PALLADIUM-CATALYZED CROSS-COUPLING FOR THE SYNTHESIS OF THIENOISOQUINOLINES

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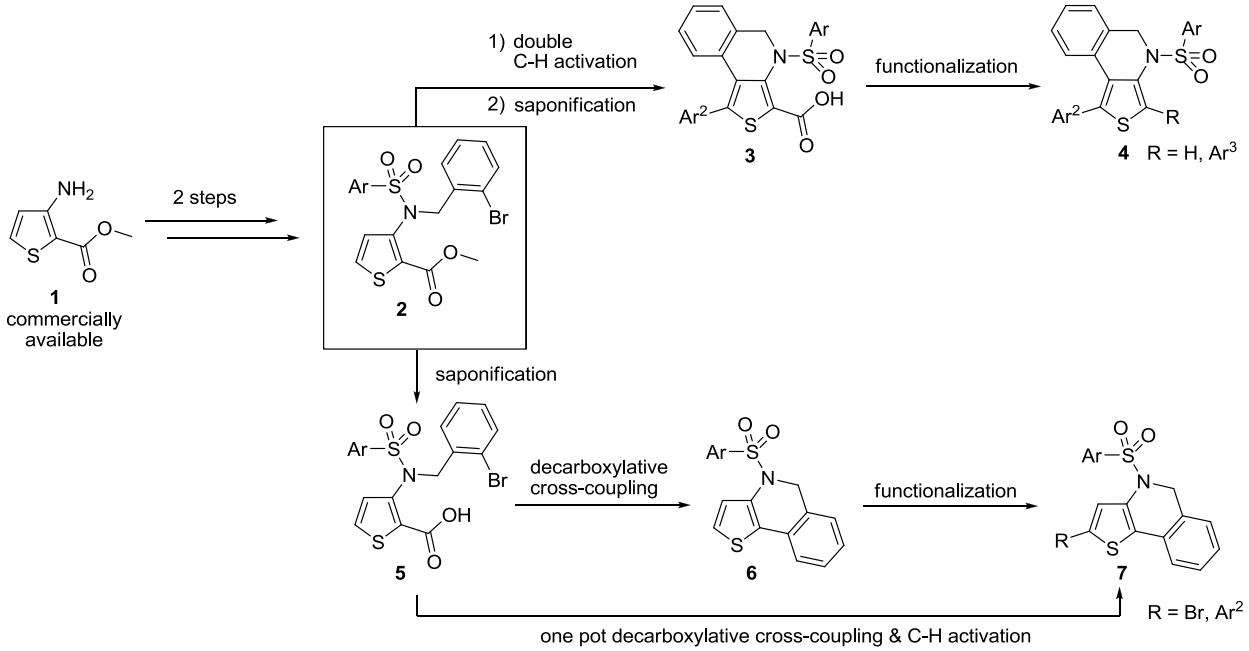
ABSTRACT

PALLADIUM-CATALYZED CROSS-COUPLING FOR THE SYNTHESIS OF THIENOISOQUINOLINES

Nicholas Wong

Thienoisoquinolines are biologically active heterocyclic systems that have potential as a breast cancer therapeutic.[1] Optimizations and syntheses of functionalized thienoisoquinolines from commercially available starting material are described. The syntheses address common limitations associated with classical palladium cross-coupling reactions such as the use of sensitive organometallic reagents and the production of high molecular weight metallic waste.



The key intermediate (2) was synthesized in 2 steps from a commercially available starting material and used in two synthetic pathways to access different thienoisoquinoline isomers. Undergoing a palladium catalyzed double C-H activation reaction allows access to the 3,4-thienoisoquinoline isomer (4). The

[1] Coghlan, R. D.; Fobare, W. F.; Trybulski, E. J., Wyeth (2006) Thienoisoquinoline-Phenylsulfonamides and their use as ER-NFkappaB Inhibitors, US 2006/0154875

ester functionality at C2 serves a dual purpose and was used both as a directing group and as a synthetic handle for further functionalization.

The key intermediate (2) can also undergo a saponification reaction first to form the carboxylic acid (5). This allows for a palladium catalyzed decarboxylative cross-coupling, generating 2,3-thienoisoquinoline systems (6). This can be further functionalized at the C5 position through a C-H activation or bromination reaction. Furthermore, these functionalized 2,3-thienoisoquinoline systems can be synthesized through a one-pot decarboxylative cross-coupling & C-H activation sequence reducing the step count and improving efficiency. In summary, an efficient synthesis of various functionalized thienoisoquinoline systems is described. Both isomers of these biologically important compounds can be obtained from a common key intermediate allowing for an efficient and modular synthesis.

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Finally I would like to thank all my previous supervisors and lab mates who have helped to shape me into the chemist that I am today.

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List of Schemes

List of Abbreviations

acac	acetylacetone
AcOH	acetic acid
Ar	aryl
CMD	concerted metallation-deprotonation
davephos	2-Dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DCM	Dichloromethane
DMA	*N,N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
dppf	1,1'- bis(diphenylphosphanyl) ferrocene
equiv.	equivalents
EtOAc	ethyl acetate
GC	gas chromatography
h	hour
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
Johnphos	(2-biphenyl)di-*tert*-butylphosphine
M	molar concentration
m/z	mass-to-charge ratio
min	minute
Mor-dalphos	di(1-adamantyl)-2-morpholinophenylphosphine
MS	mass spectrometry
n	normal
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
petey	(η-5-2,4-Cyclopentadien-1-yl)[(1,2,3-η)-1-phenyl-2-propenyl]-palladium
Ph	phenyl
pK_a	logarithmic acid dissociation constant
ppm	parts per million
T	temperature
t	time
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
tert (^{t})	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
δ	chemical shift in parts per million
µw	microwave

CHAPTER 1 – INTRODUCTION

Chapter 1.1 – Green Chemistry

Mankind has always sought the advancement of technology to further increase their quality of life. However, this advancement of technology has consumed a large portion of the planet's natural resources. Recently, with an emerging understanding of the human footprint on the planet, the implementation of procedures to minimize waste has become increasingly important. Similarly, an increasing amount of attention has been placed on research and the pharmaceutical industry. These concerns and environmental consciousness has since developed into the principles of green chemistry.

The principles of green chemistry involve development of new chemistry and processes to minimize or completely eliminate by-product formation helping to reduce environmental impact.[2] Emphasizing renewable starting materials, less dependence on fossil fuels and non-renewable chemical feedstock can lead to a self-sustained carbon neutral process. To guide future research and development, 12 principles of green chemistry were devised by Anastas and co-workers from the environmental protection agency in 1998 and are listed below.[3]

1) Prevention
2) Atom Economy
3) Less Hazardous Chemical Syntheses
4) Design Safer Chemicals
5) Safer Solvents and Auxiliaries
6) Design for Energy Efficiency
7) Use of Renewable Feedstocks

[2] Green chemistry website http://www.greenchemistry.ca/ Accessed June 19, 2012.
[3] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, 30.

8) Reduce Derivatives

9) Catalysis

10) Designed for Degradation

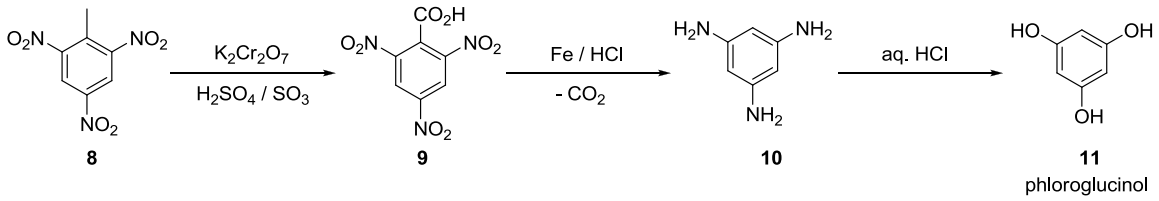
11) Real Time Analysis for Pollution Prevention

12) Inherently Safer Chemistry for Accident Prevention

These principles can be summarized into a single statement; "green chemistry uses reagents from preferably a renewable source producing minimal amounts of waste and toxic by-products towards the production of chemical products which have minimal toxicity for the environment."[2]

Although these twelve principles appear to be simple to implement, practical applications only allow for the employment of a fraction of these strategies for any one process. These principles were developed to improve upon chemistry which was initially discovered and optimized in the early 20th century when the toxicity of many solvents and reagents were not well known and environmental consciousness was of little concern.

The industrial process for the production of phloroglucinol was an example of an inefficient and environmentally detrimental process.[4] This method of transforming 2,4,6-trinitrotoluene (8) through a series of oxidations and reductions was used up until the mid 1980s.



8 **9** **10** **11** phloroglucinol

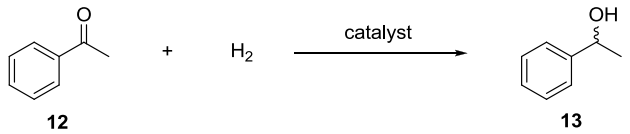
Scheme 1 – Industrial process for the production of phloroglucinol

[4] Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437.

From a classical point of view, this process to produce phloroglucinol is efficient, generating the desired product in an overall yield of >90%. However, when considering all reagents used in the synthesis, this process also produces 40 kg of waste per kilogram of product formed which translates to only 5% of the overall mass of products formed. From an atom economy perspective, the great majority of the mass formed is by-product containing metallic wastes. These waste products were found to be too costly to properly dispose and this process was subsequently retired.[4]

Large portions of waste produced in the synthesis of phloroglucinol (Scheme 1) are inorganic salts associated with the oxidizing and reducing agents. These commonly used reactions employ the use of metal based redox reagents used in stoichiometric or higher equivalents producing an equal amount of high molecular weight inorganic salts as by-product. As such, modern methods need to be established to replace these important reactions in efforts to minimize the impact on the environment.

Catalysis has more recently been a major focus of research in efforts to develop new and more efficient reactions. To minimize waste production in efforts to make reactions and processes greener, reactions employing catalytic rather than stoichiometric equivalents have recently been developed. As an example, the hydrogenation of benzaldehyde (12) using a metal catalyst is a highly atom economical process (Scheme 2). All atoms of the reagents are incorporated into the final product and there are no functional groups being eliminated as a by-product. The use of a metal catalyst also allows for isolation and the possibility of recycling rather than disposed as waste.



Scheme 2 – Catalytic hydrogenation as an atom economical process

Recent advances in catalysis have been focused on the development of carbon-carbon bond forming reactions.

Chapter 1.2 - Palladium Cross-Coupling

Carbon-carbon bonds have always had an important impact on the field of synthetic organic chemistry in the development of new methods, natural product synthesis and medicinal chemistry. More recently, transition metal catalyzed carbon-carbon bond forming reactions have been established as an alternative to classical methods to generate these bonds. To demonstrate the importance of these reactions in the development of therapeutics, a study of the reactions used by GlaxoSmithKline pharmaceuticals, AstraZeneca and Pfizer in the synthesis of 128 drug candidates was performed by Carey and co-workers in 2006.[5]

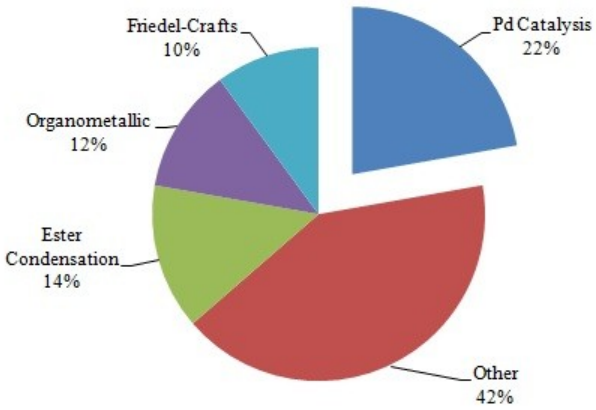


Figure 1 – Breakdown of C-C bond forming reactions

When categorizing all of the reactions performed, 11% of the reactions were carbon-carbon bond forming. Further analysis of this set of reactions revealed that 22% of those carbon-carbon bond forming reactions were palladium catalyzed (Figure 1).

To further emphasize the importance of palladium catalyzed carbon-carbon bond forming reactions, a second study was performed by Cooper and co-workers at GlaxoSmithKline. This study surveyed reactions used towards the synthesis of clinical candidates for respiratory diseases.[6]

[5] Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
[6] Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 8082.

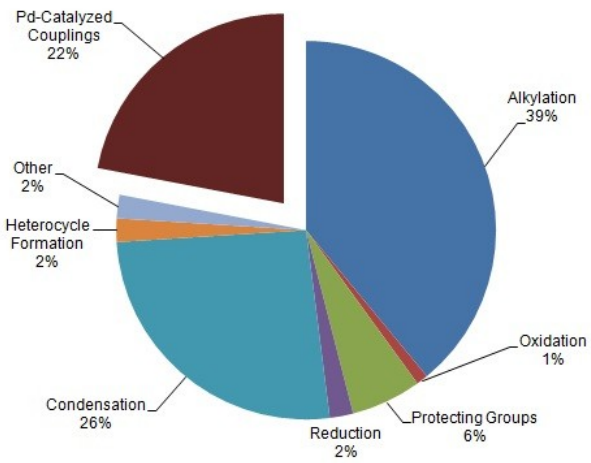
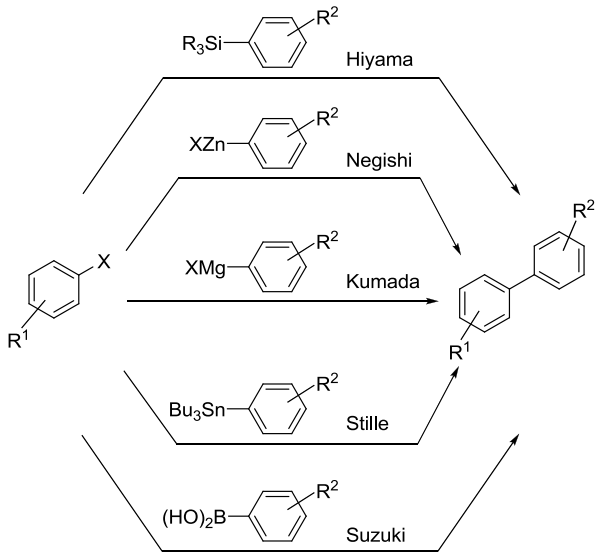


Figure 2 – Survey of reactions used at GlaxoSmithKline towards respiratory disease clinical candidates

Cooper also found that 22% of the reactions performed were palladium-catalyzed, which demonstrated the importance of these transformations (Figure 2). The two studies performed encompassed the synthesis of different therapeutics for different disease areas, further demonstrating the versatility and applicability of palladium-catalysis in drug discovery.

This class of reactions can be classified into two groups; classical methods and modern methods. Classical methods are composed of transformations such as the Suzuki, Hiyama, Negishi, Stille and Kumada reactions that employed the use of an organometallic species coupling with an aryl halide. These reactions facilitated and improved the synthesis of the aryl aryl bond (Scheme 3).[7] These cross-coupling reactions are chemioselective with aryl halides or oxygen-based leaving groups, commonly known as pseudo halides, and the corresponding organometallic group. These reactions also are typically tolerant of other functional groups, thus allowing for broad applicability with a variety of substrates.

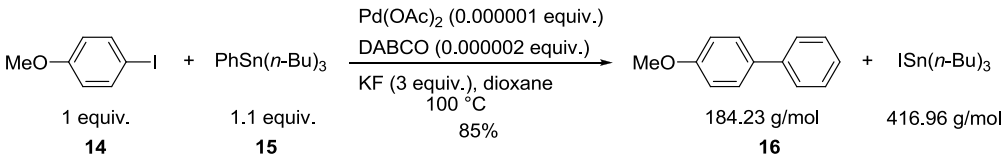
[7] For a review on palladium catalysis see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.



Scheme 3 – Traditional Cross-Coupling Reactions

These reactions employ the use of organosilianes (Hiyama), organozincs (Negishi), Grignard reagents (Kumada), organotins (Stille), and arylboronic acids/esters (Suzuki). These organometallic cross-coupling partners typically employ high molecular weight metals and are typically functionalized resulting in the production of a stoichiometric amount of the corresponding metal salt as waste.

In 2005, Li and co-workers presented an "efficient" Stille cross-coupling reaction for the formation of bi-aryls (Scheme 4).[8]



Scheme 4 – An "efficient" Stille cross-coupling reaction

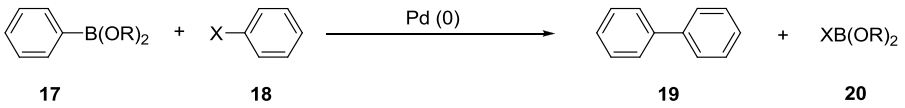
This reaction, through a classical evaluation is excellent since very low palladium catalyst loadings are required to generate the product in excellent yields. However, when evaluating this reaction with the twelve principles of green chemistry, it employs a low catalyst loading which in turn produces minimal metallic waste. However, the reaction also employs a higher than stoichiometric amount of phenyl-

[8] Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832.

tributyltin (15) in the reaction, generating 10% wasted reagent. KF was added as an additive to the reaction in 3 equivalents and none of the mass associated with this reagent is incorporated into the final product. Finally, comparing the molecular weight of the product and the stoichiometric metallic by-product, approximately 2 g of inorganic salts are produced for every 1 g of desired product. Similarly, other reactions employing organometallic reactions (Scheme 3) also produce stoichiometric amounts of high molecular weight inorganic salts as by-products.

Chapter 1.3 - Suzuki Reaction

The Suzuki reaction has gained more attention than any other classical cross-coupling reaction and along with the Heck and Negishi reactions was awarded the Nobel Prize in chemistry in 2010.[9,10] The reason for the success of the Suzuki reaction is in part due to the thermal stability of boronic acids/esters and[11] their inertness to water and oxygen allowing these reagents to be synthesized and stored long term without special precautions. Furthermore, functionalized boronic acids and esters have been made commercially available, increasing their access to researchers. These boronic acids have been applied to a wide range of cross-couplings, between two alkenes,[12] an aryl group and an alkene,[13] and more recently alkyl-alkyl couplings.[14] Despite the wide range of reactivity, the Suzuki reaction is primarily known for the coupling of two aryl groups.[15]

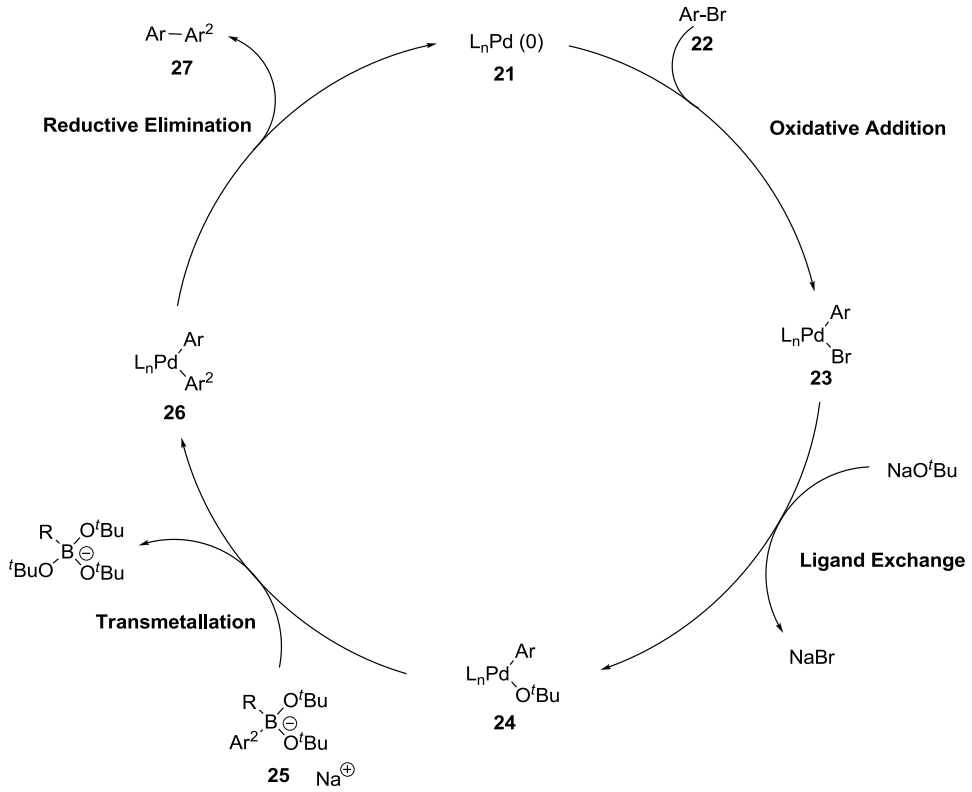


Scheme 5 – A general Suzuki reaction

A general Suzuki reaction employs the use of organoboronic acids or boronic esters (17) and is reacted with an aryl halide (18) under palladium (0) catalysis conditions to yield bi-aryls (19) and a boron based salt (20). Comparing the atom economy of the Suzuki reaction (Scheme 5) to the atom economy of the Stille reaction (Scheme 4), the Suzuki reaction can be considered a greener process based on the twelve principles of green chemistry. The boron salts (20) that are formed as by-products of the Suzuki reaction are of much lower molecular weight than the tin salts formed in the Stille reaction. The palladium in

[9] Nobelprize.org http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/ accessed June 19, 2012.
[10] For an excellent review see: Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.
[11] Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, *95*, 2457.
[12] Honeycutt, J. B.; Riddle, J. M. *J. Am. Chem. Soc.* **1959**, *81*, 2593.
[13] Larock, R. C.; Riefling, B. *J. Org. Chem.* **1978**, *43,* 1468.
[14] a) Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F. *J. Am. Chem. Soc.* **2010**, *132*, 6855. b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794.
[15] Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149.

both cases is regenerated as the active Pd (0) species after each reaction cycle allowing for catalytic amounts of the metal to be employed and the potential to recycle the catalyst.

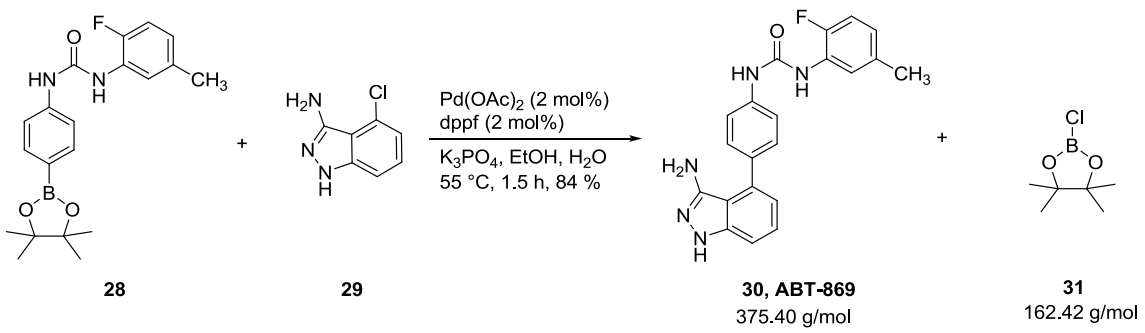


Scheme 6 – Mechanism for a typical Suzuki reaction

These classical cross-coupling reactions typically proceed via closely related mechanisms. As an example, a Suzuki reaction starts with a Pd (0) species (21) typically obtained through a reduction of Pd (II) through a ligand association/dissociation process. Phosphine or nitrogen based ligands are commonly used for these types of reactions. This Pd (0) species (21) undergoes an oxidative addition into an aryl halide bond (22) forming a Pd (II) species. This species then undergoes a ligand exchange followed by a transmetallation with the organometallic species (25). Finally this bi-aryl palladium species (26) proceeds through a reductive elimination forming a new carbon-carbon bond between two aryl groups and regenerates the active Pd (0) species (21). This regeneration of Pd (0) allows for the use of a catalytic amount of palladium. Therefore, palladium is not consumed in the reaction and

theoretically can be reused indefinitely. However, in practice, turnover of the palladium catalyst is limited, leading to a small amount of metallic waste.

These characteristics and the advantages previously outlined have allowed the Suzuki reaction to attract significant interest from researchers and have led to its use in industrial applications. Researchers at the Abbott process research and development laboratories have applied the use of a Suzuki reaction in their synthesis of ABT-869, a tyrosine kinase inhibitor.[16] This molecule was found to have inhibitory effects on tyrosine kinase, which is essential in the process of angiogenesis associated with developing cancerous cells. As such, this small molecule (30) was seen as a potential cancer therapeutic and the synthesis was scaled up to produce 100 kg.



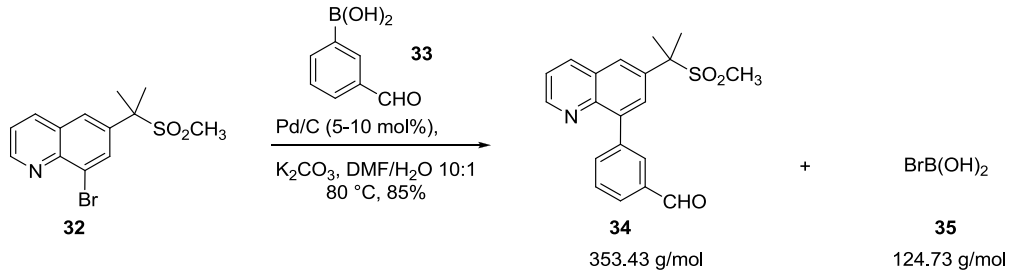
Scheme 7 – Abbott synthesis of ABT-869, a tyrosine kinase inhibitor

This industrial synthesis of ABT-869 employed a late stage Suzuki reaction of advanced intermediate boronic ester (28) and chlorinated indazole (29). The synthesis employed the use of 2 mol% of palladium acetate as a catalyst with 1,1'-Bis(diphenylphosphino)ferocene (dppf) as a ligand producing the desired inhibitor ABT-869 in a yield of 84% after purification. As a by-product of the reaction, a borate salt is obtained and has a molar mass of 162.42 g/mol (31). This by-product, discarded as waste, constitutes approximately 30% of the mass balance of the reaction, not including the use of additional

[16] Kruger, A. W.; Rozema, M. J.; Chu-Kung, A.; Gandarilla, J.; Haight, A. R.; Kotecki, B. J.; Richter, S. M.; Schwartz, A. M.; Wang, Z. *Org. Process Res. Dev.* **2009**, *13*, 1419.

reagents. As such, the production of 100 kg of ABT-869 also produces an additional 30 kg of borate salt as by-product that would have to be subsequently disposed.

A second example was performed in collaboration between the process laboratories of Merck Research Laboratories and Merck Frosst. They describe an efficient scalable synthesis of a PDE4 inhibitor that could be used as a therapeutic for inflammation in the treatment of pulmonary diseases.[17]



Scheme 8 – Merck's synthesis of advanced intermediate (34) for the synthesis of a PDE4 inhibitor.

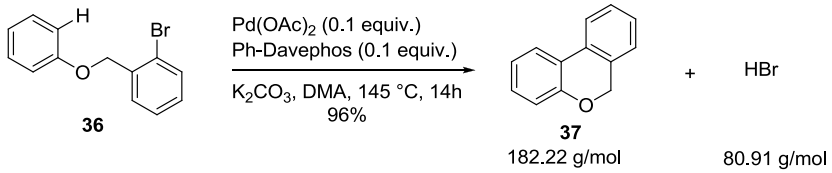
Brominated intermediate (32), was reacted with boronic acid (33) under palladium catalysis conditions to provide advanced intermediate (34). To minimize palladium leeching into the final product, Merck employed a strategy of using a carbon mounted palladium complex as a heterogeneous catalyst optimized from an original reaction employing $Pd(OAc)_2$ as a homogeneous catalyst. This strategy of employing a heterogeneous catalyst helps to facilitate the recycling of palladium. After the reaction was completed, the mixture was filtered and the filter cake was washed, separating the solid palladium from the desired product in solution. As with the synthesis of ABT-869 (Scheme 7), a borate salt is produced as a corresponding by-product of the reaction. This synthesis demonstrates a slight increase in mass efficiency since the borate salt only composes 26% of the produced mass balance.[17] Furthermore, the use of a heterogeneous catalyst decreases the environmental impact by minimizing palladium leeching

[17] Conlon, D. A.; Drahus-Paone, A.; Ho, G.-J.; Pipik, B.; Helmy, R.; McNamara, J. M.; Shi, Y.-J.; Williams, J. M.; Macdonald, D.; Deschênes, D.; Gallant, M.; Mastracchio, A.; Roy, B.; Scheigetz, J. *Org. Process Res. Dev.* **2006**, *10*, 36.

into the reaction mixture. This reduces the requirements for further subsequent purification steps to remove the metal contaminant.

Chapter 1.4 - C-H Activation

Although the atom economy of the Suzuki reaction can be improved through the use of lower molecular weight boronic acids or boronic esters and less massive halogens or pseudo halides, the production of these boronate salts is an intrinsic limitation of the Suzuki reaction that cannot be overcome. As such, recent developments in palladium cross-coupling chemistry have been focused on the elimination of the requirement for stoichiometric organometallic cross-coupling partners. Pioneering work by the Fagnou research group at the University of Ottawa in 2004, demonstrated the intramolecular cross-coupling between an unactivated aryl group and an aryl bromide (36).[18]

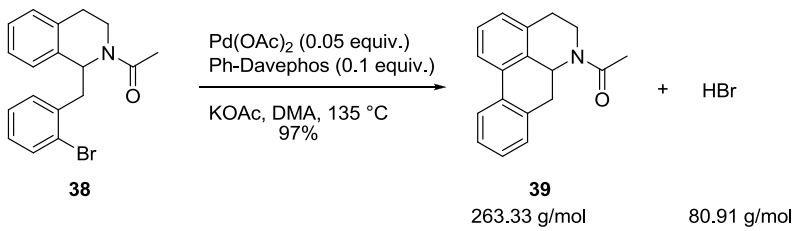


Scheme 9 – C-H activation of a tethered bi-aryl.

This novel reactivity requires no organometallic component and produces no metallic waste other than the catalyst. As such, this reaction demonstrates a step forward in the efficiency of palladium cross-coupling reactions.

Later that year, the intramolecular C-H activation of a tethered bi-aryl was applied towards the synthesis of aporphine alkaloids, which were found to have activity as serotonergic, dopaminergic, antiplatelet and vasorelaxing agents (Scheme 10).[19]

[18] Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.
[19] Lafrance, M.; Blaquière, N.; Fagnou, K. *Chem. Comm.* **2004**, 2874.



38 **39**

263.33 g/mol 80.91 g/mol

Scheme 10 – C-H activation towards the synthesis of aporphine alkaloids

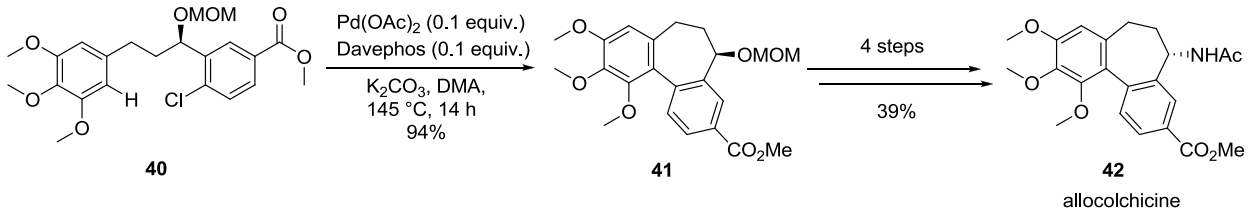
Synthesis of these natural products further demonstrates the applicability and utility of this greener palladium cross-coupling reaction. C-H activation was performed late in the synthesis demonstrating the ability for both cross-coupling partners to be carried through multiple step syntheses which is typically not facile for classical cross-coupling reactions.

The scope of potentially reactive aryl halides was extended to aryl chlorides in the following years, by repeating the synthesis of tethered bi-aryl compounds.[20] Optimized conditions were established using an *N*-heterocyclic carbene ligand resulting in the synthesis of 5 and 6 membered centre rings in high yields. This method was subsequently applied towards the synthesis of allocolchicine, a microtubule depolymerisation agent that has potential as anti-tumour agents.[21]

The synthesis of allocolchicine presented a new challenge to the application of C-H activation since it contained a difficult 7-membered medium sized ring (Scheme 11). Previously, only 5 and 6 membered rings were prepared employing this chemistry. Seven membered rings typically suffer from unfavorable entropic effects and produce ring strain, increasing the difficulty of formation.[22] Entropic difficulties arise from changing the conformation of linear chains with high flexibility and rotation to a ring system that minimizes free rotation. Enthalpic effects associated with ring strain are also a factor that must be overcome for the synthesis of these medium sized rings. The ring conformation forces substituents to be closer in space, increasing steric hindrance for larger substituents. As such, the synthesis of the

[20] Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857.
[21] Leblanc, M.; Fagnou, K. *Org. Lett*. **2005**, *7*, 2849.
[22] Dale, J. *Angew. Chem. Int. Ed., Engl.* **1966**, *5*, 1000.

seven membered ring in allocolchicine represents a significant advancement in the field of direct arylation.

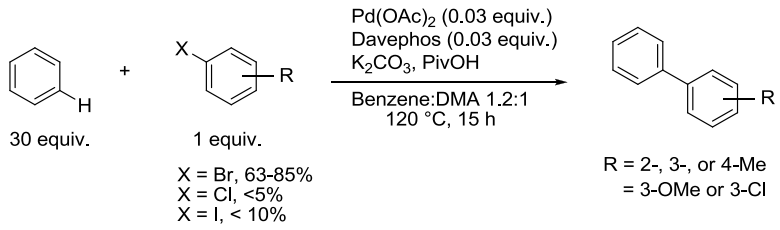


Scheme 11 – Synthesis of allocolchicine from an advanced intermediate (41)

Advanced intermediate (40) was synthesized in 5 steps with an overall yield of 54%. This substrate was then subjected to direct arylation using $Pd(OAc)_2$ as a palladium source and Davephos as a ligand, producing the desired 7-membered ring (41) in 94% yield. The 7-membered ring was subsequently transformed into allocolchicine (42) over 4 steps with an overall yield of 39%. This substrate demonstrated the versatility of direct arylation by synthesizing a difficult medium sized ring and also employing the use of chlorine as a halogen, which is typically less reactive than the corresponding bromide or iodide. However, the chemistry is limited to tethered bi-aryl syntheses and can only be applied to intramolecular arylations.

In 2006, a series of papers addressed the issue of tethered direct arylations allowing for the direct intermolecular arylation of 6-membered aromatic rings (Scheme 12).[23] Optimizations of the reaction found that PivOH was an essential additive to the reaction increasing conversions from <5% to approximately 100%. Furthermore, due to the typical inertness of aromatic hydrogens and potential for aryl bromide homocoupling, a large excess of benzene is required to obtain high yields. The scope of the reaction was also determined, demonstrating high tolerance for a variety of aryl bromides

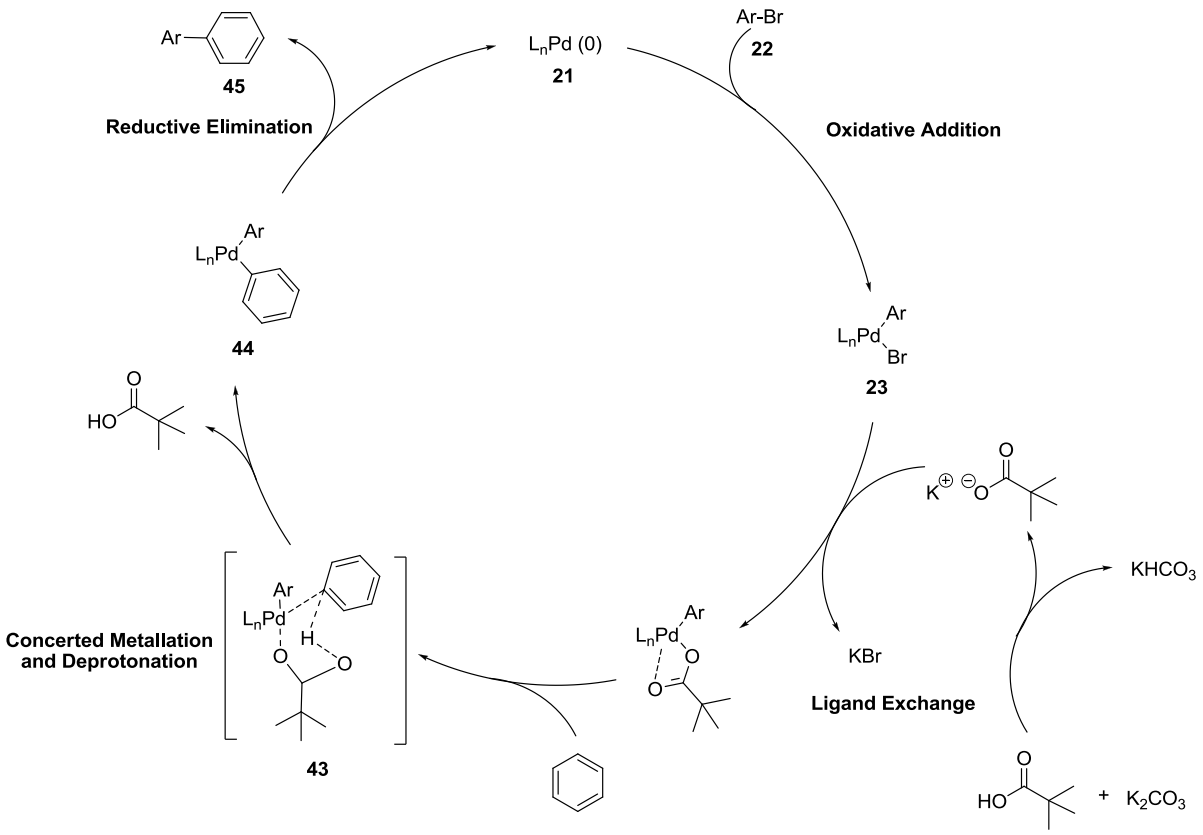
[23] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.



Scheme 12 – Intermolecular C-H activation of benzene

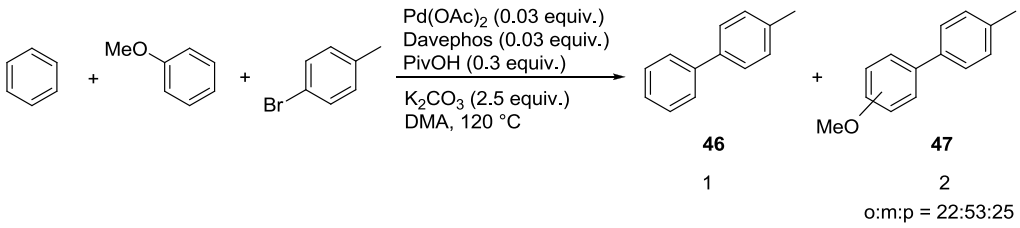
The scope of the reaction is relatively broad and tolerant to different steric effects all in excellent yields. Electron-rich and -poor aryl bromides are also well tolerated in good to excellent yields. Different halides however were less well tolerated; the typically more reactive iodide resulted in less than 10% yield and the aryl chlorides, which functioned excellently in intramolecular arylation, resulted in less than 5% yield. Pivalic acid was found to play an important role helping with the deprotonation step and the metallation of the aryl group to generate a palladium bi-aryl species common to previous cross-coupling reactions.

Related to the mechanism for the Suzuki reaction (Scheme 6), the mechanism for C-H activation begins with a Pd (0) catalyst (21). This Pd (0) species then undergoes an oxidative addition into an Ar-Br (22) bond providing a Pd (II) species (23). Ligand exchange on Pd(II) occurs with pivalate generated through the deprotonation of pivalic acid. Benzene then coordinates to the Pd (II) species (43) and the oxygen of pivalate then in a concerted mechanism undergoes a deprotonation and metallation. This releases pivalic acid, which can be deprotonated to re-enter the cycle, and generates a bi-arylated palladium species (44). This then undergoes reductive elimination regenerating the Pd (0) catalyst (21) and forming a C-C bond between two aryl species (45).



Scheme 13 – Proposed mechanism for C-H activation

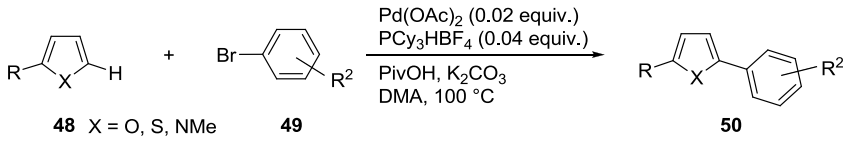
A competition experiment where an electron-rich anisole was reacted alongside benzene with *para*-bromotoluene revealed that electron-rich aromatic rings undergo C-H activation less likely than electron-neutral aromatic rings. Furthermore, electron deficient aromatics are preferentially arylated. However issues arise when these conditions are applied to aromatic compounds with multiple non-equivalent hydrogens. These reactive hydrogens allow for non-selective C-H activation leading to a mixture of products (Scheme 14).



Scheme 14 – C-H activation of non equivalent hydrogens

C-H activation of anisole, containing different reactive hydrogens, with bromotoluene gives a mix of regioisomers. The ratio obtained for *meta* and *para*-arylation, 50% and 25% respectively, suggests that electron donating substituents have little effect on the overall reactivity since the ratio obtained is consistent with the ratio of reactive hydrogens. *Ortho* substitution, however, obtained in 22%, is the least reactive position and does not correspond to the ratio of hydrogens. If the distribution of regioisomers was dependent solely on the ratio of hydrogens, a similar ratio for *ortho* and *meta* substitution would be expected. This observation however can be explained through steric effects. Both pivalate and palladium need to coordinate to the hydrogen being deprotonated, thus an *ortho* substituent will cause steric repulsion effects to the large *tert*-butyl group present on the pivalate and the large phosphine ligands present on palladium. This demonstrates that, although the regioselectivity of the reaction can be somewhat controlled through steric effects, mixtures of regioisomers will be obtained when more than one reactive hydrogen is present.

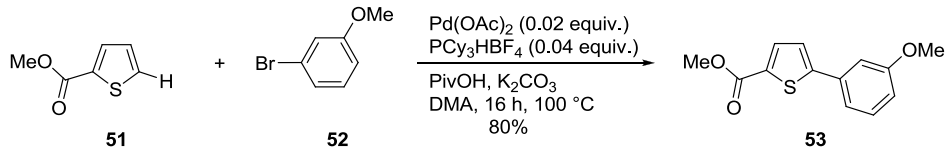
The scope and utility of C-H activation was further expanded in 2009 to a variety of heteroaromatics with different aryl bromides (Scheme 15).[24] This reaction was found to be effective for heteroaromatics of all types including thiophene, furan, *N*-substituted pyrroles, *N*-substituted imidazole, triazole, thiazole and oxazole and aryl bromides with various electron-donating and -withdrawing substituents. However, the general scheme presented in the paper (Scheme 15, R=H) is slightly misleading as the heteroaromatic has reactive hydrogens on both the 2 and 5 position of the ring.



Scheme 15 – C-H activation on heteroaromatics with aryl bromides

[24] Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

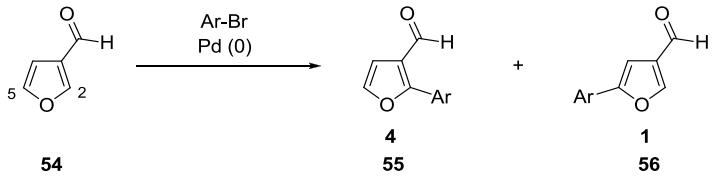
Having both C2 and C5 hydrogens present in a non symmetrical heteroaromatic would typically generate a mix of regioisomers resulting in mixtures of products and increasing the difficulty of purifications. As such, to alleviate the problems with a lack of regioselectivity, Fagnou and co-workers employed the use of blocking groups at either position, reducing the reactive sites to one. This strategy allows for selective C-H activation of a specific hydrogen without generating mixes of regioisomeric products.



Scheme 16 – C-H activation of methyl thiophene-2-carboxylate (51) with 3-bromoanisole (52)

As an example, the reaction of methyl thiophene-2-carboxylate (51) with 3-bromoanisole (52) gives *mono*-arylation at the 2 position since the 5 position of the thiophene is blocked with a methyl ester. This has proven to be an effective strategy for regioselective arylation and an improvement in the utility and applicability of C-H activation.

Another solution to the regioselectivity issues attributed to C-H activation of heteroaromatics was presented by Doucet and co-workers in 2010. Varying the steric environment at the C3 position allowed the influencing of C-H activation to the C2 or C5 positions.[25]



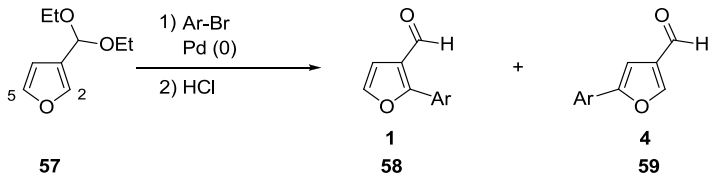
Scheme 17 – Regioselective control using a C3 aldehyde

With activated hydrogens at the C2 and C5 position of the furan, typically an equimolar amount of arylation would occur giving a mixture of regioisomers. However, by varying substituents on C3, the regioselectivity of the reaction can be influenced. Having a non-sterically encumbered aldehyde at C3

[25] Dong, J. J.; Doucet, H. *Eur. J. Org. Chem.* **2010**, *611*, 615.

allows for minimal steric interference and results typically in a 4 to 1 ratio of arylation favoring the C2 position.

Switching the C3 substituent to the bulkier acetal substituent increases steric interference and therefore the C2 position is less favourable for C-H activation. Thus the regioselectivity of C-H activation can be reversed giving a 4 to 1 ratio in favour of the C5 position. The acetal is subsequently hydrolyzed to reveal the aldehyde.



57 **1** **58** **4** **59**

Scheme 18 – Regioselective control using a C3 acetal

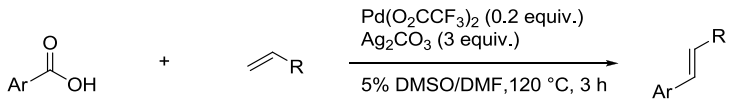
Regioselectivity of C-H activation can be controlled through the use of different blocking groups minimizing reactive sites and through the use of different sterically hindered groups at the C3 position. However, these strategies suffer from limitations. Installation of a blocking group at a desired position and timing can prove to be difficult in larger more complex molecules limiting the utility of this strategy. The use of different sterically hindered groups at C3 to direct arylation is also not an ideal strategy since it still results in a mixture of regioisomers and is typically difficult to purify.

C-H activation has proven to be an effective method in arylation, requiring no pre-activation or the use of traditional organometallic cross-coupling partners reducing waste production. This method has since been widely applied to a number of different aromatic and heteroaromatic substrates including total syntheses of natural products. Strategies have also been developed to circumvent the limitations associated with regioselectivity through the use of blocking or directing groups. However, these strategies suffer from limitations allowing for improvement in the area of green arylation without the use of organometallic cross-coupling partners.

Chapter 1.5 - Decarboxylative Cross-Coupling

To address the common limitations associated with classical methods of cross-couplings, such as the production of stoichiometric metallic waste and the use of sensitive organometallic reagents, modern alternatives such as C-H activation were developed to alleviate these issues. However, it also suffers from limitations with regioselectivity hindering applicability and versatility. To address these limitations associated with classical methods and C-H activation, alternative organometallic replacements have been investigated. It was found that carboxylic acids could mimic the metal portion of an organometallic reagent, allowing for cross-couplings to occur. Carboxylic acids are typically stable functional groups that can easily be protected as esters to be carried through multiple step syntheses, allowing for arylation at desired points in the synthetic route. However, this intrinsic stability translates to a high energy barrier that has to be overcome to facilitate the reaction.

An early example of a catalytic decarboxylative-cross coupling reaction was described by Myers and co-workers in 2002. They found that an aromatic carboxylic acid could be cross-coupled in a decarboxylative Heck type coupling with various olefins using a catalytic amount of palladium with silver carbonate (Scheme 19).[26]

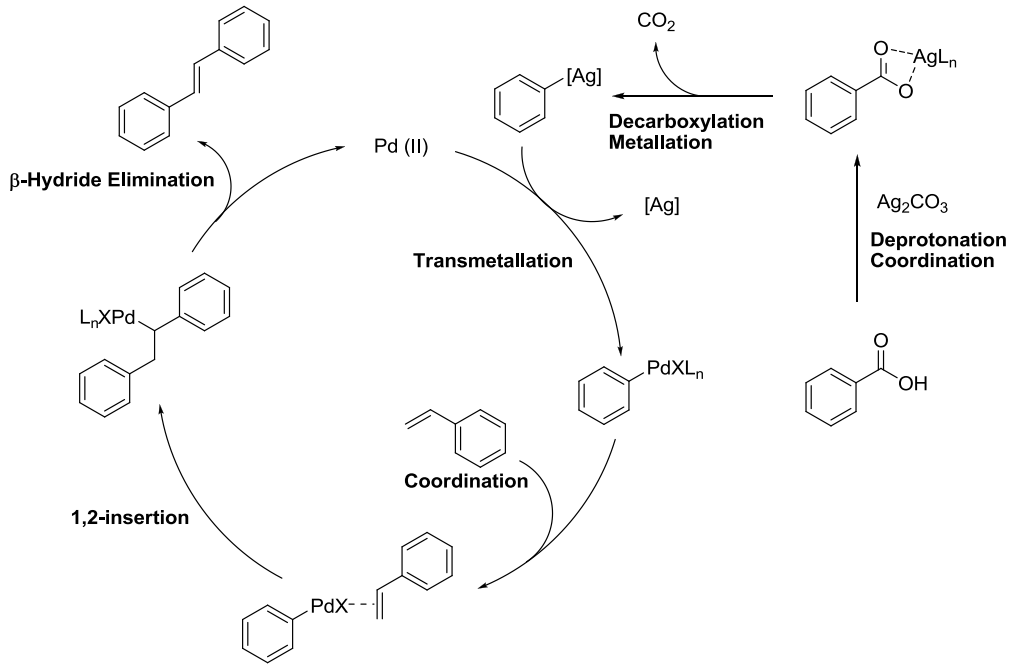


Scheme 19 – Myers decarboxylative Heck reaction

Palladium sources were screened for their ability to promote decarboxylative coupling between 2,4,5-trimethoxybenzoic acid and styrene. They found that heating the mixture of the acid, styrene, palladium and copper (II) trifluoroacetate provided the desired product in 82% yield. However, this reaction was found to be more difficult with less electron-rich carboxylic acids, where only recovered starting material was obtained. As such, it was determined the decarboxylation step was the main difficulty of

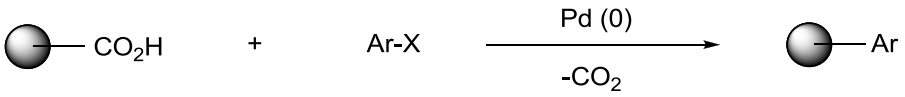
[26] Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

the reaction. Switching the base and additive to Ag_2CO_3 was found to be instrumental in improving the decarboxylation step. This suggests the silver coordinates the carboxylic acid and lowers the energy barrier for decarboxylation (Scheme 20).



Scheme 20 – Proposed mechanism for Myers decarboxylative Heck reaction

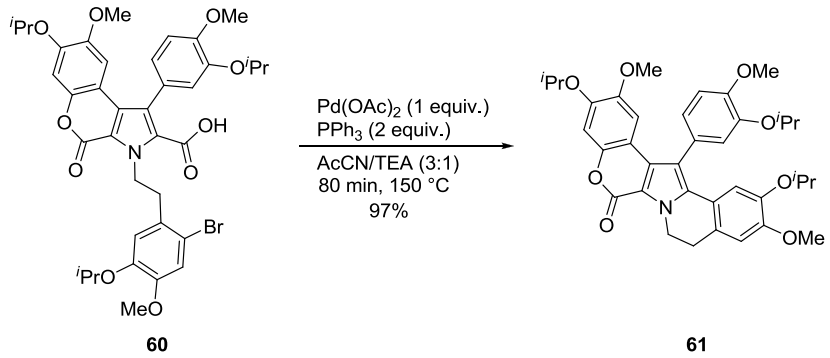
The two metals in the reaction work in concert, starting with the silver coordinating to the carboxylic acid allowing a decarboxylation metallation sequence substituting silver for the carboxylic acid. The subsequent aryl silver complex undergoes a transmetallation with palladium generating an aryl palladium species and a silver complex. This aryl palladium then can coordinate the olefin and undergo a 1,2-insertion across the double bond. This species then undergoes a *β*-hydride elimination giving the desired product and releasing the Pd (II) catalyst. This reactivity allowed for the coupling of different aromatic carboxylic acids with different olefins however the process differs in mechanism and was not optimized for the cross-coupling of aromatics. A general decarboxylative cross-coupling of aromatics could be envisioned to follow a similar strategy employing the use of a metal additive to facilitate decarboxylative metallation (Scheme 21).



Scheme 21 – General decarboxylative cross-coupling

The aromatic carboxylic acid substituent could undergo a decarboxylative metallation, allowing the formation of an organometallic cross-coupling partner in situ and thus avoiding the need for pre-activation. This species could then undergo transmetallation with an aryl palladium complex generating a bi-aryl palladium species common to previous cross-coupling reactions leading to the formation of an aryl aryl bond. Although the reaction is slightly less atom economical than C-H activation, the only by-product of the reaction is carbon dioxide. Furthermore, the production of carbon dioxide gas also makes the reaction irreversible and drives the reaction forward.

In contrast to work performed by Myers, an early report by Steglich and co-workers demonstrated the intramolecular decarboxylative cross-coupling of two aryl groups for the synthesis of lamellarin L without the use of a metal additive.[27] Lamellarin L is a hexacyclic alkaloid isolated from prosobranch mollusks that have been found to inhibit the growth of several tumor cell lines.



60 **61**

Scheme 22 – Intramolecular decarboxylative cross-coupling in the synthesis of lamellarin L.

An advanced intermediate (60) was heated with a stoichiometric amount of palladium acetate and a phosphine ligand at 150 °C for 80 min facilitating the decarboxylative cross-coupling between a tethered aryl bromide and a carboxylic acid present on the 2 position of the pyrrole. Alternatively C-H activation

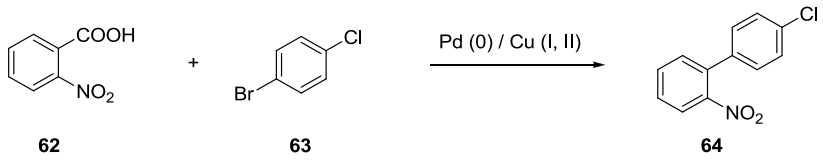
[27] Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. -Eur. J.* **2000**, *6*, 1147.

could also have been used; however, as demonstrated by Fagnou and co-works (Scheme 14) sterically hindered, *ortho*-substituted aryl halides typically generated the product in low yields. Although a stoichiometric use of palladium for cross-coupling reactions is not ideal, this example represented a proof of principle for the development of a catalytic decarboxylative cross-coupling reaction without the use of metal additives.

Utilizing principles demonstrated by Myers in the decarboxylative Heck reaction and Steglich in the synthesis of lamellarin L, carbon-carbon bond forming reactions between two aryl groups using a decarboxylative cross-coupling was established by three different groups around the same time. The works of Gooßen and co-workers focused primarily on the decarboxylative cross-coupling of benzoic acids using a copper palladium system, the group of Becht employed a silver palladium system and the group of Forgione and Bilodeau focused primarily on the decarboxylative cross-coupling of heteroaromatic carboxylic acids with palladium.

Chapter 1.6 - Gooßen decarboxylative cross-coupling

Decarboxylation of benzoic acids using copper was initially established by Nilsson and co-workers in 1966. They described an aryl copper species that was captured with an excess amount of iodobenzene, producing bi-phenyl products.[28] Since Ullmann-type chemistry had intrinsic limitations such as low selectivity for heterocoupling and uses stoichiometric amounts of copper, Gooßen and co-workers envisioned the use of a bi-metallic catalyst system to facilitate decarboxylative cross-coupling. In 2006, they described a decarboxylative cross-coupling of benzoic acids with aryl bromides to generate bi-phenyl motifs.[29,30] Bi-phenyls were a common motif among some of the top selling drugs of the time, demonstrating the importance and potential impact of this transformation. Using a bi-metallic catalyst system employing copper and palladium, it was found the copper would initially coordinate with the carboxylic acid to facilitate decarboxylation to form an aryl copper bond. This aryl copper species then undergoes a transmetallation with palladium (II) generating a di-arylated palladium species, a common intermediate of cross-coupling reactions. Optimization studies of the decarboxylative cross-coupling reaction using 2-nitrobenzoic acid (62) and 4-bromochlorobenzene (63) as a model reaction was evaluated, which could be used towards the synthesis of Boscalid.



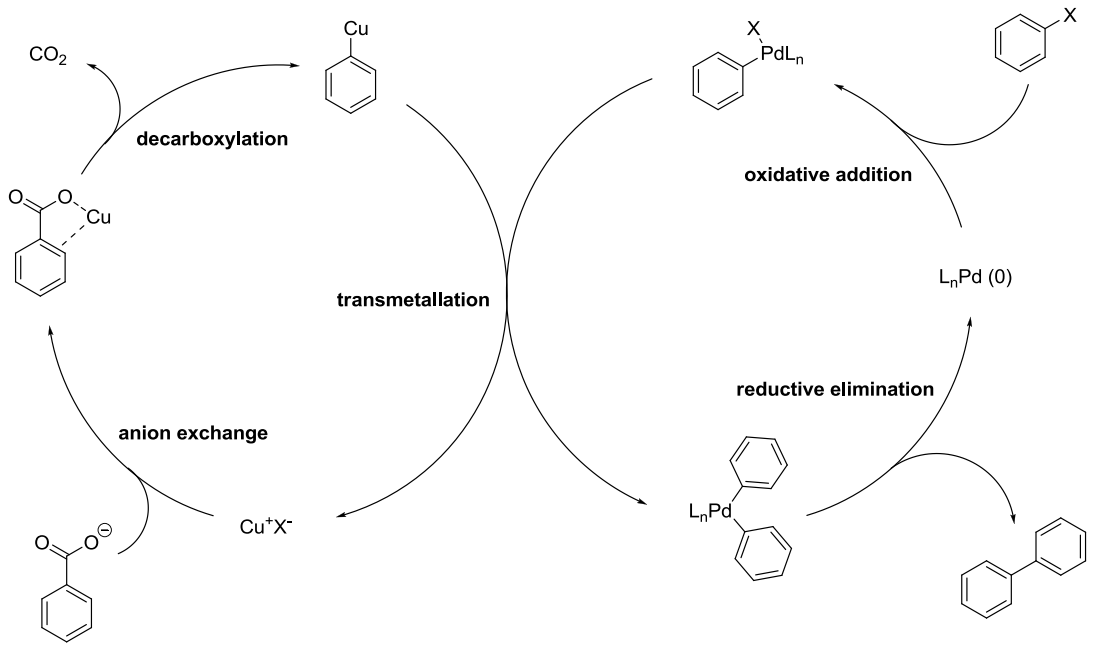
62 **63** **64**

Scheme 23 – Synthesis of Boscalid intermediate using decarboxylative cross-coupling

Formation of the desired bi-aryl compound (64) was not observed when heated with a palladium source and a phosphine ligand, nor was it observed when just heated with a copper (II) source in the absence of palladium. The combination of both metals proved to be effective in the synthesis of the desired bi-

[28] Nilsson, M. *Acta Chem. Scand. A* **1966**, *20*, 423.
[29] Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
[30] Gooßen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824.

aryls and optimization of the reaction conditions were then performed. They found that $Pd(acac)_2$, P(*i*-Pr)Ph_2, $CuCO_3$, KF and molecular sieves in NMP to be the optimal conditions. However, the stoichiometric use of Cu(II) was undesirable and as such optimizations for the use of sub-stoichiometric amount was attempted. The active copper species could theoretically be regenerated after transmetallation with the palladium allowing for a catalytic amount of copper to be used. This however was found to be unsuccessful as the Cu (II) species would irreversibly reduce to Cu (I) which proved to be unreactive under these conditions. As such, the conditions were re-optimized using the less reactive Cu (I) species at an increased temperature. The optimal conditions, CuI (1 mol%), $Pd(acac)_2$ (0.5 mol%) and phenanthroline (3 mol%) in NMP, was then applied to a variety of aryl carboxylic acids and coupled with aryl bromides.



Scheme 24 - Gooßen decarboxylative cross-coupling mechanism

Bearing some similarities to the decarboxylative Heck reaction described by Myers, the decarboxylative cross-coupling reaction requires the use of two metals in the mechanism, but in catalytic amounts rather than stoichiometric. Similar to the silver used by Myers to facilitate decarboxylation, Gooßen

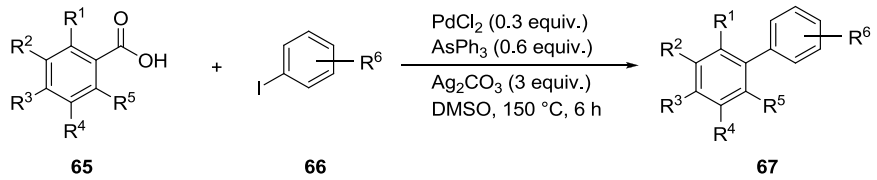
employed the use of a copper species for a similar purpose. A copper (I) species was shown to be more stable than either copper (II) sources or silver and as such the decarboxylation requires higher temperatures to occur. Copper (I) undergoes an anion exchange with the carboxylate and subsequently facilitates a decarboxylation metallation giving an aryl copper species. This then undergoes a transmetallation with an aryl palladium (II) species that was generated through the oxidative addition into the aryl halide bond. Transmetallation regenerates the active copper species and produces a diarylated palladium (II) complex. This complex then undergoes reductive elimination producing the desired aryl aryl bond and regenerating palladium (0).

The use of a catalytic amount of metal for decarboxylation proves to be advantageous in minimizing the amount of copper required for reactivity. This regeneration of copper also reduces the amount of metallic waste produced and as such renders the reaction more environmentally friendly. The scope of this method for the formation of bi-aryls was later expanded to α-oxocarboxylates,[31] chlorides[32] and tosylates.[33]

[31] Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043.
[32] Gooßen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103.
[33] Gooßen, L. J.; Rodriguez, N.; Lang, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111

Chapter 1.7 - Becht decarboxylative cross-coupling

In 2007, Becht and co-workers developed a decarboxylative cross-coupling reaction between a variety of benzoic acids and aryl iodides.[34] They employed the use of silver to help facilitate decarboxylation and metallation. The aryl silver species subsequently undergoes a transmetallation with palladium and to facilitate the cross-coupling.



Scheme 25 – Becht decarboxylative cross-coupling

Becht and co-workers employed the use of silver carbonate to serve a dual purpose, acting as both a base and to co-ordination to the carboxylic acid and facilitate decarboxylation. Similar to previously reported palladium catalyzed decarboxylative cross-coupling reactions elevated temperatures were required to overcome the intrinsic stability of carboxylic acids. Optimizations of the palladium source and ligand found that palladium chloride was optimal but required loadings of 30 mol%. Lower palladium loadings were found to be detrimental to the yield of the desired cross-coupling product. Initial results employing phosphine-based ligands gave moderate yields and optimizations with a variety of ligands found that triphenylarsine was the preferred ligand. Similar to the mechanism presented by Gooßen (Scheme 20) silver was employed to facilitate the decarboxylation of benzoic acids (65). The aryl silver species then undergoes a transmellation with an aryl bound palladium (II) species, generating a bis-arylated palladium (67). This species then undergoes a reductive elimination, regenerating the palladium (0) catalyst and forming the carbon-carbon bond.

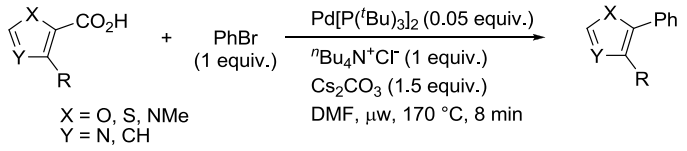
This method gave a wide range of substituted bi-aryl products from good to excellent yields. However, the requirement for high palladium and ligand loadings were not ideal from an environmental

[34] Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

perspective limiting industrial applications of this process. As such, focus was placed on the more efficient Gooßen decarboxylative cross-coupling and the Forgione and Bilodeau decarboxylative cross-coupling reactions.

Chapter 1.8 - Forgione and Bilodeau decarboxylative cross-coupling

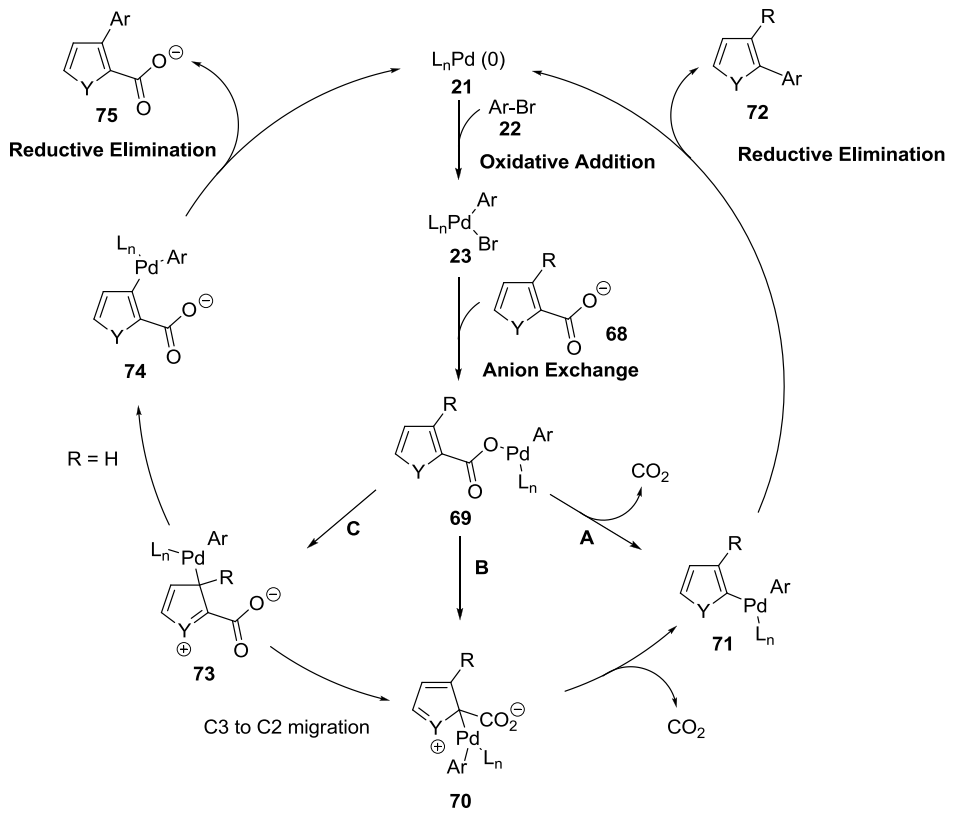
A different decarboxylative cross-coupling was developed by Forgione and Bilodeau at Boehringer Ingelheim in 2006, which formed carbon-carbon bonds between heteroaromatic and aromatic compounds.[35]



Scheme 26 – Forgione and Bilodeau decarboxylative cross-coupling

Similar to the previous decarboxylative cross-coupling reactions, an aromatic carboxylic acid was reacted with an aryl halide with palladium to generate a new carbon-carbon bond. Although this reaction is a related decarboxylative cross-coupling there are significant differences from the previous bi-metallic systems. The only metal present in the reaction is palladium which suggests a different mechanism for decarboxylation. Another significant difference is the short reaction times for this reaction compared to alternatives and the use of microwave heating rather than conventional thermal heating. The final major difference is the use of tetrabutylammonium chloride as an additive that was found to minimize unwanted C3 arylation. Having only catalytic equivalents of a single metal present in the reaction and the observation of a bis-C2 and C3 arylated product, Forgione and Bilodeau proposed a mechanism to explain these observations.[36]

[35] Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.
[36] Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550.



