DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF MEDICINALLY RELEVANT HETEROCYCLES

A THESIS

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By

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DELHI TECHNOLOGICAL UNIVERSITY

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DECLARATION

This is to declare that the work presented in this thesis entitled of **"Design, Synthesis and Biological Evaluation of Medicinally Relevant Heterocycles" is original and has been carried out by me for the degree of Doctor of Philosophy** under the supervision of **Dr. Saurabh Mehta**, **Assistant Professor**, Department of Applied Chemistry. This thesis is a contribution to my original research work. Wherever research contribution of others is involved, every effort has been made to clearly indicate the same. To the best of my Knowledge, this research work has not been submitted in part or full for the award of any degree or diploma in Delhi Technological University or in any other university/institution.

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CERTIFICATE

This is to certify that the thesis entitled **"Design, Synthesis and Biological Evaluation of Medicinally Relevant Heterocycles"** submitted to the Delhi Technological University, Delhi-110042, in fulfilment of the requirement for the award of the degree of **Doctor of Philosophy** by the candidate **Mr. Dhirendra Brahmchari**, (Reg. No. 2K13/PhD/AC/06) under the supervision of **Dr. Saurabh Mehta**, **Assistant Professor**, Department of Applied Chemistry. It is further certified that the work embodied in this thesis has been neither partially nor fully submitted to any other university or institution for the award of any degree or diploma.

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Dedicated to

My parents & family...

ACKNOWLEDGMENTS

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(Dhirendra Brahmchari)

ABSTRACT

New methodologies for the synthesis of nitrogenous heterocyclic compounds, namely Isoindolin-1-ones have been reported. The methodologies involve the base-mediated iodoaminocyclization of 2-(1-alkynyl)benzamides. The first methodology involves *n*-BuLi as an efficient base and leads to the *N*-cyclization of *o*-alkynylbenzamides. Interestingly, the second methodology involving the Phosphazene superbase P_4-*t*-Bu works under milder reaction conditions, and quickly affords diverse isoindolin-1-ones in good to excellent yields, in a regio- and stereoselective manner. The reactions are easy to perform, accommodate a variety of sensitive functional groups (including TMS, halogens, *etc*.), work with other halogen electrophiles (such as ICl, Br_2, NBS, *etc*.), and are also scalable. An interesting reaction mechanism involving the intimate ion pair has been proposed in order to explain the exclusive formation of *Z*-geometric isomers. The methodology involving the superbase has also been extended for the synthesis of Aristolactams, an important class of natural products. The synthesized isoindolinones have also been evaluated (virtual screening) for their potential biological activities against important cancer drug targets.

THESIS ORGANIZATION

The thesis has been divided into five chapters. The background of the work as well as the relevant literature survey including several reported methodologies for the synthesis of isoindolin-1-ones and aristolactams is summarized in ***Chapter 1***. A simple and straightforward synthesis of isoindolin-1-ones using *n*-BuLi-I_2/ICl for the regio- and stereoselective iodocyclization of 2-(1-alkynyl)benzamides has been reported in ***Chapter 2***. Another robust methodology involving a superbase-mediated electrophilic cyclization/iodocyclization of functionally substituted alkynes for the regio- and stereoselective synthesis of isoindolin-1-ones is described in ***Chapter 3***. The ***Chapter 4*** deals with the evaluation of the isoindolinone compounds for various ADME parameters including Lipinski's parameters, and *in silico* evaluation (docking) of the cyclized compounds against important cancer drug targets. The conclusions and the future scope of the work have been presented in the ***Chapter 5*** of the thesis.

LIST OF PUBLICATIONS AND CONFERENCES

Journal Articles:

1. **Dhirendra Brahmchari**, Akhilesh K. Verma and Saurabh Mehta, Regio- and Stereoselective Synthesis of Isoindolin-1-ones through BuLi-Mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides. *J. Org. Chem.* **2018**, *83,* 3339–3347.
2. Saurabh Mehta and **Dhirendra Brahmchari**, Phosphazene Superbase-Mediated Regio- and Stereoselective Iodoaminocyclization of 2-(1-Alkynyl)benzamides for the Synthesis of Isoindolin-1-ones. *J. Org. Chem.* **2019**, *84,* 5492-5503.

Publications in conference/workshop proceeding:

1. Saurabh Mehta, **Dhirenda Brahmchari** and Mange Ram Mangyan, Iodocyclization of 2-(1-alkynyl)benzamides: Synthesis of cyclic imidates and isoindolinones., *American Chemical Society National Meeting in Boston MA, USA 256*.
2. **Dhirendra Brahmchari**, Mange Ram Mangyan, Akhilesh K. Verma and Saurabh Mehta, Synthesis of Isoindolin-1-ones through BuLi-mediated Iodocyclization of 2-(1-alkynyl)benzamides. *Emerging Trends in Drugs Development and Natural-Products (ETDDNP-2018)* January 12th -14th, 2018, University of Delhi, Delhi, India.
3. **Dhirendra Brahmchari** and Saurabh Mehta, Synthesis of Isoindolin-1-ones through Base-mediated Cyclization of 2-(1-alkynyl)benzamides. *1st International Conference on New Frontiers in Engineering, Science and Technology (NFEST-2018),* January 8th – 12th, 2018, Delhi Technological University, Delhi, India.
4. Participated in the *International Conference on Advances in Analytical Sciences* (ICAAS-2018) Organized by Indian Society of Analytical Scientists (ISAS)-Delhi Chapter & CSIR-Indian Institute of Petroleum Dehradun, India, March 15th -17th, 2018.

INDEX

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

ADME	Absorption Dissolution Metabolism Excretion
aq.	Aqueous
ALK	Anaplastic Lymphoma Kinase
Ar	argon
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Bn	benzyl
BRD	Bromodomain
Bu	butyl
n-BuLi	*n*-Butyllithium
t-Bu	*tert.*-butyl
°C	degrees celsius
calcd	calculated
cat.	catalytic
CTAB	cetyltrimethylammonium bromide
δ	chemical shift
D	deuterium
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPA	diisopropylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	Electron Ionization
eq.	equation
equiv	equivalent

E	electrophile
EGFR	Epidermal Growth Factor Receptor
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour (s)
H	hydrogen
HAT	Histone Acetyltransferase
HDAC	Histone Deacetylase
HRMS	High Resolution Mass Spectroscopy
Hz	hertz
IR	infrared
m	meta
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	millilitre
mmol	millimole(s)
mp	melting point
MW	microwave
NMR	Nuclear Magnetic Resonance
o	ortho
OMe	methoxy
p	para
Pd	palladium

PDB	Protein Data Bank
Ph	phenyl
PKC	Protein Kinase C
PPh_3	triphenylphosphine
s	singlet
Satd.	Saturated
SBDD	structure based drug design
TBAB	tetra-*n*-butylammonium bromide
TEATFB	tetraethylammonium tetrafluoroborate
Temp	temperature
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TPK	Tyrosine Protein Kinase
UV	ultraviolet

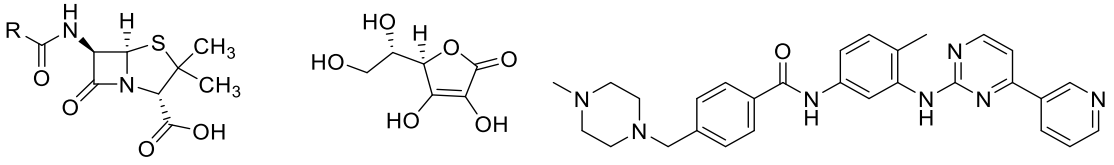
CHAPTER 1

INTRODUCTION

1.1 Heterocyclic Compounds

The organic compounds having a ring system containing at least one heteroatom (N, O, S, *etc.*) in place of the carbon atom are termed as heterocyclic compounds. They may either contain simple aromatic rings or non-aromatic rings. Heterocycles are extensively found in the nature in the essential molecules of life, primarily in plant alkaloids, nucleic acids, flavones, anthocyanins, DNA, chlorophyll, heme, *etc*.[1,2] Various naturally occurring as well as synthetically designed heterocycles are used in pharmaceuticals,[3] agrochemicals, and play an important role in human life.[4–8] A few examples of important heterocycles are shown in figure 1.1.

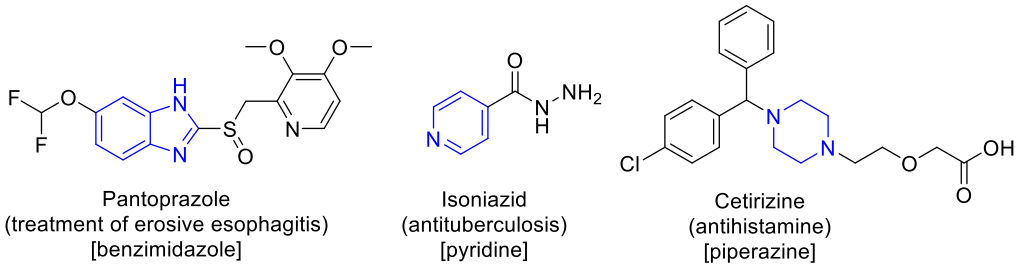
Figure 1.1 Biologically active heterocyclic compounds: Selected examples[9,10]



1.1.1 Nitrogen-containing heterocycles

Nitrogen-containing heterocycles, owing to their structural diversity and biological importance have been attractive targets for synthesis.[1] These compounds are found in several naturally occurring products.[1,5,6] Due to their therapeutic and pharmacological properties, nitrogen heterocycles and their derivatives occupy an important place in the field of natural products and synthetic organic chemistry. Numerous building blocks containing nitrogen heterocycles have applications in pharmaceutical research, drug discovery, and agriculture science.[5,6] Examples of some important nitrogen-containing compounds/scaffolds are shown in Figure 1.2.[2,3,11,12]

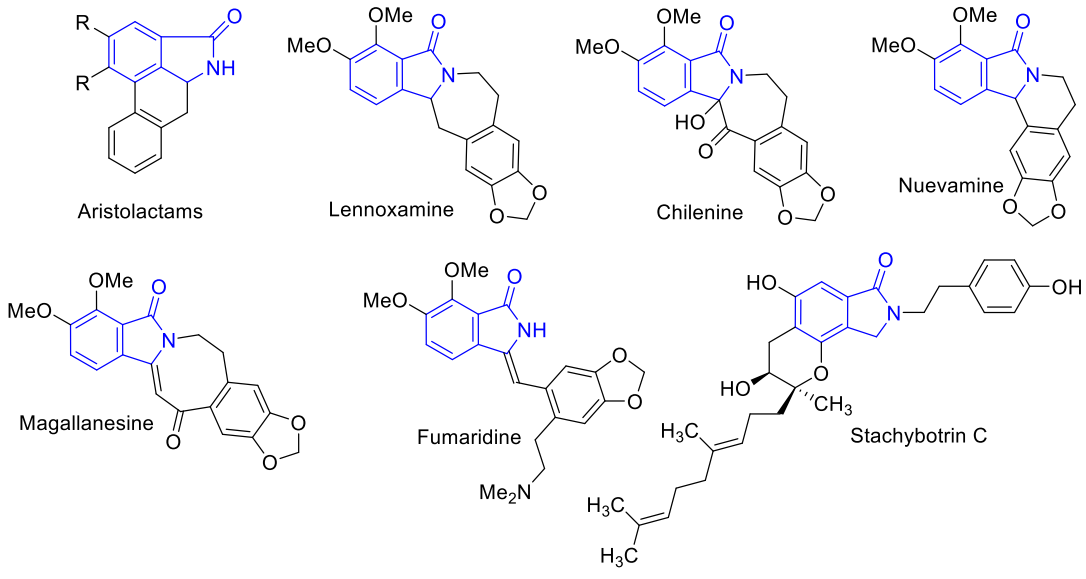
Figure 1.2 Examples of important compounds containing nitrogen heterocycles



1.1.1.1 Isoindolinones

Isoindolinones or phthalimidines represent an important class of nitrogen-containing heterocycles. Lactams (cyclic amides), particularly, isoindolinones comprise the core structure in a large number of biologically active natural products and pharmaceutically interesting compounds (Figure 1.3).[1,13] Various naturally occurring compounds, containing isoindolin-1-one core include Aristolactams,[14,15] Lennoxamine,[16] Chilenine,[16] Nuevamine,[17] Magallanesine,[18] Fumaridine,[16] Stachybotrin C,[19] Isoindolinomycin,[20] *etc*.[21]

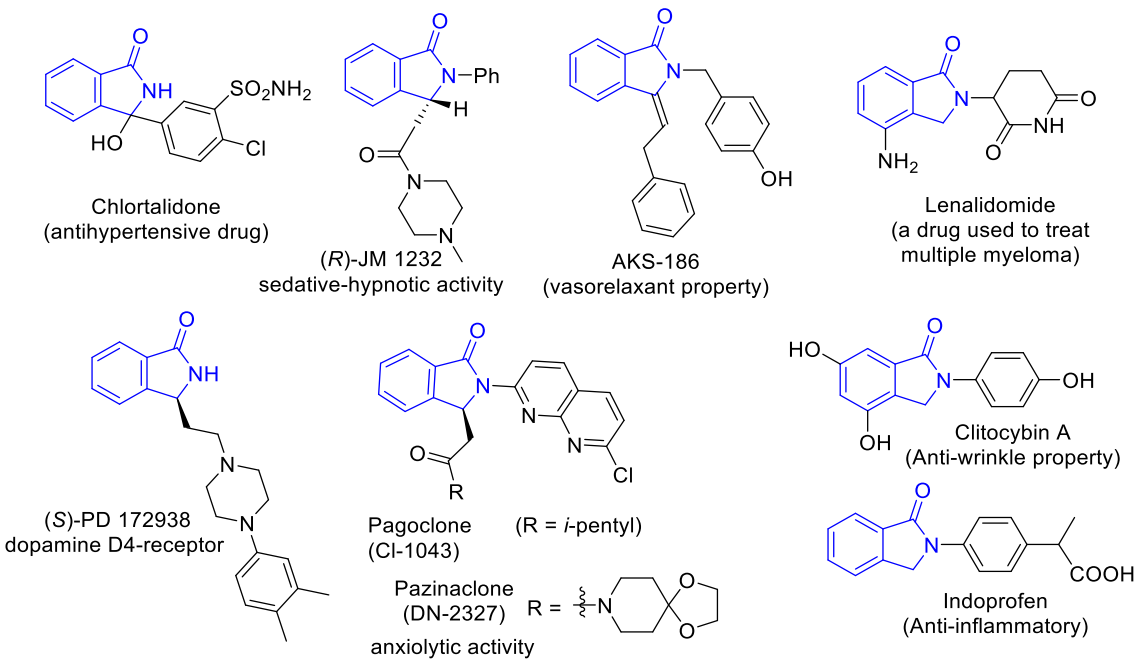
Figure 1.3 Naturally occurring isoindolin-1-ones



Moreover, numerous molecules containing isoindolin-1-one fragment exhibit a wide array of important biological activities such as antihypertensive,[22] antiulcer,[23] anesthetic,[24] antipsychotic,[25,26] vasodilatory agents,[27] treatment of cardiac arrhythmias,[28]

anti-HIV,[29] antileukemic,[30] anti-inflammatory,[31] antimicrobial,[32] antihyperglycemic,[33] anxiolytic,[34] anticonvulsant,[35] sedative & hypnotic,[36] antiviral,[37] anti-wrinkle effects,[38] *etc.*[39] A few specific examples of such medicinally important compounds containing isoindolin-1-one core are indicated in Figure 1.4, namely, Chlortalidone (antihypertensive drug),[40] JM-1232 (sedative-hypnotic property),[41] AKS 186 (vasorelaxant property),[42,43] Lenalidomide (treatment of multiple myeloma),[44] (*S*)-PD 172938 (dopamine D4-receptor inhibitor),[45] Pagoclone (anxiolytic activity),[46] Pazinaclone (anxiolytic activity),[26,47] Clitocybin A (anti-wrinkle property),[38] indoprofen (anti-inflammatory),[48] *etc*.

Figure 1.4 Biologically active compounds with the isoindolin-1-one skeleton[38,44,48–52]

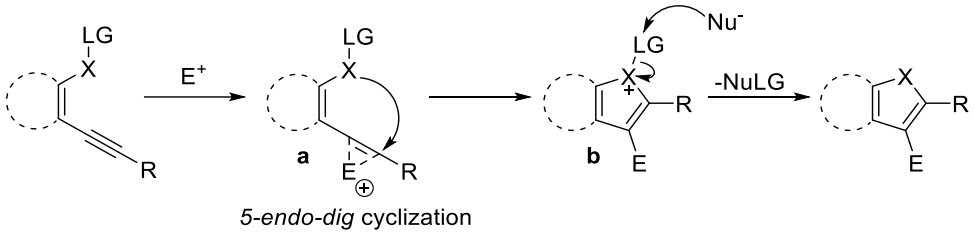


1.2 Alkyne Annulation and Electrophilic Cyclization

In organic chemistry, the reactions involving the formation of a new ring are known as annulation reactions. The reactions involving suitably substituted alkynes as starting substrate for the cyclization reactions are known as alkyne annulation reactions.[53] Electrophilic cyclization reactions involve the activation of the carbon-carbon multiple bonds by the electrophile, which is followed by the intramolecular annulation by an

internal nucleophile to form the cyclized products.[53] Electrophilic cyclizations that are promoted by the halogen electrophiles are known as halocyclization reactions. In the past few decades, halocyclization[53,54] reactions have emerged as efficient pathways for synthesizing highly functionalized scaffolds including furan, indole, thiophene, pyrrole, *etc*. using several halogen-containing electrophiles like I_2, Br_2, ICl, NIS, NBS or other organochalcogen derivatives.[55–57] Usually, the alkyne halocyclization reactions are initiated by the formation of a cyclic halonium intermediate by the halonium ions which is followed by the backside attack of the neighboring nucleophile leading to the ring-opening of the formed halonium intermediate ring (Scheme 1.1). The halocyclization products contain halogen that are useful handles for further structural elaboration.

Scheme 1.1 Halocyclization. A general mechanistic pathway[54]



X = NH, O, S, Se, etc.
R = alkyl, aryl, TMS, heterocyclic, etc.
LG = leaving group
E^+ = I, Br, etc.

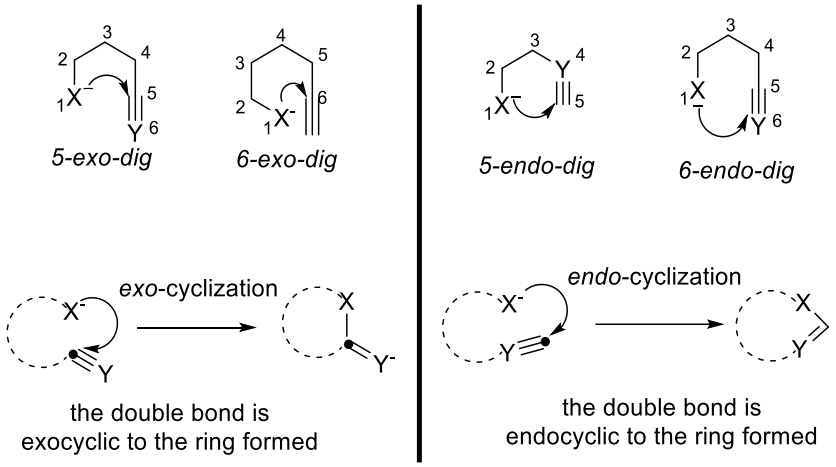
1.2.1 Iodocyclization

Over the past few decades, molecular iodine has emerged as a powerful and robust electrophilic reagent for synthesizing a wide range of iodofunctionalized heterocyclic compounds.[54] Iodine, as a reagent, provides several advantages over the other electrophiles. It is readily available, highly cost-effective, non-toxic, and is easy-to-handle. Moreover, the reactions are generally carried out at ambient conditions, are completed in few min/hours, and accomodate important functional groups. Additionally, the C-I bond is known to be a preferred site for metal-catalyzed coupling reactions.[54,58]

1.3 Baldwin Rules

Ring-forming reactions are the most encountered processes in organic synthesis. Baldwin's work[59,60] defined a series of guidelines which govern the formation of heterocyclic/carbocyclic rings.

Figure 1.5 Baldwin's classification of ring-closing reactions



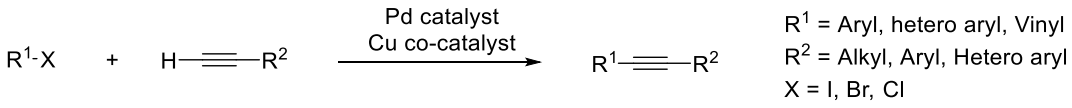
According to Baldwin, the cyclization mode is represented as combination of three independent variables (prefixes), e.g., *5-exo-dig.* The number of atoms which are a part of the newly formed ring is provided by the first numerical prefix. The position of the resulting bond is represented by the second prefix (*endo* or *exo*), where *exo-* represents that the breaking bond lies outside to the newly formed ring and the prefix *endo-* indicate that the breaking bond lies inside the newly formed ring. The information about the hybridization/type of bond of the atom, which is the ring closure point is provided by the third prefix (*-dig*, *-trig* and *-tet*), where *-dig* (digonal) represents an sp-hybridized atom; *–trig* (trigonal) represents an sp^2-hybridized atom; *–tet* (tetrahedral) represents sp^3-hybridized atom.

1.4 Sonogashira Reaction

Palladium-catalyzed reactions have been extensively used in organic chemistry as robust methodologies for the making of C-C bonds.[61–63] The '*Sonogashira coupling*', named after Kenkichi Sonogashira,[61] is a palladium-catalyzed carbon-carbon bond

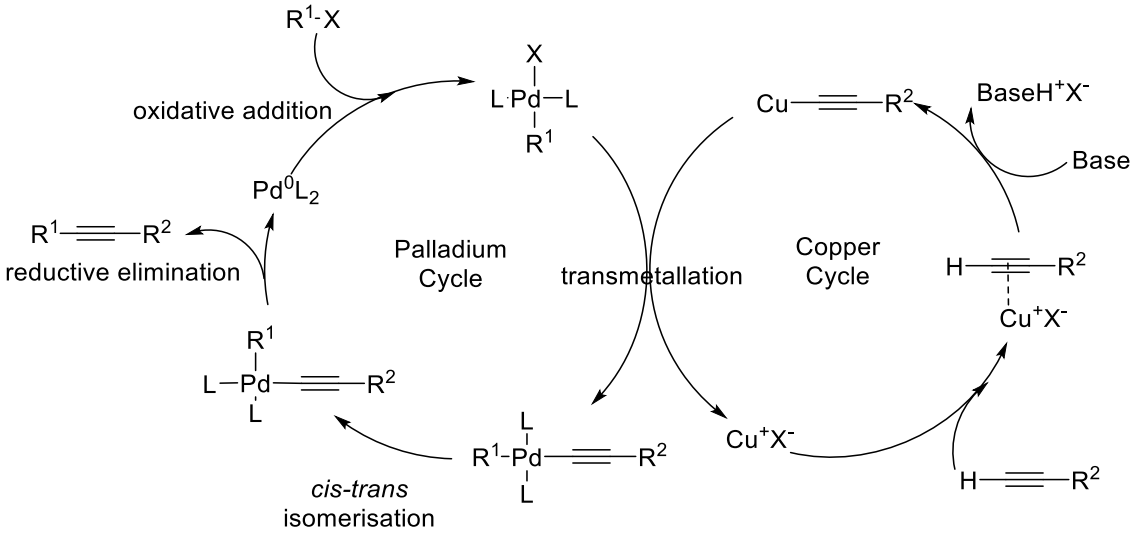
formation process where the carbon (sp^2 hybrid) of an aryl or vinyl halide (R-X) is coupled with a terminal carbon (sp hybrid) of an alkyne to form the Sonogashira products. The reaction is catalyzed by a palladium source such as $PdCl_2(PPh_3)_2$ and CuI (co-catalyst) in a suitable solvent.

Scheme 1.2 Sonogashira coupling. **General representation**



Over time various modifications have been made to the Sonogashira reaction employing different catalysts and reaction conditions.[64,65] The general mechanism of the Pd-Cu catalyzed Sonogashira reaction is shown below:

Scheme 1.3 Mechanism of Pd-Cu catalyzed Sonogashira reaction



The generally accepted mechanism involves two independent catalytic cycles (palladium cycle & copper cycle). The Pd catalyst is activated under the reaction conditions to generate reactive Pd^0 complex. The palladium complex [$Pd(0)L_2$] undergoes oxidative addition of the halide to form the Pd(II) species which upon transmetallation with the copper acetylide complex forms the Pd-acetylene complex. This Pd-complex undergoes *cis-trans* isomerization[66,67] to form the *cis*-oriented Pd-complex which on

reductive elimination results in the formation of the carbon-carbon coupled compound and regenerating the Pd^0 catalyst for further catalytic cycles. The copper-cycle in this reaction is not well known. However, it is believed that in the presence of the base, a π-alkyne complex is formed, thereby, increasing the acidity of the terminal hydrogen and paving the way for the generation for the copper acetylide complex. The copper-acetylene complex undergoes transmetallation with the Pd-intermediates.

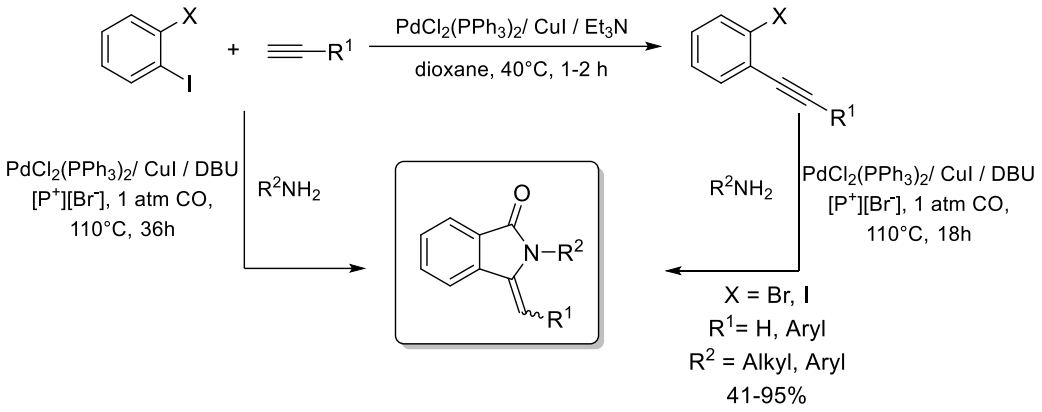
1.5 Literature Survey

Owing to the widespread medicinal importance of isoindolinones, there has been a continuous interest in designing and developing new syntheses of isoindolin-1-ones with improved accessibility to a broad array of structurally related analogs. In the past, several research groups have developed various interesting approaches (>200 research articles in the recent literature) for the synthesis of the isoindolin-1-ones.[68,69] More particularly, alkyne annulation reactions have been used for the synthesis of isoindolinones, *e.g.*, through metal-catalyzed, including Pd-catalyzed,[70–74] Cu-catalyzed/mediated,[75–79] Ru-catalyzed;[80] base-mediated annulations,[81–88] *etc*.[89,90] The relevant research literature with respect to the synthesis of isoindolinones *via* several alkyne annulations reactions of the *o*-(alkynyl)benzamides is discussed here.

Following the traditional base-catalyzed methodology, two different approaches have been adopted by Cao *et al.*[70] for the synthesis of isoindolinones (Scheme 1.4) under mild conditions using phosphonium salt ionic liquids (PSIL). The first multistep approach involved the formation of alkyne adducts *via* Sonogashira coupling followed by the palladium-catalyzed carbonylation-intramolecular hydroamination reaction in the PSIL. Another method was a one-pot strategy involving tandem Sonogashira coupling, carbonylation, and intramolecular hydroamination chemistry in sequential steps to form

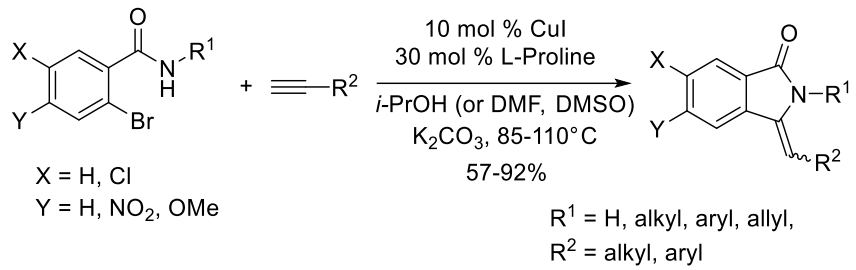
the substituted isoindolinone products. Both the methodologies resulted in the formation of highly stereoselective (*Z*-isomers) products along with good yields.

Scheme 1.4



Li *et al.*[91] reported a copper-catalyzed coupling/additive cyclization cascade reaction for synthesizing 3-methyleneisoindolin-1-ones from 2-bromobenzamides and terminal alkynes (Scheme 1.5). The methodology was diverse enough to tolerate variation at *N*-atom, aromatic ring, and alkyne terminal to form the desired isoindolinones in good yields (Scheme 1.5). The products exhibited *Z*-geometry, except in case of nitro-substituted aryl bromides and *N*, *N*-diethylethylene-substituted aryl bromide substrates, where *E*-isomers were isolated as a major product. The developed methodology was extended for the synthesis of Lennoxamine.

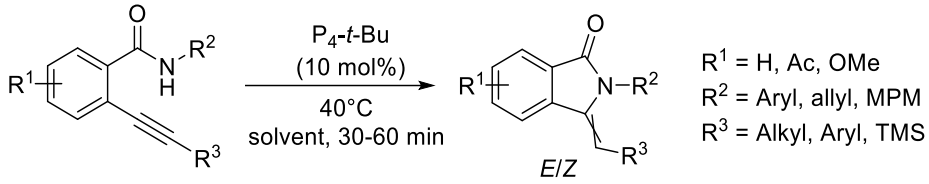
Scheme 1.5



The superbase mediated intramolecular cyclization of *o*-alkynylbenzamides has been reported by Terada and Kanazawa[81] that permitted dichotomous control of the *E*/*Z*-geometry at the *exo*-vinylidene isoindolin-1-one substrates (Scheme 1.6). The role of

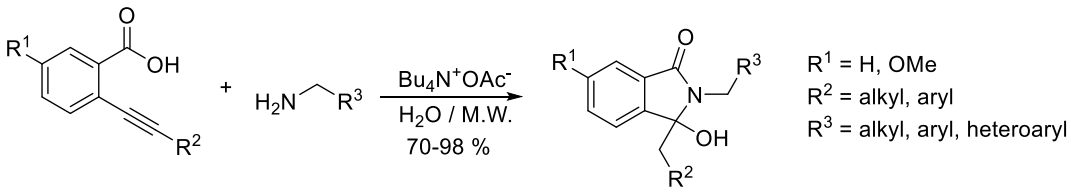
water, coupled with P_4-*t*-Bu superbase was found to be important in controlling the geometry of exocyclic double bond in the resulting products. In the presence of water, the kinetically favored *Z*-isomers were formed while in the absence of water, the steric interaction of the substituents introduced at the alkynyl terminus and the nitrogen atom was responsible for the high *E*-selectivity. The *E*/*Z*-selectivity of the product was markedly influenced not only by the solvents and organic bases employed but also by the concentration of the reactants along with electronic properties and steric demand of the substituents.

Scheme 1.6



Zhou *et al.*[92] reported an atom-economical and environmentally friendly methodology for the formation of 3-hydroxyisoindolin-1-ones from *o*-alkynyl benzoic acid and primary amines. The methodology provided the products with high regioselectivity (Scheme 1.7). The products formed on dehydration yielded *Z*-isomers as the major product. The methodology was highly flexible to work smoothly with a wide range of aromatic as well as aliphatic substrates.

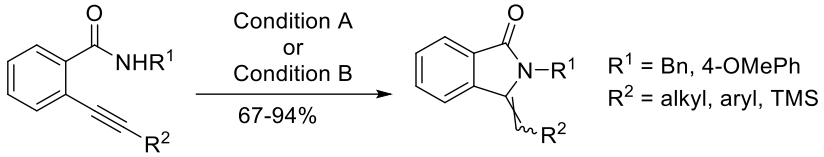
Scheme 1.7



Bianchi *et al.*[93] reported chemo- and stereo-5-*exo*-*dig* conversion of *o*-(1-alkynyl)benzamides to (*Z*)-3-aryl-/vinylidene-isoindolinones (Scheme 1.8). In presence of the electrogenerated base, the formation of the (*Z*)-geometric isoindolinone products

was observed. However, when the reaction was promoted by *t*-BuONa in DMF, the (*E*)-3-arylideneisoindolinone derivatives were formed, probably due to the steric hindrance. The choice of a suitable base provided a choice for the selection of different geometrical products. Additionally, the isomerization of the (*Z*)-isomeric product of (Z)-3-alkylideneisoindolone to the corresponding (*E*)-isomer occurred under the strongly basic conditions for both the reported procedures.

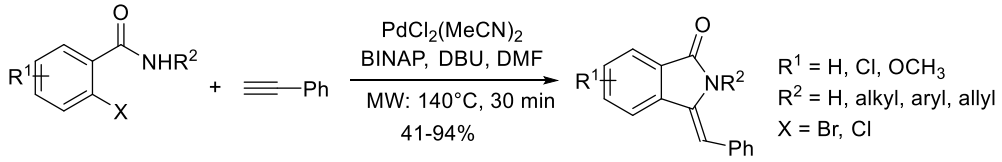
Scheme 1.8



Condition A - Electrolyses in CH_3CN, 0.1M TEATFB solutions at 0°C with Pt electrodes, current (2.0 $F \cdot mol^{-1}$), reaction time 0.1 h.
Condition B - Reaction in DMF at room temperature in the presence of *t*-BuONa

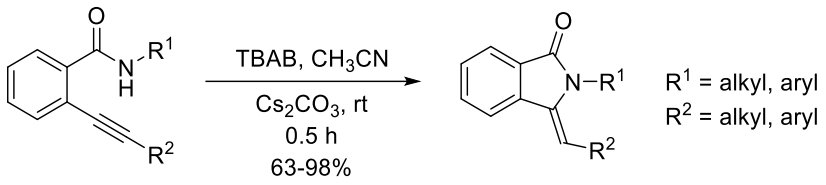
Cuny and Hellal[94] reported an interesting method for the preparation of isoindolin-1-ones that involved a tandem Sonogashira reaction (copper-free) followed by cycloisomerization using microwave heating conditions to give *Z*-isomer isoindolinones as the major product in good to excellent yield (Scheme 1.9). The methodology involves readily available starting materials, thereby making it a cost-effective protocol.

Scheme 1.9



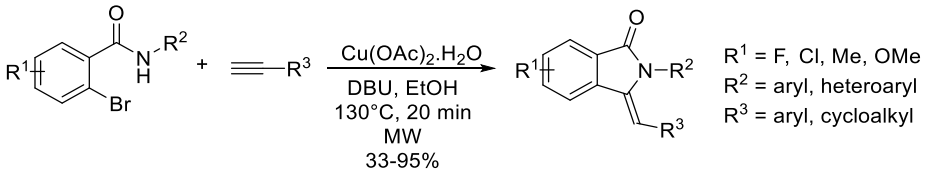
Hu *et al.*[95] reported a metal-free intramolecular hydroamination of 2-alkynyl benzamides using TBAB (phase-transfer-catalyst) leading to the formation of 3-methyleneisoindoline-1-one in good to excellent yield under ambient reaction conditions (Scheme 1.10). The reactions were easy to perform, tolerant of a variety of functional groups and possessed the advantages of being environment-friendly.

Scheme 1.10



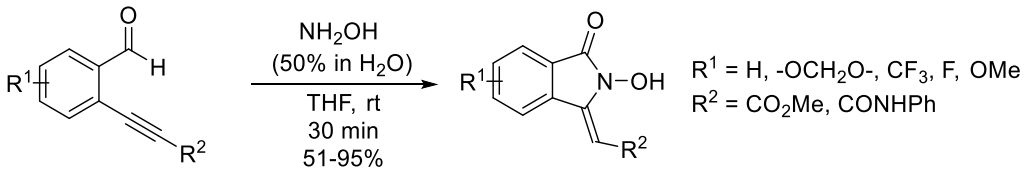
Zhang *et al*.[76] developed a quick and convenient synthetic route for the exclusive preparation of (*Z)*-3-methyleneisoindolin-1-ones. The $Cu(OAc)_2 \bullet H_2O$ catalyzed cascade reaction of *N*-benzyl-2-bromobenzamide and phenylacetylene in the presence of DBU under microwave irradiation in ethanol solvent lead to the formation of corresponding *Z*-isoindolinone products (Scheme 1.11). Importantly, DBU played a dual role as a base and as a ligand for copper. This methodology was tolerant to various substituted benzamides and ring substitutions including heteroaryl, aryl acetylenes and aliphatic alkynes, to yield highly stereoselective products in good yield in a short period.

Scheme 1.11



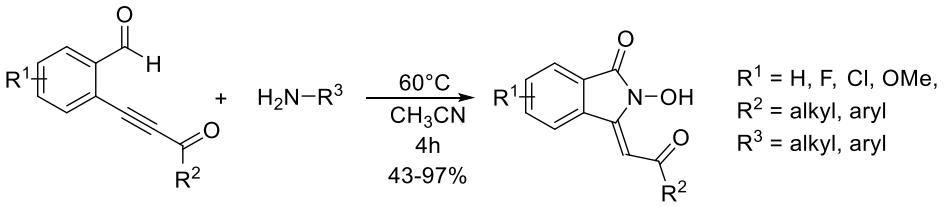
Royo *et al.*[96] reported that the reaction of aryl-aldehydes possessing *ortho*-substituted propiolate fragments undergoes reaction with hydroxylamine to form carbinolamine intermediates which experience a nucleophilic *aza*-conjugate addition reaction under ambient reaction conditions to form *N*-hydroxy-isoindolinones in moderate to excellent yields (Scheme 1.12).

Scheme 1.12



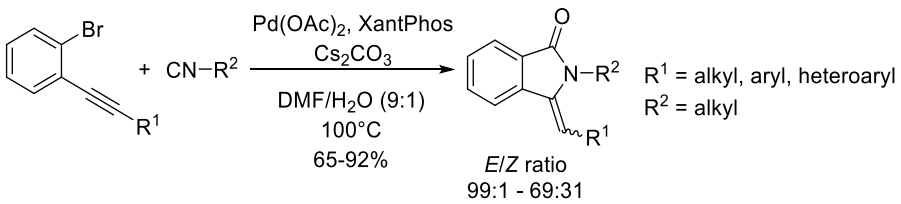
Cao *et al.*[89] reported a transition-metal-free reaction of *ortho* alkynyl-substituted arylaldehydes with primary amines followed by intramolecular *aza*-conjugate addition furnished a variety of functionalized isoindolin-1-one derivatives in good to excellent yields (Scheme 1.13). It is noteworthy that the choice of the primary amine was very crucial for the success of the reaction. Primary amines containing small groups generated isoindolinones whereas the bulky amines hindered the conjugate addition of the -NH group, thereby blocking the isoindolinone formation pathway.

Scheme 1.13



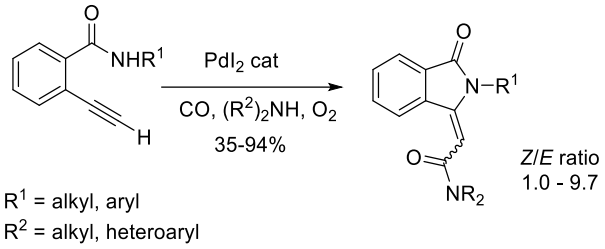
Pathare *et al.*[97] utilized isocyanide as useful amide surrogates for synthesizing isoindolinones in a one-pot tandem process using palladium-catalyst and Xantphos as the ligand (Scheme 1.14). The process involved the sequential insertion of the isocyanide group followed by hydrolysis for the in situ generation the amide group, which is followed by 5-*exo-dig* cycloisomerization leading to the formation of isoindolin-1-ones in excellent yields. The electrophilicity of alkyne was the driving force for the hydroamination, and a lack of electrophilic assistance led to the formation of corresponding amides instead of the isoindolin-1-ones.

Scheme 1.14



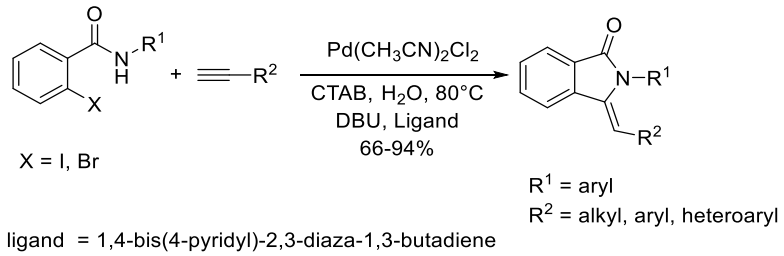
Gabriele and co workers[98] synthesized isoindolin-1-one derivatives *via* a tandem oxidative monoaminocarbonylation of *N*-alkyl-2-ethynylbenzamides (Scheme 1.15). The methodology used PdI_2/KI as a catalyst which was followed by *5-endo-dig* intramolecular conjugate addition *via N*-atom of the aryl amido group to the alkynyl group leading to the formation of the racemic mixture (*Z*/*E* ratio 1.0 - 9.7) of isoindolin-1-ones in good to excellent yield. However, when *N*-*tert*-butyl-2-ethynylbenzamide was subjected to the optimized reaction conditions, the steric effect exerted by the bulky substituent (*tert*-butyl group) resulted in the formation of only *E* isomeric isoindolin-1-one product.

Scheme 1.15



Sarkar *et al.*[99] reported a one-pot, environmentally friendly and straightforward methodology for the synthesis of (*Z*)-3-methyleneisoindolinones under aerobic conditions (Scheme 1.16).

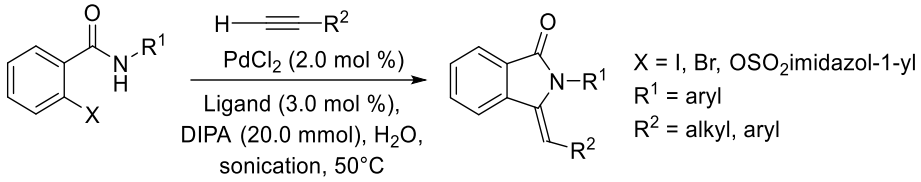
Scheme 1.16



Chatterjee *et al.*[100] reported a Cu-free cascade Sonogashira-cross-coupling reaction of aryl imidazol-1-yl-sulphonates with aryl/alkyl-substituted terminal alkynes which underwent cyclization reaction for the synthesis of isoindoline-1-ones, in a stereoselective manner (Scheme 1.17). The reactions were carried using water as the only

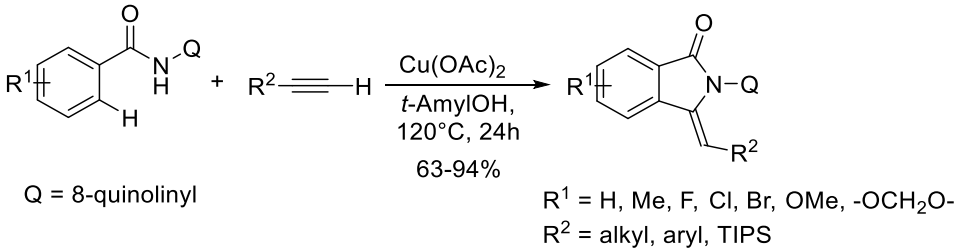
solvent under sonication. The methodology used a green reaction condition (sonication in aqueous medium) to give excellent products yield in a short duration.

Scheme 1.17



You *et al.*[101] took advantage of an 8-aminoquinoline residue for the bidentate-chelation assistance to establish a copper-mediated cascade oxidative carbon-carbon coupling followed by annulation of unactivated arenes and terminal alkynes resulting in the formation of the isoindolin-1-one scaffolds with a *Z*-geometry (Scheme 1.18). The methodology was highly economical, tolerated high functional group, displayed an exclusive chemo-, regio- and stereoselectivity. Additionally, the use of other ligands, base, and additive was also eliminated. In this transformation $Cu(OAc)_2$ plays a dual role as a promoter and the terminal oxidant.

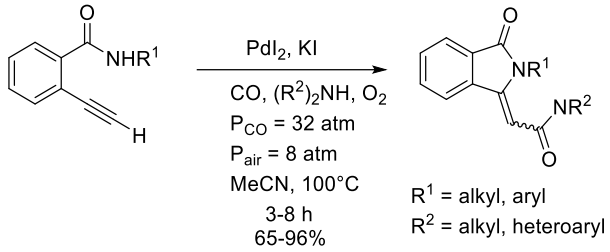
Scheme 1.18



Mancuso *et al.*[72] reported a divergent, multicomponent carbonylative approach, mediated by transition metal for the formation of isoindolin-1-ones (Scheme 1.19). The starting 2-ethynylbenzamides reacted with carbon monoxisde, a nucleophile (secondary amine), and oxygen in the presence of palladium catalyst. An oxidative monoaminocarbonylation occurred at the triple bond, which was followed by conjugate addition leading to *N*-cyclization and resulted in similar isoindolin-1-one products.

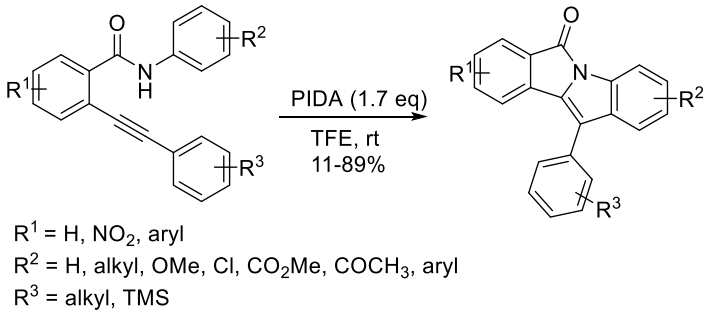
However, the methodology was not stereospecific and resulted in the formation of *Z*:*E* products, where *Z*-isomer was found to be a major product in most of the cases. It is to be noted that some reactions were exclusively selective towards the formation of the *Z* or *E*-isomeric product.

Scheme 1.19



Dev and Maurya[102] developed a metal-free pathway to construct tetracyclic fused isoindolinone derivatives under the hypervalent iodine (PIDA) mediated cascade oxidative cyclization of 2-(1-arylethynyl)benzamides *via* C–N and C–C bond formation at room temperature (Scheme 1.20). The methodology worked well with various alkynes, aromatic benzene ring as well as *N*-atom of the amide group. The electron-withdrawing groups favored the reaction, and a better yield was obtained as compared to electron-donating groups. Presence of EWGs does not support the reaction mostly due to the destabilization of nitrenium ion formed during the course of the reaction.

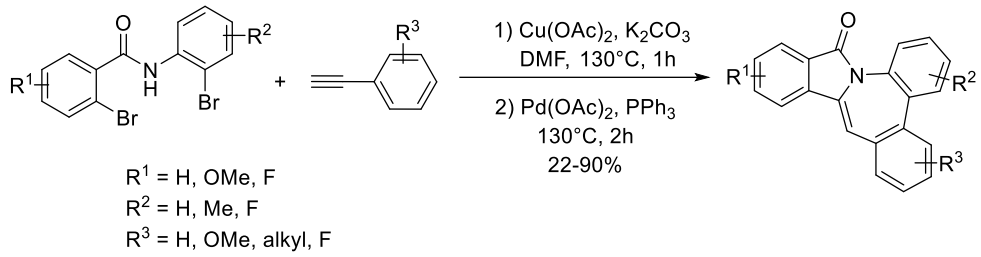
Scheme 1.20



Saini *et al.*[103] reported a tandem one-pot sequential copper and palladium-catalyzed synthesis of azepino-fused isoindolinones (Scheme 1.21). The initial copper-catalyzed Sonogashira coupling resulted in the formation of the *o*-alkynyl benzamides,

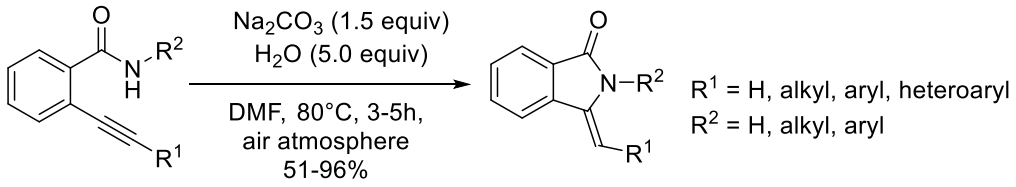
which was followed by the intramolecular hydroamination and palladium-catalyzed intramolecular direct arylation reaction to form the desired isoindolinone products.

Scheme 1.21



Tan *et al.*[104] reported a highly regio- and chemoselective reaction that involved the transition-metal free conversion of *o*-alkynyl benzamides to (*Z*)-3-alkylideneisoindolin-1-one derivatives (Scheme 1.22).

Scheme 1.22

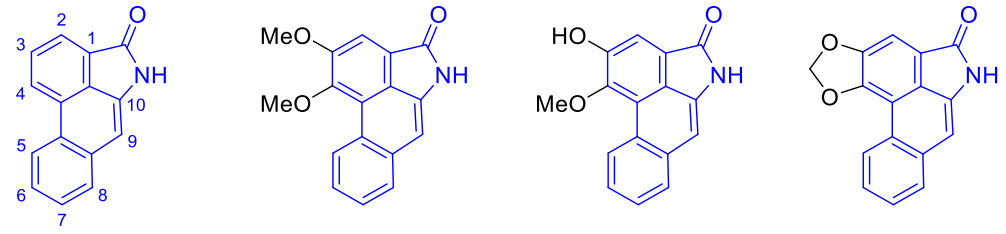


The above methodologies reported the intramolecular cyclization reactions/annulations, leading to the formation of the isoindolin-1-ones. However, in all these methodologies, none of the approaches involved the use of iodine as an efficient electrophile for the iodoaminocyclization of *o*-(alkynyl)benzamides for the formation of the isoindolinone derivatives. Therefore, after a thorough literature survey, it was concluded that the iodocyclization of the *o*-(alkynyl)benzamides remained an unexplored area for the synthesis of isoindolin-1-ones. After reviewing literature, we became interested in the synthesis of some nitrogen-containing heterocycles, especially, isoindolinones *via* electrophilic cyclization of the suitably substituted alkynes.

1.6 Aristolactams

The aristolactams are the compounds containing the phenanthrene core and comprise of a tetracyclic skeleton which is a common structural motif occurring in many classes of bioactive natural products.[105,106] Aristolactams occurring in many classes of bioactive natural products are found exclusively among the plants of the family *Aristolochiaceae*.[105] Several other plants, including Annonaceae, Monimimaceae, Menispermaceae, and Piperaceae are the significant source of aristolactams.[107] Traditionally, plants containing aristolactam-type alkaloids have been employed as the main ingredients for many remedy formulations in folk medicine practices.[106,108,109] Due to this, aristolactams and their derivatives have earned significant attention from both synthetic chemists and biochemists for both their structural novelty and wide range of biological properties. The structural complexities of aristolactams made them challenging synthetic targets.

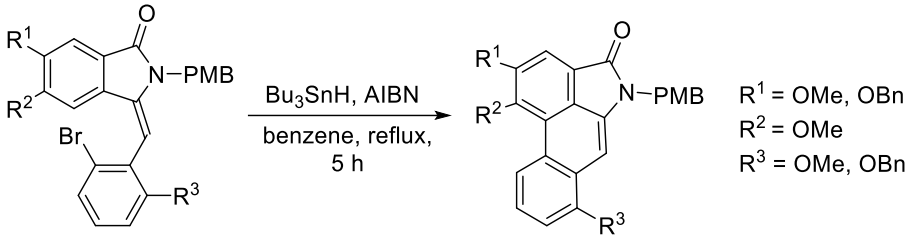
Figure 1.6 Naturally occurring/Biologically active Aristolactams[105]



Axel Couture has been the pioneer in the synthesis of Aristolactams *via* free radical cyclization reactions. Couture *et al.*[14] reported that subjecting suitably halogen substituted isoindolin-1-one compounds to the free radical cyclization lead to the formation of the corresponding phenanthrene ring containing aristolactams (Scheme 1.23). The radical cyclization was accomplished through dropwise mixing of a benzene solution of Bu_3SnH and AIBN to a refluxing benzene solution of the corresponding

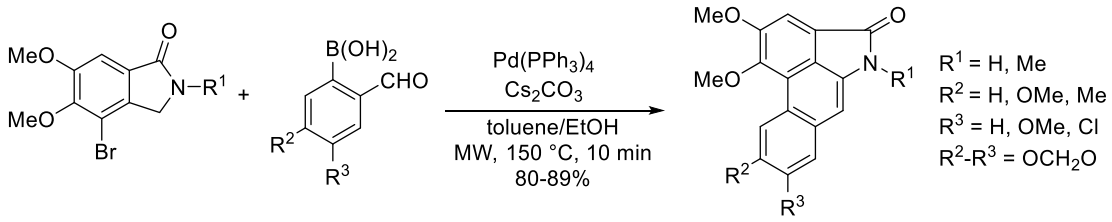
isoindolinone under argon atmosphere to deliver the fused aristolactams with reasonable yields.

Scheme 1.23



Kim *et al.*[110] reported the synthesis of phenanthrene lactams in a direct one-pot reaction. The reaction proceeded *via* a series of cascade reactions, Suzuki-Miyaura coupling of isoindolin-1-one with 2-formylphenylboronic acid, followed by the aldol condensation reaction constructed the core phenanthrene ring system (Scheme 1.24). Several aristolactams derivatives, including aristolactam BIII, aristolactam BII, aristolactam FI, and *N*-methyl piperolactam A were prepared in excellent yields.

Scheme 1.24



Upon a thorough literature search, it was observed that there is tremendous interest in the synthesis of isoindolinone scaffold. As shown in the literature survey above, a few papers reported base catalyzed/mediated intramolecular cyclization of *o*-alkynylbenzamides for the synthesis of isoindolinones. It was observed that due to the ambident nature of amide functionality the *N*-cyclization of amide group is sometimes challenging. Moreover, in many cases, mixtures of *E/Z* stereoisomers were obtained as a result of cyclization reaction of *o*-alkynylbenzamides. Also, the synthesis of isoindolinones has not been accomplished *via* iodocyclization of functionally substituted

alkynes. We thought that such methodology would be useful in expanding the chemical space with respect to this medicinally previleged scaffold. This research gap encouraged us to test the applicability of electrophilic iodocyclization of *o*-alkynyl benzamides for the synthesis of novel isoindolinone derivatives.

1.7 References

(1) Van Order, R. B.; Lindwall, H. G. *Chem. Rev.* **1942**, *30*, 69–96.

(2) Janosik, T.; Rannug, A.; Rannug, U.; Wahlström, N.; Slätt, J.; Bergman, J. *Chem. Rev.* **2018**, *118*, 9058–9128.

(3) Das, P.; Delost, M. D.; Qureshi, M. H.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2019**, *62*, 4265–4311.

(4) Katritzky, A. R.; Drum, C. A. *Compr. Heterocycl. Chem.* **2009**, 47–82.

(5) Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958–3043.

(6) Eftekhari-Sis, B.; Zirak, M. *Chem. Rev.* **2015**, *115*, 151–264.

(7) Chattopadhyay, S. K. *Green Synth. Approaches Biol. Relev. Heterocycles,* **2015**, 291–315.

(8) Eicher, T.; Hauptmann, S.; Speicher, A. **2003**, 2nd Edition, *Wiley-VC*H, Weinheim.

(9) Speck, K.; Magauer, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078.

(10) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1–35.

(11) Hein, J. *Clin Drug Investig.* **2011**, *31*, 655–664.

(12) Vitaku, M. E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257-10274.

(13) Ranjani, G.; Nagarajan, R. *Org. Lett.* **2019**, *21*, 675–678.

(14) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128–3132.

(15) Reddy, M. C.; Jeganmohan, M. *Chem. Sci.* **2017**, *8*, 4130–4135.

(16) Yao, T.; Guo, Z.; Liang, X.; Qi, L. *J. Org. Chem.* **2018**, *83*, 13370–13380.

(17) Islas-Jácome, A.; Cárdenas-Galindo, L.; Jerezano, A.; Tamariz, J.; González-Zamora, E.; Gámez-Montaño, R. *Synlett* **2012**, *23*, 2951–2956.

(18) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S.; Kurihara, T. *Tetrahedron*, **1996**, *52*, 14563–14576.

(19) Nozawa, Y.; Yamamoto, K.; Ito, M.; Sakai, N.; Mizoue, K.; Mizobe, F.; Hanada, K. *The Journal of Antibiotics*, **1997**, 50, 635-640.

(20) Thong, W. L.; Shin-ya, K.; Nishiyama, M.; Kuzuyama, T. *ACS Chem. Biol.* **2018**, *13*, 2615–2622.

(21) Kim, Y. H.; Kim, M.; Yoo, M.; Kim, J. E.; Lee, H. K.; Heo, J.-N.; Lee, C. O.; Yoo, M.; Jung, K.-Y.; Yun, C.-S.; *et al. Biochem. Biophys. Res. Commun.* **2018**, *503*, 882–887.

(22) Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361–365.

(23) Lippmann, W. U.S. Patent 4, 267, 189, 1981; *Chem. Abstr*. **1981**, 95, 61988m. US4267189 A.

(24) Laboratori Baldacci, S. P. A. Japanese Patent 5, 946, 268, 1984; *Chem. Abstr.* **1984**, 101, 54922.

(25) Zhuang, Z.; Kung, M.-P.; Mu; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166.

(26) Linden, M.; Hadler, D.; Hofmann, S. *Hum. Psychopharmacol. Clin. Exp.* **1997**, *12*, 445–452.

(27) Achinami, K.; Ashizawa, N.; Kobayasui, F. Japanese Patent 03, 133, 955, 1991; *Chem. Abstr*. **1991**, 115, 255977j.

(28) Bjore, A.; Bostrom, J.; Davidsson, O.; Emtenas, H.; Gran, U.; Iliefski, T.; Kajanus, J.; Olsson, R.; Sandberg, L.; Strandlund, G.; Sundell. J.; Kuan, Z.-Q. WO 2008/008022 A1; *Chem. Abstr*. **2008**, 148, 168577.

(29) Zhao, X. Z.; Maddali, K.; Marchand, C.; Pommier, Y.; Burke, T. R. *Bioorg. Med. Chem.* **2009**, *17*, 5318–5324.

(30) Hardcastle, I. R.; Liu, J.; Valeur, E.; Watson, A.; Ahmed, S. U.; Blackburn, T. J.; Bennaceur, K.; Clegg, W.; Drummond, C.; Endicott, J. A; *et al. J. Med. Chem.* **2011**, *54*, 1233–1243.

(31) Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyano Gongye* **1985**, 16, 543; *Chem. Abstr.* **1986**, *105*, 6378n.

(32) Suyavaran, A.; Ramamurthy, C.; Mareeswaran, R.; Shanthi, Y. V.; Selvakumar, J.; Mangalaraj, S.; Kumar, M. S.; Ramanathan, C. R.; Thirunavukkarasu, C. *Bioorg. Med. Chem.* **2015**, *23* (3), 488–498.

(33) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1992**, *35*, 4613–4627.

(34) Hussein, Z.; Mulford, D. J.; Bopp, B. A.; Granneman, G. R. *Br J Clin Pharmac* **1993**, *36*, 357–361.

(35) Carlson, J. N.; Haskew, R.; Wacker, J.; Maisonneuve, I. M.; Glick, S. D.; Jerussi, T. P. *Eur. J. Pharmacol.* **2001**, *415*, 181–189.

(36) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. *Chem. Pharm. Bull.* **2007**, *55*, 1682–1688.

(37) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517.

(38) Lee, J.-E.; Lee, I.-S.; Kim, K.-C.; Yoo, I.-D.; Yang, H.-M. *J. Microbiol. Biotechnol.* **2017**, *27*, 933–938.

(39) Egbertson, M. S.; Hartman, G. D.; Gould, R. J.; Bednar, B.; Bednar, R. A.; Cook, J. J.; Gaul, S. L.; Holahan, M. A.; Libby, L. A.; Lynch, J. J., Jr.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Vassallo, L. M. *Bioorg. Med. Chem. Lett.* **1996**, 6, 2519.

(40) The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research

Group. *JAMA J. Am. Med. Assoc.* **2002**, *288* (23), 2981–2997.

(41) Uemura, S.; Fujita, T.; Sakaguchi, Y.; Kumamoto, E. *Biochem. Biophys. Res. Commun.* **2012**, *418*, 695–700.

(42) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060–2062.

(43) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003–2006.

(44) Armoiry, X.; Aulagner, G.; Facon, T. *J. Clin. Pharm. Ther.* **2008**, *33*, 219–226.

(45) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; *et al. Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502.

(46) Stuk, T. L.; Assink, B. K.; Bates, R. C.; Erdman, D. T.; Fedij, V.; Jennings, S. M.; Lassig, J. A.; Smith, R. J.; Smith, T. L. *Org. Process Res. Dev.* **2003**, *7*, 851–855.

(47) Linden, M.; Hadler, D.; Hofmann, S. *Hum. Psychopharmacol. Clin. Exp.* **1997**, *12*, 445–452.

(48) Tian, Y.; Wei, J.; Wang, M.; Li, G.; Xu, F. *Tetrahedron Lett.* **2018**, *59*, 1866–1870.

(49) Park, J. S.; Moon, S. C.; Baik, K. U.; Cho, J. Y.; Yoo, E. S.; Byun, Y. S.; Park, M. H. *Arch. Pharm. Res.* **2002**, *25*, 137–142.

(50) Lawrence, N. J.; Liddle, J.; Bushell, S. M.; Jackson, D. A. *J. Org. Chem* **2002**, *67*, 457–464.

(51) J.J. Baldwin, D.A. Claremon, C.M. Tice, S. Cacatian, L.H. Dillard, A.V.Ishchenko, J. Yuan, Z. Xu, G. Mcgeehan, W. Zhao, *et al.*, WO2008156816, **2008**.

(52) A. Bjoere, J. Bostroem, O. Davidsson, H. Emtenaes, H. Gran, T. Iliefski, J.Kajanus, R. Olsson , L. Sandberg , G. Strandlund, *et al*., WO2008008022, **2008**.

(53) Larock, R. C. In *Acetylene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA:

Weinheim, FRG, 2005; Vol. 106, pp 51–99.

(54) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980.

(55) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141–1147.

(56) Mehta, S.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 10938–10944.

(57) Wirth, T. *Angew. Chemie Int. Ed.* **2005**, *44*, 3656–3665.

(58) Aggarwal, T.; Kumar, S.; Verma, A. K. *Org. Biomol. Chem.* **2016**, *14*, 7639–7653.

(59) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, No. 18, 734.

(60) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Commun.* **1976**, No. 18, 736.

(61) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(62) Miyaura, N.; Yamada, K.; Suzuki, A. *OPergamon Press Ltd*, **1979**.

(63) Heck, R. F. In *Org. React.*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1982; pp 345–390.

(64) Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871.

(65) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

(66) Craig, N. C.; Chen, A.; Suh, K. H.; Klee, S.; Mellau, G. C.; Winnewisser, B. P.; Winnewisser, M. *J. Am. Chem. Soc.* **1997**, *119*, 4789–4790.

(67) Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 535–540.

(68) Couture, A.; Deniau, E.; Lamblin, M.; Lorion, M.; Grandclaudon, P. *Synthesis (Stuttg).* **2007**, *2007*, 1434–1437.

(69) Suneja, A.; Bisai, V.; Singh, V. K. *J. Org. Chem.* **2016**, *81*, 4779–4788.

