UNIVERSITÉ DU QUÉBEC À MONTRÉAL

NOUVELLE MÉTHODOLOGIE DE SYNTHÈSE DE PYRIDINES POLYSUBSTITUÉES EN DEUX ÉTAPES À PARTIR D'ÉNONES IODÉES

MÉMOIRE

PRÉSENTÉ

COMME EXIGENCE PARTIELLE

DE LA MAÎTRISE EN CHIMIE

PAR

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Merci Jésus

DÉDICACE

« I’m just a simple man trying to make my way in the universe »

Jango Fett

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LISTE DES ABRÉVIATIONS, DES SIGLES ET DES ACRONYMES

Ac	Acétyle
ACN	Acétonitrile
API	Ingrédient Actif Pharmaceutique (Active Pharmaceutical ingredient)
Ar*	Argon (dans les conditions réactionnelles et le texte)
Ar*	Aryle (dans les structures organiques et les tableaux)
Boc	Tert-butoxycarbonyl
Bu	Butyle
CuI	Iodure de Cuivre
DBU	1,8-diazabicyclo[5.4.0]undéc-7-ène
DCM	Dichlorométhane
DEAD	Diéthyl azodicarboxylate
DEL	Diode Électro Luminescente
DIPEA	Diisopropyléthylamine
equiv.	Équivalents
Et	Éthyle
Et_3N	Triéthylamine
EtOH	Éthanol
FDA	Food and Drug Administration
$FeCl_3$	Chlorure de fer (III)

H	Hydrogène
H_2O	Eau
HNO_3	Acide nitrique
iPr	Isopropyle
$iPrNH_2$	Diisopropylamine
K_2CO_3	Carbonate de potassium
KOAc	Acétate de potassium
LiCl	Chlorure de lithium
*m*CPBA	Acide métachloroperbenzoïque
Me	Méthyle
MeO	Méthoxy
MeOH	Méthanol
mol%	Pourcentage molaire
MS	Tamis moléculaire (molecular sieves)
NIS	N-iodosuccinimide
nosyl	nitrobenzenesulfonyl
o-Ns	2-nitrobenzenesulfonyl
p-ClPh	4-chlorophényle
$PdCl_2(PPh_3)_2$	Dichlorobis(triphenylphosphine)palladium(II)
Ph	Phényl
PhSH	Thiophénol

PIDA	Diacétate de Phényliodure (III)
p-Ns	4-nitrobenzenesulfonyl
PPh_3	Triphénylphosphine
Py	Pyridine
r.r	Ratio de régioisomères
$SnCl_2$	Chlorure d'étain (II)
t.p.	Température pièce
tBuOK	tert-butanolate de potassium
THF	Tétrahydrofurane
Ts	Toluènesulphonyl

RÉSUMÉ

Ce travail porte sur le développement d'une nouvelle méthodologie de synthèse de pyridines substituées en deux étapes à partir d'iodo-énones et iodo-énals. Les produits naturels et composés synthétiques contenant des pyridines détiennent des propriétés thérapeutiques variées et intéressantes. L'ajout de pyridines à des composés biologiquement actifs peut aussi rehausser ou moduler ses propriétés biologiques telles que la stabilité, la perméabilité membranaire et l'activité biologique. Le développement de nouvelles méthodes de synthèse des pyridines permet d'accéder à une plus grande gamme de pyridines naturelles et synthétiques intéressantes au niveau pharmacologique. Les nouvelles méthodes de synthèse peuvent aussi donner l'accès à des produits naturels dont les propriétés biologiques sont peu connues afin de vérifier leurs propriétés biologiques. La synthèse de pyridines à partir de couplage de propargylamines avec des iodo-énones serait la première en son genre.

La synthèse de pyridines à partir d'iodo-énones se fait en deux étapes par réaction de Sonogashira en premier lieu suivie d'une déprotection de Fukuyama, qui provoque une réaction en cascade de Michael-rétro-Michael, condensation et isomérisation dirigée par le thiophénol. Le couplage de Sonogashira entre une iodo-énone, un iodo-énal ou un iodo-acrylate et une propargylamine nosylée sera étudié dans ce travail. L'optimisation de la formation de pyridines par réaction avec le thiophénol ainsi que la portée de cette méthodologie seront subséquemment présentées. La synthèse de pyridines polysubstituées à quatre des cinq positions possibles s'effectue grâce au couplage de Sonogashira avec une propargylamine substituée. La méthodologie est aussi efficace avec un iodo-acrylate donnant une 2-pyridone. Le substituant thiophényle démontre une réactivité pour la réduction, l'oxydation et les couplages au nickel.

Il est donc possible de synthétiser des pyridines polysubstituées et même des 2-pyridones à partir de carbonyles α-iodo-α,β-insaturées. Ces pyridines offrent une réactivité unique grâce à leur substituant 4-thiophényle.

Mots clés : Pyridines, Sonogashira, Iodo-énones, Cascade Michael, Propargylamine, 2-Pyridone, Synthèse d'hétérocycles

ABSTRACT

This work is about the development of a novel pyridine synthesis in two steps from iodo-enones or iodo-enals. Pyridine containing natural products and synthetic compounds possess varied and interesting therapeutic properties. Addition of pyridine heterocycles to biologically active compounds can increase or modulate its biological properties such as stability, membrane permeability and biological activity. Development of new synthetic methodologies of pyridines can lead to a broader range of pharmacologically interesting synthetic and natural pyridines. New methods of synthesis can also give access to scarcely studied natural products opening up the possibility of the study of their biological properties. The synthesis of pyridines based on the Sonogashira coupling of propargylamines and iodo-enones would be the first of its kind.

The synthesis of pyridines is accomplished from iodo-enones in two steps with a Sonogashira coupling first, then a Fukuyama deprotection, Michael-retro-Michael cascade reaction, condensation and isomerization mediated by thiophenol. The Sonogashira coupling between an iodo-enone, iodo-enal or iodo-acrylate and nosyl protected propargylamines is studied in this work. Optimization of the pyridine formation as well the scope of the methodology are subsequently presented. The synthesis of polysubstituted pyridines at four of the five positions is made possible by the coupling of substituted propargylamines. This methodology is also applicable to iodo-acrylate giving access to the synthesis 2-pyridones. The thiophenyl substituent demonstrates reactivity in reduction, oxidation and nickel coupling.

As such, it is possible to synthesize polysubstituted pyridines as well as 2-pyridones from α-iodo-α,β-unsaturated carbonyls. These pyridines offer a unique reactivity through their 4-thiophenyl substituent.

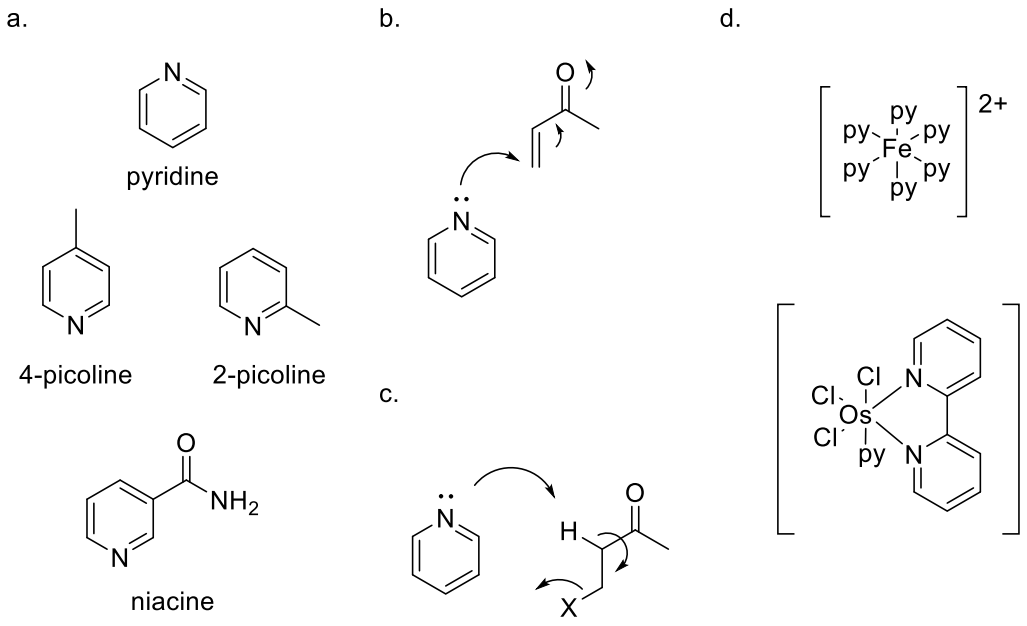
Keywords : Pyridine, Sonogashira, Iodo-enones, Michael-cascade, Propargylamine, 2-Pyridone, Heterocycle synthesis

INTRODUCTION

0.1 Les Pyridines

La pyridine est un hétérocycle aromatique à six membres contenant un atome d'azote (**Schéma 0.1a**) premièrement isolée, sous forme de picoline en 1846, d'huile d'os.[1] Une pyridine est différente du benzène dû à l'atome d'azote présent. Celui-ci, par son doublet d'électrons libres, lui confère des propriétés nucléophiles (**0.1b**), telles que lors d'un mécanisme de type Baylis-Hilman[2] ou basique lors d'une réaction d'élimination(E1cB) (**0.1c**). Ce doublet d'électrons libres peut aussi être donné à un atome métallique permettant aux pyridines (Py) de faire office de ligand (**0.1d**).[3] Les pyridines possèdent des propriétés chimiques uniques qui confèrent des effets et usages variés. Par exemple, La niacine (**0.1a**), plus communément appelée vitamine B3, est d'une grande utilité et permet la prévention de la démence et de la dermatite.[1]

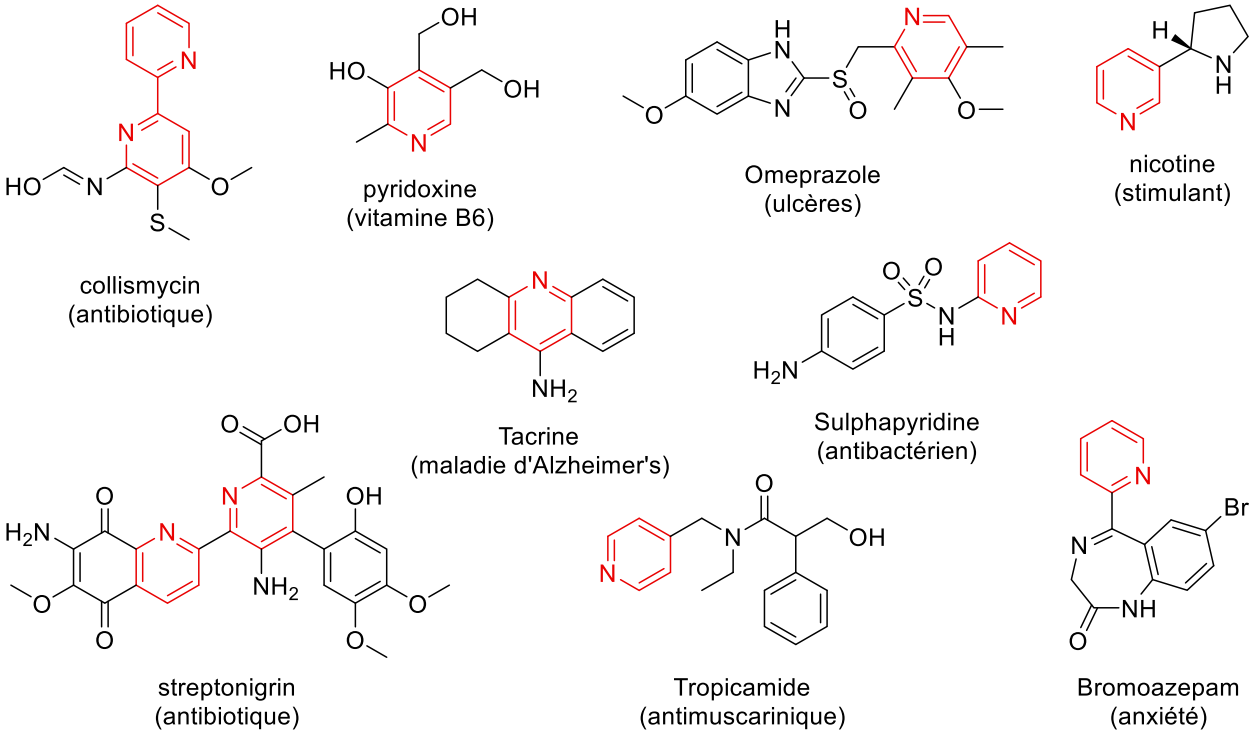
Schéma 0.1 Pyridines simples et propriétés du doublet d'électrons libres



Les pyridines se retrouvent dans une vaste gamme d'applications comme la synthèse organique, la catalyse, la polymérisation,[1] la modulation des effets pharmacologiques, la production de médicaments, et l'agrochimie.[4] Les pyridines sont particulièrement importantes dans la production d'agents thérapeutiques. Selon la banque de données de la « Food and Drug Administration » (FDA), les pyridines

comptent pour 14% des N-hétérocycles dans les médicaments.[5] Les pyridines se retrouvent aussi dans divers produits naturels possédant des propriétés biologiques intéressantes et agents thérapeutiques [4-6] (**Schéma 0.2**). Les composés contenant des pyridines ont été identifiés avec plusieurs activités biologiques : blocage des canaux calciques,[7] baisse du cholestérol sanguin,[8] antibactérienne,[9] antidiabétique[10] et anti-inflammatoire[11] parmi tant d'autres.

Schéma 0.2 Quelques produits naturels et agents thérapeutiques contenant des pyridines



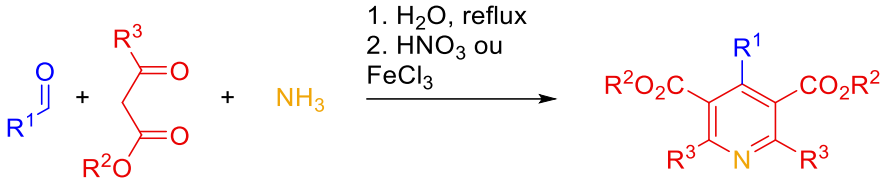
Les pyridines sont alors les sujets d'études des chimistes, biochimistes et biologistes pour leurs potentiels effets pharmacologiques depuis longtemps, prenant une place non négligeable dans le développement de nouveaux agents thérapeutiques. La synthèse de ceux-ci nécessite d'autant plus des méthodes variées de synthèse des pyridines, qui seront un outil versatile pour le chimiste de synthèse voulant développer un tel composé.

0.2 La synthèse des Pyridines

Afin de pouvoir synthétiser des produits naturels ayant des effets biologiques avantageux ou pour développer la voie de synthèse d'un « Active Pharmaceutical Ingredient » (API). Le développement de différentes méthodologies de synthèse ouvre la porte à une panoplie de différents composés. Le

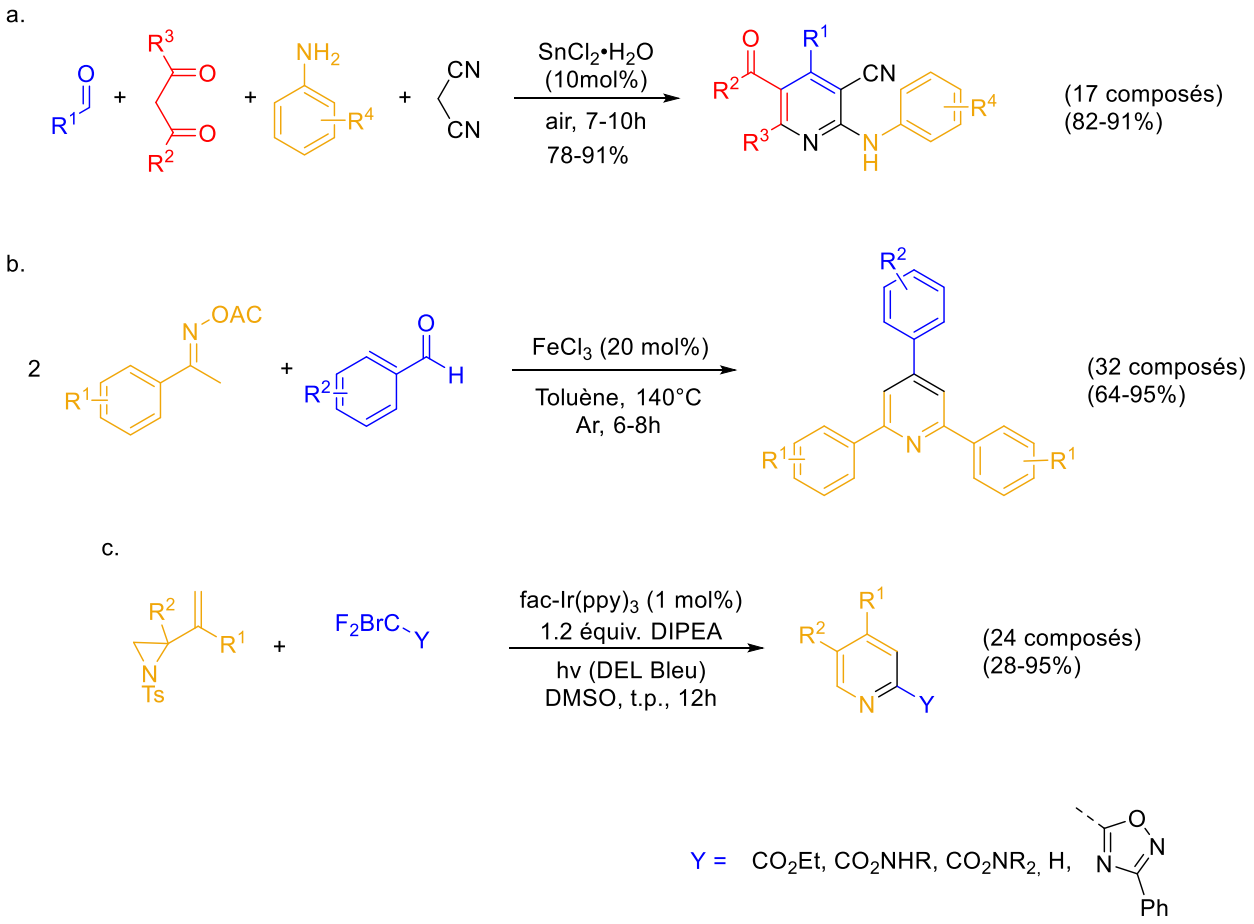
développement de réactions permettant la synthèse de pyridines fait l'objet d'une étude continue et de multiples nouvelles méthodes ont été développées depuis la découverte de la pyridine. La plus célèbre des méthodes a été développée il y a plus d'un siècle. Il s'agit de la synthèse des pyridines des Hantzsch qui permet la condensation d'ammoniac, d'un aldéhyde et deux équivalents de β-céto-ester pour obtenir une dihydropyridine facilement oxydable en pyridine[12] (**Schéma 0.3**).

Schéma 0.3 Synthèse des pyridines de Hantzsch



Depuis, de nombreuses méthodes ont été développées permettant la formation du N-hétérocycle.[4] La synthèse de 3-cyanopyridines polysubstituées par catalyse à l'étain, en conditions douces, est rapportée par Pal et al.[13] Cette méthode permet d'accéder à des pyridines ayant des propriétés médicinales avec de hauts rendements (**Schéma 0.4a**). La synthèse verte des pyridines est aussi possible à partir d'acétates de kétoximes et de benzaldéhydes par catalyse au fer (III) (**0.4b**).[14] Les vinylazyridines (**0.4c**) peuvent être utilisées afin d'introduire l'azote lors de la formation de pyridine par réaction de photo-oxydoréduction à l'iridium avec des difluorohalogénures d'alkyles.[15] Cette méthode est limitée lorsque des substituants sont sur les carbones de l'aziridine, cependant la quantité de catalyseur utilisée est faible. Le ruthénium a permis la synthèse de pyridines polysubstituées (**0.4d**), tel que décrit par Wang et al.,[16] avec une grande efficacité, apportant la possibilité de substituer sur chaque position du cycle.

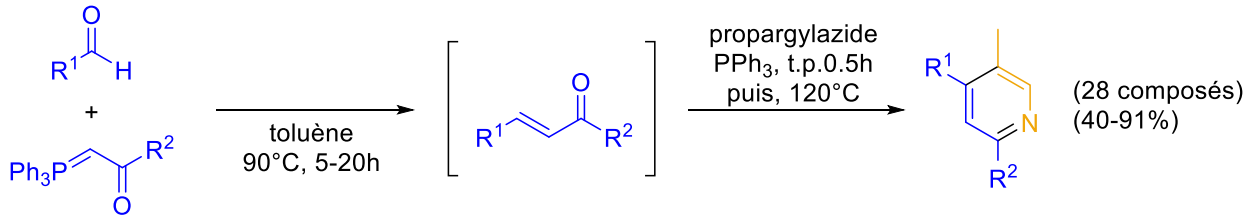
Schéma 0.4 Synthèse de pyridines polysubstituées



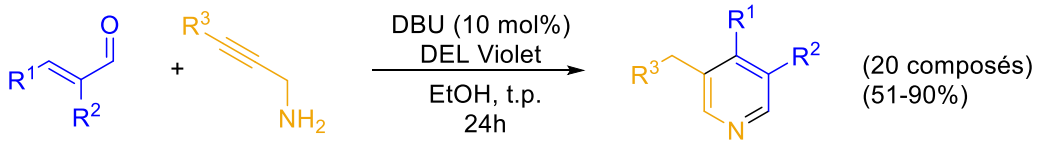
La synthèse sans métaux de pyridines peut s'accomplir à partir d'une réaction « One-Pot » (**Schéma 0.5**) entre un ylure de phosphore, un azoturede propargyle et un aldéhyde (**0.5a**).[17] La propargylamine, similaire a l'azoture de propargyle, est aussi utilisée dans plusieurs autres synthèses de pyridine, souvent couplée à une stratégie d'électro-cyclisation a une énone ou un énal comme décrit par la méthode précédente où la cétone α,β-insaturée est formée lors de la réaction. Zang et al. décrivent une méthode utilisant la photo-oxydoréduction sans métaux produisant la synthèse des aldéhydes de picolines (**0.5b**).[18] Watkins et al. avaient déjà utilisé cette stratégie en 2019 permettant la synthèse verte de pyridine avec de bons rendements (**0.5c**).[19] La (-)-actinidine a été synthétisée avec 85% de rendement grâce à cette méthode.

Schéma 0.5 Synthèse [4+2] de pyridines à partir de propargylamines et dérivés de propargylamines

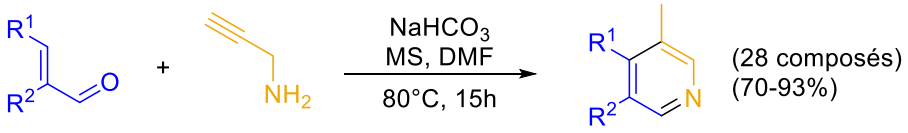
a.



b.

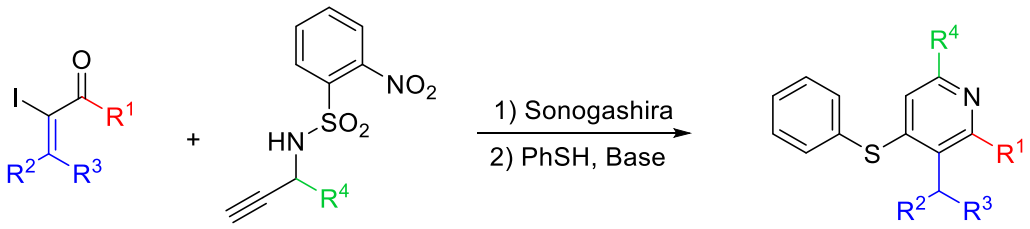


c.



Dans ce travail, la synthèse de pyridines a été étudiée et plus spécifiquement à partir de propargylamines et carbonyles α,β-insaturés. Cette stratégie différera de ce qui est courant dans la littérature, car la synthèse de pyridines se fera en deux étapes. Premièrement, la propargylamine sera couplée à une iodo-énone par couplage de Sonogashira suivi d'une cascade de Michael-rétro-Michael, avec le thiophénol (PhSH), pour donner une pyridine (**Schéma 0.6**).

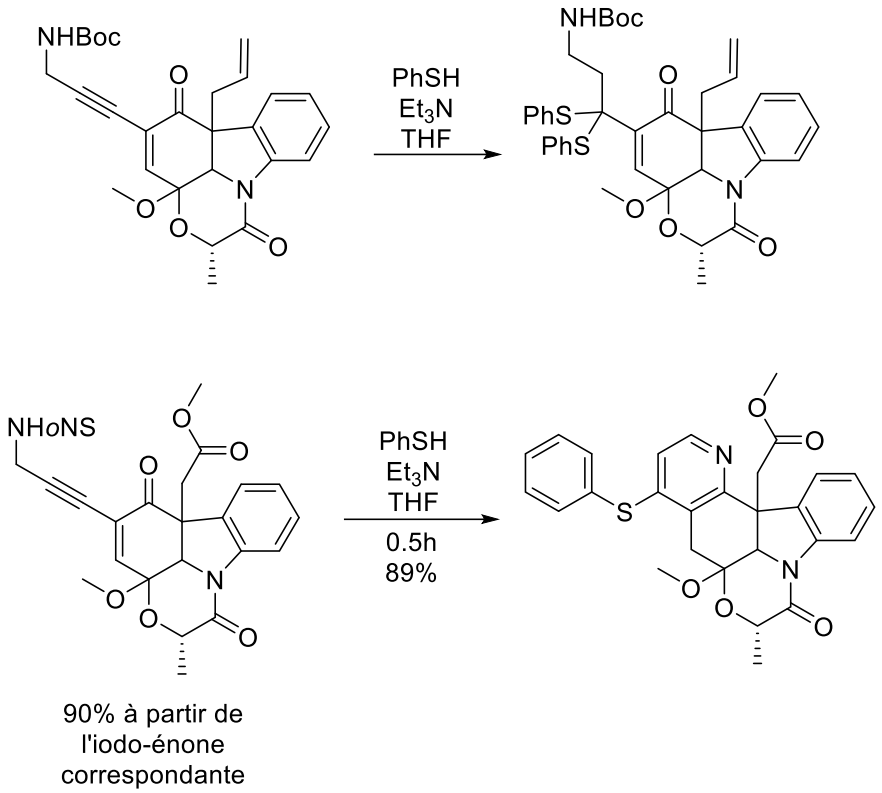
Schéma 0.6 Synthèse en deux étapes de pyridine à partir d'iodo-énones



Dans le cadre de la synthèse des vindolines, qui a été investiguée dans le groupe de recherche Canesi, une sous-réaction fut identifiée lors d'une tentative de double addition de PhSH. Dans le cas où le groupe protecteur sur la propargylamine couplé est un tert-butoxycarbonyl (Boc), la double addition se déroule comme prévu. Cependant, quand le groupement protecteur de la propargylamine est un nitrobenzenesulfonyl (nosyl), une réaction de Fukuyama[20] en conjonction avec une addition de Michael

et rétro-Michael a produit une pyridine sur l'intermédiaire avancé (**Schéma 0.7, Annexe C**). La formation de pyridines à partir d'énynes semblait possible grâce à cette découverte.

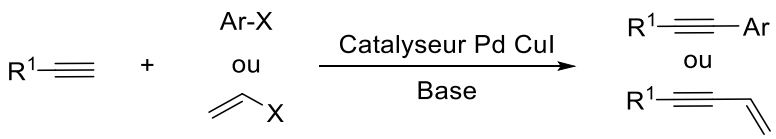
Schéma 0.7 Découverte de la formation de pyridines



0.3 Le Couplage de Sonogashira

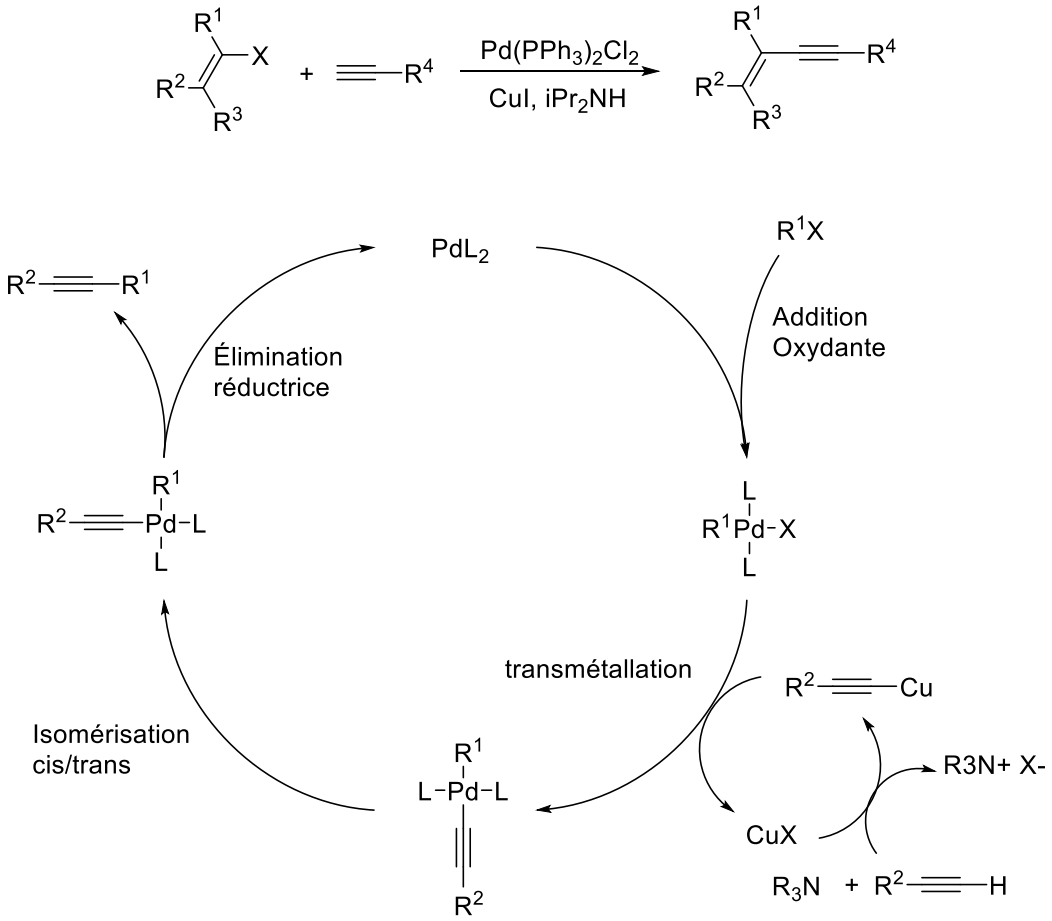
Le couplage de Sonogashira est le couplage d'un alcyne terminal (carbone sp) avec un halogénoalcène ou halogénoaryl (carbone sp2) (**Schéma 0.8**). Le couplage de Sonogashira permet un couplage de carbone sp et sp^2.[21] À cause de son utilité, ce couplage est très utilisé en synthèse organique pour synthétiser des alcynes conjugués. Le couplage de Sonogashira est catalysé par le palladium et le cuivre. Le cuivre, souvent sous forme d'iodure de cuivre dans les versions plus simples, sert à activer l'alcyne terminal

Schéma 0.8 Couplage de Sonogashira



Le mécanisme du couplage de Sonogashira (**Schéma 0.9**) débute par l'addition oxydante du palladium (0) dans la liaison Ar-X ou alcyne-X. Il est possible que le palladium utilisé soit sous forme Pd(II), dans ce cas deux équivalents d'alcynes activés[21] ou deux équivalents de base permettent la conversion vers le palladium (0). Par la suite, une *trans*-métallation avec un alcyne activé par le cuivre s'opère, suivie d'une isomérisation et d'une élimination réductrice. Le produit de couplage est obtenu et nous retrouvons le palladium (0) complétant le cycle catalytique.

Schéma 0.9 Mécanisme du couplage de Sonogashira

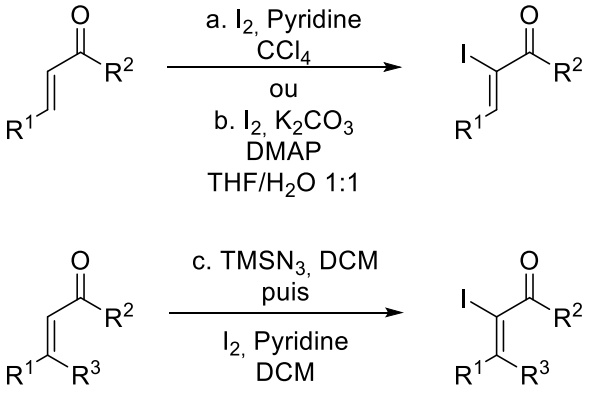


Dans cet ouvrage, sera étudié le couplage de Sonogashira entre les proparylamines avec un groupement protecteur 2-nitrobenzenesulfonyl (*o*-Ns) et des carbonyles α,β-insaturés.

0.4 La Synthèse de Carbonyles α,β-Insaturés α-Iodés

Afin de pouvoir synthétiser des pyridines, il faudra effectuer un couplage de Sonogashira sur un carbonyl α,β-insaturé. Ces composés sont plutôt difficiles à obtenir commercialement. Il faudra les synthétiser à partir de méthodes connues de la littérature. L'iodation d'énones ou d'énals peut se faire par iodation directe en employant un agent d'iodation tel que l'iode, le N-iodoscuccinimide (NIS) et d'autres. Parmi ces méthodes est l'iodation de cétones conjuguées avec de l'iode et de la pyridine[22] (**Schéma 0.10a**). La réaction se déroule selon le mécanisme de Baylis-Hillman, donnant un énolate pouvant attaquer l'iode électrophile. Un autre équivalent de pyridine peut effectuer une réaction E1cBpour reformer la double liaison conjuguée. Il existe deux autres variantes de cette méthode. Kraft et Cran ont développé une méthode plus douce et rapide avec une portée plus limitée pour les cétones (**0.10b**).[23] Sha et Huang décrivent l'ajout de triméthylsilylazide ($TMSN_3$) pour synthétiser des α-iodocycloaklenone β-substituées (**0.10c**).[24]

Schéma 0.10 Synthèse de α-iodoénones par iodation directe d'énones

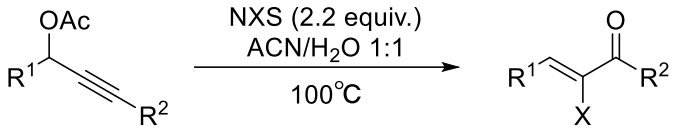


Une autre manière d'obtenir des énones α-iodées est de faire la déaromatisation oxydante d'un *o*-iodophénol[25] pour en obtenir la dienone (**Schéma 0.11**). Les diénones sont des intermédiaires facilement fonctionnalisables sur toutes les positions, les rendant très intéressantes pour la synthèse totale de produits naturels.[26]

Schéma 0.11 Déaromatization oxydante du *o*-iodophénol

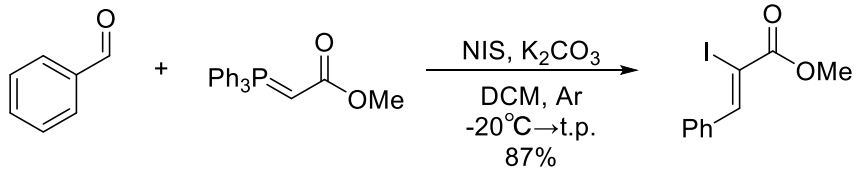
D'autres méthodes utilisent le réarrangement de Meyer-Shuster pour former des α-haloénones à partir d'alcools propargyliques acétylés. Une de ces méthodes, rapportée par Sadhukhan et Baire, démontre la transformation de ces substrats en α-haloénones avec le NIS dans un mélange d'acétonitrile (ACN) et d'eau (H_2O) à reflux[27] (**Scéhma 0.12**).

Schéma 0.12 Synthèse d'α-haloénones par réarrangement de Meyer-Shuster



La synthèse d'ester α,β-insaturés α-iodés est possible par réaction de Wittig avec formation d'halogéno-ylure de phosphore *in situ*[28] (**Schéma 0.13**). Cette méthodologie ouvre la porte à de nouveaux intermédiaires, car la synthèse d'ester α-iodés conjugués est difficile normalement.[23]

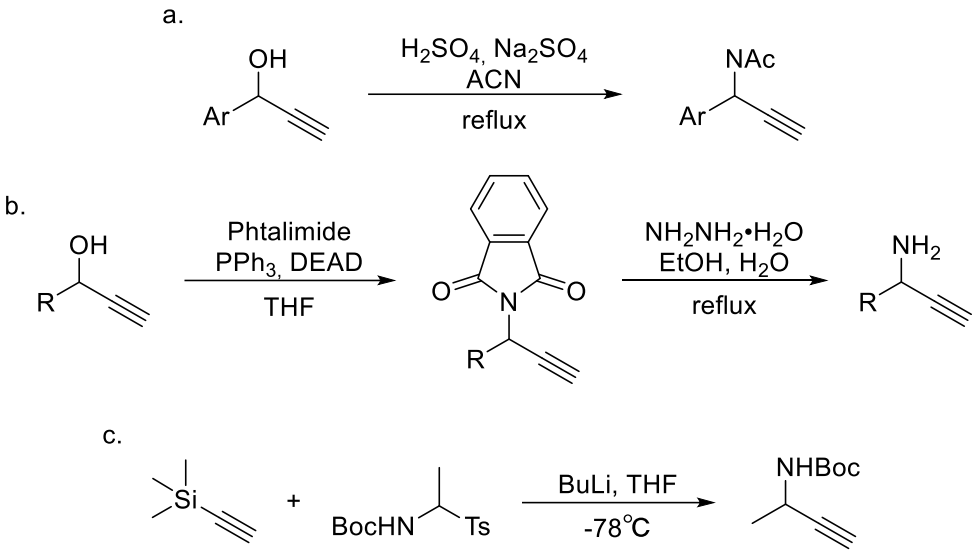
Schéma 0.13 Réaction de Wittig avec formation d'halo-ylure de phosphore *in situ*



0.5 La Synthèse de Propargylamines substituées

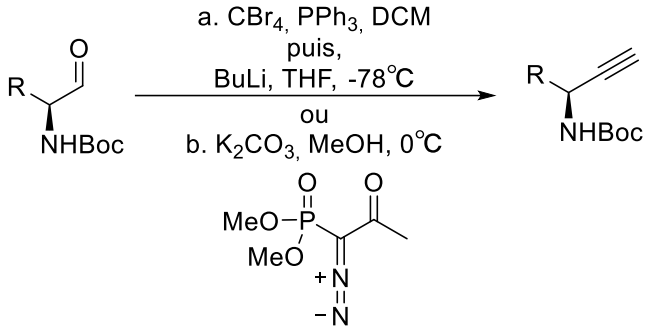
La synthèse des propargylamines substitués est possible par plusieurs stratégies. Celles-ci peuvent être préparées à partir d'alcools propargyliques (**Schéma 0.14**) par réaction de Ritter[29] (**0.14a**), par réaction de Mitsunobu[30] (**0.14b**) ou par addition d'organolithien sur une α-aminosulfone[31] (**0.14c**).

Schéma 0.14 Synthèse de propargylamines à partir d'alcools propargyliques



La synthèse de propargylamines substituées peut s'accomplir à partir d'acides aminés (**Schéma 0.15**). Une fois que la fonction acide carboxylique est transformée en aldéhyde, une réaction de Corey-Fuchs[32] ou de Seyfert-Gilbert[33] permet l'obtention de propargylamines substituées. Cette voie de synthèse offre autant de variété qu'il y a d'acides aminés, en plus de conserver la stéréochimie naturelle de l'acide aminé de départ.

Schéma 0.15 Synthèse de propargylamines à partir d'acides aminés



La synthèse de ces précurseurs permettront, dans le cadre de cette recherche de potentiellement synthétiser des pyridines substituées à quatre des cinq positions.

CHAPITRE 1

Article : Two-Step Formation of Substituted Pyridines from Iodo-Enones

Carl Malenfant, Maxime Denis and Sylvain Canesi*

Article soumis pour publication dans le journal Organic Letters

1.1 Mise en contexte

Dans ce chapitre se trouve l'article scientifique intitulé « Two Step Formation of substituted Pyridines from Iodo-Enones », écrit en anglais, qui est la synthèse de la recherche de ce mémoire. La pyridine, découverte en 1846 sous la forme de picoline,[1] est un cycle aromatique dont l'un des carbones est remplacé par un atome d'azote. Les pyridines (**Schéma 1**) sont d'importantes molécules dans un vaste nombre de domaines et particulièrement en pharmaceutique. [4,6] Certes, les pyridines présentent diverses activités biologiques[5] et l'addition de cette structure dans un composé biologiquement actif peut améliorer divers facteurs tels que; l'activité biologique[34] et la stabilité métabolique.[35] De nombreux composés actifs et produits naturels (**Schéma 2**) sont identifiés et synthétisés pour ces propriétés. La synthèse des pyridines est alors un sujet de recherche actif et varié. Parmi les méthodes de synthèse (**Schéma 3**) les plus connues se trouvent la synthèse des pyridines de Hantzsch.[12] qui, par condensation à reflux avec l'ammoniac, un aldéhyde et deux équivalents de β-cétoester donne une dihydropyridine qui est facilement oxydée en pyridine. Des méthodes plus modernes (**Schéma 4 et 5**) permettent la formation de cyanopyridines substituées par catalyse à l'étain en conditions douces[13] ou la synthèse de 3-méthylpyridines à partir de propargylamine et d'énals à partir de réactifs verts et peu onéreux. [19] Les nouvelles méthodes permettent aussi la synthèse totale de produits naturels contenant des pyridines dont les propriétés biologiques sont peu étudiées. La synthèse des pyridines reste un sujet d'actualité aujourd'hui pour l'élaboration de méthodes plus efficaces, vertes et peu couteuses, comme pour le développement et la découverte de nouveaux composés biologiquement actifs. Une nouvelle méthodologie de synthèse des pyridines en deux étapes à partir d'iodo-énones et autres carbonyles α,β-insaturés sera étudiée dans ce chapitre. L'étude de la méthode se portera sur la portée des deux étapes réactionnelles ainsi que sur l'optimisation de l'étape de formation de pyridine et la réactivité du thioéther formé.

1.2 Contributions des auteurs

Auteur principal : Carl Malenfant

Carl Malenfant fut responsable de la grande majorité des manipulations expérimentales requises pour ce projet et de la production de l'article.

Co-auteur

Maxime Denis fut responsable de la production des pyridines **8e**, **8k** et les produits de Sonogashira correspondants ainsi que leur caractérisation et de l'élaboration, en partie, des conditions réactionnelles permettant d'obtenir le produit **15**.

Auteur Correspondant

Sylvain Canesi : Direction de la recherche, production et révision de l'article.

1.3 Article – Two-Step Formation of Substituted Pyridines From Iodo-Enones

JOC The Journal of Organic Chemistry

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Two-Step Formation of Substituted Pyridines from Iodoenones

Carl Malenfant, Maxime Denis, and Sylvain Canesi*

Cite This: https://doi.org/10.1021/acs.joc.4c02502 Read Online

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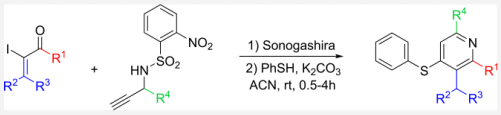
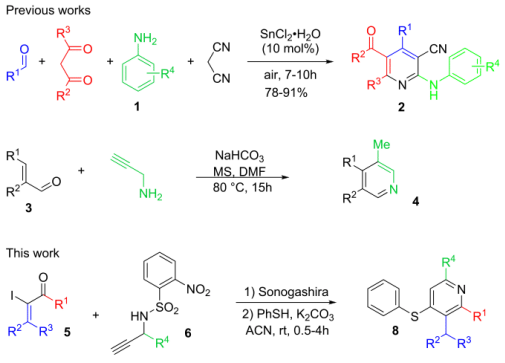
ABSTRACT: A new access to substituted pyridines was developed from iodoenones. This two-step procedure involves a Sonogashira coupling with a free alkyne containing a nosylamide followed by a thiophenol treatment in basic conditions that triggers nosyl deprotection, a Michael−retro-Michael process, condensation, and isomerization in cascade to yield the heterocycle. This method enables the introduction of different substituents at several pyridine positions. This approach offers new synthetic opportunities to produce heterocycles present in many bioactive compounds.



INTRODUCTION

Pyridines are important heterocycles present in several pharmaceuticals and natural products.[1,2] Pyridine-containing natural products and therapeutic agents have been reported to provide a vast array of biological activities, such as antibacterial,[3] anticancer,[4] antidiabetic,[5] and anti-inflammatory properties.[6] Pyridine is also inserted into bioactive compounds to improve the pharmacological profile and has been shown to increase biological activity and metabolic stability.[7] Therefore, the synthesis of pyridines[8] is of great importance, and various methods have been discovered and developed throughout the years. The most famous is the Hantzsch pyridine synthesis, developed more than a century ago.[9] More recent methods have achieved the synthesis of pyridines via a tin-catalyzed multicomponent reaction to yield substituted cyanopyridines **2**[10] (Scheme 1). A noteworthy approach by Watkins et al.[11] was reported in mild and metal-free conditions. This concise method enables the rapid formation of substituted pyridines but is limited to enals **3** and propargylamine for the formation of 3-methylpyridine cores **4**. Furthermore, a remarkable 3-alkyl-pyridine synthesis with unsaturated aldehydes through a tandem condensation/alkyne isomerization/6π 3-azatriene electrocyclization sequence enabled the total synthesis of suaveoline alkaloids.[8b] Our interest in the total synthesis of natural products involving dienones as key species[12] led us to develop a new alternative to synthesize elaborated pyridines **8** from an iodoenone precursor **5**. Therefore, we wondered if the missing atoms to generate such a heterocycle could be introduced with a linear chain containing several unsaturations, such as an alkyne and a protected amine, which could be further redesigned into a pyridine moiety by unsaturation rearrangements and amine condensation. This approach could be useful to produce substituted pyridines present in natural products.[13] In this paper, we report the synthesis of several substituted pyridines from iodo-α,β-unsaturated carbonyls that were easily obtained by a direct iodination of enones/enals[14] or by oxidative dearomatization of 2-iodophenols.[15] This approach involves a Sonogashira coupling[16] to introduce a protected amino-unsaturated side chain that is necessary for the heterocycle elaboration. A subsequent one-pot process triggered by a Fukuyama nosylamide deprotection[17] with thiophenol enabled Michael−retro-Michael equilibrium, amine condensation, and alkene isomerization in cascade to produce pyridines **8** (Scheme 1).

Scheme 1. Pyridine Syntheses



RESULTS AND DISCUSSION

First, we synthesized numerous substituted α,β-unsaturated carbonyl compounds **7** from their iodoenone/enal deriva-

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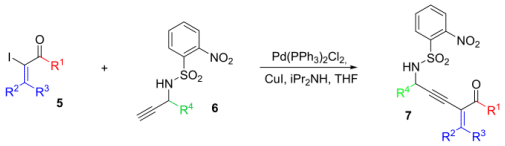
tives[18] **5** through a standard Sonogashira protocol[16] in the presence of *ortho*-nosyl protected propargylamines. Sonogashira adducts **7** were obtained in moderate to good yields. It appeared that due to the high reactivity of both the substrate and products, anhydrous and inert conditions did not improve the process. The reaction proceeded quickly, ending within 1 to 4 h. Bromoenones were not competent substrates for the coupling reaction due to their reduced reactivity, affording low yields. The coupling with iodocholestenone **7j** was less prone to degradation, sometimes observed by the formation of an unidentified tar. Dienones were the best substrates for the coupling reaction, affording **7k,l** in good yields. Furthermore, substituted propargylic amines **7m−p** slowed the rate of degradation, which substantively increased the yield of the process. Poor results were observed with a simple aliphatic substrate such as 2-iodo-hexanal. The use of *para*-nosyl-protected propargylamine **9** (R^4 = H) instead of its *ortho*-nosyl derivative **6** was studied with compound **5a** to yield the analogue **7a'**, in a similar yield of **7a** (Table 1).

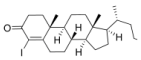
With enynes **7a−p** in hand, we decided to generate pyridines mediated by a nosylamide deprotection in the presence of thiophenolate. In such conditions, a poly-Michael addition process that would produce a more flexible sp^3 center containing a thioether as a double bond precursor by an E1cB mechanism yielded pyridines **8a−p**. To our delight, direct formation of pyridine **8a** was observed during the Fukuyama deprotection step. Several conditions were investigated to improve this process, leading to heterocycle **8a**. The best results were observed with condition 3, which allowed a rapid conversion of the reaction. The process seemed incomplete or slow with a weaker base such as triethylamine. The reaction was slower in the presence of *para*-methoxy-thiophenol, resulting in a lower yield. In this case, the transformation was interrupted, and a dihydropyridine adduct **21** readily oxidized by air on silica gel was recovered as a byproduct. The inability of this reagent to promote pyridine formation could be explained by the fact that *para*-methoxy-thiophenol is a better nucleophile and therefore a worse leaving group than thiophenol (α effect), avoiding the necessary retro-Michael process to generate aromaticity. This intermediate can be used as a clue to determine the mechanistic pathway of this transformation. Like *para*-methoxy-thiophenol, aliphatic thiols, such as benzyl mercaptan, did not complete the process because they are a worse leaving group than thiophenol, which seems to be the reagent of choice (Table 2).

With these conditions in hand, we have extended this process to different substrates **7b−p** to produce substituted pyridines **8b−p** at several positions. In almost all cases, the reaction proceeded smoothly, affording various pyridines in good yields. Cinnamaldehyde derivatives were competent substrates for this transformation. Dienones **7k,l** afforded good yields and emerged as promising intermediates for the synthesis of complex natural products. Aromatic substitution on propargylic amine **7m** at the R^4 position seemed to prevent the formation of pyridine in normal conditions, yielding only a deprotected intermediate with no Michael addition. Heating the reaction and using a stronger base like DBU degraded the reaction. The reaction tolerated alkyl substituents on the propargylic amine, giving 6-substituted pyridines **8n−p** in good yield (Table 3).

We also investigated whether this approach could be extended to the formation of a pyridone **15** from an iodoacrylate derivative[19] **13**. The acrylate Sonogashira adduct **14** was then subjected to the standard reaction conditions but afforded only a deprotected mono-Michael addition adduct. Therefore, the reaction was achieved with the addition of stronger bases, such as *t*-BuOK or DBU, granting 2-pyridone **15** (Scheme 2).

Table 1. Sonogashira Adducts[a]



Entry	R^1	R^2	R^3	R^4	T (h)	Y (%)
7a	H	Ph	H	H	1.5	54
7a'					2.5[b]	49[b]
7b					1	67
7c					1	50
7d	Me	Ph	H	H	2	37
7e	*i*Pr	Ph	H	H	1.5	48
7f	Ph	Ph	H	H	2	59
7g				H	3.5	45
7h	Me	-ClPh	H	H	3.5	34
7i	Et		H	H	2	33[c]
7j				H	2.5	59[c]
7k				H	4	71
7l				H	1.5	87
7m	H	Ph	H	*p*-ClPh	1.5	78
7n	H	Ph	H	Me	3	72
7o	H	Ph	H		3	73
7p	H	Ph	H	Bu	1.5	83

[a]$Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), $iPrNH_2$ (3 equiv), and THF. [b]Yield using *p*-nosyl-protected propargylamine **9**. [c]Pd-$(PPh_3)_2Cl_2$ (20 mol %) and CuI (40 mol %).

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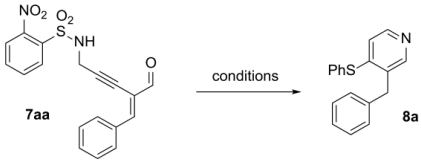
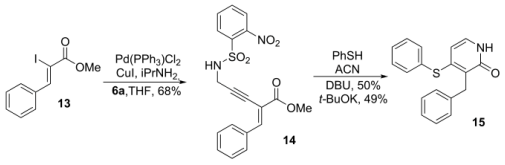
Table 2. Pyridine Synthesis Optimization



Entry	Thiol	Base	Solvent	T (h)	Yield (%)
1	PhSH	Et_3N (17 equiv)	THF	3	0
2	PhSH	Et_3N (17 equiv)	THF	20	55
3	**PhSH**	**K_2CO_3(4 equiv)**	**ACN**	**2.5**	**88**
4	4-MeO-thiophenol	K_2CO_3 (4 equiv)	ACN	4	44
5	4-MeO-thiophenol	K_2CO_3 (4 equiv)	ACN	0.25	0[a]
6	benzyl mercaptan	K_2CO_3 (4 equiv)	ACN	4	0[b]

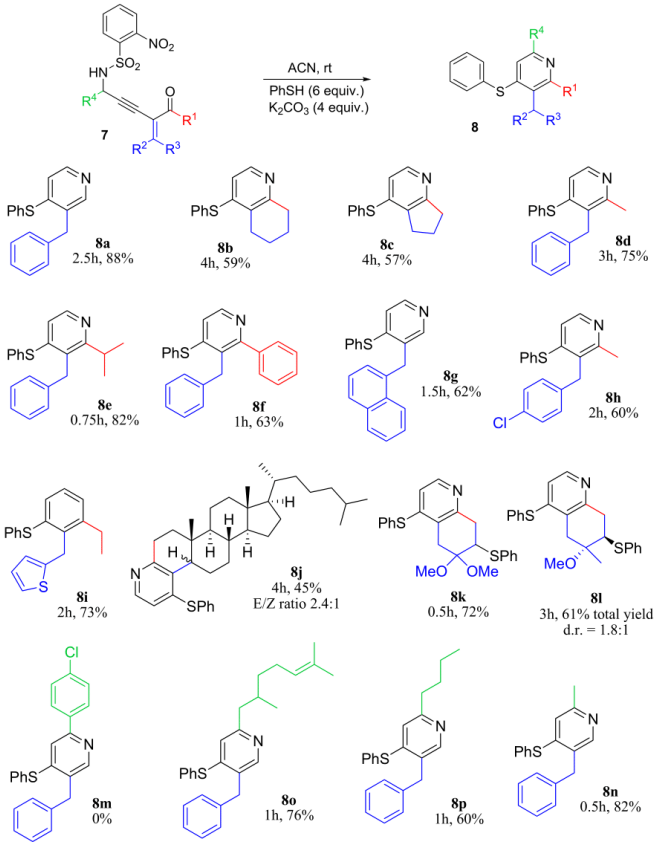
[a]Pyridine oxidized from the imine intermediate was obtained instead. [b]Imine was observed by LRMS during the reaction.

Scheme 2. Synthesis of a Substituted 2-Pyridone



The thioether subunit opens up new opportunities in synthesis to generate new bonds. Indeed, it can be reduced by a Raney nickel treatment and oxidized to the sulfone by *m*CPBA or it can promote cross-coupling transformations mediated by nickel from aryl bromides to yield 4-substituted pyridines.[20] In addition, thioethers can undergo several different cross-couplings with alkyl or aryl organometallics such as organozincs, organostannanes, organomagnesiums, and organoborons, demonstrating the importance of this functionality for further elaborations.[21] Therefore, it appeared that our method enabled us to introduce different substituents at four of the five positions of the pyridine moiety. That could be an

Table 3. Pyridine Synthesis Scope



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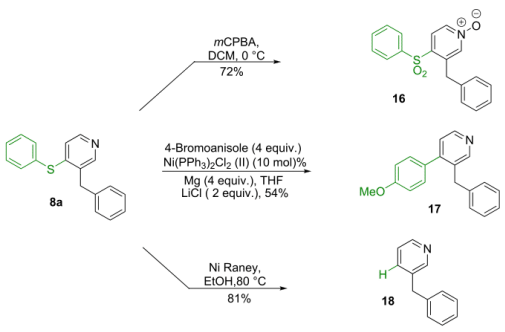
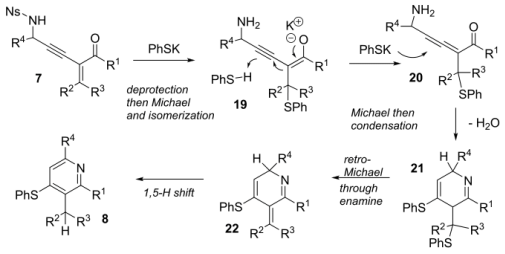
asset to synthesize complex pyridines or natural products (Scheme 3).

Scheme 3. Thioether Opportunities in Synthesis



A potential mechanism would involve a cascade, starting with the presence of thiophenol under basic conditions. First, a nosylamide deprotection, an initial 1,4-addition, and an alkene isomerization would lead to **20**. A second Michael addition followed by an amine condensation on the carbonyl would yield imine **21**. This species would trigger a retro-Michael process that would lead to the formation of compound **22**. A final 1,5-hydride shift would produce heterocycle **8**. It should be noted that the nosyl protecting group was necessary both to allow Sonogashira coupling and to release a free amine in the presence of thiophenolate, which would trigger the formation of the main ring of heterocycle **22** upon condensation. If no amine deprotection occurred during the process, only a poly-Michael adduct was observed. It appeared that at least seven transformations driven by the pyridine formation would occur in up to 88% yield (Scheme 4).

Scheme 4. Proposed Mechanism



CONCLUSION

In summary, a new approach to pyridine was developed from α,β-unsaturated carbonyls through the use of Sonogashira coupling in tandem with a Fukuyama nosylamide deprotection that triggered a cascade of transformations leading to the heterocycle. This method allowed the production of substituted pyridines in four of the five substitutable positions. We hope that this research will help scientists produce pyridine moieties from simple enones/enals. Further developments and applications in the total synthesis of natural products are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in parts per million on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), and m (multiplet) and further qualified as app (apparent), br (broad), and c (complex). Coupling constants (J) are reported in Hz. HRMSs were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer.

General Procedure for the Synthesis of Sonogashira Adducts (7a-P, 14). To a stirred solution of α-iodoenone, enal or acrylate (0.10 mmol, 1 equiv), nosyl-protected propargylamine (0.20 mmol, 2 equiv), $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol, 5 mol %), and CuI (1.9 mg, 0.010 mmol, 10 mol %) in THF (0.25 mL), $iPrNH_2$ (40 μL, 0.30 mmol, 3 equiv) was added. Upon completion, the reaction mixture was diluted with EtOAc and washed twice with brine, and the solvent was removed under reduced pressure. The residue was then purified by column chromatography with a mixture of EtOAc and hexanes to give the corresponding Sonogashira adduct.

General Procedure for the Pyridine Formation (8a-P). To a stirred solution of Sonogashira adduct **7a−p** (0.0500 mmol, 1 equiv) in acetonitrile (500 μL) with K_2CO_3 (27.6 mg, 0.200 mmol, 4 equiv), thiophenol (30 μL, 0.294 mmol, 6 equiv) was then added and the reaction was stirred at room temperature. When the reaction no longer progressed (shown by TLC), the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$, the organic layer was extracted with EtOAc, then washed with brine, and the solvents were removed under reduced pressure. The residue was then purified by column chromatography with a mixture of EtOAc/hexanes to give the corresponding pyridine.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c02502.

^{1}H and ^{13}C NMR spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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CONCLUSION

Une nouvelle méthodologie de synthèse des pyridines en deux étapes à partir d'iodo-énones a été développée. Cette méthodologie s'accomplit grâce à un couplage de Sonogashira suivi d'une déprotection de Fukuyama et d'une réaction cascade Michael-rétro-Michael. Le couplage de Sonogashira est impraticable avec les bromo-énones, mais fonctionne avec des rendements modestes à très bons avec des iodo-énones. Les diénones sont particulièrement de bons substrats pour le couplage, notamment en présence d'une propargylamine substituée, ce qui limite la formation de sous-produits et augmente le rendement. Il a été démontré que les meilleures conditions pour la formation de pyridines sont le thiophénol et le carbonate de potassium dans l'acétonitrile, permettant d'obtenir 15 différentes pyridines polysubstituées avec des rendements pouvant aller jusqu'à 84%. Le groupement *p*-chlorophényl sur la propargylamine semble empêcher la formation de pyridines (**chapitre 1. Composé 8p**), même lors de l'ajout d'une base plus forte ou du chauffage de la réaction. La méthodologie s'applique aussi dans le cas des iodo-acrylates donnant des 2-pyridones en utilisant le DBU ou le tBuOK comme base. Le thioether obtenu sur la pyridine synthétisée peut participer à un couplage au nickel permettant l'ajout d'un substituant aryle à la position 4 de la pyridine.

Cette nouvelle méthode permet la synthèse de pyridines poly-substituées à quatre des cinq positions. Il est envisagé que cette méthodologie aidera la communauté scientifique intéressée à produire des pyridines variées, depuis des iodo-énones et iodo-énals. La prochaine étape sera d'appliquer cette méthodologie en synthèse de produits naturels contenant des pyridines.

Puisque cette méthodologie est aussi applicable à la synthèse de 2-pyridones, il reste encore à évaluer la portée de cette méthode pour la synthèse de 2-pyridones ainsi que la réactivité du substituant thiophényle qui l'accompagne. La variété des thiols pouvant être utilisés comme nucléophiles lors de la formation de pyridines devrait être étudiée ainsi que d'autres nucléophiles et d'autres groupements protecteurs de l'azote. De plus, serait-il possible de synthétiser des 2-aminopyridines et des 2-thiopyridines à partir d'acrylonitriles et de thioacides α-iodés-α,β-insaturés en utilisant cette méthodologie ouvrant la porte à d'autres hétérocycles?

ANNEXE A PARTIE EXPÉRIMENTALE DE L'ARTICLE

Two-Step Formation of Substituted Pyridines from Iodo-Enones

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Supporting Information

Table of Contents

I. General Information

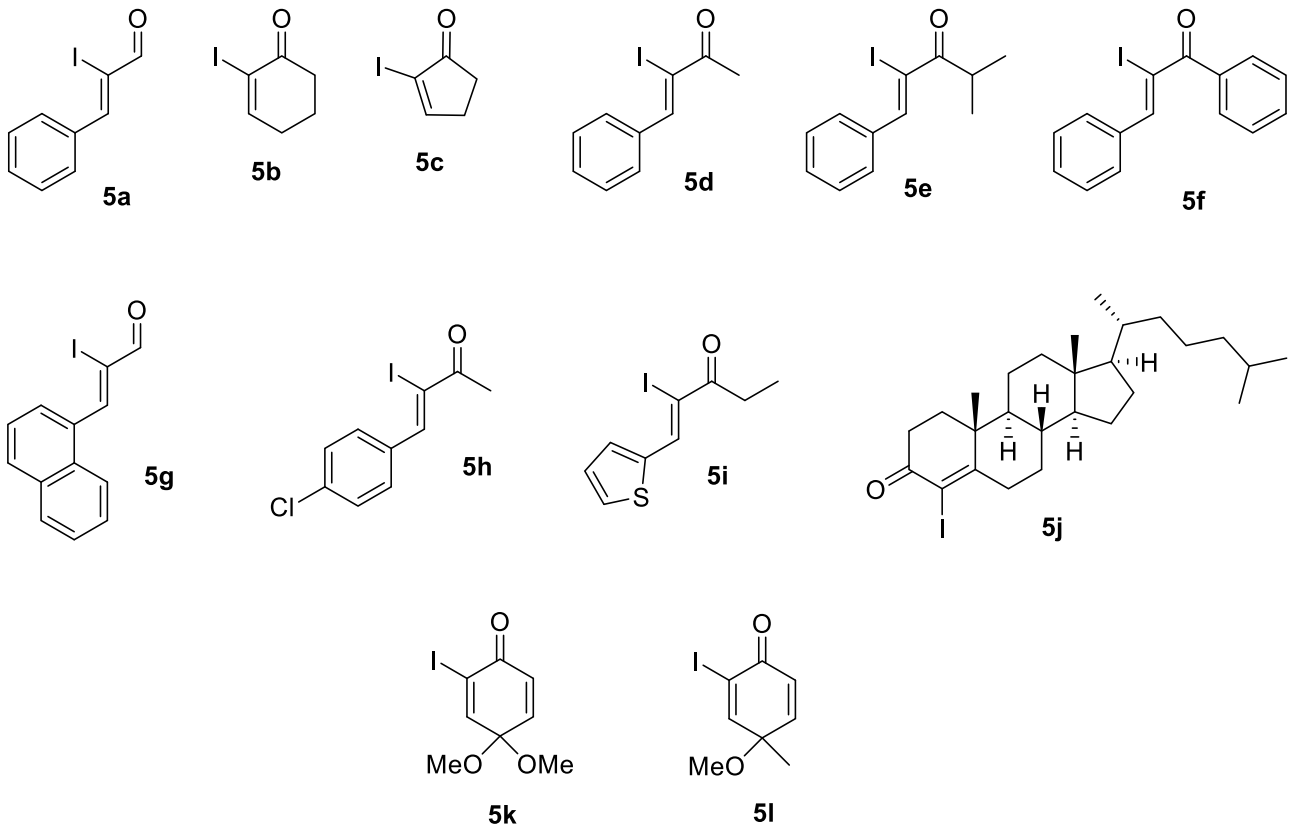
Unless otherwise indicated, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet), and further qualified as app (apparent), br (broad). Coupling constants, J, are reported in Hz. IR spectra (cm^{-1}) were recorded from thin films. Mass spectra (m/z) were measured in the electrospray (ESI) mode on a LC-UV-TOF-MS spectrometer.