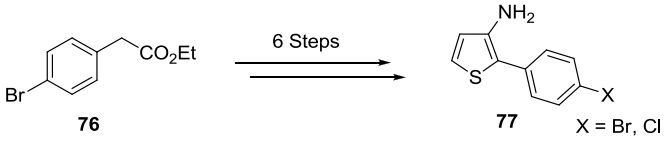
Scheme 27 – Forgione and Bilodeau decarboxylative cross-coupling mechanism

The mechanism starts with a Pd (0) complex (21) which undergoes oxidative addition into an aryl bromide bond (22). Anion ligand exchange with the palladium (II) species (23) then occurs producing a palladium carboxylate species (69). From this intermediate (69), three different potential pathways were possible; path A: direct extrusion of CO_2, path B: C2 electrophilic palladation and path C: C3 electrophilic palladation. Path A, a direct extrusion of CO_2 would allow for immediate C2 palladation (71) that could undergo reductive elimination, regenerating palladium (0) (21) and giving the desired product (72). This pathway however was believed to not be the mechanism of action since it does not make use of the heteroatom present in the aromatic ring that was shown to be essential for this transformation. Direct extrusion of CO_2 would also allow benzoic acids to be reactive substrates under these conditions, however they were found to not be reactive, supporting an alternative mechanistic pathway. Pathway B employed the use of the heteroatom present in the ring to facilitate a C2 electrophilic palladation (71). This could then undergo irreversible decarboxylation to restore

aromaticity and generate the same diarylated compound formed in pathway A. This intermediate then undergoes reductive elimination to form a new carbon-carbon bond. The final pathway, path C, was proposed based on a by-product isolated from the reaction. C3 electrophillic palladation was found to occur which can be explained through the delocalization of electrons from the heteroatom. If the C3 substituent is hydrogen, this can be deprotonated to regenerate aromaticity giving rise to a C3 palladium aryl species. This then undergoes reductive elimination to regenerate palladium (0) (21) and form a C3-aryl bond (75) leaving the carboxylate present, which can re-enter the catalytic cycle and undergo subsequent arylation at C2, providing the observed 2,3-diarylated by-product.

This decarboxylative cross-coupling represents a more efficient and greener process than the previously mentioned methods since it employs low palladium loadings and does not require a second metal as a base or a co-catalyst. This method also employs microwave heating over traditional thermal heating for short reaction times, which consumes less energy. Forgione, Bilodeau and co-workers elaborated on the scope of the reaction demonstrating with a variety of heteroaromatic, aryl halides and pseudo halides.[36]

Further demonstrating the efficiency and applicability of this reactivity, work by Mitchell and co-workers applied this chemistry towards the industrial synthesis of an important key intermediate for an undisclosed drug synthesis.[37]

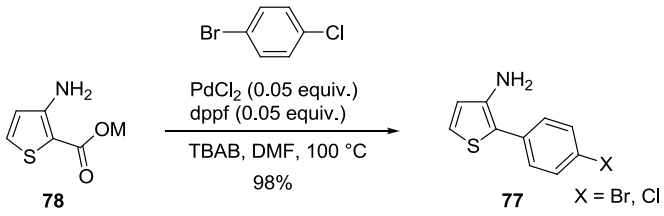


Scheme 28 – Mitchell generation 1 synthesis of key intermediate

The generation 1 synthesis started from 4-bromophenyl-ethylacetate (76) and after 6 steps, key intermediate (77) was generated in an overall yield of 34%. As a low yielding process, this synthesis

[37] Mitchell, D.; Coppert, D. M.; Moynihan, H. A.; Lorenz, K. T.; Kissane, M.; McNamara, O. A.; Maguire, A. R. *Org. Process. Res. Dev.* **2011**, *15*, 981.

generated significant amounts of waste and by-products that was not desired from both an industrial and environmental perspective. Due to these factors, Mitchell and co-workers explored various options for the synthesis of the key intermediate (77). They found that starting with 3-aminothiophene-2-carboxylate they could undergo a decarboxylative cross-coupling with an aryl halide to efficiently generate the desired key intermediate in a single step.



Scheme 29 – Mitchell generation 2 synthesis of key intermediate

Optimizations of a decarboxylative cross-coupling between carboxylate (78) and 4-chloro bromobenzene produced the desired key intermediate (77) in a 98% yield. When compared to the 6 step 34% yield generation 1 synthesis, the amount of waste produced is dramatically reduced and the efficiency of the process is increased. Furthermore, the synthetic route was reduced from 6 steps to a single step which allowed greater access of the desired key intermediate (77).

Decarboxylative cross-coupling has proven itself as a green alternative to classical cross-coupling methods. It also circumvents the limitations associated with C-H activation and has been proven to be effective on an industrial scale. However, decarboxylative cross-coupling is a relatively novel reaction that requires further development and applications.

CHAPTER 2 – RESULTS AND DISCUSSION

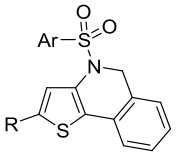
Chapter 2.1 – Project introduction

Thienoisoquinoline systems have been found to have interesting biological activity as a potential breast cancer therapeutic.[1] However, these heterocyclic tricycles are scarcely reported in the literature and present an interesting area of potential research opportunity. Furthermore, designing novel syntheses of these compounds should employ the principles of green chemistry to facilitate sustainable syntheses of these important molecules.

3,4-thienoisoquinoline 2,3-thienoisoquinoline

Figure 3 – Thienoisoquinolines

Previous structure activity relationship and biological activity studies performed by Wyeth in 2006[1] demonstrated the inhibitory activity of functionalized thienoisoquinolines against estrogen receptor NFκB.



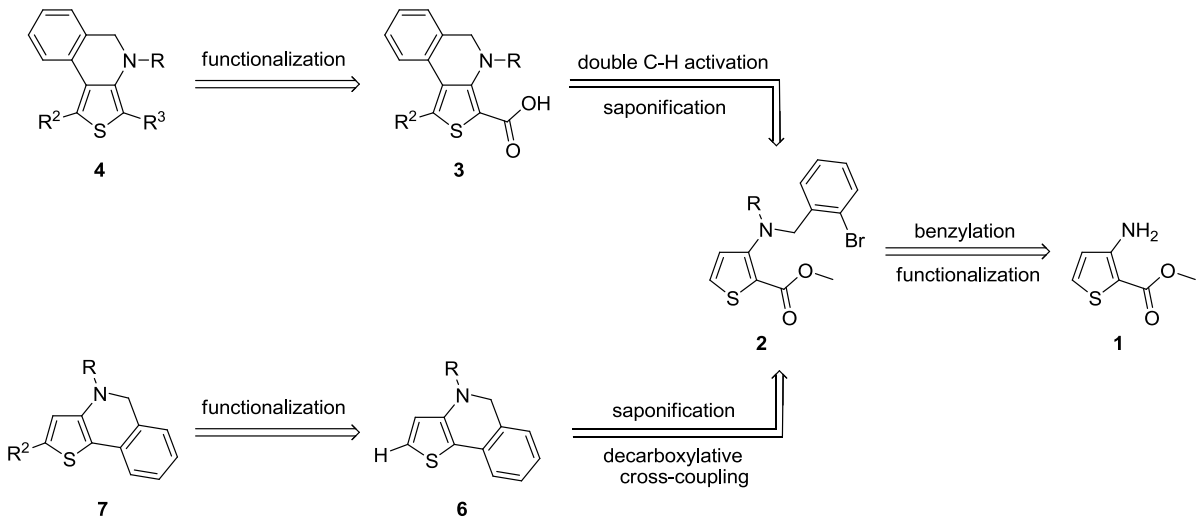
Ar = 4-OH-C_6H_4, 4-MeO-C_6H_4
R = Ar^2, H, Br

Figure 4 – Example of estrogen receptor NFκB inhibitors

Inhibition of this receptor can lead to potential therapeutics for the treatment of breast cancer, inflammation associated with congestive heart failure, inflammatory bowel disease and arthritis. [38] Other potential therapeutic areas include type II diabetes,[39] osteoarthritis,[40] asthma,[41] Alzheimer's

[38] Biswas, D. K.; Shi, Q.; Baily, S.; Strickland, I.; Ghosh, S.; Pardee, A. B.; Iglehart, J. D. *Proc. Nat. Acad. Sci.* **2004**, *101*, 10137.
[39] Yuan, M.; Konstantopoulos, N.; Lee, J.; Hansen, L.; Li, Z. W.; Karin, M.; Shoelson, S. E. *Science* **2001**, *293,* 1673.

disease, and autoimmune diseases.[1,42] Thus the synthesis of these compounds presents an important area of research with unexplored potential. Previously, there has only been a single report of the synthesis of 3,4-thienoisoquinolines[48] and a few reports of 2,3-thienoisoquinolines.[1] However, previous syntheses of these compounds did not facilitate functionalization and typically employed harsh synthetic conditions or lengthy syntheses. Therefore a retrosynthesis of the two isomers was envisioned from a single common intermediate which would allow for easy access of either functionalized thienoisoquinoline isomer.



Scheme 30 – Retrosynthesis of both thienoisoquinolines

The 3,4-thienoisoquinoline isomer (4) can be functionalized from the versatile carboxylic acid through a variety of transformations. The carboxylic acid (3) can undergo protodecarboxylation or arylated using a decarboxylative cross-coupling reaction. Furthermore, it can be functionalized to a bromine through a Hunsdiecker reaction or to an amine employing a Curtius rearrangement. The carboxylic acid (3) can be obtained through the saponification of the corresponding ester. The thienoisoquinoline system could then be obtained through an intramolecular C-H activation on the typically less reactive C4 position and

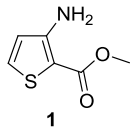
[40] a) Pelletier, J.-P.; Martel-Pelletier, J.; Abramson, S. B. *Arthritis Rheum.* **2001**, *44*, 1237. b) Felson, D. T.; Nevitt, M. C. *Curr. Opinion Rheum.* **1998**, *10*, 269.
[41] Ching-Chi, L.; Ching Yuang, L.; Hsiao-Yu, M. *Immunol. Lett.* **2000**, *73*, 57.
[42] Roth, A.; Schaffner, W.; Hertel, C. *J. Neurosci. Res.* **1999**, *57*, 399.

functionalization at C5 can also be obtained through a C-H activation reaction. This C4-H activation could be facilitated due to the blocking group employed on the C2 position preventing arylation. Furthermore, the formation of a 6-membered ring through an intramolecular process should be favored over intermolecular C5-arylation. 3,4-thienoisoquinolines could be obtained through the C4-H activation of the common intermediate (2) which can be obtained through the benzylation of the corresponding functionalized amine. The functionalized amine can also be obtained from the corresponding primary amine (1). The regioselectivity of the C-H activation of the common intermediate (2) can be controlled through the use of blocking groups. C-H activation can occur in the presence of an external aryl bromide selectively due to the differences in reaction rates of intramolecular and intermolecular reactions. The use of a blocking group at C2 removes the potentially reactive hydrogen that typically would lead to a mixture of products.

Similarly functionalized 2,3-thienoisoquinolines (7) can be obtained through derivatization of the C5 position through C-H activation or bromination reactions of the unfunctionalized thienoisoquinoline (6). The thienoisoquinoline (6) can be obtained through the decarboxylative cross-coupling of the corresponding carboxylic acid which could be obtained through the saponification of the ester of the common intermediate (2). The common intermediate (2) can be obtained as previously described. Decarboxylative cross-couplings were shown to react selectively between a carboxylic acid and an aryl halide in the presence of reactive hydrogens that can undergo C-H activation.[35] This reactivity would lead to the synthesis of 2,3-thienoisoquinolines employing the ester functionality as a synthetic handle rather than a blocking group as with the synthesis of 3,4-thienoisoquinolines.

Chapter 2.2 – Synthesis of the key intermediate

The goal of the project was to develop and optimize a synthetic route towards the two isomers of these heterocycles. For either of the desired isomer, synthesis of the key intermediate (2) was important. Also important to this process was the ease of large scale synthesis and environmentally friendly purification that would allow for timely access of key intermediate (2), allowing efforts to be focused on optimizing cross-coupling reactions in the synthesis, the development of the double C-H activation reaction and the decarboxylative cross-coupling reaction. The synthesis of the key intermediate was envisioned to begin from a commercially available thiophene.

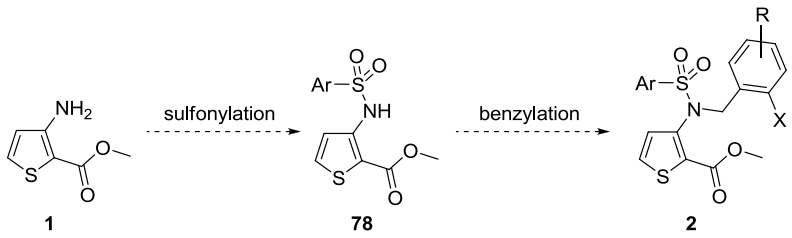


1

methyl 3-aminothiophene-2-carboxylate

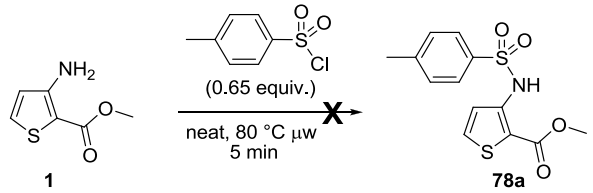
Figure 5 – Commercially available starting material

A survey of commercially available functionalized thiophene derivatives that could be employed as starting material for the synthesis resulted in methyl-3-aminothiophene-2-carboxylate (1). This commercially available thiophene contained an easily functionalizable primary amine and an ester group present at C2 that could serve the dual purpose of a blocking group and be used as a synthetic handle. With a commercially available starting material determined, initial steps towards the synthesis of the key intermediate (2) were undertaken. The first step was the functionalization of the primary amine with groups similar to the biologically active compounds published by Wyeth.



Scheme 31 – Proposed synthesis of key intermediate (2)

The synthesis was envisioned to start with the sulfonylation of commercially available methyl 3-aminothiophene-2-carboxylate (1) resulting in the desired sulfonamide (78). This intermediate could then be benzylated with various substituted benzyl halides giving the desired key intermediate (2). Initial attempts at functionalization of the primary amine with a sulfonyl-chloride were made following a procedure by Saibal and co-workers.[43] They described a neat reaction employing heating through microwave irradiation resulting in sulfonamide formation in short reaction times.

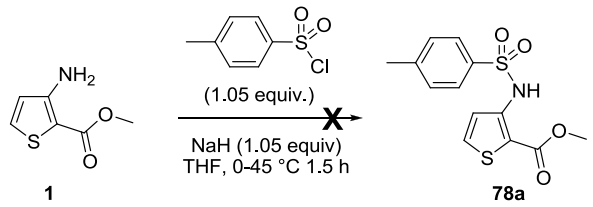


Scheme 32 – Microwave sulfonamide synthesis

The procedure was initially appealing from a green perspective since it did not require the use of any solvent and had low reaction times. However, these conditions were unsuccessful and the reaction was found to not occur. The crude mixture was analyzed by proton NMR and signals which could be attributed to the product were not observed. Typically a solvent is used in a reaction to solubilise reactants allowing for improved molecular contact. However, in a neat reaction, typically one or more of the reactants acts as the solvent to facilitate the reaction. Although *para*-toluenesulfonyl chloride was liquid under the reaction conditions, it is probable that the HCl by-product produced in the reaction would protonate the primary amine and reduces the nucleophilicity of the amine. Further difficulty in the reaction can be found in the nucleophilicity of the primary amine. Since the heteroaromatic ring contains an electron withdrawing ester substituent that draws electron density away from the ring and in turn reducing the nucleophilicity of the amine.

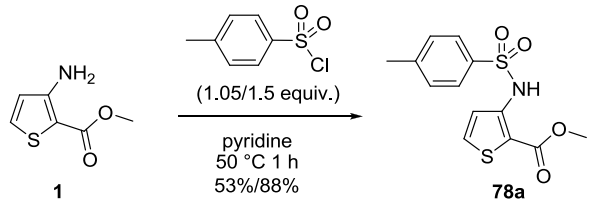
[43] Sharma, A. K., Kumar Das. S. *Synth. Comm.* **2004**, *34*, 3807.

To overcome the poor nucleophilicity of the amine, one equivalent of sodium hydride, a strong base, was used to deprotonate the amine and to form the highly nucleophilic amine anion. When considering the pKa of H_2 (~36), the conjugate acid of sodium hydride, and the pKa of an aromatic amine (~31),[44] the first deprotonation of the primary amine is favoured which should lead to the desired amine anion nucleophile.



Scheme 33 – Sodium hydride as a base in sulfonamide synthesis

Unfortunately the addition of a strong base gave unexpected results and resulted in the decomposition of the starting materials to a complex mixture of products was found to occur. Since initial attempts were unsuccessful, a more extensive survey of current literature was performed to search for milder reaction conditions, revealing a procedure by Tondi and co-workers.[45]

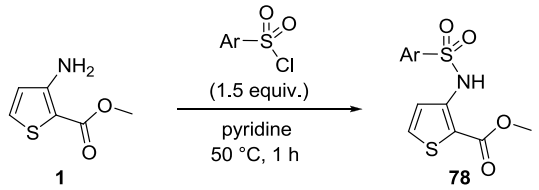


Scheme 34 – Optimizations of sulfonamide synthesis

This procedure employed the use of pyridine both as a base and as a solvent. The initial nucleophilic attack of the primary amine on the sulfonyl-chloride would result in cationic amine which was neutralized by pyridine resulting in the desired product. Initial efforts employing literature conditions proved to be successful, resulting in an isolated yield of 53%. Although this procedure gave the desired sulfonamide (78a), the moderate yield obtained was not practical for large scale synthesis of these early

[44] pKa table.1 evans.harvard.edu/pdf/evans_pka_table.pdf Accessed June 20, 2012. D. H. Ripin, D. A. Evans, (2005)
[45] Tondi, D.; Morandi, F.; Bonnet, R.; Costi, M. P.; Shoichet, B. K. *J. Am. Chem. Soc.* **2005**, *127*, 4632.

intermediates. Optimizations were attempted, increasing the equivalents of sulfonyl-chloride used. It was found that at 1.5 equivalents was optimal and the desired product could be isolated in a 88% yield. Furthermore, the reaction was performed on a multigram scale and purified through recrystalization. The ability to perform the reaction on multigram scale demonstrates the potential for future industrial development. Also purification through recrystalization rather than traditional purification methods such as column chromatography not only presents a more environmentally friendly alternative but further demonstrates the possibility for industrial scale synthesis. Column chromatography employs large quantities of silica gel and solvent that on industrial scale syntheses are impractical. Recrystalization presents an alternative purification that does not require silica gel and uses less solvent. With an increased yield and established purification methods, these optimized conditions were applied to a variety of sulfonyl-chlorides.

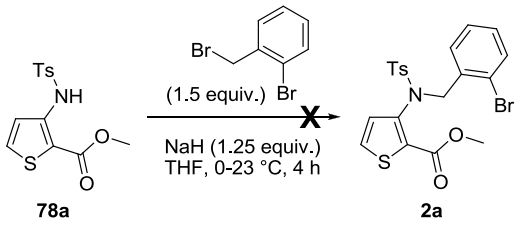


Entry	Ar	Yield (%)
1	4-$CH_3C_6H_4$	83
2	3-$CH_3C_6H_4$	83
3	2-$CH_3C_6H_4$	92
4	4-$MeOC_6H_4$	81
5	4-FC_6H_4	65
6	4-$NO_2C_6H_4$	46
7	2-thiophene	69

Table 1 – Scope of sulfonamide synthesis

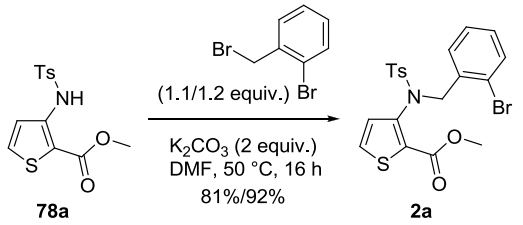
A variety of sulfonyl-chlorides were used to synthesize sulfonamides (78), in modest to excellent yields. Different sterically demanding substituents (Table 1, entries 1-3) were synthesized in good to excellent yields. Similarly electron rich aromatic rings (Table 1, entry 4) were well tolerated. Electronically poor aromatic rings (Table 1, entries 5, 6) however were less successful generating the sulfonamides (78) in modest yields. Finally, heteroaromatic substituents were also tolerated in good yields. With optimized

conditions established for sulfonamide synthesis and the scope of the reaction explored, benzylation of sulfonamides were attempted. Sulfonamides (78), were then subjected to benzylation conditions reported by Becalli and co-workers.[46]



Scheme 35 – Benzylation using sodium hydride as base

Similar to the synthesis of sulfonamides (Scheme 33), sodium hydride was used as a strong base in efforts to deprotonate the sulfonamide and increase nucleophilicity for subsequent benzylation. However, the desired reaction was found to not occur, giving a complex mixture of products. Thus a survey of the literature was performed revealing a procedure by Fawzi and co-worker which employed the use of potassium carbonate as a base with dimethylformamide as a solvent.[47]

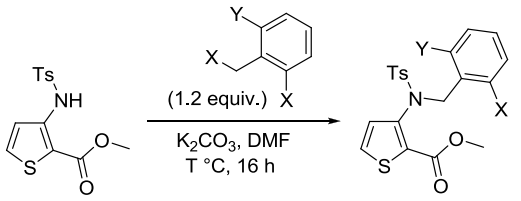


Scheme 36 – Optimization of benzylation reaction

Although initial attempts proceeded in a good yield of 81%, minor optimizations were attempted by increasing the equivalents of benzyl bromide. The addition of 1.2 equivalents of benzyl-bromide was found to slightly increase the yield to 92%. After reaction optimization, different purification methods were attempted. The original purification method employing silica gel chromatography was replaced by recrystalization allowing for multigram syntheses and greater potential for industrial application. With

[46] Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Synthesis* **2008**, *1*, 136.
[47] Coppo, F. T.; Fawzi, M. M. *J. Heterocyclic Chem*. **1998**, *35*, 983.

conditions established for the synthesis of the key intermediates (2), the scope of the reaction was explored.



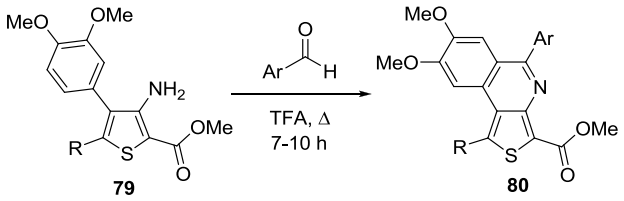
Entry	X	Y	T (°C)	Yield (%)
1	Br	H	50	92
2	Cl	H	80	87
3	Cl	F	80	99
4	Cl	Cl	80	83

Table 2 – Scope of benzylation reaction

Benzylation can be extended to chloro-benzyl-halides by increasing the reaction temperature to 80 °C. Different *ortho*-substituents were found to be well tolerated by the reaction conditions generating good to excellent yields (entries 3, 4) similar to benzyl-bromides (entry 1). With a variety of key intermediates synthesized, efforts were made towards the synthesis of 3,4-thienoisoquinolines and the optimization of a double C-H activation reaction.

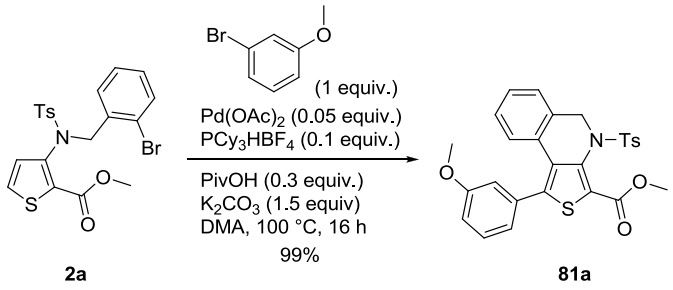
Chapter 2.3 – Synthesis of 3,4-thienoisoquinolines

A survey of the literature revealed only a single synthesis of these important compounds reported by Bogza and co-workers in 2009.[48] However, the reported synthesis was specific for a single 3,4-thienoisoquinoline system and not designed for library synthesis. Furthermore, the synthesis required the use of harsh acidic conditions to facilitate cyclization. Therefore, the application of this method on an industrial scale or for small molecule inhibitor development was not ideal.



Scheme 37 – Bogza synthesis of 3,4-thienoisoquinolines

The previous synthesis employed the use of advanced intermediate (79) heating in trifluoro-acetic acid for an extended period of time. These harsh acidic conditions resulted in low functional group tolerance and would be difficult for large scale applications. As such, a synthesis employing less harsh conditions was envisioned employing palladium catalysis to form multiple bonds in a single step.



Scheme 38 – Double C-H activation reaction towards the synthesis of 3,4-thienoisoquinolines.

In the development of a double C-H activation reaction, initial conditions were derived from the intermolecular C-H activation of heteroaromatics reported by Fagnou and co-worker.[49] Subjecting key

[48] Zinchenko, S. Y.; Efimenko, R. A.; Suikov, S. Y.; Kobrakov, K. I.; Bogza, S. A. *Chem. Heterocyclic Cmpds* **2009**, *45*, 365.
[49] Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

intermediate (2a), to palladium catalysis conditions with the addition of 3-bromo-anisole was found to give the desired thienoisoquinoline (81a) without the requirement for further optimization. The thienoisoquinolines were identified using NMR analysis and further evidence of the synthesis of these compounds by double C-H activation was provided by X-ray crystallography.

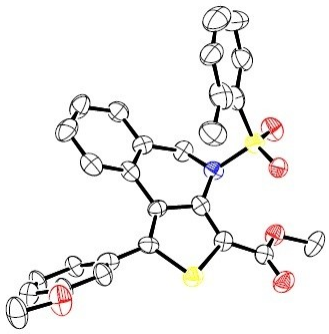
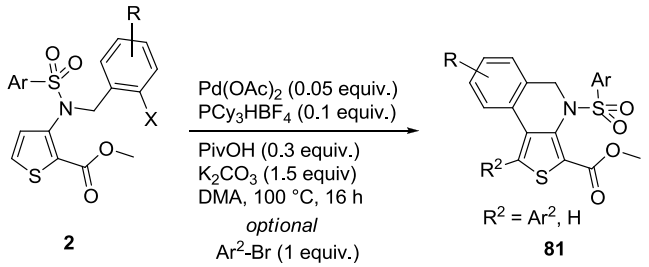


Figure 6 – X-ray structure of a substituted 3,4-thienoisoquinoline

The X-ray structure of a substituted 3,4-thienoisoquinoline (Table 3, entry 7) clearly portrays the two arylations. An intramolecular C-H activation at C4 generating the unfunctionalized 3,4-thienoisoquinoline and the arylation at C5. Thus, with optimized conditions established and identification of these compounds, the scope of the reaction was explored employing various sulfonamides, aryl bromides and benzyl substituents.[50]

[50] Wong, N. W. Y.; Forgione, P. *Org. Lett.* **2012**, *14*, 2738.

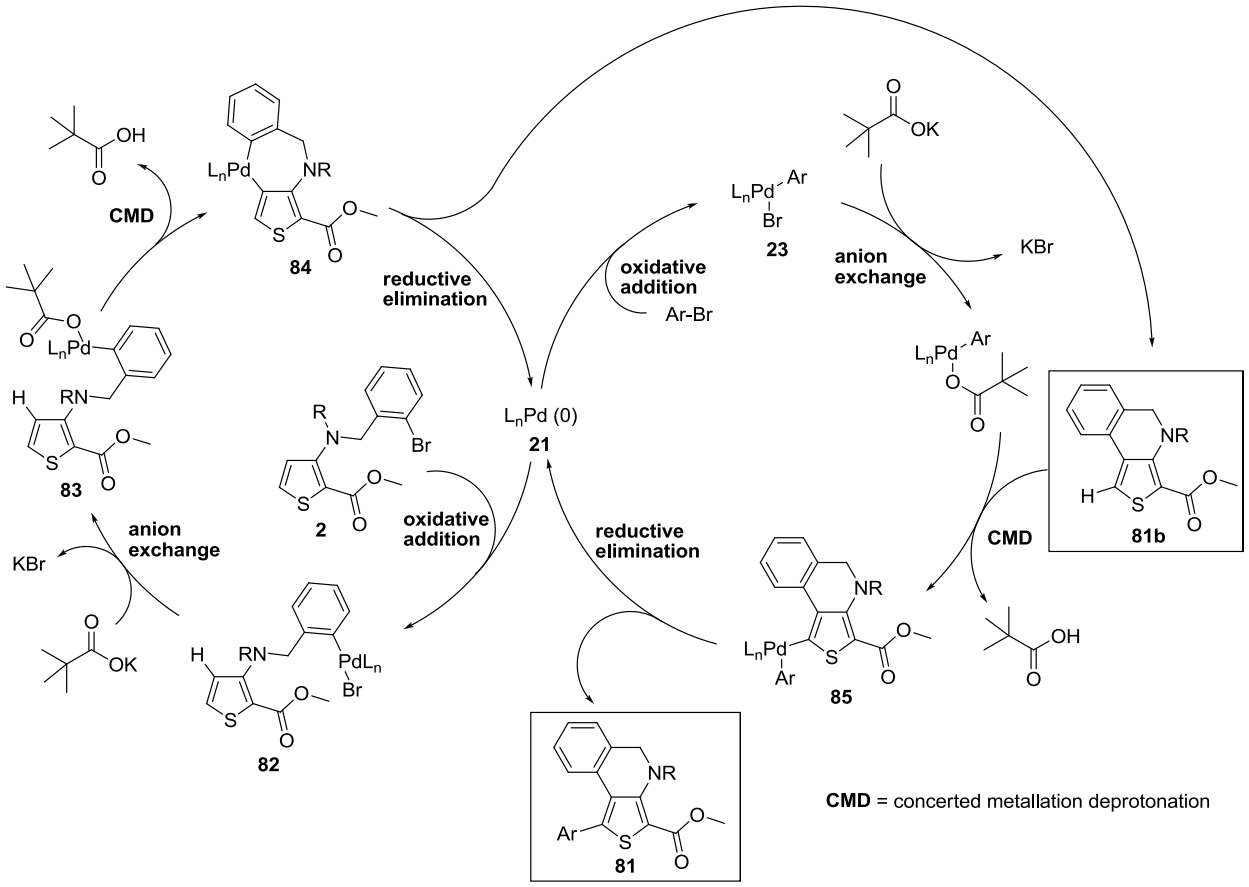


Entry	Ar	R	X	R^2	Yield (%)
1	4-Me-C_6H_4	H	Br	C_6H_5	64
2	4-Me-C_6H_4	H	Br	3-MeO-C_6H_4	99
3	4-Me-C_6H_4	H	Br	4-MeO-C_6H_4	90
4	4-Me-C_6H_4	H	Br	3-EtOOC-C_6H_4	97
5	4-Me-C_6H_4	H	Br	4-EtOOC-C_6H_4	81
6	3-Me-C_6H_4	H	Br	3-MeO-C_6H_4	80
7	2-Me-C_6H_4	H	Br	3-MeO-C_6H_4	81
8	4-MeO-C_6H_4	H	Br	3-MeO-C_6H_4	79
9	4-F-C_6H_4	H	Br	3-MeO-C_6H_4	90
10	4-Me-C_6H_4	H	Br	H	96
11	4-Me-C_6H_4	H	Cl	3-MeO-C_6H_4	0
12	4-Me-C_6H_4	F	Cl	3-MeO-C_6H_4	0
13	4-Me-C_6H_4	Cl	Cl	3-MeO-C_6H_4	0

Table 3 – Scope of double C-H activation reaction

The reaction was found to work with a large variety of Ar^2 substituents with different steric encumbrance (entries 1-7) and with a variety of electronically differing aryl bromides. Most aryl bromides were well tolerated giving excellent yields. However, bromobenzene (Table 3, entry 1) was found to proceed in lower yields. Furthermore, different sulfonamide substituents were well tolerated resulting in good to excellent yields for electronically neutral (Table 3, entries 2, 6-7), donating (Table 3, entry 8) and withdrawing (Table 3, entry 9) substituents. This reaction was also found to proceed in excellent yields in the absence of an external aryl bromide. Unfortunately, under the reaction conditions, aryl chlorides were found to be unsuitable cross-coupling partners resulting in 0% isolated yields (entries 11-13). Overall, double C-H activation was found to occur for a wide scope of substrates.

Although the mechanism of this transformation has not been studied, a proposed mechanism can be established based on previous work on C-H activation by Fagnou and co-workers.[23]

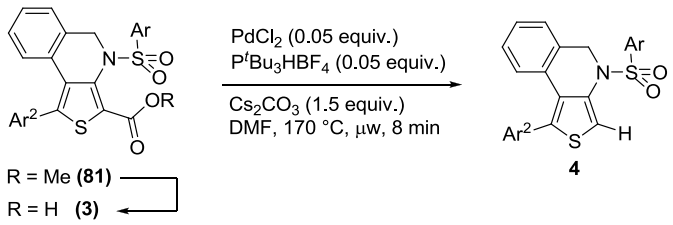


Scheme 39 – Proposed mechanism for double C-H activation reaction

The mechanism can be envisioned as a continuous cycle where the product of the first C-H activation can undergo C-H activation through the second cycle. Palladium undergoes oxidative addition into the aryl bromide bond of the key intermediate (2). This then undergoes an anion exchange followed by a concerted metallation deprotonation sequence to form a 7-membered palladacycle (91). Finally this palladacycle undergoes reductive elimination regenerating the palladium (0) catalyst (21) and generating an unsubstituted 3,4-thienoisoquinoline (81b). The catalyst either continues in the intramolecular C-H activation cycle or undergoes intermolecular C-H activation. Similarly the intermolecular C-H activation follows the same sequence of steps. First an oxidative addition into the external aryl bromide bond can occur, then anion exchange and a concerted metallation deprotonation sequence with the C5-H of the unsubstituted 3,4-theinoisoquinoline (81b) occurs. The metallated

intermediate (85) finally undergoes reductive elimination forming the desired carbon-carbon bond and regenerate the palladium (0) catalyst.

With the desired 3,4-thienoisoquinolines prepared, focus was placed on the functionalization of these systems using the masked carboxylic acid at C2. Unmasking the carboxylic acid would allow functionalization through a variety of reactions such as protodecarboxylation to remove the acid, decarboxylative cross-coupling to introduce an aryl group, Hunsdiecker reaction for bromination and a Curtius rearrangement for amination. Focusing on metal catalyzed reactions, the acid was unmasked and was subjected to protodecarboxylation conditions. Fortunately, the first set of conditions attempted, derived from Forgione and Bilodeau, proved to be successful generating the product in modest to good yields.[35]



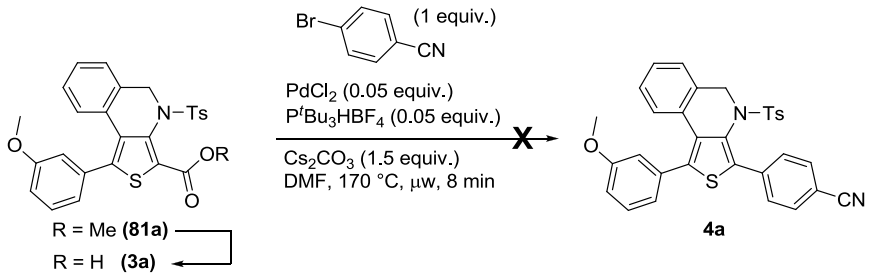
Entry	Ar	Ar^2	Yield (%)
1	4-Me-C_6H_4	C_6H_5	55
2	4-Me-C_6H_4	3-MeO-C_6H_4	65
3	4-Me-C_6H_4	4-MeO-C_6H_4	78
4	4-Me-C_6H_4	3-HOOC-C_6H_4	84
5	4-Me-C_6H_4	4-HOOC-C_6H_4	70
6	3-Me-C_6H_4	3-MeO-C_6H_4	69
7	2-Me-C_6H_4	3-MeO-C_6H_4	70
8	4-MeO-C_6H_4	3-MeO-C_6H_4	68
9	4-F-C_6H_4	3-MeO-C_6H_4	78

Table 4 – Scope of protodecarboxylation reaction

Palladium coordinates to the carboxylic acid and helps to lower the activation energy barrier facilitating protodecarboxylation. Protodecarboxylation occurred for a variety of electronically demanding substituents for Ar and Ar^2 with a large substrate scope. The most surprising results were entries 4 and

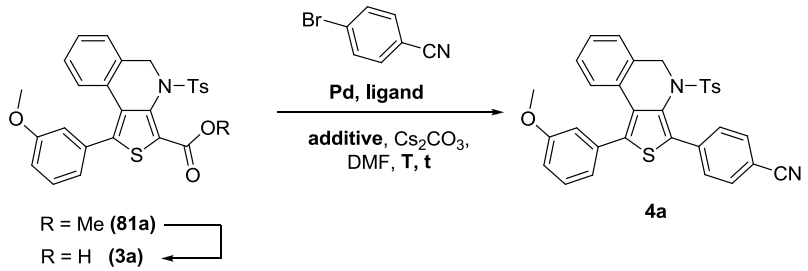
5 where Ar^2 was substituted with a carboxylic acid. Under these specific conditions, only the desired heteroaromatic carboxylic acid was decarboxylated without affecting the Ar^2 carboxylic acid substituent.

With conditions for protodecarboxylation established and scope explored, decarboxylative cross-coupling was explored as a second reaction to functionalize at the C2 position. Initial attempts were made using conditions for protodecarboxylation with the addition of an aryl bromide cross-coupling partner.



Scheme 40 – Initial attempt at decarboxylative cross-coupling

Unfortunately, these conditions failed to give the desired product, instead resulting in significant protodecarboxylation of the substrate. As such, optimizations of palladium source, ligand, additives, temperature and equivalents of Ar-Br were performed in efforts to increase the yield of the decarboxylative cross-coupling.



Entry	Pd source	Ligand	Additive	T (°C)	t (h)	Equiv. Ar-Br	Yield (%)
1	$PdCl_2$ (5 mol%)	dppf (6 mol%)	TBAB (15 mol%)	80	3	1	0
2	$PdCl_2$ (5 mol%)	dppf (6 mol%)	TBAB (15 mol%)	100	3	1	22
3	$PdCl_2$ (5 mol%)	dppf (6 mol%)	TBAB (15 mol%)	120	3	1.5	0
4	$Pd(OAc)_2$ (5 mol%)	dppf (6 mol%)	TBAB (15 mol%)	120	1	1.5	0
5	$Pd(OAc)_2$ (5 mol%)	$P^tBu_3HBF_4$ (6 mol%)	TBAB (15 mol%)	120	3	1.5	0
6	$PdCl_2$ (5 mol%)	dppf (6 mol%)	TBAC (15 mol%)	100	1	1.2	0
7	$PdCl_2$ (10 mol%)	CH_3CN (12 mol%)	TBAB (15 mol%)	100	1	1.2	17

Table 5 – Optimizations of decarboxylative cross-coupling reaction

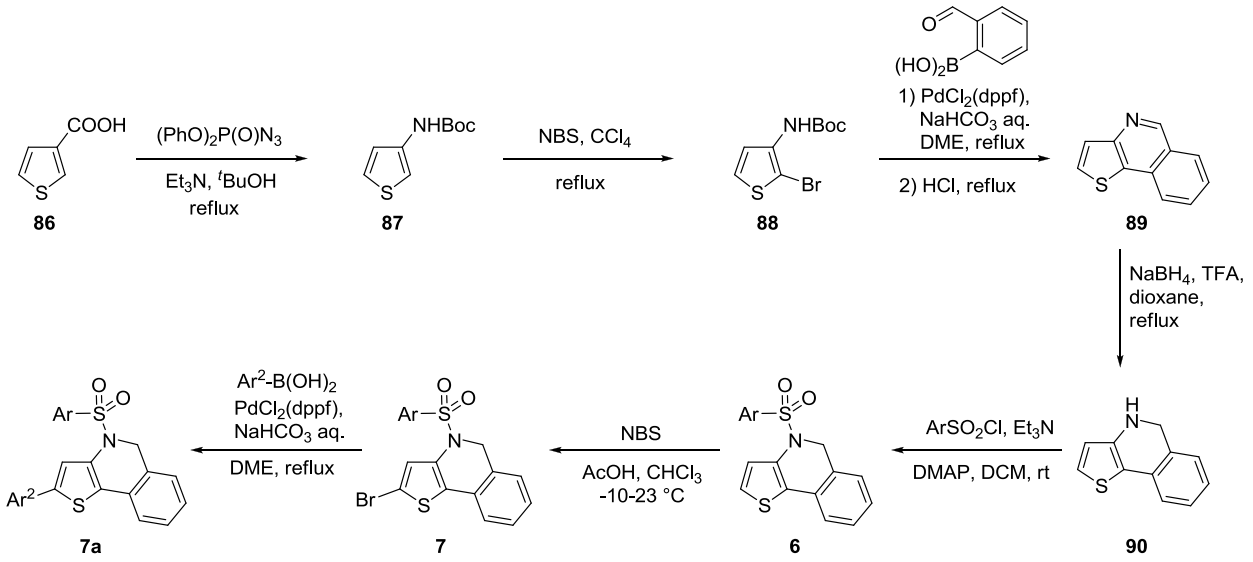
Initial screenings found that protodecarboxylation occurred more readily at higher temperatures decreasing cross-coupling. Therefore, initial changes to reduce temperature were attempted. However, reducing the temperature to 80 °C (Table 5, entry 1) proved to be very detrimental to the reaction and resulted in no product formation. Increasing the temperature to 100 °C (Table 5, entry 2) resulted in a slight increase in yield however further increase in temperature (Table 5, entry 3) resulted in protodecarboxylation and no product formation. Similarly, changing the palladium source (Table 5, entry 4), ligand (Table 5, entry 5), or additive (Table 5, entry 6) resulted in no product formation. It was then hypothesized that the nitrile of the Ar-Br was coordinating to palladium and mimicking a ligand and reducing reactivity. Acetonitrile was added as a ligand (Table 5, entry 7) and resulted in some reactivity giving 17% yield. Further attempts at the optimization of reaction conditions proved to be unsuccessful.

In summary, a robust method to synthesize 3,4-thienoisoquinolines from commercially available starting materials was established. The 3 step synthesis to access these heterocycles employed the use of a double C-H activation reaction which allows for quick diversification of aromatic substituents at the C5 position of thiophene. Furthermore, the methyl ester present at the C2 position can be unmasked revealing a carboxylic acid moiety which can be protodecarboxylated. Initial work demonstrated that

the carboxylic acid can undergo decarboxylative cross-coupling however further optimizations were necessary. Other unexplored functionalization of the carboxylic acid can include bromination through a Hunsdiecker reaction or amination through a Curtius rearrangement. Although more functionalization could be explored, efforts were focused on the synthesis of the other isomer of thienoisoquinolines.

Chapter 2.4 – Synthesis of 2,3-thienoisoquinolines

Similar to 3,4-thienoisoquinolines, the 2,3-thienoisoquinoline isomer was scarcely reported in the literature but has recently gained significant attention due to its potential as a therapeutic against breast cancer.[1] Previous syntheses of these compounds relied on the synthesis of the thiophene itself[51] limiting the ease of late stage diversification. Other syntheses required the use of fused thiophene bicycles[46,52,53] limiting diversification. One synthesis focusing on synthesizing a library of these compounds for SAR purposes was reported by Wyeth.[1]

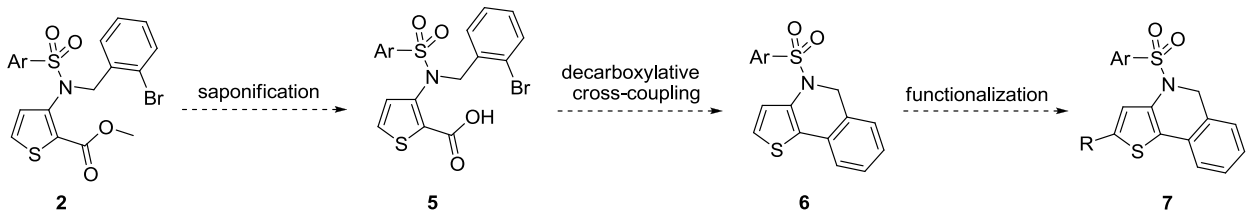


Scheme 41 – Wyeth synthesis of substituted 2,3-thienoisoquinolines

The Wyeth synthesis starts with commercially available thiophene-3-carboxylate (86) that undergoes a Curtius rearrangement in ^{t}BuOH generating the Boc protected amine (87). The thiophene is then brominated at C2 selectively using NBS. Brominated thiophene (88) then undergoes a Suzuki coupling reaction followed by imine formation and aromatization. Imine (89) was then reduced to the secondary amine (90) which was substituted with various sulfonyl-chlorides. Sulfonamide (6) was brominated at C5 to facilitate a second Suzuki reaction to introduce various C5-aryl substituents. Although this

[51] Kim, B. S.; K. K. *J. Org. Chem.* **2000**, *65*, 3690.
[52] McBurney, R. T.; Slawin, A. M. Z.; Smart, L. A.; Yu, Y.; Walton, J. C. *Chem. Comm.* **2011**, *47*, 7974.
[53] Li, L.; Chua, W. K. S. *Tetrahedron Lett.* **2011**, *52*, 1574.

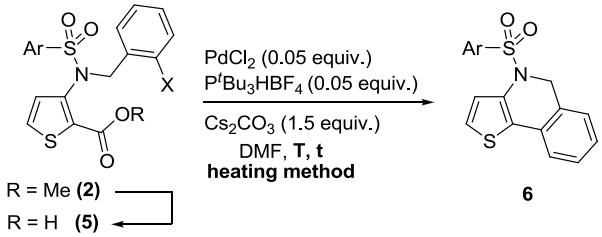
synthesis allows for the late stage diversification at the C5 position, the requirement of a two-step arylation extends the length of the synthesis. Furthermore, arylation is limited by the amount of commercially available boronic acid cross-coupling partners. Therefore, an alternative synthesis was envisioned to shorten the number of synthetic steps and increase the potential for diversification at the C5 position.



Scheme 42 – Proposed synthesis of 2,3-thienoisoquinolines

From previously synthesized key intermediate (2), the acid can be unmasked revealing a carboxylic acid. The carboxylic acid (5) can be subjected to decarboxylative cross-coupling conditions to close the centre ring and generate the desired 2,3-thienoisoquinoline system. Using a decarboxylative cross-coupling rather than a C-H activation reaction would allow for selective coupling at the C2 position rather than a potential mixture of isomers derived from arylation at C2 and C4. The C4-H was previously shown to be reactive under C-H activation conditions (Table 3). The 2,3-thienoisoquinoline can then be functionalized at the C5 position through C-H activation or bromination.

The previously synthesized key intermediate (2), was saponified under basic conditions to reveal the carboxylic acid (5). The carboxylic acid was then subjected to palladium cross-coupling conditions without further purification to form the desired 2,3-thienoisoquinoline (6). Initial conditions were derived from the decarboxylative cross-coupling reported by Forgione and co-workers.[35] Fortunately, first attempts were successful generating the desired product in excellent yields. Optimizations determined that the originally required additive ($^{n}Bu_4NCl$) was not essential to the reaction, further improving the atom economy of the reaction.

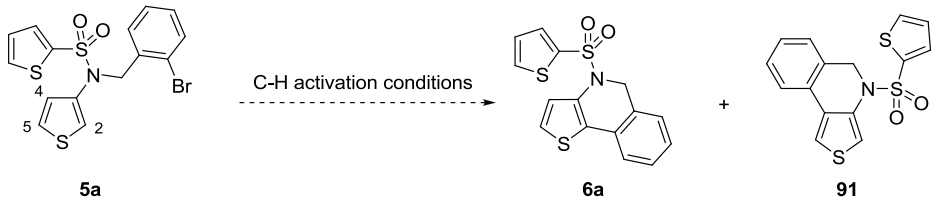


Entry	Ar	X	T (°C)	t (min)	Heating Method	Yield (%)
1	4-$CH_3C_6H_4$	Br	170	8	microwave	99
2	3-$CH_3C_6H_4$	Br	170	8	microwave	76
3	2-$CH_3C_6H_4$	Br	170	8	microwave	84
4	4-$CH_3OC_6H_4$	Br	170	8	microwave	99
5	4-FC_6H_4	Br	170	8	microwave	56
6	4-$NO_2C_6H_4$	Br	170	8	microwave	0
7	2-thiophene	Br	170	8	microwave	83
8	4-$CH_3C_6H_4$	Cl	170	8	microwave	0
9	4-$CH_3C_6H_4$	Br	100	960 (16 h)	thermal	83
10	4-$CH_3C_6H_4$	Br	140	60	thermal	99
11	3-$CH_3C_6H_4$	Br	140	60	thermal	98
12	2-$CH_3C_6H_4$	Br	140	60	thermal	97

Table 6 – Scope and optimizations of decarboxylative cross-coupling reaction

Decarboxylative cross-coupling proved to be effective for a wide scope of sulfonamides. Different sterically demanding sulfonamide aryl substituents were used (Table 6, entries 1-3) resulting in good to excellent yields. Electron-donating substituents (Table 6, entry 4) were also well tolerated resulting in excellent yields. However, electron-withdrawing substituents (Table 6, entry 5) was less well tolerated resulting in lower yields. The strongly electron-withdrawing nitro substituent (Table 6, entry 6) was found to stop the reaction from occurring. The potential for the nitro substituent to co-ordinate with palladium could potentially prevent the co-ordination of palladium with the carboxylate thus hindering activity. Heteroaromatic substituents (Table 6, entry 7) were found to also be well tolerated giving excellent yields. This further demonstrates the advantages of decarboxylative cross-coupling over C-H activation. If a decarboxylative cross-coupling was not employed and a reactive hydrogen was present at C2, under C-H activation conditions, it is probable that a mix of regioisomers would be obtained for the intramolecular cross-coupling reaction. Arylation at C2 would generate the desired 2,3-thienoisoquinoline (6a) however, as previously demonstrated in Scheme 38, the C4 position of the

thiophene is also reactive under C-H activation conditions generating 3,4-thienoisoquinolines. Therefore, a mix of regioisomers is expected to occur when not employing a decarboxylative cross-coupling.



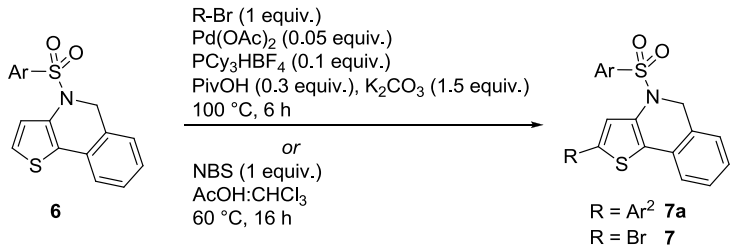
Scheme 43 – Regioselectivity issues when employing C-H activation

Furthermore, with an additional thiophene substituent present on the sulfonamide, numerous reactive hydrogens are present increasing the potential for undesired intermolecular arylation. Therefore, to obtain selective arylation and minimize the potential for undesired by-products, the selectivity of decarboxylative cross-coupling is required.

Switching aryl bromides to the less reactive aryl chloride (Table 6, entry 8) also proved to stop the reaction under these reaction conditions. Although using microwave as a heating method produced in general excellent results in a short reaction time, the limited size of the microwave reactor presented a challenge for larger scale reactions. Thermal heating conditions would have to be optimized to allow for further development as a pharmaceutical agent. Therefore, thermal heating options were explored by reducing the temperature to 100 °C and heating for a longer period of time (Table 6, entry 9). This proved to be effective, generating the desired product in 83% yield over a period of 16 h. Furthermore, this demonstrated a low temperature decarboxylative cross-coupling that was previously not widely reported. Although this procedure provided an excellent thermal alternative, the long reaction times were undesirable. To circumvent the long reaction times, the temperature of the reaction was increased to augment reaction rates (Table 6, entry 10). Heating the reaction at 140 °C for 1 h resulted in excellent yields in a short amount of time. In summary, the initial conditions reported by Forgione

and co-workers proved to be effective on small scale reactions. The reaction was further optimized to employ thermal heating conditions to facilitate larger scale reactions. Furthermore, the decarboxylative cross-coupling was found to proceed at lower temperatures than previous examples.

With the desired 2,3-thienoisoquinolines synthesized, efforts were focused on the functionalization of these compounds at the C5 position. This functionalization would be important for structure activity relationship studies towards the development of these compounds as potential therapeutics. To obtain similar substrates developed by Wyeth,[1] 2,3-thienoisoquinolines (6) were functionalized with aryl groups through C-H activation or brominated using NBS.



Entry	Ar	R	Yield (%)
1	4-$CH_3C_6H_4$	C_6H_5	78
2	4-$CH_3C_6H_4$	3-$MeOC_6H_4$	99
3	4-$CH_3C_6H_4$	4-$MeOC_6H_4$	99
4	4-$CH_3C_6H_4$	3-$COOEtC_6H_4$	87
5	4-$CH_3C_6H_4$	4-$COOEtC_6H_4$	87
6	4-$CH_3C_6H_4$	Br	60
7	4-$MeOC_6H_4$	Br	59

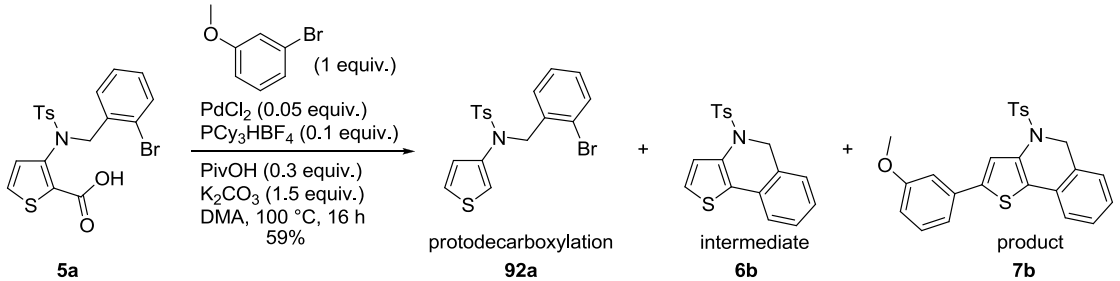
Table 7 – Functionalization of 2,3-thienoisoquinolines

Firstly, the C5 position of the thienoisoquinoline was arylated through C-H activation (entries 1-5) resulting in good to excellent yields. The reaction was well tolerant of different electronically demanding aryl bromides including electron rich (Table 7, entries 2-3) and electron poor (Table 7, entries 4-5). However, electronically neutral species (Table 7, entry 1) proved to be more difficult resulting in slightly lower yields. Furthermore, the C5 position could be brominated using NBS resulting in the brominated inhibitors that were previously reported. Bromination of 2,3-thienoisoquinoline was achieved in good yields (Table 7, entries 6, 7) with two different sulfonamide derivatives.

In summary, a five-step synthesis of functionalized 2,3-thienoisoquinolines was achieved employing a decarboxylative cross-coupling for selective ring closure followed by a functionalization using C-H activation or bromination. This synthesis improves upon a previous synthesis reported by Wyeth by 3 steps while maintaining late stage diversification.

Although this synthesis improves upon previous routes towards these biologically active compounds, there are possibilities for further improvements by further reducing the synthetic steps towards these inhibitors. The final three steps of the previous synthesis involve a saponification followed by a palladium-catalyzed decarboxylative cross-coupling then functionalization through a second palladium-catalyzed arylation. With two sequential palladium-catalyzed cross-coupling reactions, a possibility exists to combine the two arylations into a single step. This would effectively reduce the step count from five to four and eliminate a purification step increasing the ease of scalability and reducing the amount of waste produced.

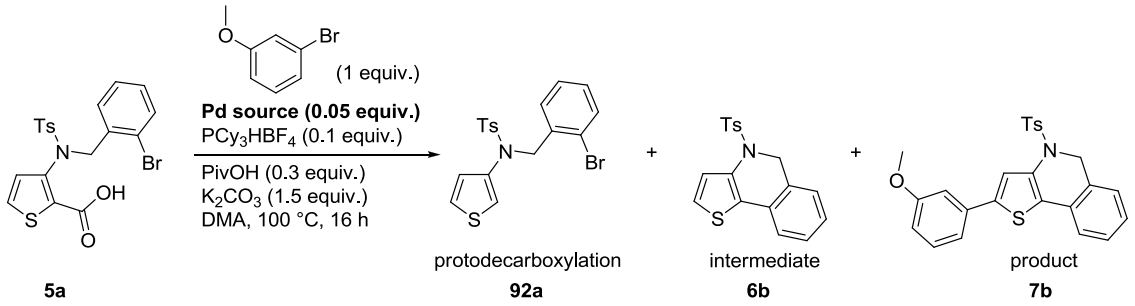
Carboxylic acid (5a) was subjected to palladium catalysis conditions with an external aryl bromide in efforts to conduct a decarboxylative cross-coupling and C-H activation in a single step. Initial conditions were derived from a combination of previously used decarboxylative cross-coupling[35,36] and C-H activation reactions.[24]



Scheme 44 – Initial attempts towards the development of a one pot decarboxylative cross-coupling C-H activation reaction

Initial conditions proved to be effective generating the desired product in a 59% yield. However, upon analysis of the unpurified mixture of products, two major by-products were also produced.

Protodecarboxylation of the starting carboxylic acid resulted in thiophene (92a) which did not react further under the reaction conditions. The second undesired product produced was the unfunctionalized 2,3-thienoisoquinoline (6b) which was not fully converted to the desired product under the reaction conditions. Therefore, in attempts to improve the yield of the functionalized 2,3-thienoisoquinoline, minimize the formation of the protodecarboxylation (92a) side product and to fully convert the unfunctionalized 2,3-thienoisoquinoline intermediate (6b), different palladium sources were screened.



		Yield (%)[a]		
Entry	**Pd Source**	**Protodecarboxylation**	**Intermediate**	**Product**
1	$PdCl_2$	1	15	59
2	$Pd(acac)_2$	2	51	14
3	Petey	1	51	24
4	$Pd(OAc)_2$	8	36	26
5	$Pd(dba)_2$	28	14	0
6	PdI_2	5	29	25
7	$Pd(OAc)_2$[b]	8	47	28

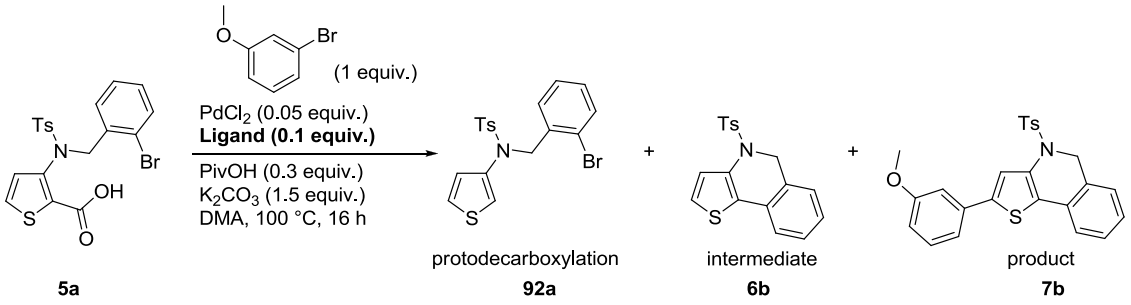
[a] Yields normalized to an isolated yield of 59% obtained for entry 1

[b] 10 mol% palladium was used

Table 8 – Optimization of palladium sources

Initial attempts using palladium chloride as catalyst generated the desired product in an isolated yield of 59% (Table 8, entry 1). However, 16% of the mass balance was attributed to the formation of protodecarboxylation and unfunctionalized intermediate products. Therefore, the yield could be potentially increased by minimizing protodecarboxylation and fully converting the unfunctionalized intermediate. To further improve the yield of the reaction, a survey of different palladium sources was conducted and the results were analyzed by GC-MS normalizing yields to an isolated yield of 59%

obtained for entry 1. Switching palladium sources from palladium chloride to $Pd(acac)_2$ (Table 8, entry 2) resulted in a decrease of desired product formation, however an increase of the amount of intermediate formation occurred. This suggests that $Pd(acac)_2$ serves as a suitable palladium source for the initial decarboxylative cross-coupling reaction however does not easily facilitate C-H activation. Changing the palladium source to Petey or palladium acetate (Table 8, entries 3, 4) gave similar results with the majority of the mass balance in the intermediate product. The more stable $Pd(dba)_2$ (Table 8, entry 5) was found to be the least effective palladium source for the desired transformation resulting in the majority of the mass balance in the protodecarboxylation side product. Changing the counter ion from chloride to iodide also proved to be detrimental to the reaction; this resulted in an equal mix of intermediate and product (Table 8, entry 6). Finally, increasing palladium acetate loading did not have a major impact on the reaction giving similar results to 5 mol% loading (Table 8, entry 4). In summary, initial use of palladium chloride proved to be the most effective source of catalyst. With a palladium source optimized, different ligands were surveyed to further optimize product formation.

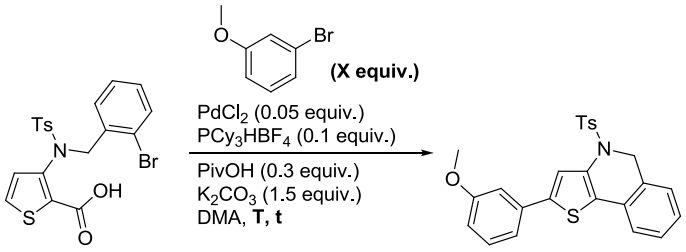


Entry	Ligand	Yield (%)[a]		
		Protodecarboxylation	Intermediate	Product
1	PCy_3HBF_4	1	15	59
2	dppf	5	71	7
3	$P^tBu_3HBF_4$	1	28	28
4	Mor-Dalphos	7	35	4
5	Johnphos	2	36	19
6	Davephos	18	26	9
7	PPh_3	10	33	8

[a] Yields normalized to an isolated yield of 59% obtained for entry 1

Table 9 – Optimization of ligand

Initial conditions (Table 9, entry 1) employed the use of tricyclohexylphosphine as a ligand and resulted in a yield of 59%. Using the bidentate ligand dppf (Table 9, entry 2) proved to be very effective in the initial decarboxylative cross-coupling step generating a substantial amount of the intermediate. However, dppf was found to be unsuitable for C-H activation generating, minimal amounts of product. Since bi-dentate ligands prove to be ineffective for the desired reaction, various monodentate phosphine ligands of different steric bulk were explored. Increasing steric bulk with a variety of ligands (Table 9, entries 3-7) did not facilitate more product formation in all cases, approximately a third of the mass balance resulted in intermediate formation with minimal product. In summary, the initial ligand, tricyclohexylphosphine, proved to be most effective for the transformation. With an optimized catalyst and ligand system established, the temperature, reaction time and equivalents of aryl bromide were optimized.



5a **7b**

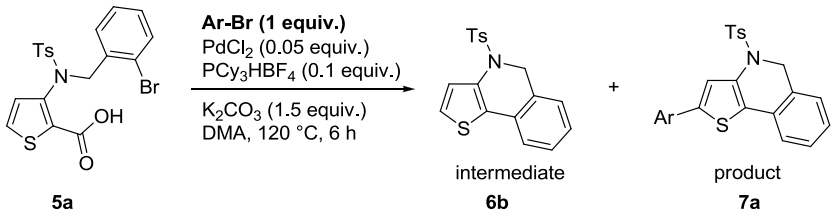
Entry	T (°C)	t (h)	Equiv. Ar-Br	Yield (%)
1	80	16	1.0	0
2	100	16	1.0	59
3	120	6	1.0	58
4	100	16	1.2	--[a]
5	100	16	1.5	--[a]
6	100	16	2.0	--[a]

[a] Unable to isolate the desired product in high purity by column chromatography.

Table 10 – Optimization of time, temperature and equivalents of Ar-Br

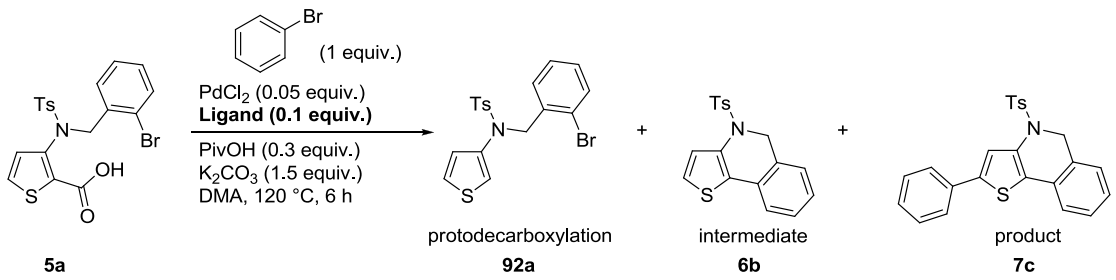
Initial conditions heating at 100 °C for 16 h with one equivalent of aryl bromide (entry 2) resulted in an isolated yield of 59%. Decreasing the temperature to 80 °C while keeping reaction time constant proved to be detrimental, resulting in minimal formation of product. However, increasing the temperature to 120 °C (entry 3) allowed a similar amount of product formation to occur in a reduced time of 6 h.

Increasing the equivalents of Ar-Br (entries 4-6) was found to increase the yield of desired product as determined by NMR. However the increase of Ar-Br also increased the formation of inseparable impurities which could not be identified and lead to the contamination of the desired product. Due to difficulties in purification associated with increasing the equivalents of Ar-Br, the addition of one equivalent of Ar-Br was determined to be optimal. As such, to reduce reaction time and increase the efficiency of optimization studies, conditions employed in entry 3 were used to explore the substrate scope of different aryl bromides.



Scheme 45 – General scheme of aryl bromide scope

Unfortunately, similar to the increase of equivalents used of aryl bromide, different substrates resulted in inseparable mixtures of the intermediate 2,3-thienoisoquinoline, the desired product and other unidentifiable impurities. As such, conditions were re-optimized with bromobenzene as a substrate rather than 3-bromoanisole. Bromobenzene under the original optimized conditions gave an inseparable mixture of products. The goal for secondary optimizations was to both minimize protodecarboxylation side product and to minimize unreacted intermediate. This would allow for an easier separation of the mixture of final products. As $PdCl_2$ was previously found to be the optimal palladium source, a survey of ligands was conducted as a first step.



5a **92a** **6b** **7c**

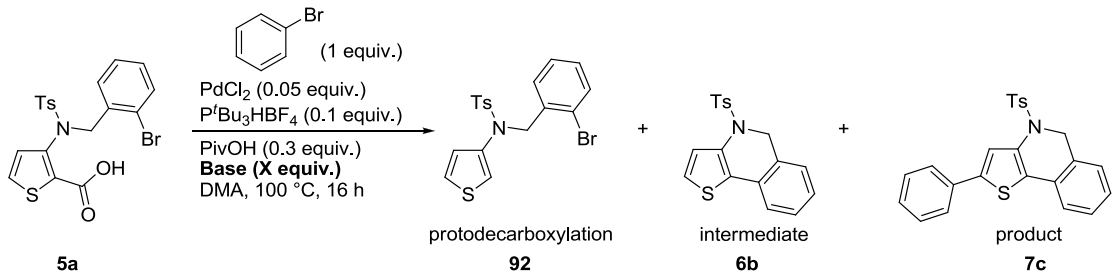
		Yield (%)[a]		
Entry	**Ligand**	**Protodecarboxylation**	**Intermediate**	**Product**
1	PCy_3HBF_4	19	9	50
2	dppf	19	29	30
3	$P^tBu_3HBF_4$	2	11	66
4	Mor-Dalphos	71	4	4
5	Johnphos	36	20	22
6	Davephos	25	9	44
7	PPh_3	30	16	32
8	$P(OC(CF_3)_2)_3$	30	19	30

[a] Yields normalized to an isolated yield of 66% obtained for entry 3

Table 11 – Second ligand optimization

With the originally optimized conditions (Table 11, entry 1) using bromobenzene as an arylating agent, 19% of the mass balance was attributed to the product formed through protodecarboxylation which could not be transformed into the desired product. Another 9% of the mass balance was found to be unfunctionalized intermediate which could potentially be fully converted to further increase the yield of the desired product. Using the bi-dentate ligand dppf, (Table 11, entry 2) again proved to be detrimental to the reaction, lowering the yield of the desired product while increasing the yield of the intermediate. This again demonstrated that dppf is a suitable ligand for decarboxylative cross-coupling but does not facilitate a subsequent C-H activation and that the results were not dependent on the aryl bromide used. A bulkier monodentate phosphine ligand, tri-*tert*-butylphosphine (Table 11, entry 3), was found to be effective, decreasing the amount of protodecarboxylation side product and decreasing the residual amount of intermediate while maintaining good yields for the desired product. With 11% of the mass balance as the unfunctionalized 2,3-thienoisoquinoline there was potential to further increase the yield of the desired product. Drastically increasing steric bulk of the ligand using the adamant-based Mor-Dalphos ligand (Table 11, entry 4) proved to be extremely detrimental to both cross-coupling reactions.

