ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
ΤΜΗΜΑ ΧΗΜΕΙΑΣ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΛΕΙΤΟΥΡΓΙΚΑ ΜΟΡΙΑ ΜΕΣΩ ΑΝΤΙΔΡΑΣΕΩΝ ΠΟΛΛΩΝ ΣΥΣΤΑΤΙΚΩΝ: ΕΦΑΡΜΟΓΕΣ ΣΤΗΝ ΦΑΡΜΑΚΕΥΤΙΚΗ ΧΗΜΕΙΑ ΚΑΙ ΧΗΜΕΙΑΣ ΥΛΙΚΩΝ

XIAOFANG LEI

ΥΠΕΥΘΥΝΟΣ ΚΑΘΗΓΗΤΗΣ: ΕΠΙΚ. ΚΑΘΗΓΗΤΗΣ
ΚΩΝΣΤΑΝΤΙΝΟΣ ΝΕΟΧΩΡΙΤΗΣ

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UNIVERSITY OF CRETE
DEPARTMENT OF CHEMISTRY

DOCTORAL THESIS

FUNCTIONALIZED MOLECULES VIA MCRS: APPLICATIONS IN DRUG DISCOVERY AND MATERIAL SCIENCE

XIAOFANG LEI

THESIS SUPERVISOR: ASS. PROFESSOR CONSTANTINOS NEOCHORITIS

HERAKLION 2023

TO THE PEOPLE WHO LOVE ME AND WHOM I LOVE

ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ

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Xiaofang Lei

July 2023

CURRICULUM VITAE

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EDUCATION

2019.10-now: University of Crete and University of Groningen, **Ph.D.** candidate. Organic Chemistry.

2016.9 - 2019.4：Shanghai University of Engineering Science, **M.Sc**. Materials Engineering.

2011.9 - 2015.6：Nanchang Hangkong University, **B.Sc.** Applied Chemistry.

PUBLICATIONS

[1] **Xiaofang Lei**, Xriatina Tomza, Constantinos G. Neochoritis and Alexander Dömling. Benzothiazepine Based MCR Chemistry. (Manuscript in preparation)

[2] **Xiaofang Lei**, Alexander Dömling, Constantinos G. Neochoritis. Novel materials via multicomponent reactions. (Manuscript in preparation)

[3] **Xiaofang Lei**, Alexander Dömling, Constantinos G. Neochoritis. The approaches towards functional TTFs. (Manuscript in preparation)

[4] **Xiaofang Lei**, Giasemi K. Angeli, Constantinos G. Neochoritis and Alexander Dömling. *Green Chemistry*, **2022**, *24*, 6168-6171.

[5] **Xiaofang Lei**, Giasemi Angeli, Alexander Dömling, Constantinos G. Neochoritis. *Eur. J. Org. Chem*. **2022**, e202200220.

[6] **Xiaofang Lei**, Panagiota Lampiri, Pravin Patil, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Chemical Communications*, **2021**, *57*, 6652-6655.

[7] **Xiaofang Lei,** Maria Thomaidi, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Synlett*, **2021**, *32*, 155-160;

[8] **Xiaofang Lei,** Yuanyuan Wang, Erkang Fan, and Zhihua Sun, *Organic Letters*, **2019**, *21(5)*, 1484-1487;

[9] Shengfeng Wu, **Xiaofang Lei**, Erkang Fan, and Zhihua Sun, *Organic Letters,* **2018**, 20(3), 522-525;

[10] Zhihua Sun, Shengfeng Wu, Yiru Dai, **Xiaofang Lei**. A synthetic method and an intermediate for an active molecule of an anti-leukemia cancer cell, CN108558862B;

[11] Xing Qiuju, Ma Jun, **Xiaofang Lei**, Yu Jian, Huang Qiong, Zou Jianping, Chen Wuhua, Yuan Qiangzhong, Pan Xianhui; A synthetic method of WS2-Bi3.84W0.16-O6.24 an ernary heterojunction of photodegradation organic catalyst, CN103962158B.

SKILLS AND TEACHING EXPERIENCE

- NMR, HRMS, IT-TOF, LC-MS, HPLC, IR, GC-MS, GC, Single-crystal diffractometer, powder X-ray diffractometer and Glove box etc;
- Microsoft office (Word, Excel, PPT), proficient in ChemDraw, MestReNova, Endnote, Jana (for XRD) and Apex;
- Knowing some knowledge of managing the laboratory, Experimenting and find literature independently and write articles;
- Working in BioDuro a global CRO/CMC as a Scientist Ⅰ in Department Chemistry (22 Apr. 2019-28 July 2019). Familiar with the synthetic route of Chiral macrocyclic compounds.

SELECTED AWARDS

2019-now:

- China Scholarship Council (CSC) 48 months.
- *"Hildegard, widow of Leonidas Zervas award"* for groundbreaking research in organic chemistry, which was awarded by the Academy of Athens. (**2022**)

2016-2018:

- First Prize scholarship once;
- Second Prize scholarship twice.

2011-2015:

- National Scholarship once;
- First Prize Scholarship 3 times;
- The First Prize in Woman's 3000-meter Race in the Sports-meeting (2012);
- The Second Prize in Woman's 1500-meter Race in the Sports-meeting 3 times;
- Merit Student 3 times.

ΠΕΡΙΛΗΨΗ

Στο πρώτο κεφάλαιο της διατριβής συντέθηκαν για πρώτη φορά 2-τετραζολο ινδόλια μέσω της αντίδρασης UT-4CR, τα οποία αποτελούν βιοϊσοστερή των 2-καρβοξυ ινδολίων. Πραγματοποιήθηκαν επιπλέον MCRs και διάφορες δευτερογενείς συνθετικές μετατροπές.

Στο δεύτερο κεφάλαιο, εκμεταλλευόμενοι τα ευρήματα της παραπάνω μελέτης, συνθέσαμε επιτυχώς ινδολο αμίδια μέσω της αντίδρασης U-4CR. Η διαδικασία είναι πράσινη και βιώσιμη.

Έπειτα (κεφάλαιο 3), πραγματοποιήθηκε η σύνθεση βιβλιοθηκών νέων παραγώγων διβενζοθειαζεπινών και βενζοθιαζινών. Αυτά αποτελούν προνομιούχες δομές και χρησιμοποιούνται ευρέως τόσο στην Φαρμακευτική Χημεία, όσο και στην Χημεία υλικών. Οι ενώσεις αξιολογήθηκαν με υπολογιστικές μελέτες.

Στο δεύτερο μέρος της διατριβής (κεφάλαια 4 και 5) πραγματοποιήθηκαν συνθέσεις παραγώγων με έμφαση στις εφαρμογές τους ως ημιαγωγοί. Αναφέρθηκαν συνθέσεις ενώσεων βασιζόμενες στις φλουορενόνες/φλουορένια (κεφάλαιο 4) και TTF (κεφάλαιο 5). Στα τελευταία παράγωγα, πραγματοποιήθηκαν εκτενείς μετρήσεις τόσο σε διάλυμα όσο και σε φιλμ ώστε να αξιολογηθεί η αγωγιμότητά τους. Πάνω από 50 διαφορετικά παράγωγα συντέθηκαν και στα δύο project.

Λέξεις κλειδιά: MCRs, σύνθεση ινδολίου, TTF, ημιαγωγοί, U-4CR, UT-4CR, αντίδραση Ugi-Joullié, αντίδραση Castagnoli-Cushman, αντίδραση GBB, αντίδραση vL, μόρια συστήματος δότη-δέκτη

ABSTRACT

Multicomponent reactions (MCRs) are highly efficient one-pot synthetic approaches for the synthesis of complex and versatile scaffolds. To date, these reactions are considered pillars of medicinal and organic chemistry. Surprisingly, their application in drug discovery and material science is still limited, considering their merits. For example, to the best of our knowledge, MCRs are barely used in material chemistry, particularly towards the synthesis of organic electronic materials such as tetrathiafulvalene (TTF)-based derivatives.

In this thesis, exploitation of the MCRs applications in both drug design and material science occurred. Compared with the traditional synthetic protocols, the proposed novel MCR procedures are of higher quality due to the following characteristics: mild conditions, speed, commercially available starting materials, easily scale up approaches and reduced purification steps. In this study, several bioactive and organic electronic materials via MCRs are developed. Herein, five chapters are dealing with the utilization of the MCRs. In summary, more than 160 molecules are obtained and most of these potential adducts are first time synthesized.

Chapter 1 deals with numerous functionalized indole tetrazole derivatives resulting via a green, easy and rapid two-step Ugi-tetrazole four component (UT-4CR) procedure from commercially available anilines, aldehydes and $TMSN_3$ in good to excellent yields. Catalytic hydrogenation and additional MCRs are employed to demonstrate the potential of this synthetic protocol. Additionally, this method is gram-scalable and one-pot feasible. Interestingly, an eIF4A3 inhibitor is obtained via this *de novo* protocol.

Chapter 2 exploits the classical Ugi four component reaction (U-4CR) to C2 functionalized indole amides. Excitingly, 20 derivatives are isolated from anilines, glyoxal dimethyl acetal, formic acid and isocyanides via an innovative 2-step protocol in good to excellent yields. These novel indole syntheses have several advantages, such as speed, highly sustainable, mild reaction conditions, low toxicity of the building blocks, high safety standards, broad substrate scope and good yields. This gram-scalable synthetic method is an easier and faster alternative in order to access numerous bioactive molecules. We have exploited

all the above by the preparation of **2t**, an anti-tuberculosis agent; it has demonstrated excellent features, such as time, amounts of inorganic and organic solvents, process mass intensity (PMI), E-factor and atom economy (AE). Additionally, the SETD2 inhibitor (**2r**) and another anti-tuberculosis agent (**2s**) are also obtained simply under our protocol.

Chapter 3 presents a library of 45 dibenzothiazepines and benzothiazepines via five different MCRs. Those scaffolds are widely used in biology and material science. Interestingly, most of these polycyclic and rigid dibenzothiapines with high complexity obey to the rule of 5 (**Ro5**) according to the CSD analysis. In addition, several single crystal structures of these compounds have been solved, offering insights for their potential binding mode.

The fluorene structural motif is widely present in numerous natural products and bioactive compounds. This scaffold is a useful candidate in materials science and drug discovery. In Chapter 4, a library of 23 fluorene-fused derivatives is depicted through IMCRs. These novel scaffolds are synthesized by functionalizing a fluorene building block. This work shows the huge potential of the MCRs in the diversity and complexity of fluorene-based compounds.

Chapter 5 expands the scope of the MCRs on the functionalization of TTF to obtain numerous electronic adducts. Herein, more than 30 TTF-fused compounds obtained via four different MCRs. In addition, the synthesis of molecules with a D-A or D-π-A system occurred (Scheme 4). This important feature allows an intramolecular charge transfer (ICT) to occur. The single X-ray structure displays a planar character that could help the electron delocalization. What's more, electronic measurements such as Hall measurement, the energy gap between the HOMO and LUMO, and the measurement of resistance are employed. So far, the applications of the TTF-based derivatives with D-A systems in organic semiconductors and molecular machines fields are limited by the efficient methods. Arguably, the new procedures will build a library of various TTF derivatives and facilitate the rapid development of novel materials.

Key words: MCRs, indole synthesis, TTF, semiconduntors, U-4CR, UT-4CR, Ugi-Joullié reaction, Castagnoli-Cushman reaction, GBB reaction, vL reaction, donor-acceptor system molecules

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AIM AND SCOPE

Multicomponent reactions (MCRs) are known as one-pot reactions employing more than two starting materials, where most of them are present in the final product regardless of the involved mechanisms. They constitute a powerful tool that provides access to various heterocyclic drugs, advanced materials and in general highly functionalized molecules. In addition, by MCR's extended molecular complexity and diversity, efficiency and high atom economy are feasible.[1] Regularly, several tags are given to MCRs (Figure 1), such as atom economy, efficiency and convergence. Therefore, MCRs are often an alternative to sequential and time-consuming multistep synthesis.

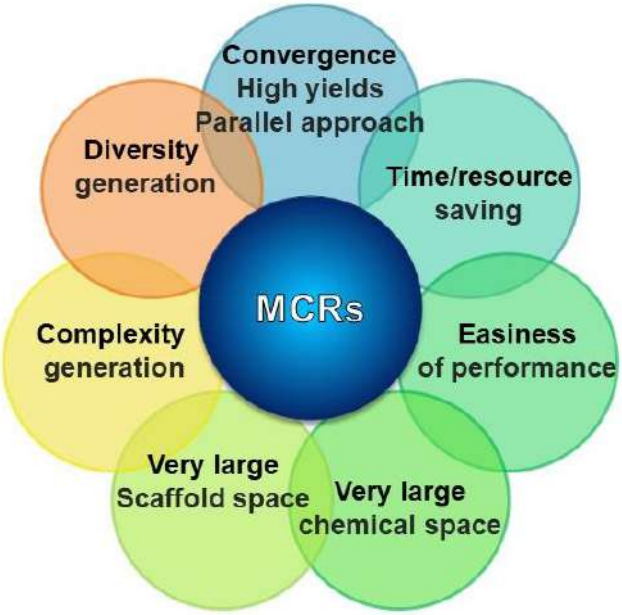


Figure 1 Basic characteristics of modern multi-component reactions (MCRs)

Surprisingly, the applications in drug discovery are limited regarding the advantages of this chemistry.[2] In fact, approximately 5% of the current drugs on the market can be synthesized via MCR despite the traditional sequential pathway.[3] Characteristic examples of drugs synthesized by MCR are lidocaine,[4] praziquantel,[5,6] telaprevir,[7] olanzapine,[8] clopidogrel,[9] lacosamide,[10] carfentanil,[11] ivosidenib[12] and levetiracetam (Figure 2).[13] Interestingly, epelsiban[14] and almorexant[15] are currently in clinical trials (Figure 2).

Moreover, MCRs lead to highly innovative functionalized structural motifs with unique features. Rational synthetic pathways using MCRs can potentially yield a range of functionalized materials with tailorable properties and numerous applications. Undoubtedly, MCR-functionalized materials can connect materials science and applied chemistry.

In the present Ph.D. thesis, the utilization of MCRs both in the synthesis of novel bioactive compounds and material science is demonstrated.

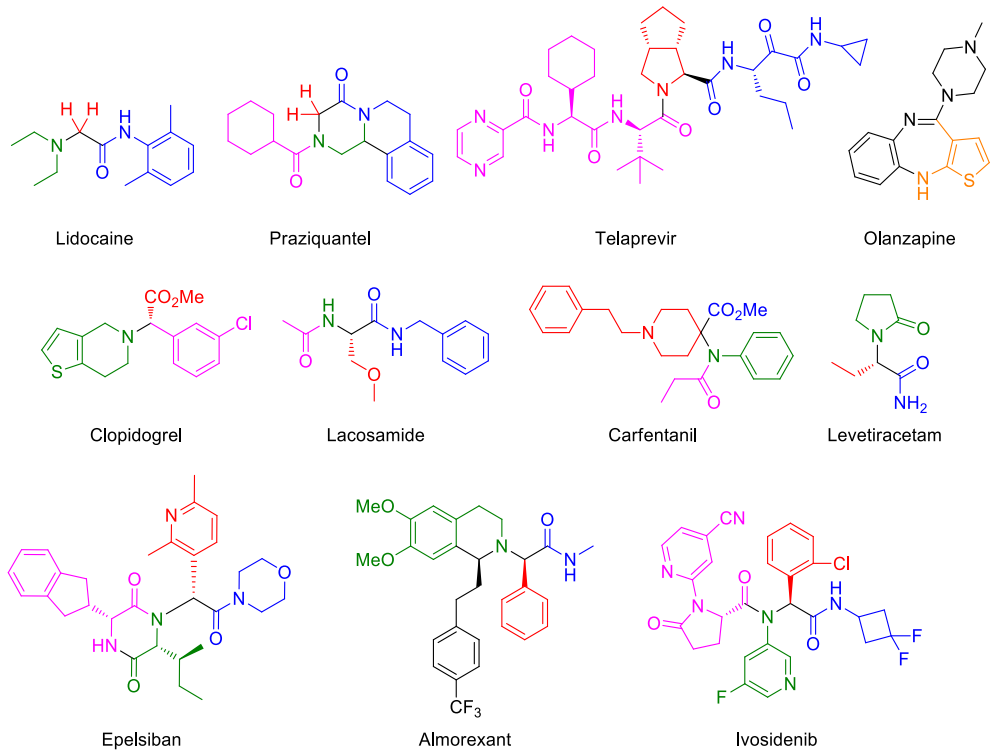


Figure 2 Drugs synthesized via multi-component reactions (MCRs)

1. Synthesis of bioactive heterocycles via MCRs

Indole is a privileged, naturally occurring heterocyclic compound, the structure of which comprises of a six-membered benzene ring tethered to a five-membered pyrrole ring. This important ring, with its 10 π-electrons, follows up the Huckel's rule of aromaticity, whereas it is more prone to electrophilic substitution reactions, similar to the benzene ring.[16,17] It was discovered in 1866 by Adolf von Baeyer[18] and both naturally occurring and synthetic indoles exhibit wide-ranging biological activity.[19] Indole containing bioactive compounds often

have a distinct binding mode to their receptors with high affinity. Of particular note, myriads applications about indoles have been found for centuries in a plethora of areas, such as: pigments, fragrances, pharmaceuticals, agrochemicals and materials.[20] Consequently, the continued development of synthetic strategies towards this divergent scaffold has been a central topic in organic synthesis over the last 100 years.[19] In addition, the current synthetic methodologies, to the best of our knowledge, often suffer from harsh reaction conditions, limited substrate scope, use of halogenated hydrocarbons as solvents or other sustainability issues. For example, the classical Fischer indole synthesis is often performed under highly acidic refluxing conditions of the precondensed phenylhydrazone derivatives.[21] Our aim is to find a milder, sustainable and more effective indole syntheses. Therefore, in Chapter 1, an unprecedented mild, two-step synthesis of 2-tetrazole substituted indoles via the Ugi-tetrazole reaction combined with an acid induced ring closure in methanesulfonic acid is reported. A library of 24 multi-substituted tetrazole indoles is generated. It is revealed that our method is rapid, easy, gram scalable with wide scope giving efficient access to functionalized indole derivatives. One pot processes are also feasible. Several post modifications are reported increasing both the diversity and the complexity of the targeted compounds. In addition, a potent eukaryotic initiation factor 4A3 (eIF4A3) inhibitor is synthesized under our synthetic pathway in only 3 steps in a good overall yield.

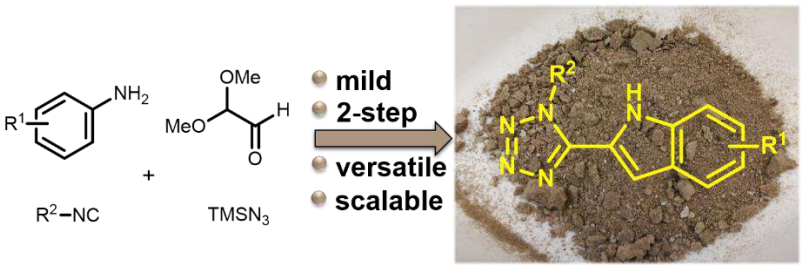


Figure 3 The UT-4CR protocol towards the tetrazole indoles.

Based on our ongoing interest in indole syntheses, as presented in Chapter 2, the application of an Ugi four-component reaction now combined with an acidic ring closure is studied. This synthesis of the indole-2-carboxamide scaffolds employs commercially available anilines, glyoxal dimethyl acetal,

formic acid and isocyanides. This protocol follows the principles of green chemistry, where factors as mass intensity (PMI), E-factor and atom economy (AE) are reported. Additionally, this synthetic methodology is rapid, atom economic and environmentally friendly compared, to the existing ones, with a high functional groups tolerance. Gram-scale and one-pot procedures are also feasible.

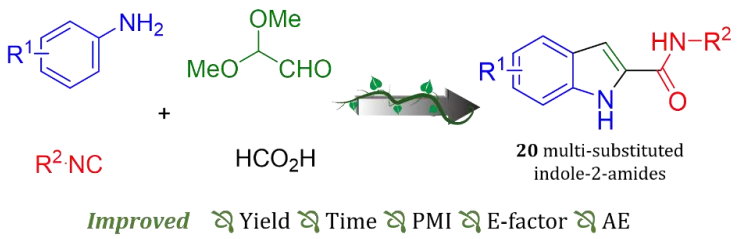
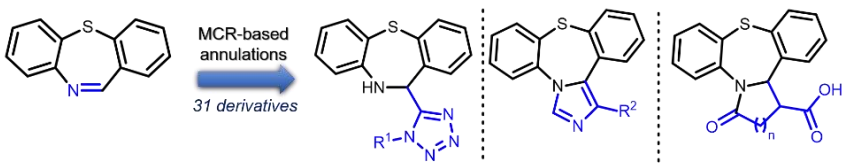


Figure 4 The U-4CR green protocol towards the indole-2-carboxamide scaffolds.

Many compounds containing the privileged benzothiazepine core, are commercially available drugs and bioactive compounds, i.e. quetiapine, metiapine and clotiapine with an antipsychotic mechanism of action.[22-27]

Initially, synthetic methods towards the synthesis of dibenzothiazepine derivatives via the MCRs are exploited. In Chapter 3, a two-step route via MCR-based annulations yields the desired dibenzothiazepine-based adducts. Hence, a library of 31 tetracyclic 1,5-tetrazole-, fused imidazo- and lactam-1,5-dibenzothiazepines is obtained, whereas scale-up and one-pot procedures are also demonstrated. Noteworthy, over 70% of this library comply with the rule of 5 (**Ro5**), by which most of the compounds have a spherical, rigid shape of high complexity. Then, we investigated the synthesis of the related six-membered ring of benzothiazines. We have successfully obtained 12 benzothiazine derivatives via an Ugi-3CR.



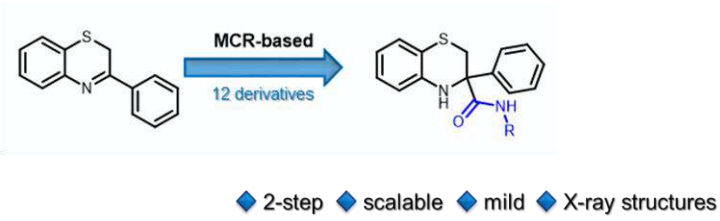


Figure 5 The synthetic protocols of the benzothiazepine-fused compounds based on the MCRs.

2. Synthesis of novel functionalized molecules via MCRs

Nowadays, fluorene adducts are in the epicenter of both functionalized organic materials such as optoelectronics,[28] solar cells[29] and bioactive compounds.[30,31] Due to their unique electronic properties, there are found in charge-transfer complexes (CTC), electron-deficient materials with semiconducting and photoconducting properties and electron transport materials.[28,29,32] Fluorenone is a privileged structure with relatively planar structure, high thermal stability and good electron-transport properties. Many of its derivatives exhibit aggregation-induced emission (AIE) and great bathochromically solid-state fluorescence.[33] In addition, the fluorene scaffold is present in multiple natural products and bioactive compounds.[34] In Chapter 4, such compounds are developed via isocyanide-based multicomponent reactions (IMCRs). Six different IMCRs are employed for a fluorene-based library in good yields and broad scope. By MCRs, we can access fluorene-based derivatives much easier than the existing, classical methods.

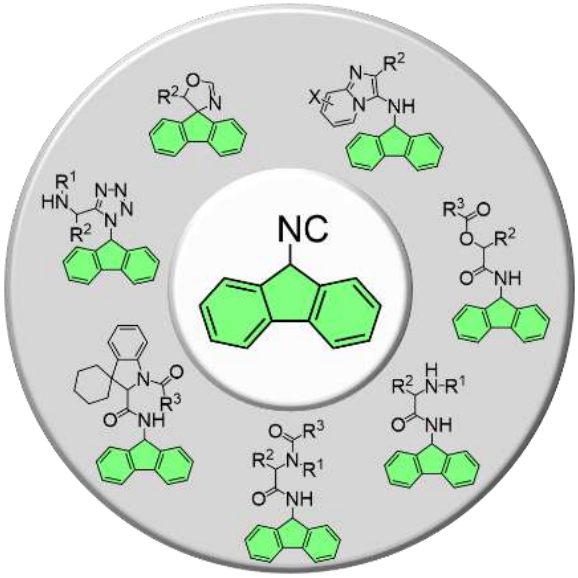


Figure 6 The synthetic protocols of the fluorene-fused compounds based on the MCRs.

Tetrathiafulvalene (TTF) consists of four sulfur atoms with remarkable redox properties.[35] This privileged structure is a central unit in molecular electronics since it is proposed as a building unit of the *first theoretical model of the single molecular* rectifier in 1974.[36] It possesses a brilliant *p*-donating ability and three stable redox states. Notably, TTF scaffolds are involved in supramolecular motifs. Therefore, in Chapter 5, the design and synthesis of a series of potential TTF-based compounds via MCRs occurred. Several x-ray structures of the synthesized TTF derivatives are obtained, revealing their planar 3D structure. The electronic character, resistance and free carrier mobility are also evaluated.

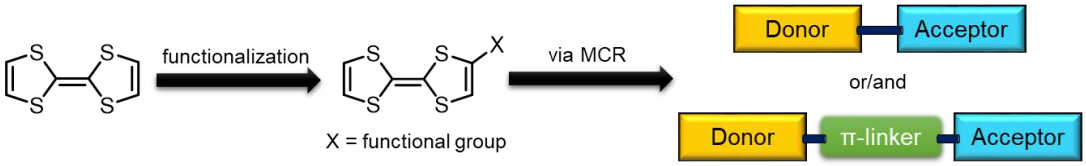


Figure 7 The synthetic protocols of the TTF-fused compounds based on the MCRs.

Key words: MCRs, Indole synthesis, benzothiazepine, fluorene, Tetrathiafulvalene (TTF), indole-2-carboxamide, Ugi-tetrazole reaction, Ugi-4CR reaction, GBB reaction, vL reaction.

REFERENCES

1. Collet, J. W., Roose, T. R., Ruijter, E., Maes, B. U. W., & Orru, R., *Angew. Chem. Int. Ed*., **2020**, *59 (2),* 540-558.
2. Brown, D. G., Boström, J., *J. Med. Chem*., **2016**, *59*, 4443-4458.
3. Zarganes-Tzitzikas, T., Dömling, *Org. Chem. Front.,* **2014**, *1*, 834-837.
4. Ugi, I., Steinbrückner, C. Ü ber Ein Neues Kondensations Prinzip., *Angew. Chem. Int. Ed*., **1960**, *72*, 267-268.
5. Dömling, A., Khoury, K., *ChemMedChem*., **2010**, *5*, 1420-1434.
6. Cao, H., Liu, H., Dömling., *Chem. - Eur. J.*, **2010**, *16*, 12296-12298.
7. Znabet, A., Polak, M. M., Janssen, E., de Kanter, F. J. J., Turner, N. J., Orru, R. V. A., Ruijter, E., *Chem. Commun.*, **2010**, *46*, 7918-7920.
8. Gewald, K., Schinke, E., Böttcher, H., *Chem. Ber.,* **1966**, *99*, 94-100.
9. Gurbel, P. A., O'Connor, C. M., Cummings, C. C., Serebruany, V. L., *Pharmacol. Res*., **1999**, *40*, 107-111.
10. Wehlan, H., Oehme, J., Schafer, A., Rossen, K., *Org. Process Res. Dev.*, **2015**, *19*, 1980-1986.
11. Varadi, A., Palmer, T. C., Haselton, N., Afonin, D., Subrath, J. J., Le Rouzic, V., Hunkele, A., Pasternak, G. W., Marrone, G. F., Borics, A., et al., *ACS Chem. Neurosci.,* **2015**, *6*, 1570-1577.
12. Popovici-Muller, J., Lemieux, R. M., Artin, E., Saunders, J. O., Salituro, F. G., Travins, J., Cianchetta, G., Cai, Z., Zhou, D., Cui, D., et al., *ACS Med. Chem. Lett.,* **2018**, *9*, 300-305.
13. Cioc, R., Schaepkens van Riempst, L., Schuckman, P., Ruijter, E., Orru, R., *Synthesis*., **2017**, *49*, 1664-1674.
14. Borthwick, A. D., Liddle, J., *Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany,* **2013**, pp 225-256.
15. Aissaoui, H., Cappi, M., Clozel, M., Fischli, W., Ralf, K., *World Patent WO2001068609A120010920*, **2000**.
16. Jyothi Dhuguru, Rachid Skouta. *Molecules,* **2020**, *25* (7), 1615.
17. Xiaofang Lei, Panagiota Lampiri, Pravin Patil, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Chemistry Communication*, **2021**, *57*, 6652-6655.

18. Baeyer, A.. *Ann. der Chemie und Pharm*., **1866**, *140*, 295-296.
19. Martyn Inman, Christopher J. Moody. *Chem. Sci.*, **2013**, *4*, 29-41.
20. Catalysis Yuan-Zheng Cheng, Qing-Ru Zhao, Xiao Zhang, Shu-Li You. *Angew. Chem*. **2019**, *131*, 18237-18242.
21. Xiaofang Lei, Giasemi K. Angeli, Constantinos G. Neochoritis, Alexander Dömling. *Green Chemistry*, **2022**, *24*, 6168-6171.
22. J. Xiao, R. B. Free, E. Barnaeva, J. L. Conroy, T. Doyle, B. Miller, M. Bryant-Genevier, M. K. Taylor, X. Hu, A. E. Dulcey, et al., *J. Med. Chem*. **2014**, *57*, 3450-3463.
23. K. Komossa, A. M. Depping, A. Gaudchau, W. Kissling, S. Leucht, *Cochrane Database Syst. Rev*. **2010**, 1-230.
24. M. Zare, A. Bazrafshan, *Cochrane Database Syst. Rev*. **2017**, 1-41.
25. G. Seminara, V. Trassari, N. Prestifilippo, R. Chiavetta, C. Calandra, *Minerva Psichiatr*. **1993**, *34*, 95-99.
26. D. Saha, G. Jain, A. Sharma, *RSC Adv*. **2015**, *5*, 70619-70639.
27. V. Devi, G. Singh, V. Monga, *J. Heterocycl. Chem*. **2020**, *57*, 3255- 3270.
28. Perepichka, I. F., Popov, A. F., Orekhova, T. V., Bryce, M. R., Andrievskii, A. M., Batsanov, A. S., Howard, J. A. K., Sokolov, N. I., *J. Org. Chem.,* **2000**, *65*, 3053-3063.
29. Lim, C. J., Lei, Y., Wu, B., Li, L., Liu, X., Lu, Y., Zhu, F., Ong, B. S., Hu, X., Ng, S.C., *Tetrahedron Lett.,* **2016**, *57*, 1430-1434.
30. Xia, J. B., Zhu, C., Chen, C., *J. Am. Chem. Soc.,* **2013**, *135*, 17494-17500.
31. Ni, S., Yuan, Y., Huang, J., Mao, X., Lv, M., Zhu, J., Shen, X., Pei, J., Lai, L., Jiang, H., Li, J.. *J. Med. Chem.,* **2009**, *52*, 5295-5298.
32. Chen, T., Chen, Z. Q., Gong, W. L., Li, C., Zhu, M. Q., *Mater. Chem. Front.,* **2017**, *1*, 1841-1846.
33. Xu, F., Wang, H., Du, X., Wang, W., Wang, D. E., Chen, S., Han, X., Li, N., Yuan, M.S., Wang, J., *Dye. Pigment.,* **2016**, *129*, 121-128.
34. Shi, Y., Gao, S.. *Tetrahedron,* **2016**, *72*, 1717-1735.
35. David Canevet, Marc Sallé, Guanxin Zhang, Deqing Zhang and Daoben Zhu, *Chem. Commun.*, **2009**, 2245-2269.
36. Coleman, L. B., Cohen, M. J., Sandman, D. J., Yamagishi, F. G., Garito, A. F., & Heeger, A. J., *Solid State Communications,* **1973***, 12 (11),* 1125-1132.

Chapter 1

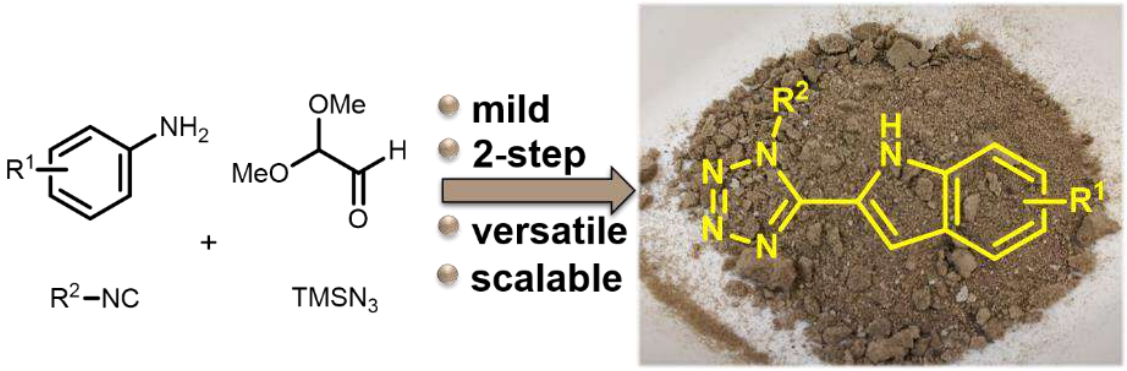
Tetrazole Indole Synthesis via MCRs

This chapter is based on the artictle: " A multicomponent tetrazolo indole synthesis*", by* **Xiaofang Lei**, Panagiota Lampiri, Pravin Patil, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Chemical Communications*, **2021**, *57*, 6652-6655.

The Academy of Athens honored this work with the "Hildegard, widow of Leonidas Zervas award" for its innovative work in organic chemistry.

ABSTRACT

According to literature, indole moieties in natural products and pharmaceuticals are of outmost importance. As such, the utilization of innovative and efficient synthetic approaches is necessary. The present work depicts an Ugi tetrazole reaction followed by an acidic closure reaction to obtain the targeted indole core. The two-step synthesis uses commercially available anilines, aldehydes and $TMSN_3$. This innovative methodology affords a variety of 2-tetrazole indoles (32 derivatives) in good to exceptional yields employing inexpensive starting materials with mild conditions. Additionally, gram-scaled synthesis and various post-reactions are reported, whereas an eIF4A3 inhibitor is obtained.



INTRODUCTION

Indole has a long history, dating back to Adolf von Baeyer's discovery over 150 years ago. It is one of the most important scaffolds because it is an essential component of many drugs and natural products.[1-3] As far as we know, indole cores are present in various pharmaceuticals, such as neurotransmitters, anticancer drugs and psychedelic drugs (Figure 1, A). Indole-based bioactive compounds, by all accounts, have a unique binding mode to the corresponding receptors. For instance, in the MDM2 and p53 interaction, the tryptophan W23 indole core acts as the adhesive between the amino acids protein domains (Figure 1, B).[22,23] It has a distinct size with a hydrogen bond donating group -NH (exemplified in the aminoacid tryptophane). Furthermore, the electron-rich 5-membered pyrrole ring undergoes electrophilic additions.

In 1883, Emil Fischer described one of the most famous and highly applicable synthetic protocols.[4] However, this synthetic procedure always performs under highly acidic refluxing conditions of precondensed phenylhydrazone derivatives.[5] The synthesis of the hazardous phenylhydrazine precursors involves the diazotization of aniline derivatives, the reduction of the resulting diazonium salt with an excess amount of sodium sulfite and the hydrolysis of phenylhydrazine sulfonic acid salts with hydrochloric acid, also known as the Fischer phenylhydrazine synthesis.[6] On the other hand, the alternative method to phenylhydrazines involves the metal catalyzed coupling of the phenyl halides.[7,8] Nowadays, there are numerous examples[9,10] of easy and efficient indole syntheses reported. One of three-component indole syntheses involving mono-substituted alkynes, bromoarenes and trifluoroacetylated anilines has been published by Senanayake's group,[11] yet, the number of multicomponent reactions (MCRs) in indole syntheses is still limited.[12,13]

A characteristic example of a reported indole synthesis constitutes the Bischler-Möhlau (BM) reaction. This method deals with the alkylation of anilines with bromoacetophenones under harsh reaction conditions and acid-induced indole formation (Figure 1, C).[14,15] Despite its success, this methodology is neither practical nor compatible with a diverse range of functional groups. Additionally, patented synthetic pathways with milder conditions involve the

cyclization of (*N*-acetylated or sulfonylated) aniline acetaldehyde diethyl acetals to indoles.[16-19] Nevertheless, this sequential synthetic approach and the limited access to aniline acetaldehyde acetals derivatives lead to this methodology lacking variability.[20,21] We are aiming for a mild multicomponent reaction approach which would allow for a greater variability of the different components and positions (R^1, R^2) to access highly substituted indoles to avoid the issues of the BM protocol. The Ugi-tetrazole four-component reaction (UT-4CR) is employed by reacting substituted anilines, isocyanides, 2,2-dimethoxyacetaldehyde in aqueous solution and $TMSN_3$. Then, the following acidic closure procedure yields the desired indole-core products under the mild and easy-going conditions (Figure 1, C). We believe that this novel method to indole synthesis has good application prospects.

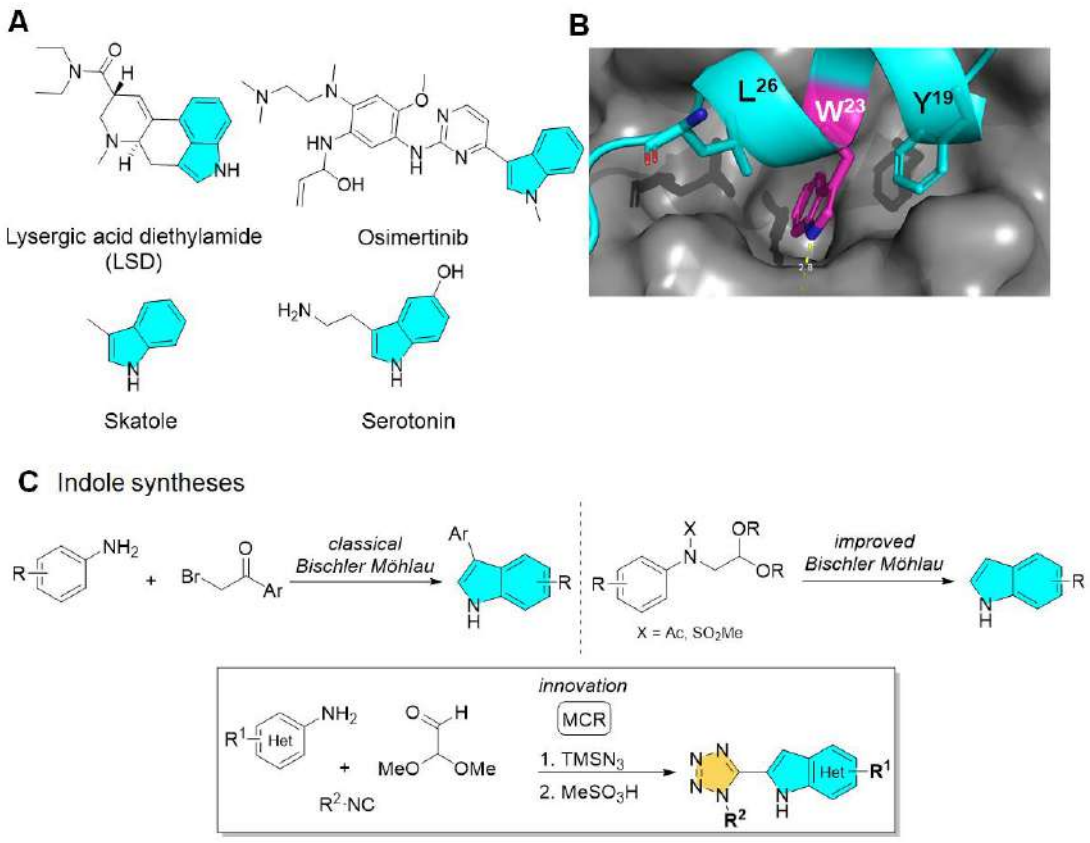
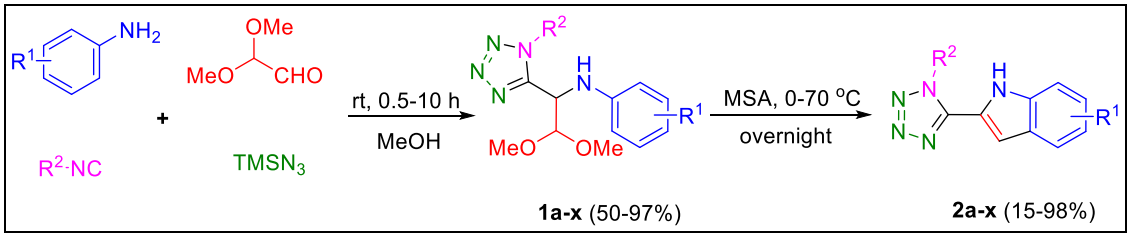


Figure 1 The nature of indole. A: Several indole-containing natural products and pharmaceuticals. B: Indole in structural biology (PDB ID 1YCR). W23 (tryptophan) binding to MDM2. C: Novel synthesis of indole.

RESULTS AND DISCUSSION

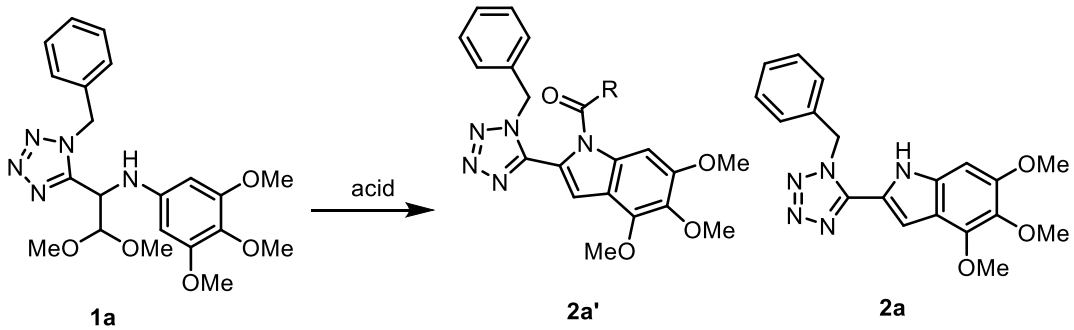
In this work, an Ugi-tetrazole four-component reaction (UT-4CR) is employed to obtain the desired indole-based compounds. We react substituted anilines, isocyanides, 2,2-dimethoxyacetaldehyde in aqueous solution and $TMSN_3$ proceeded smoothly at room temperature, yielding the derivatives **1a-x** in good to excellent yields (Scheme 1).

After testing several acidic closure conditions, the optimized one includes heating at 70 °C in anhydrous methanesulfonic acid.[24-28] Notably, formic and acetic acids can also be employed. However, the isolation of the *N*-formylated or acetylated tetrazole indoles instead of the free tetrazole indole has occurred (see Table 1).



Scheme 1 the protocol towards the indole tetrazoles.

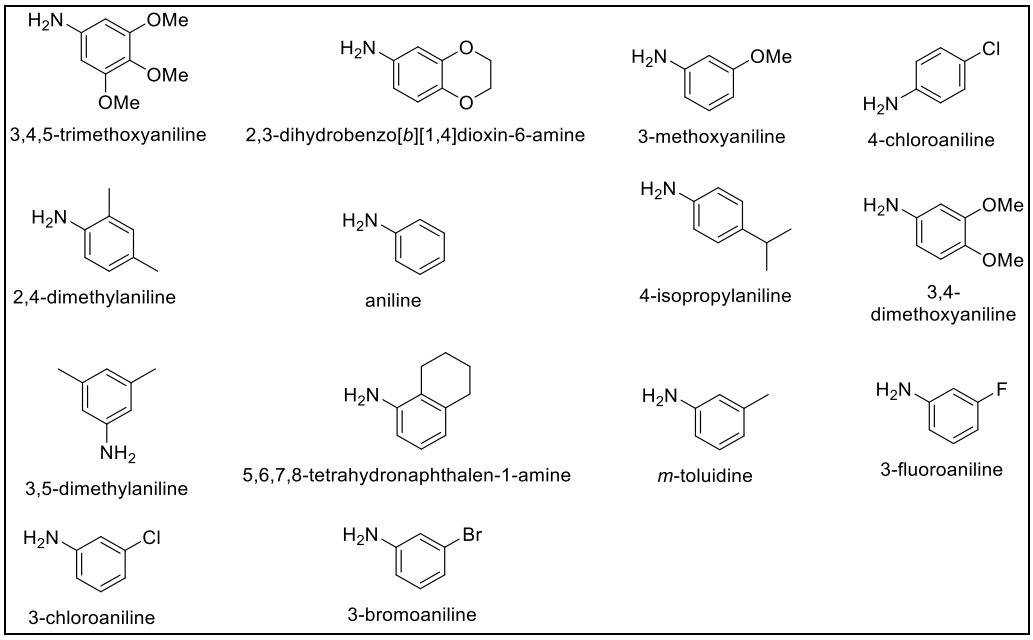
Table 1 Acidic closure reaction



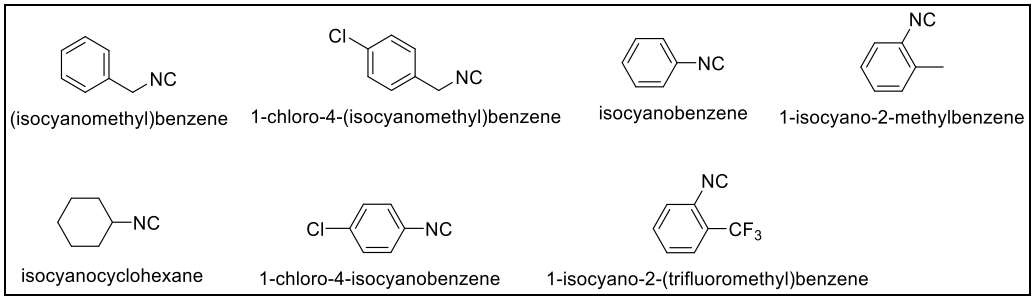
Entry	Acid	Catalyst	Temperature (°C)	Time	Solvent	Yield
1	formic acid	none	80	overnight	-	**2a'**:**2a** (65%: 22%)

2	acetic acid	$ZnCl_2$	120	48 h	-	**2a'**:**2a** (30%:30%)
3	acetic acid	$ZnCl_2$	rt	48 h	-	-
4	HCl	none	50	24 h	dioxane	**2a**: 30%
5	HCl	none	50	24 h	water	**2a**: 41%
6	HCl	none	50	24 h	isopropanol	**2a**: 45%
7	$TiCl_4$	none	rt	48 h	DCM	traces
8	methanesulfonic acid	none	45	15 h	-	**2a**: 90%
9	methanesulfonic acid	none	70	2 h	-	**2a**: 91%

This versatile protocol utilizes various substituted anilines and isocyanides. The substitution of isocyanides and anilines consists of both electron-donating (EDG) and withdrawing groups (EWG) as shown below (Schemes 2, 3).



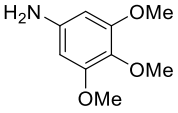
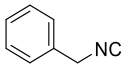
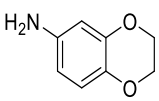
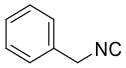
Scheme 2 Employed anilines in the 1st step.

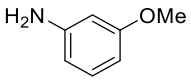
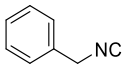
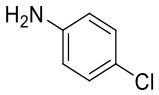
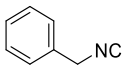
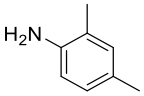
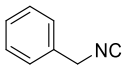
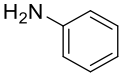
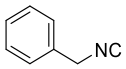
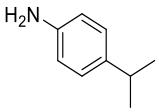
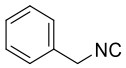
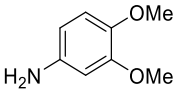
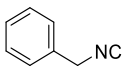
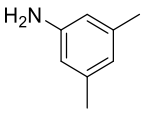
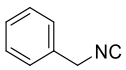
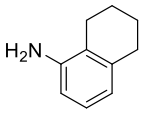
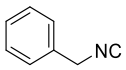
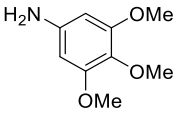
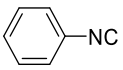
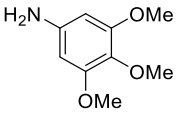
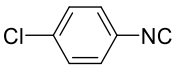
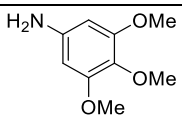
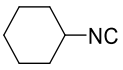
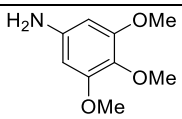
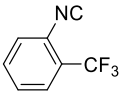
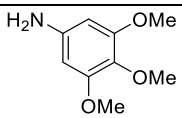


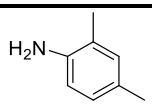
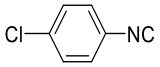
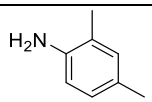
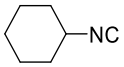
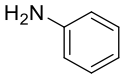
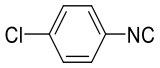
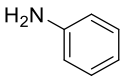
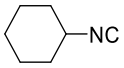
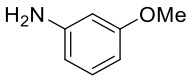
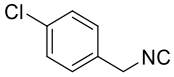
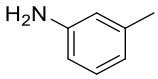
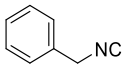
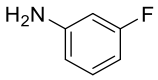
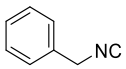
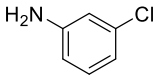
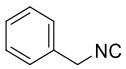
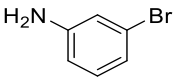
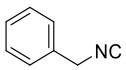
Scheme 3 Employed isocyanides in the 1st step.

The targeted multi-substituted 2-tetrazole indole derivatives **2a-x** are isolated successfully and very efficiently under this two-step manner in good to excellent yields. In several cases, UT-4CR intermediates and final products precipitated after a short reaction time (see EXPERIMENTAL SECTION). Various substituted isocyanides prove efficient for this synthetic methodology, such as aryl, benzylic, and aliphatic. EDGs on substituted anilines are used because of the presumed electrophilic ring closure mechanism. Anilines with EWGs, i.e., entry **d**, reacted insufficiently. Indole scaffolds derived from *meta*-substituted anilines, such as **b-c, h**, **t-x** and **2y,** yield two different regio isomers. After several optimization attempts of the reaction temperature (in the case of **2**) or selective precipitation (in the case of **c**, **v**, and **2y**), the major isomer is isolated in 77%, 79%, 50% and 69% yield, respectively. Products deriving from **u**, **w** and **x** are obtained as mixtures of the regioisomers (see EXPERIMENTAL SECTION)

Table 2 The yields of Ugi-Tetrazole products (1st step) and 2-tetrazole indole (2nd step)

Entry	Aniline	Isocyanide	1st step yield (%)	2nd step yield (%)
a			97	91
b[1]			81	92 *(regio isomer ratio:5:1)*

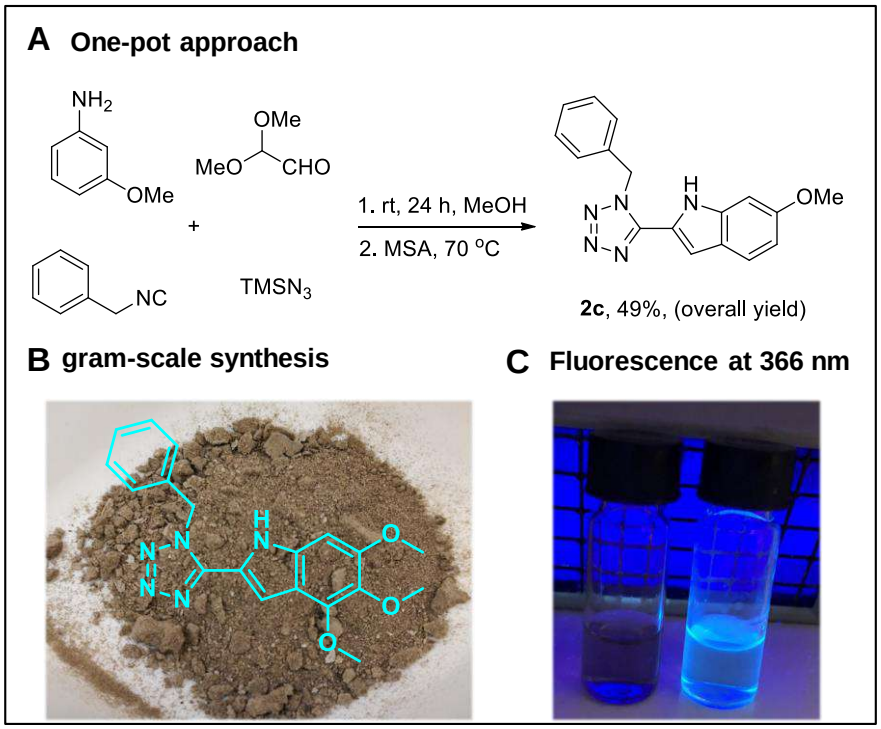
c[1]			94	87 *(regio isomer ratio:10:1)*
d			91	15
e			95	67
f			82	51
g			85	71
h[1]			94	97 *(regio isomer ratio: 5:1)*
i			95	86
j			81	98
k			67	91
l			96	81
m			79	77
n			53	67
o			91	84

p			66	71
q			50	75
r			53	51
s			52	66
t[1]			89	88 *(regio isomer ratio: 9:1)*
u[1]			97	96 *(regio isomer ratio: 3:2)*
v[1]			91	92 *(regio isomer ratio: 6:5)*
w[1]			90	86 *(regio isomer ratio: 5:4)*
x[1]			83	94 *(regio isomer ratio: 2:1)*

The yields of both steps are reported (*first and second step, respectively*), [1]*obtained as regiosomers (ratio shown in parenthesis, yield refers to the mixture), structure of the major regioisomer is given in*

EXPERIMENTAL SECTION

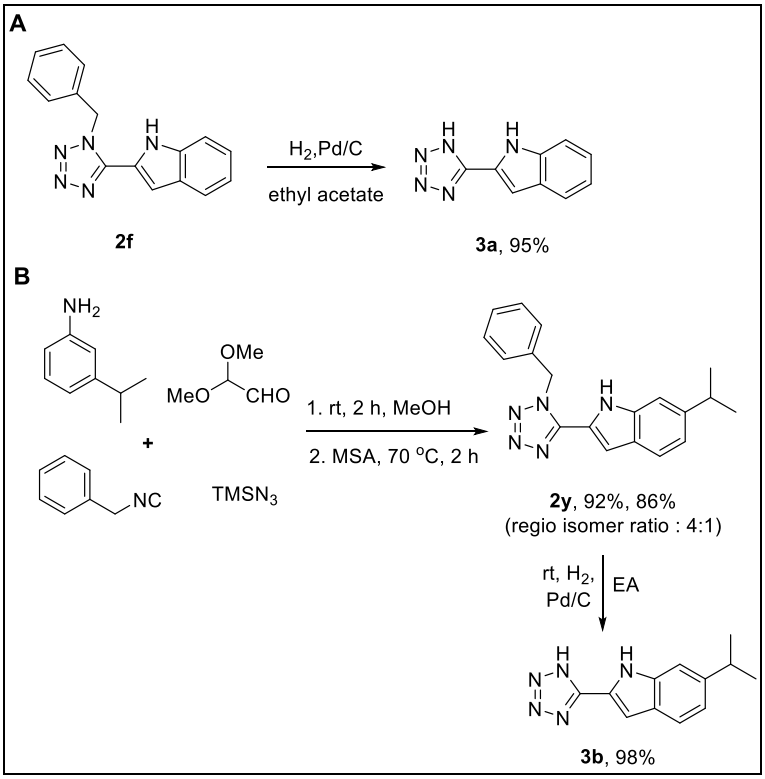
Then, the feasibility of the one-pot procedure is investigated; compound **2c** is isolated in a one-pot procedure with a 49% yield (Scheme 4, A). Furthermore, this protocol is successfully scaled up for compounds **1a** (10 mmol, 4.15 g, 97%) and **2a** (5 mmol, 2.15 g, 91%). In matter of fact, scaffolds **1a** and **2a** precipitated as brown solids without further purification (Scheme 4, B). Noteworthy, compounds **2**a-**y** exhibit a characteristic fluorescence at 366 nm (Scheme 4, C).



Scheme 4 A: One-pot approach for the isolation of **2c** without intermediate purification. B. Scaled up synthesis of **2a**. C. Fluorescent sample **2a** (right) in acetone compared to the non-fluorescent starting material (left).

Frequently, 2-indole carboxylic acids are present as effective inhibitors against numerous targets. Additionally, 1,5-disubstituted tetrazoles are considered bioisosteres of carboxylic acids.[29-32] Therefore, the 2-indole carboxylic acid bioisostere **3a** is isolated after hydrogenation under Pd/C (Scheme 5, A). Then, an UT-4CR yielded the desired indole-based scaffold **2y**, followed by catalytic hydrogenation yielded the bioactive tetrazole indole **3b** via benzyl isocyanide cleavage. This compound is a potent eukaryotic initiation

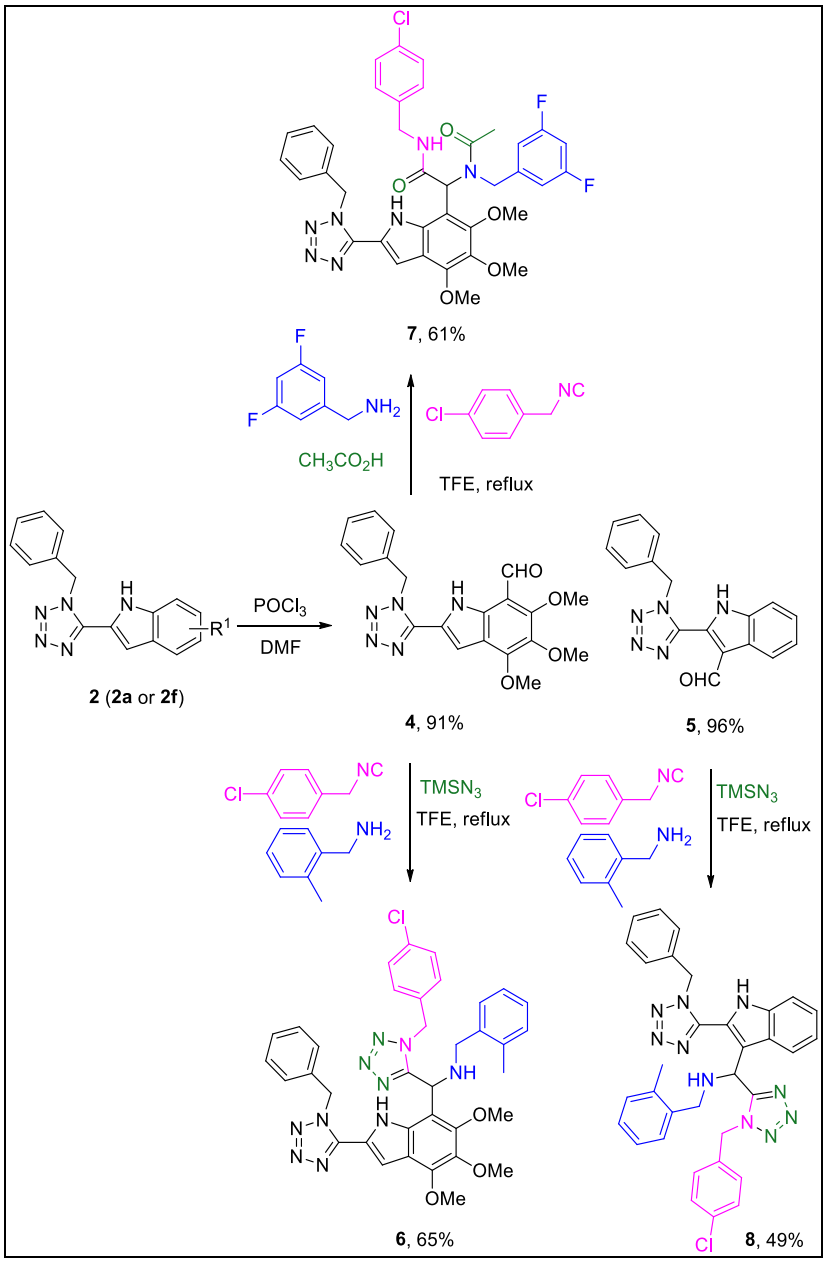
factor 4A3 (eIF4A3) inhibitor.[33] The overall synthesis is completed in only three steps with an overall yield of 62% (Scheme 5, B).



Scheme 5 **A**. Synthesis of the 2-indole carboxylic acid bioisostere **3a**. **B**. Synthesis of the eIF4A3 inhibitor **3b**

To further demonstrate the potential of our synthetic protocol, functionalization of the tetrazole indole derivatives **2** occurred, via the Vilsmeier-Haack reaction. Initially, a formylation reaction is used to functionalize the tetrazole indole moiety, and then a second MCR took place. The design of this synthetic methodology is based on the well-known union of MCRs.[34] Interestingly, **2a** gives a mixture (ratio: 1:1) of two formylated adducts on the 3- and 7 positions of the indole core under this formylation procedure. This is probably due to the electron-rich aromatic ring of **2a** (shown in EXPERIMENTAL SECTION). Tuning the formylation by changing the addition ratio of $POCl_3$ and temperature, we formylate exclusively the 7-position of the indole ring, yielding compound **4** in 91% yield. Under the same experimental conditions, compounds **2f**, yielded the indole derivative **5** with a 96% yield (Scheme 6). Then, the additional UT-4CR and the classical Ugi four component reaction (U-

4CR) are employed to the formylated indoles. To our satisfaction, the UT-CR and U-4CR adducts **6**, **7** and **8**, respectively are obtained to increase the complexity and variety of our initial 2-tetrazole indoles (Scheme 6).



Scheme 6 Functionalization of the formyl indole derivatives **4** and **5** via additional UT-4CR and U-4CR

In support of the obtained scaffolds **2** and **4**, the crystal structure of the latter is solved (Figure 2). An intramolecular H-bond of 2.3 Å between the -NH and the -CHO is revealed.

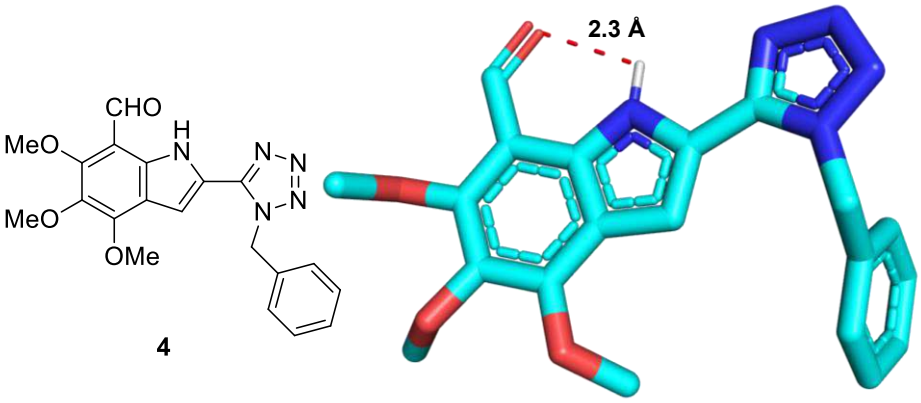


Figure 2 Crystal structure of the formylated tetrazolo-indole **4** (CCDC 2077271)

The novel approach reported in the present work is a significant improvement over the previous Bischler-Möhlau-type indole synthesis due to the mildness of the reaction conditions and also offers access to 1,5-disubsubstituted tetrazoles with beneficial physicochemical properties[35] and bioisosterism to carboxylic acids.[36] Furthermore, several tetrazole-indole derivatives have been reported as selective ATP-competitive eIF4A3 inhibitors,[37] angiotensin II-1 antagonists,[38] nociceptin/orphanin FQ (N/OFQ) receptor antagonists[39] and potential antiallergy agents.[40]

CONCLUSIONS

In summary, we developed a diverse and scalable indole synthesis protocol, which can be added to the toolbox of indole syntheses. The method reported in the present study provides an easy and rapid access to functionalized indole derivatives that can be potentially used in drug discovery as bioisosters of 2-indole carboxylic acids and amides, amongst other applications. Moreover, a multi-gram synthesis and several post-modifications are demonstrated which exponentially increase the variety and complexity of the targeted compounds.

REFERENCES

1. Baeyer, A., *Ann. der Chemie und Pharm.*, **1866**, *140*, 295-296.
2. Thanikachalam, P. V., Maurya, R. K., Garg, V., Monga, V., *Eur. J. Med. Chem.*, **2019**, *180*, 562-612.
3. Dorababu, A., *RSC Med. Chem.*, **2020**, *11*, 1335-1353.
4. Fischer, E., Jourdan, F., *Berichte der Dtsch. Chem. Gesellschaft*, **1883**, *16*, 2241-2245.
5. B. Robinson, *Chemical Reviews*, **1963**, *63*, 373-401.
6. E. Fischer, *Berichte der deutschen chemischen Gesellschaft*, **1875**, *8*, 589-594.
7. S. V. Kumar and D. Ma, *Chinese Journal of Chemistry*, **2018**, *36*, 1003-1006.
8. J. Y. Wang, K. Choi, S. J. Zuend, K. Borate, H. Shinde, R. Goetz and J. F. Hartwig, *Angewandte Chemie International Edition*, **2021**, *60*, 399-408.
9. Humphrey, G. R., Kuethe, J. T., *Chem. Rev.* **2006**, *106*, 2875-2911.
10. Inman, M., Moody, C. J., *Chem. Sci.* **2013**, *4*, 29-41.
11. Lu, B. Z., Zhao, W., Wei, H.-X., Dufour, M., Farina, V., Senanayake, C. H., *Org. Lett.*, **2006**, *8*, 3271-3274.
12. Leogane, O., Lebel, H., *Angew. Chem. Int. Ed.*, **2008**, *47*, 350-352.
13. Liu, Y. Y., Yu, X. Y., Chen, J. R., Qiao, M. M., Qi, X., Shi, D. Q., Xiao, W. J., *Angew. Chem. Int. Ed.*, **2017**, *56*, 9527-9531.
14. Bischler, A., *Chem. Gesellschaft*, **1892**, *25*, 2860-2879.
15. Möhlau, R.,*Berichte der Dtsch. Chem. Gesellschaft*, **1881**, *14*, 171-175.
16. Jendza, K., Kato, M., Salcius, M., Srinivas, H., De Erkenez, A., Nguyen, A., McLaughlin, D., Be, C., Wiesmann, C., Murphy, J., et al., *Nat. Chem. Biol.*, **2019**, *15*, 666-668.
17. Pete, B., Simig, G., Poszávácz, L., Toke, L., *Heterocycles*, **2003**, *60*, 2441.
18. Richardson, B. G., Jain, A. D., Potteti, H. R., Lazzara, P. R., David, B. P., Tamatam, C. R., Choma, E., Skowron, K., Dye, K., Siddiqui, Z., et al, *J. Med. Chem.*, **2018**, *61*, 8029-8047.
19. Kassis, P., Brzeszcz, J., Bénéteau, V., Lozach, O., Meijer, L., Le Guével, R., Guillouzo, C., Lewiński, K., Bourg, S., Colliandre, L., et al, *Eur. J. Med. Chem.*, **2011**, *46*, 5416-5434.

20. Bardiot, D. A. M.-E., Bonfanti, J.-F., Kesteleyn, B. R. R., Marchand, A. D. M., Raboisson, P. J.-M. B., Patent, WO2018215315A1, Nove. 29, **2018**.
21. Wiles, Jason, A., Phadke, Avinash, S., Deshpande, M., Agarwal, A., Chen, D., Gadhachanda, Venkat, R., Hashimoto, A., Pais, G., Wang, Q., Wang, X., et al., US Patent, US11084800B2, Aug. 10, **2021**.
22. Welsch, M. E., Snyder, S. A., Stockwell, B. R., *Curr. Opin. Chem. Biol.*, **2010**, *14*, 347-361.
23. Zhao, H., Dietrich, J., *Expert Opin. Drug Discov.*, **2015**, *10*, 781-790.
24. Wang, W., Ollio, S., Herdtweck, E., Dömling, *J. Org. Chem.*, **2011**, *76*, 637-644.
25. Tyagi, V., Khan, S., Bajpai, V., Gauniyal, H. M., Kumar, B., Chauhan, P. M. S., *J. Org. Chem.* **2012**, *77*, 1414-1421.
26. El Kaim, L., Gageat, M., Gaultier, L., Grimaud, L., *Synlett.,* **2007**, No. 3, 0500-0502.
27. Wang, H., Ganesan, A., *Org. Lett.* **1999**, *1*, 1647-1649.
28. Cárdenas-Galindo, L., Islas-Jácome, A., Alvarez-Rodríguez, N., El Kaim, L., Gámez-Montaño, R. Synthesis of 2-Tetrazolylmethyl-2,3,4,9-Tetrahydro-1H-β-Carbolines by a One-Pot Ugi-Azide/Pictet-Spengler Process. *Synthesis* **2013**, *46*, 49-56.
29. Sparey, T., Abeywickrema, P., Almond, S., Brandon, N., Byrne, N., Campbell, A., Hutson, P. H., Jacobson, M., Jones, B., Munshi, S., et al. The Discovery of Fused Pyrrole Carboxylic Acids as Novel, Potent d-Amino Acid Oxidase (DAO) Inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3386-3391.
30. Kariya, T., Grisar, J. M., Wiech, N. L., Blohm, T. R. Hypocholesterolemic Indole-2-Carboxylic Acids. *J. Med. Chem.* **1972**, *15*, 659-662.
31. Moore, J. D., Potter, A. Pin1 Inhibitors: Pitfalls, Progress and Cellular Pharmacology. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4283-4291.
32. Holt, D. A., Yamashita, D. S., Konialian-Beck, A. L., Luengo, J. I., Abell, A. D., Bergsma, D. J., Brandt, M., Levy, M. A. Benzophenone- and Indolecarboxylic Acids: Potent Type-2 Specific Inhibitors of Human Steroid 5.Alpha.-Reductase. *J. Med. Chem.* **1995**, *38*, 13-15.
33. Ito, M., Iwatani, M., Kamada, Y., Sogabe, S., Nakao, S., Tanaka, T., Kawamoto, T., Aparicio, S., Nakanishi, A., Imaeda, Y. Discovery of Selective

ATP-Competitive EIF4A3 Inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 2200-2209.

34. Zarganes-Tzitzikas, T., Chandgude, A. L., Dömling, A. Multicomponent Reactions, Union of MCRs and Beyond. *Chem. Rec.* **2015**, *15*, 981-996.
35. Schroeder, G. M., Marshall, S., Wan, H., Purandare, A. V. Improved Conditions for Converting Sterically Hindered Amides to 1,5-Disubstituted Tetrazoles. *Tetrahedron Lett.* **2010**, *51*, 1404-1406.
36. C. G. Neochoritis, T. Zhao and A. Dömling, *Chem. Rev.*, **2019**, *119 (3),* 1970-2042.
37. Ito, M., Iwatani, M., Kamada, Y., Sogabe, S., Nakao, S., Tanaka, T., Kawamoto, T., Aparicio, S., Nakanishi, A., Imaeda, Y. Discovery of Selective ATP-Competitive EIF4A3 Inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 2200-2209.
38. Russell Stabler, S., Jahangir. Preparation of N -Arylated Heterocycles by Nucleophilic Aromatic Substitution. *Synth. Commun.* **1994**, *24*, 123-129.
39. Sugimoto, Y., Shimizu, A., Kato, T., Satoh, A., Ozaki, S., Ohta, H., Okamoto, O. Design, Synthesis, and Biological Evaluation of Indole Derivatives as Novel Nociceptin/Orphanin FQ (N/OFQ) Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3569-3573.
40. Unangst, P. C., Connor, D. T., Stabler, S. R., Weikert, R. J., Carethers, M. E., Kennedy, J. A., Thueson, D. O., Chestnut, J. C., Adolphson, R. L., Conroy, M. C. Novel Indolecarboxamidotetrazoles as Potential Antiallergy Agents. *J. Med. Chem.* **1989**, *32*, 1360-1366.

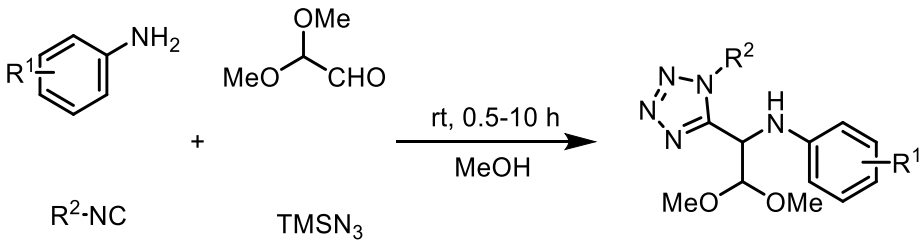
EXPERIMENTAL SECTION

1. General methods and materials

All the reagents and solvents are purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and are used without further purification. Isocyanides are synthesized as previously described by us. All microwave irradiation reactions are carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography is performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra are recorded on Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz) }. Chemical shifts for ^{1}H NMR are reported as δ values and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak. Flash chromatography is performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra are measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). High resolution mass spectra are recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

2. Synthetic procedures and analytical data

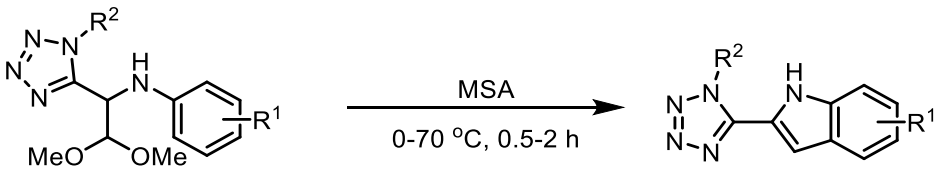
General Procedure for the UT-4CR



1a-y

To a stirred solution of 2,2-dimethoxyacetaldehyde (2.0 mmol) in MeOH (2.0 mL), the corresponding aniline (2.0 mmol), isocyanide (2.0 mmol) and trimethylsilyl azide (2.0 mmol) are added. The reaction mixture is stirred vigorously for 2 h. Then, if solid appears, half of the solvent is removed under reduced pressure. The resulting solid is filtered and washed with Et_2O. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 2:1-1:1) to give the compounds **1a-y**.

General Procedure for the Pictet-Spengler cyclization

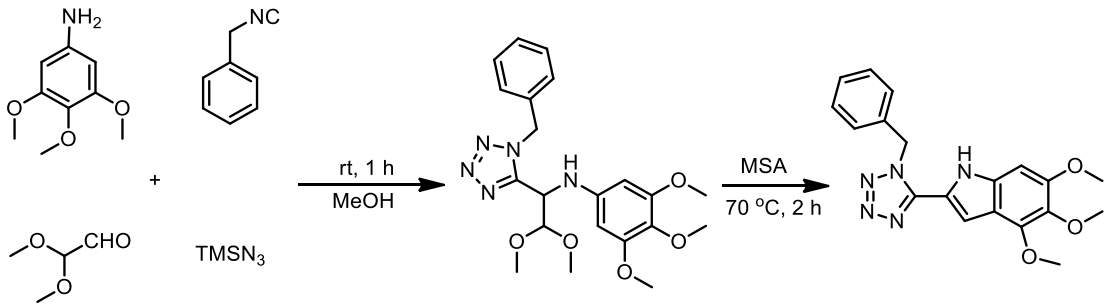


2a-z

The corresponding tetrazole derivatives (1.0 mmol) are dissolved into methanesulfonic acid (MSA) (1.0 mL) at 0 °C and then heated up to 70 °C for 0.5 - 2.0 h. Then, the reaction mixture is cooled to room temperature and neutralized with an aqueous solution of $NaHCO_3$, followed by extractions with ethyl acetate. The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. If solid appears, the resulting solid is filtered and washed with Et_2O. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 3:1-1:1) to give the compounds **2a-z**.

In case of meta-substituted anilines, mixture of isomers is obtained (see analytical data)

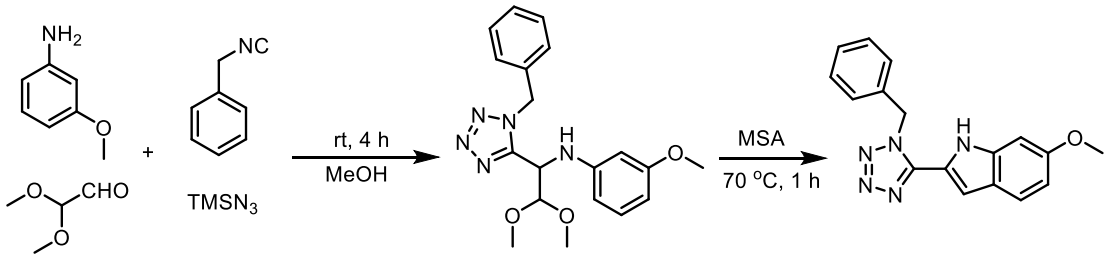
The gram-scale synthesis of 1a and 2a



1a **2a**

To a stirred solution of 2,2-dimethoxyacetaldehyde (10.0 mmol, 1.04 g) in MeOH (10.0 mL), the 3,4,5-trimethoxyaniline (10.0 mmol, 1.83 g), benzyl isocyanide (10.0 mmol, 1.17 g) and trimethylsilyl azide (10.0 mmol, 1.15 g) are added in a 50 mL flask. The reaction mixture is stirred vigorously for 2 h. Then, half of the solvent is removed under reduced pressure, the resulting solid is filtered and washed with Et_2O to give the compound **1a** (4.15 g, 97%) as gray solid. Afterwards, the *N*- (1- (1-benzyl-1*H*-tetrazol-5-yl) -2,2-dimethoxyethyl) -3,4,5-trimethoxyaniline (**1a**, 5.0 mmol, 2.15 g) is dissolved into methanesulfonic acid (5.0 mL) at 0 °C and then heated up to 70 °C for 2 h. Then, the reaction mixture is cooled to room temperature neutralized with an aqueous solution of $NaHCO_3$ to pH 7, followed by extractions with ethyl acetate (3 x 30 mL). The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The resulting solid is filtered and washed with Et_2O to give the compound **2a** (1.67 g, 91%) as brown solid.

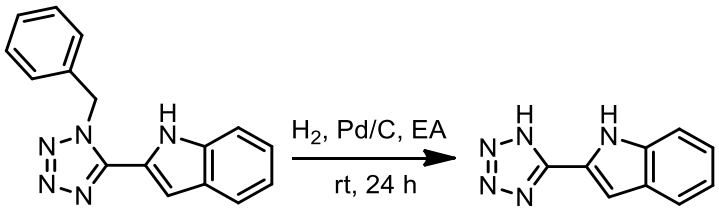
One-pot approach of 2-(1-benzyl-1*H*-tetrazol-5-yl)-6-methoxy-1*H*-indole (2c)



1c **2c**

To a stirred solution of 2,2-dimethoxyacetaldehyde (1.0 mmol) in MeOH (1.0 mL), the 3-methoxyaniline (1.0 mmol), benzyl isocyanide (1.0 mmol) and trimethylsilyl azide (1.0 mmol) are added in a 5.0 mL vial. The reaction mixture is stirred vigorously for 4 h. Then, the solvent is removed under reduced pressure and the compound **1c**, obtained as brown solid, is directly used in the next step without further purification. Afterwards, the methanesulfonic acid (1.0 mL) is added at 0 ^{o}C and heated up to 70 ^{o}C for 1 h. The reaction mixture is neutralized with an aqueous solution of $NaHCO_3$, followed by extractions with ethyl acetate. The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The resulting solid is purified by column chromatography (PE-EA, 3:1) to give compound **2c** (149 mg, 49% in 2-steps) as white solid, as mixture of isomers as indicated above.

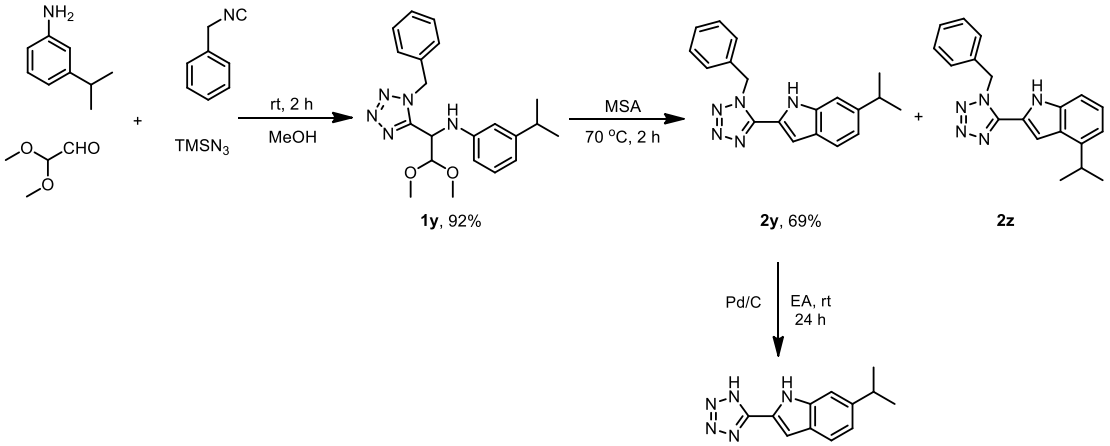
Synthesis of the 2-(1*H*-tetrazol-5-yl)-1*H*-indole



2f **3a**

To a stirred solution of 2- (1-benzyl-1*H*-tetrazol-5-yl) -1*H*-indole (**2f**, 1.0 mmol) in ethyl acetate (15.0 mL), Pd/C (10% w/w, 0.2 mmol) is added at room temperature under H_2 atmosphere at 1 atm. The reaction mixture is stirred for 24 h. Then, filtration via celite followed by purification with column chromatography (PE-EA, 1:7) gave the compound **3a** (175 mg, 95%) as yellow solid.

Synthesis of the 6-isopropyl-2-(1*H*-tetrazol-5-yl)-1*H*-indole (ATP-competitive eIF4A3 inhibitor 3b)

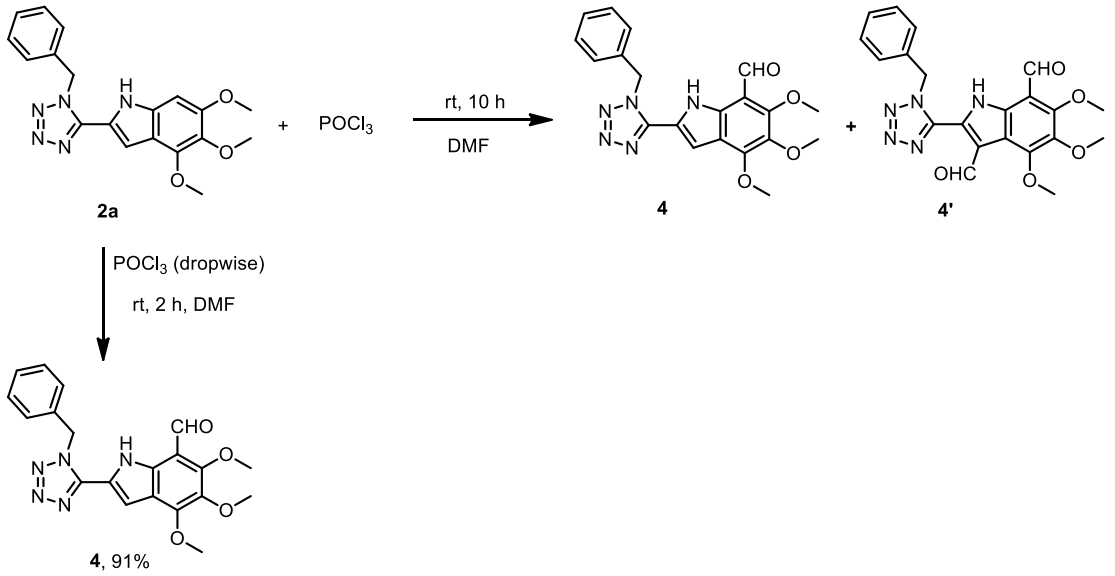


1y is synthesized according to the general procedure of UT-4CR, 3-isopropylaniline (2.0 mmol), (isocyanomethyl) benzene (2.0 mmol), 2,2-dimethoxyacetaldehyde (2.0 mmol) and trimethylsilyl azide (2.0 mmol) as starting materials, isolated in 92% yield as a yellow solid.

2y and **2z** are synthesized according to the general procedure for the Pictet-Spengler cyclization, **1y** (1.0 mmol), **2y** and **2z** are obtained as mixture of isomers in 4:1 ratio (86% yield, yellow solid), pure **2y** is obtained (69% yield, white solid) after ishing with ether.

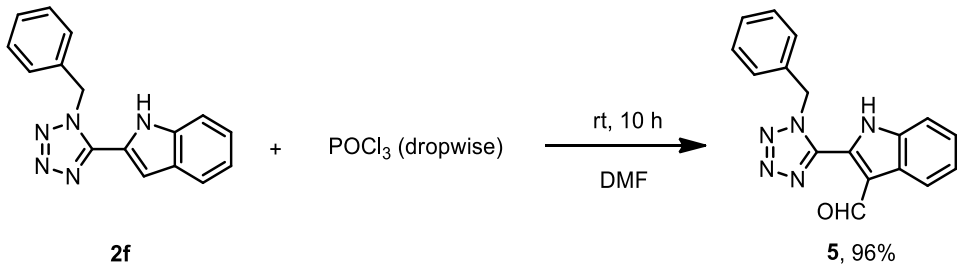
To a stirred solution of 2- (1-benzyl-1*H*-tetrazol-5-yl) -6-isopropyl-1*H*-indole (**2y**, 0.2 mmol) in ethyl acetate (2.0 mL), Pd/C (10%w/w, 0.04 mmol) is added at room temperature under H_2 atmosphere at 1 atm. The reaction mixture is stirred for 24 h. Then, filtration with celite and remove the solvent to give the compound **3b** (44 mg, 98%) as white solid.

Procedure for the formylation reactions



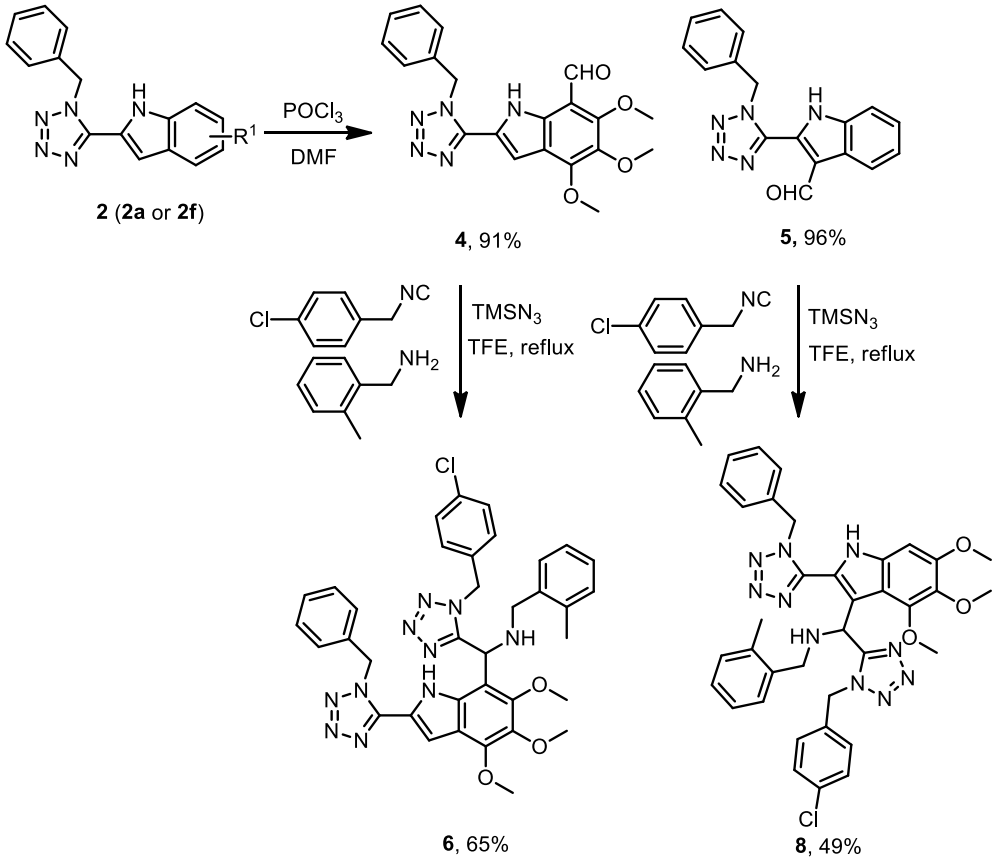
To a stirred solution of **2a** (1.0 mmol) in DMF (1.0 mL), phosphorus oxychloride (1.2 mmol) is added at room temperature and the reaction mixture is stirred for 10 h. Then, the reaction is quenched with $NaHCO_3$ solution to pH 7 and extracted with ethyl acetate (3 x 10 mL). The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The resulting solid is purified by column chromatography (PE-EA, 1:1) to give the compound mixture **4** and **4'** as a brown solid in a ratio 1:1.[2]

To a stirred solution of **2a** (1.0 mmol) in DMF (1.0 mL), the phosphorus oxychloride (1.2 mmol in 0.4 mL DMF) is added dropwise. The reaction mixture is stirred vigorously for 2 h at room temperature, then the reaction is quenched with $NaHCO_3$ solution to pH 7 and extracted with ethyl acetate (3 x 10 mL). The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The resulting solid is washed with ethyl acetate to give compound **4** (358 mg, 91%) as a green solid.[1]



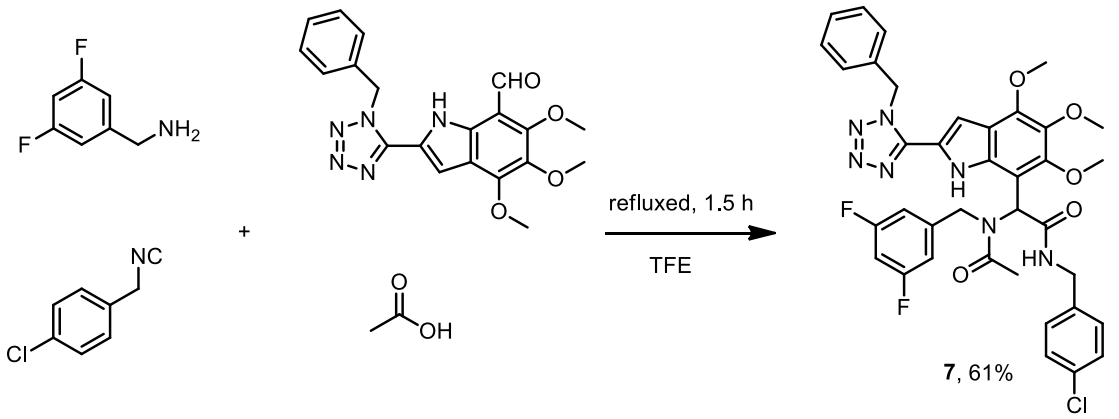
To a stirred solution of **2f** (1.0 mmol) in DMF (1.0 mL), the phosphorus oxychloride (1.2 mmol in 0.4 mL DMF) is added dropwise and the reaction mixture is stirred vigorously for 10 h at room temperature. Then, the reaction is quenched with $NaHCO_3$ solution to pH 7 and extracted with ethyl acetate (3 x 10 mL). The compound **5** (291 mg, 96%) is obtained as brown oil and used directly in the next step without further purification.

General procedure for the UT-4CR post-modification



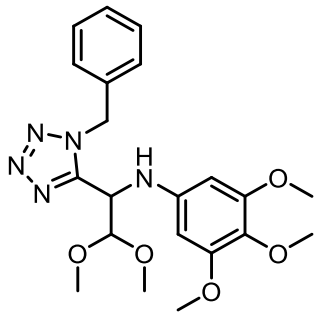
To a stirred solution of corresponding aldehyde (1.0 mmol) in TFE (1.0 mL), the *o*-tolylmethanamine (1.0 mmol), 1-chloro-4- (isocyanomethyl) benzene (1.0 mmol) and trimethylsilyl azide (1.0 mmol) are added at room temperature. Then the reaction mixture is warmed up to 80 ^{o}C and stirred vigorously for 2 h. Afterwards, the solvent is removed under reduced pressure and the resulting solid is purified by column chromatography (PE-EA, 2:1) to give compounds **6** and **8** in 65% and 49% yield, respectively.

General procedure for the U-4CR post-modification



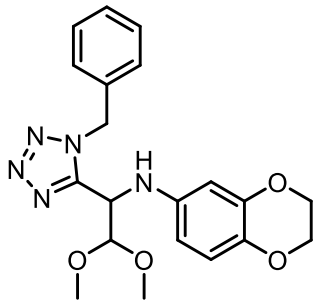
To a stirred solution of 2- (1-benzyl-1*H*-tetrazol-5-yl) -4,5,6-trimethoxy-1*H*-indole-7-carbaldehyde (1.0 mmol) in TFE (1.0 mL), the (3,5-difluorophenyl) methanamine (1.0 mmol), 1-chloro-4- (isocyanomethyl) benzene (1.0 mmol) and acetic acid (1.0 mmol) are added at room temperature. Then, the reaction mixture is warmed up to 80 ^{o}C and stirred vigorously for 1.5 h. Afterwards, the solvent is removed under reduced pressure and the resulting solid is purified by column chromatography (PE-EA, 4:1) to give the compound **7** (445 mg, 61%) as a brown solid.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3,4,5-trimethoxyaniline (1a)



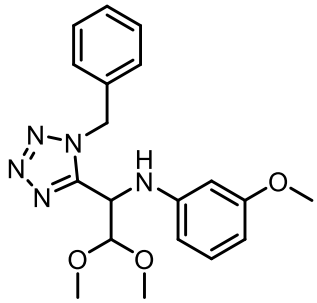
832 mg, 97% yield, gray solid. mp 131 - 134 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 - 7.25 (m, 3H), 7.08 (dd, *J* = 6.4, 3.0 Hz, 2H), 5.76, 5.61 (ABq, *J* = 15.5 Hz, 2H), 5.68 (s, 2H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.55 (d, *J* = 5.1 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 6H), 3.41 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 153.7, 142.3, 134.1, 131.7, 129.0, 128.7, 127.6, 105.3, 92.1, 61.1, 56.9, 56.1, 55.8, 53.9, 51.6. **HRMS** (ESI) m/z calcd for $C_{21}H_{28}N_5O_5$ $[M + H]^+$ = 430.2085, found 430.2081.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-2,3-dihydrobenzo[*b*][1,4] dioxin-6-amine (1b)



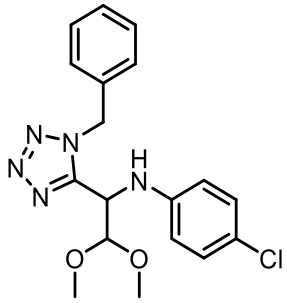
644 mg, 81% yield, white solid. mp 134 - 135 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.38 - 7.32 (m, 3H), 7.24 - 7.23 (m, 2H), 6.48 (d, *J* = 8.5 Hz, 1H), 6.18 (d, *J* = 2.7 Hz, 1H), 6.01 (dd, *J* = 8.5, 2.7 Hz, 1H), 5.89 (d, *J* = 8.9 Hz, 1H), 5.79, 5.71 (ABq, *J* = 15.4 Hz, 2H), 5.11 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.70 (d, *J* = 5.9 Hz, 1H), 4.14 - 4.12 (m, 2H), 4.08 - 4.07 (m, 2H), 3.39 (s, 3H), 3.23 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 154.5, 143.6, 141.2, 135.4, 134.8, 128.6, 128.1, 117.0, 106.5, 106.3, 104.4, 104.3, 102.3, 101.7, 64.3, 63.7, 56.0, 55.8, 51.2, 50.2. **HRMS** (ESI) m/z calcd for $C_{20}H_{24}N_5O_4$ $[M + H]^+$ = 398.1823, found 398.1820.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-methoxyaniline (1c)



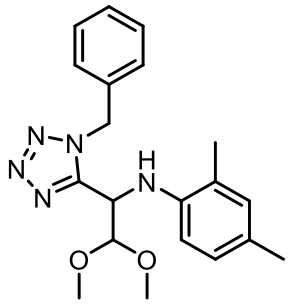
694 mg, 94% yield, brown oil. mp 110 - 113 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 - 7.30 (m, 3H), 7.17 - 7.15 (m, 2H), 6.89 (t, *J* = 8.2 Hz, 1H), 6.27 (ddd, *J* = 8.2, 2.4, 0.5 Hz, 1H), 6.00 (t, *J* = 2.4 Hz, 1H), 5.84 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.76, 5.57 (ABq, *J* = 15.2 Hz, 2H), 4.93 (dd, *J* = 6.8, 5.1 Hz, 1H), 4.53 (d, *J* = 5.1 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 3.38 (s, 3H), 3.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.8, 153.8, 147.1, 133.9, 130.3, 129.1, 128.7, 127.9, 106.2, 105.3, 104.9, 100.2, 57.0, 55.3, 55.2, 52.8, 51.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{24}N_5O_3$ $[M + H]^+$ = 370.1874, found 370.1872.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-4-chloroaniline (1d)



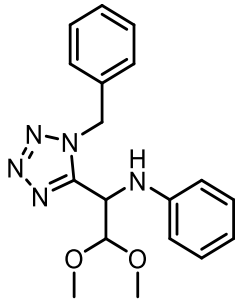
678 mg, 91% yield, gray solid. mp 98 - 100 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 - 7.31 (m, 3H), 7.17 - 7.15 (m, 2H), 6.91 - 6.88 (m, 2H), 6.12 - 6.10 (m, 2H), 5.81,5.54 (ABq, *J* = 15.2 Hz, 2H), 4.81 (dd, *J* = 7.5, 5.3 Hz, 1H), 4.57 (d, *J* = 5.3 Hz, 1H), 4.52 (d, *J* = 7.5 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.7, 144.3, 133.7, 129.3, 129.2, 129.0, 128.02, 127.97, 124.1, 115.0, 105.6, 57.2, 55.5, 52.8, 51.6. **HRMS** (ESI) m/z calcd for $C_{18}H_{21}ClN_5O_2$ $[M + H]^+$ = 374.1378, found 374.1378.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-2,4-dimethylaniline (1e)



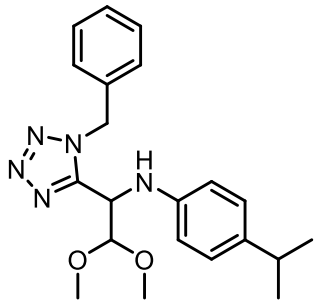
704 mg, 96% yield, white solid. mp 105 - 110 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 - 7.29 (m, 3H), 7.16 - 7.14 (m, 2H), 6.83 (s, 1H), 6.61 - 6.60 (m, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 5.77, 5.57 (ABq, *J* = 15.2 Hz, 2H), 4.93 (t, *J* = 5.7 Hz, 1H), 4.57 (d, *J* = 5.3 Hz, 1H), 4.27 (d, *J* = 6.1 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 141.5, 133.9, 131.4, 129.1, 128.7, 128.4, 128.0, 127.4, 123.7, 111.4, 105.4, 56.9, 55.0, 53.1, 51.5, 20.4, 17.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{26}N_5O_2$ $[M + H]^+$ = 368.2081, found 368.2079.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl) aniline (1f)



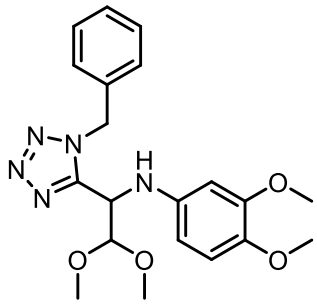
556 mg, 82% yield, white solid. mp 112 - 115 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 - 7.32 (m, 3H), 7.21 - 7.18 (m, 2H), 7.03 - 6.99 (m, 2H), 6.73 - 6.70 (m, 1H), 6.30 - 6.29 (m, 2H), 5.81, 5.59 (ABq, *J* = 15.2 Hz, 2H), 4.95 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.59 (d, *J* = 5.2 Hz, 1H), 4.55 (d, *J* = 7.0 Hz, 1H), 3.41 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.9, 145.7, 133.8, 129.4, 129.1, 128.8, 128.0, 119.3, 113.9, 105.4, 57.0, 55.2, 52.7, 51.6. **HRMS** (ESI) m/z calcd for $C_{18}H_{22}N_5O_2$ $[M + H]^+$ = 340.1768, found 340.1767.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-4-isopropylaniline (1g)



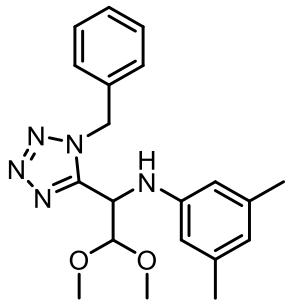
648 mg, 85% yield, colorless solid. mp 123 - 126 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 - 7.28 (m, 3H), 7.16 - 7.14 (m, 2H), 6.87 - 6.86 (m, 2H), 6.26 - 6.23 (m, 2H), 5.77, 5.57 (ABq, *J* = 15.2 Hz, 2H), 4.92 (t, *J* = 5.8 Hz, 1H), 4.54 (d, *J* = 5.2 Hz, 1H), 4.41 (d, *J* = 6.4 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.77 - 2.71 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 143.6, 140.0, 133.9, 129.1, 128.7, 128.0, 127.3, 114.0, 105.3, 56.9, 55.1, 53.1, 51.6, 33.2, 24.2. **HRMS** (ESI) m/z calcd for $C_{21}H_{28}N_5O_2$ $[M + H]^+$ = 382.2238, found 382.2237.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3,4-dimethoxyaniline (1h)



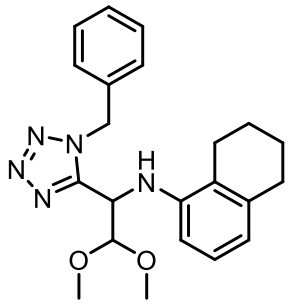
750 mg, 94% yield, gray solid. mp 120 - 125 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 - 7.27 (m, 3H), 7.13 - 7.11 (m, 2H), 6.49 (d, *J* = 8.6 Hz, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 5.76, 5.58 (ABq, *J* = 15.3 Hz, 2H), 5.71 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.86 (t, *J* = 5.1 Hz, 1H), 4.54 (d, *J* = 5.2 Hz, 1H), 4.26 (d, *J* = 5.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 150.0, 143.1, 140.3, 134.0, 129.1, 128.7, 127.9, 112.8, 105.4, 104.9, 100.7, 57.0, 56.6, 55.8, 55.4, 54.0, 51.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{26}N_5O_4$ $[M + H]^+$ = 400.1979, found 400.1978.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3,5-dimethylaniline (1i)



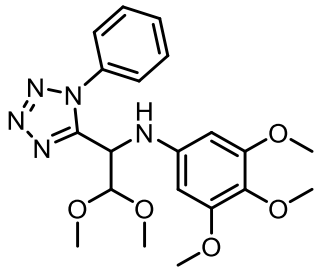
698 mg, 95% yield, white solid. mp 127 - 129 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 - 7.29 (m, 3H), 7.18 - 7.17 (m, 2H), 6.37 (s, 1H), 6.00 (s, 2H), 5.75, 5.60 (ABq, *J* = 15.2 Hz, 2H), 4.94 (dd, *J* = 6.7, 5.2 Hz, 1H), 4.53 (d, *J* = 5.1 Hz, 1H), 4.39 (d, *J* = 6.8 Hz, 1H), 3.37 (s, 3H), 3.37 (s, 3H), 2.10 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.9, 145.8, 139.2, 134.0, 129.1, 128.7, 128.0, 121.5, 111.8, 105.4, 56.9, 55.2, 52.8, 51.5, 21.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{26}N_5O_2$ $[M + H]^+$ = 368.2081, found 368.2079.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-5,6,7,8-tetrahydro naphthalen-1-amine (1j)



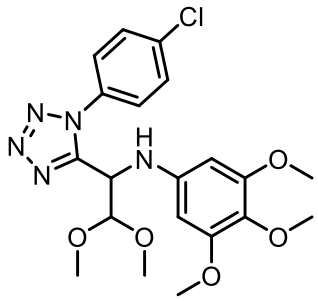
636 mg, 81% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 - 7.26 (m, 3H), 7.13 - 7.11 (m, 2H), 6.71 (t, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.82 - 5.76 (m, 1H), 5.79, 5.58 (ABq, *J* = 15.2 Hz, 2H), 4.99 (t, *J* = 5.5 Hz, 1H), 4.59 (d, *J* = 5.1 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 1.88 - 1.80 (m, 2H), 1.73 - 1.68 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 143.5, 138.1, 133.9, 129.0, 128.6, 127.9, 126.1, 122.5, 120.3, 108.0, 105.3, 56.9, 55.1, 52.7, 51.5, 30.1, 23.9, 23.1, 22.6. **HRMS** (ESI) m/z calcd for $C_{22}H_{28}N_5O_2$ $[M + H]^+$ = 394.2238, found 394.2234.

N-(2,2-dimethoxy-1-(1-phenyl-1*H*-tetrazol-5-yl)ethyl)-3,4,5-trimethoxyaniline (1k)



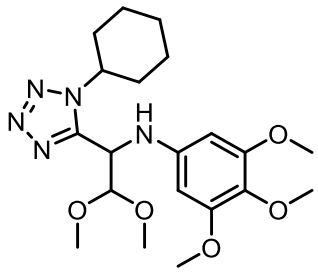
556 mg, 67% yield, gray solid. mp 133 - 135 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 - 7.53 (m, 3H), 7.50 - 7.48 (m, 2H), 5.62 (s, 2H), 4.94 - 4.91 (m, 1H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 3.70 (s, 3H), 3.60 (s, 6H), 3.47 (s, 3H), 3.43 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.7, 154.0, 142.1, 134.0, 131.6, 130.7, 129.7, 125.9, 105.8, 92.1, 61.1, 57.4, 56.0, 55.2, 52.5. **HRMS** (ESI) m/z calcd for $C_{20}H_{26}N_5O_5$ $[M + H]^+$ = 416.1928, found 416.1928.

N-(1-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3,4,5-trimethoxyaniline (1l)



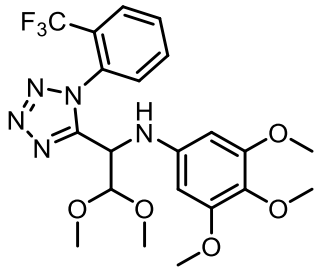
862 mg, 96% yield, gray solid. mp 162 - 166 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 5.60 (s, 2H), 4.92 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.80 (d, *J* = 5.9 Hz, 1H), 4.17 (d, *J* = 8.9 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 6H), 3.48 (s, 3H), 3.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.6, 154.1, 141.9, 137.0, 132.5, 131.7, 129.8, 127.4, 105.6, 92.0, 61.2, 57.3, 56.0, 55.6, 52.8. **HRMS** (ESI) m/z calcd for $C_{20}H_{25}ClN_5O_5$ $[M + H]^+$ = 450.1539, found 450.1538.

N-(1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3,4,5-trimethoxyaniline (1m)



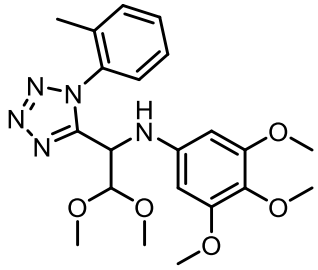
664 mg, 79% yield, gray solid. mp 133 - 135 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83 (s, 2H), 5.00 (dd, *J* = 6.0, 4.8 Hz, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.58 (tt, *J* = 11.6, 3.8 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 3.72 (s, 6H), 3.70 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H), 2.02 - 1.0 (m, 5H), 1.71 - 1.64 (m, 2H), 1.30 - 1.19 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 152.6, 142.8, 131.5, 105.6, 91.8, 65.9, 61.1, 58.8, 56.9, 56.4, 56.1, 53.9, 33.3, 33.0, 25.59, 25.55, 25.0, 15.4. **HRMS** (ESI) m/z calcd for $C_{20}H_{32}N_5O_5$ $[M + H]^+$ = 422.2398, found 422.2396.

N-(2,2-dimethoxy-1-(1-(2-(trifluoromethyl) phenyl)-1*H*-tetrazol-5-yl)ethyl)-3,4,5-trimethoxyaniline (1n)



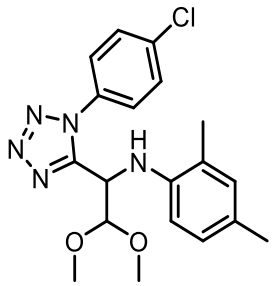
512 mg, 53% yield, yellow solid. mp 134 - 136 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.27 (d, *J* = 14.2 Hz, 1H), 5.71 (s, 2H), 4.81 - 4.75 (m, 1H), 4.71 (s, 1H), 4.12 (s, 1H), 3.72 (s, 3H), 3.69 (s, 6H), 3.42 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 154.0, 142.3, 132.6, 131.7, 131.5, 131.1, 127.9, 127.7, 123.5, 121.3, 105.7, 92.1, 61.1, 57.0, 56.1, 53.7. **HRMS** (ESI) m/z calcd for $C_{21}H_{25}F_3N_5O_5$ $[M + H]^+$ = 484.1802, found 484.1802.

N-(2,2-dimethoxy-1-(1-(*o*-tolyl)-1*H*-tetrazol-5-yl)ethyl)-3,4,5-trimethoxyaniline (1o)



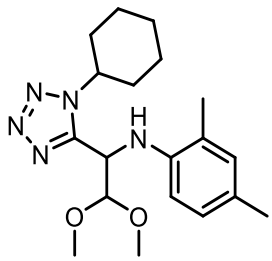
780 mg, 91% yield, gray solid. mp 149 - 151 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (td, *J* = 7.6, 1.2 Hz, 1H), 7.35 - 7.29 (m, 2H), 7.13 (d, *J* = 6.3 Hz, 1H), 5.71 (s, 2H), 4.78 - 4.73 (m, 2H), 4.07 (d, *J* = 9.1 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 6H), 3.44 (s, 3H), 3.42 (s, 3H), 1.84 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.0, 154.0, 142.2, 136.6, 132.8, 131.9, 131.5, 131.1, 127.4, 126.7, 105.6, 92.8, 61.1, 57.1, 56.0, 53.3, 17.2. **HRMS** (ESI) m/z calcd for $C_{21}H_{28}N_5O_5$ $[M + H]^+$ = 430.2085, found 430.2082.

N-(1-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-2,4-dimethylaniline (1p)



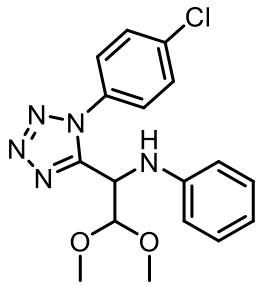
510 mg, 66% yield, colorless solid. mp 119 - 121 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 - 7.46 (m, 2H), 7.33 - 7.30 (m, 2H), 6.83 (s, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.08 (d, *J* = 8.1 Hz, 1H), 4.95 (dd, *J* = 8.4, 5.8 Hz, 1H), 4.84 (d, *J* = 5.8 Hz, 1H), 4.07 (d, *J* = 8.4 Hz, 1H), 3.44 (s, 6H), 2.17 (s, 3H), 1.99 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.0, 141.0, 136.9, 132.6, 131.7, 129.7, 128.7, 127.5, 127.3, 123.9, 111.4, 105.6, 57.1, 55.1, 52.1, 20.4, 17.3. **HRMS** (ESI) m/z calcd for $C_{19}H_{23}ClN_5O_2$ $[M + H]^+$ = 388.1535, found 388.1537.

N-(1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-2,4-dimethylaniline (1q)



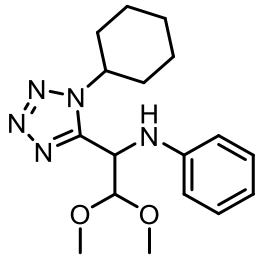
359 mg, 50% yield, white solid. mp 129 - 133 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 5.07 (t, *J* = 5.2 Hz, 1H), 4.71 (d, *J* = 4.8 Hz, 1H), 4.66 (tt, *J* = 11.6, 3.8 Hz, 1H), 4.36 (d, *J* = 5.6 Hz, 1H), 3.48 (s, 3H), 3.45 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 2.06 - 1.80 (m, 5H), 1.74 - 1.62 (m, 2H), 1.41 - 1.26 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.8, 141.8, 131.5, 128.4, 127.5, 123.5, 111.3, 105.6, 58.7, 56.9, 56.1, 53.4, 33.2, 33.1, 25.64, 25.61, 25.0, 20.4, 17.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{30}N_5O_2$ $[M + H]^+$ = 360.2394, found 360.2393.

N-(1-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl) aniline (1r)



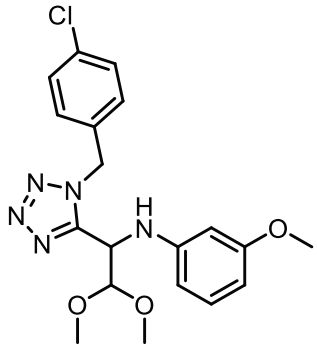
381 mg, 53% yield, white solid. mp 165 - 163 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 - 7.49 (m, 2H), 7.39 - 7.36 (m, 2H), 7.08 - 7.06 (m, 2H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 2H), 4.95 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.81 (d, *J* = 5.9 Hz, 1H), 4.34 (d, *J* = 8.9 Hz, 1H), 3.43 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.6, 145.3, 137.0, 132.5, 129.8, 129.5, 127.4, 119.6, 113.9, 105.7, 57.2, 55.2, 51.8. **HRMS** (ESI) m/z calcd for $C_{17}H_{19}ClN_5O_2$ $[M + H]^+$ = 360.1222, found 360.1222.

N-(1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl) aniline (1s)



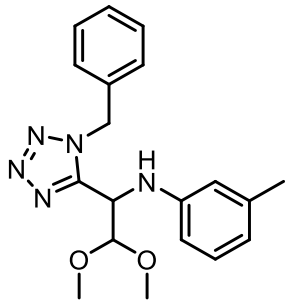
344 mg, 52% yield, white solid. mp 131 - 133 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 - 7.12 (m, 2H), 6.78 - 6.75 (m, 1H), 6.62 - 6.60 (m, 2H), 5.03 (dd, *J* = 6.3, 4.8 Hz, 1H), 4.67 (d, *J* = 4.8 Hz, 1H), 4.61 - 4.56 (m, 2H), 3.47 (s, 3H), 3.44 (s, 3H), 2.01 - 1.82 (m, 5H), 1.72 - 1.68 (m, 1H), 1.67-1.64 (m, 1H), 1.38 - 1.26 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.6, 146.1, 129.6, 119.5, 113.8, 105.7, 58.7, 57.0, 56.3, 53.2, 33.3, 33.1, 25.63, 25.55, 25.0. **HRMS** (ESI) m/z calcd for $C_{17}H_{26}N_5O_2$ $[M + H]^+$ = 332.2081, found 332.2079.

N-(1-(1-(4-chlorobenzyl)-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-methoxyaniline (1t)



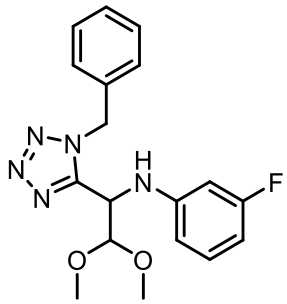
717 mg, 89% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 - 7.22 (m, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.96 - 6.92 (m, 1H), 6.31 - 6.29 (m, 1H), 5.93 - 5.91 (m, 2H), 5.72, 5.55 (ABq, *J* = 15.3 Hz, 2H), 4.95 (d, *J* = 4.7 Hz, 1H), 4.61 (d, *J* = 4.7 Hz, 1H), 3.69 (s, 3H), 3.42 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.9, 153.7, 146.9, 134.7, 132.4, 130.4, 129.2, 106.6, 105.4, 105.0, 100.4, 57.1, 55.8, 55.2, 53.2, 50.9. **HRMS** (ESI) m/z calcd for $C_{19}H_{23}ClN_5O_3$ $[M + H]^+$ = 404.1484, found 404.1483.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-methylaniline (1u)



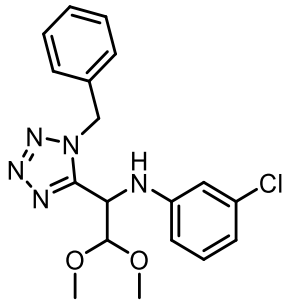
685 mg, 97% yield, white solid. mp 124 - 129 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 - 7.31 (m, 3H), 7.18 - 7.16 (m, 2H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 6.20 (s, 1H), 6.07 (dd, *J* = 8.0, 2.3 Hz, 1H), 5.77, 5.59 (ABq, *J* = 15.2 Hz, 2H), 4.93 (dd, *J* = 6.9, 5.2 Hz, 1H), 4.55 (d, *J* = 5.2 Hz, 1H), 4.44 (d, *J* = 6.9 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.9, 145.8, 139.3, 133.93, 129.3, 129.1, 128.8, 128.0, 120.4, 114.8, 110.8, 105.4, 57.0, 55.2, 52.8, 51.6, 21.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{24}N_5O_2$ $[M + H]^+$ = 354.1925, found 354.1922.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-fluoroaniline (1v)



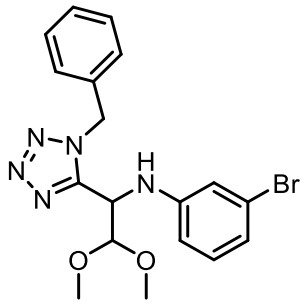
649 mg, 91% yield, yellow solid. mp 106 - 109 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 - 7.32 (m, 3H), 7.18 - 7.16 (m, 2H), 6.93 - 6.89 (m, 1H), 6.39 - 6.35 (m, 1H), 6.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.92 (dt, *J* = 11.1, 2.3 Hz, 1H), 5.81,5.56 (ABq, *J* = 15.2 Hz, 2H), 4.84 (dd, *J* = 7.3, 5.2 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 5.2 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.8 (d, $^{1}J_{C-F}$ = 244.7 Hz), 153.6, 147.5 (d, $^{3}J_{C-F}$ = 10.4 Hz), 133.6, 130.6 (d, $^{3}J_{C-F}$ = 10.1 Hz), 129.3, 129.0, 127.9, 109.5 (d, $^{4}J_{C-F}$ = 2.4 Hz), 106.0 (d, $^{2}J_{C-F}$ = 21.5 Hz), 105.6, 100.9 (d, $^{2}J_{C-F}$ = 25.5 Hz), 57.2, 55.6, 52.6, 51.7.**^{19}F NMR** (471 MHz, $CDCl_3$) δ -112.11. **HRMS** (ESI) m/z calcd for $C_{18}H_{21}FN_5O_2$ $[M + H]^+$ = 358.1674, found 358.1674.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-chloroaniline (1w)



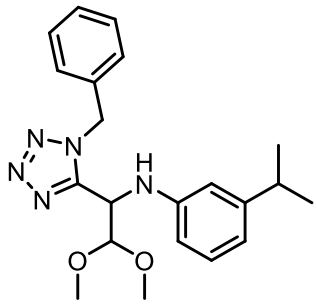
671 mg, 90% yield, yellow solid. mp 121 - 125 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 - 7.32 (m, 3H), 7.16 - 7.14 (m, 2H), 6.88 (t, *J* = 8.1 Hz, 1H), 6.66 - 6.64 (m, 1H), 6.29 (t, *J* = 2.1 Hz, 1H), 6.08 (ddd, *J* = 8.2, 2.3, 0.6 Hz, 1H), 5.80, 5.57 (ABq, *J* = 15.2 Hz, 2H), 4.84 (dd, *J* = 7.3, 5.2 Hz, 1H), 4.57 - 4.55 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 146.9, 135.1, 133.6, 130.4, 129.3, 129.0, 127.9, 119.4, 113.9, 111.8, 105.6, 57.2, 55.7, 52.6, 51.7. **HRMS** (ESI) m/z calcd for $C_{18}H_{21}ClN_5O_2$ $[M + H]^+$ = 374.1378, found 374.1378.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-bromoaniline (1x)



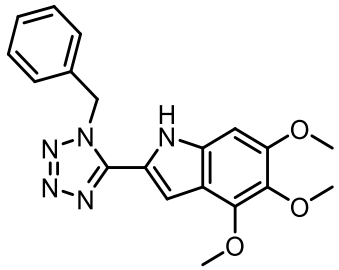
692 mg, 83% yield, yellow solid. mp 129 - 132 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 - 7.32 (m, 3H), 7.16 - 7.14 (m, 2H), 6.83 - 6.80 (m, 2H), 6.49 - 6.48 (m, 1H), 6.12 - 6.09 (m, 1H), 5.79, 5.57 (ABq, *J* = 15.2 Hz, 2H), 4.83 (dd, *J* = 7.3, 5.1 Hz, 1H), 4.57 - 4.59 (m, 2H), 3.41 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.5, 147.0, 133.6, 130.7, 129.3, 129.0, 127.8, 123.3, 122.3, 116.9, 112.1, 105.6, 57.2, 55.7, 52.5, 51.7. **HRMS** (ESI) m/z calcd for $C_{18}H_{21}BrN_5O_2$ $[M + H]^+$ = 418.0873, found 418.0873.

N-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-isopropylaniline (1y)



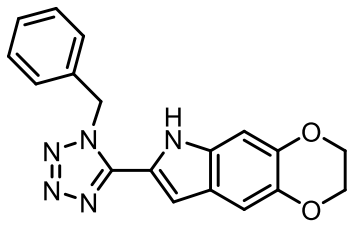
701 mg, 92% yield, yellow solid. mp 98 - 103 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 - 7.29 (m, 3H), 7.16 - 7.14 (m, 2H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.344 - 6.337 (m, 1H), 6.03 - 6.01 (m, 1H), 5.77, 5.58 (ABq, *J* = 15.2 Hz, 2H), 4.98 - 4.96 (m, 1H), 4.55 (d, *J* = 5.1 Hz, 1H), 4.47 (d, *J* = 5.0 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.69 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.14 (dd, *J* = 6.9, 3.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.9, 150.4, 145.8, 134.0, 129.4, 129.1, 128.7, 128.0, 117.7, 112.7, 110.8, 105.4, 57.0, 55.3, 52.9, 51.6, 34.2, 23.98, 23.96. **HRMS** (ESI) m/z calcd for $C_{21}H_{28}N_5O_2$ $[M + H]^+$ = 382.2238, found 382.2238.

2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole (2a)



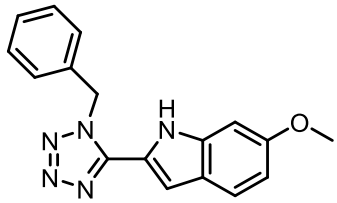
332 mg, 91% yield, white solid. mp 255 - 260 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.38 - 7.35 (m, 2H), 7.31 - 7.30 (m, 1H), 7.20 (d, J = 7.1 Hz, 2H), 7.04 (d, J = 1.4 Hz, 1H), 6.70 (s, 1H), 6.00 (s, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 3.67 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 152.7, 148.2, 145.5, 135.3, 134.6, 129.0, 128.2, 127.1, 117.9, 114.9, 103.2, 89.5, 60.9, 60.3, 55.8, 50.9. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}N_5O_3$ $[M + H]^+$ = 366.1561, found 366.1558.

7-(1-benzyl-1*H*-tetrazol-5-yl)-3,6-dihydro-2*H*-[1,4]dioxino[2,3-*f*]indole (2b-1)



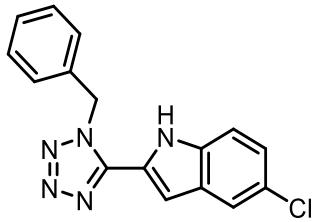
Mixture of isomers is formed in 5:1 ratio, but compound **2b-1** (77% yield, white solid) is obtained as only one isomer after ishing with chloroform. 306 mg, 92% yield (both isomers before ishing steps), yellow solid. mp 220 - 223 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.37 - 7.28 (m, 3H), 7.20 (d, J = 7.1 Hz, 2H), 7.01 (s, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 5.96 (s, 2H), 4.23 - 4.21 (m, 2H), 4.20 - 4.19 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.4, 142.7, 139.5, 134.5, 128.9, 128.2, 127.1, 122.0, 106.6, 104.3, 98.6, 64.2, 63.8, 50.8. **HRMS** (ESI) m/z calcd for $C_{18}H_{16}N_5O_2$ $[M + H]^+$ = 334.1299 found 334.1299.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6-methoxy-1*H*-indole (2c-1)



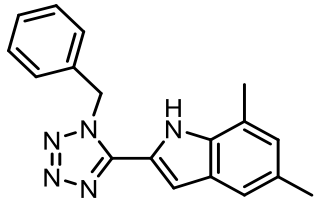
Mixture of isomers is formed in 10:1 ratio, but **2c-1** (79% yield, white solid) is obtained as only one isomer after ishing with ether. 149 mg, 87% yield (both isomers before ishing steps), white solid. mp 207 - 211 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.41 - 7.33 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.09 (s, 1H), 6.97 (s, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.99 (s, 2H), 3.80 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 157.5, 148.3, 138.3, 134.4, 128.9, 128.1, 127.1, 122.1, 121.8, 118.7, 105.2, 94.0, 55.2, 50.8. **HRMS** (ESI) m/z calcd for $C_{17}H_{16}N_5O$ $[M + H]^+$ = 306.1349, found 306.1349.

2-(1-benzyl-1*H*-tetrazol-5-yl)-5-chloro-1*H*-indole (2d)



46 mg, 15% yield, colorless solid. mp 205 - 209 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.37 - 7.30 (m, 3H), 7.24 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.22 - 7.18 (m, 2H), 7.14 (d, *J* = 1.6 Hz, 1H), 5.97 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.2, 135.8, 134.4, 129.2, 128.7, 128.5, 127.4, 124.9, 124.4, 121.7, 120.6, 114.0, 104.7, 51.2. **HRMS** (ESI) m/z calcd for $C_{16}H_{13}ClN_5O$ $[M + H]^+$ = 310.0854, found 310.0854.

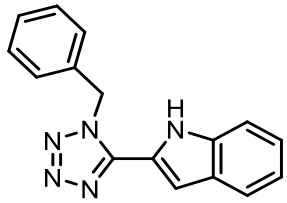
2-(1-benzyl-1*H*-tetrazol-5-yl)-5,7-dimethyl-1*H*-indole (2e)



203 mg, 67% yield, colorless solid. mp 183 - 185 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.41 - 7.34 (m, 3H), 7.26 - 7.23 (m, 3H), 6.95 (s, 1H), 6.80 - 6.79 (m, 1H), 5.84 (s, 2H), 2.47 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ

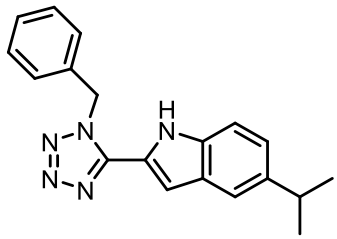
148.7, 135.3, 133.5, 130.9, 129.5, 128.9, 127.9, 127.7, 126.9, 121.0, 119.7, 118.7, 105.6, 51.7, 21.5, 16.9. **HRMS** (ESI) m/z calcd for $C_{18}H_{18}N_5$ $[M + H]^+$ = 304.1557, found 304.1556.

2-(1-benzyl-1*H*-tetrazol-5-yl)-1*H*-indole (2f)



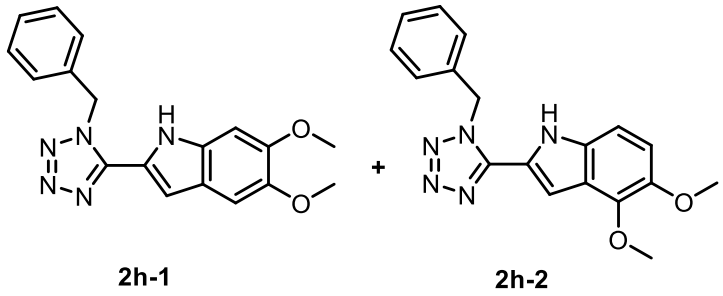
140 mg, 51% yield, white solid. mp 204 - 210 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.49 - 7.48 (m, 1H), 7.37 - 7.30 (m, 3H), 7.24 - 7.21 (m, 3H), 7.14 (dd, J = 2.3, 0.9 Hz, 1H), 7.08 - 7.07 (m, 1H) 6.00 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.4, 137.2, 134.4, 129.0, 128.2, 127.5, 127.2, 124.1, 121.4, 120.3, 120.0, 112.3, 105.0, 50.9. **HRMS** (ESI) m/z calcd for $C_{16}H_{14}N_5$ $[M + H]^+$ = 276.1244, found 276.1243.

2-(1-benzyl-1*H*-tetrazol-5-yl)-5-isopropyl-1*H*-indole (2g)



226 mg, 71% yield, white solid. mp 202 - 206 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.42 - 7.37 (m, 3H), 7.26 - 7.23 (m, 3H), 6.83 (d, J = 1.4 Hz, 1H), 5.87 (s, 2H), 3.04 - 2.97 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 142.0, 135.8, 133.5, 129.5, 128.9, 128.2, 126.9, 125.1, 120.0, 118.3, 112.0, 105.4, 51.8, 34.2, 24.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}N_5$ $[M + H]^+$ = 318.1713, found 318.1712.

2-(1-benzyl-1*H*-tetrazol-5-yl)-5,6-dimethoxy-1*H*-indole (2h-1) and 2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5-dimethoxy-1*H*-indole (2h-2)

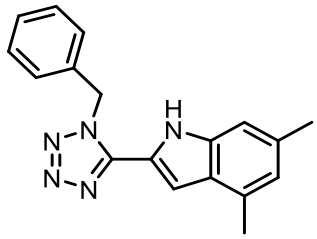


2h-1 **2h-2**

(**2h-1** : **2h-2** = 9 : 1)

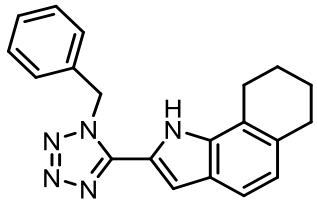
Mixture of isomers is formed in 5:1 ratio, but **2h** is obtained as the mixture of **2h-1** and **2h-2** in 9:1 ratio, after ishing steps with chloroform. **2h-1** + **2h-2**: 324 mg, 97% yield (both isomers before ishing steps), cream white solid. **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ 10.89 (s, 0.82H), 10.81 (s, 0.10H), 7.42 - 7.37 (m, 2H), 7.35 - 7.32 (m, 1H), 7.30 - 7.29 (m, 2H), 7.12 (s, 1H), 7.08 (s, 0.92H), 6.99 (s, 0.11H), 6.969 - 6.965 (m, 0.84H), 6.942 - 6.938 (m, 0.11H), 5.99 (s, 2H), 3.89 (d, *J* = 5.2 Hz, 0.43H), 3.84 (s, 2.74H), 3.80 (s, 3H). **^{13}C NMR** (126 MHz, $(CD_3)_2CO$) δ150.8, 149.5, 147.4, 135.7, 133.4, 129.94, 129.91, 129.2, 128.0, 127.9, 122.1, 119.4, 105.9, 103.5, 95.5, 56.4, 56.2, 51.9. **HRMS** (ESI) m/z calcd for $C_{18}H_{18}N_5O_2[M + H]^+$ = 336.1455, found 336.1455.

2-(1-benzyl-1*H*-tetrazol-5-yl)-5,7-dimethyl-1*H*-indole (2i)



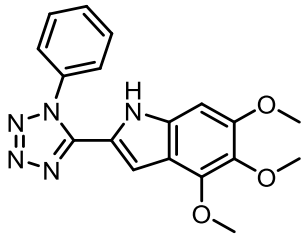
261 mg, 86% yield, white solid. mp 203 - 206 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 7.37 - 7.35 (m, 2H), 7.32 - 7.29 (m, 1H), 7.24 (d, *J* = 7.3 Hz, 2H), 7.11 - 7.10 (m, 1H), 7.08 (s, 1H), 6.70 (s, 1H), 6.01 (s, 2H), 2.41 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.5, 137.6, 134.6, 133.7, 130.0, 128.9, 128.3, 127.4, 127.3, 125.8, 122.3, 118.7, 109.4, 103.9, 51.0, 21.5, 18.3. **HRMS** (ESI) m/z calcd for $C_{18}H_{18}N_5$ $[M + H]^+$ = 304.1557, found 304.1556.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6,7,8,9-tetrahydro-1*H*-benzo[*g*]indole (2j)



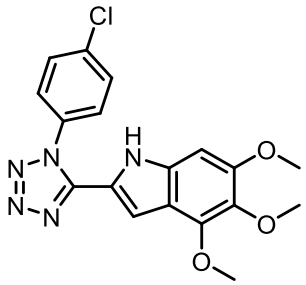
322 mg, 98% yield, white solid. mp 173 - 177 °C. **^{1}H NMR** (500 MHz, (CD_3) $_2$CO) δ 10.58 (s, 1H), 7.40 - 7.31 (m, 4H), 7.29 - 7.27 (m, 2H), 7.04 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.99 (s, 2H), 3.03 (t, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 6.1 Hz, 2H), 1.91 - 1.88 (m, 2H), 1.85 - 1.83 (m, 2H). **^{13}C NMR** (126 MHz, (CD_3) $_2$CO) δ149.6, 137.9, 135.7, 133.8, 130.0, 129.3, 128.1, 126.8, 123.8, 121.5, 121.4, 120.6, 119.5, 106.8, 52.1, 25.0, 24.1, 23.6. **HRMS** (ESI) m/z calcd for $C_{20}H_{20}N_5$ $[M + H]^+$ = 330.1713, found 330.1713.

4,5,6-trimethoxy-2-(1-phenyl-1*H*-tetrazol-5-yl)-1*H*-indole (2k)



319 mg, 91% yield, yellow solid. mp 208 - 211 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.07 (d, *J* = 1.8 Hz, 1H), 7.78 - 7.70 (m, 5H), 6.71 (s, 1H), 6.00 - 5.99 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.64 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 152.8, 148.4, 145.1, 135.4, 134.5, 134.2, 131.4, 130.2, 126.7, 118.2, 114.8, 102.5, 89.6, 60.9, 60.2, 55.8. **HRMS** (ESI) m/z calcd for $C_{18}H_{18}N_5O_3$ $[M + H]^+$ = 352.1404, found 352.1403.

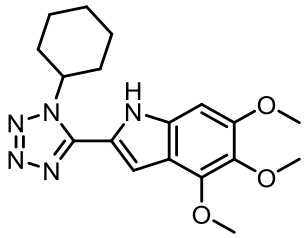
2-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole (2l)



312 mg, 81% yield, yellow solid. mp 250 - 255 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.81 - 7.78 (m, 4H), 6.71 (d, *J* = 0.5 Hz, 1H), 6.10 (s, 1H),

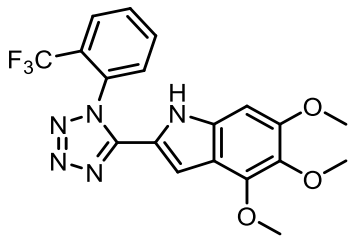
3.80 (s, 6H), 3.65 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 152.9, 148.4, 145.2, 135.9, 135.4, 134.5, 133.1, 130.2, 128.6, 118.1, 114.8, 102.6, 89.6, 60.9, 60.2, 55.8. **HRMS** (ESI) m/z calcd for $C_{18}H_{17}ClN_5O_3$ $[M + H]^+$ = 386.1014, found 386.1013.

2-(1-cyclohexyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole (2m)



275 mg, 77% yield, white solid. mp 215 - 223 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.12 (s, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 4.71 (tt, *J* = 11.5, 3.7 Hz, 1H), 4.15 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 2.27 - 2.24 (m, 2H), 2.17 - 2.09 (m, 2H), 2.06 - 2.03 (m, 2H), 1.86 - 1.83 (m, 1H), 1.60 - 1.52 (m, 2H), 1.45 - 1.39 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.8, 147.7, 145.8, 136.5, 134.7, 118.5, 116.3, 102.1, 90.5, 61.6, 61.2, 59.1, 56.3, 32.7, 25.4, 25.1. **HRMS** (ESI) m/z calcd for $C_{18}H_{24}N_5O_3$ $[M + H]^+$ = 358.1874, found 358.1873.

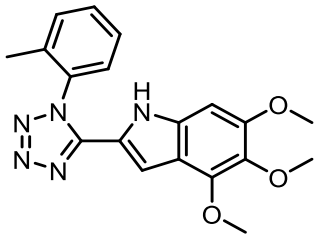
4,5,6-trimethoxy-2-(1-(2-(trifluoromethyl) phenyl)-1*H*-tetrazol-5-yl)-1*H*-indole (2n)



281 mg, 67% yield, yellow solid. mp 247 - 250 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.18 (d, *J* = 1.8 Hz, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 8.09 - 8.06 (m, 3H), 6.69 (s, 1H), 5.68 (d, *J* = 2.2 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 153.1, 149.5, 145.1, 135.4, 135.0, 134.6, 133.0, 131.2, 130.7, 128.4, 125.8, 123.6, 121.4, 117.8, 114.9, 102.4, 89.6, 60.9, 60.1,

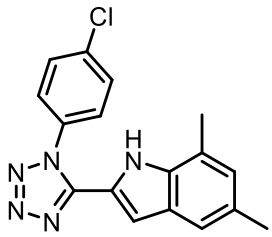
55.9. **^{19}F NMR** (471 MHz, DMSO-d_6) δ -58.32, -59.06. **HRMS** (ESI) m/z calcd for $C_{19}H_{17}F_3N_5O_3$ $[M + H]^+$ = 420.1277, found 420.1277.

4,5,6-trimethoxy-2-(1-(*o*-tolyl)-1*H*-tetrazol-5-yl)-1*H*-indole (2o)



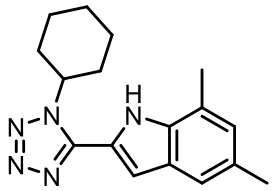
281 mg, 84% yield, yellow solid. mp 173 - 180 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.69 (td, *J* = 7.5, 1.3 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 2H), 7.56 - 7.53 (m, 1H), 6.70 (s, 1H), 5.78 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 1.92 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 153.0, 148.6, 145.1, 135.4, 135.0, 134.6, 133.3, 131.8, 127.9, 127.7, 118.1, 114.9, 101.9, 89.6, 60.9, 60.1, 55.8,16.5. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}N_5O_3$ $[M + H]^+$ = 366.1561, found 366.1557.

2-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-5,7-dimethyl-1*H*-indole (2p)



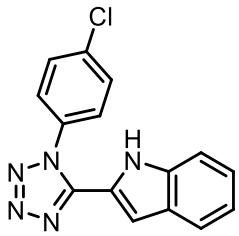
229 mg, 71% yield, cream white solid. mp 152 - 156 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.66 - 7.63 (m, 2H), 7.54 - 7.51 (m, 2H), 7.15 (s, 1H), 6.96 (s, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 2.51 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 137.6, 135.2, 132.9, 131.0, 130.6, 128.0, 127.7, 120.9, 119.6, 118.8, 106.0, 21.5, 16.8. **HRMS** (ESI) m/z calcd for $C_{17}H_{15}ClN_5$ $[M + H]^+$ = 324.1010, found 324.1010.

2-(1-cyclohexyl-1*H*-tetrazol-5-yl)-5,7-dimethyl-1*H*-indole (2q)



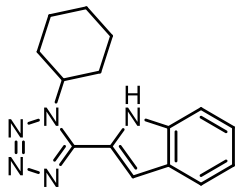
221 mg, 75% yield, colorless white solid. mp 133 - 136 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.28 (s, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.87 (s, 1H), 4.73 (tt, *J* = 11.4, 3.7 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H), 2.10 (d, *J* = 11.9 Hz, 2H), 1.90 - 1.83 (m, 4H), 1.68 (d, *J* = 12.9 Hz, 1H), 1.52 - 1.44 (m, 2H), 1.31 - 1.26 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 147.8, 129.1, 127.8, 126.3, 121.4, 120.2, 118.1, 104.8, 57.8, 32.4, 24.61, 24.57, 21.1, 17.1. **HRMS** (ESI) m/z calcd for $C_{17}H_{22}N_5$ $[M + H]^+$ = 296.1870, found 296.1869.

2-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-1*H*-indole (2r)



151 mg, 51% yield, brown solid. mp 244 - 248 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.23 (s, 1H), 7.82 - 7.80 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.23 - 7.20 (m, 1H), 7.03 - 7.00 (m, 1H), 6.20 (dd, *J* = 2.0, 0.7 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.6, 137.2, 136.0, 133.0, 130.3, 128.6, 127.2, 124.2, 121.4, 120.3, 120.1, 112.2, 104.8. **HRMS** (ESI) m/z calcd for $C_{15}H_{11}ClN_5$ $[M + H]^+$ = 296.0697, found 296.0698.

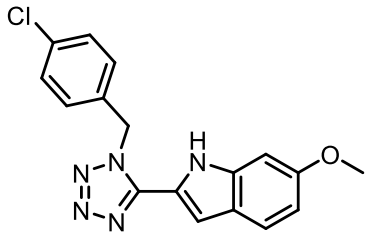
2-(1-cyclohexyl-1*H*-tetrazol-5-yl)-1*H*-indole (2s)



176 mg, 66% yield, colorless solid. mp 239 - 245 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.29 - 7.23

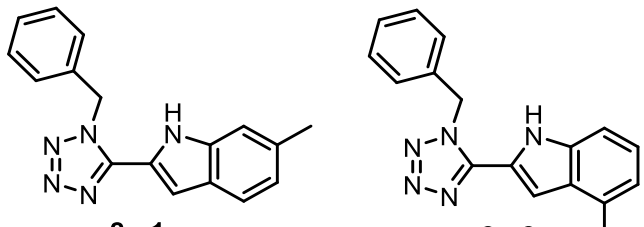
(m, 1H), 7.19 (s, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 4.85 - 4.76 (m, 1H), 2.15 (d, *J* = 11.5 Hz, 2H), 1.94 - 1.85 (m, 4H), 1.70 (d, *J* = 13.0 Hz, 1H), 1.58 - 1.50 (m, 2H), 1.31 - 1.28 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 147.6, 137.2, 127.6, 123.9, 121.4, 120.4, 120.2, 112.2, 104.4, 57.8, 32.3, 24.6, 24.5. **HRMS** (ESI) m/z calcd for $C_{15}H_{18}N_5$ $[M + H]^+$ = 268.1557, found 268.1556.

2-(1-(4-chlorobenzyl)-1*H*-tetrazol-5-yl)-6-methoxy-1*H*-indole (2t-1)



Mixture of isomers is formed in 9:1 ratio, but **2t-1** is obtained as only one isomer after ishing with ether. 298 mg, 88% yield (both isomers before ishing step), yellow solid. mp 207 - 211 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.27 - 7.25 (m, 2H), 7.07 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.97 (s, 2H), 3.78 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 157.6, 148.3, 138.4, 133.4, 132.9, 129.2, 129.0, 122.2, 121.9, 118.6, 111.6, 105.3, 94.0, 55.2, 50.2. **HRMS** (ESI) m/z calcd for $C_{17}H_{15}ClN_5O$ $[M + H]^+$ = 340.0960, found 340.0958.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6-methyl-1*H*-indole (2u-1) and 2-(1-benzyl-1*H*-tetrazol-5-yl)-4-methyl-1*H*-indole (2u-2)



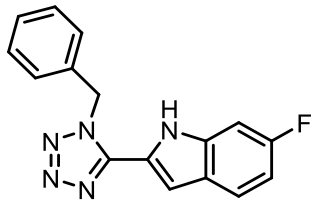
2u-1 **2u-2**

(**2u-1** : **2u-2** = 3:2)

The mixture of **2u-1** + **2u-2** is formed in 3:2 ratio. 277 mg, 96% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.24 (s, 0.37H), 10.09 (s, 0.57H), 7.50 (d, *J* = 8.2 Hz, 0.60H), 7.45 (d, *J* = 8.3 Hz, 0.43H), 7.43 - 7.36 (m, 3H), 7.30 - 7.22 (m, 2H),

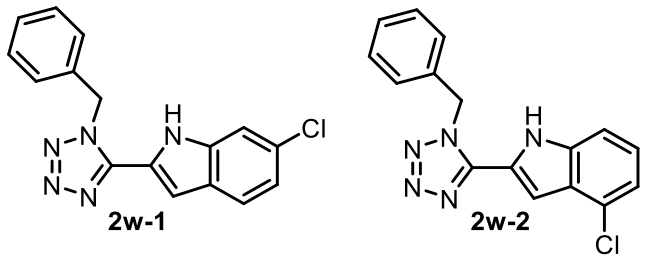
6.99 (d, *J* = 8.1 Hz, 0.57H), 6.95 (d, *J* = 7.0 Hz, 0.40H), 6.89 (s, 0.83H), 6.84 (s, 1.24H), 5.90 (s, 0.83H), 5.86 (s, 1.24H), 2.51 (s, 1.16H), 2.48 (s, 1.77H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 137.7, 137.0, 135.6, 133.54, 133.47, 131.2, 129.5, 129.0, 128.9, 128.2, 127.1, 127.0, 125.9, 125.5, 123.2, 121.3, 121.1, 119.4, 119.3, 112.0, 109.9, 105.5, 104.3, 51.9, 51.8, 22.1, 18.7. **HRMS** (ESI) m/z calcd for $C_{17}H_{16}N_5$ $[M + H]^+$ = 290.1400, found 290.1399.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6-fluoro-1*H*-indole (2v-1)



Mixture of isomers is formed in 6:5 ratio, but **2v-1** is obtained as only one isomer after ishing with dichloromethane. 269 mg, 92% yield (both isomers before ishing step), brown solid. mp 206 - 207 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.27 (s, 1H), 7.65 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.38 - 7.35 (m, 2H), 7.32 - 7.29 (m, 1H), 7.23 - 7.19 (m, 4H), 6.97 - 6.93 (m, 1H), 5.98 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 160.3 (d, $^{1}J_{C\text{-}F}$ = 239.0 Hz), 148.2, 137.3 (d, $^{3}J_{C\text{-}F}$ = 13.2 Hz), 134.4, 129.0, 128.3, 127.2, 124.4, 123.0 (d, $^{3}J_{C\text{-}F}$ = 10.3 Hz), 120.8, 109.4 (d, $^{2}J_{C\text{-}F}$ = 25.0 Hz), 105.2, 99.6, 97.9 (d, $^{2}J_{C\text{-}F}$ = 25.9 Hz), 51.0. **^{19}F NMR** (471 MHz, DMSO-d_6) δ -117.47. **HRMS** (ESI) m/z calcd for $C_{16}H_{13}FN_5$ $[M + H]^+$ = 294.1150, found 294.1149.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6-chloro-1*H*-indole (2w-1) and 2-(1-benzyl-1*H*-tetrazol-5-yl)-4-chloro-1*H*-indole (2w-2)

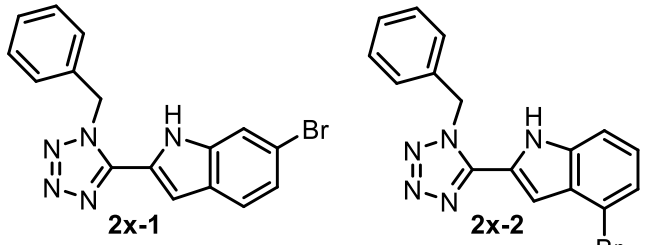


2w-1 **2w-2**

(**2w-1** : **2w-2** = 4:1)

Mixture of isomers is formed in 5:4 ratio, but **2w** is obtained as a mixture of **2w-1** and **2w-2** (4:1 ratio) after ishing with dichloromethane. **2w-1** + **2w-2**: 266 mg, 86% yield (both isomers before ishing steps), brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.56 (s, 0.24H), 12.34 (s, 0.87H), 7.65 (d, J = 8.5 Hz, 0.79H), 7.50 (s, 0.79H), 7.46 (d, J = 8.2 Hz, 0.23H), 7.39 - 7.29 (m, 3H), 7.25 - 7.21 (m, 2H), 7.19 (d, J = 1.9 Hz, 0.76H), 7.15 (d, J = 7.5 Hz, 0.18H), 7.09 (dd, J = 8.5, 1.8 Hz, 1H), 6.03 (s, 0.36H), 5.99 (s, 1.58H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.1, 137.5, 134.3, 129.0, 128.8, 128.3, 127.23, 127.19, 126.3, 123.0, 121.1, 120.8, 111.7, 105.1, 99.6, 51.0. **HRMS** (ESI) m/z calcd for $C_{16}H_{13}ClN_5$ $[M + H]^+$ = 310.0854, found 310.0854.

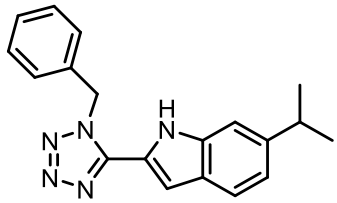
2-(1-benzyl-1*H*-tetrazol-5-yl)-6-bromo-1*H*-indole (2x-1) and 2-(1-benzyl-1*H*-tetrazol-5-yl)-4-bromo-1*H*-indole (2x-2)



(**2x-1** : **2x-2** = 1:1)

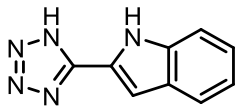
Mixture of isomers is formed in 2:1 ratio, but **2x** is obtained as a mixture of **2x-1** and **2x-2** in 1:1 ratio after ishing with dichloromethane. **2x-1** + **2x-2**: 332 mg, 94% yield (both isomers before ishing step), brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.58 (s, 0.49H), 12.34 (s, 0.50H), 7.65 (s, 0.45H), 7.60 (d, J = 8.5 Hz, 0.47H), 7.50 (d, J = 8.2 Hz, 0.51H), 7.40 - 7.30 (m, 3.43H), 7.23 - 7.16 (m, 3.42H), 6.99 (s, 0.48H), 6.03 (s, 1H), 5.99 (s, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 148.1, 138.0, 137.5, 134.4, 134.3, 129.04, 129.01, 128.4, 128.3, 128.0, 127.24, 127.19, 126.5, 125.3, 123.34, 123.28, 123.0, 121.00, 120.97, 116.9, 114.7, 114.2, 111.9, 105.2, 104.7, 51.2, 51.0. **HRMS** (ESI) m/z calcd for $C_{16}H_{13}BrN_5$ $[M + H]^+$ = 354.0349, found 354.0348.

2-(1-benzyl-1*H*-tetrazol-5-yl)-6-isopropyl-1*H*-indole (2y)



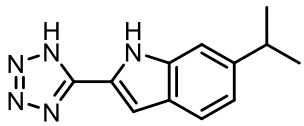
Mixture of isomers is formed in 4:1 ratio, but **2y** is obtained as only one isomer after ishing with ether. 273 mg, 86% yield (both isomers before ishing step), white solid. mp 169 - 174 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.41 - 7.35 (m, 4H), 7.26 - 7.24 (m, 2H), 7.07 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.84 (d, *J* = 1.4 Hz, 1H), 5.87 (s, 2H), 3.08 - 3.00 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 147.0, 137.5, 133.5, 129.5, 128.9, 127.0, 126.3, 121.5, 120.9, 119.6, 109.1, 105.4, 51.8, 34.7, 24.4. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}N_5$ $[M + H]^+$ = 318.1713, found 318.1714.

2-(1*H*-tetrazol-5-yl)-1*H*-indole (3a)



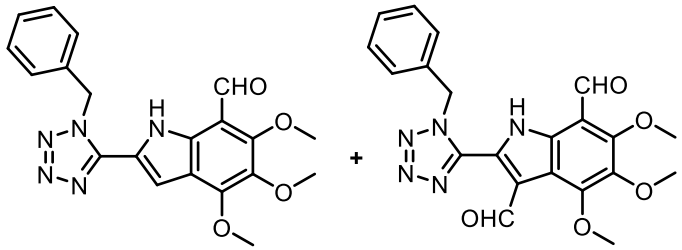
175 mg, 95% yield, yellow solid. Spectral data are in accordance to reported data. [3] **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 - 7.13 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H).

6-isopropyl-2-(1*H*-tetrazol-5-yl)-1*H*-indole (3b)



44 mg, 98% yield, white solid. Spectral data are in accordance to reported data. [4] **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.94 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.07 (d, *J* = 1.5 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.5 Hz, 1H), 2.97 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 144.2, 137.8, 125.8, 121.8, 120.9, 119.6, 109.0, 103.3, 33.8, 24.3.

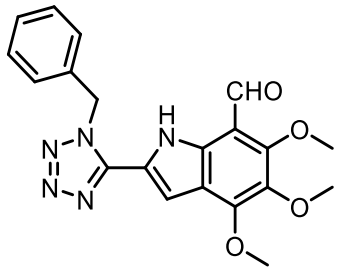
2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole-7-carbaldehyde (4) and 2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole-3,7-dicarbaldehyde (4')



4 (**4** : **4'** = 1:1) **4'**

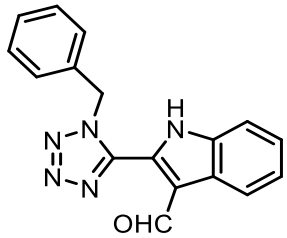
The mixture of **4** and **4'** is formed in 1:1 ratio. 374 mg, 94% yield, brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.00 (s, 1H), 11.46 (s, 1H), 10.32 (s, 1H), 10.29 (s, 1H), 10.24 (s, 1H), 7.34 - 7.26 (m, 4H), 7.24 - 7.22 (m, 3H), 7.19 - 7.17 (m, 2H), 7.14 - 7.12 (m, 2H), 5.95 (s, 2H), 5.43 (s, 2H), 4.22 (s, 3H), 4.18 (s, 3H), 4.06 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 188.5, 188.4, 186.1, 157.6, 153.7, 153.3, 148.0, 147.8, 140.1, 136.8, 134.3, 133.9, 132.5, 128.9, 128.4, 128.3, 128.3, 128.1, 127.4, 120.5, 118.3, 116.3, 115.6, 111.0, 108.3, 104.8, 63.3, 63.2, 61.5, 61.2, 61.2, 60.4, 51.1, 50.9.

2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indole-7-carbaldehyde (4)



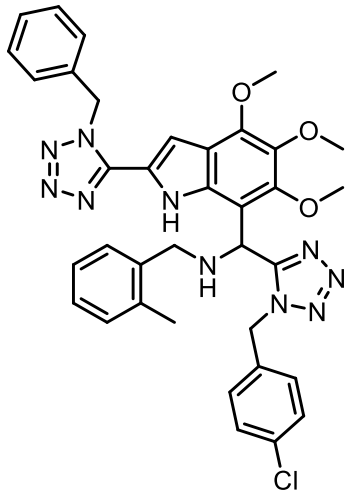
369 mg, 92% yield, brown solid. mp 198 - 199 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.47 (s, 1H), 10.25 (s, 1H), 7.34 - 7.29 (m, 4H), 7.19 - 7.17 (m, 2H), 5.95 (s, 2H), 4.22 (s, 3H), 4.02 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 188.4, 157.6, 153.7, 147.8, 136.8, 134.3, 132.5, 128.9, 128.3, 127.4, 120.5, 115.6, 108.4, 104.8, 63.2, 61.2, 60.4, 51.1. **HRMS** (ESI) m/z calcd for $C_{20}H_{20}N_5O_4$ $[M + H]^+$ = 394.1510, found 394.1505.

2-(1-benzyl-1*H*-tetrazol-5-yl)-1*H*-indole-3-carbaldehyde (5)



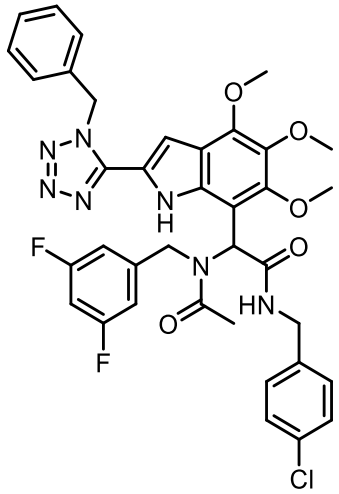
291 mg, 96% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.92 (s, 1H), 10.10 (s, 1H), 8.23 - 8.21 (m, 1H), 7.50 - 7.48 (m, 1H), 7.41 - 7.35 (m, 2H), 7.27 - 7.21 (m, 3H), 7.06 - 7.04 (m, 2H), 5.64 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 184.8, 147.6, 136.9, 133.0, 129.4, 129.3, 128.1, 126.1, 125.9, 125.2, 124.1, 120.9, 118.4, 112.8, 52.8. **HRMS** (ESI) m/z calcd for $C_{17}H_{14}N_5O$ $[M + H]^+$ = 304.1193, found 304.1192.

1-(2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indol-7-yl)-1-(1-(4-chlorobenzyl)-1*H*-tetrazol-5-yl)-*N*-(2-methylbenzyl)methanamine (6)



449 mg, 65% yield, white solid. mp 102 - 105 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.37 - 7.30 (m, 3H), 7.22 - 7.21 (m, 2H), 7.17 - 7.15 (m, 3H), 7.10 - 7.09 (m, 2H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.90 - 5.80 (m, 3H), 5.50, 5.40 (ABq, *J* = 15.5 Hz, 2H), 4.01 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.69, 3.58 (ABq, *J* = 13.6 Hz, 2H), 2.32 (s, 1H), 2.10 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.4, 150.1, 148.2, 147.2, 138.9, 136.7, 134.7, 133.6, 132.4, 132.2, 130.8, 129.3, 129.2, 128.8, 128.6, 128.5, 127.7, 126.9, 126.1, 120.3, 119.0, 103.5, 62.0, 61.4, 60.9, 51.6, 50.0, 49.2, 48.7, 18.9. **HRMS** (ESI) m/z calcd for $C_{36}H_{35}ClN_{10}NaO_3$ $[M + Na]^+$ = 713.2474, found 713.2477.

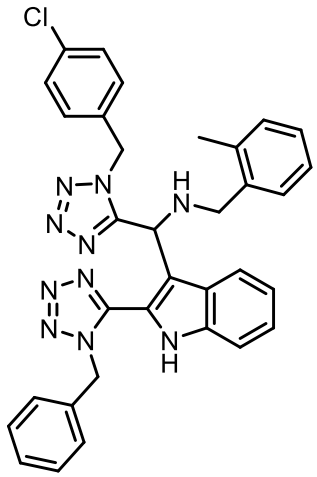
2-(2-(1-benzyl-1*H*-tetrazol-5-yl)-4,5,6-trimethoxy-1*H*-indol-7-yl)-*N*-(4-chlorobenzyl)-2-(*N*- (3,5-difluorobenzyl)acetamido)acetamide (7)



445 mg, 61% yield, brown solid. mp 154 - 158 °C. *Mixture of rotamers observed*. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.38 (s, 0.35H), 11.04 (s, 0.64H), 9.04 (s, 0.37H), 8.77 (s, 0.64H), 7.38 - 7.30 (m, 3.46H), 7.28 - 7.26 (m, 4H), 7.21 - 7.19 (m, 2H), 7.06 (s, 0.65H), 7.00 (s, 0.33H), 6.74 (t, *J* = 9.0 Hz, 0.58H), 6.54 (s, 0.38H), 6.34 (d, *J* = 6.3 Hz, 1.2H), 6.10 (d, *J* = 7.2 Hz, 0.79H), 5.99 - 5.97 (m, 2.35H), 5.04 (d, *J* = 16.4 Hz, 0.33H), 4.75, 4.57 (ABq, *J* = 18.5 Hz, 1.24H), 4.49 - 4.37 (m, 1H), 4.30 - 4.24 (m, 1.4H), 4.04 - 4.01 (m, 0.5H), 3.87 - 3.84 (m, 3H), 3.77 - 3.74 (m, 3H), 3.63 (s, 1.18H), 3.51 (s, 2H), 2.27 (s, 1H), 2.00 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 171.8, 162.9, 161.2, 160.9, 151.3, 147.8, 146.4, 143.1, 138.6, 138.3, 138.1, 134.5, 131.5, 131.2, 129.5, 129.2, 129.1, 129.0, 128.3, 128.2, 128.0, 127.2, 119.7, 117.6, 108.3, 103.5, 101.6, 60.8, 60.6, 60.5,

59.8, 57.3, 54.5, 51.0, 49.3, 46.4, 42.1, 41.9, 22.1, 22.0, 20.8, 14.1. ^{19}F NMR (471 MHz, DMSO-d_6) δ -110.29, -111.51. **HRMS** (ESI) m/z calcd for $C_{37}H_{35}ClF_2N_7O_5$ $[M + H]^+$ = 730.2351, found 730.2352.

1-(2-(1-benzyl-1*H*-tetrazol-5-yl)-1*H*-indol-3-yl)-1-(1-(4-chlorobenzyl)-1*H*-tetrazol-5-yl)-*N*-(2-methylbenzyl) methanamine (8)



294 mg, 49% yield, white solid. mp 93 - 94 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.42 - 7.39 (m, 2H), 7.23 - 7.18 (m, 3H), 7.17 - 7.14 (m, 1H), 7.10 (t, *J* = 7.1 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.02 - 6.99 (m, 3H), 6.84 - 6.80 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.79 - 5.76 (m, 1H), 5.69 - 5.60 (m, 3H), 5.47 - 5.44 (m, 1H), 3.61 - 3.55 (m, 2H), 2.97 (s, 1H), 2.13 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.9, 148.1, 137.2, 134.3, 134.0, 132.2, 130.7, 129.9, 129.8, 129.6, 129.2, 128.9, 128.6, 128.4, 127.7, 127.6, 126.0, 125.4, 121.8, 120.3, 117.8, 112.0, 51.9, 50.1, 49.0, 48.3, 19.0. **HRMS** (ESI) m/z calcd for $C_{33}H_{30}ClN_{10}$ $[M + H]^+$ = 601.2338, found 601.2337.

3. Single crystal x-ray structure determination

*Data for compound **4***

A specimen of $C_{20}H_{21}N_5O_4$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å). A total of 1692 frames are collected. The total exposure time is 2.35 hours. The frames are integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 10266 reflections to a maximum θ angle of 50.51° (1.00 Å resolution), of which 1965 are independent (average redundancy 5.224, completeness = 99.6%, R_{int} = 4.96%, R_{sig} = 3.84%) and 1606 (81.73%) are greater than 2σ (F^2). The final cell constants of a = 9.5268 (3) Å, b = 25.0880 (8) Å, c = 8.4177 (3) Å, β = 111.280 (2) °, volume = 1874.73 (11) $Å^3$, are based upon the refinement of the XYZ-centroids of 5363 reflections above 20 σ (I) with 7.047° < 2θ < 100.7°. Data are corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission is 0.808.

The structure is solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{20}H_{21}N_5O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 269 variables converged at R1 = 6.56%, for the observed data and wR2 = 19.34% for all data. The goodness-of-fit is 1.435. The largest peak in the final difference electron density synthesis is 0.212 $e^-/Å^3$ and the largest hole is -0.435 $e^-/Å^3$ with

an RMS deviation of 0.058 $e^-/Å^3$. On the basis of the final model, the calculated density is 1.401 g/cm^3 and F (000), 832 e^-. CCDC number: 2077271

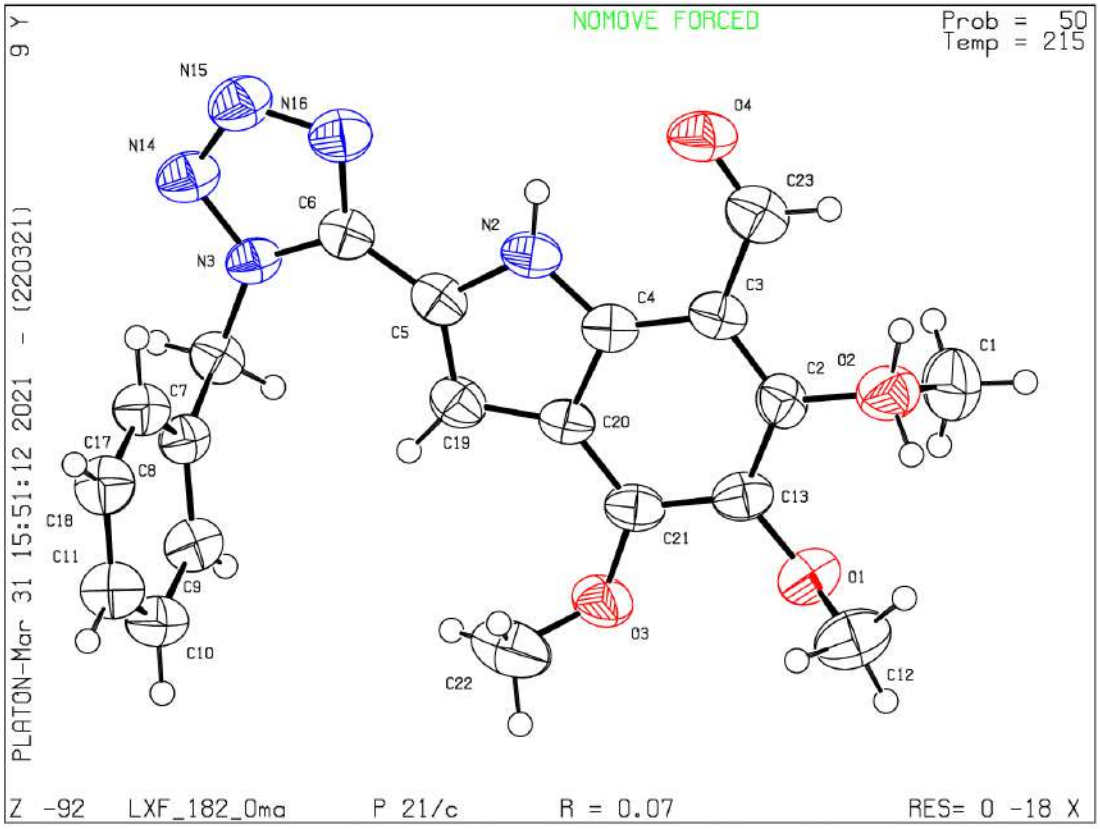


Table 1. Sample and crystal data for **4**

Identification code	**4** (LXF_182)
Chemical formula	$C_{20}H_{21}N_5O_4$
Formula weight	395.42 g/mol
Temperature	215 (2) K
Wavelength	1.54178 Å
Crystal system	monoclinic
Space group	P 1 21/c 1

Unit cell dimensions	a = 9.5268 (3) Å	α = 90°
	b = 25.0880 (8) Å	β = 111.280 (2) °
	c = 8.4177 (3) Å	γ = 90°
Volume	1874.73 (11) $Å^3$	
Z	4	
Density (calculated)	1.401 g/cm^3	
Absorption coefficient	0.831 mm^{-1}	
F (000)	832	

Table 2. Data collection and structure refinement for **4**

Theta range for data collection	3.52 to 50.51°
Index ranges	-9<=h<=9, -24<=k<=25, -8<=l<=8
Reflections collected	10266
Independent reflections	1965 [R (int) = 0.0496]
Coverage of independent reflections	99.6%
Absorption correction	Multi-Scan
Structure solution technique	direct methods
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)

Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	$\Sigma w (F_o^2 - F_c^2)^2$	
Data / restraints / parameters	1965 / 0 / 269	
Goodness-of-fit on F^2	1.435	
Δ/σ_{max}	0.002	
Final R indices	1606 data, $I>2\sigma(I)$	R1 = 0.0656, wR2 = 0.1793
	all data	R1 = 0.0822, wR2 = 0.1934
Weighting scheme	$w=1/[\sigma^2 (F_o^2) + (0.1000P)^2]$ where $P= (F_o^2+2F_c^2) /3$	
Largest diff. peak and hole	0.212 and -0.435 eÅ^{-3}	
R.M.S. deviation from mean	0.058 eÅ^{-3}	

REFERENCES

1. Patil, P., Ahmadian-Moghaddam, M., & Dömling, A. *Green Chemistry*. **2020**, 22, 6902-6911.
2. Lanke, V., & Ramaiah Prabhu, K. *Organic Letters*, **2015**, *15 (24),* 6262-6265.
3. Kou, X., Zhao, M., Qiao, X., Zhu, Y., Tong, X., Shen, Z. *Chemistry - A European Journal*, **2013**, *19*, 16880.
4. Ito, M., Iwatani, M., Kamada, Y., Sogabe, S., Nakao, S., Tanaka, T., Imaeda, Y. *Bioorganic & Medicinal Chemistry,* **2017**, *25 (7),* 2200-2209.

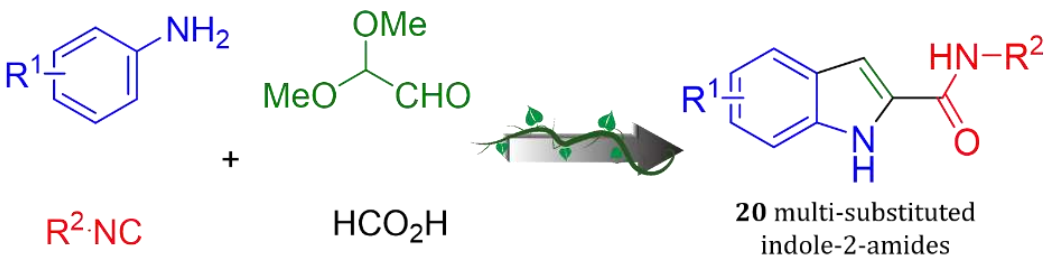
Chapter 2

Sustainable multicomponent indole synthesis with broad scope

*This chapter is based on the artictl*e: “Sustainable multicomponent indole synthesis with broad scope*”, by* **Xiaofang Lei**, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Green Chemistry,* **2022**, *24*, 6168-6171.

ABSTRACT

Herein an innovative 2-step reaction for accessing indole amides is reported. The proposed synthesis implements commercially available anilines and carboxylic acids, glyoxal dimethyl acetal and isocyanides. Our strategy is based on the combination of IMCRs, followed by an acid-induced cyclization. Compared to the already reported indole syntheses, this procedure takes place without a catalyst under mild and green conditions and is suitable for a wide range of substituted anilines and isocyanides. In the present work, 20 indole-2-carboxamide derivatives are synthesized.



Improved Yield Time PMI E-factor AE

INTRODUCTION

The indole moiety has been involved in numerous small molecules used in biochemicals, dyes, medicines, natural products, material science and agrochemicals (Figure 1).[1] This moiety has been found in the essential proteinogenic amino acid tryptophan (**3**), which plays an important role in many biochemical pathways, the anticancer drug Osimertinib (**4**),[2] the natural hallucinogenic Psilocin (**2**), for the latent treatment of series of mental illnesses,[3] the OLEDs material INDY **6**,[4] plant hormone indoleacetic acid (IAA,**1**) and Tadalafil (**5**).

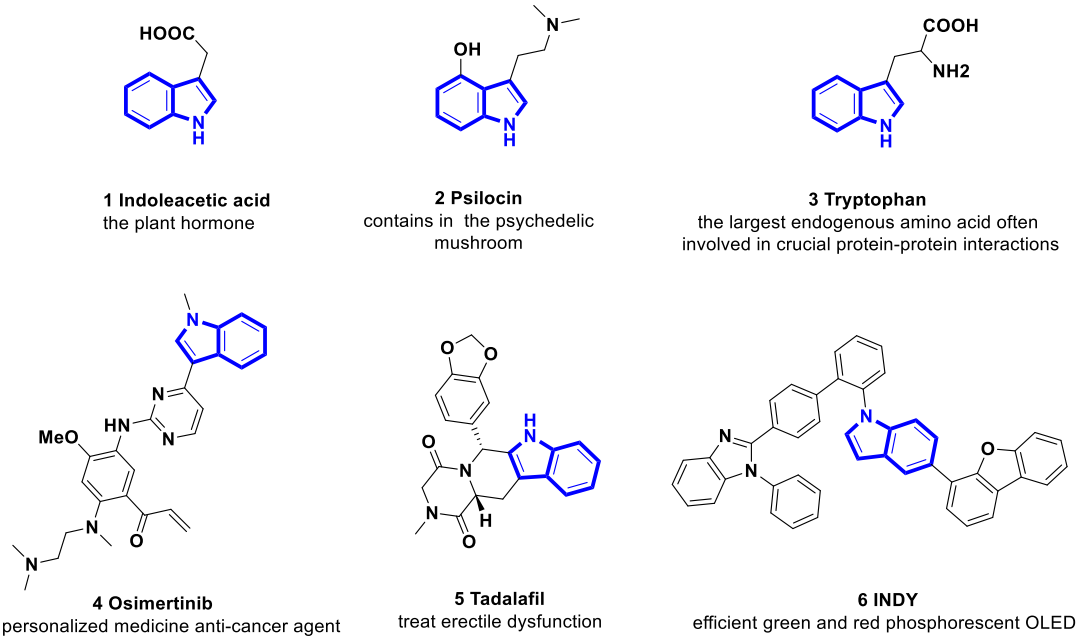


Figure 1 Selected examples of molecules containing indole core.

Therefore, an efficient synthetic methodology towards the indole core is of outmost importance. So far, indole syntheses include high-temperature reaction conditions, limited ranges of substrates and halogenated solvents.[5] The aforementioned synthetic procedure occurs under highly acidic refluxing conditions in high concentrations of the phenylhydrazone.[6] This protocol needs catalyst and an excess amount of sodium sulfite.[7-8]

One of the prospects of modern organic synthesis is sustainability. In this regard, MCRs can achieve efficiency catalyst-free, low waste production, reduced purification steps, broad scope and substrate compatibility.[11] Notably,

there are not many MCRs procedures for the synthesis of the indole scaffold (Figure 2). So far, the groups of Takahashi, Zhang and Fan, Sorensen, Kalinski, Chen and ourselves reported synthetic pathways for indole-based scaffolds via MCRs.[12-17] Takahashi *et al.* report an approach to get 2,3-disubstituted indoles through a 3-component coupling of amine, aryl iodide, and o-alkenylphenyl isocyanide with a palladium catalyst.[12] Zhang *et al.* synthesize the 3-cyano-1*H*-indoles via ammonia with 1-bromo-2- (2,2-dibromovinyl) -benzenes and aldehydes.[13] Sorensen *et al.*, depict the acid-mediated imine formation of anilines and aldehydes followed by ring closure with tert-butyl isocyanide.[14] Kalinski *et al.* report that the desired indoles are accessed from isocyanides, cinnamaldehydes and *o*-bromoanilines via an U-3CR in the presence of formic acid. The MCR reaction is followed by a Heck reaction.[15] Recently, Chen *et al.* report a one-pot method to synthesize functionalized indoles via an U-4CR.[16] Our recent work depicts the synthesis of 2-tetrazole substituted indoles from the corresponding anilines, glyoxal dimethyl acetal, isocyanides and TMS-azide via UT-4CR (Figure 2).[17]

Indole-2-carboxamide derivatives are widely used in medicine as allosteric antagonists,[18] CB2 agonists,[19] SETD2 inhibitors[20] and antitubercular agents.[21] As previously stated, MCRs adhere to several aspects of the twelve principles of green chemistry. Herein, a fast 2-step indole core is synthesized based on the U-4CR and the ring closure procedure from various anilines, glyoxal dimethyl acetal, formic acid and isocyanides. Considering previous indole-2-carboxamide synthetic protocols, the present method stands out for its mild reaction conditions, low toxicity, increased yields and broad substrate scope.

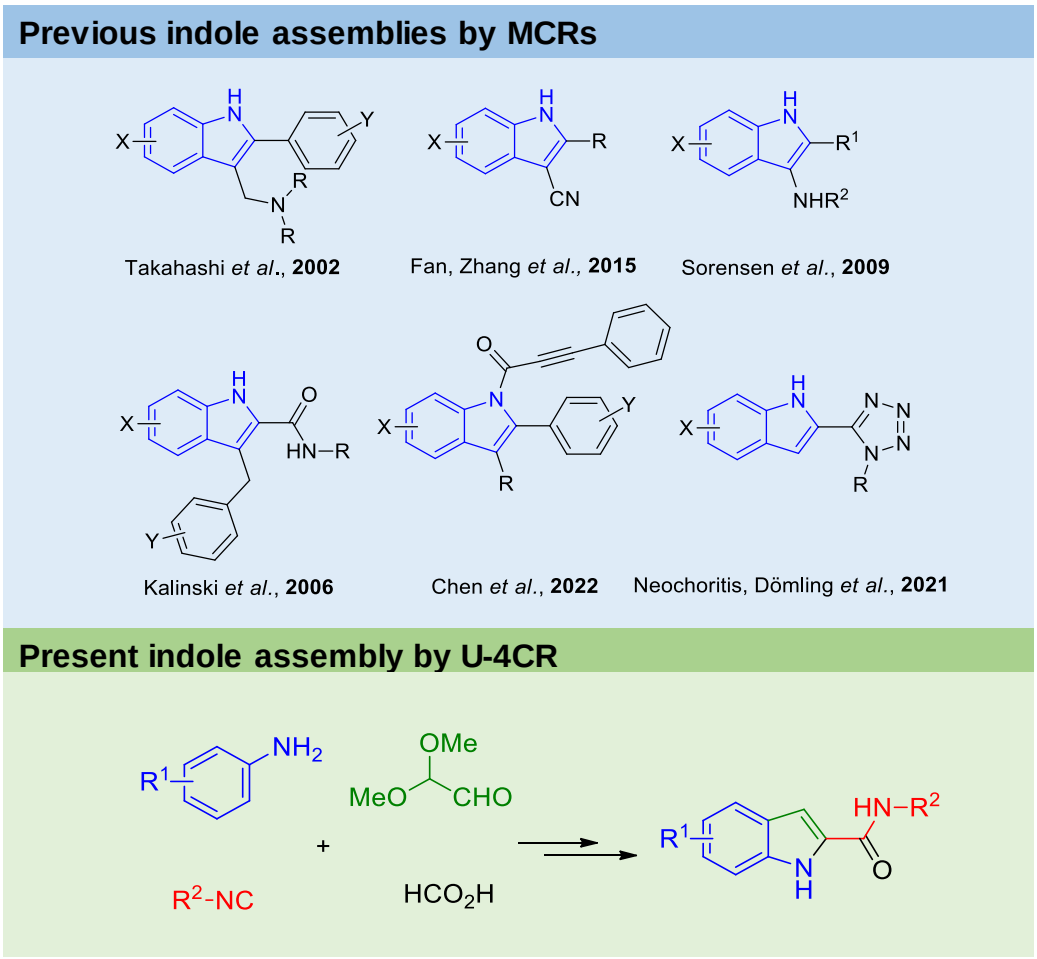


Figure 2 MCR protocols to assemble the indole core.

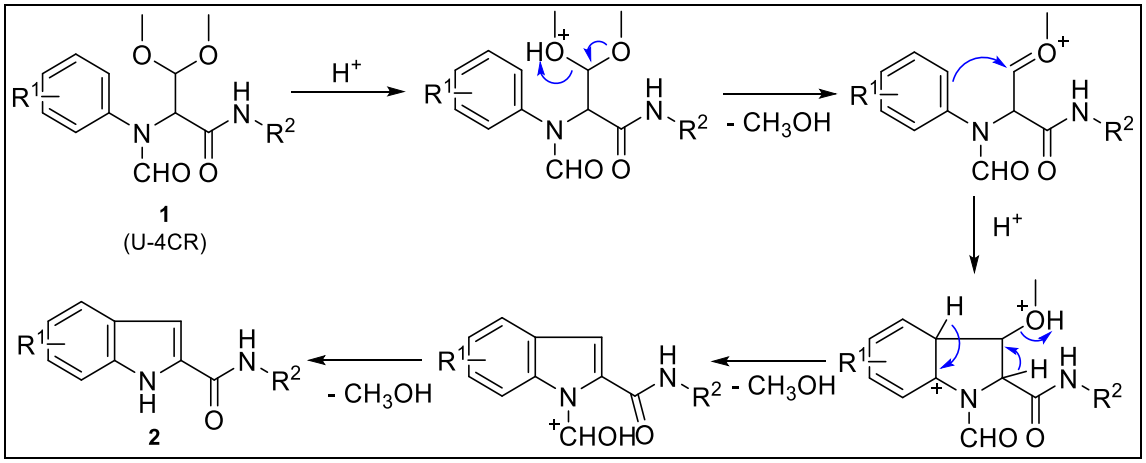
RESULTS AND DISCUSSION

Firstly, in the first step the U-4CR is utilized to obtain the intermediate products **1a**-**t** from the substituted anilines and various isocyanides at room temperature in good to excellent yields (74-96%) (Table 1). Interestingly, the targeted multi-substituted products **2a**-**t** are successfully obtained in methanesulfonic acid (MSA, ≥ 99% purity, freshly opened bottle) at 70 ºC in 22-96% yield. The MSA is crucial for the acidic cyclization reaction (see Chapter 1). In several cases, the desired products precipitate quickly and are isolated by filtration (see EXPERIMENTAL SECTION). Additionally, acetic acid and benzoic acid display the same behavior as formic acid in the first step and the following acid-catalyzed cyclization.

After the successful model reaction **2a**, several diverse substituted anilines and isocyanides are assessed. In fact, a library of 20 multi-substituted indole-2-carboxamides is developed. Observed in our previous work,[17] substituted anilines with electron-donating groups (EDGs) in *meta* position show a better behavior (See mechanism), while anilines with electron-withdrawing groups (EWGs) or *para-substituted* anilines with EDGs (**2m** and **2o**-**p**) react poorly or not at all during the cyclization step. Interestingly, the degradation of the U-4CR adducts is occurring, recovering the corresponding anilines. As expected, *meta*-substituted anilines lead to two different regio indole isomers (**2j**-**m**).[17] To our delight, the major regio isomers (**j**-**l**) precipitated in 42%, 84%, and 81% yield, respectively (Table 1). However, **2m** gives the mixture of regioisomers (see EXPERIMENTAL SECTION).

Mechanism

The proposed mechanism in this study involves an U-4CR, followed by an acidic closure step (Scheme 1).

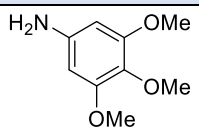
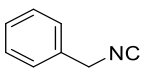
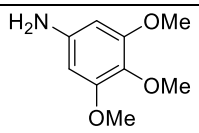
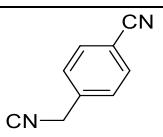


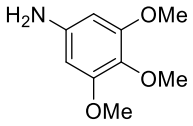
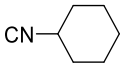
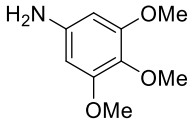
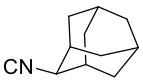
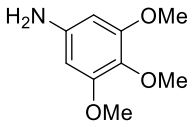
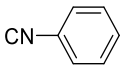
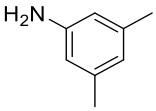
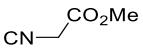
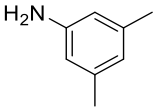
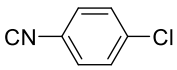
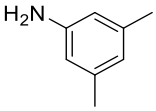
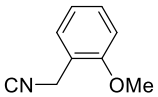
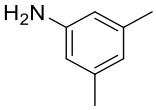
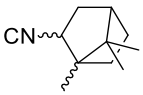
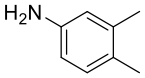
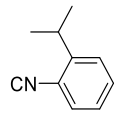
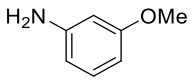
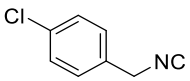
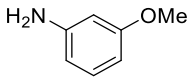
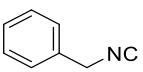
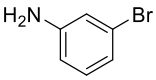
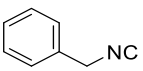
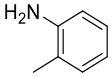
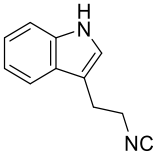
Scheme 1 Reaction mechanism

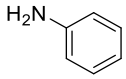
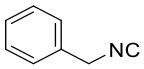
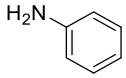
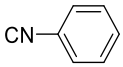
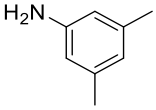
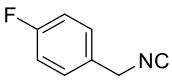
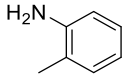
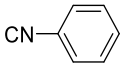
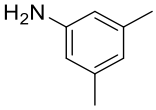
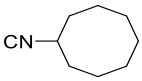
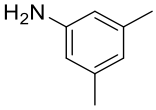
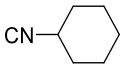
Isocyanides with diverse substituents, aryl (**e**, **g**, **j**, **p**, and **r**), benzylic (**a**-**b**, **h**, **k**-**m**, **o** and **q**) and aliphatic (**c**-**d**, **f**, **l** and **s**-**t**) afford the desired Ugi products, without interfering with the acidic closure reaction. Also, camphor (**i**) is successfully employed. Furthermore, this strategy gives access to the "double" free NH indole compound (**n**) and can be extended to other heterocycles as well. Overall, Table 1 demonstrates the *de novo* construction of the multi-substituted indole-2-carboxamides.

The one-pot two-step approach is also examined. In fact, compounds **a**, **d**, and **q**-**t** can be isolated in one pot in 81%, 84%, 64%, 57%, 82%, and 86% yield, respectively (Table 1). Additionally, this protocol can be easily scaled-up, thus isolation of 4.06 g of **1a** (10 mmol, 94%) and 1.55 g of **2a** (5 mmol, 91% yield) is achieved after purification by column chromatography (Figure 3, A).

Table 1 The MCR-based indole 2-amide **2** synthesis.

Entry	Aniline	Isocyanide	1st step yield (%)	2nd step yield (%)
a			92	81
b			93	92

c			96	91
d			One pot	84%
e			90	92
f			87	76
g			89	74
h			90	62
i			86	72
j			74	62 (regio isomer ratio:5:2)
k			89	96 (regio isomer ratio:15:1)
l			90	93 (regio isomer ratio:16:1)
m			85	39 (regio isomer ratio:7:5)
n			90	53

o			82	22
p			76	43
q			One pot	64
r			One pot	57
s			One pot	82
t			One pot	86 (regio isomer ratio:9:1)

The yields of both steps and the ratio of the regioisomers are given in the table, the second yield refers to the regio isomer mixture if the isomers appeared. Some one-pot two-step approach only give the overall yield at the second step for without isolation of the intermediate Ugi adduct.

Utilization of this protocol yields the SETD2 inhibitor (**2r**) and two anti-tuberculosis agents (**2s** and **2t**)[20, 21] in a mild, rapid and straightforward fashion with 57%, 82%, and 86% yields, respectively (Figure 3, B-D). In literature, the synthesis of these molecules proceeds upon the generation of 2-indole acetic acid, starting from phenyl hydrazines, and a subsequent amide formation. This methodology often employs inaccessible and expensive starting materials and a strong basic environment over 140 ^{o}C, [20] expensive catalysts and dry reaction conditions.[22] To date, all the reported approaches include more than 4 synthetic steps.

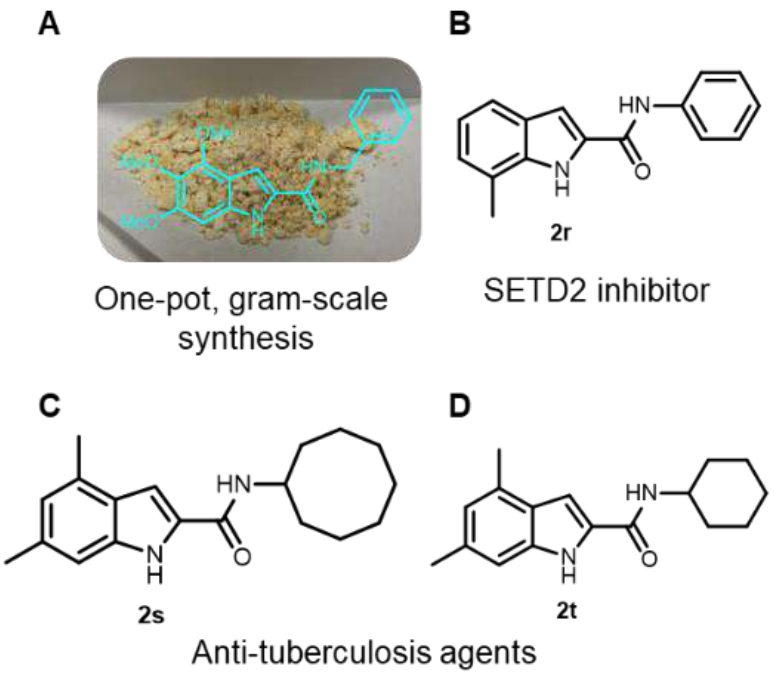


Figure 3 Applications of our innovative indole syntheses. (A) The gram-scale synthesis of **2a**, (B-D) easy access to the bioactive compounds **2r** (SETD2 inhibitor), **2s** (anti-tuberculosis agent) and **2t** (anti-tuberculosis agent) via our strategy.

The synthetic methodology proposed in the present study complies with the green chemistry principles. To evaluate this concept, analysis of several reaction parameters occurs (namely, time (h), E-factor and atom economy (AE), process mass intensity (PMI), total product yield, and the amounts of inorganic and organic solvents (ml) (Figure 4 and EXPERIMENTAL SECTION). In this regard, indole amide **2t** is selected as a model compound (Figure 4). Compared to other methods,[23-25] the proposed synthetic approach takes place in 2 steps or a two-step one-pot procedure with inexpensive starting materials (Table 1). Impressively, this protocol outstands in every category, such as the E-factor, AE, reaction time, amount of solvents (organic and inorganic) and total yield, even if we take into account the additional isocyanides synthesis (see EXPERIMENTAL SECTION). In fact, the cyclohexyl isocyanide is commercially available and inexpensive.

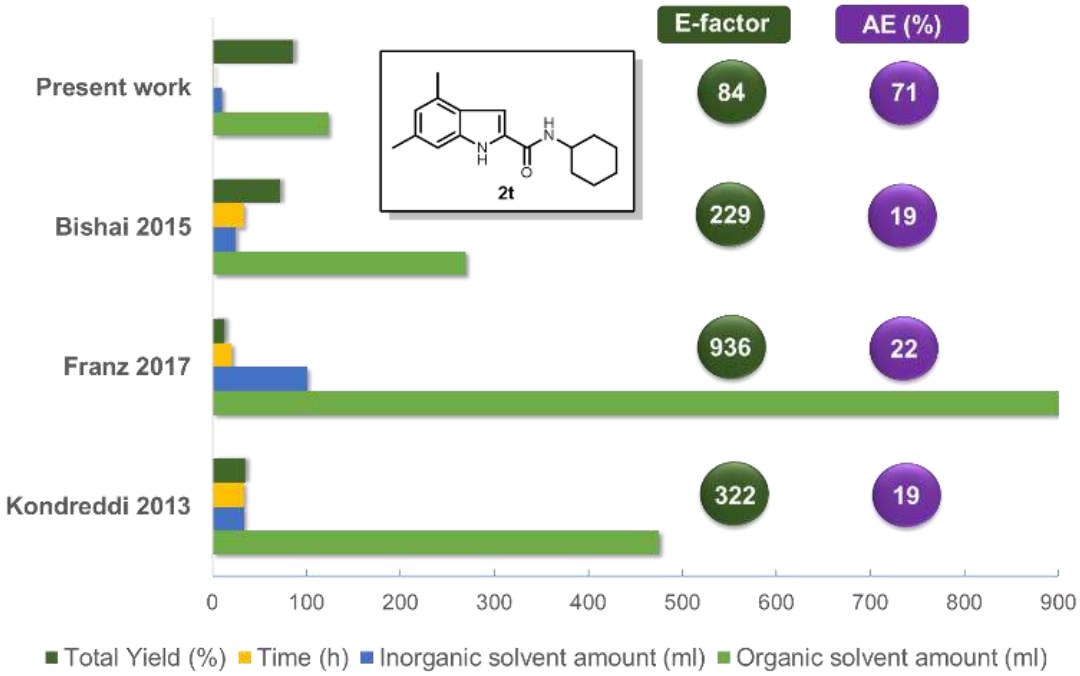


Figure 4 MCR-footprint supremacy. Bar chart comparing three representative procedures with ours (incl. the isocyanide synthesis) for the synthesis of **2t** including the total yield, time, inorganic and organic waste the E-factor and atom economy (AE).

For scaffolds **2f** and **2g** single-crystal X-ray structures are obtained (Table 1). The X-ray structures show that the solid-state conformations of the molecular scaffold involve intermolecular bifurcated hydrogen bonds involving the indole-*NH* and the 2-carbonyl of two adjacent molecules forming non-covalent dimers (Figure 5).

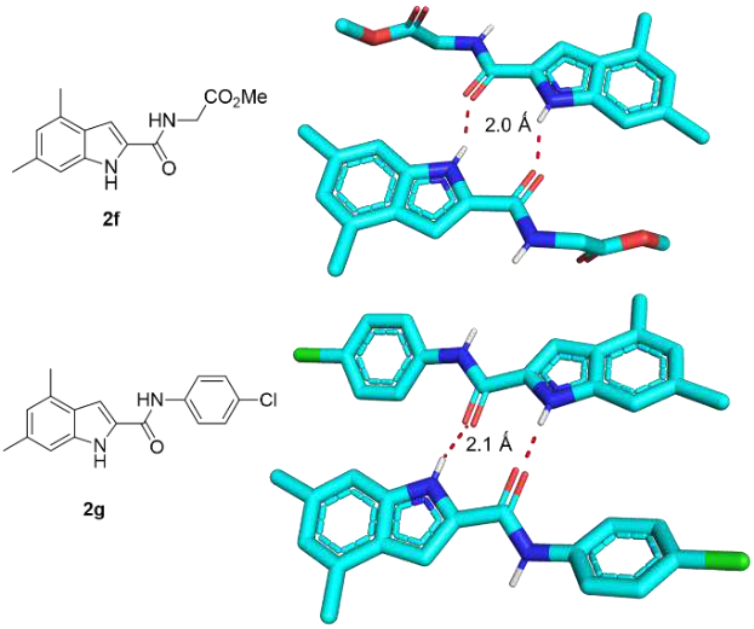


Figure 5 Hydrogen bonding-induced dimer formation of **2f** (CCDC 2174979) and **2g** (CCDC 2174980) in solid state.

CONCLUSIONS

In brief, the development of a short, rapid, mild, economic, and scalable MCR-based procedure occurs toward C2 functionalized indole amides. This novel protocol complies with the green chemistry merits principles. In addition, numerous bioactive compounds can be synthesized easily and rapidly in just two steps or one-pot two-step reactions in good to excellent yield. The library of 20 indole-2-carboxamide derivatives displays that this procedure is suitable for a wide range of scaffolds in benign reacted conditions. As such, the advantages of this *de novo* indole syntheses will make this method a handy addition to existing indole syntheses methodologies.

REFERENCES

1. E. Vitaku, D. T. Smith and J. T. Njardarson, *Journal of Medicinal Chemistry*, **2014**, *57*, 10257-10274.
2. S. S. Ramalingam, J. Vansteenkiste, D. Planchard, B. C. Cho, J. E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Cheiskulyong, R. Shah, M. Cobo, K. H. Lee, P. Cheema, M. Tiseo, T. John, M. C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov and J. C. Soria, *The New England journal of medicine*, **2020**, *382*, 41-50.
3. H. A. Geiger, M. G. Wurst and R. N. Daniels, *ACS Chemical Neuroscience*, **2018**, *9*, 2438-2447.
4. Y. Chen, X. Wei, J. Cao, J. Huang, L. Gao, J. Zhang, J. Su and H. Tian, *ACS Applied Materials & Interfaces*, **2017**, *9*, 14112-14119.
5. E. Fischer and F. Jourdan, Ber. Dtsch. Chem. Ges., **1883**, *16*, 2241-2245.
6. B. Robinson, *Chemical Reviews*, **1963**, *63*, 373-401.
7. E. Fischer, *Berichte der deutschen chemischen Gesellschaft*, **1875**, *8*, 589-594.
8. S. V. Kumar and D. Ma, *Chinese Journal of Chemistry*, **2018**, *36*, 1003-1006.
9. J. Y. Wang, K. Choi, S. J. Zuend, K. Borate, H. Shinde, R. Goetz and J. F. Hartwig, *Angewandte Chemie International Edition*, **2021**, *60*, 399-408.
10. Shengfeng Wu, Xiaofang Lei, Erkang Fan, and Zhihua Sun, *Org. Lett*. **2018**, *20*, 522-525.
11. R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chemistry*, **2014**, *16*, 2958-2975.
12. K. Onitsuka, S. Suzuki and S. Takahashi, *Tetrahedron Letters*, **2002**, *43*, 6197-6199.
13. B. Li, S. Guo, J. Zhang, X. Zhang and X. Fan, *The Journal of Organic Chemistry*, **2015**, *80*, 5444-5456.
14. J. S. Schneekloth, J. J. Kim and E. J. Sorensen, *Tetrahedron*, **2009**, *65*, 3096-3101.
15. C. Kalinski, M. Umkehrer, J. Schmidt, G. Ross, J. Kolb, C. Burdack, W. Hiller and S. D. Hoffmann, *Tetrahedron Letters*, **2006**, *47*, 4683-4686.

16. S. P. Murugan, H.-J. Zhong, C.-Y. Wu, H.-W. Pan, C. Chen and G.-H. Lee, *ACS Omega*, **2022**, *7*, 5713-5729.
17. X. Lei, P. Lampiri, P. Patil, G. Angeli, C. G. Neochoritis and A. Dömling, *Chemical Communications*, **2021**, *57*, 6652-6655.
18. Silvano E, Millan MJ, Mannoury la Cour C, Han Y, Duan L, Griffin SA, Luedtke RR, Aloisi G, Rossi M, Zazzeroni F, Javitch JA, Maggio R., *Mol Pharmacol*. **2010 Nov**,*78 (5)* :925-934.
19. Ying Shi, Yanhui Duan, Yueyang Ji, Zhilong Wang, Yanran Wu, Hendra Gunosewoyo, Xiaoyu Xie, Jianzhong Chen, Fan Yang, Jing Li, Jie Tang, Xin Xie, and Lifang Yu, *J. Med. Chem.,* **2017**, *60*, 7067-7083.
20. R. R. Kondreddi, J. Jiricek, S. P. S. Rao, S. B. Lakshminarayana, L. R. Camacho, R. Rao, M. Herve, P. Bifani, N. L. Ma, K. Kuhen, A. Goh, A. K. Chatterjee, T. Dick, T. T. Diagana, U. H. Manjunatha and P. W. Smith, *Journal of Medicinal Chemistry*, **2013**, *56*, 8849-8859.
21. O. K. Onajole, M. Pieroni, S. K. Tipparaju, S. Lun, J. Stec, G. Chen, H. Gunosewoyo, H. Guo, N. C. Ammerman, W. R. Bishai and A. P. Kozikowski, *Journal of Medicinal Chemistry*, **2013**, *56*, 4093-4103.
22. N. D. Franz, J. M. Belardinelli, M. A. Kaminski, L. C. Dunn, V. Calado Nogueira de Moura, M. A. Blaha, D. D. Truong, W. Li, M. Jackson and E. J. North, *Bioorganic & Medicinal Chemistry*, **2017**, *25*, 3746-3755.
23. Kondreddi, Ravinder Reddy et al, *Journal of Medicinal Chemistry*, **2013**, *56 (21),* 8849-8859.
24. N.D. Franz et al, *Bioorganic & Medicinal Chemistry*, **2017**, *25*, 3746-3755.
25. BISHAI, William R. et al, WO2015164482 (A1) PCT/US **2015**/027053.

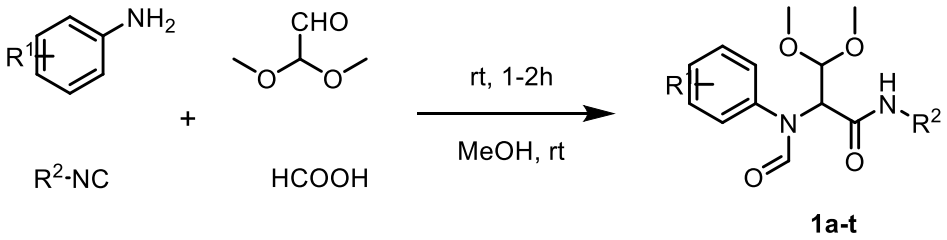
EXPERIMENTAL SECTION

1. General methods and materials

All the reagents and solvents are purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and are used without further purification. Isocyanides are synthesized as previously described by us. All microwave irradiation reactions are carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography is performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra are recorded on Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz) }. Chemical shifts for ^{1}H NMR are reported as δ values and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak. Flash chromatography is performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra are measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). High resolution mass spectra are recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

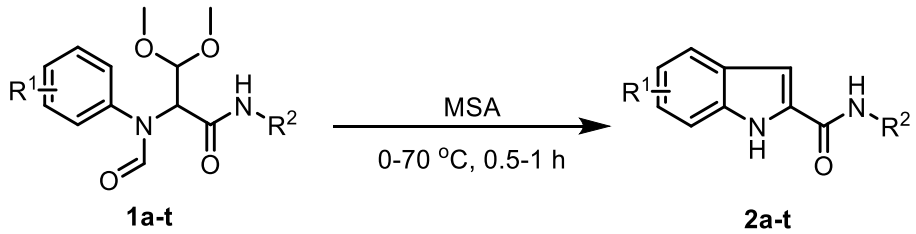
2. Synthetic procedures and analytical data

General procedure for the Ugi 4-component reaction (U-4CR)



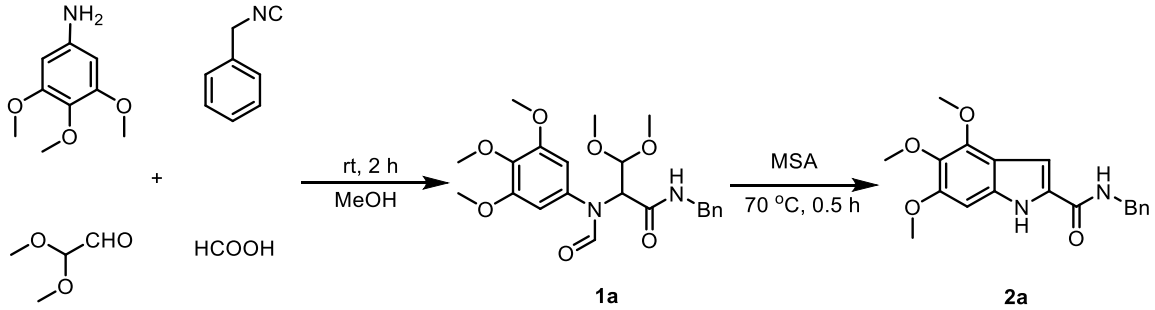
To a stirred solution of the corresponding aniline (1.0 mmol) in MeOH (1.0 mL), 2,2-dimethoxyacetaldehyde (1.0 mmol), the corresponding isocyanide (1.0 mmol) and formic acid (1.0 mmol) are added at room temperature. The reaction mixture is stirred vigorously for 1-2 h. The solvent is removed under reduced pressure and the reaction mixture is purified with column chromatography (PE-EA 4:1-1:1) to give compounds **1a**-**t**.

General procedure for the cyclization



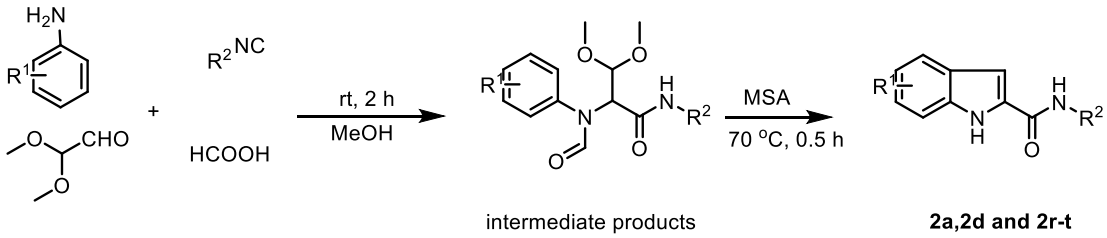
The corresponding indole-2-carboxamides (1.0 mmol) are dissolved into methanesulfonic acid (MSA) (1.0 mL) at 0 °C and then heated up to 70 °C for 0.5 - 1.0 h. Then, the reaction mixture is cooled to room temperature and neutralized with an aqueous solution of $NaHCO_3$, followed by extractions with ethyl acetate. The organic layer is dried with Na_2SO_4, the solvent is removed under reduced pressure. If solid appears, the resulting solid is filtered and washed with Et_2O or hexane. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 8:1-1:1) to give the compounds **2a-t**.

The gram-scale synthesis of 1a and 2a



To a stirred solution of 2,2-dimethoxyacetaldehyde (10.0 mmol, 1.04 g) in MeOH (10.0 mL), the 3,4,5-trimethoxyaniline (10.0 mmol, 1.83 g), benzyl isocyanide (10.0 mmol, 1.17 g) and formic acid (10.0 mmol, 0.46 g) are added in a 50 mL flask. The reaction mixture is stirred vigorously for 2 h. Then, the solvent is removed under reduced pressure and the reaction mixture is purified with column chromatography (PE-EA 4:1-1:1) to give compound **1a** (4.06 g, 94%) as yellow solid. Afterwards, the *N*-benzyl-3,3-dimethoxy-2- (*N*- (3,4,5-trimethoxyphenyl) formamido) propanamide (**1a**, 5.0 mmol, 2.16 g) is dissolved into methanesulfonic acid (5.0 mL) at 0 °C and then heated up to 70 °C for 0.5 h. Then, the reaction mixture is cooled to room temperature neutralized with an aqueous solution of $NaHCO_3$ to pH 7, followed by extractions with ethyl acetate (3 x 30 mL). The organic layer is dried with Na_2SO_4 and the solvent is removed under reduced pressure. The reaction mixture is purified with column chromatography (PE-EA 4:1-1:1) to give compound **2a** (1.55 g, 91%) as yellow solid.

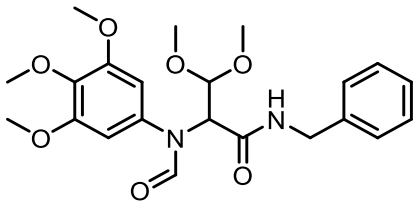
One-pot two-step approach towards 2a, 2d and 2q-t



To a stirred solution of 2,2-dimethoxyacetaldehyde (1.0 mmol) in MeOH (1.0 mL), the the corresponding aniline (1.0 mmol), the corresponding isocyanide (1.0 mmol) and formic acid (1.0 mmol) are added in a 5.0 mL vial. The reaction mixture is stirred vigorously for 2 h. Then, the solvent is removed under reduced

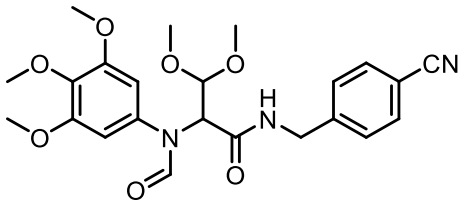
pressure and the intermediate products are obtained, directly used in the next step without further purification. Afterwards, the methanesulfonic acid (1.0 mL) is added at 0 °C and heated up to 70 °C for 0.5 h. The reaction mixture is neutralized with an aqueous solution of $NaHCO_3$, followed by extractions with ethyl acetate. The organic layer is dried with $MgSO_4$ and the solvent is removed under reduced pressure. The resulting solid is purified by column chromatography (PE-EA, 4:1-1:1) to give compounds **2a**, **2d** and **2q-t** in 2-steps.

N-benzyl-3,3-dimethoxy-2-(*N*-(3,4,5-trimethoxyphenyl)formamido) propenamide (1a)



397 mg, 92% yield, yellow solid, mp 86-90 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.36 - 7.33 (m, 2H), 7.32 - 7.29 (m, 3H), 7.18 - 7.16 (m, 1H), 6.63 (s, 2H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.82 (d, *J* = 8.3 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 6H), 3.44 (s, 3H), 3.31 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 163.6, 153.4, 138.0, 137.7, 135.4, 128.7, 127.6, 127.4, 104.9, 104.6, 103.5, 100.9, 60.9, 60.7, 56.38, 56.2, 55.7, 54.1, 43.5, 43.3. **HRMS** (ESI) m/z calcd for $C_{22}H_{29}N_2O_7$ $[M + H]^+$ 433.1969, found 433.1963.

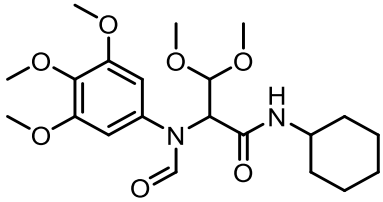
N-(4-cyanobenzyl)-3,3-dimethoxy-2-(*N*-(3,4,5-trimethoxyphenyl)formamido)propenamide (1b)



425 mg, 93% yield, yellow solid, mp 111-114 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.36 (t, *J* = 5.8 Hz, 1H), 6.64 (s, 2H), 5.02 (d, *J* = 8.1 Hz, 1H), 4.76 (d, *J* = 8.1 Hz, 1H), 4.62 (dd, *J* = 15.9, 6.0 Hz, 1H), 4.52 (dd, *J* = 15.9, 6.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 6H), 3.44 (s, 3H), 3.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.8, 163.6, 153.5,

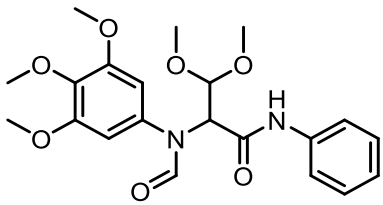
143.6, 137.8, 135.5, 132.5, 127.8, 118.7, 111.2, 104.5, 101.0, 61.3, 60.9, 56.3, 55.5, 54.6, 43.1. **HRMS** (ESI) m/z calcd for $C_{23}H_{27}NaN_3O_7$ $[M + Na]^+$ 480.1741, found 480.1735.

N-cyclohexyl-3,3-dimethoxy-2-(*N*-(3,4,5-trimethoxyphenyl)formamido)propenamide (1c)



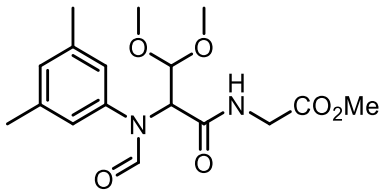
407 mg, 96% yield, white solid, mp 131-134 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.66 - 6.65 (m, 3H), 4.92 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 8.4 Hz, 1H), 3.85 - 3.84 (m, 9H), 3.82 - 3.78 (m, 1H), 3.45 (s, 3H), 3.27 (s, 3H), 1.92 - 1.89 (m, 2H), 1.70 - 1.67 (m, 2H), 1.61 - 1.57 (m, 1H), 1.41 - 1.34 (m, 2H), 1.26 - 1.18 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 163.6, 153.4, 137.7, 135.5, 104.6, 101.1, 61.0, 60.7, 56.3, 55.9, 54.0, 48.3, 32.8, 32.7, 25.6, 24.6. **HRMS** (ESI) m/z calcd for $C_{21}H_{32}NaN_2O_7$ $[M + Na]^+$ 447.2102, found 447.2097.

3,3-dimethoxy-*N*-phenyl-2-(*N*-(3,4,5-trimethoxyphenyl)formamido)propenamide (1e)



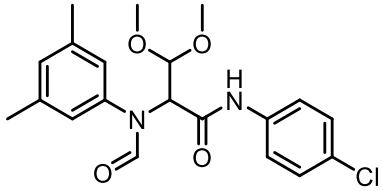
376 mg, 90% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.38 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.16 - 7.15 (m, 1H), 6.67 (s, 2H), 5.10 (d, *J* = 8.2 Hz, 1H), 4.89 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 6H), 3.53 (s, 3H), 3.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.4, 163.8, 153.5, 137.8, 137.6, 135.4, 129.0, 124.6, 120.0, 104.6, 101.0, 62.0, 61.0, 56.3, 56.0, 54.3. **HRMS** (ESI) m/z calcd for $C_{21}H_{26}NaN_2O_7$ $[M + Na]^+$ 441.1632, found 441.1624.

methyl(2-(*N*-(3,5-dimethylphenyl)formamido)-3,3-dimethoxypropanoyl)glycinate (1f)



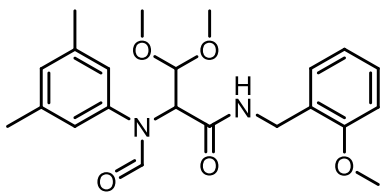
306 mg, 87% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.52 (s, 1H), 6.96 (s, 3H), 5.13 (d, *J* = 8.3 Hz, 1H), 4.70 (d, *J* = 8.3 Hz, 1H), 4.16 (dd, *J* = 18.3, 5.3 Hz, 1H), 4.08 (dd, *J* = 18.3, 5.3 Hz, 1H), 3.78 (s, 3H), 3.50 (s, 3H), 3.33 (s, 3H), 2.34 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.1, 167.5, 163.6, 140.3, 139.2, 129.4, 123.8, 100.6, 61.6, 55.3, 54.1, 52.3, 41.4, 21.3. **HRMS** (ESI) m/z calcd for $C_{17}H_{24}NaN_2O_6$ $[M + Na]^+$ 375.1527, found 375.1522.

N-(4-chlorophenyl)-2-(*N*-(3,5-dimethylphenyl)formamido)-3,3-dimethoxypropanamide (1g)



347 mg, 89% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.36 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.31 - 7.29 (m, 1H), 7.00 - 6.98 (m, 3H), 5.14 (d, *J* = 8.2 Hz, 1H), 4.83 (d, *J* = 8.2 Hz, 1H), 3.51 (s, 3H), 3.34 (s, 3H), 2.35 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.5, 164.1, 139.8, 139.3, 136.3, 129.7, 129.4, 129.0, 124.0, 121.3, 101.0, 62.5, 55.7, 54.2, 21.3. **HRMS** (ESI) m/z calcd for $C_{20}H_{23}ClNaN_2O_4$ $[M + Na]^+$ 413.1239, found 413.1234.

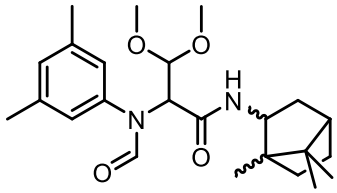
2-(*N*-(3,5-dimethylphenyl)formamido)-3,3-dimethoxy-*N*-(2-methoxybenzyl)propenamide (1h)



360 mg, 90% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.31 - 7.26 (m, 3H), 6.95 - 6.92 (m, 2H), 6.90 - 6.88 (m, 1H), 6.85 (s, 2H), 4.99 (d, *J* =

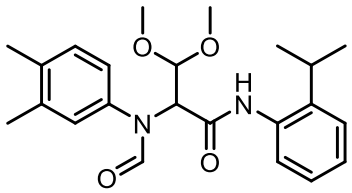
8.4 Hz, 1H), 4.78 (d, *J* = 8.4 Hz, 1H), 4.55, 4.45 (ABq, *J* = 14.6, 6.0 Hz, 2H), 3.88 (s, 3H), 3.42 (s, 3H), 3.28 (s, 3H), 2.30 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 163.5, 157.5, 139.7, 139.1, 129.6, 129.5, 128.8, 126.1, 124.3, 120.6, 110.2, 100.7, 60.5, 55.6, 55.3, 53.4, 39.6, 21.2. **HRMS** (ESI) m/z calcd for $C_{22}H_{29}N_2O_5$ $[M + H]^+$ 401.2071, found 401.2069.

2-(*N*-(3,5-dimethylphenyl)formamido)-3,3-dimethoxy-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) propanamide (1i)



334 mg, 86% yield, yellow oil, *dr~1:4.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.33 (s, 0.2H), 8.32 (s, 0.8H), 7.10 - 6.97 (m, 4H), 5.09 - 5.04 (m, 1H), 4.67 - 4.62 (m, 1H), 4.30 - 4.25 (m, 1H), 3.96 - 3.91 (m, 1H), 3.47 - 3.44 (m, 3H), 3.30 - 3.27 (m, 3H), 2.34 - 2.33 (m, 6H), 1.91 - 1.69 (m, 3H), 1.65 - 1.40 (m, 2H), 1.34 - 1.15 (m, 2H), 0.96 (d, *J* = 3.1 Hz, 3H), 0.89 (d, *J* = 4.9 Hz, 2H), 0.86 - 0.82 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 166.3, 163.8, 163.7, 163.6, 140.3, 139.1, 129.4, 129.3, 129.3, 129.2, 123.9, 123.8, 123.6, 100.8, 100.7, 56.8, 56.7, 55.2, 55.1, 54.0, 53.9, 48.7, 48.5, 47.1, 44.9, 39.1, 39.0, 37.6, 37.5, 36.0, 35.9, 28.3, 28.1, 27.1, 21.3, 20.3, 20.1, 19.8, 18.7, 13.8, 13.6, 11.9, 11.8. **HRMS** (ESI) m/z calcd for $C_{24}H_{36}NaN_2O_4$ $[M + Na]^+$ 439.2567, found 439.2547.

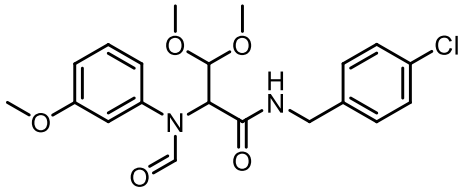
2-(*N*-(3,4-dimethylphenyl)formamido)-*N*-(2-isopropylphenyl)-3,3-dimethoxypropanamide (1j)



294 mg, 74% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.39 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.25 - 7.14 (m, 5H), 5.13 (d, *J* = 8.2 Hz, 1H), 4.98 (d, *J* = 8.2 Hz, 1H), 3.52 (s, 3H), 3.36 (s, 3H), 3.12 - 3.07 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.31 - 1.28 (m, 6H). **^{13}C NMR** (126

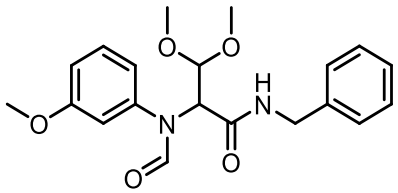
MHz, $CDCl_3$) δ 165.9, 163.9, 139.7, 137.9, 137.6, 136.6, 134.2, 130.4, 127.6, 126.3, 125.7, 125.4, 124.0, 123.9, 100.9, 61.6, 55.7, 53.9, 27.8, 23.1, 23.0, 19.9, 19.4. **HRMS** (ESI) m/z calcd for $C_{23}H_{31}N_2O_4$ $[M + H]^+$ 399.2278, found 399.2272.

N-(4-chlorobenzyl)-3,3-dimethoxy-2-(*N*-(3-methoxyphenyl)formamido)propenamide (1k)



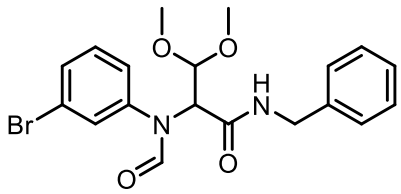
361 mg, 89% yield, yellow solid, mp 88-91 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.32 - 7.29 (m, 3H), 7.25 - 7.17 (m, 3H), 6.94 - 6.89 (m, 3H), 5.02 (d, *J* = 8.3 Hz, 1H), 4.81 (d, *J* = 8.3 Hz, 1H), 4.52 - 4.44 (m, 2H), 3.81 (s, 3H), 3.42 (s, 3H), 3.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 163.6, 160.3, 141.0, 136.6, 133.2, 130.1, 128.9, 128.8, 118.6, 113.5, 112.2, 100.8, 60.7, 55.5, 55.4, 53.9, 42.9. **HRMS** (ESI) m/z calcd for $C_{20}H_{23}ClNaN_2O_5$ $[M + H]^+$ 429.1188, found 429.1184.

N-benzyl-3,3-dimethoxy-2-(*N*-(3-methoxyphenyl)formamido) propenamide (1l)



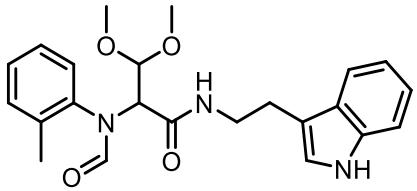
334 mg, 90% yield, white solid, mp 87-92 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.37 - 7.34 (M, 1H), 7.32 - 7.28 (m, 4H), 7.16 (s, 1H), 6.96 (t, *J* = 2.1 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.91 - 6.89 (m, 1H), 5.03 (d, *J* = 8.3 Hz, 1H), 4.84 (d, *J* = 8.3 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 3H), 3.43 (s, 3H), 3.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 163.6, 160.3, 141.1, 138.0, 130.1, 128.7, 127.5, 127.4, 118.7, 113.6, 112.2, 100.8, 60.7, 55.6, 55.4, 53.8, 43.6. **HRMS** (ESI) m/z calcd for $C_{20}H_{24}NaN_2O_5$ $[M + Na]^+$ 395.1577, found 395.1574.

N-benzyl-2-(*N*(3-bromophenyl)formamido)-3,3-dimethoxypropanamide (1m)



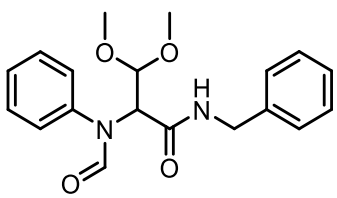
409 mg, 85% yield, yellow solid, mp 83-86 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57 (t, *J* = 1.8 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.38 - 7.33 (m, 3H), 7.31 - 7.26 (m, 4H), 7.17 - 7.15 (m, 1H), 4.98 (d, *J* = 8.2 Hz, 1H), 4.81 (d, *J* = 8.2 Hz, 1H), 4.56 - 4.47 (m, 2H), 3.42 (s, 3H), 3.29 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.9, 163.2, 141.2, 137.9, 131.1, 130.6, 129.9, 128.7, 128.5, 127.50, 127.48, 125.5, 122.7, 100.8, 60.6, 55.5, 54.0, 43.7. **HRMS** (ESI) m/z calcd for $C_{19}H_{21}BrNaN_2O_4$ $[M + Na]^+$ 443.0577, found 443.0573.

N-(2-(1*H*-indol-3-yl)ethyl)-3,3-dimethoxy-2-(*N*-*o*-tolylformamido)propenamide (1n)



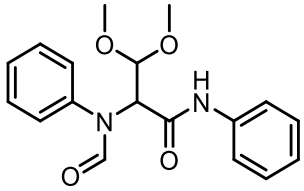
368 mg, 90% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.05 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 6.3 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 - 7.27 (m, 2H), 7.25 - 7.20 (m, 2H), 7.15 - 7.11 (m, 2H), 7.02 (s, 1H), 5.05 - 4.78 (m, 1H), 4.88 (s, 1H), 4.57 (s, 1H), 3.68 (d, *J* = 6.2 Hz, 2H), 3.29 (s, 3H), 3.22 (s, 3H), 3.04 (t, *J* = 6.9 Hz, 2H), 2.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.3, 136.4, 136.0, 131.3, 128.6, 128.4, 127.3, 126.9, 122.2, 122.1, 119.4, 118.8, 112.9, 111.2, 39.9, 25.2, 17.9. **HRMS** (ESI) m/z calcd for $C_{23}H_{27}NaN_3O_4$ $[M + Na]^+$ 432.1894, found 432.1890.

N-benzyl-3,3-dimethoxy-2-(*N*-phenylformamido) propenamide (1o)



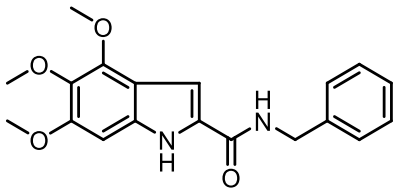
280 mg, 82% yield, colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 0.9 Hz, 1H), 7.42 - 7.39 (m, 2H), 7.37 - 7.33 (m, 5H), 7.31 - 7.26 (m, 3H), 7.21 (s, 1H), 4.97 (d, *J* = 8.3 Hz, 1H), 4.88 (d, *J* = 8.3 Hz, 1H), 4.52 (d, *J* = 5.7 Hz, 2H), 3.41 (d, *J* = 0.9 Hz, 3H), 3.25 (d, *J* = 0.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 163.7, 139.8, 138.0, 129.4, 128.7, 127.9, 127.5, 127.4, 126.8, 100.8, 60.4, 55.7, 53.7, 43.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{22}NaN_2O_4$ $[M + Na]^+$ 365.1472, found 365.1469.

3,3-dimethoxy-*N*-phenyl-2-(*N*-phenylformamido) propenamide (1p)



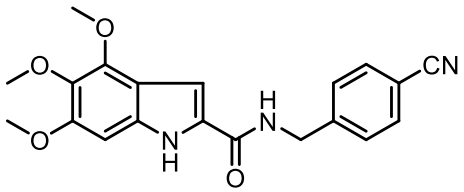
249 mg, 76% yield, red oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.40 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.46 - 7.39 (m, 4H), 7.37 - 7.34 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 5.06 (d, *J* = 8.3 Hz, 1H), 4.97 (d, *J* = 8.3 Hz, 1H), 3.51 (s, 3H), 3.31 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.5, 164.0, 139.7, 137.7, 129.5, 129.0, 128.0, 126.7, 124.5, 120.1, 100.9, 61.5, 56.0, 53.9. **HRMS** (ESI) m/z calcd for $C_{18}H_{20}NaN_2O_4$ $[M + Na]^+$ 351.1315, found 351.1310.

N-benzyl-4,5,6-trimethoxy-1*H*-indole-2-carboxamide (2a)



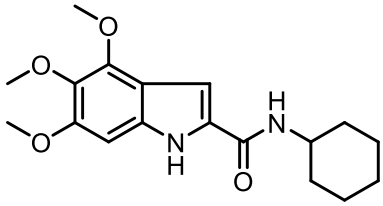
303 mg, 89% yield, yellow solid, mp 182-184 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.39 (d, *J* = 4.3 Hz, 4H), 7.36 - 7.32 (m, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.66 (s, 1H), 6.44 (t, *J* = 5.6 Hz, 1H), 4.71 (d, *J* = 5.6 Hz, 2H), 4.10 (s, 3H), 3.88 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4, 153.4, 138.0, 133., 128.9, 127.8, 127.7, 115.5, 100.3, 89.3, 61.5, 60.9, 56.1, 43.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{21}N_2O$ $[M + H]^+$ 341.1496, found 341.1493.

N-(4-cyanobenzyl)-4,5,6-trimethoxy-1*H*-indole-2-carboxamide (2b)



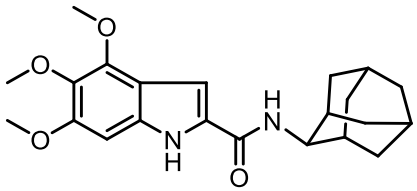
336 mg, 92% yield, colorless solid, mp 184-186 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.64 (s, 1H), 6.57 (t, *J* = 5.8 Hz, 1H), 4.74 (d, *J* = 6.2 Hz, 2H), 4.11 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5, 153.7, 146.3, 143.7, 136.4, 133.6, 132.6, 128.1, 118.7, 115.6, 111.5, 100.7, 89.2, 61.5, 60.9, 56.2, 43.1. **HRMS** (ESI) m/z calcd for $C_{20}H_{20}N_3O_4$ $[M + H]^+$ 366.1448, found 366.1446.

N-cyclohexyl-4,5,6-trimethoxy-1*H*-indole-2-carboxamide (1c)



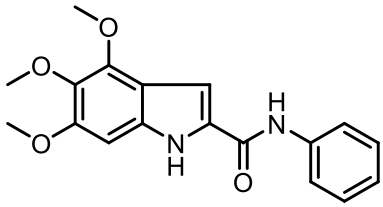
302 mg, 91% yield, brown solid, mp 230-233 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.66 (s, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 4.13 (s, 3H), 4.03 - 4.00 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.09 - 2.06 (m, 2H), 1.82 - 1.78 (m, 2H), 1.72 - 1.70 (m, 1H), 1.49 - 1.41 (m, 2H), 1.33 - 1.24 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.6, 153.2, 146.2, 136.2, 133.4, 129.3, 115.5, 99.6, 89.4, 61.5, 60.9, 56.1, 48.5, 33.3, 25.5, 25.0. **HRMS** (ESI) m/z calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1809, found 333.1805.

N-((1*R*,3*S*,5*r*,7*r*)-adamantan-2-yl)-4,5,6-trimethoxy-1*H*-indole-2-carboxamide (2d)



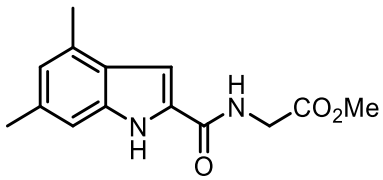
323 mg, 84% yield, white solid, mp 209-212 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.33 (s, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.40 (s, 1H), 6.67 (s, 1H), 4.09 - 4.08 (m, 1H), 4.02 (s, 3H), 3.80 (s, 3H), 3.70 (s, 3H), 2.15 (d, J = 12.5 Hz, 2H), 1.99 - 1.98 (m, 2H), 1.86 - 1.84 (m, 6H), 1.74 (s, 2H), 1.55 (d, J = 12.5 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 161.0, 152.5, 146.2, 135.4, 134.1, 130.4, 114.9, 102.0, 90.2, 61.3, 60.8, 56.2, 54.1, 37.7, 37.4, 31.9, 31.6, 27.3. **HRMS** (ESI) m/z calcd for $C_{22}H_{28}NaN_2O_4$ $[M + Na]^+$ 407.1941, found 407.1937.

4,5,6-trimethoxy-*N*-phenyl-1*H*-indole-2-carboxamide (2e)



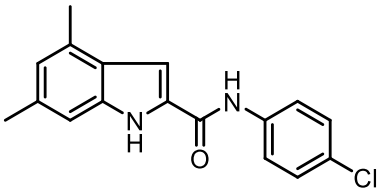
301 mg, 92% yield, brown solid, mp 229-232 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.81 (s, 1H), 7.69 (d, J = 8.2 Hz, 2H), 7.42 (t, J = 7.9 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 1.2 Hz, 1H), 6.66 (s, 1H), 4.16 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 153.8, 146.3, 137.6, 129.2, 128.8, 124.5, 120.0, 100.8, 89.3, 61.5, 61.0, 56.1. **HRMS** (ESI) m/z calcd for $C_{18}H_{19}N_2O_4$ $[M + H]^+$ 327.1339, found 327.1336.

methyl(4,6-dimethyl-1*H*-indole-2-carbonyl)glycinate (2f)



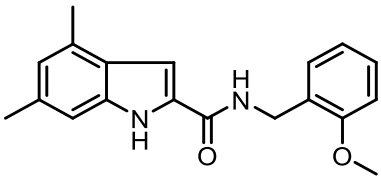
198 mg, 76% yield, pink solid, mp 189-191 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.88 (t, J = 5.9 Hz, 1H), 7.16 (s, 1H), 7.04 (s, 1H), 6.69 (s, 1H), 4.05 (d, J = 5.9 Hz, 2H), 3.67 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 171.0, 162.1, 137.3, 133.4, 130.5, 130.3, 125.7, 122.3, 110.0, 102.3, 100.0, 52.2, 22.0, 18.9. **HRMS** (ESI) m/z calcd for $C_{14}H_{17}N_2O_3$ $[M + H]^+$ 261.1234, found 261.1231.