(70) Cao, H.; McNamee, L.; Alper, H. *Org. Lett.* **2008**, *10*, 5281–5284.

(71) Chatterjee, N.; Sarkar, S.; Pal, R.; Sen, A. K. *Tetrahedron Lett.* **2013**, *54*, 3748–3751.

(72) Mancuso, R.; Ziccarelli, I.; Armentano, D.; Marino, N.; Giofrè, S. V.; Gabriele, B.

J. Org. Chem. **2014**, *79*, 3506–3518.

(73) Ling, F.; Li, Z.; Zheng, C.; Liu, X.; Ma, C. *J. Am. Chem. Soc.* **2014**, *136*, 10914–10917.

(74) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812.

(75) Sun, L. X.; Zeng, T.; Jiang, D.; Dai, L.-Y.; Li, C.-J. *Can. J. Chem.* **2012**, *90*, 92–99.

(76) Zhang, L.; Zhang, Y.; Wang, X.; Shen, J. *Molecules* **2013**, *18*, 654–665.

(77) Sarkar, S.; Chatterjee, N.; Roy, M.; Pal, R.; Sarkar, S.; Sen, A. K. *RSC Adv.* **2014**, *4*, 7024–7029.

(78) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884–2887.

(79) Mancuso, R.; Pomelli, C. S.; Raut, D. S.; Marino, N.; Giofrè, S. V.; Romeo, R.; Sartini, S.; Chiappe, C.; Gabriele, B. *ChemistrySelect* **2017**, *2*, 894–899.

(80) Hong, S. Y.; Jeong, J.; Chang, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 2408–2412.

(81) Kanazawa, C.; Terada, M. *Chem. Asian J.* **2009**, *4*, 1668–1672.

(82) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. P. *Adv. Synth. Catal.* **2010**, *352*, 136–142.

(83) Bubar, A.; Estey, P.; Lawson, M.; Eisler, S. *J. Org. Chem.* **2012**, *77*, 1572–1578.

(84) Li, L.; Janesko, B. G. *J. Org. Chem.* **2016**, *81*, 10802–10808.

(85) Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, *55*, 13193–13200.

(86) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587.

(87) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803–2805.

(88) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem. Int. Ed.* **2006**,

45, 944–947.

(89) Cao, Z.; Zhu, H.; Meng, X.; Guan, J.; Zhang, Q.; Tian, L.; Sun, X.; Chen, G.; You, J. *Chem. Eur. J.* **2016**, *22*, 16979–16985.

(90) Rubio-Marqués, P.; Rivero-Crespo, M. A.; Leyva-Pérez, A.; Corma, A. *J. Am. Chem. Soc.* **2015**, *137*, 11832–11837.

(91) Li, L.; Li, L.; Wang, M.; Wang, M.; Zhang, X.; Zhang, X.; Jiang, Y.; Jiang, Y. *Synlett* **2009**, 1–4.

(92) Zhou, Y.; Zhai, Y.; Li, J.; Ye, D.; Jiang, H.; Liu, H. *Green Chem.* **2010**, *12*, 1397.

(93) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, *352*, 136–142.

(94) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508–5511.

(95) Hu, J.; Liu, L.; Wang, X.; Hu, Y.; Yang, S.; Liang, Y. *Green Sustain. Chem.* **2011**, *01*, 165–169.

(96) Royo, S.; Chapman, R. S. L.; Sim, A. M.; Peacock, L. R.; Bull, S. D. *Org. Lett.* **2016**, *18*, 1146–1149.

(97) Pathare, R. S.; Sharma, S.; Elagandhula, S.; Saini, V.; Sawant, D. M.; Yadav, M.; Sharon, A.; Khan, S.; Pardasani, R. T. *Eur. J. Org. Chem.* **2016**, *2016*, 5579–5587.

(98) Gabriele, B.; Mancuso, R.; Ziccarelli, I.; Salerno, G. *Tetrahedron Lett.* **2012**, *53*, 6694–6696.

(99) Sarkar, S.; Dutta, S.; Dey, R.; Naskar, S. *Tetrahedron Lett.* **2012**, *53*, 6789–6792.

(100) Chatterjee, N.; Sarkar, S.; Pal, R.; Sen, A. K. *Tetrahedron Lett.* **2013**, *54*, 3748–3751.

(101) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884–2887.

(102) Dev, K.; Maurya, R. F *RSC Adv.* **2015**, *5*, 13102–13106.

(103) Saini, H. K.; Nandwana, N. K.; Dhiman, S.; Rangan, K.; Kumar, A. *European J.*

Org. Chem. **2017**, *2017*, 7277–7282.

(104) Tan, J.; Tong, Y.; Chen, Z. *ChemistrySelect* **2018**, *3*, 3886–3890.

(105) Kumar, V.; Poonam; Prasad, A. K.; Parmar, V. S. *Nat. Prod. Rep.* **2003**, *20*, 565.

(106) Choi, Y. L.; Kim, J. K.; Choi, S.-U.; Min, Y.-K.; Bae, M.-A.; Kim, B. T.; Heo, J.-N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036–3040.

(107) Mix, D. B.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 657–666.

(108) Iqbal, E.; Lim, L. B. L.; Salim, K. A.; Faizi, S.; Ahmed, A.; Mohamed, A. J. *J. King Saud Univ.-Sci.* **2018**, *30*, 41–48.

(109) Zhang, H. C.; Liu, R.; An, Z. peng; Li, H.; Zhang, R.; Zhou, F. *Biochem. Syst. Ecol.* **2016**, *65*, 198–201.

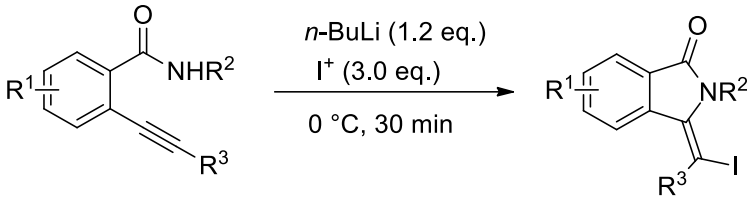
(110) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J. *Org. Lett.* **2008**, *10*, 3543–3546.

CHAPTER 2

Regio- and Stereoselective Synthesis of Isoindolin-1-ones through BuLi-mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides

Based on a paper published in the *Journal of Organic Chemistry*[33]

Abstract



R^1 = H, OMe; R^2 = H, R^3 = H, alkyl, alkenyl, aryl, *etc.*
$R^2 \neq$ Me, Ph

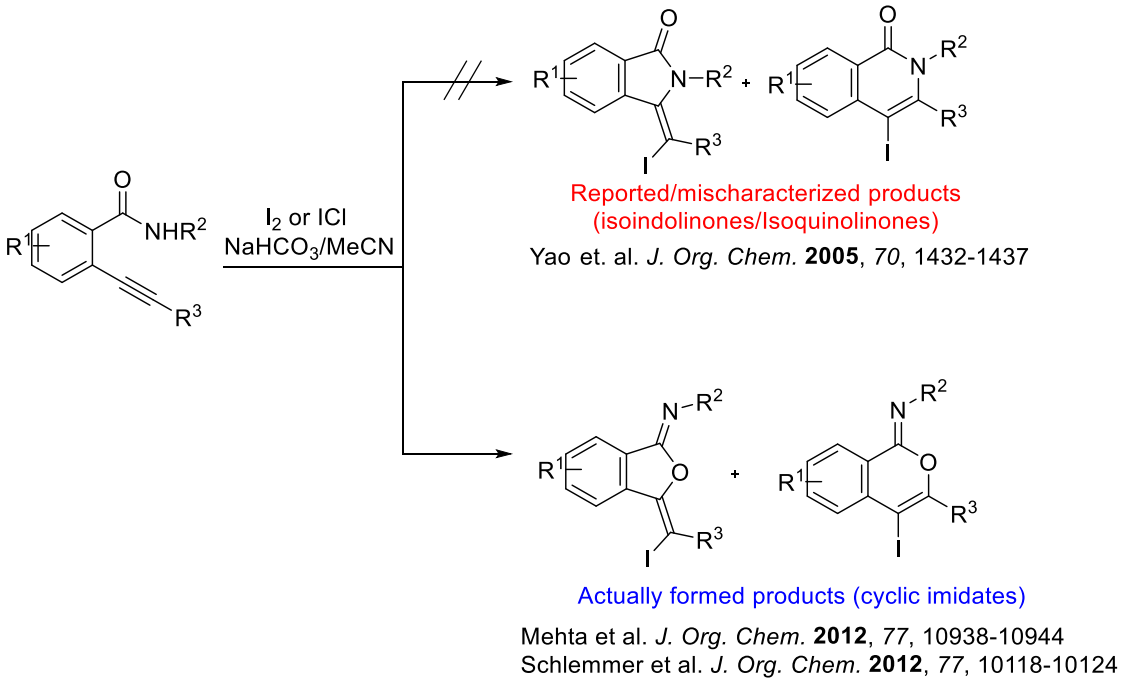
A simple and straightforward iodocyclization methodology for the synthesis of isoindolin-1-ones has been reported. Exclusive *N*-cyclization of the amide functional group, an ambident nucleophile, was accomplished for the cyclization of 2-(1-alkynyl)benzamides using *n*-BuLi/I_2 (or ICl) leading to the formation of corresponding isoindolinones. The methodology worked with primary amide and afforded the desired isoindolinones in yields of 38-94%. Interestingly, the isolated products exhibited a *Z*-stereochemistry across the exocyclic C=C double bond in the resulting products. The reaction mechanism involving the formation of either a vinylic anion or an intimate ion pair was also proposed.

2.1 Introduction

Electrophilic cyclization, particularly the iodocyclization of alkynes has emerged as a useful methodology for synthesizing important compounds.[1-3] The use of iodine as electrophile has several practical advantages including the fact that the resulting products contain iodine atom, which provides an easy handle for various metal-catalyzed coupling reactions.[4] This interesting methodology was studied by several research groups and have been used to make a variety of interesting heterocyclic compounds in the past.[5,6] Moreover,

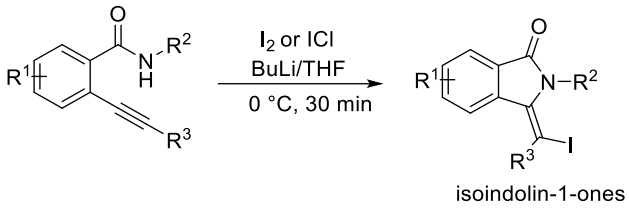
efforts have been made previously by Yao *et al.* for the iodocyclization of *o*-(1-alkynyl)benzamides for the synthesis of isoindolin-1-ones.[7] However, later it was found that the methodology resulted in the cyclization *via* the *O*-atom (rather than *N*-atom) of the amide group leading to the formation of the cyclic imidates instead of isoindolin-1-ones, which was later on confirmed and corrected by Mehta *et. al.* and others (Scheme 2.1).[8,9]

Scheme 2.1 Previous work[7-9]

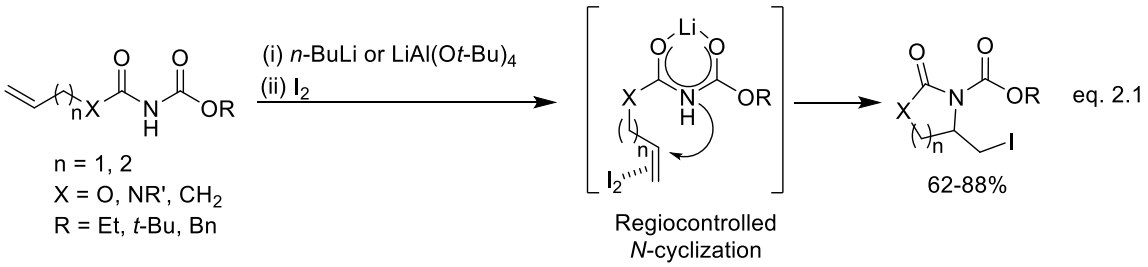


Furthermore, after a thorough literature survey it was found that the synthesis of isoindolin-1-ones has not been accomplished *via* iodocyclization, probably due to the challenges posed by the ambident nucleophilic nature of the amide functionality (*N*- Vs. *O*-cyclization). Nevertheless, such methodology would lead to diverse isoindolin-1-ones with unique substitution pattern that may not be accessible by the existing synthetic routes. Continuing with the interest in developing new methodologies for heterocyclic synthesis, it was encouraging to tune the reactivity of 2-(1-alkynyl)benzamides to achieve a regioselective synthesis of isoindolinones, and the findings have been reported in this chapter.

Scheme 2.2 Present work

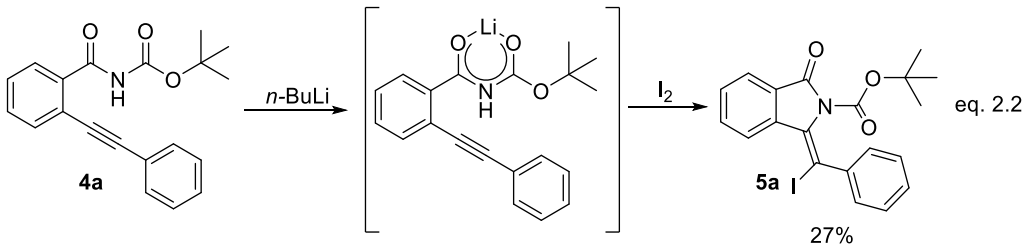


Amide group (–$CONH_2$) is a well-known ambident nucleophile and is known to undergo *N* vs *O* cyclization in alkyne annulation reactions,[10,11] thus, for successfully tuning the reactivity of the nucleophilic site, the choice of the suitable reagents has been important.[12] The efforts were directed towards the development of a suitable methodology employing iodonium ion (I^+) as an efficient electrophile for the regiocontrolled *N*-cyclization of 2-(1-alkynyl)benzamides to furnish isoindolin-1-ones. During a thorough literature survey, an interesting methodology developed by Fujita *et al.* was found, that involved a regiocontrolled iodoaminocyclization of the protected amide group at the activated double bond (eq 2.1).[13] A rationale of *N*- Vs *O*-cyclization of unsaturated amides based on HSAB theory was also presented by the authors. Furthermore, the authors achieved regiocontrol (*N*-cyclization) in the iodocyclization of allyl or homoallyl carbamates, *etc*. through the use of suitable base/additives, *n*-BuLi/LiAl(O*t*-Bu)$_4$ (eq. 2.1). The authors postulated that the reaction proceeded through the formation of a metal imino alkolate intermediate and explained the achieved regiocontrol (*N*-cyclization over *O*-cyclization) through the increased reactivity of the amide nitrogen atom.



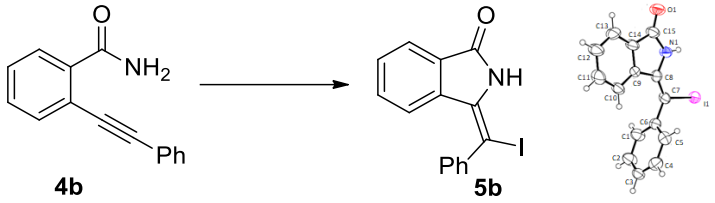
2.2 Results and Discussion

Inspired by the methodology developed by Fujita *et al.*, a similar intramolecular iodoaminocyclization of 2-(1-alkynyl)benzamide derivatives was proposed. Initially, reactions were started (eq. 2.2) with the cyclization of *tert*-butyl(2-(phenylethynyl)benzoyl)carbamate (**4a**), which involved the (-CO-NH-CO-) group for the formation of metal imino alkolate intermediate with metallic base which makes the nitrogen atom more nucleophilic, leading to the formation of *N*-cyclized product. Although the reaction was successful, however, the product formed (**5a**) was not stable enough, and it resulted in poor yield (27%). The formation of unstable product and low reaction yield was attributed to the presence of the labile protecting group (*N*-Boc) and/or the sterically hindered substrate, and it was decided to use the unprotected amide group instead.



2-(1-phenylethynyl)benzamide (**4b**) was taken as model substrate to determine optimized conditions/reagents for iodocyclization reaction, using I_2/ICl as the iodine source (Table 2.1). Surprisingly, the use of *n*-BuLi as a base worked, and the cyclized product **5b** was isolated with a yield of 67% at 0 °C in 30 min (entry 1). The cyclized product was thoroughly characterized using spectroscopy (IR, ^{1}H-NMR, ^{13}C-NMR), mass spectrometry (HRMS) as well as single-crystal X-ray crystallography (see ORTEP diagram in Table 2.1).

Table 2.1 Optimization Studies: Iodocyclization of 2-Phenylethynyl-benzamide[a]



S.No.	Base	Solvent	temp (°C)	time (min)	I^+	Isolated Yield (%)
1.	***n*-BuLi**	**THF**	**0**	**30**	**I_2**	**67** [b]
2.	*n*-BuLi	THF	-78	30	I_2	64[c]
3.	*n*-BuLi	THF	0	60	I_2	67
4.	*n*-BuLi	THF	0	180	I_2	62
5.	*n*-BuLi	THF	0	30	ICl	63
6.	*n*-BuLi	THF	0	30	Br_2	- [d]
7.	LDA	THF	-78	30	I_2	< 5[d]
8.	LDA	THF	-10	30	I_2	18
9.	DBU	THF	-10	30	I_2	nr
10.	DBU	THF	0	30	I_2	nr
11.	DBU	THF	25	30	I_2	30[e]
12.	DABCO	THF	0	30	I_2	nr
13.	DABCO	EtOH	0	30	I_2	nr
14.	$KOBu^t$	THF	0	30	I_2	16
15.	NaH	THF	0	30	I_2	33
16.	NaOH	THF	0	30	I_2	18
17.	NaOH	EtOH:H_2O (1:1)	25	30	I_2	42
18.	KOH	THF	0	30	I_2	15
19.	KOH	EtOH:H_2O (1:1)	25	30	I_2	38
20.	Na_2CO_3	THF	0	30	I_2	-[d]
21.	$NaHCO_3$	THF	0	30	I_2	-[d]
22.	K_2CO_3	THF	0	30	I_2	-[d]

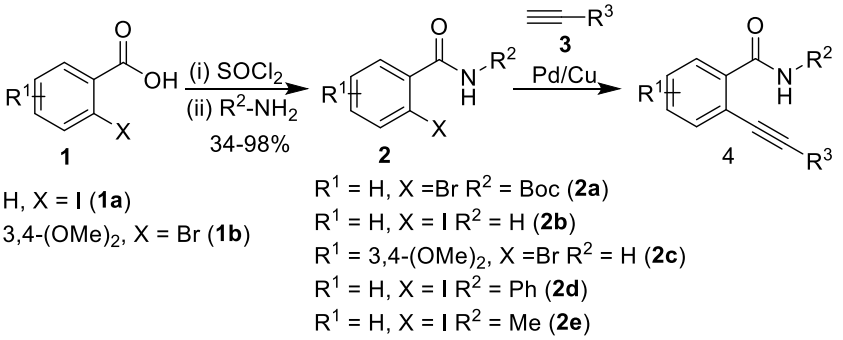
[a]All reactions were run using 0.25 mmol of 2-(1-alkynyl)benzamide in 2 mL THF and 1.2 equiv of *n*-BuLi (1.6 M in hexane), stirred for 10 min, followed by the dropwise addition (approx.1 min) of 3.0 equiv I_2/ICl

in 1 mL THF at 0 °C for 20 min in argon atmosphere (total reaction time 30 min). [b]similar yield was obtained when the reaction was performed at 1.1 mmol (250 mg) scale. [c]formation of another geometrical isomer (*E*) was also observed (*E*/*Z* = 1:9). [d]complex reaction mixture was obtained. [e]mixture of geometrical isomers (*E*/*Z* = 1:5). nr = no reaction.

It was notable that the reaction at a lower temperature (-78 ^{o}C) resulted in low reaction yield along with the mixture of stereoisomers (*E:Z* 1:9%, entry 2), where the *Z*-geometric compound was formed as the major product. There was no change in the product yield when the reaction was run for 60 min (entry 3). However, the longer reaction times (180 min) resulted in the lower yield (entry 4) of the product, probably, due to some side reactions. The reaction also worked with ICl as the source of I^+ ions; however, the yield was slightly lower (63%) in this case (entry 5). It was attempted to improve the reaction yield through the use of other organic bases (LDA, DBU, DABCO, KOBu^t; entries 7-14) as well as inorganic bases (NaH, NaOH, KOH), *etc*. (entries 15-19) and other reaction parameters (reaction time, temperature) and the details are summarized in the optimization Table 2.1. Moreover, reactions with carbonate bases, *e.g.*, Na_2CO_3, $NaHCO_3$, K_2CO_3, *etc*. (entries 20-22) did not yield the desired products (either no reaction occurred or complex reaction mixtures were obtained). Overall, the yield could not be improved for this substrate. Therefore, it was decided to proceed further and to study the scope of the reaction using the same reaction conditions. Thus the optimized reaction conditions for the iodocyclization were 2-(1-alkynyl)benzamide (1.0 eq), *n*-BuLi (1.2 eq), I_2/ICl (3.0 eq) in THF at 0 °C for 30 min under argon atmosphere. It was noted that the cyclized product **5b** was found to possess *Z*-geometrical configuration across the exocyclic C=C bond (See ORTEP diagram). Having optimized the reaction conditions, the scope of the developed iodocyclization was investigated.

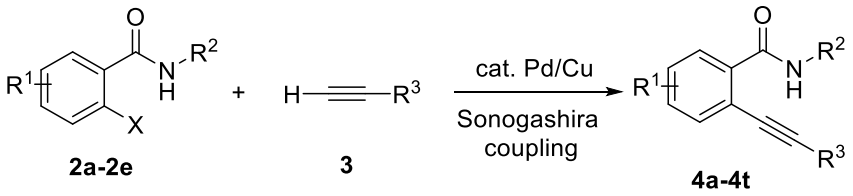
The required alkyne substrates were conveniently prepared from the commercially available starting materials using the following approach (Scheme 2.3).

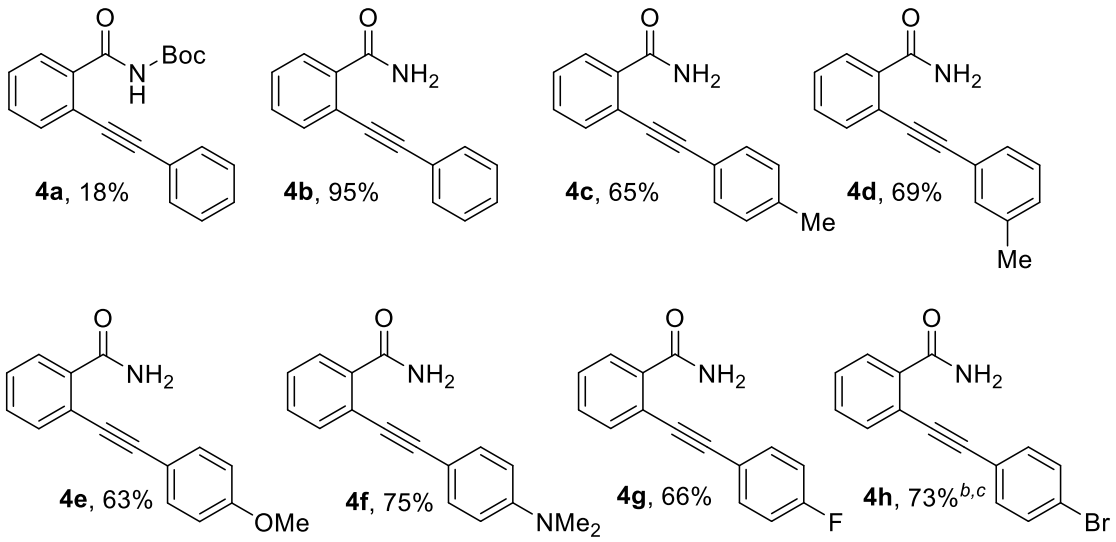
Scheme 2.3 Two-step Strategy for preparing 2-(1-alkynyl)benzamides

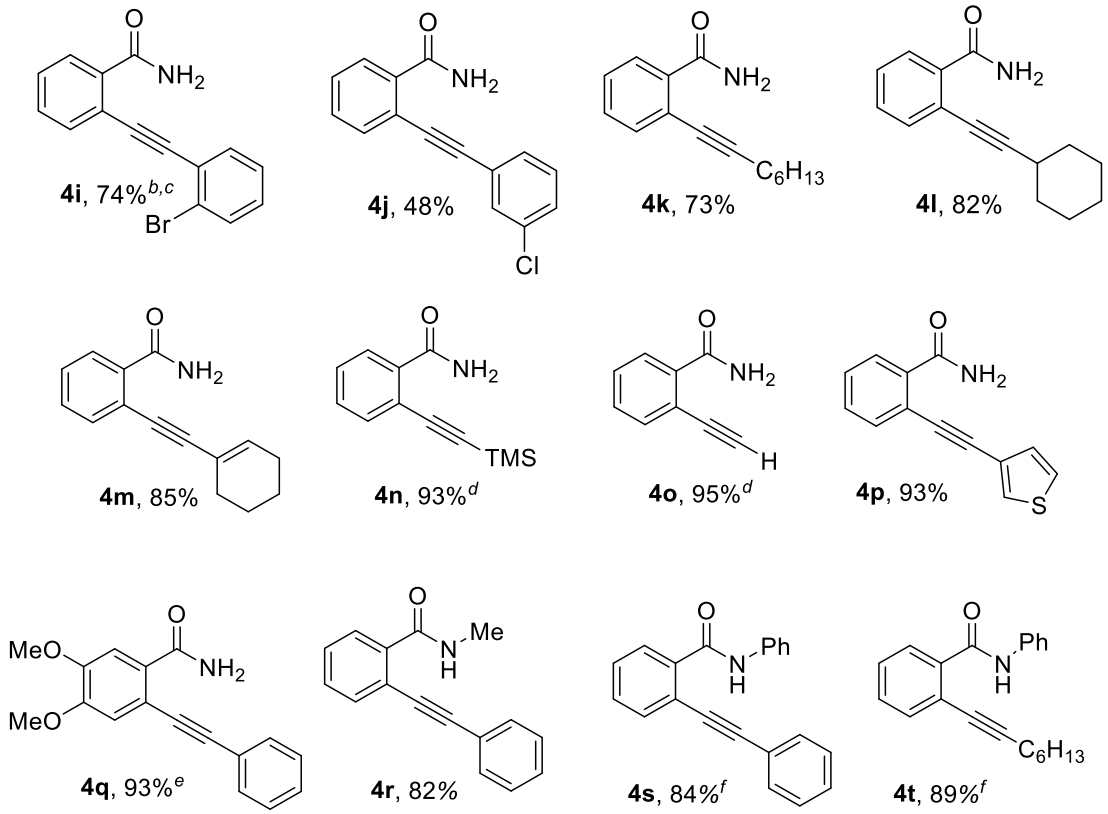


The starting *o*-halobenzamides required for the Sonogashira reaction were prepared by the reaction of commercially available *o*-halobenzoic acids (**1a**−**1b**) with thionyl chloride, followed by the reaction with ammonia/primary amine. The palladium/copper-catalyzed Sonogashira cross coupling[14] of the *o*-halobenzamides **2a-2e** with corresponding terminal alkynes **3** resulted in the formation of alkynes **4a-4t** in yields ranging from 48-95% and results are reported in Table 2.2.

Table 2.2 Preparation of 2-(1-alkynyl)benzamides[a]



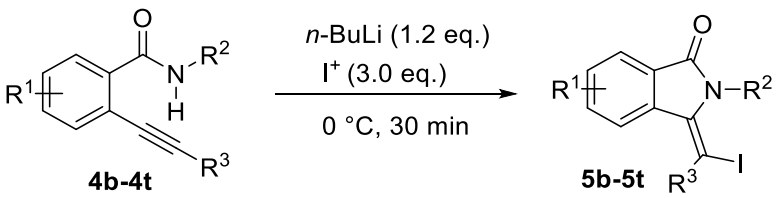


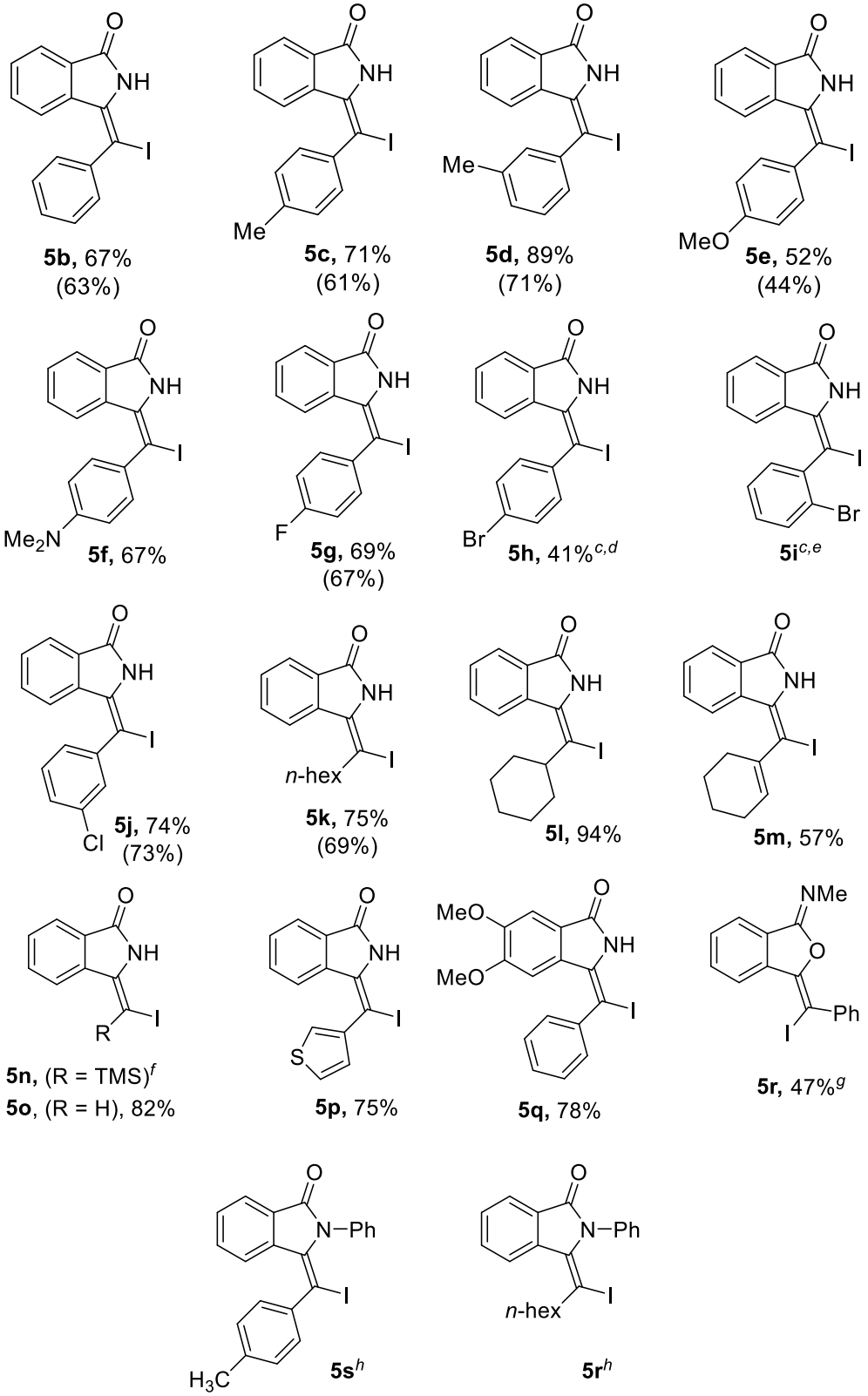


[a]All reactions were performed using 0.25 mmol of 2-halo benzamide and 1.2 equiv of alkyne, $PdCl_2(PPh_3)_2$ (4 mol%), CuI (2 mol%), 4 equiv of TEA in DMF for 2 h at 70 °C.[b]THF: DIPA (50:1) was used as a solvent. [c]alkyne (in THF) was added over 30 min. [d]TMS deprotection was carried out to obtain the corresponding terminal alkyne **4o** [e] $PdCl_2(PPh_3)_2$ (15 mol%) was used. [f]DCE was used as a solvent. [f]reaction temperature 80 °C.

The substrate scope of the iodocyclization reaction was investigated using the optimized reaction conditions, and a variety of 2-(1-alkynyl)benzamides were transformed into the corresponding isoindolin-1-ones in good yields. The results are reported in Table 2.3.

Table 2.3 BuLi-mediated Iodocyclization of 2-(1-Alkynyl)benzamides[a, b]





[a]All reactions were run using 0.25 mmol of 2-(1-alkynyl)benzamide in 2 mL of THF and 1.2 equiv of *n*-BuLi (1.6 M in hexane), stirred for 10 min, followed by the dropwise addition (approx 1 min) of 3.0 equiv I_2/ICl in 1 mL of THF, at 0 °C for 20 min in argon atmosphere (total reaction time 30 min). [b]The yields in parentheses correspond to the reactions that were performed using 3.0 equiv of ICl as the electrophile. [c]1.0 equiv of *n*-BuLi (1.6 M in hexane) was used. [d]Corresponding debrominated product was also formed (yield: 9%). [e]Only the corresponding debrominated product was isolated (yield: 38%). [f]Corresponding desilylated

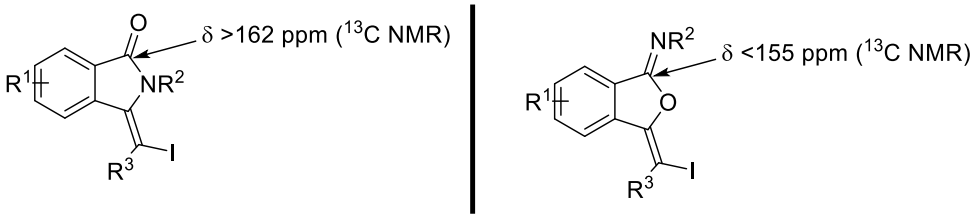
product was isolated (yield: 75%). [g]O-cyclized product was formed (yield: 47%). [h]Complex reaction mixture was obtained.

The presence of the methyl group at the *para*-position (**5c**) led to a slight increase in the yield than the parent system. Presence of an electron-donating methyl group (-CH_3) at the *meta*-position generated the cyclized product **5d** in good yields 89 & 71%, respectively. However, the presence of a more electron-donating *para*-methoxy group (**5e**) showed a drop in the product yield. When –NMe_2 group is present at *para*-position, a satisfactory yield of **5f** was obtained. The substrate **4g** with electron-withdrawing fluorine atom at the 4-position of the aromatic ring also provided desired product (**5g**) in comparable yield to that of the parent system. While the 4-bromophenyl substrate **4h** cyclized to give a lower product yield (**5h**) accompanied with the formation of the debrominated product (**5b**) whereas the substrate **4i** with the 2-bromophenyl group, only the debrominated product (**5b**, 38%) was isolated. An electron-withdrawing chloro-group in **4j** at *meta*-position of distal phenyl ring resulted in the corresponding cyclization product (**5j**) in good yields. The substrate **4k** with alkyl (*n*-hexyl) group at the distal end of the alkyne was cyclized to give good yield (**5k**). Even a cyclohexyl group containing substrate **4l** was successfully cyclized with an excellent yield of **5l**. Cyclization of alkyne substrate **4m** with unsaturation (cyclohexenyl group) resulted in the formation of the product (**5m**) in moderate yield. The cyclization of the substrate **4n** with TMS group resulted in the formation of only desilylated product (**5b**) in 75% yield. The reaction worked well for the terminal alkyne **4o**, and the expected product (**5o**) was isolated in 82% yield. The methodology also worked for the substrate with a heterocyclic moiety (3-thienyl) **4p** and resulted in good product yield (**5p**). The substrates containing electron-donating methoxy groups at the benzamide ring in substrate **4q** was successfully converted to the desired product (**5q**) in 78% yield.

The cyclization of secondary amides (**4r-4t**) was also attempted. The *N*-Me substituted amide **4r** underwent cyclization; however, the product was found to be the corresponding imidate (*O*-cyclized product) instead of the expected isoindolin-1-one. Furthermore, the cyclization of *N*-phenyl substituted amides **4s** and **4t** resulted in the formation of complex mixtures that could not be resolved. These results of cyclization with secondary amides indicated that the steric hindrance due to the methyl or phenyl substituent on the nitrogen atom of the amide group presumably disfavored the desired *N*-cyclization under these reaction conditions.

All the amides, Sonogashira products, as well as cyclized products, were thoroughly characterized using the spectroscopic techniques (IR, ^{1}H-NMR, and ^{13}C-NMR) and Mass Spectrometry (HRMS). The stereochemistry of the cyclized products was assigned by correlating the spectroscopic data with that of **5b**. Notably, all the cyclized products were confirmed to be arising from the *N*-cyclization reactions, and this was also confirmed by the presence of the diagnostic signals in the ^{13}C-NMR spectra of these compounds (Figure 2.1).

Figure 2.1 ^{13}C NMR data for the identification of *N* vs *O*-cyclized products

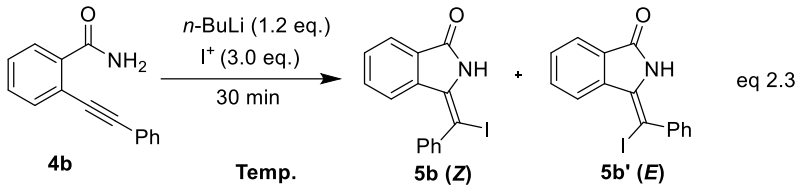


The results of the presented methodology were quite interesting with respect to the exclusive *N*-cyclization, selective *5-exo-dig* cyclization, and especially the observed stereochemistry of the cyclized products. As mentioned above, the cyclization reaction yields the cyclized products with *Z*-stereochemistry, and the products with *E*-configuration were not isolated except for one case involving the model substrate. During

the attempt to rationalize the observations from a mechanistic perspective, the possibility of the formation of a vinylic cation or an alkyne iodonium intermediate for these cyclization reactions were considered. Both of these species have been reported in the literature as possible intermediates in iodocyclization reactions.[15] The possibility that the reaction might follow an anionic pathway for the cyclization was also considered.[16-18] Moreover, in recent literature, an article was published, in which while using metallaaromatic compounds, Wang *et al.* have captured and characterized the key intermediates in the base-mediated alkyne iodocyclization reactions.[19] With the help of X-ray structural evidence of an isolated intermediate, it was claimed that the involvement of an intimate ion pair intermediate is likely instead of the generally accepted iodonium ion. Considering the possibility of the formation of an intimate ion pair vs an alkyne iodonium intermediate for the reported cyclization reaction, a few simple experiments were also performed/repeated to shed some more information on the possible mechanism of the cyclization reaction. The observations were:

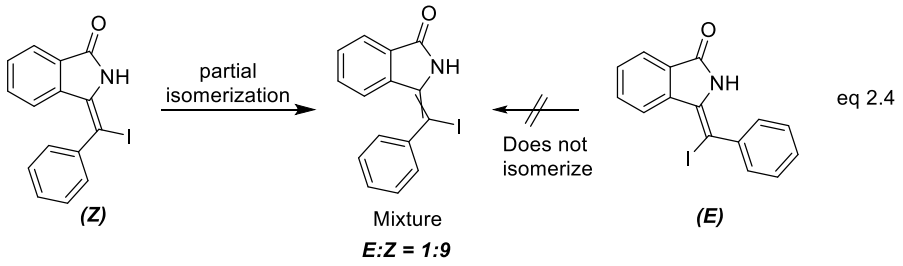
a) At 0 °C only the *Z*-isomer was obtained.

b) At a lower temperature, the *E* isomer was also formed as a minor product (*E*/*Z* ratio 1:9). It must be noted that this happened only in the case of the model system. In other cases, only one isomer (*Z*) was formed exclusively (eq 2.3).



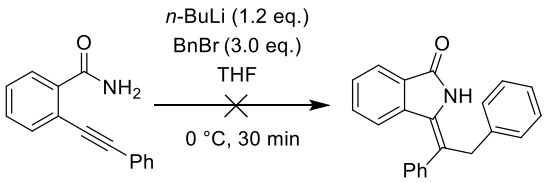
c) The *Z* isomer partially isomerized at to *E*-isomer (*E*:*Z* 1:9) over time, whereas the pure *E*-isomer did not isomerize to the *Z*-isomer. It indicated that *Z*-isomer was formed directly as a kinetically favorable product of the iodocyclization reaction,

and the possibility of the initial formation of *E*-isomer followed by the isomerization to the *Z*-isomer may be ruled out (eq 2.4).



eq 2.4

d) Assuming the possibility of the involvement of the vinylic anion intermediate, it was attempted to quench the vinylic anion using benzyl bromide (instead of I_2) as an electrophile. However, the reaction resulted in a complex mixture, and the desired product could not be isolated (eq 2.5).

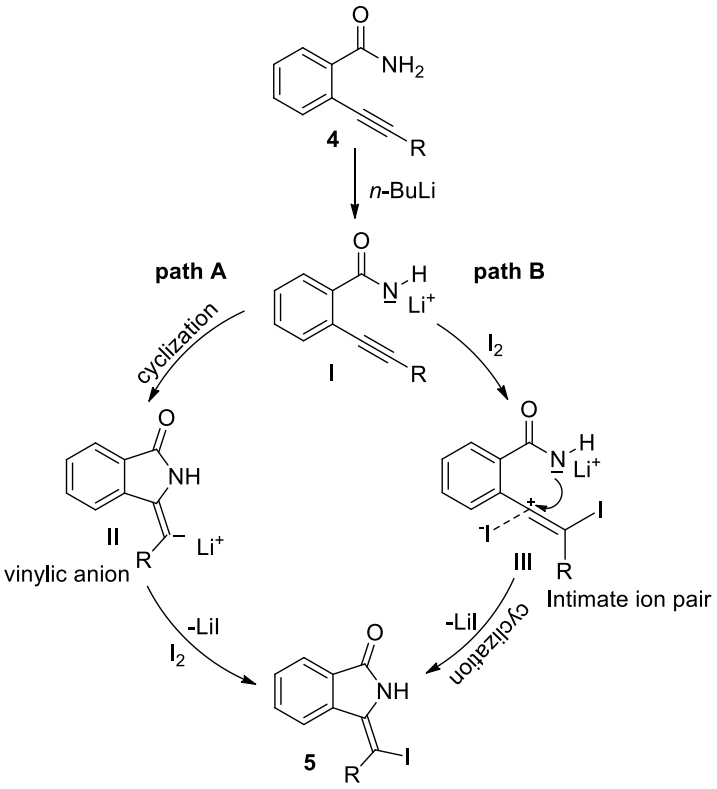


eq 2.5

Similarly, the reaction with Br_2 also led to the formation of a complex reaction mixture.

e) Furthermore, the cyclization reaction of the model substrate **4b** was repeated while keeping all the parameters the same except that the sequence of the addition of the base and I_2 was reversed. As a result, the reaction did not yield **5b,** and the TLC analysis suggested the formation of a different product that seemed unstable and could not be purified (probably the corresponding *O*-cyclized product).

Scheme 2.4. Plausible mechanism



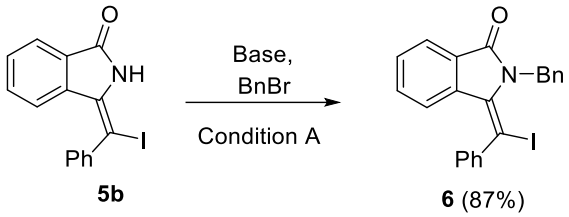
In view of the evidence presented in the literature[20-22] as well as the experimental observations in the laboratory, a plausible mechanism was proposed (Scheme 2.4) where the alkynyl amide **4** is first deprotonated by BuLi, yielding the corresponding amide anion (I). It is believed that the amide anion (I) either underwent *5-exo-dig* cyclization *via* path A leading to the formation of vinylic anion intermediate (II) which, on reaction with iodine, generated the iodine-containing isoindolin-1-one **5**. Alternatively, the amide anion (I) might react with iodine, leading to the formation of an intimate ion pair (III) *via* path B, followed by the aminocyclization to yield the corresponding iodinated isoindolinone **5** with the *Z*-stereochemistry.

The resulting products contained iodine as well as a -NH group, which provided potential sites for further structural modifications. This was explored and was demonstrated in Scheme 2.5. Thus, the resulting iodine-containing isoindolin-1-ones were diversified *via N*-benzylation (Scheme 2.5a), and by using conventional palladium-

catalyzed transformations, including Sonogashira alkynylation (Scheme 2.5b) and Suzuki-Miyaura (Scheme 2.5c) reactions. All these reactions resulted in the multi-substituted isoindolin-1-ones in good yields.

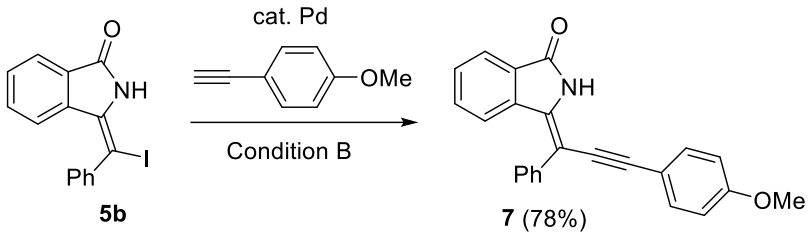
Scheme 2.5 Diversification of iodine-containing Isoindolin-1-ones[a,b,c]

a) *N*-Benzylation[a]



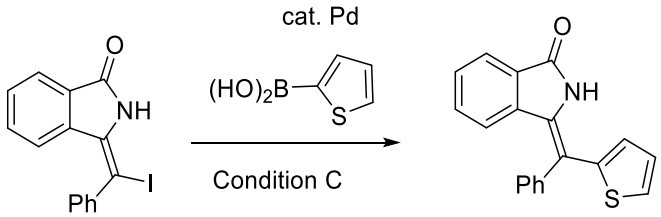
5b **6** (87%)

b) Sonogashira coupling[b]



5b **7** (78%)

c) Suzuki Miyaura coupling[c]



5b **8** (86%)

[a]Condition A: NaH (1.2 equiv), Benzyl bromide (1.1 equiv), DMF, 0 °C, 2 h. [b]Condition B: 3 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, DIPA (4 equiv), 1-ethynyl-4-methoxybenzene (1.2 equiv), DMF, 70 °C, 2 h. [c]Condition B: 5 mol % $PdCl_2$, Cs_2CO_3 (1.4 equiv), thiophen-2-ylboronic acid (1.2 equiv), 4:1 DMF/H_2O, 80 °C, 2 h.

2.3 Conclusions

This methodology represented the first successful iodoaminocyclization of easily accessible 2-(1-alkynyl)benzamides, to yield the corresponding isoindolin-1-ones. The reported electrophilic cyclization reactions efficiently cyclized 2-(1-alkynyl)benzamides,

exclusively *via N*-cyclization, leading to the formation of isoindolin-1-ones, with excellent regio- and stereoselectivity. The presence of free –NH as well as iodine group in the resulting products provided the scope for further elaboration to more complex products using known substitution reactions and/or organopalladium chemistry.

2.4 Experimental Section

General. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 25 °C at 400 MHz and 100 MHz, respectively, with Me_4Si as an internal standard. The chemical shifts (δ) and coupling constants (J) were given in ppm and in Hz, respectively. Thin-layer chromatography was performed using commercially prepared 60-100-mesh silica gel plate, and visualization was effected with short wavelength UV light (254 nm). Compounds were purified by column chromatography. All melting points were uncorrected.

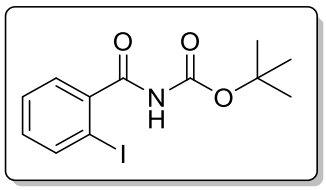
***Reagents*.** All commercial reagents were used as received.

***Solvents*.** All solvents were used as obtained commercially.

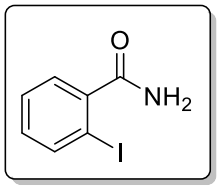
2-halobenzoic acids. **1a** and **1b** were commercially available and were used as received.

***Terminal alkyne building blocks*.** Commercially available terminal alkynes (3) were used as received.

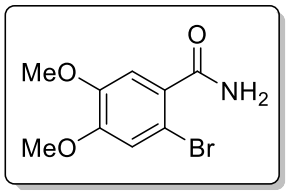
Procedure for the Preparation of 2-Halobenzamides. 2-Halobenzoic acid (1 gm) was refluxed $SOCl_2$ for 7 h. The solvent was evaporated, and the resulting yellow oil was treated with the corresponding primary amines at 0 °C. The resulting white solid was filtered and dried overnight in hot air oven at 50 °C. 2-Bromobenzamide was commercially available and used as such.



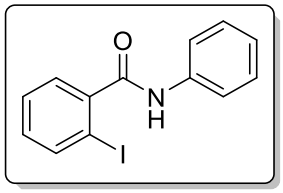
tert-Butyl (2-iodobenzoyl)carbamate (2a). Yield: (477 mg, 34%); light yellow solid; TLC R_f = 0.22 (20% EtOAc:Hexanes, UV); mp 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.37-7.33 (m, 1H), 7.28-7.26 (m, 1H), 7.10-7.05 (m, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.9, 149.3, 141.0, 139.1, 131.0, 127.7, 127.5, 91.9, 82.7, 27.8.



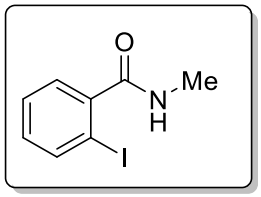
2-Iodobenzamide (2b).[23] Yield: (966 mg, 97%); white solid; TLC R_f = 0.15 (30% EtOAc:Hexanes, UV); mp 183-185 °C; 1H NMR (400 MHz, CDCl3) δ = 7.90 (d, J = 10.4 Hz, 1H), 7.48-7.46 (m, 1H), 7.41-7.37 (m, 1H), 7.14-7.10 (m, 1H), 5.88 (s, 2H).



2-Bromo-4,5-dimethoxybenzamide (2c).[24] Yield: (976 mg, 98%); white solid; TLC R_f = 0.26 (40% EtOAc:Hexanes, UV); mp 177-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (s, 1H), 7.98 (s, 1H), 6.54 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ = 168.6, 151.0, 148.2, 127.6, 115.8, 113.2, 110.1, 56.2, 56.0.



2-Iodo-N-phenylbenzamide (2d).[23] Yield: (1.211 g, 93%); white solid; TLC R_f = 0.33 (10% EtOAc:Hexanes, UV); mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 7.2 Hz, 1H), 7.63-7.61 (m, 3H), 7.50-7.48 (m, 1H), 7.42-7.35 (m, 3H), 7.19-7.10 (m, 2H).



2-Iodo-N-methylbenzamide (2e).[23] Yield: (998 mg, 95%); white solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145-147 °C)[25]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.0 Hz, 1H), 7.38-7.31 (m, 2H), 7.10-7.03 (m, 1H), 5.99 (s, 1H), 2.97 (d, J = 4.8 Hz, 3H).

Representative Sonogashira procedure. To a solution of the appropriate iodo/bromo starting material (0.25 mmol) in DMF (2 mL) were added $PdCl_2(PPh_3)_2$ (4 mol %) and CuI (2 mol %). The reaction vial was flushed with Argon, and the reaction mixture was stirred for 5 min at room temperature. TEA (4.0 equiv) was added by syringe. The reaction mixture was heated to 70 °C. A solution of the corresponding terminal alkyne (1.2 equiv) in DMF (1 mL) was added dropwise over 5 min, and the mixture was allowed to stir at 70 °C for 2 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was cooled, diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using Hexane-EtOAc as the eluent.

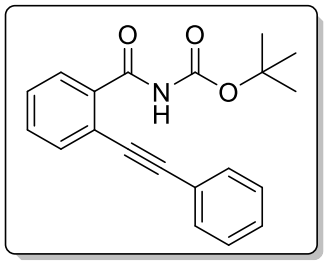
*Sonogashira Coupling Procedure for the Preparation of **4h** and **4i***. Both **4h** and **4i** were synthesized using the slightly modified procedure as the reaction was performed at 50 °C

and the corresponding terminal alkyne (1.2 equiv) in THF (1 mL) was added dropwise over 30 min.

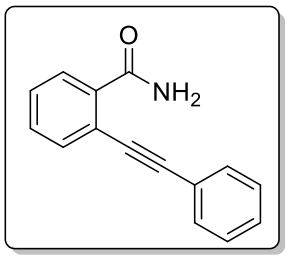
*Procedure for the synthesis of terminal alkyne **4o**.* A modified literature procedure was used.[26] To a solution of compound **4n** (0.25 mmol) in methanol (5 mL), $KF{\cdot}2H_2O$ (6 equiv) was added, and the reaction mixture was stirred for 30 min at 25 °C. After the reaction was over, methanol was removed under vacuum, and the residue was extracted with EtOAc (3 x 25 mL), washed with 0.1M HCl and brine, dried (anhydrous Na_2SO_4), filtered, and the solvent was removed under vacuum. Purification by flash chromatography afforded the product.[27]

*Sonogashira Coupling Procedure for the Preparation of **4q**.* This compound was synthesized using the slightly modified procedure where $PdCl_2(PPh_3)_2$ (15 mol %) was used and the reaction was carried at 80 °C.

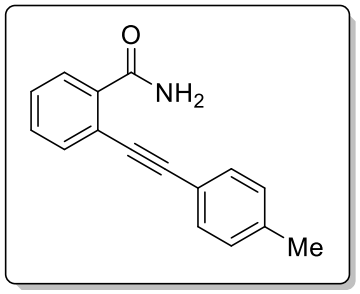
*Sonogashira Coupling Procedure for the Preparation of **4s** and **4t**.* General Sonogashira was followed with the difference that DCE was used as solvent.



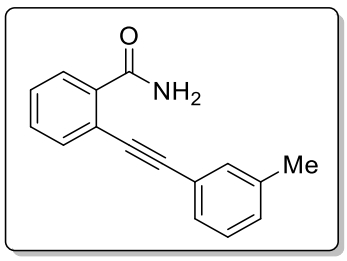
***tert*-Butyl (2-(phenylethynyl)benzoyl)carbamate (4a)**. Yield: (14.4 mg, 18%); yellow solid; TLC R_f = 0.5 (20% EtOAc:Hexanes, UV); mp 108-110 °C; IR ($CHCl_3$, cm^{-1}) 3265, 2978, 1761, 1693, 1220; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.28 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.62-7.59 (m, 3H), 7.52-7.42 (m, 2H), 7.40-7.34 (m, 3H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 164.9, 149.3, 139.3, 133.2, 131.6, 131.4, 130.4, 129.2, 128.9, 128.3, 121.7, 119.8, 86.5, 82.5, 67.4, 27.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_3$ 322.1438; Found 322.1449.



2-(Phenylethynyl)benzamide (4b).[28] Yield: (51.3 mg, 95%); yellow solid; TLC R_f = 0.26 (30% EtOAc:Hexanes, UV); mp 146-148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.82 (s, 1H), 7.62-7.60 (m, 2H), 7.58-7.55 (m, 1H), 7.54-7.52 (m, 2H), 7.49-7.47 (m, 2H), 7.46-7.45 (m, 1H), 7.44-7.43 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ = 169.5, 139.9, 132.9, 131.7, 130.0, 129.3, 129.1, 129.0, 128.1, 122.9, 120.2, 93.2, 88.5; MS (*m/z*) 222 $(M+H)^+$.

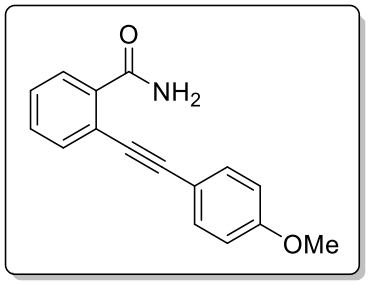


2-(p-Tolylethynyl)benzamide (4c) [29] Yield: (38.2 mg, 65%); yellow solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 142-144 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.82 (s, 1H), 7.59-7.54 (m, 3H), 7.47-7.40 (m, 4H), 7.26 (d, *J* = 7.88 Hz, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ = 169.5, 139.7, 139.1, 132.8, 131.6, 130.0, 129.8, 128.8, 128.1, 120.3, 119.9, 93.4, 87.9, 21.5; MS (*m/z*) 236 $(M+H)^+$.

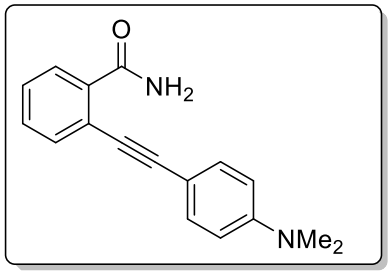


2-(m-Tolylethynyl)benzamide (4d). Yield: (40.6 mg, 69%); yellow solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 128-129 °C; IR ($CHCl_3$, cm^{-1}) 3374, 3177, 2902, 2208, 1644; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.83 (s, 1H),

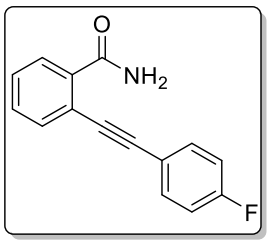
7.61-7.56 (m, 3H), 7.50-7.43 (m, 2H), 7.35-7.32 (m, 3H), 7.26-7.24 (m, 1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 169.5, 139.9, 138.4, 132.8, 132.1, 130.0, 130.0, 129.0, 128.9, 128.8, 128.1, 122.8, 120.2, 93.3, 88.2, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1068.



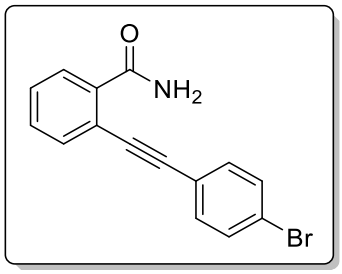
2-((4-Methoxyphenyl)ethynyl)benzamide (4e).[28] Yield: (39.6 mg, 63%); yellow solid; TLC R_f = 0.23 (30% EtOAc:Hexanes, UV); mp 123-124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.82 (s, 1H), 7.58-7.55 (m, 3H), 7.48-7.44 (m, 4H), 7.02-6.99 (m, 2H), 3.80 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 169.5, 160.1, 139.6, 138.5, 133.3, 132.7, 130.0, 128.5, 128.2, 120.6, 114.8, 93.5, 87.2, 55.7; MS (*m/z*) 252 $(M+H)^+$.



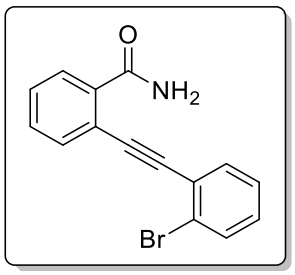
2-((4-(Dimethylamino)phenyl)ethynyl)benzamide (4f). Yield: (49.6 mg, 75%); brown yellow solid; TLC R_f = 0.22 (30% EtOAc:Hexanes, UV); mp 151-153 °C; IR ($CHCl_3$, cm^{-1}) 3025, 2940, 2204, 1662, 1218; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.79 (s, 1H), 7.58-7.52 (m, 3H), 7.44-7.32 (m, 4H), 6.73-6.71 (m, 2H), 2.96 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 169.6, 150.7, 138.9, 132.8, 132.5, 130.0, 128.2, 128.0, 121.1, 112.2, 108.9, 95.3, 86.5, 40.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2O$ 265.1335; Found 265.1345.



2-((4-Fluorophenyl)ethynyl)benzamide (4g).[29] Yield: (39.4 mg, 66%); yellow solid; TLC R_f = 0.21 (30% EtOAc:Hexanes, UV); mp 159-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.84 (s, 1H), 7.60-7.54 (m, 5H), 7.47-7.30 (m, 2H), 7.28-7.26 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ = 169.5, 163.7, 161.3, 139.9, 134.1, 134.0, 132.8, 130.0, 129.0, 128.2, 120.1, 119.4, 119.4, 116.5, 116.3, 92.1, 88.3; MS (*m/z*) 240 $(M+H)^+$.

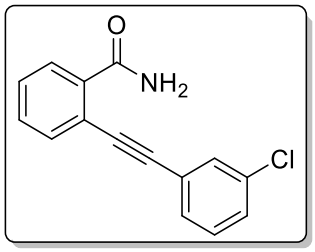


2-((4-Bromophenyl)ethynyl)benzamide (4h). Yield: (54.7 mg, 73%); brown yellow solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 178-180 °C; IR ($CHCl_3$, cm^{-1}) 3455, 3177, 2890, 2217, 1652; ^{1}H NMR (400 MHz, DMSO-d_6) δ =7.89 (s, 1H), 7.71-7.69 (m, 2H), 7.67-7.65 (m, 1H), 7.62-7.60 (m, 2H), 7.54-7.50 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ = 169.4, 139.9, 133.6, 132.9, 132.2, 130.1, 129.2, 128.2, 122.7, 122.2, 119.9, 92.0, 89.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}BrNO$ 300.0019; Found 300.0002.

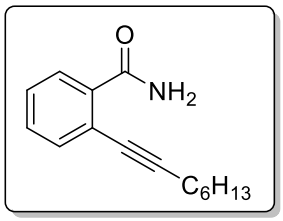


2-((2-Bromophenyl)ethynyl)benzamide (4i). Yield: (55.5 mg, 74%); white solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 177-179°C; IR ($CHCl_3$, cm^{-1}) 3446, 3161, 2926, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16-8.13 (m,

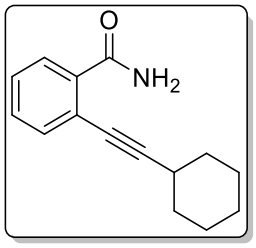
1H), 7.69-7.67 (m, 1H), 7.64-7.57 (m, 2H), 7.50-7.48 (m, 3H), 7.35-7.32 (m, 1H), 7.26-7.22 (m, 2H, including solvent protons), 6.20 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.8, 134.3, 133.8, 133.6, 132.5, 131.0, 130.4, 130.3, 129.2, 127.2, 125.1, 124.3, 119.7, 94.2, 91.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}BrNO$ 300.0019; Found 300.0002.



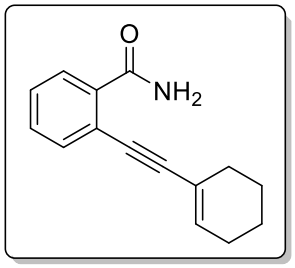
2-((3-Chlorophenyl)ethynyl)benzamide (4j).[25] Yield: (30.7 mg, 48%); brown yellow solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 139-141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.87 (s, 1H), 7.63-7.57 (m, 4H), 7.50-7.48(m, 5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 169.4, 140.1, 133.7, 133.0, 131.1, 131.1, 130.3, 130.1, 129.4, 129.3, 128.2, 124.9, 119.7, 91.5, 89.9; MS (*m/z*) 256 $(M+H)^+$, 258.



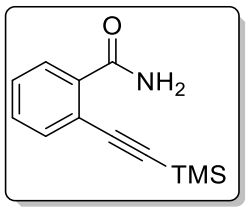
2-(Oct-1-yn-1-yl)benzamide (4k).[30] Yield: (41.8 mg, 73%); yellow solid; TLC R_f = 0.32 (30% EtOAc:Hexanes, UV); mp 88-89 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.68 (s, 1H), 7.53-7.51 (m, 2H), 7.42-7.37 (m, 3H), 2.44-2.40 (m, 2H), 1.55-1.52 (m, 2H), 1.44-1.41 (m, 2H), 1.30-1.29 (m, 4H), 0.90-0.87 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 169.4, 139.3, 133.1, 129.9, 128.1, 128.0, 121.0, 95.2, 79.5, 31.2, 28.4, 28.4, 22.4, 19.3, 14.3; MS (*m/z*) 230 $(M+H)^+$.