However, this catalyst ligand system was found to be effective in facilitating protodecarboxylation. Buchwald-type ligands (Table 11, entries 5, 6) were also attempted resulting in a mixture of all three products in similar equivalents. Similarly, different phosphine ligands (Table 11, entries 7, 8) also gave mixtures of all three products. In summary, although the original ligand choice of tricyclohexylphosphine gave reasonable yields, the amount of protodecarboxylation side product and unfunctionalized intermediate produced decreased yields of the desired product and complicated final purification. As such, the more sterically hindered tri-*tert*-butylphosphine ligand was found to be the optimal ligand for this system generating the best ratio of product, intermediate and protodecarboxylation. With an optimized palladium/ligand system, the base that was previously not optimized was examined.



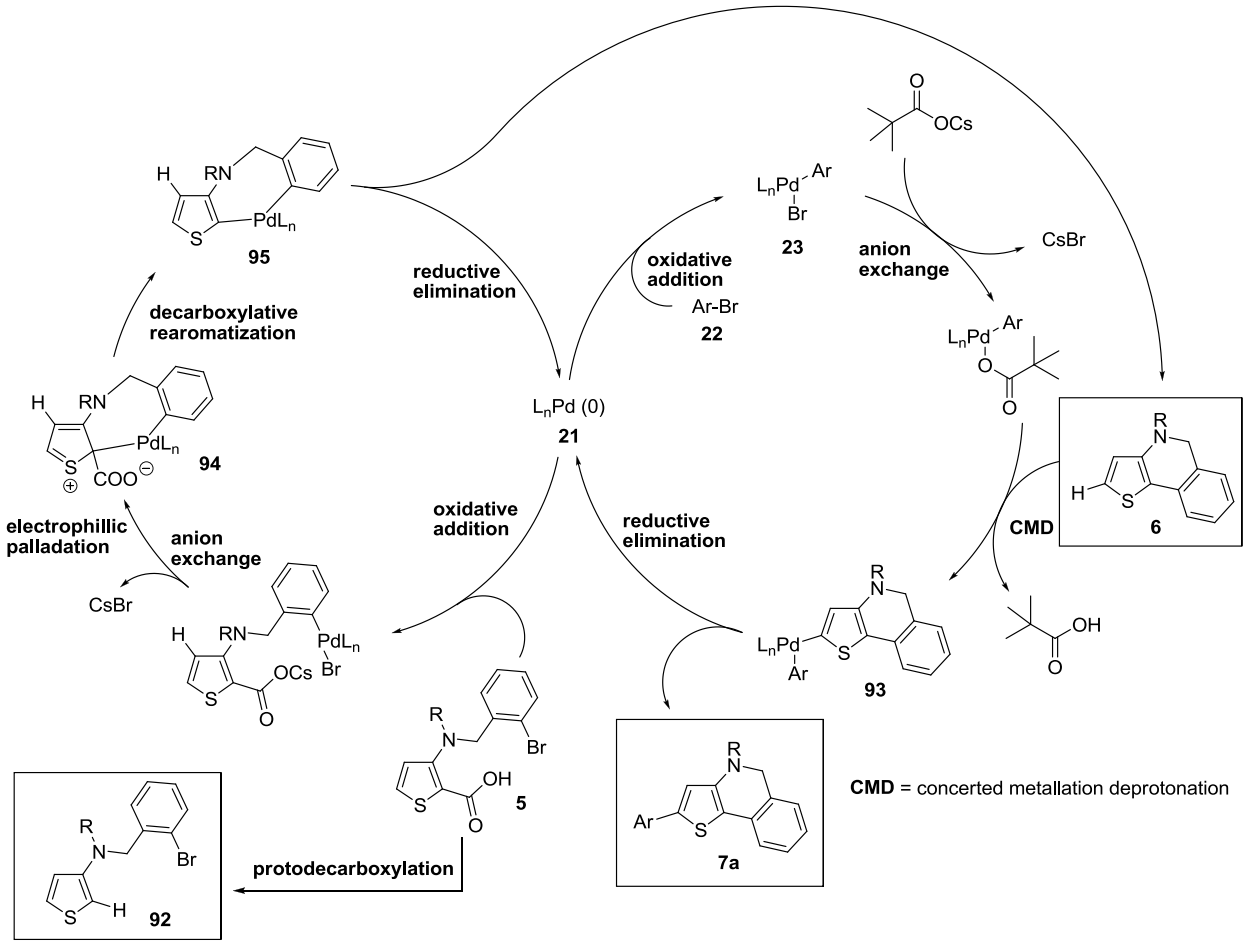
		Yield (%)[a]		
Entry	**Base**	**Protodecarboxylation**	**Intermediate**	**Product**
1	K_2CO_3 (3.0 equiv.)	2	11	66
2	Na_2CO_3 (3.0 equiv.)	2	10	18
3	Cs_2CO_3 (3.0 equiv.)	1	2	80
4	NaOH (3.0 equiv.)	0	0	0
5	Cs_2CO_3 (2.0 equiv.)	1	5	37
6	Cs_2CO_3 (1.5 equiv.)	5	11	21
7	Cs_2CO_3 (1.0 equiv.)	1	6	7
8	Cs_2CO_3 (0.5 equiv.)	2	17	0
9	Et_3N (2.0 equiv.)	4	56	0

[a] Yields normalized to an isolated yield of 80% obtained for entry 3

Table 12 – Optimization of bases

Different carbonate bases were explored to determine the effect of counter-ions on the system. Switching the original base K_2CO_3 to Na_2CO_3 (Table 12, entry 2), was found to severely hinder the reaction in all aspects, decreasing the yield of both cross-coupling reactions and decreasing the amount

of protodecarboxylation product formed. Increasing the size of the counter-ion using Cs_2CO_3 (Table 12, entry 3) as the base proved to be beneficial to the reaction. Using cesium carbonate as a base resulted in the formation of a similar amount of protodecarboxylation product. However, it was found that Cs_2CO_3 facilitated C-H activation converting the majority of the unfunctionalized intermediate to the desired product. As such, Cs_2CO_3, appears to be effective in C-H activation as high amounts of product and minimal amounts of intermediate is observed. A different inorganic base, sodium hydroxide (Table 12, entry 4), was attempted however no desired reactions was observed. An attempt to decrease the equivalents of Cs_2CO_3, required for the reaction (Table 12, entries 5-8) proved to be detrimental to the reaction, limiting the amount of cross-coupling product observed. Finally, an organic base (Et_3N, Table 12, entry 9) was attempted. This base however was found to facilitate only the first step of decarboxylative cross-coupling and did not facilitate the subsequent C-H activation. In summary, cesium carbonate proved to be the most effective base when used in 3 equivalents. Lowering the equivalents of the base or employing smaller counter-ions proved to be detrimental to final product formation. With the information gathered during optimization studies, a mechanism can be proposed based on previously known mechanisms for decarboxylative cross-coupling and C-H activation.



Scheme 46 – Proposed mechanism for a one-pot decarboxylative cross-coupling C-H activation reaction

Similar to the proposed mechanism for double C-H activation (Scheme 39) this one-pot reaction can be seen as two catalytic cycles occurring in tandem both mediated by a palladium (0) catalyst. The carboxylic acid can be subjected to two pathways; firstly protodecarboxylation resulting in an unwanted side product (92) or the palladium (0) catalyst can undergo an oxidative insertion into the aryl bromide (5) bond. The oxidative addition would allow for the palladium to be in close proximity to the carboxylate facilitating co-ordination and anion exchange. Electrons on the heteroatom then delocalize and undergo a nucleophilic attack onto the electrophilic palladium species metallating at the C2 position (94). The carboxylate then undergoes decarboxylation to restore aromaticity. The seven membered palladacycle (95) then undergoes reductive elimination forming the 2,3-thienoisoquinoline intermediate

(6) and regenerating the active palladium (0) catalyst (21). The catalyst then undergoes oxidative addition into an external aryl bromide (22) bond which upon anion exchange with pivalate can undergo a concerted metallation deprotonation sequence with the C5 position of the newly formed 2,3-thienoisoquinoline (6). The resulting palladated species (93) can then undergo a reductive elimination forming the carbon-carbon bond and regenerating the active palladium (0) catalyst (21).

With extensive optimizations and a proposed mechanism complete, future directions of this project are aimed towards the exploration of the scope of this one-pot process and biological testing of these active compounds for potential therapeutic use.

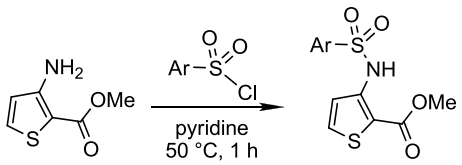
CHAPTER 3 – EXPERIMENTAL

General Considerations: All glassware was flame dried under argon prior to reaction set-up unless otherwise stated. Solids were weighed open to air and added to a septum sealed round bottle flask that was then purged with argon gas. Liquids were transferred using plastic or glass syringes and stainless steel syringe needles to maintain an inert atmosphere. Flash chromatography was carried out using 40-63 µm silica gel (Silicycle).

Materials: All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and were stored under an inert atmosphere with activated 3Å molecular sieves. Molecular sieves were activated by heating at 150 °C for 16 h under high vacuum. Distilled water was obtained from an in-house water distillery. All other reagents and chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification.

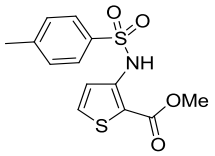
Instrumentation: ^{1}H (500MHz) and ^{13}C (125MHz) NMR spectra were recorded in $CDCl_3$ using a Varian Inova 500MHz spectrometer. Spectra were referenced to the residual solvent signal or internal TMS signal. Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet); coupling constants (*J*, Hz); number of protons; assignment based on chemical shifts of proton signals. High resolution mass spectra (HRMS) were obtained using a LC-Tof ESI positive mode mass spectrometer. Infrared (IR) spectra were obtained on a Nicolet 6700 FT-IR spectrometer as % transmittance as neat thin films loaded with $CDCl_3$ and allowed to dry on a sodium chloride window. Spectral features are tabulated by wavenumber (cm^{-1}). Microwave reactions were carried out using Biotage initiator 2.3 build 6250 system with a 400 watt magnetron.

General procedure for the synthesis of sulfonamides (Procedure 1)



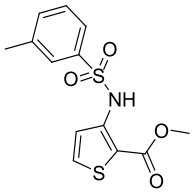
A procedure by Tondi and co-workers was used with modifications.[45] Pyridine (0.8 M) was added to aryl sulfonyl chloride (1.5 equiv.) and 3-amino-thiophene-2-methyl-carboxylate (1 equiv.) and heated to 50 °C for 1 hour. After 1 hour the resulting mixture was cooled to 23 °C then was diluted in EtOAc and washed with distilled water. The aqueous phase was extracted with EtOAc and the combined organics were washed 5 times with distilled water. The organics were then dried over anhydrous sodium sulfate, filtered over a cotton plug and the solvent was removed under reduced pressure. The resulting mixture was recrystalized using EtOAc and hexanes.

Synthesis of NW-060 (78a)



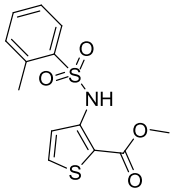
NW-060 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 31.8 mmol (5.0 g) scale. Yield 83 % colourless crystalline solid. (m.p. 149-150 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.74 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 2H), 7.25 (d, *J* = 80 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.2, 144.1, 143.4, 136.2 (2C), 131.9, 129.7 (2C), 126.8, 120.3, 110.4, 51.9, 21.4. (IR (NaCl): 3201, 3118, 2956, 1671, 1597, 1546, 1400, 1163, 1032, 876. HRMS (EI): Exact mass calculated for $C_{13}H_{13}NO_4S_2$ $[M + H]^+$: 312.03588 found 312.03625.

Synthesis of NW-151 (78b)



NW-151 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 83 % beige solid. (m.p. 96-97 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.68-7.65 (m, 2H), 7.39 (s, 2H), 7.35-7.34 (m, 2H), 3.84 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.2, 143.4, 139.4, 139.1, 134.0, 131.9, 128.9, 127.2, 124.0, 120.4, 110.5, 52.0, 21.2. (IR (NaCl): 3241, 2954, 1676, 1548, 1448, 1384, 1276, 1244, 1162, 1096, 1035. HRMS (EI): Exact mass calculated for $C_{13}H_{13}NO_4S_2$ $[M + H]^+$: 312.03588 found 312.03571.

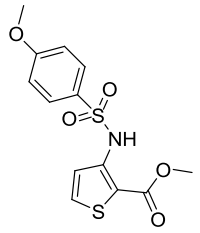
Synthesis of NW-150 (78c)



NW-150 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 68 % pink solid. (m.p. 127-128 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.02 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.34-7.33 (m, 1H), 7.31-7.25 (m, 3H), 3.87 (s, 3H), 2.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.3, 143.3, 137.3, 133.3, 132.7, 132.0, 129.5, 126.5, 126.1,

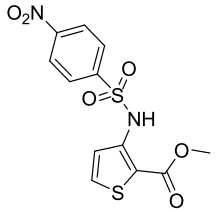
119.7, 109.5, 52.0, 20.0. (IR (NaCl): 3234, 3131, 2952, 1679, 1547, 1404, 1375, 1243, 1171, 1033. HRMS (EI): Exact mass calculated for $C_{13}H_{13}NO_4S_2$ $[M + H]^+$: 312.03588 found 312.03457.

Synthesis of NW-2-010 (78d)



NW-2-010 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 81 % beige solid. (m.p. 99-100 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.39 (s, 2H), 7.36 (m, 2H), 6.91-6.88 (m, 2H) 3.81 (s, 3H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.2, 163.2, 143.6 (2C), 131.8 (2C), 130.7, 129.1, 120.5, 114.3, 110.5, 55.5, 52.0. (IR (NaCl): 3244, 2361, 2338, 1675, 1577, 1383, 1243, 1161, 1093, 1032. HRMS (EI): Exact mass calculated for $C_{13}H_{13}NO_5S_2$ $[M + H]^+$: 328.03079 found 328.03105.

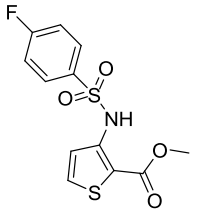
Synthesis of NW-149 (78e)



NW-149 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 68 % pink solid. (m.p. 137-138 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm

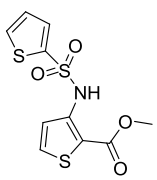
8.30 (d, *J* = 9.0 Hz, 2H), 8.05-8.03 (m, 2H), 7.44 (m, 2H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.3, 150.4, 144.9 (2C). 142.4, 132.4 (2C), 128.3, 124.4, 120.5, 111.8, 52.3. (IR (NaCl): 3192, 3106, 2955, 1678, 1530, 1403, 1351, 1243, 1168, 1089. HRMS (EI): Exact mass calculated for $C_{12}H_{10}N_2O_6S_2$ $[M + H]^+$: 343.0053 found 343.0055.

Synthesis of NW-2-053 (78f)



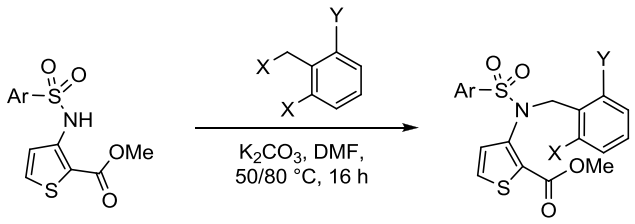
NW-2-053 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 65 % beige solid. (m.p. 88-89 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 9.60 (br s, 1H), 7.87-7.84 (m, 2H), 7.42-7.36 (m, 2H), 7.14-7.09 (m, 2H) 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 166.3, 164.2, 143.1 (2C), 135.3 (2C), 132.0, 129.7, 120.5, 116.3, 111.1, 52.1. (IR (NaCl):3238, 3106, 2955, 1680, 1593, 1545, 1494, 1449, 1404, 1277, 1240, 1170, 1157, 1090, 1034, 950. HRMS (EI): Exact mass calculated for $C_{12}H_{10}FNO_4S_2$ $[M + H]^+$: 316.0108 found 316.01132.

Synthesis of NW-152 (78g)



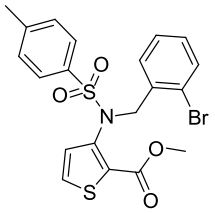
NW-152 was prepared following the general procedure for the preparation of sulfonamides (procedure 1) on a 6.36 mmol (1.0 g) scale. Yield: 69 % beige solid. (m.p. 115-116 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.62-7.61 (m, 1H), 7.56-7.54 (m, 1H), 7.46-7.44 (m, 2H), 7.04-7.02 (m, 1H) 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 164.2, 143.0, 139.9, 132.7, 132.6, 131.9, 127.4, 120.7, 111.2, 52.1. (IR (NaCl): 3193, 3118, 1668, 1551, 1451, 1384, 1256, 1156, 1037. HRMS (EI): Exact mass calculated for $C_{10}H_9NO_4S_3$ $[M + H]^+$: 303.97655 found 303.97687.

General procedure for benzylation (Procedure 2)



A procedure by Fawzi and co-workers was used with modifications.[47] Benzyl bromides and benzyl chlorides (1.2 equiv.) were added to a mixture of sulfonamide (1 equiv.) and K_2CO_3 (2 equiv.) in DMF (0.3 M) then heated to 50 °C or 80 °C. The resulting mixture was cooled to 23 °C then diluted with EtOAc and was brought to pH = 2 with 1 M $HCl_{(aq.)}$. The phases were then separated and the aqueous phase was extracted with EtOAc. The combined organics were washed three times with water then were dried over anhydrous sodium sulfate, filtered over a cotton plug and the solvent was removed under reduced pressure. The resulting mixture was recrystalized with EtOAc and hexanes.

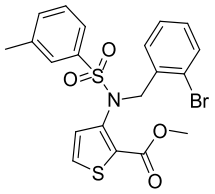
Synthesis of NW-104 (2a)



NW-104 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 9.64 mmol (3.0 g) scale. Yield: 92 % beige solid. (m.p. 118-119 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.67 (dd, *Js* = 2,0 Hz, *Jl* = 8,0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.41 (dd, *Js* = 2.0 Hz, *Jl* = 8.0 Hz, 1H), 7.33 (d, *J* = 5.0 Hz 1H), 7.29-7.26 (m, 3H), 7.08 (m, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 5.02 (s, 2H), 3.60 (s, 3H), 2.43 (s,

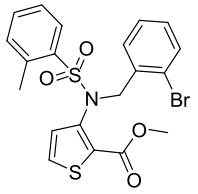
3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.5, 143.4 (2C), 140.4, 136.3 (2C), 135.8, 132.6 (2C), 131.2, 130.8, 129.1, 129.0, 128.5, 127.6, 127.5, 123.6, 54.6, 51.9, 21.5. (IR (NaCl): 3110, 2950, 1721, 1598, 1522, 1438, 1352, 1264, 1164, 1091. HRMS (EI): Exact mass calculated for $C_{20}H_{18}BrNO_4S_2$ $[M + H]^+$: 479.99334 found 479.99419.

Synthesis of NW-160 (2b)



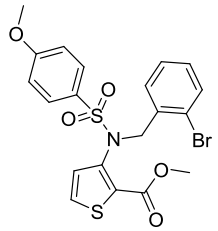
NW-160 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.64 mmol (0.2 g) scale. Yield: 83 % colourless needles. (m.p. 123-124 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.67 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.41 (dd, *Js* = 1.5 Hz, *J* = 8.0 Hz, 1H), 7.37-7.33 (m, 3H), 7.28 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.08 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 6.92 (d, *J* = 5.5 Hz, 1H), 5.03 (s, 2H), 3.59 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.5, 140.3, 139.1, 138.8, 135.8, 133.4, 132.6, 131.3, 130.9, 129.1, 129.0, 128.6, 127.9, 127.5, 124.7, 123.6, 104.9, 54.6, 51.8, 21.2. (IR (NaCl): 2950, 1721, 1438, 1352, 1158, 1086. HRMS (EI): Exact mass calculated for $C_{20}H_{18}BrNO_4S_2$ $[M + H]^+$: 479.99334 found 479.99152.

Synthesis of NW-154 (2c)



NW-154 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.64 mmol (0.2 g) scale. Yield: 95 % colourless needles. (m.p. 108-109 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.76 (dd, *Js* = 1.0 Hz, *Jl* = 8.0 Hz, 1H), 7.68 (dd, *Js* = 1.0 Hz, *Jl* = 8.0 Hz, 1H), 7.43-7.39 (m, 2H), 7.30-7.22 (m, 4H), 7.08 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 6.96 (d, *J* = 5.5 Hz, 1H), 5.16 (s, 2H), 3.58 (s, 3H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.5, 140.1, 138.2 (2C), 137.7, 136.0, 132.6, 132.5, 131.9, 131.1, 130.2, 129.2, 128.8, 128.6, 127.6, 125.9, 123.9, 54.6, 51.9, 21.1. (IR (NaCl): 3062, 2950, 1719, 1522, 1438, 1396, 1347, 1265, 1231, 1164, 1061. HRMS (EI): Exact mass calculated for $C_{20}H_{18}BrNO_4S_2$ [M + H]$^{+}$: 479.99334 found 479.99446.

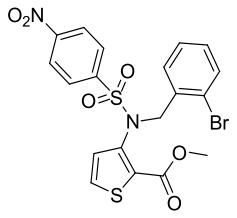
Synthesis of NW-2-067 (2d)



NW-2-067 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 2.44 mmol (0.8 g) scale. Yield: 98 % colourless crystal. (m.p. 125-126 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.67-7.62 (m, 3H), 7.40 (dd, *Js* = 2.0 Hz, *Jl* = 8.0 Hz, 1H), 7.32 (d, *J* = 5.5 Hz, 1H), 7.26 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.06 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 6.94-6.91 (m, 3H), 5.01 (s, 2H), 3.85 (s, 3H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 163.0, 160.5, 140.5 (2C), 135.8 (2C), 132.5, 131.1, 130.8 (2C),

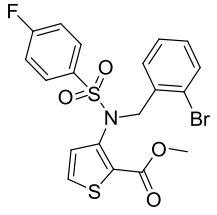
129.7, 129.1, 129.0, 128.4, 127.5, 123.5, 113.8, 55.5, 54.5, 51.9. (IR (NaCl): 3109, 2949, 2840, 2362, 1720, 1596, 1498, 1438, 1351, 1260, 1159, 1092, 1023. HRMS (EI): Exact mass calculated for $C_{20}H_{18}BrNO_5S_2$ $[M + H]^+$: 495.98825 found 495.98608.

Synthesis of NW-153 (2e)



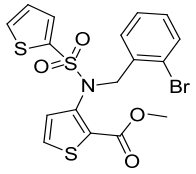
NW-153 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.58 mmol (0.2 g) scale. Yield: 98 % colourless crystal. (m.p. 188-189 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.30 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.57 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.44 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.36 (d, *J* = 5.0 Hz, 1H), 7.28 (td, *Js* = 1.0 Hz, *Jl* = 8.0 Hz, 1H), 7.10 (td, *Js* = 1.0 Hz, *Jl* = 8.0 Hz, 1H), 6.95 (d, *J* = 5.0 Hz, 1H), 5.08 (s, 2H), 3.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.2, 150.1, 144.9 (2C), 139.7, 135.0 (2C), 132.8, 131.7 (2C), 131.0, 129.5 (2C), 128.8, 127.8, 127.6, 123.9, 54.6, 52.0. (IR (NaCl): 3107, 1711, 1531, 1437, 1350, 1169, 1090. HRMS (EI): Exact mass calculated for $C_{19}H_{15}BrN_2O_6S_2$ $[M + H]^+$: 510.96277 found 510.96379.

Synthesis of NW-2-066 (2f)



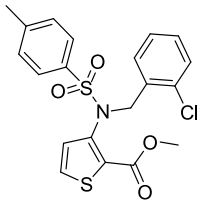
NW-2-066 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 1.60 mmol (0.5 g) scale. Yield: 94 % colourless crystal. (m.p. 162-163 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.74-7.70 (m, 2H), 7.62 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.41 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.33 (d, *J* = 5.5 Hz, 1H), 7.27 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.16-7.11 (m, 2H), 7.07 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 6.94 (d, *J* = 5.5 Hz, 1H), 5.04 (s, 2H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 166.2, 164.1, 160.3, 140.2 (2C), 135.6, 135.3, 132.6, 131.4 (2C), 130.8, 130.3, 129.2, 128.2, 127.5, 123.7, 115.9, 54.6, 51.9. (IR (NaCl): 3237, 3106, 2955, 1678, 1593, 1548, 1494, 1448, 1388, 1277, 1243, 1172, 1090, 1035. HRMS (EI): Exact mass calculated for $C_{19}H_{15}BrFNO_4S_2$ $[M + H]^+$: 483.96827 found 483.96693.

Synthesis of NW-161 (2g)



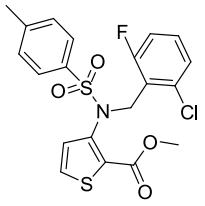
NW-161 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.66 mmol (0.2 g) scale. Yield: 91 % colourless needles. (m.p. 125-126 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.63 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.60 (d, *J* = 5.5 Hz, 1H), 7.47 (dd, *Js* = 1.5 Hz, *Jl* = 4.0 Hz, 1H), 7.42 (dd, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 7.27 (td, *Js* = 1.5 Hz, *Jl* = 8.0 Hz, 1H), 7.10-7.06 (m, 2H), 6.92 (d, *J* = 5.5 Hz, 1H), 5.06 (s, 2H), 3.68 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.6, 139.9, 139.7, 135.5, 132.6, 132.5, 132.2, 131.2, 130.9, 129.3 129.2, 128.7, 127.5, 127.3, 123.7, 54.7, 52.1. (IR (NaCl): 3108, 2950, 2362, 2337, 1719, 1522, 1437, 1357, 1263, 1227, 1159, 1091, 1019. HRMS (EI): Exact mass calculated for $C_{17}H_{14}BrNO_4S_3$ $[M + H]^+$: 471.93411 found 471.93194.

Synthesis of NW-171 (2h)



NW-171 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 2.41 mmol (0.75 g) scale. Yield: 88 % colourless powder. (m.p. 110-111 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.63-7.58 (m, 3H), 7.31 (d, *J* = 5.5 Hz, 1H), 7.26-7.25 (m, 2H), 7.23-7.19 (m, 2H), 7.16-7.13 (m, 1H), 6.91 (d, *J* = 5.5 Hz, 1H), 5.02 (s, 2H), 3.60 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.5, 143.4 (2C), 140.4 (2C), 136.3, 134.1, 133.6, 131.1 (2C), 130.8, 129.3, 129.2, 129.0, 128.9, 128.5, 127.6, 126.8, 52.1, 21.5. (IR (NaCl): 3110, 2951, 1721, 1522, 1438, 1353, 1165, 1092, 1030, 924, 814. HRMS (EI): Exact mass calculated for $C_{20}H_{18}ClNO_4S_2$ $[M + H]^+$: 436.04385 found 436.04186.

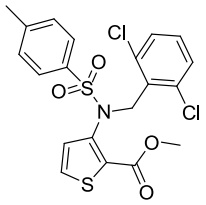
Synthesis of NW-131 (2i)



NW-131 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.94 mmol (0.3 g) scale. Yield: 99 % colourless powder. (m.p. 113-114 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.60 (d, *J* = 8.0 Hz, 2H), 7.29-7.25 (m, 3H), 7.15-7.06 (m, 2H), 6.86-6.81 (m, 2H), 5.09 (s, 2H), 3.57 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 163.1, 161.1, 160.6, 143.3 (2C), 139.9, 136.5, 136.3, 131.4, 130.0, 129.5, 129.2, 128.7, 127.7, 125.3, 122.1, 114.0, 51.8, 45.6, 21.5. (IR (NaCl): 3110,

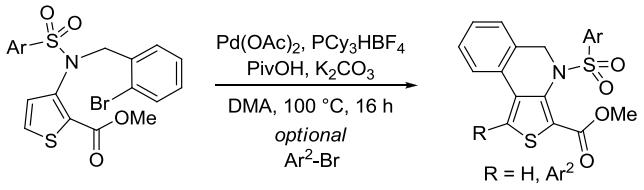
2951, 1723, 1506, 1456, 1437, 1358, 1162, 1091. HRMS (EI): Exact mass calculated for $C_{20}H_{17}ClFNO_4S_2$ [M + H]$^+$: 454.03443 found 454.03288.

Synthesis of NW-130 (2j)



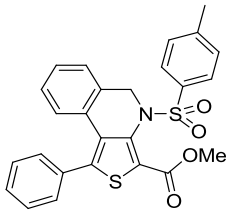
NW-130 was prepared following the general procedure for benzylation of sulfonamides (procedure 2) on a 0.96 mmol (0.3 g) scale. Yield: 83.1 % colourless crystal. (m.p. 175-176 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.60 (d, *J* = 8.5 Hz, 2H), 7.26-7.24 (m, 3H), 7.18 (s, 1H), 7.16 (s, 1H), 7.08-7.05 (m, 1H), 6.80 (d, *J* = 5.5 Hz, 1H), 5.25 (s, 2H), 3.56 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 160.5, 143.2 (2C), 139.4 (2C), 137.0, 136.5, 131.5, 131.3, 130.2 (2C), 129.6, 129.1, 128.6, 128.3, 127.8 (2C), 51.7, 49.2, 21.4. (IR (NaCl): 2950, 1723, 1703, 1437, 1355, 1164, 1093, 928, 777, 671, 562, 545. HRMS (EI): Exact mass calculated for $C_{20}H_{17}Cl_2NO_4S_2$ [M + H]$^+$: 470.00488 found 470.00309.

General procedure for double C-H activation (Procedure 3)



Procedure adapted from a method reported by Fagnou and co-workers.[24] Aryl bromide (1 equiv.) was added to a solution of the benzyl sulfonamide (1 equiv.), $Pd(OAc)_2$ (0.05 equiv.), $PCy_3 \cdot HBF_4$ (0.1 equiv.), pivalic acid (0.3 equiv), K_2CO_3 (1.5 equiv.) in DMA (0.1 M). The resulting mixture was heated to 100 °C for 16 h, was cooled to 23 °C and filtered over a packed pad of celite. The round bottom flask was further rinsed with EtOAc and was poured over the pad of celite. The filtrate was then washed with water. The aqueous phase was then extracted with EtOAc and the combined organic phases were washed 3 times with water. Organics were dried over anhydrous sodium sulfate, filtered over a cotton plug and solvent was removed under reduced pressure. The resulting compounds were purified by column chromatography, 20% EtOAc in hexanes or triturated using 50% EtOAc in hexanes.

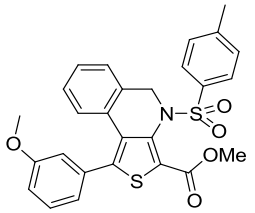
Synthesis of NW-2-081 (81a)



NW-2-081 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.42 mmol (0.2 g) scale. Yield: 64 % colourless solid. (m.p. 209-210 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.44-7.38 (m, 5H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.94-6.86 (m, 2H), 6.77-6.69 (m, 4H), 4.82 (br s, 2H), 3.99

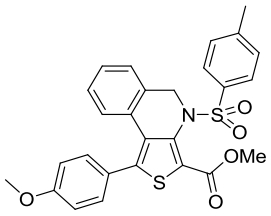
(s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.4, 143.2 (2C), 141.3 (2C), 137.6, 135.2 (2C), 133.4 (2C), 130.4 (2C), 129.1, 129.0, 128.9, 128.7, 128.6, 128.2, 127.3 (2C), 126.8, 126.5, 125.0, 52.4, 51.0, 21.2. (IR (NaCl): 3063, 2951, 2256, 1731, 1704, 1577, 1457, 1358, 1241, 1166, 1114, 1088. HRMS (EI): Exact mass calculated for $C_{26}H_{21}NO_4S_2$ $[M + H]^+$: 476.09848 found 476.09795.

Synthesis of NW-2-074 (81c)



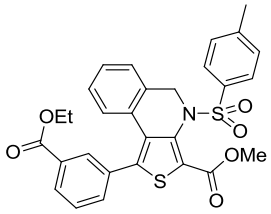
NW-2-074 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.42 mmol (0.2 g) scale. Yield: 99 % yellow solid. (m.p. 219-220 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.33-7.29 (m, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.01-6.99 (m, 1H), 6.96-6.71 (m, 3H), 6.87-6.86 (m, 1H), 6.77-6.73 (m, 4H), 4.82 (br s, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.4, 159.9, 143.2 (2C), 141.1, 137.6, 135.2 (2C), 134.6 (2C), 130.4, 130.1, 128.6 (2C), 128.2, 127.3, 126.7, 126.4, 125.5, 125.1, 121.2, 114.9, 114.2, 55.3, 52.4, 51.0, 21.2. (IR (NaCl): 2951, 1731, 1703, 1597, 1438, 1358, 1252, 1165, 1087, 1046. HRMS (EI): Exact mass calculated for $C_{27}H_{23}NO_5S_2$ $[M + H]^+$: 506.10904 found 506.10909.

Synthesis of NW-2-080 (81d)



NW-2-080 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.42 mmol (0.2 g) scale. Yield: 90 % colourless solid. (m.p. 182-183 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.34 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.93-6.90 (m, 3H), 6.87-6.85 (m, 1H), 6.77-6.73 (m, 4H), 4.81 (br s, 2H), 3.98 (s, 3H), 3.85 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.4, 160.3, 143.2, 141.5 (2C), 137.6, 135.1, 130.3 (2C), 130.1 (2C), 128.8, 128.5, 127.7, 127.2, 127.1 (2C), 126.7, 126.4, 125.5, 124.9, 124.8, 114.4, 55.3, 52.2, 50.9, 21.1. (IR (NaCl): 3003, 2951, 2839, 2256, 1730, 1703, 1608, 1558, 1517, 1458, 1439, 1164, 1088, 1032, 911. HRMS (EI): Exact mass calculated for $C_{27}H_{23}NO_5S_2$ $[M + H]^+$: 506.10904 found 506.10893.

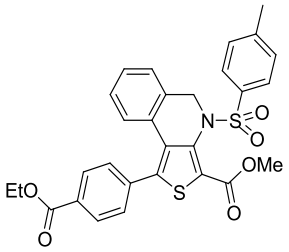
Synthesis of NW-2-017 (81e)



NW-2-017 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.63 mmol (0.3 g) scale. Yield: 97 % clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.12-8.09 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.94-6.87 (m, 2H), 6.76-6.72 (m, 3H), 6.62 (d, *J* = 8.0 Hz, 1H) 4.83 (br s, 2H), 4.38 (q, *J* = 7.5 Hz, 2H), 3.99 (s, 3H), 2.12 (s, 3H), 1.38 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 165.8, 162.3, 143.3 (2C), 139.7 (2C), 137.7 (2C), 135.2,

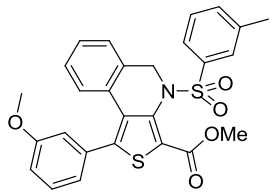
133.8, 133.2, 131.5 (2C), 130.5, 130.1, 129.9, 129.1, 128.7 (2C), 127.5, 127.3, 126.9, 126.1, 124.8, 61.3, 52.4, 51.0, 21.2, 14.3. (IR (NaCl): 2982, 2951, 1719, 1559, 1384, 1231, 1166, 1086, 1031. HRMS (EI): Exact mass calculated for $C_{29}H_{25}NO_6S_2$ $[M + H]^+$: 548.11961 found 548.12059.

Synthesis of NW-2-153 (81f)



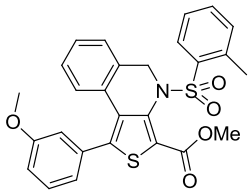
NW-2-153 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.62 mmol (0.3 g) scale. Yield: 81 % yellow solid (m.p. 110-111 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.06 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.95-6.86 (m, 2H), 6.76-6.65 (m, 4H), 4.81 (br s, 2H), 4.40 (q, *J* = 7.5 Hz, 2H), 3.98 (s, 3H), 2.11 (s, 3H), 1.40 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 165.9, 162.2, 143.3 (2C), 139.6 (2C), 137.9, 137.8, 135.1, 130.9 (2C), 130.5, 130.2, 128.9, 128.8, 128.6, 128.3, 127.6 (2C), 127.2, 126.8, 126.6, 126.3, 125.0, 61.2, 52.4, 50.9, 21.2, 14.2. (IR (NaCl): 2951,1715, 1360, 1271, 1166, 1109, 1028. HRMS (EI): Exact mass calculated for $C_{29}H_{25}NO_6S_2$ $[M + H]^+$: 548.11961 found 548.11746.

Synthesis of NW-2-083 (81g)



NW-2-083 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.31 mmol (0.15 g) scale. Yield: 80 % yellow solid. (m.p. 171-172 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.31 (t, *J* = 8.0 Hz, 1H), 7.06-7.04 (m, 1H), 7.00-6.84 (m, 8H), 6.75-6.74 (m, 2H), 4.85 (br s, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.4, 159.9, 141.1, 138.3, 137.8, 137.5, 134.6, 133.2, 130.1, 130.0, 128.5, 128.3, 127.8, 127.6, 127.4, 127.1, 126.3, 125.6, 125.0, 124.5, 121.2, 114.9, 114.2, 55.3, 52.4, 51.1, 20.9. (IR (NaCl): 3446, 2951, 2837, 1732, 1703, 1598, 1487, 1462, 1437, 1358, 1253, 1161, 1086, 1046, 959. HRMS (EI): Exact mass calculated for $C_{27}H_{23}NO_5S_2$ $[M+H]^+$: 506.10904 found 506.11036.

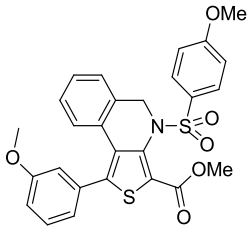
Synthesis of NW-2-098 (81h)



NW-2-098 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.42 mmol (0.2 g) scale. Yield: 81 % colourless solid. (m.p. 178-179 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.71 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.07-6.92 (m, 6H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.73 (t, *J* = 8.0 Hz, 2H), 4.78 (s, 2H), 3.95 (s, 3H), 3.78 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.4, 159.9, 141.2, 137.9, 137.7, 137.6, 134.6 (2C), 132.5, 132.2, 130.5, 130.2, 128.6, 128.4, 127.5, 127.2, 125.8, 125.6, 125.0, 124.6, 121.2, 114.9, 114.2, 55.3, 52.3, 50.5, 20.3. (IR (NaCl):

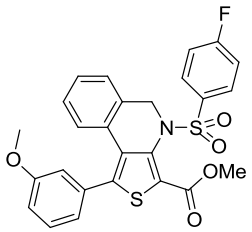
3061, 3002, 2951, 2837, 1731, 1703, 1597, 1578, 1462, 1439, 1354, 1254, 1166, 1047. HRMS (EI): Exact mass calculated for $C_{27}H_{23}NO_5S_2$ [M +H]$^+$: 506.10904 found 506.10876.

Synthesis of NW-2-075 (81i)



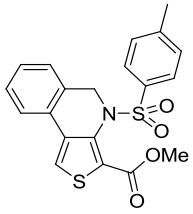
NW-2-075 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.40 mmol (0.2 g) scale. Yield: 79 % yellow solid. (m.p. 219-220 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.31 (td, *Js* = 1.5 Hz, *Jl* = 7.5 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.01-6.90 (m, 5H), 6.81-6.76 (m, 2H), 6.41 (d, *J* = 9.0 Hz, 2H), 4.83 (br s, 2H), 3.99 (s, 3H), 3.77 (s, 3H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.6, 162.4, 159.9, 141.1, 137.7, 134.7 (2C), 130.4, 130.1, 129.8, 129.4, 128.6, 128.2, 127.5, 127.0, 126.4 (2C), 125.5, 125.2, 121.2, 114.9, 114.2, 113.3, 55.4, 55.3, 52.4, 51.0. (IR (NaCl): 2949, 2841, 2362, 1731, 1701, 1595, 1578, 1497, 1438, 1384, 1259, 1160, 1090, 1027, 781. HRMS (EI): Exact mass calculated for $C_{27}H_{23}NO_6S_2$ [M +H]$^+$: 522.10396 found 522.10364.

Synthesis of NW-2-070 (81j)



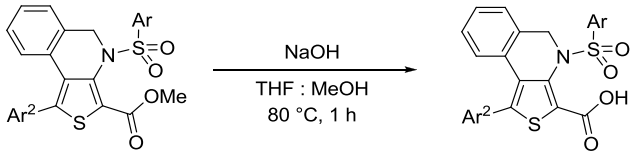
NW-2-070 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.62 mmol (0.3 g) scale. Yield: 78 % yellow solid. (m.p. 199-200 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.31 (t, *J* = 7.5 Hz, 1H), 7.23-7.20 (m, 2H), 7.00-6.93 (m, 5H), 6.83-6.78 (m, 2H), 6.62 (t, *J* = 8.5 Hz, 2H), 4.84 (br s, 2H), 3.98 (s, 3H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 165.8, 163.7, 162.2, 159.9, 141.4, 137.1, 134.3, 134.1, 130.2, 130.0 (2C), 128.5, 128.1, 127.6, 127.2, 126.4, 125.7, 125.2, 121.1, 115.2, 115.0 (2C), 114.1, 55.3, 52.4, 51.1. (IR (NaCl): 2951, 2362, 2337, 1731, 1302, 1590, 1491, 1361, 1253, 1170, 1155, 1087. HRMS (EI): Exact mass calculated for $C_{26}H_{20}BrFNO_5S_2$ $[M+H]^+$: 510.08397 found 510.08421.

Synthesis of NW-3-043 (81b)



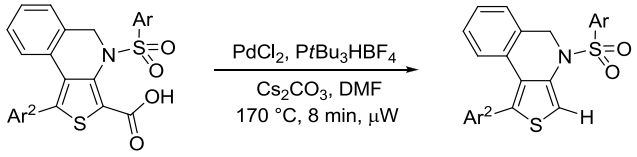
NW-3-043 was prepared following the general procedure for double C-H functionalization (procedure 3) on a 0.21 mmol (0.1 g) scale. Yield: 96 % colourless solid. (m.p. 168-169 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.53 (s, 1H), 7.17-7.03 (m, 5H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 4.82 (br s, 2H), 3.96 (s, 3H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.2, 143.4 (2C), 136.7, 134.9, 133.5 (2C), 129.1, 128.7, 128.4, 127.8, 127.5, 127.4, 127.1, 126.2, 123.0, 120.9, 52.4, 50.6, 21.2. (IR (NaCl): 2951, 2256, 1707, 1597, 1560, 1446, 1386, 1357, 1255, 1197, 1166.

General procedure for saponification (Procedure 4)



A 1 : 2 : 1 mixture of 2 M $NaOH_{(aq.)}$ (5 equiv.), THF, MeOH (overall concentration 0.1 M) was added to the methyl ester (1 equiv.) and heated to reflux for 1 h. The mixture was cooled to 23 °C then diluted with EtOAc and brought to pH = 2 with 1 M $HCl_{(aq.)}$. The mixture was separated, and the aqueous phase was extracted with EtOAc. Combined organics were then washed three times with water, dried over anhydrous sodium sulfate and filtered over a plug of cotton. Solvent was removed under reduced pressure and used without further purification.

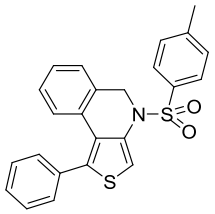
General procedure for protodecarboxylation (Procedure 5)



Conditions were based upon decarboxylative cross-coupling conditions established by Forgione and Bilodeau.[35] The carboxylic acid (1 equiv.) in DMF (0.1 M) was added to a microwave vial containing $P^tBu_3{\cdot}HBF_4$ (0.05 equiv.), Cs_2CO_3 (1.5 equiv.) and $PdCl_2$ (0.05 equiv.). The vial was then purged with argon and sealed with a microwave septum. The mixture was then irradiated in the microwave at 170 °C for 8 minutes. The resulting mixture was cooled to 23 °C then filtered over a packed pad of celite. The microwave vial was rinsed with EtOAc and was filtered over the celite. The filtrate was washed once with water and the aqueous phase was extracted with EtOAc. The organics were then combined and washed three times with water, dried over anhydrous sodium sulfate and filtered over a plug of cotton.

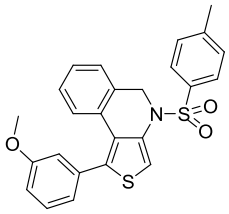
Solvent was then removed under reduced pressure. The compounds were purified by column chromatography using 20% EtOAc in hexanes as the eluent.

Synthesis of NW-158 (4b)



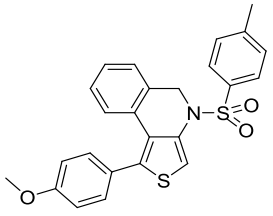
NW-158 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.17 mmol (0.1 g) scale. Yield: 55 % clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.51 (s, 1H), 7.44-7.41 (m, 2H), 7.38-7.35 (m, 3H), 7.14-7.08 (m, 3H), 7.03-7.00 (m, 1H), 6.81-6.75 (m, 4H), 4.87 (s, 2H), 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 143.1 (2C), 137.3(2C), 135.6 (2C), 134.9, 134.4, 130.3 (2C), 129.4, 129.0, 128.9, 128.6, 128.4, 127.0 (3C), 126.7, 126.4, 125.0, 116.7, 51.2, 21.3. (IR (NaCl): 3122. 3062, 1597, 1578, 1555, 1498, 1455, 1353, 1165, 1089, 1062, 912. HRMS (EI): Exact mass calculated for $C_{24}H_{19}NO_2S_2$ $[M + H]^+$: 418.093 found 418.09153.

Synthesis of NW-2-169 (4c)



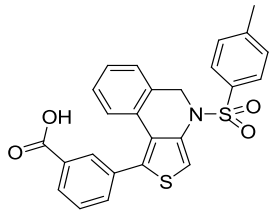
NW-2-169 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.17 mmol (0.1 g) scale. Yield: 65 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.49 (s, 1H), 7.29-7.26 (m, 1H), 7.13-7.07 (m, 3H), 7.03-6.99 (m, 2H), 6.96-6.95 (m, 1H), 6.91-6.89 (m, 1H), 6.83-6.78 (m, 4H), 4.86 (s, 2H), 3.76 (s, 3H), 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.8, 143.1 (2C), 137.2, 135.6, 135.5, 134.9, 130.2 (2C), 129.9, 129.3, 128.6, 127.0 (2C), 126.9, 126.7, 126.3, 125.1, 121.4, 116.7, 114.3, 113.1, 55.3, 51.1, 21.2. (IR (NaCl): 2922, 1598, 1578, 1494, 1353, 1164, 1090, 1048, 952. HRMS (EI): Exact mass calculated for $C_{25}H_{21}NO_3S_2$ $[M + H]^+$: 448.10356 found 448.10153.

Synthesis of NW-136 (4d)



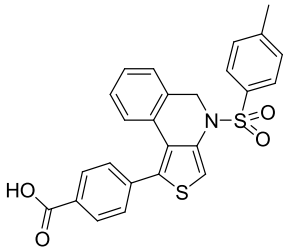
NW-136 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.21 mmol (0.12 g) scale. Yield: 78 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.45 (s, 1H), 7.35-7.31 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.03-6.99 (m, 1H), 6.91-6.88 (m, 2H), 6.81-6.77 (m, 4H), 4.85 (s, 2H), 3.84 (s, 3H), 2.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.7, 143.0 (2C), 137.4 (2C), 135.4 (2C), 134.9 (2C), 130.2 (2C), 129.5, 128.5, 127.0, 126.8, 126.6, 126.4, 126.2, 124.7 (2C), 116.0, 114.3, 55.3, 51.1, 21.2. (IR (NaCl): 3123, 2935, 2837, 1608, 1513, 1351, 1291, 1249, 1164, 1034, 911. HRMS (EI): Exact mass calculated for $C_{25}H_{21}NO_3S_2$ $[M + H]^+$: 448.10356 found 448.10347.

Synthesis of NW-2-027 (4e)



NW-2-027 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.16 mmol (0.1 g) scale. Yield: 84 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.19 (s, 1H), 8.12-8.10 (m, 1H), 7.68-7.66 (m, 1H), 7.57 (s, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.15-7.03 (m, 4H), 6.81-6.79 (m, 3H), 6.70-6.69 (m, 1H), 4.89 (s, 2H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 170.4, 143.2 (2C), 135.8, 135.6, 135.1, 134.9, 134.4, 130.6, 130.5, 130.0, 129.9, 129.2, 129.0, 128.7, 127.4, 127.3, 127.1, 127.0, 126.6, 124.7 (2C), 117.4, 51.1, 21.3. (IR (NaCl): 2955, 2924, 2854, 1623, 1461, 1164, 1046. HRMS (EI): Exact mass calculated for $C_{25}H_{19}NO_4S_2$ $[M + H]^+$: 462.08283 found 462.08375.

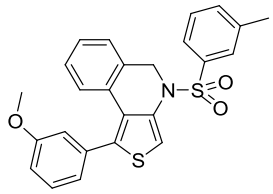
Synthesis of NW-2-033 (4f)



NW-2-033 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.16 mmol (0.1 g) scale. Yield: 70 % yellow oil.^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.10 (d, *J* = 8.0 Hz, 2H), 7.59-7.56 (m, 3H),

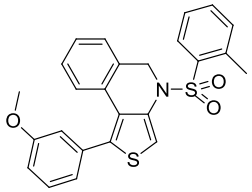
7.14-7.06 (m, 4H), 6.84-6.75 (m, 4H), 4.88 (s, 2H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 170.7, 143.2 (2C), 140.0, 136.1, 135.7 (2C), 134.9, 130.8 (2C), 130.6, 129.0, 128.9, 128.8, 128.7, 127.8, 127.5, 127.1 (2C), 127.0, 126.6, 125.1, 117.9, 51.1, 21.3. (IR (NaCl): 2986, 1690, 1605, 1419, 1353, 1293, 1164, 1089, 928. HRMS (EI): Exact mass calculated for $C_{25}H_{19}NO_4S_2$ $[M + H]^+$: 462.08283 found 462.08277.

Synthesis of NW-2-007 (4g)



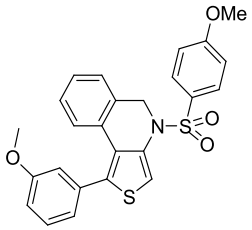
NW-2-007 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.17 mmol (0.1 g) scale. Yield: 69 % yellow solid. (m.p. 114-115 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.51 (s, 1H), 7.28 (t, *J* = 8.5 Hz, 1H), 7.11-7.10 (m, 1H), 7.05-8.85 (m, 8H), 6.81-6.77 (m, 2H), 4.88 (s, 2H), 3.76 (s, 3H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.8, 138.2, 137.5, 137.2, 135.6, 135.5, 133.0, 130.0, 129.9, 129.2, 127.7, 127.4, 127.0, 126.8, 126.3, 125.0 (2C), 124.2, 121.4, 117.1, 114.4, 114.1, 55.3, 51.2, 20.9. (IR (NaCl): 3122, 3065, 2937, 2835, 2256, 1599, 1576, 1464, 1353, 1224, 1224, 1047. HRMS (EI): Exact mass calculated for $C_{25}H_{21}NO_3S_2$ $[M + H]^+$: 448.10356 found 448.10361.

Synthesis of NW-2-021 (4h)



NW-2-021 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.17 mmol (0.1 g) scale. Yield: 70 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.69 (dd, *Js* = 1.0 Hz, *Jl* = 8.0 Hz, 1H), 7.31-7.25 (m, 2H), 7.15 (td, *Js* = 1.5 Hz, *Jl* = 7.5 Hz, 1H), 7.05-6.97 (m, 6H), 6.93-6.85 (m, 3H), 4.87 (s, 2H), 3.76 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.8, 137.4 (2C), 137.2, 135.4, 132.5, 132.3, 130.8, 130.0, 129.9, 129.4, 127.3, 127.1, 126.6, 126.0, 125.7, 125.1 (2C), 121.5, 114.6, 114.2, 105.0, 55.3, 50.3, 20.2. (IR (NaCl): 3063, 2937, 2836, 1605, 1578, 1555, 1494, 1464, 1349, 1224, 1164, 1065, 920. HRMS (EI): Exact mass calculated for $C_{25}H_{21}NO_3S_2$ $[M + H]^+$: 448.10356 found 448.10419.

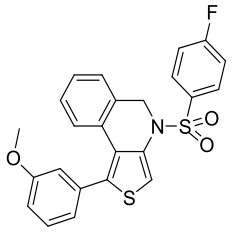
Synthesis of NW-156 (4i)



NW-156 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.20 mmol (0.12 g) scale. Yield: 68 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.49 (s, 1H), 7.29-7.26 (m, 1H), 7.16-7.13 (m, 2H), 7.11-7.09 (m, 1H), 7.05-6.99 (m, 2H), 6.96-6.89 (m, 2H), 6.85-6.79 (m, 2H), 6.46-6.43 (m, 2H), 4.86 (s, 2H), 3.76 (s, 3H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.5, 159.8, 137.2 (2C),

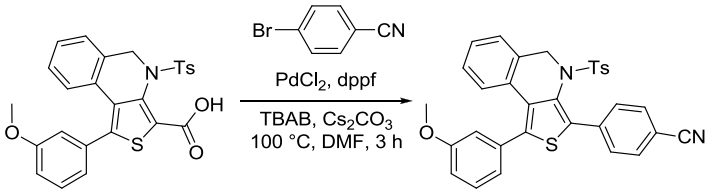
135.6 (2C), 130.2 (2C), 129.9, 129.3, 129.1, 127.1 (2C), 126.8, 126.3, 125.1 (2C), 121.4, 116.8, 114.3, 114.1, 113.2, 55.3 (2C), 51.1. (IR (NaCl): 3121, 2941, 2838, 1596, 1578, 1496, 1463, 1352, 1261, 1160, 1091, 1049, 1028. HRMS (EI): Exact mass calculated for $C_{25}H_{21}NO_4S_2$ [M + H]$^+$: 464.09848 found 464.09842.

Synthesis of NW-2-103 (4j)



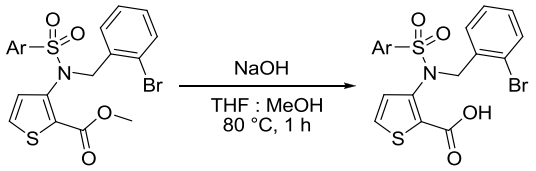
NW-2-103 was prepared following the general procedure for saponification (procedure 4) and the crude product was used in the general procedure for protodecarboxylation (procedure 5) on a 0.17mmol (0.1 g) scale. Yield: 78 % clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.53 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21-7.19 (m, 2H), 7.11-6.94 (m, 5H), 6.86-6.81 (m, 2H), 6.64 (t, *J* = 8.5 Hz, 2H), 4.88 (s, 2H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.8, 137.6 (2C), 135.4, 135.2, 130.0 (2C), 129.9, 129.7, 129.6, 129.2, 127.4, 127.2, 126.7, 126.4, 125.2, 121.4, 117.5, 115.2, 115.0, 114.4, 114.2, 55.3, 51.3. (IR (NaCl): 2923, 2851, 1589, 1492, 1356, 1224, 1168, 1156, 1047. HRMS (EI): Exact mass calculated for $C_{24}H_{18}FNO_3S_2$ [M + H]$^+$: 452.07849 found 452.07859.

Procedure for decarboxylative cross-coupling (Procedure 6) (4a)



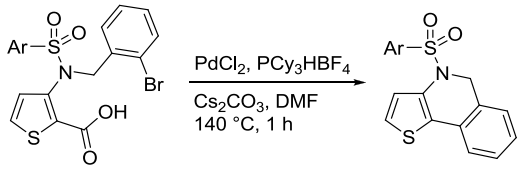
Original conditions by Mitchell and co-workers were used with modifications.[37] DMF (0.1 M) was added to a mixture of the carboxylic acid (0.102 mmol, 50 mg), $PdCl_2$ (0.0051 mmol, 1 mg), dppf (0.0061 mmol, 3.4 mg), Cs_2CO_3 (0.153 mmol, 50 mg) and 4-bromobenzonitrile (0.204 mmol, 37.2mg). The mixture was then heated to 100 °C for 3 h. The resulting mixture was cooled to room temperature, filtered over a packed pad of celite and the filtrate was washed once with water and the aqueous phase was extracted with EtOAc. The combined organics were then washed three times with water, dried over anhydrous sodium sulfate and filtered over a plug of cotton. Solvent was then removed under reduced pressure resulting in a yellow solid. Yield 62%. The solid was then purified by recrystalization with EtOAc and hexanes resulting in a yellow solid. Yield 22%. (m.p. 242-243 °C) ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 8.01 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7,31 (t, *J* = 9.0 Hz, 1H), 7.06-6.94 (m, 7H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.71-6.68 (m, 3H), 4.93 (br s, 2H), 3.78 (s, 3H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 159.9, 143.2 (2C), 138.2, 137.6, 134.9 (2C), 134.3, 134.2, 132.4 (2C), 132.2 (2C), 130.1, 130.0, 129.1 (2C), 128.4, 128.3 (2C), 127.4, 127.3, 126.8, 126.6, 125.5, 121.3, 118.9, 114.4, 111.0, 55.4, 51.8, 21.3. (IR (NaCl): 2921, 2226. 1603, 1578. 1490, 1355, 1287, 1184, 1165, 1089.

General procedure for saponification (Procedure 7)



A 1:2:1 mixture of 2 M $NaOH_{(aq.)}$ (5 equiv.), THF, MeOH (overall concentration 0.1 M) was added to methyl ester (1 equiv.) and heated to reflux for 1 h. The mixture was diluted with EtOAc and brought to pH = 2 with 1 M $HCl_{(aq.)}$. The mixture was separated, and the aqueous phase was extracted with EtOAc. Combined organics were then washed three times with water, dried over sodium sulphate and filtered. Solvent was removed under reduced pressure and used without further purification.

General procedure for decarboxylative cross-coupling (Procedure 8)

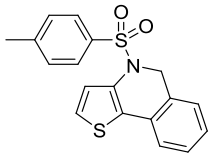


Original conditions by Forgione and Bilodeau were used with modifications.[54] The carboxylic acid (1 equiv.) in DMF (0.1 M) was added to a flame dried round bottom flask containing $P^tBu_3{\cdot}HBF_4$ (0.05 equiv.), Cs_2CO_3 (1.5 equiv.) and $PdCl_2$ (0.05 equiv.). The mixture was then heated to 170 °C and stirred for 1 h. The resulting mixture was filtered over a hard pad of celite and the filtrate was washed once with water and the aqueous phase was extracted with EtOAc. The combined organics were then washed

[54] Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* ***2006****, 128*, 11350

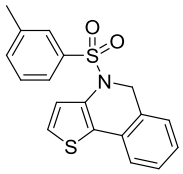
three times with water, dried over sodium sulphate and filtered. Solvent was then removed under reduced pressure. The resulting crude mixtures were purified by column chromatography using 20% EtOAc in hexanes as an eluent.

Synthesis of NW-2-077 (6b)



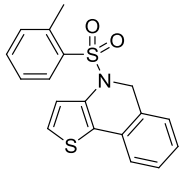
NW-2-077 was prepared following the general procedure for saponification (procedure 7) and the crude product was used in the general procedure for decarboxylative cross coupling (procedure 8) on a 0.43 mmol (0.2 g) scale. Yield: 99 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.37 (d, *J* = 5.5 Hz, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 7.12-7.01 (m, 5H), 6.93-6.91 (m, 1H), 6.79-6.78 (m, 2H), 4.88 (s, 2H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 143.3 (2C), 135.4, 134.0, 130.5 (2C), 128.5, 128.2, 127.9, 127.6, 127.4, 127.0, 126.0, 125.8, 122.9, 122.1, 50.9, 21.2. (IR (NaCl): 2923, 2853, 1490, 1457, 1354, 1167, 1089, 1067, 1028, 954, 768, 662, 582, 548. HRMS (EI): Exact mass calculated for $C_{18}H_{15}NO_2S_2$ $[M + H]^+$: 342.0617 found 342.06038.

Synthesis of NW-4-132 (6c)



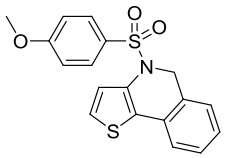
NW-4-132 was prepared following the general procedure for saponification (procedure 7) and the crude product was used in the general procedure for decarboxylative cross coupling (procedure 8) on a 0.43 mmol (0.2 g) scale. Yield: 98 % yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.56 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 5.5 Hz, 1H), 7.17 (d, J = 5.5 Hz, 1H), 7.14-6.95 (m, 6H), 6.90-6.89 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 137.5, 136.7, 135.4, 132.6, 132.3, 129.7, 129.6, 128.4, 128.3, 128.1, 127.5, 125.7, 125.5, 125.5, 123.0, 122.2, 50.4, 20.3,. (IR (NaCl): 3099, 2926, 2361, 1457, 1351, 1167, 1065, 955, 600

Synthesis of NW-4-133 (6d)



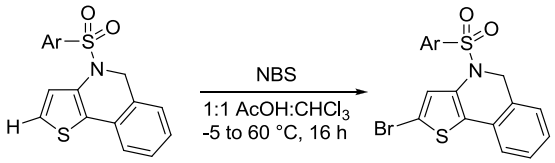
NW-4-133 was prepared following the general procedure for saponification (procedure 7) and the crude product was used in the general procedure for decarboxylative cross coupling (procedure 8) on a 0.43 mmol (0.2 g) scale. Yield: 97 % green oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.36 (d, *J* = 5.5 Hz, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 7.08-6.86 (m, 8H), 4.88 (s, 2H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 138.3, 136.7, 135.4, 133.2, 130.7, 128.1, 127.9, 127.7, 127.7, 127.5, 127.4, 126.1, 125.8, 124.2, 122.9, 122.1, 51.0, 20.9. (IR (NaCl): 3097, 2921, 1457, 1354, 1162, 1085, 1027, 954, 767, 601.

Synthesis of NW-2-109 (6e)



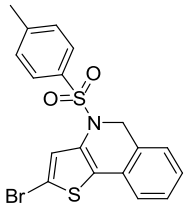
NW-2-109 was prepared following the general procedure for saponification (procedure 7) and the crude product was used in the general procedure for decarboxylative cross coupling (procedure 8) on a 0.62 mmol (0.3 g) scale. Yield: 99 % brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.36-7.34 (m, 1H), 7.21-7.19 (m, 1H), 7.13-7.11 (m, 2H), 7.08-7.01 (m, 3H), 6.94-6.93 (m, 1H), 6.44 (d, *J* = 7.0 Hz, 2H), 4.86 (s, 2H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.7, 135.5 (2C), 130.5 (2C), 129.0, 128.4, 128.1, 127.8, 127.7, 127.4, 126.0, 125.7, 122.8, 122.1, 113.1, 55.3, 50.8. (IR (NaCl): 3100, 2927, 2841, 1595, 1577, 1497, 1355, 1258, 1166, 1091, 1025, 954, 833, 768, 664, 623, 554. HRMS (EI): Exact mass calculated for $C_{18}H_{15}NO_3S_2$ $[M + H]^+$: 358.05661 found 358.05548.

General procedure for bromination (Procedure 9)



NBS (1 equiv.) was added to a mixture of thienoisoquinoline-phenylsulfonamide (1 equiv.) in a 1:1 mixture of acetic acid to chloroform (0.2 M) at -5 °C. The mixture was allowed to reach 23 °C before subsequent heating to 60 °C and allowed to stir for 16 h. The reaction mixture was cooled to 23 °C and basified to pH = 9 with sodium bicarbonate. The resulting biphasic mixture was partitioned between EtOAc and water and extracted. The water phase was extracted with EtOAc and the combined organic phases were washed three times with water. The combined organics was then dried using sodium sulphate, filtered and solvent was removed under reduced pressure. Samples were purified by recrystalization using EtOAc and Hexanes.

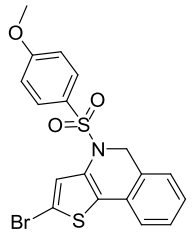
NW-2-150 (6a)



NW-2-150 was prepared following the general procedure for bromination (procedure 9) on a 0.43 mmol (0.15 g) scale. Yield: 60 % colourless needles. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.37 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.09-6.99 (m, 3H), 6.84-6.79 (m, 3H), 4.84 (s, 2H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 143.6 (2C), 134.9 (2C), 131.7 (2C), 128.7 (2C), 127.8, 127.7, 127.5, 127.5, 127.0, 125.9, 121.9, 110.7,

50.6, 21.2,. (IR (NaCl): 3107, 3049, 2894, 1597, 1532, 1459, 1356, 1166, 1089, 1034, 921, 812, 767, 664, 583, 548. HRMS (EI): Exact mass calculated for $C_{18}H_{14}BrNO_2S_2$ $[M + H]^+$: 419.97221 found 419.9717.

NW-2-125 (6f)

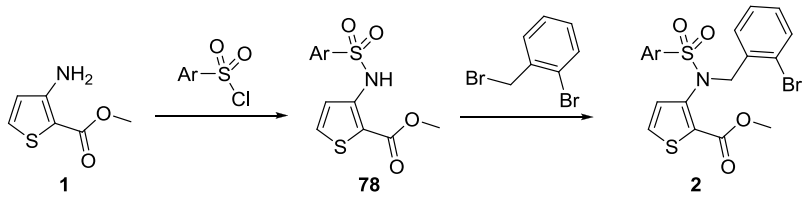


NW-2-125 was prepared following the general procedure for bromination (procedure 9) on a 0.56 mmol (0.2 g) scale. Yield: 59 % colourless crystal. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm 7.36 (s, 1H), 7.17 (d, *J* = 9.0 Hz, 2H), 7.10-7.01 (m, 3H), 6.83-6.82 (d, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 9.0 Hz, 2H), 4.83 (s, 2H), 3.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 162.9, 135.1 (2C), 131.9 (2C), 129.1, 128.8, 128.0, 127.8 (2C), 127.5, 125.9, 121.9 (2C), 113.3, 110.7, 55.4, 50.6. (IR (NaCl): 2943, 2840, 1595, 1496, 1355, 1261, 1160, 1030, 832, 668, 585,555. HRMS (EI): Exact mass calculated for $C_{18}H_{14}BrNO_3S_2$ $[M + H]^+$: 435.96712 found 435.96669.

CHAPTER 4 – CONCLUSION

In summary, methods have been developed for the synthesis of two isomers of thienoisoquinolines. The syntheses employed the use of modern palladium cross-coupling reactions that are more environmentally friendly compared to their predecessors. These reactions do not require preactivation in the form of organometallic reagents minimizing the quantity of metallic waste produced.