N-(4-chlorophenyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (2g)



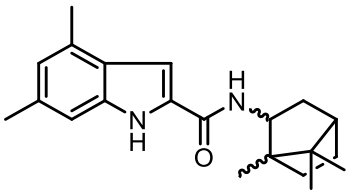
221 mg, 74% yield, yellow solid, mp 258-261 °C. **^{1}H NMR** (500 MHz, Acetone-d_6) δ 10.80 (s, 1H), 9.69 (s, 1H), 7.92 - 7.90 (m, 2H), 7.40 - 7.39 (m, 2H), 7.35 (s, 1H), 7.21 (s, 1H), 6.77 (s, 1H), 2.50 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (126 MHz, Acetone-d_6) δ159.9, 138.2, 137.6, 134.3, 130.7, 128.6, 127.7, 125.9, 122.4, 121.2, 121.2, 109.5, 109.5, 102.1, 21.1, 17.8. **HRMS** (ESI) m/z calcd for $C_{17}H_{16}ClN_2O$ $[M + H]^+$ 299.0946, found 299.0948.

N-(2-methoxybenzyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (2h)



192 mg, 62% yield, white solid, mp 199-202 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.39 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.32 (td, *J* = 8.0, 1.7 Hz, 1H), 7.07 (s, 1H), 6.98 (td, *J* = 7.5, 0.9 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.80 - 6.79 (dd, *J* = 2.7, 1.8 Hz, 2H), 6.64 (s, 1H), 3.94 (s, 5H), 2.52 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5, 157.7, 136.5, 134.7, 131.0, 129.9, 129.7, 129.1, 126.1, 125.7, 122.8, 120.8, 110.5, 109.1, 100.3, 55.5, 39.5, 21.8, 18.6. **HRMS** (ESI) m/z calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$ 309.1598, found 309.1599.

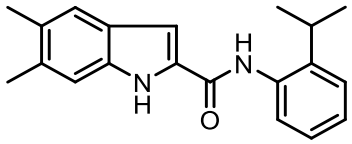
4,6-dimethyl-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-1*H*-indole-2-carboxamide (2i)



213 mg, 72% yield, white solid, mp 126-128 °C, *dr~1:5:15.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.68 (s, 0.2H), 9.63 (s, 0.6H), 9.53 (s, 0.05H), 7.13 (s, 0.2H), 7.12 (s, 0.6H), 6.85 (d, *J* = 1.4 Hz, 0.2H), 6.81 (d, *J* = 3.7 Hz, 0.8H), 6.71 (d, *J* = 1.4 Hz,

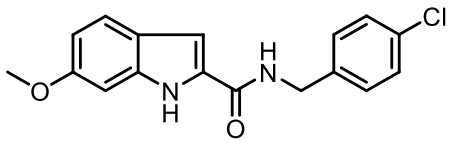
0.6H), 6.29 (d, *J* = 6.8 Hz, 0.03H), 6.22 (d, *J* = 9.0 Hz, 0.2H), 6.13 (d, *J* = 8.9 Hz, 0.6H), 4.59 - 4.54 (m, 0.12H), 4.40 - 4.34 (m, 0.02H), 4.24 - 4.19 (m, 0.6H), 2.56 - 2.55 (m, 3H), 2.46 - 2.45 (m, 3H), 2.03 - 1.99 (m, 1H), 1.87 - 1.68 (m, 4H), 1.53 - 1.41 (m, 1H), 1.36 - 1.24 (m, 0.1H), 1.09 - 1.07 (m, 3H), 0.97 - 0.92 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.00, 161.2, 136.7, 134.5, 130.9, 130.8, 129.9, 125.7, 125.7, 122.8, 109.4, 109.3, 99.9, 99.5, 56.9, 54.0, 49.8, 49.1, 48.3, 47.2, 45.02, 44.99, 39.2, 37.9, 36.0, 28.5, 28.2, 27.1, 21.9, 20.4, 20.3, 19.9, 18.73, 18.66, 13.8, 11.9. **HRMS** (ESI) m/z calcd for $C_{21}H_{29}N_2O$ $[M + H]^+$ 325.2274, found 325.2276.

N-(2-isopropylphenyl)-5,6-dimethyl-1*H*-indole-2-carboxamide (2j)



190 mg, 62% yield, Colorless solid, mp 159-162 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.31 - 7.28 (m, 2H), 7.24 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.20 - 7.16 (m, 2H), 7.09 - 7.05 (m, 2H), 6.99 (s, 1H), 3.27 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.0, 138.3, 137.8, 133.4, 132.4, 131.3, 130.5, 128.7, 123.8, 123.0, 122.1, 122.1, 122.0, 117.9, 108.2, 27.1, 22.8, 20.0, 19.1. **HRMS** (ESI) m/z calcd for $C_{20}H_{23}N_2O$ $[M + H]^+$ 307.1805, found 307.1806.

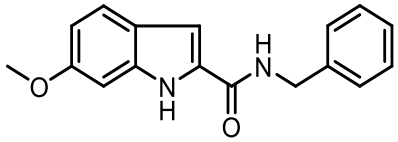
N-(4-chlorobenzyl)-6-methoxy-1*H*-indole-2-carboxamide (2k)



301 mg, 96% (ratio=15:1) yield, White soild, mp 208-211 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.44 (s, 1H), 8.95 (t, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.11 (s, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.2 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 161.7, 157.5, 139.3, 137.9, 131.8, 130.8, 129.5,

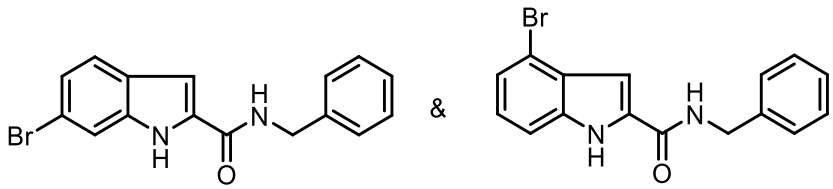
128.7, 122.8, 122.7, 121.8, 111.5, 111.4, 103.5, 94.5, 55.6, 41.9. **HRMS** (ESI) m/z calcd for $C_{17}H_{16}ClN_2O_2$ $[M + H]^+$ 315.0895, found 315.0896.

N-benzyl-6-methoxy-1*H*-indole-2-carboxamide (2l)



260 mg, 93% (ratio=16:1) yield, White solid, mp 206-208 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.89 (t, *J* = 6.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 4.2 Hz, 4H), 7.27-7.24 (m, 1H), 7.11 (d, *J* = 1.4 Hz, 1H), 6.89 (d, *J* = 1.6 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.51 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 161.6, 157.5, 140.2, 137.9, 131.0, 128.8, 127.7, 127.2, 122.7, 121.9, 111.4, 103.4, 94.6, 55.6, 42.6. **HRMS** (ESI) m/z calcd for $C_{17}H_{17}N_2O_2$ $[M + H]^+$ 281.1285, found 281.1288.

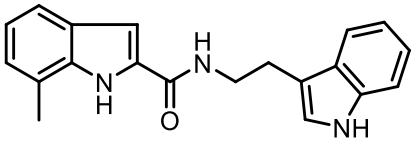
N-benzyl-6-bromo-1*H*-indole-2-carboxamide (2m)



2m **2m'**

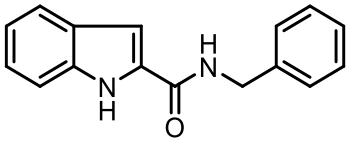
128 mg, 39% (2m:2m' (3:2)) yield, ice cream solid. **^{1}H NMR** (500 MHz, Acetone-d_6) δ 11.21 (s, 0.2H), 11.02 (s, 0.3H), 8.52 (s, 0.4H), 8.39 (s, 0.6H), 7.78 (s, 0.6H), 7.61 - 7.58 (m, 1H), 7.43 - 7.39 (m, 2H), 7.37 - 7.32 (m, 5H), 7.30 (s, 0.3H), 7.27 - 7.16 (m, 3H), 4.67 (d, *J* = 6.1 Hz, 0.8H), 4.64 (d, *J* = 6.1 Hz, 1.6H). **^{13}C NMR** (126 MHz, Acetone-d_6) δ 160.9, 160.8, 139.5, 137.5, 137.0, 128.345766, 128.345763, 127.5087, 127.5086, 126.9330, 126.9329, 124.6172, 124.6169, 123.3135, 123.3121, 123.1896, 123.1895, 122.7897, 122.7896, 116.69513, 116.69508, 114.8611, 114.8610, 102.2391, 102.2388, 101.9828, 101.9826, 42.7. **HRMS** (ESI) m/z calcd for $C_{16}H_{14}BrN_2O$ $[M + H]^+$ 329.0284, found 329.0284.

N-(2-(1*H*-indol-2-yl)ethyl)-7-methyl-1*H*-indole-2-carboxamide (2n)



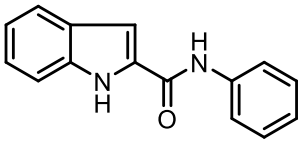
168 mg, 53% yield, yellow oil. *Mixture of rotamers observed.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.44 (s, 0.4H), 8.33 (s, 0.4H), 7.45 - 7.44 (m, 0.5H), 7.39 (s, 0.5H), 7.31 - 7.23 (m, 6H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.01 - 6.95 (m, 2H), 6.79 (dd, *J* = 7.9, 4.2 Hz, 1H), 5.60 (dd, *J* = 8.1, 5.3 Hz, 1H), 4.16 - 4.07 (m, 1H), 4.00 - 3.93 (m, 1H), 3.45 - 3.36 (m, 1H), 2.53 - 2.46 (m, 1H), 2.43 (s, 1.5H), 2.38 (s, 1.5H), 1.90 - 1.83 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.1, 162.9, 159.5, 158.3, 142.8, 142.6, 139.5, 136.0, 135.5, 133.6, 133.0, 132.3, 131.5, 131.2, 129.0, 128.8, 128.7, 128.2, 128.1, 127.6, 127.1, 126.9, 125.5, 125.3, 122.8, 122.4, 115.8, 109.5, 109.4, 46.1, 45.1, 18.4. **HRMS** (ESI) m/z calcd for $C_{20}H_{20}N_3O$ $[M + H]^+$ 318.1601, found 318.1602.

N-benzyl-1*H*-indole-2-carboxamide (2o)



56 mg, 22% yield, ice cream solid, mp 204-207 °C. **^{1}H NMR** (500 MHz, Acetone-d_6) δ 10.83 (s, 1H), 8.32 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.41 - 7.33 (m, 4H), 7.28 - 7.22 (m, 2H), 7.18 (s, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 4.64 (d, *J* = 6.2 Hz, 2H). **^{13}C NMR** (126 MHz, Acetone-d_6) δ139.7, 128.3, 127.5, 126.9, 123.6, 121.6, 120.0, 112.2, 102.1, 42.6. **HRMS** (ESI) m/z calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$ 251.1179, found 251.1183.

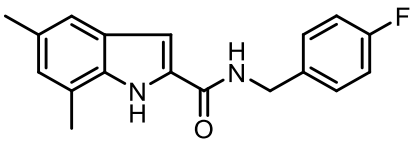
N-phenyl-1*H*-indole-2-carboxamide (2p)



101 mg, 43% yield, ice cream solid, mp 217-219 °C. **^{1}H NMR** (500 MHz, Acetone-d_6) δ 11.14 (s, 1H), 7.57 - 7.51 (m, 3H), 7.46 - 7.38 (m, 5H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR** (126

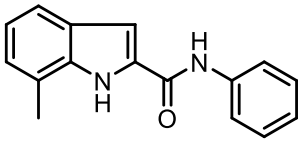
MHz, Acetone-d_6) δ141.2, 133.3, 132.8, 129.3, 125.7, 125.6, 122.4, 122.0, 121.5, 119.5, 119.4, 114.7, 107.3. **HRMS** (ESI) m/z calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1022, found 237.1027.

N-(4-fluorobenzyl)-5,7-dimethyl-1*H*-indole-2-carboxamide (2q)



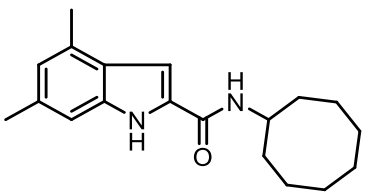
189 mg, 64% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.35 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.26 (s, 1H), 7.08 - 7.04 (m, 2H), 6.95 (s, 1H), 6.80 (d, *J* = 2.1 Hz, 1H), 6.53 (s, 1H), 4.66 - 4.14 (m, 1H), 2.48 (s, 3H), 2.43 (s, 3H), 2.36 - 2.28 (m, 1H), . **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{C\text{-}F}$ = 245.7 Hz), 161.8, 134.6, 133.9 (d, $^4J_{C\text{-}F}$ = 2.5 Hz), 130.4, 130.1, 129.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 127.5, 127.1, 121.0, 118.8, 115.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 102.2, 43.0, 21.4, 16.6. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.72. **HRMS** (ESI) m/z calcd for $C_{18}H_{18}FN_2O$ $[M + H]^+$ 297.1398, found 297.1400.

7-methyl-*N*-phenyl-1*H*-indole-2-carboxamide (2r)



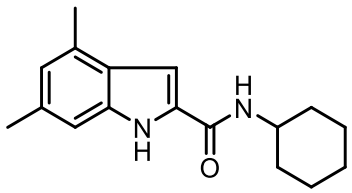
143 mg, 57% yield, yellow solid, mp 129-134 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.46 - 7.44 (m, 1H), 7.41 - 7.39 (m, 1H), 7.35 - 7.29 (m, 2H), 7.28 - 7.26 (m, 3H), 7.21 - 7.18 (m, 1H), 7.12 (td, *J* = 7.5, 1.1 Hz, 1H), 7.03 (s, 1H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.1, 138.5, 134.0, 131.5, 131.4, 131.3, 126.9, 125.8, 125.6, 124.2, 123.3, 122.1, 122.0, 115.2, 108.1, 17.9. **HRMS** (ESI) m/z calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$ 251.1179, found 251.1174.

N-cyclooctyl-4,6-dimethyl-1*H*-indole-2-carboxamide (2s)



244 mg, 82% yield, colorless oil. Spectral data are in accordance to reported data. [1] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.10 (s, 1H), 6.80 (d, *J* = 1.1 Hz, 2H), 6.13 (d, *J* = 8.0 Hz, 1H), 4.31 - 4.26 (m, 1H), 2.54 (s, 3H), 2.45 (s, 3H), 2.03 - 1.98 (m, 2H), 1.77 - 1.60 (m, 12H). **HRMS** (ESI) m/z calcd for $C_{19}H_{27}N_2O$ $[M + H]^+$ 299.2118, found 299.2121.

N-cyclohexyl-4,6-dimethyl-1*H*-indole-2-carboxamide (2t)



248 mg, 86% yield, white soild, mp 217-220 ºC. Spectral data are in accordance to reported data. [1] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.08 (s, 1H), 6.80 (dd, *J* = 2.2, 0.8 Hz, 2H), 6.01 (d, *J* = 7.8 Hz, 1H), 4.09 - 3.95 (m, 1H), 2.54 (s, 3H), 2.45 (s, 3H), 2.11 - 2.05 (m, 2H), 1.84 - 1.78 (m, 2H), 1.74 - 1.68 (m, 1H), 1.48 (ddt, *J* = 11.9, 9.9, 6.1 Hz, 2H), 1.34 - 1.24 (m, 3H). **HRMS** (ESI) m/z calcd for $C_{17}H_{23}N_2O$ $[M + H]^+$ 271.1805, found 271.1809.

Reaction Parameters Calculations:

Environmental factor (**E-factor**), Process Mass Intensity (**PMI**) and Atom Economy (**AE**) calculations

For this method, utilization of already reported reaction conditions for N-cyclohexyl-4,6-dimethyl-1H-indole-2-carboxamide (**2t**) occurred.[23-25] While calculating the E-factors, the amount of silica gel for flash column chromatography is not considered.

In this study, for a 1 mmol scale reaction, 15 g of 100 - 200 mesh size silica are used (one-pot synthesis of **2t**). However, the amount of silica gel employed in the other three methods is considerably higher. Therefore, silica gel waste would considerably increase the difference in the E-factor between our novel synthesis and the previous ones.

Calculations of the E-factor, PMI and AE (atom economy) values for the *N*-cyclohexyl-4,6-dimethyl-1*H*-indole-2-carboxamide syntheses:

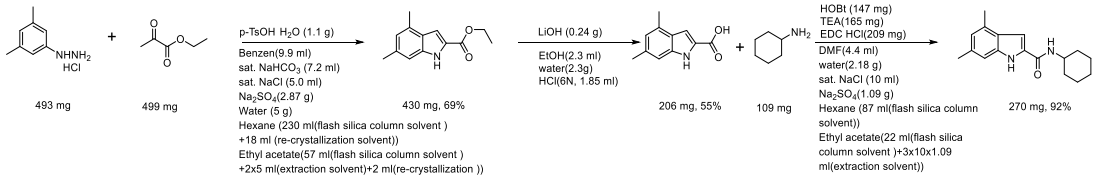
E-factor = Mass (waste) /Mass (product)

PMI = Mass (total) /Mass (product) = E-factor + 1

AE = (Molecular mass of desired product/Sum of molecular masses of all reactants) X 100%

For the AE calculation, any material that is incorporated into an intermediate or product during the synthesis is taken into account. This includes protecting groups, catalysts used in stoichiometric quantities, and acids or bases used for hydrolysis. Solvents, reagents, or materials used in catalytic quantities are omitted from the analysis, as they do not contribute atoms to an intermediate and/or product. [8]

1. Kondreddi, Ravinder Reddy et al, *Journal of Medicinal Chemistry*, **2013**, *56 (21),* 8849-8859.

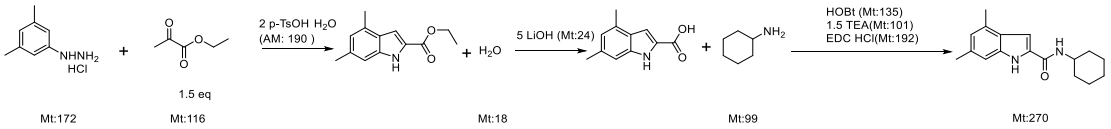


Reagents	Amount
3,5-dimethylphenylhydrazine hydrochloride	0.5 g
ethyl pyruvate	0.5 g
p-Toluenesulfonic acid monohydrate	1.1 g
Benzen (assuming 90% recovery)	9.9 ml x (0.876 g/ml) x 10% = 0.9 g
Sat. $NaHCO_3$ sol. (calculated by weight)	7.2 ml x 1.1 g/ml = 7.9 g
Sat. NaCl sol. (calculated by weight)	15.0 ml x 1.2 g/ml = 18 g
Water	5 g + 2.3 g + 2.18 g = 9.5 g
LiOH	0.2 g
HCl (aq) (6N)	1.85 ml x 1.1 g/ml = 2.0 g
HOBt	0.2 g
TEA	0.2 g
EDC·HCl	0.2 g
cyclohexanamine	0.1 g
DMF	4.4 ml x 0.944 g/ml = 4.1 g
Na_2SO_4 used for drying (assuming 1g/mmol)	2.87 g + 1.09 g = 4.0 g
EtOH (assuming as 90% recovery)	2.3 ml x (0.789 g/ml) x 10% = 0.2 g
Hexane (assuming as 90% recovery)	335ml x (0.661 g/ml) x 10% = 26.4 g
EtOAc (assuming as 90% recovery)	124 ml x (0.902 g/ml) x 10% = 11.2 g
Total	**87.2 g**

Amount of product = **0.27 g**

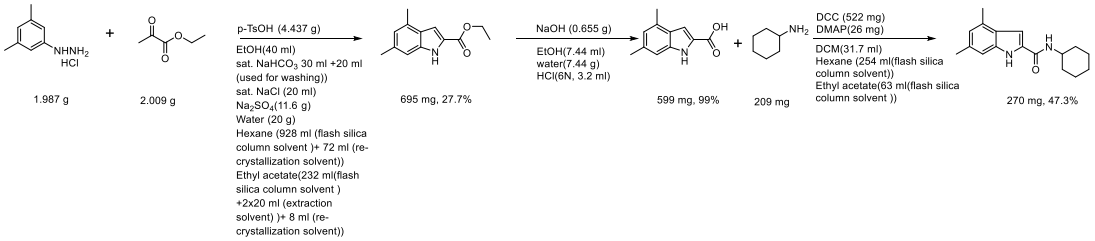
E-Factor = Amount of waste/Amount of product = (87.2-0.27) g/0.27 g = 322.0

E-factor = **322.0**



AE = (270/(172+1.5x116+2x190+18+5x24+99+135+1.5x101+192)) x 100% = (270/1441.5) x 100% = **18.7%**

2. N.D. Franz et al, *Bioorganic & Medicinal Chemistry*, **2017**, *25*, 3746-3755.



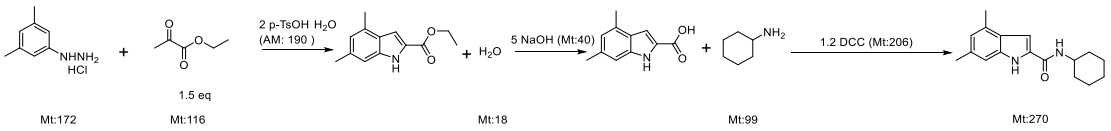
Reagents	Amount
3,5-dimethylphenylhydrazine hydrochloride	2.0 g
ethyl pyruvate	2.0 g
p-Toluenesulfonic acid monohydrate	4.4 g
EtOH (assuming as 90% recovery)	47.44 ml x (0.789 g/ml) x 10% = 3.7 g
Sat. $NaHCO_3$ sol.	50 ml x 1.1 g/ml = 55 g
Sat. NaCl sol.	20 ml x 1.2 g/ml = 24.0 g
Water	27.4 ml x 1.0 g/ml = 27.4 g
NaOH	0.7 g
HCl (aq) (6N)	3.2 ml x 1.1 g/ml = 3.5 g
DCC	0.5 g
DMAP	0.1 g
cyclohexanamine	0.2 g

DCM (assuming as 90% recovery)	31.7 ml x (1.33 g/ml) x 10% = 4.2 g
Na_2SO_4 used for drying (assuming 1g/mmol)	11.6 g
Hexane (assuming as 90% recovery)	1254 ml x (0.661 g/ml) x 10% = 82.9 g
EtOAc (assuming as 90% recovery)	343 ml x (0.902 g/ml) x 10% = 30.9 g
Total	**253.1 g**

Amount of product = **0.27 g**

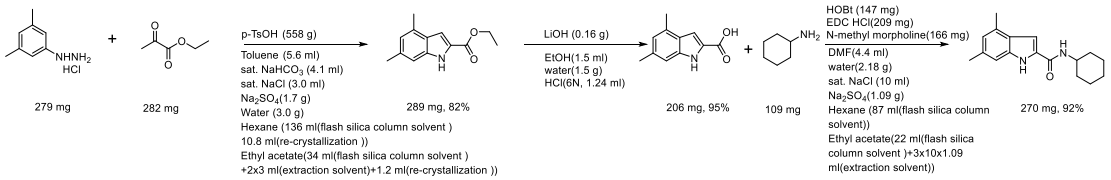
E-Factor = Amount of waste/Amount of product = (253.1-0.27) g/0.27 g = 936.4

E-factor = **936.4**



AE = (270/ (172+1.5x116+2x190+18+5x40+99+1.2x206)) x 100%= (270/1249) x 100% = **21.6%**

3. BISHAI, William R. et al, WO2015164482 (A1) PCT/US**2015**/027053



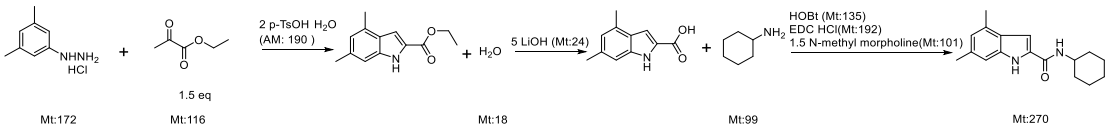
Reagents	Amount
3,5-dimethylphenylhydrazine hydrochloride	0.3 g
ethyl pyruvate	0.3 g
p-Toluenesulfonic acid monohydrate	0.6 g
Toluene (assuming 90% recovery)	5.6 ml x (0.876 g/ml) x 10% = 0.5 g

Sat. $NaHCO_3$ sol. (calculated by weight)	4.1 ml x 1.1 g/ml= 4.5 g
Sat. NaCl sol. (calculated by weight)	13.0 ml x 1.2 g/ml = 15.6 g
Water	3 g + 1.5 g + 2.18 g = 6.7 g
LiOH	0.2 g
HCl (aq) (6N)	1.24 ml x 1.1 g/ml = 1.4 g
N-methyl morpholine	0.2 g
HOBt	0.2 g
EDC·HCl	0.2 g
cyclohexanamine	0.1 g
DMF	4.4 ml x 0.944 g/ml = 4.1 g
Na_2SO_4 used for drying (assuming 1g/mmol)	1.7 g + 1.09 g = 2.8 g
EtOH (assuming as 90% recovery)	1.5 ml x (0.789 g/ml) x 10% = 0.1 g
Hexane (assuming as 90% recovery)	193.8 ml x (0.661 g/ml) x 10% = 12.8 g
EtOAc (assuming as 90% recovery)	63.9 ml x (0.902 g/ml) x 10% = 5.6 g
Total	**62.0 g**

Amount of product = **0.27 g**

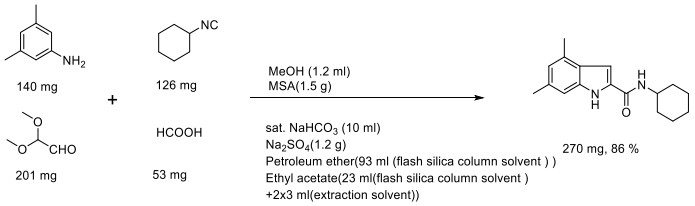
E-Factor = Amount of waste/Amount of product = (62.0-0.27) g/0.27 g = 228.6

E-factor = **228.6**



AE = (270/ (172+1.5x116+2x190+18+5x24+99+135+1.5x101+192)) x 100% = (270/1441.5) x 100% = **18.7%**

4. Our current work

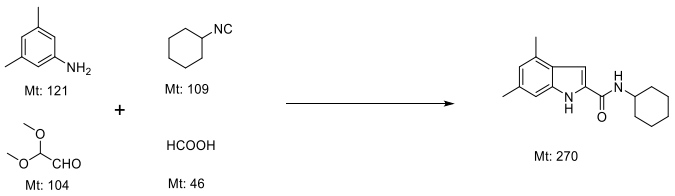


Reagents	Amount
3,5-dimethylaniline	0.1 g
2,2-dimethoxyacetaldehyde	0.2 g
isocyanocyclohexane	0.1 g
formic acid	0.1 g
MSA	1.5 g
Sat. $NaHCO_3$ sol. (calculated by weight)	10 ml x 1.1 g/ml = 11 g
Na_2SO_4 used for drying (assuming 1g/mmol)	1.2 g
MeOH (assuming as 90% recovery)	1.2 ml x (0.792 g/ml) x 10% = 0.1 g
Petroleum ether (assuming as 90% recovery)	93 ml x (0.653 g/ml) x 10% = 6.1 g
EtOAc (assuming as 90% recovery)	29 ml x (0.902 g/ml) x 10% = 2.6 g
Total	**23 g**

Amount of product = **0.27 g**

E-Factor = Amount of waste/Amount of product = (23-0.27) g/0.27 g = 84.2

E-factor = **84.2**



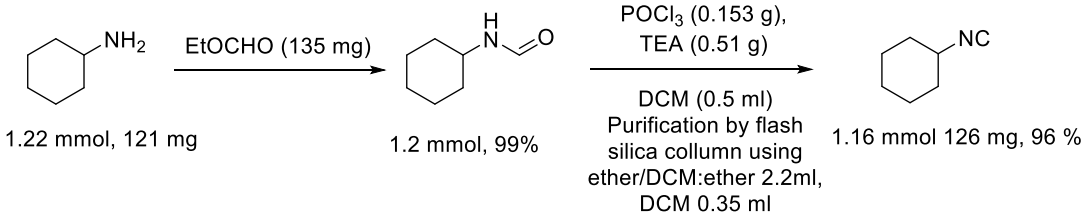
AE = (270/ (121+104+109+46)) x 100%= (270/380) x 100% = **71.1%**

Note: The experimental procedures of **1**-**3** follow the Fischer indole synthesis, the differences are based on the solvents, timeframes and various additives. The amounts are calculated based on the experimental procedures reported on each paper or the references mentioned there. Importantly, inclusion of the phenylhydrazine syntheses (many of which are not commercially available or quite expensive) would considerably worsen the PMI and E-factors of the competing procedures.

Thus, herein we summarize the E-factor, PMI and AE calculations of the various literature process of *N*-cyclohexyl-4,6-dimethyl-1*H*-indole-2-carboxamide synthesis.

Entry	Reference	E-factor	PMI	AE (%)
1	Kondreddi *et al.* **2013**	322.0	323.0	18.7
2	Franz *et al.* **2017**	936.4	937.4	21.6
3	Bishai *et al*. **2015**	228.6	229.6	18.7
4	Present work	84.2	85.2	71.1

Isocyanide E-factor calculation



Reagents	Amount
cyclohexanamine	0.1 g
EtOCHO	0.1 g
TEA	0.5 g
$POCl_3$	0.2 g
diethyl ether (assuming as 90% recovery)	2.2 ml x (0.706 g/ml) x 10% = 0.2 g

DCM (assuming as 90% recovery)	0.85 ml x (1.33 gm/ml) x 10% = 0.1 g
Total	**1.2 g**

Amount of product = **0.27 g**

E-Factor = Amount of waste/Amount of product = 1.2 g/0.27 g = 4.4

E-factor = **4.4**

3. Single crystal x-ray structure determination

Data for compound **2f**

Single crystals of $C_{14}H_{16}N_2O_3$ (**2f**) are carefully collected under a microscope. A suitable crystal is selected and measured with a Bruker APEX-II CCD diffractometer. The crystal is kept at 210.00 K during data collection. Using Olex2,[3] the structure is solved with the SHELXT[2] structure solution program using Intrinsic Phasing and refined with the SHELXL[4] refinement package using Least Squares minimization. All non-H atoms are refined with anisotropic thermal parameters. H-atoms are introduced at calculated positions and allowed to ride on their carrier atoms. Crystal data and structure refinement parameters for **2f** are given in **table 1** (CCDC No: 2174979).

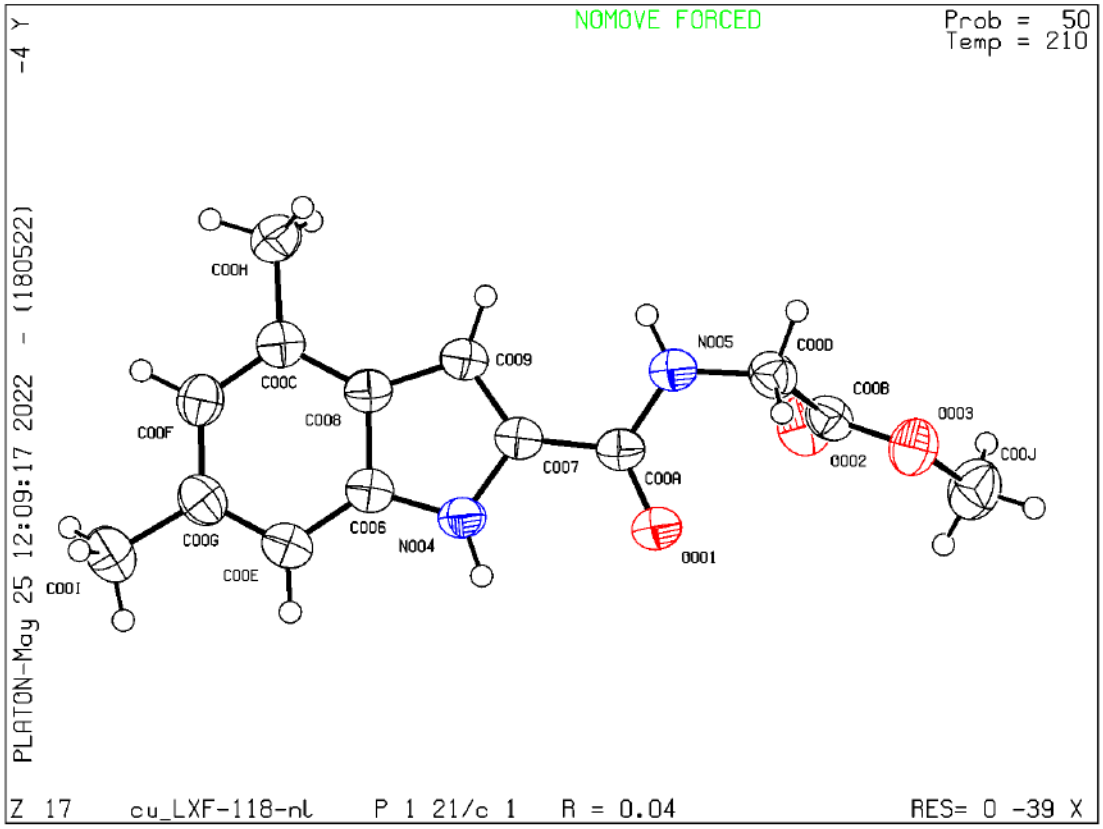
Crystal structure determination of 2f

Crystal Data for $C_{14}H_{16}N_2O_3$ (M =260.29 g/mol) : monoclinic, space group $P2_1/c$ (no. 14), a = 15.1633 (10) Å, b = 5.1388 (3) Å, c = 17.4106 (11) Å, β = 101.494 (3) °, V = 1329.45 (14) Å^3, Z = 4, T = 209.99 K, μ (CuKα) = 0.760 mm^{-1}, *Dcalc* = 1.300 g/cm^3, 11578 reflections measured (5.948° ≤ 2Θ ≤ 118.014°), 1910 unique (R_{int} = 0.0360, R_{sigma} = 0.0268) which are used in all calculations. The final R_1 is 0.0384 (I > 2σ (I)) and wR_2 is 0.1248 (all data)

Table 1 Crystal data and structure refinement for **2f**.

Identification code	cu_lxf_118nl_2_0m_a
Empirical formula	$C_{14}H_{16}N_2O_3$
Formula weight	260.29
Temperature/K	209.99
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.1633 (10)
b/Å	5.1388 (3)
c/Å	17.4106 (11)

α/°	90
β/°	101.494 (3)
γ/°	90
Volume/Å^3	1329.45 (14)
Z	4
ρ_{calc}g/cm^3	1.300
μ/mm^{-1}	0.760
F (000)	552.0
Crystal size/mm^3	0.06 × 0.04 × 0.02
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	5.948 to 118.014
Index ranges	-16 ≤ h ≤ 16, -5 ≤ k ≤ 5, -19 ≤ l ≤ 19
Reflections collected	11578
Independent reflections	1910 [R_{int} = 0.0360, R_{sigma} = 0.0268]
Data/restraints/parameters	1910/0/176
Goodness-of-fit on F^2	1.142
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.1097
Final R indexes [all data]	R_1 = 0.0426, wR_2 = 0.1248
Largest diff. peak/hole / e Å^{-3}	0.18/-0.19



Data for compound **2g**

Single crystals of $C_{17}H_{15}ClN_2O$ (**2g**) are carefully collected under a microscope. A suitable crystal is selected and measured with a Bruker APEX-II CCD diffractometer. The crystal is kept at 200.00 K during data collection. Using Olex2,[3] the structure is solved with the SHELXT[2] structure solution program using Intrinsic Phasing and refined with the SHELXL[4] refinement package using Least Squares minimization. All non-H atoms are refined with anisotropic thermal parameters. H-atoms are introduced at calculated positions and allowed to ride on their carrier atoms. Crystal data and structure refinement parameters for **2g** are given in **table 2** (CCDC No: 2174980).

Crystal structure determination of **2g**

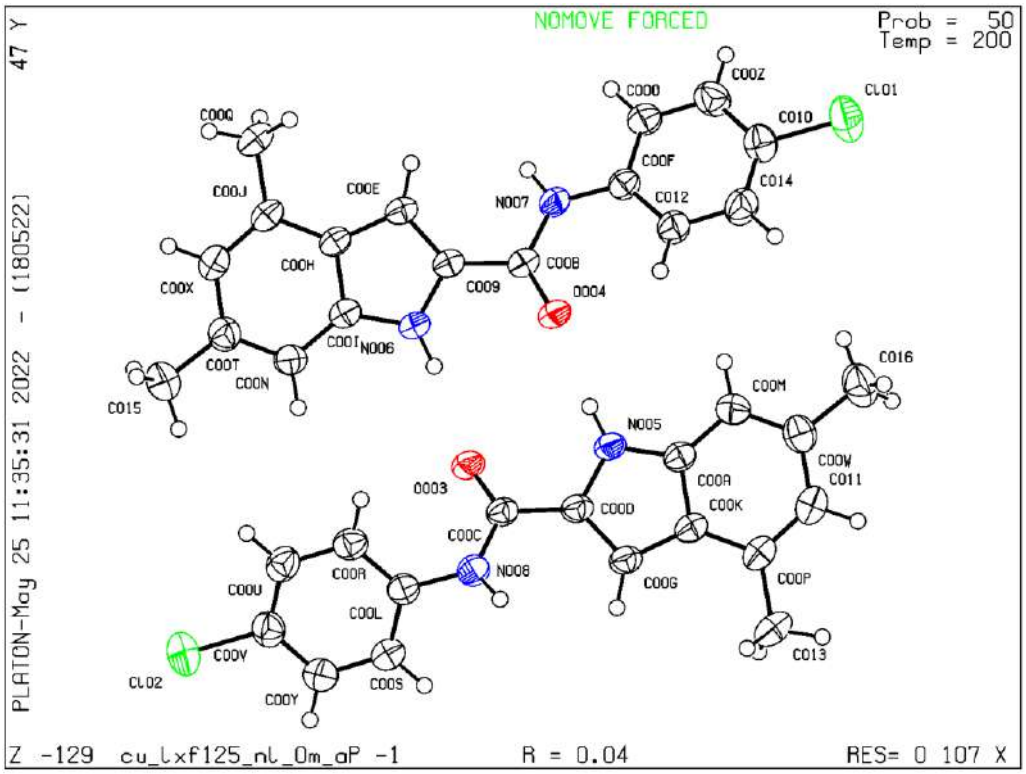
Crystal Data for $C_{17}H_{15}ClN_2O$ (*M* =298.76 g/mol) : triclinic, space group P-1 (no. 2), *a* = 9.4666 (3) Å, *b* = 9.9691 (3) Å, *c* = 16.3110 (4) Å, *α* = 100.1530 (10) °, *β* = 104.0720 (10) °, *γ* = 92.7510 (10) °, *V* = 1463.08 (7) Å^3, *Z* = 4, *T* = 199.98 K, μ (CuKα) = 2.304 mm^{-1}, *Dcalc* = 1.356 g/cm^3, 36534 reflections measured (5.694° ≤ 2Θ ≤ 149.102°), 5942 unique (R_{int} = 0.0245, R_{sigma} =

0.0157) which are used in all calculations. The final R_1 is 0.0375 (I > 2σ (I)) and wR_2 is 0.1122 (all data).

Table 2 Crystal data and structure refinement for **2g.**

Identification code	cu_LXF125_nl_0m_a
Empirical formula	$C_{17}H_{15}ClN_2O$
Formula weight	298.76
Temperature/K	199.98
Crystal system	triclinic
Space group	P-1
a/Å	9.4666 (3)
b/Å	9.9691 (3)
c/Å	16.3110 (4)
α/°	100.1530 (10)
β/°	104.0720 (10)
γ/°	92.7510 (10)
Volume/Å^3	1463.08 (7)
Z	4
ρ_{calc}g/cm^3	1.356
μ/mm^{-1}	2.304
F (000)	624.0
Crystal size/mm^3	0.06 × 0.04 × 0.02
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	5.694 to 149.102
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -20 ≤ l ≤ 20
Reflections collected	36534
Independent reflections	5942 [R_{int} = 0.0245, R_{sigma} = 0.0157]
Data/restraints/parameters	5942/0/384
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0375, wR_2 = 0.1080

Final R indexes [all data]	R_1 = 0.0413, wR_2 = 0.1122
Largest diff. peak/hole / e Å^{-3}	0.23/-0.30



REFERENCES

1. Oluseye K. Onajole et al, *J. Med. Chem.* **2013**, *56*, 4093-4103.
2. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H., *J. Appl. Cryst*. **2009**, *42*, 339-341.
3. BISHAI, William R. et al, WO2015164482 (A1) PCT/US **2015**/027053.
4. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. *Acta Cryst.* **2015**, *A71*, 59-75.
5. Sheldrick, G.M. Acta Cryst. **2015**, *C71*, 3-8.
6. Andrew P. Dicks, ISBN 978-3-319-10499-7, **2015**, p18.

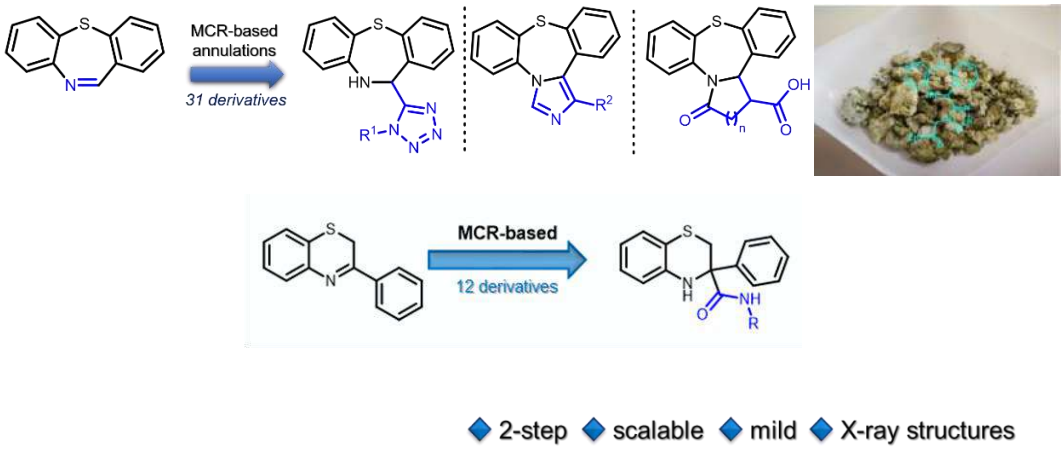
Chapter 3

Benzothiazepines based MCR chemistry

*This chapter is based on the artictl*e: “Dibenzothiazepines based on MCR chemistry*”, by* **Xiaofang Lei**, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling*, Eur. J. Org. Chem*., **2022**, *20*, e202200220.

ABSTRACT

In this study, several functionalized 1,5-dibenzothiazepines and 1,4-benzothiazines are synthesized via MCRs. As such, a highly efficient two-step, catalyst-free and green synthetic protocol is presented. A library of 43 tetracyclic 1,5-tetrazolo-, fused imidazo- and lactam-1,5-dibenzothiazepines and C3 functionalized tetrazolo- and amides benzo[*b*][1,4]thiazine derivatives are synthesized. The reported procedures are scalable and applicable to one-pot protocols. X-ray crystallography confirmed the conformation of the scaffolds.



INTRODUCTION

1,5-Dibenzothiazepines and 1,4-benzothiazines are scaffolds with unique properties and conformations (Figure 1, A).[1,2] As a continuation of the quest for exploring different areas of the chemical space[3] for novel entities with interesting dynamic properties, we spot the 1,5-dibenzothiazepines which are widely used in medicinal chemistry research.[4] In fact, the dibenzothiazepine scaffold possess three unique features: a secondary amine, an oxidizable sulfur atom in a tricyclic ring system, and a "butterfly" conformation (Figure 1, A, B).[5,6] The benzothiazepine core is also frequently found in several commercial drugs, for instance, antipsychotic (**a**),[7-10] electronic molecular (**b**),[11] antidepressant analogs (**c**),[12] anti-hypertensive (**d**),[13] calcium antagonists (**e**)[14] and anti-fungal agents (**f**)[15] (Figure 1 C).

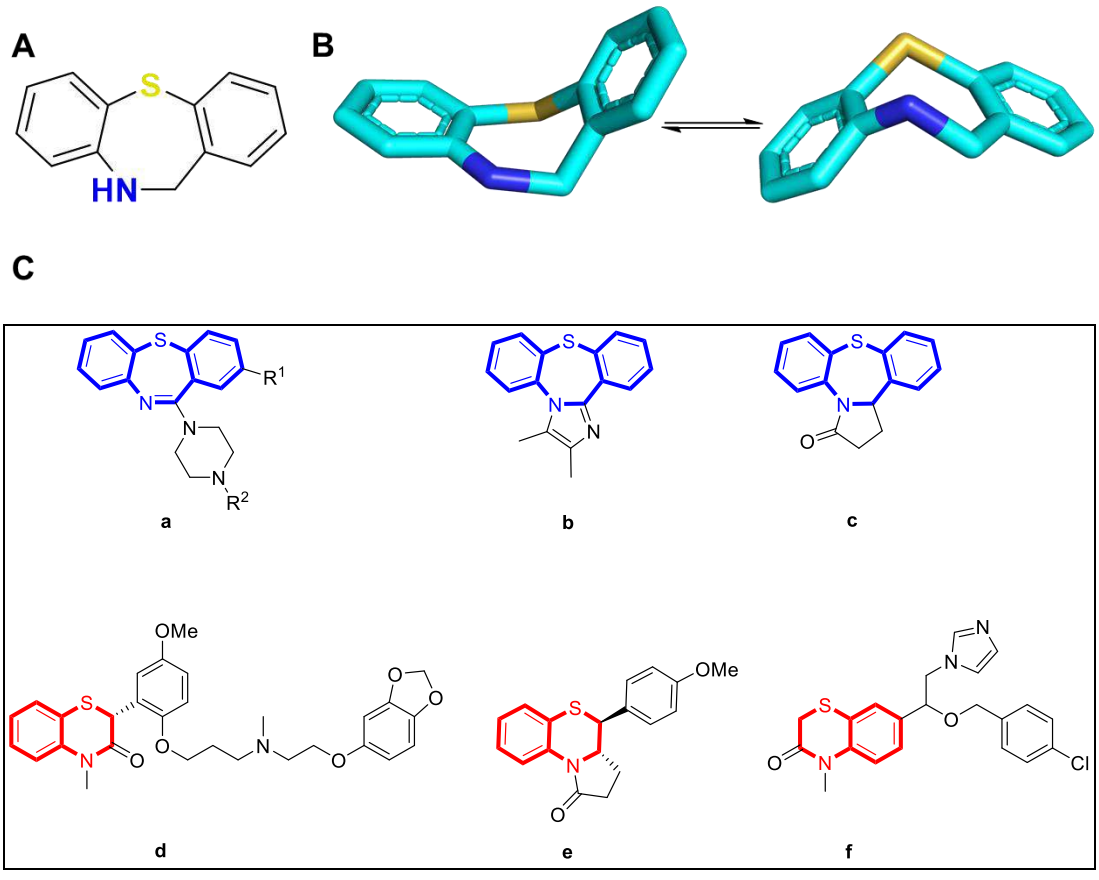


Figure 1 **A.** The privileged structure of the tricyclic dibenzothiazepine with the secondary NH and the oxidizable sulfur atom, **B.** The "butterfly" conformation of the ring with the isomer interconversion, **C**. Examples of molecules of interest based on the specific dibenzothiazepine and benzothiazepine core.

The focus turned to MCR-based annulation of the 1,5-dibenzodiazepine derivatives due to their unique conformational equilibrium[5,6,16-18] and atropisomers. The substitution of this core could potentially result in molecules with high-energy interconversion and separation. Interestingly, their thermodynamic profile can be improved upon addition of extra rings, since those restrict the inversion of the core's seven-membered ring.[1] Additionally, this core offers a unique binding mode in numerous targets (Figure 2).[19,20] Figure 2A shows the antiviral activity of the dibenzothiazepine DBT1 against the capsid protein of the Hepatitis B Virus (HBV) (PDB ID 6WFS). Impressively, an NH-π interaction of Trp102 (grey sticks) with the aromatic ring of 3.4 Å along with hydrogen bonds with Thr128 (grey sticks) and Ser121 (grey sticks) is observed. Next, figure 2B displays the antifungal activity of a dibenzothiazepinone against the BET protein Bdf1. Appealingly, a hydrogen bond network between the carbonyl groups of the small molecule with Asn291 (gray sticks) and certain molecules of water (orange spheres) of 3.0 Å, 2.8 Å, 3.3 Å, and 3.1 Å is revealed (PDB ID 5N17). In medicinal chemistry, atropisomers are becoming more and more important, although challenging to construct selectively.[21]

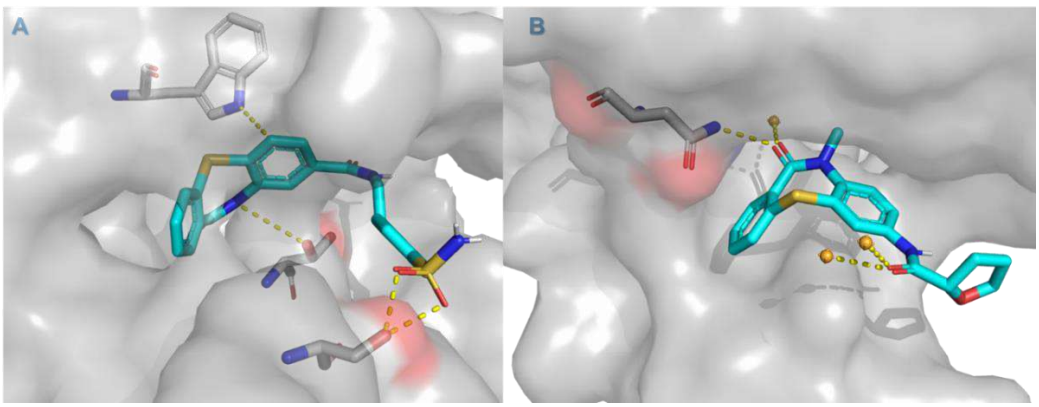
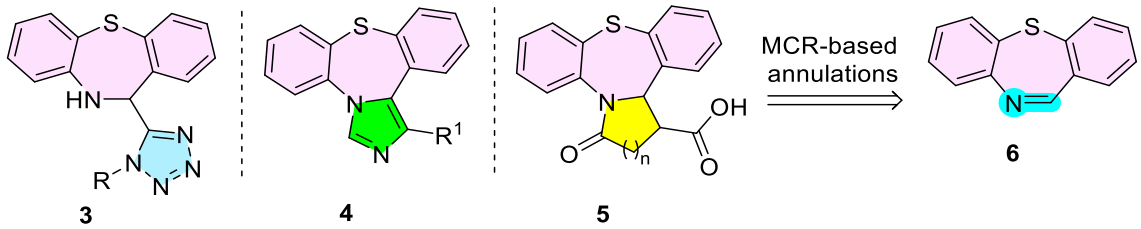


Figure 2 Dibenzothiazepine-receptor bind modes

So far, there are several sequential methodologies reported for 1,5-dibenzodiazepine derivatives. However, rapid synthetic approaches of versatile libraries for screening docks are limited.[1,2,22,23] In this concept, MCRs[24] offer rapid and convergent routes to polycyclic, diverse and complex products.[25-28] Interestingly, MCRs have been utilized in the synthesis of the 1,5-

dibenzothiazepine scaffold, e.g. the Ugi-Joullie three-component reaction (UJ-3CR), Mannich, Strecker, Pudovik reaction and aza-Henry.[29-34] Yet, only one MCR-based annulation is reported for the preparation of this scaffold.[35]

The tetracyclic dibenzothiazepine scaffolds **3**-**5** are widely used in synthetic pharmaceuticals, bioactive analogues[36-39] and material science.[11] Our retrosynthetic plan towards distinct cycles such as the tetrazole, imidazole, γ- and δ-lactams rings consists of MCR-based annulations, starting from the versatile building block **6** and targeting the imine bond (Scheme 1).[40]



Scheme 1 Retrosynthetic plans towards the privileged tetracyclic scaffolds of **3**, **4** and **5** bearing a tetrazole (cyan), imidazole (green) and lactam (yellow) ring, respectively based on the dibenzothiazepine imine **6**.

RESULTS AND DISCUSSION

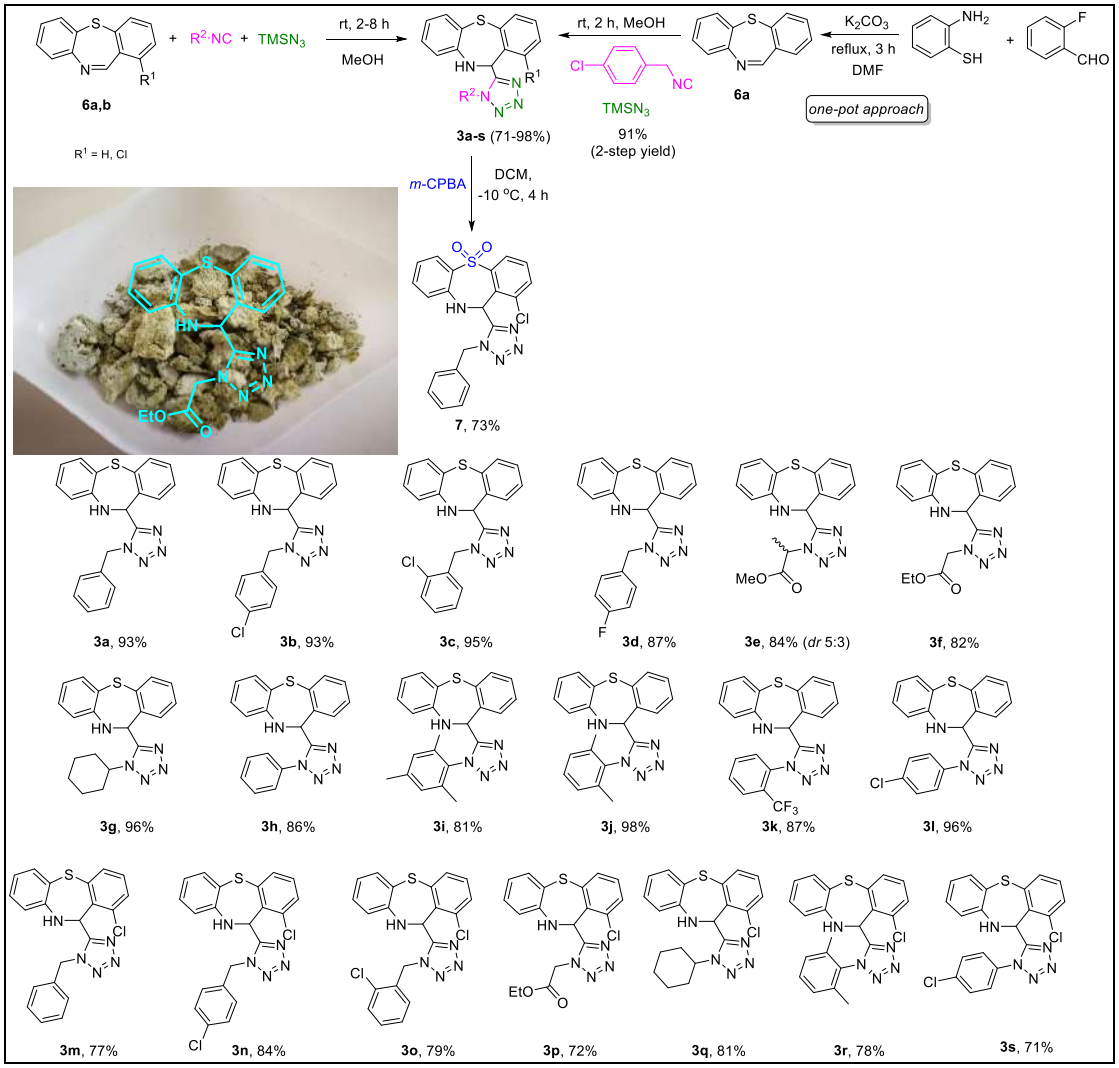
Firstly, the synthesis of 1,5-tetrazole dibenzothiazepines **3** is investigated**.** Interestingly, the tetrazole ring serves as a bioisostere to carboxylic acids and cis-amides[42,43] and offers significant improvement in the physicochemical properties of the synthesized libraries.[44] Notably, these fused tetracyclic tetrazole dibenzothiazepine derivatives demonstrates mild analgesic activity.[45]

The initial plan involved the direct reaction of *o*-aminothiophenol, *o*-fluorobenzaldehyde, the corresponding isocyanides and $TMSN_3$ and then cyclization. Unfortunately, this procedure failed with unreacted starting materials and byproducts. To overcome this issue, the study initiated from the imines **6a,b** with TMS-azide and a range of different isocyanides towards the desired 1,5-tetrazolodibenzothiazepines under mild conditions in good to excellent yields (Scheme 2, 71-98%).

The selection of isocyanides included benzylic (**3a-d, 3m-o**), aliphatic (**3e-g**, **3p-q**), and aryl (**3h-l**, **3r-s**) bearing both electron-withdrawing (EWG) and donating groups (EDG) (Scheme 2). Interestingly, alanine-fused isocyanides also comply with this protocol and give a mixture of diastereomers (*dr* 5:3). To demonstrate the potential of this synthetic strategy, **6b** with chlorine on the 1-position of the aromatic ring explored to obtain the desired scaffolds in slightly lower yields, probably due to solubility issues.

To our delight, the one-pot two-step approach afforded the desired product (**3b**) with an excellent yield of over 90% (without purifying the intermediate imine). Noteworthy, imine **6a** is obtained upon refluxing *o*-fluorobenzaldehyde and *o*-aminothiophenol with K_2CO_3,[46] without the additives (Scheme 2).[29]

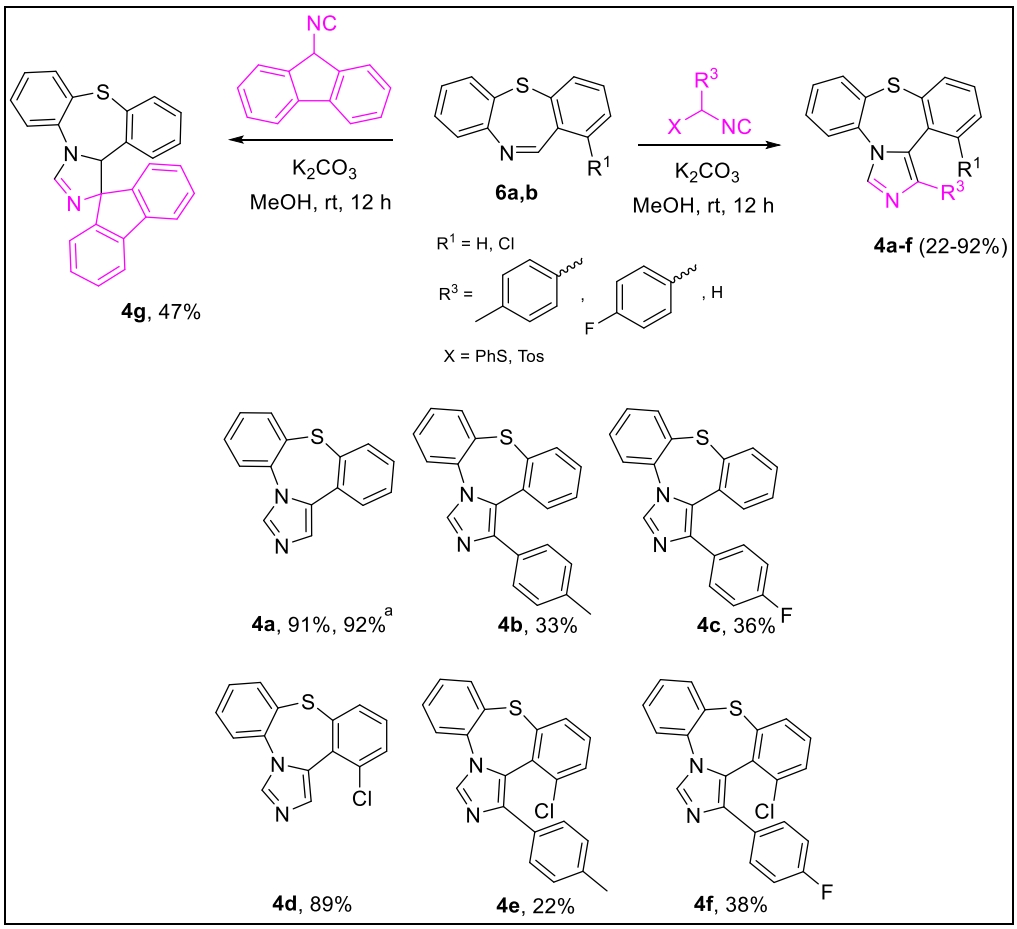
Next, post-modification on the initial UT scaffold take place (Scheme 2) due to the biological activities that benzo[*f*][1,2]thiazepinedioxides possess.[1] Oxidization of the sulfur atom of the thiazepine ring with *m*-CPBA yields **7** in 73% yield (Scheme 2). In addition, this approach is also scalable (Scheme 2, left image) and we obtain the adduct **3f** on a 5 mmol scale (81% yield, 2.97 g).



Scheme 2 The Ugi tetrazole reaction of the imines **6** towards the tetracyclic tetrazolo dibenzothiazepines **3**. An example of the one-pot approach is also shown. The scale-up of the reaction (left picture) and the oxidation of **3m** to the dioxide derivative **7** are shown.

Then, the fused tetracyclic imidazo-1,5-dibenzothiazepines **4** are synthesized based on the van Leusen imidazole reaction.[47] It has been reported that fused imidazo-azepines acted as selective GABAA receptor antagonists (e.g. Flumazenil),[48] antiviral and antibacterial agents.[49] Fortunately, the desired polycyclic thiazepines **4a**-**g** are isolated under mild conditions in 22-91% yields (Scheme 3). In this procedure, TosMIC isocyanide and its substituted derivatives, other acidic isocyanides such as the phenylsulfane (related to AsMIC),[50] and the fluorene isocyanides are also applicable. Interestingly, AsMIC and TosMIC yield the same product, **4a**, whereas the thiophenolate acts as the

leaving group. As expected, the substituted TosMICs (**4b**-**c**, **4e**-**f**) lead to reduced yields due to their increased instability in the reactions conditions (prone to dimerization).[51] Recently, the fluorene isocyanide is explored[52] and afford the complexed 7-membered spiro thiazepine **4g** (Scheme 3). In the present thesis, imidazole thiazepines are isolated in all cases instead of the corresponding imidazoline derivatives, compared with Sharma's group.[36]



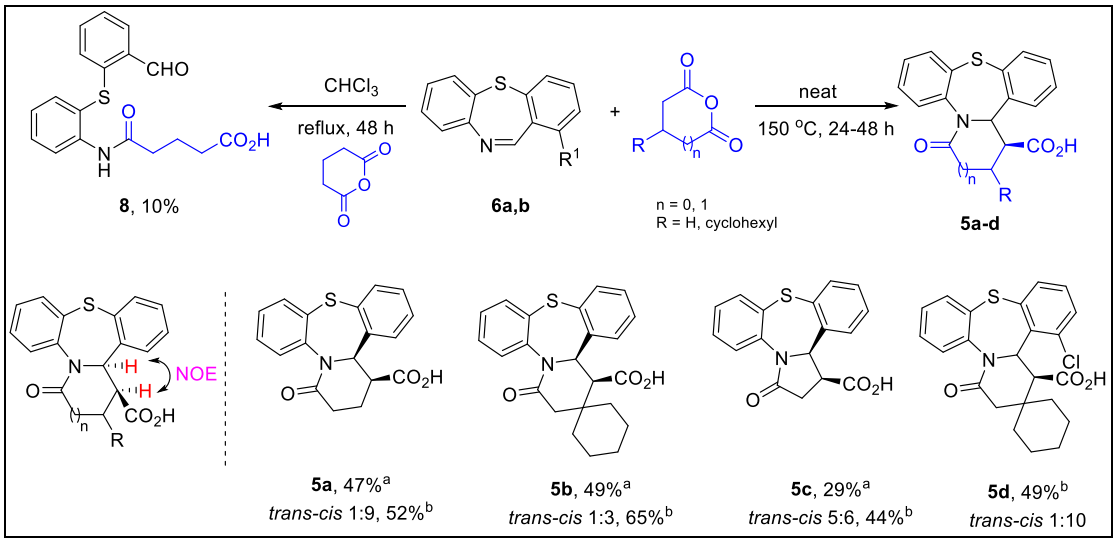
[a]*The first yield refers to the reaction with TosMIC, whereas the second yield refers to the reaction with AsMIC*

Scheme 3 The van Leusen reaction of the imines **6** with various acidic isocyanides towards the fused polycyclic dibenzothiazepines **4**.

Starting with the well-known Castagnoli-Cushman reaction (CCR) for the preparation of polysubstituted lactam carboxylic acids from imines and α-C-H cyclic anhydrides.[53-59] Subsequently, γ- and δ-lactam carboxylic acids **5** are

synthesized with the pre-prepared dibenzothiapine and the commercial cyclic anhydrides.

Several scaffolds are synthesized from three different commercial cyclic anhydrides and imines **6a** and **6b** under high temperature, neat conditions in one step with good yields (Scheme 4). As shown in Scheme 4, the reaction proceeds in a relatively diastereoselective way. Interestingly, the *cis*-isomer is the major isomer via analyzing by NOE experiments (see NOE spectrums) and the characteristic ^{1}H NMR patterns. Nevertheless, the CCR often gives rise to the *trans*-isomer under similar reaction conditions.[60] Isolation of the cis isomer via recrystallization with EtOH occurs (except **5d).**[57] The lower boiling point solvents such as chloroform or toluene give the ring-opening adducts in low yield (product **8**).[56] Surprisingly, adducts **5** are traced under reflux in bromobenzene (Scheme 4).

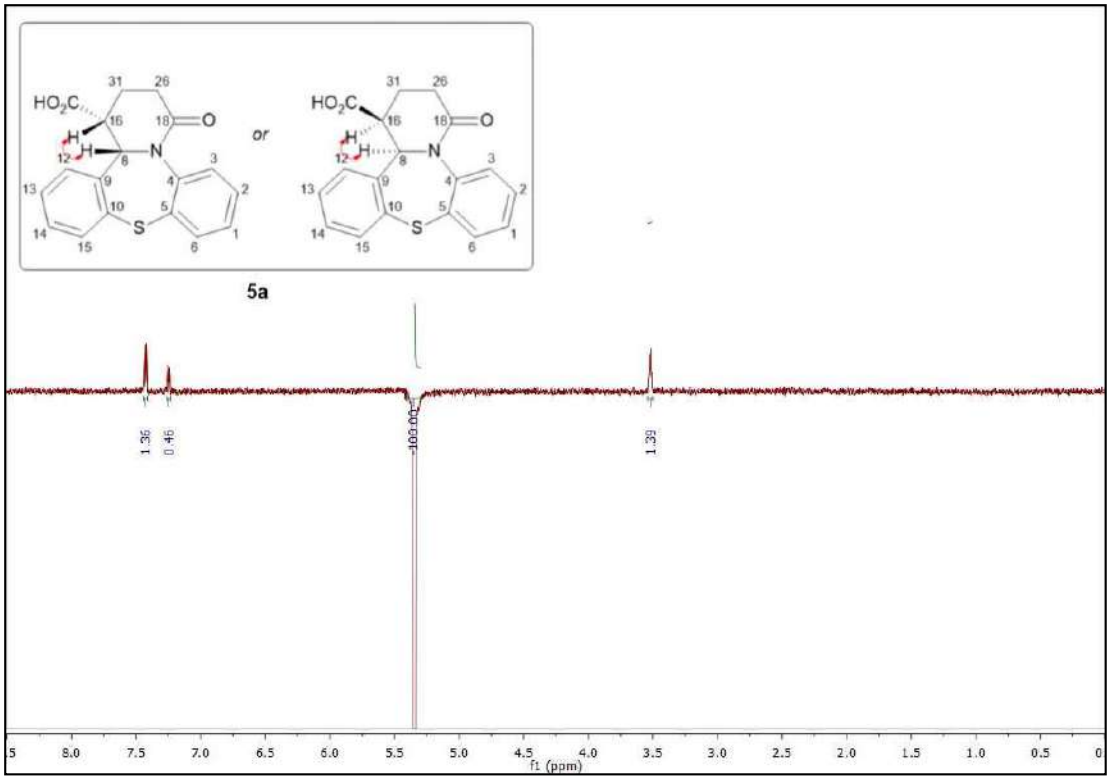


[a]Isolated yield of the cis-isomer, [b]Yield of the mixture trans-cis isomers

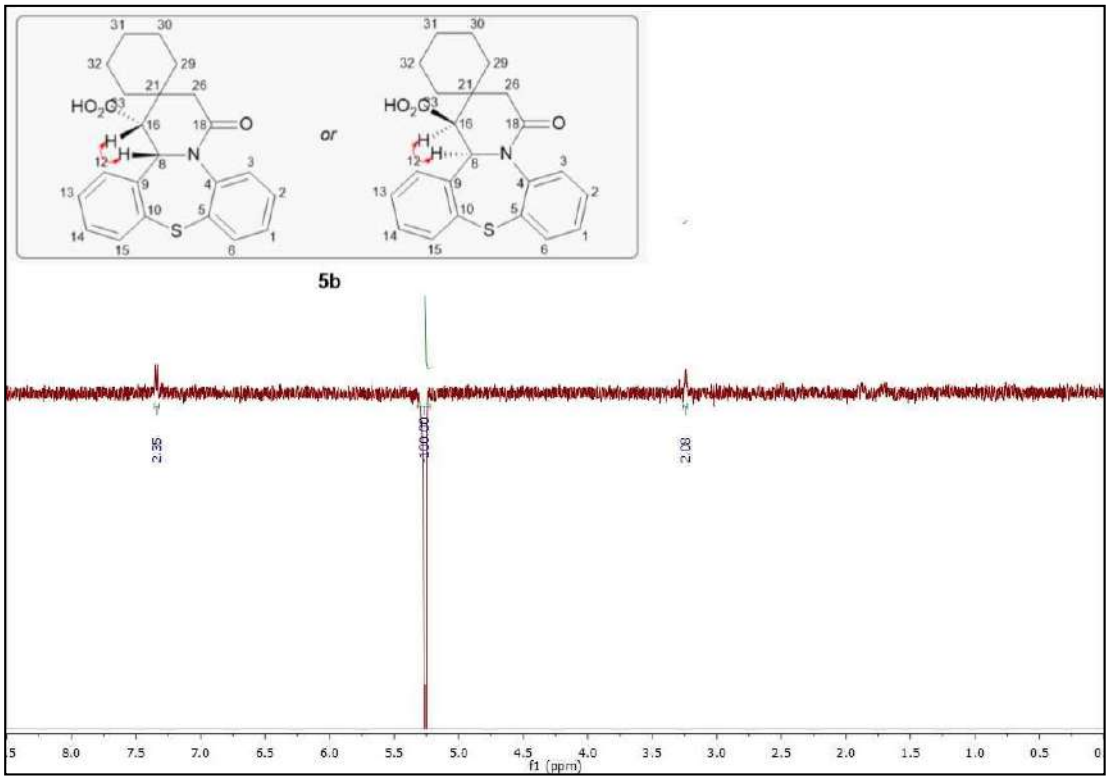
Scheme 4 The Castagnoli-Cushman reaction of the imines **6** towards the γ- and δ-lactams **5**. In most of the cases the major *cis*-isomer is isolated.

Representative NOE experiments for structure elucidation

*Irradiation of the H8 proton of **5a** resonating at 5.34 ppm results to signal enhancement of the aromatic H12 at 7.43 ppm, of the aromatic H13 at 7.25 ppm, of the H16 at 3.52 ppm.*

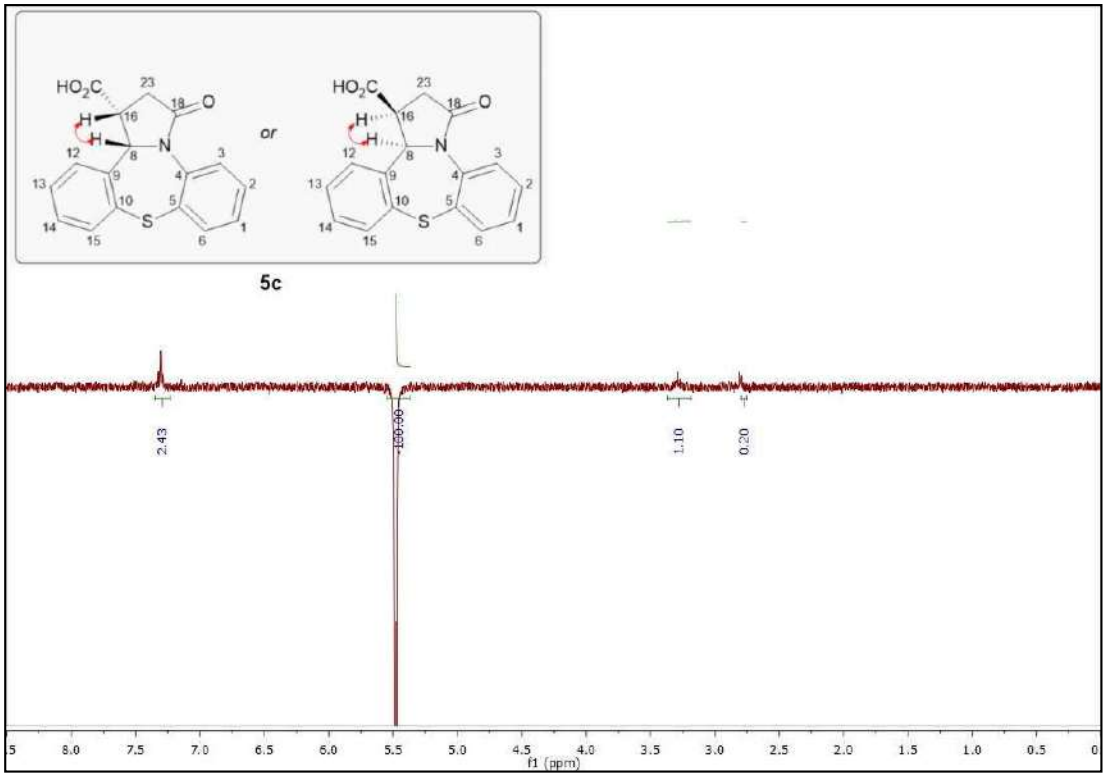


*Irradiation of the H8 proton of **5b** resonating at 5.26 ppm results to signal enhancement of the aromatic H12 at 7.33 ppm, of the H16 at 3.24 ppm.*

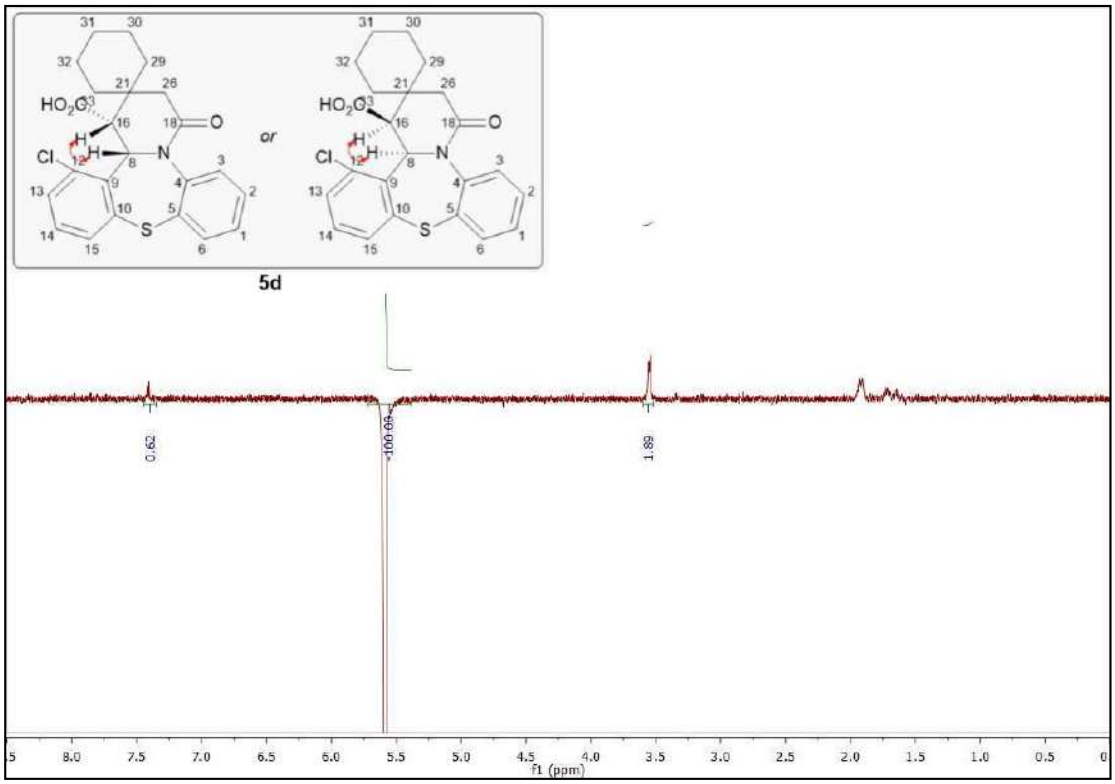


*Irradiation of the H8 proton of **5c** resonating at 5.48 ppm results to signal*

enhancement of the aromatic H12 at 7.31 ppm, of the H16 at 3.29 ppm, of the methyl H23 at 2.81 ppm.



*Irradiation of the H8 proton of **5d** resonating at 5.58 ppm results to signal enhancement of the aromatic H12 at 7.45 ppm, of the H16 at 3,54 ppm.*



The crystal structures of the **3g, 7**, and **4b** confirmed the conformational behavior of the current cores (Figure 4). The conformers in all cases are present in the unit cell.[18] The dibenzothiazepine ring adopts the expected butterfly conformation and the geometrical features (verified by the “Mogul geometry check” of the CCDC suite). In addition, **7** has an intramolecular hydrogen bond of 2.2 Å between the oxygen atom from the -SO_2 group and the polar hydrogen atom of the N-H. Compared to **3g** and **7,** the fused bicyclic adduct **4b** shows increased rigidity due to the extra fused ring.

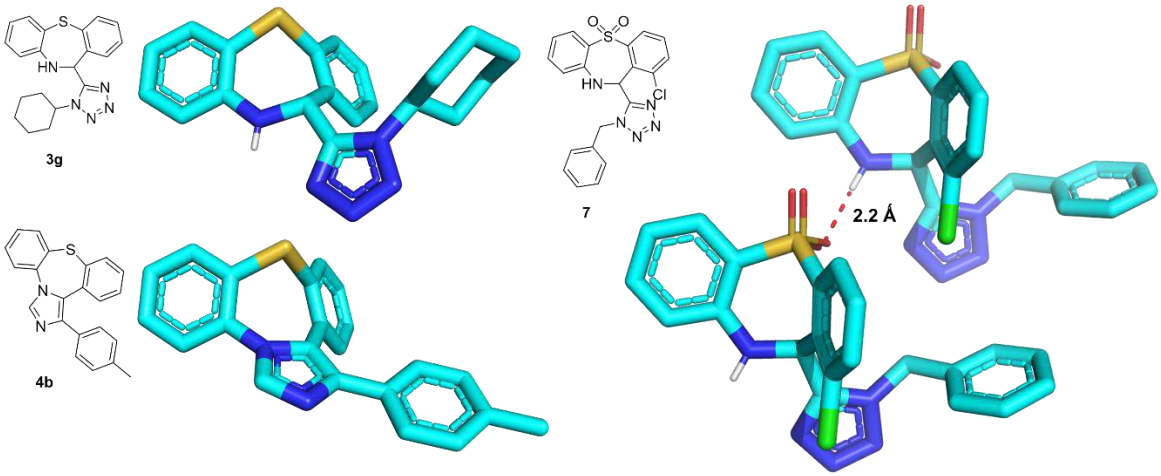


Figure 4 General structure of the dibenzothiazepine and crystal structures of the **3g** (CCDC 2123183), **4b** (CCDC 2123182) and **7** (CCDC 2123184).

Additionally, we performed a generation of conformers via the CCDC suite for each of the three different 3D structures we managed to solve. It is calculated that compound **4b** has only six different conformers compared with the thirty-one and fifteen of compounds **3g** and **7**, respectively. The conformational behavior of the dibenzothiazepines is key to the core structures' behavior on a molecular level and understanding the connectivity with a biological target.[17] Cambridge Structural Database (CSD)[41] data is firstly used to analyze the solid-stay of this tricyclic scaffold. In fact, the conformation of the

seven-membered ring and the relative arrangement of the fused aromatic rings defined this scaffold's overall shape.[16,17] Also, the tricyclic rings' folding is affected by X (Figure 3, X = C, N, O, S).[5] The dihedral angles $R^1$16-N14-C13-C12 and $R^2$17-C15-C3-C2 reveals a relatively planar conformation.

Analysis and data mining in Cambridge Structural Database (CSD)

A thorough analysis in CSD (CSD version 5.41 + 3 updates) on the dibenzoazepine derivatives (79 hits) is performed with the following parameters: 3D coordinates determined, R factor ≤ 0.1, only non-disordered, no errors, not polymeric, no ions, only single crystal structures and organics.

As an indication of the folding of the two aromatic rings, namely A (cyan) and B (yellow), their relative disposition is investigated by measuring the angle (ANG2) between their mean planes (Figure 3). Moreover, the angles that each of the two aromatic rings form with the plane of the seven-membered ring (as set by X-N14-C15), namely ANG3 (angle of the aromatic ring A with the plane of 7-membered ring) and ANG4 (angle of the aromatic ring B with the plane of 7-membered ring) are considered (Figure 4). The scatterplot of ANG2 with ANG3 reveals that as ANG2 increases from 50º to 65º, the ANG3 appears as two different value subgroups, the first ranges from 5º-10º and the second from 40º-65º. The majority of compounds in the first subgroup includes mostly benzoxazepines (X = O, cyan spots) or benzothiazepines (X = S, red spots). The majority of the second subgroup includes benzodiazepines (X = N, blue spots). The opposite phenomenon is observed in the scatterplot of ANG2 vs ANG4. Particularly, the ANG3 tends to decrease whereas the ANG4 increases when we move from N to S (Figure 5). It is clear that indeed the heteroatom X influences the folding of the ring. Finally, dihedral angles $R^1$16-N14-C13-C12 and $R^2$17-C15-C3-C2 are taken into account, with mean values of -6.1º and -3.2º, respectively revealing a relative planar conformation (Figure 6).

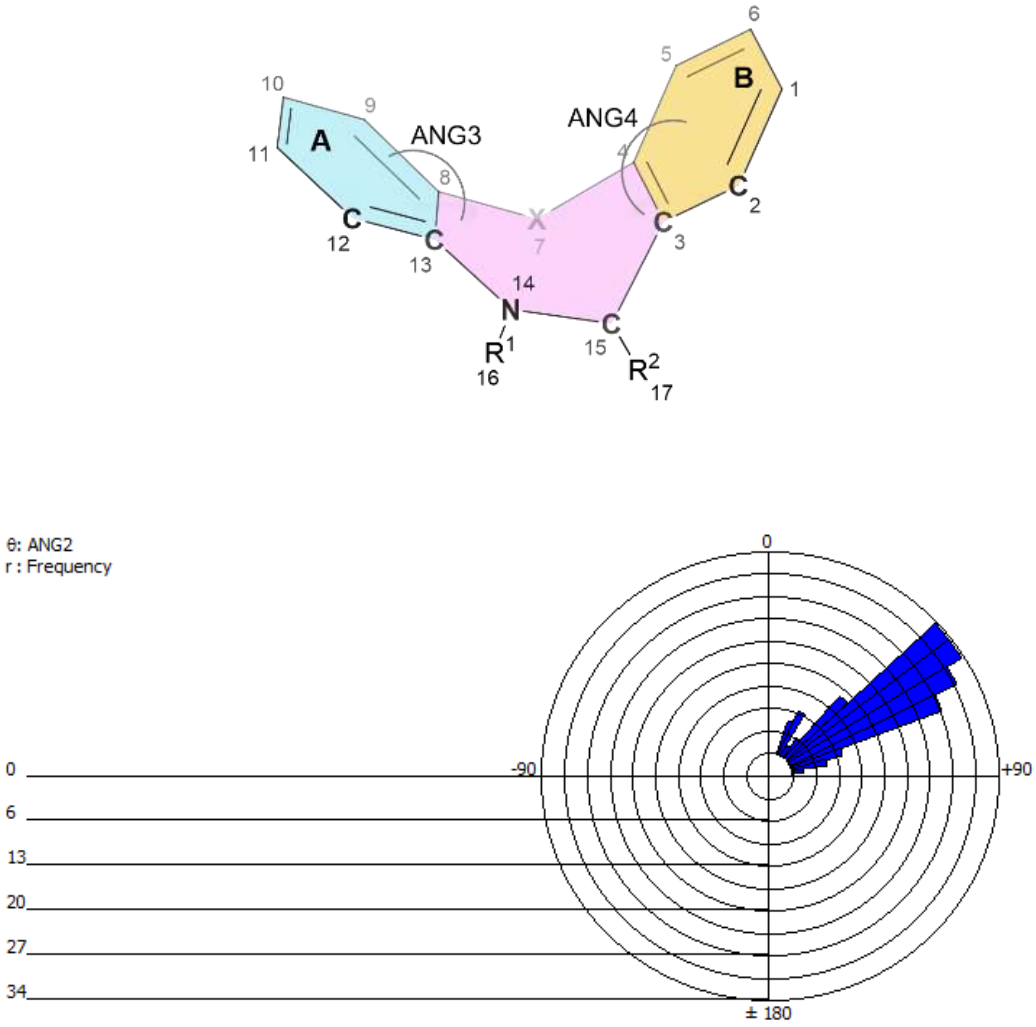


Figure 3 Polar histogram of ANG2 (angle between the mean planes of rings A and B) with a mean value of 55.197º).

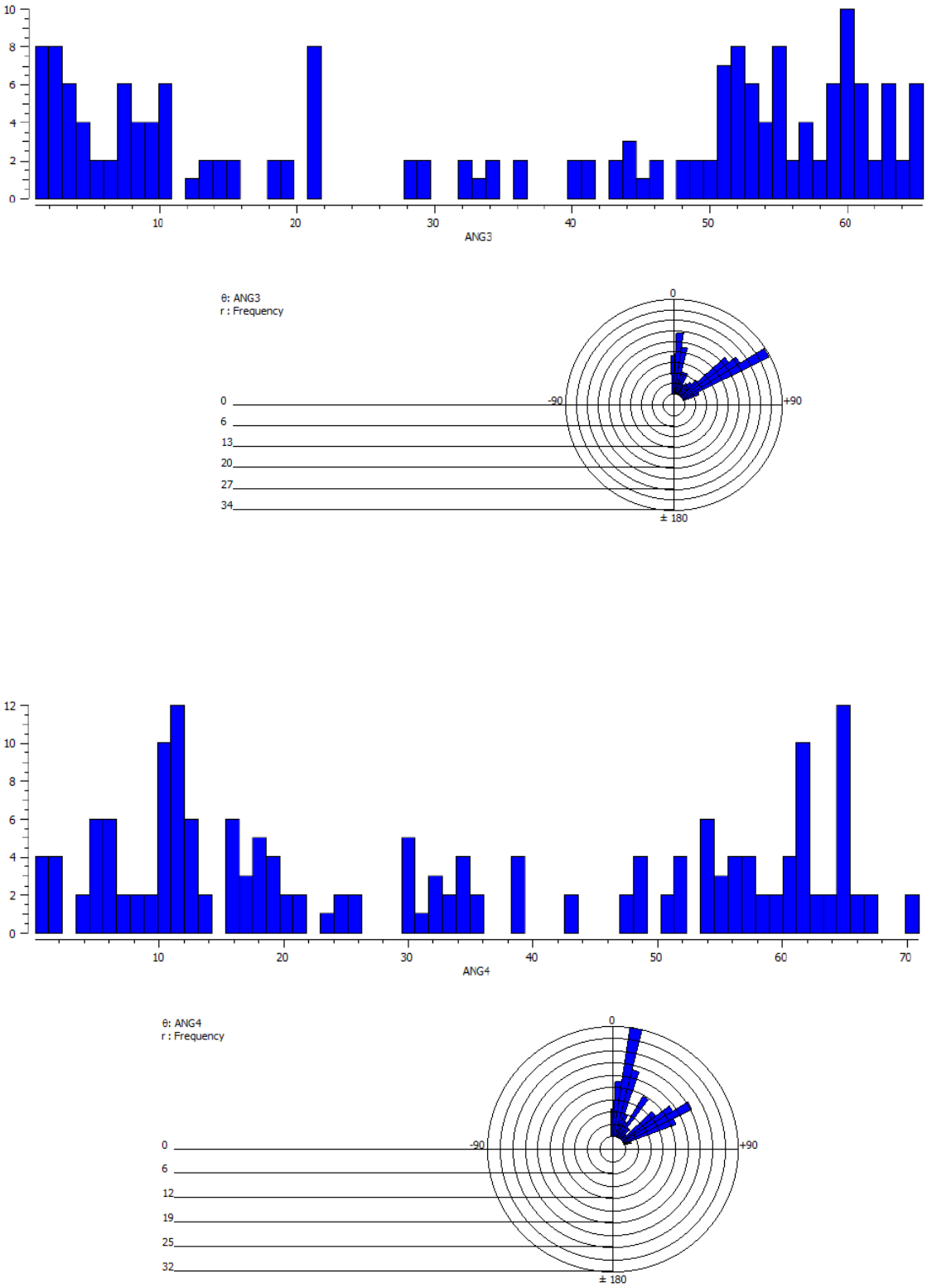


Figure 4 Histograms and polar histograms of ANG3 and ANG4 (with mean values of 35.794º and 33.172º, respectively).

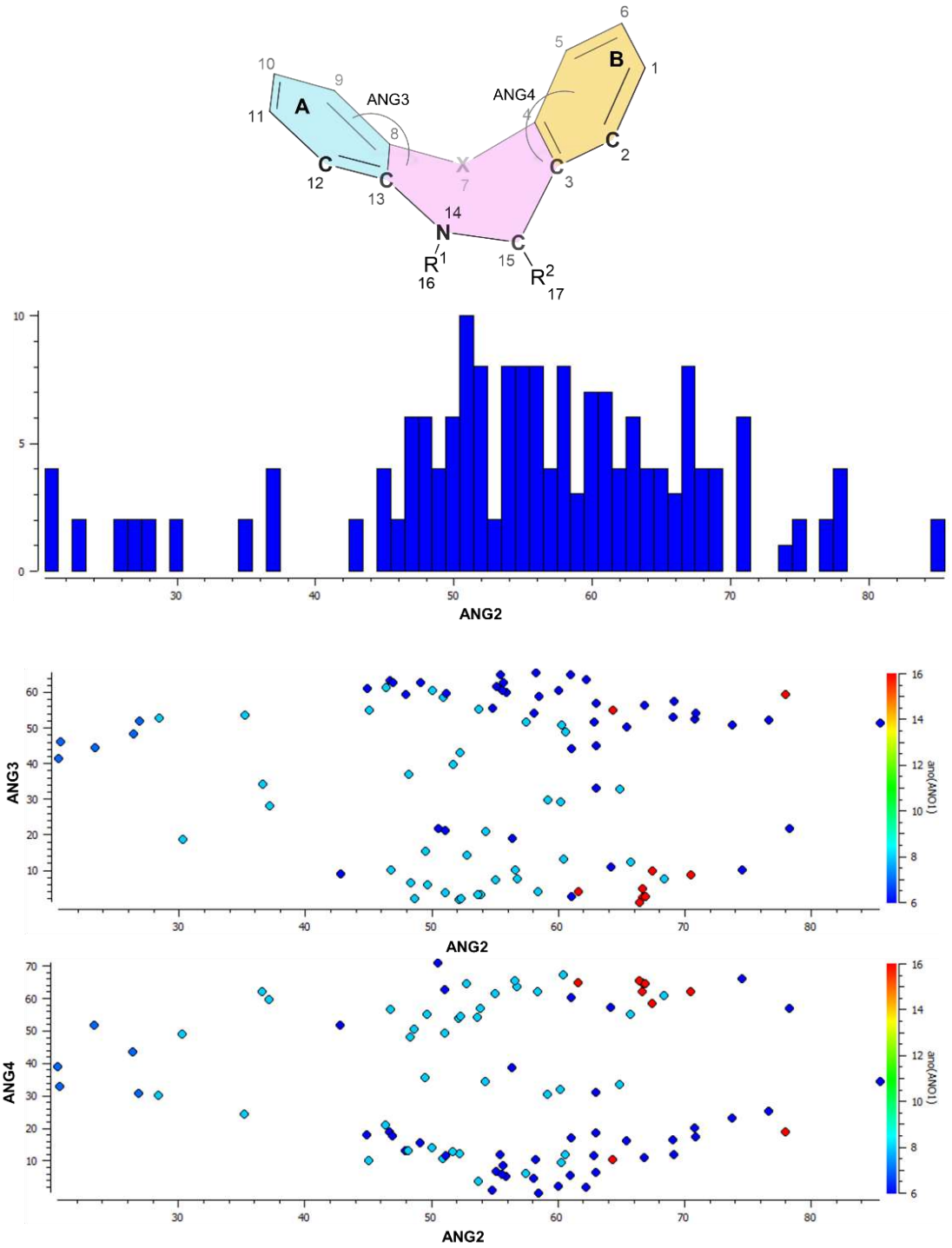


Figure 5 CSD analysis of dibenzoazepines (68 hits), Histogram of the angle of the mean plane of the two aromatic rings, A and B (ANG2) that indicates their folding, Scatterplots of ANG2 *vs* ANG3 and ANG4 (shown in sketch) that reveal the influence of the heteroatom X (C, N, O and S) on the rigidity of the system, Scatterplot of ANG3 *vs* the atom which indicates the conformational folding.

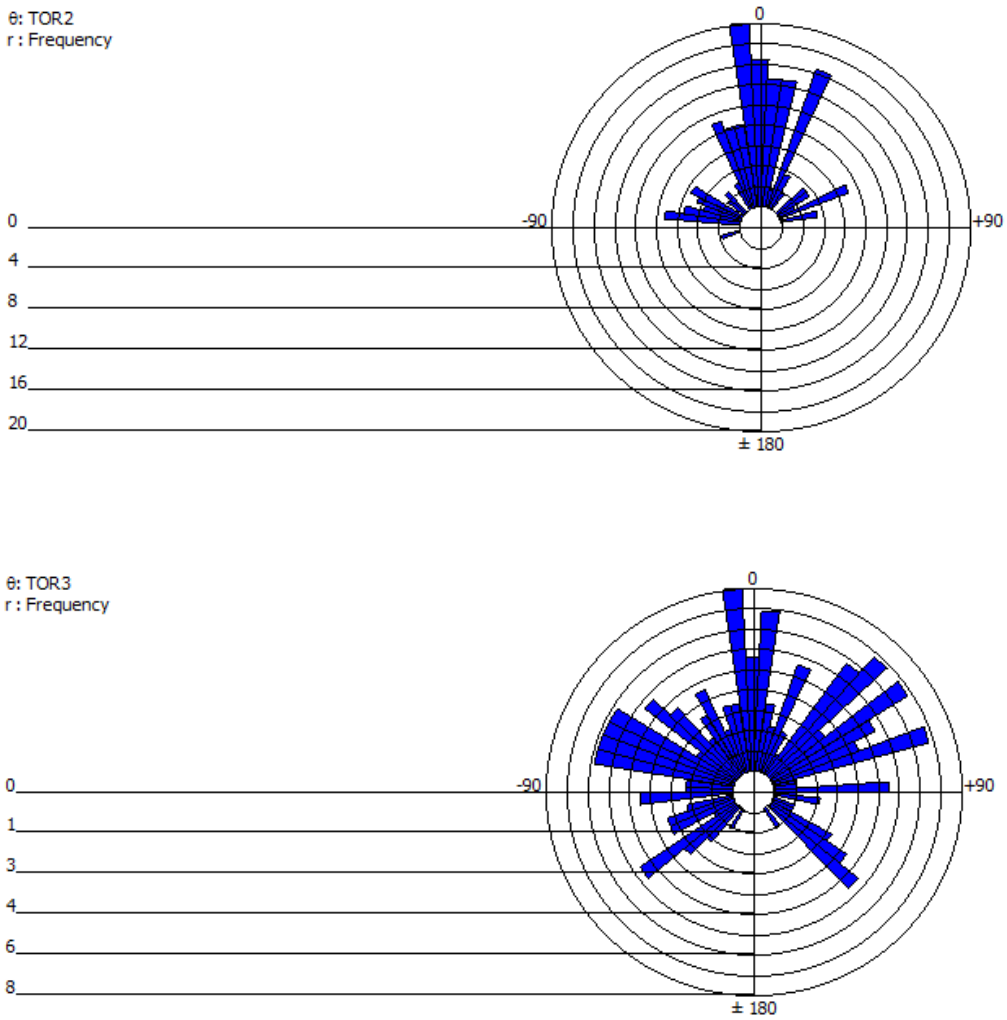
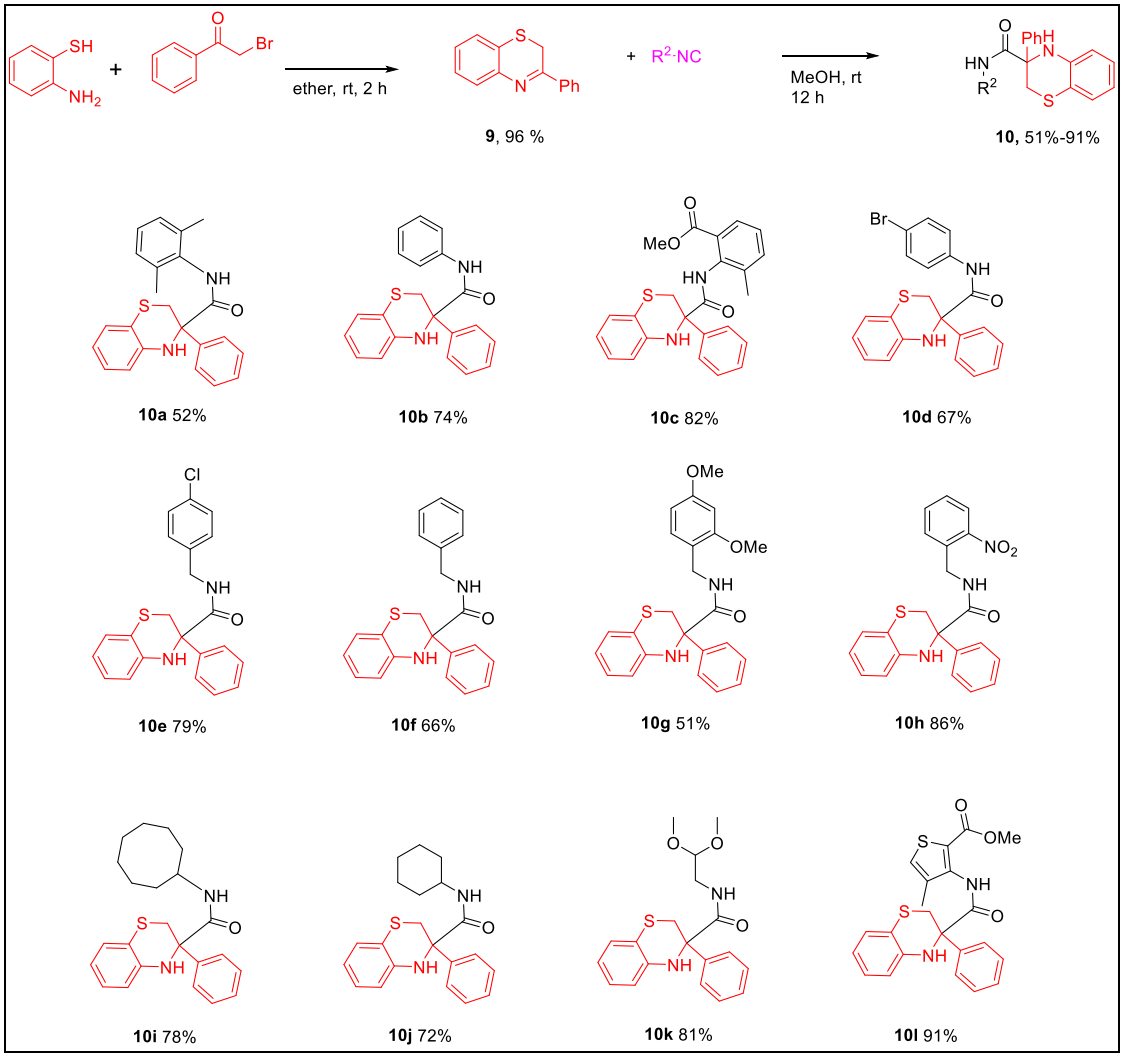


Figure 6 Polar histograms of the dihedral angles $R^1$16-N14-C13-C12 (namely TOR1, mean value 6.130°) and $R^2$17-C15-C3-C2 (namely TOR2, mean value 3.164°).

Then, we turned to the six-membered benzothiazine scaffold synthesis. The Ugi-3CR is employed in order to access those entities as shown in Scheme 5.[13-15] Imine **9** is obtained following the existing straightforward protocol via stirring the *o*-aminothiophenol and phenacyl bromide in ether at room temperature and simply flitration.[61] The Ugi-3CR adducts are synthesized mostly under mild conditions in methanol at room temperature in good to very good yields. To our delight, the range of isocyanides that have been used is

broad, i.e. aryl (**10a** and **10f**), benzylic (**10c**-**d**), aliphatic (**10b** and **10e**) and heterocyclic (**10g**) with different substituents and functional groups (Scheme 5).



Scheme 5 The Ugi tetrazole reaction of the imine **9** towards the tetracyclic tetrazolo benzothiazepines **10**.

CONCLUSIONS

In this study, five straightforward MCR approaches towards various and complex benzothiapine derivatives took place. An extended library of 42 adducts obtained under these one-pot protocols in good to excellent yields. Notably, several polycyclic and rigid dibenzothiapines with high complexity obey the rule of 5 (**Ro5**). There are several advantages of this method, such as mild conditions, short reaction time, easy access to starting materials, gram scale, and reduced purification steps. As such, this method is a useful tool in the field of benzothiapine synthesis.

REFERENCES

1. D. Saha, G. Jain, A. Sharma, *RSC Adv.* **2015**, *5*, 70619-70639.
2. V. Devi, G. Singh, V. Monga, *J. Heterocycl. Chem.* ***2020***, *57*, 3255-3270.
3. J.-L. Reymond, R. van Deursen, L. C. Blum, L. Ruddigkeit, *Medchemcomm,* **2010**, *1*, 30-38.
4. M. K. Parai, G. Panda, *Tetrahedron Letters*, **2009**, *50*, 4703-4705.
5. M. Altamura, A. Guidi, L. Jierry, P. Paoli, P. Rossi, *CrystEngComm,* **2011**, *13*, 2310-2317.
6. M. Altamura, P. Dapporto, A. Guidi, N. J. S. Harmat, L. Jierry, E. Libralesso, P. Paoli, P. Rossi, *New J. Chem.*, **2008**, *32*, 1617-1627.
7. J. Xiao, R. B. Free, E. Barnaeva, J. L. Conroy, T. Doyle, B. Miller, M. Bryant-Genevier, M. K. Taylor, X. Hu, A. E. Dulcey, et al., *J. Med. Chem.*, **2014**, *57*, 3450-3463.
8. K. Komossa, A. M. Depping, A. Gaudchau, W. Kissling, S. Leucht, *Cochrane Database Syst. Rev.,* **2010**, 1-230.
9. M. Zare, A. Bazrafshan, *Cochrane Database Syst. Rev.,* **2017**, 1-41.
10. G. Seminara, V. Trassari, N. Prestifilippo, R. Chiavetta, C. Calandra, *Minerva Psichiatr.*, **1993**, *34*, 95-99.
11. E. D. Baranoff, M. Graetzel, M. K. Nazeeruddin, *Light Emitting Materials for Electronics*, *WO2012019948A1*, **2012**.
12. Hadou, Abderrahmane, Hamid, Abdulkareem, Mathouet, Hilarion, Deida, Mohamed-Fadel, Daich, Adam, *Heterocycles***, 2008,** *76 (2),* 1017 - 1022.
13. Morino, T., Yamamoto, T. *J. Chem. Eng. Jpn.* **1997**, *30*, 1005.
14. Corelli, F., Manetti, F., Tafi, A., Campiani, G., Nacci, V., Botta, M., *J. Med. Chem.* **1997**, *40*, 125.
15. Macchiarulo, A., Costantino, G., Fringuelli, D., Vecchiarelli, A., chiaffella, F., Fringuelli, R. *Bioorg. Med. Chem.* **2002**, *10*, 3415.

16. M. Altamura, A. Guidi, L. Jierry, P. Paoli, P. Rossi, *Acta Crystallogr. Sect. E Struct*. Reports Online **2012**, *68*, o3133-o3134.
17. M. Altamura, V. Fedi, D. Giannotti, P. Paoli, P. Rossi, *New J. Chem.*, **2009**, *33*, 2219-2231.
18. J. Irurre, F. Marquillas, A. Alvarez-Larena, J. F. Piniella, *Can. J. Chem.*, **1994**, *72*, 334-338.
19. C. J. Schlicksup, P. Laughlin, S. Dunkelbarger, J. C. Y. Wang, A. Zlotnick, *ACS Chem. Biol.*, **2020**, *15*, 1708-1717.
20. F. Mietton, E. Ferri, M. Champleboux, N. Zala, D. Maubon, Y. Zhou, M. Harbut, D. Spittler, C. Garnaud, M. Courçon, et al., *Nat. Commun.*, **2017**, *8*, 15482.
21. J. K. Cheng, S.-H. Xiang, S. Li, L. Ye, B. Tan, *Chem. Rev.*, **2021**, *121*, 4805-4902.
22. M. A. Mironov, M. N. Ivantsova, M. I. Tokareva, V. S. Mokrushin, *Russ. Chem. Bull.*, **2004**, *53*, 1232-1236.
23. J. Yadav, A. P. Pawar, Y. K. Nagare, E. Iype, K. Rangan, J. Ohshita, D. Kumar, I. Kumar, *J. Org. Chem.*, **2020**, *85*, 14094-14108.
24. A. Dömling, W. Wang, K. Wang, *Chem. Rev.*, **2012**, *112*, 3083-3135.
25. W. Wang, S. Ollio, E. Herdtweck, A. Dömling, *J. Org. Chem.*, **2011**, *76*, 637-644.
26. K. Wang, D. Kim, A. Dömling, *J. Comb. Chem.*, **2010**, *12*, 111-118.
27. P. Patil, K. Khoury, E. Herdtweck, A. Dömling, Bioorg. *Med. Chem.*, **2015**, *23*, 2699-2715.
28. Q. Wang, K. C. Mgimpatsang, M. Konstantinidou, S. V Shishkina, A. Dömling, *Org. Lett.*, **2019**, *21*, 7320-7323.
29. Q. Zheng, A. Boltjes, A. Dömling, *Synthesis*, **2021**, *53*, 1980-1988.
30. D. Saha, P. Wadhwa, A. Sharma, *RSC Adv.*, **2015**, *5*, 33067-33076.
31. Z. F. Deng, B. Huang, H. Xu, F. Shi, Y. Q. Wang, *Asian J. Org. Chem.*, **2017**, *6*, 1460-1469.

32. C. Lluna-Galán, G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, C. Vila, *Adv. Synth. Catal.*, **2018**, *360*, 3662-3666.
33. D. Saha, T. Kaur, N. Singh, U. P. Singh, A. Sharma, *Asian J. Org. Chem.*, **2016**, *5*, 82-90.
34. L. Cai, Y. L. Pan, L. Chen, J. P. Cheng, X. Li, *Chem. Commun.*, **2020**, *56*, 12383-12386.
35. Y. D. Shao, D. D. Han, X. Y. Yang, D. Di Zhou, T. Wang, D. J. Cheng, *Eur. J. Org. Chem.*, **2019**, 1957-1961.
36. D. Saha, T. Kaur, A. Sharma, Asian *J. Org. Chem.*, **2017**, *6*, 527- 533.
37. C. G. Wermuth, in Analog. Drug Discov., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2006**, pp. 1-23.
38. J. R. Proudfoot, in Analog. Drug Discov., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2006**, pp. 25-52.
39. H. Kubinyi, in Analog. Drug Discov., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2006**, pp. 53-68.
40. R. B. Moffett, *J. Heterocycl. Chem.*, **1980**, *17*, 341-349.
41. D. Dar'in, O. Bakulina, S. Nikolskaya, I. Gluzdikov, M. Krasavin, *RSC Adv.*, **2016**, *6*, 49411-49415.
42. G. M. Schroeder, S. Marshall, H. Wan, A. V. Purandare, *Tetrahedron Lett.*, **2010**, *51*, 1404-1406.
43. C. G. Neochoritis, T. Zhao, A. Dömling, *Chem. Rev.*, **2019**, *119*, 1970-2042.
44. M. T. Nazeri, H. Farhid, R. Mohammadian, A. Shaabani, *ACS Comb. Sci.*, **2020**, DOI 10.1021/acscombsci.0c00046.
45. X. Lei, P. Lampiri, P. Patil, G. Angeli, C. G. Neochoritis, A. Dömling, *Chem. Commun.*, **2021**, *57*, 6652-6655.
46. L. Crawley, S. R. Safir, *J. Heterocycl. Chem.*, **1975**, *12*, 1075-1076.
47. J.-H. Ye, P. Bellotti, T. O. Paulisch, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.*, **2021**, *60*, 13671-13676.

48. A. M. Van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem.*, **1977**, *42*, 1153-1159.
49. D. Bentué-Ferrer, M. Bureau, A. Patat, H. Allain, *CNS Drug Rev.*, **1996**, *2*, 390-414.
50. C. Dechambre, J. M. Chezal, E. Moreau, F. Estour, B. Combourieu, G. Grassy, A. Gueiffier, C. Enguehard, V. Gaumet, O. Chavignon, et al., *Tetrahedron Lett.*, **2002**, *43*, 9119-9123.
51. L. G. Mueller, A. Chao, E. Alwedi, M. Natrajan, F. F. Fleming, *Org. Lett.*, **2021**, *23*, 1500-1503.
52. A. D. Mathiyazhagan, G. Anilkumar, *Org. Biomol. Chem.*, **2019**, *17*, 6735-6747.
53. X. Lei, M. Thomaidi, G. K. Angeli, A. Dömling, C. G. Neochoritis, *Synlett*., **2022**, *33*, 155-160.
54. D. O'Hagan, *Nat. Prod. Rep.*, **2000**, *17*, 435-446.
55. E. Kroon, J. O. Schulze, E. Süß, C. J. Camacho, R. M. Biondi, A. Dömling, *Angew. Chem. Int. Ed.*, **2015**, *54*, 13933-13936.
56. M. Cushman, N. Castagnoli, *J. Org. Chem.*, **1973**, *38*, 440-448.
57. N. Castagnoli, *J. Org. Chem.*, **1969**, *34*, 3187-3189.
58. A. Lepikhina, O. Bakulina, D. Dar'In, M. Krasavin, *RSC Adv.*, **2016**, *6*, 83808-83813.
59. A. Firsov, E. Chupakhin, D. Dar'In, O. Bakulina, M. Krasavin, *Org. Lett.*, 2019, *21*, 1637-1640.
60. Z. Li, Y. Feng, Z. Li, L. Jiang, *Synlett*, **2014**, *25*, 2899-2902.
61. Loredana Leone, Orlando Crescenzi, Riccardo Amorati, Luca Valgimigli, Alessandra Napolitano, Vincenzo Barone and Marco d'Ischia, *Org. Lett.,* **2013**, *15*, *19*, 4944-4947.
62. Nutt, R. F., Joullié, M. M. *J. Am. Chem. Soc.*, **1982**, *104*, 5852-5853.

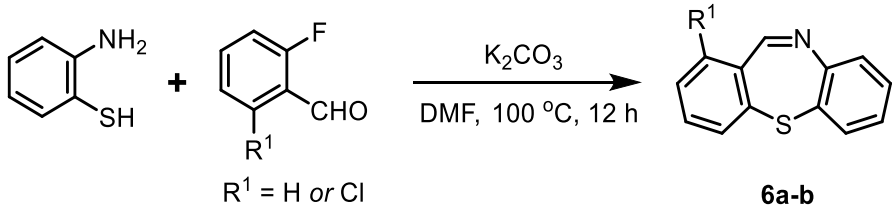
EXPERIMENTAL SECTION

1. General methods and materials

All the reagents and solvents are purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and are used without further purification. Isocyanides are synthesized as previously described by us. All microwave irradiation reactions are carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography is performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra are recorded on Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)}. Chemical shifts for ^{1}H NMR are reported as δ values and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak. Flash chromatography is performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra are measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). High resolution mass spectra are recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

2. Synthetic procedures and analytical data

General procedure for the synthesis of dibenzothiazepines

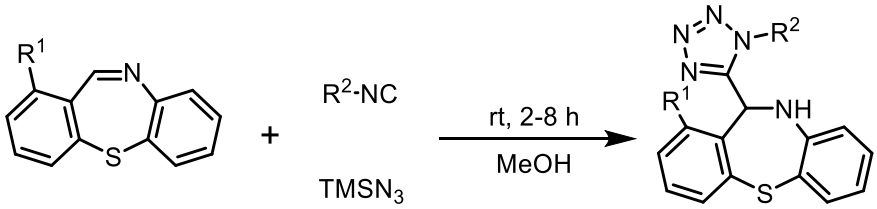


R^1 = H *or* Cl

6a-b

To a stirred solution of 2-aminobenzenethiol (1.0 mmol) in DMF (3.0 mL), the corresponding 2-fluorobenzaldehyde (1.0 mmol) and K_2CO_3 (1.5 mmol) are added and then warmed up to 100 °C for 3 - 12 h. The mixture is washed with water (2 x 10.0 mL), extracted with ethyl acetate (3 x 5.0 mL), the organic layer is dried over Na_2SO_4 and filtered. The solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 10:1-4:1) to give compounds **6a-b**.

General procedure for the Ugi tetrazole reactions (UT-3CR)



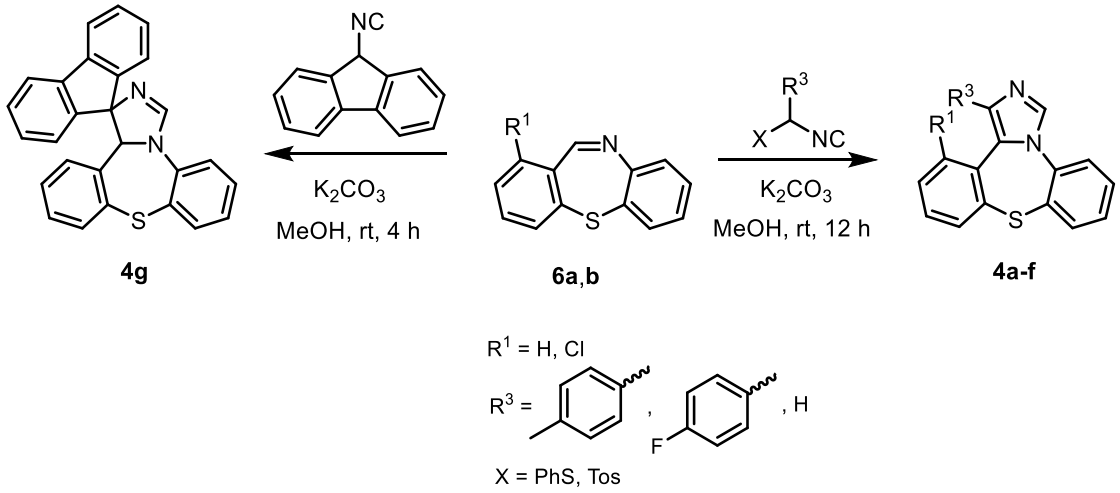
6a-b

R^1= H *or* Cl

3a-s

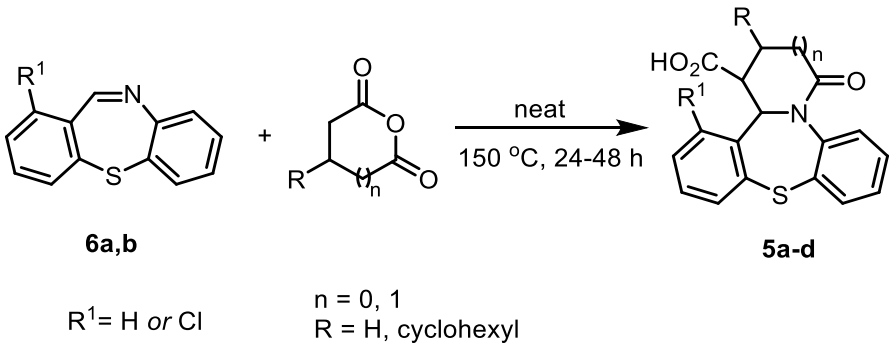
To a stirred solution of the corresponding dibenzothiazepine **6a-b** (1.0 mmol) in MeOH (1.0 mL), the corresponding isocyanide (1.0 mmol) and trimethylsilyl azide (1.0 mmol) are added. The reaction mixture is stirred vigorously for 2 - 8 h. Then, if solid appears, half of the solvent is removed under reduced pressure. The resulting solid is filtered and washed with Et_2O. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 4:1-1:1) to give compounds **3a-s**.

General procedure for the Van Leusen reactions



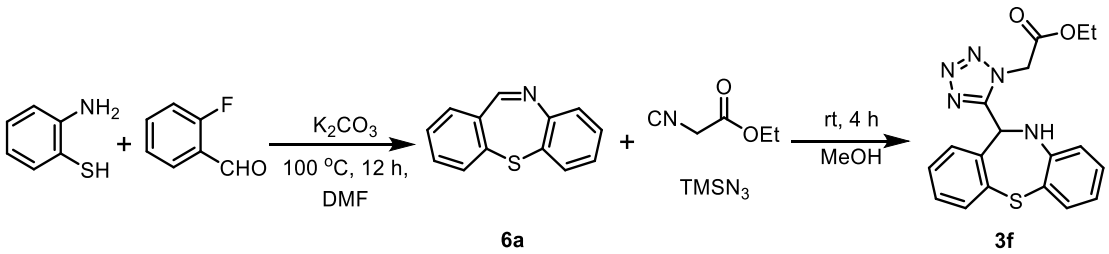
To a stirred solution of the corresponding dibenzothiazepine **6a**-**b** (1.0 mmol) in MeOH (3.0 mL), the corresponding isocyanide (1.0 mmol) and K_2CO_3 (1.5 mmol) are added at room temperature. The reaction mixture is stirred vigorously for 4 h or 12 h. Then, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 4:1-1:1) to give compounds **4a**-**g**.

General procedure for Castagnoli-Cushman reactions (CC-3CR)



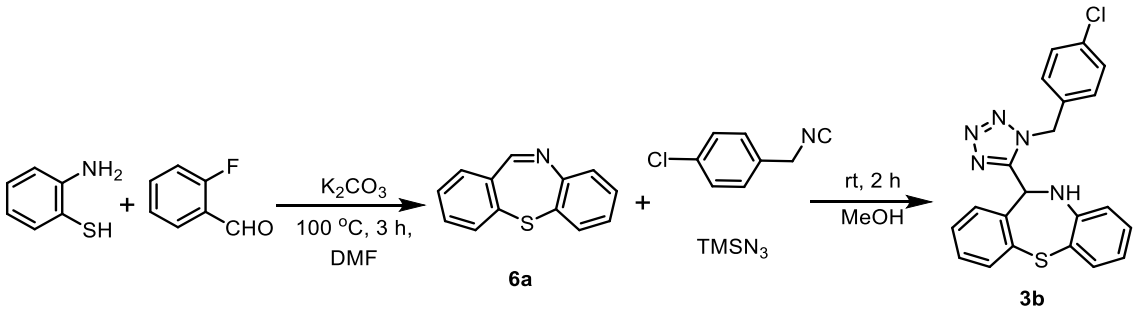
The corresponding dibenzothiazepine (1.0 mmol) and anhydride (1.0 mmol) are stirred at room temperature. Then, the reaction is heated up to 150 °C under neat conditions for 24 - 48 h. The residue is purified by column chromatography (DCM-MeOH, 1:0-20:1) to give compounds **5a**-**d**.

The gram-scale synthesis of 6a and 3f



To a stirred solution of 2-aminobenzenethiol (10.0 mmol) in DMF (30.0 mL), the 2-fluorobenzaldehyde (10.0 mmol) and K_2CO_3 (15 mmol) are added and then warmed up to 100 °C for 12 h. The mixture is washed with water (2 x 100.0 mL), extracted with ethyl acetate (3 x 25.0 mL), the organic layer is dried over Na_2SO_4 and filtered. The solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 8:1-4:1) to give compound **6a** (1.96 g, 93%) as yellow solid. Afterwards, to a stirred solution of the dibenzothiazepine **6a** (5.0 mmol, 1.06 g) in MeOH (5.0 mL), the ethyl 2-isocyanoacetate (5.0 mmol, 0.57 g) and trimethylsilyl azide (5.0 mmol, 0.57 g) are added. The reaction mixture is stirred vigorously for 4 h. Then, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 4:1-1:1) to give compound **3f** (2.97 g, 81%) as green solid.

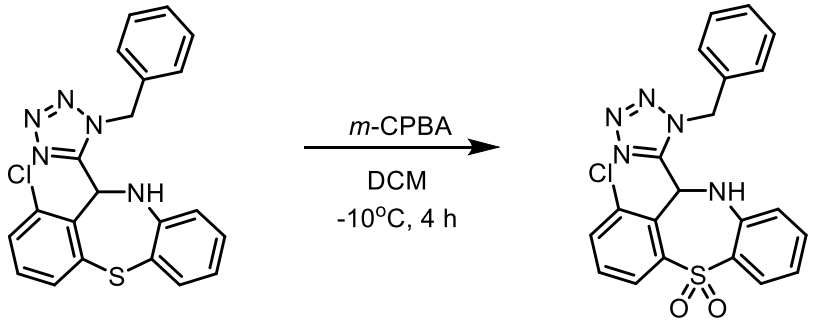
One-pot approach of 11- (1- (4-chlorobenzyl) -1*H*-tetrazol-5-yl) -10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3b)



To a stirred solution of 2-aminobenzenethiol (1.0 mmol) in DMF (3.0 mL), the 2-fluorobenzaldehyde (1.0 mmol) and K_2CO_3 (1.5 mmol) are added and then

warmed up to 100 °C for 3 h. The mixture is washed with water (2 x 10.0 mL), extracted with ethyl acetate (3 x 5.0 mL), the organic layer is dried over Na_2SO_4 and filtered. The solvent is removed under reduced pressure and the obtained, as yellow solid, **6a** directly used in the next step without further purification. Afterwards, to a stirred solution of the **6a** (~1.0 mmol) in MeOH (1.0 mL), the 1-chloro-4- (isocyanomethyl) benzene (1.0 mmol) and trimethylsilyl azide (1.0 mmol) are added. The reaction mixture is stirred vigorously for 2 h. Then, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 8:1-2:1) to give compound **3b** (91%) as white solid.

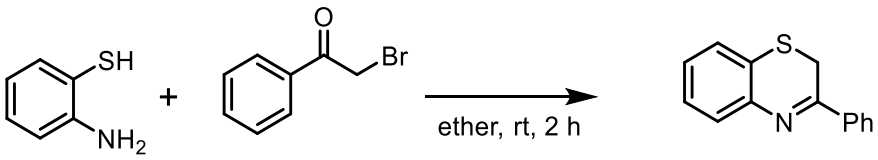
Synthesis of the 11-(1-benzyl-1*H*-tetrazol-5-yl)-1-chloro-10,11-dihydrodibenzo-[*b*,*f*][1,4]thiazepine 5,5-dioxide



3m **7**, 73%

To a stirred solution of **3m** (1.0 mmol) in DCM (3.0 mL), the *m*-CPBA (2.2 mmol) dissolved in DCM (2.0 mL) is added dropwise at 0 °C. The reaction mixture is allowed to stir for 4 h at 0 °C. The reaction suspension is quenched with the aqueous solution of $Na_2S_2O_3$ (5 mL) and stirred at room temperature for 0.5 h, then extracted with DCM (3 x 5.0 mL), the organic layer is dried over Na_2SO_4 and filtered. The solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 10:1-1:1) to give the compound **7** (73%) as colorless solid.

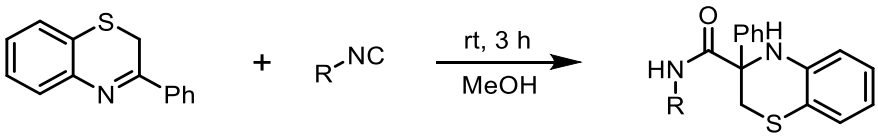
General procedure for the synthesis of dibenzothiazepines



9, 96 %

To a stirred solution of the 2-bromo-1-phenylethan-1-one (11.0 mmol) in diethyl ether (25.0 mL), the 2-aminobenzenethiol (10.0 mmol) dissolved in diethyl ether (5.0 mL) is added at room temperature. After 2 h, the reaction mixture is filtered and the yellow solid is washed with Et_2O and dried.

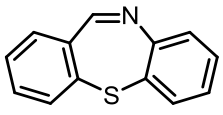
General procedure for the Ugi three-component reactions (U-3CR)



9 **10a-l**

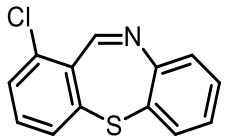
To a stirred solution of the benzothiazepine **9** (1.0 mmol) in MeOH (2.0 mL), the corresponding isocyanide (1.0 mmol) is added. The reaction mixture is stirred vigorously for 3 h. Then, if solid appears, half of the solvent is removed under reduced pressure. The resulting solid is filtered and washed with Et_2O. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA, 4:1-1:1) to give compounds **10a-l**.

Dibenzo[*b*,*f*][1,4]thiazepine (6a)



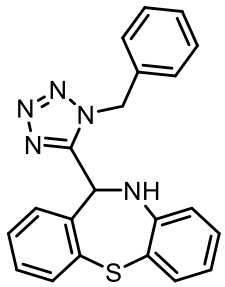
194 mg, 92%, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.45 - 7.35 (m, 5H), 7.34 - 7.31 (m, 2H), 7.19 - 7.16 (m, 1H). The experimental data are in agreement with literature reports.[1]

1-Chlorodibenzo[*b*,*f*][1,4]thiazepine (6b)



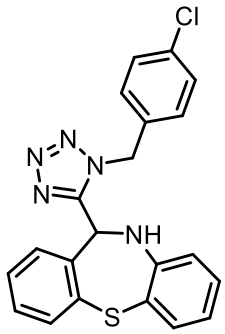
210 mg, 86% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.42 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.35 - 7.26 (m, 5H), 7.17 - 7.14 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.2, 148.6, 143.1, 134.9, 134.07, 132.9, 132.1, 130.2, 129.8, 129.7, 128.5, 127.1, 126.3. The experimental data are in agreement with literature reports.[2]

11-(1-Benzyl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3a)



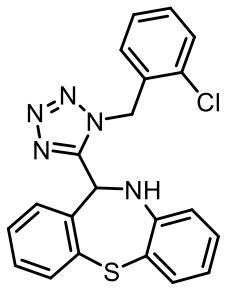
345 mg, 93% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.43 (s, 1H), 7.31 - 7.23 (m, 4H), 7.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.14 (td, *J* = 7.5, 1.1 Hz, 1H), 7.05 - 7.03 (m, 2H), 7.00 - 6.96 (m, 1H), 6.62 (td, *J* = 7.5, 1.0 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.39 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.52, 5.12 (ABq, *J* = 15.1 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 144.8, 140.3, 136.7, 133.0, 132.6, 131.9, 129.7, 129.5, 129.3, 129.2, 128.2, 125.5, 119.4, 118.5, 115.6, 51.9, 51.5. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{17}N_5NaS^+$ $[M + Na]^+$ 394.1102, found 394.1093.

11-(1-(4-Chlorobenzyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3b)



377 mg, 93% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.42 (d, *J* = 5.8 Hz, 1H), 7.29 (td, *J* = 7.6, 1.3 Hz, 1H), 7.19 - 7.15 (m, 3H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 7.00 - 6.94 (m, 3H), 6.62 (td, *J* = 7.7, 1.3 Hz, 1H), 6.51 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.32 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.41, 5.18 (ABq, *J* = 15.2 Hz, 2H), 5.09 (d, *J* = 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 144.7, 140.1, 136.6, 135.5, 133.1, 132.6, 130.4, 129.8, 129.64, 129.56, 129.5, 129.3, 125.6, 119.6, 118.7, 115.8, 51.5, 51.2. **HRMS** (ESI^+) *m/z* calcd. for $C_{21}H_{16}ClN_5NaS^+$ $[M + Na]^+$ 428.0713, found 428.0699.

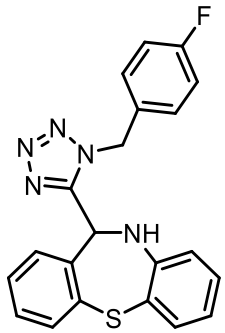
11-(1-(2-Chlorobenzyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3c)



385 mg, 95% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.43 (d, *J* = 6.0 Hz, 1H), 7.28 - 7.12 (m, 6H), 7.05 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.00 - 6.96 (m, 1H), 6.62 (td, *J* = 7.6, 1.3 Hz, 1H), 6.53 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.40 (dd, *J* = 7.7, 1.3 Hz, 1H), 5.58, 5.39 (ABq, *J* = 15.5 Hz, 2H), 5.20 (d, *J* = 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.3, 144.8, 140.2,

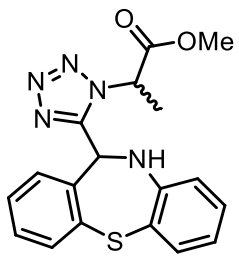
136.9, 133.0, 132.7, 130.7, 130.4, 130.1, 129.7, 129.4, 129.2, 127.6, 125.4, 119.5, 118.6, 115.8, 51.6, 49.3. **HRMS** (ESI$^+$) *m/z* calcd for $C_{21}H_{17}ClN_5S^+$ [M + H]$^+$ 406.0888, found 406.0881.

11-(1-(4-Fluorobenzyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3d)



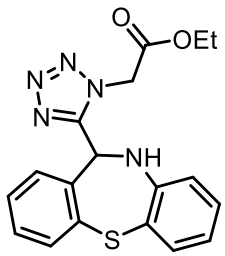
342 mg, 87% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.45 (s, 1H), 7.32 - 7.29 (m, 1H), 7.21 - 7.19 (m, 1H), 7.12 (td, *J* = 7.6, 1.1 Hz, 1H), 7.03 - 6.97 (m, 3H), 6.92 - 6.89 (m, 2H), 6.65 - 6.62 (td, *J* = 7.8, 1.2 Hz, 1H), 6.53 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.35 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.44, 5.18 (d, *J* = 15.2 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{C\text{-}F}$ = 249.5 Hz), 153.9, 144.7, 140.2, 136.6, 133.0, 132.6, 130.2 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 129.7, 129.5, 129.3, 127.8 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 125.6, 119.6, 118.6, 116.2 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 115.7, 51.5, 51.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -111.77. **HRMS** (ESI$^+$) *m/z* calcd for $C_{21}H_{17}FN_5S^+$ [M + H]$^+$ 390.1189, found 390.1192.

2-Methyl 2-(5-(10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1*H*-tetrazol-1-yl) propanoate (3e)



308 mg, 84% yield, yellow solid, *dr>5:3.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.2 Hz, 0.6H), 7.63 (dd, *J* = 7.7, 1.2 Hz, 0.4H), 7.50 (s, 0.6H), 7.47 (s, 0.4H), 7.37 - 7.30 (m, 1H), 7.27 - 7.23 (m, 2H), 7.06 - 7.03 (m, 1H), 6.72 - 6.68 (m, 1.6H), 6.64 - 6.61 (m, 1H), 6.57 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.23 (q, *J* = 7.5 Hz, 0.5H), 4.84 (q, *J* = 7.5 Hz, 0.5H), 3.69 (s, 2H), 3.55 (s, 1H), 1.86 (d, *J* = 7.5 Hz, 1H), 1.81 (d, *J* = 7.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.0, 167.8, 154.6, 144.8, 139.7, 136.4, 136.1, 133.0, 132.80, 132.79, 132.6, 129.8, 129.6, 129.31, 129.28, 129.1, 126.7, 125.7, 120.1, 119.9, 119.02, 118.95, 116.9, 56.2, 55.9, 53.5, 53.1, 52.1, 51.9, 17.3, 16.4. **HRMS** (ESI^+) *m/z* calcd for $C_{18}H_{18}N_5O_2S^+$ $[M + H]^+$ 368.1181, found 368.1172.

Ethyl 2-(5-(10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1*H*-tetrazol-1yl) acetate (3f)



303 mg, 82% yield, yellow solid. mp 72 - 73 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.18, 4.80 (ABq, *J* = 17.6 Hz, 2H), 5.01 (d, *J* = 6.0 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.2, 155.7, 144.9, 139.5, 136.3, 133.1, 133.0, 130.0, 129.53, 129.45, 127.2, 120.2, 119.0, 117.1, 63.0, 53.1, 48.8, 14.1. **HRMS** (ESI^+) *m/z* calcd for $C_{18}H_{18}N_5O_2S^+$ $[M + H]^+$ 368.1181, found 368.1169.

11-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3g)

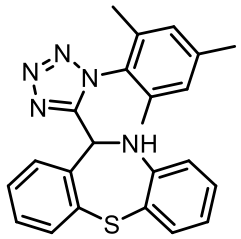
348 mg, 96% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 - 7.65 (m, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.34 (td, *J* = 7.6, 1.0 Hz, 1H), 7.27 - 7.22 (m, 2H), 7.04 - 7.01 (m, 1H), 6.68 (td, *J* = 7.6, 0.7 Hz, 1H), 6.59 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.51 (dd, *J* = 7.7, 1.3 Hz, 1H), 5.18 (d, *J* = 6.0 Hz, 1H), 3.96 - 3.90 (m, 1H), 2.01 - 1.89 (m, 4H), 1.81 - 1.79 (m, 1H), 1.70 - 1.61 (m, 2H), 1.36 - 1.22 (m, 2H), 1.17 - 1.08 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.3, 145.1, 140.8, 136.3, 133.0, 132.7, 129.8, 129.37, 129.35, 125.8, 119.8, 119.0, 116.7, 58.6, 51.7, 33.2, 32.2, 25.3, 25.2, 24.8. **HRMS** (ESI$^+$) *m/z* calcd for $C_{20}H_{22}N_5S^+$ $[M + H]^+$ 364.1596, found 364.1584.

11-(1-Phenyl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3h)

307 mg, 86% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.0 Hz, 1H), 7.60 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.52 - 7.44 (m, 3H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 - 7.25 (m, 1H), 7.24 - 7.22 (m, 2H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.01 - 6.97 (m, 1H), 6.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.63 (td, *J* = 7.6, 1.3 Hz, 1H), 6.54 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.09 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.2, 144.7, 141.3, 136.4, 133.4, 133.0, 132.7, 130.8, 130.0, 129.8,

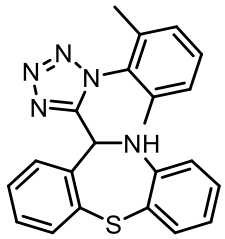
129.6, 129.1, 125.9, 124.4, 119.6, 118.8, 115.8, 51.4. **HRMS** (ESI^+) *m/z* calcd for $C_{20}H_{15}N_5NaS^+$ $[M + Na]^+$ 380.0946, found 380.0937.

11-(1-Mesityl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3i)



323 mg, 81% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 - 7.52 (m, 1H), 7.29 - 7.23 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.05 (s, 1H), 7.00 - 6.96 (m, 2H), 6.86 (s, 1H), 6.61 (td, *J* = 7.5, 1.0 Hz, 1H), 6.49 (dd, *J* = 8.1, 1.2 Hz, 1H), 2.35 (s, 3H), 2.00 (s, 3H), 1.60 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.7, 144.9, 141.4, 140.5, 137.0, 135.5, 135.2, 133.2, 132.7, 129.9, 129.8, 129.6, 129.3, 129.1, 128.7, 126.2, 119.5, 118.9, 116.1, 51.0, 21.3, 17.50, 17.46. **HRMS** (ESI^+) *m/z* calcd for $C_{23}H_{21}N_5NaS^+$ $[M + Na]^+$ 422.1415, found 422.1406.

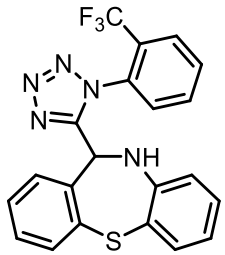
11-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4]thia-zepine (3j)



377 mg, 98% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.28 - 7.21 (m, 3H), 7.15 - 7.12 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.01 - 6.95 (m, 2H), 6.61 (td, *J* = 7.6, 1.2 Hz, 1H), 6.49 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.89 (d, *J* = 7.7 Hz, 1H), 2.04 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.7, 144.8, 140.3, 136.8, 135.9, 135.5, 133.1,

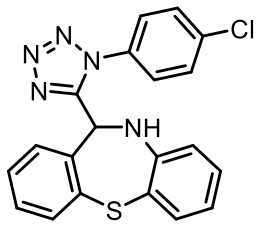
132.6, 131.3, 131.2, 129.6, 129.3, 129.11, 129.08, 129.0, 126.3, 119.5, 118.8, 116.0, 51.3, 17.6, 17.5. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{20}N_5S^+$ $[M + H]^+$ 386.1439, found 386.1429.

11-(1-(2-(Trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] - thiazepine (3k)



370 mg, 87% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.31 - 7.24 (m, 2H), 7.13 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.06 (s, 1H), 6.98 (s, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.71 (s, 1H), 6.61 (td, *J* = 7.6, 1.2 Hz, 1H), 6.34 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.1, 144.6, 140.6, 136.1, 132.93, 132.90 (d, $^3J_{C\text{-}F}$ = 5.0 Hz), 131.5, 130.0, 129.4, 129.2 (d, $^2J_{C\text{-}F}$ = 17.6 Hz), 127.6 (d, $^3J_{C\text{-}F}$ = 5.0 Hz), 127.2, 122.6 (d, $^1J_{C\text{-}F}$ = 274.7 Hz), 119.6, 118.3, 115.7, 53.4. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -59.80. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{15}F_3N_5S^+$ $[M + H]^+$ 426.1000, found 426.0986.

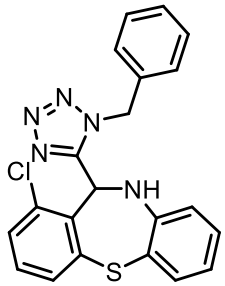
11-(1-(4-Chlorophenyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3l)



375 mg, 96% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 - 7.59 (m, 1H), 7.56 (d, *J* = 6.9 Hz, 1H), 7.43 - 7.40 (m, 2H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H), 7.26

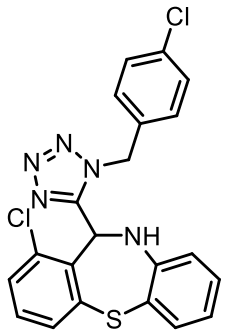
(td, *J* = 7.6, 1.6 Hz, 1H), 7.18 - 7.15 (m, 3H), 7.00 - 6.97 (m, 1H), 6.76 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.63 (td, *J* = 7.7, 1.3 Hz, 1H), 6.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.09 (d, *J* = 6.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.4, 144.6, 141.0, 136.9, 136.4, 133.0, 132.8, 131.8, 130.6, 130.2, 129.9, 129.6, 129.2, 126.0, 125.7, 122.6, 119.7, 118.8, 115.8, 51.6. **HRMS** (ESI^+) *m/z* calcd for $C_{20}H_{14}ClN_5NaS^+$ $[M + Na]^+$ 414.0556, found 414.0548.

11-(1-Benzyl-1*H*-tetrazol-5-yl)-1-chloro-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine (3m)



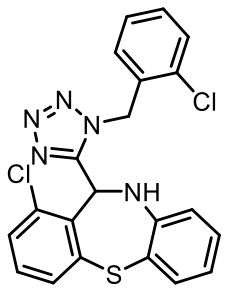
311 mg, 77% yield, colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 - 7.29 (m, 5H), 7.27 - 7.18 (m, 2H), 7.06 (td, *J* = 8.0, 1.5 Hz, 1H), 6.97 - 6.95 (m, 2H), 6.73 (td, *J* = 6.0, 1.0 Hz, 1H), 6.54 (s, 1H), 6.50 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.50, 5.40 (ABq, *J* = 15.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.7, 144.6, 138.1, 136.2, 133.7, 133.6, 133.0, 131.6, 130.5, 130.3, 129.7, 129.1, 128.7, 126.9, 121.0, 119.0, 118.0, 52.0, 51.8. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{16}ClN_5NaS^+$ $[M + Na]^+$ 428.0713, found 428.0704.

1-Chloro-11-(1-(4-chlorobenzyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3n)



369 mg, 84% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 - 7.33 (m, 2H), 7.29 - 7.22 (m, 3H), 7.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.75 (td, *J* = 7.6, 1.2 Hz, 1H), 6.58 - 6.54 (m, 2H), 5.40 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.8, 144.9, 144.5, 136.3, 134.6, 133.6, 133.1, 132.1, 131.7, 130.6, 130.4, 129.9, 129.2, 128.2, 121.0, 119.0, 52.1, 51.1. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{16}Cl_2N_5S^+$ $[M + H]^+$ 440.0503, found 440.0492.

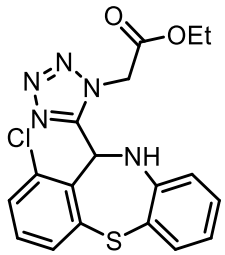
1-Chloro-11-(1-(2-chlorobenzyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (2o)



347 mg, 79% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 - 7.26 (m, 1H), 7.21 (td, *J* = 7.6, 1.5 Hz, 1H), 7.18 - 7.12 (m, 3H), 7.05 - 7.02 (m, 1H), 6.74 -6.69 (m, 2H), 6.56 - 6.55 (m, 2H), 5.58, 5.47 (ABq, *J* = 16.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.2, 144.5, 137.9, 135.8, 133.5, 132.9, 132.2, 131.6, 131.5, 130.4, 130.3, 129.7, 129.6, 128.0,

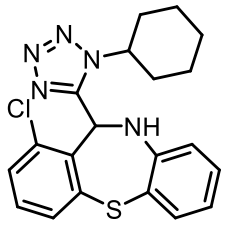
127.3, 120.9, 119.2, 117.7, 52.0, 49.0. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{16}Cl_2N_5S^+$ $[M + H]^+$ 440.0503, found 440.0492.

Ethyl 2-(5-(1-chloro-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepin-11-yl)-1*H*-tetrazol-1-yl) acetate (3p)



289 mg, 72% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 - 7.45 (m, 2H), 7.31 - 7.29 (m, 1H), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.11 - 7.08 (m, 1H), 6.74 (td, *J* = 7.5, 1.0 Hz, 1H), 6.61 - 6.58 (m, 2H), 5.21, 5.10 (ABq, *J* = 17.7 Hz, 2H), 4.30 - 4.18 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.4, 157.2, 144.6, 138.2, 137.0, 133.9, 133.5, 132.1, 130.8, 130.5, 130.0, 120.9, 118.5, 117.0, 62.7, 52.1, 49.7, 14.3. **HRMS** (ESI^+) *m/z* calcd for $C_{18}H_{16}ClN_5NaO_2S^+$ $[M + Na]^+$ 424.0611, found 424.0601.

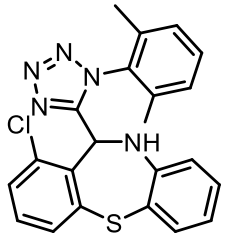
1-Chloro-11-(1-cyclohexyl-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3q)



322 mg, 81% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.39 - 7.37 (m, 1H), 7.30 - 7.27 (m, 2H), 7.07 (td, *J* = 7.0, 1.5 Hz, 1H), 6.82 (td, *J* = 7.5, 1.0 Hz, 1H), 6.70 (d, *J* = 7.0 Hz, 1H), 6.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 3.76 (tt, *J* = 11.6, 3.6 Hz, 1H), 1.81 - 1.76 (m, 2H), 1.74 - 1.70 (m, 2H), 1.59 - 1.56 (m, 2H), 1.19 - 1.10 (m, 2H), 0.96

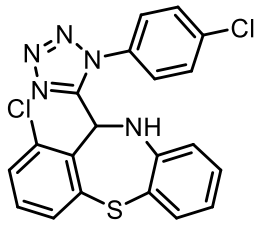
- 0.88 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 145.3, 137.5, 135.0, 134.3, 132.2, 130.9, 130.1, 129.8, 129.7, 122.2, 120.7, 58.9, 52.8, 33.2, 32.4, 25.6, 25.5, 24.8. **HRMS** (ESI^+) *m/z* calcd for $C_{20}H_{21}ClN_5S^+$ $[M + H]^+$ 398.1206, found 398.1194.

1-Chloro-11-(1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*] [1,4]thiazepine (3r)



327 mg, 78% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.18 - 7.14 (m, 2H), 7.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.99 - 6.94 (m, 2H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.33 (dd, *J* = 8.0, 1.0 Hz, 2H), 1.92 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.9, 144.6, 137.9, 137.1, 135.9, 135.4, 133.7, 132.8, 132.5, 132.1, 130.4, 130.0, 129.4, 129.0, 128.4, 119.8, 117.9, 114.8, 51.8, 17.8, 17.6. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{19}ClN_5S^+$ $[M + H]^+$ 420.1050, found 420.1041.

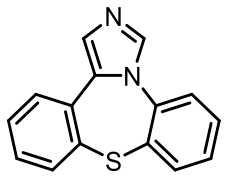
1-Chloro-11-(1-(4-chlorophenyl)-1*H*-tetrazol-5-yl)-10,11-dihydrodibenzo[*b*,*f*][1,4] thiazepine (3s)



302 mg, 71% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 - 7.23 (m, 3H), 7.19 - 7.18 (m, 1H), 7.15 - 7.09 (m, 4H), 7.05 - 7.02 (m, 1H), 6.74 (td, *J* = 7.6, 1.2 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.51

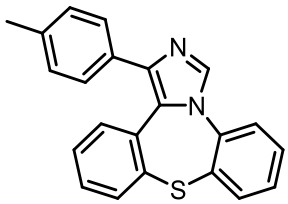
(d, *J* = 5.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4, 144.5, 137.4, 136.6, 136.2, 133.8, 132.5, 131.3, 130.4, 129.8, 129.6, 129.3, 126.9, 121.1, 119.6, 117.7, 52.3. **HRMS** (ESI^+) *m/z* calcd for $C_{20}H_{13}Cl_2N_5NaS^+$ $[M + Na]^+$ 448.0166, found 448.0157.

Dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4a)



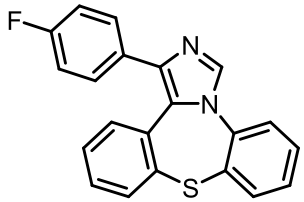
228 mg, 91% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.0 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.61 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.45 - 7.28 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.0, 138.4, 135.0, 134.2, 133.3, 132.6, 131.9, 130.2, 129.9, 129.3, 129.3, 129.0, 128.6, 125.0. **HRMS** (ESI^+) *m/z* calcd for $C_{15}H_{11}N_2S^+$ $[M + H]^+$ 251.0643, found 251.0637.

1-(*p*-Tolyl)dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4b)



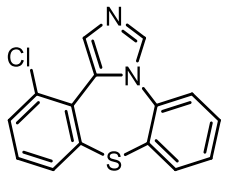
112 mg, 33% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.69 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.49 - 7.43 (m, 4H), 7.36 - 7.32 (m, 2H), 7.29 - 7.26 (m, 1H), 7.19 - 7.16 (m, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.4, 138.7, 137.4, 137.0, 136.5, 134.1, 133.8, 133.0, 132.8, 132.3, 131.5, 130.2, 129.2, 128.94, 128.92, 128.4, 128.2, 127.8, 124.9, 21.4. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{17}N_2S^+$ $[M + H]^+$ 341.1112, found 341.1103.

1-(4-Fluorophenyl)dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4c)



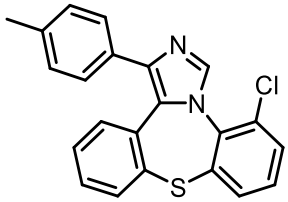
124 mg, 36% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.76 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.72 - 7.70 (m, 1H), 7.56 - 7.54 (m, 2H), 7.50 - 7.45 (m, 2H), 7.36 (td, *J* = 7.5, 2.0 Hz, 1H), 7.32 - 7.29 (m, 2H), 7.21 - 7.18 (m, 1H), 7.03 - 7.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.4 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 138.5, 137.4, 136.7, 134.2, 133.3, 133.1, 132.9, 132.2, 130.3, 130.0 (d, $^{3}J_{C\text{-}F}$ = 7.6 Hz), 129.2, 129.0, 128.7, 128.1, 124.9, 115.4 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.88. **HRMS** (ESI^{+}) *m/z* calcd for $C_{21}H_{13}FN_2NaS^{+}$ [M + Na]$^{+}$ 367.0681, found 367.0672.

13-Chlorodibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4d)



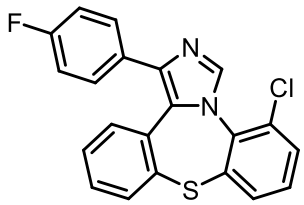
253 mg, 89% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 0.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.58 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.49 - 7.48 (m, 3H), 7.40 - 7.36 (m, 1H), 7.20 (t, *J* = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7, 138.1, 134.6, 133.8, 133.1, 132.7, 131.7, 131.5, 131.3, 130.5, 128.9, 128.8, 128.5, 125.2. **HRMS** (ESI^{+}) *m/z* calcd for $C_{15}H_{10}ClN_2S^{+}$ [M + H]$^{+}$ 285.0253, found 285.0248.

5-Chloro-1-(*p*-tolyl)dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4e)



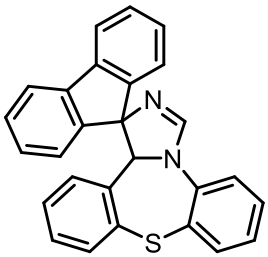
82 mg, 22% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.5 - 7.57 (m, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 - 7.36 (m, 3H), 7.34 - 7.32 (m, 1H), 7.28 - 7.25 (m, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.1, 138.1, 137.5, 135.8, 134.1, 133.5, 131.8, 131.6, 131.4, 130.7, 129.9, 129.4, 128.9, 126.7, 124.8, 124.5, 21.5. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{15}ClN_2NaS^+$ $[M + Na]^+$ 397.0542, found 397.0533.

5-Chloro-1-(4-fluorophenyl)dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine (4f)



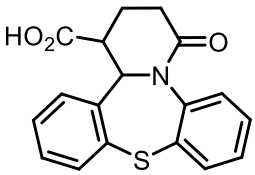
144 mg, 38% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.59 - 7.57 (m, 1H), 7.53 - 7.57 (m, 1H), 7.50 - 7.46 (m, 2H), 7.38 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 - 7.32 (m, 1H), 7.29 - 7.26 (m, 1H), 7.03 - 7.00 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ162.7 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 141.2, 137.9, 137.6, 135.6, 134.2, 133.4, 131.7, 131.5, 131.2, 130.8, 130.2, 129.2, 128.6 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 124.9 (d, $^{4}J_{C\text{-}F}$ = 2.5 Hz), 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 29.8. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -114.33. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{13}ClFN_2S^+$ $[M + H]^+$ 379.0472, found 379.0464.

13b*H*-Spiro[dibenzo[*b*,*f*]imidazo[1,5-*d*][1,4]thiazepine-1,9'-fluorene] (4g)



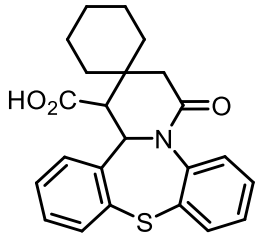
189 mg, 47% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 - 7.68 (m, 4H), 7.51 - 7.46 (m, 5H), 7.33 - 7.30 (m, 2H), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (td, *J* = 7.5, 0.5 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.61 - 6.58 (m, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 5.61 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.8, 144.6, 142.6, 142.0, 139.8, 132.7, 132.1, 130.8, 130.4, 129.2, 128.7, 128.3, 127.8, 127.69, 127.67, 127.5, 127.1, 125.4, 124.8, 124.6, 120.2, 119.5, 73.2. **HRMS** (ESI^+) *m/z* calcd for $C_{27}H_{19}N_2S^+$ $[M + H]^+$ 403.1269, found 403.1258.

cis-4-Oxo-2,3,4,14b-tetrahydro-1*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]thiazepine-1-carboxylic acid (5a)



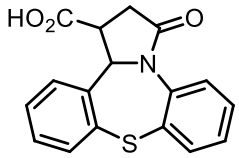
169 mg, isolated yield 52% (*trans*/*cis*: *dr* 1:9), pure *cis*-isomer is obtained after crystallization from aqueous ethanol, yellow solid. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.63 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.51 - 7.45 (m, 2H), 7.41 - 7.31 (m, 3H), 7.29 - 7.26 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 2.5 Hz, 1H), 3.53 (d, *J* = 3.0 Hz, 1H), 2.73 - 2.66 (m, 1H), 2.55 - 2.50 (m, 1H), 2.33 - 2.29 (m, 1H), 1.99 - 1.92 (m, 1H). **^{13}C NMR** (126 MHz, MeOD-d_4) δ 172.7, 145.8, 139.2, 137.6, 135.3, 133.8, 132.7, 131.4, 130.2, 129.8, 129.12, 129.08, 128.7, 64.2, 47.8, 30.2, 20.6. **HRMS** (ESI^+) *m/z* calcd for $C_{18}H_{16}NO_3S^+$ $[M + H]^+$ 326.0845, found 326.0846.

cis-4'-Oxo-1',3',4',14b'-tetrahydrospiro[cyclohexane-1,2'-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]thiazepine]-1'-carboxylic acid (5b)



255 mg, isolated yield 65% (*trans*/*cis*: *dr* 1:3), pure *cis*-isomer is obtained after crystallization from aqueous ethanol, white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.61 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 - 7.35 (m, 3H), 7.31 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.26 - 7.20 (m, 2H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 3.26 (d, *J* = 5.5 Hz, 1H), 2.73, 2.38 (ABq, *J* = 17.5 Hz, 2H), 1.92 - 1.88 (m, 1H), 1.74 - 1.72 (m, 2H), 1.60 - 1.56 (m, 2H), 1.46 - 1.38 (m, 4H), 1.33 - 1.29 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 172.0, 168.8, 142.9, 138.3, 137.7, 134.9, 133.1, 132.0, 130.7, 130.1, 127.9, 127.8, 127.0, 59.5, 36.4, 34.1, 33.9, 25.5, 21.0, 20.8. **HRMS** (ESI$^+$) *m/z* calcd for $C_{23}H_{24}NO_3S^+$ $[M + H]^+$ 394.1471, found 394.1467.

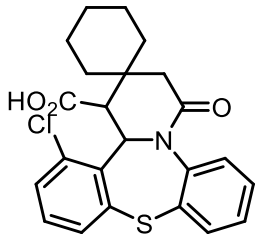
cis-3-Oxo-1,2,3,13b-tetrahydrodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]thiazepine-1-carboxylic acid (5c)



137 mg, isolated yield 44% (*trans*/*cis*: *dr* 5:6), pure *cis*-isomer is obtained after crystallization from aqueous ethanol, brown solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.56 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 - 7.29 (m, 3H), 7.28 - 7.24 (m, 1H), 5.49 (d, *J* = 7.0 Hz, 1H), 3.36 - 3.35 (m, 1H), 2.83 (d, *J* = 9 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 173.3, 171.4, 139.3, 138.9, 134.2, 133.0,

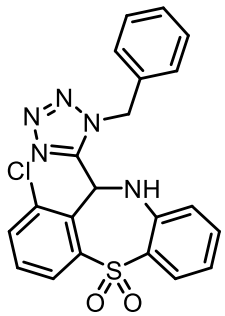
132.0, 129.8, 129.4, 129.1, 128.8, 128.2, 128.0, 63.9, 46.7, 33.6. **HRMS** (ESI^+) *m/z* calcd for $C_{17}H_{14}NO_3S^+$ $[M + H]^+$ 312.0689, found 312.0687.

trans/cis-14-Chloro-4-oxo-1,3,4,14b-tetrahydro-2*H*-dibenzo[*b*,*f*]pyrido[1,2-*d*][1,4]thiaze-pine-1-carboxylic acid (5d)



209 mg, isolated yield 49% (*trans*/*cis*: *dr* 1:10), white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ for *cis*-isomer 12.19 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.51 - 7.47 (m, 1H), 7.44 - 7.43 (m, 2H), 7.37 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 5.60 (d, *J* = 6.0 Hz, 1H), 3.57 (d, *J* = 5.5 Hz, 1H), 2.87,2.37 (ABq, *J* = 17.6 Hz, 2H), 1.96 - 1.92 (m, 1H), 1.75 - 1.71 (m, 1H), 1.67 - 1.65 (m, 2H), 1.52 - 1.35 (m, 6H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ *cis*-isomer 171.6, 168.5, 142.2, 138.8, 138.4, 133.7, 133.6, 133.0, 131.9, 130.34, 130.28, 130.1, 128.4, 128.1, 57.5, 36.2, 34.1, 33.9, 25.4, 21.2, 20.8, 19.8. **HRMS** (ESI^+) *m/z* calcd for $C_{23}H_{22}ClNO_3S^+$ $[M + H]^+$ 428.1082, found 428.1076.

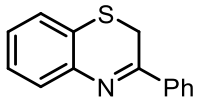
11-(1-Benzyl-1*H*-tetrazol-5-yl)-1-chloro-10,11-dihydrodibenzo[*b*,*f*][1,4]thiazepine 5,5-dioxide (7)



319 mg, 73% yield, colorless solid.**^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.10 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.78 - 7.71 (m, 3H), 7.47 - 7.44 (m,

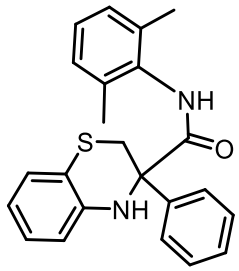
1H), 7.35 - 7.29 (m, 3H), 7.27 - 7.26 (m, 2H), 7.03 - 6.94 (m, 3H), 5.79, 5.73 (ABq, *J* = 15.5 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 154.1, 143.1, 141.3, 135.6, 135.3, 134.1, 133.8, 131.1, 129.6, 128.6, 128.1, 127.9, 126.1, 125.3, 121.2, 120.0, 50.9, 50.6. **HRMS** (ESI$^+$) *m/z* calcd for $C_{21}H_{17}ClN_5O_2S^+$ $[M + H]^+$ 438.0786, found 438.0778.

3-phenyl-2*H*-benzo[*b*][1,4]thiazine(9)



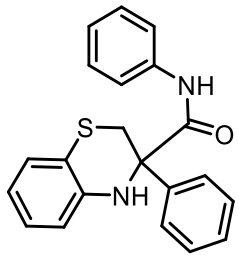
216 mg, 96% yield, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.52 - 8.50 (m, 2H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 2H), 7.50 - 7.44 (m, 3H), 4.16 (d, *J* = 2.0 Hz, 2H).

N-(2,6-dimethylphenyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10a)



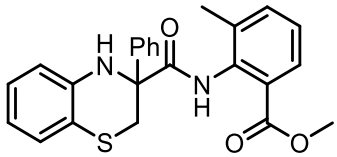
194 mg, 52% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.48 - 7.41 (m, 3H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.11 - 7.05 (m, 4H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.89 - 3.86 (m, 1H), 2.92 (d, *J* = 12.4 Hz, 1H), 2.15 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 142.0, 139.6, 135.4, 133.9, 129.4, 128.9, 128.4, 127.4, 126.4, 126.0, 119.7, 117.2, 116.3, 68.0, 32.7, 29.9, 18.8. **HRMS** (ESI$^+$) *m/z* calcd for $C_{23}H_{23}N_2OS$ $[M + H]^+$ 375.1531, found 375.1531.

N,3-diphenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10b)



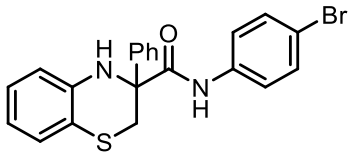
256 mg, 74% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.61 - 7.59 (m, 4H), 7.45 - 7.33 (m, 5H), 7.22 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.16 - 7.13 (m, 1H), 7.09 (td, *J* = 8.0, 1.4 Hz, 1H), 6.84 - 6.79 (m, 2H), 3.93 (d, *J* = 12.4 Hz, 1H), 2.92 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.5, 141.9, 139.6, 137.3, 129.3, 129.2, 129.0, 128.9, 126.5, 125.9, 124.8, 120.1, 119.7, 117.5, 116.2, 68.9, 32.5. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{19}N_2OS$ $[M + H]^+$ 347.1218, found 347.1213.

methyl 3-methyl-2-(3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamido) benzoate (10c)



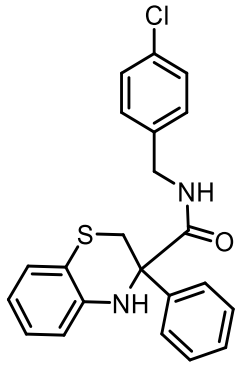
343 mg, 82% yield, orange solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.74 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.65 - 7.64 (m, 2H), 7.44 - 7.37 (m, 4H), 7.21 - 7.18 (m, 2H), 7.09 - 7.06 (m, 1H), 6.84 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.78 (td, *J* = 7.8, 1.0 Hz, 1H), 3.86 (d, *J* = 12.4 Hz, 1H), 3.71 (s, 3H), 3.03 (d, *J* = 12.4 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 167.7, 141.9, 140.0, 136.3, 136.1, 135.4, 129.1, 128.6, 128.5, 128.0, 126.4, 126.0, 125.7, 124.6, 119.0, 116.4, 116.1, 67.7, 52.2, 32.2, 19.5. **HRMS** (ESI^+) *m/z* calcd for $C_{24}H_{23}N_2O_3S$ $[M + H]^+$ 419.1429, found 419.1420.

N-(4-bromophenyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10d)



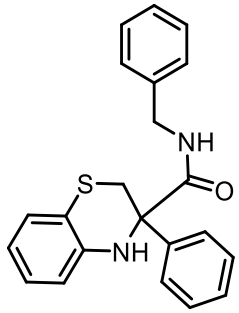
284 mg, 67% yield, brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.57 - 7.56 (m, 2H), 7.51 - 7.49 (m, 2H), 7.45 - 7.40 (m, 4H), 7.27 - 7.21 (m, 1H), 7.11 - 7.08 (m, 1H), 6.83 (td, *J* = 7.6, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.60 - 6.58 (m, 1H), 3.90 (d, *J* = 12.5 Hz, 1H), 2.90 (d, *J* = 12.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.6, 141.6, 139.5, 136.3, 132.0, 129.4, 129.2, 129.0, 126.6, 125.8, 121.7, 119.8, 117.5, 117.4, 116.2, 69.1, 32.5. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{18}BrN_2OS$ $[M + H]^+$ 425.0323, found 425.0316.

N-(4-chlorobenzyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10e)



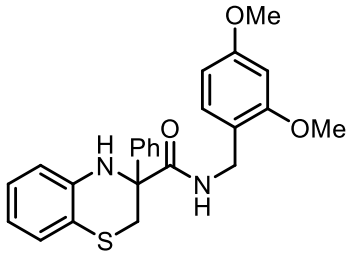
311 mg, 79% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 - 7.50 (m, 3H), 7.43 - 7.38 (m, 3H), 7.24 - 7.19 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.03 - 7.00 (m, 1H), 6.79 (td, *J* = 7.7, 1.0 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.54 - 4.41 (m, 2H), 3.80 (d, *J* = 12.4 Hz, 1H), 2.89 (d, *J* = 12.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.4, 141.8, 139.7, 136.6, 133.1, 129.2, 128.81, 128.76, 128.73, 128.68, 126.3, 125.9, 119.3, 116.9, 116.0, 67.7, 43.0, 32.5. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{20}ClN_2OS$ $[M + H]^+$ 395.0985, found 395.0978.

N-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10f)



238 mg, 66% yield, colorless solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 - 7.55 (m, 2H), 7.44 - 7.38 (m, 4H), 7.31 - 7.21 (m, 5H), 7.04 - 7.00 (m, 1H), 6.80 - 6.77 (m, 1H), 6.65 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.63 - 4.52 (m, 2H), 4.37 (s, 1H), 3.86 (d, *J* = 12.3 Hz, 1H), 2.91 (d, *J* = 12.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.2, 142.0, 139.7, 138.1, 129.2, 128.9, 128.8, 128.7, 128.6, 128.0, 127.7, 127.6, 127.4, 126.3, 126.2, 125.9, 119.2, 118.9, 117.0, 116.0, 67.9, 43.7, 32.5. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{21}N_2OS$ $[M + H]^+$ 361.1375, found 361.1369.

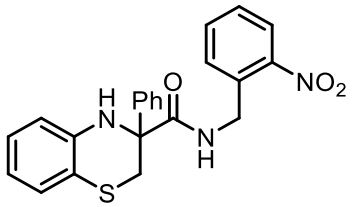
N-(2,4-dimethoxybenzyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10g)



214 mg, 51% yield, brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 - 7.48 (m, 3H), 7.39 - 7.36 (m, 3H), 7.18 - 7.15 (m, 2H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.42 - 6.39 (m, 2H), 4.55 - 4.51 (m, 1H), 4.42 - 4.34 (m, 2H), 3.81 (d, *J* = 1.0 Hz, 3H), 3.61 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.7, 142.2, 140.1, 130.3, 129.1, 126.1, 118.9, 115.7,

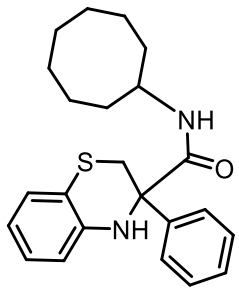
103.7, 98.5, 67.4, 55.4, 55.1, 39.6, 32.3, 29.7. **HRMS** (ESI$^+$) *m/z* calcd for $C_{24}H_{25}N_2O_3S$ $[M + H]^+$ 421.1586, found 421.1581.

N-(2-nitrobenzyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10h)



348 mg, 86% yield, white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.85 (t, *J* = 6.0 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 - 7.36 (m, 6H), 7.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.06 - 7.02 (m, 1H), 6.77 (td, *J* = 7.6, 1.2 Hz, 1H), 6.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.94 - 4.90 (m, 2H), 4.38 (s, 1H), 3.78 (d, *J* = 12.3 Hz, 1H), 2.91 (d, *J* = 12.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.7, 141.6, 139.5, 133.9, 133.5, 131.7, 129.2, 128.7, 128.54, 128.48, 126.4, 125.8, 125.1, 119.4, 116.6, 116.1, 67.5, 41.7, 32.5. **HRMS** (ESI$^+$) *m/z* calcd for $C_{22}H_{20}N_3O_3S$ $[M + H]^+$ 406.1225, found 406.1220.

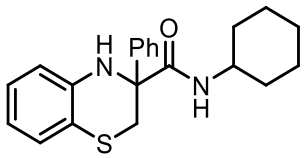
N-cyclooctyl-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10i)



297 mg, 78% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5 Hz, 2H), 7.42 - 7.36 (m, 3H), 7.19 - 7.17 (m, 1H), 7.05 - 7.02 (m, 2H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.35 (s, 1H), 4.10 - 4.07 (m, 1H), 3.80 (d,

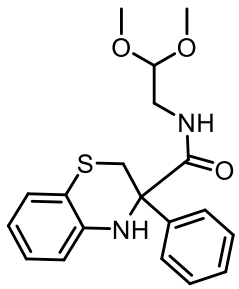
J = 12.3 Hz, 1H), 2.89 (d, *J* = 12.3 Hz, 1H), 1.86 - 1.80 (m, 2H), 1.66 - 1.49 (m, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.8, 142.3, 140.0, 129.3, 128.9, 128.7, 126.3, 126.1, 119.2, 117.2, 115.9, 67.5, 50.0, 32.7, 32.6, 32.4, 27.3, 27.2, 25.6, 23.8, 23.7. **HRMS** (ESI^+) *m/z* calcd for $C_{23}H_{29}N_2OS$ $[M + H]^+$ 381.2001, found 381.1957.

N-cyclohexyl-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10j)



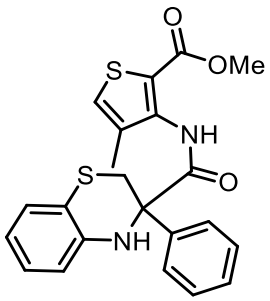
253 mg, 72% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 - 7.53 (m, 2H), 7.42 - 7.34 (m, 3H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.06 - 7.02 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.77 (td, *J* = 7.6, 1.2 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.1 Hz, 1H), 3.91 - 3.86 (m, 1H), 3.80 (d, *J* = 12.3 Hz, 1H), 2.88 (d, *J* = 12.3 Hz, 1H), 1.96 - 1.88 (m, 2H), 1.70 - 1.68 (m, 1H), 1.63 - 1.59 (m, 2H), 1.42 - 1.34 (m, 2H), 1.24 - 1.10 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.1, 142.2, 139.9, 129.1, 128.8, 128.5, 126.2, 126.0, 119.1, 117.1, 115.7, 67.6, 48.6, 33.0, 32.9, 32.6, 25.5, 24.8, 24.6. **HRMS** (ESI^+) *m/z* calcd for $C_{21}H_{25}N_2OS$ $[M + H]^+$ 353.1688, found 353.1684.

N-(2,2-dimethoxyethyl)-3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamide (10k)



290 mg, 81% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 2H), 7.43 - 7.37 (m, 3H), 7.31 - 7.29 (m, 1H), 7.16 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.05 - 7.02 (m, 1H), 6.76 (td, *J* = 7.7, 1.0 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.40 (s, 1H), 4.38 - 4.36 (m, 1H), 3.79 (d, *J* = 12.3 Hz, 1H), 3.58 - 3.53 (m, 1H), 3.42 - 3.38 (m, 1H), 3.36 (s, 3H), 3.25 (s, 3H), 2.92 (d, *J* = 12.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.5, 141.8, 139.6, 129.2, 128.7, 128.6, 126.3, 125.9, 119.1, 116.5, 115.9, 103.1, 67.4, 55.3, 54.3, 41.6, 32.1. **HRMS** (ESI^+) *m/z* calcd for $C_{19}H_{23}N_2O_3S$ $[M + H]^+$ 359.1429, found 359.1424.

methyl 4-methyl-3-(3-phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine-3-carboxamido) thiophene-2-carboxylate (10l)



386 mg, 91% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.67 - 7.65 (m, 2H), 7.45 - 7.37 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.08 - 7.05 (m, 1H), 6.82 - 6.76 (m, 2H), 3.90 - 3.85 (m, 2H), 3.72 (d, *J* = 1.4 Hz, 3H), 3.02 (dd, *J* = 12.3, 1.3 Hz, 1H), 2.27 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.5, 163.1, 141.7, 139.7, 136.5, 129.2, 128.7, 127.5, 126.4, 125.8, 119.2, 118.5, 116.4, 116.2, 67.9, 51.8, 31.8, 15.9. **HRMS** (ESI^+) *m/z* calcd for $C_{22}H_{21}N_2O_3S_2$ $[M + H]^+$ 425.0994, found 425.0989.

3. Single crystal x-ray structure determination

*Data for compound **4b***

A specimen of $C_{22}H_{16}N_2S$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å). The integration of the data using a monoclinic unit cell yielded a total of 10844 reflections to a maximum θ angle of 54.18° (0.95 Å resolution), of which 2016 are independent (average redundancy 5.379, completeness = 99.5%, R_{int} = 1.84%, R_{sig} = 1.35%) and 1953 (96.88%) are greater than 2σ (F^2). The final cell constants of a = 7.49800 (10) Å, b = 11.1798 (2) Å, c = 20.0199 (4) Å, β = 96.2350 (10) °, volume = 1668.26 (5) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ (I). The structure is solved and refined using the Bruker SHELXTL Software Package, using the space groupP 1 21/n 1, with Z = 4 for the formula unit, $C_{22}H_{16}N_2S$. The final anisotropic full-matrix least-squares refinement on F^2 with 227 variables converged at R1 = 3.20%, for the observed data and wR2 = 12.93% for all data. The goodness-of-fit is 1.261. The largest peak in the final difference electron density synthesis is 0.204 $e^-/Å^3$ and the largest hole is -0.282 $e^-/Å^3$ with an RMS deviation of 0.041 $e^-/Å^3$. On the basis of the final model, the calculated density is 1.355 g/cm^3 and F (000), 712 e^-. The CCDC access number is: 2123182.

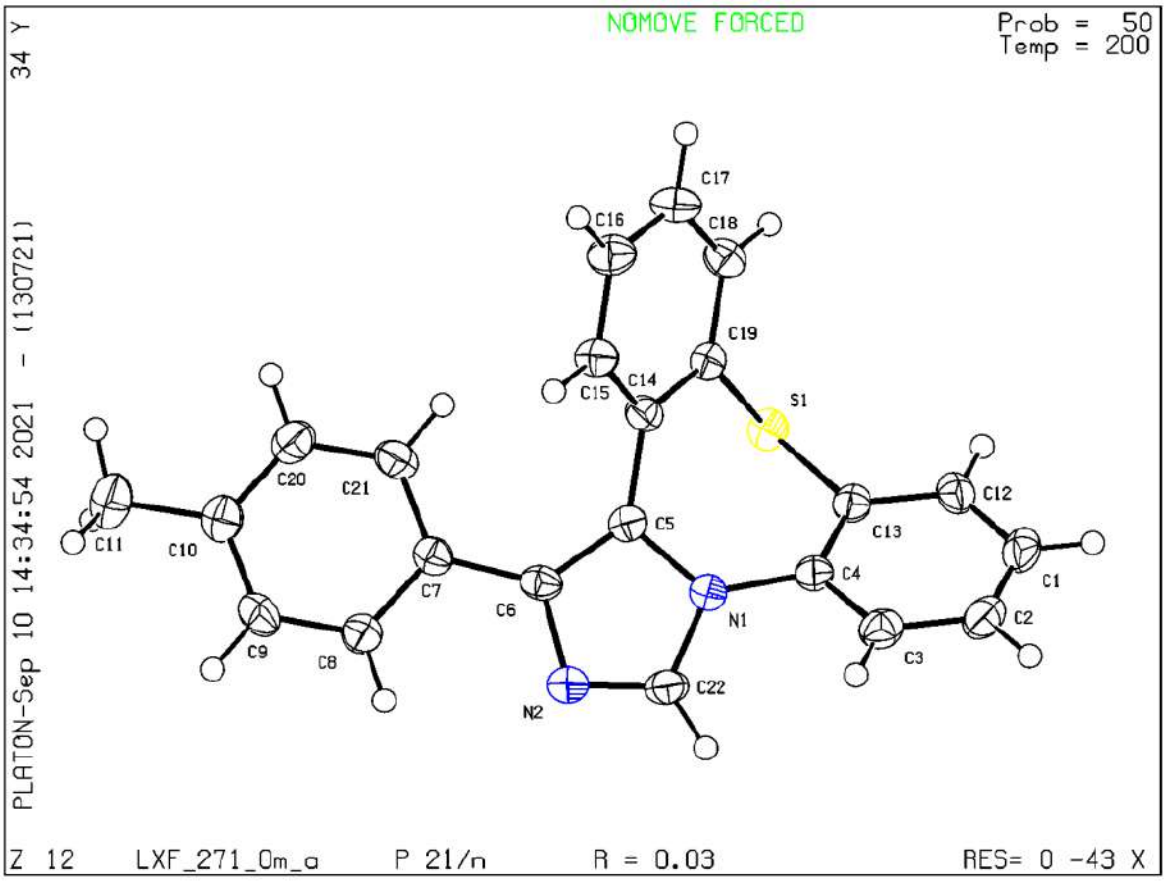


Table 1 Sample and crystal data for **4b**.

Identification code	LXF_271	
Chemical formula	$C_{22}H_{16}N_2S$	
Formula weight	340.43 g/mol	
Temperature	200 (2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 7.49800 (10) Å	α = 90°
	b = 11.1798 (2) Å	β = 96.2350 (10) °

	c = 20.0199 (4) Å	γ = 90°
Volume	1668.26 (5) $Å^3$	
Z	4	
Density (calculated)	1.355 g/cm^3	
Absorption coefficient	1.751 mm^{-1}	
F (000)	712	

Table 2 Data collection and structure refinement for **4b**.

Theta range for data collection	4.44 to 54.18°
Index ranges	-7<=h<=7, -11<=k<=11, -21<=l<=21
Reflections collected	10844
Independent reflections	2016 [R (int) = 0.0184]
Structure solution technique	direct methods
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)
Function minimized	$\Sigma w (F_o^2 - F_c^2)^2$
Data / restraints / parameters	2016 / 0 / 227
Goodness-of-fit on F^2	1.261

Δ/σ_{max}	0.001	
Final R indices	1953 data, I>2σ (I)	R1 = 0.0320, wR2 = 0.1274
	all data	R1 = 0.0327, wR2 = 0.1293
Weighting scheme	$w=1/[\sigma^2 (F_o^2) + (0.1000P)^2]$ where $P= (F_o^2+2F_c^2) /3$	
Largest diff. peak and hole	0.204 and -0.282 eÅ^{-3}	
R.M.S. deviation from mean	0.041 eÅ^{-3}	

*Data for compound **3g***

A specimen of $C_{20}H_{21}N_5S$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å). The integration of the data using a monoclinic unit cell yielded a total of 15201 reflections to a maximum θ angle of 65.20° (0.85 Å resolution), of which 3144 are independent (average redundancy 4.835, completeness = 99.6%, R_{int} = 3.52%, R_{sig} = 2.73%) and 2951 (93.86%) are greater than 2σ (F^2). The final cell constants of a = 13.9465 (6) Å, b = 10.9246 (4) Å, c =12.7740 (5) Å, β = 108.4690 (10) °, volume = 1846.00 (13) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ (I). The structure is solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{20}H_{21}N_5S$. The final anisotropic full-matrix least-squares refinement on F^2 with 242 variables converged at R1 = 4.31%, for the observed data and wR2 = 15.75% for all data. The goodness-of-fit is 1.386. The largest peak in the final difference electron density synthesis is 0.347 e$^-$/Å^3 and the largest hole is -0.378 e$^-$/Å^3 with an RMS deviation of 0.060 e$^-$/Å^3. On the

basis of the final model, the calculated density is1.308 g/cm^3 and F (000), 768 e$^-$. The CCDC access number is: 2123183.

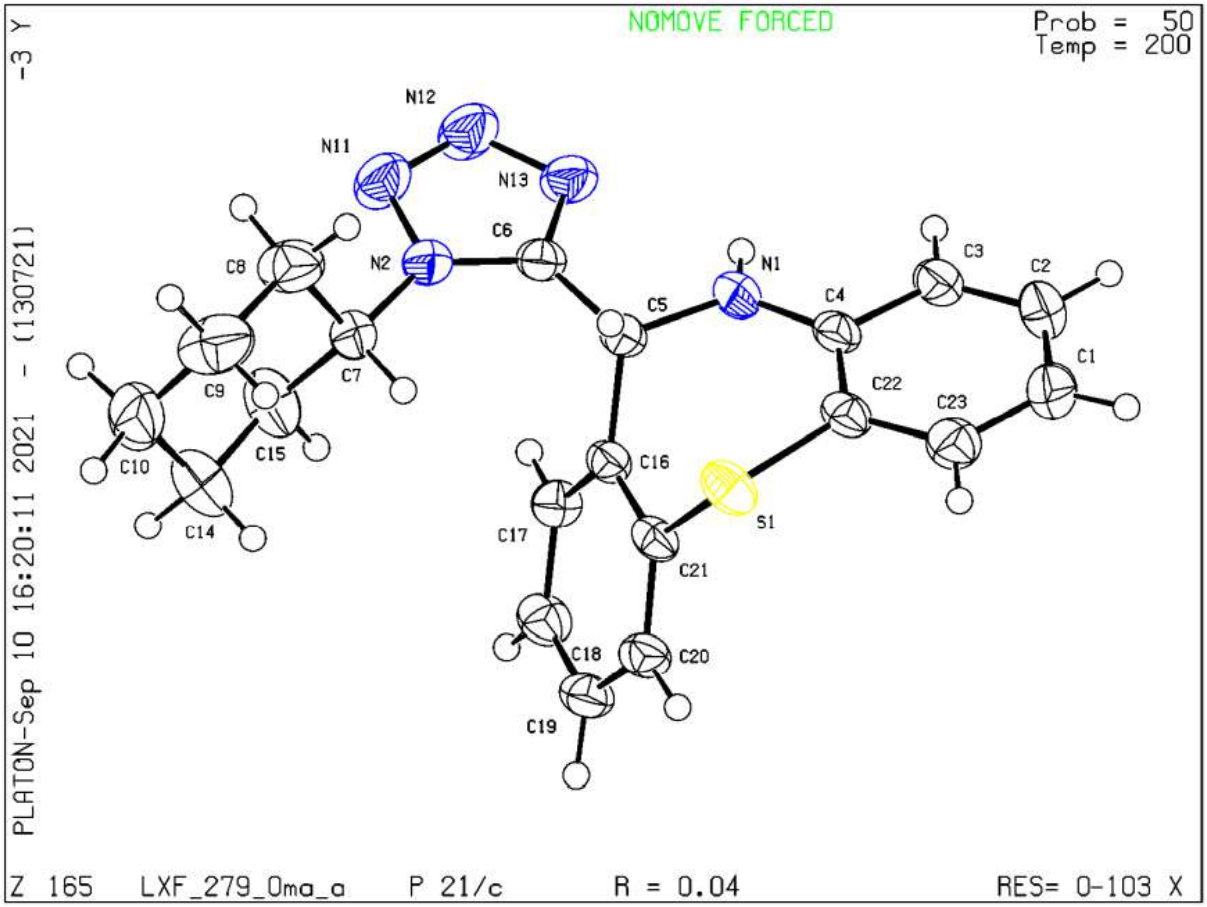


Table 3 Sample and crystal data for **3g**.

Identification code	LXF_279
Chemical formula	$C_{20}H_{21}N_5S$
Formula weight	363.48 g/mol
Temperature	200 (2) K
Wavelength	1.54178 Å
Crystal system	monoclinic

Space group	P 1 21/c 1	
Unit cell dimensions	a = 13.9465 (6) Å	α = 90°
	b = 10.9246 (4) Å	β = 108.4690 (10) °
	c = 12.7740 (5) Å	γ = 90°
Volume	1846.00 (13) $Å^3$	
Z	4	
Density (calculated)	1.308 g/cm^3	
Absorption coefficient	1.657 mm^{-1}	
F (000)	768	

Table 4 Data collection and structure refinement for **3g**.

Theta range for data collection	5.25 to 65.20°
Index ranges	-15<=h<=16, -12<=k<=12, -15<=l<=14
Reflections collected	15201
Independent reflections	3144 [R (int) = 0.0352]
Structure solution technique	direct methods

Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	Σ w (F_o^2 - F_c^2) ^{2}	
Data / restraints / parameters	3144 / 0 / 242	
Goodness-of-fit on F^2	1.386	
Final R indices	2951 data, I>2σ (I)	R1 = 0.0431, wR2 = 0.1530
	all data	R1 = 0.0452, wR2 = 0.1575
Weighting scheme	w=1/[σ^2 (F_o^2) + (0.1000P) ^{2}] where P= (F_o^2+2F_c^2) /3	
Largest diff. peak and hole	0.347 and -0.378 eÅ^{-3}	
R.M.S. deviation from mean	0.060 eÅ^{-3}	

*Data for compound **7***

A specimen of $C_{21}H_{16}ClN_5O_2S$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å). The crystal is kept at 200.02 K during data collection. Using Olex2 [1], the structure is solved with the olex2.solve [2] structure solution program using Charge Flipping and refined

with the SHELXL [3] refinement package using Least Squares minimization. Crystal Data for $C_{21}H_{16}ClN_5O_2S$ (*M* =437.90 g/mol) : triclinic, space group P-1 (no. 2), *a* = 6.5091 (2) Å, *b* = 11.8470 (3) Å, *c* = 12.2806 (3) Å, *α* = 89.7040 (10) °, *β* = 85.3440 (10) °, *γ* = 82.9030 (10) °, *V* = 936.63 (4) Å^3, *Z* = 2, *T* = 200.02 K, μ (CuKα) = 3.114 mm^{-1}, *Dcalc* = 1.553 g/cm^3, 15310 reflections measured (7.52° ≤ 2Θ ≤ 117.952°), 2672 unique (R_{int} = 0.0186, R_{sigma} = 0.0152) which are used in all calculations. The final R_1 is 0.0288 (I > 2σ (I)) and wR_2 is 0.0762 (all data). The CCDC access number is: 2123184.

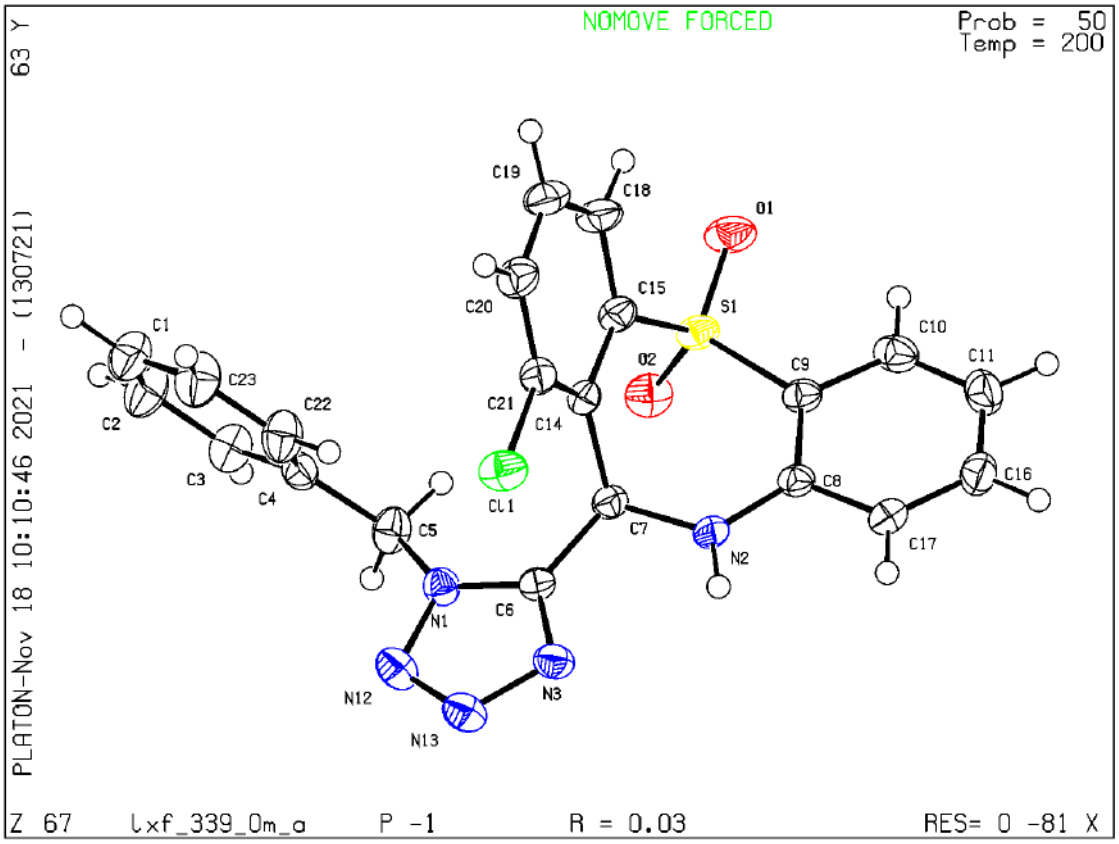


Table 5 Crystal data and structure refinement for **7**.

Identification code	LXF_339_0m_a
Empirical formula	$C_{21}H_{16}ClN_5O_2S$
Formula weight	437.90

Temperature/K	200.02
Crystal system	triclinic
Space group	P-1
a/Å	6.5091 (2)
b/Å	11.8470 (3)
c/Å	12.2806 (3)
α/°	89.7040 (10)
β/°	85.3440 (10)
γ/°	82.9030 (10)
Volume/$Å^3$	936.63 (4)
Z	2
$\rho_{calc}g/cm^3$	1.553
μ/mm^{-1}	3.114
F (000)	452.0
Crystal size/mm^3	0.2 × 0.08 × 0.04
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.52 to 117.952
Index ranges	-7 ≤ h ≤ 7, -13 ≤ k ≤ 13, -13 ≤ l ≤ 13
Reflections collected	15310
Independent reflections	2672 [R_{int} = 0.0186, R_{sigma} = 0.0152]
Data/restraints/parameters	2672/0/271
Goodness-of-fit on F^2	1.029

Final R indexes [I>=2σ (I)]	R_1 = 0.0288, wR_2 = 0.0760
Final R indexes [all data]	R_1 = 0.0290, wR_2 = 0.0762
Largest diff. peak/hole / e Å^{-3}	0.36/-0.39

Table 6 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **7**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U (eq)
Cl1	8037.7 (7)	3302.5 (4)	7676.4 (4)	34.42 (15)
S1	2013.8 (6)	2496.9 (4)	5006.9 (4)	26.69 (14)
O1	631 (2)	3212.3 (11)	4369.4 (11)	38.1 (3)
O2	1139.7 (18)	1617.1 (11)	5640.1 (10)	33.4 (3)
N1	5111 (2)	1172.3 (12)	8480.1 (11)	25.4 (3)
N2	6635 (2)	1250.0 (12)	5533.7 (11)	25.4 (3)
N3	8072 (2)	643.9 (12)	7581.5 (12)	27.8 (3)
C1	830 (3)	4116.0 (17)	11092.5 (17)	41.1 (5)
C2	-340 (3)	3252.2 (18)	10946.1 (17)	41.7 (5)
C3	372 (3)	2383.4 (17)	10208.2 (15)	34.7 (4)
C4	2261 (3)	2381.0 (15)	9603.6 (14)	27.2 (4)
C5	2873 (3)	1429.0 (16)	8784.5 (15)	31.0 (4)
C6	6182 (3)	1145.6 (14)	7495.9 (13)	22.7 (4)
C7	5291 (3)	1639.8 (14)	6486.6 (13)	23.3 (4)

Atom	*x*	*y*	*z*	U (eq)
C8	6099 (3)	1413.5 (13)	4475.2 (13)	22.4 (4)
C9	4162 (3)	1903.4 (14)	4131.8 (14)	24.4 (4)
C10	3842 (3)	1974.5 (15)	3015.4 (15)	31.5 (4)
C11	5393 (3)	1589.1 (16)	2234.8 (15)	35.8 (5)
N12	6400 (2)	678.6 (14)	9206.3 (12)	32.2 (4)
N13	8164 (2)	371.8 (13)	8660.3 (12)	32.3 (4)
C14	4779 (3)	2940.6 (14)	6495.8 (13)	23.2 (4)
C15	3169 (3)	3399.6 (15)	5873.5 (14)	25.9 (4)
C16	7313 (3)	1135.6 (15)	2563.3 (15)	32.1 (4)
C17	7657 (3)	1045.2 (14)	3647.3 (14)	26.8 (4)
C18	2555 (3)	4561.9 (15)	5815.1 (16)	32.7 (4)
C19	3554 (3)	5303.2 (16)	6380.8 (16)	35.2 (4)
C20	5221 (3)	4890.9 (15)	6944.9 (15)	32.3 (4)
C21	5840 (3)	3726.7 (15)	6986.2 (14)	26.3 (4)
C22	3441 (3)	3249.9 (17)	9761.5 (16)	37.6 (5)
C23	2725 (3)	4112.0 (18)	10504.7 (17)	43.2 (5)

Table 7 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **7**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	31.1 (3)	30.8 (3)	42.8 (3)	-2.99 (19)	-13.1 (2)	-2.86 (19)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	19.2 (2)	25.7 (2)	34.7 (3)	-1.36 (18)	-6.46 (18)	1.91 (17)
O1	30.6 (7)	34.5 (7)	48.4 (8)	-2.2 (6)	-16.6 (6)	7.8 (6)
O2	21.0 (6)	37.4 (7)	42.3 (8)	1.5 (6)	-2.5 (5)	-5.3 (5)
N1	23.9 (8)	28.8 (8)	23.8 (8)	0.4 (6)	-2.7 (6)	-3.7 (6)
N2	22.1 (7)	27.1 (8)	24.3 (8)	-0.9 (6)	-2.2 (6)	7.2 (6)
N3	25.5 (8)	27.3 (8)	29.9 (8)	4.5 (6)	-3.8 (6)	0.6 (6)
C1	46.0 (12)	36.6 (11)	39.6 (11)	-10.2 (9)	3.2 (9)	-5.2 (9)
C2	34.8 (11)	44.5 (12)	44.4 (12)	-10.2 (10)	10.0 (9)	-7.2 (9)
C3	32.0 (10)	35.5 (11)	37.4 (11)	-5.6 (8)	1.9 (8)	-9.7 (8)
C4	28.2 (9)	30.6 (10)	22.7 (9)	1.8 (7)	-4.1 (7)	-2.4 (8)
C5	23.6 (9)	39.7 (11)	29.9 (10)	-5.2 (8)	0.6 (7)	-6.1 (8)
C6	24.4 (9)	18.9 (8)	24.7 (9)	-0.1 (7)	-2.0 (7)	-2.2 (7)
C7	22.0 (9)	22.6 (9)	24.6 (9)	-0.9 (7)	-1.8 (7)	0.3 (7)
C8	25.3 (9)	16.5 (8)	25.5 (9)	0.0 (7)	-2.8 (7)	-2.5 (7)
C9	25.6 (9)	19.3 (8)	28.6 (9)	-0.7 (7)	-4.2 (7)	-2.7 (7)
C10	36.0 (10)	26.3 (10)	33.8 (10)	0.9 (8)	-13.6 (8)	-3.6 (8)
C11	50.8 (12)	33.5 (11)	24.2 (9)	-1.2 (8)	-6.3 (9)	-7.1 (9)
N12	32.2 (9)	37.5 (9)	27.8 (8)	5.9 (7)	-7.0 (7)	-5.7 (7)
N13	31.0 (9)	33.6 (9)	32.5 (9)	6.2 (7)	-7.3 (7)	-2.1 (7)
C14	22.1 (9)	23.7 (9)	22.1 (8)	-0.3 (7)	2.3 (7)	1.1 (7)
C15	21.8 (9)	25.9 (9)	28.6 (9)	-1.7 (7)	-0.3 (7)	1.2 (7)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C16	39.7 (11)	28.6 (10)	27.2 (10)	-4.4 (8)	3.4 (8)	-4.6 (8)
C17	26.4 (9)	22.5 (9)	30.4 (10)	-2.9 (7)	-0.4 (7)	0.1 (7)
C18	28.9 (10)	26.5 (10)	41.0 (11)	-0.3 (8)	-6.9 (8)	6.5 (8)
C19	39.7 (11)	21.6 (9)	42.3 (11)	-1.2 (8)	-3.8 (9)	4.3 (8)
C20	37.6 (11)	25.0 (10)	34.4 (10)	-4.2 (8)	-2.4 (8)	-5.0 (8)
C21	25.4 (9)	28.1 (10)	24.8 (9)	-0.2 (7)	-2.2 (7)	-0.6 (7)
C22	36.8 (11)	42.7 (11)	34.1 (11)	-3.8 (9)	5.3 (9)	-13.1 (9)
C23	50.2 (13)	38.8 (12)	42.9 (12)	-7.6 (9)	3.5 (10)	-19.0 (10)

Table 8 Bond Lengths for **7**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C21	1.7415 (18)	C4	C22	1.382 (3)
S1	O1	1.4353 (13)	C6	C7	1.497 (2)
S1	O2	1.4427 (13)	C7	C14	1.536 (2)
S1	C9	1.7679 (17)	C8	C9	1.417 (2)
S1	C15	1.7837 (18)	C8	C17	1.407 (2)
N1	C5	1.469 (2)	C9	C10	1.404 (3)

Atom	Atom	Length/ Å	Atom	Atom	Length/Å
N1	C6	1.344 (2)	C10	C11	1.371 (3)
N1	N12	1.355 (2)	C11	C16	1.388 (3)
N2	C7	1.445 (2)	N12	N13	1.294 (2)
N2	C8	1.380 (2)	C14	C15	1.401 (2)
N3	C6	1.311 (2)	C14	C21	1.392 (3)
N3	N13	1.366 (2)	C15	C18	1.389 (3)
C1	C2	1.370 (3)	C16	C17	1.369 (3)
C1	C23	1.377 (3)	C18	C19	1.377 (3)
C2	C3	1.385 (3)	C19	C20	1.373 (3)
C3	C4	1.383 (3)	C20	C21	1.390 (3)
C4	C5	1.509 (3)	C22	C23	1.384 (3)

Table 9 Bond Angles for **7**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O1	S1	O2	116.90 (8)	N2	C8	C17	115.96 (15)
O1	S1	C9	108.39 (8)	C17	C8	C9	116.68 (15)
O1	S1	C15	107.47 (8)	C8	C9	S1	125.30 (13)
O2	S1	C9	110.38 (8)	C10	C9	S1	114.33 (13)
O2	S1	C15	110.23 (8)	C10	C9	C8	120.34 (16)
C9	S1	C15	102.45 (8)	C11	C10	C9	121.12 (17)

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C6	N1	C5	130.52 (15)	C10	C11	C16	118.90 (17)
C6	N1	N12	107.81 (14)	N13	N12	N1	106.39 (13)
N12	N1	C5	120.47 (14)	N12	N13	N3	110.97 (14)
C8	N2	C7	123.84 (14)	C15	C14	C7	116.80 (15)
C6	N3	N13	105.53 (14)	C21	C14	C7	127.25 (15)
C2	C1	C23	119.53 (19)	C21	C14	C15	115.75 (15)
C1	C2	C3	120.25 (19)	C14	C15	S1	119.91 (13)
C4	C3	C2	120.59 (18)	C18	C15	S1	117.39 (14)
C3	C4	C5	117.03 (16)	C18	C15	C14	122.39 (16)
C22	C4	C3	118.87 (17)	C17	C16	C11	121.10 (17)
C22	C4	C5	124.07 (16)	C16	C17	C8	121.83 (17)
N1	C5	C4	115.51 (15)	C19	C18	C15	119.63 (17)
N1	C6	C7	123.54 (15)	C20	C19	C18	119.66 (17)
N3	C6	N1	109.29 (15)	C19	C20	C21	120.15 (17)
N3	C6	C7	127.16 (15)	C14	C21	Cl1	121.63 (13)
N2	C7	C6	109.88 (13)	C20	C21	Cl1	116.25 (14)
N2	C7	C14	111.34 (13)	C20	C21	C14	122.12 (16)
C6	C7	C14	114.96 (14)	C4	C22	C23	120.21 (18)
N2	C8	C9	127.36 (15)	C1	C23	C22	120.54 (19)

Table 10 Torsion Angles for **7**.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	C9	C10	C11	177.56 (14)	C7	N2	C8	C9	-4.5 (3)
S1	C15	C18	C19	-173.26 (15)	C7	N2	C8	C17	175.78 (15)
O1	S1	C9	C8	161.82 (14)	C7	C14	C15	S1	-6.7 (2)
O1	S1	C9	C10	-16.57 (15)	C7	C14	C15	C18	179.92 (16)
O1	S1	C15	C14	-172.33 (13)	C7	C14	C21	Cl1	1.0 (2)
O1	S1	C15	C18	1.34 (17)	C7	C14	C21	C20	-179.65 (16)
O2	S1	C9	C8	-68.97 (16)	C8	N2	C7	C6	169.85 (14)
O2	S1	C9	C10	112.64 (13)	C8	N2	C7	C14	-61.6 (2)
O2	S1	C15	C14	59.24 (15)	C8	C9	C10	C11	-0.9 (3)
O2	S1	C15	C18	-127.09 (14)	C9	S1	C15	C14	-58.24 (15)
N1	C6	C7	N2	-166.82 (15)	C9	S1	C15	C18	115.43 (15)
N1	C6	C7	C14	66.7 (2)	C9	C8	C17	C16	-1.1 (2)
N1	N12	N13	N3	-0.44 (19)	C9	C10	C11	C16	-0.8 (3)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N2	C7	C14	C15	82.46 (18)	C10	C11	C16	C17	1.5 (3)
N2	C7	C14	C21	-92.2 (2)	C11	C16	C17	C8	-0.5 (3)
N2	C8	C9	S1	3.9 (3)	N12	N1	C5	C4	70.3 (2)
N2	C8	C9	C10	-177.85 (16)	N12	N1	C6	N3	0.72 (19)
N2	C8	C17	C16	178.59 (16)	N12	N1	C6	C7	-178.46 (15)
N3	C6	C7	N2	14.2 (2)	N13	N3	C6	N1	-0.95 (18)
N3	C6	C7	C14	-112.37 (19)	N13	N3	C6	C7	178.19 (16)
C1	C2	C3	C4	-0.6 (3)	C14	C15	C18	C19	0.2 (3)
C2	C1	C23	C22	0.7 (3)	C15	S1	C9	C8	48.40 (16)
C2	C3	C4	C5	-177.45 (18)	C15	S1	C9	C10	-129.98 (13)
C2	C3	C4	C22	1.1 (3)	C15	C14	C21	Cl1	-173.70 (12)
C3	C4	C5	N1	-156.75 (16)	C15	C14	C21	C20	5.7 (2)
C3	C4	C22	C23	-0.7 (3)	C15	C18	C19	C20	3.8 (3)
C4	C22	C23	C1	-0.1 (3)	C17	C8	C9	S1	-176.45 (13)
C5	N1	C6	N3	-166.56 (17)	C17	C8	C9	C10	1.8 (2)
C5	N1	C6	C7	14.3 (3)	C18	C19	C20	C21	-2.9 (3)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C5	N1	N12	N13	168.64 (15)	C19	C20	C21	Cl1	177.43 (15)
C5	C4	C22	C23	177.70 (19)	C19	C20	C21	C14	-2.0 (3)
C6	N1	C5	C4	-123.82 (19)	C21	C14	C15	S1	168.53 (13)
C6	N1	N12	N13	-0.16 (18)	C21	C14	C15	C18	-4.8 (2)
C6	N3	N13	N12	0.87 (19)	C22	C4	C5	N1	24.8 (3)
C6	C7	C14	C15	-151.76 (15)	C23	C1	C2	C3	-0.3 (3)
C6	C7	C14	C21	33.6 (2)					

Table 11 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **7**.

Atom	*x*	*y*	*z*	U (eq)
H2	7867.41	887.1	5634.43	30
H1	338.25	4713.6	11596.06	49
H2A	-1645.51	3248.95	11352.16	50
H3	-443.29	1783.97	10116.61	42
H5A	2356.02	731.33	9087.33	37
H5B	2163.66	1626.21	8113.51	37

Atom	*x*	*y*	*z*	U (eq)
H7	3950.76	1321.23	6428.41	28
H10	2529.03	2295.04	2797.2	38
H11	5156.94	1631.7	1481.49	43
H16	8405.96	883.84	2027.13	39
H17	8984.38	724.9	3846.09	32
H18	1453.01	4844.08	5387.29	39
H19	3090.54	6095.74	6380.56	42
H20	5954.48	5402.37	7307.92	39
H22	4749.33	3255.67	9358.67	45
H23	3546.4	4705.56	10609.91	52

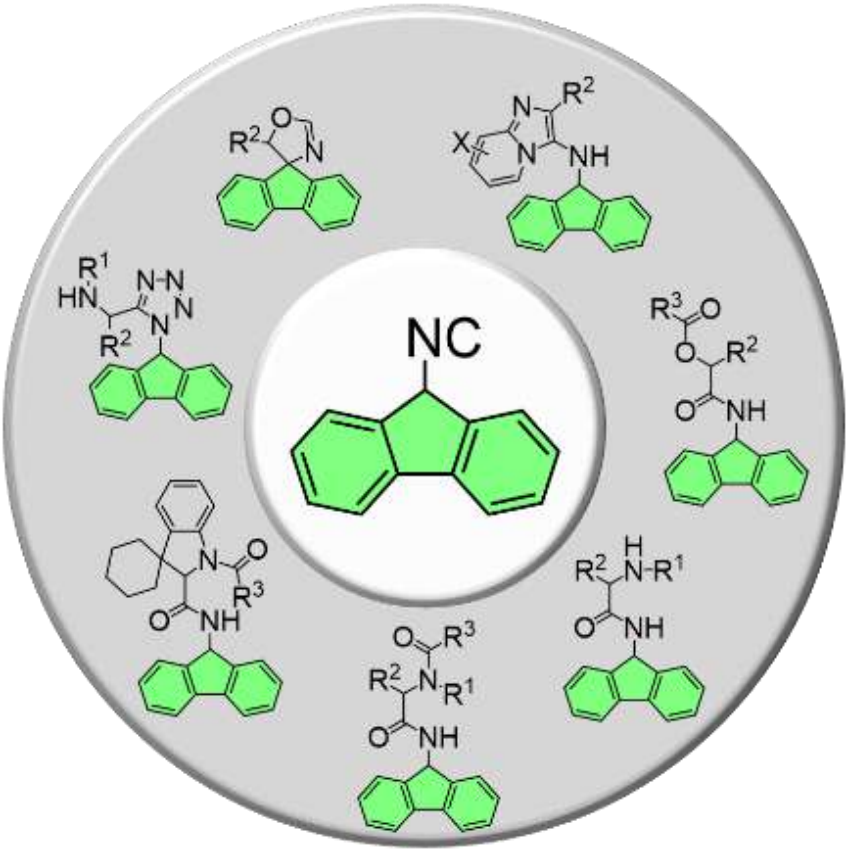
Chapter 4

Fluorene-based multicomponent reactions

*This chapter is based on the artictl*e:“Fluorene-based Multicomponent Reactions*”, by* **Xiaofang Lei**, Maria Thomaidi, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Synlett,* **2022**, *33 (02),* 155-160.

ABSTRACT

Based on our ongoing interest in molecules with special characteristics, we focused on fluorene-fused compounds that are widely used in drug discovery and material science. The functionalization of these entities is highly important. Novel adducts containing those structures based on IMCRs are reported in this work. 23 Fluorene-fused adducts are synthesized via six different IMCRs. These new protocols are efficient and rapid. The X-ray crystallography of several fluorene-based scaffolds revealed their solid-state conformation.



INTRODUCTION

Fluorene has been involved in various research fields, such as optoelectronics,[1] solar cells,[2] synthetic chemistry[3] and drug discovery.[4] Interestingly, molecules incorporating a fluorene core are used as semiconducting and photoconducting charge-transfer complexes (CTC) and electron transport materials (Figure 1, A).[1,2,5] Fluorenone especially, is considered to be a privileged structure as it is relatively planar with high thermal stability and good electron-transport properties. Many of its derivatives exhibit both aggregation-induced emission (AIE) and great bathochromically solid-state fluorescence.[6] This core is widely present in numerous natural products and bioactive compounds.[7] Figure 1, A shows characteristic examples of this unique core such as the natural product dendroflorin with high antioxidant activity[8] and the anti-myocardial ischemia activity drug, caulophine.[9] In addition, many effective inhibitors contain this scaffold, i.e. cyclophorin A (CypA), [4] fibril formation of human transthyretin (TTR)[10] and glycoside hydrolases (GHs) (Figure 1, B).[11,12] Notably, in synthesis, fluorene derivatives have been utilized in the archetypical protective groups Fmoc.[13] Herein, several synthetic methods, including one-pot strategies and catalyst-assisted towards the fluorene-based cores are reported.[14-22]

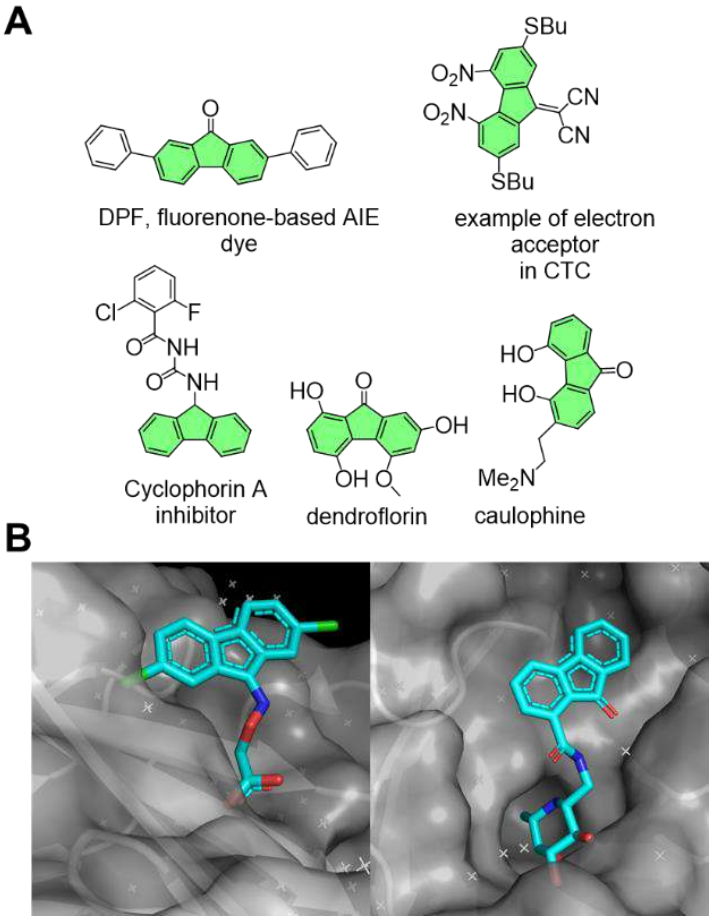


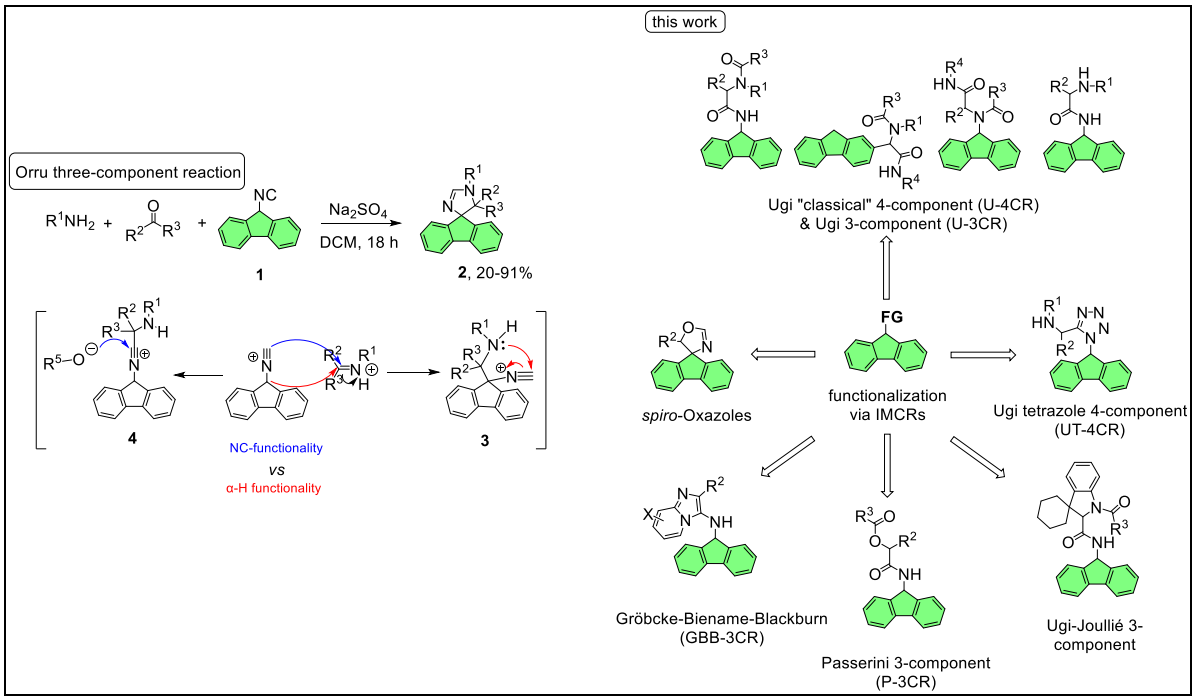
Figure 1 **A**. Fluorene-based derivatives in applied materials and natural products, **B**. Fluorene-based molecules in drug discovery, left: Inhibitor of TTR (PDB ID: 5E4A), right: α-l-fucosidase inhibitor (PDB ID: 2XII).

Orru and co-workers,[23] in their pioneering work, took advantage of the acidic nature of 9-isocyano-1H-fluorene (1, pKa = 12.3 in DMSO), which becomes aromatic after deprotonation,[24-26] and are able to synthesize the druglike spiro-2-imidazolines **2** through a three-component reaction, now known as the Orru reaction (Oru-3CR, Scheme 1).[23,27-29] Due to the acidic nature of the isocyanide, in which the isocyano functionality competes with α-H acidity, the Mannich-type intermediate **3** is probably formed. Intramolecular attack by the nucleophilic

amine on the isocyanide carbon of 3 is the driving force toward cyclization to give fluoreno-2-imidazolines 2 (Scheme 1, red arrows).[23]

As we aforementioned many times, MCRs are valuable tools for complex and diverse scaffolds in one-pot and reduced purification steps manner.[30] Incorporation of fluorene-fused derivatives by IMCRs gives rise to diverse products. IMCRs methodology is not yet fully explored.[31-36] Additionally, the development of new products and technologies is enormously important for structural diversity and complexity in fluorene-based libraries.

Considering this, the focus turned to the widely used IMCRs to build the fluorene cores derivatives. Firstly, 9-isocyanofluorene **1** constituted a versatile building block for our study. Subsequently, synthesis of the isocyano function (Scheme 1, blue arrows, intermediate **4**) and investigation of the formation of the 2-imidazoline under the corresponding conditions occurs. Interestingly, the reduction of the nucleophilicity of the amine in the Ugi reaction leads the reaction towards the classic pathway of the bisamides (Scheme 1, intermediate **4**).[35,23] Herein, a series of IMCRs reported: the classical Ugi reaction, U-3CR,[37] Ugi-Joullié reaction,[38] Ugi-Smiles four-component,[39-41] UT-4CR,[42] GBB-3CR[43-45] and P-3CR.[46] Also, synthesis of the *spiro*-oxazolidine derivatives via the isocyano moiety of the 9-isocyanofluorene takes place.



Scheme 1 α-H *versus* NC-functionality of the isocyanofluorene **1** yielding the Orru-3CR and our proposed IMCR-based employment of fluorenes, including the synthesis of *spiro*-oxazoles

RESULTS AND DISCUSSION

Compound **1** is prepared from the corresponding formamide **1a**. It is worth noting that compound **1a** is obtained from the 9-fluorenone via the Leuckart-Wallach procedure (Figure 2, A).[47] The standard synthetic procedure[23] of the isocyanides (RNCs) starts with the formylation of the amines. However, the 9-amino fluorene is commercially available as its hydrochloric salt (CAS 5978-75-6, 69.60 €/5 g) and is substantially much more expensive than the corresponding 9-fluorenone (CAS 486-25-9, 18.50 €/5 g). Compound **1** is yielded as an odorless solid via dehydration of **1a** on a gram-scale in 92% yield. Surprisingly, the solution of **1a** in DCM gives a characteristic bright blue glow at 366 nm, while the solution of the RNC in DCM appears as light green at 254 nm (Figure 2, B, C).

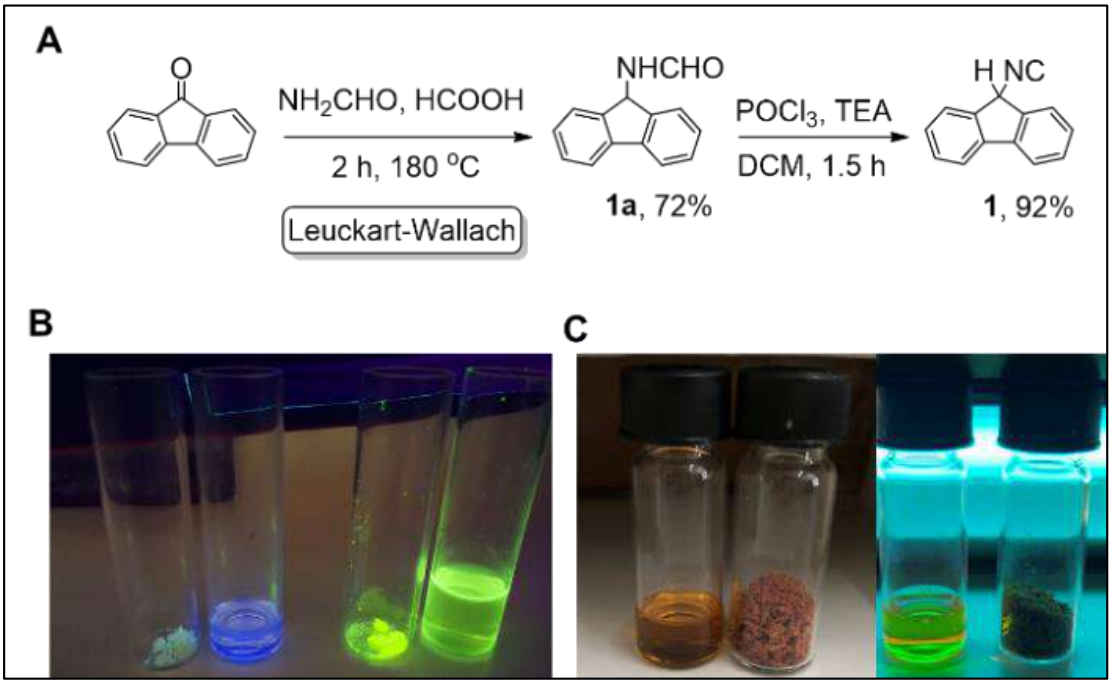


Figure 1 (**A**) Access to the isocyanide **1** via the Leuckart-Wallach reaction of 9H-fluoren-9-one. (**B**) Fluorescence of 9H-fluoren-9-one (green color, right-hand vial) and formamide **1a** (blue color, left-hand vial) on excitation at 366 nm, both as a solid and as a solution in CH_2Cl_2. (**C**) Fluorescence of 9-isocyanofluorene on excitation by visible light (left) and at 254 nm (right) both as a solid and as a solution in DCM.

First, employment of an U-4CR occurs. The four diversity points of the reaction can give access to extensive libraries, while the U-4CR adduct can an excellent hub for numerous secondary transformations.[48,49] Isocyanide **1**, the fluorene-based aldehyde and amine are employed to build the library of the targeted bisamides **5a-c** in 34-89% yield. Noteworthy, in **5c**, the fluorene scaffold appeared in three building blocks, demonstrating the great architectural aspect of the reaction (Scheme 2). Surprisingly, adduct **2a** is obtained instead of the U-4CR product when aliphatic aldehydes are used (Figure 3). This because the 5-chloropentanal could increase the nucleophilicity of the nitrogen of the corresponding amine.

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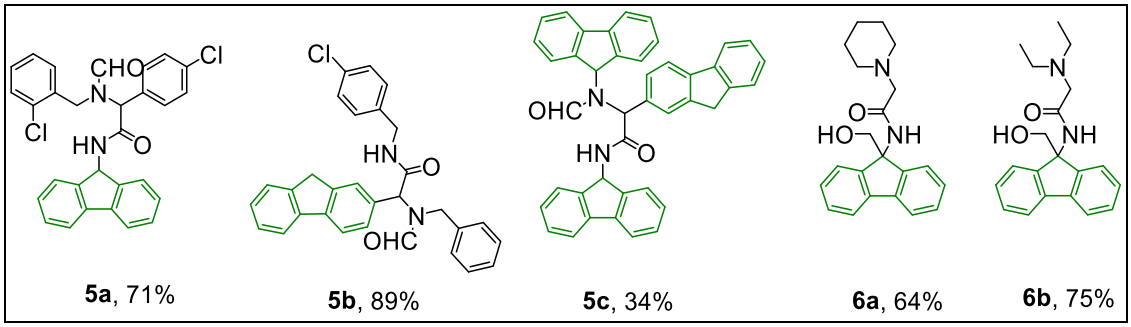
The difference between the U-3CR and U-4CR is that the water acts as the nucleophile instead of the acid in the former. The presence of α-aminoacylamides in several bioactive molecules and commercially available drugs leads to improved pharmacokinetic/ pharmacodynamic (PKPD) properties, such as oral bioavailability and water solubility, due to incorporating a basic amine.[50] Considering this, the focus turned into the U-3CR and obtain the α-aminoacylamides **6a,b** in 64% and 75% yield (Scheme 2). To access caine-type compounds the secondary amines are employed in an aqueous solution of formaldehyde without catalysts, no additives or other solvents. Interestingly, an additional formaldehyde is added to the U-3CR as a hydroxyl methylene scaffold via a Mannich-type addition. The acidic proton of the fluorene-fused and the aqueous reaction condition attribute this result.



5a, 71% **5b**, 89% **5c**, 34% **6a**, 64% **6b**, 75%

Scheme 2 Synthesis of U-4CR **5a**-**c** and U-3CR **6a**,**b** adducts utilizing fluorene moieties as isocyanide, aldehyde and amine components

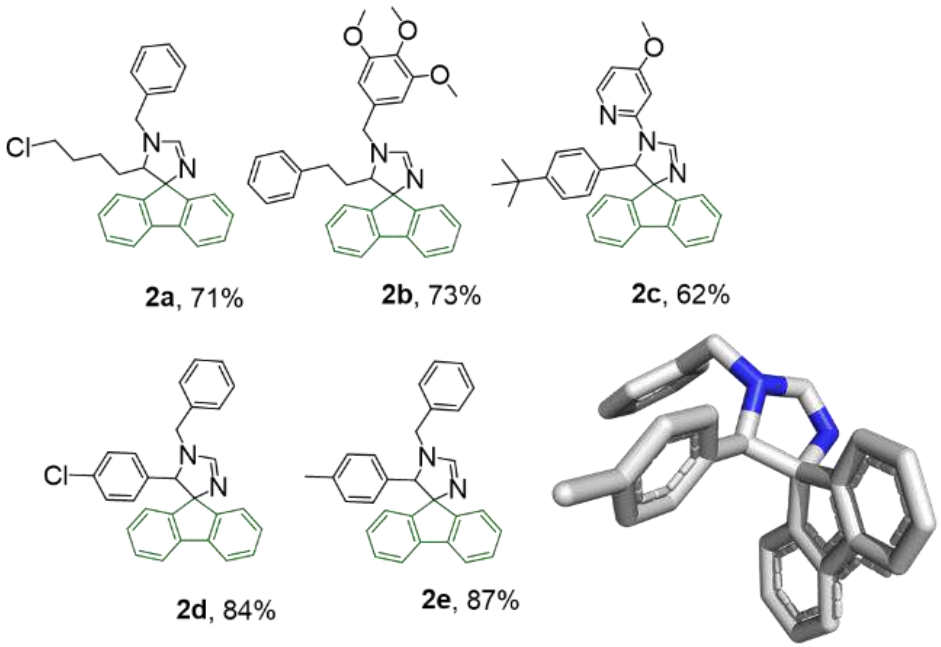
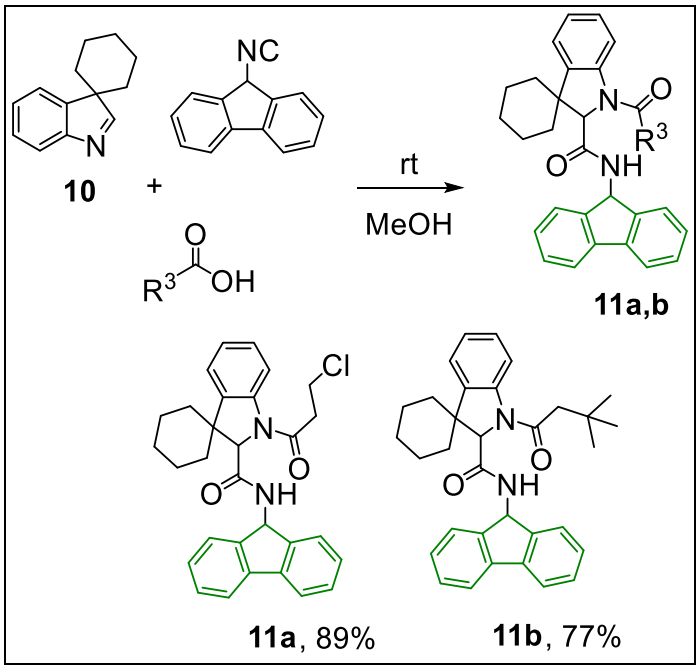


Figure 3 Synthesis of imidazolines **2a**-**e** via an Orru-3CR and an x-ray structure of compound **2e** (CCDC 2065539)

The Ugi-Joullié reaction[38] is a highly versatile cyclic variation of the Ugi reaction, which produces conformationally constrained peptidomimetics and antibacterial depsipeptides.[51] So far, the Ugi-Joullié reaction has been widely utilized in various post-transformations of an initial MCR.[52] Herein, spiroindolenine **10**, obtained via a Fischer indole synthesis, with unique 3D character[53] has been explored with the fluorene-fused isocyanides. Interestingly, adducts **11a** and **11b** are isolated with good yields (Scheme 3).



Scheme 3 Ugi-Joullié adducts **11a,b** employing the 9-isocyanofluorene

Over the last years, the 3D-shaped alicyclic building structure has received considerable attention in drug discovery ("escape from the flatland"), and the *spiro* molecules are of high importance.[54,55] Therefore, the combination of the α-acidity of **1** with its isocyano functional group occurs. A similar fashion as the van Leusen oxazole approach[56] is employed with an aldehyde and TosMIC (Figure 4). In fact, the targeted *spiro*-oxazolidines **12a-c** (Figure 4) are successfully obtained in good to excellent yields, with K_2CO_3 at room temperature. In addition, the crystal structure of **12c** is solved to support the proposed scaffold (Figure 4).

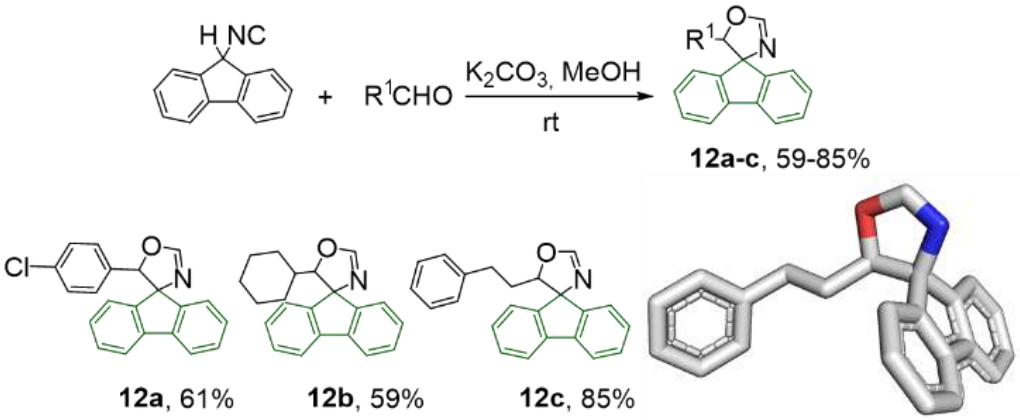


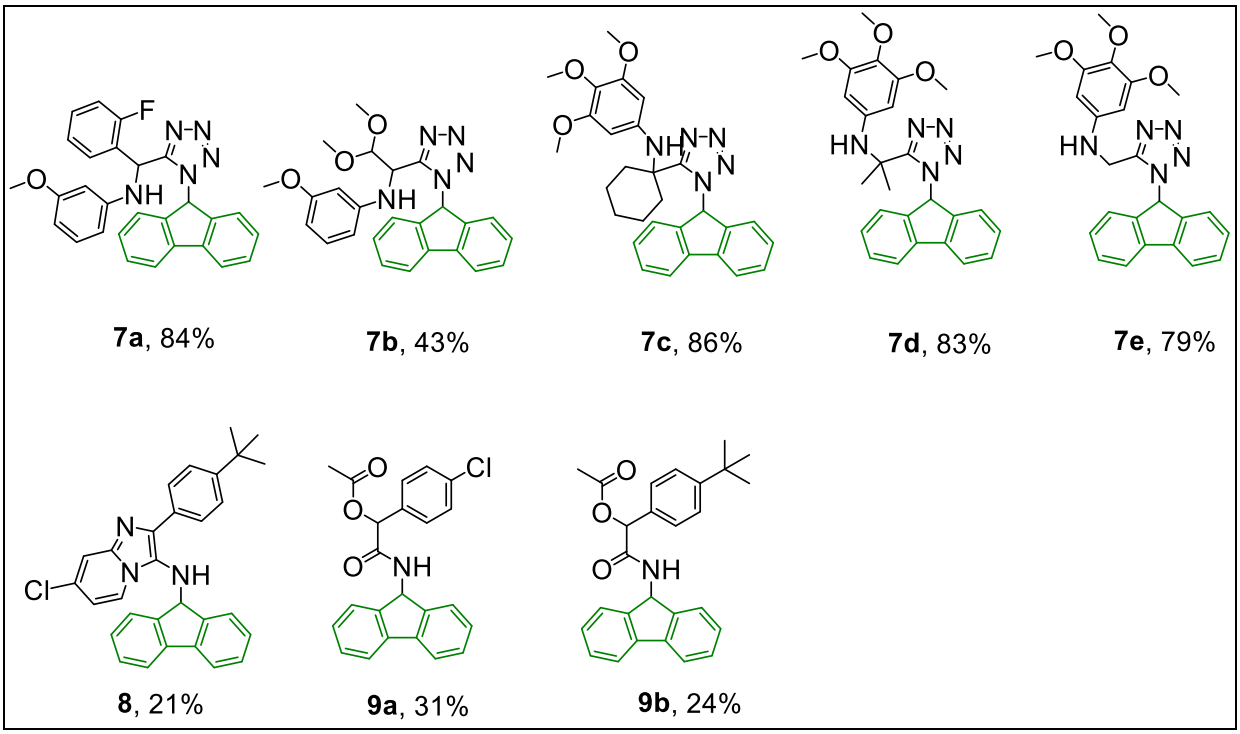
Figure 4 Synthesis of the spiro-oxazolidines 12a-c and the x-ray structure of **12c** (CCDC 2065540)

Arguably, the Ugi tetrazole reaction (UT-4CR) is one of the most well-known variations of the Ugi reaction. The tetrazole core is a very important bioisostere to carboxylic acid and cis-amide moiety. The UT-4CR gives efficient access to fluorene-tetrazole scaffolds in a single step. Notably, tetrazole derivatives show enhanced metabolic stability and beneficial physicochemical characteristics.[57] The desired fluorene-tetrazole adducts **7a**-**e** are obtained in good to excellent yields from various aryl amines, aldehydes, and ketones (Scheme 4). Adducts **7a** and **b** contain additional functional groups that can allow various post-modifications (for example, the S_NAr and deprotection of the acetal part). Surprisingly, **2b** is formed instead of the desired adducts when 3-phenylpropanal and 3,4,5-trimethoxy benzylamine are employed (Figure 3).