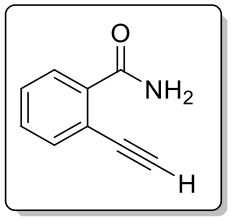
2-(Cyclohexylethynyl)benzamide (4l).[29] Yield: (46.6 mg, 82%); white solid; TLC R_f = 0.31 (30% EtOAc:Hexanes, UV); mp 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14-8.11 (m, 1H), 7.75 (s, 1H), 7.50-7.48 (m, 1H), 7.41-7.38 (m, 2H), 6.44 (s, 1H), 2.70-2.63 (m, 1H), 1.92-1.89 (m, 2H), 1.77-1.71 (m, 2H), 1.56-1.53 (m, 2H), 1.39-1.35 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.2, 133.8, 133.6, 130.8, 130.2, 128.0, 120.9, 101.7, 79.6, 32.2, 29.8, 25.6, 24.8.



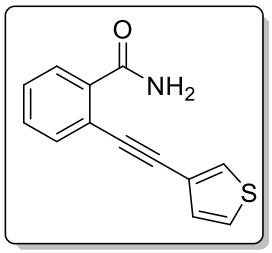
2-(Cyclohex-1-en-1-ylethynyl)benzamide (4m).[28] Yield: (47.8 mg, 85%); white solid; TLC R_f = 0.28 (30% EtOAc:Hexanes, UV); mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12-8.09 (m, 1H), 7.57 (s, 1H), 7.50-7.48 (m, 1H), 7.43-7.36 (m, 2H), 6.56 (s, 1H), 6.27-6.25 (m, 1H), 2.22-2.19 (m, 2H), 2.17-2.14 (m, 2H), 1.69-1.60 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.3, 137.0, 133.9, 133.3, 130.8, 130.2, 128.2, 120.6, 119.9, 97.9, 85.2, 28.7, 25.7, 22.0, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO$ 226.1226; Found 226.1214.



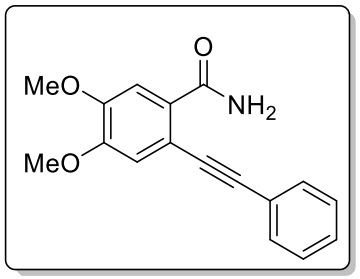
2-((Trimethylsilyl)ethynyl)benzamide (4n).[28] Yield: (50 mg, 93%); white solid; R_f = 0.55 (30% EtOAc:Hexanes); mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.13-8.11 (m, 1H), 7.70 (s, 1H), 7.55-7.52 (m, 1H), 7.42-7.40 (m, 2H), 6.46 (s,1H), 0.26 (s, 9H).



2-Ethynylbenzamide (4o).[28] Yield: (34.8 mg, 95%); yellow solid; TLC R_f = 0.16 (30% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145- 147 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.06 (m, 1H), 7.60-7.58 (m, 1H), 7.49-7.43 (m, 2H), 7.34 (s, 1H), 6.30 (s, 1H), 3.52 (s, 1H).

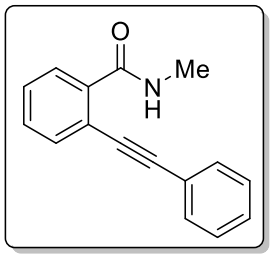


2-(Thiophen-3-ylethynyl)benzamide (4p).[28] Yield: (52.8 mg, 93%); white solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99-7.84 (m, 2H), 7.51-7.44 (m, 2H), 7.37-7.18 (m, 3H), 7.14-7.04 (m, 1H), 6.70 (d, J = 21.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 168.5, 139.9, 134.5, 133.3, 131.8, 130.8, 129.9, 129.6, 129.4, 128.6, 125.8, 90.8, 87.0.

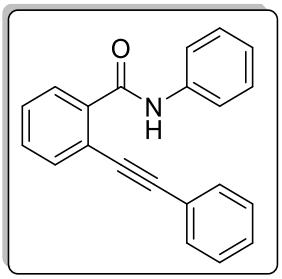


4,5-Dimethoxy-2-(phenylethynyl)benzamide (4q). Yield: (65.4 mg, 93%); brown solid; TLC R_f = 0.20 (50% EtOAc:Hexanes, UV); mp 148-150 °C; IR ($CHCl_3$, cm^{-1}) 3445, 3170, 2995, 1666, 1216, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.68-7.63 (m, 1H), 7.53-7.51 (m, 2H), 7.47-7.43 (m, 1H), 7.39-7.37 (m, 2H), 7.04 (s, 1H), 6.10 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 167.5, 150.9, 149.5, 132.1, 132.0, 131.4, 129.1, 128.6, 128.4, 115.1, 112.9,

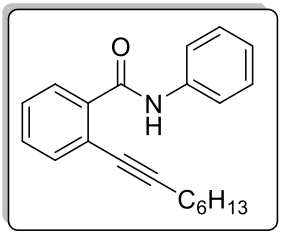
94.7, 88.0, 56.1, 56.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3$ 282.1125; Found 282.1120.



N-Methyl-2-(phenylethynyl)benzamide (4r).[8] Yield: (48 mg, 82%); white solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 105-106 °C (lit. mp 103-105 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ =8.02-8.00 (m, 1H), 7.59-7.56 (m, 1H), 7.52-7.50 (m, 2H), 7.43-7.30 (m, 5H), 3.06 (d, *J* = 4.8 Hz, 3H).

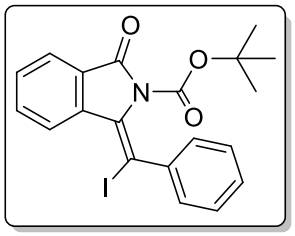


N-Phenyl-2-(phenylethynyl)benzamide (4s).[8] Yield: (62.4 mg, 84%); white solid; TLC R_f = 0.60 (20% EtOAc:Hexanes, UV); mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (s, 1H), 8.13-8.11 (m, 1H), 7.68-7.63 (m, 3H), 7.50-7.44 (m, 4H), 7.41-7.32 (m, 5H), 7.16-7.12 (m, 1H).

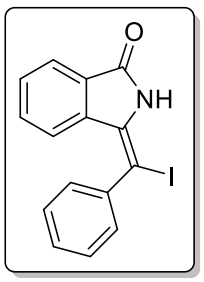


2-(Oct-1-yn-1-yl)-N-phenylbenzamide (4t).[8] Yield: (68 mg, 89%); brown semi-solid; TLC R_f = 0.64 (20% EtOAc:Hexanes, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43 (s, 1H), 8.09-8.07 (m, 1H), 7.69-7.67 (m, 2H), 7.50-7.48 (m, 1H), 7.40-7.34 (m, 4H), 7.16-7.12 (m, 1H), 2.51-2.47 (m, 2H), 1.62-1.55 (m, 2H), 1.44-1.36 (m, 2H), 1.28-1.21 (m, 4H), 0.89-0.85 (m, 3H).

Representative Procedure for the Cyclization Reaction. All cyclization reactions were performed using the appropriate alkyne starting material (0.25 mmol) in THF at 0 °C and flushed with argon. 1.2 equiv of *n*-BuLi (1.6 M in hexane). After 10 min, I_2 (3 equiv)/ [ICl (1.0 molar in THF)] (3 equiv), was added dropwise (approx. 1 min) and stirred for 20 min (total reaction time 30 min). After completion, the reaction mixture was quenched with satd. aq. NH_4Cl solution, diluted with EtOAc, washed with satd. aq. $Na_2S_2O_3$ and dried. The solvent was evaporated and the product was isolated by column chromatography on silica gel.

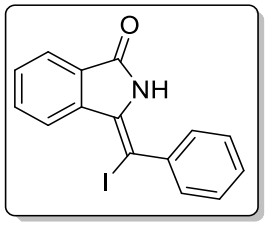


(E)-tert-Butyl 1-(iodo(phenyl)methylene)-3-oxoisoindoline-2-carboxylate (5a). Yield: (30.2 mg, 27%); yellow solid; TLC R_f = 0.5 (10% EtOAc:Hexanes, UV); mp 171-173 °C; IR ($CHCl_3$, cm^{-1}) 2925, 2854, 1816, 1710, 1470, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.08 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.77-7.73 (m, 1H), 7.62-7.59 (m, 1H), 7.45-7.42 (m, 2H), 7.36-7.32 (m, 2H), 7.24-7.21 (m, 1H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 165.2, 148.1, 144.3, 137.9, 133.8, 133.1, 130.2, 129.9, 129.2, 128.6, 128.3, 124.8, 124.0, 84.5, 84.0, 27.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}INO_3$ 448.0404; Found 448.0416.

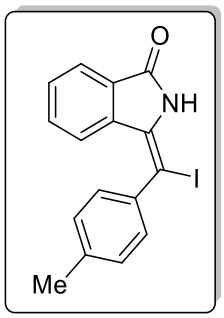


(Z)-3-(Iodo(phenyl)methylene)isoindolin-1-one (5b). Yield: (75.5 mg, 67%); yellow solid; TLC R_f = 0.62 (30% EtOAc:Hexanes, UV); mp 165-167 °C; IR ($CHCl_3$, cm^{-1}) 3184, 3068, 2965, 1703, 1469; ^1H NMR (400 MHz, DMSO-d_6) δ = 10.26

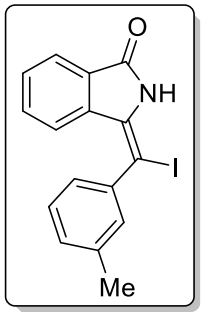
(s, 1H), 7.70 (d, J = 7.48 Hz, 1H), 7.52-7.40 (m, 6H), 7.33-7.29 (m, 1H), 6.29 (d, J = 7.96 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ = 167.9, 142.6, 139.0, 135.1, 132.5, 131.8, 129.7, 129.6, 129.6, 129.4, 123.5, 123.1, 78.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}INO$ 347.9880; Found 347.9869.



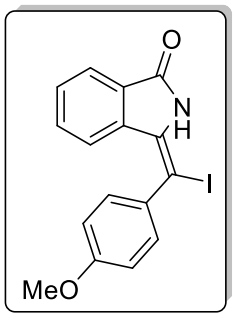
(E)-3-(Iodo(phenyl)methylene)isoindolin-1-one (5b'). yellow solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 172-173 °C; IR ($CHCl_3$, cm^{-1}) 3257, 3059, 2961, 1705, 1470; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.95 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.76-7.74 (m, 1H), 7.63-7.61 (m, 1H), 7.59 (s, 1H), 7.44-7.40 (m, 4H), 7.37-7.33 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 166.0, 141.9, 136.1, 135.4, 132.0, 131.0, 130.1, 129.2, 129.1, 128.9, 123.8, 123.7, 72.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}INO$ 347.9880; Found 347.9869.



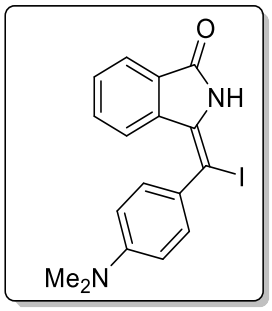
(Z)-3-(Iodo(p-tolyl)methylene)isoindolin-1-one (5c). Yield: (64.1 mg, 71%); white solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 192-194 °C; IR ($CHCl_3$, cm^{-1}) 3189, 2956, 2925, 1704, 1469; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 7.6 Hz, 1H), 7.73 (s, 1H), 7.43-7.39 (m, 1H), 7.34-7.32 (m, 2H), 7.28-7.25 (m, 3H), 6.60 (d, J = 8.4 Hz, 1H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.2, 139.4, 138.0, 137.4, 134.5, 132.1, 131.7, 129.8, 129.3, 129.2, 123.7, 123.2, 79.4, 21.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO$ 362.0036; Found 362.0025.



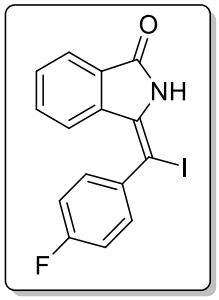
(Z)-3-(Iodo(m-tolyl)methylene)isoindolin-1-one (5d). Yield: (80.4 mg, 89%); white solid; TLC R_f = 0.65 (30% EtOAc:Hexanes, UV); mp 146-148 °C; IR ($CHCl_3$, cm^{-1}) 3175, 3060, 2891, 1703, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78-7.76 (m, 2H), 7.41-7.38 (m, 1H), 7.35-7.31 (m, 1H), 7.26-7.21(m, 3H), 6.53 (d, J = 7.6 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.2, 140.7, 138.9, 137.4, 134.5, 132.1, 131.7, 130.0, 130.0, 129.2, 128.9, 126.4, 123.7, 123.2, 79.1, 21.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO$ 362.0036; Found 362.0065.



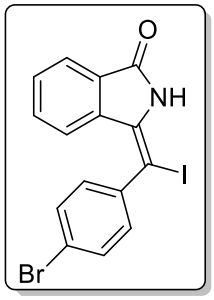
(Z)-3-(Iodo(4-methoxyphenyl)methylene)isoindolin-1-one (5e). Yield: (49 mg, 52%); brown solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 175-177 °C; IR ($CHCl_3$, cm^{-1}) 3196, 2917, 2849, 1708, 1471, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.43-7.36 (m, 4H), 6.98-6.96 (m, 2H), 6.62 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.2, 160.1, 137.4, 134.5, 133.2, 132.2, 131.7, 131.0, 129.2, 123.7, 123.1, 114.4, 79.4, 55.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO_2$ 377.9985; Found 377.9978.



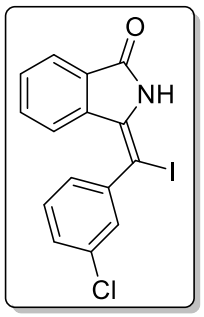
(Z)-3-((4-(Dimethylamino)phenyl)iodomethylene)isoindolin-1-one (5f). Yield: (65.4 mg, 67%); brown solid; TLC R_f = 0.57 (30% EtOAc:Hexanes, UV); mp 192-193 °C; IR ($CHCl_3$, cm^{-1}) 3019, 2917, 2850, 1707, 1466, 1364, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 8.35-8.33 (m, 1H), 7.99-7.97 (m, 1H), 7.76-7.71 (m, 1H), 7.51-7.47 (m, 1H), 7.41-7.39 (m, 3H), 6.76 (d, J = 8.4 Hz, 1H), 3.04 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.5, 150.9, 143.1, 139.1, 133.7, 131.5, 130.2, 127.6, 126.9, 125.3, 124.5, 111.2, 75.2, 40.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}IN_2O$ 391.0302; Found 391.0325.



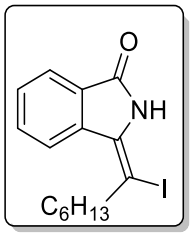
(Z)-3-((4-Fluorophenyl)iodomethylene)isoindolin-1-one (5g). Yield: (63 mg, 69%); yellow solid; TLC R_f = 0.55 (30% EtOAc:Hexanes, UV); mp 145-147 °C; IR ($CHCl_3$, cm^{-1}) 3193, 3068, 1708, 1471, 1229; ^1H NMR (400 MHz, DMSO-d_6) δ = 10.27 (s, 1H), 7.70 (d, J = 7.44 Hz, 1H), 7.49-7.46 (m, 3H), 7.39-7.31 (m, 3H), 6.35 (d, J = 7.88 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ = 167.9, 163.7, 139.4, 139.1, 139.1, 135.0, 132.7, 132.0, 131.9, 129.8, 123.5, 123.1, 116.8, 116.5, 77.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}FINO$ 365.9786; Found 365.9809.



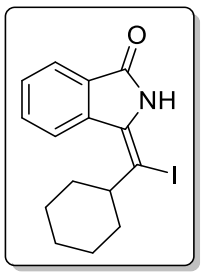
(Z)-3-((4-Bromophenyl)iodomethylene)isoindolin-1-one (5h). Yield: (43.6 mg, 41%); yellow solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 164-166 °C; IR ($CHCl_3$, cm^{-1}) 3204, 3015, 1708, 1470; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.78 (m, 1H), 7.74 (s, 1H), 7.60-7.56 (m, 2H), 7.45-7.42 (m, 1H), 7.33-7.28 (m, 3H), 6.60 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.1, 139.9, 138.0, 134.2, 132.4, 131.7, 131.2, 130.7, 129.5, 123.9, 123.5, 123.1, 86.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}BrINO$ 425.8985; Found 425.8978.



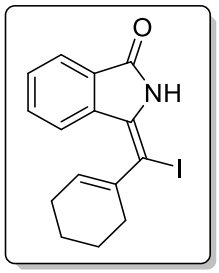
(Z)-3-((3-Chlorophenyl)iodomethylene)isoindolin-1-one (5j). Yield: (70.6 mg, 74%); brown solid; TLC R_f = 0.59 (30% EtOAc:Hexanes, UV); mp 148-150 °C; IR ($CHCl_3$, cm^{-1}) 3192, 2961, 1709, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.77 (m, 2H), 7.46-7.44 (m, 2H), 7.42-7.40 (m, 2H), 7.34-7.29 (m, 2H), 6.57 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.2, 142.5, 138.3, 134.7, 134.2, 132.4, 131.7, 130.4, 129.7, 129.5, 129.4, 127.8, 123.9, 123.1, 75.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}ClINO$ 381.9490; Found 381.9475.



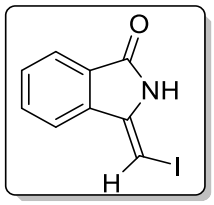
(Z)-3-(1-Iodoheptylidene)isoindolin-1-one (5k). Yield: (66.6 mg, 75%); yellow solid; TLC R_f = 0.69 (30% EtOAc:Hexanes, UV); mp 88-89 °C; IR ($CHCl_3$, cm^{-1}) 3191, 2955, 2927, 2856, 1700, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.86-7.84 (m, 1H), 7.80-7.78 (m, 1H), 7.68 (s, 1H), 7.66-7.60 (m, 1H), 7.55-7.51 (m, 1H), 1.75-1.67 (m, 2H), 1.46-1.43 (m, 2H), 1.36-1.34 (m, 6H), 0.92-0.88 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 166.8, 135.9, 134.0, 132.5, 132.2, 129.0, 124.2, 123.0, 89.9, 40.1, 31.5, 29.5, 28.3, 22.5, 14.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}INO$ 356.0506; Found 356.0541.



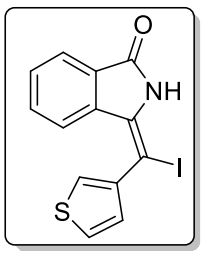
(Z)-3-(Cyclohexyliodomethylene)isoindolin-1-one (5l). Yield: (83 mg, 94%); white solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 118-119 °C; IR ($CHCl_3$, cm^{-1}) 3186, 2927, 2853, 1697, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.87-7.79 (m, 3H), 7.65-7.58 (m, 1H), 7.54-7.50 (m, 1H), 2.76-2.72 (m, 1H), 1.90-1.88 (m, 2H), 1.78-1.71 (m, 2H), 1.54-1.48 (m, 4H), 1.29-1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 166.8, 134.7, 134.1, 132.5, 132.3, 129.1, 124.3, 123.0, 102.1, 42.7, 34.5, 25.8, 25.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}INO$ 354.0349; Found 354.0371.



(Z)-3-(Cyclohex-1-en-1-yliodomethylene)isoindolin-1-one (5m). Yield: (50 mg, 57%); white solid; TLC R_f = 0.65 (30% EtOAc:Hexanes, UV); mp 165-167 °C; IR ($CHCl_3$, cm^{-1}) 3159, 3015, 2932, 2854, 1711, 1652, 1465; ^1H NMR (400 MHz, $CDCl_3$) δ = 10.8 (s, 1H), 8.35-8.33 (m, 1H), 7.93-7.91 (m, 1H), 7.74-7.70 (m, 1H), 7.51-7.47 (m, 1H), 5.96-5.94 (m, 1H), 2.34-2.32 (m, 2H), 2.26-2.24 (m, 2H), 1.88-1.83 (m, 2H), 1.78-1.72 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.4, 145.3, 138.9, 136.6, 133.6, 132.5, 131.2, 127.4, 126.9, 124.6, 74.5, 27.6, 25.0, 22.4, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}INO$ 352.0193; Found 352.0175.

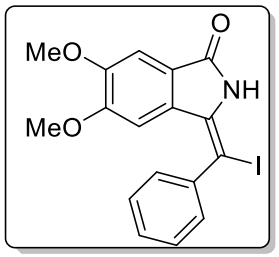


(Z)-3-(Iodomethylene)isoindolin-1-one (5o). Yield: (56 mg, 82%); white solid; TLC R_f = 0.33 (10% EtOAc:Hexanes, UV); mp 191-193 °C; IR ($CHCl_3$, cm^{-1}) 3019, 2880, 1709, 1467; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.80 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.84-7.79 (m, 1H), 7.68-7.64 (m, 1H), 7.61-7.56 (m, 1H), 6.22 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 165.8, 140.7, 135.3, 132.5, 132.3, 130.2, 124.3, 123.8, 54.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for C_9H_7INO 271.9567; Found 271.9563.

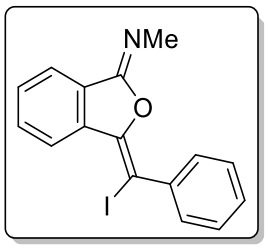


(Z)-3-(Iodo(thiophen-3-yl)methylene)isoindolin-1-one (5p). Yield: (66.3 mg, 75%); yellow solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 162-164 °C; IR ($CHCl_3$, cm^{-1}) 3208, 2928, 1708, 1471; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d,

J = 4.0 Hz, 1H), 7.72 (s, 1H), 7.48-7.42 (m, 3H), 7.34-7.30 (m, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.0, 140.7, 138.4, 134.6, 132.3, 131.4, 129.4, 128.3, 126.8, 125.8, 123.8, 122.9, 72.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_9INOS$ 353.9444; Found 353.9426.

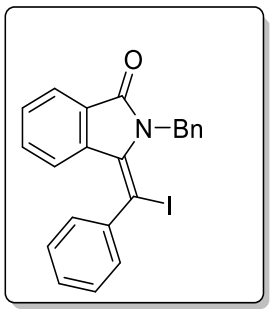


(Z)-3-(Iodo(phenyl)methylene)-5,6-dimethoxyisoindolin-1-one (5q). Yield: (79.4 mg, 78%); yellow solid; TLC R_f = 0.48 (50% EtOAc:Hexanes, UV); mp 206-207 °C; IR ($CHCl_3$, cm^{-1}) 3220, 3019, 2838, 1701, 1496, 1217; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.46-7.45 (m, 4H), 7.41-7.39 (m, 1H), 7.17 (s, 1H), 5.86 (s, 1H), 3.88 (s, 3H), 3.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.5, 152.3, 150.5, 141.1, 137.8, 129.7, 129.1, 129.0, 128.5, 124.6, 105.2, 104.7, 76.0, 56.1, 55.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}INO_3$ 408.0091; Found 408.0079.



N-((E)-3-(Iodo(phenyl)methylene)isobenzofuran-1(3H)-ylidene)methanamine (5r).[8] Yield: (42.4 mg, 47%); white solid; TLC R_f = 0.27 (30% EtOAc:Hexanes, UV); mp 121-124 °C; IR ($CHCl_3$, cm^{-1}) 3017, 2877, 1708, 1217; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.58-7.53 (m, 3H), 7.49-7.45 (m, 1H), 7.33-7.29 (m, 1H), 7.22-7.18 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 154.7, 147.1, 140.5, 135.9, 131.6, 131.1, 130.5, 130.1, 128.2, 127.9, 124.9, 122.9, 73.4, 34.9.

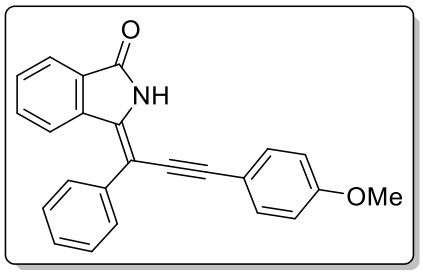
Procedure for the Synthesis of (Z)-2-Benzyl-3-(iodo(phenyl)methylene)isoindolin-1-one (6). To an ice cooled suspension of NaH (1.2 equiv) in DMF was added **5b** (0.25 mmol). After 15 min, benzyl bromide (1.1 equiv) was added slowly. Reaction mixture was stirred for 2h. After completion, added 1 mL methanol to the reaction mixture and diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography.



(Z)-2-Benzyl-3-(iodo(phenyl)methylene)isoindolin-1-one (6). Yield: (92.2 mg, 87%); white solid; TLC R_f = 0.66 (30% EtOAc: Hexane, UV); m.p.150-152°C; IR ($CHCl_3$, cm^{-1}) 3068, 3029, 2928, 1709, 1470; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76-7.74 (m, 1H), 7.31-7.05 (m, 13H)(solvent peak included), 5.89 (d, J = 8.0 Hz, 1H), 5.61 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =169.5, 145.0, 139.4, 137.6, 137.4, 132.1, 129.3, 129.1, 129.0, 128.9, 128.4, 128.1, 126.9, 126.4, 123.8, 122.9, 87.1, 44.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{17}INO$ = 438.0349; Found 438.0363.

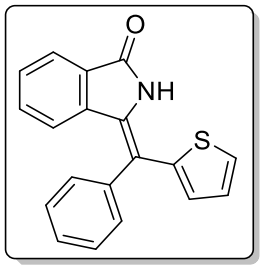
Procedure for the Synthesis of (Z)-3-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ylidene)isoindolin-1-one (7). To a solution of the **5b** (0.25 mmol) in DMF (2 mL) were added $PdCl_2(PPh_3)_2$ (4 mol %) and CuI (3 mol %). The reaction vial was flushed with Argon, and the reaction mixture was stirred for 5 min at room temperature. TEA (4.0 equiv) was added by a syringe. The reaction mixture was heated to 80 °C. A solution of the 4-ethynylanisole (1.2 equiv) in DMF (1 mL) was added, and the mixture was stirred

at 80 °C for 2 h (the reaction progress was monitored by TLC). After cooling, the reaction mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried and concentrated to give the crude product, which was purified by column chromatography.



(Z)-3-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ylidene)isoindolin-1-one (7). Yield: (68.5 mg, 78%); yellow solid; TLC R_f = 0.67 (30% EtOAc: Hexane, UV); m.p. 194-195°C; IR ($CHCl_3$, cm^{-1}) 3183, 3019, 2928, 2184, 1703, 1471, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.74(s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.58-7.55 (m, 2H), 7.51-7.46 (m, 5H), 7.42-7.38 (m, 1H), 7.30-7.27 (m, 1H), 6.90-6.86 (m, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.2, 160.0, 138.0, 135.7, 135.0, 133.2, 131.8, 130.6, 129.7, 129.2, 128.9, 128.6, 123.6, 114.6, 114.1, 105.4, 99.7, 86.5, 55.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1332; Found 328.1355.

Procedure for the Synthesis of (Z)-3-(Phenyl(thiophen-2-yl)methylene)isoindolin-1-one (8). To a suspension of **5b** (0.25 mmol) and thiophen-2-ylboronic acid (1.2 equiv) in 2 mL DMF:H_2O (4:1) was added $PdCl_2$ (5 mol %) and Cs_2CO_3 (1.4 equiv). The reaction was heated to 80 °C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product, which was purified.



(Z)-3-(Phenyl(thiophen-2-yl)methylene)isoindolin-1-one (8).

Yield: (65.2 mg, 86%); White Solid; TLC R_f = 0.47 (30% EtOAc: Hexane, UV); m.p. 158-160 °C; IR ($CHCl_3$, cm^{-1}) 3196, 3081, 1700, 1607, 1472, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 7.85 (d, J = 4.0 Hz, 1H), 7.50-7.47(m, 3H), 7.41-7.35 (m, 4H), 7.24-7.20 (m, 1H), 7.08-7.06 (m, 1H), 7.03-7.02 (m, 1H), 6.35 (d, J = 8.0 Hz, 1H) ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 167.9, 142.8, 138.8, 136.8, 131.9, 131.7, 130.4, 130.1, 129.0, 128.8, 128.6, 128.3, 127.7, 127.2, 123.7, 123.4, 117.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}NOS$ 304.0791; Found 304.0810).

X-ray Crystallographic Data for (Z)-3-(Iodo(phenyl)methylene)isoindolin-1-one (5b).

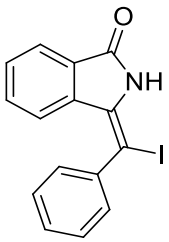
Data collection and structure solution

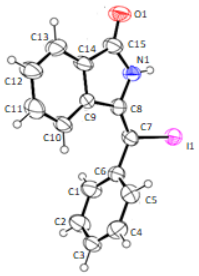
Single crystals of **5b** of suitable quality were grown by slow evaporation of the solvent mixture of dichloromethane and diethyl ether (*v:v* = 2:5) solvent solutions containing **5b** at room temperature. Compound **5b** was dissolved in DCM at ambient temperature. Subsequently, diethyl ether was added carefully on top of the dichloromethane solution, and two layers were observed. The vial was kept to allow slow evaporation of solvents until crystals were formed that were suitable for X-ray diffraction analysis. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre, and CCDC deposit number for **5b** is **1561244**.

X-ray data collection was performed with Oxford Xcalibur, Sapphire3 Diffractometer equipped Mo (Kα) (λ = 0.71073 Å) radiation. Cell refinement and data reduction were carried out using CrysAlisPro 1.171.38.46 (Rigaku OD, 2015) program.

Empirical absorption correction was performed using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. Crystal structures were solved by SHELXT-2014 (Sheldrick, 2014) and refined using SHELXL-2014 (Sheldrick, 2014) computer program using the WinGX graphical user interface.[31] Molecular graphics were drawn using ORTEP3.[32] The relevant data is given in Table 2.4. All aromatic hydrogens were fixed geometrically at calculated positions and refined as riding model with C—H distance of 0.93 Å, Uiso(H) = 1.2Ueq(C), whereas the hydrogen on Nitrogen atom was located from the electron density peaks and refined freely with N-H distance restrained at 0.85 Å within an allowed standard deviation of 0.02 Å. The ORTEP diagram was drawn at 40% probability level.

Figure 2.2. Molecular structure of 5b





CCDC 1561244

Table 2.4. Crystal data and structure refinement of 5b

Identification	B37	
Empirical form.	$C_{15.25}H_{10}INO_{1.75}$	
Formula wt.	362.14	
Temp.	296(2) K	
Wavelength (λ)	0.71073 Å	
Crystal system	Triclinic	
Space gp.	P-1	
Unit cell dimensions	a = 13.8012(4) Å	α= 90.852(2)°.

	b = 14.1127(5) Å β= 104.066(2)°.
	c = 15.8686(6) Å γ = 103.825(2)°.
Vol.	2902.49(18) $Å^3$
Z	8
Density (calcd)	1.657 mg/m^3
Absorption coeff.	2.202 mm^{-1}
F(000)	1404
Crystal size	0.200 x 0.150 x 0.100 mm^3
Theta range for data collection	2.300 to 24.999°.
Index ranges	-16<=h<=16, -16<=k<=16, -18<=l<=18
Reflections collected	61748
Independent reflections	10202 [R(int) = 0.0463]
Completeness to theta = 24.999°	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.6350
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10202 / 98 / 712
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0501, wR2 = 0.1282
R indices (all data)	R1 = 0.0838, wR2 = 0.1562
Extinction coeff.	n/a
Largest diff. peak and hole	0.966 and -0.993 $e.Å^{-3}$

2.5 References

(1) Larock, R. C. In *Acetylene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2005; Vol. 106, pp 51–99.

(2) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980.

(3) Aggarwal, T.; Kumar, S.; Verma, A. K. *Org. Biomol. Chem.* **2016**, *14*, 7639–7653.

(4) Mehta, S.; Waldo, J. P.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2013**, *15*, 247–254.

(5) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141–1147.

(6) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658.

(7) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432–1437.

(8) Mehta, S.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 10938–10944.

(9) Schlemmer, C.; Andernach, L.; Schollmeyer, D.; Straub, B. F.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 10118–10124.

(10) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681–13736.

(11) Bian, M.; Yao, W.; Ding, H.; Ma, C. *J. Org. Chem.* **2010**, *75*, 269–272.

(12) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, 352, 136−142.

(13) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330–7335.

(14) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(15) Volpe, R.; Aurelio, L.; Gillin, M. G.; Krenske, E. H.; Flynn, B. L. *Chemistry - A European Journal* **2015**, *21*, 10191–10199.

(16) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, 50, 11803−11812.

(17) Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, 55, 13193−13200.

(18) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571−1587.

(19) Wang, T.; Zhang, H.; Han, F.; Long, L.; Lin, Z.; Xia, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 9251–9255.

(20) Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* **2010**, *75*, 5250–5258.

(21) Breugst, M.; Zipse, H.; Guthrie, J. P.; Mayr, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5165–5169.

(22) Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6470–6505.

(23) Songsichan, T.; Promsuk, J.; Rukachaisirikul, V.; Kaeobamrung, J. *Org. Biomol. Chem.* **2014**, *12*, 4571–4575.

(24) Donaldson, L. R.; Wallace, S.; Haigh, D.; Patton, E. E.; Hulme, A. N. *Org. Biomol. Chem.* **2011**, *9*, 2233–2239.

(25) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777–4792.

(26) Spivey, A. C.; McKendrick, J.; Srikaran, R.; Helm, B. A. *J. Org. Chem.* **2003**, *68*, 1843–1851.

(27) Varela-Fernández, A.; Varela, J.; Saá, C. *Synthesis* **2012**, *44*, 3285–3295.

(28) Long, Y.; She, Z.; Liu, X.; Chen, Y. *J. Org. Chem.* **2013**, *78*, 2579–2588.

(29) Minami, H.; Sueda, T.; Okamoto, N.; Miwa, Y.; Ishikura, M.; Yanada, R. *Eur. J. Org. Chem.* **2016**, *2016*, 541–548.

(30) Praveen, C.; Dheenkumar, P.; Perumal, P. T. *J. Chem. Sci.* **2013**, *125*, 71–83.

(31) Farrugia, L. J. *J. Appl. Cryst.* **1999**, 32, 837–838.

(32) Farrugia, L. J. *J. Appl. Cryst.* **1997**, 30, 565–565.

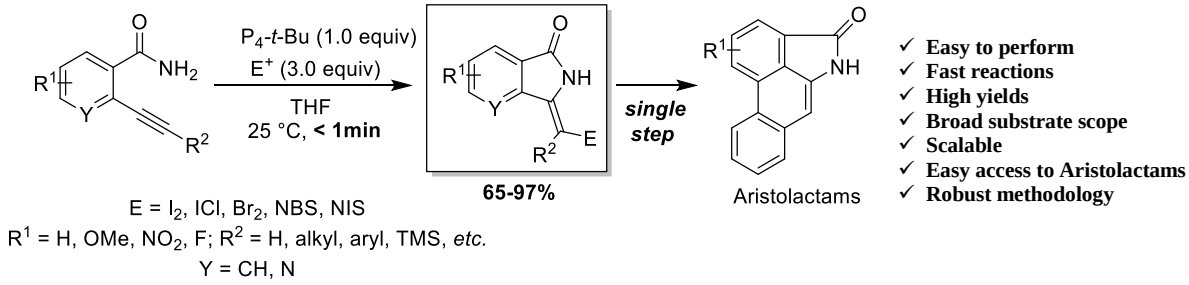
(33) Brahmchari, D.; Verma, A. K.; Mehta, S. *J. Org. Chem.* **2018**, 83, 3339−3347.

CHAPTER 3

Phosphazene Superbase-Mediated Regio- and Stereoselective Iodoaminocyclization of 2-(1-Alkynyl)benzamides for the Synthesis of Isoindolin-1-ones

Based on a paper published in the *Journal of Organic Chemistry*[53]

Abstract



A simple, quick and robust iodoaminocyclization of 2-(1-alkynyl)benzamides, mediated by phosphazene superbase P$_4$-*t*-Bu, has been reported for the synthesis of isoindolin-1-ones. The reaction worked under ambient conditions and instantaneously resulted in the synthesis of isoindolin-1-ones in 65-97% yields, in a regio- and stereoselective manner. The resulting isoindolinone products were found to exhibit an exclusive *Z*-geometry across the exocyclic C=C bond (confirmed through X-ray crystallography). The methodology also provided an easy access to aristolactams, an important class of natural products. This was successfully demonstrated by synthesizing two aristolactam derivatives (including Cepharanone B).

3.1 Introduction

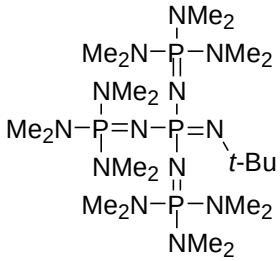
Electrophilic cyclization reactions of functionalized alkynes have emerged as very useful synthetic tools in organic chemistry.[1-3] Over the years, there has been continuous interest in developing novel strategies for the synthesis of heterocyclic and polyheterocyclic compounds through iodocyclization methodology.[4,5] The electrophilic cyclization reactions of *o*-alkynyl benzamides have been particularly studied and

explored by several research groups for the synthesis of isoindolinones and their regio-isomeric cyclic imidates.[6-10] In this context, it may be noted that the amide group (−$CONH_2$) is known to be an ambident nucleophile.[11-17] Previous studies showed that the cyclization of *o*-alkynyl benzamides resulted in the *O*-cyclization, thereby, yielding the corresponding cyclic imidates, when the cyclization was carried out in the absence of a base (using NIS in DCM),[6] or in the presence of weak base (using I_2/ICl with $NaHCO_3$ in MeCN) (Scheme 3.1a).[7-9] Notably, in previous studies[7] some of these cyclic imidates were mischaracterized as isoindolinones and isoquinolones which was later on corrected by Mehta *et al.* and also by Opatz *et al.*[8,9] Furthermore, it was later accomplished that using a stronger base *n*-BuLi with I_2/ICl successfully accomplished the *N*-cyclization of *o*-alkynyl benzamide substrates and resulted in the formation of isoindolinones (Scheme 3.1b).[10] While the *n*-BuLi worked well, the scope of the methodology was found to be limited with respect to the substrate functionality. The substrates with labile trimethylsilyl (TMS) or bromo (-Br) groups did not yield the desired products and/or resulted in the formation of corresponding debrominated or desilylated products, respectively. Also, the reaction yields were moderate in most cases. Besides, *n*-BuLi being a highly reactive reagent, it is difficult to handle and is not a preferred choice of synthetic/industrial chemists.

The amide group (-$CONH_2$), due to its ambident nature has always been a synthetic challenge for the chemists and tuning the reactivity of amide group is still a synthetic challenge to accomplish an efficient and regioselective *N*-cyclization (vs possible *O*-cyclization) for the alkynyl amides and related substrates.[14-17] Furthermore, there was still scope for the development of a robust and straightforward methodology for the synthesis of isoindolin-1-ones, especially one that tolerates labile functional groups, easy to perform, comparative increment in product yields, allows further

diversification, and possible extension to natural product synthesis. Therefore, it was decided to develop a simple, straightforward, and efficient methodology for the iodoaminocyclization of *o*-alkynyl benzamides. It was speculated that the use of an organic, non-nucleophilic superbase would be suitable for such iodocyclizations. Phosphazene superbases consist of an important class of such bases, which are extremely strong, are metal-free, non-nucleophilic bases, and many of these are commercially available.[18-20] P_4-*t*-Bu, a member of the phosphazene superbase family (Figure 3.1), is particularly established as an extremely strong (pK_a = 42.7 in MeCN) and useful superbase in organic synthesis.[21,22]

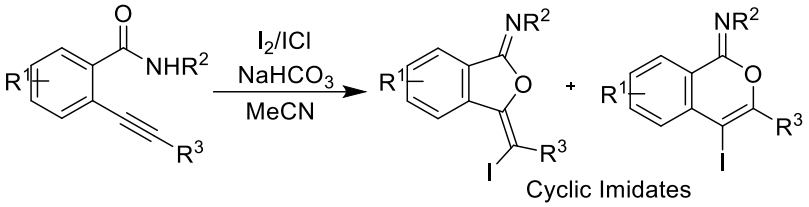
Figure 3.1 Phosphazene superbase P_4-*t*-Bu



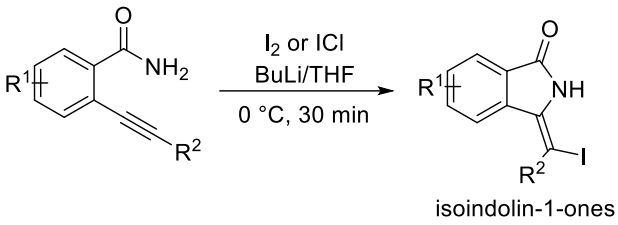
After a thorough literature search, there was no report found for the use of a superbase in iodocyclization of functionally-substituted alkynes. Although a few papers were found where Terada *et al.* reported superbase-catalyzed intramolecular cyclization of *o*-alkynylphenyl ethers[23] and *o*-alkynylbenzamides,[24] no electrophiles (other than H^+) were explored for that methodology. Also, in many cases, the cyclization reaction of *o*-alkynylbenzamides resulted in the formation of mixtures of *E*/*Z* stereoisomers (Scheme 3.1c).[24] Therefore, it was decided to explore the use of P_4-*t*-Bu superbase in halocyclization reactions, and the results of the studies on superbase P_4-*t*-Bu mediated stereo- and regioselective halocyclization reactions of 2-(1-alkynyl) benzamides were reported (Scheme 3.1d).

Scheme 3.1 Base Mediated Cyclizations of 2-(1-Alkynyl)benzamides

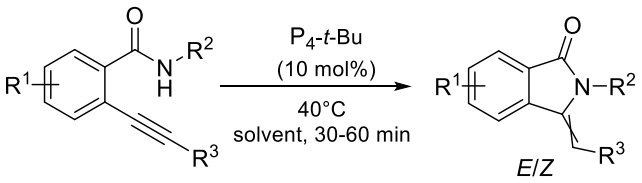
(a) Electrophilic Cyclization of 2-(1-Alkynyl)benzamides yielding Cyclic Imidates[33]



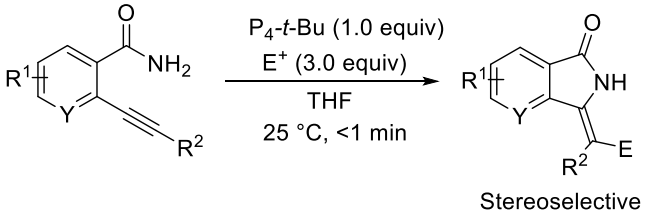
(b) *n*-Butyl Lithium-mediated Iodocyclization of 2-(1-Alkynyl)benzamides generating Isoindolin-1-ones[35]



(c) P4-*t*-Bu Catalyzed Cyclization of *o*-Alkynylbenzamide forming isoindolinones[49]



(d) Present work. P4-*t*-Bu mediated Stereoselective Electrophilic Cyclization of *o*-Alkynylbenzamides

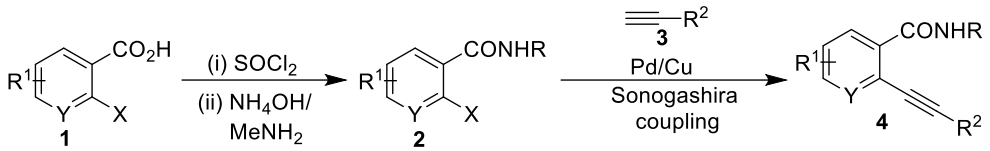


3.2 Results and Discussion

The starting materials, 2-(1-alkynyl)benzamides, were prepared through a two-step strategy (Scheme 3.2). The reaction of commercially available *o*-halobenzoic acids **(1a-1e)** with thionyl chloride, followed by the reaction with ammonia/primary amine, resulted in the formation of *o*-halobenzamides **(2a-2g),** which were then subjected to

Sonogashira coupling[25] with appropriate terminal alkyne **(3)** to afford *o*-alkynylbenzamides **(4a-4aa)** in good to excellent yields (Table 3.1).

Scheme 3.2 Strategy for the Synthesis of 2-(1-alkynyl)benzamides

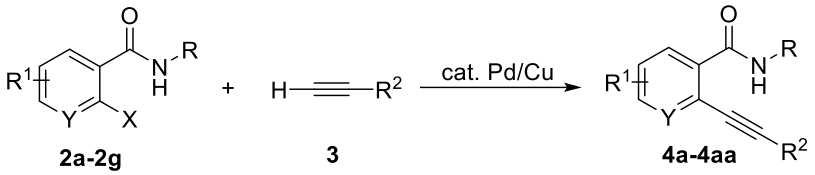


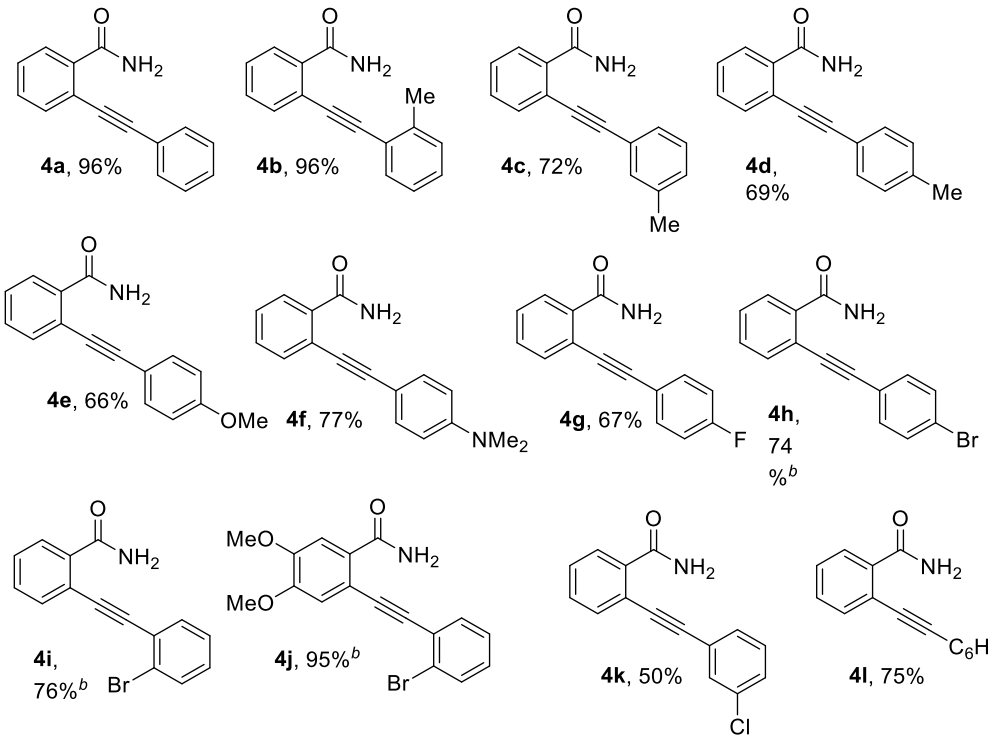
R^1 = H, X = I, Y = CH (**1a**)
R^1 = 5-F, X = I, Y = CH (**1b**)
R^1 = 5-NO_2, X = Br, Y = CH (**1c**)
R^1 = H, X = Br, Y = N (**1d**)
R^1 = 4,5-$(OMe)_2$, X = I, Y = CH (**1e**)

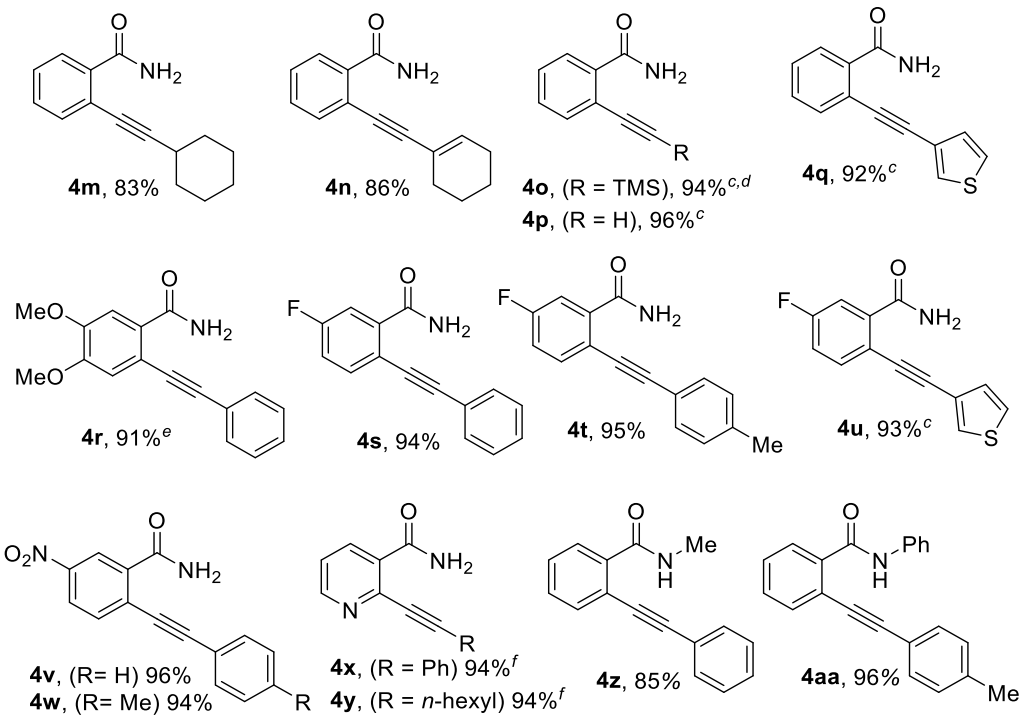
R^1 = H, R^2 = H, X = I, Y = CH (**2a**)
R^1 = 5-F, R^2 = H, X = I, Y = CH (**2b**)
R^1 = 5-NO_2, R^2 = H, X = Br, Y = CH (**2c**)
R^1 = H, R^2 = H, X = Br, Y = N (**2d**)
R^1 = 4,5-$(OMe)_2$, R^2 = H, X = I, Y = CH (**2e**)
R^1 = H, R^2 = Me, X = I, Y = CH (**2f**)
R^1 = H, R^2 = Ph, X = I, Y = CH (**2g**)

R^1 = H, OMe, NO_2, *etc.*
R^2 = alkyl, aryl, TMS, *etc.*
R = H, Me

Table 3.1 Preparation of 2-(1-Alkynyl)benzamides[a]



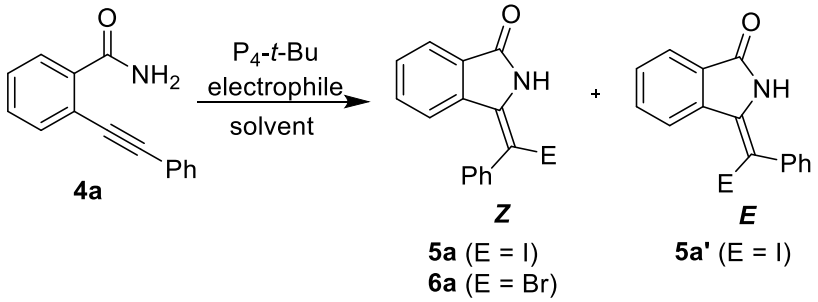




[a]All reactions were carried using 0.50 mmol *o*-iodo/bromo amide substrate in THF (see Experimental Section for details). [b]The reaction was carried out in THF:DIPA (50:1) as a solvent. [c]Compound **4o** (2 mmol) was used for preparing **4p** through TMS group deprotection. [d]This reaction was performed on a 3 mmol scale. [e]15 mol% of catalyst was used, and the reaction was carried out at 80 °C. [f]THF was used as a solvent at 50 °C.

To explore the use of P_4-*t*-Bu in halocyclization reactions 2-(phenylethynyl)benzamide (**4a**) was taken as the model substrate for the cyclization reaction. The summary of the results of the optimization studies is compiled in Table 3.2.

Table 3.2 Optimization Studies for Halocyclization Reaction[a,b]



S. No.	base equiv	solvent	temp (°C)	time (min)	electro phile	total isolated yield (5a + 5a') or (6a) (%)	*Z*/*E ratio* (5a:5a')
1	0.10	THF	25	30	I_2	63[c]	82/18
2	0.10	THF	25	1	I_2	63[c]	82/18

3	0.20	THF	25	1	I_2	72[c]	82/18
4	0.20	THF	25	30	I_2	72[c]	82/18
5	0.30	THF	25	1	I_2	78[c]	84/16
6	0.30	THF	25	30	I_2	78[c]	84/16
7	0.50	THF	25	1	I_2	85	88/12
8	0.50	THF	25	30	I_2	85	88/12
9	**1.0**	**THF**	**25**	**1**	**I_2**	**87**	**100/0**
10	1.0	THF	25	30	I_2	87	100/0
11	1.0	THF	0	1	I_2	87	90/10
12	1.0	THF	50	1	I_2	83	100/0
13	1.0	THF	25	1	1 I_2	72[c]	71/29
14	1.0	THF	25	1	2 I_2	84	73/27
15	1.0	THF	25	1	ICl	82	100/0
16	1.0	THF	25	30	ICl	82	100/0
17	1.0	THF	25	1	NIS	81	100/0
18	1.0	THF	25	1	Br_2	71[d]	-
19	1.0	THF	25	1	NBS	68[d]	-
20	1.0	DCM	25	1	I_2	78	100/0
21	1.0	MeCN	25	1	I_2	73	100/0

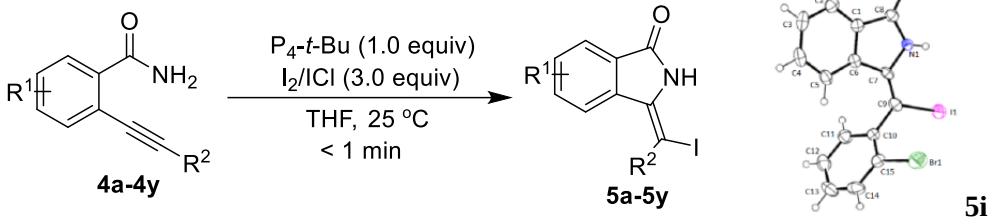
[a]Unless otherwise indicated all reactions were performed on a 0.25 mmol scale using 3.0 equiv of the electrophile. [b]Unless otherwise indicated the reactions were complete in less than 1 min; however, for the uniform comparison of yields, the reactions were stopped after 1 min/30 min**.** [c]Starting material was not consumed completely. [d]Only *Z*-isomer (**6a**) was obtained.

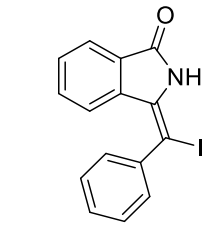
Initially, the cyclization was attempted by using a catalytic amount (10%) of P_4-*t*-Bu superbase (entry 1). Surprisingly, the cyclization occurred *via* the *N*-atom of the amide group leading to the formation of the desired isoindolinone (**5**), the structure of which was confirmed by comparing its spectroscopic data with the previously published results.[35] It may be noted, the major product (**5a**) was found to have a *Z*-configuration across the exocyclic C=C bond. When the reaction was stopped after 1 min (entry 2), the same result was obtained. Notable, the improvement in the product yield and stereoselectivity was observed on increasing the amount of the base (entries 3-8).

However, it was noted that starting material was not completely consumed and/or the *E*-isomer of the product (**5a'**) was also formed in small quantities for all of the experiments where catalytic amount (10-50%) of P_4-*t*-Bu was used (entries 1-8). When 1 equiv of the superbase was used, the best-isolated yield of the exclusively formed *Z*-isomer (87%) was obtained (entry 9). The same result was obtained when the reaction was run for 30 min (entry 10). During optimization studies, it was observed that lowering the reaction temperature resulted in the formation of the *E*-isomer as a minor coproduct (entry 11), whereas a slight reduction in product yield was noted when the reaction was carried at the increased temperature (entry 12). On reducing the amount of the electrophile (I_2), the reaction either did not complete (starting material was remaining with 1 equiv) or a significant amount of *E*-isomer was also formed (entries 13 and 14). The methodology also worked well with ICl and NIS (entries 15-17). The cyclization with bromine electrophiles such as Br_2 and NBS (entries 18 and 19) worked well, although the product yield was lower as compared to reactions with I_2. The brief screening of solvents (such as DCM and MeCN, entries 20 and 21) also resulted in the formation of the desired product, but the yield could not be further improved. In all cases, the product yield remained unchanged when the reaction was run for longer duration (30 min). Therefore, the optimized conditions involved stirring of *o*-alkynylbenzamide (1.0 equiv), P_4-*t*-Bu superbase (1.0 equiv) and I_2 (3.0 equiv) in THF at ambient temperature.

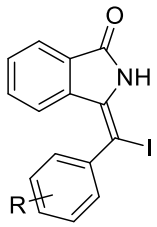
Having optimized the reaction conditions, the scope of the iodocyclization reaction was studied. The reactions were performed with the *o*-alkynyl benzamide substrates (**4a-4aa**) using an iodine electrophile, and the results are presented below (Table 3.3), where the structures of the products along with the isolated yields are indicated. Additionally, a few reactions were also performed using ICl as an electrophile, and where applicable, the corresponding yields were reported in parentheses.

Table 3.3 Scope for P_4-*t*-Bu Mediated Iodocyclization Reaction[a]





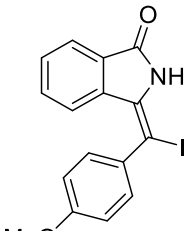
5a, 87% (82%)



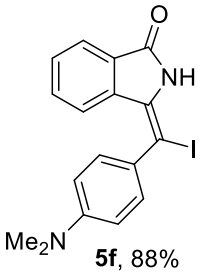
5b (R = *o*-Methyl), 86% (84%)

5c (R = *m*-Methyl), 93% (83%)

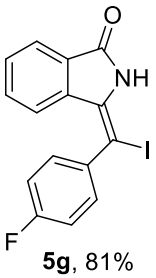
5d (R = *p*-Methyl), 86% (84%)



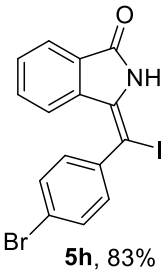
5e, 72% (65%)



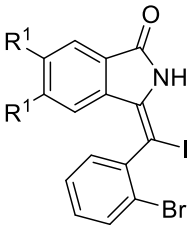
5f, 88% (82%)



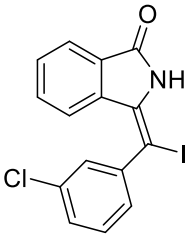
5g, 81% (75%)



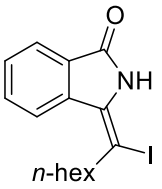
5h, 83% (79%)



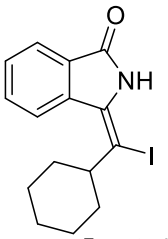
5i (R^1 = H), 86%
5j (R^1 = OMe), 96%



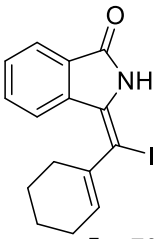
5k, 89% (84%)



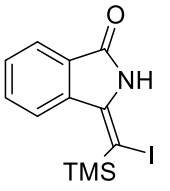
5l, 91% (84%)



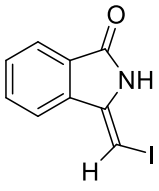
5m, 94% (80%)



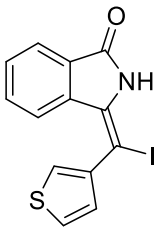
5n, 73% (69%)



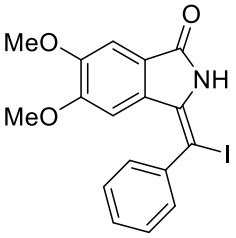
5o, 91% (88%)



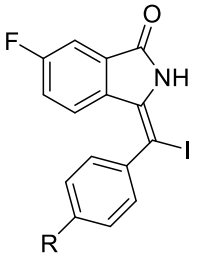
5p,[c] 94% (85%)



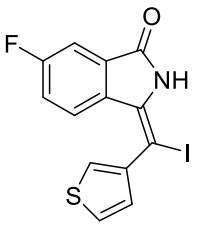
5q, 90%



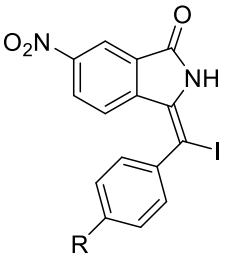
5r, 91% (91%)



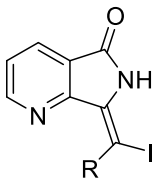
5s, R = H, 90%
5t, R = Me, 96%



5u, 96%



5v, R = H, 97%
5w, R = Me, 93%



5x, R = Ph, 94%
5y, R = *n*-hexyl, 91%

---

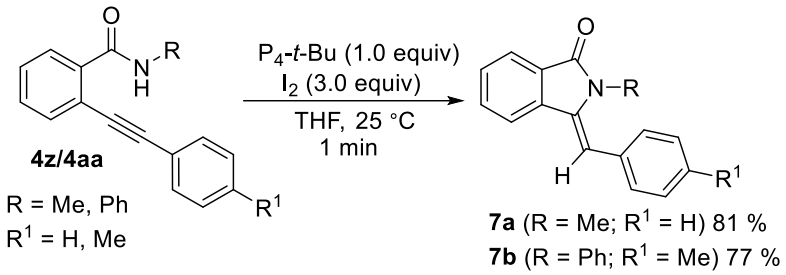
[a]All reactions were run using 0.25 mmol of *o*-(alkynyl)benzamide and 1.0 equiv of P_4-*t*-Bu (0.8 M in hexane) and 3.0 equiv of I_2 in dry THF at 25 °C. [b]The yields in parentheses correspond to the reactions that were performed using 3.0 equiv of ICl as the electrophile. [c]This reaction was also performed at 1 mmol scale (isolated yield: 96%).

When the starting alkyne substrates containing the electron-donating groups (Me, OMe, NMe_2) as well as electron-withdrawing groups (F, Br) on the phenyl ring at the distal end of the alkyne were subjected to the cyclization conditions, the desired isoindolin-1-ones were formed (**5b**-**5k**) in good yields (Table 3.3). Halogen-containing substrates were well tolerated and were efficiently cyclized to give the corresponding desired products **5g**-**5k**. Even the fluoro (-F) group was well tolerated, and the cyclization resulted in the formation of the desired product **5g** in 81% yield. It is also noteworthy that the substrates containing the bromo and chloro groups were efficiently transformed into corresponding cyclized products (**5h-5j**, 83-96%) and **5k** (89%) in good yields and no dehalogenated product was observed in either case. The alkyne substrate containing an aliphatic chain (*n*-hexyl) was also successfully cyclized to give the corresponding product **5l** in 91% yield. The reaction was also successful with alkyne substrate containing a cyclohexyl group to give the desired product **5m** in excellent yield (94%). Even the cyclohexenyl group was well tolerated to give product **5n** in good yield (73%). Alkynyl substrate containing highly labile trimethylsilyl functional group cyclized smoothly and resulted in the formation of cyclized product **5o** in 91% yield, with the TMS group intact. The cyclized product **5p** was formed in excellent yield (94%) on subjecting the terminal alkyne (**4p**) to the cyclization conditions. This reaction was also performed at a higher

scale (1 mmol) and afforded the desired product at an even higher isolated yield of 96%. The substrate containing the heterocyclic moiety (3-thienyl) also worked well under the reaction conditions and resulted in the thienyl containing isoindolin-1-one **5q** in 90% yield. The presence of various electron-donating (**5r**) and withdrawing groups (**5s-5w**) on the benzamide ring of the alkynyl substrates worked efficiently under the given reaction conditions. With fluoro (-F) substitution on the benzamide ring, the substrates containing the phenyl, *p*-tolyl, and even 3-thienyl groups at the alkyne-terminal afforded the corresponding products **5s**-**5u** in excellent yields (90-96%). Substrates having an electron-withdrawing nitro group on the benzamide ring afforded the cyclized products **5v** and **5w** in excellent yields, in 97 and 93%, respectively. The benzamide ring having a heteroatom (nitrogen) was also well accommodated, and the reaction resulted in the isolation of the desired heteroatom-containing isoindolinone derivatives **5x** and **5y** in 94 and 91% yield, respectively. A few reactions that were performed with ICl as the source of the electrophile (indicated above) also afforded the desired products; however, the yields were generally slightly lower as compared to the reactions when iodine was used. All these results indicated that iodine is the electrophile of choice for this methodology.