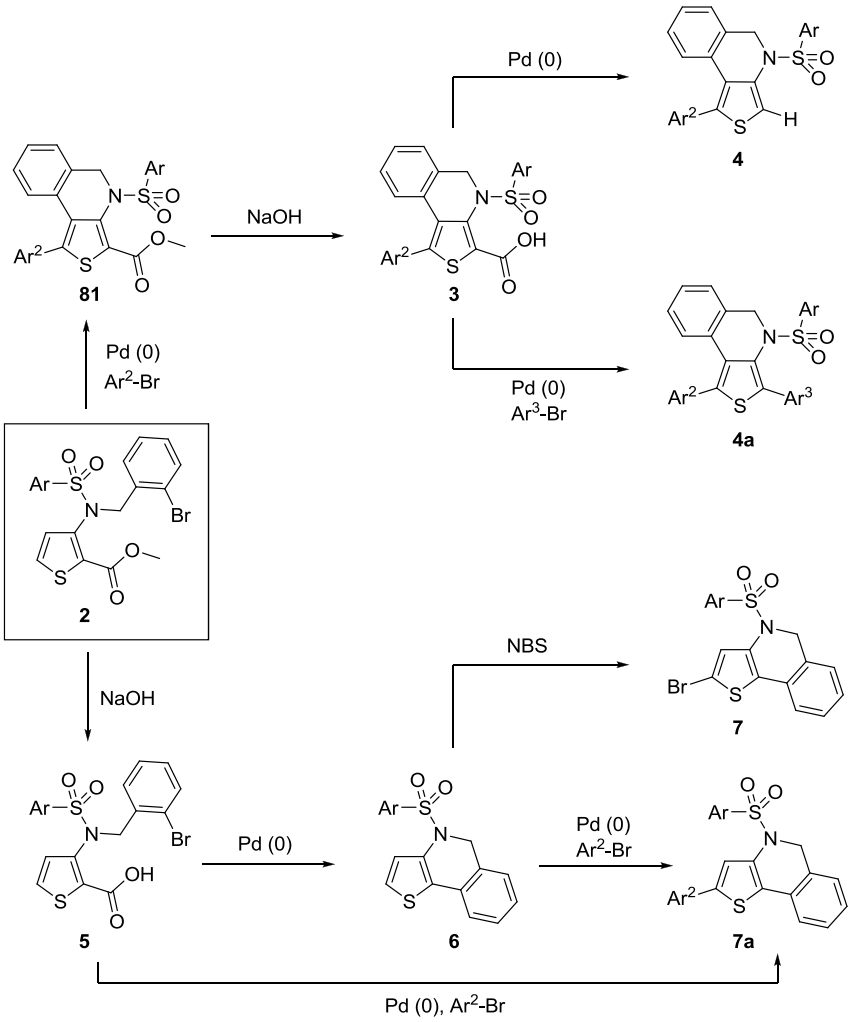
Starting from a commercially available thiophene, the key intermediate of both isomers was obtained in 2 steps.



Scheme 47 – Synthesis of key intermediate

Synthesis of the key intermediate began with commercially available 3-amino-2-methyl-thiophenecarboxylate (1) and functionalized with a sulfonyl-chloride generating different sulfonamides (78). Sulfonamides were benzylated using bromobenzylbromide, generating the key intermediate (2). This two step synthesis was conducted on multigram scale using only recrystalization as a purification method. Recrystalization is a green purification alternative to silica gel chromatography using less solvent and without the requirement of silica gel.

The key intermediate (2) was subjected to two different sequences of reactions giving different isomers, which lead to a variety of functionalized thienoisoquinolines.



Scheme 48 – Summary of the syntheses of functionalized thienoisoquinolines

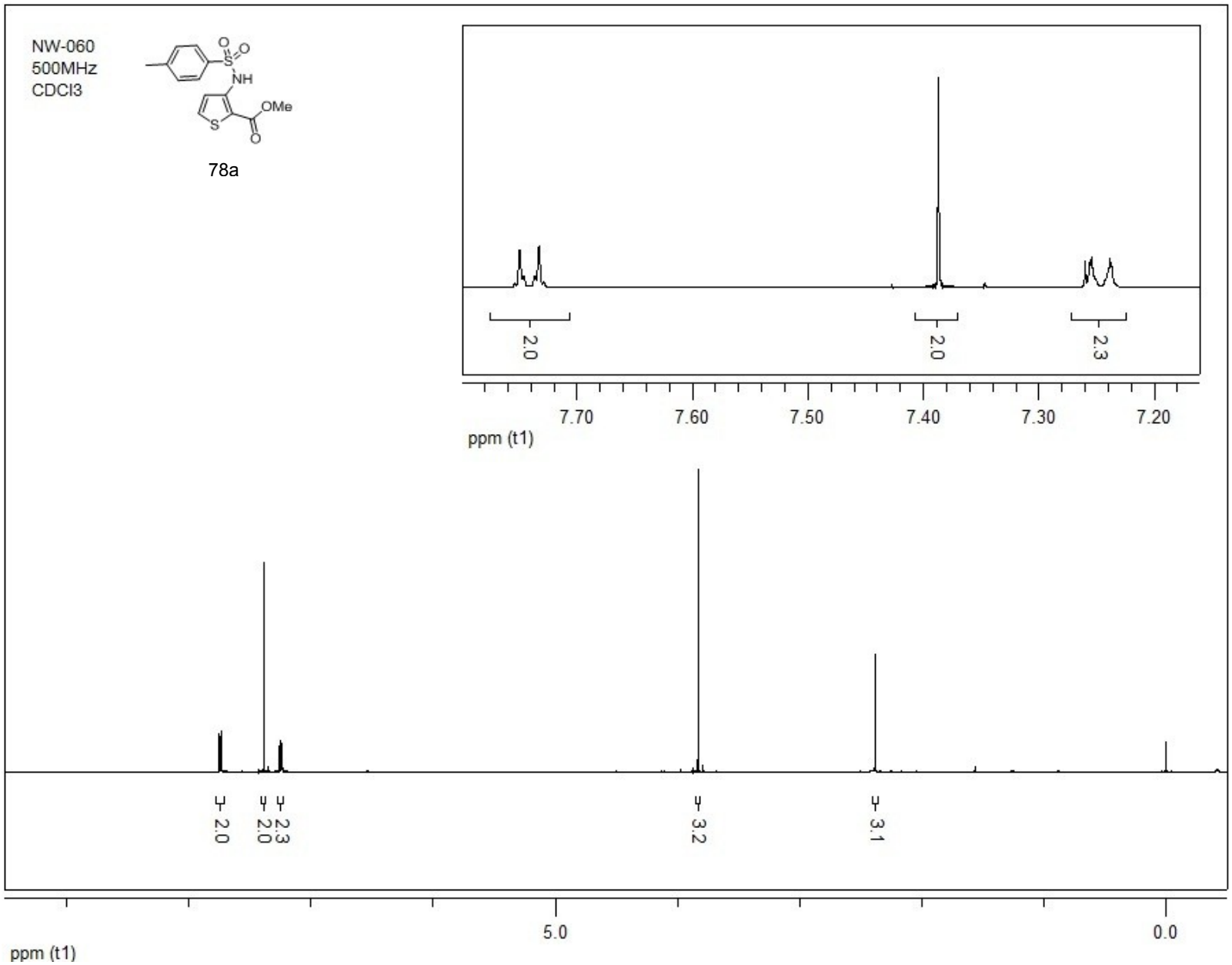
Subjecting the key intermediate to palladium catalysis conditions with a second aryl bromide facilitates a double C-H activation reaction. An intramolecular C-H activation occurs forming a carbon-carbon bond at generally less reactive C4 position due to an ester functionality at C2 acting as a blocking group. The second C-H activation can occur at the C5 position of the 3,4-thienoisoquinoline functionalizing with a variety of aromatic substituents. The overall process occurred in good to excellent yields for a variety of electronically and sterically different substituents. The ester could be saponified revealing the carboxylic acid giving a synthetic handle for further transformations. The acid can be protodecarboxylated to functionalize the C2 position with a hydrogen that was found to occur readily

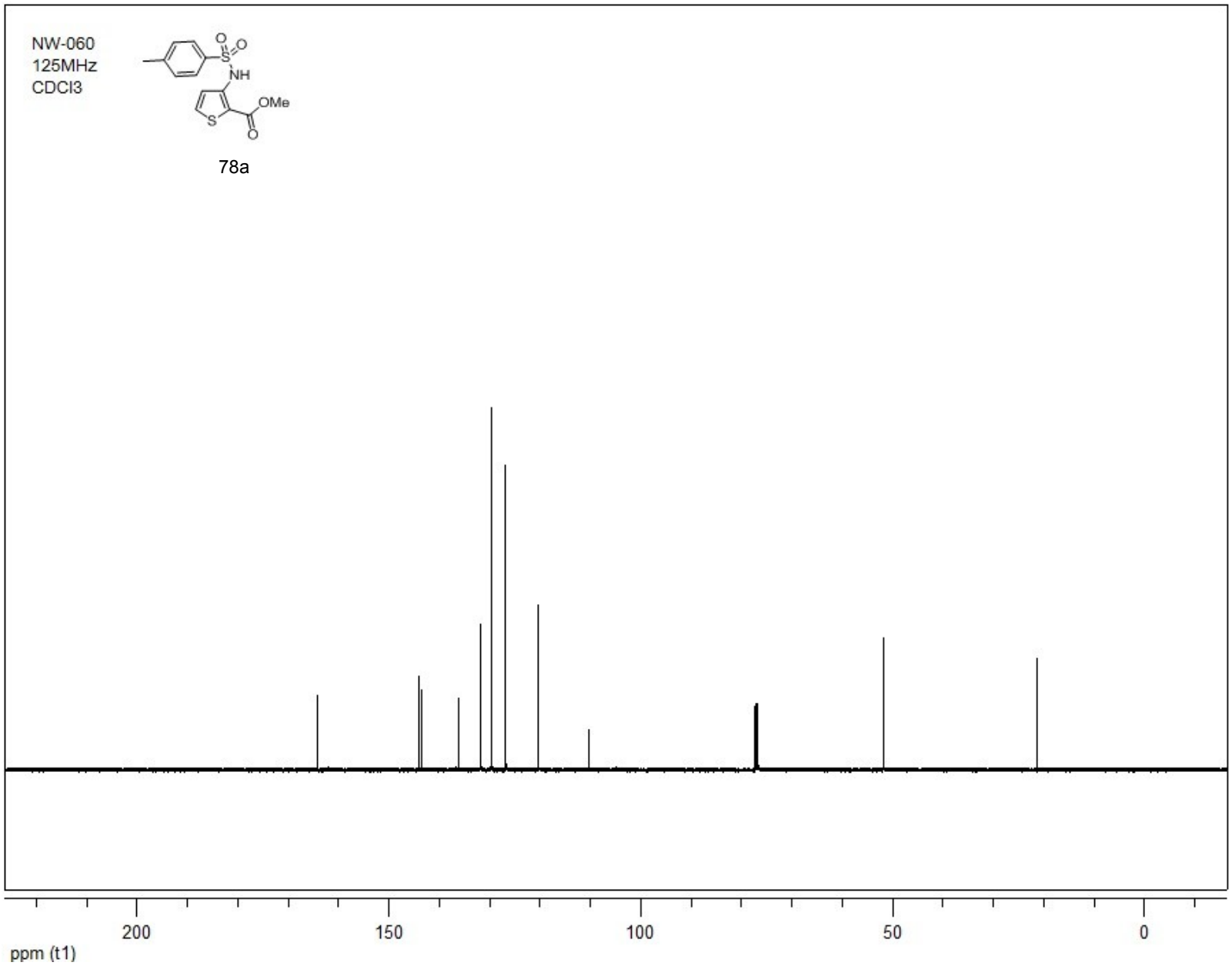
with a variety of Ar and Ar^2 substituents. The acid could also be subjected under palladium catalysis conditions to undergo a decarboxylative cross-coupling to substitute the C2 position with different aryl substituents. Although the resulting yield was low, further optimization studies are required to increase yield of the transformation.

Altering the order of reactions performed on the key intermediate allowed for the synthesis of functionalized 2,3-thienoisoquinolines (7). The carboxylic acid was unmasked through a saponification of the corresponding ester. Decarboxylative cross-coupling was then performed on the acid to form unfunctionalized 2,3-thienoisoquinolines. These intermediates (6) were brominated with NBS resulting in functionalization with a bromine at C5. Furthermore, the intermediates (6), were also functionalized at C5 with a variety of aryl functionalities using C-H activation. The synthesis was further improved by combining both decarboxylative cross-coupling and functionalization through C-H activation into a single set of conditions. For the one-pot transformation, a palladium/ligand combination, base, reaction temperature and time were optimized. Future work involves the determination of the substrate scope of the transformation.

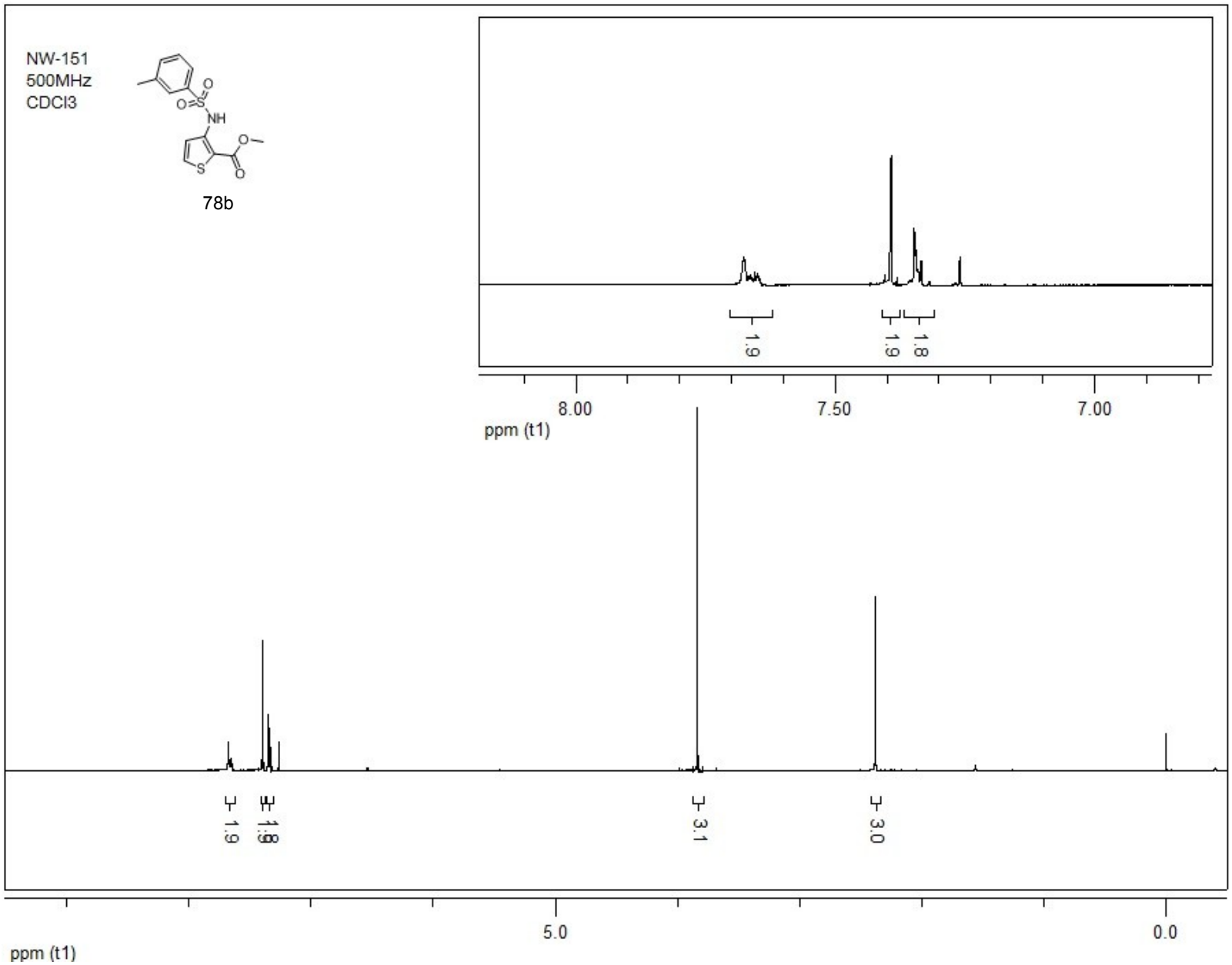
Presented are two complimentary routes to access different functionalized thienoisoquinoline systems, which have been shown to be biologically active against breast cancer. The syntheses of both isomers employ modern alternatives to classical cross-coupling reactions, C-H activation and decarboxylative cross-coupling. This modular system allows for the generation a library of these important compounds while minimizing environmental impact

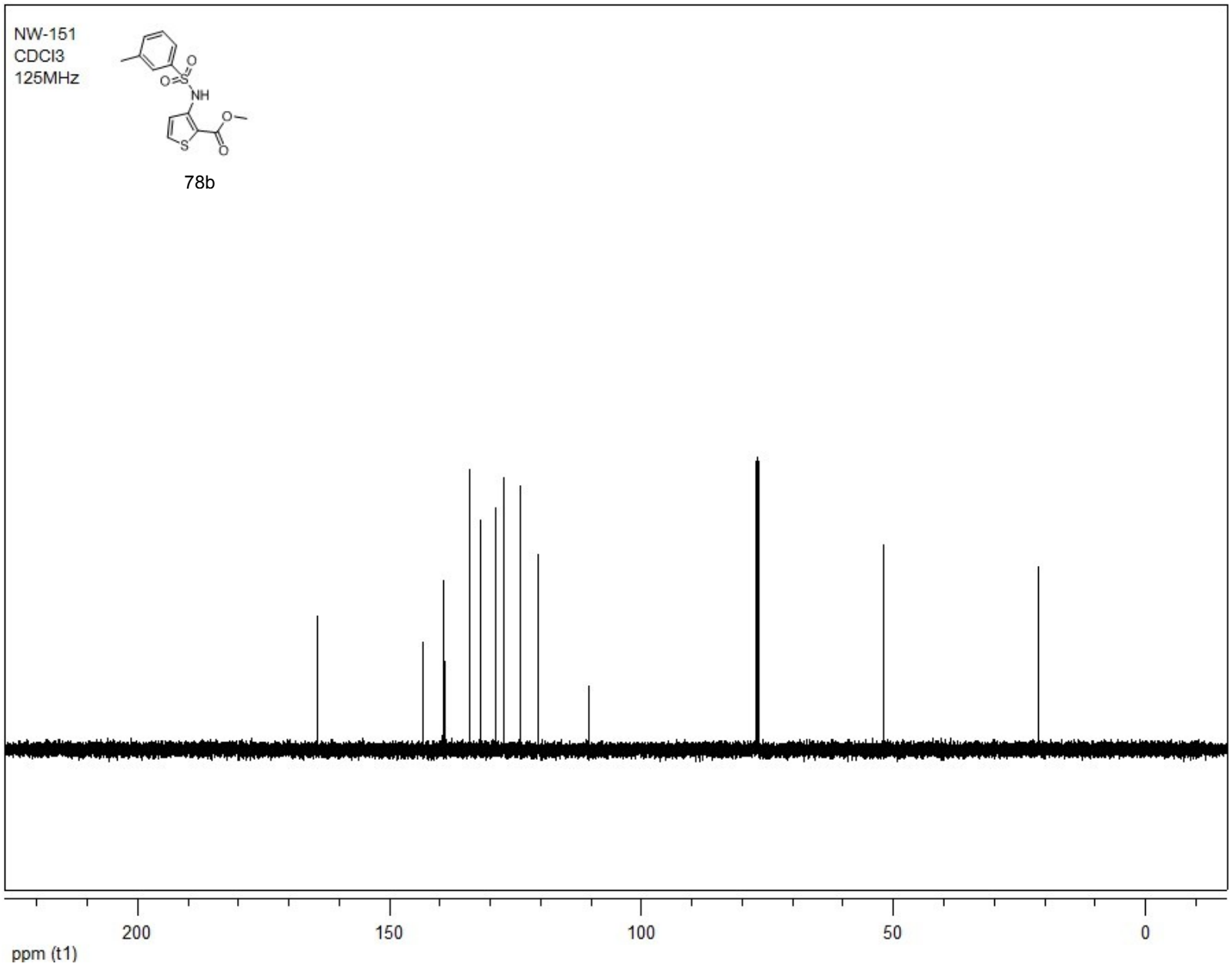
APPENDIX


NW-060
500MHz
CDCl3
NH
OMe
78a
2.0
2.0
2.3
7.70
7.60
7.50
7.40
7.30
7.20
ppm (t1)
2.0
2.3
2.0
3.2
3.1
5.0
0.0
ppm (t1)

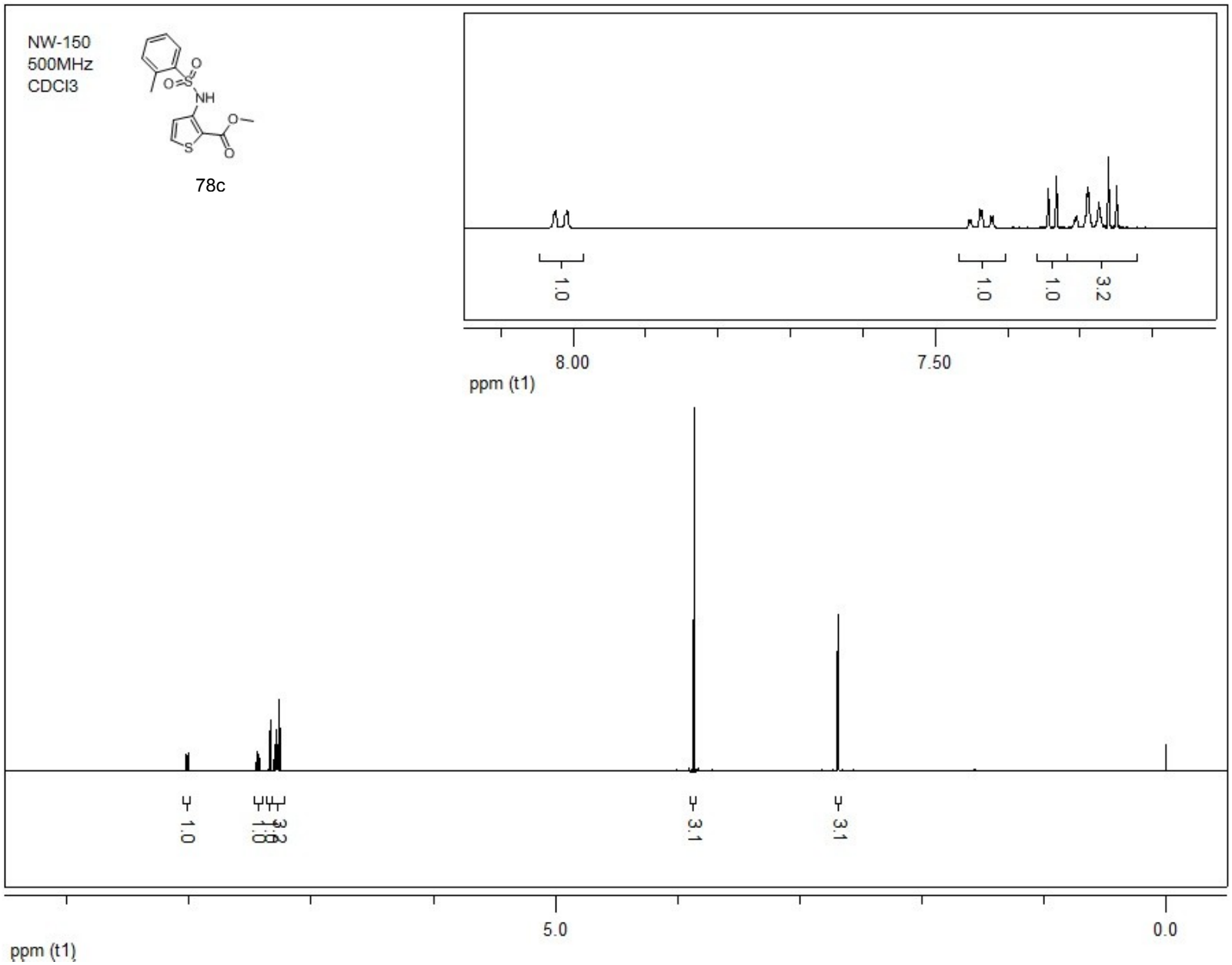


78a


NW-151
500MHz
CDCl3
78b
1.9
1.9
1.8
8.00
7.50
7.00
ppm (t1)
1.9
1.8
3.1
3.0
5.0
0.0
ppm (t1)



78b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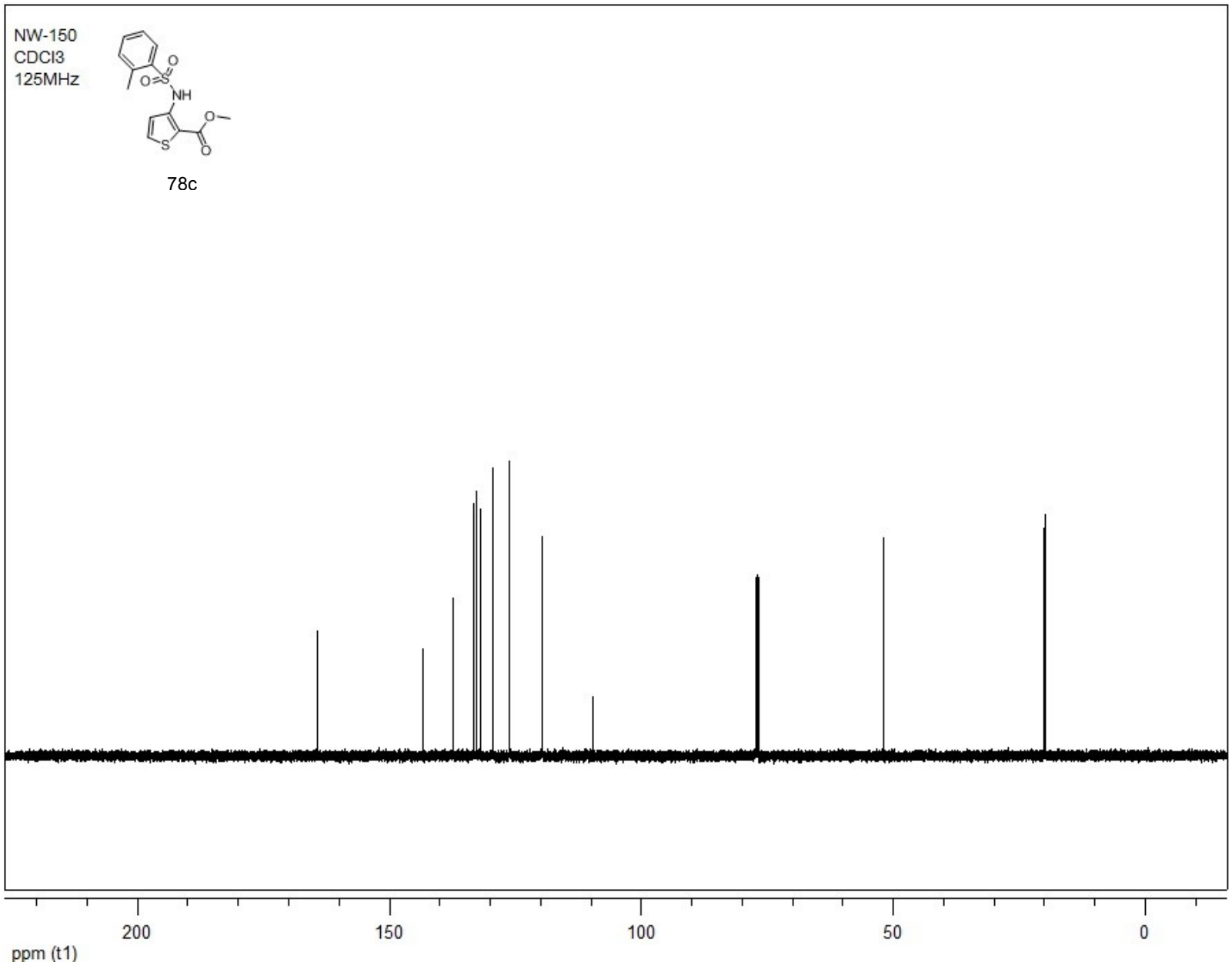
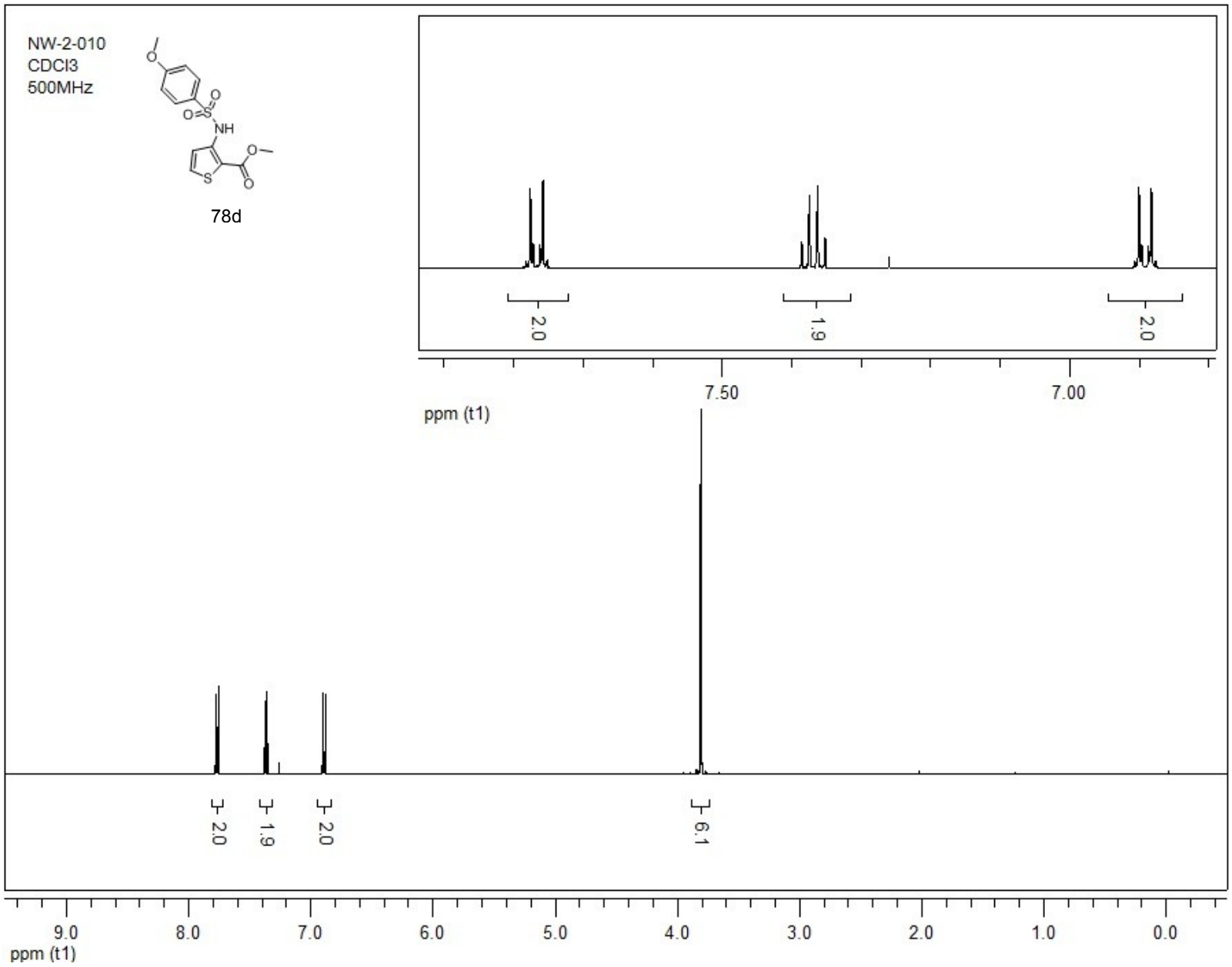
500MHz
CDCl3
NH
O
O
O
O
S
S
O
78c
1.0
1.0
1.0
3.2
8.00
7.50
ppm (t1)
1.0
3.2
1.8
1.0
3.1
3.1
5.0
0.0
ppm (t1)


NW-150
CDCl3
125MHz
O
O
S
NH
O
O
S
O
78c
200
150
100
50
0
ppm (t1)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78d
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1.9
2.0
7.50
7.00
ppm (t1)
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1.9
2.0
6.1
9.0
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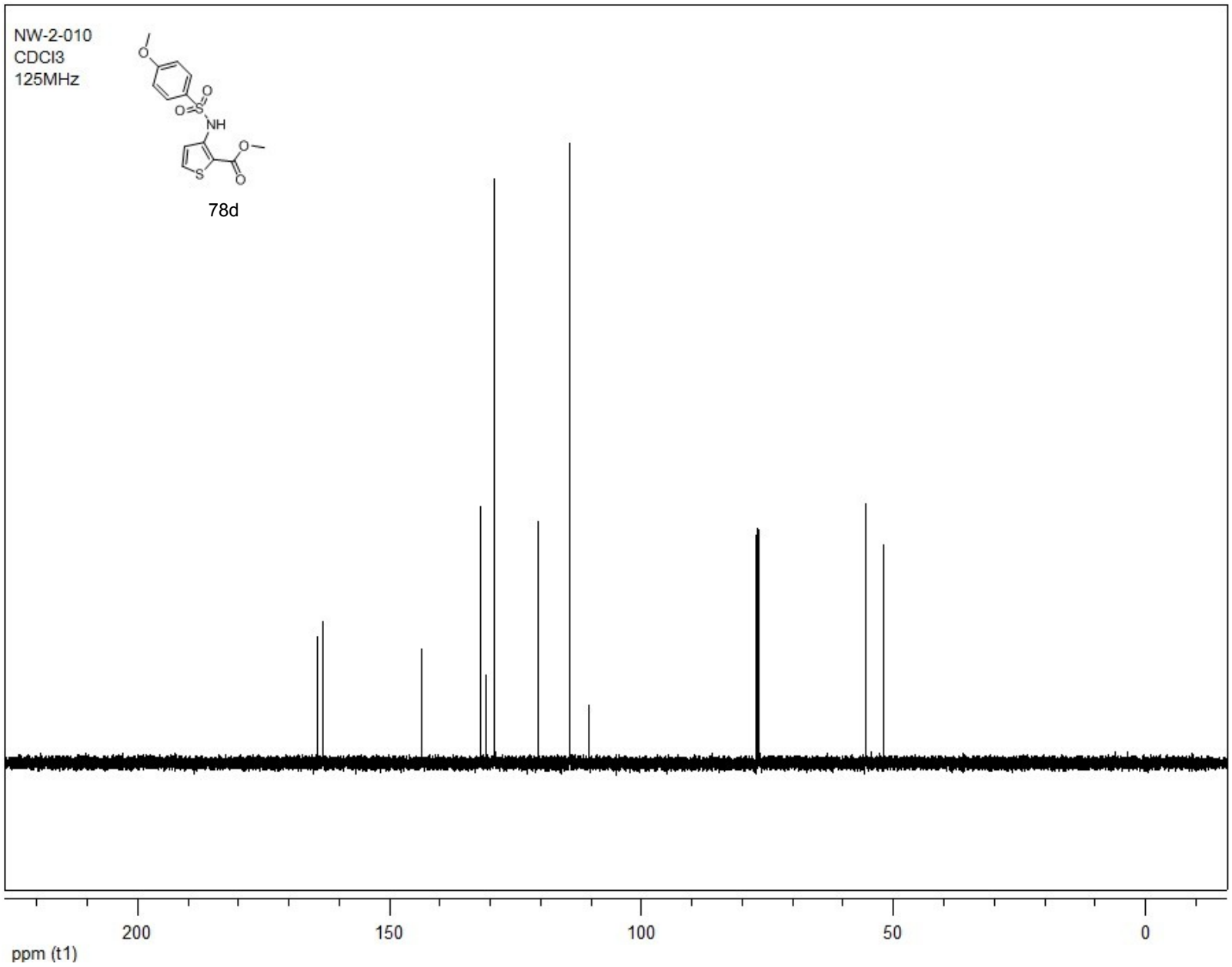
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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125MHz
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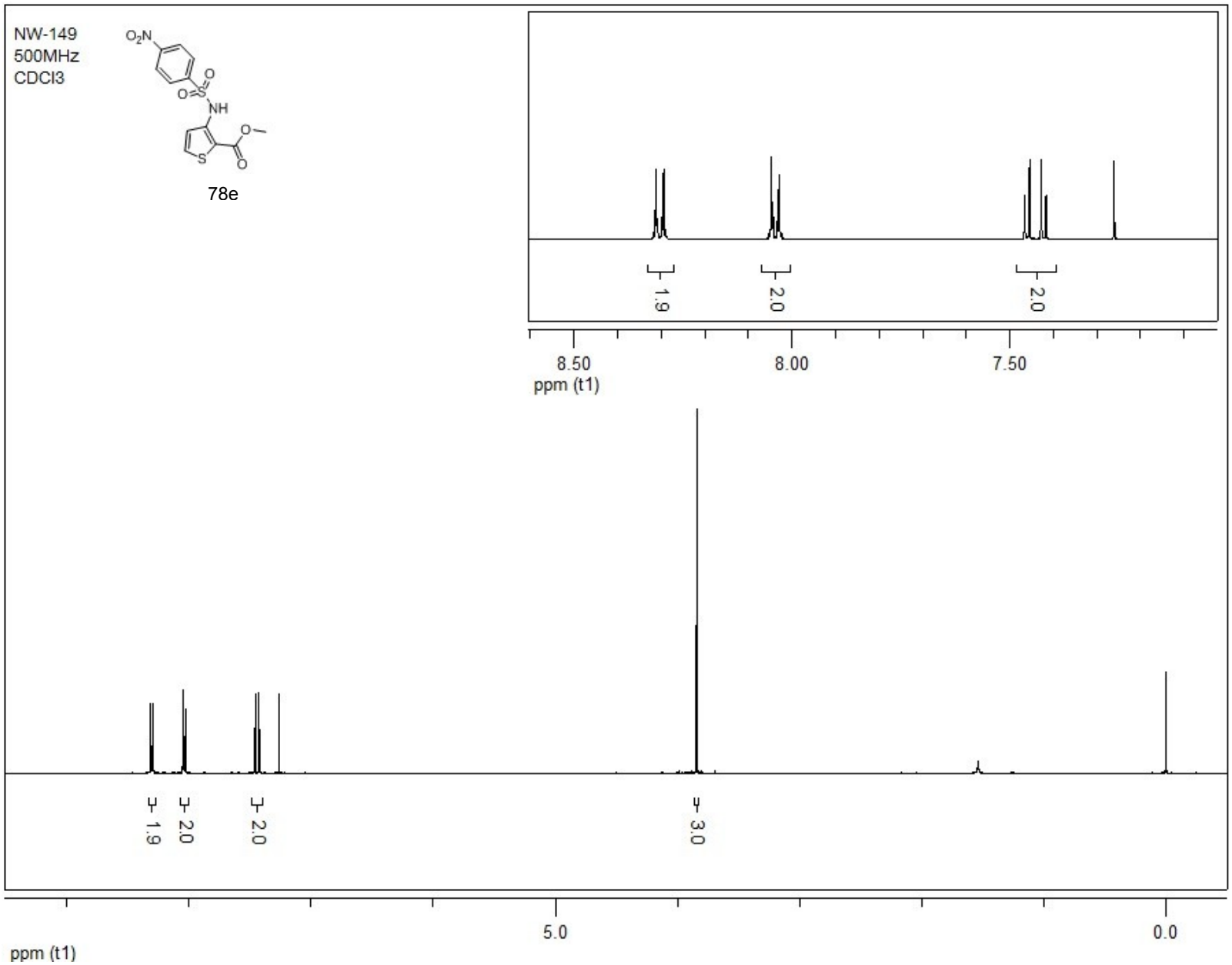
O
S
O
NH
O
O
S
O
78d
200
150
100
50
0
ppm (t1)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ppm (t1)
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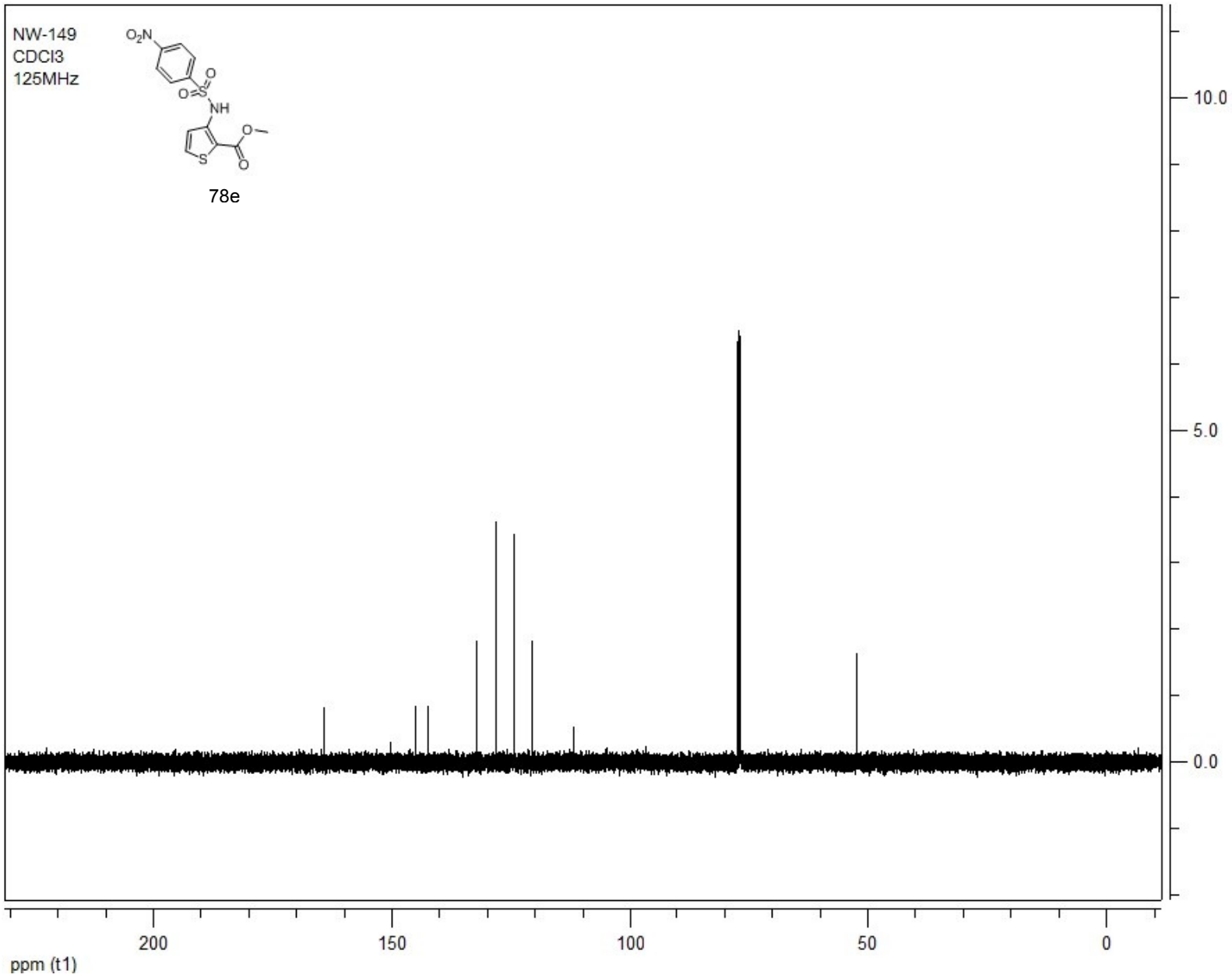
2.0
2.0
3.0
5.0
0.0
ppm (t1)

X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O_2N
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S
NH
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S
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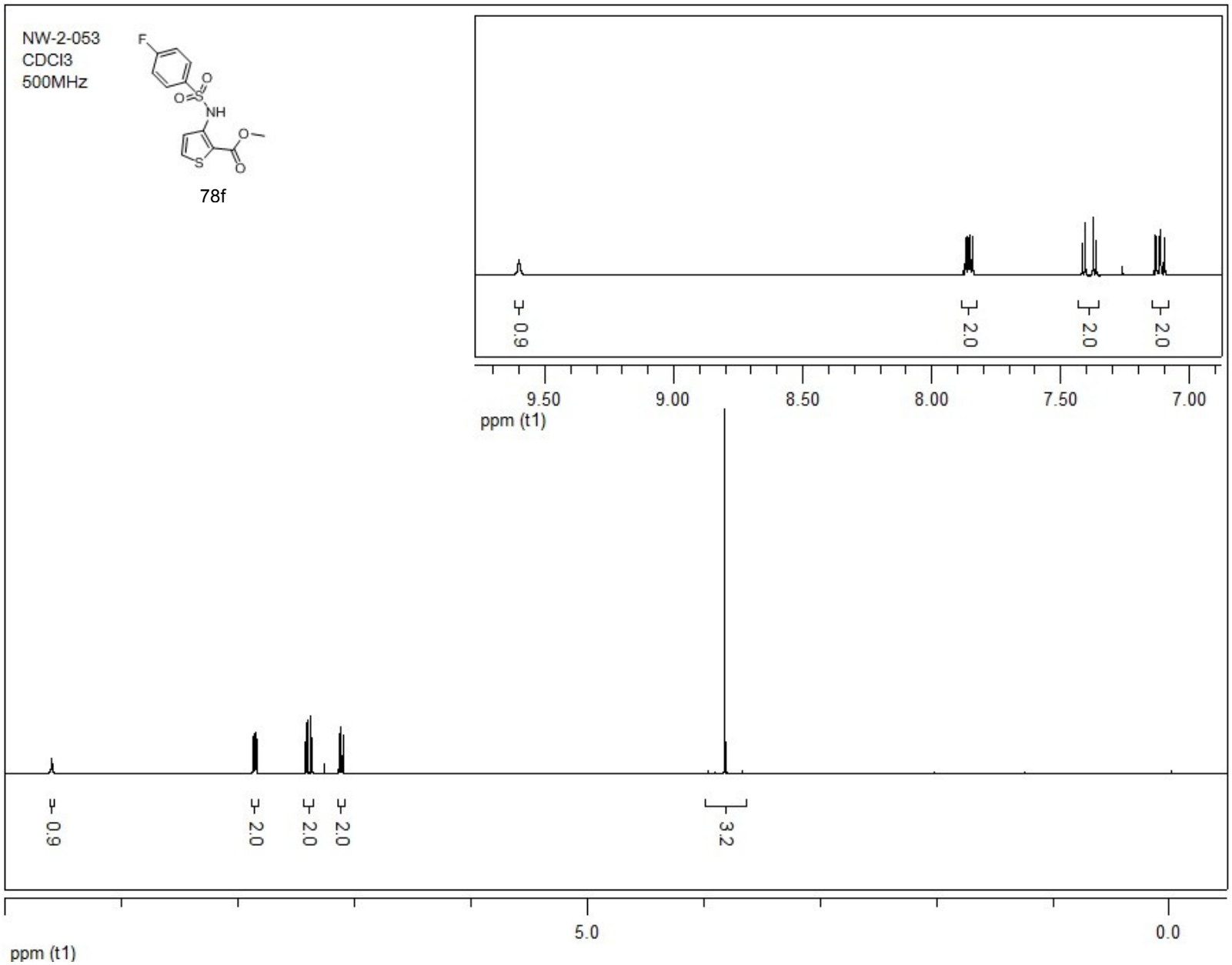
200
150
100
50
0
ppm (t1)

78e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CDCl3
500MHz
F
O
O
S
NH
O
O
S
O
78f
0.9
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2.0
2.0
9.50
9.00
8.50
8.00
7.50
7.00
ppm (t1)
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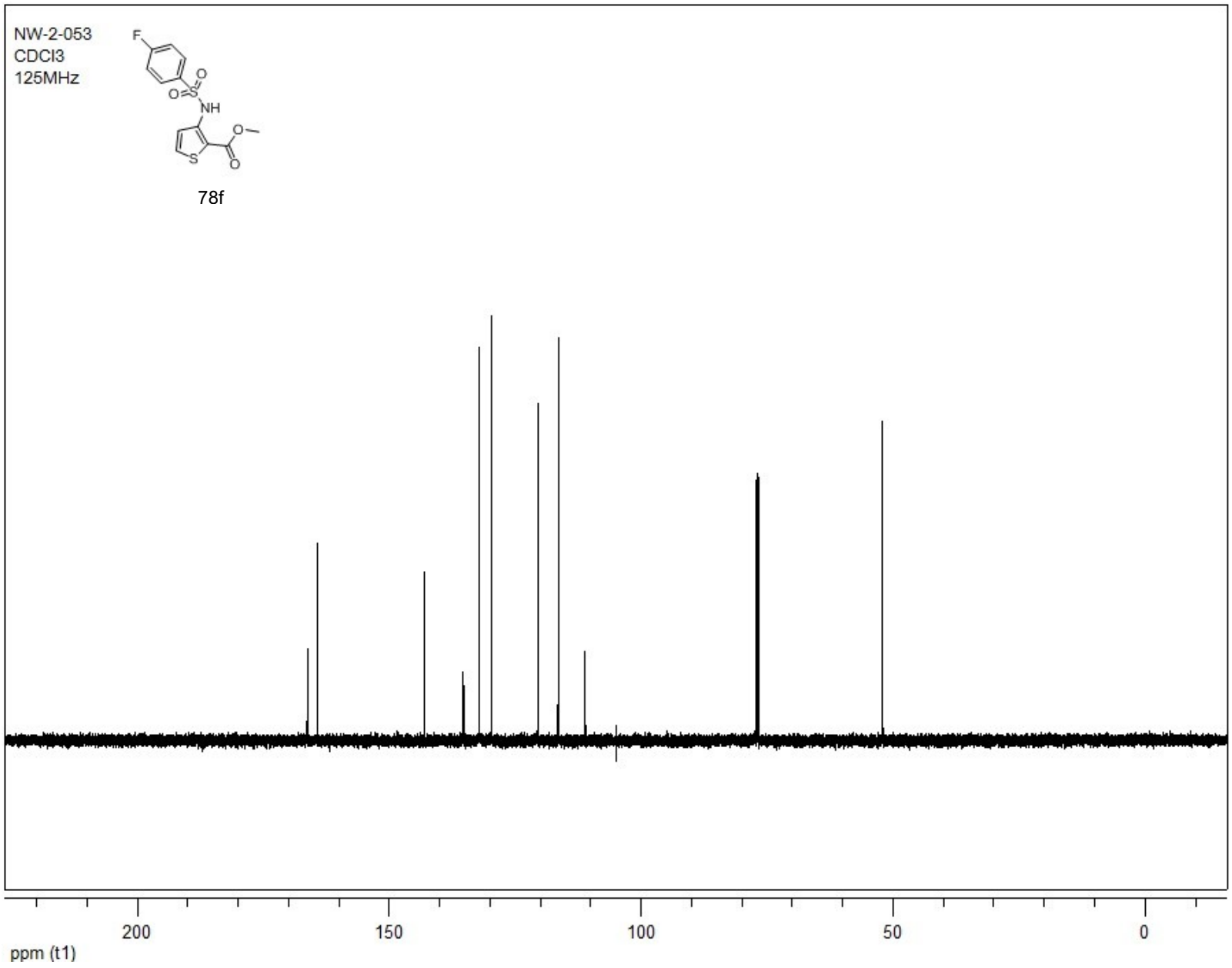
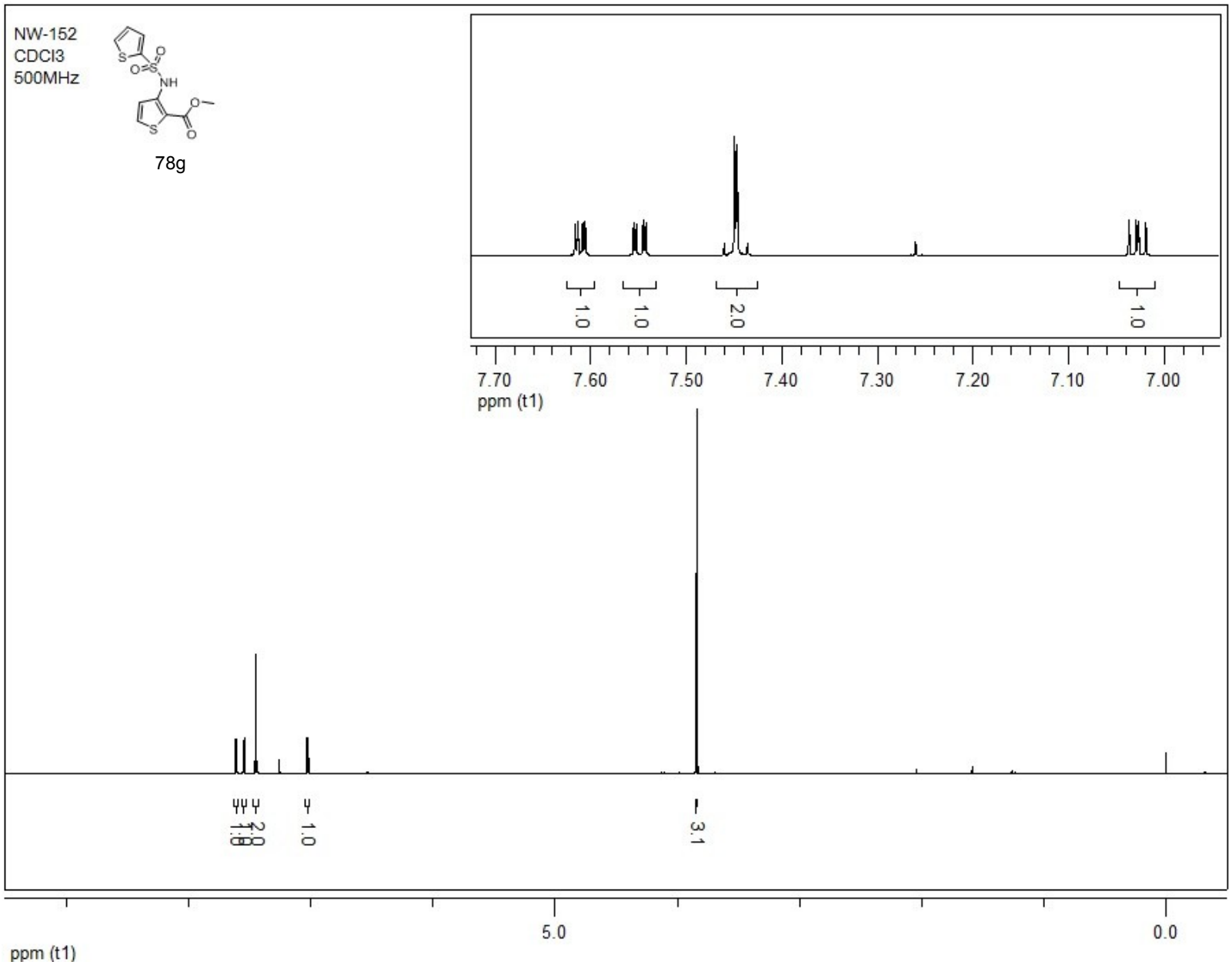
2.0
2.0
2.0
3.2
5.0
0.0
ppm (t1)