II. Experimental Procedures

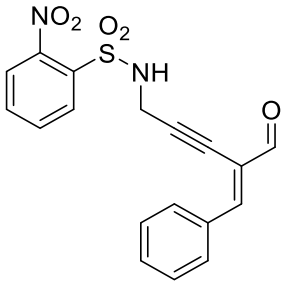
a) General Procedure for the synthesis of Sonogashira adducts (7a-p, 14)

To a stirred solution of α-iodo-enone, enal or acrylate (1 equiv), nosyl protected propargylamine (2 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) in THF (0.4M), $iPrNH_2$ (3 equiv.) was added. Upon completion, reaction mixture was diluted with EtOAc, washed twice with brine and solvent were removed under reduced pressure. The residue was then purified by column chromatography with a mixture of EtOAc/hexanes to give the corresponding Sonogashira adduct.

Structures of α-iodo-enones and enals (7a-l)

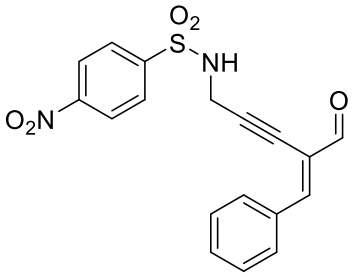


Unless specified, the propargyl amine used is ***6a***[42]*; 2-nitro-N-2-propyn-1-ylbenzenesulfonamide*

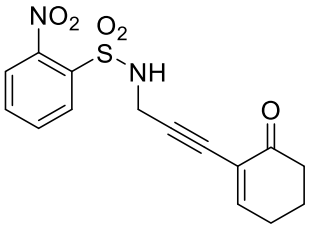


(E)-N-(4-formyl-5-phenylpent-4-en-2-yn-1-yl)-2-nitrobenzenesulfonamide (7a). From starting material **5a**[23, 43] (1.16 mmol, 300.0 mg) and a 1.5h reaction time, an orange oil was isolated (0.420 mmol, 155.4 mg, 54% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.18 – 8.08 (m, 1H), 7.93 – 7.80 (m, 2H), 7.62 (dd, *J* = 5.3, 4.0 Hz, 1H), 7.56 – 7.38 (m, 5H), 7.34 (s, 1H), 6.10 (s, 1H), 4.39 (d, *J* = 5.0 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 190.8, 153.2, 147.8, 133.8, 133.6, 133.4, 132.8, 132.2, 131.4, 130.5, 129.0, 125.5, 121.4, 94.8, 78.5, 34.5. HRMS (ESI): Calc. for $C_{18}H_{15}N_2O_5S$ $(M+H)^+$: 371.0696 found: 371.0687.

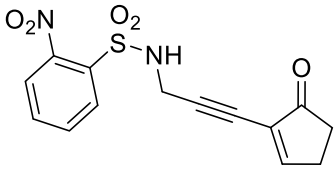
This reaction was also tested at a 3.92 mmol scale. The reaction was stopped after 2h yielding **7a**. (1.82 mmol, 673.8 mg, 46% yield). NMR spectra was consistent with previously obtained data for **7a**.



(E)-N-(4-formyl-5-phenylpent-4-en-2-yn-1-yl)-4-nitrobenzenesulfonamide (7a'). From starting materials **5a** (0.710 mmol, 183.1 mg) and *para*-nosyl propargylamine **9**[44] and a 2.5h reaction time, an orange oil was isolated (0.345 mmol, 127.6 mg, 49% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, acetone-d6) δ 9.45 (s, 1H), 8.22 – 8.08 (m, 4H), 7.97 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.65 (s, 1H), 7.56 (s, 1H), 7.48 (dt, *J* = 14.1, 6.0 Hz, 3H), 4.36 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d6) δ 191.5, 153.9, 150.7, 147.5, 134.7, 132.6, 131.3,129.7, 129.5, 125.0, 122.8, 96.7, 78.6, 34.2. HRMS (ESI): Calc. for $C_{18}H_{15}N_2O_5S$ $(M+H)^+$: 371.0696 found: 371.0685.

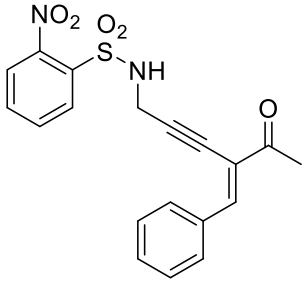


2-nitro-N-(3-(6-oxocyclohex-1-en-1-yl)prop-2-yn-1-yl)benzenesulfonamide (7b). From starting material **5b**[23] (0.315 mmol, 70.0 mg) and a 1h reaction time, an orange oil was isolated (0.140 mmol, 46.8 mg, 67% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.16 (m, 1H), 7.94 – 7.86 (m, 1H), 7.78 – 7.68 (m, 2H), 6.95 (t, *J* = 4.3 Hz, 1H), 5.85 (t, *J* = 6.1 Hz, 1H), 4.18 (d, *J* = 6.2 Hz, 2H), 2.57 – 2.19 (m, 4H), 1.95 (q, *J* = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.2, 155.4, 148.0, 134.1, 133.6, 133.1, 131.7, 125.6, 124.2, 85.7, 79.8, 37.9, 34.4, 26.4, 22.3. HRMS (ESI): Calc. for $C_{15}H_{15}N_2O_5S$ $(M+H)^+$: 335.0696 found: 335.0682.

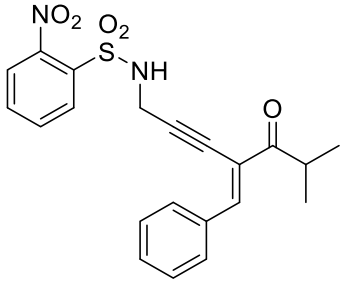


2-nitro-N-(3-(5-oxocyclopent-1-en-1-yl)prop-2-yn-1-yl)benzenesulfonamide (7c). From starting material **5c**[23] (0.962 mmol, 200.0 mg) and a 1h reaction time, a brown-orange oil was isolated (0.328 mmol, 105.2 mg, 50% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR

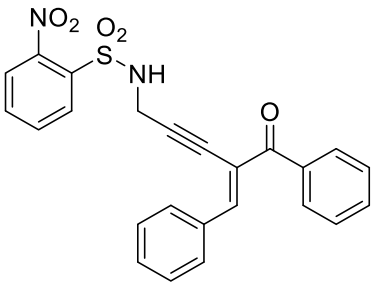
(300 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 1H), 7.94 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.54 (t, *J* = 2.9 Hz, 1H), 5.81 (t, *J* = 5.9 Hz, 1H), 4.24 (d, *J* = 6.2 Hz, 2H), 2.66 (dd, *J* = 7.7, 4.3 Hz, 2H), 2.43 – 2.36 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 205.1, 166.2, 148.1, 134.1, 133.7, 133.2, 131.7, 129.0, 125.8, 89.6, 76.0, 34.4, 33.9, 27.4. HRMS (ESI): Calc. for $C_{14}H_{13}N_2O_5S$ $(M+H)^+$: 321.0540 found: 321.0530.



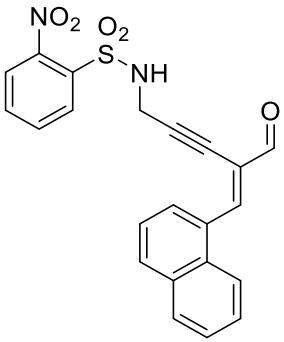
(E)-N-(4-benzylidene-5-oxohex-2-yn-1-yl)-2-nitrobenzenesulfonamide (7d). From starting material **5d**[23] (0.383 mmol, 104.1 mg) and a 2h reaction time, a white solid was isolated (0.143 mmol, 54.9 mg, 37% yield), TLC (30% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.05 (m, 1H), 7.79 (dd, *J* = 7.5, 1.8 Hz, 2H), 7.61 (t, *J* = 4.6 Hz, 2H), 7.52 – 7.46 (m, 2H), 7.40 (d, *J* = 7.1 Hz, 3H), 6.01 (t, *J* = 6.3 Hz, 1H), 4.40 (d, *J* = 6.4 Hz, 2H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 195.6, 147.8, 144.56 ,134.0, 133.8, 133.7, 132.8, 131.3, 130.4, 128.8, 125.4, 118.9, 92.9, 82.2, 34.6, 27.7. HRMS (ESI): Calc. for $C_{19}H_{17}N_2O_5S$ $(M+H)^+$: 385.0853 found: 385.0843.



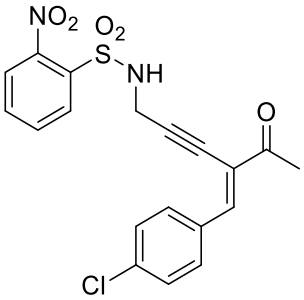
(E)-N-(4-benzylidene-6-methyl-5-oxohept-2-yn-1-yl)-2-nitrobenzenesulfonamide (7e). From starting material **5e**[22] (0.103 mmol, 31.0 mg) and a 2h reaction time, an orange oil was isolated (0.0496 mmol, 20.4 mg, 48% yield), TLC (40% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.63 (s, 1H), 7.58 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 – 7.37 (m, 5H), 5.90 (t, *J* = 6.3 Hz, 1H), 4.39 (d, *J* = 6.4 Hz, 2H), 3.24 (hept, *J* = 6.8 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 201.5, 145.1, 134.1, 133.7, 132.8, 131.3, 131.2, 130.4, 128.8, 125.5, 118.2, 92.5, 82.4, 36.7, 34.7, 18.6. HRMS (ESI): Calc. for $C_{21}H_{21}N_2O_5S$ $(M+H)^+$: 413.1166 found: 413.1150.



(E)-N-(4-benzoyl-5-phenylpent-4-en-2-yn-1-yl)-2-nitrobenzenesulfonamide (7f). From starting material **5f**[22] (0.658 mmol, 220.0 mg) and a 2h reaction time, an orange oil was isolated (0.256 mmol, 111.3 mg, 59% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 6.0, 3.3 Hz, 1H), 7.82 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.77 (s, 1H), 7.75 (d, *J* = 1.5 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.52 – 7.40 (m, 7H), 7.34 (s, 1H), 5.85 (t, *J* = 6.2 Hz, 1H), 4.33 (d, *J* = 6.3 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 193.0, 147.8, 146.6, 136.6, 134.1, 134.0, 133.6, 133.0, 132.9, 131.4, 131.2, 130.1, 129.7, 128.9, 128.4, 125.6, 119.8, 94.1, 82.2, 34.7. HRMS (ESI): Calc. for $C_{24}H_{19}N_2O_5S$ $(M+H)^+$: 447.1009 found: 447.1001.

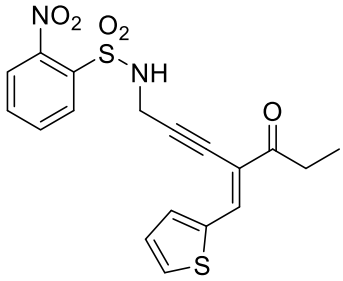


(E)-N-(4-formyl-5-(naphthalen-1-yl)pent-4-en-2-yn-1-yl)-2-nitrobenzenesulfonamide (7g). From starting material **5g**[23] (0.0828 mmol, 25.5 mg) and a 3.5h reaction time, an orange oil was isolated (0.0376 mmol, 14.5 mg, 45% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.23 (d, *J* = 7.3 Hz, 1H), 8.19 (s, 1H), 8.09 – 7.95 (m, 4H), 7.71 – 7.60 (m, 2H), 7.58 – 7.51 (m, 1H), 7.42 – 7.31 (m, 2H), 7.20 (dd, *J* = 11.1, 4.4 Hz, 1H), 5.87 (t, *J* = 6.3 Hz, 1H), 4.37 (d, *J* = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 190.5, 149.6, 147.6, 133.9, 133.6, 133.4, 132.6, 132.4, 131.4, 131.4, 129.7, 129.3, 128.0, 127.6, 126.8, 125.4, 125.4, 123.4, 122.7, 93.6, 78.5, 34.6. HRMS (ESI): Calc. for $C_{22}H_{17}N_2O_5S$ $(M+H)^+$: 421.0853 found: 421.0852.

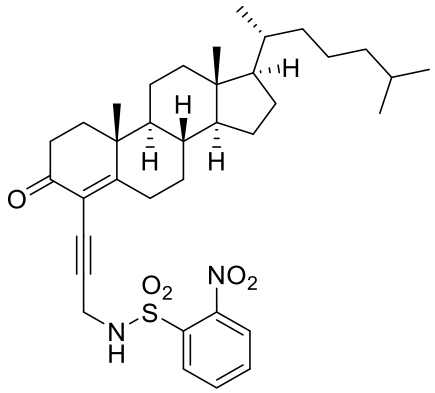


(E)-N-(4-(4-chlorobenzylidene)-5-oxohex-2-yn-1-yl)-2-nitrobenzenesulfonamide (7h). From starting material **5h**[22] (0.153 mmol, 47.0 mg) and a 3h reaction time, a yellow solid was isolated (0.0525 mmol, 22.0 mg, 34% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.12 (m, 1H), 7.79 – 7.69 (m, 3H), 7.57 (dt, *J* = 2.1, 1.7 Hz, 3H), 7.41 –

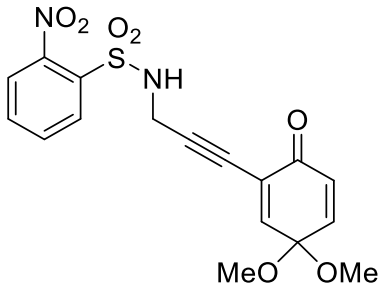
7.33 (m, 2H), 5.96 (t, *J* = 6.3 Hz, 1H), 4.40 (d, *J* = 6.3 Hz, 2H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 195.4, 143.1, 137.2, 134.1, 133.8, 132.9, 132.3, 131.6, 131.3, 129.1, 125.4, 119.3, 93.7, 82.0, 34.5, 27.8. HRMS (ESI): Calc. for $C_{19}H_{16}ClN_2O_5S$ $(M+)^+$: 419.0463 found: 419.0459.



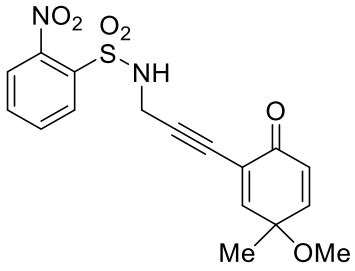
(E)-2-nitro-N-(5-oxo-4-(thiophen-2-ylmethylene)hept-2-yn-1-yl)benzenesulfonamide (7i). From starting material **5i**[22] (0.192 mmol, 56.0 mg), 20% of palladium catalyst and 40% of copper catalyst were used, and a 5h reaction time, an orange solid was isolated (0.0957 mmol, 38.7 mg, 33% yield), TLC (40% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.92 (s, 1H), 7.74 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.46 (s, 2H), 2.60 (q, *J* = 7.2 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 197.6, 147.9, 138.5, 137.8, 135.6, 134.2, 133.7, 132.8, 131.7, 131.5, 127.6, 125.3, 115.5, 95.9, 82.5, 34.9, 33.5, 8.1. HRMS (ESI): Calc. for $C_{18}H_{17}N_2O_5S_2$ $(M+H)^+$: 405.0573 found: 405.0562.



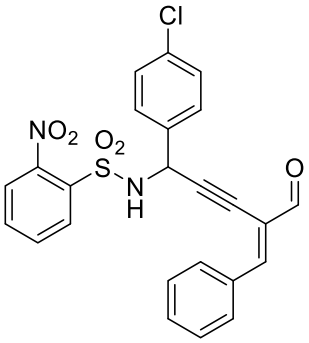
N-(3-((8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-4-yl)prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (7j). From starting material **5j**[24] (0.451 mmol, 230 mg), 20% of palladium catalyst and 40% of copper catalyst were used, and a 2.5h reaction time, a beige solid was isolated (59 mmol, 111.3 mg, 59% yield), TLC (40% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.89 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.76 – 7.65 (m, 2H), 5.81 (t, *J* = 5.9 Hz, 1H), 4.24 (d, *J* = 6.1 Hz, 2H), 2.85 (d, *J* = 13.7 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.13 – 1.76 (m, 6H), 1.68 – 1.23 (m, 12H), 1.21 – 1.07 (m, 9H), 0.94 – 0.86 (m, 10H), 0.71 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 195.2, 175.8, 148.0, 134.1, 133.5, 133.0, 131.7, 125.5, 117.8, 89.5, 79.3, 56.1, 55.9, 54.0, 42.4, 39.6, 39.6, 39.5, 36.2, 35.8, 35.2, 34.6, 34.5, 33.6, 31.8, 30.7, 28.3, 28.1, 24.2, 23.9, 22.9, 22.6, 21.1, 18.7, 17.8, 12. HRMS (ESI): Calc. for $C_{36}H_{51}N_2O_5S$ $(M+H)^+$: 623.3513 found: 623.3498.



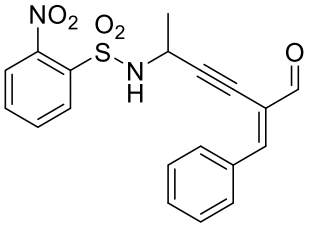
N-(3-(3,3-dimethoxy-6-oxocyclohexa-1,4-dien-1-yl)prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (7k). From starting material **5k**[25] (0.300 mmol, 84.0 mg) and a 4h reaction time, a yellow solid was isolated (0.300 mmol, 117.6 mg, 71% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.90 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.76 – 7.64 (m, 2H), 6.78 (dd, *J* = 10.4, 3.2 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.19 (d, *J* = 10.4 Hz, 1H), 5.82 (t, *J* = 6.2 Hz, 1H), 4.22 (d, *J* = 6.3 Hz, 2H), 3.32 (s, 6H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 181.0, 146.2, 143.2, 134.1, 133.8, 133.2, 131.7, 129.3, 125.8, 124.1, 92.3, 88.7, 78.4, 77.6, 77.2, 76.7, 50.5, 34.3. HRMS (ESI): Calc. for $C_{17}H_{17}N_2O_7S$ $(M+H)^+$: 393.0751 found: 393.0739.



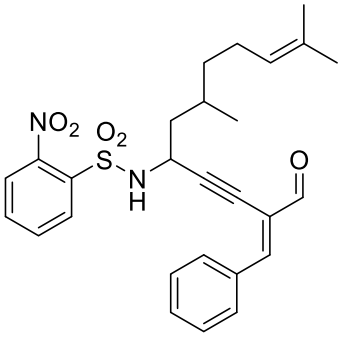
N-(3-(3-methoxy-3-methyl-6-oxocyclohexa-1,4-dien-1-yl)prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (7l). From starting material **5l**[25] (0.259 mmol, 68.4 mg) and a 1.5h reaction time, a yellow solid was isolated (0.225 mmol, 84.6 mg, 87% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 – 8.20 (m, 1H), 7.98 – 7.87 (m, 1H), 7.79 – 7.69 (m, 2H), 6.75 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 6.27 (d, *J* = 10.1 Hz, 1H), 5.86 (t, *J* = 6.0 Hz, 1H), 4.25 (d, *J* = 6.2 Hz, 2H), 3.15 (s, 3H), 1.39 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 181.2, 155.4, 151.6, 134.2, 133.7, 133.1, 131.8, 129.8, 125.7, 124.9, 87.9, 78.5, 72.8, 53.7, 34.4, 26.4. HRMS (ESI): Calc. for $C_{17}H_{17}N_2O_6S$ $(M+H)^+$: 377.0802 found: 377.0792.



(E)-N-(1-(4-chlorophenyl)-4-formyl-5-phenylpent-4-en-2-yn-1-yl)-2-nitrobenzenesulfonamide (7m). From starting materials **5a** (0.233 mmol, 60.0 mg) and **6b** and a 1.5h reaction time, an amber solid was isolated (0.194 mmol, 93.3 mg, 78% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.02 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.58 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.41 – 7.33 (m, 4H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.03 (d, *J* = 5.7 Hz, 1H), 6.53 (s, 1H), 6.40 (d, *J* = 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 188.7, 147.9, 142.9, 139.8, 136.2, 135.6, 135.6, 134.7, 134.0, 131.9, 131.8, 131.7, 129.0, 129.0, 128.8, 128.7, 127.2, 124.4, 116.6, 54.7. HRMS (ESI): Calc. for $C_{24}H_{18}ClN_2O_5S$ $(M+H)^+$: 481.0619 found: 481.0612.

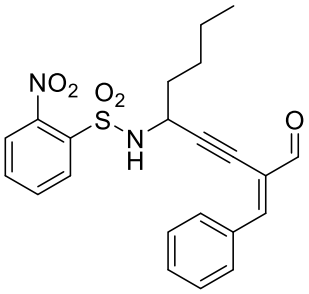


(E)-N-(5-formyl-6-phenylhex-5-en-3-yn-2-yl)-2-nitrobenzenesulfonamide (7n). From starting materials **5a** (0.202 mmol, 52.0 mg) and **6c** and a 2h reaction time, a yellow solid was isolated (0.146 mmol, 56 mg, 72% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.19 – 8.14 (m, 1H), 7.88 – 7.82 (m, 2H), 7.67 – 7.63 (m, 1H), 7.57 – 7.41 (m, 5H), 7.32 (s, 1H), 5.89 (d, *J* = 9.2 Hz, 1H), 4.83 – 4.67 (m, 1H), 1.68 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 190.4, 152.6, 147.8, 133.9, 133.4, 132.8, 132.1, 131.4, 130.4, 128.9, 125.5, 121.4, 98.9, 77.9, 42.9, 22.7. HRMS (ESI): Calc. for $C_{19}H_{17}N_2O_5S$ $(M+H)^+$: 385.0853 found: 385.0837.

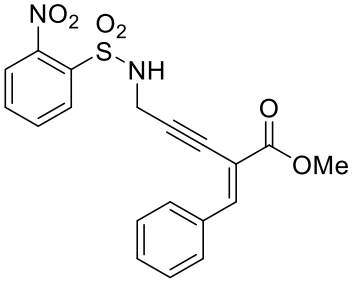


(E)-N-(2-formyl-7,11-dimethyl-1-phenyldodeca-1,10-dien-3-yn-5-yl)-2-nitrobenzenesulfonamide (7o). From from starting materials **5a** (0.484 mmol, 125.0 mg) and **6d** and a 2h reaction time, an orange oil was isolated (0.354 mmol, 174.9 mg, 73% yield), as a mixture of diastereoisomers, TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.83 (dd, *J* = 6.5, 4.8 Hz, 2H), 7.71 – 7.40 (m, 6H), 7.30 (d, *J* = 3.6 Hz, 1H), 5.86 (dd, *J* = 15.9, 9.9 Hz, 1H), 4.67 (dd, *J* = 15.6, 8.2 Hz, 1H), 1.92 – 1.79 (m, 4H), 1.58

– 1.48 (m, 7H), 1.44 – 1.38 (m, 2H), 1.04 – 0.97 (m, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 190.3, 190.3, 152.4, 152.4, 147.9, 134.2, 134.1, 133.5, 133.5, 133.4, 132.8, 132.1, 131.5, 131.4, 130.4, 128.9, 125.6, 125.5, 121.5, 98.6, 98.3, 89.3, 78.7, 78.4, 45.8, 45.4, 43.4, 40.5, 36.6, 29.5, 29.0, 25.6, 25.6, 25.5, 20.9, 20.9, 19.1, 18.8. HRMS (ESI): Calc. for $C_{27}H_{31}N_2O_5S$ $(M+H)^+$: 495.1948 found: 495.1958.

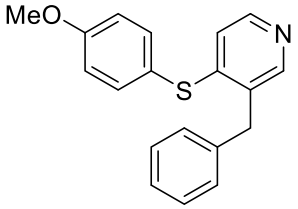


(E)-N-(2-formyl-1-phenylnon-1-en-3-yn-5-yl)-2-nitrobenzenesulfonamide (7p). From starting materials **5a** (0.399 mmol, 103.0 mg) and **6e** and a 1.5h reaction time, an orange oil was isolated (0.333 mmol, 142.1 mg, 83% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.19 – 8.10 (m, 1H), 7.89 – 7.79 (m, 2H), 7.64 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.60 – 7.38 (m, 5H), 7.31 (s, 1H), 5.87 (d, *J* = 9.8 Hz, 1H), 4.59 (dt, *J* = 9.7, 7.0 Hz, 1H), 1.91 (dd, *J* = 15.2, 7.3 Hz, 2H), 1.55 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.39 (dd, *J* = 14.5, 7.3 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 190.3, 152.4, 147.8, 134.1, 133.5, 133.4, 132.8, 132.0, 131.4, 130.4, 128.9, 125.6, 121.5, 98.4, 78.6, 47.3, 35.8, 27.6, 22.1, 13.9. HRMS (ESI): Calc. for $C_{22}H_{23}N_2O_5S$ $(M+H)^+$: 427.1322 found: 427.1314.

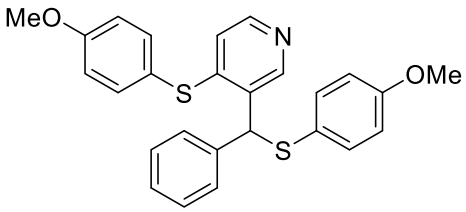


(E)-methyl 2-benzylidene-5-(2-nitrophenylsulfonamido)pent-3-ynoate (14). From starting material **13**[28] (1.00 mmol, 288.9 mg) and a 2.5h reaction time, an orange solid was isolated (0.678 mmol, 271.5 mg, 68% yield), TLC (30% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 – 8.07 (m, 1H), 7.76 (d, *J* = 6.6 Hz, 2H), 7.72 (s, 1H), 7.63 – 7.55 (m, 1H), 7.52 – 7.43 (m, 2H), 7.43 – 7.33 (m, 3H), 6.00 (t, *J* = 6.0 Hz, 1H), 4.36 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7, 147.7, 146.8, 134.0, 133.6, 133.5, 132.7, 131.4, 131.2, 130.2, 128.7, 125.3, 111.4, 91.7, 80.6, 52.9, 34.6. HRMS (ESI): Calc. for $C_{19}H_{17}N_2O_6S$ $(M+H)^+$: 401.0802 found: 401.0787.

b) Optimization of the pyridine formation



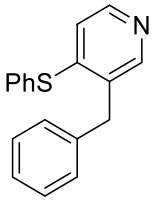
3-benzyl-4-((4-methoxyphenyl)thio)pyridine (25). To a stirred solution of Sonogashira adduct **7a** (0.141 mmol, 52.3 mg, 1 equiv.) in acetonitrile (1.4 mL, 0.1M) with K_2CO_3 (0.565 mmol, 78.1 mg, 4 equiv.), Thiophenol (0.813 mmol, 90 µL, 5,77 equiv.) was then added, and the reaction was stirred at room temperature. After 4h, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$, the organic layer was extracted with EtOAc, then washed with brine and the solvents were removed under reduced pressure. The residue was then purified by column chromatography (20 → 30% EtOAc/hexanes), the product was further purified by preparative chromatography (3% MeOH/DCM) to afford pure **25** as a yellow oil was isolated (0.0618 mmol, 19.0 mg, 44% yield), TLC (40% EtOAc/Hexanes and 3% MeOH/DCM). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.18 (d, *J* = 5.2 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.39 – 7.24 (m, 5H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 5.3 Hz, 1H), 4.12 (s, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.1, 151.0, 149.8, 147.7, 138.6, 137.6, 129.1, 128.7, 126.6, 119.9, 119.7, 115.7, 55.6, 36.9. HRMS (ESI). Calc for $C_{19}H_{18}NOS$ $(M+H)^+$: 308.1104 found :.308.1104.



4-((4-methoxyphenyl)thio)-3-(((4-methoxyphenyl)thio)(phenyl)methyl)pyridine (26). To a stirred solution of Sonogashira adduct **7a** (0.303 mmo1, 112.4 mg, 1 equiv.) in acetonitrile (3.0 mL, 0.1M) with K_2CO_3 (0.608 mmol, 84.1 mg, 2 equiv.), 4-Methoxythiophenol (0.894 mmol, 110 µL, 2.95 equiv.) was then added and the reaction was stirred at room temperature. After 15min, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$, the organic layer was extracted with EtOAc, then washed with brine and the solvents were removed under reduced pressure. The residue was then purified by column chromatography (20 → 30% EtOAc/hexanes), to afford unpure **26** (61.7 mg). Part of the product (20.3 mg) was further purified by preparative chromatography (3% MeOH/DCM) to afford **26** as a yellow oil was isolated (0.0182 mmol, 8.1 mg, 18% yield based on the ratio of unpure product purified by preparative chromatography), TLC (40% EtOAc/Hexanes and 3% MeOH/DCM). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.13 (s, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.29 (m, 7H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H), 5.82 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H).

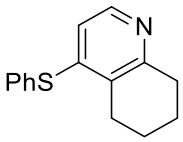
c) General Procedure for the pyridine formation (8a-p)

To a stirred solution of Sonogashira adduct **7a-p** (1 equiv.) in acetonitrile (0.1M) with K_2CO_3 (4 equiv.), thiophenol (6 equiv.) was then added, and the reaction was stirred at room temperature. Upon completion, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$, the organic layer was extracted with EtOAc, then washed with brine and the solvents were removed under reduced pressure. The residue was then purified by column chromatography with a mixture of EtOAc/hexanes to give the corresponding pyridine.



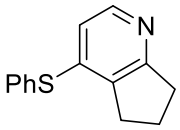
3-benzyl-4-(phenylthio)pyridine (8a). From Sonogashira adduct **7a**. (0.546 mmol, 202.1 mg) and a 2.5h reaction time, a yellow solid was isolated (0.461 mmol, 127.8 mg, 84% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.20 (d, *J* = 5.3 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.49 – 7.43 (m, 3H), 7.39 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H), 6.66 (d, *J* = 5.4 Hz, 1H), 4.13 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.1, 149.7, 147.8, 138.6, 135.4, 132.9, 130.0, 130.0, 129.7, 129.1, 128.7, 126.7, 120.8, 37.0. HRMS (ESI): Calc. for $C_{18}H_{16}NS$ $(M+H)^+$: 278.0998 found: 278.0994.

This reaction was also tested at a 1.26 mmol scale. The reaction was stopped after 2.5h yielding **8a** (1.11 mmol, 308.1 mg, 88% yield). NMR spectra was consistent with previously obtained data for **8a**.

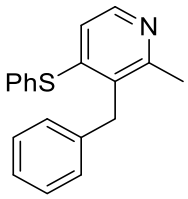


4-(phenylthio)-5,6,7,8-tetrahydroquinoline (8b). From Sonogashira adduct **7b** (0.144 mmol, 48.1 mg) and a 4h reaction time, a yellow-white oil was isolated (0.0854 mmol, 20.6 mg, 59% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 4.9 Hz, 1H), 7.54 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.47 (dd, *J* = 4.2, 2.4 Hz, 3H), 6.43 (d, *J* = 5.3 Hz, 1H), 2.93 (s, 2H), 2.75 (s, 2H), 1.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 149.8, 146.2, 135.5, 130.1, 130.0, 129.6, 129.2, 128.8, 117.8, 33.0, 26.3, 22.9, 22.8. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.6, 149.8, 146.2,

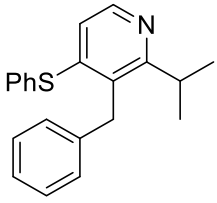
135.5, 130.1, 130.0, 129.6, 128.8, 117.8, 33.0, 26.3, 22.9, 22.8. HRMS (ESI): Calc. for $C_{15}H_{16}NS$ $(M+H)^+$: 242.0998 found: 242.0989.



4-(phenylthio)-6,7-dihydro-5H-cyclopenta[b]pyridine (8c). From Sonogashira adduct **7c** (0.161 mmol, 51.5 mg) and a 4h reaction time, a white oil was isolated (0.0915 mmol, 20.8 mg, 57% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 5.4 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.49 – 7.42 (m, 3H), 6.47 (d, *J* = 5.4 Hz, 1H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.17 (q, *J* = 7.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.9, 147.8, 145.8, 135.0, 133.9, 129.9, 129.9, 129.4, 117.8, 34.5, 29.8, 22.5. HRMS (ESI): Calc. for $C_{14}H_{14}NS$ $(M+H)^+$: 228.0841 found: 228.0833.

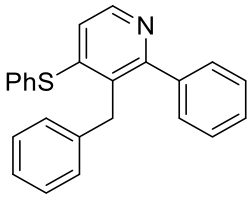


3-benzyl-2-methyl-4-(phenylthio)pyridine (8d). From Sonogashira adduct **7d**. (0.0909 mmol, 32.2 mg) and a 3h reaction time, a yellow oil was isolated (0.0624 mmol, 18.2 mg, 75% yield), TLC (50% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 5.3 Hz, 1H), 7.52 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.48 – 7.41 (m, 3H), 7.36 – 7.21 (m, 3H), 7.17 (d, *J* = 6.9 Hz, 2H), 6.60 (d, *J* = 5.4 Hz, 1H), 4.27 (s, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 157.6, 150.4, 146.8, 138.2, 135.2, 130.8, 130.6, 130.0, 129.5, 128.7, 128.2, 126.4, 119.5, 35.5, 23.0. HRMS (ESI): Calc. for $C_{19}H_{18}NS$ $(M+H)^+$: 292.1154 found: 292.1145.

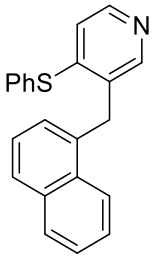


3-benzyl-2-isopropyl-4-(phenylthio)pyridine (8e). From Sonogashira adduct **7e**. (0.0243 mmol, 10.0 mg) and a 0.75h reaction time, a yellow solid was isolated (0.0207 mmol, 6.6 mg, 82% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.3 Hz, 1H), 7.49 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.42 (dd, *J* = 6.4, 3.7 Hz, 3H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 6.54 (d, *J* = 5.3 Hz, 1H), 4.29 (s, 2H), 3.24 (hept, *J* = 6.8 Hz, 1H), 1.17 (d, *J* = 6.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5, 147.1,

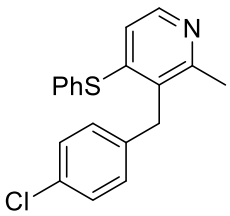
138.9, 135.3, 130.8, 130.0, 129.5, 128.9, 128.7, 128.2, 126.4, 119.1, 34.7, 31.5, 22.4. HRMS (ESI): Calc. for $C_{21}H_{22}NS$ $(M+H)^+$: 320.1467 found: 320.1461.



3-benzyl-2-phenyl-4-(phenylthio)pyridine (8f). From Sonogashira adduct **7f**. (0.218 mmol, 94.5 mg) and a 1h reaction time, a yellow oil was isolated (0.137 mmol, 48.5 mg, 63% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.3 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.46 – 7.32 (m, 8H), 7.31 – 7.20 (m, 3H), 7.06 (d, *J* = 6.9 Hz, 2H), 6.70 (d, *J* = 5.3 Hz, 1H), 4.26 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.7, 152.1, 147.1, 140.5, 139.3, 135.4, 130.6, 130.0, 129.7, 129.6, 128.9, 128.6, 128.3, 128.2, 128.2, 126.2, 120.2, 36.2. HRMS (ESI): Calc. for $C_{24}H_{20}NS$ $(M+H)^+$: 354.1311 found: 354.1297.

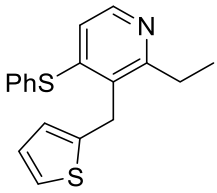


3-(naphthalen-1-ylmethyl)-4-(phenylthio)pyridine (8g). From Sonogashira adduct **7g**. (0.0502 mmol, 21.1 mg) and a 1.5h reaction time, a yellow oil was isolated (0.0312 mmol, 10.2 mg, 62% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.95 (ddd, *J* = 12.5, 6.3, 3.4 Hz, 3H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.44 (m, 8H), 7.26 (d, *J* = 7.0 Hz, 1H), 6.76 (d, *J* = 3.9 Hz, 1H), 4.55 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.2, 149.3, 147.2, 135.4, 134.1, 134.0, 132.1, 130.2, 129.9, 129.6, 129.0, 127.8, 127.2, 126.5, 126.0, 125.7, 123.9, 34.1. HRMS (ESI): Calc. for $C_{22}H_{18}NS$ $(M+H)^+$: 328.1154 found: 328.1151.

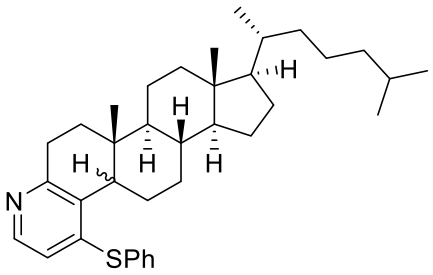


3-(4-chlorobenzyl)-2-methyl-4-(phenylthio)pyridine (8h). From Sonogashira adduct **7h**. (0.0504 mmol, 21.1 mg) and a 2h reaction time, an orange solid was isolated (0.0298 mmol, 9.7 mg, 60% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 4.1 Hz, 1H), 7.56 – 7.43 (m, 5H), 7.29 (d, *J* = 5.1 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 5.4 Hz, 1H), 4.22 (s, 2H), 2.51 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$)

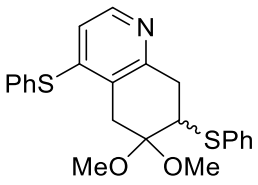
δ 157.3, 150.8, 146.8, 136.6, 135.3, 132.3, 130.4, 130.1, 129.7, 129.5, 128.9, 119.5, 34.9, 22.8. HRMS (ESI): Calc. for $C_{19}H_{17}ClNS$ $(M+H)^+$: 326.0765 found: 326.0764.



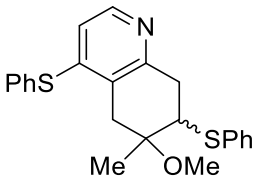
2-ethyl-4-(phenylthio)-3-(thiophen-2-ylmethyl)pyridine (8i). From Sonogashira adduct **7i**. (0.0846 mmol, 34.2 mg) and a 2h reaction time, a yellow-orange solid was isolated (0.0620 mmol, 19.3 mg, 73% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 3.3 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.47 – 7.41 (m, 3H), 7.18 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.79 (dd, *J* = 3.4, 1.1 Hz, 1H), 6.59 (d, *J* = 5.3 Hz, 1H), 4.42 (s, 2H), 2.91 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.7, 150.2, 147.3, 141.7, 135.1, 131.0, 129.9, 129.4, 126.9, 125.2, 123.9, 119.7, 29.8, 28.6, 13.6. HRMS (ESI): Calc. for $C_{18}H_{18}NS_2$ $(M+H)^+$: 312.0875 found: 312.0866.



(6aR,6bS,8aR,9R,11aS,11bS)-6a,8a-dimethyl-9-((R)-6-methylheptan-2-yl)-1-(phenylthio)-6,6a,6b,7,8,8a,9,10,11,11a,11b,12,13,13a-tetradecahydro-5H-cyclopenta[5,6]naphtho[2,1-f]quinoline (8j). From Sonogashira adduct **7j**. (0.153 mmol, 95.5 mg) and a 4h reaction time, a brown solid was isolated (0.0853 mmol, 45.2 mg, 45% yield), as a mixture of diastereoisomers (E/Z) 1.2:1, TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (45% d, *J* = 3.5 Hz, 1H), 8.00 (55%, d, *J* = 3.5 Hz, 1H), 7.56 – 7.38 (m, 5H), 6.55 (55% d, *J* = 5.0 Hz, 1H), 6.50 (45%, d, *J* = 5.0 Hz, 1H), 3.23 – 2.54 (m, 3H), 2.08 – 1.79 (m, 5H), 1.72 – 1.49 (m, 6H), 1.44 – 1.26 (m, 7H), 1.22 – 1.10 (m, 7H), 0.97 – 0.86 (m, 13H), 0.72 (55%, s, 3H), 0.71 (45%, s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 135.4, 134.9, 132.5, 131.0, 129.9, 129.8, 129.4, 129.2, 58.3, 56.6 56.4, 56.2, 54.0, 49.4, 46.9, 43.1, 43.0, 42.6, 40.3, 39.9, 39.6, 36.4, 36.3, 36.0, 35.9, 35.8, 34.4, 33.1, 32.0, 31.2, 30.5, 29.4, 28.5, 28.3, 28.1, 25.4, 25.0, 24.4, 24.2, 24.0, 23.0, 22.7, 22.1, 21.9, 20.8, 18.9, 18.8, 15.5, 12.4, 12.0. HRMS (ESI): Calc. for $C_{36}H_{52}NS$ $(M+H)^+$: 530.3815 found: 530.3816.



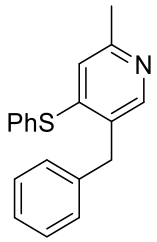
6,6-dimethoxy-4,7-bis(phenylthio)-5,6,7,8-tetrahydroquinoline (8k). From Sonogashira adduct **7k**. (0.112 mmol, 43.9 mg) and a 0.5h reaction time, a yellow oil was isolated (0.0806 mmol, 33mg, 72% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 5.5 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.49 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.44 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.29 (dd, *J* = 7.1, 5.3 Hz, 3H), 6.54 (d, *J* = 5.5 Hz, 1H), 3.92 (dd, 1H), 3.40 (d, *J* = 3.8 Hz, 1H), 3.38 (s, 3H), 3.30 – 3.20 (m, 5H), 3.00 (d, *J* = 17.3 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.0, 144.7, 135.6, 133.5, 133.4, 130.3, 130.2, 129.3, 128.7, 128.0, 125.8, 118.3, 100.5, 48.6, 48.5, 47.5, 35.6, 31.2. HRMS (ESI): Calc. for $C_{23}H_{24}NO_2S_2$ $(M+H)^+$: 410.1243 found: 410.1253.



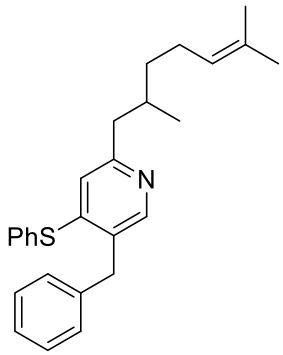
6-methoxy-6-methyl-4,7-bis(phenylthio)-5,6,7,8-tetrahydroquinoline (8l). From Sonogashira adduct **7l**. (0.209 mmol, 78.6 mg) and a 3h reaction time, two diastereoisomers were isolated (0.127 mmol, 50.1 mg, 61% total yield, d.r. = 1.8:1).

8l-1; A yellow oil was isolated (0.0808 mmol, 31.8 mg), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 5.3 Hz, 1H), 7.59 – 7.44 (m, 7H), 7.34 – 7.25 (m, 3H), 6.48 (d, *J* = 5.3 Hz, 1H), 3.64 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.45 – 3.16 (m, 6H), 2.73 – 2.60 (m, 1H), 1.56 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.4, 149.8, 146.9, 135.4, 135.1, 132.9, 130.1, 129.7, 129.7, 129.1, 127.4, 125.7 118.3, 74.9, 53.4, 49.7, 37.2, 35.4, 23.1. HRMS (ESI): Calc. for $C_{23}H_{24}NOS_2$ $(M+H)^+$: 394.1294 found: 394.1284.

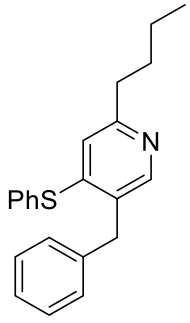
8l-2; A yellow oil was isolated (0.0465 mmol, 18.3 mg), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 5.3 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.52 – 7.45 (m, 5H), 7.36 – 7.27 (m, 3H), 6.48 (d, *J* = 5.3 Hz, 1H), 3.77 (t, *J* = 4.3 Hz, 1H), 3.46 (dd, *J* = 17.7, 5.1 Hz, 1H), 3.33 (s, 3H), 3.10 (dd, *J* = 17.8, 4.3 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.89 (d, *J* = 17.3 Hz, 1H), 1.57 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.6, 149.9, 146.8, 135.5, 134.8, 132.7, 130.1, 129.7, 129.2, 127.5, 125.9, 118.2, 75.5, 51.0, 49.5, 36.5, 34.9, 21.5. HRMS (ESI): Calc. for $C_{23}H_{24}NOS_2$ $(M+H)^+$: 394.1294 found: 394.1295.



5-benzyl-2-methyl-4-(phenylthio)pyridine (8n). From Sonogashira adduct **7n**. (0.124 mmol, 47.5 mg) and a 0.5h reaction time, a cream solid was isolated (0.101 mmol, 29.5 mg, 82% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.52 – 7.41 (m, 5H), 7.37 – 7.23 (m, 5H), 6.56 (s, 1H), 4.10 (s, 2H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 156.5, 149.5, 139.0, 135.0, 130.4, 130.3, 130.0, 129.4, 129.0, 128.7, 126.5, 120.6, 36.7, 24.1. HRMS (ESI): Calc. for $C_{19}H_{18}NS$ $(M+H)^+$: 292.1154 found: 292.1147.



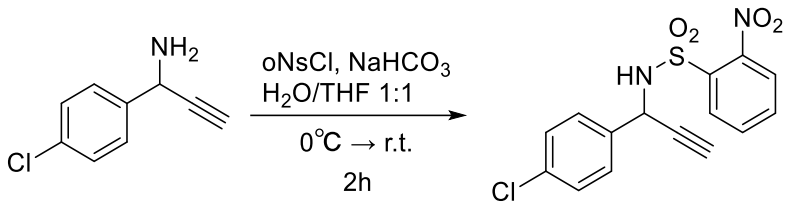
5-benzyl-2-(2,6-dimethylhept-5-en-1-yl)-4-(phenylthio)pyridine (8o). From Sonogashira adduct **7o**. (0.165 mmol, 81.7 mg) and a 1h reaction time, a yellow oil was isolated (0.125 mmol, 50.1 mg, 76% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.51 – 7.42 (m, 5H), 7.41 – 7.13 (m, 6H), 6.53 (s, 1H), 4.11 (s, 2H), 2.60 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.36 (dd, *J* = 13.3, 8.2 Hz, 1H), 1.90 – 1.73 (m, 3H), 1.53 (s, 6H), 1.33 – 1.27 (m, 2H), 0.79 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 159.3, 149.7, 149.0, 139.0, 134.7, 130.8, 130.7, 129.9, 129.3, 129.0, 128.7, 126.5, 121.2, 89.4, 45.5, 40.5, 36.7, 33.4, 25.6, 25.6, 21.2, 19.3. HRMS (ESI): Calc. for $C_{27}H_{32}NS$ $(M+H)^+$: 402.2250 found: 402.2251.



5-benzyl-2-butyl-4-(phenylthio)pyridine (8p). From Sonogashira adduct **7p**. (0.254 mmol, 108.3 mg) and a 1h reaction time, a yellow oil was isolated (0.152 mmol, 50.6 mg, 60% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.51 – 7.36 (m, 5H), 7.34 – 7.17 (m, 5H), 6.54 (s, 1H), 4.07 (s, 2H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.54 (dt, *J* = 15.4, 7.5 Hz, 2H), 1.27 (dt, *J* = 14.9, 7.4 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 149.7, 149.1, 139.0, 134.8, 130.7, 130.5, 129.9, 129.3, 129.0, 128.6, 126.5, 120.2, 37.7, 36.7, 31.8, 22.4, 14.0. HRMS (ESI): Calc. for $C_{22}H_{24}NS$ $(M+H)^+$: 334.1624 found: 334.1626.

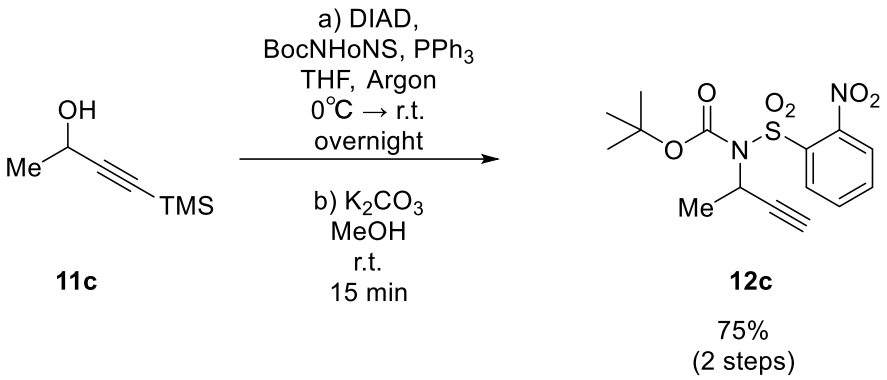
d) General and Experimental procedures for the synthesis of substituted propargyl amines

N-(1-(4-chlorophenyl)prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (6b).

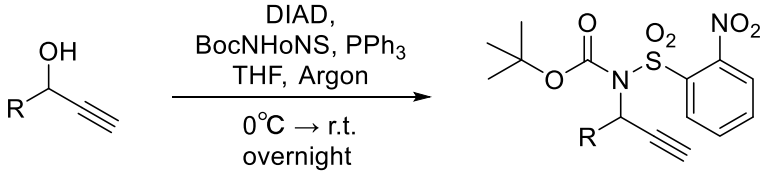


10 **6b**

4-Chloro-α-ethynylbenzenemethanamine[29] **10** (1.26 mmol, 208.0 mg, 1.00 equiv.) was dissolved in THF/H_2O 1:1 (4.2 mL, 0.3M) and cooled to 0°C in an ice bath. $NaHCO_3$ (2.53 mmol, 213 mg, 2.01 equiv.) was added followed by 2-nitrobenzenesulfonyl chloride (1.23 mmol, 272 mg, 0.97 equiv.). The reaction was let back to room temperature and stirred for 2 hours. The mixture was diluted with EtOAc, washed twice with a sat. NH_4Cl and washed twice with brine. The solvents were removed under reduced pressure. The beige solid obtained which was already quite pure by NMR was passed through column chromatography (20% EtOAc, 0.1% Et_3N /hexanes → 50% EtOAc, 0.1% Et_3N /hexanes) to afford pure **6b** as a white solid (1.12 mmol, 355.4 mg, 91% yield), TLC (40% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.08 (m, 1H), 8.02 – 7.88 (m, 1H), 7.83 – 7.70 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.01 (d, *J* = 9.6 Hz, 1H), 5.47 (dd, *J* = 9.6, 2.2 Hz, 1H), 2.30 (d, *J* = 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 135.0, 134.8, 134.2, 133.9, 133.0, 131.6, 129.1, 128.8, 125.6, 79.2, 75.8, 49.3. HRMS (ESI): Calc. for $C_{15}H_{11}ClN_2NaO_4S$ $(M+Na)^+$: 373.0020 found: 373.0025.

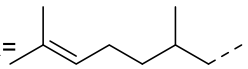


tert-butyl but-3-yn-2-yl((2-nitrophenyl)sulfonyl)carbamate (12c). Substituted propargylic alcohol **11c**[46] (1.42 mmol, 202.5 mg, 1.0 equiv.) N-(tert-Butoxycarbonyl)-2-nitrobenzenesulfonamide[47a] (1.71 mmol, 516 mg, 1.2 equiv.) and PPh_3 (1.71 mmol, 448 mg, 1.2 equiv.) were diluted in dry THF (9.5 mL, 0.15M) under argon and cooled to 0°C in an ice bath. Diisopropyl azidocarboxylate (1.71 mmol, 340µL, 1.2 equiv.) was then added dropwise. The reaction was let back to room temperature and stirred overnight. The solvents were evaporated under reduced pressure and the liquid residue was purified by column chromatography using a mixture of EtOAc/hexanes to give the boc/nosyl protected substituted propargyl amine which was then dissolved in MeOH (6mL, 1M) and K_2CO_3 (1.42 mmol, 197 mg, 1 equiv.) was added. The reaction was stirred for 1.5h after which the reaction mixture was diluted with water, extracted three times with EtOAc, washed once with brine and the solvents were removed under reduced pressure. The crude was purified by column chromatography (15 → 30% EtOAc/hexanes) to afford **12c** as a pink oil (1.07 mmol, 378.5 mg, 75% yield over 2 steps), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 8.28 (m, 1H), 7.85 – 7.72 (m, 3H), 5.29 (qd, *J* = 7.0, 2.5 Hz, 1H), 2.42 (d, *J* = 2.5 Hz, 1H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.8, 148.0, 134.3, 133.8, 133.0, 132.1, 124.7, 85.8, 82.1, 71.6, 46.1, 28.0, 21.9. HRMS (ESI): Calc. for $C_{15}H_{18}N_2NaO_6S$ $(M+Na)^+$: 377.0778 found: 377.0773.



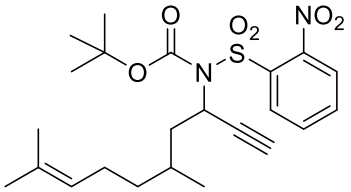
11d,e **12d,e**

11d: R=

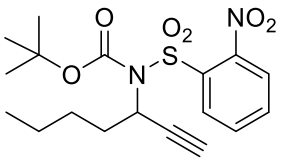


11e: R=Bu

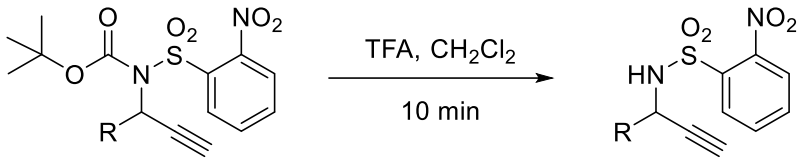
Substituted propargylic alcohol **11**[48,49] (1.0 equiv.) N-(tert-Butoxycarbonyl)-2-nitrobenzenesulfonamide[47a] (1.2 equiv.) and PPh_3 (1.2 equiv.) were diluted in dry THF (0.15M) under argon and cooled to 0°C in an ice bath. Diisopropyl azidocarboxylate (1.2 equiv.) was then added dropwise. The reaction was let back to room temperature and stirred overnight. The solvents were evaporated under reduced pressure and the liquid residue was purified by column chromatography using a mixture of EOAc/hexanes to give the boc-nosyl protected substituted propargylic amines **12d,e**.



tert-butyl-(5,9-dimethyldec-8-en-1-yn-3-yl)((2-nitrophenyl)sulfonyl)-carbamate (12d). From propargylic alcohol **11d**. (2.88 mmol, 518.3 mg), a white solid was isolated (2.19 mmol, 1017.1 mg, 76% yield), as a mixture of diastereoisomers, TLC (20% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 – 8.28 (m, 1H), 7.86 – 7.73 (m, 3H), 5.22 (ddt, *J* = 10.1, 5.0, 2.6 Hz, 1H), 5.14 (t, *J* = 7.0 Hz, 1H), 2.45 (dd, *J* = 3.9, 2.4 Hz, 1H), 2.12 – 1.97 (m, 3H), 1.77 – 1.68 (m, 4H), 1.64 (s, 3H), 1.51 – 1.45 (m, 1H), 1.43 (50%, s, 9H), 1.41 (50%, s, 9H), 1.38 – 1.18 (m, 2H), 1.04 (dd, *J* = 6.5, 1.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.8, 149.6, 148.1, 148.0, 134.2, 134.2, 133.7, 132.4, 132.1, 132.1, 131.4, 131.3, 124.6, 124.6, 124.5, 85.7, 85.7, 81.3, 80.8, 72.7, 72.5, 49.3, 49.2, 42.2, 42.0, 37.4, 36.3, 30.1, 29.9, 27.9, 27.9, 25.7, 25.4, 25.3, 19.9, 18.9, 17.7, 17.7. HRMS (ESI): Calc. for $C_{23}H_{33}N_2O_6S$ $(M+H)^+$: 465.2054 found: 465.2021.

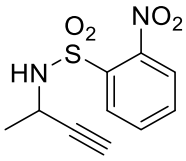


tert-butyl hept-1-yn-3-yl((2-nitrophenyl)sulfonyl)carbamate (12e). From propargylic alcohol **11e**. (1.54 mmol, 172.9 mg), a yellow oil was isolated (1.32 mmol, 521.9 mg, 85% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 – 8.29 (m, 1H), 7.88 – 7.68 (m, 3H), 5.10 (ddd, *J* = 8.9, 6.7, 2.4 Hz, 1H), 2.45 (d, *J* = 2.4 Hz, 1H), 2.19 (ddd, *J* = 14.5, 9.2, 4.6 Hz, 1H), 2.13 – 1.95 (m, 1H), 1.60 – 1.47 (m, 4H), 1.43 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.5, 147.9, 134.3, 133.4, 132.1, 132.0, 124.5, 85.6, 80.9, 72.5, 50.6, 34.7, 28.4, 27.7, 21.9, 13.8. HRMS (ESI): Calc. for $C_{18}H_{25}N_2O_6S$ $(M+H)^+$: 397.1428 found: 397.1391.



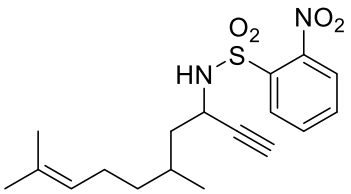
12c-e **6c-e**

Boc-nosyl protected substituted propargyl amines **12c-e** was dissolved in DCM (0.2M). Trifluoroacetic acid (0.2M) was added under agitation. After 10 minutes the solvents were quickly evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexanes with 0.1% of Et_3N) to afford the nosyl protected substituted propargylic amine.

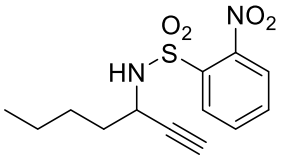


N-(but-3-yn-2-yl)-2-nitrobenzenesulfonamide (6c). From boc-nosyl protected substituted propargyl amines **12c** (1.01 mmol, 359.3 mg), a white solid was isolated (0.851 mmol, 216.5 mg, 84% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 1H), 7.96 – 7.88 (m, 1H), 7.77 (dd, *J* = 5.7, 3.6 Hz, 2H), 5.66 (d, *J* = 9.4 Hz, 1H), 4.43 – 4.29 (m, 1H), 2.00 (d, *J* = 2.2 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ

148.0, 134.2, 133.9, 133.0, 131.7, 125.5, 82.0, 72.4, 42.0, 23.1. HRMS (ESI): Calc. for $C_{10}H_{11}N_2O_4S$ $(M+H)^+$: 255.0434 found: 255.0426.

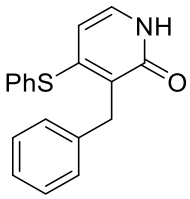


N-(5,9-dimethyldec-8-en-1-yn-3-yl)-2-nitrobenzenesulfonamide (6d). From boc-nosyl protected substituted propargyl amines **12d** (1.57 mmol, 730.3 mg), an orange oil was isolated (1.46 mmol, 531.4 mg, 93% yield), as a mixture of diastereoisomers, TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 1H), 7.94 – 7.85 (m, 1H), 7.81 – 7.71 (m, 2H), 5.61 (dd, *J* = 11.5, 10.1 Hz, 1H), 4.33 – 4.21 (m, 1H), 1.95 (dd, *J* = 6.7, 2.2 Hz, 1H), 1.85 – 1.66 (m, 4H), 1.55 (s, 3H), 1.54 (s, 3H), 1.39 – 1.24 (m, 3H), 0.94 (50%, d, *J* = 6.1 Hz, 3H), 0.92 (50%, d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.5, 156.5, 156.0, 156.0, 147.9, 134.2, 134.2, 133.9, 133.0, 131.6, 125.5, 124.4, 116.4, 112.6, 89.4, 81.4, 81.0, 73.2, 72.8, 44.8, 44.4, 43.5, 43.4, 40.4, 36.5, 36.4, 29.3, 28.9, 25.6, 25.5, 20.9, 20.8, 19.0, 18.8. HRMS (ESI): Calc. for $C_{18}H_{25}N_2O_4S$ $(M+H)^+$: 365.1530 found: 365.1519.



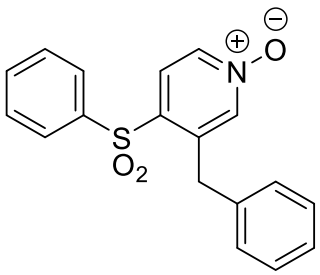
N-(hept-1-yn-3-yl)-2-nitrobenzenesulfonamide (6e). From boc-nosyl protected substituted propargyl amines **12e** (1.14 mmol, 451.6 mg), a yellow oil was isolated (1.04 mmol, 309.5 mg, 92% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.9, 3.4 Hz, 1H), 7.91 (dd, *J* = 5.8, 3.5 Hz, 1H), 7.76 (dd, *J* = 5.9, 3.4 Hz, 2H), 5.63 (d, *J* = 9.7 Hz, 1H), 4.21 (dtd, *J* = 9.3, 7.0, 2.2 Hz, 1H), 1.97 (d, *J* = 2.3 Hz, 1H), 1.82 – 1.68 (m, 2H), 1.47 – 1.29 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.9, 134.2, 133.9, 133.0, 131.6, 125.5, 81.2, 73.0, 46.3, 35.9, 27.4, 22.0, 13.9. HRMS (ESI): Calc. for $C_{13}H_{17}N_2O_4S$ $(M+H)^+$: 297.0904 found: 297.0890.

e) Experimental procedure for the 2-pyridone synthesis

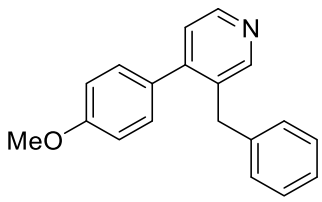


3-benzyl-4-(phenylthio)pyridin-2(1H)-one (15). To a solution stirred of acrylate Sonogashira adduct **14** (0.024 mmol, 9.8 mg, 1 equiv.) in acetonitrile (250µL, 0.1M) under argon was added DBU (0.20 mmol, 20µL, 8 equiv.) followed by thiophenol (0.15 mmol, 6 15 µL, equiv.). When the reaction completed (shown by TLC), a saturated solution of $Na_2S_2O_3$ was added to quench the reaction mixture. Then, EtOAc was added and the organic phase was separated and washed once with brine.The solvents were removed under reduced pressure. The residue was purified by column chromatography (60% EtOAc/hexane with 0.1% Et_3N → 0.1% Et_3N and 2% MeOH/EtOAc) to give the 2-pyridone **15** as a white solid (0.012 mmol, 3.6 mg, 50% yield), TLC (40% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.46 – 7.39 (m, 5H), 7.29 (t, *J* = 7.3 Hz, 3H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 5.74 (d, *J* = 7.0 Hz, 1H), 4.16 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.4, 152.6, 139.5 (s), 135.3, 131.3, 130.6, 129.8, 129.6, 128.9, 128.4, 126.2, 106.1, 33.1, 29.9. HRMS (ESI): Calc. for $C_{18}H_{16}NOS$ $(M+H)^+$: 294.0947 found: 294.0931.