The Gröbcke-Blackburn-Bienaymé reaction (GBB-3CR) which just emerged in two decades is one of the newest but nevertheless very useful IMCRs.[58-60] It is coined independently by three research teams, Groebke (Switzerland), Blackburn (USA) and Bienaymé (France)) in 1998.[61-63] Over the past 20 years, the GBB reaction is widely used to synthesize the 3-amino-substituted imidazo[1,2-a]-pyridines, -pyrazines and -pyrimidines respectively from aminoazines or aminoazoles, aldehyde and isocyanides. The reaction

proceeds through imine formation and subsequent formal [4 + 1] cycloaddition in the presence of a Lewis or Brønsted acid.[64] The synthetic potential of this kind IMCR and the excellent biological and photophysical properties of GBB adducts highlight the importance of this reaction.[65] For instance, the [1,2-a]pyridine scaffold exhibits auto-fluorescence in UV , a property that can be applied in enzymatic fluorescence detection assays.[66] As known, the imidazo[1,2-a]-heterocycles are present in numerous late-stage clinical trial drugs.[67] Herein, GBB adduct **8** is designed and obtained from 4-chloropyridin-2-amine (Scheme 4). Interestingly, **2c** is obtained when 4-methoxypyridin-2-amine is used, pointing the aforementioned mechanistic assumptions out (Figure 3). Noteworthy, only **2d** and **2e** adducts are produced via the Ugi-Smiles reaction. The crystal structure of **2e** confirms the different pathways taken in this reaction (Figure 3).

The Passerini reaction (P-3CR) is one of the classic IMCRs, due to its access to α-acyloxy carboxamides. Employment of the fluorene scaffold in the Passerini methodology yields adducts **9a**-**b** (Scheme 4). Additionally, the utilization of acetic acid and substituted aromatic aldehydes with electron-donating and withdrawing groups is presented in this study.



Scheme 4 Synthesis of UT-4CR **7a**-**e**, GBB-3CR **8** and P-3CR **9a**,**b** adducts utilizing fluorene moieties as isocyanide, aldehyde and amine components.

CONCLUSIONS

In summary, 23 unprecedented fluorene derivatives with different scaffolds are successfully obtained via functionalization of the fluorene moiety through IMCRs. The potentiality of MCR chemistry is further exploited and showed its potential in both material science and drug discovery. The mild conditions, high yields, reduced purification steps, and inexpensive starting material make this method a handy tool for the construction of fluorene derivatives.

REFERENCES

1. Perepichka, I. F., Popov, A. F., Orekhova, T. V., Bryce, M. R., Andrievskii, A. M., Batsanov, A. S., Howard, J. A. K., Sokolov, N. I., *J. Org. Chem.,* **2000**, *65*, 3053-3063.
2. Lim, C. J., Lei, Y., Wu, B., Li, L., Liu, X., Lu, Y., Zhu, F., Ong, B. S., Hu, X., Ng, S.-C., *Tetrahedron Lett*., **2016**, *57*, 1430-1434.
3. Xia, J.-B., Zhu, C., Chen, C., *J. Am. Chem. Soc*., **2013**, *135*, 17494-17500.
4. Ni, S., Yuan, Y., Huang, J., Mao, X., Lv, M., Zhu, J., Shen, X., Pei, J., Lai, L., Jiang, H., Li, J., *J. Med. Chem*., **2009**, *52*, 5295-5298.
5. Chen, T., Chen, Z.-Q., Gong, W.-L., Li, C., Zhu, M.-Q., *Mater. Chem. Front*., **2017**, *1*, 1841-1846.
6. Xu, F., Wang, H., Du, X., Wang, W., Wang, D.-E., Chen, S., Han, X., Li, N., Yuan, M.-S., Wang, *J., Dye. Pigment*., **2016**, *129*, 121-128.
7. Shi, Y., Gao, S., *Tetrahedro,* **2016**, *72*, 1717-1735.
8. Fan, C., Wang, W., Wang, Y., Qin, G., Zhao, W., *Phytochemistry*, **2001**, *57*, 1255-1258.
9. Wang, S., Wen, B., Wang, N., Liu, J., He, L., *Arch. Pharm. Res*., **2009**, *32*, 521-526.
10. Ciccone, L., Nencetti, S., Rossello, A., Stura, E. A., Orlandini, E. *J. Enzyme Inhib. Med. Chem.,* **2016**, *31*, 40-51.
11. Lammerts van Bueren, A., Popat, S. D., Lin, C.-H., Davies, G. J., *ChemBioChem,* **2010**, *11*, 1971-1974.
12. Zechel, D. L., Boraston, A. B., Gloster, T., Boraston, C. M., Macdonald, J. M., Tilbrook, D. M. G., Stick, R. V, Davies, G. J., *J. Am. Chem. Soc.,* **2003**, *125*, 14313-14323.
13. Wuts, P. G. M., Greene, T. W., *Greene's Protective Groups in Organic Synthesis, 4th ed*, Wiley: Hoboken, **2007**.

14. Zhou, A.-H., Pan, F., Zhu, C., Ye, L.-W., *Chem. - A Eur. J.,* **2015**, *21*, 10278-10288.
15. Dong, K., Fan, X., Pei, C., Zheng, Y., Chang, S., Cai, J., Qiu, L., Yu, Z.-X., Xu, X., *Nat. Commun.,* **2020**, *11*, 2363.
16. Liu, T.-P., Liao, Y.-X., Xing, C.-H., Hu, Q.-S., *Org. Lett.,* **2011**, *13*, 2452-2455.
17. Li, H., Zhu, R.-Y., Shi, W.-J., He, K.-H., Shi, Z.-J., *Org. Lett.,* **2012**, *14*, 4850-4853.
18. Ye, F., Haddad, M., Michelet, V., Ratovelomanana-Vidal, V., *Org. Lett.,* **2016**, *18*, 5612-5615.
19. Zhou, Z.-Z., Jin, D.-P., Li, L.-H., He, Y.-T., Zhou, P.-X., Yan, X.-B., Liu, X.-Y., Liang, Y.-M., *Org. Lett.,* **2014**, *16*, 5616-5619.
20. Kumar, R., Raghuvanshi, K., Verma, R. K., Singh, M. S., *Tetrahedron Lett.,* **2010**, *51*, 5933-5936.
21. Rong, L., Han, H., Jiang, H., Tu, S., *Synth. Commun.,* **2009**, *39*, 3493-3499.
22. Nishida, M., Lee, D., Shintani, R., *J. Org. Chem.,* **2020**, *85 (13),* 8489-8500.
23. Bon, R. S., Hong, C., Bouma, M. J., Schmitz, R. F., de Kanter, F. J. J., Lutz, M., Spek, A. L., Orru, R. V. A., *Org. Lett.,* **2003**, *5*, 3759-3762.
24. Janssen, G. V., Janssen, E., Vande Velde, C. M. L., Ehlers, A. W., Slootweg, J. C., Ruijter, E., Lammertsma, K., Orru, R. V. A., *Org. Lett.,* **2014**, *16*, 5116-5119.
25. Konstandaras, N., Dunn, M. H., Guerry, M. S., Barnett, C. D., Cole, M. L., Harper, J. B., *Org. Biomol. Chem.,* **2020**, *18*, 66-75.
26. Janssen, G. V., Vicente-García, E., Vogel, W., Slootweg, J. C., Ruijter, E., Lammertsma, K., Orru, R. V. A., *European J. Org. Chem.,* **2014**, *2014*, 3762-3766.

27. Bon, R. S., van Vliet, B., Sprenkels, N. E., Schmitz, R. F., de Kanter, F. J. J., Stevens, C. V., Swart, M., Bickelhaupt, F. M., Groen, M. B., Orru, R. V. A., *J. Org. Chem.,* **2005**, *70*, 3542-3553.
28. Mooijman, M., Bon, R., Sprenkels, N., van Oosterhout, H., de Kanter, F., Groen, M., Ruijter, E., Orru, R., *Synlett,* **2012**, *2012*, 80-84.
29. Elders, N., Schmitz, R. F., de Kanter, F. J. J., Ruijter, E., Groen, M. B., Orru, R. V. A., *J. Org. Chem.,* **2007**, *72*, 6135-6142.
30. (a) S. M. Sheehan, J. J. Masters, M. R. Wiley, S. C. Young, J. W. Liebeschuetz, S. D. Jones, C. W. Murray, J. B. Franciskovich, D. B. Engel, W. W. Weber, J. Marimuthu, J. A. Kyle, J. K. Smallwood, M. W. Farmen and G. F. Smith, *Bioorg., Med. Chem. Lett.,* **2003**, *13*, 2255-2259, (b) T. Nixey and C. Hulme, *Tetrahedron Lett.,* **2002**, *43*, 6833-6835, (c) T. P. Ribelin, A. S. Judd, I. Akritopoulou-Zanze, R. F. Henry, J. L. Cross, D. N. Whittern and S. W. Djuric, *Org. Lett.,* **2007**, *9*, 5119-5122, (d) L. El Kaim, L. Grimaud and J. Oble, *Angew. Chem., Int. Ed.,* **2005**, *44*, 7961-7964, (e) K. Khoury, M. K. Sinha, T. Nagashima, E. Herdtweck and A. Dömling, *Angew. Chem., Int. Ed.* **2012**, *51*, 10280-10283, (f) L. Banfi, G. Guanti, R. Riva, A. Basso and E. Calcagno, *Tetrahedron Lett.,* **2002**, *43*, 4067-4069.
31. Hussein, E. M., El Guesmi, N., Ahmed, S. A., *RSC Adv.,* **2019**, *9*, 40118-40130.
32. Hosseini, H., Bayat, M., *RSC Adv.,* **2018**, *8*, 41218-41225.
33. Meerakrishna, R. S., Periyaraja, S., Shanmugam, P., *European J. Org. Chem.,* **2016**, *2016*, 4516-4525.
34. Zhu, Z., Seidel, D., *Org. Lett.,* **2016**, *18*, 631-633.
35. Mehta, V. P., Modha, S. G., Ruijter, E., Van Hecke, K., Van Meervelt, L., Pannecouque, C., Balzarini, J., Orru, R. V. A., Van der Eycken, E., *J. Org. Chem.,* **2011**, *76*, 2828-2839.
36. Rezayan, A. H., Hariri, S., Azerang, P., Ghavami, G., Portugal, I., Sardari, S., *Iran. J. Pharm. Res. IJPR,* **2017**, *16*, 745-755.

37. Ugi, I., Steinbrückner, C., *Angew. Chemie,* **1960**, *72*, 267-268.
38. Nutt, R. F., Joullie, M. M., *J. Am. Chem. Soc.,* **1982**, *104*, 5852-5853.
39. El Kaïm, L., Grimaud, L., Oble, J., *Angew. Chemie Int. Ed.,* **2005**, *117*, 8175-8178.
40. El Kaim, L., Grimaud, L., *Tetrahedron,* **2009**, *65*, 2153-2171.
41. El Kaïm, L., Gizolme, M., Grimaud, L., Oble, J., *J. Org. Chem.,* **2007**, *72*, 4169-4180.
42. Ugi, I., Meyr, R., *Chem. Ber.,* **1961**, *94*, 2229-2233.
43. Gröebke, K., Weber, L., Mehlin, F., *Synlett,* **1998**, 661-663.
44. Blackburn, C., Guan, B., Fleming, P., Shiosaki, K., Tsai, S., *Tetrahedron Lett.,* **1998**, *39*, 3635-3638.
45. Bienaymé, H., Bouzid, K., *Angew. Chemie Int. Ed.,* **1998**, *37*, 2234-2237.
46. Passerini, M., *Gazz. Chim. Ital.,* **1921**, *51*, 181-188.
47. Neochoritis, C. G., Zarganes-Tzitzikas, T., Stotani, S., Dömling, A., Herdtweck, E., Khoury, K., Dömling, A., *ACS Comb. Sci.,* **2015**, *17*, 493-499.
48. Fouad, M. A., Abdel-Hamid, H., Ayoup, M. S., *RSC Adv.,* **2020**, *10*, 42644-42681.
49. Younus, H. A., Al-Rashida, M., Hameed, A., Uroos, M., Salar, U., Rana, S., Khan, K. M., *Expert Opin. Ther. Pat.,* **2021**, *31 (3),* 267-289.
50. Tripolitsiotis, N. P., Thomaidi, M., Neochoritis, C. G., *European J. Org. Chem.,* **2020**, *2020*, 6525-6544.
51. Gazzotti, S., Rainoldi, G., Silvani, A., *Expert Opin. Drug Discov.,* **2019**, *14*, 639-652.
52. Zarganes-Tzitzikas, T., Chandgude, A. L., Dömling, A., *Chem. Rec.,* **2015**, *15*, 981-996.
53. Estévez, V., Kloeters, L., Kwietniewska, N., Vicente-García, E., Ruijter, E., Orru, R., *Synlett,* **2016**, *28*, 376-380.

54. Chalyk, B. A., Butko, M. V, Yanshyna, O. O., Gavrilenko, K. S., Druzhenko, T. V, Mykhailiuk, P. K., *Chem. - A Eur. J.,* **2017**, *23*, 16782-16786.
55. Lovering, F., Bikker, J., Humblet, C., *J. Med. Chem.,* **2009**, *52*, 6752-6756.
56. van Leusen, A. M., Hoogenboom, B. E., Siderius, H., *Tetrahedron Lett.,* **1972**, *13*, 2369-2372.
57. Neochoritis, C. G., Zhao, T., Dömling, A., *Chem. Rev.,* **2019**, *119*, 1970-2042.
58. Boltjes, A., Dömling, A., *Eur. J. Org. Chem.,* **2019**, *2019*, 7007-7049.
59. Rostamnia, S., *RSC Adv.,* **2015**, 5, 97044-97065.
60. Rostamnia, S., Hassankhani, A*., RSC Adv.,* **2013**, 3, 18626-18629.
61. K. Groebke, L. Weber, F. Mehlin, *Synlett*, **1998**, 661-663.
62. C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.*, **1998**, *39*, 3635-3638.
63. H. Bienaymé, K. Bouzid, *Angew. Chem. Int. Ed.*, **1998**, *37*, 2234-2237.
64. A. Boltjes, A. Dömling, *Eur. J. Org. Chem.*, **2019**, 7007-7049.
65. Manpreet Kaur, Rahul Singh, Madhuri T. Patil, Kushvinder Kumar, Subash Chandra Sahoo, Kamal Nain Singh, Vinod D. Chaudhari, Deepak B. Salunke, *J Heterocyclic Chem.*, **2022**, *59*, 319-328.
66. O. N. Burchak, L. Mugherli, M. Ostuni, J. J. Lacapere, M. Y. Balakirev, *J. Am. Chem. Soc.*, **2011**, *133*, 10058-10061.
67. Konstantinidou, M., Boiarska, Z., Butera, R., Neochoritis, C. G., Kurpiewska, K., Kalinowska-Tłuscik, J., Dömling, A., *European J. Org. Chem.,* **2020**, *2020*, 5601-5605.

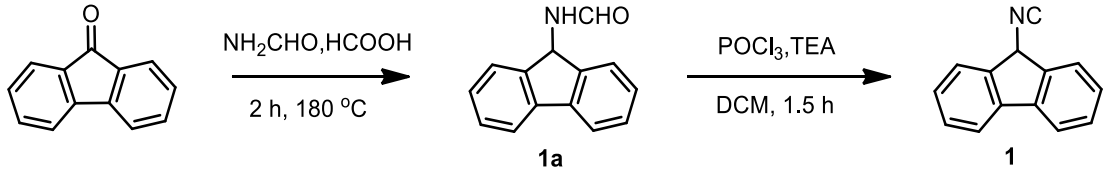
EXPERIMENTAL SECTION

1. General methods and materials

All the reagents and solvents are purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and are used without further purification. All microwave irradiation reactions are carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography is performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra are recorded on Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz) }. Chemical shifts for ^{1}H NMR are reported as δ values and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak. Flash chromatography is performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra are measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). High resolution mass spectra are recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

2. Synthetic procedures and analytical data

General Procedure for the synthesis of 9-isocyano-9H-fluorene



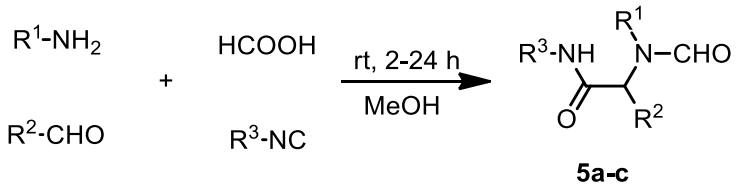
Reductive amination of 9H-fluoren-9-one

To a stirred solution of 9*H*-fluoren-9-one (10.0 mmol) in formamide (120.0 mmol), formic acid (80.0 mmol) is added and then refluxed at 180 °C for 2 h. The mixture is extracted with DCM (3 x 50.0 mL) after cooling down. The organic layer is separated, washed with water, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude product is washed with diethyl ether and compound **1a** is obtained as white solid in 72% yield.[1]

Dehydration towards the 9-isocyano-9H-fluorene

To a stirred solution of *N*- (9*H*-fluoren-9-yl) formamide (5.0 mmol) and triethyl amine (25.0 mmol) in DCM (15.0 mL), phosphoryl chloride (6.0 mmol) is added dropwise at 0 °C. The mixture is warmed up to room temperature and stirred about 1.5 h. Then, the reaction mixture is poured onto ice with $NaHCO_3$ (15.0 mmol) and then stirred about 2 h at room temperature. The aqueous layer is extracted with DCM (2 x 10.0 mL). The combined organic layers are dried over Na_2SO_4 and removed under reduced pressure. The 9-isocyano-9*H*-fluorene **1** is obtained as red solid in 92% yield and is used directly without further purification.[1]

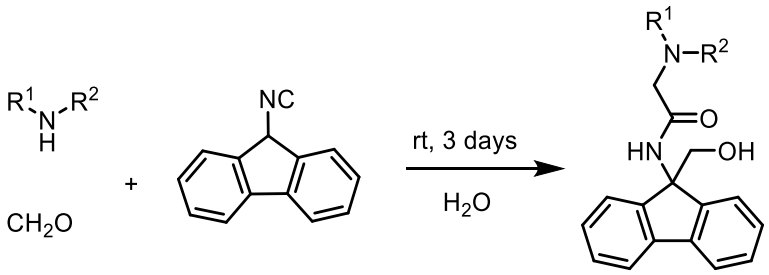
General procedure for the Ugi 4-component reaction (U-4CR)



5a-c

To a stirred solution of the corresponding amine (1.0 mmol) in MeOH (1.0 mL), the corresponding aldehyde (1.0 mmol), isocyanide (1.0 mmol) and acid (1.0 mmol) are added at room temperature. The reaction mixture is stirred vigorously for 2-24 h. The solvent is removed under reduced pressure and the reaction mixture is purified with column chromatography (PE-EA 1:1) to give compounds **5a**-**c** and **2a**.

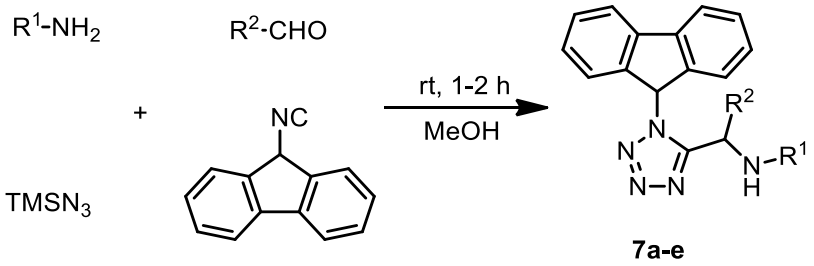
General procedure for the Ugi 3-component reaction (U-3CR)



6a,b

To a stirred solution of corresponding secondary amine (1.0 mmol) into aqueous formaldehyde (10.0 mmol), 9-isocyano-9*H*-fluorene (1.0 mmol) is added at room temperature. The reaction mixture is stirred vigorously for 3 days. The residue is extracted with DCM twice. The combined organic layers are washed with water and dried over Na_2SO_4. Then, the solvent is removed under reduced pressure and the reaction mixture is purified with column chromatography (DCM-MeOH 20:1) compounds **6a**,**b**.

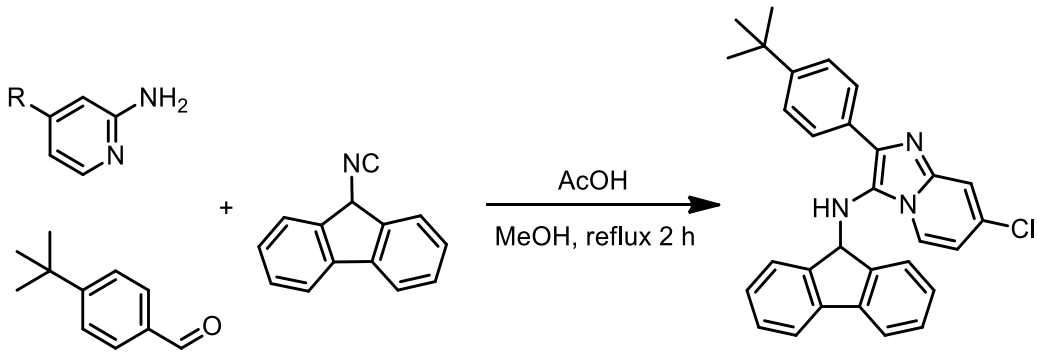
General procedure for the Ugi tetrazole 4-component reaction reaction (UT-4CR)



7a-e

To a stirred solution of the corresponding aldehyde (1.0 mmol) in MeOH (1.0 mL), the corresponding aniline (1.0 mmol), isocyanide (1.0 mmol) and trimethylsilyl azide (1.0 mmol) are added at room temperature. The reaction mixture is stirred vigorously for 1-2 h. Then, half of the solvent is removed under reduced pressure and in case that solid residue appeared, it is filtered and washed with Et_2O. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA 1:1) to give the compounds **7a**-**e** and **2b**.

General procedure for the Groebke-Blackburn-Bienaymé (GBB) reaction



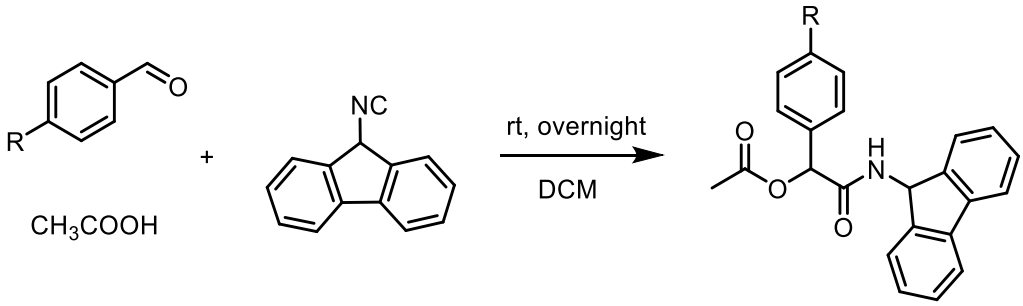
8

R= -Cl, OMe

To a stirred solution of substituted pyridin-2-amine (1.0 mmol) in MeOH (1.0 mL), acetic acid (0.2 mmol), 4- (*tert*-butyl) benzaldehyde (1.0 mmol) and 9-isocyano-9*H*-fluorene (1.0 mmol) are added at room temperature. Then, the reaction mixture is refluxed for 2 h. The solvent is removed under reduced

pressure and the residue is purified by column chromatography (PE-EA 4:1) to give the compounds **8** and **2c**.

General procedure for the Passerini 3-component reaction

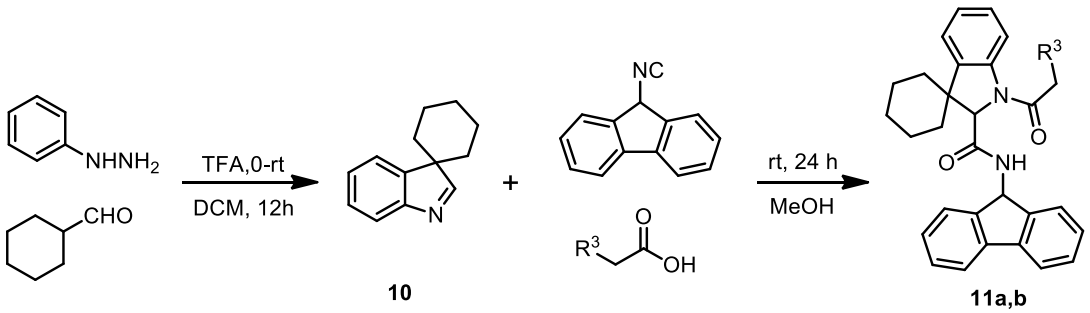


R = Cl or *tert*-butyl

9a,**b**

To a stirred solution of 9-isocyano-9*H*-fluorene (1.0 mmol) in DCM (2.0 mL), the corresponding aldehyde (1.0 mmol) and acetic acid (1.0 mmol) are added at room temperature. The reaction mixture is stirred vigorously overnight. The solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA 2:1) to give the corresponding Passerini adducts **9a**,**b**.

General procedure for the Ugi-Joullié reaction



R^3= -Cl, -^{t}Bu

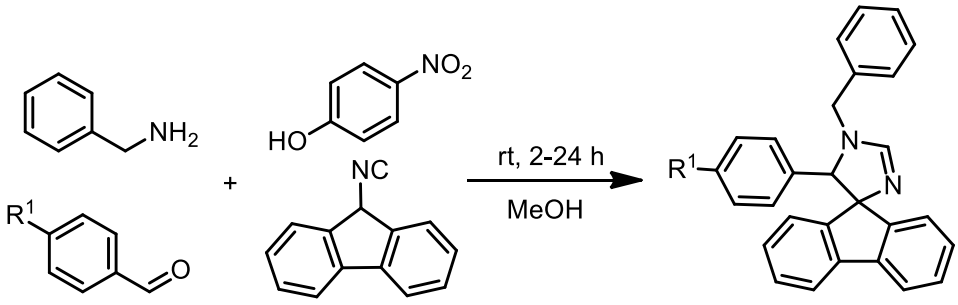
Synthesis of the spiroindolenine 10

To stirred solution of phenylhydrazine (2.0 mmol) and cyclohexanecarbaldehyde (2.0 mmol) in DCM (20.0 mL), trifluoroacetic acid (TFA, 4.0 mmol) is added dropwise at 0 °C. The reaction mixture is then warmed to room temperature for 12 h. Subsequently, the mixture is diluted with water (20.0 mL) and DCM (20.0 mL) and neutralized with Na_2CO_3 (6.0 mmol). The combined aqueous layers are extracted by DCM (2 x 10.0 mL). The organic layers are washed with water and brine, dried over Na_2SO_4 and the solvent is removed under reduced pressure. The crude compound **10** is obtained and used directly in the next step without further purification.[2]

Synthesis of adduct 11

To a stirred solution of **10** (1.0 mmol) in MeOH (4.0 mL), 9-isocyano-9*H*-fluorene (1.0 mmol) and the corresponding acid (1.0 mmol) are added at room temperature for 24 h. The solvent is removed under reduced pressure and the residue is washed with diethyl ether. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA 8:1) to give the compounds **11a,b**.

General procedure for the Ugi-Smile reaction



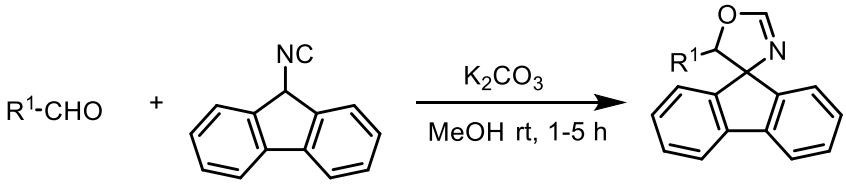
R[1]= -Cl, -Me

2d,e

To a stirred solution of benzylamine (1.0 mmol) in MeOH (2.0 mL), the corresponding aldehyde (1.0 mmol), 9-isocyano-9*H*-fluorene (1.0 mmol) and *p*-

nitro-phenol (1.0 mmol) are added at room temperature for 2-24 h. The solvent is removed under reduced pressure and the reaction mixture is purified by column chromatography (PE-EA 2:1) to give compounds **2d**,**e**.

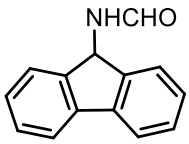
General procedure for the synthesis of oxazoles



12a-c

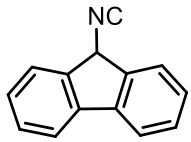
To a stirred solution of the corresponding aldehyde (1.0 mmol) and 9-isocyano-9*H*-fluorene (1.0 mmol) in MeOH (3.0 mL), K_2CO_3 (1.5 mmol) is added at rt. The reaction mixture is stirred vigorously for 1-5 h. Then, the solvent is removed under reduced pressure and the residue is filtered and washed with Et_2O affording the targeted compound. Alternatively, the solvent is removed under reduced pressure and the residue is purified by column chromatography (PE-EA 4:1) to give the compounds **12a**-**c**. We have to mention that compound **12a** proved to be not particular stable after long storage.

N-(9*H*-fluoren-9-yl)formamide (1a)



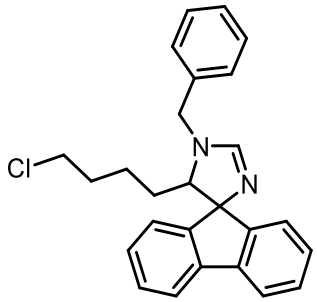
1.51 g, 72%, white solid. *Mixture of rotamers observed.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.52 (s, 0.2H), 8.49 (s, 0.8H), 7.72 (d, *J* = 7.5 Hz, 0.3H), 7.68 (d, *J* = 7.5 Hz, 1.7H), 7.56 (dd, *J* = 7.5, 0.7 Hz, 1.7H), 7.50 (dd, *J* = 7.5, 0.7 Hz, 0.3H), 7.45 (t, *J* = 7.5 Hz, 0.3H), 7.40 (t, *J* = 7.5 Hz, 1.7H), 7.36 (td, *J* = 7.5, 1.0 Hz, 0.3H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1.7H), 6.28 (d, *J* = 9.1 Hz, 0.8H), 5.83 (s, 0.8H), 5.69 (s, 0.2H), 5.45 (d, *J* = 9.1 Hz, 0.2H).

9-isocyano-9*H*-fluorene (1)



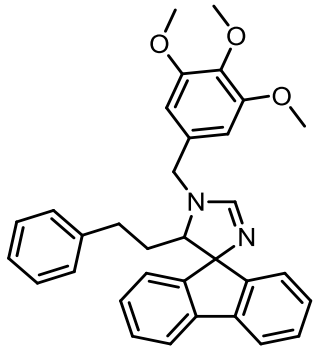
879 mg, 92% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 - 7.70 (m, 4H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.40 (td, *J* = 7.5, 1.0 Hz, 2H), 5.63 (s, 1H).

1'-benzyl-5'-(4-chlorobutyl)-1',5'-dihydrospiro[fluorene-9,4'-imidazole] (2a)



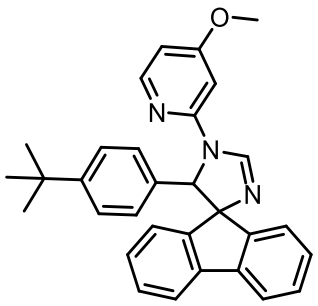
284 mg, 71% yield, yellow solid. mp 169 - 173 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.44 - 7.31 (m, 8H), 7.26 - 7.21 (m, 2H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.61 (d, *J* = 15.2 Hz, 1H), 4.14 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.97 - 2.87 (m, 2H), 1.74 - 1.67 (m, 1H), 1.49 - 1.41 (m, 1H), 1.18 - 1.01 (m, 2H), 0.58 - 0.49 (m, 1H), 0.42 - 0.33 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7, 145.3, 140.4, 140.1, 139.9, 133.1, 130.5, 130.3, 129.4, 129.0, 128.9, 128.3, 128.2, 125.8, 124.3, 120.8, 120.5, 74.7, 68.0, 50.3, 43.8, 31.3, 26.7, 21.4. **MS** (ESI) m/z calcd for $C_{26}H_{26}ClN_2$ $[M + H]^+$ 401.18, found 401.20.

5'-phenethyl-1'-(3,4,5-trimethoxybenzyl)-1',5'-dihydrospiro[fluorene-9,4'-imidazole] (2b)



368 mg, 73% yield, brown solid. mp 77 - 81 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.43 - 7.34 (m, 3H), 7.28 - 7.21 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.00 - 6.99 (m, 3H), 6.50 (s, 2H), 6.34 - 6.31 (m, 2H), 4.58 (d, *J* = 15.0 Hz, 1H), 4.42 (s, 1H), 4.23 (d, *J* = 15.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 6H), 3.83 - 3.79 (m, 1H), 1.94 - 1.87 (m, 1H), 1.73 - 1.65 (m, 2H), 1.57 - 1.51 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 153.8, 149.0, 143.7, 140.7, 140.6, 140.2, 137.9, 131.1, 129.2, 129.0, 128.3, 128.2, 128.0, 127.6, 125.9, 125.8, 124.5, 120.5, 120.2, 105.1, 80.5, 66.7, 61.1, 56.4, 50.5, 31.0, 30.9. **MS** (ESI) m/z calcd for $C_{33}H_{33}N_2O_3$ $[M + H]^+$ 505.25, found 505.10.

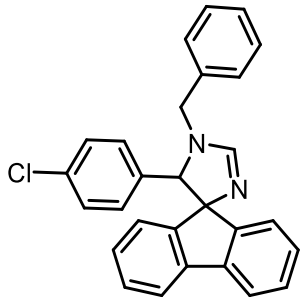
5'-(4-(*tert*-butyl)phenyl)-1'-(4-methoxypyridin-2-yl)-1',5'-dihydrospiro[fluorene-9,4'-imidazole] (2c)



285 mg, 62% yield, red oil. **^{1}H NMR** (500 MHz, DMSO) δ 8.79 (s, 1H), 8.07 (d, *J* = 5.8 Hz, 1H), 7.79 - 7.77 (m, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.44 - 7.41 (m,

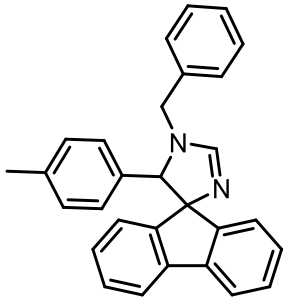
2H), 7.36 - 7.34 (m, 1H), 7.15 (td, *J* = 7.5, 0.8 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.77 (td, *J* = 7.5, 0.8 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 2H), 6.57 (dd, *J* = 5.8, 2.2 Hz, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 5.57 (s, 1H), 3.64 (s, 3H), 1.14 (s, 9H). **^{13}C NMR** (126 MHz, DMSO) δ 166.8, 153.0, 152.1, 149.9, 149.8, 149.5, 144.4, 140.1, 139.1, 133.9, 128.8, 128.3, 128.1, 126.5, 126.3, 124.7, 123.4, 119.9, 119.6, 104.5, 95.5, 84.9, 68.3, 55.3, 34.1, 31.0. **MS** (ESI) m/z calcd for $C_{31}H_{30}N_3O$ $[M + H]^+$ 460.24, found 460.20.

1'-benzyl-5'-(4-chlorophenyl)-1',5'-dihydrospiro[fluorene-9,4'-imidazole] (2d)



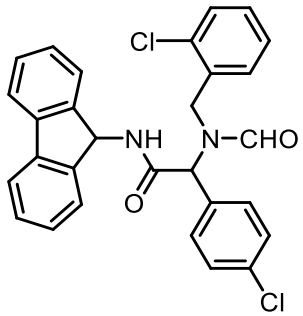
353 mg, 84% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.43 - 7.40 (m, 4H), 7.33 (td, *J* = 7.4, 1.2 Hz, 1H), 7.27 - 7.25 (m, 3H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.11 (td, *J* = 7.4, 1.2 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.00 -6.99 (m, 3H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.76 (s, 1H), 4.70 (d, *J* = 14.5 Hz, 1H), 4.08 (d, *J* = 14.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.5, 149.1, 144.4, 140.9, 139.8, 135.1, 133.4, 133.2, 129.1, 128.80, 128.78, 128.42, 128.40, 128.3, 128.1, 128.0, 127.0, 126.1, 124.1, 119.7, 119.6, 84.2, 72.1, 50.8. **MS** (ESI) m/z calcd for $C_{28}H_{22}ClN_2$ $[M + H]^+$ 421.15, found 421.20.

1'-benzyl-5'-(*p*-tolyl)-1',5'-dihydrospiro[fluorene-9,4'-imidazole] (2e)



348 mg, 87% yield, yellow solid. mp 72 - 73 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.93 (s, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.50 - 7.49 (m, 1H), 7.42 - 7.39 (m, 2H), 7.36 - 7.32 (m, 2H), 7.27 (td, *J* = 7.4, 1.1 Hz, 1H), 7.22 - 7.20 (m, 2H), 7.11 - 7.06 (m, 3H), 7.02 - 6.98 (m, 1H), 6.81 (d, *J* = 7.8 Hz, 2H), 6.58 (d, *J* = 7.8 Hz, 2H), 4.77 (d, *J* = 14.7 Hz, 1H), 4.61 (s, 1H), 3.97 (d, *J* = 14.7 Hz, 1H), 2.07 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 159.9, 149.7, 145.3, 140.3, 139.2, 136.1, 135.8, 131.8, 128.7, 128.54, 128.51, 128.4, 127.9, 127.8, 126.6, 126.4, 126.1, 123.9, 119.6, 119.5, 84.1, 71.4, 49.4, 20.6. **MS** (ESI) m/z calcd for $C_{29}H_{25}N_2$ $[M + H]^+$ 401.20, found 401.20.

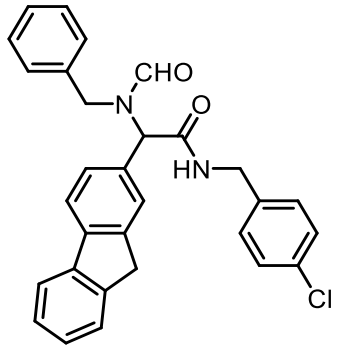
2- (*N*-(2-chlorobenzyl) formamido)-2-(4-chlorophenyl)-*N*-(9*H*-fluoren-9-yl) acetamide (5a)



355 mg, 71% yield, orange solid. mp 194 - 196 °C. *Mixture of rotamers observed.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 1.4 Hz, 1H), 8.25 (d, *J* = 1.4 Hz, 1H), 7.73 - 7.68 (m, 2H), 7.55 - 7.28 (m, 9H), 7.24 - 7.17 (m, 3H), 6.96 - 6.94 (m, 1H), 6.83 (d, *J* = 8.7 Hz, 0.3H), 6.48 (d, *J* = 8.7 Hz, 0.6H), 6.22 - 6.17 (m, 1H), 5.82 (s, 0.6H), 5.12 (s, 0.3H), 4.71 - 4.65 (m, 1H), 4.54 - 4.47 (m, 1H).

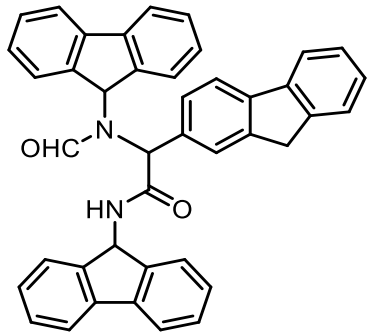
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 163.9, 163.8, 143.7, 140.6, 140.6, 138.8, 135.2, 134.5, 132.2, 131.0, 130.1, 130.0, 129.9, 129.5, 129.1, 128.9, 128.9, 128.4, 128.1, 127.9, 127.9, 127.8, 127.7, 126.6, 125.6, 125.2, 125.0, 125.0, 120.2, 120.2, 120.1, 120.1, 64.3, 59.9, 55.1, 54.9, 49.8, 46.9. **MS** (ESI) m/z calcd for $C_{29}H_{23}Cl_2N_2O_2$ $[M + H]^+$ 501.11, found 501.10.

2-(*N*-benzylformamido)-*N*-(4-chlorobenzyl)-2-(9*H*-fluoren-2-yl) acetamide (5b)



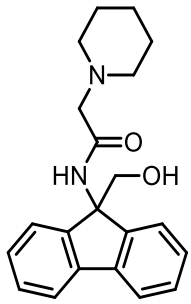
427 mg, 89% yield, white solid. mp 199 - 201 °C. *Mixture of rotamers observed*. **^{1}H NMR** (500 MHz, DMSO) δ 8.84 (t, *J* = 5.9 Hz, 0.7H), 8.74 (t, *J* = 5.9 Hz, 0.3H), 8.38 (s, 0.3H), 8.21 (s, 0.7H), 7.86 (d, *J* = 7.5 Hz, 0.7H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 0.3H), 7.57 - 7.54 (m, 1H), 7.37 - 7.18 (m, 11.5H), 7.03 - 7.02 (m, 1H), 6.90 - 6.88 (m, 0.5H), 5.92 (s, 0.3H), 5.31 (s, 0.7H), 4.72 - 4.66 (m, 1H), 4.43 - 4.38 (m, 1H), 4.3o - 4.26 (m, 2H), 3.90 - 3.78 (m, 1.7H), 3.70 - 3.65 (m, 0.3H). **^{13}C NMR** (126 MHz, DMSO) δ 168.9, 163.7, 143.4, 143.3, 141.1, 140.4, 137.9, 137.1, 134.5, 131.5, 129.3, 129.1, 128.3, 128.28, 128.27, 127.9, 127.8, 127.1, 127.0, 126.8, 125.2, 125.1, 120.3, 120.2, 63.4, 47.1, 41.9, 36.3. **MS** (ESI) m/z calcd for $C_{30}H_{26}ClN_2O_2$ $[M + H]^+$ 481.99, found 483.50.

2-(*N*-(9*H*-fluoren-9-yl)formamido)-2-(9*H*-fluoren-2-yl)-*N*-(9*H*-fluoren-9-yl) acetamide (5c)



242 mg, 34% yield, white solid. mp 174 - 179 °C. **^{1}H NMR** (500 MHz, DMSO) δ 8.68 (s, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 7.97 - 7.95 (m, 2H), 7.88 - 7.84 (m, 2H), 7.74 - 7.71 (m, 2H), 7.61 - 7.52 (m, 5H), 7.48 - 7.42 (m, 2H), 7.38 - 7.33 (m, 4H), 7.32 - 7.27 (m, 3H), 7.25 - 7.21 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.80 (d, *J* = 6.5 Hz, 1H), 6.75 (s, 1H), 5.84 (d, *J* = 8.1 Hz, 1H), 4.35 (s, 1H), 3.96 - 3.84 (m, 2H). **^{13}C NMR** (126 MHz, DMSO) δ 170.1, 166.0, 165.1, 147.5, 144.2, 143.4, 143.3, 141.0, 140.3, 139.9, 135.8, 135.4, 128.9, 128.5, 127.7, 127.6, 127.4, 127.1, 126.9, 126.2, 125.2, 125.1, 124.8, 120.5, 120.3, 120.2, 120.0, 99.5, 59.6, 57.0, 54.2, 36.4. **MS** (ESI) m/z calcd for $C_{42}H_{31}N_2O_2$ $[M + H]^+$ 595.24, found 595.00.

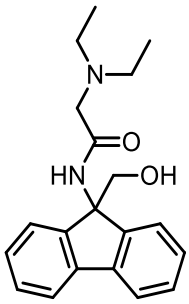
N-(9-(hydroxymethyl)-9*H*-fluoren-9-yl)-2- (piperidin-1-yl) acetamide (6a)



215 mg, 64%, white solid. mp 158 - 160 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.43 (td, *J* = 7.5, 1.1 Hz, 2H), 7.32 (td, *J* = 7.5, 1.1 Hz, 2H), 5.21 (s, 1H), 3.95 (s, 2H), 2.99 (s, 2H),

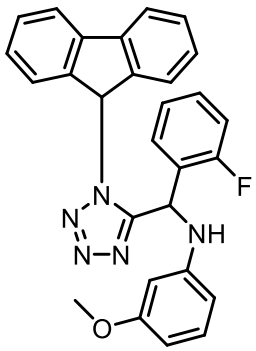
2.44 (s, 4H), 1.46 - 1.41 (m, 4H), 1.37 - 1.32 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.2, 139.6, 129.2, 128.1, 124.8, 120.4, 69.2, 68.3, 62.6, 54.8, 29.8, 26.0, 23.6. **MS** (ESI) m/z calcd for $C_{21}H_{24}N_2NaO_2$ $[M + Na]^+$ 359.17, found 359.13.

2-(diethylamino)-*N*-(9-(hydroxymethyl)-9*H*-fluoren-9-yl) acetamide (6b)



243 mg, 75% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.72 - 7.70 (m, 2H), 7.62 - 7.60 (m, 2H), 7.42 (td, *J* = 7.5, 1.1 Hz, 2H), 7.32 (td, *J* = 7.5, 1.1 Hz, 2H), 5.41 (t, *J* = 7.0 Hz, 1H), 3.95 (d, *J* = 7.0 Hz, 2H), 3.07 (s, 2H), 2.49 (q, *J* = 7.1 Hz, 4H), 0.90 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.1, 146.2, 139.6, 129.2, 128.1, 124.9, 120.4, 69.4, 68.2, 57.9, 49.0, 12.4. **MS** (ESI) m/z calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.19, found 325.10.

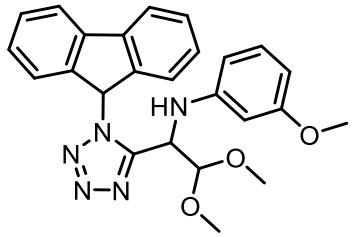
N-((1- (9*H*-fluoren-9-yl)-1*H*-tetrazol-5-yl)(2-fluorophenyl) methyl)-3-methoxyaniline (7a)



778 mg, 84% yield, yellow solid. mp 124 - 127 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.96 (dd, *J* = 7.6, 4.3 Hz, 2H), 7.54 - 7.46 (m, 4H), 7.29 - 7.22 (m, 5H), 7.15 (s, 1H), 6.96 (t, *J* = 8.0 Hz, 2H), 6.83 (s, 1H), 6.35 (s, 2H), 6.20 (dd, *J* = 8.1, 1.8

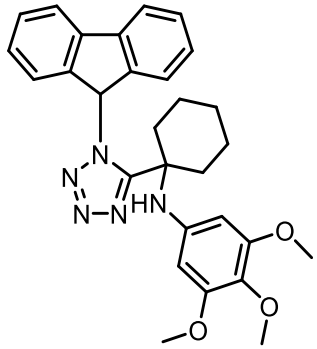
Hz, 1H), 3.63 (s, 3H), 2.81 (s, 1H). **^{13}C NMR** (126 MHz, DMSO) δ 161.3, 160.7, 148.2, 140.64, 140.61, 130.31, 130.25, 130.2, 128.7, 128.6, 125.3, 125.2, 121.4, 116.1, 115.9, 107.0, 103.3, 100.3, 61.8, 55.2, 50.5. **^{19}F NMR** (471 MHz, DMSO) δ -113.99. **MS** (ESI) m/z calcd for $C_{28}H_{22}FN_5NaO$ $[M + Na]^+$ 486.17, found 486.10.

N-(1-(1-(9*H*-fluoren-9-yl)-1*H*-tetrazol-5-yl)-2,2-dimethoxyethyl)-3-methoxyaniline (7b)



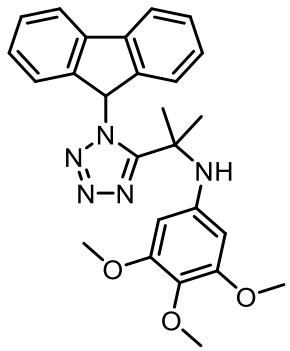
381 mg, 43% yield, yellow solid. mp 152 - 154 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.95 (dd, *J* = 11.7, 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 7.6, 0.9 Hz, 1H), 7.27 (s, 1H), 7.16 - 7.11 (m, 2H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 6.44 - 6.40 (m, 2H), 6.28 - 6.26 (m, 1H), 5.64 - 5.61 (m, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 3.65 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 160.4, 155.0, 147.9, 141.9, 141.7, 140.12, 140.08, 129.9, 129.54, 129.45, 128.1, 128.0, 124.54, 124.48, 120.8, 120.7, 106.1, 104.4, 103.1, 99.4, 61.5, 56.2, 55.3, 54.8, 51.0. **MS** (ESI) m/z calcd for $C_{25}H_{25}N_5NaO_3$ $[M + Na]^+$ 466.19, found 466.13.

N-(1-(1-(9*H*-fluoren-9-yl)-1*H*-tetrazol-5-yl)cyclohexyl)-3,4,5-trimethoxyaniline (7c)



427 mg, 86% yield, gray solid. mp 216 - 218 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.26 (s, 1H), 7.12 (s, 2H), 6.39 (s, 2H), 5.72 (s, 2H), 3.59 (s, 3H), 3.47 (s, 6H), 2.87 (s, 1H), 2.61 - 2.58 (m, 2H), 2.352 - 2.348 (m, 2H), 1.80 - 1.69 (m, 5H), 1.47 - 1.44 (m, 1H). **^{13}C NMR** (126 MHz, DMSO) δ 160.3, 153.6, 141.6, 141.5, 140.0, 129.7, 129.5, 128.0, 124.1, 120.8, 91.6, 61.9, 60.5, 55.5, 53.5, 45.5, 24.8, 20.9. **MS** (ESI) m/z calcd for $C_{29}H_{31}N_5NaO_3$ $[M + Na]^+$ 520.23, found 520.07.

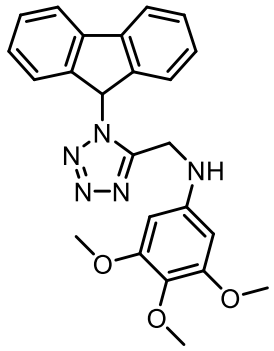
N-(2-(1-(9*H*-fluoren-9-yl)-1*H*-tetrazol-5-yl)propan-2-yl)-3,4,5-trimethoxyaniline (7d)



379 mg, 83% yield, gray solid. mp 236 - 238 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.25 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 2H), 6.56 (s, 1H), 6.50 (s, 2H), 5.68 (s, 2H), 3.59 (s, 3H), 3.48 (s, 6H), 2.02 (s, 6H). **^{13}C NMR** (126 MHz, DMSO) δ 160.1, 153.6, 141.9, 141.5, 140.0, 129.9,

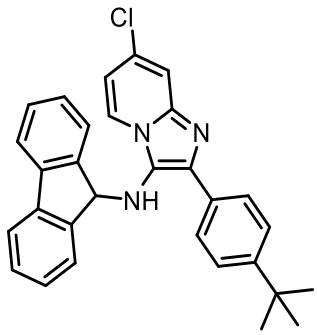
129.5, 128.0, 124.2, 120.8, 91.8, 62.0, 60.5, 55.5, 51.0, 45.5, 28.5. **MS** (ESI) m/z calcd for $C_{26}H_{27}N_5NaO_3$ $[M + Na]^+$ 480.20, found 480.07.

N-((1-(9*H*-fluoren-9-yl)-1*H*-tetrazol-5-yl) methyl)-3,4,5-trimethoxyaniline (7e)



339 mg, 79% yield, white solid. mp 96 - 97 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.10 (s, 1H), 6.35 (t, *J* = 5.7 Hz, 1H), 5.97 (s, 2H), 4.82 (s, 2H), 3.65 (s, 6H), 3.53 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 153.5, 143.9, 140.9, 140.2, 129.7, 128.1, 125.0, 120.8, 90.6, 61.1, 60.21, 55.6, 36.8. **MS** (ESI) m/z calcd for $C_{24}H_{23}N_5NaO_3$ $[M + Na]^+$ 452.17, found 452.10.

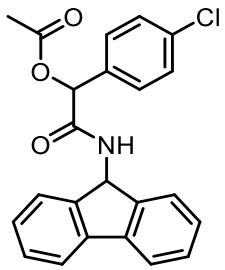
2-(4-(*tert*-butyl)phenyl)-7-chloro-*N*-(9*H*-fluoren-9-yl)imidazo[1,2-*a*]pyridin-3-amine (8)



121 mg, 31% yield, yellow solid. mp 183 - 184 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 - 7.98 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.63 (dd, *J* = 7.3, 0.5 Hz, 1H),

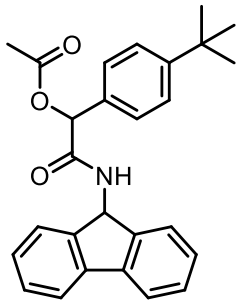
7.56 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.45 - 7.43 (m, 2H), 7.37 - 7.34 (m, 2H), 7.16 - 7.12 (m, 4H), 6.58 (dd, *J* = 7.3, 2.0 Hz, 1H), 5.25 (d, *J* = 7.6 Hz, 1H), 3.72 (d, *J* = 7.6 Hz, 1H), 1.34 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.8, 144.4, 141.2, 140.5, 136.8, 131.0, 130.3, 128.9, 127.8, 126.9, 125.7, 125.04, 125.01, 122.9, 120.2, 116.3, 113.1, 61.4, 34.7, 31.4. **MS** (ESI) m/z calcd for $C_{30}H_{27}ClN_3$ $[M + H]^+$ 464.19, found 464.10.

2-((9*H*-fluoren-9-yl) amino)-1-(4-chlorophenyl)-2-oxoethyl acetate (9a)



121 mg, 31% yield, white solid. mp 216 - 218 °C. **^{1}H NMR** (500 MHz, DMSO) δ 8.98 (d, *J* = 8.6 Hz, 1H), 7.85 - 7.83 (m, 2H), 7.55 - 7.54 (m, 2H), 7.51 - 7.49 (m, 2H), 7.44 - 7.32 (m, 4H), 7.25 (td, *J* = 7.4, 0.9 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 5.95 (d, *J* = 8.5 Hz, 1H), 5.88 (s, 1H), 2.13 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 169.8, 168.9, 144.4, 144.1, 140.1, 140.0, 134.8, 133.4, 129.2, 128.6, 128.52, 128.49, 127.69, 127.65, 124.8, 124.3, 120.3, 74.5, 53.9, 20.6. **MS** (ESI) m/z calcd for $C_{23}H_{18}ClNNaO_3$ $[M + Na]^+$ 414.09, found 414.07.

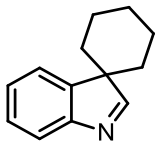
2-((9*H*-fluoren-9-yl) amino)-1-(4-(*tert*-butyl) phenyl)-2-oxoethyl acetate (9b)



99 mg, 24% yield, red oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.5, 3.3 Hz, 2H), 7.51 - 7.47 (m, 2H), 7.44 - 7.39 (m, 6H), 7.34 - 7.29 (m, 2H), 6.42 (d,

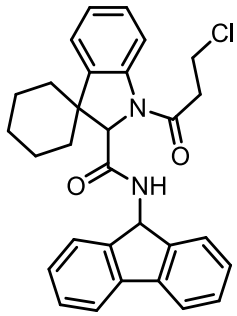
J = 8.7 Hz, 1H), 6.25 (d, *J* = 9.1 Hz, 1H), 6.19 (s, 1H), 2.10 (s, 3H), 1.33 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.7, 169.4, 152.3, 144.01, 143.96, 140.8, 140.7, 132.6, 130.2, 128.98, 128.95, 128.0, 127.4, 126.0, 125.6, 125.23, 125.21, 120.2, 120.1, 75.1, 54.6, 34.8, 31.4, 21.2. **MS** (ESI) m/z calcd for $C_{27}H_{27}NNaO_3$ $[M + Na]^+$ 436.19, found 436.10.

5'-(4-chlorophenyl)-5'*H*-spiro[fluorene-9,4'-oxazole] (10)



248 mg, 67% yield, brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.26 - 7.24 (m, 1H), 1.94-1.91 (m, 2H), 1.78-1.67 (m, 5H), 1.32 - 1.22 (m, 3H).

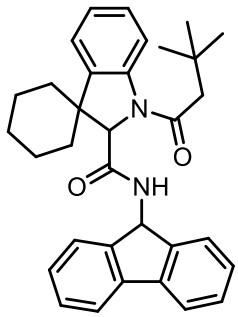
5'-(4-chlorophenyl)-5'*H*-spiro[fluorene-9,4'-oxazole] (11a)



431 mg, 89% yield, yellow oil. **^{1}H NMR** (500 MHz, DMSO) δ 9.30 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 - 7.39 (m, 3H), 7.35 - 7.31 (m, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.03 (d, *J* = 8.2 Hz, 1H), 4.88 (s, 1H), 3.96 - 3.86 (m, 2H), 3.20 - 3.14 (dt, *J* = 16.6, 6.4 Hz, 1H), 2.87 (dt, *J* = 16.6, 6.4 Hz, 1H), 1.97 (s, 2H), 1.70 - 1.59 (m, 3H), 1.56 - 1.47 (m, 3H), 1.28 - 1.19 (m, 2H). **^{13}C NMR** (126 MHz, DMSO) δ 168.7, 167.9, 144.0, 142.3, 140.7, 140.3, 140.2, 128.7, 128.7, 127.9, 127.8, 127.2, 125.1, 124.8, 123.6, 122.0, 120.4, 120.3,

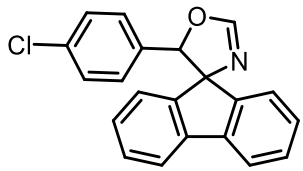
115.9, 69.0, 54.0, 47.9, 37.7, 37.3, 29.7, 25.1, 23.3, 21.8. **MS** (ESI) m/z calcd for $C_{30}H_{30}ClN_2O_2$ $[M + H]^+$ 485.20, found 485.30.

1'-(3,3-dimethylbutanoyl)-*N*-(9*H*-fluoren-9-yl)spiro[cyclohexane-1,3'-indoline]-2'-carboxamide (11b)



379 mg, 77% yield, yellow oil. *Mixture of rotamers observed*. **^{1}H NMR** (500 MHz, DMSO) δ 9.28 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.4 - 7.33 (m, 6H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.02 (d, *J* = 8.3 Hz, 1H), 4.87 (s, 1H), 2.15 - 1.12 (m, 1H), 2.06 (s, 1H), 1.96 - 1.95 (m, 2H), 1.68 - 1.67 (m, 2H), 1.56 - 1.46 (m, 4H), 1.32 - 1.22 (m, 2H), 0.99 (s, 6H) 0.99 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 173.2, 170.0, 168.9, 144.2, 143.9, 142.7, 140.6, 140.3, 140.2, 128.7, 127.8, 127.7, 127.1, 124.9, 124.8, 123.2, 121.7, 120.4, 116.1, 69.6, 53.9, 47.6, 47.4, 46.5, 31.3, 30.0, 29.6, 29.4, 29.3, 25.2, 23.2, 21.7. **MS** (ESI) m/z calcd for $C_{33}H_{36}ClN_2NaO_2$ $[M + Na]^+$ 515.27, found 515.60.

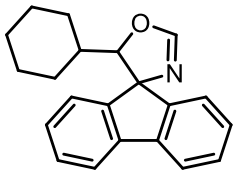
5'-(4-chlorophenyl)-5'*H*-spiro[fluorene-9,4'-oxazole] (12a)



201 mg, 61% yield, yellow oil. **^{1}H NMR** (500 MHz, DMSO) δ 7.95 (s, 1H), 7.81 (dd, *J* = 6.7, 0.9 Hz, 1H), 7.68 - 7.63 (m, 2H), 7.49 - 7.42 (m, 2H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 - 7.11 (m, 2H), 6.99 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 - 6.79

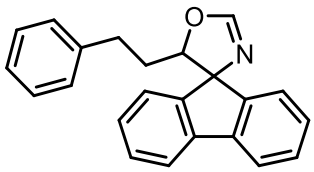
(m, 3H), 5.97 (s, 1H). **^{13}C NMR** (126 MHz, DMSO) δ 158.1, 147.5, 143.3, 140.3, 139.5, 134.9, 132.0, 129.2, 128.6, 128.3, 127.9, 127.0, 126.4, 126.0, 124.6, 120.2, 119.9, 86.1, 82.5. **MS** (ESI) m/z calcd for $C_{21}H_{15}ClNO$ $[M + H]^+$ 332.08, found 332.10.

5'-cyclohexyl-5'*H*-spiro[fluorene-9,4'-oxazole] (12b)



179 mg, 59% yield, yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 2H), 7.44 - 7.42 (m, 1H), 7.40 - 7.39 (m, 1H), 7.37 - 7.33 (m, 2H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 - 7.16 (m, 1H), 5.86 - 5.84 (m, 1H), 5.08 (s, 1H), 2.00 - 1.94 (m, 2H), 1.36 - 1.18 (m, 6H), 0.92 - 0.85 (m, 2H), 0.68 - 0.63 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 149.0, 143.9, 140.4, 132.7, 128.9, 128.8, 128.2, 126.9, 124.0, 121.4, 120.1, 119.7, 88.4, 81.3, 25.5, 24.6, 22.1, 21.7. **MS** (ESI) m/z calcd for $C_{21}H_{21}NKO$ $[M + K]^+$ 342.13, found 342.10.

5'-phenethyl-5'*H*-spiro[fluorene-9,4'-oxazole] (12c)



276 mg, 85% yield, white solid. mp 161 - 163 °C. **^{1}H NMR** (500 MHz, DMSO) δ 7.89 - 7.83 (m, 2H), 7.69 (s, 1H), 7.43 - 7.27 (m, 6H), 7.10 - 7.05 (m, 3H), 6.76 (d, *J* = 6.9 Hz, 2H), 4.68 - 4.65 (m, 1H), 2.30 - 2.25 (m, 1H), 2.13 - 2.07 (m, 1H), 1.89 - 1.88 (m, 1H), 1.32 - 1.28 (m, 1H). **^{13}C NMR** (126 MHz, DMSO) δ 158.2, 148.1, 143.5, 140.6, 140.0, 139.9, 129.0, 128.9, 128.23, 128.18, 128.0, 127.4, 126.0, 125.9, 124.5, 120.5, 120.2, 85.1, 80.6, 32.9, 31.5. **MS** (ESI) m/z calcd for $C_{23}H_{19}NNaO$ $[M + Na]^+$ 348.14, found 348.10.

3. Single crystal x-ray structure determination

Data for compound ***12c***

A specimen of $C_{23}H_{19}NO$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å).

The frames are integrated with the Bruker SAINT software package using a narrow-frame algorithm.

The integration of the data using a monoclinic unit cell yielded a total of 15804 reflections to a maximum θ angle of 50.40^{o} (1.00Å resolution), of which 1781 are independent (average redundancy 8.874, completeness =100.0%, R_{int}=2.63%, R_{sig}=1.28%) and 1653 (92.81%) are greater than 2σ (F^2). The final cell constants of a=12.5179 (4) Å, b=10.3390 (3) Å, c = 13.2660 (4) Å, β =98.7970 (10) ^{o}, volume = 1696.72 (9) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ (I).

The structure is solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/n 1, with Z =4 for the formula unit, $C_{23}H_{19}NO$. The final anisotropic full-matrix least-squares refinement on F^2 with 226 variables converged at R1 = 3.69%, for the observed data and wR2 =11.75% for all data. The goodness-of-fit is 1.100. The largest peak in the final difference electron density synthesis is 0.083 e^-/Å^3 and the largest hole is -0.214 e^-/Å^3 with an RMS deviation of 0.042e^-/Å^3. On the basis of the final model, the calculated density is 1.274g/cm^3 and F (000), 688e^-. CCDC No.: 2065540.

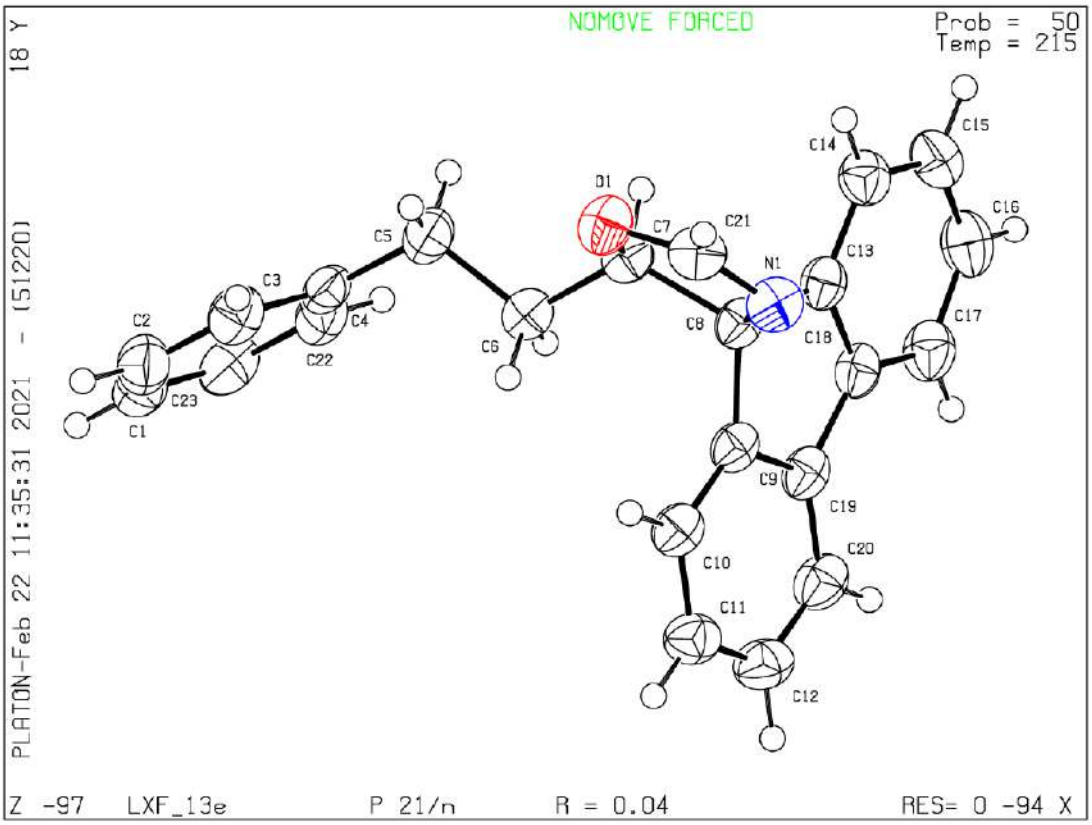


Table 1 Sample and crystal data for **12c**

Identification code	**12c** (LXF_13e)	
Chemical formula	$C_{23}H_{19}NO$	
Formula weight	325.39 g/mol	
Temperature	215 (2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 12.5179 (4) Å	α = 90°

	b = 10.3390 (3) Å	β = 98.7970 (10) °
	c = 13.2660 (4) Å	γ = 90°
Volume	1696.72 (9) $Å^3$	
Z	4	
Density (calculated)	1.274 g/cm^3	
Absorption coefficient	0.603 mm^{-1}	
F (000)	688	
Theta range for data collection	4.52 to 50.40°	
Index ranges	-12<=h<=12, -9<=k<=10, -13<=l<=13	
Reflections collected	15804	
Independent reflections	1781 [R (int) = 0.0263]	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma w (F_o^2 - F_c^2)^2$	

Data / restraints / parameters	1781 / 0 / 226	
Goodness-of-fit on F^2	1.100	
Δ/σ_{max}	0.007	
Final R indices	1653 data, I>2σ (I)	R1 = 0.0369, wR2 = 0.1129
	all data	R1 = 0.0390, wR2 = 0.1175
Weighting scheme	$w=1/[\sigma^2 (F_o^2) + (0.1000P)^2]$ where $P= (F_o^2+2F_c^2) /3$	
Largest diff. peak and hole	0.083 and -0.214 eÅ^{-3}	
R.M.S. deviation from mean	0.042 eÅ^{-3}	

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*Data for compound **2e***

The frames are integrated with the Bruker SAINT software package using a narrow-frame algorithm.

A specimen of $C_{29}H_{24}N_2$ is used for the X-ray crystallographic analysis. The X-ray intensity data are measured (λ = 1.54178 Å).

The integration of the data using a triclinic unit cell yielded a total of 15823 reflections to a maximum θ angle of 48.75° (1.03Å resolution), of which 2206 are independent (average redundancy 7.173, completeness =100.0%, R_{int}=2.63%, R_{sig}=1.60%) and 2009 (91.07%) are greater than 2σ (F^2). The final cell constants of a =9.3897 (2) Å, b=10.5292 (3) Å, c = 12.5854 (3) Å, α =84.5700 (10) °, β =80.9700 (10) °, γ = 67.6540 (10) °, volume =1135.46 (4) Å^3,

are based upon the refinement of the XYZ-centroids of 9899 reflections above 20 σ (I) with 7.117° < 2θ <97.40°. Data are corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission is 0.878.

The structure is solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z =2 for the formula unit, $C_{29}H_{24}N_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 298 variables converged at R1 =4.31%, for the observed data and wR2 =9.09% for all data. The goodness-of-fit is 1.058. The largest peak in the final difference electron density synthesis is 0.161 $e^-/Å^3$and the largest hole is -0.196$e^-/Å^3$ with an RMS deviation of 0.037$e^-/Å^3$. On the basis of the final model, the calculated density is 1.218 g/cm^3 and F (000), 444 e^-. CCDC No.: 2065539.

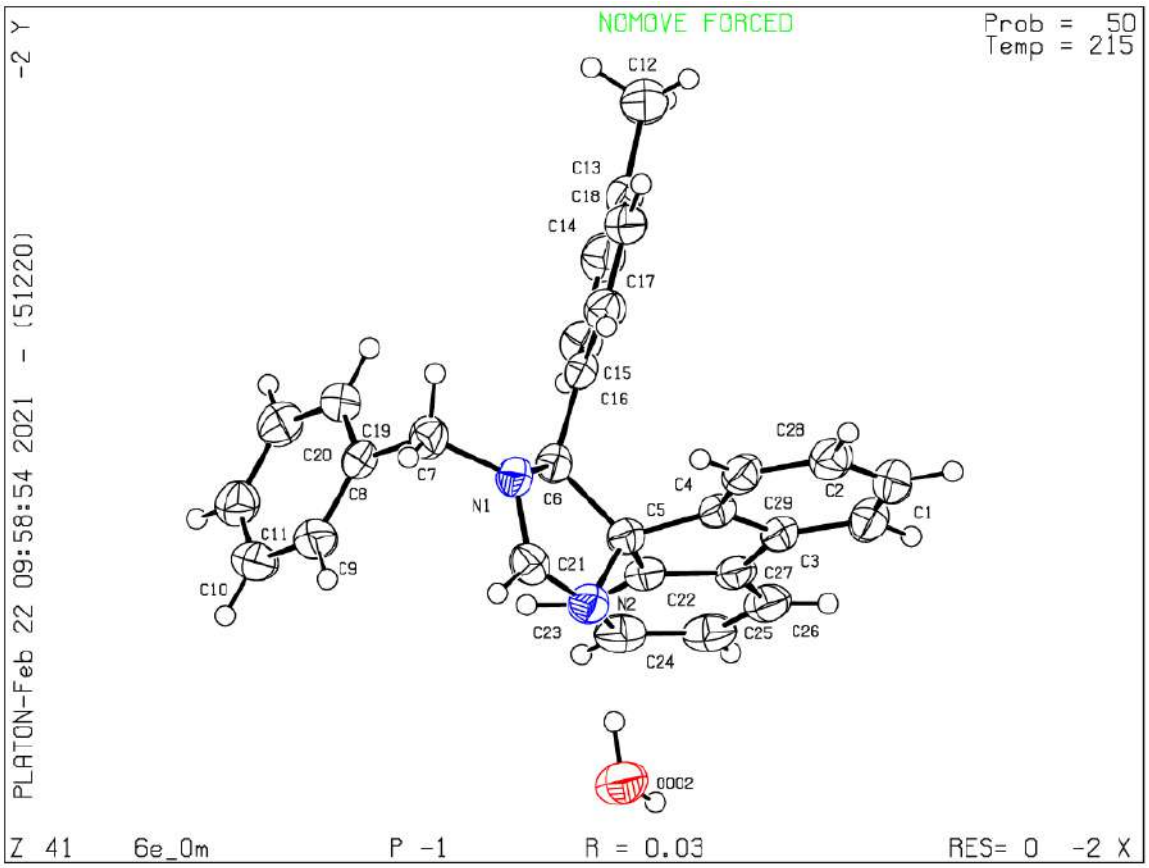

Table 2 Sample and crystal data for **2e**

Identification code	**2e** (LXF_6e)	
Chemical formula	$C_{29}H_{24}N_2O$	
Formula weight	416.50 g/mol	
Temperature	215 (2) K	
Wavelength	1.54178 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.3890 (2) Å	α = 84.5730 (10) °
	b = 10.5280 (2) Å	β = 80.9730 (10) °
	c = 12.5854 (3) Å	γ = 67.6500 (10) °
Volume	1135.71 (4) $Å^3$	
Z	2	
Density (calculated)	1.224 g/cm^3	
Absorption coefficient	0.577 mm^{-1}	
F (000)	440	
Theta range for data collection	3.56 to 48.75°	
Index ranges	-8<=h<=8, -9<=k<=9, -11<=l<=11	
Reflections collected	13943	

Independent reflections	1801 [R (int) = 0.0249]	
Coverage of independent reflections	99.9%	
Absorption correction	Multi-Scan	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	Σ w (Fo2 - Fc2) 2	
Data / restraints / parameters	2206 / 0 / 298	
Goodness-of-fit on F2	1.058	
Δ/σmax	5.943	
Final R indices	1660 data, I>2σ (I)	R1 = 0.0431, wR2 = 0.1095
	all data	R1 = 0.0457, wR2 = 0.1180
Weighting scheme	$w=1/[\sigma^2 (F_o^2) + (0.1000P)^2]$ where $P= (F_o^2+2F_c^2) /3$	
Largest diff. peak and hole	0.161 and -0.196 $eÅ^{-3}$	
R.M.S. deviation from mean	0.037 $eÅ^{-3}$	

REFERENCES

1. Neochoritis, C. G., Zarganes-Tzitzikas, T., Stotani, S., Dömling, A., Herdtweck, E., Khoury, K., Dömling, A. *ACS Combinatorial Science* **2015**, *17 (9),* 493-499.
2. Ruijter, E., Orru, R., Estévez, V., Kloeters, L., Kwietniewska, N., & Vicente-García, E. *Synlett* **2016**, *28 (03),* 376-380.

Chapter 5

Synthesis of novel TTF-based scaffolds via MCRs

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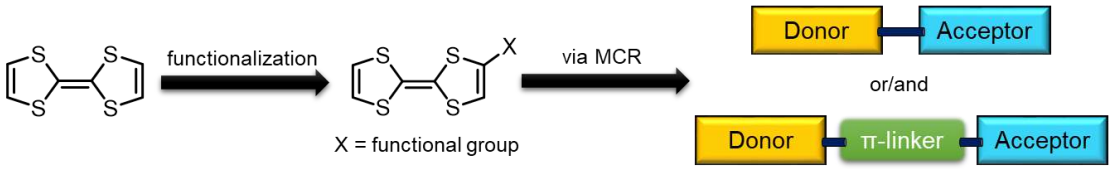
Manuscript in preparation

ABSTRACT

In this chapter, several novel TTF-based derivatives are reported. Utilization of the vL, GBB, U-4CR and UT-4CR reactions yielded the functionalized TTF-fused derivatives. Interestingly, the x-ray structures of few TTF derivatives showed their intermolecular stacking. The electronic properties of substituted TTF-phenyl-oxazole compounds are measured via the Hall measurement. In addition, UV spectra and DFT calculations are employed on those molecules.



INTRODUCTION

Small organic molecules as semiconductors and superconductors have attracted the attention of researchers.[1] Over the last fifty years, tetrathiafulvalene (TTF) and TTF-fused compounds are some of the most common and widespread frameworks present in material science. This electron-rich skeleton constitutes the major part of many organic semiconductors due to its planar 3D structure, extended delocalized π-orbitals and stable mixed-valency.[2] Additionally, the π-π stacking between the TTF molecules affects the conductivity, as the latter belongs to the so called p-type charge carriers.[3] Furthermore, TTF has high redox potential and presents good solubility qualities.[4] Interestingly, the neutral TTF with 14-π-electrons is non-aromatic, however, in its oxidation states TTF^{+} and TTF^{2+} are aromatic stable (Hückel's rule).[5] These unique physical and chemical properties renders TTF and TTF analogs useful in various fields. They are not only utilized as conductors, but also widely employed as supramolecular gels,[6] molecular electronic devices,[7] photovoltaics,[8] solid catalysts,[9] magnetic materials,[10] molecular near-infrared (NIR) dyes[11] and artificial molecular machines.[12]

The first donor-acceptors (D-A) systems were designed as molecular diodes by Aviram and Ratner in 1974 (Figure 1, **3**).[13] Later on, those donor-acceptor (D-A) systems were employed in many cutting-edge fields whereas TTF, due to its strong electron-donating properties, is a suitable donor partner in such systems (Figure 1). These D-A type dyads are well known due to their plenty advantages, such as a low HOMO-LUMO gap,[14-15] well-defined structures and photogeneration.[16] In addition, donor and acceptor moieties in one molecule are becoming more and more popular in quantum information science (QIS),[16] artificial photosynthetic models, molecular chromophores with nonlinear optical (NLO)[17] and semiconducting MOFs.[18]

Nevertheless, the design and synthesis of these privileged scaffolds is limited.[19] Arguably, the limitation of synthetic methods of the TTF-based compounds so far seriously affects their broad application. We considered, in this chapter, applying our MCR tactics towards novel TTF derivatives syntheses.[20] Thus, few TTF-based libraries of potential (semi) conductors are obtained.

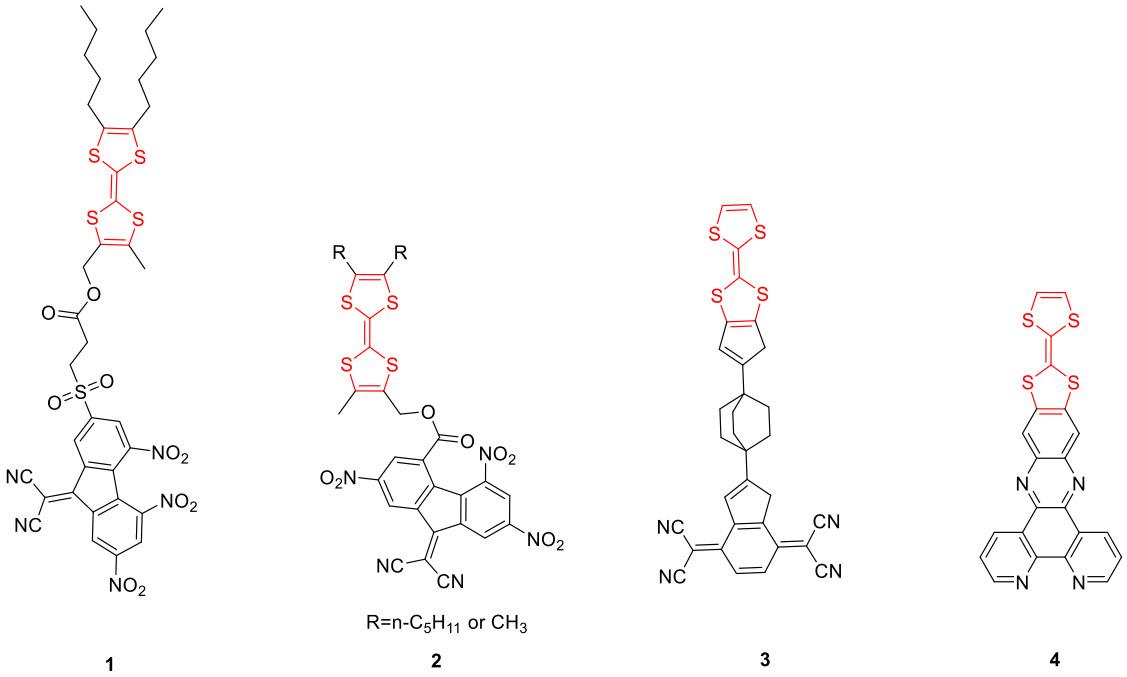


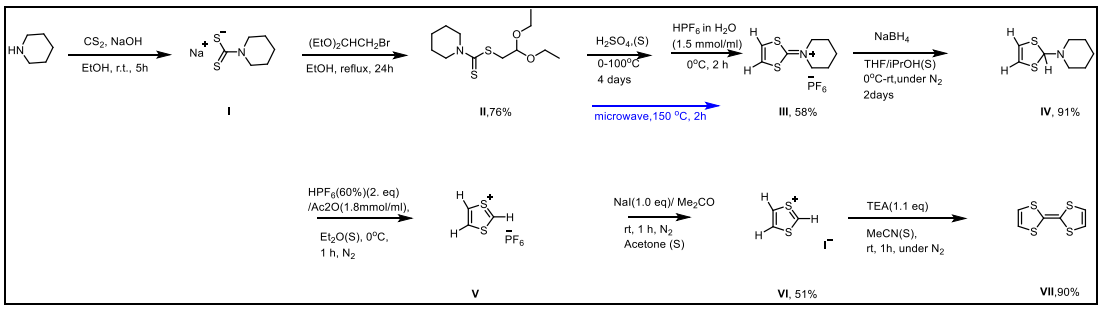
Figure 1 The molecules with the donor (TTF-red) and acceptor moieties.

RESULTS AND DISCUSSION

Part 1 *Access to TTF-based derivatives via IMCR*

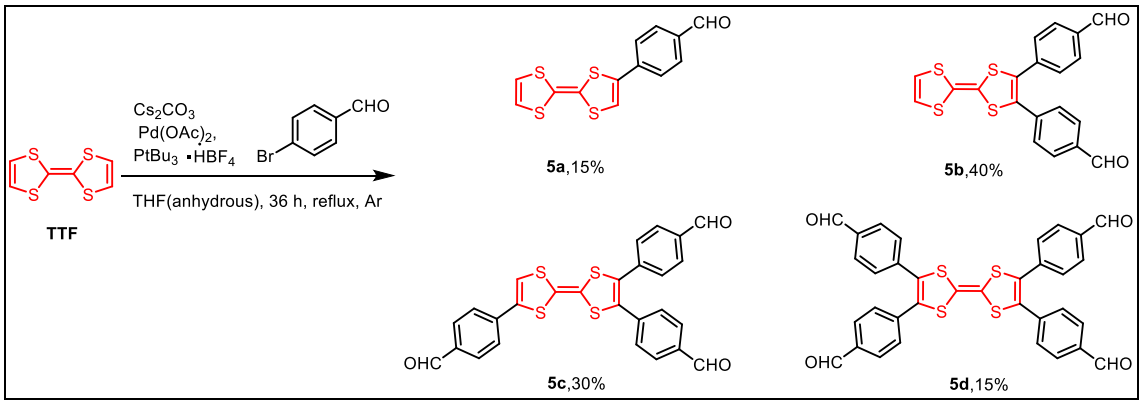
In general, TTF with low $E^1_{1/2}$ and $E^2_{1/2}$ values have three different redox-states. When TTF-based derivatives are fused with electron acceptors, they form the corresponding donor-acceptor (D-A) systems, therefore an intramolecular charge transfer or photo induced electron transfer may occur. Additionally, the π-donor ability of the TTF derivatives can be adjusted upon substitution. The adjustable π-donor ability opens the door to develop a variety of switchable molecular and supramolecular architectures. As far as we know, a synthetic breakthrough of the construction of novel TTF derivatives will permit the significant step forward in molecular machines and molecular-level devices.[21]

For these reasons, we design to employ MCR chemistry towards TTF-based compounds syntheses. Firstly, we have obtained the TTF precursor either by a gram-scale 8-step synthesis (Scheme 1)[22] or by a commercial source. Notably the temperature of the third step is very important in the TTF synthesis. Compound **III** cannot be obtained when the temperature reaches below 70 ºC. Alternatively, as shown in the Scheme 1, we can obtain the **III** via microwave irradiation only in 2 hours with similar yields as the conventional procedure.



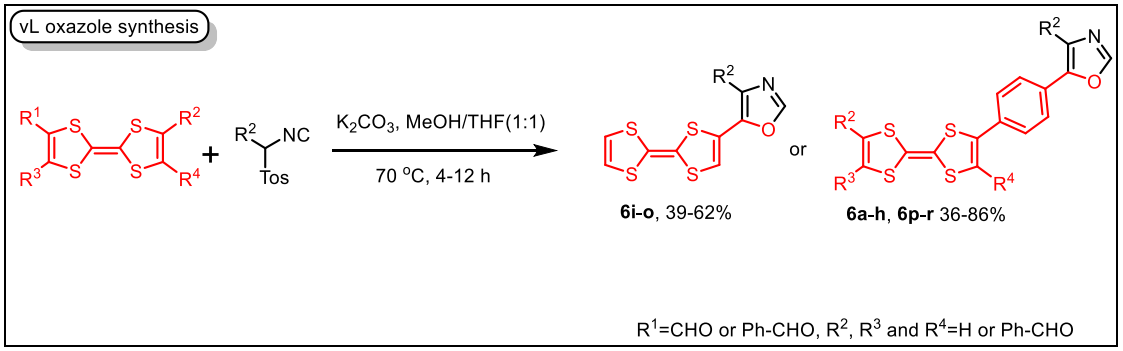
Scheme 1 The synthetic procedure towards TTF.

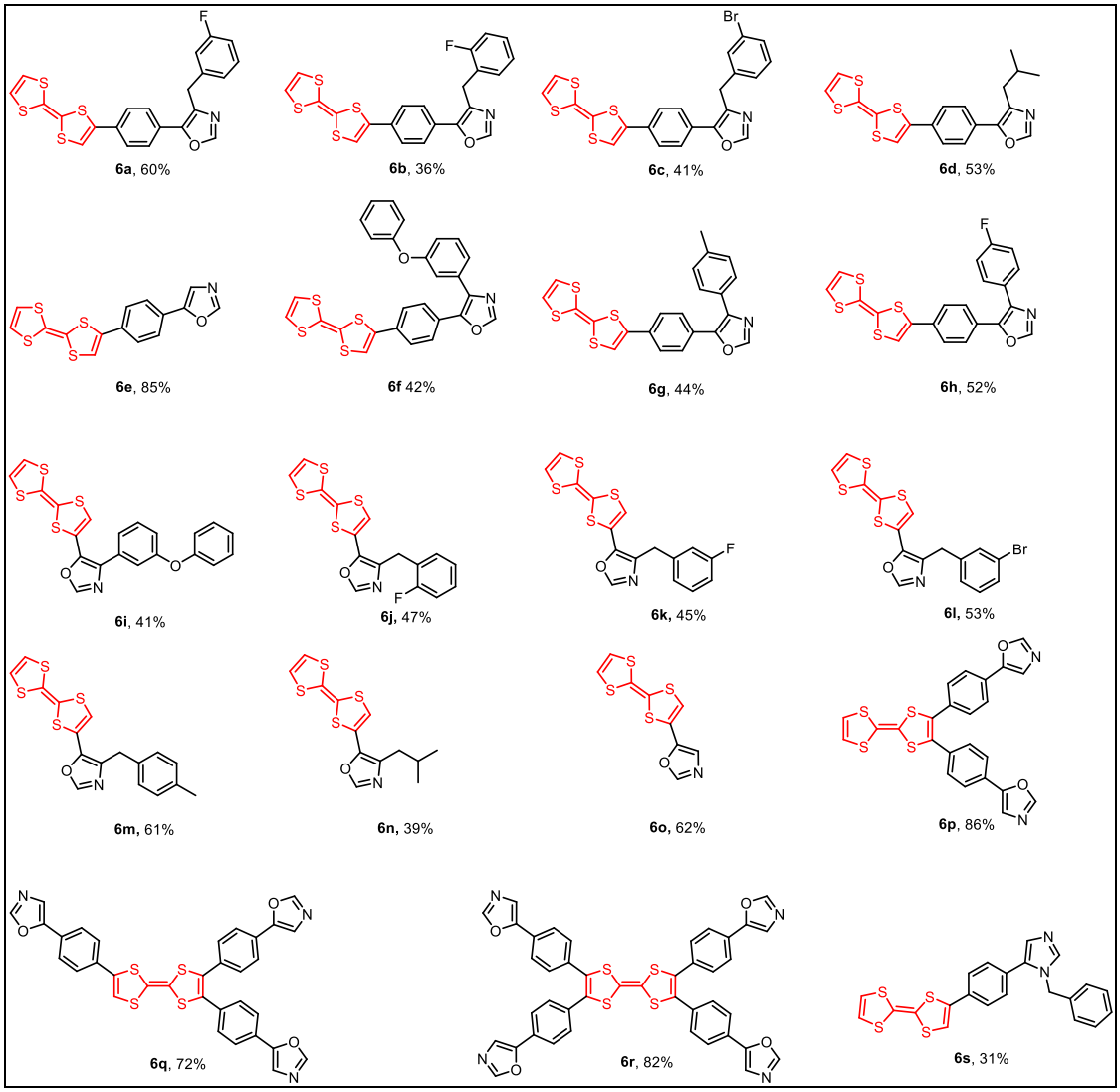
Then, the TTF-fused aldehydes (**5a-d** shown in Scheme 2) are prepared through the existing procedures.[23] During this procedure, Cs_2CO_3 is added to the mixture of $Pd(OAc)_2$, P*t*Bu_3·HBF_4, TTF and 4-bromobenzadehyde in a two-neck round bottom flask at room temperature. The system is subjected to three cycles of evacuation and refilling with nitrogen and reflux for 36 hours. The aldehydes are separated by column chromatography (silica gel, DCM 100%).



Scheme 2 Formylation of the TTF.

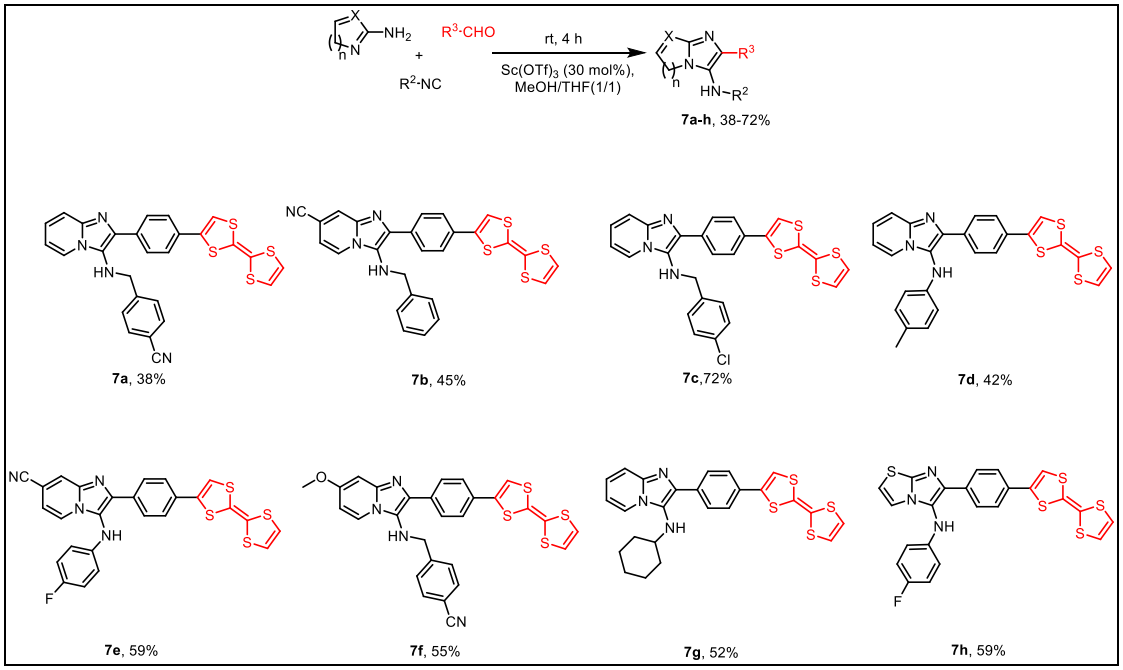
After functionalizing the TTF, we combine the TTF aldehyde and α-acidic isocyanides at 70 ºC which yield the desired vL-oxazole adducts (Scheme 3) in good to very good yields. As shown in Scheme 3, the scope of the isocyanides is quite broad. The tosylmethyl isocyanide (TosMIC) and various TosMIC derivatives are employed. The synthesized TTF-fused oxazoles contain the aryl (**6f**-**l**), benzylic (**6a**-**c**, **6j**-**m**) and aliphatic (**6d**, **6n**) moieties with different substituents. These TTF adducts include both a π-linker (**6a**-**h**, **6p**-**r**) and without (**6i**-**o**) are synthesized via our protocol. Notably, the di, tri and tetra-substituted TTF benzyl aldehydes and their corresponding oxazoles are also obtained in very good yields. However, the gram-scale reactions of these multi-substituted TTF-fused oxazoles are not successful due to poor solubility of the TTF-fused aldehydes (Scheme 3).





Scheme 3 The vL procedure towards TTF-fused oxazoles and the library of TTF-fused oxazoles.

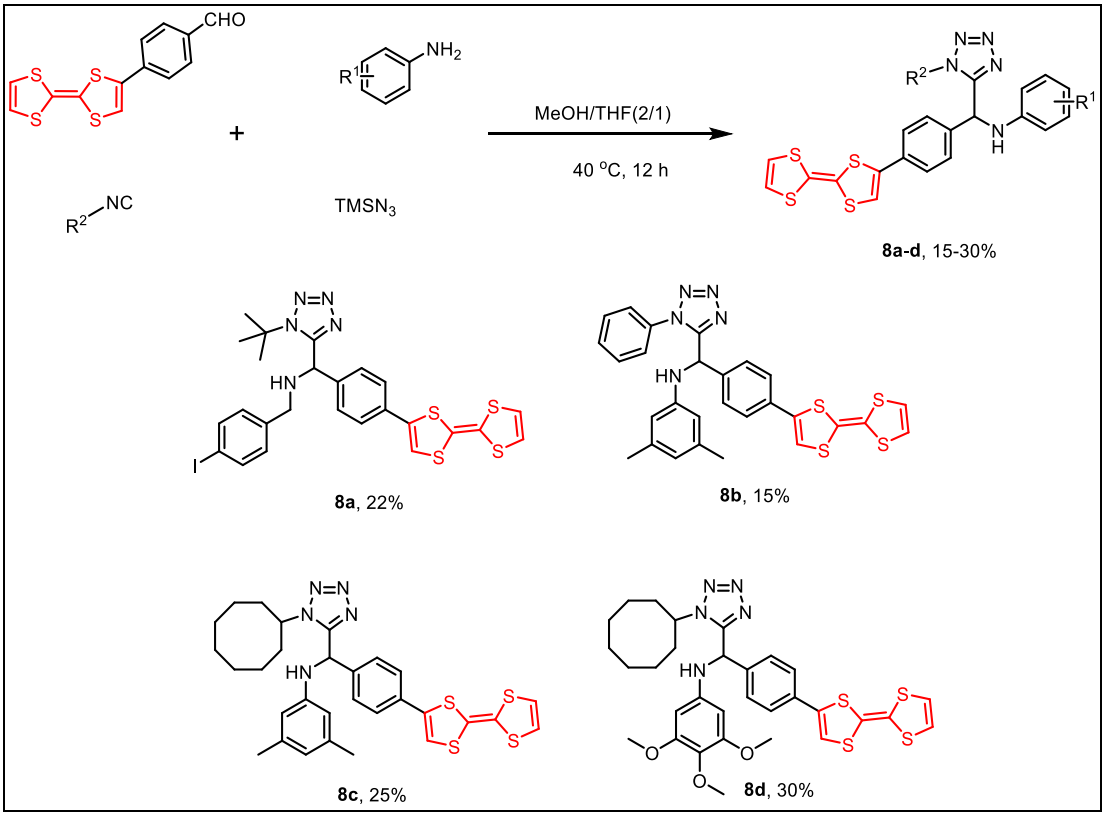
Then, the GBB-3CR is employed towards the synthesis of TTF derivatives; the reaction of the mono-substituted TTF benzyl aldehyde, aminopyridines and isocyanides in the presence of the Lewis acid scandium triflate in a mixture of solvents (MeOH/THF: 2:1) at room temperature takes place. To our satisfaction, 8 different TTF-fused GBB products are obtained in good yields. The aminopyridines with both electron donating and electron withdrawing groups are applicable whereas, the thiazol-2-amine (**7h**) works as well. The variety of isocyanides is broad as well including aryl (**7d**-**e**, **7h**), benzylic (**7a**-**c**, **7f**) and aliphatic (**7g**) as shown in the Scheme 4.



Scheme 4 the procedure towards the TTF-fused GBB adducts and the products.

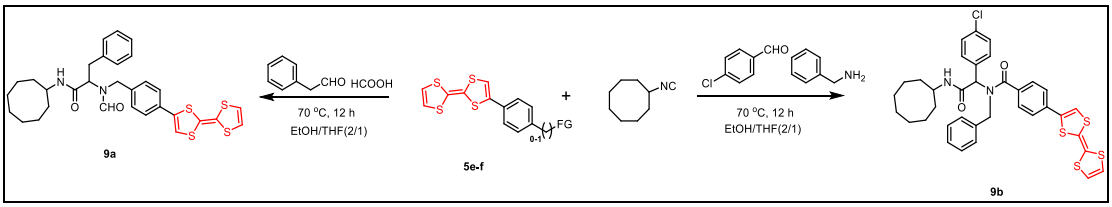
The UT-4CR is considered as a variant of the U-4CR. The potential and features of the tetrazole core has been aforementioned many times in Chapter 1, 3 and 4. Therefore, we tried to employ this reaction with the reactants **5a**, the corresponding anilines, isocyanides and trimethylsilyl azide. Unfortunately, all the isolated yields are low, despite of the many efforts of optimization. The microwave irradiation, different temperatures and solvents conditions have

been screened as well. The adducts **8a**, **8c-d** are obtained via this protocol (Scheme 5).



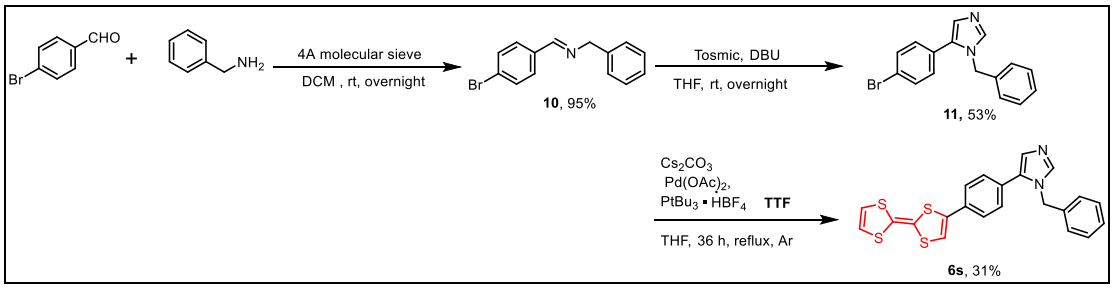
Scheme 5 The procedure towards the TTF-fused UT adducts and the products.

As a continuation, we synthesized the amino **5e** and the carboxy **5f** following the existing procedures (see EXPERIMENTAL SECTION).[23] Then, these two functionalized TTF derivatives are employed in an U-4CR. Here, 2 U-4CR adducts are obtained under mild conditions (Scheme 6). The conditions will be optimized in a future work.



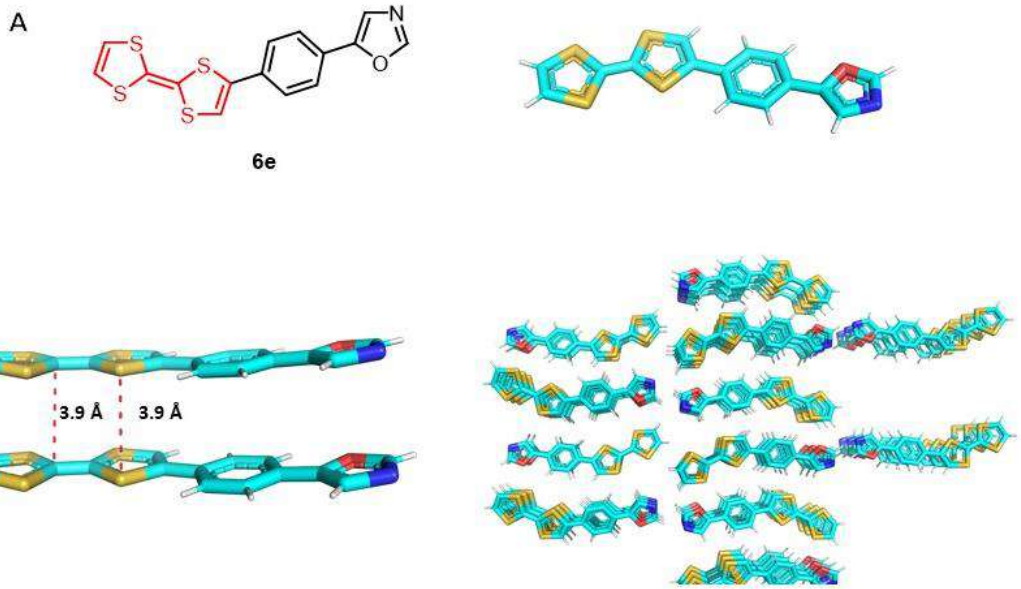
Scheme 6 The procedure towards the TTF-fused U-4CR adducts and the products.

To solve issues of some difficult syntheses, we tried to change the sequence of MCRs and the functionalization of the TTF. This strategy helped us get a few compounds which cannot be synthesized with our standrd procedures, such as the **6s** (Scheme 7). Notably, we utilized this strategy in the UT-4CR (**9a**), GBB-3CR (**8b**) and vL (**6e**), obtaining those derivatives in slightly lower yields than the previous procedure. Nevertheless, this method offers an alternative way to some adducts which is difficult obtained under the normal procedures.



Scheme 7 The procedure towards **6s**.

Several crystal structures of the isolated TTF-based molecules (**6e**, **6g**, **6h** and **5b**) are obtained during this project (shown Figure 2). The single-crystal structures of the latter show very important information for the design of electronic devices, for example, the TTF-based field-effect transistors.[24-25] Compound **2e** (Figure 2, A) has a planar conformation with short intermolecular distances of around 3.9 Å and a head to head π-π stacking. Compound **6g** has the same stack distance as **2e** with a head-to-head π-π stacking as well. However, the layer-to-layer of **6g** is S-S stacking. In addition, the whole molecule is not planar as shown in Figure 2, B. Regarding **6h**, we can observe a head to tail 3D crystal structure probably because of the halogen bond (Figure 2: C). As we know, the way of the stacking can affect the device's properties.[26] These various TTF-fused molecule stacking ways will be utilized in the near future.


A
S
S
S
S
N
O
6e
3.9 Å
3.9 Å
B
S
S
S
S
N
O
6g

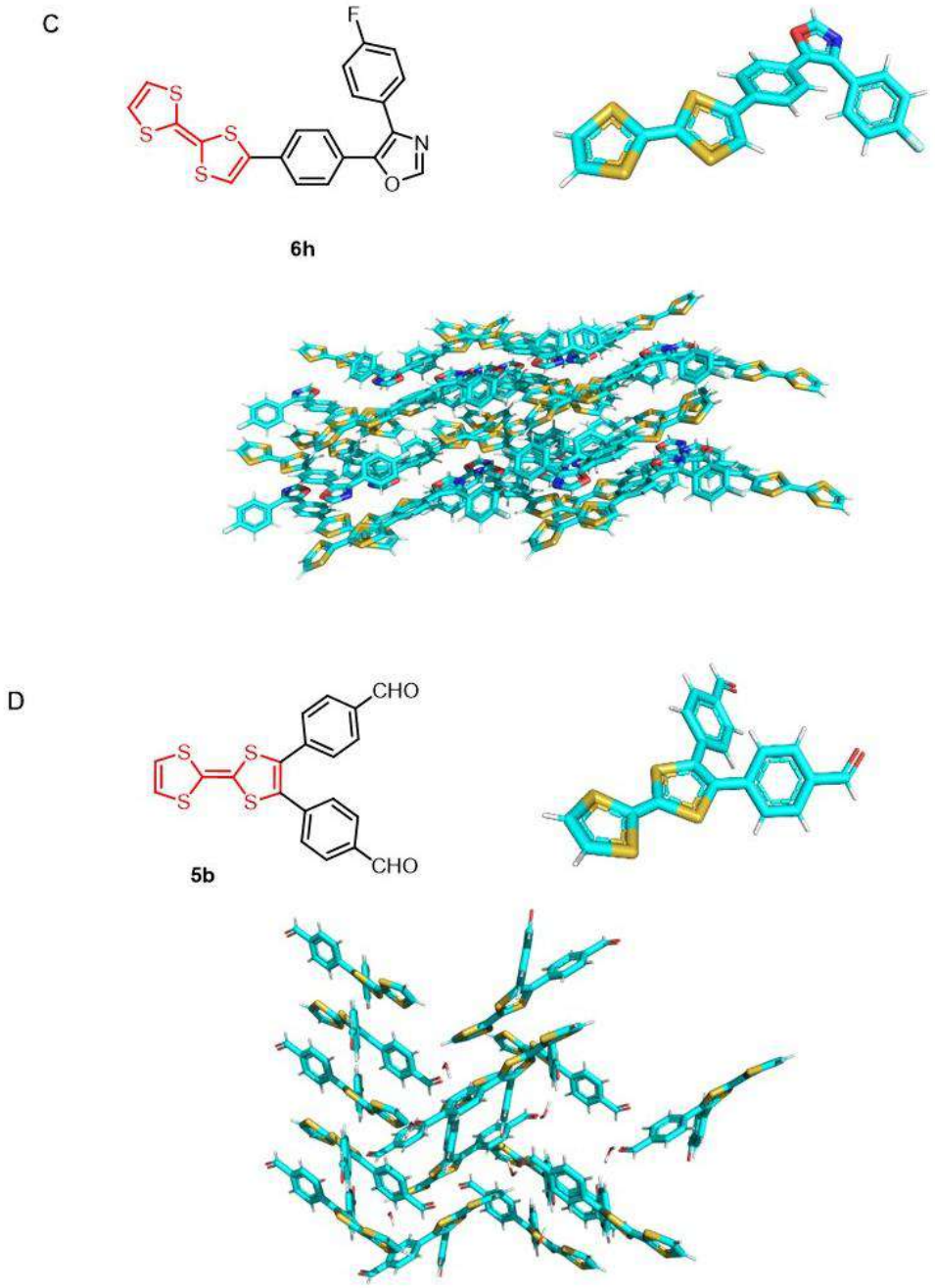
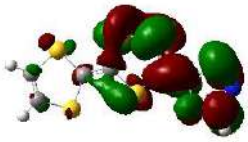
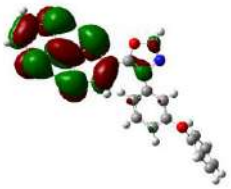
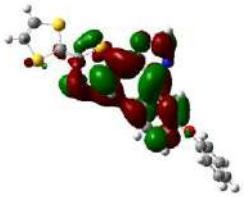
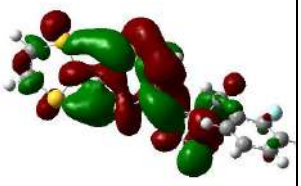
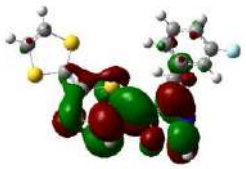
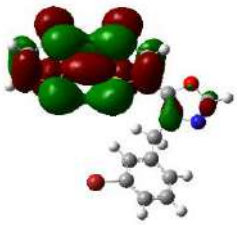
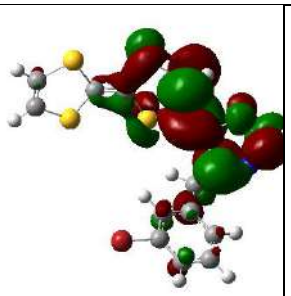
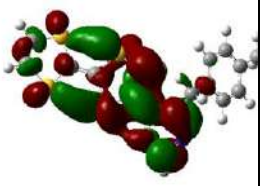
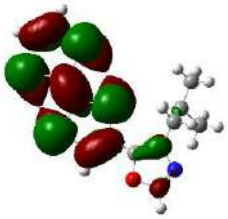
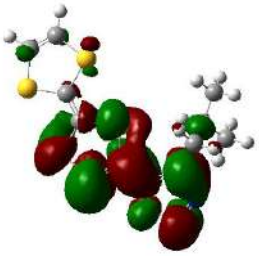


Figure 2 The single crystal X-ray structures of the TTF derivatives.

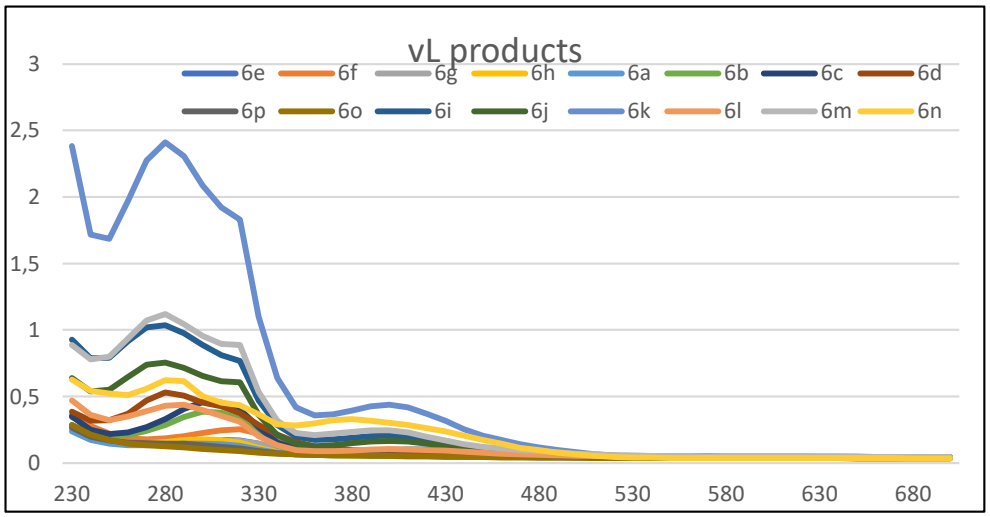
In addition, another important parameter, the electronic properties of donor-acceptor (D-A) molecular system, were calculated via DFT B3LYP/631G* level. The energy of the molecule's HOMO, LUMO and gap of the HOMO-LUMO is shown in Table 1.

Table 1 The DFT calculations of the D-A TTF derivatives.

Compound	Energy (Hartrees)	HOMO	LUMO	ΔE {LUMO-HOMO}
6o	-2068.62	 - 4.738 eV	 -1.323 eV	3.415
6i	-2605.94	 - 4.704 eV	 -1.527 eV	3.177
6j	-2438.22	 - 4.723 eV	 -1.230 eV	3.493
6k	-2438.22	 - 4.819 eV	 -1.296 eV	3.523

6l	-4910.09	 - 4.798 eV	 -1.313eV	3.485
6m	-2378.31	 - 4.653 eV	 -1.177 eV	3.476
6n	-2225.88	 - 4.697 eV	 -1.196 eV	3.501

To evidence the occurrence of donor-to-acceptor ICT, solution UV measurements are performed (Figure 3). This figure depicts the absorption band of some TTF-based molecules. Most of the TTF derivatives absorb around the 280-330 nm and demonstrate double absorption bands. Notably, some compounds' absorption broadband appear at the visible region, such as **6k** and **6n**. In future, this phenomenon could be beneficial to OL materials research for the demand of high transmittance in visible-light regions (400-700 nm).



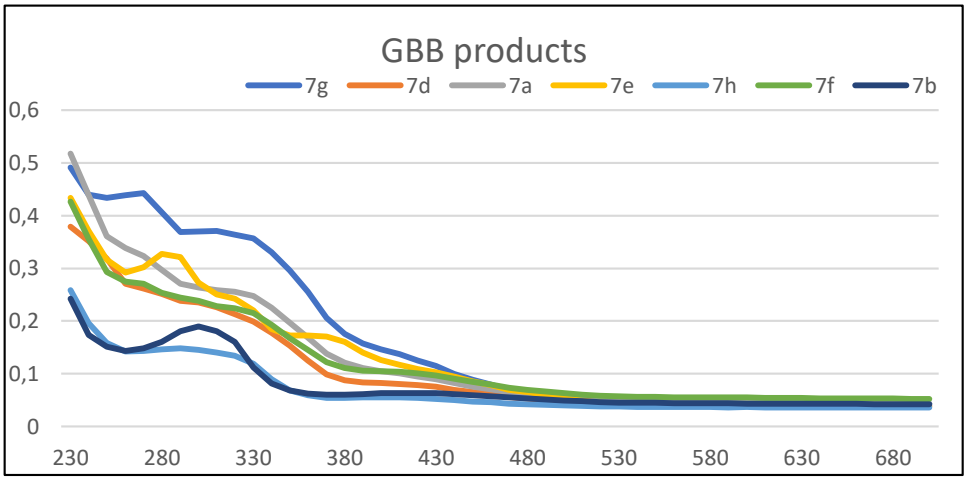


Figure 3 The UV-vis absorption spectra of the TTF-based compounds.

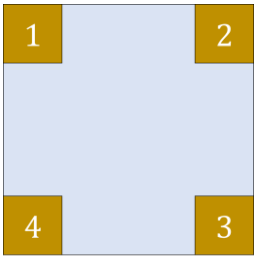
Part 2 *Electrochemical properties measurements*

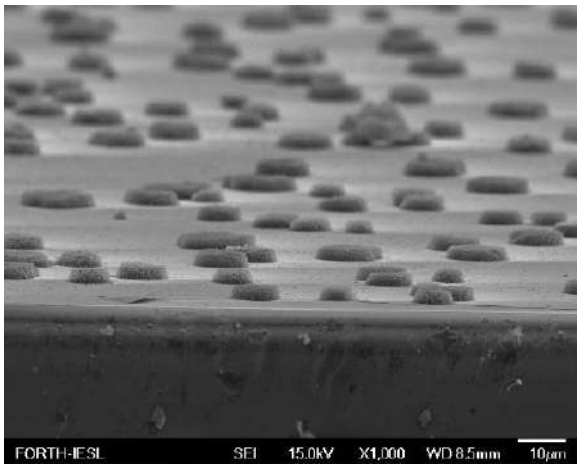
Charge transfer salts exhibit metallic conductivity and even superconductivity when they form the π-stacked molecular crystals.[27] This discovery revolutionized the field of organic superconductivity and has been extensively studied for its potential applications in the development of novel electronic materials and devices. Such as, the TTF-TCNQ (Tetrathiafulvalene-Tetracyano-*p*-Quinodimethane) complex is a good example of how the combination of TTF and electron-acceptor molecules can lead to the formation of new materials with unique electronic properties. This potential complex is used in studying the organic charge-transfer systerm. Herein, we seek to the materials of high charge mobility based on our large library of the TTF derivatives. In doing so, some synthesized TTF-fused compounds are mixed with TCNQ or tetracyanoethylene (TCNE) to form charge transfer salts. Thus, a number of electrochemical properties are examined as follows.

Deposition of TTF-based films

For the deposition of TTF-based films on glass substrates, the substrates are cleaned with Hellmanex, DI water, acetone and isopropanol via sonication and then quickly dried up under nitrogen gas. Before deposition, the substrates are treated with oxygen-plasma to increase their hydrophilic character. Our procedure continues with the deposition of the films of the TTF scaffold derivatives and their complexes with TCNQ or TCNE. Compared to other solvents (such as DMF, toluene, acetonitrile and chlorobenzene), the DMSO provides a higher solubility of these compounds and uniformity after deposition. The SEM images (in Figure 4) indicate that the film quality of **6e** in DMSO is better than that in DMF. Herein, for preparing all the films investigated here, we

choose DMSO as the solvent {**6e** (69 mg/mL), **6e**: TCNE (92 mg/mL), **6e**: TCNQ (107 mg/mL)}. The films are prepared by depositing 60 μL of the solutions on a 0.5 x 0.5 cm square glass substrate via spin-coating technique at 2000 rpm for 30 sec. Dynamic deposition helps to avoid non-uniformity, particularly at the edges of the substrate. After deposition, we anneal the deposited films at 65 °C for 5 minutes in ambient conditions. The next step, the Au contacts are deposited via RF-Sputtering in Argon atmosphere. Finally, we place special gold squares on each film, as shown in the right picture.





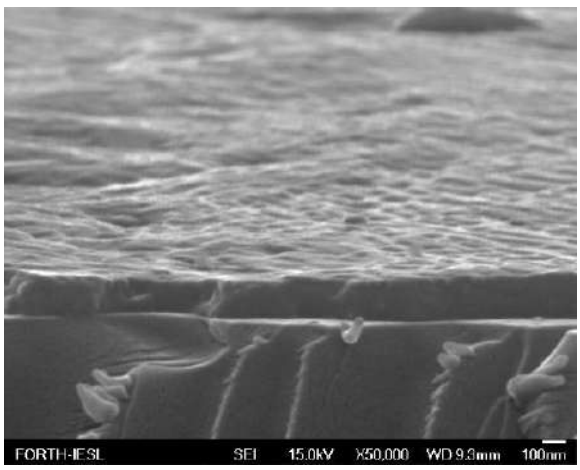


Figure 4 **6e**'s film in DMF solvent (left) and DMSO solvent (right).

Hall Measurements

In order to proceed to the electrical characterization of the TTF-based D-A molecules, we checked the electrical conductivity of the prepared films following the Hall Van Der Pauw method[28-29] using a magnetic field at 0.7 Tesla. (see EXPERIMENTAL SECTION. The final films are appeared as the one shown in Figure 5. Unfortunately, some of the prepared films are still not suitable for further studies even lots of efforts have been made in order to improve their quality such as, changing the solvent, temperature and the speed of spin-coating technique (shown in Figure 6).

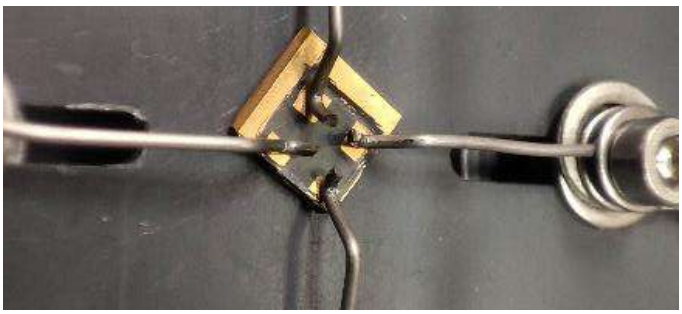


Figure 5 The final film of **6e**.

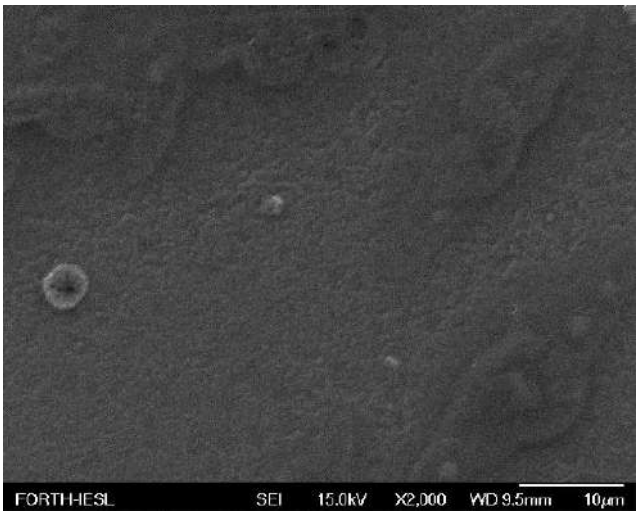


Figure 6 The surface of film of **6e**:TCNE.

To our delight, the complex of **6e**:TCNQ (1:1) demonstrates conductivity properties. Their resistance, the free carrier's mobility and the thickness are obtained. The μ-value of this complex is better compared with those of ordinary organic semiconductors (such as, the anthracene's μ-value is around 1 cm^2/Vs). The thickness of the film from the complex of **6e**:TCNQ is 325 nm according to the SEM images (Figure 7). The data demonstrates that the complex of **6e**:TCNQ (1:1) belongs to p-type charge carriers as well.

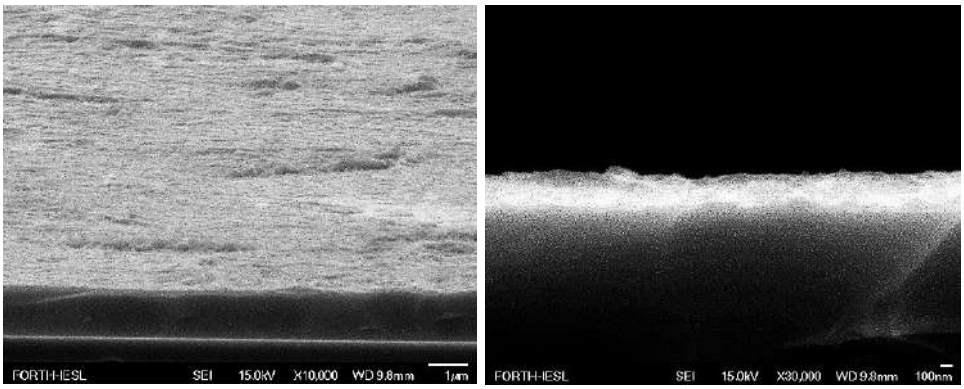


Figure 7 The complex of **6e**:TCNQ surface (left) and cross section image (right).

Table 2 The electrical characterizations of the complex **6e**:TCNQ (1:1).

Thickness (t)	325	nm
Specific resistance (ρ)	1.27	Ωcm
Sheet resistance (Rs)	3.90E+04	Ω/SQUARE
Free carrier density (N)	8.97E+17	cm^{-3}
Surface free carrier density (Ns)	2.92E+13	cm^{-2}
Free carrier mobility (μ)	5.50E+00	cm^2/Vs

The luminous transmittance is a very important characteristic measuring the amount of light that passes through a transparent material. In general, adhesives used in electro-optical interconnects must have a high transmittance. The *total light transmittance* through a material is equal to the total incident light less the light that is absorbed and light that is scattered.[30] The results of our selected materials, **6e**, **6e**:TCNQ, **6e**:TCNE, are shown in Figure 8. It displays that all of the TTF-based molecules and their complexes with TCNQ or TCNE absorb more light than the TTF.

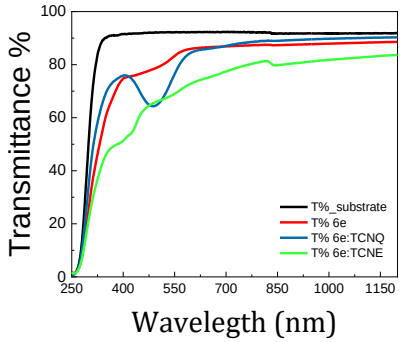


Figure 8 The transmittance of the materials.

CONCLUSIONS

During this work, 33 TTF derivatives are synthesized via simple IMCRs under mild reaction conditions in good to excellent yields. To our delight, the single-crystal XRD analyses of the compounds display most of the vL adducts (the D-A molecules) with planar geometry which is beneficial for the electron delocalization. The potential of an intramolecular charge transfer is demonstrated through DFT calculations and the UV spectroscopy. Further investigations on the electronic and physical characteristics include Hall measurements and luminous transmittance.

REFERENCES

1. Huibiao Liu, Junbo Li, Changshi Lao, Changshui Huang, Yuliang Li, Zhong Lin Wang and Daoben Zhu, *Nanotechnology,* **2007**,*18*, 495704.
2. Yan Zhou, Fei Yu, Jian Su, Mohamedally Kurmoo, Jing-Lin Zuo, *Angew. Chem.* **2020**, *132*, 18922-18926.
3. Xiang-Yu Gao, Yu-Lin Li, Tian-Fu Liu, Xin-Song Huang and Rong Cao, *CrystEngComm*, **2021**, *23*, 4743-4747.
4. Weikang Hu, Jiaqi Xu, Nanjie Chen, Zongcai Deng, Yuekun Lai, Dongyang Chen*, Green Energy & Environment, DOI:* 0.1016/j.gee.2022.10.005
5. David Canevet, Marc Sallé, Guanxin Zhang, Deqing Zhang and Daoben Zhu, *Chem. Commun.*, **2009**, 2245-2269.
6. Yang, G. Zhang, L. Li, D. Zhang, L. Chi and D. Zhu, *Small*, **2012**, *8*, 578-584.
7. T. Akutagawa, K. Kakiuchi, T. Hasegawa, S. Noro, T. Nakamura, H. Hasegawa, S. Mashiko and J. Becher, *Angew. Chem., Int. Ed.*, **2005**, *44*, 7283-7287.
8. Yuejie Zhu, Long Zhao, Zhengyin Du, GuanFan Chen, Yuexin Li, Lejia Wang, Xunwen Xiao, *Synthetic Metals*, **2021**, *282*, 116946.
9. Souto, A. Santiago-Portillo, M. Palomino, I. J. VitóricaYrezábal, B. J. C. Vieira, J. C. Waerenborgh, S. Valencia, S. Navalón, F. Rey, H. García and G. Mínguez Espallargas, *Chem. Sci.*, **2018**, *9*, 2413-2418.
10. H. Y. Wang, J. Y. Ge, C. Hua, C. Q. Jiao, Y. Wu, C. F. Leong, D. M. D'Alessandro, T. Liu and J. L. Zuo, *Angew. Chem., Int. Ed.*, **2017**, *56*, 5465-5470.
11. Lauren E. McNamara, Jan-Niklas Boyn, Christopher Melnychuk, Sophie W. Anferov, David A. Mazziotti, Richard D. Schaller, and John S. Anderson, *J. Am. Chem. Soc.* **2022**, *144*, 16447-16455.

12. Hendrik V. Schröder and Christoph A. Schalley, *Beilstein J. Org. Chem*., **2018**, *14*, 2163-2185.
13. Viram, A. & M.A. Ratner, *Chem. Phys. Lett.*, **1974**, *29*, 277-283.
14. Anupama Ghosh, K. Venkata Rao, Rakesh Voggu, Subi J. George, *Chemical Physics Letters*, **2010**, *488*, 198-201.
15. Gregory Ho, James R. Heath, Mykola Kondratenko, Dmitrii F. Perepichka, Karin Arseneault, Michel Pzolet, and Martin R. Bryce, *Chem. Eur. J.*, **2005**, *11*, 2914-2922.
16. Juan P. Villabona-Monsalve, Nikolai A. Tcyrulnikov, Emmaline R. Lorenzo, Nicole LaBine, Ryan Burdick, Matthew D. Krzyaniak, Ryan M. Young, Michael R. Isielewski, and Theodore Goodson, *J. Phys. Chem. C*, **2022**, *126*, 6334-6343.
17. Raquel Andreu, Ana I. de Lucas, Javier Garín, Nazario Martín, Jesús Ordun, Luis Sánchez, Carlos Seoane, *Synthetic Metals*, **1997**, *86*, 1817-1818.
18. Yan Zhou, Fei Yu, Jian Su, Mohamedally Kurmoo und Jing-Lin Zuo, *Angew. Chem.*, **2020**, *132*, 18922-18926.
19. François Riobé, Philippe Grosshans, Helena Sidorenkova, Michel Geoffroy, Narcis Avarvari, *Chem. Eur. J.*, **2009**, *15*, 380-387.
20. Xiaofang Lei, Giasemi K. Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Green Chem.*, **2022**, *24*, 6168-6171.
21. David Canevet, Marc Sallé, Guanxin Zhang, Deqing Zhang and Daoben Zhu, *Chem. Commun.*, **2009**, 2245-2269.
22. Adrian J. Moore, Martin R. Bryce, *Synthesis*. **1997**, 407-409.
23. Cai, Song-Liang, Zhang Yue-Biao, Andrew B. Pun, He Bo, Yang Jinhui, Francesca M. Toma, Ian D. Sharp, Omar M. Yaghi, Fan Jun, Zheng Sheng-Run, Zhang Wei-Guang and Liu Yi, *Chemical Science*, **2014** , *5 (12),* 4693-4700.

24. M. Mas-Torrent, M. Durkut, P. Hadley, X. Ribas, C. Rovira, *J. Am. Chem. Soc.*, **2004**, *126*, 984-985.
25. M. Mas-Torrent, C. Rovira, *J. Mater. Chem.*, **2006**, *16*, 433-436.
26. Xiang-Yu Gao, Yu-Lin Li, Tian-Fu Liu, Xin-Song Huang and Rong Cao, *CrystEngComm*, **2021**, *23*, 4743-4747.
27. Tarun C. Narayan, Tomoyo Miyakai, Shu Seki, and Mircea Dincă, *J. Am. Chem. Soc.*, **2012**, *134*, 12932-12935.
28. M. Nelkon and P. Parker, Magnetic field and Force on Conductor, Hall effect, [M], *Advanced Level Physics, Heinemann Educational*, **1995**, pp. 316-319.
29. J.Wilson and J.Wawkes, Optoelectronics: An Introduction (3rd Edition), [M], **1998**.
30. James J. Licari, Dale W. Swanson, Adhesives Technology for Electronic Applications (Second Edition), [M], **2011**, *Chapter 7*.

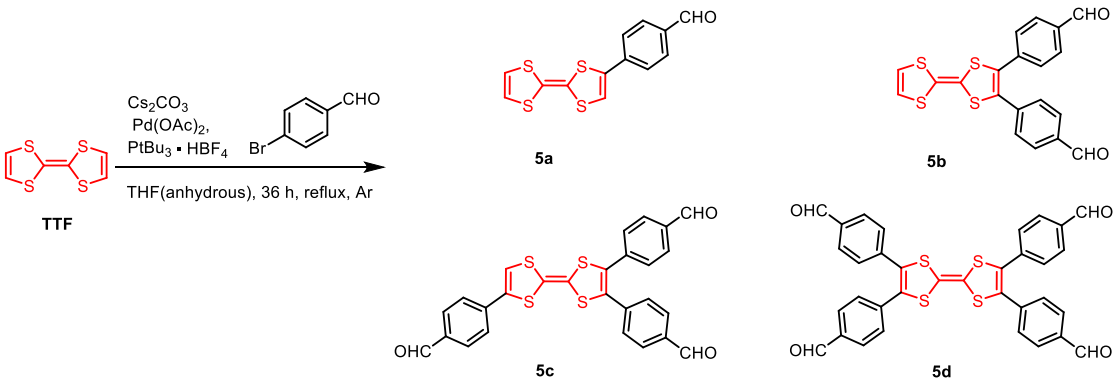
EXPERIMENTAL SECTION

1. General methods and materials

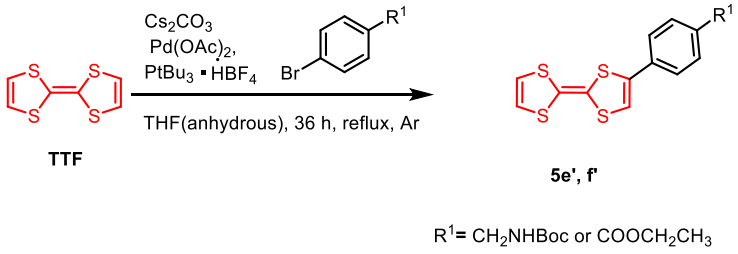
All the reagents and solvents are purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and are used without further purification. All microwave irradiation reactions are carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography is performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra are recorded on a Bruker Avance 500 spectrometers {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz) }. Chemical shifts for ^{1}H NMR are reported as δ values and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR are reported in ppm relative to the solvent peak. Flash chromatography is performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra are measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 µm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 µm particle size). High resolution mass spectra are recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

2. Synthetic procedures and analytical data

Synthetic procedure of the 5a-f



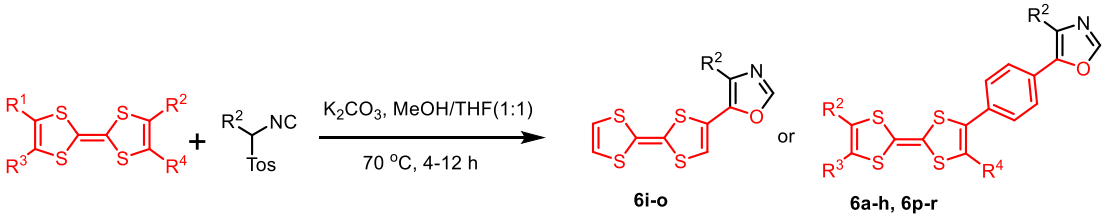
The mixture of TTF (2.0 mmol), 4-bromobenzaldehyde (10.0 mmol), $Pd(OAc)_2$ (0.5 mmol), $PtBu_3HBF_4$ (1.1 mmol), and $CsCO_3$ (3.8 mmol) in 20 ml THF is degassed by freeze-pump-thaw cycles, purged with argon, and refluxed 36 hrs. 100 ml DCM is used to extracted the mixture in two times, then the combined organic layers are washed with brine. The organic layer is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel with dichloromethane as eluent to afford the **5a-d**.



The mixture of TTF (1.0 mmol), the corresponding 4-bromobenzyl compounds (1.0 mmol), $Pd(OAc)_2$ (0.25 mmol), $PtBu_3HBF_4$ (0.55 mmol), and $CsCO_3$ (1.85 mmol) in 10 ml THF is degassed by freeze-pump-thaw cycles, purged with argon, and refluxed 36 hrs. 50 ml DCM is used to extracted the mixture in two times, then the combined organic layers are washed with brine. The organic layer is dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. The residue is purified by column chromatography on silica gel with dichloromethane as eluent to afford the **5e'**, **f'**. Then the **5e'**, **f'** follow the existing deprotected procedures to get the **5e**, **f** in ~95% yields.[1-2]

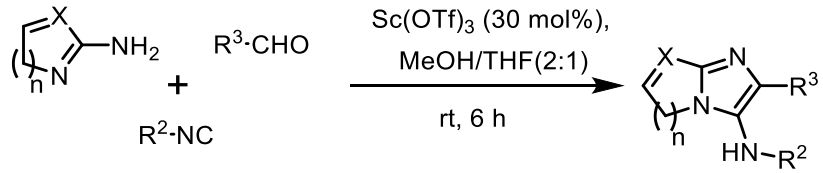
Synthetic procedure of the vL oxazole synthesis



R^1=CHO or Ph-CHO, R^2, R^3 and R^4=H or Ph-CHO

In a 10 mL vial, the corresponding tetrathiofulvalene aldehyde (1.0 mmol), TosMIC (1.1 mmol) and K_2CO_3 (2.0 mmol) are dissolved in MeOH-THF (4 mL, 3:1). The reaction mixture is stirred at 70 °C for 12 h. Afterwards, the solvent is evaporated and the residue is purified with column chromatography on silica gel eluted with PE-EA (5:1-1:1) affording the targeted compounds **6a**-**r**.

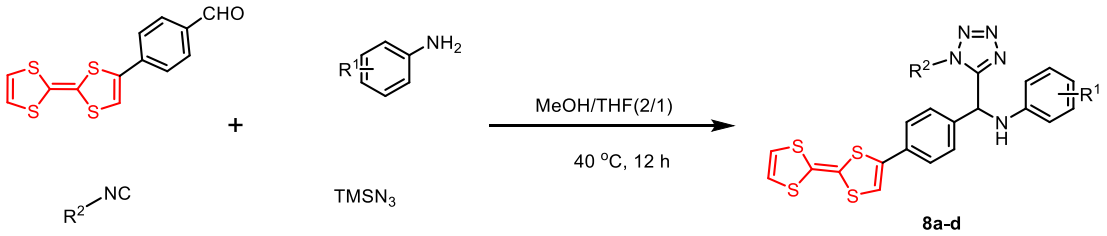
Synthetic procedure of the GBB-3CR



7a-h

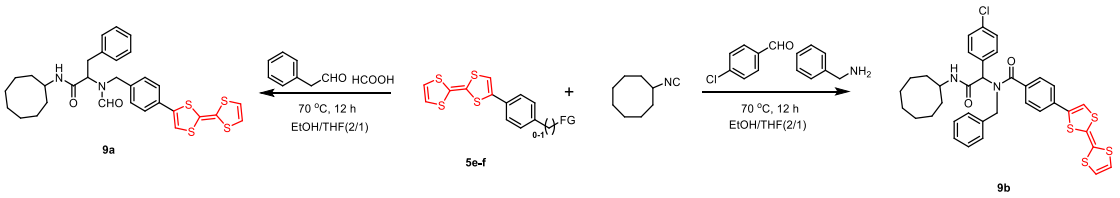
In a 10 mL vial, the corresponding 2-aminopyridine or 2-aminothiazole (1.0 mmol), tetrathiofulvalene aldehyde (1.0 mmol), isocyanide (1.0 mmol) and $Sc(OTf)_3$ (30 mol%) are dissolved in MeOH-THF (4 mL, 2:1 at room temperature and stirred for 6 h. Afterwards, the solvent is evaporated and the residue is purified with column chromatography on silica gel eluted with PE-EA (4:1-1:1) affording the targeted compounds **7a**-**h**.

Synthetic procedure of the UT-4CR synthesis



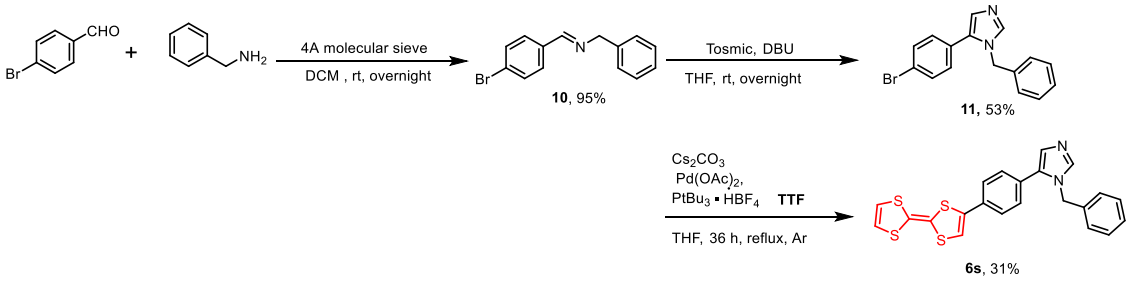
In a 10 mL vial, the corresponding aniline (1.0 mmol), 4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)benzaldehyde (1.0 mmol), the corresponding isocyanide (1.0 mmol) and TMS-azide (1.0 mmol) are dissolved in MeOH-THF (4 mL, 3:1) at room temperature. Then, the reaction mixture is stirred at 40 °C for 12 h. Afterwards, the solvent is evaporated and the residue is purified with column chromatography on silica gel eluted with PE-EA (5:1-1:1) affording the targeted compounds **8a**-**d**.

Synthetic procedure of the U-4CR synthesis



In a 10 mL vial, the corresponding amine (1.0 mmol), the corresponding aldehyde (1.0 mmol), isocyanocyclooctane (1.0 mmol) and the corresponding acid (1.0 mmol) are dissolved in EtOH-THF (4 mL, 2:1). Then, the reaction mixture is stirred at 70 °C for 12 h. Afterwards, the solvent is evaporated and the residue is purified with column chromatography on silica gel eluted with PE-EA (5:1-1:1) affording the targeted compounds **9a**, **b**.

Synthetic procedure of the 6s

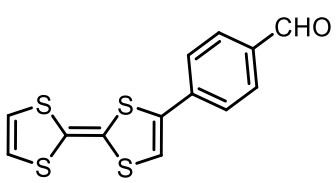


To a stirred solution of 4-bromobenzaldehyde (4.0 mmol) and phenylmethanamine (4.0 mmol) in DCM (30.0 mL), 4Å molecular sieve (500 mg) is added at room temperature and the reaction mixture is stirred overnight. Then, the mixture is filtrated and the solvent is removed under reduced pressure. The crude product **10** is obtained and used directly in the next step.

To a stirred solution of **10** (2.0 mmol) and TosMIC (2.2 mmol) in THF (2.0 mL), DBU (3.0 mmol) is added at room temperature and and the reaction mixture is stirred overnight. Afterwards, the solvent is evaporated and the residue is purified with column chromatography on silica gel with PE-EA (4:1-1:1) as eluent to afford the **11** as yellow solid in 53% yield.

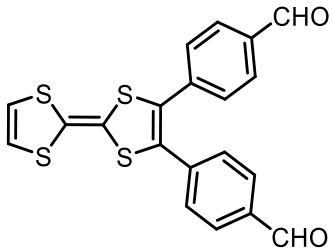
The mixture of TTF (1.0 mmol), **11** (1.0 mmol), $Pd(OAc)_2$ (0.25 mmol), $PtBu_3HBF_4$ (0.55 mmol), and $CsCO_3$ (1.85 mmol) in 10 ml THF is degassed by freeze-pump-thaw cycles, purged with argon, and refluxed 36 h. 50 ml DCM is used to extracted the mixture in two times, then the combined organic layers are washed with brine. The organic layer is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue is purified with column chromatography on silica gel with PE-EA (4:1-1:1) as eluent to afford the **6s** as black solid in 31% yield.

4-([2,2'-bi(1,3-dithiolylidene)]-4-yl) benzaldehyde (5a)



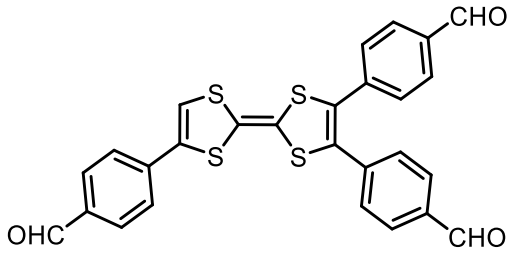
92 mg, 15% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 6.77 (s, 1H), 6.38 (s, 2H).

4,4'-([2,2'-bi(1,3-dithiolylidene)]-4,5-diyl)dibenzaldehyde (5b)



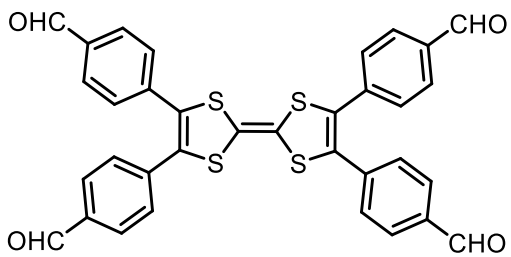
330 mg, 40% yield, red solid.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.04 (s, 2H), 7.92 (d, *J* = 8.4 Hz, 4H), 7.59 (d, *J* = 8.3 Hz, 4H), 6.80 (s, 2H).

4,4',4''-([2,2'-bi (1,3-dithiolylidene)]-4,4',5-triyl)tribenzaldehyde (5c)



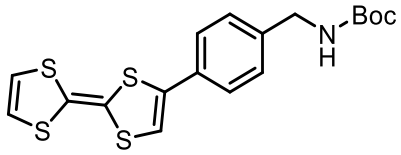
310 mg, 30% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 10.00 (s, 2H), 7.93 - 7.89 (m, 2H), 7.79 (dd, *J* = 8.3, 1.7 Hz, 4H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, *J* = 8.3, 2.3 Hz, 4H), 6.81 (s, 1H).

4,4',4'',4'''-([2,2'-bi(1,3-dithiolylidene)]-4,4',5,5'-tetrayl) tetrabenzaldehyde (5d)



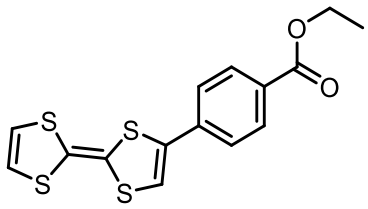
186 mg, 15% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.00 (s, 4H), 7.80 (d, *J* = 8.2 Hz, 8H), 7.40 (d, *J* = 8.2 Hz, 8H).

tert-butyl (4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)benzyl)carbamate (5e')



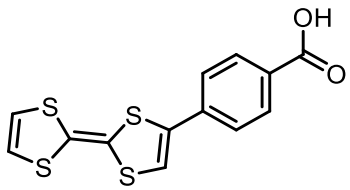
327 mg, 80% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 - 7.37 (m, 2H), 7.29 (d, *J* = 6.4 Hz, 2H), 6.51 (s, 1H), 6.35 (s, 2H), 4.33 (d, *J* = 5.1 Hz, 2H), 1.48 (s, 9H).

ethyl 4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)benzoate (5f')



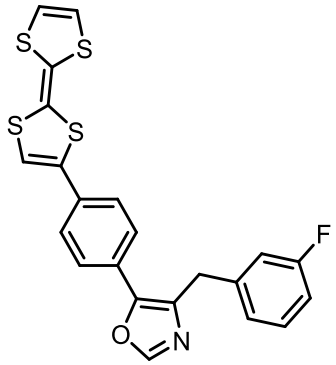
141 mg, 40% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.68 (s, 1H), 6.36 (s, 2H), 4.40 (t, *J* = 3.6 Hz, 2H), 1.42 (s, 3H).

4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)benzoic acid (5f)



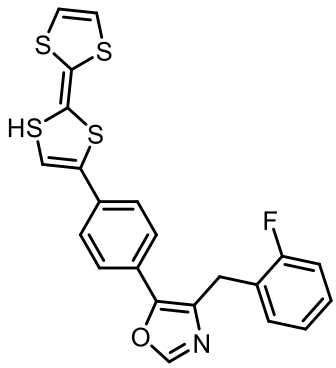
308 mg, 95% yield, black solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.47 (s, 1H), 6.77 (s, 2H).

5-(4-([2,2'-bi (1,3-dithiolylidene)]-4-yl)phenyl)-4-(3-fluorobenzyl) oxazole (6a)



272 mg, 60% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.06 - 7.03 (m, 1H), 6.98 - 6.90 (m, 2H), 6.58 (s, 1H), 6.34 (s, 2H), 4.15 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.2 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 149.9, 146.2, 140.9, 140.8, 135.4, 133.9, 132.3, 130.2 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 129.3, 128.1, 126.8, 126.6, 126.1, 124.2(d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 119.2, 119.2, 115.3(d, $^{2}J_{C\text{-}F}$ = 22.7 Hz), 114.7, 113.8, 113.6, 112.4, 108.6, 32.9. **HRMS** (ESI) m/z calculated for $C_{22}H_{14}FNOS_4$ $[M]^+$: 454.9937, found $[M]^+$: 454.9936.

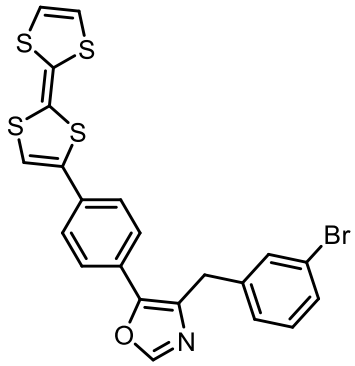
5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-(2-fluorobenzyl) oxazole (6b)



163 mg, 36% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.60 - 7.54 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.00 - 6.86 (m, 2H), 6.58 (s, 1H), 6.36 (d, *J* = 17.6 Hz, 1H), 4.15 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.2 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 149.9, 146.2,

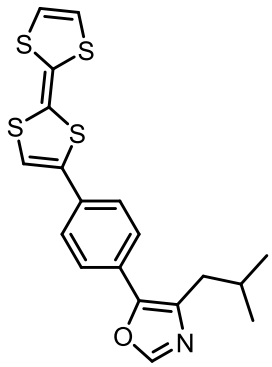
140.9, 140.9, 134.0, 130.3 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 129.9, 126.9, 126.1, 124.2, 119.3, 119.2, 115.5 (d, $^{2}J_{C\text{-}F}$ = 22.7 Hz), 113.7 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 32.9. **HRMS** (ESI) m/z calculated for $C_{22}H_{14}FNOS_4$ $[M]^+$: 454.9937, found $[M]^+$: 454.9937.

5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-(3-bromobenzyl) oxazole (6c)



210 mg, 41% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.51 - 7.35 (m, 4H), 7.21 (d, *J* = 7.0 Hz, 2H), 6.35 (s, 2H), 4.15 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.9, 146.2, 140.7, 133.8, 131.6, 130.3, 129.9, 127.2, 126.8, 126.1, 122.9, 119.2, 114.7, 32.8. **HRMS** (ESI) m/z calculated for $C_{22}H_{14}BrNOS_4$ $[M]^+$: 514.9136, found $[M]^+$: 514.9134.

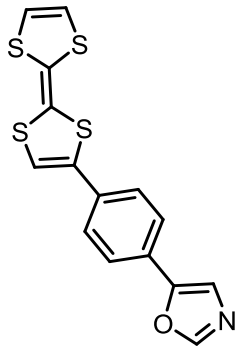
5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-isobutyloxazole (6d)



214 mg, 53% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.57 (s, 1H), 6.33 (s, 2H), 2.66 (d, *J* = 7.2 Hz, 2H), 2.21 - 2.08 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.4, 145.5, 136.0, 135.6, 129.0, 126.7, 126.0, 119.2, 119.2,

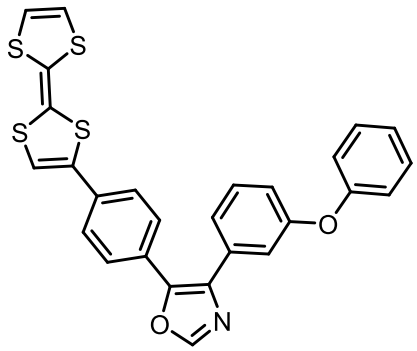
114.3, 36.2, 28.5, 22.7. **HRMS** (ESI) m/z calculated for $C_{19}H_{18}NOS_4$ $[M+H]^+$: 404.0266, found $[M+H]^+$: 404.0261.

5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)oxazole (6e)



295 mg, 85% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.38 (s, 1H), 6.59 (s, 1H), 6.35 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.8, 135.4, 132.6, 127.6, 126.8, 124.8, 122.2, 119.2, 119.2, 114.6, 29.8. **HRMS** (ESI) m/z calculated for $C_{15}H_9NOS_4$ $[M]^+$: 346.9562, found $[M]^+$: 346.9562.

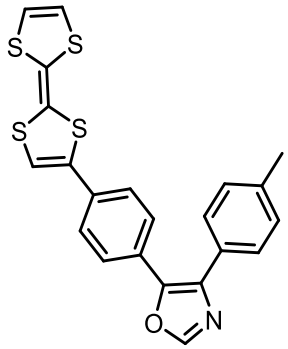
5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-(3-phenoxyphenyl) oxazole (6f)



216 mg, 42% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.63 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 3H), 7.24 (s, 1H), 7.19 - 7.14 (m, 2H), 7.01 - 6.94 (m, 2H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.55 (s, 1H), 6.34 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7, 154.6, 149.8, 146.6,

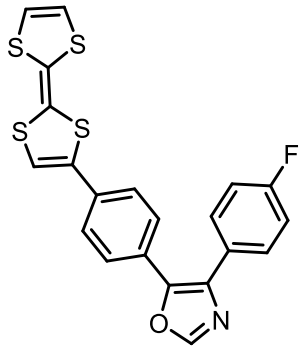
135.7, 132.2, 131.9, 131.5, 130.4, 130.2, 129.6, 128.7, 126.3, 126.2, 124.3, 124.0, 123.2, 119.4, 119.2, 119.2, 119.1, 118.3, 114.3, 112.2, 108.8. **HRMS** (ESI) m/z calculated for $C_{27}H_{17}NO_2S_4$ $[M]^+$: 515.0137, found $[M]^+$: 515.0135.

5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-(p-tolyl) oxazole (6g)



192 mg, 44% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.57 (s, 1H), 6.34 (s, 2H), 2.40 (s, 3H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 144.8, 138.5, 135.6, 135.5, 132.5, 129.5, 129.2, 128.7, 128.0, 126.9, 126.5, 119.2, 119.2, 114.5, 112.2, 108.6, 21.5. **HRMS** (ESI) m/z calculated for $C_{22}H_{15}NOS_4$ $[M]^+$: 437.0031, found $[M]^+$: 437.0029.

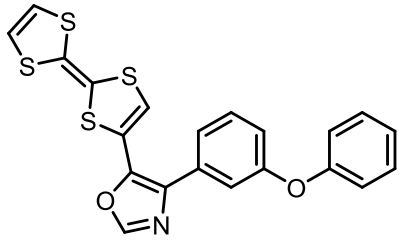
5-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-4-(4-fluorophenyl) oxazole (6h)



229 mg, 52% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.65 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 6.60 (s, 1H), 6.36 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ

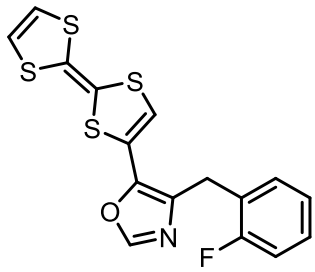
162.9 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 150.0, 145.1, 135.3, 134.6, 132.7, 130.1, 130.0, (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 128.3, 128.2 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 126.9, 126.6, 119.21, 119.16, 115.9 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 114.8, 112.4, 108.5. **HRMS** (ESI) m/z calculated for $C_{21}H_{12}FNOS_4$ $[M]^+$: 440.9780, found $[M]^+$: 440.9777.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-(3-phenoxyphenyl) oxazole (6i)



180 mg, 41% yield, red solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.54 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.40 - 7.37 (m, 1H), 7.28 - 7.18 (m, 3H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.50 (s, 1H), 6.33 - 6.30 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9, 155.2, 149.6, 132.2, 130.9, 130.4, 129.8, 123.6, 123.5, 122.6, 119.8, 119.3, 119.1, 119.1, 119.0, 118.2. **HRMS** (ESI) m/z calculated for $C_{21}H_{13}NO_2S_4$ $[M]^+$: 438.9824, found $[M]^+$: 438.9823.

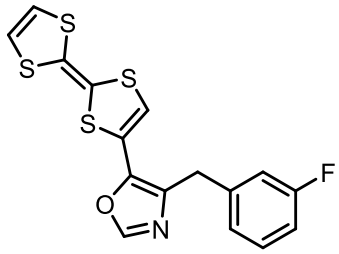
5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-(2-fluorobenzyl) oxazole (6j)



178 mg, 47% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.21 (t, *J* = 7.0 Hz, 2H), 7.07 (m, 2H), 6.57 (s, 1H), 6.33 (s, 2H), 4.07 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.8 (d, $^{1}J_{C\text{-}F}$ = 210.4 Hz), 161.3, 160.0, 149.8, 140.4, 134.4, 130.8(d, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 128.7(d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 124.4 (d, $^{4}J_{C\text{-}F}$ = 3.8

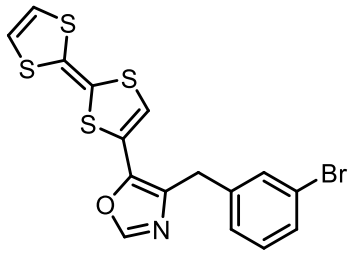
Hz), 121.9, 119.3, 119.2, 117.6, 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 26.0, 25.9. **HRMS** (ESI) m/z calculated for $C_{16}H_{10}FNOS_4$ $[M]^+$: 378.9624, found $[M]^+$: 378.9624.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-(3-fluorobenzyl) oxazole (6k)



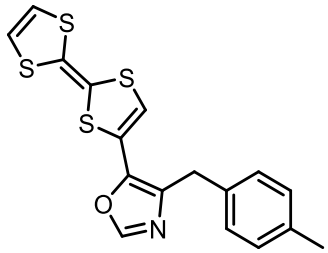
171 mg, 45% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.27 - 7.25(m, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 9.8 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.56 (s, 1H), 6.35 (s, 2H), 4.05 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 130.3(d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 124.5, 119.3, 119.2, 117.6, 115.8(d, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 114.0, 113.8, 32.6. **HRMS** (ESI) m/z calculated for $C_{16}H_{11}FNOS_4$ $[M+H]^+$: 379.9702, found $[M+H]^+$: 379.9701.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-(3-bromobenzyl) oxazole (6l)



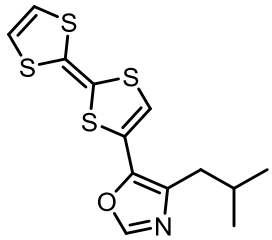
233 mg, 53% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.41 (s, 1H), 7.35 (s, 1H), 7.21 - 7.16 (m, 2H), 6.56 (s, 1H), 6.34 (s, 2H), 4.02 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 140.4, 134.8, 131.9, 130.4, 130.1, 128.6, 127.5, 122.9, 121.8, 119.3, 119.2, 117.7, 32.5. **HRMS** (ESI) m/z calculated for $C_{16}H_{11}BrNOS_4$ $[M+H]^+$: 439.8901, found $[M+H]^+$: 439.8900.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-(4-methylbenzyl) oxazole (6m)



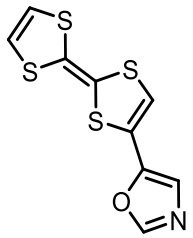
229 mg, 61% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 6.34 (s, 2H), 4.01 (s, 2H), 2.31 (s, 3H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.8, 136.4, 136.0, 135.1, 129.6, 128.7, 122.1, 119.3, 119.2, 117.2, 113.9, 32.6, 21.3. **HRMS** (ESI) m/z calculated for $C_{17}H_{14}NOS_4$ $[M+H]^+$: 375.9953, found $[M+H]^+$: 375.9951.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-4-isobutyloxazole (6n)



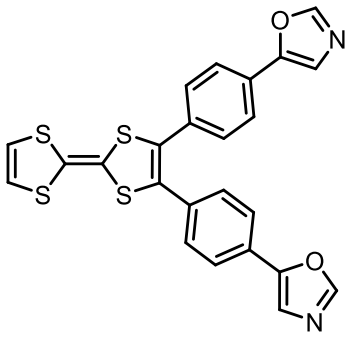
128 mg, 39% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 6.55 (s, 1H), 6.35 (s, 2H), 2.54 (d, *J* = 7.1 Hz, 2H), 2.07 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 7H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.5, 136.7, 130.4, 122.6, 119.3, 119.2, 116.4, 113.4, 35.7, 28.8, 22.6. **HRMS** (ESI) m/z calculated for $C_{13}H_{13}NOS_4$ $[M]^+$: 326.9875, found $[M]^+$: 326.9876.

5-([2,2'-bi(1,3-dithiolylidene)]-4-yl) oxazole (6o)



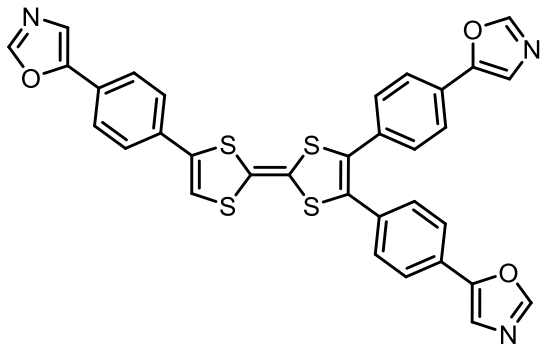
168 mg, 62% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.00 (s, 1H), 6.69 (s, 1H), 6.35 (s, 2H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.3, 153.9, 150.6, 124.3, 123.6, 119.3, 117.0. **HRMS** (ESI) m/z calculated for $C_9H_6NOS_4$ $[M+H]^+$: 271.9327, found $[M+H]^+$: 271.9325.

4,5-bis(4-(oxazol-5-yl)phenyl)-2,2'-bi(1,3-dithiolylidene) (6p)



421 mg, 86% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.67 - 7.63 (m, 4H), 7.50 - 7.46 (m, 4H), 7.39 (s, 2H), 6.63 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.9, 150.5, 135.8, 129.6, 126.4, 125.2, 125.1, 121.8. **HRMS** (ESI) m/z calculated for $C_{24}H_{14}N_2O_2S_4$ $[M]^+$: 489.9938, found $[M]^+$: 489.9931.

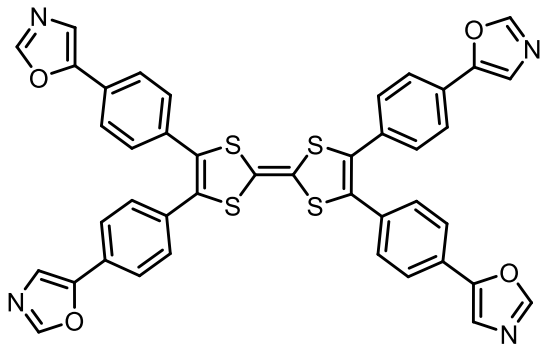
5,5',5''-([2,2'-bi(1,3-dithiolylidene)]-4,4',5-triyltris(benzene-4,1-diyl))tris (oxazole) (6q)



455 mg, 72% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.93 (s, 2H), 7.68 (d, *J* = 8.1 Hz, 3H), 7.57 (d, *J* = 8.1 Hz, 3H), 7.50 (d, *J* = 8.0 Hz, 3H), 7.41 (s, 1H), 7.37 (s, 2H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 3H), 6.65 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 132.5, 129.7, 127.6, 126.8, 124.8, 124.6,

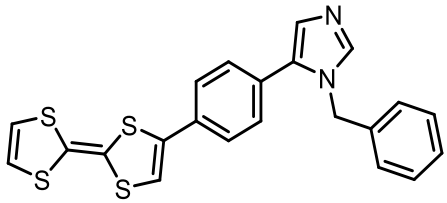
122.3, 122.1, 114.7. **HRMS** (ESI) m/z calculated for $C_{33}H_{19}N_3O_3S_4$ $[M]^+$: 633.0309, found $[M]^+$: 633.0309.

4,4',5,5'-tetrakis(4-(oxazol-5-yl)phenyl)-2,2'-bi(1,3-dithiolylidene) (6r)



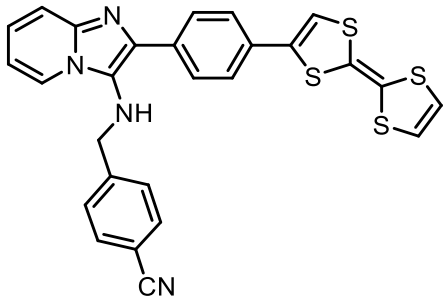
636 mg, 82% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (s, 4H), 7.59 - 7.54 (m, 8H), 7.37 (s, 4H), 7.33 (dd, *J* = 6.6, 1.8 Hz, 8H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 132.7, 129.9, 129.7, 129.2, 127.8, 126.3, 124.7, 124.6, 124.5, 122.3, 122.2. **HRMS** (ESI) m/z calculated for $C_{42}H_{24}N_4O_4S_4$ $[M]^+$: 776.0675, found $[M]^+$: 776.0679.

5-(4-([2,2'-b(1,3-dithiolylidene)]-4-yl)phenyl)-1-benzyl-1*H*-imidazole (6s)



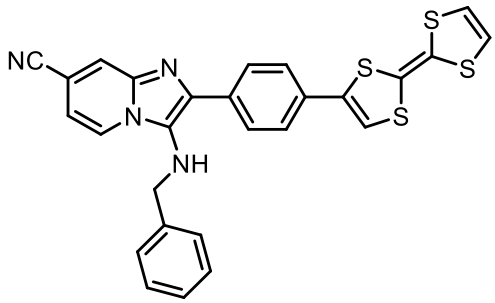
163 mg, 31% yield, black solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.46 - 7.39 (m, 2H), 7.35 (dd, *J* = 7.2, 5.2 Hz, 2H), 7.32 - 7.29 (m, 2H), 7.23 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.05 (d, *J* = 6.0 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.68 (m, 1H), 6.59 (s, 0.5H), 6.53 (d, *J* = 3.9 Hz, 0.6H), 6.36 (d, *J* = 3.5 Hz, 2H), 5.20 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.2, 133.1, 132.8, 129.1, 128.9, 127.4, 126.8, 126.6, 120.0, 119.1, 114.5, 40.2. **HRMS** (ESI) m/z calculated for $C_{22}H_{17}N_2S_4$ $[M+H]^+$: 437.0275, found $[M+H]^+$: 437.0275.

4-(((2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl) imidazo[1,2-a]pyridin-3-yl) amino) methyl) benzonitrile (7a)



200 mg, 38% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 6.9 Hz, 3H), 7.58 - 7.53 (m, 3H), 7.45 (d, *J* = 6.7 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.17 - 7.14 (m, 1H), 6.77 (t, *J* = 6.7 Hz, 1H), 6.59 (s, 1H), 6.35 (s, 2H), 4.23 (s, 2H), 3.58 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.5, 140.2, 134.3, 133.6, 132.7, 132.2, 132.0, 130.3, 129.1, 127.0, 126.7, 126.1, 125.2, 120.2, 118.9, 116.4, 115.7, 112.1, 111.9, 109.8, 106.8, 50.8. **HRMS** (ESI) m/z calculated for $C_{27}H_{18}N_4S_4$ $[M]^+$: 526.0407, found $[M]^+$: 526.0409.

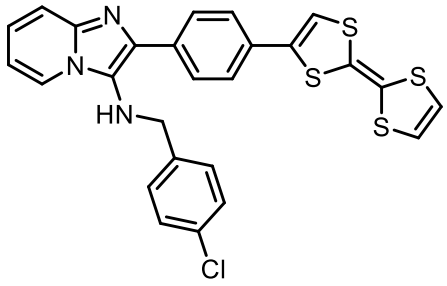
2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-3-(benzylamino)imidazo[1,2-a]pyridine-7-carbonitrile (7b)



237 mg, 45% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 - 7.92 (m, 4H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.29 (m, 5H), 6.86 (dd, *J* = 7.1, 1.3 Hz, 1H), 6.61 (s, 1H), 6.37 (s, 2H), 4.23 (d, *J* = 4.8 Hz, 2H), 3.63 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.3, 138.9, 138.3, 135.7, 133.1, 129.1, 128.3, 128.2, 128.1, 127.5, 126.7, 123.6, 123.0, 119.2, 119.2, 118.1, 114.3, 112.2, 106.4, 52.4.

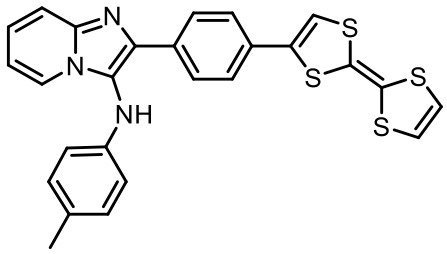
HRMS (ESI) m/z calculated for $C_{27}H_{19}N_4S_4$ $[M+H]^+$: 527.0487, found $[M+H]^+$: 527.0487.

2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-*N*-(4-chlorobenzyl)imidazo[1,2-*a*]pyridin-3-amine (7c)



385 mg, 72% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 3H), 7.58 - 7.54 (m, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.26 (dd, *J* = 19.2, 8.0 Hz, 4H), 7.20 - 7.15 (m, 1H), 6.78 (t, *J* = 6.7 Hz, 1H), 6.59 (d, *J* = 0.4 Hz, 1H), 6.36 (d, *J* = 0.7 Hz, 2H), 4.16 (d, *J* = 5.9 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.5, 137.3, 135.8, 133.6, 131.4, 129.5, 128.8, 127.9, 127.2, 126.4, 125.5, 124.8, 122.3, 119.1, 119.1, 117.3, 113.7, 112.2, 111.7, 109.1, 51.7. **HRMS** (ESI) m/z calculated for $C_{26}H_{19}ClN_3S_4$ $[M+H]^+$: 536.0150, found $[M+H]^+$: 536.0146.

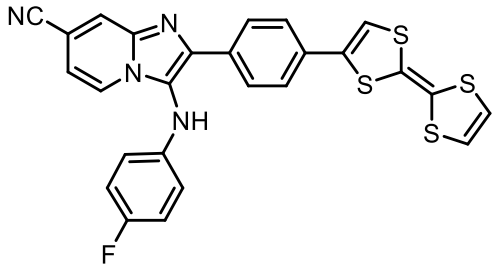
2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-*N*-(p-tolyl)imidazo[1,2-a]pyridin-3-amine (7d)



210 mg, 42% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 6.8 Hz, 1H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.24 (s, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.78 (s, 1H), 6.56 - 6.51 (m, 4H), 6.36 (s, 2H), 2.18 (d, *J* = 2.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.0, 141.8, 136.3,

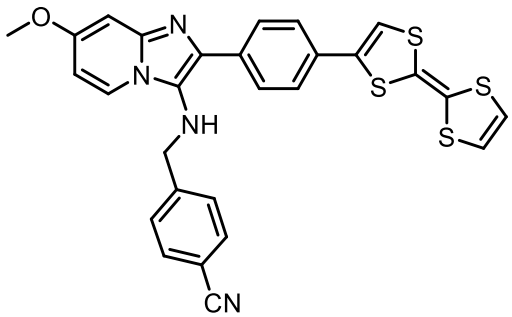
134.2, 133.6, 130.6, 130.0, 127.2, 126.8, 126.1, 125.5, 123.2, 123.1, 119.9, 117.2, 115.7, 113.1, 112.9, 111.9, 106.7, 20.1. **HRMS** (ESI) m/z calculated for $C_{26}H_{19}N_3S_4$ $[M]^+$: 501.0456, found $[M]^+$: 501.0456.

2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-3-((4-fluorophenyl)amino)imidazo[1,2-a]pyridine-7-carbonitrile (7e)



313 mg, 59% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$, DMSO-*d6*) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 2H), 7.70 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.89 (t, *J* = 8.6 Hz, 2H), 6.66 (s, 1H), 6.54 (dd, *J* = 8.8, 4.3 Hz, 2H), 6.39 (s, 2H), **^{13}C NMR** (126 MHz, DMSO-*d6*) δ 156.9, 155.1, 141.1, 139.8, 139.3, 134.0, 132.5, 131.3, 127.3, 126.3, 124.4, 123.7, 121.9, 118.1, 116.4, 116.3, 116.1, 114.5, 114.3, 112.6, 112.0, 106.6. **HRMS** (ESI) m/z calculated for $C_{26}H_{15}FN_4S_4$ $[M]^+$: 530.0158, found $[M]^+$: 530.0156.

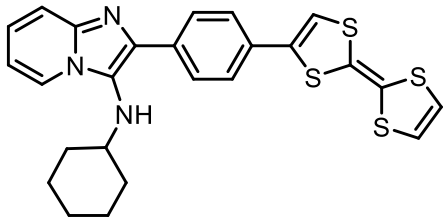
4-(((2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-7-methoxyimidazo[1,2-*a*]pyridin-3-yl) aminomethyl)benzonitrile (7f)



306 mg, 55% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$, DMSO-*d6*) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.89 (s, 1H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.53 (s, 2H), 7.51 - 7.37 (m, 4H), 6.76 (s, 1H), 6.70 (s, 1H), 6.44 (d, *J* = 23.4 Hz, 3H), 4.19 (s, 2H), 3.84

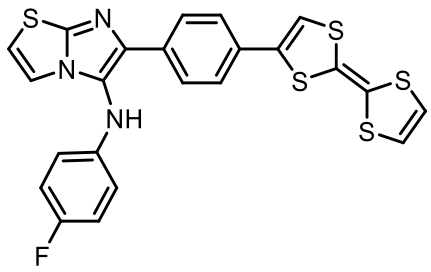
(d, *J* = 5.7 Hz, 3H), **^{13}C NMR** (126 MHz, $CDCl_3$, DMSO-*d6*) δ 158.1, 144.5, 142.5, 135.4, 133.5, 131.9, 130.7, 128.7, 126.8, 126.0, 124.6, 122.9, 118.9, 118.9, 118.5, 113.4, 111.4, 110.8, 108.4, 107.0, 93.9, 55.4, 51.6. **HRMS** (ESI) m/z calculated for $C_{28}H_{21}N_4OS_4$ $[M+H]^+$: 557.0593, found $[M+H]^+$: 557.0590.

2-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-*N*-cyclohexylimidazo[1,2-a]pyridin-3-amine (7g)



256 mg, 52% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.11 - 8.07 (m, 3H), 7.54 (d, *J* = 9.1 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.16 - 7.13 (m, 1H), 6.79 (t, *J* = 6.7 Hz, 1H), 6.58 (s, 1H), 6.34 (s, 2H), 3.07 (s, 1H), 2.98 (s, 1H), 1.83 (d, *J* = 12.7 Hz, 2H), 1.70 (d, *J* = 6.0 Hz, 2H), 1.29 - 1.18 (m, 6H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.7, 136.1, 135.7, 134.6, 131.2, 127.3, 126.4, 125.4, 124.4, 122.8, 119.2, 119.1, 117.5, 113.4, 111.9, 111.6, 109.3, 57.0, 34.3, 25.8, 24.9. **HRMS** (ESI) m/z calculated for $C_{25}H_{24}N_3S_4$ $[M+H]^+$: 494.0848, found $[M+H]^+$: 494.0842.

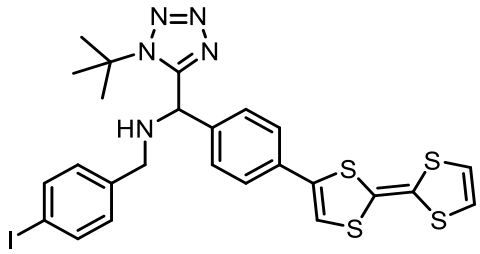
6-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-*N*-(4-fluorophenyl)imidazo[2,1-b]thiazol-5-amine (7h)



301 mg, 59% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$, DMSO-*d6*) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 4.5 Hz, 1H), 6.92 (t, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 4.4 Hz, 1H), 6.62 (d, *J* = 4.4 Hz, 2H), 6.53 (s, 1H), 6.34

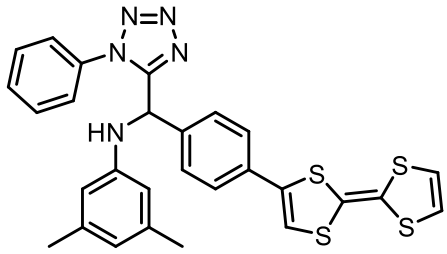
(s, 2H), 6.18 (s, 1H), **^{13}C NMR** (126 MHz, DMSO) δ 145.6, 141.7, 137.0, 133.8, 133.5, 129.6 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 129.5, 125.7(d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 125.7, 125.6, 125.3, 121.4, 114.9, 111.5, 106.4. **HRMS** (ESI) m/z calculated for $C_{23}H_{15}FN_3S_5$ $[M+H]^+$: 511.9854, found $[M+H]^+$: 511.9800.

1-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)-1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-*N*-(4-iodobenzyl) methanamine (8a)



143 mg, 22% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 6.34 (s, 2H), 5.20 (s, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.62 (d, *J* = 13.6 Hz, 1H), 1.52 (s, 9H), **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.0, 138.5, 137.7, 135.2, 132.7, 130.5, 128.7, 126.9, 119.2, 119.2, 114.7, 112.2, 108.6, 92.9, 61.6, 56.9, 50.8. **HRMS** (ESI) m/z calculated for $C_{25}H_{24}IN_5S_4$ $[M]^+$: 648.9954, found $[M]^+$: 648.9951.

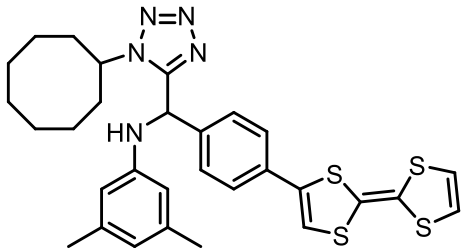
N-((4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)(1-phenyl-1*H*-tetrazol-5-yl)methyl)-3,5-dimethylaniline (8b)



84 mg, 15% yield, red solid. 15% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.56 - 7.53 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 6.9 Hz,

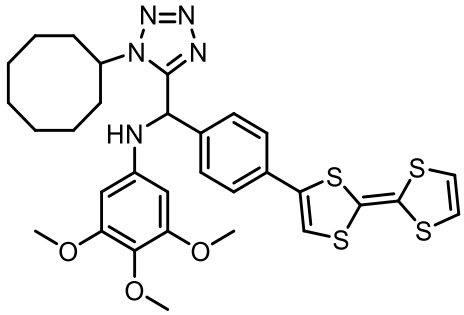
3H), 6.90 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.75 (s, 1H), 6.63 (s, 1H), 6.37 (s, 1H), 6.13 (d, *J* = 2.7 Hz, 1H), 5.84 (s, 2H), 2.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.7, 148.3, 138.4, 135.8, 135.7, 135.1, 133.0, 130.0, 129.4, 128.9, 127.1, 126.6, 123.1, 119.1, 119.1, 117.4, 116.5, 29.1, 21.4, 21.1. **HRMS** (ESI) m/z calculated for $C_{28}H_{23}N_5S_4$ $[M+H]^+$: 558.0915, found $[M+H]^+$: 558.0910.

N-((4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)(1-cyclooctyl-1*H*-tetrazol-5-yl)methyl)-3,5-dimethylaniline (8c)



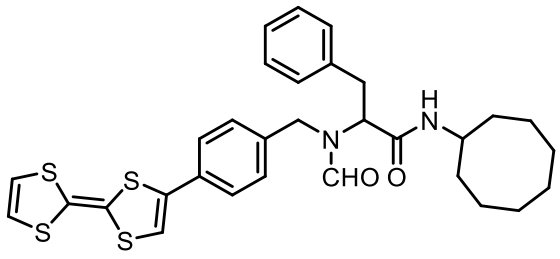
148 mg, 25% yield, red oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 - 7.38 (m, 4H), 6.55 (s, 1H), 6.47 (s, 1H), 6.35 (s, 2H), 6.32 (s, 2H), 5.91 (d, *J* = 6.4 Hz, 1H), 4.60 (ddd, *J* = 9.8, 6.4, 3.5 Hz, 1H), 2.26 (s, 1H), 2.22 (s, 6H), 2.10 - 2.02 (m, 1H), 1.92 (d, *J* = 2.8 Hz, 1H), 1.90 - 1.84 (m, 2H), 1.76 - 1.69 (m, 3H), 1.53 (dd, *J* = 11.0, 3.5 Hz, 5H), 1.43 - 1.37 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.8, 145.6, 139.2, 138.1, 135.0, 133.0, 127.7, 127.0, 121.5, 119.0, 114.7, 112.0, 59.4, 53.5, 33.2, 33.1, 31.8, 26.5, 25.9, 24.4, 24.0, 23.0, 21.4. **HRMS** (ESI) m/z calculated for $C_{30}H_{33}N_5S_4$ $[M]^+$: 591.1613, found $[M]^+$: 591.1613.

N-((4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)phenyl)(1-cyclooctyl-1*H*-tetrazol-5-yl)methyl)-3,4,5-trimethoxyaniline (8d)



196 mg, 30% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (q, *J* = 8.5 Hz, 4H), 6.57 (s, 1H), 6.35 (s, 1H), 5.96 (s, 1H), 5.93 (s, 2H), 5.87 (s, 1H), 4.64 - 4.53 (m, 1H), 3.83 (s, 2H), 3.77 (s, 5H), 3.75 (s, 2H), 2.27 - 2.20 (m, 1H), 2.05 - 1.99 (m, 1H), 1.85 (d, *J* = 10.2 Hz, 1H), 1.73 - 1.68 (m, 2H), 1.65 - 1.58 (m, 3H), 1.55 - 1.48 (m, 4H), 1.35 (d, *J* = 3.9 Hz, 1H), 0.93 - 0.86 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 153.9, 153.6, 142.1, 137.8, 134.9, 133.2, 131.8, 127.7, 127.0, 119.1, 119.0, 115.0, 92.9, 92.3, 61.0, 59.5, 56.1, 56.0, 54.2, 33.2, 33.0, 26.5, 26.4, 25.9, 24.4, 24.0. **HRMS** (ESI) m/z calculated for $C_{31}H_{35}N_5O_3S_4$ $[M]^+$: 653.1623, found $[M]^+$: 653.1617.

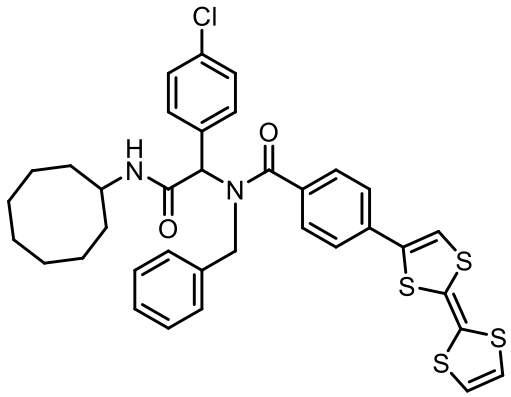
2-(*N*-(4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)benzyl)formamido)-*N*-cyclooctyl-3-phenylpropanamide (9a)



178 mg, 30% yield, black oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 0.26H), 8.27 (s, 0.71H), 7.36 - 7.29 (m, 3H), 7.28 - 7.22 (m, 3H), 7.15 - 7.09 (m, 3H), 6.15 (d, *J* = 7.8 Hz, 0.69H), 5.08 (d, *J* = 8.0 Hz, 0.18H), 4.48 - 4.33 (m, 1H), 4.09 (d, *J* = 14.9 Hz, 1H), 3.89 - 3.74 (m, 2H), 3.42 - 2.99 (m, 2H), 1.58 - 1.42 (m, 14H).

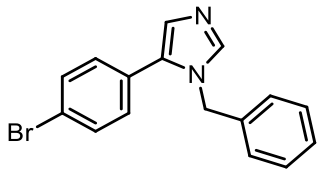
HRMS (ESI) m/z calculated for $C_{31}H_{35}N_2O_2S_4$ $[M+H]^+$: 595.1581, found $[M+H]^+$: 595.1581.

4-([2,2'-bi(1,3-dithiolylidene)]-4-yl)-*N*-benzyl-*N*-(1-(4-chlorophenyl)-2-(cyclooctylamino)-2-oxoethyl) benzamide (9b)



276 mg, 40% yield, red solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 4.4 Hz, 2H), 7.35 - 7.31 (m, 1H), 7.28 (dd, *J* = 5.1, 3.0 Hz, 3H), 7.24 - 7.18 (m, 3H), 7.08 (d, *J* = 6.4 Hz, 2H), 6.46 (d, *J* = 97.5 Hz, 2H), 5.74 (s, 1H), 5.43 (s, 1H), 4.09 - 3.96 (m, 1H), 1.79 (d, *J* = 21.8 Hz, 2H), 1.56 (dd, *J* = 22.1, 14.0 Hz, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.5, 167.4, 134.7, 131.0, 129.0, 128.5, 127.4, 127.3, 126.3, 119.1, 119.0, 115.2, 50.0, 32.2, 32.1, 29.7, 27.1, 27.0, 25.4, 23.7. **HRMS** (ESI) m/z calculated for $C_{36}H_{36}ClN_2O_2S_4$ $[M+H]^+$: 691.1348, found $[M+H]^+$: 691.1348

1-benzyl-5-(4-bromophenyl)-1H-imidazole (11)



156 mg, 50% yield, yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 - 7.39 (m, 2H), 7.33 (d, *J* =

8.1 Hz, 1H), 7.29 - 7.28 (m, 3H), 7.17 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H).

THE CACULATION THEORY OF THE CARRIER'S MOBILITY

The calculation theory is following the equations *(1) - (6).*

$$R_{ij,kl} = \frac{V_{kl}}{I_{ij}} \text{ (1)}$$

The equation for the sheet resistance:

$$Rs = \frac{\pi}{ln2}\frac{1}{8}\left[\left(R_{21,34} - R_{12,34} + R_{32,41} - R_{23,41}\right)f_A + \left(R_{43,12} - R_{34,12} + R_{14,23} - R_{41,23}\right)f_B\right]$$

(2)

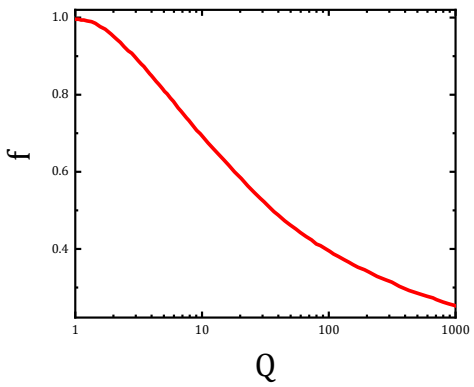
The equation for the specific resistance:

$$\rho = t \cdot Rs \rightarrow$$

$$\rho = \frac{\pi t}{ln2}\frac{1}{8}\left[\left(R_{21,34} - R_{12,34} + R_{32,41} - R_{23,41}\right)f_A + \left(R_{43,12} - R_{34,12} + R_{14,23} - R_{41,23}\right)f_B\right] \text{ (3)}$$

t is the thickness of the sample.

For the fA and fB factors we used the diagram below:



Calculation of Q_A, Q_B:

$$Q_A = \frac{R_{21,34} - R_{12,34}}{R_{32,41} - R_{23,41}}, Q_B = \frac{R_{43,12} - R_{34,12}}{R_{14,23} - R_{41,23}} \text{ (4)}$$

Then, we applied magnetic field vertically on the sample surface (on both directions, up (+B) and down (-B) and measured the surface hall coefficient and hall coefficient respectively.

$$R_{Hs} = \frac{1}{B}\left[\frac{R_{31,42(+B)} - R_{13,42(+B)} + R_{42,13(+B)} - R_{24,13(+B)} + R_{13,42(-B)} - R_{31,42(-B)} + R_{24,13(-B)} - R_{42,13(-B)}}{8}\right],$$

$$R_H = \frac{t}{B}\left[\frac{R_{31,42\,(+B)} - R_{13,42(+B)} + R_{42,13(+B)} - R_{24,13(+B)} + R_{13,42(-B)} - R_{31,42(-B)} + R_{24,13(-B)} - R_{42,13(-B)}}{8}\right] \text{ (5)}$$

For the free carrier density, as known, $N_s = \frac{1}{qR_{Hs}}$ and N= $\frac{1}{qR_H}$, then the free carrier's mobility could be obtained as following:

$$\mu = \frac{1}{q \cdot \rho \cdot N} \text{ . (6)}$$

REFERENCES

1. Del Olmo, E., Molina-Salinas, G. M., Escarcena, R., Alves, M., López-Pérez, J. L., Hernandez-Pando, R., Feliciano, A. S. *Bioorganic & Medicinal Chemistry Letters,* **2009**,*19(19), 5764-5768.*
2. Atta, Ananta Kumar; Kim, Seul-Bi; Cho, Dong-Gyu, *Bulletin of the Korean Chemical Society*, **2011**, *32(6)*, 2070 - 2072.

CONTRIBUTIONS

In Chapter 1, I performed the syntheses and collected the analytical data. Panagiota Lampiri assisted me in purifying some products. Pravin Patil gave some advice in the condition optimization. Alexander Dömling, Constantinos G. Neochoritis and I conceptualized and directed the project and contributed to the manuscript writing. Giasemi Angeli determined the single crystal X-ray structure. In Chapter 2 and Chapter 3, I performed the syntheses and collected the analytical data as the project leader. Alexander Dömling, Constantinos G. Neochoritis conceptualized and directed the project. Giasemi Angeli determined the single crystal X-ray structure. Alexander Dömling, Constantinos G. Neochoritis and I contributed to the manuscript writing. In Chapter 4, I was the project leader, Maria Thomaidi and I performed the syntheses and collected the analytical data. Constantinos G. Neochoritis conceptualized and directed the project. Giasemi Angeli determined the single crystal X-ray structure. Alexander Dömling, Constantinos G. Neochoritis and I contributed to the manuscript writing. In the Chapter 5, Qian wang, Constantinos G. Neochoritis and I performed the syntheses and collected the analytical data. Alexander Dömling, Constantinos G. Neochoritis and I conceptualized and directed the project. Constantinos Stoumpos, Emmanuel G. Manidalis and I performed the electrochemical properties measurements. Constantinos Stoumpos and I determined the single crystal X-ray structure. Alexander Dömling, Constantinos G. Neochoritis and I contributed to the manuscript writing.

LIST OF PUBLICATIONS

[1] **Xiaofang Lei**, Xriatina Tomza, Constantinos G. Neochoritis and Alexander Dömling. Benzothiazepine Based MCR Chemistry. (Manuscript in preparation)

[2] **Xiaofang Lei**, Alexander Dömling, Constantinos G. Neochoritis. Novel materials via multicomponent reactions. (Manuscript in preparation)

[3] **Xiaofang Lei**, Alexander Dömling, Constantinos G. Neochoritis. The approaches towards functional TTFs. (Manuscript in preparation)

[4] **Xiaofang Lei**, Giasemi K. Angeli, Constantinos G. Neochoritis and Alexander Dömling. *Green Chemistry*, 2022, *24*, 6168-6171.

[5] **Xiaofang Lei**, Giasemi Angeli, Alexander Dömling, Constantinos G. Neochoritis. *Eur. J. Org. Chem*. 2022, e202200220.

[6] **Xiaofang Lei**, Panagiota Lampiri, Pravin Patil, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Chemical Communications*, 2021, *57*, 6652-6655.

[7] **Xiaofang Lei,** Maria Thomaidi, Giasemi Angeli, Constantinos G. Neochoritis and Alexander Dömling, *Synlett*, 2021, *32*, 155-160.

Before Groningen

[1] **Xiaofang Lei,** Yuanyuan Wang, Erkang Fan, and Zhihua Sun, *Organic Letters*, 2019, *21(5)*, 1484-1487.

[2] Shengfeng Wu, **Xiaofang Lei**, Erkang Fan, and Zhihua Sun, *Organic Letters,* 2018, 20(3), 522-525.

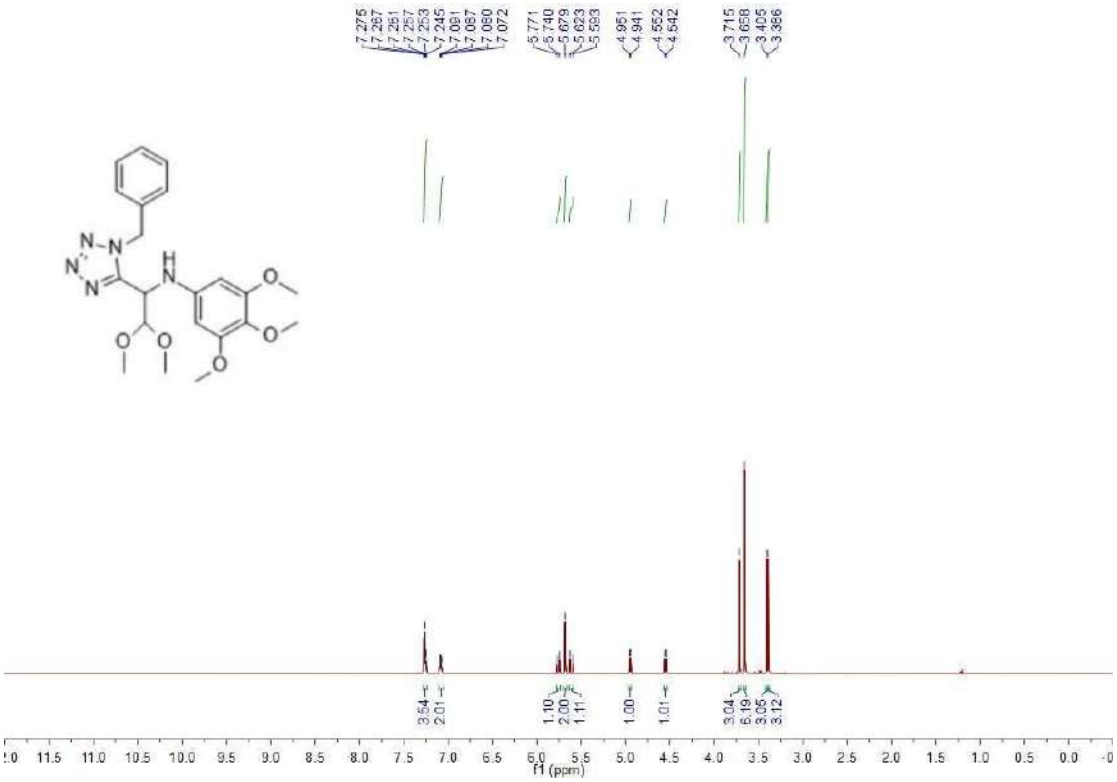
[3] Zhihua Sun, Shengfeng Wu, Yiru Dai, **Xiaofang Lei**. A synthetic method and an intermediate for an active molecule of an anti-leukemia cancer cell, CN108558862B.

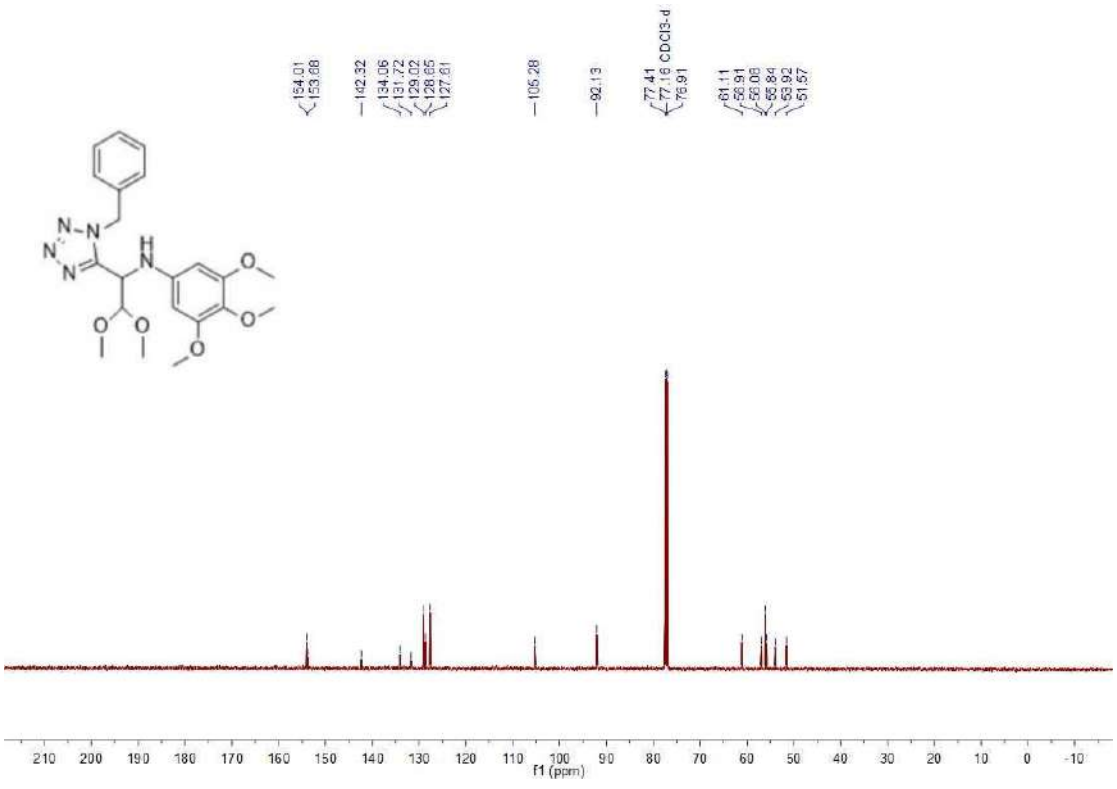
[4] Xing Qiuju, Ma Jun, **Xiaofang Lei**, Yu Jian, Huang Qiong, Zou Jianping, Chen Wuhua, Yuan Qiangzhong, Pan Xianhui; A synthetic method of WS2-Bi3.84W0.16-O6.24 an ernary heterojunction of photodegradation organic catalyst, CN103962158B.