The iodocyclization of secondary amide substrates was also attempted (Scheme 3.3). Although the substrates underwent cyclization *via* the nitrogen atom of the amide group to form the corresponding isoindolinones, the iodine atom (C-I bond) was found to be absent in the isolated product. Also, the geometry of the resulting products **7a** and **7b** was found to be different (the nitrogen atom is *trans* with respect to the incoming H) as compared to the products (**5a-5y**) obtained from primary amide substrates (where the nitrogen atom is *cis* with respect to the incoming I). This observation has been discussed in the mechanism section (Scheme 3.4).

Scheme 3.3 Cyclization of *N*-Substituted *o*-Alkynylbenzamides



Thus, the above results indicated that it is an efficient methodology for the synthesis of isoindolin-1-ones, and it is superior to the previously reported BuLi-mediated iodocyclization on several important criteria. These included ambient reaction conditions, ease of setting up the reactions, as well as having metal-free conditions. Also, the reactions generally afforded better yields, were faster, were cleaner, and were scalable. The present methodology also had a broader scope, as the trimethylsilyl group, as well as the halogens, were well tolerated. The tolerance of halogens, particularly the bromo group, offered the possibility of further expansion of the present methodology for the synthesis of more complex derivatives as well as natural products. This type of expansion was not possible for the BuLi mediated iodocyclization methodology, due to the debromination of the bromo-containing substrates during the reaction.

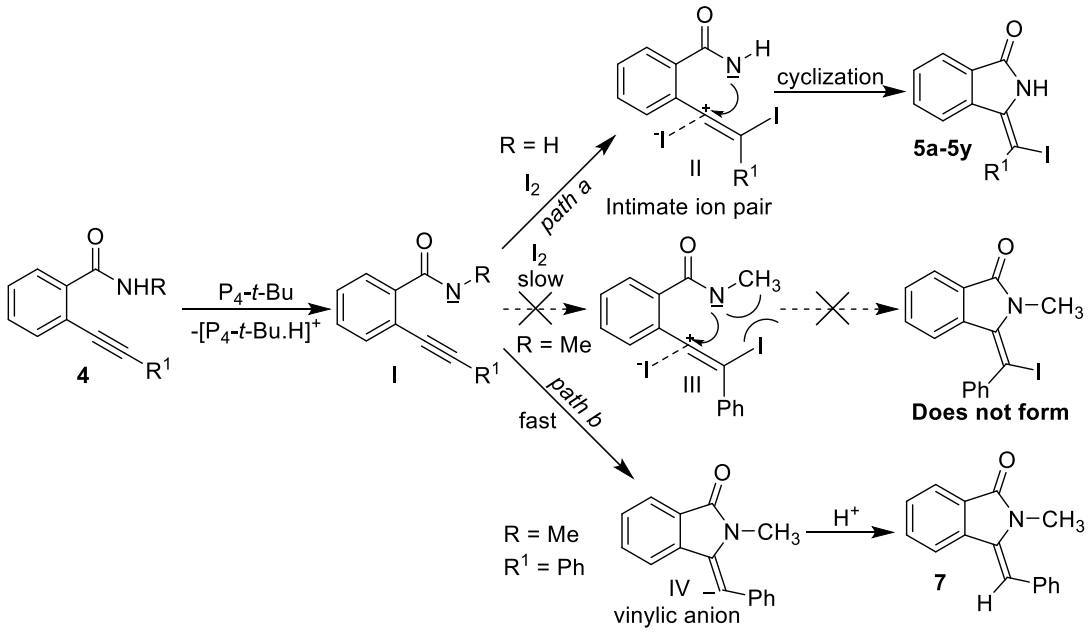
Moreover, the present methodology also worked with a secondary amide group, leading to the formation of the desired isoindolinone (although without the incorporation of an iodo group). Thus, the new and successful substrates in this work either expanded the scope of this methodology and/or provided insights for the possible mechanism of the reaction. Overall, these results reported here constituted a significant advancement in the area of electrophilic cyclization of alkynes and will further advance this interesting area of organic synthesis.

In order to explain the interesting results obtained through the superbase mediated electrophilic cyclization reaction, various factors were considered that affected the

reaction as well as the various types of intermediates that might be involved.[10,26] Moreover, the recent literature reported the evidence for the formation of an intimate ion pair intermediate that was reported to be isolated and characterized through X-ray crystallography,[27] for a base mediated iodocyclization reaction of a metallabenzene. Given the literature evidence available in this regard, along with our combined observations with bases BuLi as well as P_4-*t*-Bu, we proposed a similar kind of intermediate, *i.e.,* an intimate ion pair intermediate for the mechanism of this reaction (Scheme 3.4). It appears that the first step of the base-mediated cyclization of 2-(1-alkynyl)benzamides involved the generation of the amide anion (I).[11-13] After that, in the presence of iodine, the aminocyclization of primary amide containing substrates proceeded through the intimate ion pair (II) intermediate (path a). As far as the quantity of the base is concerned, it seems that a stoichiometric amount of superbase is required for the quick and complete generation of the intermediate, as well as for the cyclization reaction. It must also be mentioned here that, while we believe that involvement of an intimate ion pair is likely, alternatively the involvement of a cationic intermediate cannot be completely ruled out.

Furthermore, in the case of the secondary amide substrates (**4z** and **4aa)**, the formation of the corresponding intimate ion pair (III) was presumably slow due to the steric hindrance. It appears that the cyclization proceeded through an alternate mechanism (path b), *i.e*., a relatively fast anionic mechanism in this case, where the vinylic anion intermediate (IV) seemed to be quenched with H^+ (presumably during the reaction workup), leading to the isolation of the corresponding isoindolinones (**7a** and **7b**) without iodine incorporation.

Scheme 3.4 Plausible Mechanism



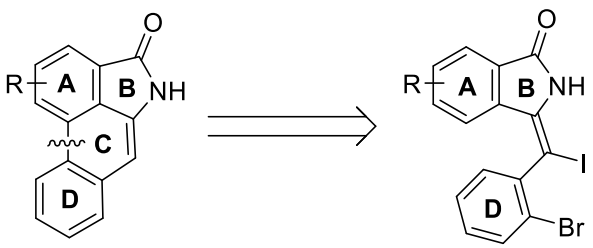
It may be noted that, when the substrate was subjected to BuLi mediated iodocyclization conditions, the *N*-cyclization was disfavored, and the reaction resulted in the isolation of the *O*-cyclized product.[10] The combined observations suggested that being a kinetically controlled reaction, the presence of a free amide group was necessary for the successful iodoaminocyclization. Any steric hindrance at the nitrogen atom of the amide functionality leads to either the *N*-cyclized product without the incorporation iodine atom (for P_4-*t*-Bu mediated cyclization) or *O*-cyclization (for BuLi mediated cyclization). Finally, the nature of the base also appeared to be an important factor for the cyclization, and interestingly, the use of P_4-*t*-Bu seemed to favor *N*-cyclization.[24]

The presence of a C-I bond as well as the free *–NH* group in the iodocyclized products provided easy handles for further functionalization. It had been previously demonstrated through through alkylation/arylation of the lactam *(–NH),*[10] as well as various metal-catalyzed transformations such as Sonogashira alkynylation, Heck reaction, Suzuki-Miyaura coupling, *etc*., on iodo-containing heterocycles[28,29] Further, the utility of this superbase mediated iodocyclization methodology for the synthesis of

important natural products was tested. As mentioned above, the isoindolinone core is prevalent in a variety of biologically active natural products, and there is still scope for the development of new and efficient methodologies for the synthesis of important natural products and their analogues. One such example is Aristolactams, which is an important class of naturally occurring phenanthrene lactam alkaloids, found in the leaves and roots of several plant families such as Aristolochiaceae, Piperaceae, *etc*.[30,31] In East Asia, traditionally the aristolactams have been used as folk medicines and have also displayed important biological properties including anticancer, anti-inflammatory, antiplatelet and neuroprotective activities.[32-34] We thought of devising a new synthetic route for aristolactams using this iodocyclization methodology. This utility was demonstrated in synthesizing a particular aristolactam derivative, namely aristolactam BII (also known as Cepharanone B), due to its known antitumor[35] and antitubercular activities.[36]

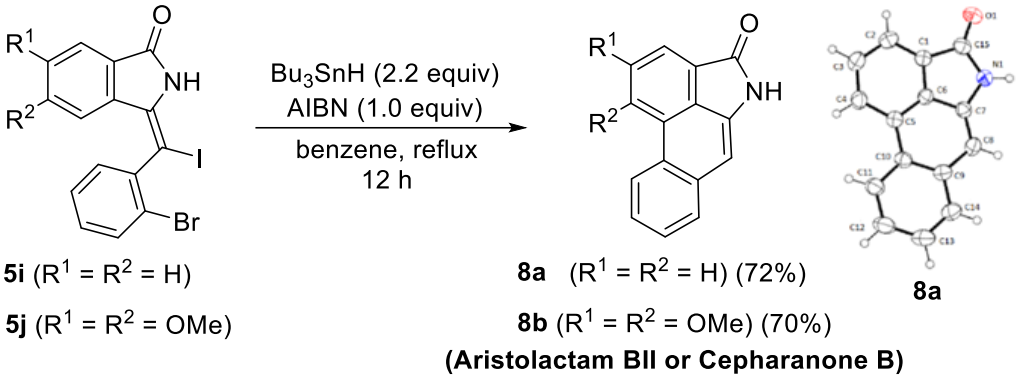
As indicated above, the substrates containing halogens were easily tolerated under the reported iodocyclization conditions (see products **5i** and **5j** in Table 3.3). This feature of resulting methodology was used for further extension. This feature was used to synthesize aristolactam derivatives. A brief retrosynthetic analysis was used (Scheme 3.5), it was envisioned that the aristolactam derivatives could indeed be conveniently synthesized by constructing the **"C"** ring (Scheme 3.5) through an annulation reaction (such as free radical-mediated annulation) of a suitably substituted isoindolinone derivative obtained from P_4-*t*-Bu superbase mediated iodocyclization methodology.

Scheme 3.5 Retrosynthetic Analysis for the Synthesis of Aristolactams from iodocyclized products



The *Z* geometry of at the exocyclic C=C double bond of the cyclized products (confirmed through the X-ray crystallographic studies of the cyclized product **5i)** seemed to be favorable for a subsequent annulation reaction.

Scheme 3.6 Synthesis of Aristolactam Derivatives



5i ($R^1 = R^2 = H$)

5j ($R^1 = R^2 = OMe$)

8a ($R^1 = R^2 = H$) (72%)

8b ($R^1 = R^2 = OMe$) (70%)

(Aristolactam BII or Cepharanone B)

8a

The isoindolinones containing a suitable substituted bromo group when subjected to free radical cyclization using tributyltin hydride and AIBN,[37,38] resulted in the formation of the aristolactam derivative and Cepharanone B/aristolactam BII in good yields of 72 and 70%, respectively. Thus, it has been demonstrated that the methodology offered scope for the synthesis of novel isoindolinones, related natural products, and their derivatives.

3.3 Conclusions

In summary, a simple and robust methodology for the regio- and stereoselective synthesis of isoindolinones was developed. This was the first report of a superbase mediated electrophilic cyclization/iodocyclization reaction. The reaction were easy to perform, accommodated a variety of sensitive functional groups (including TMS, halogens, *etc*.), worked with other halogen electrophiles (such as ICl, Br_2, NBS, *etc*.), and was also scalable. It may be noted that in addition to the broader scope, the yields were generally higher (on average 15-20%) as compared to the yields obtained through *n*-BuLi mediated iodoaminocyclization. Moreover, the suitably substituted iodocyclized

isoindolinones were conveniently transformed into the corresponding aristolactam derivatives.

3.4 Experimental Section

General Information. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained at 400 and 100 MHz, respectively, with tetramethylsilane (TMS) as the internal standard, using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. Crystal structure analysis were performed on single needle X-ray diffractometer. Reaction progress was monitored by thin-layer chromatography (TLC) analysis, which was performed on commercially available silica gel 60 F_{254} 0.25 mm precoated aluminum foil plates, and visualization was done with short wavelength UV light (254 nm). HRMS data were recorded on an Agilent G6530A (LC-HRMS-Q-TOF) mass spectrometer equipped with an electrospray source with a mass accuracy > 2 ppm having an HPLC pressure of 600 bar and an MS pressure of 10^{-4} to 10^{-5} Torr. Compound purification was performed by column chromatography using commercially available silica having mesh size 100-200, and using ethyl acetate-hexane as a solvent. All melting points were uncorrected.

Reagents and Solvents. Unless otherwise indicated, all reagents and solvents were used as obtained commercially.

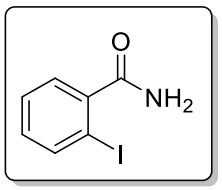
*2-Halobenzoic Acids (**1a**-**1e**).* Commercially available and used as received.

*Terminal Alkynes (**3**).* Commercially available terminal alkynes were used as received.

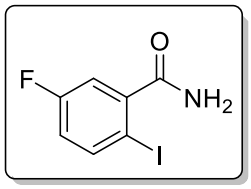
Superbase P_4-*t*-Bu (0.8 M in hexane) was used as received (Sigma Aldrich, SKU 79421).

Procedure for the synthesis of 2-Halobenzamides. To an oven-dried round-bottom flask, the corresponding 2-Halobenzoic acid **1a**-**1e** (1 g) was added followed by the addition of 5 mL of thionyl chloride ($SOCl_2$). The solution was allowed to reflux for 7 h. After the completion of the reaction, the excess of thionyl chloride was removed under reduced

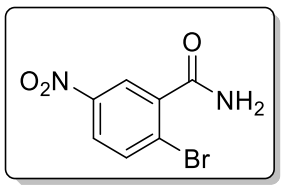
pressure and the residue was cooled to 0 °C using an ice-bath. The corresponding primary amine was added dropwise while vigorously stirring the reaction mixture. The amide (**2a-2g)** was formed as white solid, which was filtered in scintered flask and washed with water several times to remove any traces of starting acid. The moist amide was dried in a hot air oven at 50 °C for 12 h, weighed, and used as such.



2-Iodobenzamide (2a).[39] This compound was prepared by performing the reaction on a 10.0 mmol scale. Yield: 2.42 g (98%); white solid; TLC R_f = 0.15 (30% EtOAc:Hexanes, UV); mp 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 10.4 Hz, 1H), 7.48-7.46 (m, 1H), 7.41-7.37 (m, 1H), 7.14-7.10 (m, 1H), 5.88 (s, 2H).

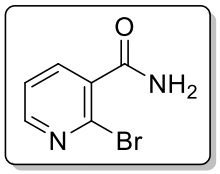


5-Fluoro-2-iodobenzamide (2b).[40] Yield: (976.3 mg, 98%); white solid; TLC R_f = 0.22 (40% EtOAc:Hexanes, UV); mp 161-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84-7.81 (m, 1H), 7.22-7.19 (m, 1H), 6.90-6.86 (m, 1H), 6.21 (s, 1H), 5.91 (s, 1H).

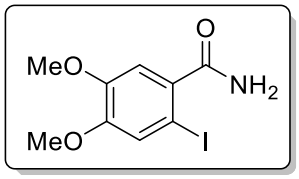


2-Bromo-5-nitrobenzamide (2c). Yield: (956.0 mg, 96%); white solid; TLC R_f = 0.18 (30% EtOAc:Hexanes, UV); mp 130-132 °C; IR (KBr, cm^{-1}) 3361, 3186, 1627, 639; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18-8.16 (m, 2H), 8.12 (s, 1H), 7.97 (d, J = 8.40 Hz, 1H), 7.85 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.6, 147.0,

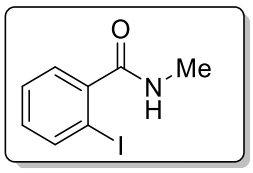
140.8, 135.0, 126.9, 125.5, 123.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_7H_6BrN_2O_3$ 244.9556; Found 244.9554.



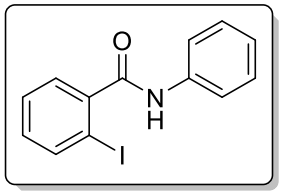
2-Bromonicotinamide (2d). Yield: (776.1 mg, 78%); white solid; TLC R_f = 0.26 (50% EtOAc:Hexanes, UV); mp 185-187 °C; IR (KBr, cm^{-1}) 3329, 3153, 1669, 629; ^1H NMR (400 MHz, DMSO-d_6) δ 8.45-8.44 (m, 1H), 8.05 (s, 1H), 7.90-7.88 (m, 1H), 7.78 (s, 1H), 7.49-7.46 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 167.4, 150.5, 146.7, 138.3, 133.9, 123.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_6H_6BrN_2O$ 200.9658; Found 200.9651.



2-Iodo-4,5-dimethoxybenzamide (2e). Yield: (966.8 mg, 97%); white solid; TLC R_f = 0.15 (40% EtOAc:Hexanes, UV); mp 186-188 °C; IR (KBr, cm^{-1}) 3364, 319, 2964, 1638, 1256 ; ^1H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.39 (s, 1H), 7.28 (s, 1H), 6.96 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.1, 149.7, 148.3, 134.6, 121.9, 111.8, 81.8, 55.9, 55.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{11}INO_3$ 307.9778; Found 307.9780.



2-Iodo-N-methylbenzamide (2f).[39] Yield: (979 mg, 93%); white solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145-147 °C)[2]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84-7.81 (m, 1H), 7.35-7.33 (m, 2H), 7.10-7.03 (m, 1H), 5.99 (s, 1H), 2.97 (d, *J* = 4.80 Hz, 3H).

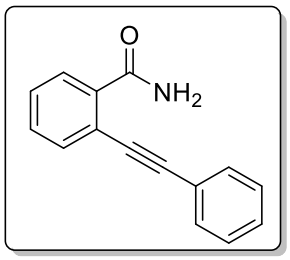


2-iodo-N-phenylbenzamide (2g).[10] Yield: (1.27 g, 98%); white solid; TLC R_f = 0.33 (10% EtOAc:Hexanes, UV); mp 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 7.2 Hz, 1H), 7.63-7.61 (m, 3H), 7.50-7.48 (m, 1H), 7.42-7.35 (m, 3H), 7.19-7.10 (m, 2H).

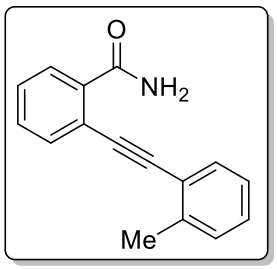
Procedure for Sonogashira Coupling

The starting bromo/iodo amide (0.50 mmol) was placed in DMF (6 mL) in an oven-dried round bottom flask. $Pd(PPh_3)_2Cl_2$ (4 mol %) and copper iodide (2 mol %) were added to the flask, and the reaction mixture was placed under Argon atmosphere. The reaction mixture was stirred (5 min) at room temperature, and triethylamine (4.0 equiv) was added by syringe. The temperature was then increased to 70 °C. The terminal alkyne (1.2 equiv) dissolved in DMF (2 mL) was added dropwise over 5 min. The reaction mixture was allowed to stir at 70 °C for 2 h, and the reaction progress was monitored by TLC to establish completion. After the reaction was over, it was allowed to cool and was quenched with aqueous NH_4Cl (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried using anhydrous Na_2SO_4, and was evaporated under reduced pressure. The crude product thus obtained was purified through column chromatography.

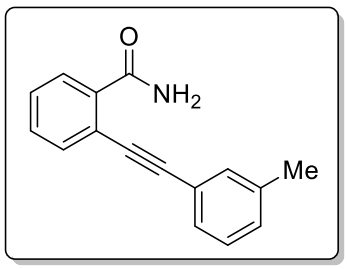
Substrates **4h, 4i** and **4j** were synthesized using the slightly modified procedure, as the reaction was carried at 50 °C in THF:DIPA (50:1) as the solvent, and that the terminal alkyne in THF (2 mL) was added very slowly over a period of 30 min. Substrate **4r** was prepared as before.[35] For preparing substrate **4x** and **4y**, the reaction was carried out at 50 °C using THF as the solvent. The terminal alkyne **4p** was prepared from **4o** as before on a 2 mmol scale, as per a modified literature procedure.[4, 41]



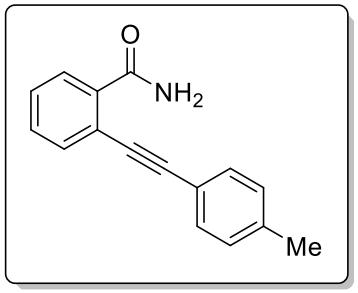
2-(Phenylethynyl)benzamide (4a).[42] Yield: (106.1 mg, 96%); yellow solid; TLC R_f = 0.26 (30% EtOAc:Hexanes, UV); mp 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13-8.11 (m, 1H), 7.64-7.62 (m, 1H), 7.55-7.53 (m, 2H), 7.50-7.43 (m, 3H), 7.40-7.36 (m, 3H), 6.23 (s, 1H).



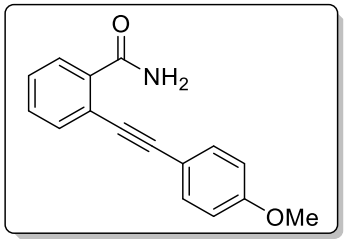
2-(o-Tolylethynyl)benzamide (4b). Yield: (112.9 mg, 96%); white solid; TLC R_f = 0.28 (30% EtOAc:Hexanes, UV); mp 131-133 °C; IR (KBr, cm^{-1}) 3380, 3179, 3019, 2214, 1650, 1397; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.58-7.56 (m, 2H), 7.52-7.49 (m, 1H), 7.46-7.38 (m, 3H), 7.28-7.27 (m, 2H), 7.22-7.16 (m, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.2, 139.9, 139.4, 132.5, 131.6, 129.6, 129.5, 128.8, 128.4, 127.5, 125.8, 122.2, 120.0, 91.7, 91.6, 20.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1081.



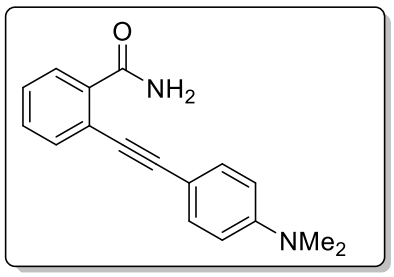
2-(m-Tolylethynyl)benzamide (4c).[10] Yield: (84.7 mg, 72%); yellow solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14-8.12 (m, 1H), 7.63-7.61 (m, 1H), 7.50-7.43 (m, 3H), 7.36-7.33 (m, 2H), 7.29-7.27 (m, 1H), 7.22-7.20 (m, 1H), 6.20 (s, 1H), 2.37 (s, 3H).



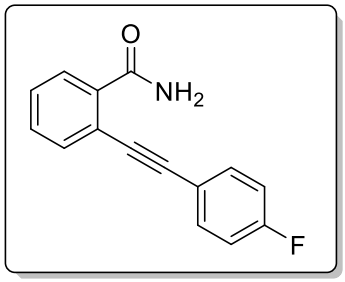
2-(p-Tolylethynyl)benzamide (4d).[43] Yield: (81.2 mg, 69%); yellow solid; TLC R_f = 0.30 (30% EtOAc:Hexanes, UV); mp 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13-8.11 (m, 1H), 7.62-7.60 (m, 1H), 7.49-7.41 (m, 5H), 7.19-7.17 (m, 2H), 6.28 (s, 1H), 2.38 (s, 3H).



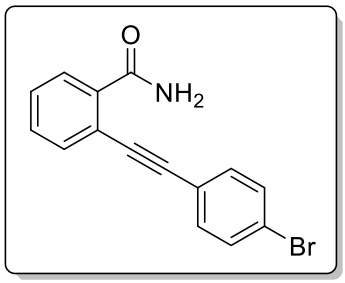
2-((4-Methoxyphenyl)ethynyl)benzamide (4e).[42] Yield: (82.9 mg, 66%); yellow solid; TLC R_f = 0.23 (30% EtOAc:Hexanes, UV); mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.05 (m, 1H), 7.58-7.55 (m, 2H), 7.45-7.38 (m, 4H), 6.97 (s, 1H), 6.87-6.85 (m, 2H), 3.79 (s, 3H).



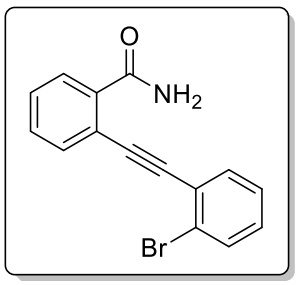
2-((4-(dimethylamino)phenyl)ethynyl)benzamide (4f).[10] Yield: (101.8 mg, 77%); brown yellow solid; TLC R_f = 0.22 (30% EtOAc:Hexanes, UV); mp 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17-8.15 (m, 1H), 7.75 (s, 1H), 7.59-7.58 (m, 1H), 7.45-7.38 (m, 4H), 6.67-6.65 (m, 2H), 6.08 (s, 1H), 3.01 (s, 6H).



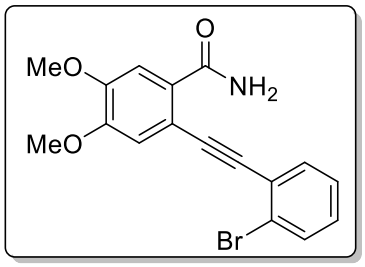
2-((4-Fluorophenyl)ethynyl)benzamide (4g).[43] Yield: (80.2 mg, 67%); yellow solid; TLC R_f = 0.21 (30% EtOAc:Hexanes, UV); mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09-8.07 (m, 1H), 7.68-7.60 (m, 2H), 7.54-7.50 (m, 2H), 7.48-7.45 (m, 2H), 7.10-7.05 (m, 2H), 6.26 (s, 1H).



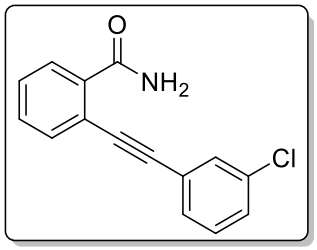
2-((4-Bromophenyl)ethynyl)benzamide (4h).[10] Yield: (111.0 mg, 74%); brown yellow solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09-8.06 (m, 1H), 7.63-7.60 (m, 1H), 7.53-7.51 (m, 2H), 7.49-7.46 (m, 2H), 7.40-7.38 (m, 2H), 7.22 (s, 1H), 5.98 (s, 1H).



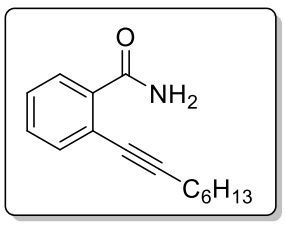
2-((2-Bromophenyl)ethynyl)benzamide (4i).[10] Yield: (114.0 mg, 76%); white solid; TLC R_f = 0.25 (30% EtOAc:Hexanes, UV); mp 177-179°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15-8.13 (m, 1H), 7.68- 7.66 (m, 1H), 7.61-7.56 (m, 2H), 7.49-7.48 (m, 3H), 7.35-7.31 (m, 1H), 7.26-7.22 (m, 2H, including solvent peak), 6.20 (s, 1H).



2-((2-Bromophenyl)ethynyl)-4,5-dimethoxybenzamide (4j). Yield: (171.0 mg, 95%); yellow solid; TLC R_f = 0.45 (30% EtOAc:Hexanes, UV); mp 138-140 °C; IR (KBr, cm^{-1}) 3436, 3150, 2961, 2202, 1671, 1263, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.70 (s, 1H), 7.60-7.54 (m, 2H), 7.32-7.28 (m, 1H), 7.22-7.18 (m, 1H), 7.04 (s, 1H), 6.56 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 150.9, 149.5, 133.4, 132.4, 130.0, 127.2, 124.9, 124.3, 115.3, 115.3, 112.8, 112.5, 93.3, 91.9, 56.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}BrNO_3$ 360.0230; Found 360.0223.

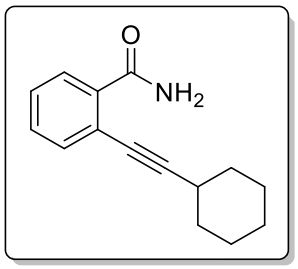


2-((3-Chlorophenyl)ethynyl)benzamide (4k).[45] Yield: (63.9 mg, 50%); brown yellowish solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 139-141 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ = 8.08-8.06 (m, 1H), 7.63-7.60 (m, 1H), 7.52-7.29 (m, 6H), 7.21 (s, 1H), 6.24 (s, 1H).

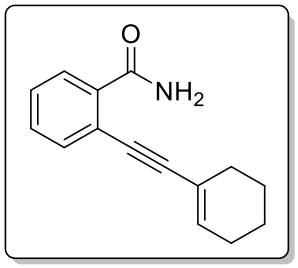


2-(Oct-1-yn-1-yl)benzamide (4l).[45] Yield: (86.0 mg, 75%); yellow solid; TLC R_f = 0.32 (30% EtOAc:Hexanes, UV); mp 88-89 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ = 8.13-8.11 (m, 1H), 7.70 (s, 1H), 7.50-7.48 (m, 1H), 7.43-7.36 (m, 2H), 6.17

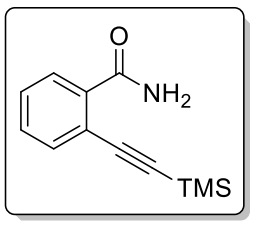
(s, 1H), 2.50-2.46 (m, 2H), 1.67- 1.59 (m, 2H), 1.49-1.41 (m, 2H), 1.36-1.25 (m, 4H), 0.92-0.88 (m, 3H).



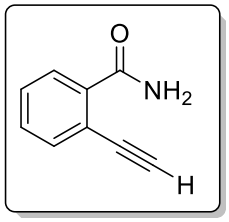
2-(Cyclohexylethynyl)benzamide (4m).[43] Yield: (94.3 mg, 83%); white solid; TLC R_f = 0.31 (30% EtOAc:Hexanes, UV); mp 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13-8.10 (m, 1H), 7.74 (s, 1H), 7.49-7.47 (m, 1H), 7.40-7.37 (m, 2H), 6.43 (s, 1H), 2.69-2.62 (m, 1H), 1.92-1.89 (m, 2H), 1.75-1.73 (m, 2H), 1.56-1.53 (m, 2H), 1.39-1.35 (m, 4H).



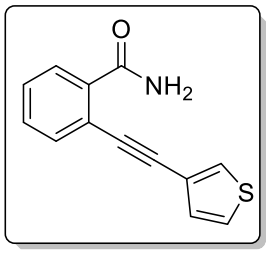
2-(Cyclohex-1-en-1-ylethynyl)benzamide (4n).[42] Yield: (96.9 mg, 86%); white solid; TLC R_f = 0.28 (30% EtOAc:Hexanes, UV); mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13-8.10 (m, 1H), 7.59 (s, 1H), 7.51-7.49 (m, 1H), 7.44-7.37 (m, 2H), 6.57 (s, 1H), 6.28-6.26 (m, 1H), 2.23-2.10 (m, 2H), 2.19-2.15 (m, 2H), 1.72-1.59 (m, 4H).



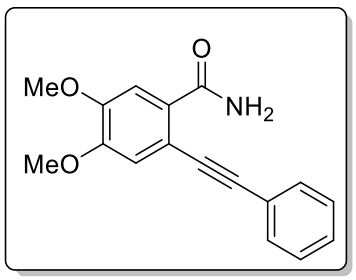
2-((Trimethylsilyl)ethynyl)benzamide (4o).[42] This reaction was performed on a 3 mmol scale. Yield: (612.7 mg, 94%); white solid; R_f = 0.55 (30% EtOAc:Hexanes); mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13-8.10 (m, 1H), 7.70 (s, 1H), 7.54-7.52 (m, 1H), 7.44-7.39 (m, 2H), 6.46 (s, 1H), 0.26 (s, 9H).



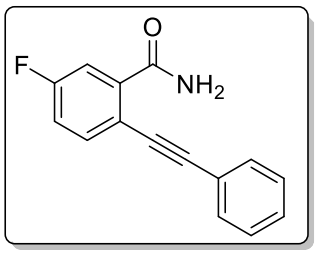
2-Ethynylbenzamide (4p).[42] This reaction was performed on a 2 mmol scale. Yield: (278.6 mg, 96%); yellow solid; TLC R_f = 0.16 (30% EtOAc:Hexanes, UV); mp 146-148 °C (lit. mp 145- 147 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.06 (m, 1H), 7.60-7.58 (m, 1H), 7.49-7.43 (m, 2H), 7.34 (s, 1H), 6.30 (s, 1H), 3.52 (s, 1H).



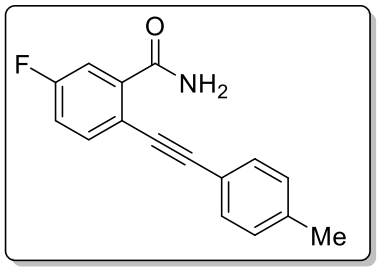
2-(Thiophen-3-ylethynyl)benzamide (4q).[42] Yield: (104.6 mg, 92%); white solid; TLC R_f = 0.24 (30% EtOAc:Hexanes, UV); mp 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06-7.91 (m, 2H), 7.58-7.51 (m, 2H), 7.43-7.25 (m, 4H, including solvent peak), 7.21-7.11 (m, 1H), 6.77-6.71 (m, 1H).



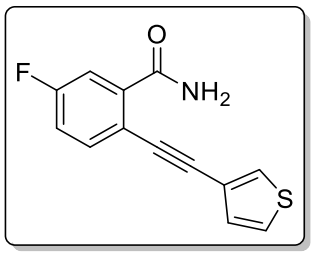
4,5-Dimethoxy-2-(phenylethynyl)benzamide (4r).[10] Yield: (127.9 mg, 91%); brown solid; TLC R_f = 0.20 (50% EtOAc:Hexanes, UV); mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.69-7.64 (m, 1H), 7.54-7.52 (m, 2H), 7.48-7.44 (m, 1H), 7.40-7.38 (m, 2H), 7.05 (s, 1H), 6.11 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H).



5-Fluoro-2-(phenylethynyl)benzamide (4s).[42] Yield: (112.4 mg, 94%); white solid; TLC R_f = 0.54 (30% EtOAc:Hexanes, UV); mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 1H), 7.63-7.60 (m, 1H), 7.53-7.51 (m, 2H), 7.41-7.37 (m, 4H), 7.21-7.17 (m, 1H), 6.35 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 163.7, 137.0, 135.5, 131.5, 129.3, 128.6, 121.7, 117.7, 117.3, 116.2, 95.6, 86.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{11}FNO$ 240.0819; Found 240.0827.

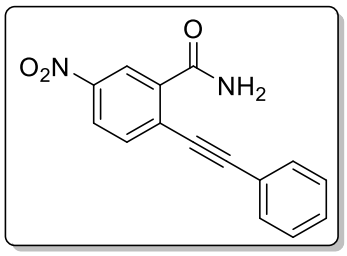


5-Fluoro-2-(p-tolylethynyl)benzamide (4t). Yield: (120.2 mg, 95%); light yellow solid; TLC R_f = 0.47 (30% EtOAc:Hexanes, UV); mp 191-193 °C; IR (KBr, cm^{-1}) 3367, 3167, 2957, 2213, 1644, 1376; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 1H), 7.62-7.58 (m, 2H), 7.42-7.40 (m, 2H), 7.20-7.15 (m, 3H), 6.31 (s, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 163.6, 139.7, 135.5, 135.4, 131.3, 129.3, 118.6, 117.6, 117.3, 116.5, 95.9, 86.0, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}FNO$ 254.0976; Found 254.0994.

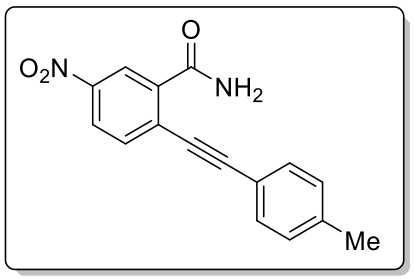


5-Fluoro-2-(thiophen-3-ylethynyl)benzamide (4u). Yield: (114.0 mg, 93%); yellow solid; TLC R_f = 0.41 (30% EtOAc:Hexanes, UV); mp 105-107

°C; IR (KBr, cm^{-1}) 3353, 3175, 2204, 1651, 1384;^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.80-7.79 (m, 1H), 7.64 (s, 1H), 7.63-7.58 (m, 2H), 7.36-7.28 (m, 2H), 7.18-7.17 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.7, 162.5, 141.6, 134.9, 134.8, 129.9, 129.5, 127.0, 121.2, 117.0, 115.0, 88.0, 86.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_9FNOS$ 246.0383; Found 246.0352.

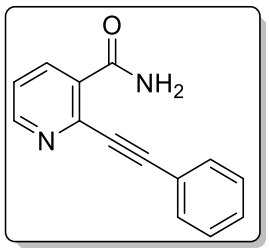


5-Nitro-2-(phenylethynyl)benzamide (4v). Yield: (127.8 mg, 96%); yellow solid; TLC R_f = 0.59 (30% EtOAc:Hexanes, UV); mp 176-177 °C; IR (KBr, cm^{-1}) 3368, 3186, 2209, 1650, 1342; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32-8.29 (m, 2H), 8.13 (s, 1H), 7.92-7.86 (m, 2H), 7.62-7.56 (m, 2H), 7.48-7.45 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.5, 146.8, 141.1, 134.4, 132.1, 130.3, 129.4, 127.0, 124.8, 123.1, 122.0, 98.0, 87.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}N_2O_3$ 267.0764; Found 267.0779.

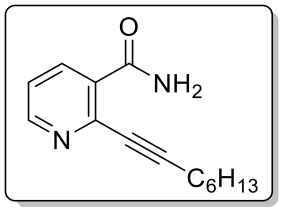


5-Nitro-2-(p-tolylethynyl)benzamide (4w). Yield: (131.7 mg, 94%); yellow solid; TLC R_f = 0.55 (30% EtOAc:Hexanes, UV); mp 217-219 °C; IR (KBr, cm^{-1}) 3373, 3203, 2925, 2209, 1641, 1350; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34-8.28 (m, 2H), 8.12 (s, 1H), 7.86-7.84 (m, 2H), 7.51-7.42 (m, 2H), 7.30-7.28 (m, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.6, 146.7, 140.8, 140.3,

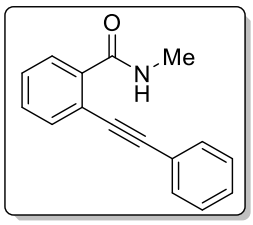
134.0, 131.9, 130.0, 127.3, 124.5, 122.5, 118.5, 98.4, 86.4, 21.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O_3$ 281.0921; Found 281.0928.



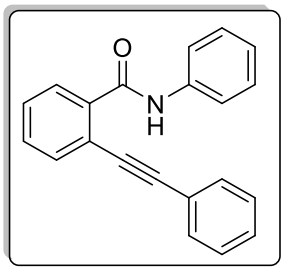
2-(Phenylethynyl)nicotinamide (4x). Yield: (93.4 mg, 84%); white solid; TLC R_f = 0.27 (50% EtOAc:Hexanes, UV); mp 201-202 °C; IR (KBr, cm^{-1}) 3370, 3173, 2223, 1648; ^1H NMR (400 MHz, DMSO-d_6) δ 8.63-8.61 (m, 1H), 8.03 (s, 1H), 7.91-7.88 (m, 1H), 7.74 (s, 1H), 7.57-7.51 (m, 2H), 7.47-7.43 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 168.0, 150.5, 139.0, 136.0, 135.4, 131.6, 129.5, 128.8, 123.1, 121.6, 91.5, 87.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{11}N_2O$ 223.0866; Found 223.0872.



2-(Oct-1-yn-1-yl)nicotinamide (4y). Yield: (103.6 mg, 90.0%); yellow viscous liquid; TLC R_f = 0.20 (30% EtOAc:Hexanes, UV); IR (KBr, cm^{-1}) 3370, 3174, 2957, 2924, 2232, 1650; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.65-8.63 (m, 1H), 8.42-8.40 (m, 1H), 7.74 (s, 1H), 7.35-7.32 (m, 1H), 6.51 (s, 1H), 2.54-2.50 (m, 2H), 1.69-1.62 (m, 2H), 1.48-1.40 (m, 2H), 1.31-1.27 (m, 4H), 0.89-0.86 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 166.6, 151.8, 139.9, 138.3, 130.3, 122.7, 98.1, 79.6, 31.2, 28.7, 27.9, 22.4, 19.5, 13.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}N_2O$ 231.1492; Found 231.1495.



N-Methyl-2-(phenylethynyl)benzamide (4z).[8] Yield: (100.0 mg, 85%); white solid; TLC R_f = 0.23 (10% EtOAc:Hexanes, UV); mp 105-106 °C (lit. mp 103-105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02-8.00 (m, 1H), 7.59-7.56 (m, 1H), 7.50-7.50 (m, 2H), 7.43-7.40 (m, 2H), 7.39-7.37 (m, 3H), 7.33 (s, 1H), 3.06 (d, J = 4.8 Hz, 3H).

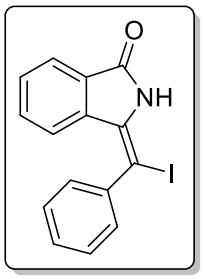


N-phenyl-2-(p-tolylethynyl)benzamide (4aa).[46] Yield: (149.4 mg, 96%); white solid; TLC R_f = 0.60 (20% EtOAc:Hexanes, UV); mp 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (s, 1H), 8.13-8.11 (m, 1H), 7.68-7.63 (m, 3H), 7.50-7.44 (m, 4H), 7.41-7.32 (m, 5H), 7.16-7.12 (m, 1H).

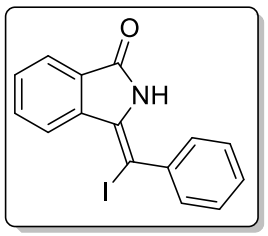
Procedure for Iodocyclization Reaction.

To an oven-dried round-bottom flask, the appropriate alkyne substrate **4** (0.25 mmol) was taken in 2 mL of THF at 25 °C and flushed with Argon. 1.0 equiv of P_4-*t*-Bu (0.8 M in hexane) superbase was added by syringe. Iodine (3 equiv)/[ICl (3 equiv; 1.0 molar in THF)] dissolved in 1 mL of THF was added by a syringe and the reaction was stirred for 1 minute (since the addition of superbase). The reaction was quenched by the addition of saturated aq. NH_4Cl (3 mL), followed by the addition of satd. aq. $Na_2S_2O_3$ (3 mL). Water (10 mL) was added, and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried using anhydrous Na_2SO_4, evaporated under

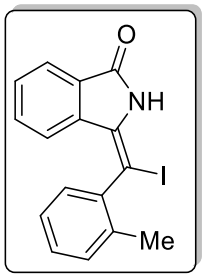
reduced pressure, and the residue was purified by column chromatography (using hexane-EtOAc as eluent) to afford the pure isoindolin-1-one product **5**.



(Z)-3-(Iodo(phenyl)methylene)isoindolin-1-one (5a).[10] Yield: (75.5 mg, 87%); yellow solid; TLC R_f = 0.62 (30% EtOAc:Hexanes, UV); mp 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79-7.77 (m, 1H), 7.69 (s, 1H), 7.46-7.39 (m, 6H), 7.24-7.22 (m, 1H), 6.51 (d, J = 8.4 Hz, 1H).

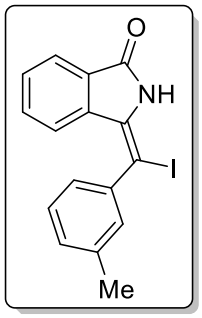


(E)-3-(Iodo(phenyl)methylene)isoindolin-1-one (5a').[10] Yield: (10 mg, 12%); white solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 172-173°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.97 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.77-7.73 (m, 1H), 7.64-7.62 (m, 1H), 7.61-7.61 (m, 1H), 7.46-7.42 (m, 4H), 7.39-7.35 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 166.2, 141.9, 136.1, 135.5, 132.0, 131.1, 130.1, 129.1, 129.1, 129.0, 123.9, 123.7, 72.8.

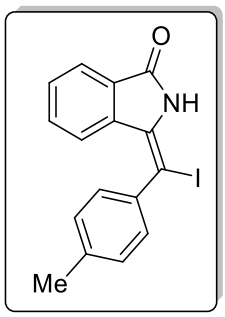


(Z)-3-(Iodo(o-tolyl)methylene)isoindolin-1-one (5b). Yield: (84.6 mg, 94%); light yellow solid; TLC R_f = 0.36 (30% EtOAc:Hexanes, UV); mp 144-145 °C; IR (KBr, cm^{-1}) 3170, 2959, 1708, 1467; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H),

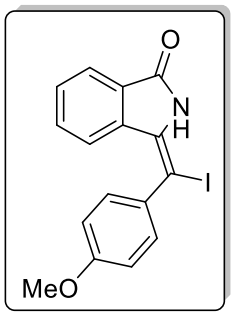
7.67 (d, *J* = 7.6 Hz, 1H), 7.45-7.41 (m, 1H), 7.37-7.28 (m, 4H), 7.26-7.21 (m, 1H), 6.02 (d, *J* = 8.0 Hz, 1H), 2.10 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 167.4, 140.8, 138.5, 135.6, 134.6, 132.4, 131.2, 130.8, 129.4, 129.3, 129.1, 127.0, 123.1, 122.0, 77.4, 18.9; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}INO$ 362.0036; Found 362.0047.



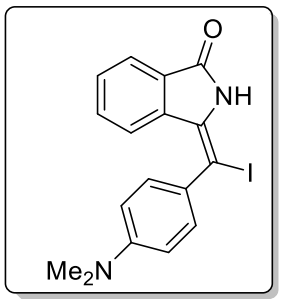
(Z)-3-(Iodo(m-tolyl)methylene)isoindolin-1-one (5c).[10] Yield: (83.9 mg, 93%); white solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78-7.72 (m, 2H), 7.41-7.38 (m, 1H), 7.35-7.31 (m, 1H), 7.25-7.21 (m, 4H), 6.53 (d, *J* = 7.6 Hz, 1H), 2.37 (s, 3H).



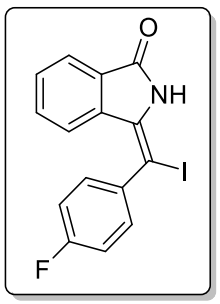
(Z)-3-(Iodo(p-tolyl)methylene)isoindolin-1-one (5d).[10] Yield: (77.6 mg, 86%); white solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.44-7.40 (m, 1H), 7.35-7.33 (m, 2H), 7.29-7.25 (m, 4H, including solvent peak), 6.61 (d, *J* = 8.0 Hz, 1H), 2.45 (s, 3H).



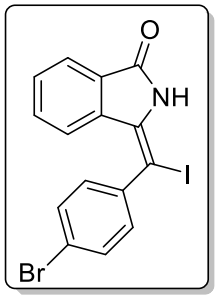
(Z)-3-(Iodo(4-methoxyphenyl)methylene)isoindolin-1-one (5e).[10] Yield: (67.9 mg, 72%); brown solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.40-7.33 (m, 3H), 7.24-7.22 (m, 1H), 6.95-6.93 (m, 2H), 6.59 (d, J = 7.6 Hz, 1H), 3.85 (s, 3H).



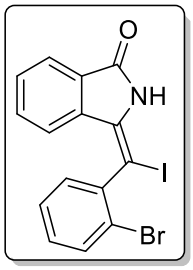
(Z)-3-((4-(Dimethylamino)phenyl)iodomethylene)isoindolin-1-one (5f).[10] Yield: (85.8 mg, 88%); brown solid; TLC R_f = 0.57 (30% EtOAc:Hexanes, UV); mp 192-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.34 (s, 1H), 8.35 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.75-7.71 (m, 1H), 7.50-7.46 (m, 1H), 7.40-7.38 (m, 3H), 6.76 (d, J = 9.2 Hz, 1H), 3.03 (s, 6H).



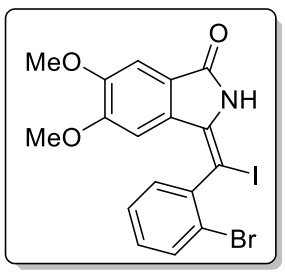
(Z)-3-((4-Fluorophenyl)iodomethylene)isoindolin-1-one (5g).[10] Yield: (73.9 mg, 81%); yellow solid; TLC R_f = 0.55 (30% EtOAc:Hexanes, UV); mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.78 (m, 2H), 7.44-7.41 (m, 3H), 7.17-7.13 (m, 3H), 6.53 (d, J = 7.6 Hz, 1H).



(Z)-3-((4-Bromophenyl)iodomethylene)isoindolin-1-one (5h).[10] Yield: (88.4 mg, 83%); yellow solid; TLC R_f = 0.60 (30% EtOAc:Hexanes, UV); mp 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.61-7.59 (m, 2H), 7.46-7.42 (m, 1H), 7.34-7.30 (m, 3H), 6.61 (d, J = 8.4 Hz, 1H).

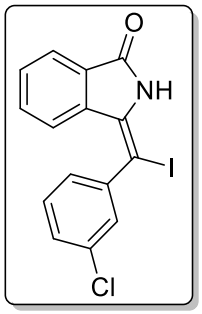


(Z)-3-((2-Bromophenyl)iodomethylene)isoindolin-1-one (5i). Yield: (91.6 mg, 86%); yellow solid; TLC R_f = 0.54 (30% EtOAc:Hexanes, UV); mp 172-174 °C; IR (KBr, cm^{-1}) 3219, 3058, 1707, 1471; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.73-7.71 (m, 1H), 7.44-7.40 (m, 4H), 7.35-7.28 (m, 1H), 6.27 (d, J = 8.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 140.4, 138.8, 134.2, 133.8, 132.6, 131.6, 131.3, 130.8, 129.5, 128.4, 124.1, 123.9, 122.7, 76.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}BrINO$ 425.8985; Found 425.8978.

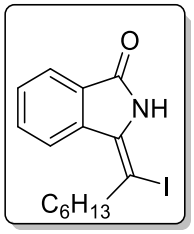


(Z)-3-((2-Bromophenyl)iodomethylene)-5,6-dimethoxyisoindolin-1-one (5j). Yield: (116.6 mg, 96%); yellow solid; TLC R_f = 0.43 (50% EtOAc:Hexanes, UV); mp 174-175 °C; IR (KBr, cm^{-1}) 3198, 2913, 1710, 1463, 1356; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 7.67-7.65 (m, 1H), 7.61-7.59 (m,

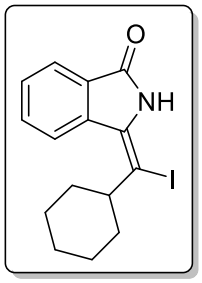
2H), 7.41-7.39 (m, 1H), 7.19 (s, 1H), 6.60 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 169.0, 153.0, 150.8, 135.1, 134.8, 132.5, 131.6, 131.3, 128.8, 127.9, 123.3, 121.4, 104.2, 103.1, 72.0, 56.2, 55.8; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}BrINO_3$ 485.9196; Found 485.9212.



(Z)-3-((3-Chlorophenyl)iodomethylene)isoindolin-1-one (5k).[10] Yield: (84.9 mg, 89%); %); brown solid; TLC R_f = 0.59 (30% EtOAc:Hexanes, UV); mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.77 (m, 2H), 7.45-7.44 (m, 2H), 7.42-7.40 (m, 2H), 7.35-7.27 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H).

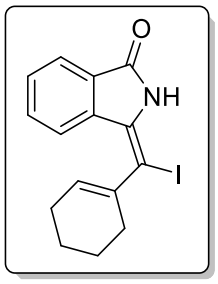


(Z)-3-(1-Iodoheptylidene)isoindolin-1-one (5l).[10] Yield: (80.8 mg, 91%); yellow solid; TLC R_f = 0.69 (30% EtOAc:Hexanes, UV); mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89-7.83 (m, 1H), 7.79-7.77 (m, 1H), 7.66 (s, 1H), 7.63-7.59 (m, 1H), 7.54-7.50 (m, 1H), 1.74-1.67 (m, 2H), 1.48-1.40 (m, 2H), 1.36-1.21 (m, 6H), 0.91-0.80 (m, 3H).

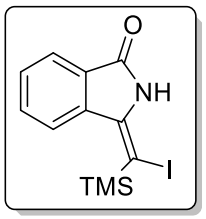


(Z)-3-(Cyclohexyliodomethylene)isoindolin-1-one (5m).[10] Yield: (83.0 mg, 94%); white solid; TLC R_f = 0.66 (30% EtOAc:Hexanes, UV); mp 118-119 °C; ^{1}H

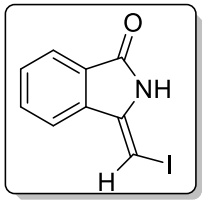
NMR (400 MHz, $CDCl_3$) δ = 7.85-7.80 (m, 3H), 7.65-7.60 (m, 1H), 7.54-7.51 (m, 1H), 2.76-2.72 (m, 1H), 1.90-1.85 (m, 2H), 1.78-1.66 (m, 2H), 1.54-1.47 (m, 4H), 1.27-1.24 (m, 2H).



(Z)-3-(Cyclohex-1-en-1-yliodomethylene)isoindolin-1-one (5n).[10] Yield: (64.0 mg, 73%); white solid; TLC R_f = 0.65 (30% EtOAc:Hexanes, UV); mp 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.43 (s, 1H), 8.35 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7-74-7.70 (m, 1H), 7.51-7.47 (m, 1H), 5.97-5.95 (m, 1H), 2.34-2.32 (m, 2H), 2.26-2.24 (m, 2H), 1.88-1.83 (m, 2H), 1.78-1.75 (m, 2H).

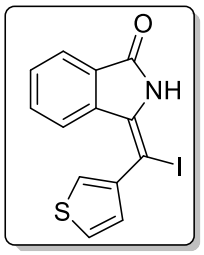


(Z)-3-(Iodo(trimethylsilyl)methylene)isoindolin-1-one (5o). Yield: (78.0 mg, 91%); yellow solid; TLC R_f = 0.37 (20% EtOAc:Hexanes, UV); mp 157-159 °C; IR (KBr, cm^{-1}) 3180, 2917, 1708, 1467; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.51-7.48 (m, 2H), 7.45-7.43 (m, 2H), 0.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.3, 140.0, 135.4, 135.1, 132.2, 131.0, 123.9, 123.9, 71.8, 0.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{15}INOSi$ 343.9962; Found 343.9978.

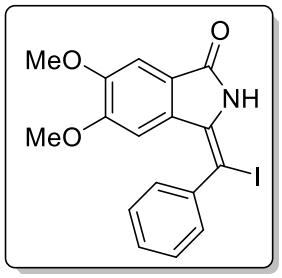


(Z)-3-(Iodomethylene)isoindolin-1-one (5p).[10] Yield: (63.7 mg, 94%), Yield at 1 mmol scale: 260.0 mg, 96%. white solid; TLC R_f = 0.33 (10% EtOAc:Hexanes,

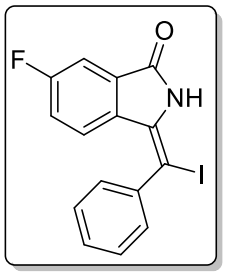
UV); mp 191-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.84-7.79 (m, 1H), 7.68-7.64 (m, 1H), 7.61-7.56 (m, 1H), 6.22 (s, 1H).



(Z)-3-(Iodo(thiophen-3-yl)methylene)isoindolin-1-one (5q).[10] Yield: (79.4 mg, 90%); yellow solid; TLC R_f = 0.58 (30% EtOAc:Hexanes, UV); mp 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, J = 7.2 Hz, 1H), 7.72 (s, 1H), 7.48-7.46 (m, 1H), 7.44-7.42 (m, 2H), 7.34-7.30 (m, 1H), 7.15-7.14 (m, 1H), 6.74 (d, J = 7.6 Hz, 1H).

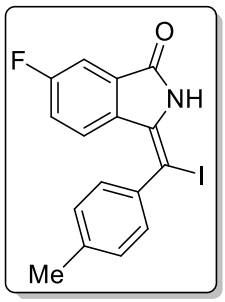


(Z)-3-(Iodo(phenyl)methylene)-5,6-dimethoxyisoindolin-1-one (5r).[10] Yield: (92.6 mg, 91%); yellow solid; TLC R_f = 0.48 (50% EtOAc:Hexanes, UV); mp 206-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.47-7.46 (m, 4H), 7.43-7.39 (m, 1H), 7.18 (s, 1H), 5.87 (s, 1H), 3.89 (s, 3H), 3.39 (s, 3H).

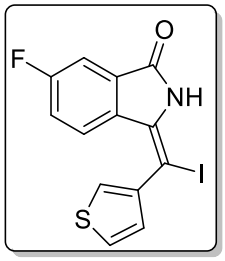


(Z)-6-Fluoro-3-(iodo(phenyl)methylene)isoindolin-1-one (5s). Yield: (82.1 mg, 90%); white solid; TLC R_f = 0.42 (30% EtOAc:Hexanes, UV); mp 176-178 °C; IR (KBr, cm^{-1}) 3342, 1706, 1478, 1362; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.49-7.41 (m, 6H), 6.95-6.90 (m, 1H), 6.47-6.43 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

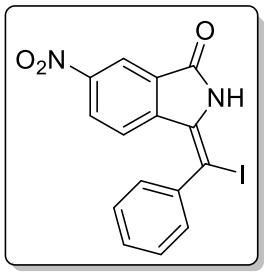
166.0, 164.2, 140.7, 136.8, 134.0, 133.9, 130.4, 129.4, 129.2, 125.2, 119.9, 119.7, 78.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}FINO$ 365.9786; Found 365.9781.



(Z)-6-Fluoro-3-(iodo(p-tolyl)methylene)isoindolin-1-one (5t). Yield: (91.0 mg, 96%); white solid; TLC R_f = 0.38 (30% EtOAc:Hexanes, UV); mp 202-204 °C; IR (KBr, cm^{-1}) 3174, 2957, 2957, 1707, 1478, 1367; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.43-7.41 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.21 (m, 3H, including solvent proton), 6.97-6.92 (m, 1H), 6.56-6.52 (m, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 164.2, 139.6, 137.8, 136.6, 133.9, 130.4, 129.9, 129.3, 125.2, 119.9, 119.6, 79.2, 24.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{12}FINO$ 379.9942; Found 379.9936.

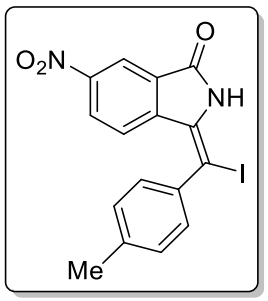


((Z)-6-Fluoro-3-(iodo(thiophen-3-yl)methylene)isoindolin-1-one (5u). Yield: (89.0 mg, 96%); white solid; TLC R_f = 0.33 (30% EtOAc:Hexanes, UV); mp 182-183 °C; IR (KBr, cm^{-1}) 3205, 1709, 1466, 1364; ^1H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.76-7.74 (m, 1H), 7.69-7.68 (m, 1H), 7.48-7.46 (m, 1H), 7.32-7.27 (m, 1H), 7.15-7.14 (m, 1H), 6.50-6.47 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.2, 163.6, 141.7, 138.3, 133.6, 130.9, 128.2, 127.8, 125.9, 124.8, 120.0, 109.7, 72.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_8FINOS$ 371.9350; Found 371.9367.



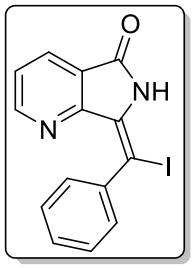
(Z)-3-(Iodo(phenyl)methylene)-6-nitroisoindolin-1-one (5v).

Yield: (95.0 mg, 97%); light yellow solid; TLC R_f = 0.45 (30% EtOAc:Hexanes, UV); mp 190-192 °C; IR (KBr, cm^{-1}) 3172, 1705, 1463, 1342; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61-8.60 (m, 1H), 8.25 (s, 1H), 8.11-8.08 (m, 1H), 7.51-7.42 (m, 5H), 6.62 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 147.9, 140.3, 138.3, 136.6, 133.0, 130.0, 129.4, 129.1, 127.0, 124.2, 119.4, 84.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}IN_2O_3$ 392.9731; Found 392.9722.

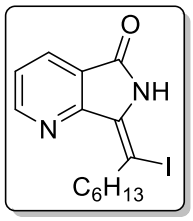


(Z)-3-(Iodo(p-tolyl)methylene)-6-nitroisoindolin-1-one (5w).

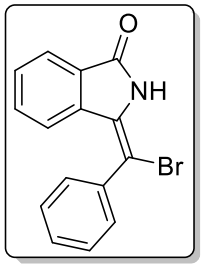
Yield: (94.4 mg, 93%); yellow solid; TLC R_f = 0.41 (30% EtOAc:Hexanes, UV); mp 235-237 °C; IR (KBr, cm^{-1}) 3167, 2924, 1704, 1342; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60-8.60 (m, 1H), 8.13-8.10 (m, 2H), 7.33-7.28 (m, 4H), 6.71 (d, J = 8.8 Hz, 1H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.1, 148.0, 139.6, 139.4, 137.9, 132.9, 130.4, 129.7, 129.4, 127.6, 124.5, 118.6, 79.7, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{12}IN_2O_3$ 406.9887; Found 406.9858.



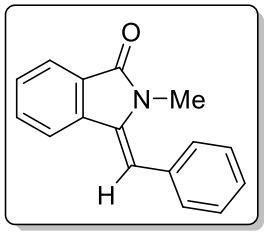
(Z)-7-(Iodo(phenyl)methylene)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (5x). Yield: (81.8 mg, 94%); light yellow solid; TLC R_f = 0.38 (50% EtOAc:Hexanes, UV); mp 221-223 °C; IR (KBr, cm^{-1}) 3427, 1702, 1466; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.05-9.04 (m, 1H), 8.58-8.55 (m, 1H), 7.58-7.52 (m, 5H), 7.47-7.44 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 161.8, 155.2, 152.4, 147.7, 137.5, 135.5, 129.5, 128.1, 122.5, 120.4, 79.2 (1 peak missing due to overlap); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{10}IN_2O$ 348.9832; Found 348.9820.



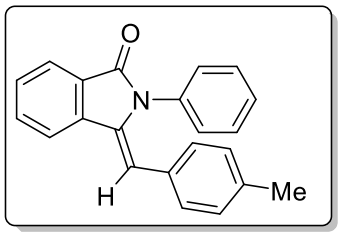
(Z)-7-(1-Iodoheptylidene)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (5y). Yield: (162.0 mg, 91.0%); light yellow solid; TLC R_f = 0.20 (30% EtOAc:Hexanes, UV); mp 142-144 °C; IR (KBr, cm^{-1}) 3310, 2958, 2924, 1707, 1459; ^1H NMR (400 MHz, $CDCl_3$) δ 11.71 (s, 1H), 9.01-9.00 (m, 1H), 8.61-8.59 (m, 1H), 7.43-7.40 (m, 1H), 1.81-1.74 (m, 2H), 1.54-1.47 (m, 2H), 1.37-1.33 (m, 2H), 1.27-1.23 (m, 4H), 0.91-0.88 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0, 155.3, 153.2, 148.2, 136.1, 121.5, 119.8, 79.5, 38.7, 31.4, 28.9, 28.3, 22.5, 14.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}IN_2O$ 357.0458; Found 357.0464.