78f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1.0
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7.10
7.00
ppm (t1)
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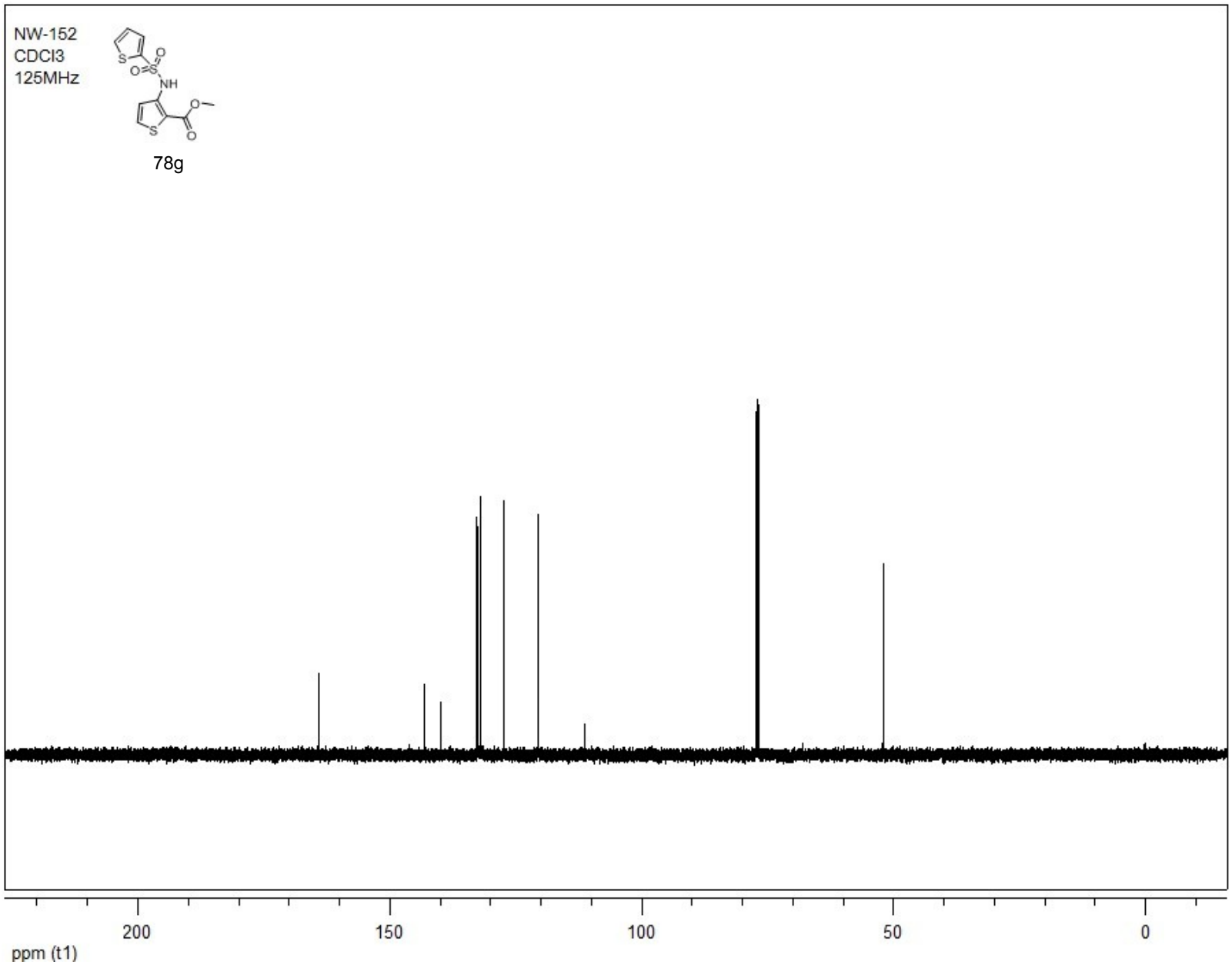
3.1
5.0
0.0
ppm (t1)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78g
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50
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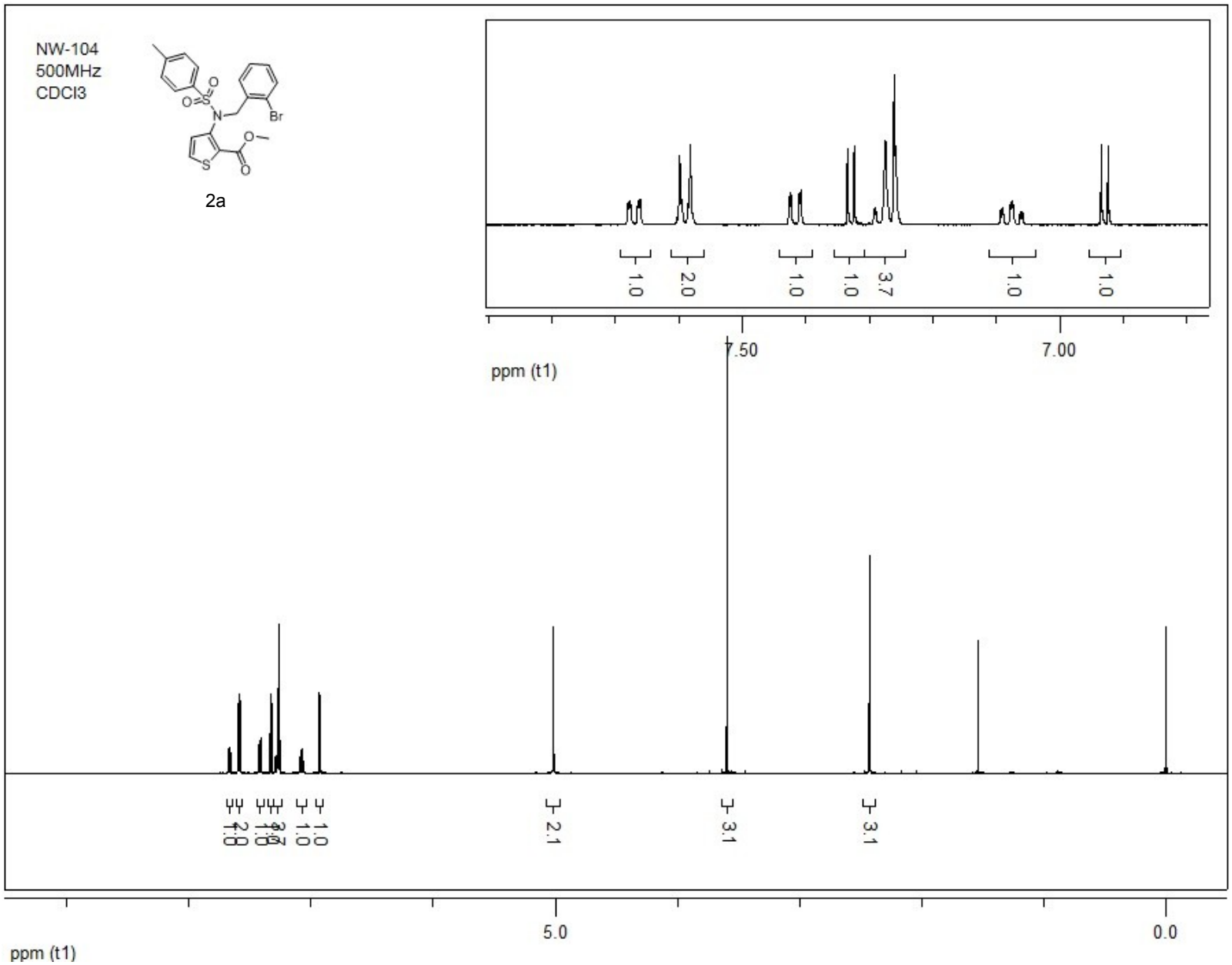
ppm (t1)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2.1
3.1
3.1
5.0
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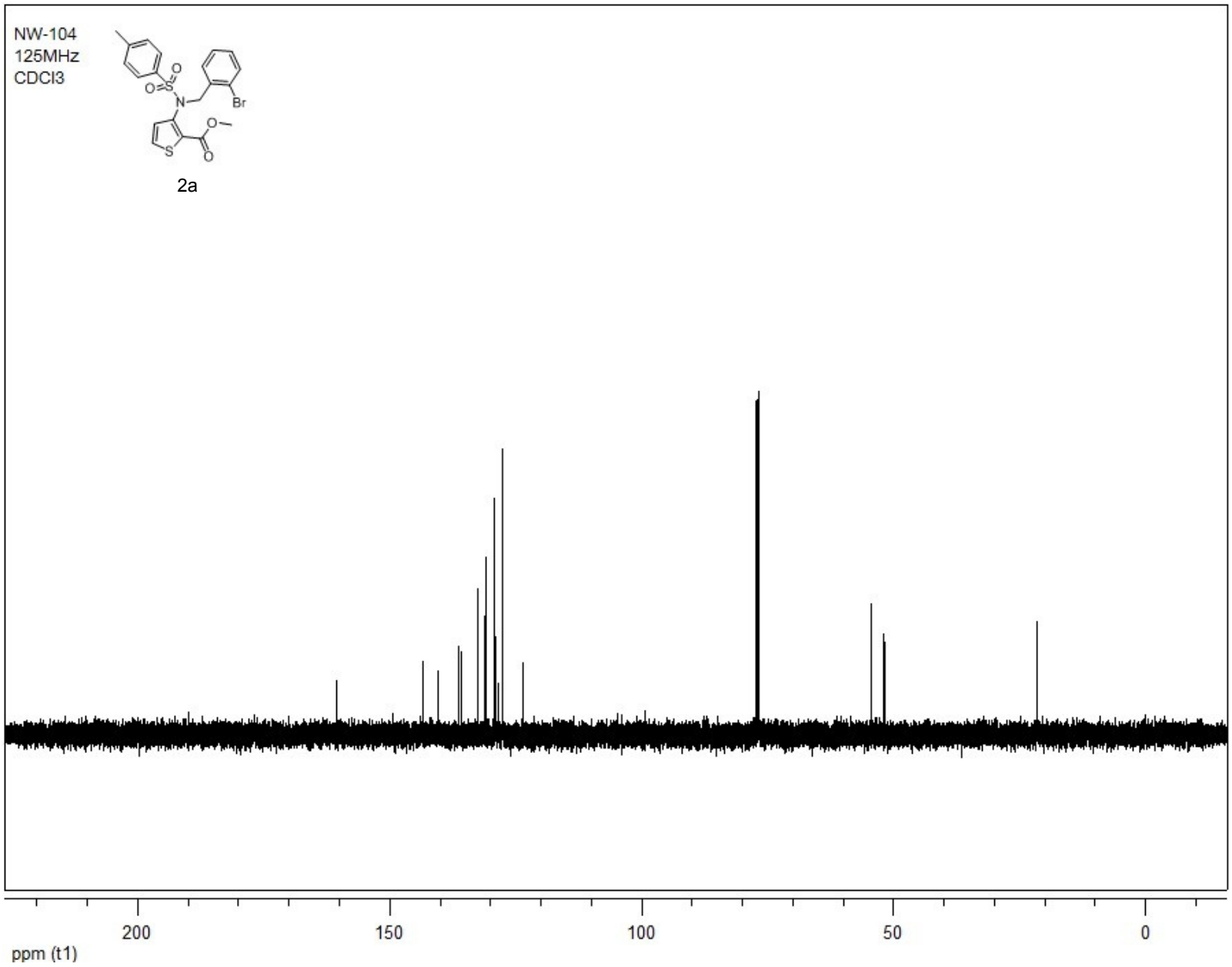
ppm (t1)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Br
2a
200
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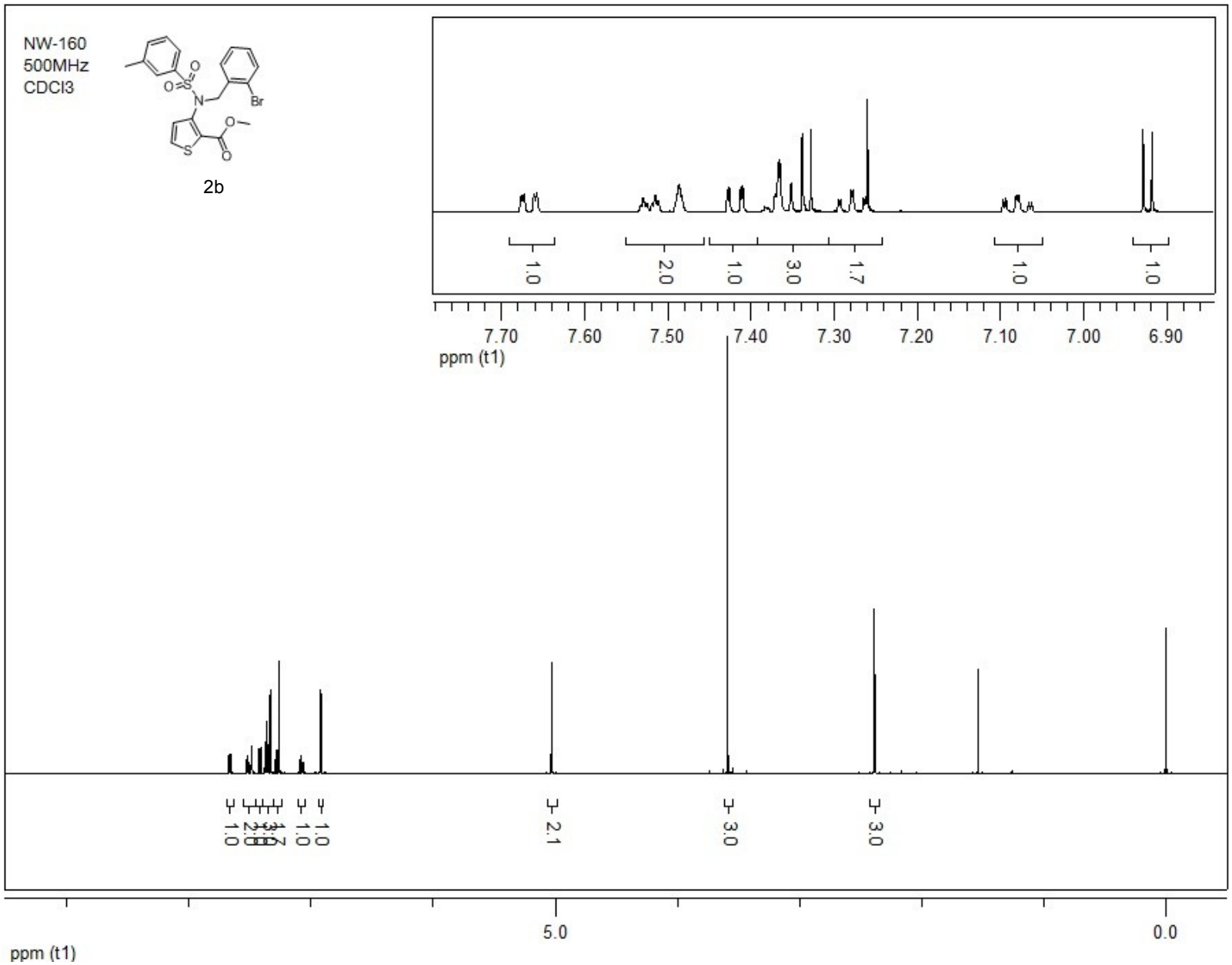
100
50
0
ppm (t1)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2.0
1.0
3.0
1.7
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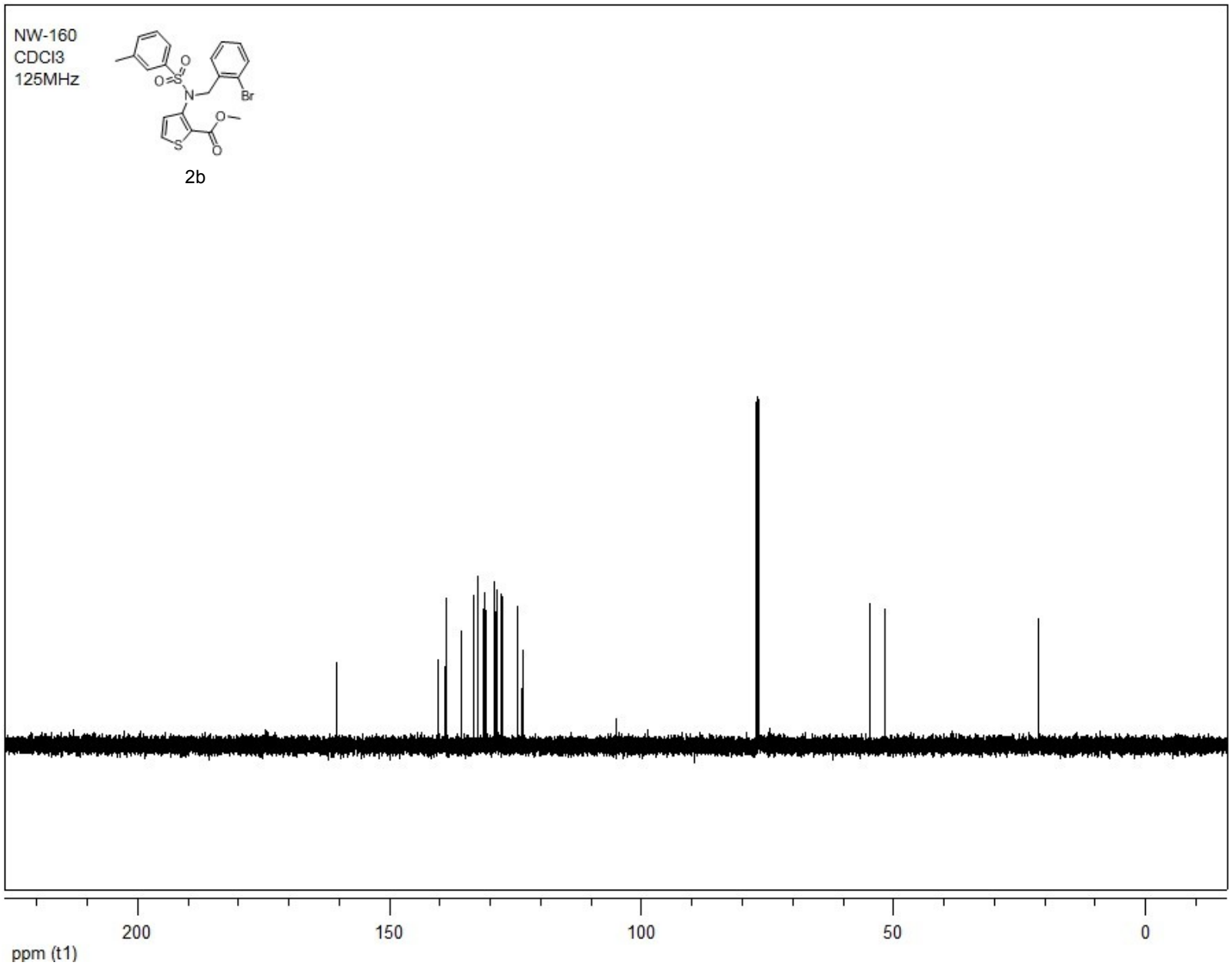
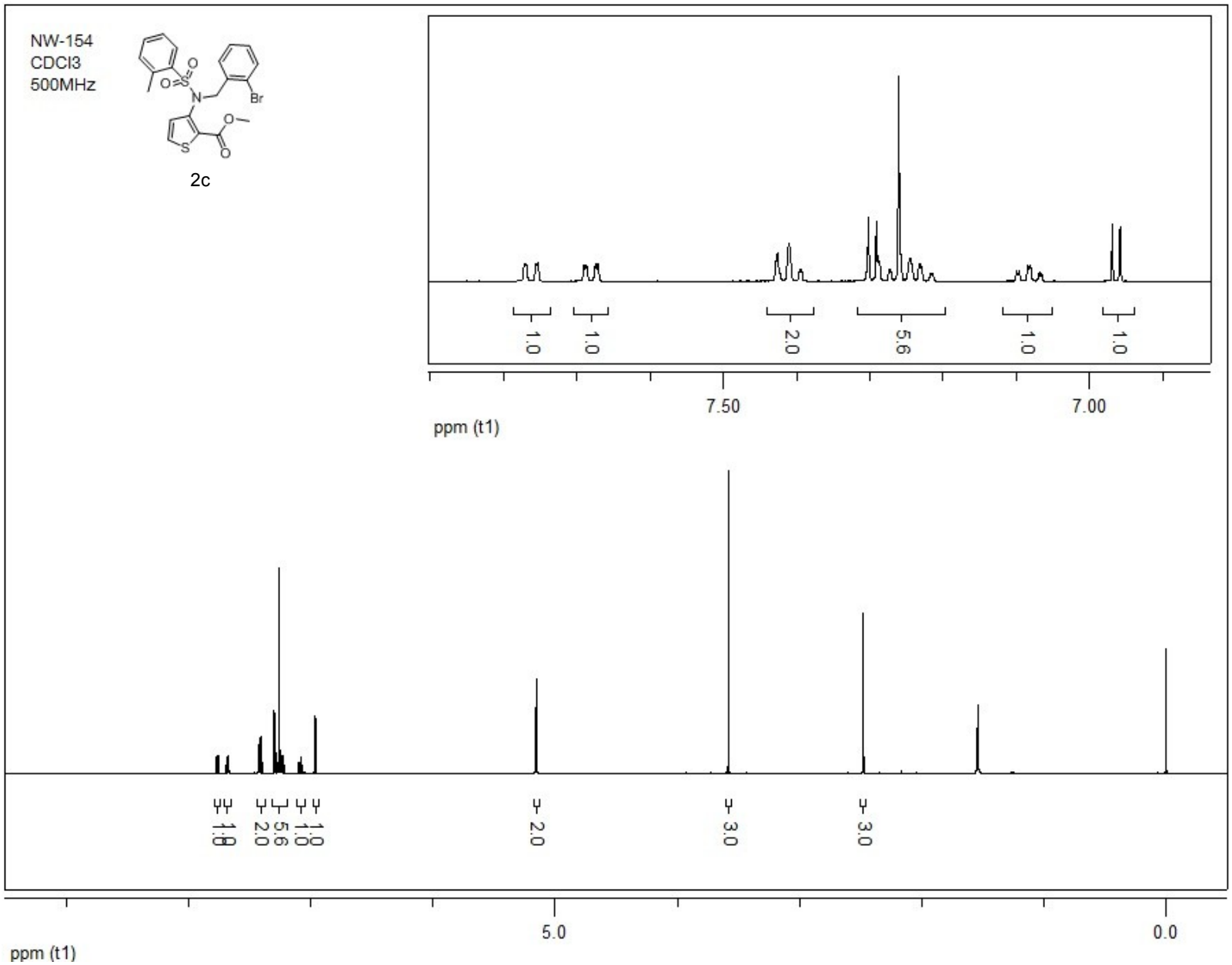
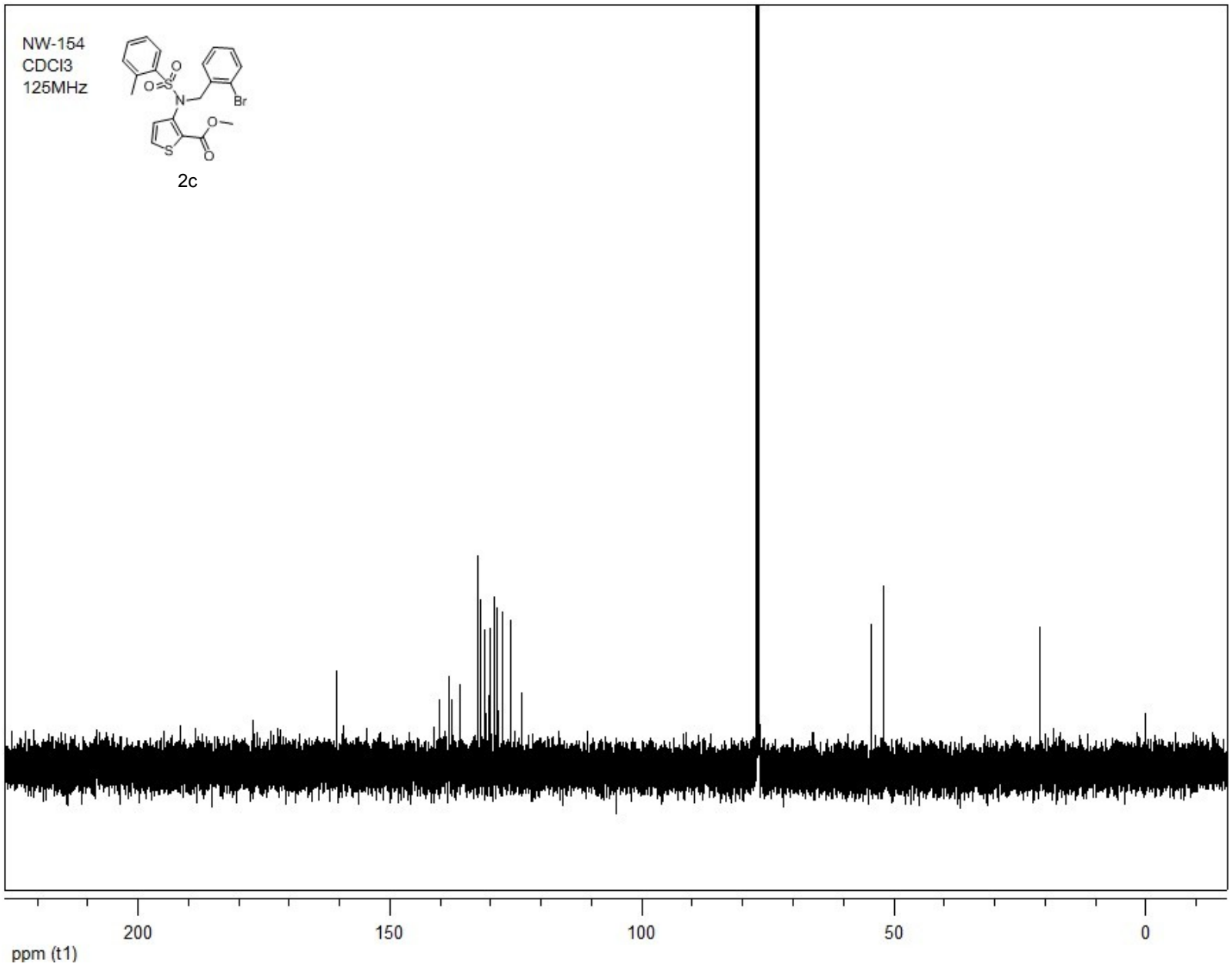
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
ppm (t1)
1.0
1.0
2.1
3.0
3.0
5.0
0.0
ppm (t1)



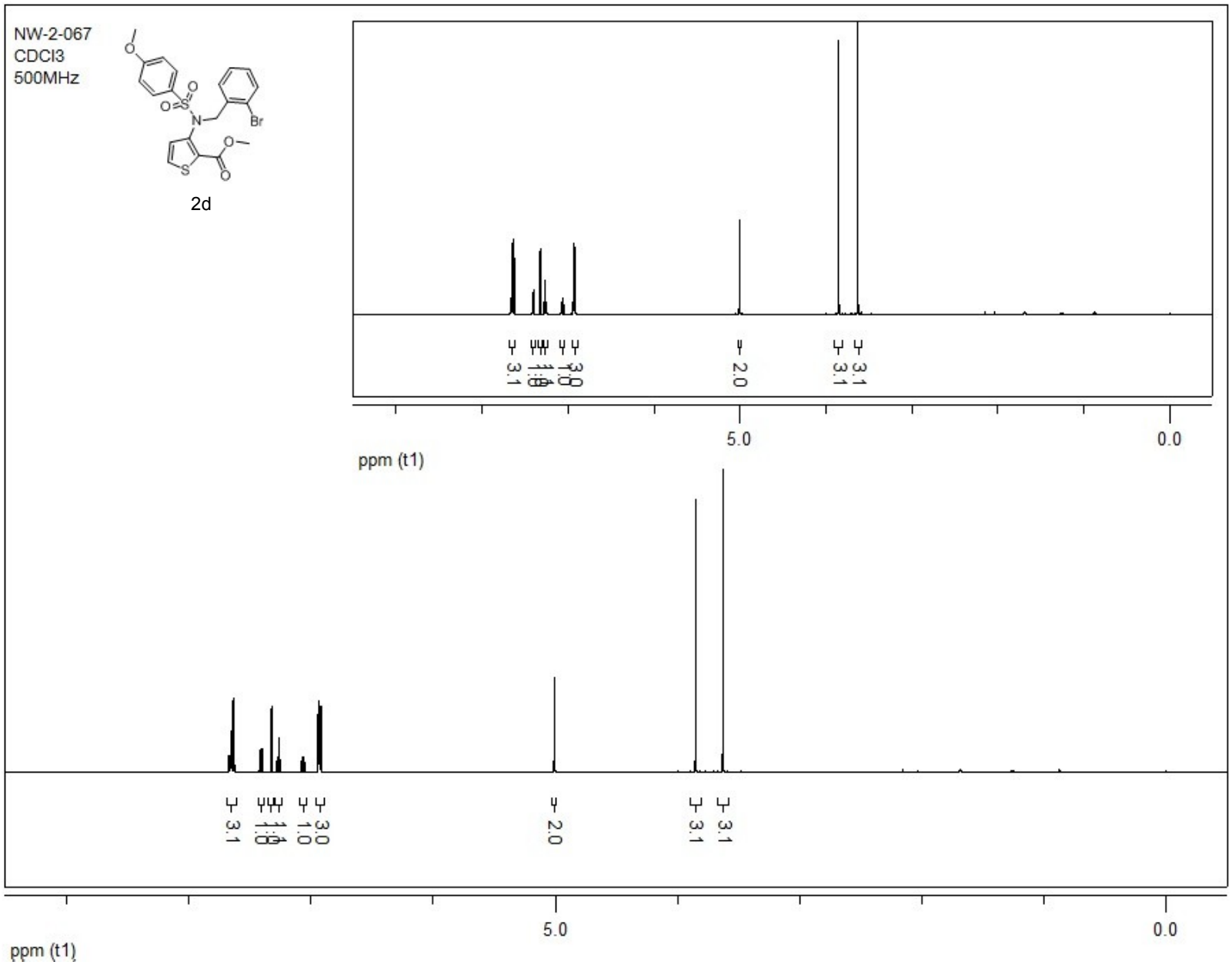
2b

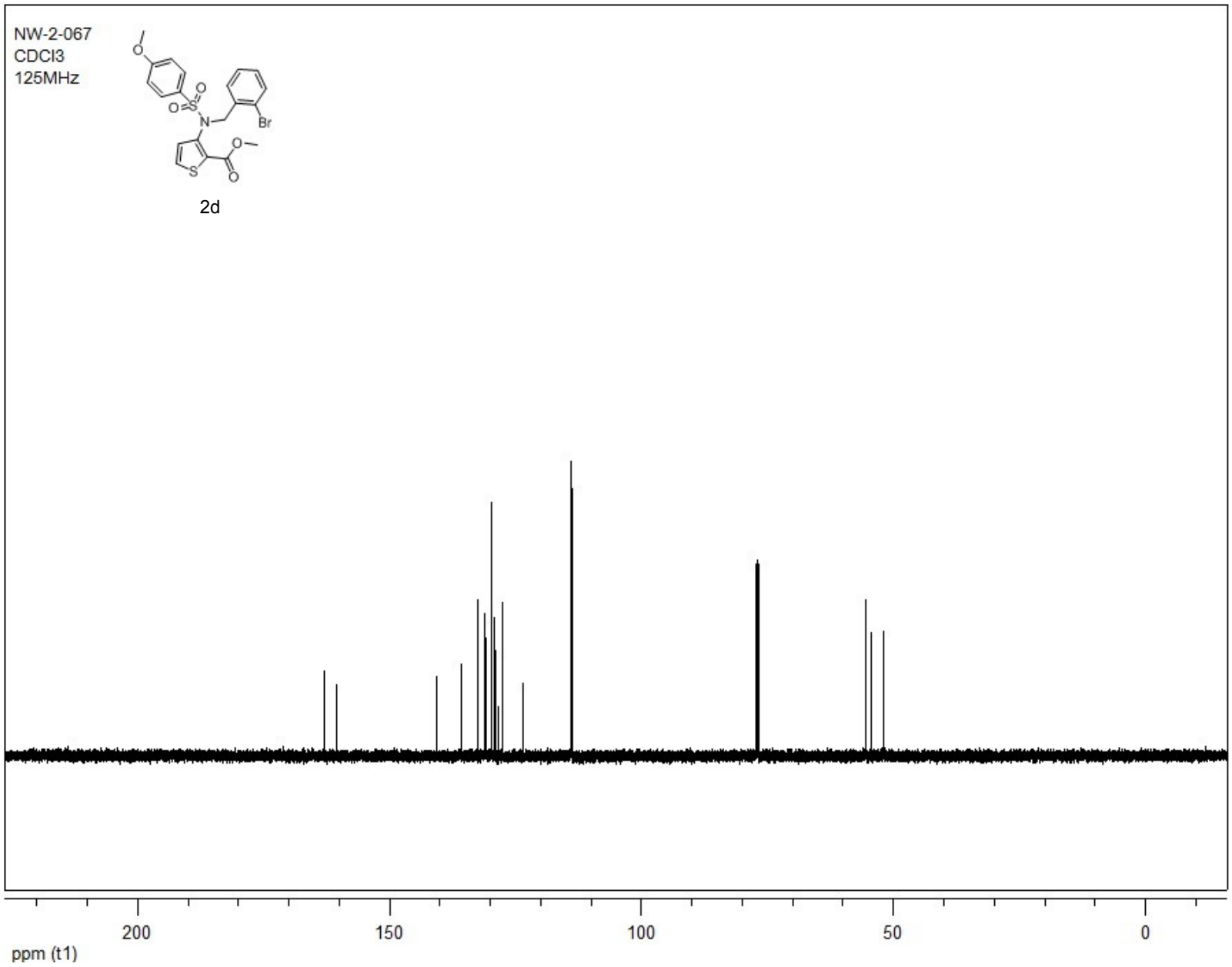

NW-154
CDCl3
500MHz
Br
O
S
N
O
O
O
S
O
2c
1.0
1.0
2.0
5.6
1.0
1.0
7.50
7.00
ppm (t1)
1.0
2.0
5.6
1.0
2.0
3.0
3.0
5.0
0.0
ppm (t1)

XX

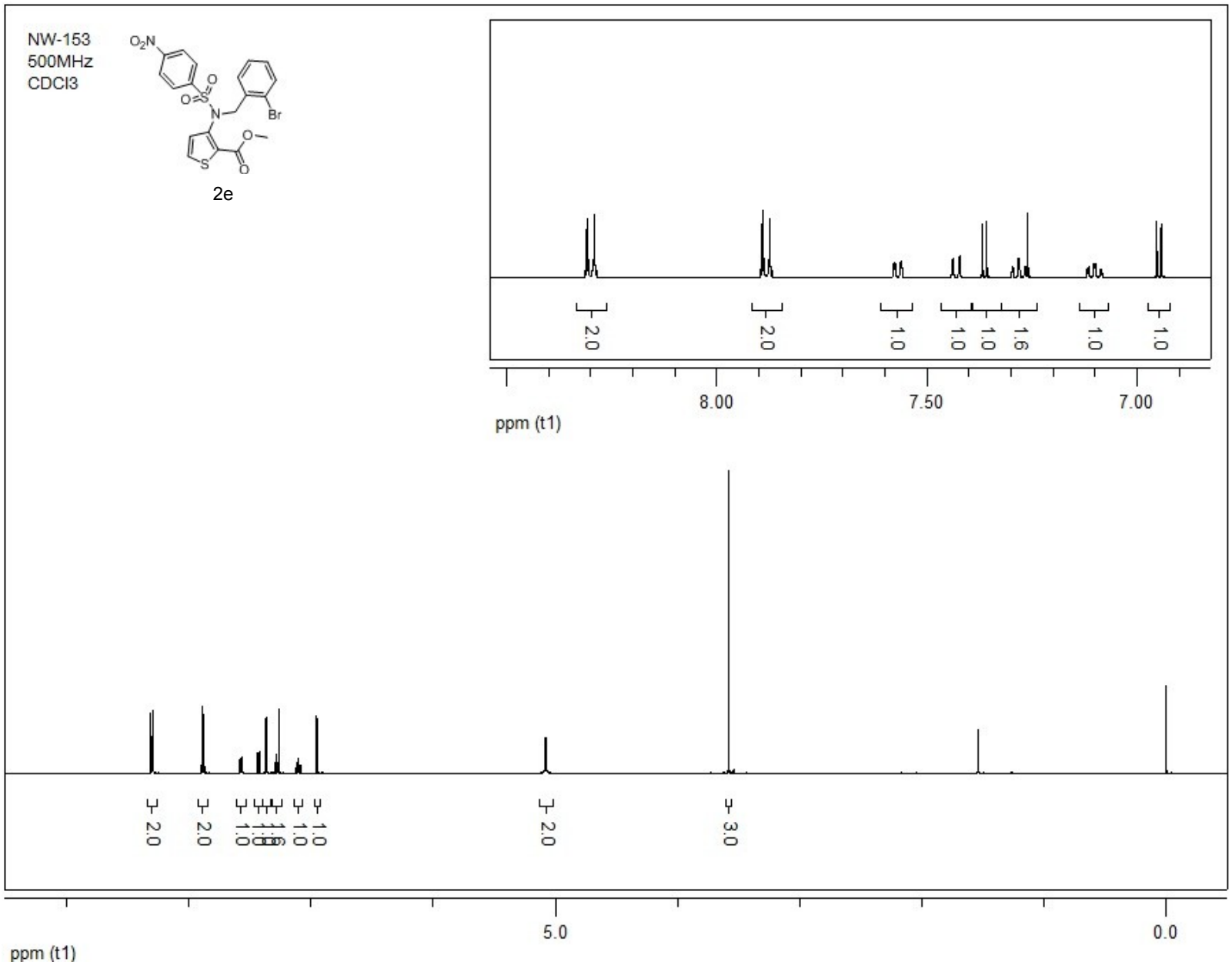


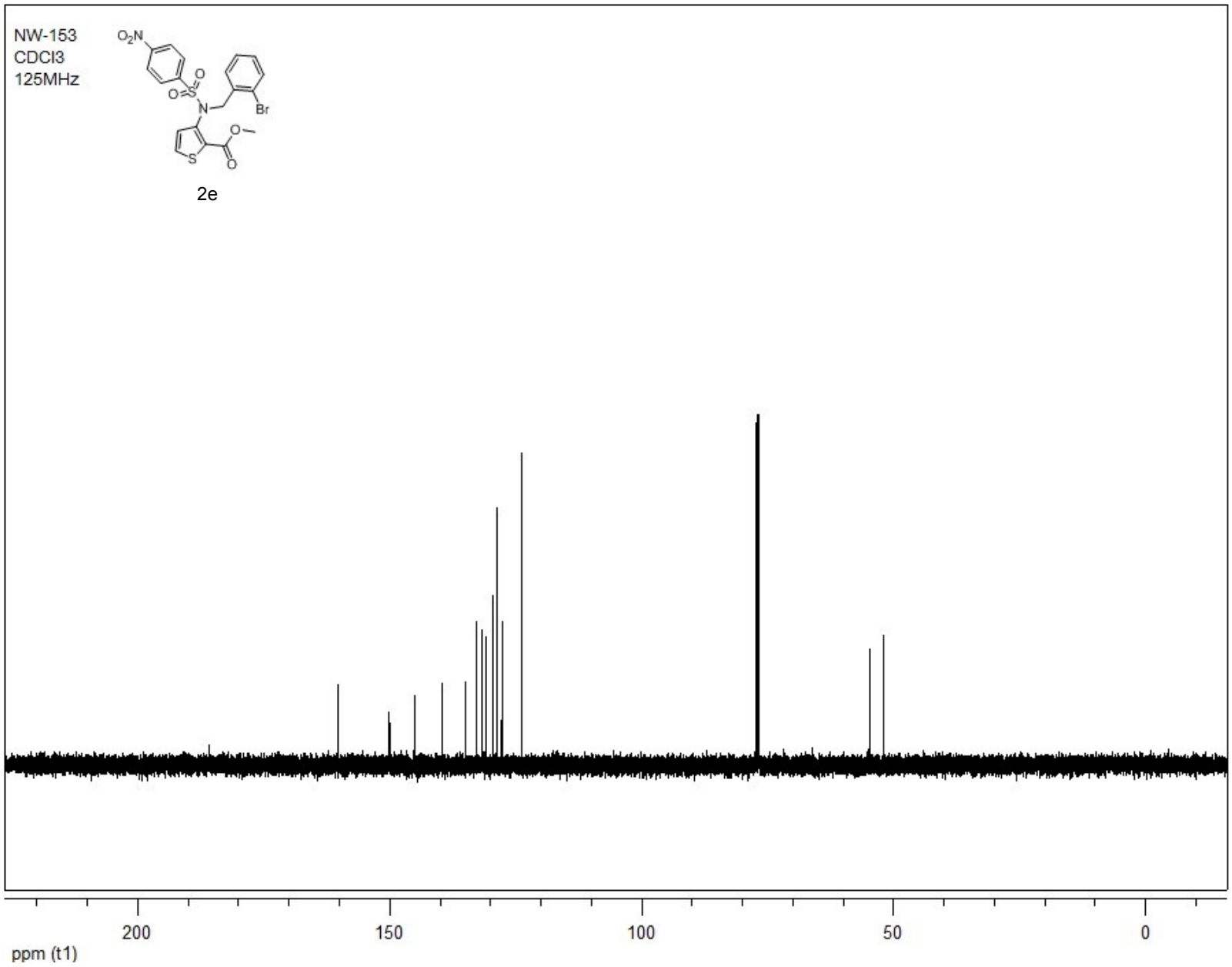
2c


NW-2-067
CDCl3
500MHz
2d
3.1
3.0
1.0
2.0
3.1
3.1
5.0
0.0
ppm (t1)

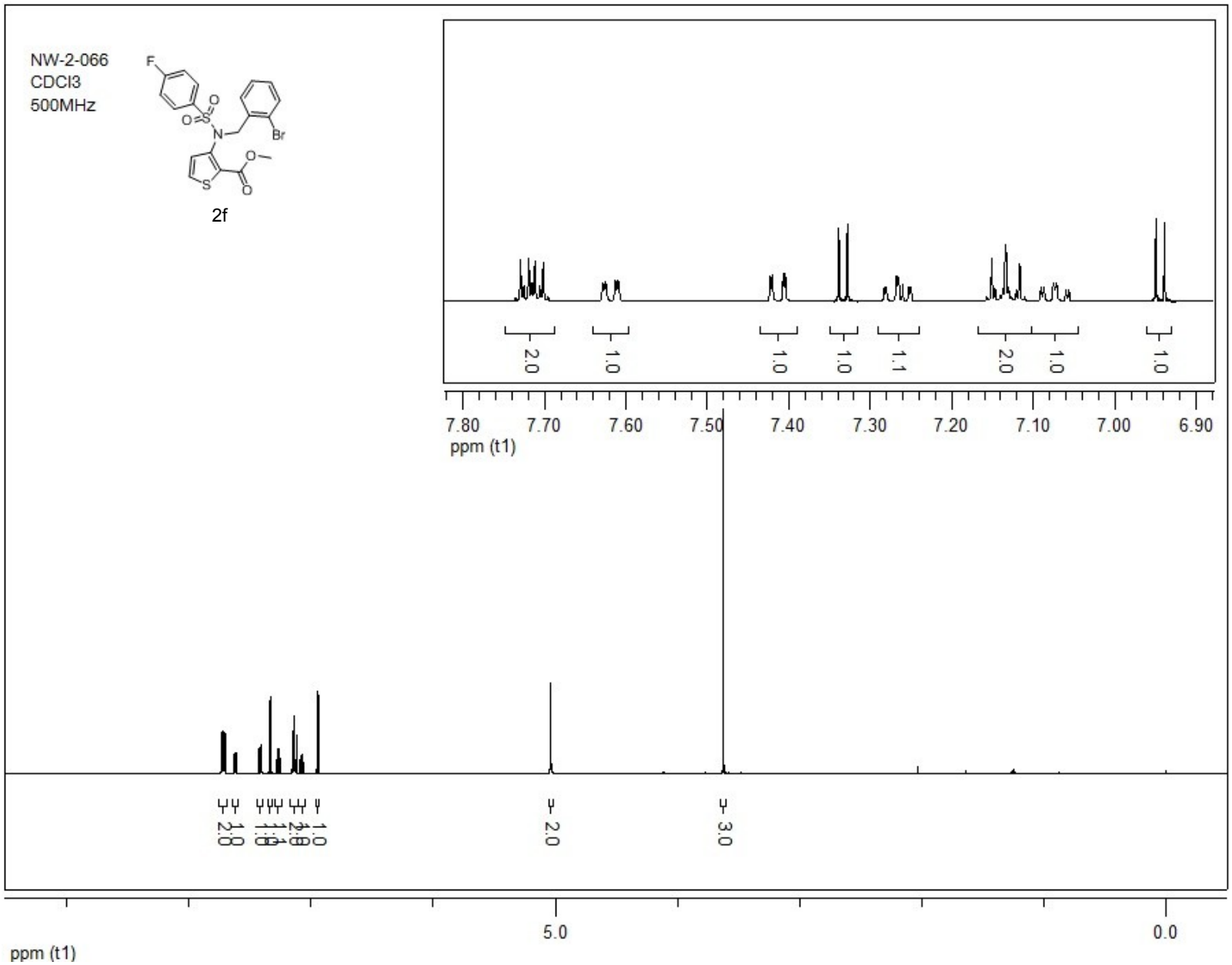


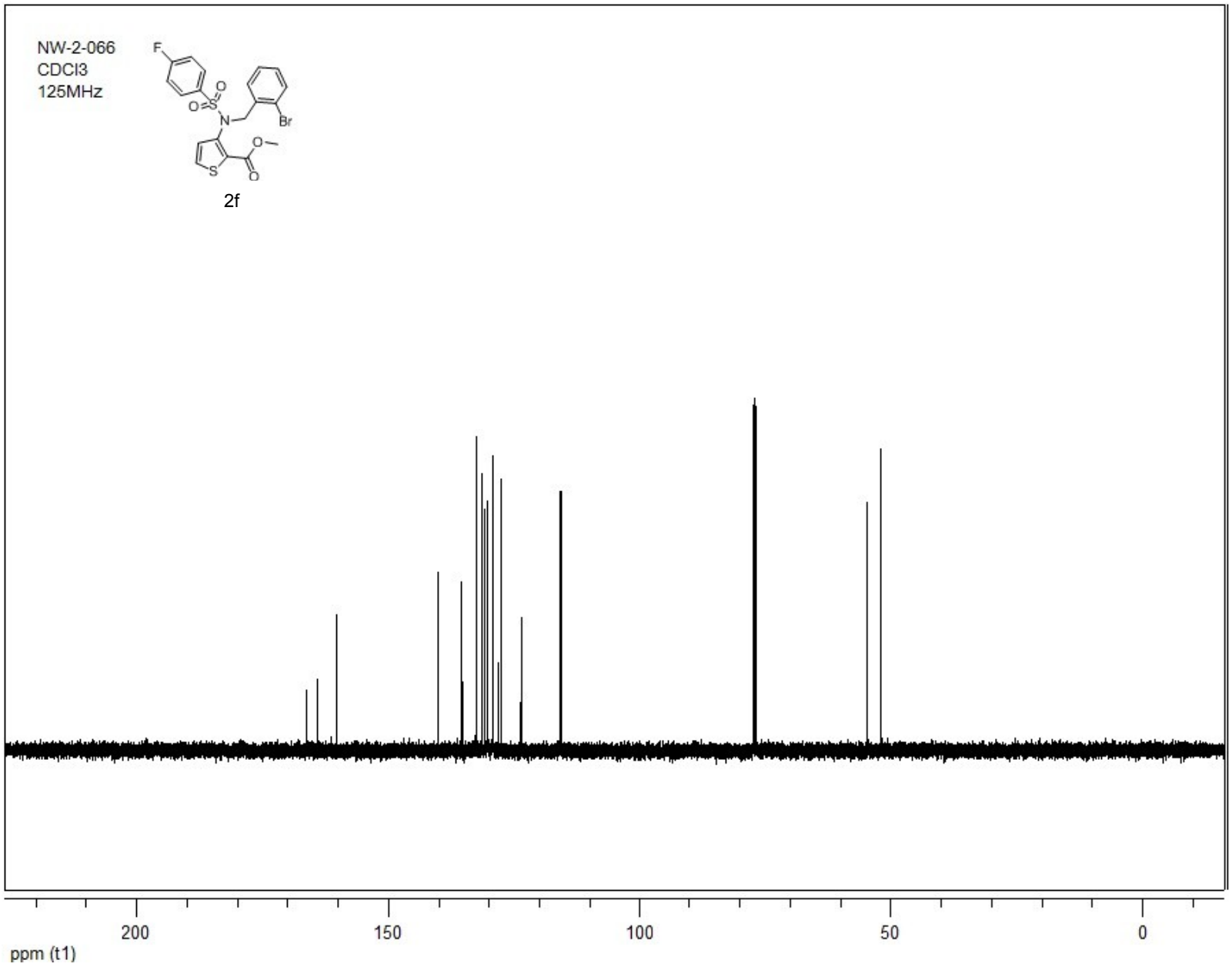
2d

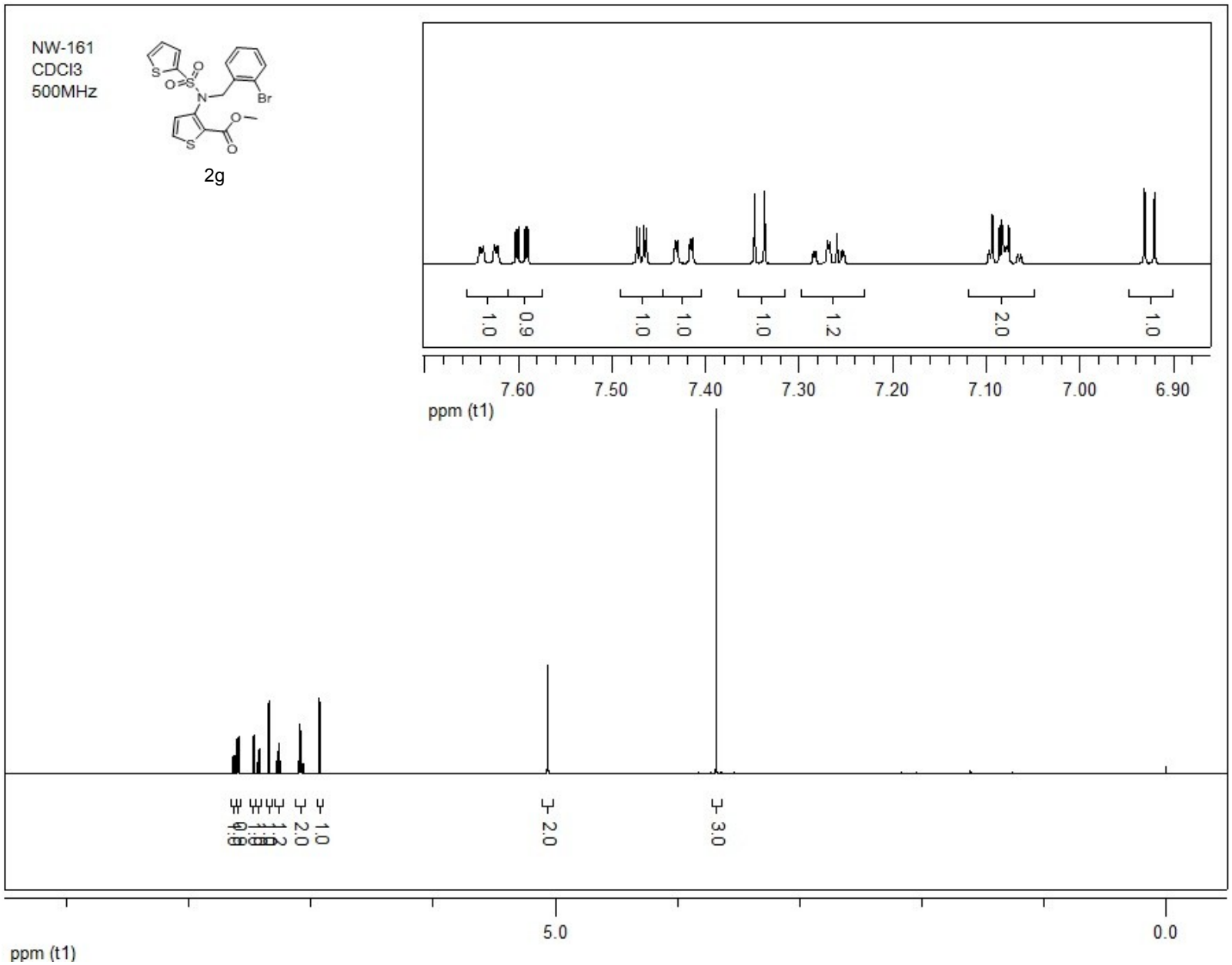

NW-153
500MHz
CDCl3
2e
8.00
7.50
7.00
ppm (t1)
5.0
0.0
ppm (t1)

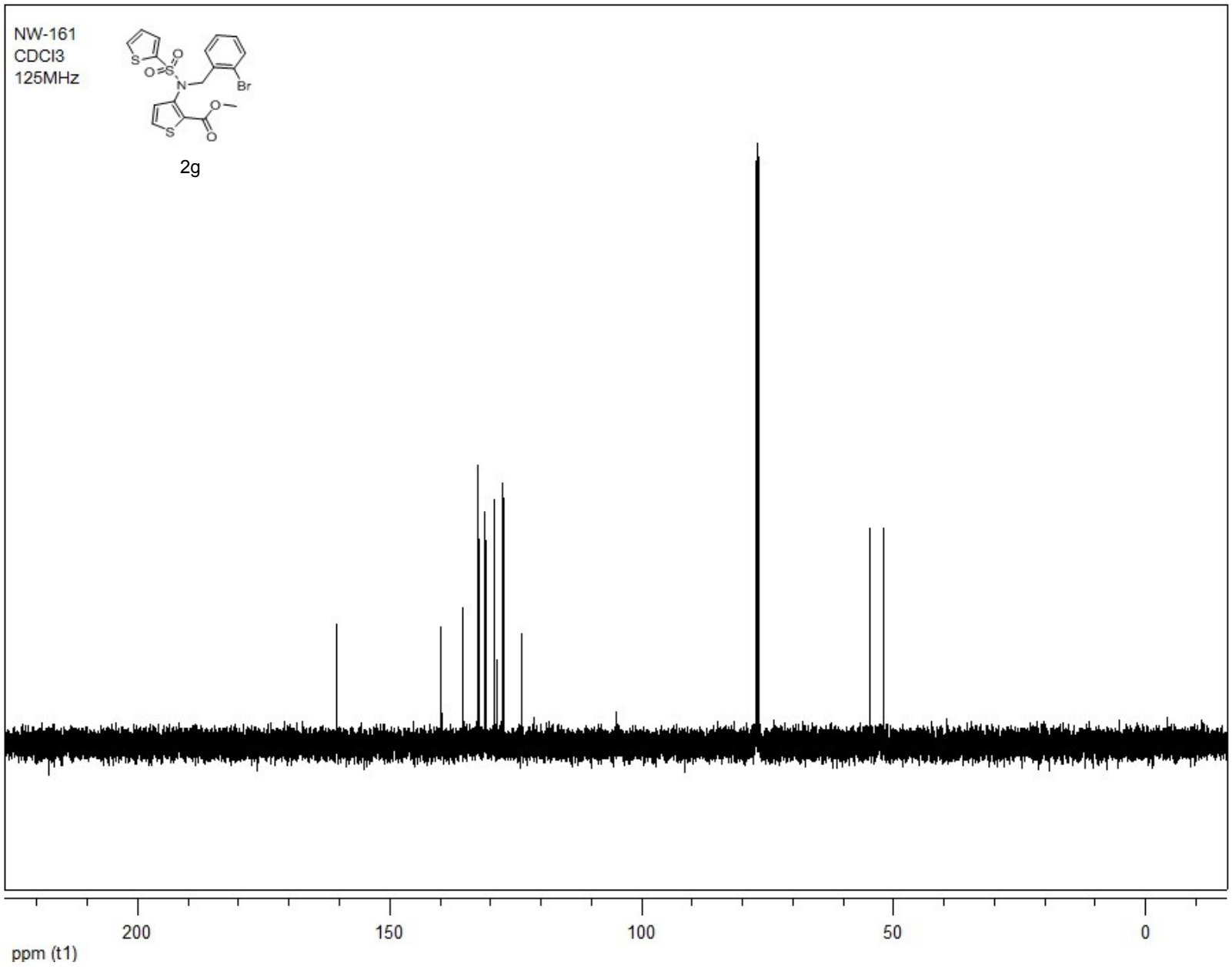


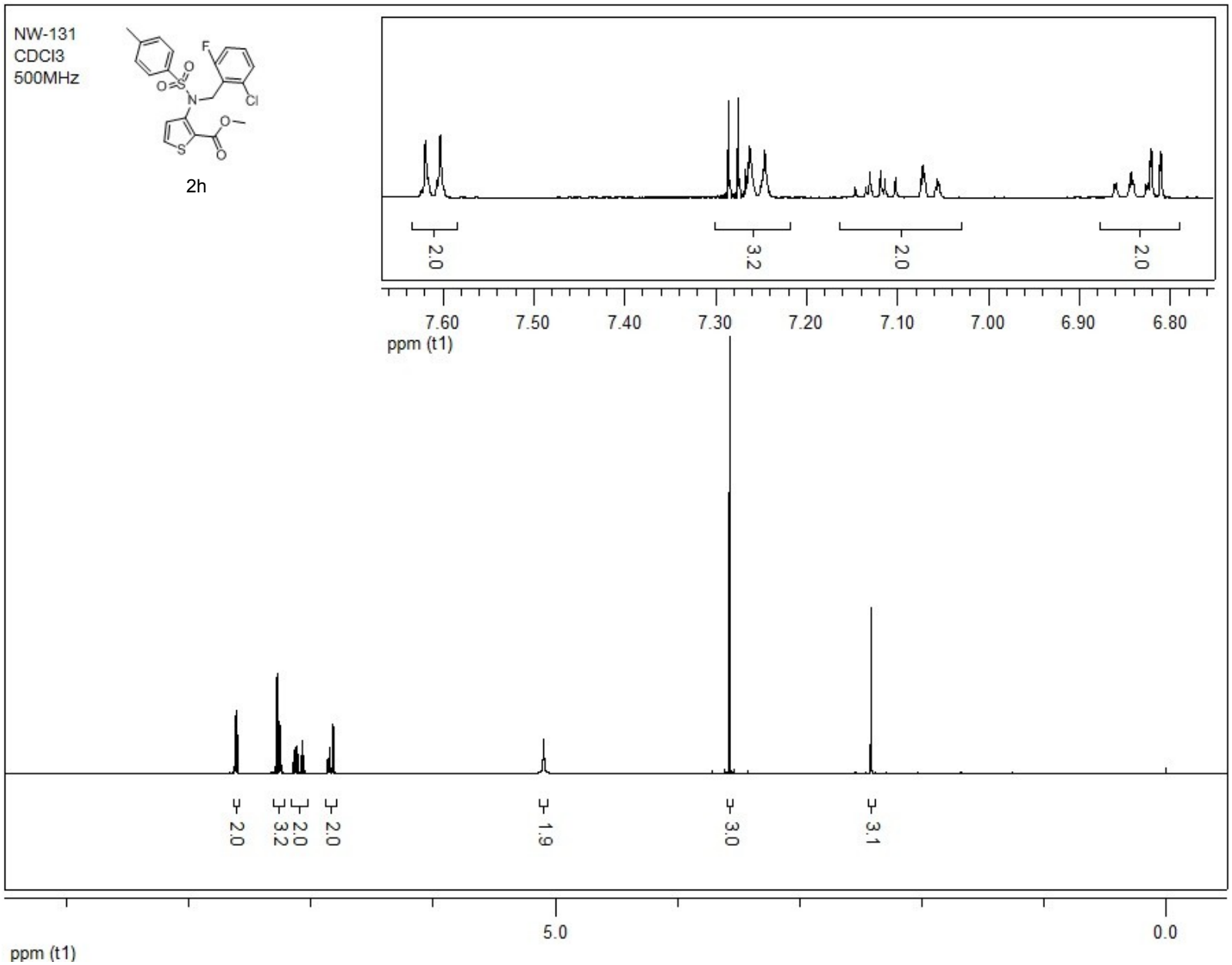
2e


NW-2-066
CDCl3
500MHz
F
O
O
S
N
Br
O
O
S
2f
2.0
1.0
1.0
1.0
1.1
2.0
1.0
1.0
7.80
7.70
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
ppm (t1)
2.0
3.0
5.0
0.0
ppm (t1)

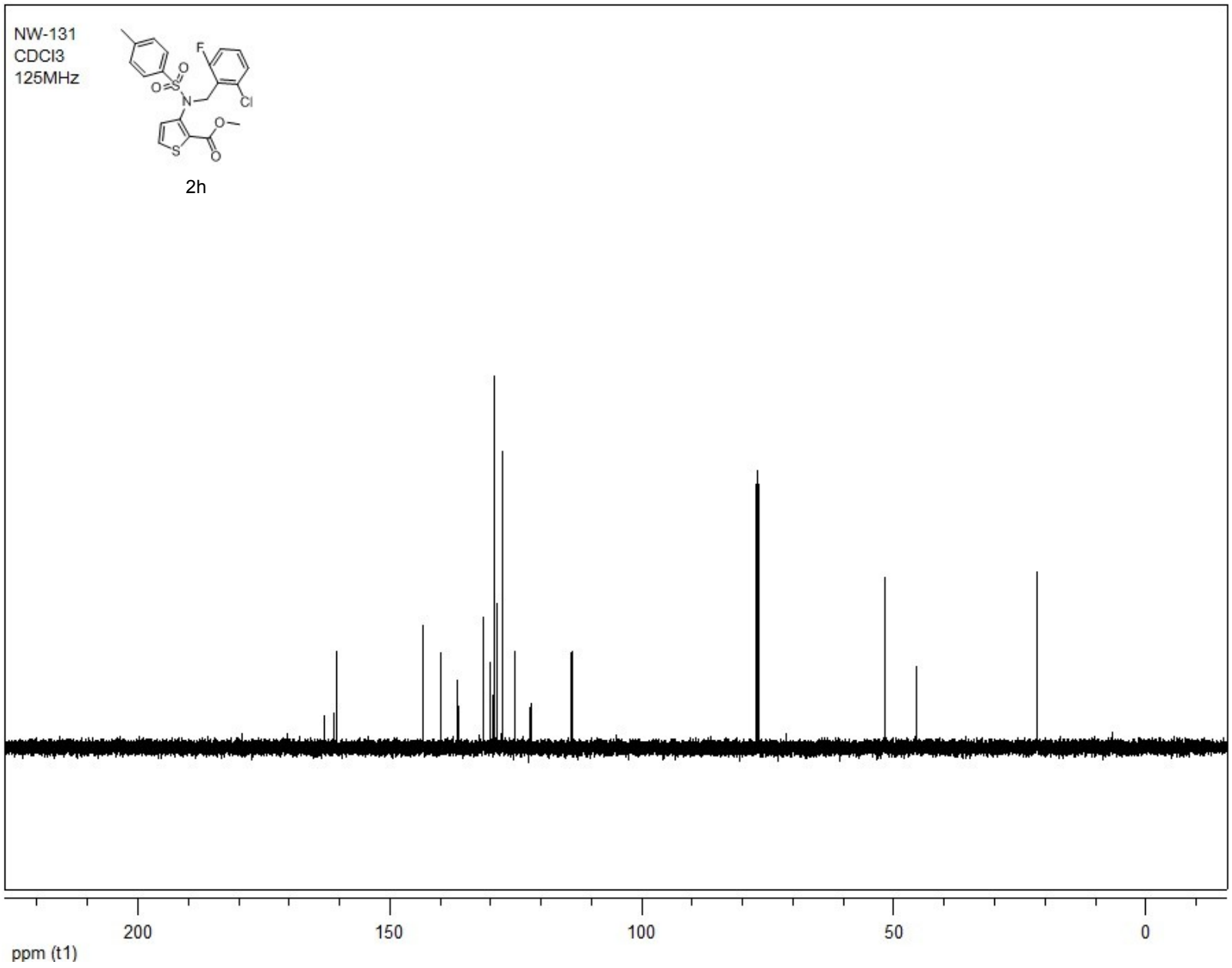

NW-2-066
CDCl3
125MHz
F
O
O
S
N
Br
O
O
S
O
2f
200
150
100
50
0
ppm (t1)


NW-161
CDCl3
500MHz
2g
1.0
0.9
1.0
1.0
1.0
1.2
2.0
1.0
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
ppm (t1)
1.0
2.0
3.0
5.0
0.0
ppm (t1)

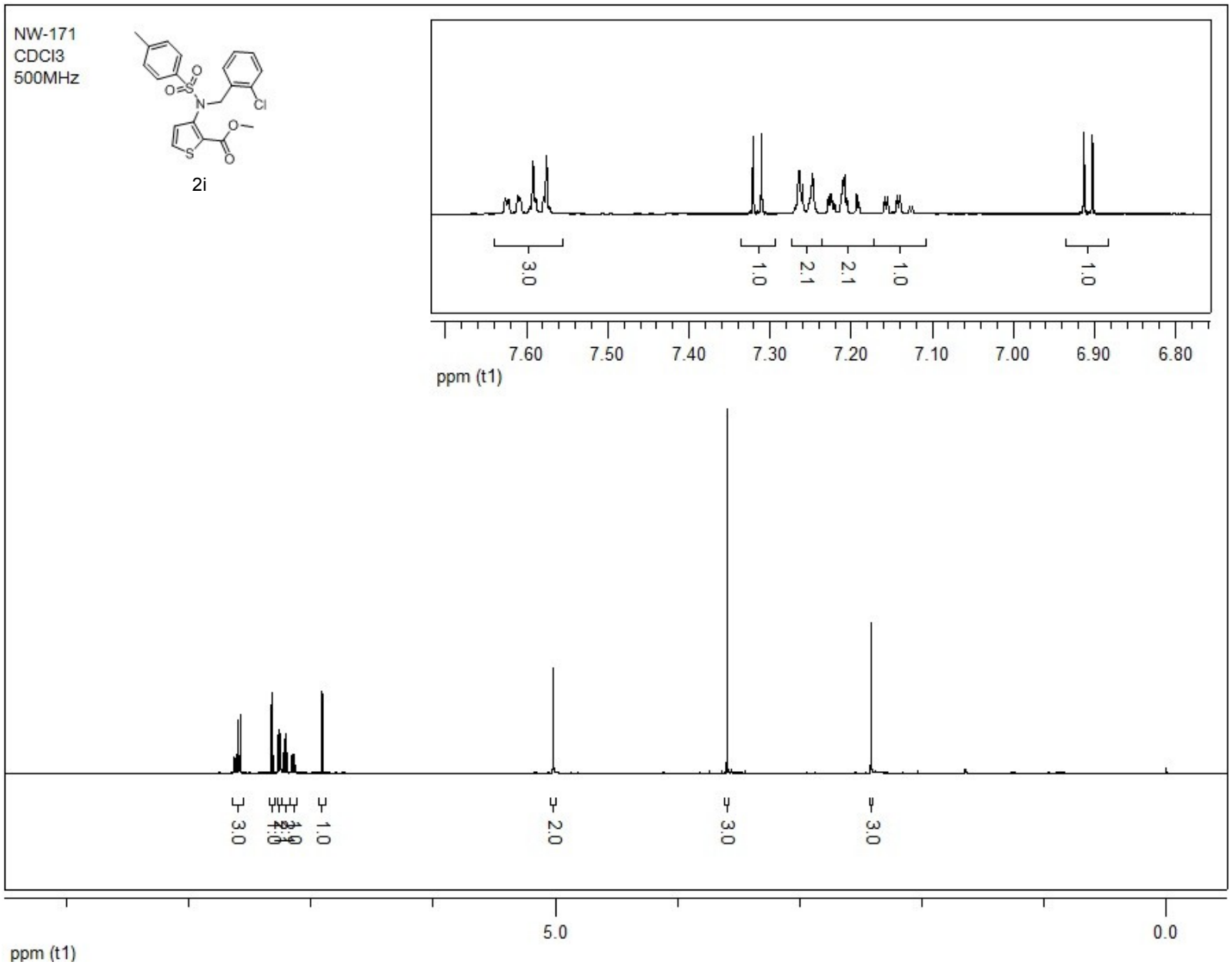

NW-161
CDCl3
125MHz
2g
200
150
100
50
0
ppm (t1)

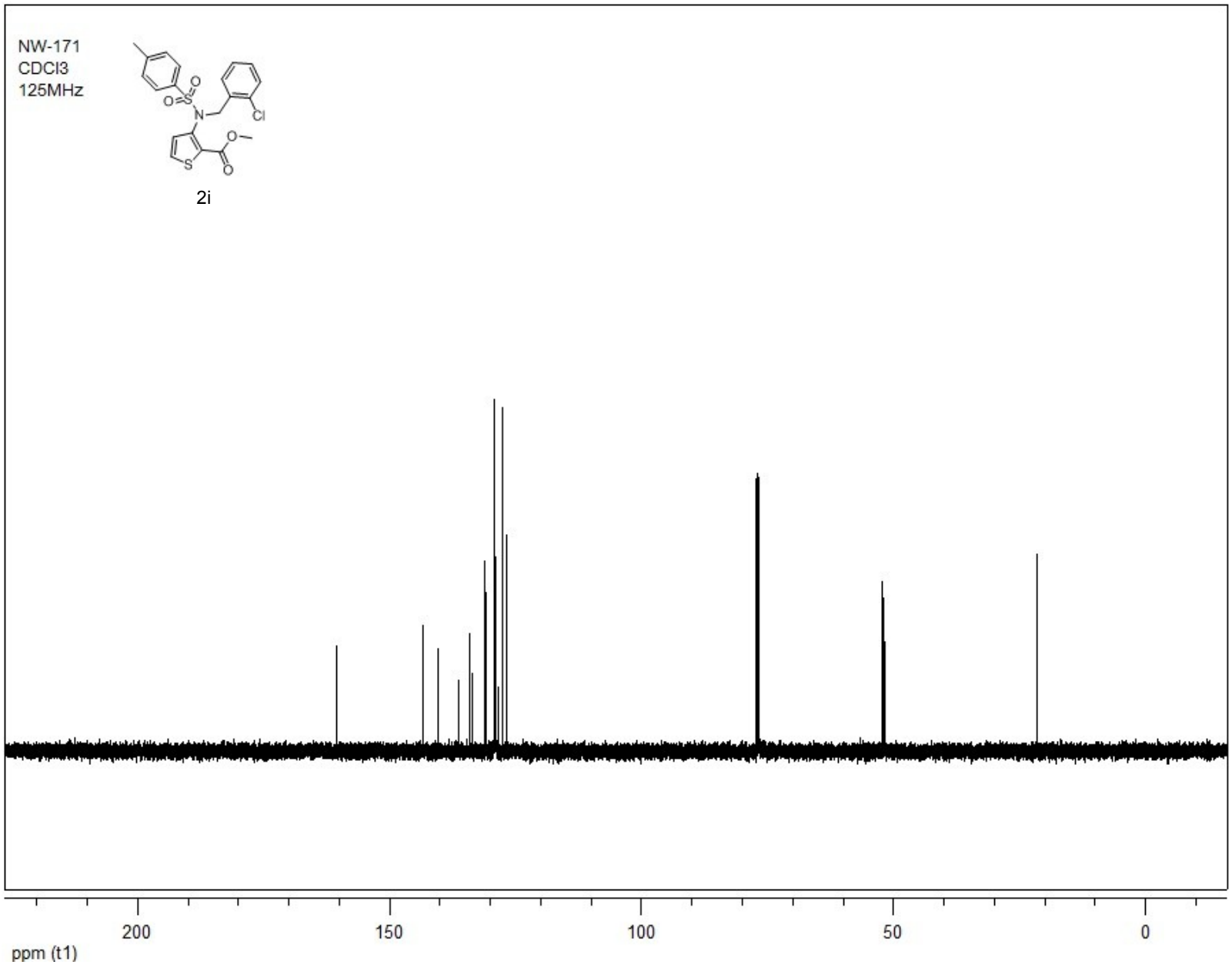

NW-131
CDCl3
500MHz
2h
2.0
3.2
2.0
2.0
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
2.0
3.2
2.0
2.0
1.9
3.0
3.1
5.0
0.0
ppm (t1)

XXX

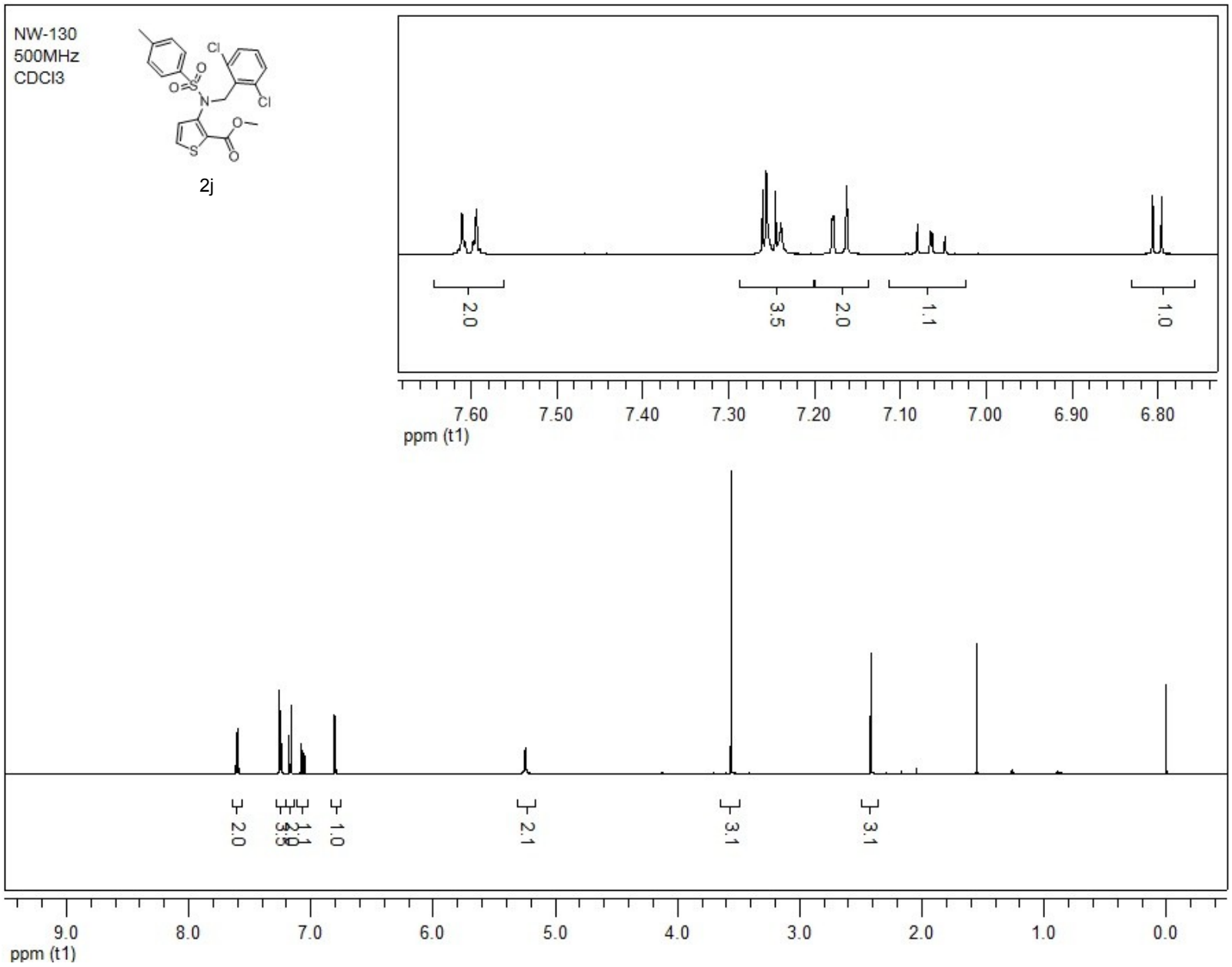


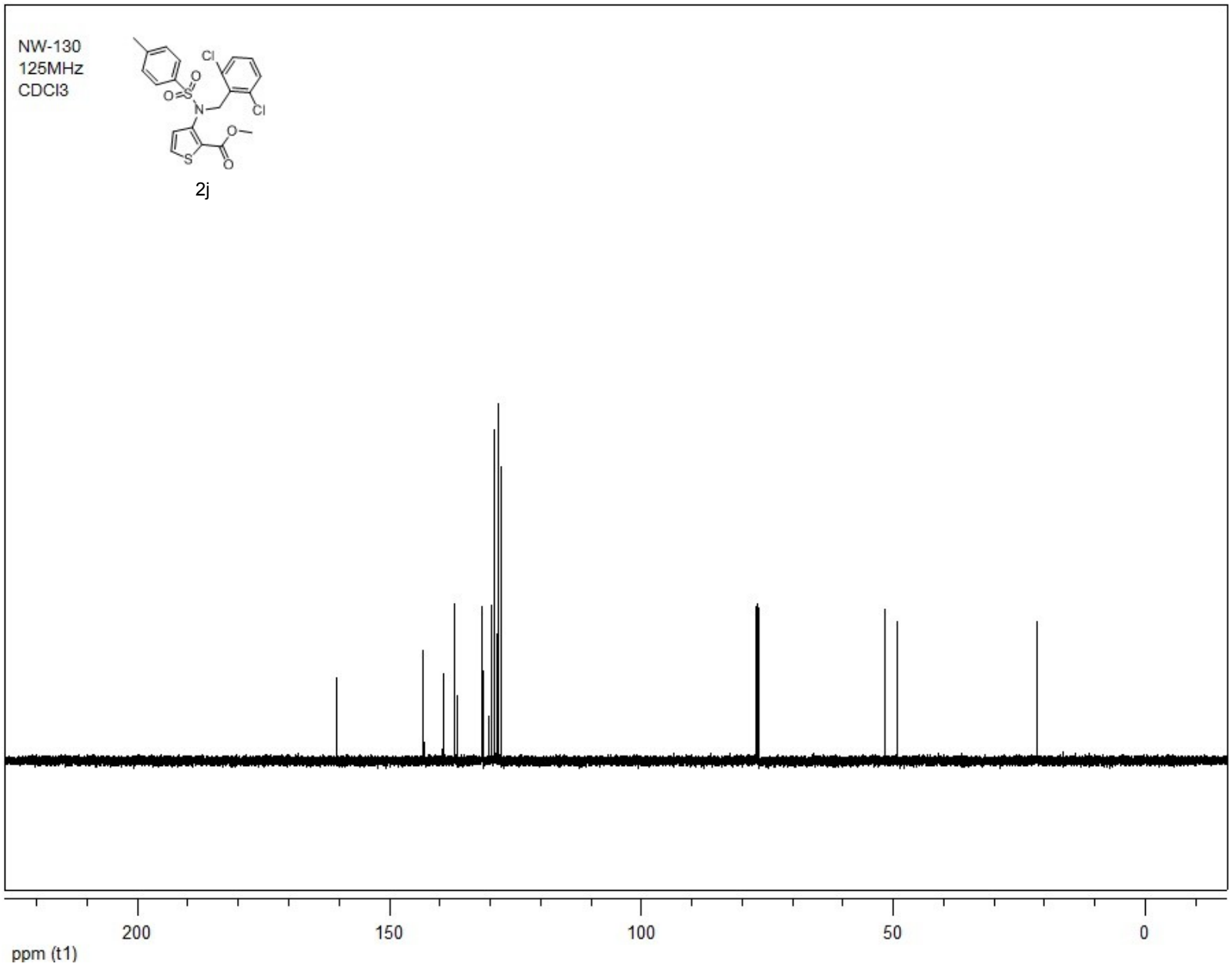
2h


NW-171
CDCl3
500MHz
2i
3.0
1.0
2.1
2.1
1.0
1.0
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
3.0
1.0
2.0
3.0
3.0
5.0
0.0
ppm (t1)