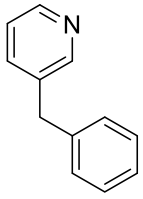
f) Experimental procedure for the synthesis of 16-18



3-benzyl-4-(phenylsulfonyl)pyridine-N-oxide (16). To a stirred solution of pyridine **8a** (0.036 mmol, 9.9 mg, 1 equiv.) in DCM (360µL, 0.1M) at 0°C, was added mCPBA (0.089 mmol, 22 mg, 2.5 equiv.). The reaction mixture was kept at 0°C in an ice bath and after 4h the reaction mixture was filtered over cellite. The filtrate was diluted with EtOAc, washed twice with sat. $Na_2S_2O_3$, twice with sat. $NaHCO_3$ and the solvents were removed under reduced pressure to afford sulfone **16** as white solid (0.026 mmol, 8.0 mg, 72% yield), TLC (50% EtOAc/Hexanes). NMR data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 6.9, 1.6 Hz, 1H), 8.07 (d, *J* = 6.9 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.74 (d, *J* = 0.6 Hz, 1H), 7.66 (dd, *J* = 8.5, 6.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.26 (dd, *J* = 5.0, 1.8 Hz, 3H), 6.93 (dd, *J* = 6.4, 2.9 Hz, 2H), 4.18 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 141.8, 140.0, 139.5, 137.5, 135.8, 135.5, 134.2, 129.7, 129.4, 129.2, 127.9, 127.6, 126.2, 35.4. HRMS (ESI): Calc. for $C_{18}H_{16}NO_3S$ $(M+H)^+$: 326.0845. found :326.0835

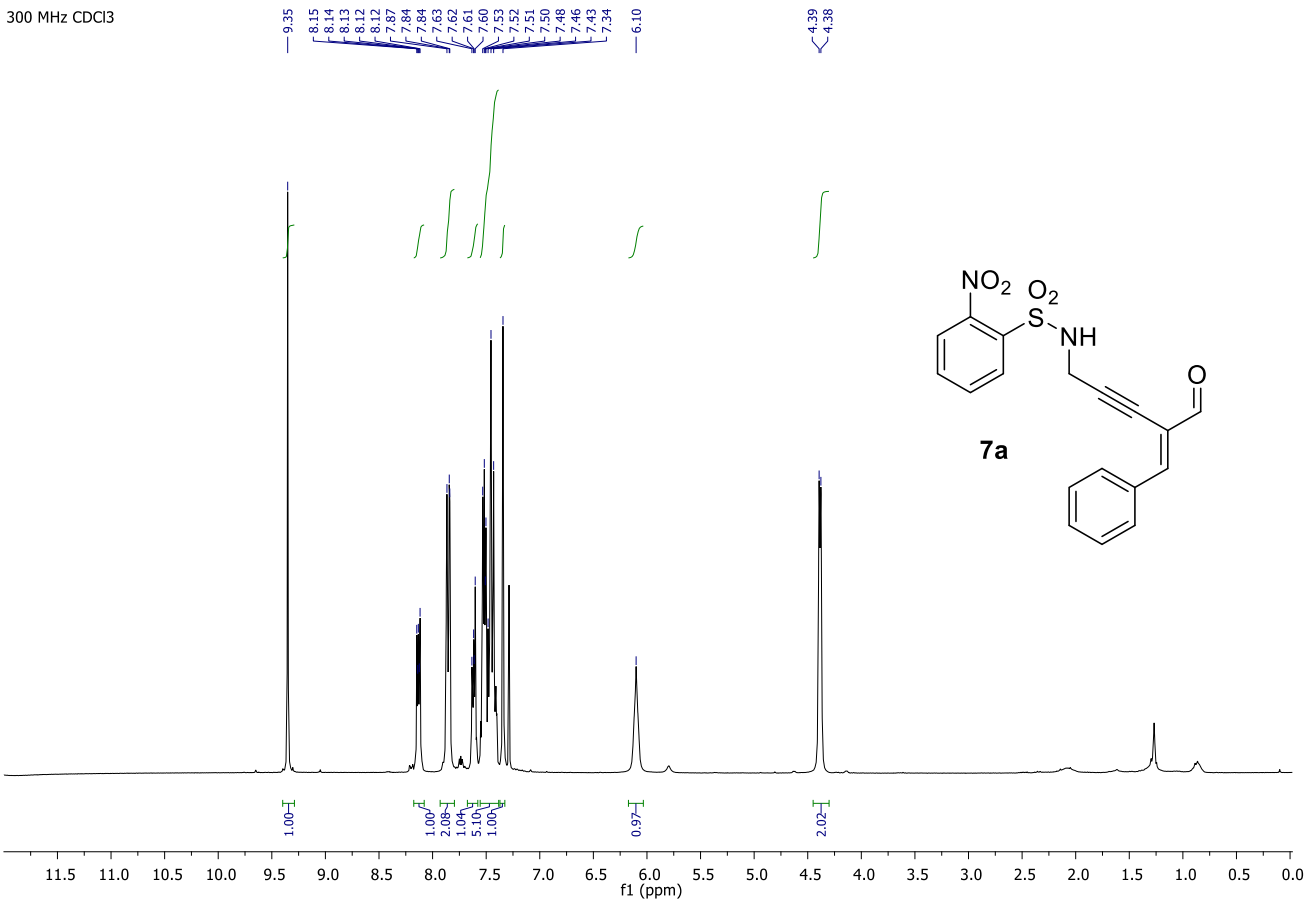


3-benzyl-4-(4-methoxyphenyl)pyridine (17). As decribed from the literature[41] A flask containing Mg (0.72 mmol, 17.5 mg, 4 equiv.) and LiCl (0.36 mmol, 15.3 mg, 2 equiv.) and a stir bar was flame dried under vacuum, cooled to room temperature and purged three times with argon. THF (600µL) was added and under stirring: pyridine **8a** (0.18 mmol, 50 mg, 1 equiv.), $Ni(PPh_3)_2Cl_2$ (0.018mmol, 12 mg, 10 mol%) were added followed by p-bromoanisole 0.72 mmol, (90µL, 4 equiv.). The reaction was stirred for 12h after which it was quench by addition of sat NH_4Cl. The mixture was extracted three times with EtOAc, washed once with brine and solvents were removed under reduced pressure to afford derivated pyridine **17** as a clear pale oil (0.098 mmol, 27 mg, 54% yield), TLC (20% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.29 – 7.16 (m, 6H), 7.02 – 6.91 (m, 4H), 4.03 (s, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.5, 151.7, 149.5 147.6, 140.4, 133.7, 131.1, 129.9, 128.6, 128.5, 126.2, 124.7, 113.9, 55.4, 36.4. HRMS (ESI): Calc. for $C_{19}H_{18}NO$ $(M+H)^+$: 276.1383 found: 276.1376.

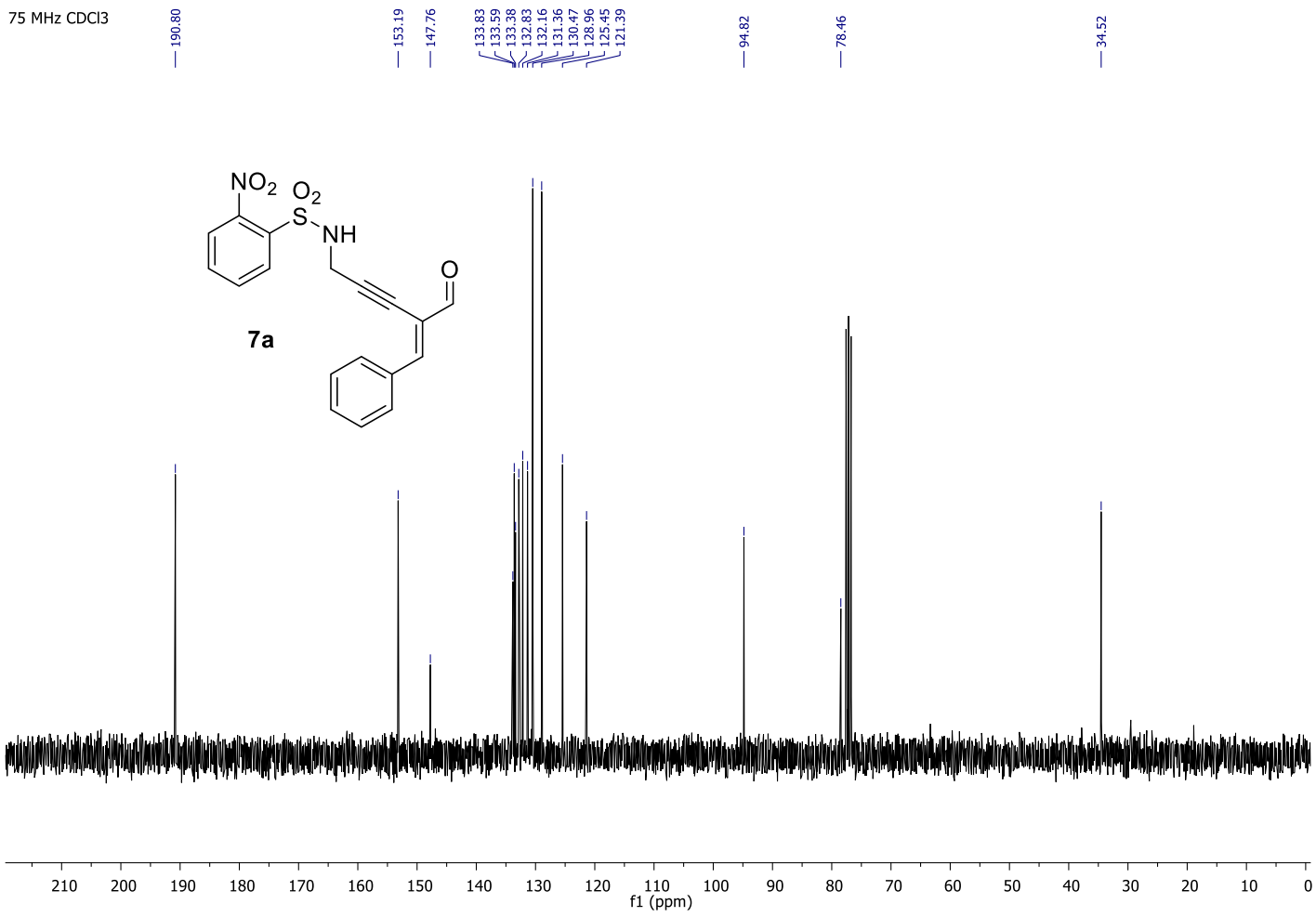


3-benzylpyridine (18). A stirred solution of pyridine **8a** (0.048 mmol, 13.1 mg, 1 equiv.) in EtOH (780µL, 0.06Mv v v) with a catalytic amount of Raney nickel, in a sealed tube, was heated to 80°C in a sand bath. After reaction completion (Raney nickel may be added during to complete the conversion), sat. $NaHCO_3$ was added and the resulting mixture was extracted three times with EtOAc and solvents were removed under reduced pressure to afford reduced pyridine **18** as a yellow oil with a pleasant and sweet smell (0.038 mmol, 6.5 mg, 81% yield), TLC (40% EtOAc/Hexanes). NMR data: ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 14.0 Hz, 2H), 7.27 (d, *J* , 1H), 7.14 – 6.96 (m, 6H), 3.79 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.1, 147.6, 139.8, 136.4, 128.9, 128.7, 126.5, 123.5, 39.1. HRMS (ESI): Calc. for $C_{12}H_{12}N$ $(M+H)^+$: 170.0964 found: 170.0964.

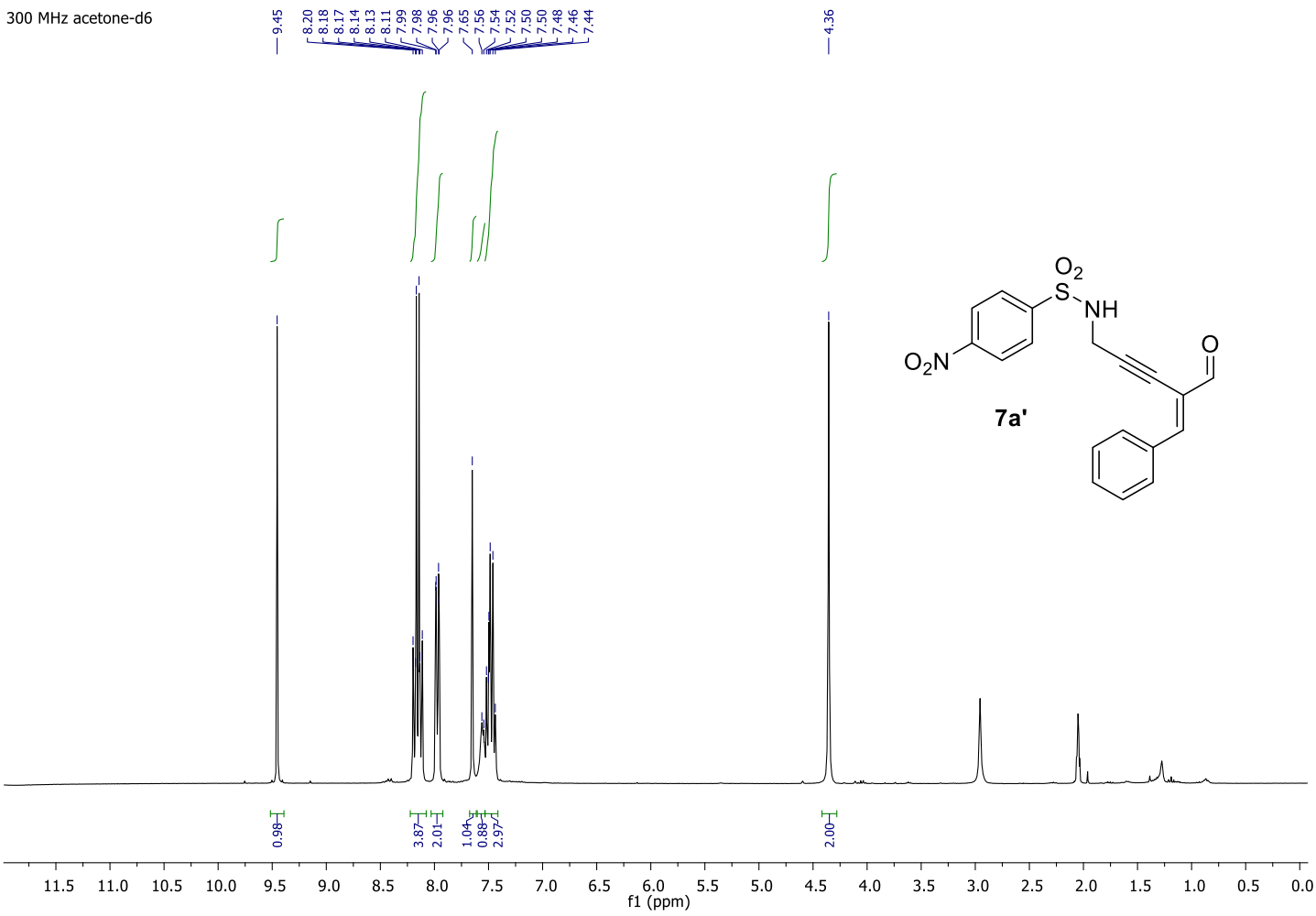
III. Copies of ^1H and ^{13}C NMR spectra for all compound


300 MHz CDCl3
9.35
8.15
8.14
8.13
8.12
8.12
7.87
7.84
7.84
7.63
7.62
7.61
7.60
7.53
7.52
7.51
7.50
7.48
7.46
7.43
7.34
6.10
4.39
4.38
NO2
O2
S
NH
O
7a
1.00
1.00
2.08
1.04
5.10
1.00
0.97
2.02
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

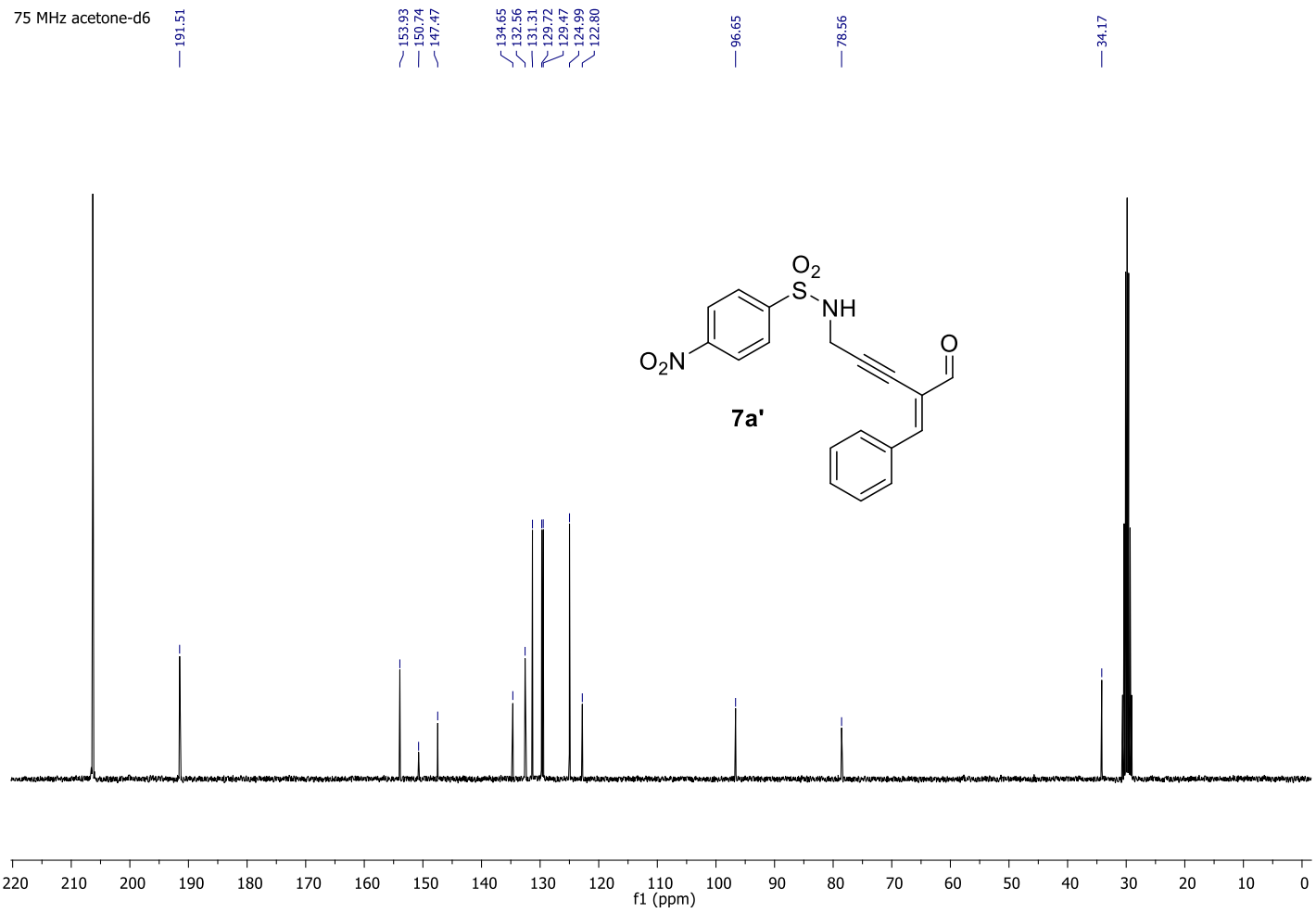
RMN ^{1}H


75 MHz CDCl3
190.80
153.19
147.76
133.83
133.59
133.38
132.83
132.16
131.36
130.47
128.96
125.45
121.39
94.82
78.46
34.52
NO2
O2
S
NH
O
7a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

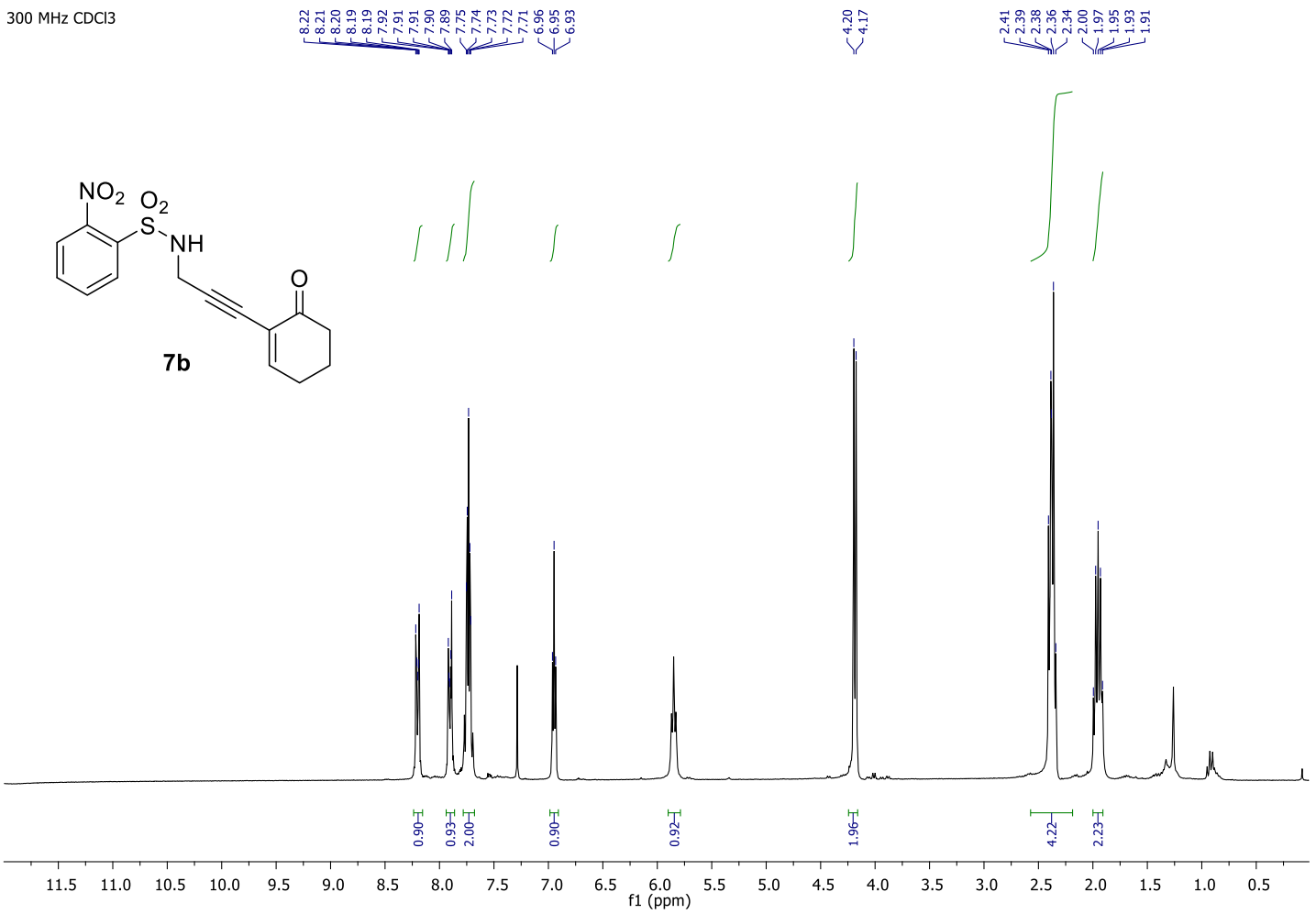
RMN $^{13}C\{^{1}H\}$


300 MHz acetone-d6
9.45
8.20
8.18
8.17
8.14
8.13
8.11
7.99
7.98
7.96
7.96
7.65
7.56
7.54
7.52
7.50
7.50
7.48
7.46
7.44
4.36
0.98
3.87
2.01
1.04
0.88
2.97
2.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
O2
S
NH
O2N
O
7a'

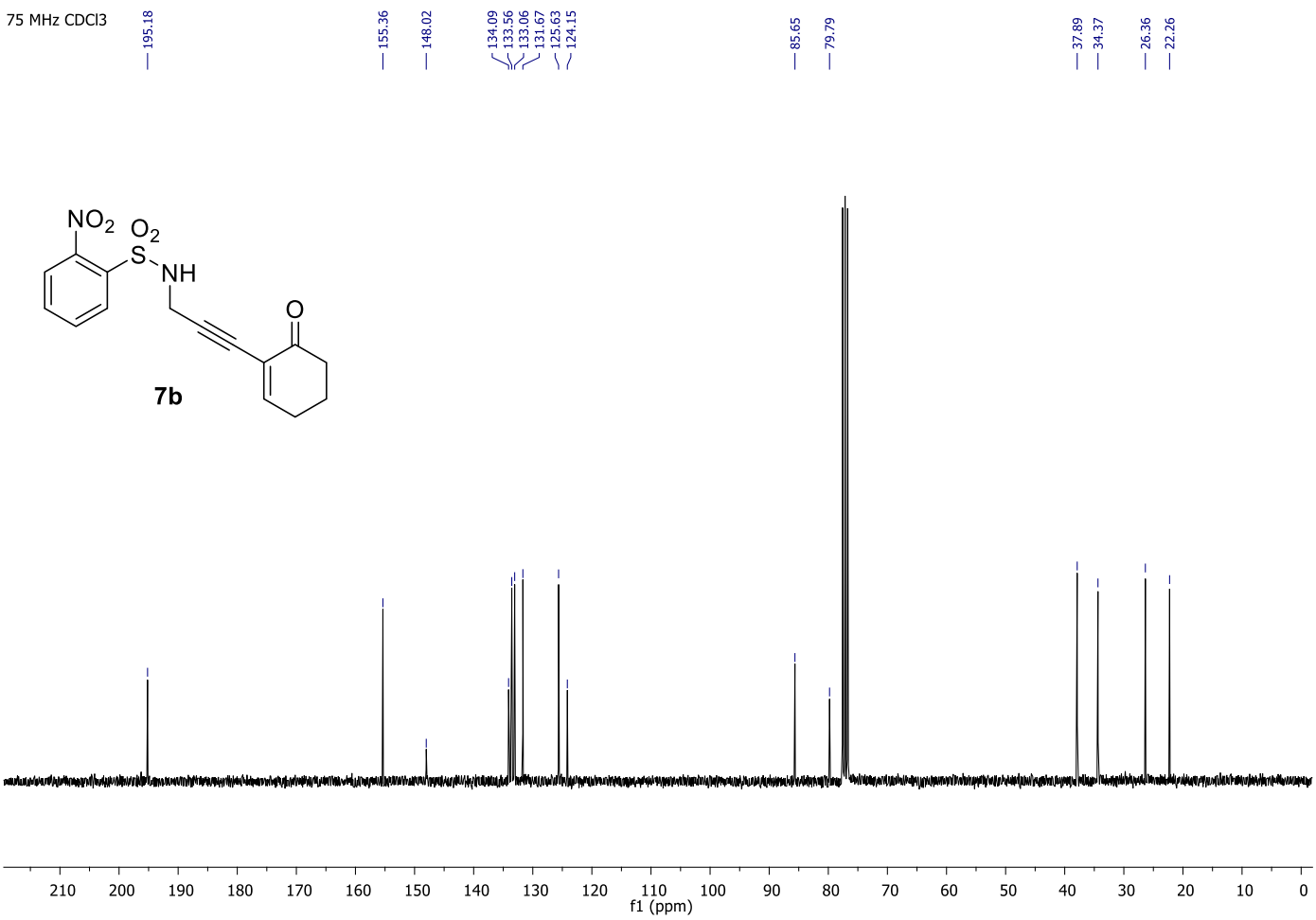
RMN ^{1}H


75 MHz acetone-d6
191.51
153.93
150.74
147.47
134.65
132.56
131.31
129.72
129.47
124.99
122.80
96.65
78.56
34.17
O2
S
NH
O2N
O
7a'
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

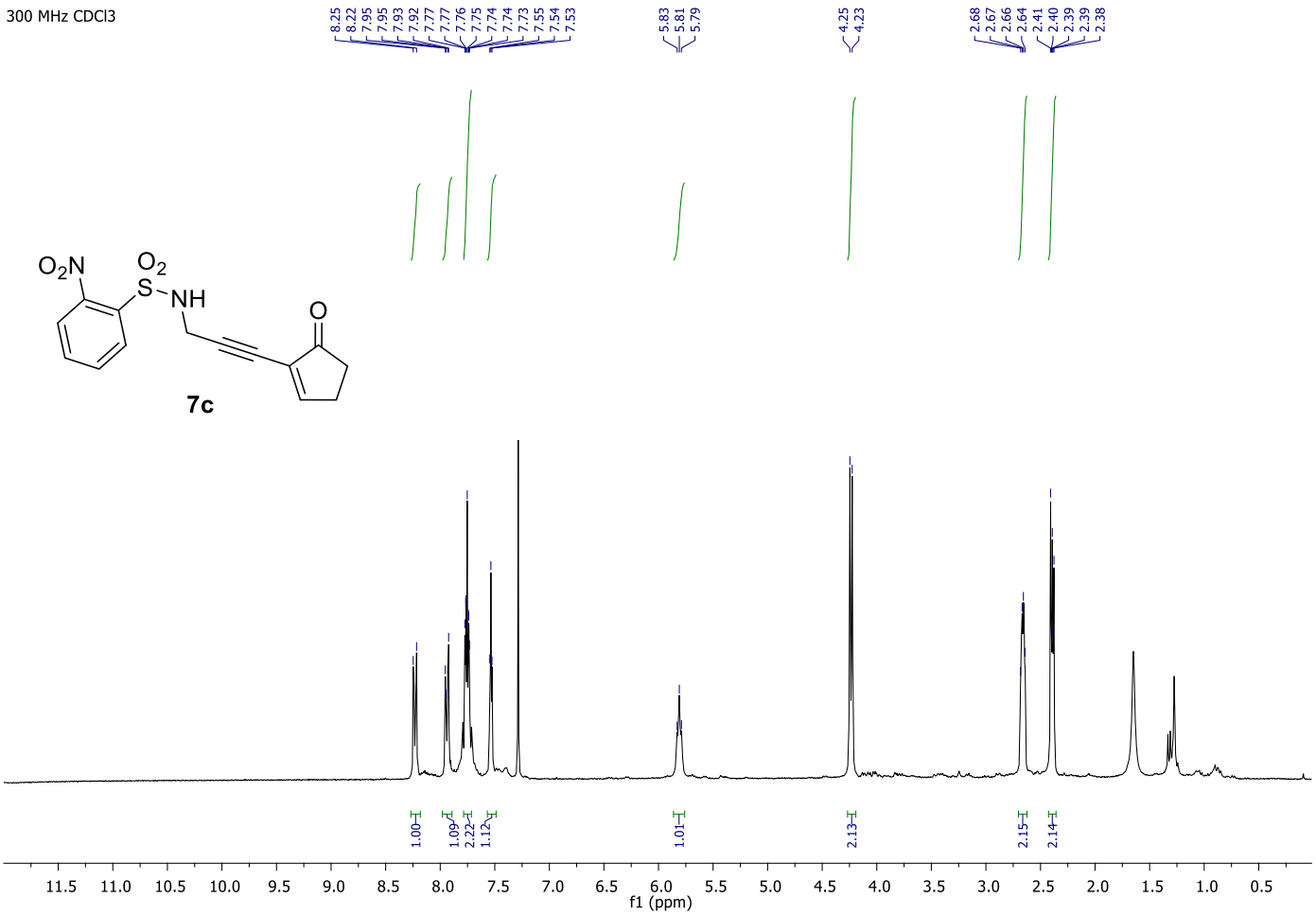
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.22
8.21
8.20
8.19
8.19
7.92
7.91
7.91
7.90
7.89
7.75
7.74
7.73
7.72
7.71
6.96
6.95
6.93
4.20
4.17
2.41
2.39
2.38
2.36
2.34
2.00
1.97
1.95
1.93
1.91
NO2
O2
S
NH
O
7b
0.90
0.93
2.00
0.90
0.92
1.96
4.22
2.23
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

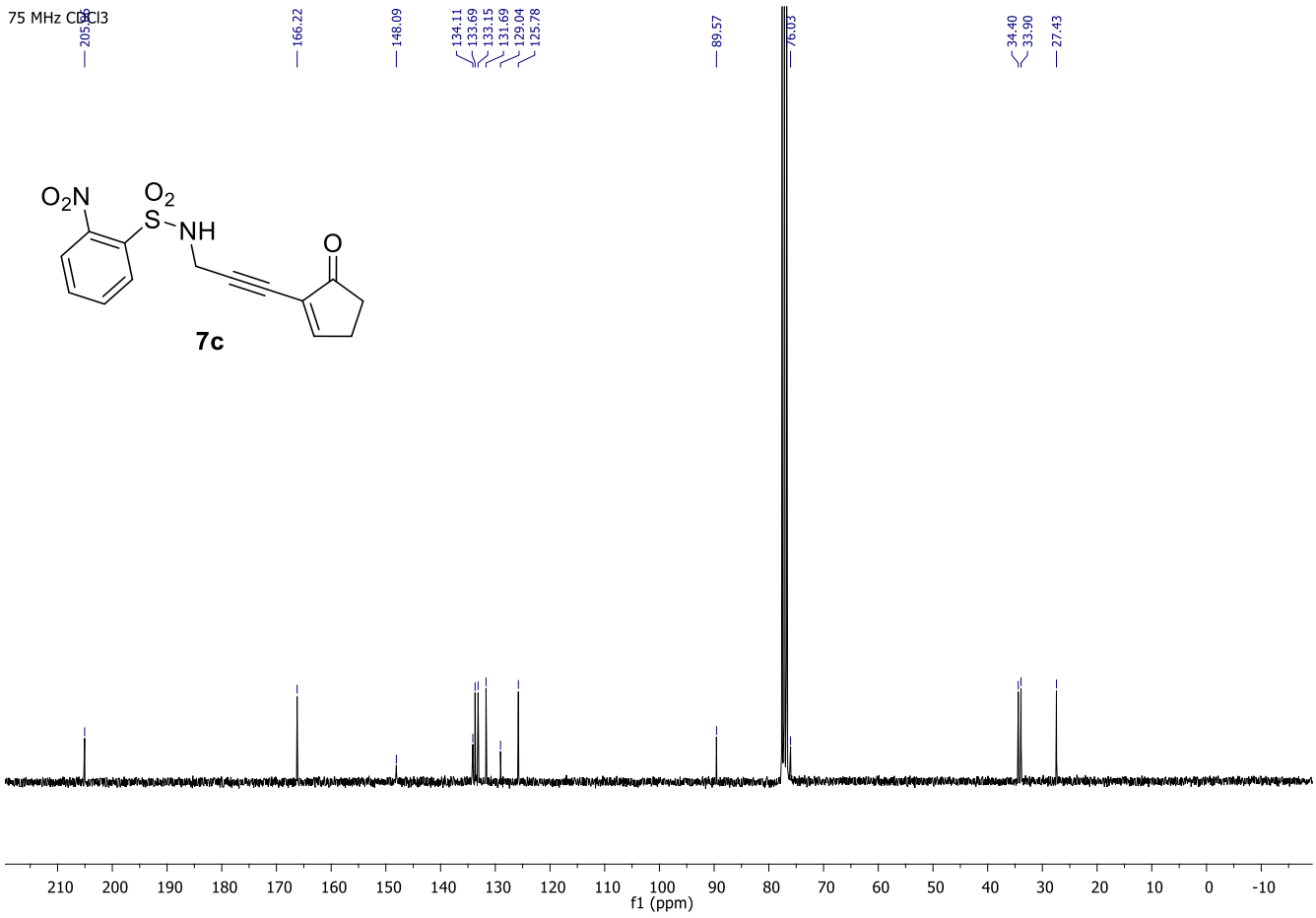
RMN ^{1}H


75 MHz CDCl3
195.18
155.36
148.02
134.09
133.56
133.06
131.67
125.63
124.15
85.65
79.79
37.89
34.37
26.36
22.26
NO2
O2
S
NH
O
7b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

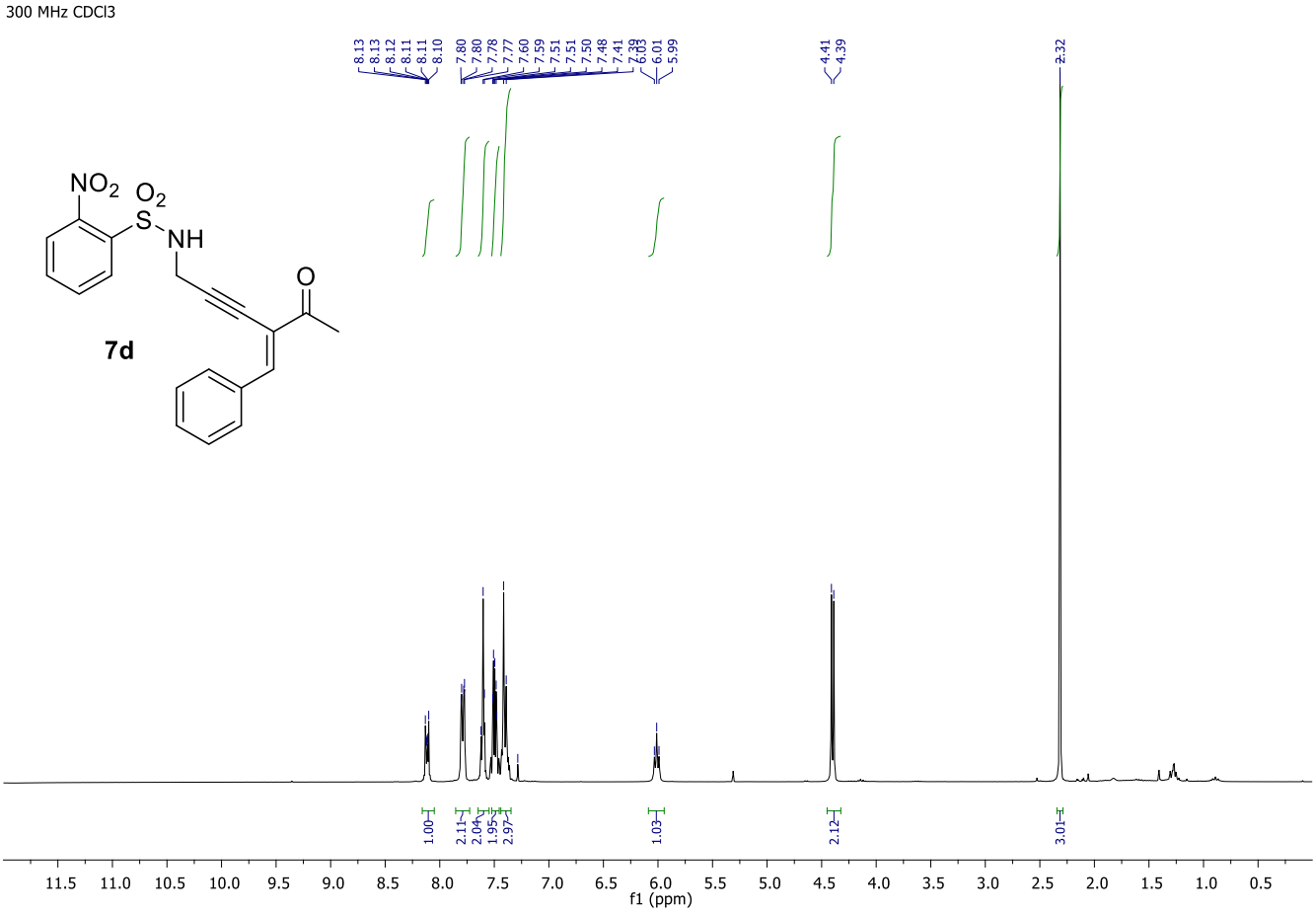
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.25
8.22
7.95
7.95
7.93
7.92
7.77
7.77
7.76
7.75
7.74
7.74
7.73
7.55
7.54
7.53
5.83
5.81
5.79
4.25
4.23
2.68
2.67
2.66
2.64
2.41
2.40
2.39
2.39
2.38
O2N
O2
S
NH
O
7c
1.00
1.09
2.22
1.12
1.01
2.13
2.15
2.14
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

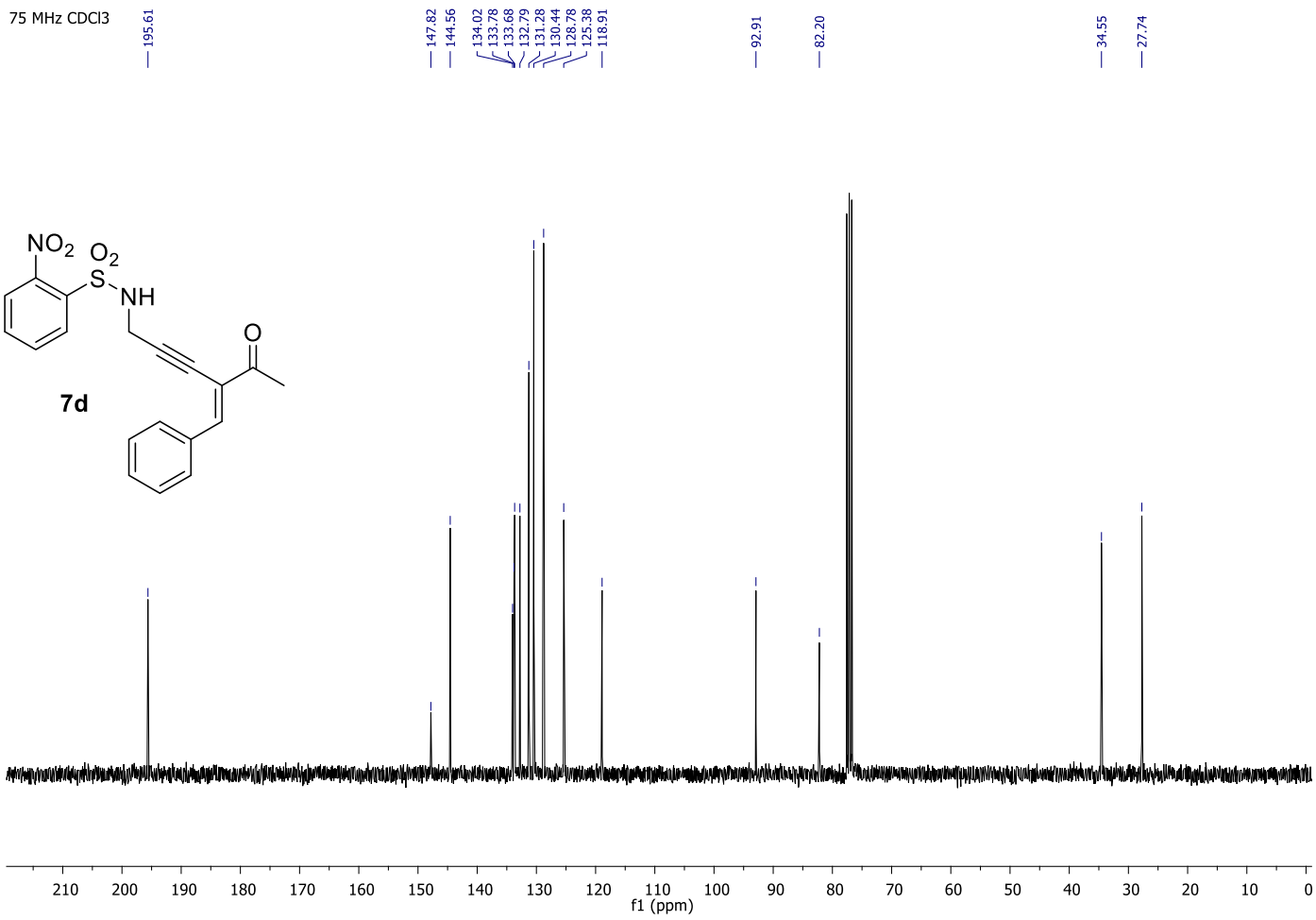
RMN ^{1}H


75 MHz CDCl3
205.49
166.22
148.09
134.11
133.69
133.15
131.69
129.04
125.78
89.57
76.03
34.40
33.90
27.43
O2N
O2
S
NH
O
7c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

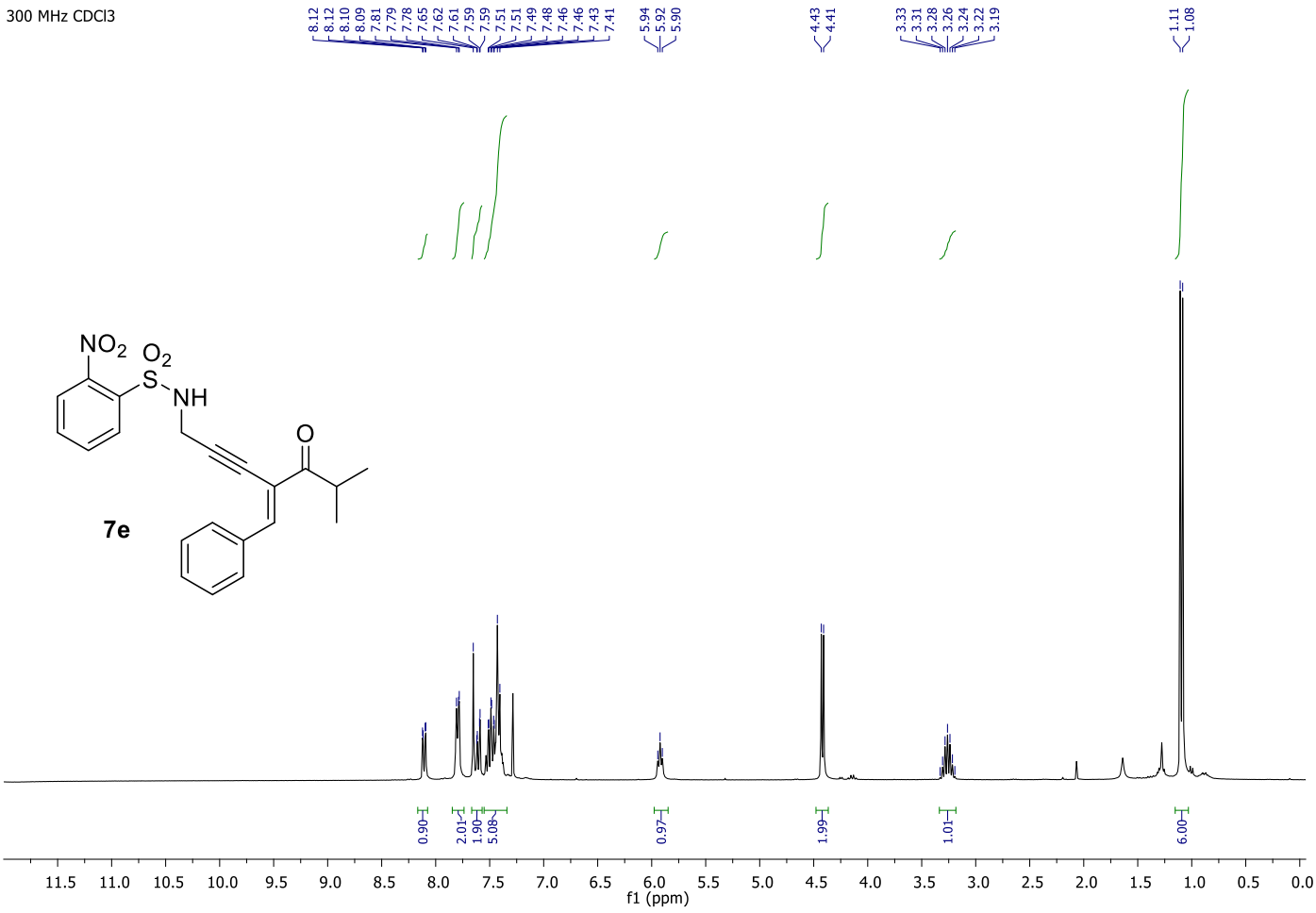
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.13
8.13
8.12
8.11
8.11
8.10
7.80
7.80
7.78
7.77
7.60
7.59
7.51
7.51
7.50
7.48
7.41
7.39
6.03
6.01
5.99
4.41
4.39
2.32
NO2
O2
S
NH
O
7d
1.00
2.11
2.04
1.95
2.97
1.03
2.12
3.01
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

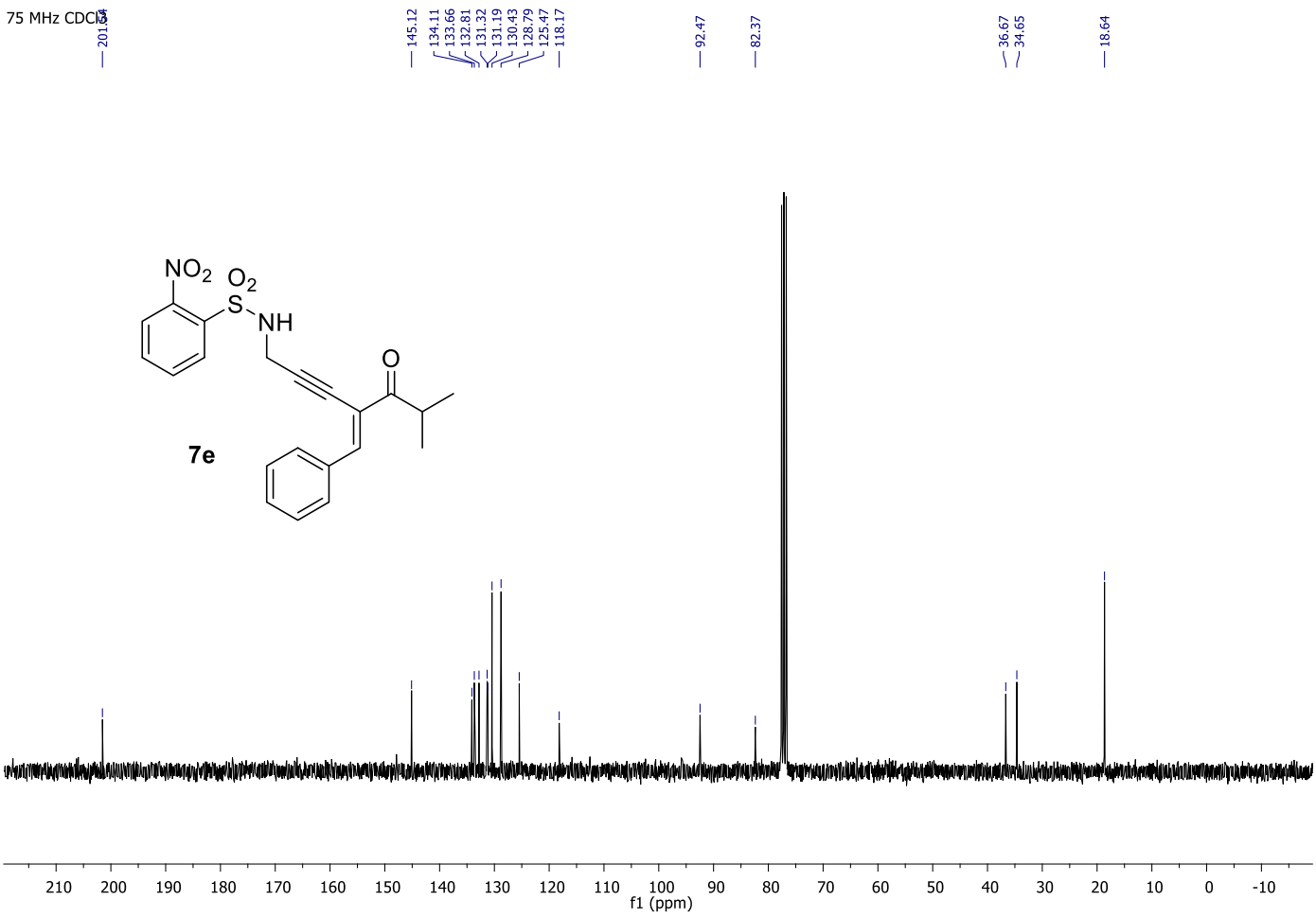
RMN ^{1}H


75 MHz CDCl3
195.61
147.82
144.56
134.02
133.78
133.68
132.79
131.28
130.44
128.78
125.38
118.91
92.91
82.20
34.55
27.74
NO2
O2
S
NH
O
7d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

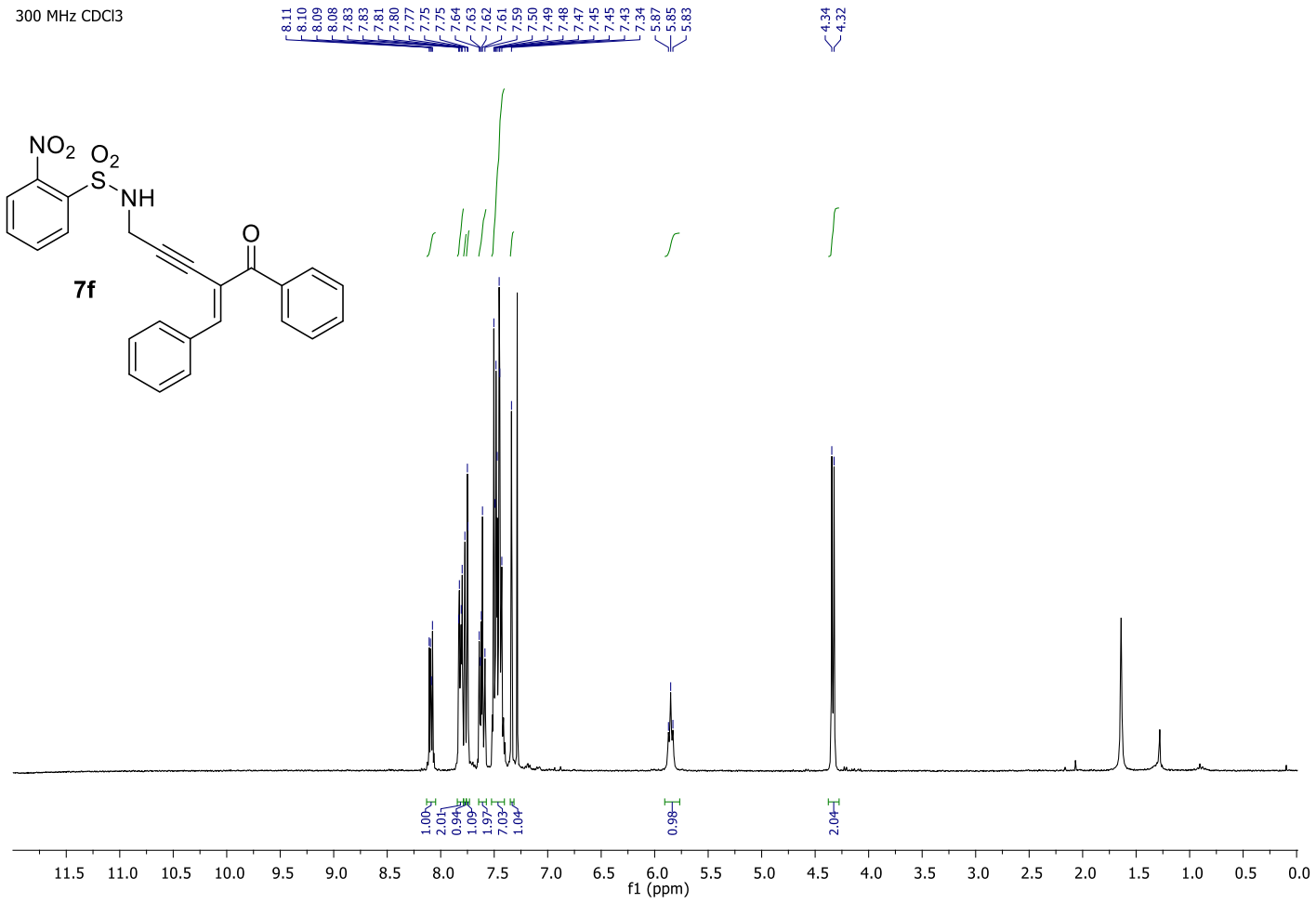
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.12
8.12
8.10
8.09
7.81
7.79
7.78
7.65
7.62
7.61
7.59
7.59
7.51
7.51
7.49
7.48
7.46
7.46
7.43
7.41
5.94
5.92
5.90
4.43
4.41
3.33
3.31
3.28
3.26
3.24
3.22
3.19
1.11
1.08
NO2
O2
S
NH
O
7e
0.90
2.01
1.90
5.08
0.97
1.99
1.01
6.00
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

RMN ^{1}H

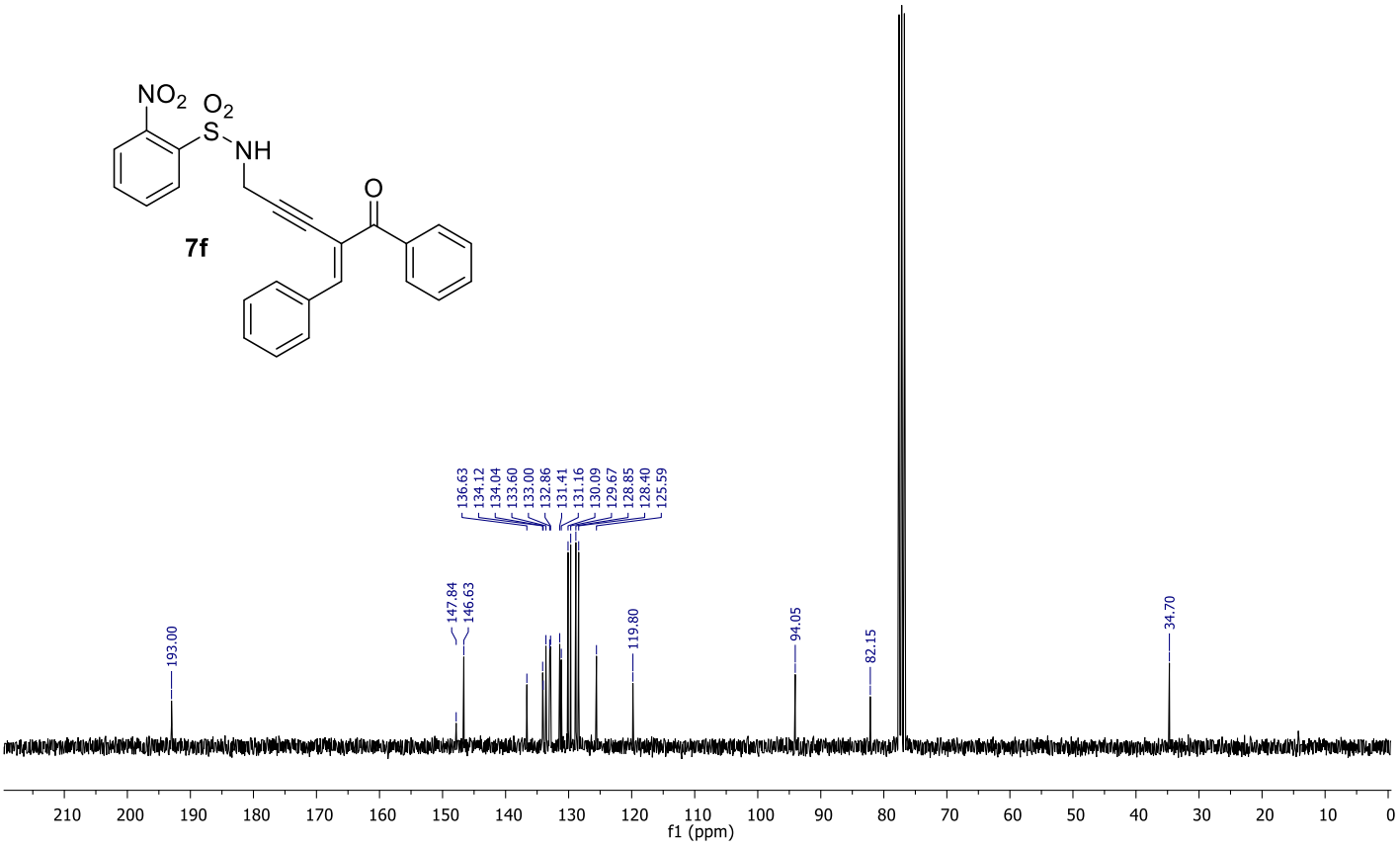

75 MHz CDCl3
201.54
145.12
134.11
133.66
132.81
131.32
131.19
130.43
128.79
125.47
118.17
92.47
82.37
36.67
34.65
18.64
NO2
O2
S
NH
O
7e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

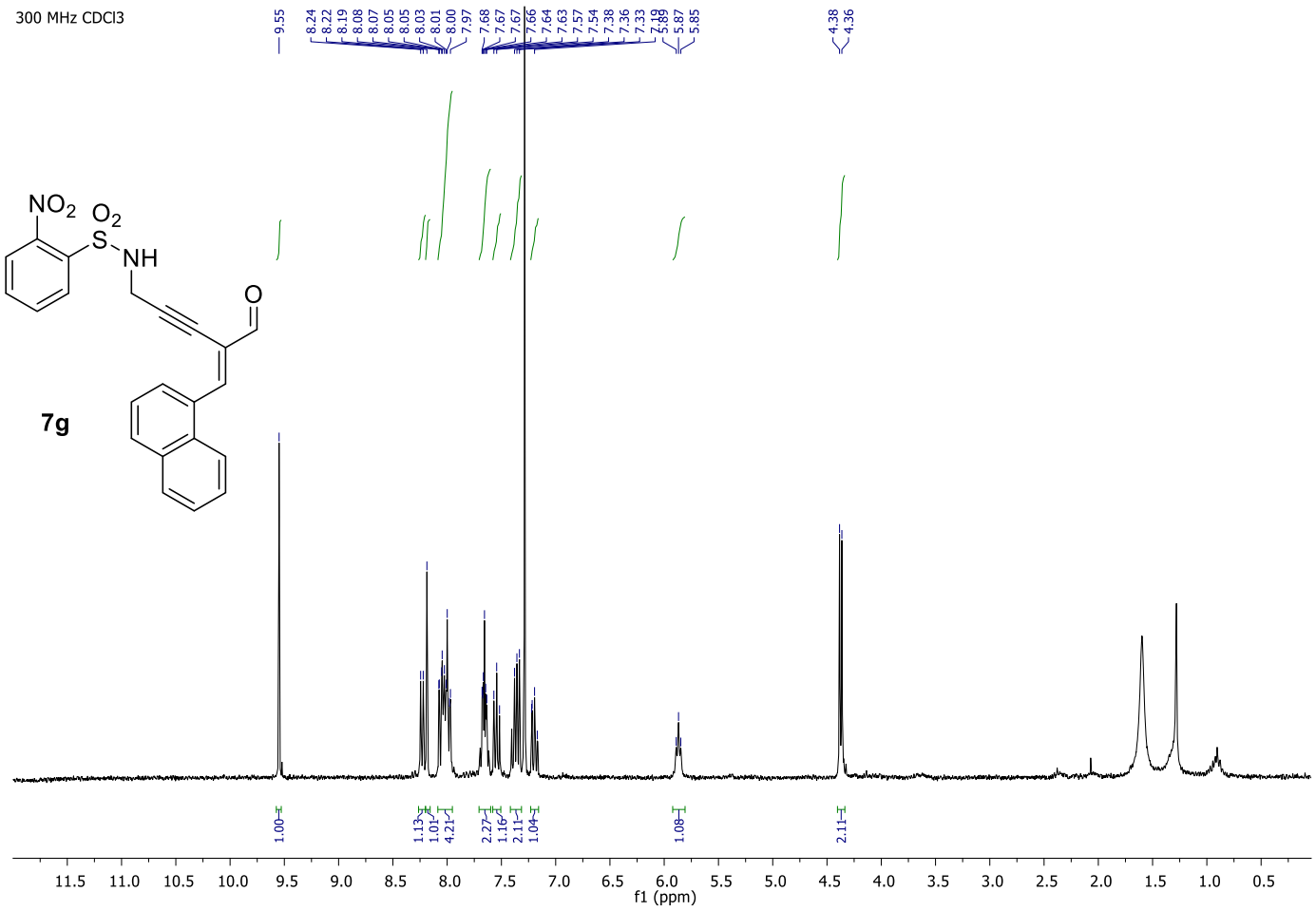

300 MHz CDCl3
8.11
8.10
8.09
8.08
7.83
7.83
7.81
7.80
7.77
7.75
7.75
7.64
7.63
7.62
7.61
7.59
7.50
7.49
7.48
7.47
7.45
7.45
7.43
7.34
5.87
5.85
5.83
4.34
4.32
NO2
O2
S
NH
O
7f
1.00
2.01
0.94
1.09
1.97
7.03
1.04
0.98
2.04
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