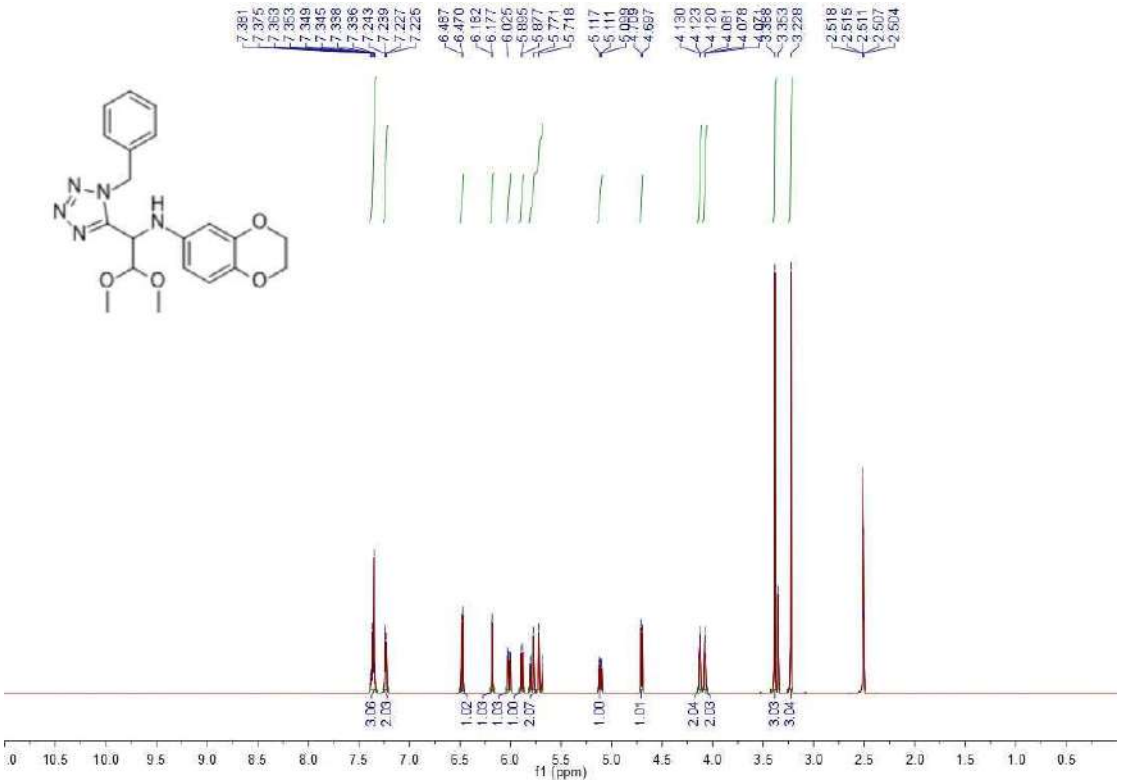
ΠΑΡΑΡΤΗΜΑ

Exemplary copies of NMR spectra of novel compounds

Chapter 1



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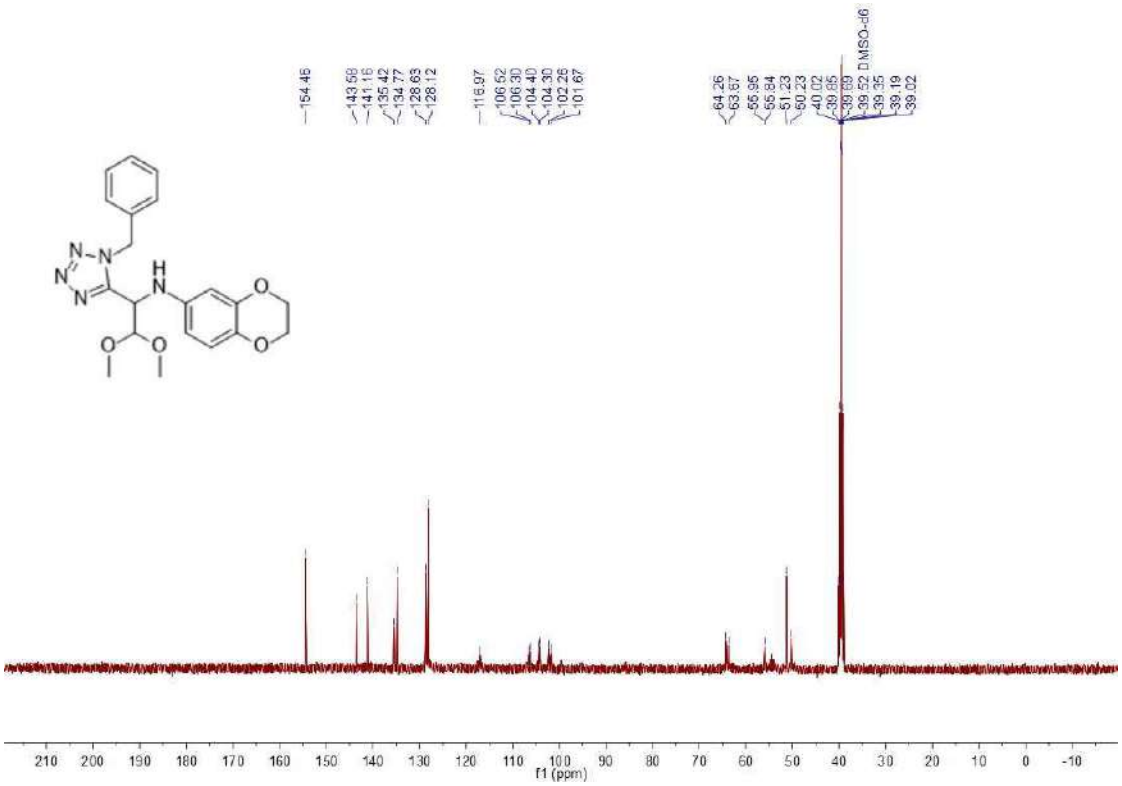
3.04
f1 (ppm)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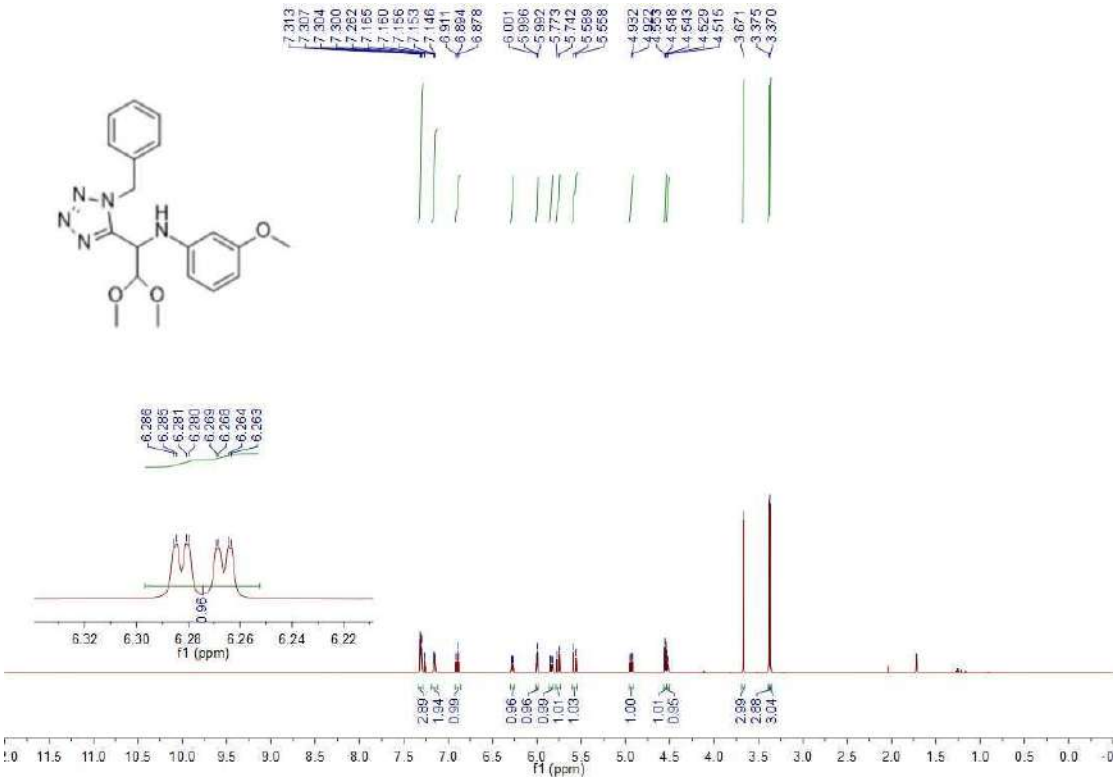
f1 (ppm)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6.22
f1 (ppm)
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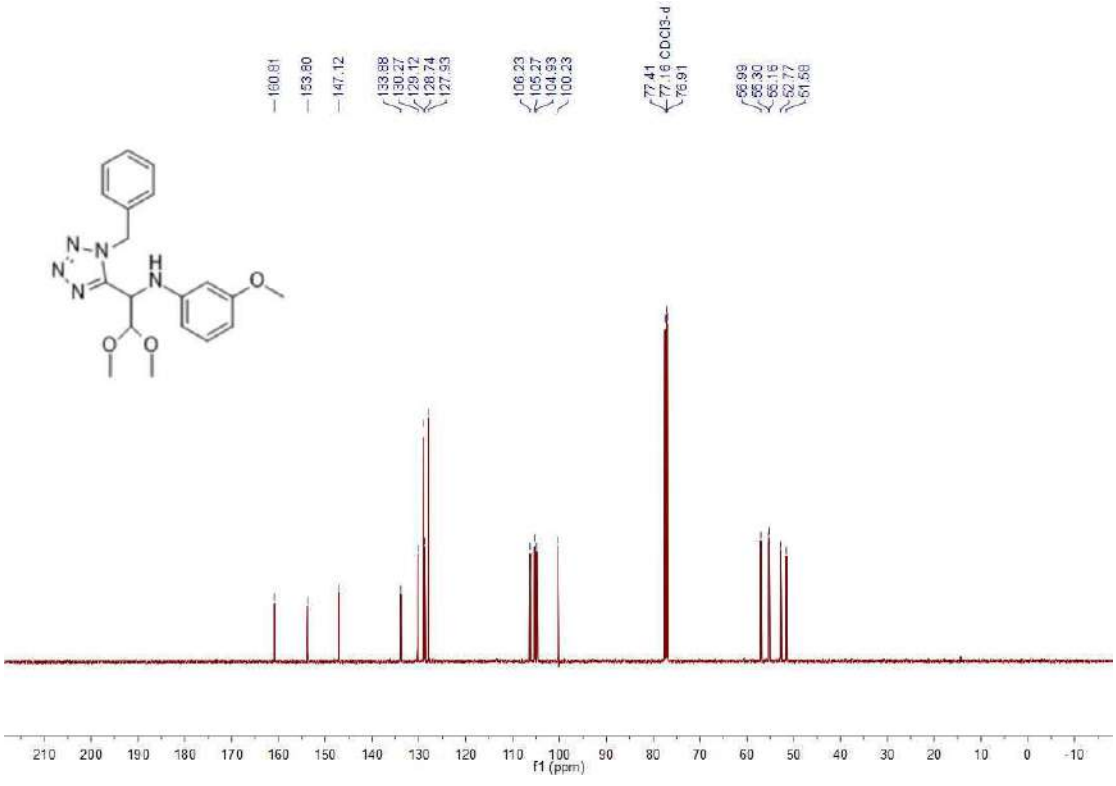
f1 (ppm)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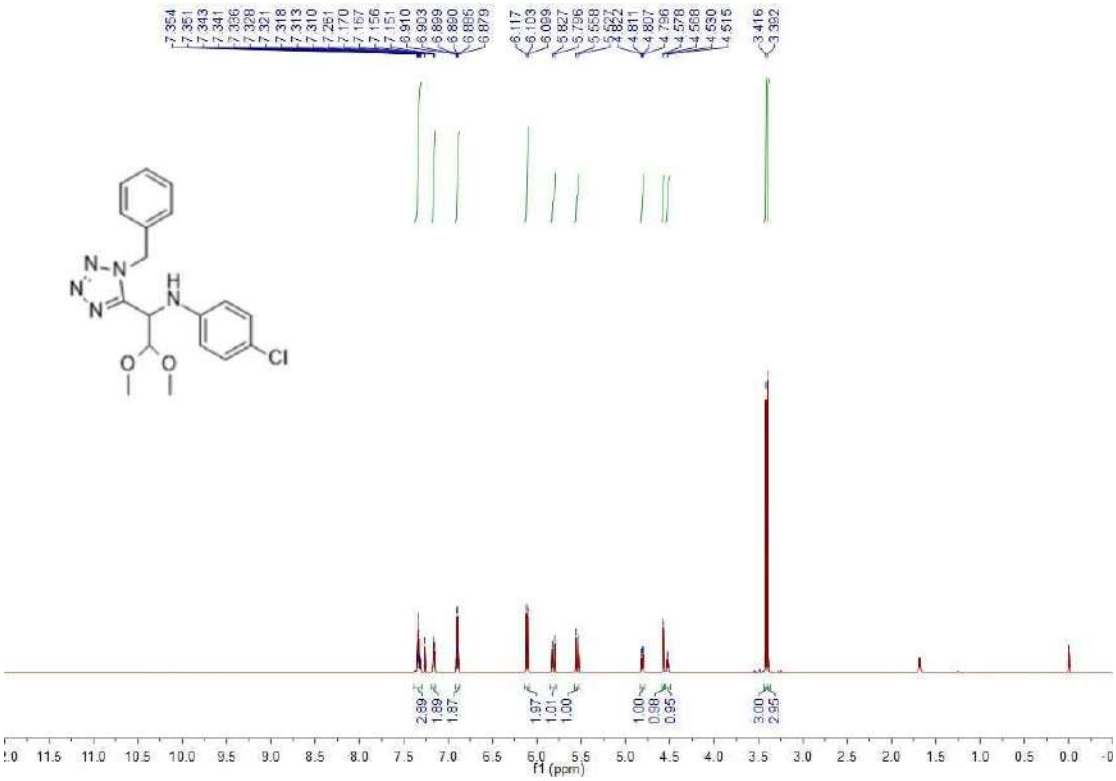
f1 (ppm)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4.515
3.416
3.392
Cl
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1.00
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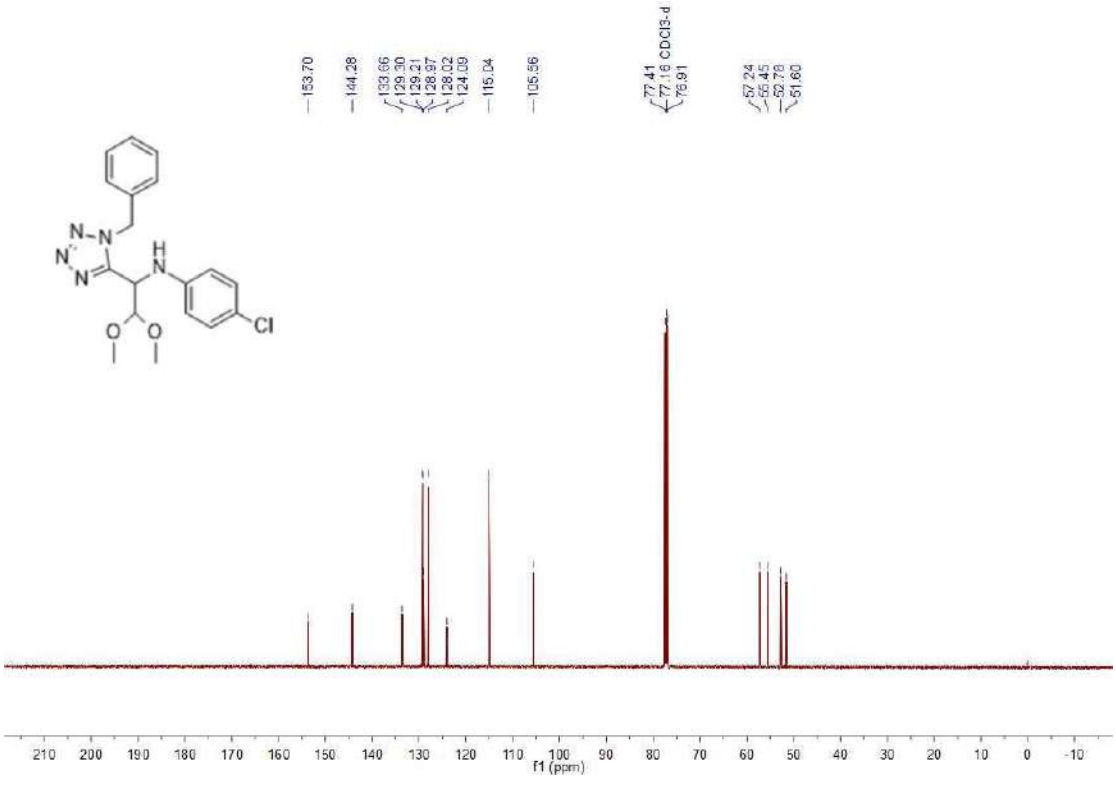
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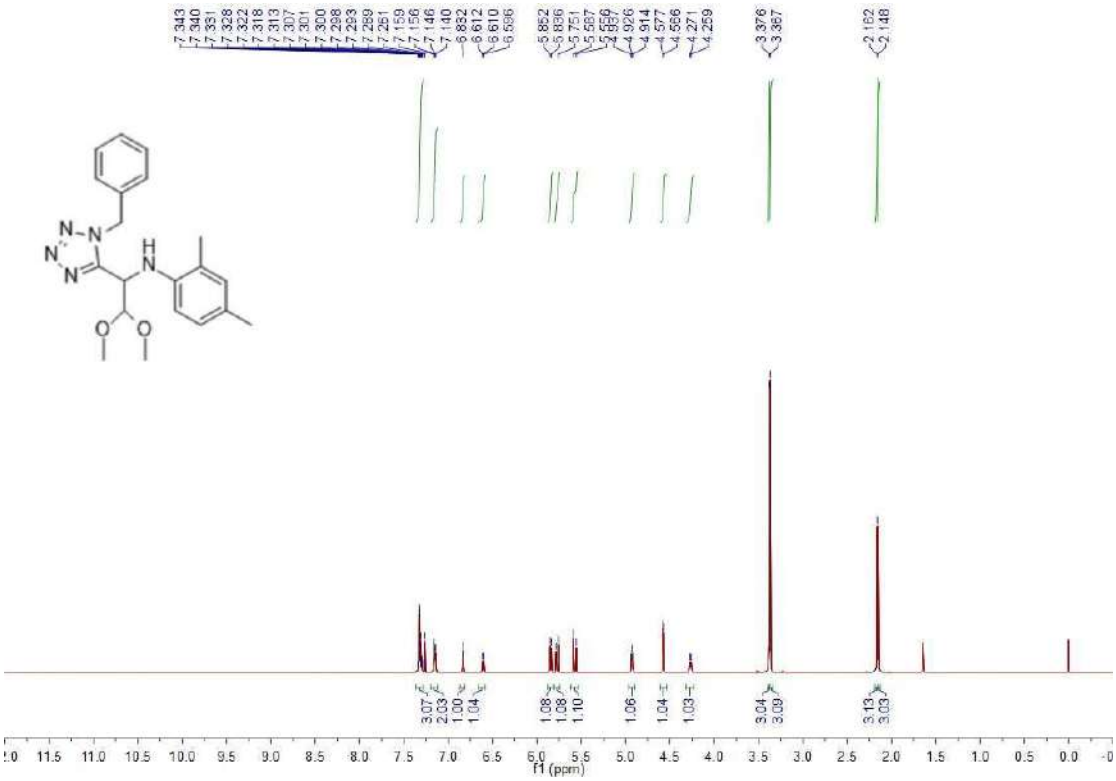
Cl
f1 (ppm)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7.293
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7.156
7.146
7.140
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6.610
6.596
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5.667
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4.914
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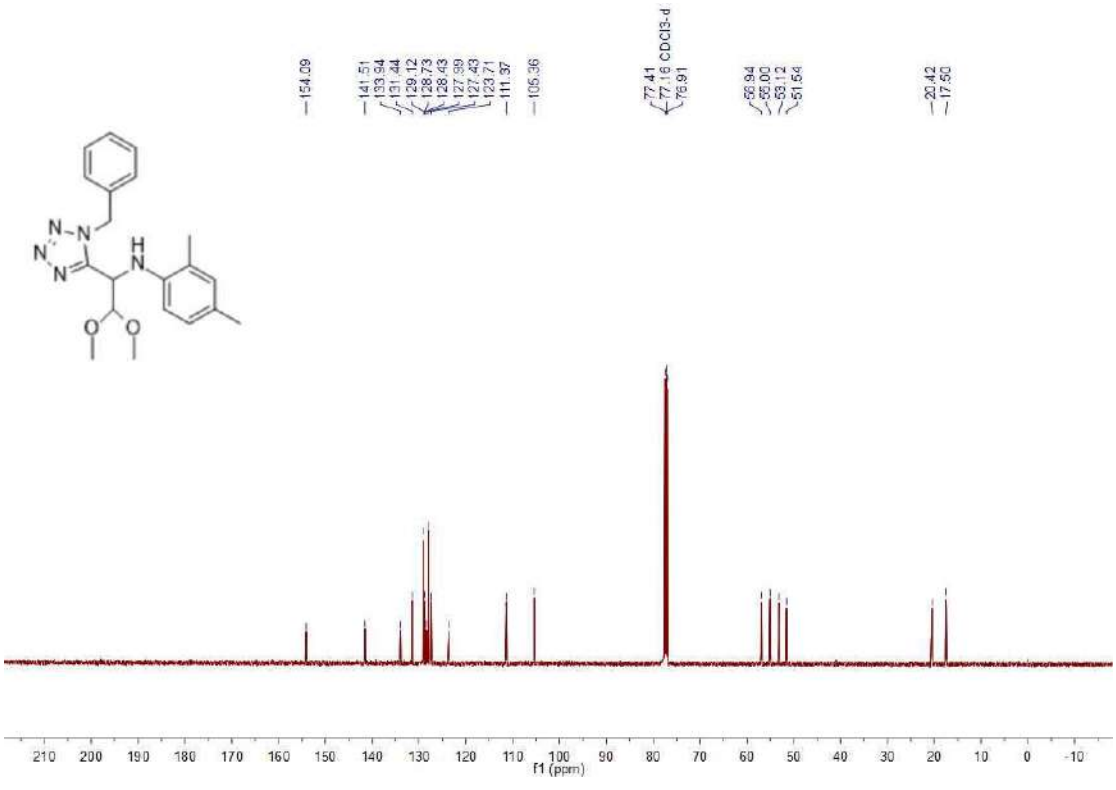
3.04
3.09
3.13
3.03
f1 (ppm)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123.71
111.97
105.36
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CDCl3-d
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51.54
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17.50
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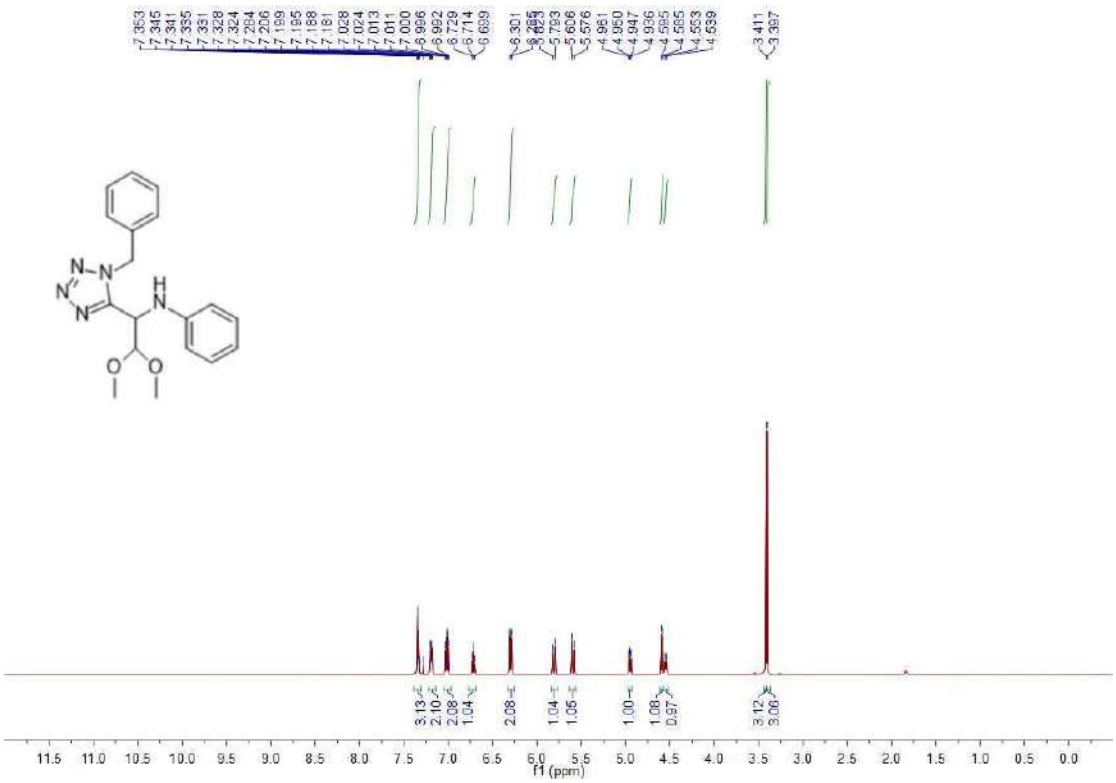
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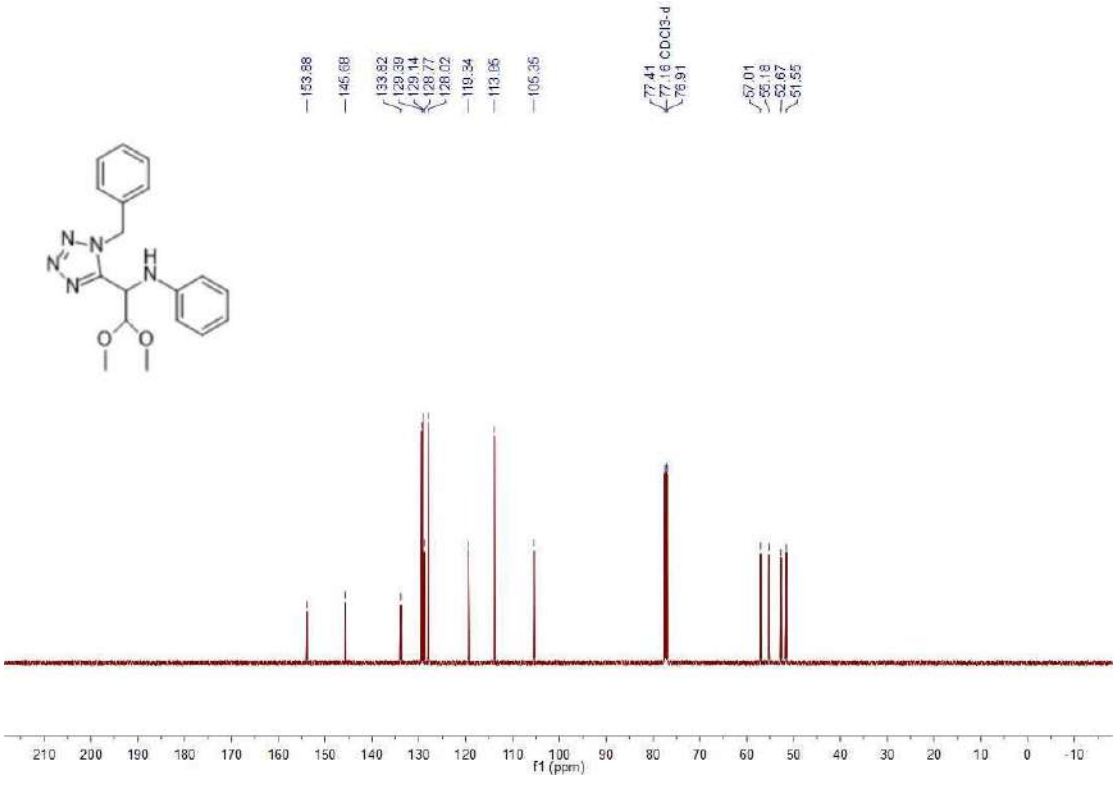
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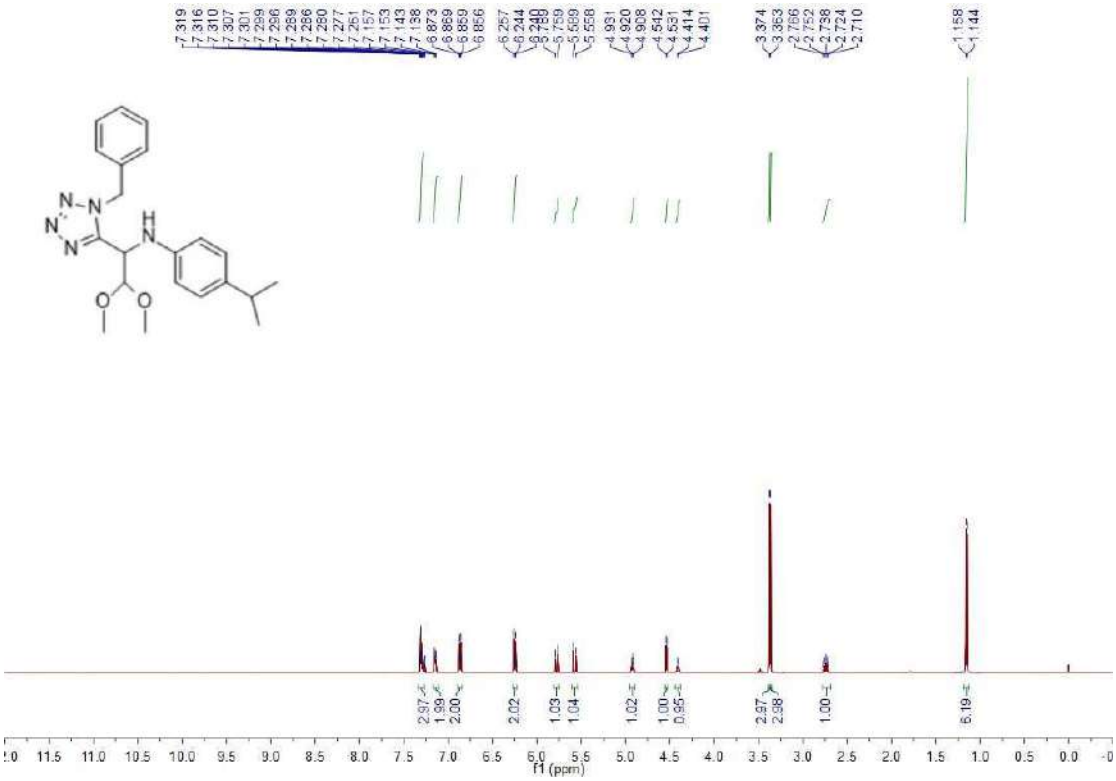
f1 (ppm)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1.99
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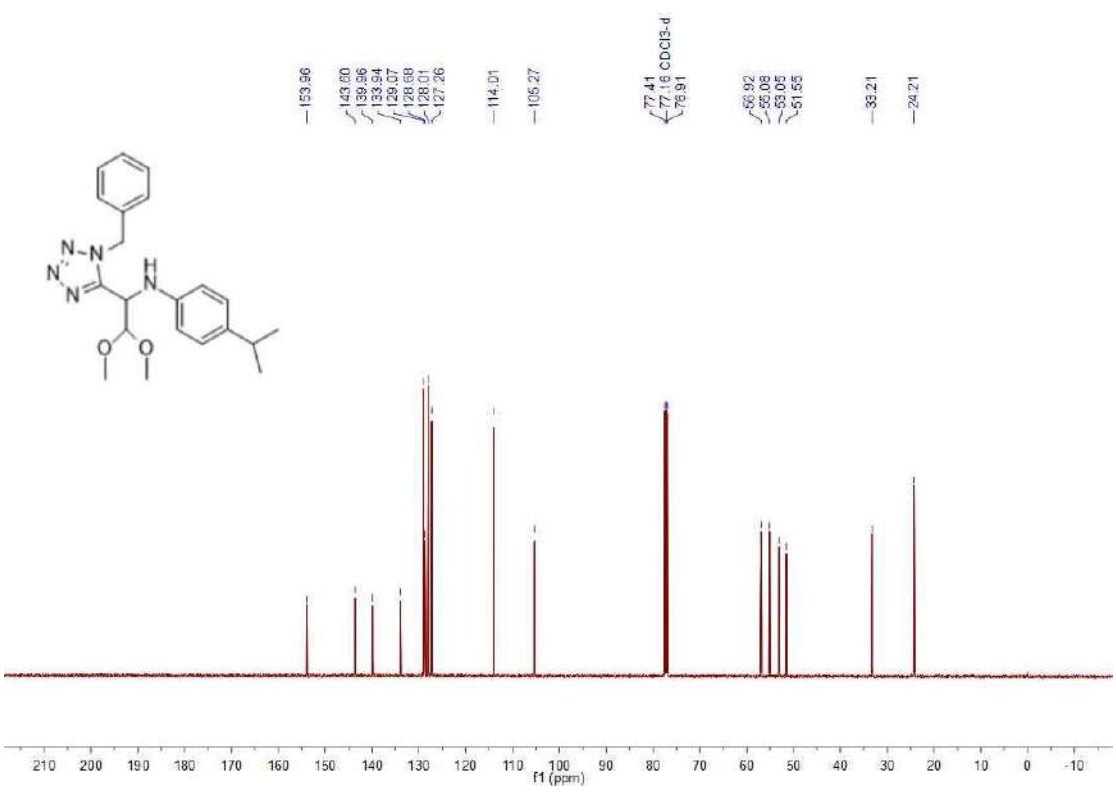
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24.21
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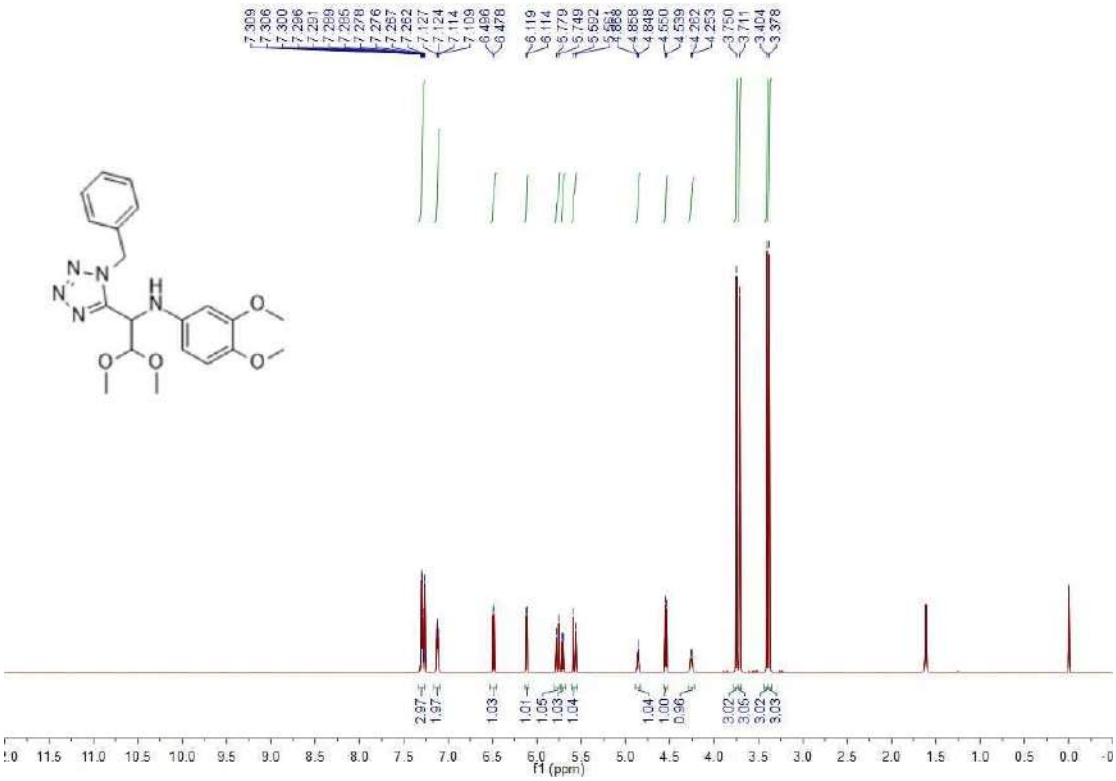
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1.03
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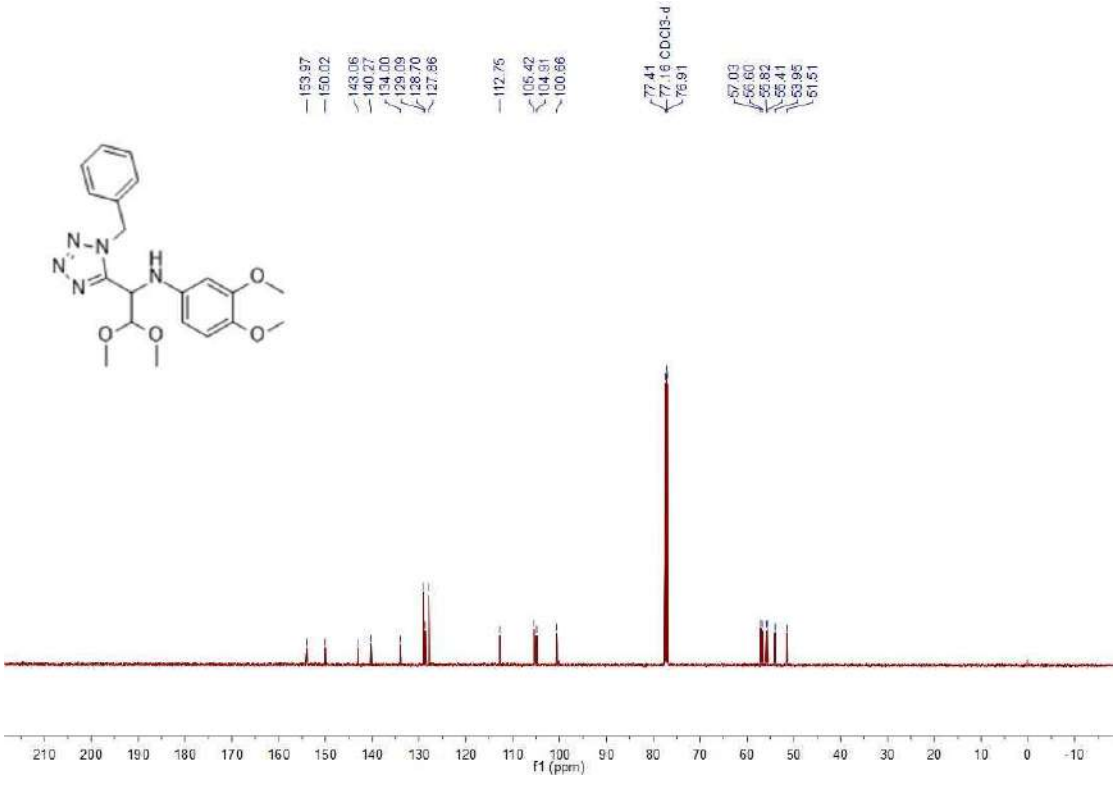
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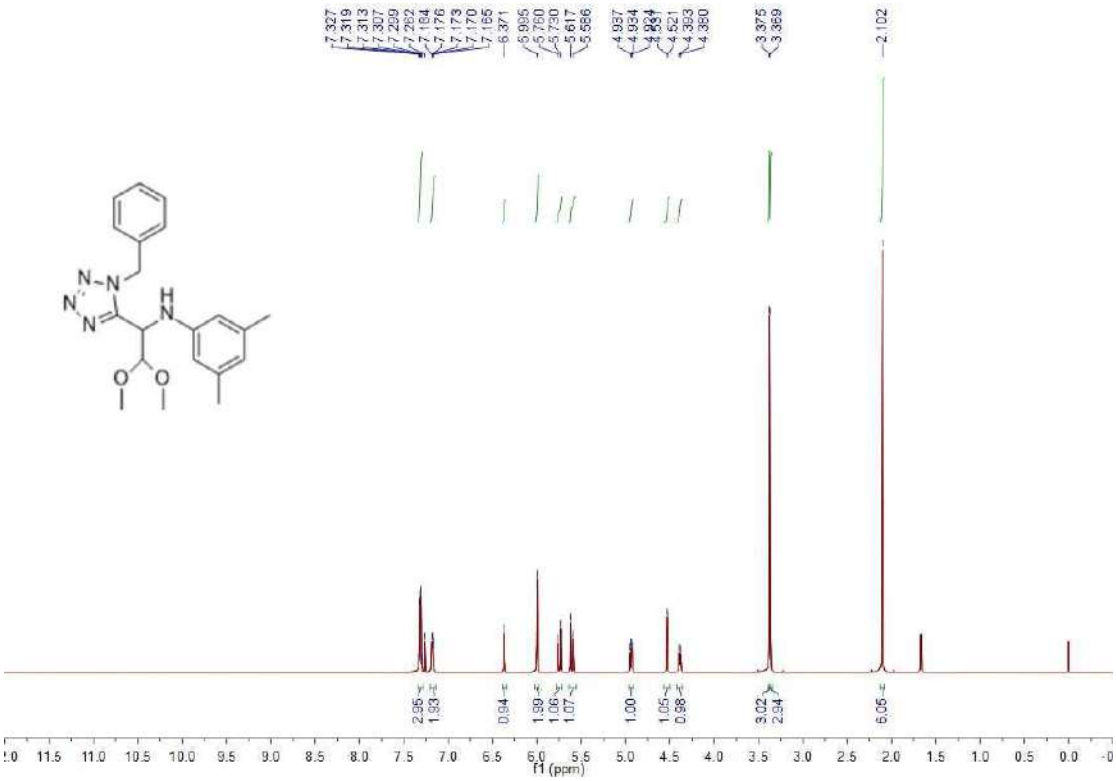
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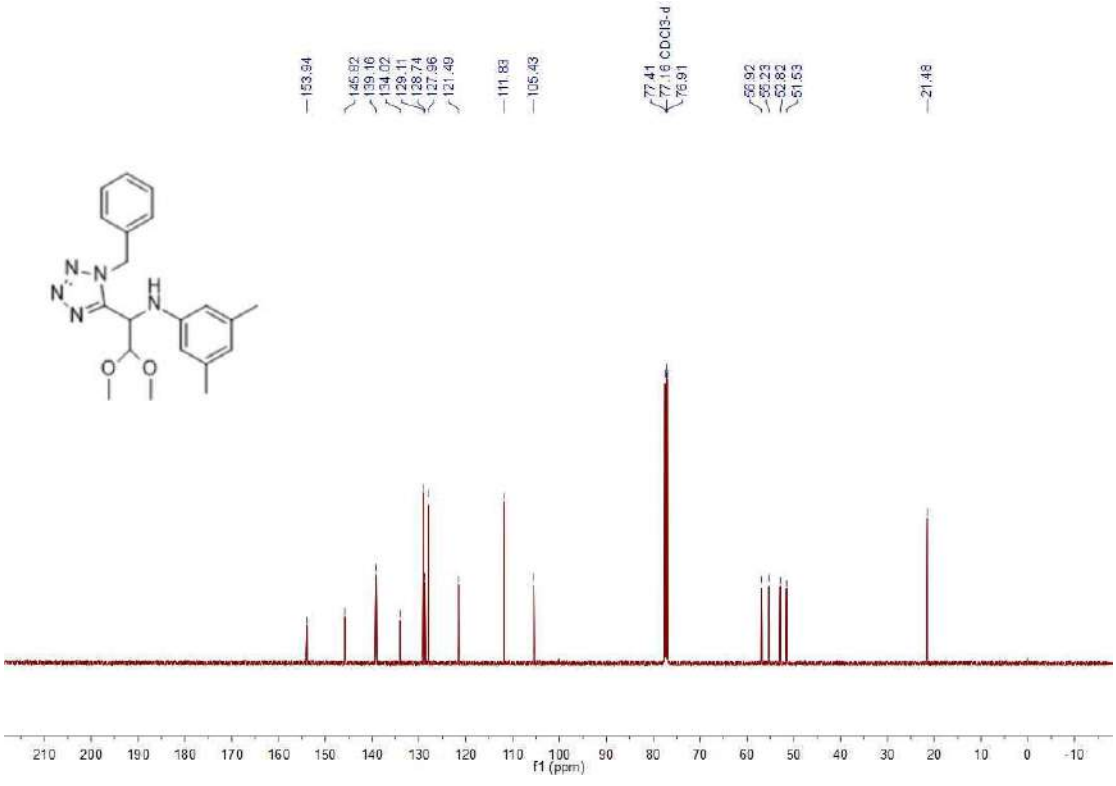
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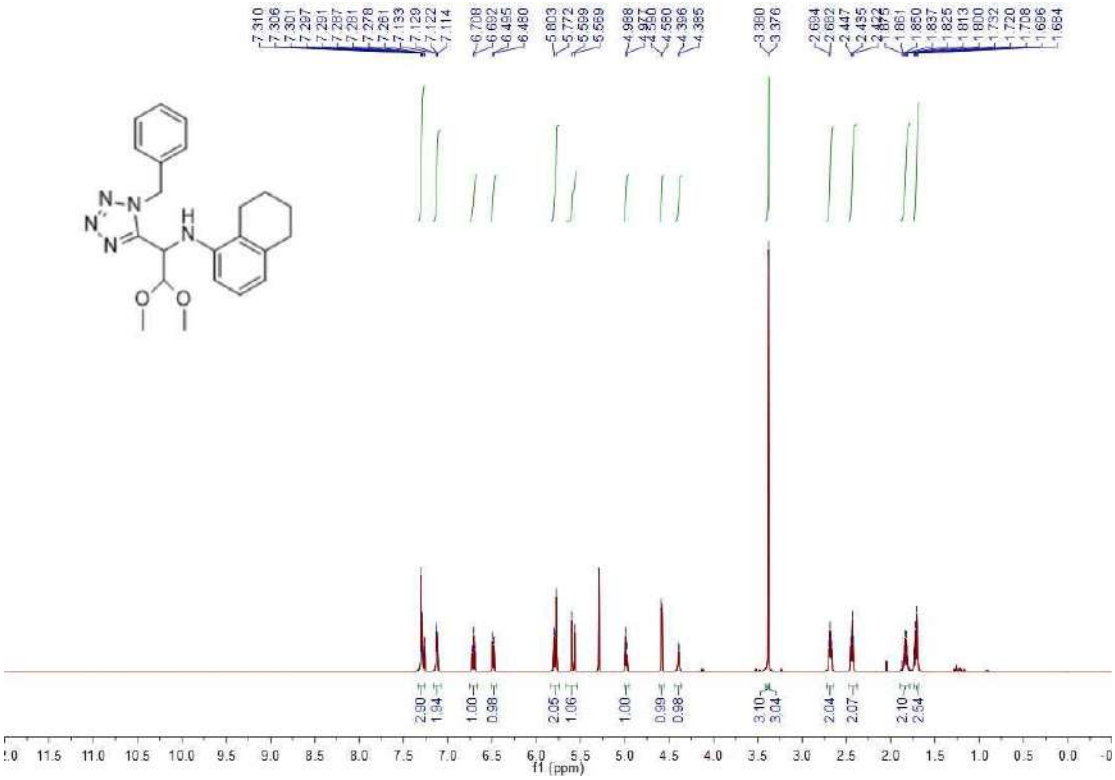
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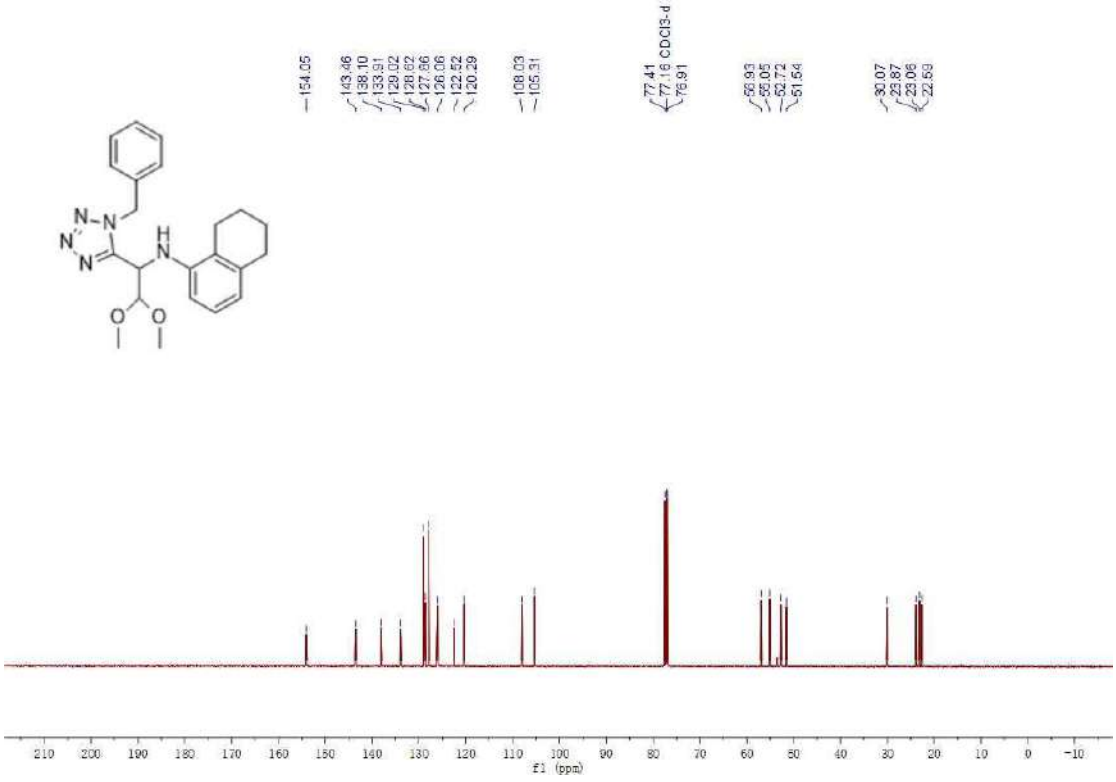
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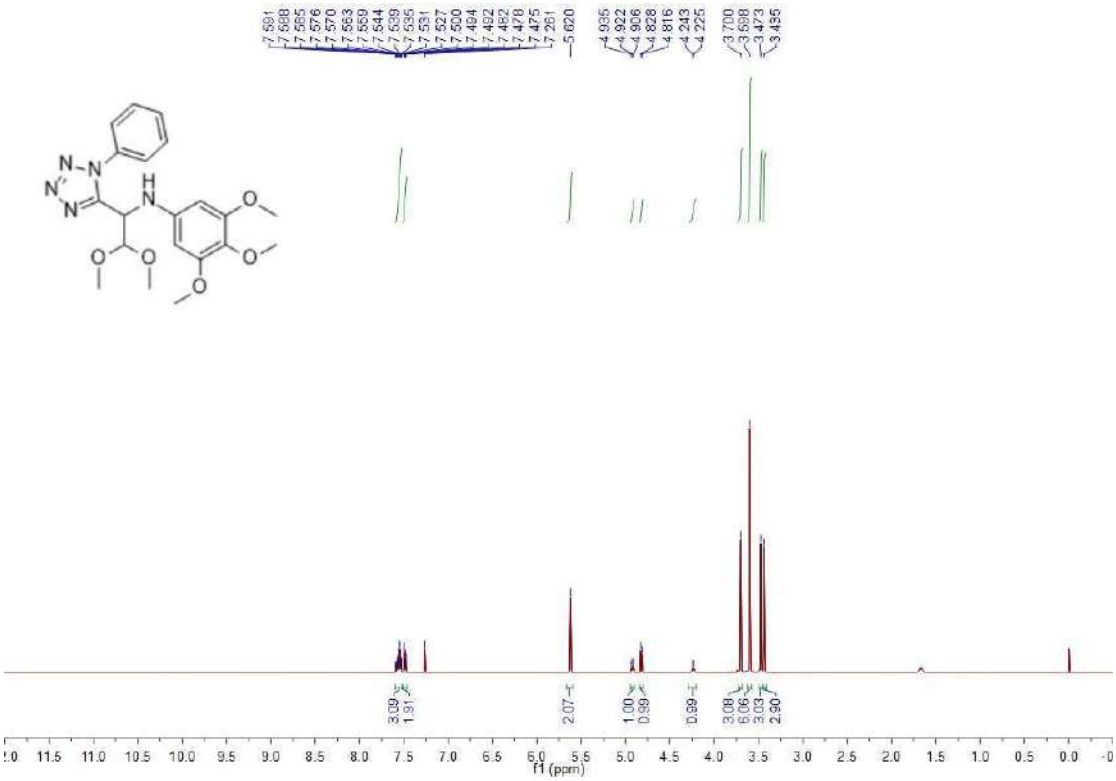
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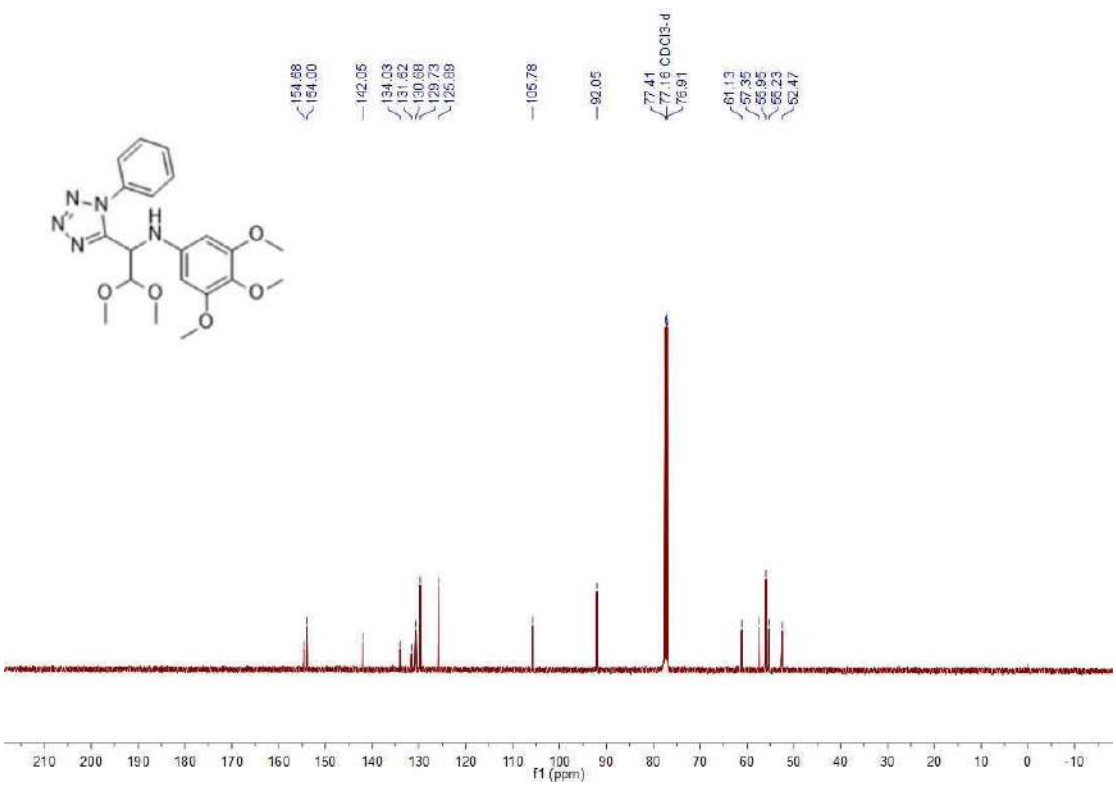
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CDCl3-d
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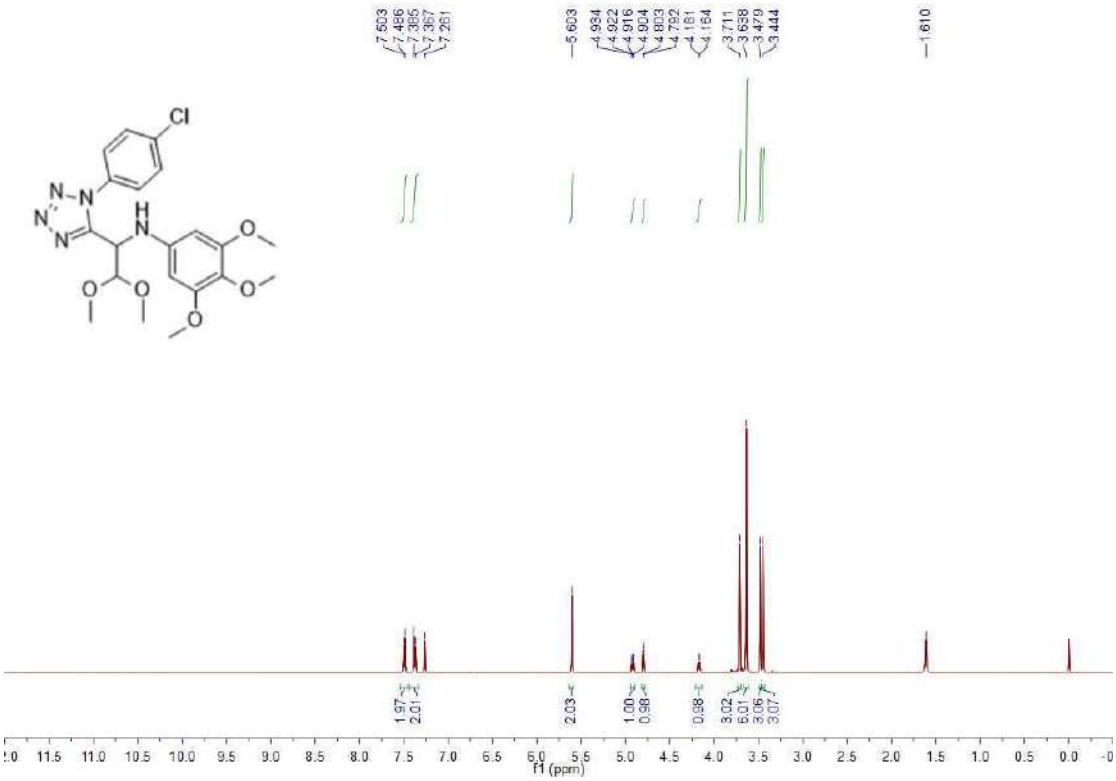
f1 (ppm)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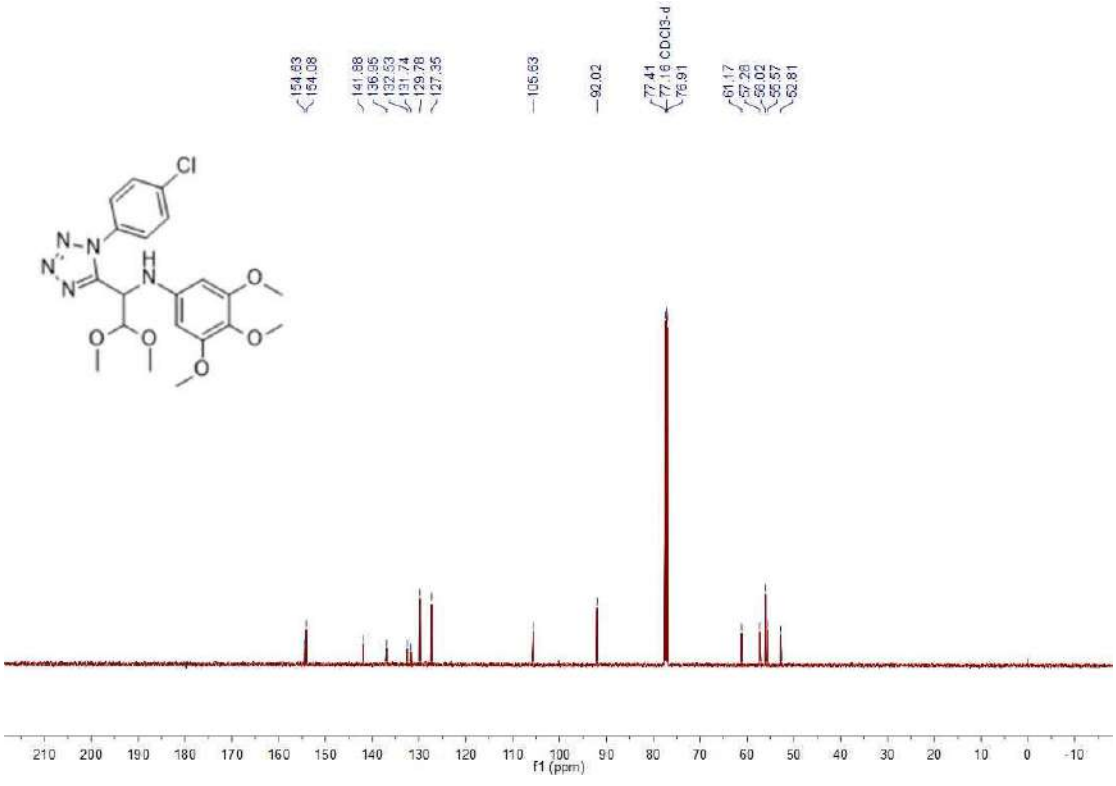
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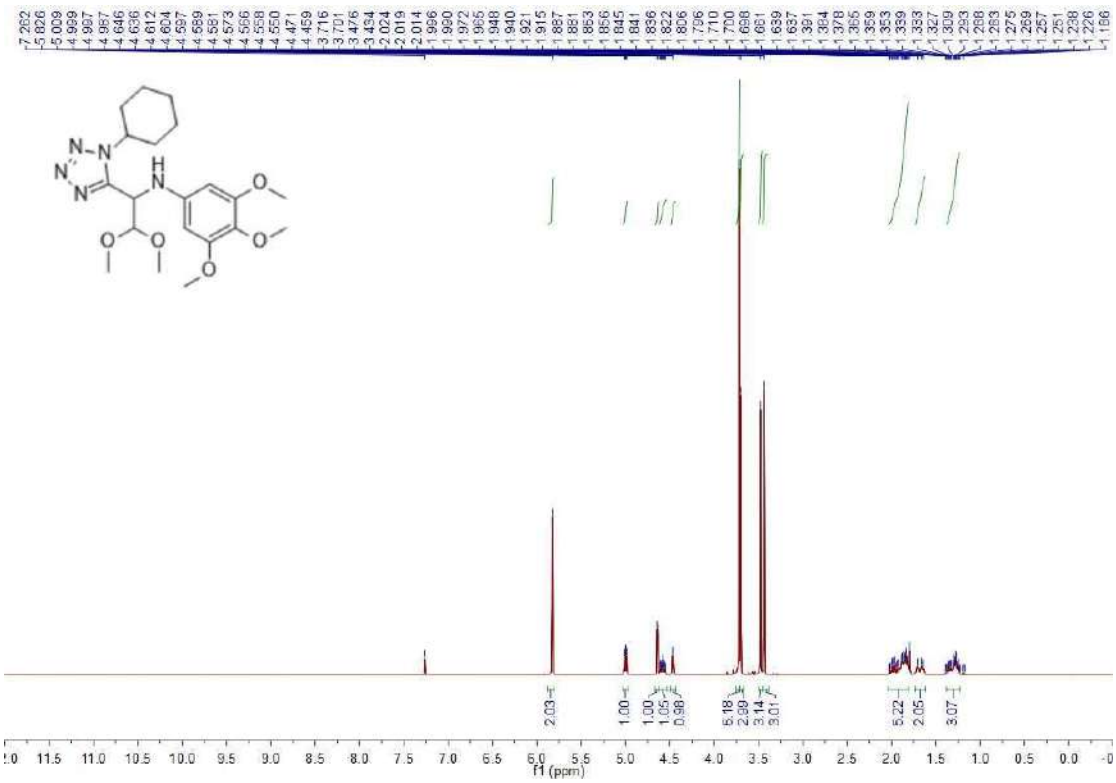
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2.03
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0.98
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2.99
3.14
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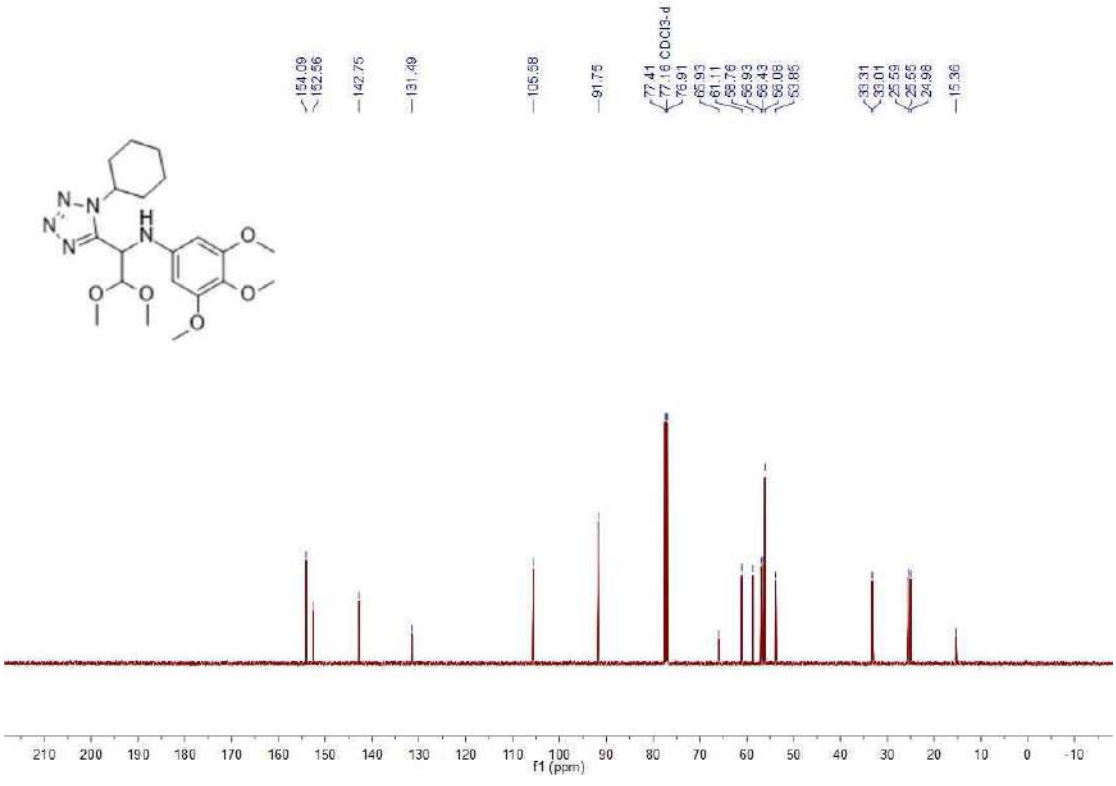
5.22
2.05
3.07
f1 (ppm)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77.16
CDCl3-d
76.91
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61.11
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56.93
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56.08
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33.31
33.01
25.59
25.55
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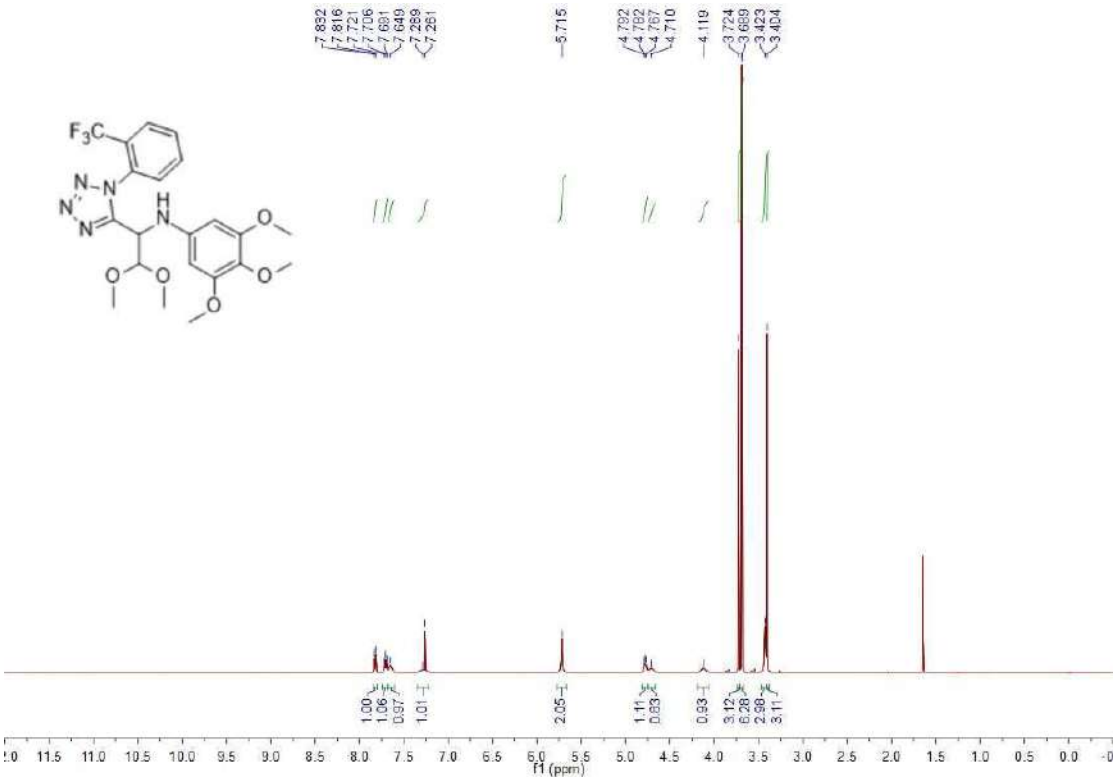
f1 (ppm)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4.710
4.119
3.724
3.689
3.423
3.404
1.00
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6.28
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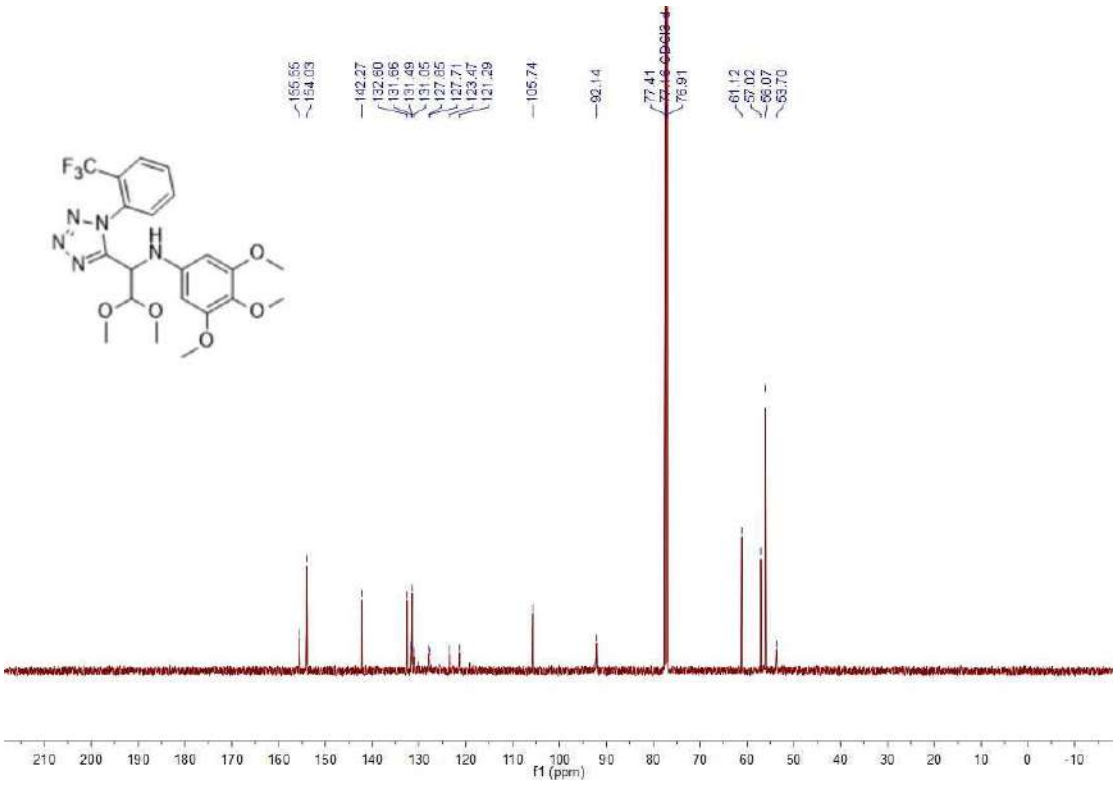
3.11
f1 (ppm)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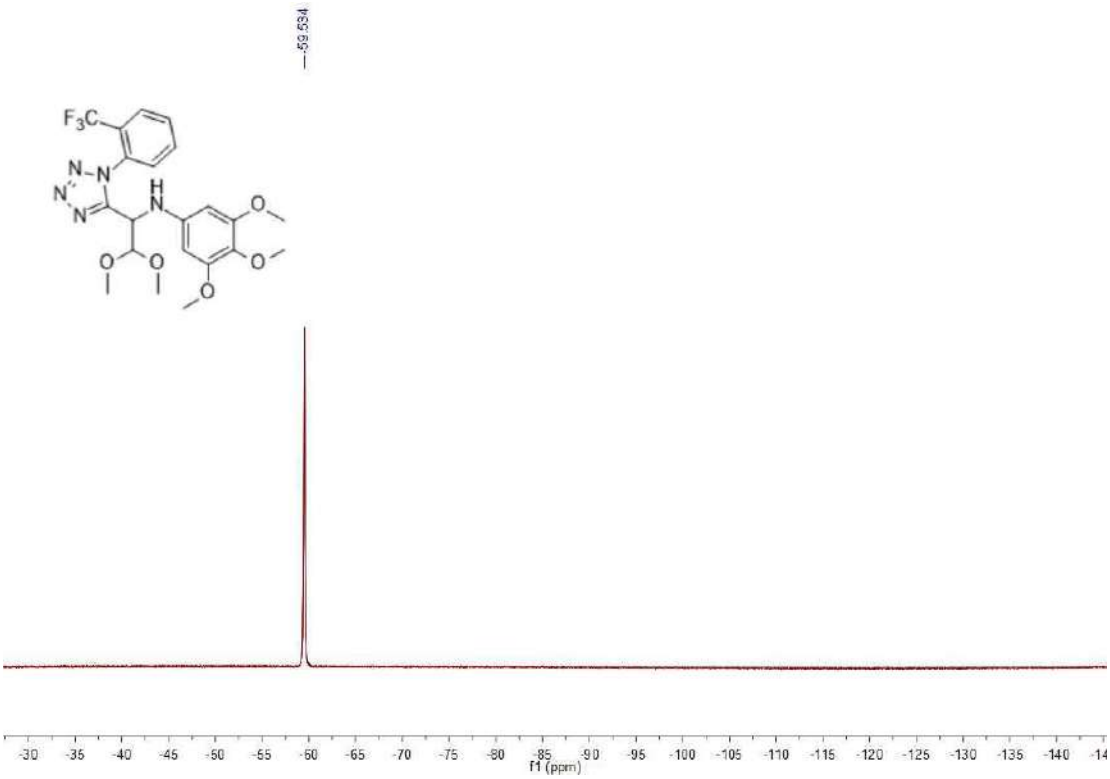
77.16
76.91
61.12
57.02
56.07
53.70
f1 (ppm)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N
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O
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O
O
-30
-35
-40
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-55
-60
-65
-70
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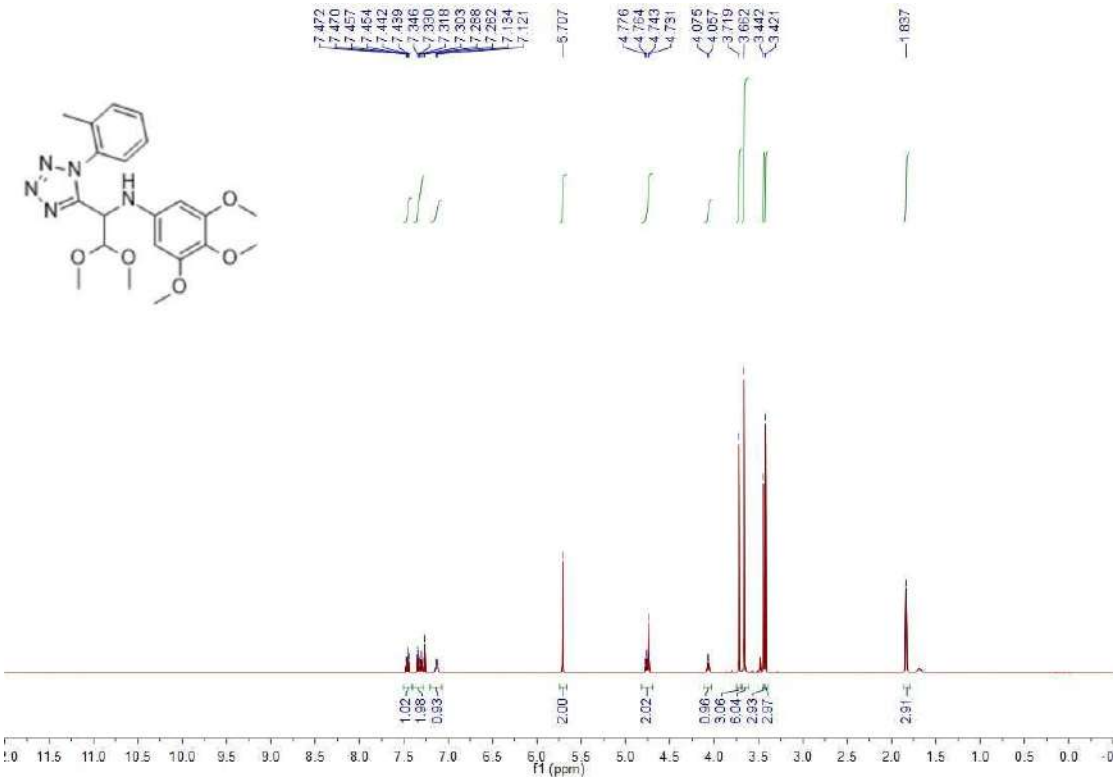
-100
-105
-110
-115
-120
-125
-130
-135
-140
f1 (ppm)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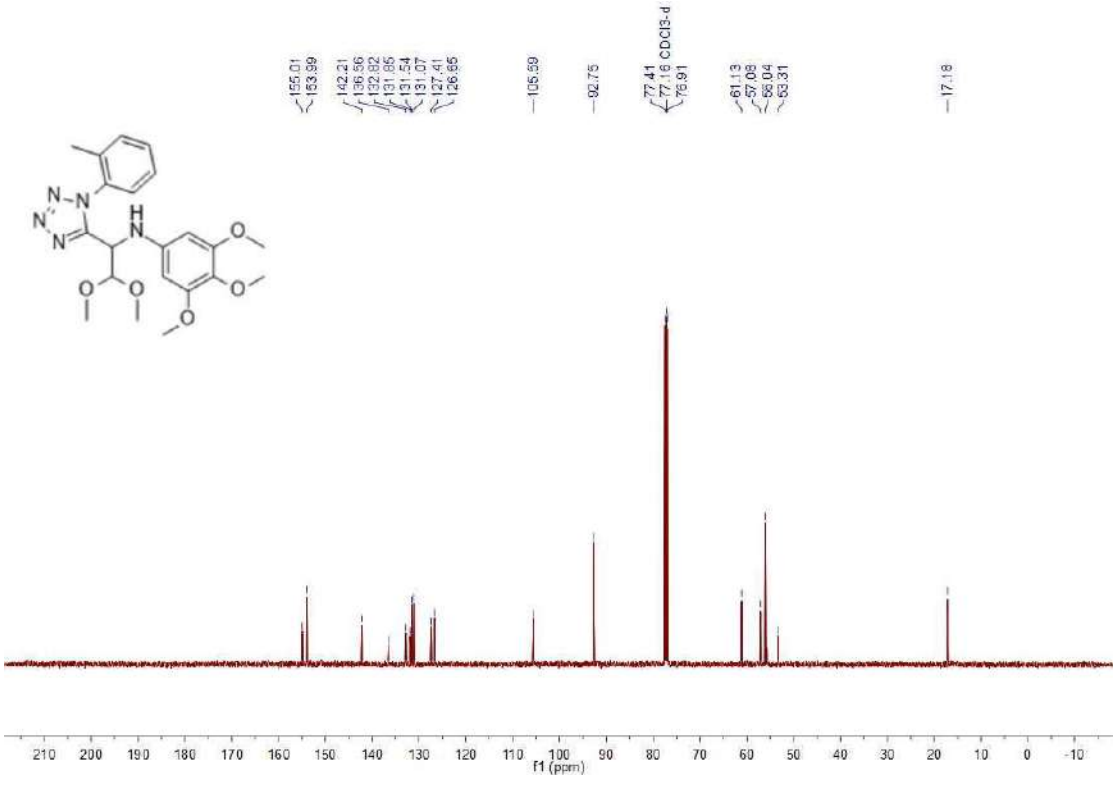
7.303
7.288
7.262
7.134
7.121
5.707
4.776
4.764
4.743
4.731
4.075
4.057
3.719
3.662
3.442
3.421
1.837
1.02
1.38
0.93
2.00
2.02
0.96
3.06
6.04
2.93
2.97
2.91
f1 (ppm)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126.85
105.59
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77.16
CDCl3-d
76.91
61.13
57.08
56.04
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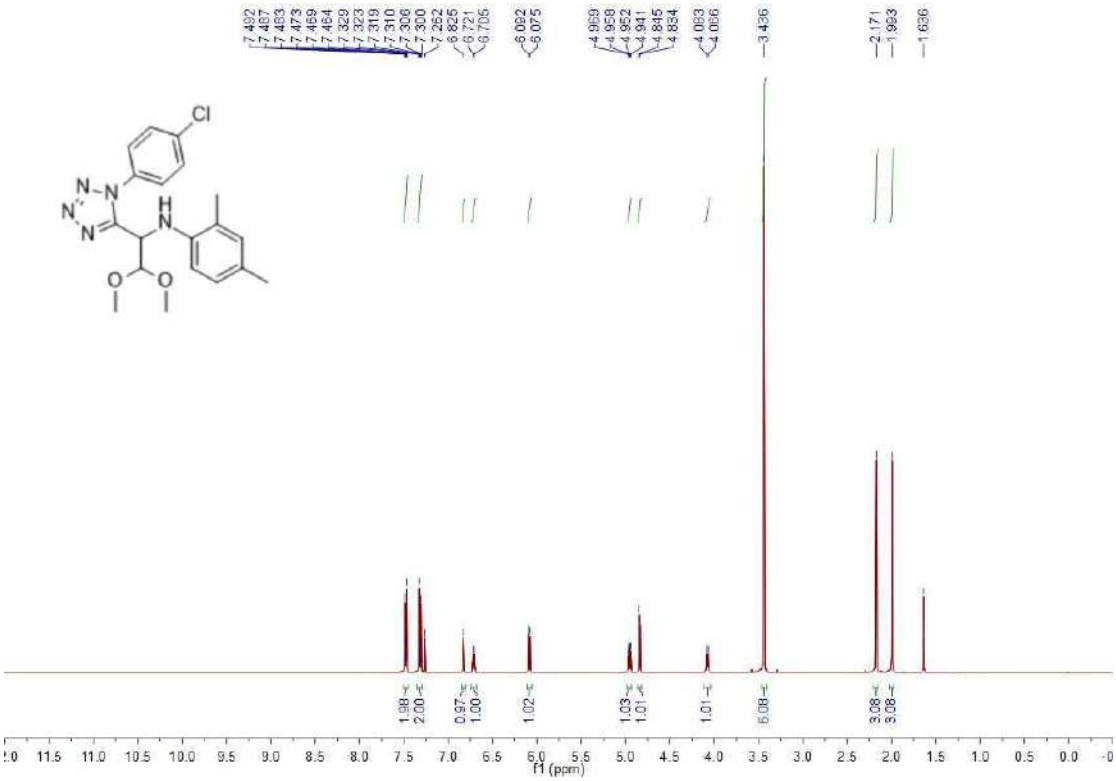
17.18
f1 (ppm)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7.306
7.300
7.262
6.825
6.721
6.705
6.092
6.075
4.969
4.958
4.952
4.941
4.845
4.834
4.083
4.066
3.436
2.171
1.993
1.636
Cl
N
N
N
H
N
O
O
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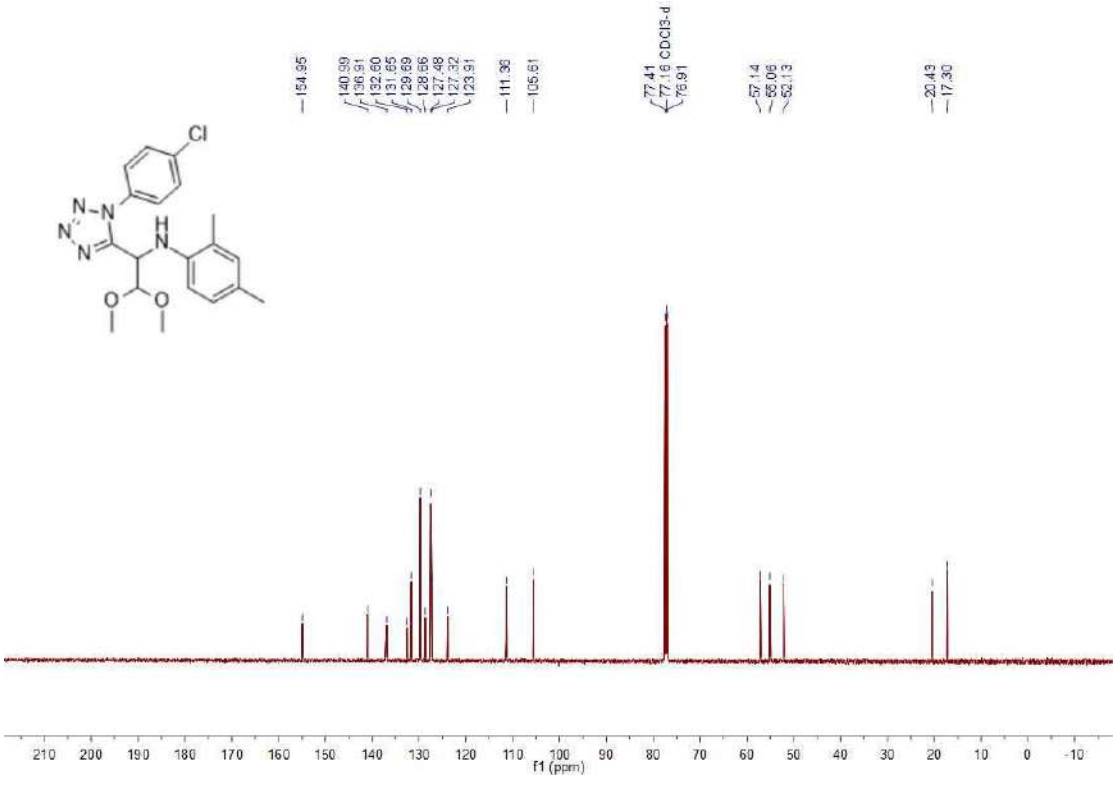
2.00
0.97
1.00
1.02
1.03
1.01
1.01
5.08
3.08
3.08
f1 (ppm)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129.89
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127.48
127.32
123.91
111.36
105.61
77.41
77.16
CDCl3-d
76.91
57.14
55.06
52.13
20.43
17.30
Cl
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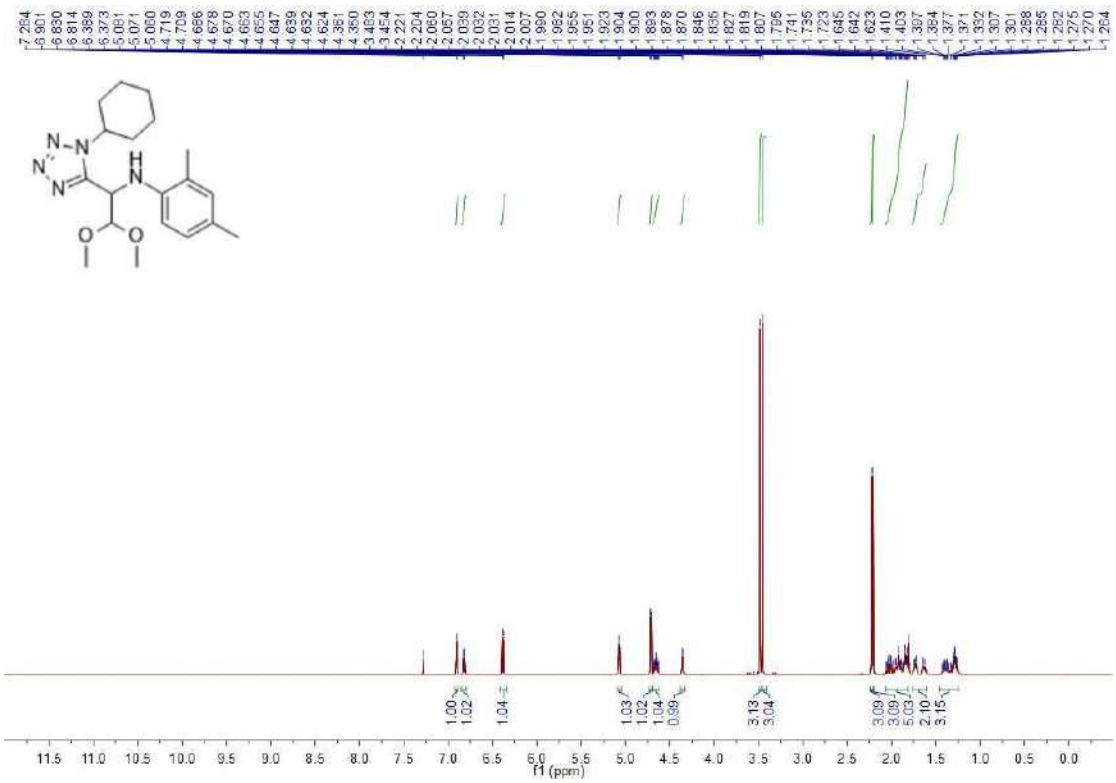
N
N
H
N
O
O
f1 (ppm)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6.814
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6.373
5.081
5.071
5.060
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4.709
4.686
4.678
4.670
4.663
4.655
4.647
4.639
4.632
4.624
4.361
4.350
3.463
3.454
2.221
2.204
2.060
2.057
2.039
2.032
2.031
2.014
2.007
1.990
1.982
1.955
1.951
1.923
1.904
1.900
1.893
1.878
1.870
1.846
1.836
1.827
1.819
1.807
1.795
1.741
1.735
1.723
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1.642
1.623
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1.403
1.397
1.384
1.377
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1.332
1.307
1.301
1.298
1.285
1.282
1.275
1.270
1.264
1.00
1.02
1.04
1.03
1.02
1.04
0.89
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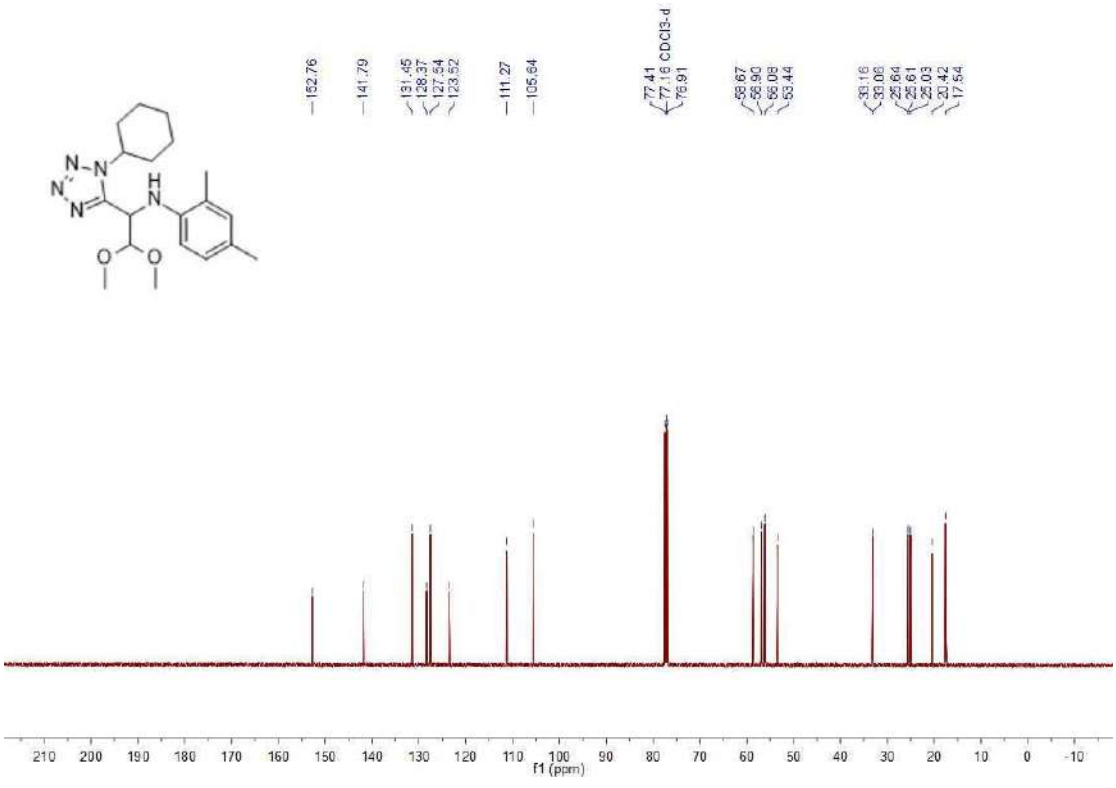
3.04
3.09
3.09
5.03
2.10
3.15
f1 (ppm)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123.52
111.27
105.64
77.41
77.16 CDCl3-d
76.91
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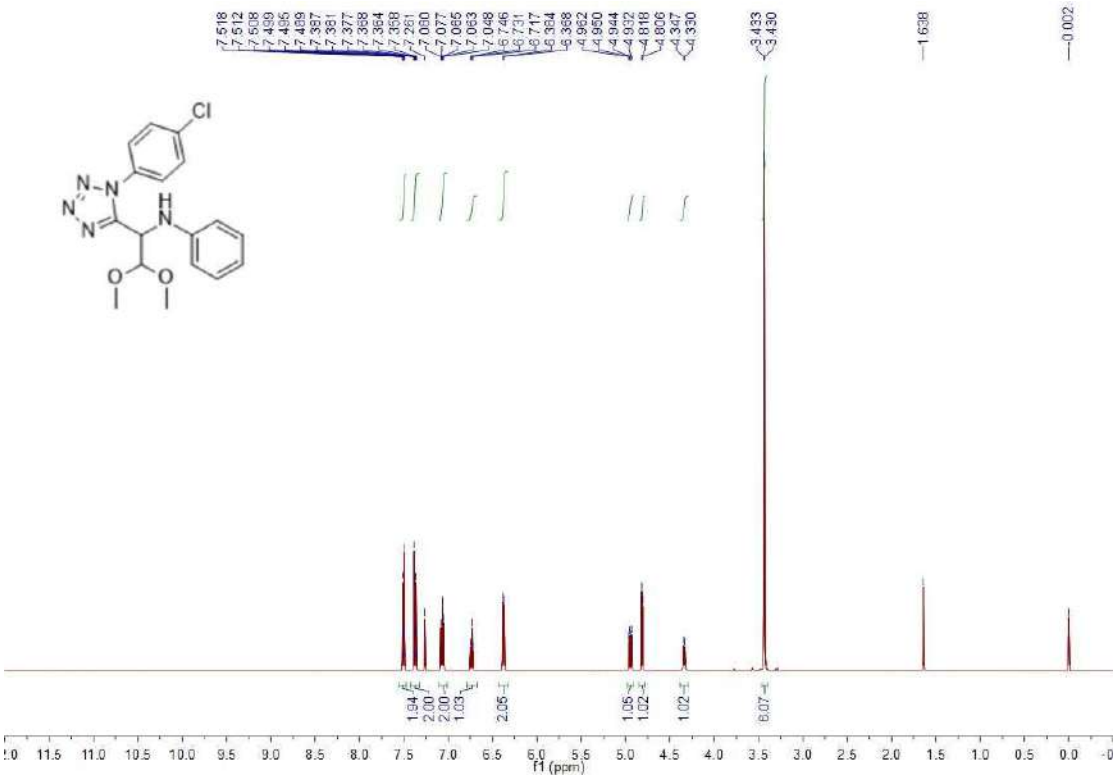
25.61
25.03
20.42
17.54
f1 (ppm)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7.409
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7.381
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7.368
7.364
7.358
7.221
7.090
7.077
7.065
7.063
7.048
6.746
6.731
6.717
6.384
6.368
4.962
4.950
4.944
4.932
4.818
4.806
4.347
4.330
3.433
3.430
1.638
0.002
Cl
N
N
N
H
N
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2.00
2.00
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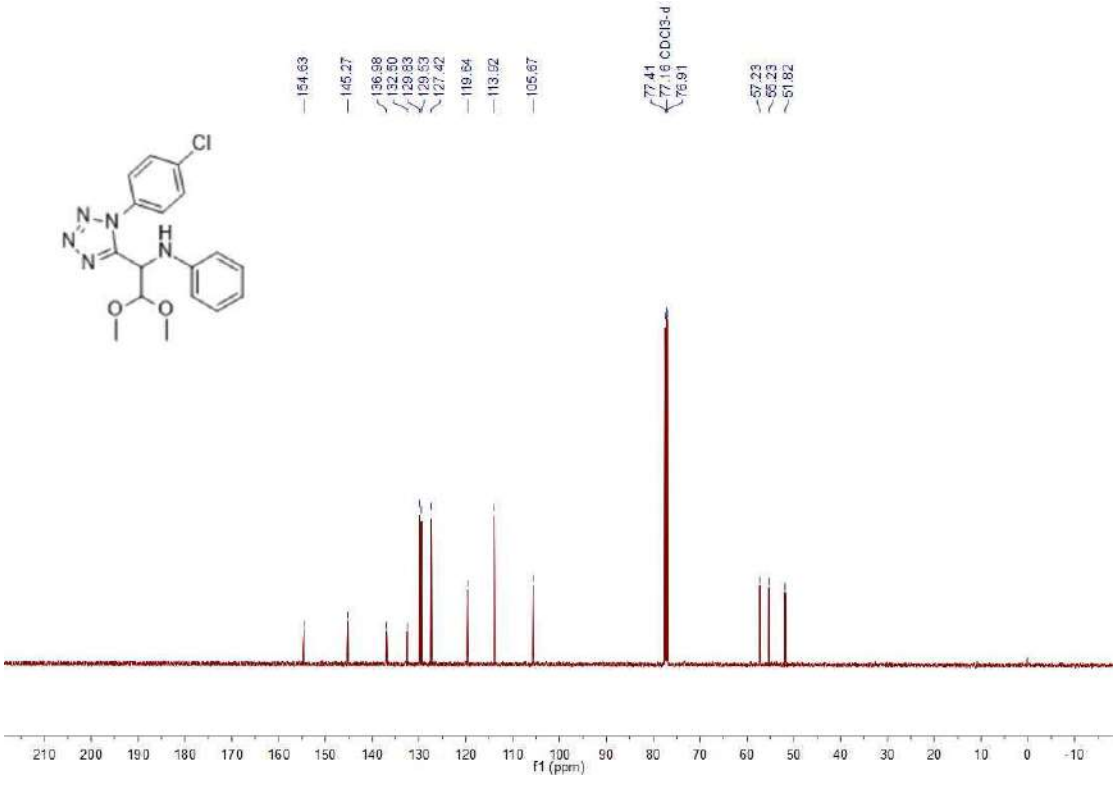
2.05
1.05
1.02
1.02
8.07
f1 (ppm)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145.27
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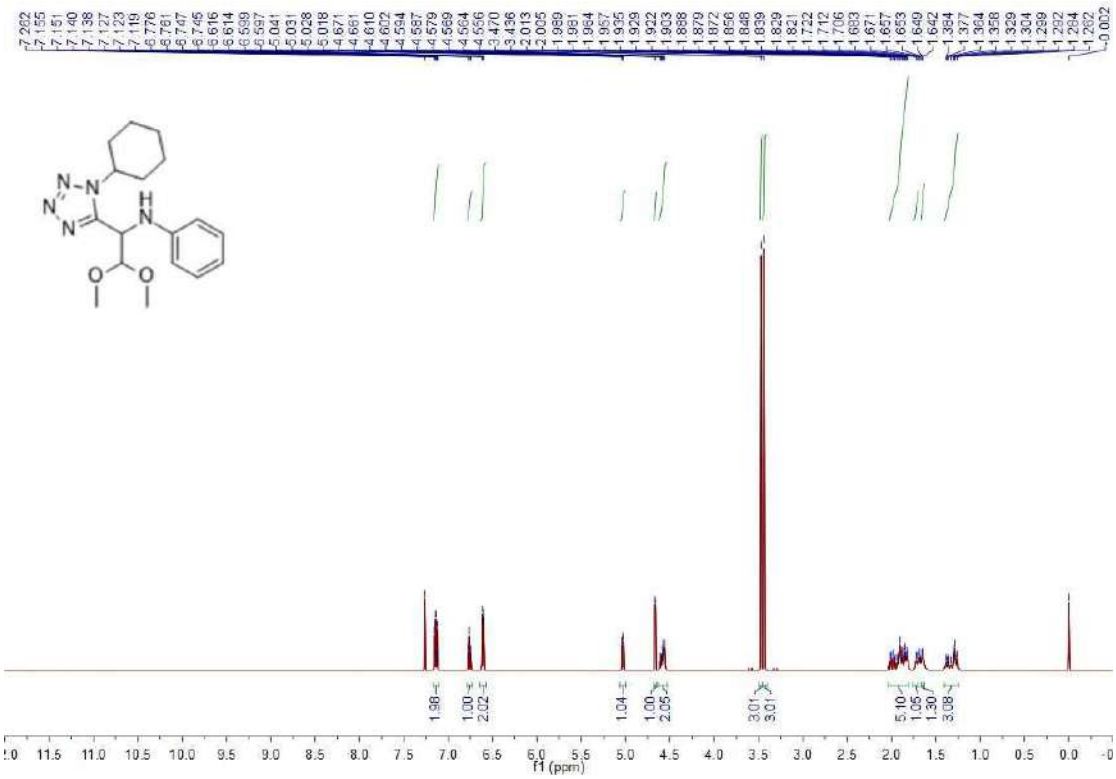
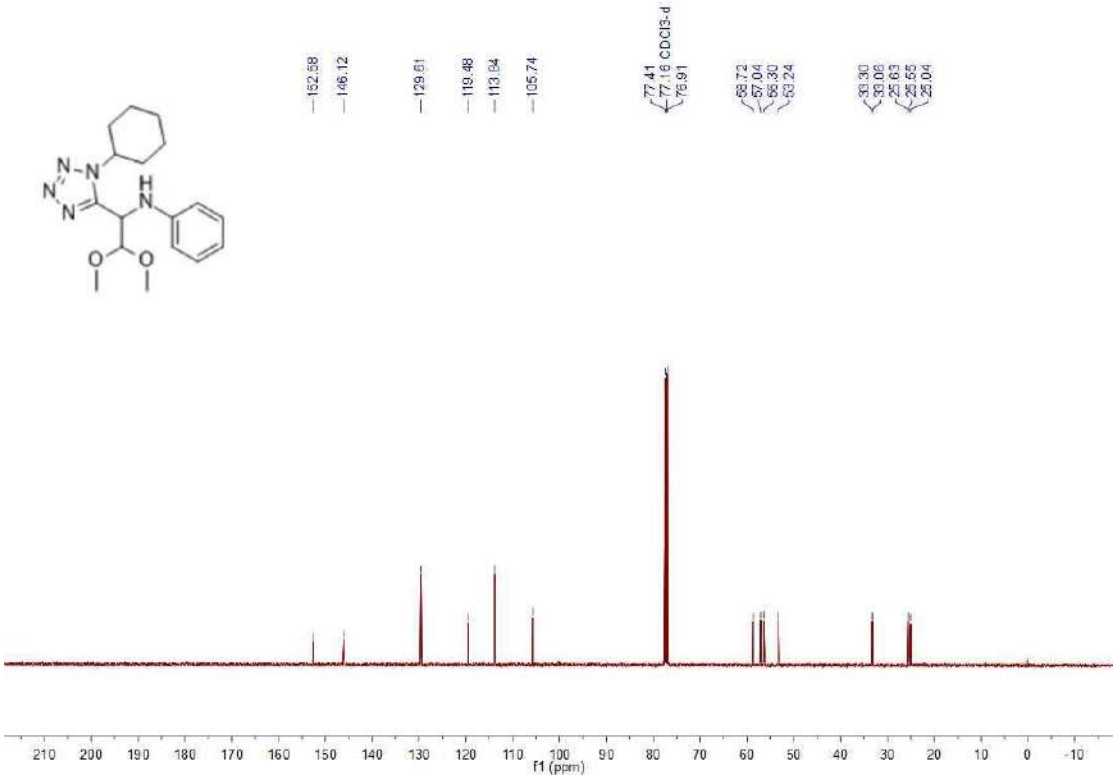
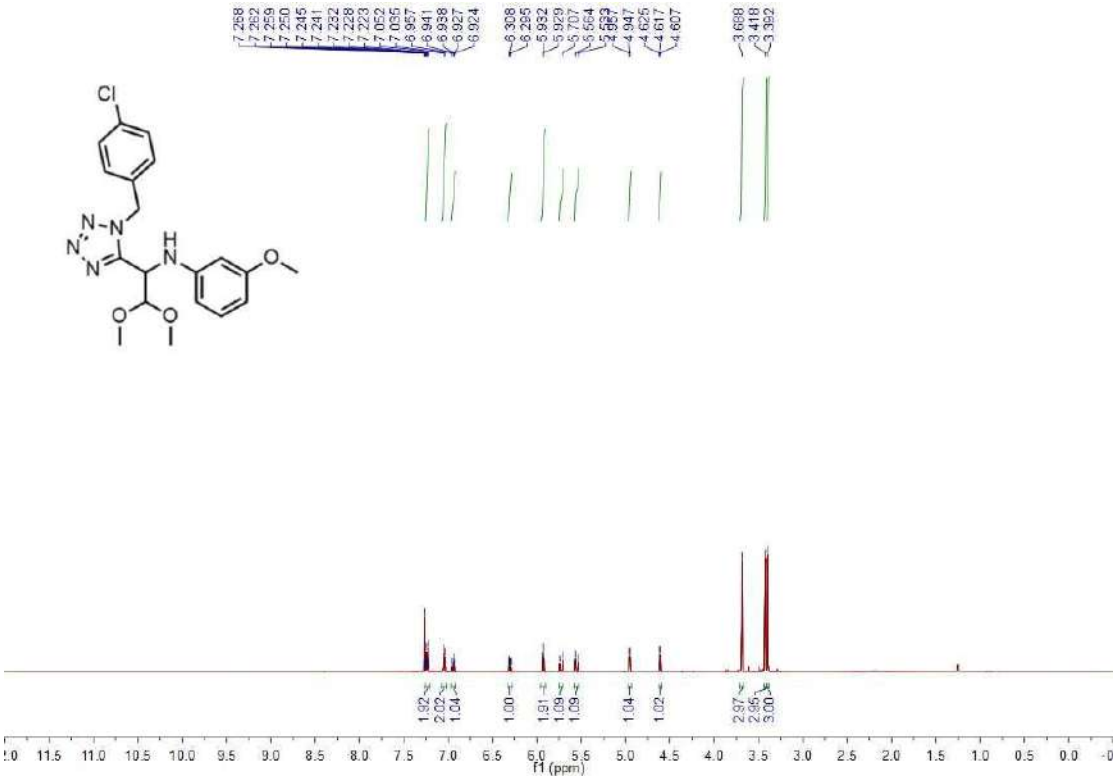
132.50
129.88
129.53
127.42
119.64
113.62
105.67
77.41
77.16
CDCl3-d
76.91
57.23
56.23
51.82
Cl
N
N
N
H
N
O
O
f1 (ppm)



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7.241
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7.228
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7.052
7.055
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6.941
6.938
6.927
6.924
6.308
6.295
5.932
5.929
5.707
5.564
4.947
4.625
4.617
4.607
3.668
3.418
3.392
Cl
N
N
N
H
O
O
O
1.92
2.02
1.04
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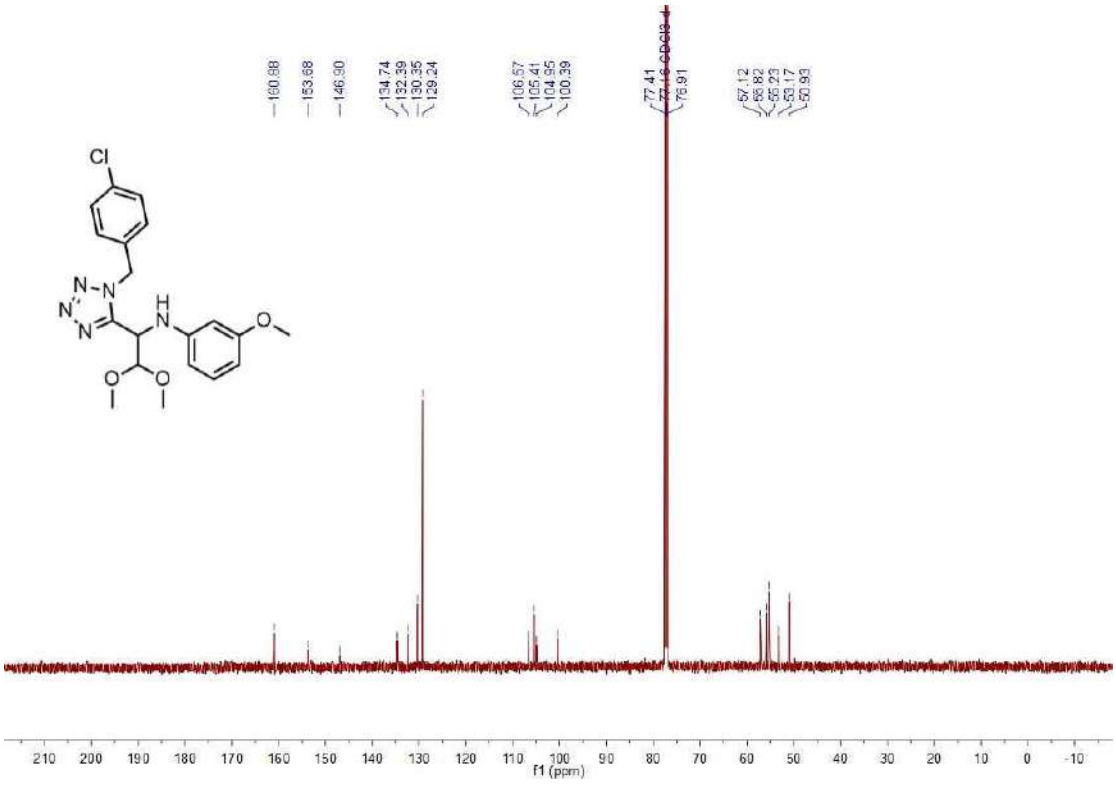
1.91
1.09
1.09
1.04
1.02
2.97
2.95
3.00
f1 (ppm)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130.35
129.24
106.57
105.41
104.95
100.39
77.41
75.91
57.12
56.82
55.23
53.17
50.93
Cl
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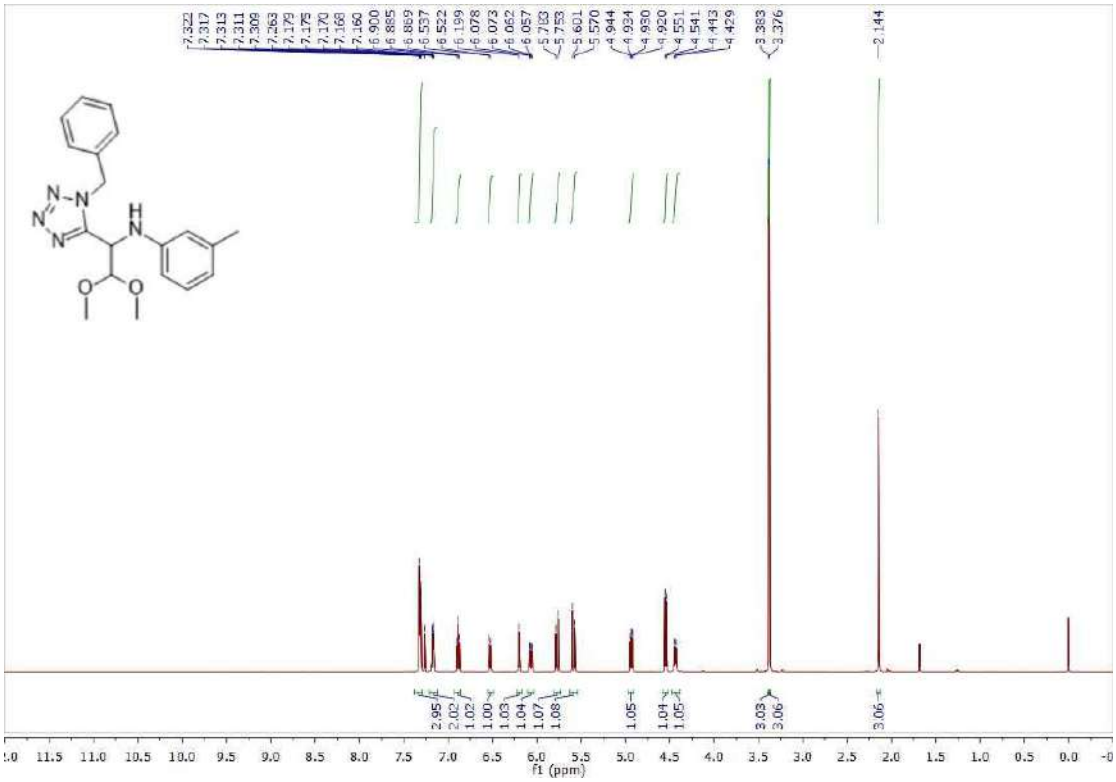
N
N
H
O
O
O
f1 (ppm)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6.885
6.859
6.537
6.522
6.199
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6.073
6.062
6.057
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5.753
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5.570
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4.934
4.930
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4.551
4.541
4.443
4.429
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3.376
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2.95
2.02
1.02
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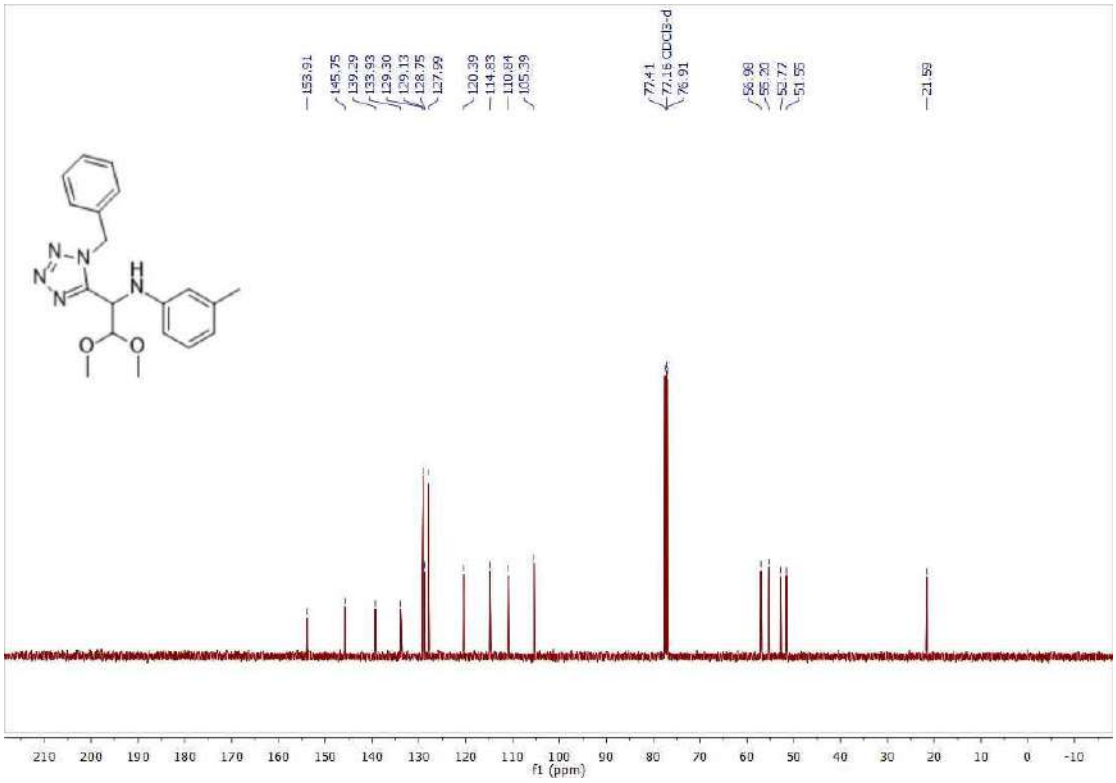
3.03
3.06
3.06
f1 (ppm)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127.99
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114.83
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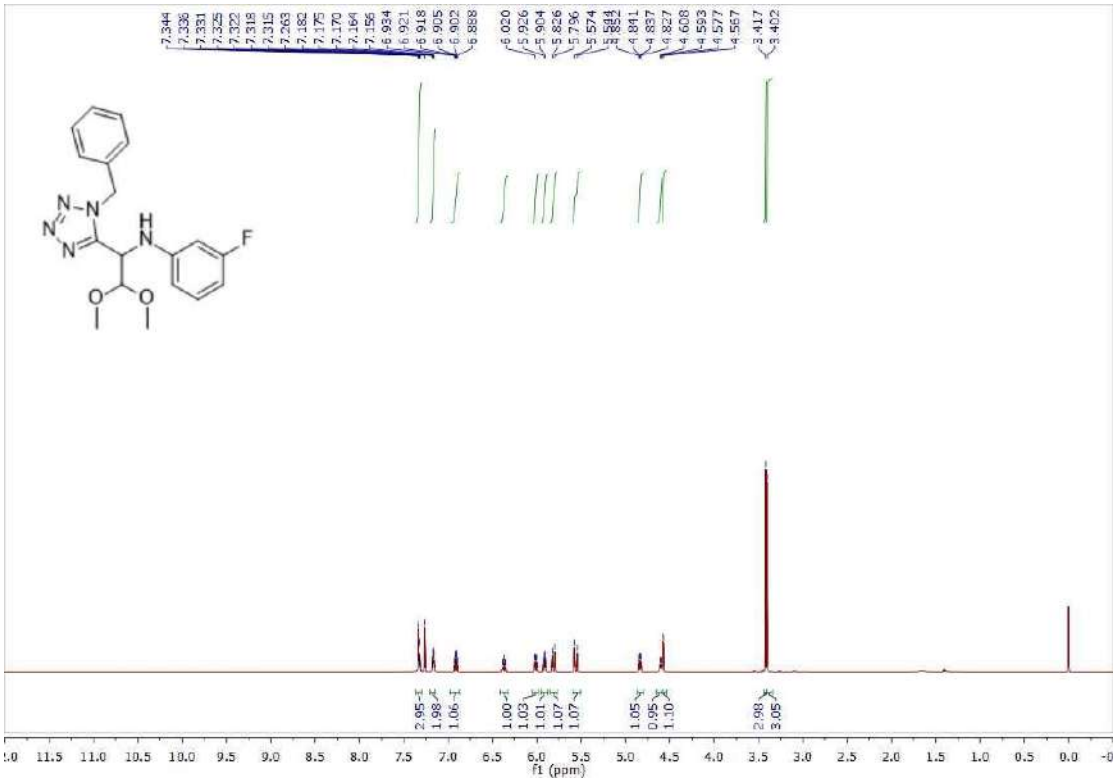
105.39
77.41
77.16 CDCl3-d
76.91
56.98
56.20
52.77
51.55
21.59
f1 (ppm)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7.156
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6.921
6.918
6.905
6.902
6.888
6.020
5.926
5.904
5.826
5.796
5.574
4.841
4.837
4.827
4.608
4.593
4.577
4.557
3.417
3.402
F
H
N
O
O
2.95
1.98
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1.01
1.07
1.07
1.05
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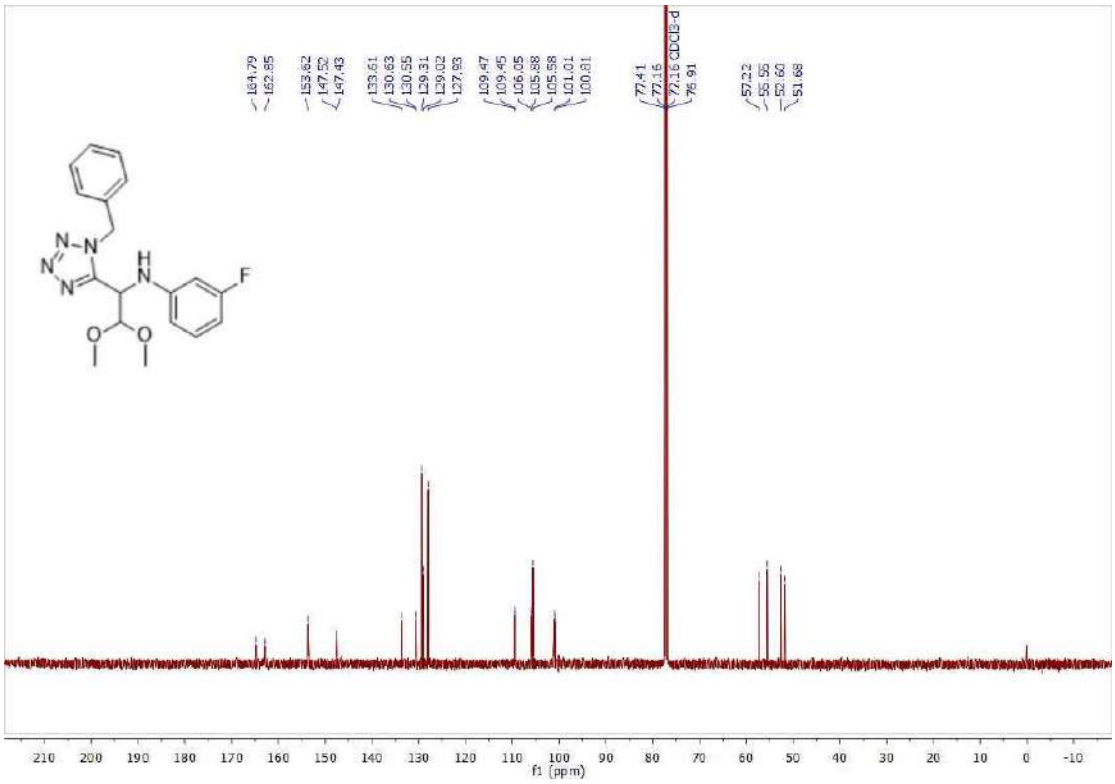
1.10
2.98
3.05
f1 (ppm)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129.02
127.93
109.47
109.45
106.05
105.88
105.58
101.01
100.81
77.41
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77.16 CDCl3-d
76.91
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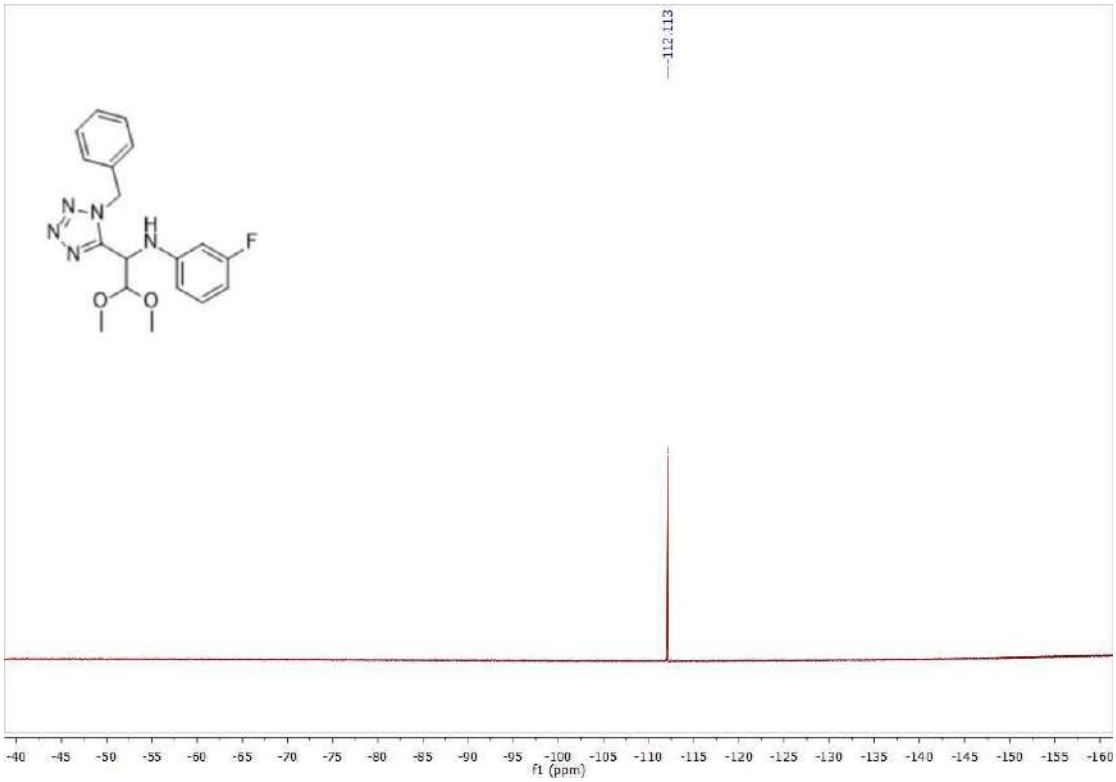
F
H
N
O
O
f1 (ppm)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N
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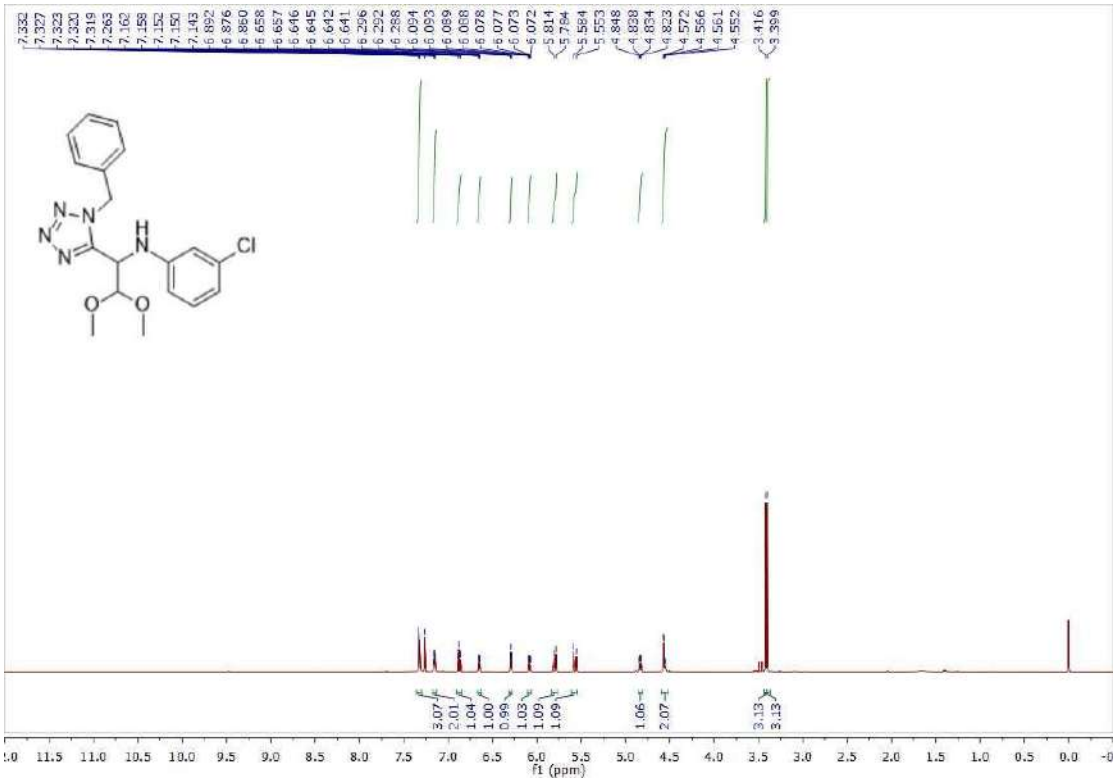
N
F
O
O
-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160
f1 (ppm)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6.068
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6.077
6.073
6.072
5.814
5.784
5.584
5.553
4.848
4.838
4.834
4.823
4.572
4.566
4.561
4.552
3.416
3.399
N
N
N
H
N
Cl
O
O
3.07
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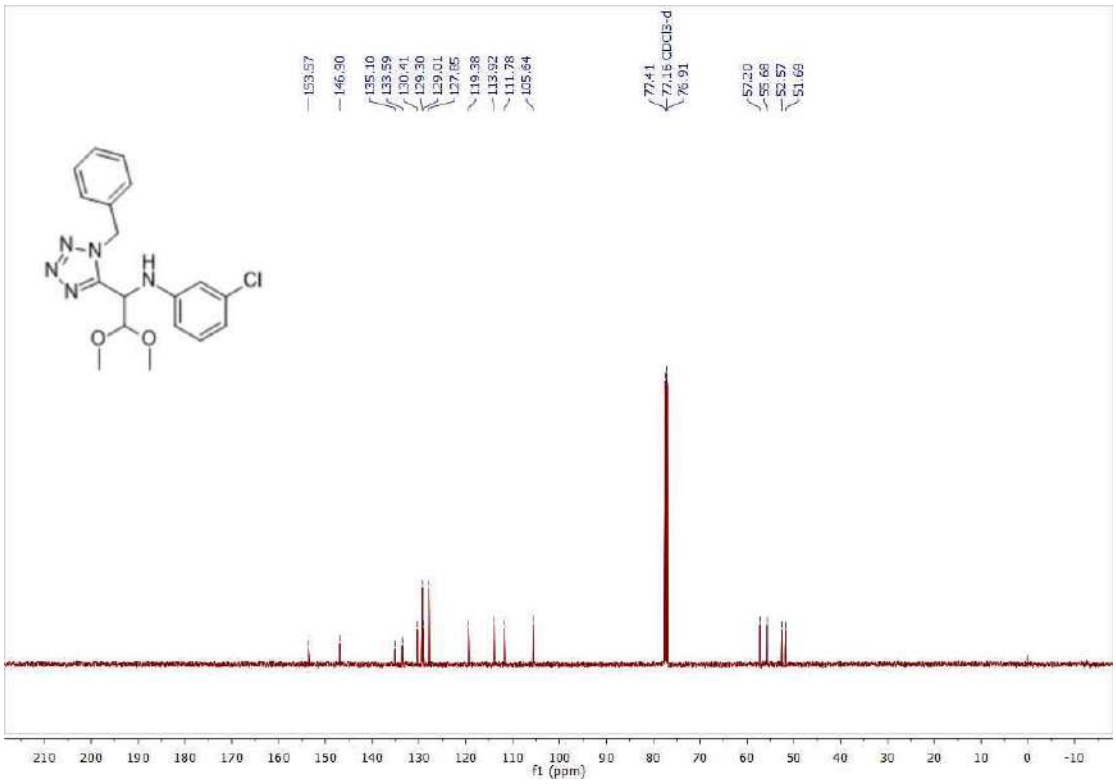
0.99
1.03
1.09
1.09
1.06
2.07
3.13
3.13
f1 (ppm)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146.90
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133.59
130.41
129.30
129.01
127.85
119.38
113.92
111.78
105.64
77.41
77.16 CDCl3-d
76.91
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55.68
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51.69
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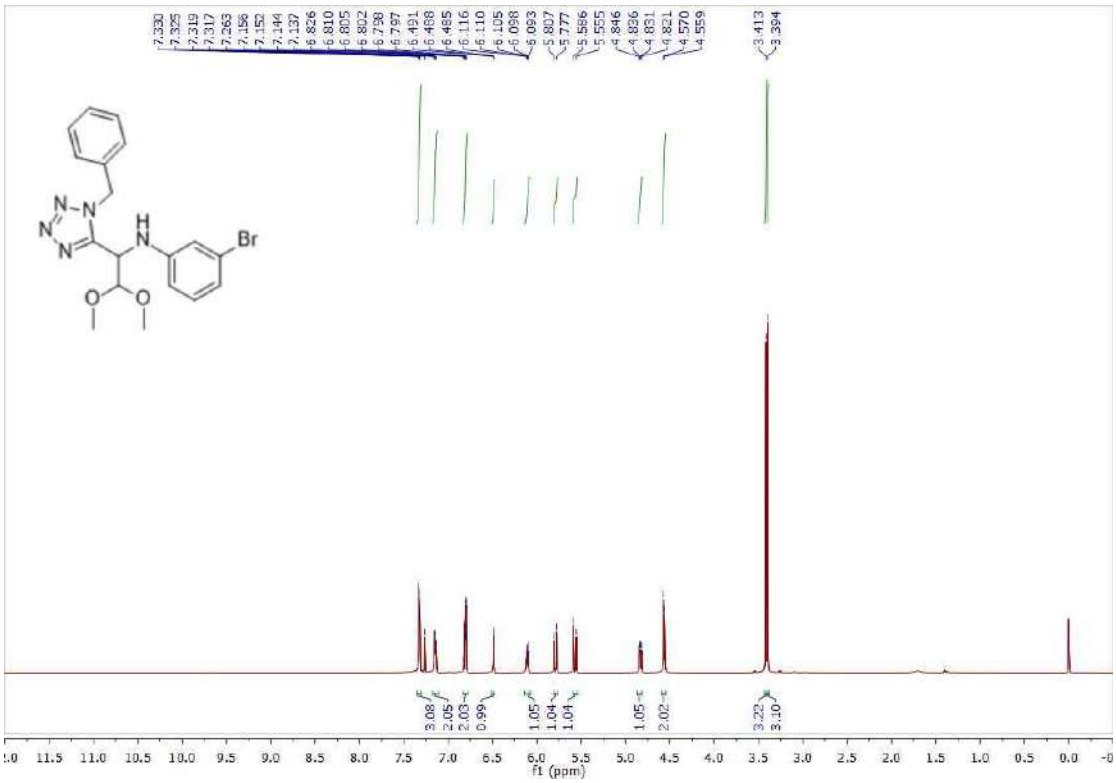
N
N
H
N
Cl
O
O
f1 (ppm)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6.802
6.798
6.797
6.491
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6.485
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6.093
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5.777
5.586
5.555
4.846
4.836
4.831
4.821
4.570
4.559
3.413
3.394
Br
3.08
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2.03
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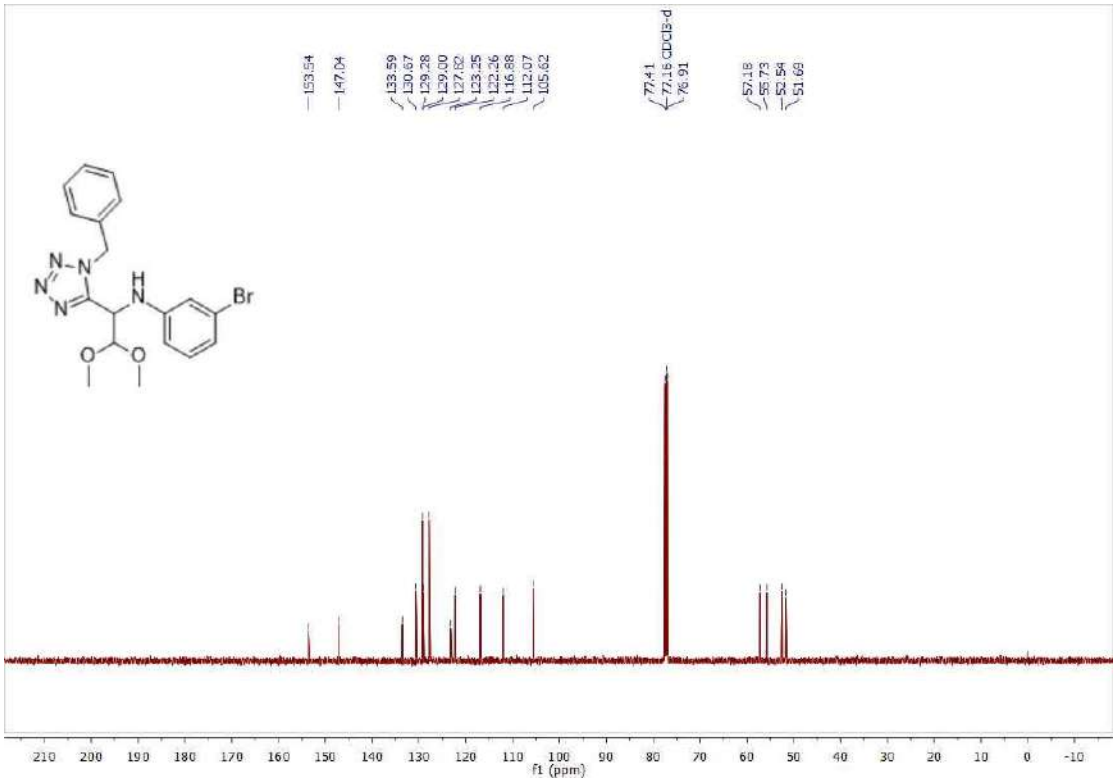
1.05
1.04
1.04
1.05
2.02
3.22
3.10
f1 (ppm)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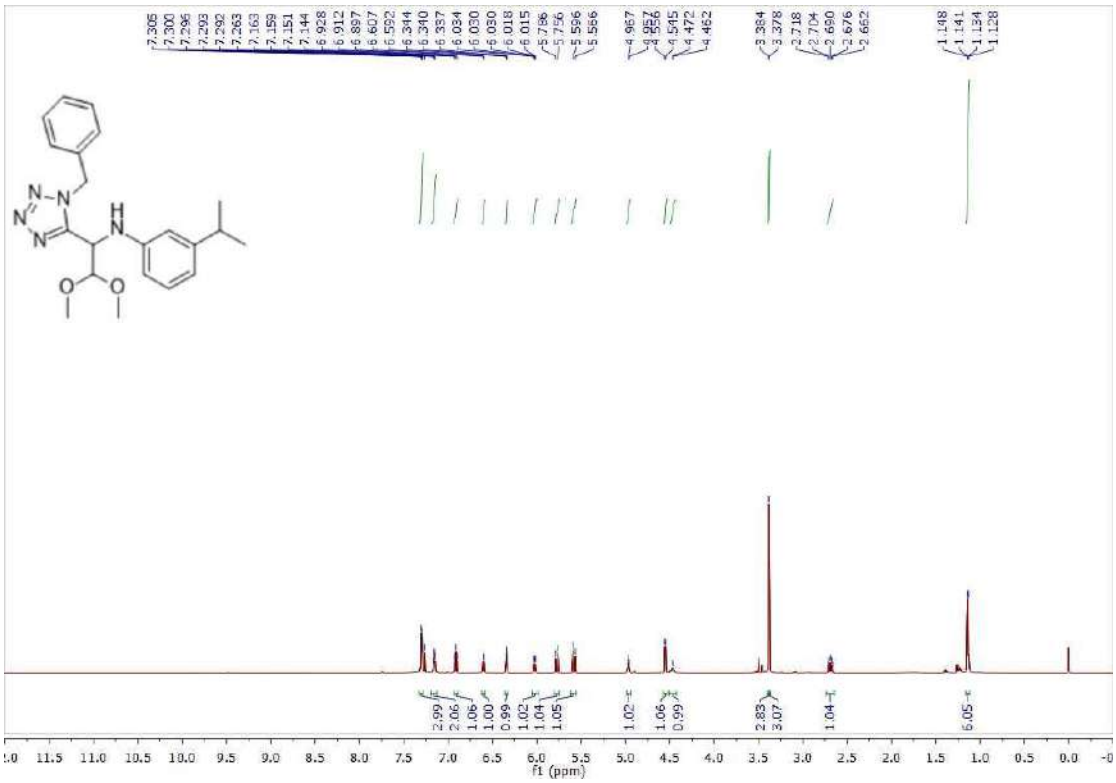
129.28
129.00
127.82
123.35
122.26
116.88
112.07
105.62
77.41
77.16 CDCl3-d
76.91
57.18
56.73
52.54
51.69
Br
f1 (ppm)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7.296
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7.163
7.159
7.151
7.144
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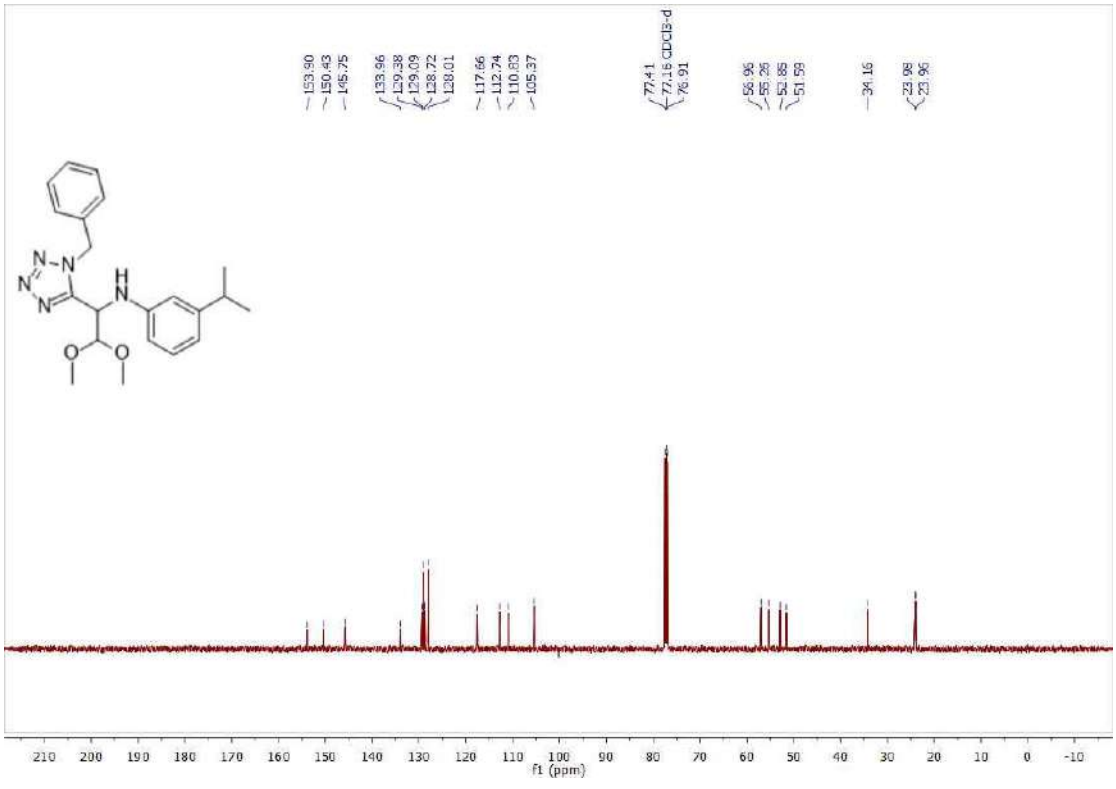
6.912
6.897
6.607
6.592
6.344
6.340
6.337
6.034
6.030
6.030
6.018
6.015
5.786
5.756
5.596
5.566
4.967
4.957
4.956
4.545
4.472
4.462
3.384
3.378
2.718
2.704
2.690
2.676
2.662
1.148
1.141
1.134
1.128
2.99
2.06
1.06
1.00
0.99
1.02
1.04
1.05
1.02
1.06
0.99
2.83
3.07
1.04
6.05
f1 (ppm)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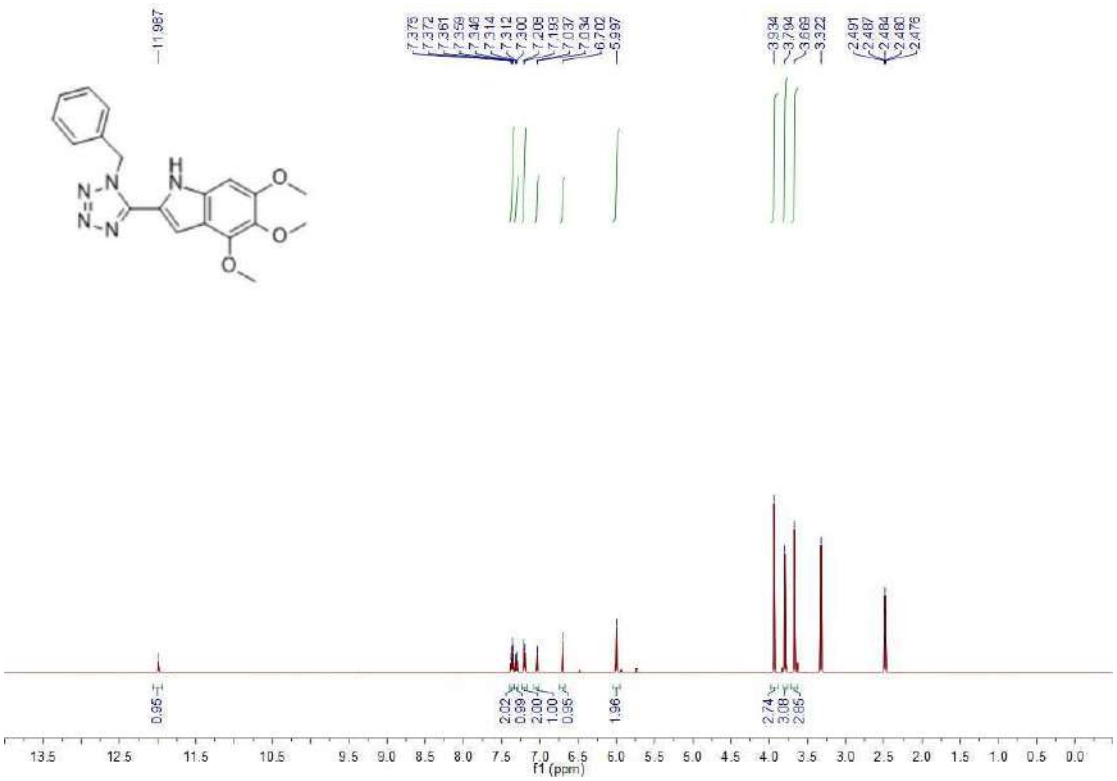
146.75
133.96
129.38
129.09
128.72
128.01
117.66
112.74
110.83
105.37
77.41
77.16 CDCl3-d
76.91
56.96
55.26
52.85
51.59
34.16
23.99
23.96
f1 (ppm)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7.346
7.314
7.312
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7.209
7.193
7.037
7.034
6.702
5.997
3.934
3.794
3.668
3.322
2.491
2.487
2.484
2.480
2.476
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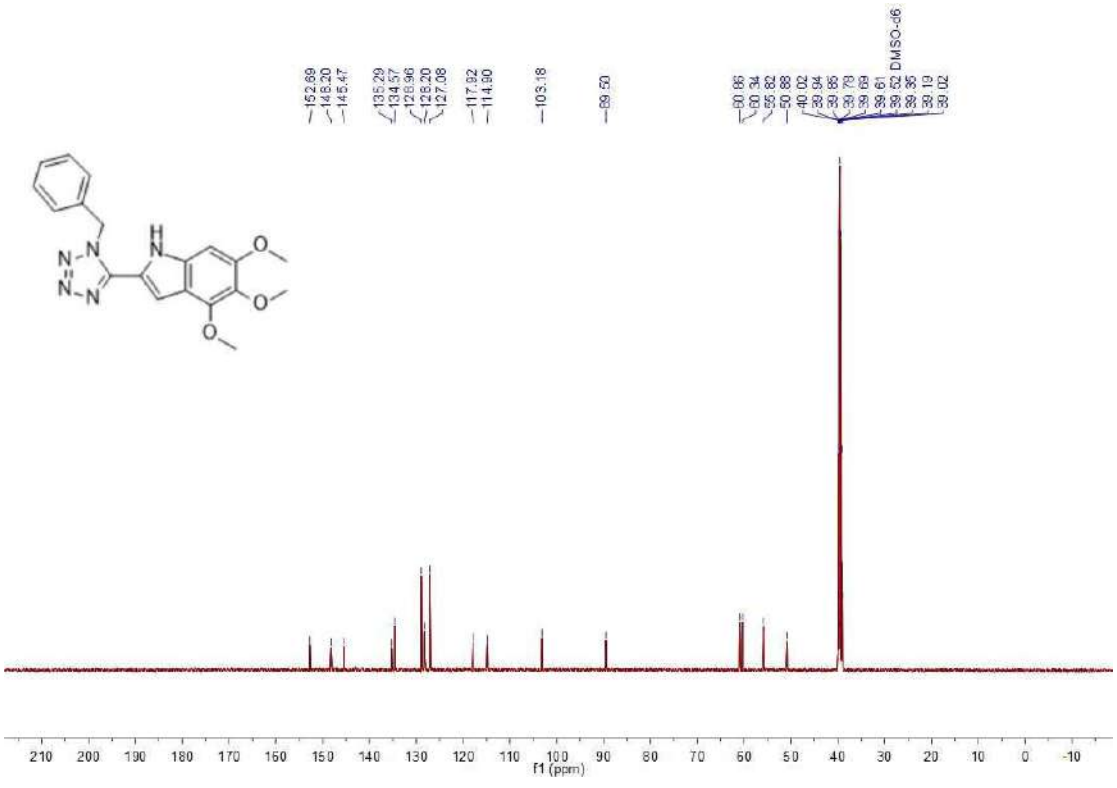
0.99
2.00
1.00
0.95
1.96
2.74
3.08
2.65
f1 (ppm)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127.08
117.92
114.90
103.18
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60.86
60.34
55.82
50.88
40.02
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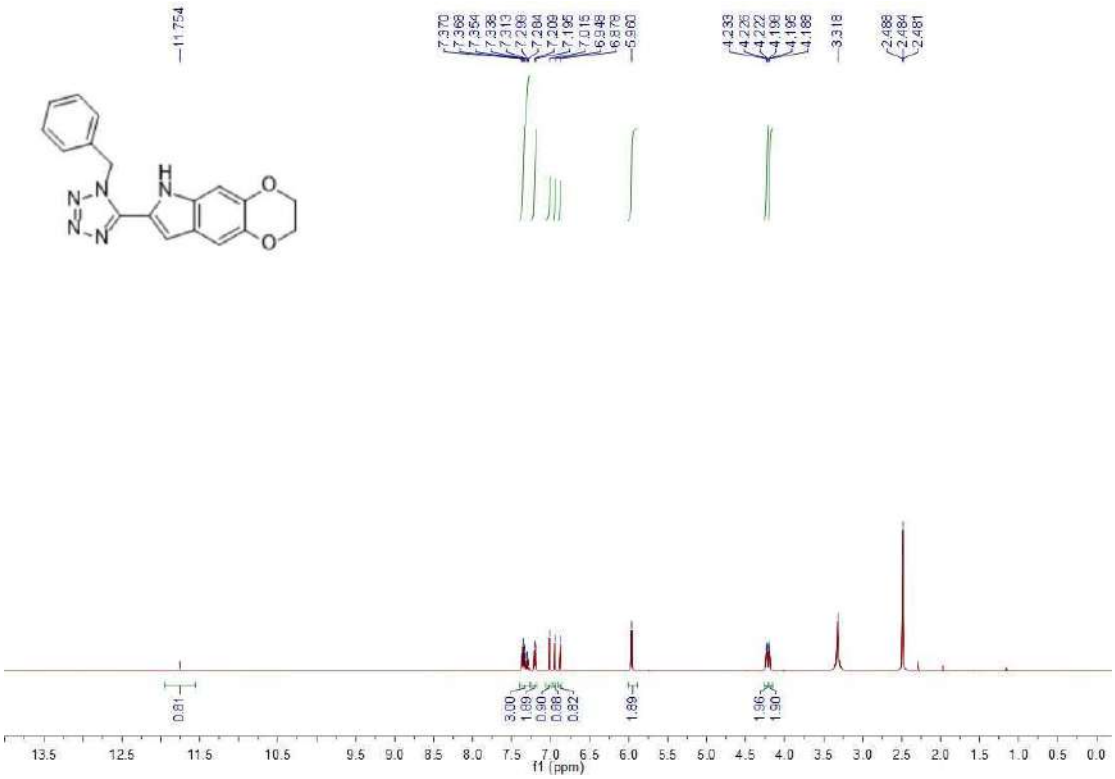
39.78
39.69
39.61
39.52
DMSO-d6
39.35
39.19
39.02
f1 (ppm)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7.209
7.196
7.015
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5.960
4.233
4.225
4.222
4.196
4.195
4.188
3.318
2.488
2.484
2.481
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3.00
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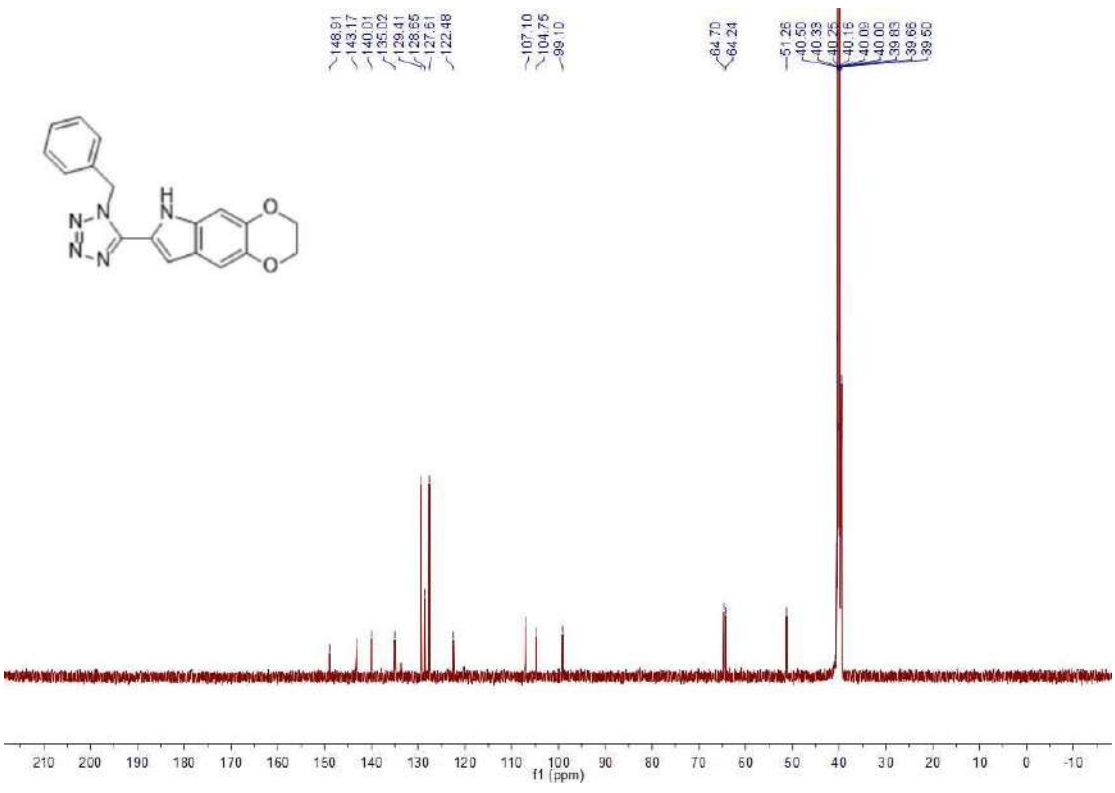
0.90
0.88
0.82
1.89
1.96
1.90
f1 (ppm)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143.17
140.01
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128.65
127.61
122.48
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104.75
99.10
64.70
64.24
51.26
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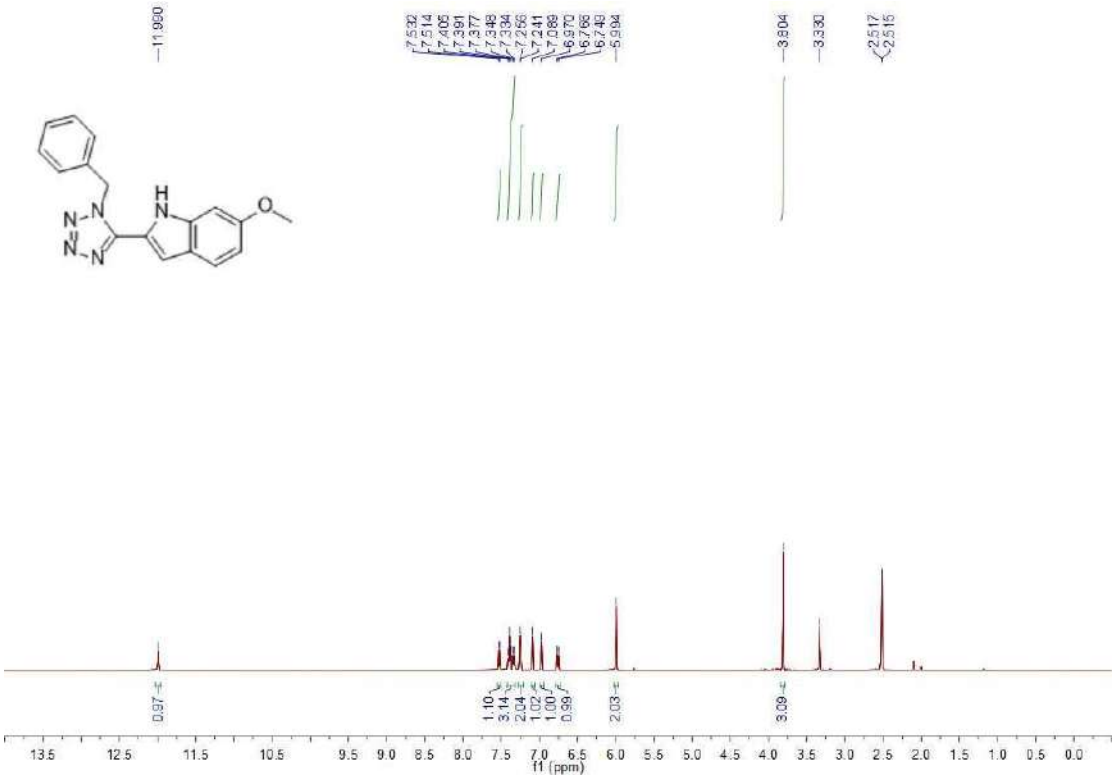
40.33
40.25
40.15
40.09
40.00
39.83
39.66
39.50
f1 (ppm)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7.514
7.405
7.391
7.377
7.348
7.334
7.255
7.241
7.088
6.970
6.766
6.749
5.994
3.804
3.330
2.517
2.515
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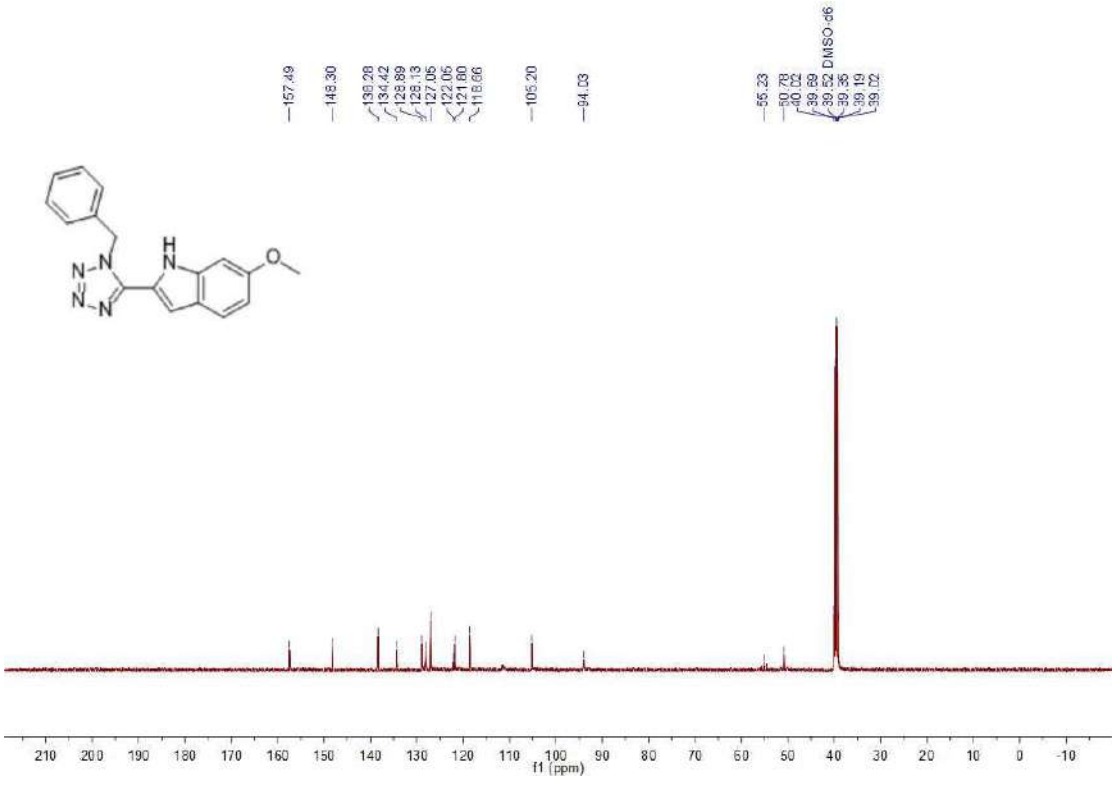
1.10
3.14
2.04
1.02
1.00
0.99
2.03
3.09
f1 (ppm)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128.89
128.13
127.05
122.05
121.80
118.66
105.20
94.03
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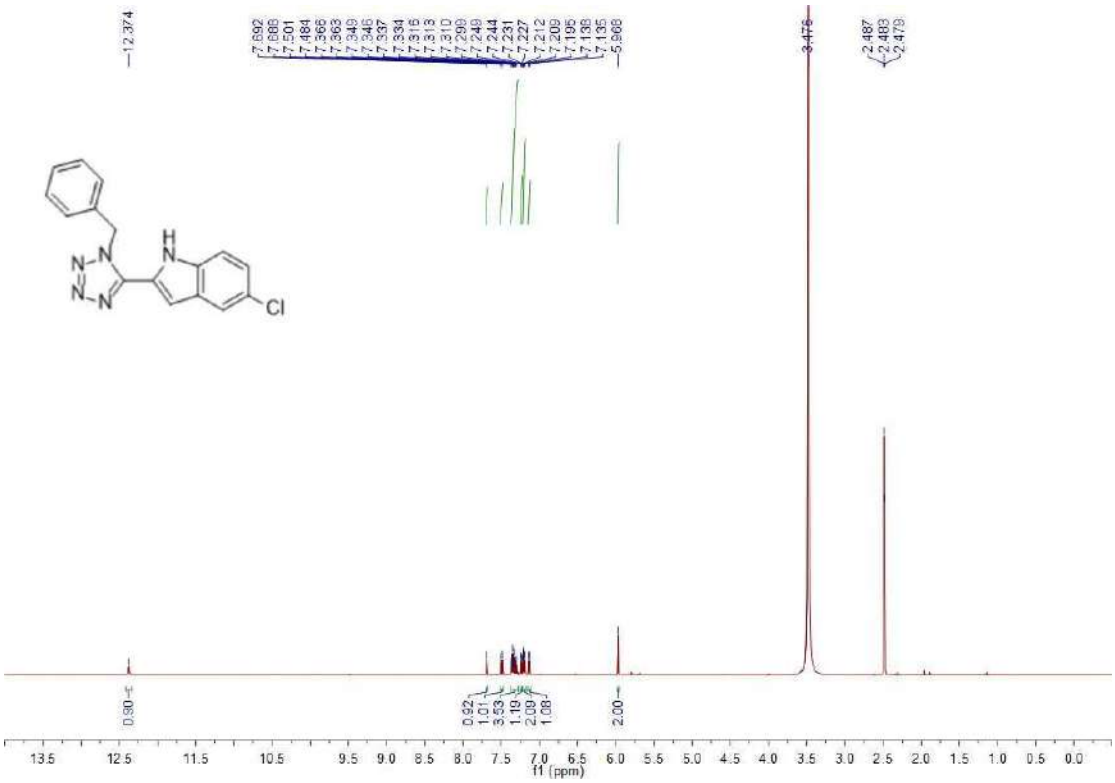
DMSO-d6
39.35
39.19
39.02
f1 (ppm)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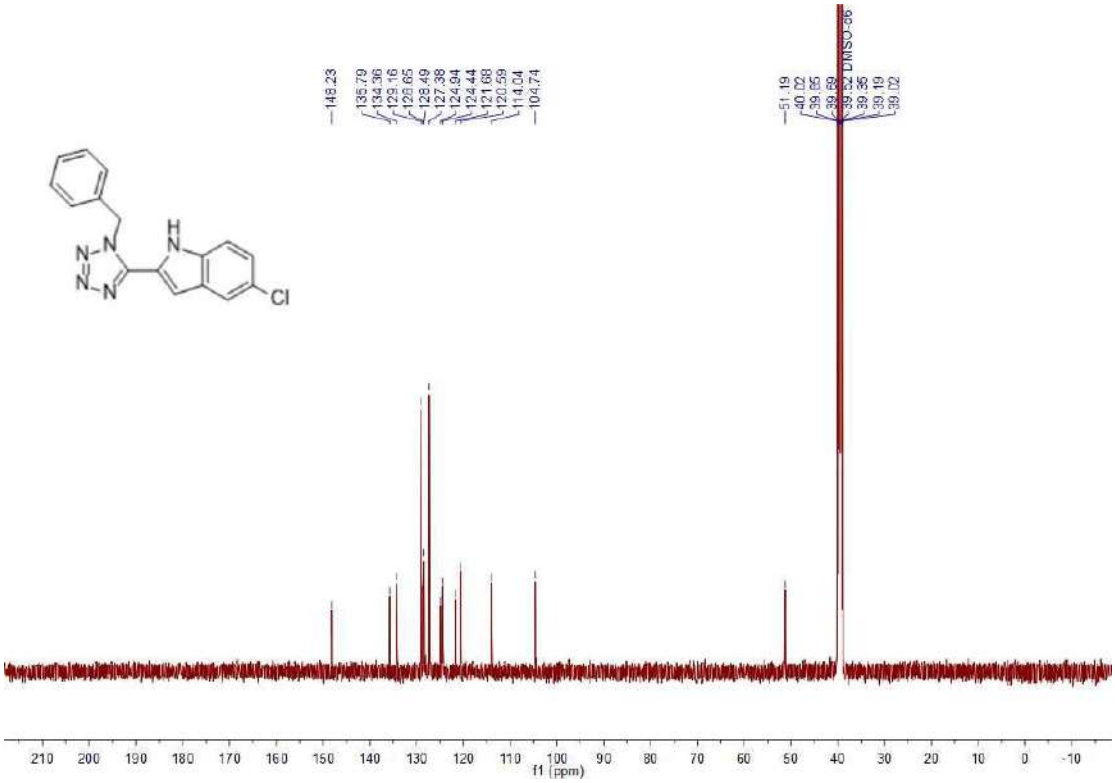
7.363
7.348
7.345
7.337
7.334
7.316
7.313
7.310
7.290
7.249
7.244
7.231
7.227
7.212
7.209
7.195
7.138
7.135
5.908
3.476
2.487
2.483
2.479
Cl
0.90
0.92
1.01
3.53
1.19
2.09
1.08
2.00
f1 (ppm)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135.79
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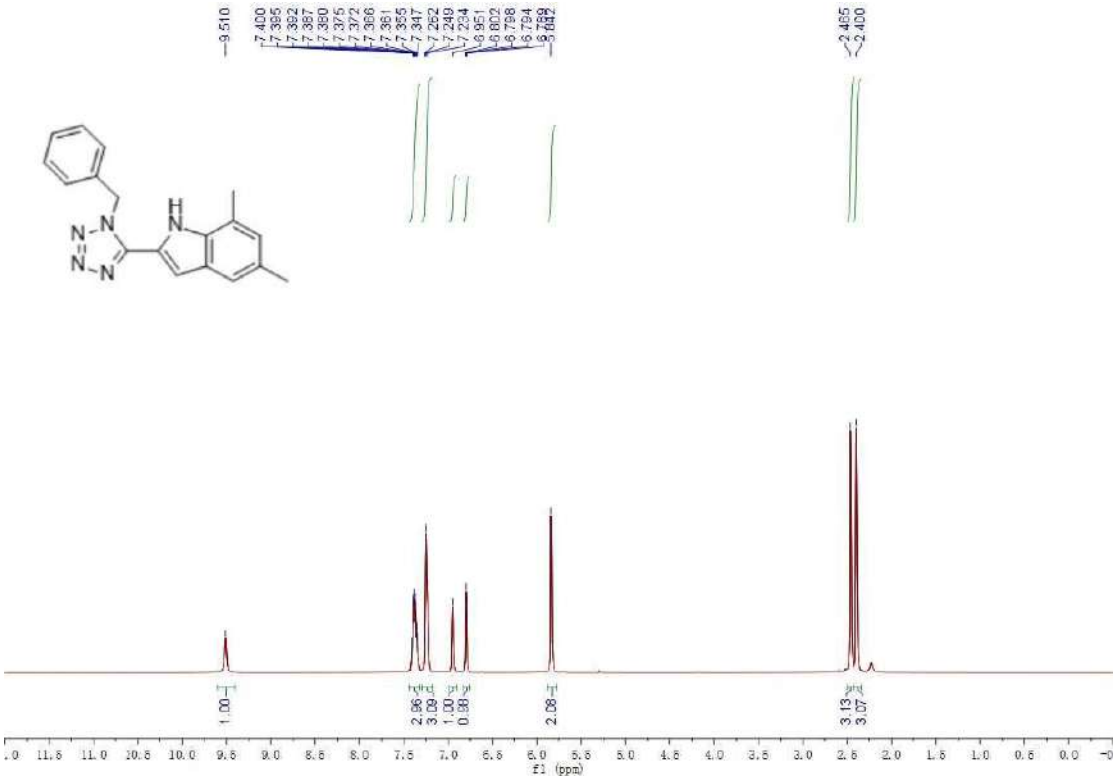
129.16
128.65
128.49
127.38
124.94
124.44
121.68
120.59
114.04
104.74
51.19
40.02
39.85
39.69
39.52 DMSO-d6
39.36
39.19
39.02
Cl
f1 (ppm)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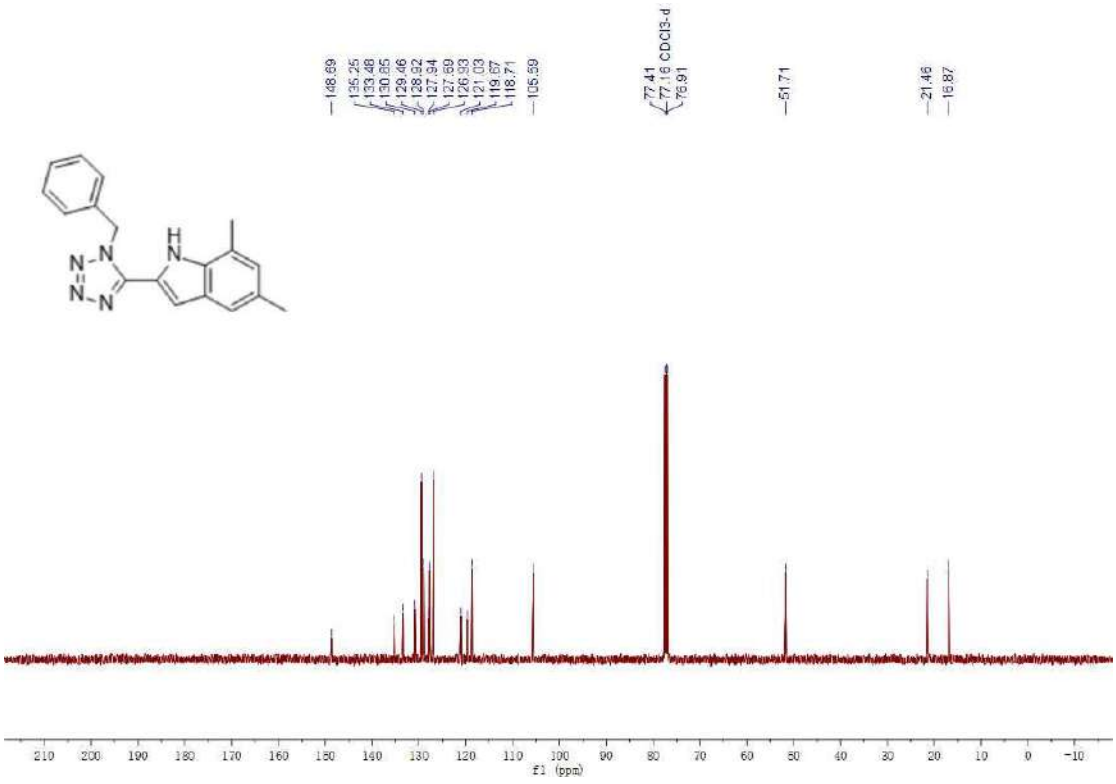
7.382
7.367
7.360
7.375
7.372
7.366
7.361
7.355
7.347
7.262
7.249
7.234
6.951
6.802
6.798
6.794
6.759
6.642
2.485
2.400
1.00
2.96
3.09
1.00
0.98
2.08
3.13
3.07
f1 (ppm)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130.85
129.46
128.92
127.94
127.69
126.93
121.03
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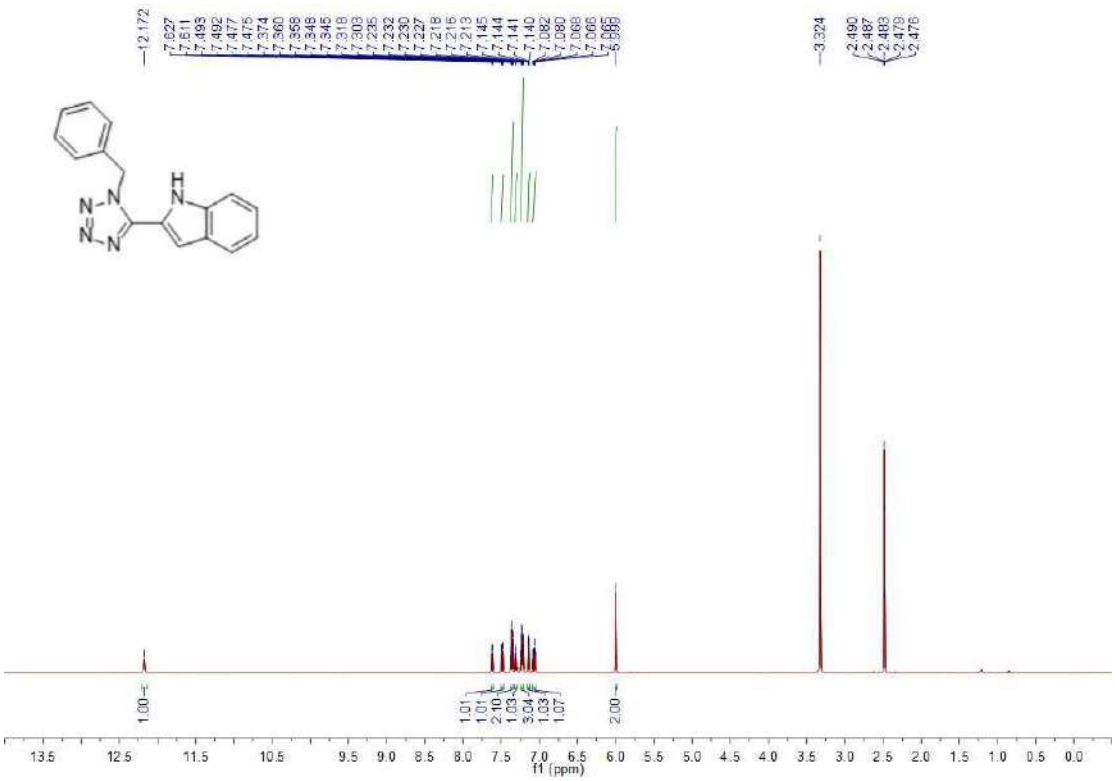
105.59
77.41
77.16
75.91
CDCl3-d
51.71
21.46
15.87
f1 (ppm)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7.611
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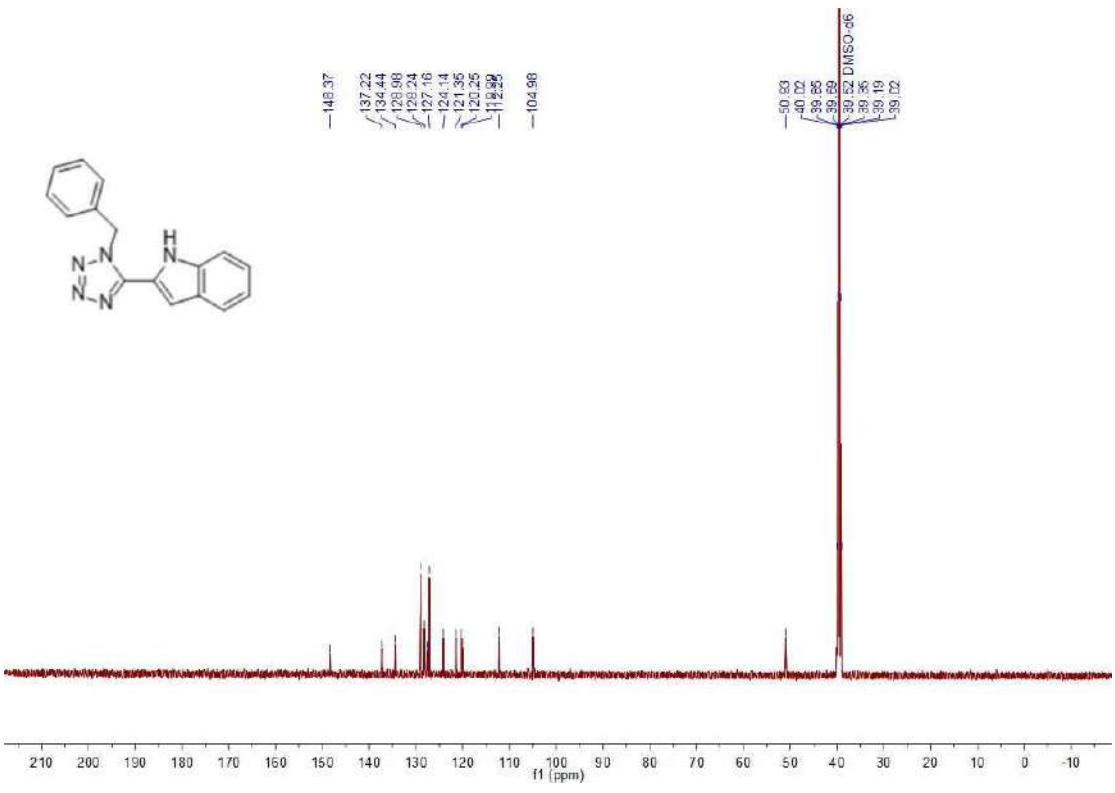
7.492
7.477
7.475
7.374
7.360
7.358
7.348
7.345
7.318
7.303
7.235
7.232
7.230
7.227
7.218
7.216
7.213
7.145
7.144
7.141
7.140
7.082
7.080
7.068
7.066
5.985
3.324
2.490
2.487
2.483
2.479
2.476
1.00
1.01
1.01
2.10
1.03
3.04
1.03
1.07
2.00
f1 (ppm)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137.22
134.44
128.98
128.24
127.16
124.14
121.35
120.25
104.98
50.93
40.02
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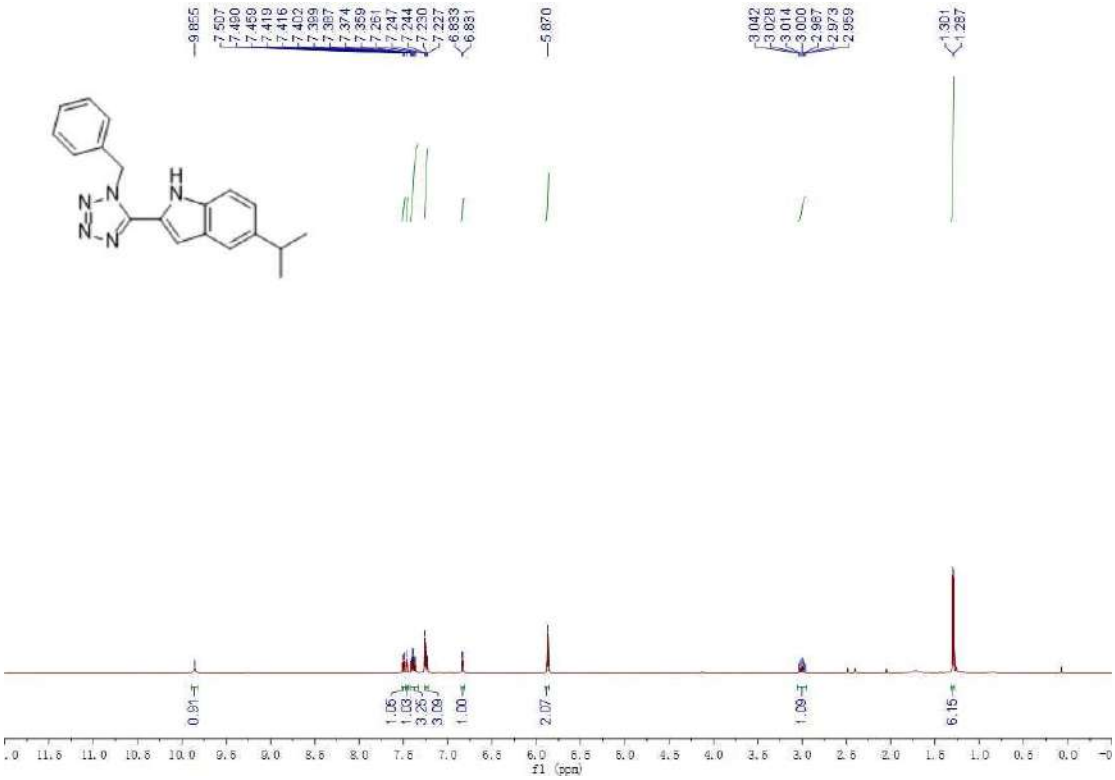
39.35
39.19
39.02
f1 (ppm)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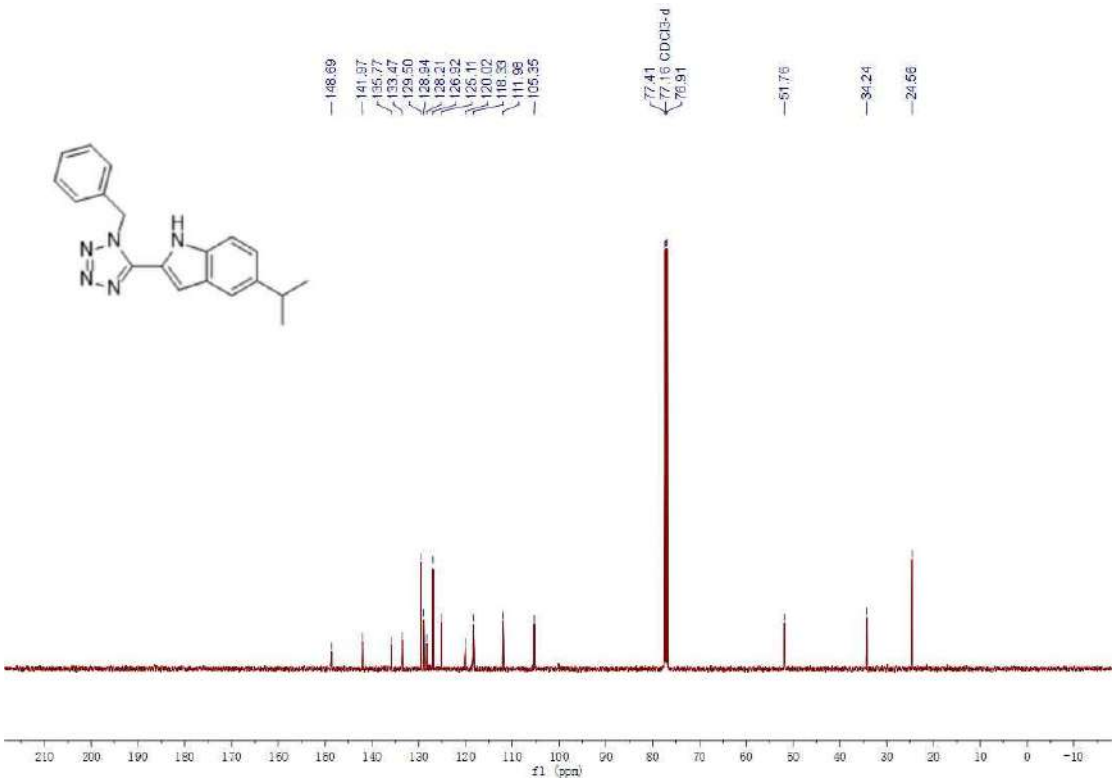
7.402
7.399
7.387
7.374
7.359
7.261
7.247
7.244
7.230
7.227
6.833
6.831
5.870
3.042
3.028
3.014
3.000
2.987
2.973
2.959
1.301
1.287
0.91
1.05
1.03
3.26
3.09
1.00
2.07
1.09
6.15
f1 (ppm)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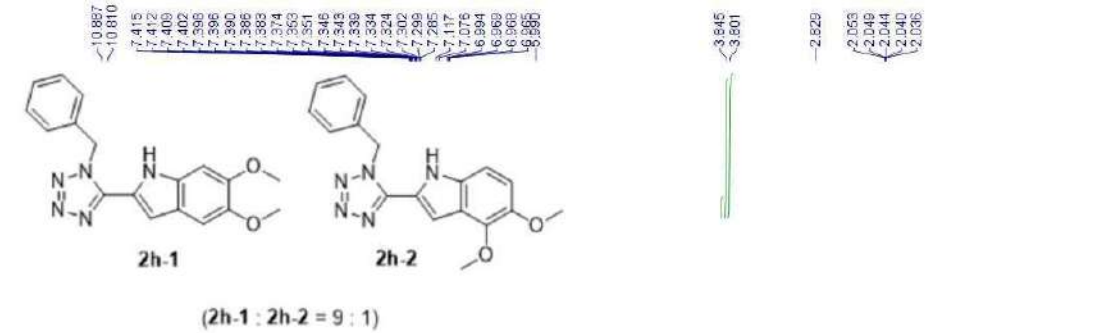
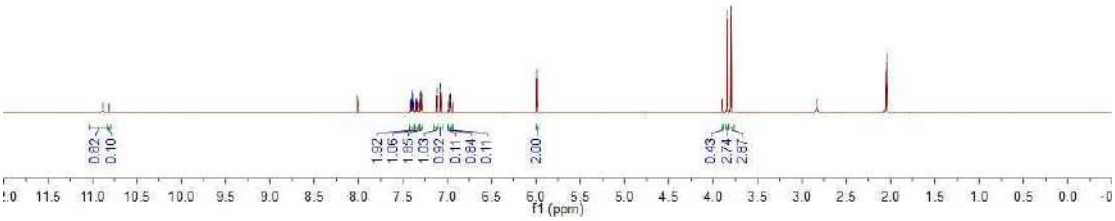
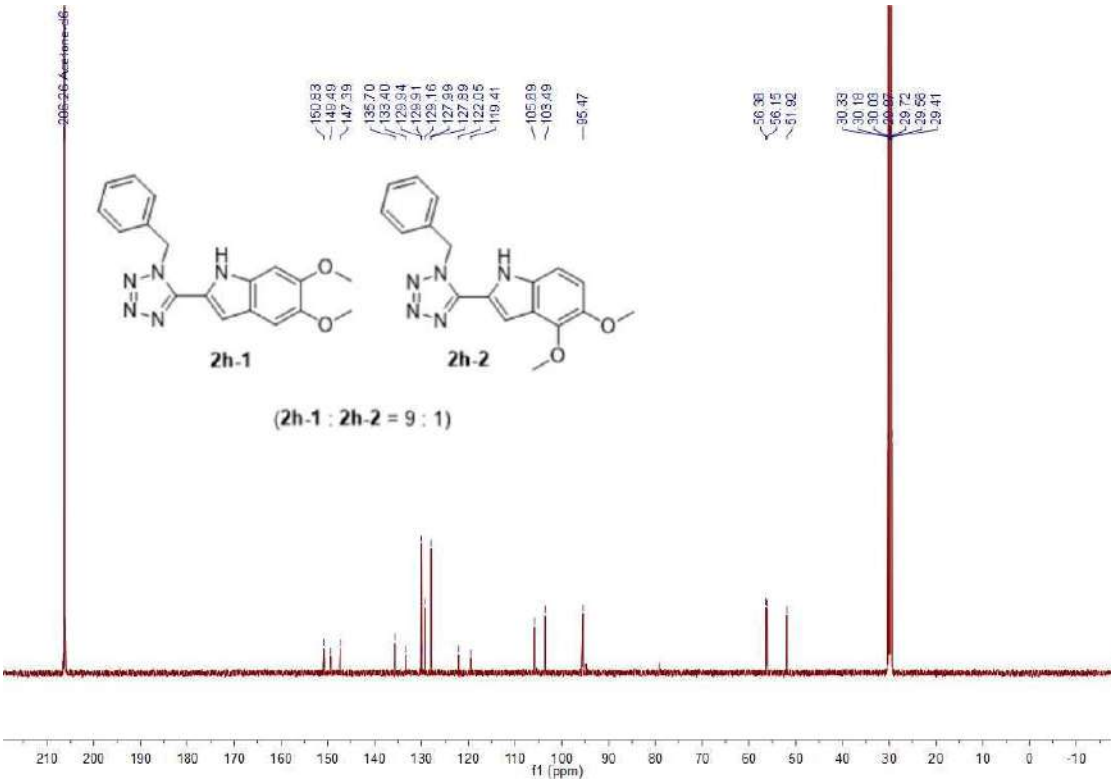
128.94
128.21
126.92
125.11
120.02
118.39
111.98
105.35
77.41
77.16
CDCl3-d
76.91
51.76
34.24
24.56
f1 (ppm)

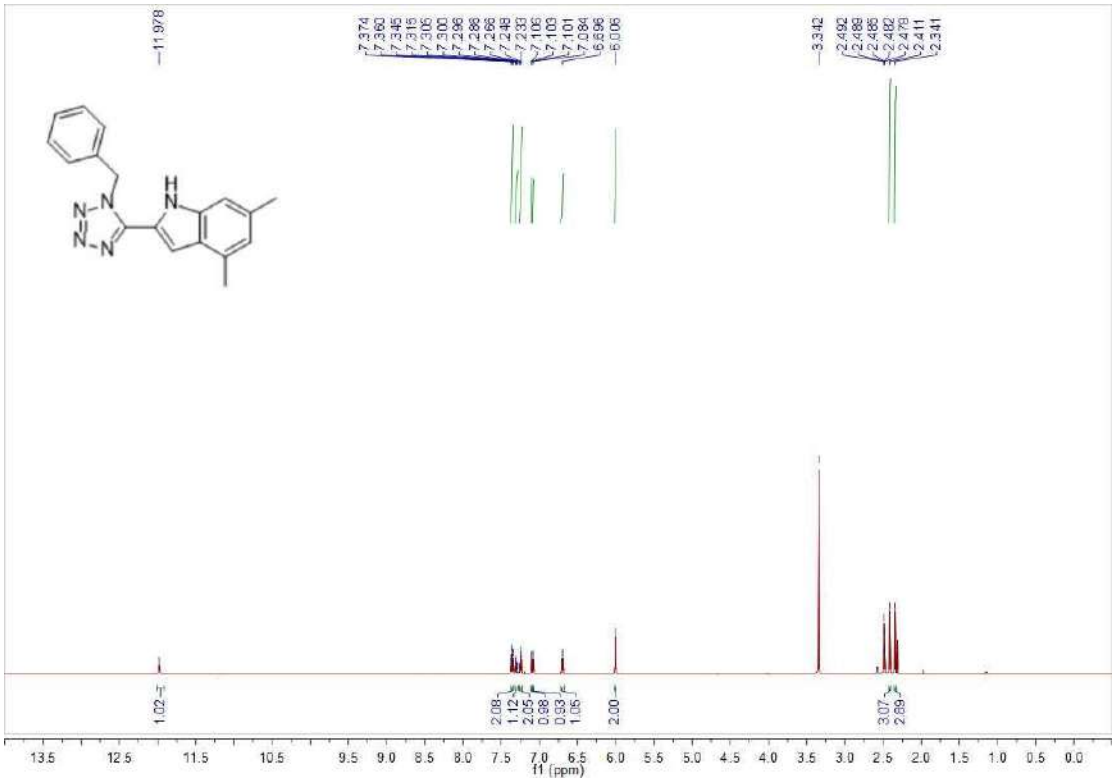


(**2h-1** : **2h-2** = 9 : 1)





(**2h-1** : **2h-2** = 9 : 1)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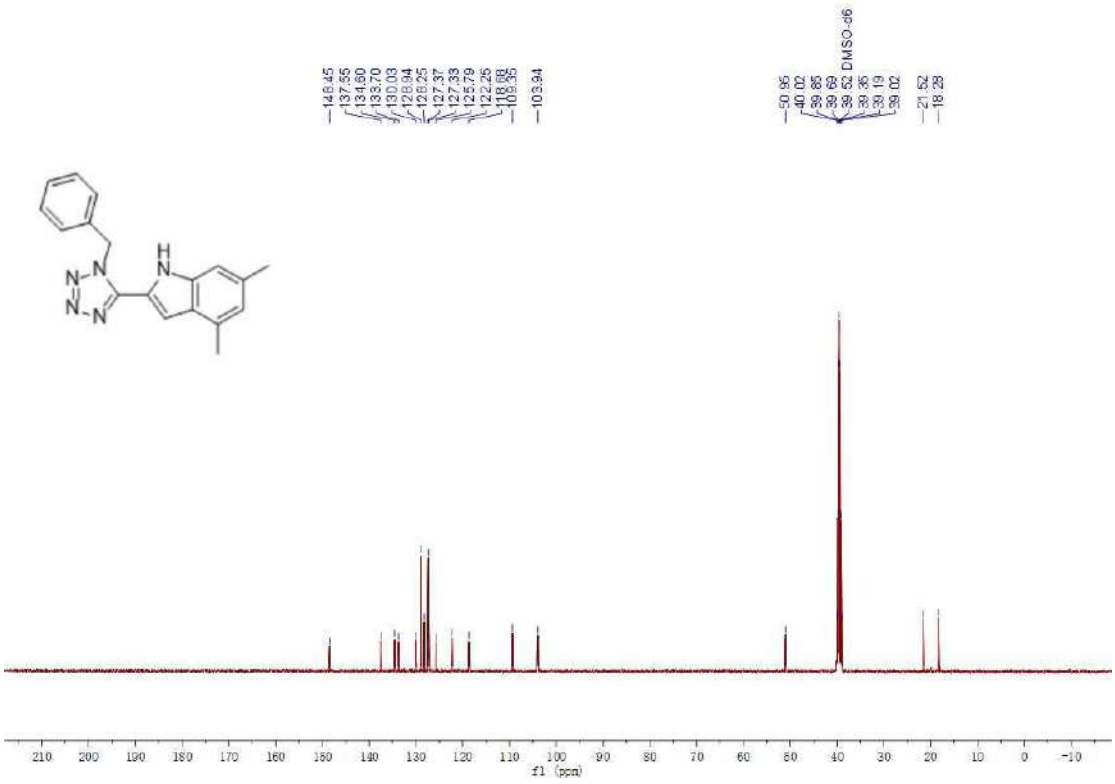
7.266
7.248
7.233
7.105
7.103
7.101
7.084
6.896
6.006
3.342
2.492
2.489
2.485
2.482
2.478
2.411
2.341
1.02
2.08
1.12
2.05
0.98
0.93
1.05
2.00
3.07
2.89
f1 (ppm)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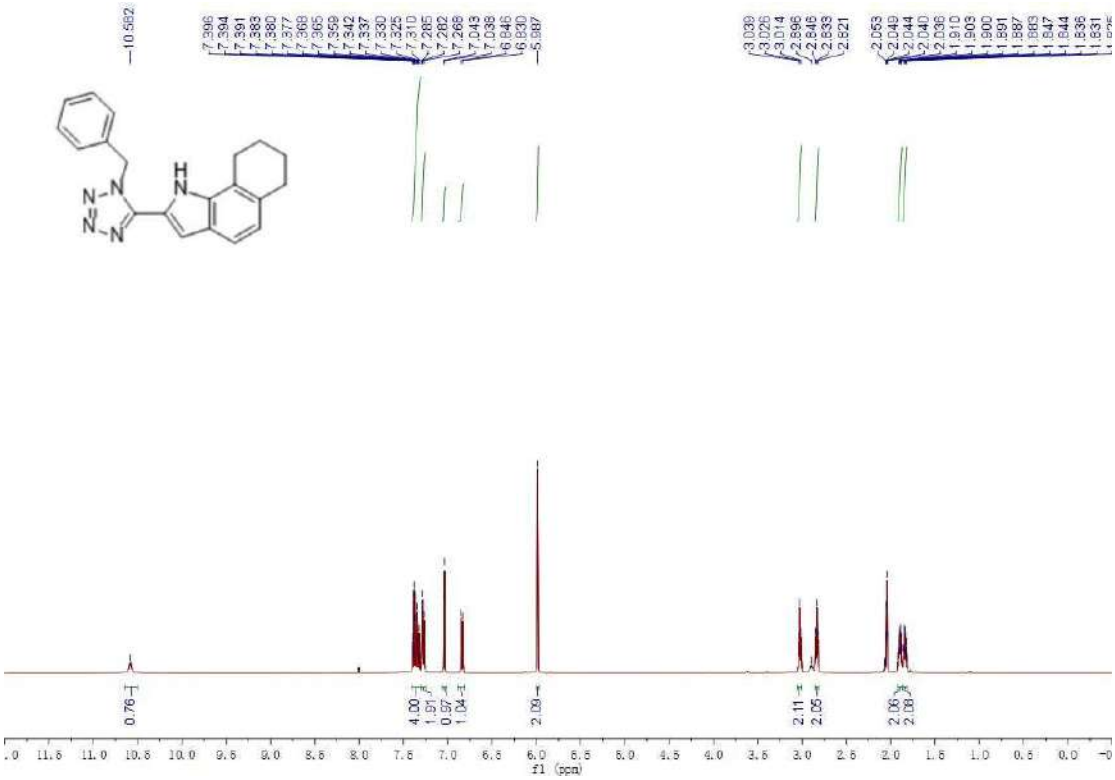
128.25
127.37
127.33
125.79
122.25
118.88
108.35
103.94
50.95
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
21.52
18.29
f1 (ppm)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7.337
7.330
7.325
7.310
7.285
7.282
7.268
7.043
7.038
6.846
6.830
5.987
3.039
3.026
3.014
2.896
2.846
2.833
2.821
2.053
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2.044
2.040
2.036
1.910
1.903
1.900
1.891
1.887
1.883
1.847
1.844
1.836
1.831
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0.97
1.04
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2.05
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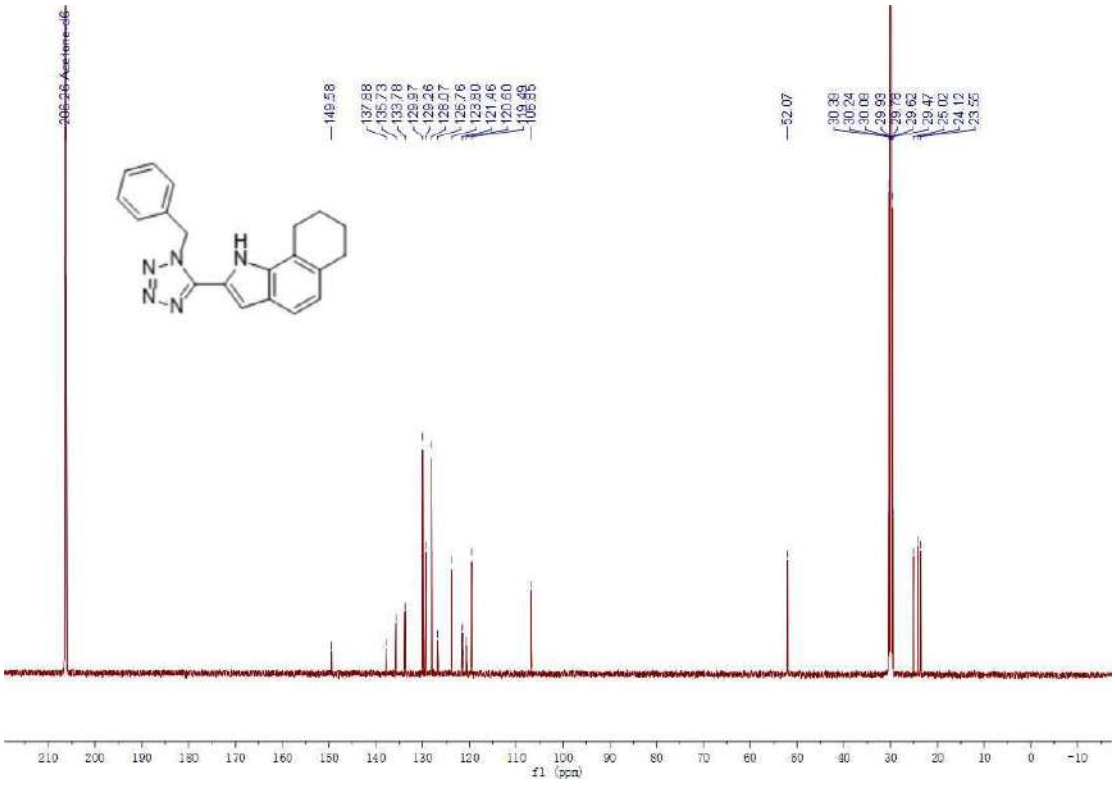
2.08
f1 (ppm)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133.78
129.97
129.26
128.07
126.76
123.80
121.46
120.60
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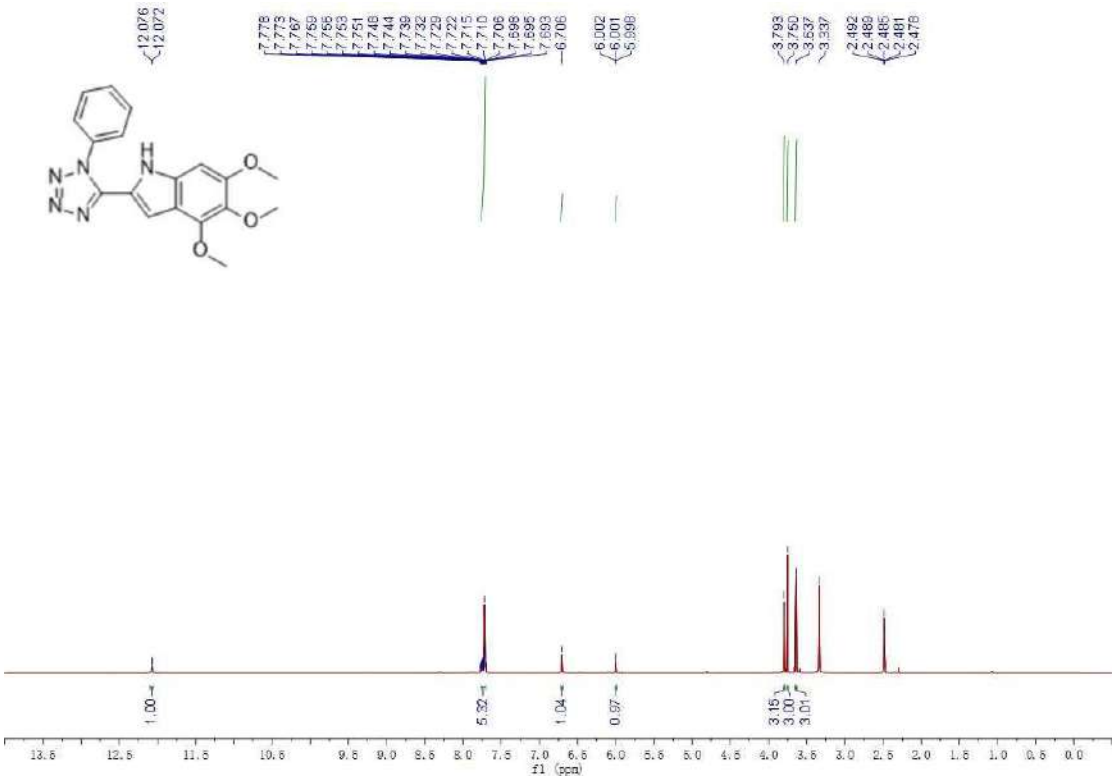
29.47
25.02
24.12
23.55
f1 (ppm)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7.753
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7.732
7.729
7.722
7.715
7.710
7.706
7.698
7.695
7.693
6.706
6.002
6.001
5.998
3.793
3.750
3.637
3.337
2.492
2.489
2.485
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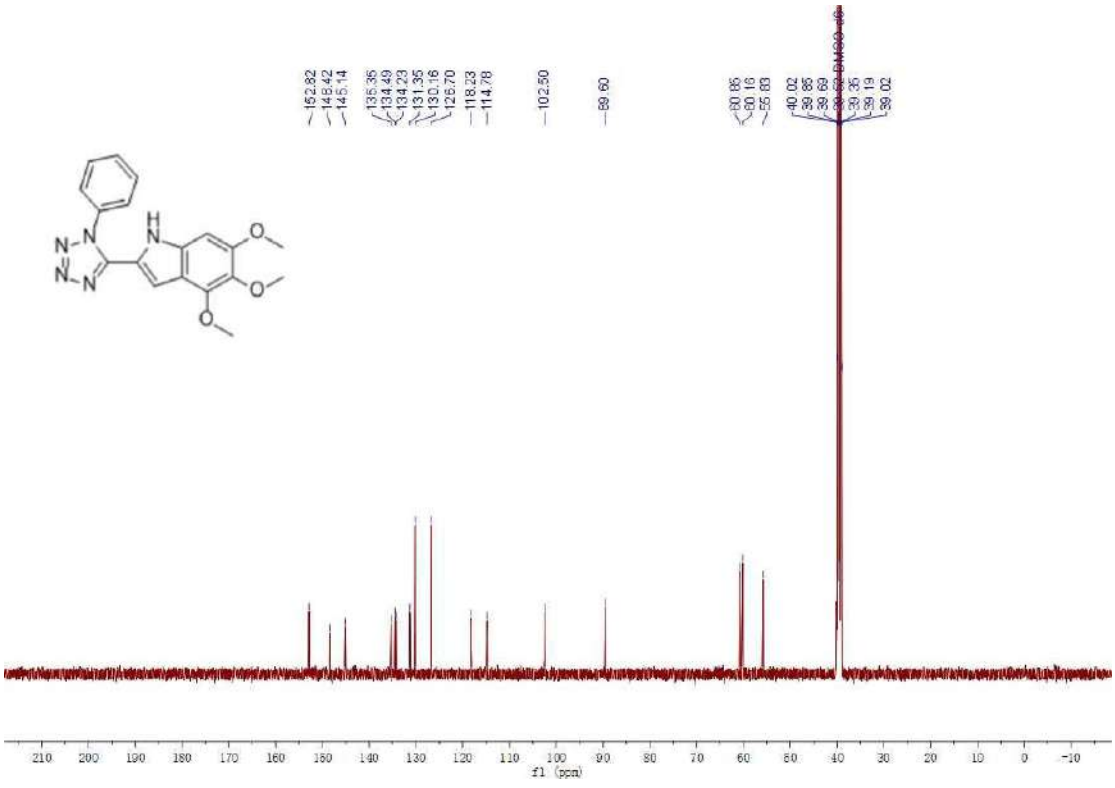
2.478
1.00
5.32
1.04
0.97
3.15
3.00
3.01
f1 (ppm)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114.78
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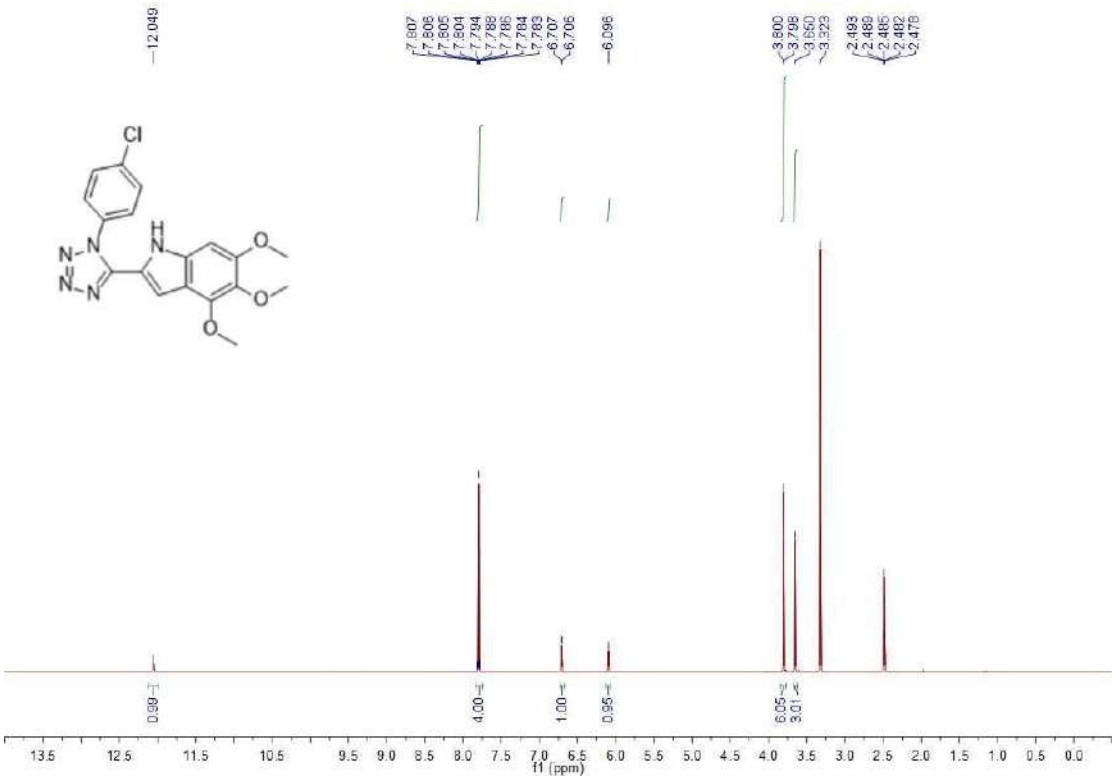
39.35
39.19
39.02
f1 (ppm)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7.794
7.788
7.786
7.784
7.783
6.707
6.706
6.096
3.800
3.798
3.650
3.323
2.493
2.489
2.485
2.482
2.478
Cl
H
N
O
O
O
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4.00
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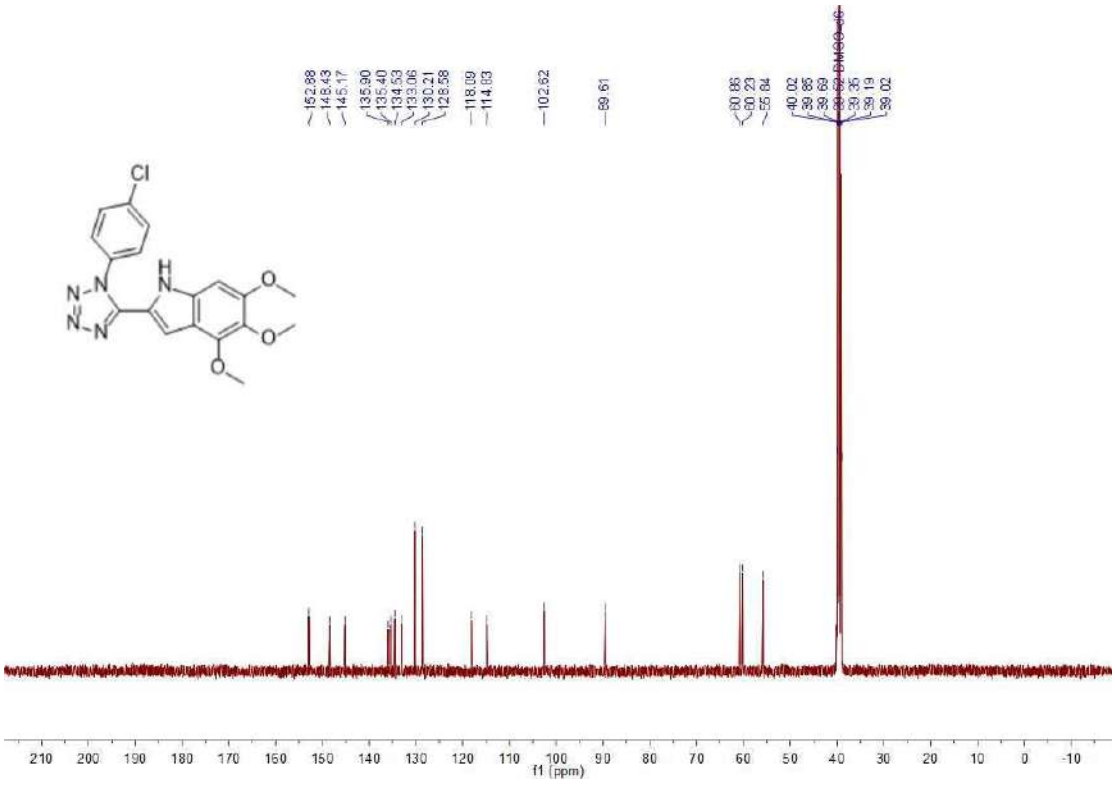
0.95
6.05
3.01
f1 (ppm)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135.40
134.53
133.06
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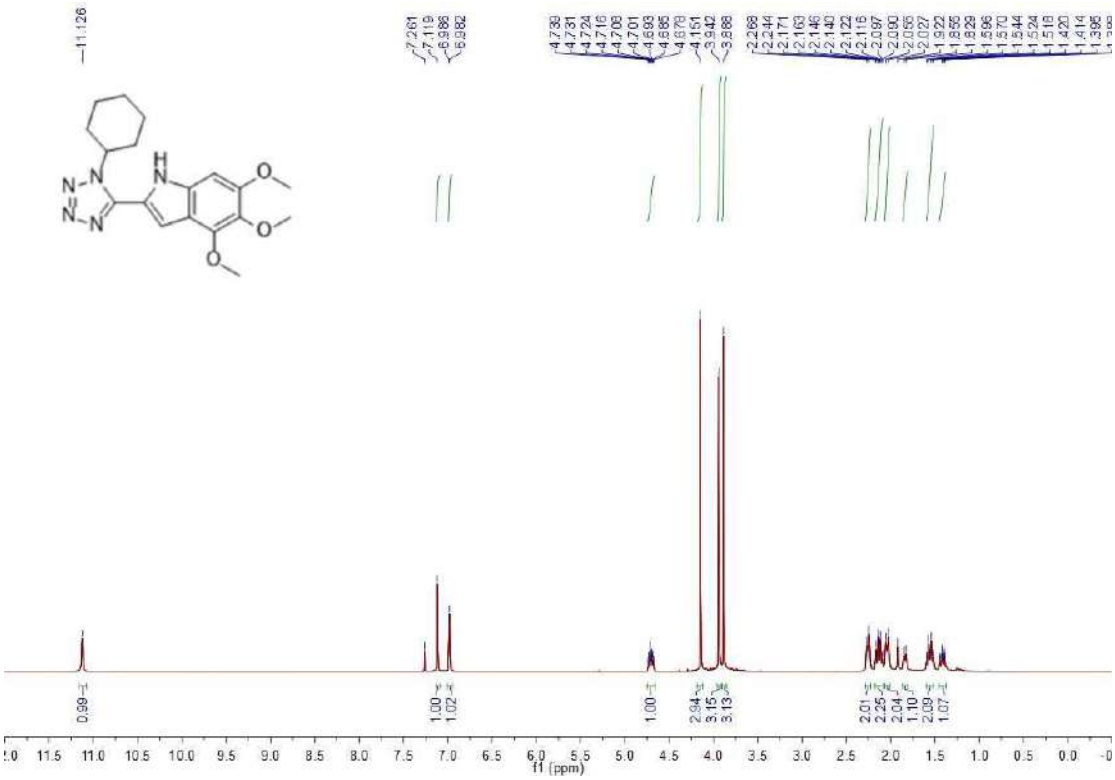
128.58
118.09
114.83
102.82
89.61
60.86
60.23
55.84
40.02
39.85
39.69
39.35
39.19
39.02
Cl
H
N
O
O
O
f1 (ppm)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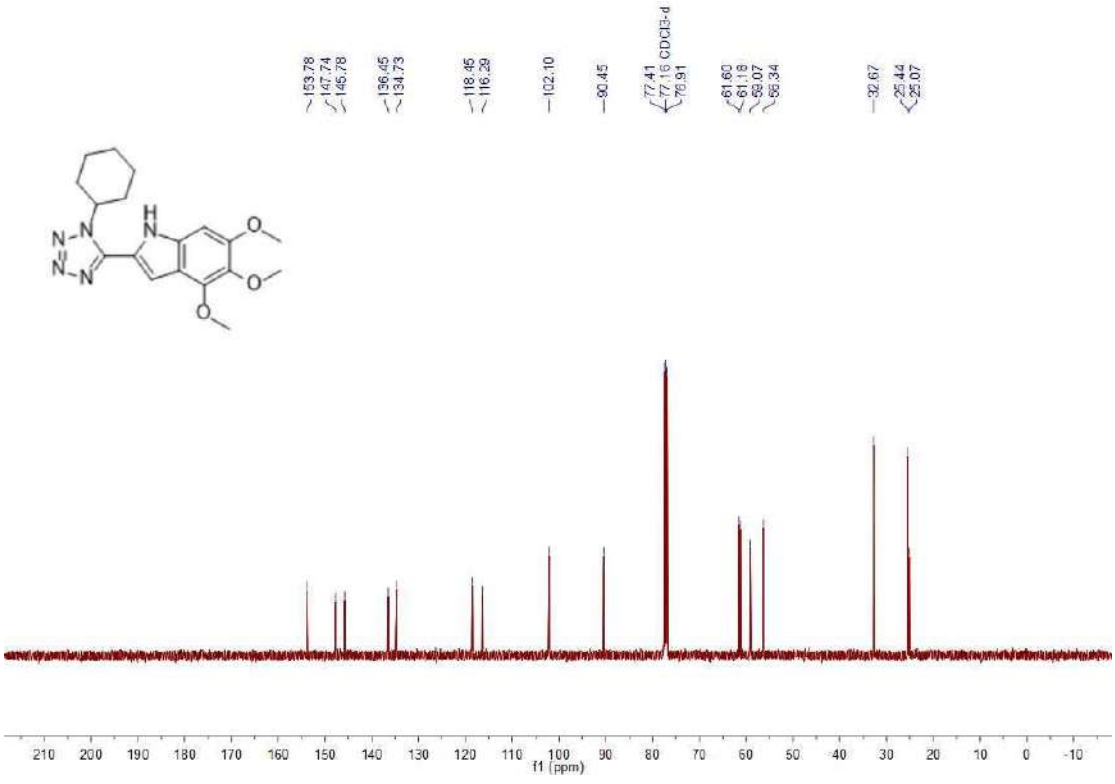
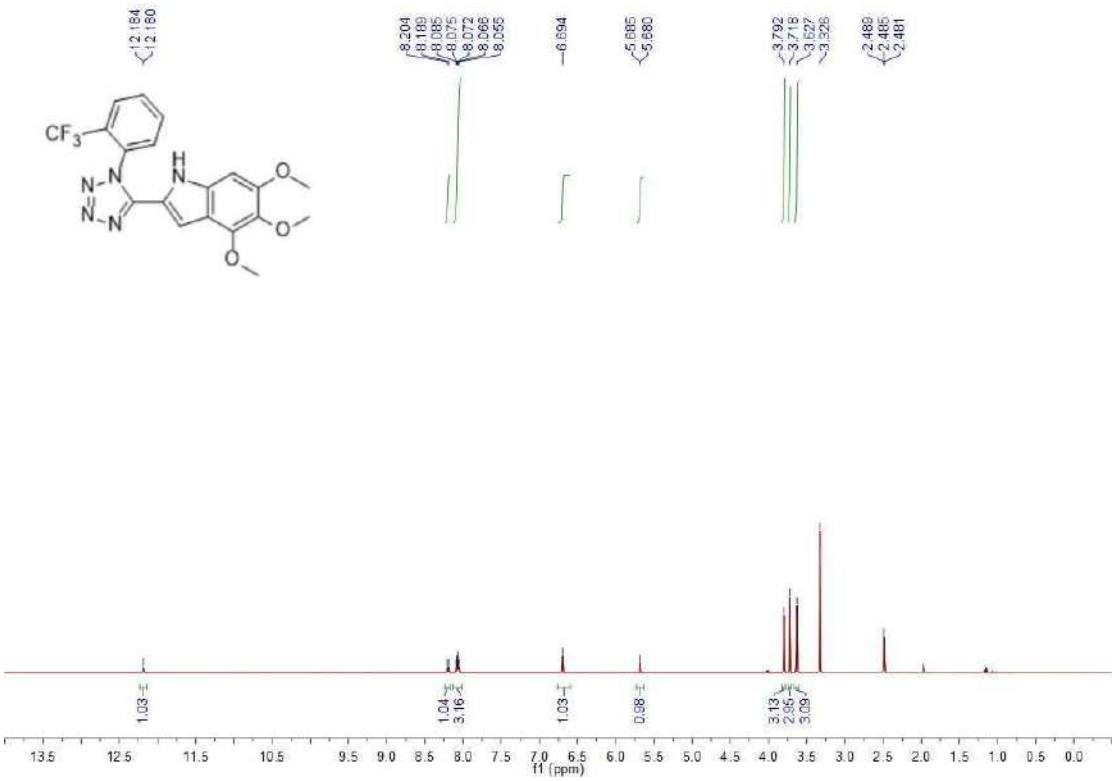
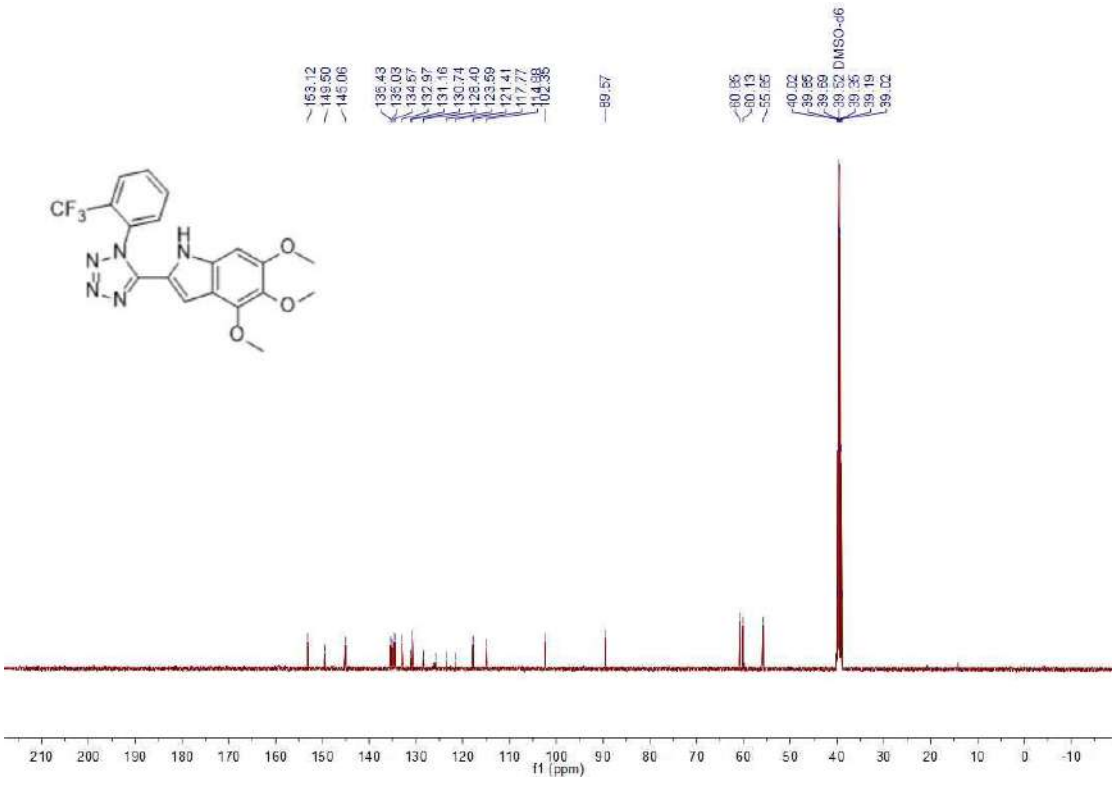
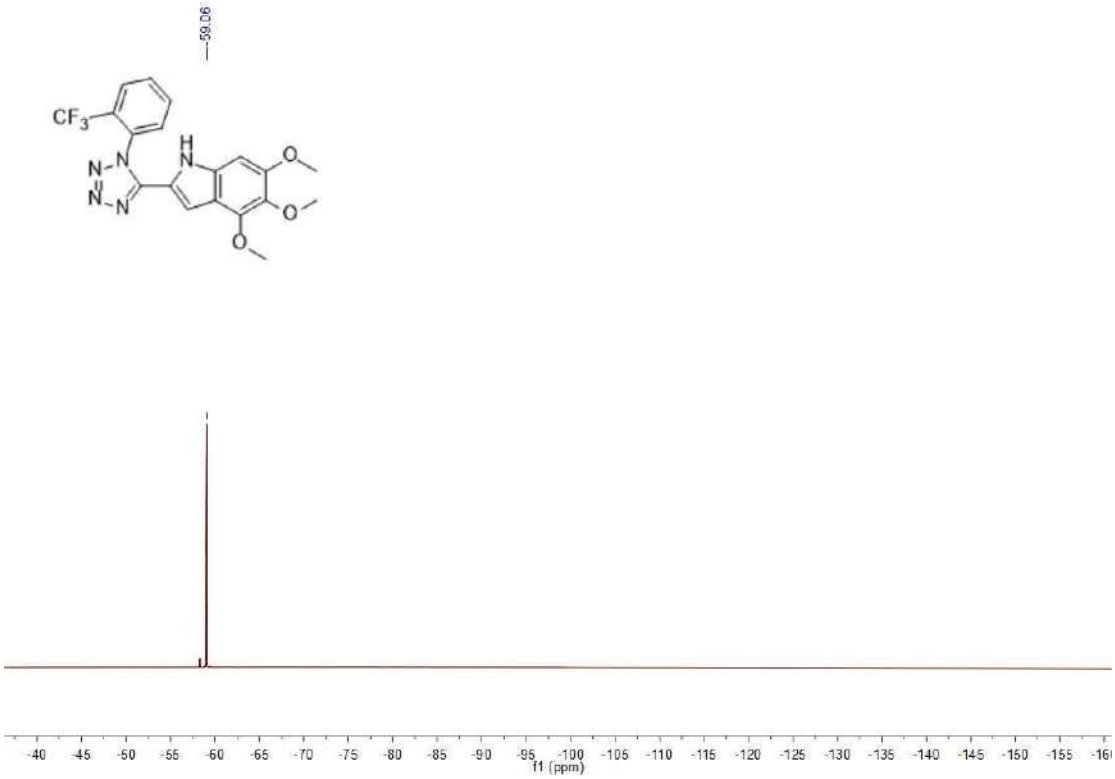
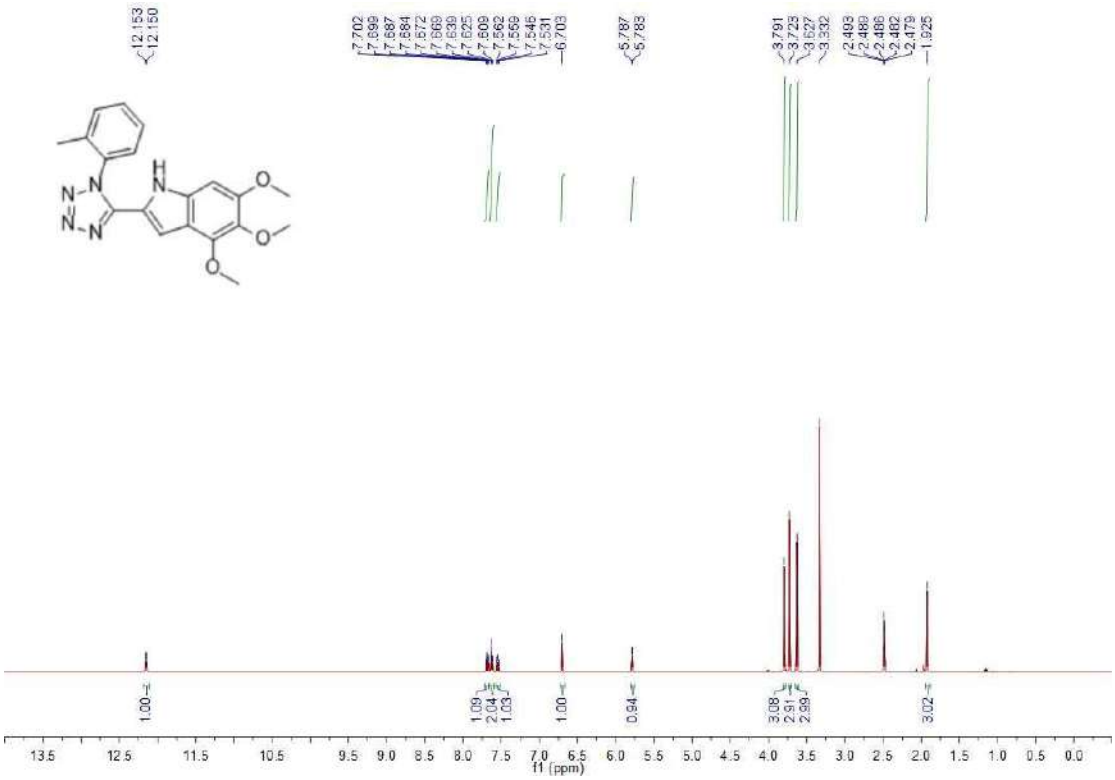
7.261
7.119
6.986
6.882
4.738
4.731
4.724
4.716
4.708
4.701
4.693
4.685
4.678
4.151
3.942
3.888
2.268
2.244
2.171
2.163
2.146
2.140
2.122
2.115
2.097
2.090
2.055
2.027
1.922
1.855
1.829
1.596
1.570
1.544
1.524
1.518
1.420
1.414
1.395
0.99
1.00
1.02
1.00
2.94
3.15
3.13
2.01
2.25
2.04
1.10
2.09
1.07
f1 (ppm)

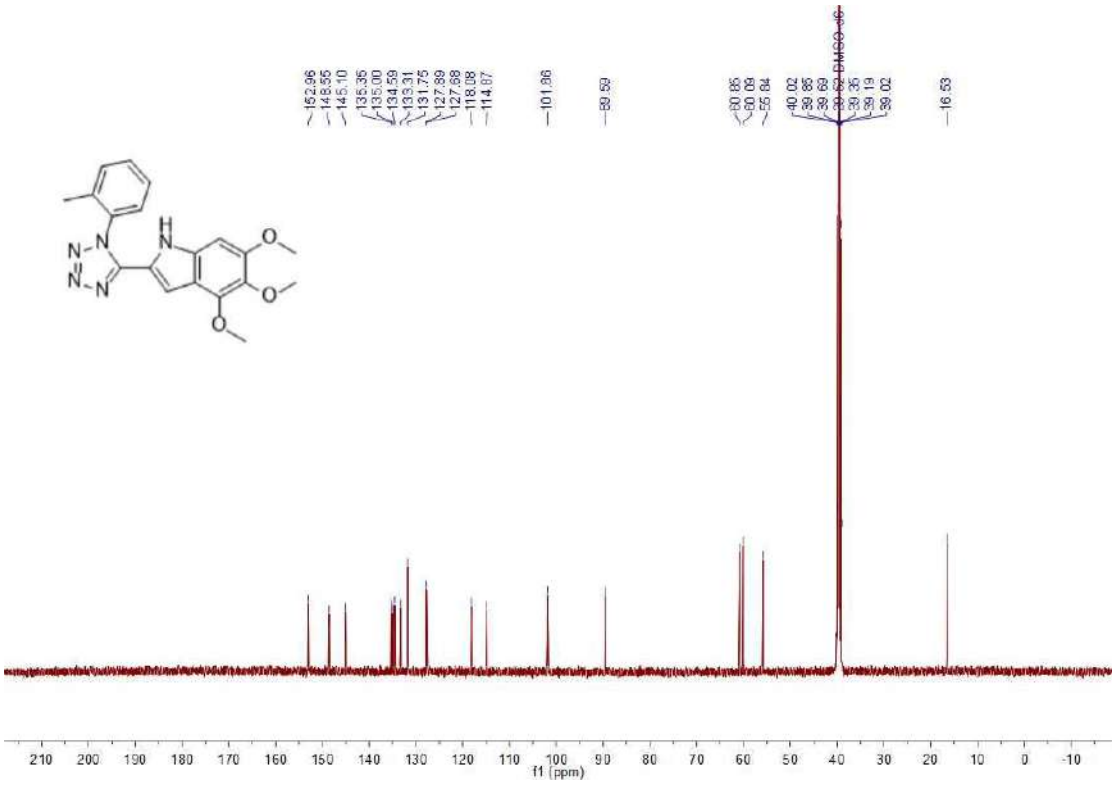

153.78
147.74
145.78
136.45
134.73
118.45
116.29
102.10
90.45
77.41
77.16 CDCl3-d
76.91
61.60
61.18
56.07
55.34
32.67
25.44
25.07
f1 (ppm)

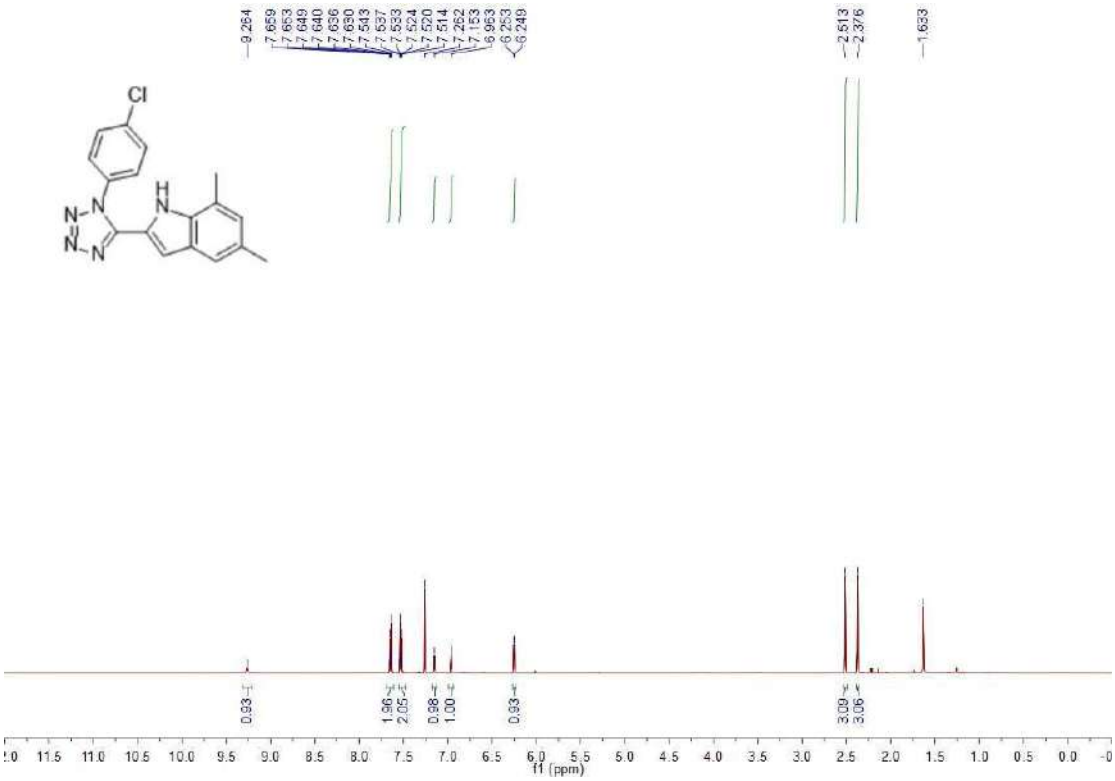

12.184
12.180
8.204
8.199
8.085
8.075
8.072
8.066
8.055
6.894
5.885
5.880
3.792
3.718
3.627
3.326
2.489
2.485
2.481
CF3
N
N
N
H
O
O
O
1.03
1.04
3.16
1.03
0.98
3.13
2.95
3.09
f1 (ppm)

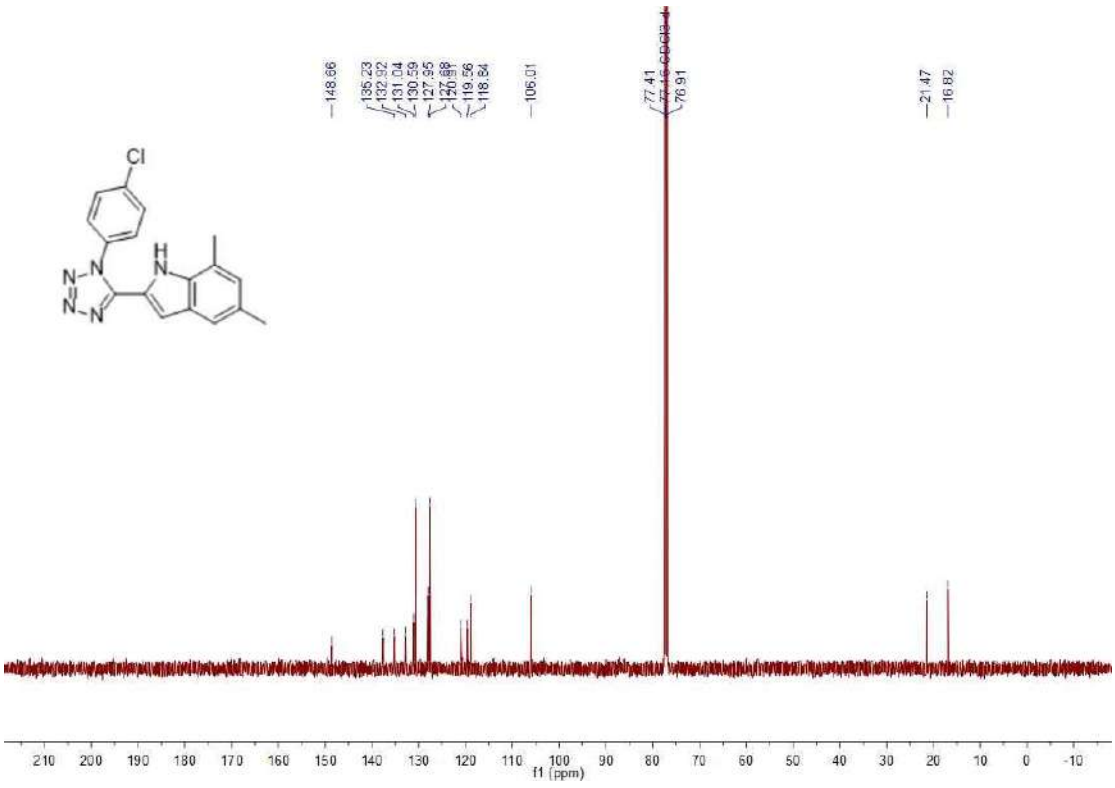

153.12
149.50
145.06
135.43
133.03
134.57
132.97
131.16
130.74
128.40
123.59
121.41
117.77
114.38
102.38
89.57
60.86
60.13
55.55
40.02
39.86
39.69
39.52 DMSO-d6
39.35
39.19
39.02
CF3
N
N
N
H
O
O
O
f1 (ppm)

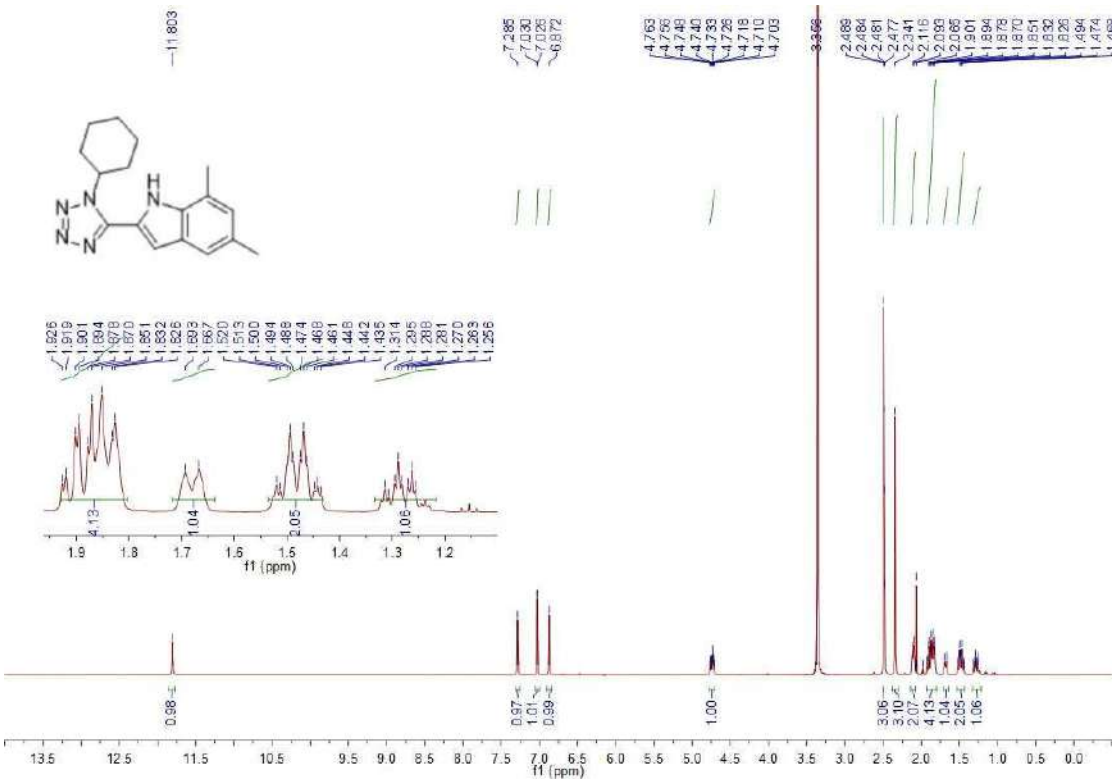

-59.06
CF3
N
N
N
H
N
O
O
O
-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155
f1 (ppm)

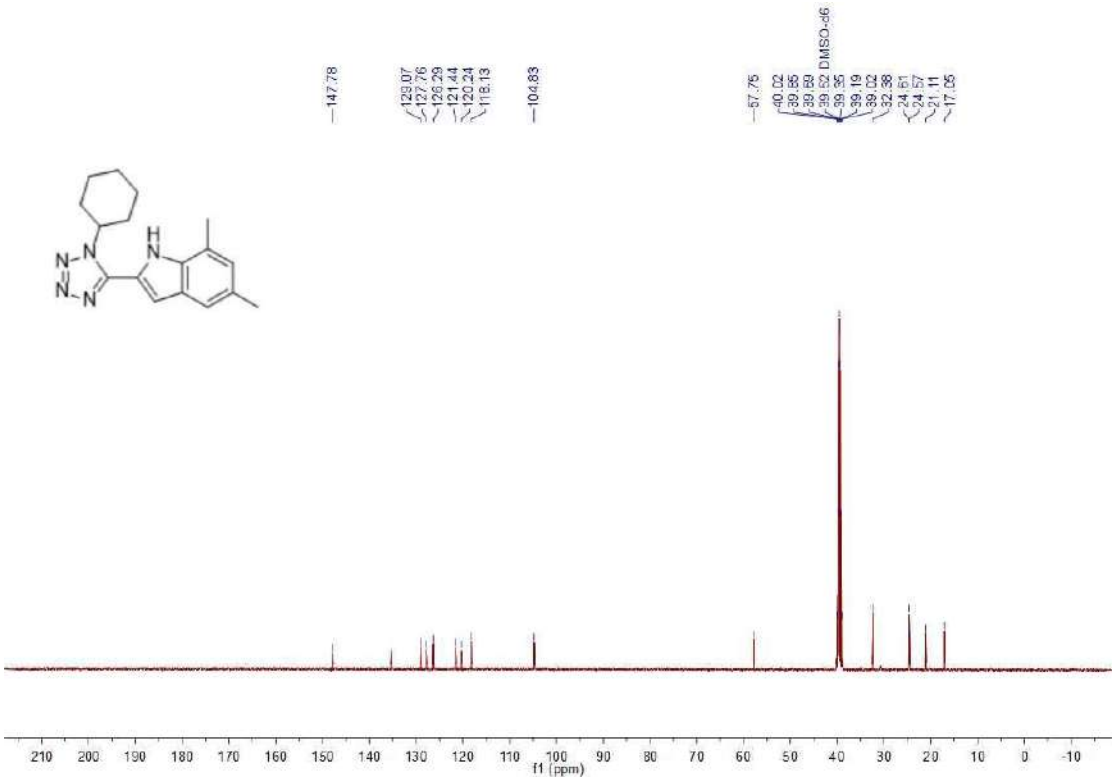

12.153
12.150
7.702
7.699
7.687
7.684
7.672
7.669
7.639
7.625
7.509
7.562
7.559
7.545
7.531
6.703
5.787
5.783
3.791
3.723
3.527
3.332
2.493
2.489
2.486
2.482
2.479
1.925
1.00
1.09
2.04
1.03
1.00
0.94
3.08
2.91
2.99
3.02
f1 (ppm)

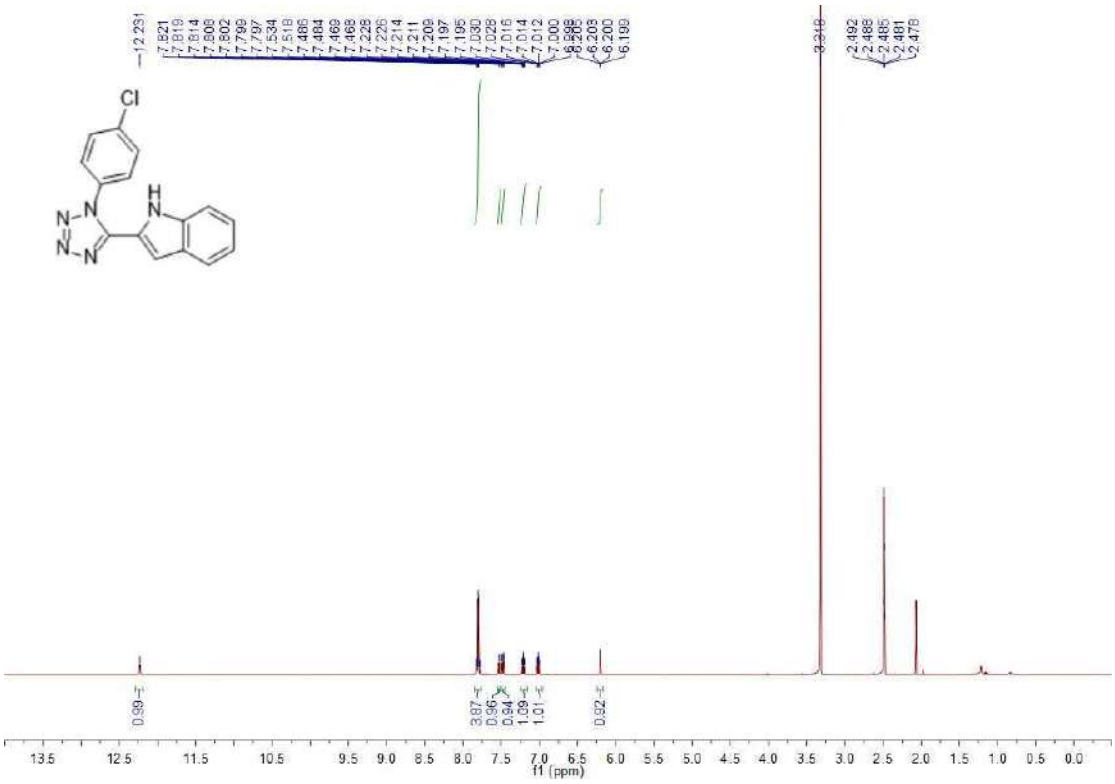

152.96
148.55
145.10
135.35
135.00
134.59
133.31
131.75
127.89
127.68
118.08
114.87
101.86
89.59
60.85
60.09
55.84
40.02
39.86
39.69
39.53
39.35
39.19
39.02
16.53
f1 (ppm)

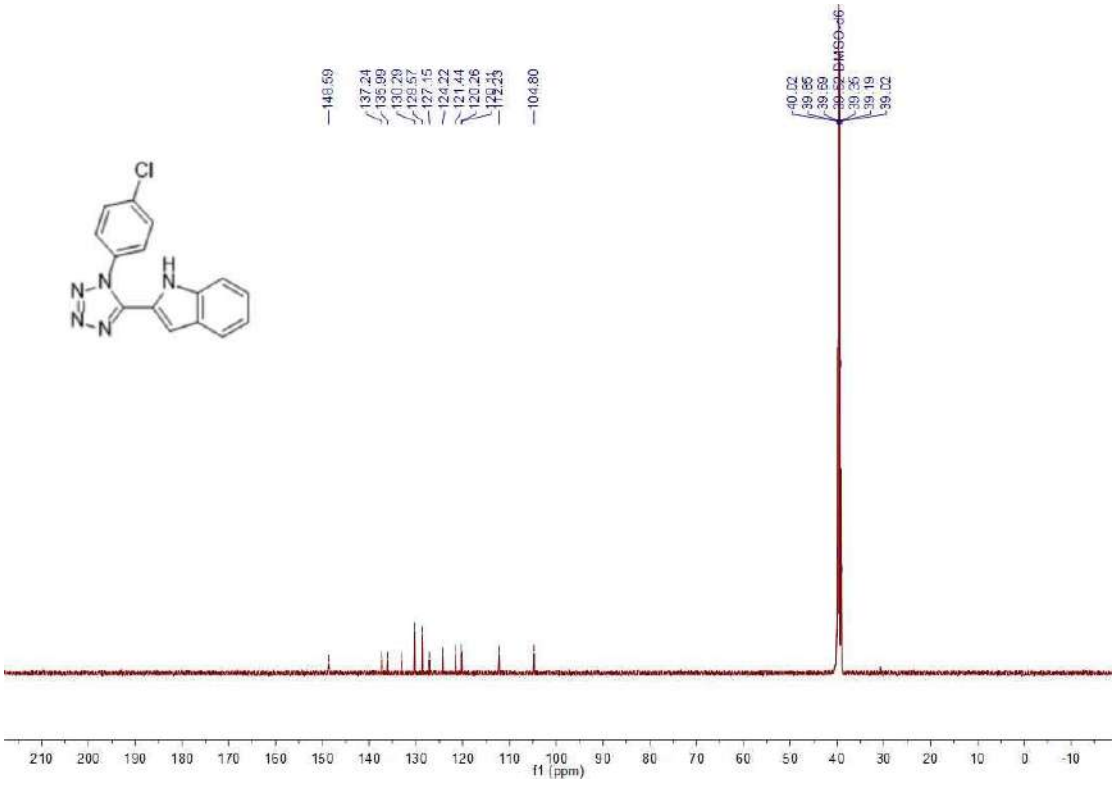

9.264
7.659
7.653
7.649
7.640
7.636
7.630
7.543
7.537
7.533
7.524
7.520
7.514
7.262
7.153
6.963
6.253
6.249
2.513
2.376
1.633
Cl
N
N
N
H
0.93
1.96
2.05
0.98
1.00
0.93
3.09
3.06
f1 (ppm)

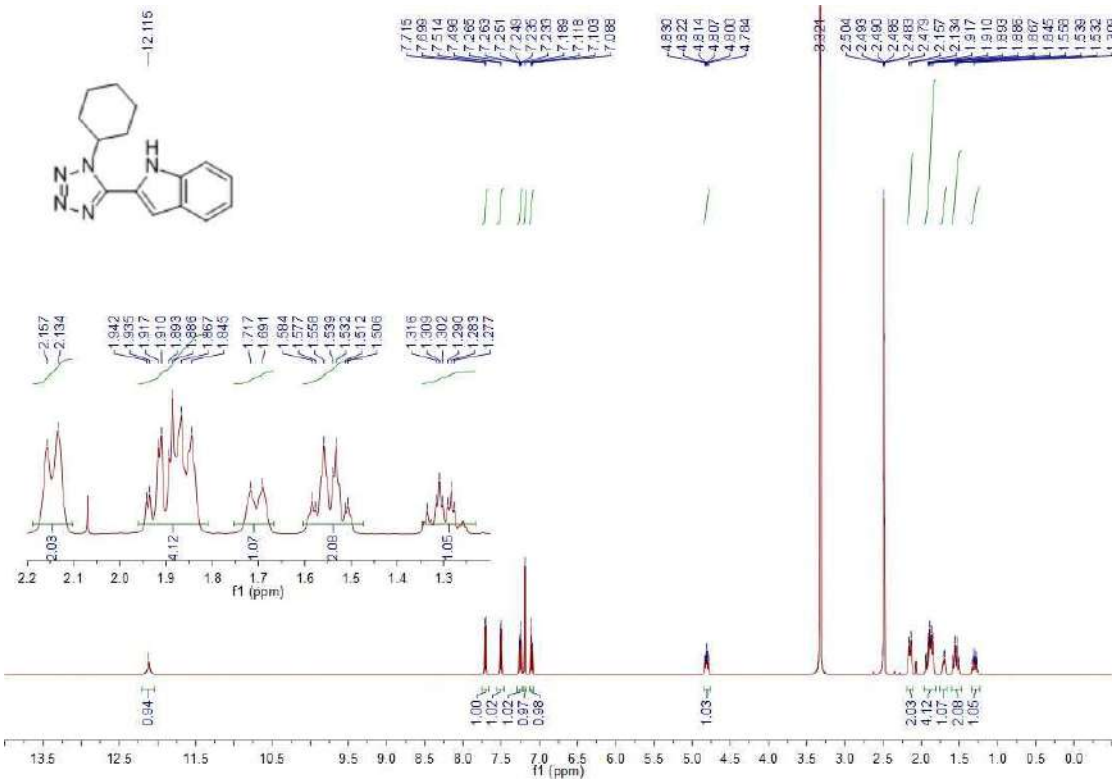

148.66
135.23
132.92
131.04
130.59
127.95
126.68
119.56
118.84
106.01
77.41
77.16
76.91
21.47
16.82
Cl
N
N
N
H
f1 (ppm)

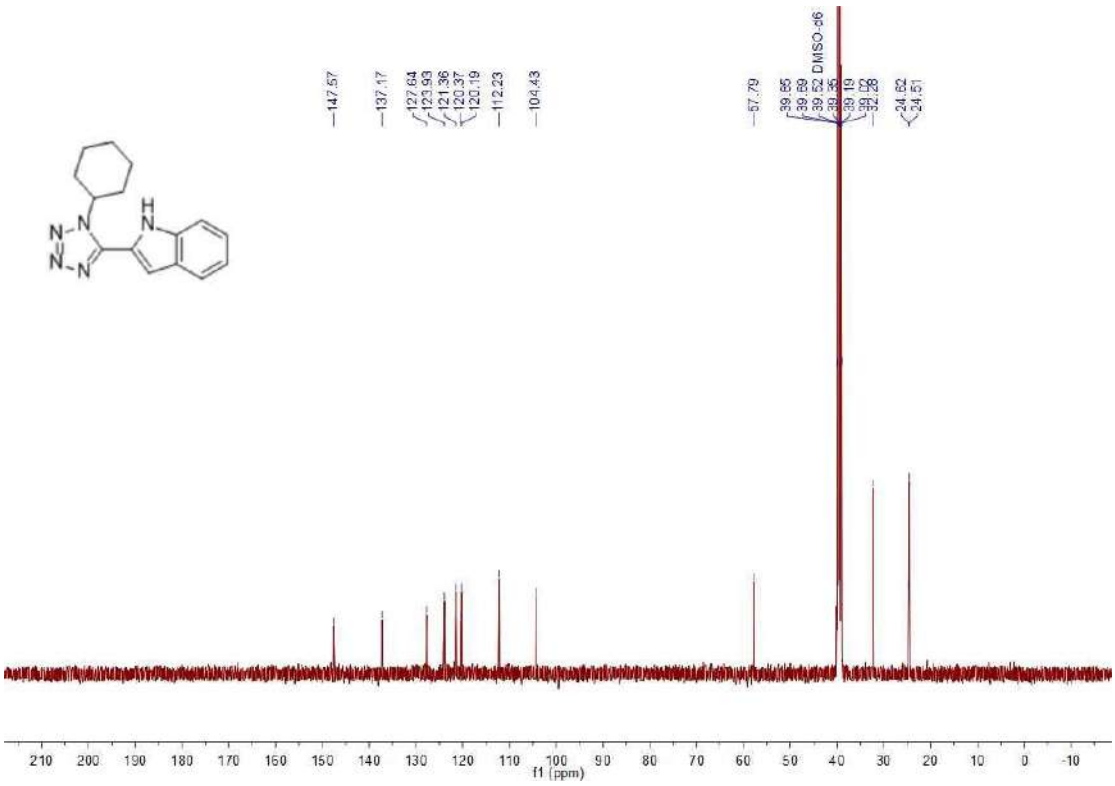

11.803
7.295
7.030
7.026
6.872
4.763
4.756
4.743
4.740
4.733
4.726
4.718
4.710
4.703
3.956
2.488
2.484
2.481
2.477
2.341
2.116
2.099
2.065
1.901
1.894
1.879
1.870
1.851
1.832
1.826
1.494
1.474
1.926
1.919
1.901
1.894
1.878
1.870
1.851
1.832
1.826
1.693
1.667
1.520
1.513
1.500
1.494
1.488
1.474
1.468
1.461
1.448
1.442
1.435
1.314
1.295
1.288
1.281
1.270
1.263
1.256
4.13
1.04
2.05
1.06
f1 (ppm)
0.98
0.97
1.01
0.99
1.00
3.06
3.10
2.07
4.13
1.04
2.05
1.06
f1 (ppm)

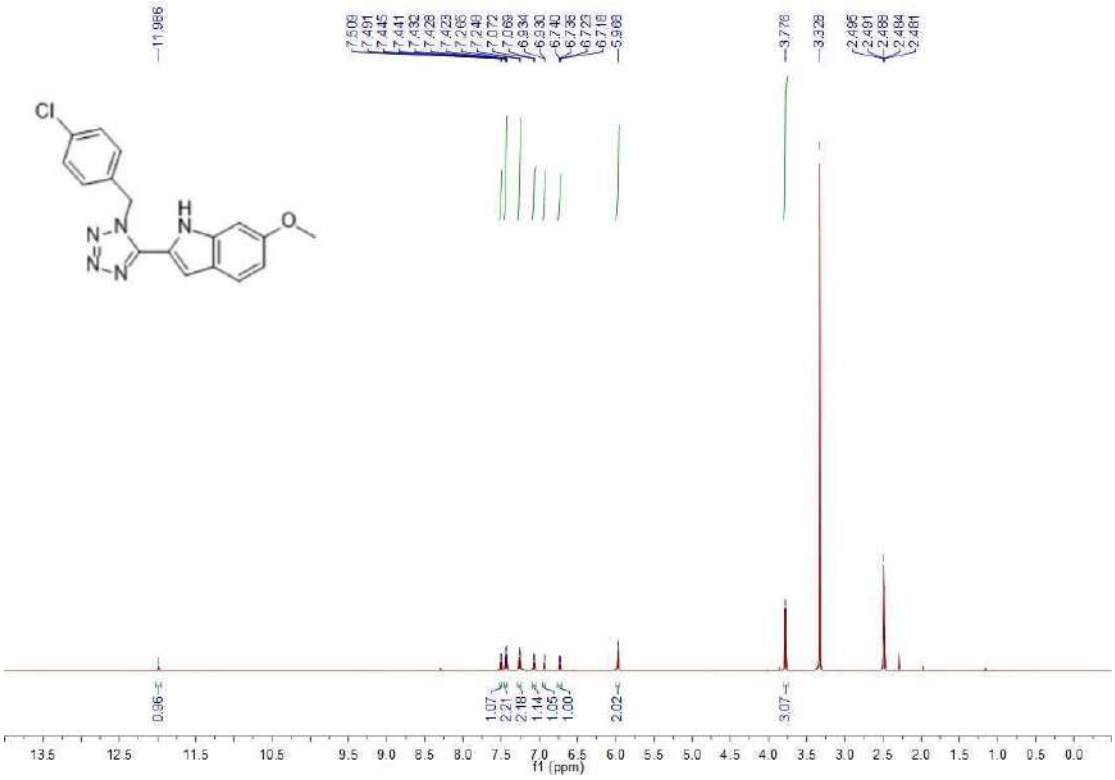

147.78
129.07
127.76
126.29
121.44
120.24
118.13
104.83
57.75
40.02
39.86
39.69
39.52 DMSO-d6
39.35
39.19
39.02
32.38
24.61
24.57
21.11
17.05
f1 (ppm)

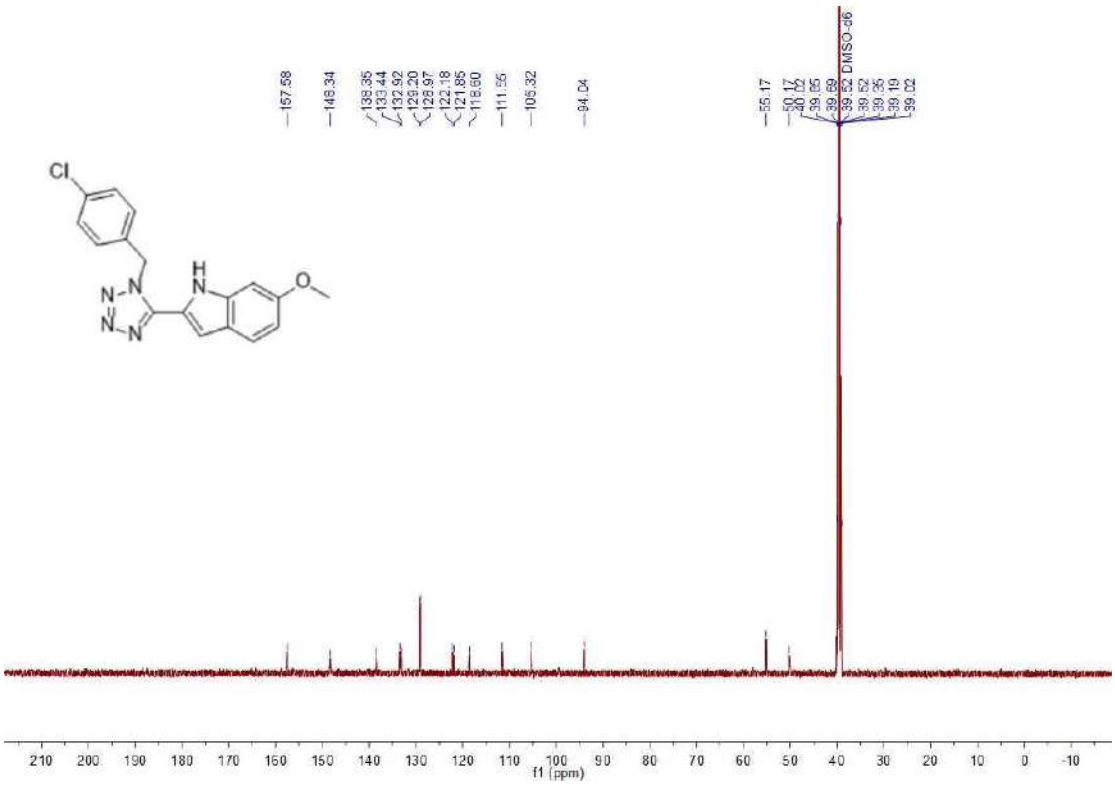

12.231
7.821
7.819
7.814
7.806
7.802
7.799
7.797
7.534
7.518
7.486
7.484
7.469
7.468
7.228
7.226
7.214
7.211
7.209
7.197
7.195
7.030
7.028
7.016
7.014
7.012
7.000
6.588
6.203
6.200
6.199
3.318
2.492
2.488
2.485
2.481
2.478
Cl
N
N
N
H
0.99
3.87
0.96
0.94
1.09
1.01
0.92
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