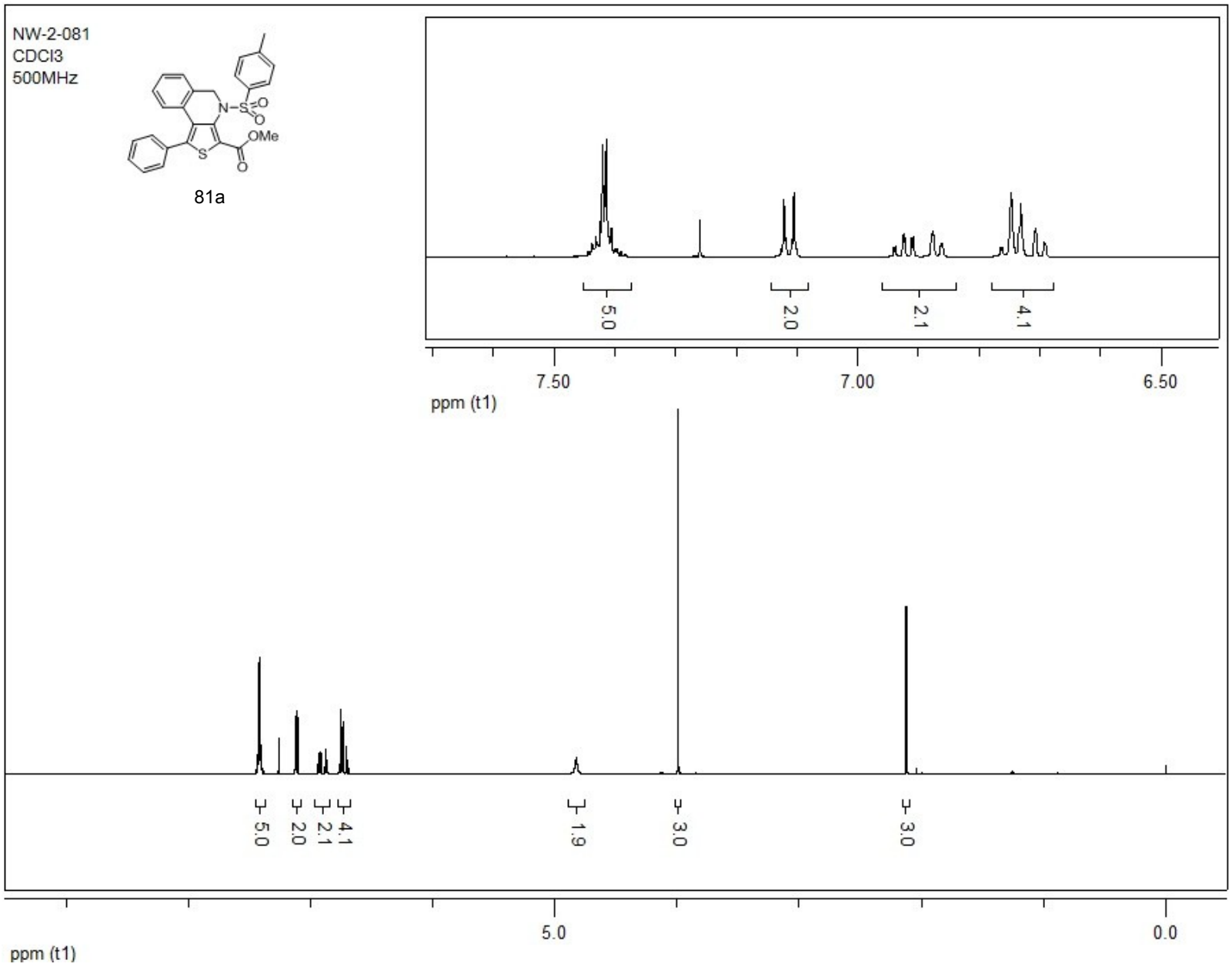


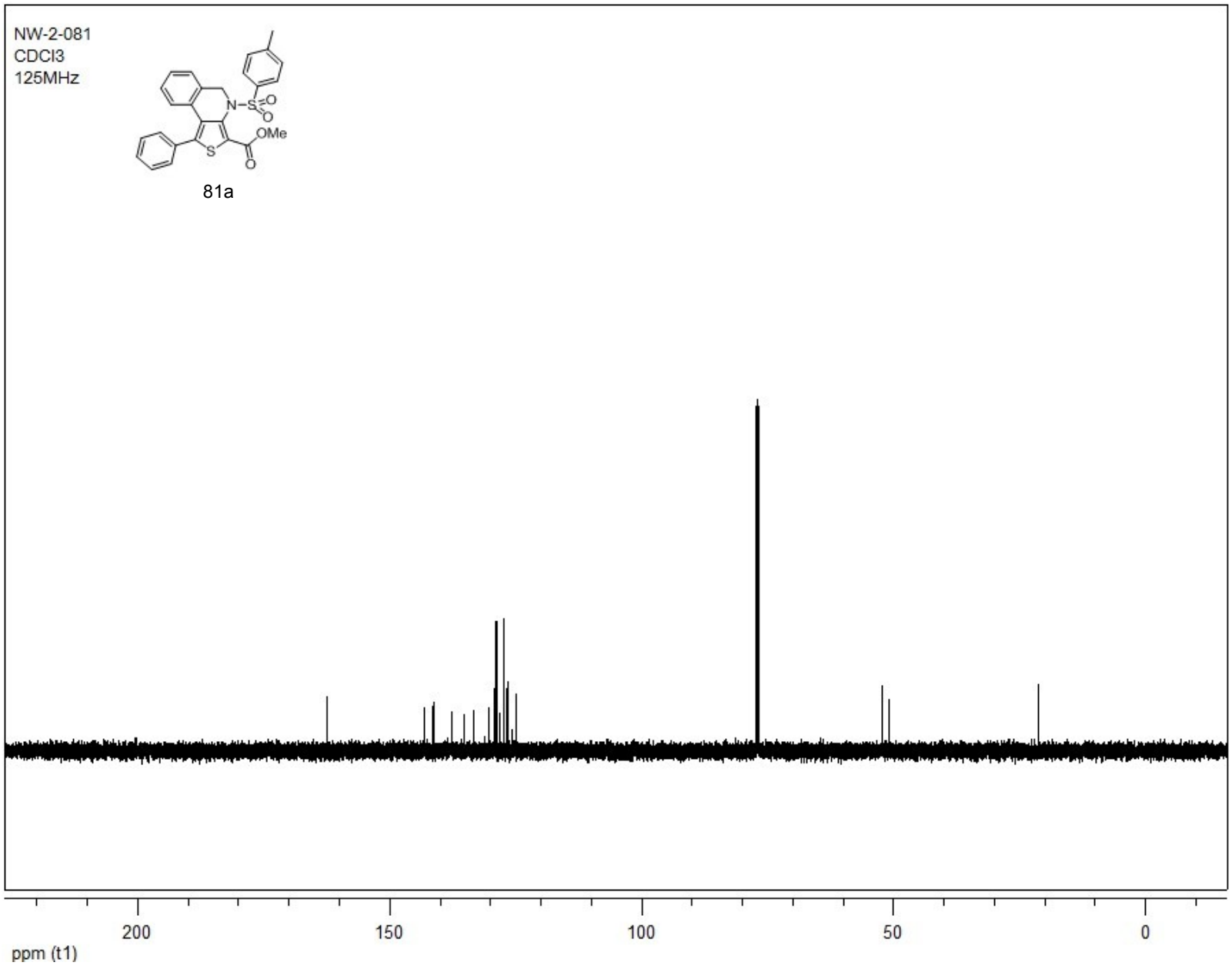
2i

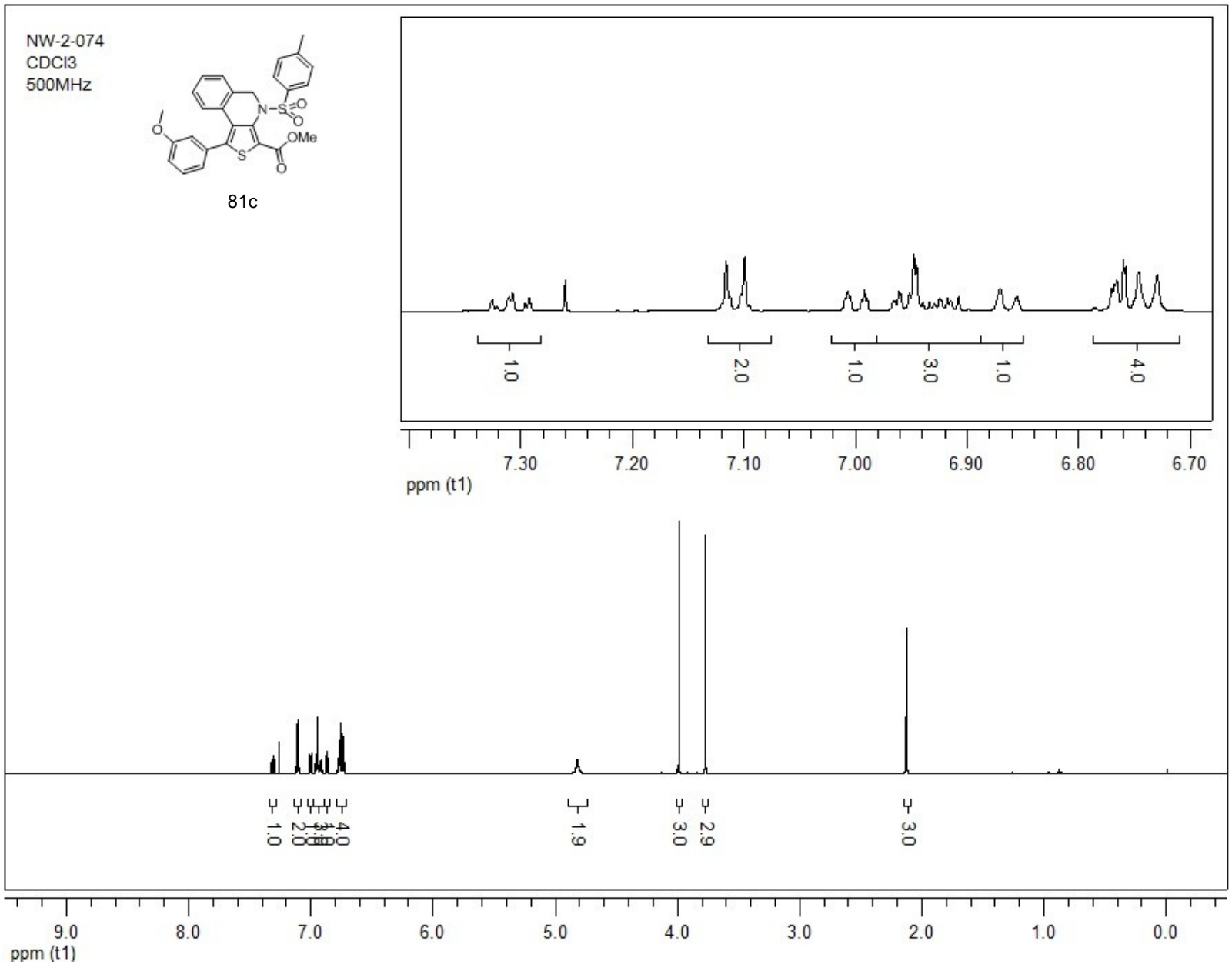

NW-130
500MHz
CDCl3
2j
2.0
3.5
2.0
1.1
1.0
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
2.0
1.0
2.1
3.1
3.1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

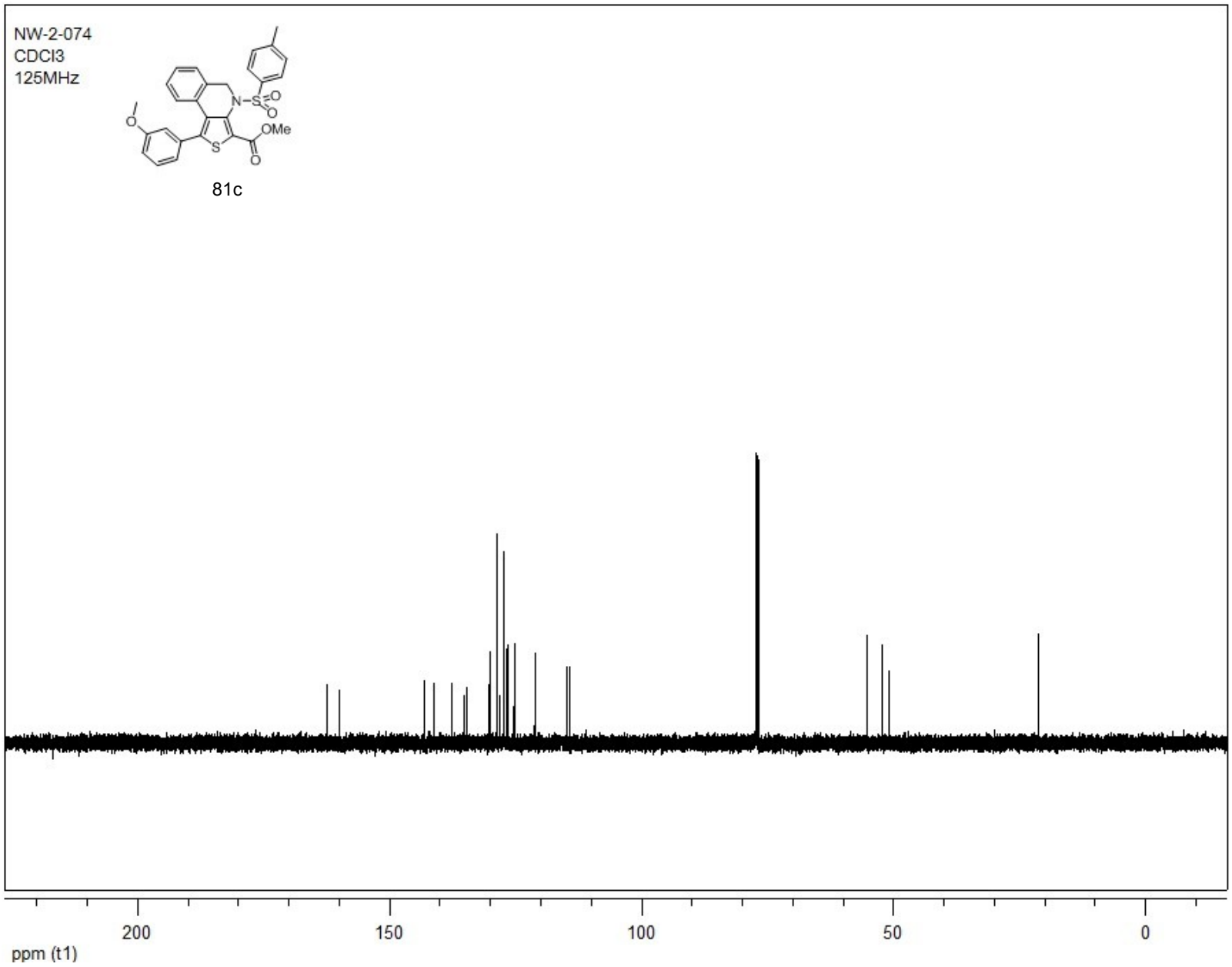


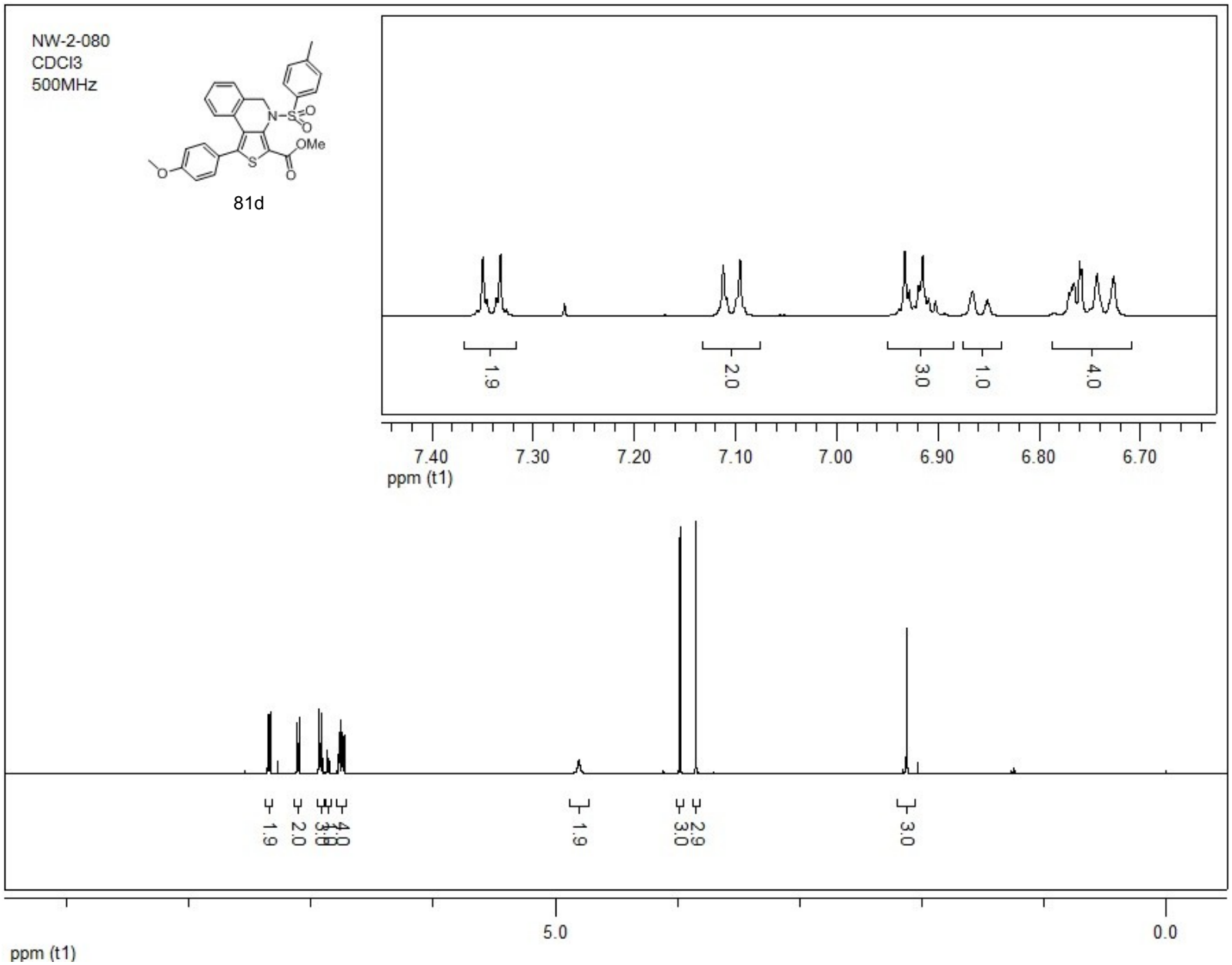
2j


NW-2-081
CDCl3
500MHz
OMe
81a
5.0
2.0
2.1
4.1
7.50
7.00
6.50
ppm (t1)
5.0
2.0
2.1
4.1
1.9
3.0
3.0
5.0
0.0
ppm (t1)

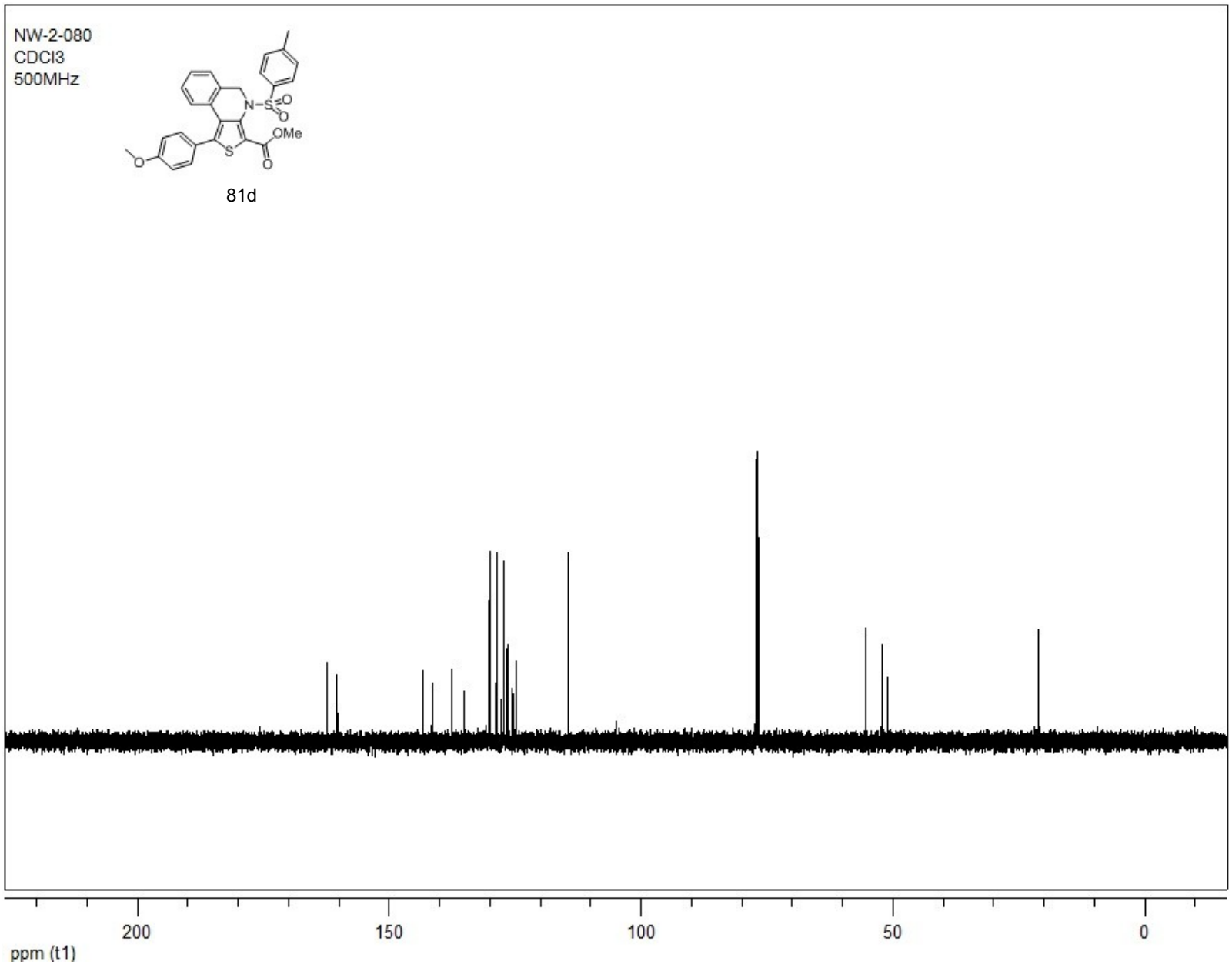

NW-2-081
CDCl3
125MHz
N
S
O
O
OMe
S
O
81a
200
150
100
50
0
ppm (t1)

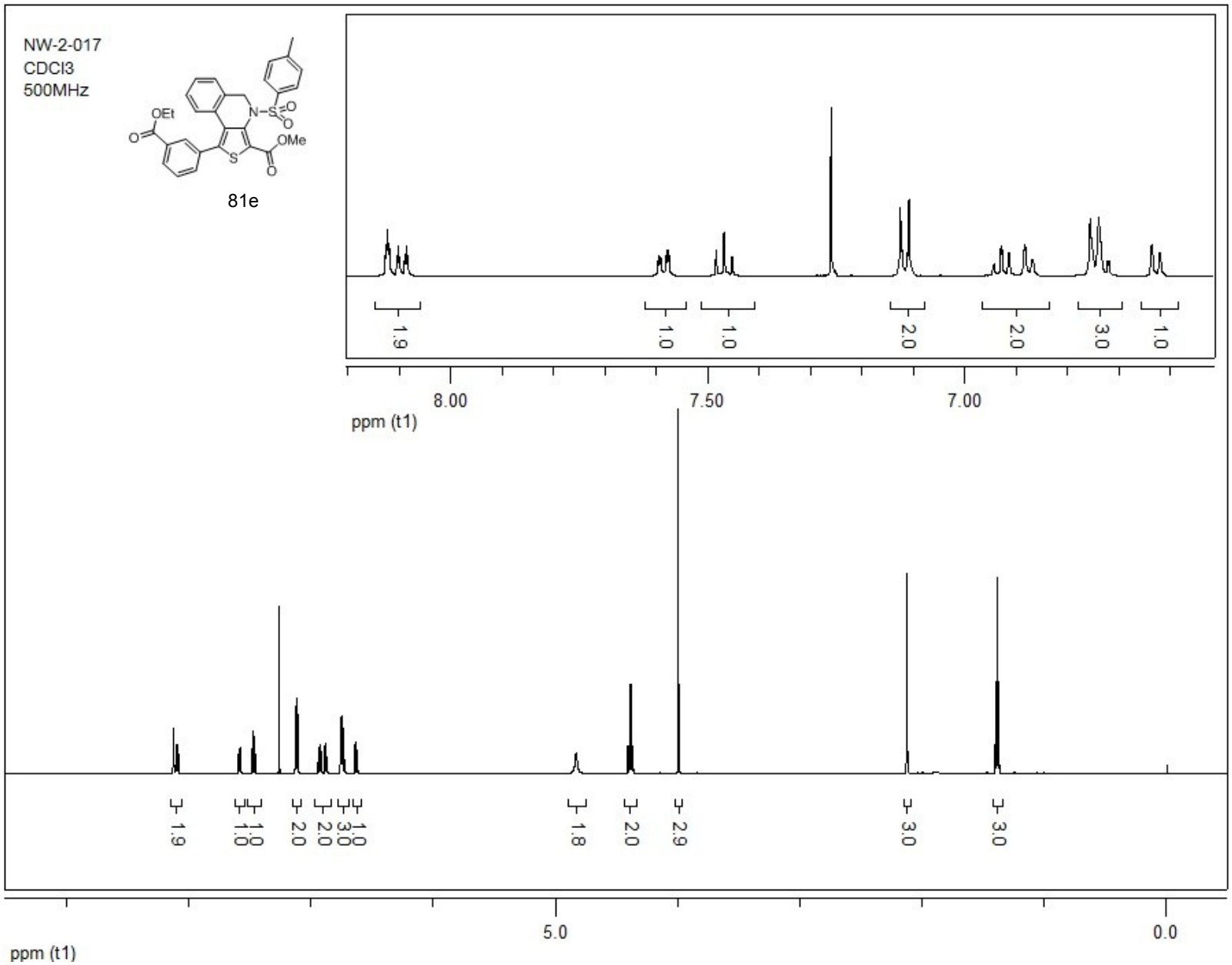

NW-2-074
CDCl3
500MHz
OMe
81c
1.0
2.0
1.0
3.0
1.0
4.0
7.30
7.20
7.10
7.00
6.90
6.80
6.70
ppm (t1)
1.0
4.0
1.9
3.0
2.9
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

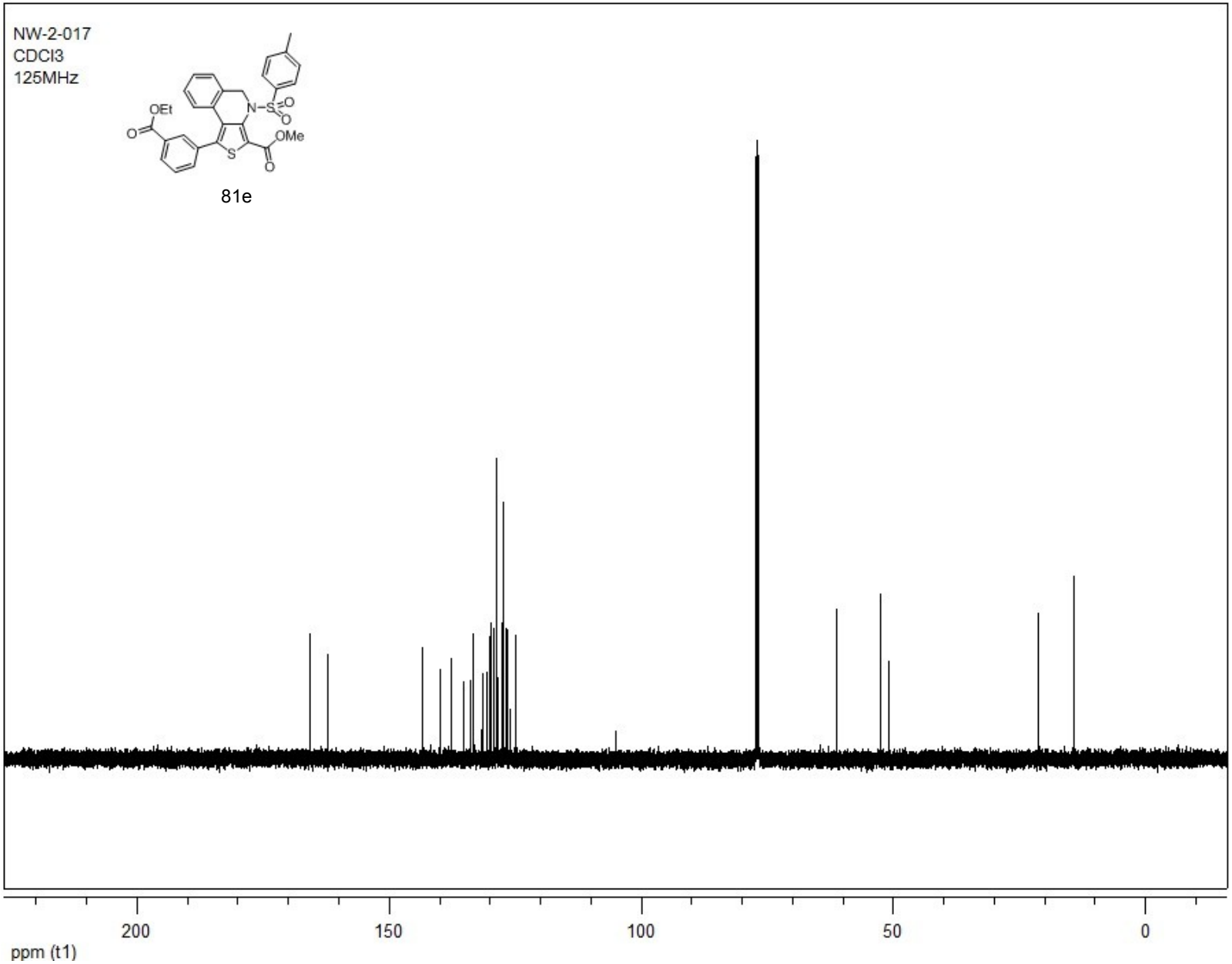

NW-2-074
CDCl3
125MHz
N
S
O
O
OMe
O
S
O
81c
200
150
100
50
0
ppm (t1)

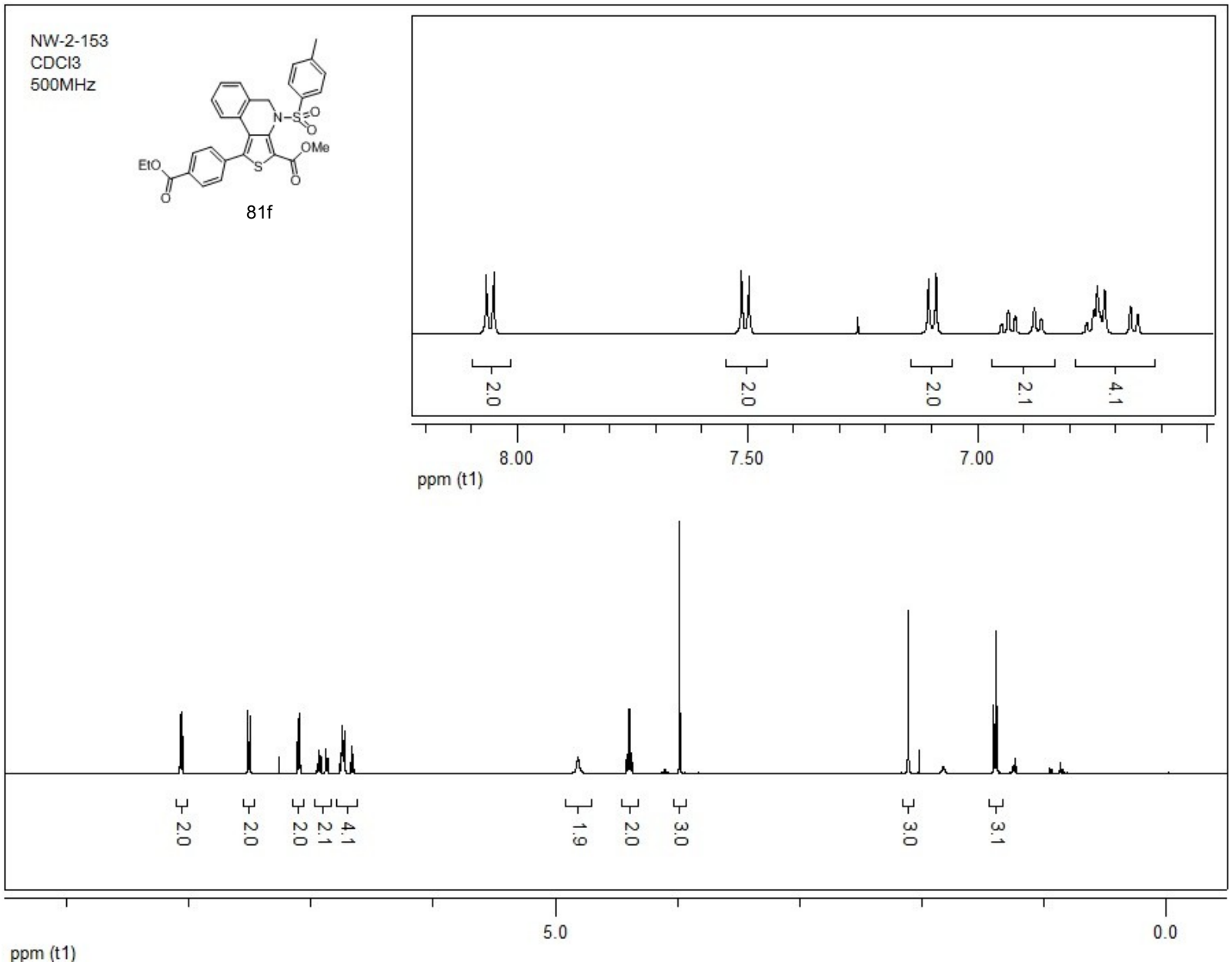

NW-2-080
CDCl3
500MHz
81d
1.9
2.0
3.0
1.0
4.0
7.40
7.30
7.20
7.10
7.00
6.90
6.80
6.70
ppm (t1)
1.9
2.0
4.0
1.9
2.9
3.0
3.0
5.0
0.0
ppm (t1)

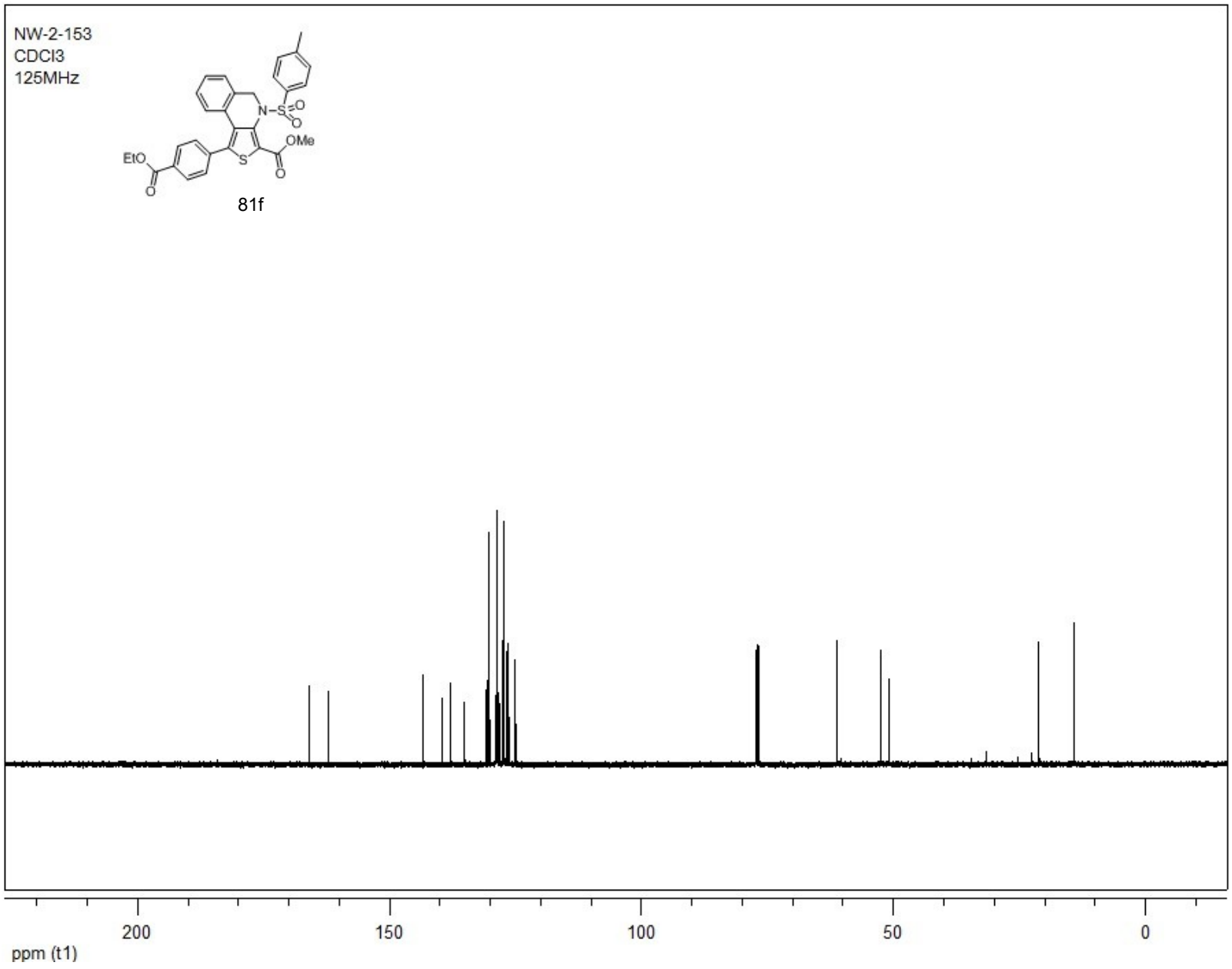
XL

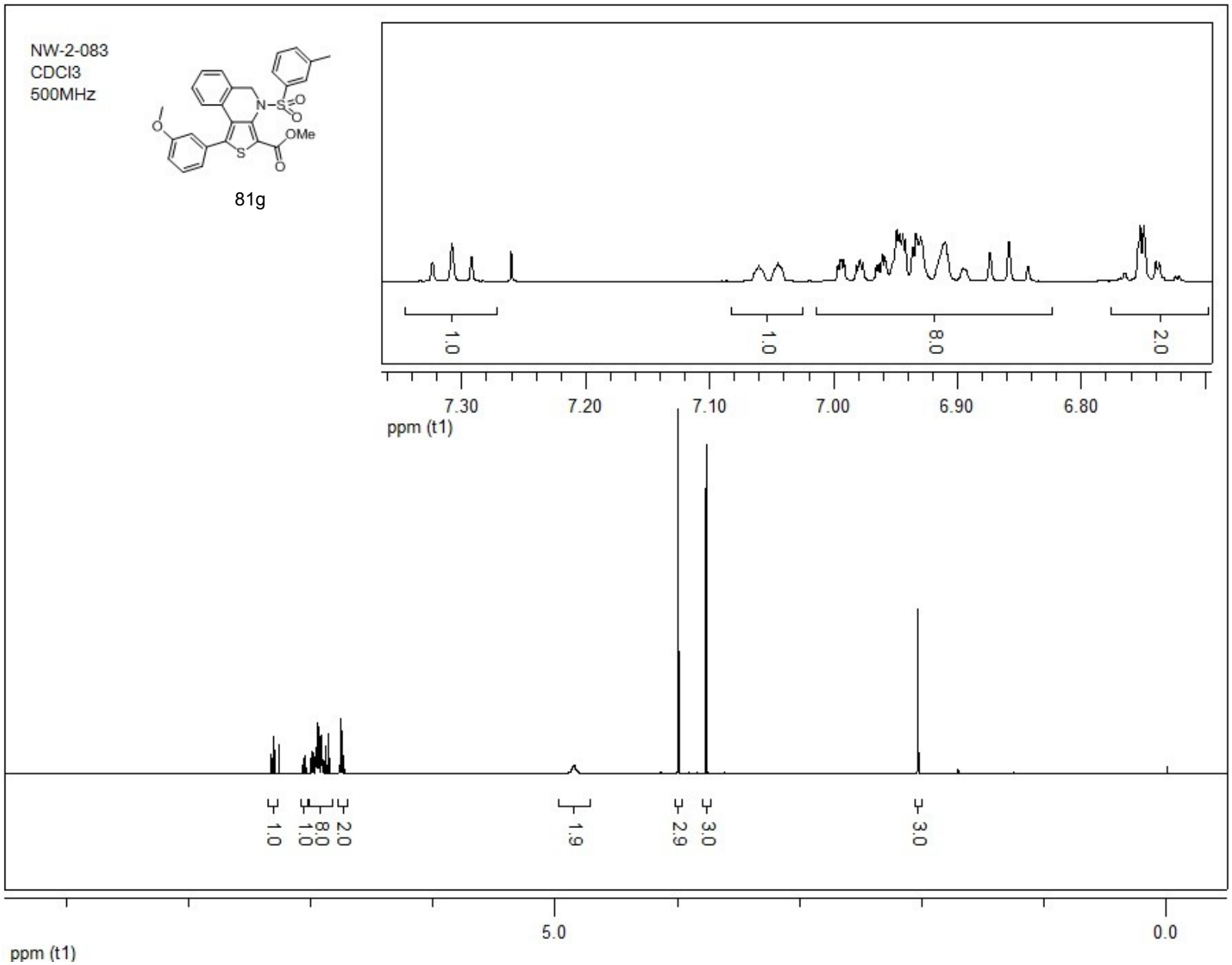

NW-2-080
CDCl3
500MHz
N
S
O
O
OMe
O
S
O
81d
200
150
100
50
0
ppm (t1)

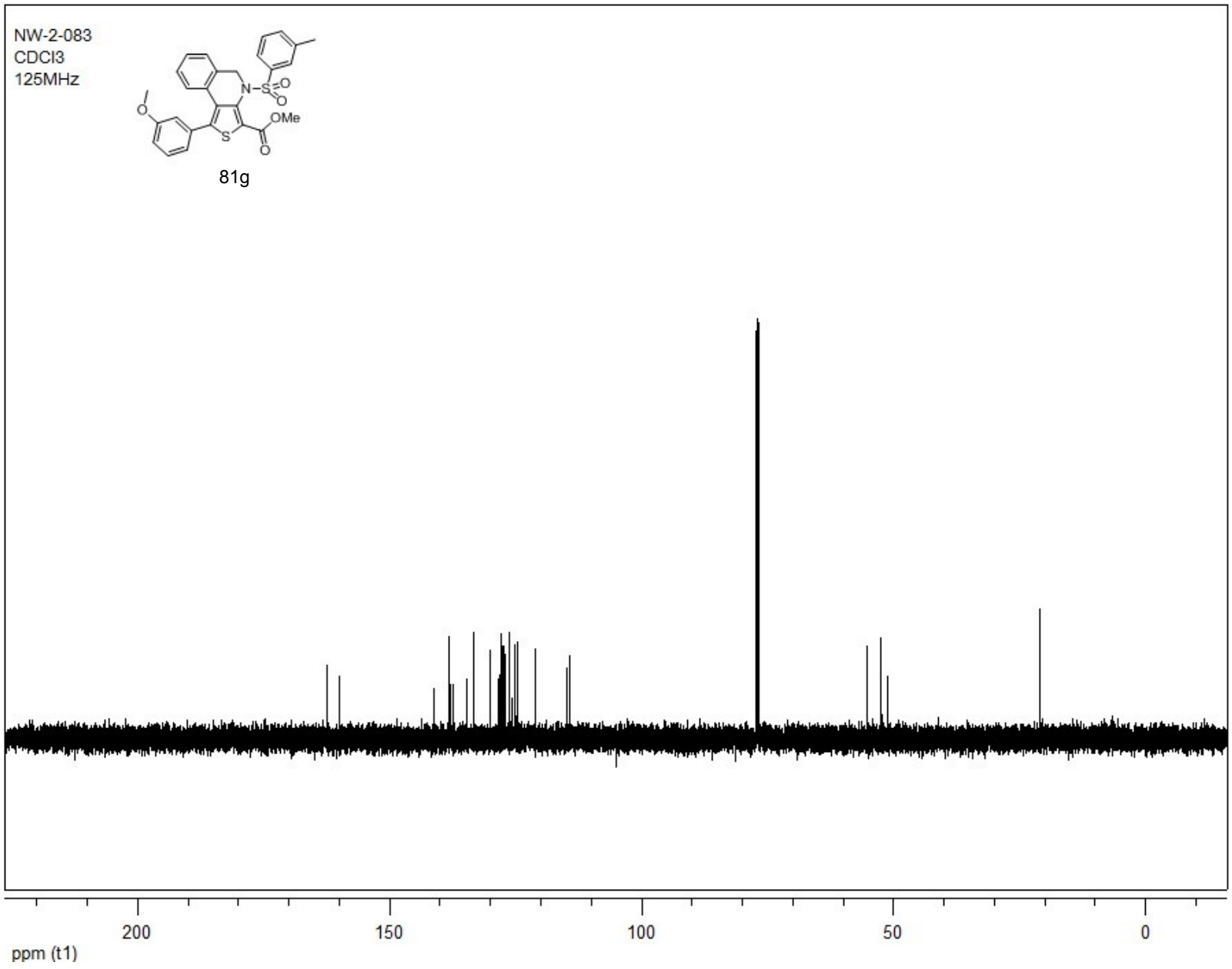

NW-2-017
CDCl3
500MHz
OEt
OMe
N
S
O
O
O
O
S
81e
1.9
1.0
1.0
2.0
2.0
3.0
1.0
8.00
7.50
7.00
ppm (t1)
1.9
1.0
1.0
2.0
2.0
3.0
1.0
1.8
2.0
2.9
3.0
3.0
5.0
0.0
ppm (t1)

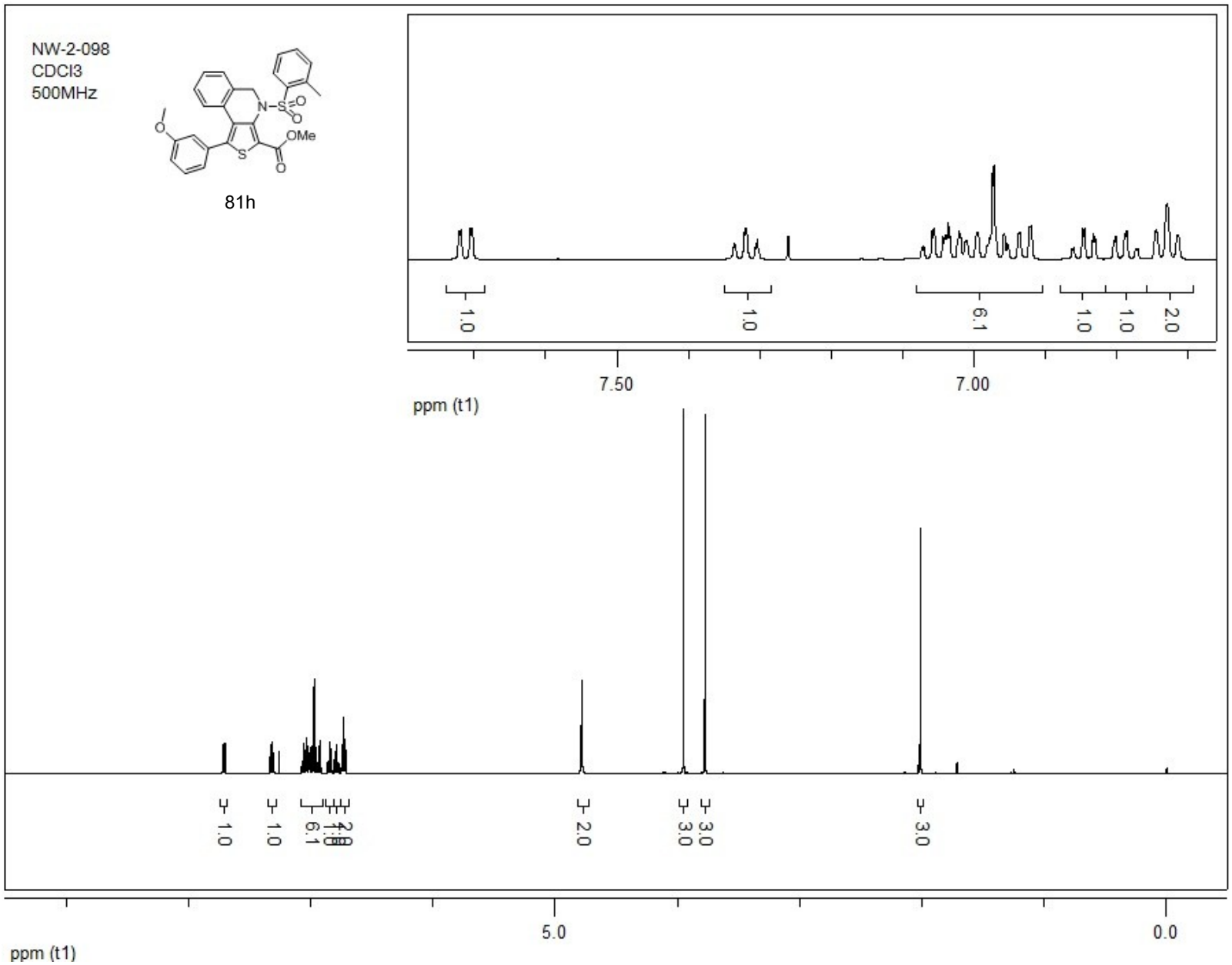

NW-2-017
CDCl3
125MHz
OEt
O
N
S
O
O
OMe
O
S
O
81e
200
150
100
50
0
ppm (t1)

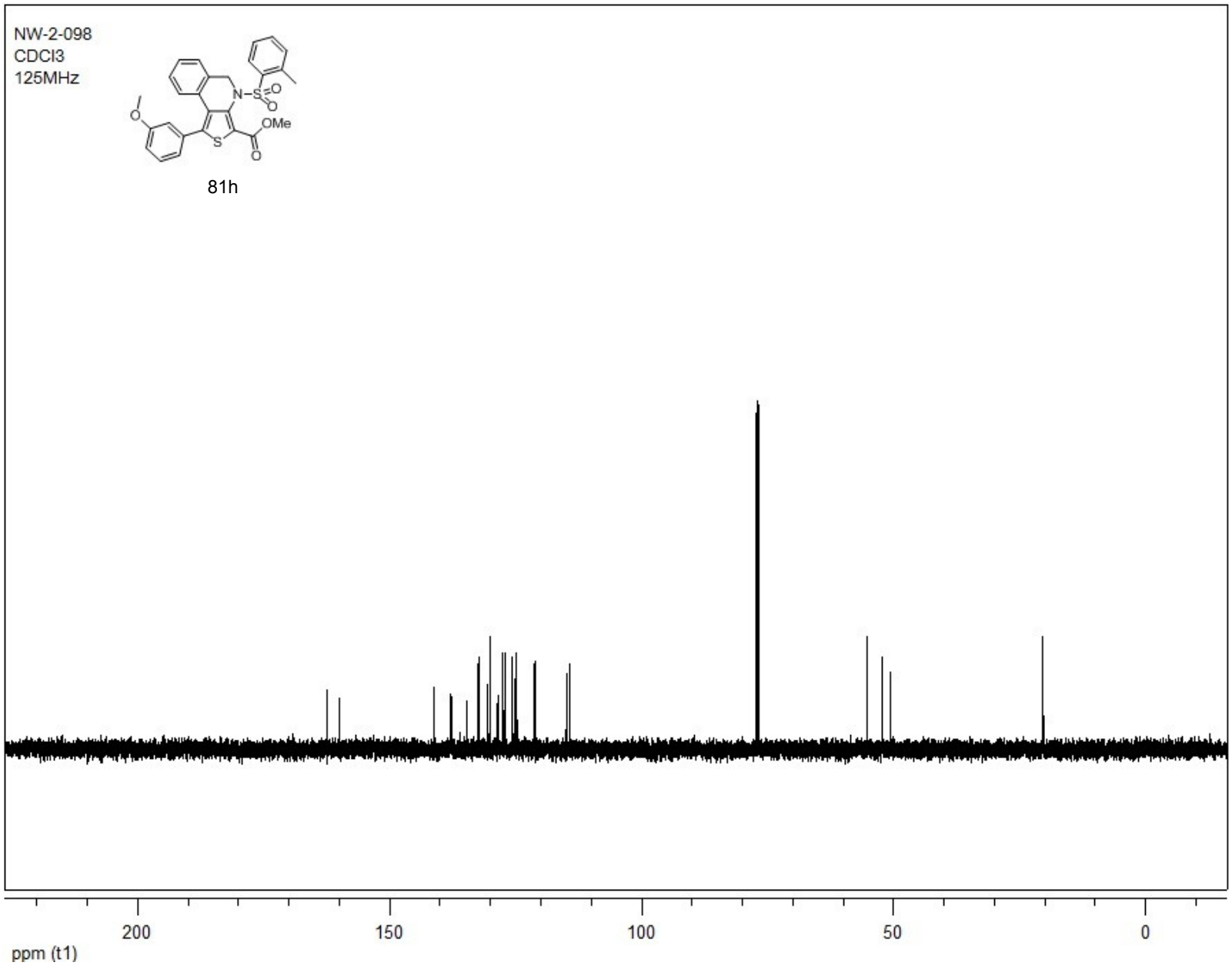

NW-2-153
CDCl3
500MHz
EtO
OMe
N
S
O
O
S
O
O
81f
2.0
2.0
2.0
2.1
4.1
8.00
7.50
7.00
ppm (t1)
2.0
2.0
2.0
2.1
4.1
1.9
2.0
3.0
3.0
3.1
5.0
0.0
ppm (t1)


NW-2-153
CDCl3
125MHz
N
S
O
O
EtO
O
S
OMe
O
81f
200
150
100
50
0
ppm (t1)

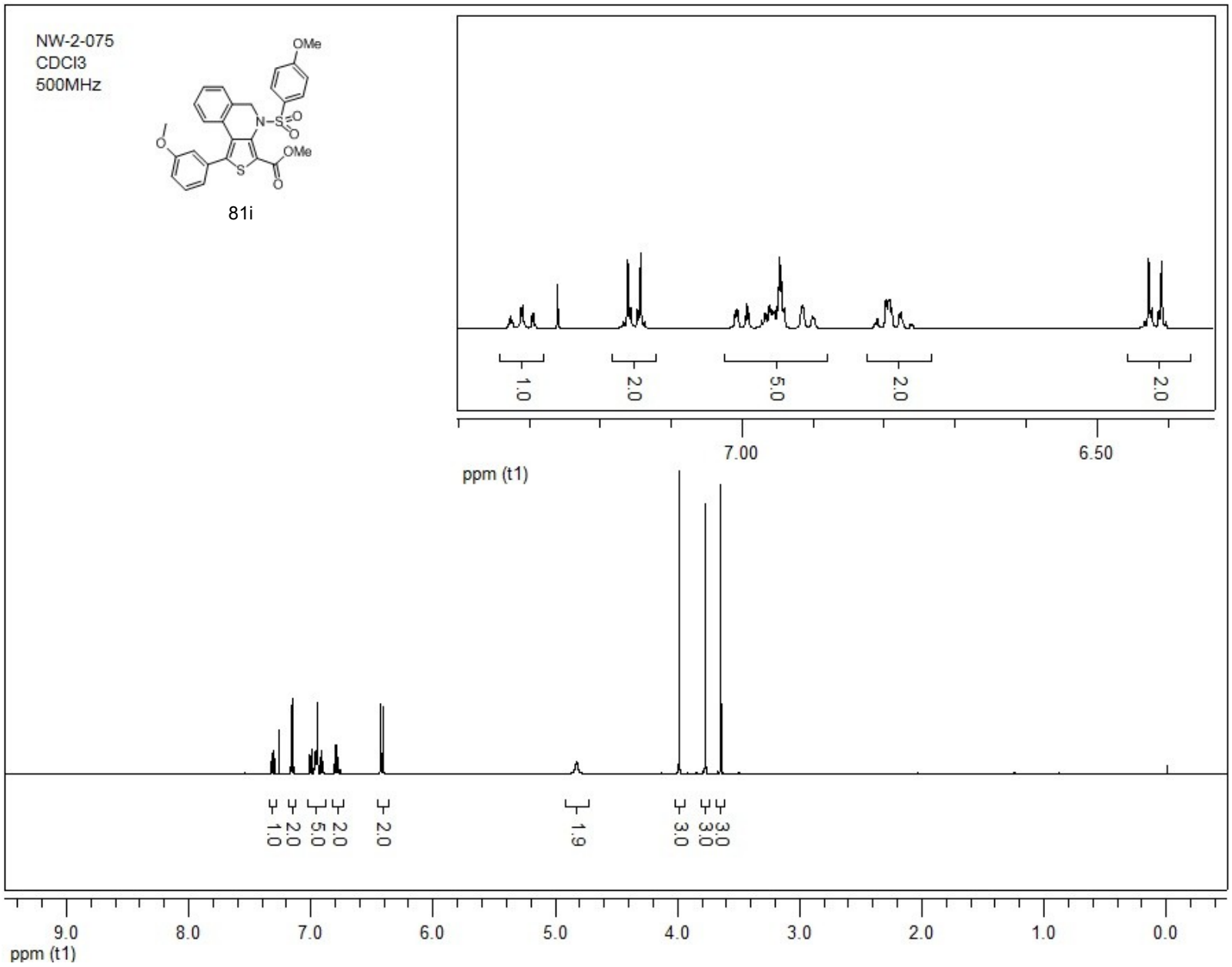

NW-2-083
CDCl3
500MHz
81g
1.0
1.0
8.0
2.0
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
1.0
1.0
8.0
2.0
1.9
2.9
3.0
3.0
5.0
0.0
ppm (t1)


NW-2-083
CDCl3
125MHz
N
S
O
O
OMe
O
S
O
81g
200
150
100
50
0
ppm (t1)

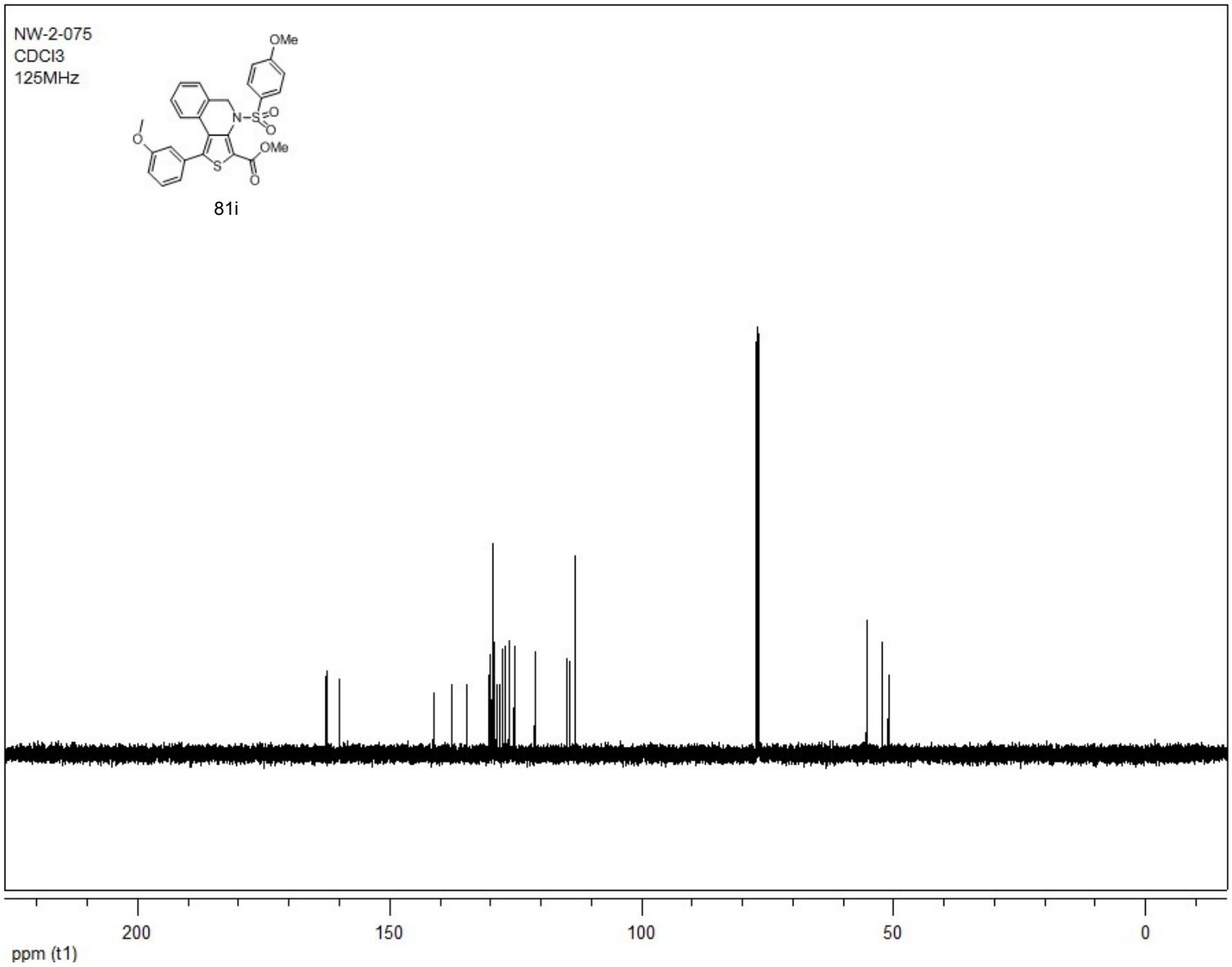

NW-2-098
CDCl3
500MHz
OMe
O
S
N
O
O
O
O
81h
1.0
1.0
6.1
1.0
1.0
2.0
7.50
7.00
ppm (t1)
1.0
1.0
6.1
2.0
3.0
3.0
3.0
5.0
0.0
ppm (t1)



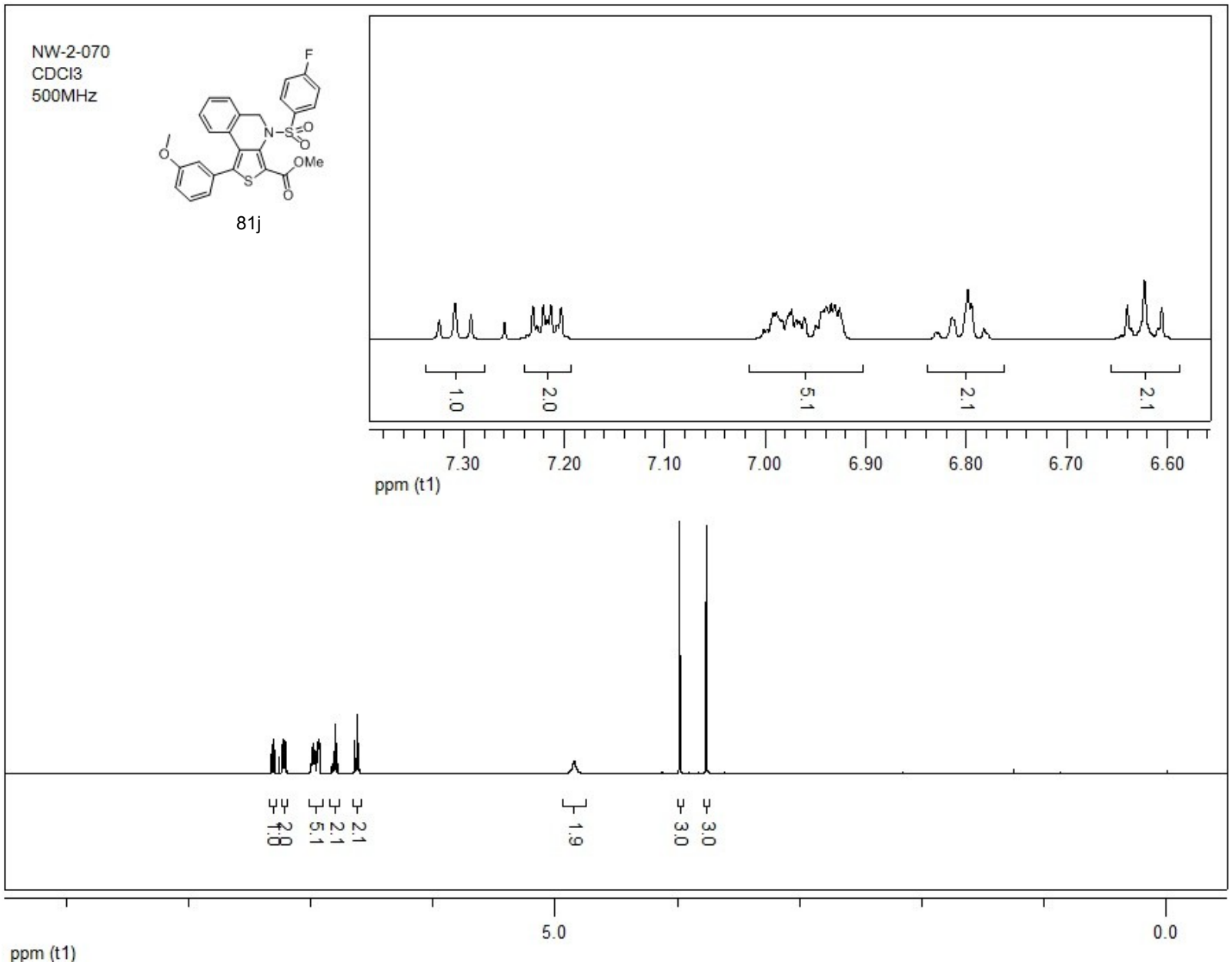
81h

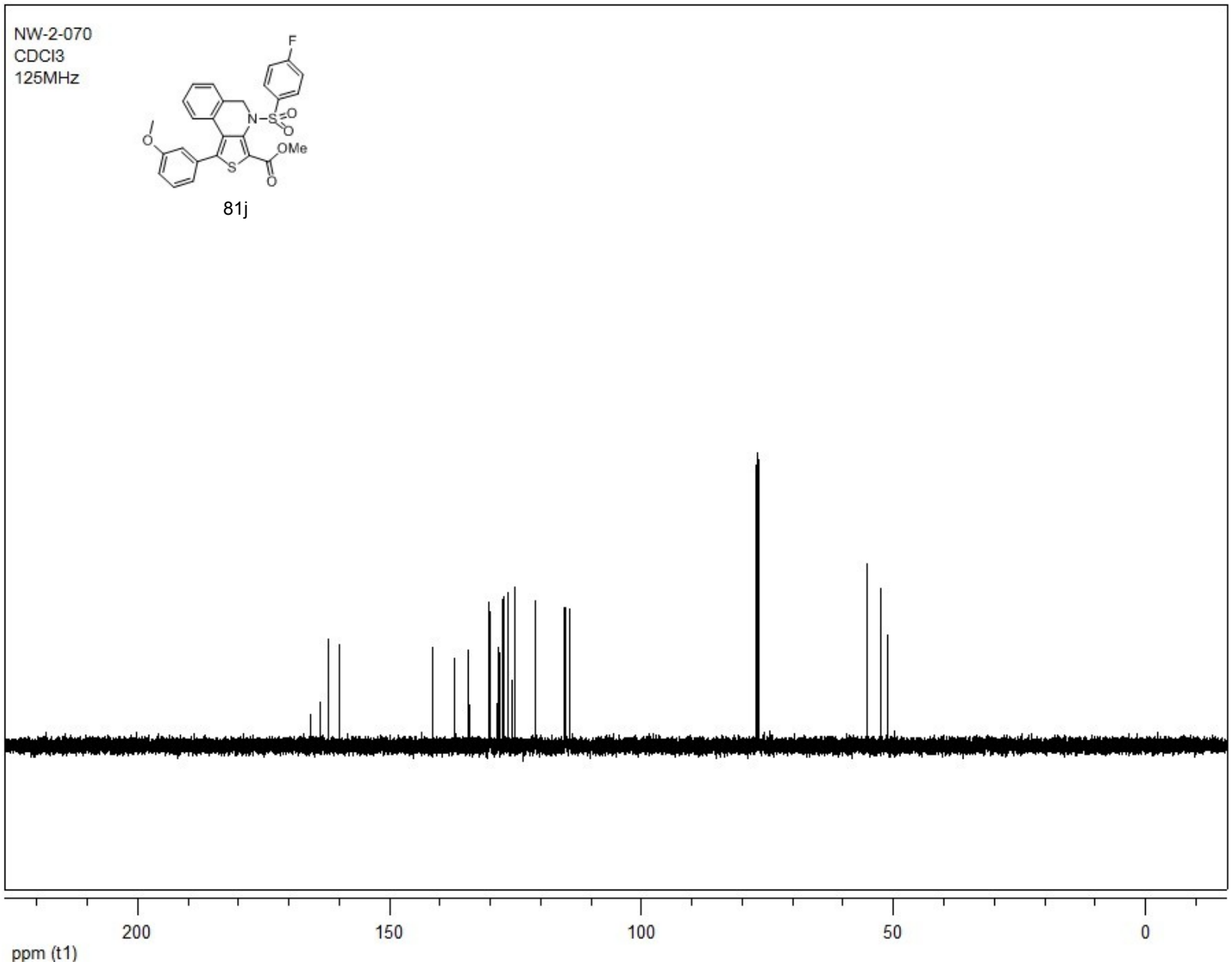

NW-2-075
CDCl3
500MHz
OMe
N
S
O
O
OMe
O
S
O
81i
1.0
2.0
5.0
2.0
2.0
7.00
6.50
ppm (t1)
1.0
2.0
5.0
2.0
2.0
1.9
3.0
3.0
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