RMN ^{1}H

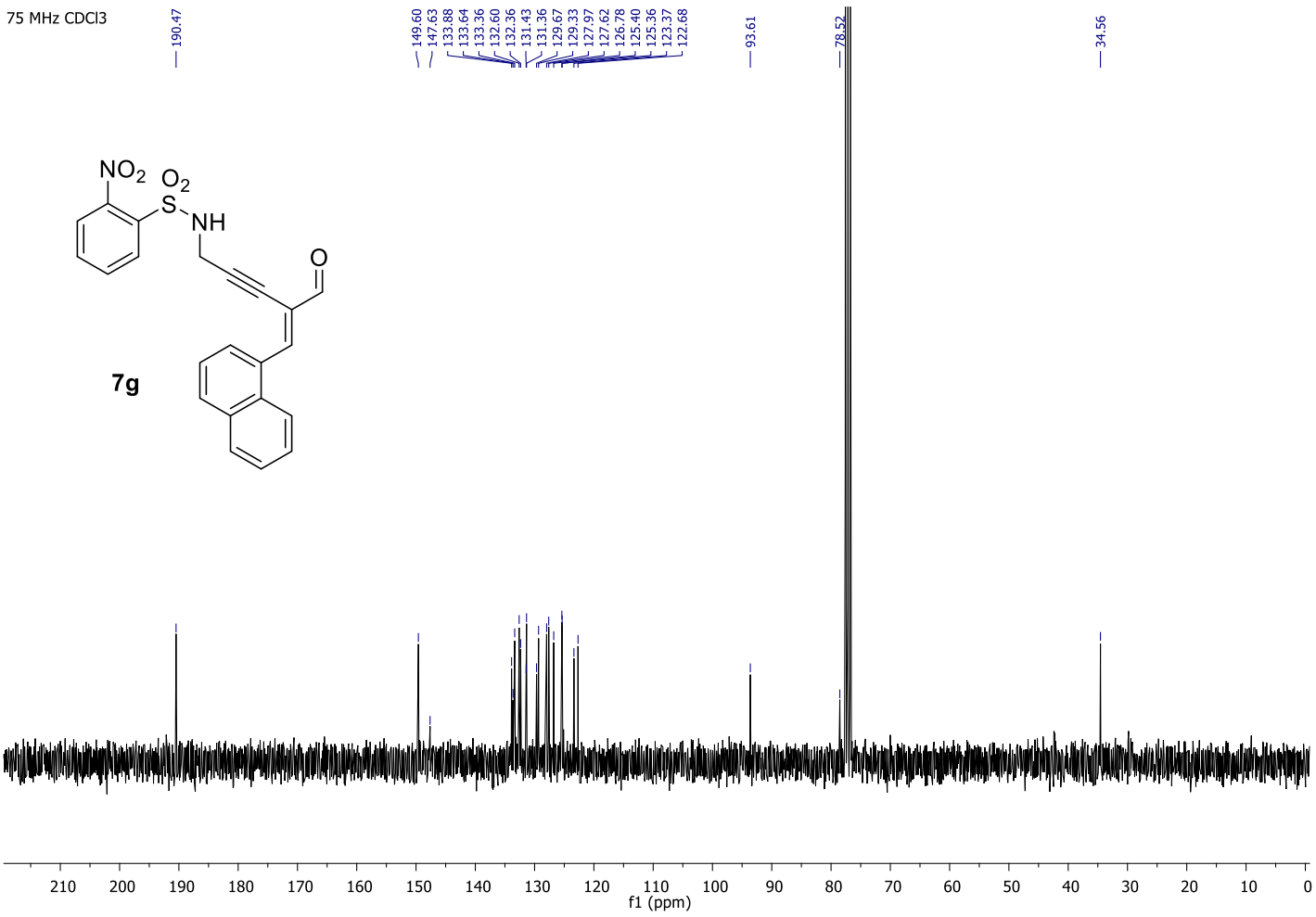
75 MHz CDCl3



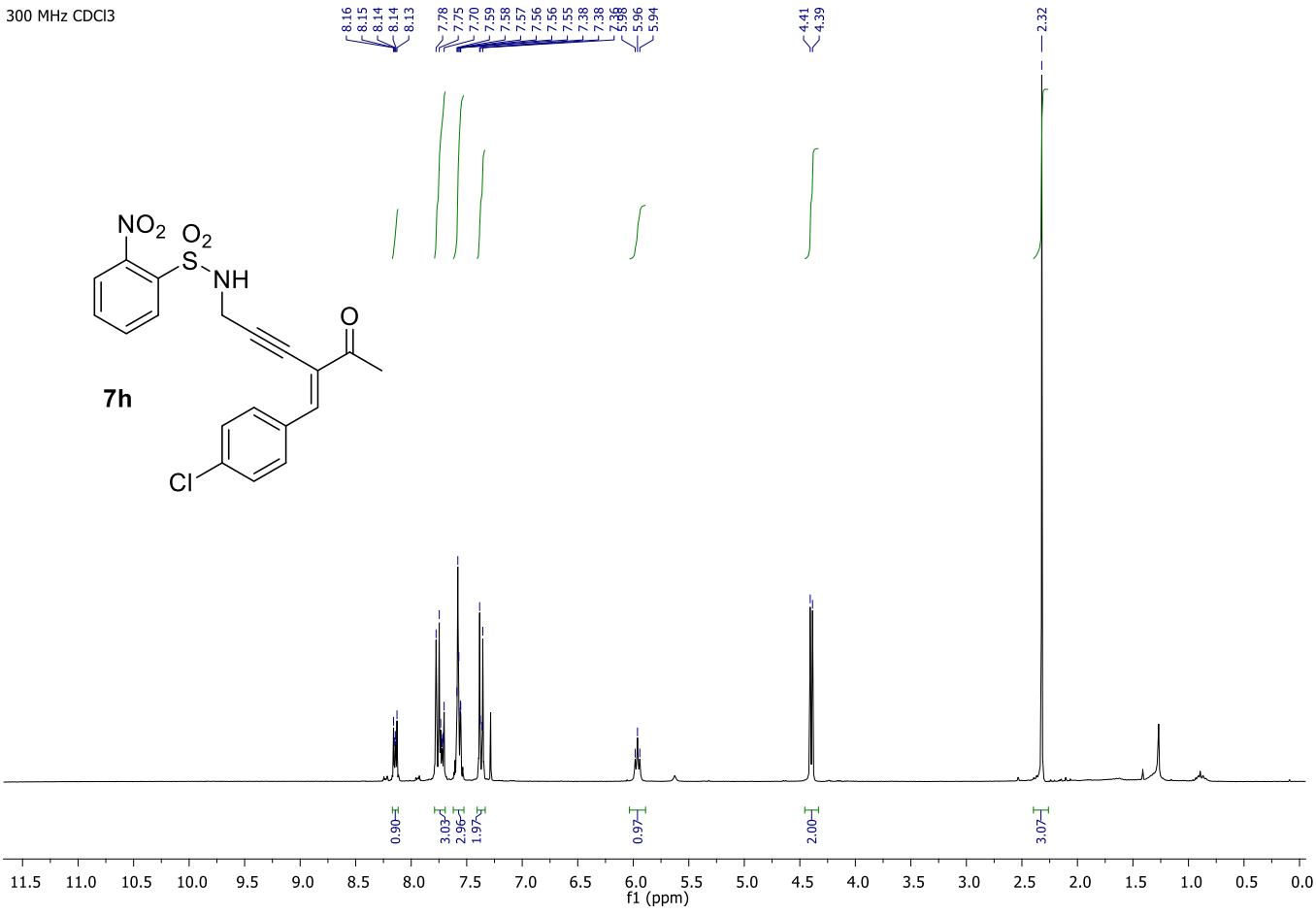
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
9.55
8.24
8.22
8.19
8.08
8.07
8.05
8.05
8.03
8.01
8.00
7.97
7.68
7.67
7.67
7.66
7.64
7.63
7.57
7.54
7.38
7.36
7.33
5.89
5.87
5.85
4.38
4.36
NO2
O2
S
NH
O
7g
1.00
1.13
1.01
4.21
2.27
1.16
2.11
1.04
1.08
2.11
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

RMN ^{1}H

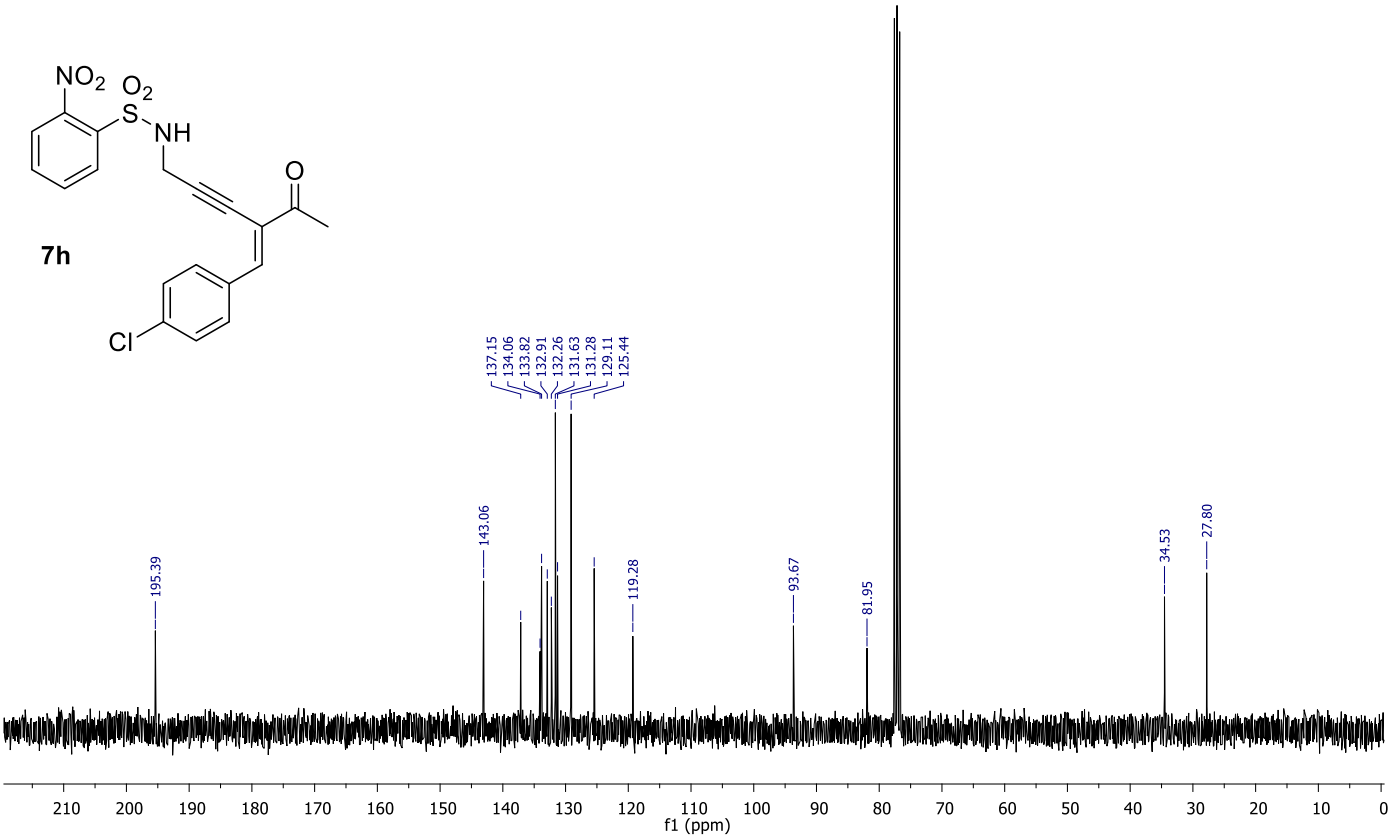

75 MHz CDCl3
190.47
149.60
147.63
133.88
133.64
133.36
132.60
132.36
131.43
131.36
129.67
129.33
127.97
127.62
126.78
125.40
125.36
123.37
122.68
93.61
78.52
34.56
NO2
O2
S
NH
O
7g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

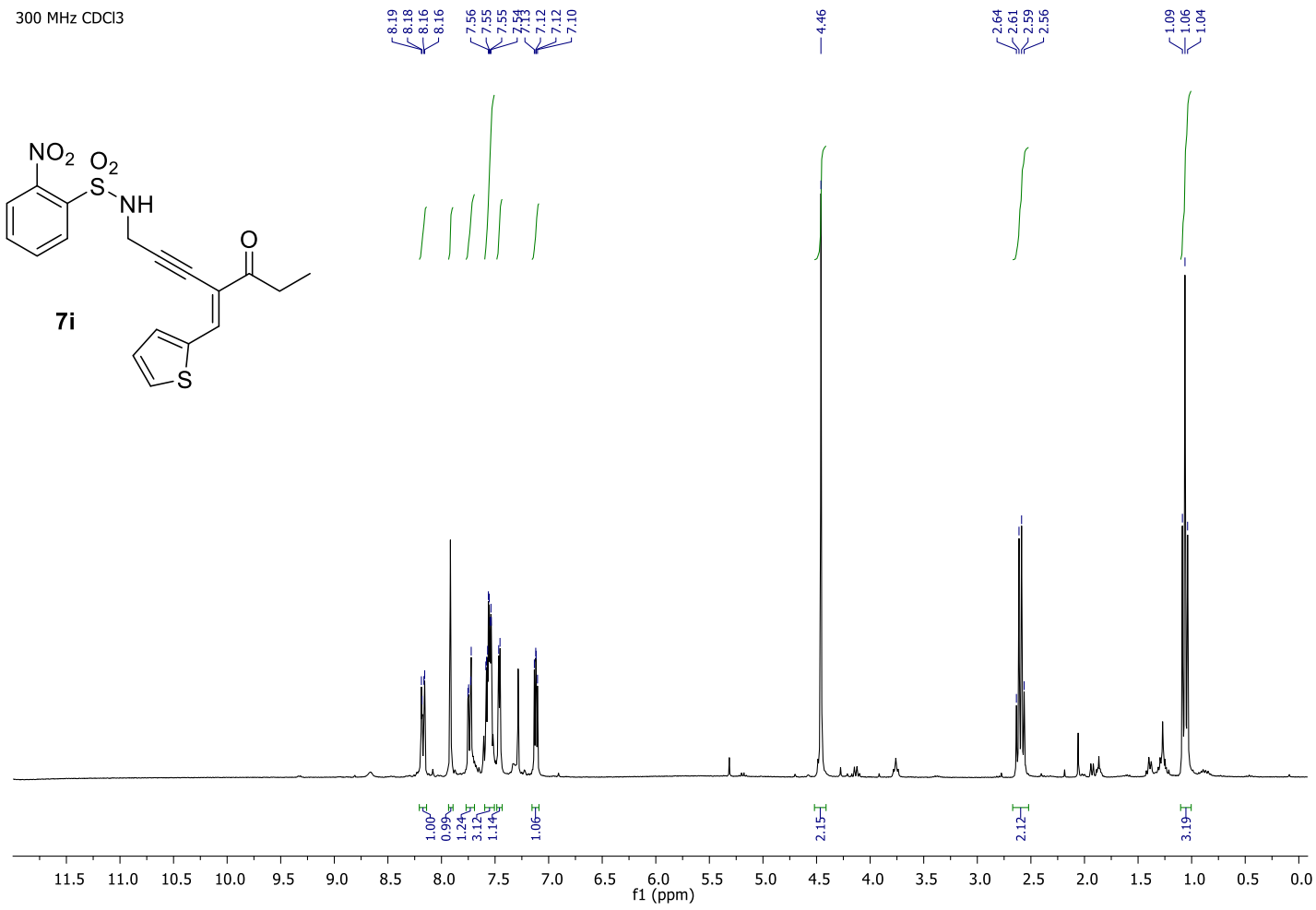

300 MHz CDCl3
8.16
8.15
8.14
8.14
8.13
7.78
7.75
7.70
7.59
7.58
7.57
7.56
7.56
7.55
7.38
7.38
5.96
5.94
4.41
4.39
2.32
NO2
O2
S
NH
O
Cl
7h
0.90
3.03
2.96
1.97
0.97
2.00
3.07
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H

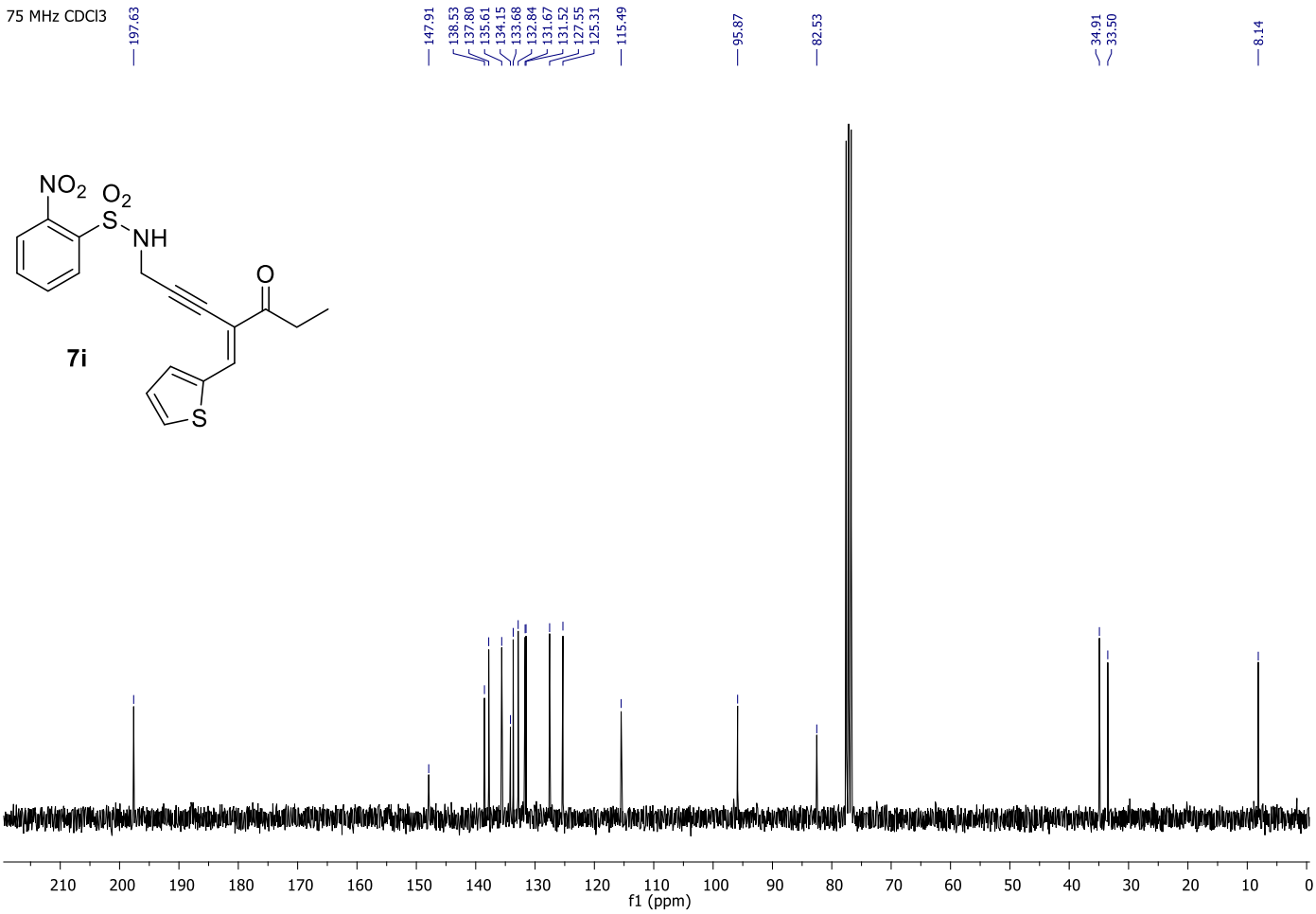
75 MHz CDCl3



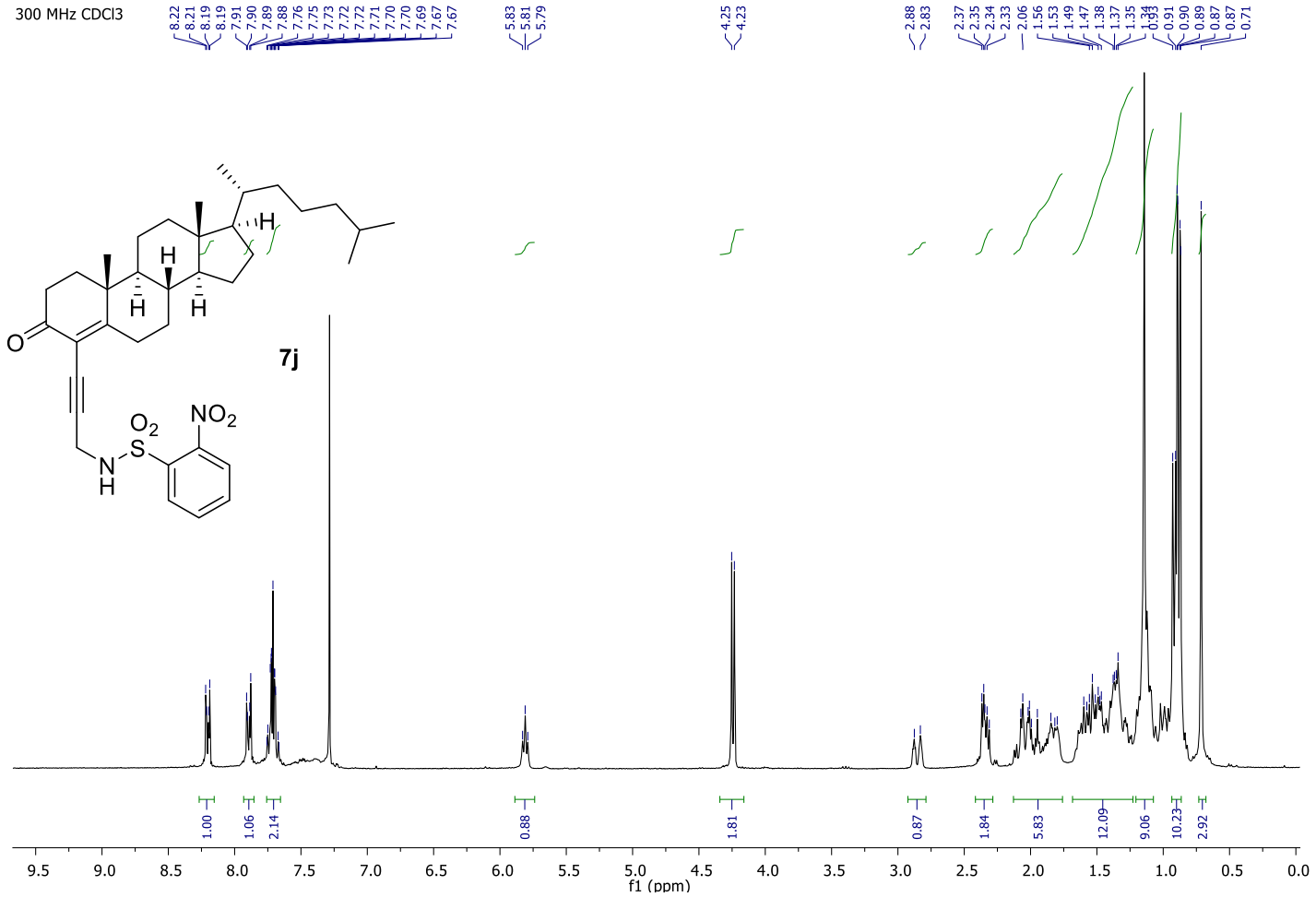
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.19
8.18
8.16
8.16
7.56
7.55
7.55
7.53
7.13
7.12
7.12
7.10
4.46
2.64
2.61
2.59
2.56
1.09
1.06
1.04
NO2
O2
S
NH
O
S
7i
1.00
0.99
1.24
3.12
1.14
1.06
2.15
2.12
3.19
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

RMN ^{1}H

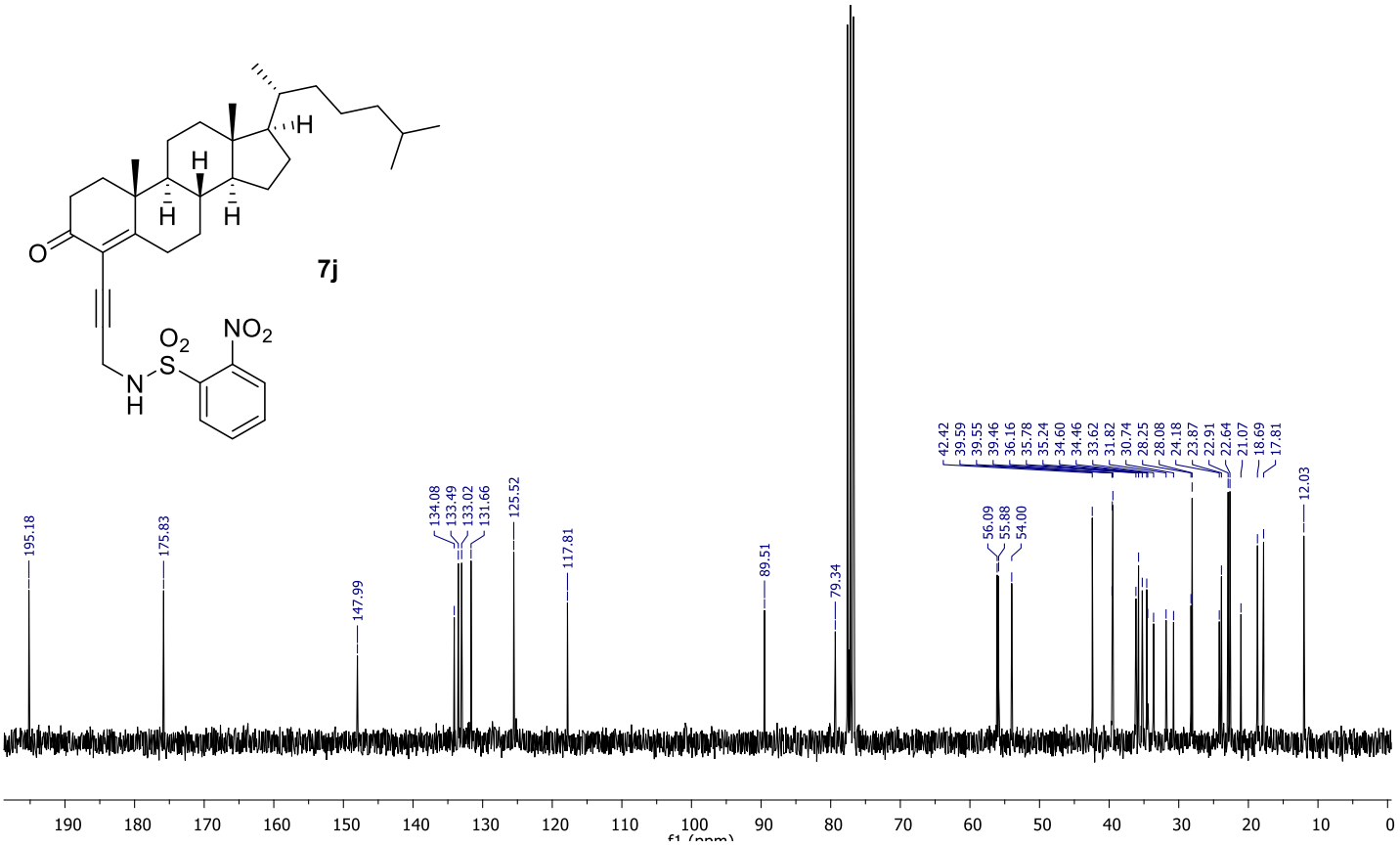

75 MHz CDCl3
197.63
147.91
138.53
137.80
135.61
134.15
133.68
132.84
131.67
131.52
127.55
125.31
115.49
95.87
82.53
34.91
33.50
8.14
NO2
O2
S
NH
O
S
7i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

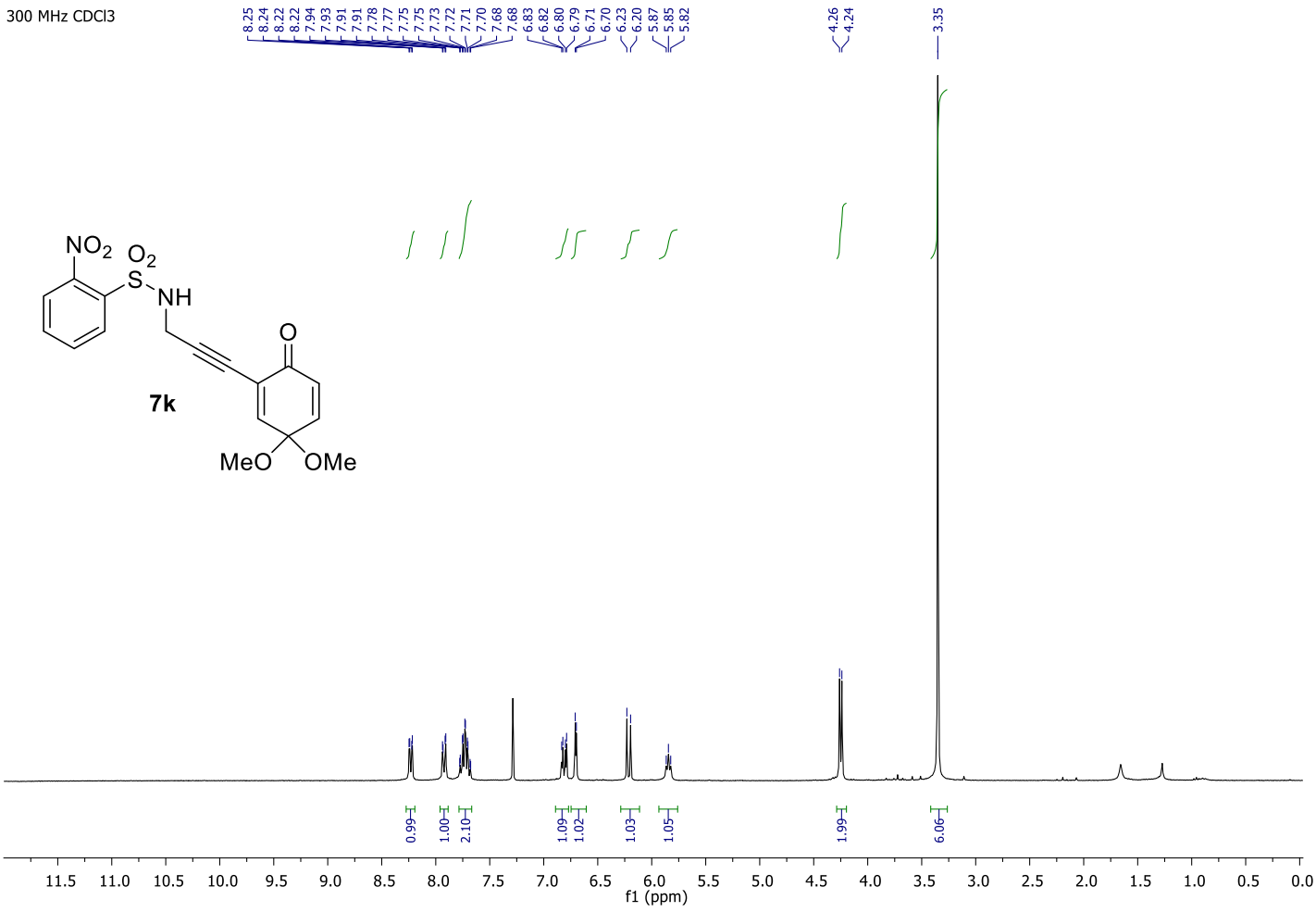

300 MHz CDCl3
8.22
8.21
8.19
8.19
7.91
7.90
7.89
7.88
7.76
7.75
7.73
7.72
7.72
7.71
7.70
7.70
7.69
7.67
7.67
5.83
5.81
5.79
4.25
4.23
2.88
2.83
2.37
2.35
2.34
2.33
2.06
1.56
1.53
1.49
1.47
1.38
1.37
1.35
1.34
0.93
0.91
0.90
0.89
0.87
0.87
0.71
7j
1.00
1.06
2.14
0.88
1.81
0.87
1.84
5.83
12.09
9.06
10.23
2.92
f1 (ppm)

RMN ^{1}H

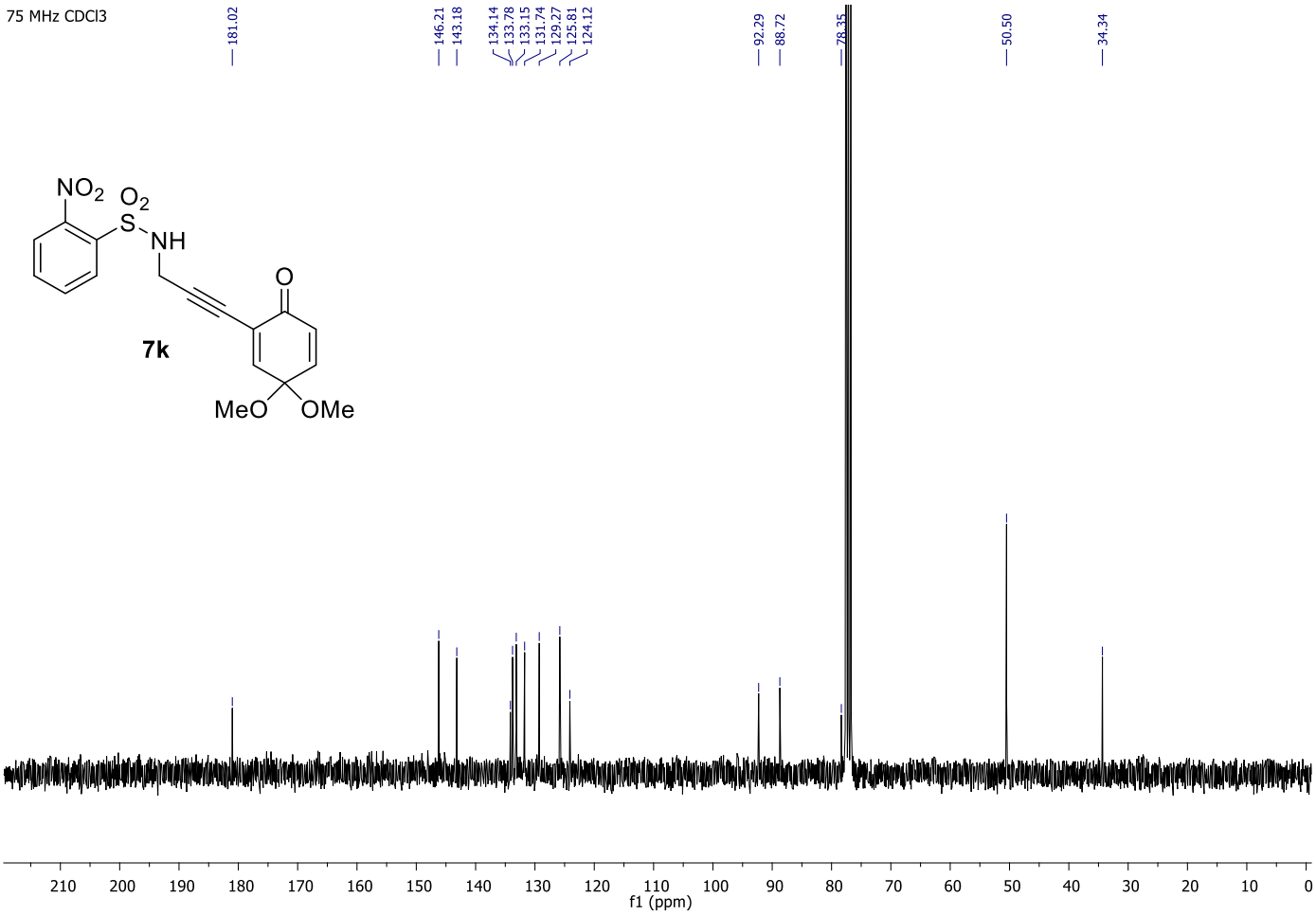
75 MHz CDCl3



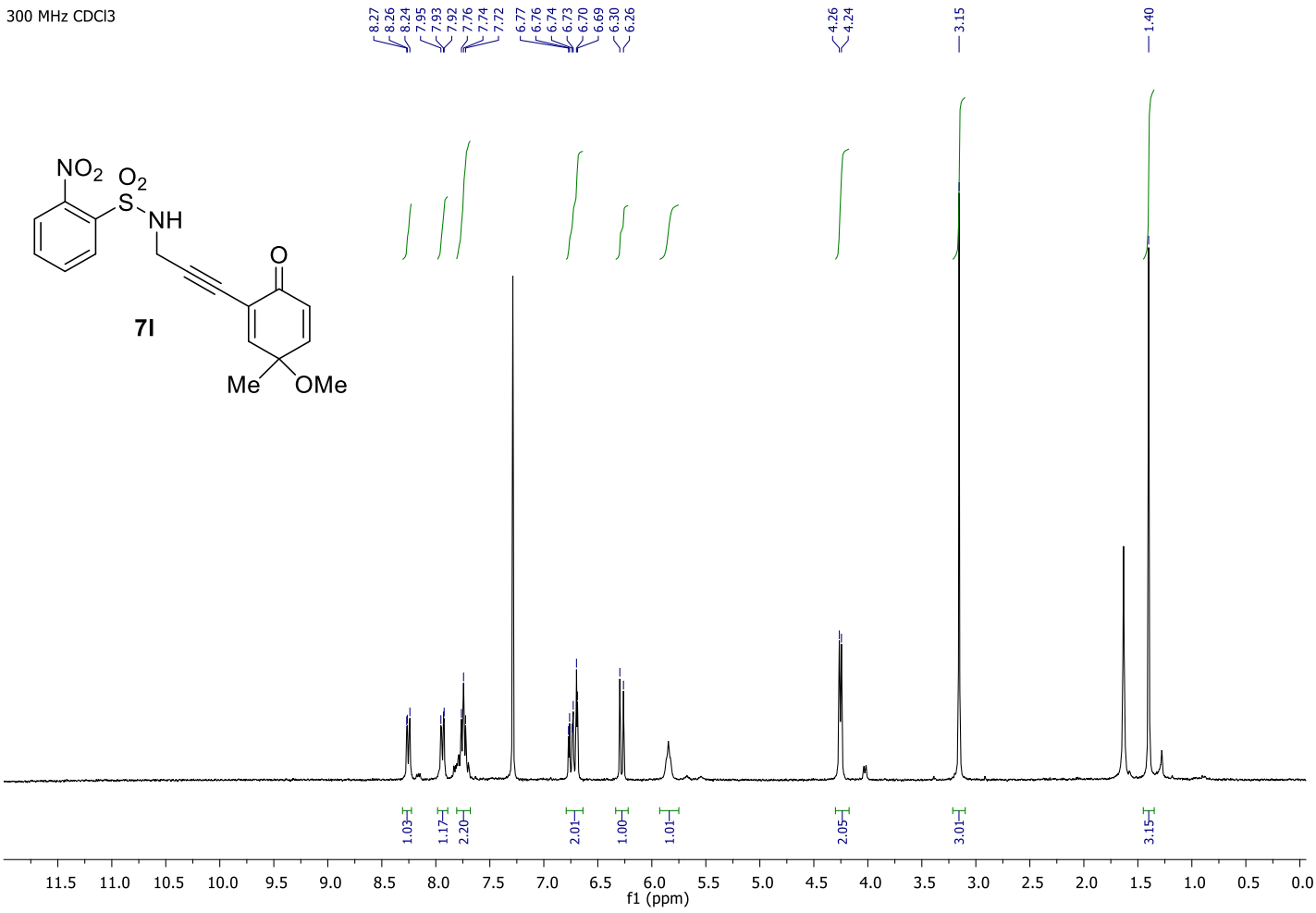
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.25
8.24
8.22
8.22
7.94
7.93
7.91
7.91
7.78
7.77
7.75
7.75
7.73
7.72
7.71
7.70
7.68
7.68
6.83
6.82
6.80
6.79
6.71
6.70
6.23
6.20
5.87
5.85
5.82
4.26
4.24
3.35
NO2
O2
S
NH
O
MeO
OMe
7k
0.99
1.00
2.10
1.09
1.02
1.03
1.05
1.99
6.06
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

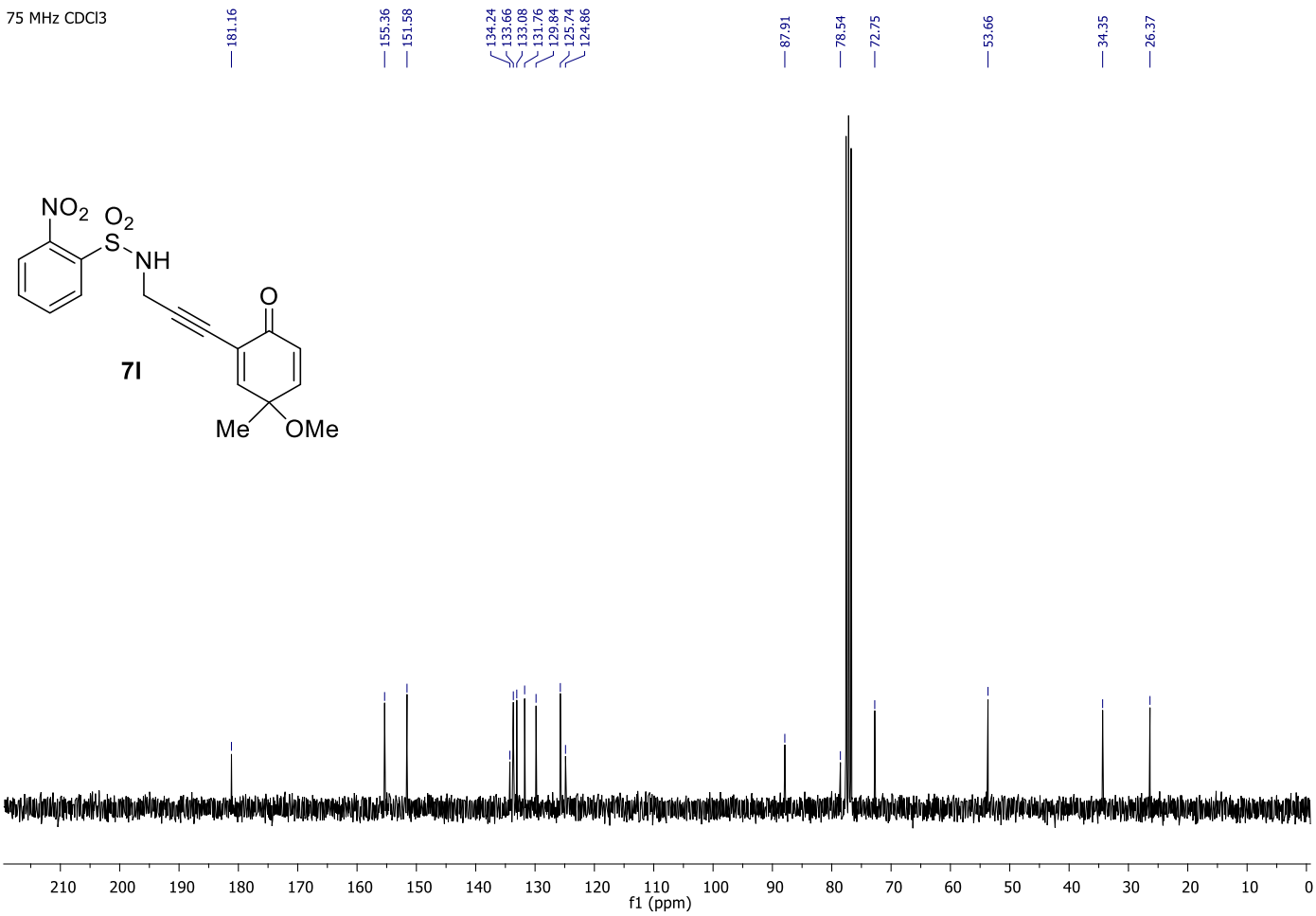
RMN ^{1}H


75 MHz CDCl3
181.02
146.21
143.18
134.14
133.78
133.15
131.74
129.27
125.81
124.12
92.29
88.72
78.35
50.50
34.34
NO2
O2
S
NH
O
7k
MeO
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

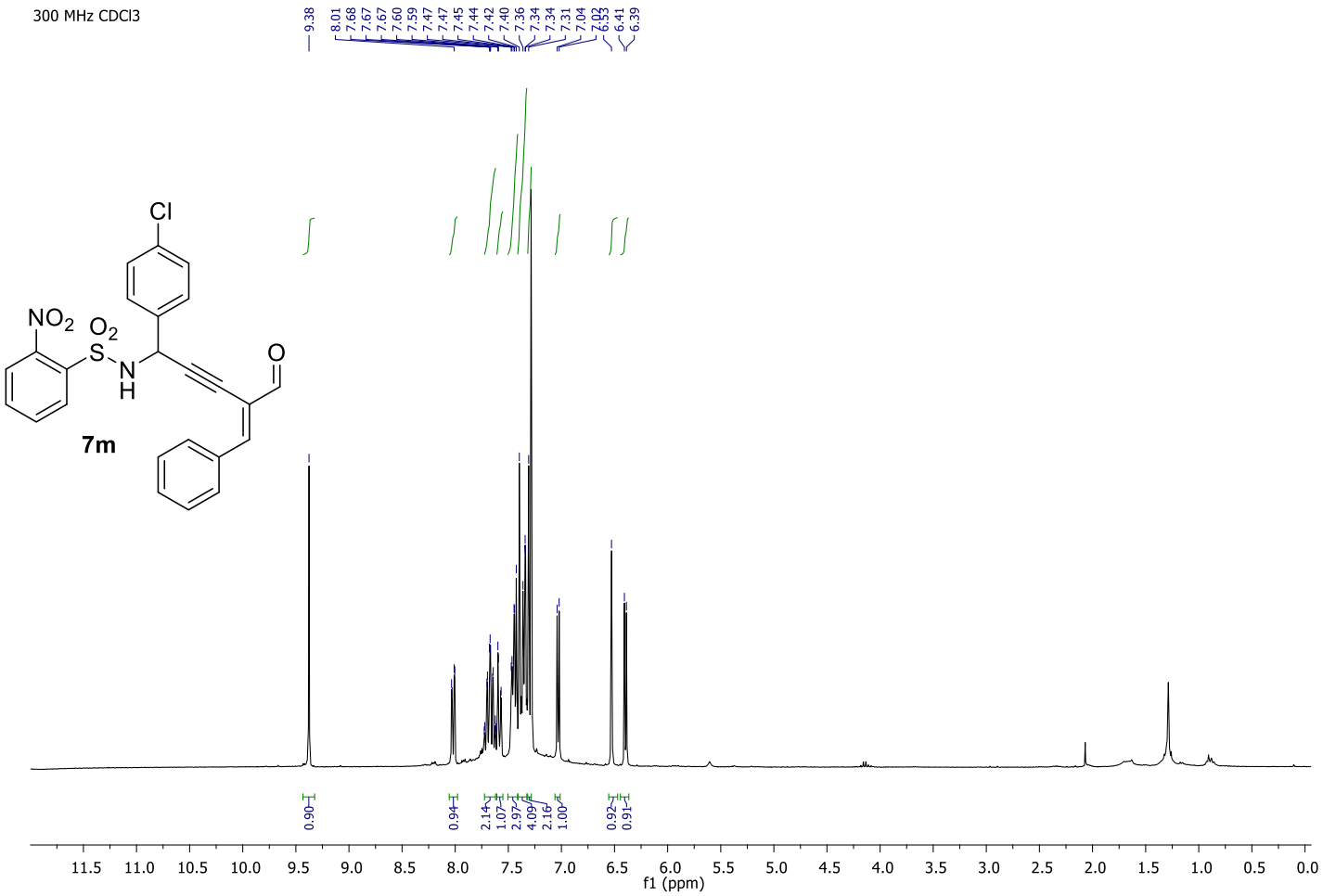
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.27
8.26
8.24
7.95
7.93
7.92
7.76
7.74
7.72
6.77
6.76
6.74
6.73
6.70
6.69
6.30
6.26
4.26
4.24
3.15
1.40
NO2
O2
S
NH
O
Me
OMe
7l
1.03
1.17
2.20
2.01
1.00
1.01
2.05
3.01
3.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

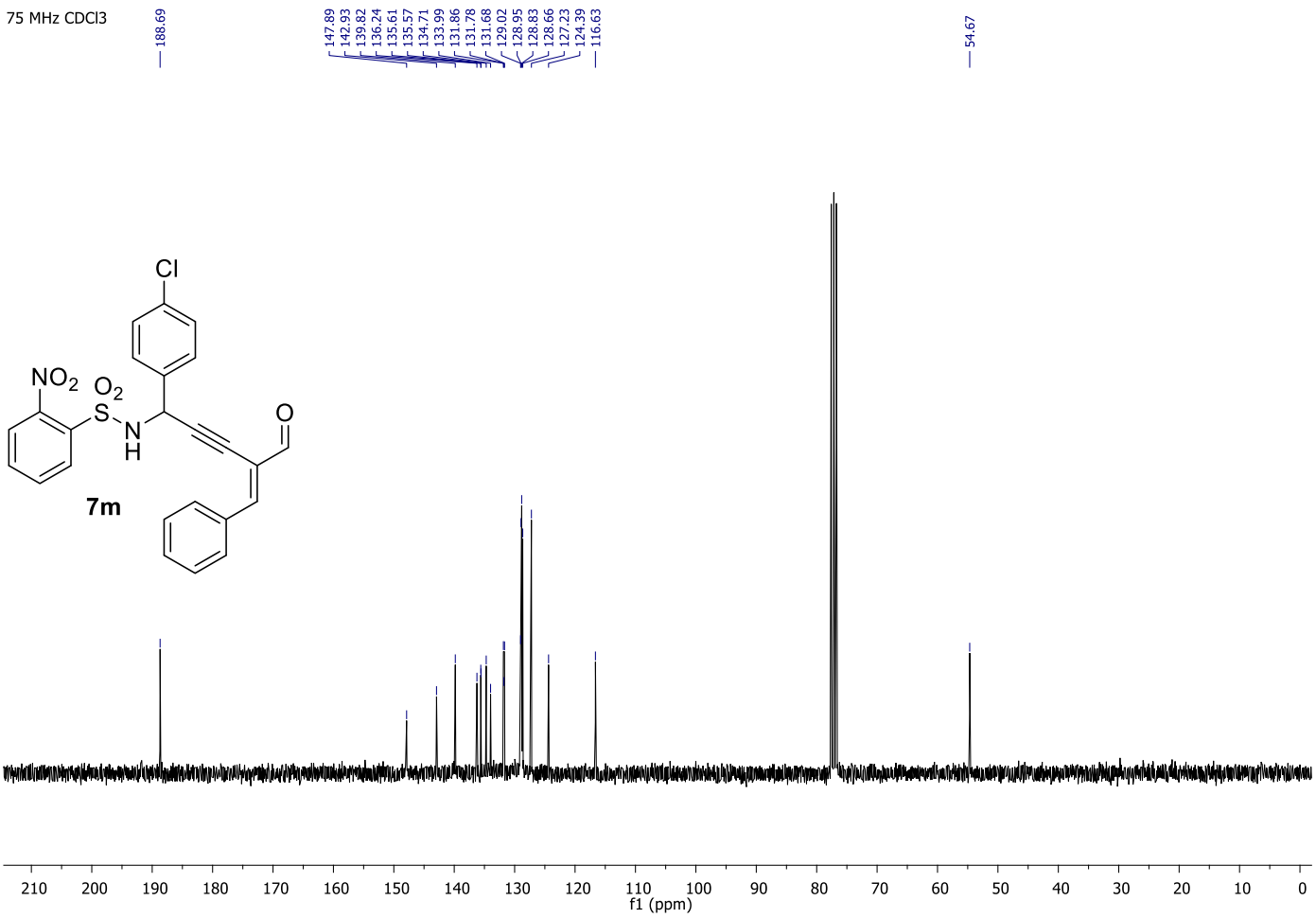
RMN ^{1}H


75 MHz CDCl3
181.16
155.36
151.58
134.24
133.66
133.08
131.76
129.84
125.74
124.86
87.91
78.54
72.75
53.66
34.35
26.37
NO2
O2
S
NH
O
Me
OMe
7I
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

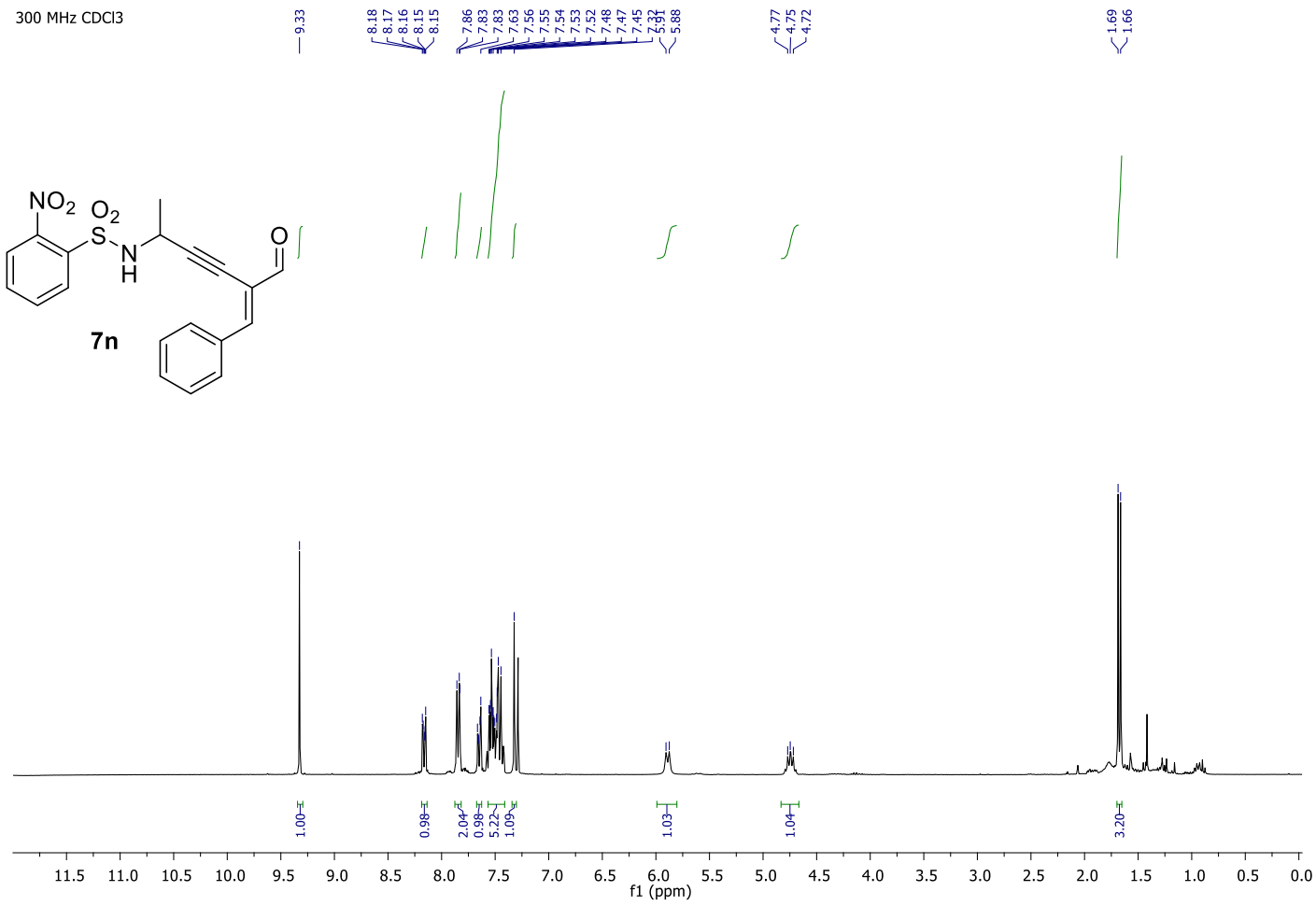
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
9.38
8.01
7.68
7.67
7.67
7.60
7.59
7.47
7.47
7.45
7.44
7.42
7.40
7.36
7.34
7.34
7.31
7.04
7.02
6.53
6.41
6.39
Cl
NO2
O2
S
N
H
O
7m
0.90
0.94
2.14
1.07
2.97
4.09
2.16
1.00
0.92
0.91
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

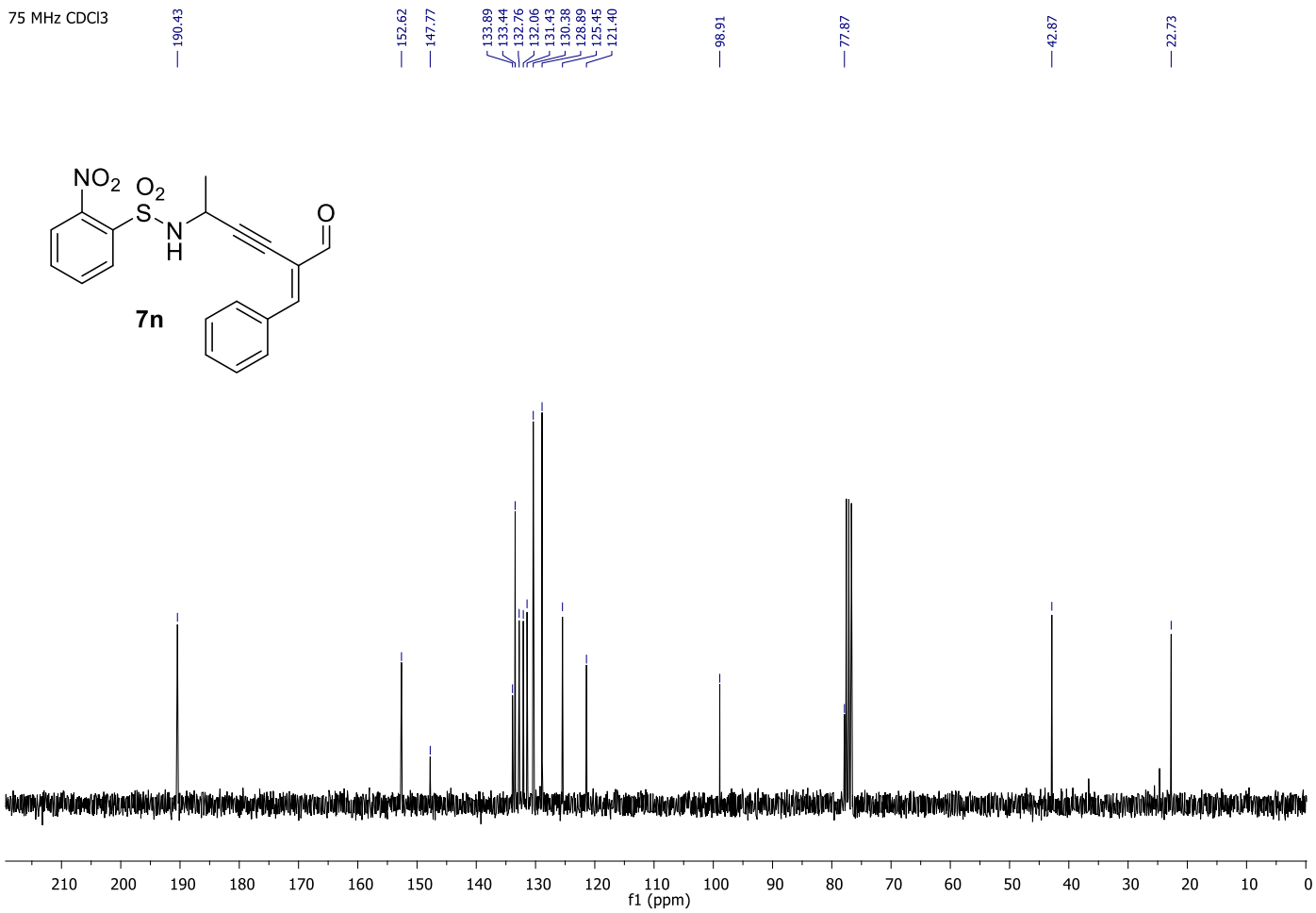
RMN ^{1}H


75 MHz CDCl3
188.69
147.89
142.93
139.82
136.24
135.61
135.57
134.71
133.99
131.86
131.78
131.68
129.02
128.95
128.83
128.66
127.23
124.39
116.63
54.67
Cl
NO2
O2
S
N
H
O
7m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

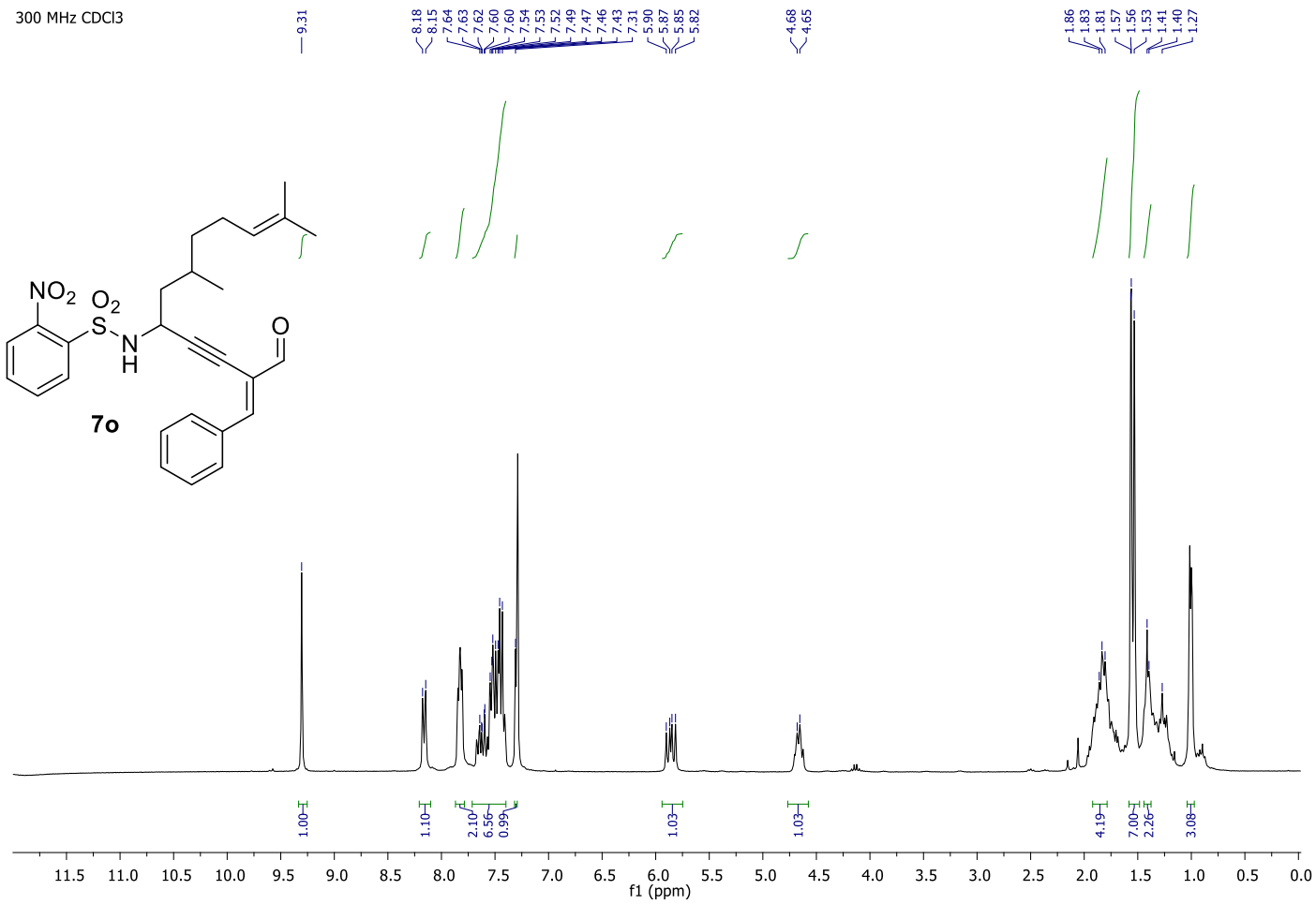
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
9.33
8.18
8.17
8.16
8.15
8.15
7.86
7.83
7.83
7.63
7.56
7.55
7.54
7.53
7.52
7.48
7.47
7.45
5.91
5.88
4.77
4.75
4.72
1.69
1.66
NO2
O2
S
N
H
O
7n
1.00
0.98
2.04
0.98
5.22
1.09
1.03
1.04
3.20
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