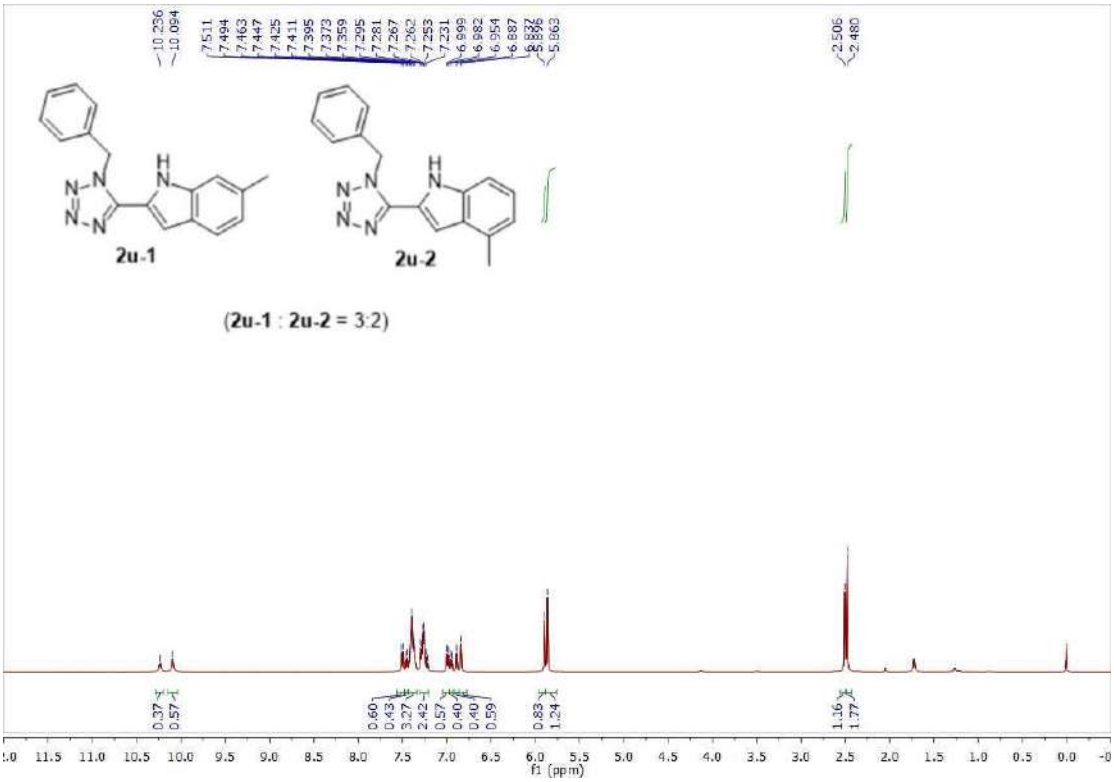

143.59
137.24
135.99
130.29
129.57
127.15
124.22
121.44
120.26
112.31
104.80
40.02
39.86
39.69
39.52
39.36
39.19
39.02
Cl
N
N
N
H
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

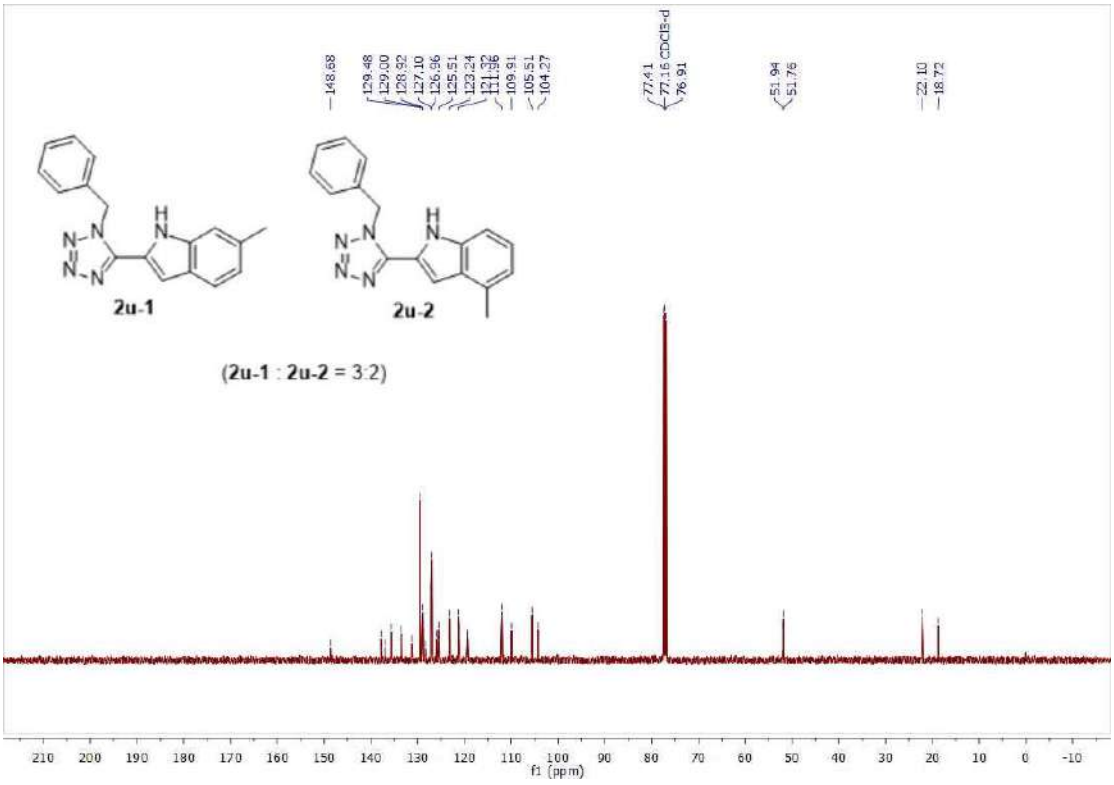


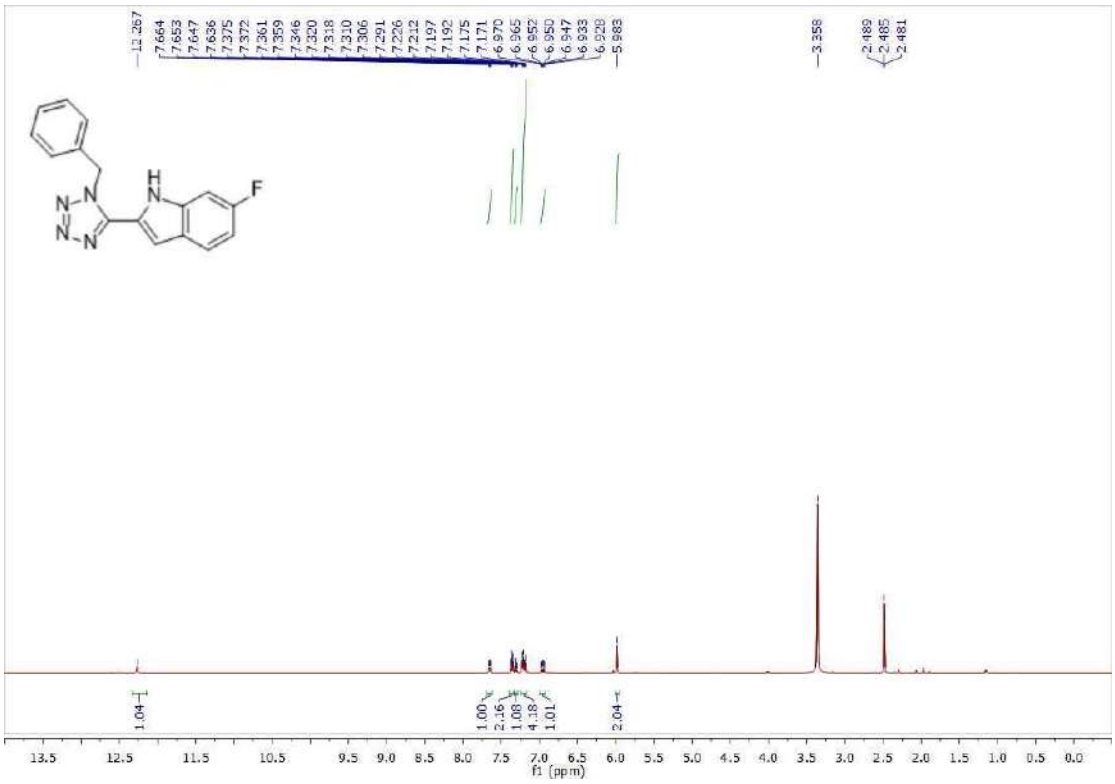


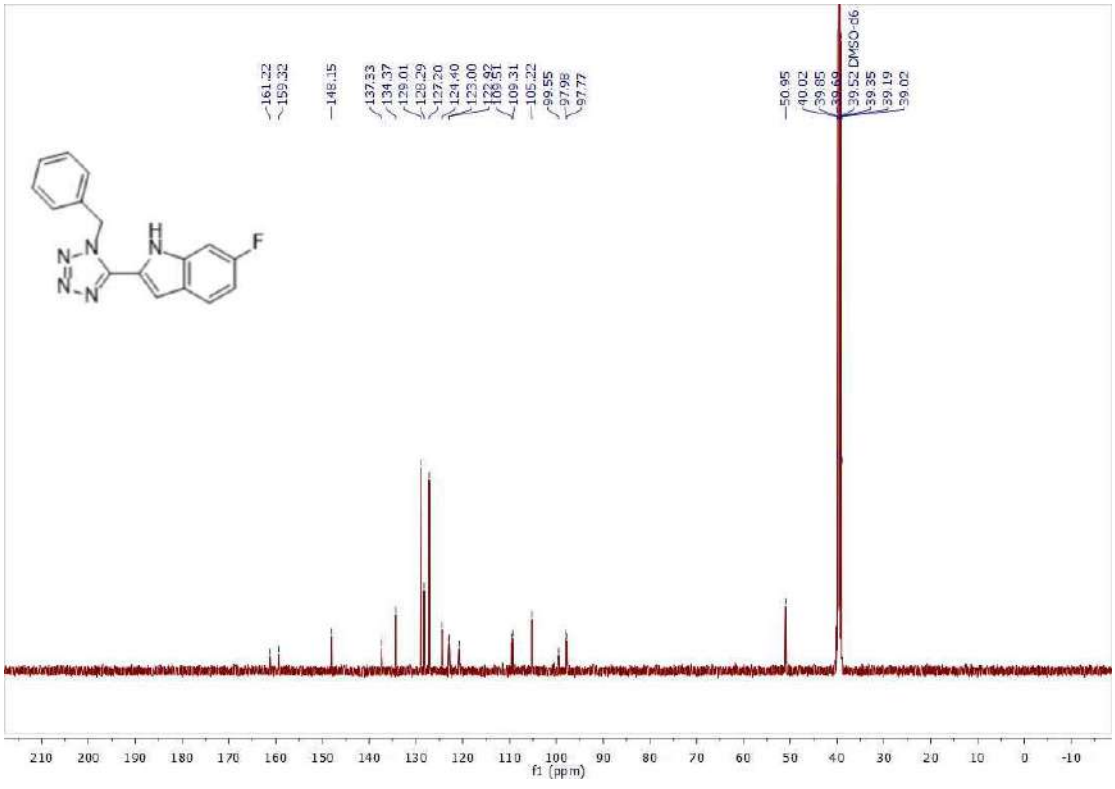

11.966
7.508
7.491
7.445
7.441
7.432
7.428
7.423
7.266
7.249
7.072
7.069
6.934
6.930
6.740
6.736
6.723
6.718
5.988
3.778
3.329
2.495
2.491
2.488
2.484
2.481
Cl
N
N
N
H
O
0.96
1.07
2.21
2.18
1.14
1.05
1.00
2.02
3.07
f1 (ppm)

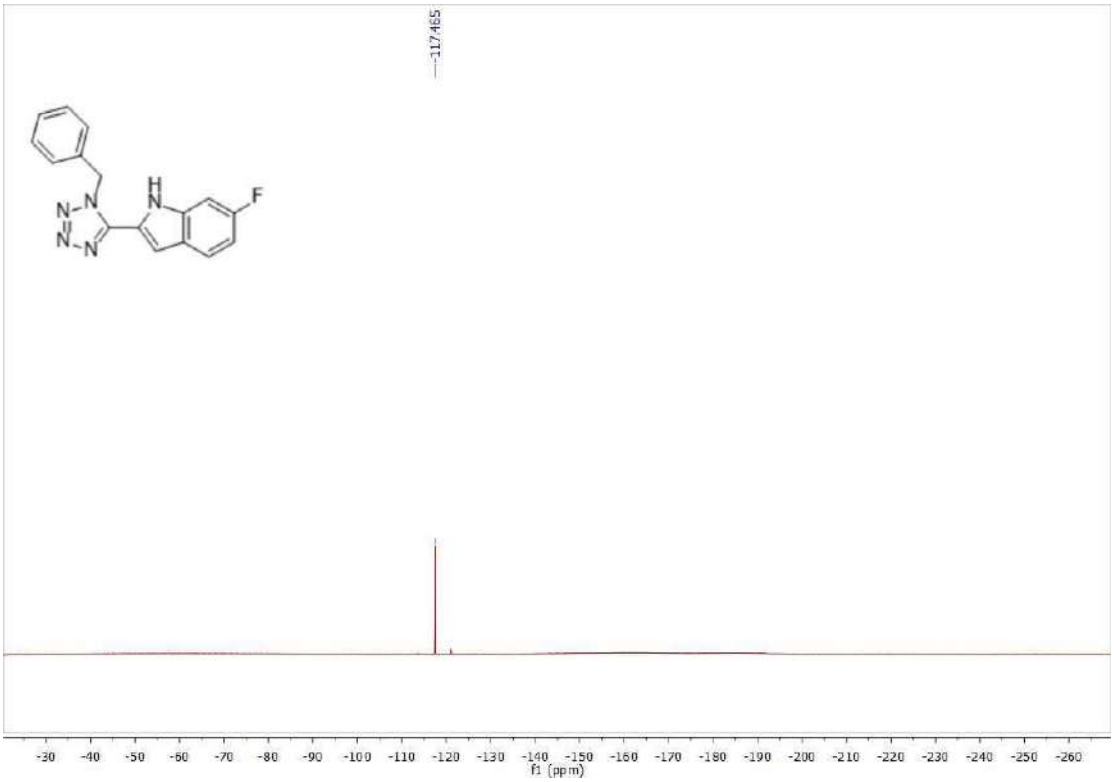

157.58
148.34
138.35
133.44
132.92
129.20
128.97
122.18
121.85
118.60
111.55
105.32
94.04
55.17
DMSO-d6
Cl
N
N
N
H
O
f1 (ppm)

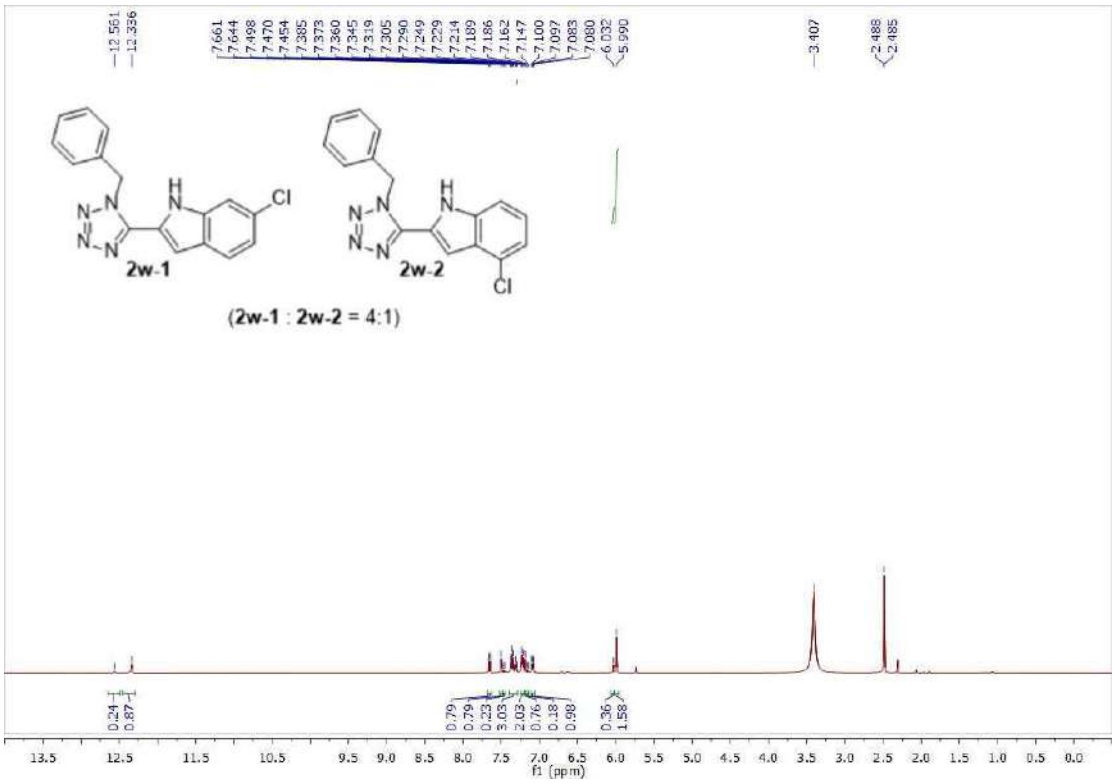

10.236
10.094
7.511
7.494
7.463
7.447
7.425
7.411
7.395
7.373
7.359
7.295
7.281
7.267
7.262
7.253
7.231
6.999
6.982
6.954
6.887
6.837
6.896
5.863
2.506
2.480
2u-1
2u-2
(2u-1 : 2u-2 = 3:2)
0.37
0.57
0.60
0.43
3.27
2.42
0.57
0.40
0.40
0.59
0.83
1.24
1.16
1.77
f1 (ppm)

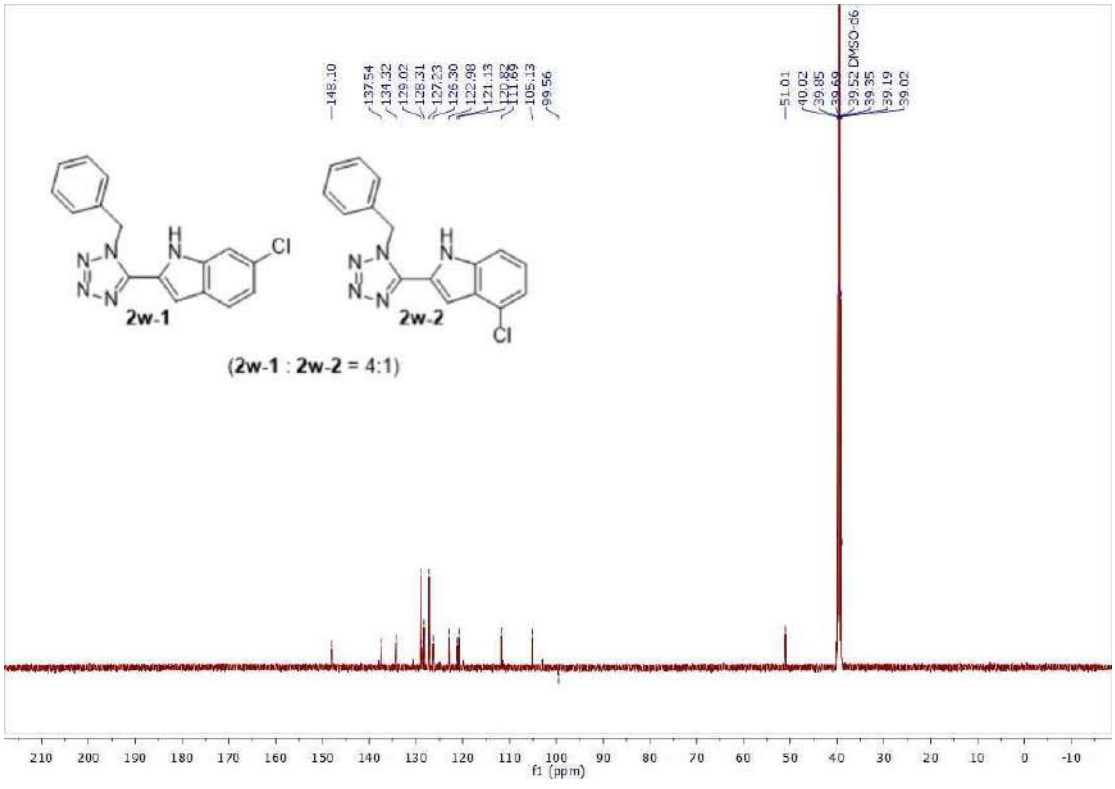

148.68
129.48
129.00
128.92
127.10
126.96
125.51
123.24
121.32
111.96
109.91
105.51
104.27
77.41
77.16 CDCl3-d
76.91
51.94
51.76
22.10
18.72
2u-1
2u-2
(2u-1 : 2u-2 = 3:2)
f1 (ppm)

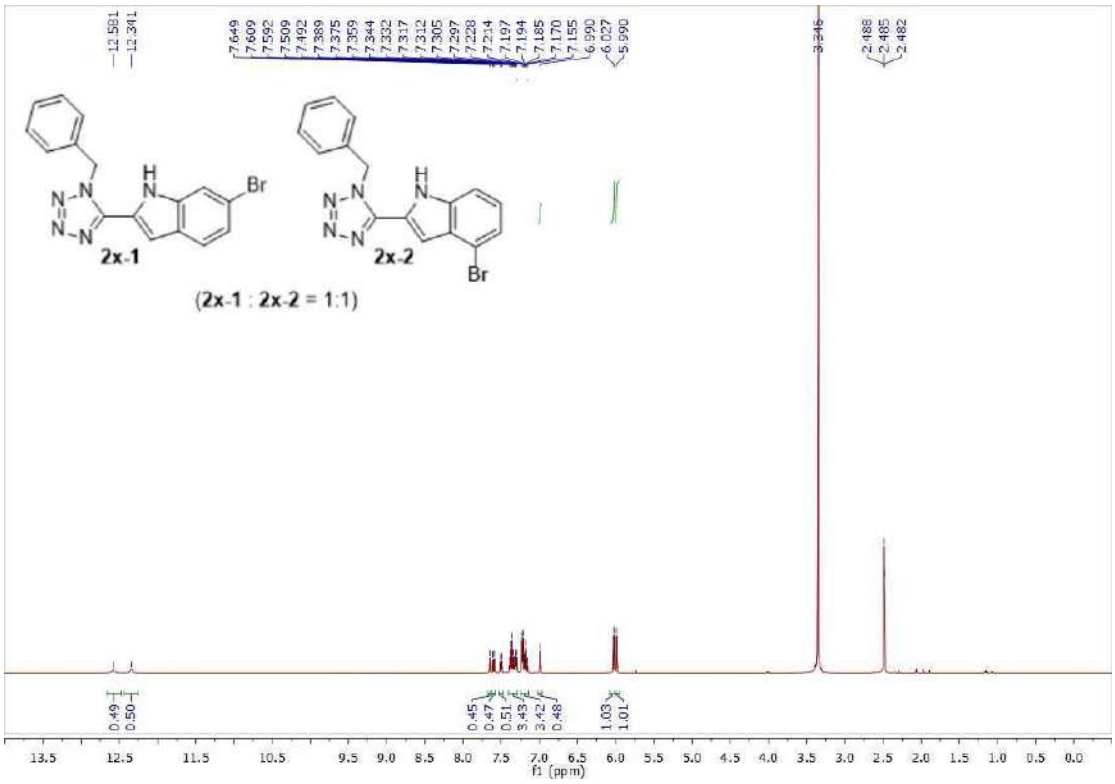

12.267
7.664
7.653
7.647
7.636
7.375
7.372
7.361
7.359
7.346
7.320
7.318
7.310
7.306
7.291
7.226
7.212
7.197
7.192
7.175
7.171
6.970
6.965
6.952
6.950
6.947
6.933
6.928
5.983
3.558
2.489
2.485
2.481
F
H
N
1.04
1.00
2.16
1.08
4.18
1.01
2.04
f1 (ppm)

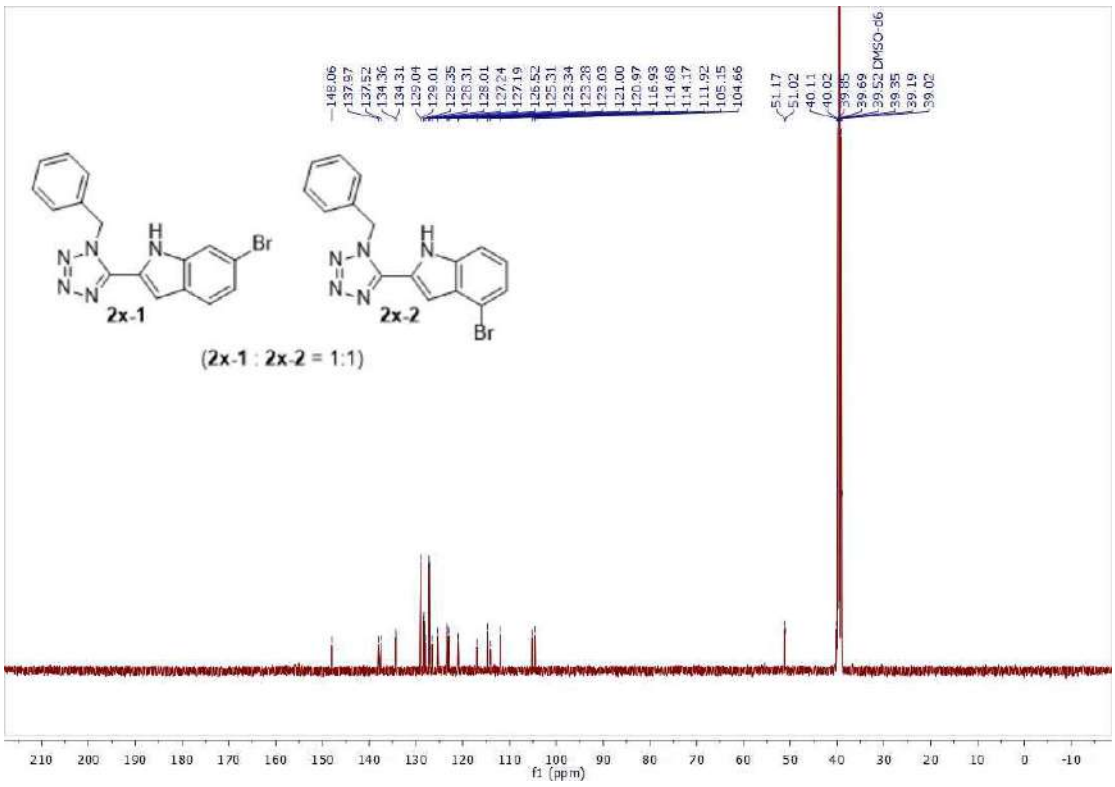

161.22
159.32
148.15
137.33
134.37
129.01
128.29
127.20
124.40
123.00
122.82
108.51
109.31
105.22
99.55
97.98
97.77
50.95
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
F
H
N
f1 (ppm)

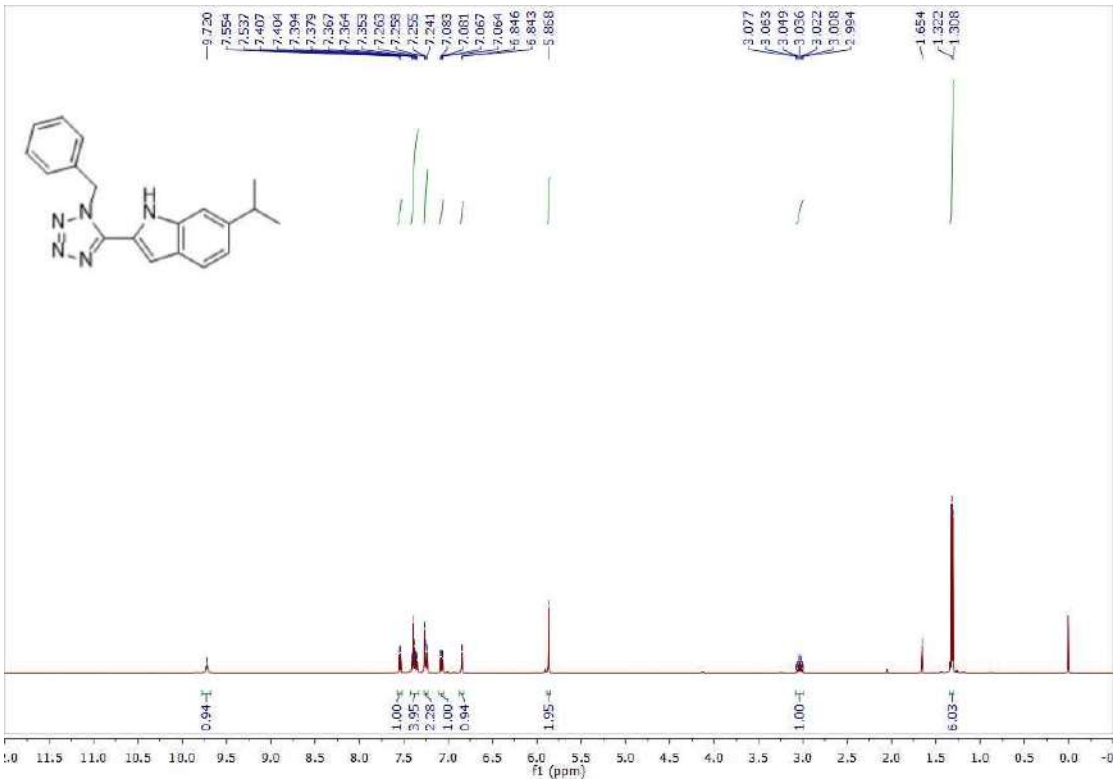

-117.465
F
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260
f1 (ppm)

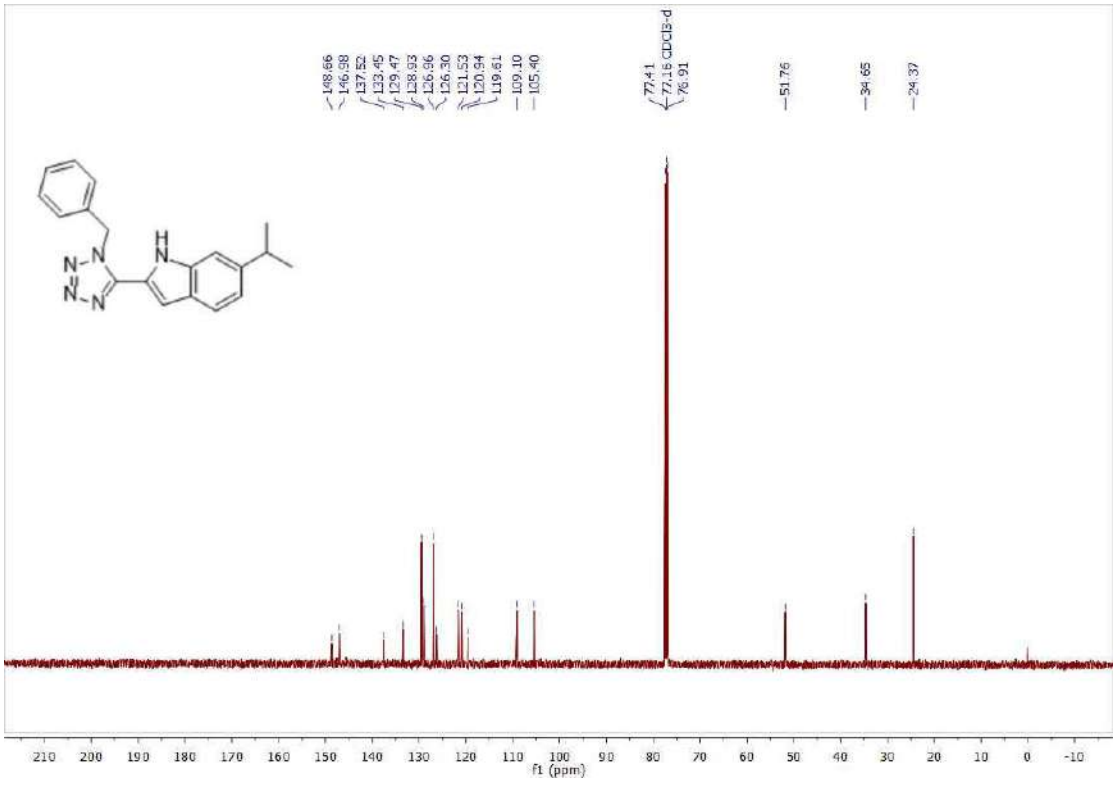

12.561
12.336
7.661
7.644
7.498
7.470
7.454
7.385
7.373
7.360
7.345
7.319
7.305
7.290
7.249
7.229
7.214
7.189
7.186
7.162
7.147
7.100
7.097
7.083
7.080
6.032
5.590
3.407
2.488
2.485
2w-1
2w-2
Cl
(2w-1 : 2w-2 = 4:1)
0.24
0.87
0.79
0.79
0.23
3.03
2.03
0.76
0.18
0.98
0.36
1.58
f1 (ppm)

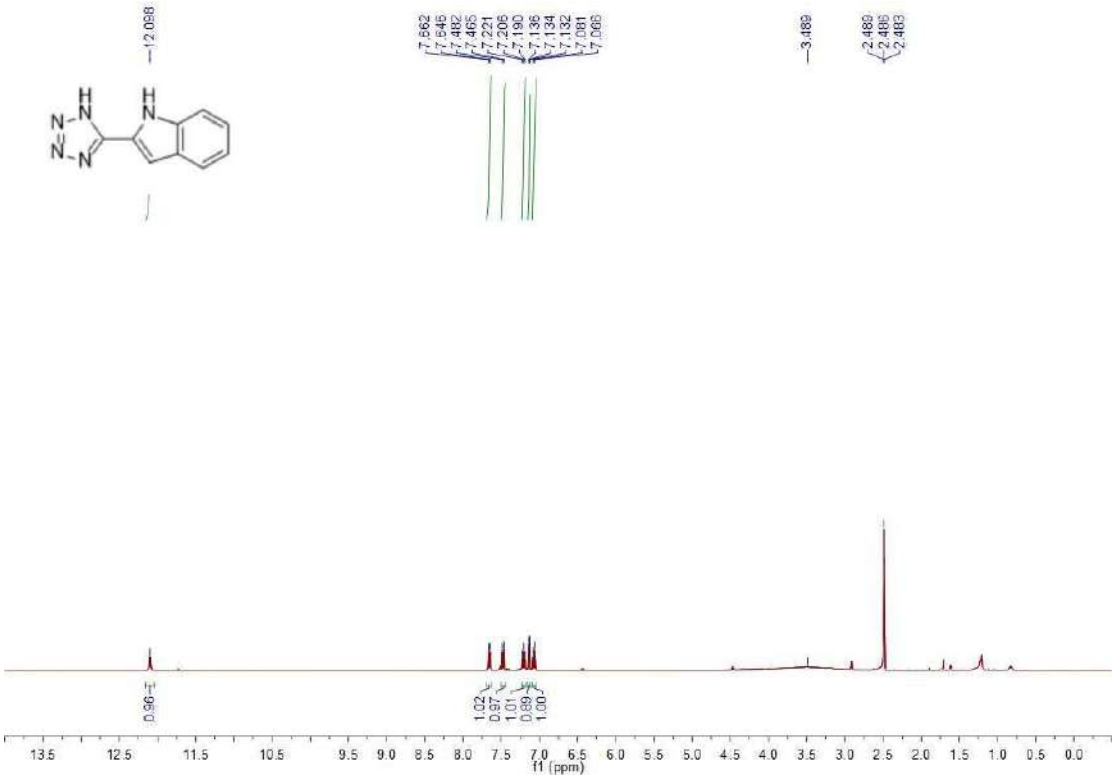

148.10
137.54
134.32
129.02
128.31
127.23
126.30
122.98
121.13
120.82
111.89
105.13
99.56
51.01
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
2w-1
2w-2
Cl
(2w-1 : 2w-2 = 4:1)
f1 (ppm)

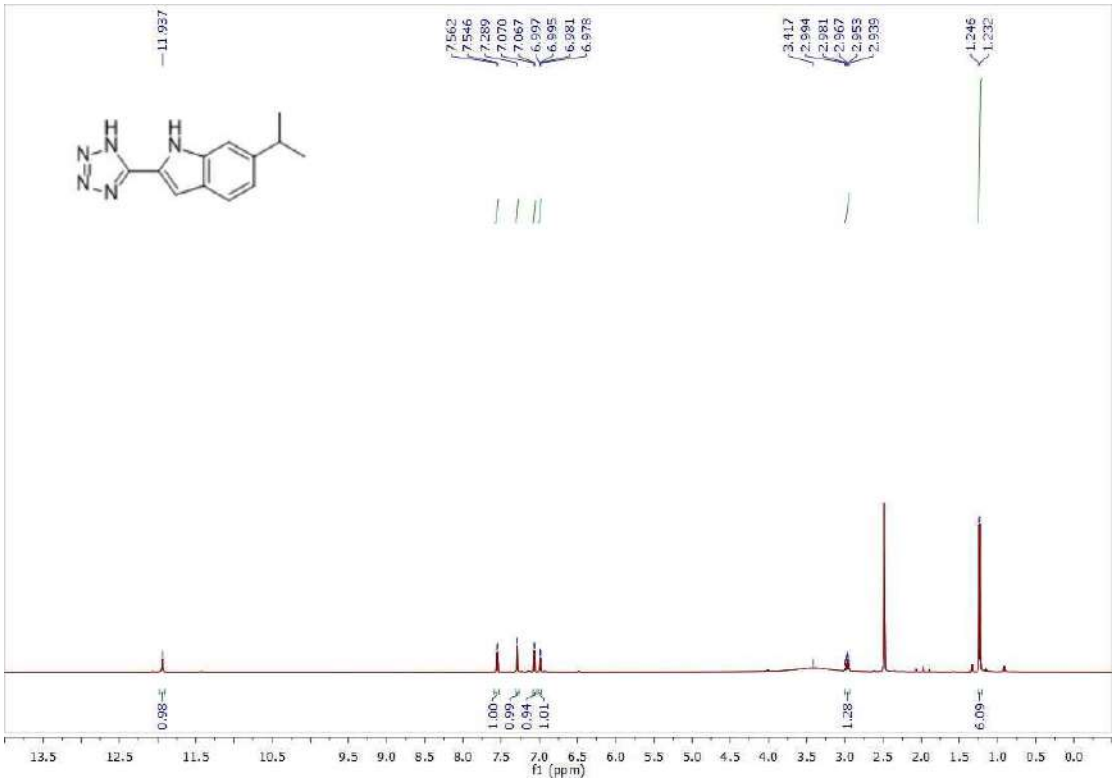

12.581
12.341
7.649
7.609
7.592
7.509
7.492
7.389
7.375
7.359
7.344
7.332
7.317
7.312
7.305
7.297
7.228
7.214
7.197
7.194
7.185
7.170
7.155
6.990
6.027
5.990
3.346
2.488
2.485
2.482
Br
2x-1
2x-2
Br
(2x-1 : 2x-2 = 1:1)
0.49
0.50
0.45
0.47
0.51
3.43
3.42
0.48
1.03
1.01
f1 (ppm)

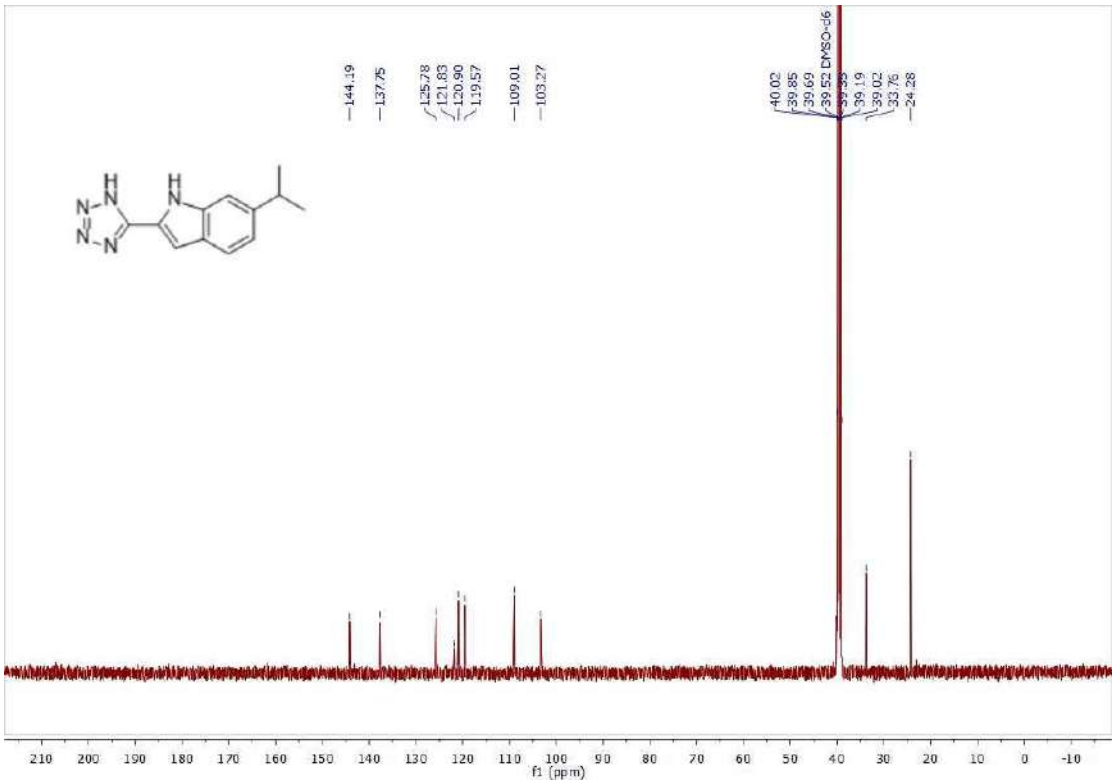

148.06
137.97
137.52
134.36
134.31
129.04
129.01
128.35
128.31
128.01
127.24
127.19
126.52
125.31
123.34
123.28
123.03
121.00
120.97
116.93
114.68
114.17
111.92
105.15
104.66
51.17
51.02
40.11
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
Br
2x-1
2x-2
Br
(2x-1 : 2x-2 = 1:1)
f1 (ppm)

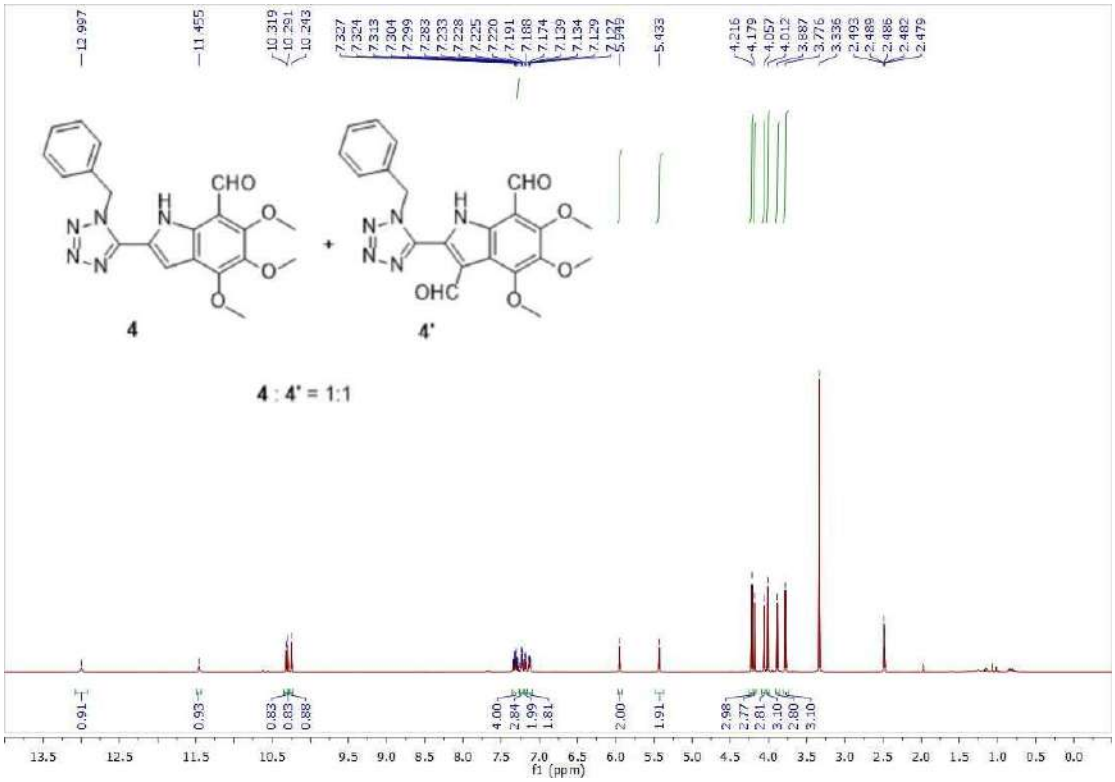

9.720
7.554
7.537
7.407
7.404
7.394
7.379
7.367
7.364
7.353
7.263
7.258
7.255
7.241
7.083
7.081
7.067
7.064
6.846
6.843
5.868
3.077
3.063
3.049
3.036
3.022
3.008
2.994
1.654
1.322
1.308
0.94
1.00
3.95
2.28
1.00
0.94
1.95
1.00
6.03
f1 (ppm)

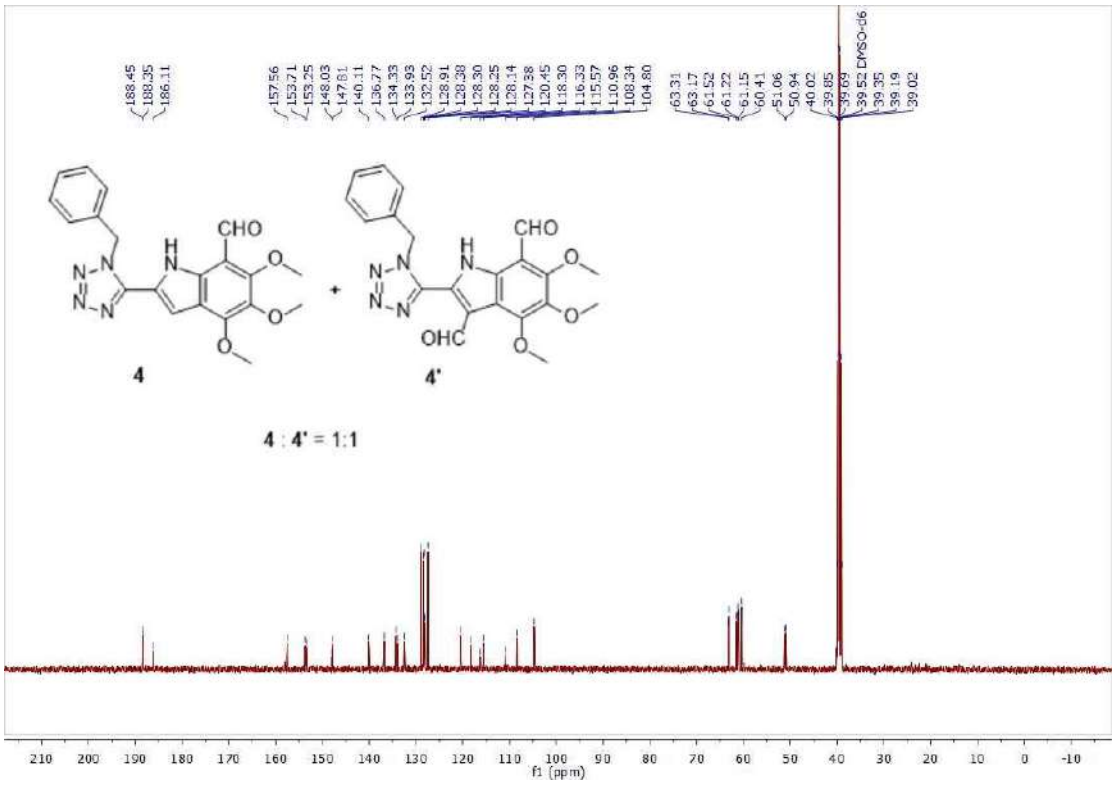

148.66
146.98
137.52
133.45
129.47
128.93
126.96
126.30
121.53
120.94
119.61
109.10
105.40
77.41
77.16 CDCl3-d
76.91
51.76
34.65
24.37
f1 (ppm)

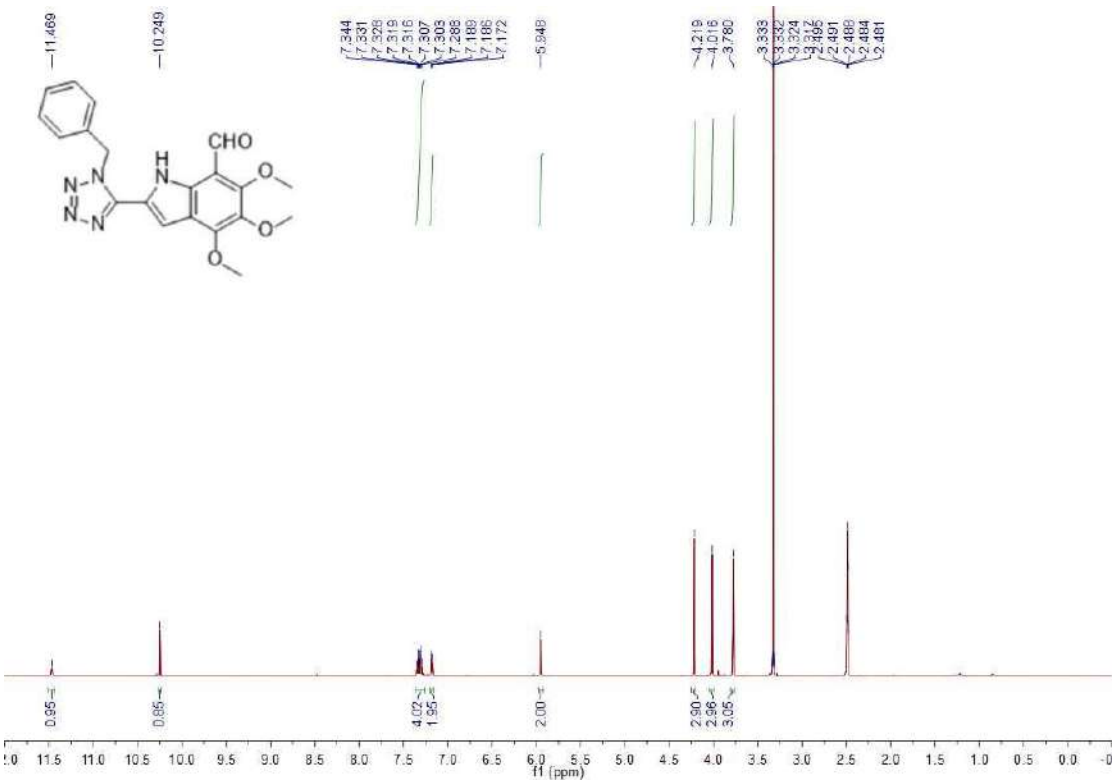

12.098
7.562
7.546
7.482
7.465
7.221
7.206
7.190
7.136
7.134
7.132
7.081
7.066
3.489
2.488
2.486
2.483
0.96
1.02
0.97
1.01
0.89
1.00
f1 (ppm)

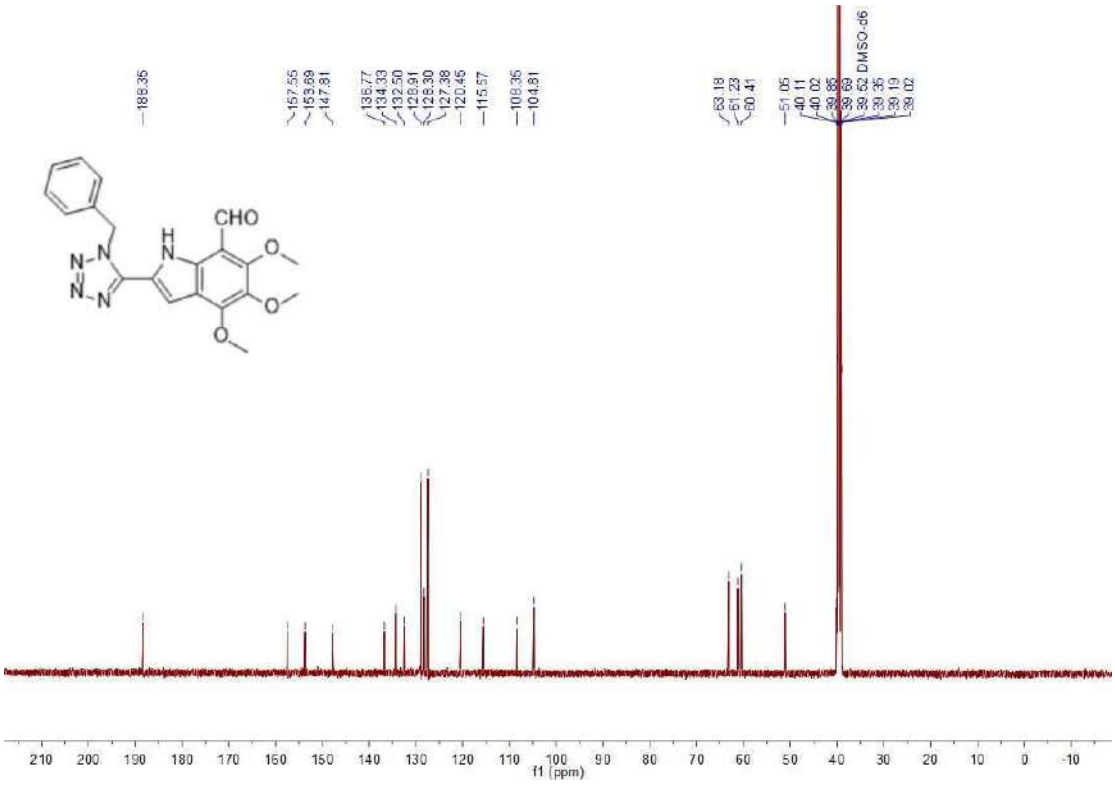

11.937
7.562
7.546
7.289
7.070
7.067
6.997
6.995
6.981
6.978
3.417
2.994
2.981
2.967
2.953
2.939
1.246
1.232
0.98
1.00
0.99
0.94
1.01
1.28
6.09
f1 (ppm)

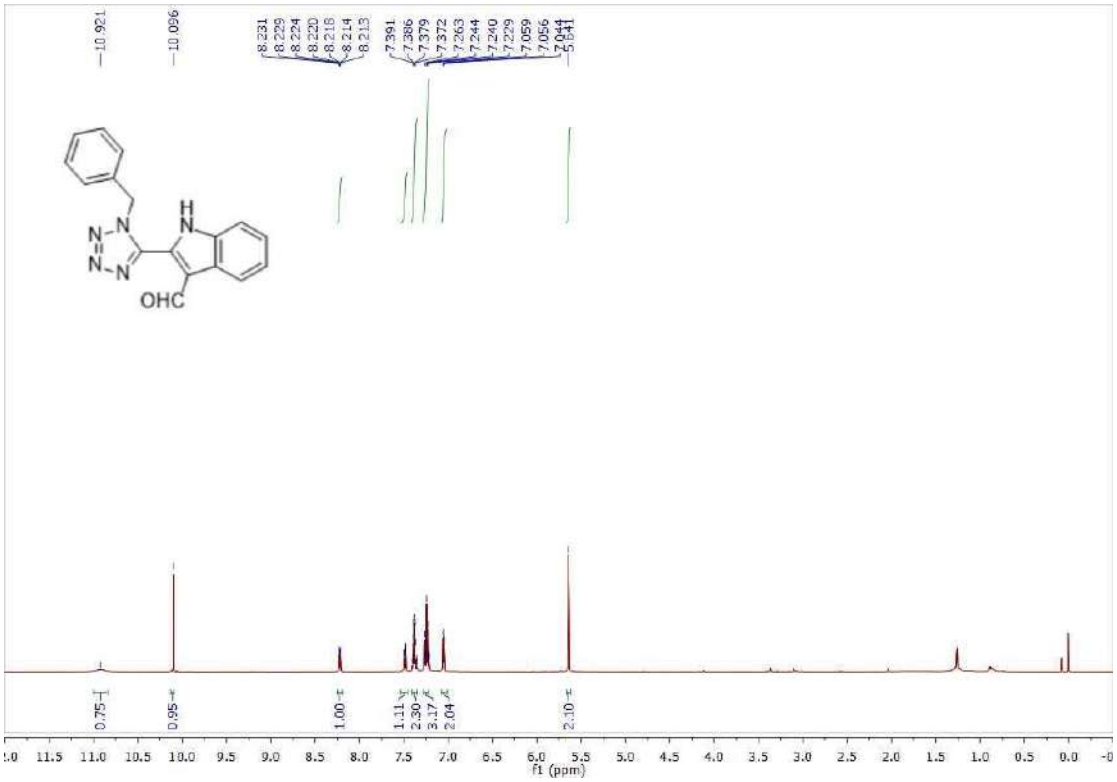

144.19
137.75
125.78
121.83
120.90
119.57
109.01
103.27
40.02
39.85
39.69
39.52 DMSO-d6
39.19
39.02
33.76
24.28
f1 (ppm)

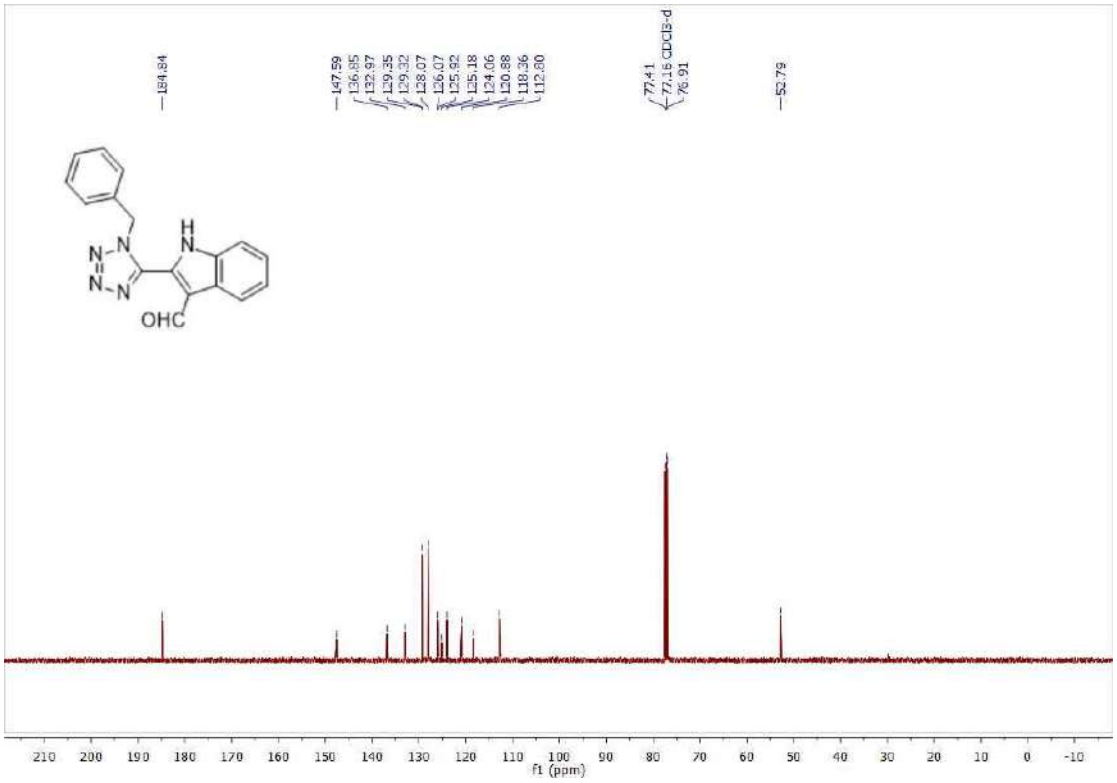

12.997
11.455
10.319
10.291
10.243
7.327
7.324
7.313
7.304
7.299
7.283
7.233
7.228
7.225
7.220
7.191
7.188
7.174
7.139
7.134
7.129
7.127
5.949
5.433
4.216
4.179
4.057
4.012
3.887
3.776
3.336
2.493
2.488
2.486
2.482
2.479
CHO
OHC
4
4'
4 : 4' = 1:1
0.91
0.93
0.83
0.83
0.88
4.00
2.84
1.99
1.81
2.00
1.91
2.98
2.77
2.81
3.10
2.80
3.10
f1 (ppm)

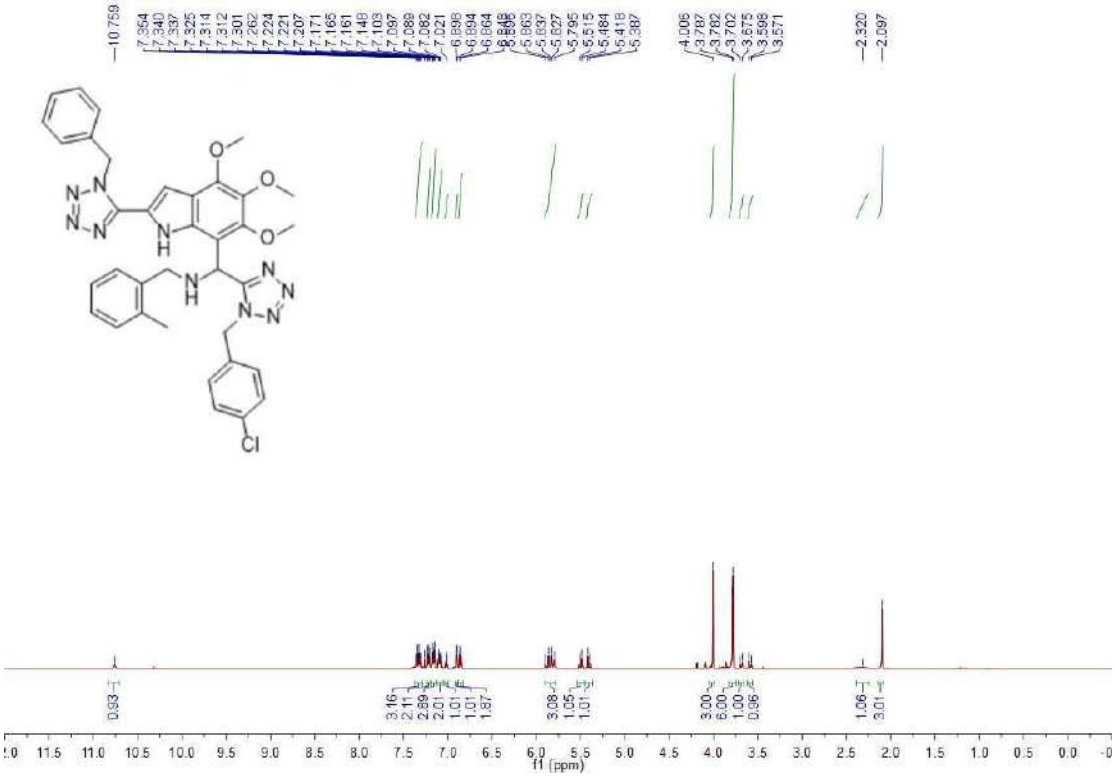

188.45
188.35
186.11
157.56
153.71
153.25
148.03
147.81
140.11
136.77
134.33
133.93
132.52
128.91
128.38
128.30
128.25
128.14
127.38
120.45
118.30
116.33
115.57
110.96
108.34
104.80
63.31
63.17
61.52
61.22
61.15
60.41
51.06
50.94
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
CHO
OHC
4
4'
4 : 4' = 1:1
f1 (ppm)

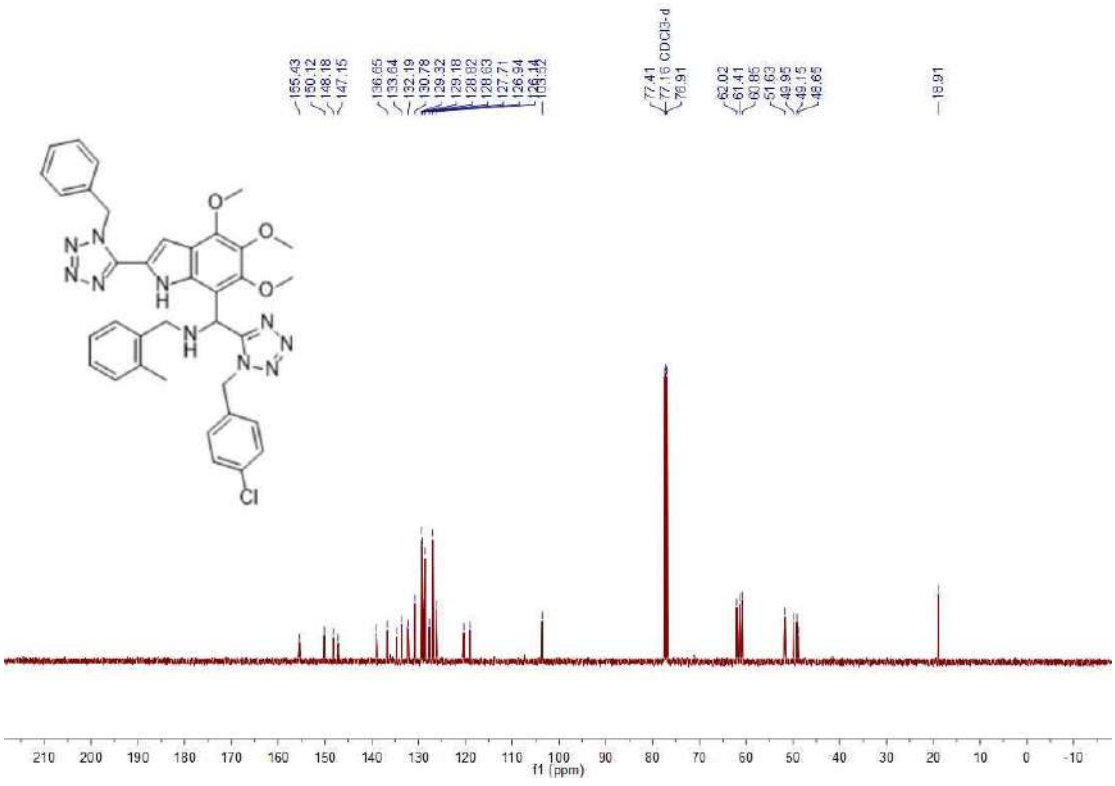

11.469
10.249
7.344
7.331
7.328
7.319
7.316
7.307
7.303
7.288
7.189
7.186
7.172
5.848
4.219
4.016
3.780
3.333
3.332
3.324
3.312
2.495
2.491
2.488
2.484
2.481
CHO
H
N
O
0.95
0.85
4.02
1.95
2.00
2.90
2.96
3.05
f1 (ppm)

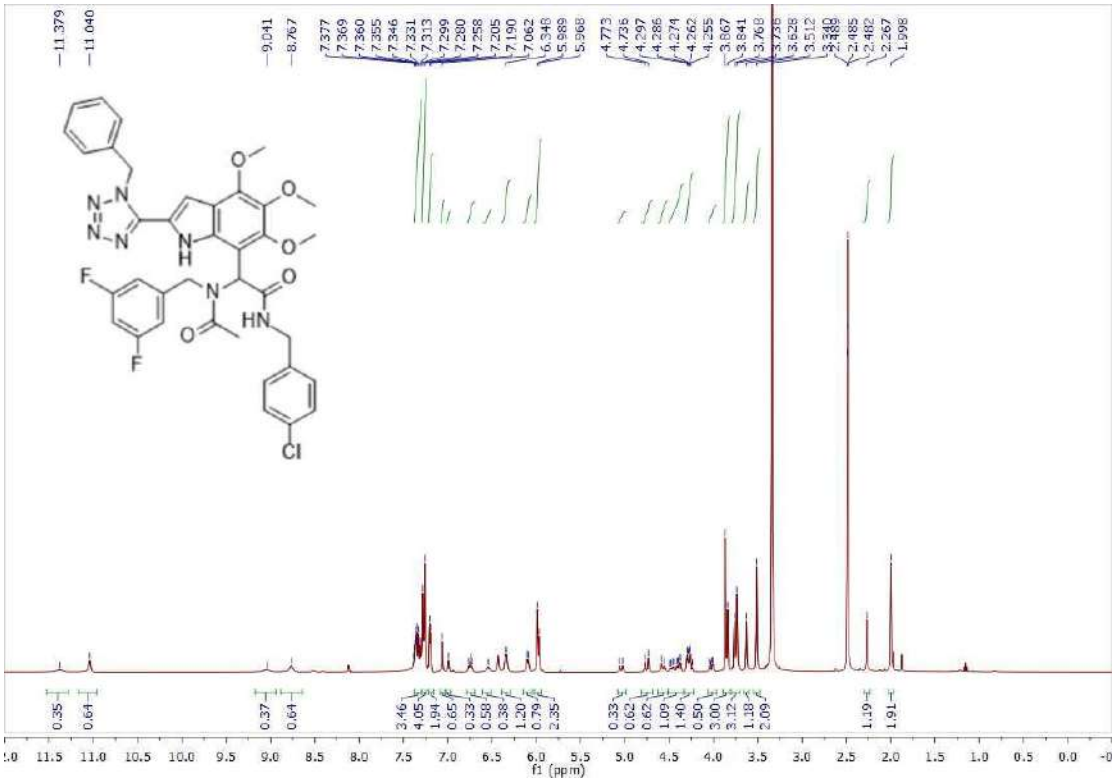

188.35
157.55
153.69
147.81
136.77
134.33
132.50
129.91
128.30
127.38
120.45
115.57
108.35
104.81
63.18
61.23
60.41
51.05
40.11
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
CHO
H
N
O
f1 (ppm)

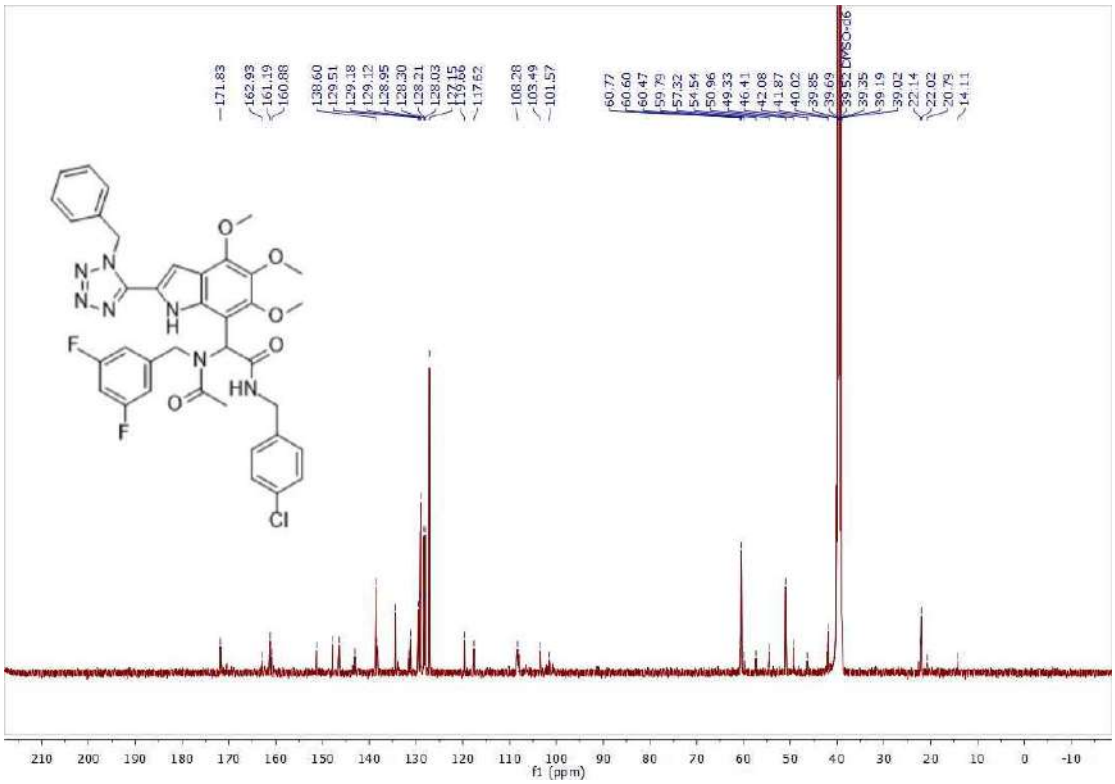

10.921
10.096
8.231
8.229
8.224
8.220
8.218
8.214
8.213
7.391
7.386
7.379
7.372
7.263
7.244
7.240
7.229
7.059
7.056
7.044
5.841
OHC
0.75
0.95
1.00
1.11
2.30
3.17
2.04
2.10
f1 (ppm)

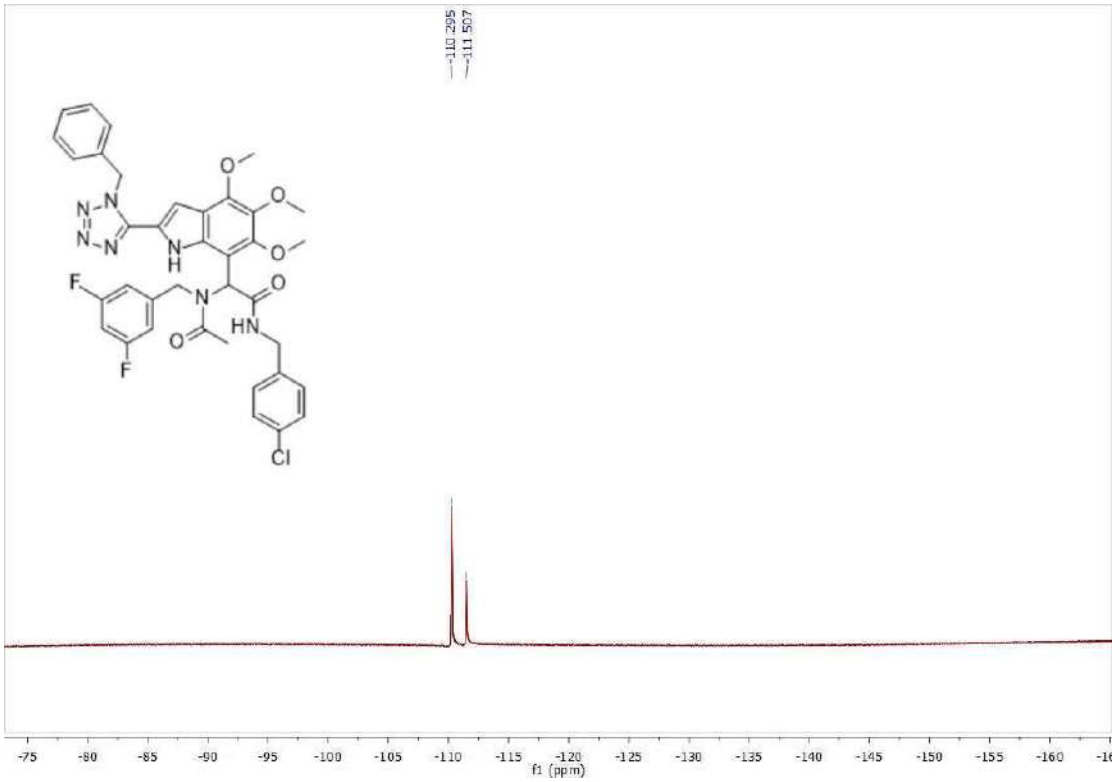

184.84
147.59
136.85
132.97
129.35
129.32
128.07
126.07
125.92
125.18
124.06
120.88
118.36
112.80
77.41
77.16 CDCl3-d
76.91
52.79
OHC
f1 (ppm)

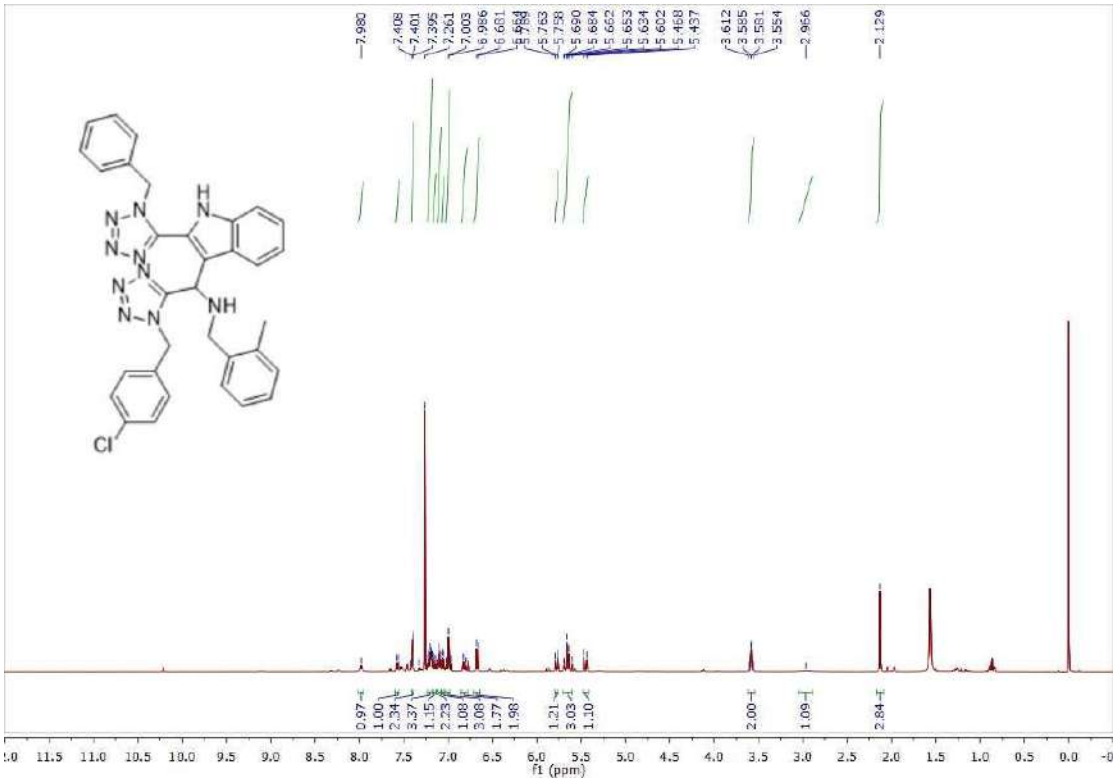

10.759
7.354
7.340
7.337
7.325
7.314
7.312
7.301
7.262
7.224
7.221
7.207
7.171
7.165
7.161
7.148
7.103
7.097
7.089
7.082
7.021
6.898
6.894
6.864
5.863
5.837
5.827
5.795
5.515
5.484
5.418
5.387
4.006
3.787
3.782
3.702
3.675
3.598
3.571
2.320
2.097
Cl
0.93
3.16
2.11
2.89
2.01
1.01
1.01
1.87
3.08
1.05
1.01
3.00
6.00
1.00
0.96
1.06
3.01
f1 (ppm)

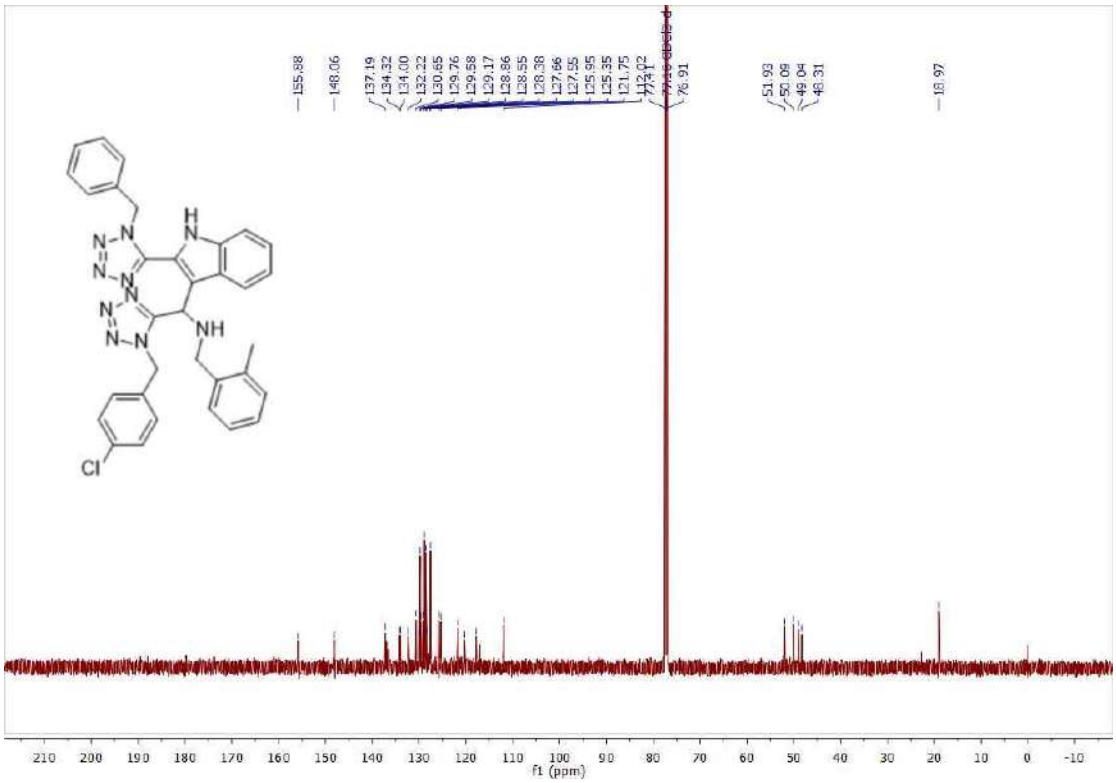

155.43
150.12
148.18
147.15
136.65
133.64
132.19
130.78
129.32
129.18
128.82
128.63
127.71
126.94
77.41
77.16 CDCl3-d
76.91
62.02
61.41
60.85
51.63
49.95
49.15
48.65
18.91
Cl
f1 (ppm)

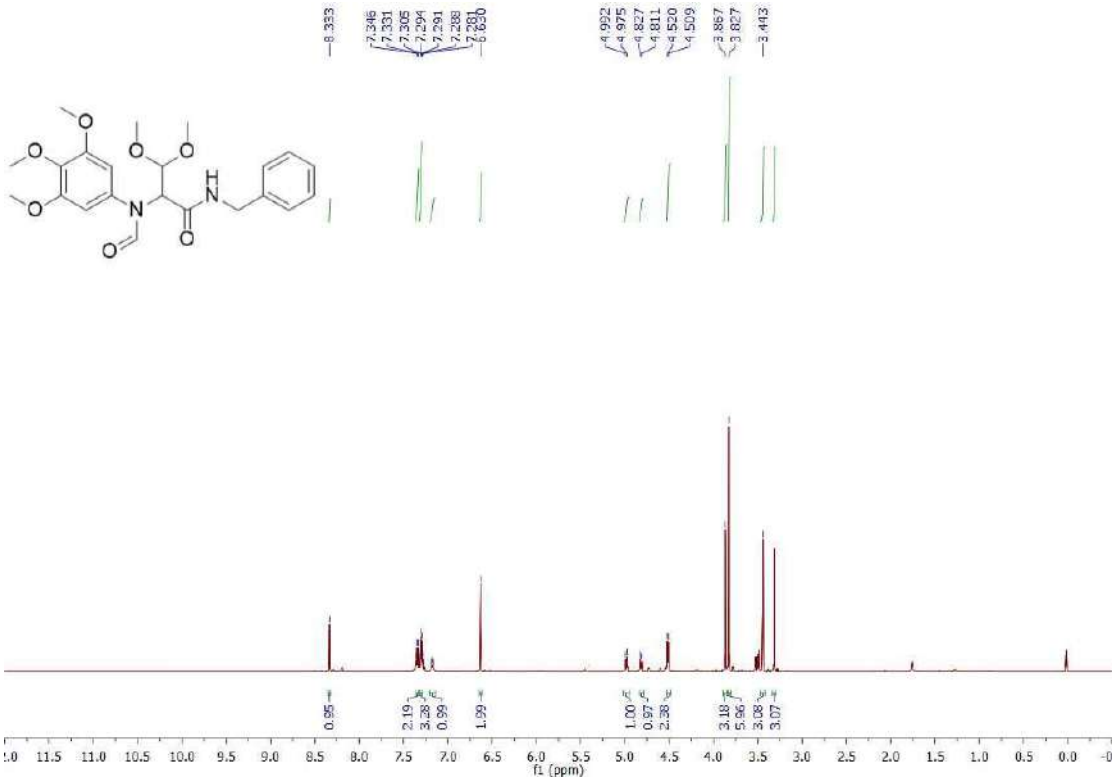

11.379
11.040
9.041
8.767
7.377
7.369
7.360
7.355
7.346
7.331
7.313
7.299
7.280
7.258
7.205
7.190
7.062
6.348
5.989
5.968
4.773
4.736
4.297
4.286
4.274
4.262
4.255
3.867
3.841
3.768
3.736
3.628
3.512
3.349
2.485
2.482
2.267
1.998
0.35
0.64
0.37
0.64
3.46
4.05
1.94
0.65
0.33
0.58
0.38
1.20
0.79
2.35
0.33
0.62
0.62
1.09
1.40
0.50
3.00
3.12
1.18
2.09
1.19
1.91
f1 (ppm)

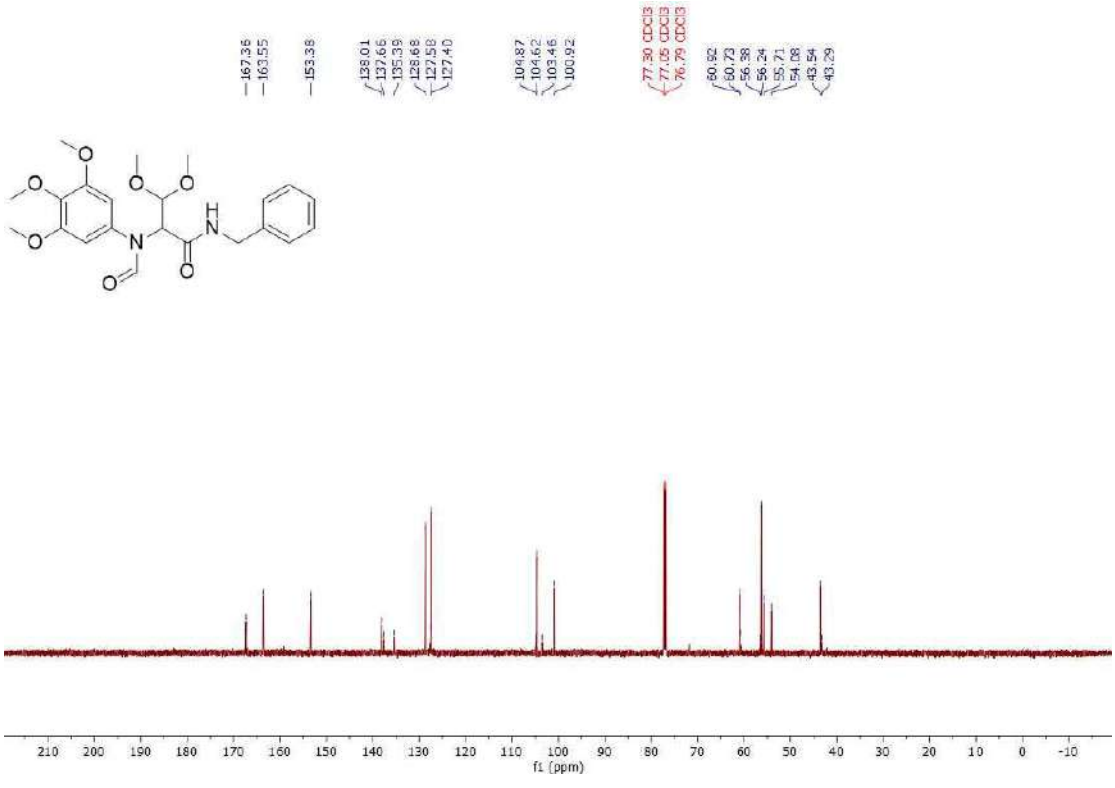

171.83
162.93
161.19
160.88
138.60
129.51
129.18
129.12
128.95
128.30
128.21
128.03
117.62
108.28
103.49
101.57
60.77
60.60
60.47
59.79
57.32
54.54
50.96
49.33
46.41
42.08
41.87
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
22.14
22.02
20.79
14.11
f1 (ppm)

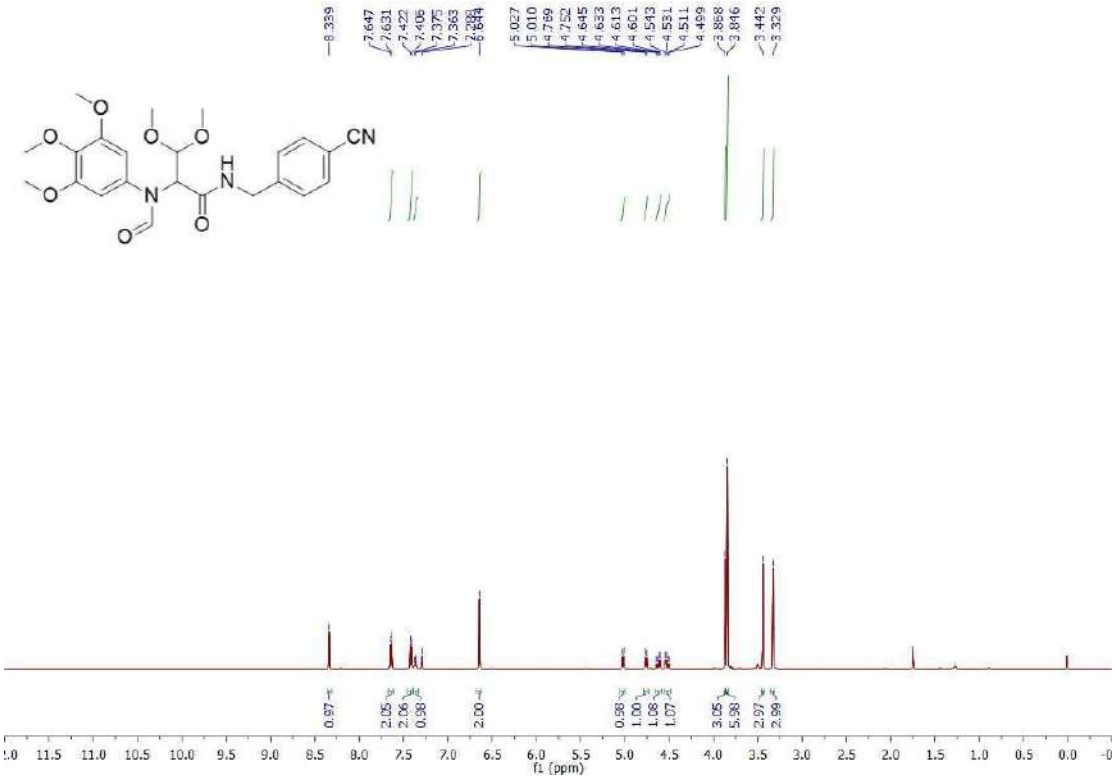

-110.295
-111.507
F
F
N
N
N
N
H
O
O
O
N
O
HN
O
Cl
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
f1 (ppm)

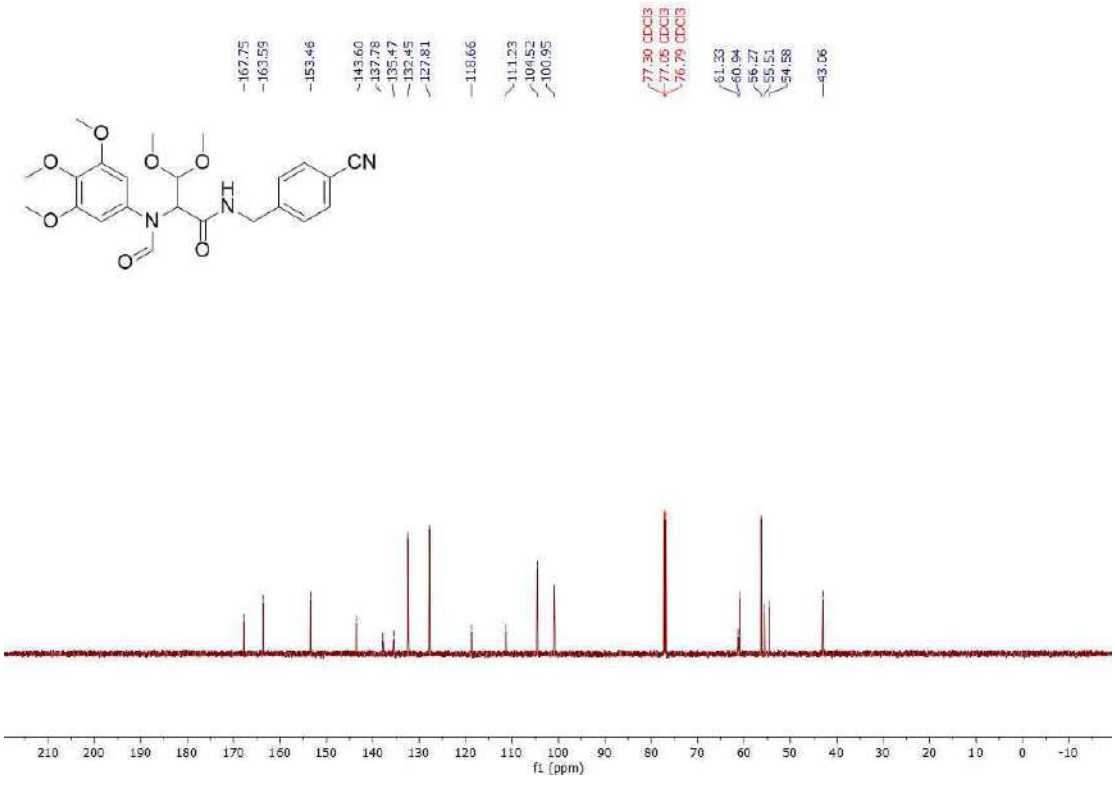

7.980
7.408
7.401
7.395
7.261
7.003
6.996
6.681
5.763
5.758
5.690
5.684
5.662
5.653
5.634
5.622
5.458
5.437
3.612
3.585
3.581
3.554
2.956
2.129
NH
Cl
0.97
1.00
2.34
3.37
1.15
2.23
1.08
3.08
1.77
1.98
1.21
3.03
1.10
2.00
1.09
2.84
f1 (ppm)

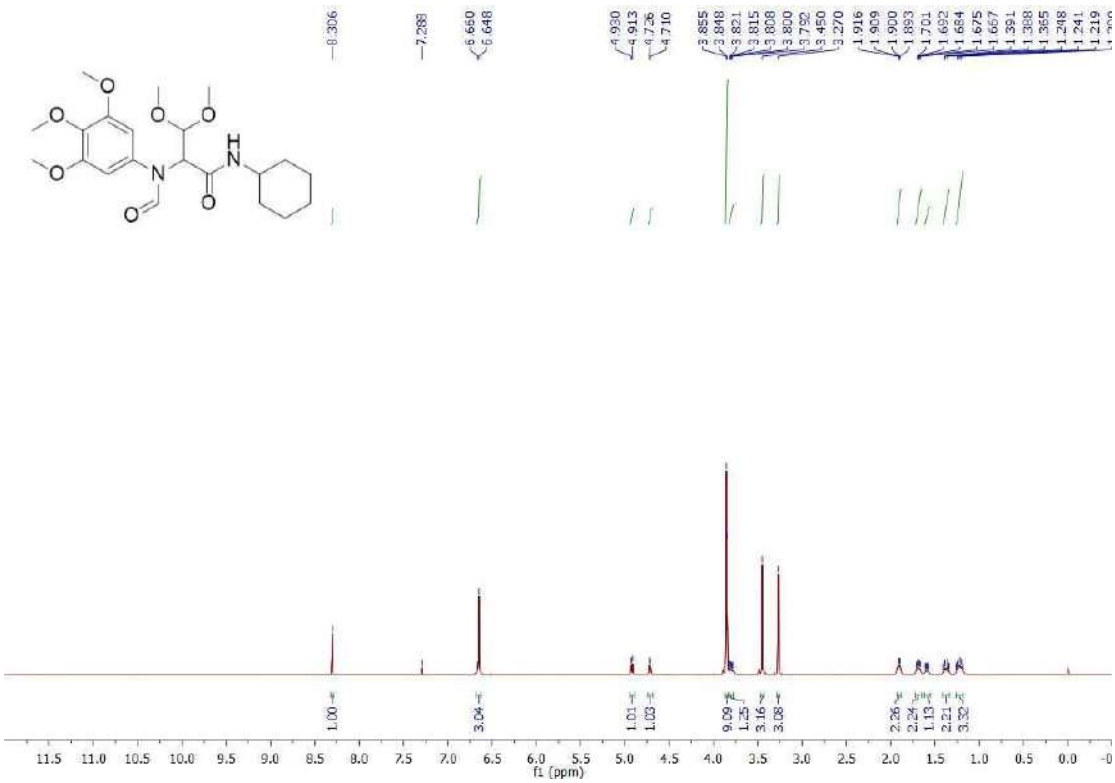

155.88
148.06
137.19
134.32
134.00
132.22
130.65
129.76
129.58
129.17
128.86
128.55
128.38
127.66
127.55
125.95
125.35
121.75
112.02
77.41
76.91
51.93
50.06
49.04
48.31
18.97
NH
Cl
f1 (ppm)

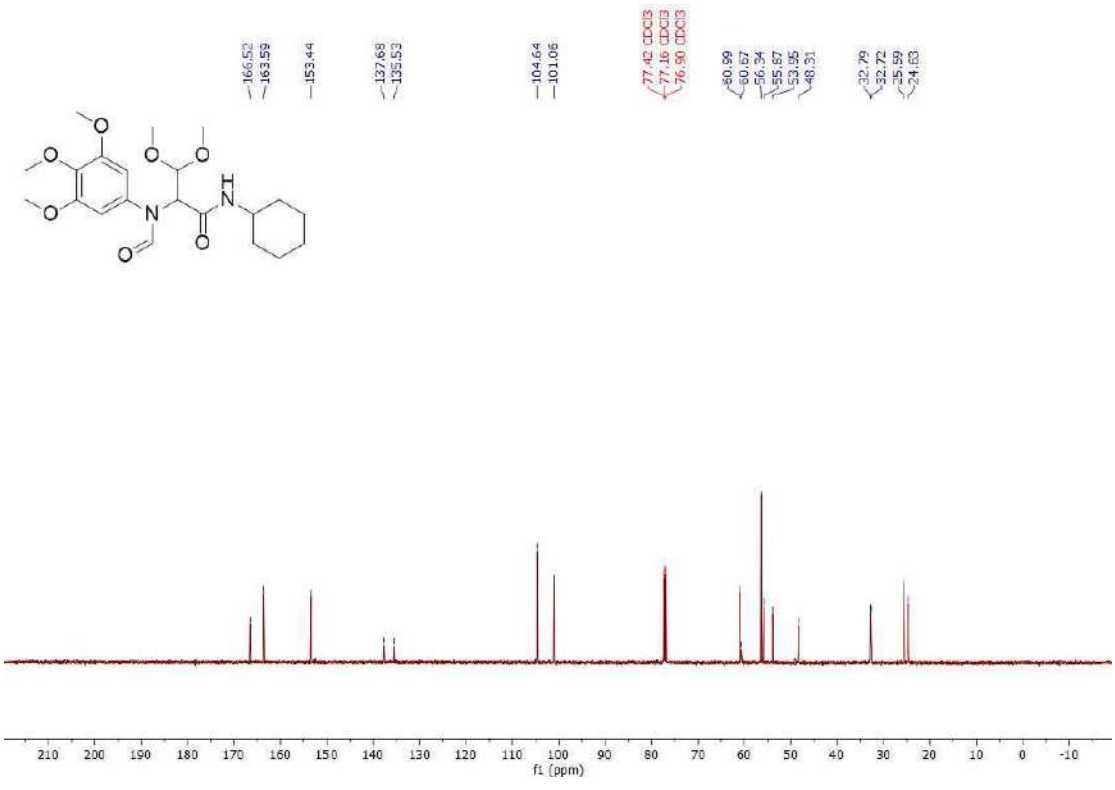

8.333
7.346
7.331
7.305
7.294
7.291
7.288
7.281
6.630
4.992
4.975
4.827
4.811
4.520
4.509
3.867
3.827
3.443
0.95
2.19
3.28
0.99
1.99
1.00
0.97
2.38
3.18
5.96
3.08
3.07
f1 (ppm)


167.36
163.55
153.38
138.01
137.66
135.39
128.68
127.58
127.40
104.87
104.62
103.46
100.92
77.30 CDCl3
77.05 CDCl3
76.79 CDCl3
60.92
60.73
56.38
56.24
55.71
54.08
43.54
43.29
f1 (ppm)


8.339
7.647
7.631
7.422
7.406
7.375
7.363
7.288
7.284
5.027
5.010
4.799
4.752
4.645
4.633
4.613
4.601
4.543
4.531
4.511
4.499
3.868
3.846
3.442
3.329
CN
0.97
2.05
2.06
0.98
2.00
0.98
1.00
1.08
1.07
3.05
5.98
2.97
2.99
f1 (ppm)


167.75
163.59
153.46
143.60
137.78
135.47
132.45
127.81
118.66
111.23
104.52
100.95
77.30 CDCl3
77.05 CDCl3
76.79 CDCl3
61.33
60.94
56.27
55.51
54.58
43.06
CN
f1 (ppm)


8.306
7.288
6.660
6.648
4.930
4.913
4.726
4.710
3.855
3.848
3.821
3.815
3.808
3.800
3.792
3.450
3.270
1.916
1.909
1.900
1.893
1.701
1.692
1.684
1.675
1.657
1.391
1.388
1.365
1.248
1.241
1.219
1.00
3.04
1.01
1.03
9.09
1.25
3.16
3.08
2.26
2.24
1.13
2.21
3.32
f1 (ppm)


166.52
163.59
153.44
137.68
135.53
104.64
101.06
77.42 CDCl3
77.16 CDCl3
76.90 CDCl3
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53.95
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32.72
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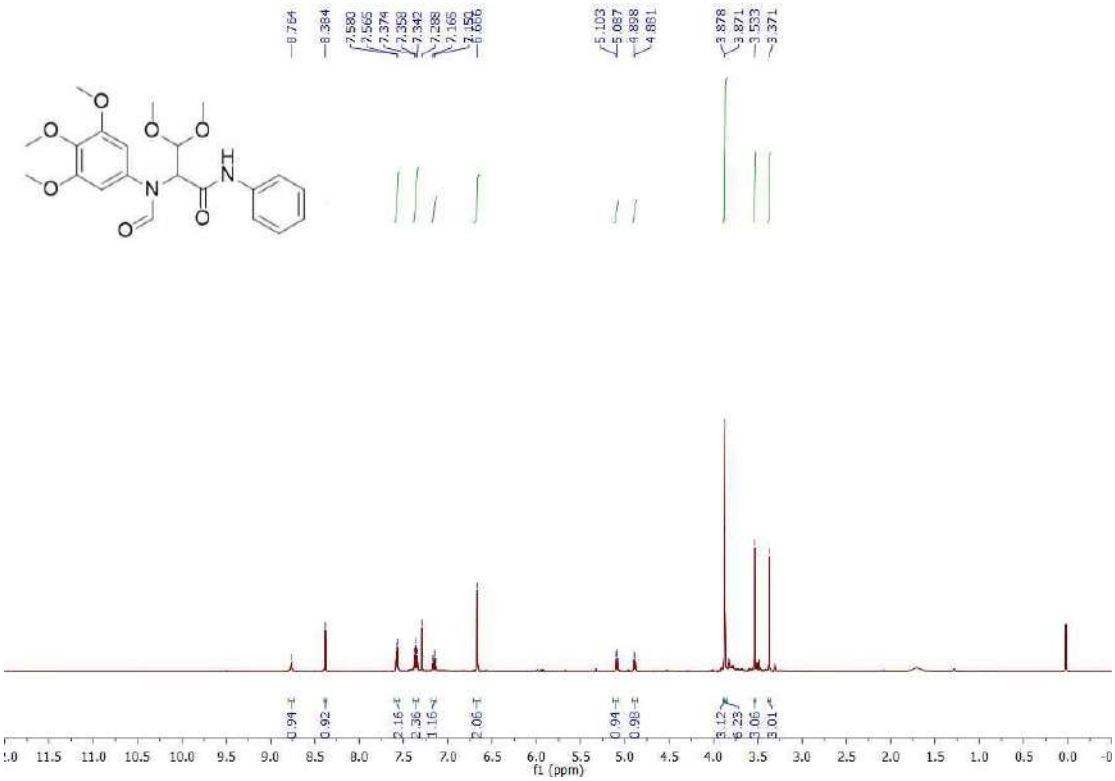
24.63
f1 (ppm)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5.087
4.898
4.881
3.878
3.871
3.533
3.371
0.94
0.92
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1.16
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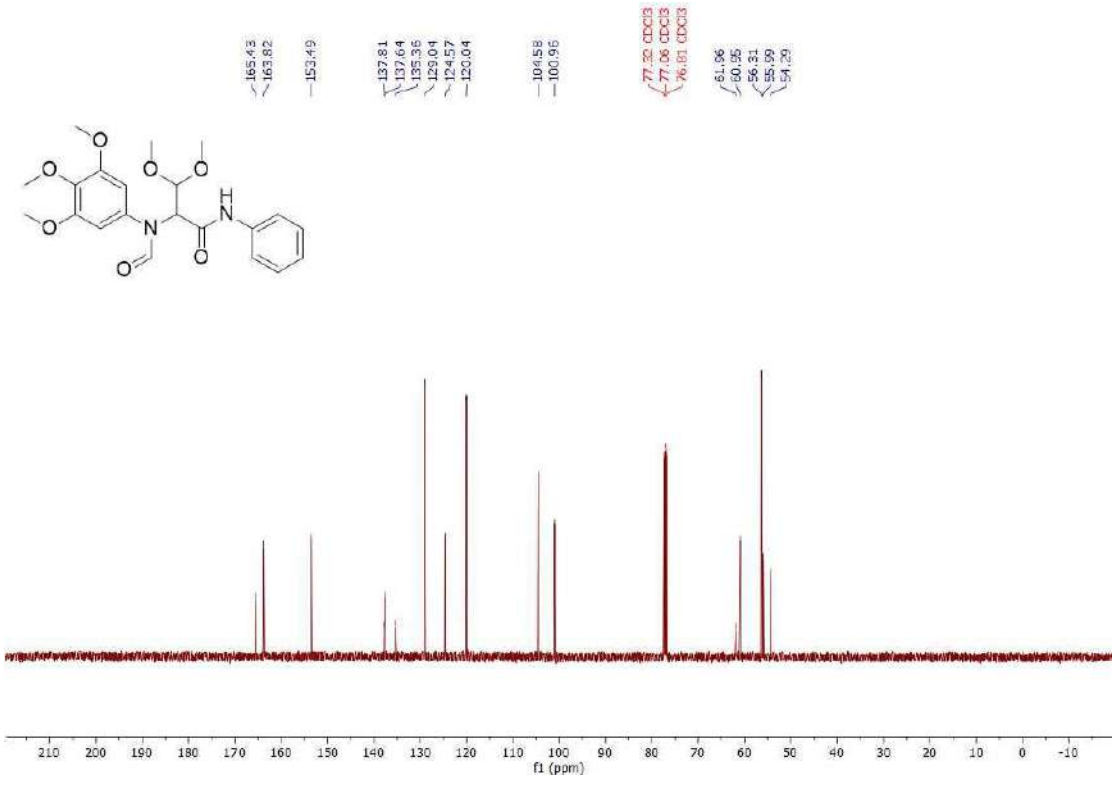
3.01
f1 (ppm)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135.36
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124.57
120.04
104.58
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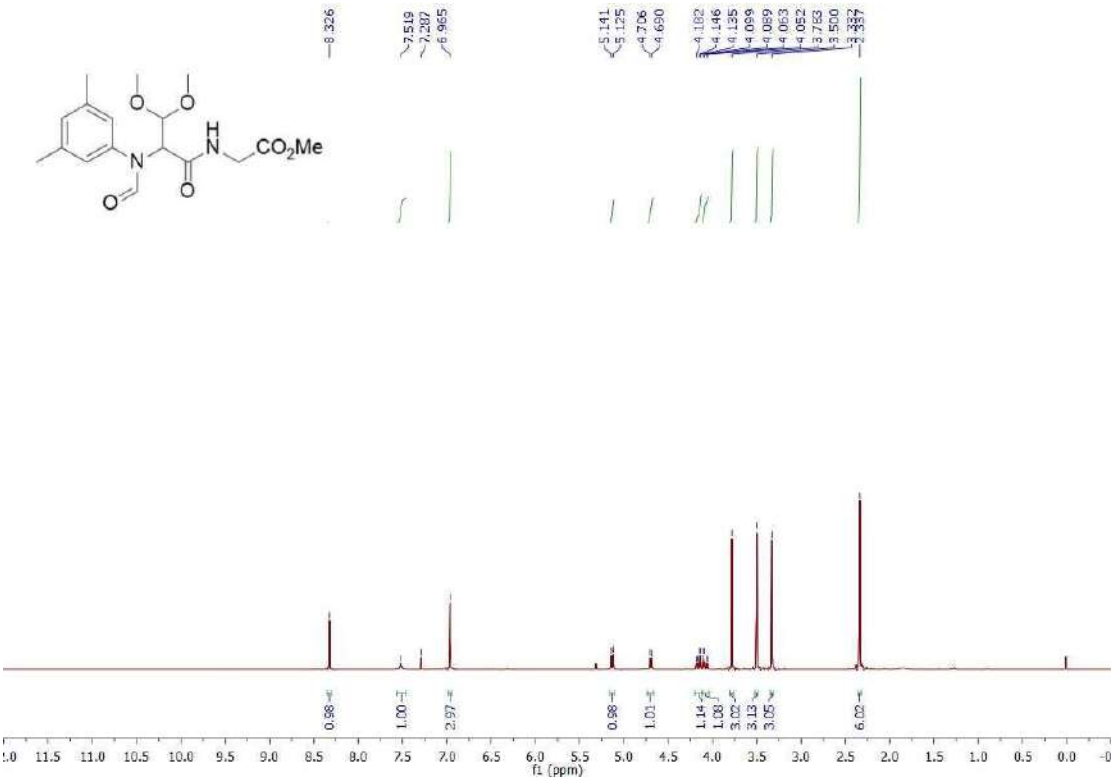
54.29
f1 (ppm)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4.089
4.063
4.052
3.783
3.500
3.332
3.317
CO2Me
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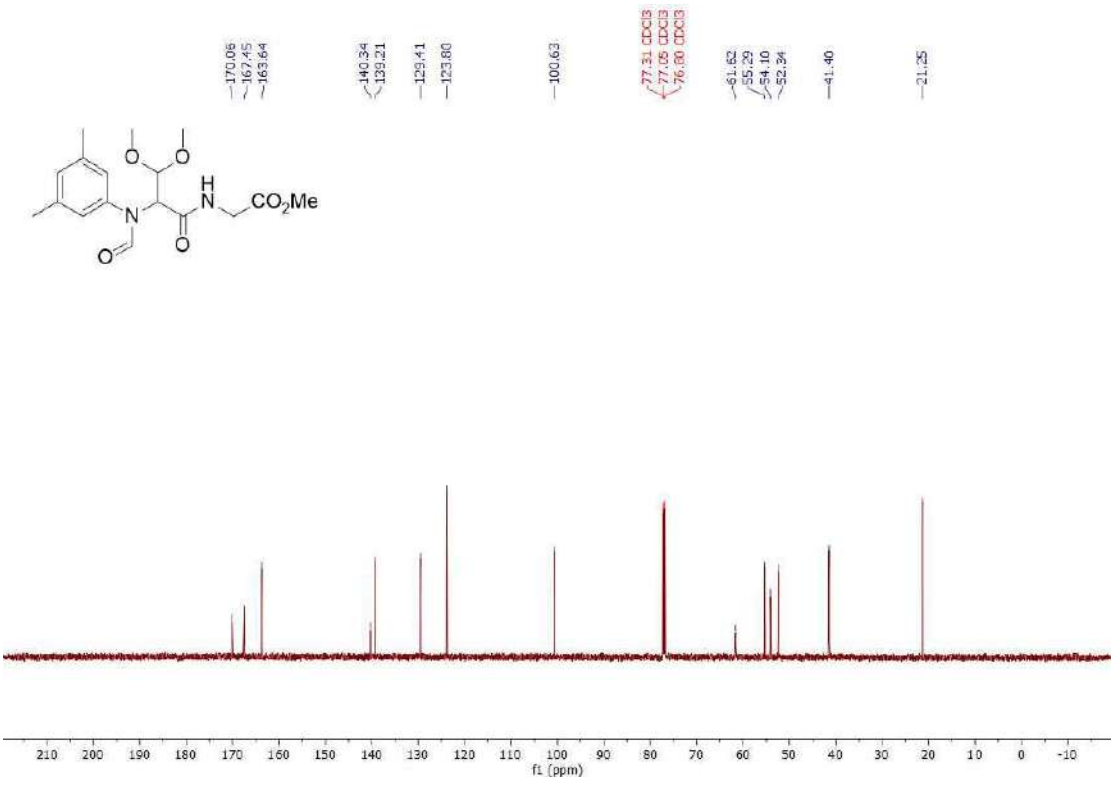
1.01
1.14
1.08
3.02
3.13
3.05
6.02
f1 (ppm)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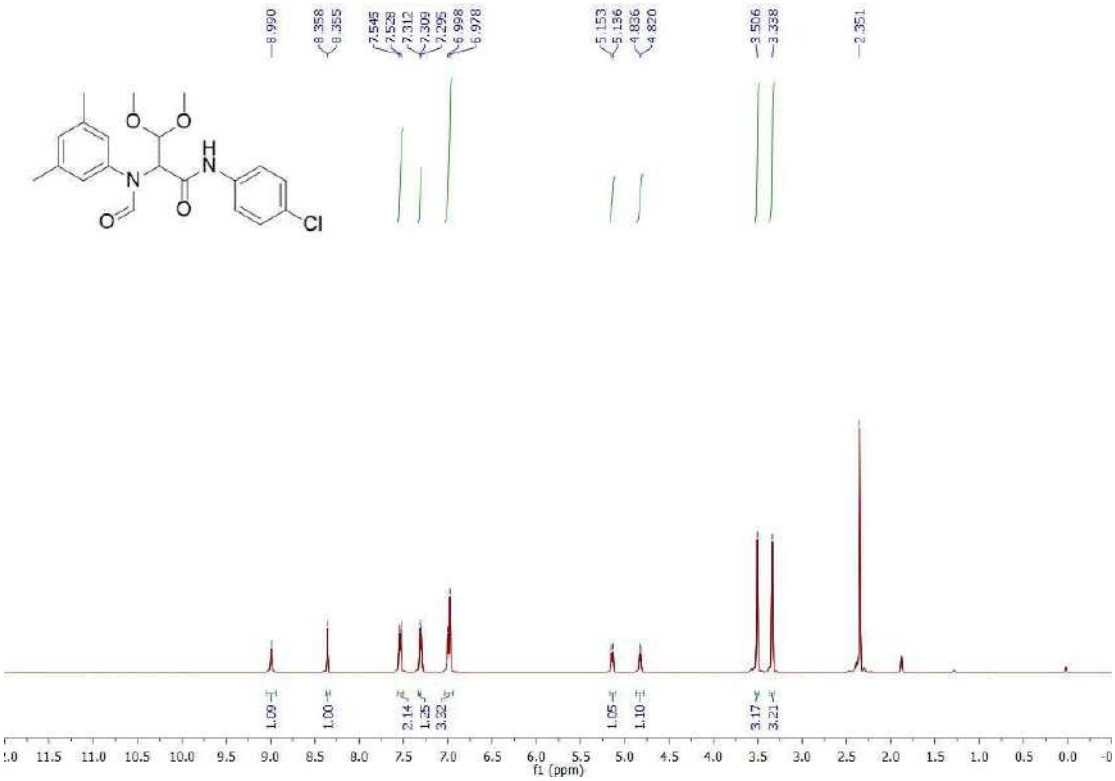
CO2Me
f1 (ppm)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5.136
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4.820
3.506
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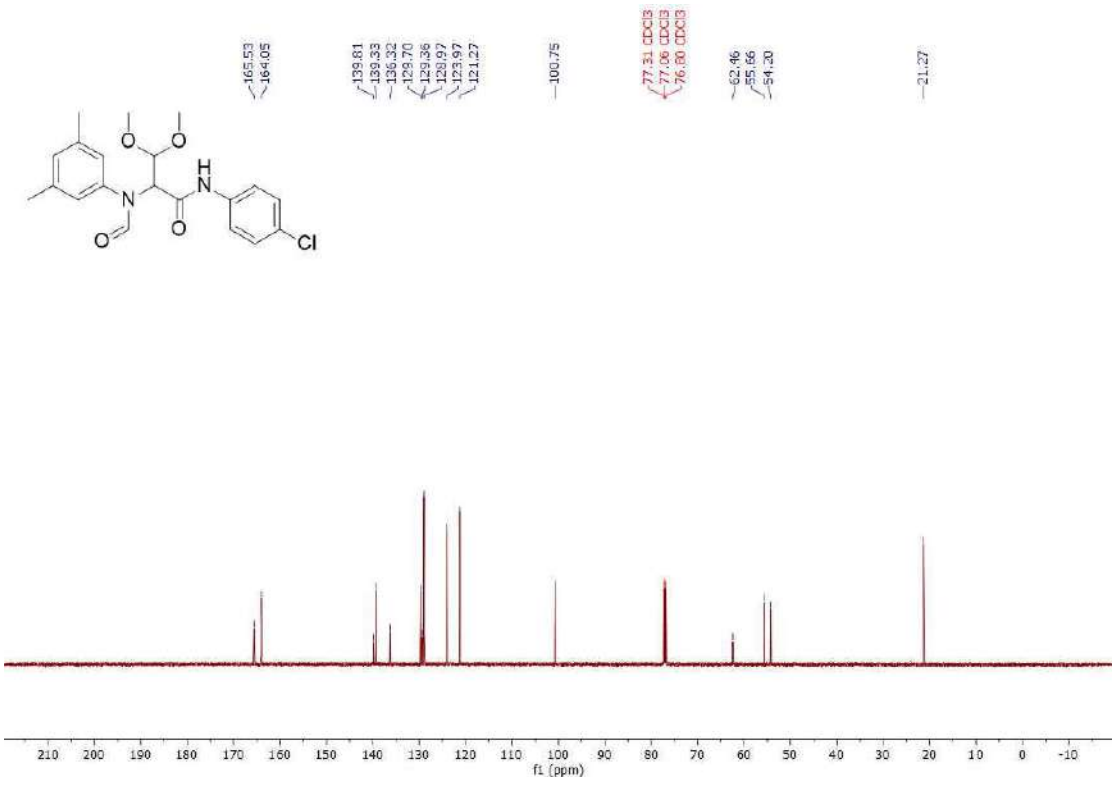
3.32
1.05
1.10
3.17
3.21
f1 (ppm)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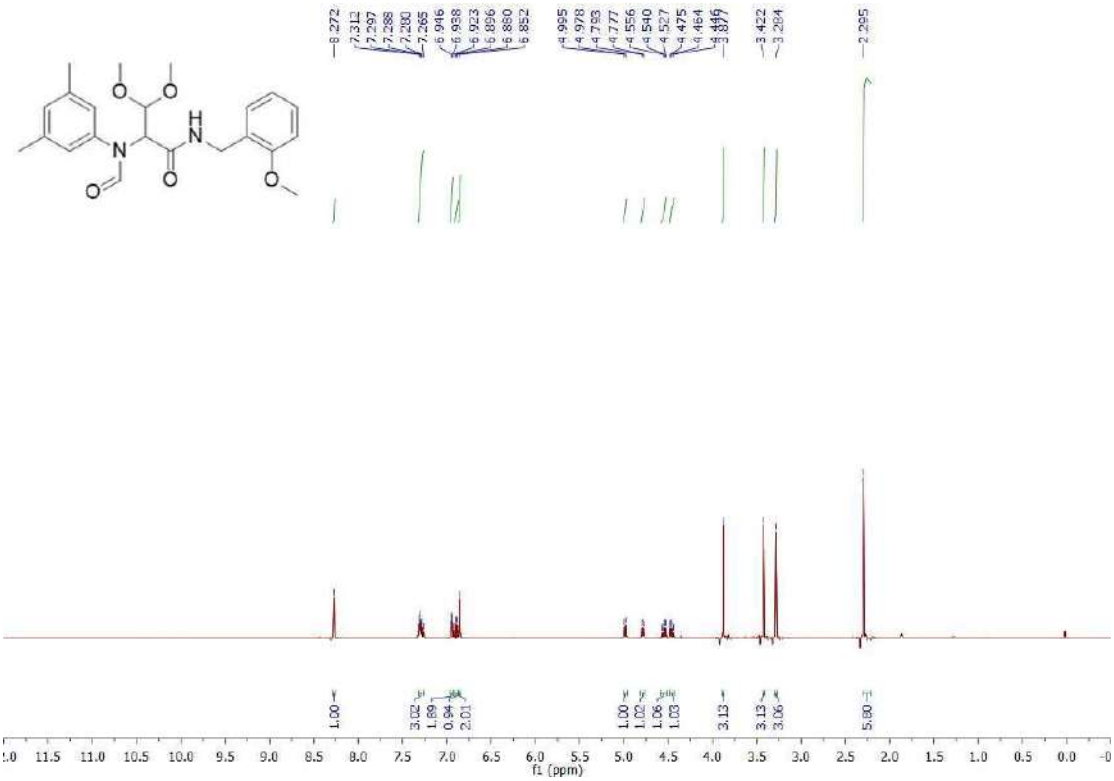
77.06 CDCl3
76.80 CDCl3
62.46
55.66
54.20
21.27
f1 (ppm)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6.852
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4.978
4.793
4.777
4.556
4.540
4.527
4.475
4.464
3.422
3.284
2.295
1.00
3.02
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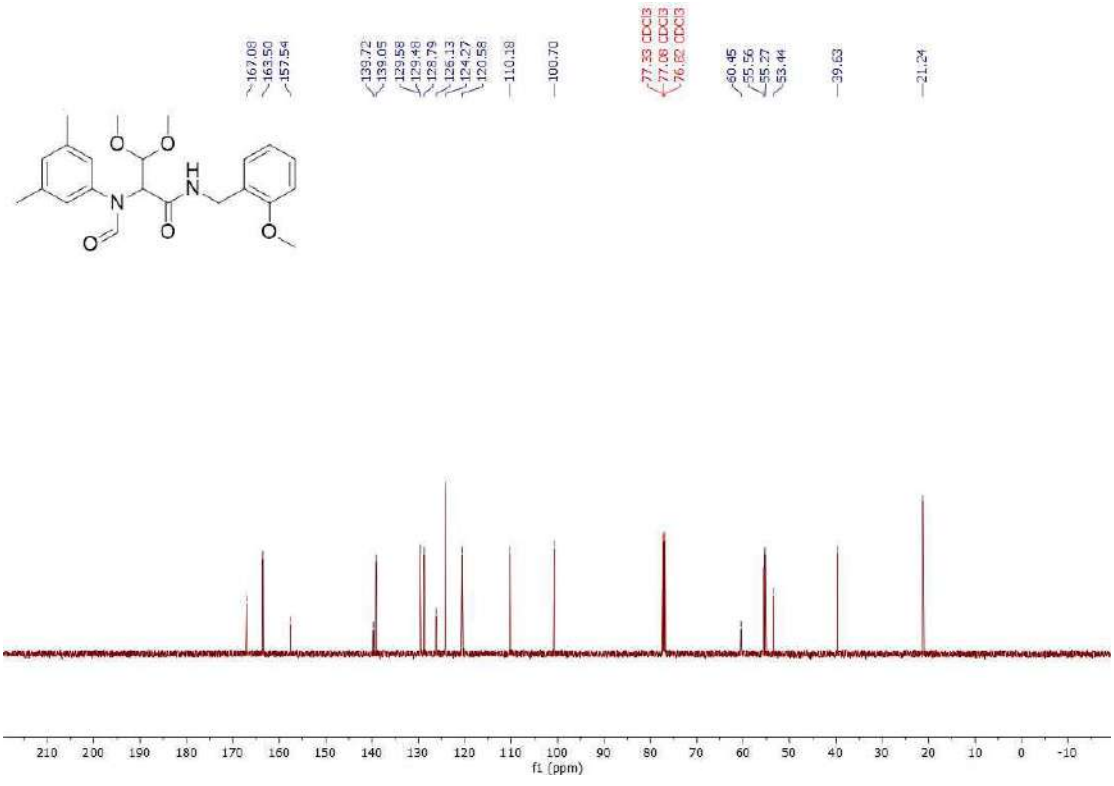
3.13
3.06
5.80
f1 (ppm)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129.58
129.48
128.79
126.13
124.27
120.58
110.18
100.70
77.33 CDCl3
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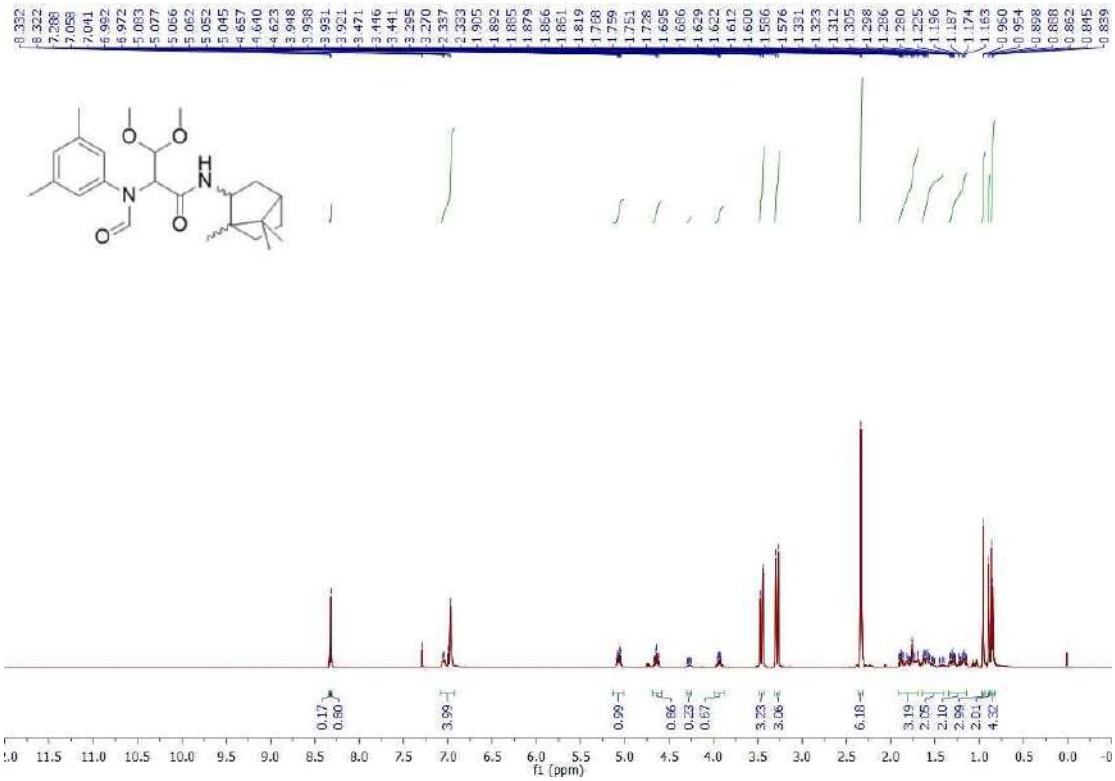
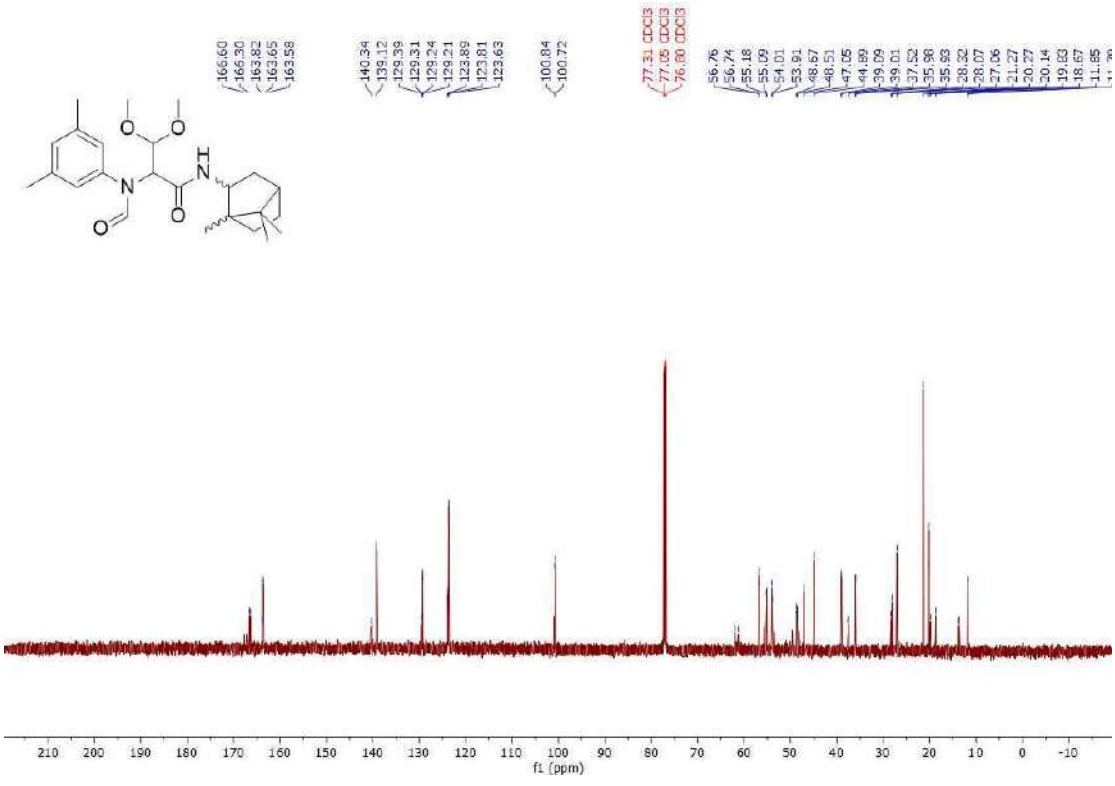
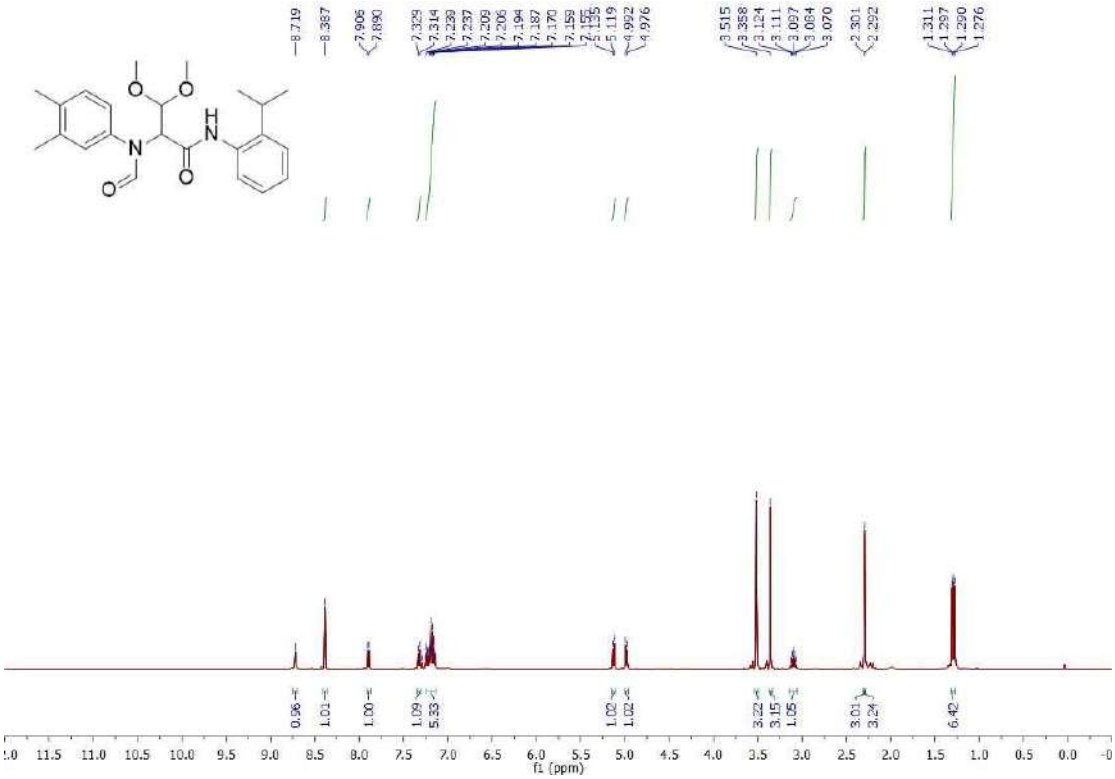
76.82 CDCl3
60.45
55.56
55.27
53.44
39.63
21.24
f1 (ppm)



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7.237
7.209
7.206
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7.187
7.170
7.159
7.155
7.135
5.119
4.992
4.976
3.515
3.358
3.124
3.111
3.097
3.084
3.070
2.301
2.292
1.311
1.297
1.290
1.276
0.96
1.01
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1.09
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1.02
1.02
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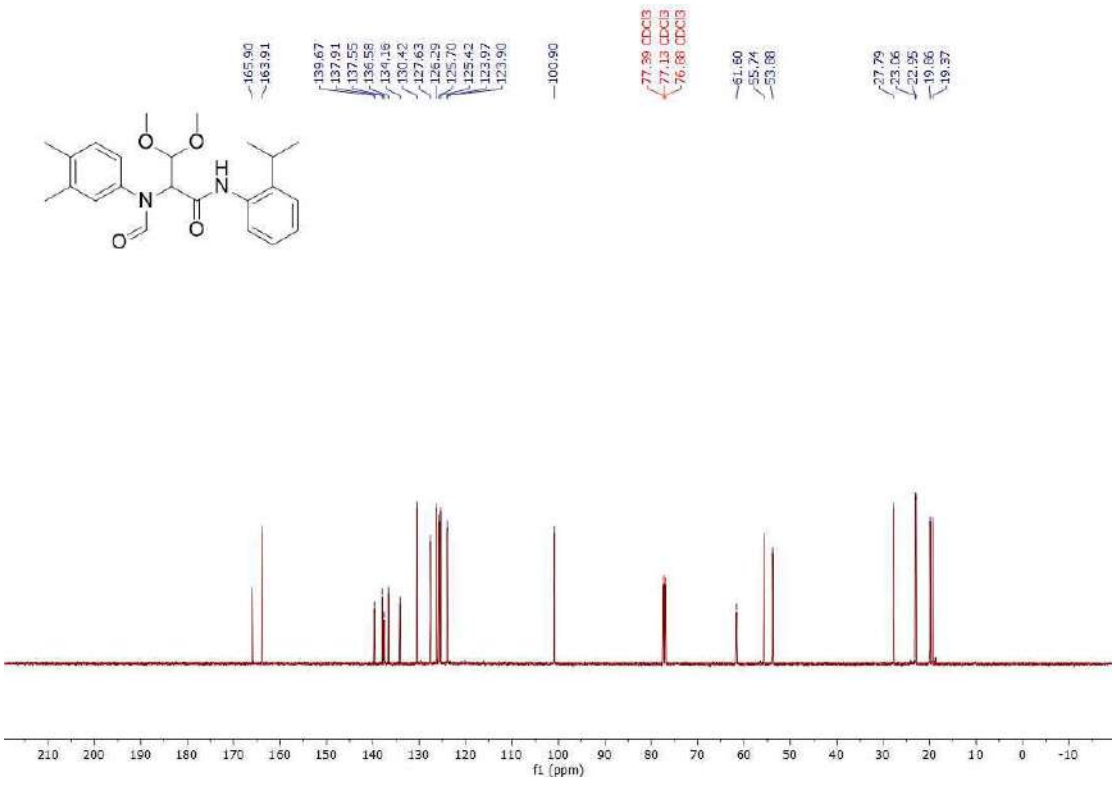
1.05
3.01
3.24
6.42
f1 (ppm)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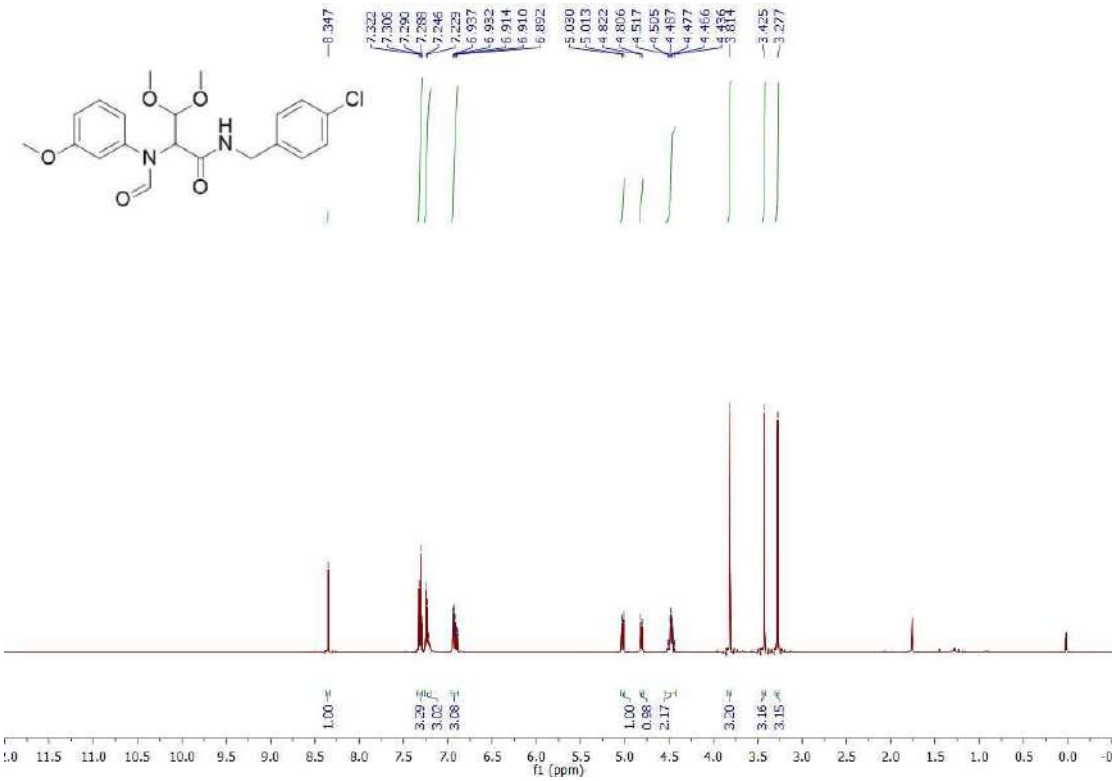
136.58
134.16
130.42
127.63
126.29
125.70
125.42
123.97
123.90
100.90
77.39 CDCl3
77.13 CDCl3
76.88 CDCl3
61.80
55.74
53.88
27.79
23.06
22.95
19.86
19.37
f1 (ppm)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7.290
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7.246
7.229
6.937
6.932
6.914
6.910
6.892
5.030
5.013
4.822
4.806
4.517
4.505
4.487
4.477
4.466
3.814
3.425
3.277
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3.08
1.00
0.88
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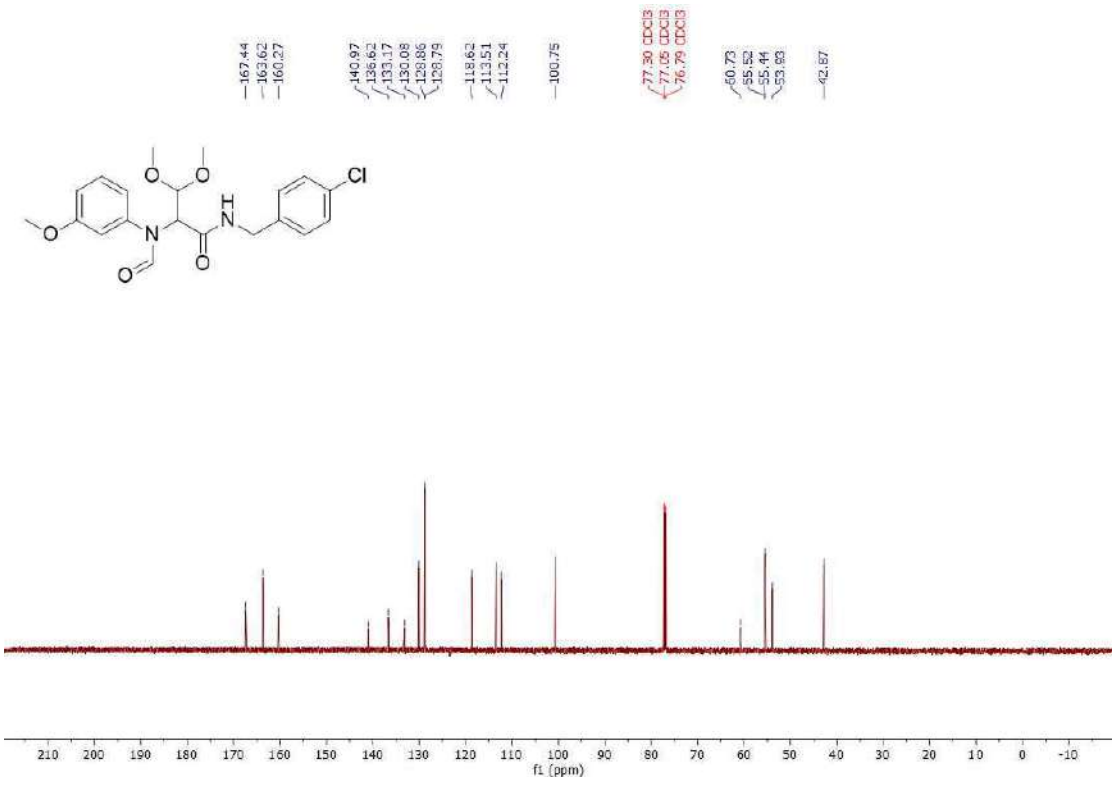
3.20
3.16
3.15
f1 (ppm)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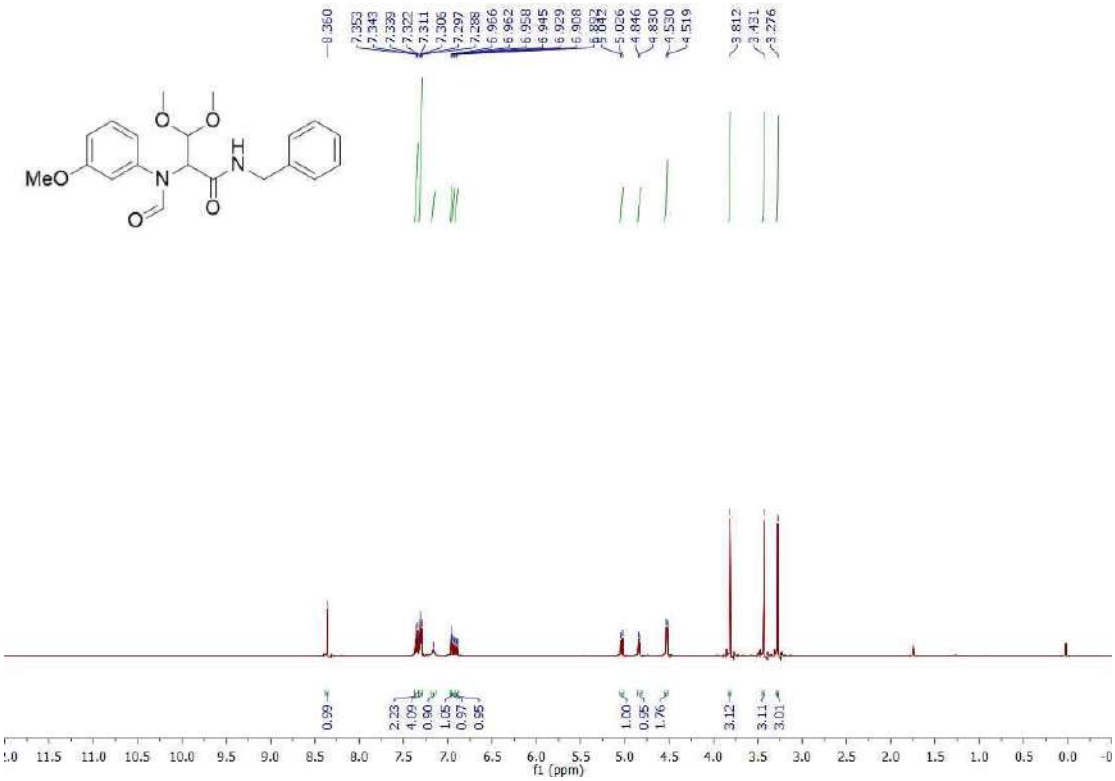
136.62
133.17
130.08
129.86
128.79
118.62
113.51
112.24
100.75
77.30 CDCl3
77.05 CDCl3
76.79 CDCl3
60.73
55.52
55.44
53.93
42.87
Cl
f1 (ppm)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6.962
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6.945
6.929
6.908
5.842
5.026
4.846
4.830
4.530
4.519
3.812
3.431
3.276
MeO
0.99
2.23
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0.97
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1.00
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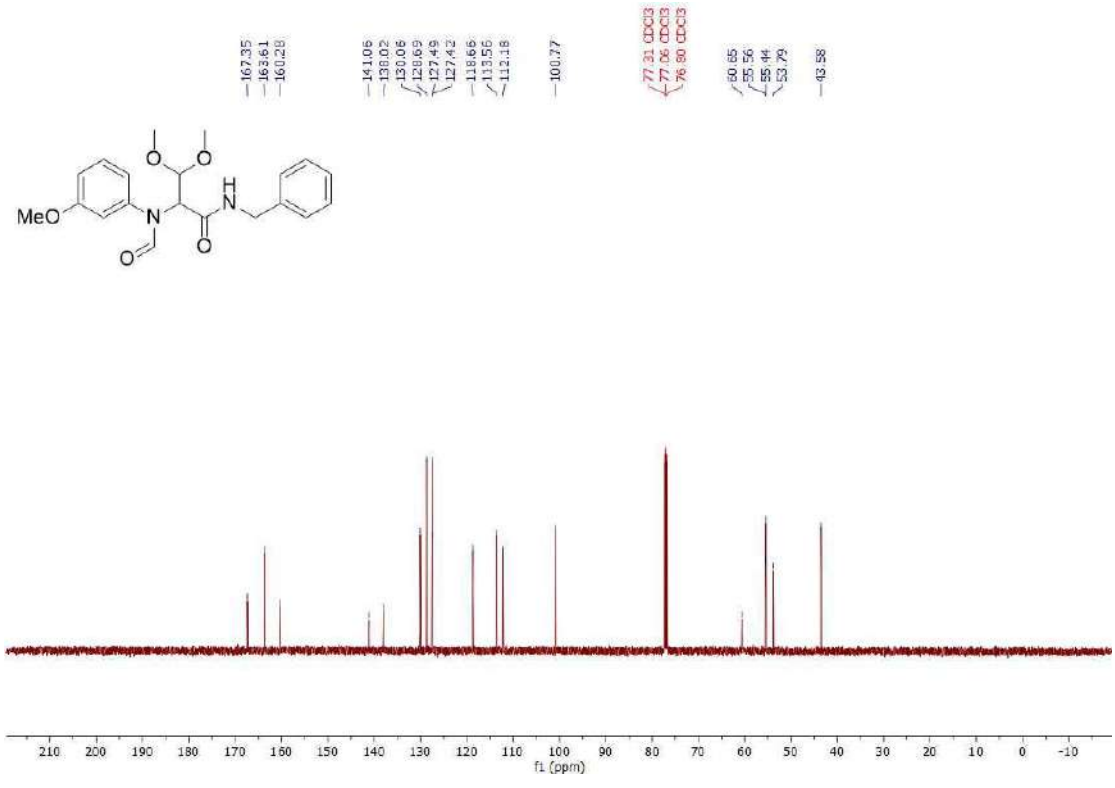
3.01
f1 (ppm)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112.18
100.77
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76.80 CDCl3
60.65
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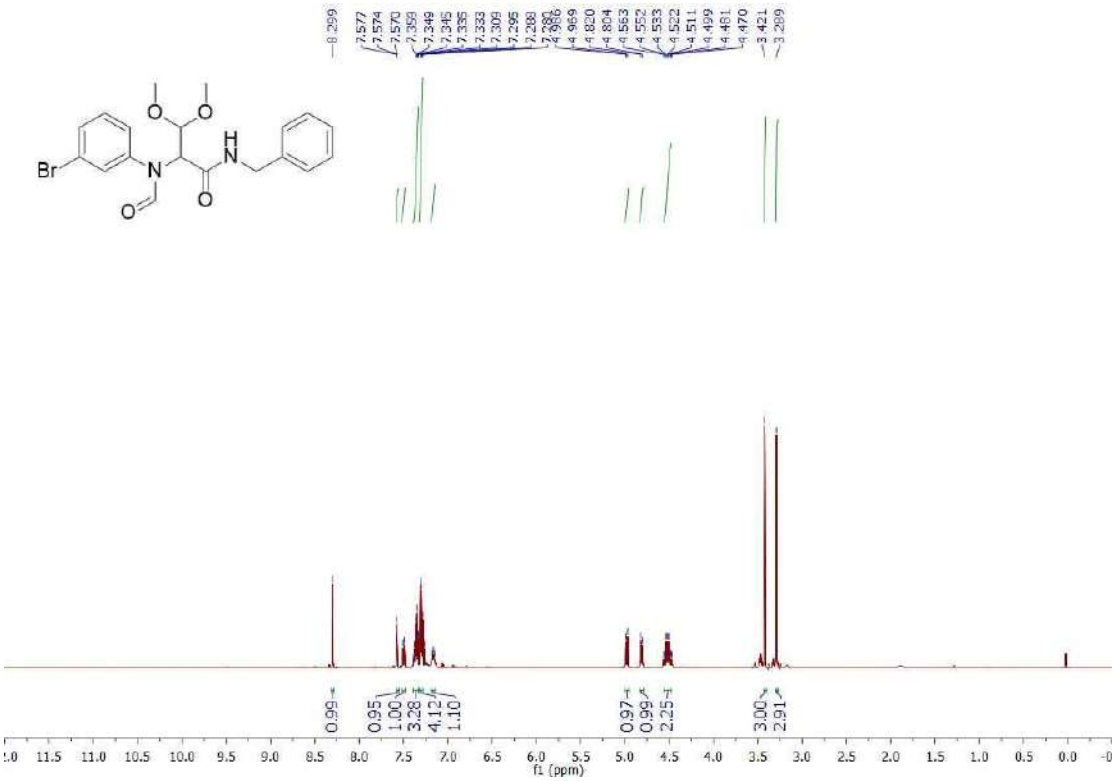
55.44
53.79
43.58
MeO
f1 (ppm)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7.309
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7.288
7.280
4.969
4.820
4.804
4.563
4.552
4.533
4.522
4.511
4.499
4.481
4.470
3.421
3.289
Br
N
O
H
N
O
O
O
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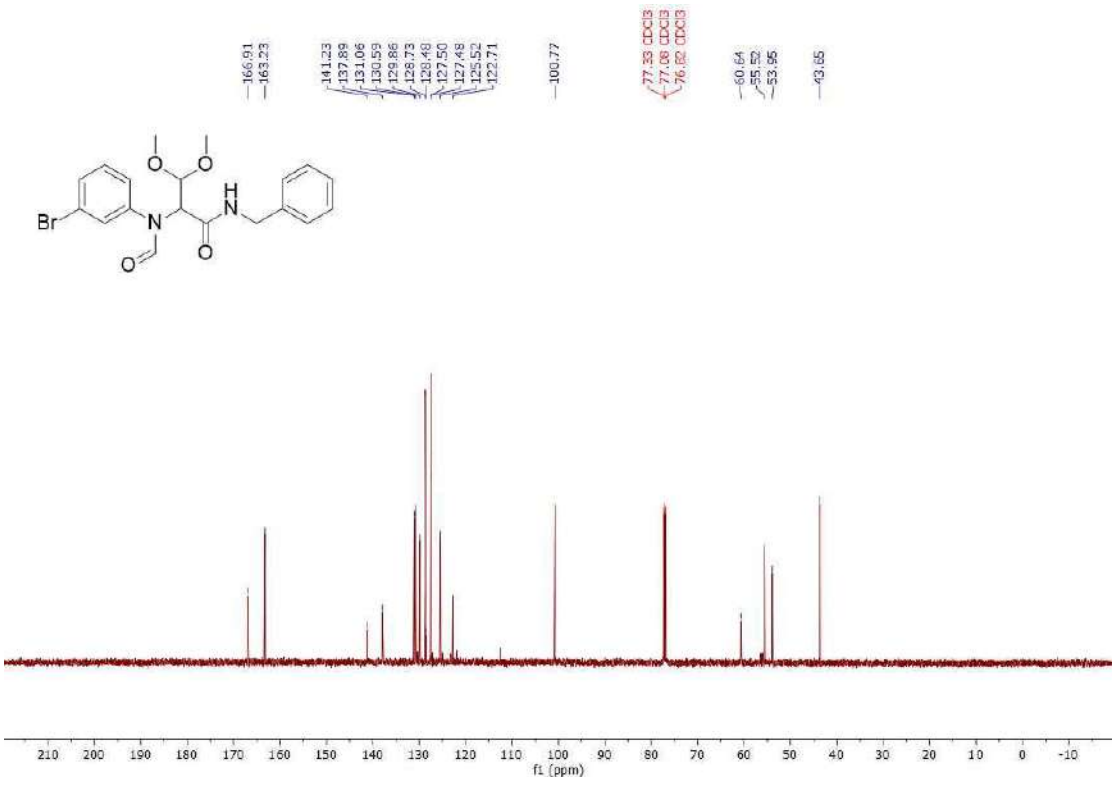
f1 (ppm)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125.52
122.71
100.77
77.33 CDCl3
77.08 CDCl3
76.82 CDCl3
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55.52
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43.65
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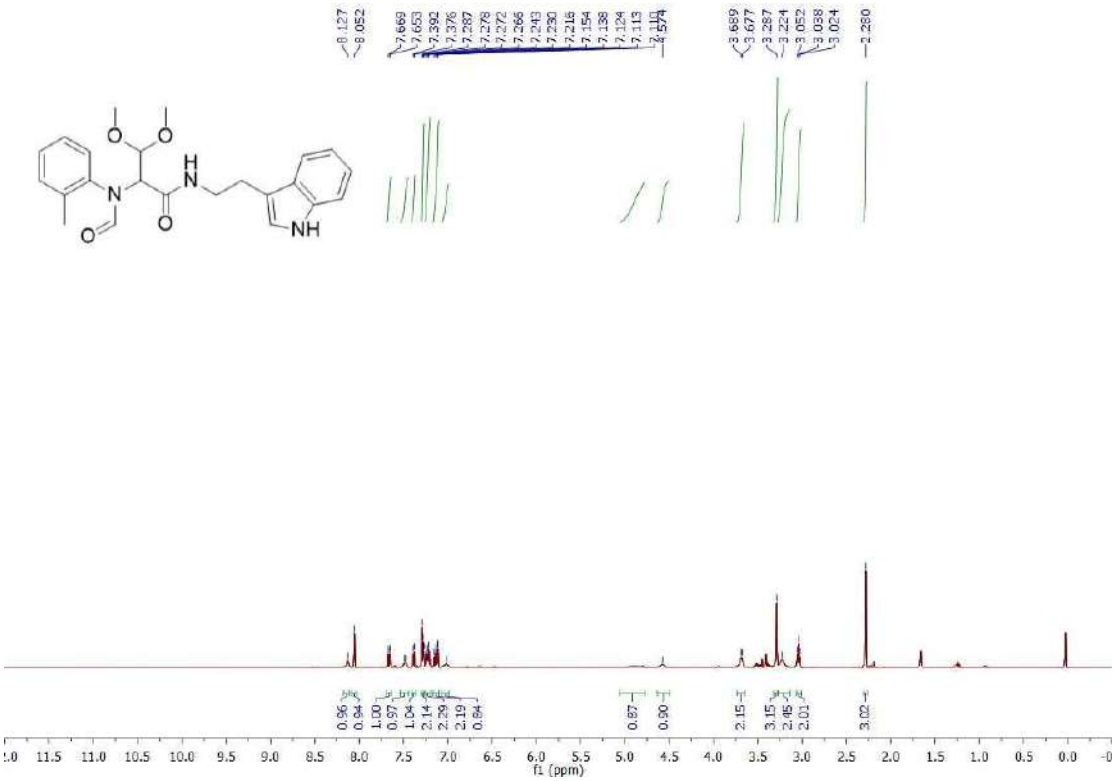
O
f1 (ppm)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7.138
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7.113
4.574
3.669
3.677
3.287
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3.052
3.038
3.024
2.280
O
O
N
O
H
N
O
NH
0.96
0.94
1.00
0.97
1.04
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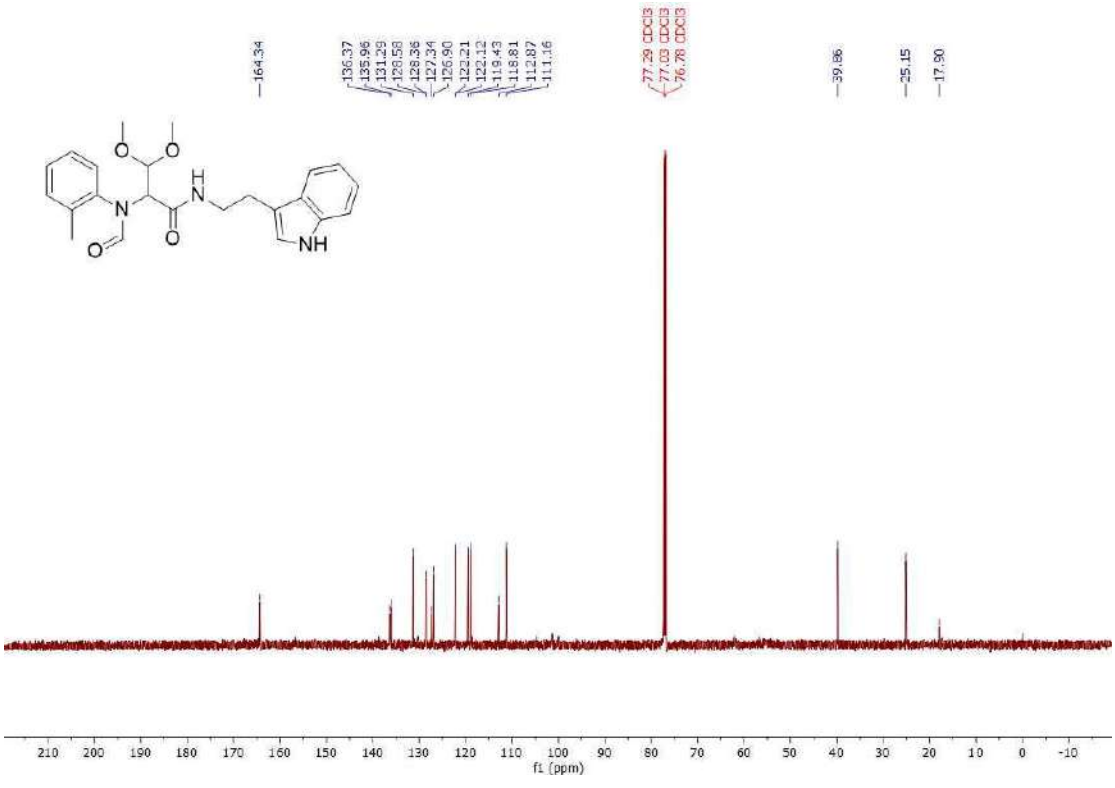
f1 (ppm)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122.12
119.43
118.81
112.87
111.16
77.29 CDCl3
77.03 CDCl3
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39.86
25.15
17.90
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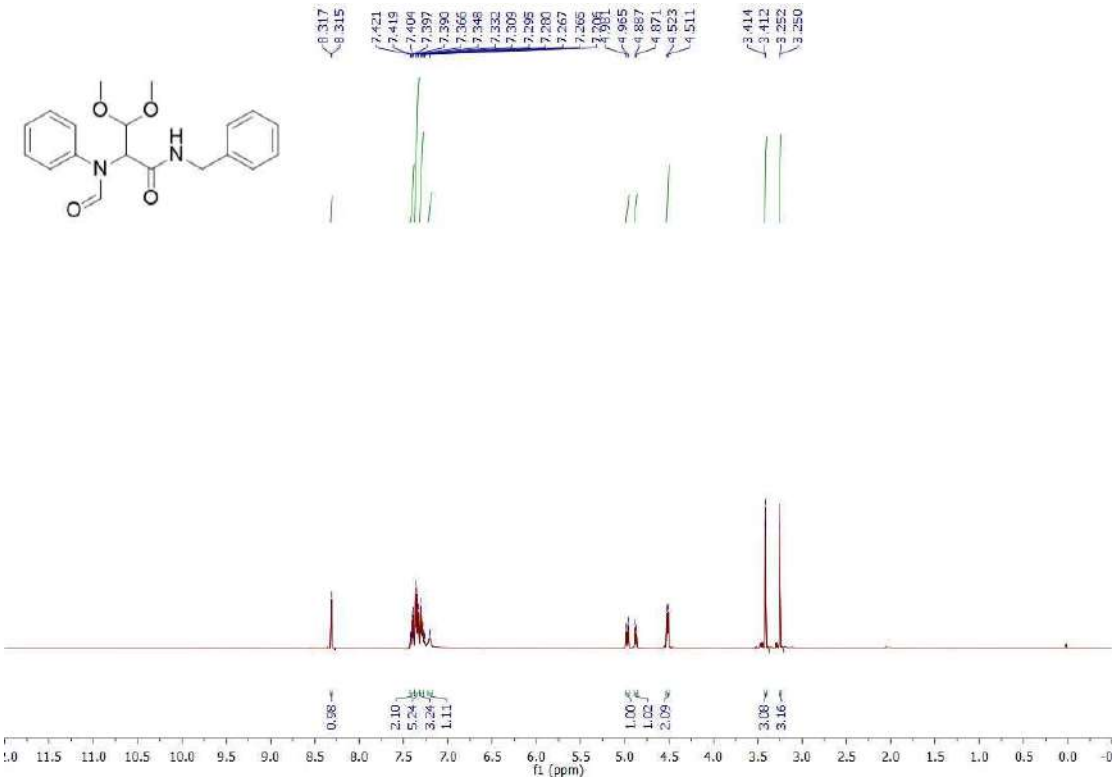
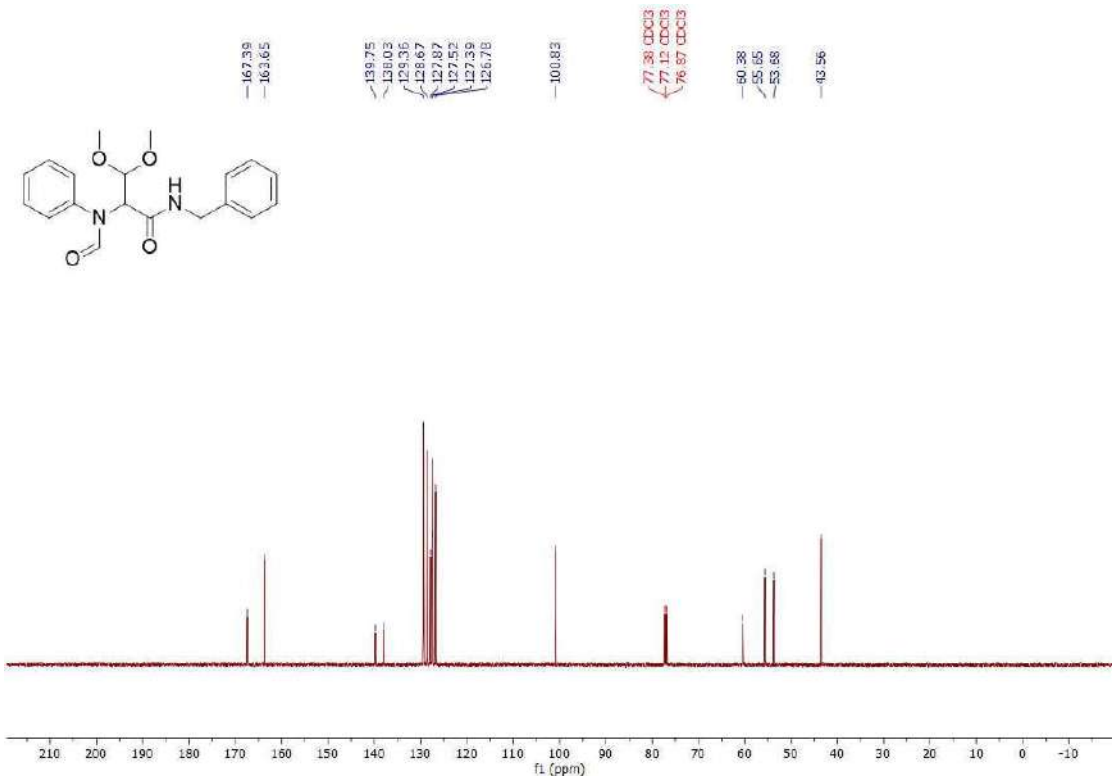
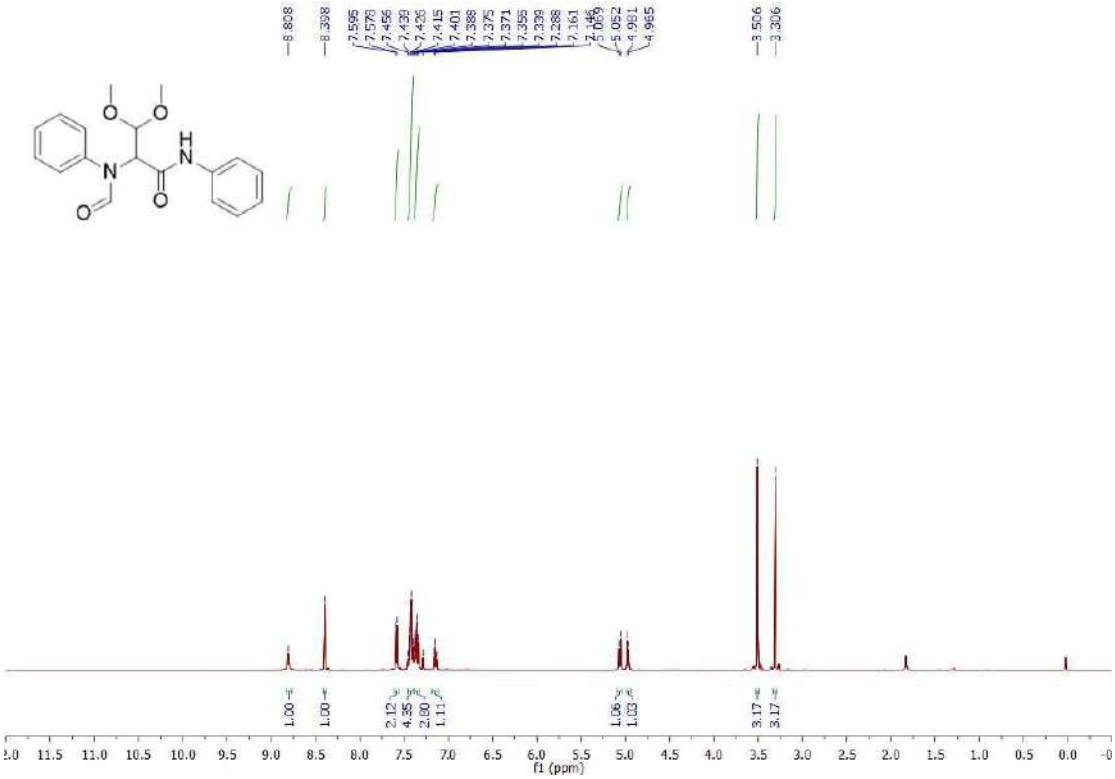
N
O
H
N
O
NH
f1 (ppm)



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7.355
7.339
7.288
7.161
7.146
7.059
5.052
4.981
4.965
3.506
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2.12
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1.03
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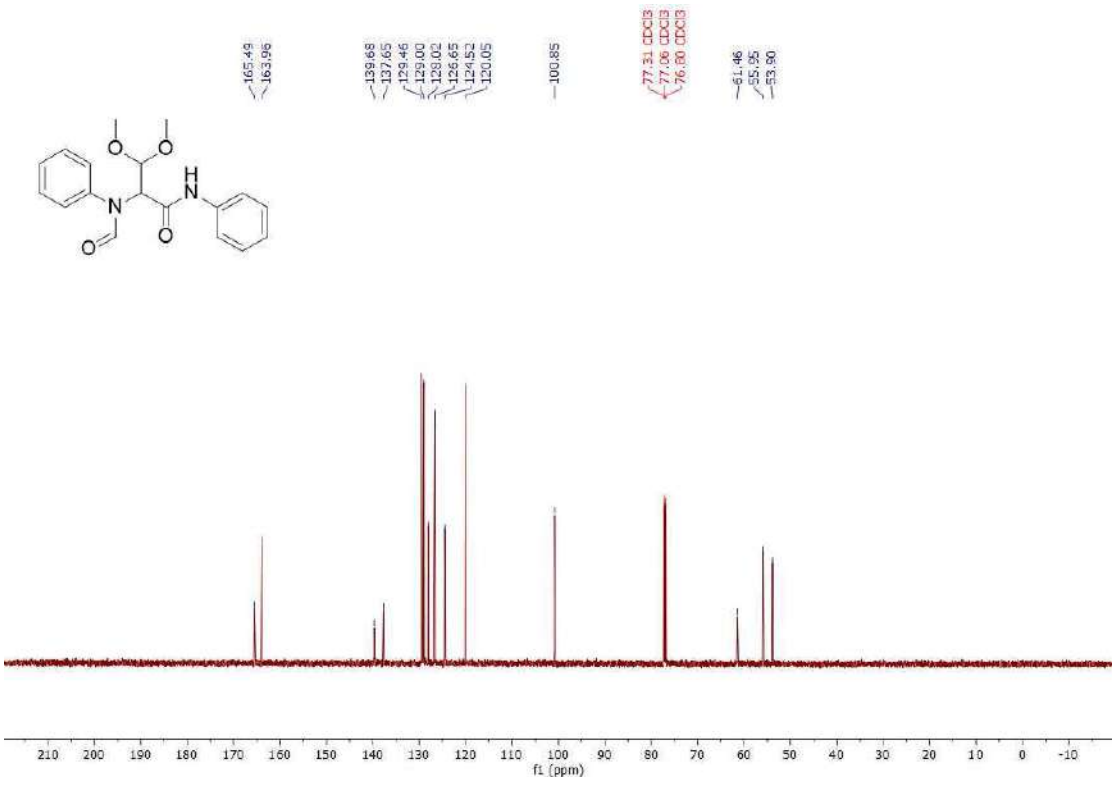
3.17
f1 (ppm)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137.65
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129.00
128.02
126.65
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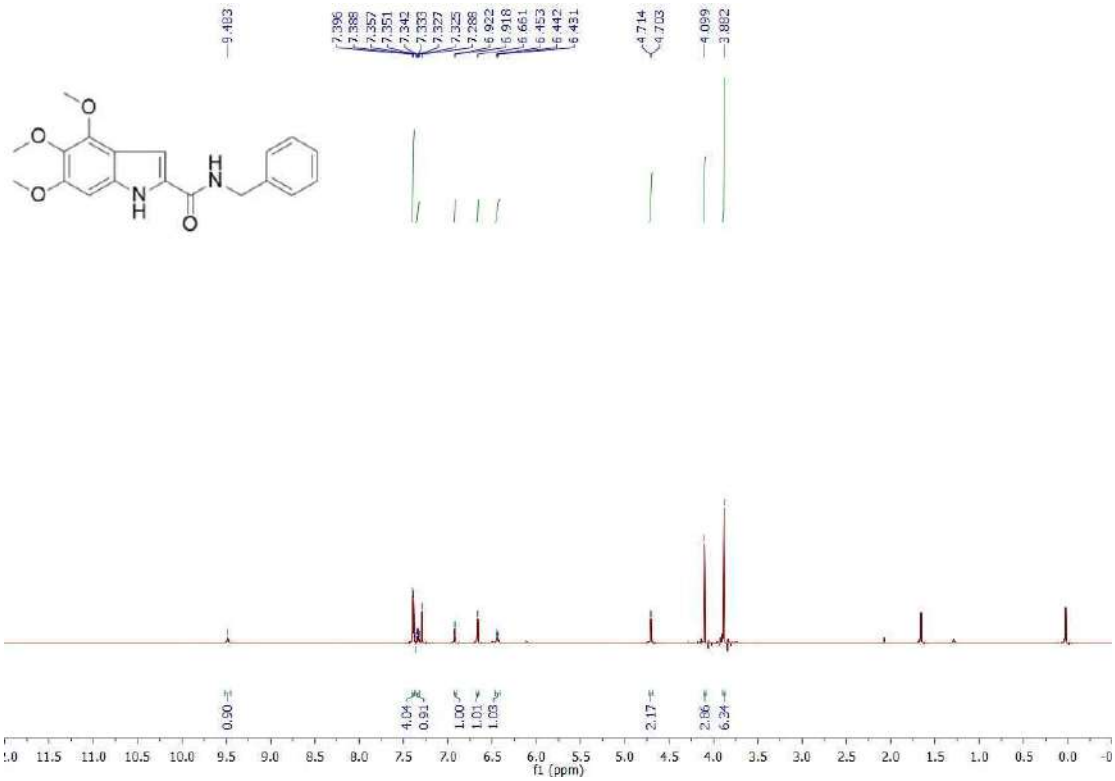
77.31 CDCl3
77.06 CDCl3
76.80 CDCl3
61.46
55.95
53.90
f1 (ppm)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6.661
6.453
6.442
6.431
4.714
4.703
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1.01
1.03
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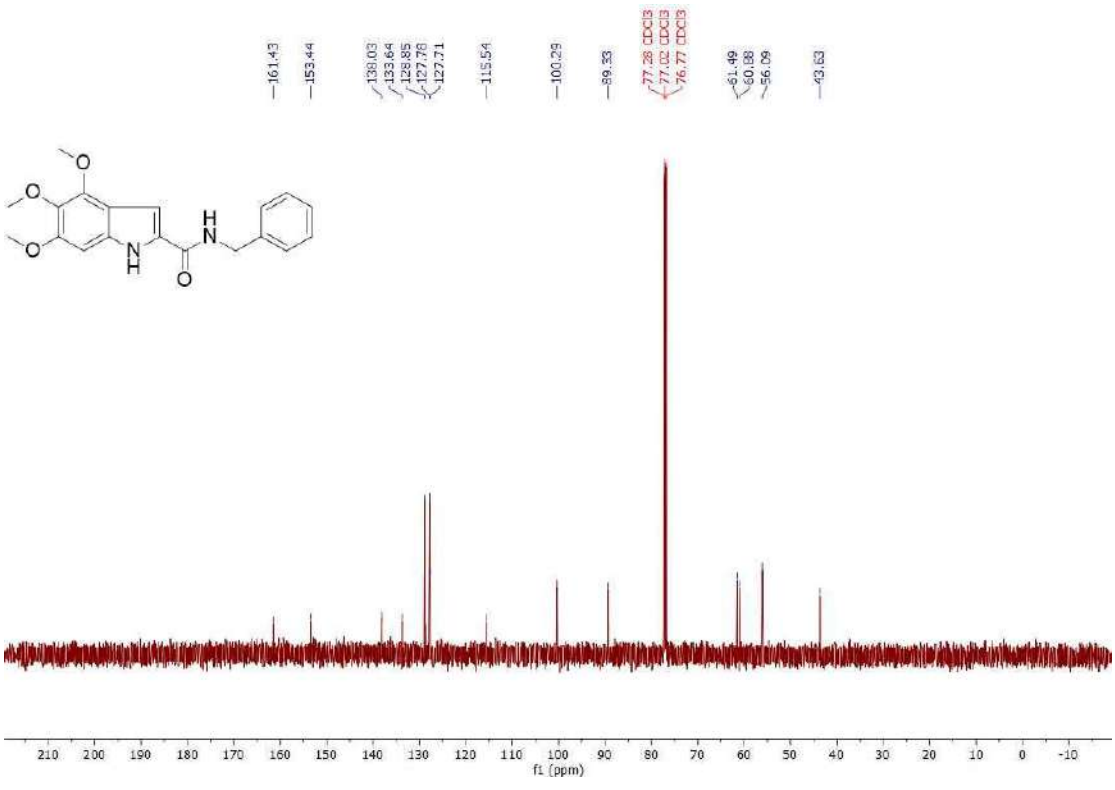
6.24
f1 (ppm)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153.44
138.03
133.64
128.85
127.78
127.71
115.54
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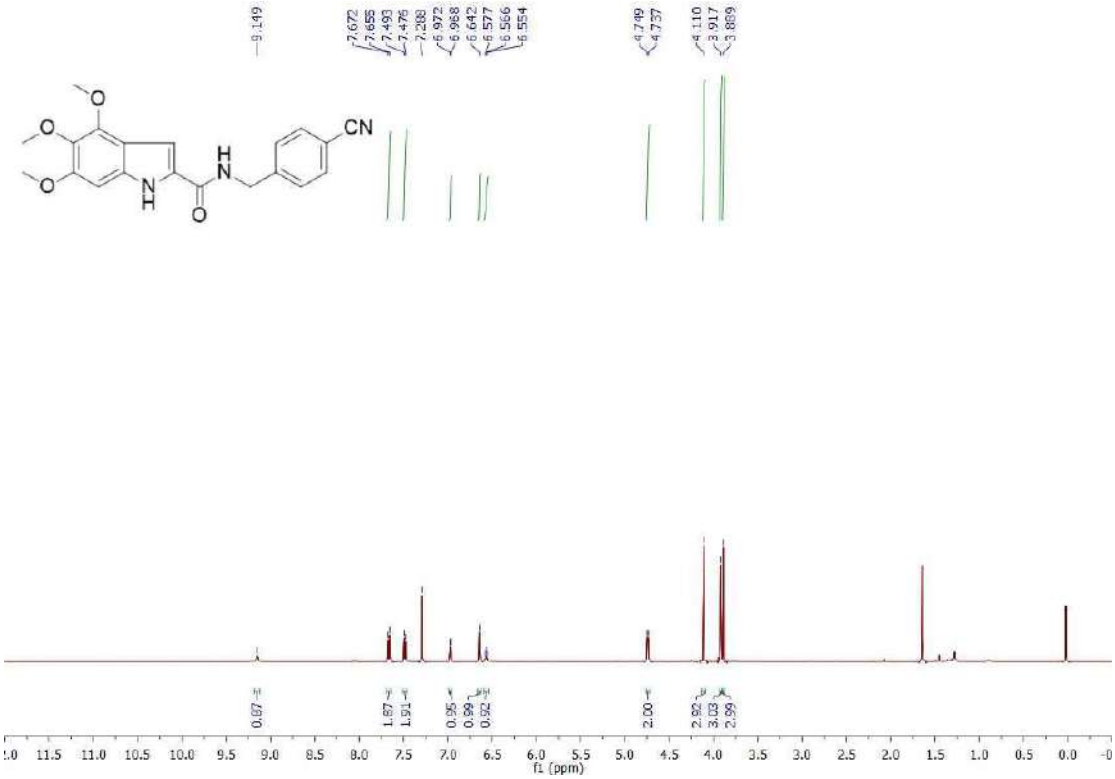
77.02 CDCl3
76.77 CDCl3
61.49
60.88
56.09
43.63
f1 (ppm)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4.749
4.737
4.110
3.917
3.889
CN
O
O
O
H
N
N
H
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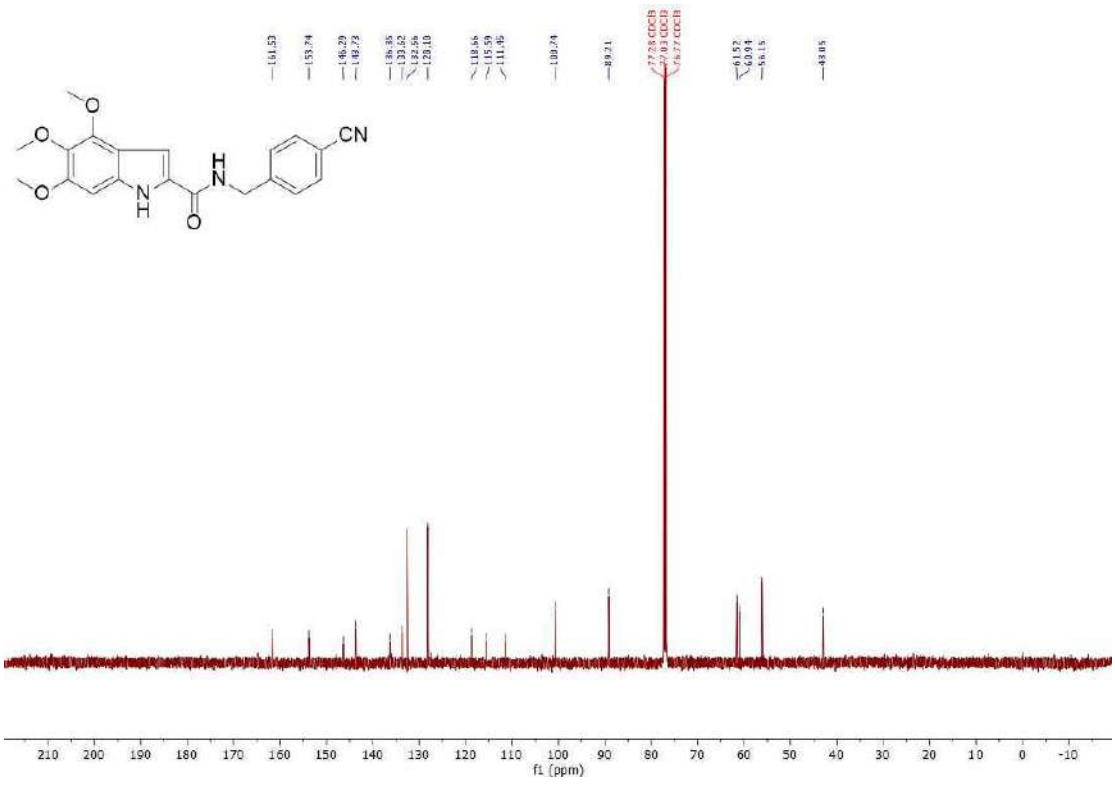
2.99
f1 (ppm)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111.46
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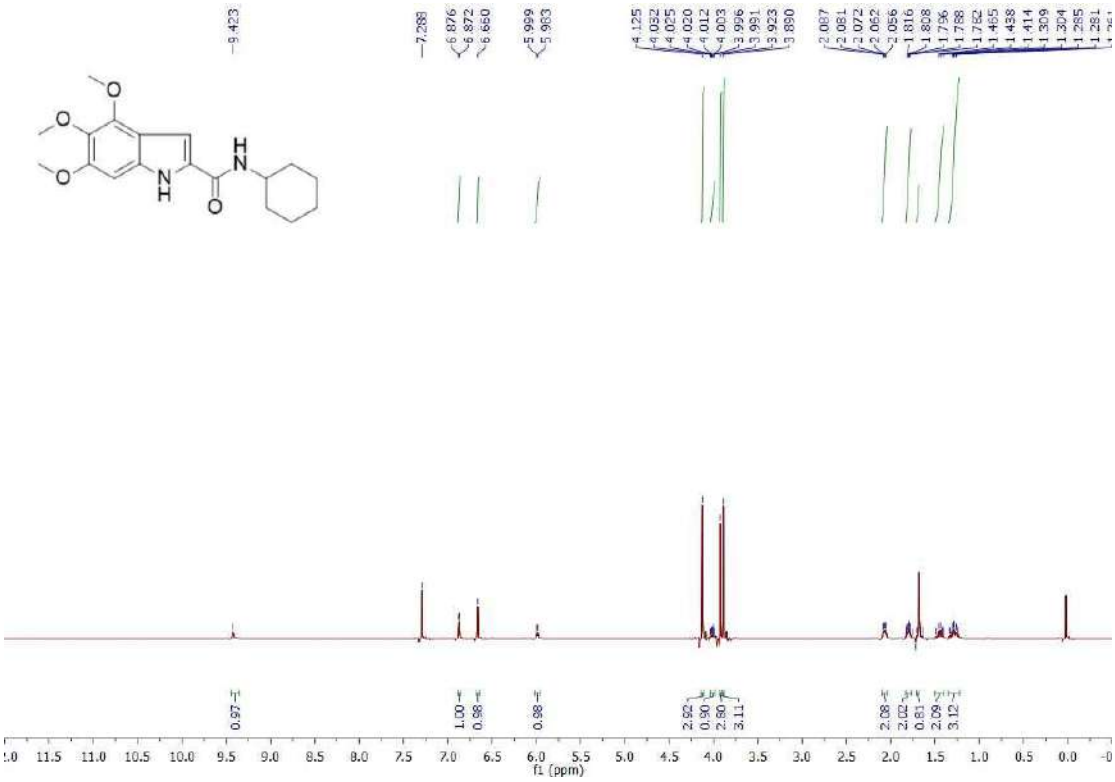
89.21
77.26 CDCl3
77.03 CDCl3
76.77 CDCl3
61.52
60.94
56.15
43.05
CN
O
O
O
H
N
N
H
O
f1 (ppm)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6.660
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5.963
4.125
4.032
4.025
4.020
4.012
4.003
3.996
3.991
3.923
3.890
2.087
2.081
2.072
2.062
2.056
1.816
1.808
1.796
1.788
1.782
1.465
1.438
1.414
1.309
1.304
1.285
1.281
0.97
1.00
0.98
0.98
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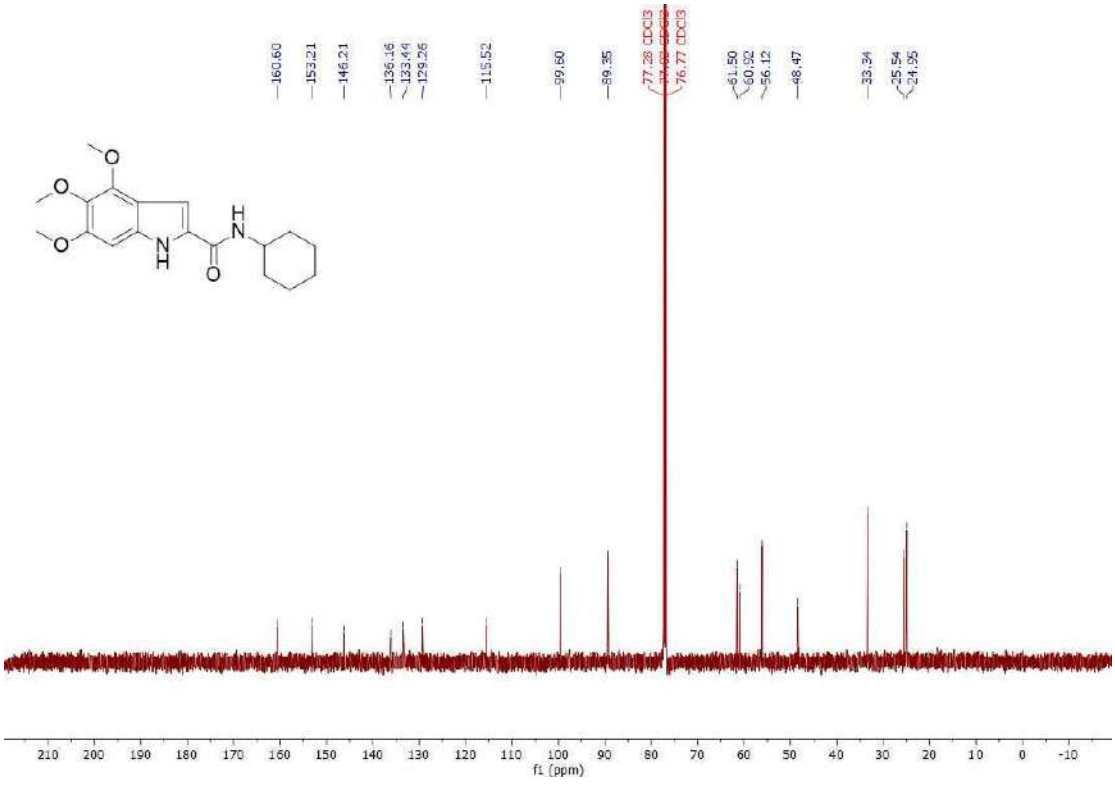
0.90
2.80
3.11
2.08
2.02
0.81
2.09
3.12
f1 (ppm)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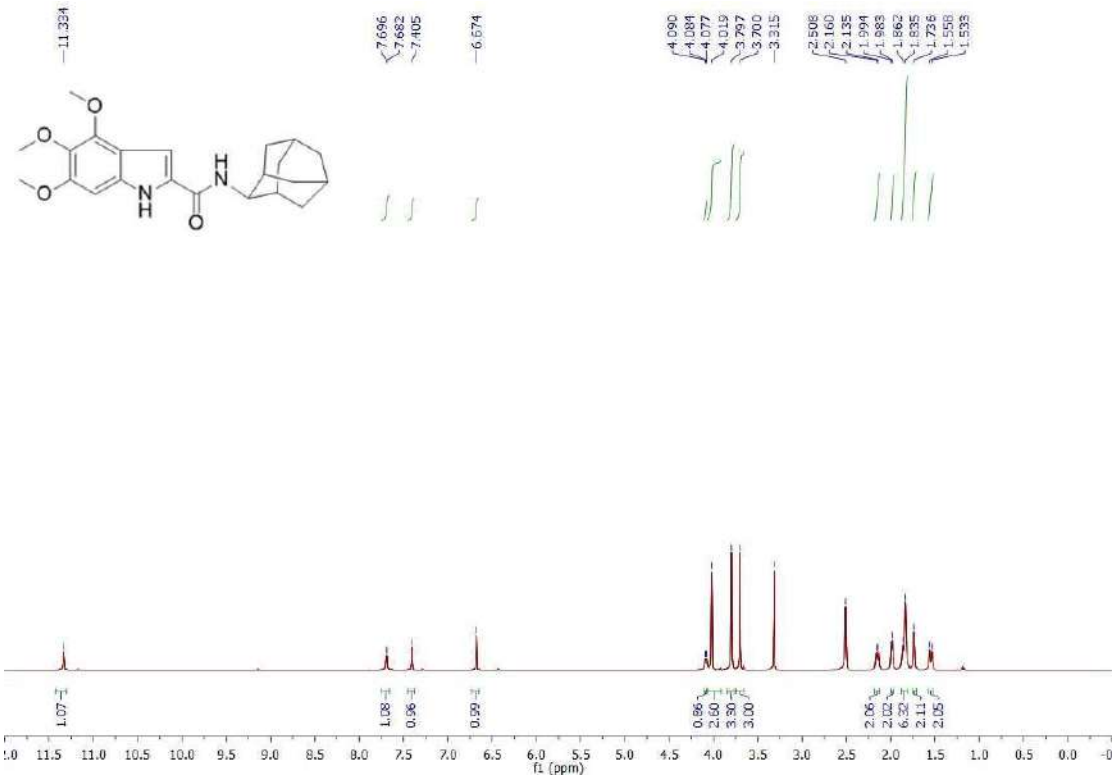
153.21
146.21
136.16
133.44
129.26
115.52
99.60
89.35
77.28 CDCl3
76.77 CDCl3
61.50
60.92
56.12
48.47
33.34
25.54
24.95
f1 (ppm)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7.682
7.405
6.674
4.090
4.084
4.077
4.019
3.797
3.700
3.315
2.508
2.160
2.135
1.994
1.983
1.862
1.835
1.736
1.598
1.533
1.07
1.08
0.96
0.99
0.86
2.60
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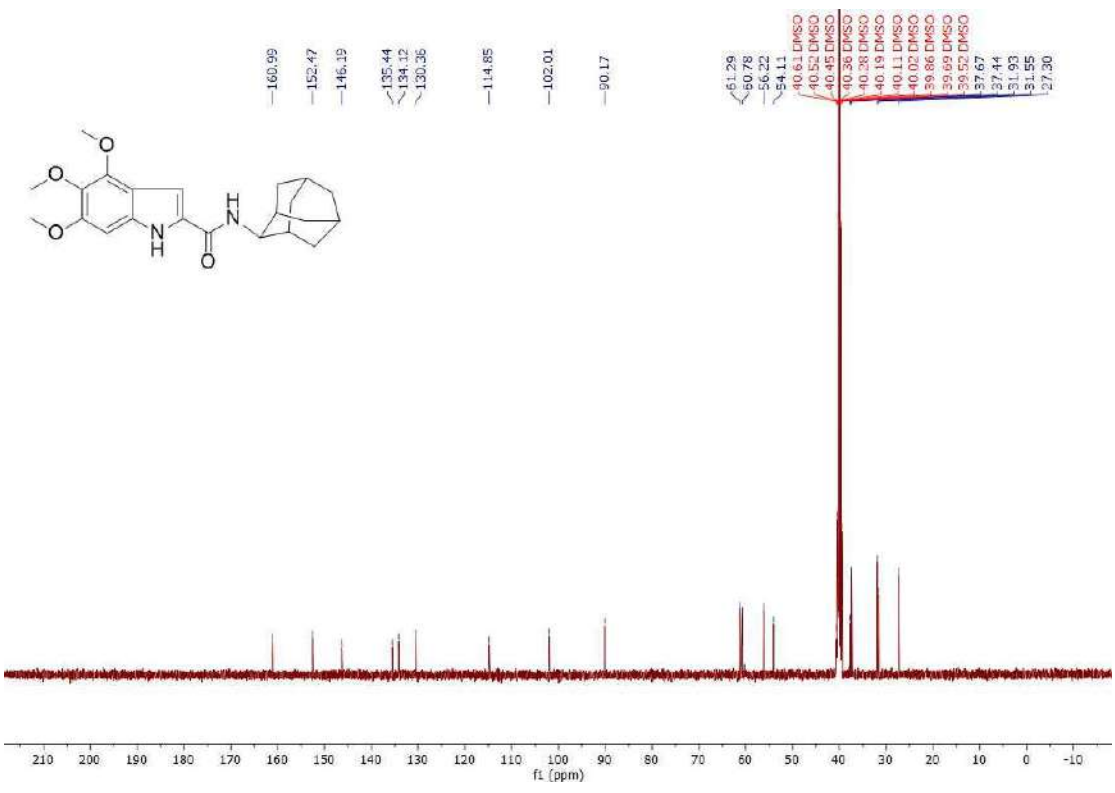
3.00
2.06
2.02
6.32
2.11
2.05
f1 (ppm)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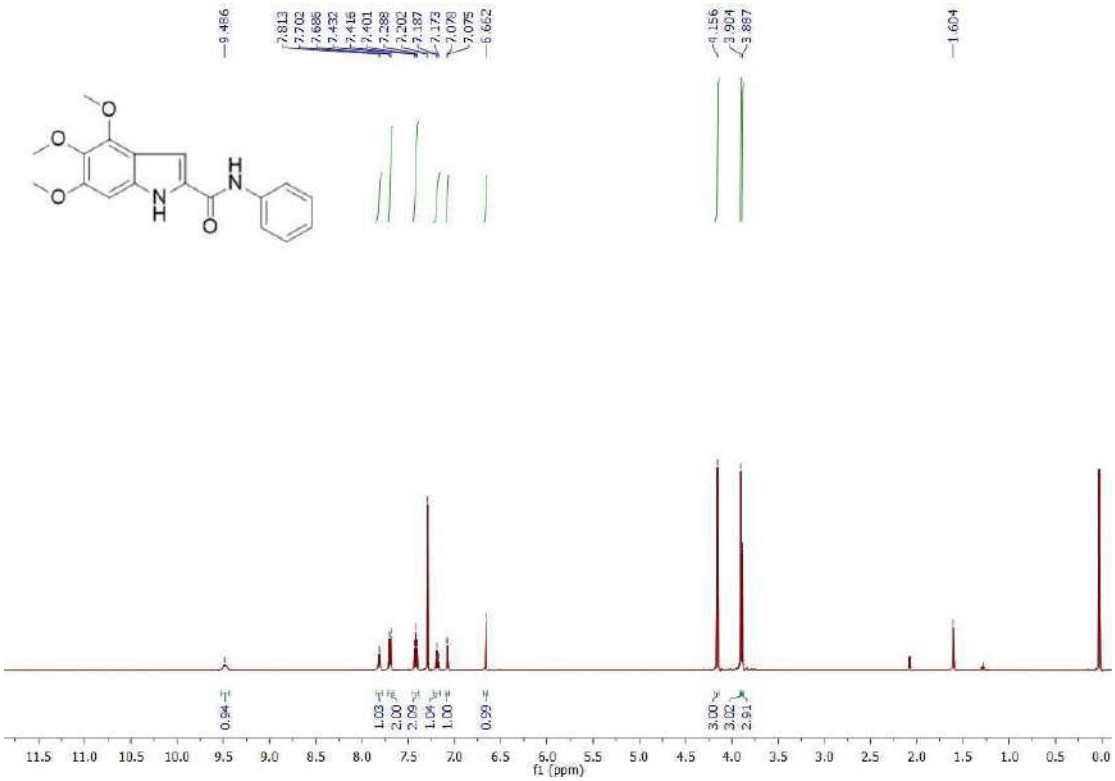
152.47
146.19
135.44
134.12
130.36
114.85
102.01
90.17
61.29
60.78
56.22
54.11
40.61 DMSO
40.52 DMSO
40.45 DMSO
40.36 DMSO
40.28 DMSO
40.19 DMSO
40.11 DMSO
40.02 DMSO
39.86 DMSO
39.69 DMSO
39.52 DMSO
37.67
27.44
31.93
31.55
27.30
f1 (ppm)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7.702
7.688
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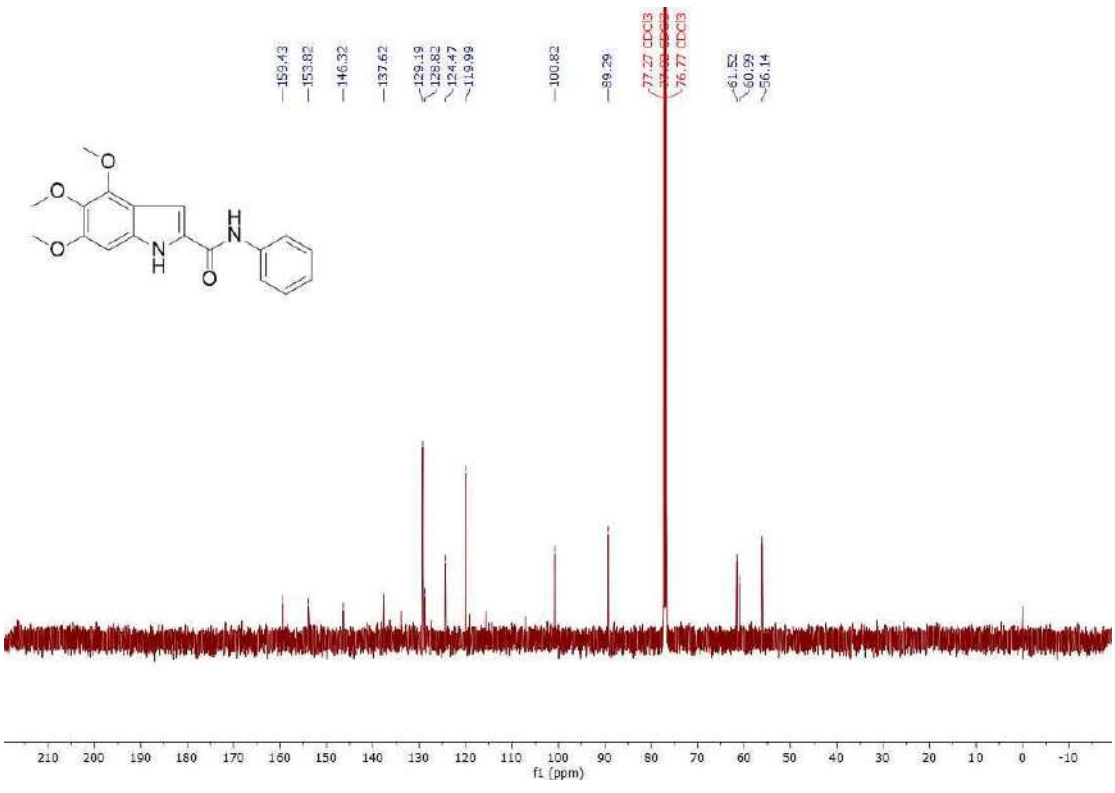
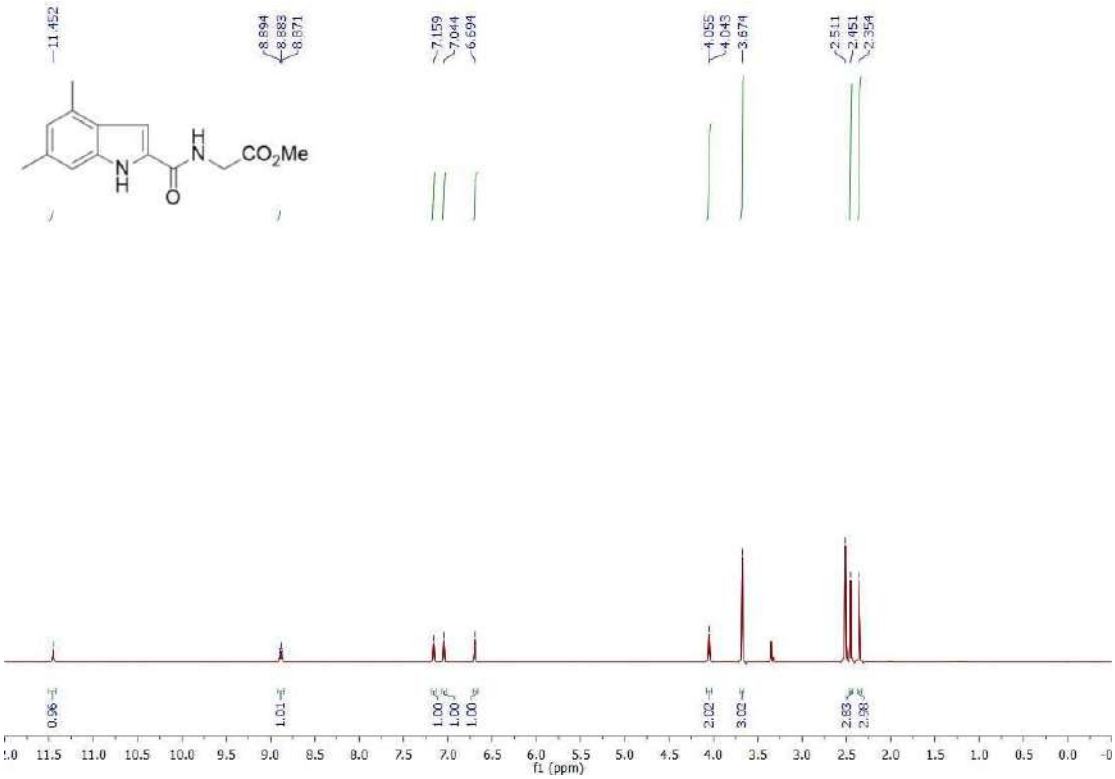
7.416
7.401
7.288
7.200
7.187
7.173
7.078
7.075
6.662
4.156
3.904
3.887
1.604
0.94
1.03
2.00
2.09
1.04
1.00
0.99
3.00
3.02
2.91
f1 (ppm)


159.43
153.82
146.32
137.62
129.19
128.82
124.47
119.99
100.82
89.29
77.27 CDCl3
76.77 CDCl3
61.52
60.99
56.14
f1 (ppm)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8.883
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7.044
6.694
4.055
4.043
3.674
2.511
2.451
2.394
CO2Me
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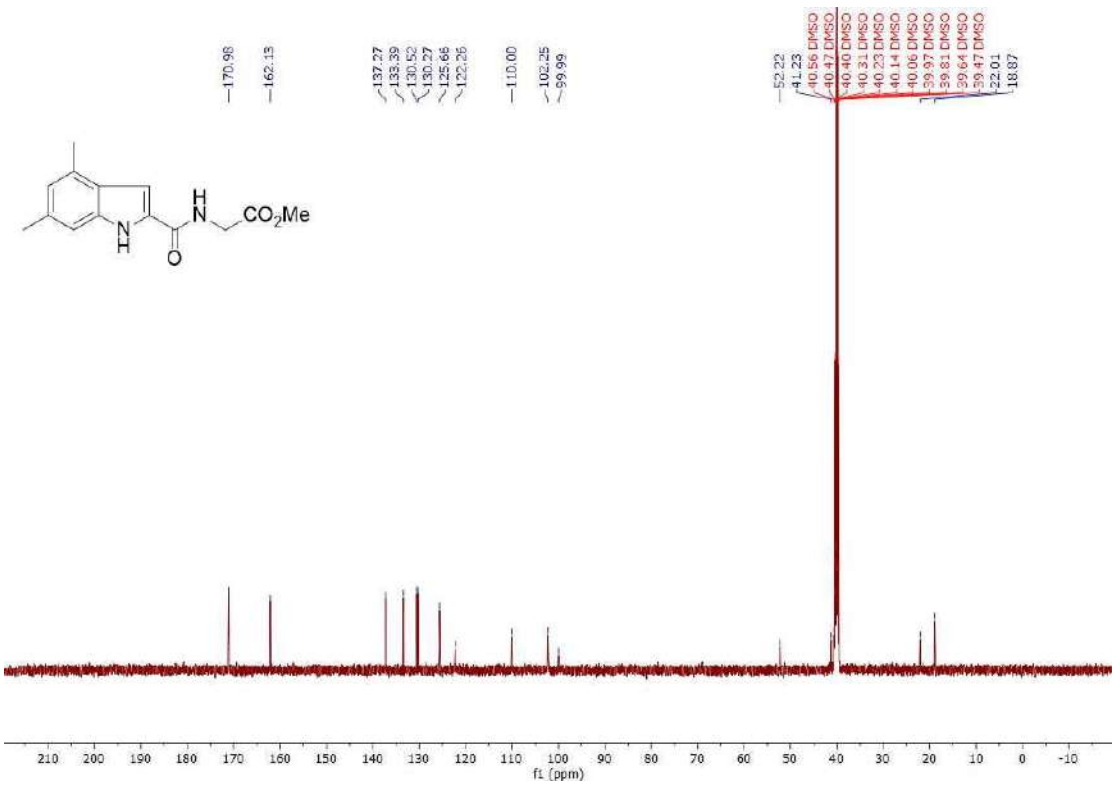
1.01
1.00
1.00
1.00
2.02
3.02
2.83
2.98
f1 (ppm)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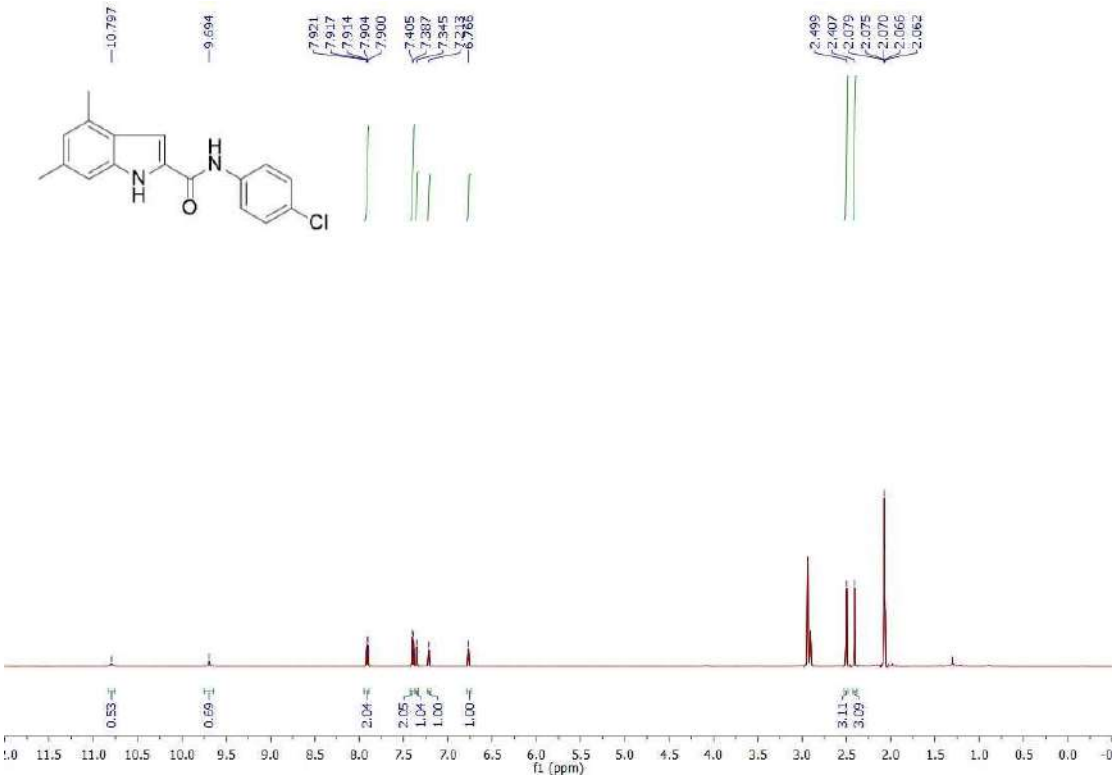
162.13
137.27
133.39
130.52
130.27
125.66
122.26
110.00
102.25
99.99
52.22
41.23
40.56 DMSO
40.47 DMSO
40.40 DMSO
40.31 DMSO
40.23 DMSO
40.14 DMSO
40.06 DMSO
39.97 DMSO
39.81 DMSO
39.64 DMSO
39.47 DMSO
22.01
18.87
CO2Me
f1 (ppm)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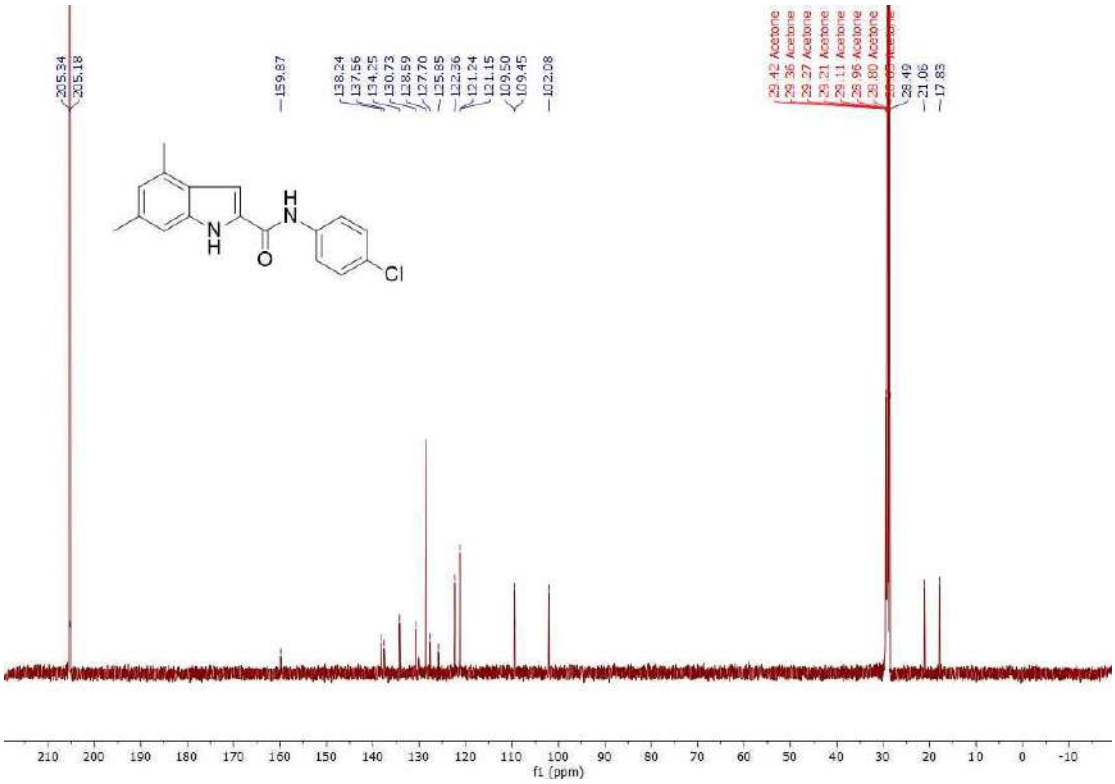
9.694
7.921
7.917
7.914
7.904
7.900
7.405
7.387
7.345
7.213
6.768
2.499
2.407
2.079
2.075
2.070
2.066
2.062
0.53
0.69
2.04
2.05
1.04
1.00
3.11
3.09
f1 (ppm)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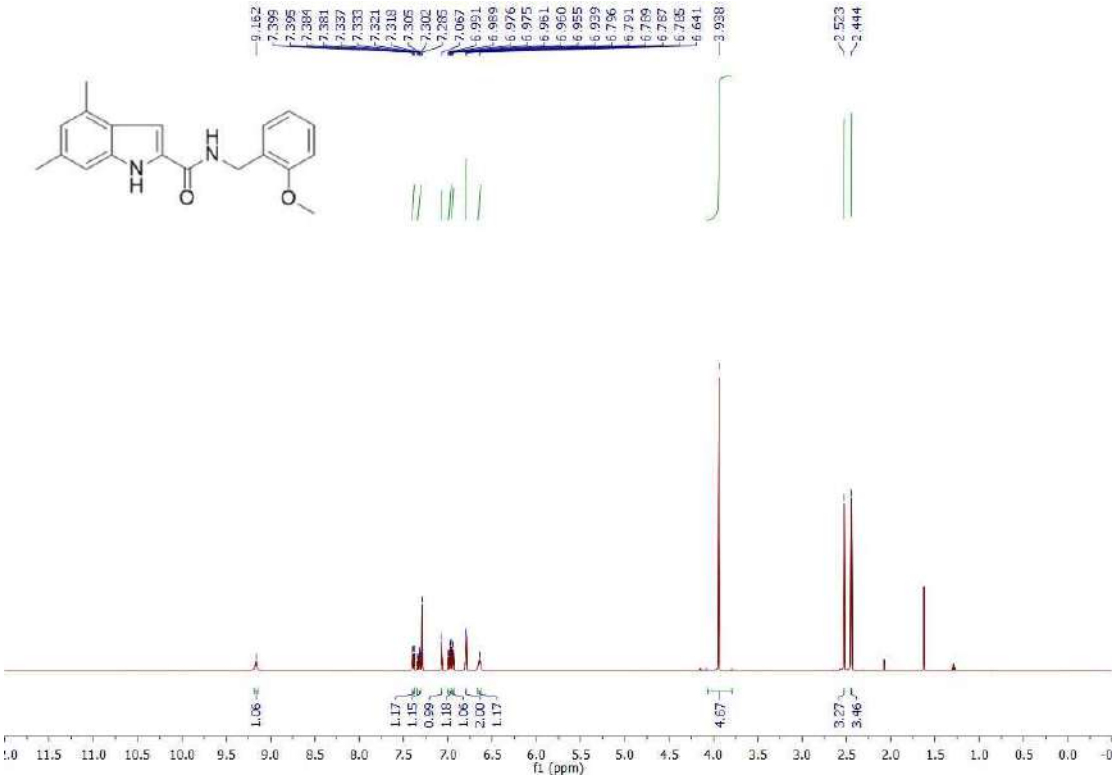
205.18
159.87
138.24
137.56
134.25
130.73
128.59
127.70
125.85
122.36
121.24
121.15
109.50
109.45
102.08
29.42 Acetone
29.36 Acetone
29.27 Acetone
29.21 Acetone
29.11 Acetone
28.96 Acetone
28.80 Acetone
28.49
21.06
17.83
f1 (ppm)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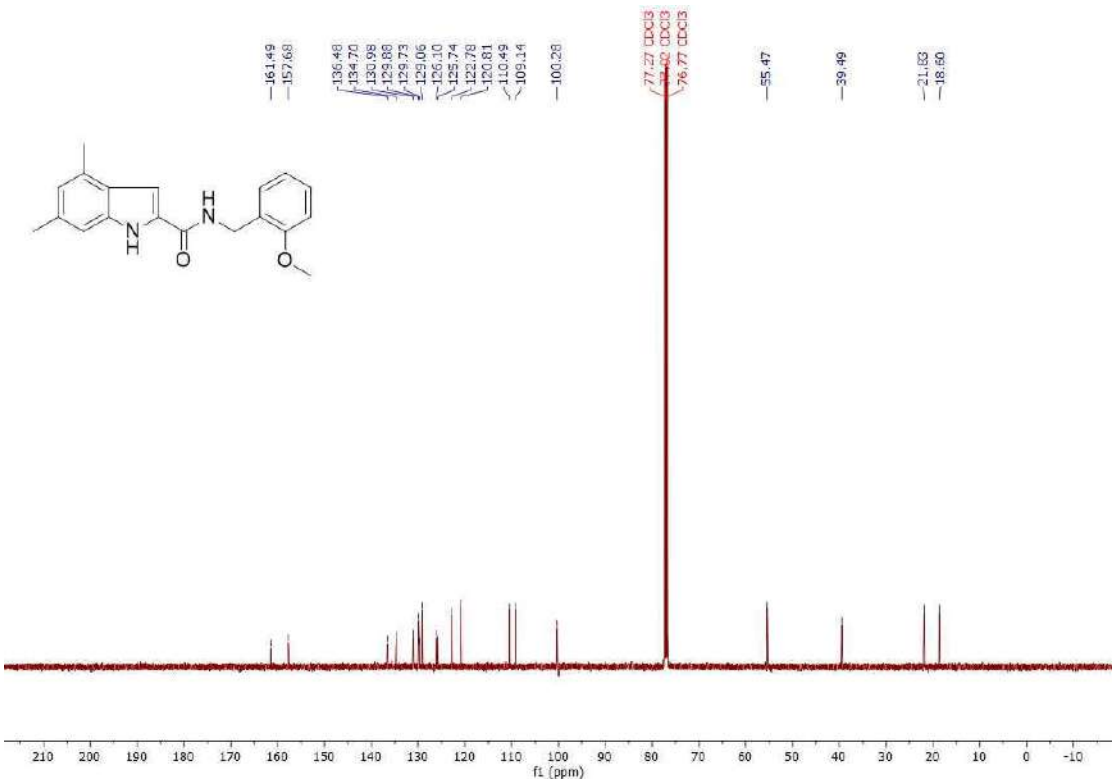
7.395
7.384
7.381
7.337
7.333
7.321
7.318
7.305
7.302
7.285
7.067
6.991
6.989
6.976
6.975
6.961
6.960
6.955
6.939
6.796
6.791
6.789
6.787
6.785
6.641
3.938
2.523
2.444
1.06
1.17
1.15
0.99
1.18
1.06
2.00
1.17
4.67
3.27
3.46
f1 (ppm)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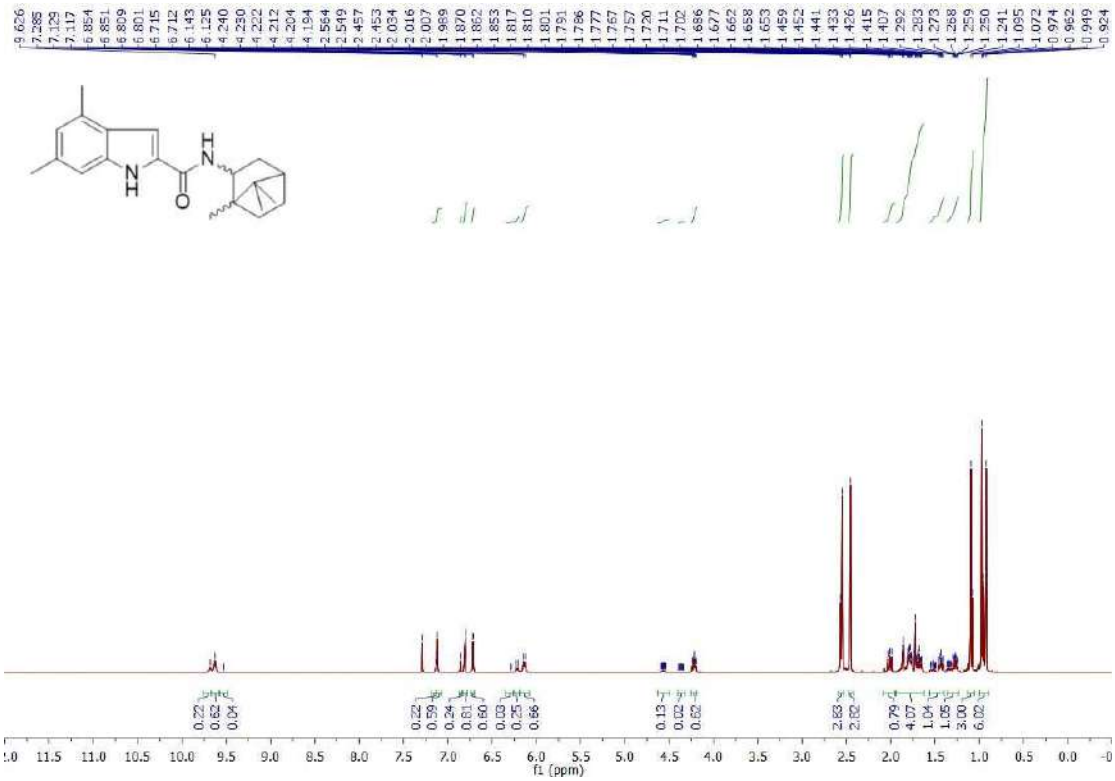
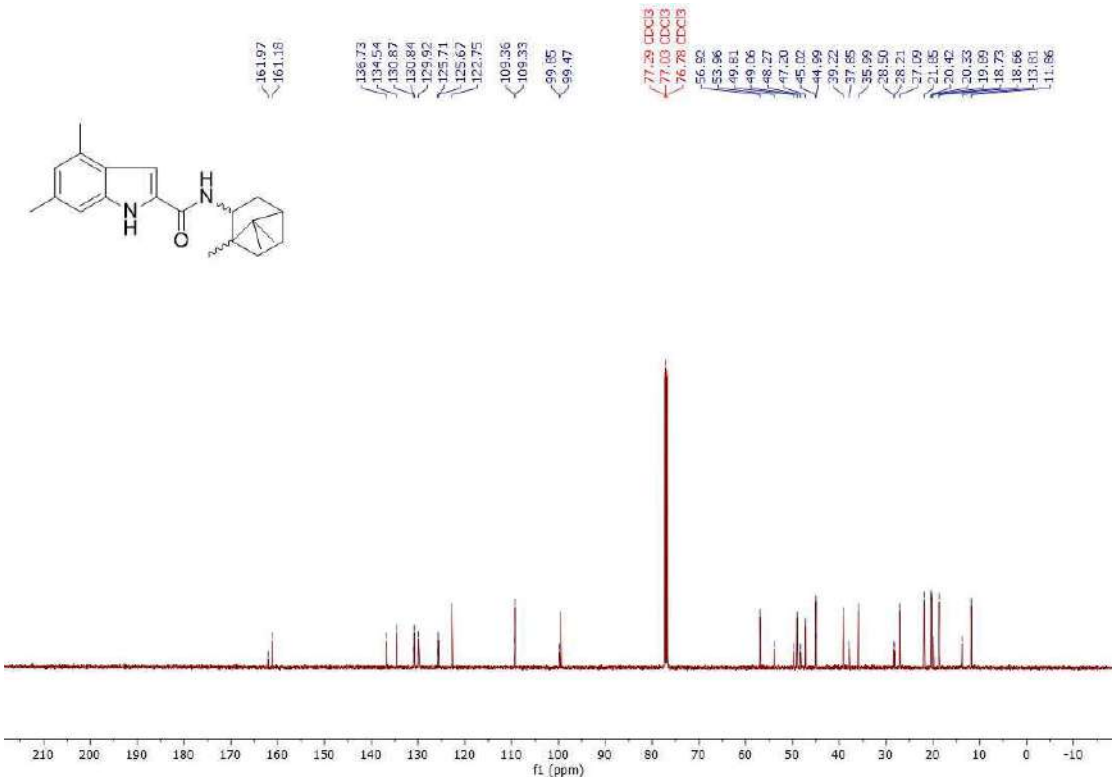
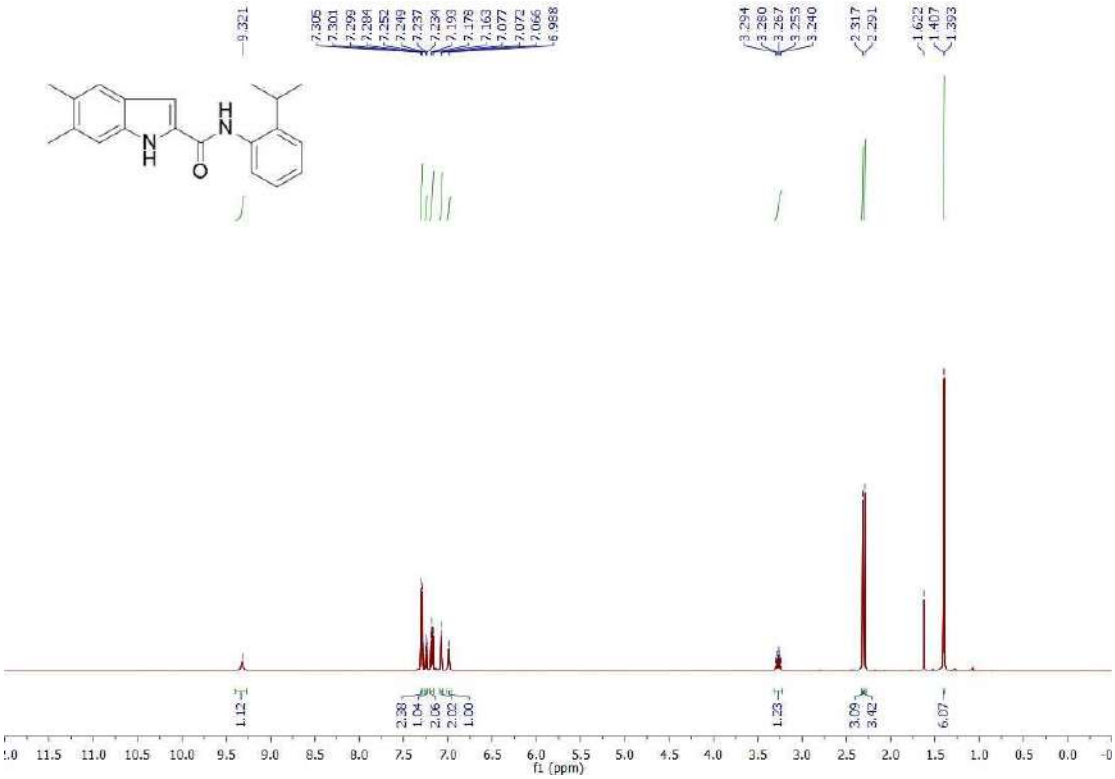
157.68
136.48
134.70
130.98
129.88
129.73
129.06
126.10
125.74
122.78
120.81
110.49
109.14
100.28
77.27 CDCl3
77.02 CDCl3
76.77 CDCl3
55.47
39.49
21.83
18.60
f1 (ppm)