(Z)-3-(Bromo(phenyl)methylene)isoindolin-1-one (6a).[46] Yield: (53.2 mg, 71%); light yellow solid; TLC R_f = 0.37 (30% EtOAc:Hexanes, UV); mp 214-216 °C; IR (KBr, cm^{-1}) 3171, 1704, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.83-7.81 (d, J = 7.6 Hz, 1H), 7.51-7.47 (m, 5H), 7.44-7.40 (m,1H), 7.29-7.25 (m, 1H), 6.65-6.63 (d, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2, 137.4, 135.0, 135.4, 132.2, 130.9, 130.1, 129.8, 129.2, 129.1, 123.8, 122.7, 103.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}BrNO$ 300.0019; Found 300.0016.



(Z)-3-Benzylidene-2-methylisoindolin-1-one (7a).[48] This reaction was performed twice. Yield: (47.6 mg, 81%); light yellow solid; TLC R_f = 0.48 (30% EtOAc:Hexanes, UV); mp 182-183 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 1H), 7.75-7.73 (m, 1H), 7.59-7.57 (m, 1H), 7.50-7.47 (m, 1H), 7.40-7.31 (m, 5H), 6.78 (s, 1H), 3.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.8, 137.9, 136.1, 134.6, 131.7, 129.5, 128.9, 128.4, 128.0, 127.4, 123.1, 119.2, 106.4, 30.4.

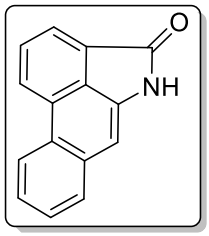


(Z)-3-(4-methylbenzylidene)-2-phenylisoindolin-1-one (7b).[49] Yield: (60.0 mg, 77%). light yellow solid; TLC R_f = 0.28 (10% EtOAc:Hexanes, UV); ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H),

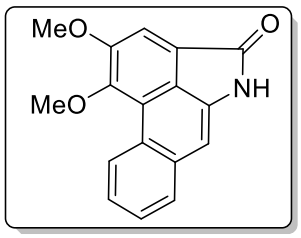
7.68-7.64 (m, 1H), 7.55-7.51 (m, 1H), 7.11-7.08 (m, 5H), 6.80 (s, 1H), 6.76-6.71 (m, 4H), 2.19 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 136.4, 135.9, 133.6, 132.3, 130.5, 129.0, 128.9, 127.8, 127.6, 127.2, 127.0, 126.7, 123.8, 119.2, 107.9, 21.1.

Procedure for the Synthesis of Aristolactam Derivatives[38]

The isoindolin-1-one derivative (**5i** or **5j**) was dissolved (0.25 mmol) in dry, degassed benzene (20 mL), and the solution was heated to reflux under argon atmosphere. A solution of Bu_3SnH (2.2 equiv, 0.55 mmol) and AIBN (1.0 equiv, 0.25 mmol) in dry, degassed benzene (4 mL) was added by syringe over 30 min. Once the addition was completed, the reaction mixture was refluxed for 12 h. After reaction completion, benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (10 mL). The solution was washed with hexane (3×50 mL) and concentrated in vacuum to give the crude product, which was purified by column chromatography using hexanes-EtOAc as the eluent.



Dibenzo[cd,f]indol-4(5H)-one (8a). Yield: (39.5 mg, 72%); light yellow solid; TLC R_f = 0.61 (30% EtOAc:Hexanes, UV); mp 154-156 °C; IR (KBr, cm^{-1}) 3414, 1707; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.86 (d, J = 8.0 Hz, 1H), 8.69 (d, J = 7.2 Hz, 1H), 8.04-8.02 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.92-7.88 (m, 1H), 7.61-7.54 (m, 2H), 7.24 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 168.9, 135.6, 134.9, 134.2, 131.7, 129.4, 129.2, 129.0, 128.6, 127.7, 126.9, 125.3, 123.5, 123.4, 105.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}NO$ 220.0757; Found 220.0774.



1,2-Dimethoxydibenzo[cd,f]indol-4(5H)-one (8b).[50] Yield: (48.9 mg, 70%); light yellow solid; TLC R_f = 0.14 (30% EtOAc:Hexanes, UV); mp 250-251°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.12-9.09 (m, 1H), 7.95-7.93 (m, 1H), 7.85 (s, 1H), 7.60-7.54 (m, 2H), 7.13 (s 1H), 4.04 (s, 3H), 4.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 168.4, 154.2, 150.4, 135.1, 134.8, 129.1, 127.5, 126.9, 125.9, 125.4, 123.3, 121.6, 119.9, 109.9, 104.6, 59.9, 56.9.

X-ray Crystallographic Data for Compounds 5i and 8a

Single crystals of **5i** of suitable quality were grown by slow evaporation of the solvent mixture of dichloromethane and diethyl ether (*v*:*v* = 2:5) solvent solutions containing **5i** at room temperature. Compound **5i** was dissolved in DCM at ambient temperature. Subsequently, Et_2O was added carefully on top of the dichloromethane solution, and two layers could be observed. The vial was kept to allow slow evaporation of solvents until crystals were formed that were suitable for X-ray diffraction analysis. X-ray crystallographic data has been deposited in the Cambridge Crystallographic Data Centre, and CCDC deposit number for **5i** is 1864768.

Single crystals of **8a** of suitable quality were grown by slow evaporation of the mixture solvent of dichloromethane and diethyl ether (*v*:*v* = 2:5) solvent solutions containing **8a** at room temperature. Compound **8a** was dissolved in DCM at ambient temperature. Subsequently, Et_2O was added carefully on top of the dichloromethane solution, and two layers could be observed. The vial was kept to allow slow evaporation of solvents until crystals were formed that were suitable for X-ray diffraction analysis. X-

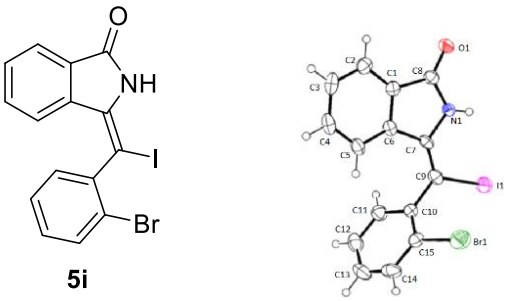
ray crystallographic data has been deposited in the Cambridge Crystallographic Data Centre, and CCDC deposit number for **8a** is 1865767.

X-ray data collection was performed with Oxford Xcalibur, Sapphire3 Diffractometer equipped Mo (Kα) (λ = 0.71073 Å) radiation. Cell refinement and data reduction were carried out using CrysAlisPro 1.171.38.46 (Rigaku OD, 2015) program. Empirical absorption correction was performed using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. Crystal structures were solved by SHELXT - 2014 (Sheldrick, 2014) and refined using SHELXL-2014 (Sheldrick, 2014) computer program using the WinGX graphical user interface.[51] Molecular graphics were drawn using ORTEP3.[52] The relevant data is given in Table (Table 3.4 and 3.5). All aromatic hydrogens were fixed geometrically at calculated positions and refined as riding model with C—H distance of 0.93 Å, Uiso(H) = 1.2Ueq(C), whereas the hydrogen on Nitrogen atom was located from the electron density peaks and refined freely with N-H distance restrained at 0.85 Å within an allowed standard deviation of 0.02 Å.

X-ray Crystallographic Data for

(*Z*)-3-((2-bromophenyl)iodomethylene)isoindolin-1-one (5i), CCDC 1864768

Figure 3.2 Molecular structure of 5i



5i

Table 3.4 Crystal data and structure refinement for Compound 5i

Identification	DHB-167
Empirical form.	$C_{15}H_9BrINO$
Formula wt.	426.04

Temperature	293(2) K
Wavelength (λ)	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.3441(4) Å α= 77.358(7)°.
	b = 8.1078(6) Å β= 82.035(7)°.
	c = 13.4140(8) Å γ = 63.503(10)°.
Vol.	696.73(10) $Å^3$
Z	2
Density (calcd)	2.031 mg/m^3
Absorption coeff.	5.156 mm^{-1}
F(000)	404
Crystal size	0.200 x 0.150 x 0.100 mm^3
Theta range for data collection	3.406 to 24.999°.
Index ranges	-8<=h<=8, -9<=k<=9, -15<=l<=15
Reflections collected	8386
Independent reflections	2454 [R(int) = 0.0728]
Completeness to theta = 24.999°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.657 and 0.457
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2454 / 1 / 176
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0599, wR2 = 0.1440
R indices (all data)	R1 = 0.0754, wR2 = 0.1561

Extinction coeff.	n/a
Largest diff. peak and hole	0.982 and -0.740 e.Å^{-3}

X-ray Crystallographic Data for dibenzo[cd,f]indol-4(5*H*)-one (8a), CCDC 1865767

Figure 3.3 Molecular structure of 8a

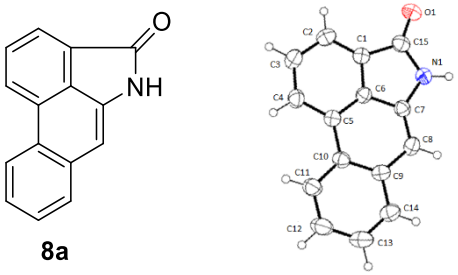


Table 3.5 Crystal data and structure refinement for Compound 8a

Identification	292	
Empirical form.	$C_{15}H_9NO$	
Formula wt.	219.23	
Temp.	293(2) K	
Wavelength (λ)	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.3645(6) Å	α= 90°.
	b = 6.7110(5) Å	β= 96.720(6)°.
	c = 17.1210(10) Å	γ = 90°.
Vol.	1068.58(12) Å^3	
Z	4	
Density	1.363 mg/m^3	
Absorption coeff.	0.086 mm^{-1}	
F(000)	456	

Crystal size	0.250 x 0.200 x 0.200 mm^3
Theta range for data collection	3.744 to 24.980°.
Index ranges	-11<=h<=11, -7<=k<=7, -20<=l<=20
Reflections collected	12321
Independent reflections	1872 [R(int) = 0.0641]
Completeness to theta = 24.980°	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0 and 0.938
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1872 / 0 / 159
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0528, wR2 = 0.1054
R indices (all data)	R1 = 0.1052, wR2 = 0.1377
Extinction coeff.	0.0070(17)
Largest diff. peak and hole	0.197 and -0.154 $e.Å^{-3}$

3.5 References

(1) Aggarwal, T.; Kumar, S.; Verma, A. K. *Org. Biomol. Chem.* **2016**, *14*, 7639–7653.

(2) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980.

(3) Issaian, A.; Tu, K. N.; Blum, S. A. *Acc. Chem. Res.*, **2017**, *50*, 2598–2609.

(4) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141–1147.

(5) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658.

(6) Chinta, B. S.; Sanapa, H.; Vasikarla, K. P.; Baire, B. *Org. Biomol. Chem.* **2018**, *16*, 3947-3951.

(7) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432−1437.

(8) Mehta, S.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 10938−10944.

(9) Schlemmer, C.; Andernach, L.; Schollmeyer, D.; Straub, B. F.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 10118−10124.

(10) Brahmchari, D.; Verma, A. K.; Mehta, S. *J. Org. Chem.* **2018**, *83*, 3339−3347 and references cited therein.

(11) Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6470−6505.

(12) Breugst, M.; Zipse, H.; Guthrie, J. P.; Mayr, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5165−5169.

(13) Breugst, M.; Tokuyasu, T.; Mayr, H. *J. Org. Chem.* **2010**, *75*, 5250−5258.

(14) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681−13736.

(15) Bian, M.; Yao, W.; Ding, H.; Ma, C. *J. Org. Chem.* **2010**, *75*, 269−272.

(16) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, *352*, 136−142.

(17) Okitsu, T.; Nakahigashi, H.; Sugihara, R.; Fukuda, I.; Tsuji, S.; In, Y.; Wada, A. *Chem. Eur. J.* **2018**, *24*, 18638-18642.

(18) Saame, J.; Rodima, T.; Tshepelevitsh, S.; Kütt, A.; Kaljurand, I.; Haljasorg, T.; Koppel, I. A.; Leito, I. *J. Org. Chem* **2016**, *81*, 7349–7361.

(19) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; John Wiley & Sons, Ltd: Chichester, UK, **2009**.

(20) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem. Int. Ed.* **1993**, *32*, 1361–1363.

(21) Kolonko, K. J.; Reich, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 9668–9669.

(22) Imahori, T.; Hori, C. Kondo, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090-1092 and references cited therein.

(23) Kanazawa, C.; Goto, K.; Terada, M. *Chem. Commun.* **2009**, 5248–5250.

(24) Kanazawa, C.; Terada, M. *Chem. Asian J.* **2009**, *4*, 1668–1672.

(25) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(26) Volpe, R.; Aurelio, L.; Gillin, M. G.; Krenske, E. H.; Flynn, B. L. *Chem. - Eur. J.* **2015**, *21*, 10191−10199.

(27) Wang, T.; Zhang, H.; Han, F.; Long, L.; Lin, Z.; Xia, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 9251–9255.

(28) Mehta, S.; Waldo, J. P.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2013**, 15, 247−254.

(29) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Comb. Chem. High Throughput Screen.* **2012**, *15*, 451-472.

(30) Houghton, P. J.; Ogutveren, M. *Phytochemistry* **1991**, *30*, 253–254.

(31) Zhang, Y.; Zhong, X.; Zheng, Z.; Hu, X.; Zuo, J.; Hu, L. *Bioorg. Med. Chem.* **2007**, *15*, 988–996.

(32) Chen, Y.; Chen, J.; Chang, Y.; Teng, C.; Lin, W.; Wu, C.; Chen, I. *Planta Med.* **2004**, *70*, 174–177.

(33) Kim, S. R.; Sung, S. H.; Kang, S. Y.; Koo, K. A.; Kim, S. H.; Ma, C. J.; Lee, H.-S.; Park, M. J.; Kim, Y. C. *Planta Med.* **2004**, *70*, 391–396.

(34) Marti, G.; Eparvier, V.; Morleo, B.; Le Ven, J.; Apel, C.; Bodo, B.; Amand, S. Dumontet, V.; Lozach, O.; Meijer, L.; Guéritte, F.; Litaudon, M. *Molecules* **2013**, *18*, 3018-3027 and references cited therein.

(35) Choi, Y. L.; Kim, J. K.; Choi, S.; Min, Y.; Bae, M.; Kim, B. T.; Heo, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036-3040.

(36) Mata, R.; Morales, I.; Pérez, O.; Rivero-Cruz, I.; Acevedo, L.; Enriquez-Mendoza, I.; Bye, R.; Franzblau, S.; Timmermann, B. *J. Nat. Prod.* **2004**; *67*, 1961–1968.

(37) Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557-3559 and references cited therein.

(38) Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2003**, *2003*, 1231–1237.

(39) Songsichan, T.; Promsuk, J.; Rukachaisirikul, V.; Kaeobamrung, J. *Org. Biomol. Chem.* **2014**, *12*, 4571–4575.

(40) Kong, L.-L.; Fan, L.-Y. *Chinese Chem. Lett.* **2016**, *27*, 827–831.

(41) Spivey, A. C.; McKendrick, J.; Srikaran, R.; Helm, B. A. *J. Org. Chem.* **2003**, *68*, 1843–1851.

(42) Long, Y.; She, Z.; Liu, X.; Chen, Y. *J. Org. Chem.* **2013**, *78*, 2579–2588.

(43) Minami, H.; Sueda, T.; Okamoto, N.; Miwa, Y.; Ishikura, M.; Yanada, R. *Eur. J. Org. Chem.* **2016**, *2016*, 541–548.

(44) Kundu, N. G.; Khan, M. W. *Tetrahedron,* **2000**, 56, 4777−4792.

(45) Praveen, C.; Dheenkumar, P.; Perumal, P. T. *J. Chem. Sci.* **2013**, *125*, 71–83.

(46) Dev, K.; Maurya, R. *RSC Adv.* **2015**, *5*, 13102–13106.

(47) Hong, S. Y.; Son, J.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 12359–12363.

(48) Munoz, S. B.; Aloia, A. N.; Moore, A. K.; Papp, A.; Mathew, T.; Fustero, S.; Olah, G. A.; Prakash, G. K. S. *Org. Biomol. Chem.* **2016**, *14*, 85–92.

(49) Gogoi, A.; Guin, S.; Rout, S. K.; Majji, G.; Patel, B. K. *RSC Adv.* **2014**, *4*, 59902–59907.

(50) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.–N. *Org. Lett.* **2008**, *10*, 3543–3546.

(51) Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837–838.

(52) Farrugia, L. J. *J. Appl. Cryst.* **1997**, *30*, 565–565.

(53) Mehta, S.; Brahmchari, D. *J. Org. Chem.* **2019**, *84*, 5492–5503.

Chapter 4

In silico Biological Evaluation of Isoindolin-1-ones

4.1 Introduction

Designing and discovering new and more efficient drugs, to combat the prevailing and/or new diseases has always been the prime focus of pharmaceutical research.[1] In the past, majority of drugs used to be discovered by either recognizing the bioactive component of natural products or by serendipity.[2,3] In modern times, the process of drug discovery has also shifted to rationale and mechanism of action based process.[4] As a result it has become very complex and expensive process, and involves a high risk of failure.[4] For a molecule to be a new drug, it has to successfully pass through various stages (lead identification, synthesis, characterization, screening for therapeutic efficacy, clinical trials, *etc*.)[5] involved in modern drug discovery and development. Presently, computational studies and analysis have also become an essential component of various drug discovery programmes. From hit identification to lead optimization, and various approaches such as ligand- or structure- based virtual screening techniques are extensively used in many drug discovery projects.[4] Molecular docking is one such highly active area of research, where small molecules are docked with the target binding sites.[6,7] Docking is predominantly used as a hit- identification method when complete information the structure (binding site) of a target is available.[6,8]

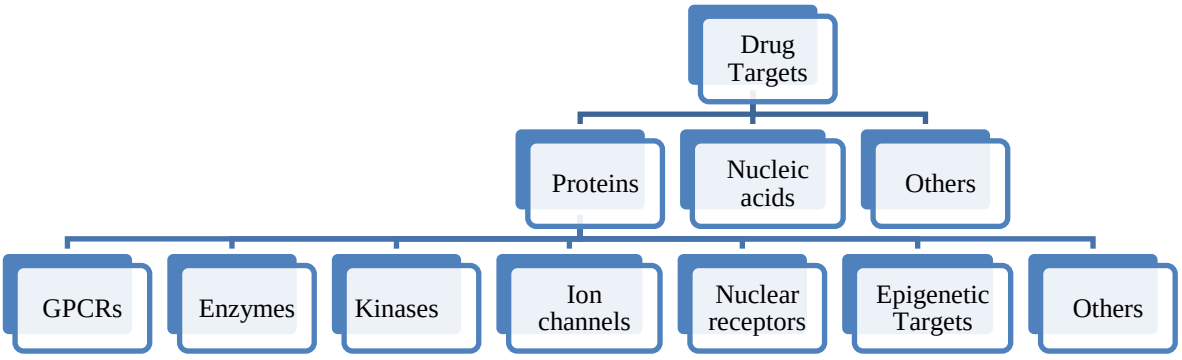
As mentioned in the previous chapters that several compounds containing the isoindolinone core have been recognized as medicinally important, and have shown important biological activities.[9,10] In the literature, there are a few reports for the association of the isoindolinone scaffold as known Kinase inhibitors,[11] particularly EGFR inhibitors[12,13] and also inhibitors of epigenetic targets (such as BRD4).[14] Therefore, we became interested in discovering novel inhibitors of these known and important cancer

drug targets. Since, Kinase, EGFR, and BRD4 are established as well as important oncotargets, so we wanted to check the inhibitory activity of our compounds against these targets. Therefore, these important drug targets such as EGFR (kinase) and BRD4 (bromodomain) proteins were chosen for our studies due to their known association with several oncologic disorders.[15,16]

Pharmacological or biological activity is the study of the medication action of a drug in living organisms. The drug consists of a pharmacophore which is primarily responsible for exerting its biological activity.[17] The biological activity of an orally dosed substance significantly depends on the fulfillment of the ADME (Absorption, Distribution, Metabolism, Excretion) standards.[18,19]

4.2 Biological Target or Drug Target

A biological target is usually a biopolymer (protein, nucleic acid) whose activity can be altered by changing its behavior and/or working pattern through its interaction by the pharmacologically active molecule.[20] Proteins and nucleic acids are known to be the most common biological targets, including proteins enzymes, ion channels, and receptors.[21] Various drug targets are broadly classified as:



4.2.1 Proteins

Proteins are essential biological macromolecules built of amino acids. Several important functions are accomplished by proteins including the regulation of cellular and physiological actions, enzymatic catalysis, transportation of ions and molecules, *etc.* in

living organisms. Proteins structure has been classified as primary, secondary, tertiary, and quaternary structures.[22] The tertiary structure of proteins is mainly responsible for the functionality of the proteins. The Protein Data Bank (PDB) is the depository for the three-dimensional structural data of drug targets including proteins. Currently, the PDB database contains >150,000 deposited structures of various target complexes.[23,24] Complete information required to specify the structure of a protein is contained in the sequence of the amino acid residues of the protein.[25] The structure of proteins along with their complexes delivers abundant insights to understand various parameters including protein structure stability, inter-residue contacts, protein folding, and possibility of structure-based drug design, *etc*.[26]

4.2.1.1 Kinases

Over the past decades, kinases have emerged as effective drug targets. Phosphorylation plays a key role in various cellular as well as extracellular processes.[27–29] The human genome comprises of >518 kinases[30] and up to one-third of these enzymes are phosphatases.[31] More than 39 kinase inhibitors have been approved as drugs till date.[32]

Kinases, during the phosphotransfer process, offer several nodes for therapeutic intervention in many abnormally controlled biological processes.[31] Deregulating the kinase functionality involving abnormal phosphorylation is known to be associated with various disorders.[33,34] In 1980s, work on Protein kinase C (PKCs), and Tyrosine protein kinases (TPKs) as oncogenes initiated the kinase drug discovery developments. Lead compounds like staurosporine[35] and tyrphostins[36] provided the foundation for the exploration of kinase inhibitors.[31-32] Presently, various small molecules as kinase inhibitors, with superior pharmaceutical properties, have gained significant clinical attention, *e.g.*, imatinib, crizotinib, lapatinib, gefitinib, erlotinib, *etc*.[29,37–40] More than 39 kinase inhibitors have been approved as drugs till date.

4.2.1.1.1 Epidermal Growth Factor Receptor (EGFR)

The EGFR is a transmembrane receptor protein of the Tyrosine Kinase family of extracellular protein ligands. The EGFR family includes four transmembrane receptors, namely EGFR, HER2, HER3 and HER4.[41] Activation of the EGFR is known to stimulate tumour growth and progression.[42] EGFR has been reported as an important target in lung cancer, ovarian cancer, *etc*.[43,44] and molecular inhibitors of EGFR signaling represent promising anticancer agents.[45]

4.2.1.1.2 Anaplastic Lymphoma Kinase (ALK)

Receptor tyrosine kinases are an important class of proteins and Anaplastic Lymphoma Kinase (ALK) represents an important member of this class. This protein is normally expressed in the intestine, brain, and testis, and is known to be associated with various types of cancer.[46]

4.2.1.2 Epigenetic Targets

The term 'Epigenetics', defined by C. H. Waddington as "*the causal interactions between genes and their products, which bring the phenotype into being*".[47] In modern era, epigenetics is defined as 'the study of heritable changes in gene expression that occur independent of changes in the primary DNA sequence'.[48] Epigenetic proteins of most interest include reader domains, histone deacetylase inhibitors (HDAC), histone acetyltransferase (HAT), poly ADP ribose polymerase (PARPs), *etc*.[49] A cell undergoes many heritable changes during cell differentiation, where the cells contain the same genetic information but possess separate identities. Recent epigenetic developments revealed that such genetic/epigenetic abnormalities alterations stimulate cancer progression.[50–54] The reversible nature of epigenetic abnormalities may be restored to their regular state by epigenetic therapy.[55] Deeper insights of epigenetic modifications accompanied by standard chemotherapy holds potential for efficacious cancer treatment.[55–57]

4.2.1.2.1 Bromodomains

The emergence of resistance in the prevailing kinase-targeting drugs has encouraged the exploration for alternate targets, such as epigenetic targets like Bromodomain containing proteins.[40] These bromodomains were reported in the *Drosophila* protein brahma (origin of the name).[58] Bromodomain proteins belong to the family of epigenetic regulator domain proteins that localizes to DNA *via* binding acetylated lysine residues, and assisted in gene expression. The structure of bromodomain comprised of approx. 110 amino acids protein domain and consist of four α helices which are linked by two loops (BC and ZA).[59] There are 61 bromodomain modules known in 42 diverse proteins of the human proteome, bromodomain and extra-terminal (BET) proteins include four family members BRD2, BRD3, BRD4, and BRDT.[26,60] BRD4 is the most extensively studied member of the BET family.[26,61]

BRD4 is a promising target for cancer therapy[62] and its overexpression have been observed in various cancers, comprising squamous cell carcinoma and glioblastoma *etc*.[63] For various diseases such as cancer, inflammations, *etc*., the recent development of BET protein inhibitors have shown promising results[64,65] and therefore these proteins are being explored as drug targets.

The importance of BRD4 in disease-related functions and therapeutic effect have encouraged the academia and the pharma companies to make significant efforts to develop effective BRD4 inhibitors, by using various strategies including virtual screening, high-throughput screening as well as through drug repurposing.

4.3 Molecular Properties and Druglikeness

Druglikeness means how "druglike" a chemical compound is with respect to factors like bioavailability.[66,67] It can be computed by analyzing the molecular structure even before the substance is even made and tested. The significance of Lipinski "Rule of

Five" has been described,[66,68] for various isoindolinone scaffolds. Various computational approaches predicting the solubility and permeability parameters for any compound have been successfully blended with the drug discovery program and development settings.

4.3.1 Lipinski's Rule of Five (RO5)

The Lipinski's Rule of Five comprises of a given set of parameters for evaluating druglikeness. In 1997, Christopher A. Lipinski, formulated the rule based on examination that most drugs are comparatively small, moderately liphophilic molecules.[66,68] The Lipinski's rule defines various molecular properties that may be essential for a drug's pharmacokinetics in the human body, including absorption, distribution, metabolism, and excretion ("ADME"). It has been observed that various drug candidates that are in agreement to the Lipinski's rule have lower failure rates through clinical trials and therefore have a better chance of making their way to the market.[68]

Components of Lipinski's Rule[66]

The Lipinski's rule states that for a drug to be orally active, the molecule should meet to the below mentioned criteria:

- The molecular mass <500 Daltons.
- It should contain < 5 Hydrogen Bond Donors.
- It should contain < 10 Hydrogen Bond Acceptors.
- Its partition coefficient (octanol/water) (log *P)* should be <5.

During drug discovery process, in order to increase the affinity, selectivity and potency of the drug like candidate, changes in the molecular weight and lipophilicity are often attempted. Therefore, during the hit and lead optimization process it is challenging to uphold drug-likeness (RO5 fulfilment). Hence it is recommended that the members of screening libraries for the discovery of probable hits must be prejudiced toward lower

molecular weight and lower lipophilicity, thereby, making it easier for the medicinal chemists to deliver the optimized drug development candidates.

The RO5 have proved to be highly effective tools for a better understanding to generate awareness about the significance of various pharmacokinetic parameters in drug development. This approach has been very attractive and can be used to provide a solid foundation for computational druggability assessments in the early stages of drug discovery.

4.4 Experimental Section

4.4.1 Determination and Calculation of Lipinski Parameters for the Synthesized Compounds[69,70]

4.4.1.1 Preparation of ligands

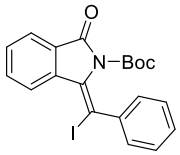
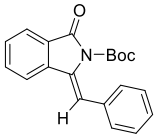
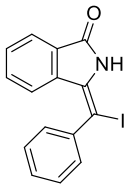
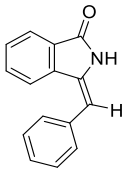
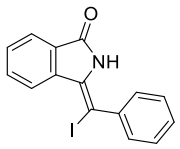
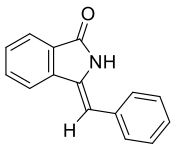
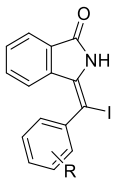
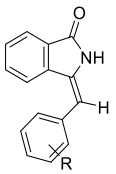
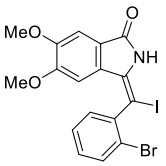
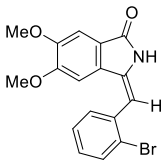
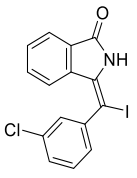
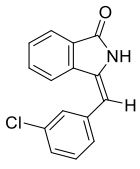
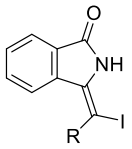
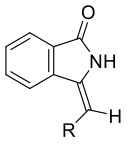
The GUI (graphical user interface) of Schrödinger Maestro (version 12.0, Schrödinger, 2019-2)[71] was used to sketch the structures of the ligands (1–59) and were saved. The LigPrep (version 2.5, Schrödinger, 2019-2) of Schrödinger software suit is a highly efficient combination of tools that utilizes the 1D (SMILES) and 2D (SDF) representation of a molecule for generating the corresponding 3D structures, generating various possible tautomers, isomers, *etc*. For the ligand minimization, Molecular Mechanics Force Fields (OPLS3e) were employed with all default settings.

4.4.1.2 Calculation of ADME properties

The program QikProp (Schrödinger 2019-2)[72] was used to make the predictions to provide an initial sense of anticipated pharmacological properties to evaluate their drug likeness. QikProp module of Schrödinger software suit is fast and highly user-friendly program for prediction of ADME properties. QikProp conveniently uses the organic molecules (individually or in library) to predict various physically significant molecular descriptors and pharmaceutically important properties. QikProp was allowed to run in the normal processing mode with default options and the resulting calculation with respect to

the properties that influence bioavailability through cell permeation, metabolism and bioavailability are presented below (Table 4.1).

Table 4.1 Library of compounds for determining Lipinski's parameters and predicting various ADME parameters

Compound ID	Structure	Compound ID	Structure
1		**33**	
2		**34**	
3		**35**	
4 (R = 2-Me) **5** (R = 3-Me) **6** (R = 4-Me) **7** (R = 4-OMe) **8** (R = 4-NMe_2) **9** (R = 4-F) **10** (R = 4-Br) **11** (R = 2-Br)		**36** (R = 2-Me) **37** (R = 3-Me) **38** (R = 4-Me) **39** (R = 4-OMe) **40** (R = 4-NMe_2) **41** (R = 4-F) **42** (R = 4-Br) **43** (R = 2-Br)	
12		**44**	
13		**45**	
14 (R = hexyl) **15** (R = cyclohexyl) **16** (R = cyclohexenyl) **17** (R = TMS) **18** (R = H) **19** (R = 3-thienyl)		**46** (R = hexyl) **47**(R = cyclohexyl) **48** (R = cyclohexenyl) **49** (R = TMS) **50** (R = H)	

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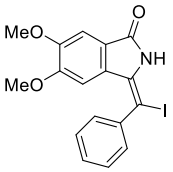
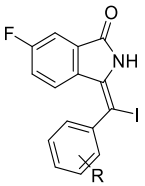


21 (R = H)
22 (R = 4-Me)



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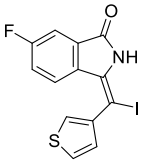

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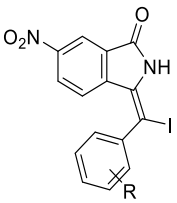
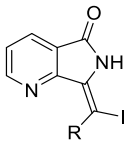
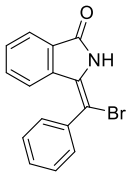
25 (R = 4-Me)



26 (R = Ph)
27 (R = hexyl)



28



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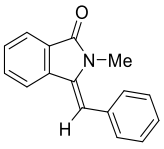

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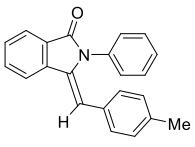
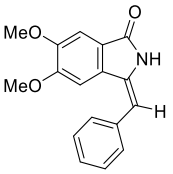
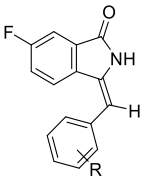


51 (R = 3-thienyl)

52



53 (R = H)
54 (R = 4-Me)



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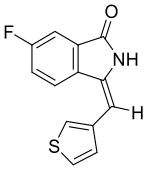
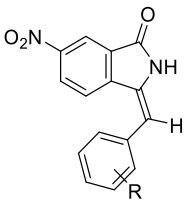
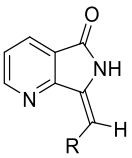


56 (R = H)
57 (R = 4-Me)



58 (R = Ph)
59 (R = hexyl)



31 (R = H)
32 (R = OMe)

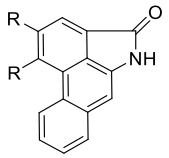


Table 4.2 Calculation of ADME properties

Comp. ID	MW[a]	HBD[b]	HBA[c]	QPlogPo/w[d]	Violations to RO5[e]	SASA[f]	QPlogS[g]	QPPCaco[h]	QPlogBB[i]	Human Oral Absorption[j]
1	447.272	0	3.0	3.7	0	598.3	-4.1	2351.3	-0.19	3
2	347.155	1	2.5	3.5	0	499.4	-4.5	1432.7	-0.17	3
3	347.155	1	2.5	3.5	0	490.6	-4.3	1835.5	-0.09	3
4	361.181	1	2.5	3.7	0	519.5	-4.8	1444.2	-0.18	3
5	361.181	1	2.5	3.8	0	530.1	-5.0	1433.7	-0.19	3
6	361.181	1	2.5	3.8	0	530.9	-5.1	1433.3	-0.20	3
7	377.181	1	3.25	3.6	0	536.5	-4.7	1433.0	-0.25	3
8	390.223	1	3.5	3.9	0	577.1	-5.4	1385.7	-0.30	3
9	365.145	1	2.5	3.7	0	508.4	-4.9	1433.1	-0.06	3
10	426.051	1	2.5	4.1	0	528.0	-5.3	1432.7	-0.01	3
11	426.051	1	2.5	3.9	0	517.1	-5.0	1455.0	-0.03	3
12	486.103	1	4.0	4.1	0	574.6	-5.2	1455.1	-0.17	3
13	381.600	1	2.5	4.0	0	521.9	-5.2	1432.9	-0.02	3
14	355.218	1	2.5	4.1	0	575.8	-5.2	1431.7	-0.51	3
15	353.202	1	2.5	3.5	0	517.8	-4.8	1440.4	-0.19	3
16	351.186	1	2.5	3.5	0	513.7	-4.7	1434.4	-0.18	3
17	343.239	1	2.5	3.3	0	502.0	-4.5	1445.0	-0.17	3
18	271.057	1	2.5	2.0	0	394.0	-2.8	1410.3	-0.04	3
19	353.177	1	2.5	3.4	0	483.3	-4.4	1436.1	-0.03	3
20	407.207	1	4.0	3.6	0	559.0	-4.7	1434.7	-0.30	3
21	365.145	1	2.5	3.7	0	508.4	-4.9	1433.0	-0.06	3
22	379.172	1	2.5	4.0	0	539.9	-5.4	1433.6	-0.09	3
23	371.167	1	2.5	3.6	0	492.3	-4.8	1436.4	0.08	3
24	392.152	1	3.5	2.8	0	538.4	-4.7	171.5	-1.19	3
25	406.179	1	3.5	3.1	0	569.6	-5.2	172.0	-1.23	3

26	348.142	1	3.5	3.0	0	501.0	-4.2	1269.6	-0.24	3
27	356.206	1	3.5	3.6	0	568.4	-4.7	1318.5	-0.52	3
28	300.154	1	2.5	3.7	0	532.1	-5.1	1432.8	-0.25	3
29	235.285	0	3.0	3.3	0	482.4	-3.5	3145.2	-0.01	3
30	311.382	0	3.0	4.7	0	557.8	-4.9	3780.2	0.06	3
31	219.242	1	2.5	3.0	0	426.4	-3.2	1326.7	-0.20	3
32	279.295	1	4.0	2.6	0	487.6	-3.8	1333.3	-0.33	3
33	321.375	0	3.0	4.7	0	578.3	-5.1	2752.3	-0.14	3
34	221.258	1	2.5	2.9	0	459.6	-3.4	1439.4	-0.32	3
35	221.258	1	2.5	3.0	0	471.1	-3.6	1906.3	-0.23	3
36	235.285	1	2.5	3.0	0	482.3	-3.8	1439.1	-0.33	3
37	235.285	1	2.5	3.1	0	489.2	-4.0	1440.6	-0.34	3
38	235.285	1	2.5	3.1	0	491.6	-4.0	1440.1	-0.35	3
39	251.284	1	3.25	2.9	0	496.3	-3.7	1439.3	-0.41	3
40	264.326	1	3.5	3.2	0	537.7	-4.3	1393.7	-0.45	3
41	239.248	1	2.5	3.0	0	468.7	-3.8	1439.7	-0.22	3
42	300.154	1	2.5	3.3	0	488.7	-4.3	1439.6	-0.16	3
43	300.154	1	2.5	3.3	0	483.2	-4.2	1437.5	-0.17	3
44	360.206	1	4.0	3.4	0	545.2	-4.4	1438.6	-0.31	3
45	255.703	1	2.5	3.2	0	483.6	-4.2	1439.5	-0.17	3
46	229.321	1	2.5	3.4	0	534.8	-4.1	1434.4	-0.64	3
47	227.305	1	2.5	2.9	0	488.4	-3.9	1442.4	-0.34	3
48	225.29	1	2.5	2.8	0	476.6	-3.7	1436.3	-0.33	3
49	217.342	1	2.5	2.7	0	471.9	-3.7	1444.0	-0.32	3
50	145.16	1	2.5	2.0	0	348.5	-2.3	1412.3	-0.20	3
51	227.28	1	2.5	2.7	0	443.2	-3.4	1442.7	-0.18	3
52	281.31	1	4.0	2.9	0	522.8	-3.8	1441.1	-0.47	3
53	239.248	1	2.5	3.0	0	468.7	-3.8	1439.8	-0.22	3
54	253.275	1	2.5	3.3	0	500.7	-4.4	1440.4	-0.24	3
55	245.271	1	2.5	2.9	0	452.2	-3.7	1443.1	-0.07	3
56	266.256	1	3.5	2.1	0	497.6	-3.6	172.7	-1.29	3
57	280.282	1	3.5	2.4	0	530.2	-4.3	172.8	-1.34	3
58	222.246	1	3.5	2.3	0	462.3	-3.2	1264.5	-0.39	3

59	230.309	1	3.5	2.9	0	538.7	-3.9	1182.4	-0.75	3

[a]Molecular weight in Dalton. [b]Hydrogen bonds that may be donated. [c]Hydrogen bonds that may be accepted. [d]Calculated partition coefficient (octanol/water). [e]Number of violations of Lipinski's rule of five. [f]Total solvent accessible surface (Å^2). [g]Aqueous solubility. [h]Calculated cell permeability. [i]partition coefficient (brain/blood). [j]Human oral absorption.

Table 4.3 Summary of results: Lipinski/ADME parameters[72]

Parameter	Mean	Range	Range/Recommended values
Mol. Weight	308.5	145.1 – 447.2	≤500
H-bond donors	0.9	0 –1	≤5
H-bond acceptors	2.8	2.5 – 4	≤10
QPlogPo/w	3.2	2.0 – 4.7	≤5
Violations to *Rule Of Five*	0	0	<1[73]
SASA	506.6	348.4 – 598.3	<1000
QPlogS	-4.3	-5.4 – -2.3	–6.5 – 0.5
QPPCaco	1455.2	171.4 – 3780.1	>500
QPlogBB	0.29	-1.34 – -0.01	<1.0
Human Oral Absorption	3.0	3	>2

Lipinski's parameters were used to evaluate the potential bioavailability of the synthesized compounds as well as their corresponding deiodinated counterparts. Various ADME parameters were calculated and compared with the optimum values described in the program for 95% of the marketed drugs. The predicted ADME values for isoindolinone compounds are shown in Table 4.2. Interestingly, the interpretation of the ADME parameters showed that all the cyclized compounds evaluated were in compliance with the Lipinski's rule and there were no violations to the *Rule of five*.

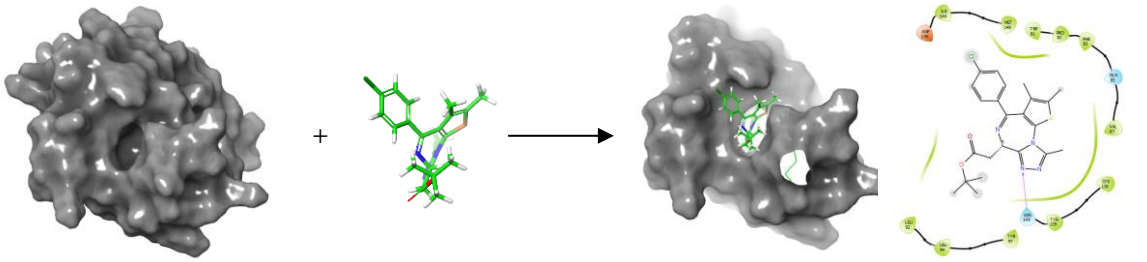
4.4.2 Molecular Docking

Understanding the interaction between the ligands and drug target in normal and diseased states is one of the fundamental goals in drug discovery today. In recent times, with the advancements in technology the understanding and structural details of various

proteins has become more efficient. Various database are publicly available with a large number of drug targets and their 3D structures based on X-ray,[74] NMR studies and model-built structures of receptors and enzymes.[75] This increase in 3D-structural information of the ligand-receptor complex is highly useful for directing efforts to make more potent compounds possessing promising physicochemical properties.

Molecular docking is known to be a useful screening tool for finding hits and also in optimizing lead compounds. This technique has gained the attention from the researchers for a better understanding of various interactions between the complex target structure and the small ligand molecule at the atomic level using the computational methods.[76,77]

Figure 4.1 Representation of Molecular docking of 3MXF with JQ1



For the molecular docking experiments, a suitable target with proper PDB format is required, which can be easily accessed *via* https://www.rcsb.org/. Information on small ligand molecules can be easily found on various databases e.g. Cambridge Structural Database (CSD), National Cancer Institute Database (NCI), MDL Drug Data Report (MDDR) and Available Chemical Directory (ACD). During docking, several conformers are generated for each structure and compared with each other.

4.4.2.1 Virtual Screening: Docking studies

Materials and methods

The Schrödinger 2019-2 software suite[78,79] was used for performing structure-based manipulations and simulations. Three PDB crystal structures of 2RGP (EGFR), 6MX8 (ALK tyrosine kinase receptor), and 5XI2 (BRD4) were chosen for docking of the compounds library. The PDBs were chosen based on important human anti-cancer targets (EGFR, BRD4, etc.) that have been fully characterized by X-ray diffraction studies, having the resolution of ~2Å.

Ligand Preparation. After generating the SMILES of all the compounds, the corresponding crystal ligand of the protein and BRD4 ligands were subjected to LigPrep (Schrödinger 2019-2) for generating various tautomeric, ionization states, and 3D conformations. Keeping all conditions to default, except for generating the ionization states at the pH of 7 ± 2. The resulting 3D ligand representations resulting from the Ligprep were transferred as SDFs followed by the assignment of the unique IDs to each canonical structures to simplify postdocking categorized data.

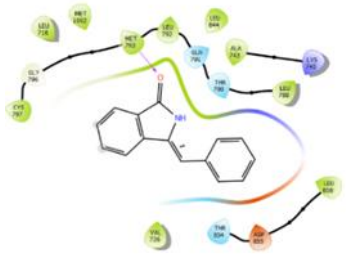
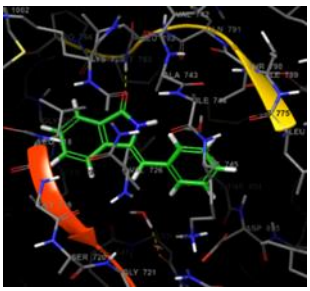
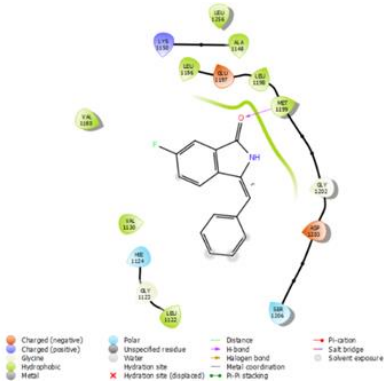
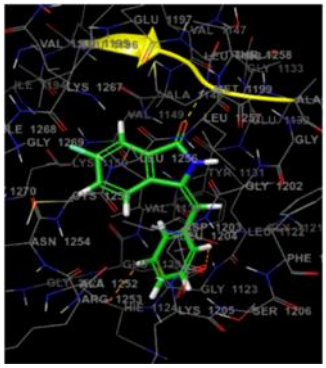
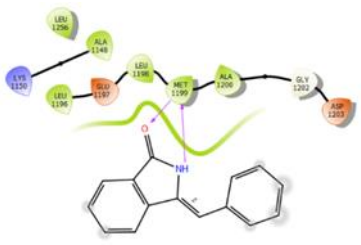
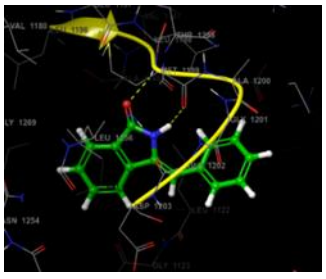
Docking Protocol. Ligand prepared file containing the ligand representations which were obtained *via* the LigPrep wizard, and were subjected to docking with the prepared protein models using Glide in standard precision (SP). All settings were kept to default, except for postdocking minimization where at most 5 poses per ligand representation were written, and comprising 25 poses per ligand were selected. After the completion of the docking, all results were transferred as text files. The docking scores were analyzed and correlated with the ligand-interaction diagrams (Table 4.5).

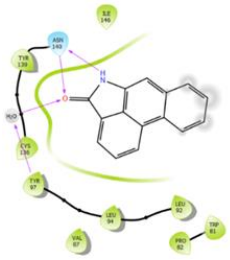
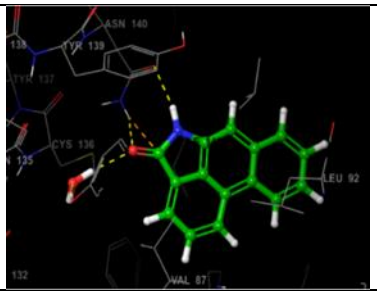
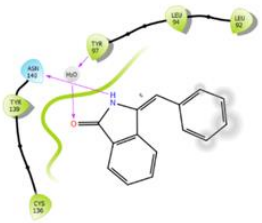
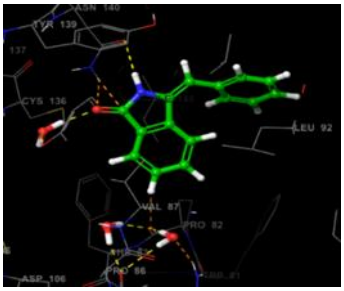
4.5 Results and Discussion

Table 4.4 Library Docking Score of top molecules

PDB ID	Family	Docking Score with crystal ligand	Compound ID	Docking Score
2RGP	EGFR	-10.053	**35**	-9.910
6MX8	ALK tyrosine Kinase receptor	-8.629	**53** **35**	-8.372 -8.309
5XI2	BRD4	-9.598	**31** **34**	-8.175 -8.146

Table 4.5 Pose view and ligand interactions

a)		b)	
c)		d)	
e)		f)	

g)		h)	
i)		j)	

a) 2RGP docking pose with compound **35.** b) Compound **35** showing conservative H-bonding interaction with (MET793) of 2RGP. c) 6MX8 docking pose with compound **53.** d) Compound **53** showing conservative H-bonding interaction with (MET1199) of 6MX8. e) 6MX8 docking pose with compound **35.** f) Compound **35** showing conservative H-bonding interaction with (MET1199) of 6MX8. g) 5XI2 docking pose with compound **31.** h) Compound **31** showing conservative H-bonding interaction with (ASN140) of 5XI2 and showing interaction with water residue. h) 5XI2 docking pose with compound **34.** i) Compound **34** showing conservative H-bonding interaction with (ASN140) of 5XI2 and showing interaction with water residue.

4.6 Conclusions

The docking method was evaluated by comparing the docking score of the known BRD4 inhibitors. The results showed that some of the synthesized library molecules showed comparable docking score and binding affinity with the protein *via* H-boding with the conservative H-bonding interaction. The docking score for docking of the library compounds with various proteins are summarized in the Table 4.4 above. The compounds **31**, **34**, **35**, and **53** have docking score comparable to that of the crystal ligands.

The results of the docking were quite interesting and suggest that this class of compounds have the potential to inhibit BRD4, an important oncology target.

4.7 References

1 Zhou, S.-F.; Zhong, W.-Z. Molecules 2017, 22, 279.

2 Pan, S.-Y.; Zhou, S.-F.; Gao, S.-H.; Yu, Z.-L.; Zhang, S.-F.; Tang, M.-K.; Sun, J.-N.; *et al. Evidence-Based Complement. Altern. Med.* **2013**, *2013*, 1–25.

3 Yuan, H.; Ma, Q.; Ye, L.; Piao, G. T *Molecules* **2016**, *21*, 559.

4 Kaur, D.; Kutum, R.; Dash, D.; Brahmachari, S. K. *Sci. Rep.* **2017**, *7*, 46595.

5 Cooper, M. A. *Nat. Rev. Drug Discov.* **2002**, *1*, 515–528.

6 Pei, J.; Yin, N.; Ma, X.; Lai, L. *J. Am. Chem. Soc.* **2014**, *136*, 11556–11565.

7 Lee, Y.; Basith, S.; Choi, S. *J. Med. Chem.* **2018**, *61*, 1–46.

8 Klon, A. E.; Glick, M.; Thoma, M.; Acklin, P.; Davies, J. W. *J. Med. Chem.* **2004**, *47*, 2743–2749.

9 Brahmchari, D.; Verma, A. K.; Mehta, S. *J. Org. Chem.* **2018**, *83*, 3339–3347.

10 Mehta, S.; Brahmchari, D. *J. Org. Chem.* **2019**, *84*, 5492–5503.

11 Curtin, M. L.; Frey, R. R.; Heyman, H. R.; Sarris, K. A.; Steinman, D. H.; Holmes, J. H. *et al.*, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 4505-4509.

12 Hao, L.; Guo, L.; Chen, X.; Mo, F.; Tian, S.; Liu, X. *Org. Process Res. Dev.*, **2019**, *23*, 397–402.

13 Jia, Y.; Yun, C.-H.; Park, E.; Ercan, D.; Manuia, M. *et al.*, *Nature*, **2016**, *534*, 129–132.

14 Montenegro, R. C.; Clark, P. G. K.; Howarth, A.; Wan, X.; Ceroni, A. *et al.*, *Oncotarget*, **2016**, *7*, 43997–44012.

15 Liu, Z.; Wang, P.; Chen, H.; Wold, E. A.; Tian, B.; Brasier, A. R.; Zhou, J. *J. Med. Chem.*, **2017**, *60*, 4533–4558.

16 Chen, L.; Fu, W.; Zheng, L.; Liu, Z.; Liang, G. *J. Med. Chem.* **2018**, *61*, 4290–4300.

17 Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem.* **2018**, *61*, 10996–11020.

18 Smith, D. A. *Mol. Pharm.* **2013**, *10*, 1162–1170.

19 Lombardo, F.; Desai, P. V.; Arimoto, R.; Desino, K. E.; Fischer, H.; Keefer, C.

E.; Petersson, C.; Winiwarter, S.; Broccatelli, F. *J. Med. Chem.* **2017**, *60*, 9097–9113.

20 Wang, Q.; Feng, Y.; Huang, J.; Wang, T.; Cheng, G. *PLoS One* **2017**, *12*, e0176486.

21 Santos, R.; Ursu, O.; Gaulton, A.; Bento, A. P.; Donadi, R. S.; Bologa, C. G.; Karlsson, A.; *et al. Nat. Rev. Drug Discov.* **2017**, *16*, 19–34.

22 Shashilov, V. A.; Lednev, I. K. *Chem. Rev.* **2010**, *110*, 5692–5713.

23 Burley, S. K.; Berman, H. M.; Kleywegt, G. J.; Markley, J. L.; Nakamura, H.; Velankar, S. *Protein Data Bank (PDB): The Single Global Macromolecular Structure Archive*; Humana Press, New York, NY, **2017**; pp 627–641

24 Bateman, A.; Martin, M. J.; O'Donovan, C.; Magrane, M.; Alpi, E.; Antunes, R.; Bely, B.; *et al*. *Nucleic Acids Res.* **2017**, *45* (D1), D158–D169.

25 Anfinsen, C. B. *Science*, **1973**, *181*, 223–230.

26 Huang, L.-T.; Gromiha, M. M. *Bioinformatics* **2010**, *26*, 2121–2127.

27 Ubersax, J. A.; Ferrell Jr, J. E. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 530–541.

28 Akinleye, A.; Furqan, M.; Mukhi, N.; Ravella, P.; Liu, D. *J. Hematol. Oncol.* **2013**, *6*, 27.

29 Kannaiyan, R.; Mahadevan, D. *Expert Rev. Anticancer Ther.* **2018**, *18*, 1249–1270.

30 Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S. *Science*, **2002**, *298*, 1912-1934.

31 Shi, Y. *Cell* **2009**, *139*, 468–484.

32 Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A.; Grant, J. R.; Sajed, T.; *et al. Nucleic Acids Res.* **2018**, *46* (D1), D1074–D1082.

33 Fruman, D. A.; Rommel, C. *Nat. Rev. Drug Discov.* **2014**, *13*, 140–156.

34 Müller, S.; Chaikuad, A.; Gray, N. S.; Knapp, S. *Nat. Chem. Biol.* **2015**, *11*, 818–821.

35 Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397–402.

36 Levitzki, A. *Biochem. Pharmacol.* **1990**, *40*, 913–918.

37 Bhullar, K. S.; Lagarón, N. O.; McGowan, E. M.; Parmar, I.; Jha, A.; Hubbard, B. P.; Rupasinghe, H. P. V. *Mol. Cancer* **2018**, *17*, 48.

38 Fabbro, D.; Cowan-Jacob, S. W.; Moebitz, H. *Br. J. Pharmacol.* **2015**, *172*, 2675–2700.

39 Ferguson, F. M.; Gray, N. S. *Nat. Rev. Drug Discov.* **2018**, *17*, 353–377.

40 Gross, S.; Rahal, R.; Stransky, N.; Lengauer, C.; Hoeflich, K. P. *J. Clin. Invest.* **2015**, *125*, 1780–1789.

41 Yarden, Y. *Eur. J. Cancer*, **2001**, *37*, 3–8.

42 Woodburn, J. R. *Pharmacol. Ther.* **1999**, *82*, 241–250.

43 Herbst, R. S. *Oncology* **2002**, *16*, 19–24.

44 Mendelsohn, J.; Baselga, J. *J. Clin. Oncol.* **2003**, *21*, 2787–2799.

45 Harari, P. M. *Endocr. Relat. Cancer* **2004**, *11*, 689–708.

46 Holla, V. R.; Elamin, Y. Y.; Bailey, A. M.; Johnson, A. M.; Litzenburger, B. C.; Khotskaya, Y. B.; *et al*. *Mol. Case Stud.* **2017**, *3*, a001115.

47 Waddington, C. H. *Int. J. Epidemiol.* **2012**, *41*, 10–13.

48 Sharma, S.; Kelly, T. K.; Jones, P. A. *Carcinogenesis* **2010**, *31*, 27–36.

49 Liu, Y.; Liu, K.; Qin, S.; Xu, C.; Min, J. *Pharmacol. Ther.* **2014**, *143*, 275–294.

50 Jones, P. A.; Martienssen, R. *Cancer Res.* **2005**, *65*, 11241–11246.

51 Feinberg, A. P.; Ohlsson, R.; Henikoff, S. *Nat. Rev. Genet.* **2006**, *7*, 21–33.

52 Jones, P. A.; Baylin, S. B. *Cell* **2007**, *128*, 683–692.

53 Jones, P. A.; Laird, P. W. *Nat. Genet.* **1999**, *21*, 163–167.

54 Aihara, H. *Genes Dev.* **2004**, *18*, 877–888.

55 Yoo, C. B.; Jones, P. A. *Nat. Rev. Drug Discov.* **2006**, *5*, 37–50.

56 Thottassery, J. V.; Sambandam, V.; Allan, P. W.; Maddry, J. A.; Maxuitenko, Y. Y.; Tiwari, K.; Hollingshead, M.; Parker, W. B. *Cancer Chemother. Pharmacol.* **2014**, *74*, 291–302.

57 Constantinides, P. G.; Jones, P. A.; Gevers, W. *Nature* **1977**, *267*, 364–366.

58 Tamkun, J. W.; Deuring, R.; Scott, M. P.; Kissinger, M.; Pattatucci, A. M.; Kaufman, T. C.; Kennison, J. A. *Cell* **1992**, *68*, 561–572.

59 Filippakopoulos, P.; Picaud, S.; Mangos, M.; Keates, T.; Lambert, J.-P.; Barsyte-Lovejoy, D.; *et al. Cell* **2012**, *149*, 214–231.

60 Owen, D. J.; Ornaghi, P.; Yang, J.; Lowe, N.; Evans, P. R.; *et al. EMBO J.* **2000**, *19*, 6141–6149.

61 Liu, Z.; Wang, P.; Chen, H.; Wold, E. A.; Tian, B.; Brasier, A. R.; Zhou, J. *J. Med. Chem.* **2017**, *60*, 4533–4558.

62 Bandopadhayay, P.; Bergthold, G.; Nguyen, B.; Schubert, S.; Gholamin, S.; Tang, Y.; Bolin, S.; Schumacher, S. E.; Zeid, R.; Masoud, S.; *et al. Clin. Cancer Res.* **2014**, *20*, 912–925.

63 Pastori, C.; Daniel, M.; Penas, C.; Volmar, C.-H.; Johnstone, A. L.; Brothers, S. P.; Graham, R. M.; *et al. Epigenetics* **2014**, *9*, 611–620.

64 Smith, S. G.; Zhou, M.-M. *ACS Chem. Biol.* **2016**, *11*, 598–608.

65 Liu, Z.; Wang, P.; Chen, H.; Wold, E. A.; Tian, B.; Brasier, A. R.; Zhou, J. *J. Med. Chem.* **2017**, *60*, 4533–4558.

66 Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25.

67 Polinsky, A. *Pract. Med. Chem.* **2008**, 244–254.

68 Lipinski, C. A. *Drug Discov. Today Technol.* **2004**, *1*, 337–341.

69 Wang, N.-N.; Dong, J.; Deng, Y.-H.; Zhu, M.-F.; Wen, M.; Yao, Z.-J.; Lu, A.-P.; Wang, J.-B.; Cao, D.-S. *J. Chem. Inf. Model.* **2016**, *56*, 763–773.

70 Zhu, L.; Zhao, J.; Zhang, Y.; Zhou, W.; Yin, L.; Wang, Y.; Fan, Y.; Chen, Y.; Liu, H. *Mol. Divers.* **2018**, *22*, 979–990.

71 Schrödinger Release 2019-2: LigPrep, Schrödinger, LLC, New York, NY, **2019**.

72 Schrödinger Release 2019-2: QikProp, Schrödinger, LLC, New York, NY, **2019**.

73 Lipinski, C. A.; Lombardo, F.; Dominy , B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.*, **2012**, *64*, 4–17.

74 Blundell, T. L.; Jhoti, H.; Abell, C. *Nat. Rev. Drug Discov.* **2002**, *1*, 45–54.

75 Westbrook, J.; Feng, Z.; Chen, L.; Yang, H.; Berman, H. M. *Nucleic Acids Res.* **2003**, *31*, 489–491.

76 Kitchen, D. B.; Decornez, H.; Furr, J. R.; Bajorath, J. *Nat. Rev. Drug Discov.* **2004**, *3*, 935–949.

77 Dar, A. M.; Mir, S. *J. Anal. Bioanal. Tech.* **2017**, *08*, 8–10.

78 Schrödinger Release 2019-2: Glide, Schrödinger, LLC, New York, NY, **2019**.

79 Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. *J. Med. Chem.* **2006**, *49*, 6177–6196.

CHAPTER 5

CONCLUSIONS AND FUTURE SCOPE OF THE WORK DONE

In this thesis, two novel approaches for the regio- and stereoselective synthesis of important isoindolon-1-ones have been reported. The synthetic methodologies involve the base- and halogen electrophile-mediated cyclization of 2-(1-alkynyl)benzamides, and lead to exclusive *N*-cyclization of the ambident nucleophile (amide group). The approaches used are quite simple and can be easily accessed by researchers to synthesize diverse isoindolinone derivatives as well as the relevant natural products. The synthesized isoindolinones have also been evaluated (virtual screening) against important anti-cancer drug targets.

The use of *n*-BuLi as an efficient base for tuning the reactivity of amide group represented the first successful iodoaminocyclization of easily accessible 2-(1-alkynyl)benzamides, for the generation of isoindolin-1-ones. The methodology resulted in an exclusive *N*-cyclization of 2-(1-alkynyl)benzamides, leading to the formation of corresponding isoindolin-1-ones in moderate to good reaction yields. Interestingly, the isolated products exhibited a *Z*-stereochemistry across the C═C double bond. The reaction mechanism involving the formation of either a vinylic anion or an intimate ion pair intermediate was proposed to describe the outcomes of the reaction. Although the use of *n*-BuLi worked well for the cyclization, however, we were interested in further improving the scope of the methodology, as well as the yields of the cyclized isoindolinones. Therefore, we further screened several inorganic as well as organic bases. Through the systematic optimization of the methodology, we found that the phosphazene superbase (P_4-*t*-Bu) was a suitable reagent for this iodoaminocyclization of 2-(1-alkynyl)benzamides, leading to the synthesis of isoindolin-1-ones with excellent regio- and stereoselectivity. It is notable that this methodology is the first ever superbase

mediated electrophilic cyclization/iodocyclization reaction. The methodology offered several advantages to our previous *n*-BuLi-mediated methodology. Phosphazene superbase mediated reactions were very easy to perform, accommodated a broad range of sensitive functional groups (including TMS, halogens, *etc*.), worked with several other halogen electrophiles (such as ICl, Br_2, NBS, *etc*.). The reactions were fast (reaction time < 1min), and were also found to be scalable. This methodology resulted on average 15-20% higher yields than our BuLi-mediated methodology. Also, this work provided further insights with respect to the reaction mechanism. Furthermore, the presence of *–NH* as well as the iodine atoms in the resulting products provides the easy handles for further diversification of the resulting isoindolinones. This was demonstrated through successful *N*-substitution as well as the Pd-catalyzed coupling reactions (Sonogashira, Suzuki coupling, *etc*.) of the iodocyclized products. Furthermore, the tolerance of labile functional groups (bromine, TMS) led into the formation of isoindolinone scaffolds which served as useful precursors and were conveniently converted into the corresponding aristolactam derivatives, including Cepharanone B (a naturally occurring alkaloid with antitumor and antitubercular properties).