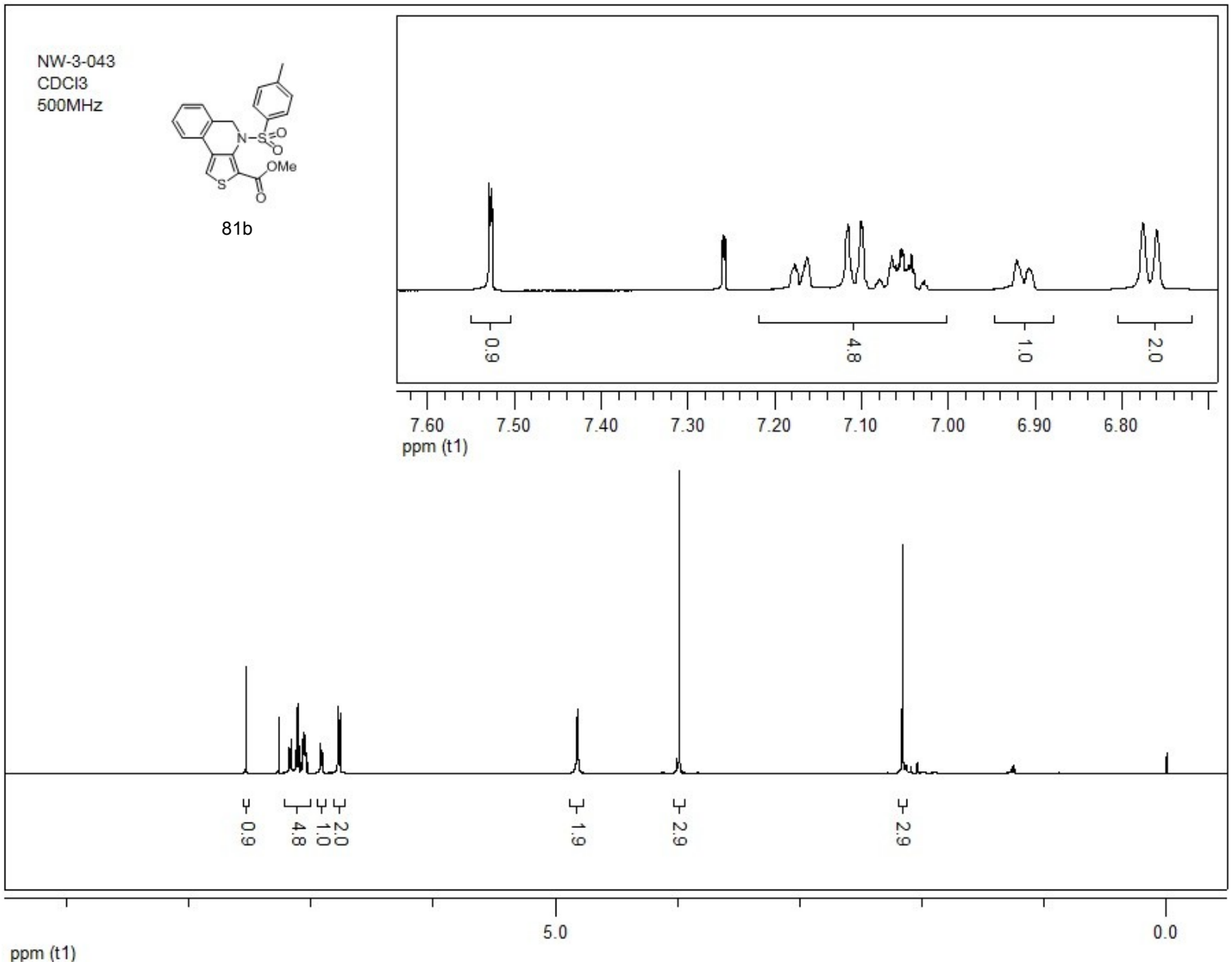
L

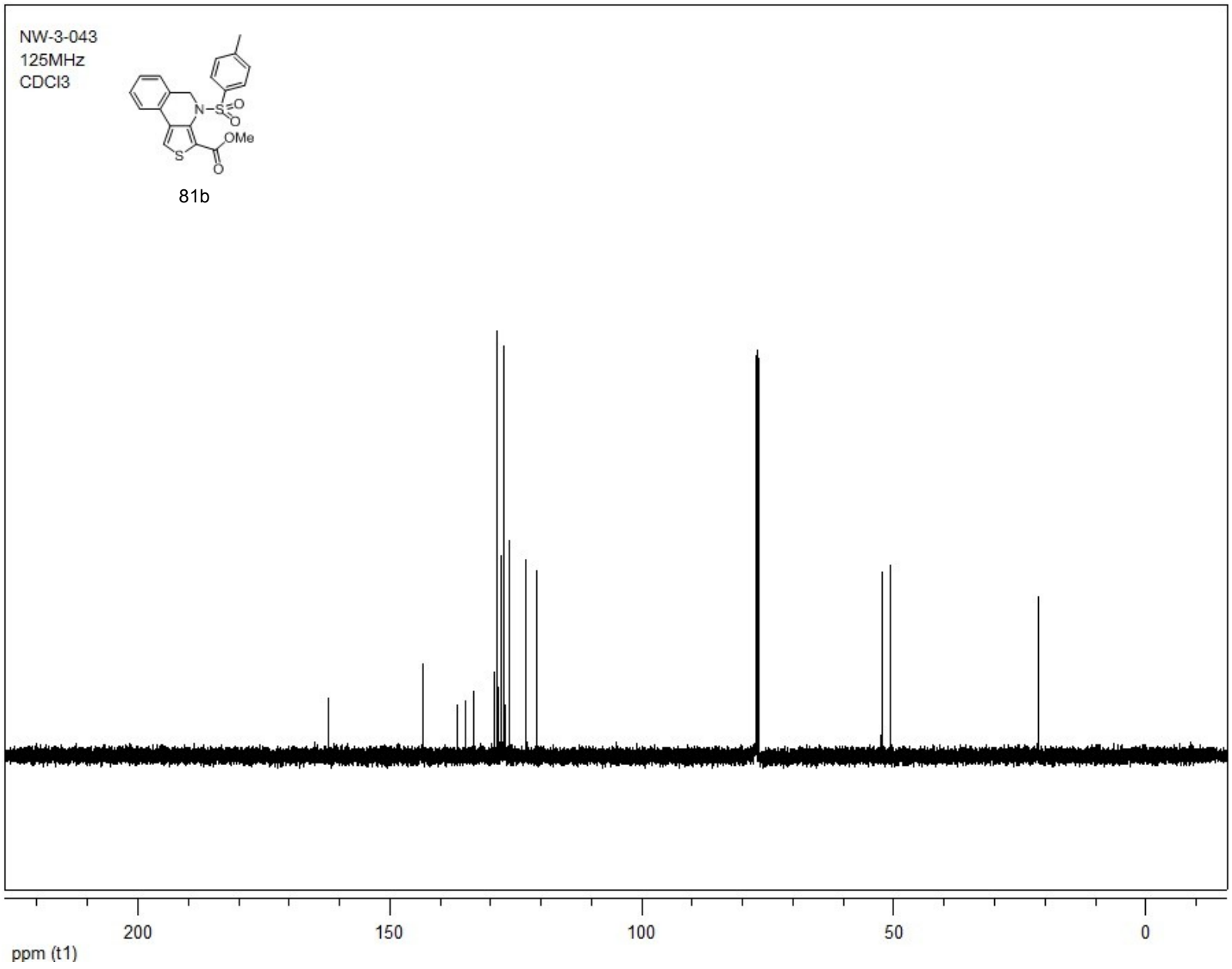

NW-2-075
CDCl3
125MHz
OMe
N
S
O
O
OMe
O
O
S
O
81i
200
150
100
50
0
ppm (t1)

LI

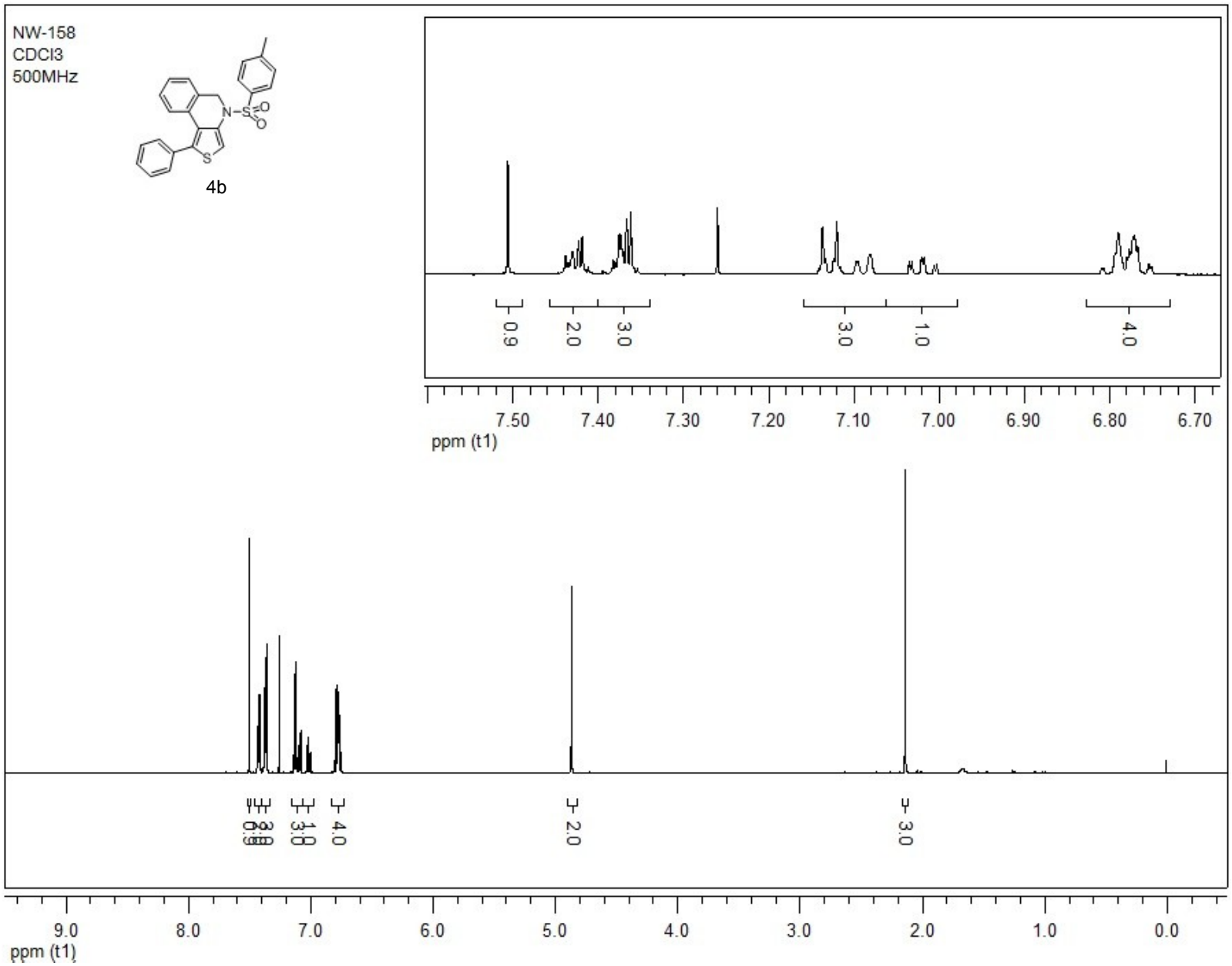

NW-2-070
CDCl3
500MHz
F
N
S
O
O
OMe
O
S
O
81j
1.0
2.0
5.1
2.1
2.1
7.30
7.20
7.10
7.00
6.90
6.80
6.70
6.60
ppm (t1)
1.8
2.0
5.1
2.1
2.1
1.9
3.0
3.0
5.0
0.0
ppm (t1)

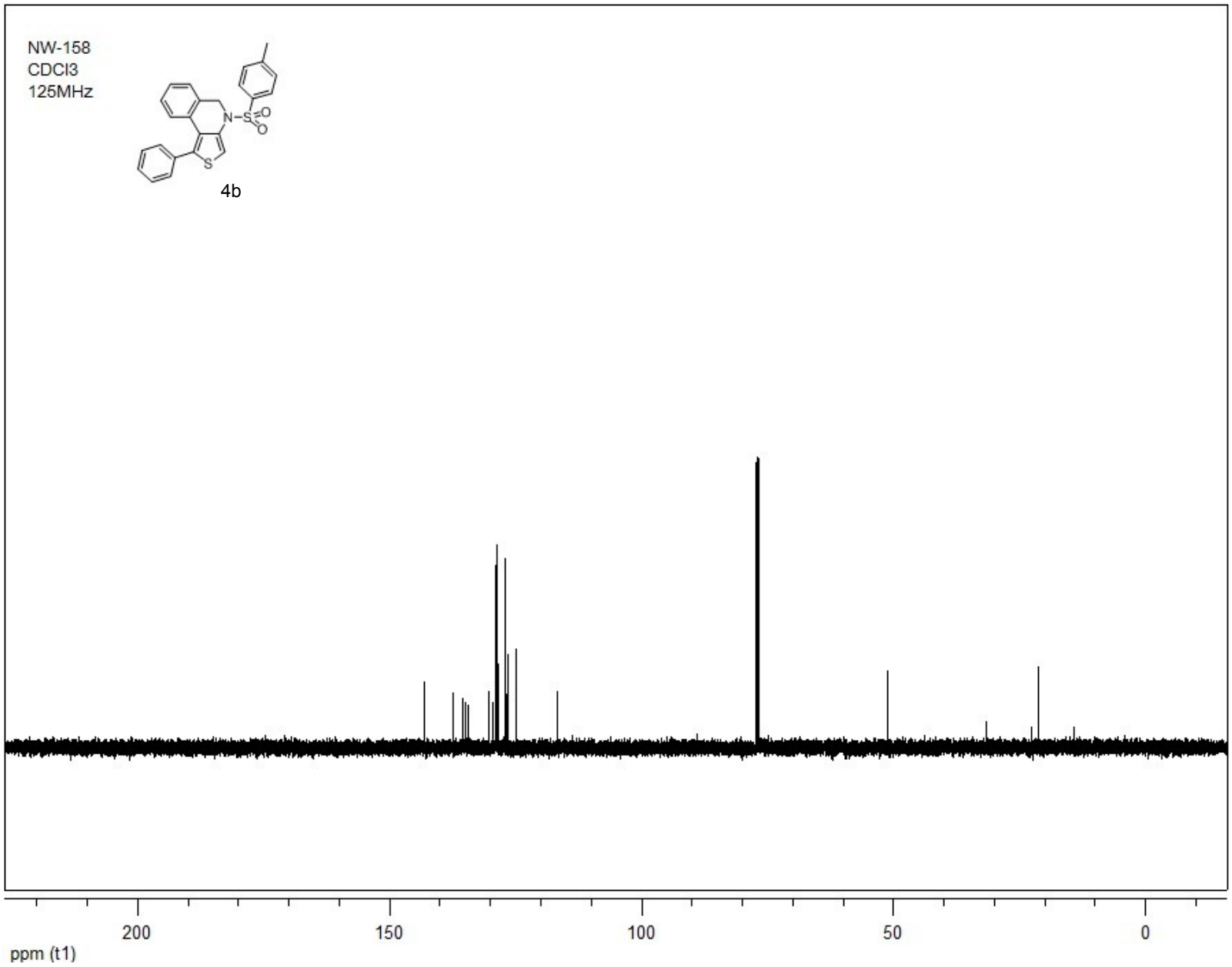

NW-2-070
CDCl3
125MHz
F
N
S
O
O
OMe
O
S
O
O
81j
200
150
100
50
0
ppm (t1)

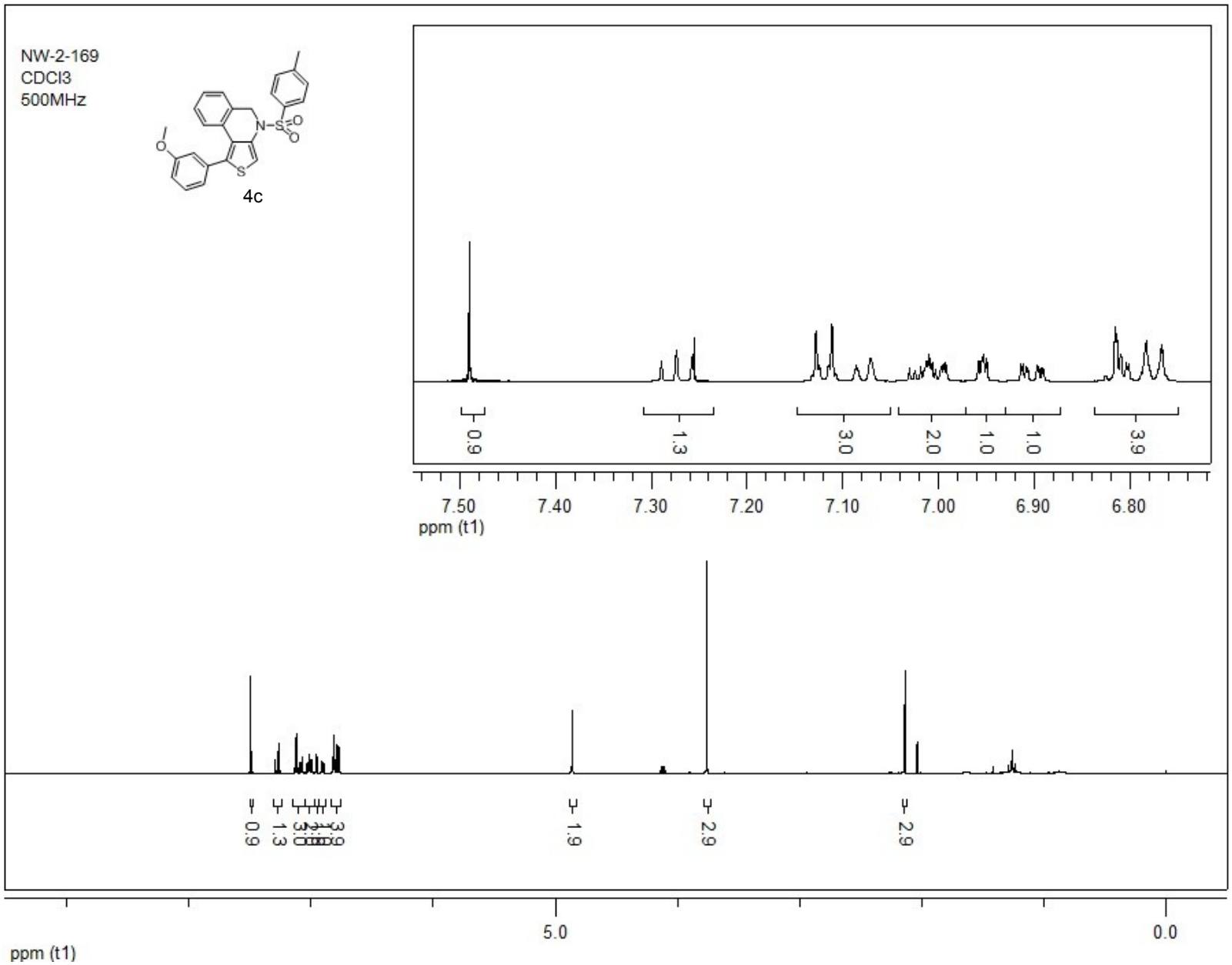

NW-3-043
CDCl3
500MHz
81b
0.9
4.8
1.0
2.0
7.60
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
0.9
4.8
1.0
2.0
1.9
2.9
2.9
5.0
0.0
ppm (t1)

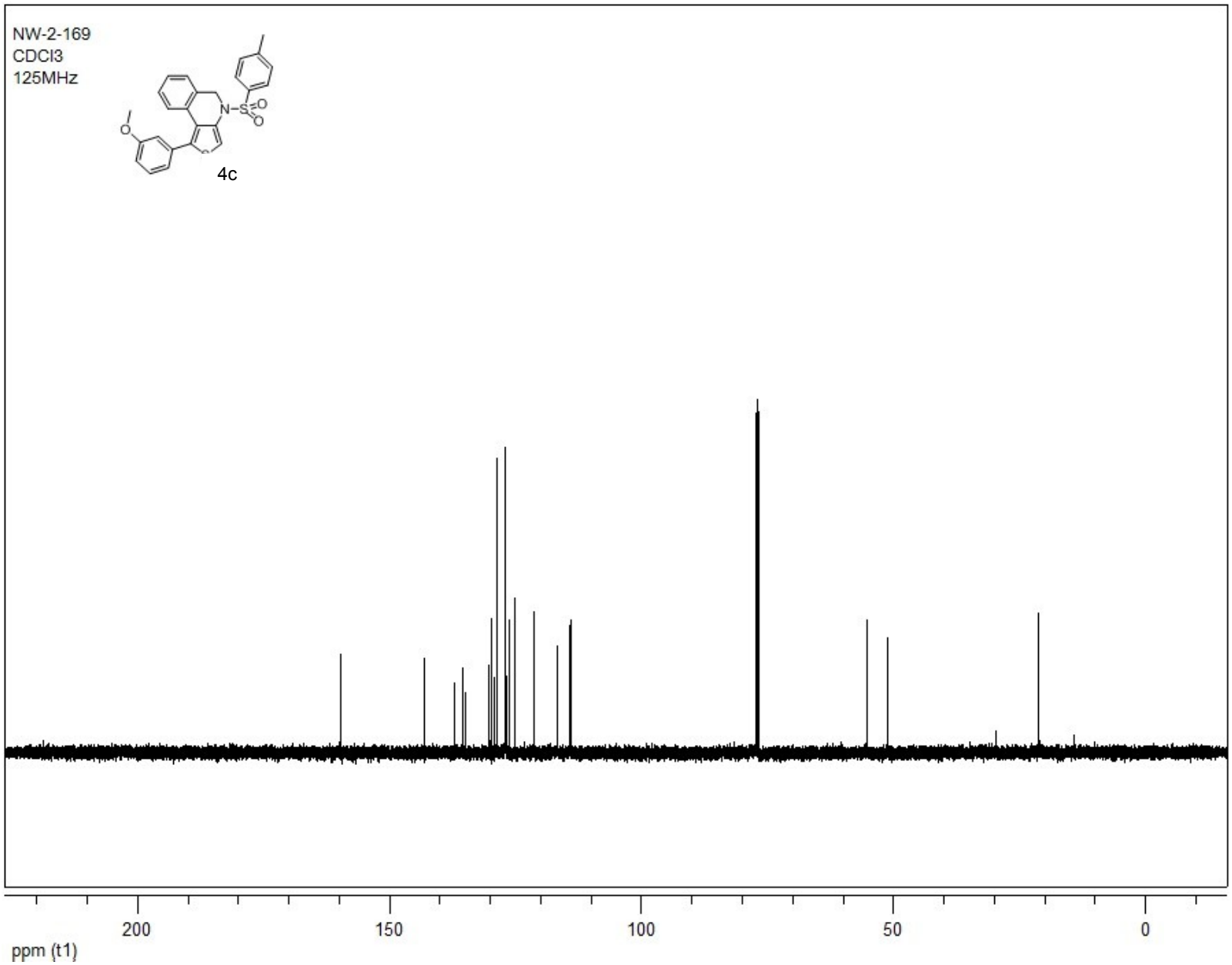


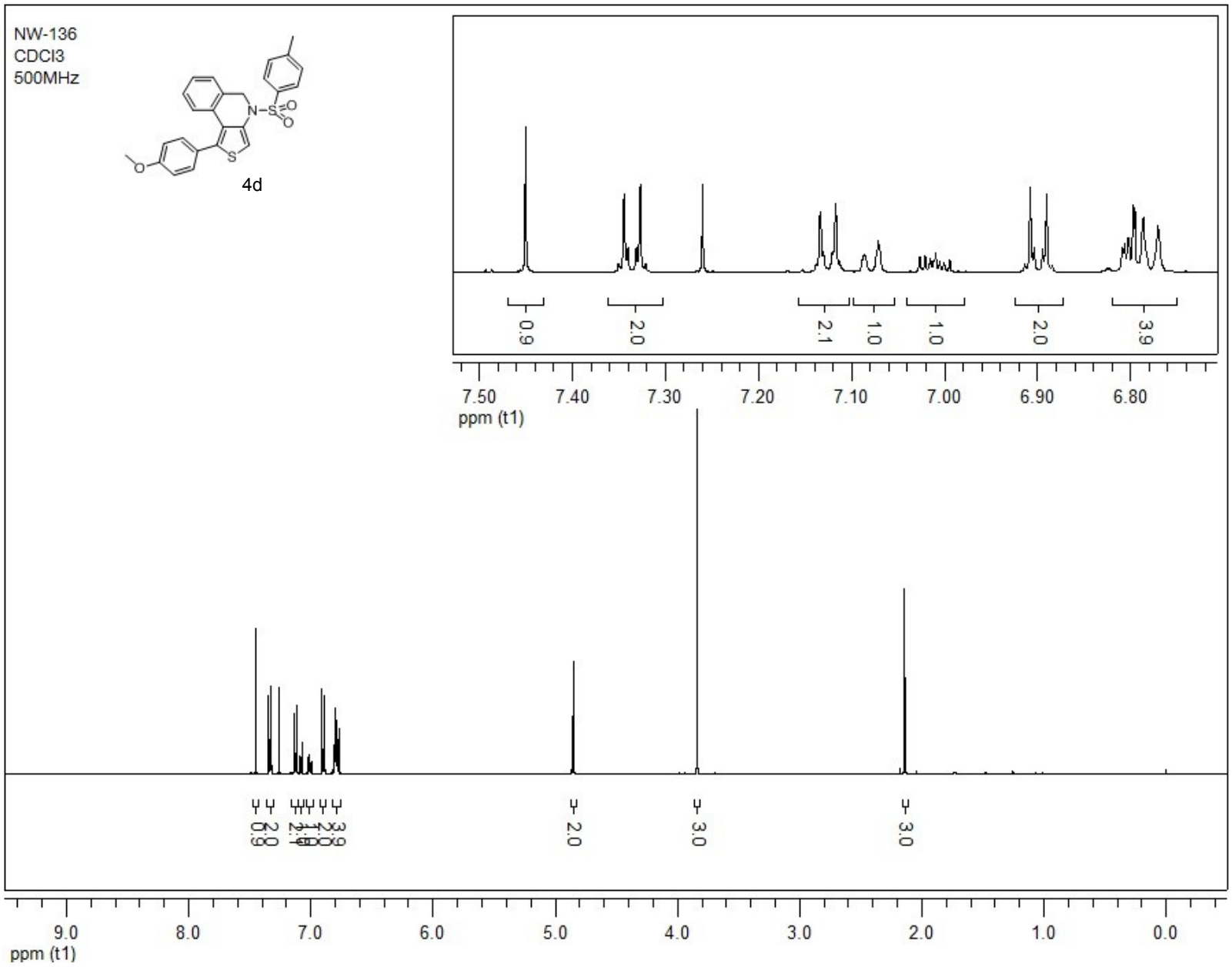
LV


NW-158
CDCl3
500MHz
4b
0.9
2.0
3.0
3.0
1.0
4.0
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
6.70
ppm (t1)
4.0
2.0
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

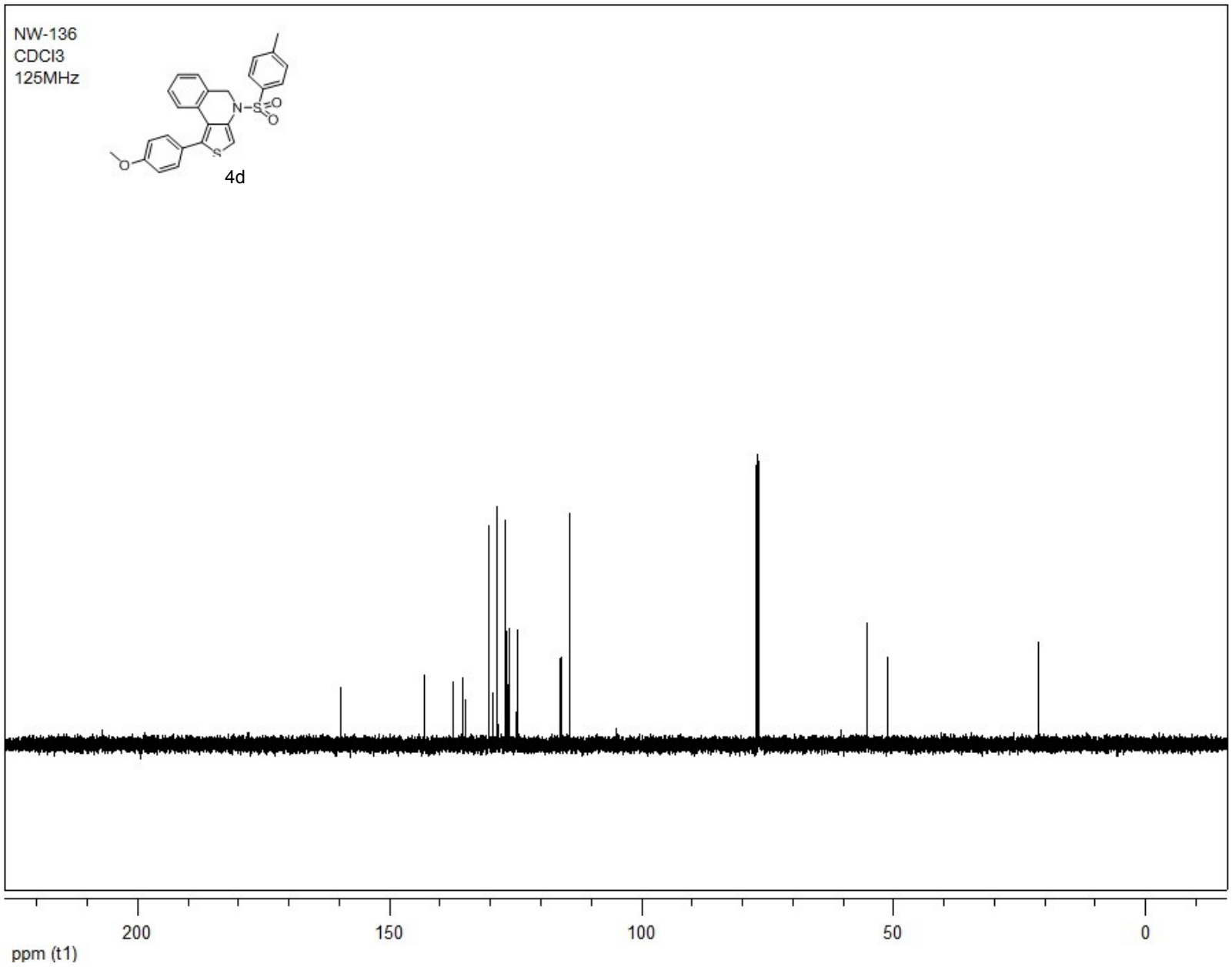

NW-158
CDCl3
125MHz
4b
200
150
100
50
0
ppm (t1)

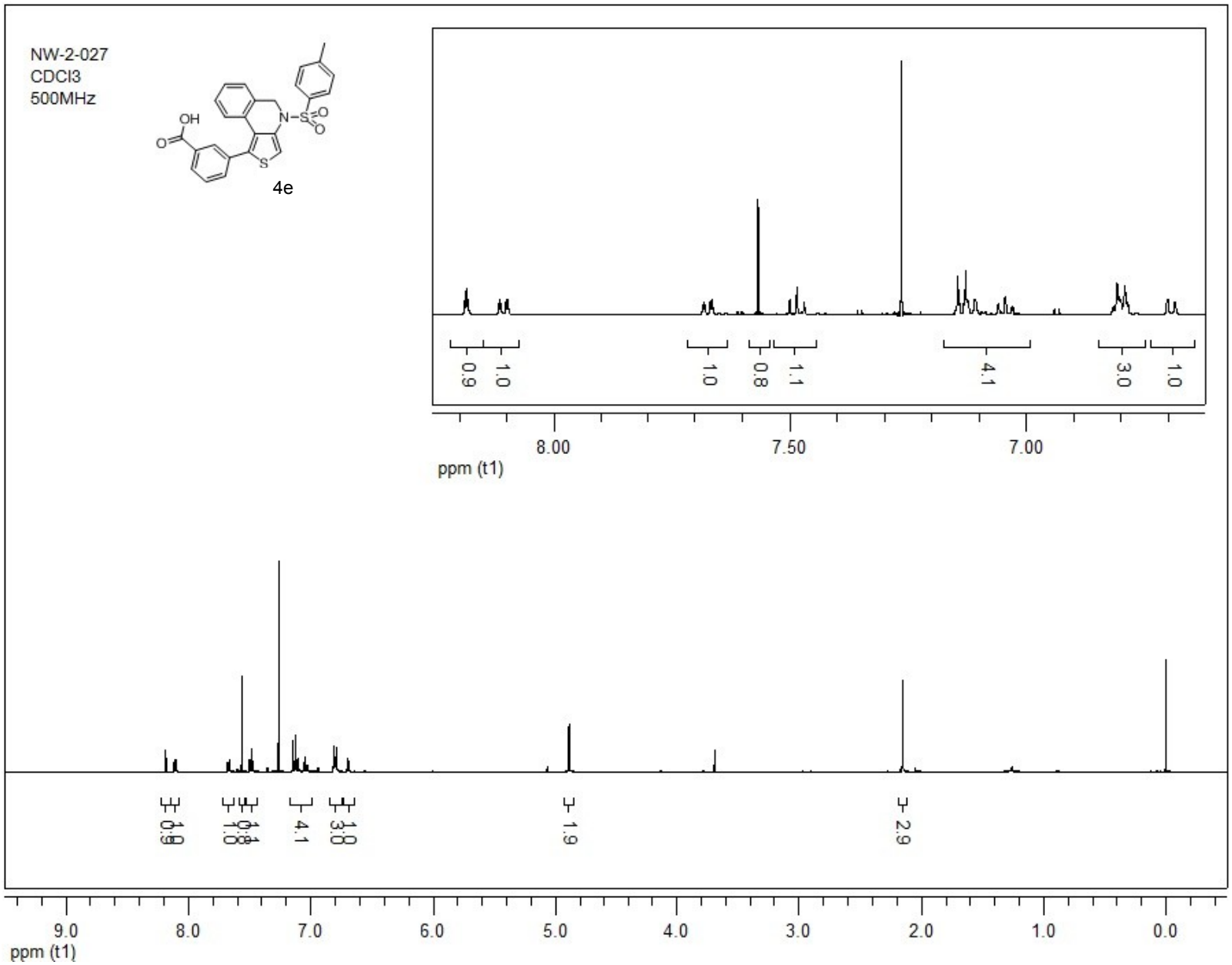

NW-2-169
CDCl3
500MHz
4c
0.9
1.3
3.0
2.0
1.0
1.0
3.9
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
0.9
1.3
3.0
3.9
1.9
2.9
2.9
5.0
0.0
ppm (t1)

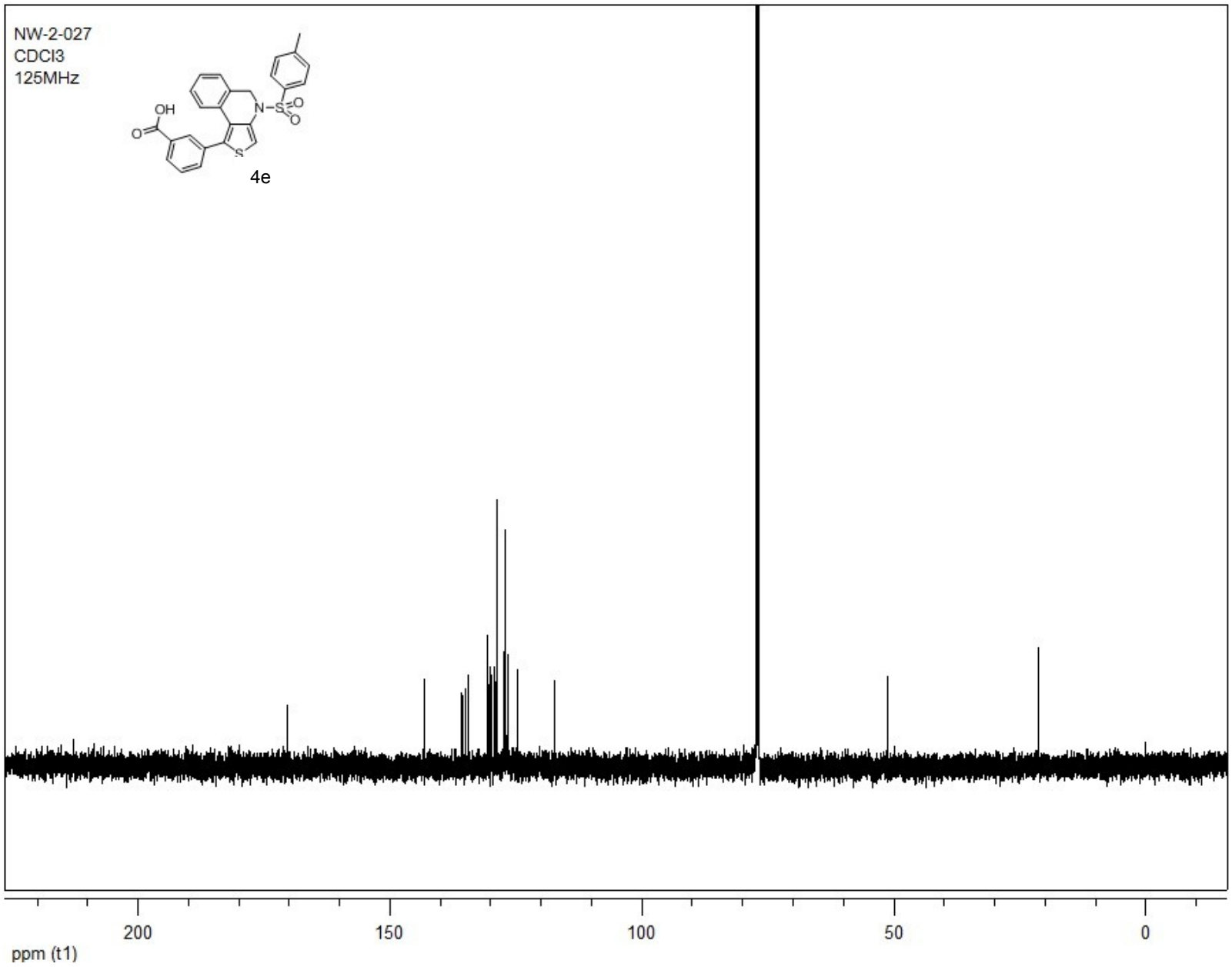

NW-2-169
CDCl3
125MHz
4c
200
150
100
50
0
ppm (t1)

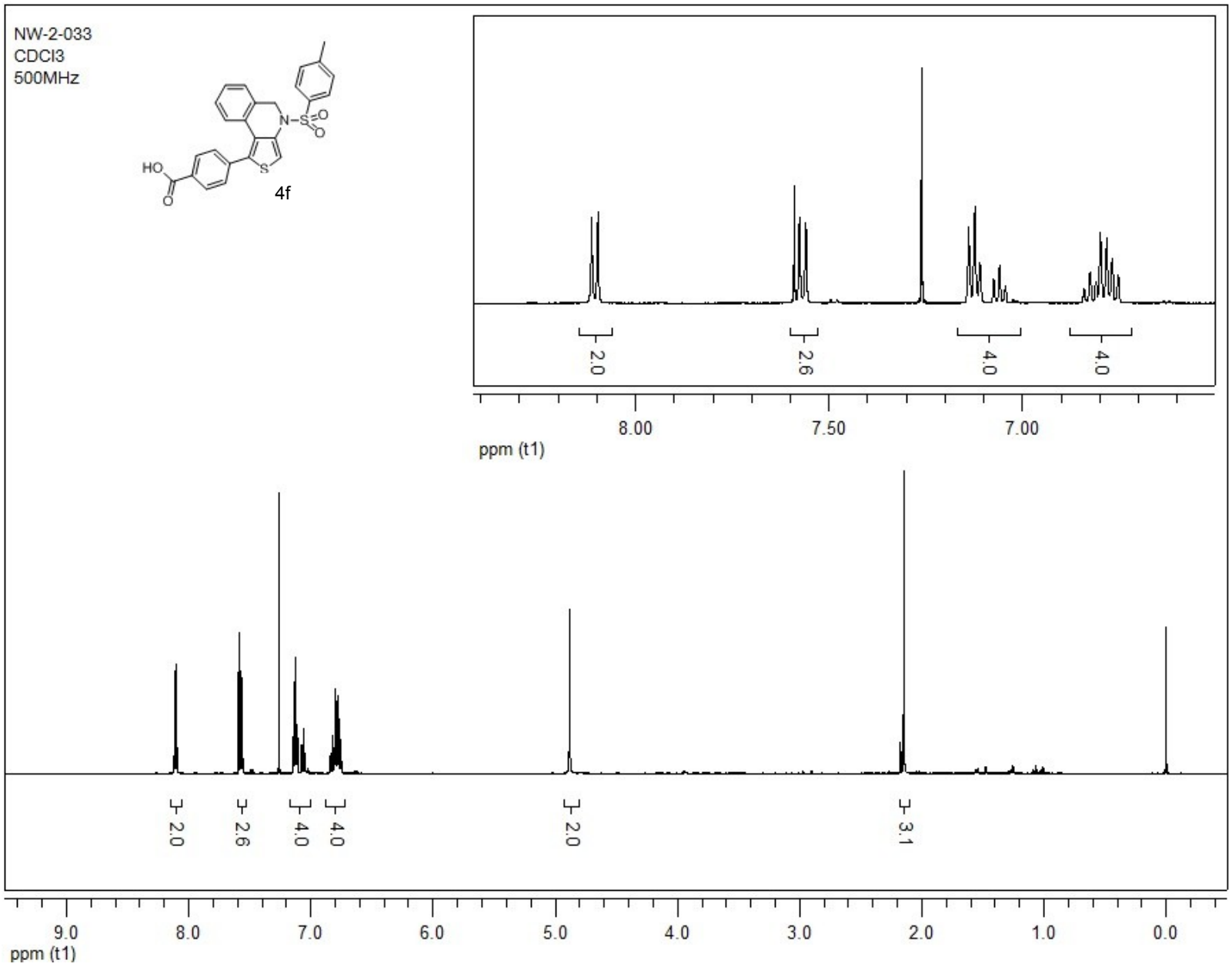

NW-136
CDCl3
500MHz
4d
0.9
2.0
2.1
1.0
1.0
2.0
3.9
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
2.0
3.0
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

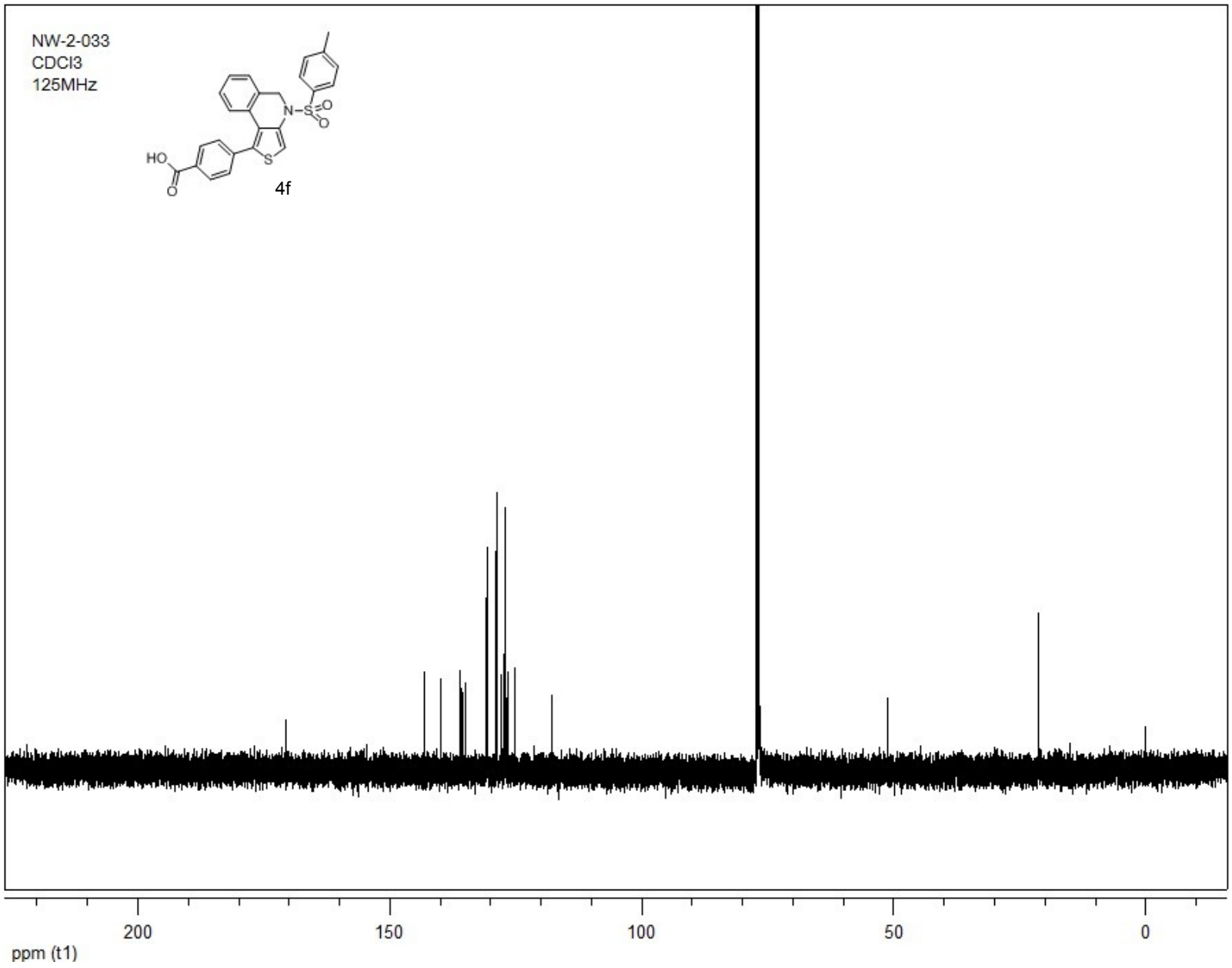
LX

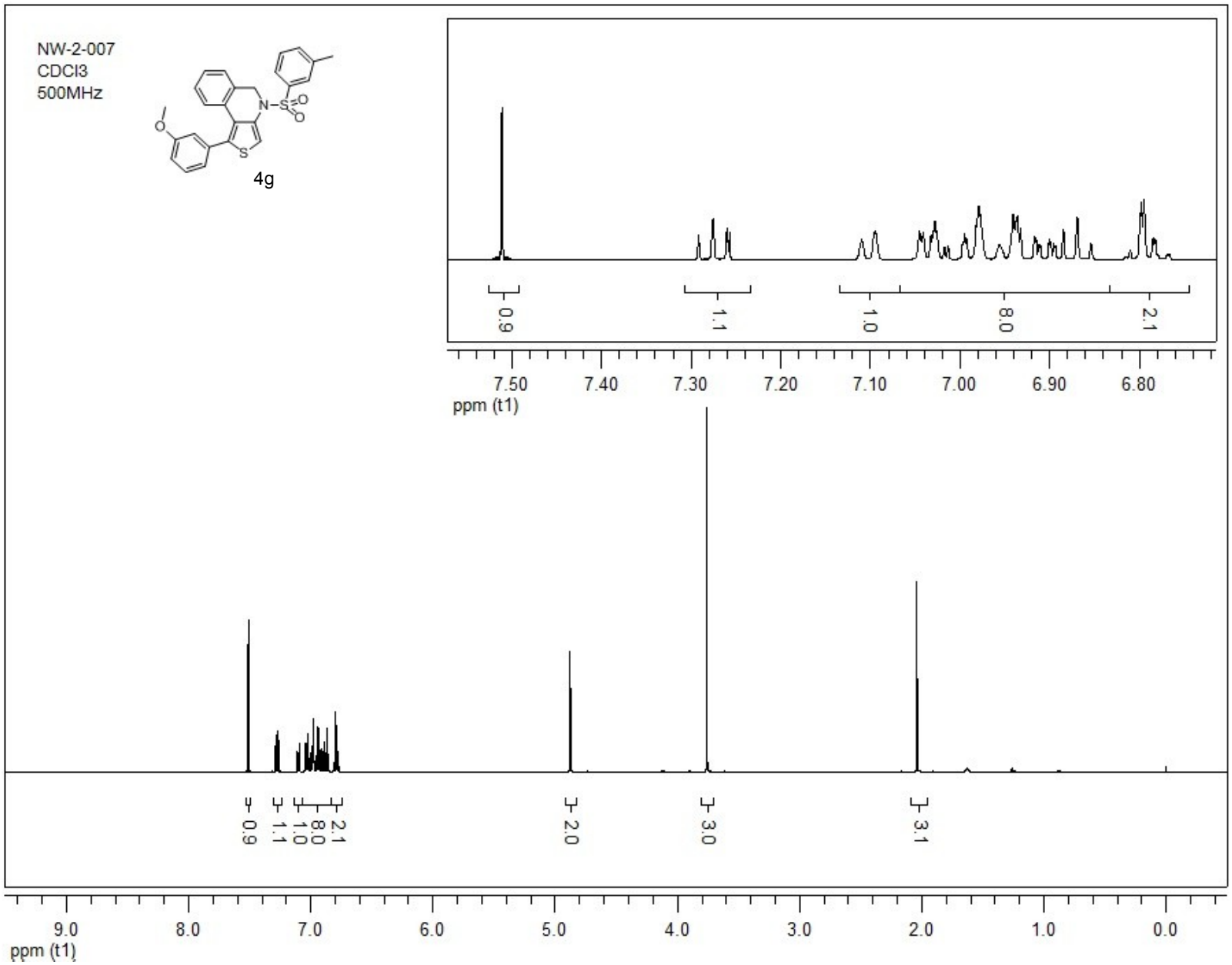

NW-136
CDCl3
125MHz
4d
200
150
100
50
0
ppm (t1)

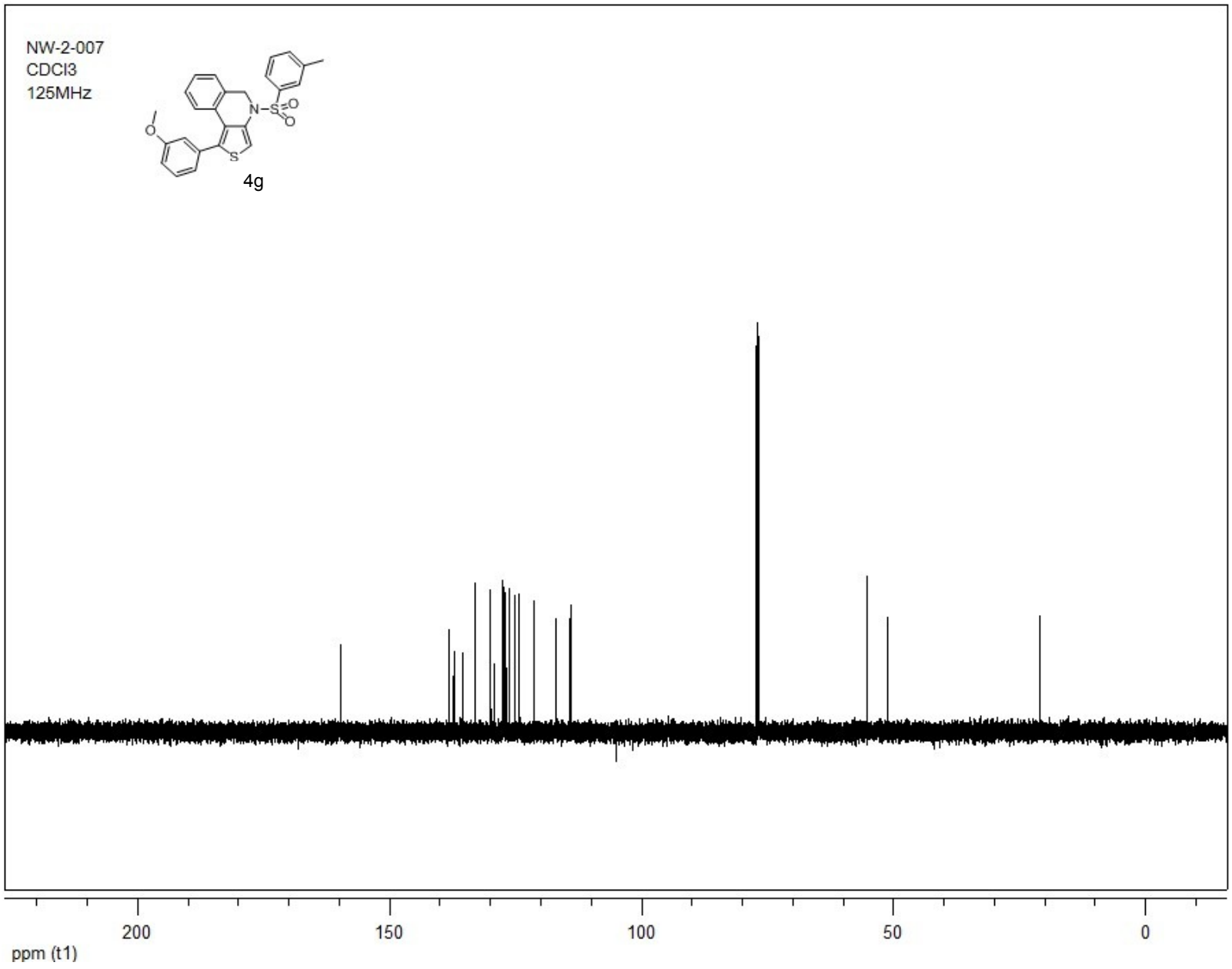

NW-2-027
CDCl3
500MHz
OH
O
N
S
O
O
S
4e
0.9
1.0
1.0
0.8
1.1
4.1
3.0
1.0
8.00
7.50
7.00
ppm (t1)
1.0
0.9
1.0
0.8
1.1
4.1
3.0
1.9
2.9
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

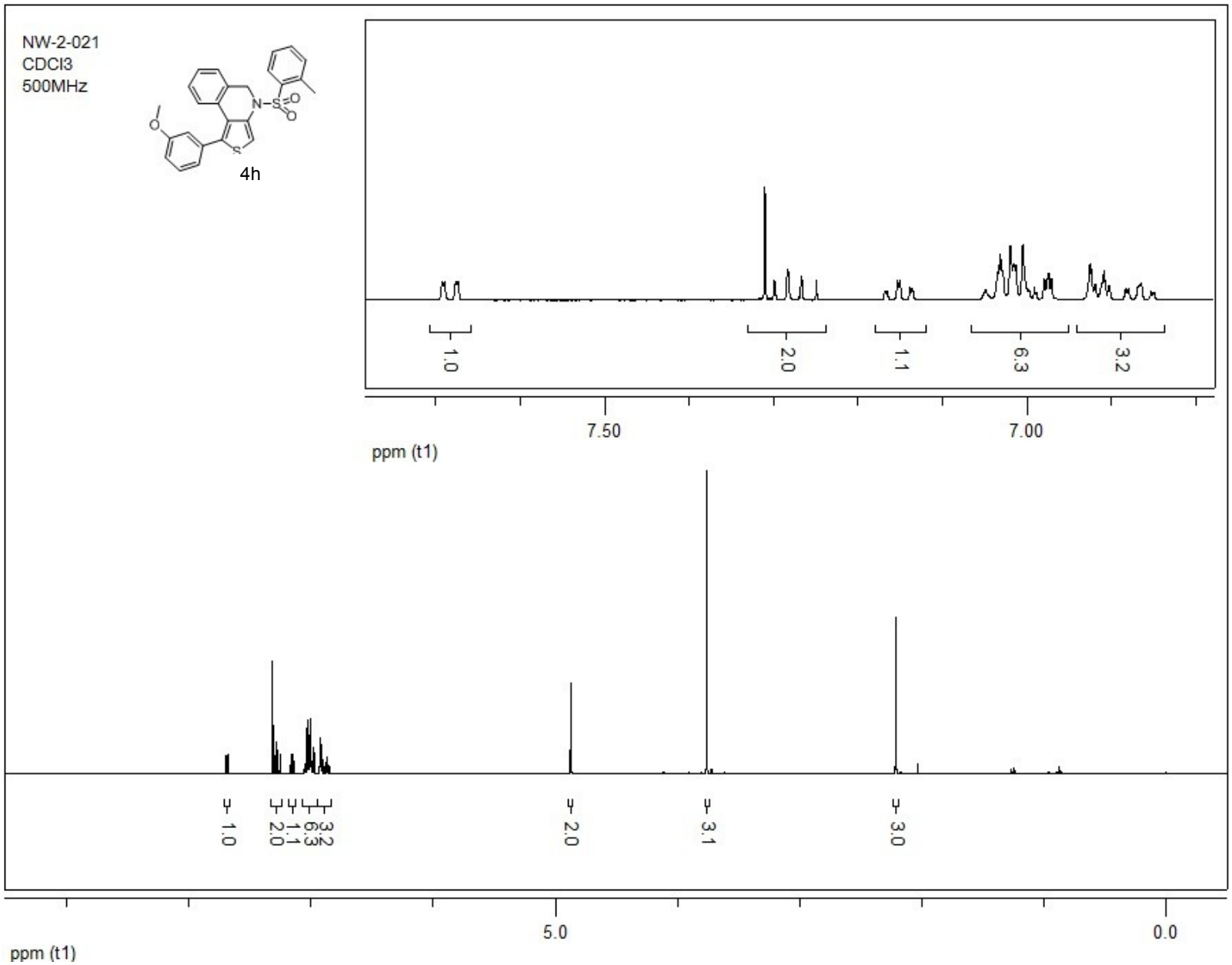

NW-2-027
CDCl3
125MHz
OH
O
N
S
O
O
S
4e
200
150
100
50
0
ppm (t1)

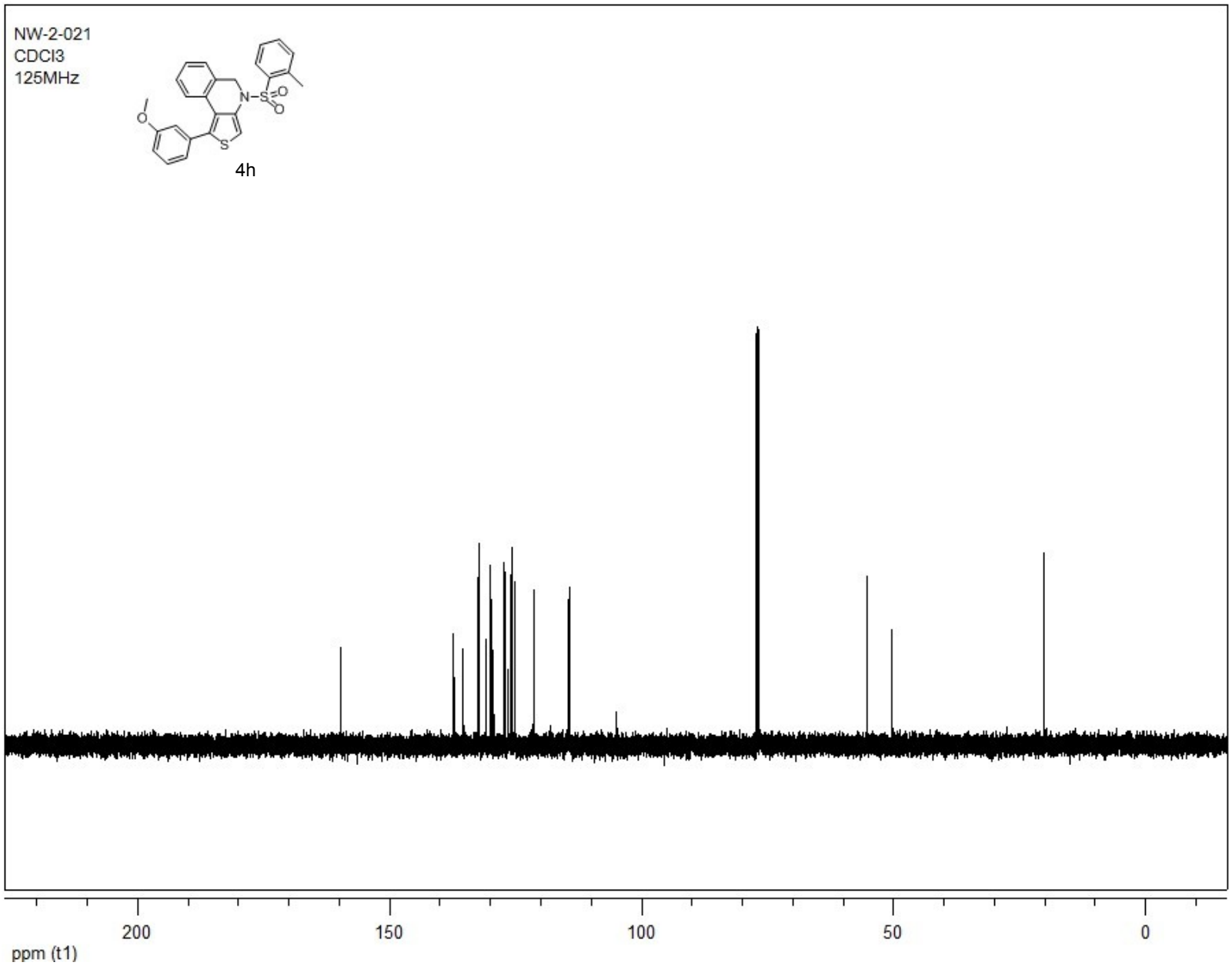

NW-2-033
CDCl3
500MHz
HO
O
O
N
S
O
O
S
4f
2.0
2.6
4.0
4.0
8.00
7.50
7.00
ppm (t1)
2.0
2.6
4.0
4.0
2.0
3.1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

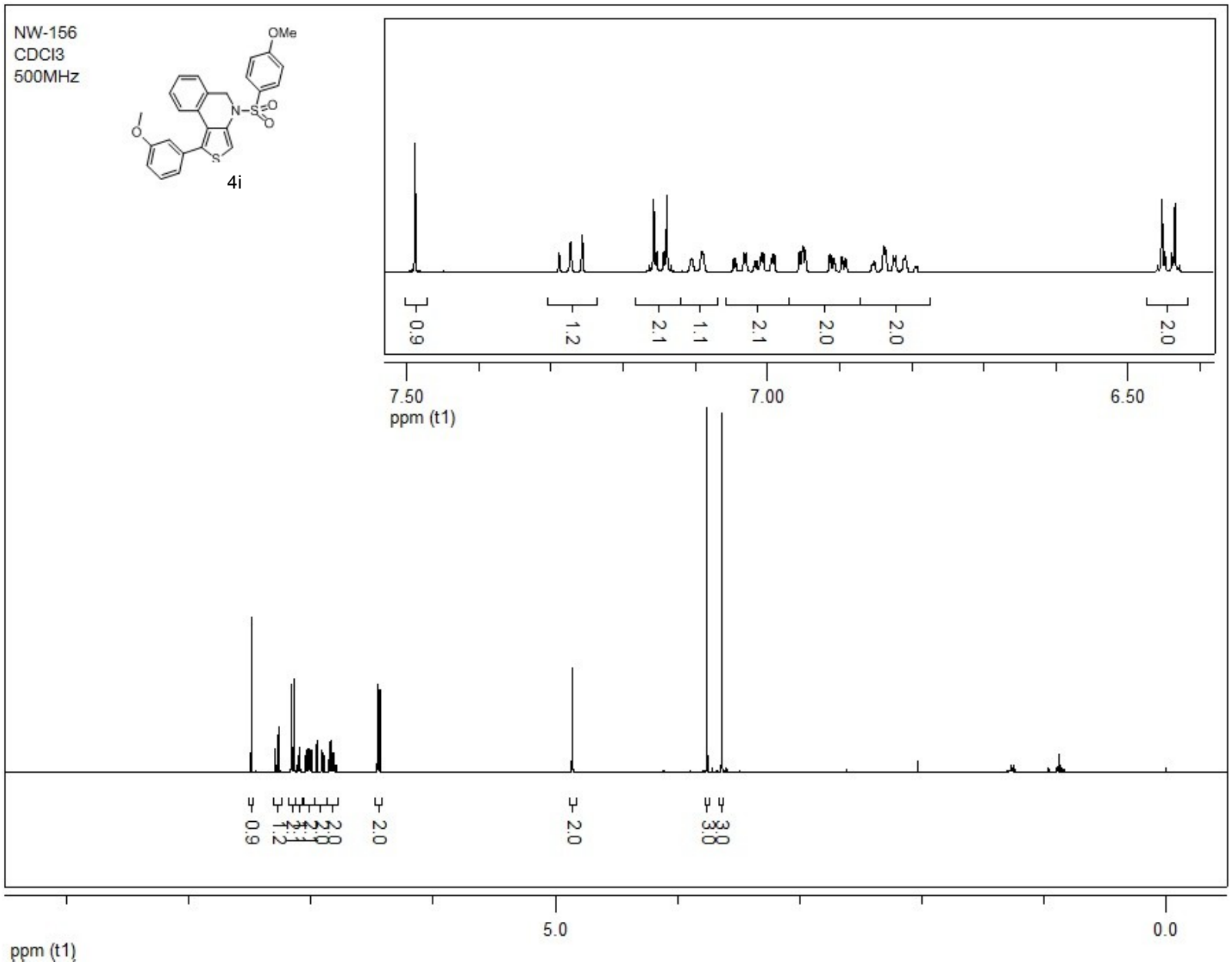

NW-2-033
CDCl3
125MHz
HO
O
S
N
O
O
4f
200
150
100
50
0
ppm (t1)