RMN ^{1}H

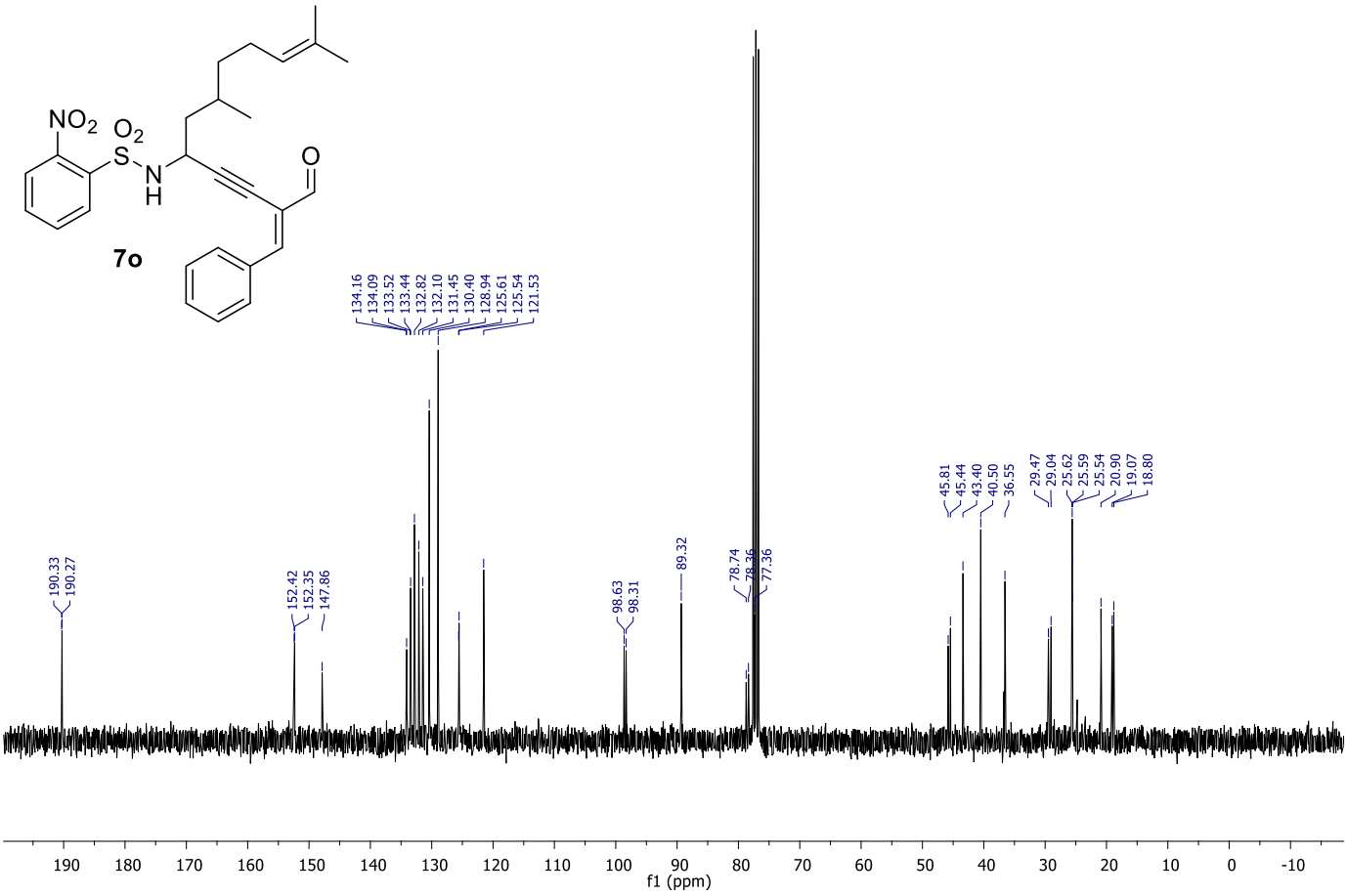

75 MHz CDCl3
190.43
152.62
147.77
133.89
133.44
132.76
132.06
131.43
130.38
128.89
125.45
121.40
98.91
77.87
42.87
22.73
NO2
O2
S
N
H
O
7n
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

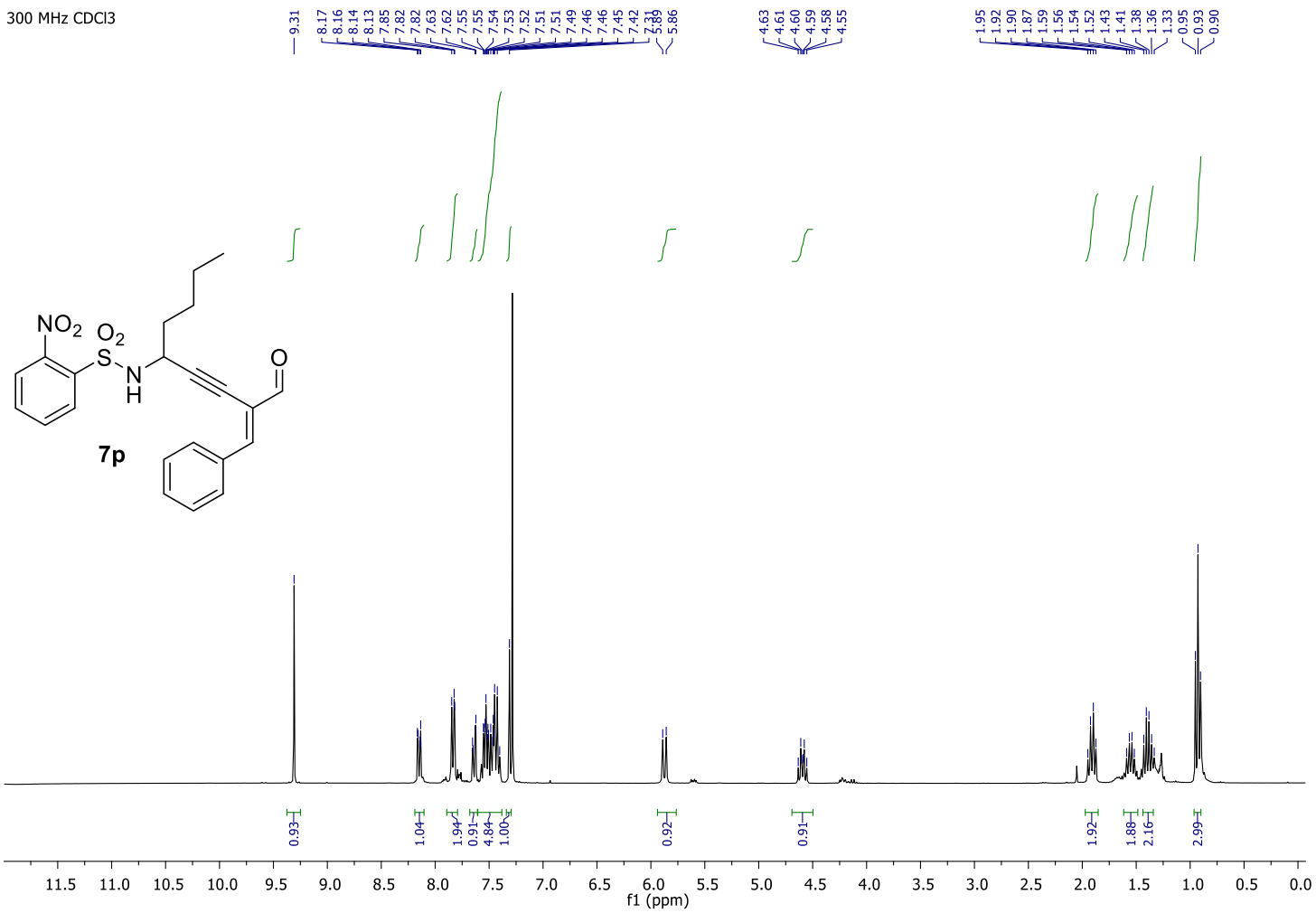

300 MHz CDCl3
9.31
8.18
8.15
7.64
7.63
7.62
7.60
7.60
7.54
7.53
7.52
7.49
7.47
7.46
7.43
7.31
5.90
5.87
5.85
5.82
4.68
4.65
1.86
1.83
1.81
1.57
1.56
1.53
1.41
1.40
1.27
NO2
O2
S
N
H
O
7o
1.00
1.10
2.10
6.56
0.99
1.03
1.03
4.19
7.00
2.26
3.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H

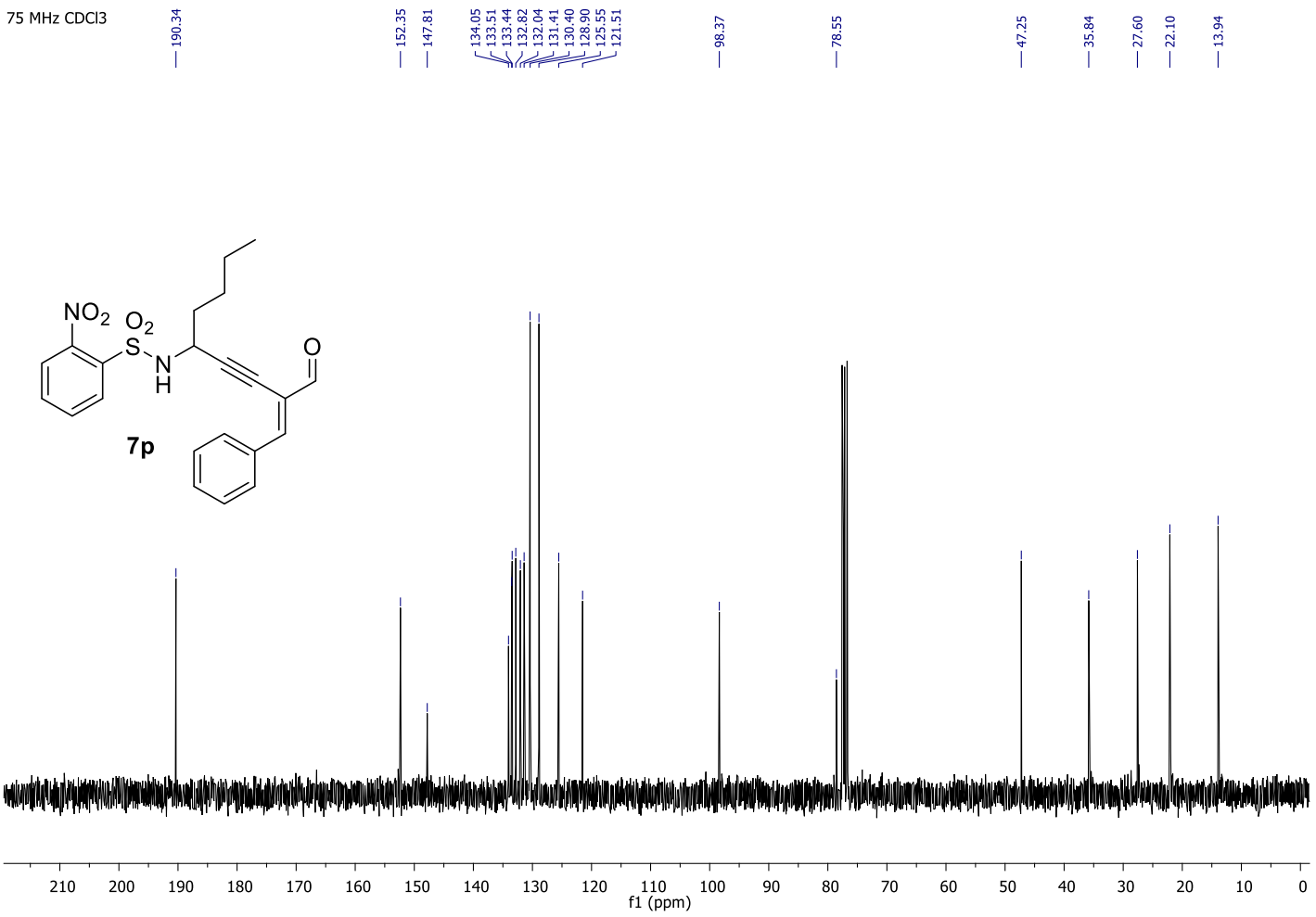
75 MHz CDCl3



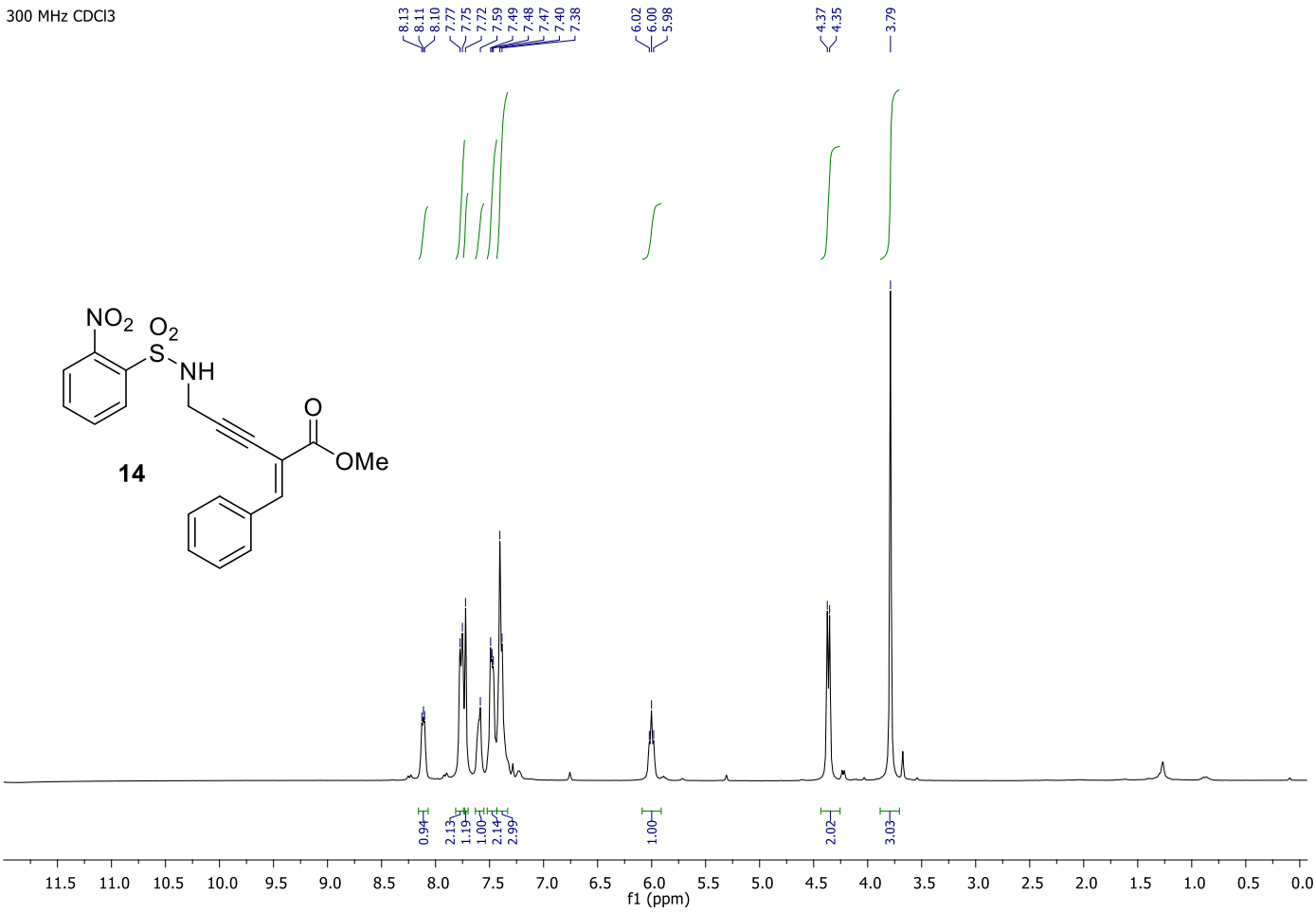
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
9.31
8.17
8.16
8.14
8.13
7.85
7.82
7.82
7.63
7.62
7.55
7.55
7.54
7.53
7.52
7.51
7.51
7.49
7.46
7.46
7.45
7.42
5.86
4.63
4.61
4.60
4.59
4.58
4.55
1.95
1.92
1.90
1.87
1.59
1.56
1.54
1.52
1.43
1.41
1.38
1.36
1.33
0.95
0.93
0.90
NO2
O2
S
N
H
O
7p
0.93
1.04
1.94
0.91
4.84
1.00
0.92
0.91
1.92
1.88
2.16
2.99
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

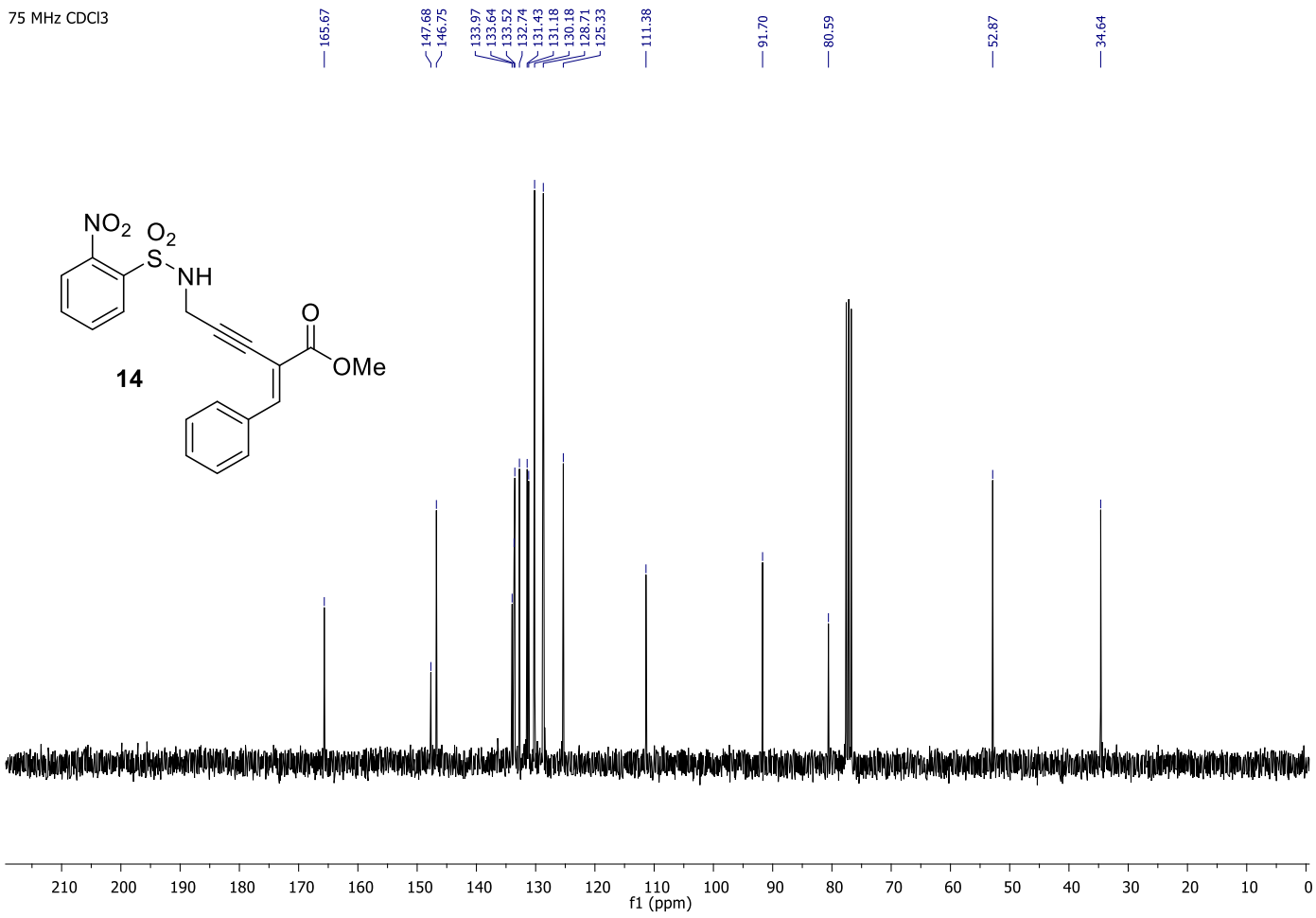
RMN ^{1}H


75 MHz CDCl3
190.34
152.35
147.81
134.05
133.51
133.44
132.82
132.04
131.41
130.40
128.90
125.55
121.51
98.37
78.55
47.25
35.84
27.60
22.10
13.94
NO2
O2
S
N
H
O
7p
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

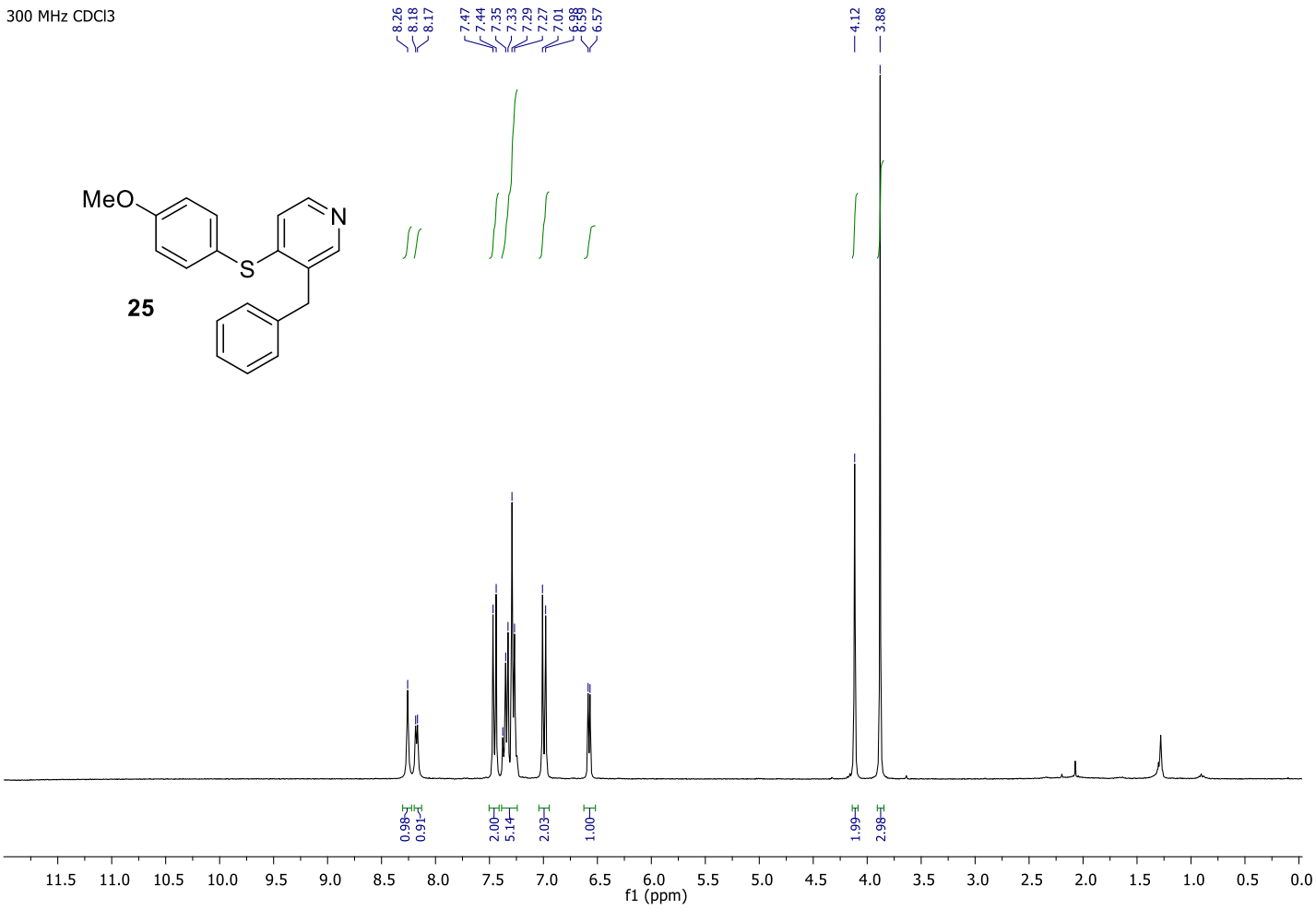
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.13
8.11
8.10
7.77
7.75
7.72
7.59
7.49
7.48
7.47
7.40
7.38
6.02
6.00
5.98
4.37
4.35
3.79
NO2
O2
S
NH
O
OMe
14
0.94
2.13
1.19
1.00
2.14
2.99
1.00
2.02
3.03
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

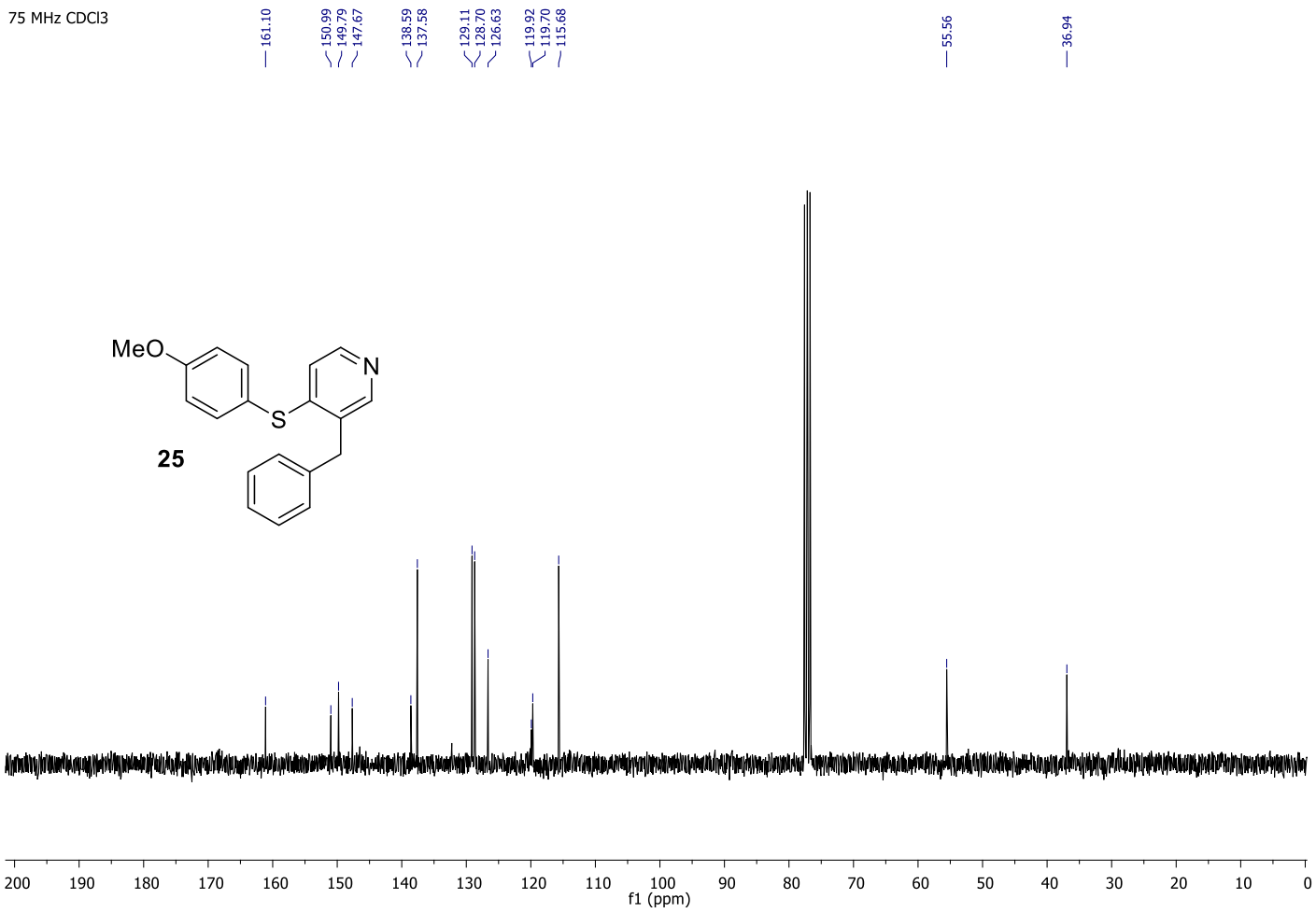
RMN ^{1}H


75 MHz CDCl3
165.67
147.68
146.75
133.97
133.64
133.52
132.74
131.43
131.18
130.18
128.71
125.33
111.38
91.70
80.59
52.87
34.64
NO2
O2
S
NH
O
OMe
14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

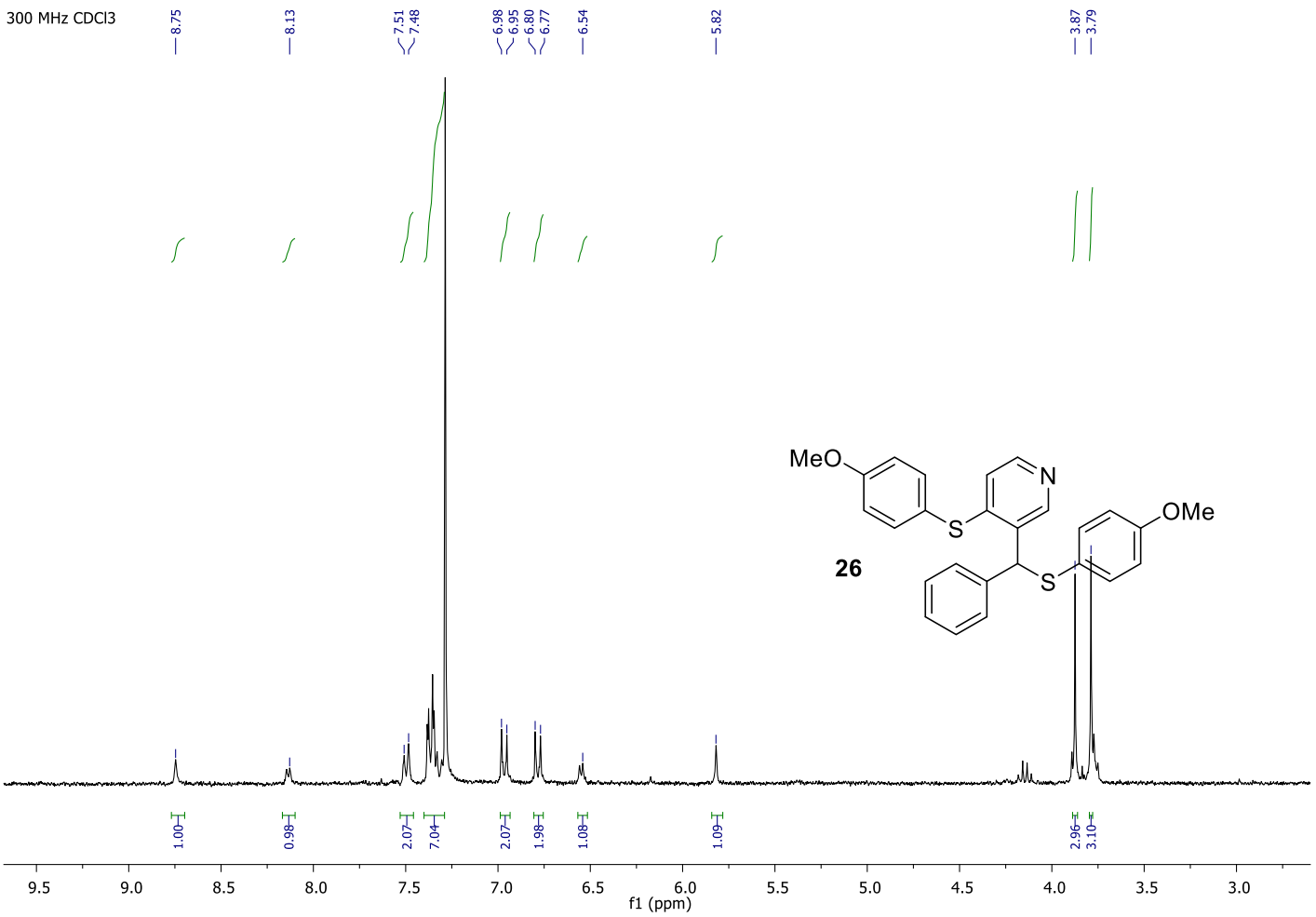
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.26
8.18
8.17
7.47
7.44
7.35
7.33
7.29
7.27
7.01
6.57
4.12
3.88
MeO
S
N
25
0.98
0.91
2.00
5.14
2.03
1.00
1.99
2.98
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

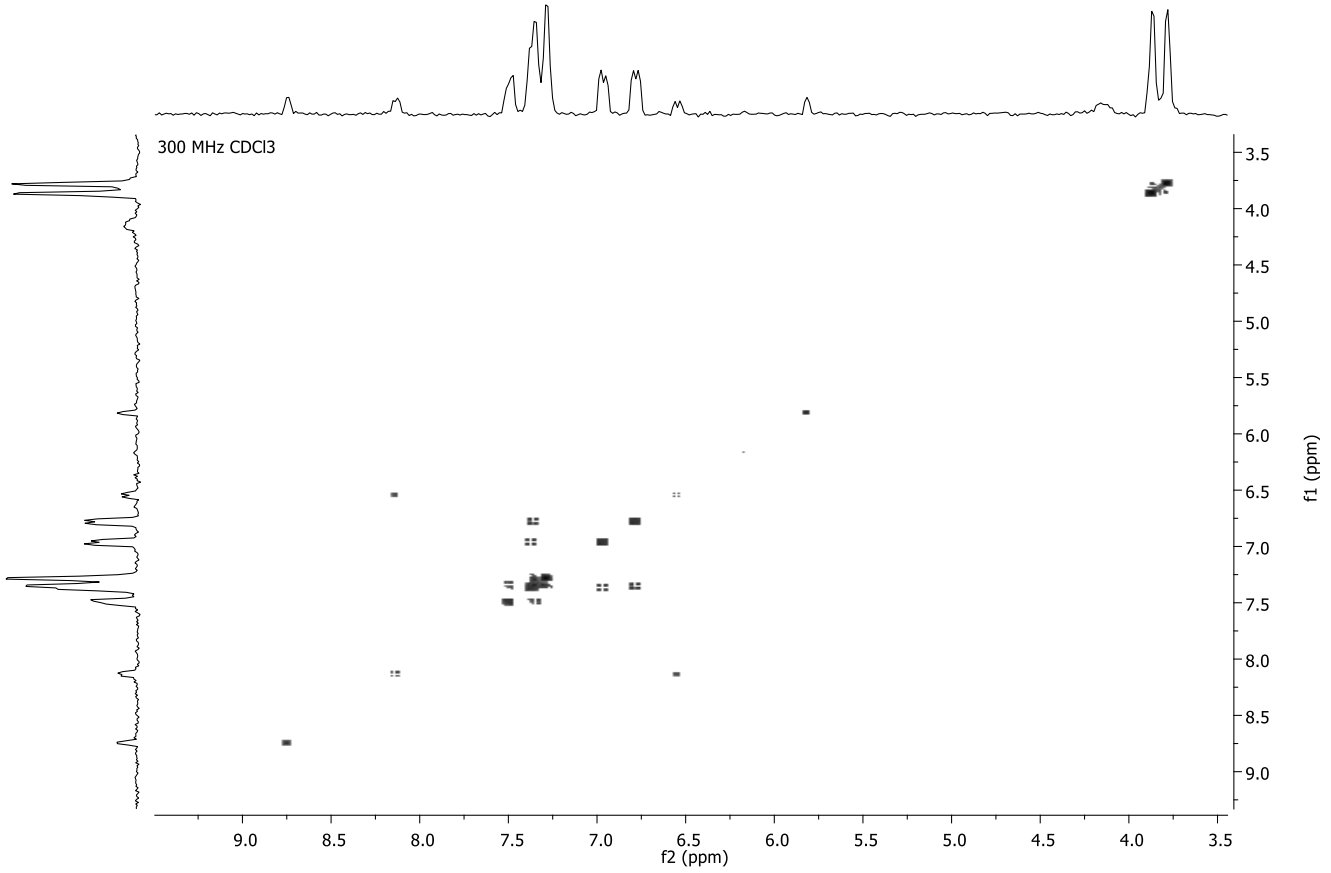
RMN ^{1}H


75 MHz CDCl3
161.10
150.99
149.79
147.67
138.59
137.58
129.11
128.70
126.63
119.92
119.70
115.68
55.56
36.94
MeO
S
N
25
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

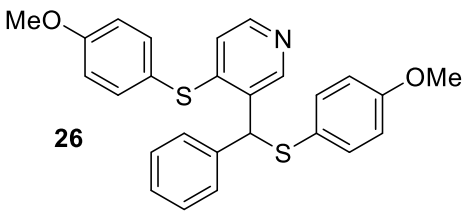
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.75
8.13
7.51
7.48
6.98
6.95
6.80
6.77
6.54
5.82
3.87
3.79
MeO
N
S
OMe
S
26
1.00
0.98
2.07
7.04
2.07
1.98
1.08
1.09
2.96
3.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

RMN ^{1}H



RMN ^{1}H – gCOSY



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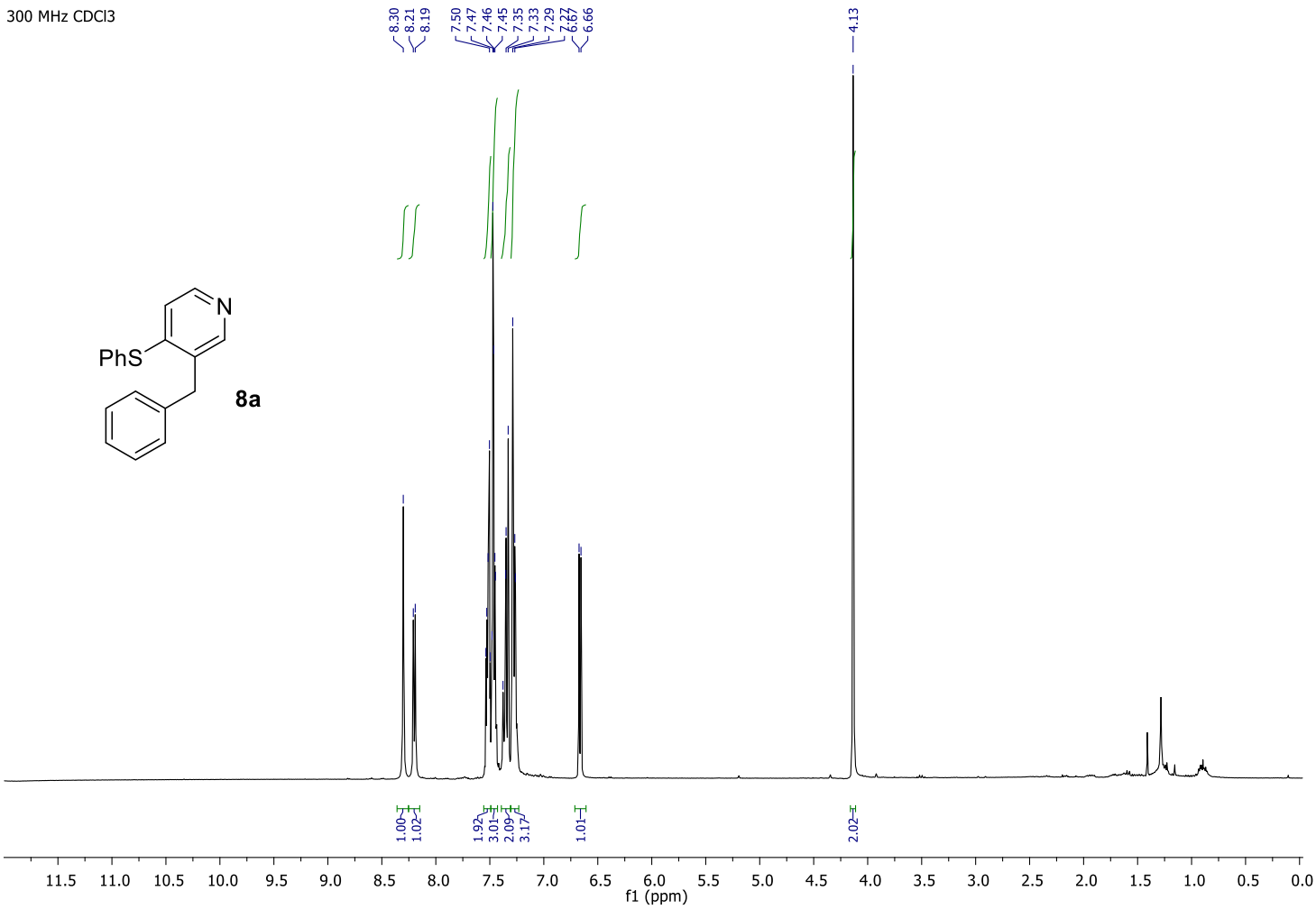
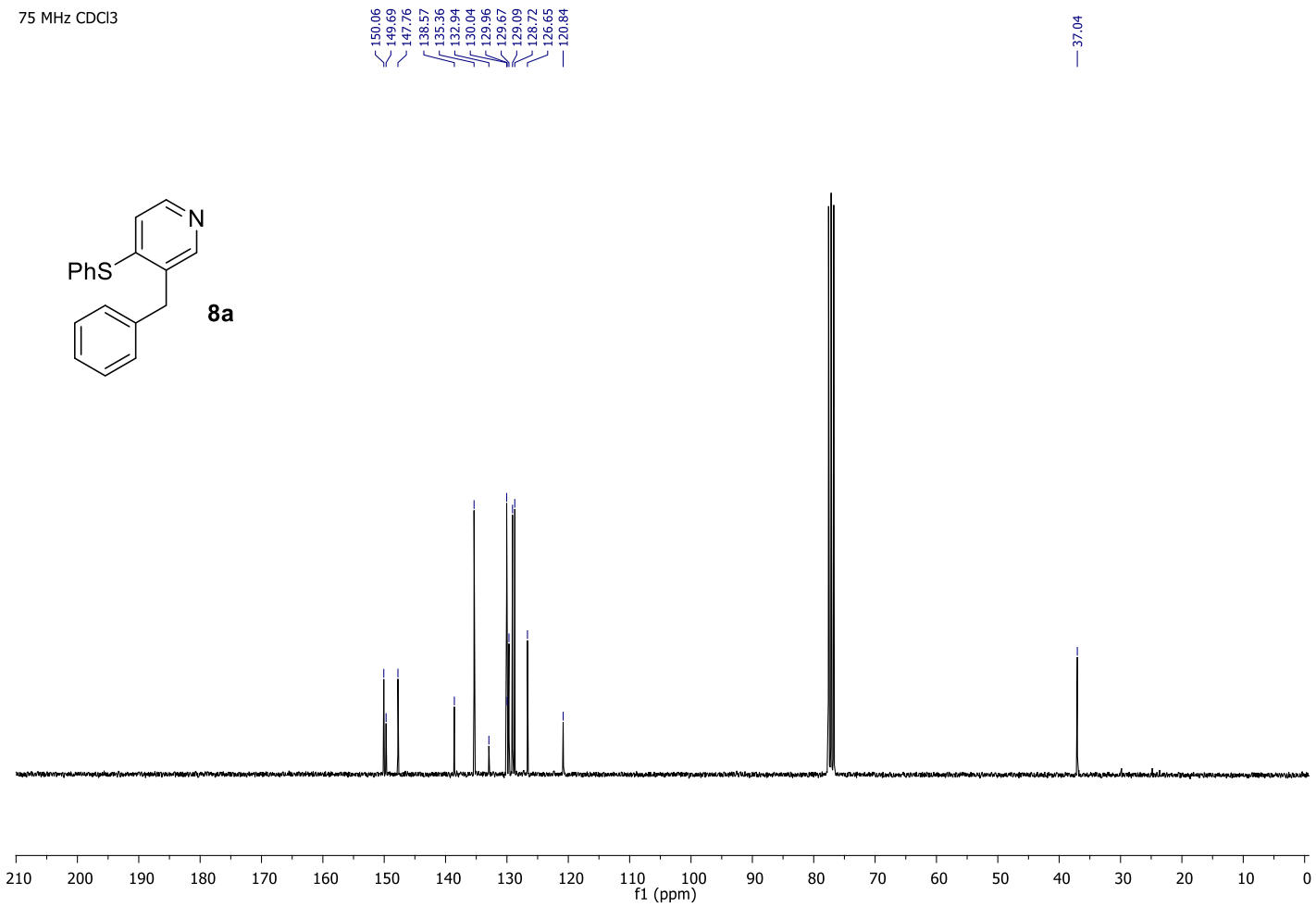
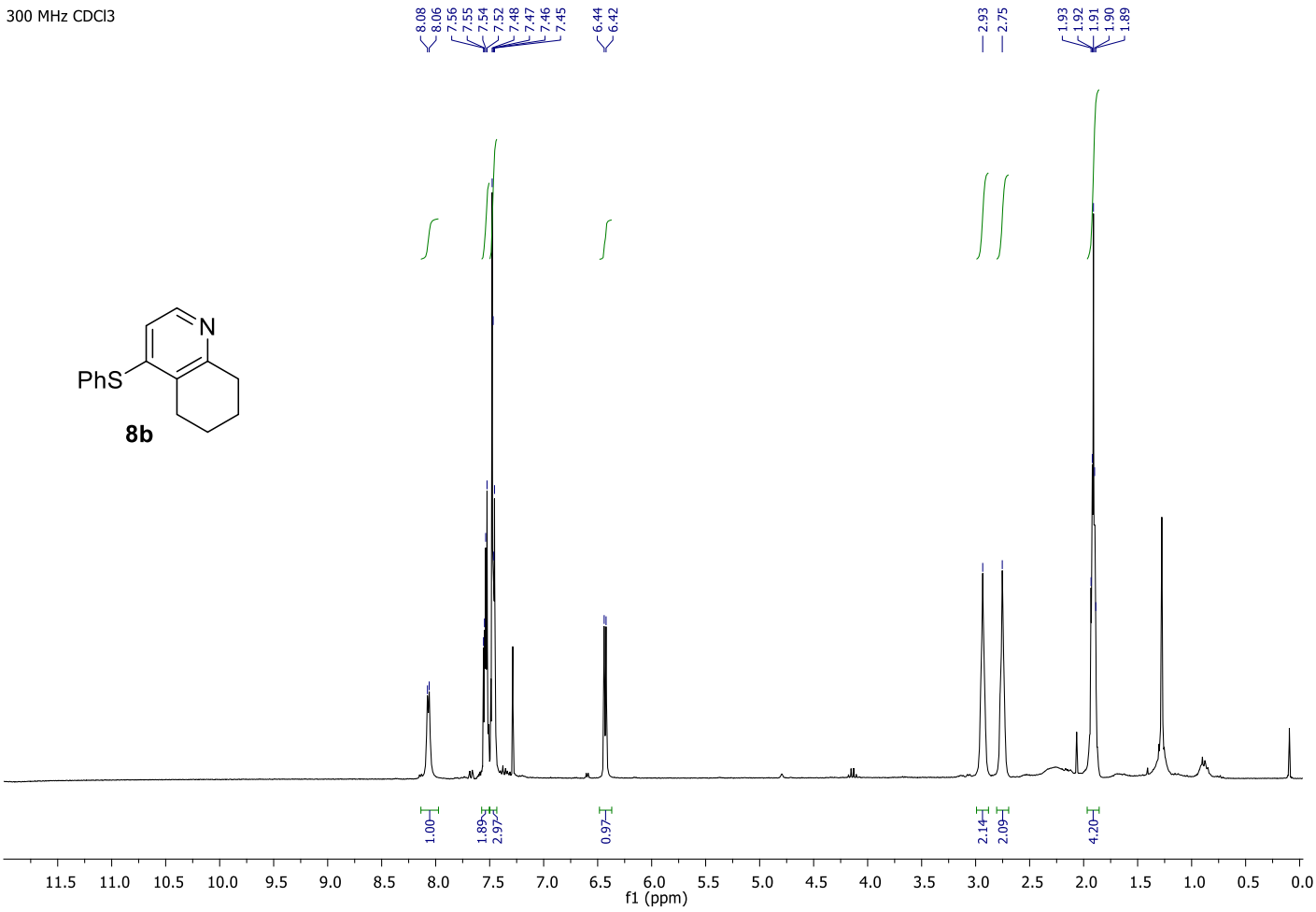

300 MHz CDCl3
8.30
8.21
8.19
7.50
7.47
7.46
7.45
7.35
7.33
7.29
6.67
6.66
4.13
N
PhS
8a
1.00
1.02
1.92
3.01
2.09
3.17
1.01
2.02
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

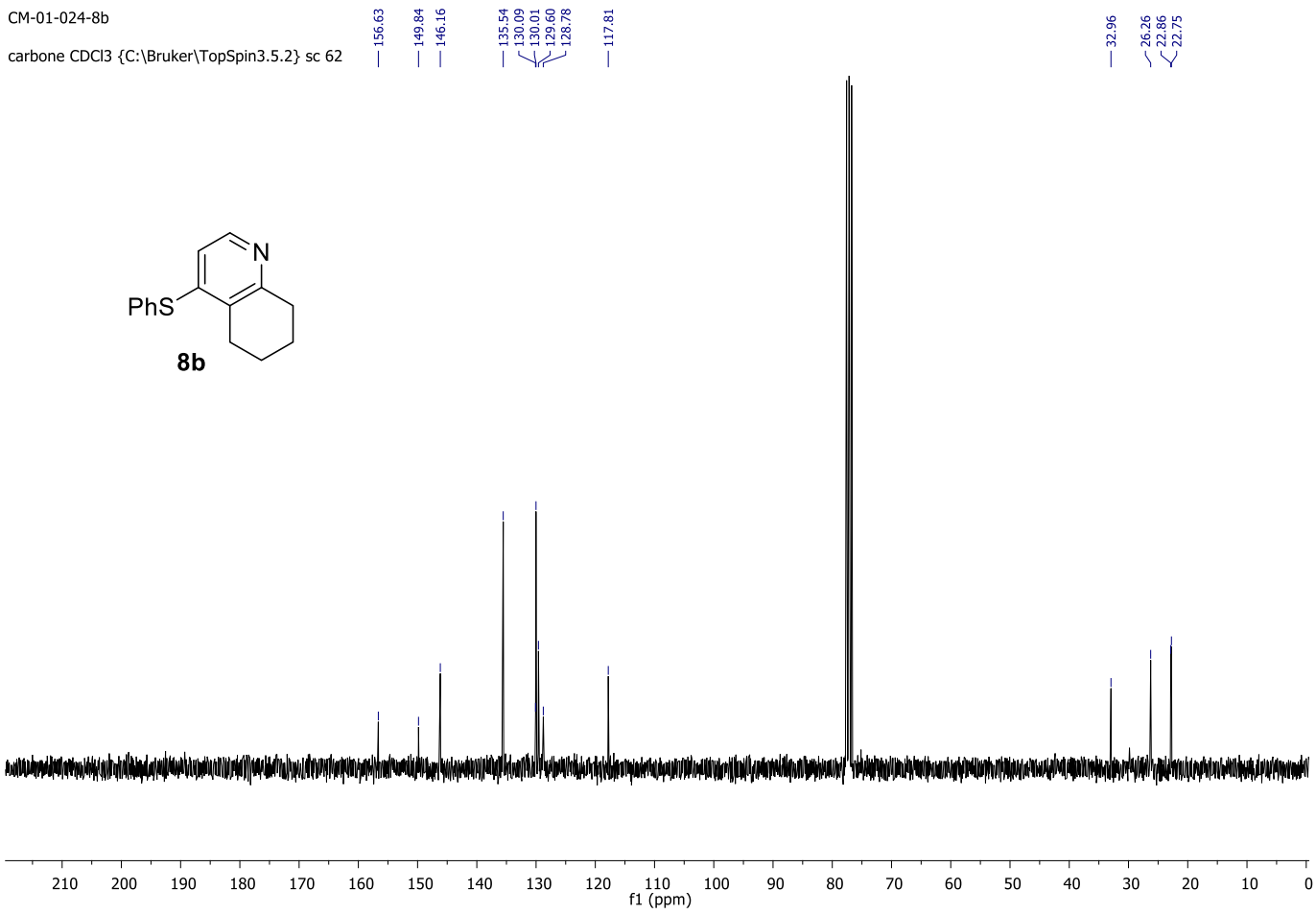
RMN ^{1}H


75 MHz CDCl3
150.06
149.69
147.76
138.57
135.36
132.94
130.04
129.96
129.67
129.09
128.72
126.65
120.84
37.04
N
PhS
8a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

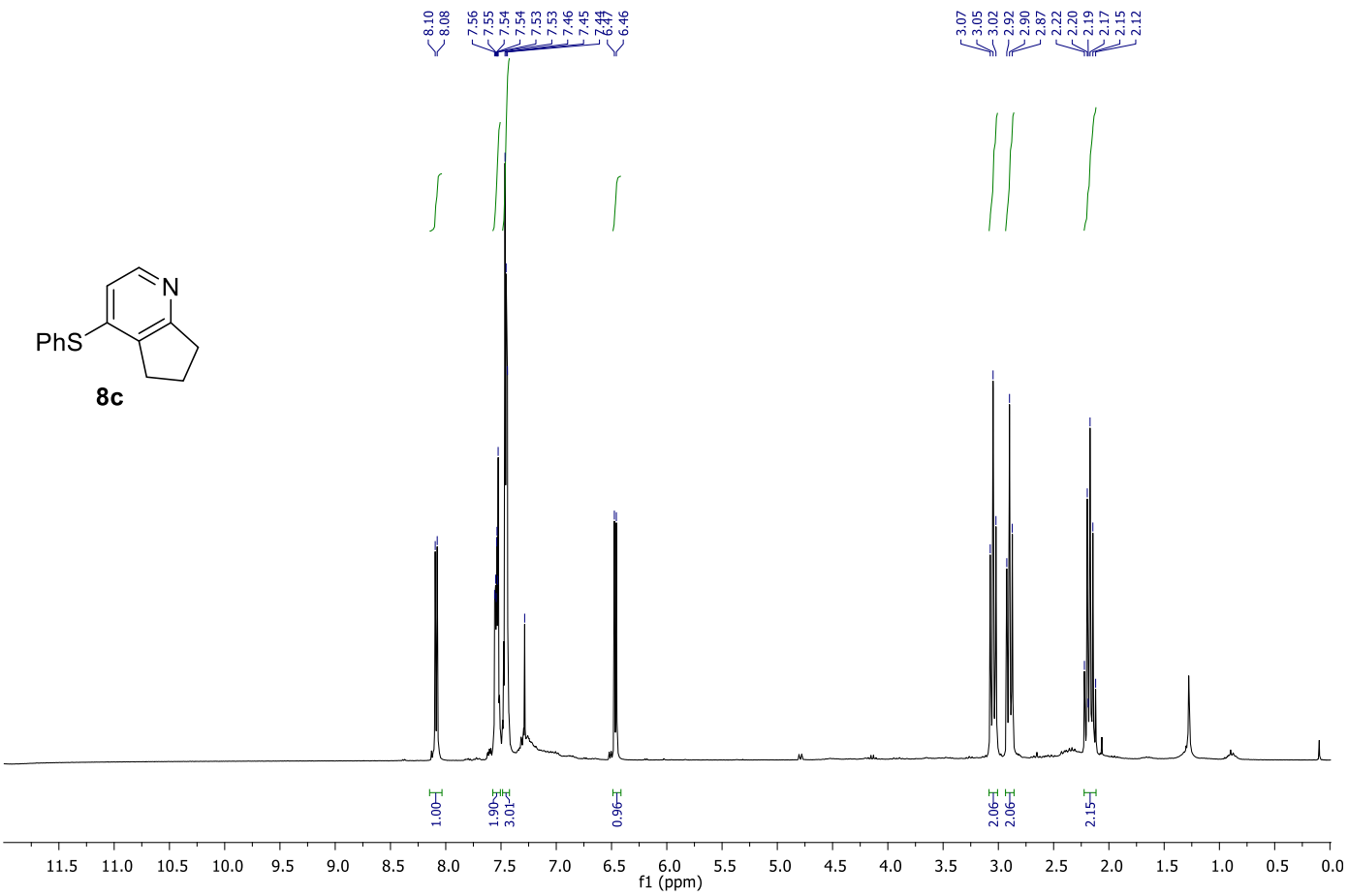

300 MHz CDCl3
8.08
8.06
7.56
7.55
7.54
7.52
7.48
7.47
7.46
7.45
6.44
6.42
2.93
2.75
1.93
1.92
1.91
1.90
1.89
N
PhS
8b
1.00
1.89
2.97
0.97
2.14
2.09
4.20
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H


CM-01-024-8b
carbone CDCl3 {C:\Bruker\TopSpin3.5.2} sc 62
156.63
149.84
146.16
135.54
130.09
130.01
129.60
128.78
117.81
32.96
26.26
22.86
22.75
N
PhS
8b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

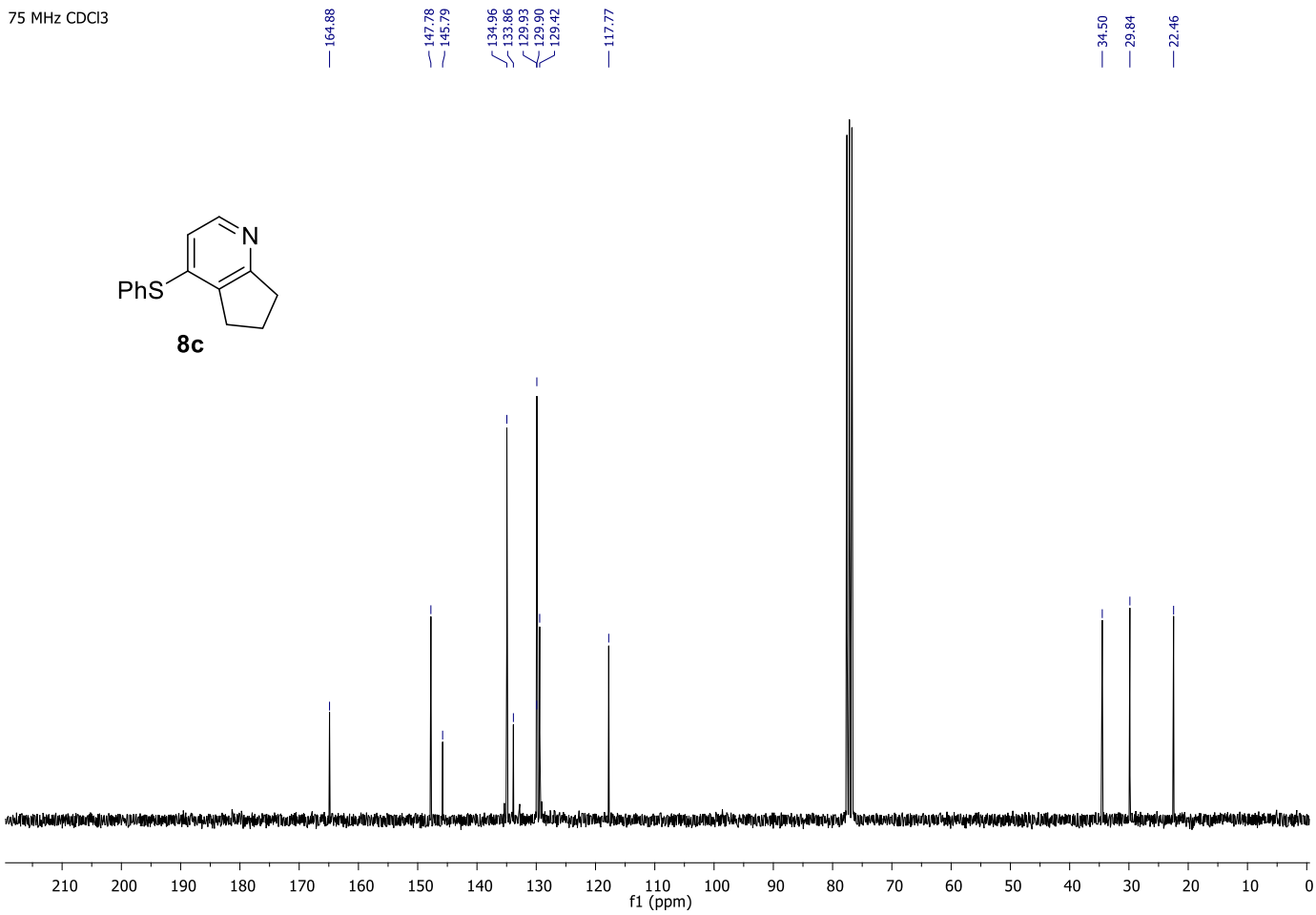
RMN $^{13}C\{^{1}H\}$

300 MHz CDCl3



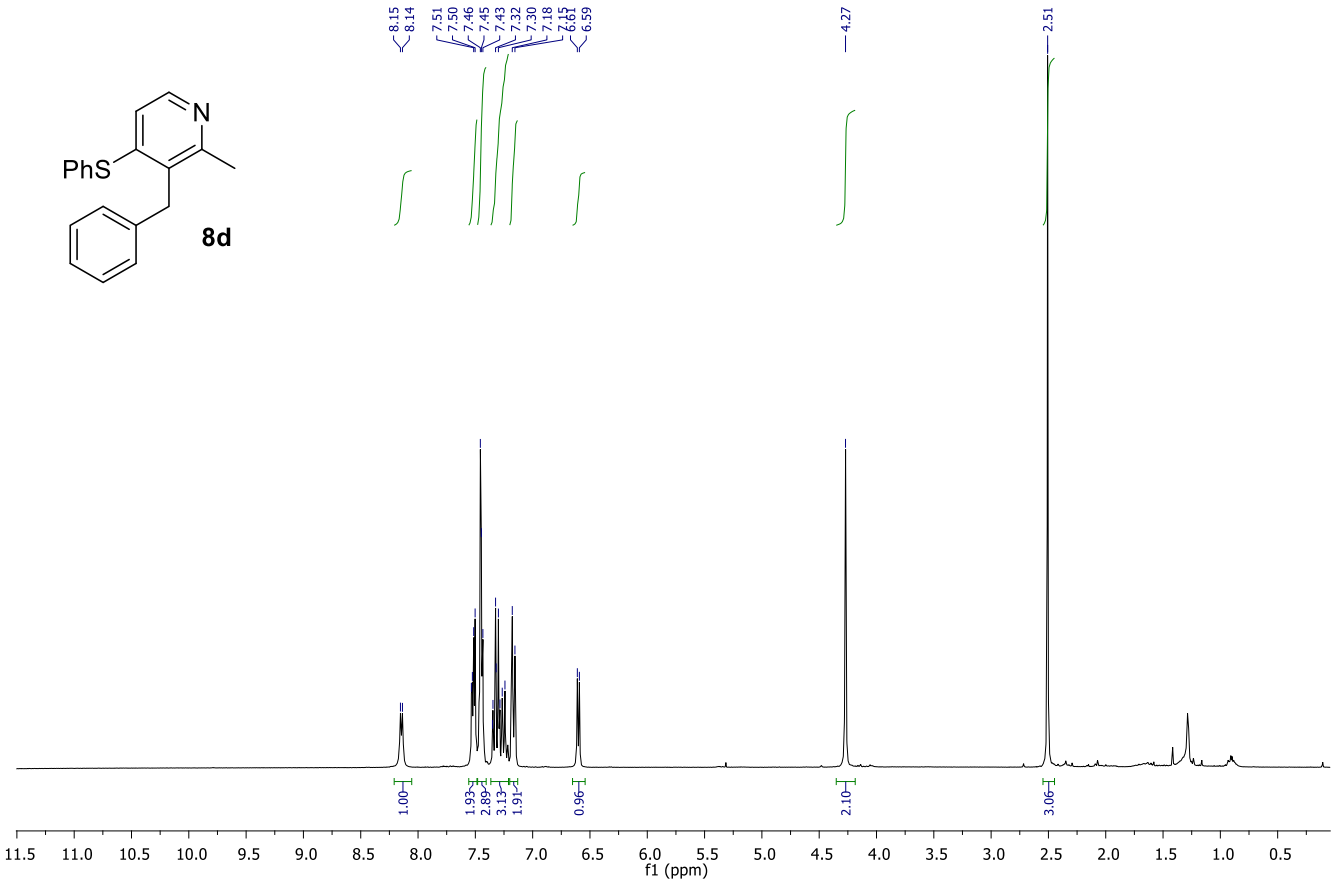
8c

RMN ^{1}H

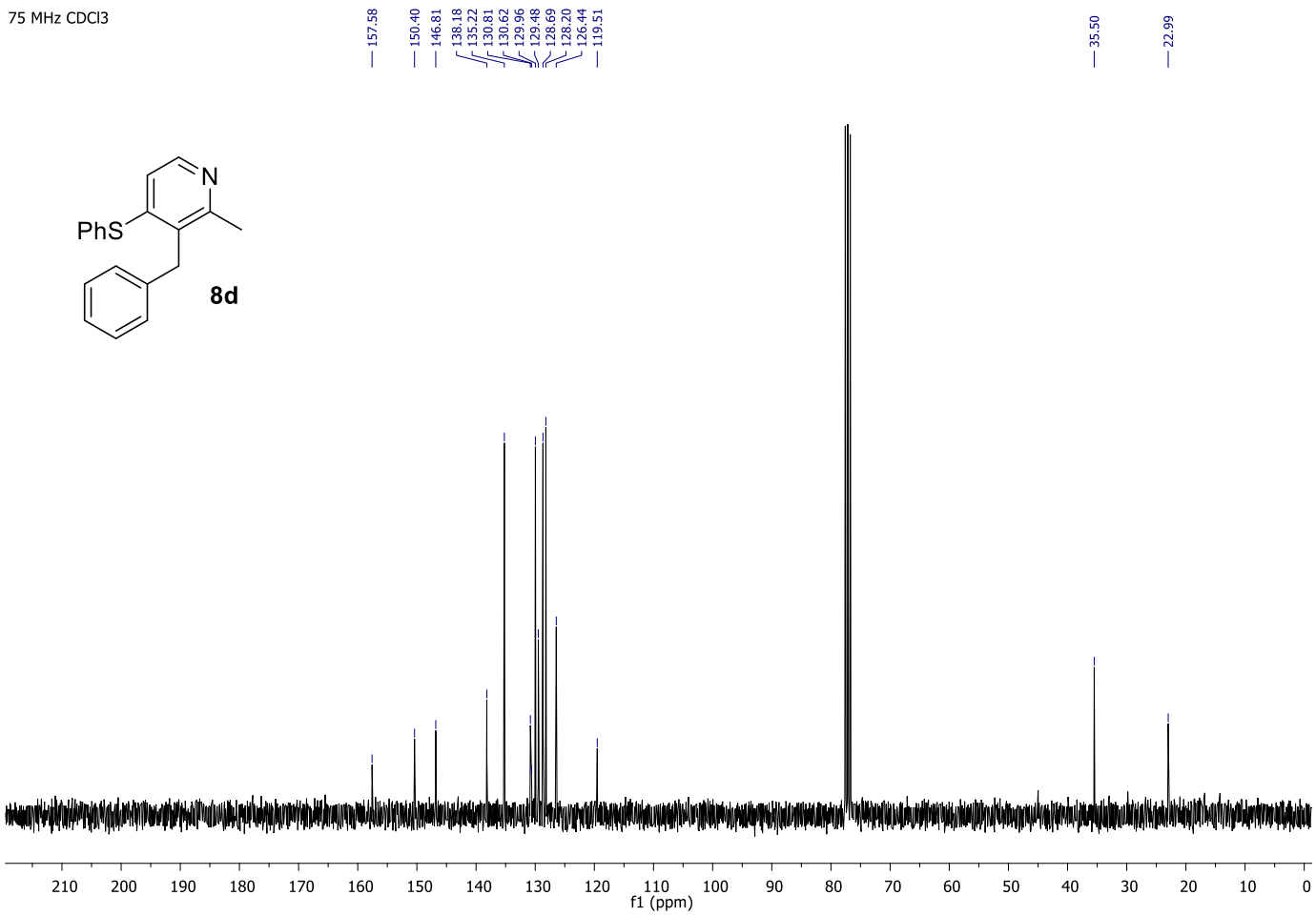

75 MHz CDCl3
164.88
147.78
145.79
134.96
133.86
129.93
129.90
129.42
117.77
34.50
29.84
22.46
N
PhS
8c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