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7.301
7.299
7.284
7.252
7.249
7.237
7.234
7.193
7.178
7.163
7.077
7.072
7.066
6.988
3.294
3.280
3.267
3.253
3.240
2.317
2.291
1.622
1.407
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1.04
2.06
2.02
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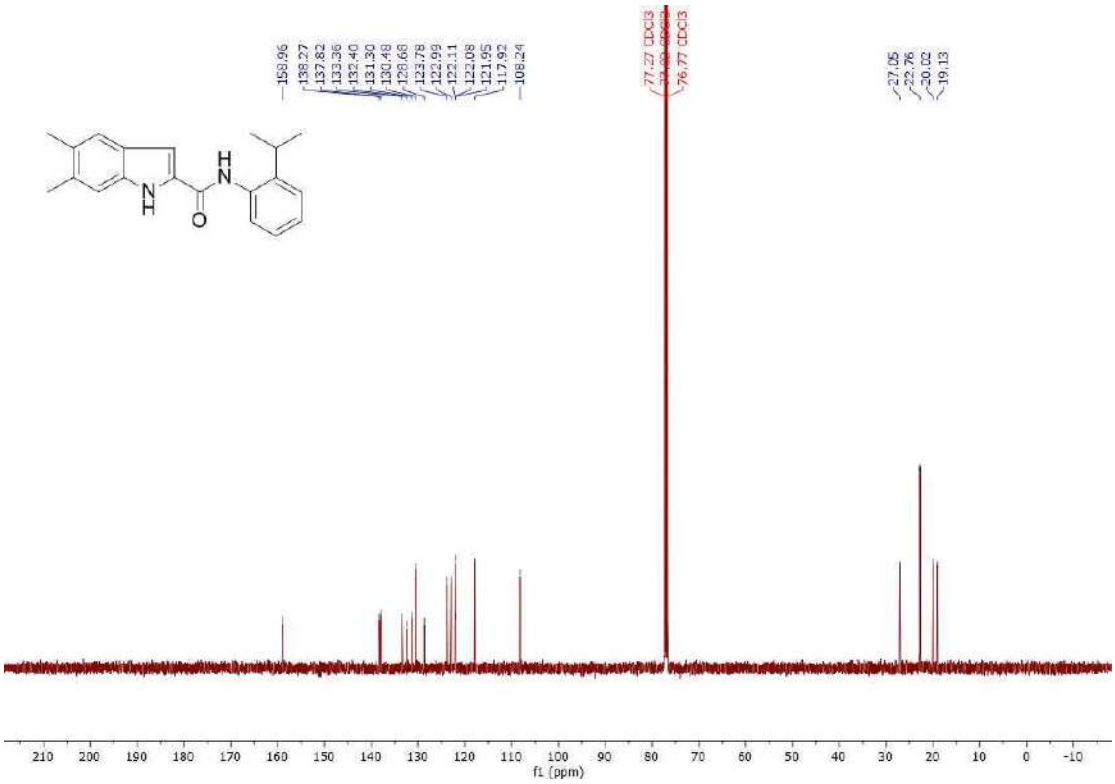
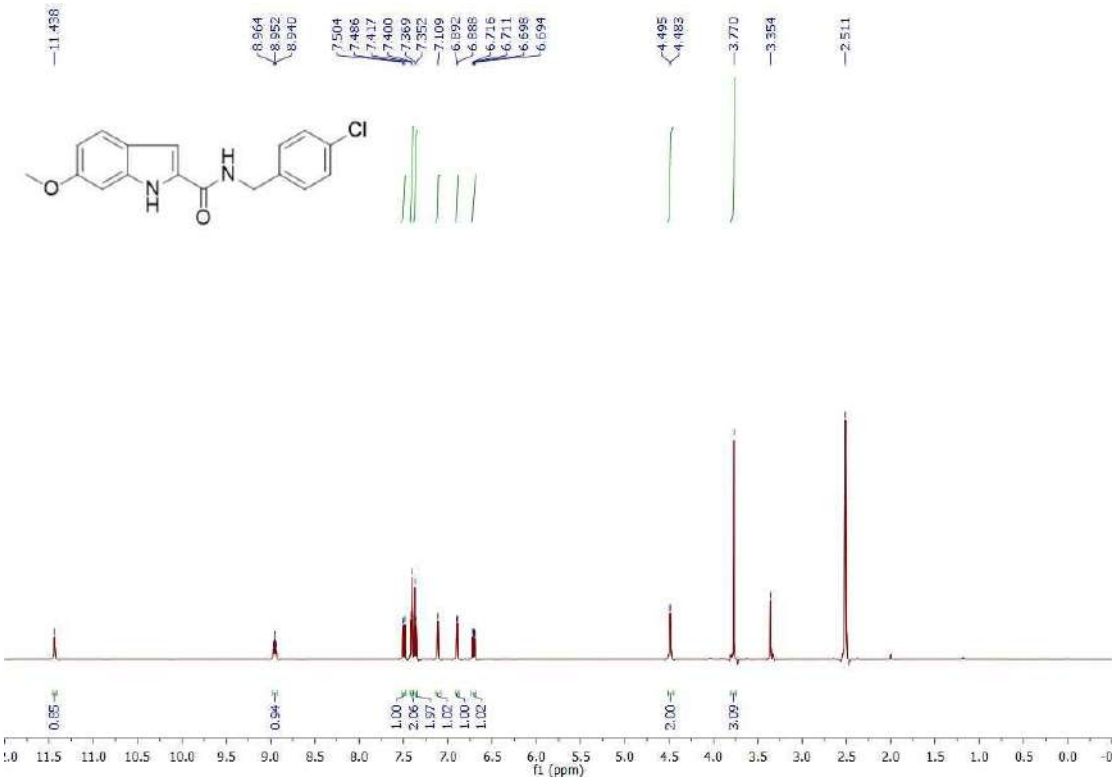
1.23
3.09
3.42
6.07
f1 (ppm)


158.96
138.27
137.82
133.36
132.40
131.30
130.48
128.68
123.78
122.99
122.11
122.08
121.95
117.92
108.24
77.27 CDCl3
76.77 CDCl3
27.05
22.76
20.02
19.13
f1 (ppm)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8.940
7.504
7.486
7.417
7.400
7.369
7.352
7.109
6.892
6.888
6.716
6.711
6.698
6.694
4.495
4.483
3.770
3.354
2.511
Cl
N
H
O
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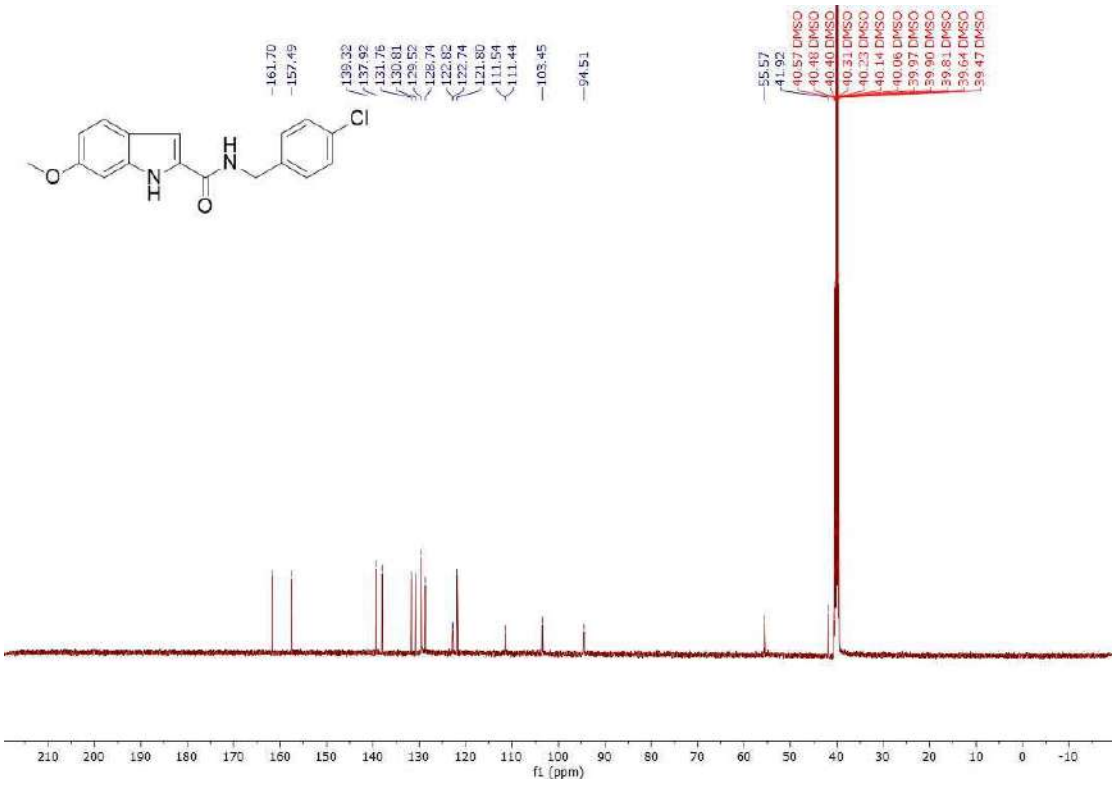
0.94
1.00
2.06
1.97
1.02
1.00
1.02
2.00
3.09
f1 (ppm)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137.92
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130.81
129.52
128.74
122.82
122.74
121.80
111.54
111.44
103.45
94.51
55.57
41.92
40.57 DMSO
40.48 DMSO
40.40 DMSO
40.31 DMSO
40.23 DMSO
40.14 DMSO
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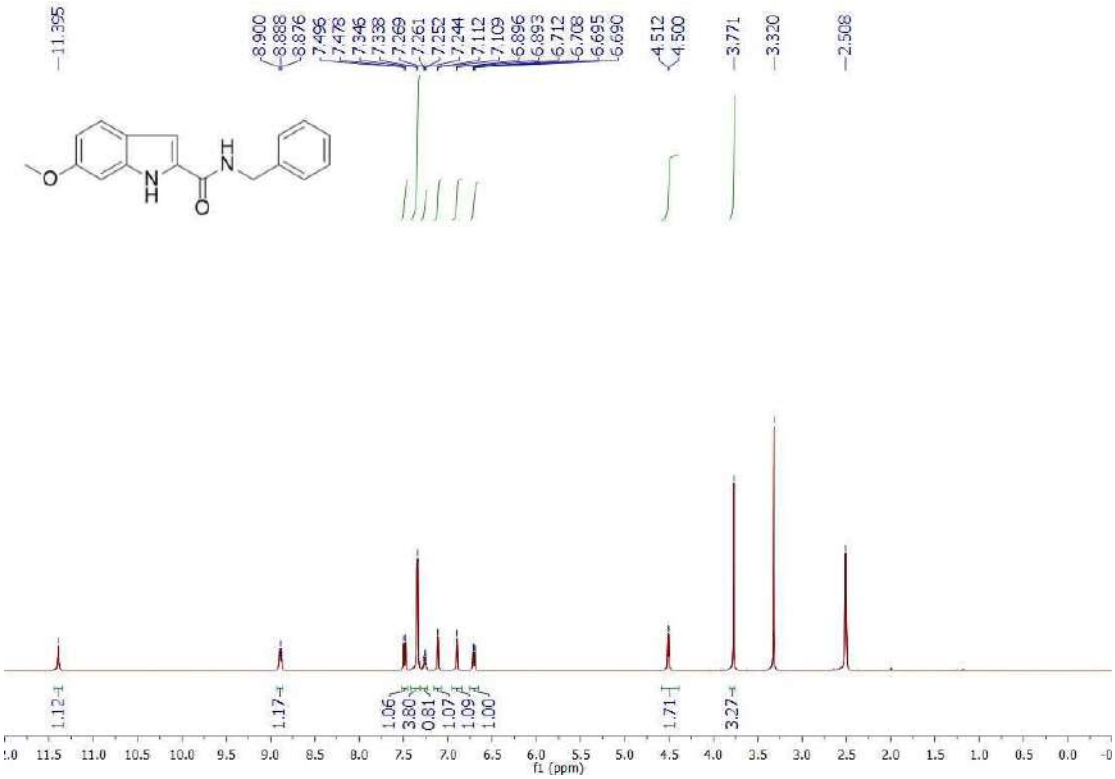
39.90 DMSO
39.81 DMSO
39.64 DMSO
39.47 DMSO
Cl
N
H
O
f1 (ppm)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7.252
7.244
7.112
7.109
6.896
6.893
6.712
6.708
6.695
6.690
4.512
4.500
3.771
3.320
2.508
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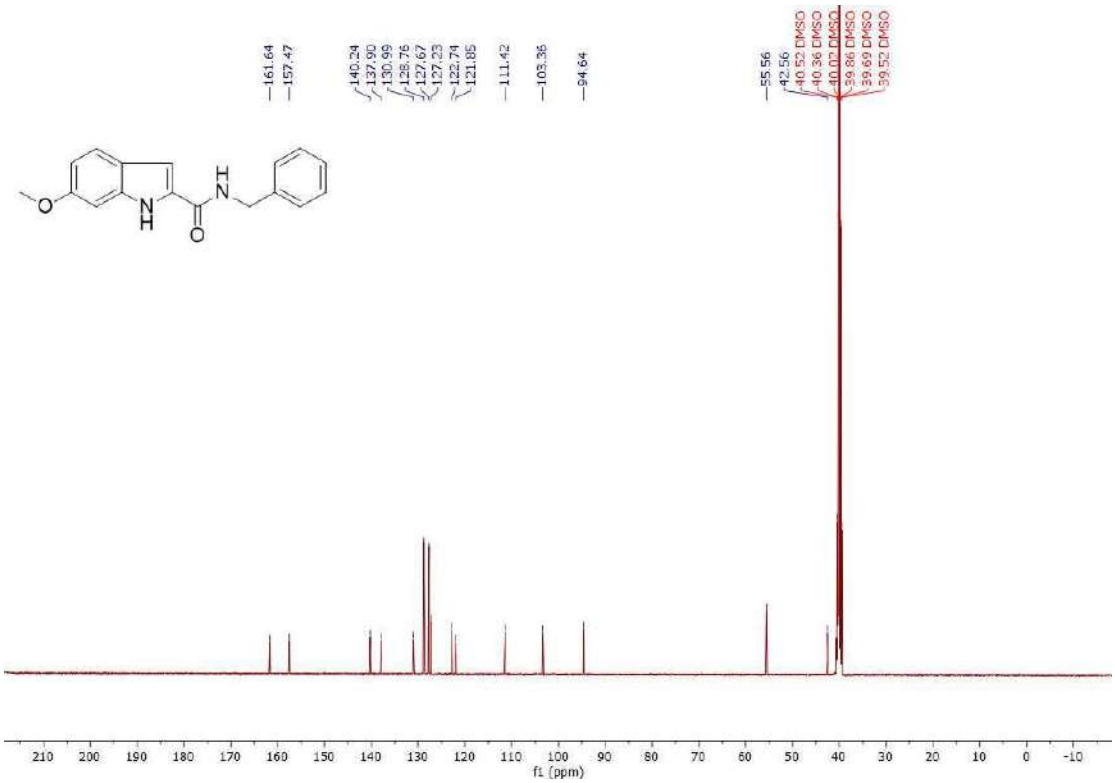
1.06
3.80
0.81
1.07
1.09
1.00
1.71
3.27
f1 (ppm)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127.67
127.23
122.74
121.85
111.42
103.36
94.64
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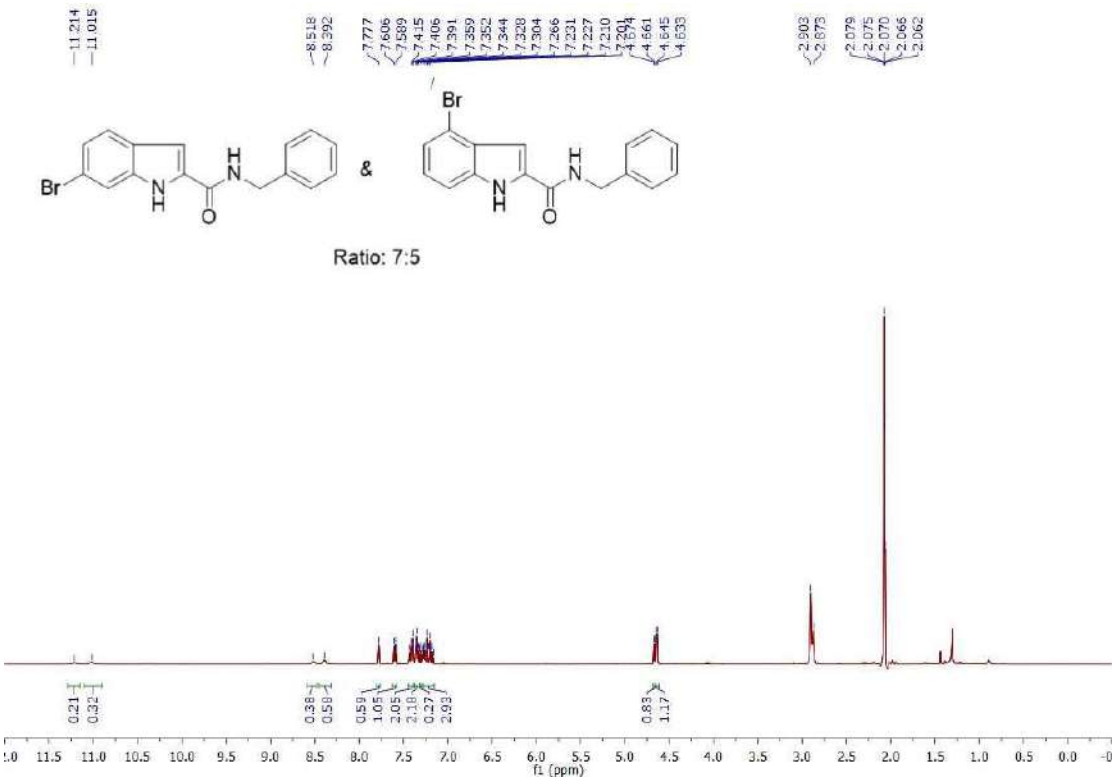
42.56
40.52 DMSO
40.36 DMSO
40.02 DMSO
39.86 DMSO
39.69 DMSO
39.52 DMSO
f1 (ppm)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7.606
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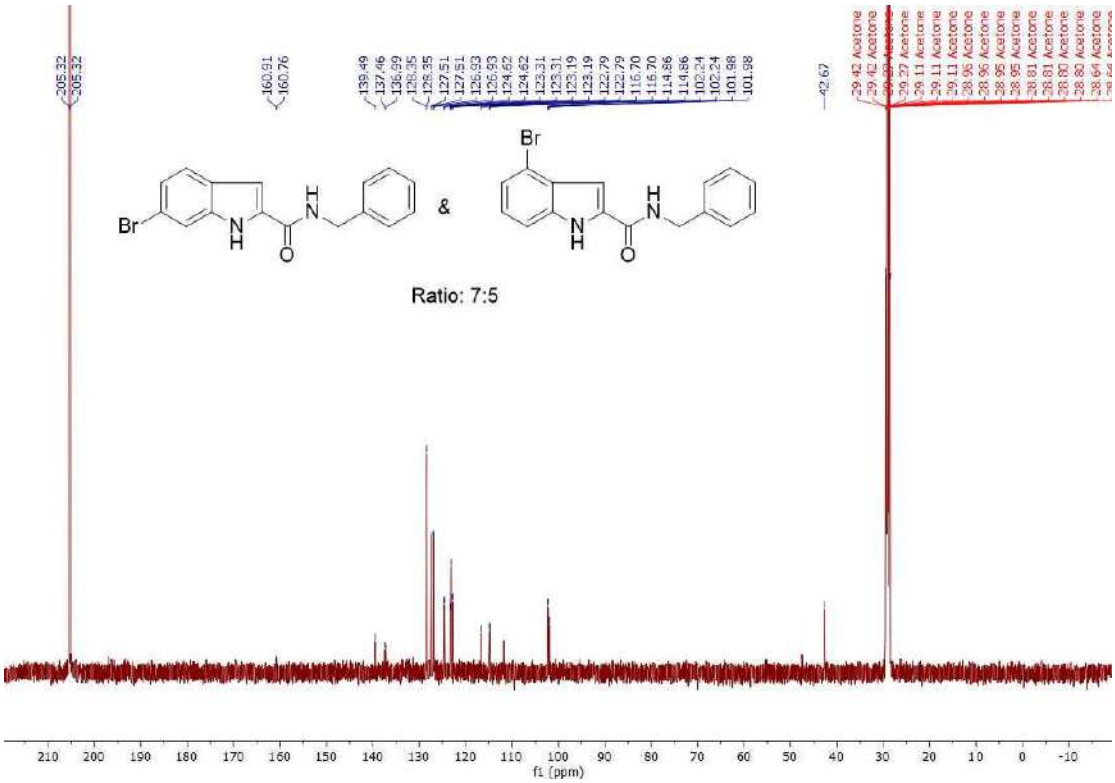
7.415
7.406
7.391
7.359
7.352
7.344
7.328
7.304
7.266
7.231
7.227
7.210
4.661
4.645
4.633
2.903
2.873
2.079
2.075
2.070
2.066
2.062
Br
&
Br
Ratio: 7:5
0.21
0.32
0.38
0.58
0.59
1.05
2.05
2.18
0.27
2.93
0.83
1.17
f1 (ppm)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205.32
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136.99
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127.51
127.51
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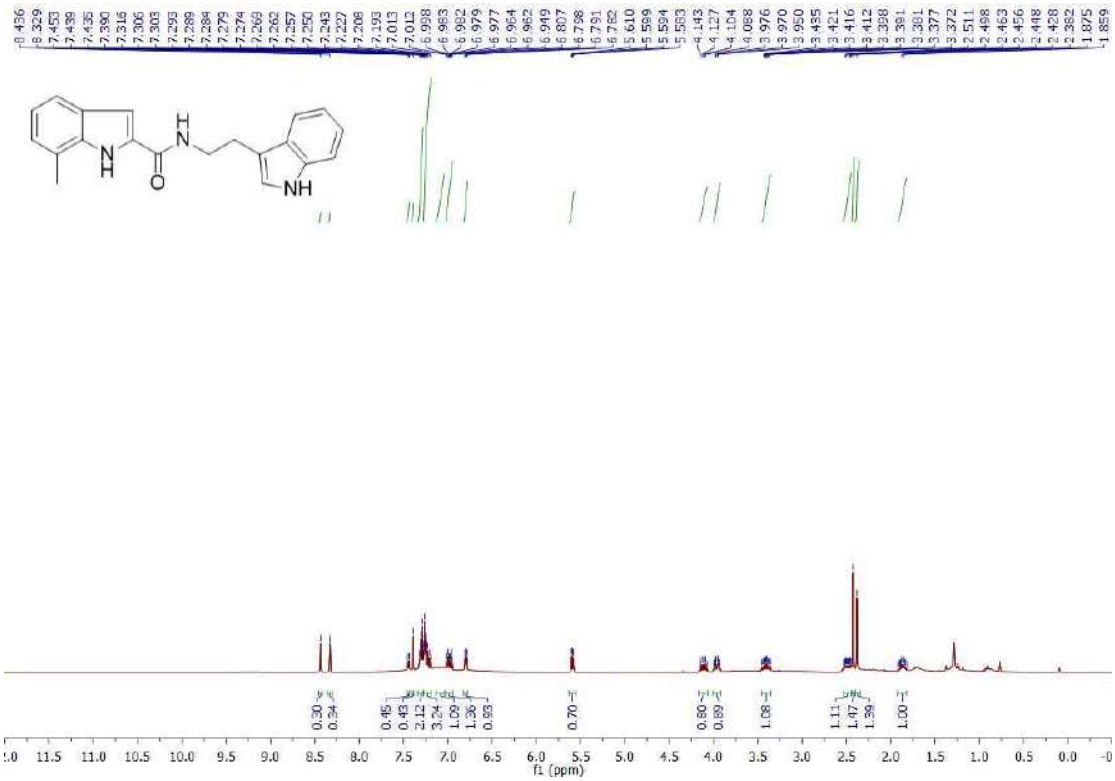
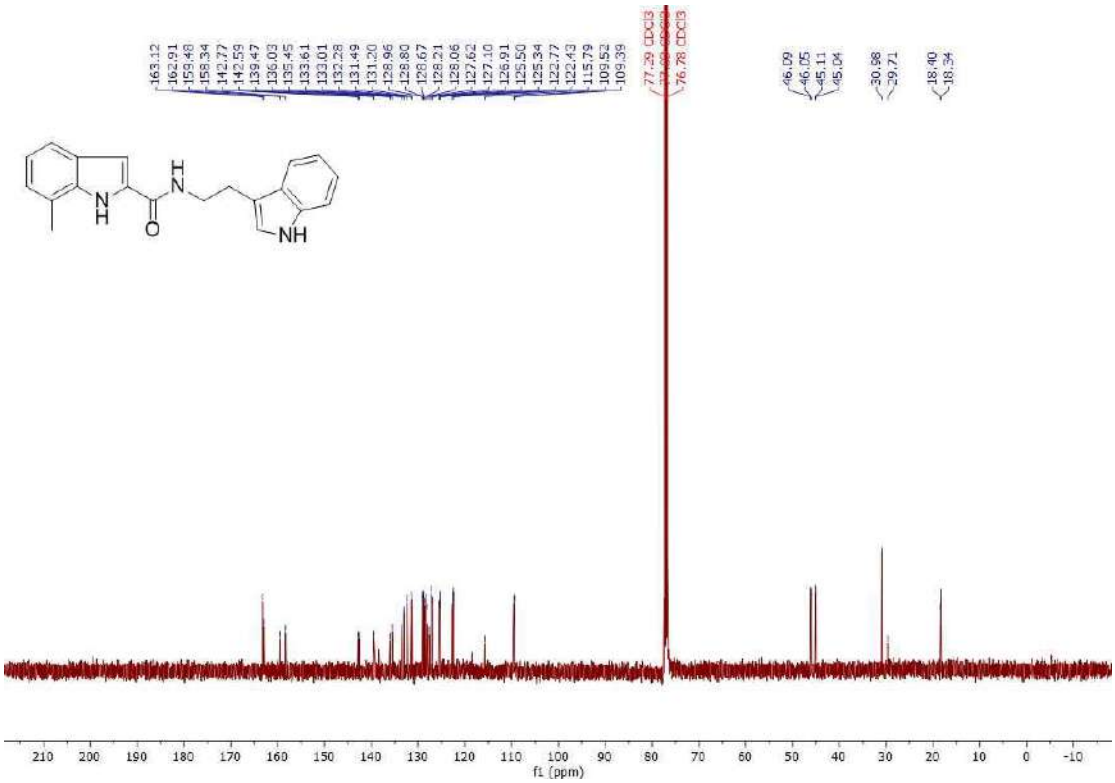
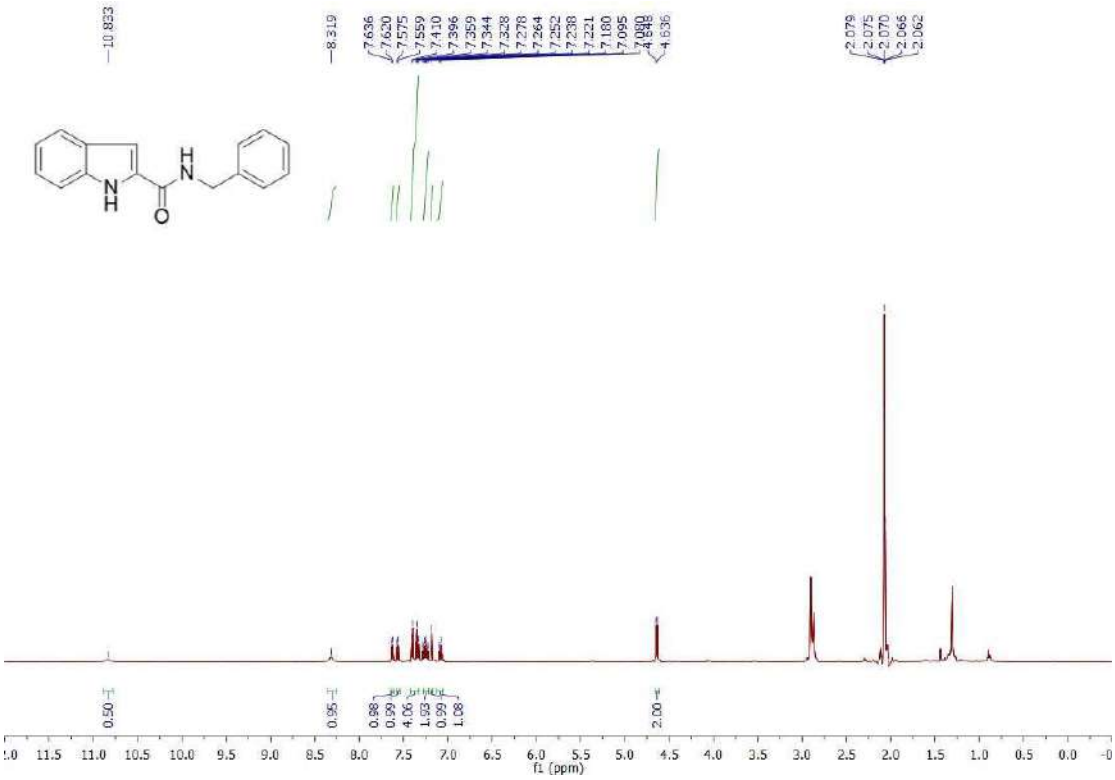
125.93
124.62
124.62
123.31
123.31
123.19
123.19
122.79
122.79
116.70
116.70
114.86
114.86
102.24
102.24
101.98
101.98
42.67
29.42 Acetone
29.42 Acetone
29.27 Acetone
29.11 Acetone
29.11 Acetone
28.96 Acetone
28.96 Acetone
28.95 Acetone
28.95 Acetone
28.81 Acetone
28.81 Acetone
28.80 Acetone
28.80 Acetone
28.64 Acetone
Br
&
Br
Ratio: 7:5
f1 (ppm)



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7.636
7.620
7.575
7.559
7.410
7.396
7.359
7.344
7.328
7.278
7.264
7.252
7.238
7.221
7.180
7.095
7.080
4.648
4.636
2.079
2.075
2.070
2.066
2.062
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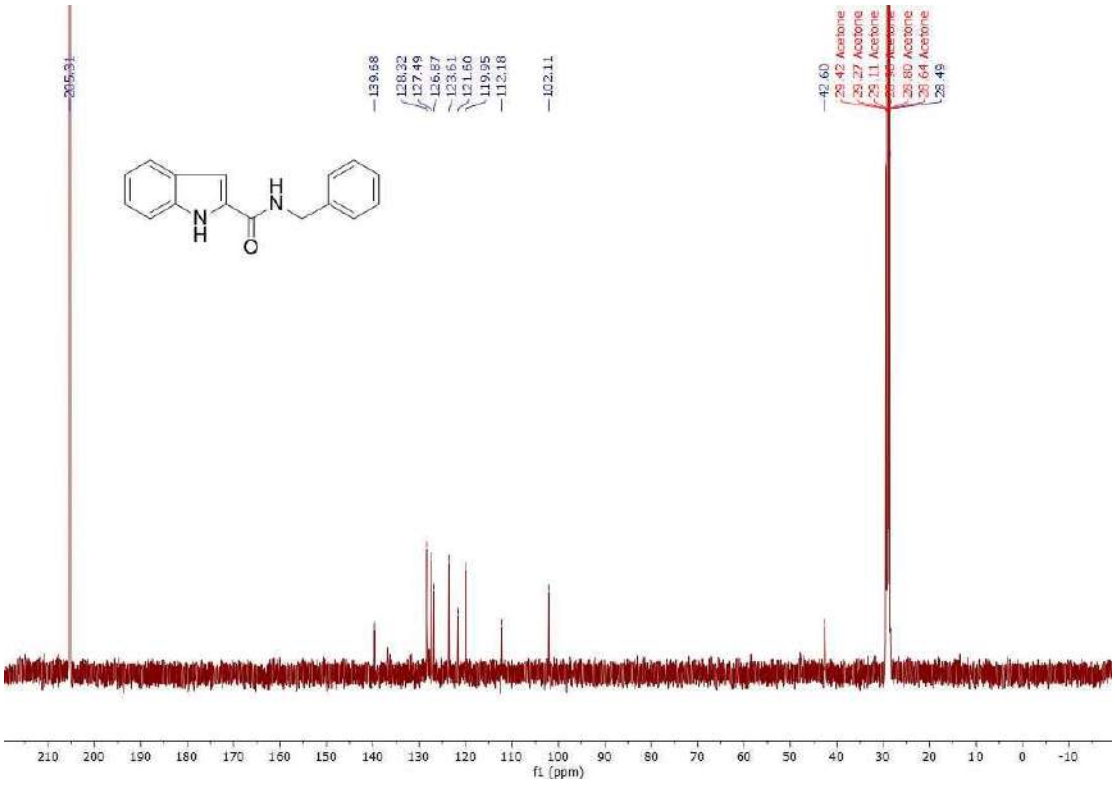
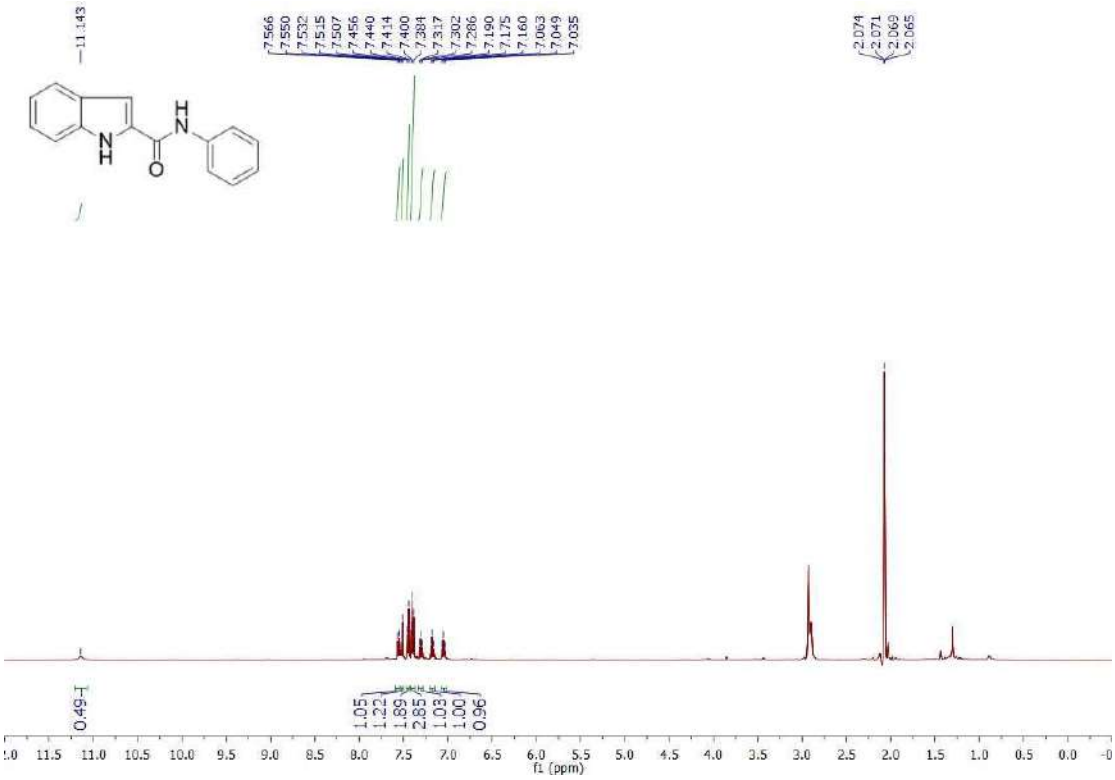
0.95
0.98
0.99
4.06
1.93
0.99
1.08
2.00
f1 (ppm)


205.31
139.68
128.32
127.49
126.87
123.61
121.60
119.95
112.18
102.11
42.60
29.42 Acetone
29.27 Acetone
29.11 Acetone
28.80 Acetone
28.64 Acetone
28.49
f1 (ppm)


11.143
7.566
7.550
7.532
7.515
7.507
7.456
7.440
7.414
7.400
7.384
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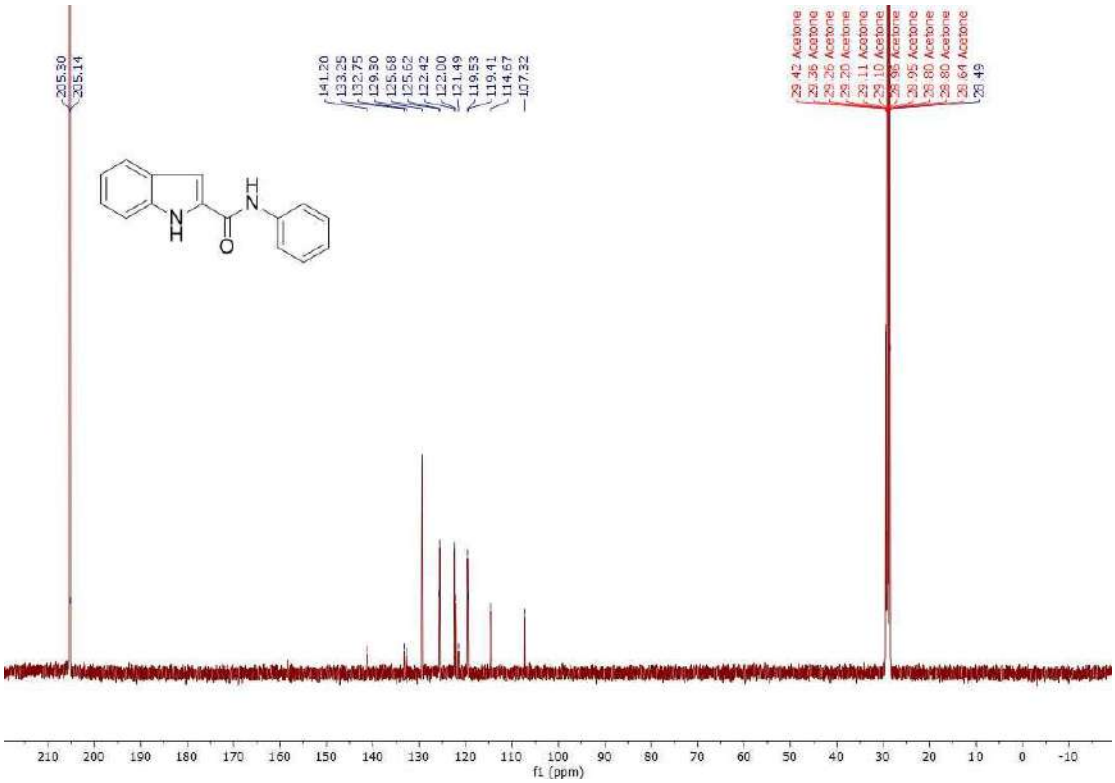
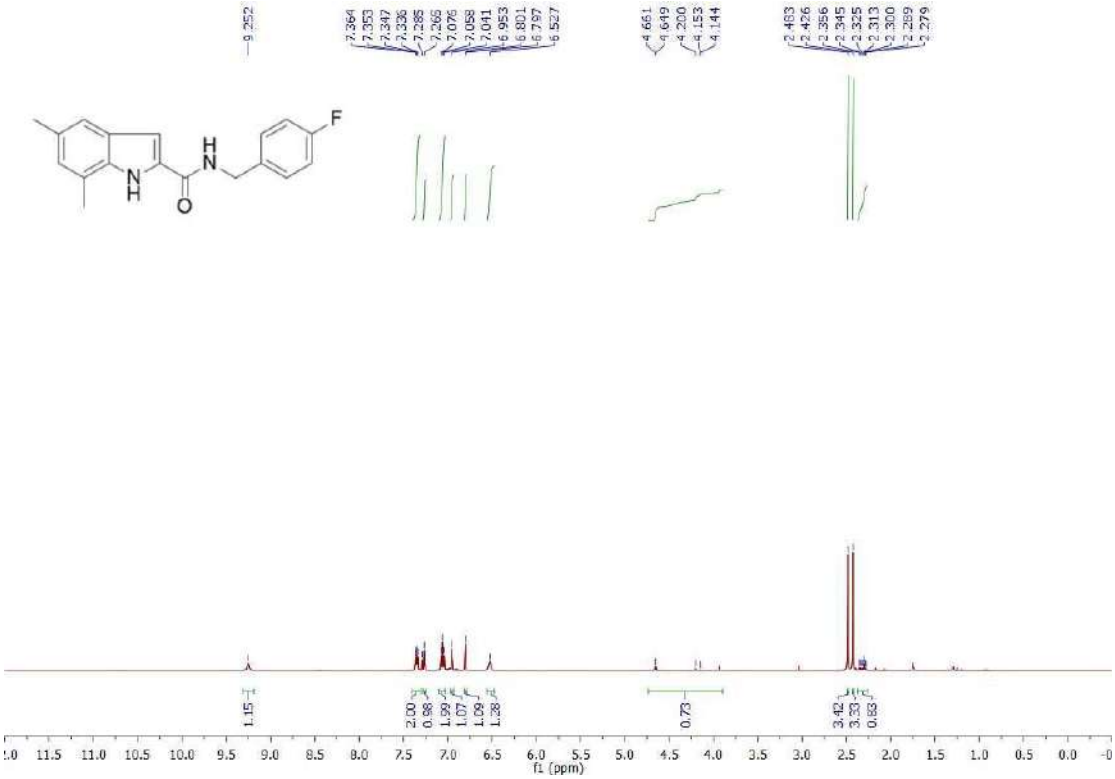
7.302
7.286
7.190
7.175
7.160
7.063
7.049
7.035
2.074
2.071
2.069
2.065
0.49
1.05
1.22
1.89
2.85
1.03
1.00
0.96
f1 (ppm)


205.30
205.14
141.20
133.25
132.75
129.30
125.68
125.62
122.42
122.00
121.49
119.53
119.41
114.67
107.32
29.42 Acetone
29.36 Acetone
29.26 Acetone
29.20 Acetone
29.11 Acetone
29.10 Acetone
28.95 Acetone
28.80 Acetone
28.64 Acetone
28.49
f1 (ppm)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6.797
6.527
4.661
4.649
4.200
4.153
4.144
2.463
2.426
2.356
2.345
2.325
2.313
2.300
2.289
2.279
F
H
N
N
H
O
1.15
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1.99
1.07
1.09
1.28
0.73
3.42
3.33
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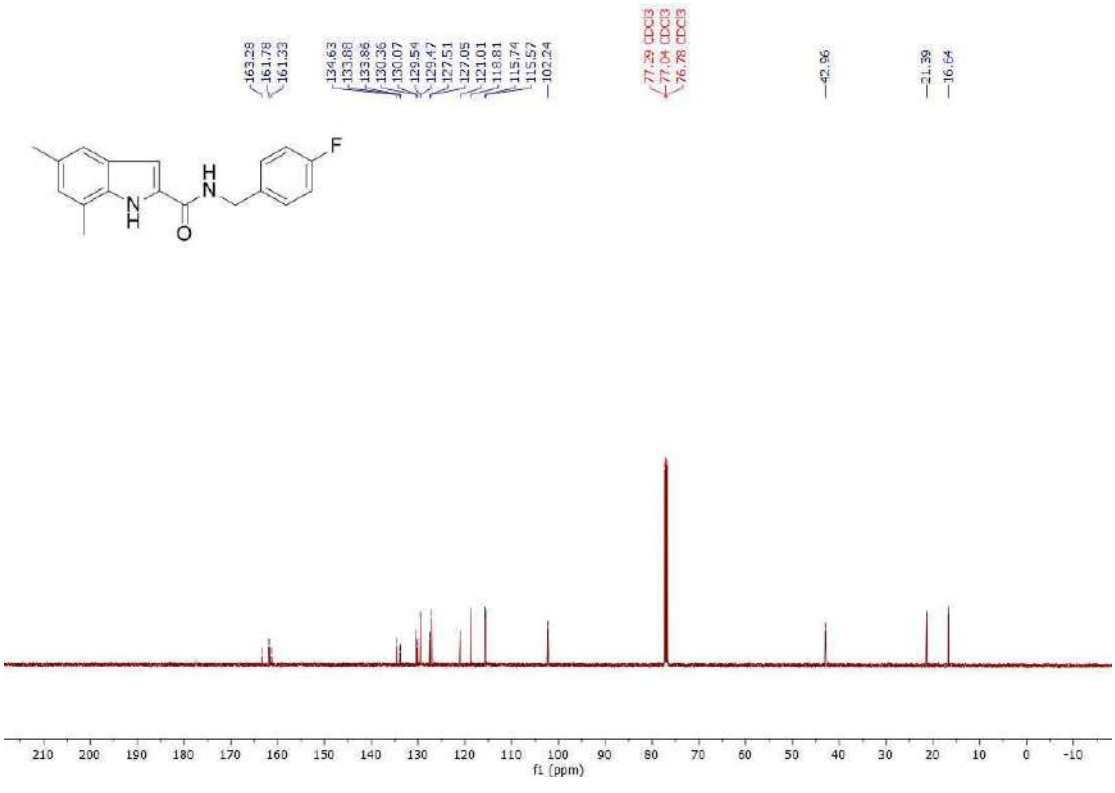
f1 (ppm)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130.07
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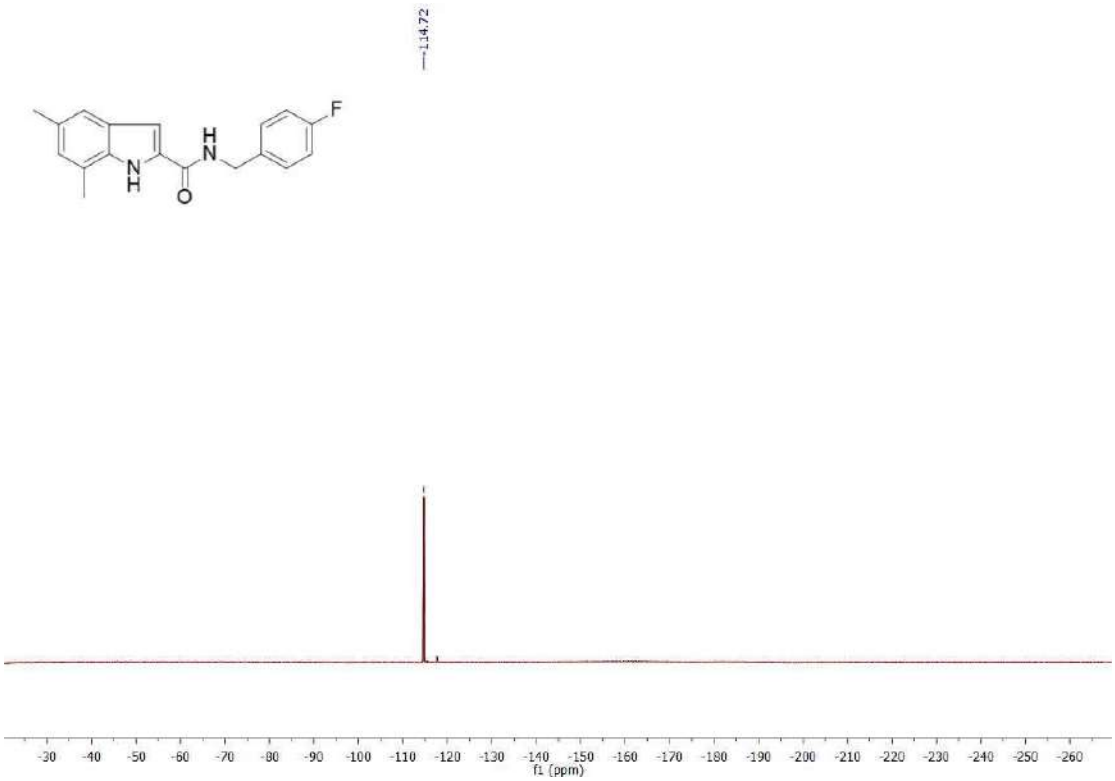
129.47
127.51
127.05
121.01
118.81
115.74
115.57
102.24
77.29 CDCl3
77.04 CDCl3
76.78 CDCl3
42.96
21.39
16.64
F
H
N
N
H
O
f1 (ppm)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N
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H
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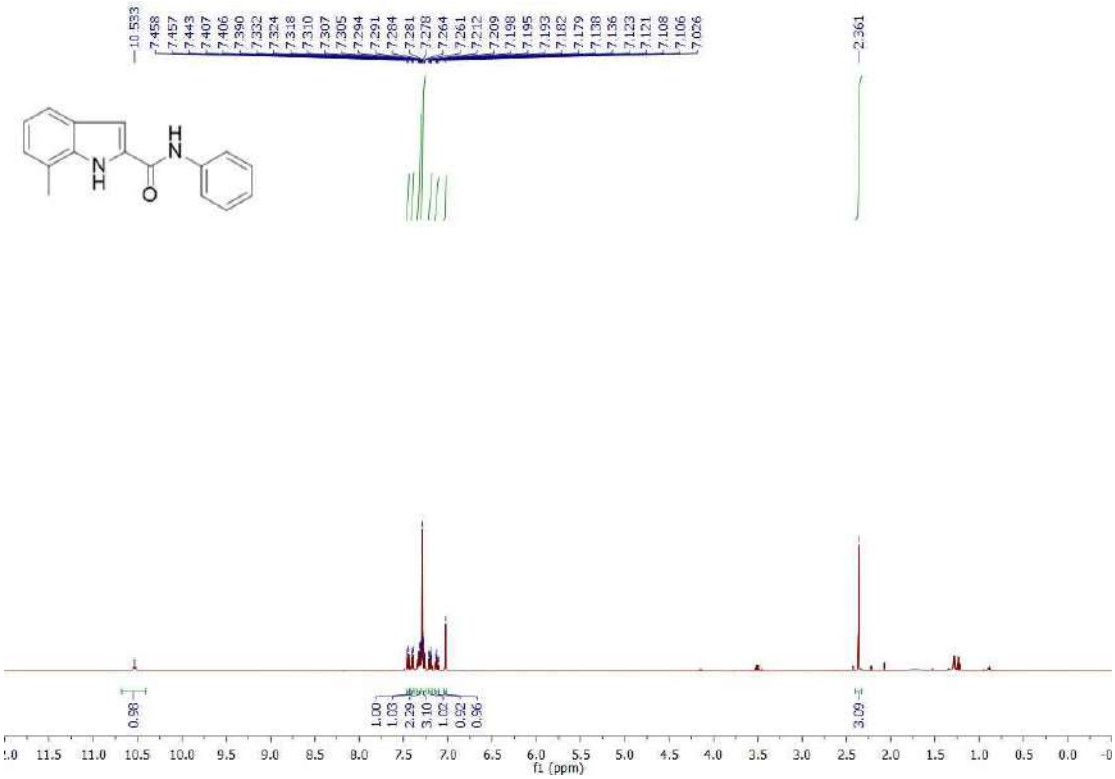
f1 (ppm)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7.307
7.305
7.294
7.291
7.284
7.281
7.278
7.264
7.261
7.212
7.209
7.198
7.195
7.193
7.182
7.179
7.138
7.136
7.123
7.121
7.108
7.106
7.026
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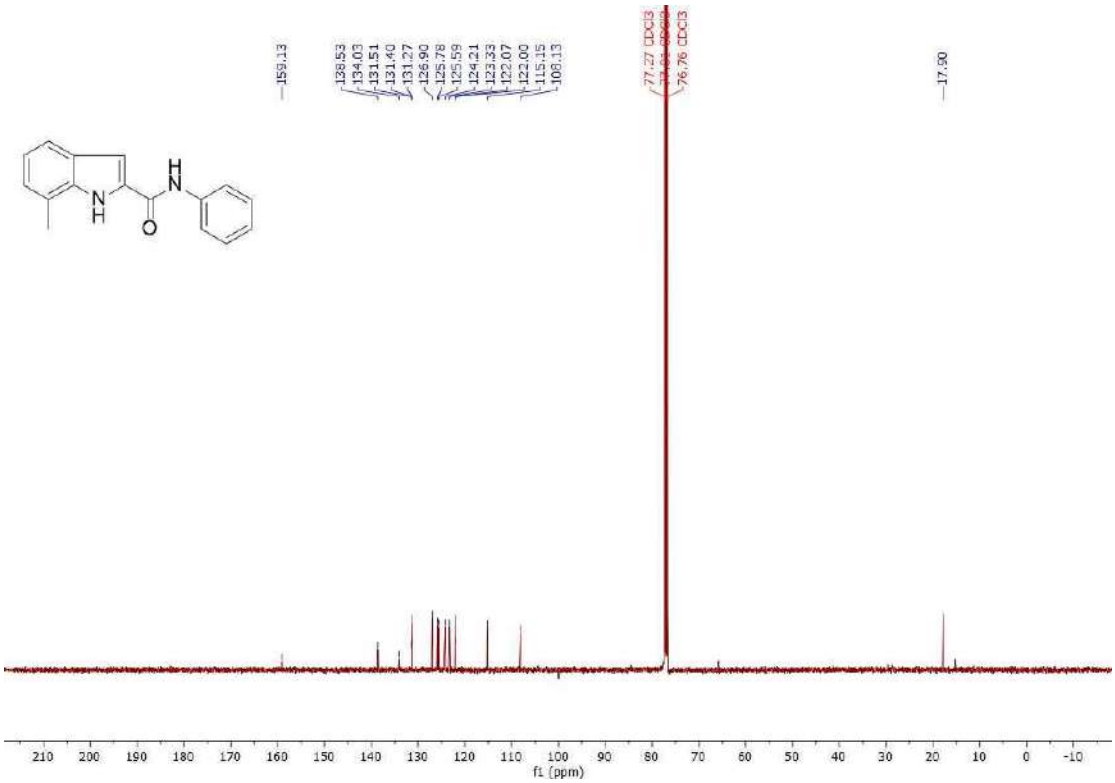
1.00
1.03
2.29
3.10
1.02
0.92
0.96
3.09
f1 (ppm)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126.90
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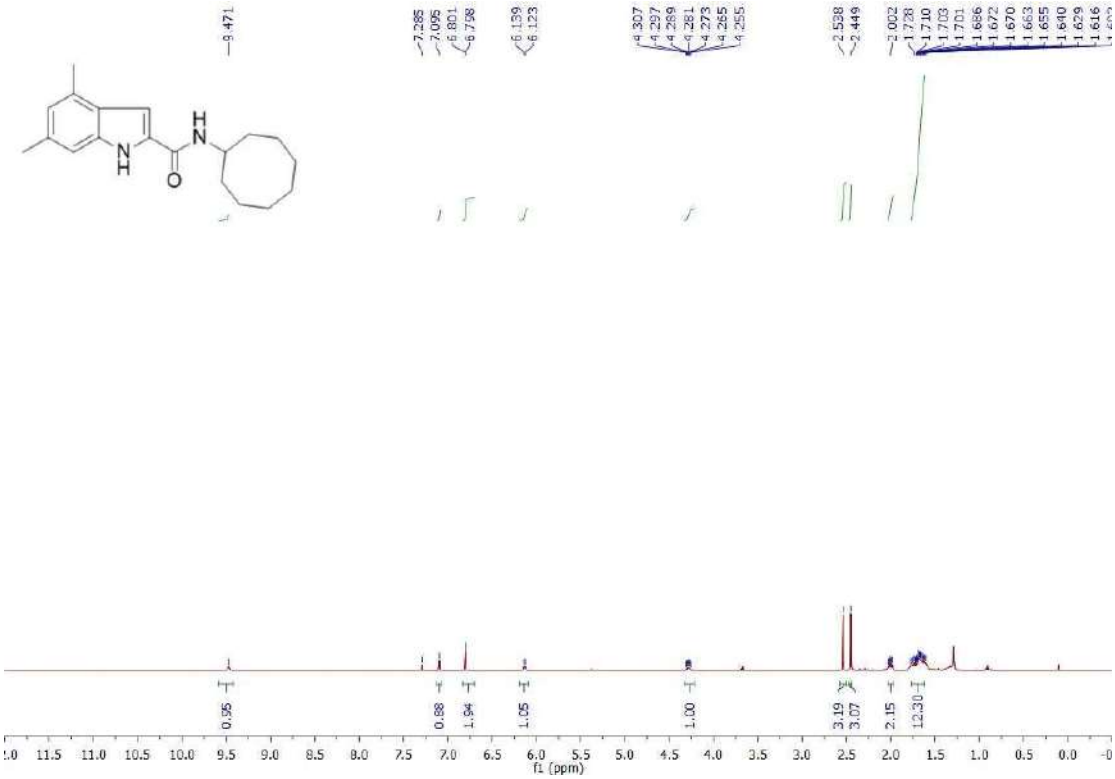
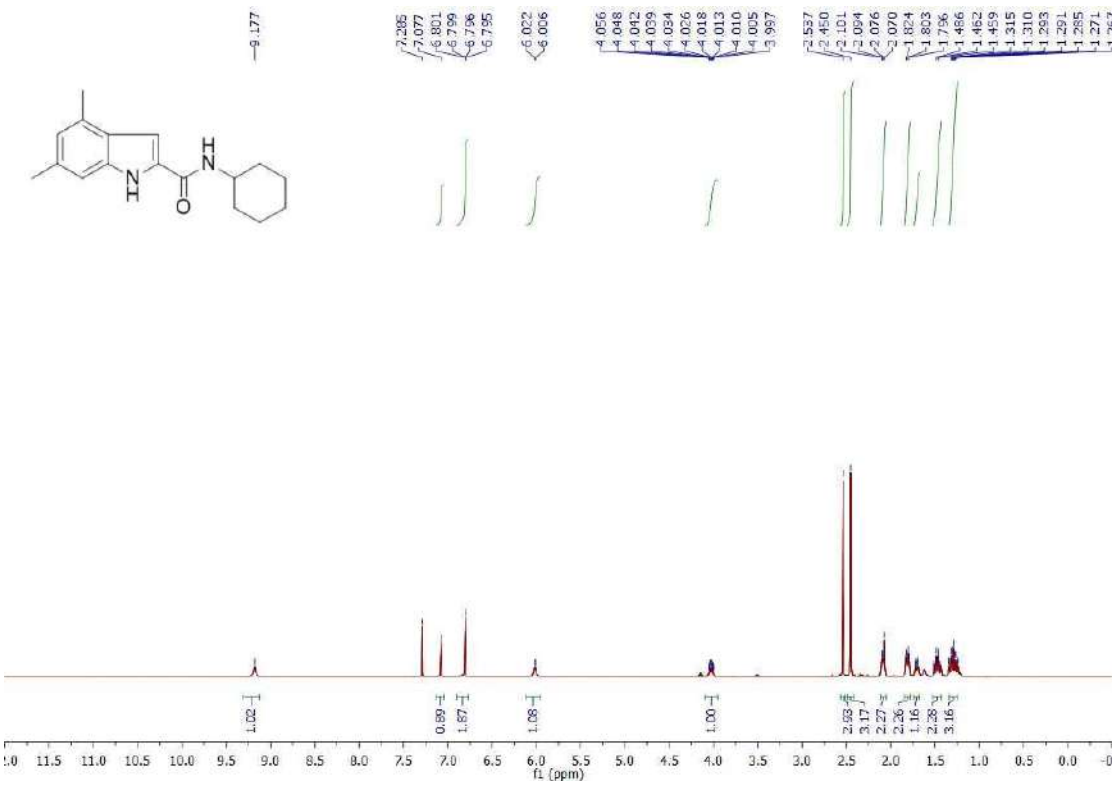
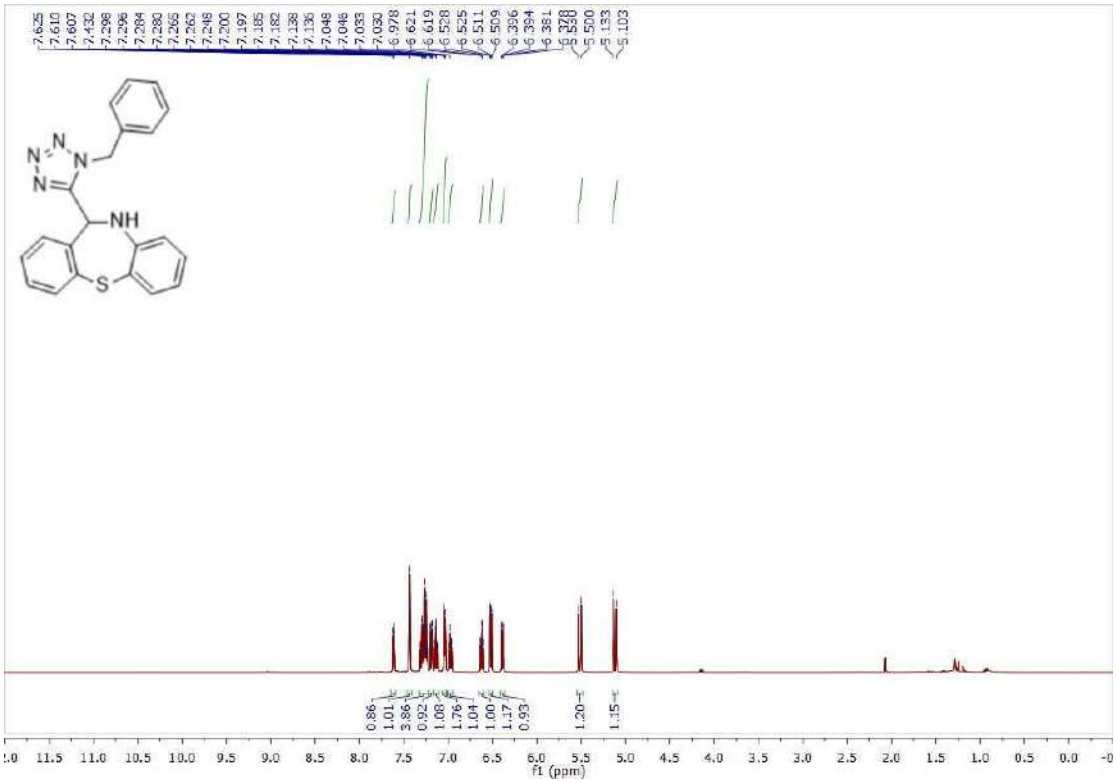
76.76 CDCl3
17.90
f1 (ppm)



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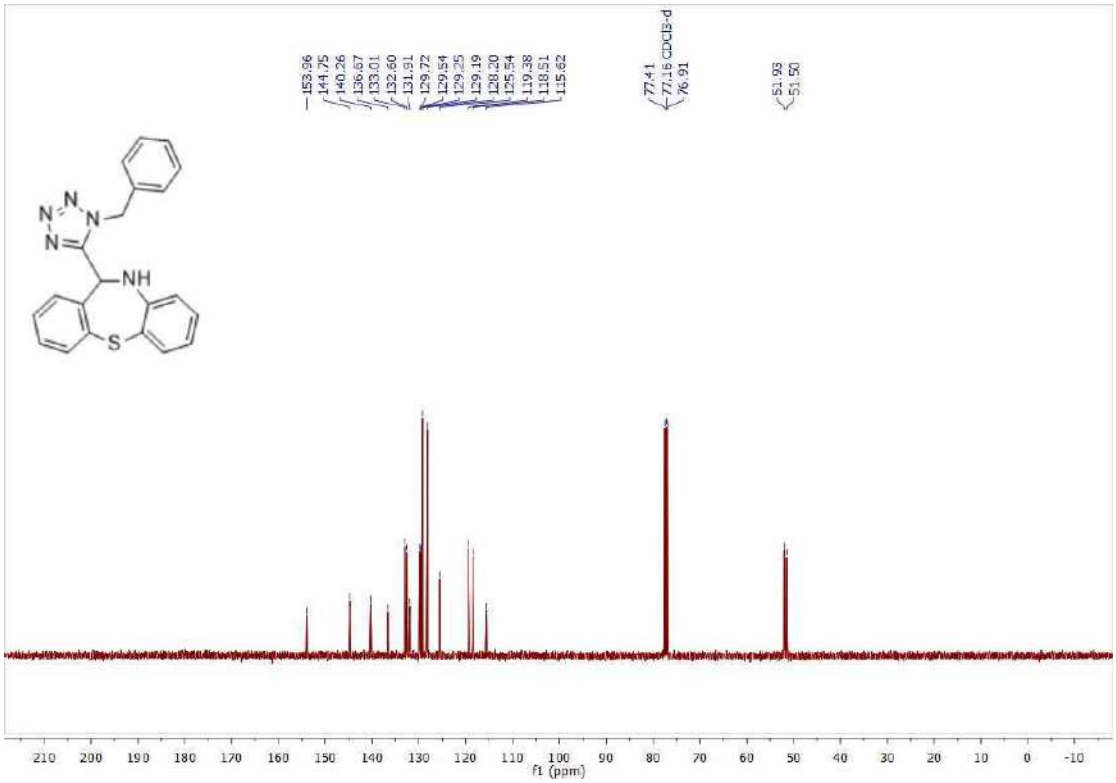
7.280
7.265
7.262
7.248
7.200
7.197
7.185
7.182
7.138
7.136
7.048
7.046
7.033
7.030
6.978
6.621
6.619
6.528
6.525
6.511
6.509
6.396
6.394
6.381
5.550
5.133
5.103
NH
S
0.86
1.01
3.86
0.92
1.08
1.76
1.04
1.00
1.17
0.93
1.20
1.15
f1 (ppm)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140.26
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132.60
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129.72
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129.25
129.19
128.20
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115.62
77.41
77.16 CDCl3-d
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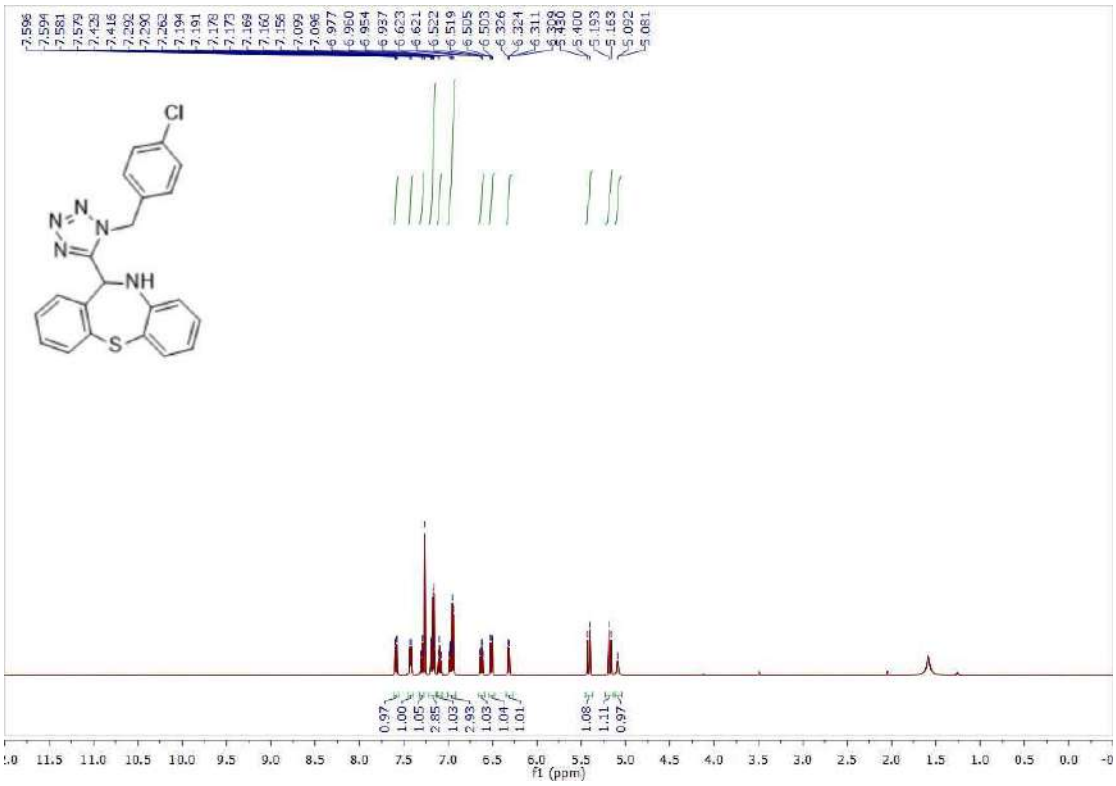
51.93
51.50
NH
S
f1 (ppm)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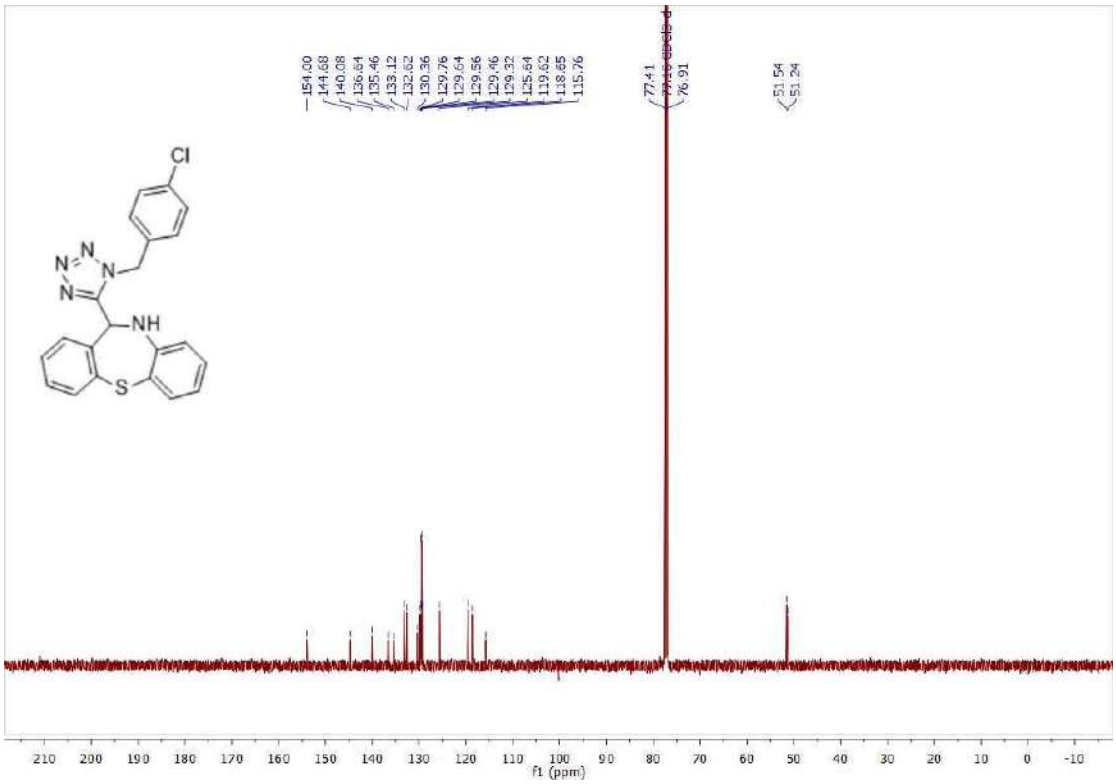
N
N
NH
S
f1 (ppm)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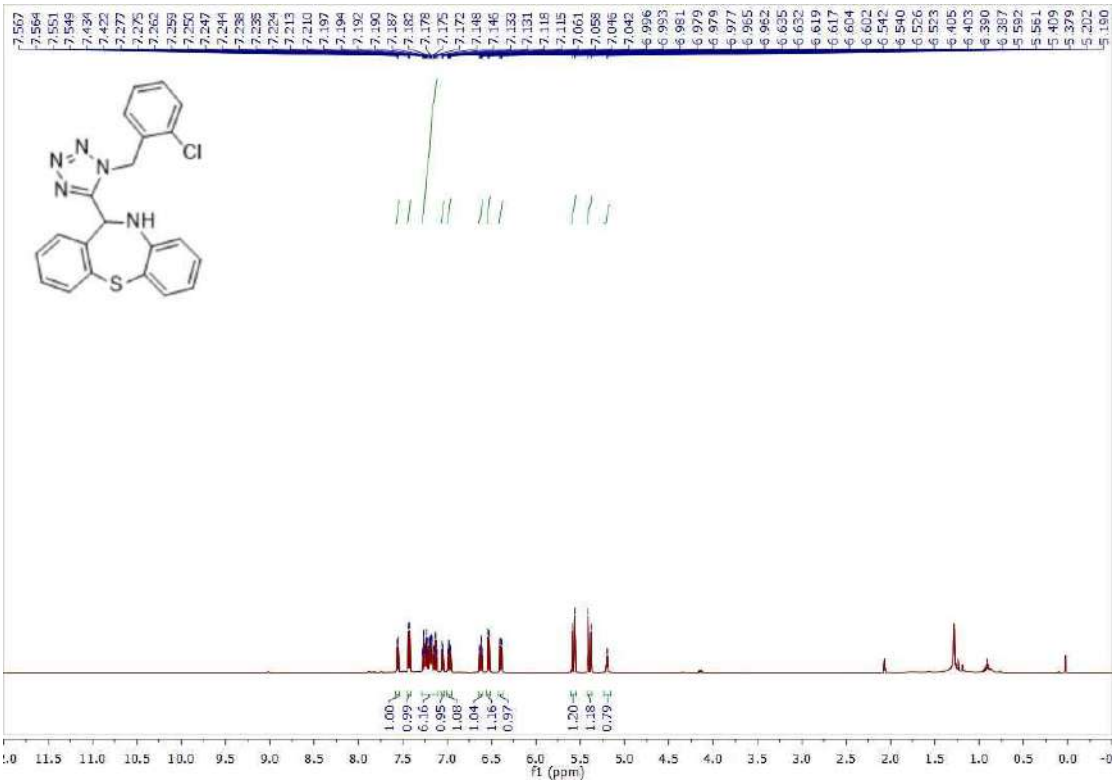
N
N
NH
S
f1 (ppm)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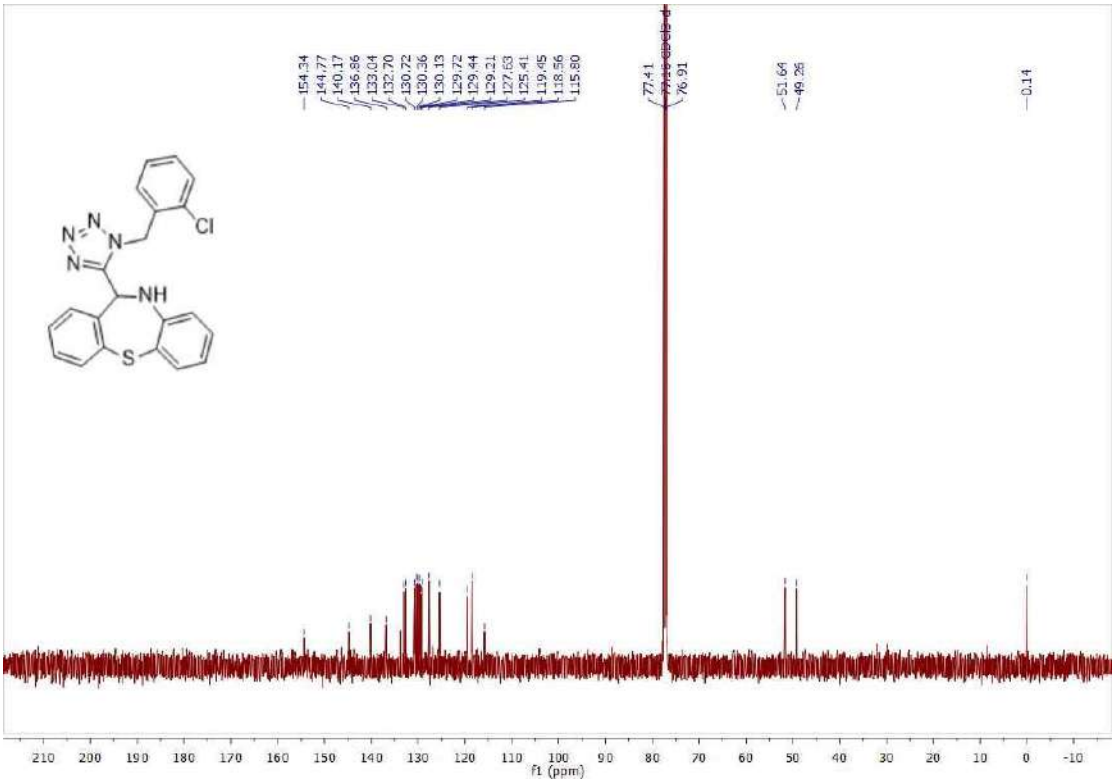
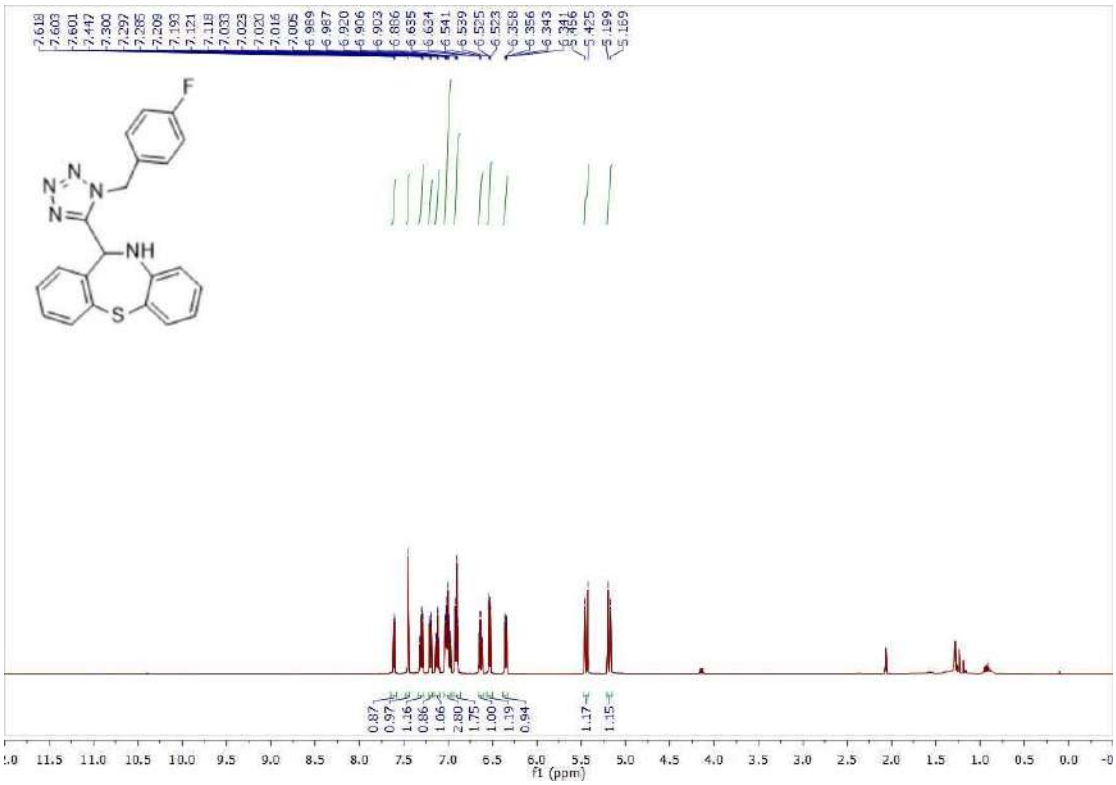
N
NH
S
f1 (ppm)


Cl
N
NH
S
f1 (ppm)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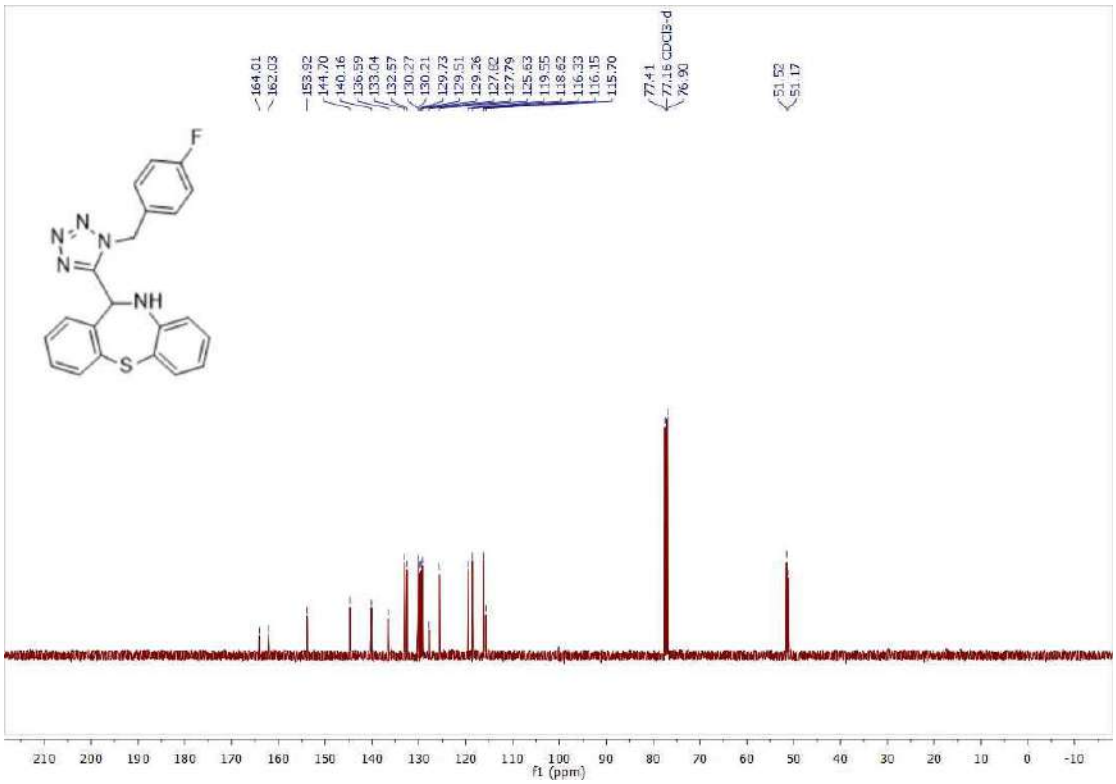
N
N
N
NH
S
f1 (ppm)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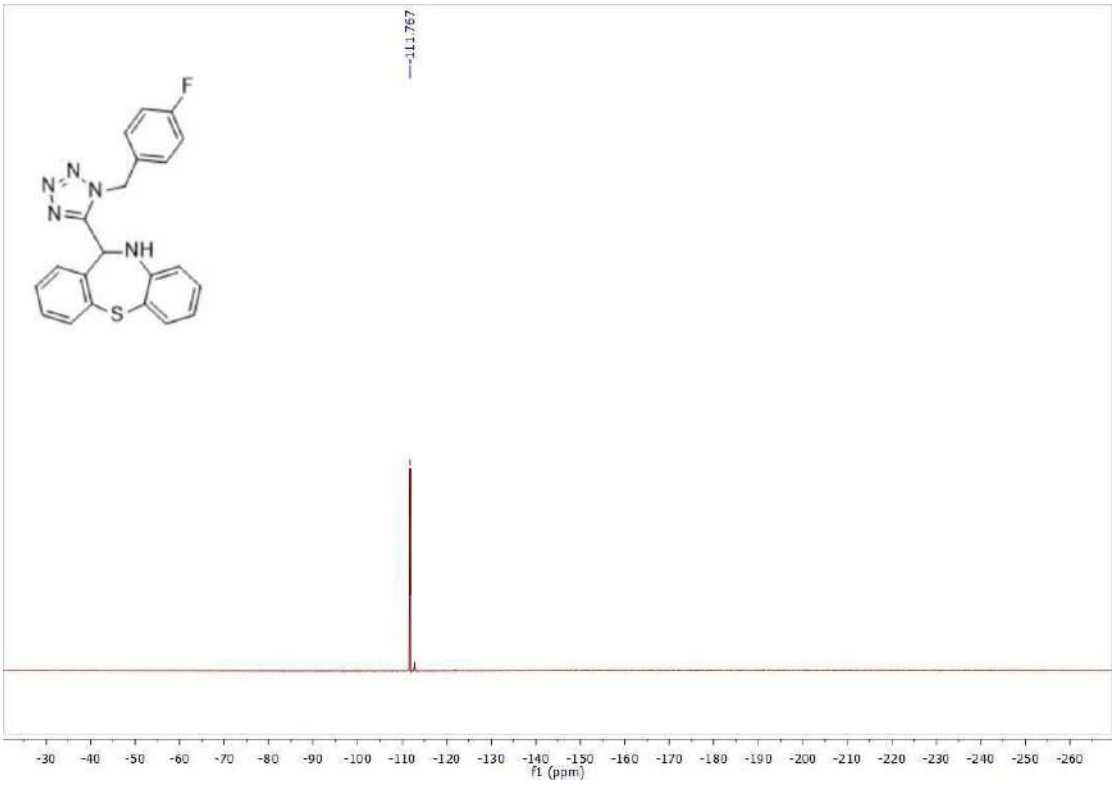
N
N
N
NH
S
f1 (ppm)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N
N
N
NH
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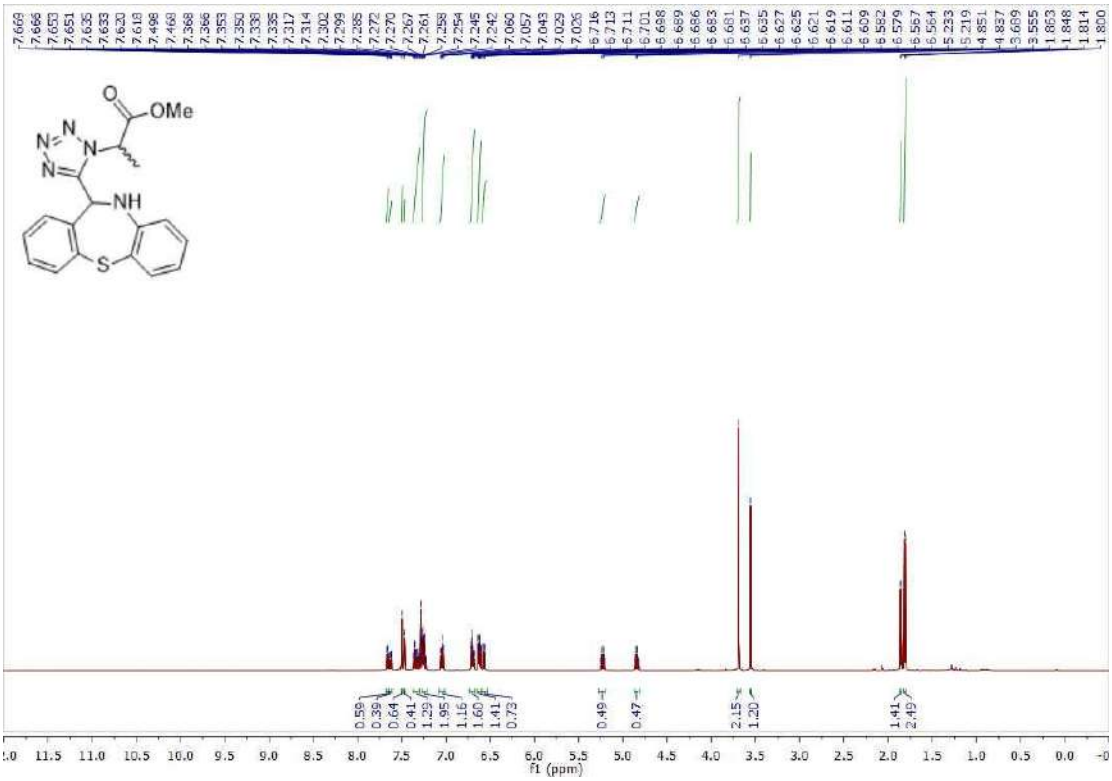
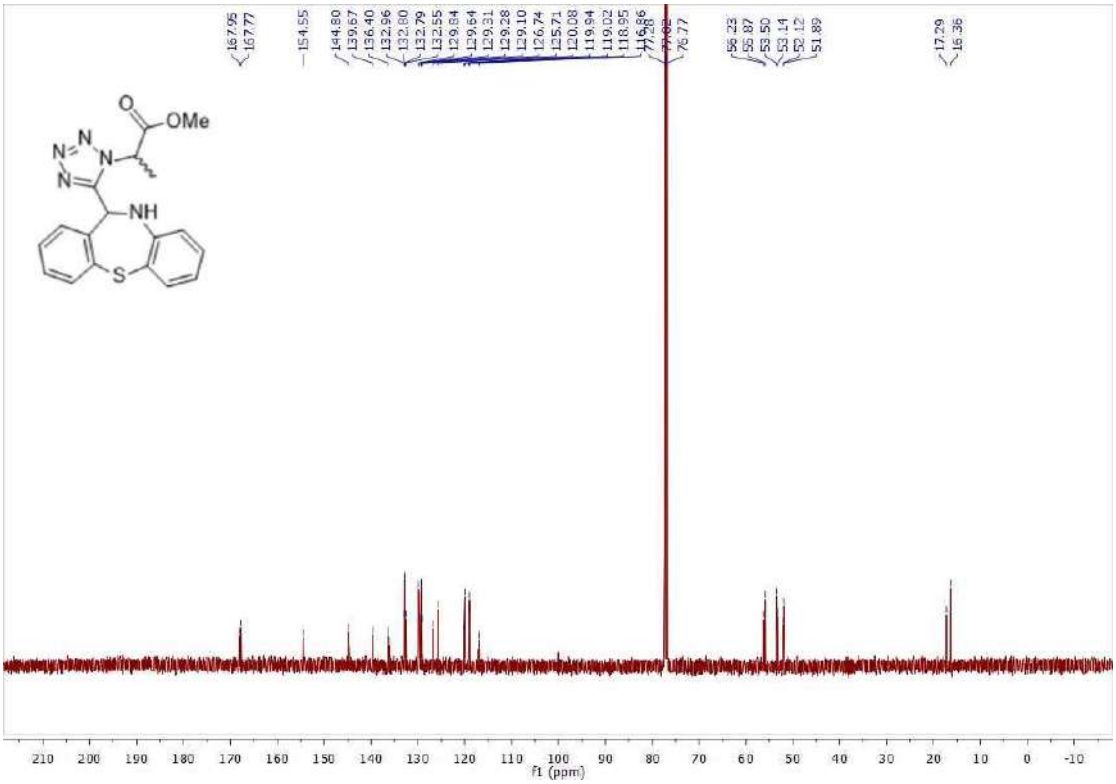
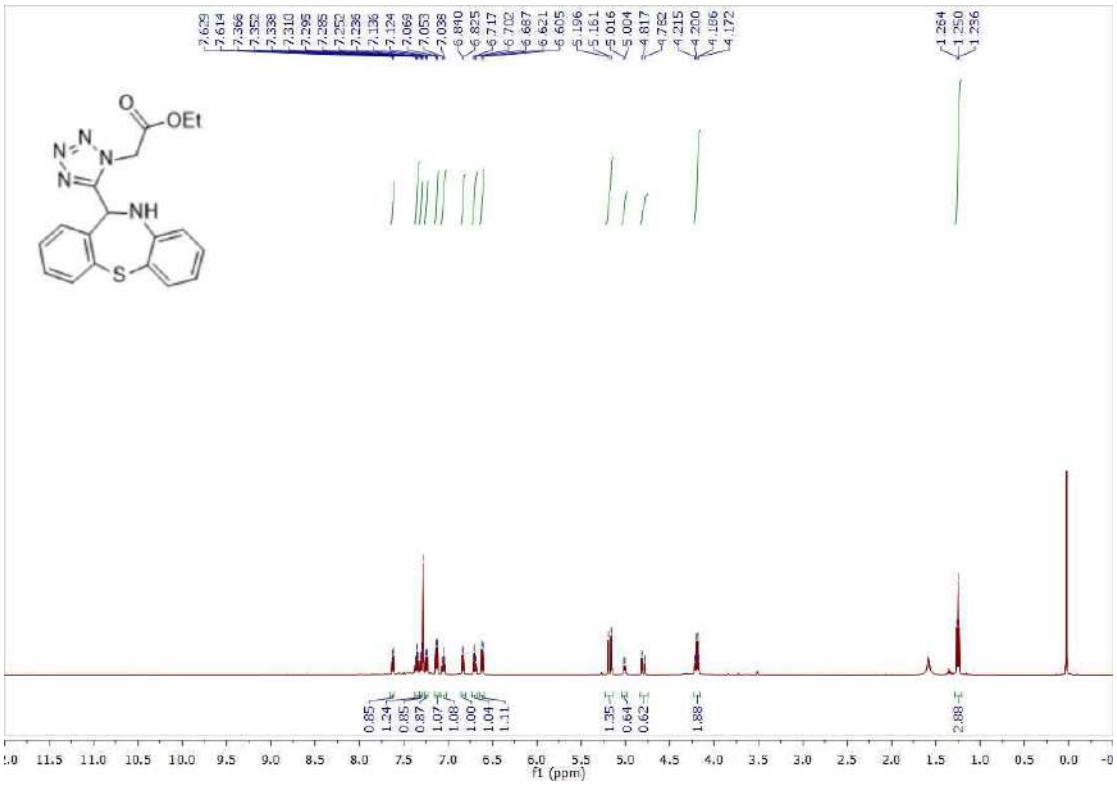
f1 (ppm)


OMe
NH
S
f1 (ppm)


OMe
NH
S
f1 (ppm)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7.124
7.069
7.053
7.038
6.840
6.825
6.717
6.702
6.687
6.621
6.605
5.196
5.161
5.016
5.004
4.817
4.782
4.215
4.200
4.186
4.172
1.264
1.250
1.236
O
OEt
N
N
N
NH
S
0.85
1.24
0.85
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1.04
1.11
1.35
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0.62
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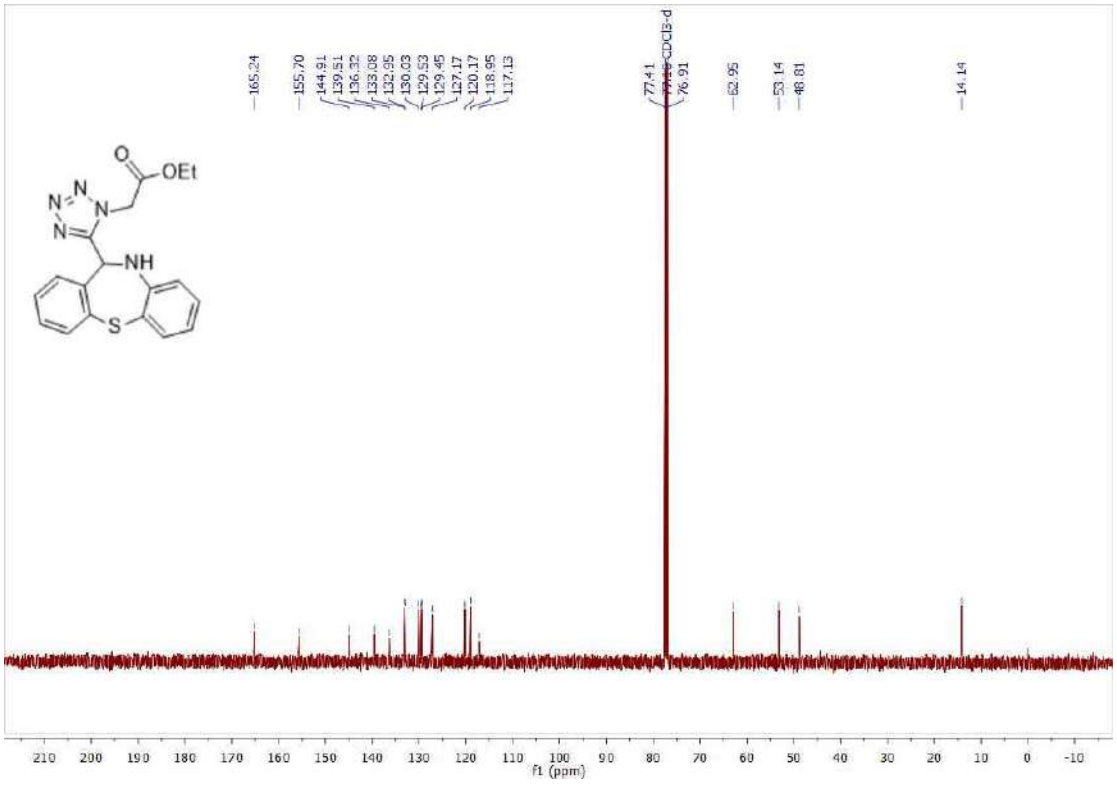
2.88
f1 (ppm)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136.32
133.08
132.95
130.03
129.53
129.45
127.17
120.17
118.95
117.13
77.41
CDCl3-d
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62.95
53.14
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14.14
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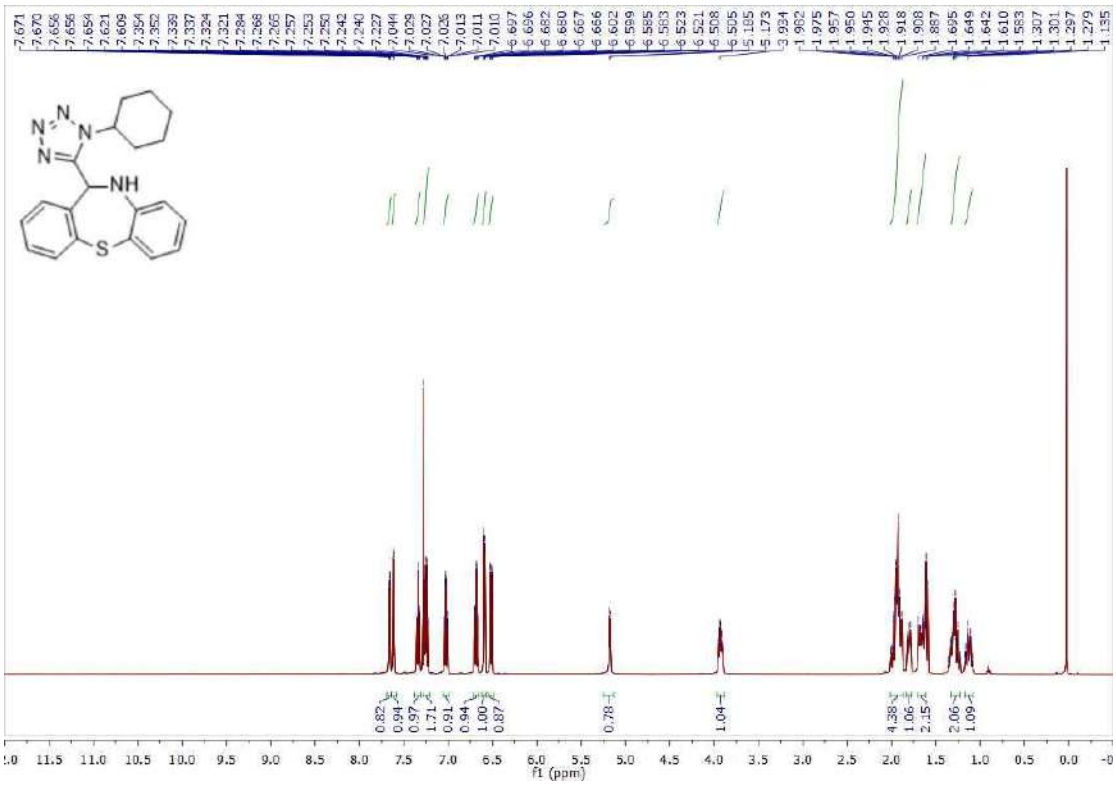
OEt
N
N
N
NH
S
f1 (ppm)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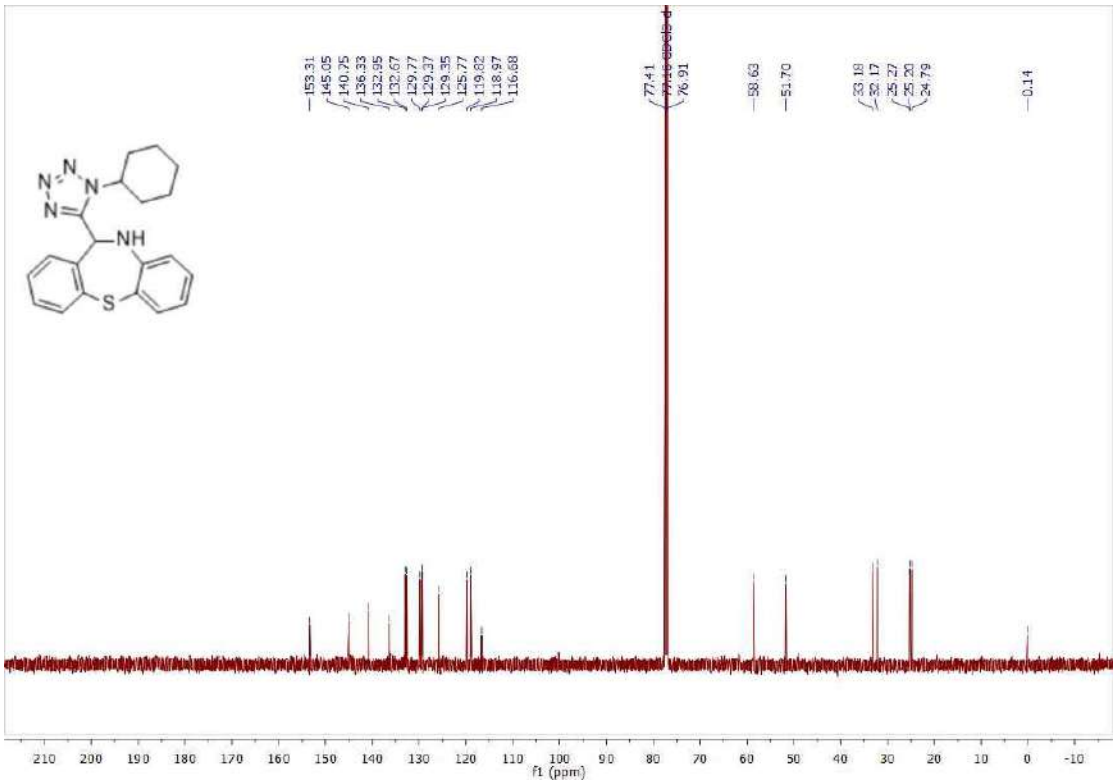
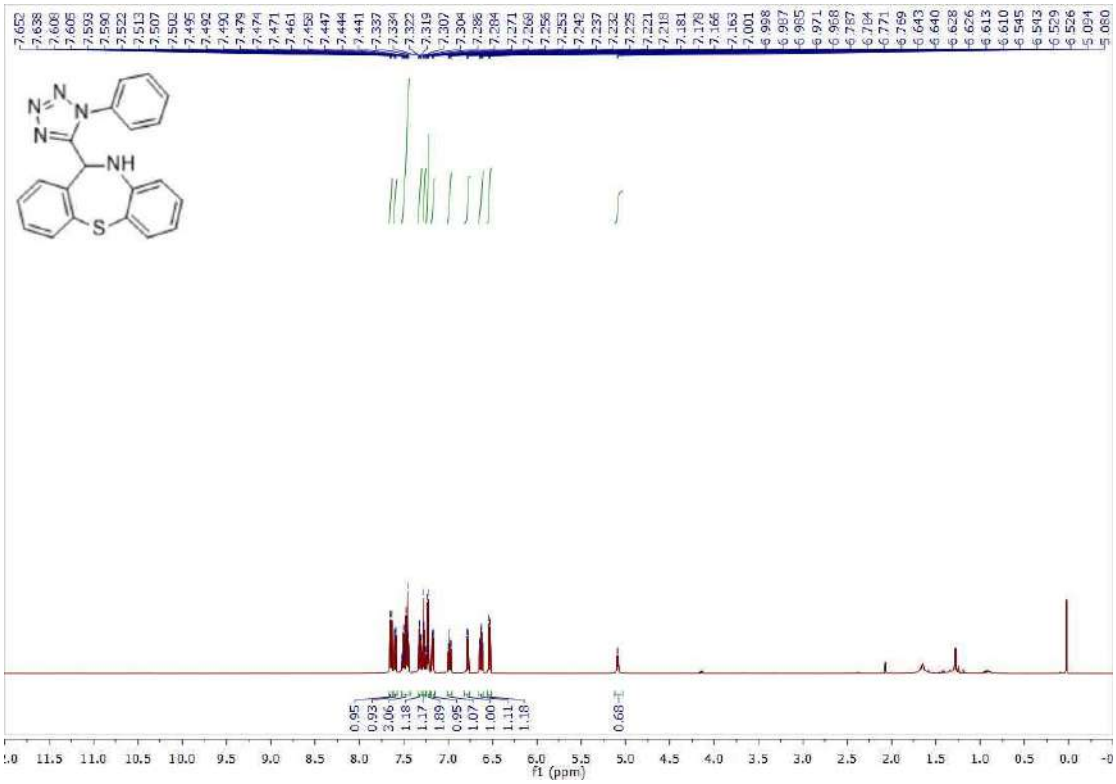
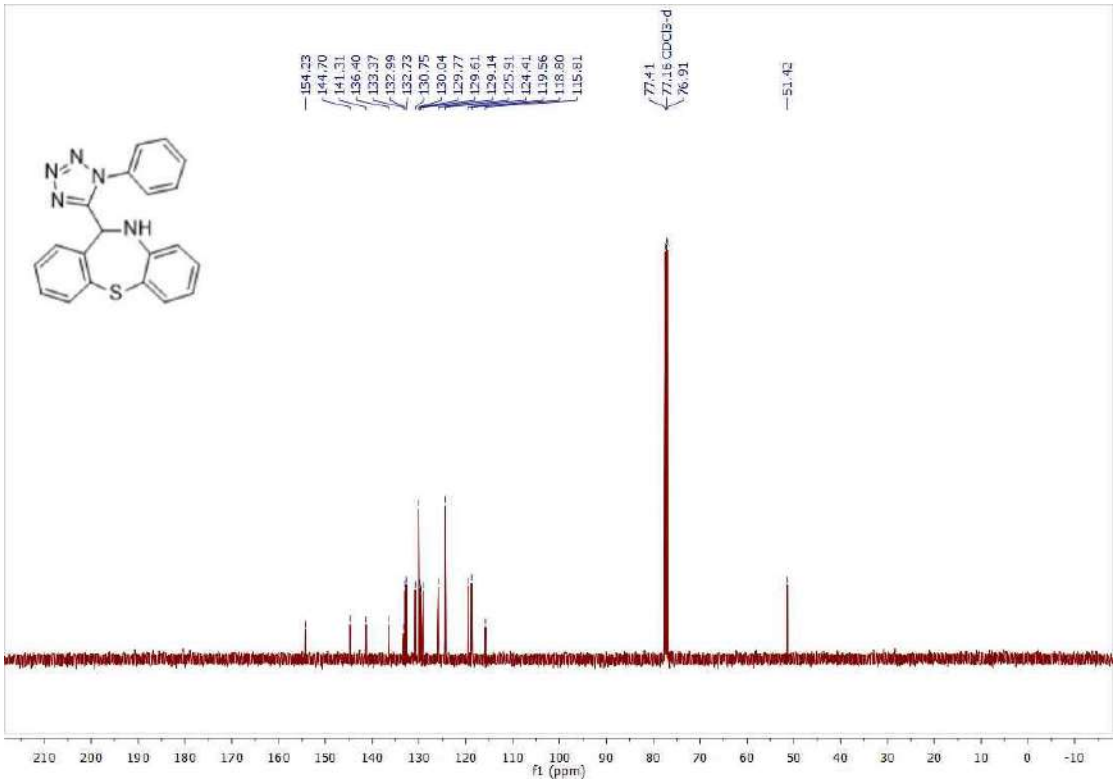
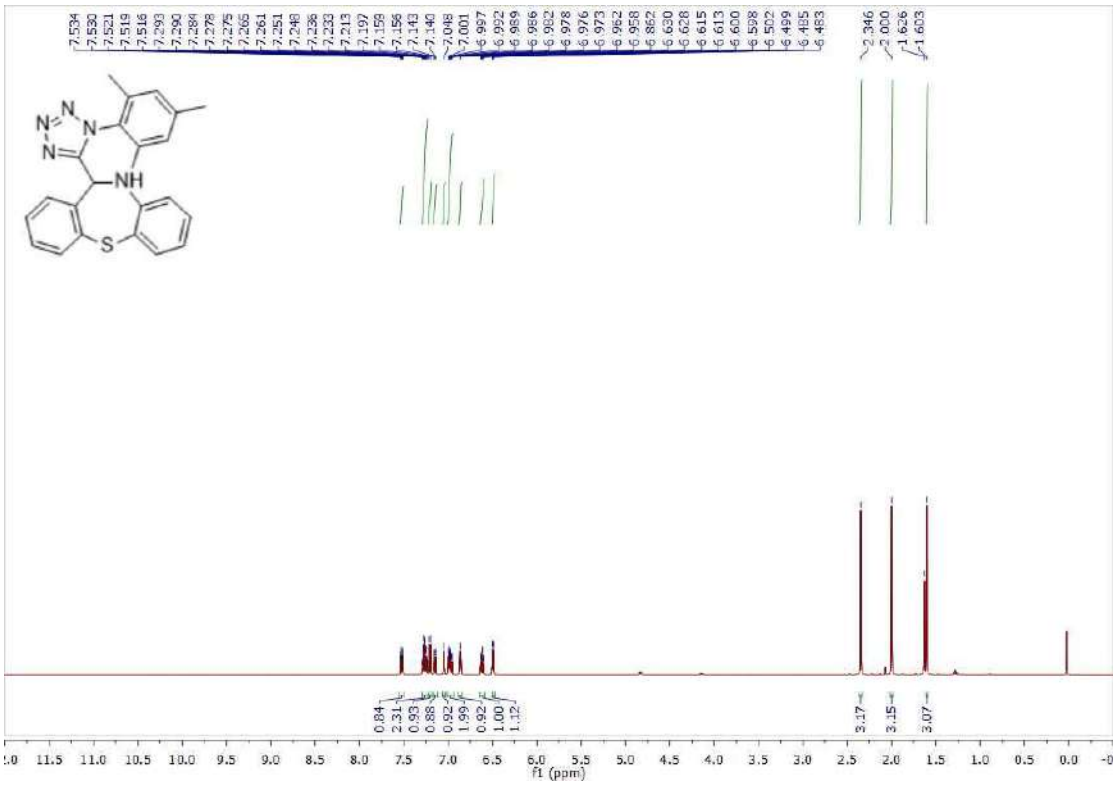
S
f1 (ppm)


NH
S
f1 (ppm)


NH
S
f1 (ppm)


NH
S
f1 (ppm)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7.248
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6.982
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6.485
6.483
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1.603
NH
S
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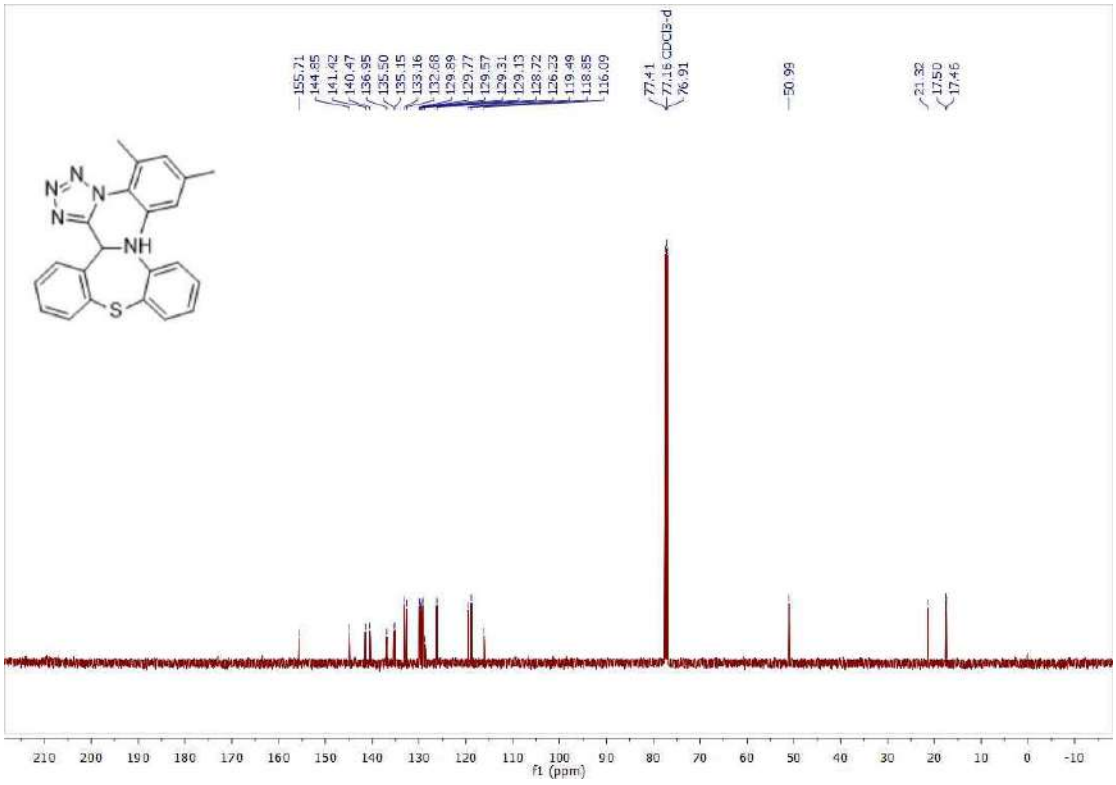
3.07
f1 (ppm)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129.57
129.31
129.13
128.72
126.23
119.49
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116.09
77.41
77.16 CDCl3-d
76.91
50.99
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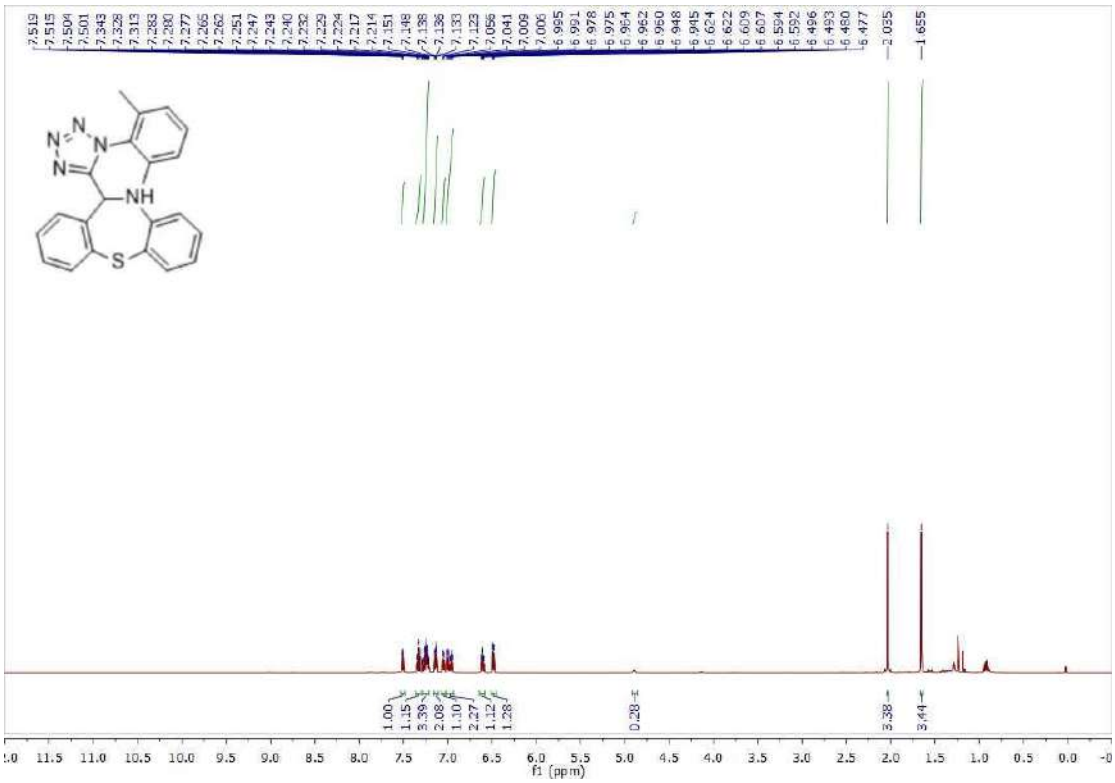
17.50
17.46
NH
S
f1 (ppm)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N
N
N
NH
S
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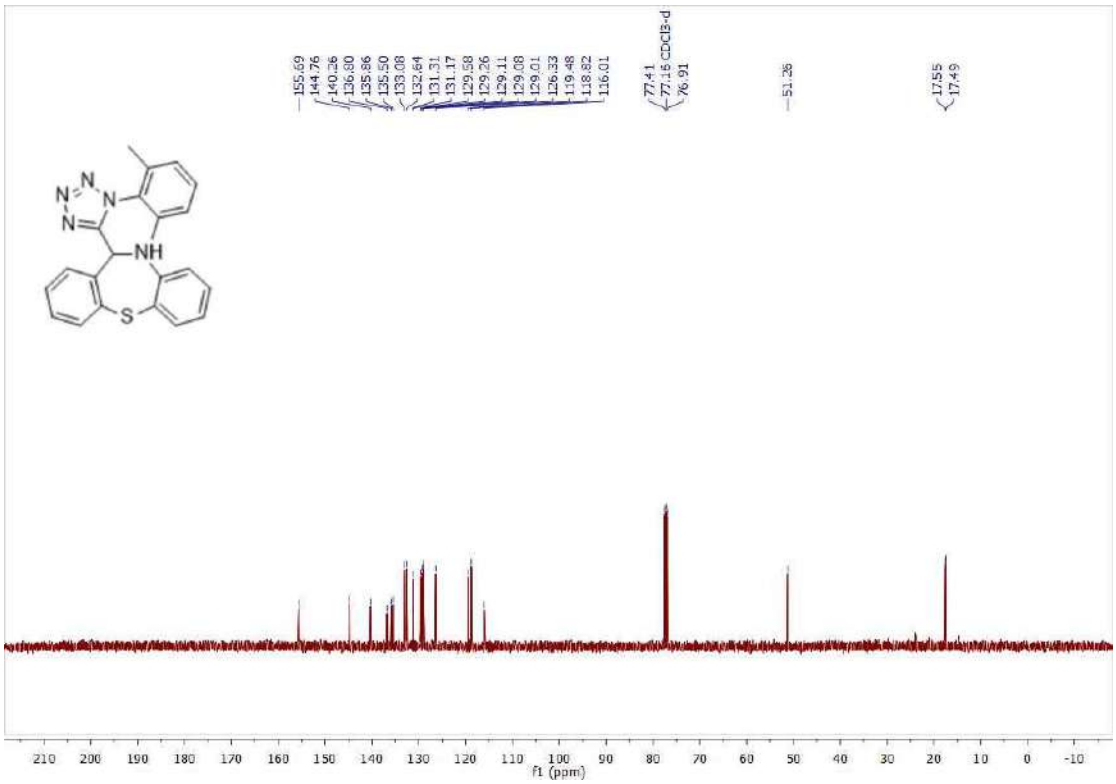
f1 (ppm)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129.11
129.08
129.01
126.33
119.48
118.82
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76.91
51.26
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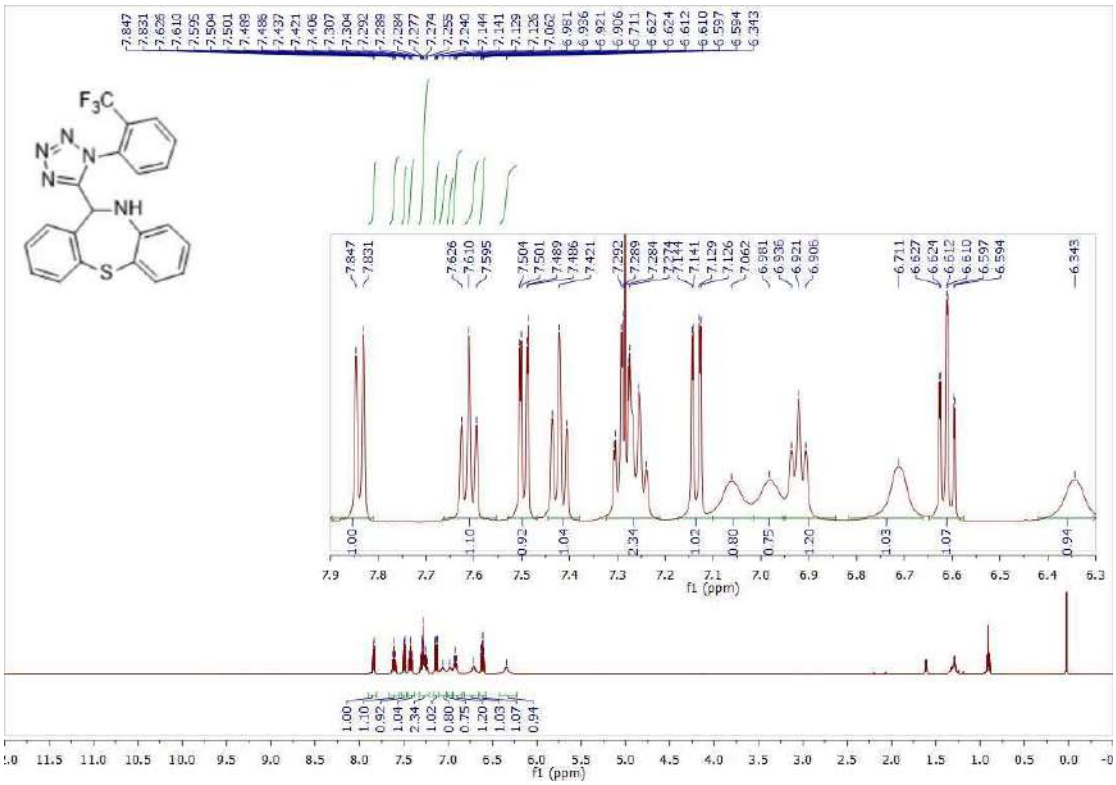
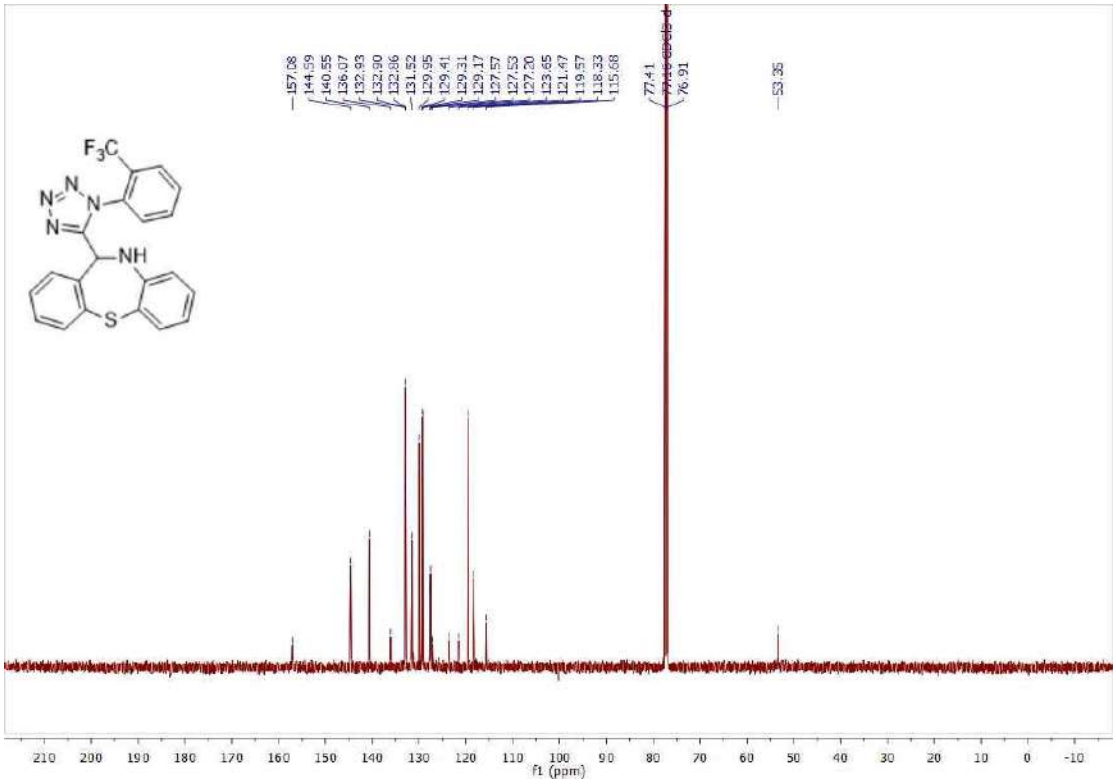
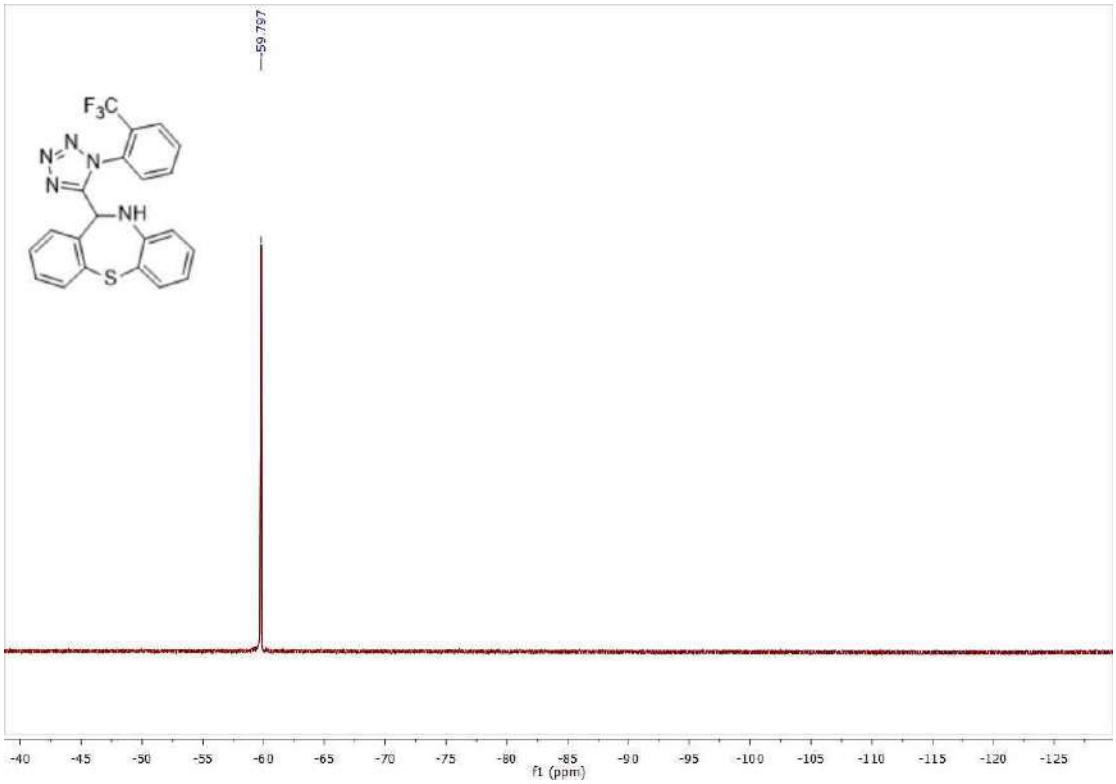
N
N
N
NH
S
f1 (ppm)


F3C
NH
S
f1 (ppm)


F3C
NH
S
f1 (ppm)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N
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S
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-110
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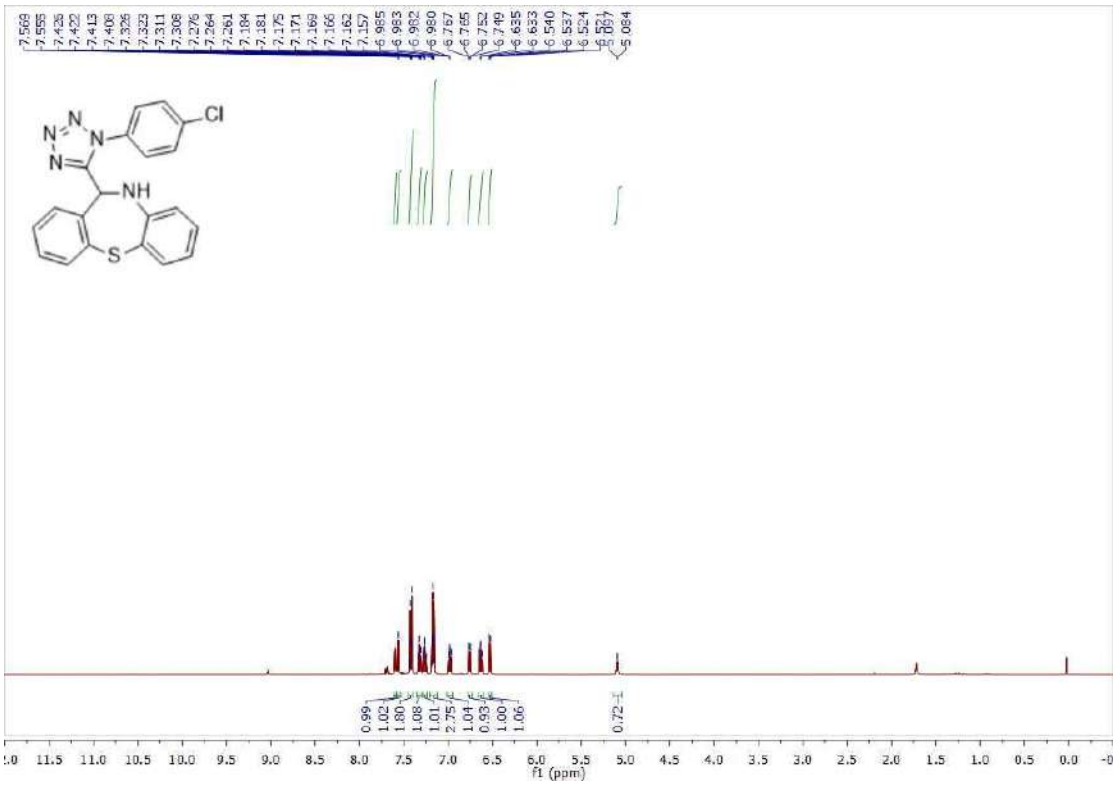
-120
-125
f1 (ppm)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7.169
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7.162
7.157
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6.983
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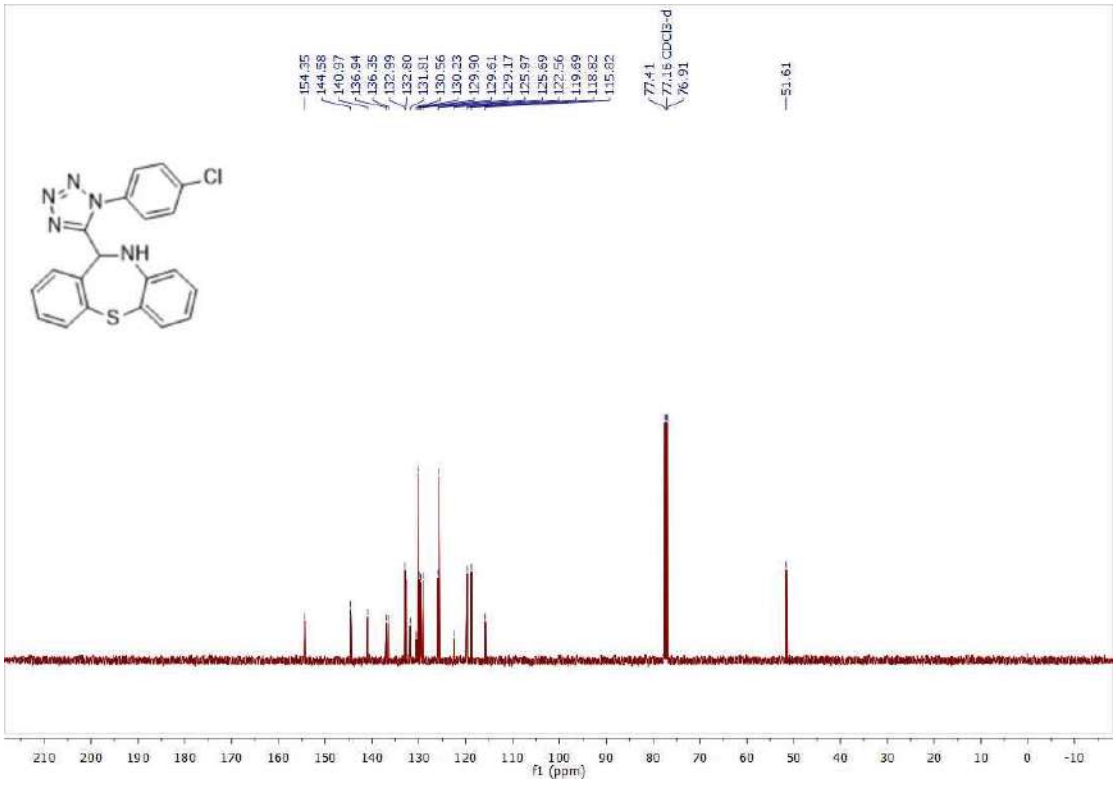
6.767
6.765
6.752
6.749
6.635
6.633
6.540
6.537
6.524
6.521
6.087
5.084
Cl
N
NH
S
0.99
1.02
1.80
1.08
1.01
2.75
1.04
0.93
1.00
1.06
0.72
f1 (ppm)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131.81
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130.23
129.90
129.61
129.17
125.97
125.69
122.56
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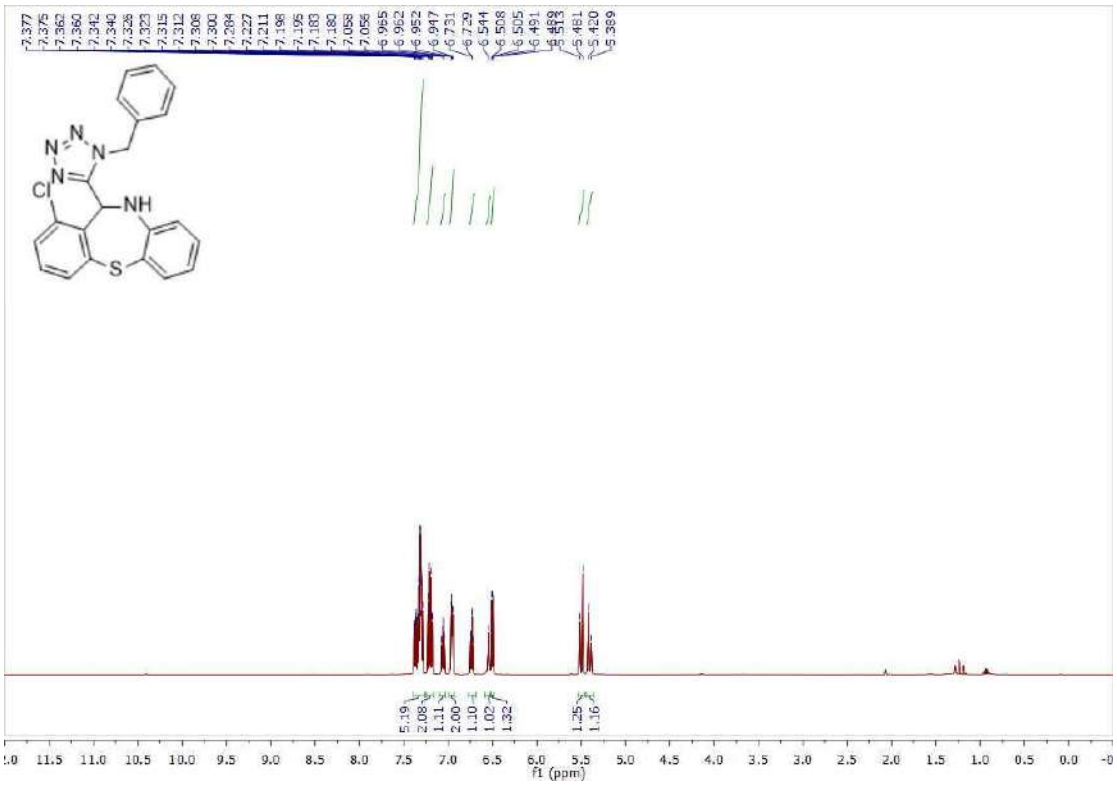
115.82
77.41
77.16 CDCl3-d
76.91
51.61
Cl
N
NH
S
f1 (ppm)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7.323
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7.312
7.306
7.300
7.284
7.227
7.211
7.198
7.195
7.183
7.180
7.058
7.055
6.965
6.962
6.952
6.947
6.731
6.729
6.544
6.508
6.505
6.491
5.481
5.420
5.389
Cl
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2.00
1.10
1.02
1.32
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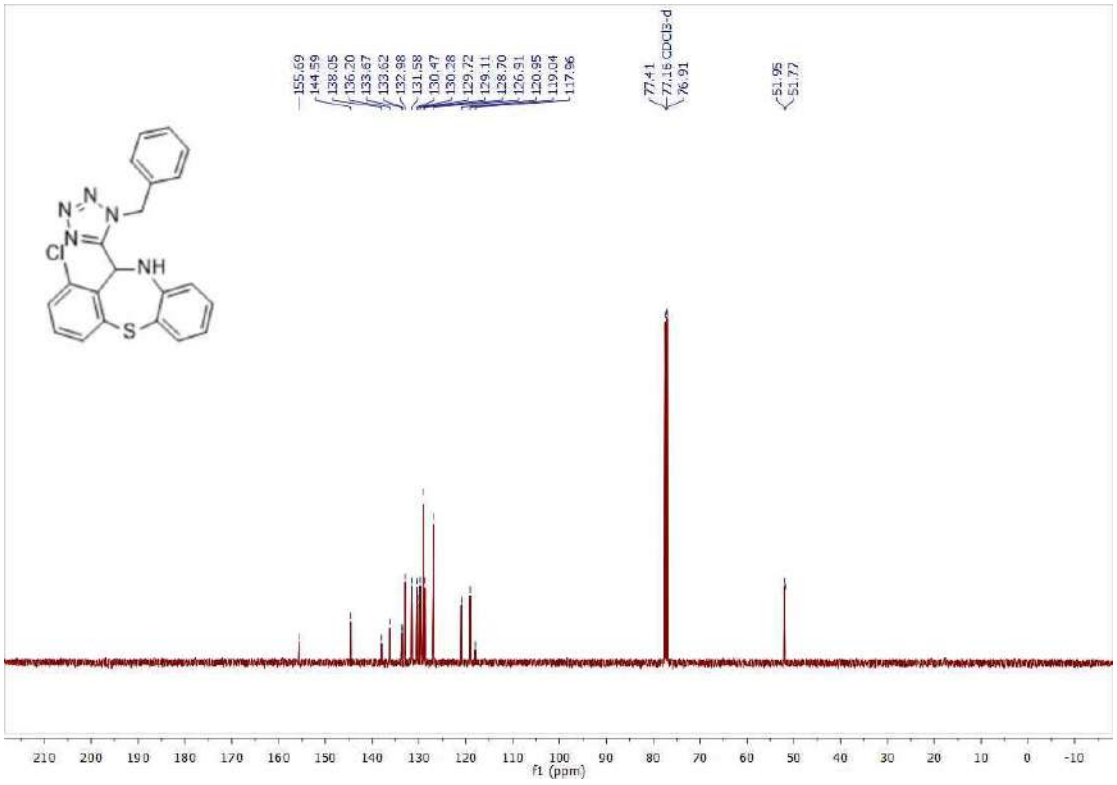
1.16
f1 (ppm)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128.70
126.91
120.95
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77.16 CDCl3-d
76.91
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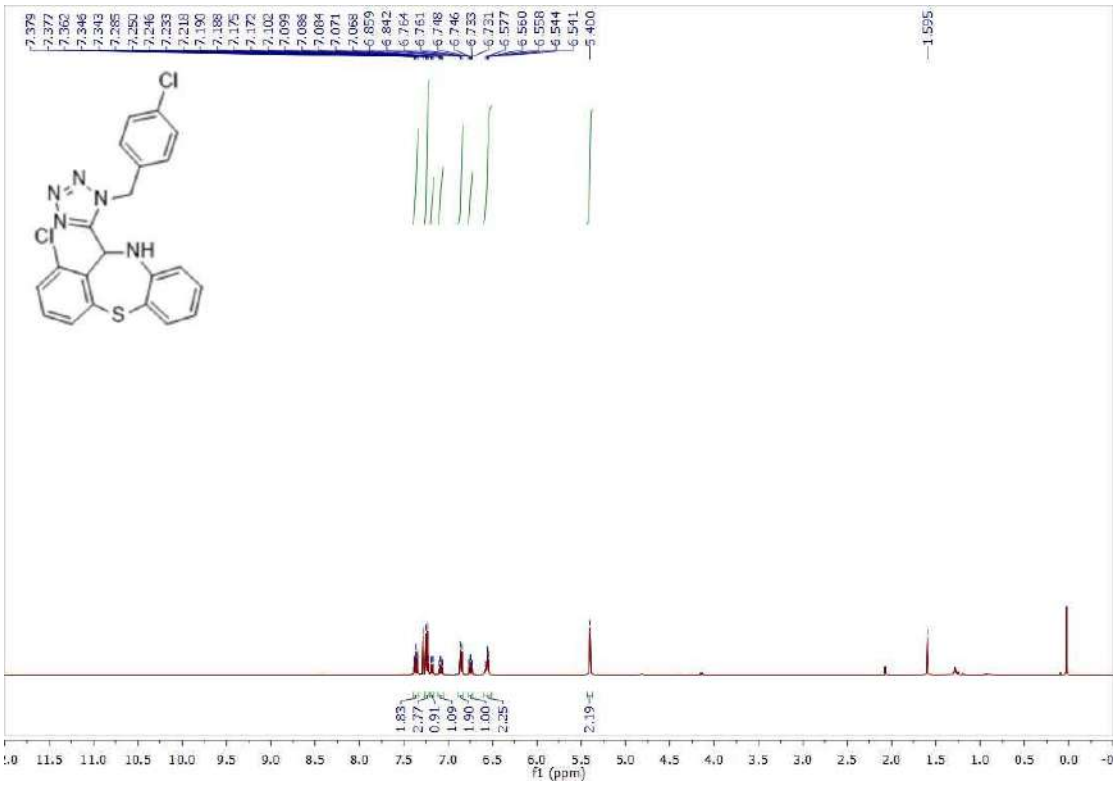
51.77
Cl
N
NH
S
f1 (ppm)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7.190
7.188
7.175
7.172
7.102
7.099
7.086
7.084
7.071
7.068
6.859
6.842
6.764
6.761
6.748
6.746
6.733
6.731
6.577
6.560
6.558
6.544
6.541
5.400
1.595
Cl
N
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Cl
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1.00
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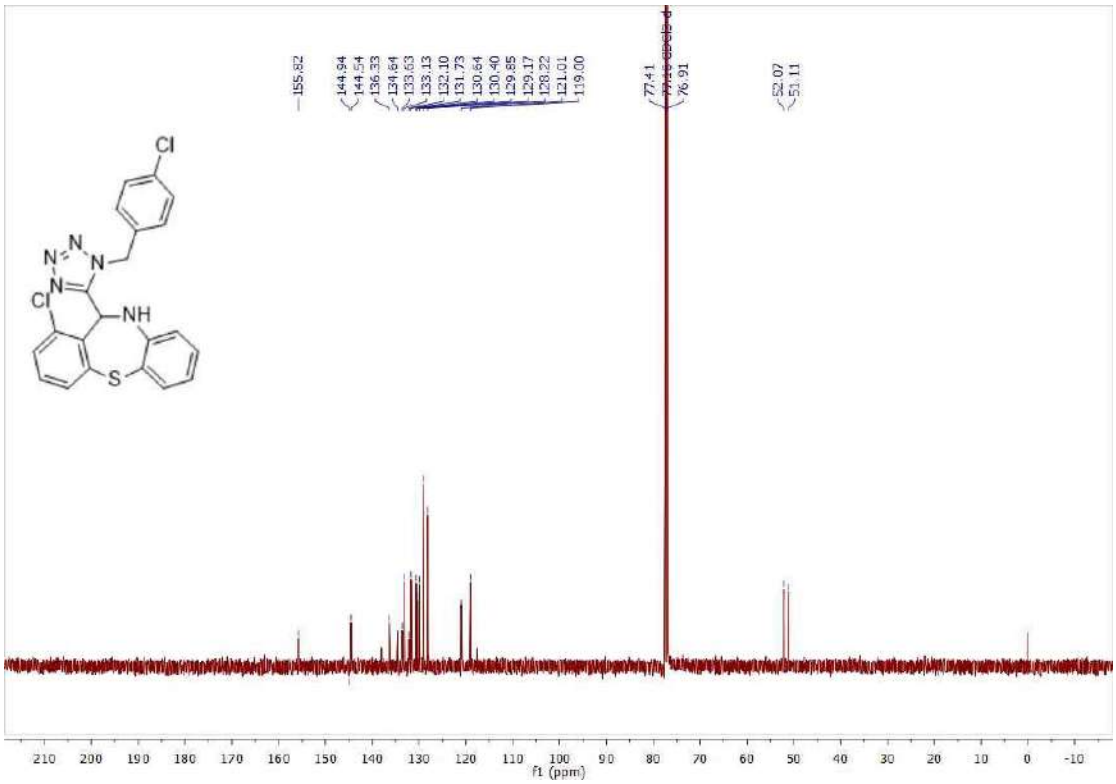
2.19
f1 (ppm)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129.85
129.17
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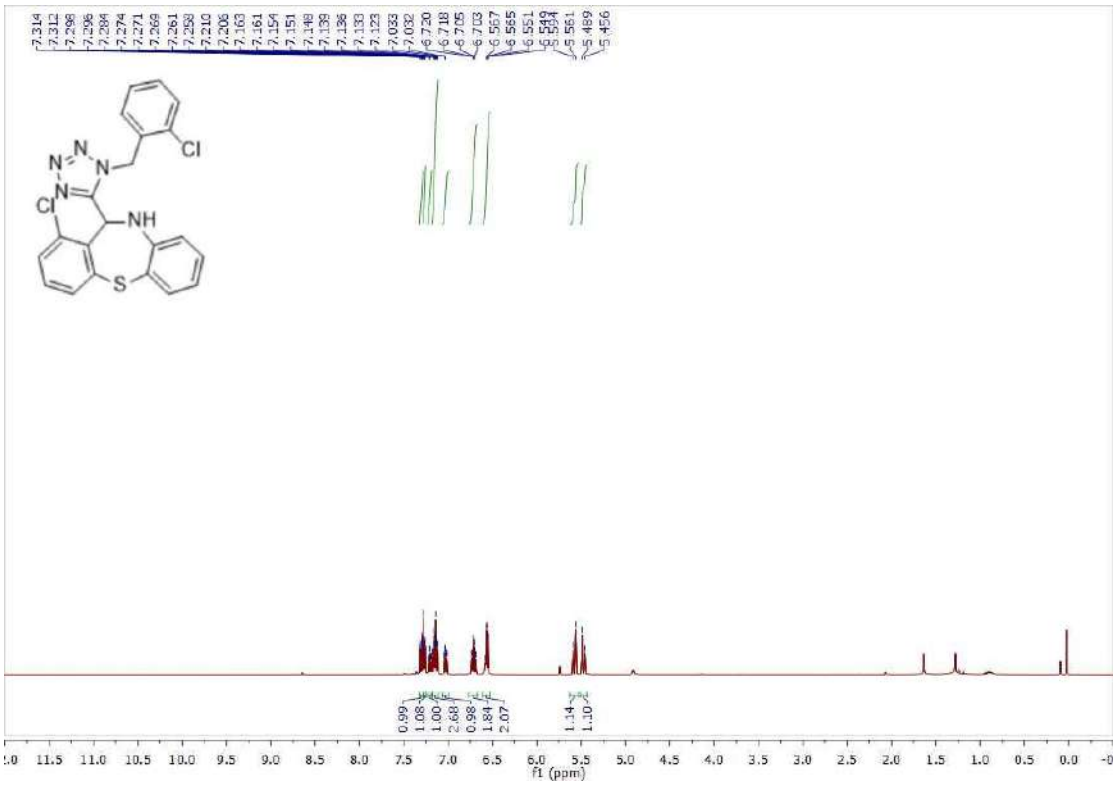
77.41
76.91
52.07
51.11
Cl
N
N
N
Cl
NH
S
f1 (ppm)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7.161
7.154
7.151
7.149
7.139
7.136
7.133
7.123
7.033
7.032
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6.718
6.705
6.703
6.567
6.565
6.551
5.549
5.534
5.561
5.489
5.456
Cl
N
N
N
Cl
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2.07
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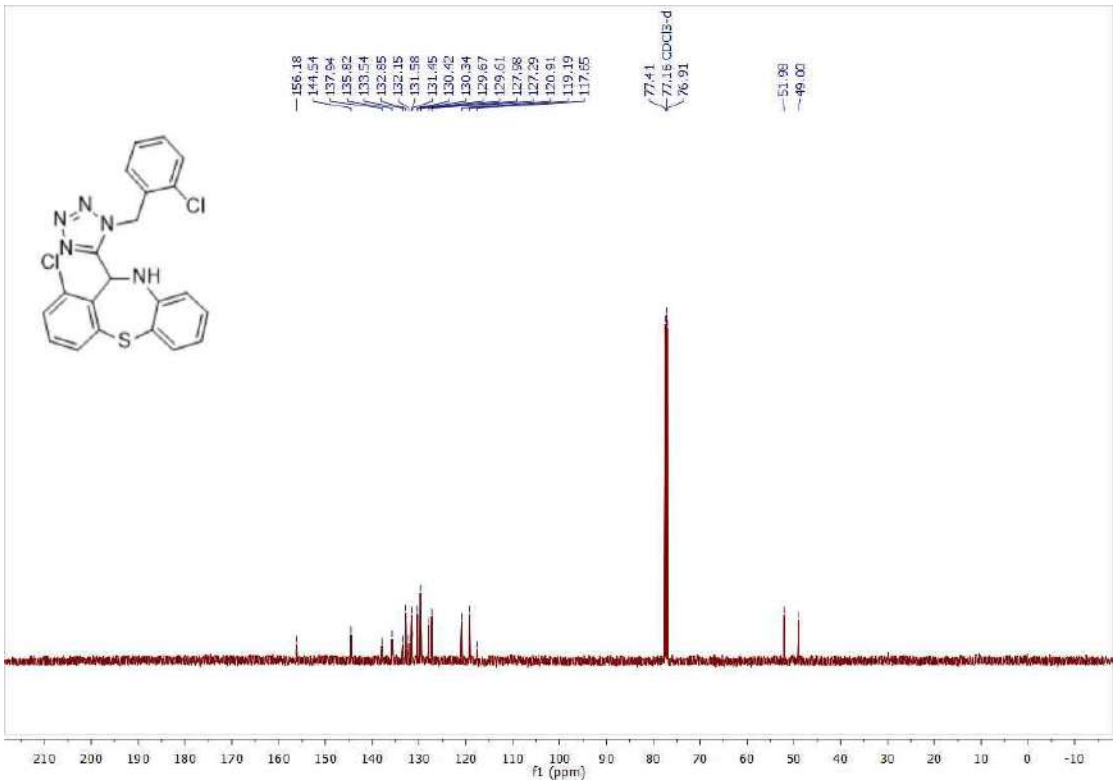
1.10
f1 (ppm)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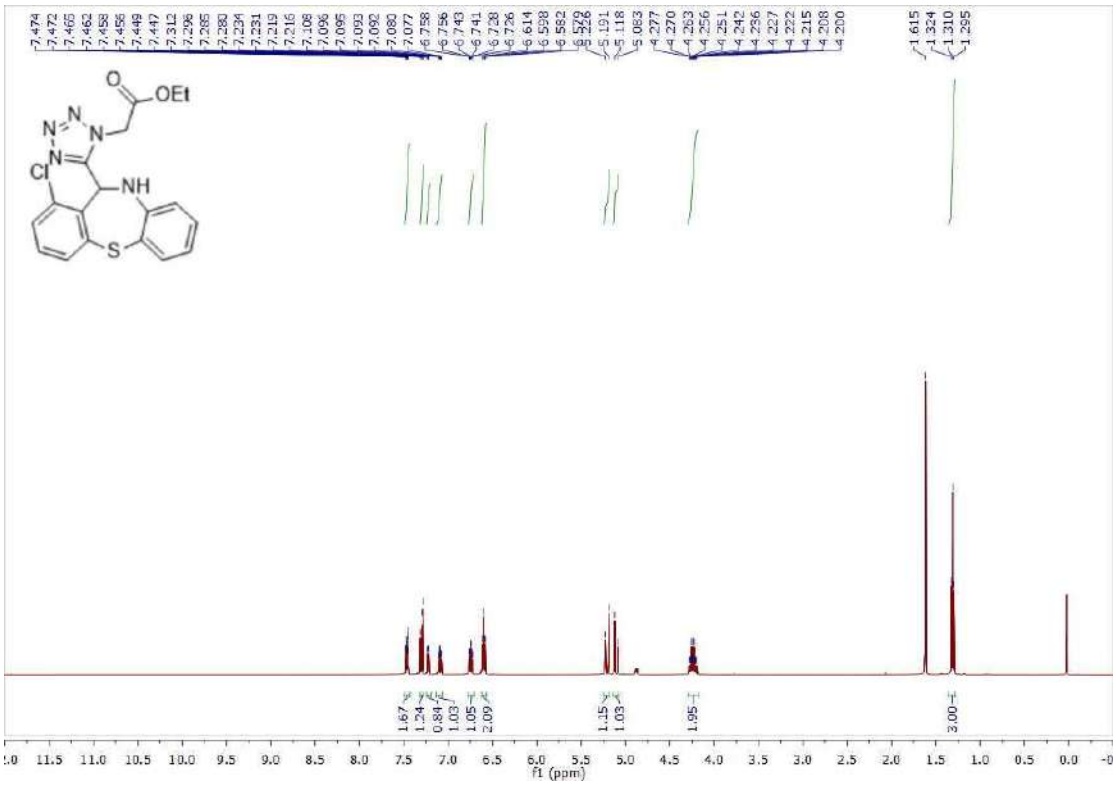
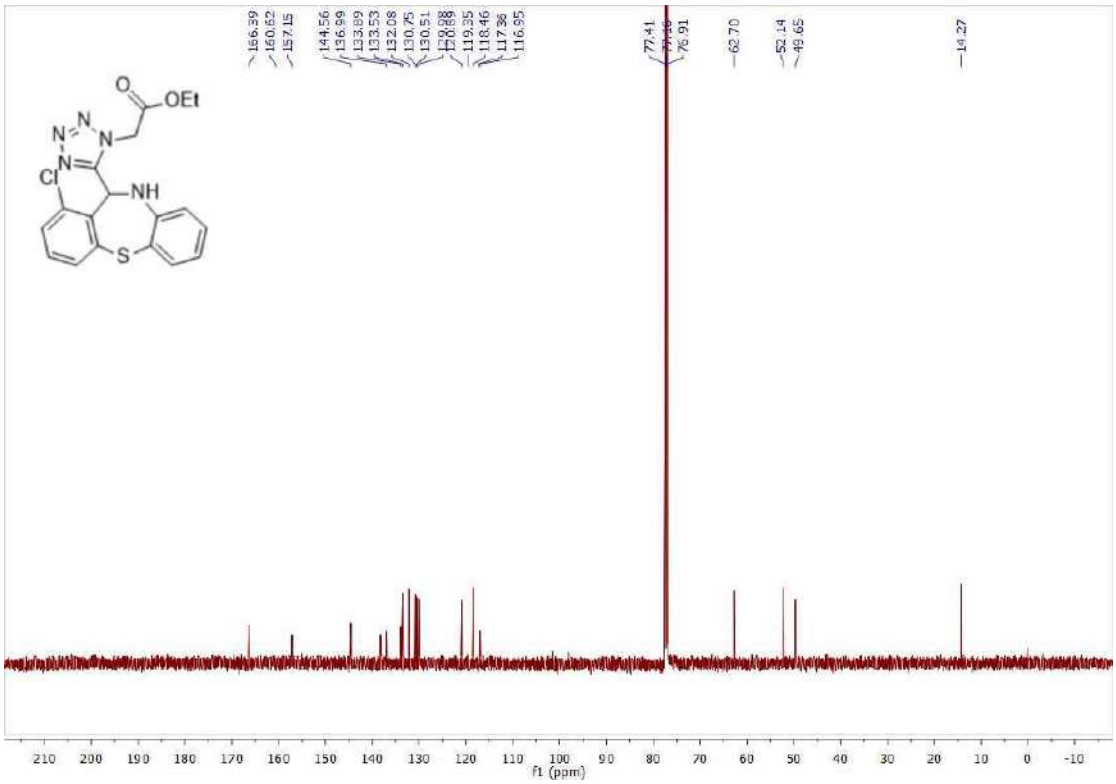
131.58
131.45
130.42
130.34
129.67
129.61
127.98
127.29
120.91
119.19
117.65
77.41
77.16 CDCl3-d
76.91
51.98
49.00
Cl
N
N
N
Cl
NH
S
f1 (ppm)


OEt
O
N
N
N
Cl
NH
S
f1 (ppm)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O
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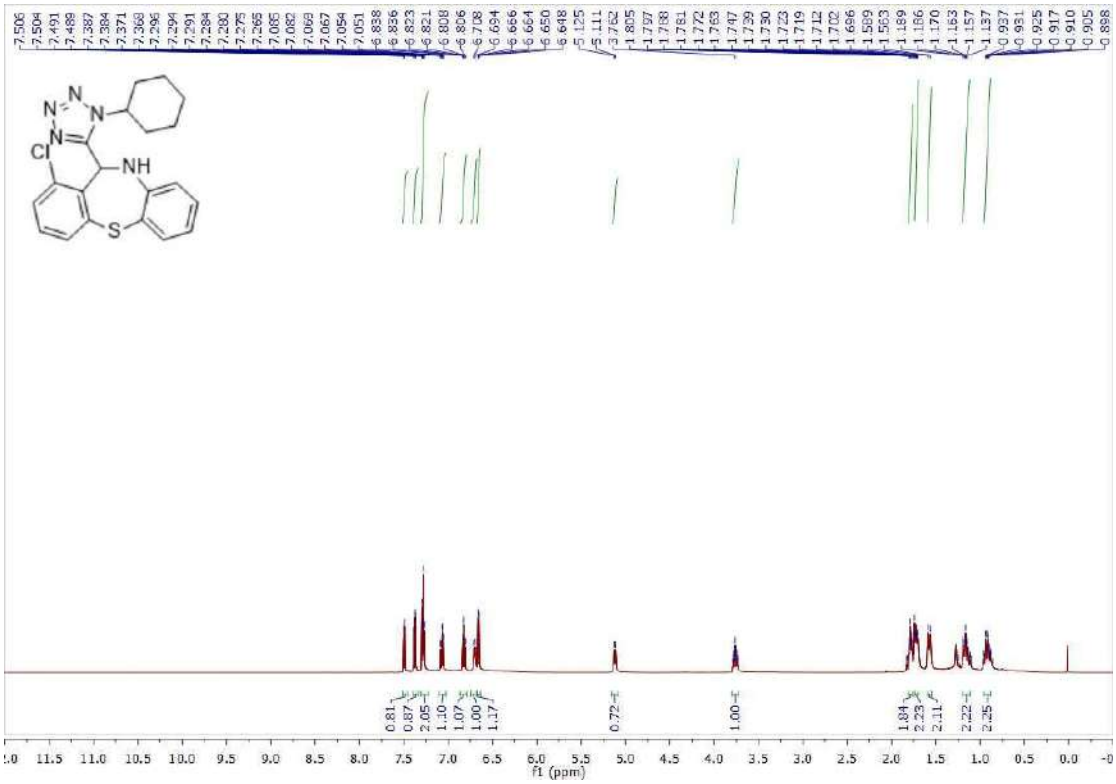
N
Cl
NH
S
f1 (ppm)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7.280
7.275
7.265
7.085
7.082
7.069
7.067
7.054
7.051
6.838
6.836
6.823
6.821
6.808
6.806
6.708
6.694
6.666
6.664
6.650
6.648
5.125
5.111
3.762
1.805
1.797
1.788
1.781
1.772
1.763
1.747
1.739
1.730
1.723
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1.712
1.702
1.696
1.589
1.563
1.189
1.186
1.170
1.163
1.157
1.137
0.937
0.931
0.925
0.917
0.910
0.905
0.898
Cl
N
N
N
NH
S
0.81
0.87
2.05
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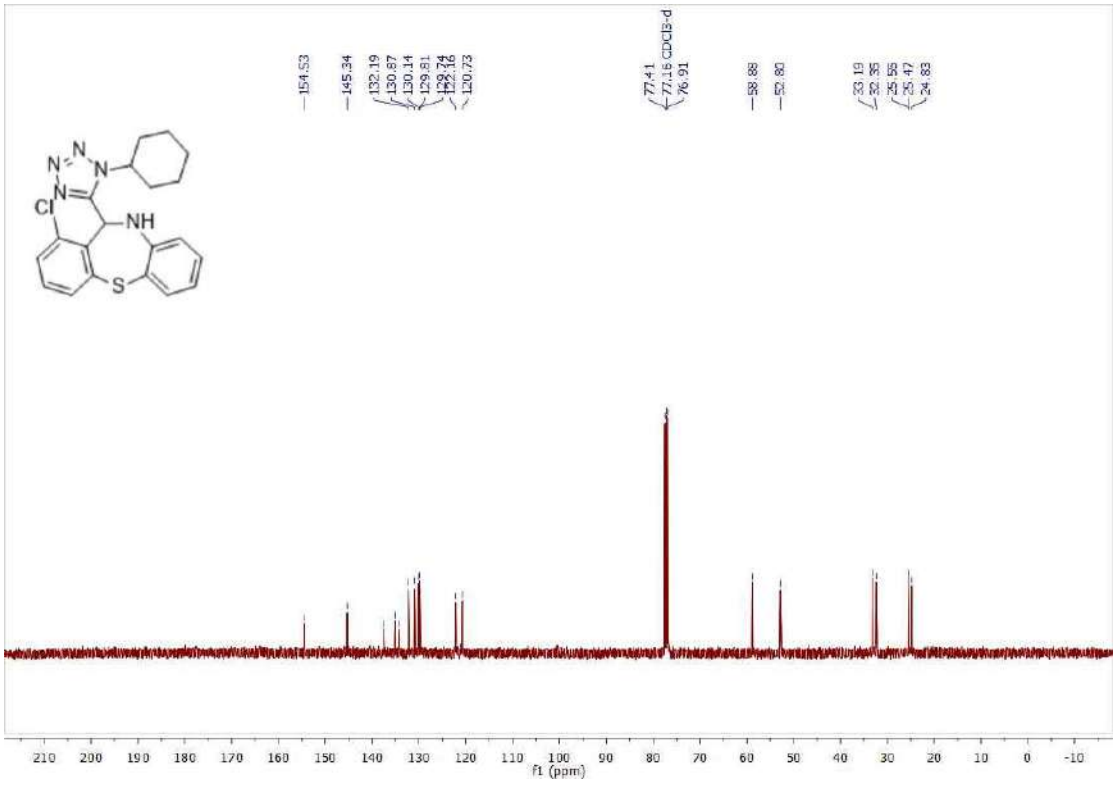
2.25
f1 (ppm)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145.34
132.19
130.87
130.14
129.81
128.74
122.18
120.73
77.41
77.16 CDCl3-d
76.91
58.88
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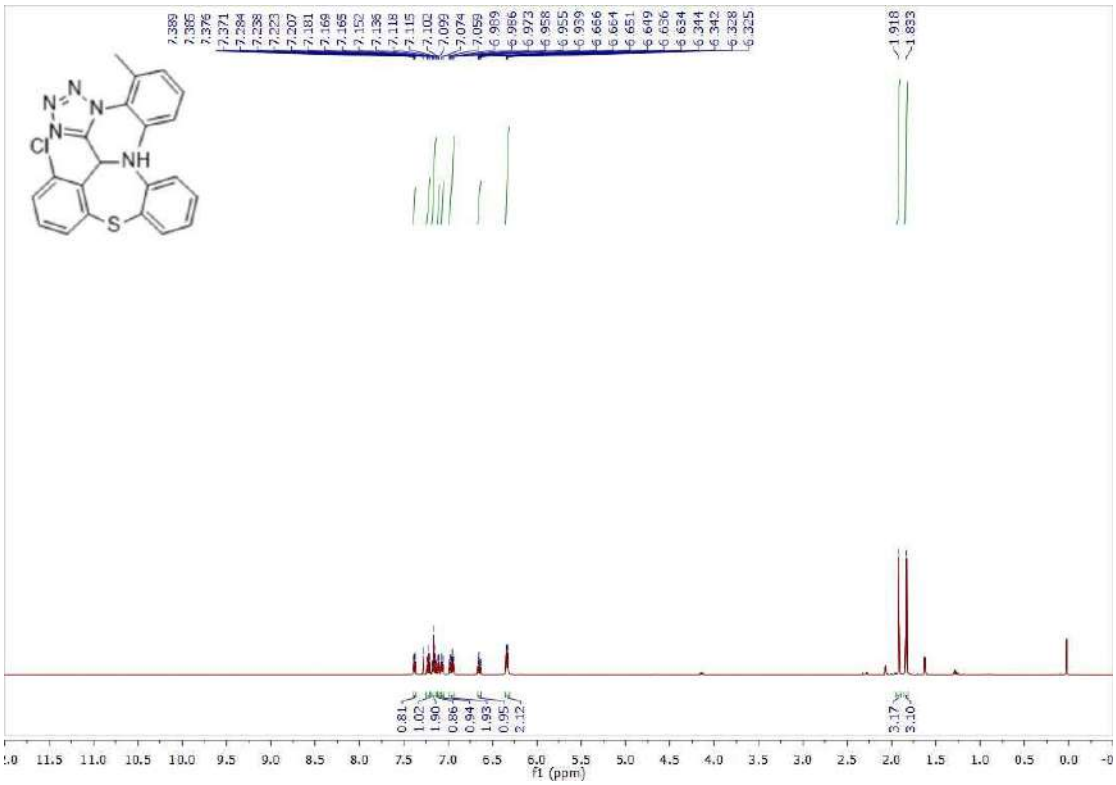
33.19
32.35
25.56
25.47
24.83
Cl
N
N
N
NH
S
f1 (ppm)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7.152
7.136
7.118
7.115
7.102
7.099
7.074
7.059
6.969
6.956
6.973
6.958
6.955
6.939
6.666
6.664
6.651
6.649
6.636
6.634
6.344
6.342
6.328
6.325
1.918
1.833
Cl
N
NH
S
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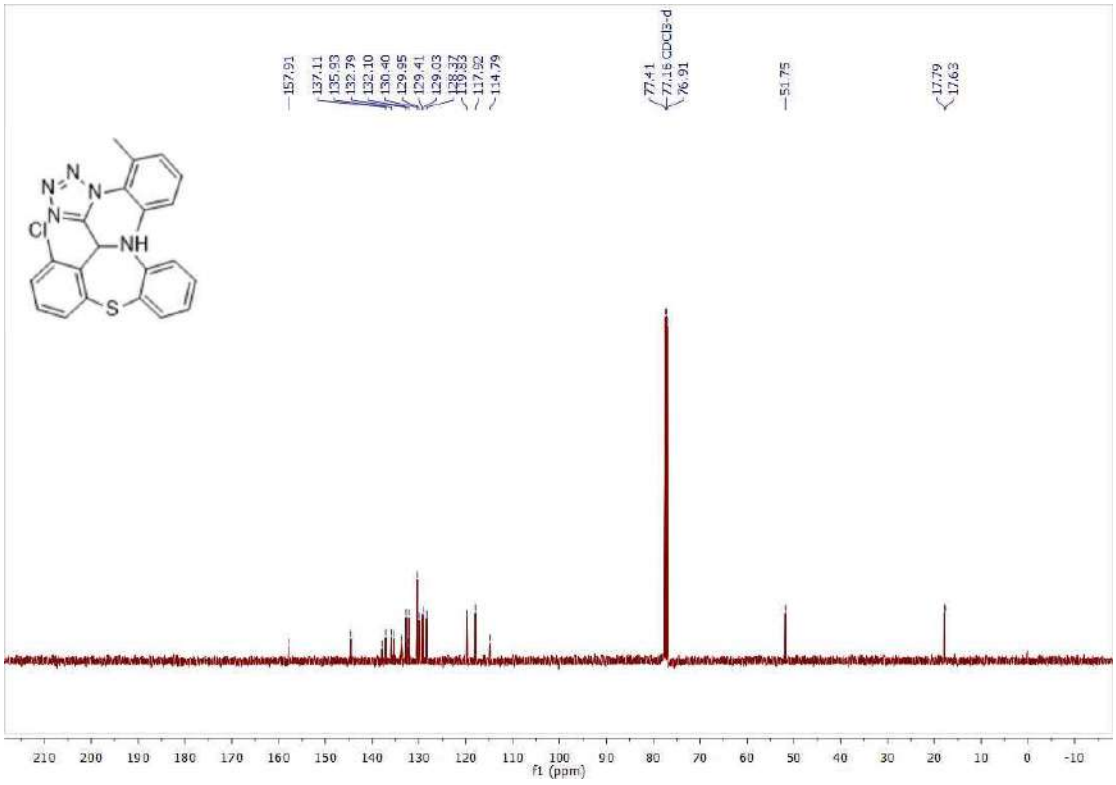
0.94
1.93
0.95
2.12
3.17
3.10
f1 (ppm)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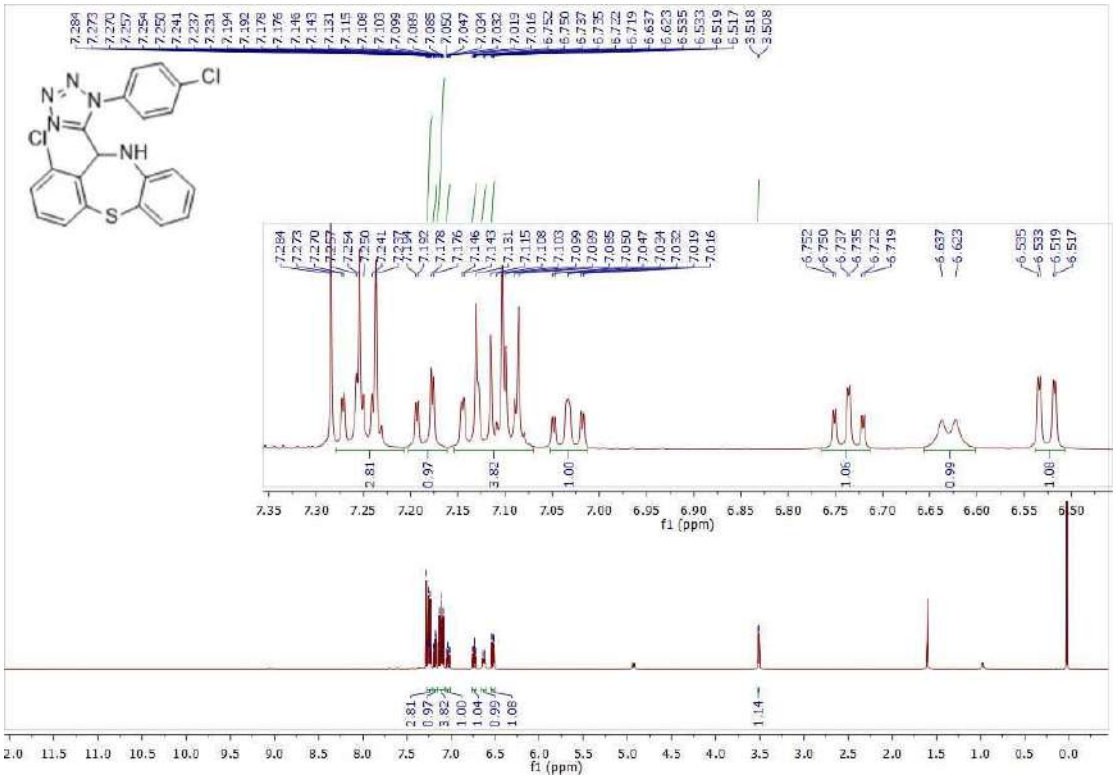
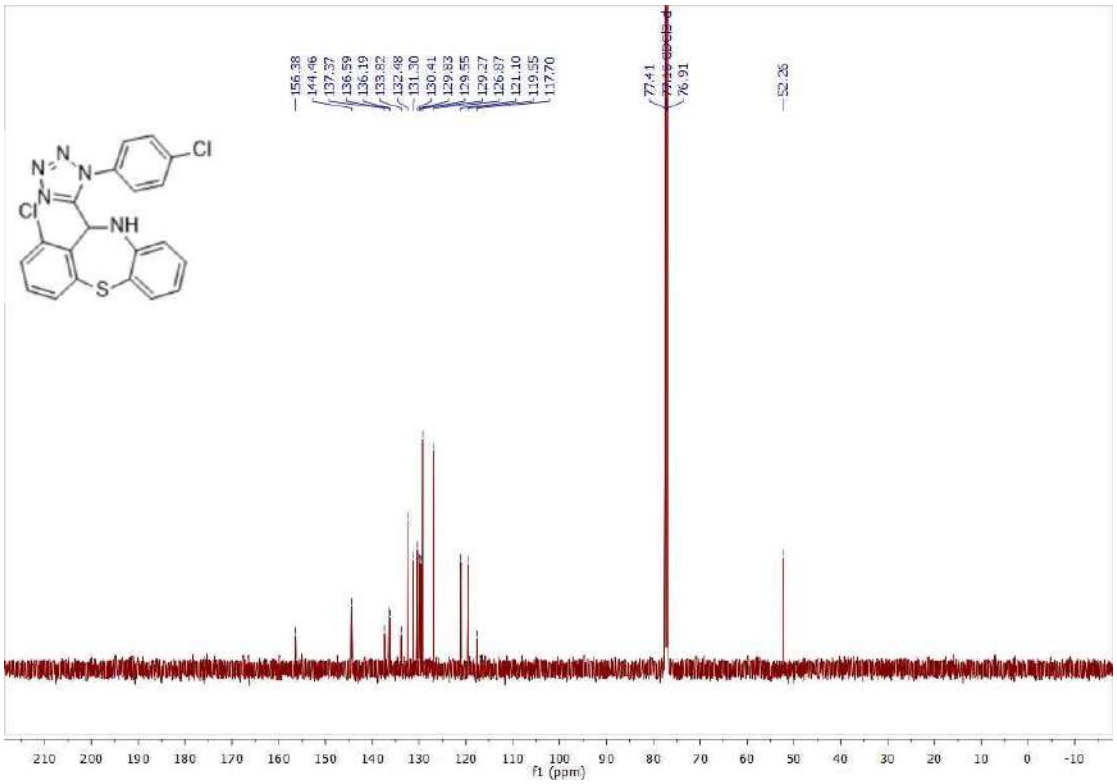
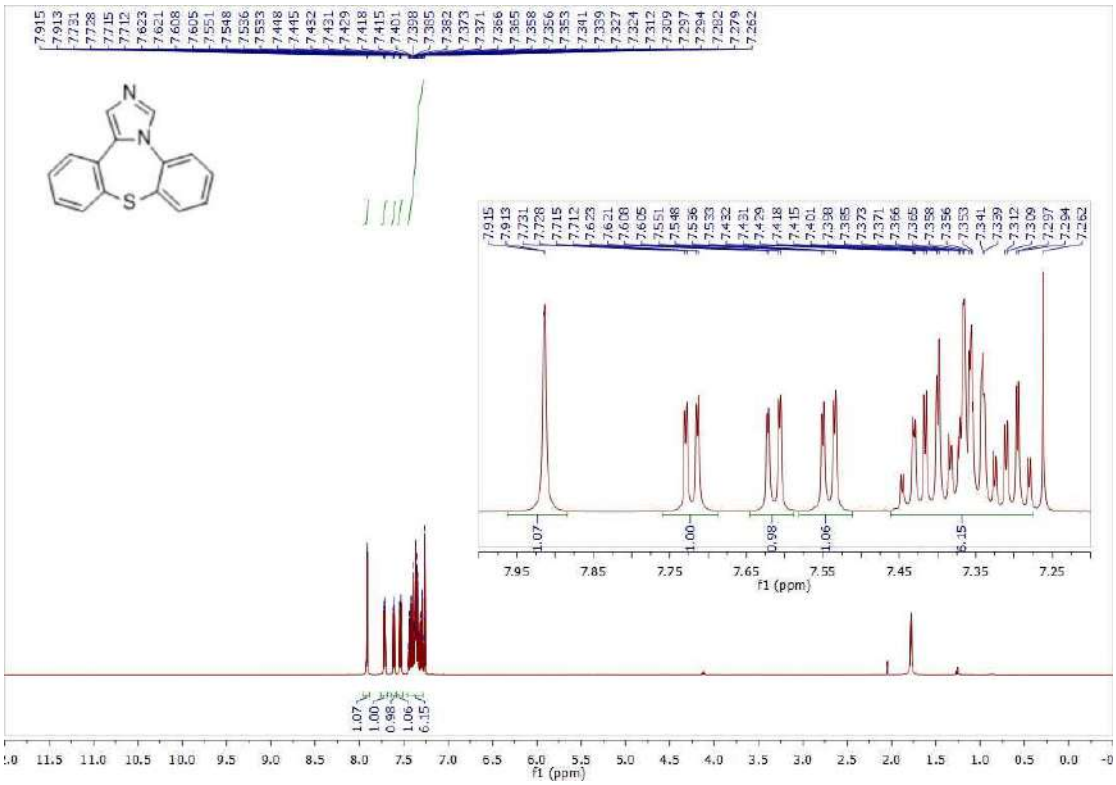
137.11
135.93
132.79
132.10
130.40
129.95
129.41
129.03
117.92
114.79
77.41
77.16 CDCl3-d
76.91
51.75
17.79
17.63
Cl
N
NH
S
f1 (ppm)


Cl
Cl
NH
S
f1 (ppm)


Cl
Cl
NH
S
f1 (ppm)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7.548
7.536
7.533
7.448
7.445
7.432
7.431
7.429
7.418
7.415
7.401
7.398
7.385
7.382
7.373
7.371
7.366
7.365
7.358
7.356
7.353
7.341
7.339
7.327
7.324
7.312
7.309
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7.282
7.279
7.262
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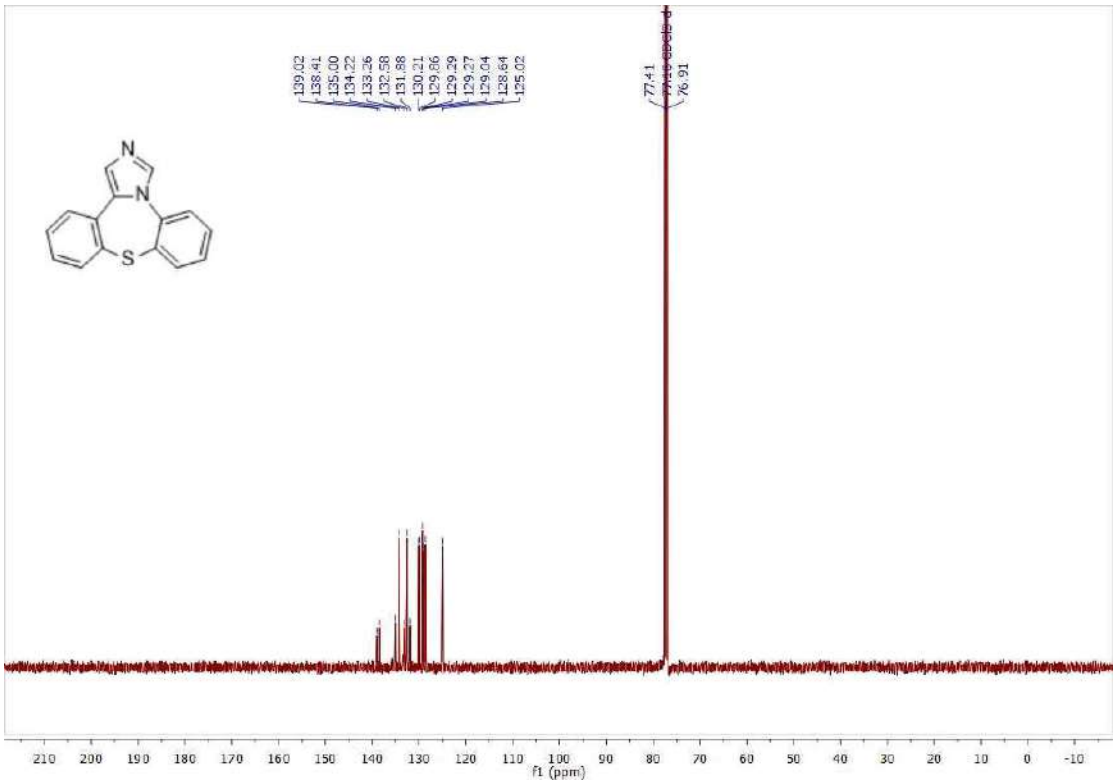
1.00
0.98
1.06
6.15
f1 (ppm)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129.27
129.04
128.64
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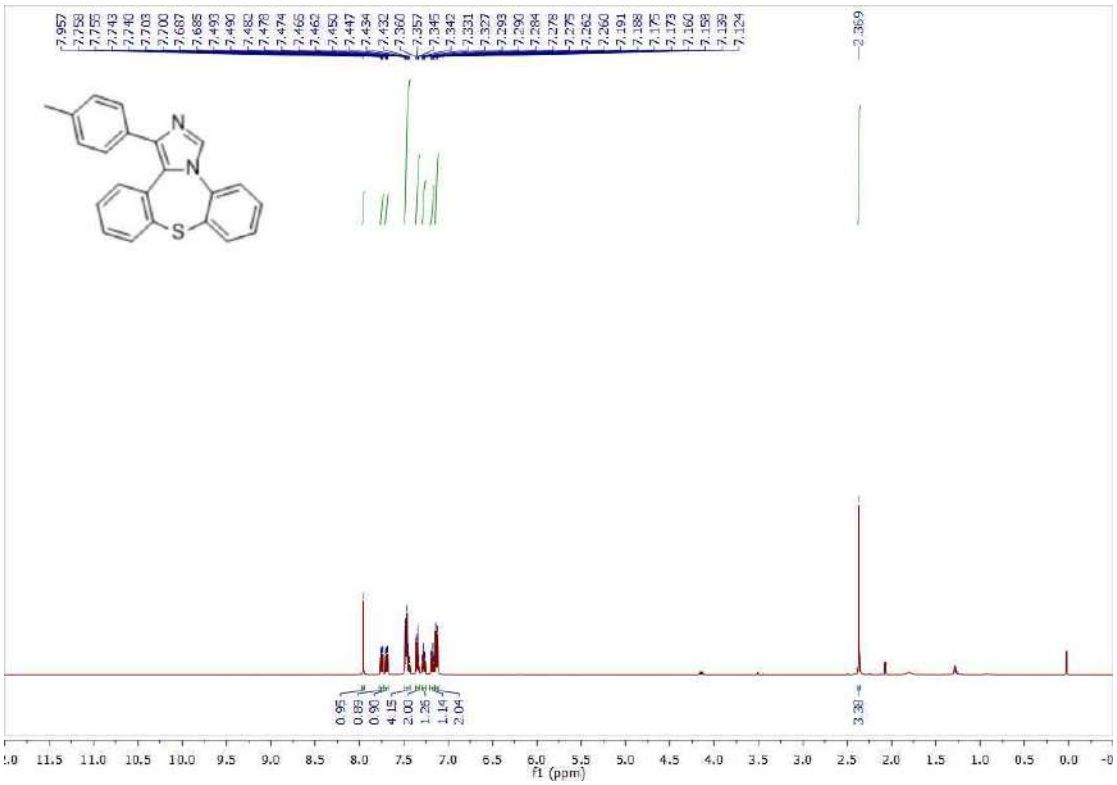
77.41
76.91
f1 (ppm)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7.474
7.466
7.462
7.450
7.447
7.434
7.432
7.360
7.357
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7.284
7.278
7.275
7.262
7.260
7.191
7.188
7.175
7.173
7.160
7.158
7.139
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0.90
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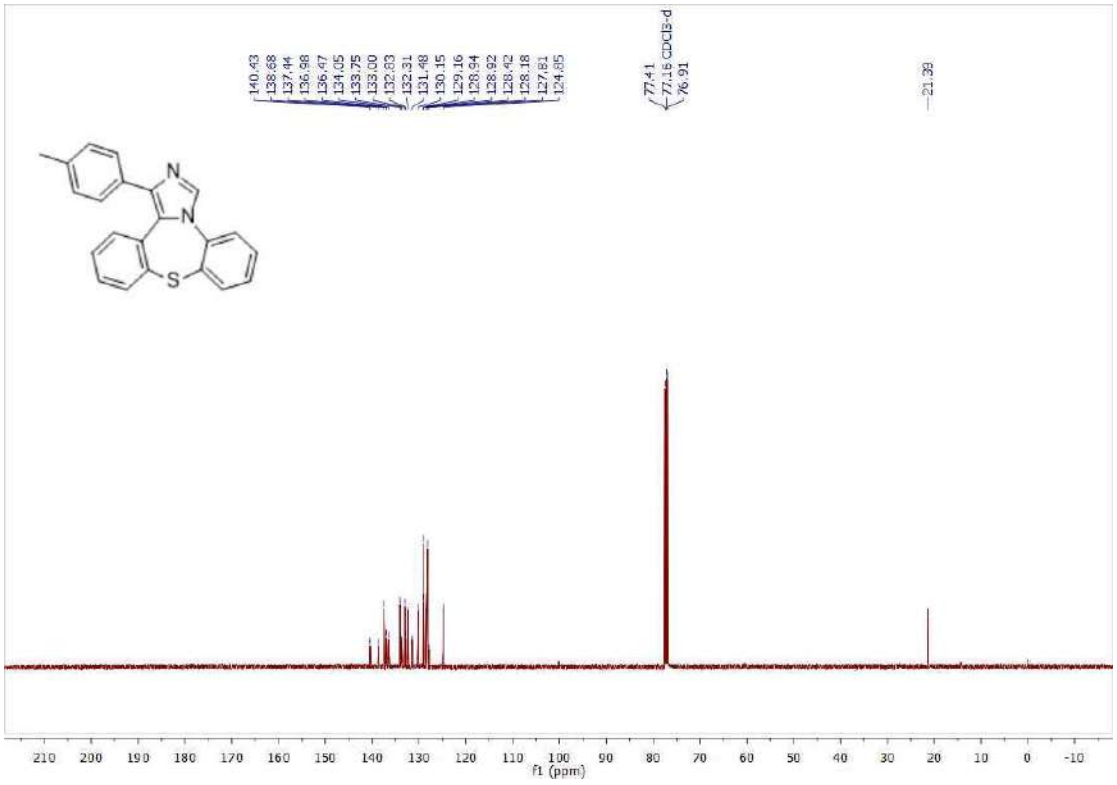
1.14
2.04
3.38
f1 (ppm)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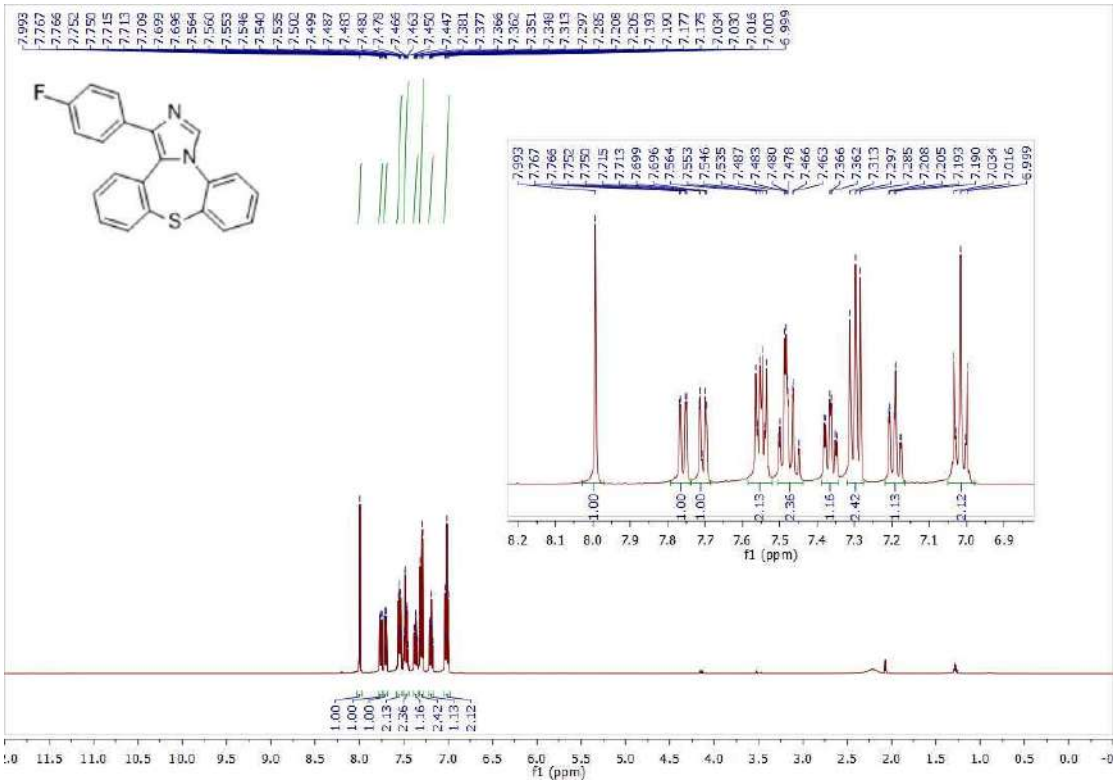
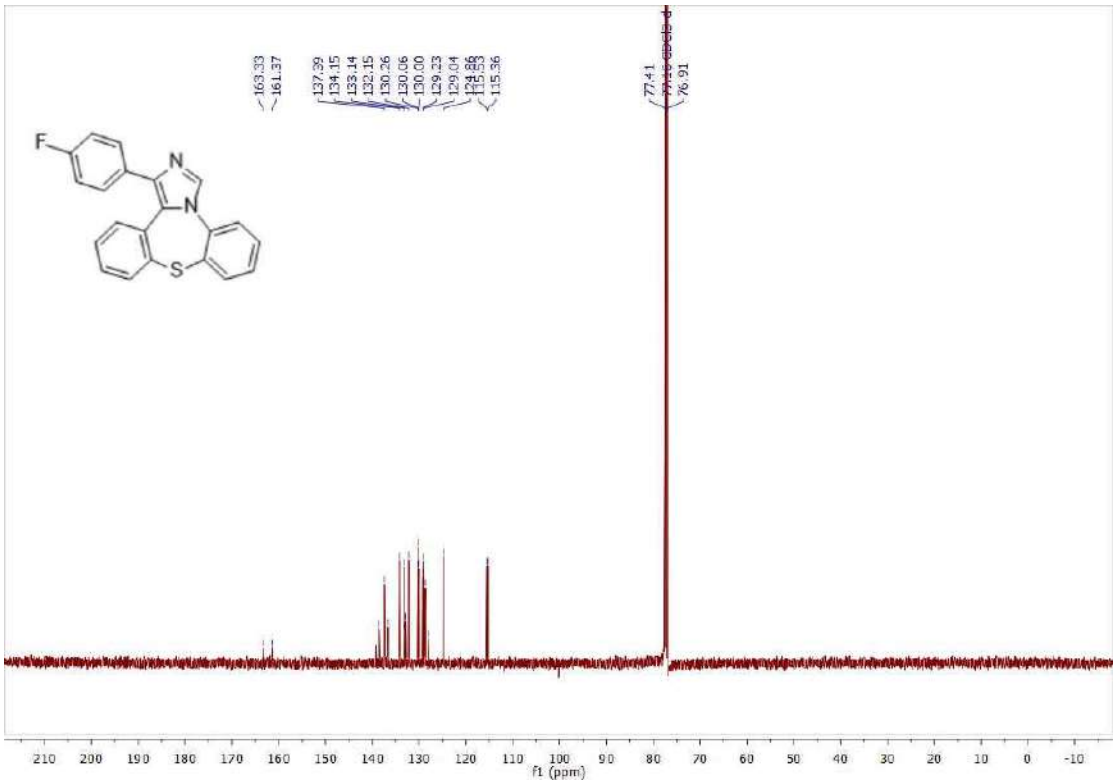
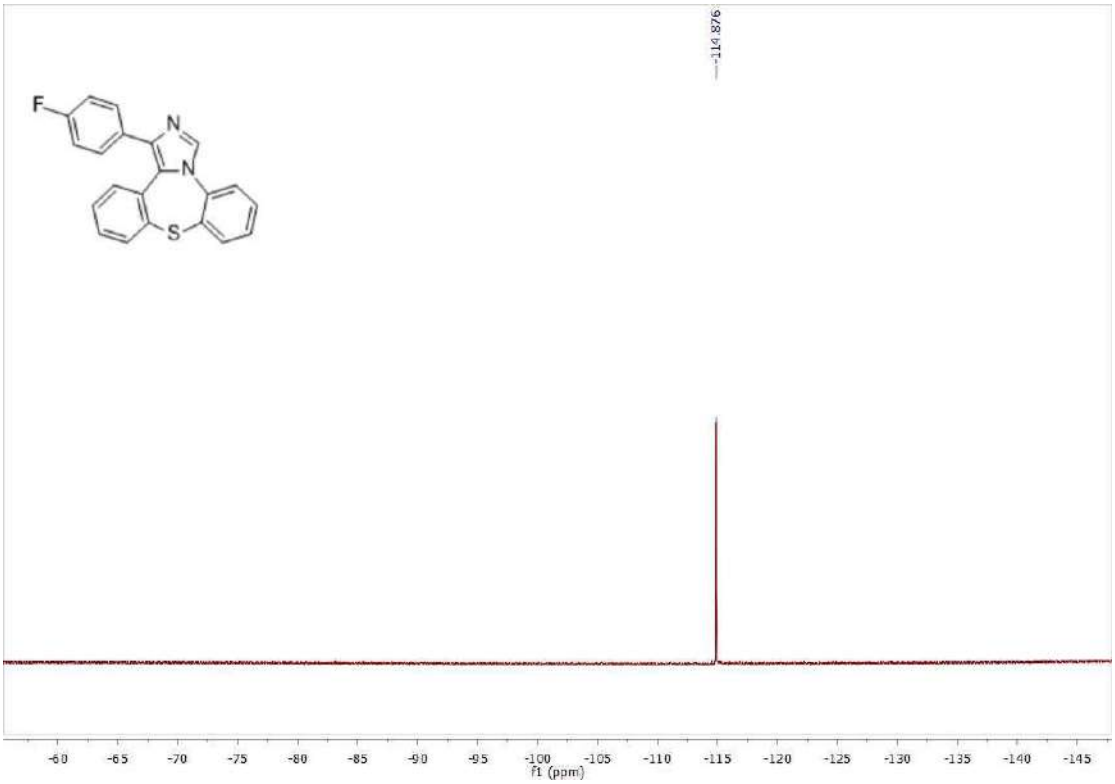
124.85
77.41
77.16 CDCl3-d
76.91
21.38
f1 (ppm)


F
N
S
f1 (ppm)


F
N
S
f1 (ppm)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N
S
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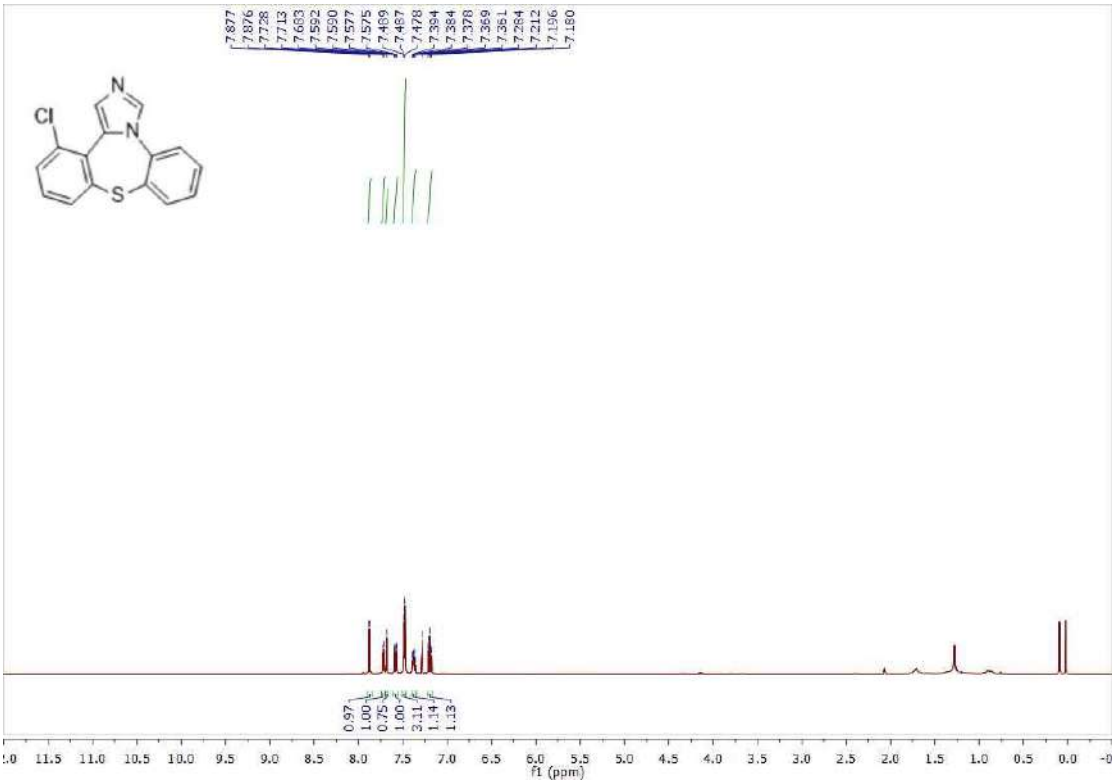
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)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7.590
7.577
7.575
7.489
7.487
7.478
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7.384
7.378
7.369
7.361
7.284
7.212
7.196
7.190
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N
S
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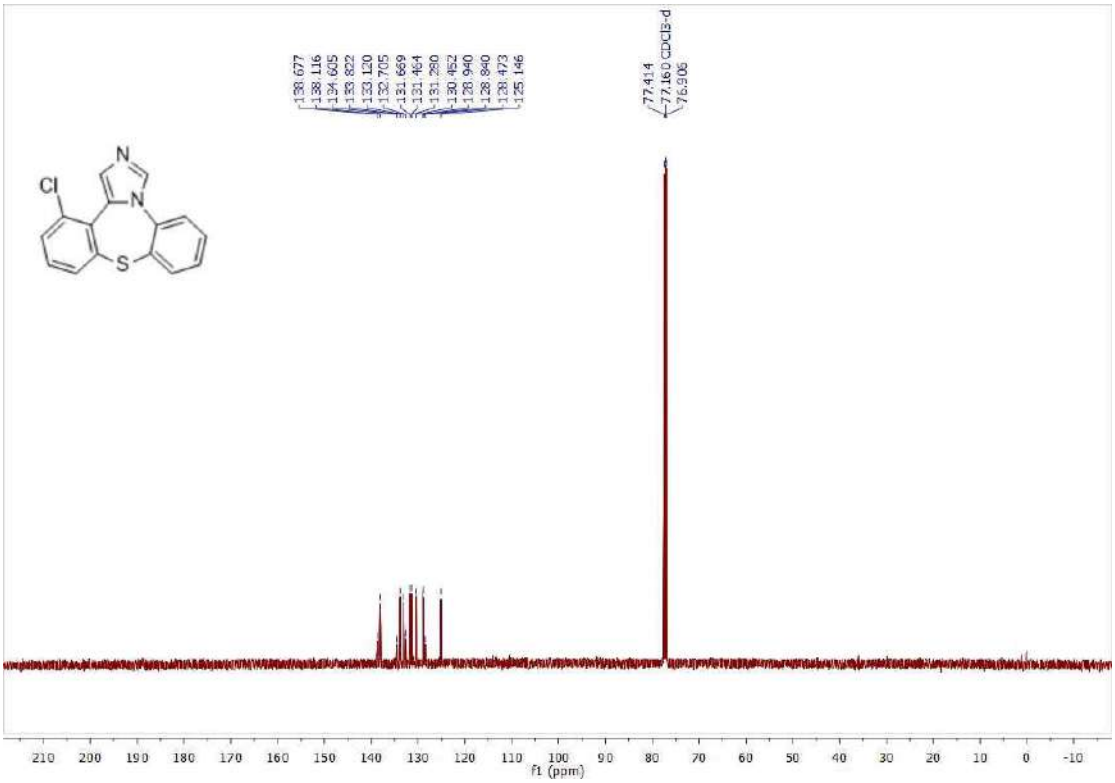
1.00
3.11
1.14
1.13
f1 (ppm)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131.280
130.452
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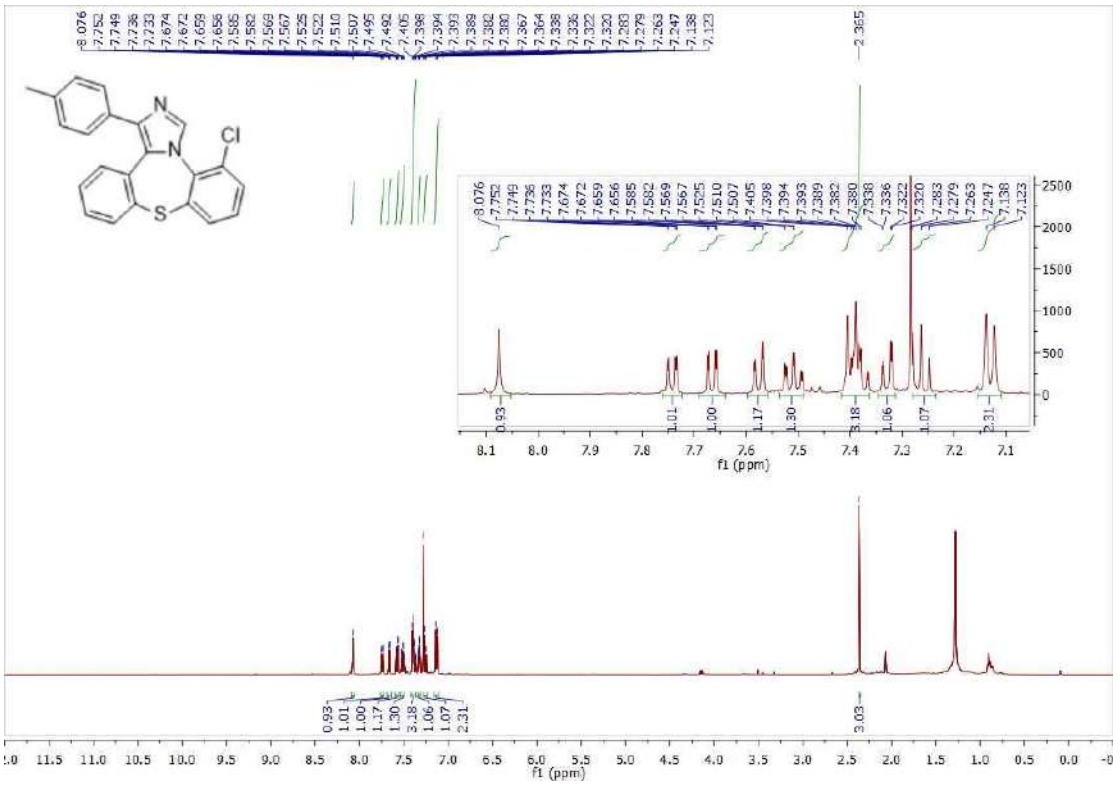
128.473
125.146
77.414
77.160 CDCl3-d
76.906
Cl
N
N
S
f1 (ppm)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7.582
7.569
7.567
7.525
7.522
7.510
7.507
7.495
7.492
7.405
7.398
7.394
7.393
7.389
7.382
7.380
7.367
7.364
7.338
7.336
7.322
7.320
7.283
7.279
7.263
7.247
7.138
7.123
2.365
N
Cl
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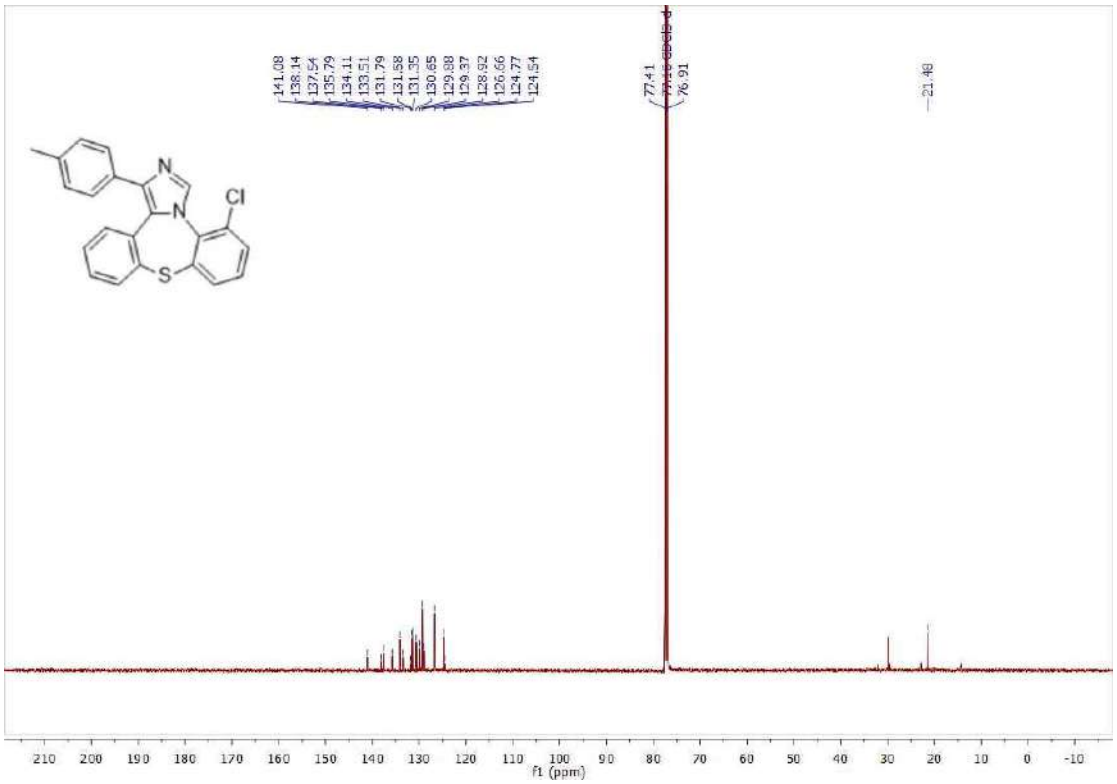
1.17
1.30
3.18
1.06
1.07
2.31
3.03
f1 (ppm)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134.11
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130.65
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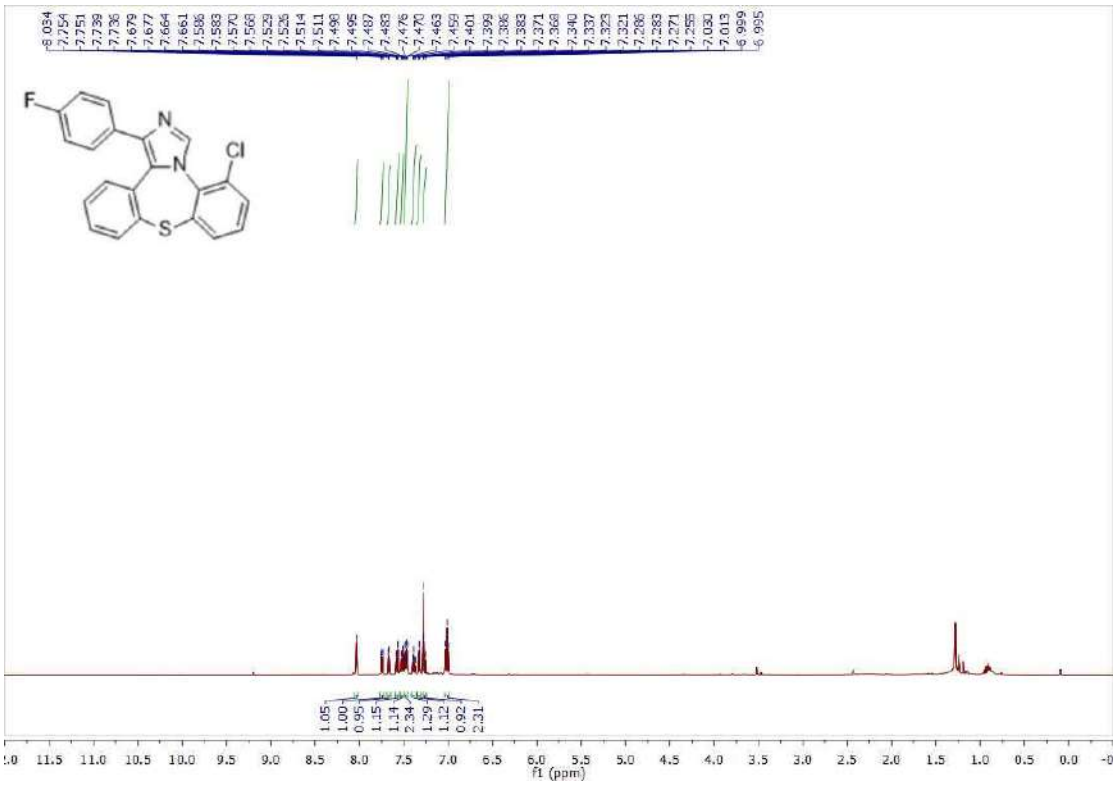
124.54
77.41
76.91
21.48
N
Cl
S
f1 (ppm)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7.661
7.586
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7.570
7.568
7.529
7.526
7.514
7.511
7.498
7.495
7.487
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7.470
7.463
7.459
7.401
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7.383
7.371
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7.340
7.337
7.323
7.321
7.286
7.283
7.271
7.255
7.030
7.013
6.999
6.995
F
N
N
Cl
S
1.05
1.00
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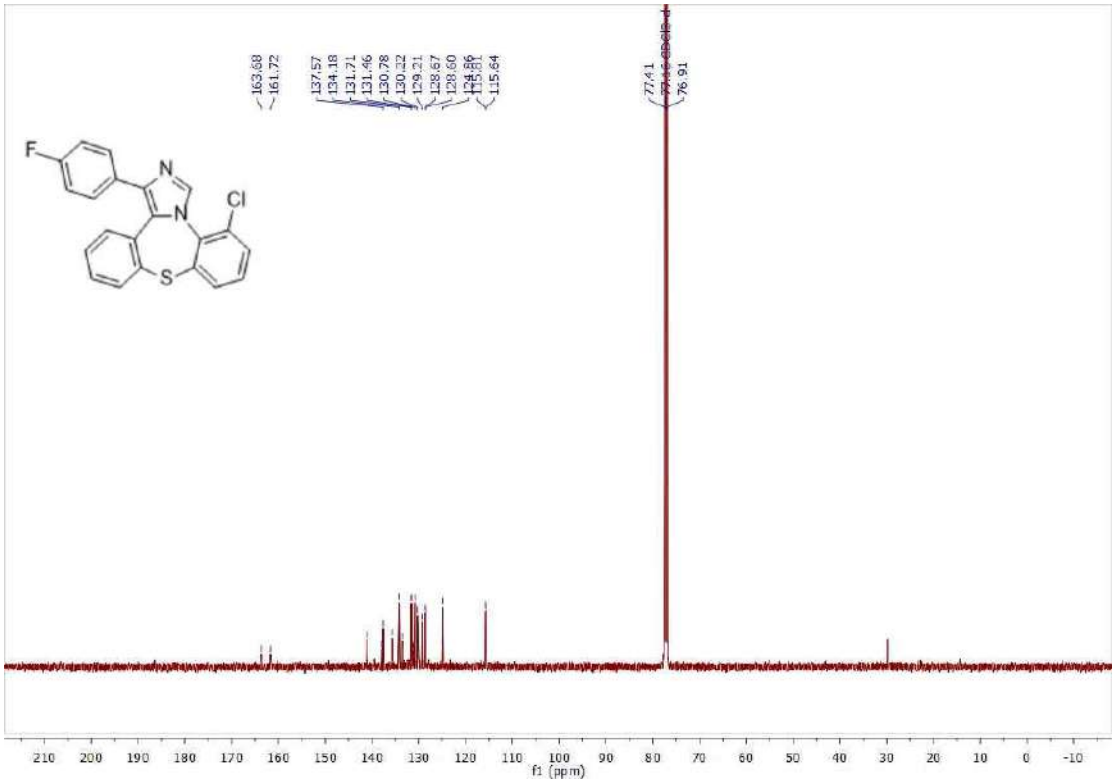
1.15
1.14
2.34
1.29
1.12
0.92
2.31
f1 (ppm)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115.64
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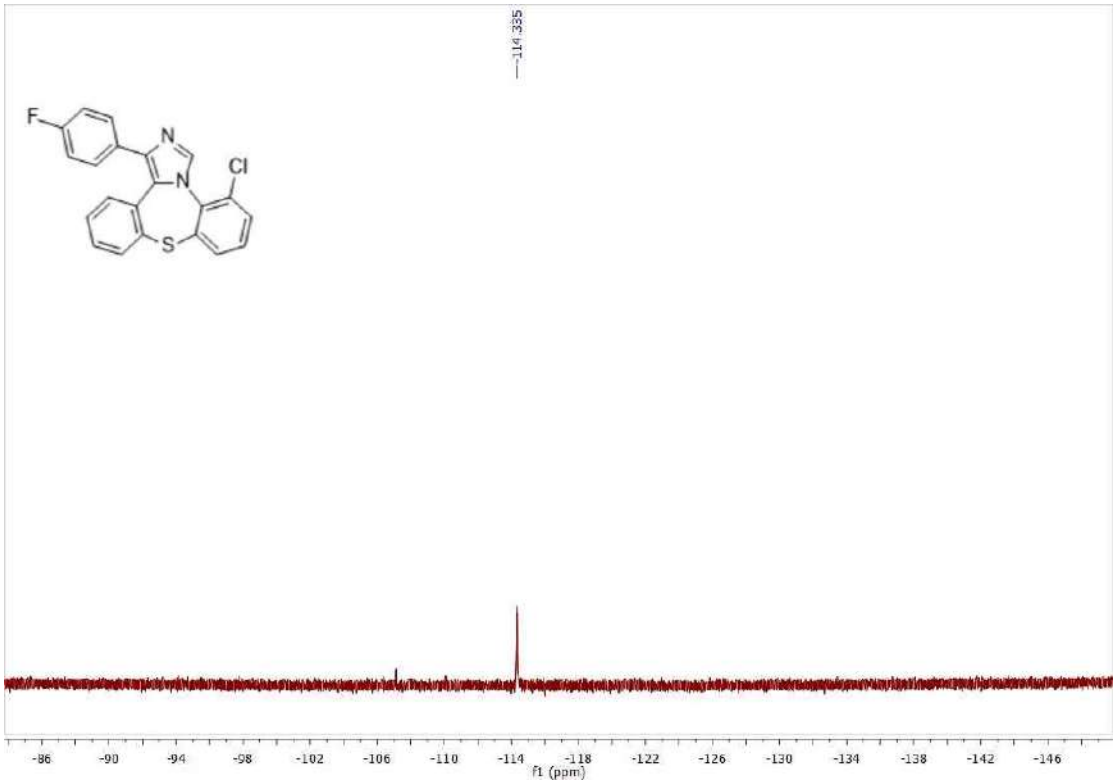
76.91
F
N
N
Cl
S
f1 (ppm)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N
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-114
-118
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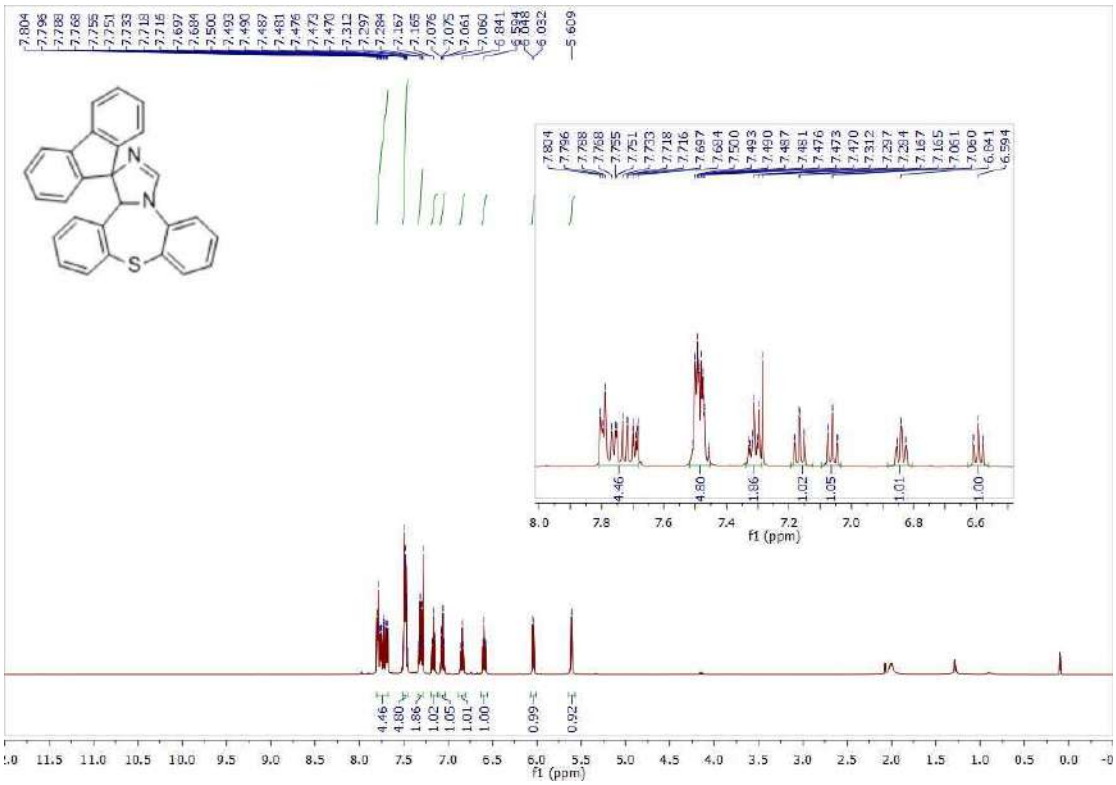
-126
-130
-134
-138
-142
-146
f1 (ppm)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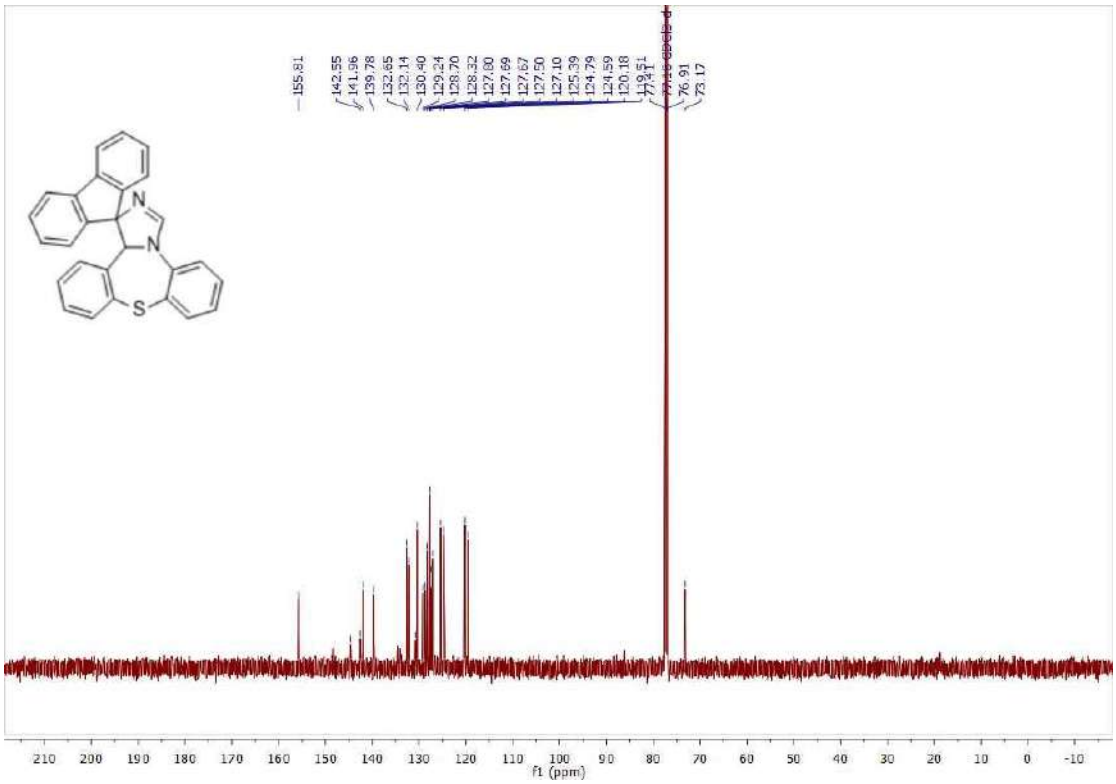
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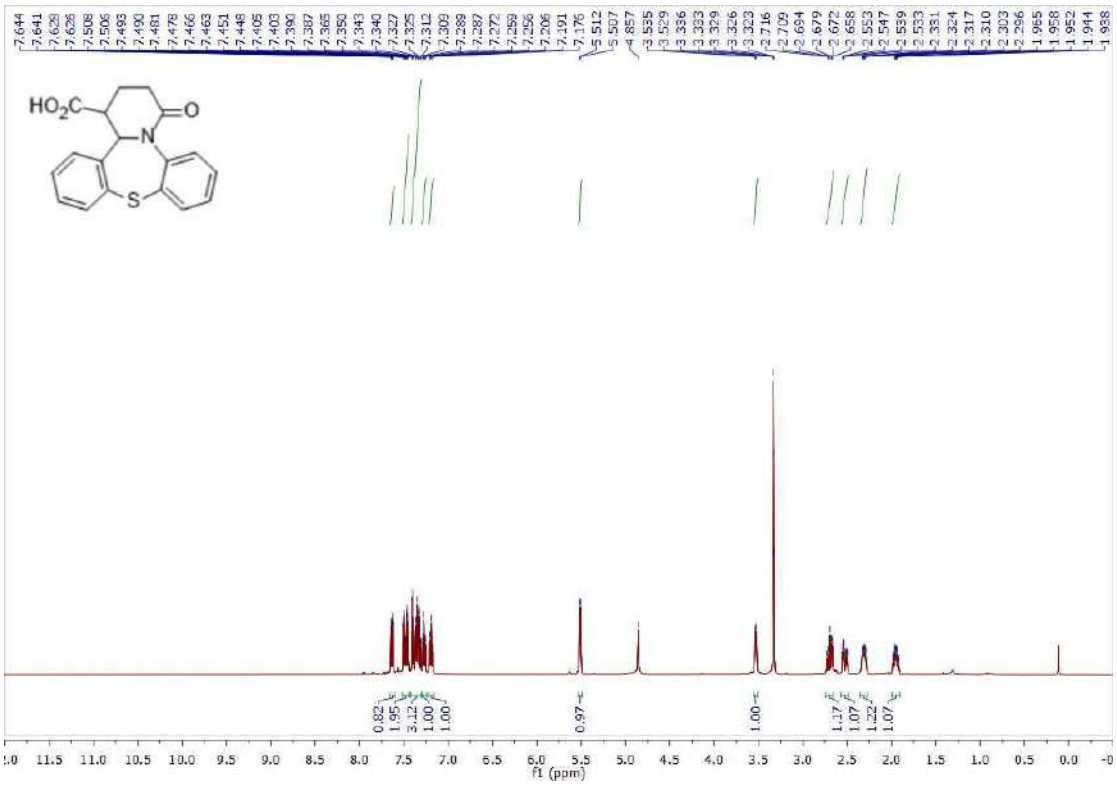
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N
S
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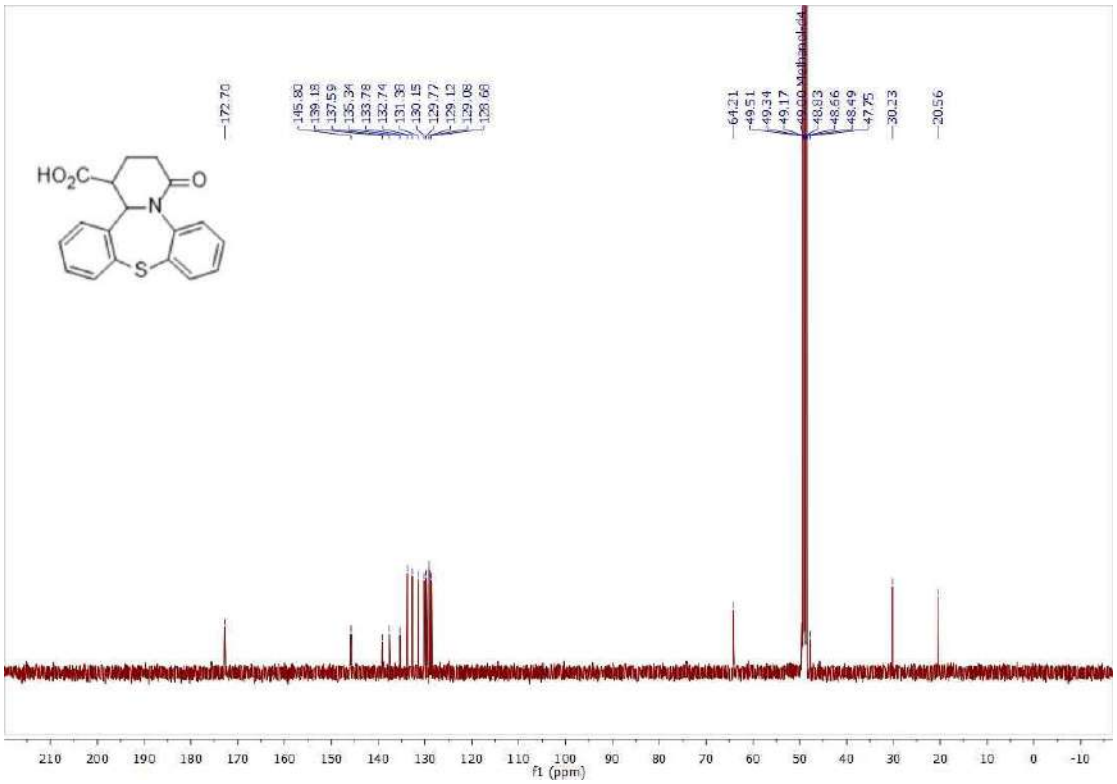
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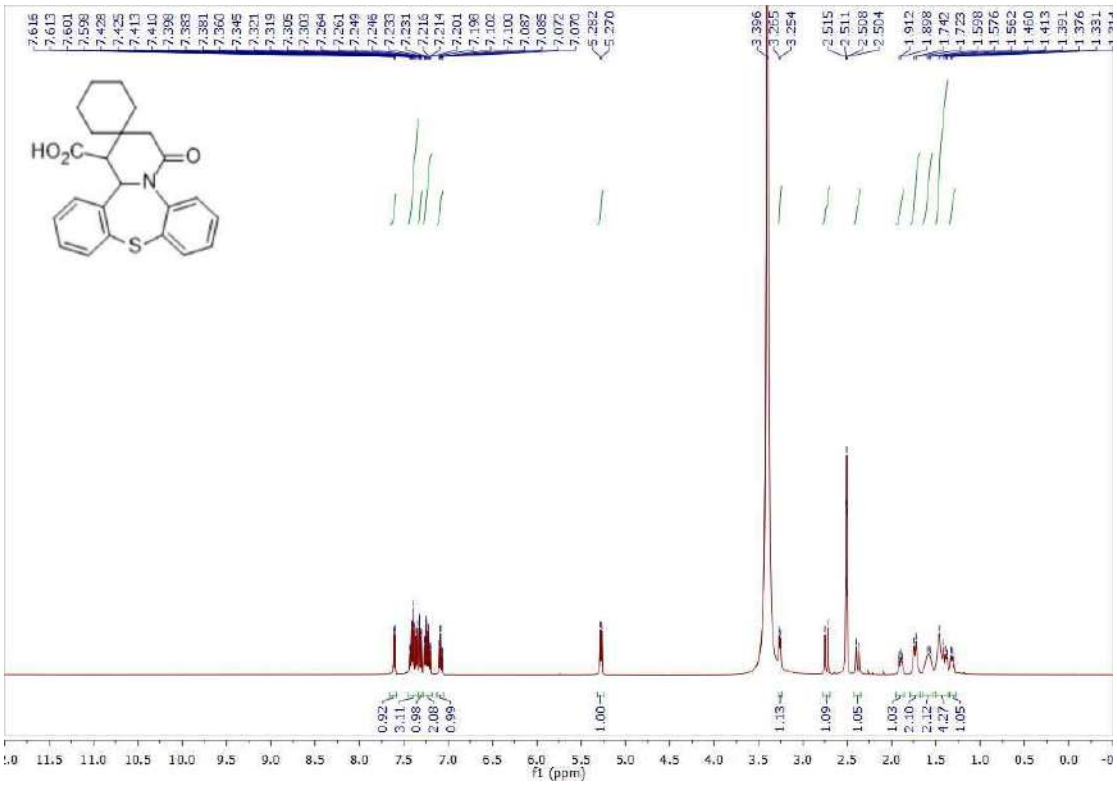
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O
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S
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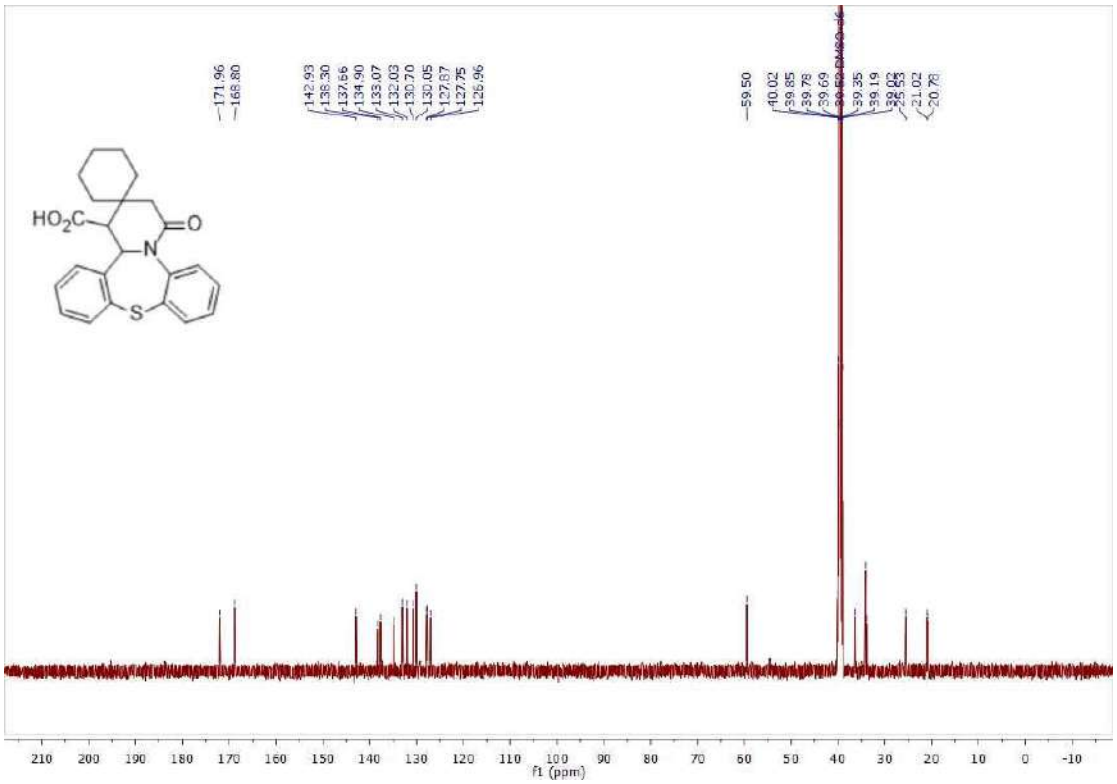
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S
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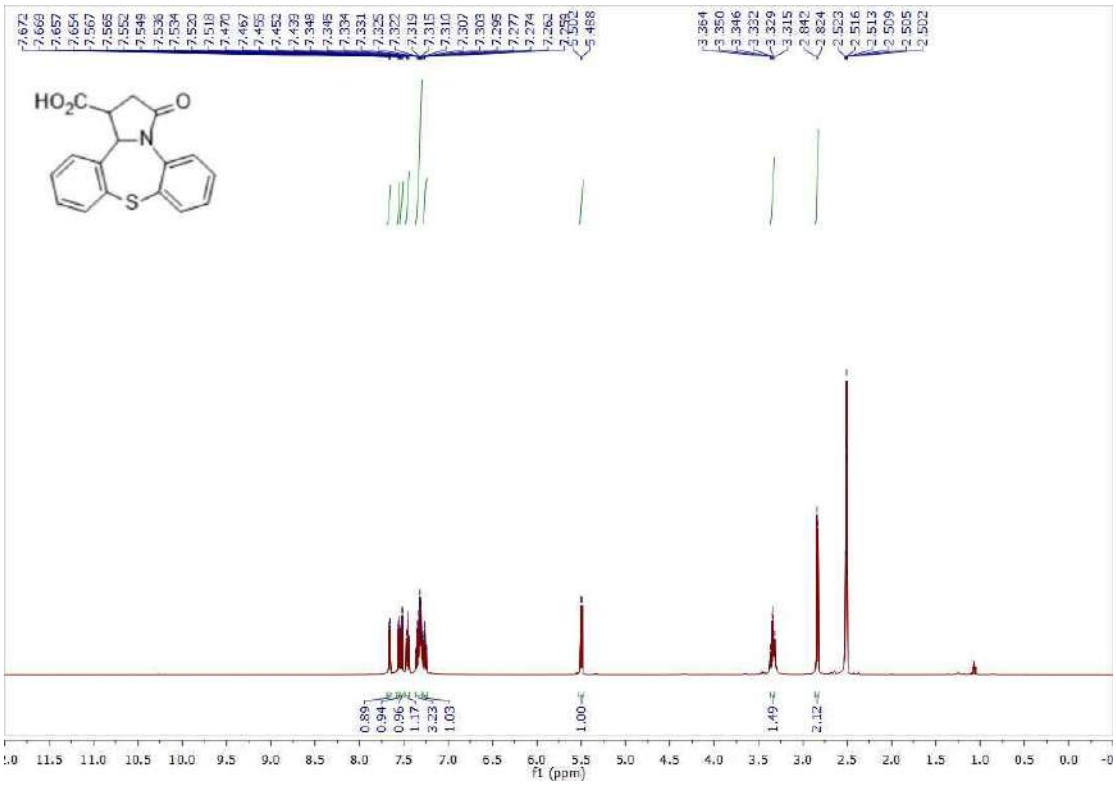
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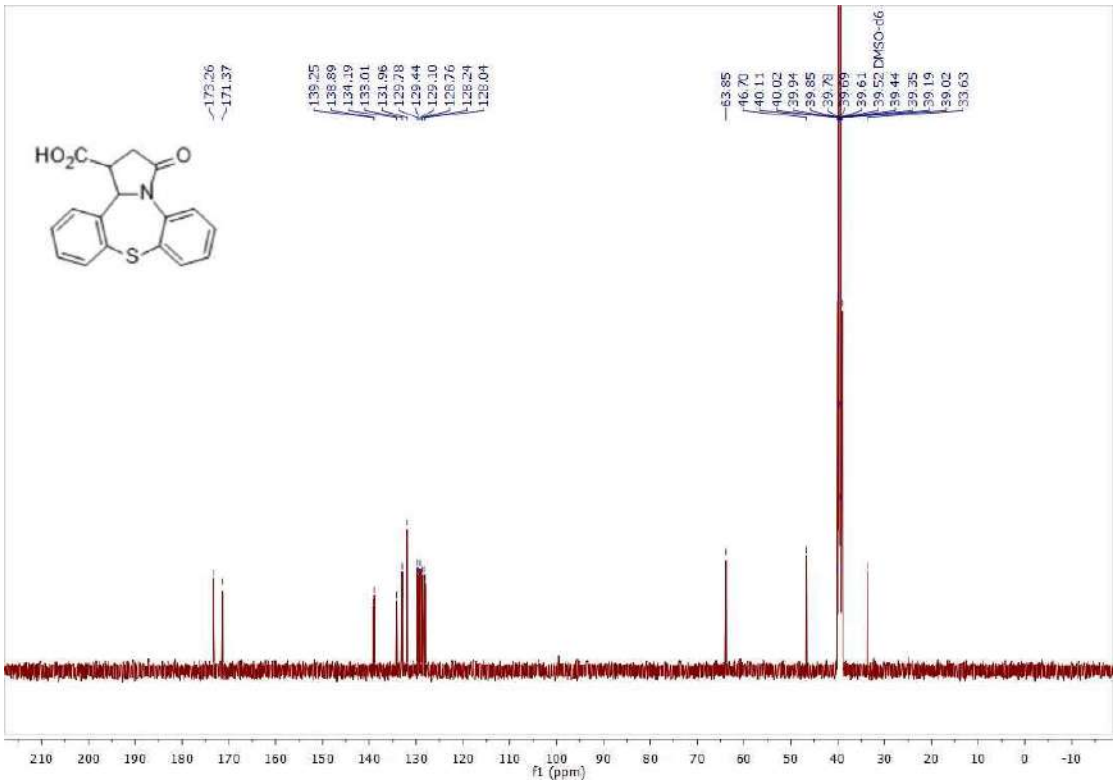
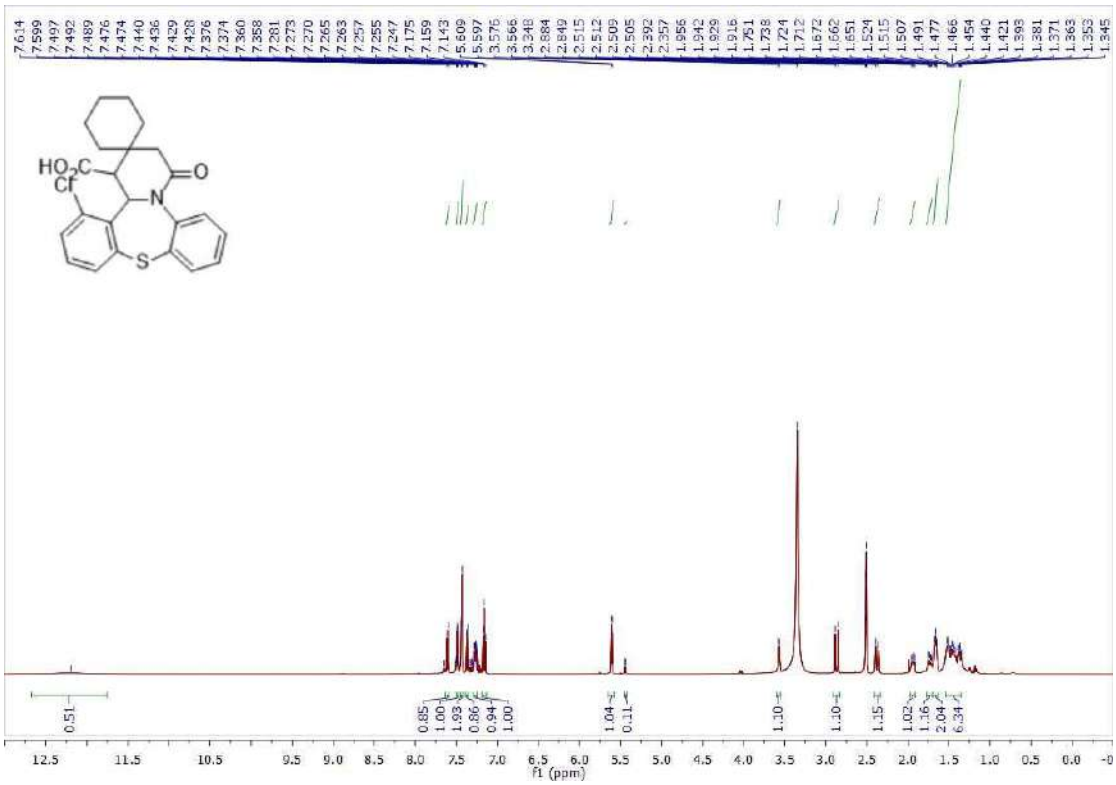
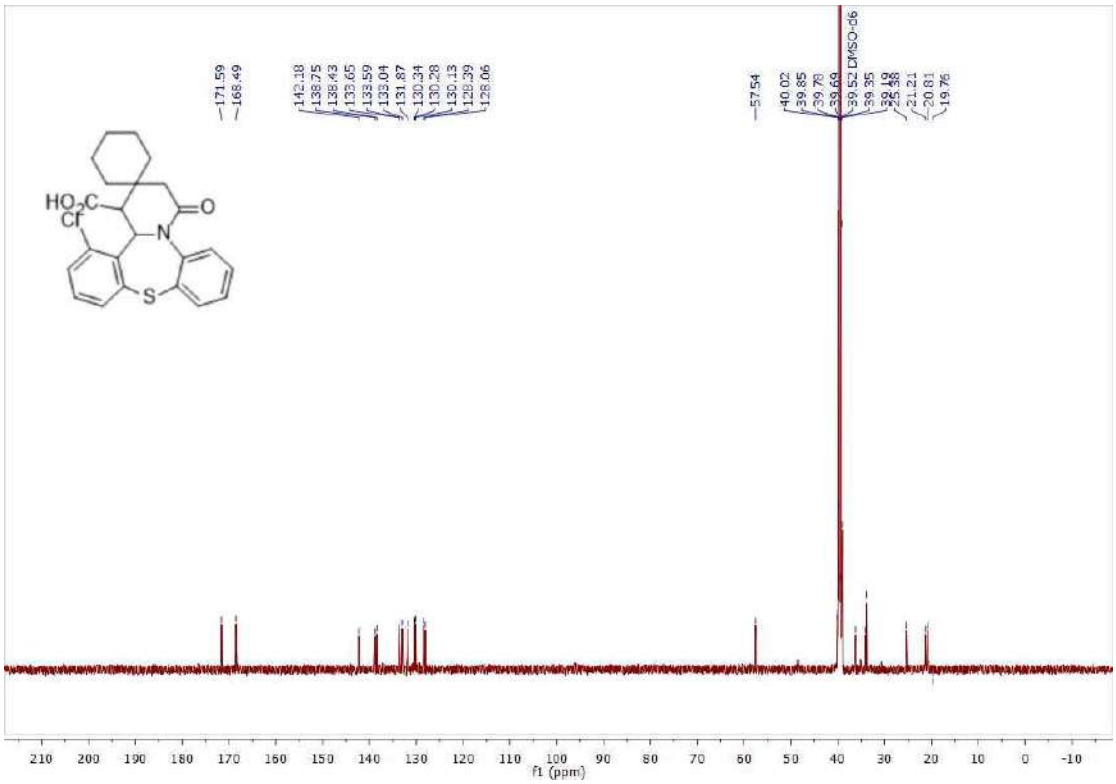
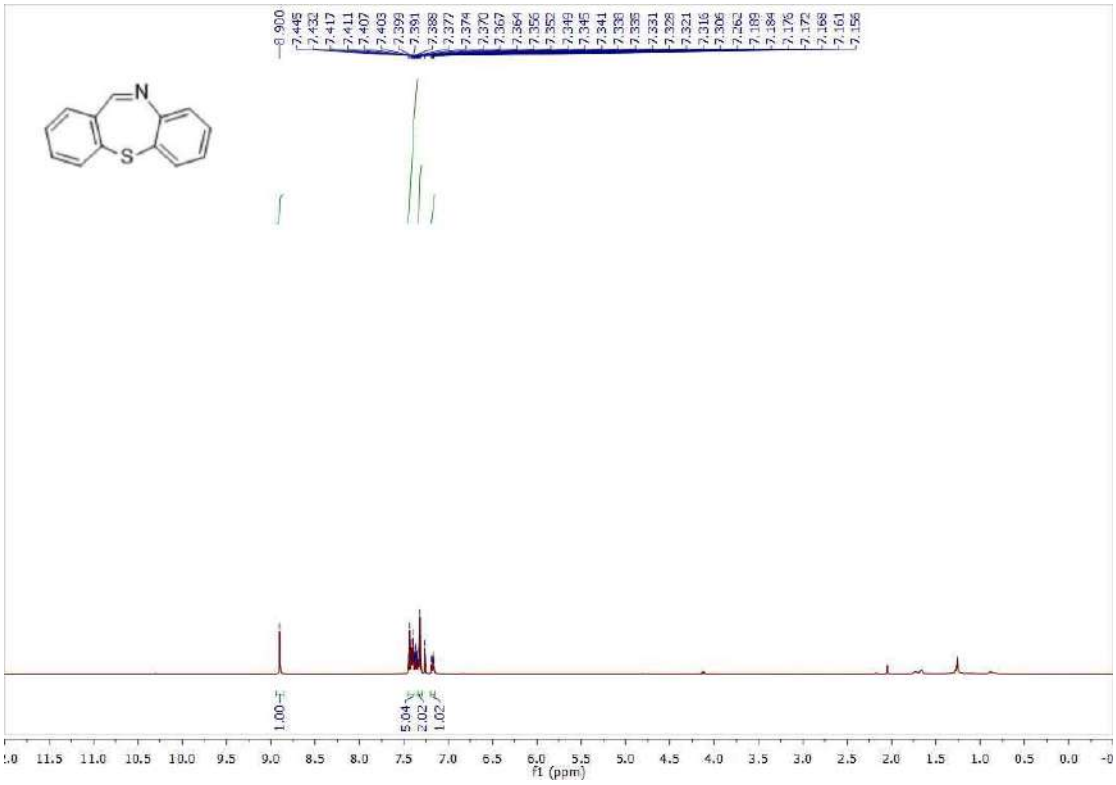
O
N
S
f1 (ppm)