Determination and evaluation of the cyclized compounds for the calculation of various Lipinski's parameters was done which showed that all the cyclized compounds were in compliance with the Lipinski's parameters, hence, passing the first phase for 'Drug likeliness'. *In silico* evaluation (docking) of the cyclized compounds was also done against important cancer drug targets, namely kinases (EGFR, ALK) as well as Bromodomains (BRD4). The virtual screening results showed good docking scores, as well as the presence of conservative target-ligand interactions found in the corresponding protein-cocrystal ligand complexes. The results are very encouraging and indicate the potential of the synthesized compounds to inhibit known oncology targets.

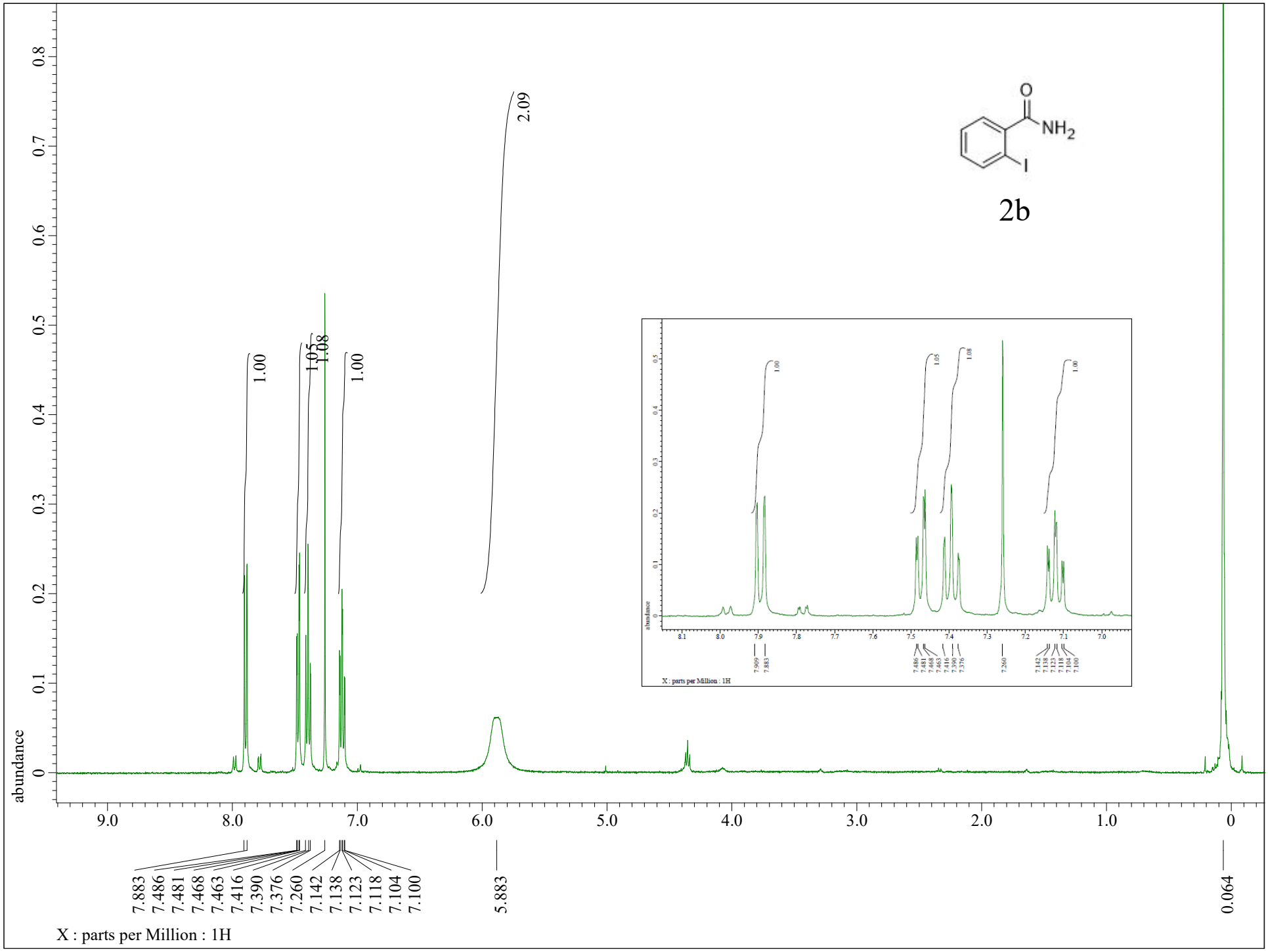
Future Scope

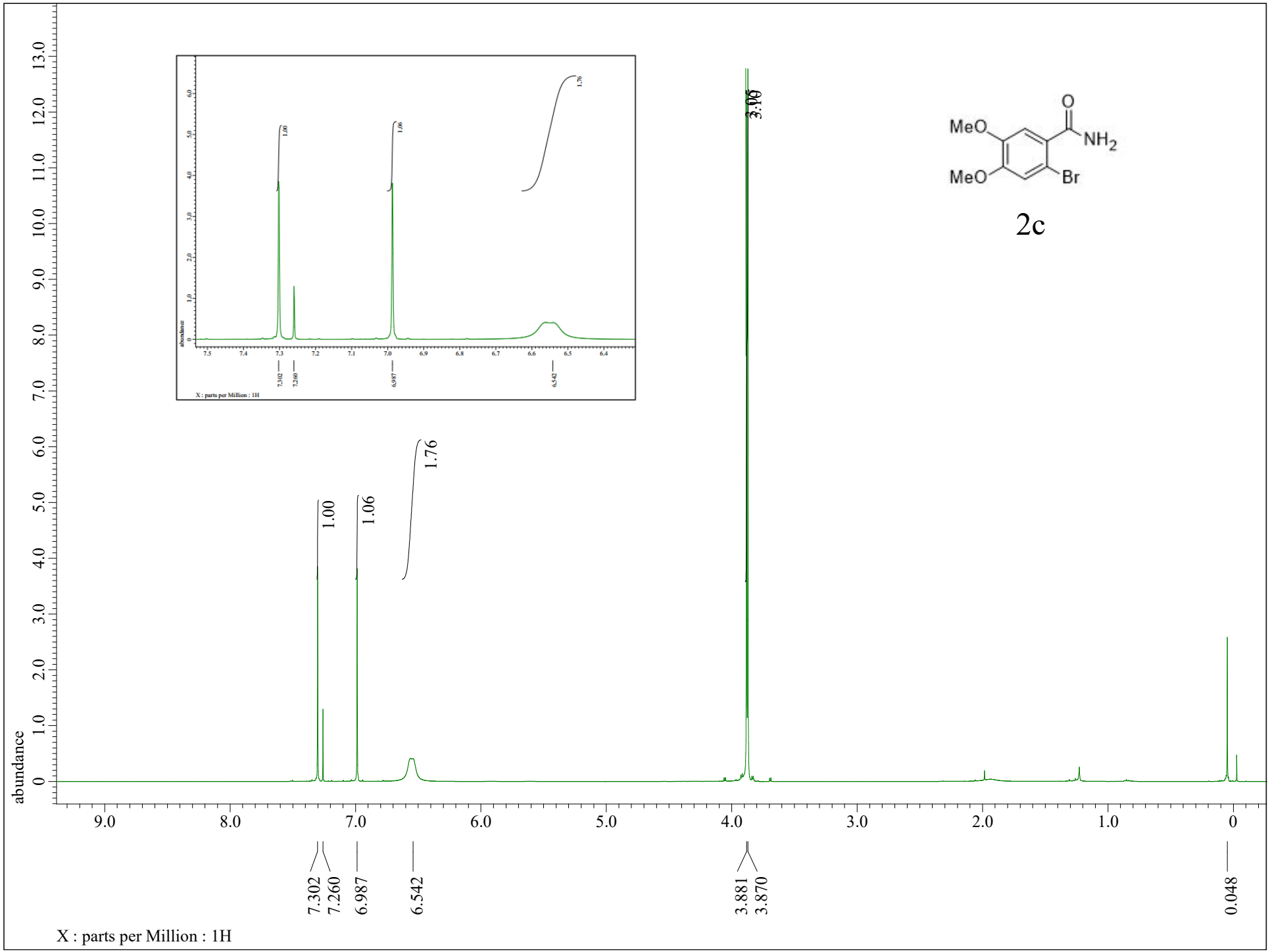
The cyclized products *i.e.* isoindolinones, contain free *–NH* group as well as halogen atom (I/Br), which provides the scope for further elaboration of these compounds to more complex products by subjecting to various reactions/metal-catalyzed couplings, generating an extensive library of the complex compounds. Moreover, the suitably substituted iodocyclized products may be useful intermediates for conveniently converting into novel aristolactam derivatives. Thus the work reported here will improve the accessibility as well as expand the chemical space with respect to the *N*-heterocyclic synthesis. The cyclized products may be used for high-throughput screening using various biochemical assays against validated drug targets. Thus, we believe that this methodology will be of interest to the synthetic/medicinal chemists, and may find applications in the pharmaceutical industry. Considering the scope and flexibility of these methodologies, and the potential applications of the resulting products, rapid advances in this area of research are anticipated.

APPENDIX A. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

2a
9.19
0.91
1.00
1.14
0.99
1.09
8.155
7.798
7.779
7.373
7.371
7.352
7.336
7.333
7.289
7.284
7.269
7.266
7.260
7.100
7.096
7.080
7.077
7.062
7.057
1.372
0.045
-0.036
abundance
X : parts per Million : 1H

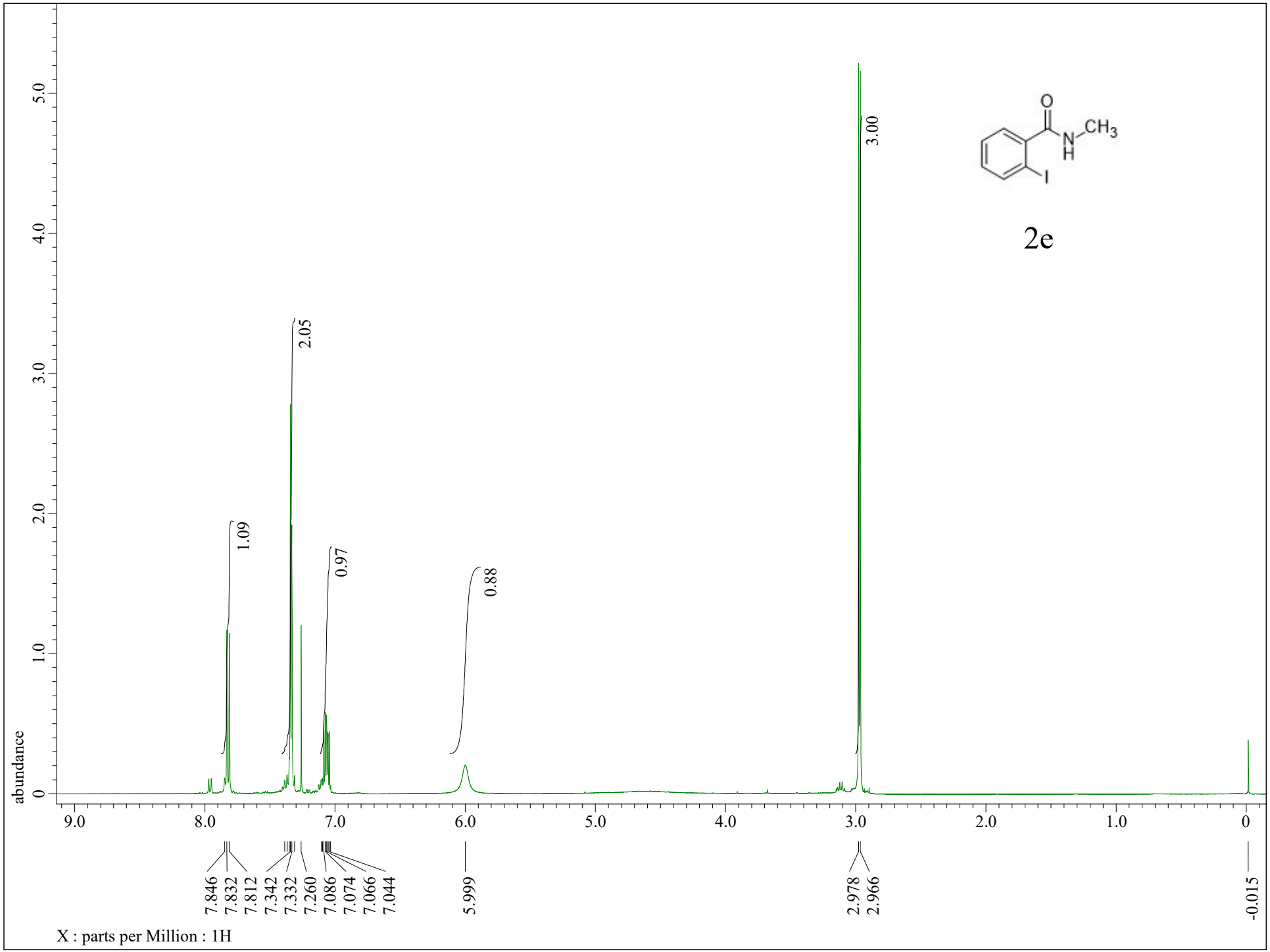
2a
abundance
4.0
3.0
2.0
1.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.961
149.320
141.053
139.146
131.071
127.781
127.581
91.988
82.721
77.315
77.000
76.676
27.802
X : parts per Million : 13C


abundance
X : parts per Million : 1H
2b
1.00
1.05
1.08
1.00
2.09
7.883
7.486
7.481
7.468
7.463
7.416
7.390
7.376
7.260
7.142
7.138
7.123
7.118
7.104
7.100
5.883
0.064


MeO
MeO
O
NH2
Br
2c
abundance
X : parts per Million : 1H
7.302
7.260
6.987
6.542
3.881
3.870
0.048
1.00
1.06
1.76

MeO
MeO
O
NH2
Br
2c
abundance
X : parts per Million : 13C
168.627
151.055
148.261
127.600
115.834
113.203
110.199
77.324
77.210
77.000
76.685
56.224
56.072
0.943

2d
abundance
X : parts per Million : 1H
1.00
1.02
3.11
2.78
2.14
7.898
7.880
7.638
7.619
7.504
7.499
7.485
7.481
7.403
7.391
7.386
7.371
7.352
7.260
7.171
7.151
7.132
7.128
0.078
0.004

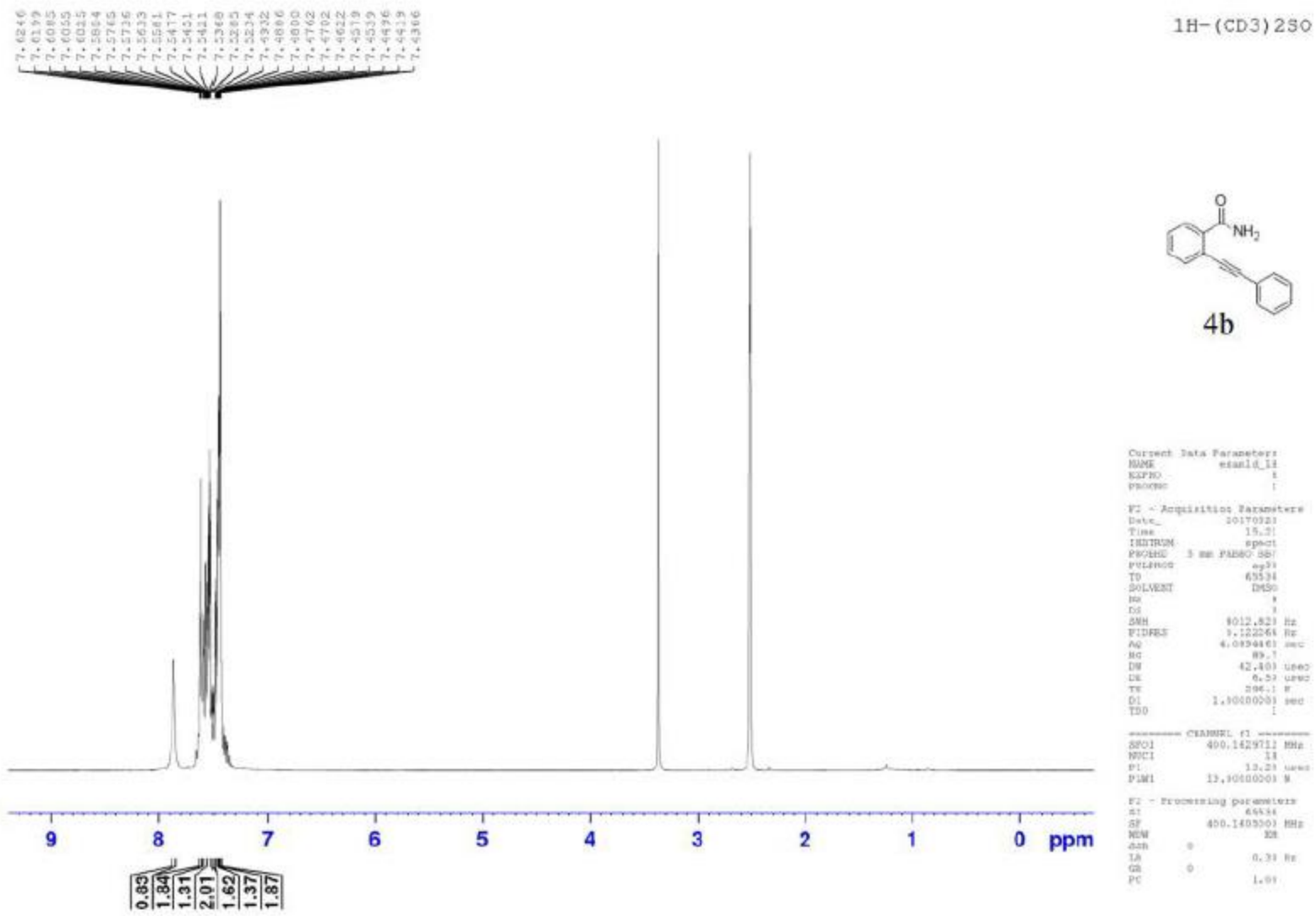

abundance
5.0
4.0
3.0
2.0
1.0
0
1.09
2.05
0.97
0.88
3.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.846
7.832
7.812
7.342
7.332
7.260
7.086
7.074
7.066
7.044
5.999
2.978
2.966
-0.015
X : parts per Million : 1H

O
N
H
CH3
I

2e

4a
abundance
X : parts per Million : 1H
9.289
8.066
8.046
7.628
7.611
7.596
7.591
7.481
7.462
7.394
7.377
7.260
1.457
0.068
0.79
0.93
3.20
3.02
1.77
9.00

4a
abundance
X : parts per Million : 13C
164.947
149.348
139.347
133.235
131.671
131.490
130.479
129.249
128.925
128.382
121.765
119.801
86.525
82.511
77.324
77.000
76.685
67.418
27.878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7.6055
7.6025
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7.5765
7.5736
7.5633
7.5581
7.5477
7.5451
7.5421
7.5360
7.5285
7.5234
7.4932
7.4886
7.4800
7.4762
7.4702
7.4622
7.4519
7.4539
7.4496
7.4419
7.4366
NH2
O
4b
9
8
7
6
5
4
3
2
1
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ppm
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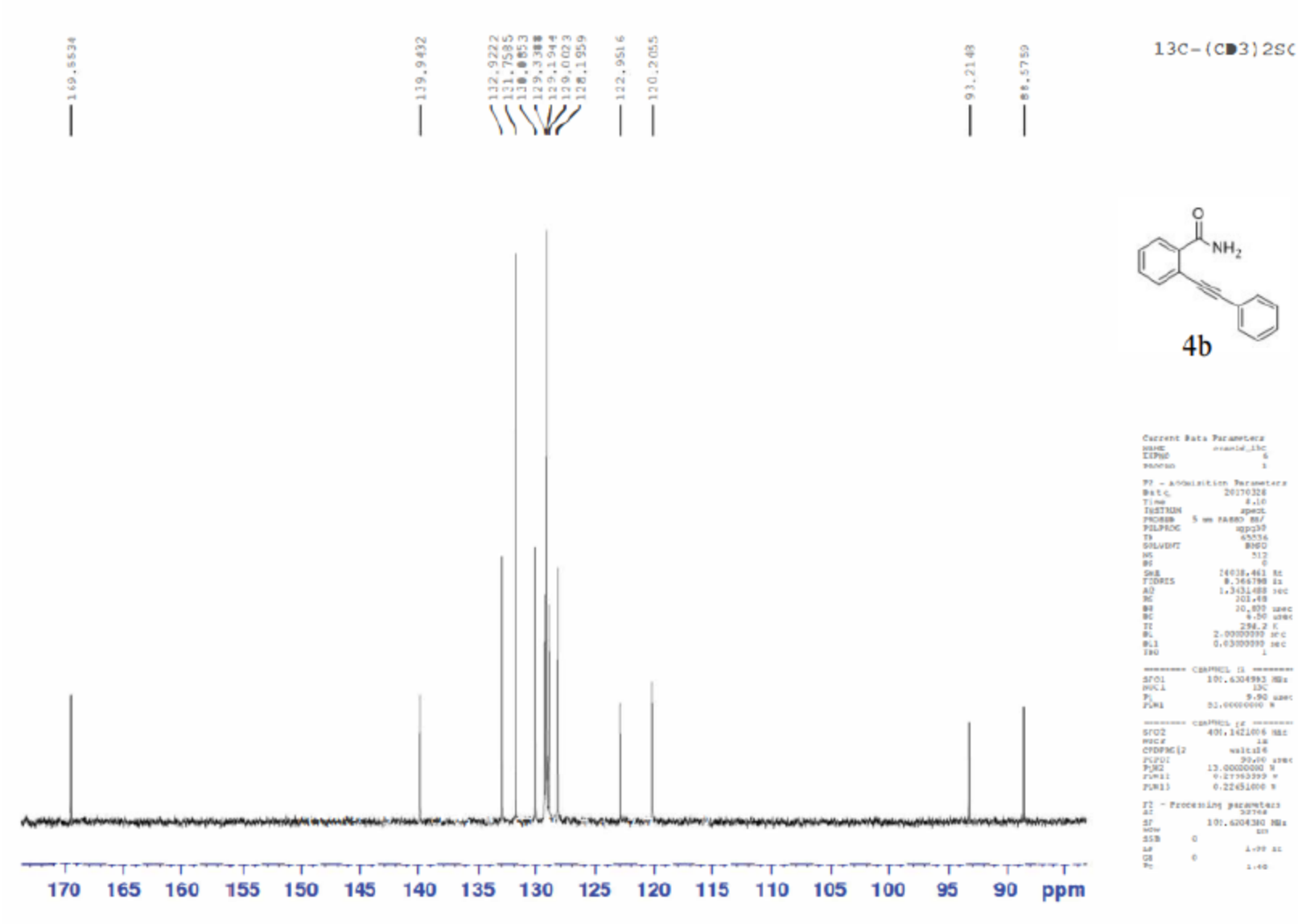
1.31
2.01
1.62
1.37
1.87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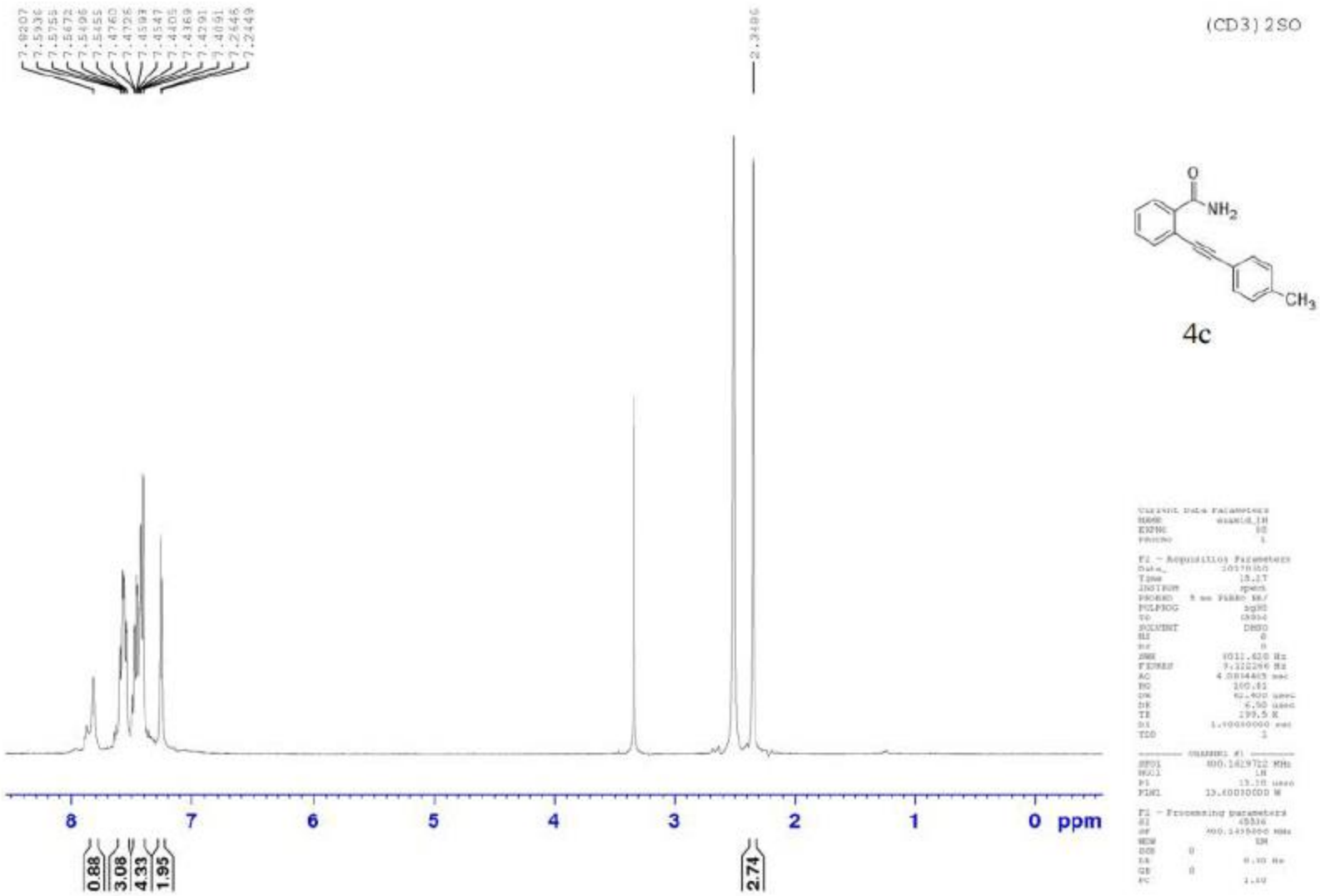
139.9432
132.9222
131.7585
129.3388
129.1944
129.0023
128.1959
122.9516
120.2055
93.2143
88.5759
13C-(CD3)2SO
NH2
4b
ppm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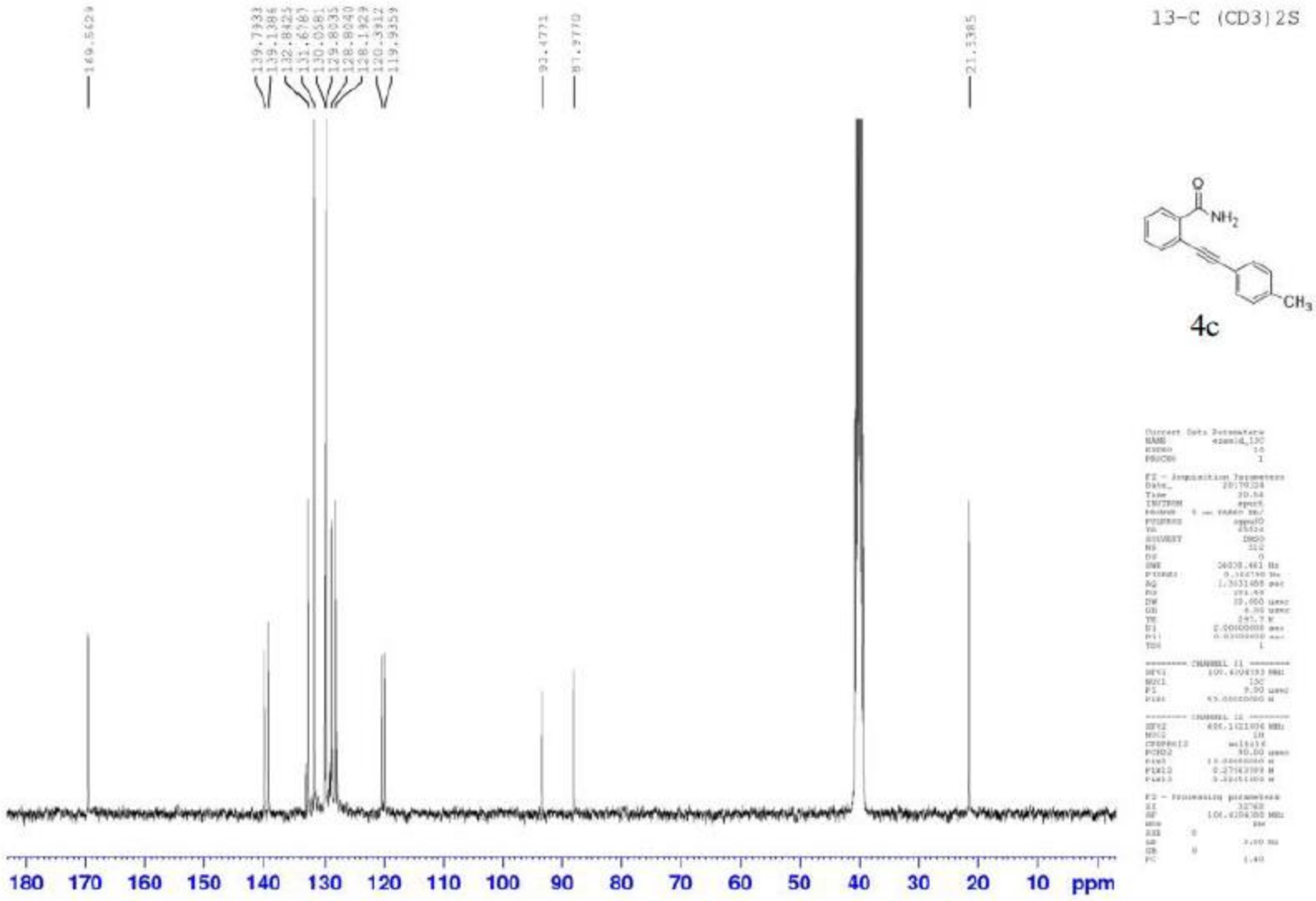
7.5936
7.5755
7.5672
7.5496
7.5455
7.4760
7.4726
7.4593
7.4547
7.4405
7.4369
7.4291
7.4091
7.2646
7.2449
2.3486
(CD3)2SO
O
NH2
CH3
4c
8
7
6
5
4
3
2
1
0 ppm
0.88
3.08
4.33
1.95
2.74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130.0581
129.8035
128.8040
128.1929
120.3912
119.9359
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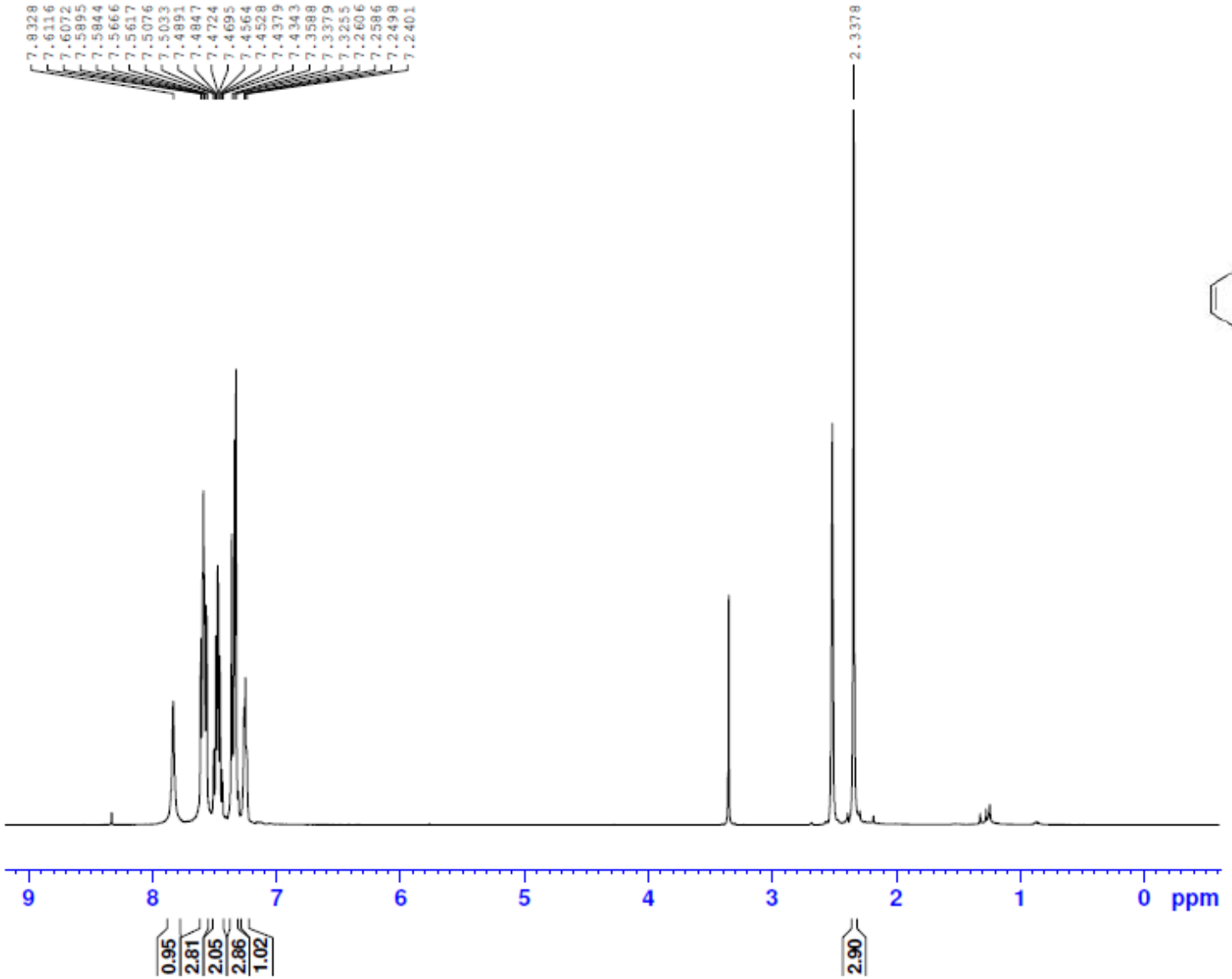
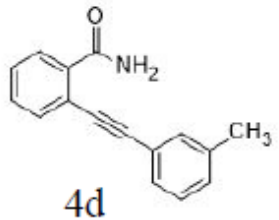
21.3385
13-C (CD3)2S
NH2
CH3
4c
ppm





4d

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PROCNO                        1

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INSTRUM                   spect
PROBHD     5 mm PABBO BB/
PULPROG                   zg30
TD                       65536
SOLVENT                   DMSO
NS                            8
DS                            0
SWH                 9012.820 Hz
FIDRES              0.122264 Hz
AQ                  4.0894465 sec
RG                        73.53
DW                       62.400 usec
DE                        6.50 usec
TE                       300.0 K
D1                  1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1              400.1629712 MHz
NUC1                        1H
P1                       13.20 usec
PLW1             13.00000000 W

F2 - Processing parameters
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WDW                          EM
SSB                   0
LB                        0.30 Hz
GB                    0
PC                        1.00
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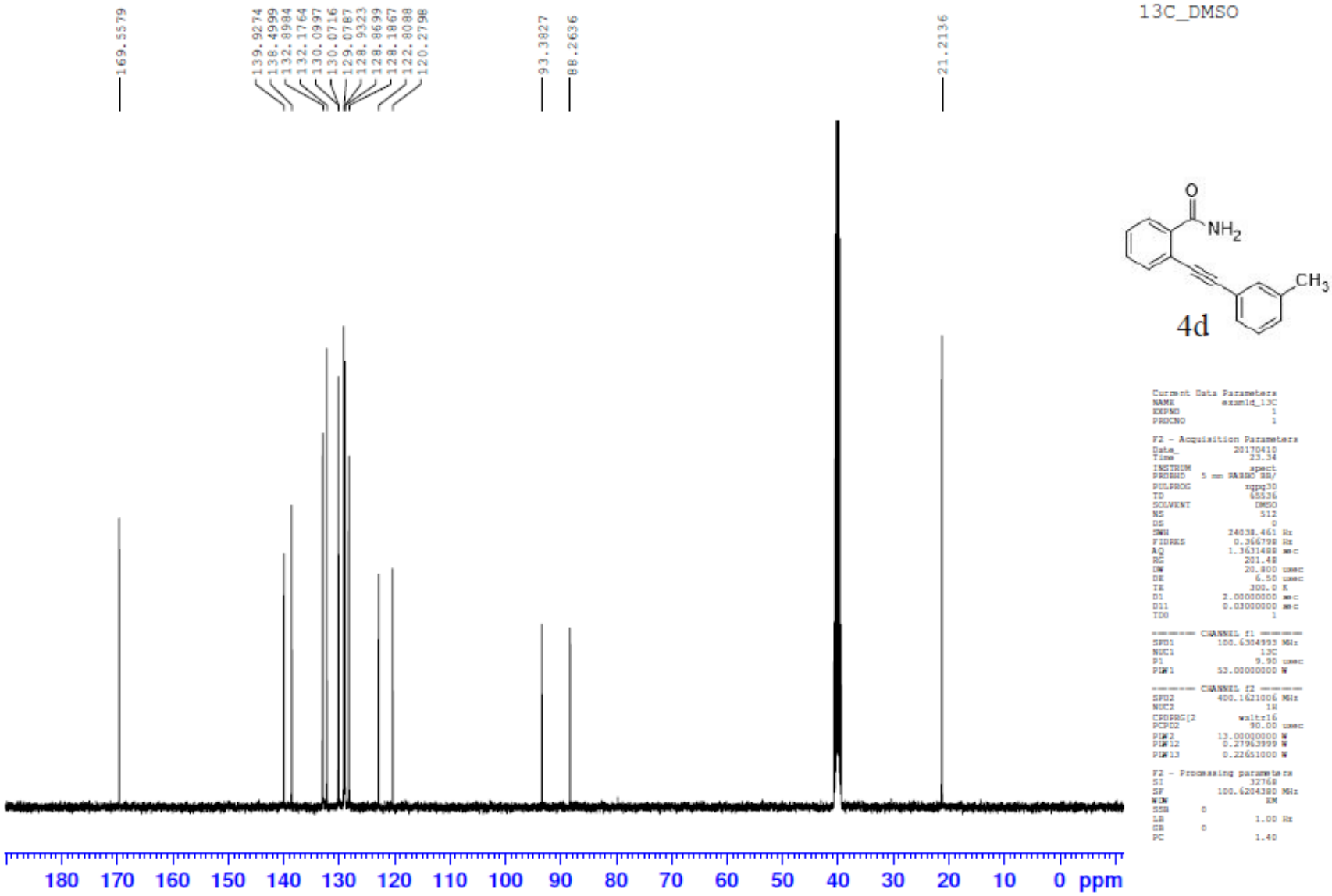
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130.0716
129.0787
128.9323
128.8699
128.1867
122.8088
120.2798
93.3827
88.2636
21.2136
O
NH2
CH3
4d
Current Data Parameters
NAME exam1d_13C
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PROCNO 1
F2 - Acquisition Parameters
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INSTRUM spect
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PULPROG zgpg30
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FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.48
DW 20.800 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6304893 MHz
NUC1 13C
P1 9.90 usec
PW1 53.00000000 W
======== CHANNEL f2 ========
SFO2 400.1621006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PW2 13.00000000 W
PW12 0.27963999 W
PW13 0.22651000 W
F2 - Processing parameters
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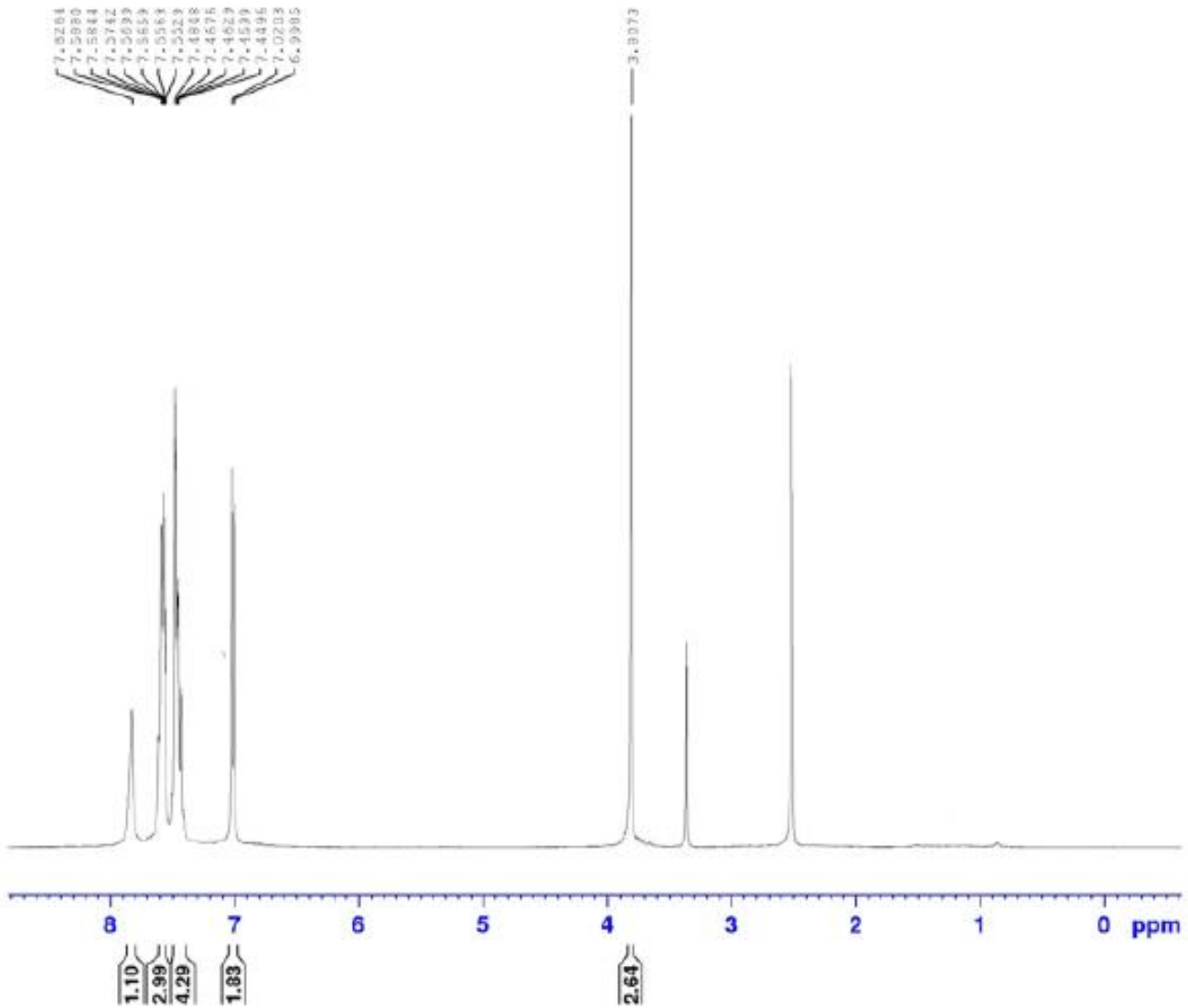

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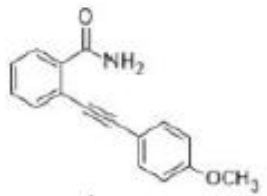

4e

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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT DMSO
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DS 2
SWH 8013.830 Hz
FIDRES 0.122264 Hz
AQ 4.0894861 sec
RG 73.53
DW 62.400 usec
DE 6.50 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 600.1629712 MHz
NUC1 1H
P1 13.20 usec
PLW1 13.60000000 W

F2 - Processing parameters
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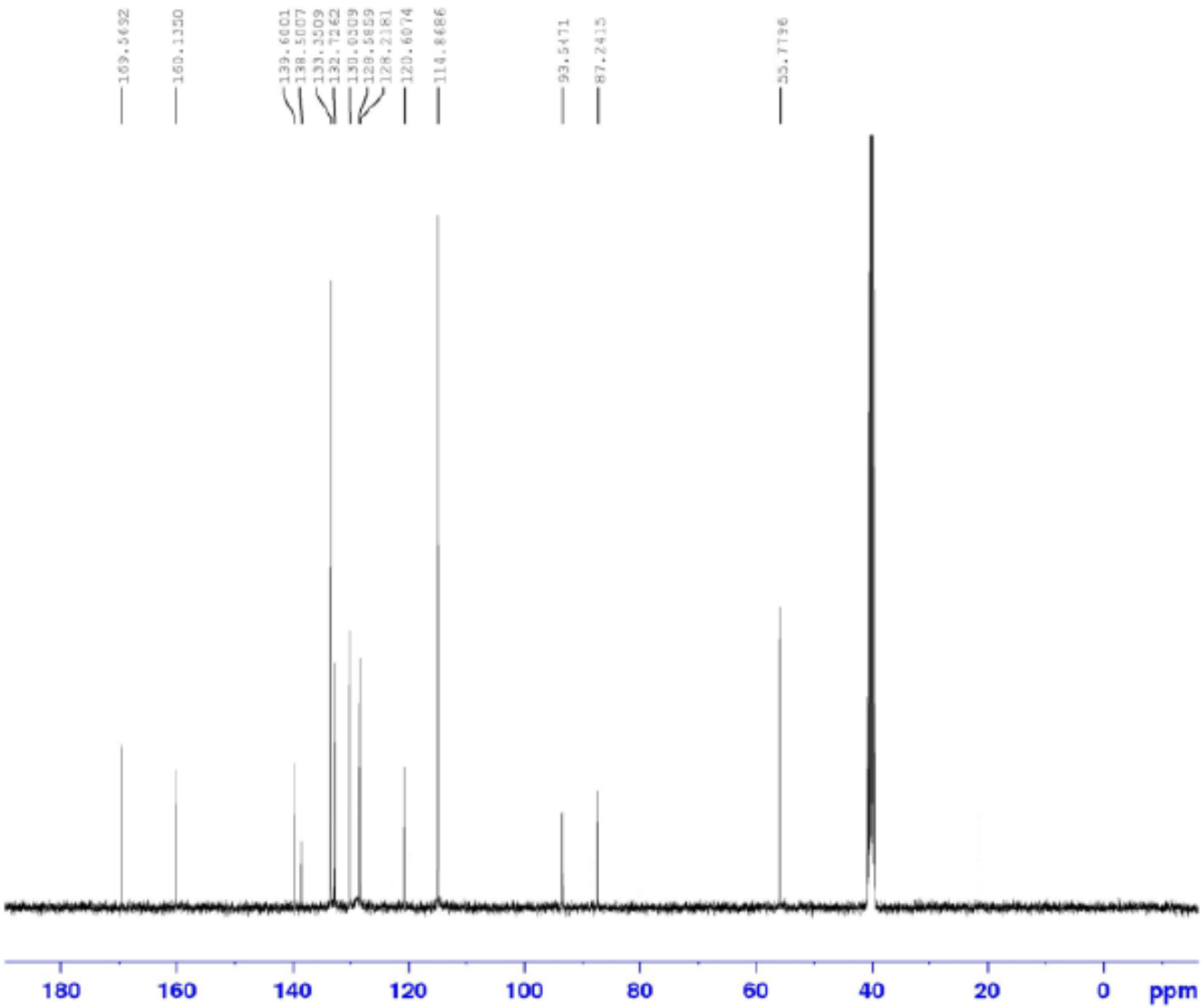
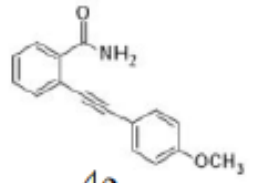
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

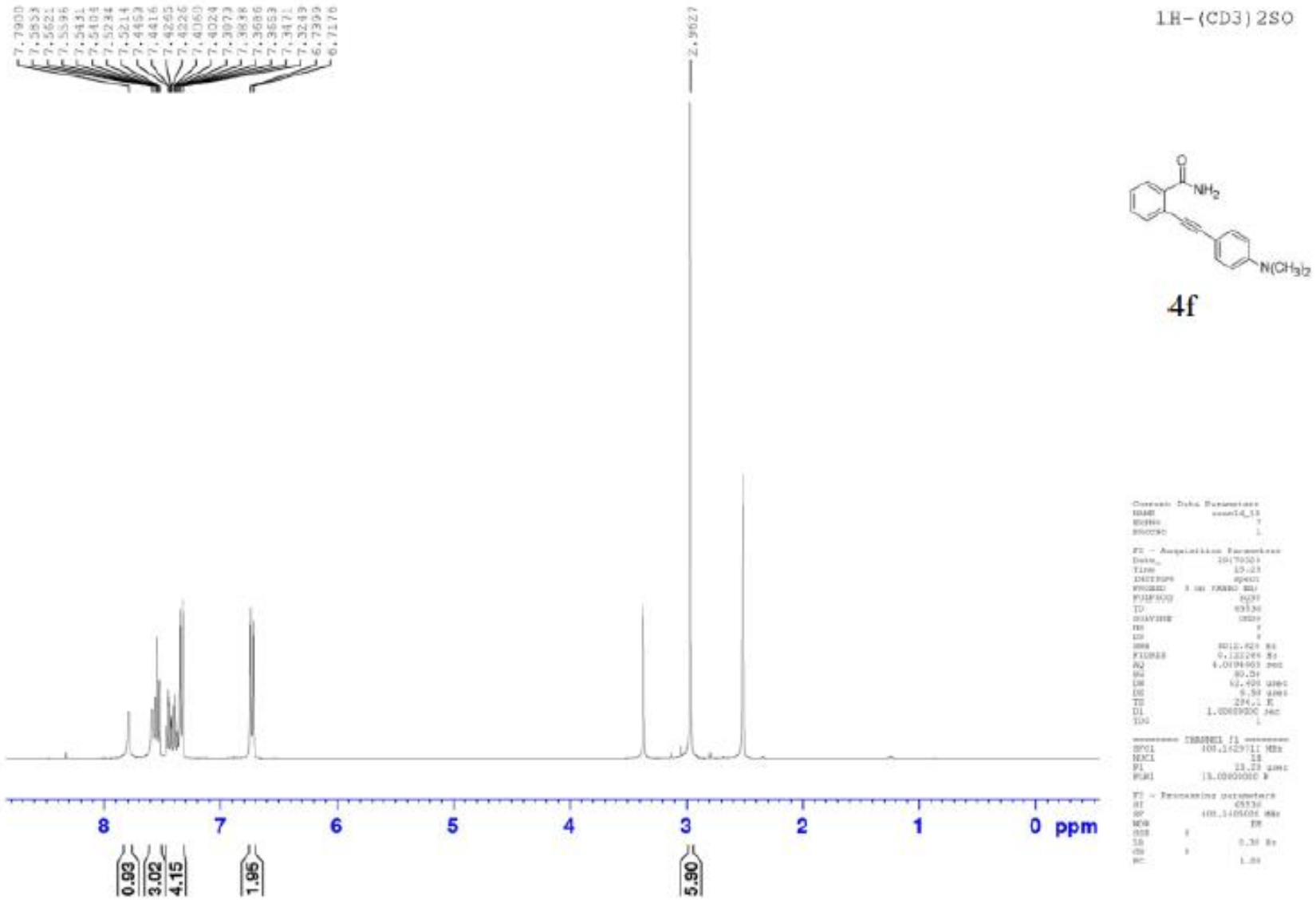


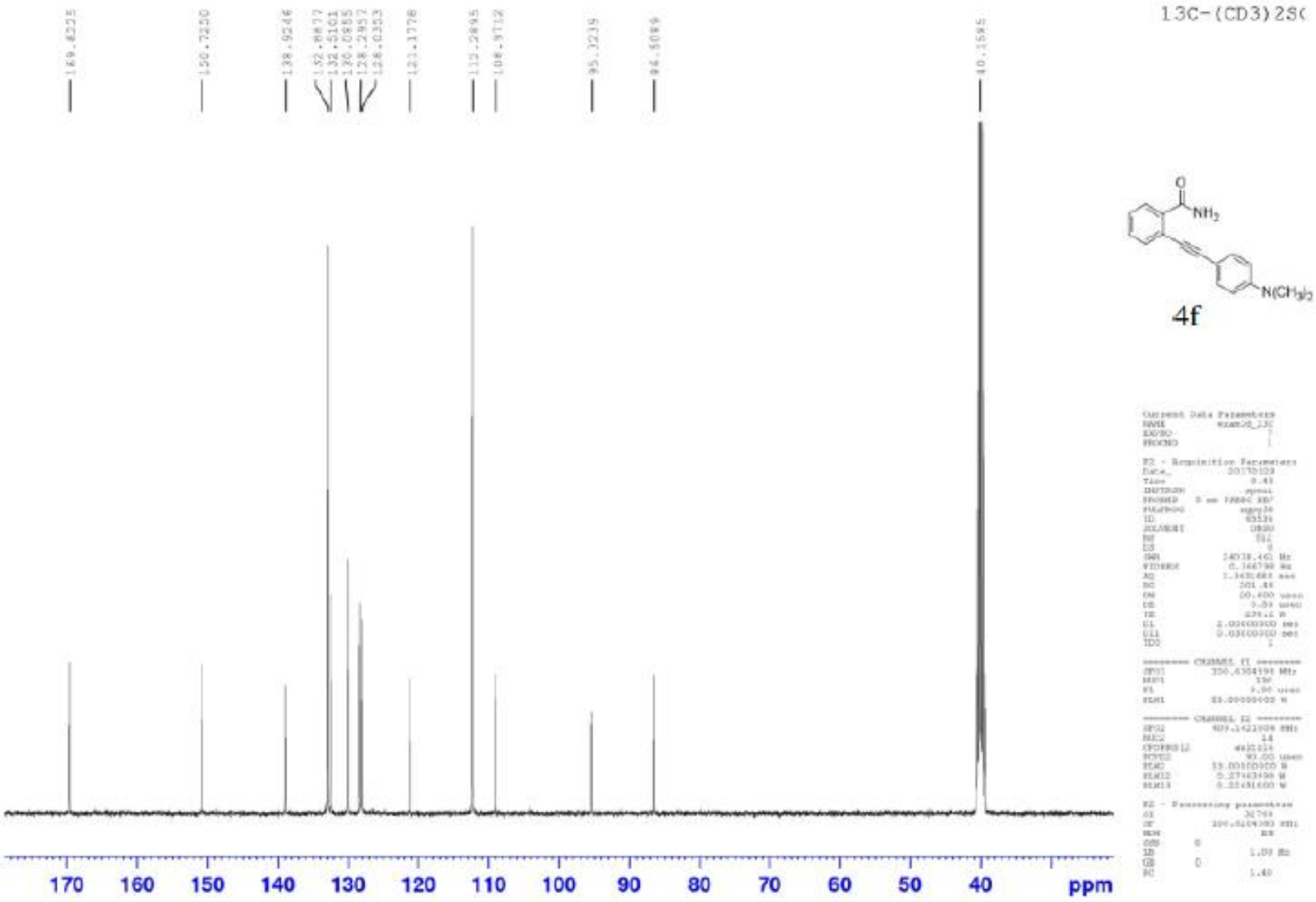
13C_DMSO

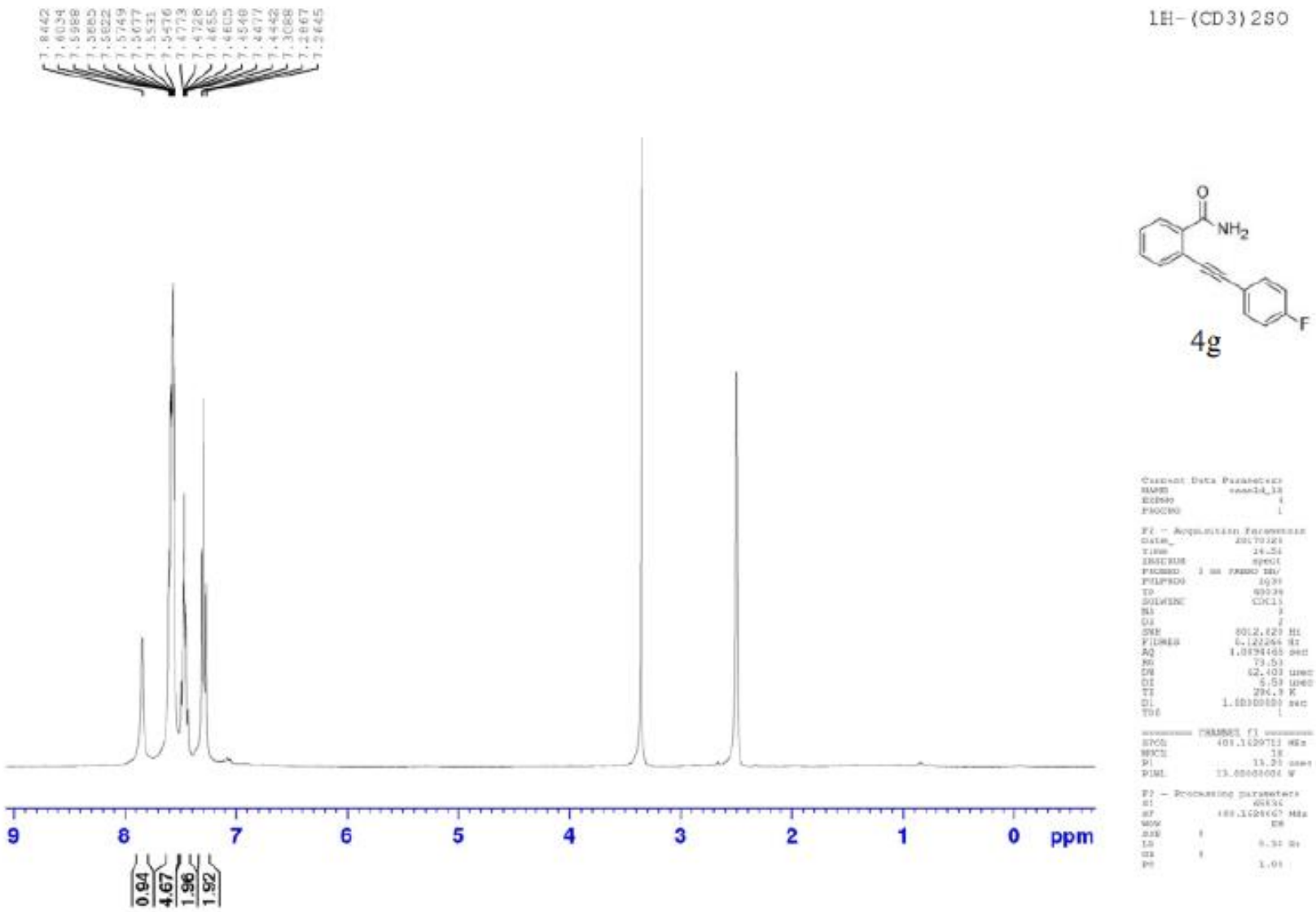


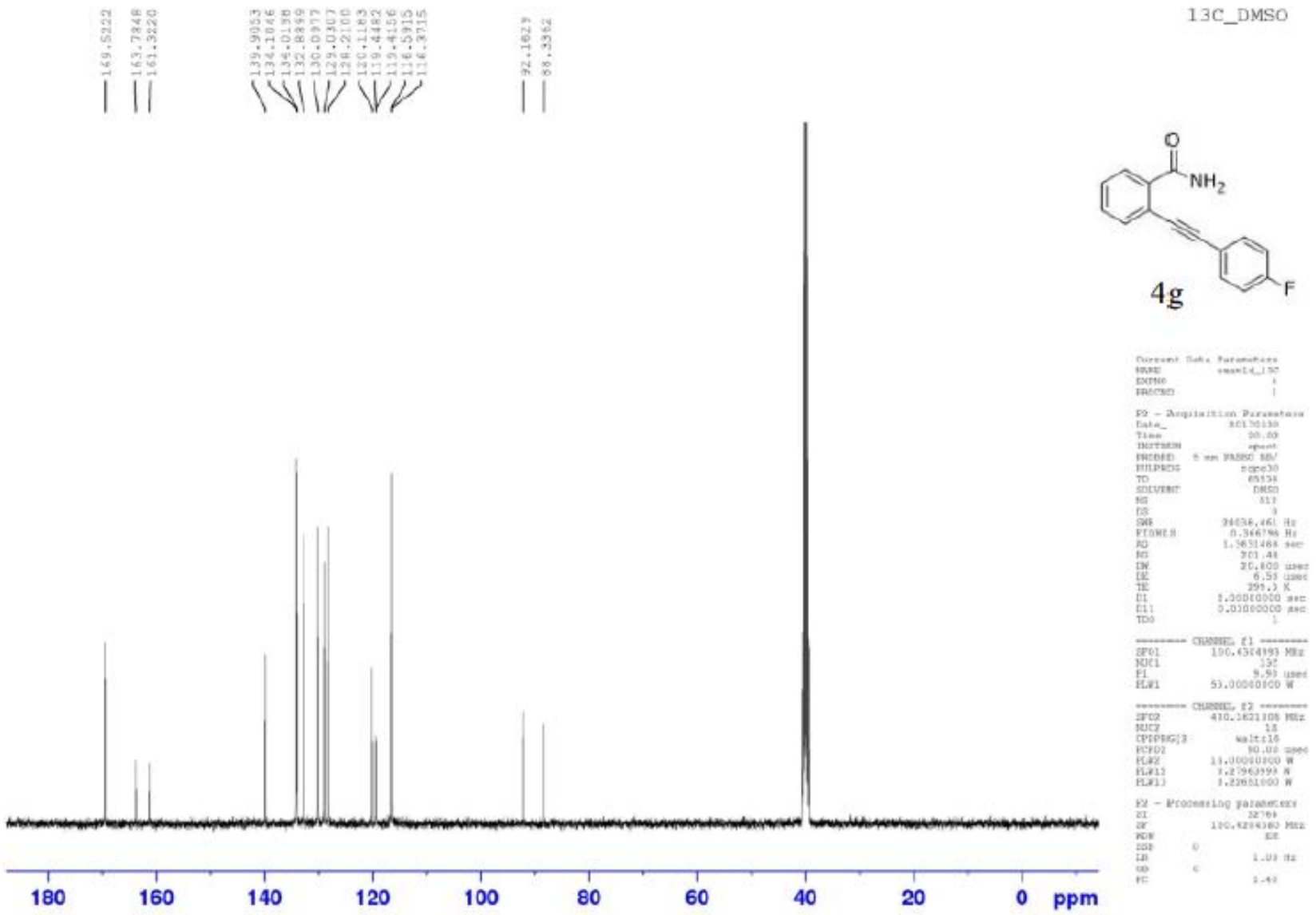
4e

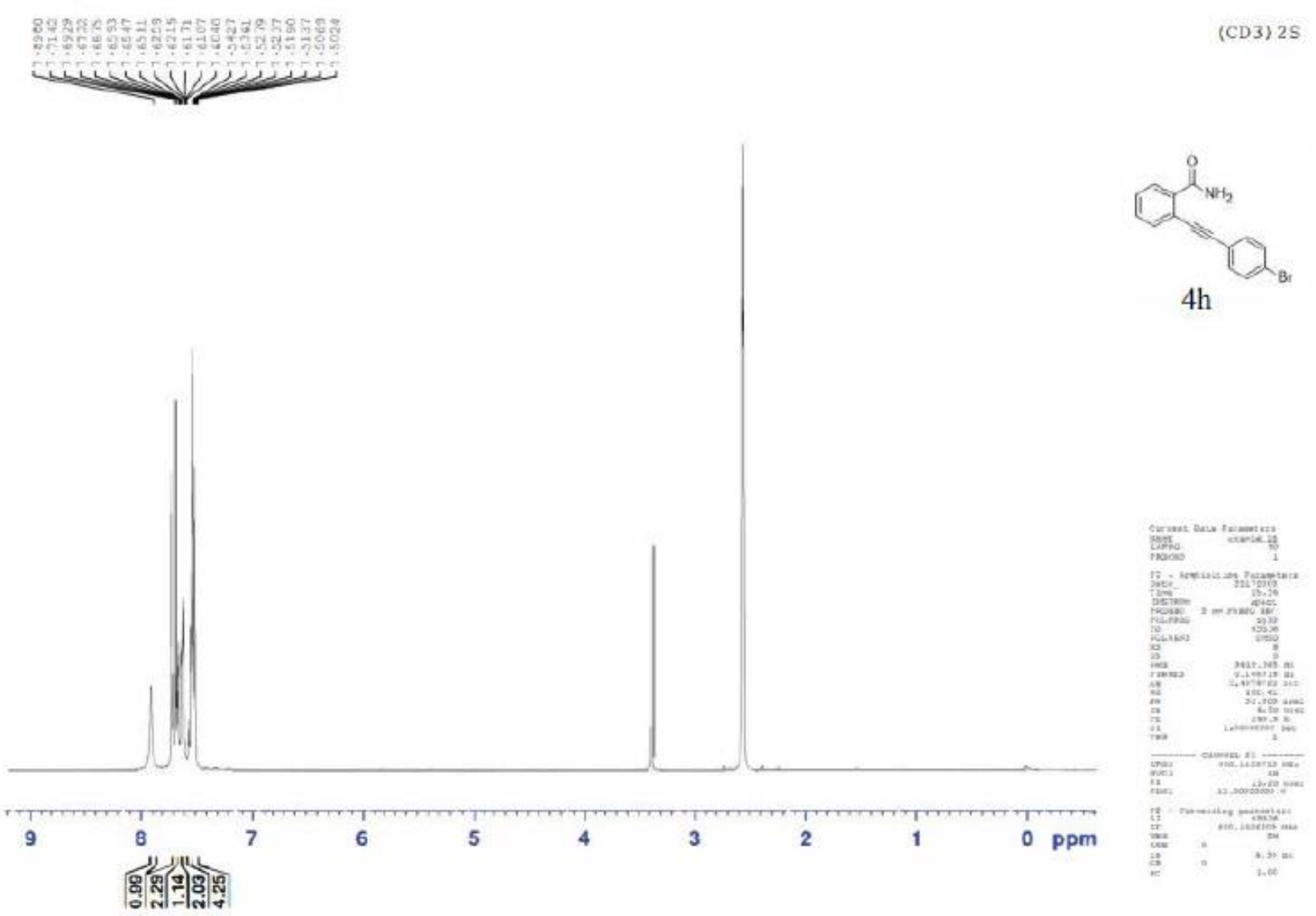
NAME	exam1d_13C
EXPNO	6
PROCNO	1
F2 - Acquisition Parameters	
Date_	20170130
Time	20.35
INSTRUM	spect
PROBHD	5 mm PABBO BB/
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	332
DS	0
SWH	34538.461 Hz
FIDRES	0.366758 Hz
AQ	1.3631488 sec
RG	201.48
DW	20.800 usec
DE	6.50 usec
TE	299.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	100.6304993 MHz
NUC1	13C
P1	9.90 usec
PLW1	53.00000000 W
======== CHANNEL f2 ========	
SFO2	400.1621006 MHz
NUC2	1H
CPDPRG[2	waltz16
PCPD2	90.00 usec
PLW2	13.00000000 W
PLW12	0.27963999 W
PLW13	0.22651000 W
F2 - Processing parameters	
SI	32768
SF	100.6204260 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