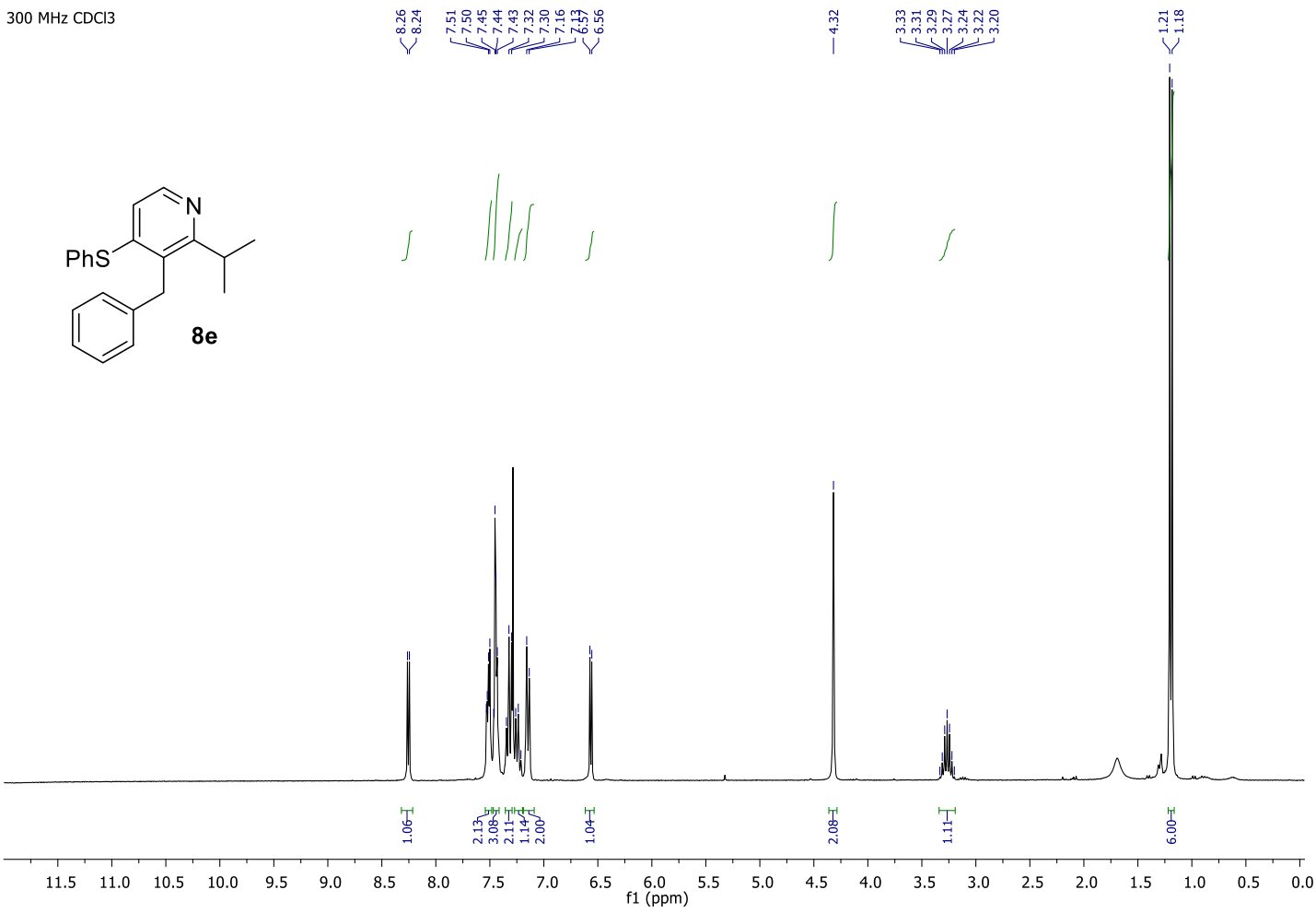
300 MHz CDCl3



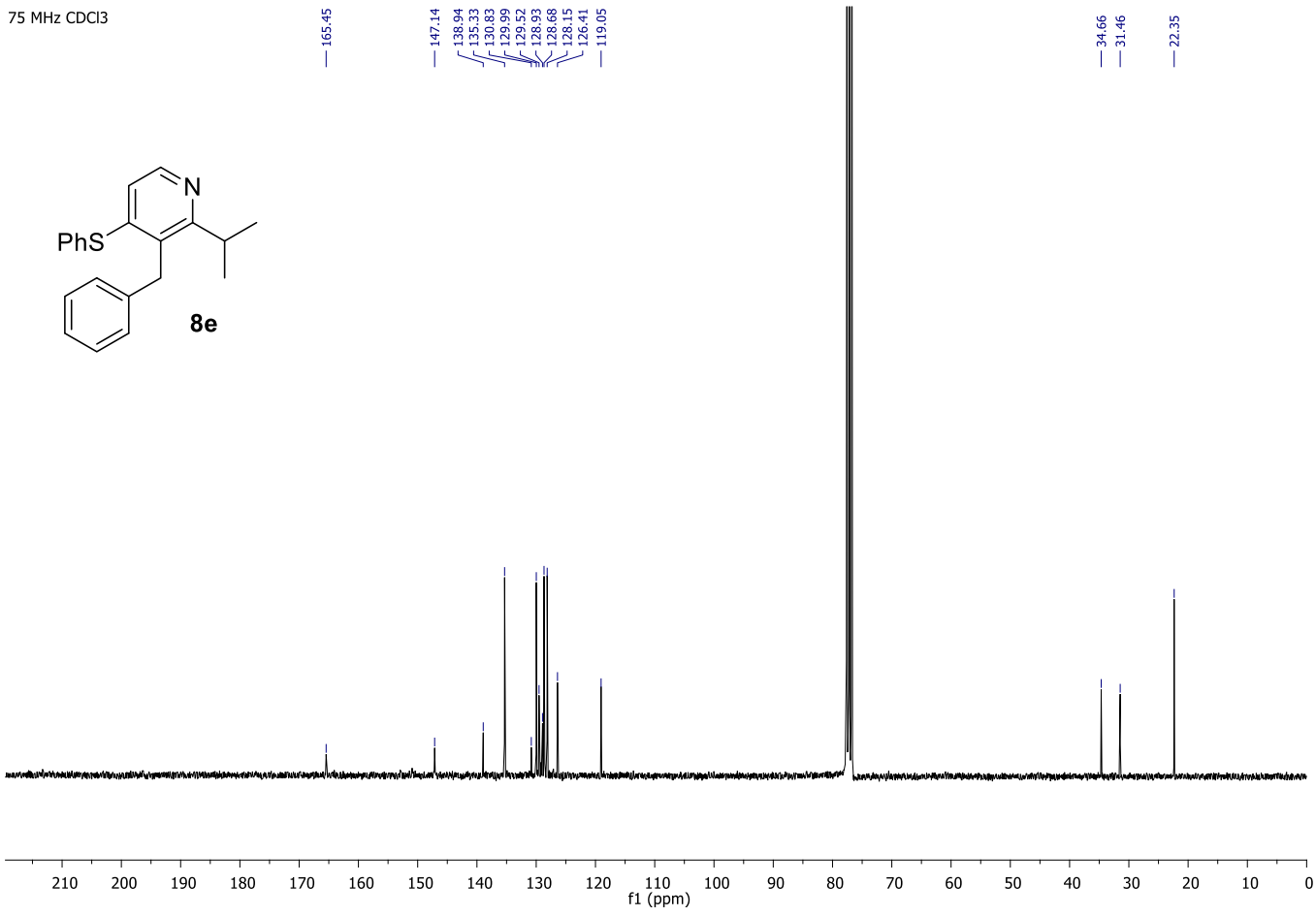
RMN ^{1}H


75 MHz CDCl3
157.58
150.40
146.81
138.18
135.22
130.81
130.62
129.96
129.48
128.69
128.20
126.44
119.51
35.50
22.99
PhS
N
8d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

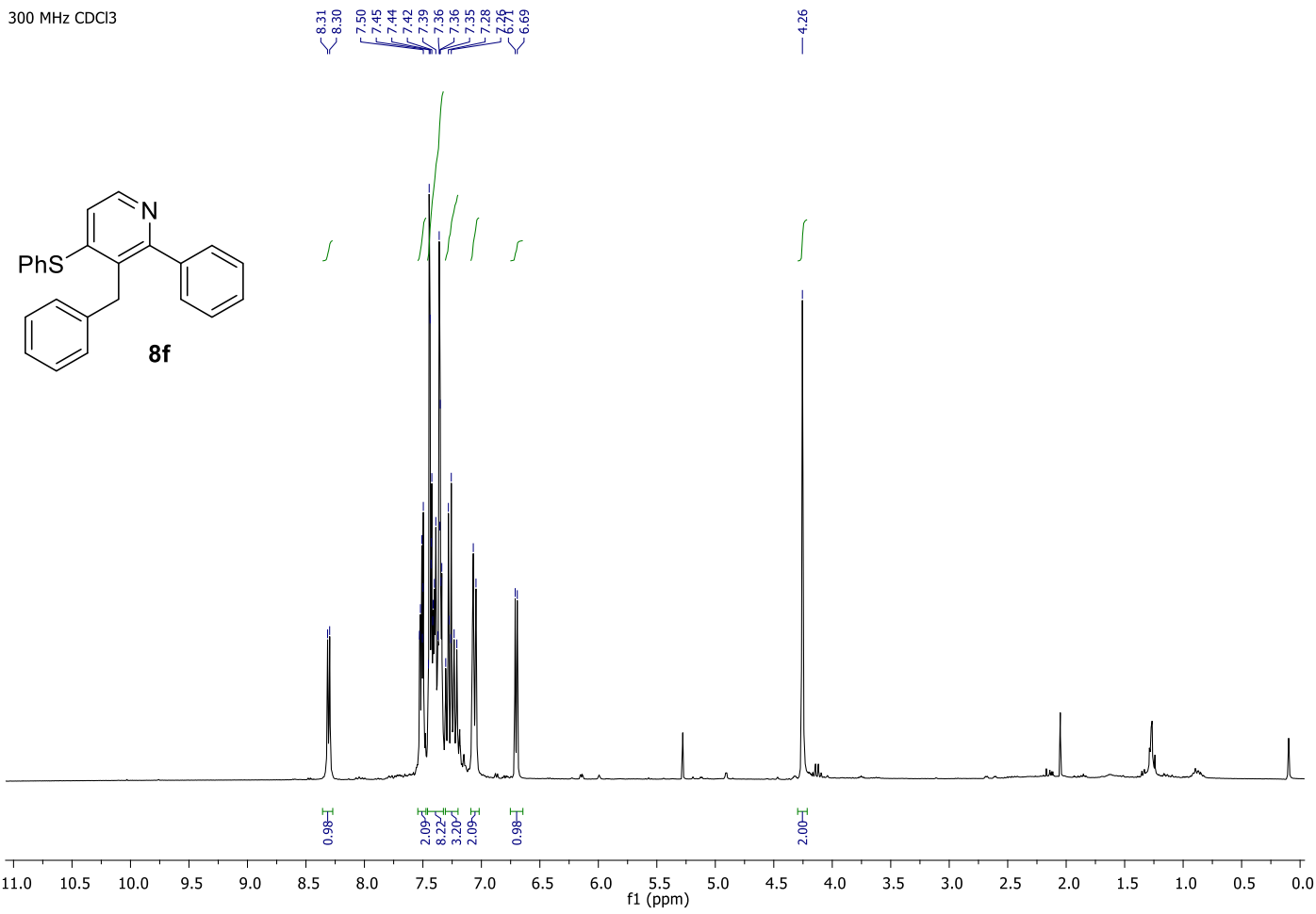
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.26
8.24
7.51
7.50
7.45
7.44
7.43
7.32
7.30
7.16
7.13
6.57
6.56
4.32
3.33
3.31
3.29
3.27
3.24
3.22
3.20
1.21
1.18
PhS
N
8e
1.06
2.13
3.08
2.11
1.14
2.00
1.04
2.08
1.11
6.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H


75 MHz CDCl3
165.45
147.14
138.94
135.33
130.83
129.99
129.52
128.93
128.68
128.15
126.41
119.05
34.66
31.46
22.35
N
PhS
8e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

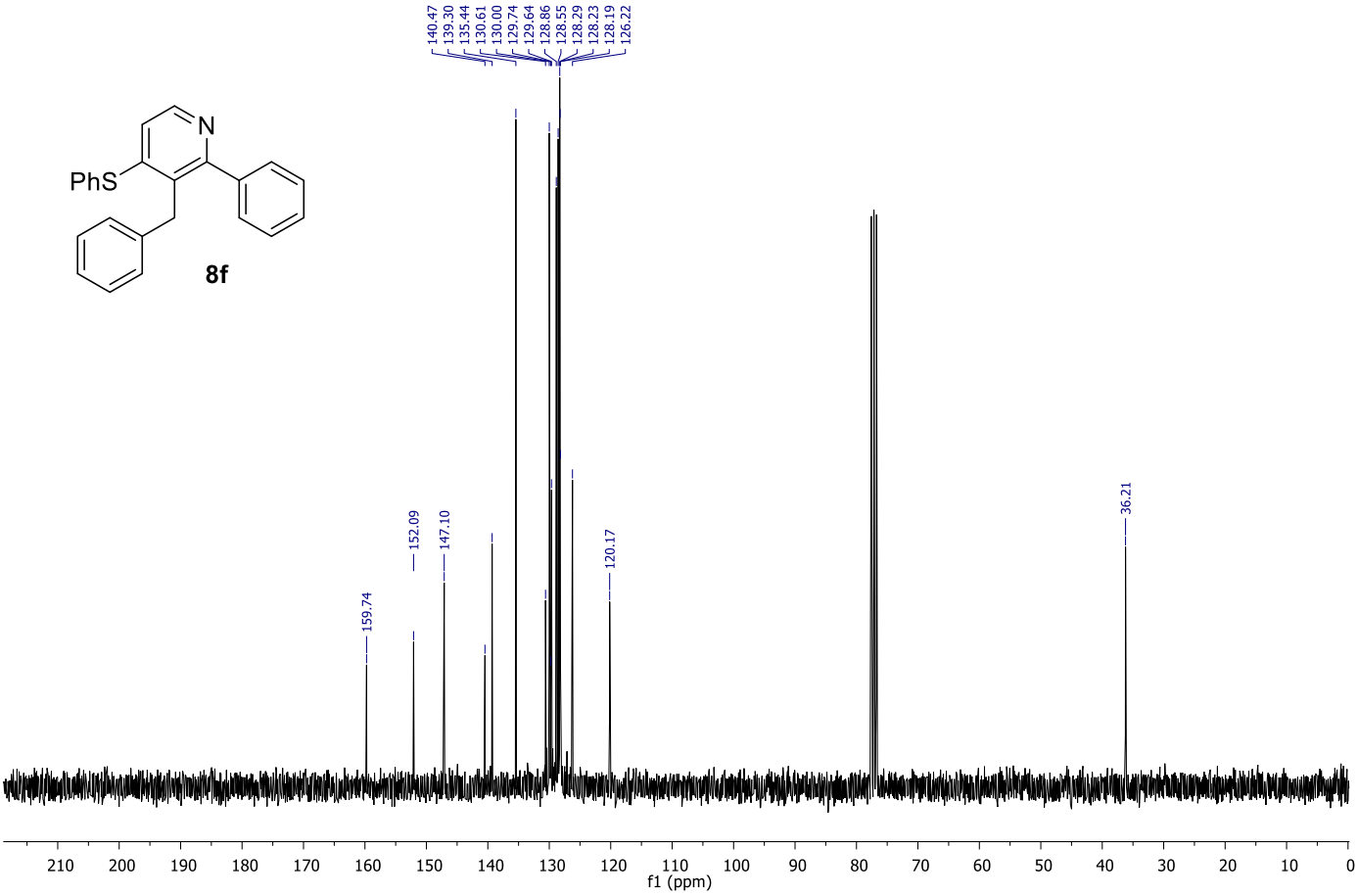
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.31
8.30
7.50
7.45
7.44
7.42
7.39
7.36
7.36
7.35
7.28
7.26
6.71
6.69
4.26
PhS
N
0.98
2.09
8.22
3.20
2.09
0.98
2.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

8f

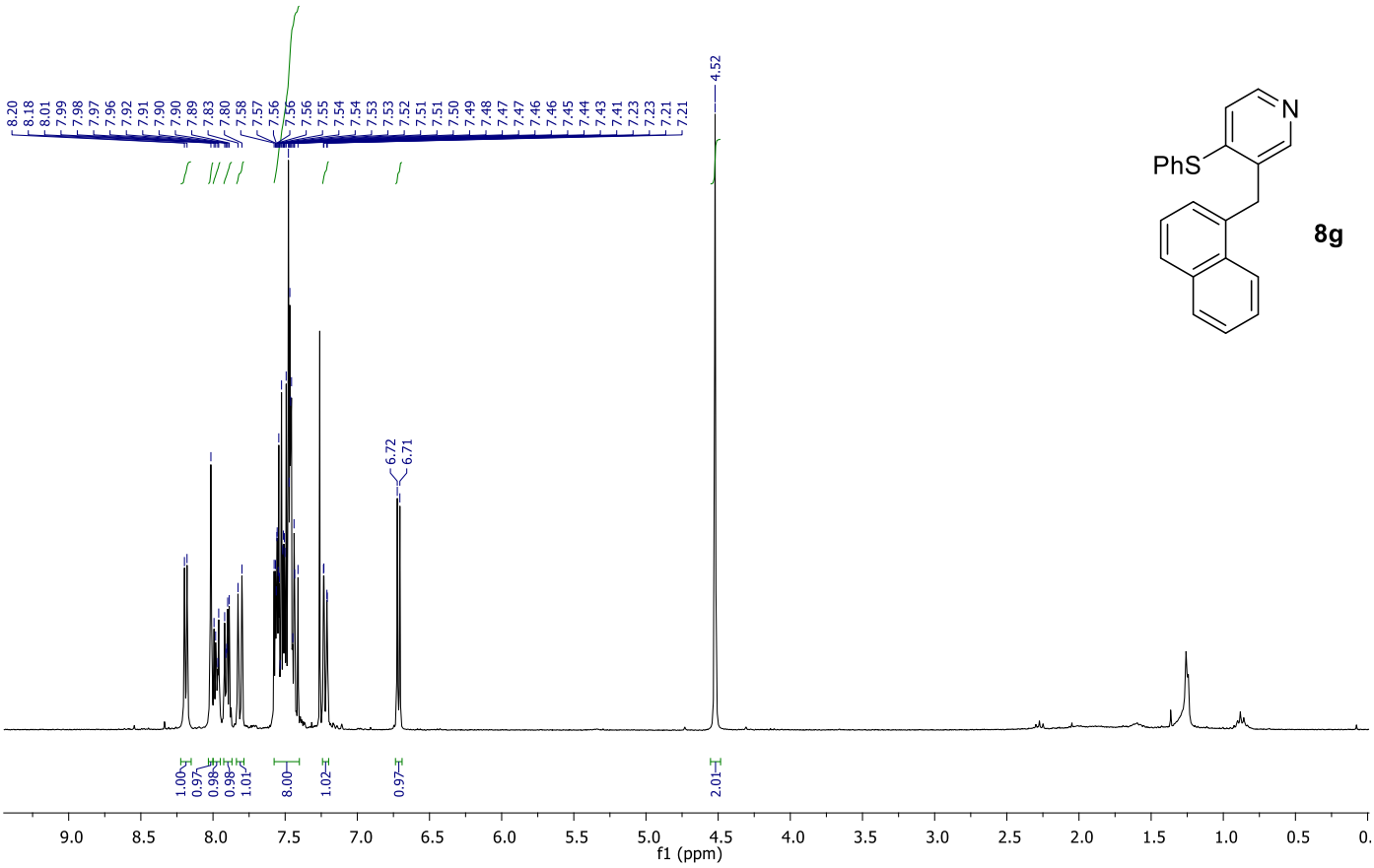
RMN ^{1}H

75 MHz CDCl3



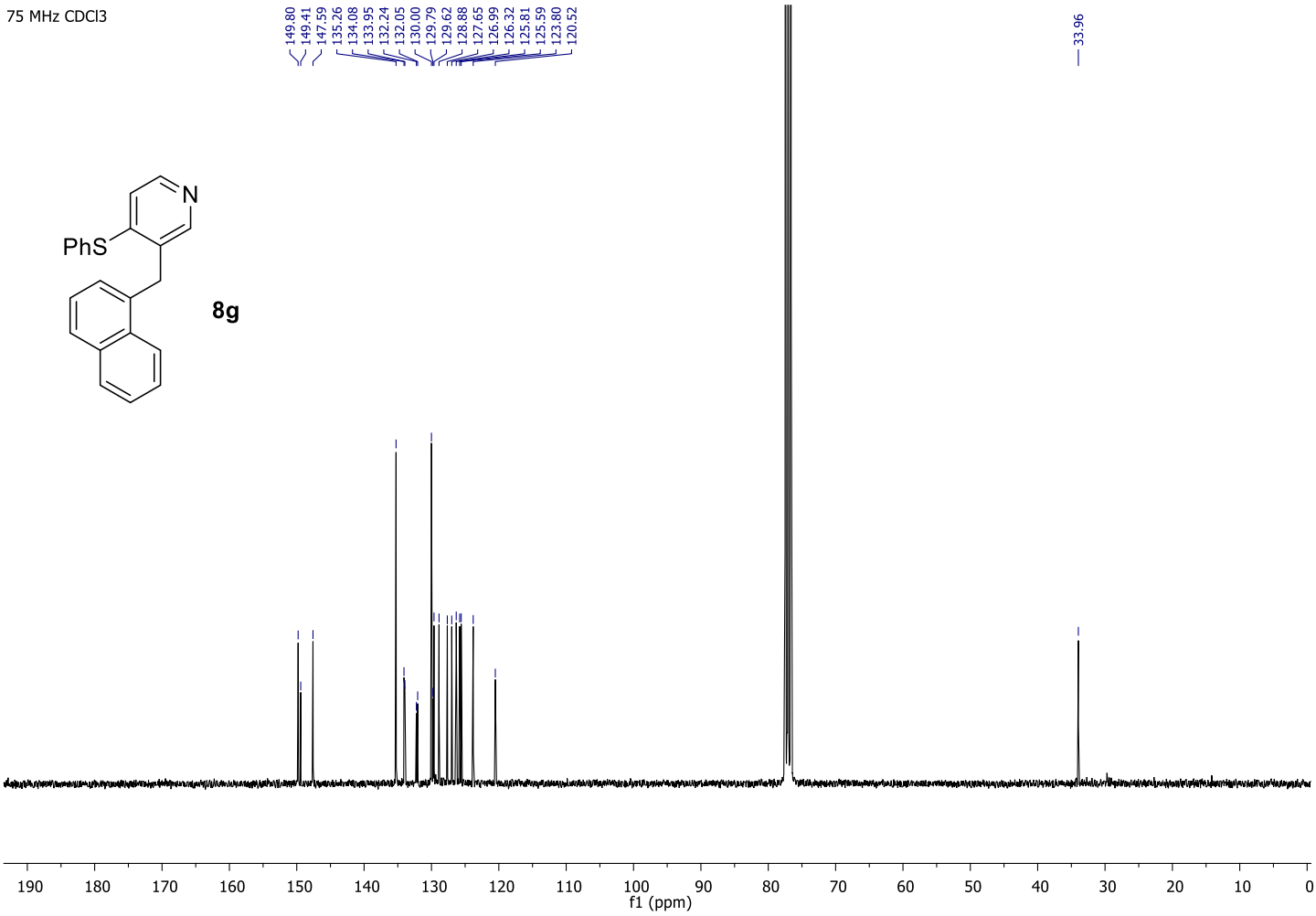
RMN $^{13}C\{^{1}H\}$

300 MHz CDCl3

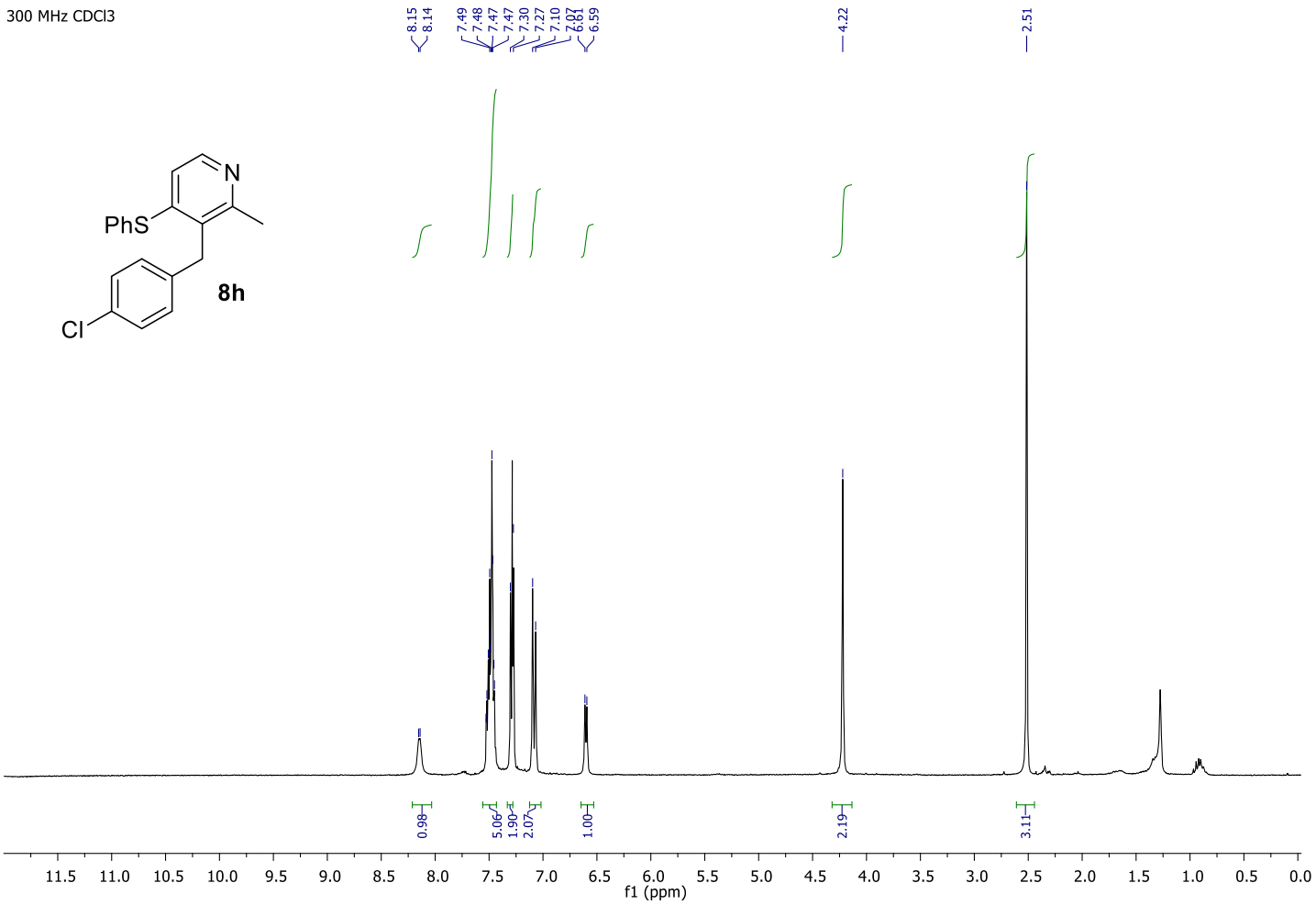


8g

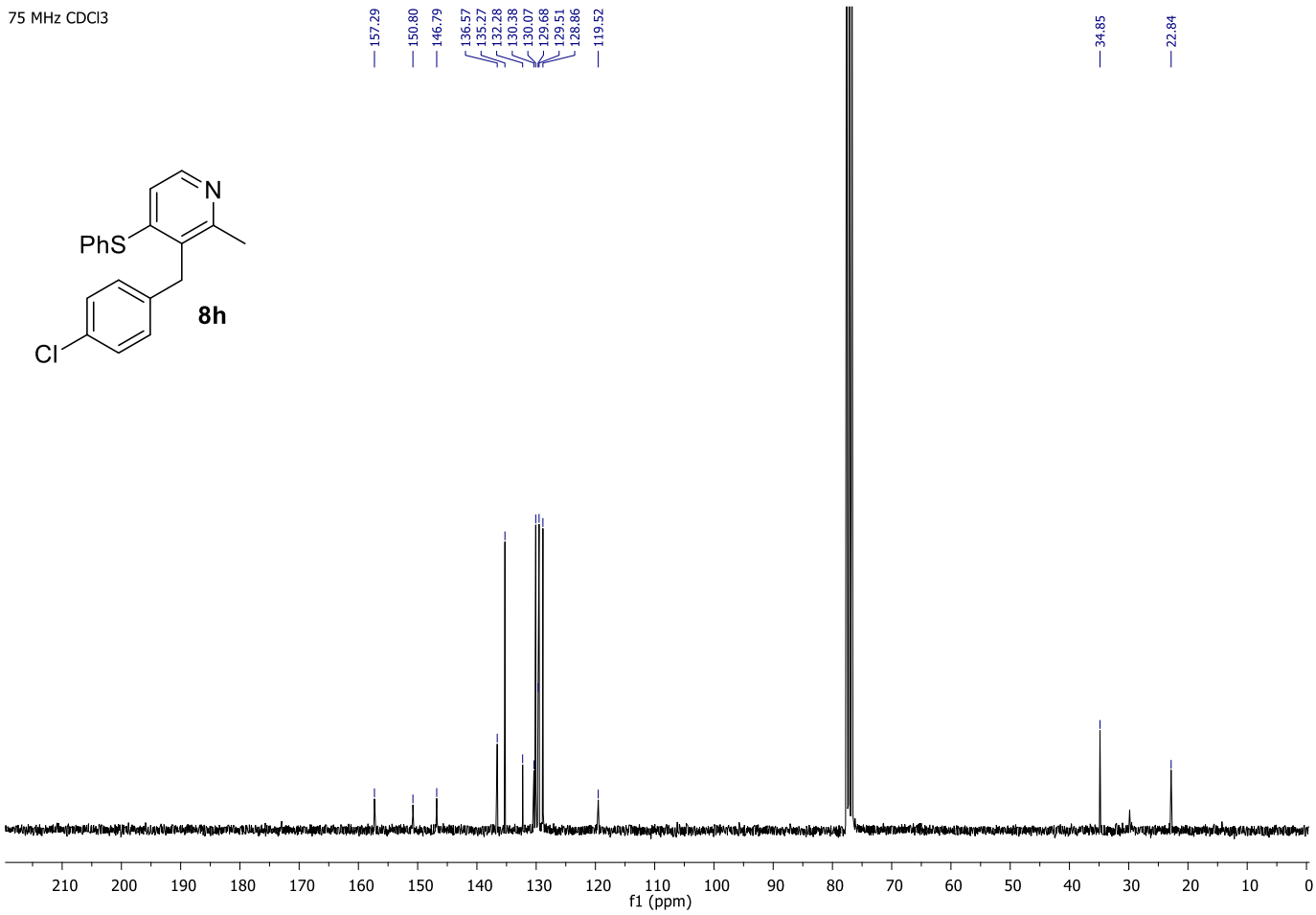
RMN ^{1}H


75 MHz CDCl3
149.80
149.41
147.59
135.26
134.08
133.95
132.24
132.05
130.00
129.79
129.62
128.88
127.65
126.99
126.32
125.81
125.59
123.80
120.52
33.96
N
PhS
8g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

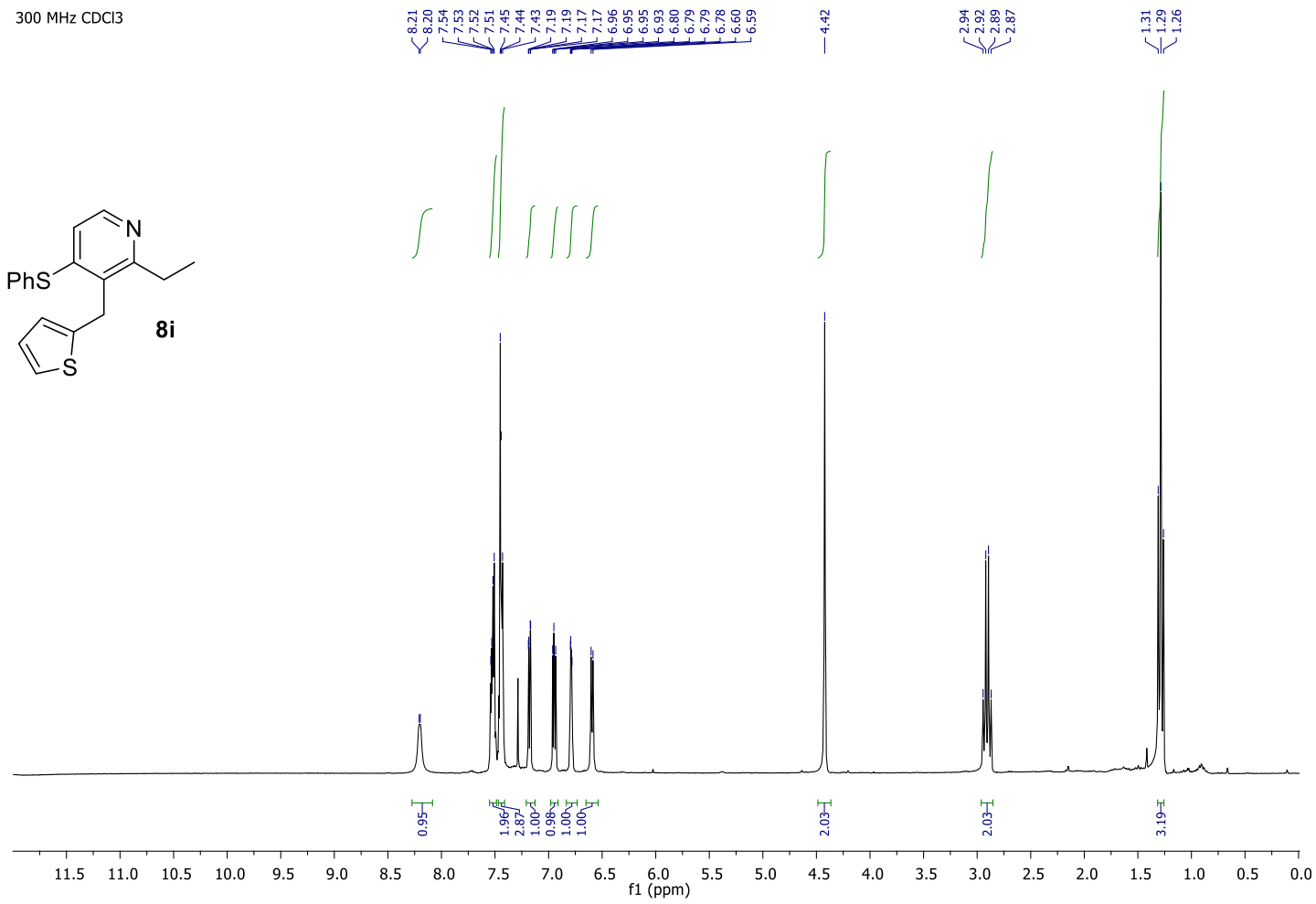
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.15
8.14
7.49
7.48
7.47
7.47
7.30
7.27
7.10
7.07
6.81
6.59
4.22
2.51
N
PhS
Cl
8h
0.98
5.06
1.90
2.07
1.00
2.19
3.11
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

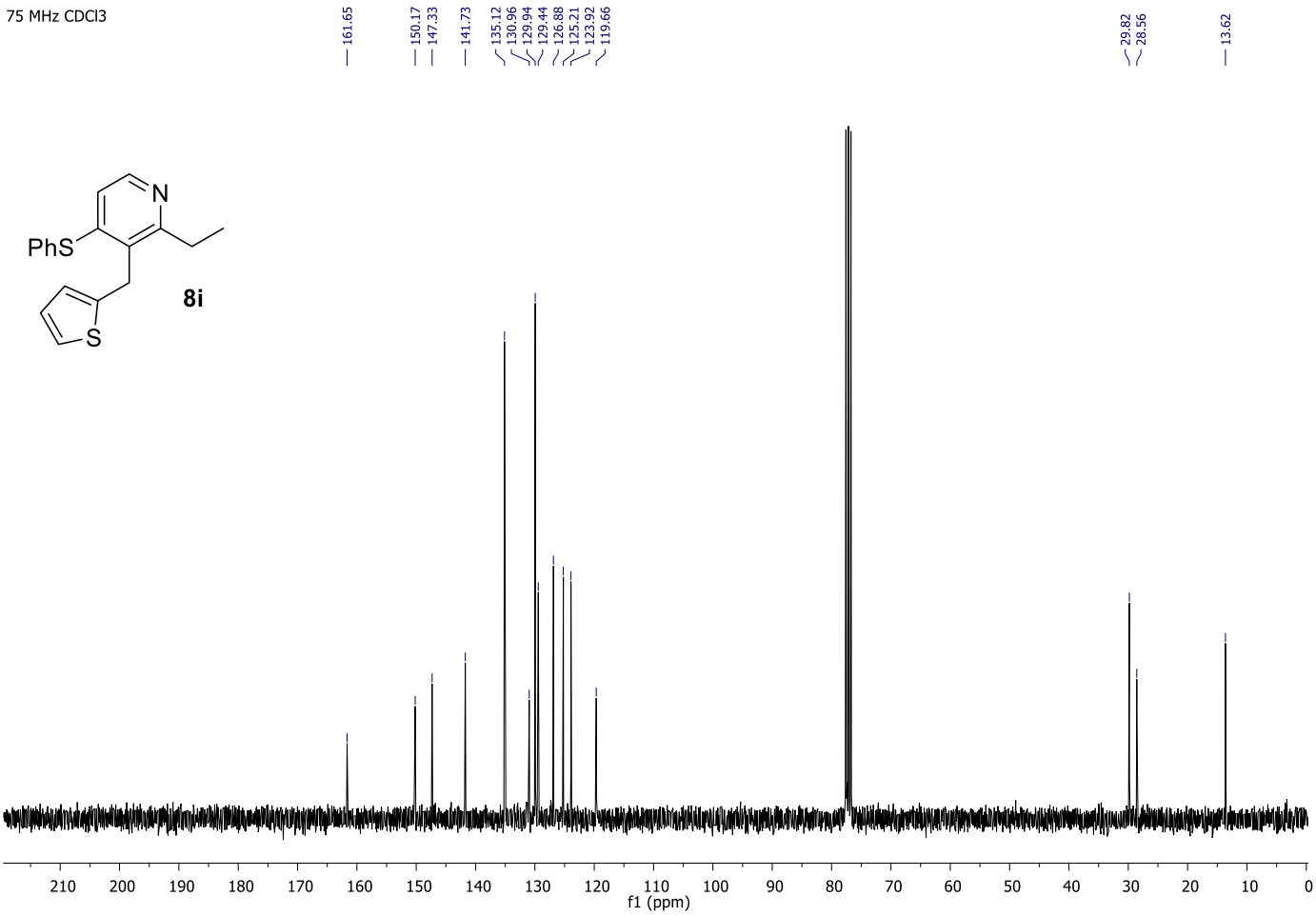
RMN ^{1}H


75 MHz CDCl3
157.29
150.80
146.79
136.57
135.27
132.28
130.38
130.07
129.68
129.51
128.86
119.52
34.85
22.84
N
PhS
Cl
8h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

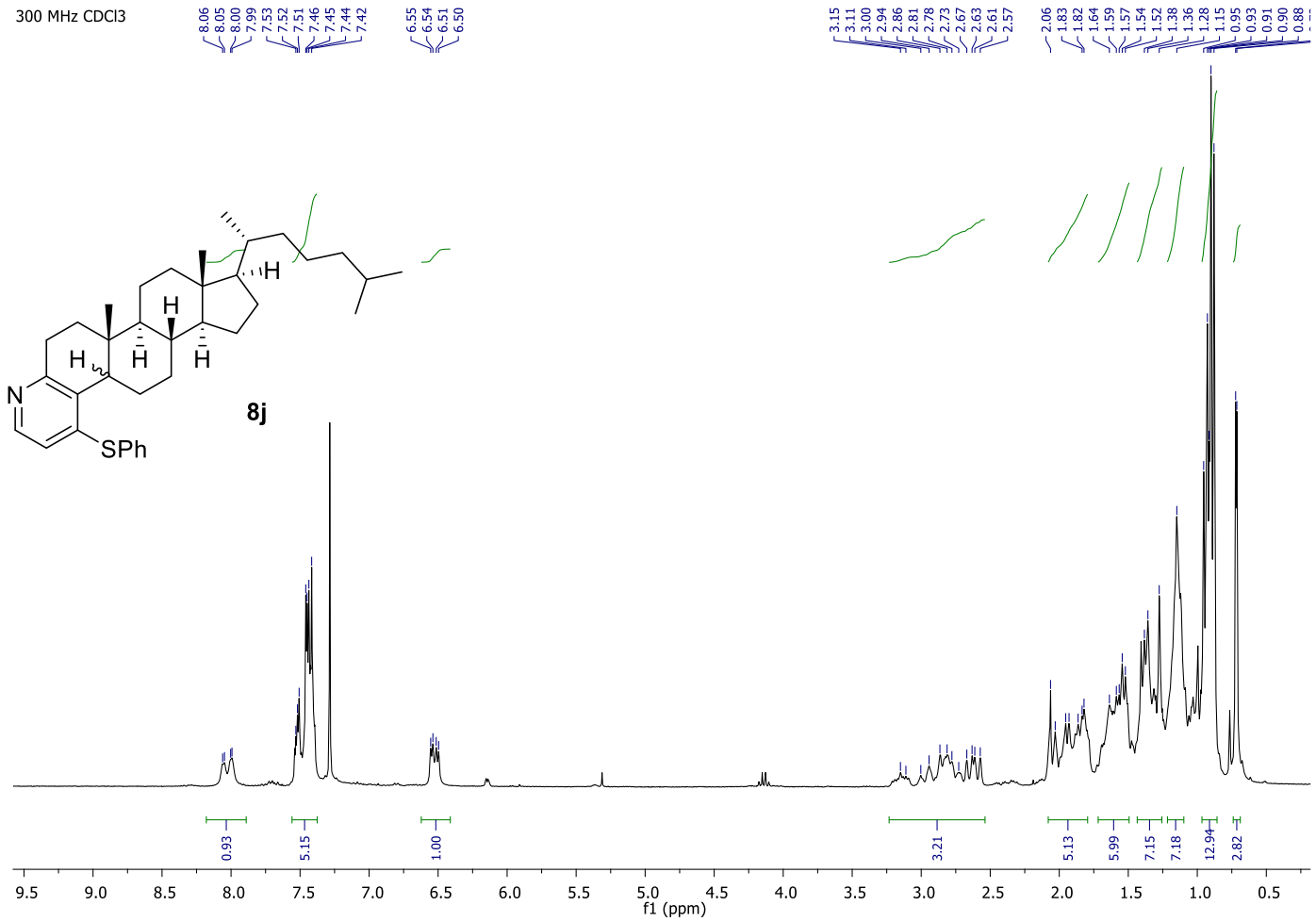
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.21
8.20
7.54
7.53
7.52
7.51
7.45
7.44
7.43
7.19
7.19
7.17
7.17
6.96
6.95
6.95
6.93
6.80
6.79
6.79
6.78
6.60
6.59
4.42
2.94
2.92
2.89
2.87
1.31
1.29
1.26
N
PhS
S
8i
0.95
1.96
2.87
1.00
0.98
1.00
1.00
2.03
2.03
3.19
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

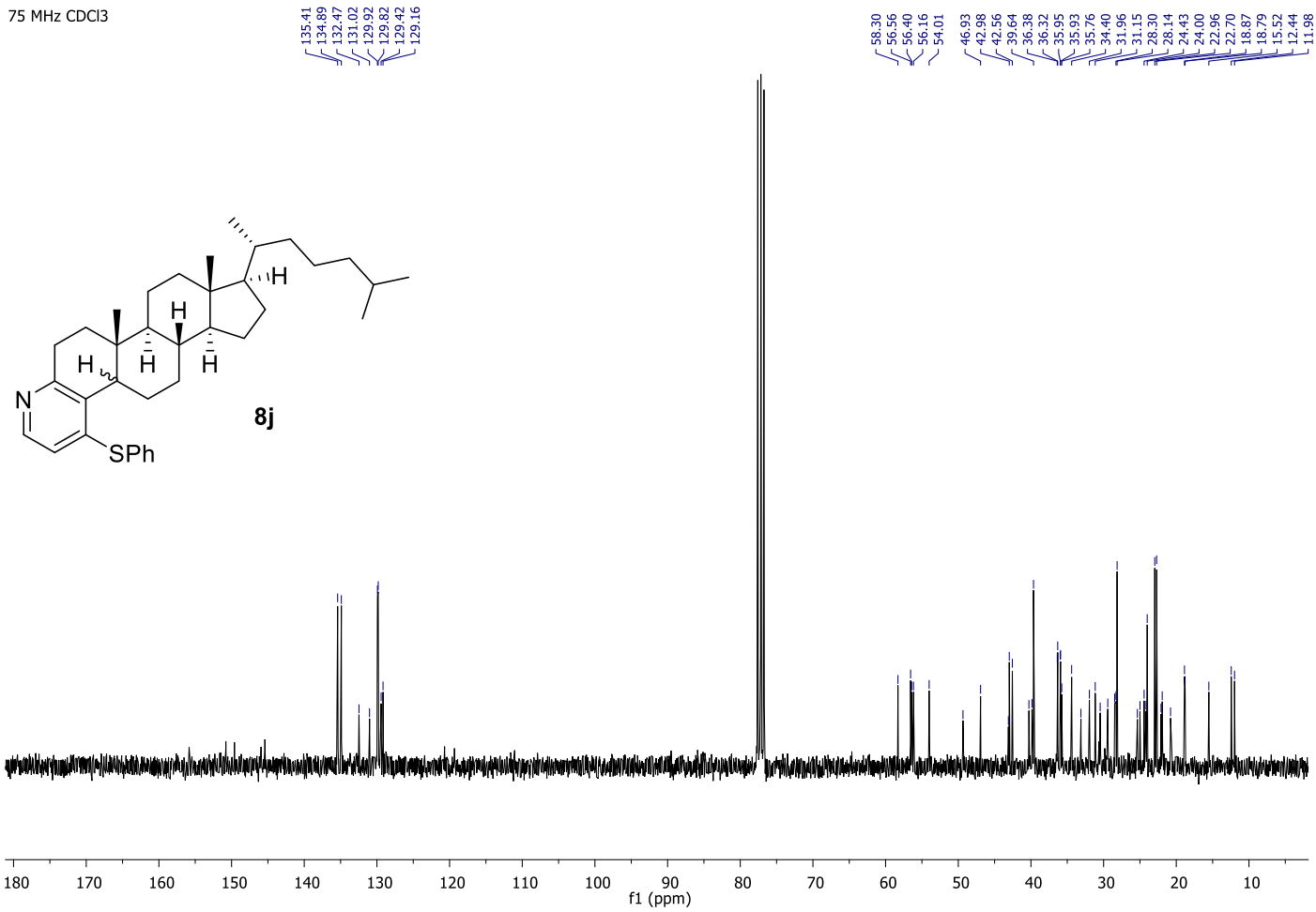
RMN ^{1}H


75 MHz CDCl3
161.65
150.17
147.33
141.73
135.12
130.96
129.94
129.44
126.88
125.21
123.92
119.66
29.82
28.56
13.62
N
PhS
S
8i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

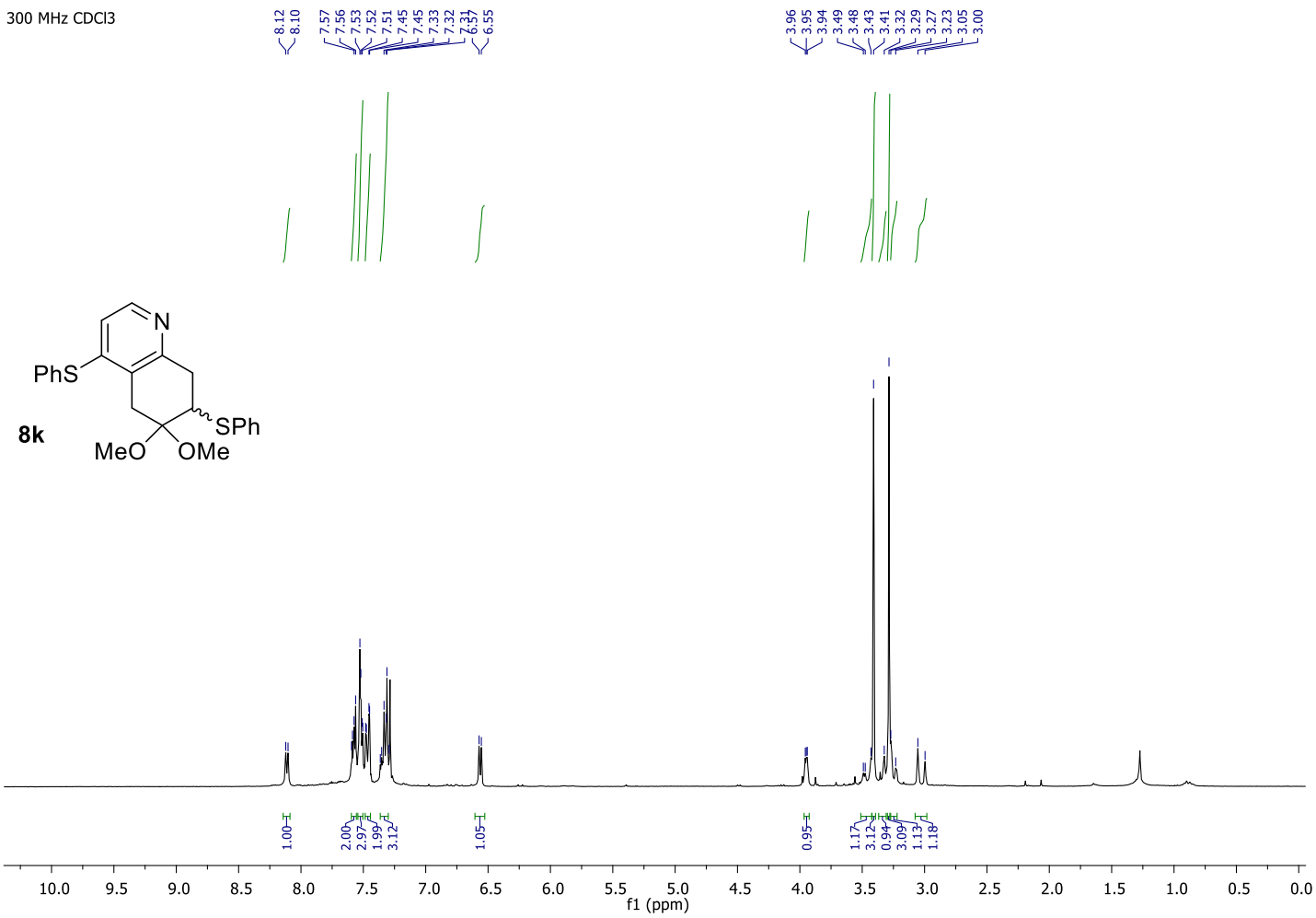
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.06
8.05
8.00
7.99
7.53
7.52
7.51
7.46
7.45
7.44
7.42
6.55
6.54
6.51
6.50
3.15
3.11
3.00
2.94
2.86
2.81
2.78
2.73
2.67
2.63
2.61
2.57
2.06
1.83
1.82
1.64
1.59
1.57
1.54
1.52
1.38
1.36
1.28
1.15
0.95
0.93
0.91
0.90
0.88
H
H
H
H
H
N
SPh
8j
0.93
5.15
1.00
3.21
5.13
5.99
7.15
7.18
12.94
2.82
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

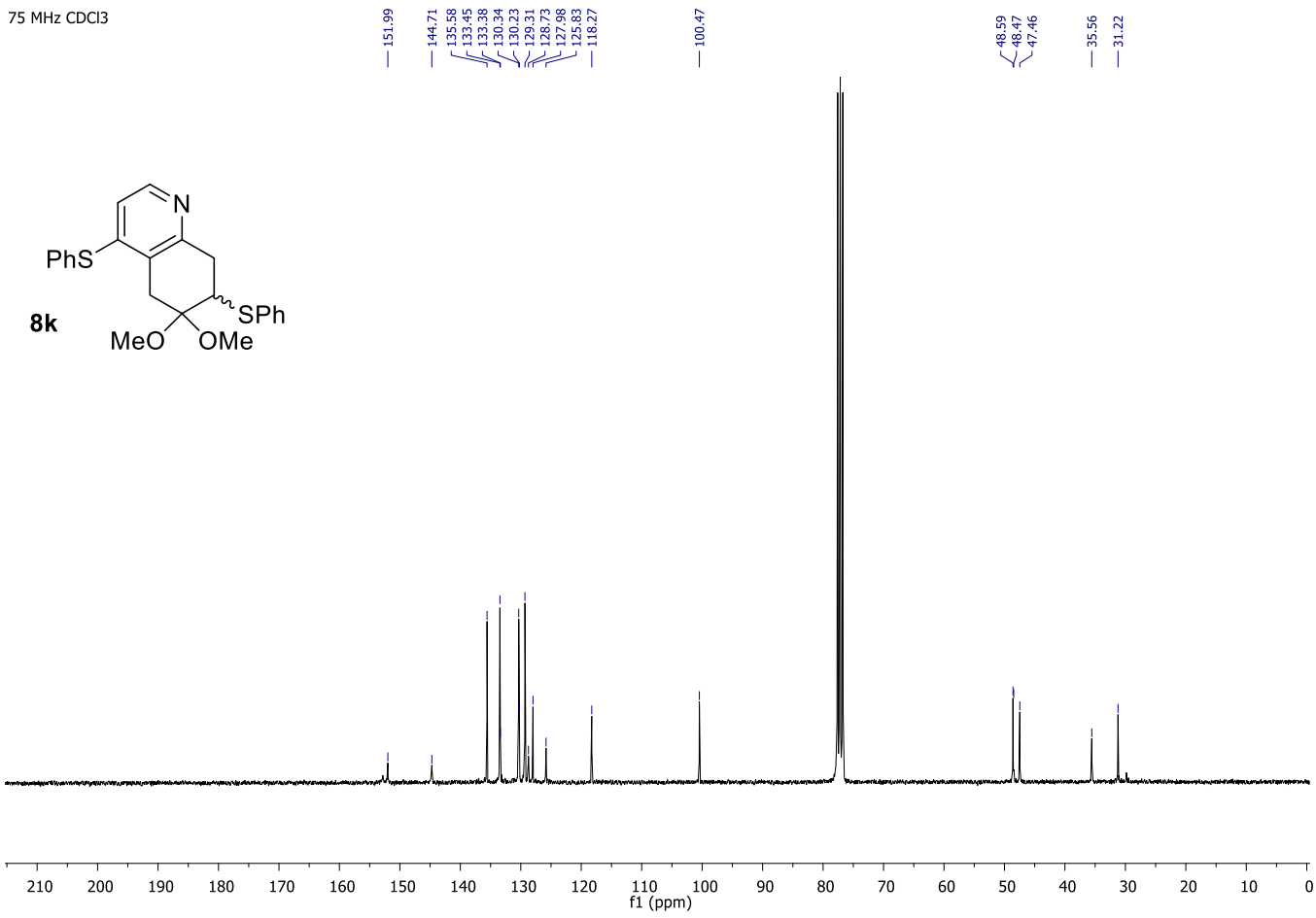
RMN ^{1}H


75 MHz CDCl3
135.41
134.89
132.47
131.02
129.92
129.82
129.42
129.16
58.30
56.56
56.40
56.16
54.01
46.93
42.98
42.56
39.64
36.38
36.32
35.95
35.93
35.76
34.40
31.96
31.15
28.30
28.14
24.43
24.00
22.96
22.70
18.87
18.79
15.52
12.44
11.98
H
H
H
H
H
N
SPh
8j
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

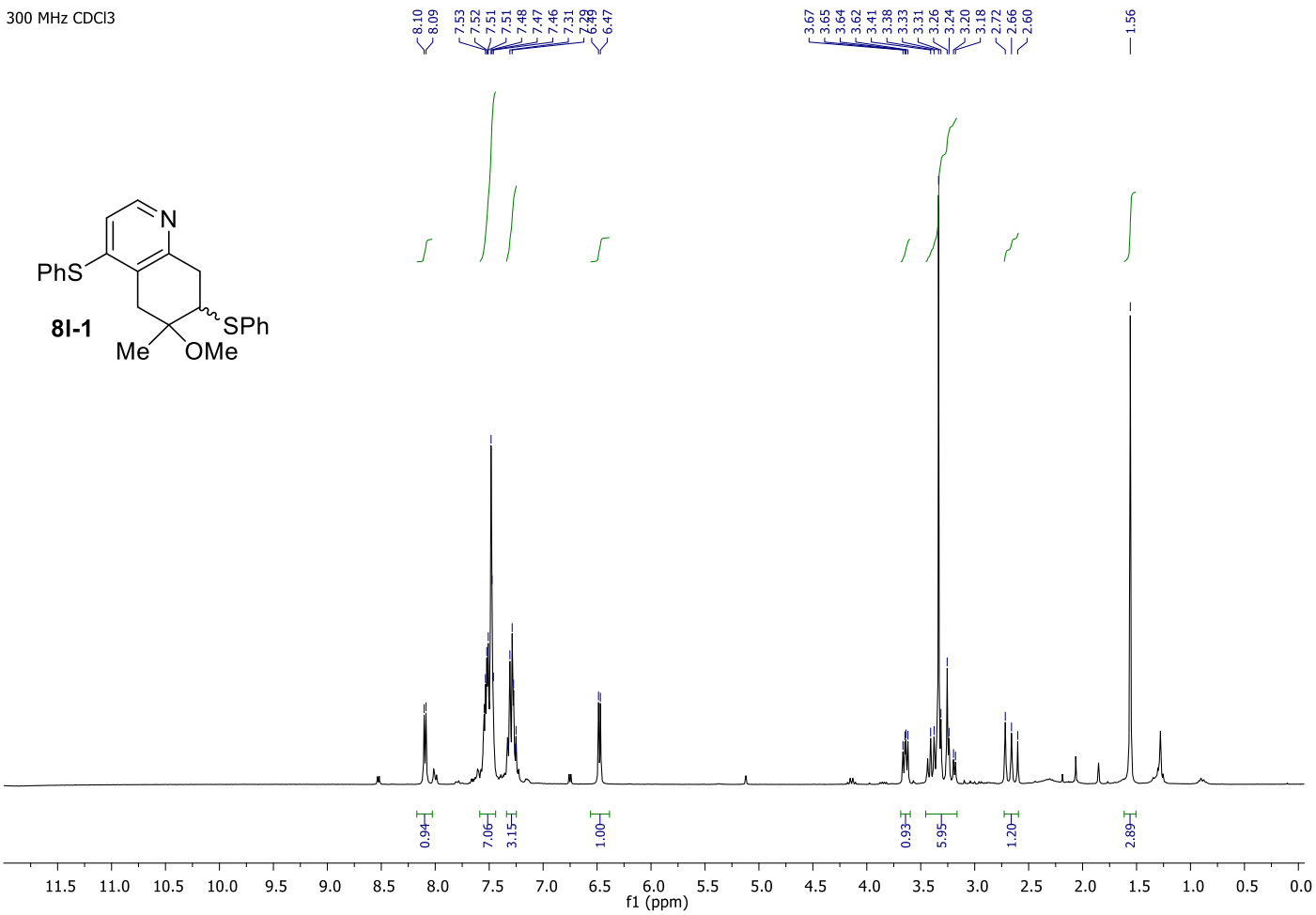
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.12
8.10
7.57
7.56
7.53
7.52
7.51
7.45
7.33
7.32
7.31
6.55
3.96
3.95
3.94
3.49
3.48
3.43
3.41
3.32
3.29
3.27
3.23
3.05
3.00
N
PhS
SPh
MeO
OMe
8k
1.00
2.00
2.97
1.99
3.12
1.05
0.95
1.17
3.12
0.94
3.09
1.13
1.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