HO2C
O
N
S
DMSO-d6
f1 (ppm)


HO2C
Cl
O
N
S
f1 (ppm)


HO2C
Cl
O
N
S
DMSO-d6
f1 (ppm)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7.370
7.367
7.364
7.356
7.352
7.349
7.345
7.341
7.338
7.335
7.331
7.328
7.321
7.316
7.306
7.262
7.189
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7.172
7.168
7.161
7.156
N
S
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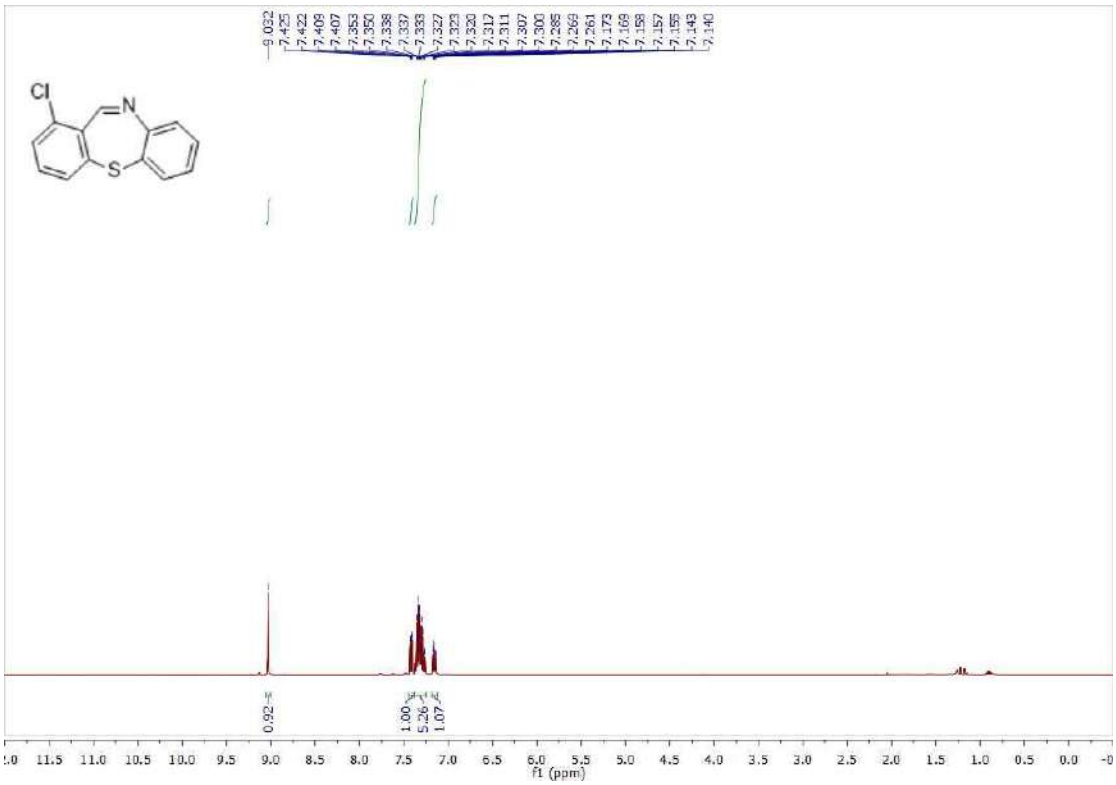
2.02
1.02
f1 (ppm)


Cl
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S
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7.327
7.323
7.320
7.312
7.311
7.307
7.300
7.285
7.269
7.261
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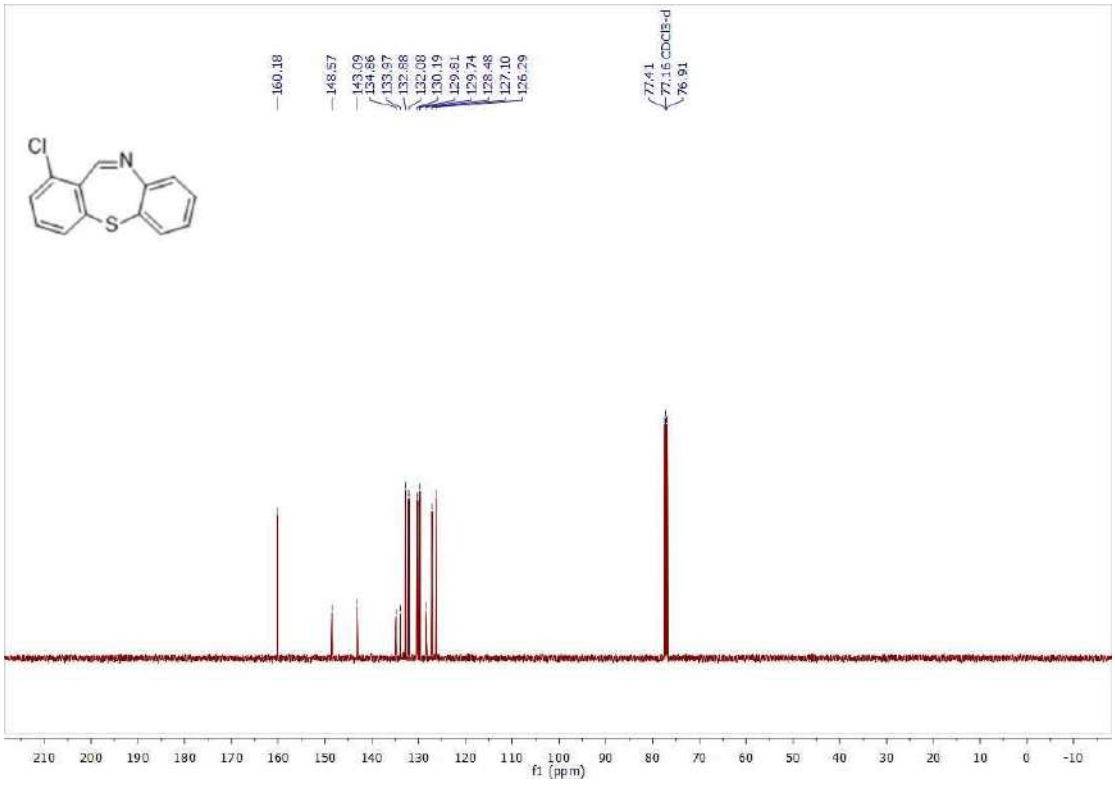
7.157
7.155
7.143
7.140
0.92
1.00
5.26
1.07
f1 (ppm)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S
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133.97
132.88
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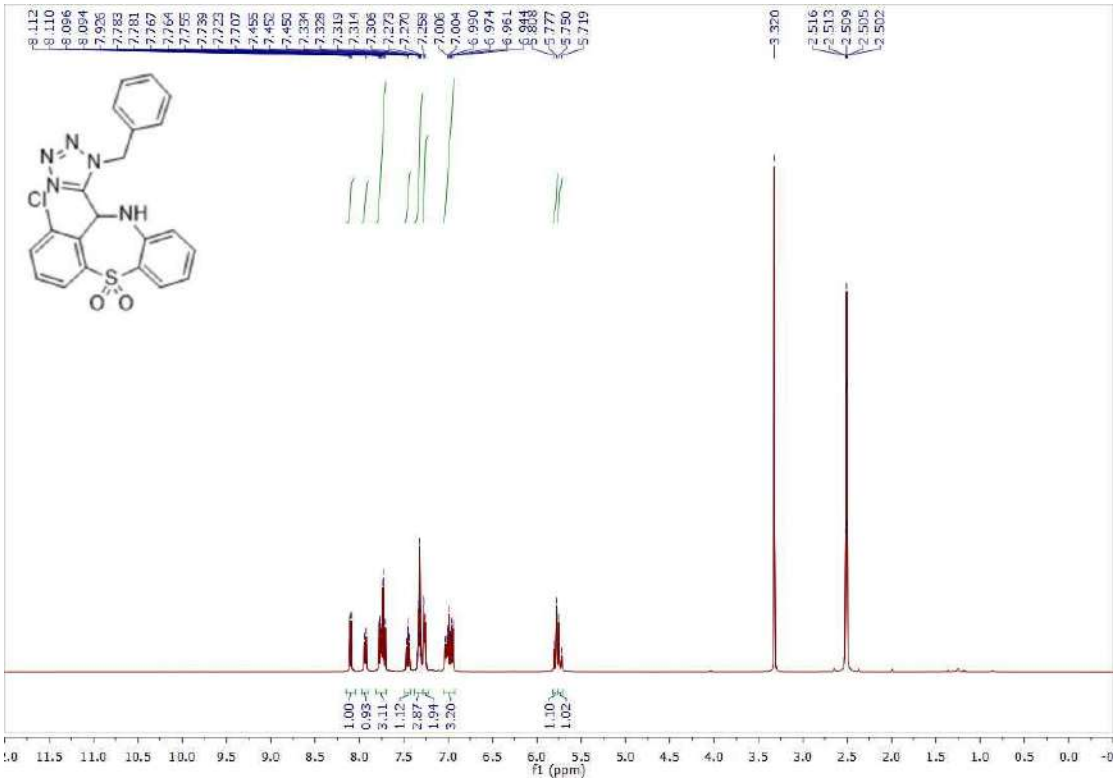
127.10
126.29
77.41
77.16 CDCl3-d
76.91
f1 (ppm)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7.739
7.723
7.707
7.455
7.452
7.450
7.334
7.328
7.319
7.314
7.306
7.273
7.270
7.258
7.006
7.004
6.990
6.974
6.961
5.777
5.750
5.719
3.320
2.516
2.513
2.509
2.505
2.502
Cl
NH
S
O
O
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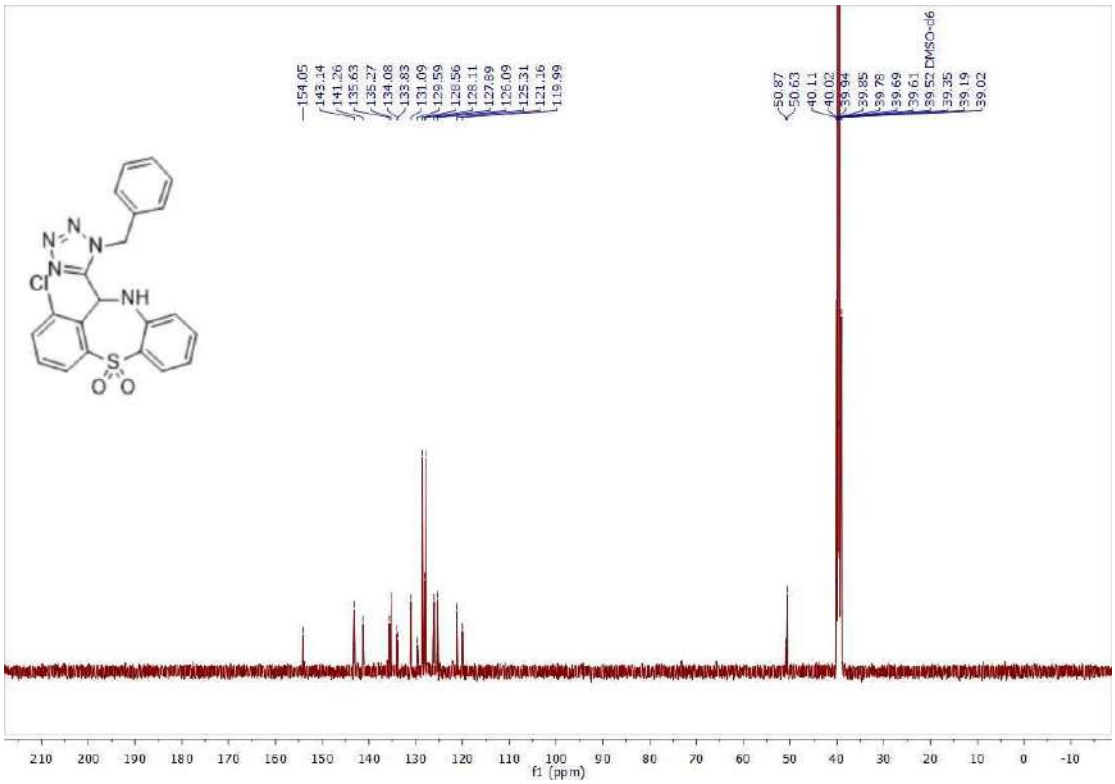
2.87
1.94
3.20
1.10
1.02
f1 (ppm)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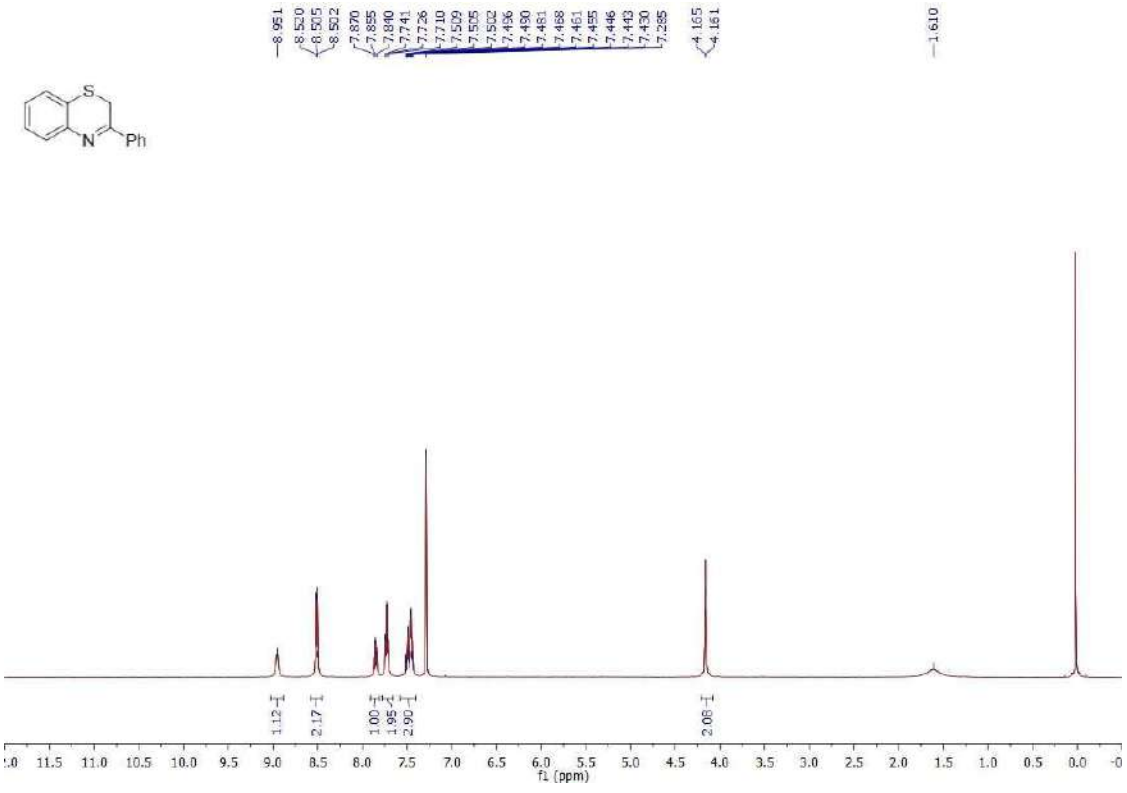
128.56
128.11
127.89
126.09
125.31
121.16
119.99
50.87
50.63
40.11
40.02
39.94
39.85
39.78
39.69
39.61
39.52 DMSO-d6
39.35
39.19
39.02
Cl
NH
S
O
O
f1 (ppm)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7.502
7.496
7.490
7.481
7.468
7.461
7.455
7.446
7.443
7.430
7.285
4.165
4.161
1.610
S
N
Ph
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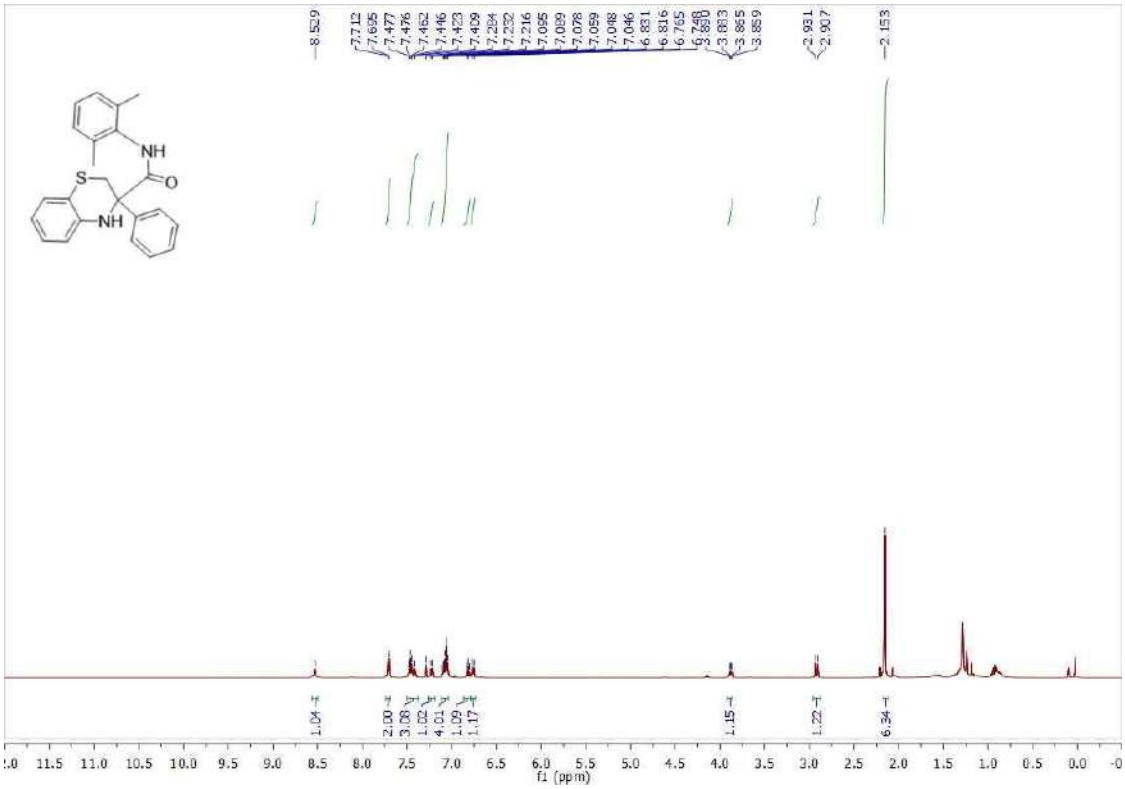
2.17
1.00
1.95
2.90
2.08
f1 (ppm)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7.095
7.089
7.078
7.059
7.048
7.046
6.831
6.816
6.765
6.748
3.880
3.863
3.855
3.859
2.931
2.907
2.153
NH
S
O
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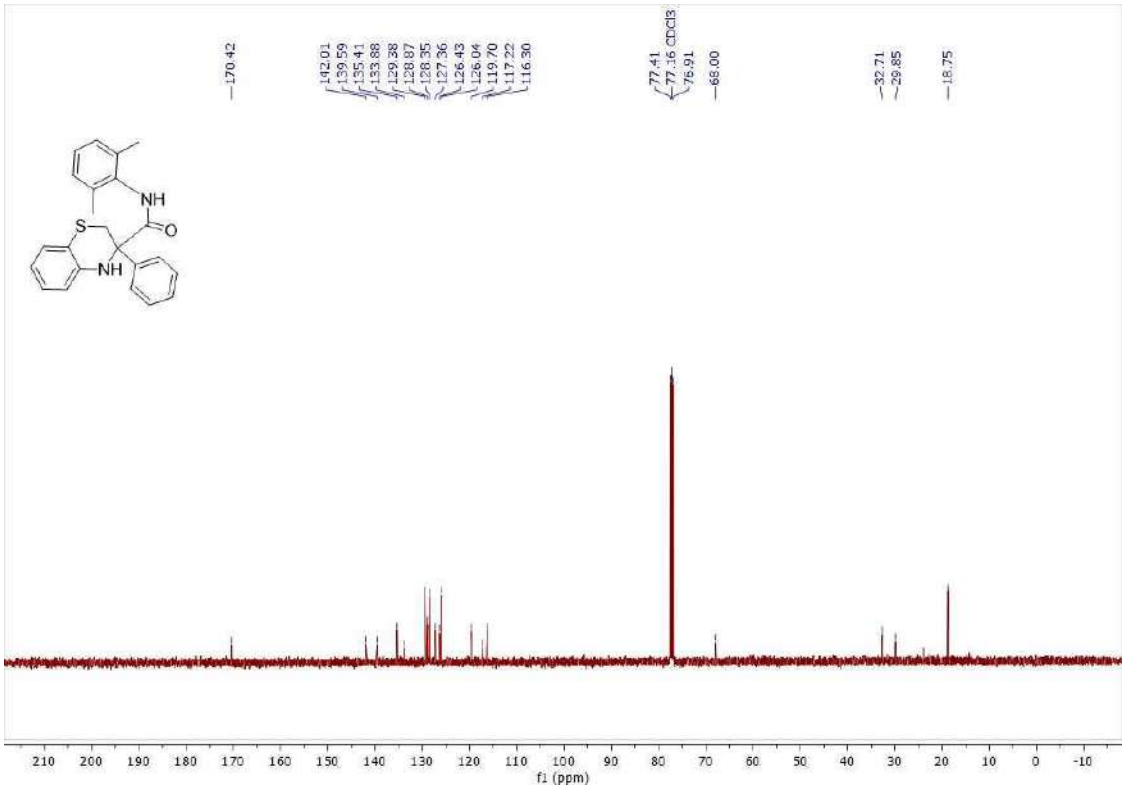
3.08
1.02
4.01
1.09
1.17
1.15
1.22
6.34
f1 (ppm)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128.35
127.36
126.43
126.04
119.70
117.22
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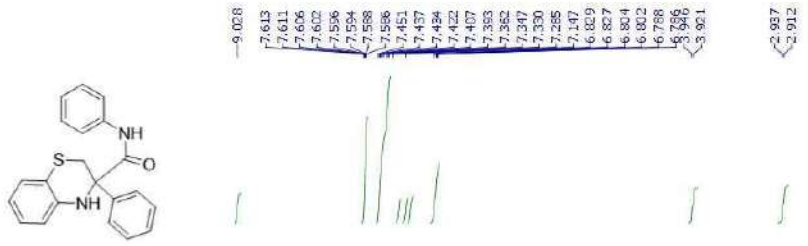
77.41
77.16 CDCl3
76.91
68.00
32.71
29.85
18.75
NH
S
O
NH
f1 (ppm)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7.434
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7.407
7.393
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7.347
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6.829
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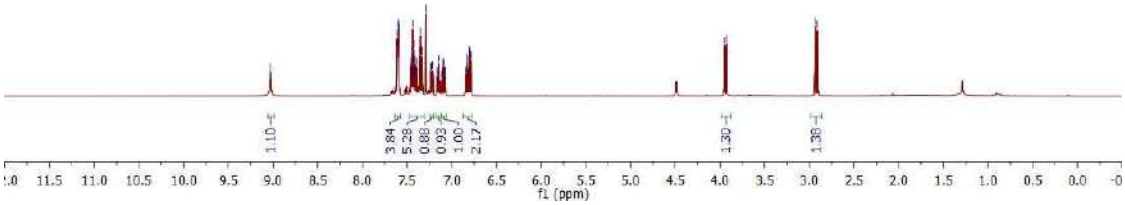
NH
S
O
NH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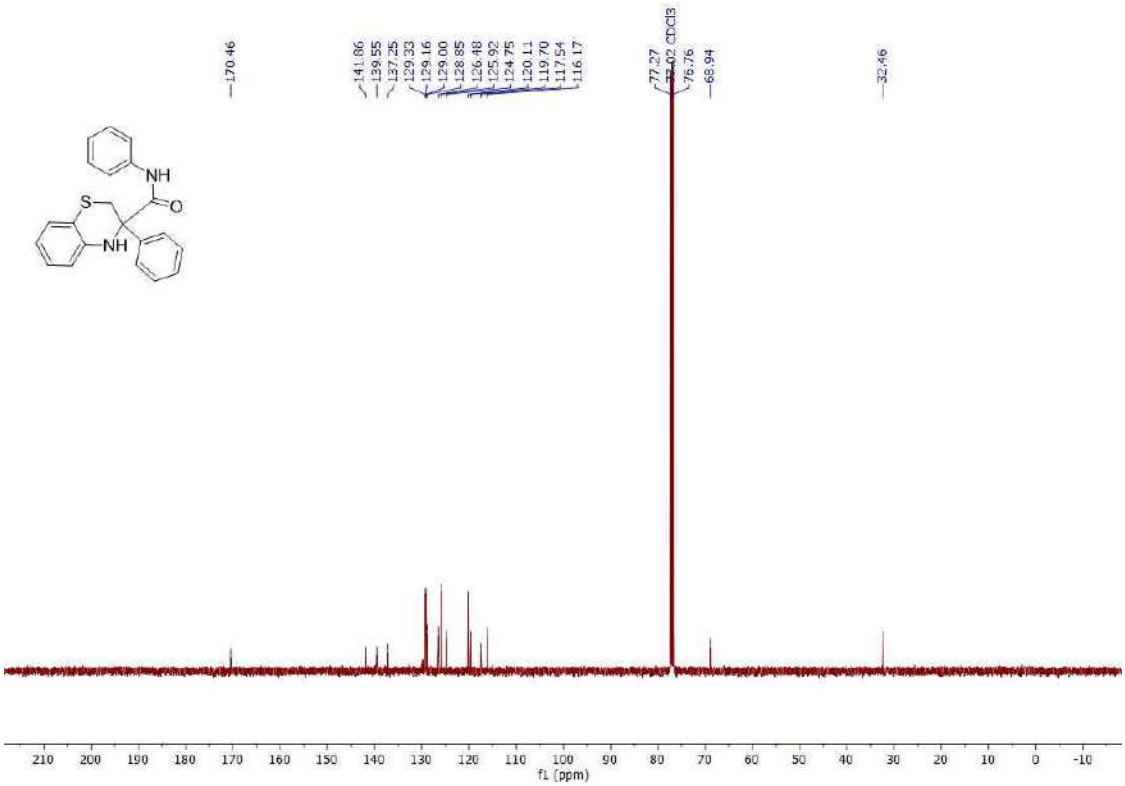
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125.92
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77.27
77.02 CDCl3
76.76
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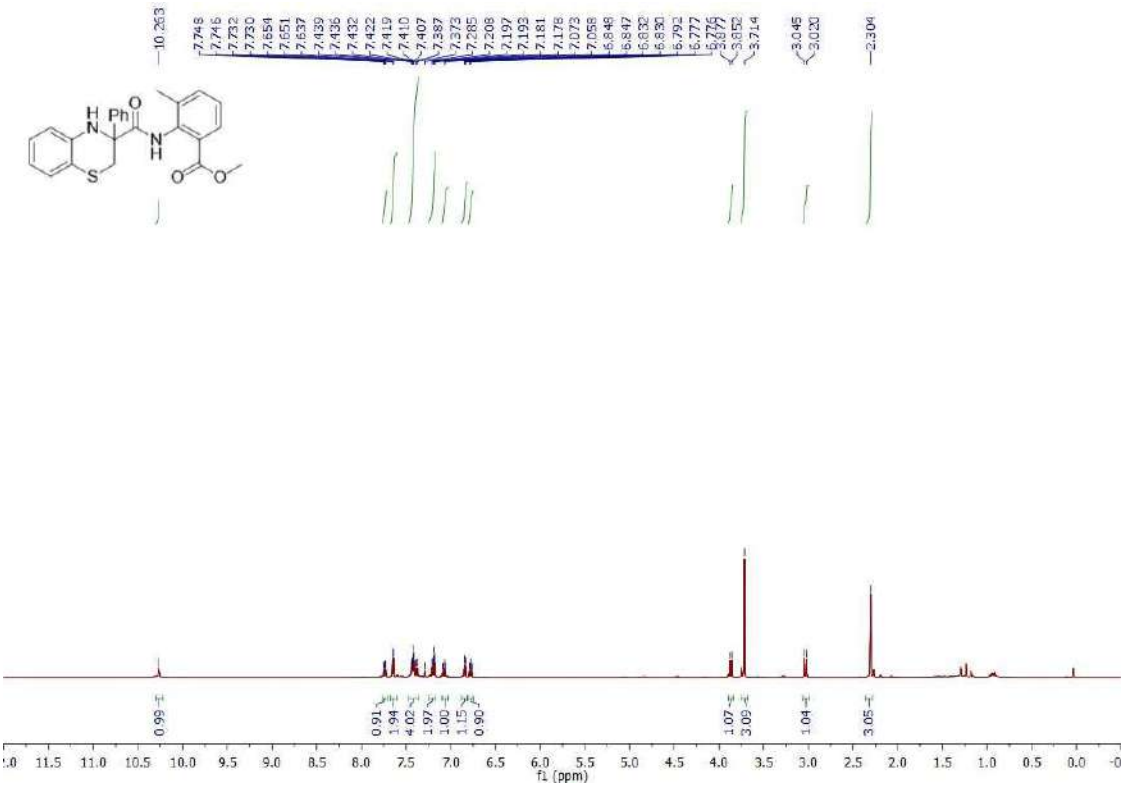
32.46
NH
S
O
NH
f1 (ppm)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7.407
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7.193
7.181
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7.073
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6.847
6.832
6.831
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3.877
3.852
3.714
3.045
3.020
2.304
Ph
O
H
N
N
H
S
O
O
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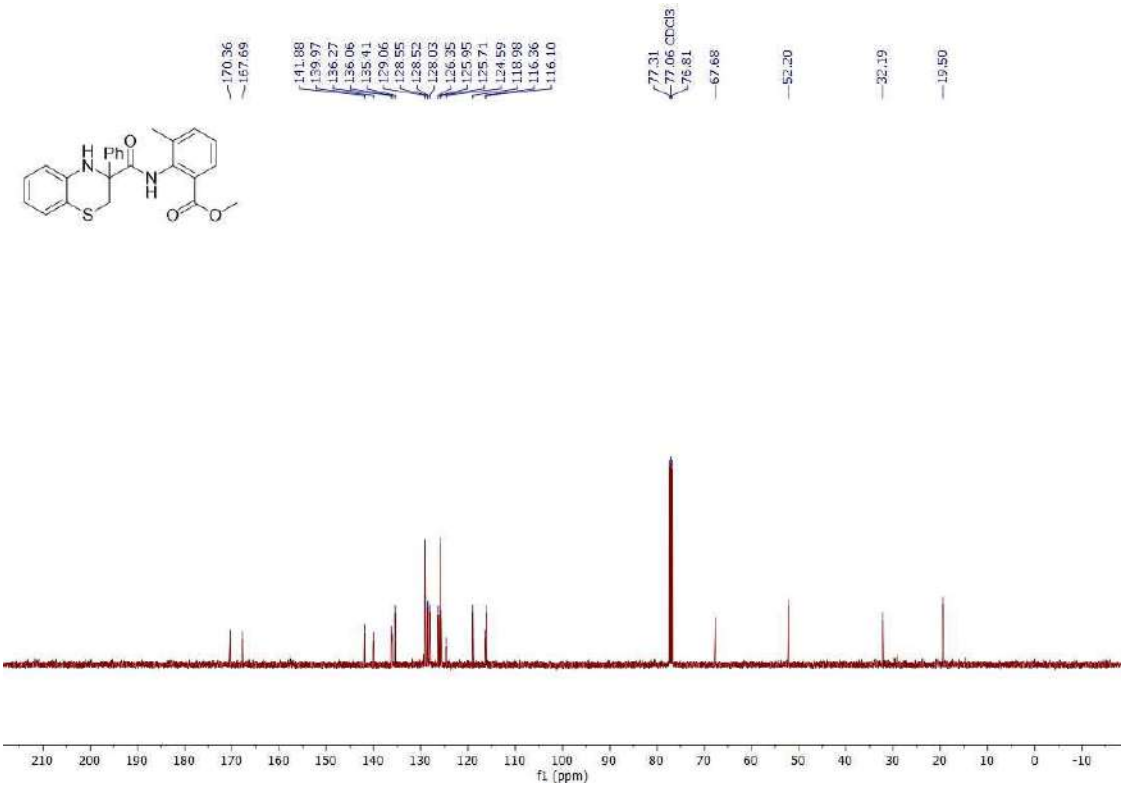
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128.03
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125.95
125.71
124.59
118.98
116.36
116.10
77.31
77.06 CDCl3
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32.19
19.50
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N
H
S
O
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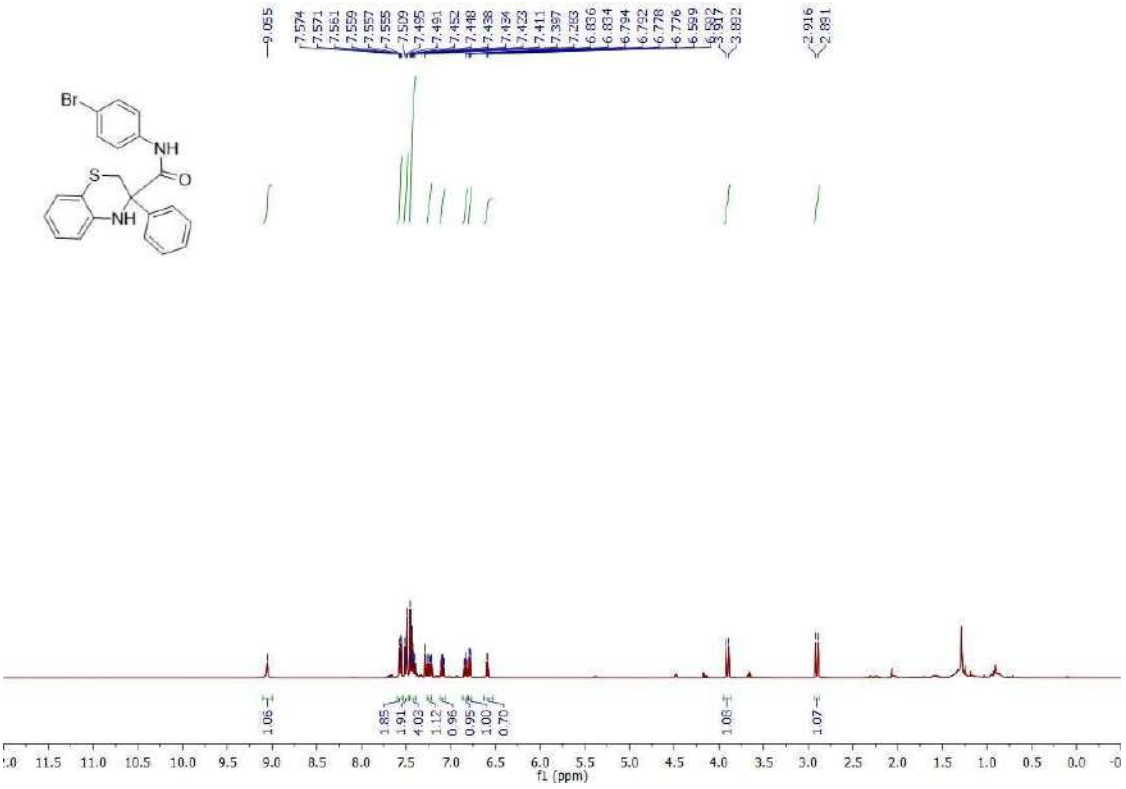
f1 (ppm)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7.434
7.423
7.411
7.397
7.293
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6.834
6.794
6.792
6.778
6.776
6.589
6.582
3.917
3.832
2.916
2.881
Br
NH
S
O
NH
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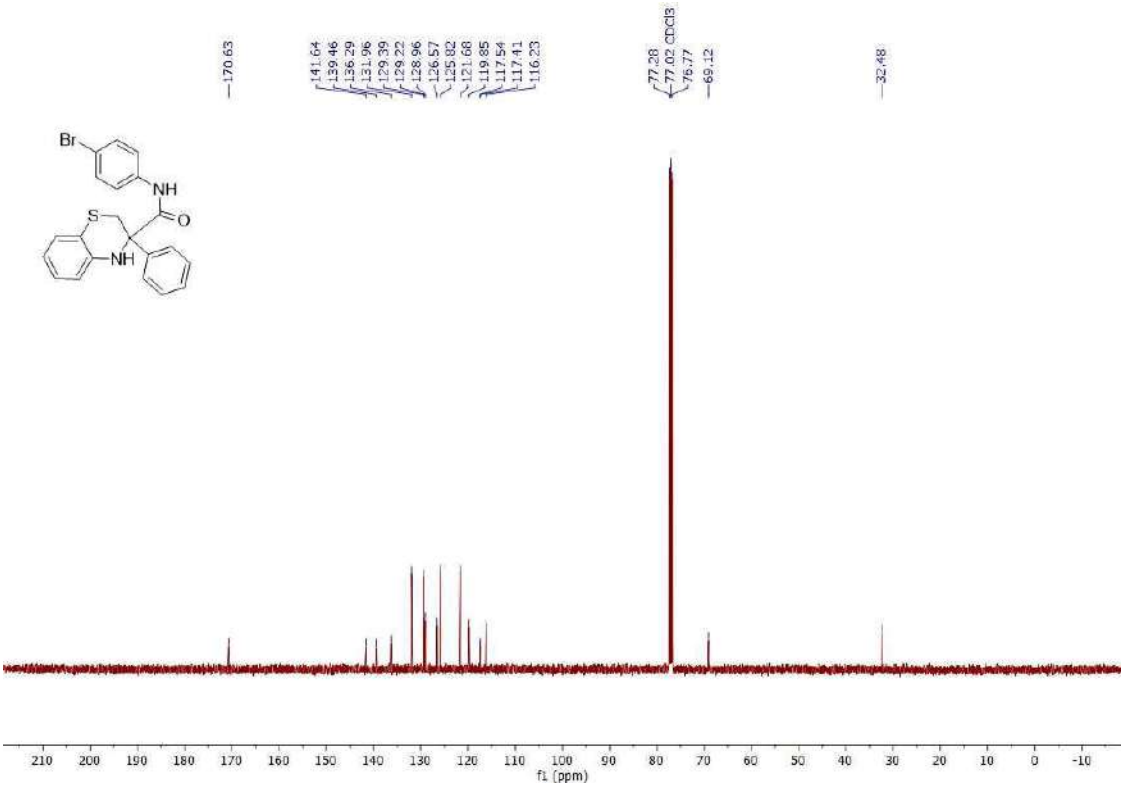
1.07
f1 (ppm)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117.54
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77.02 CDCl3
76.77
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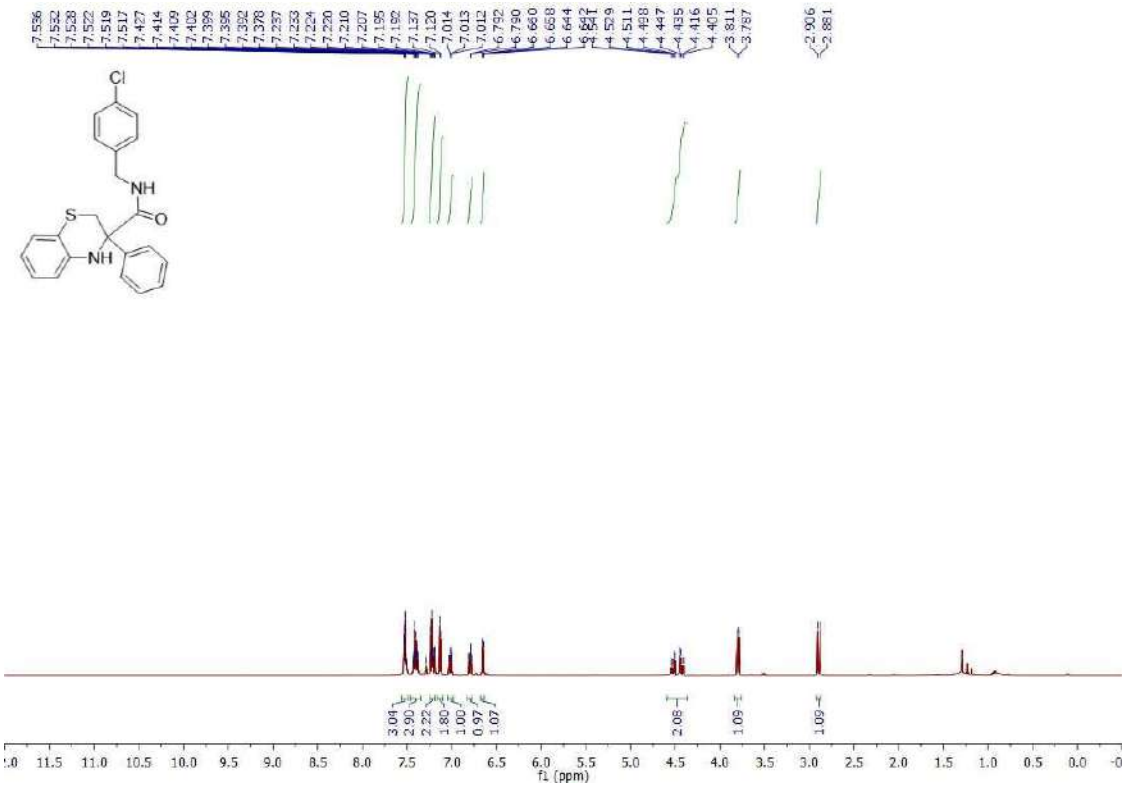
Br
NH
S
O
NH
f1 (ppm)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7.392
7.378
7.237
7.233
7.224
7.220
7.210
7.207
7.195
7.192
7.137
7.120
7.014
7.013
7.012
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6.790
6.660
6.658
6.644
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4.511
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4.447
4.435
4.416
4.405
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3.787
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2.881
Cl
NH
O
S
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1.09
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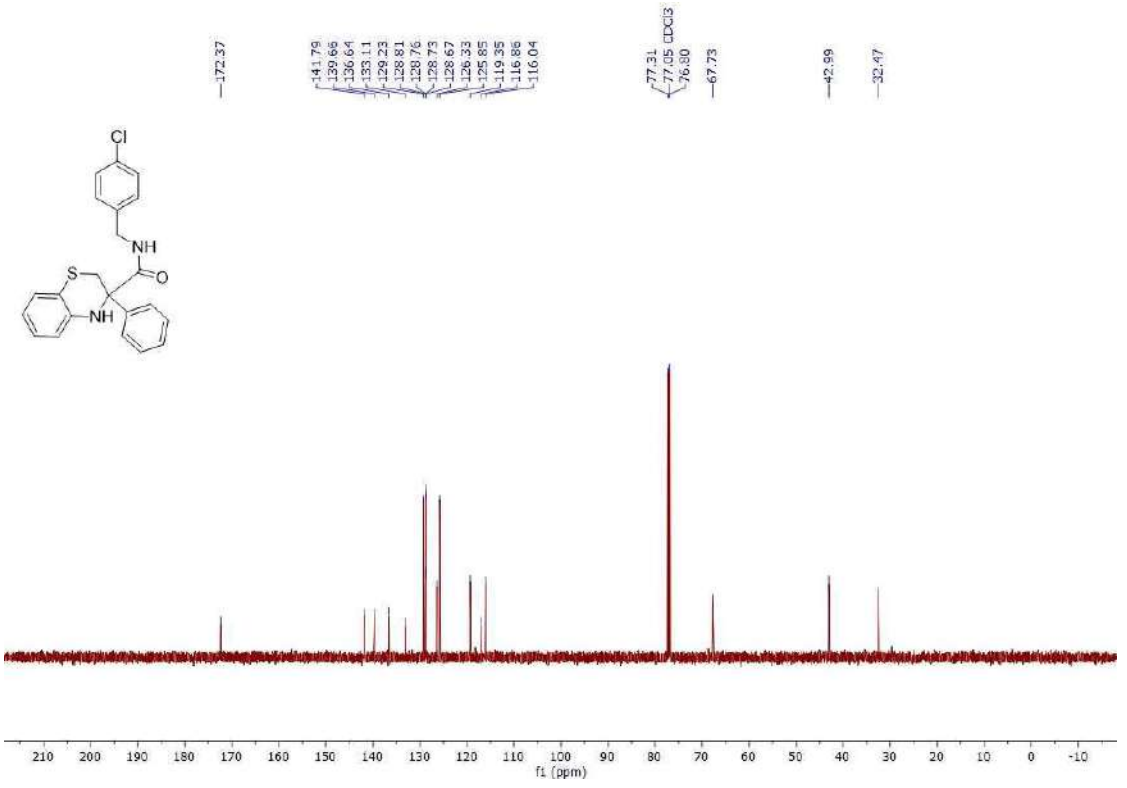
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119.35
116.86
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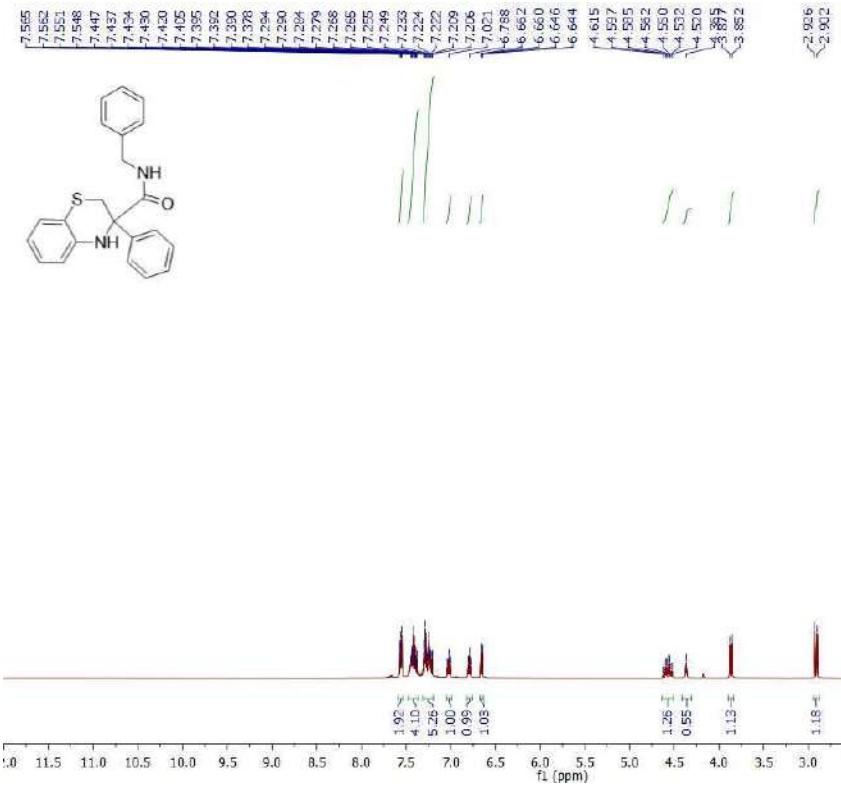
O
S
NH
f1 (ppm)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4.520
3.885
3.877
3.852
2.926
2.902
NH
S
O
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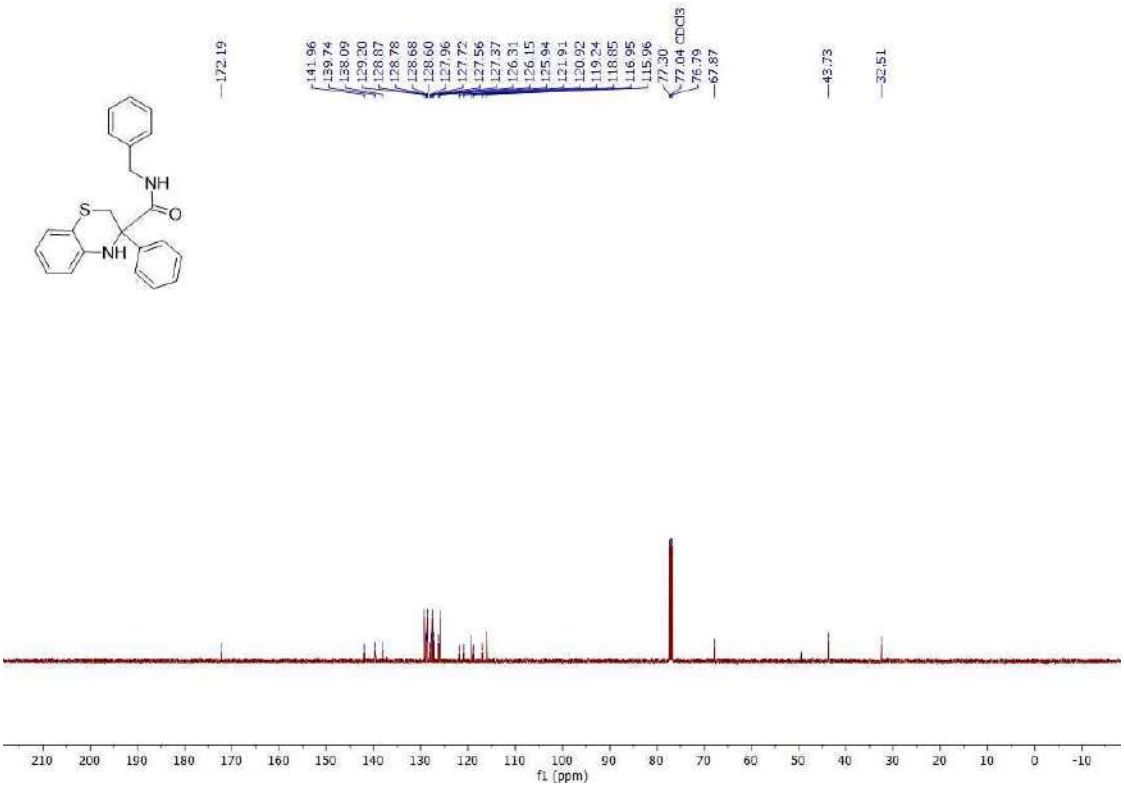
fl (ppm)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121.91
120.92
119.24
118.85
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76.79
67.87
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32.51
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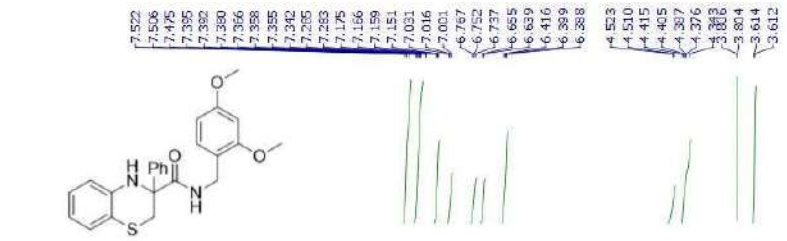
O
NH
fl (ppm)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7.175
7.166
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7.031
7.016
7.001
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6.416
6.399
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4.523
4.510
4.415
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3.804
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3.612
Ph
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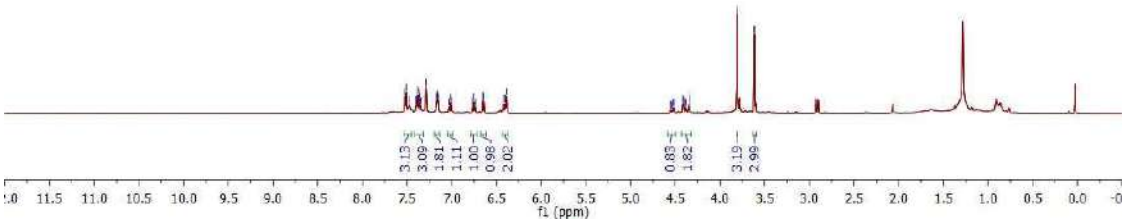
H
S
O
O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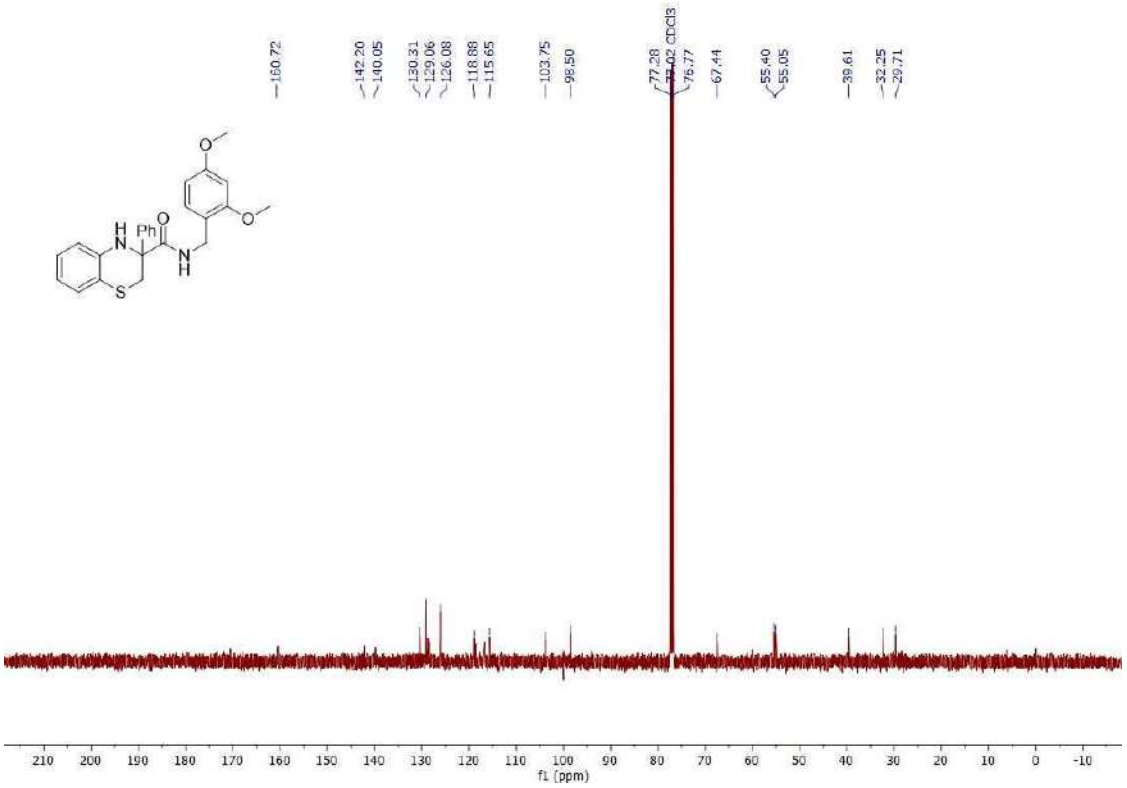
2.99
f1 (ppm)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77.02 CDCl3
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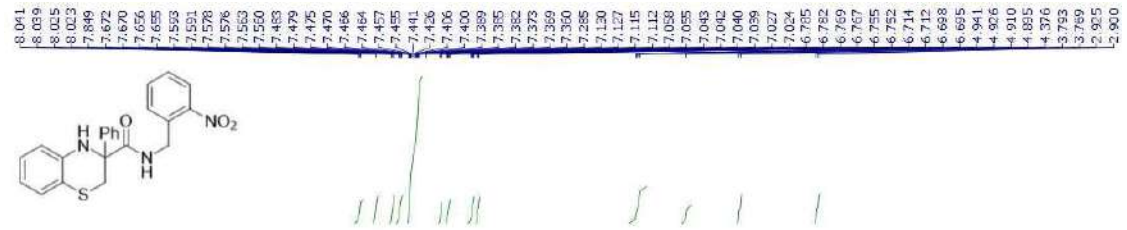
N
H
S
O
O
f1 (ppm)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7.127
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7.112
7.058
7.055
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7.042
7.040
7.039
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Ph
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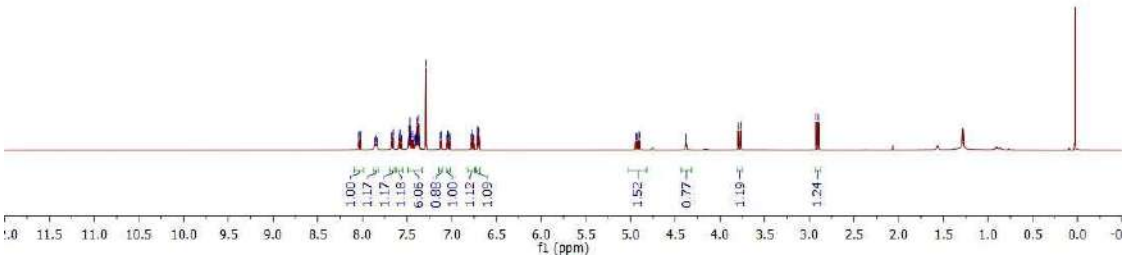
H
S
NO2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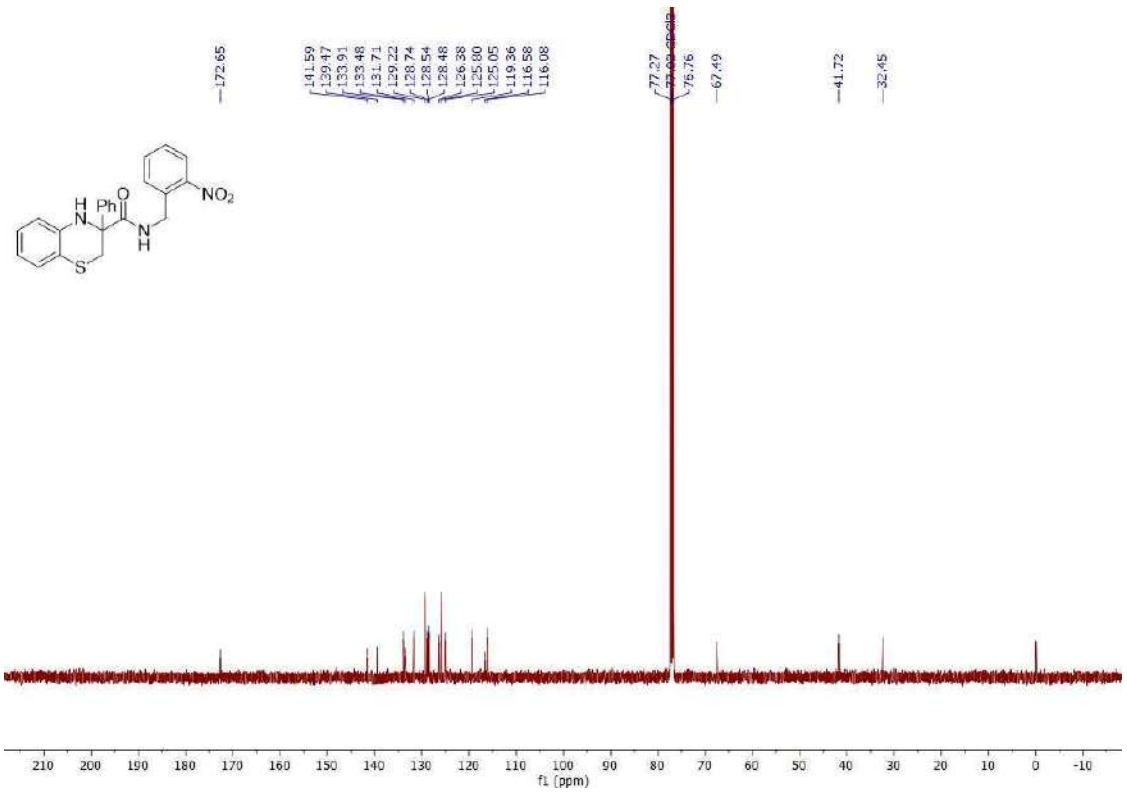
1.24
f1 (ppm)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119.36
116.58
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67.49
41.72
32.45
Ph
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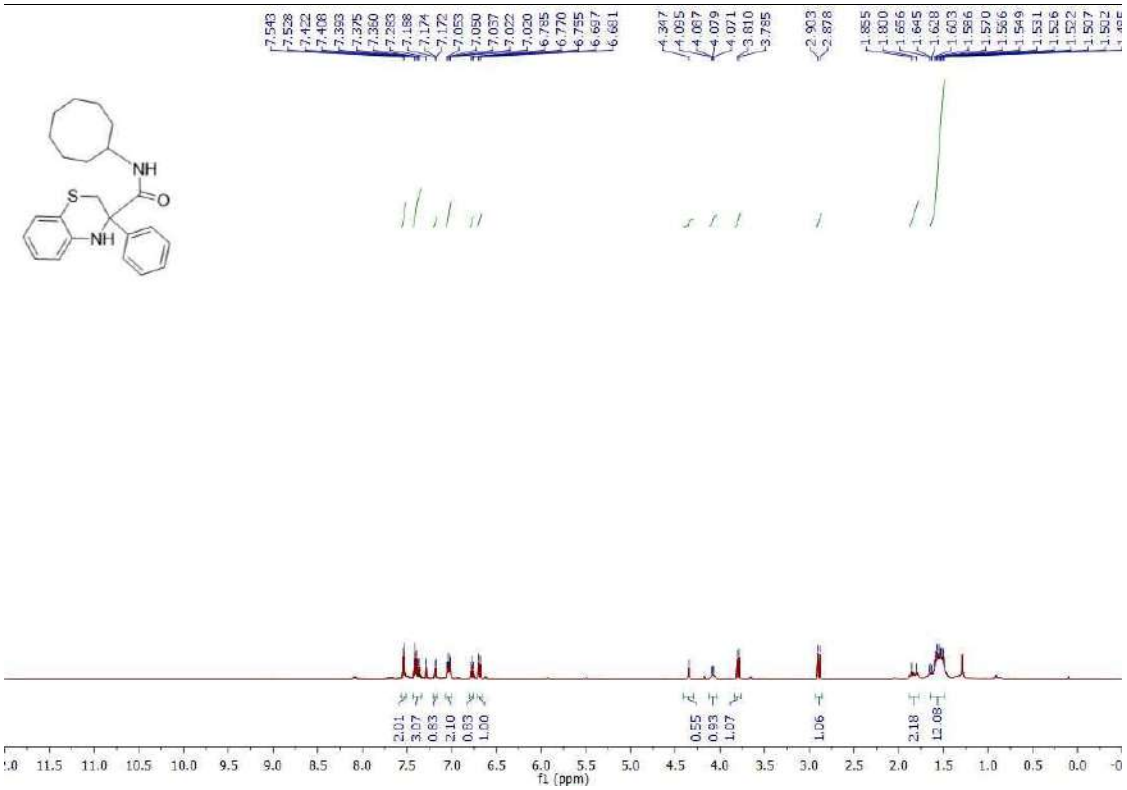
N
H
N
H
S
NO2
f1 (ppm)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O
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7.172
7.053
7.050
7.037
7.022
7.020
6.795
6.770
6.755
6.697
6.681
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4.065
4.067
4.039
4.071
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3.785
2.903
2.878
1.855
1.900
1.656
1.645
1.628
1.603
1.586
1.570
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1.549
1.531
1.526
1.502
1.507
1.502
2.01
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0.83
2.10
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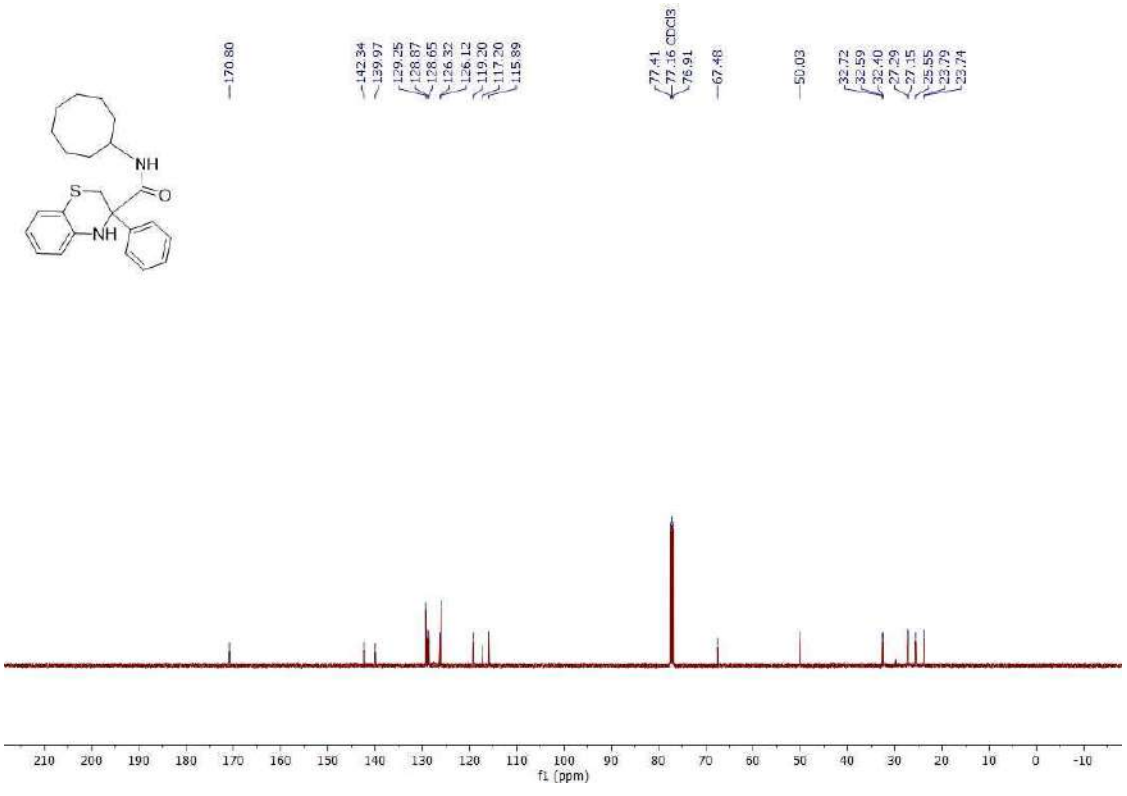
1.00
0.55
0.93
1.07
1.06
2.18
12.08
f1 (ppm)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126.12
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117.20
115.89
77.41
77.16 CDCl3
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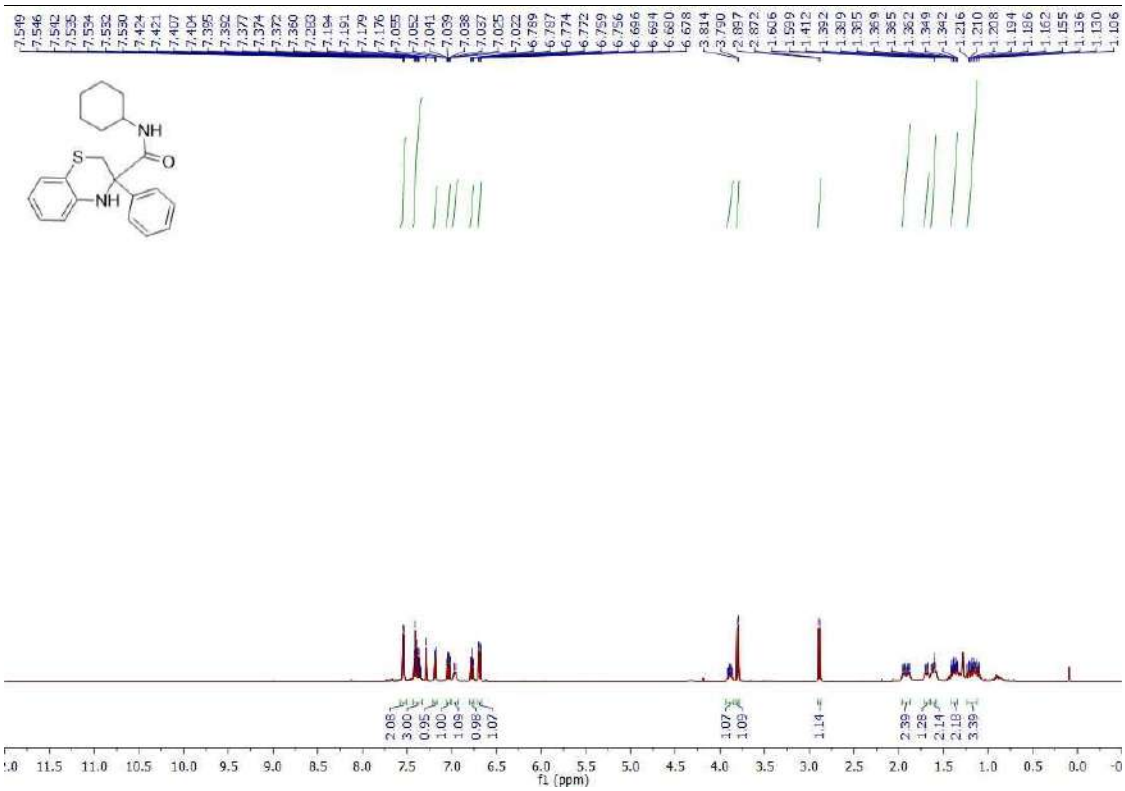
32.40
27.29
27.15
25.55
23.79
23.74
f1 (ppm)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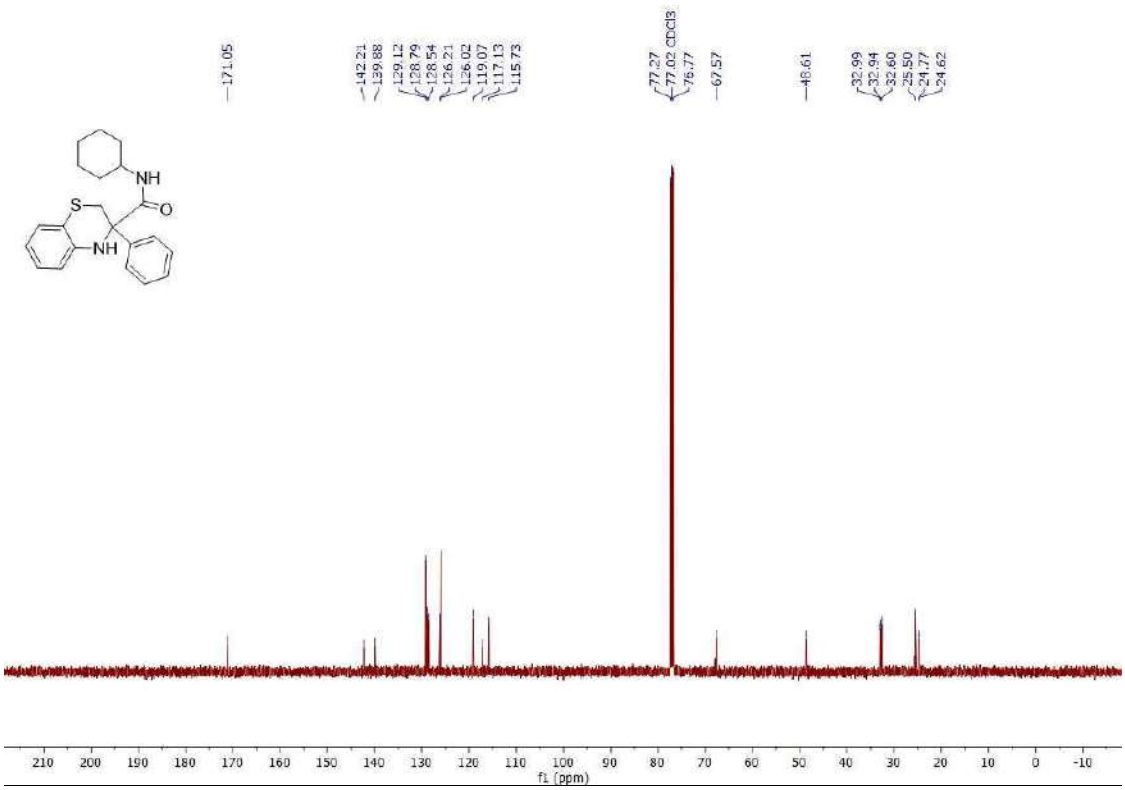
O
S
NH
f1 (ppm)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77.02 CDCl3
76.77
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25.50
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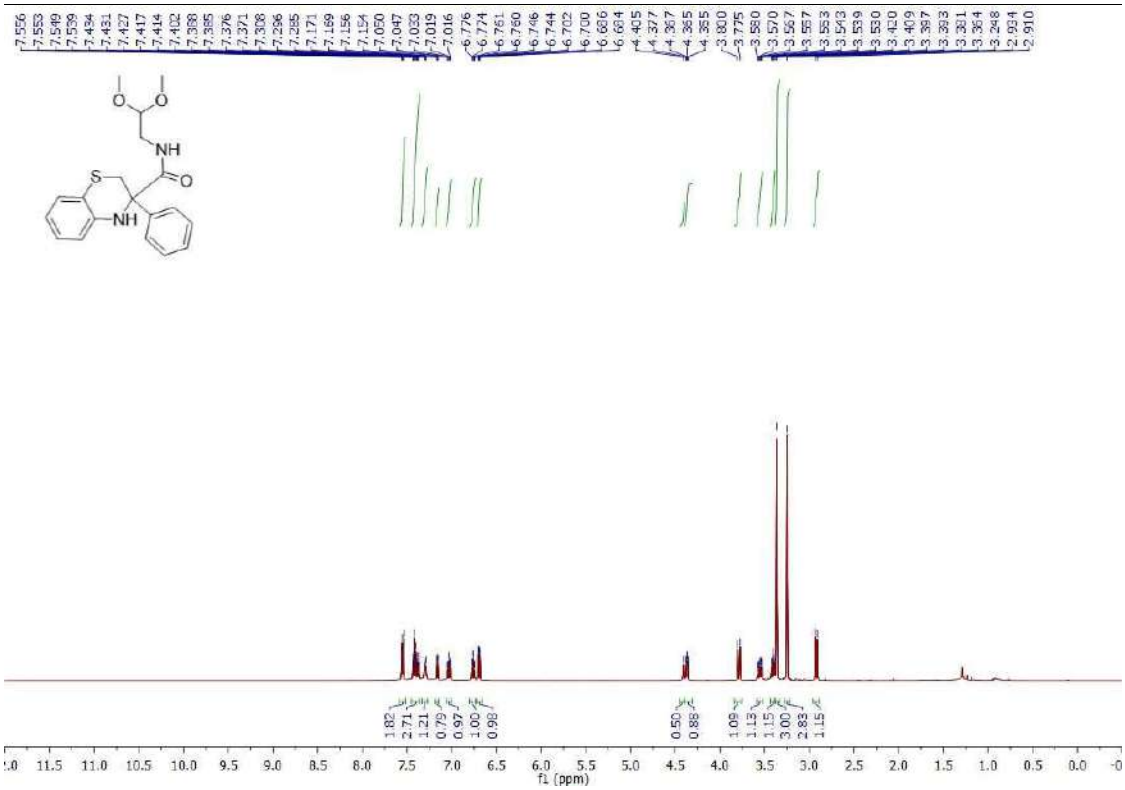
24.62
NH
O
S
NH
f1 (ppm)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7.295
7.171
7.169
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7.154
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7.016
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6.774
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6.760
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6.684
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3.553
3.543
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3.530
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3.393
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O
O
NH
O
S
NH
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2.71
1.21
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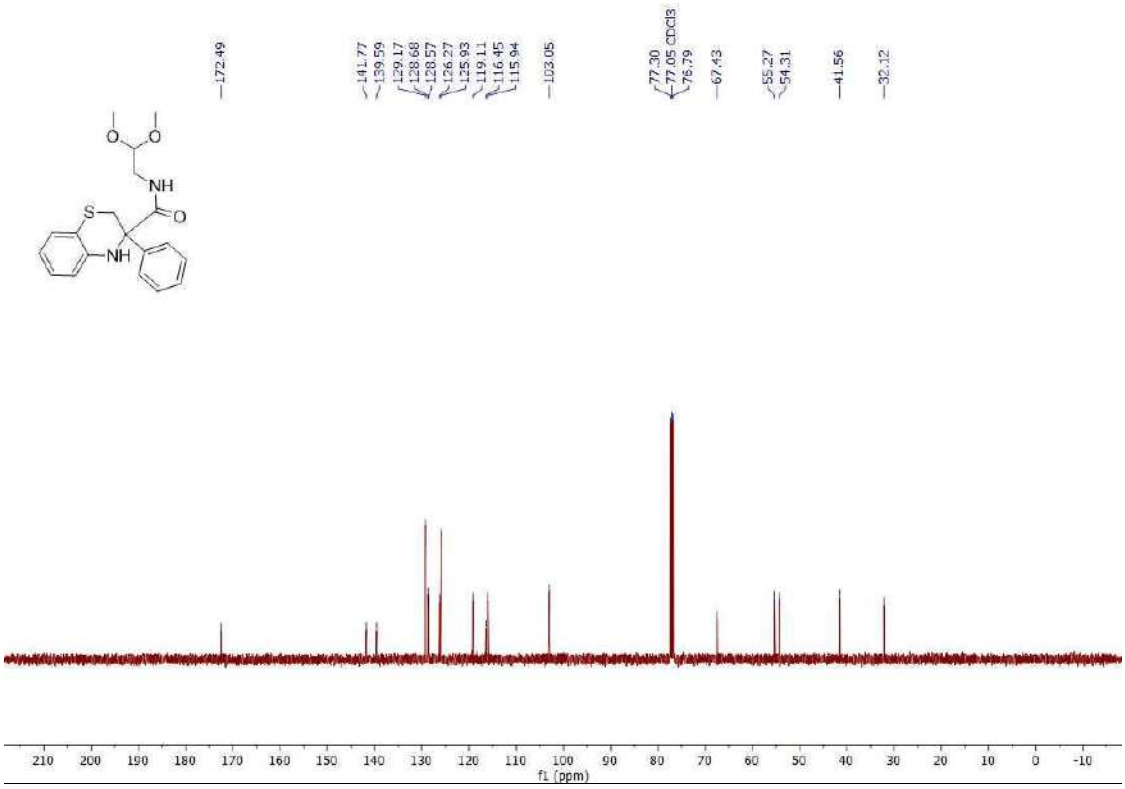
f1 (ppm)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77.30
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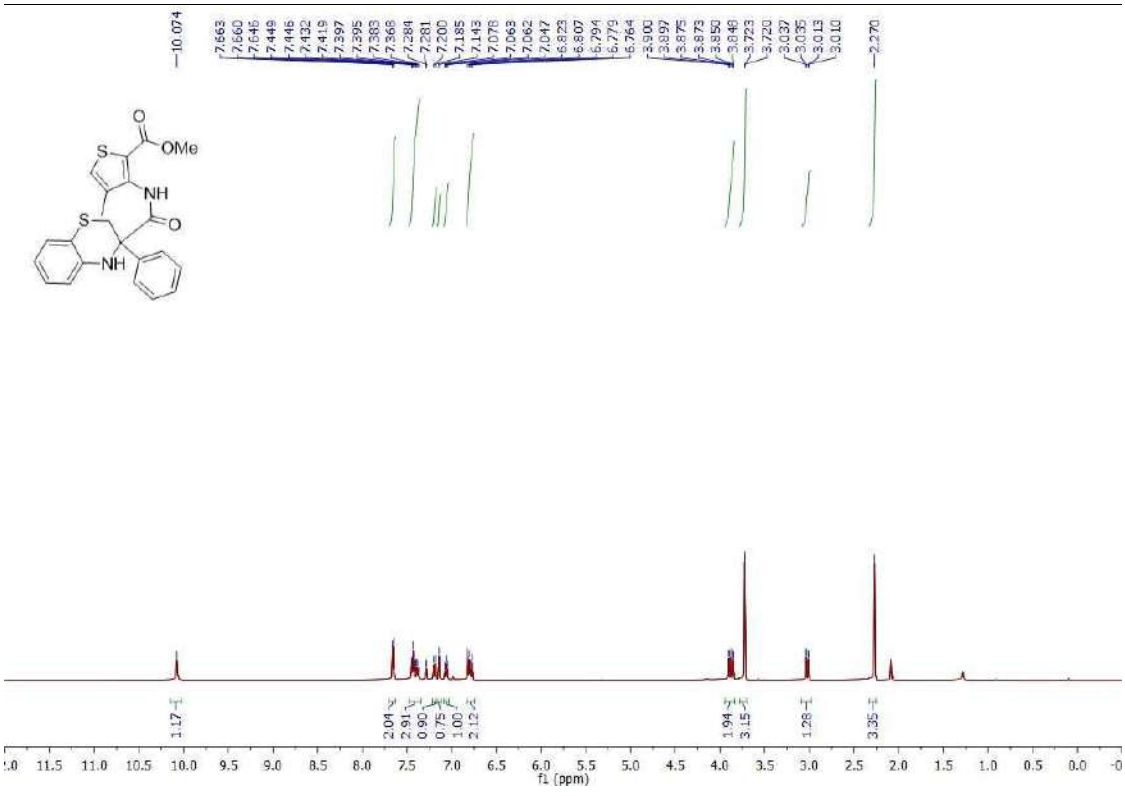
O
O
NH
O
S
NH
f1 (ppm)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3.013
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OMe
NH
S
NH
O
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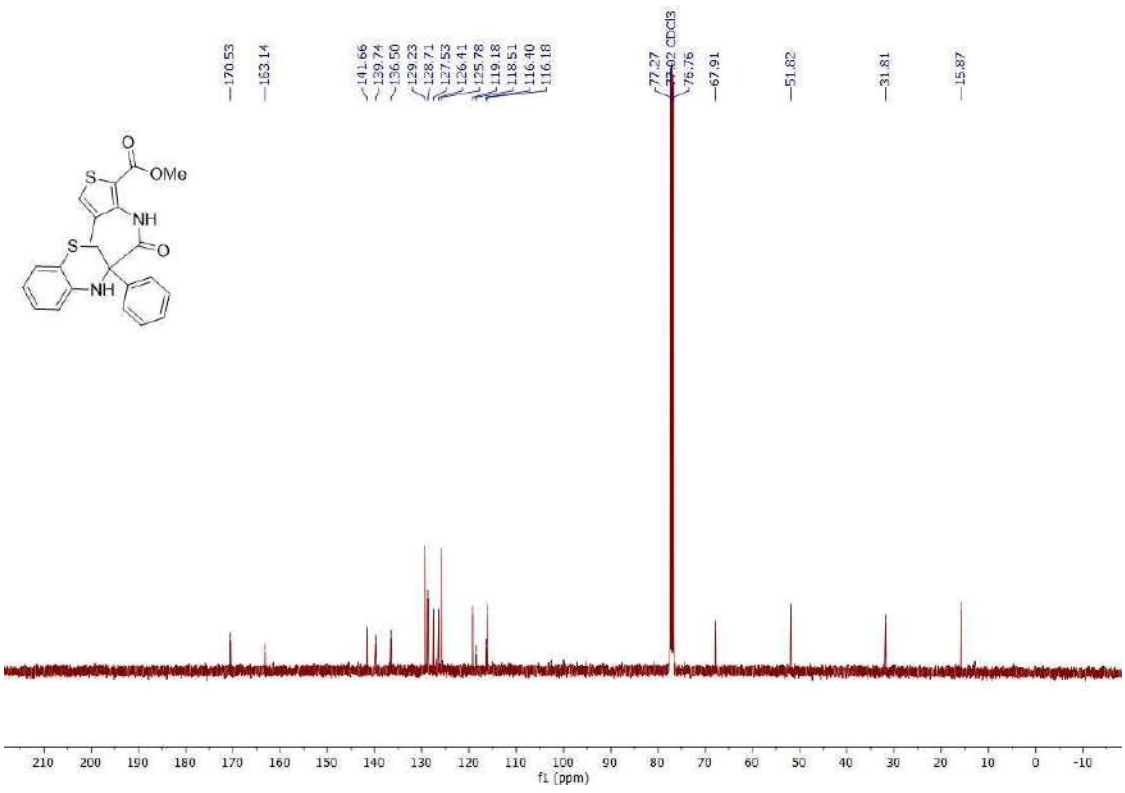
f1 (ppm)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116.40
116.18
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67.91
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OMe
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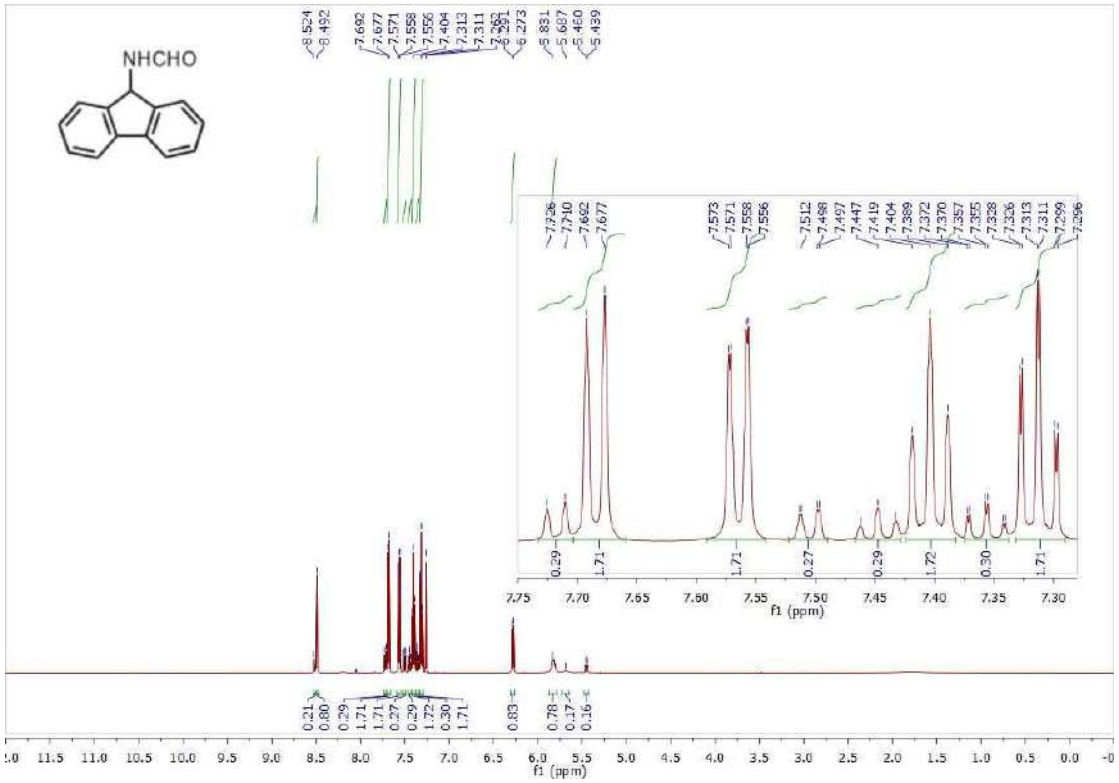
S
NH
O
f1 (ppm)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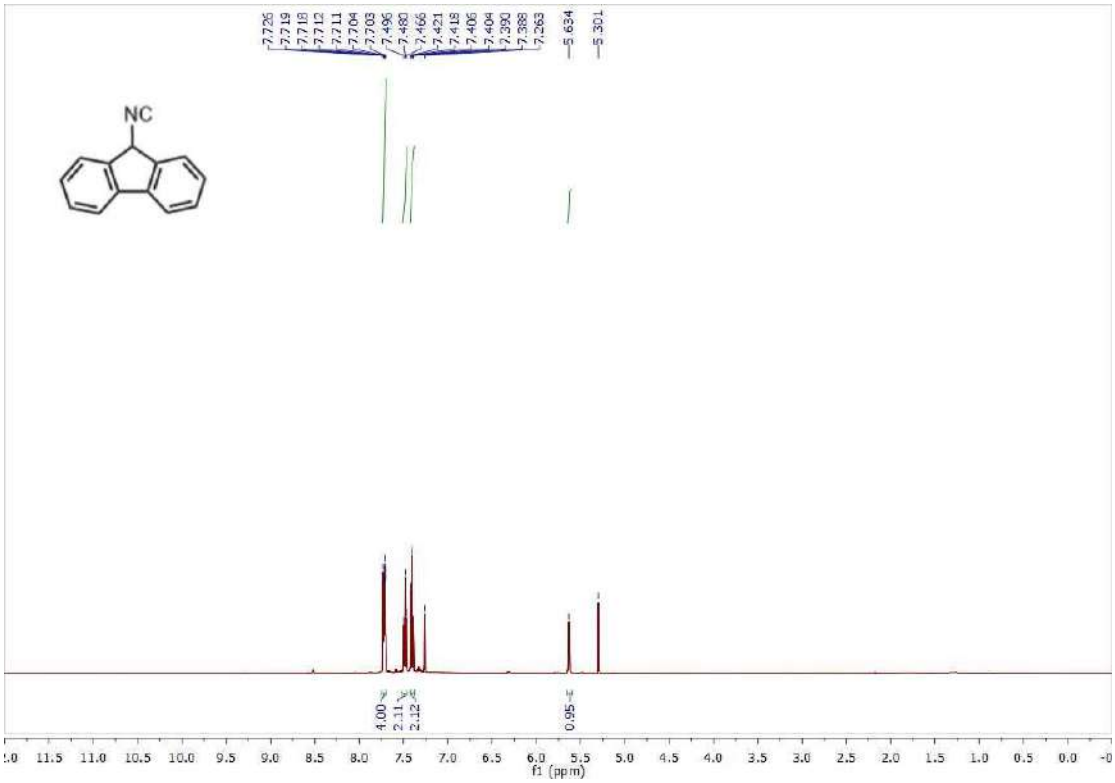
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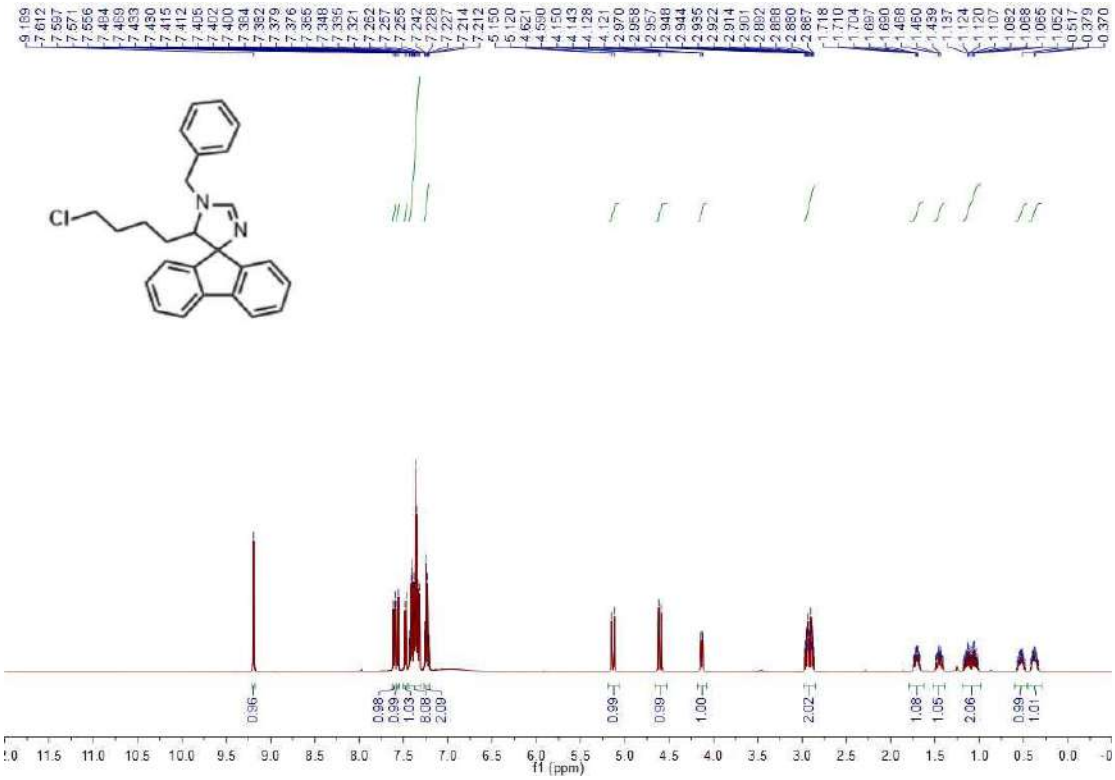
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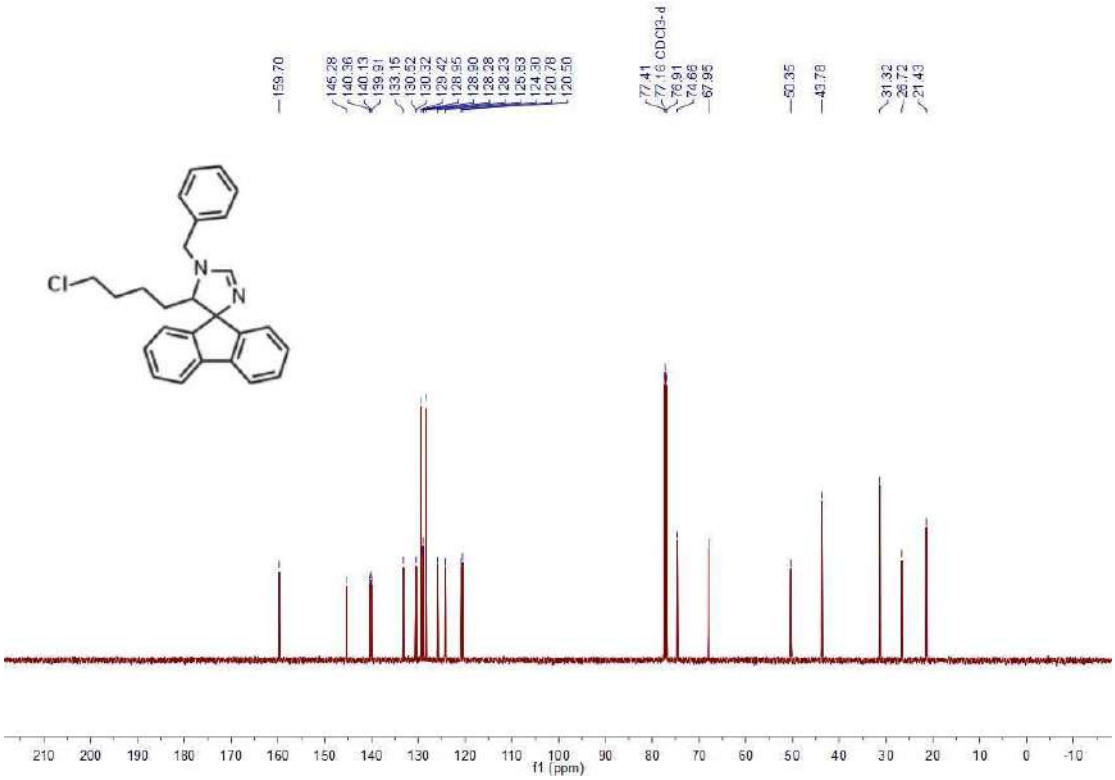
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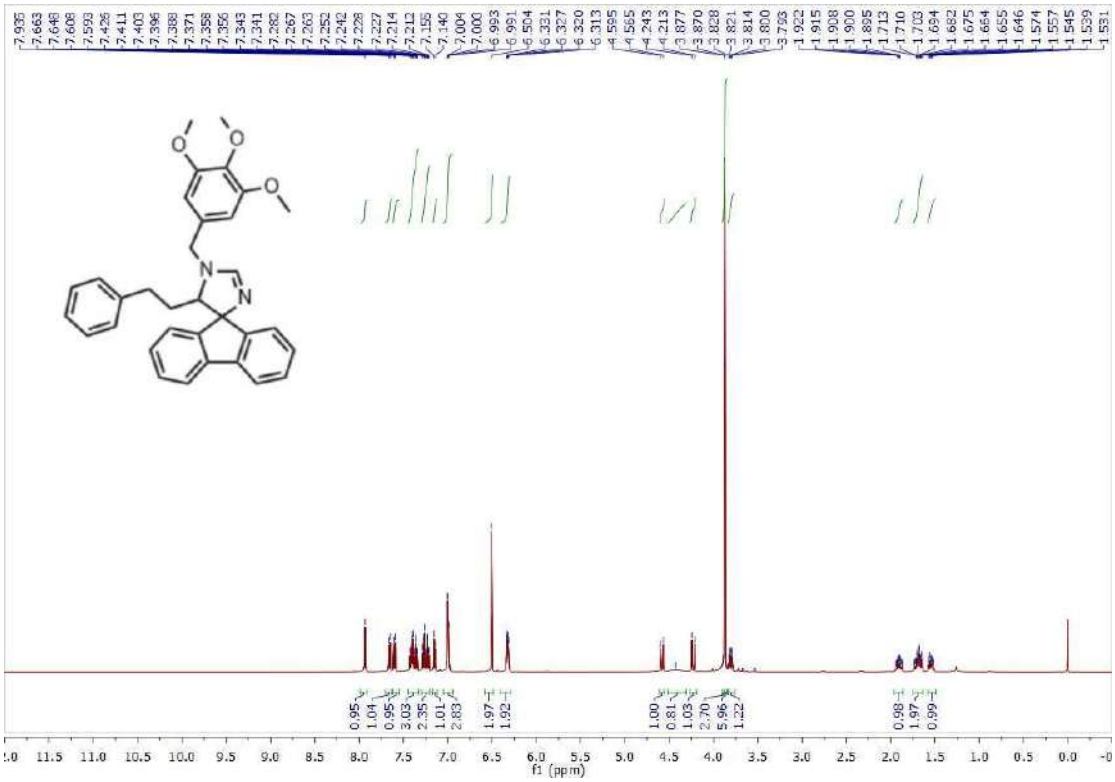
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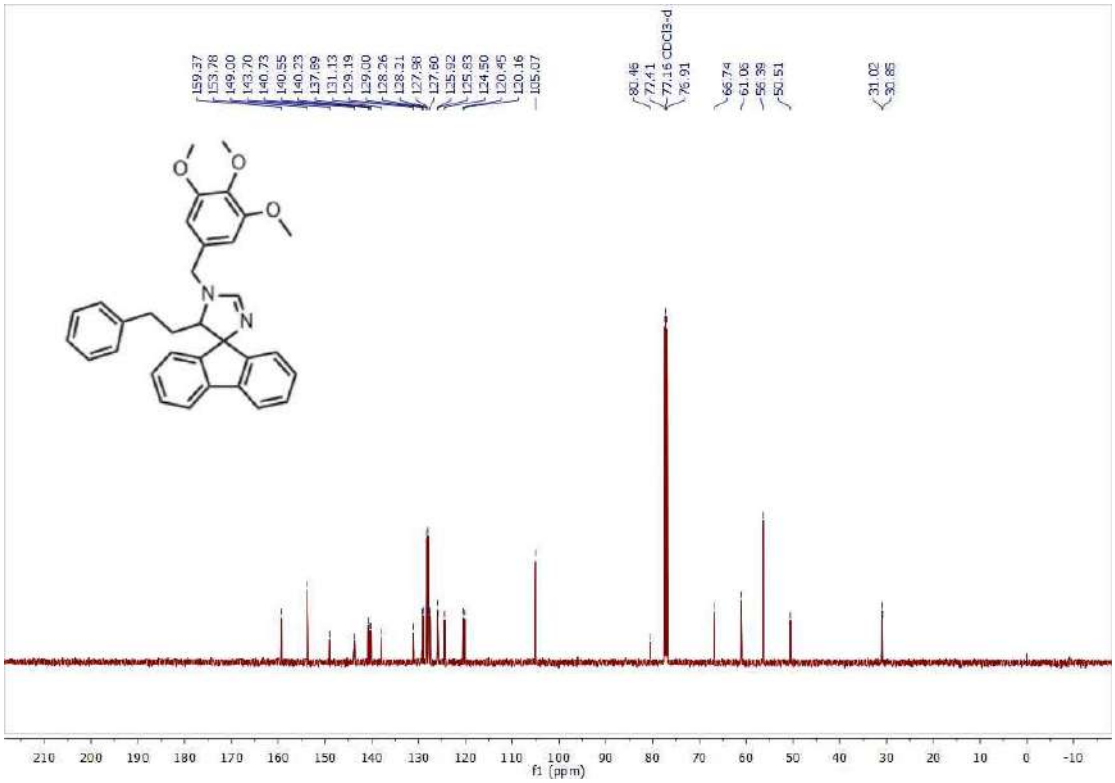
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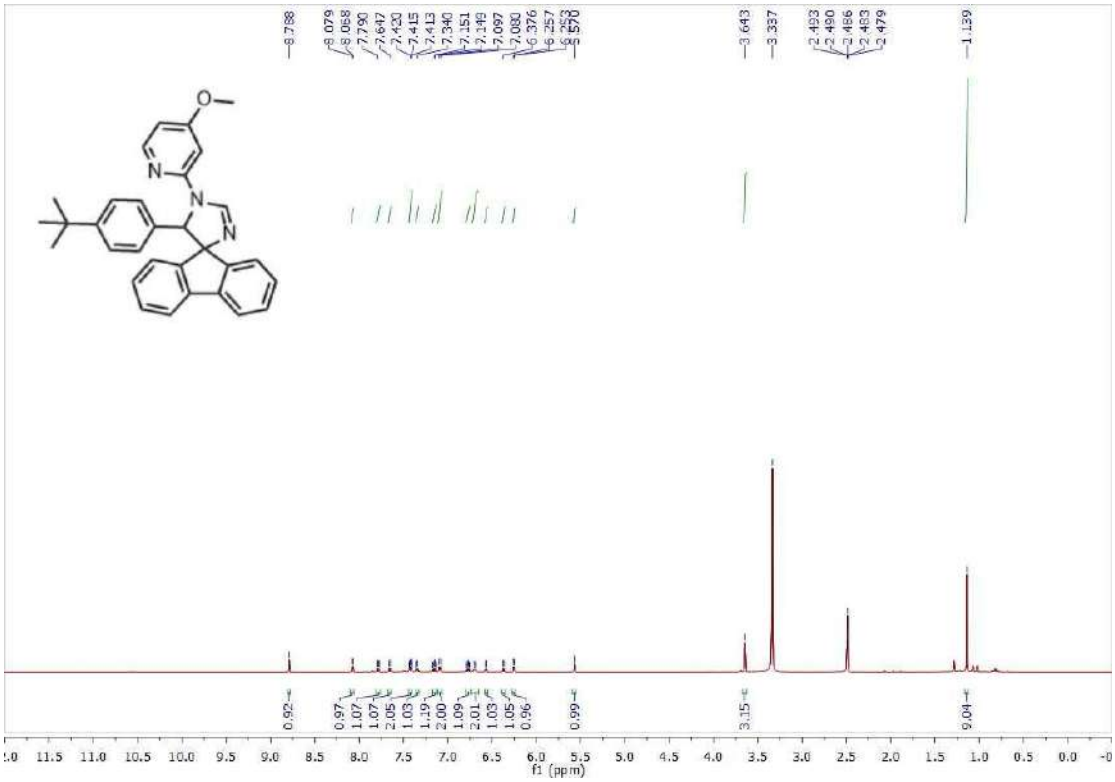
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6.257
5.570
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3.337
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2.490
2.486
2.483
2.479
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0.97
1.07
1.07
2.05
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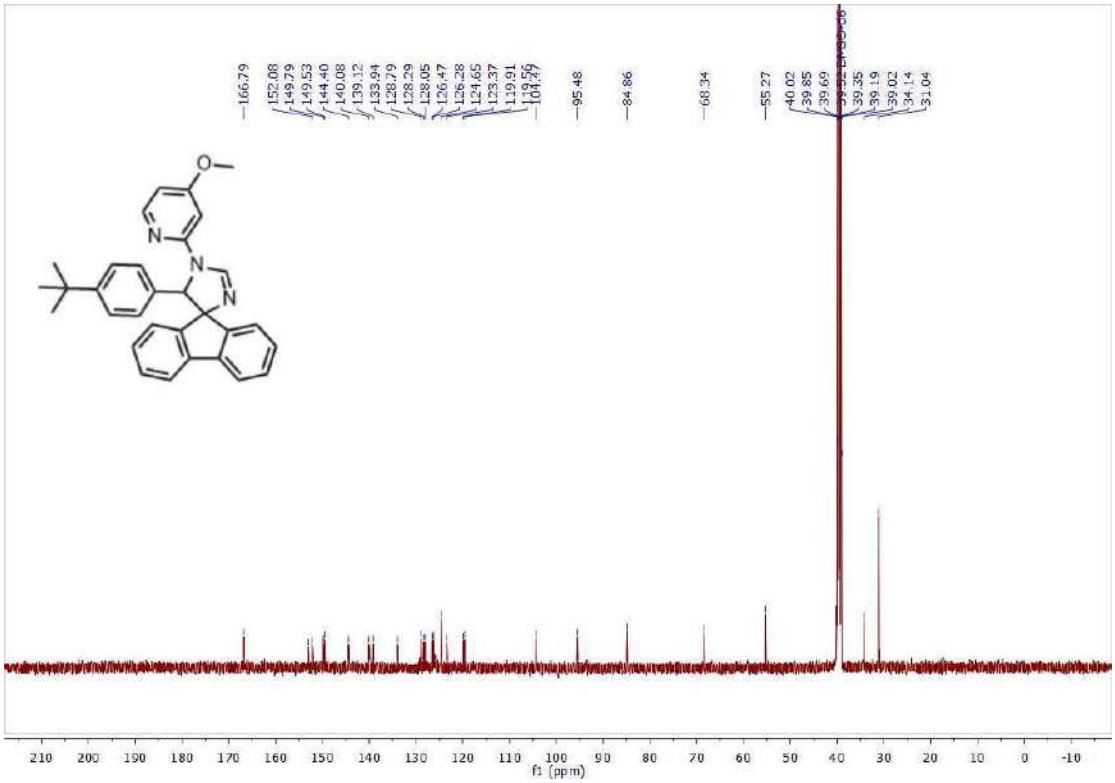
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39.02
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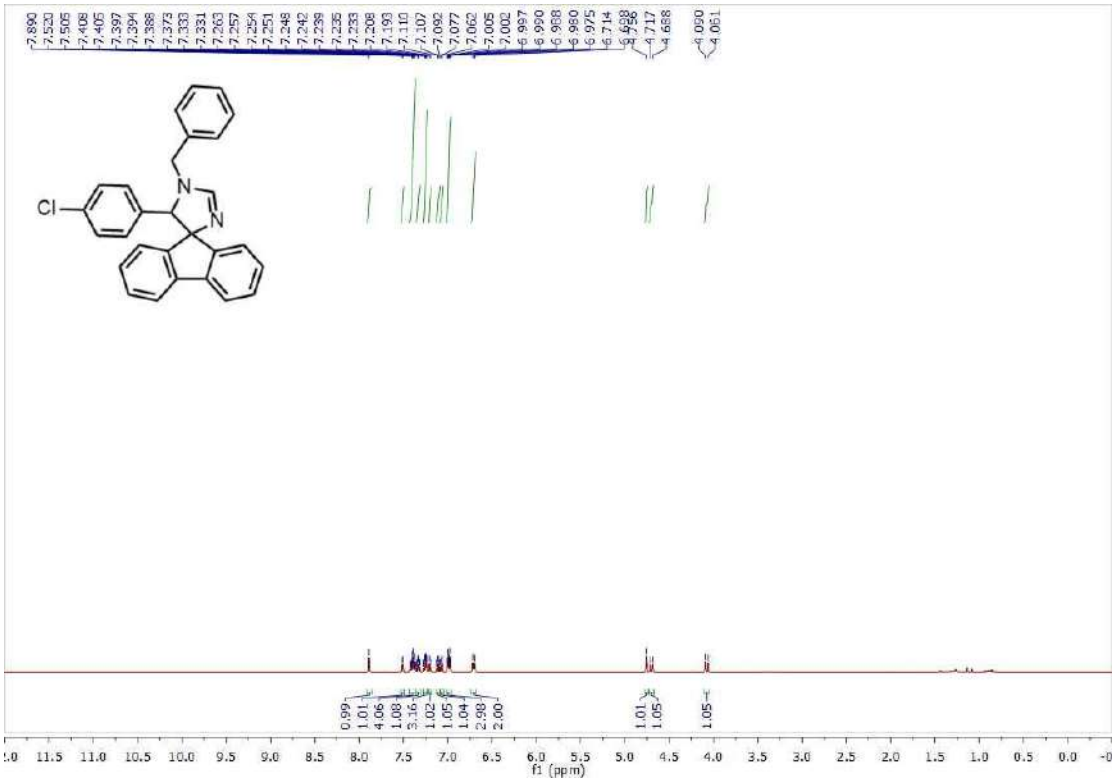
31.04
f1 (ppm)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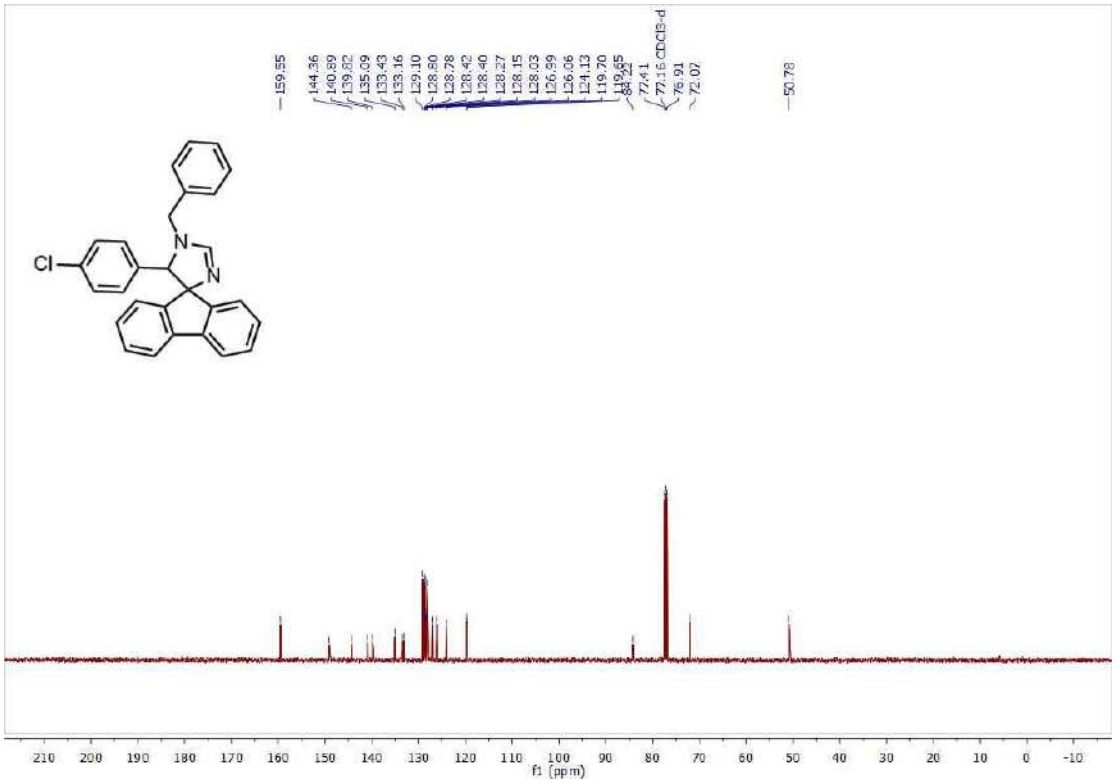
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126.06
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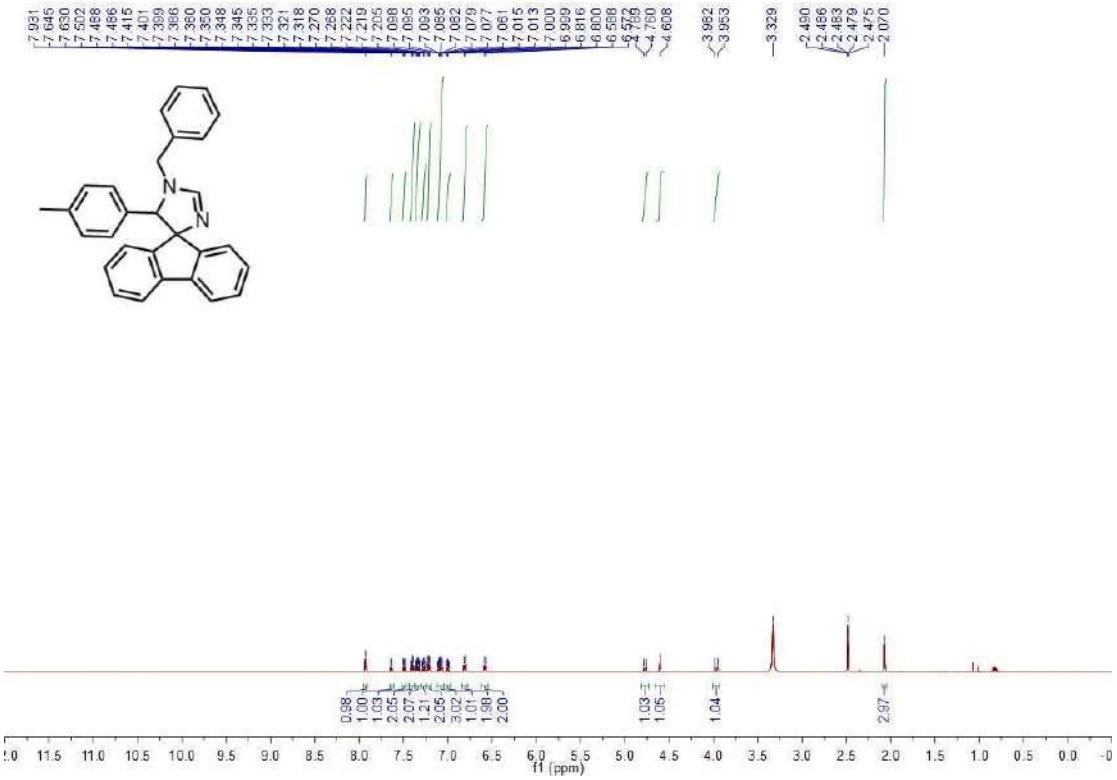
Cl
N
N
f1 (ppm)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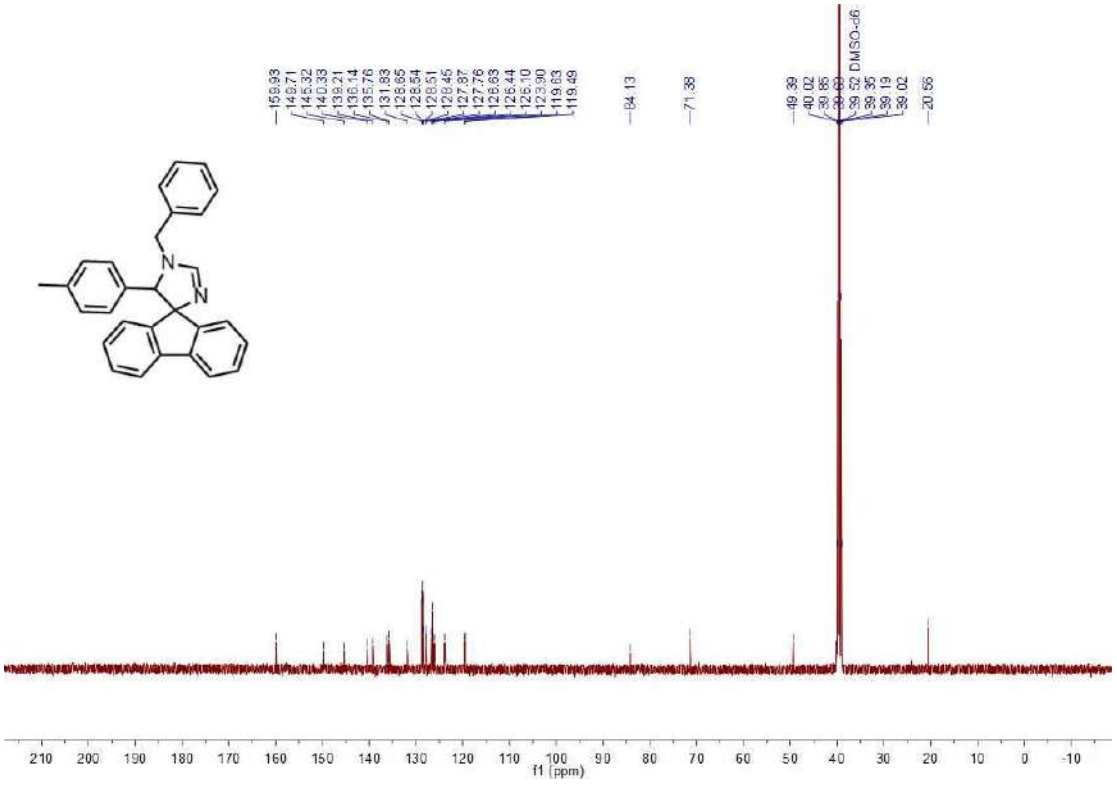
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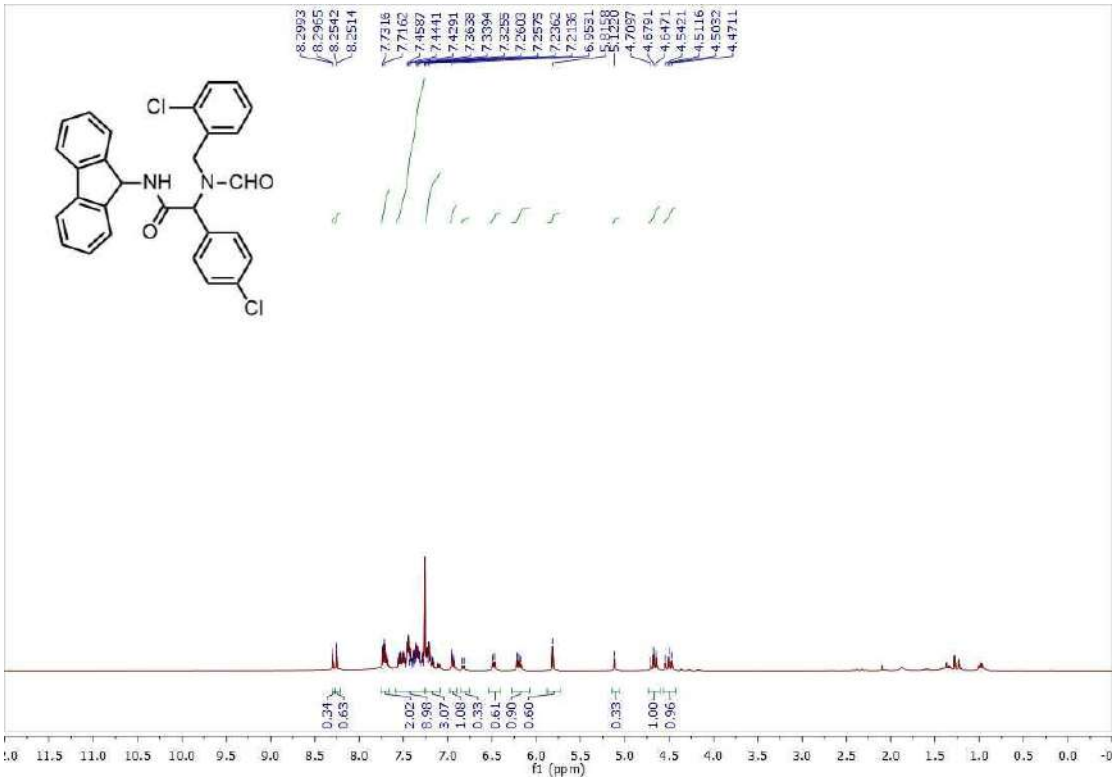
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N-CHO
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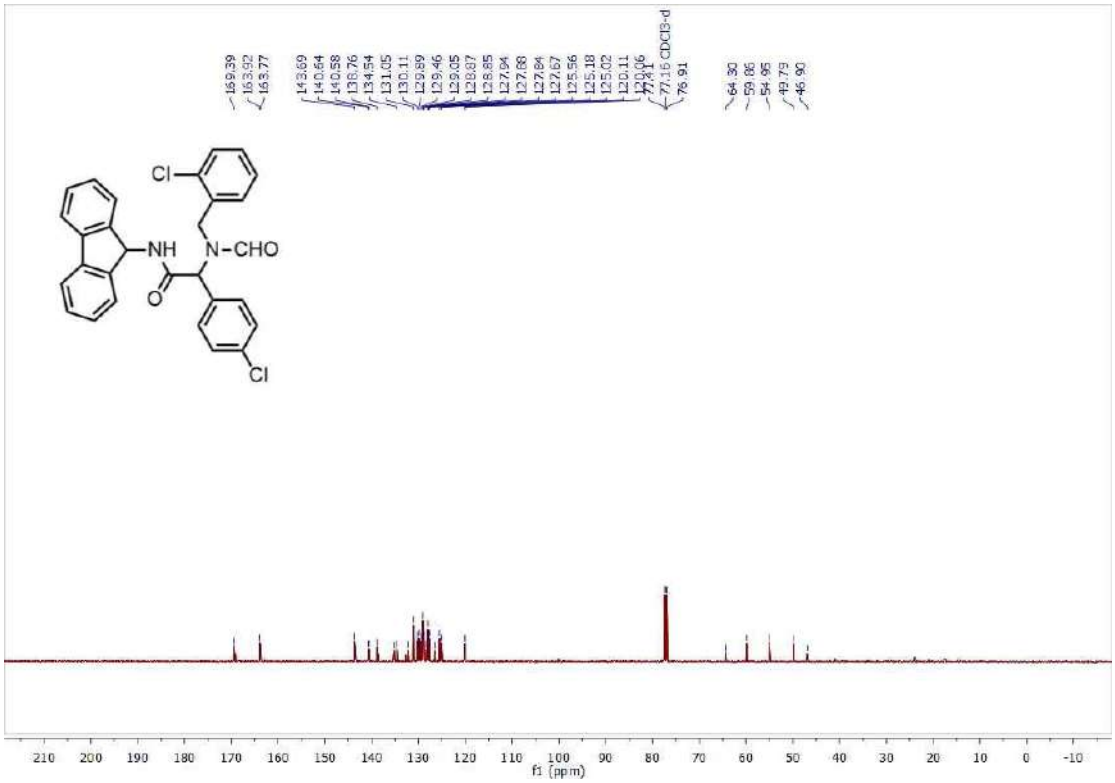
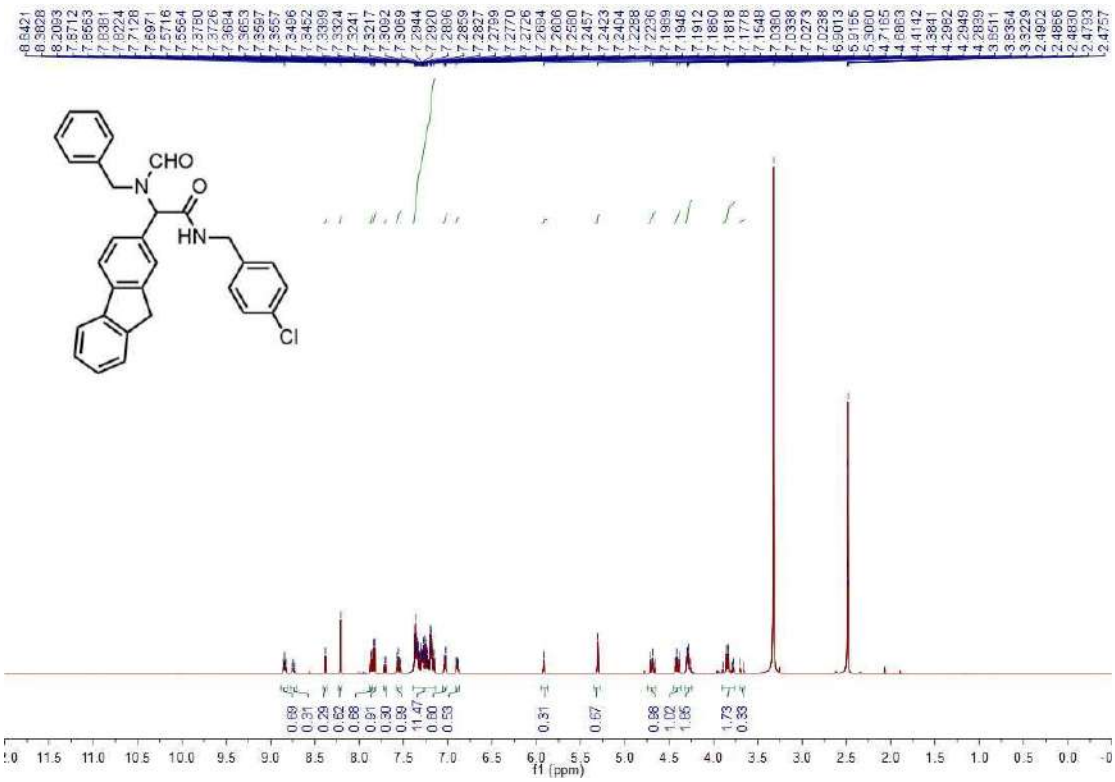
Cl
f1 (ppm)


Cl
NH
N-CHO
O
Cl
CDCl3-d
f1 (ppm)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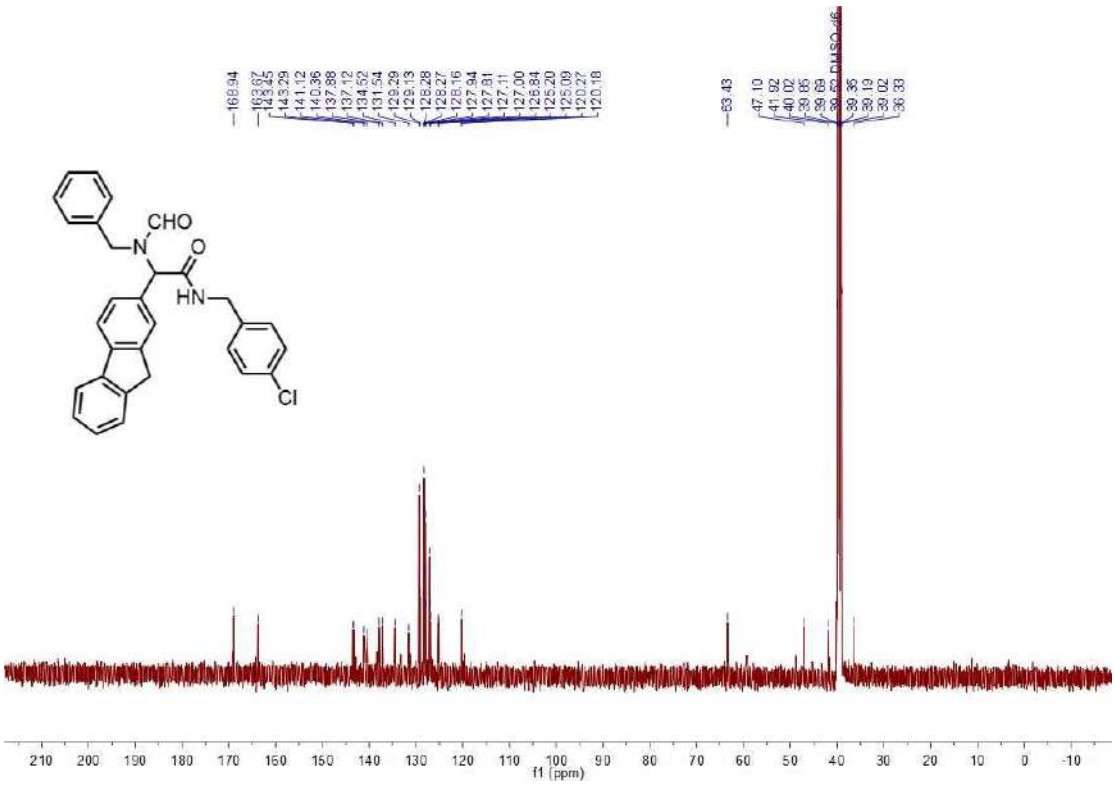
N
O
HN
Cl
f1 (ppm)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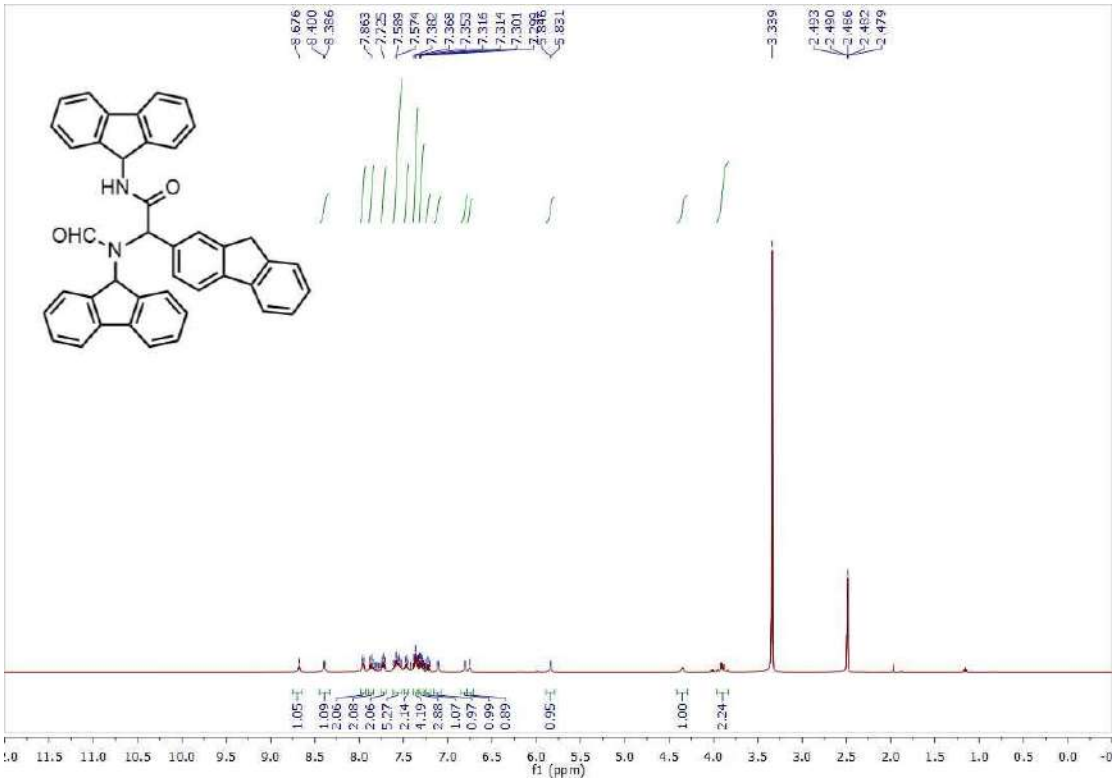
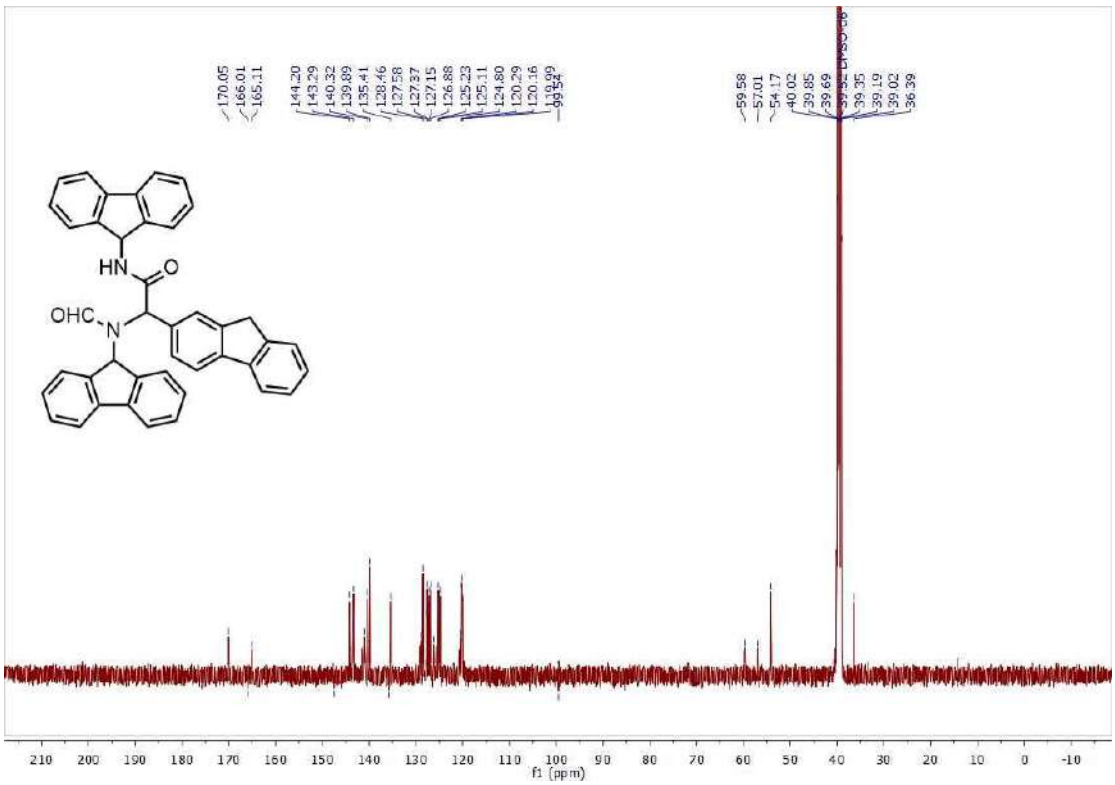
N
O
HN
Cl
f1 (ppm)


HN
O
OHC
N
f1 (ppm)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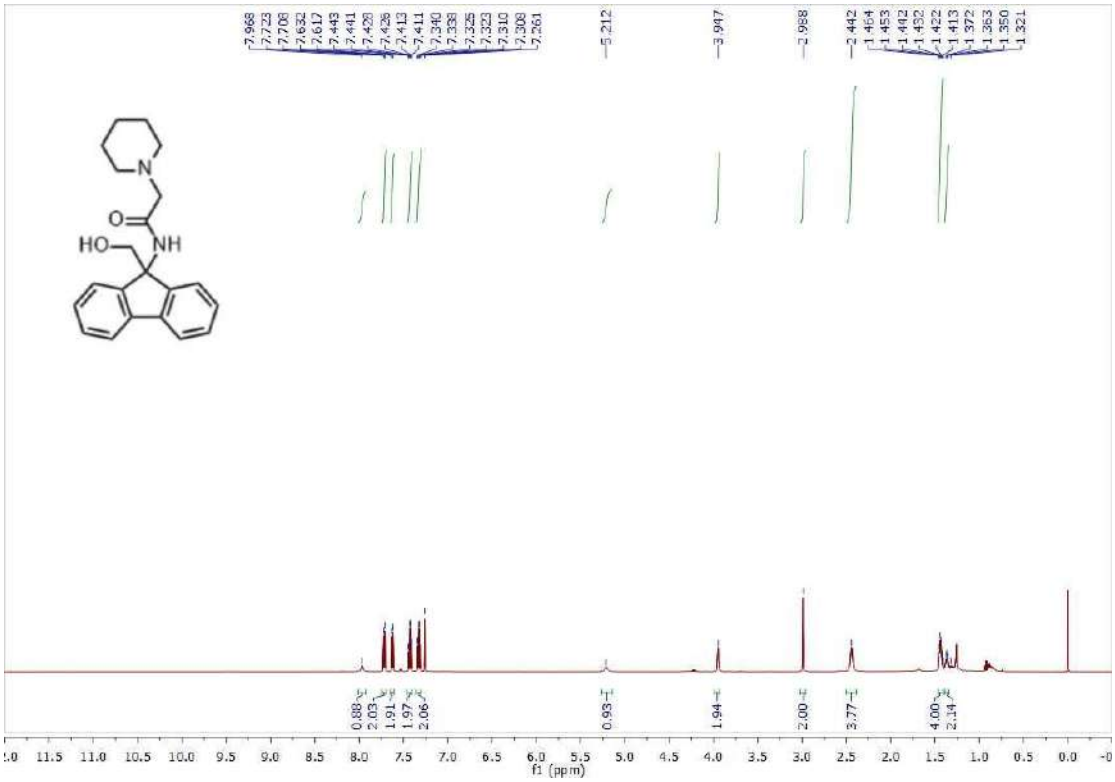
O
OHC
N
f1 (ppm)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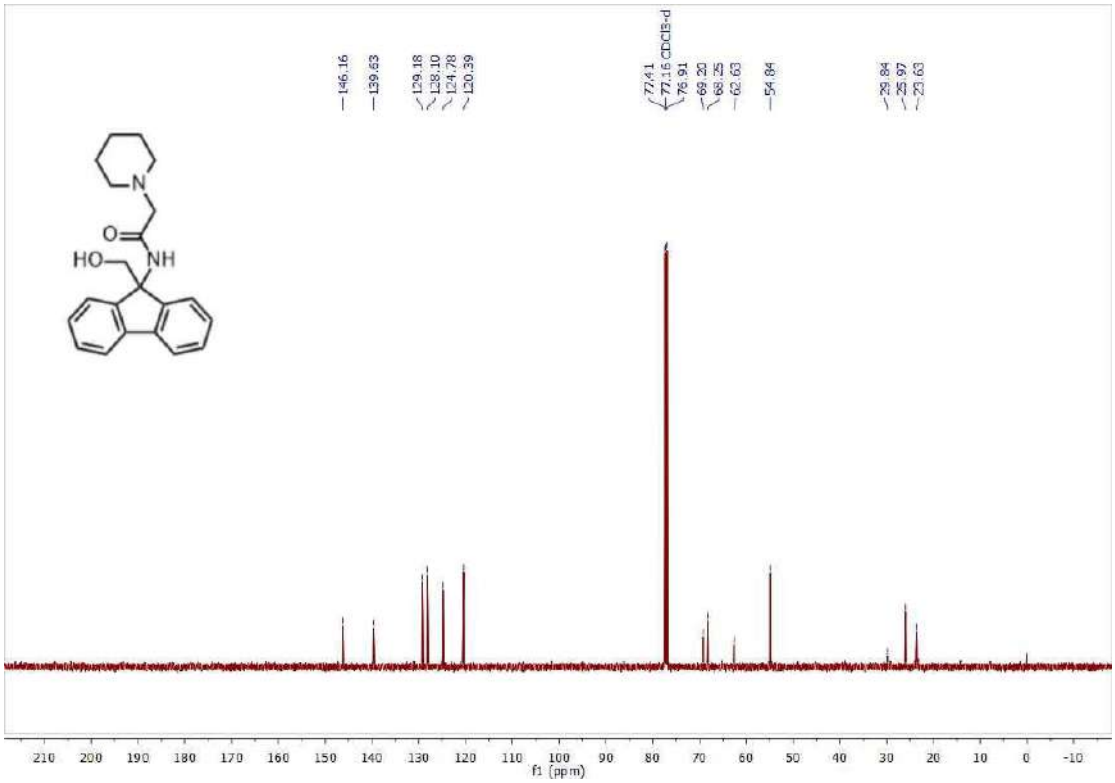
7.428
7.426
7.413
7.411
7.340
7.338
7.325
7.323
7.310
7.308
7.261
5.212
3.947
2.988
2.442
1.464
1.453
1.442
1.432
1.422
1.413
1.372
1.363
1.350
1.321
HO
NH
O
N
0.88
2.03
1.91
1.97
2.06
0.93
1.94
2.00
3.77
4.00
2.14
f1 (ppm)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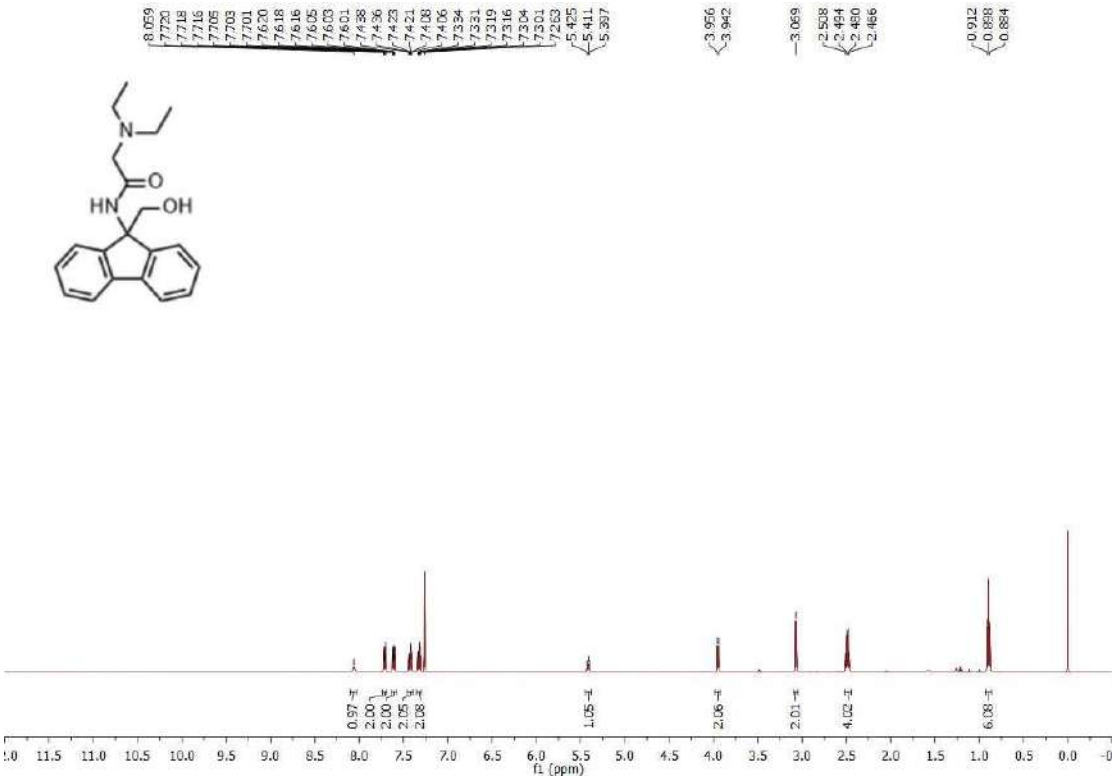
139.63
129.18
128.10
124.78
120.39
77.41
77.16 CDCl3-d
76.91
69.20
68.25
62.63
54.84
29.84
25.97
23.63
HO
NH
O
N
f1 (ppm)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7.718
7.716
7.705
7.703
7.701
7.620
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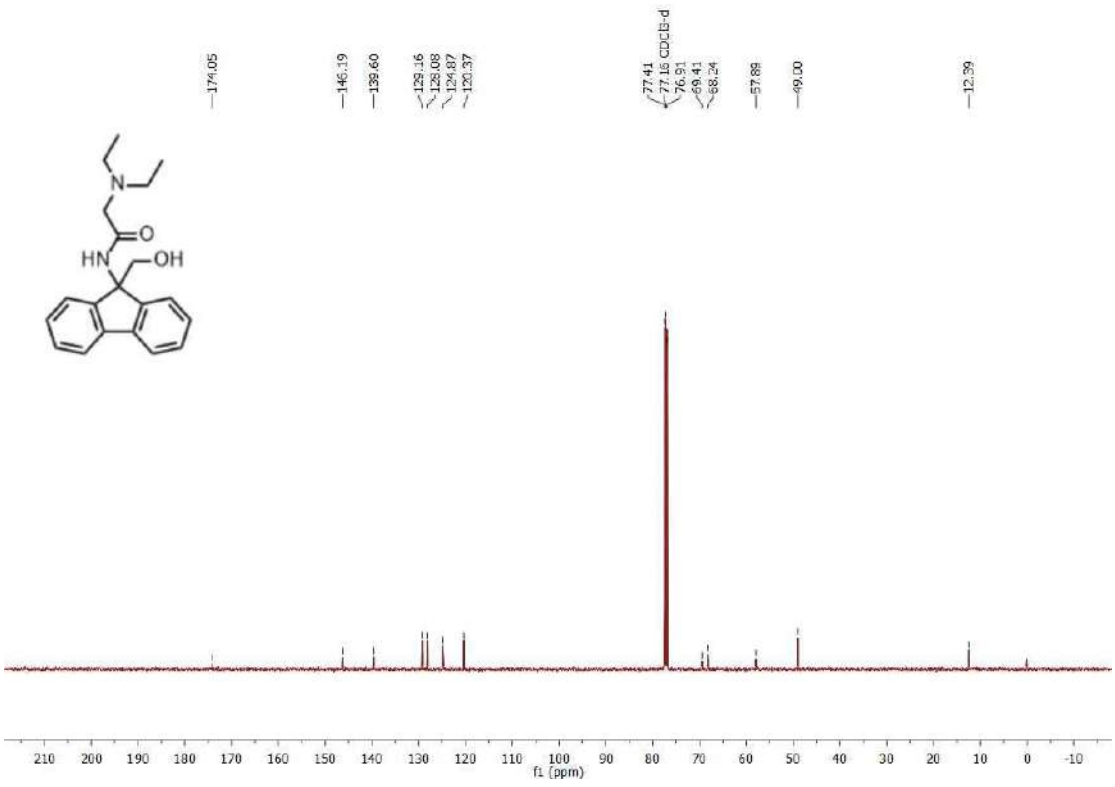
7.616
7.605
7.603
7.601
7.438
7.436
7.423
7.421
7.408
7.406
7.334
7.331
7.319
7.316
7.304
7.301
7.263
5.425
5.411
5.397
3.956
3.942
3.069
2.508
2.464
2.460
2.456
0.912
0.898
0.884
N
O
HN
OH
0.97
2.00
2.00
2.05
2.08
1.05
2.06
2.01
4.02
6.08
f1 (ppm)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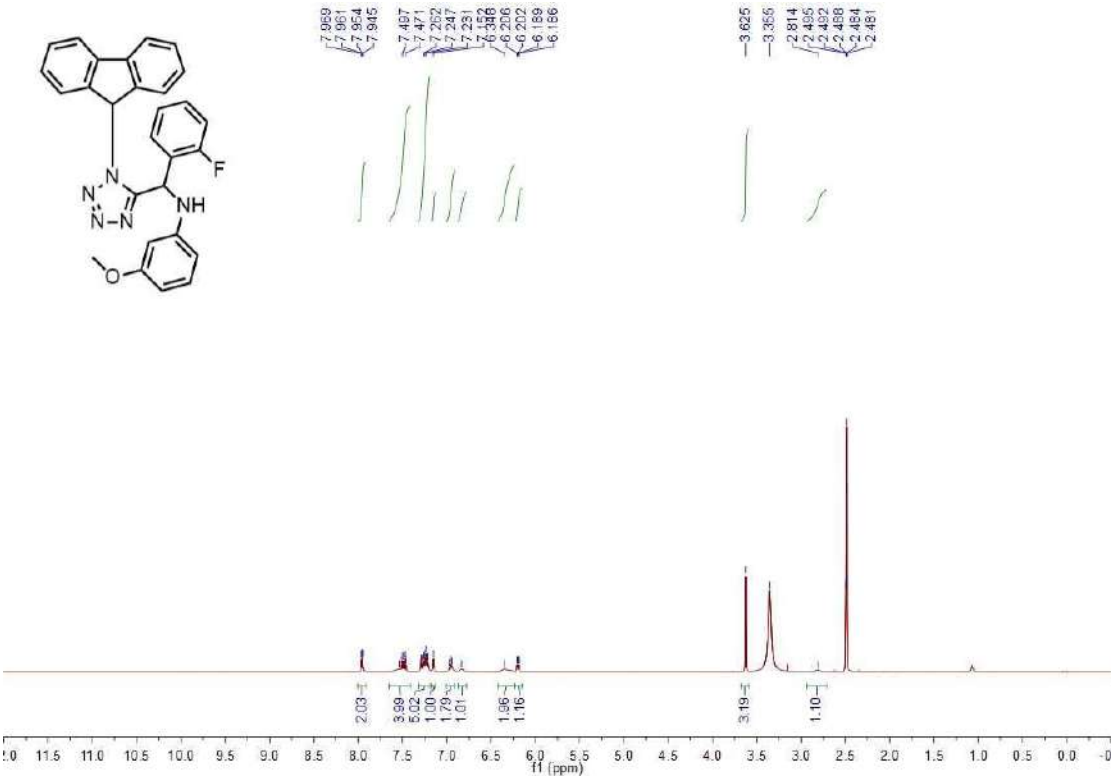
146.19
139.60
129.16
128.08
124.87
120.37
77.41
77.16 CDCl3-d
76.91
69.41
68.24
57.89
49.00
12.39
N
O
HN
OH
f1 (ppm)


F
NH
O
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7.961
7.954
7.945
7.497
7.471
7.252
7.247
7.231
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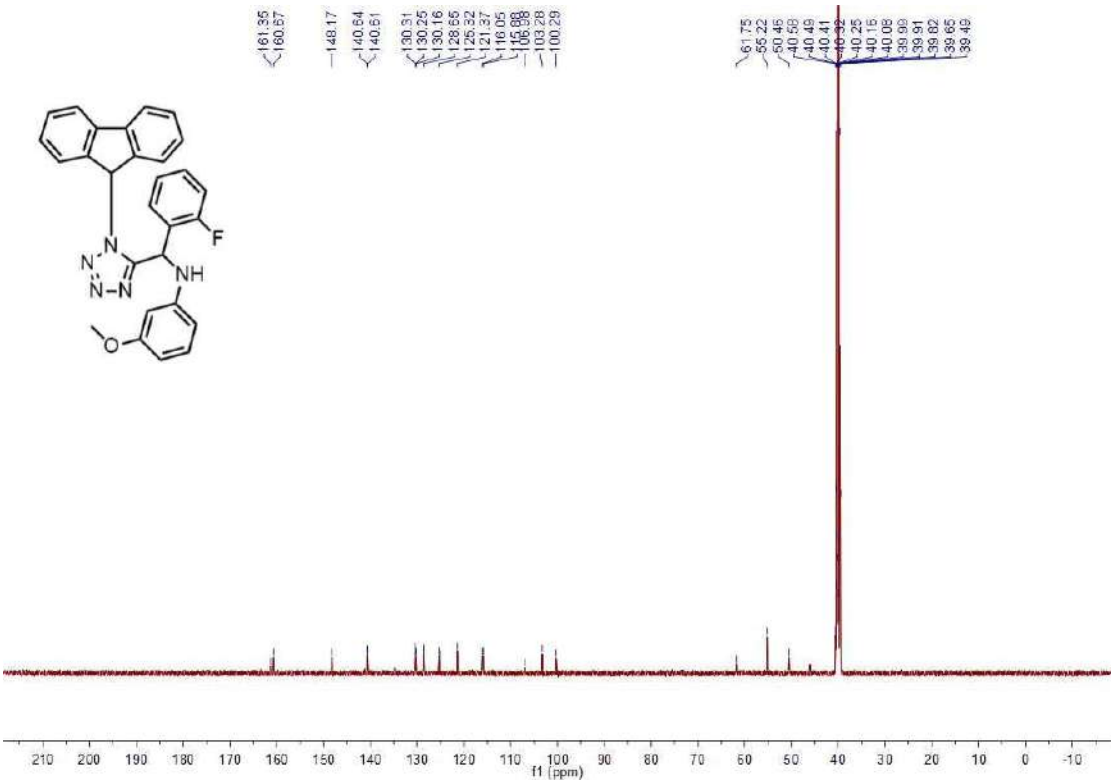
6.206
6.202
6.189
6.186
3.625
3.355
2.814
2.495
2.492
2.488
2.484
2.481
2.03
3.99
5.02
1.00
1.79
1.01
1.96
1.16
3.19
1.10
f1 (ppm)


F
NH
O
161.35
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148.17
140.64
140.61
130.31
130.25
130.16
128.65
125.52
121.37
116.05
115.88
108.98
103.28
100.29
61.75
55.22
50.45
40.59
40.49
40.41
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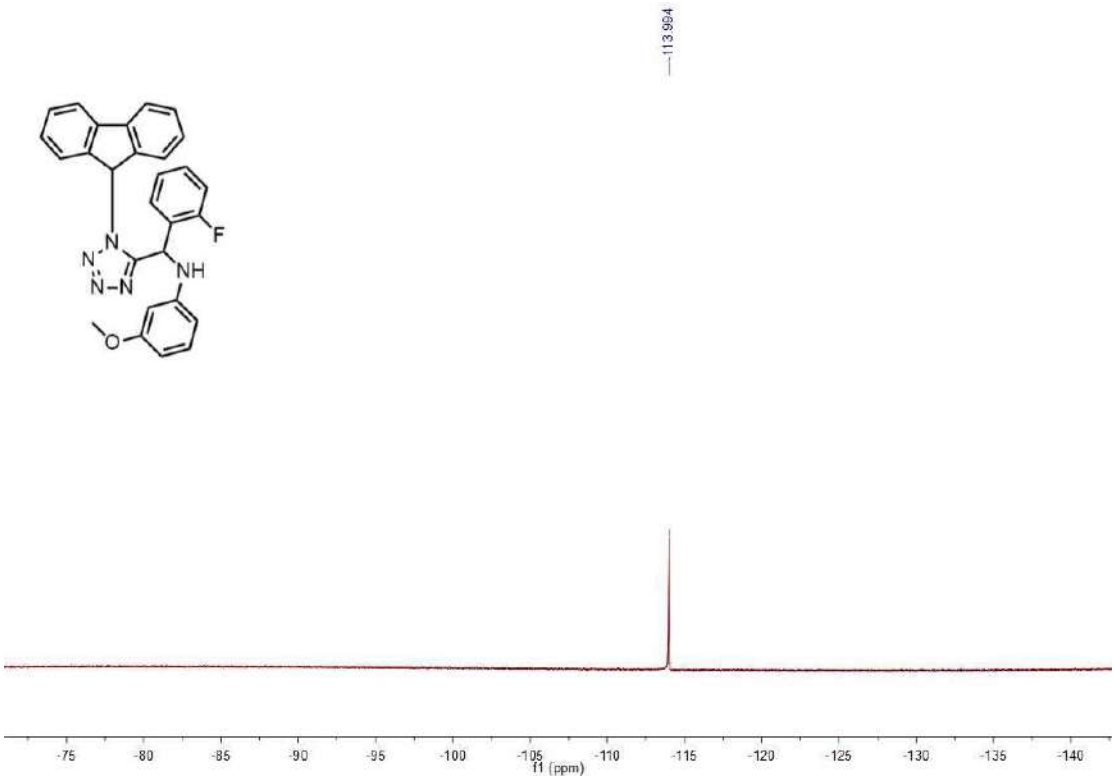
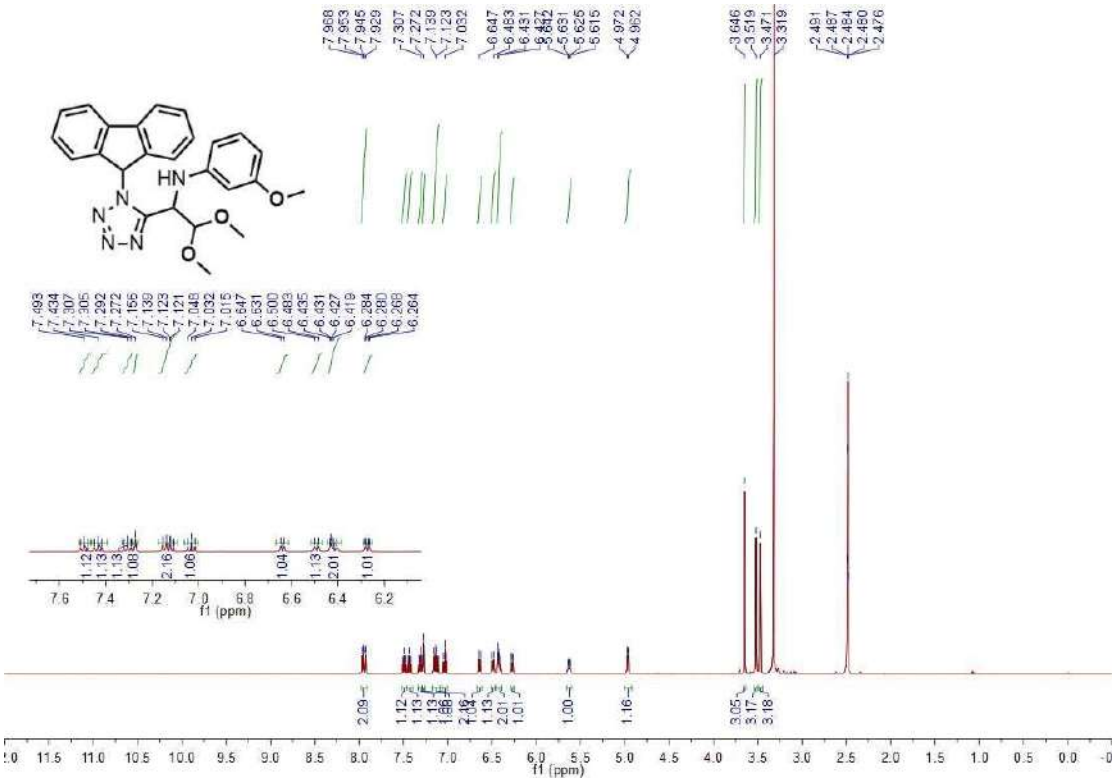
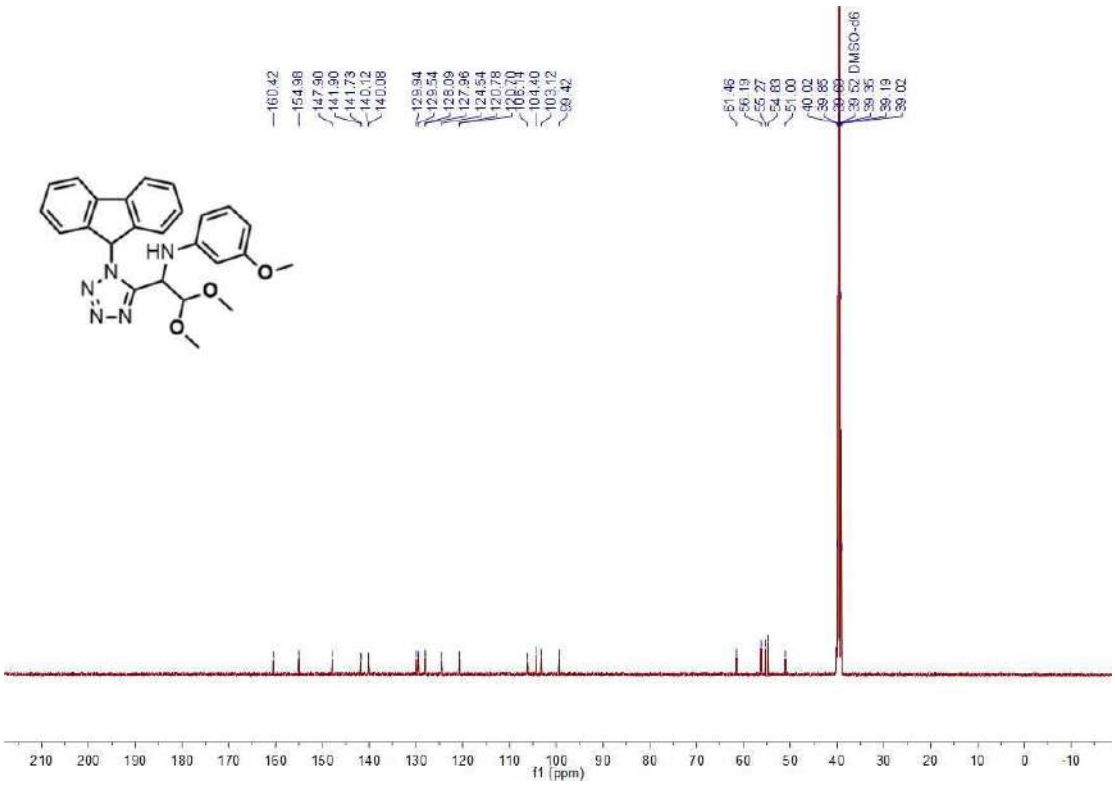
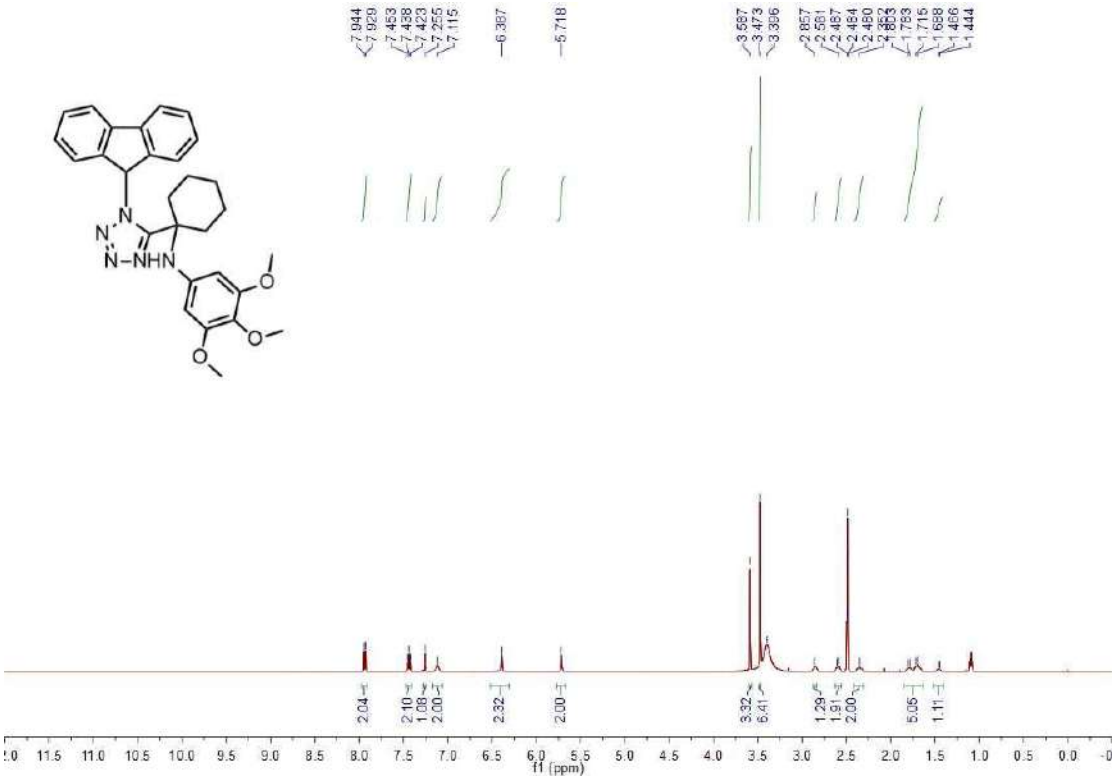
40.25
40.15
40.08
39.99
39.91
39.82
39.65
39.49
f1 (ppm)


-113.994
F
N
N
N
N
NH
O
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
f1 (ppm)


HN
O
O
O
N
N
N
N
f1 (ppm)


HN
O
O
O
N
N
N
N
DMSO-d6
f1 (ppm)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7.438
7.423
7.255
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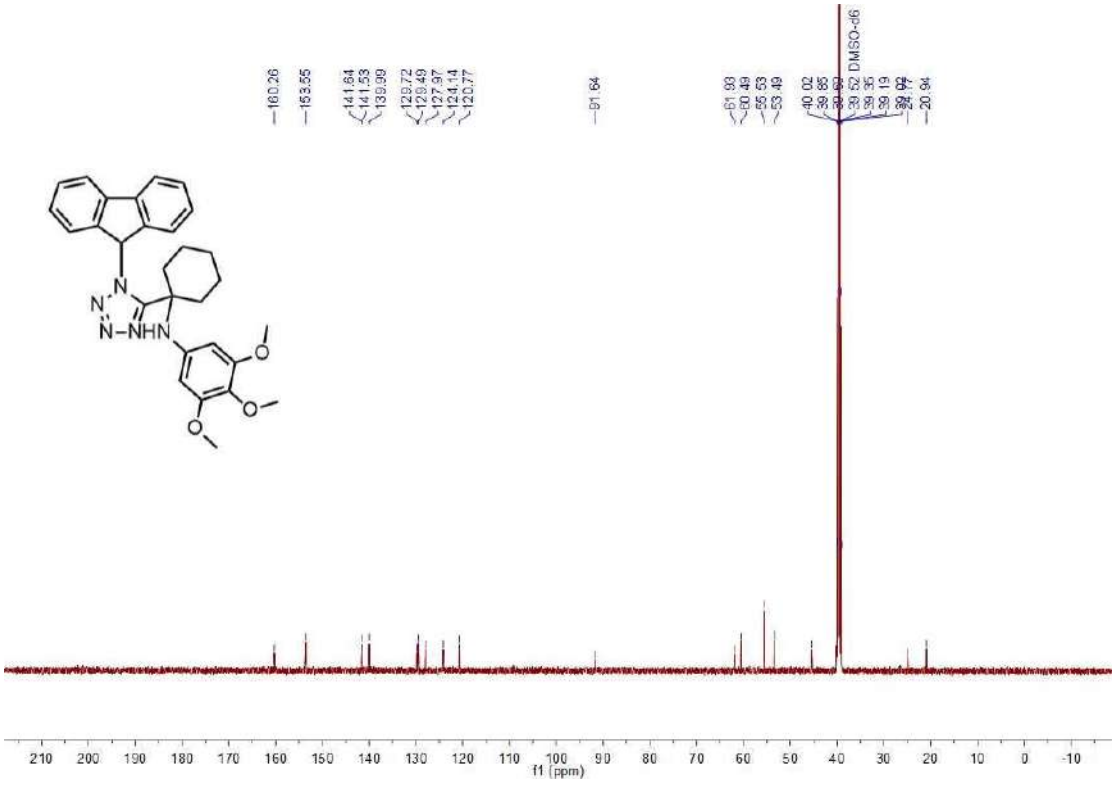
6.387
5.718
3.587
3.473
3.396
2.857
2.581
2.487
2.484
2.450
1.753
1.715
1.688
1.456
1.444
2.04
2.10
1.08
2.00
2.32
2.00
3.32
6.41
1.29
1.91
2.00
5.05
1.11
f1 (ppm)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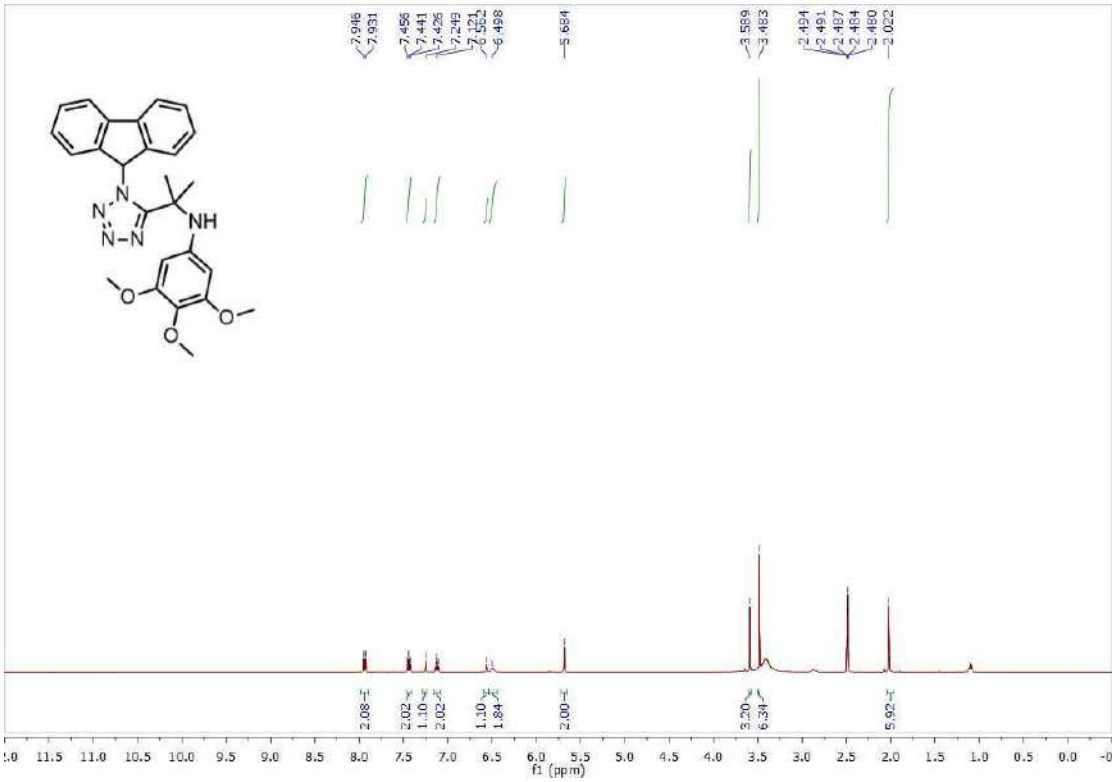
141.64
141.53
139.99
129.72
129.49
127.97
124.14
120.77
91.64
61.93
60.49
55.53
53.49
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
20.94
f1 (ppm)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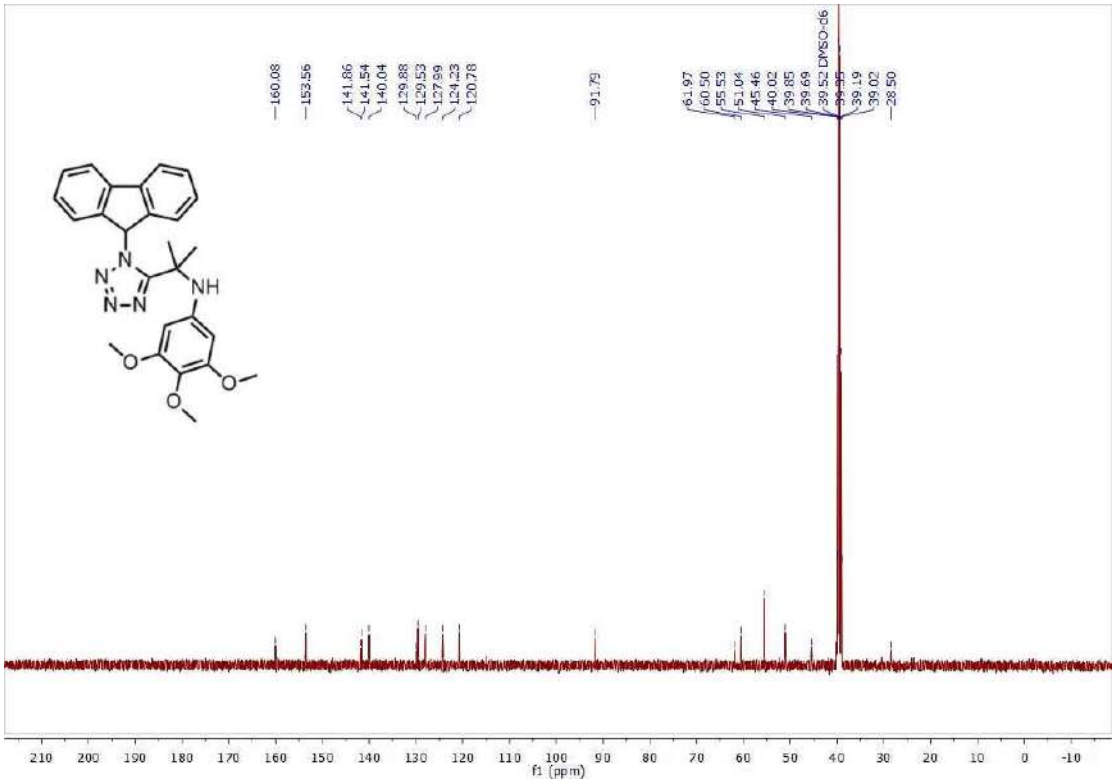
7.441
7.435
7.249
7.121
6.562
6.498
5.684
3.589
3.483
2.494
2.491
2.487
2.484
2.480
2.022
NH
2.08
2.02
1.10
2.02
1.10
1.84
2.00
3.20
6.34
5.92
f1 (ppm)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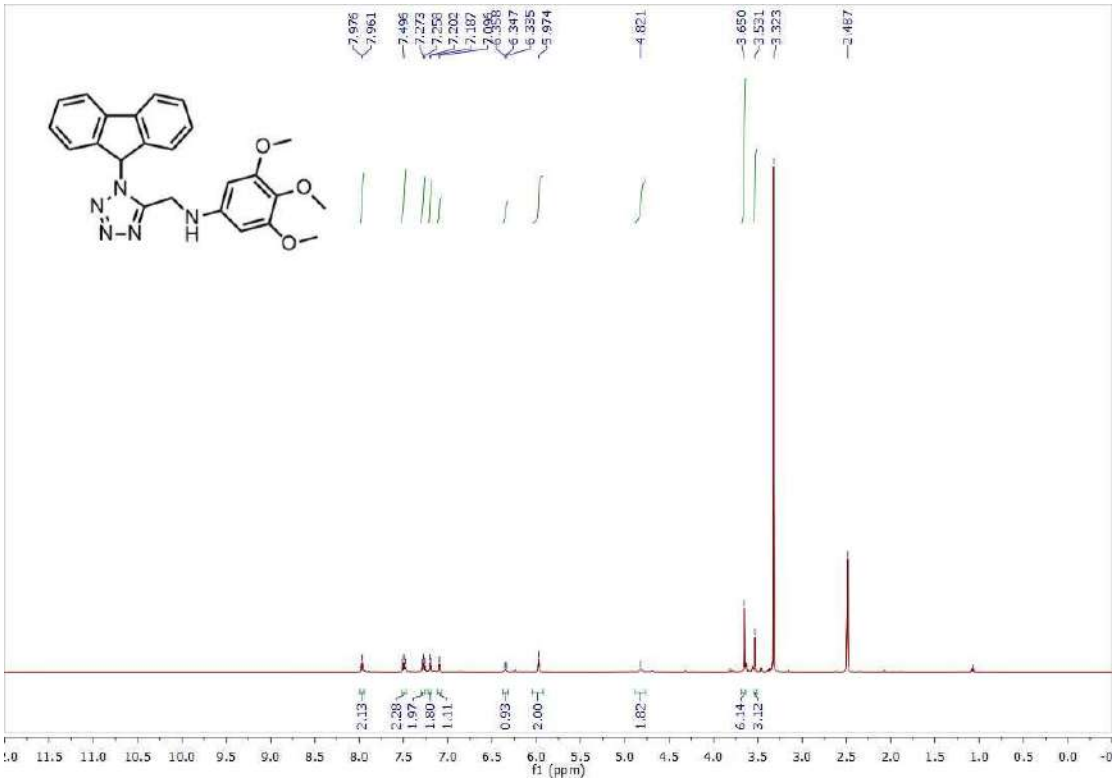
141.54
140.04
129.88
129.53
127.99
124.23
120.78
91.79
61.97
60.50
55.53
51.04
45.46
40.02
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
28.50
NH
f1 (ppm)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7.273
7.258
7.202
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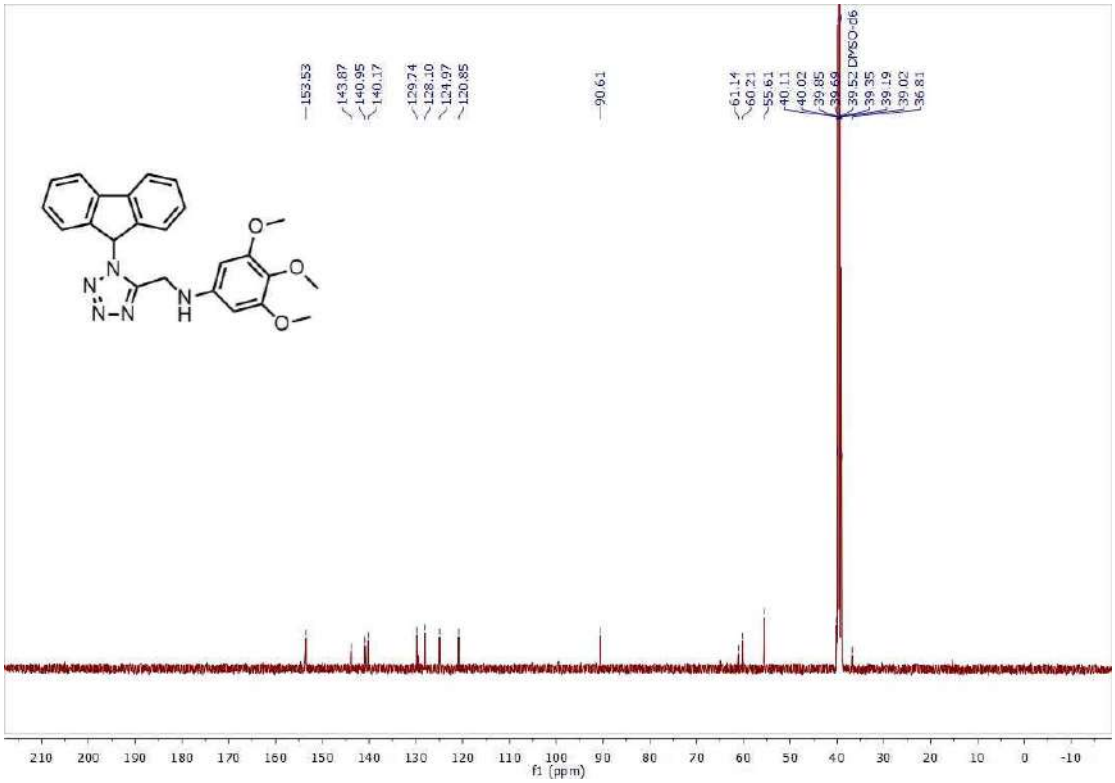
7.095
6.358
6.347
6.335
5.974
4.821
3.650
3.521
3.323
2.487
2.13
2.28
1.97
1.80
1.11
0.93
2.00
1.82
6.14
3.12
f1 (ppm)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120.85
90.61
61.14
60.21
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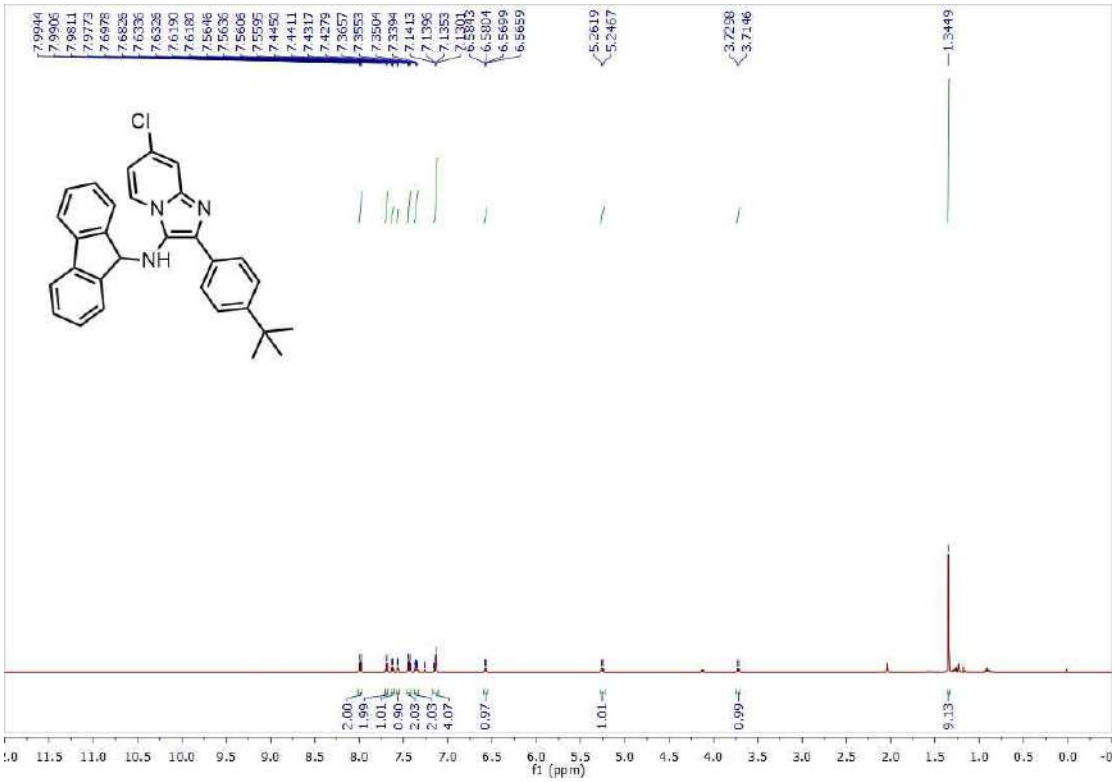
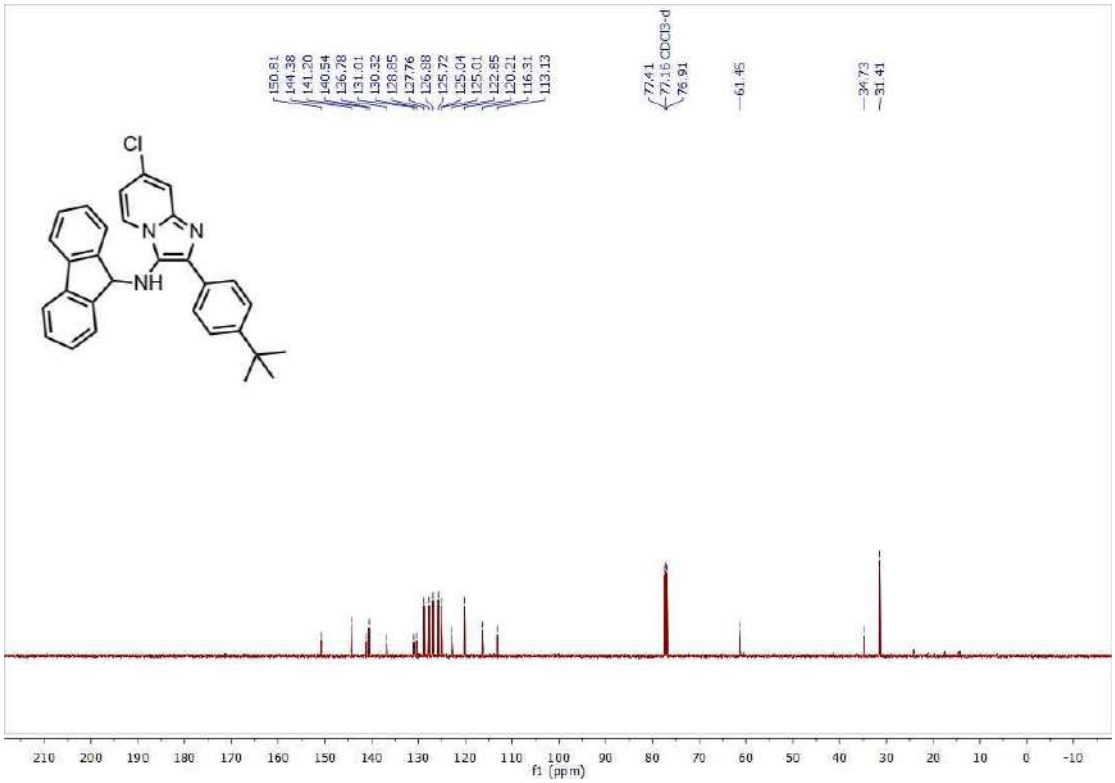
39.85
39.69
39.52 DMSO-d6
39.35
39.19
39.02
36.81
f1 (ppm)


Cl
N
N
NH
f1 (ppm)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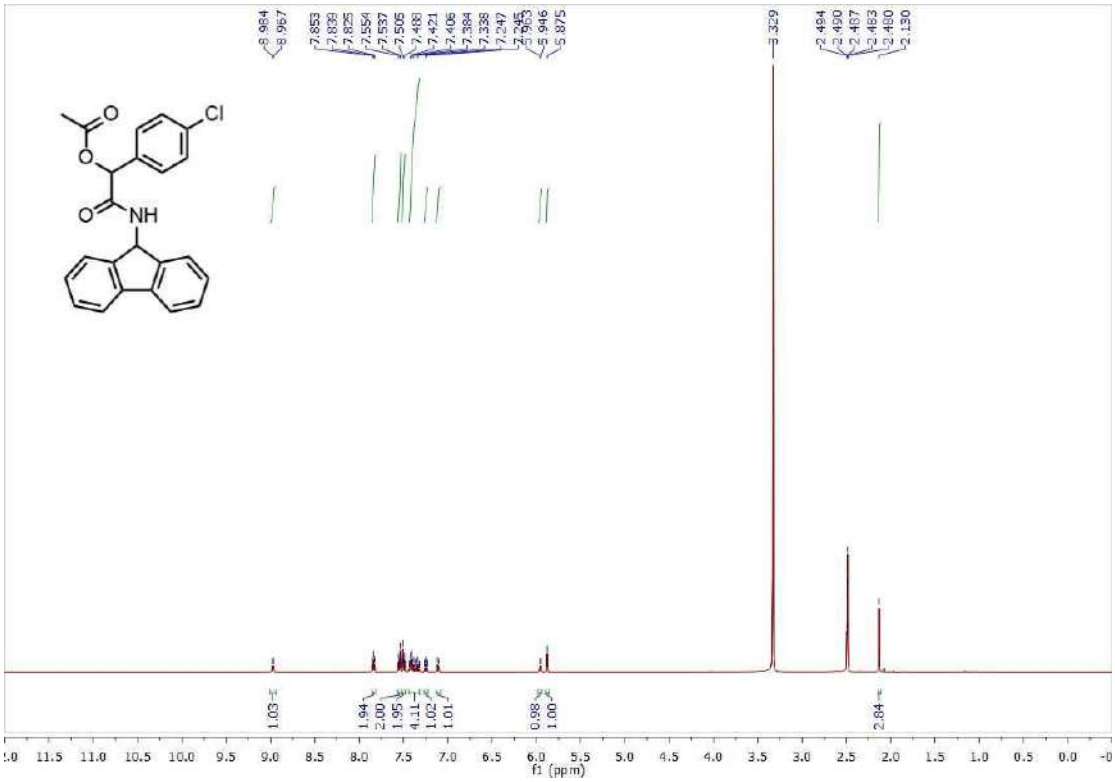
N
N
NH
CDCl3-d
f1 (ppm)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7.421
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7.384
7.338
7.247
7.245
5.953
5.946
5.875
3.329
2.484
2.490
2.487
2.483
2.480
2.130
Cl
O
O
NH
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4.11
1.02
1.01
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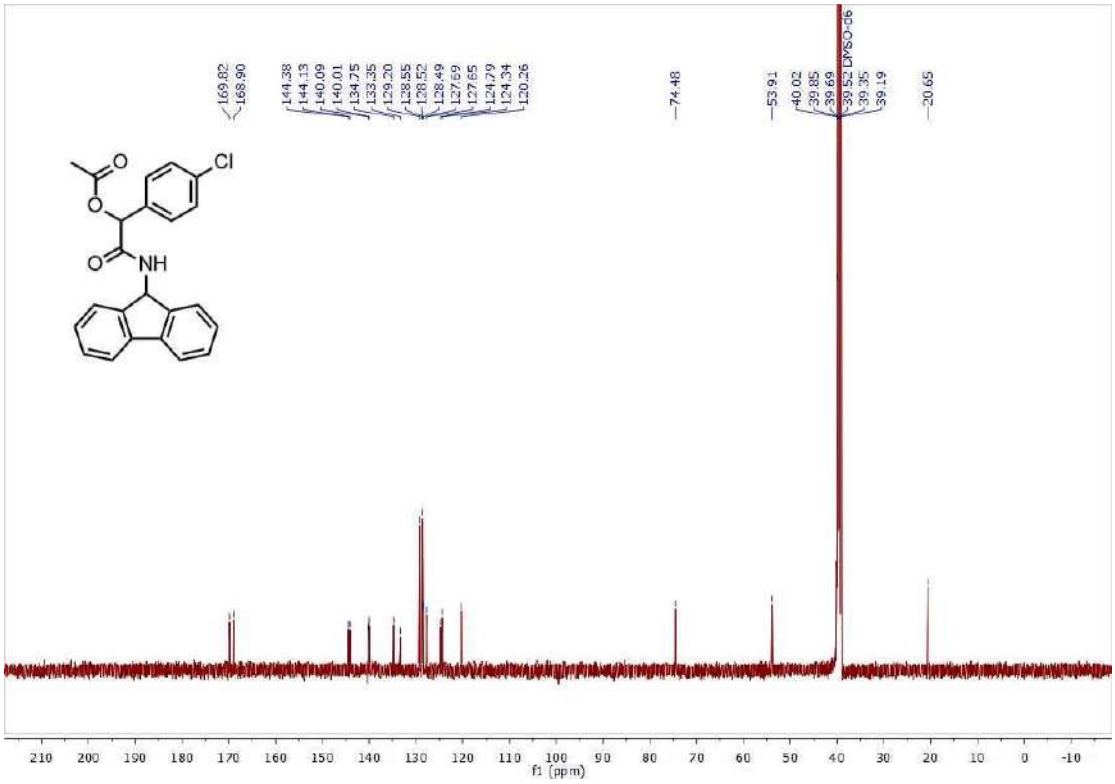
1.00
2.84
f1 (ppm)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140.01
134.75
133.35
129.20
128.55
128.52
128.49
127.69
127.65
124.79
124.34
120.26
74.48
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40.02
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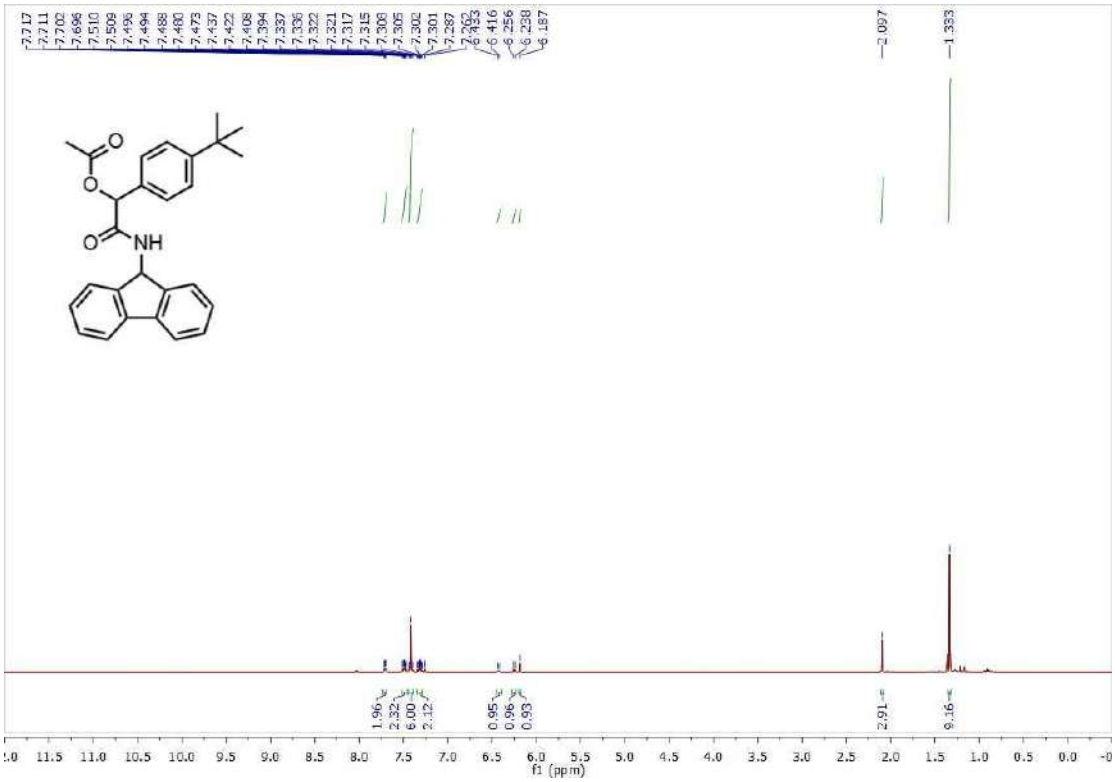
39.69
39.52 DMSO-d6
39.35
39.19
20.65
Cl
O
O
NH
f1 (ppm)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7.494
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7.480
7.473
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7.408
7.394
7.337
7.336
7.322
7.321
7.317
7.315
7.308
7.305
7.302
7.301
7.287
6.416
6.256
6.238
6.187
2.097
1.333
O
O
NH
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6.00
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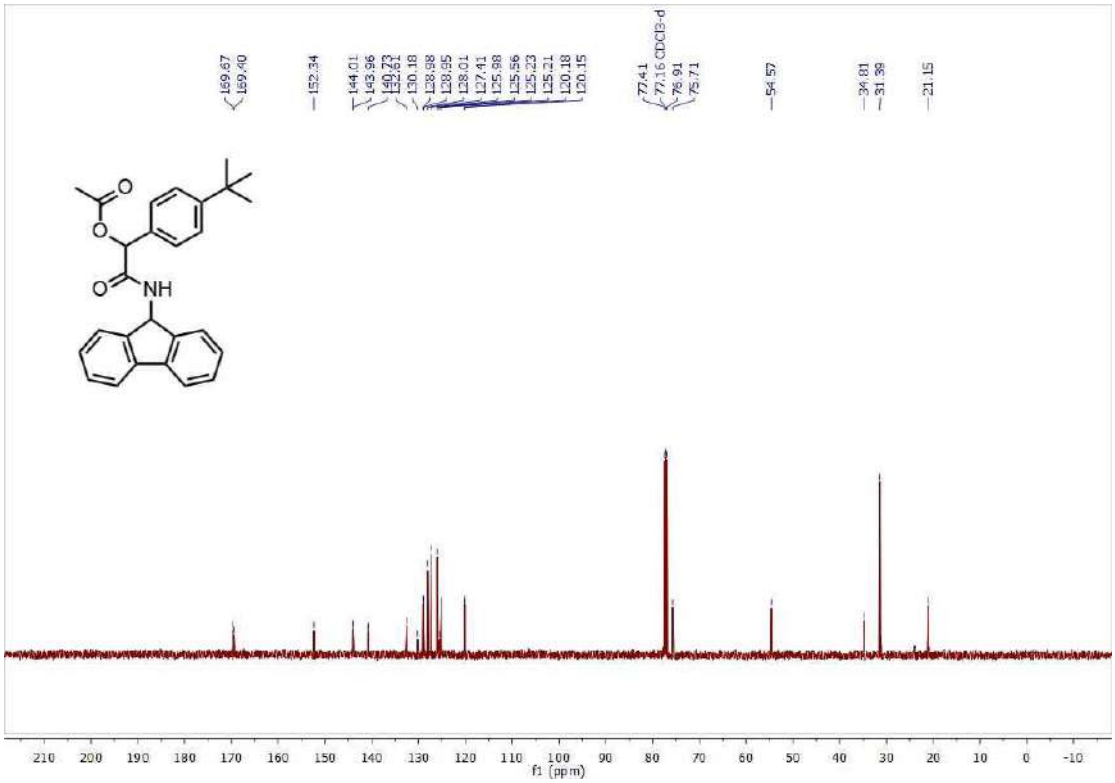
0.96
0.93
2.91
9.16
f1 (ppm)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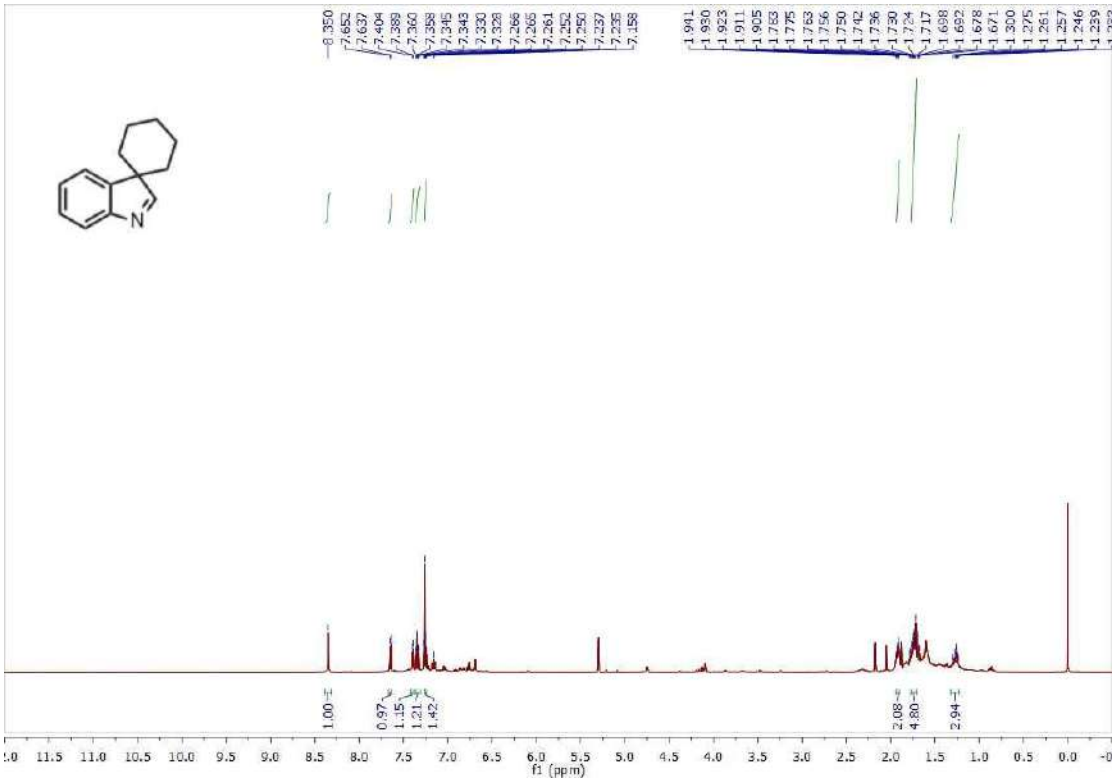
140.23
132.61
130.18
128.98
128.95
128.01
127.41
125.98
125.56
125.23
125.21
120.18
120.15
77.41
77.16 CDCl3-d
76.91
75.71
54.57
34.81
31.39
21.15
O
O
NH
f1 (ppm)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7.345
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7.265
7.261
7.252
7.250
7.237
7.235
7.158
1.941
1.930
1.923
1.911
1.905
1.783
1.775
1.763
1.756
1.750
1.742
1.736
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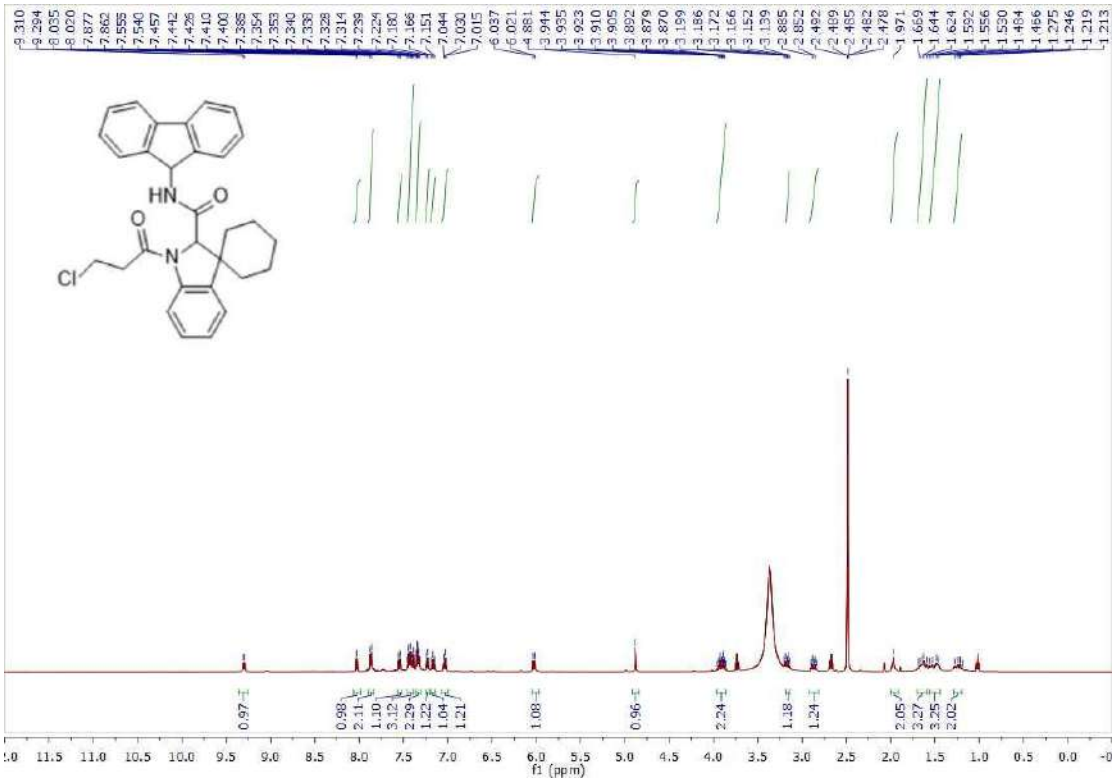
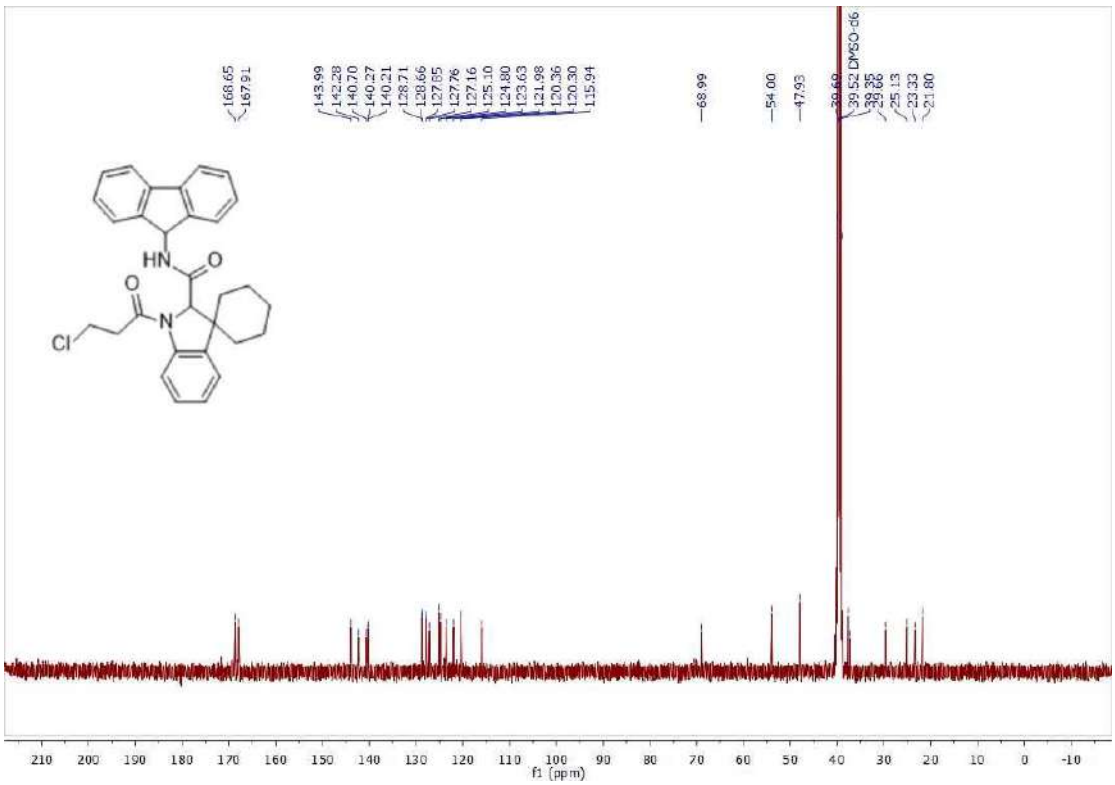
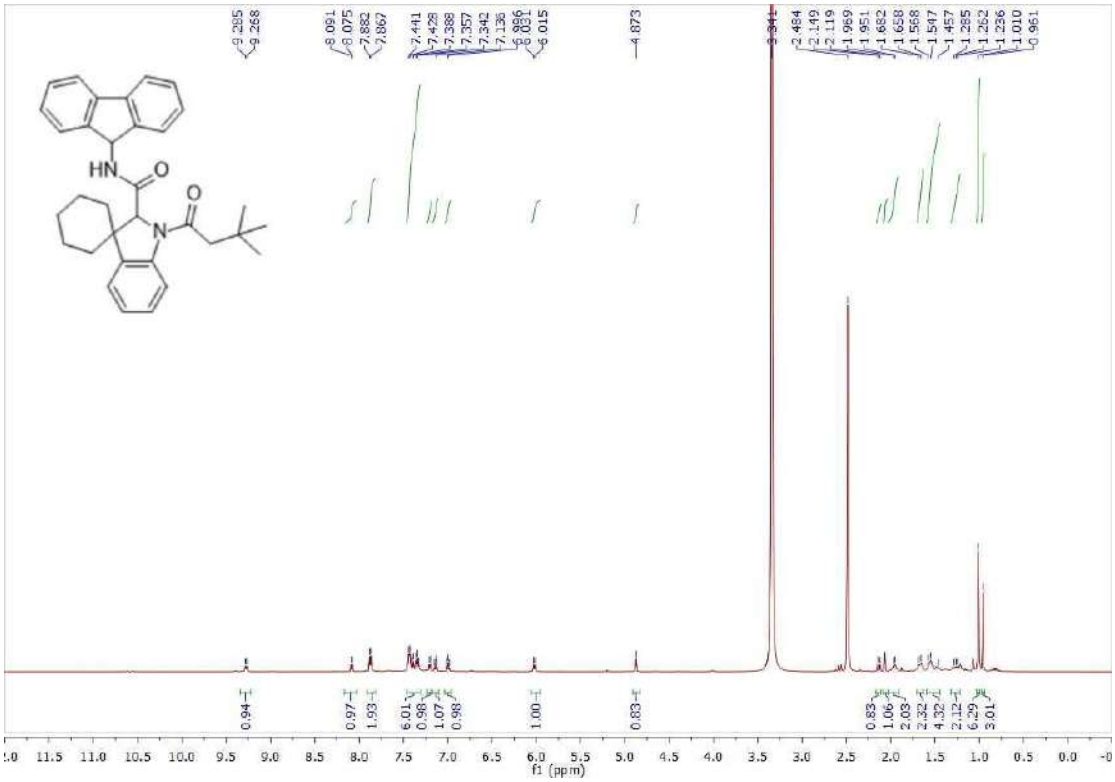
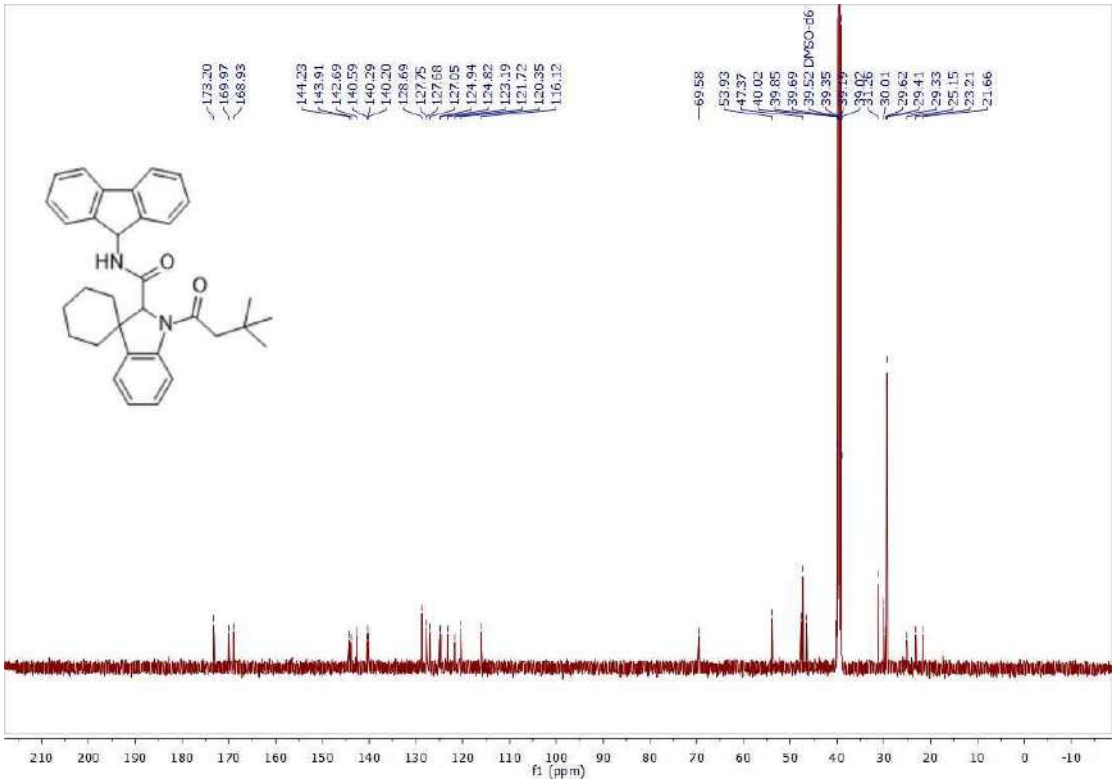
1.724
1.717
1.698
1.692
1.678
1.671
1.300
1.275
1.261
1.257
1.246
1.229
1.00
0.97
1.15
1.21
1.42
2.08
4.80
2.94
f1 (ppm)


HN
O
O
N
Cl
f1 (ppm)


HN
O
O
N
Cl
f1 (ppm)