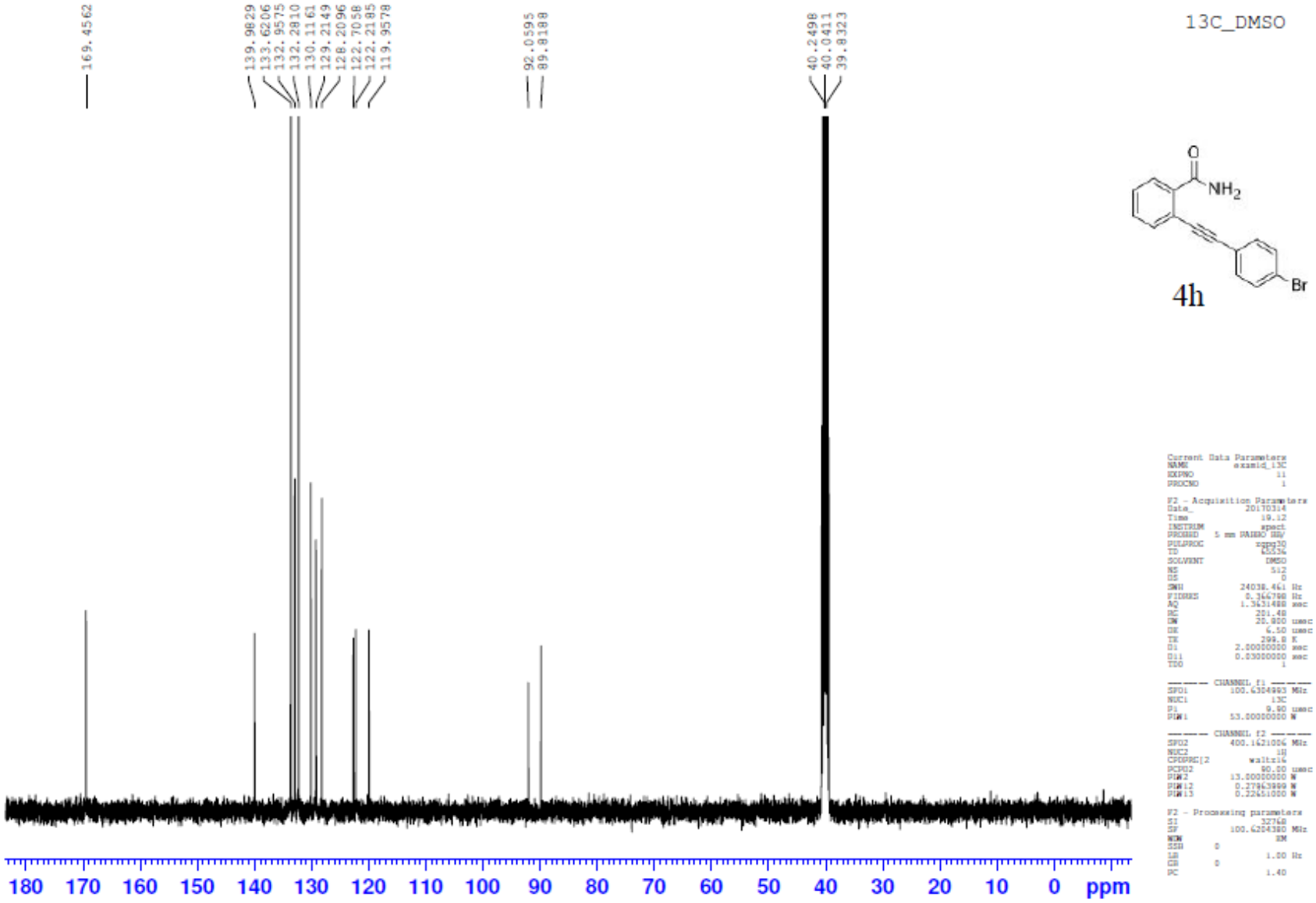

7.7930
7.3853
7.5621
7.5596
7.5431
7.5403
7.5234
7.5214
7.4459
7.4416
7.4265
7.4226
7.4060
7.4024
7.3973
7.3838
7.3586
7.3553
7.3471
7.3249
6.7399
6.7176
2.9627
1H-(CD3)2SO
NH2
N(CH3)2
4f
8
7
6
5
4
3
2
1
0 ppm
0.93
3.02
4.15
1.95
5.90

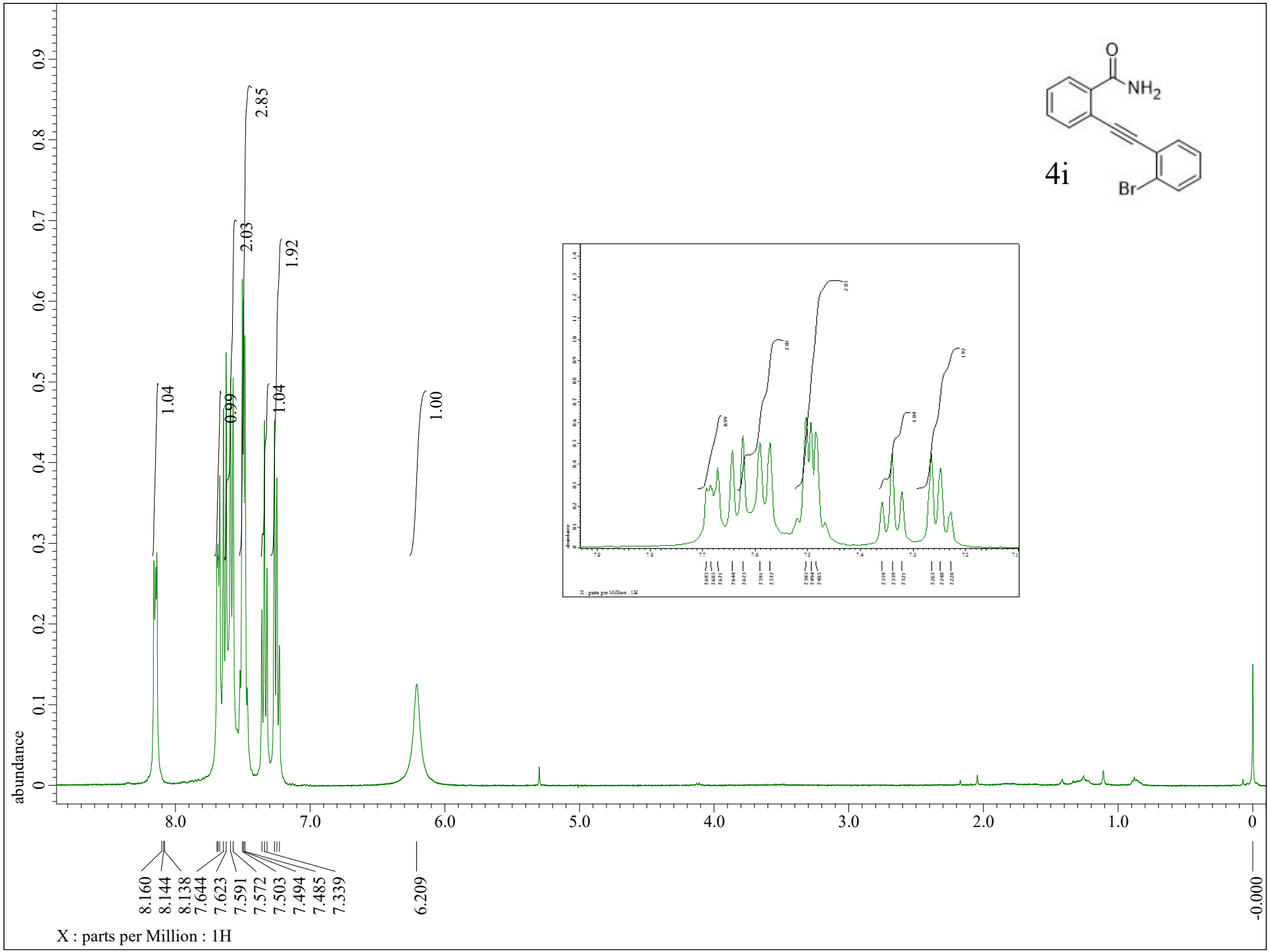

169.8225
150.7850
138.9246
132.8877
132.5161
130.0885
128.2957
126.0353
121.1778
111.2895
106.9712
95.3239
84.5069
40.1585
13C-(CD3)2SO
O
NH2
N(CH3)2
4f
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


7.8442
7.8034
7.5988
7.5885
7.5822
7.5749
7.5677
7.5531
7.5476
7.4773
7.4728
7.4655
7.4605
7.4540
7.4477
7.4442
7.3068
7.2867
7.2645
1H-(CD3)2SO
O
NH2
F
4g
9
8
7
6
5
4
3
2
1
0
ppm
0.94
4.67
1.96
1.92

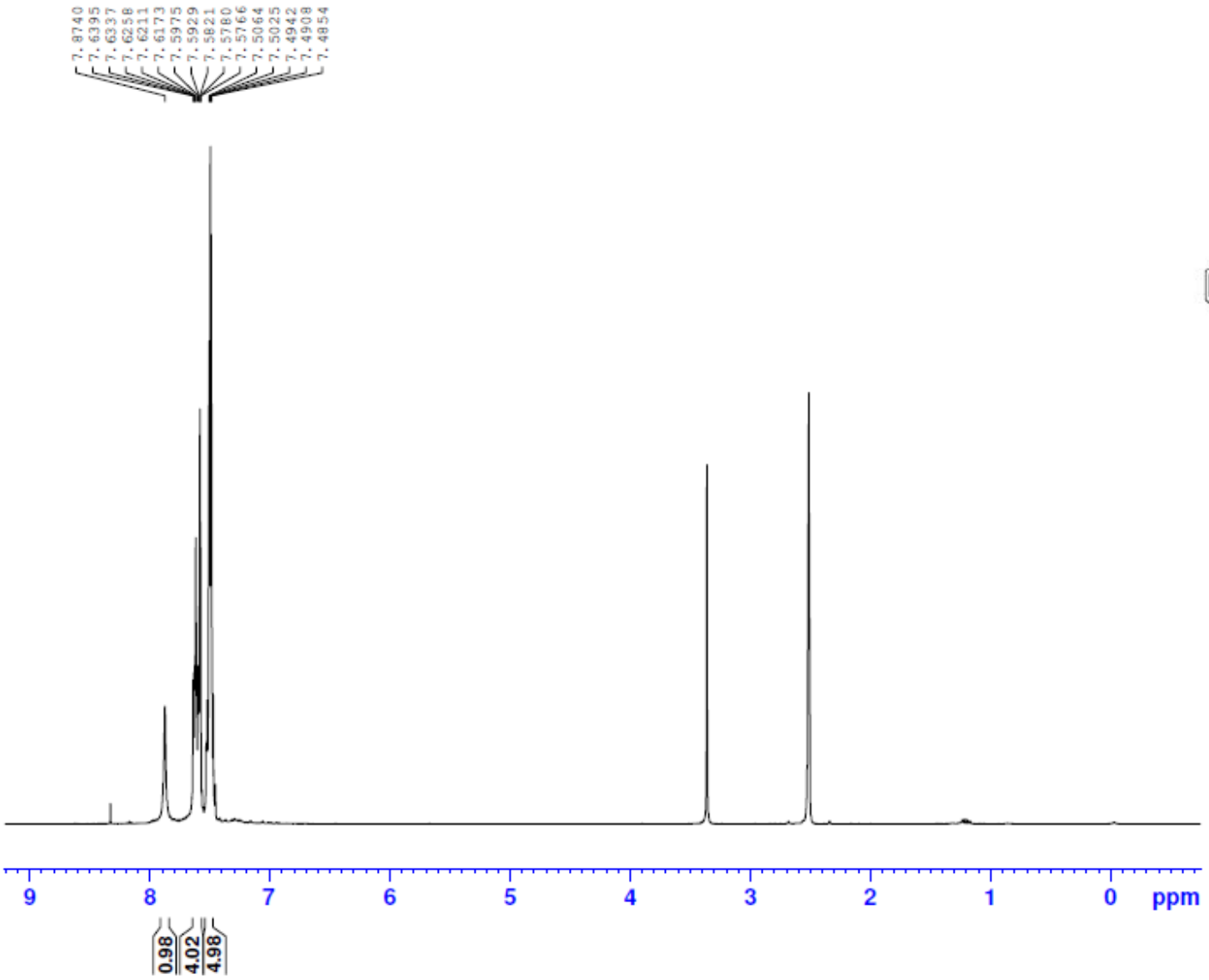

13C_DMSO
169.5222
163.7848
161.3220
139.9053
134.1046
134.0198
132.8899
130.0977
129.0307
128.2100
120.1183
119.4482
119.4156
116.5915
116.3715
92.1629
88.3362
O
NH2
F
4g
180
160
140
120
100
80
60
40
20
0
ppm


(CD3)2S
4h
9
8
7
6
5
4
3
2
1
0 ppm
0.99
2.29
1.14
2.03
4.25

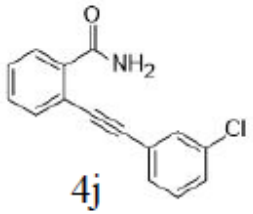

169.4562
139.9829
133.6206
132.9575
132.2810
130.1161
129.2149
128.2096
122.7058
122.2185
119.9578
92.0595
89.8188
40.2498
40.0411
39.8323
13C_DMSO
O
NH2
Br
4h
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


4i
NH2
O
Br
abundance
1.04
0.99
2.03
2.85
1.92
1.04
1.00
8.160
8.144
8.138
7.644
7.623
7.591
7.572
7.503
7.494
7.485
7.339
6.209
-0.000
X : parts per Million : 1H

O
NH2
Br
4i
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.807
134.331
133.864
133.635
132.587
131.032
130.451
130.308
129.240
127.295
125.197
124.368
119.715
94.258
91.721
77.315
77.000
76.685
X : parts per Million : 13C

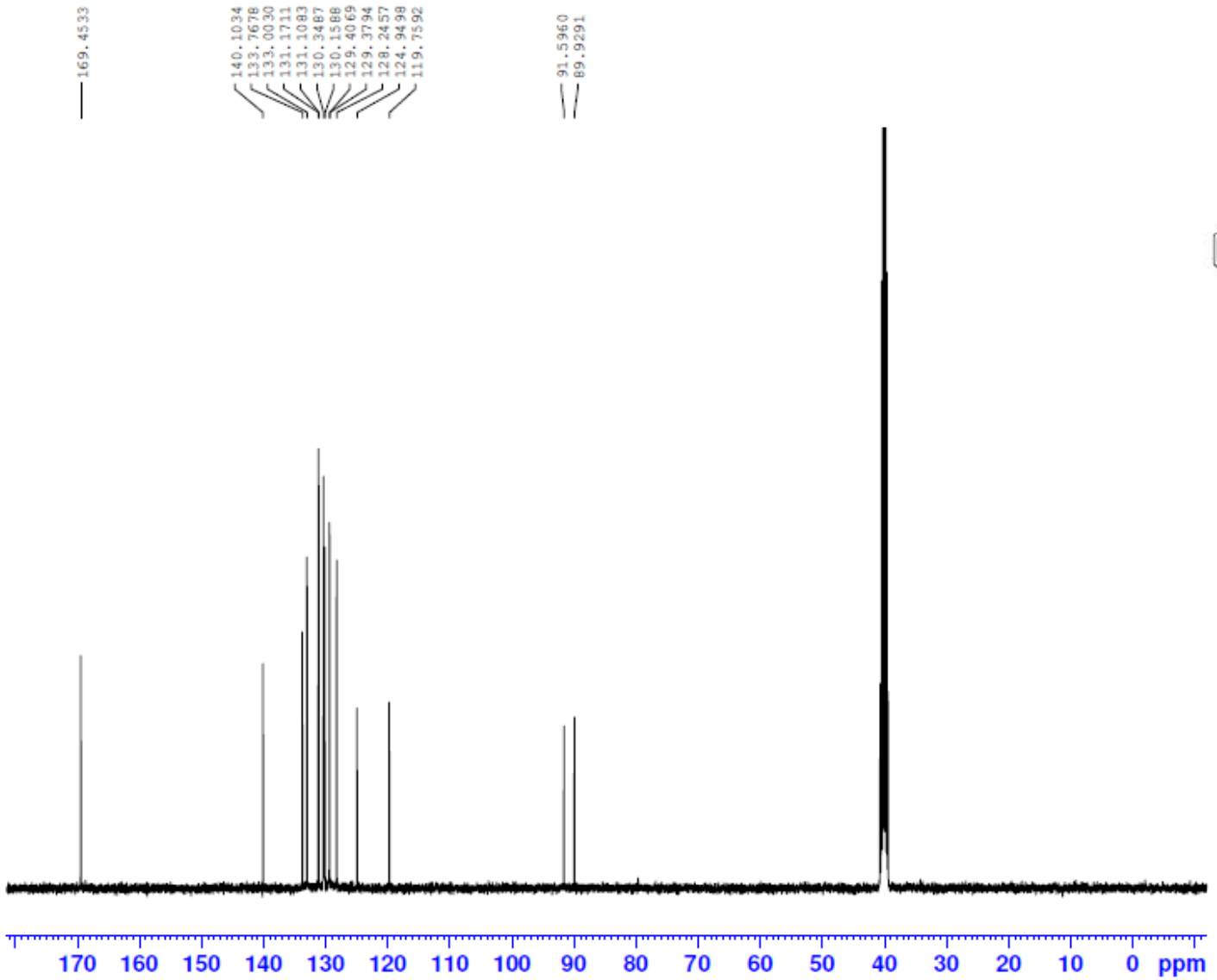


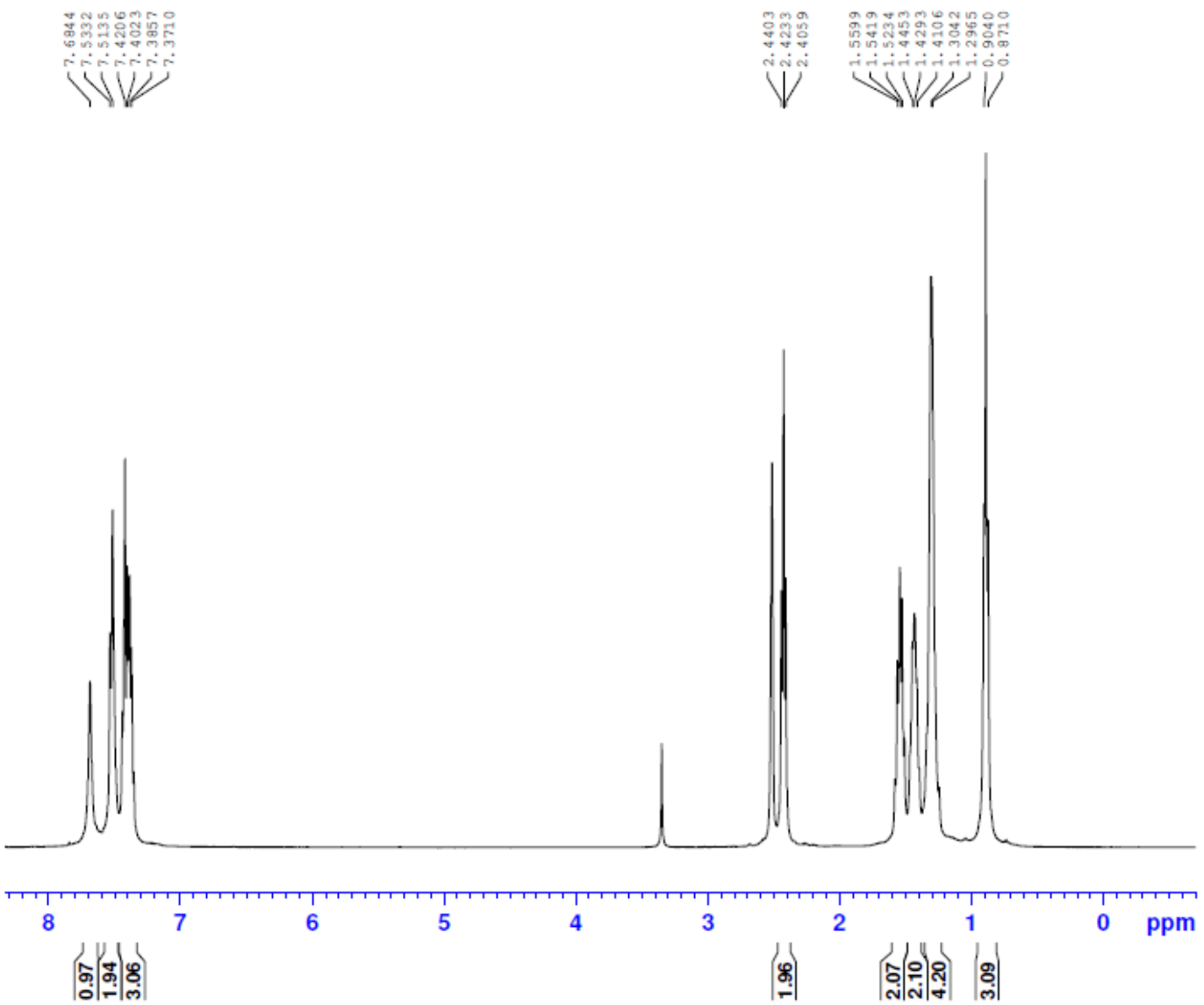
1H_DMSO



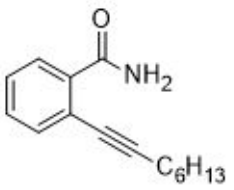
4j

```
Current Data Parameters
NAME                  examld_1H
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20170331
Time                      14.24
INSTRUM                    spect
PROBHD    5 mm PABBO BB/
PULPROG                    zg30
TD                        65536
SOLVENT                    DMSO
NS                            8
DS                            0
SWH                    8012.820 Hz
FIDRES                 0.122266 Hz
AQ                     4.0894465 sec
RG                        80.54
DW                        62.400 usec
DE                         6.50 usec
TE                       297.8 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                 400.1629712 MHz
NUC1                          1H
P1                        13.20 usec
PLW1                 13.00000000 W

F2 - Processing parameters
SI                        65536
SF                   400.1605000 MHz
WDW                          EM
SSB                   0
LB                            0.30 Hz
GB                    0
PC                            1.00
```


169.4533
140.1034
133.7678
133.0030
131.1711
131.1083
130.3487
130.1588
129.4069
129.3794
128.2457
124.9498
119.7592
91.5960
89.9291
13C_DMSO
O
NH2
Cl
4j
Current Data Parameters
NAME examld_13C
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170404
Time 2.02
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 0
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 201.48
DW 20.800 usec
DE 6.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 100.6304993 MHz
NUC1 13C
P1 9.90 usec
PLW1 53.00000000 W
CHANNEL f2
SFO2 400.1621006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 13.00000000 W
PLW12 0.27963999 W
PLW13 0.22651000 W
F2 - Processing parameters
SI 32768
SF 100.6204380 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

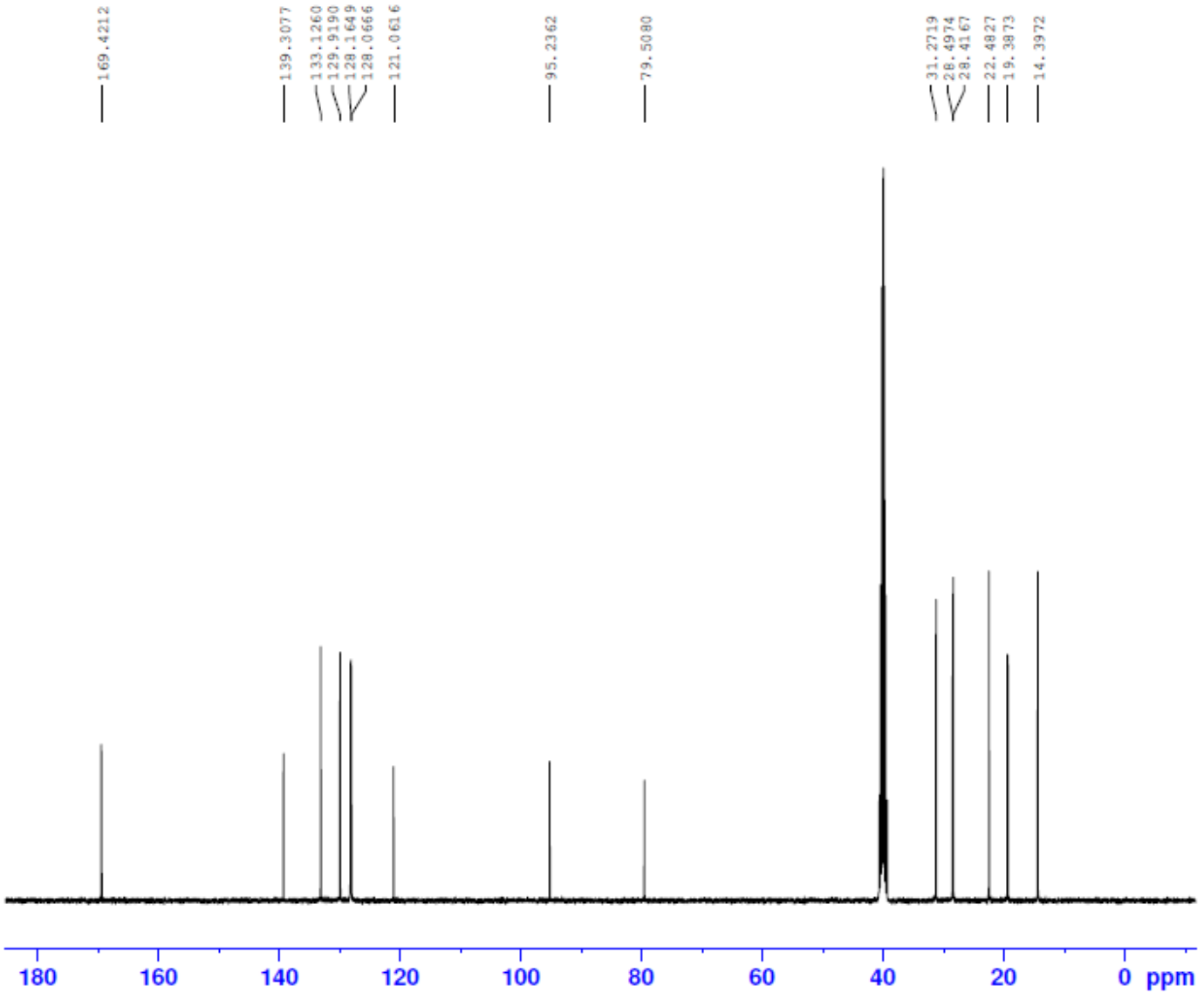


1H_(CD3)2S(

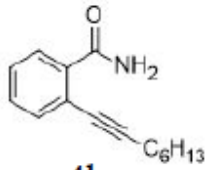


4k

```
Current Data Parameters
NAME                  examld_1H
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20170331
Time                      14.28
INSTRUM                   spect
PROBHD     5 mm PABBO BB/
PULPROG                   zg30
TD                       65536
SOLVENT                   DMSO
NS                            8
DS                            0
SWH                    8012.820 Hz
FIDRES                 0.122266 Hz
AQ                     4.0894465 sec
RG                        31.99
DW                       62.400 usec
DE                        6.50 usec
TE                       297.8 K
D1                    1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                 400.1629712 MHz
NUC1                         1H
P1                        13.20 usec
PLW1                 13.00000000 W

F2 - Processing parameters
SI                        65536
SF                   400.1605000 MHz
WDW                          EM
SSB                   0
LB                            0.30 Hz
GB                    0
PC                            1.00
```