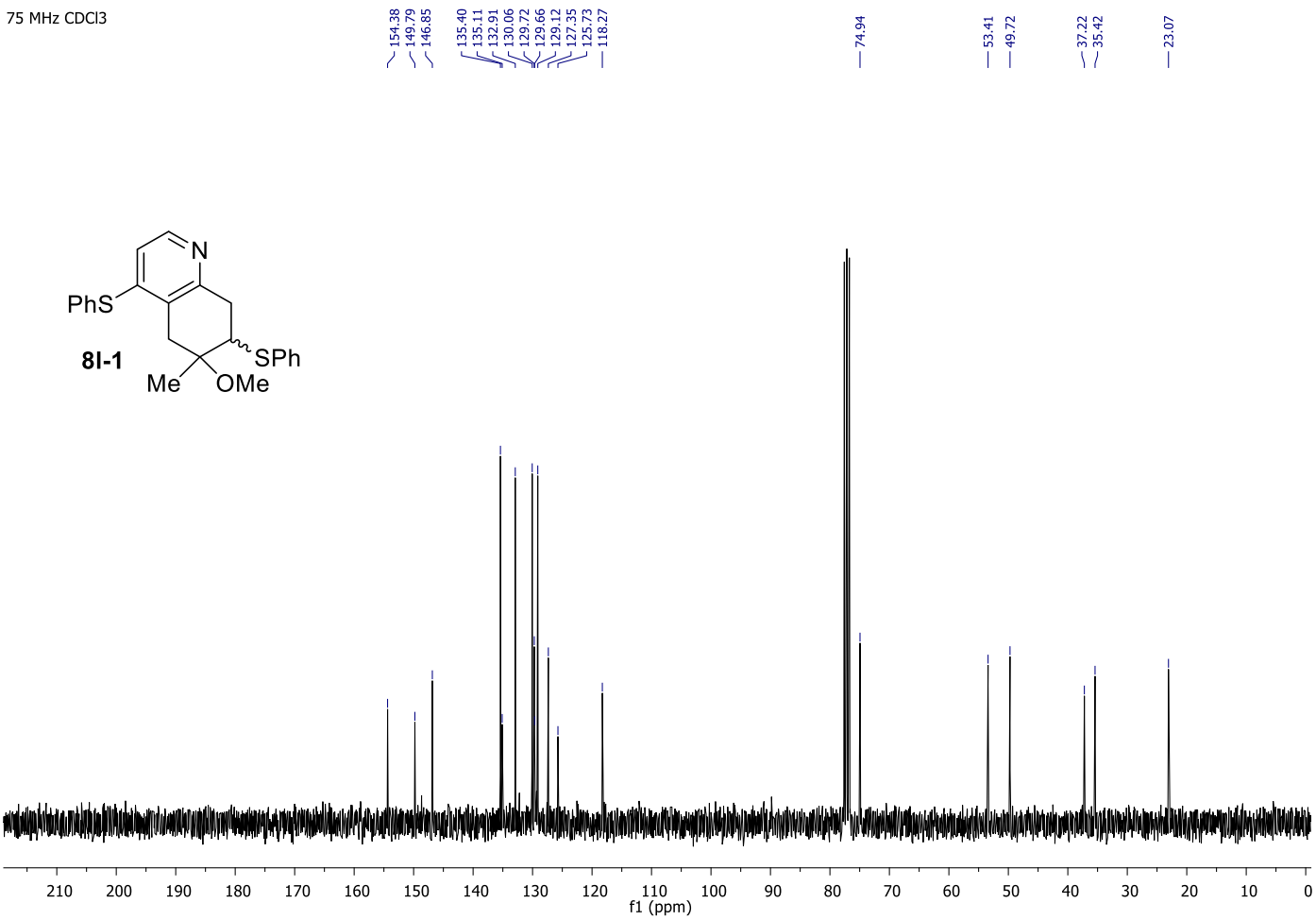
RMN ^{1}H


75 MHz CDCl3
151.99
144.71
135.58
133.45
133.38
130.34
130.23
129.31
128.73
127.98
125.83
118.27
100.47
48.59
48.47
47.46
35.56
31.22
N
PhS
SPh
MeO
OMe
8k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

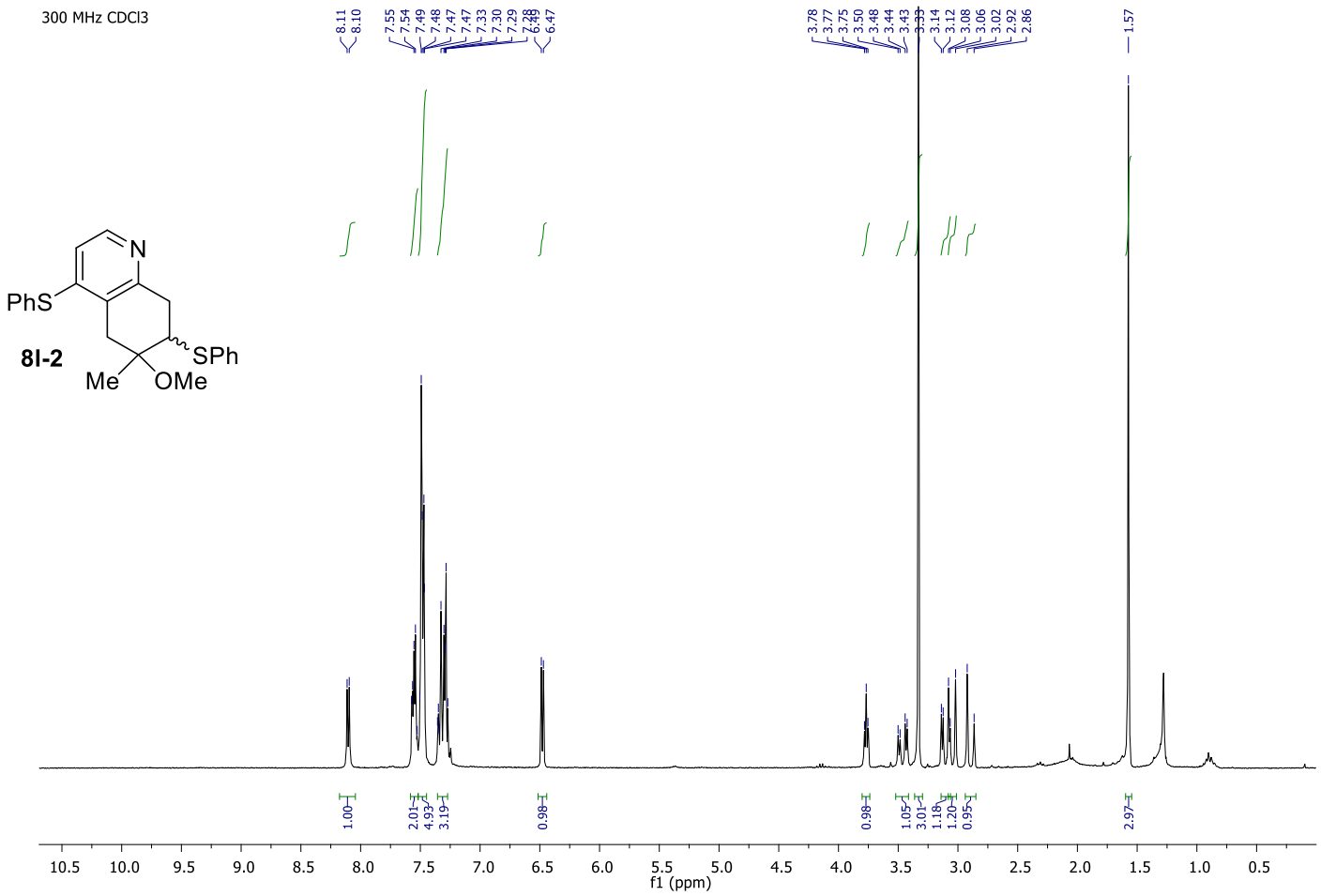
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.10
8.09
7.53
7.52
7.51
7.51
7.48
7.47
7.46
7.31
6.49
6.47
3.67
3.65
3.64
3.62
3.41
3.38
3.33
3.31
3.26
3.24
3.20
3.18
2.72
2.66
2.60
1.56
N
PhS
SPh
Me
OMe
8I-1
0.94
7.06
3.15
1.00
0.93
5.95
1.20
2.89
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H

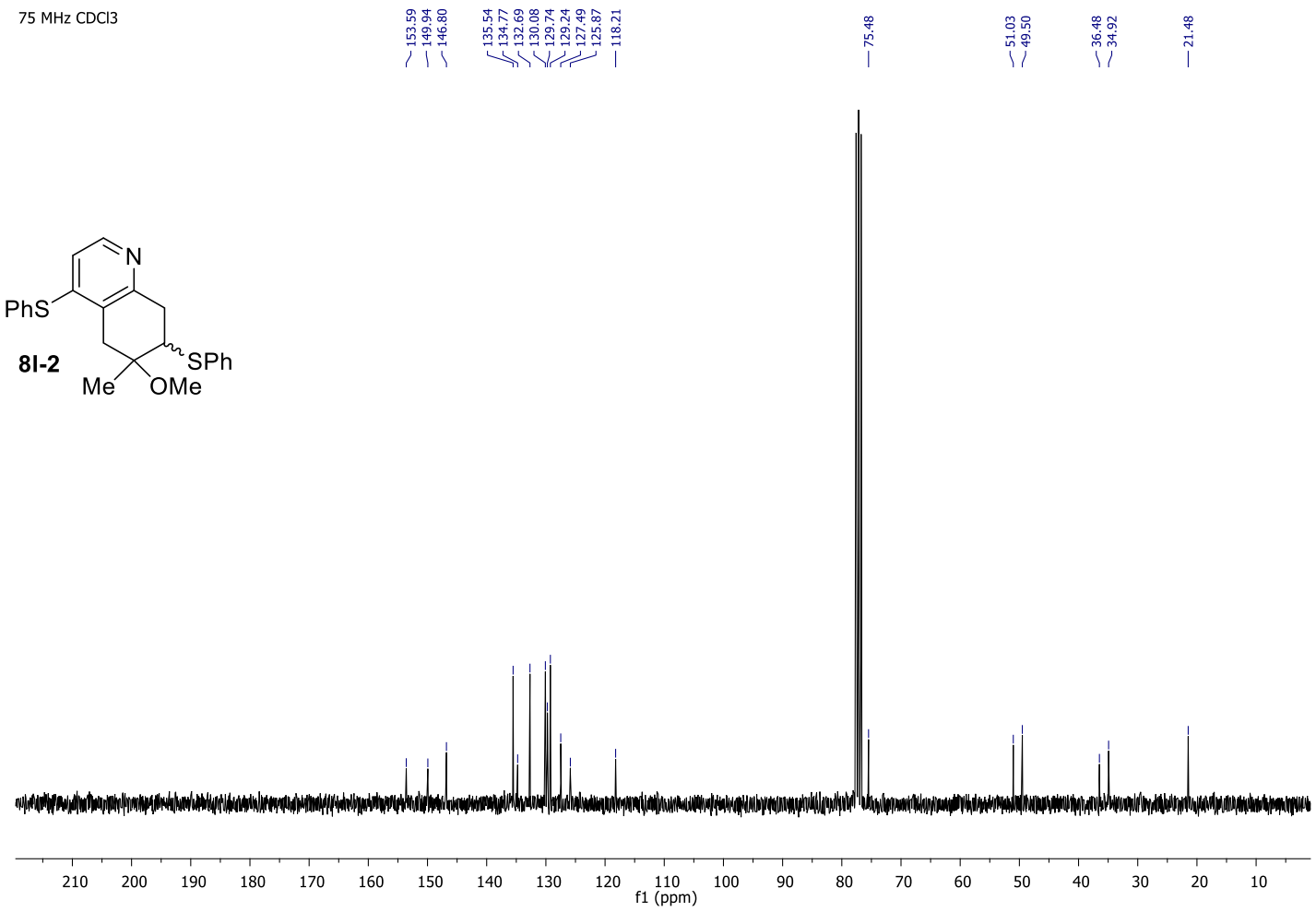

75 MHz CDCl3
154.38
149.79
146.85
135.40
135.11
132.91
130.06
129.72
129.66
129.12
127.35
125.73
118.27
74.94
53.41
49.72
37.22
35.42
23.07
N
PhS
SPh
Me
OMe
8I-1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

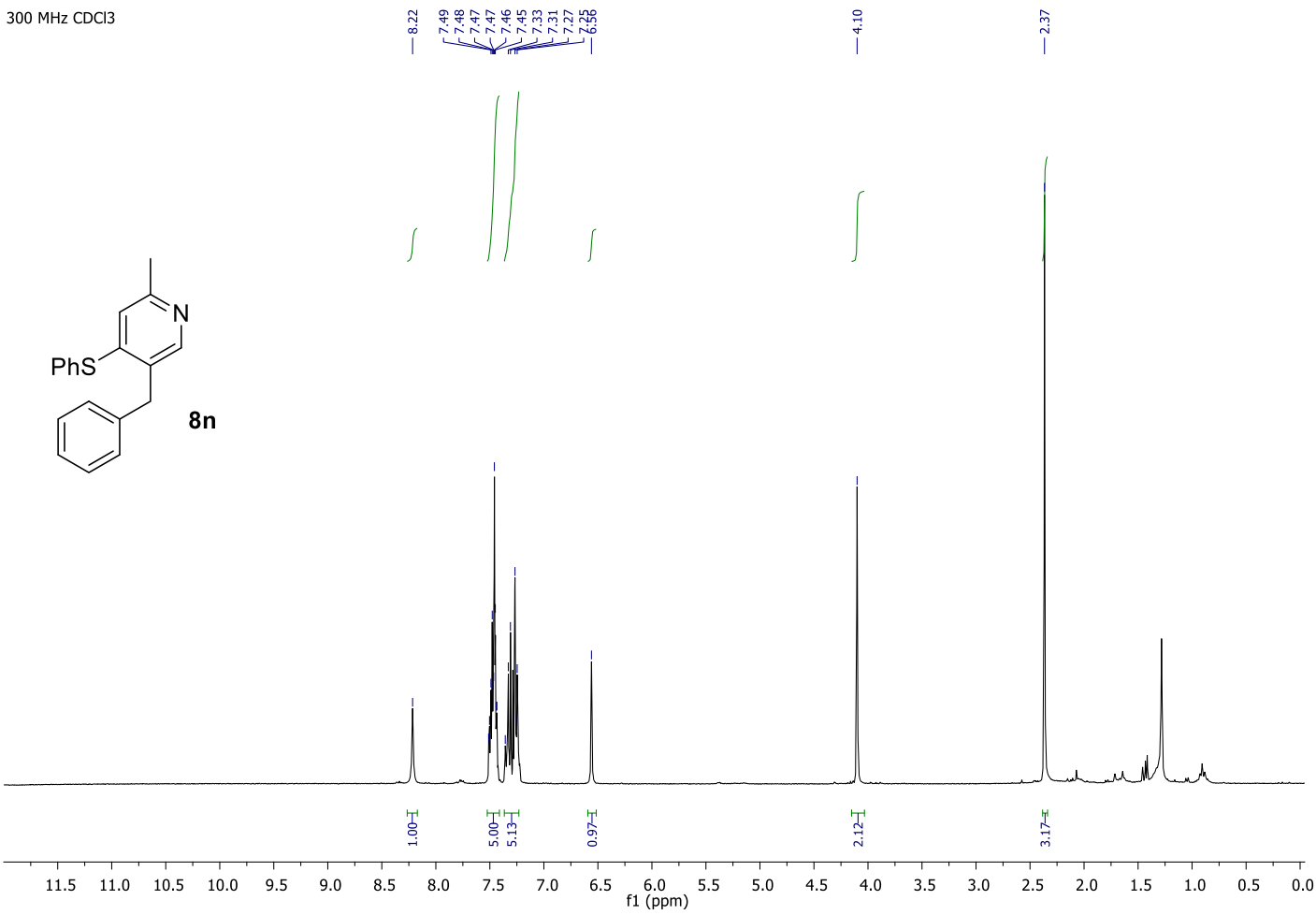

300 MHz CDCl3
8.11
8.10
7.55
7.54
7.49
7.48
7.47
7.47
7.33
7.30
7.29
6.48
6.47
3.78
3.77
3.75
3.50
3.48
3.44
3.43
3.33
3.14
3.12
3.08
3.06
3.02
2.92
2.86
1.57
N
PhS
SPh
Me
OMe
1.00
2.01
4.93
3.19
0.98
0.98
1.05
3.01
1.18
1.20
0.95
2.97
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

8l-2

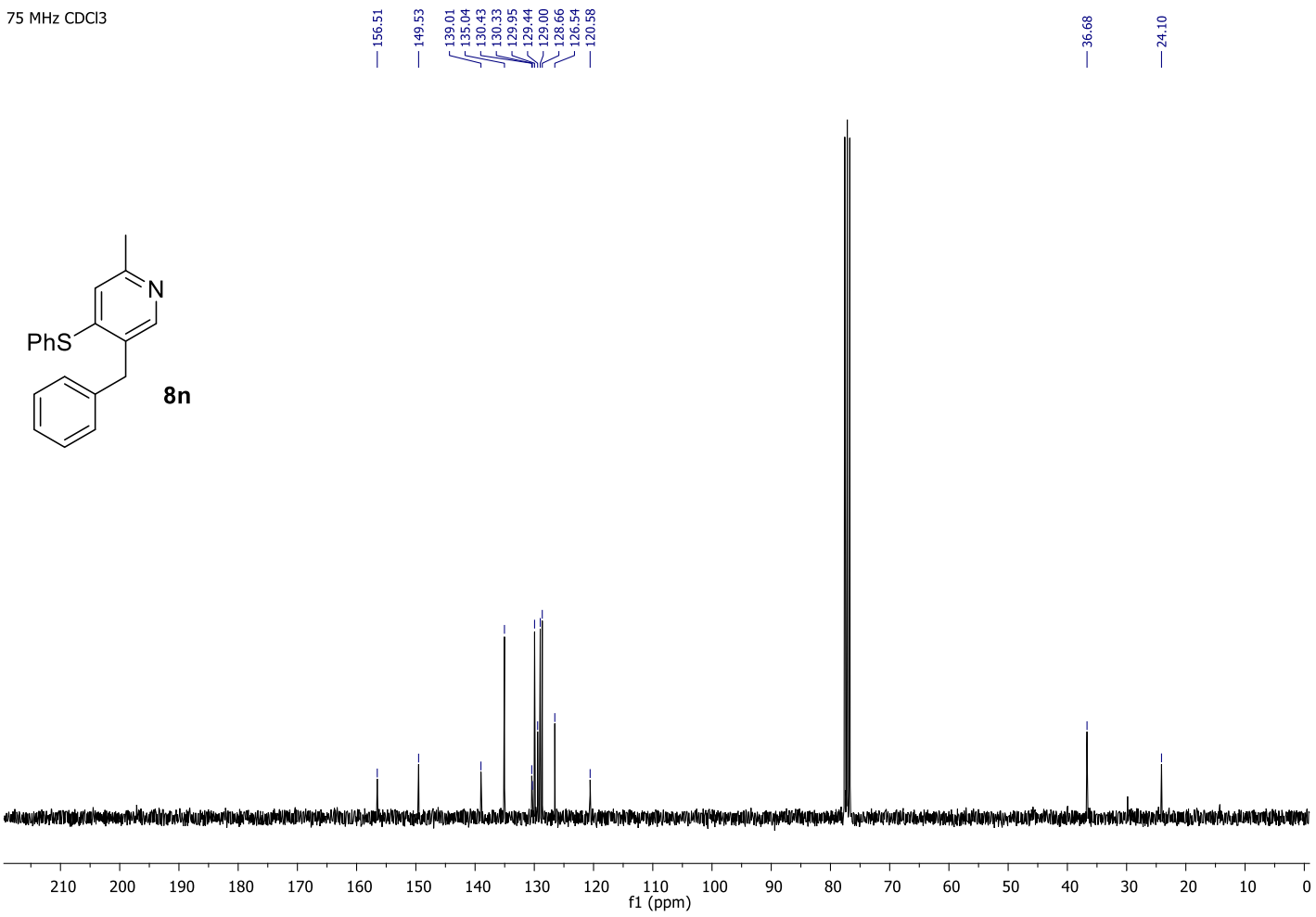
RMN ^{1}H


75 MHz CDCl3
153.59
149.94
146.80
135.54
134.77
132.69
130.08
129.74
129.24
127.49
125.87
118.21
75.48
51.03
49.50
36.48
34.92
21.48
N
PhS
SPh
Me
OMe
8I-2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

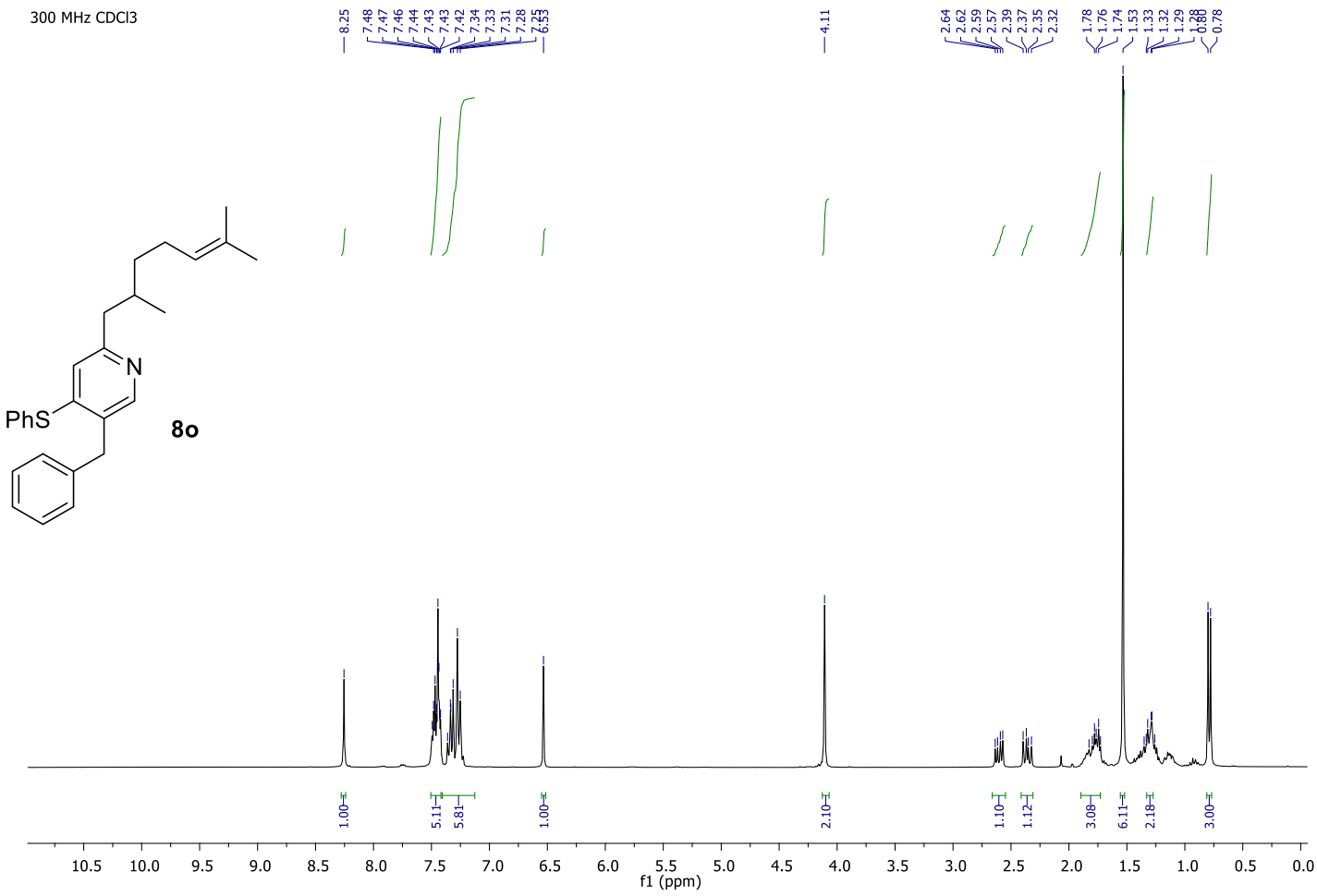
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.22
7.49
7.48
7.47
7.47
7.46
7.45
7.33
7.31
7.27
7.25
6.56
4.10
2.37
N
PhS
8n
1.00
5.00
5.13
0.97
2.12
3.17
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

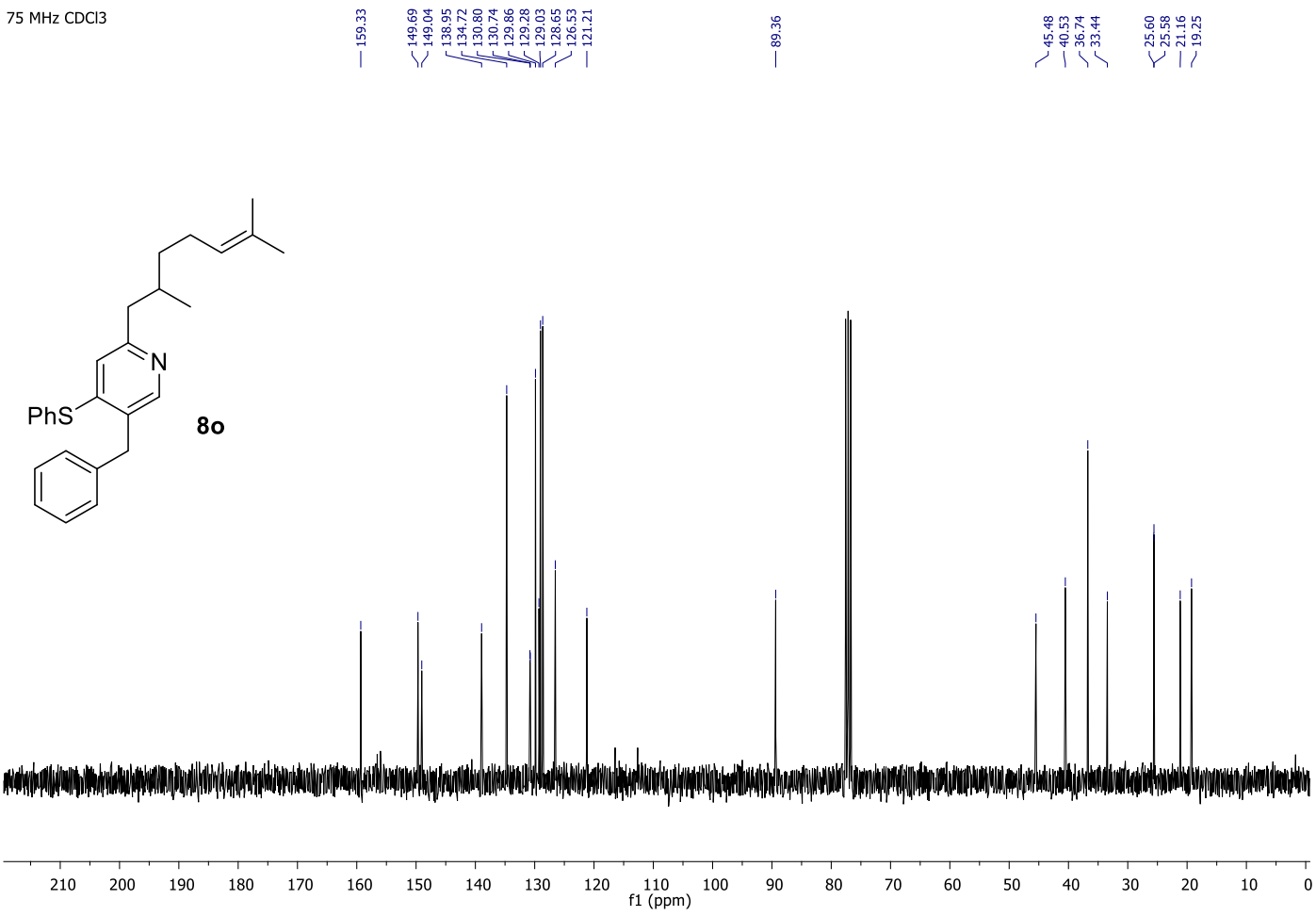
RMN ^{1}H


75 MHz CDCl3
156.51
149.53
139.01
135.04
130.43
130.33
129.95
129.44
129.00
128.66
126.54
120.58
36.68
24.10
PhS
N
8n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

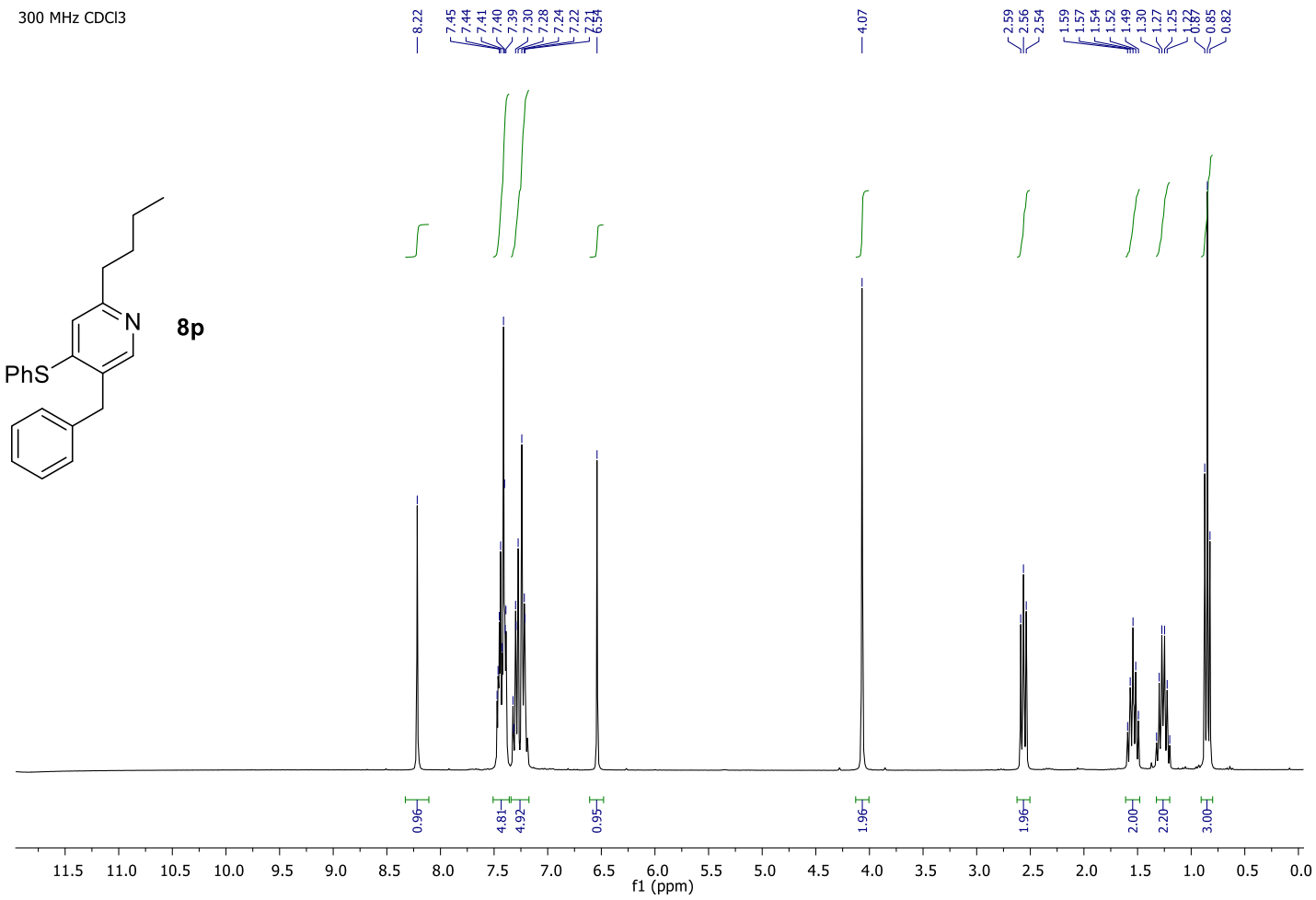
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.25
7.48
7.47
7.46
7.44
7.43
7.43
7.42
7.34
7.33
7.31
7.28
7.25
6.53
4.11
2.64
2.62
2.59
2.57
2.39
2.37
2.35
2.32
1.78
1.76
1.74
1.53
1.33
1.32
1.29
0.88
0.88
0.78
N
PhS
8o
1.00
5.11
5.81
1.00
2.10
1.10
1.12
3.08
6.11
2.18
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

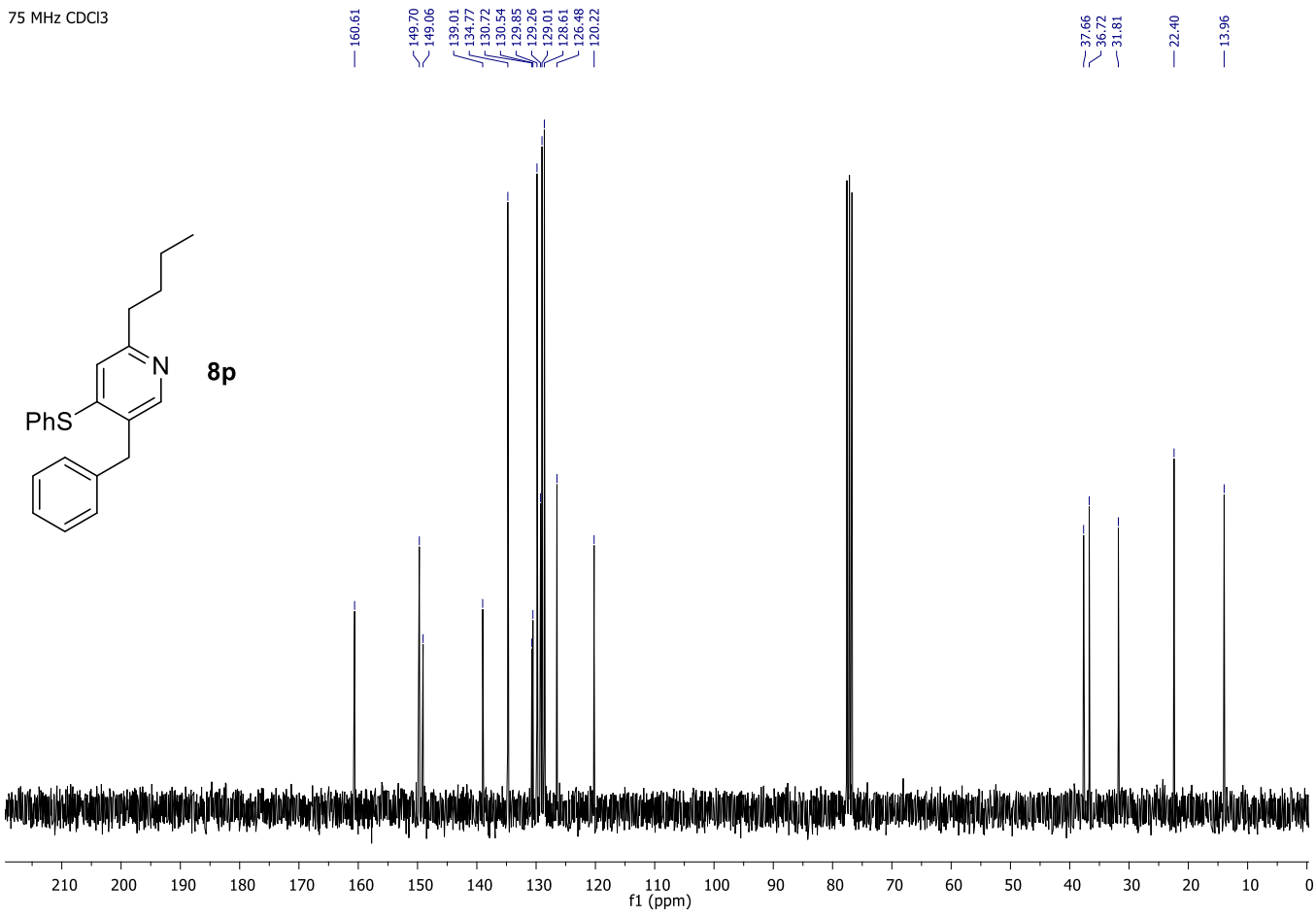
RMN ^{1}H


75 MHz CDCl3
159.33
149.69
149.04
138.95
134.72
130.80
130.74
129.86
129.28
129.03
128.65
126.53
121.21
89.36
45.48
40.53
36.74
33.44
25.60
25.58
21.16
19.25
N
PhS
8o
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

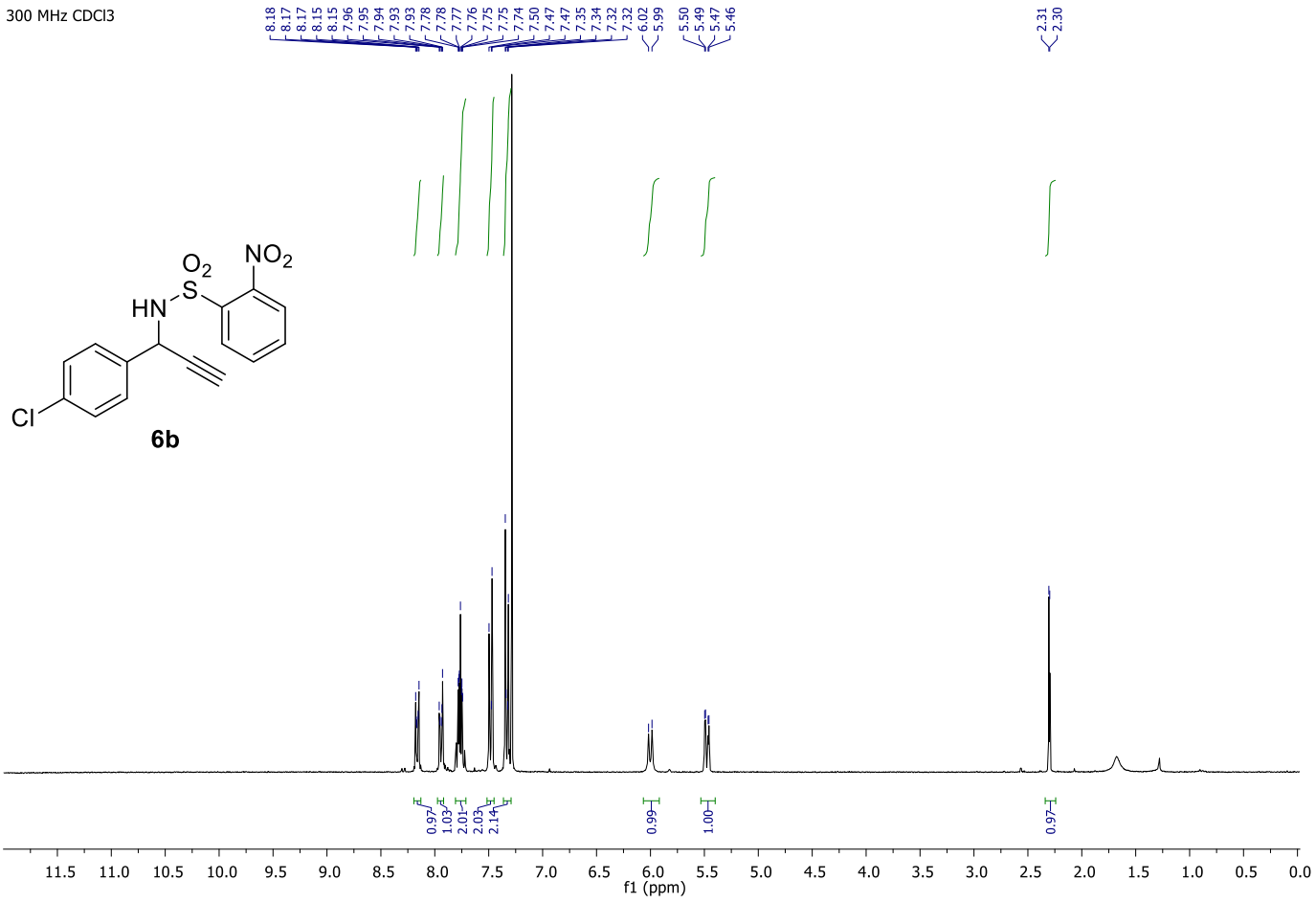
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.22
7.45
7.44
7.41
7.40
7.39
7.30
7.28
7.24
7.22
7.21
6.54
4.07
2.59
2.56
2.54
1.59
1.57
1.54
1.52
1.49
1.30
1.27
1.25
0.87
0.85
0.82
N
PhS
8p
0.96
4.81
4.92
0.95
1.96
1.96
2.00
2.20
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

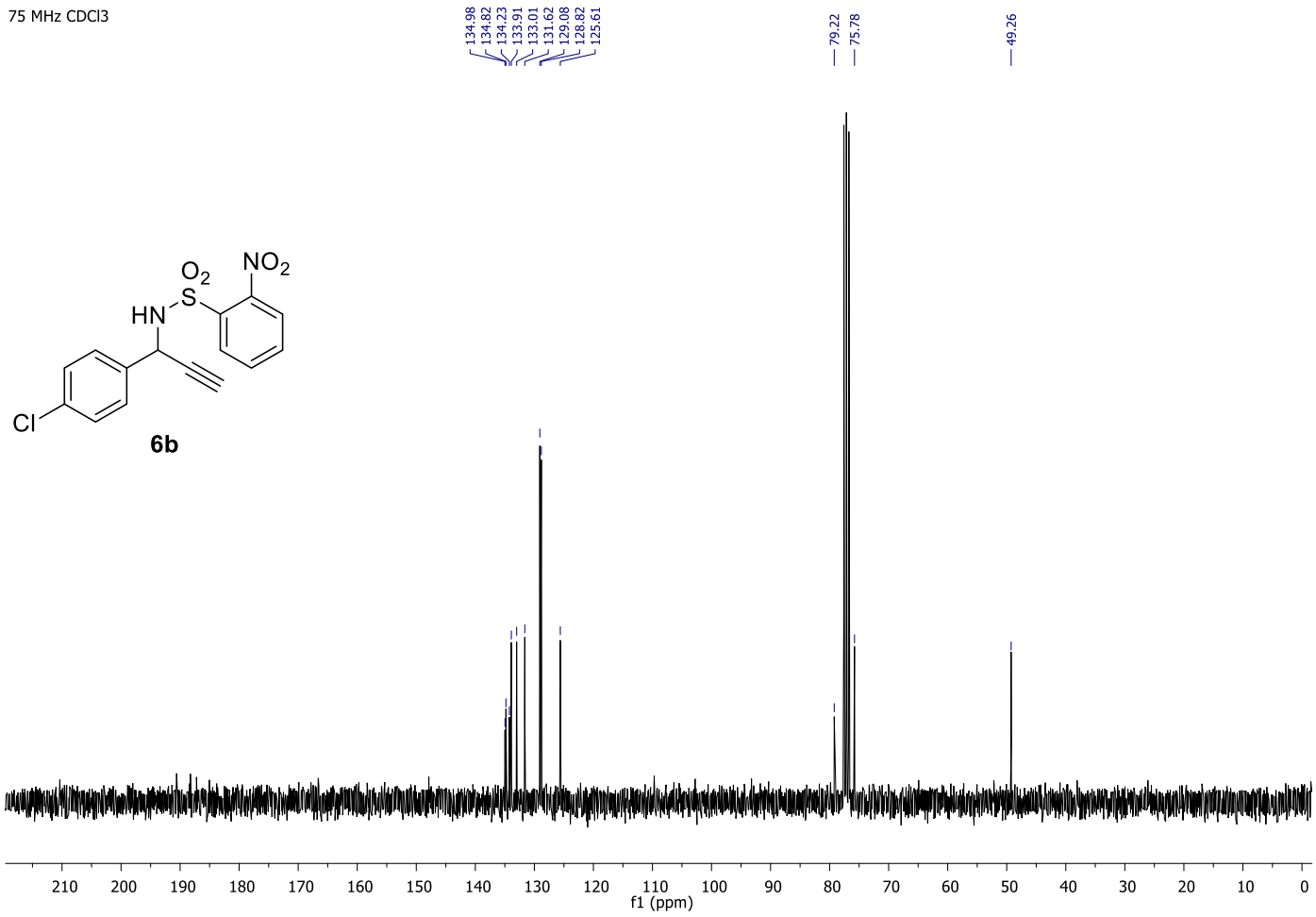
RMN ^{1}H


75 MHz CDCl3
160.61
149.70
149.06
139.01
134.77
130.72
130.54
129.85
129.26
129.01
128.61
126.48
120.22
37.66
36.72
31.81
22.40
13.96
N
PhS
8p
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

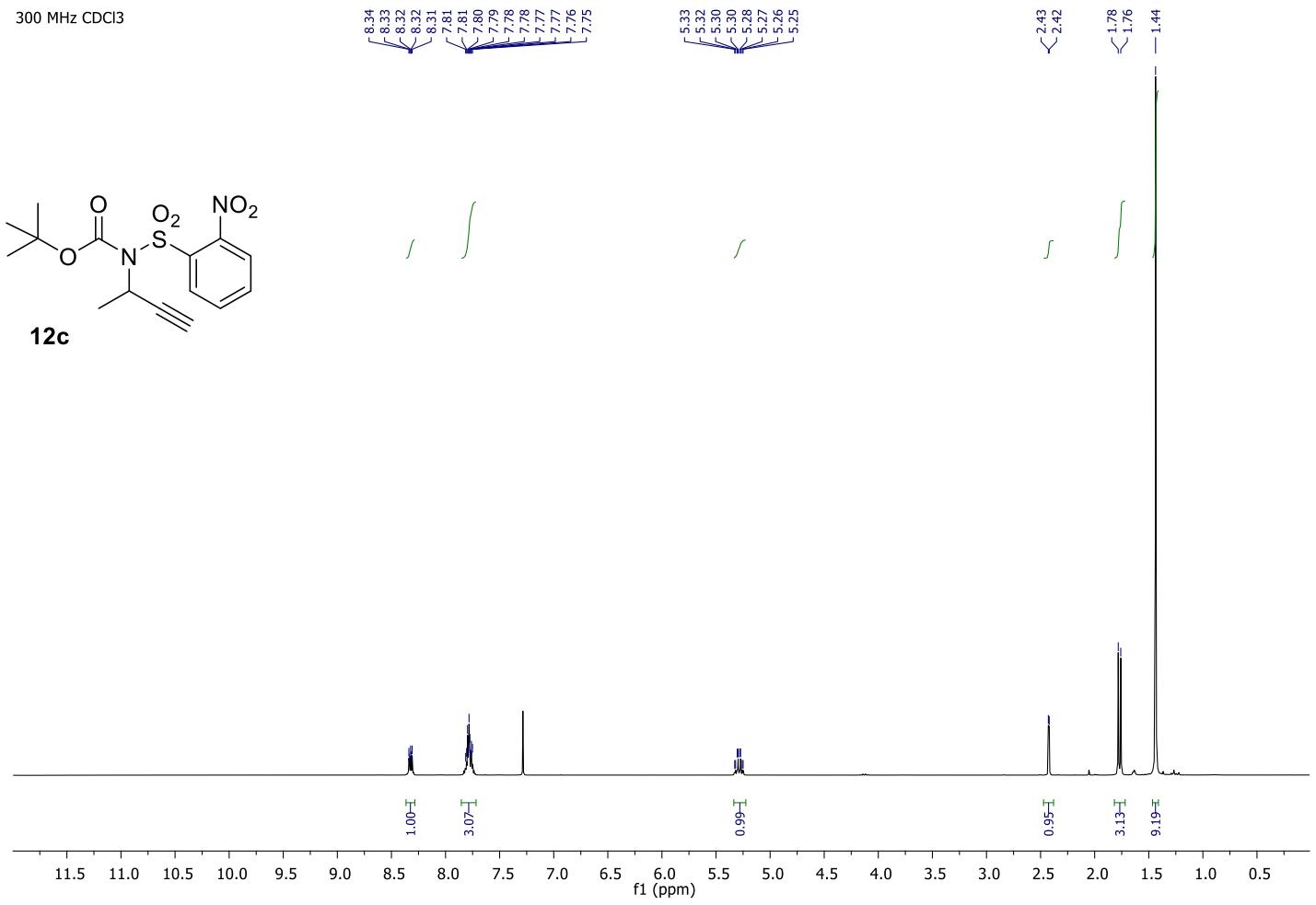
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.18
8.17
8.17
8.15
8.15
7.96
7.95
7.94
7.93
7.93
7.78
7.78
7.77
7.76
7.75
7.75
7.74
7.50
7.47
7.47
7.35
7.34
7.32
7.32
6.02
5.99
5.50
5.49
5.47
5.46
2.31
2.30
O2
NO2
S
HN
Cl
6b
0.97
1.03
2.01
2.03
2.14
0.99
1.00
0.97
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

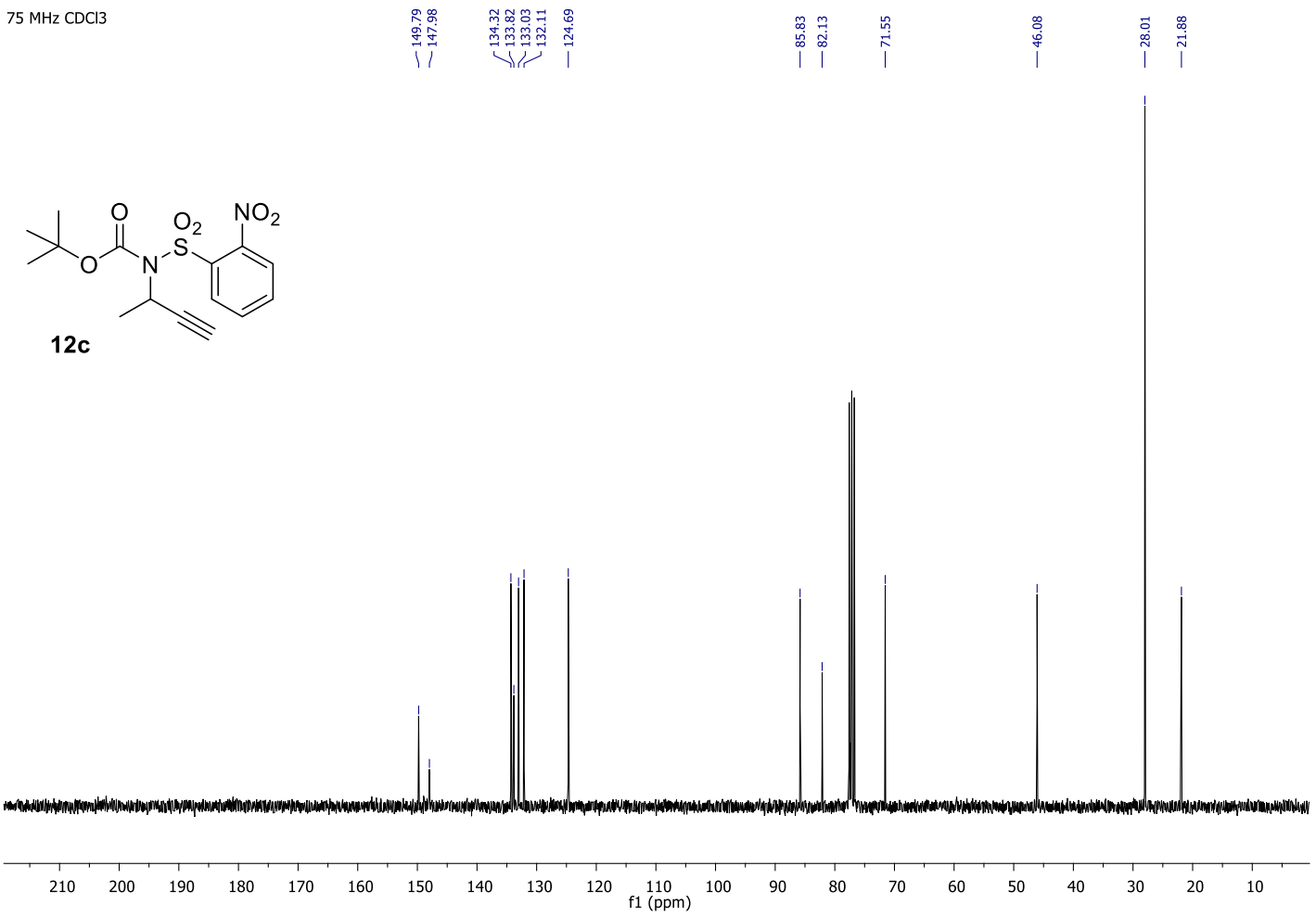
RMN ^{1}H


75 MHz CDCl3
134.98
134.82
134.23
133.91
133.01
131.62
129.08
128.82
125.61
79.22
75.78
49.26
O2
NO2
S
HN
Cl
6b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

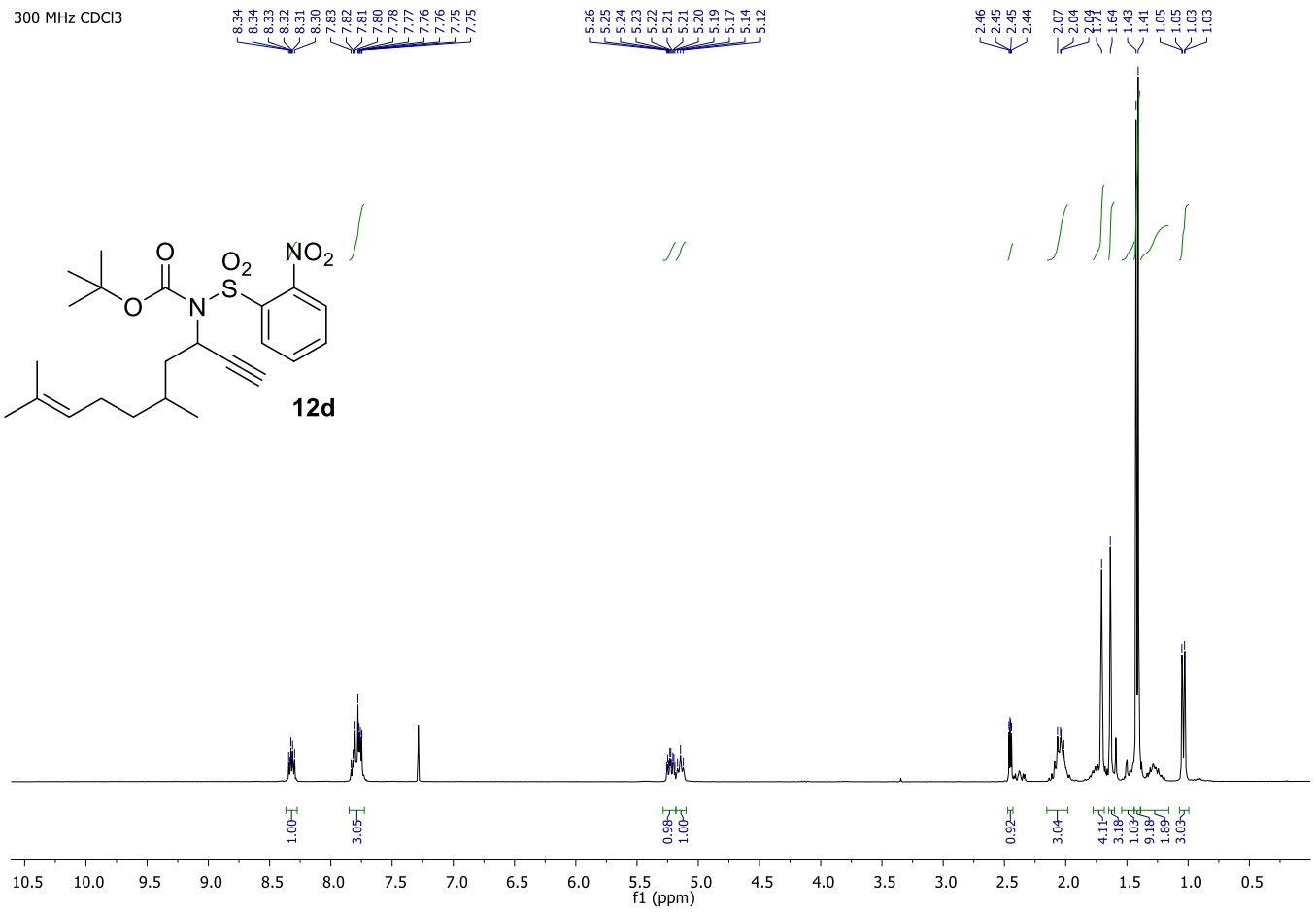
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.34
8.33
8.32
8.32
8.31
7.81
7.81
7.80
7.79
7.78
7.78
7.77
7.77
7.76
7.75
5.33
5.32
5.30
5.30
5.28
5.27
5.26
5.25
2.43
2.42
1.78
1.76
1.44
O
O
N
S
O2
NO2
12c
1.00
3.07
0.99
0.95
3.13
9.19
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

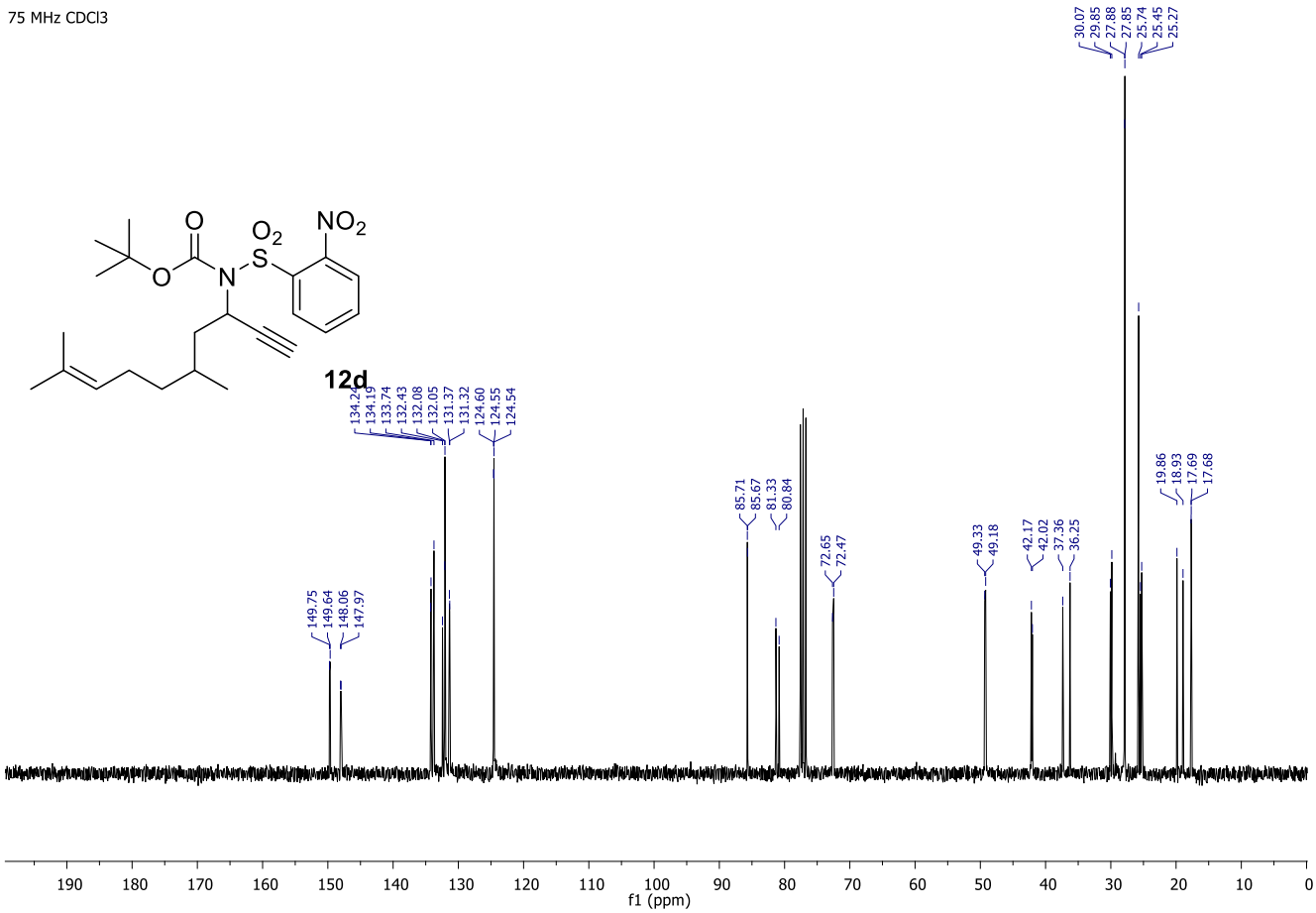
RMN ^{1}H


75 MHz CDCl3
149.79
147.98
134.32
133.82
133.03
132.11
124.69
85.83
82.13
71.55
46.08
28.01
21.88
O
O
O2
S
N
NO2
12c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

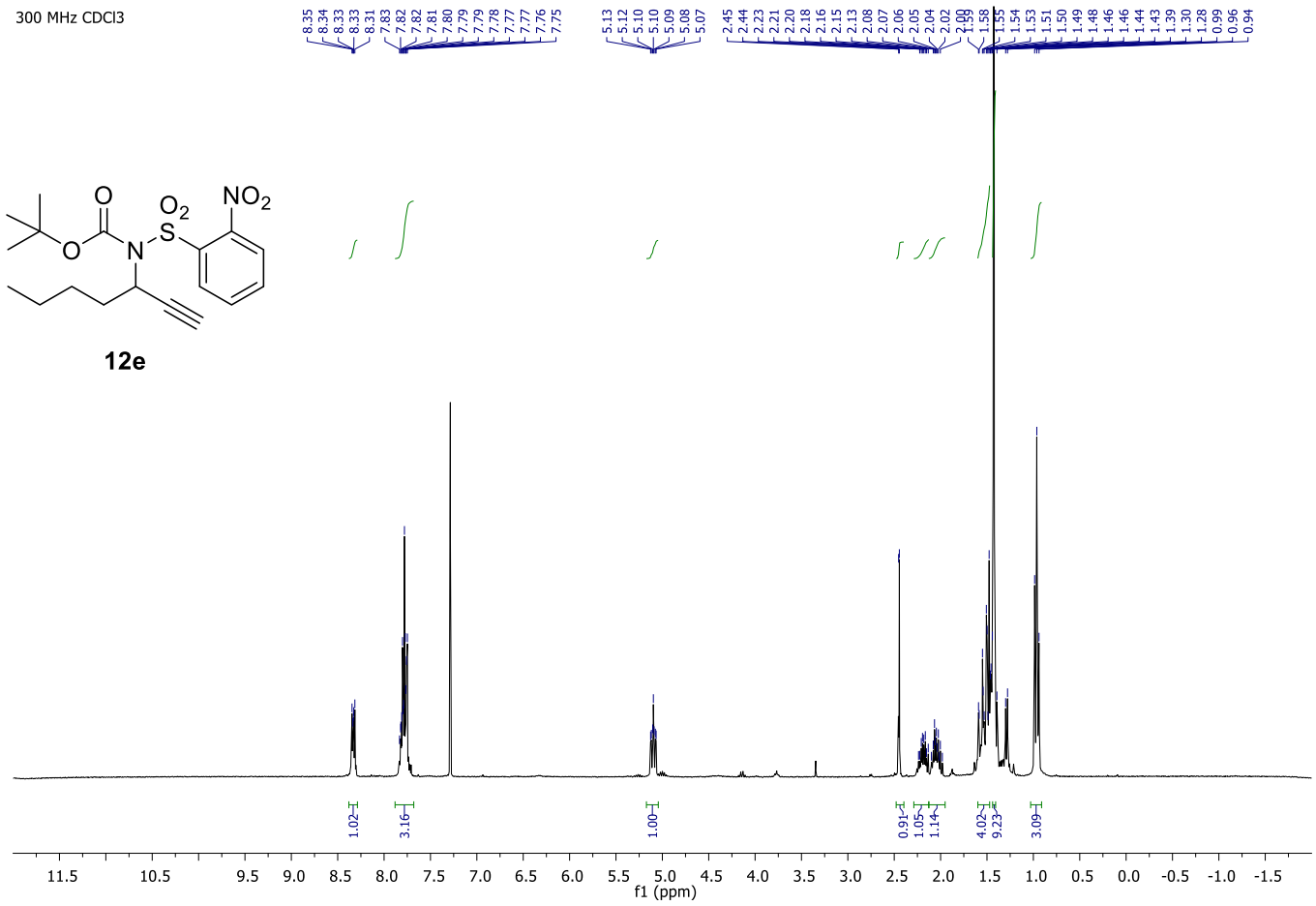
RMN $^{13}C\{^{1}H\}$



RMN ^{1}H

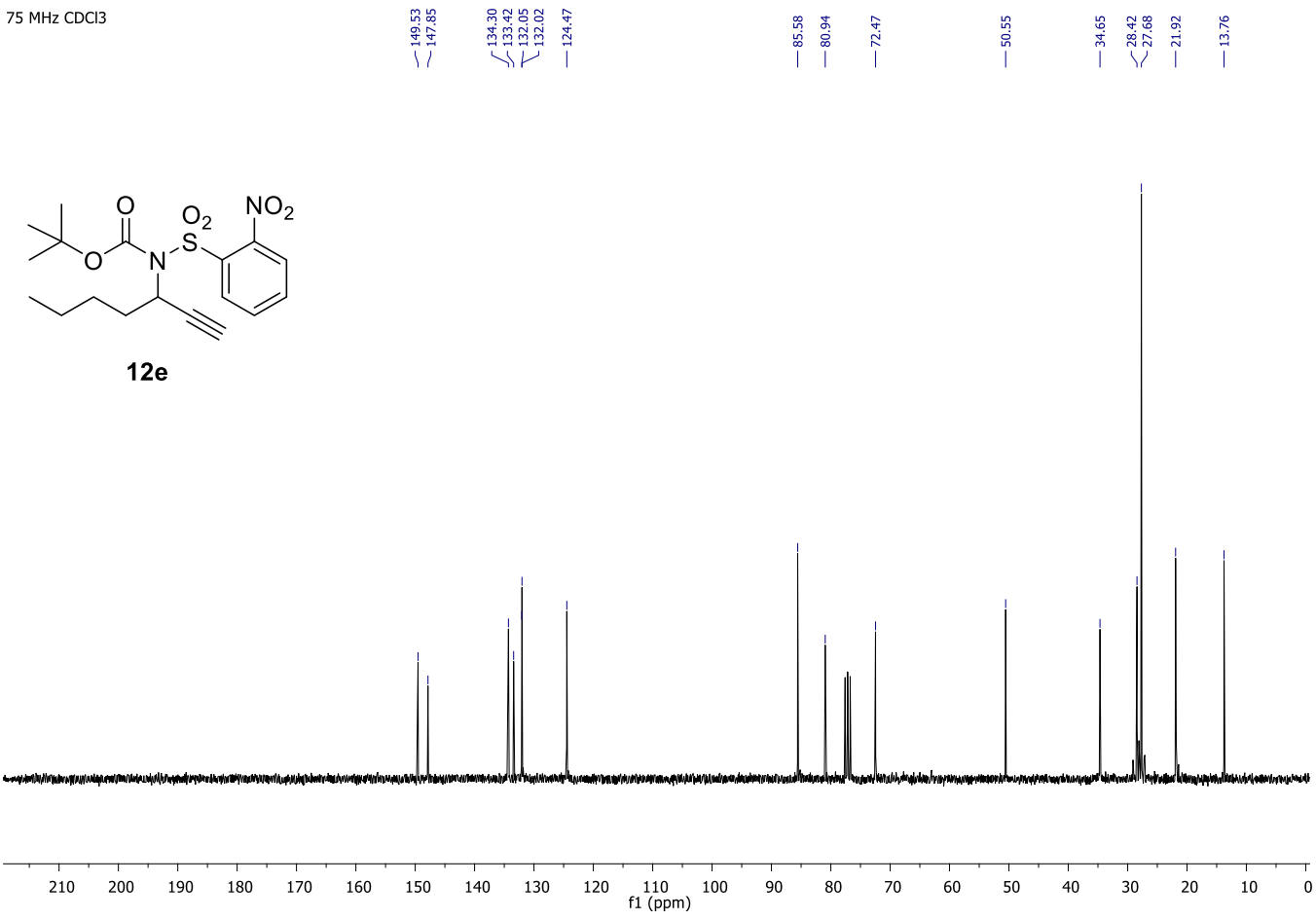

75 MHz CDCl3
12d
30.07
29.85
27.88
27.85
25.74
25.45
25.27
134.24
134.19
133.74
132.43
132.08
132.05
131.37
131.32
124.60
124.55
124.54
85.71
85.67
81.33
80.84
72.65
72.47
49.33
49.18
42.17
42.02
37.36
36.25
19.86
18.93
17.69
17.68
149.75
149.64
148.06
147.97
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$