HN
O
O
N
f1 (ppm)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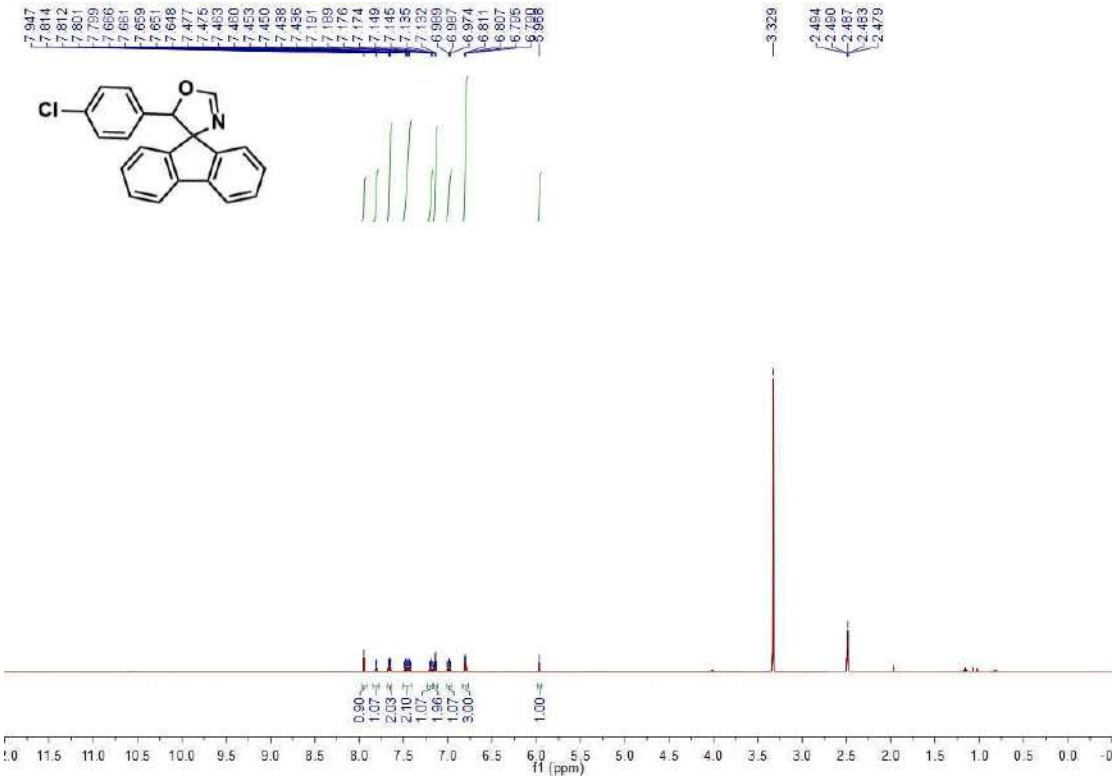
O
O
N
DMSO-d6
f1 (ppm)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7.812
7.801
7.799
7.666
7.661
7.659
7.651
7.648
7.477
7.475
7.463
7.460
7.453
7.450
7.438
7.436
7.191
7.189
7.176
7.174
7.149
7.145
7.135
7.132
6.989
6.987
6.974
6.811
6.807
6.795
6.788
3.958
3.329
2.494
2.490
2.487
2.483
2.479
Cl
O
N
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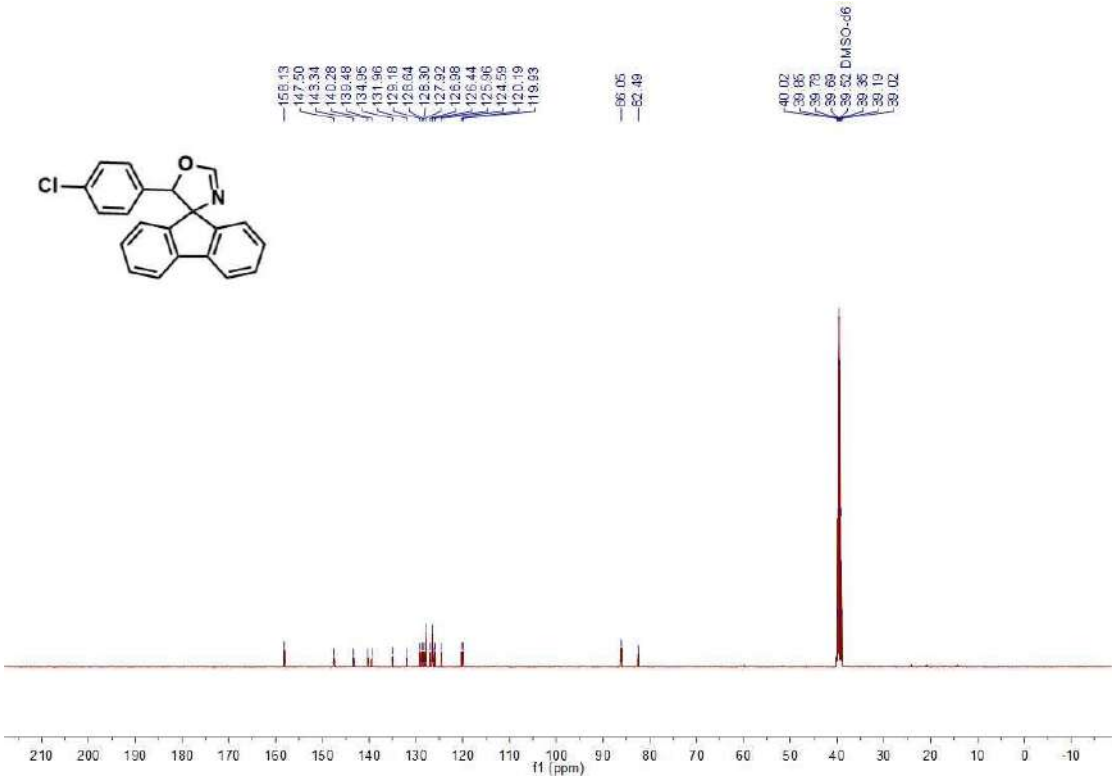
2.03
2.10
1.07
1.96
1.07
3.00
1.00
f1 (ppm)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129.18
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126.44
125.96
124.59
120.19
119.93
96.05
82.49
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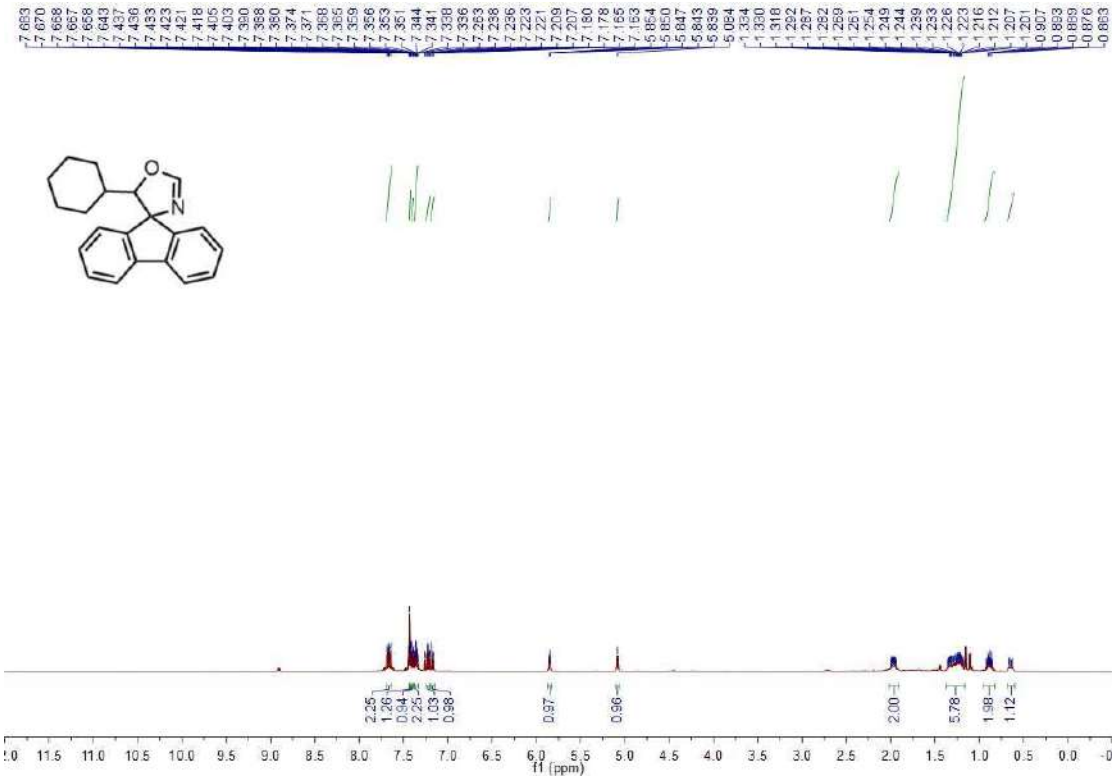
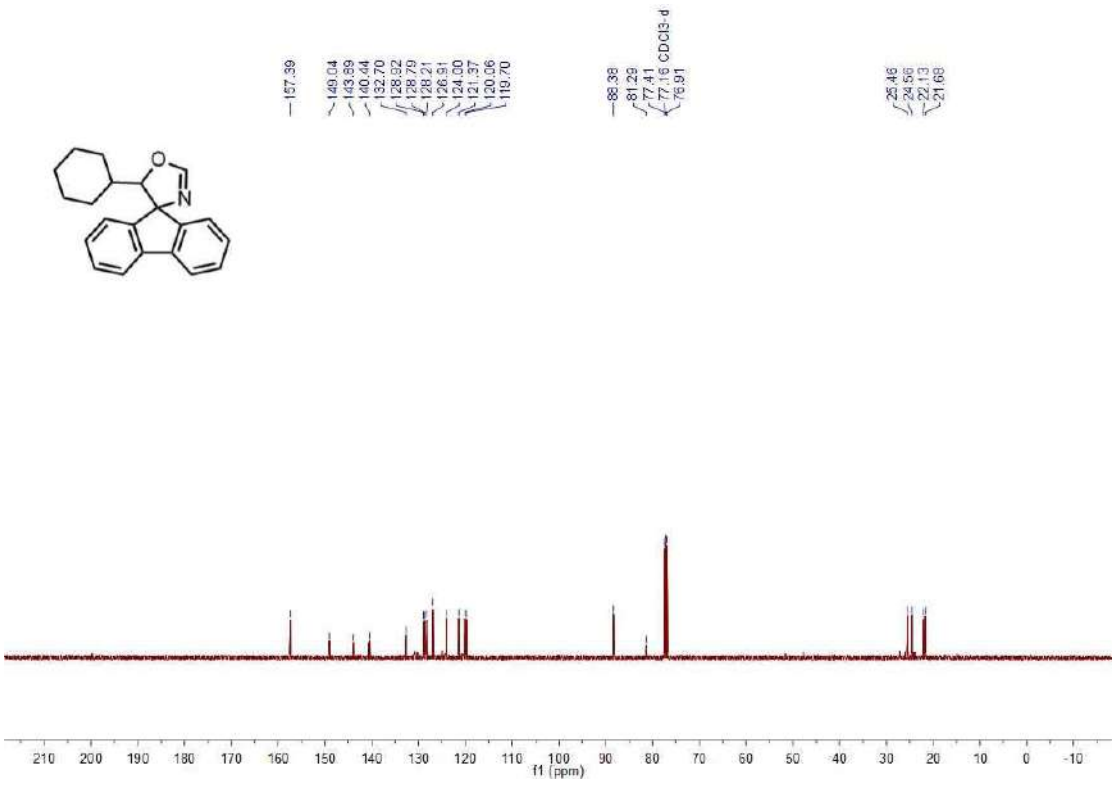
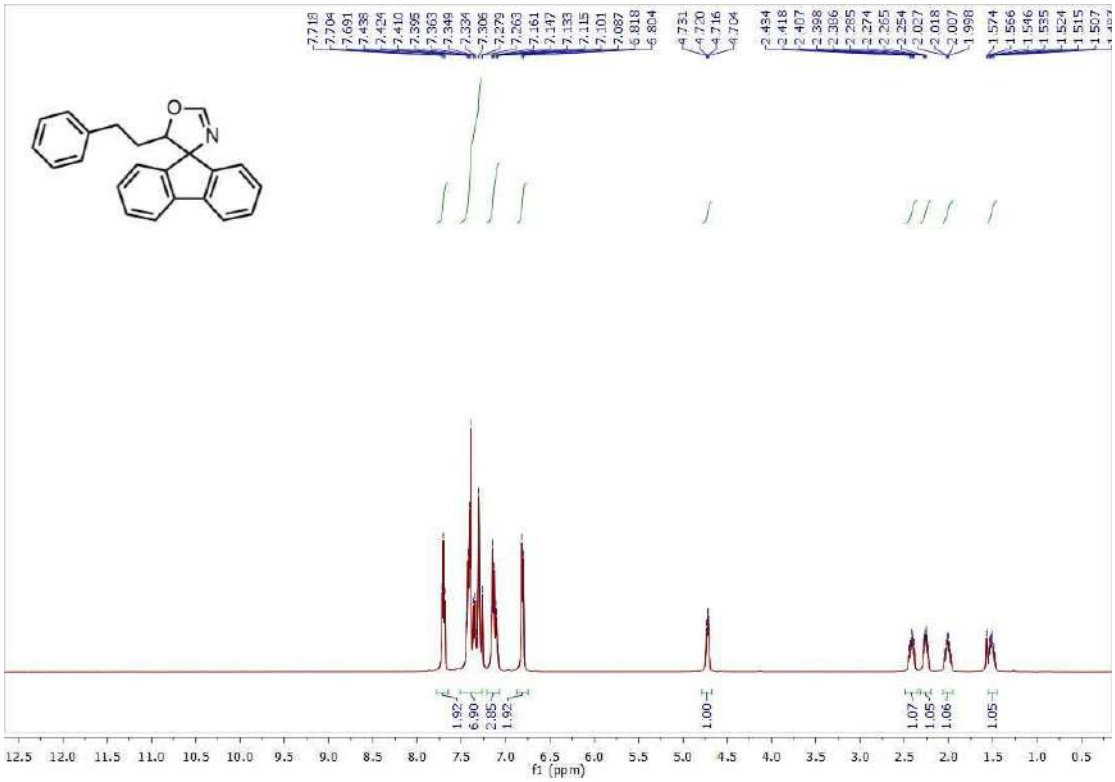
39.73
39.69
39.52 DMSO-d6
39.36
39.19
39.02
Cl
O
N
f1 (ppm)



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7.334
7.306
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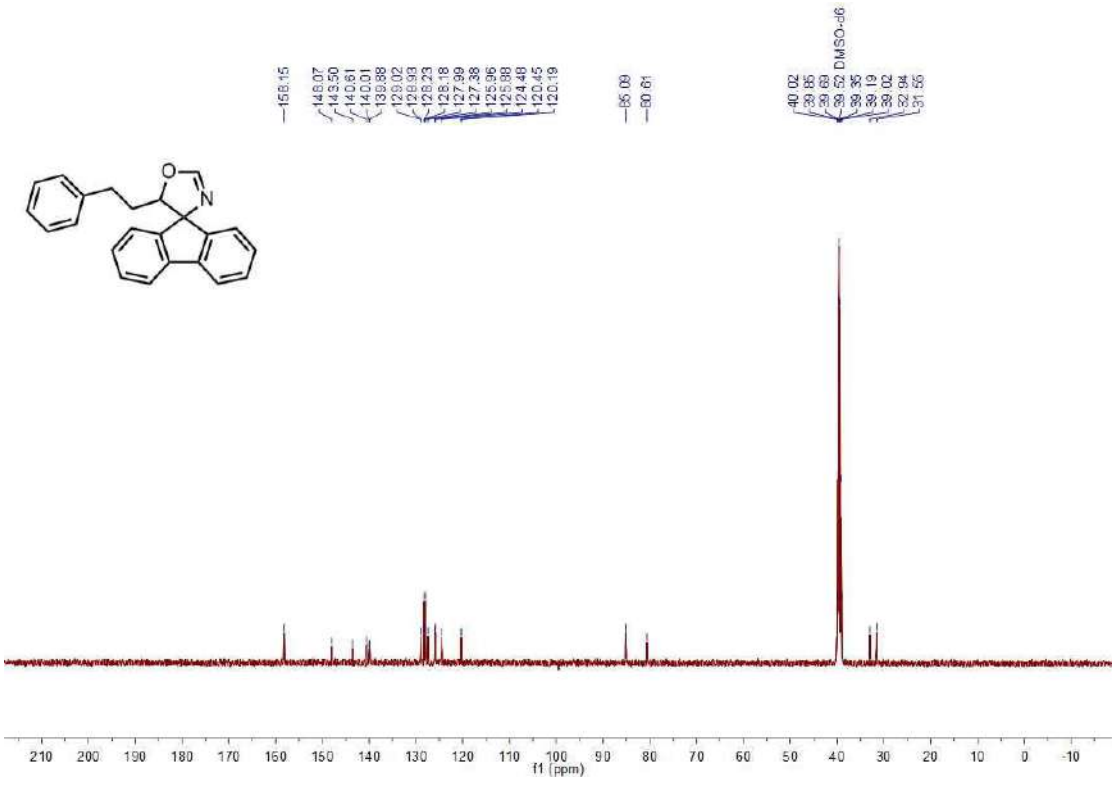
7.263
7.161
7.147
7.133
7.115
7.101
7.087
6.818
6.804
4.731
4.720
4.716
4.704
2.434
2.418
2.407
2.398
2.386
2.285
2.274
2.265
2.254
2.027
2.018
2.007
1.998
1.574
1.566
1.546
1.535
1.524
1.515
1.507
O
N
1.92
6.90
2.85
1.92
1.00
1.07
1.05
1.06
1.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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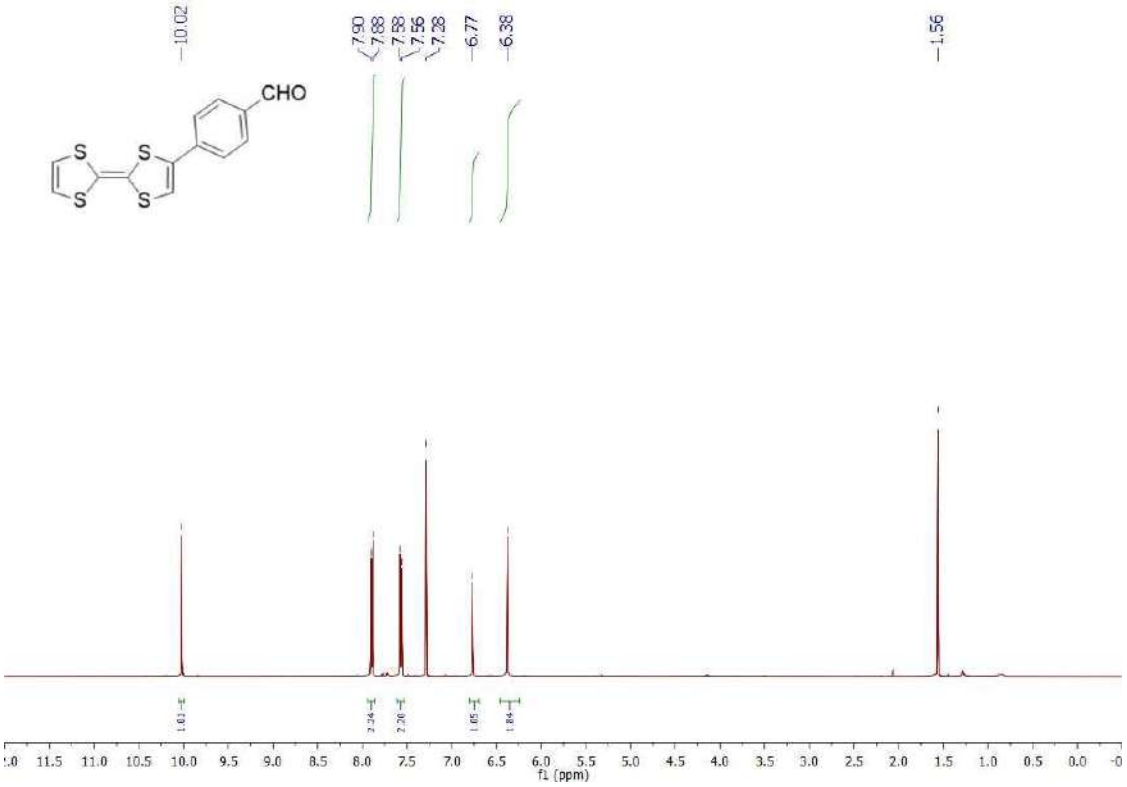
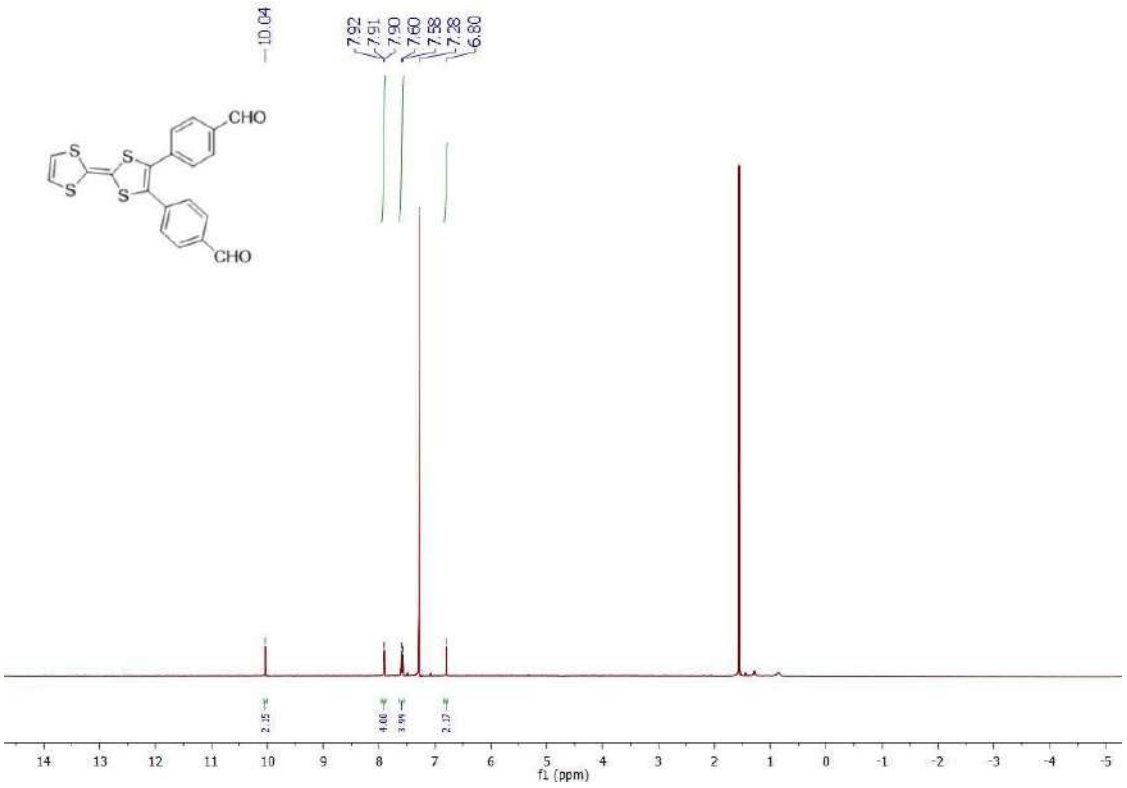
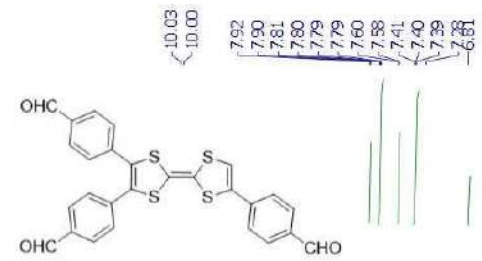
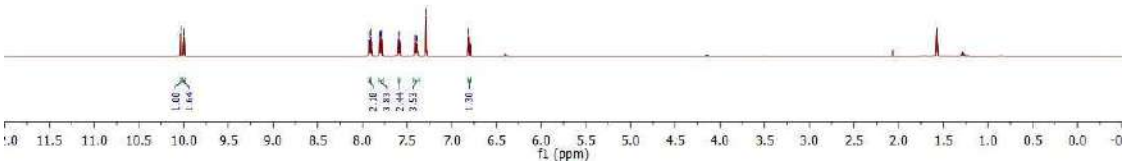
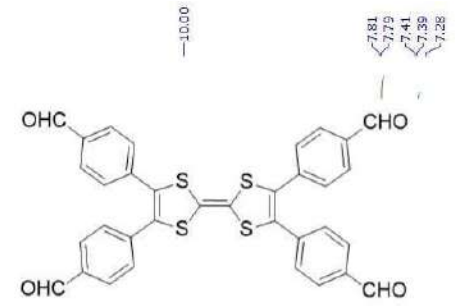
128.93
128.23
128.18
127.99
127.38
125.96
125.88
124.48
120.45
120.19
85.09
80.61
40.02
39.85
39.69
39.52
DMSO-d6
39.35
39.19
39.02
32.94
31.55
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

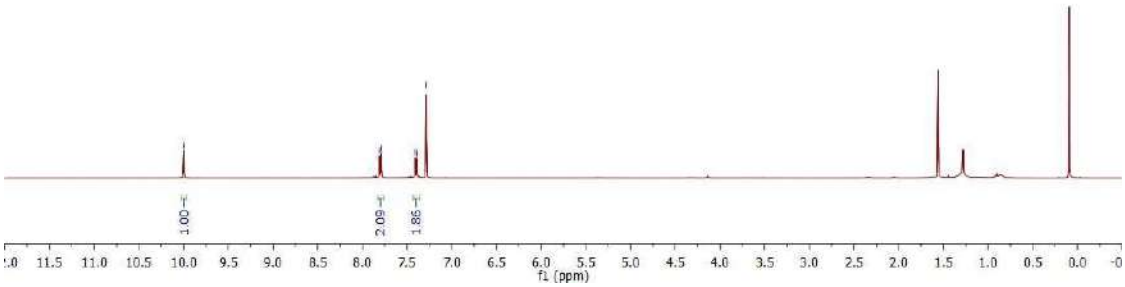

10.02
7.90
7.88
7.58
7.56
7.28
6.77
6.38
1.56
CHO
S
S
S
S
f1 (ppm)

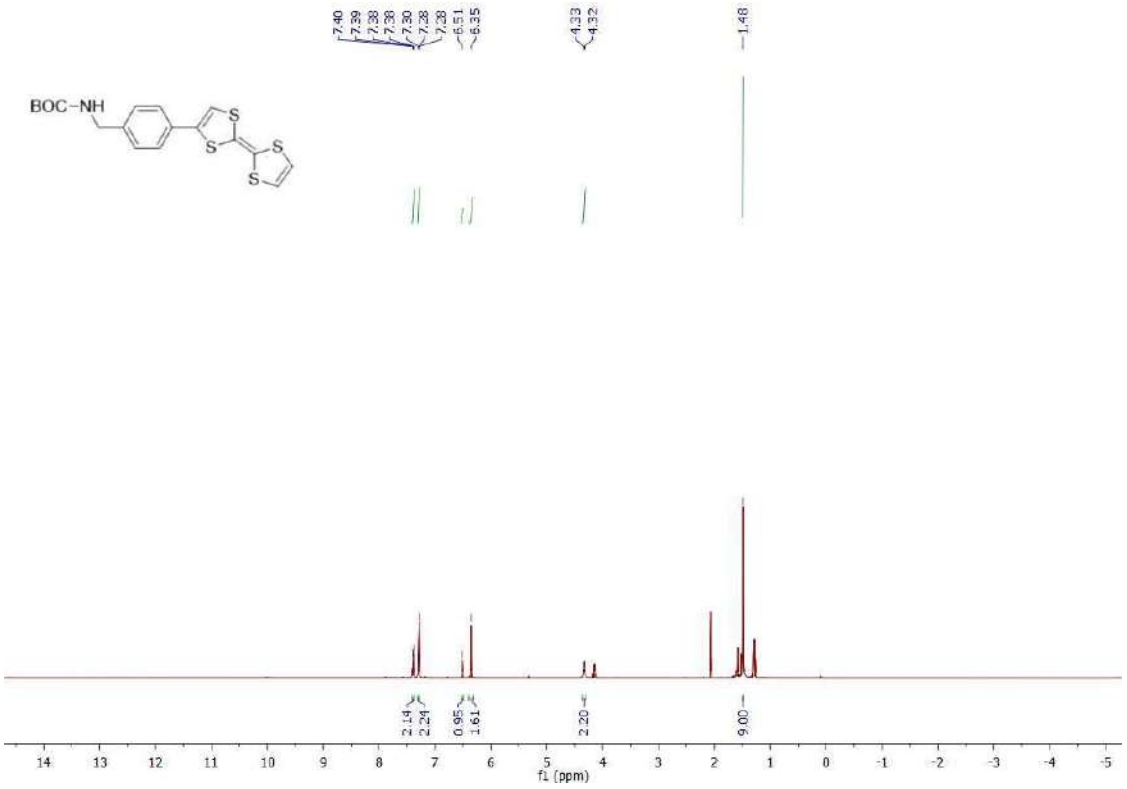

10.04
7.92
7.91
7.90
7.60
7.58
7.28
6.80
CHO
CHO
S
S
S
S
f1 (ppm)

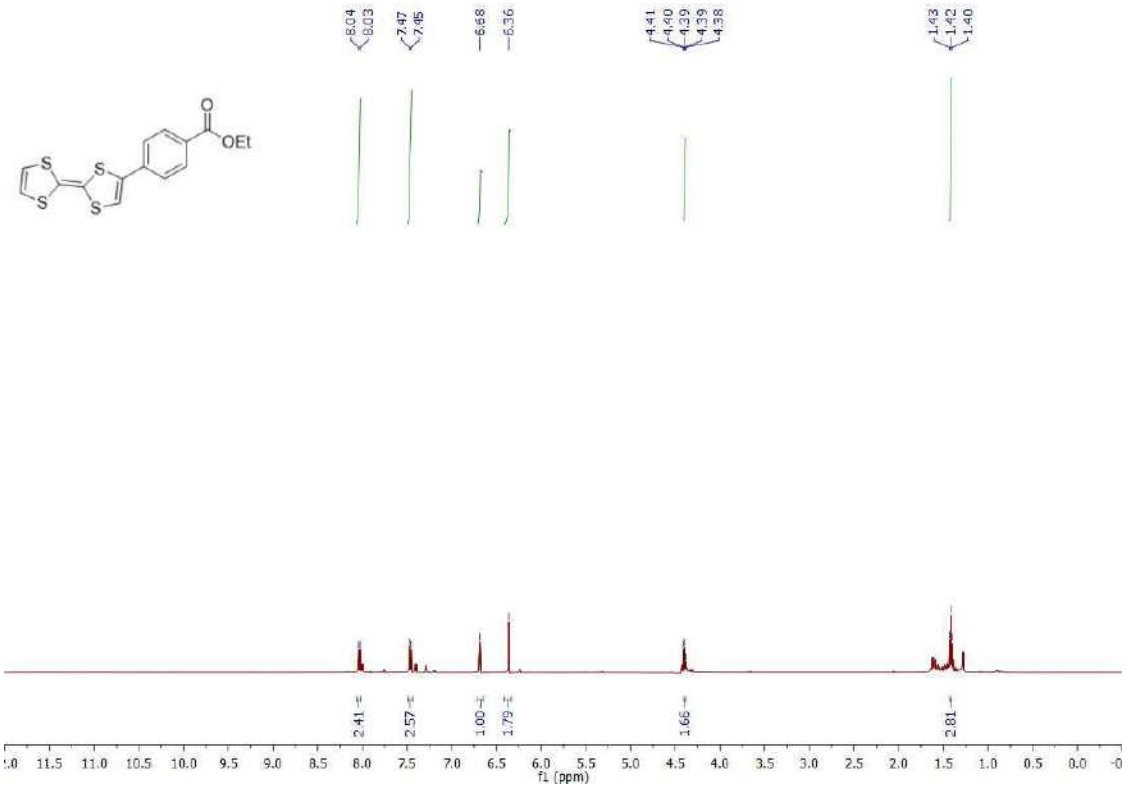

10.03
10.00
7.92
7.90
7.81
7.80
7.79
7.79
7.60
7.58
7.41
7.40
7.39
7.28
6.81
OHC
OHC
CHO
S
S
S
S

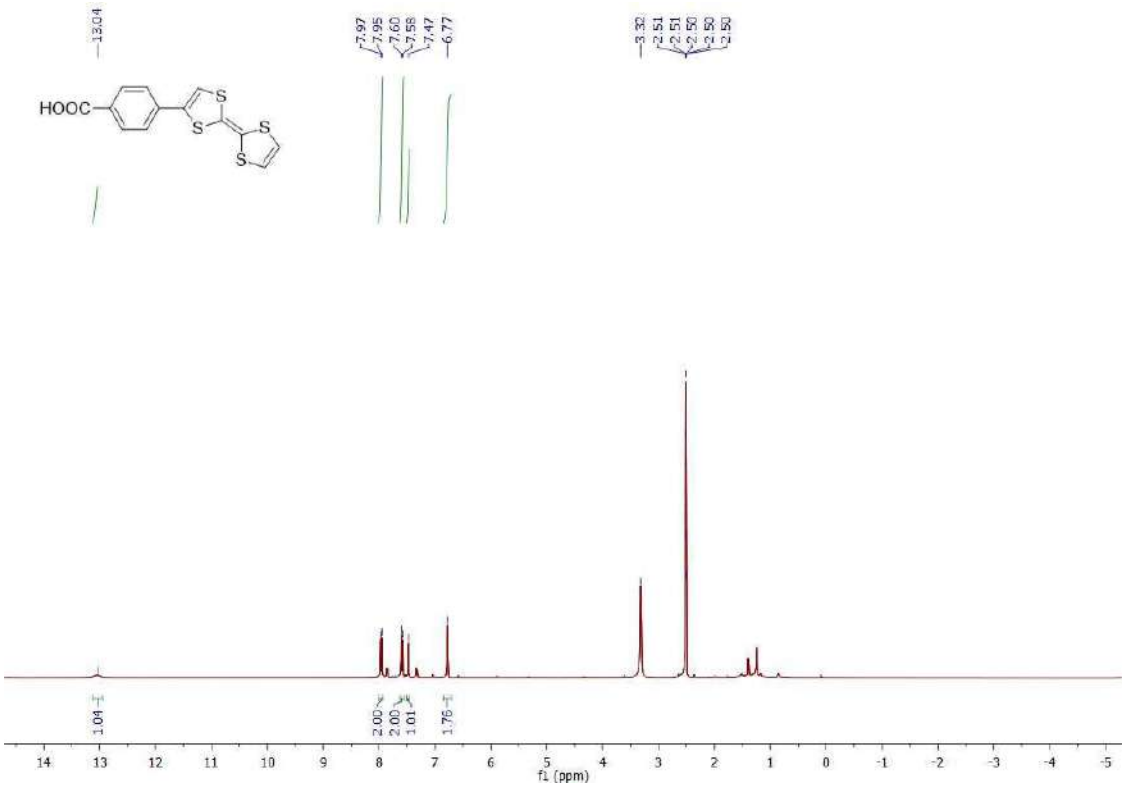

1.00
1.64
2.16
3.83
2.44
3.53
1.30
f1 (ppm)

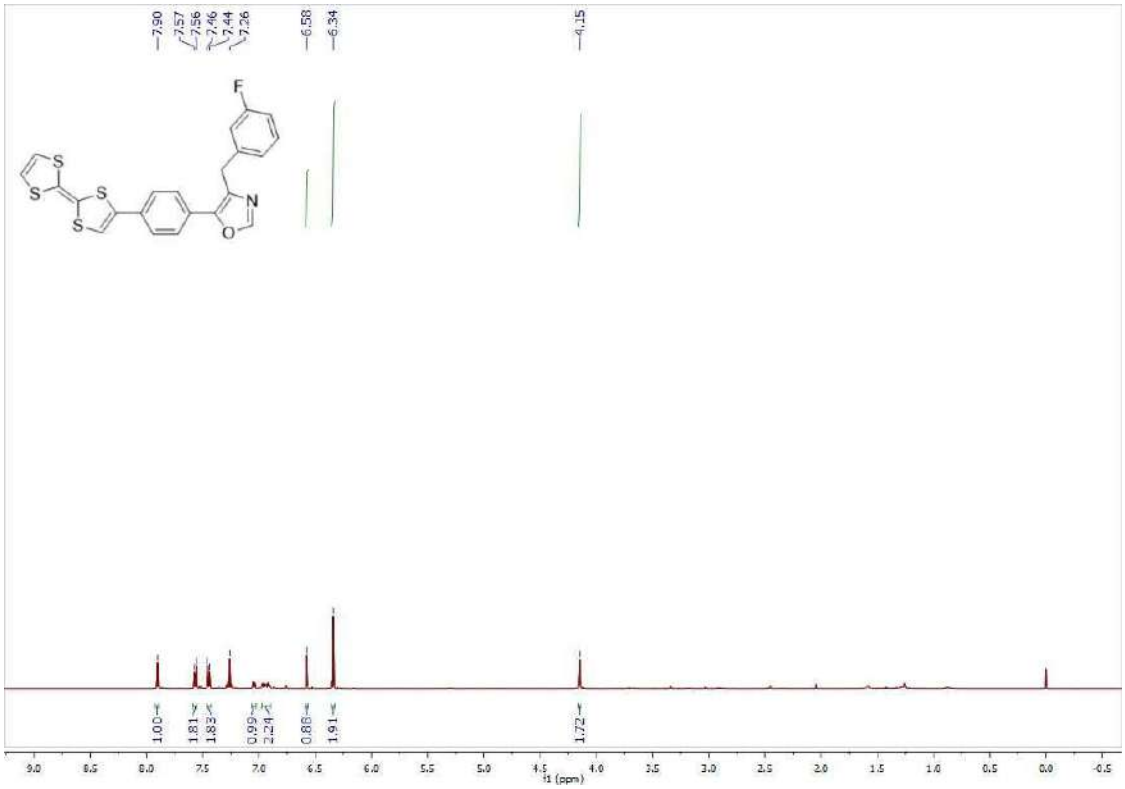

10.00
7.81
7.79
7.41
7.39
7.28
OHC
OHC
CHO
CHO
S
S
S
S

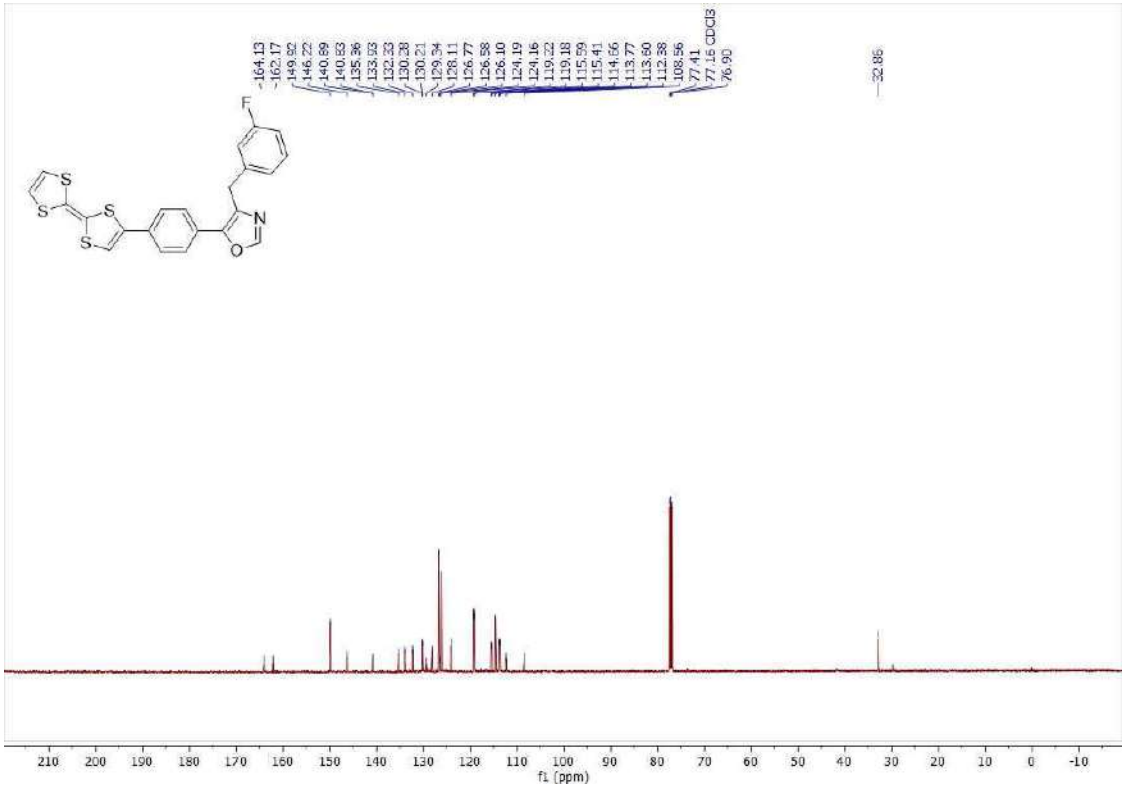

1.00
2.09
1.85
f1 (ppm)


BOC–NH
S
S
S
S
7.40
7.39
7.38
7.38
7.30
7.28
7.28
6.51
6.35
4.33
4.32
1.48
2.19
2.24
0.95
1.61
2.20
9.00
f1 (ppm)


O
OEt
S
S
S
S
8.04
8.03
7.47
7.45
6.68
6.36
4.41
4.40
4.39
4.39
4.38
1.43
1.42
1.40
2.41
2.57
1.00
1.79
1.66
2.81
f1 (ppm)


13.04
7.97
7.95
7.60
7.58
7.47
6.77
3.32
2.51
2.51
2.50
2.50
2.50
HOOC
S
S
S
S
1.04
2.00
2.00
1.01
1.76
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
f1 (ppm)


7.90
7.57
7.56
7.46
7.44
7.26
6.58
6.34
4.15
F
S
S
S
S
N
O
1.00
1.81
1.83
0.99
2.24
0.86
1.91
1.72
f1 (ppm)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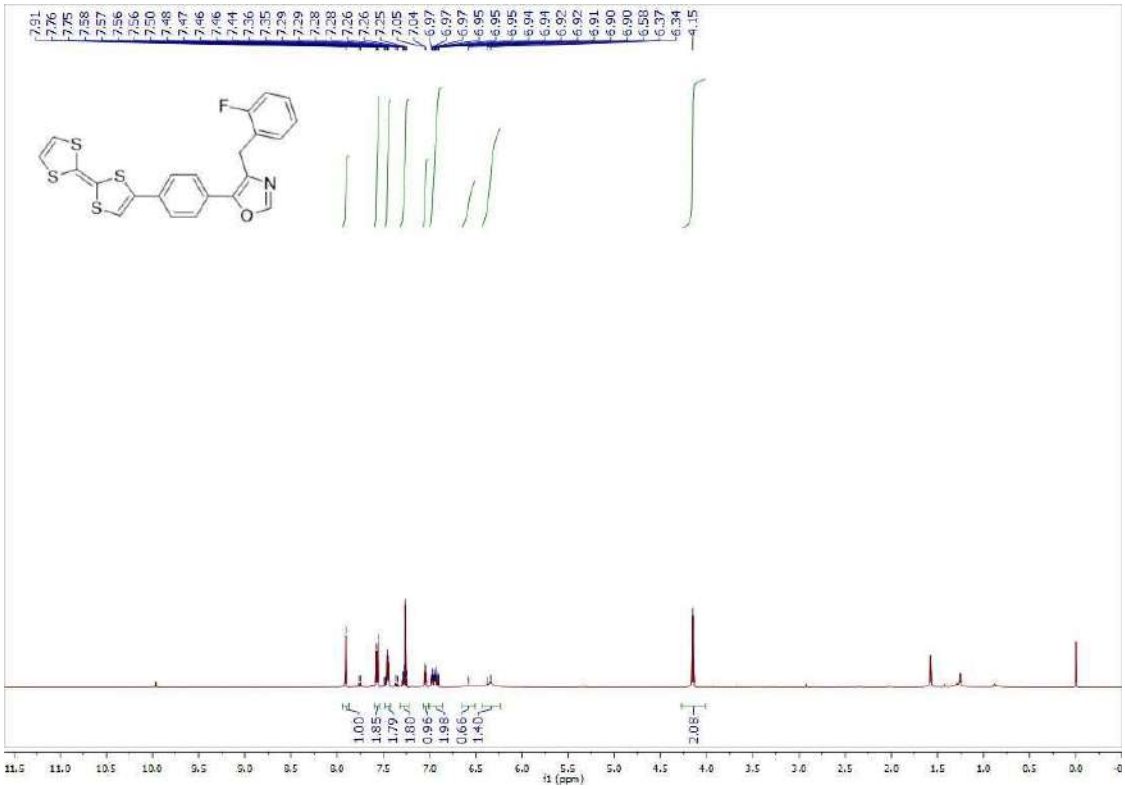
162.17
149.92
146.22
140.89
140.83
135.36
133.93
132.33
130.38
130.21
129.34
128.11
126.77
126.58
126.10
124.19
124.16
119.22
119.18
115.59
115.41
114.66
113.77
113.60
112.38
108.56
77.41
77.16 CDCl3
76.90
32.86
F
S
S
S
S
N
O
f1 (ppm)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7.57
7.56
7.56
7.50
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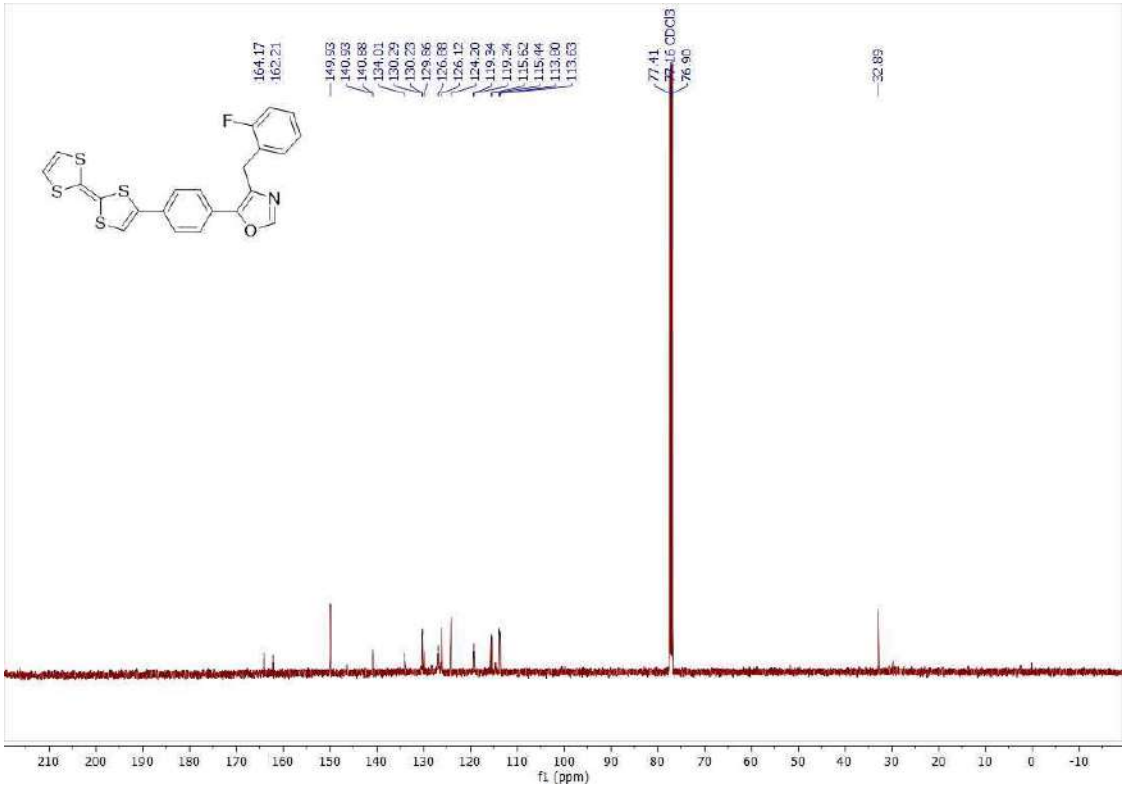
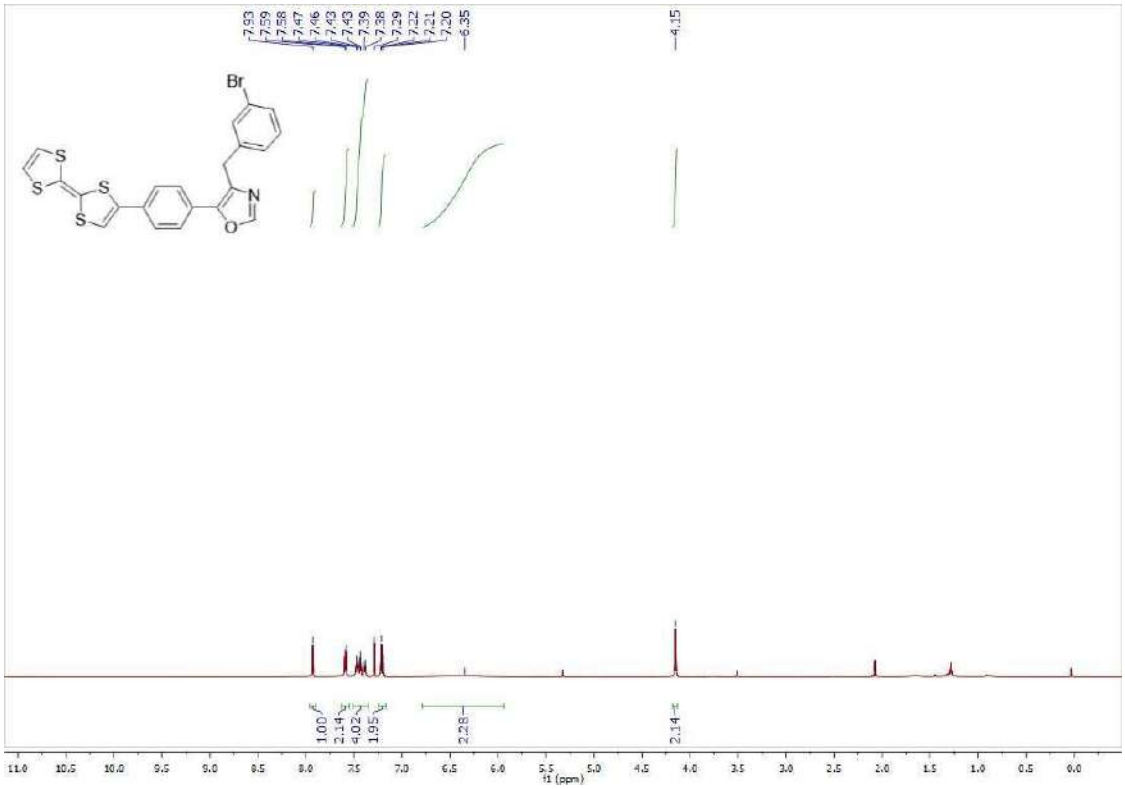
7.47
7.46
7.46
7.44
7.36
7.35
7.29
7.29
7.28
7.28
7.26
7.26
7.25
7.05
7.04
6.97
6.97
6.97
6.95
6.95
6.95
6.94
6.94
6.92
6.92
6.91
6.90
6.90
6.58
6.37
6.34
4.15
F
S
S
S
S
N
O
1.00
1.85
1.79
1.80
0.96
1.98
0.66
1.40
2.08
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.17
162.21
149.93
140.93
140.88
134.01
130.29
130.23
129.86
126.88
126.12
124.20
119.34
119.24
115.62
115.44
113.80
113.63
77.41
77.16 CDCl3
76.90
32.83
F
S
S
S
S
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.58
7.47
7.46
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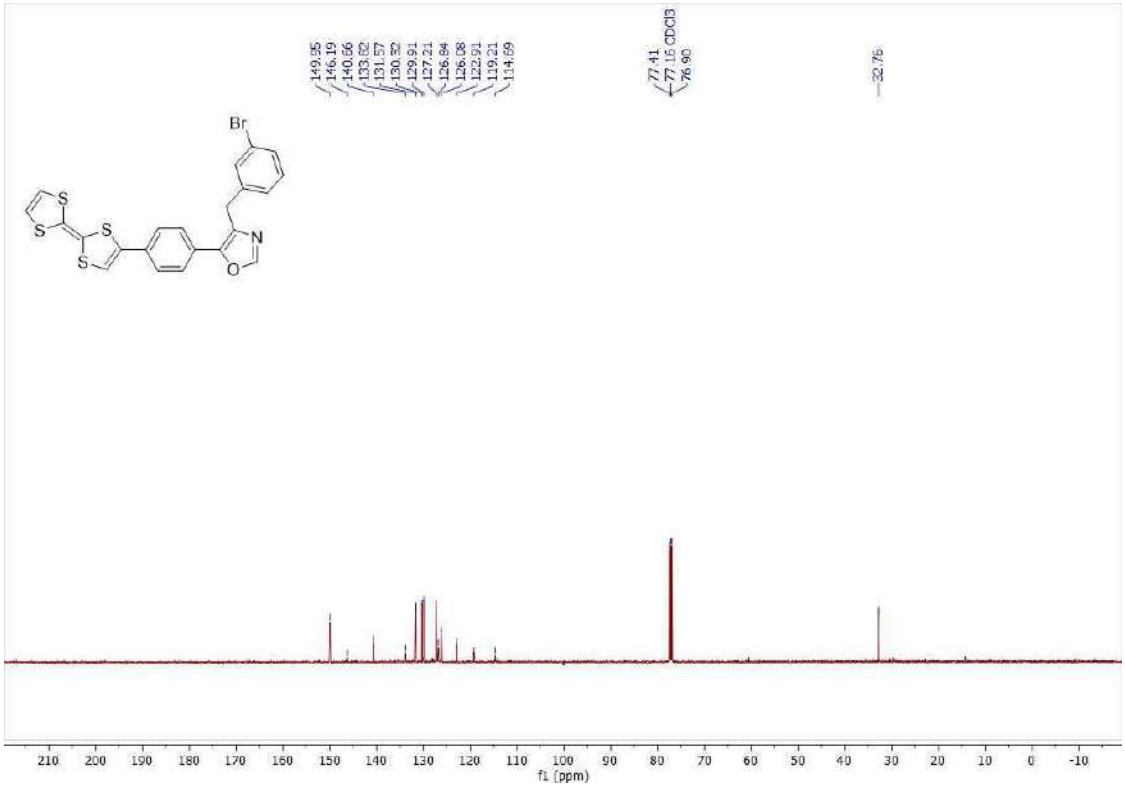
7.43
7.39
7.38
7.29
7.22
7.21
7.20
6.35
4.15
Br
S
S
S
S
N
O
1.00
2.14
4.02
1.95
2.28
2.14
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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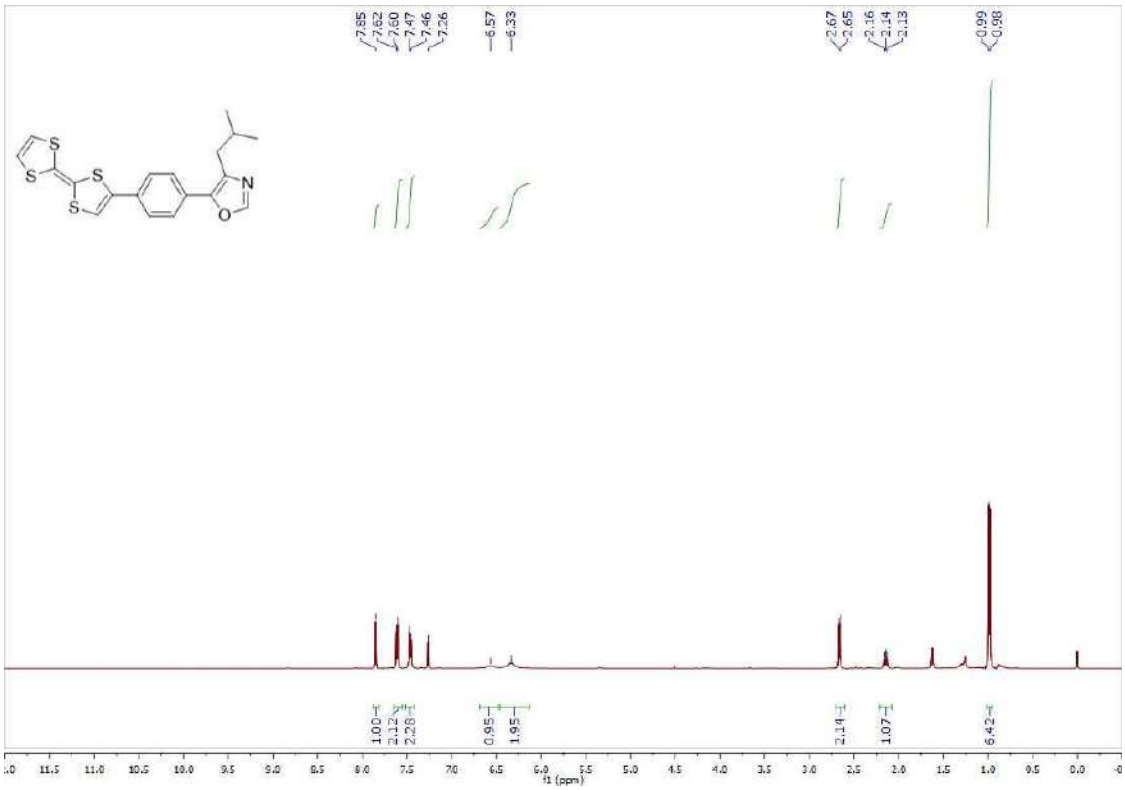
130.32
129.91
127.21
126.84
126.08
122.91
119.21
114.69
77.41
77.15 CDCl3
76.90
32.76
Br
S
S
S
S
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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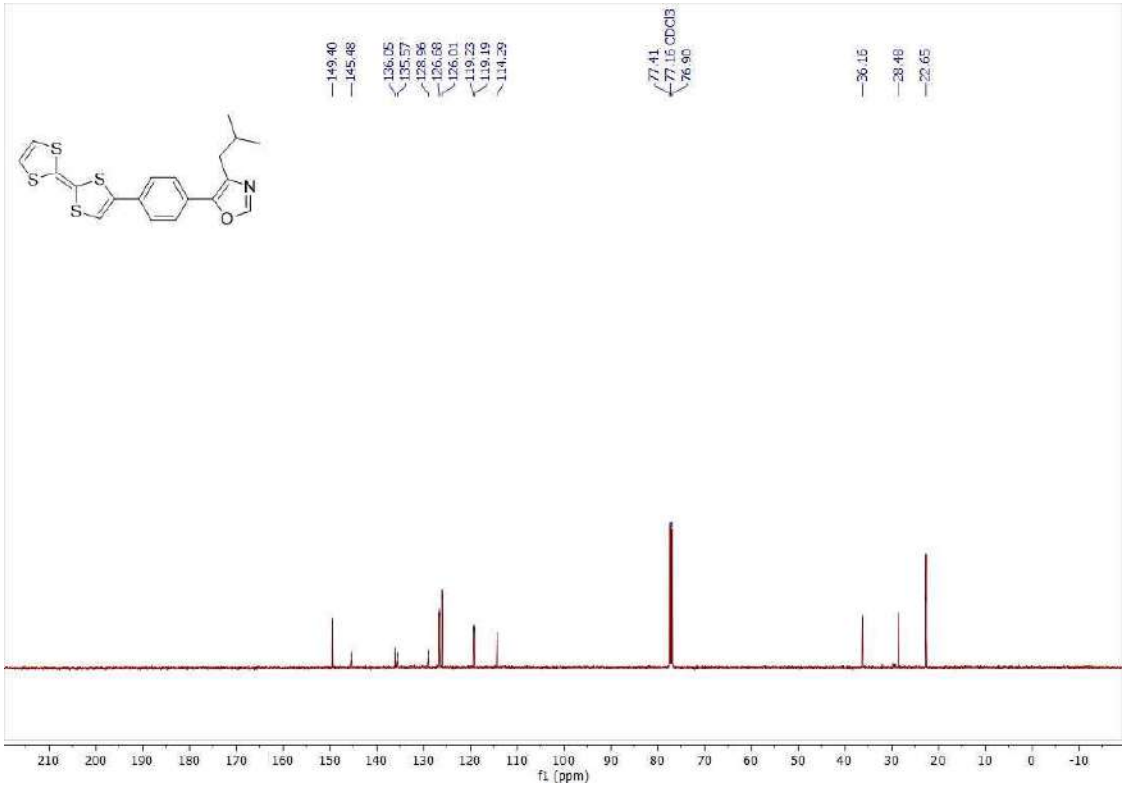
7.46
7.26
6.57
6.33
2.67
2.65
2.16
2.14
2.13
0.99
0.98
1.00
2.12
2.28
0.95
1.95
2.14
1.07
6.42
f1 (ppm)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128.96
126.68
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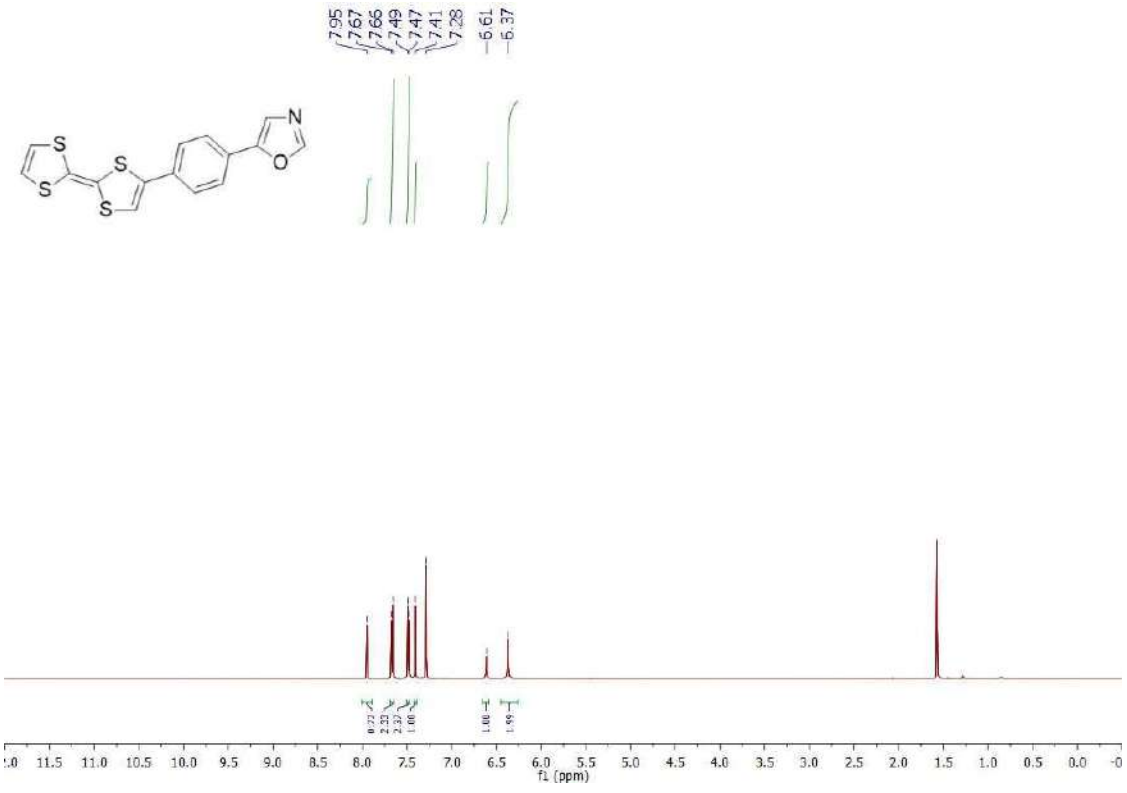
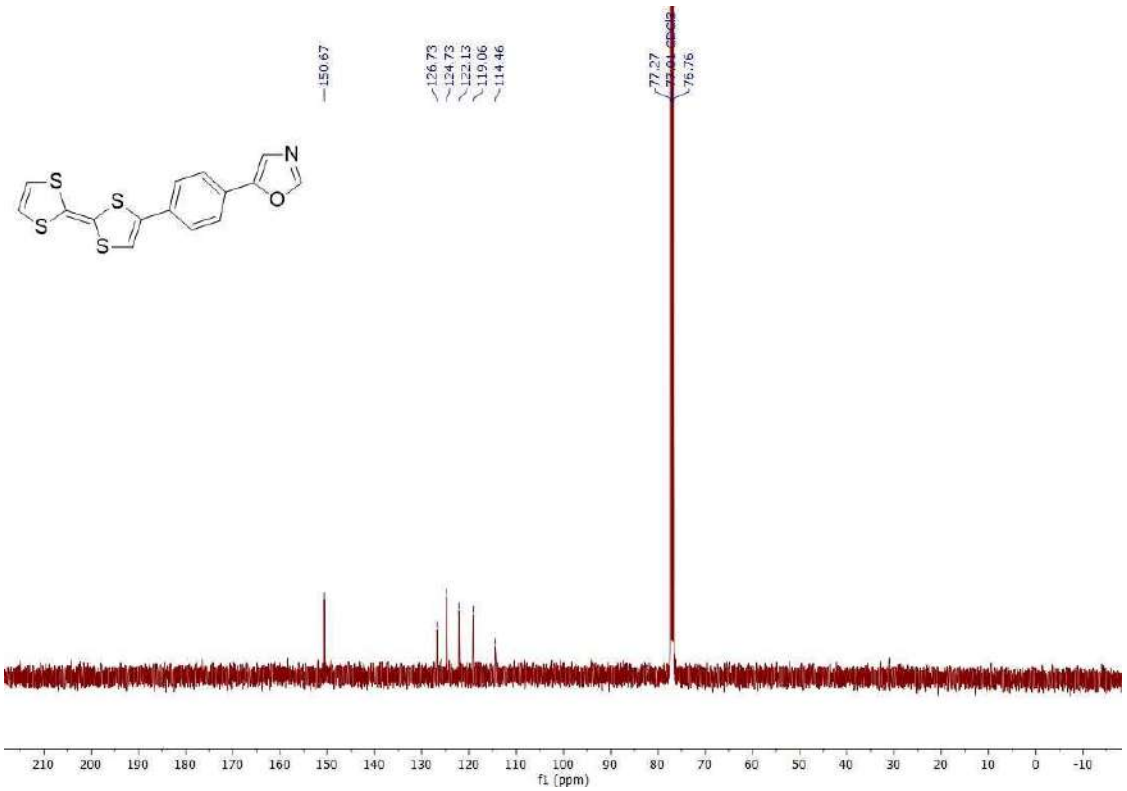
119.19
114.29
77.41
77.16 CDCl3
76.90
36.16
28.48
22.65
f1 (ppm)


7.95
7.67
7.66
7.49
7.47
7.41
7.28
6.61
6.37
S
S
S
S
N
O
f1 (ppm)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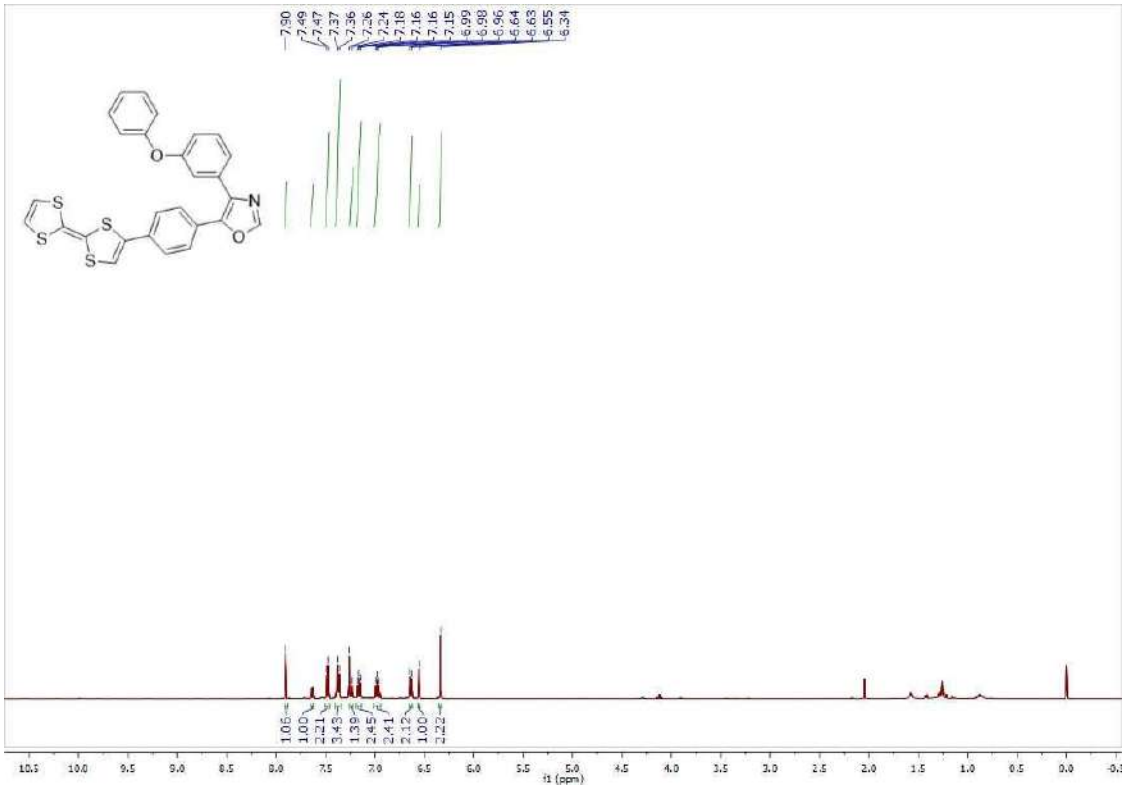
124.73
122.13
119.06
114.46
77.27
76.76
S
S
S
S
N
O
f1 (ppm)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7.49
7.47
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7.36
7.26
7.24
7.18
7.16
7.16
7.15
6.99
6.98
6.96
6.64
6.63
6.55
6.34
O
N
S
S
S
S
O
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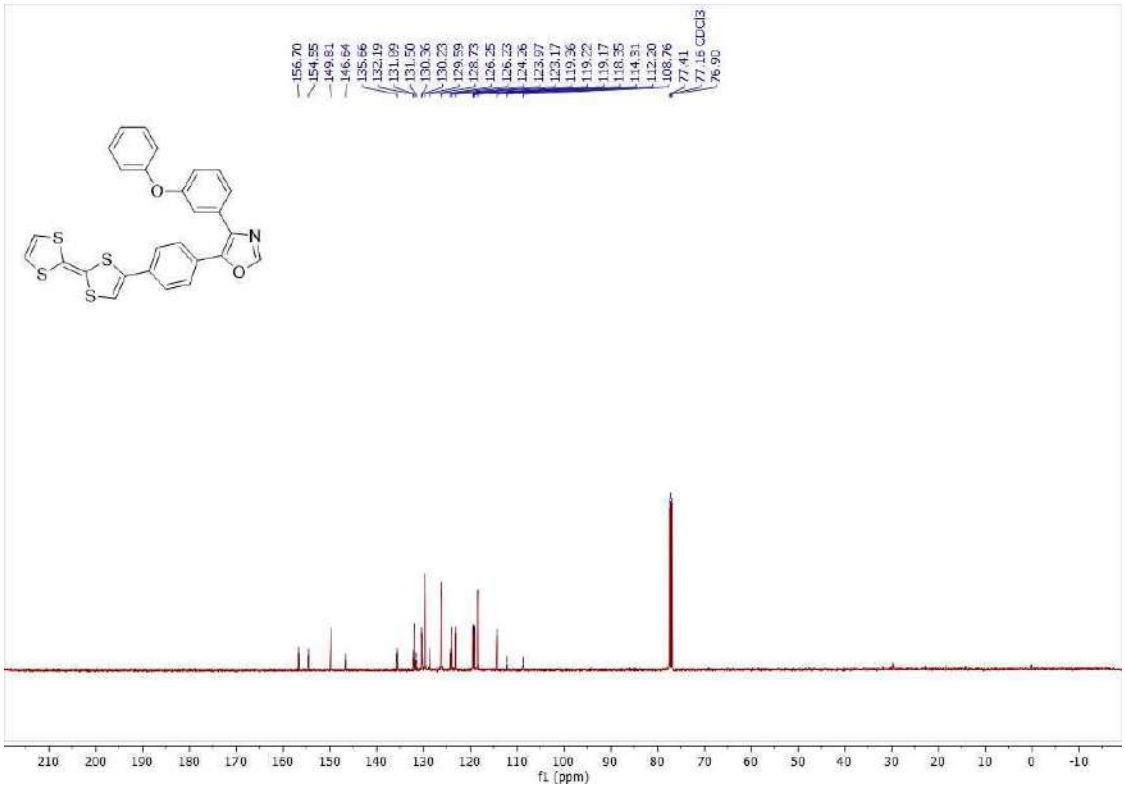
2.41
2.13
1.00
2.22
f1 (ppm)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132.19
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131.50
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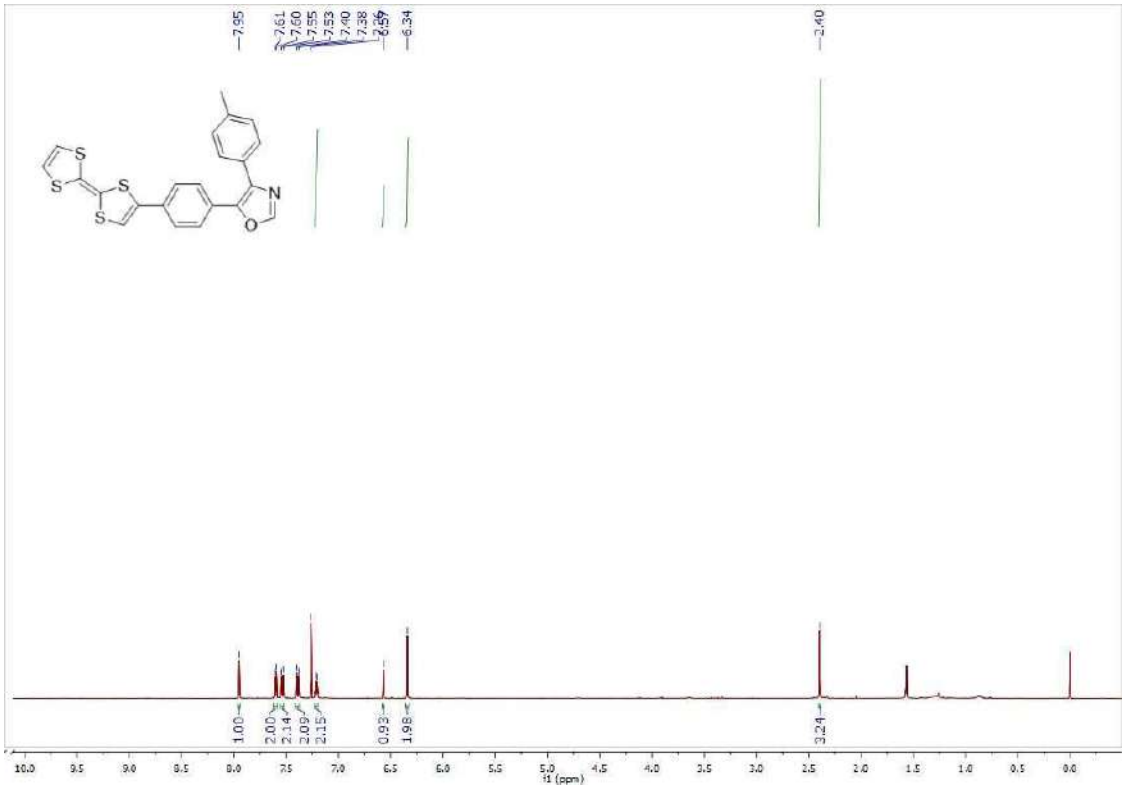
130.23
129.59
128.73
126.25
126.23
124.26
123.97
123.17
119.36
119.22
119.17
118.35
114.31
112.20
108.76
77.41
77.16 CDCl3
76.90
O
N
S
S
S
S
O
f1 (ppm)


7.95
7.61
7.60
7.55
7.53
7.40
7.38
6.59
6.34
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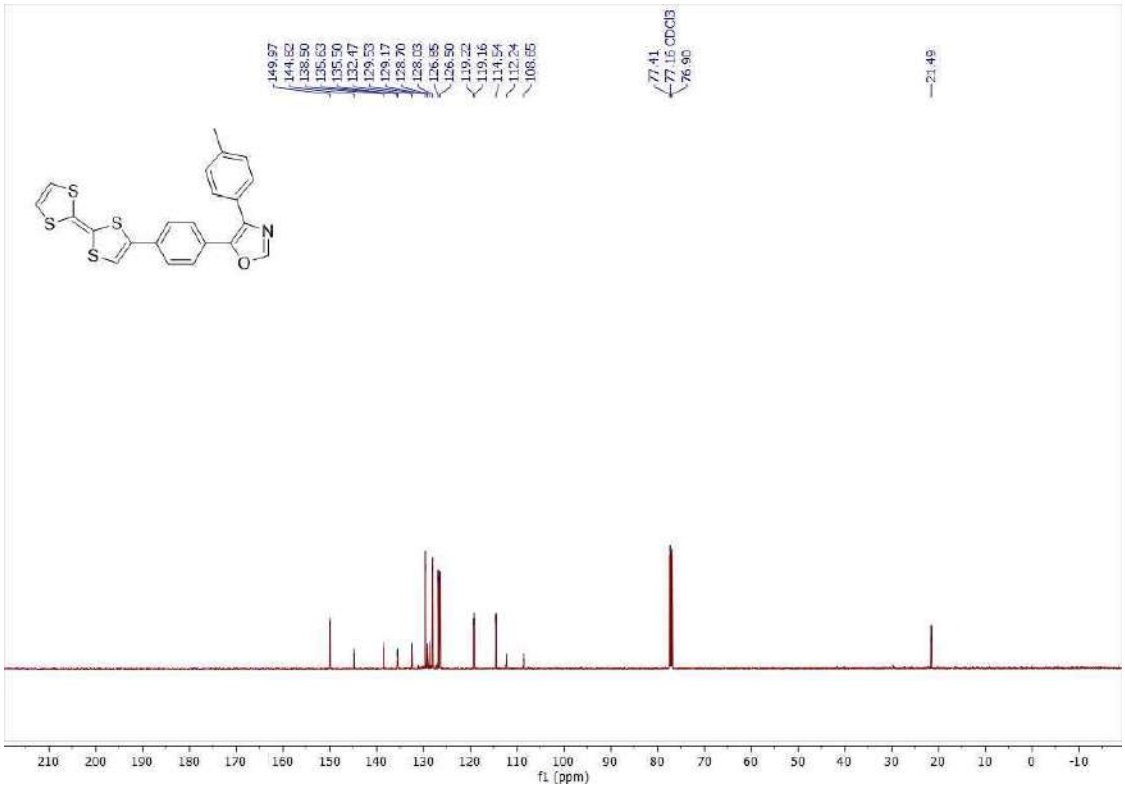
1.00
2.00
2.14
2.09
2.15
0.93
1.98
3.24
f1 (ppm)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128.03
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126.50
119.22
119.16
114.54
112.24
108.65
77.41
77.16 CDCl3
76.90
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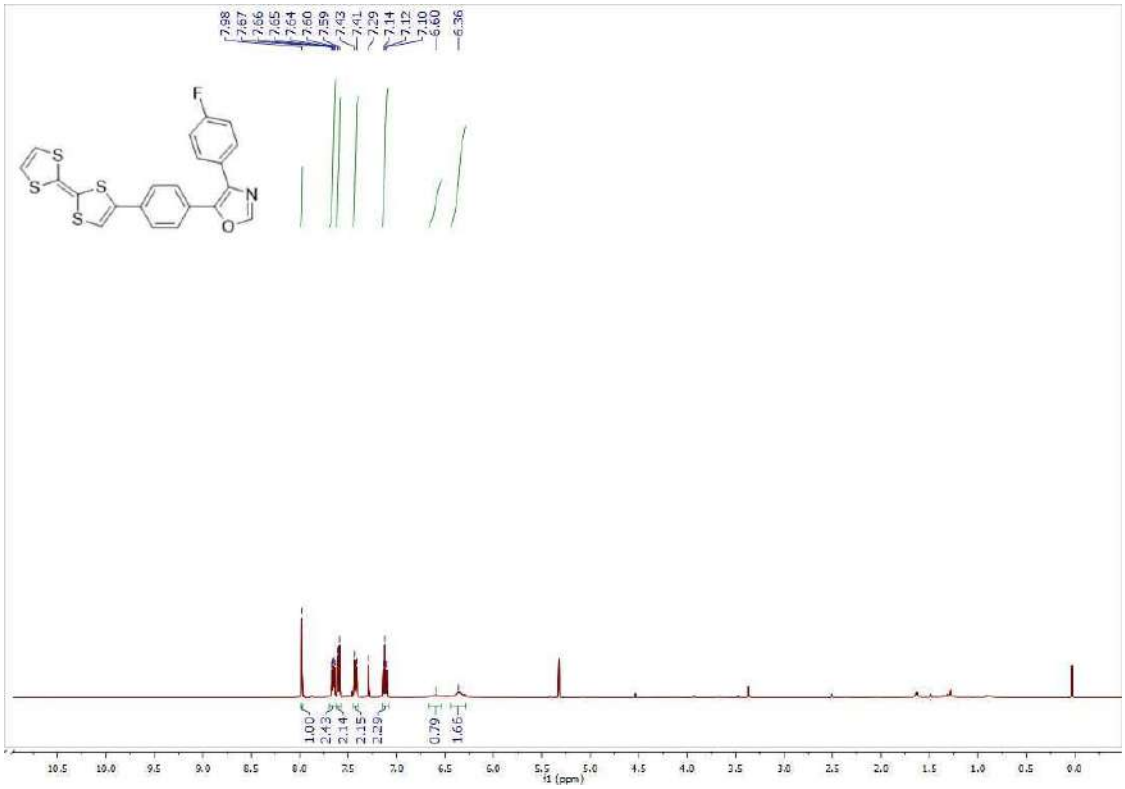
f1 (ppm)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7.10
6.80
6.36
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S
N
O
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2.43
2.14
2.15
2.29
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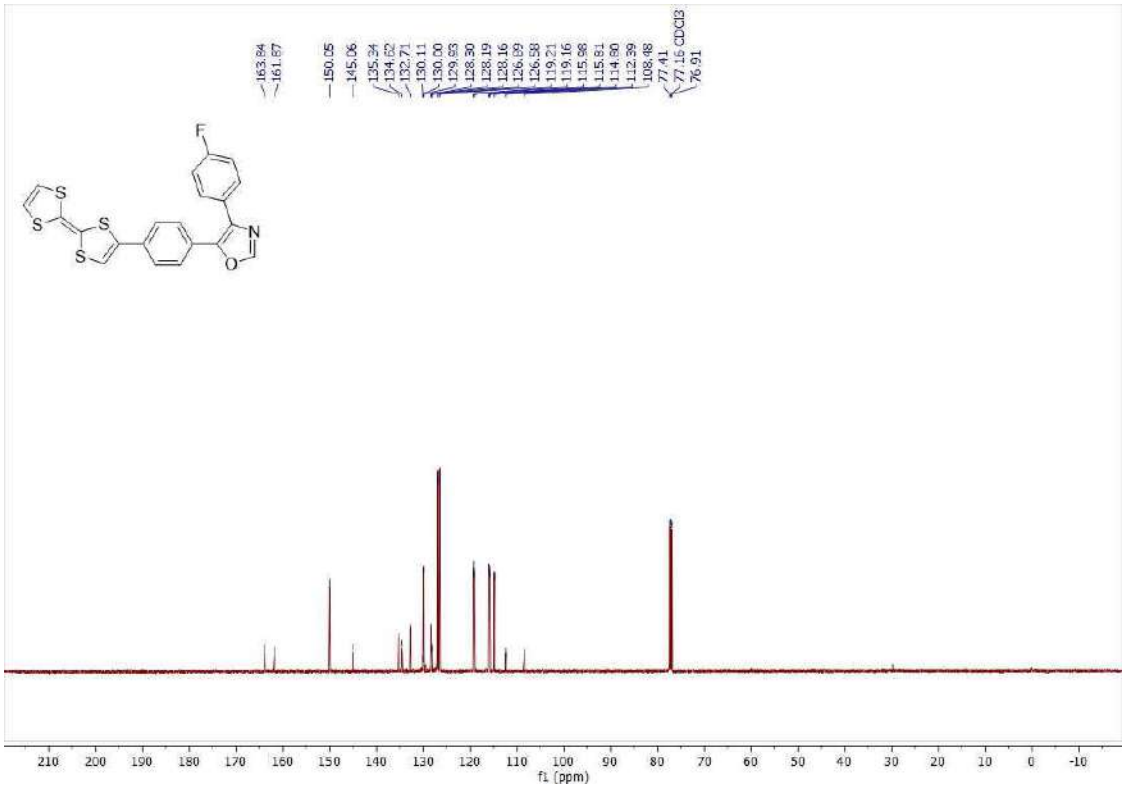
1.65
f1 (ppm)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128.19
128.16
126.89
126.58
119.21
119.16
115.98
115.81
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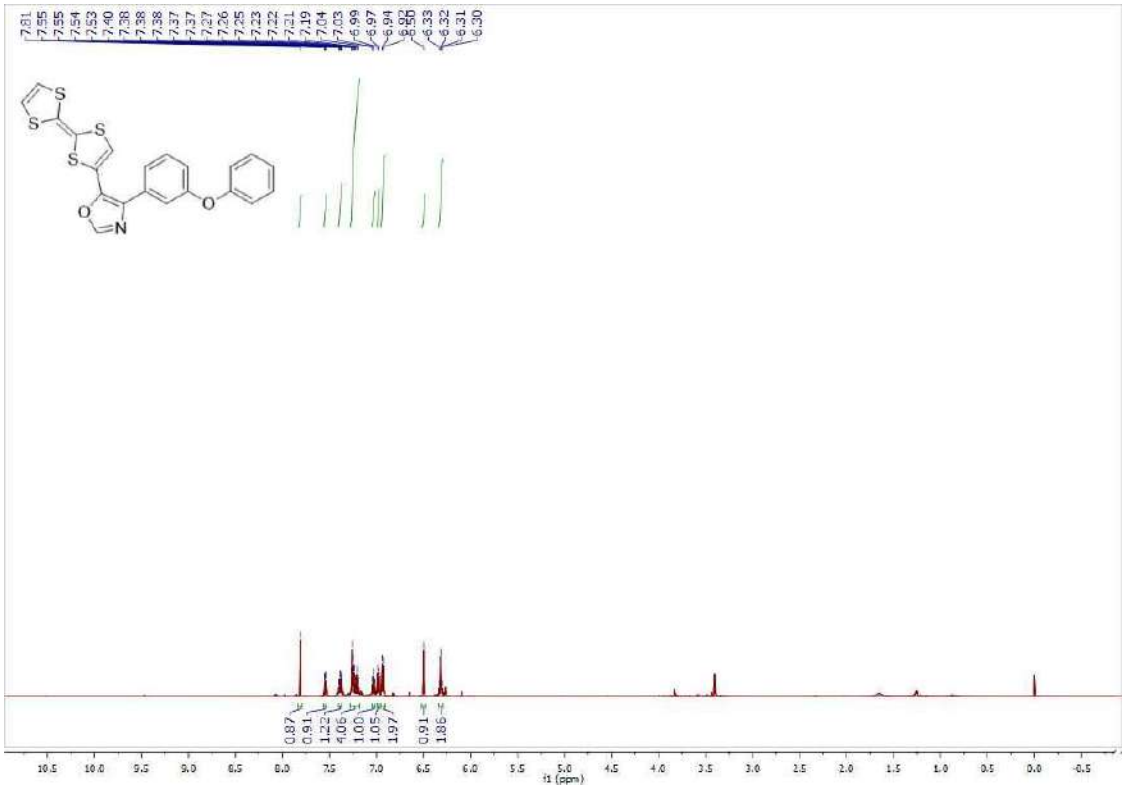
77.41
77.16 CDCl3
76.91
F
S
S
S
S
N
O
f1 (ppm)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7.26
7.25
7.23
7.22
7.21
7.19
7.04
7.03
6.99
6.97
6.94
6.92
6.56
6.33
6.32
6.31
6.30
S
S
S
S
O
N
O
0.87
0.91
1.22
4.06
1.00
1.05
1.97
0.91
1.86
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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2.0
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0.5
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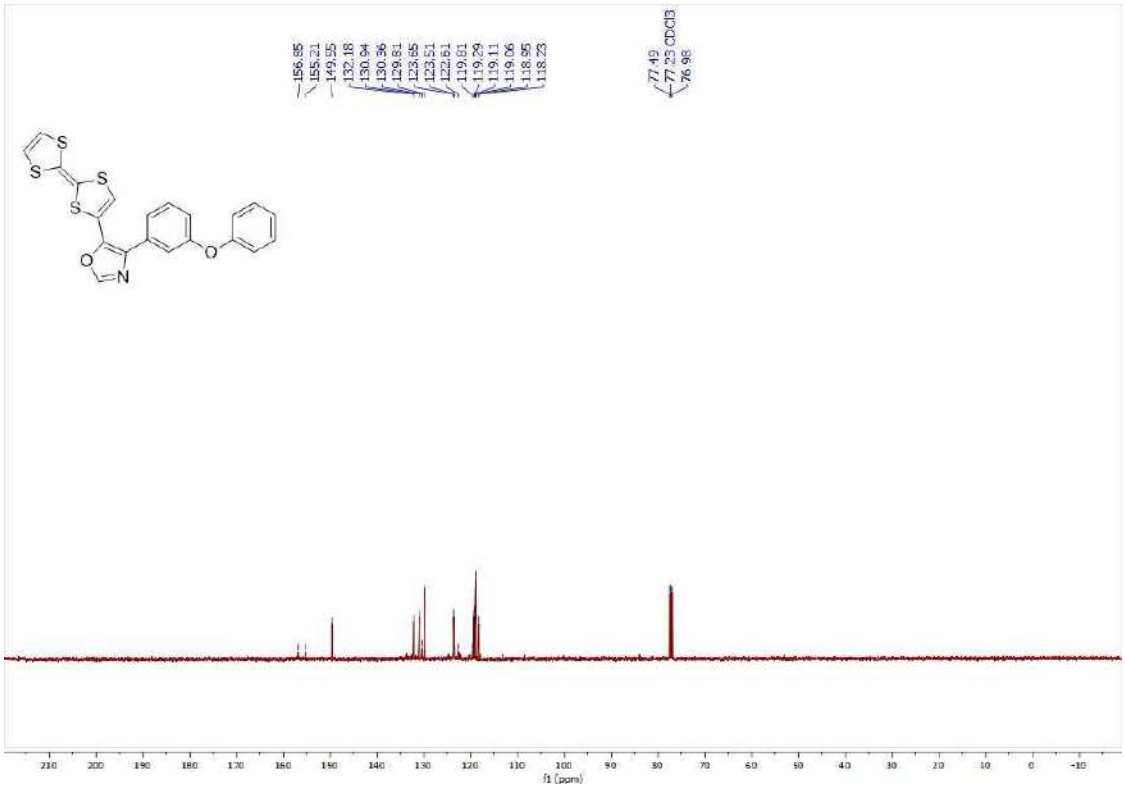
-0.5
f1 (ppm)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123.85
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119.11
119.06
118.95
118.23
77.49
77.23 CDCl3
76.98
S
S
S
S
O
N
O
210
200
190
180
170
160
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120
110
100
90
80
70
60
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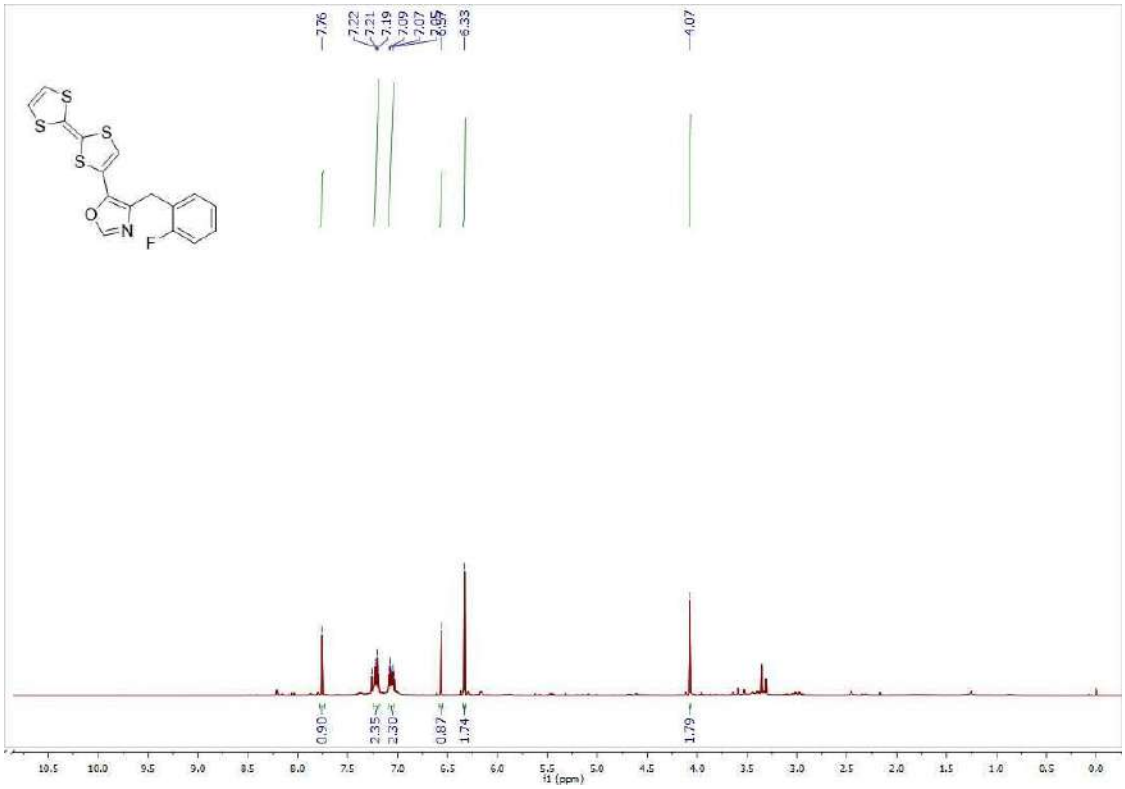
40
30
20
10
0
-10
f1 (ppm)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7.22
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6.33
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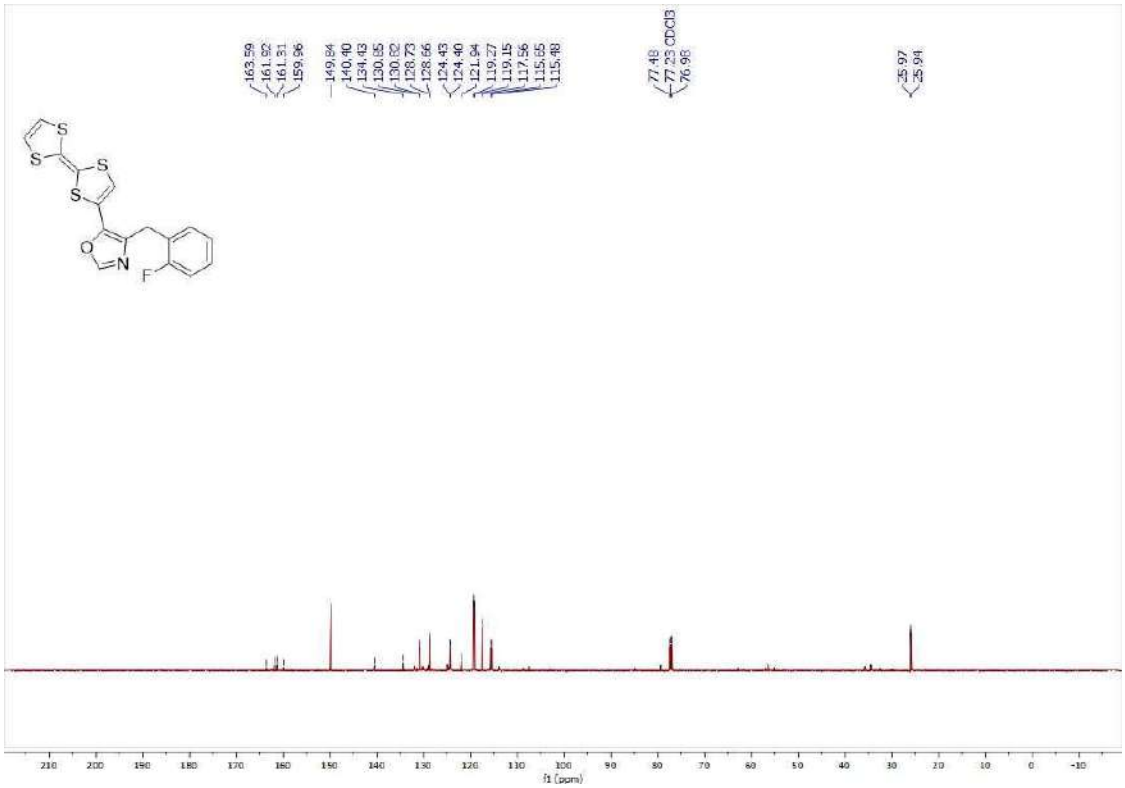
0.90
2.35
2.30
0.87
1.74
1.79
f1 (ppm)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124.40
121.94
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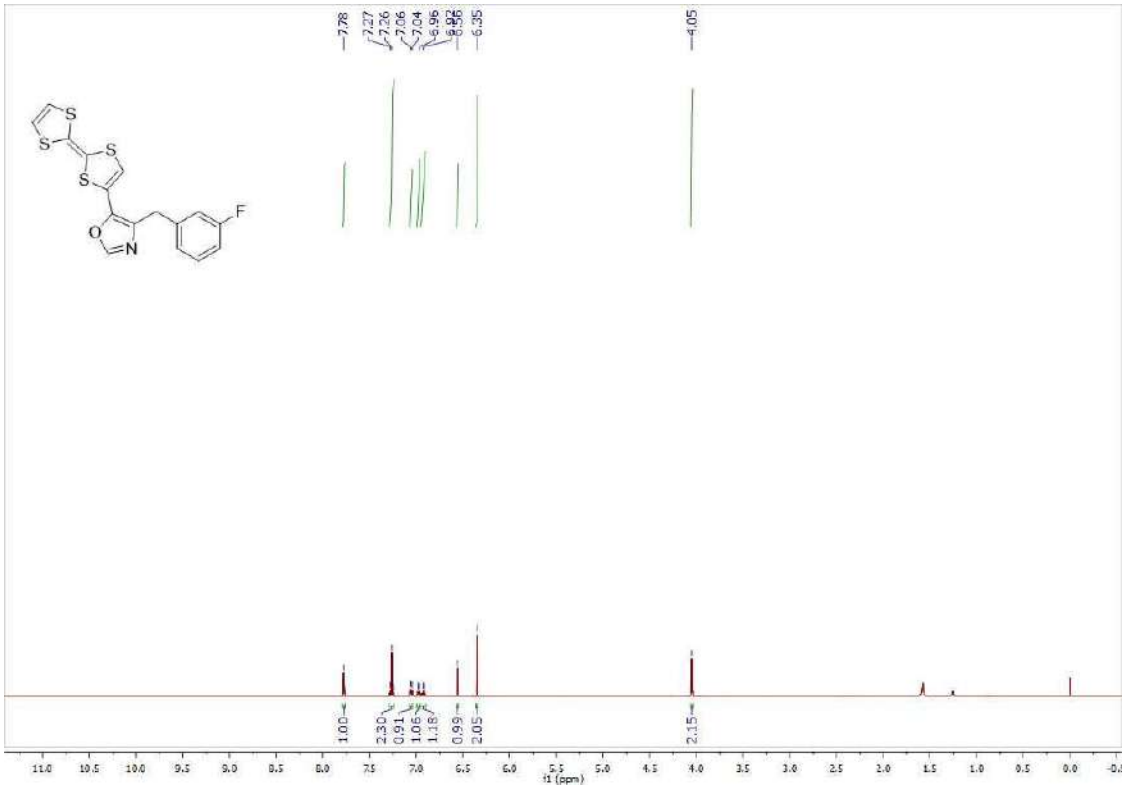
117.56
115.65
115.48
77.48
77.23 CDCl3
76.98
25.97
25.94
f1 (ppm)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7.27
7.26
7.06
7.04
6.96
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6.35
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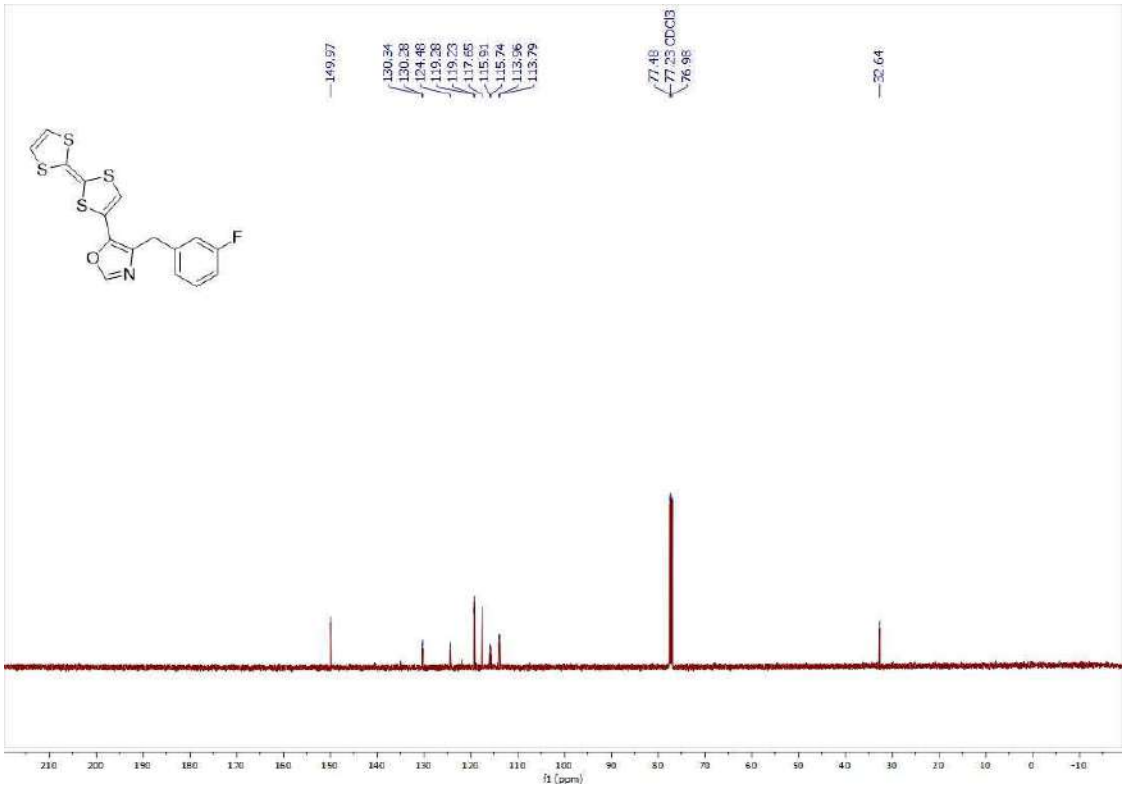
1.00
2.30
0.91
1.06
1.18
0.99
2.05
2.15
f1 (ppm)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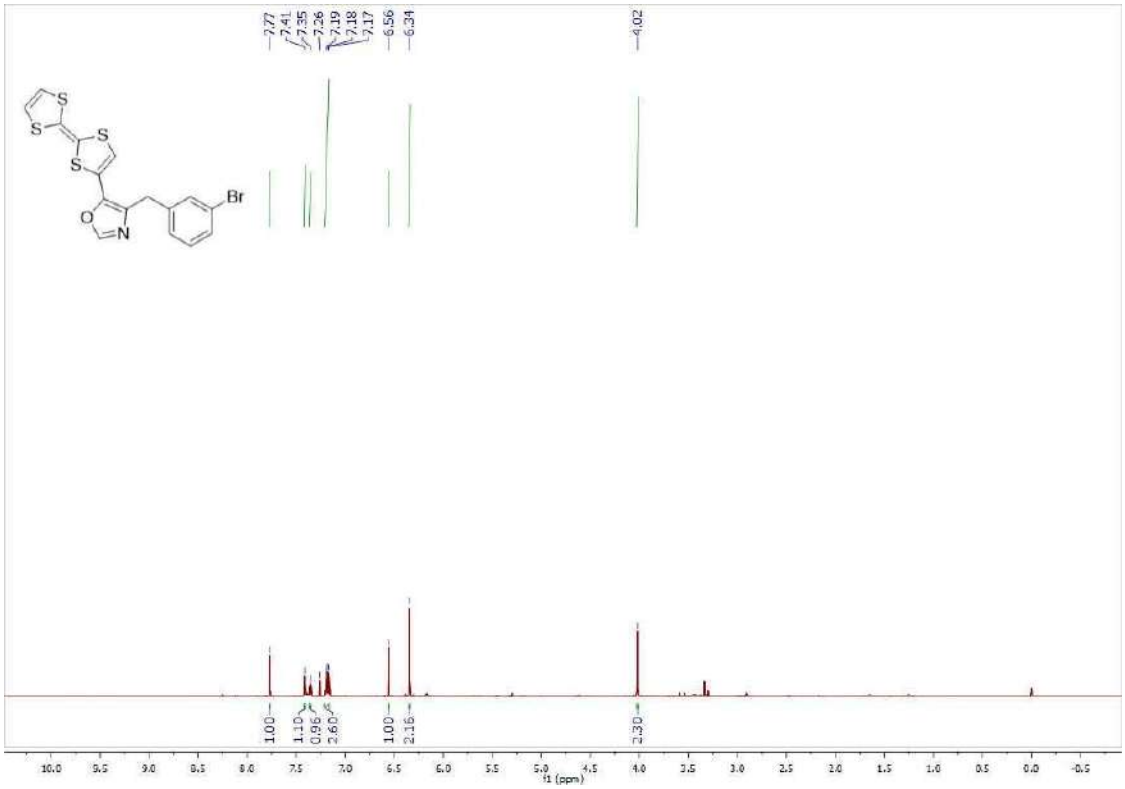
130.34
130.28
124.48
119.28
119.23
117.65
115.91
115.74
113.96
113.79
77.48
77.23 CDCl3
76.98
30.64
f1 (ppm)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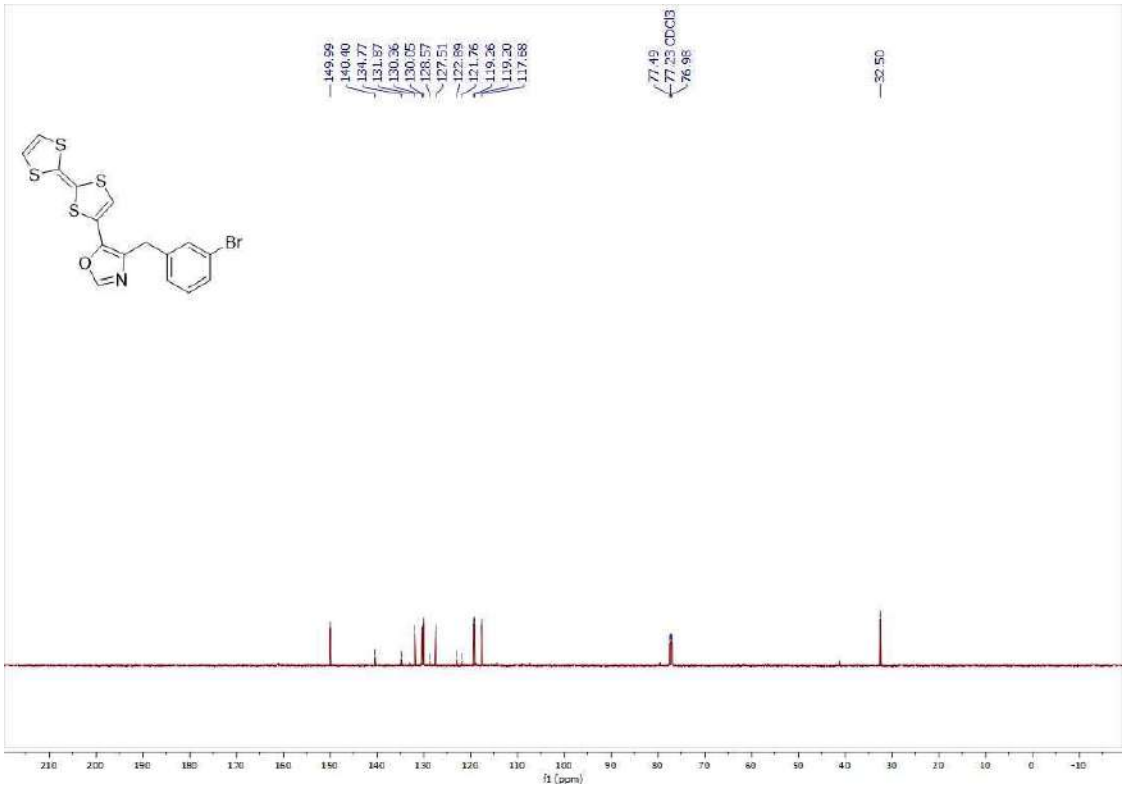
7.35
7.26
7.19
7.18
7.17
6.56
6.34
4.02
Br
1.00
1.10
0.96
2.60
1.00
2.16
2.30
f1 (ppm)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130.36
130.05
128.57
127.51
122.89
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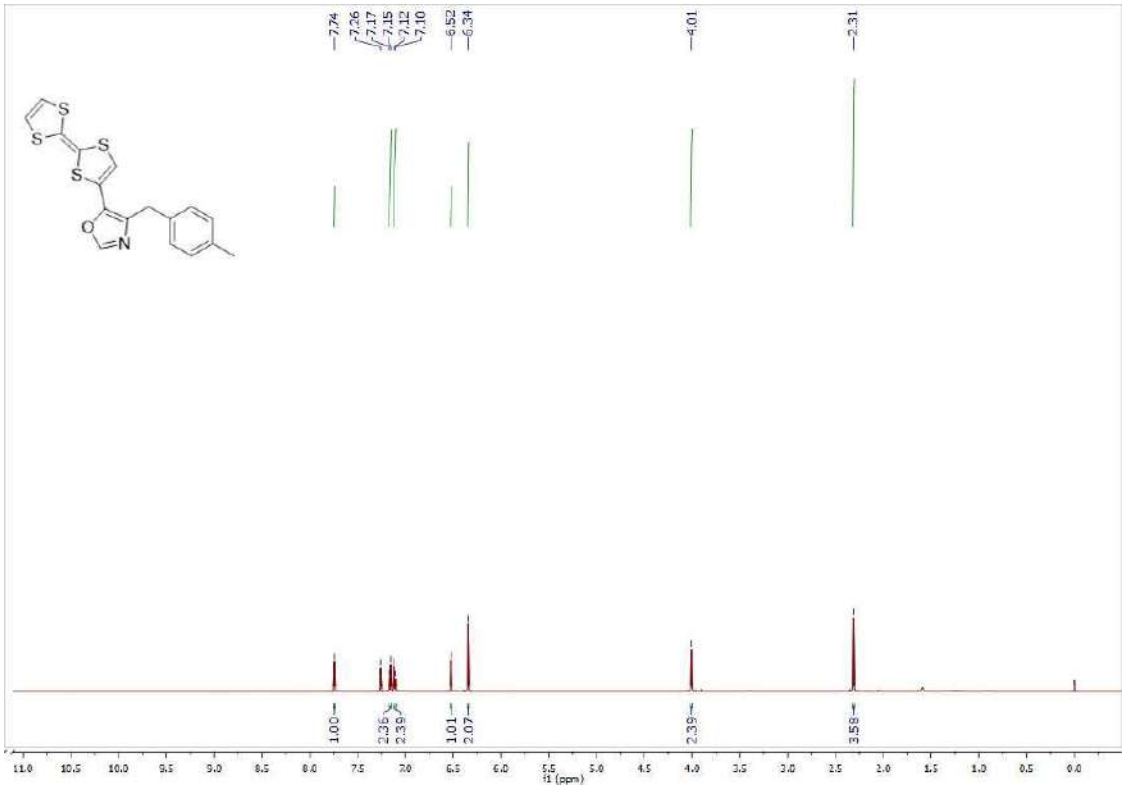
119.26
119.20
117.68
77.49
77.23 CDCl3
76.98
32.50
Br
f1 (ppm)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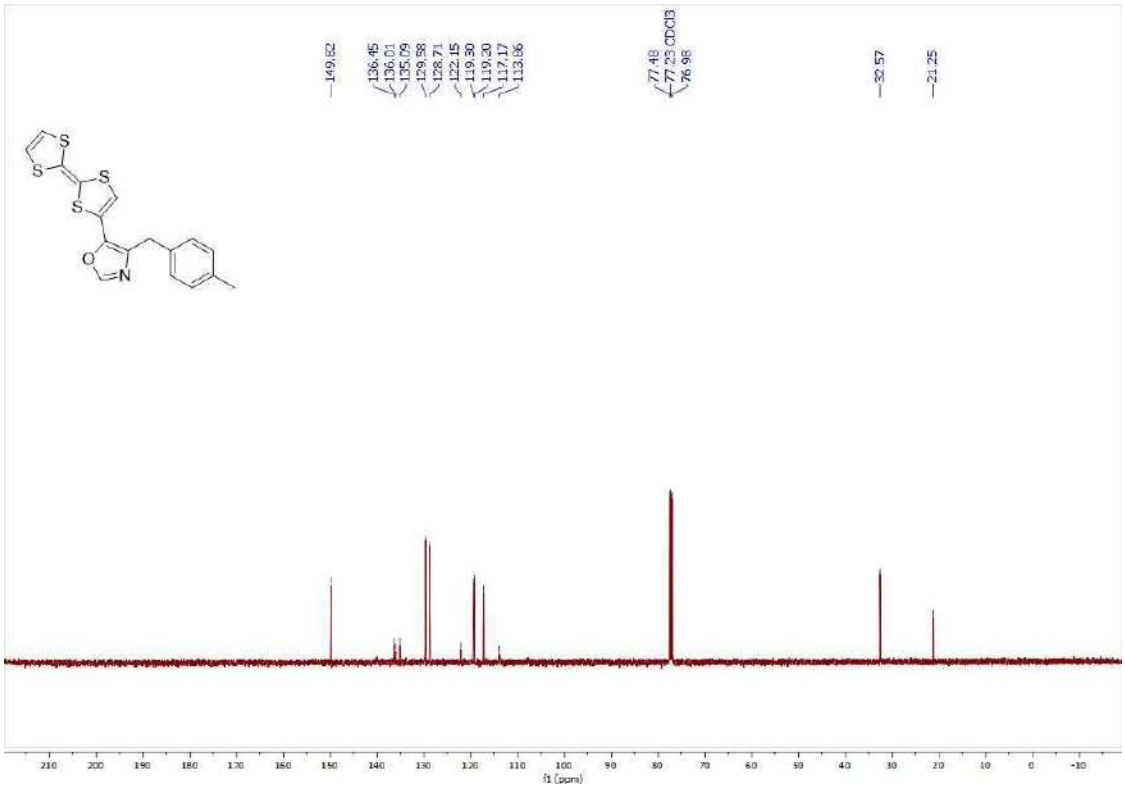
7.26
7.17
7.15
7.12
7.10
6.52
6.34
4.01
2.31
1.00
2.36
2.39
1.01
2.07
2.39
3.58
f1 (ppm)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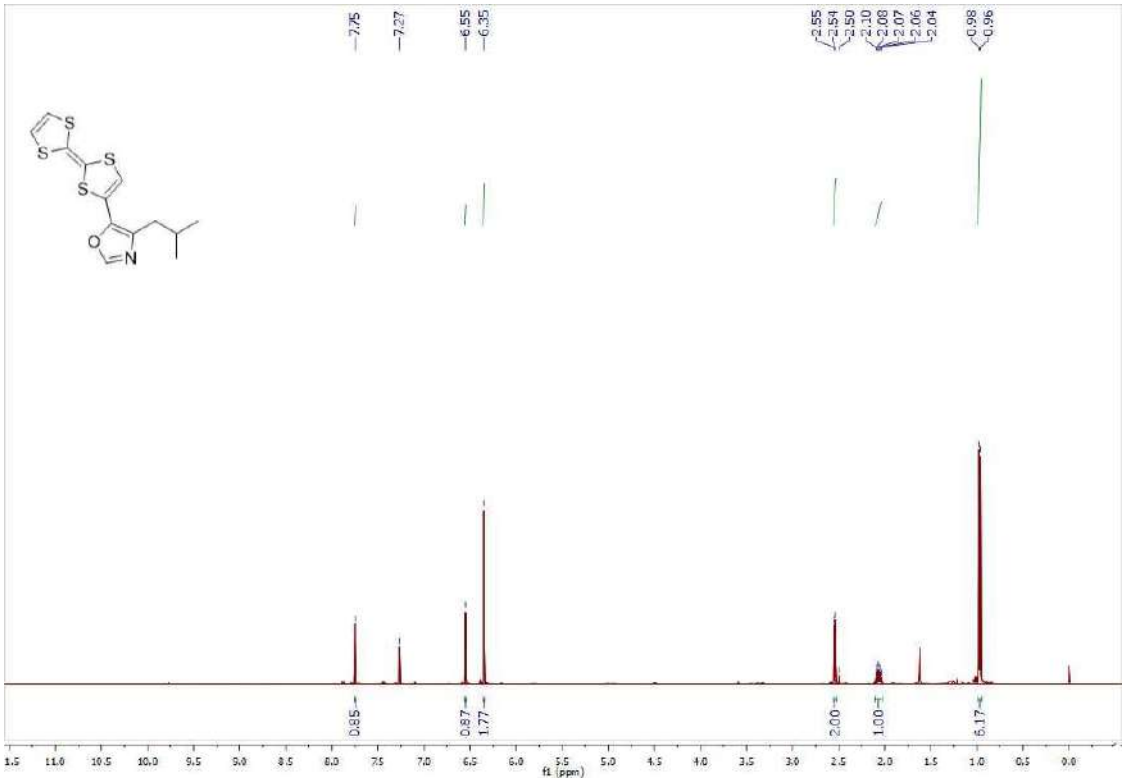
117.17
113.86
77.48
77.23 CDCl3
76.98
32.57
21.25
f1 (ppm)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7.27
6.55
6.35
2.55
2.54
2.50
2.10
2.08
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2.06
2.04
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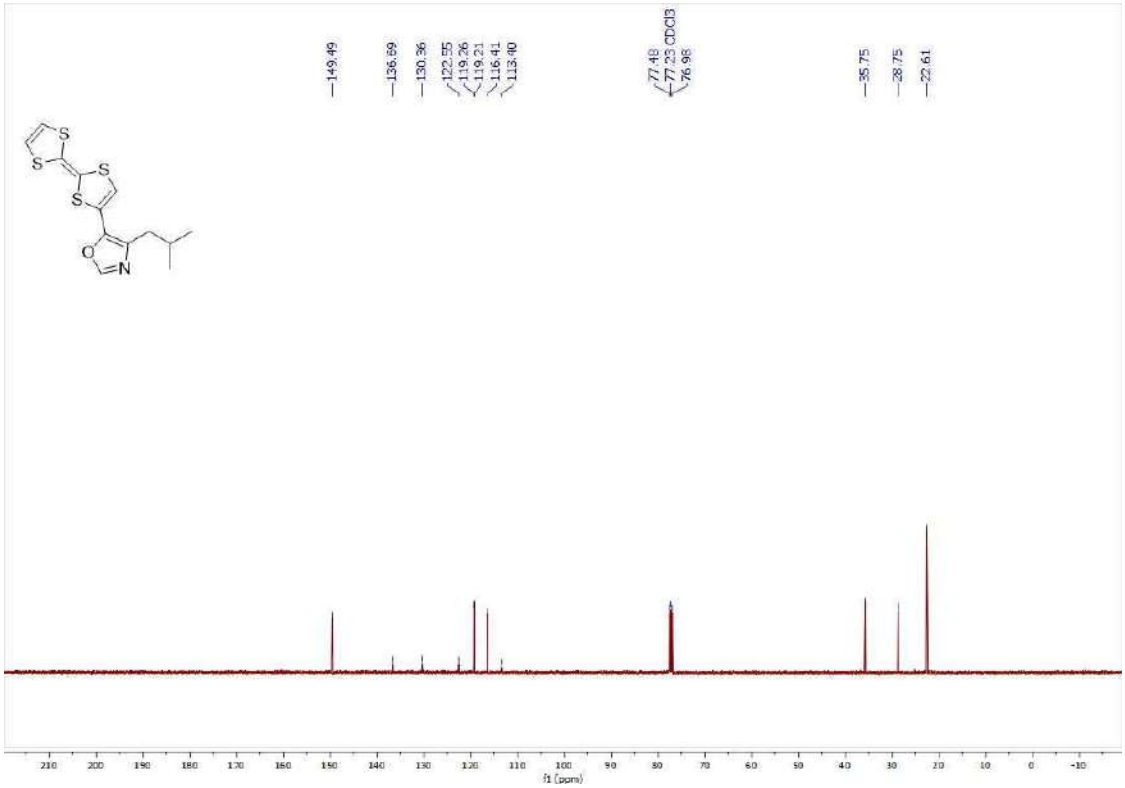
0.96
0.85
0.87
1.77
2.00
1.00
6.17
f1 (ppm)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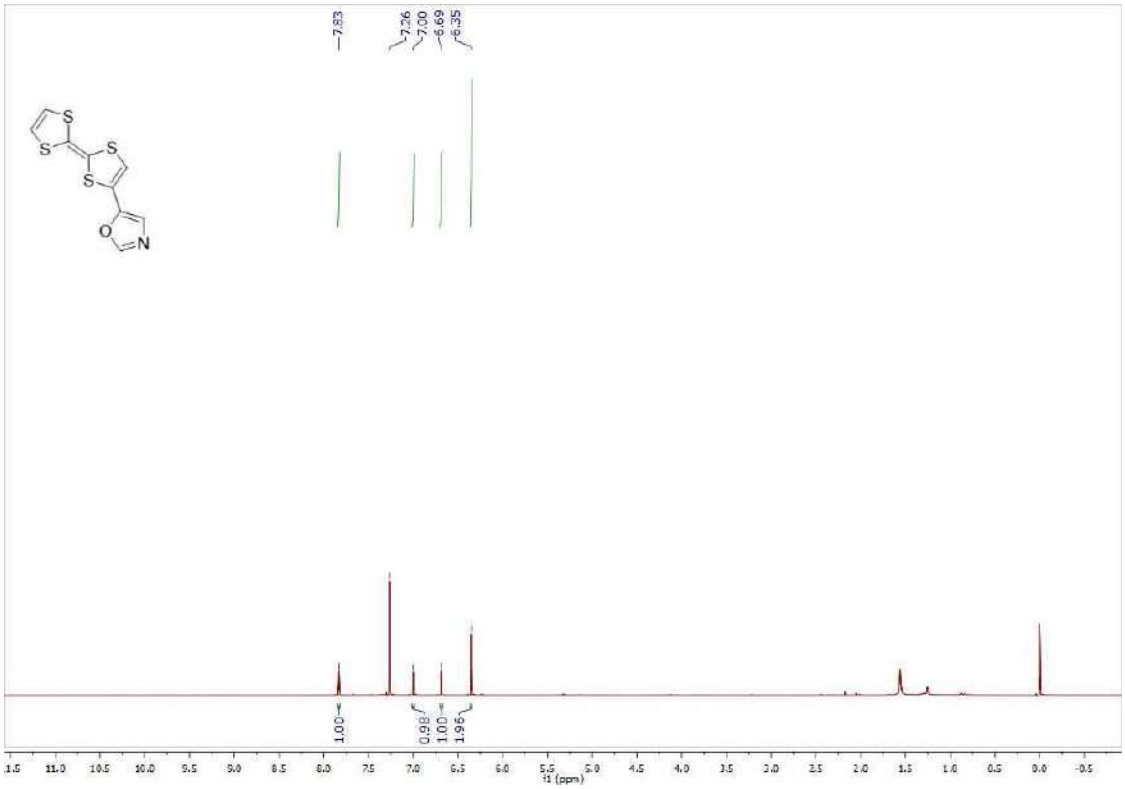
119.21
116.41
113.40
77.48
77.23 CDCl3
76.98
35.75
28.75
22.61
f1 (ppm)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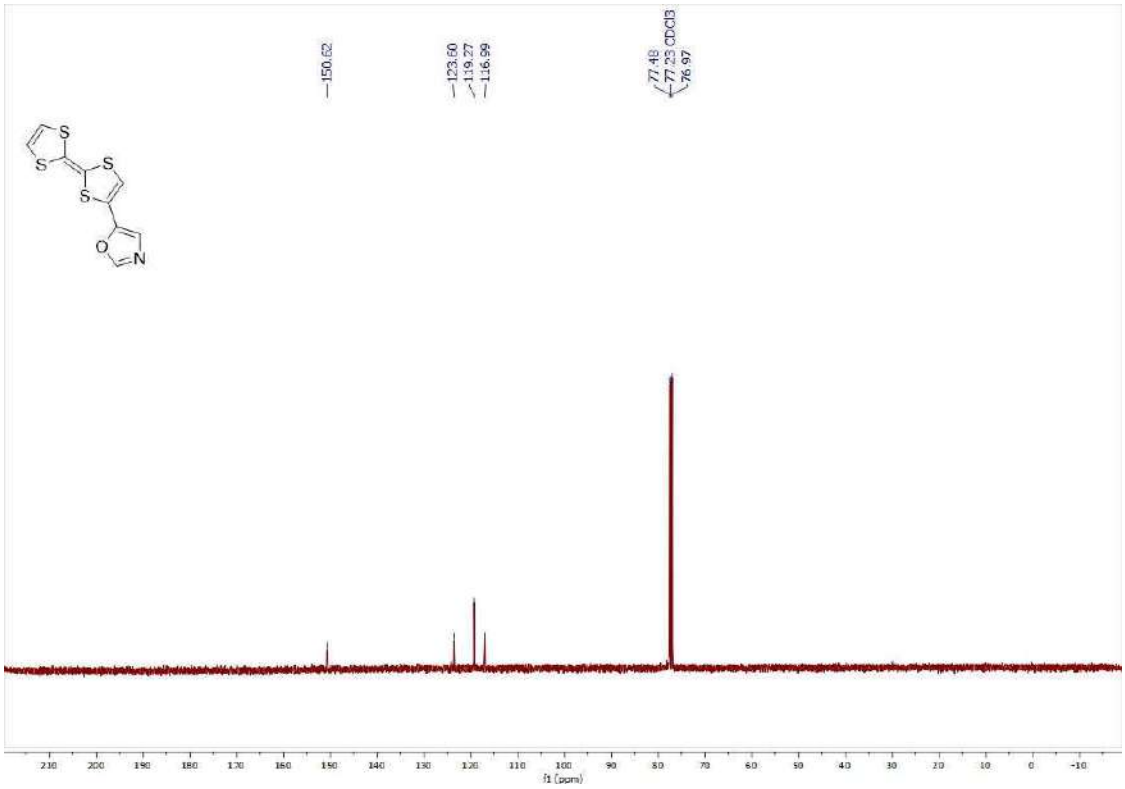
6.69
6.35
1.00
0.98
1.00
1.96
f1 (ppm)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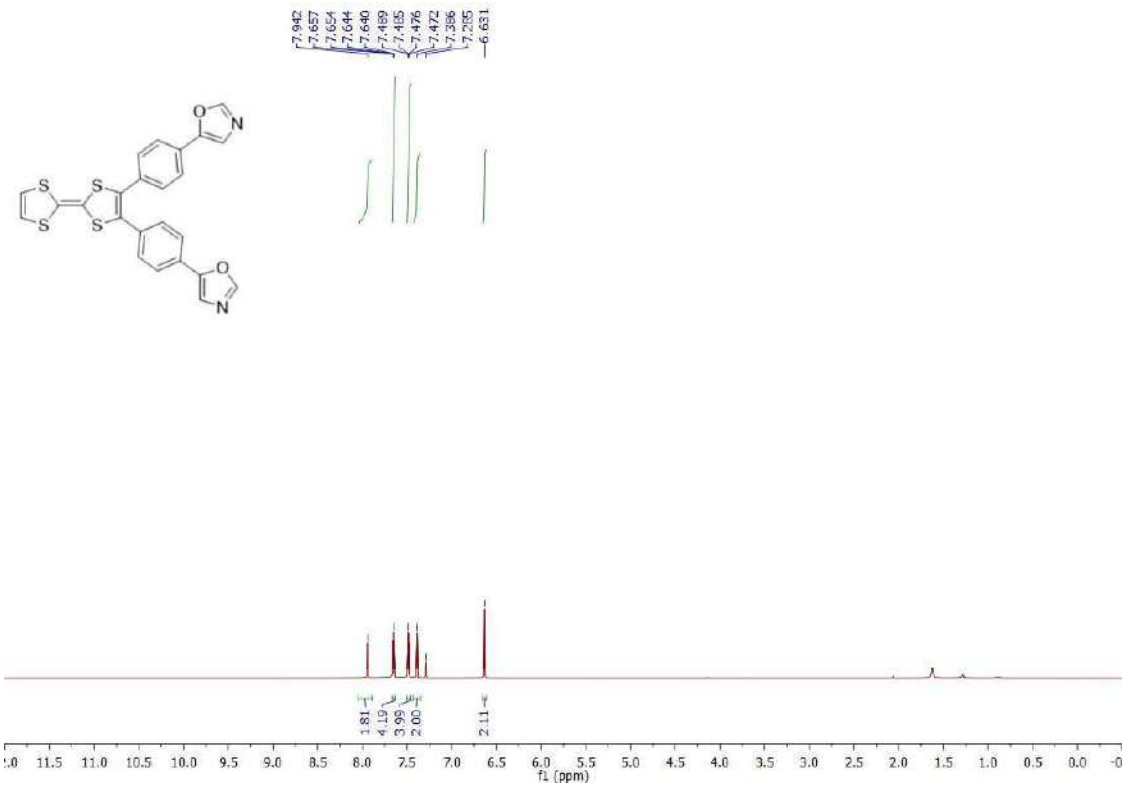
116.99
77.48
77.23 CDCl3
76.97
f1 (ppm)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7.644
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7.485
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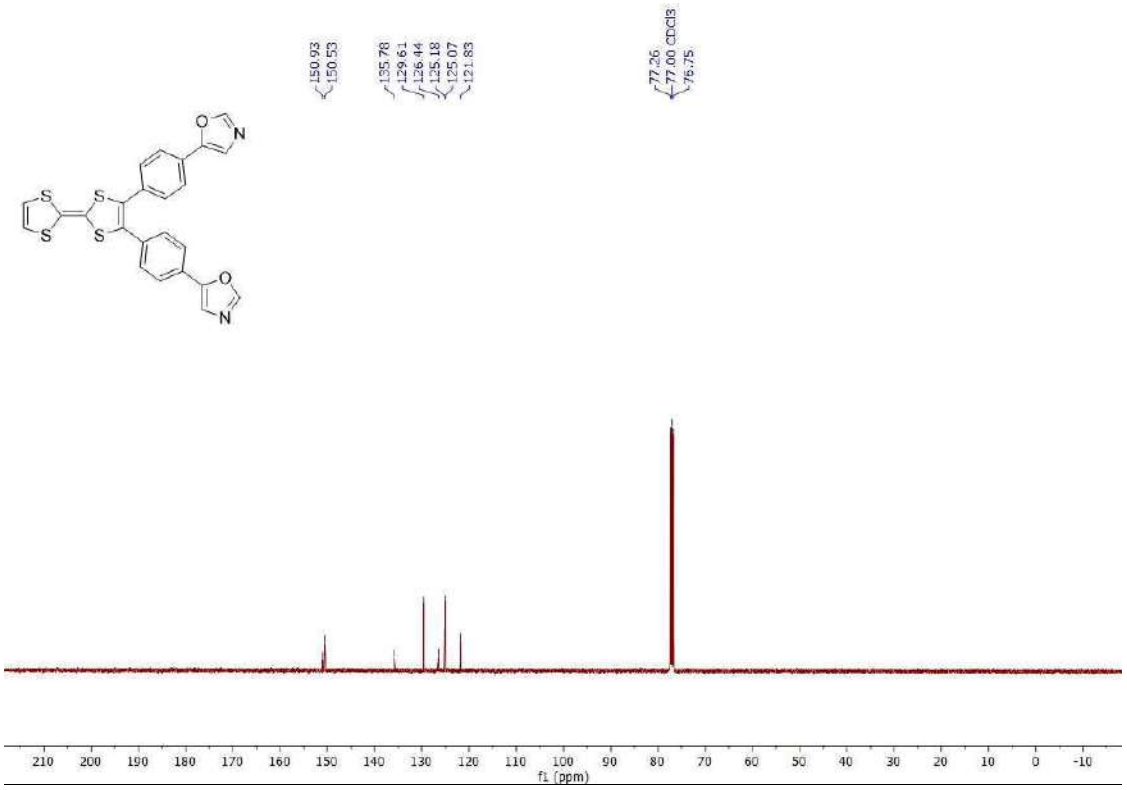
7.386
7.285
6.631
1.81
4.19
3.99
2.00
2.11
f1 (ppm)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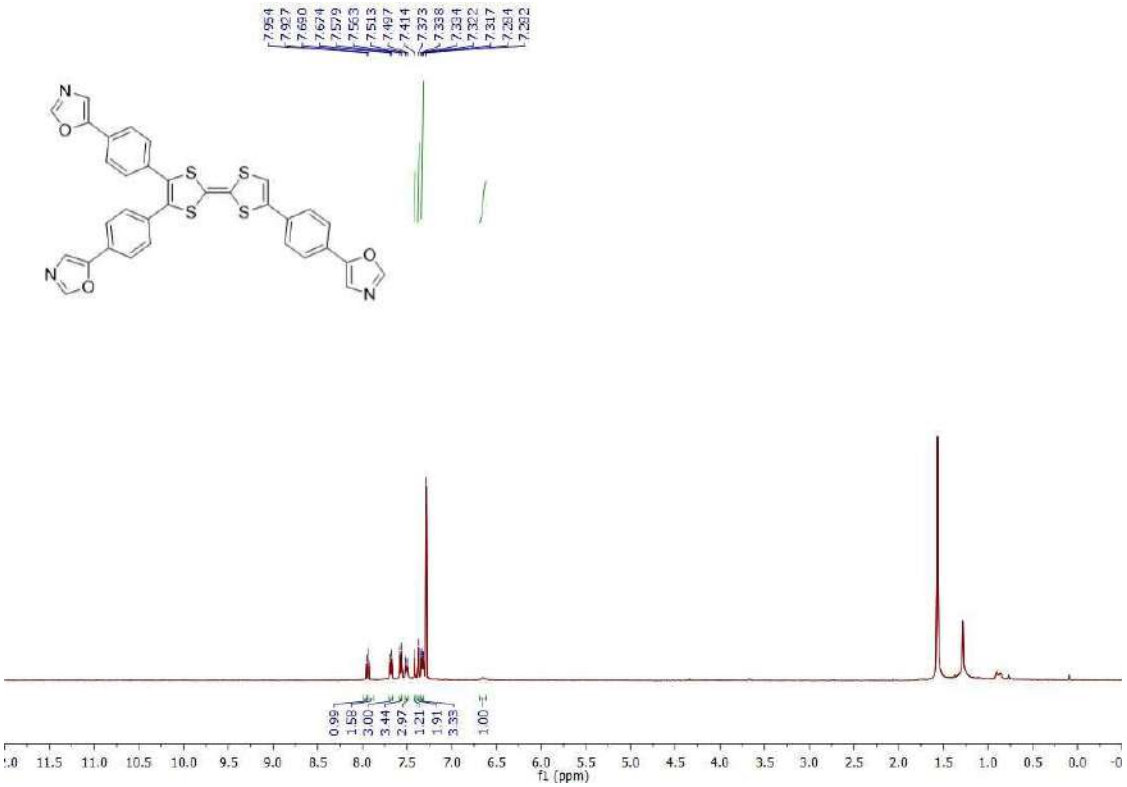
126.44
125.18
125.07
121.83
77.26
77.00 CDCl3
76.75
f1 (ppm)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7.497
7.414
7.373
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7.334
7.322
7.317
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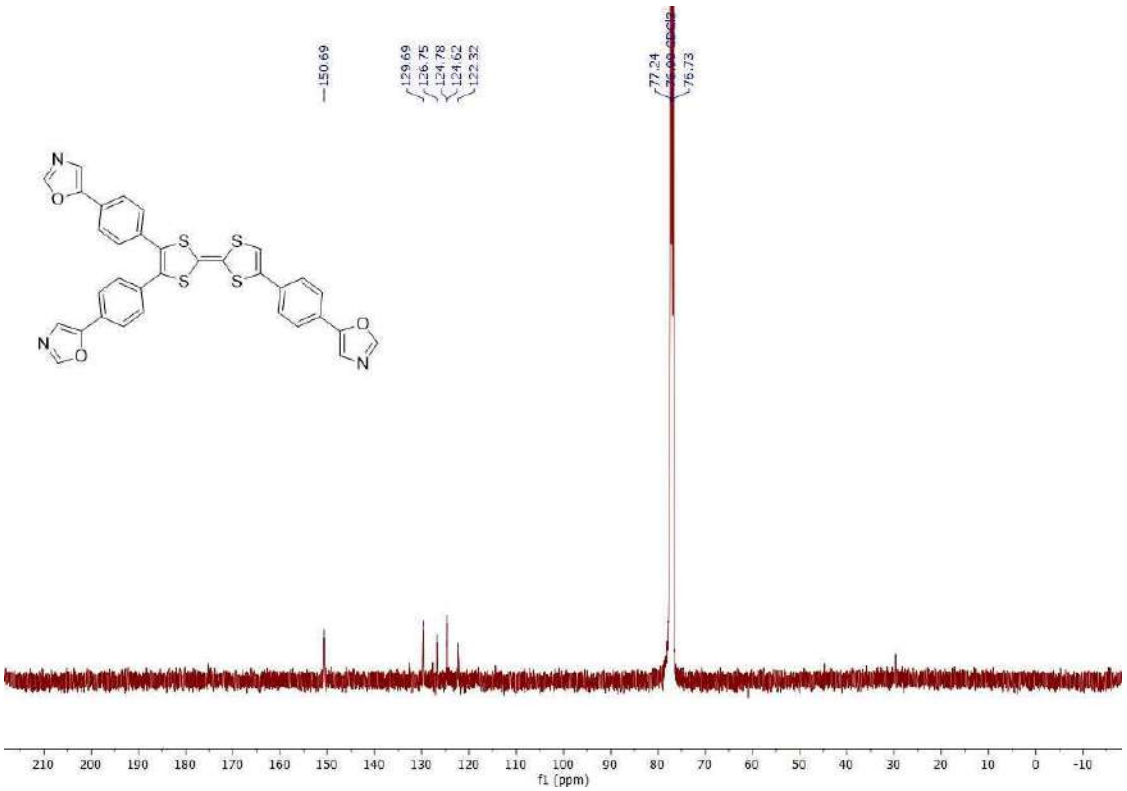
3.00
3.44
2.97
1.21
1.91
3.33
1.00
f1 (ppm)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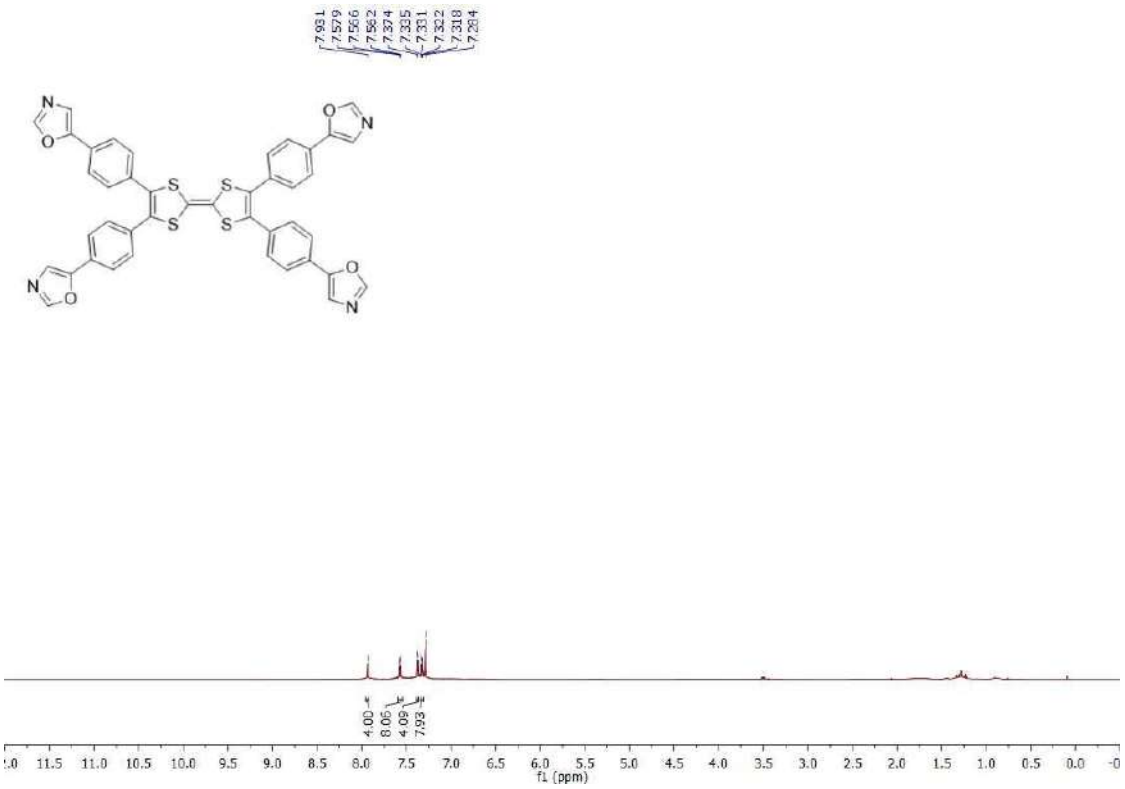
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7.294
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8.05
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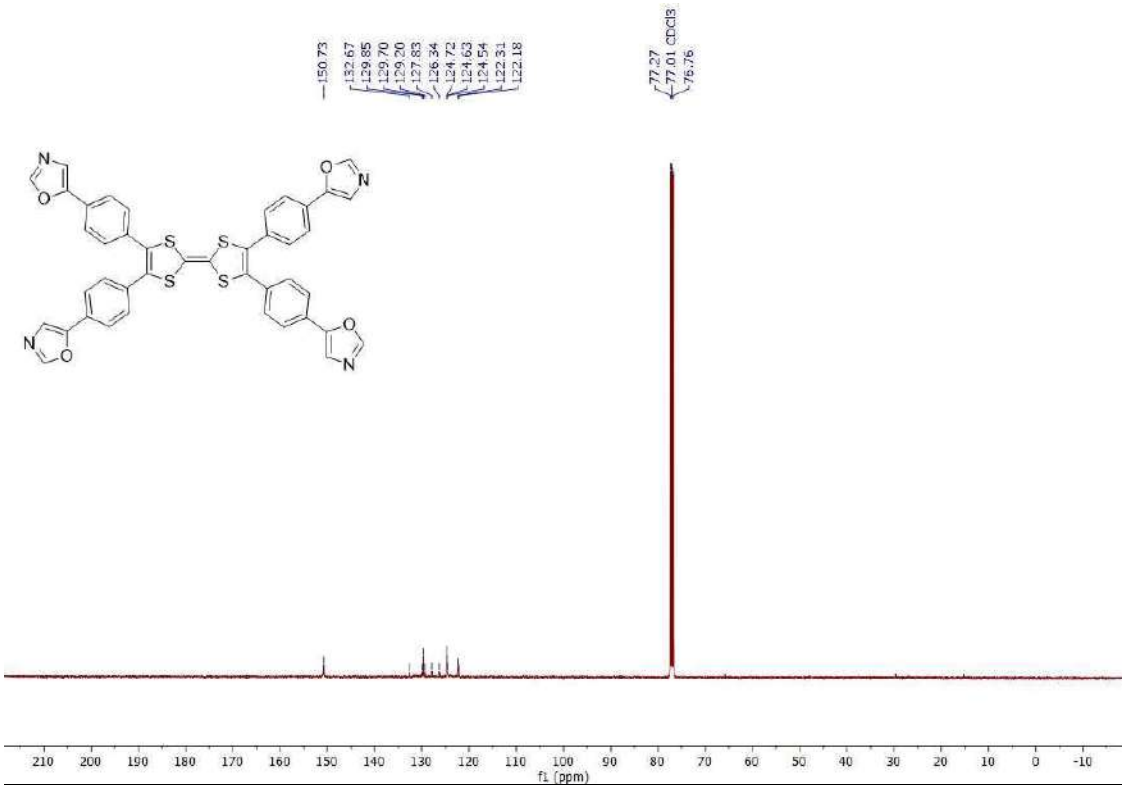
7.93
f1 (ppm)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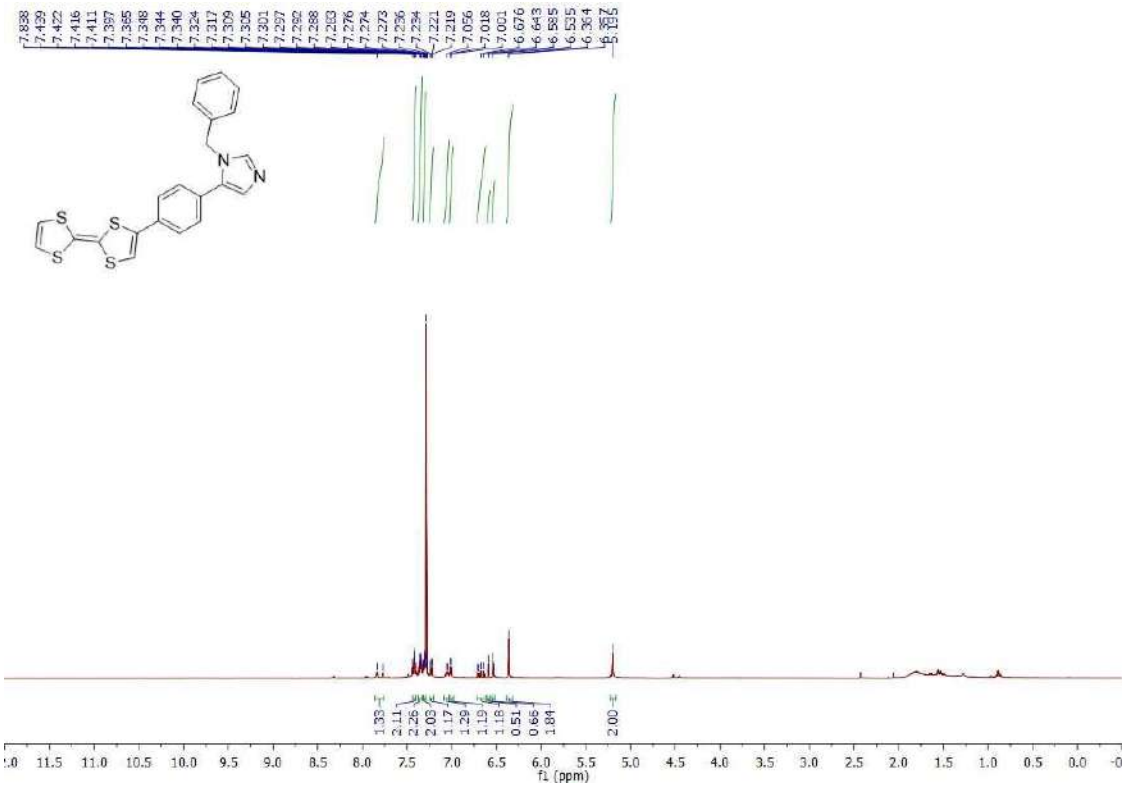
122.18
77.27
77.01
CDCl3
76.76
f1 (ppm)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7.234
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6.364
6.357
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1.33
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1.29
1.19
1.18
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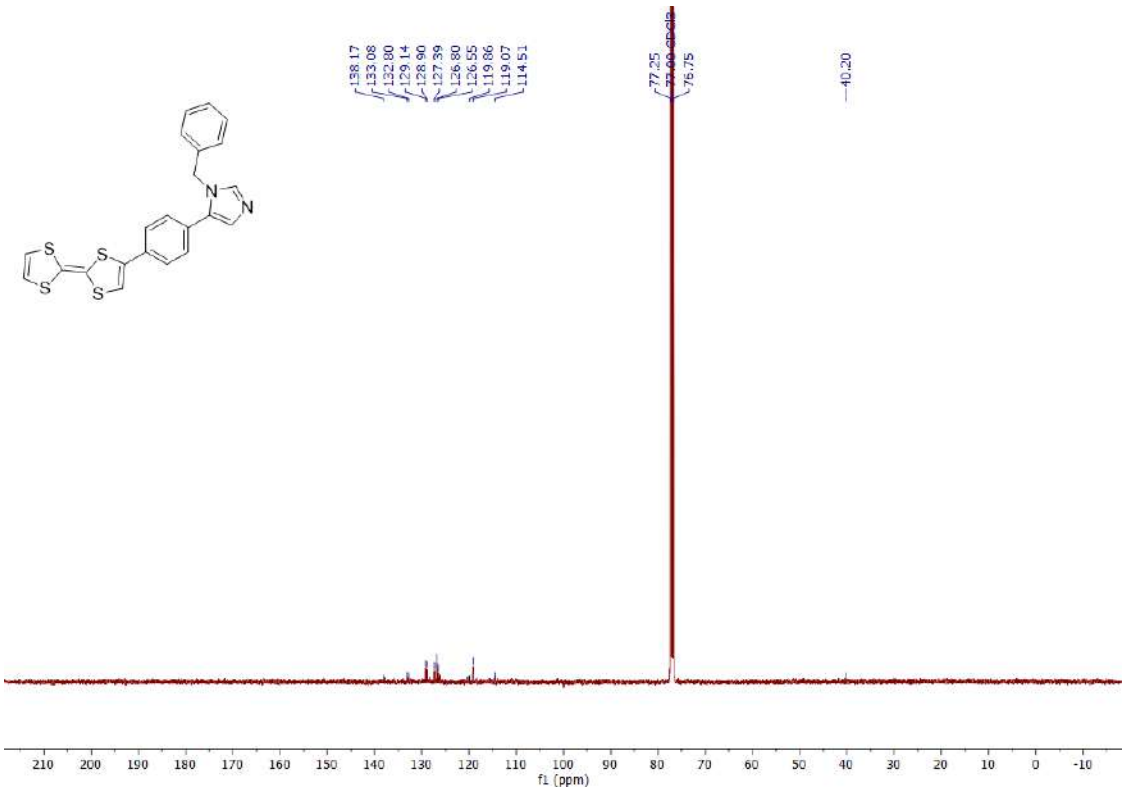
2.00
f1 (ppm)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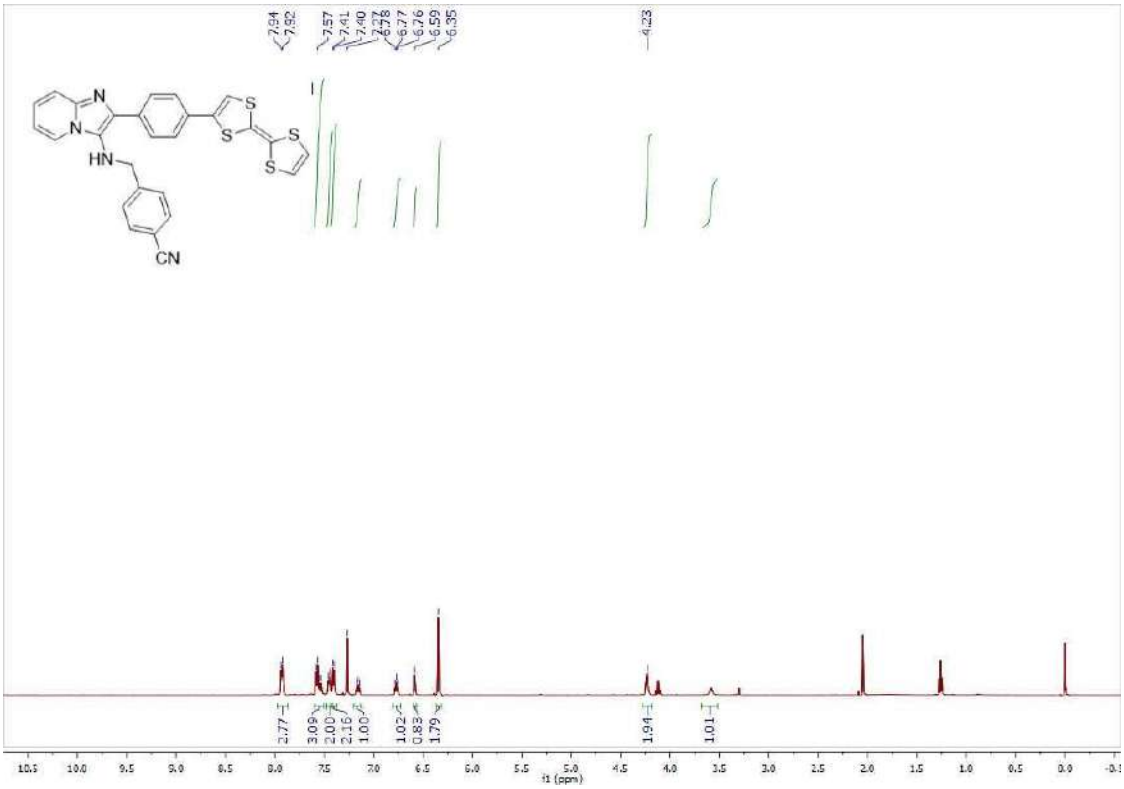
76.75
40.20
f1 (ppm)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6.77
6.76
6.59
6.35
4.23
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CN
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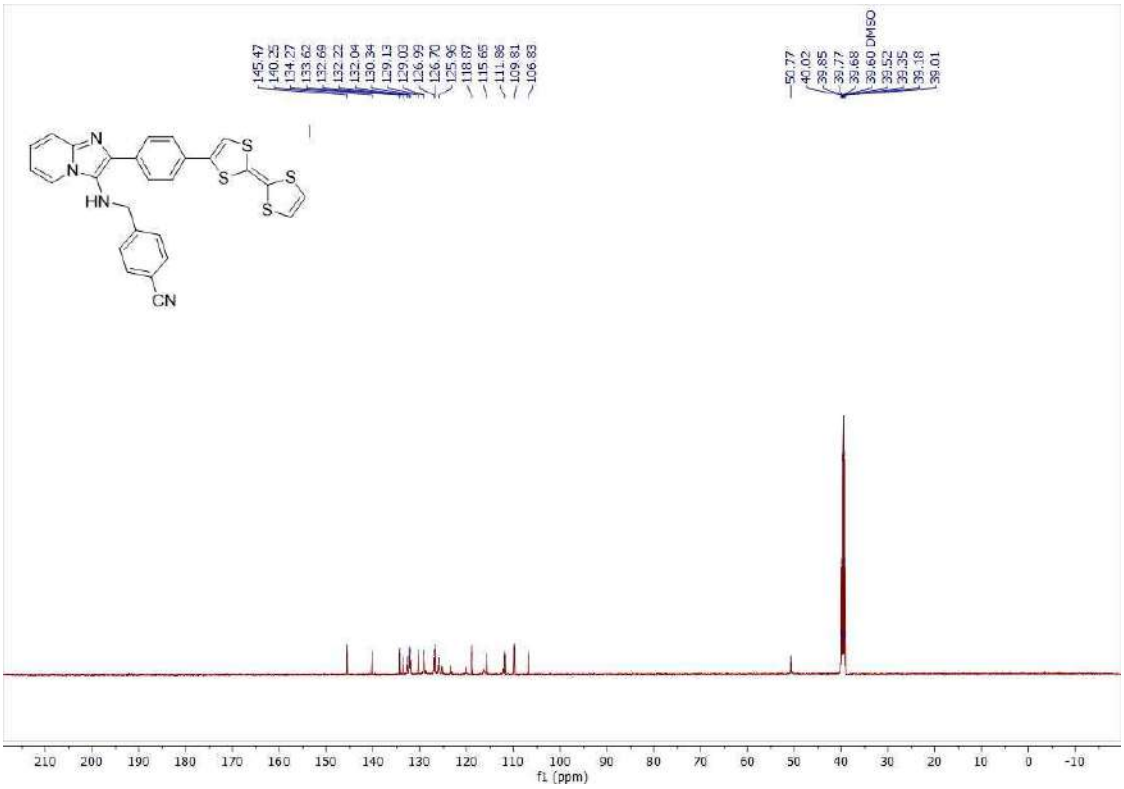
1.79
1.94
1.01
f1 (ppm)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109.81
106.83
50.77
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39.18
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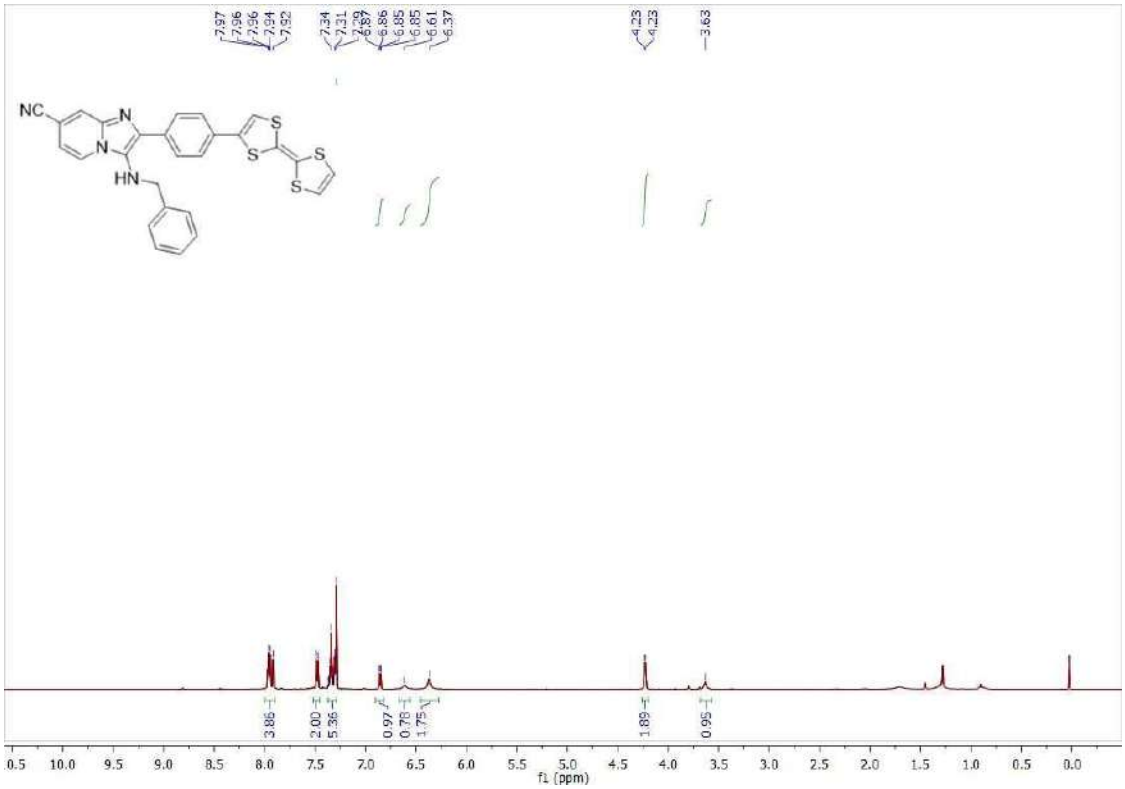
HN
CN
f1 (ppm)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6.85
6.61
6.37
4.23
4.23
3.63
NC
N
N
HN
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S
S
S
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2.00
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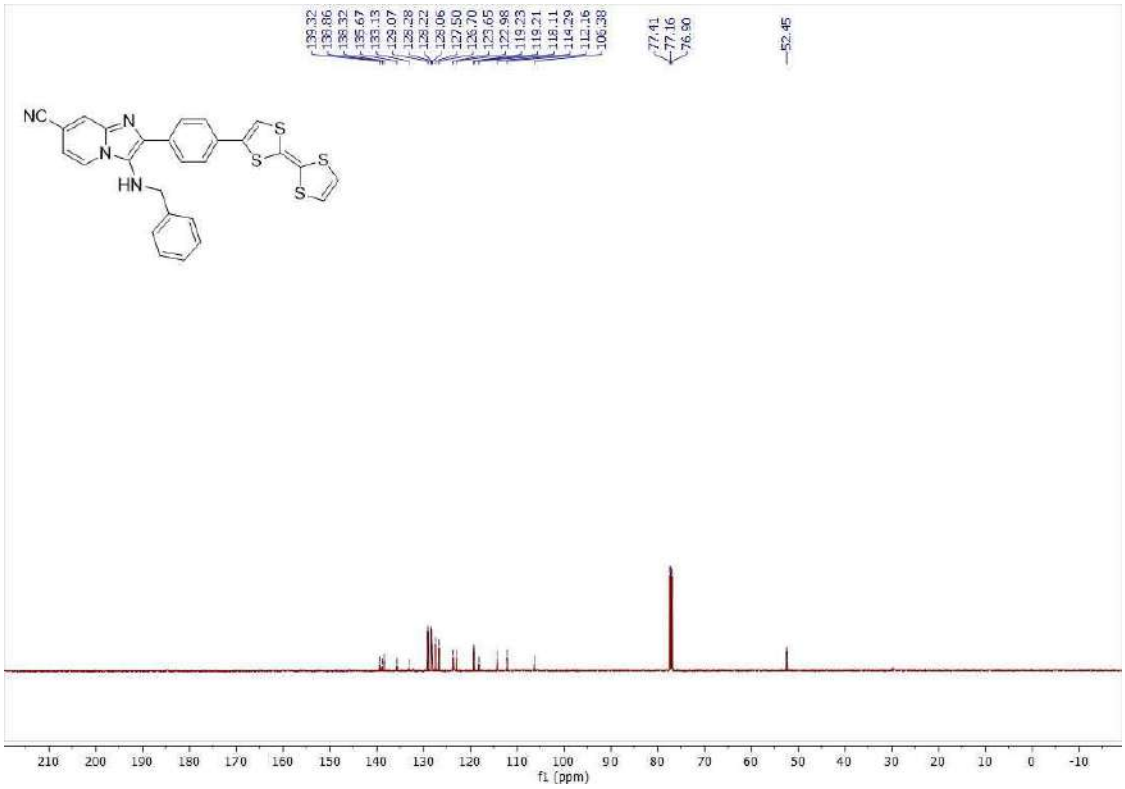
1.89
0.95
f1 (ppm)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122.98
119.23
119.21
118.11
114.29
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77.16
76.90
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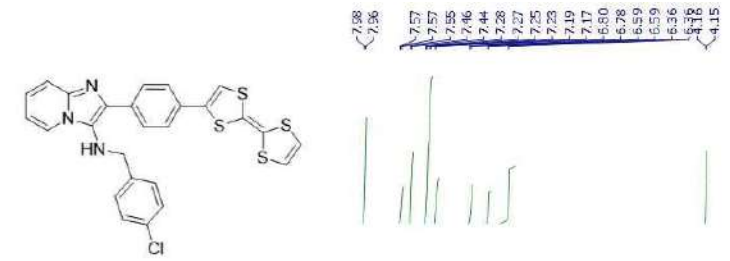
NC
N
N
HN
S
S
S
S
f1 (ppm)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7.19
7.17
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6.59
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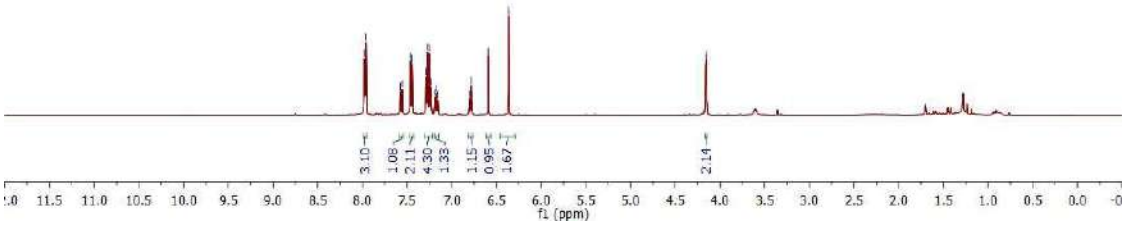
6.36
4.16
4.15
N
N
HN
S
S
S
S
Cl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9.5
9.0
8.5
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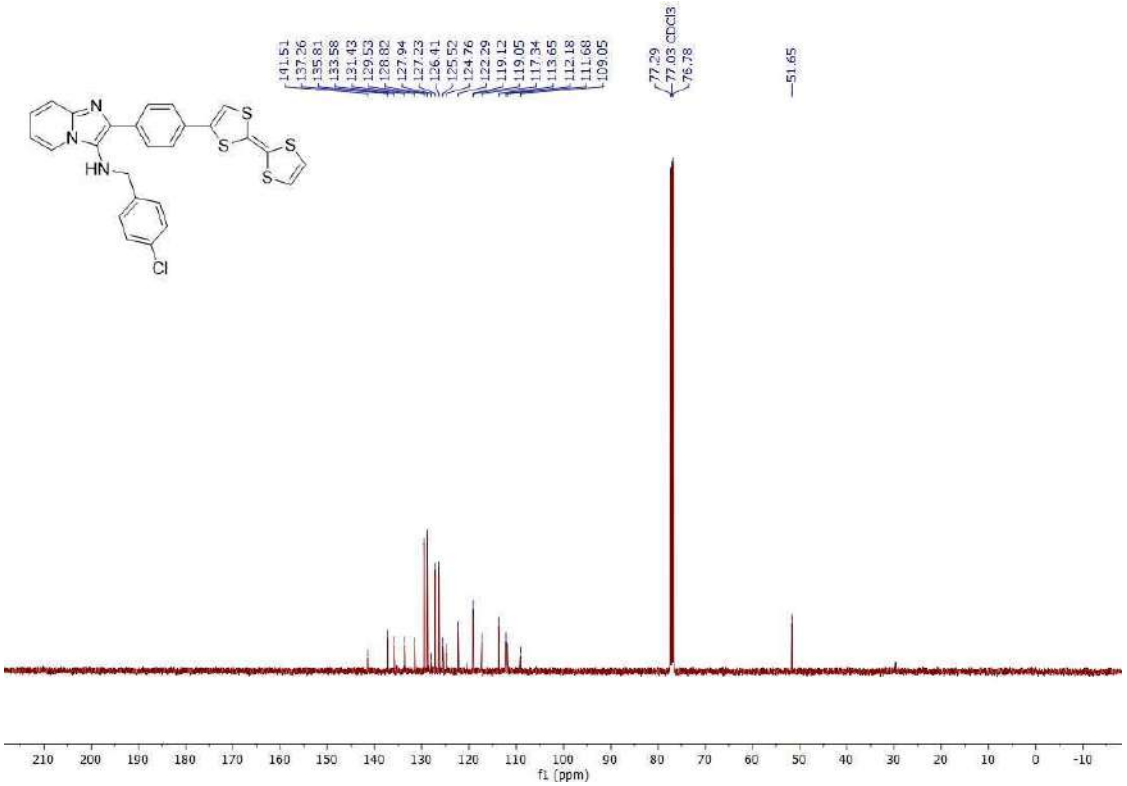
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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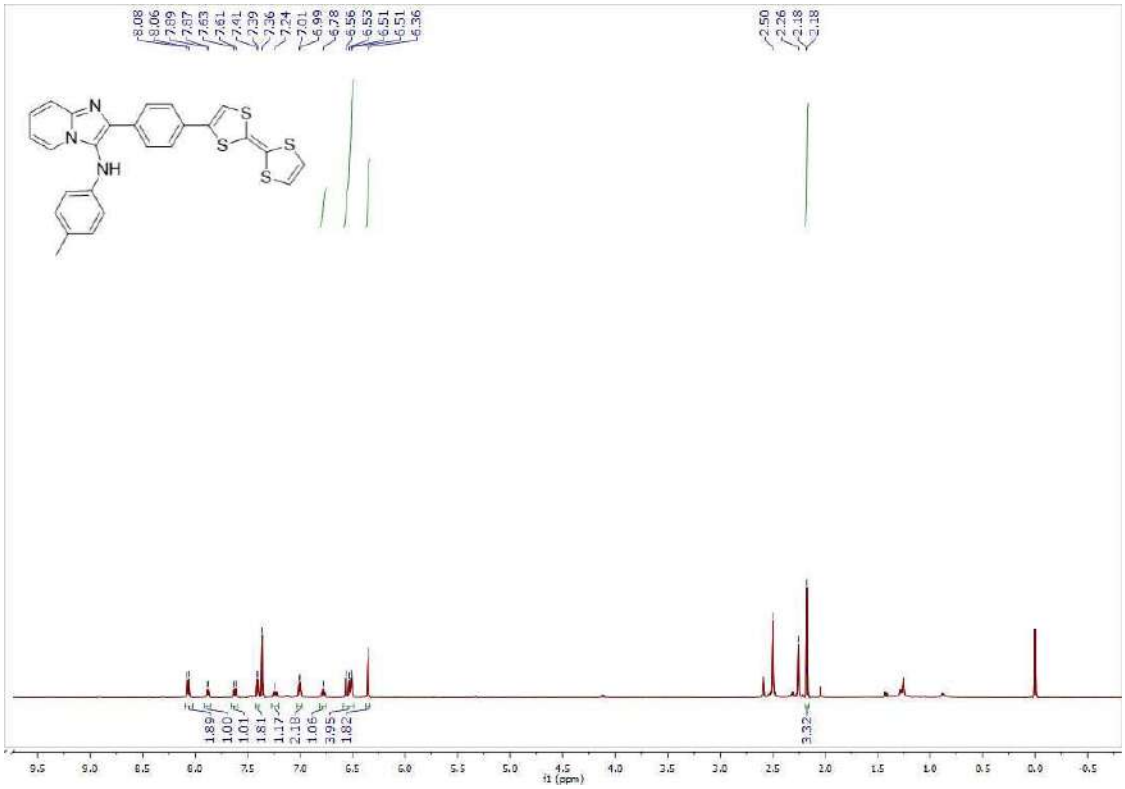
137.26
135.81
133.58
131.43
129.53
128.82
127.94
127.23
126.41
125.52
124.76
122.29
119.12
119.05
117.34
113.65
112.18
111.68
109.05
77.29
77.03
CDCl3
76.78
51.65
N
N
HN
S
S
S
S
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.06
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7.87
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7.61
7.41
7.39
7.36
7.24
7.01
6.99
6.78
6.56
6.53
6.51
6.51
6.36
2.50
2.26
2.18
2.18
NH
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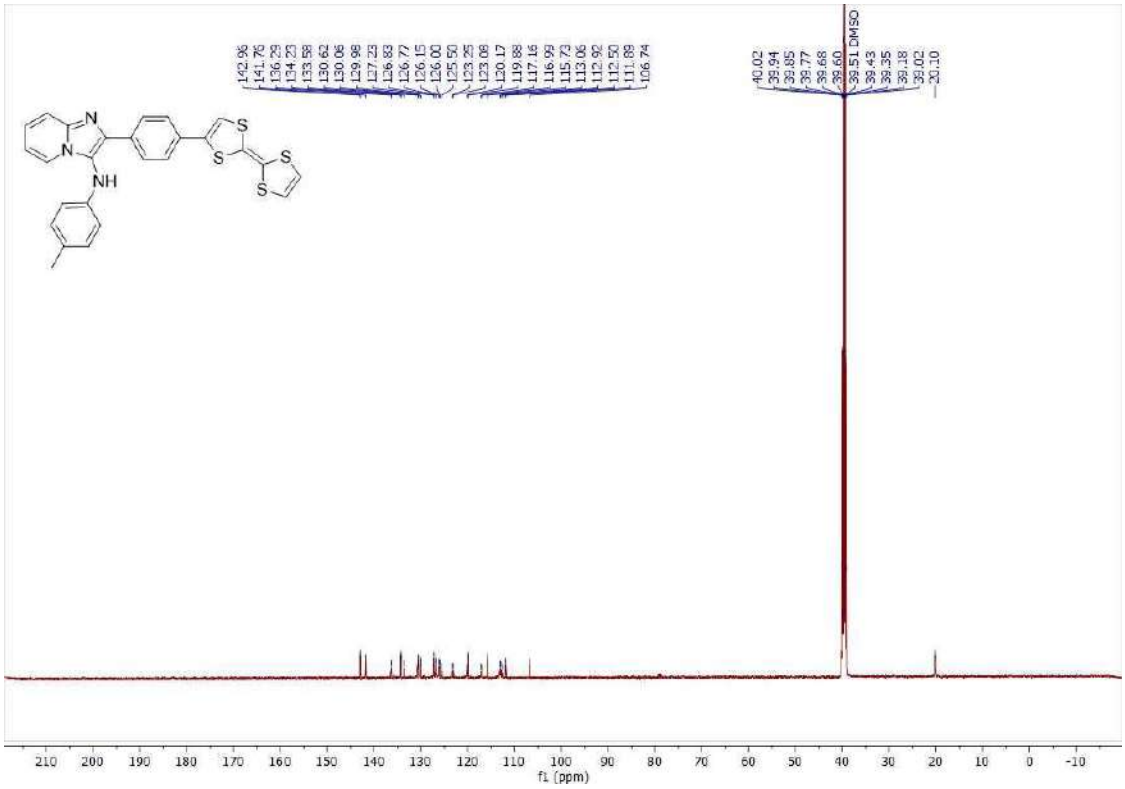
1.01
1.81
1.17
2.18
1.06
3.95
1.82
3.32
f1 (ppm)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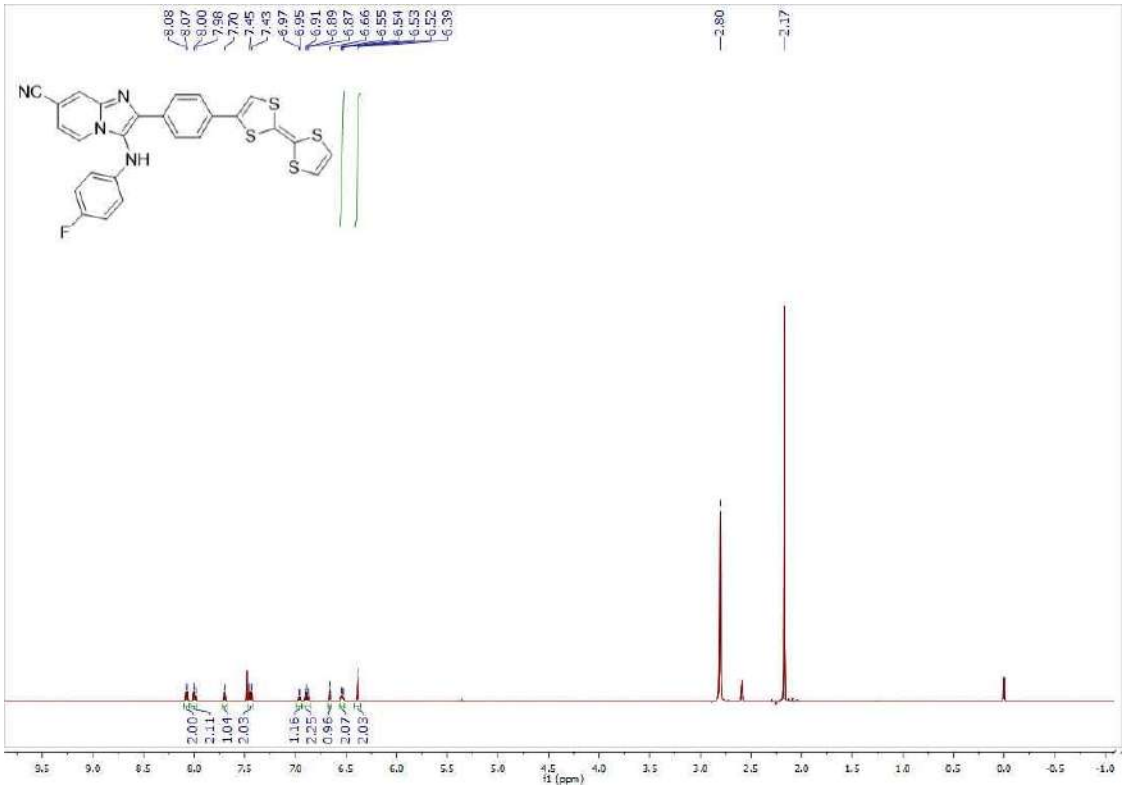
130.62
130.06
129.98
127.23
126.83
126.77
126.15
126.00
125.50
123.25
123.08
120.17
119.88
117.16
116.99
115.73
113.06
112.92
112.50
111.89
106.74
40.02
39.94
39.85
39.77
39.68
39.60
39.51 DMSO
39.43
39.35
39.18
39.02
20.10
NH
f1 (ppm)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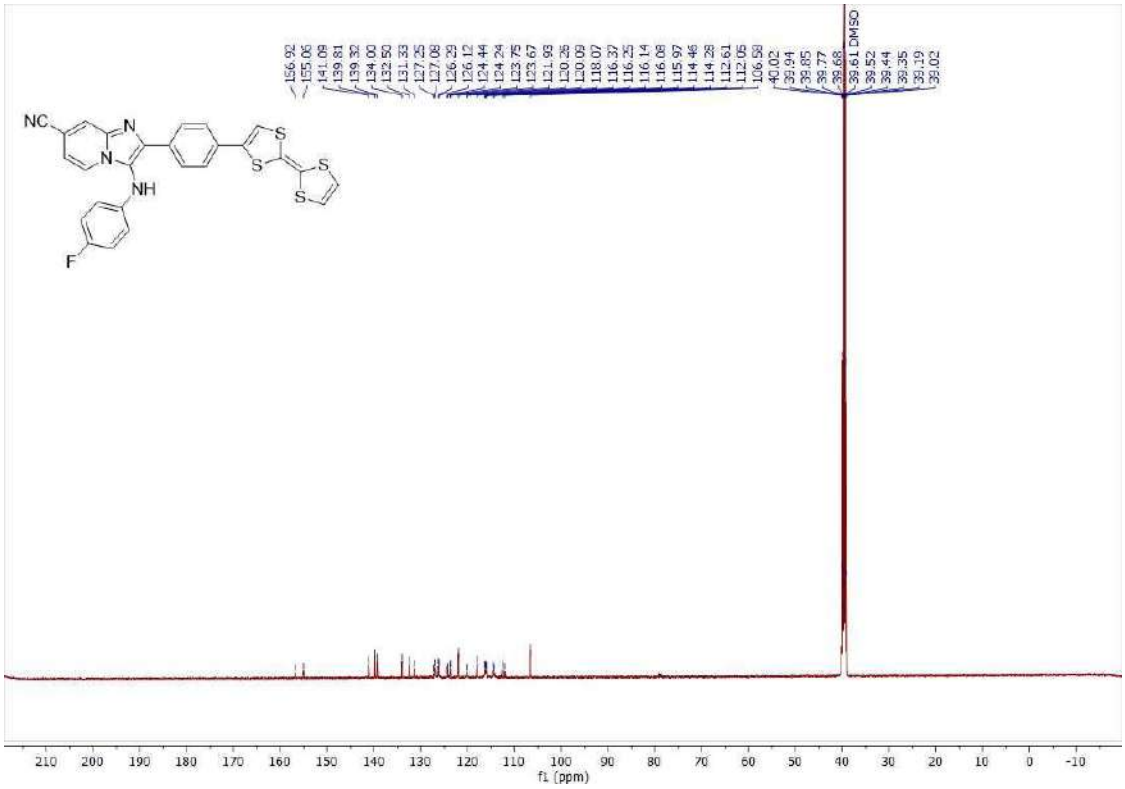
8.07
8.00
7.98
7.70
7.45
7.43
6.97
6.95
6.91
6.89
6.87
6.66
6.55
6.54
6.53
6.52
6.39
2.80
2.17
NC
N
N
NH
F
S
S
S
S
2.00
2.11
1.04
2.03
1.16
2.25
0.96
2.07
2.03
f1 (ppm)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155.06
141.08
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139.32
134.00
132.50
131.33
127.25
127.08
126.29
126.12
124.44
124.24
123.75
123.67
121.98
120.26
120.09
118.07
116.37
116.25
116.14
116.08
115.97
114.46
114.28
112.61
112.06
106.58
40.02
39.94
39.85
39.77
39.68
39.61 DMSO
39.52
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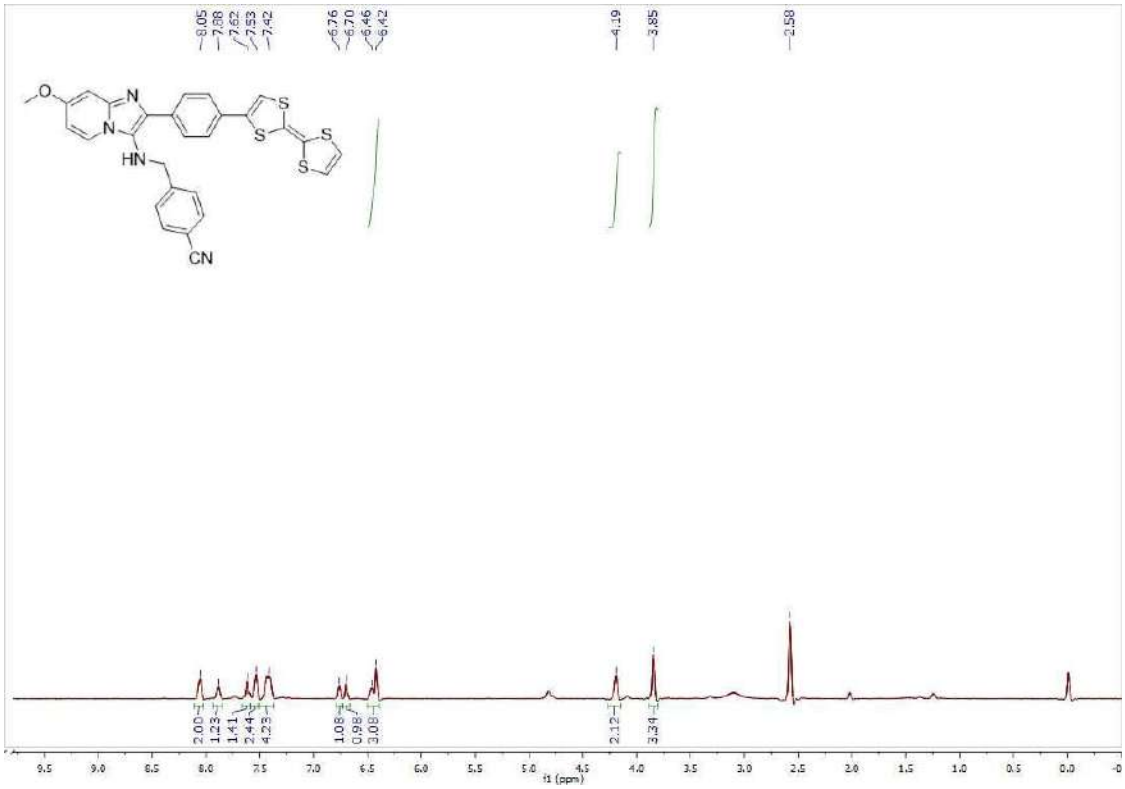
39.35
39.19
39.02
NC
N
N
NH
F
S
S
S
S
f1 (ppm)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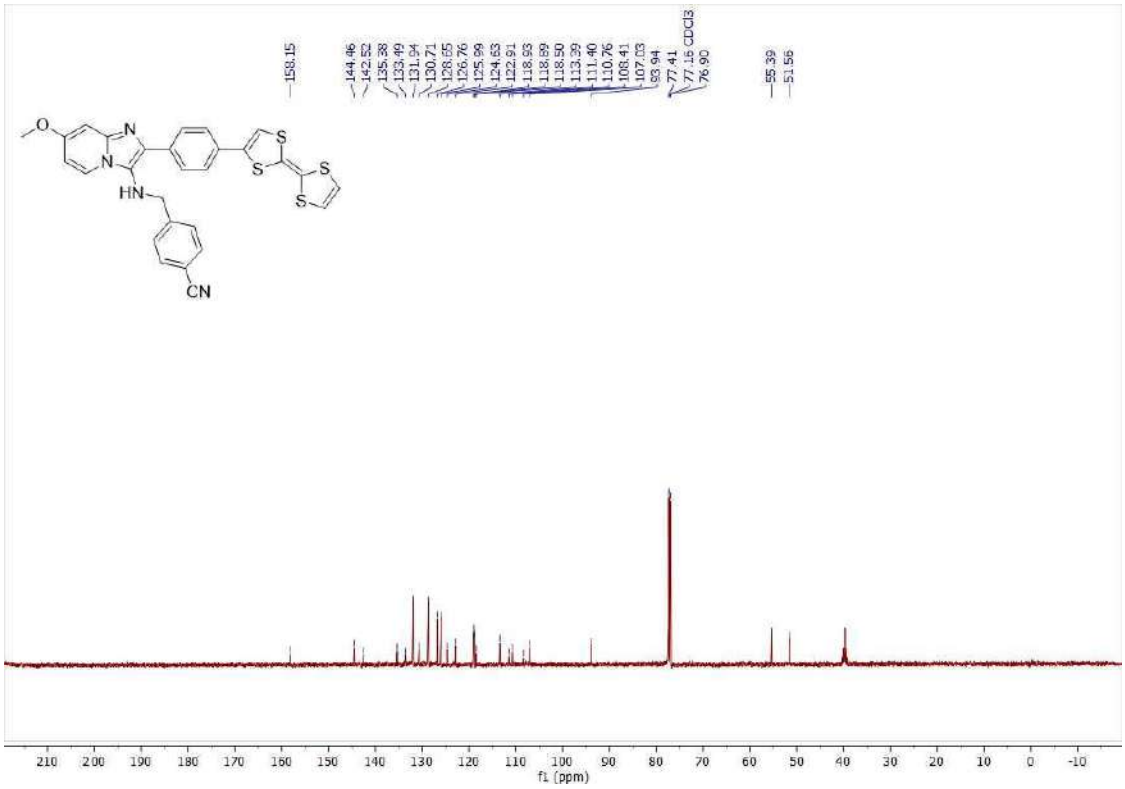
7.88
7.62
7.53
7.42
6.76
6.70
6.46
6.42
4.19
3.85
2.58
HN
CN
2.00
1.23
1.41
2.44
4.23
1.08
0.98
3.08
2.12
3.34
f1 (ppm)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142.52
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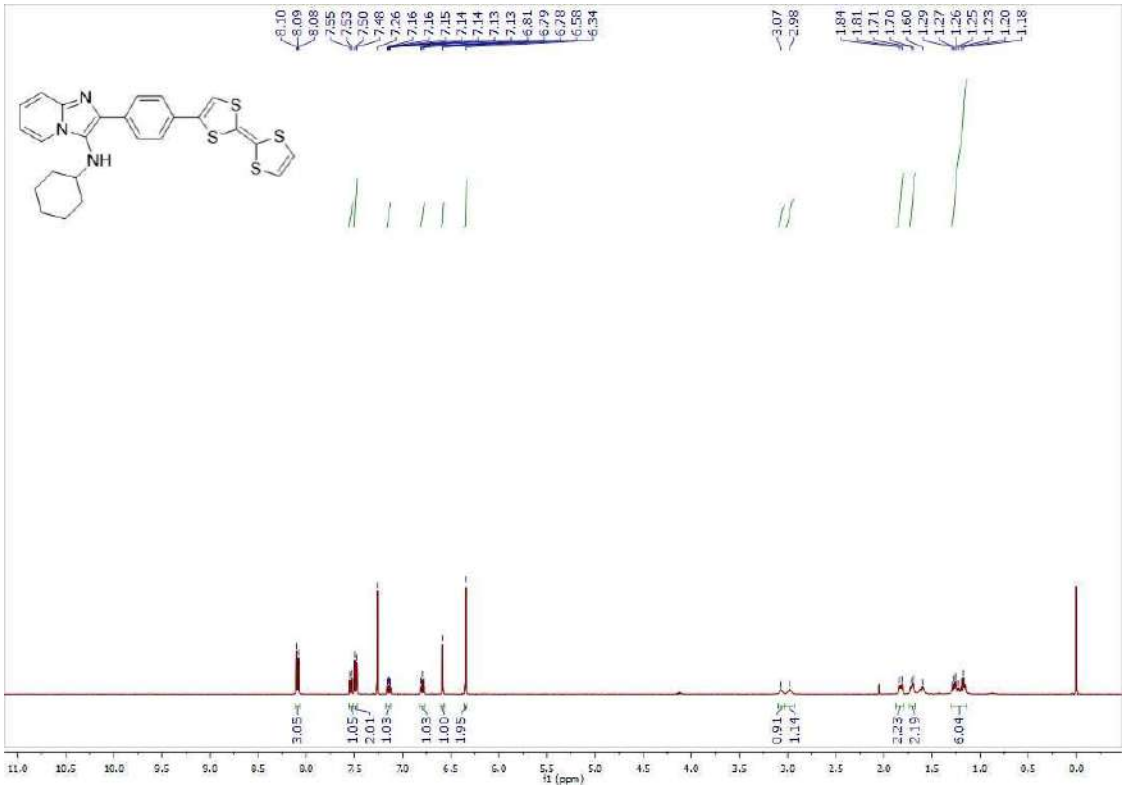
133.49
131.94
130.71
128.65
126.76
125.99
124.63
122.91
118.93
118.89
118.50
113.39
111.40
110.76
108.41
107.03
93.94
77.41
77.16 CDCl3
76.90
55.39
51.56
HN
CN
f1 (ppm)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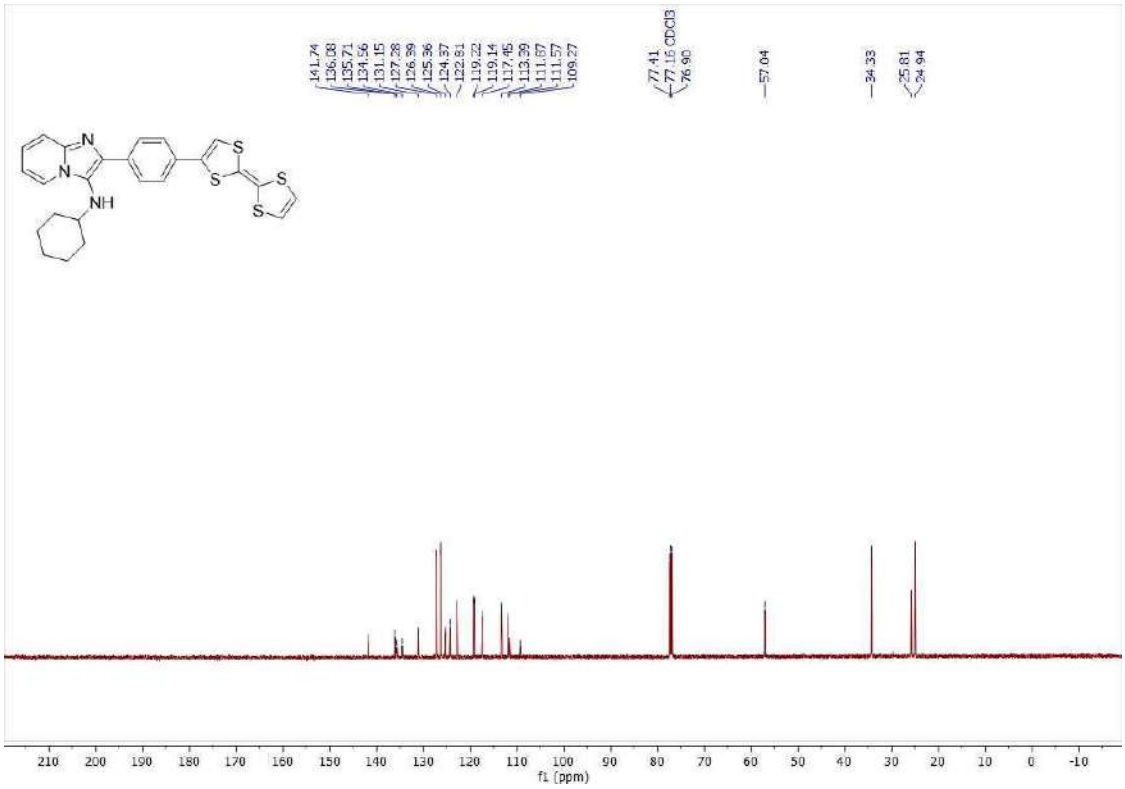
8.09
8.08
7.55
7.53
7.50
7.48
7.26
7.16
7.16
7.15
7.14
7.14
7.13
7.13
6.81
6.79
6.78
6.58
6.34
3.07
2.98
1.84
1.81
1.71
1.70
1.60
1.29
1.27
1.26
1.25
1.23
1.20
1.18
N
S
S
S
S
NH
3.05
1.05
2.01
1.03
1.03
1.00
1.95
0.91
1.14
2.23
2.19
6.04
f1 (ppm)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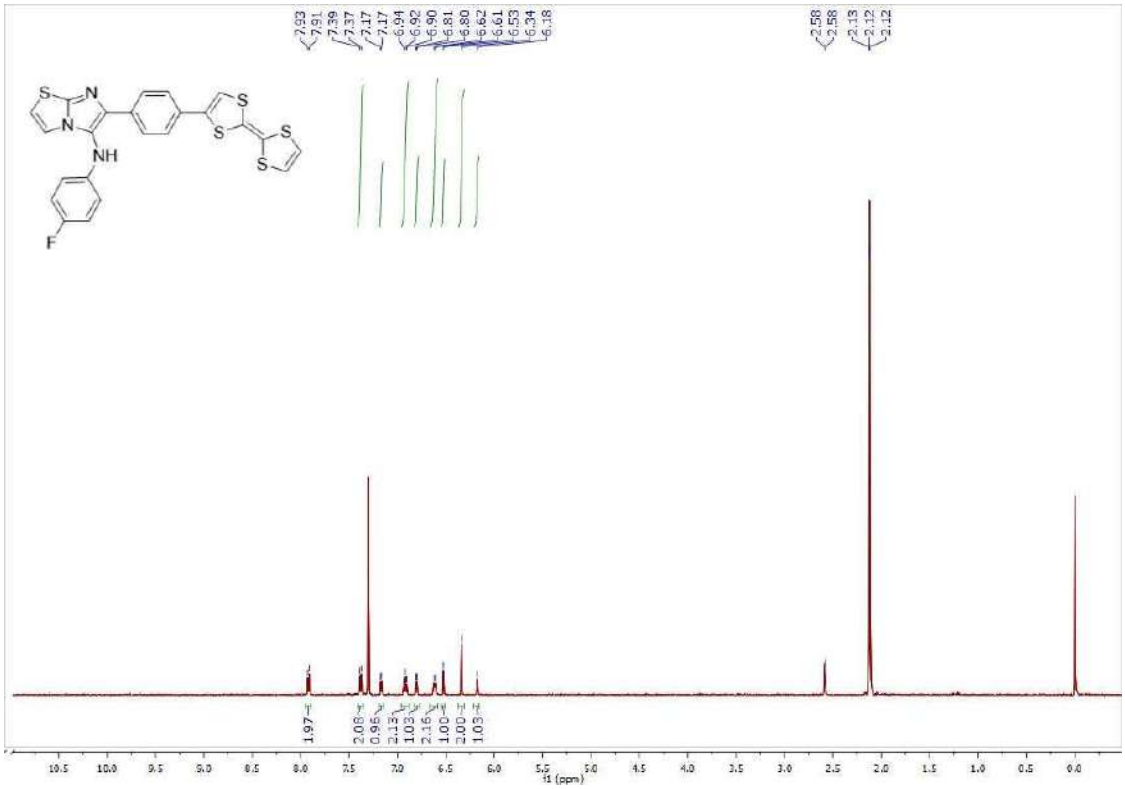
127.28
126.59
125.36
124.37
122.81
119.22
119.14
117.45
113.39
111.87
111.57
109.27
77.41
77.16 CDCl3
76.90
57.04
34.33
25.81
24.94
N
S
S
S
S
NH
f1 (ppm)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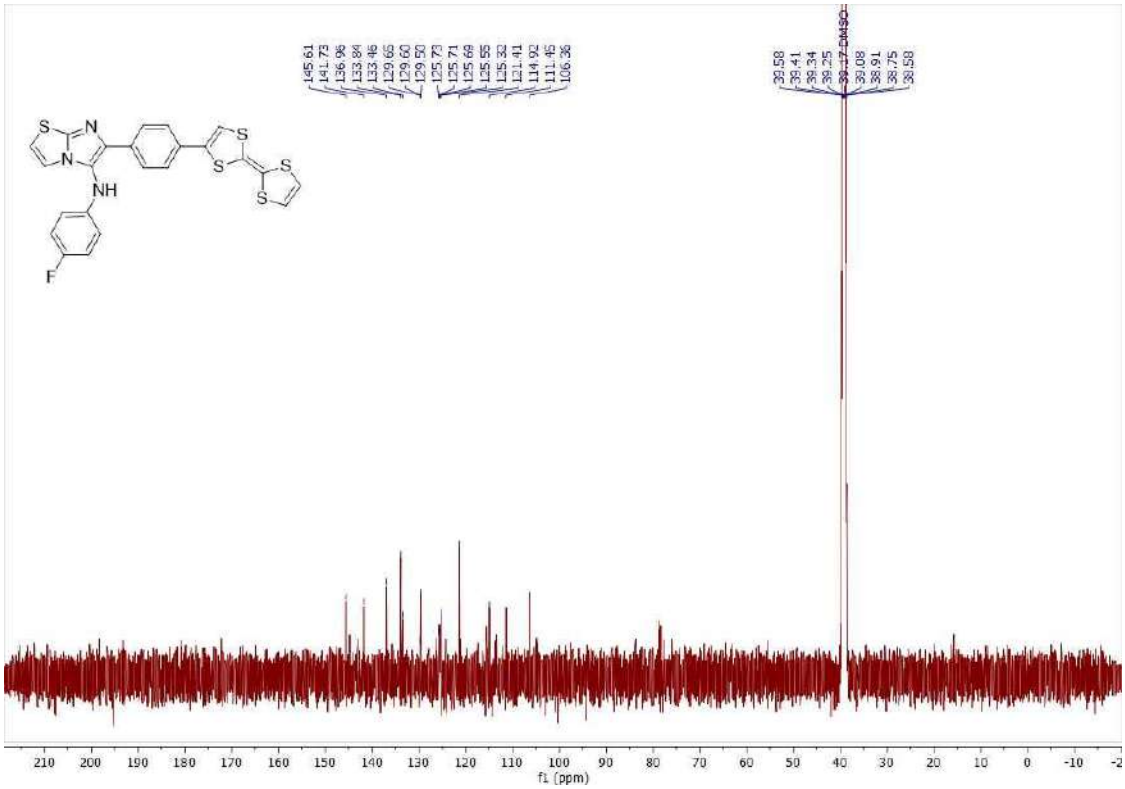
7.91
7.39
7.37
7.17
7.17
6.94
6.92
6.90
6.81
6.80
6.62
6.61
6.53
6.34
6.18
2.58
2.58
2.13
2.12
2.12
NH
F
1.97
2.08
0.96
2.13
1.03
2.15
1.00
2.00
1.03
f1 (ppm)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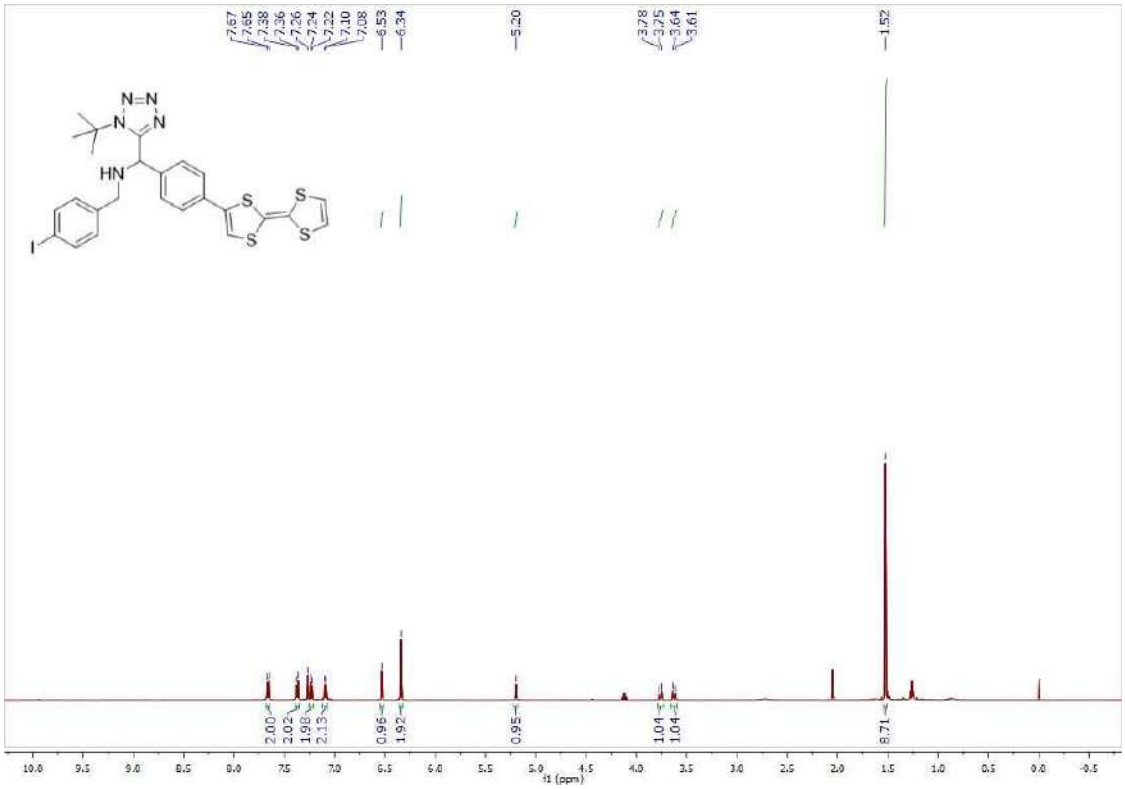
136.96
133.84
133.46
129.65
129.60
129.50
125.73
125.71
125.69
125.55
125.32
121.41
114.92
111.45
106.36
39.58
39.41
39.34
39.25
39.08
38.91
38.75
38.58
NH
F
f1 (ppm)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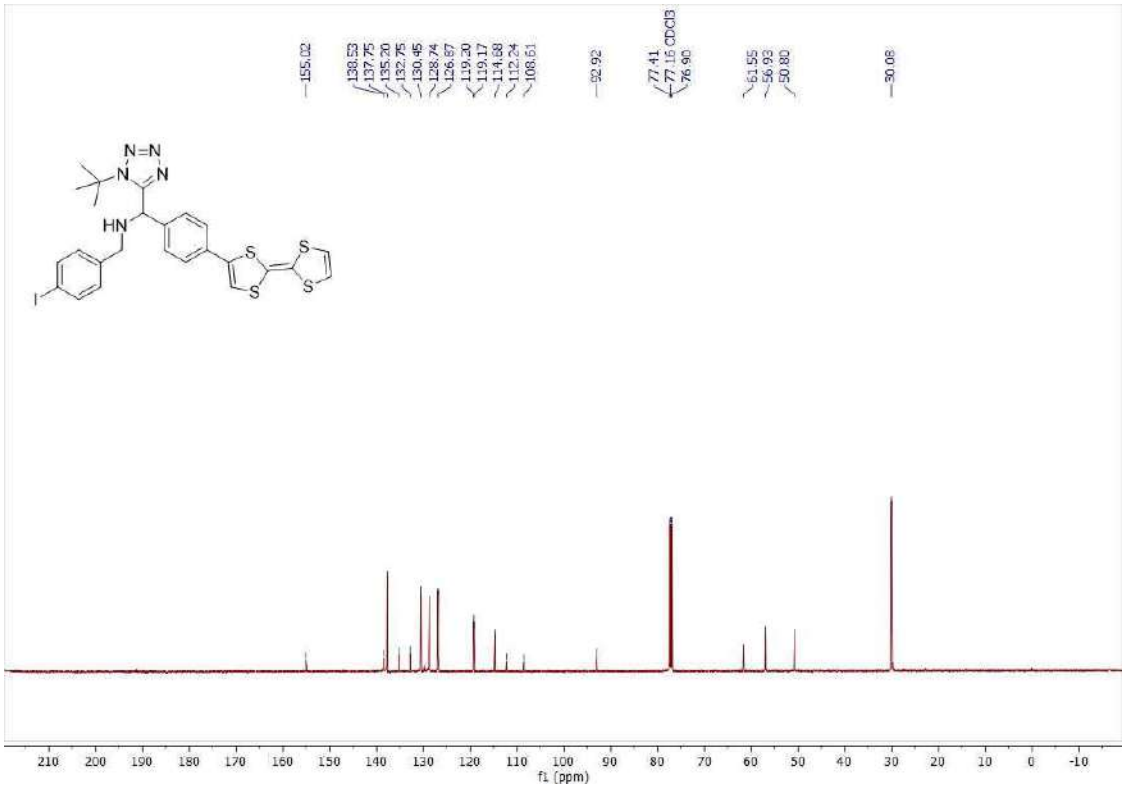
7.65
7.38
7.36
7.26
7.24
7.22
7.10
7.08
6.53
6.34
5.20
3.78
3.75
3.64
3.61
1.52
HN
I
S
S
S
S
N=N
N
N
2.00
2.02
1.98
2.13
0.96
1.92
0.95
1.04
1.04
8.71
f1 (ppm)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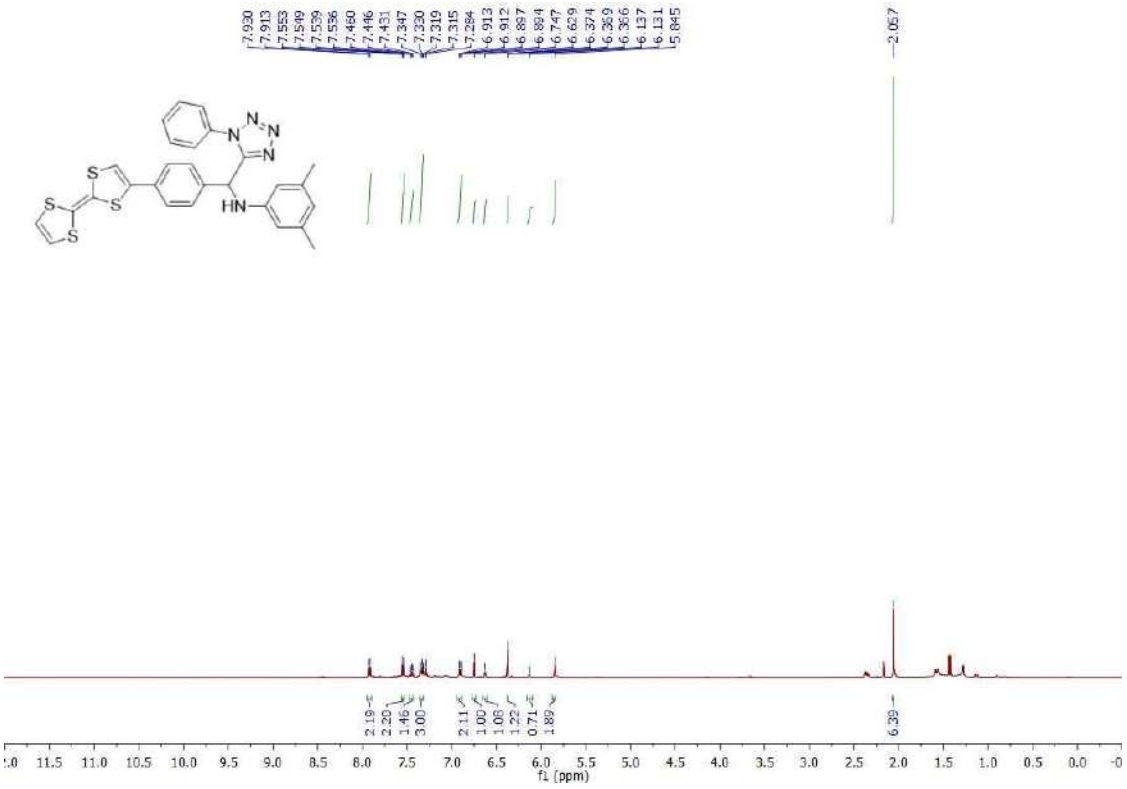
138.53
137.75
135.20
132.75
130.45
128.74
126.87
119.20
119.17
114.68
112.24
108.61
92.92
77.41
77.16 CDCl3
76.90
61.55
56.93
50.80
30.08
HN
I
S
S
S
S
N=N
N
N
f1 (ppm)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7.536
7.460
7.446
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7.347
7.330
7.319
7.315
7.284
6.913
6.912
6.897
6.884
6.747
6.629
6.374
6.369
6.366
6.137
6.131
5.845
2.057
HN
2.19
2.20
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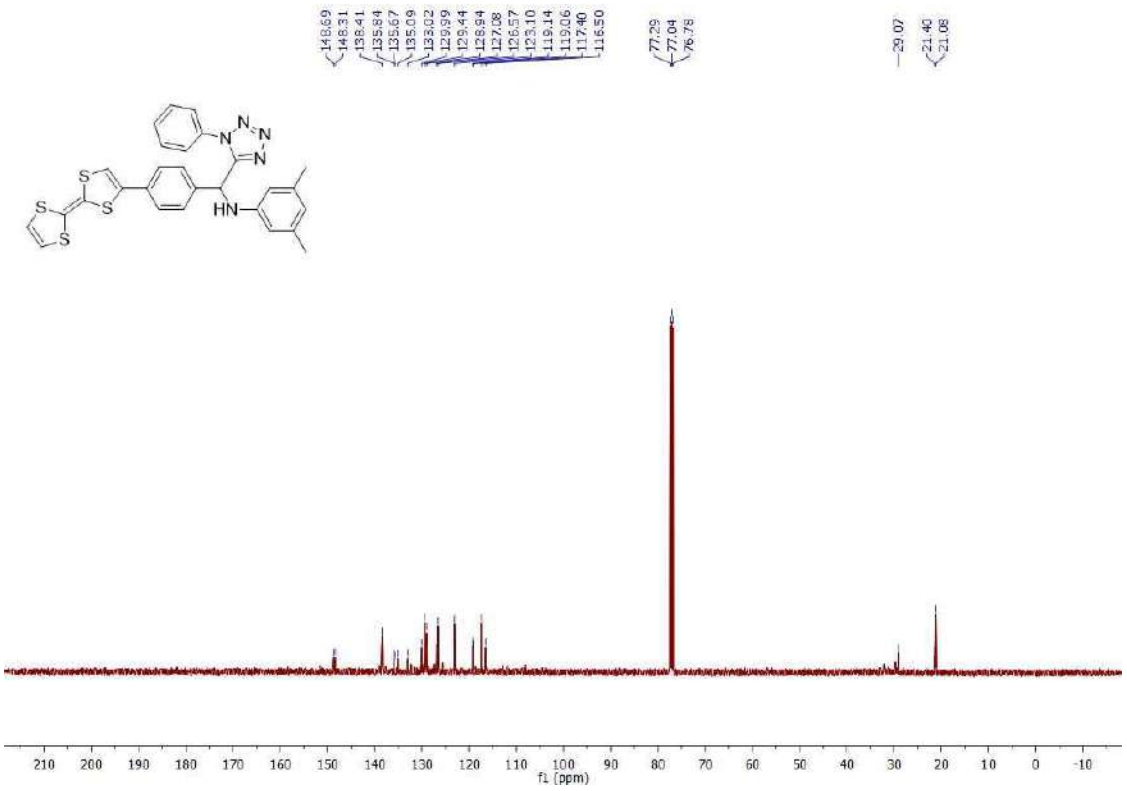
3.00
2.11
1.00
1.08
1.22
0.71
1.89
6.39
f1 (ppm)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135.67
135.09
133.02
129.99
128.44
128.04
127.08
126.57
123.10
119.14
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117.40
116.50
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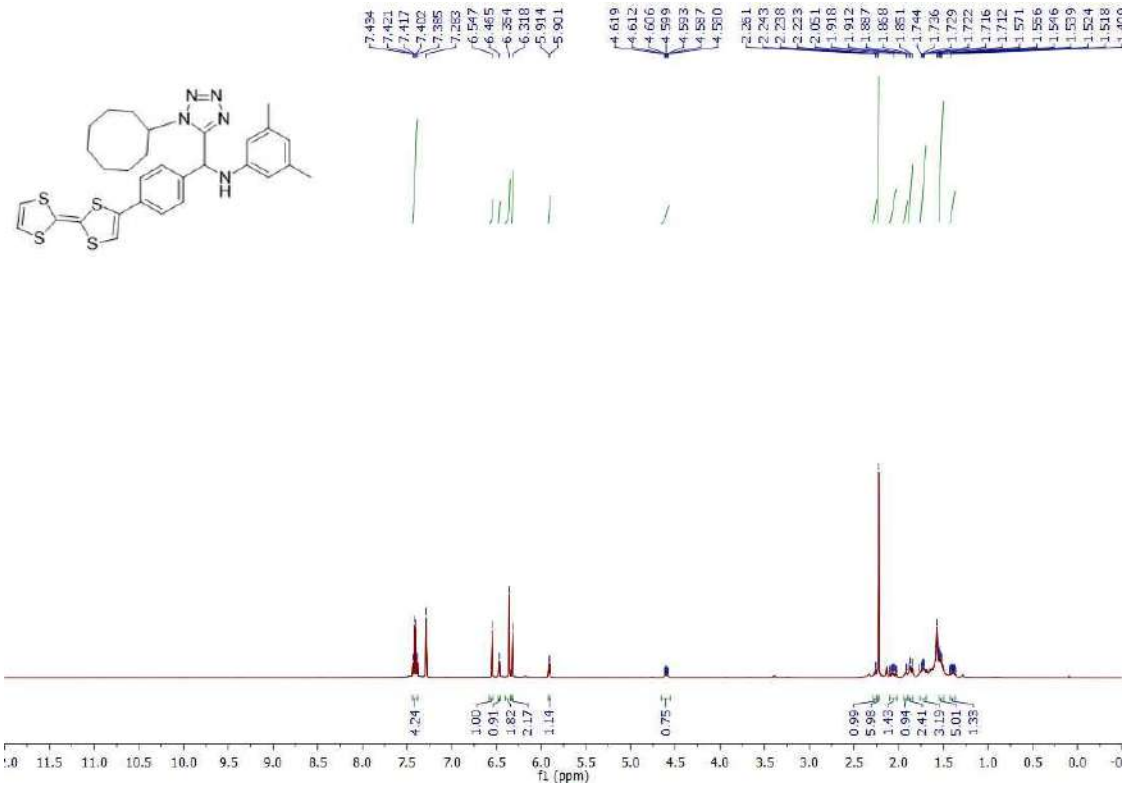
77.04
76.78
29.07
21.40
21.08
HN
f1 (ppm)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7.417
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7.283
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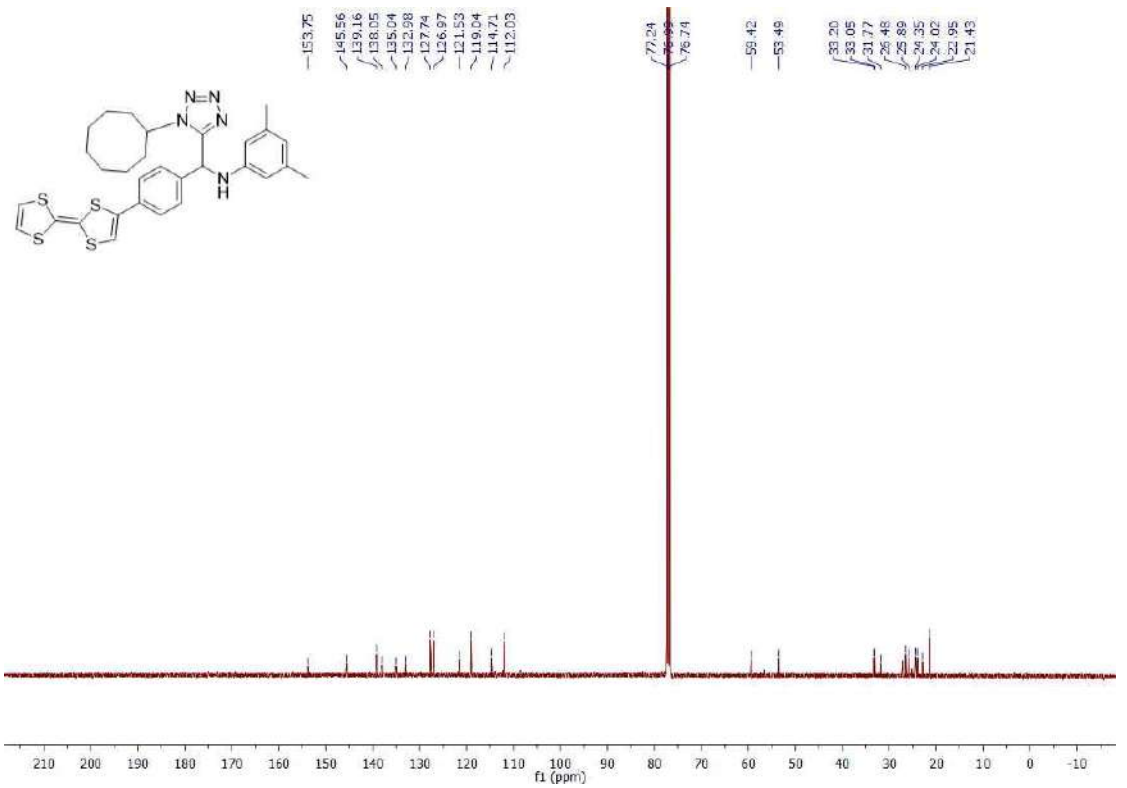
6.465
6.384
6.318
5.914
5.901
4.619
4.612
4.606
4.599
4.593
4.587
4.580
2.261
2.243
2.238
2.223
2.051
1.918
1.912
1.887
1.868
1.851
1.744
1.736
1.729
1.722
1.716
1.712
1.571
1.556
1.546
1.539
1.524
1.518
4.24
1.00
0.91
1.82
2.17
1.14
0.75
0.99
5.98
1.43
0.94
2.41
3.19
5.01
1.33
f1 (ppm)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132.98
127.74
126.97
121.53
119.04
114.71
112.03
77.24
76.99
76.74
58.42
53.49
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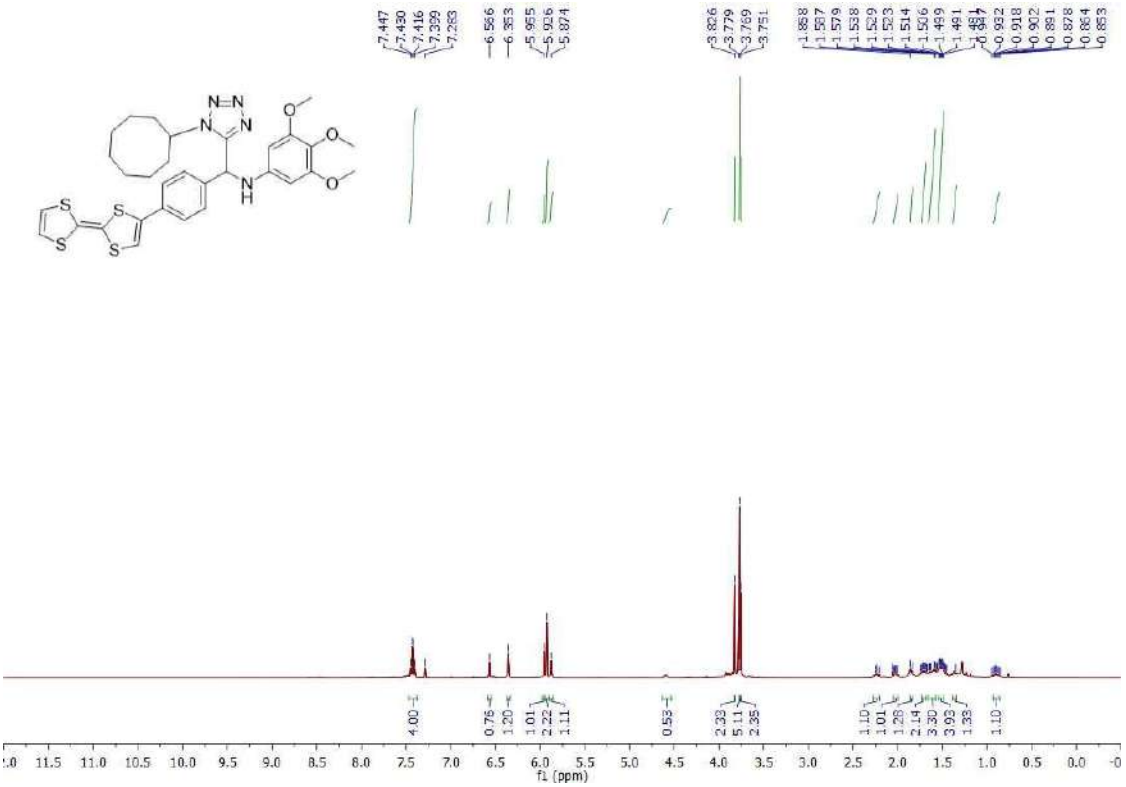
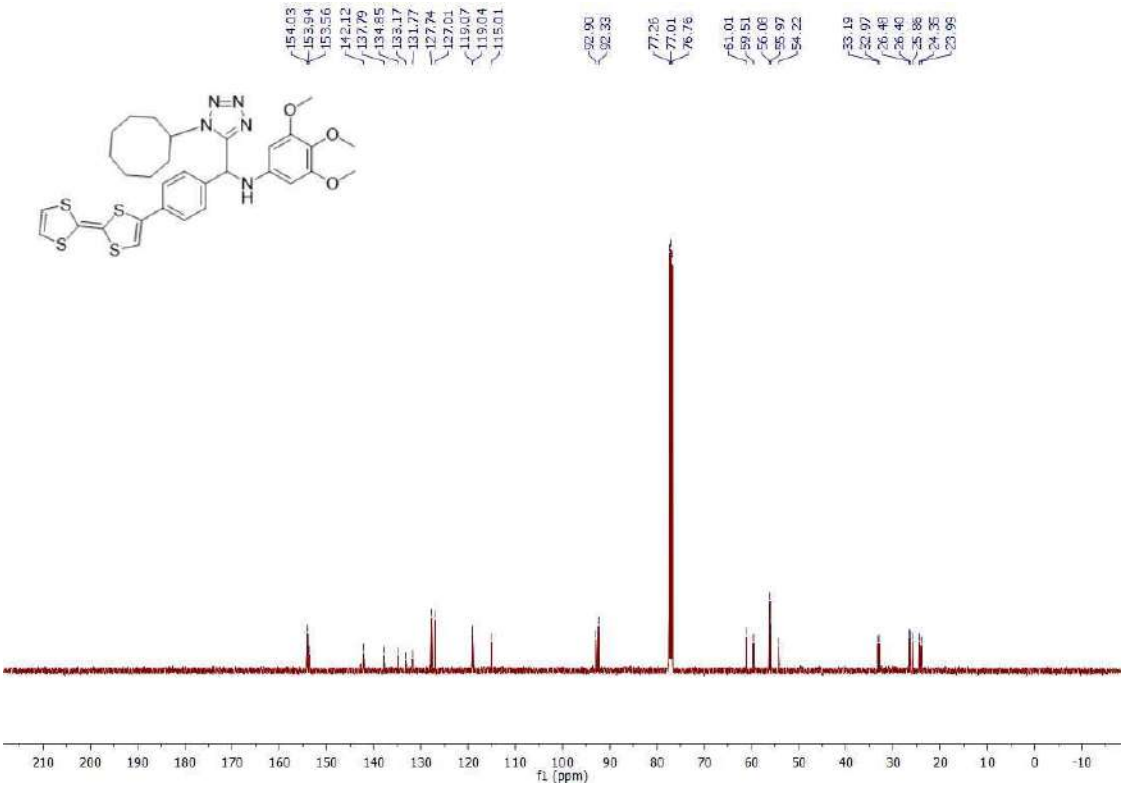
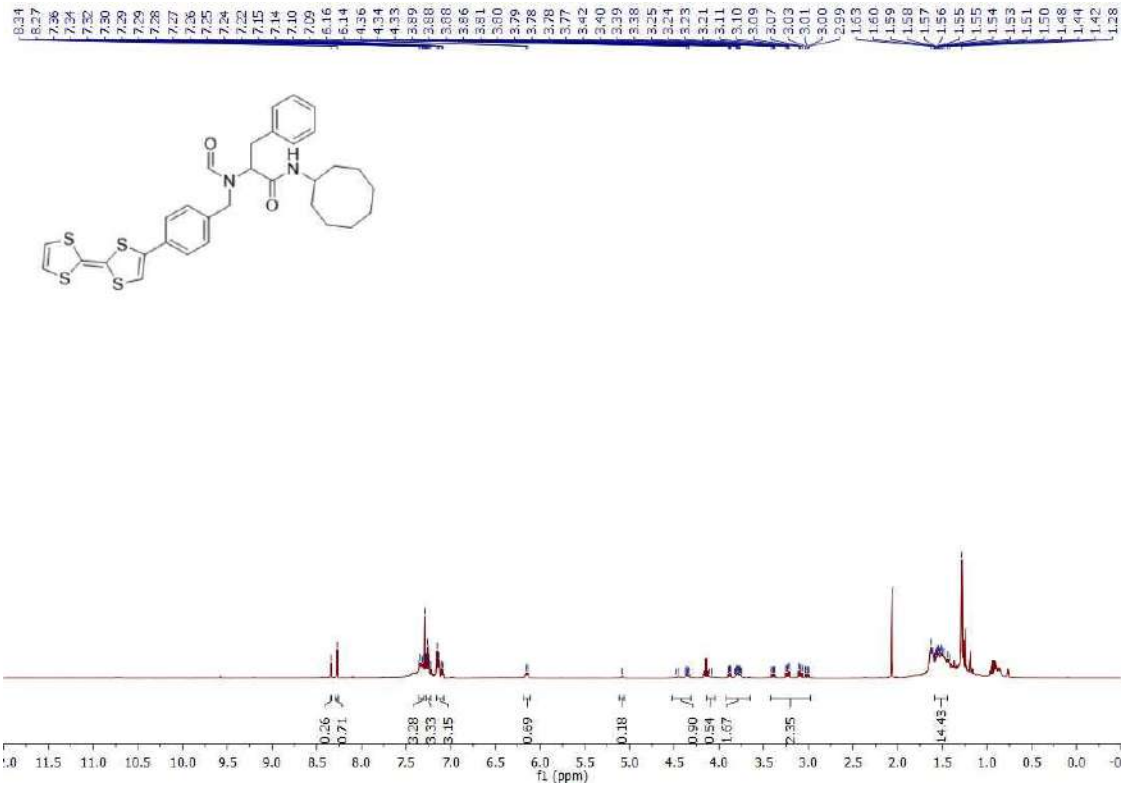
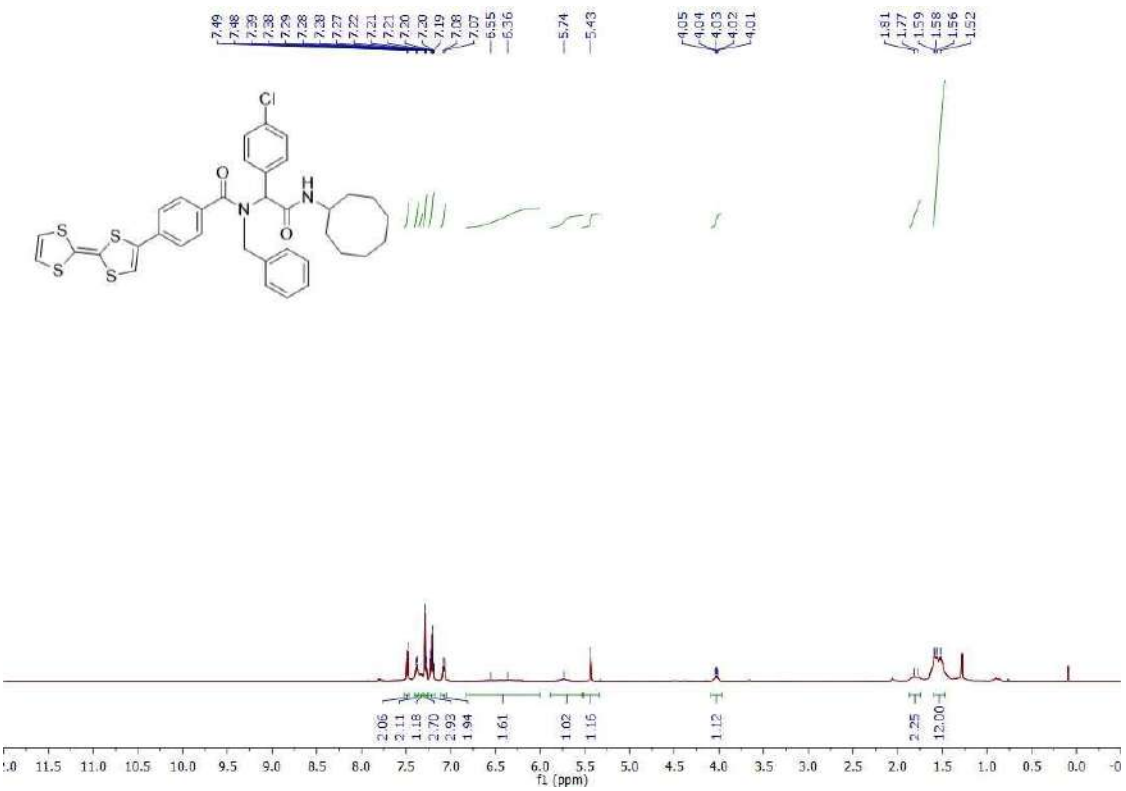
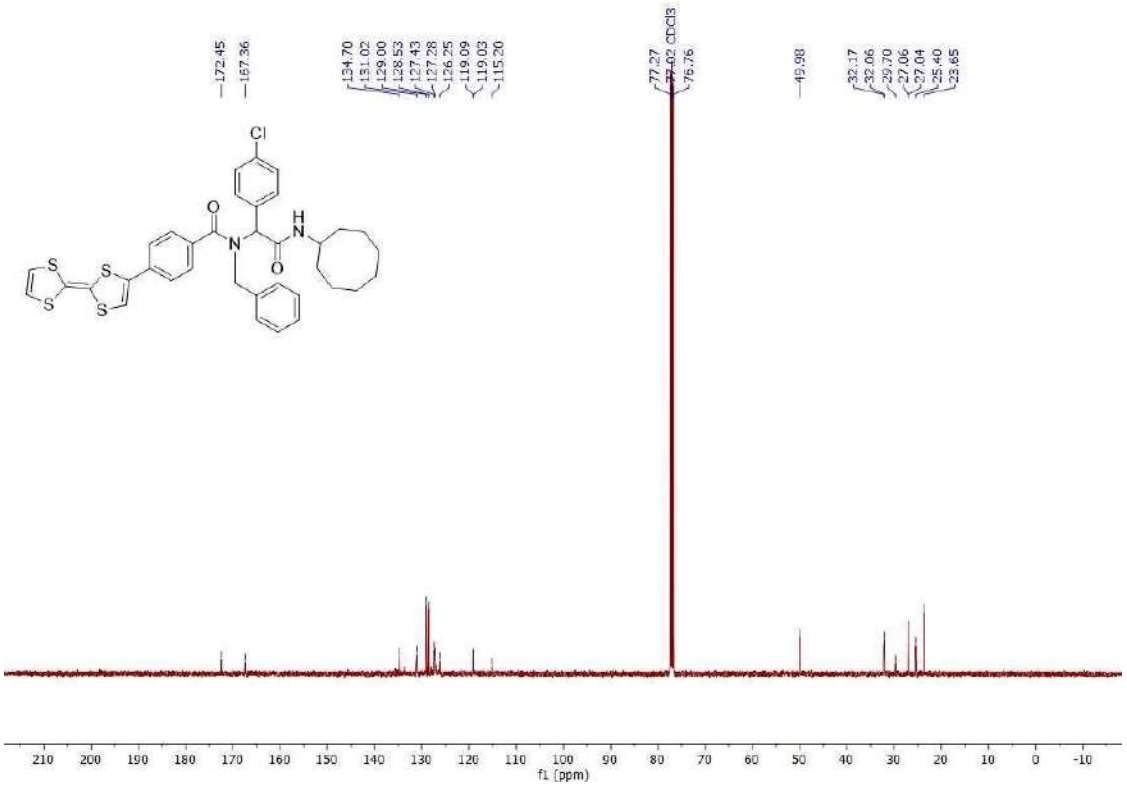
33.05
31.77
26.48
25.89
24.35
24.02
22.95
21.43
f1 (ppm)







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167.36
134.70
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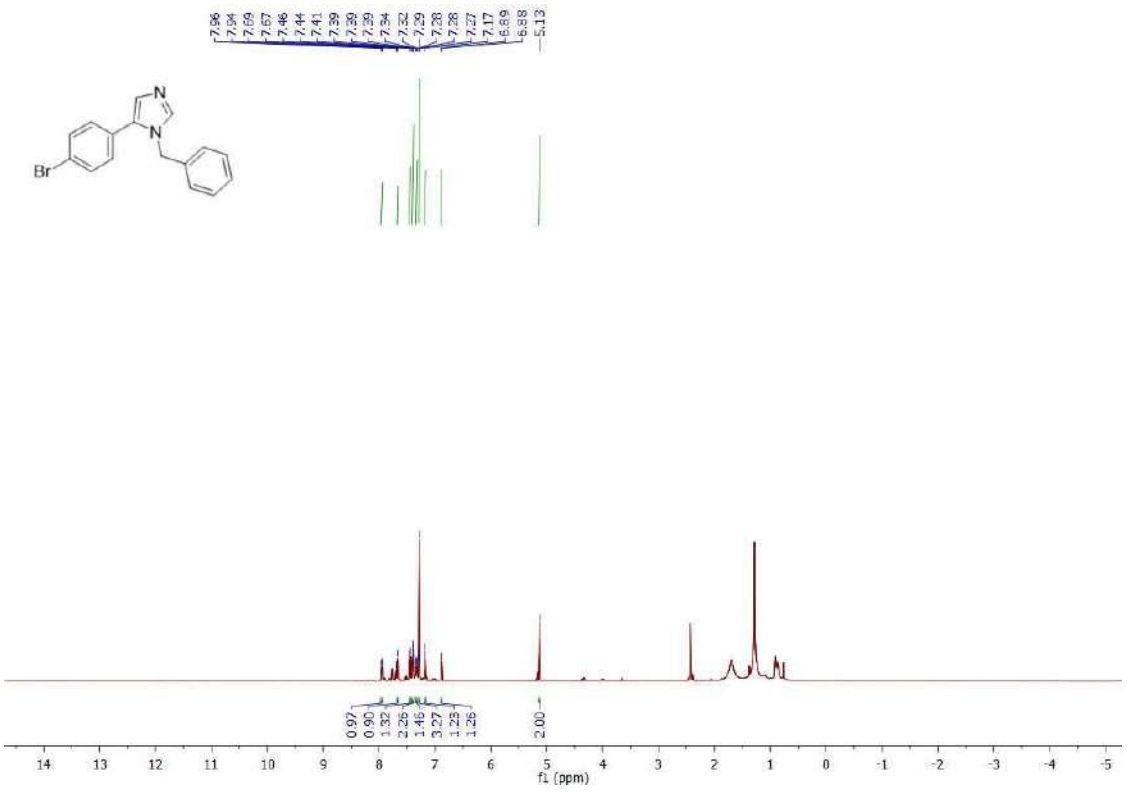
129.00
128.53
127.43
127.28
126.25
119.09
119.03
115.20
77.27
77.02 CDCl3
76.76
49.98
32.17
32.06
29.70
27.06
27.04
25.40
23.65
Cl
O
N
H
N
O
S
S
S
S
f1 (ppm)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7.94
7.69
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7.46
7.44
7.41
7.39
7.38
7.29
7.34
7.32
7.29
7.28
7.28
7.27
7.17
6.89
6.88
5.13
N
N
Br
0.97
0.90
1.32
2.26
1.46
3.27
1.23
1.26
2.00
f1 (ppm)