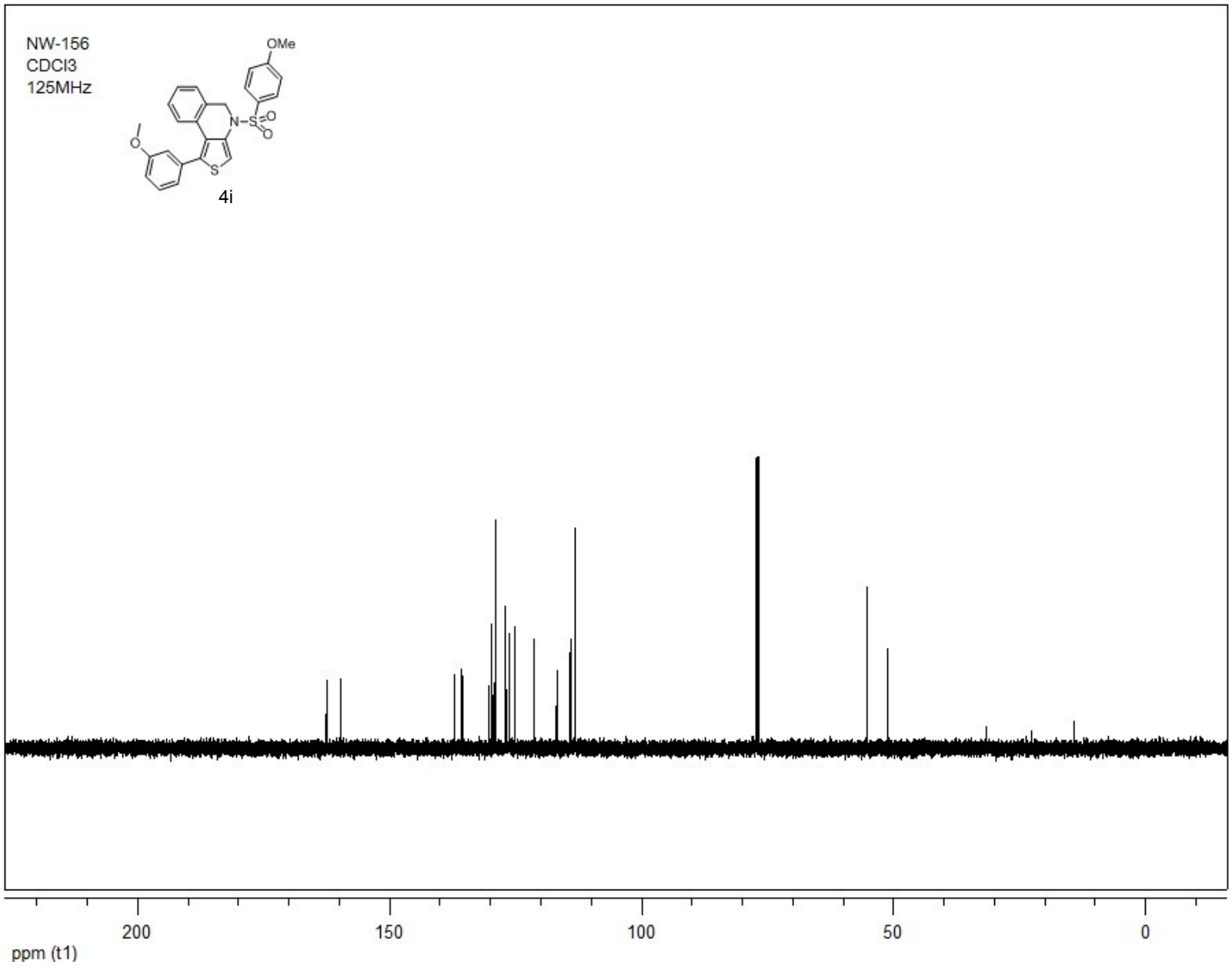

NW-2-007
CDCl3
500MHz
4g
0.9
1.1
1.0
8.0
2.1
7.50
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
0.9
1.1
1.0
8.0
2.1
2.0
3.0
3.1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

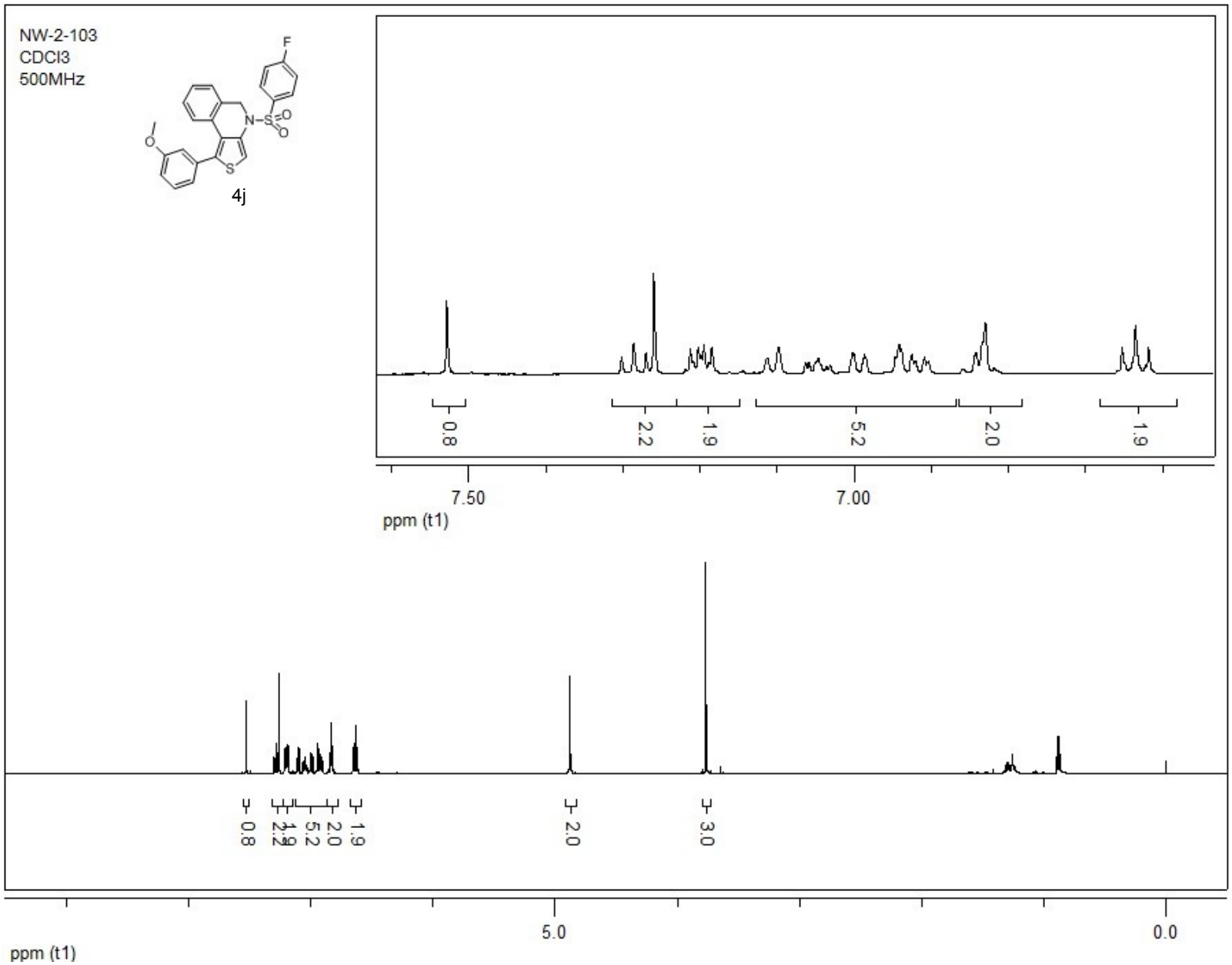

NW-2-007
CDCl3
125MHz
4g
200
150
100
50
0
ppm (t1)

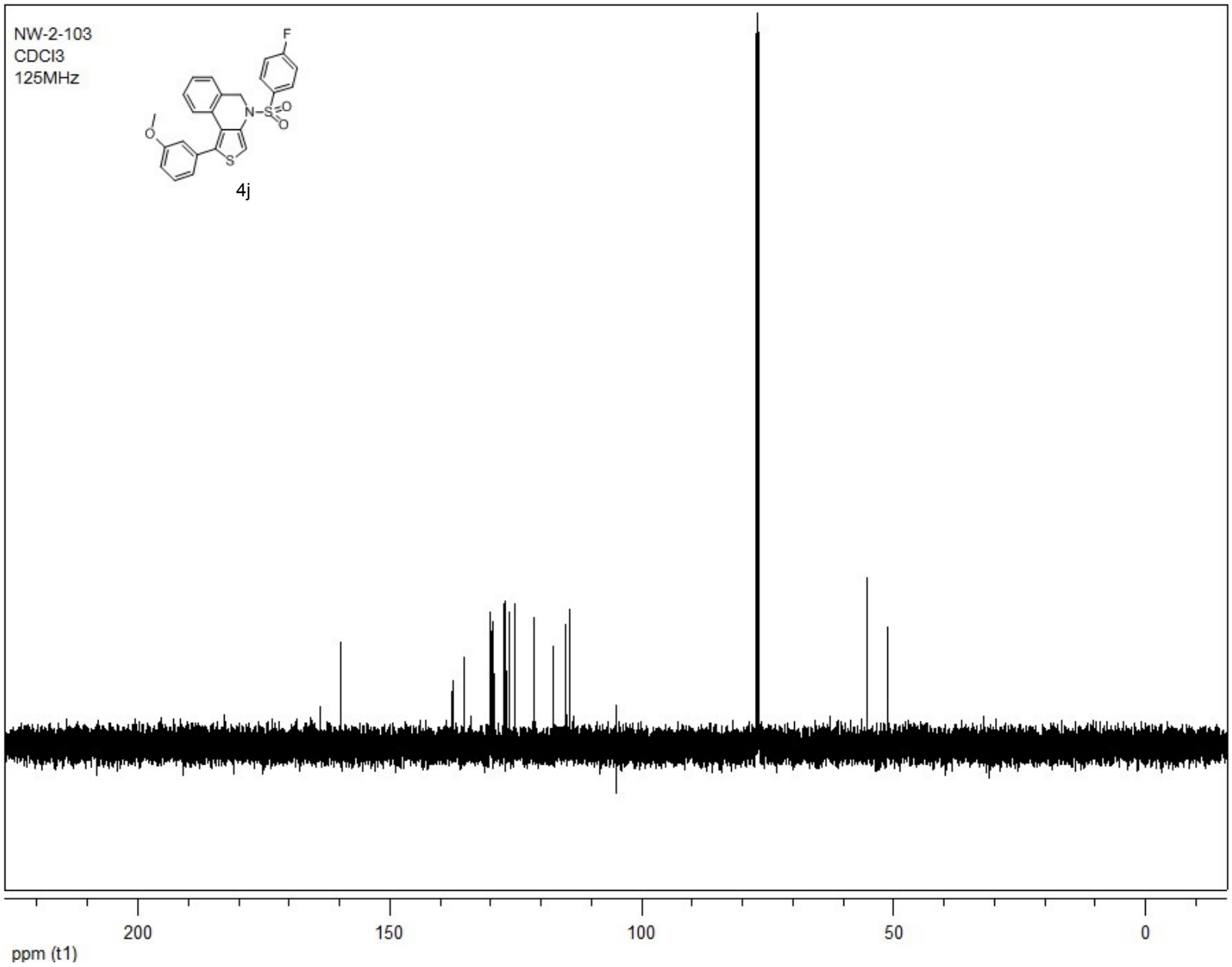

NW-2-021
CDCl3
500MHz
4h
1.0
2.0
1.1
6.3
3.2
7.50
7.00
ppm (t1)
1.0
2.0
1.1
6.3
3.2
2.0
3.1
3.0
5.0
0.0
ppm (t1)

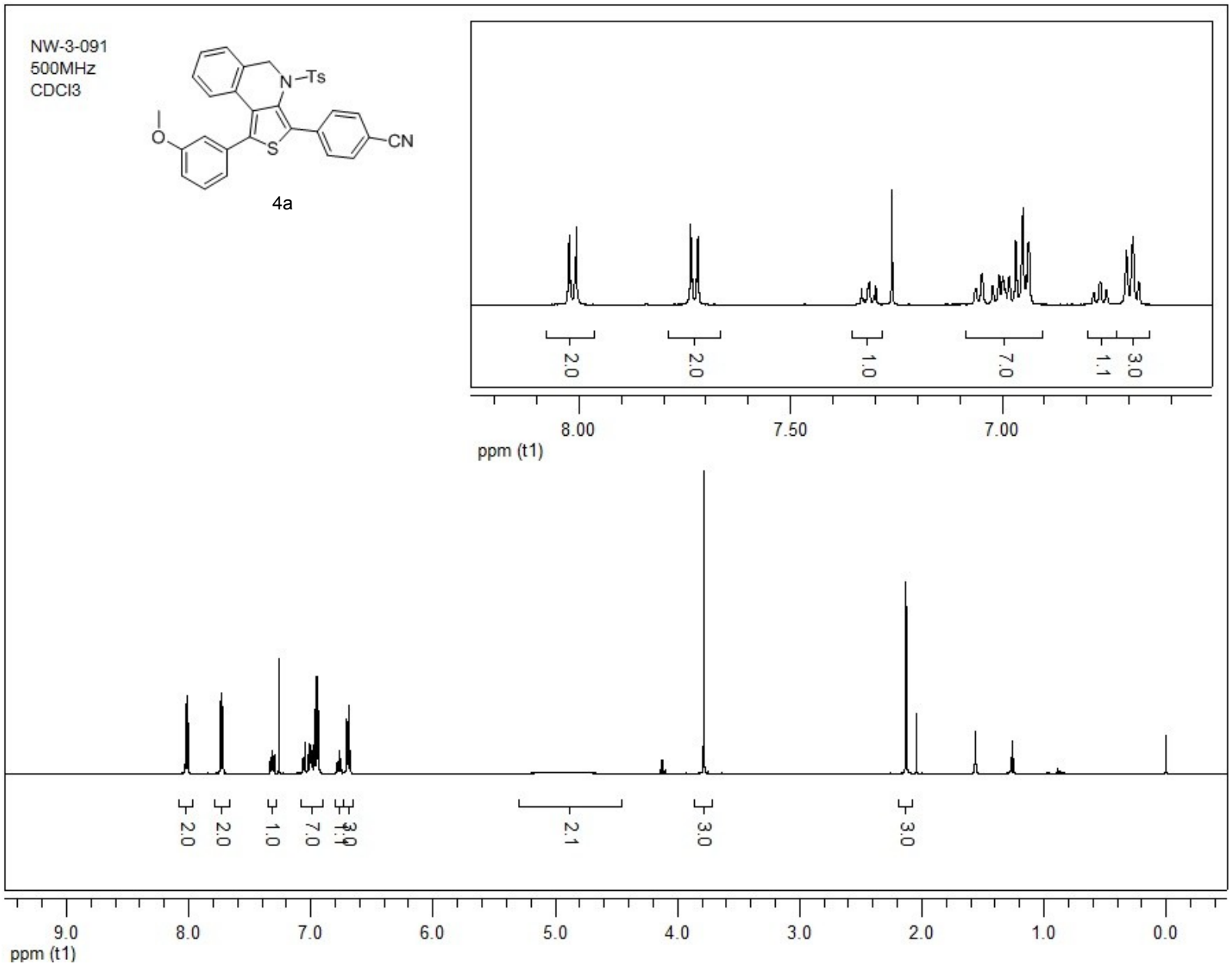

NW-2-021
CDCl3
125MHz
4h
200
150
100
50
0
ppm (t1)

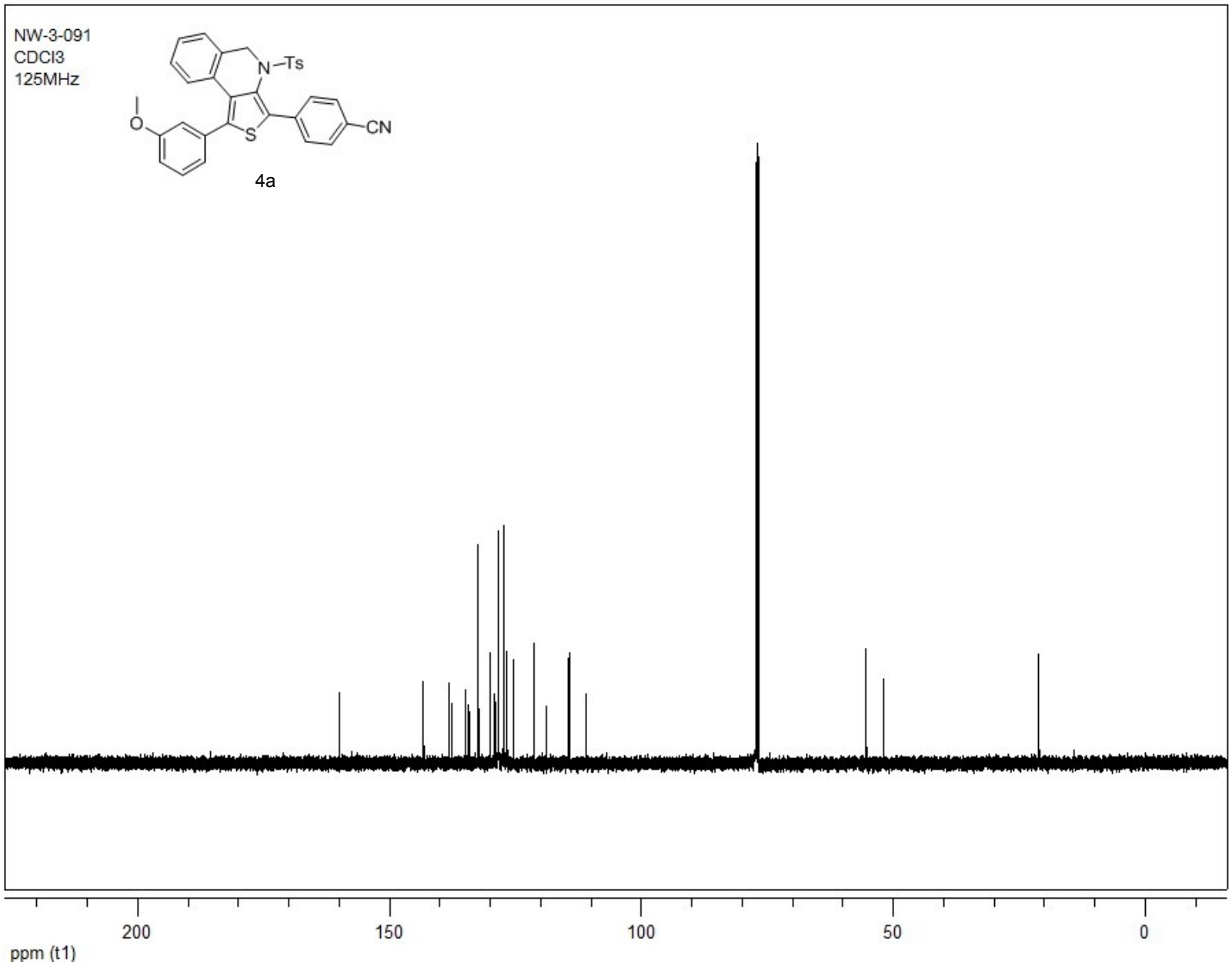

NW-156
CDCl3
500MHz
OMe
N
S
O
O
O
S
4i
0.9
1.2
2.1
1.1
2.1
2.0
2.0
2.0
7.50
7.00
6.50
ppm (t1)
0.9
1.2
2.0
2.0
3.0
5.0
0.0
ppm (t1)

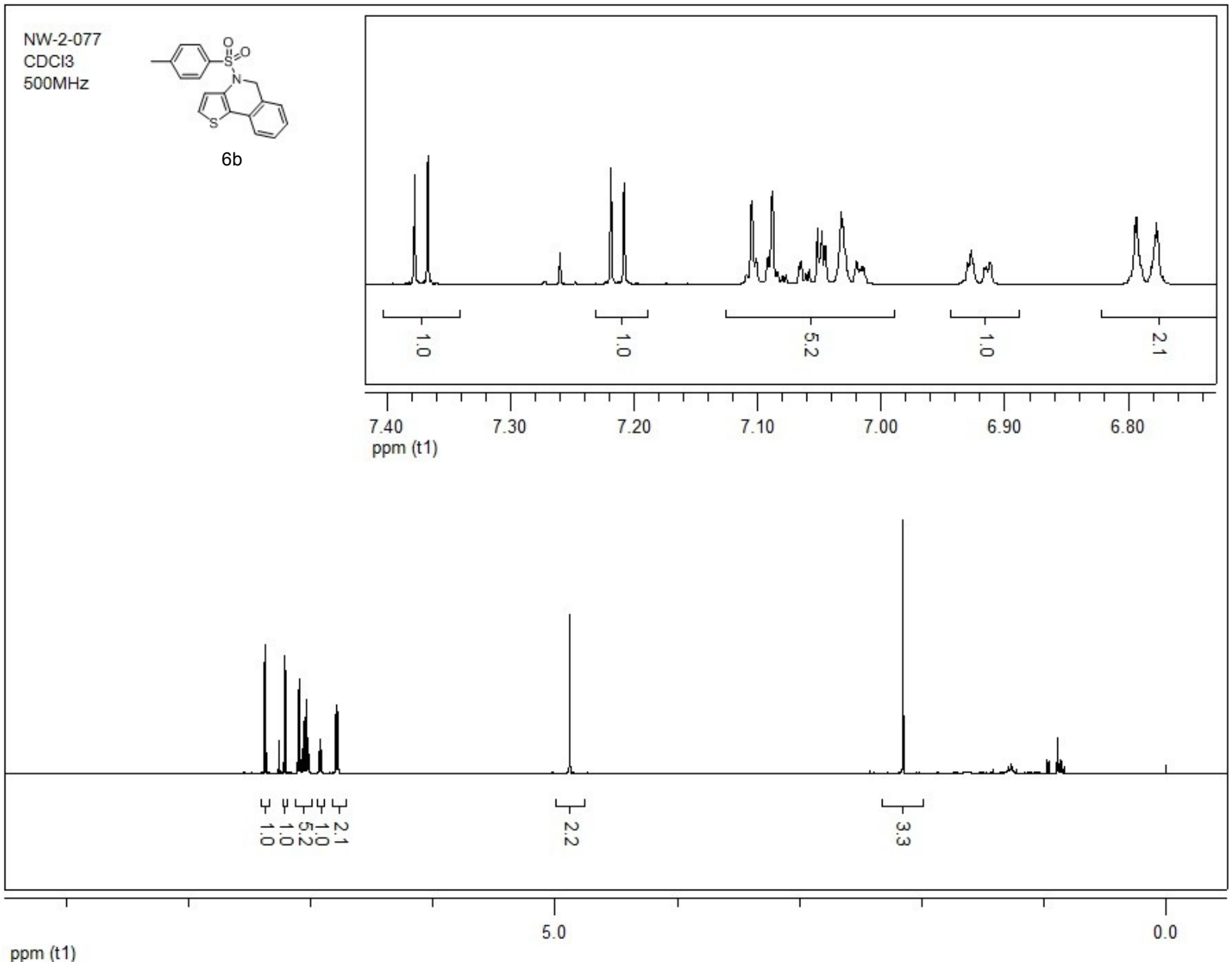

NW-156
CDCl3
125MHz
OMe
O
N
S
O
O
S
4i
200
150
100
50
0
ppm (t1)

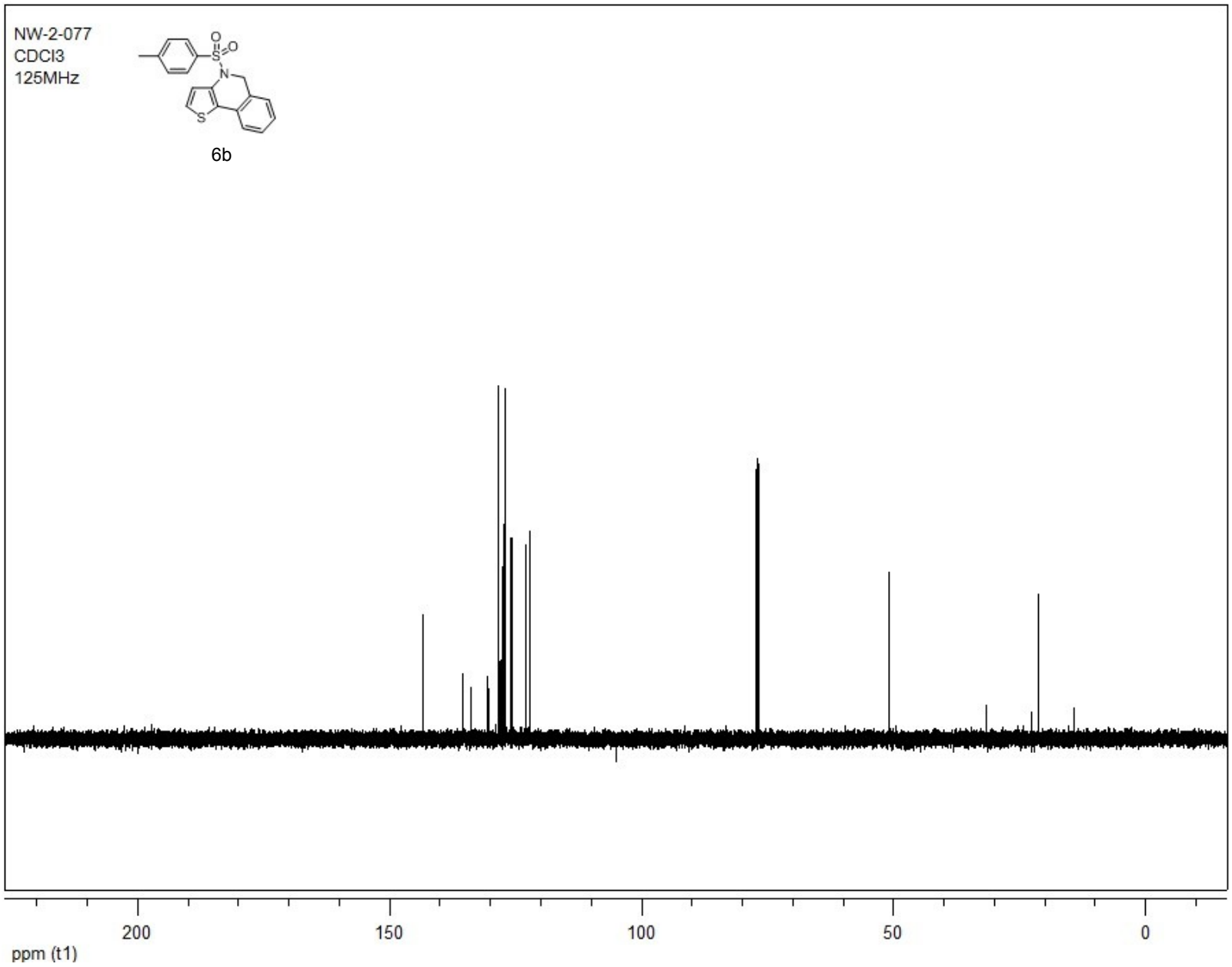

NW-2-103
CDCl3
500MHz
F
O
N
S
O
O
S
4j
0.8
2.2
1.9
5.2
2.0
1.9
7.50
7.00
ppm (t1)
0.8
2.2
1.9
5.2
2.0
1.9
2.0
3.0
5.0
0.0
ppm (t1)

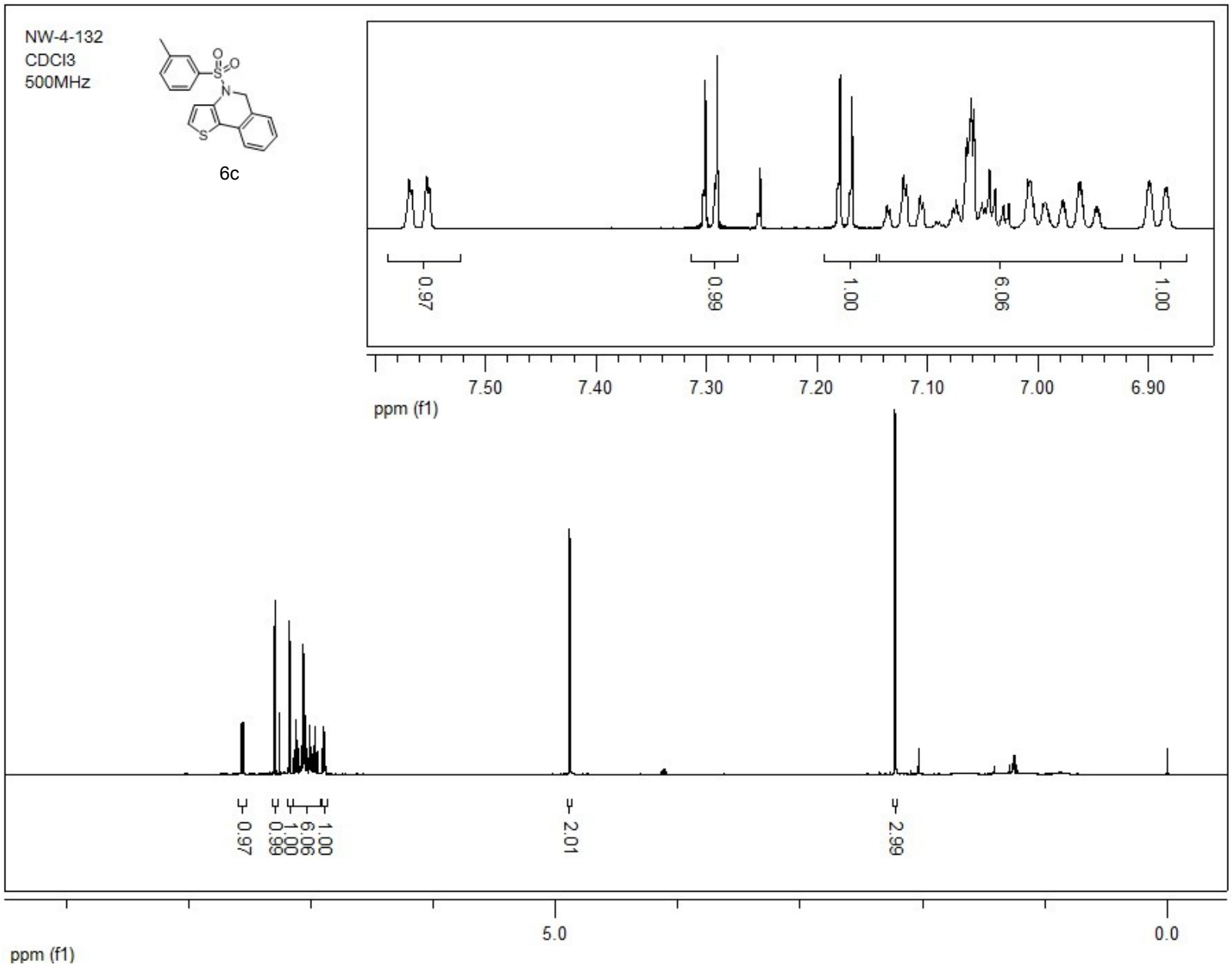

NW-2-103
CDCl3
125MHz
F
O
N
S
O
O
S
4j
200
150
100
50
0
ppm (t1)

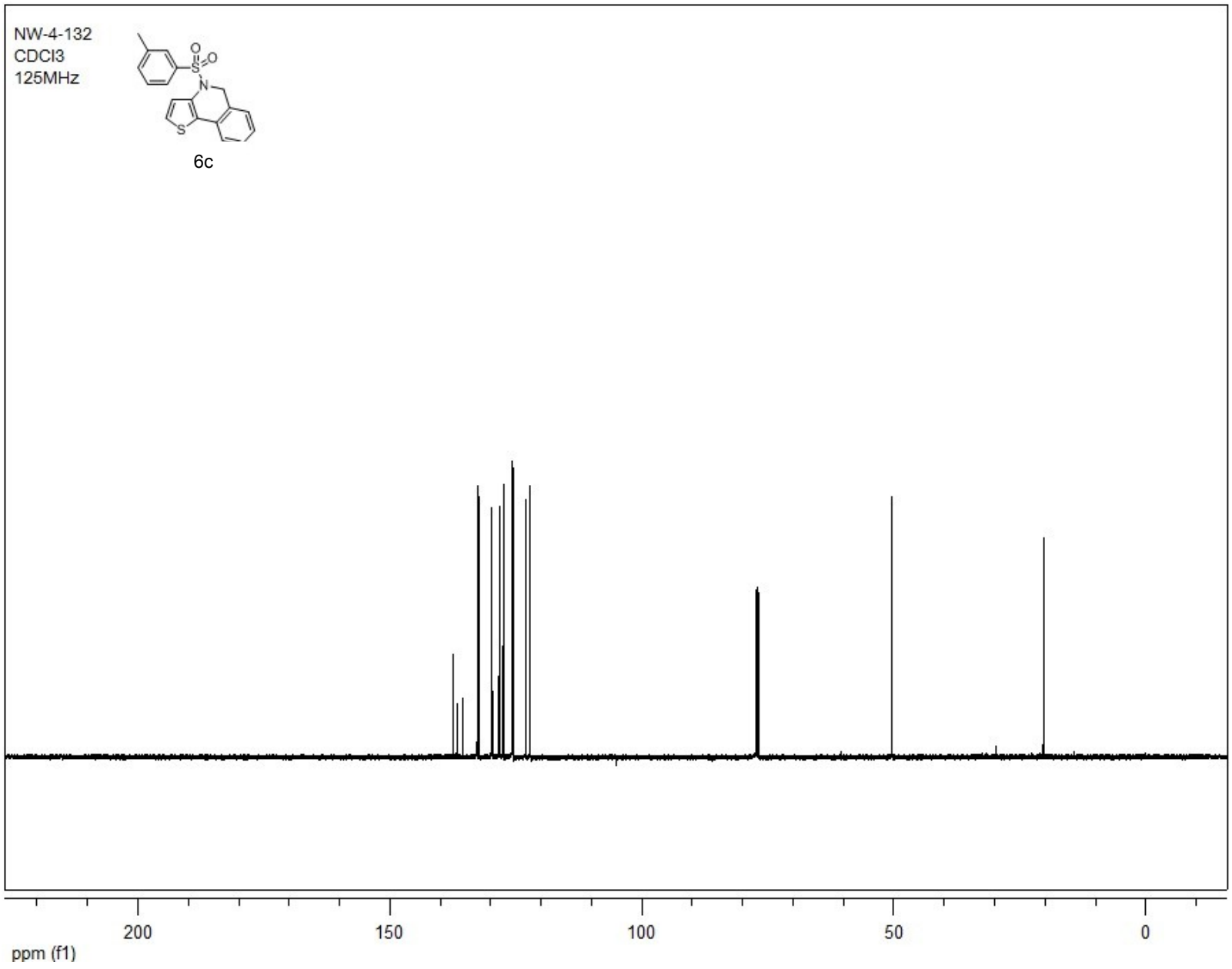

NW-3-091
500MHz
CDCl3
N–Ts
O
S
CN
4a
2.0
2.0
1.0
7.0
1.1
3.0
8.00
7.50
7.00
ppm (t1)
2.0
2.0
1.0
7.0
1.1
3.0
2.1
3.0
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

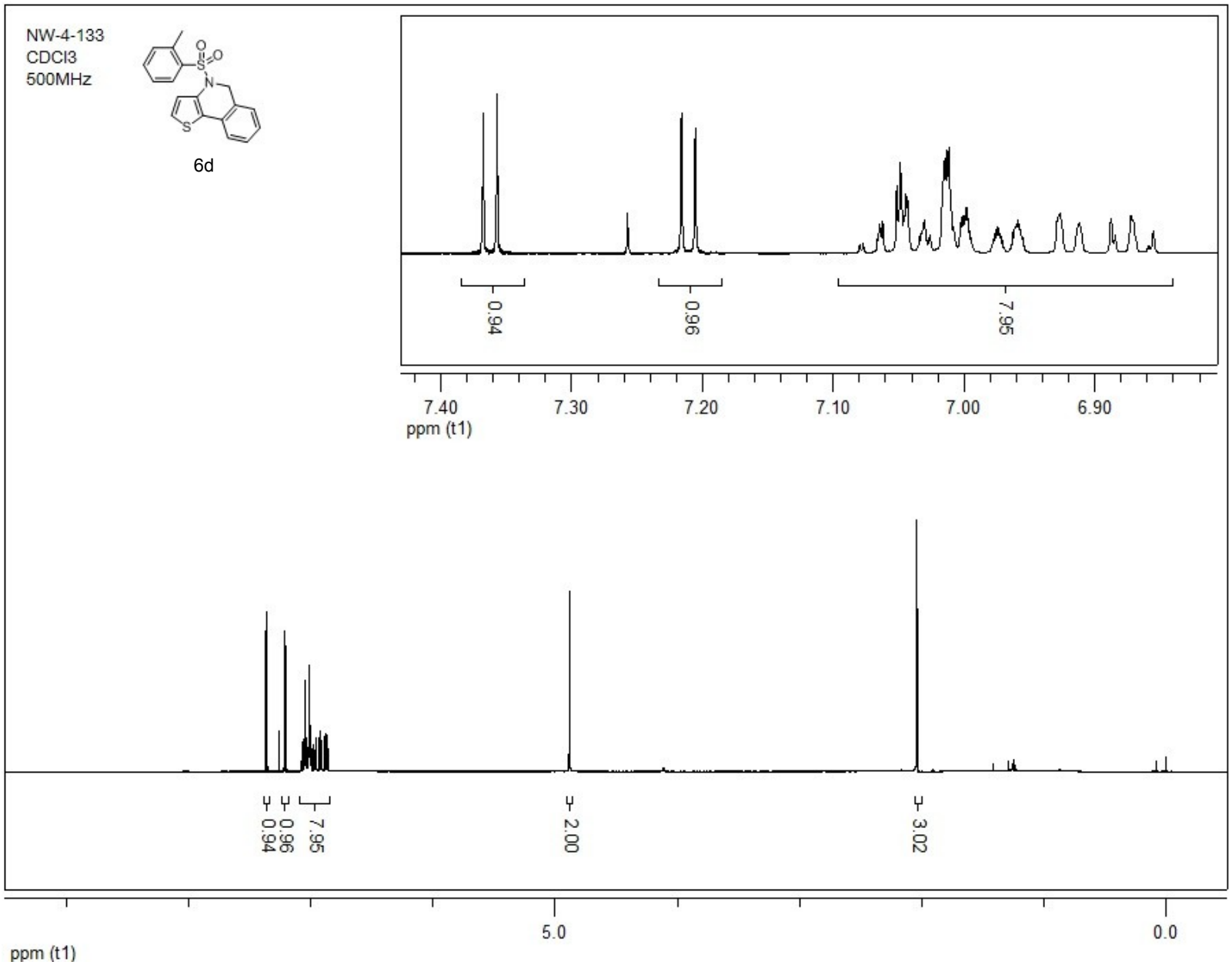

NW-3-091
CDCl3
125MHz
N
Ts
O
S
CN
4a
200
150
100
50
0
ppm (t1)

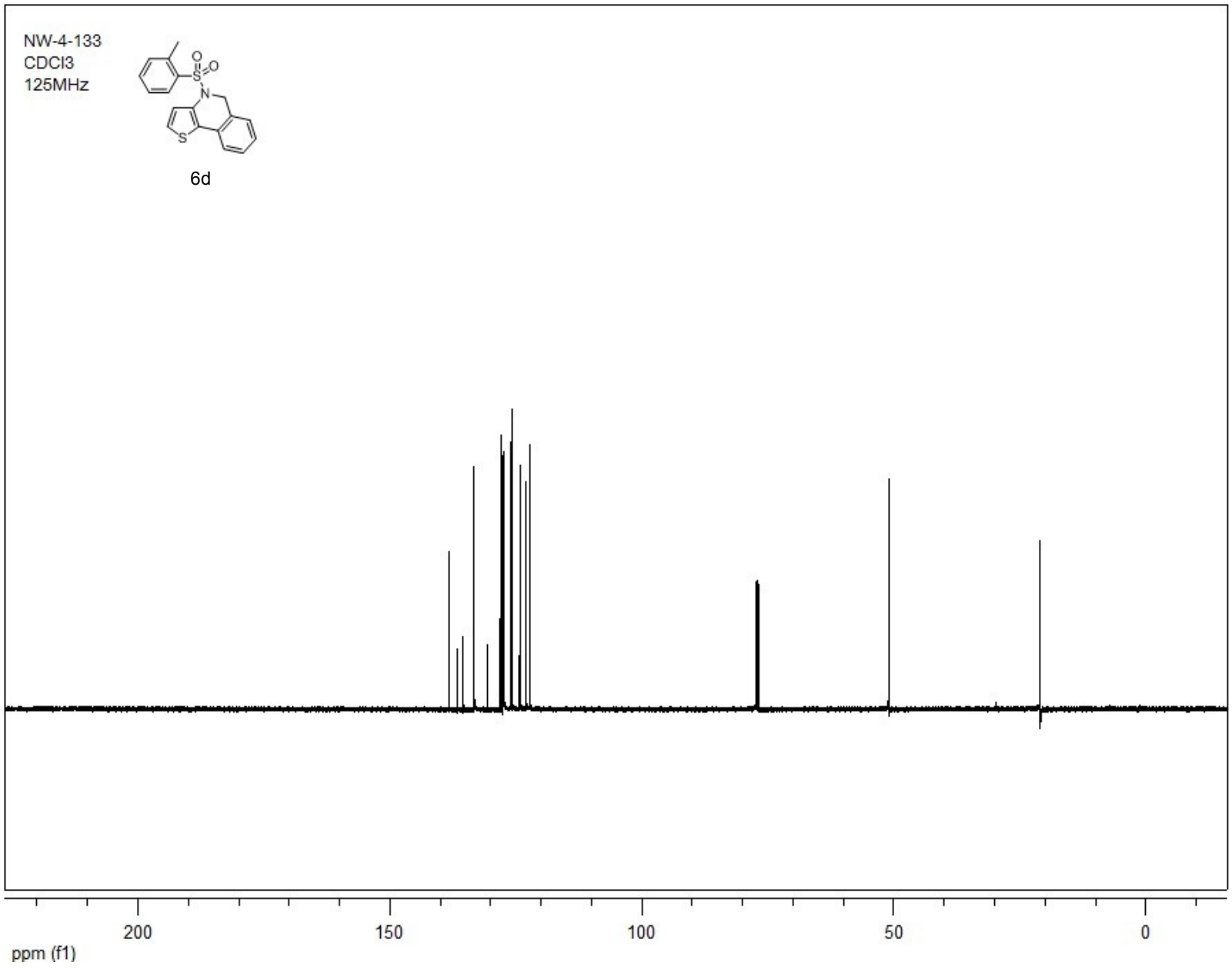

NW-2-077
CDCl3
500MHz
6b
1.0
1.0
5.2
1.0
2.1
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
1.0
1.0
5.2
1.0
2.1
2.2
3.3
5.0
0.0
ppm (t1)

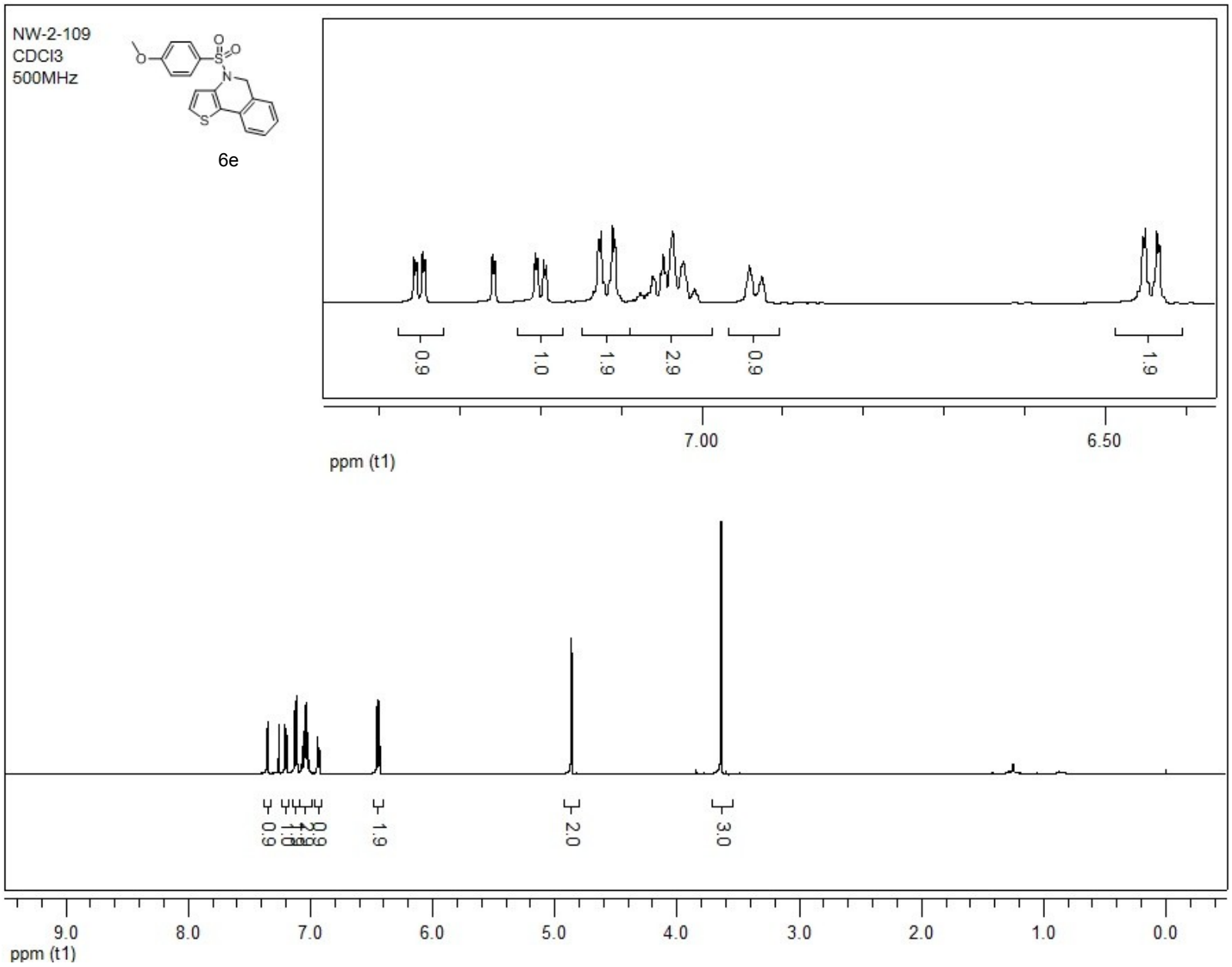

NW-2-077
CDCl3
125MHz
6b
200
150
100
50
0
ppm (t1)

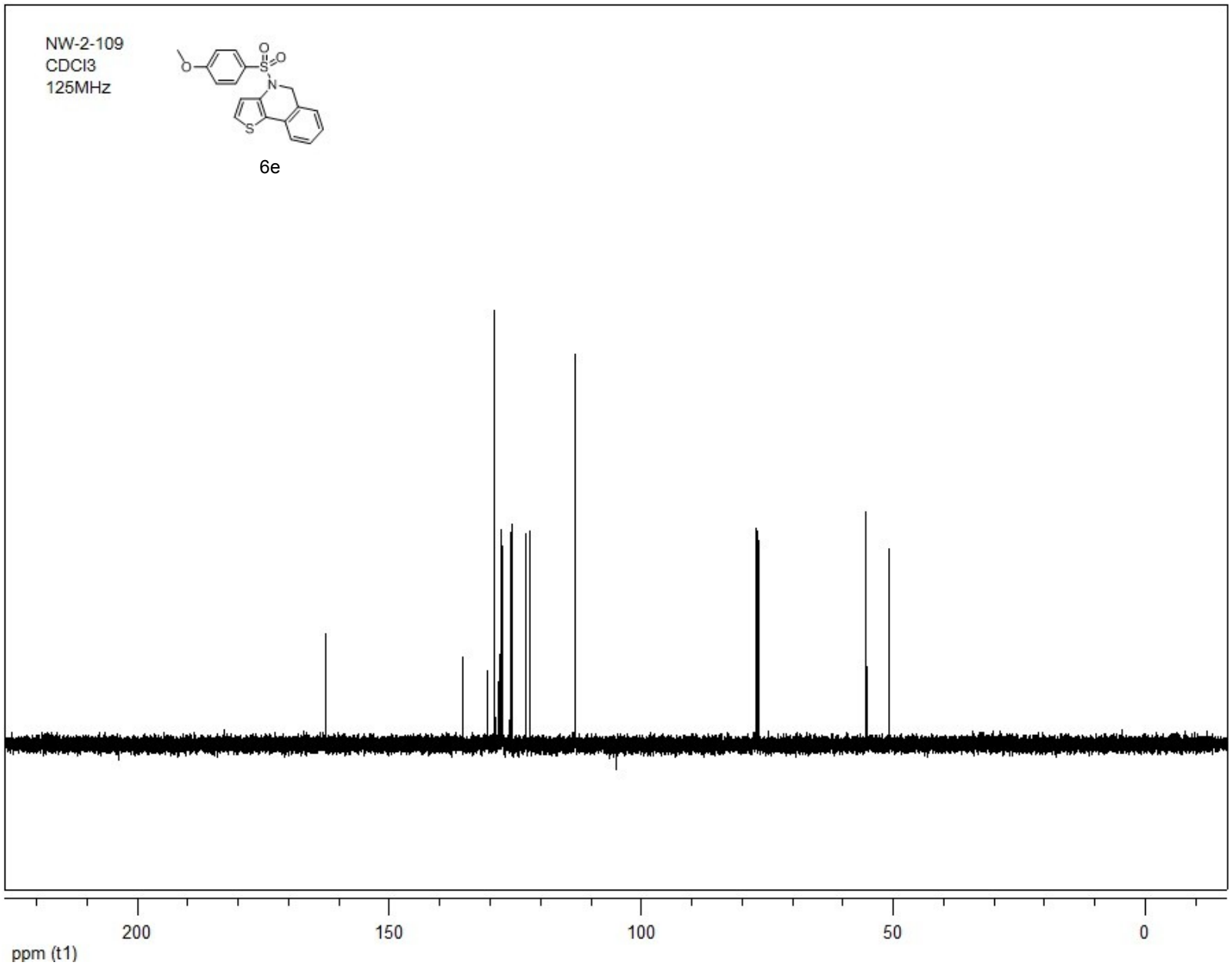

NW-4-132
CDCl3
500MHz
6c
0.97
0.99
1.00
6.06
1.00
7.50
7.40
7.30
7.20
7.10
7.00
6.90
ppm (f1)
0.97
0.99
1.00
6.06
1.00
2.01
2.99
5.0
0.0
ppm (f1)

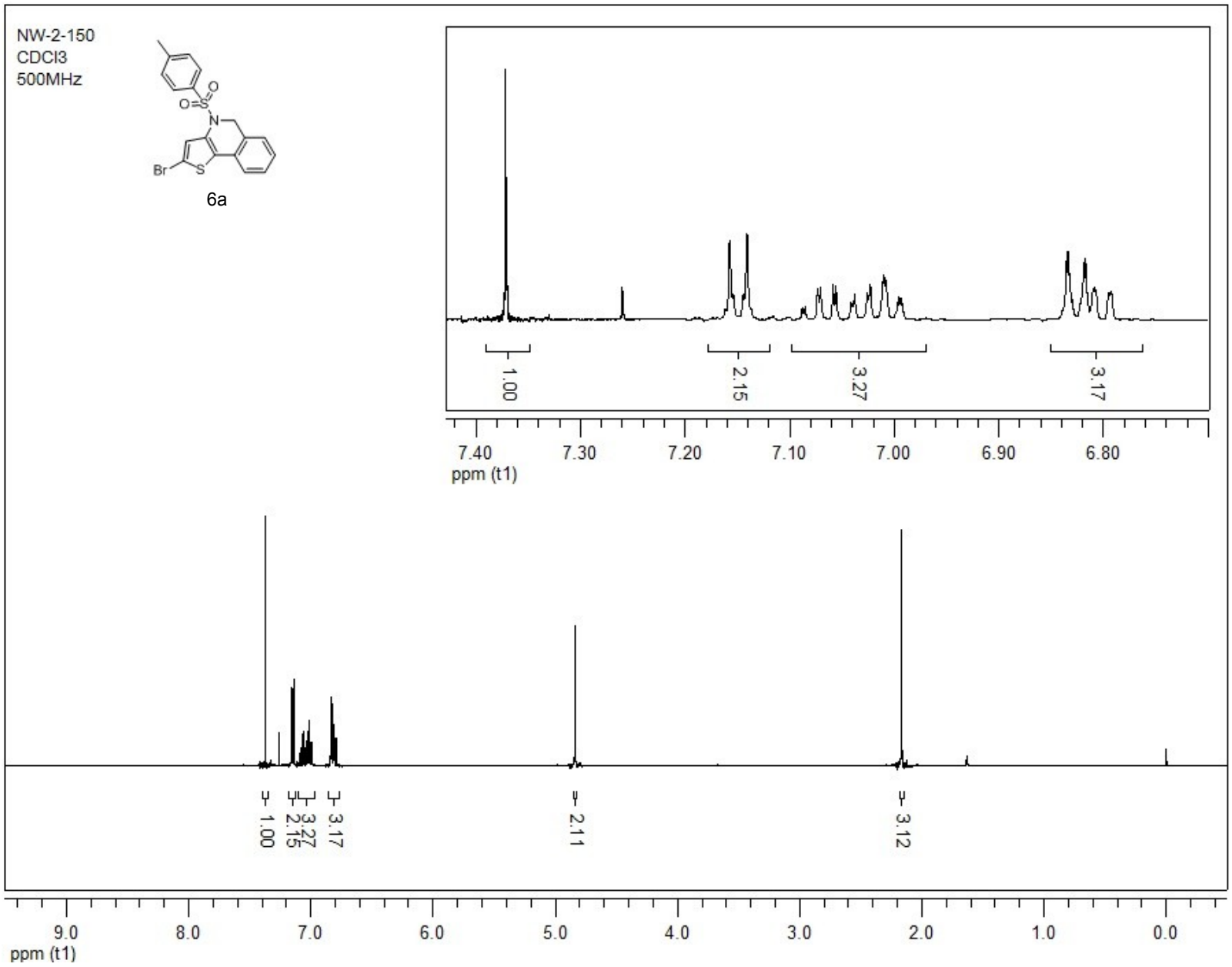

NW-4-132
CDCl3
125MHz
O
S
O
N
S
6c
200
150
100
50
0
ppm (f1)

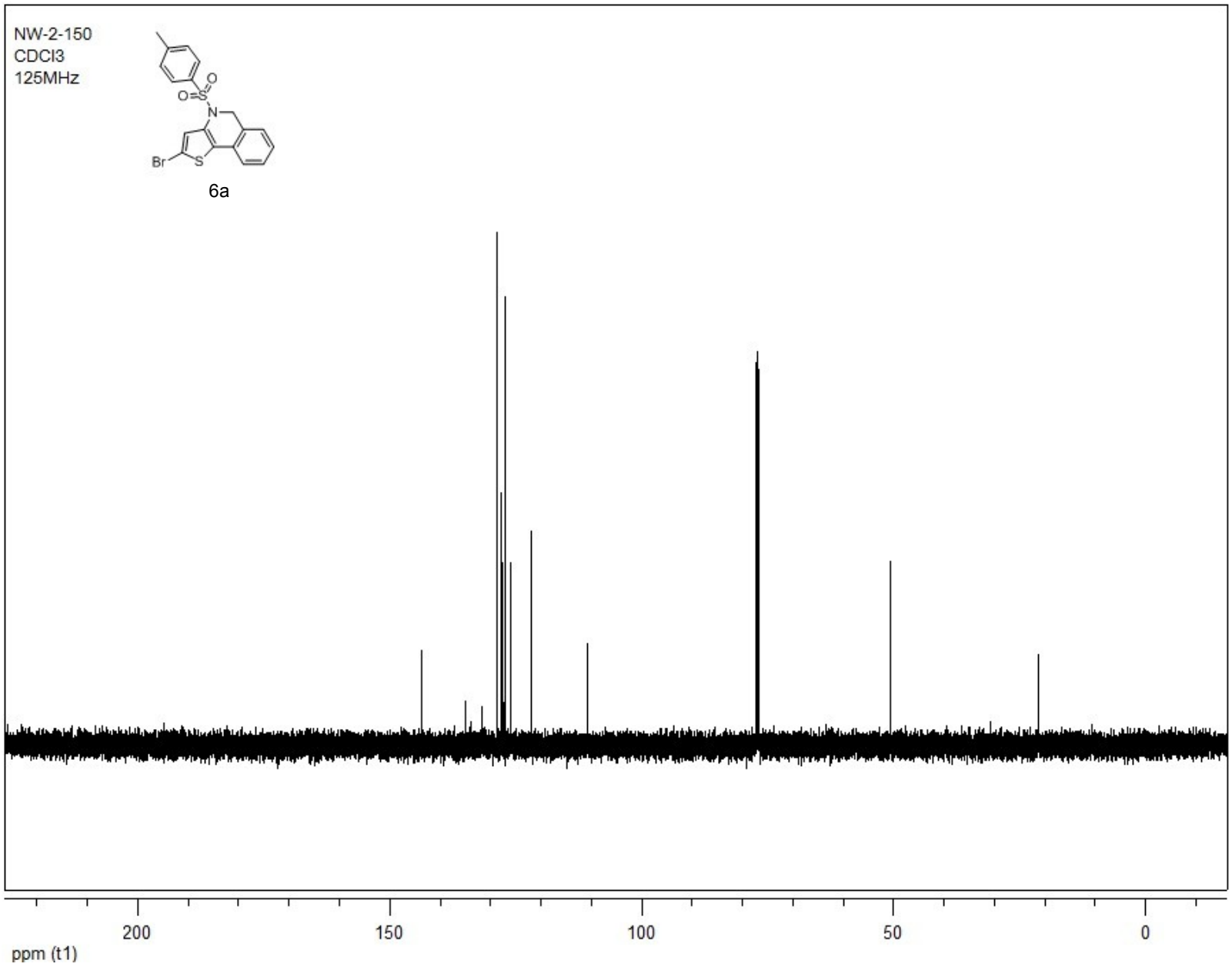

NW-4-133
CDCl3
500MHz
6d
0.94
0.96
7.95
7.40
7.30
7.20
7.10
7.00
6.90
ppm (t1)
= 0.94
= 0.96
7.95
= 2.00
= 3.02
5.0
0.0
ppm (t1)

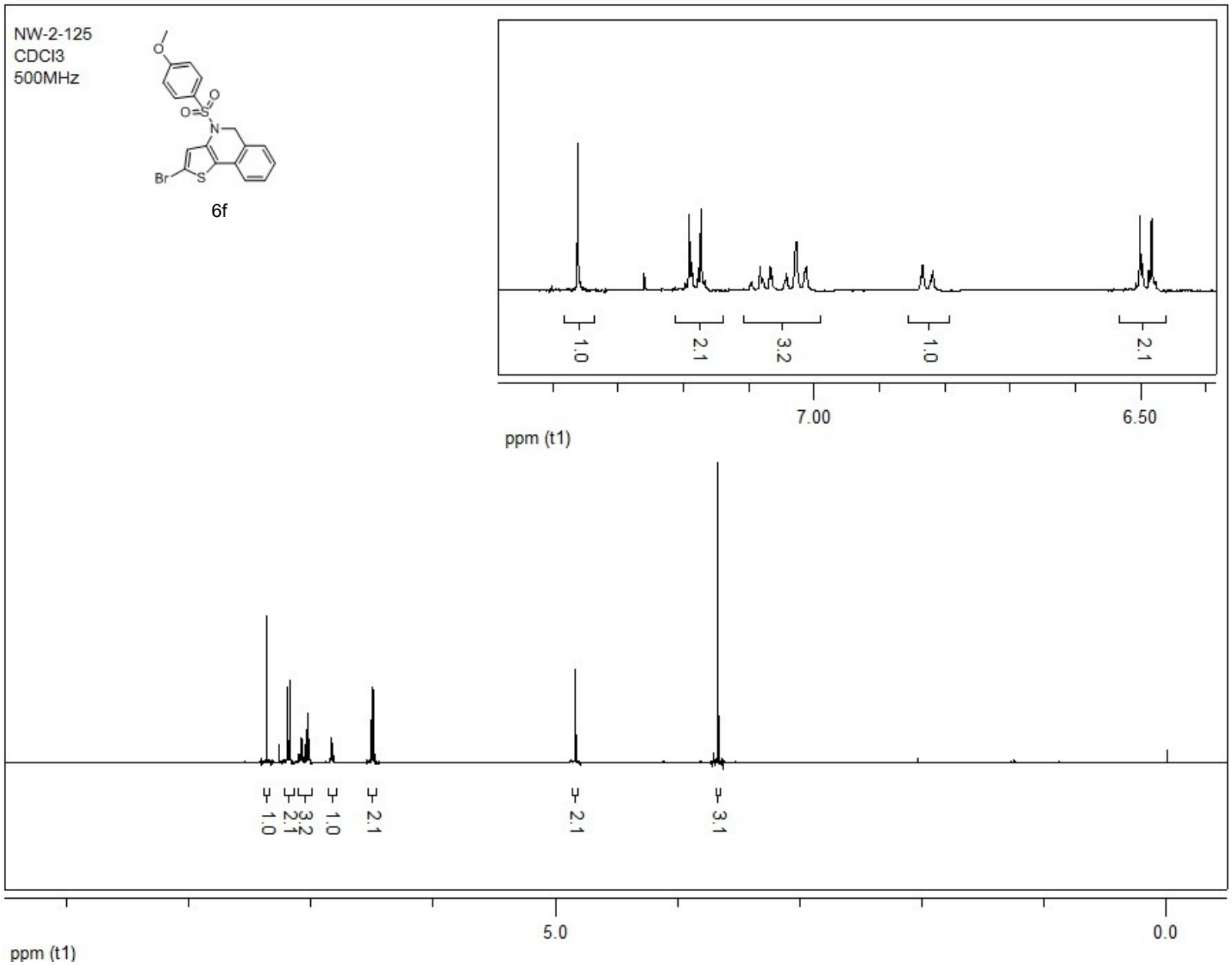

NW-4-133
CDCl3
125MHz
O
S
O
N
S
6d
200
150
100
50
0
ppm (f1)

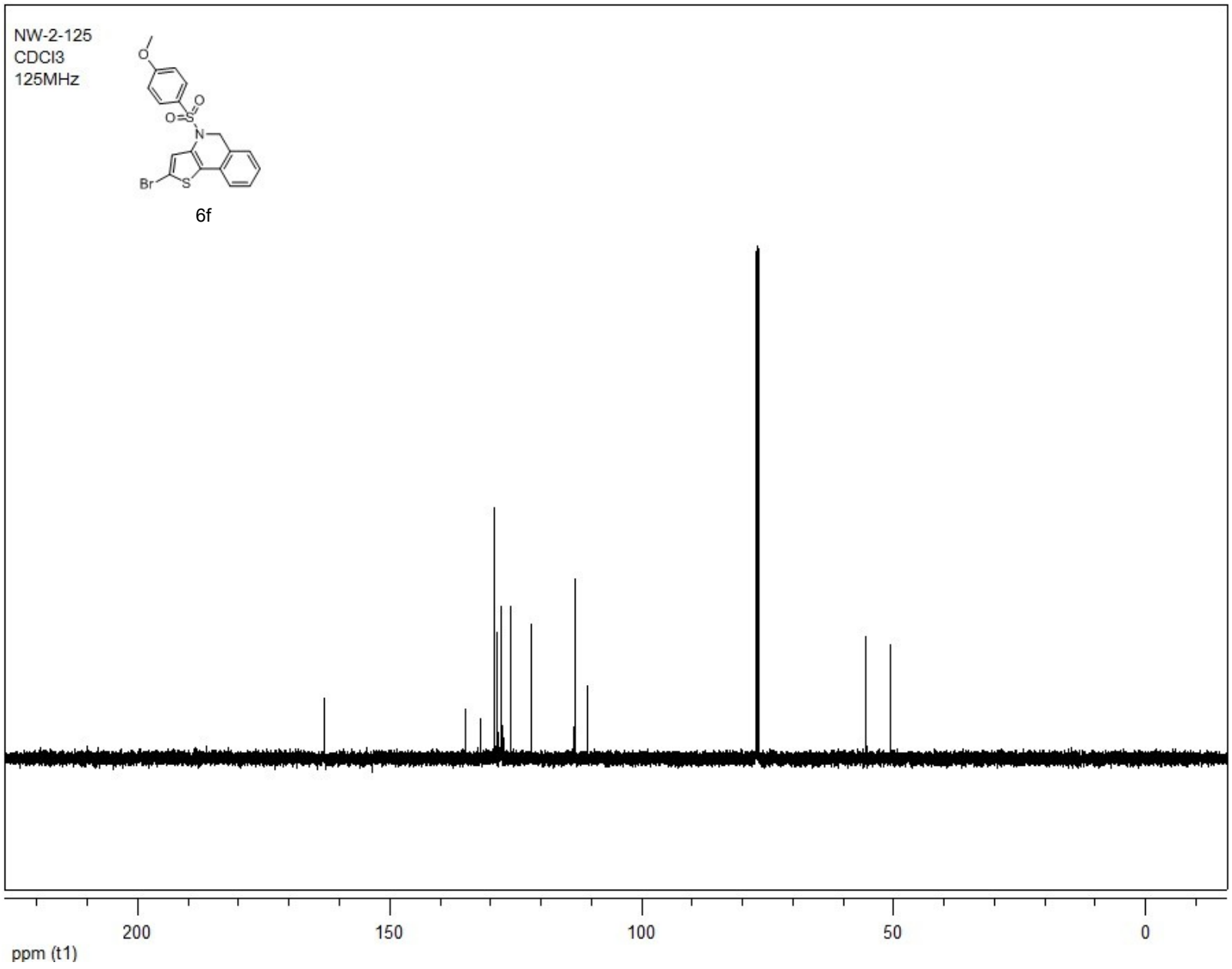

NW-2-109
CDCl3
500MHz
6e
0.9
1.0
1.9
2.9
0.9
1.9
7.00
6.50
ppm (t1)
0.9
1.9
2.0
3.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


NW-2-109
CDCl3
125MHz
O
S
O
O
N
S
6e
200
150
100
50
0
ppm (t1)


NW-2-150
CDCl3
500MHz
6a
1.00
2.15
3.27
3.17
7.40
7.30
7.20
7.10
7.00
6.90
6.80
ppm (t1)
1.00
2.15
3.27
3.17
2.11
3.12
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


NW-2-150
CDCl3
125MHz
O
O=S
N
Br
S
6a
200
150
100
50
0
ppm (t1)


NW-2-125
CDCl3
500MHz
6f
1.0
2.1
3.2
1.0
2.1
7.00
6.50
ppm (t1)
1.0
2.1
3.2
1.0
2.1
2.1
3.1
5.0
0.0
ppm (t1)


NW-2-125
CDCl3
125MHz
O
O=S
O
N
Br
S
6f
200
150
100
50
0
ppm (t1)