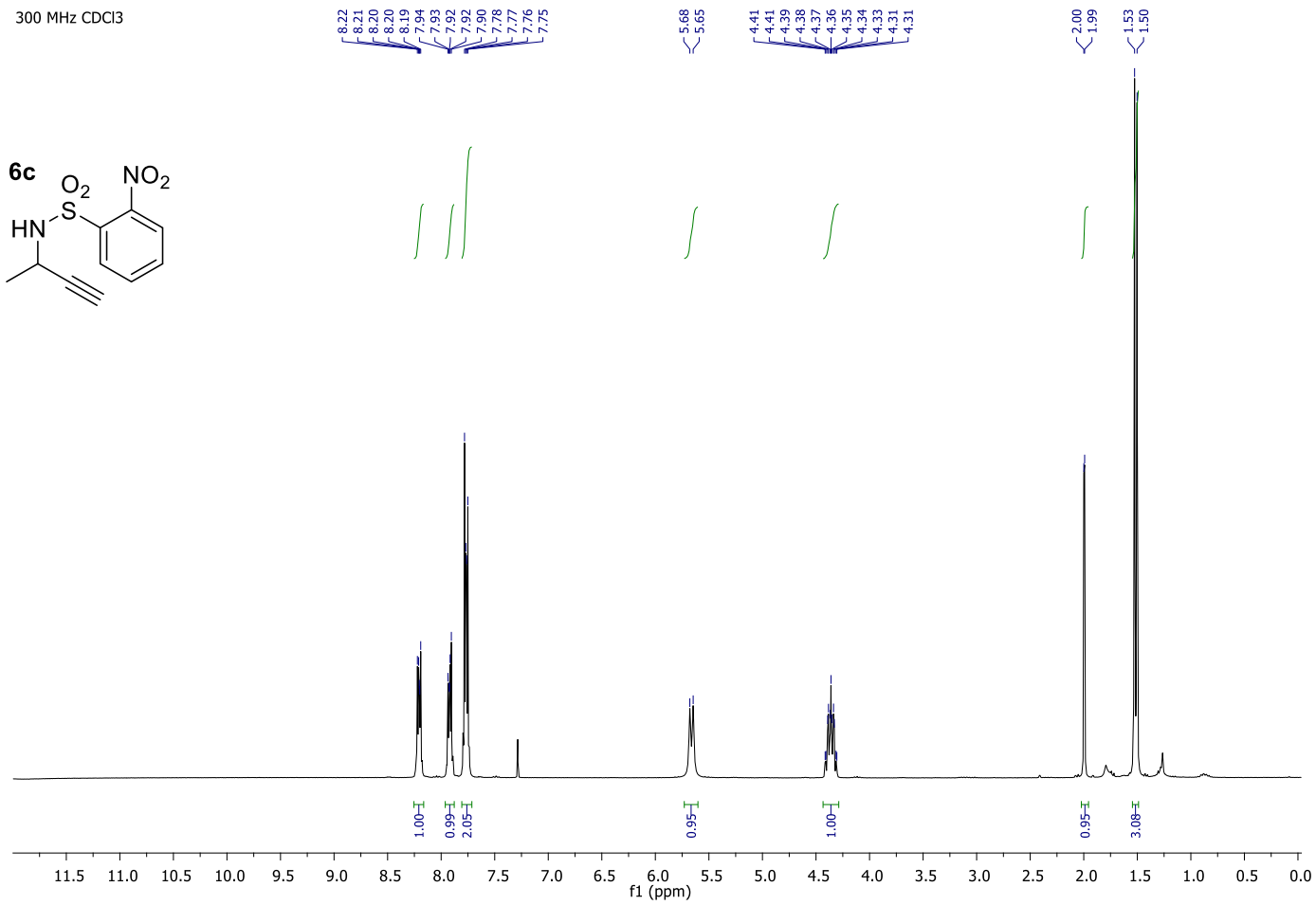
RMN ^{1}H

75 MHz CDCl3

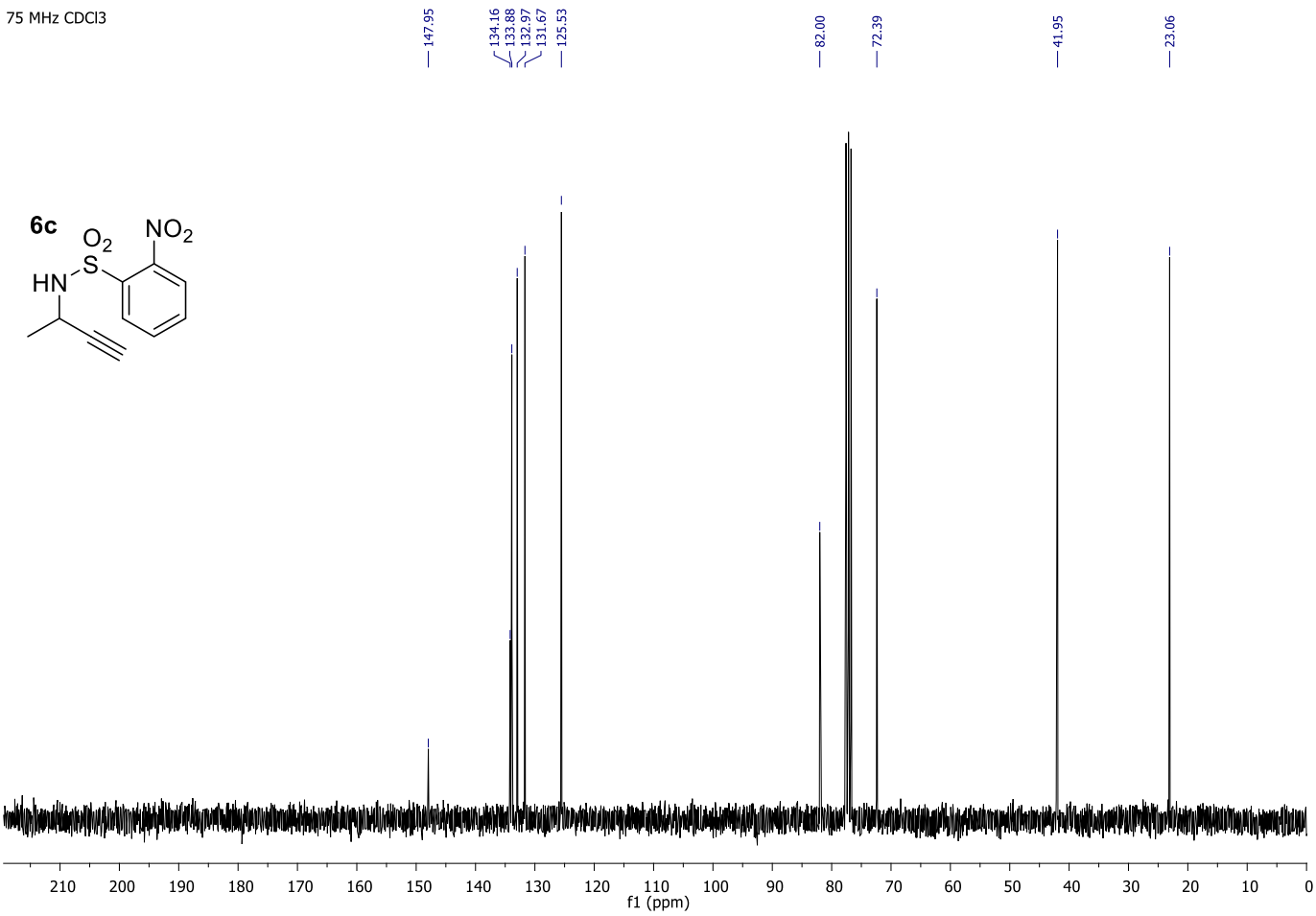


12e

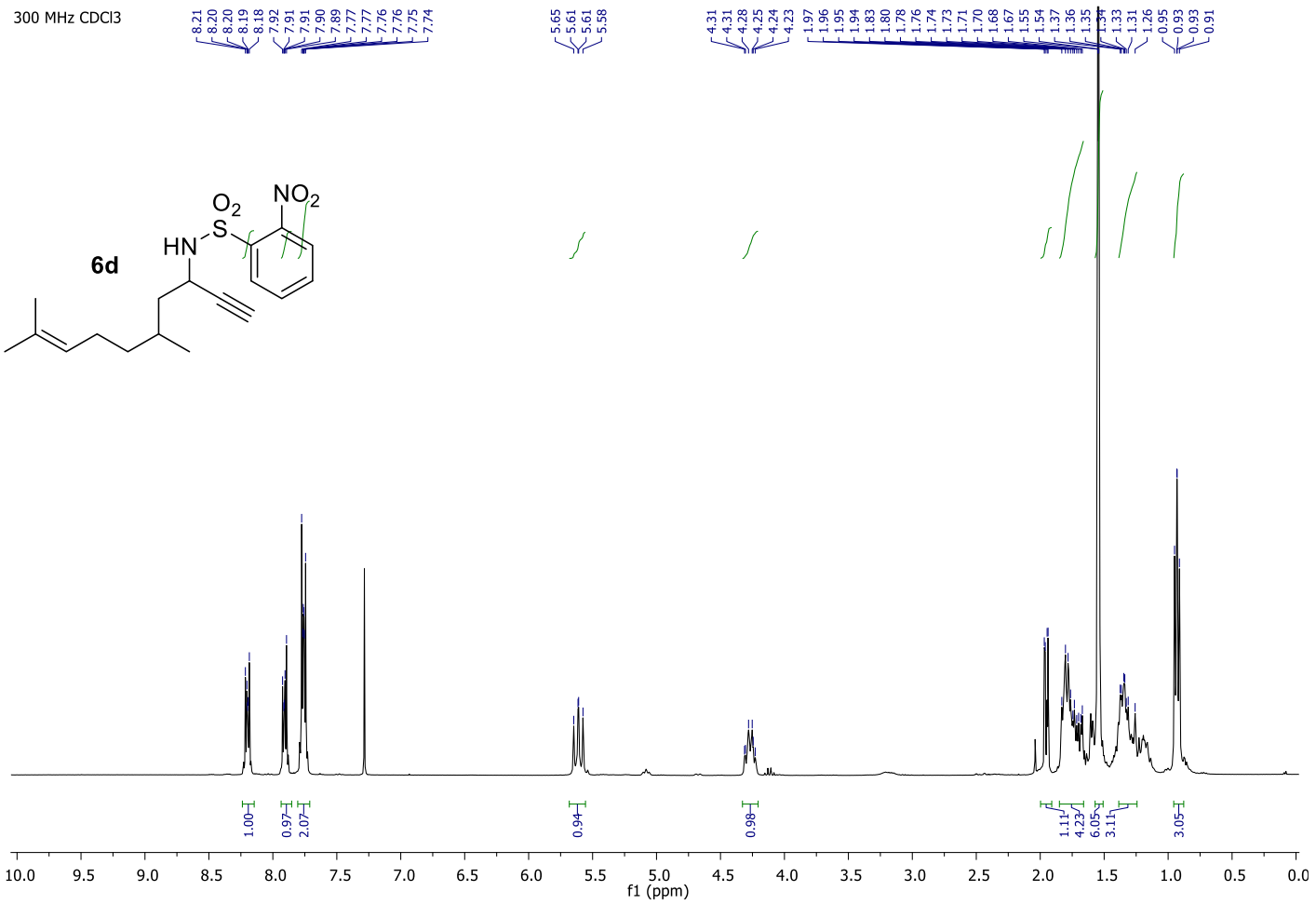
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
6c
8.22
8.21
8.20
8.20
8.19
7.94
7.93
7.92
7.92
7.90
7.78
7.77
7.76
7.75
5.68
5.65
4.41
4.41
4.39
4.38
4.37
4.36
4.35
4.34
4.33
4.31
4.31
2.00
1.99
1.53
1.50
1.00
0.99
2.05
0.95
1.00
0.95
3.08
f1 (ppm)

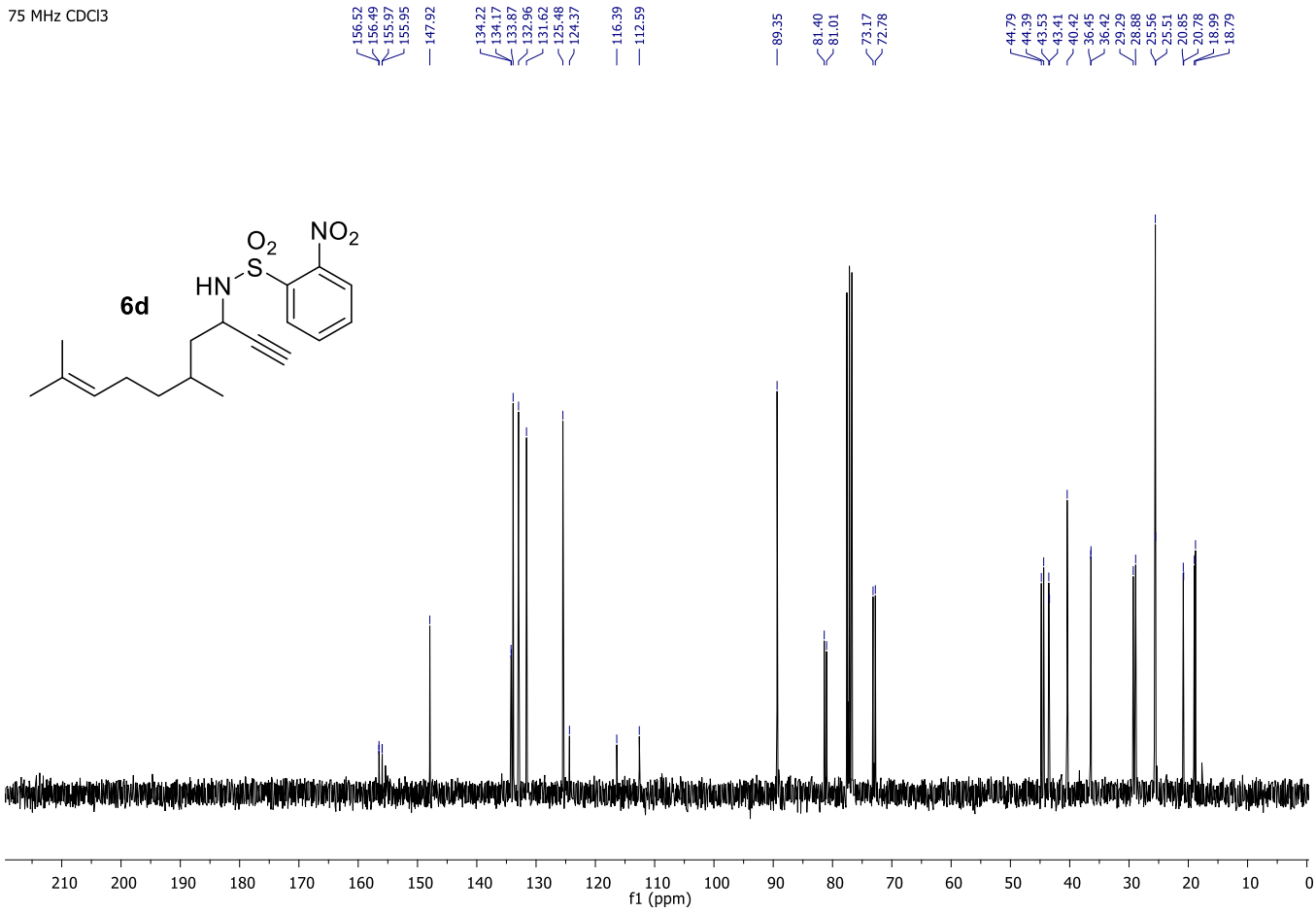
RMN ^{1}H


75 MHz CDCl3
147.95
134.16
133.88
132.97
131.67
125.53
82.00
72.39
41.95
23.06
6c
O2
NO2
S
HN
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

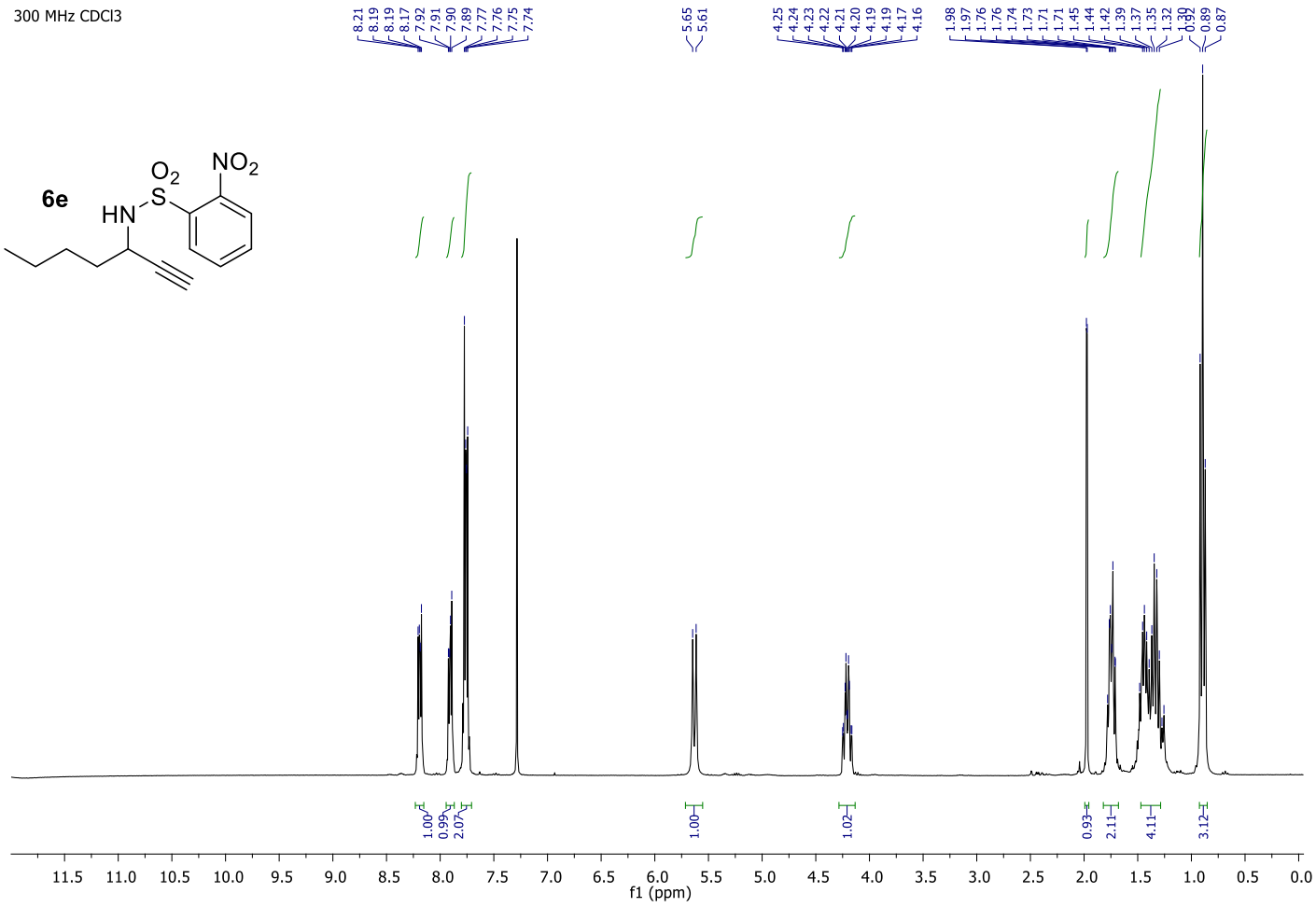
RMN $^{13}C\{^{1}H\}$



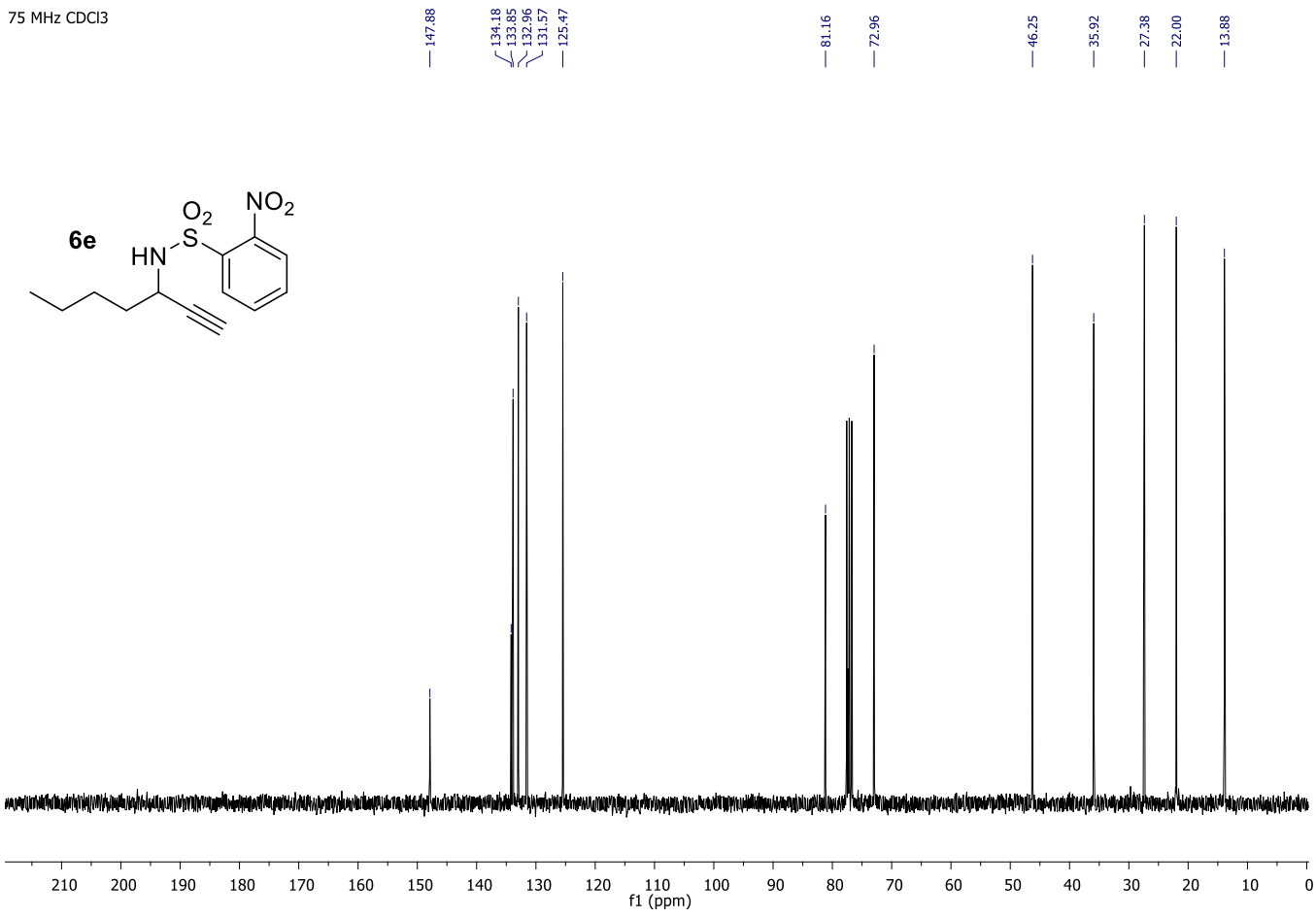
RMN ^{1}H


75 MHz CDCl3
156.52
156.49
155.97
155.95
147.92
134.22
134.17
133.87
132.96
131.62
125.48
124.37
116.39
112.59
89.35
81.40
81.01
73.17
72.78
44.79
44.39
43.53
43.41
40.42
36.45
36.42
29.29
28.88
25.56
25.51
20.85
20.78
18.99
18.79
6d
O2
S
HN
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

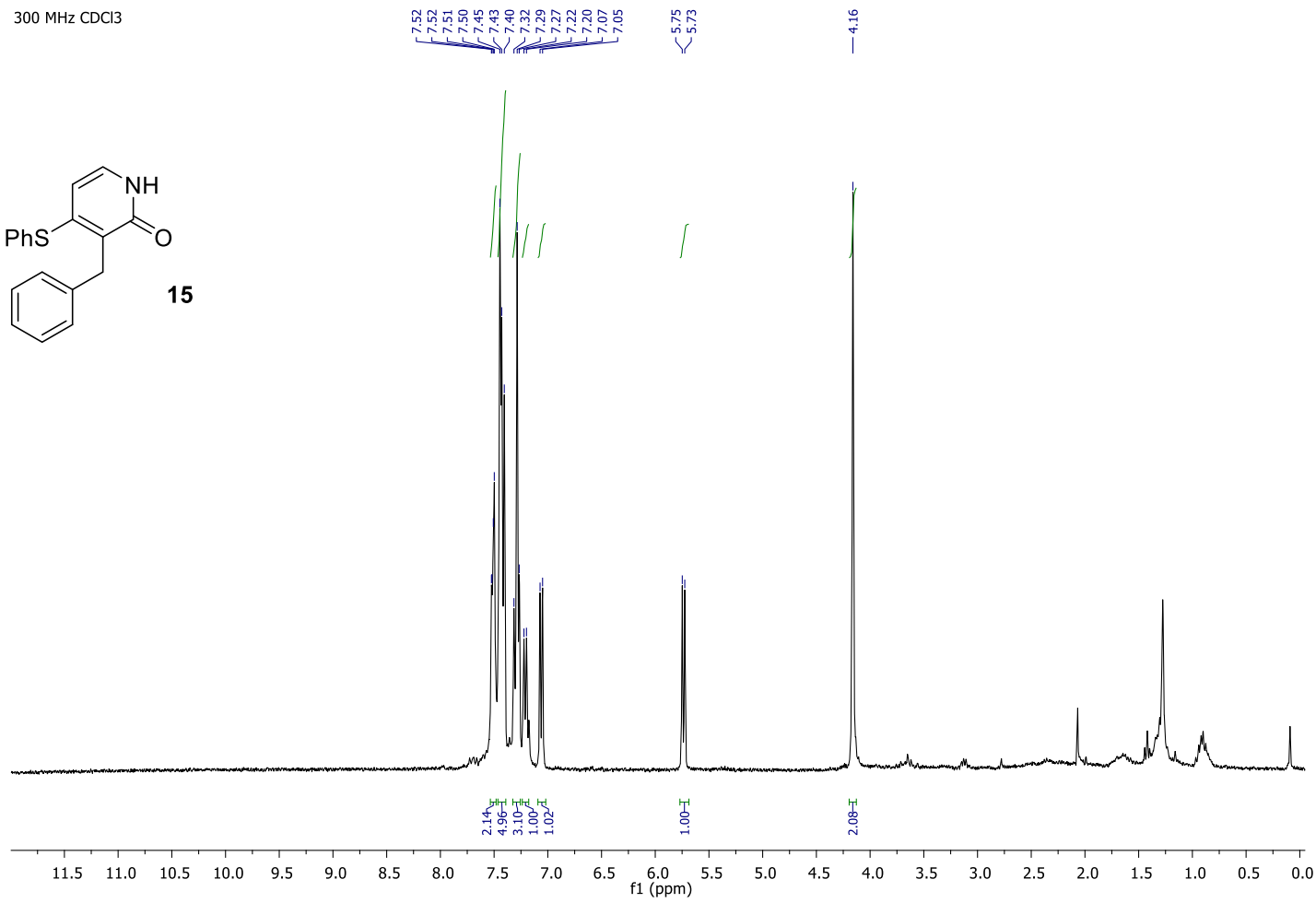
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
6e
O2
NO2
HN
S
8.21
8.19
8.17
7.92
7.91
7.90
7.89
7.77
7.76
7.75
7.74
5.65
5.61
4.25
4.24
4.23
4.22
4.21
4.20
4.19
4.19
4.17
4.16
1.98
1.97
1.76
1.76
1.74
1.73
1.71
1.71
1.45
1.44
1.42
1.39
1.37
1.35
1.32
1.30
0.92
0.89
0.87
1.00
0.99
2.07
1.00
1.02
0.93
2.11
4.11
3.12
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

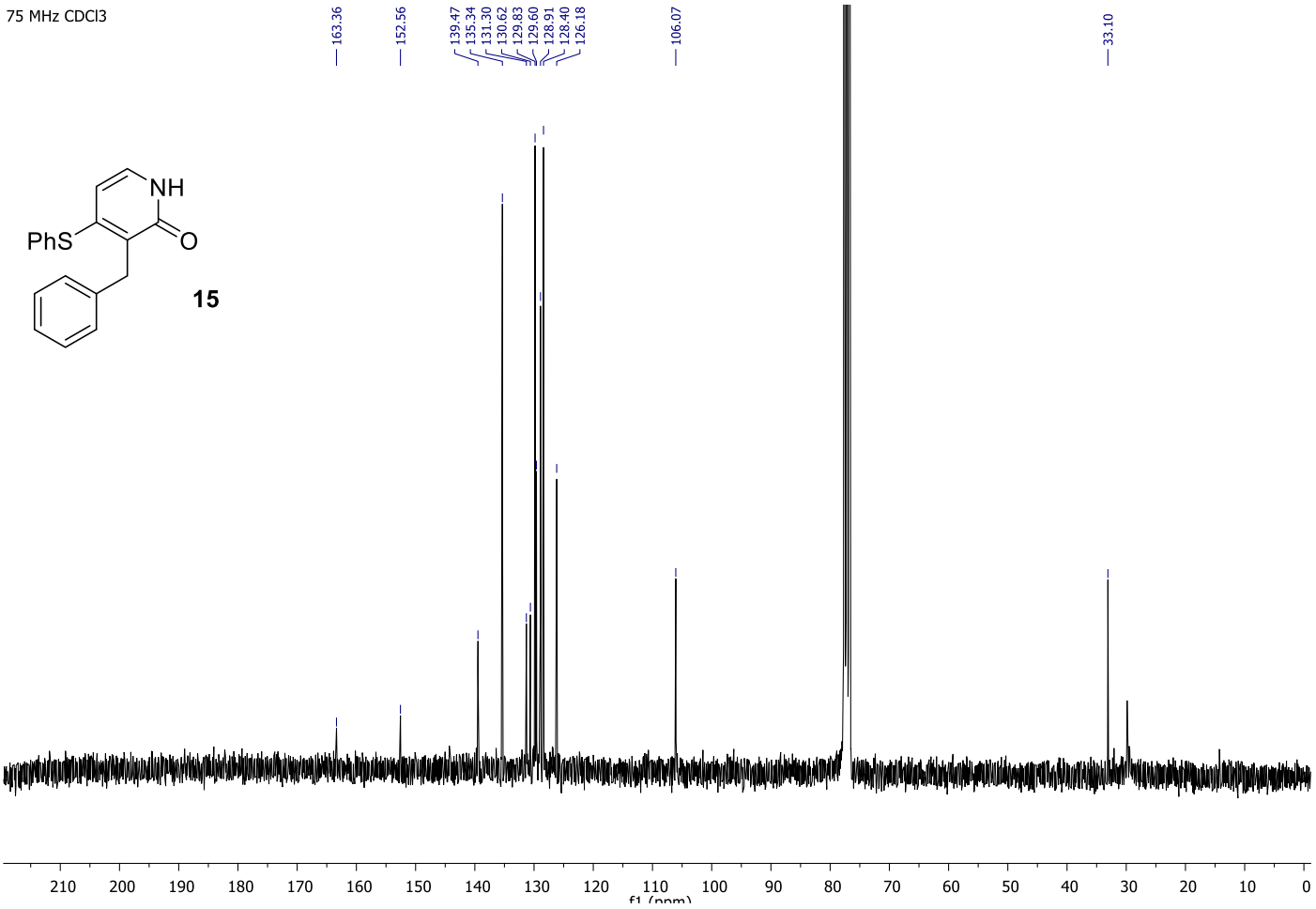
RMN ^{1}H


75 MHz CDCl3
147.88
134.18
133.85
132.96
131.57
125.47
81.16
72.96
46.25
35.92
27.38
22.00
13.88
6e
HN
S
O2
NO2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

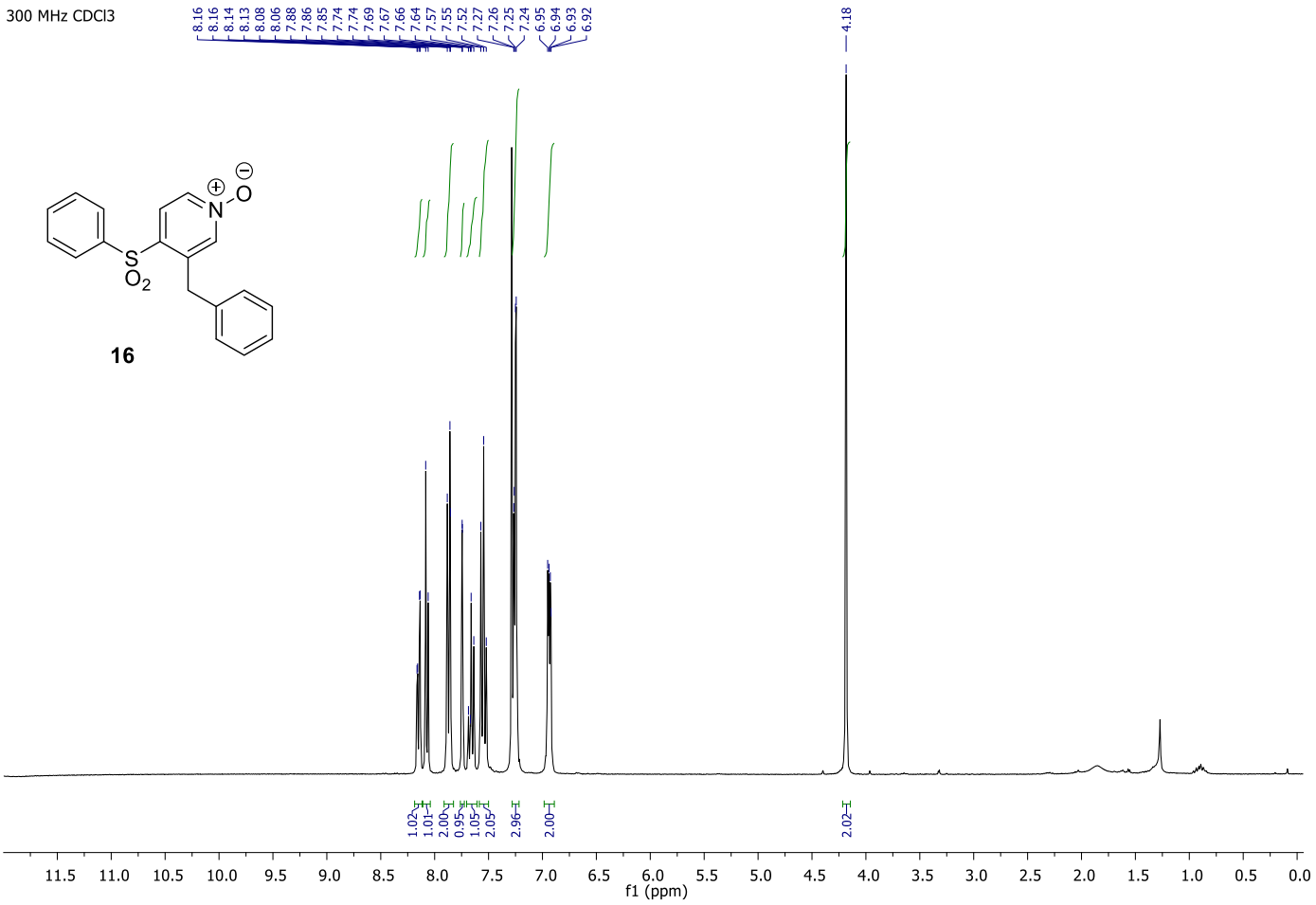
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
7.52
7.52
7.51
7.50
7.45
7.43
7.40
7.32
7.29
7.27
7.22
7.20
7.07
7.05
5.75
5.73
4.16
NH
PhS
O
15
2.14
4.96
3.10
1.00
1.02
1.00
2.08
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

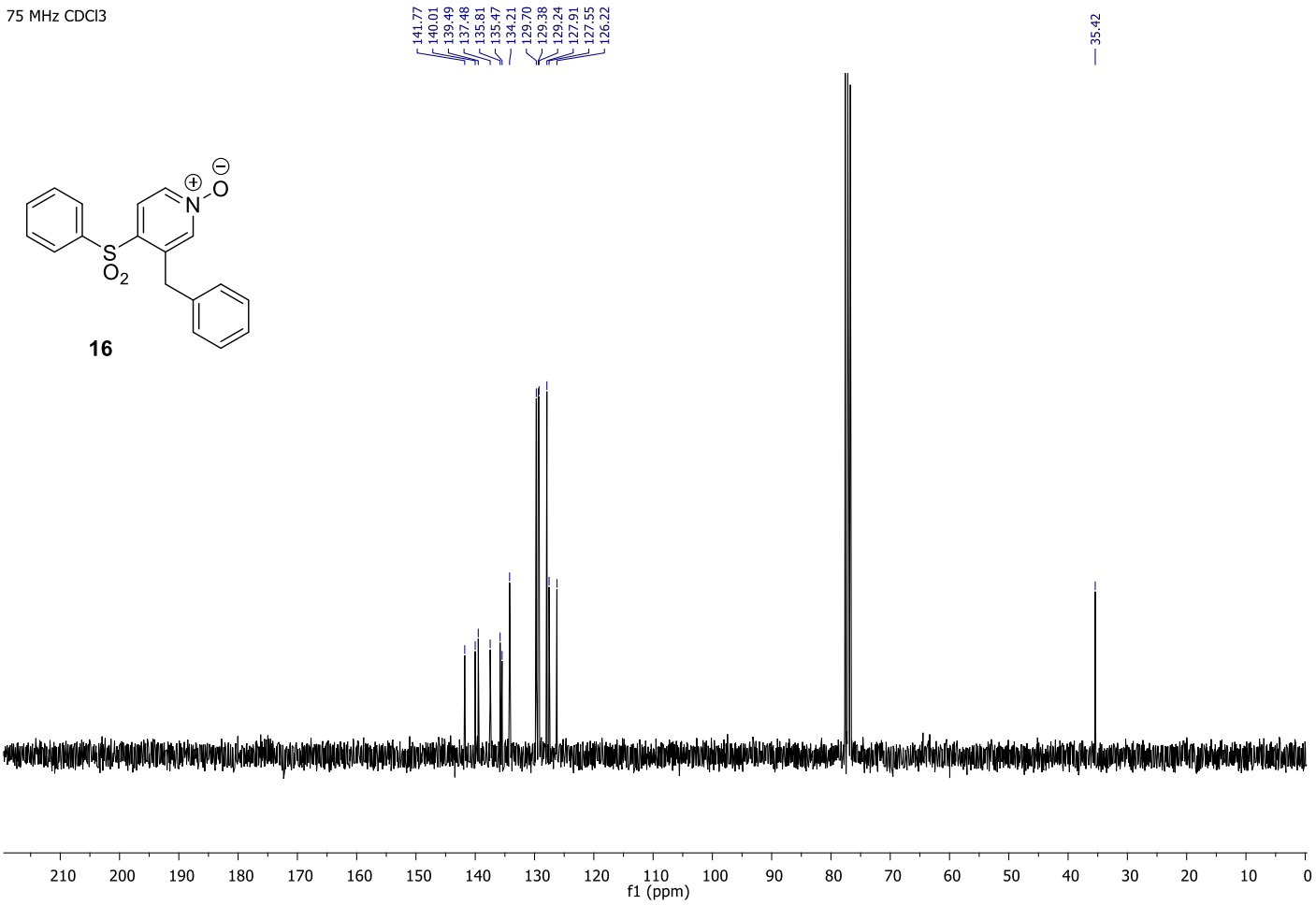
RMN ^{1}H


75 MHz CDCl3
163.36
152.56
139.47
135.34
131.30
130.62
129.83
129.60
128.91
128.40
126.18
106.07
33.10
NH
PhS
O
15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

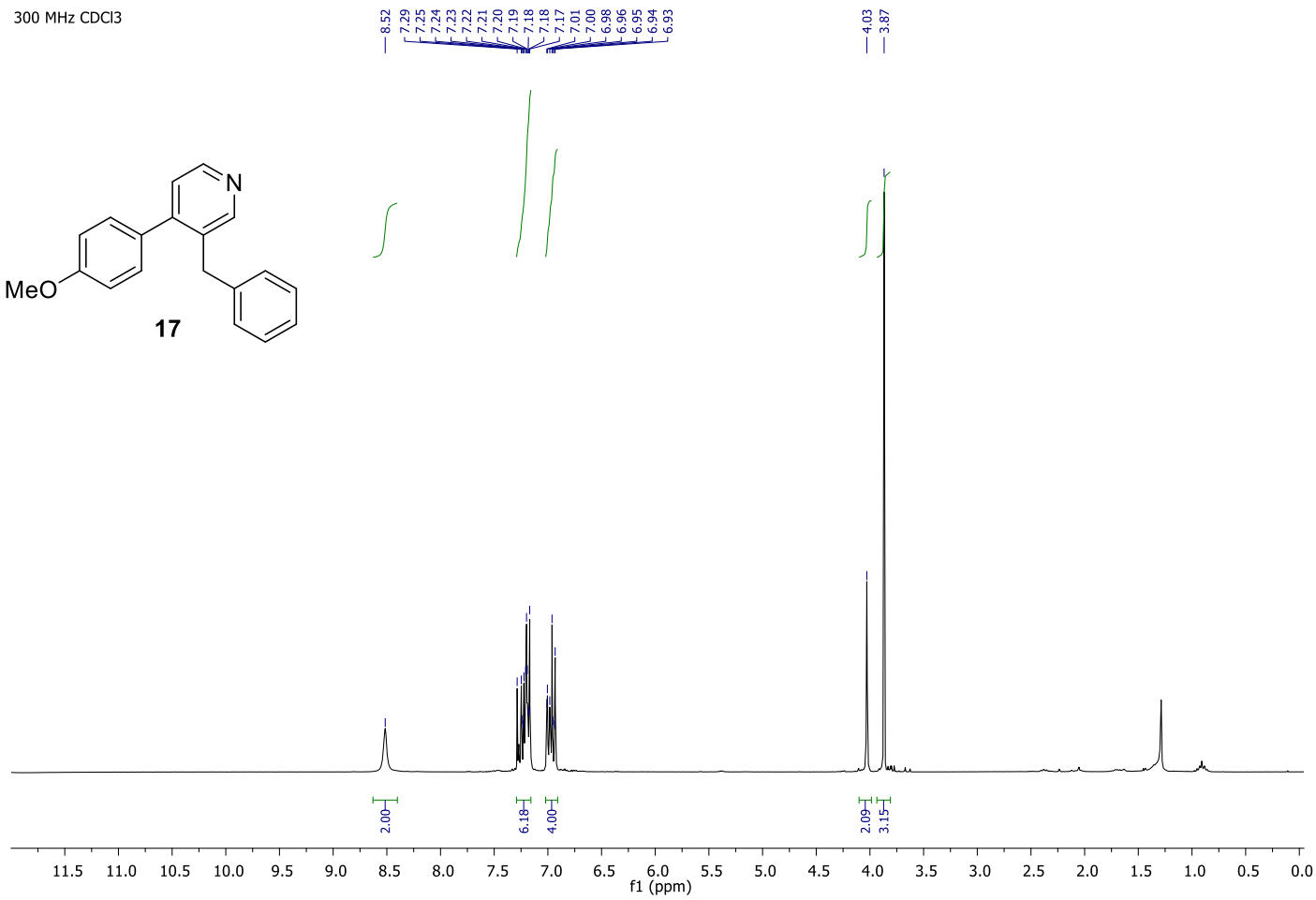
RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.16
8.16
8.14
8.13
8.08
8.06
7.88
7.86
7.85
7.74
7.74
7.69
7.67
7.66
7.64
7.57
7.55
7.52
7.27
7.26
7.25
7.24
6.95
6.94
6.93
6.92
4.18
16
1.02
1.01
2.00
0.95
1.05
2.05
2.96
2.00
2.02
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

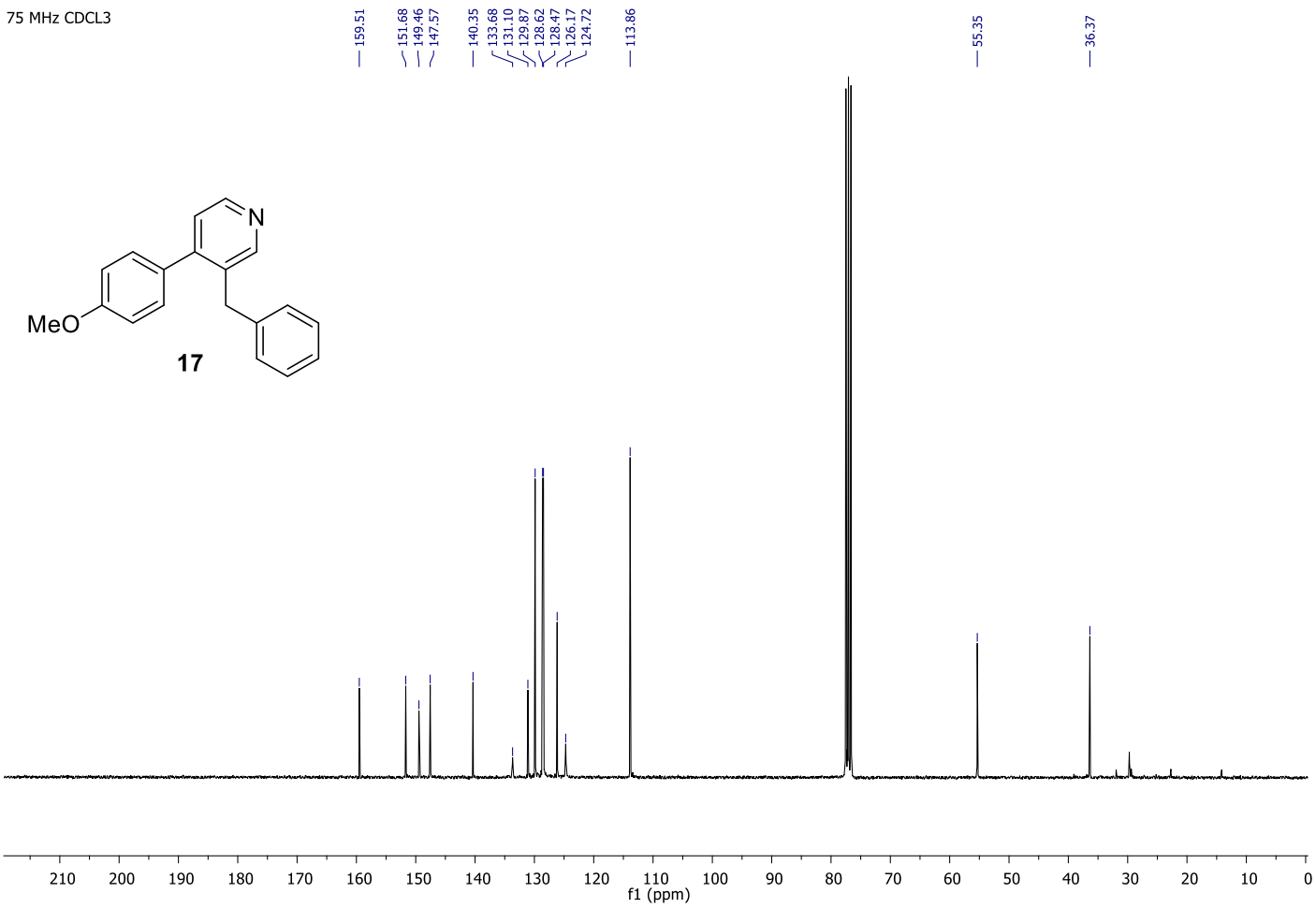
RMN ^{1}H


75 MHz CDCl3
141.77
140.01
139.49
137.48
135.81
135.47
134.21
129.70
129.38
129.24
127.91
127.55
126.22
35.42
16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.52
7.29
7.25
7.24
7.23
7.22
7.21
7.20
7.19
7.18
7.18
7.17
7.01
7.00
6.98
6.96
6.95
6.94
6.93
4.03
3.87
N
MeO
17
2.00
6.18
4.00
2.09
3.15
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

RMN ^{1}H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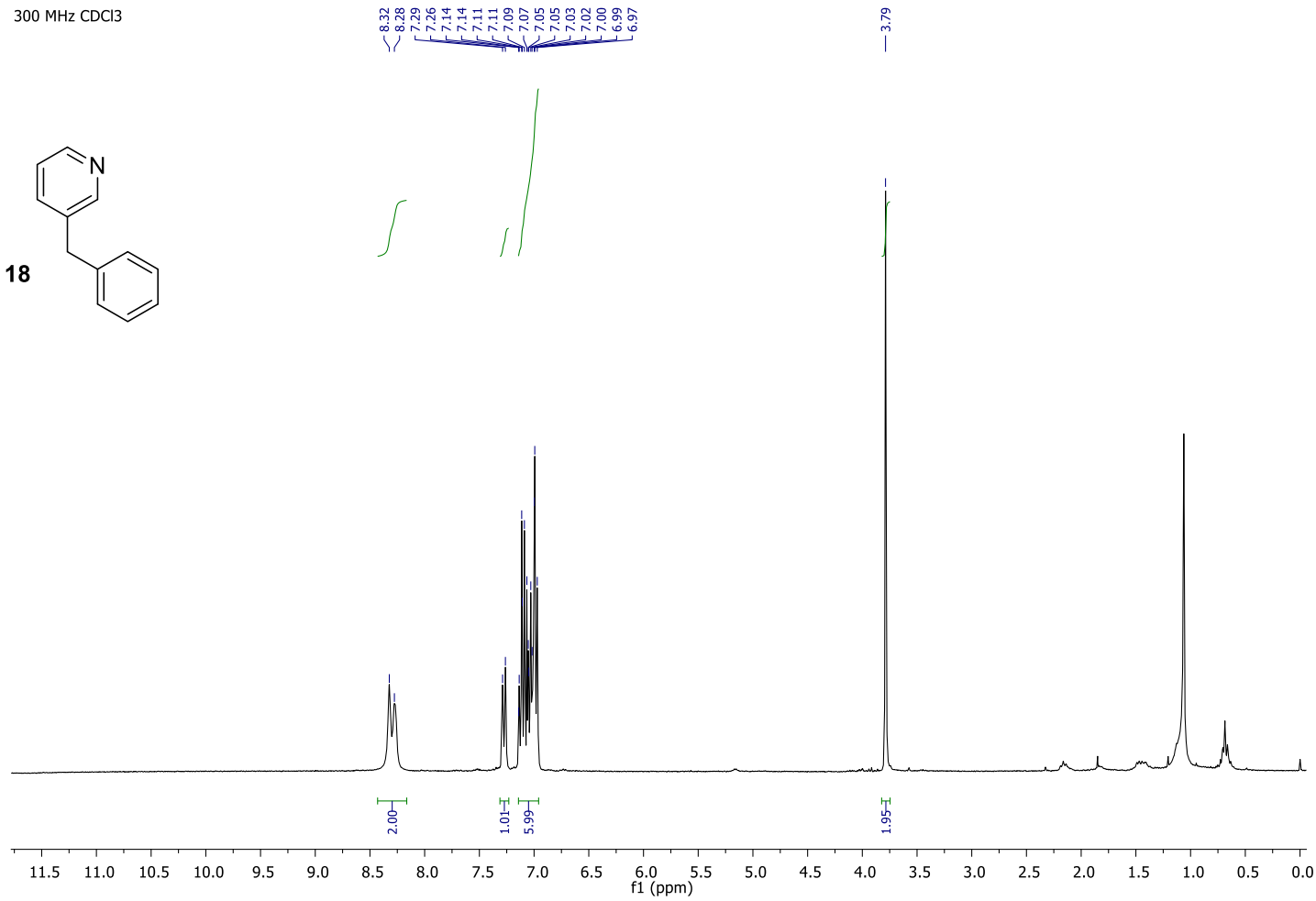
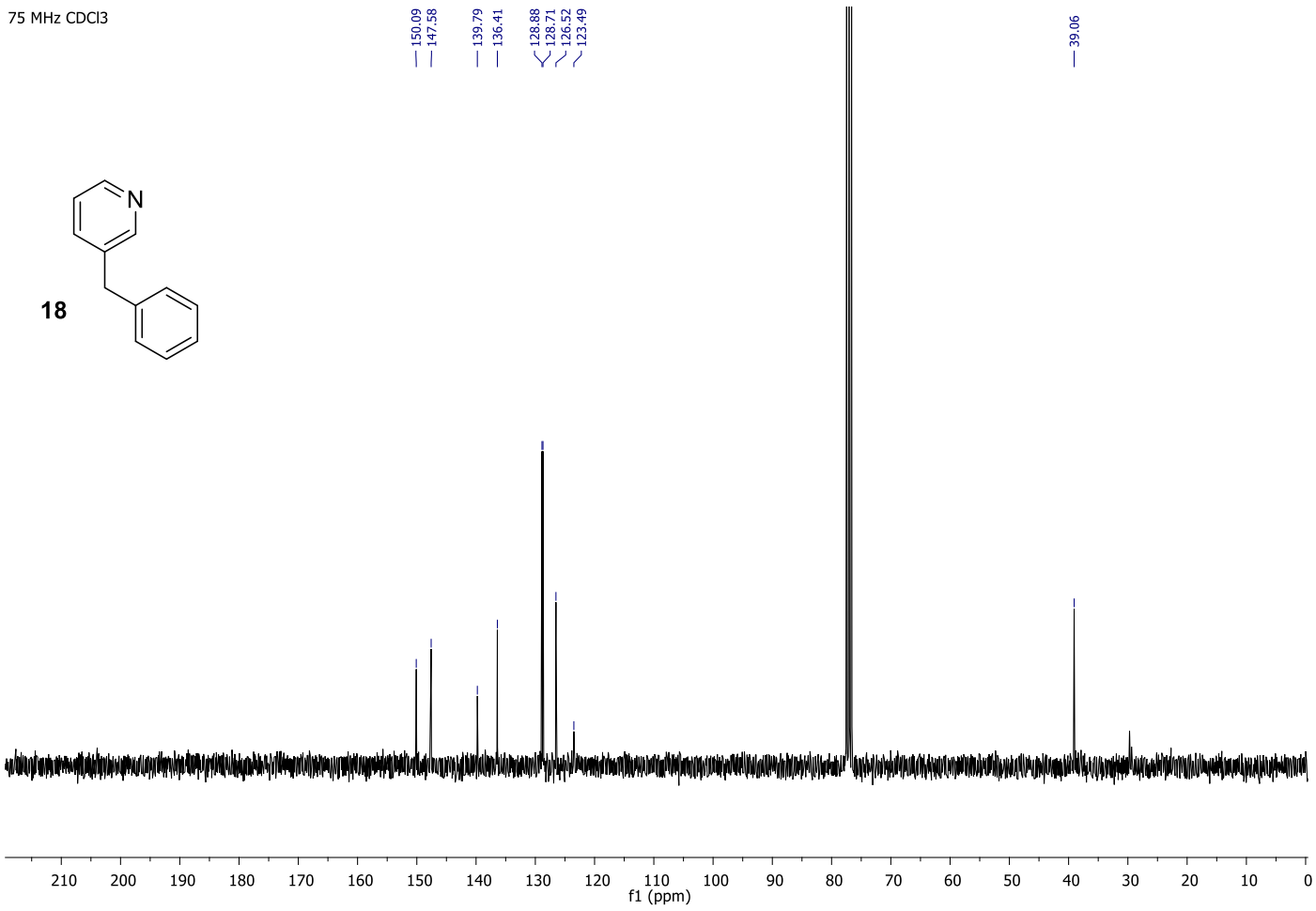
159.51
151.68
149.46
147.57
140.35
133.68
131.10
129.87
128.62
128.47
126.17
124.72
113.86
55.35
36.37
N
MeO
17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$


300 MHz CDCl3
8.32
8.28
7.29
7.26
7.14
7.11
7.11
7.09
7.07
7.05
7.05
7.03
7.02
7.00
6.99
6.97
3.79
N
18
2.00
1.01
5.99
1.95
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

RMN ^{1}H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139.79
136.41
128.88
128.71
126.52
123.49
39.06
N
18
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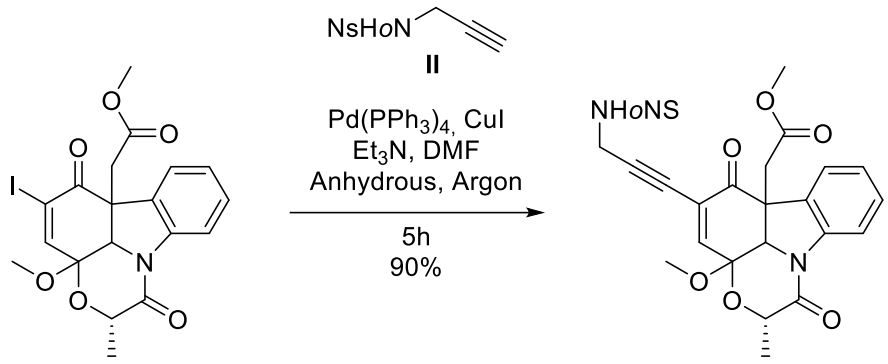
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

RMN $^{13}C\{^{1}H\}$

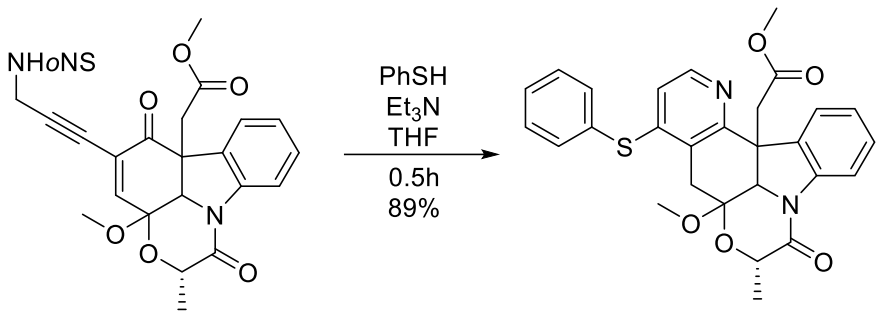
)

ANNEXE B PROTOCOLES SYNTHÉTIQUES ADDITIONNELS

Cette annexe contient les protocoles, en anglais, ainsi que les caractérisations en forme de paragraphe pour la synthèse de la pyridine du **schéma 0.7** (spectre non-inclus).



Preparation of methyl 2-((2S,3aS,3a1R,6aS)-3a-methoxy-2-methyl-5-(3-((2-nitrophenyl) sulfonamido)prop-1-yn-1-yl)-1,6-dioxo-1,2,3a,6-tetrahydro-[1,4]oxazino[2,3,4-jk]carbazo -6a(3a1H)-yl)acetate. To a round-bottomed flask was added $Pd(PPh_3)_4$ (17.2 mg, 2 mol %) and CuI (5.5 mg, 4 mol %). After the flask had been purged with argon, it was charged with a solution of **I** (350 mg, 0.725 mmol, 1 eq.) in degassed triethylamine (1.45 mL, 0.5 M), followed by **II** (174 mg, 0.725 mmol, 1 eq.) in anhydrous DMF (1.45 mL, 0.5 M). The mixture was stirred at rt for 5 hr, at which time the reaction was diluted with DCM (5 mL) and washed with H_2O (3 x 5 mL). The organic layer was washed with sat. aq. NaCl (5 mL), dried (Na_2SO_4) and concentrated to dryness. Purification by column chromatography (*n*-Hex, to 50:50 *n*-Hex/EtOAc) gave 390 mg of the title compound **III** (90%). 1H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.90 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.82 – 7.64 (m, 2H), 7.38 – 7.26 (m, 2H), 7.10 (t, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 5.76 (s, 1H), 4.84 (d, *J* = 2.2 Hz, 1H), 4.51 (q, *J* = 6.5 Hz, 1H), 4.18 (s, 2H), 3.59 (s, 3H), 3.46 (s, 3H), 3.25 (d, *J* = 2,2 Hz, 2H), 1.54 (d, *J* = 6.9 Hz, 3H).



III **IV**

Preparation of methyl 2-((5aS,5a1R,7S,13bS)-5a-methoxy-7-methyl-8-oxo-4-(phenylthio) -5a,5a1,7,8-tetrahydro-[1,4]oxazino[4,3,2-lm]pyrido[3,2-c]carbazol-13b(5H)-yl)acetate. To a solution of **III** (150 mg, 0,251 mmol, 1 eq.) in THF (2.5 mL) was added triethylamine (0,59 mL, 4.27 mmol, 17 eq.) and thiophenol (0,51 mL, 5.02 mmol, 20 eq.). The reaction mixture was stirred at room temperature for 0.5 h. Then the reaction mixture was diluted with DCM (5 mL) and washed with NH_4Cl (5 mL). The aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to dryness. Purification by column chromatography (*n*-Hex, to 50:50 *n*-Hex/EtOAc) afforded 112 mg of the title compound **IV** (89%). 1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.8 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.35 (m, 5H), 7.26 (m, 2H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 5.3 Hz, 1H), 4.85 (d, *J* = 2.6 Hz, 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.75 (d, *J* = 15.6 Hz, 1H), 3.62 (dd, *J* = 16.6, 2.7 Hz, 1H), 3.49 (s, 3H), 3.35 (s, 3H), 3.28 (d, *J* = 15.6 Hz, 1H), 2.42 (d, *J* = 16.6 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H).

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