13C_DMSO



4k

```
Current Data Parameters
NAME                 exam1d_13C
EXPNO                         3
PROCNO                        1

F2 - Acquisition Parameters
Date_               20170404
Time                    2.34
INSTRUM                spect
PROBHD    5 mm PABBO BB/
PULPROG             zgpg30
TD                   65536
SOLVENT                DMSO
NS                       512
DS                         0
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                     201.48
DW                   20.800 usec
DE                    6.50 usec
TE                    300.0 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1            100.6304993 MHz
NUC1                    13C
P1                     9.90 usec
PLW1            53.00000000 W

======== CHANNEL f2 ========
SFO2            400.1621006 MHz
NUC2                    1H
CPDPRG[2             waltz16
PCPD2                 90.00 usec
PLW2            13.00000000 W
PLW12            0.27963999 W
PLW13            0.22651000 W

F2 - Processing parameters
SI                     32768
SF              100.6204380 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

O
NH2
41
abundance
X : parts per Million : 1H
1.00
0.98
1.03
2.03
1.00
1.00
2.01
2.01
2.04
3.94
8.140
8.123
8.116
7.750
7.480
7.409
7.404
7.398
7.386
6.442
2.701
2.692
2.678
2.669
2.659
2.645
2.636
1.903
1.758
1.753
1.745
1.569
1.564
1.538
1.394
1.372
1.353
-0.000

O
NH2
41
abundance
0
0.1
0.2
0.3
0.4
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.284
133.893
133.683
130.880
130.260
128.039
120.935
101.704
79.660
77.315
77.000
76.685
32.273
29.832
25.666
24.817
X : parts per Million : 13C

4m
abundance
X : parts per Million : 1H
1.04
0.96
1.05
1.98
1.03
1.00
2.05
2.00
3.96
8.121
8.102
8.098
7.500
7.483
7.416
7.413
7.399
7.384
6.563
6.270
6.260
6.250
2.220
2.214
2.199
2.174
2.165
2.159
2.149
2.144
1.689
1.686
1.674
1.670
1.630
1.626
1.617
0.063
-0.011

4m
abundance
X : parts per Million : 13C
168.332
137.020
133.902
133.340
130.889
130.270
128.229
120.697
119.982
97.967
85.257
77.315
77.000
76.685
28.726
25.742
22.071
21.261

O
NH2
TMS

4n

abundance
X : parts per Million : 1H
1.00
0.66
1.05
2.09
0.81
8.73
8.135
8.127
8.124
8.117
8.111
7.427
7.421
7.417
7.415
7.404
7.260
6.463
0.264
0.062

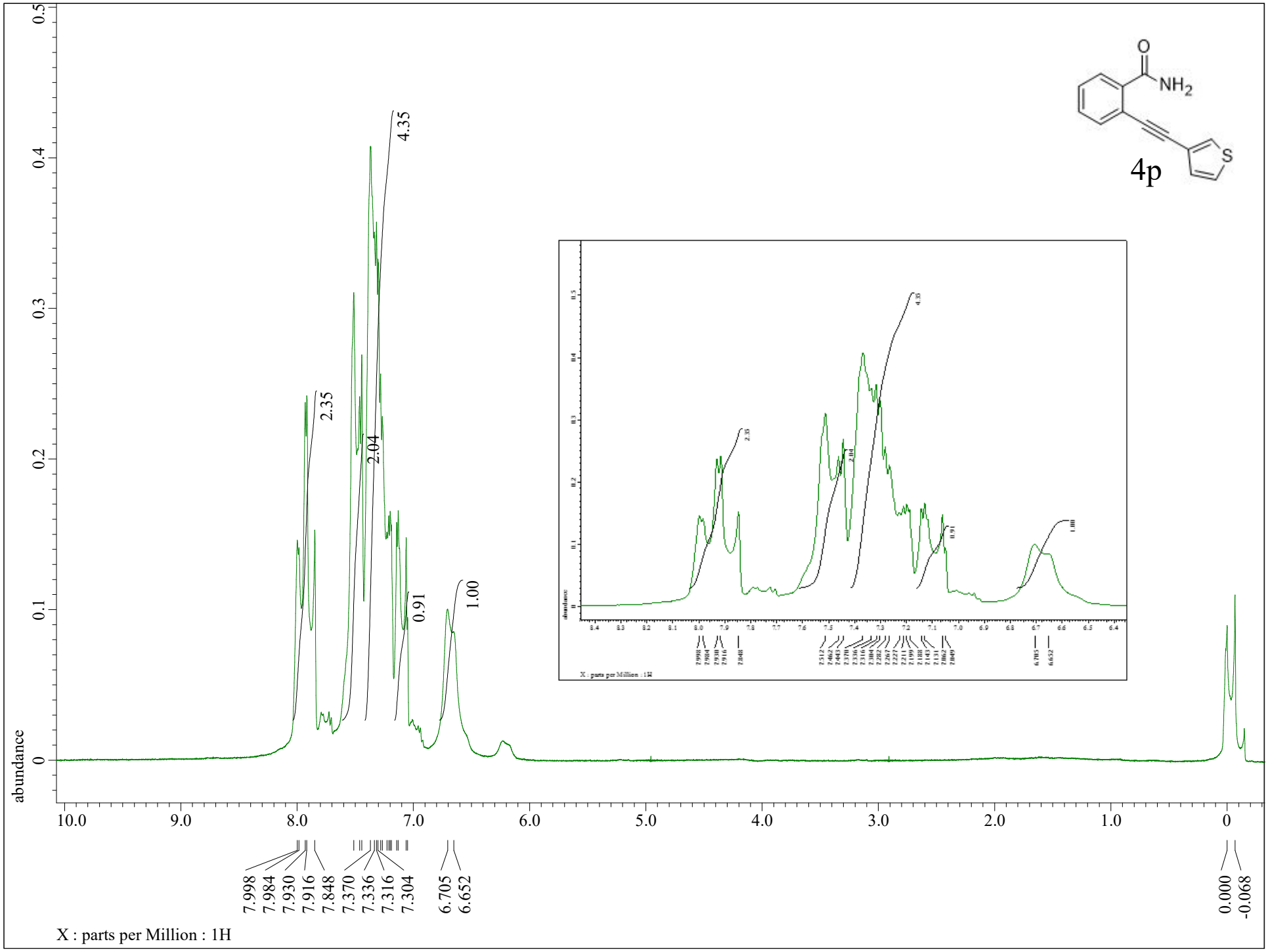
4o

abundance

1.00
2.05
0.92
0.87
0.91
0.99

8.084
8.078
8.076
8.070
8.065
8.060
7.582
7.476
7.471
7.463
7.454
7.260
6.306
3.522
-0.007

X : parts per Million : 1H


4p
abundance
X : parts per Million : 1H
2.35
2.04
4.35
0.91
1.00
7.998
7.984
7.930
7.916
7.848
7.370
7.336
7.316
7.304
6.705
6.652
0.000
-0.068

O
NH2
S
4p
abundance
0
0.1
0.2
0.3
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.522
139.900
134.570
133.302
131.881
130.842
129.993
129.621
129.421
128.611
125.836
90.882
87.059
77.315
77.000
76.676
0.914
0.847
X : parts per Million : 13C

4q
X : parts per Million : 1H
abundance

4q
abundance
X : parts per Million : 13C
167.531
150.922
149.501
132.129
132.034
131.414
129.116
128.620
128.430
115.148
112.907
94.763
88.003
77.324
77.210
77.000
76.685
56.176
56.129

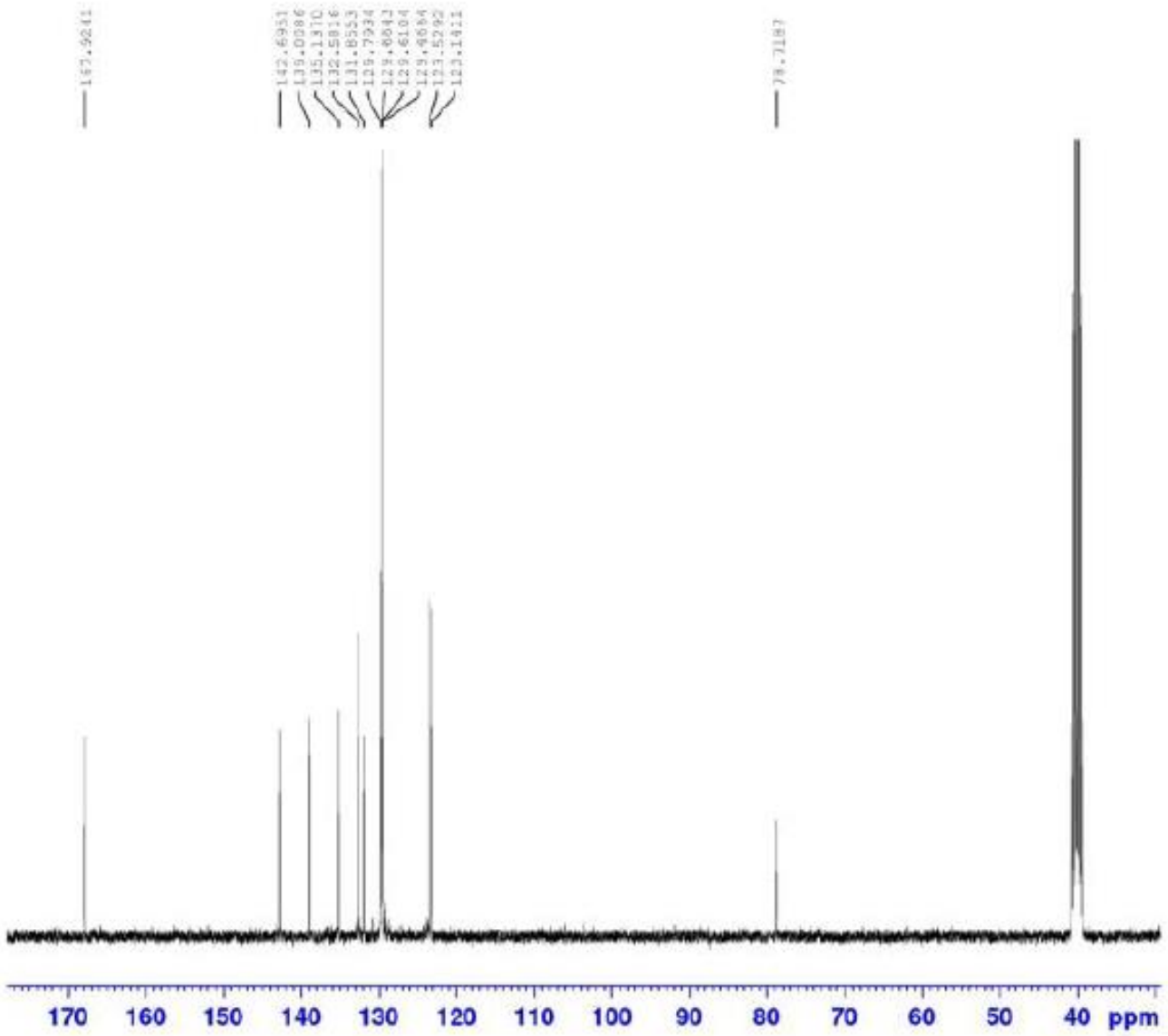
4r
abundance
X : parts per Million : 1H
1.00
0.81
1.88
5.94
3.22
8.025
8.019
8.013
8.002
7.519
7.510
7.501
7.432
7.425
7.420
7.408
7.394
7.387
7.378
3.069
3.057
-0.005

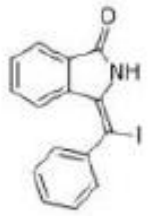
4s
abundance
X : parts per Million : 1H
1.00
1.01
3.14
4.00
4.96
1.05
9.225
8.137
8.133
8.123
8.115
7.688
7.669
7.509
7.505
7.490
7.485
7.482
7.370
7.359
7.350
7.340
0.100
0.017

4t
abundance
X : parts per Million : 1H
1.00
0.99
2.00
0.96
4.00
1.00
2.04
2.09
2.02
4.02
3.04
9.430
8.094
8.089
8.080
8.078
8.071
7.678
7.482
7.396
7.392
7.384
7.373
7.367
7.350
7.346
7.142
2.514
2.497
2.479
1.592
1.259
1.254
1.246
1.236
0.891
0.874
0.856
0.124
0.007

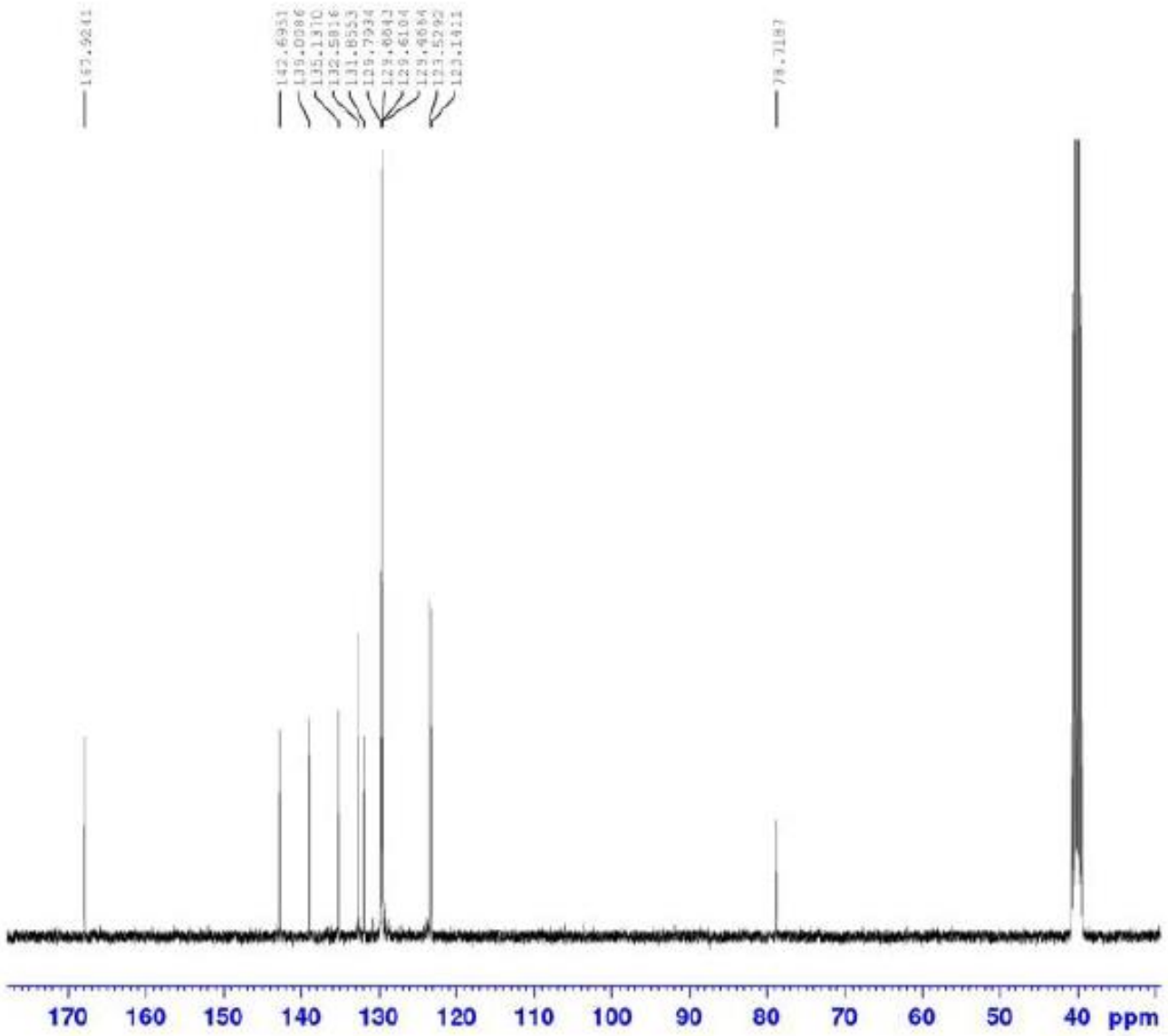
5a
abundance
X : parts per Million : 1H
9.084
9.065
7.943
7.920
7.757
7.605
7.450
7.433
7.422
7.362
7.344
7.323
7.260
7.249
7.230
7.212
1.192
0.073
1.00
1.05
1.10
1.10
2.20
2.17
0.90
9.08

5a
abundance
X : parts per Million : 13C
165.290
148.109
144.314
137.993
133.874
133.187
130.241
129.907
129.297
128.639
128.344
124.806
124.063
84.551
84.017
77.324
77.000
76.685
27.363

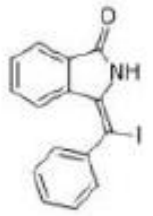

167.9241
142.6951
139.0086
135.1370
132.5816
131.8553
129.7934
129.8043
129.6104
123.5292
123.1411
78.7187
(CD3)2SO
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


O
NH
I

5b

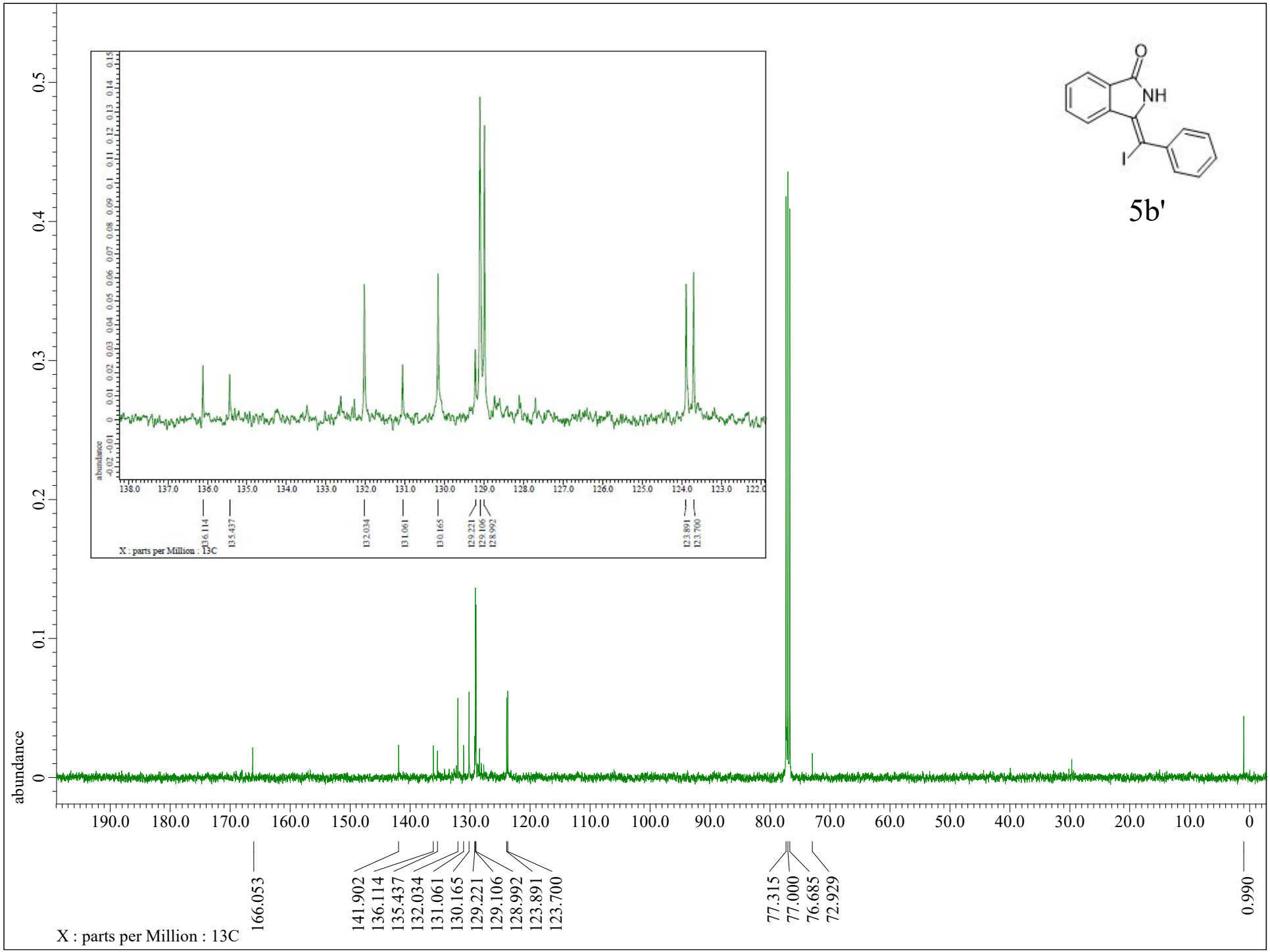

167.9241
142.6951
139.0086
135.1370
132.5816
131.8553
129.7934
129.8043
129.6104
123.5292
123.1411
78.7187
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

(CD3)2SO


O
NH
I

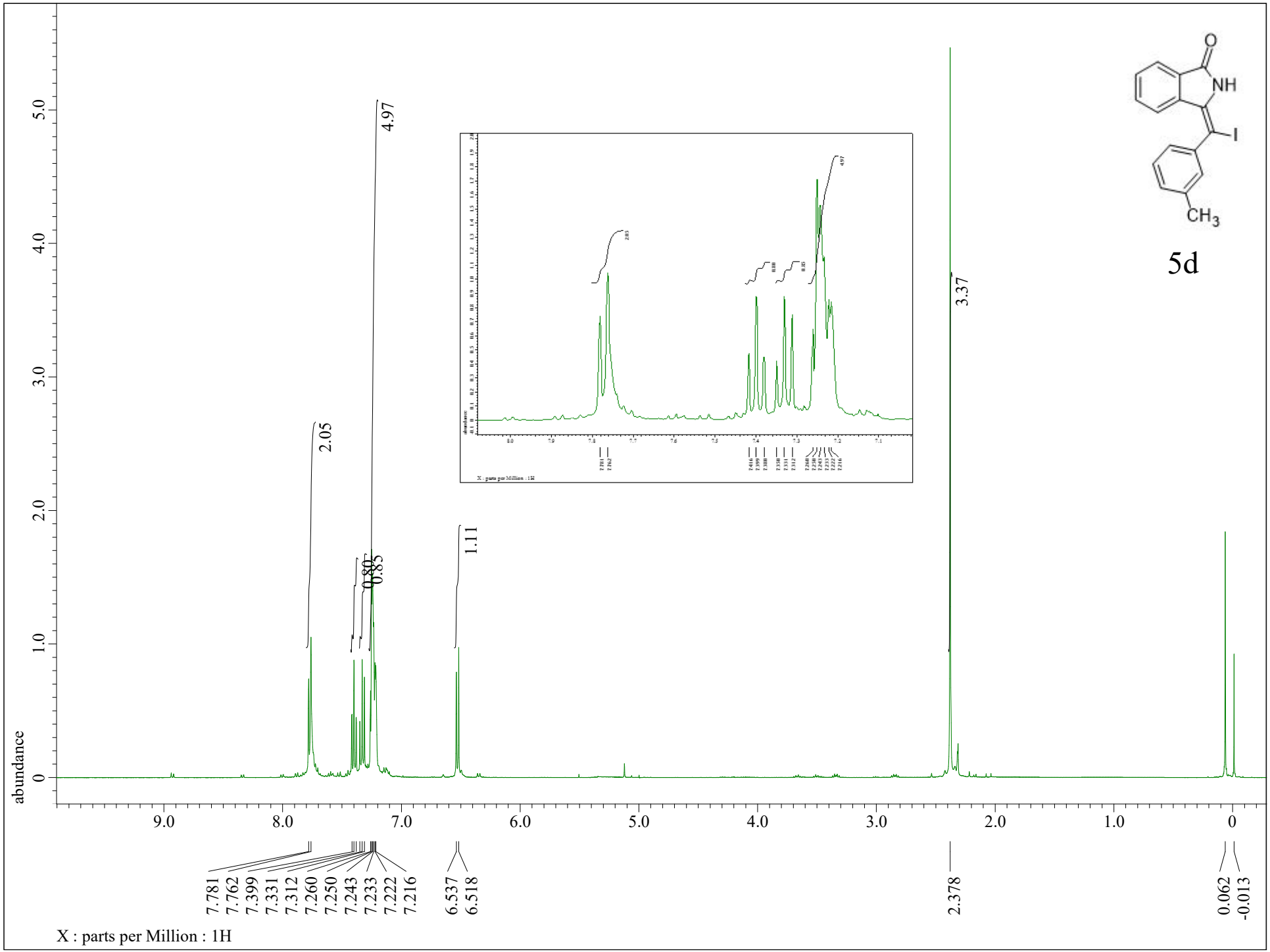
5b

O
NH
I
5b'
abundance
X : parts per Million : 1H
1.00
1.07
0.87
0.55
1.12
0.87
4.10
8.957
8.937
7.906
7.887
7.766
7.760
7.744
7.615
7.613
7.595
7.442
7.427
7.423
7.352
7.264
0.072
-0.000


O
NH
I
5b'
abundance
X : parts per Million : 13C
166.053
141.902
136.114
135.437
132.034
131.061
130.165
129.221
129.106
128.992
123.891
123.700
77.315
77.000
76.685
72.929
0.990

O
NH
I
H3C
5c
4.31
1.99
1.01
0.99
0.99
3.00
abundance
X : parts per Million : 1H
7.794
7.775
7.737
7.433
7.414
7.395
7.345
7.326
7.280
7.269
7.263
7.250
6.605
6.584
2.448
-0.000

O
NH
I
H3C
5c
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.254
139.461
138.031
137.411
134.532
132.167
131.748
129.812
129.393
129.221
123.729
123.233
79.431
77.315
77.000
76.676
21.461
X : parts per Million : 13C


5d
abundance
X : parts per Million : 1H
2.05
4.97
0.80
0.85
1.11
3.37
7.781
7.762
7.399
7.331
7.312
7.260
7.250
7.243
7.233
7.222
7.216
6.537
6.518
2.378
0.062
-0.013

O
NH
I
CH3
5d
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
167.283
140.796
138.956
137.459
134.513
132.196
131.728
130.098
130.003
129.221
128.963
126.456
123.719
123.252
79.136
77.315
77.000
76.676
21.347
X : parts per Million : 13C

5e
abundance
X : parts per Million : 1H
4.23
2.01
1.06
1.01
0.85
3.00
7.791
7.771
7.708
7.434
7.415
7.395
7.384
7.363
7.291
7.271
7.260
7.252
6.981
6.960
6.628
6.609
3.890
0.069
-0.003

O
NH
I
H3CO

5e

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
167.235
160.180
137.459
134.570
133.216
132.205
131.767
131.013
129.221
123.767
123.195
114.480
79.489
77.324
77.000
76.685
55.414
X : parts per Million : 13C

5f

abundance

1.01
1.17
0.98
0.96
1.14
2.70
1.16
6.00

9.397
8.359
8.355
8.338
7.996
7.975
7.740
7.510
7.492
7.418
7.395
7.265
6.765
6.744
3.042
0.084
0.008

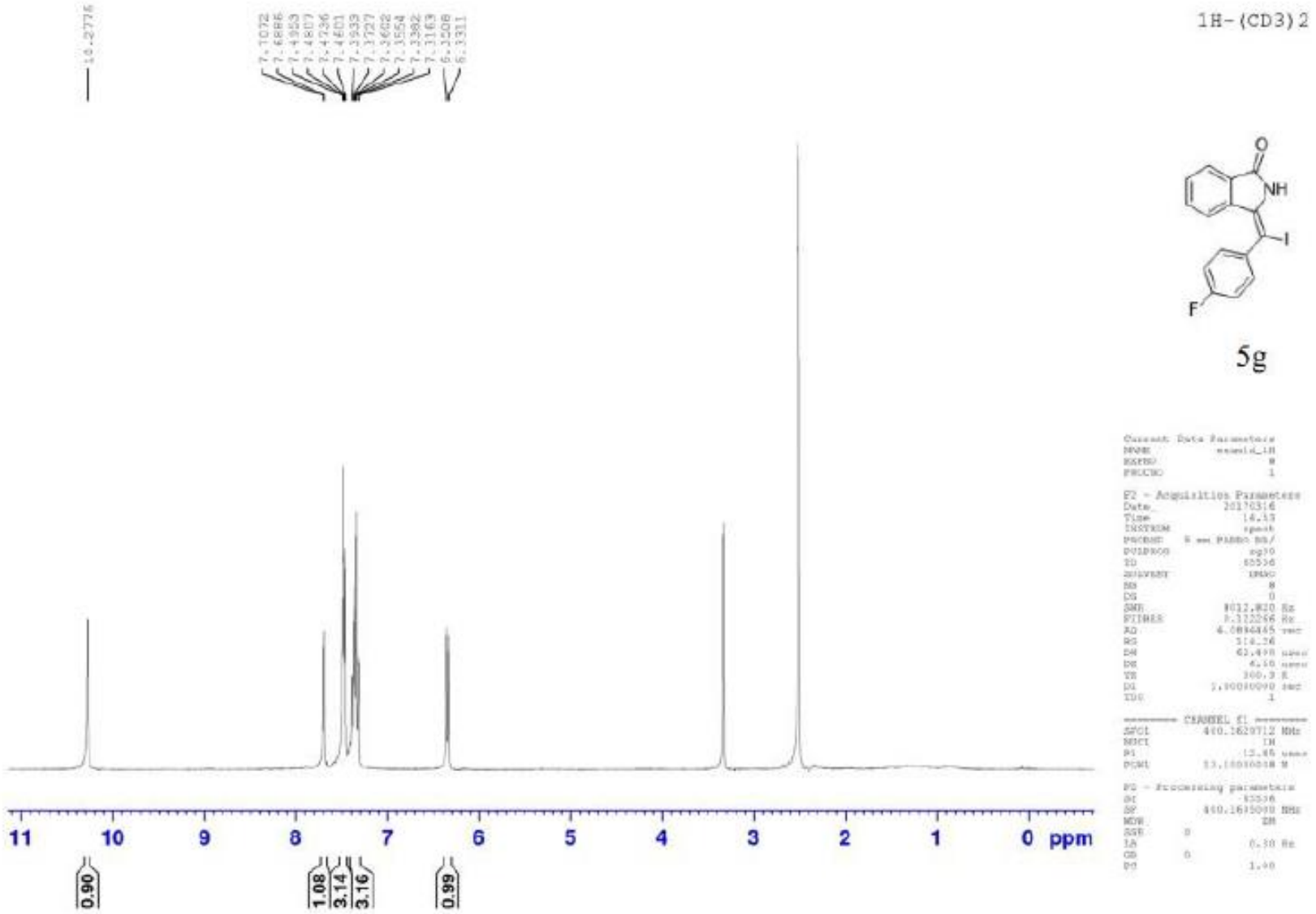
X : parts per Million : 1H

5f

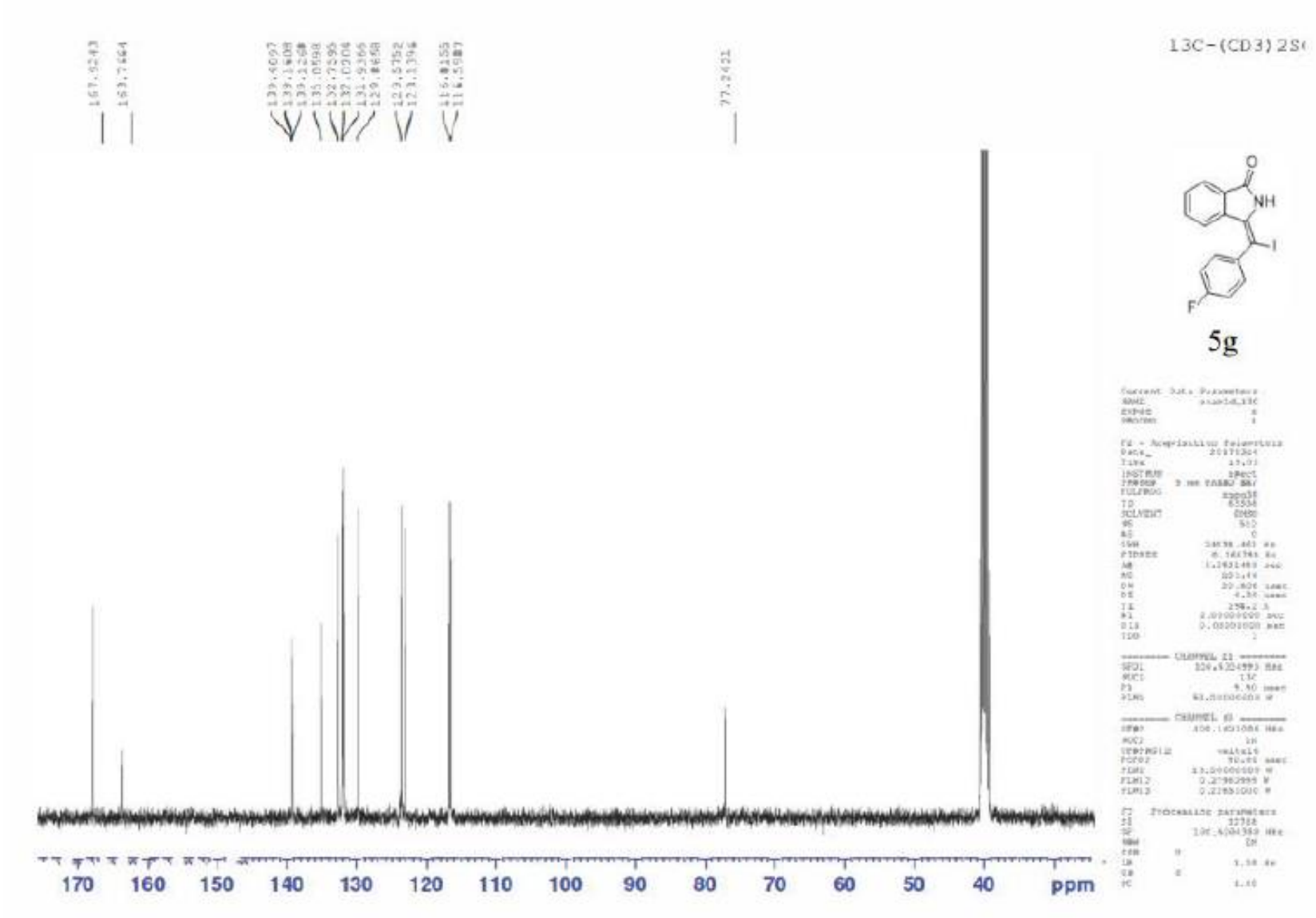
abundance

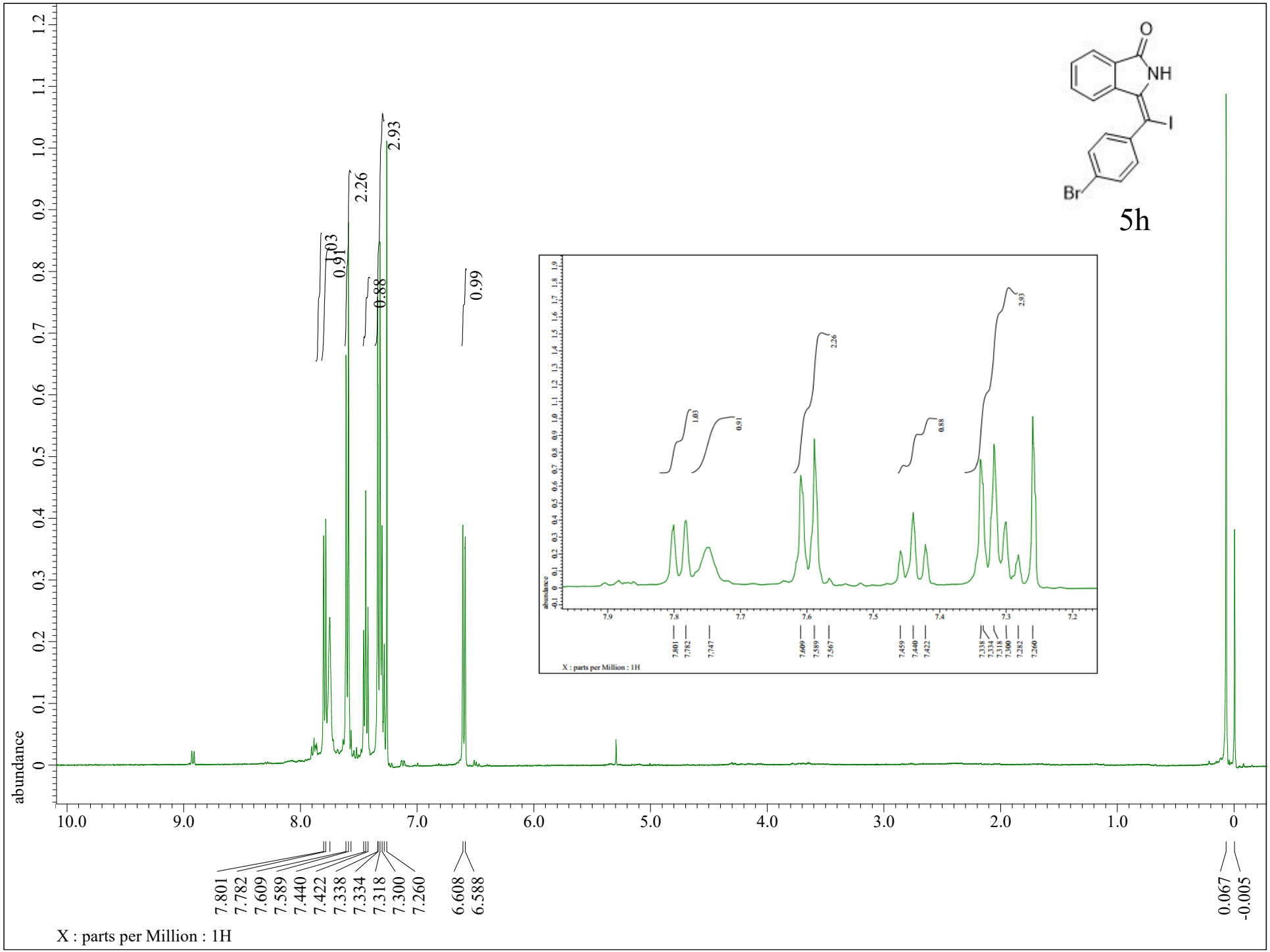
X : parts per Million : 13C

162.516
150.912
143.170
139.118
133.712
131.585
130.289
127.619
126.942
125.331
124.558
111.229
77.315
77.000
76.685
75.236
40.149

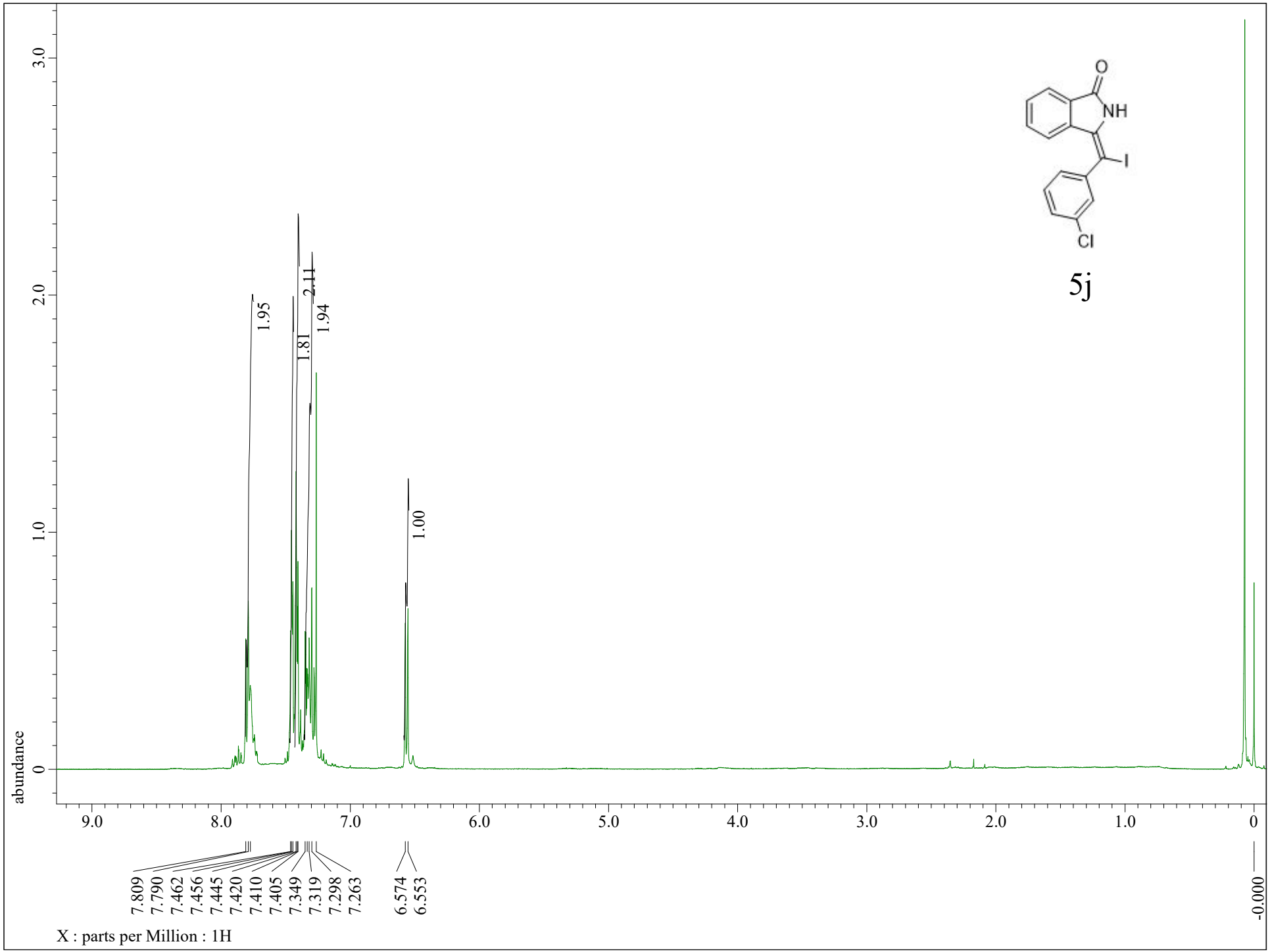

1H-(CD3)2
10.2776
7.7072
7.6886
7.4953
7.4807
7.4236
7.4601
7.3939
7.3727
7.3662
7.3554
7.3382
7.3163
6.3508
6.3331
NH
O
I
F
11
10
9
8
7
6
5
4
3
2
1
0 ppm
0.90
1.08
3.14
3.16
0.99

5g

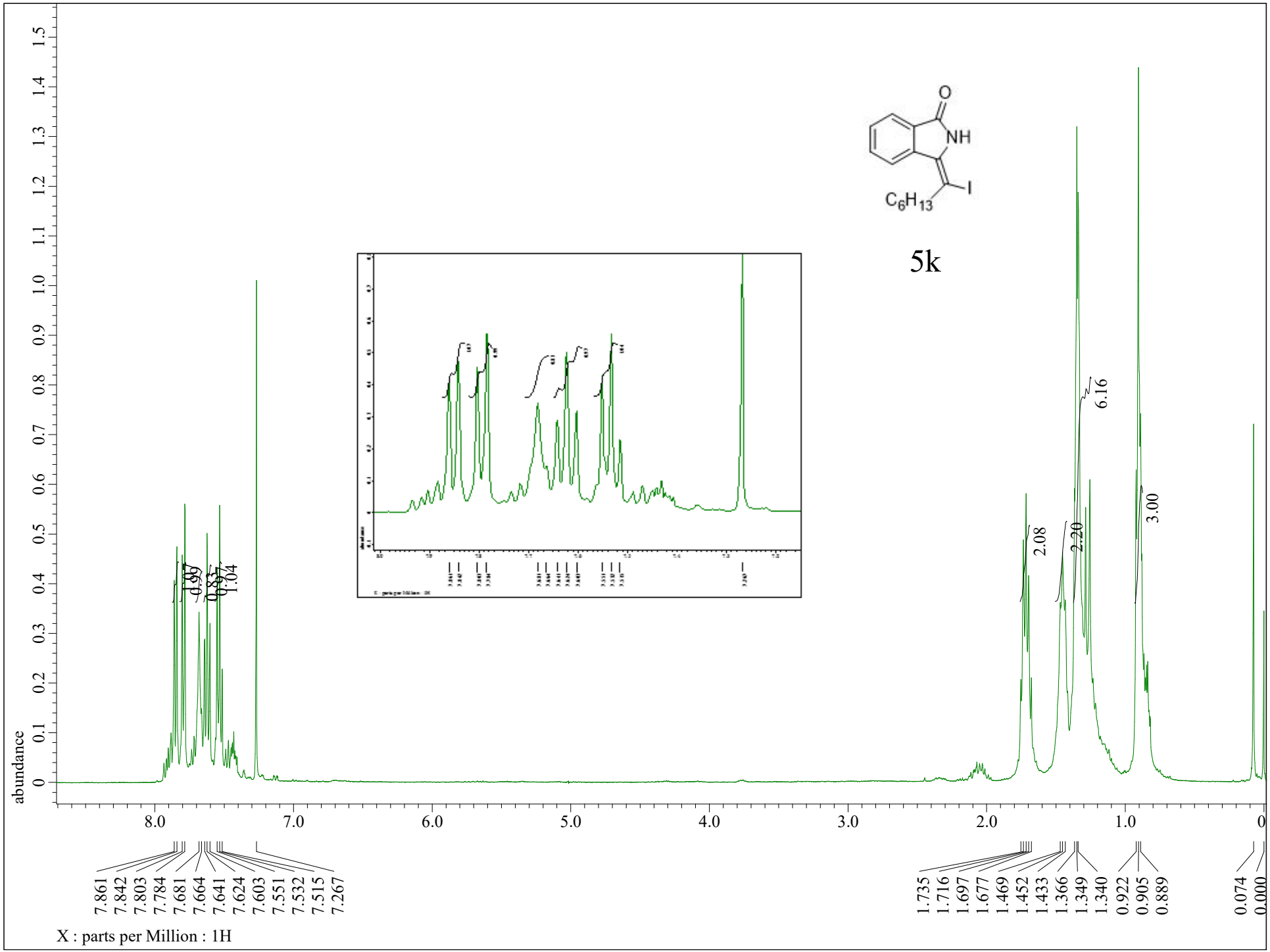

13C-(CD3)2S(
167.9243
163.7464
139.4697
139.1408
139.1268
135.0598
132.7596
132.0204
131.9365
129.8658
123.5752
123.1396
116.8155
116.5587
77.2421
O
NH
I
F
5g
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


O
NH
I
Br
5h
1.03
0.91
2.26
0.88
2.93
0.99
abundance
X : parts per Million : 1H
7.801
7.782
7.609
7.589
7.440
7.422
7.338
7.334
7.318
7.300
7.260
6.608
6.588
0.067
-0.005

O
NH
I
Br
5h
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.188
139.909
138.079
134.284
132.425
131.786
131.290
130.718
129.583
123.967
123.557
123.100
86.897
77.324
77.000
76.685
1.000
X : parts per Million : 13C


O
NH
I
Cl
5j
1.95
1.81
2.11
1.94
1.00
abundance
3.0
2.0
1.0
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.809
7.790
7.462
7.456
7.445
7.420
7.410
7.405
7.349
7.319
7.298
7.263
6.574
6.553
-0.000
X : parts per Million : 1H

O
NH
I
Cl
5j
abundance
0
0.1
0.2
0.3
0.4
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
167.235
142.569
138.336
134.770
134.236
132.415
131.757
130.413
129.707
129.583
129.469
127.819
123.948
123.109
77.315
77.000
76.685
75.789
X : parts per Million : 13C


O
NH
I
C_6H_{13}
5k
abundance
X : parts per Million : 1H
7.861
7.842
7.803
7.784
7.681
7.664
7.641
7.624
7.603
7.551
7.532
7.515
7.267
1.735
1.716
1.697
1.677
1.469
1.452
1.433
1.366
1.349
1.340
0.922
0.905
0.889
0.074
0.000
2.08
2.20
6.16
3.00

O
NH
I
C6H13
5k
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
166.844
135.981
134.045
132.587
132.215
129.068
124.292
123.023
89.910
77.315
77.000
76.685
40.168
31.596
29.518
28.374
22.519
14.024
X : parts per Million : 13C

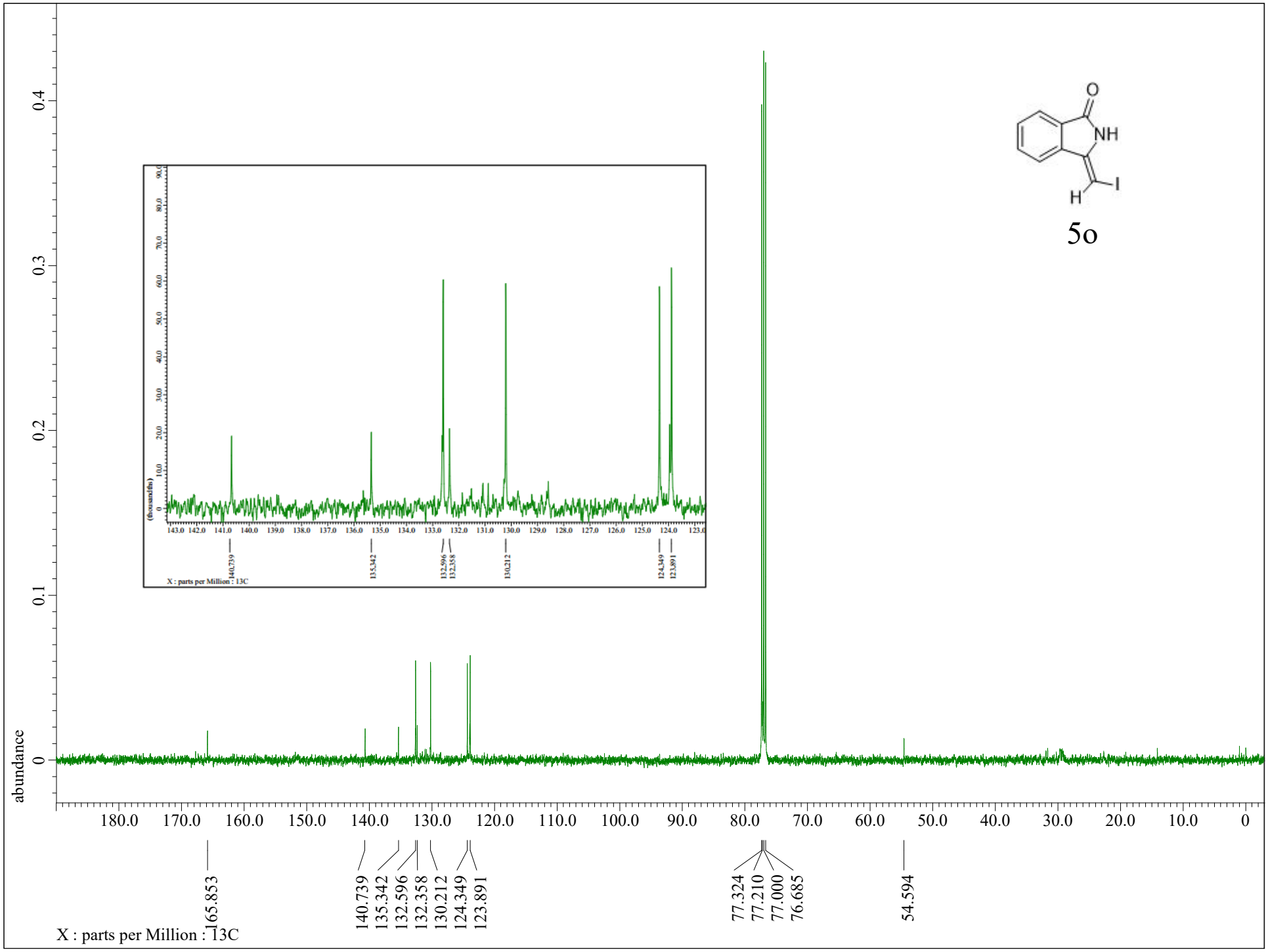
O
NH
I
51
3.04
1.04
1.07
1.00
2.05
2.10
4.03
1.92
abundance
X : parts per Million : 1H
7.849
7.832
7.829
7.818
7.798
7.624
7.621
7.546
7.527
7.260
2.762
2.743
2.735
2.727
1.903
1.888
1.742
1.722
1.718
1.543
1.519
1.506
1.482
0.065
-0.013

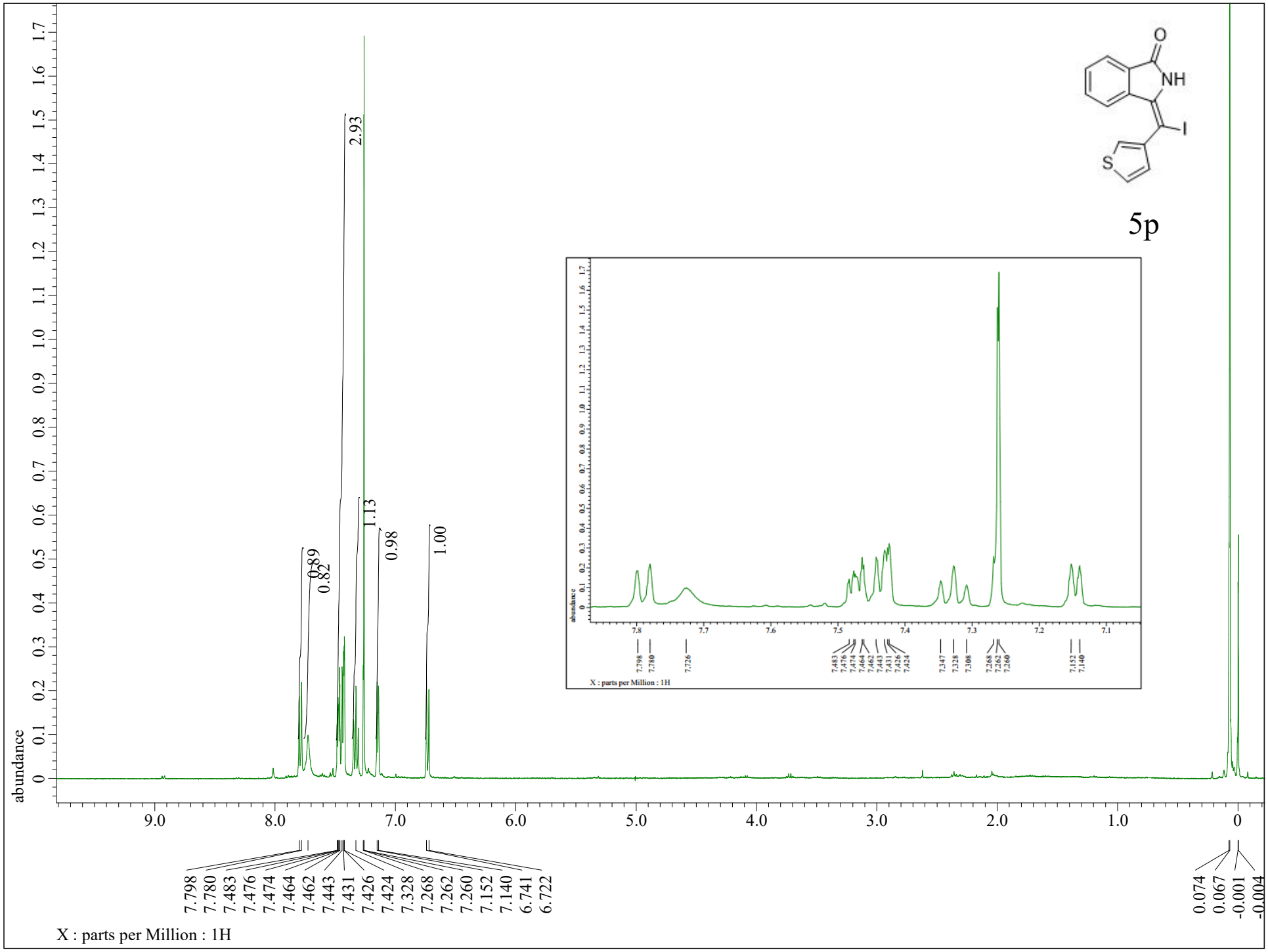
O
NH
I
51
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
166.873
134.732
134.141
132.510
132.348
129.126
124.311
123.033
102.114
77.315
77.000
76.685
42.790
34.533
25.828
25.427
X : parts per Million : 13C

O
NH
I
5m
abundance
X : parts per Million : 1H
10.821
8.355
8.352
8.334
7.932
7.911
7.724
7.514
7.493
7.476
7.260
5.968
5.958
5.955
5.949
2.348
2.327
2.268
2.262
2.252
2.247
1.863
1.857
1.848
1.842
1.770
1.756
-0.003
1.00
1.03
1.07
1.00
0.98
0.99
2.03
1.99
2.04
2.00

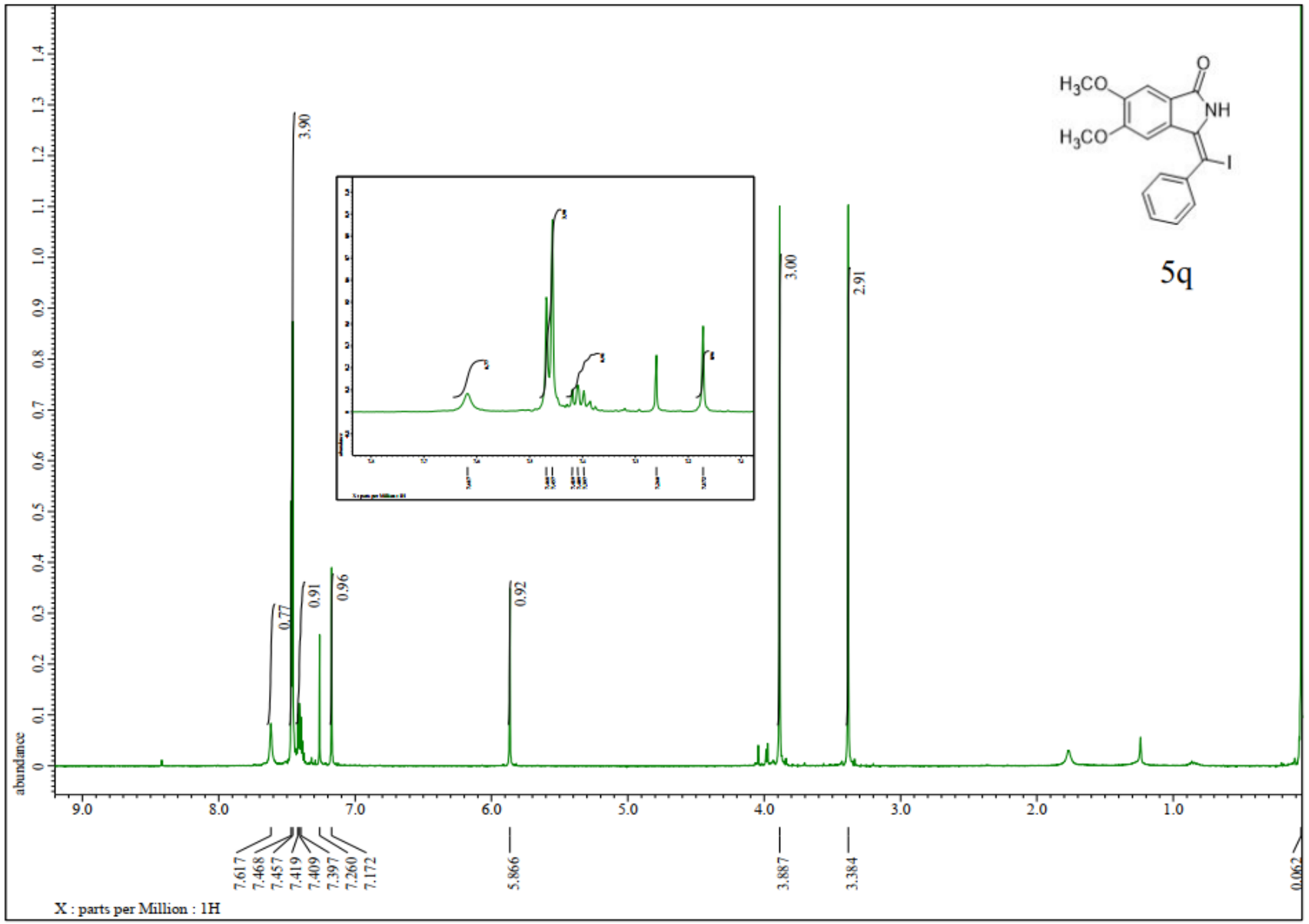
O
NH
I
5m
abundance
0
0.1
0.2
0.3
0.4
0.5
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
163.450
145.344
138.965
136.629
133.664
132.501
131.223
127.428
126.971
124.606
77.315
77.000
76.676
74.597
27.659
25.094
22.462
21.595
0.990
X : parts per Million : 13C

O
NH
I
H
5o
abundance
X : parts per Million : 1H
8.804
8.784
7.842
7.824
7.686
7.667
7.647
7.604
7.584
7.566
7.260
6.221
-0.008
1.00
0.92
1.13
1.06
1.12
0.65


O
NH
I
H
5o
abundance
0
0.1
0.2
0.3
0.4
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
165.853
140.739
135.342
132.596
132.358
130.212
124.349
123.891
77.324
77.210
77.000
76.685
54.594
X : parts per Million : 13C


5p
abundance
X : parts per Million : 1H
2.93
1.13
0.98
1.00
0.89
0.82
7.798
7.780
7.483
7.476
7.474
7.464
7.462
7.443
7.431
7.426
7.424
7.328
7.268
7.262
7.260
7.152
7.140
6.741
6.722
0.074
0.067
-0.001
-0.004

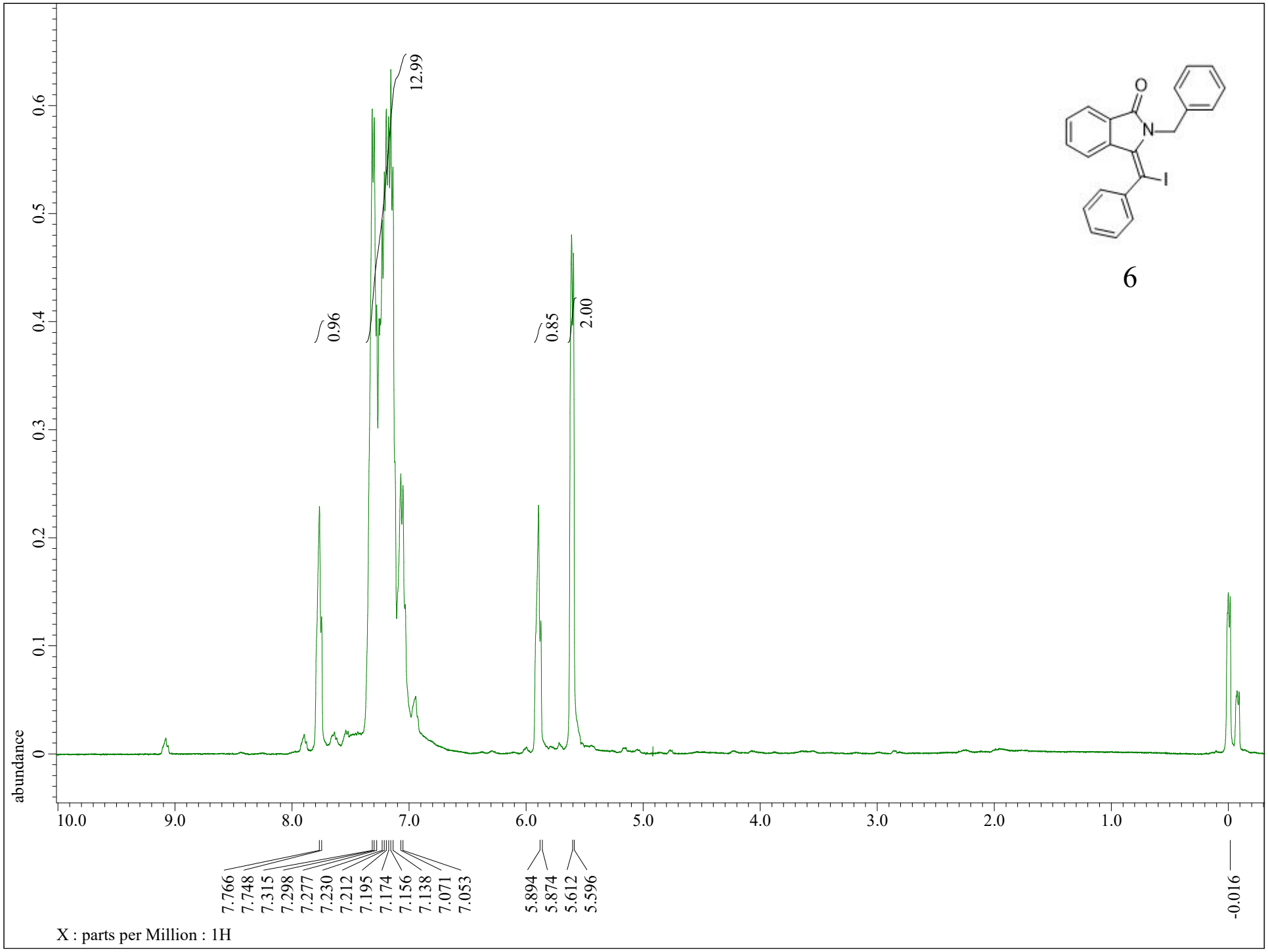
O
NH
I
S
5p
(thousandths)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.054
140.710
138.489
134.627
132.396
131.452
129.488
128.363
126.818
125.846
123.834
122.995
77.315
77.200
77.000
76.676
72.109
1.000
X : parts per Million : 13C


5q
abundance
X : parts per Million : 1H
3.90
0.77
0.91
0.96
0.92
3.00
2.91
7.617
7.468
7.457
7.419
7.409
7.397
7.260
7.172
5.866
3.887
3.384
0.062

H3CO
H3CO
O
NH
I
5q
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.579
152.342
150.502
141.120
137.840
129.745
129.135
129.049
128.525
124.692
105.280
104.774
77.324
77.210
77.000
76.685
76.075
56.176
55.433
0.971
X : parts per Million : 13C

NMe
O
Ph
I
5r
abundance
X : parts per Million : 1H
1.00
1.10
1.16
2.99
1.94
1.67
3.01
8.762
8.741
7.566
7.558
7.555
7.549
7.534
7.477
7.474
7.333
7.314
7.294
7.209
7.186
3.077
0.000

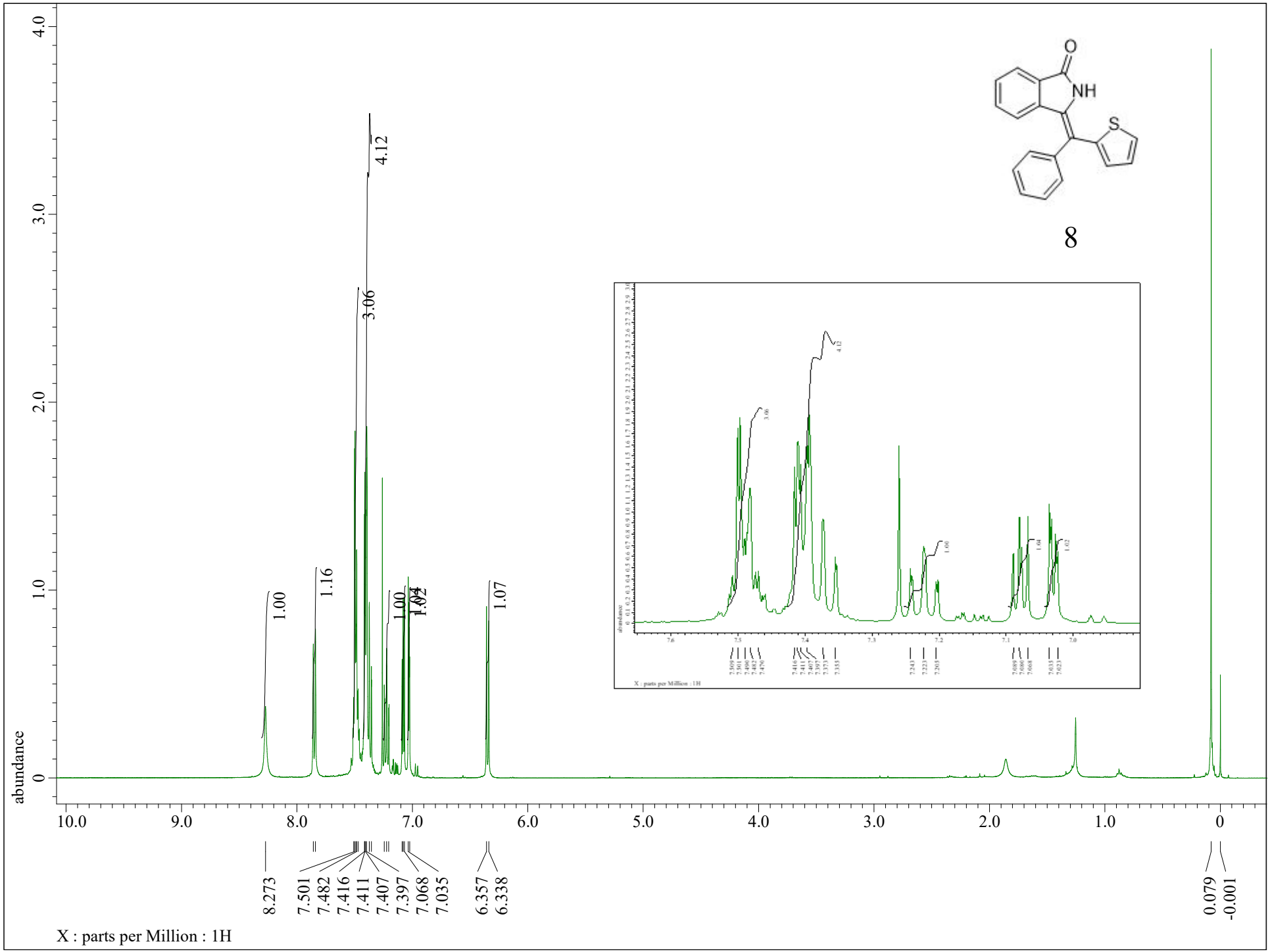
NMe
O
Ph
I
5r
abundance
X : parts per Million : 13C
154.745
147.165
140.558
135.914
131.662
131.175
130.518
130.108
128.229
127.905
124.940
122.938
77.315
77.000
76.685
73.425
34.905


abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
0.96
12.99
0.85
2.00
7.766
7.748
7.315
7.298
7.277
7.230
7.212
7.195
7.174
7.156
7.138
7.071
7.053
5.894
5.874
5.612
5.596
-0.016
X : parts per Million : 1H
O
N
I
6

O
N
I
6
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
169.590
145.077
139.413
137.678
137.440
132.148
129.316
129.154
129.049
128.935
128.420
128.134
126.923
126.427
123.872
122.985
87.154
77.324
77.200
77.000
76.743
76.685
44.592
X : parts per Million : 13C

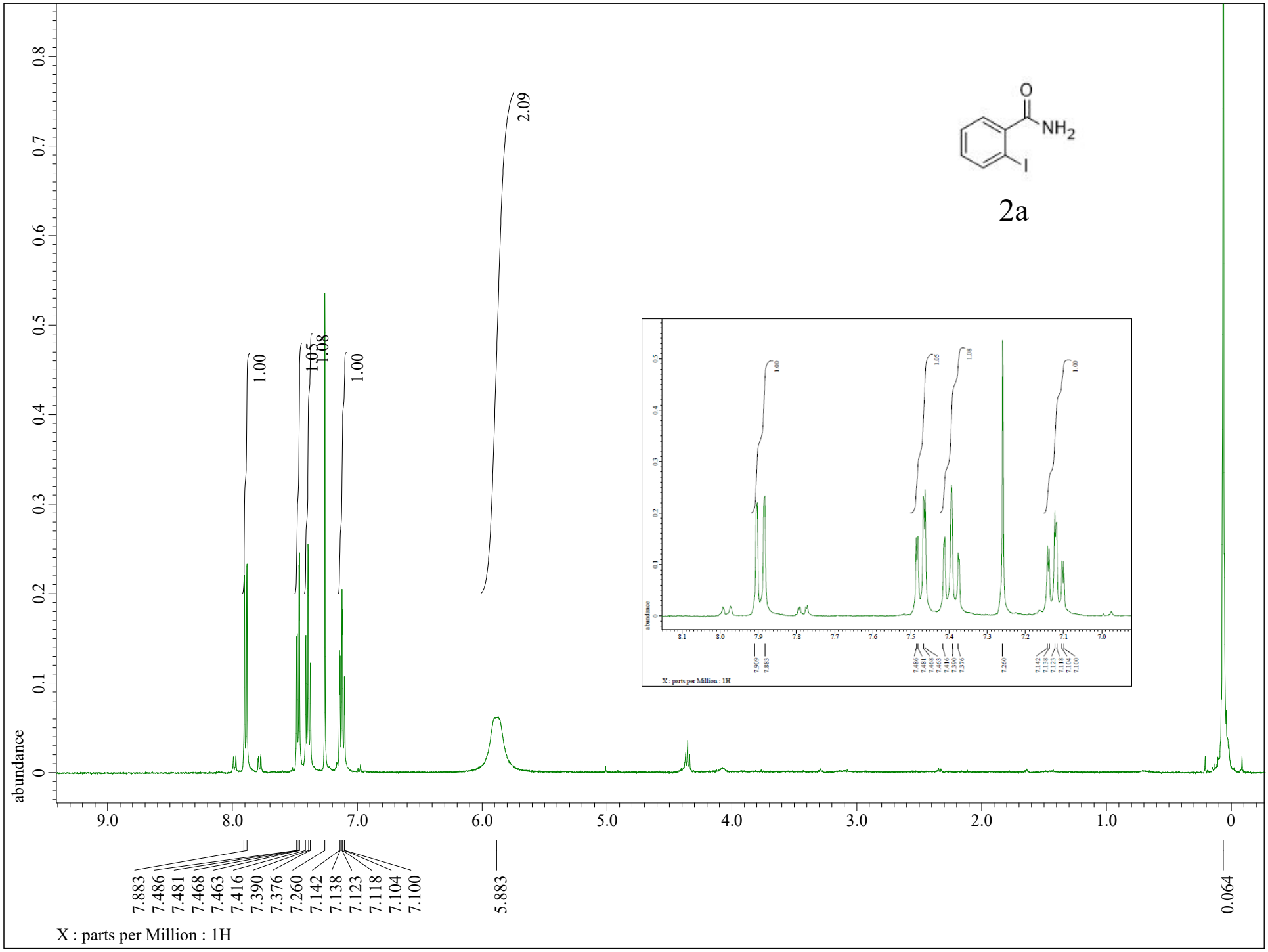
O
NH
O
7
abundance
5.0
4.0
3.0
2.0
1.0
0
0.89
0.92
2.02
4.99
1.00
0.69
3.04
3.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.741
7.564
7.502
7.487
7.481
7.474
7.470
7.260
6.903
6.881
6.860
3.826
0.083
0.003
X : parts per Million : 1H

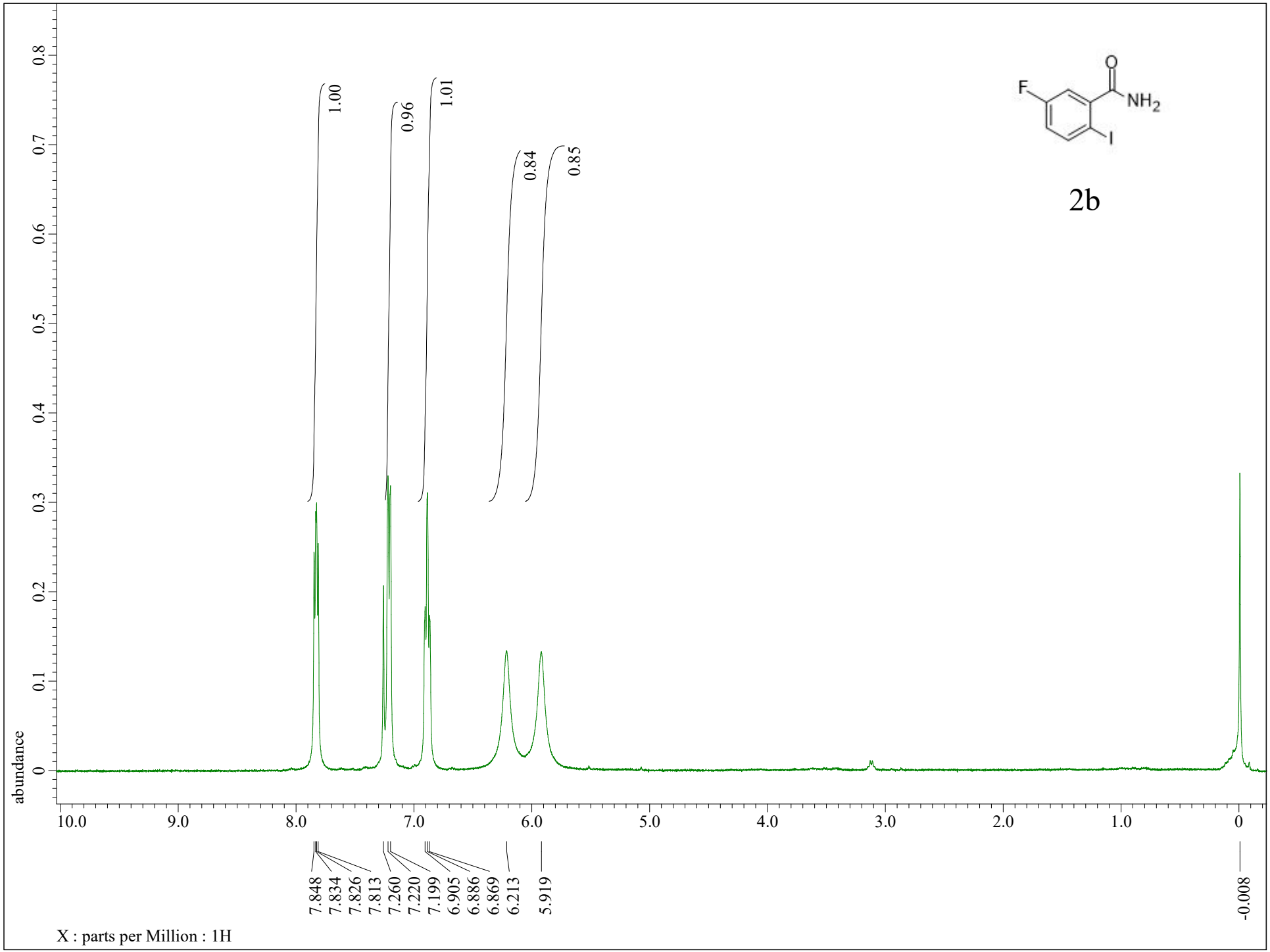
O
NH
O
7
abundance
-0.01
0.01
0.03
0.05
0.07
0.09
0.11
0.13
0.15
0.17
0.19
0.21
0.23
0.25
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
167.273
160.075
138.088
133.225
131.852
130.699
129.745
129.259
128.963
128.639
123.615
114.633
114.128
105.499
99.778
86.525
77.324
77.067
77.000
76.743
76.685
55.309
X : parts per Million : 13C

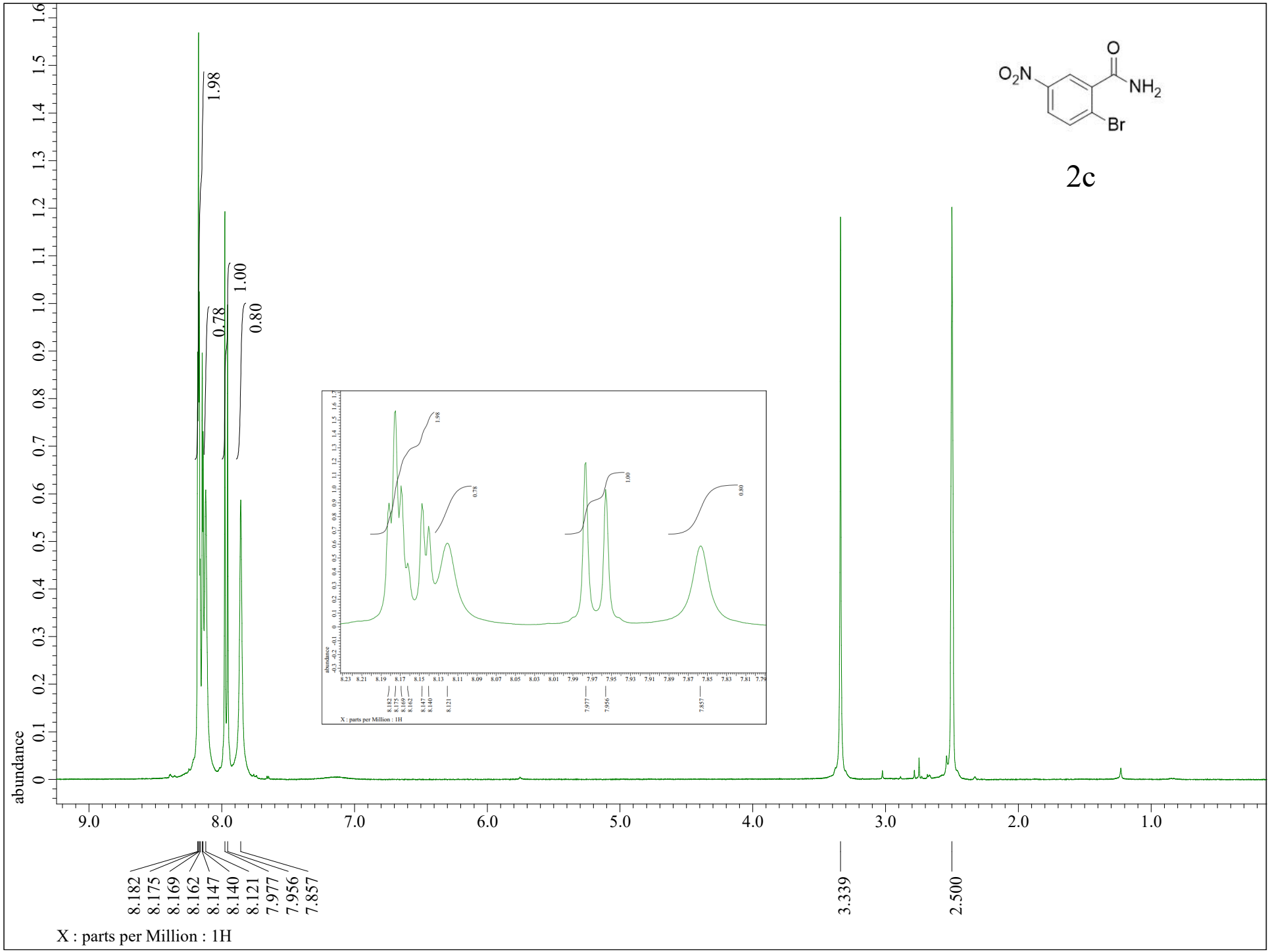

O
NH
S
8
abundance
X : parts per Million : 1H
1.00
1.16
3.06
4.12
1.00
1.02
1.04
1.07
8.273
7.501
7.482
7.416
7.411
7.407
7.397
7.068
7.035
6.357
6.338
0.079
-0.001

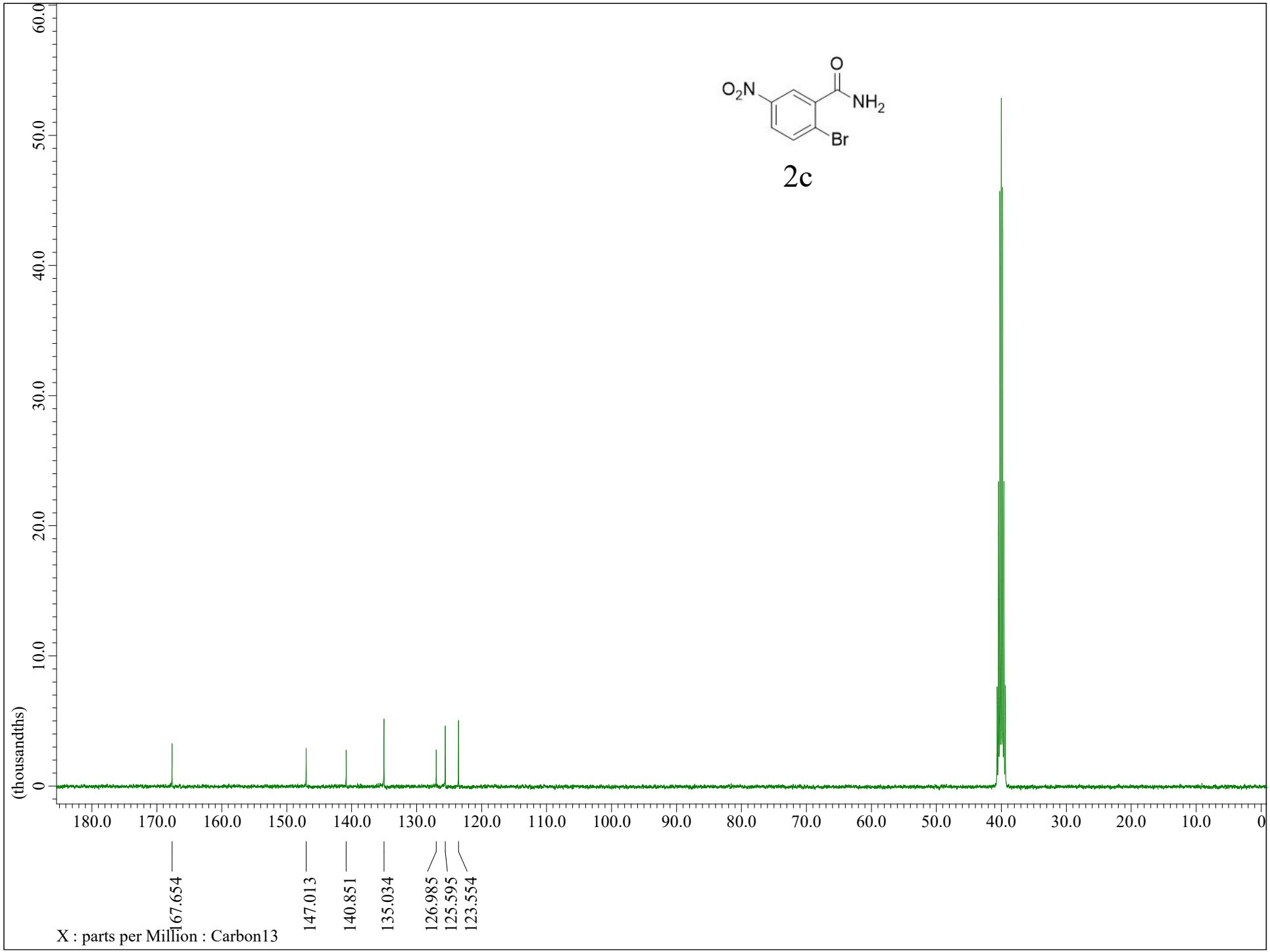
O
NH
S
8
abundance
0.6
0.5
0.4
0.3
0.2
0.1
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
167.988
142.893
138.841
136.839
131.900
131.738
130.403
130.184
129.068
128.801
128.677
128.325
127.724
127.266
123.710
123.433
117.360
77.324
77.210
77.000
76.685
0.981
X : parts per Million : 13C

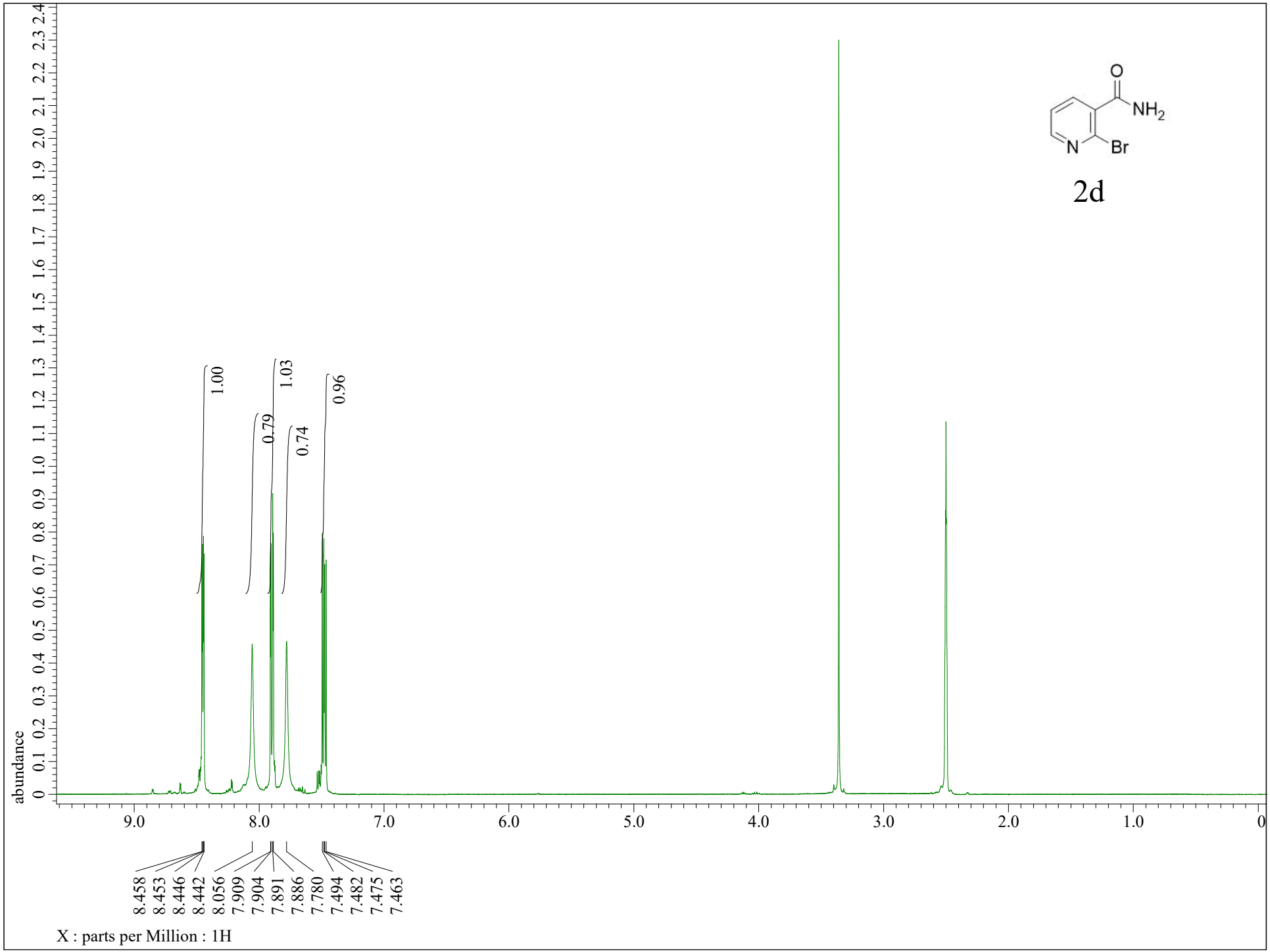
APPENDIX B. CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA


2a
abundance
X : parts per Million : 1H
1.00
1.05
1.08
1.00
2.09
7.883
7.486
7.481
7.468
7.463
7.416
7.390
7.376
7.260
7.142
7.138
7.123
7.118
7.104
7.100
5.883
0.064

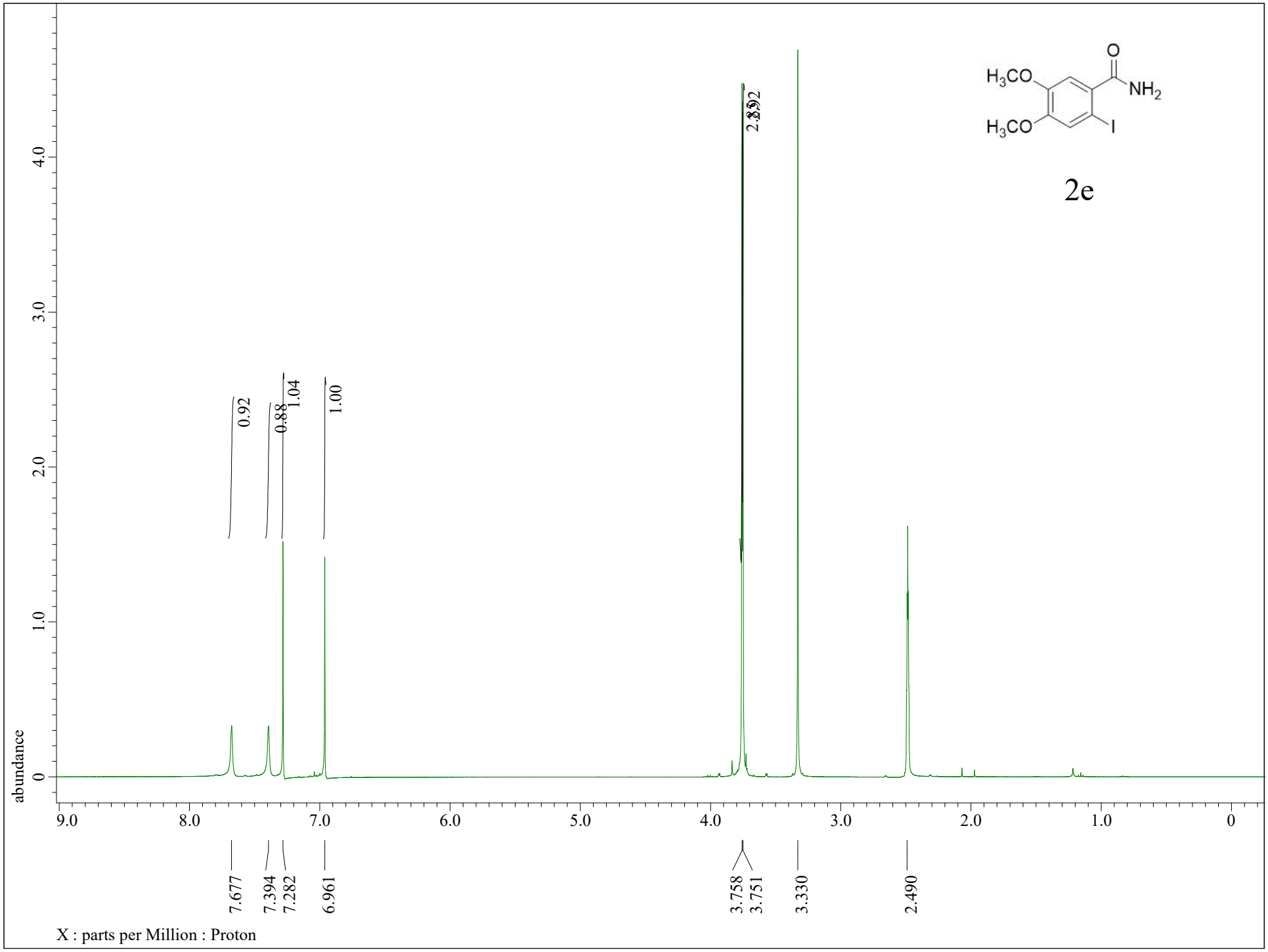

1.00
0.96
1.01
0.84
0.85
F
O
NH2
I
2b
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.848
7.834
7.826
7.813
7.260
7.220
7.199
6.905
6.886
6.869
6.213
5.919
-0.008
X : parts per Million : 1H

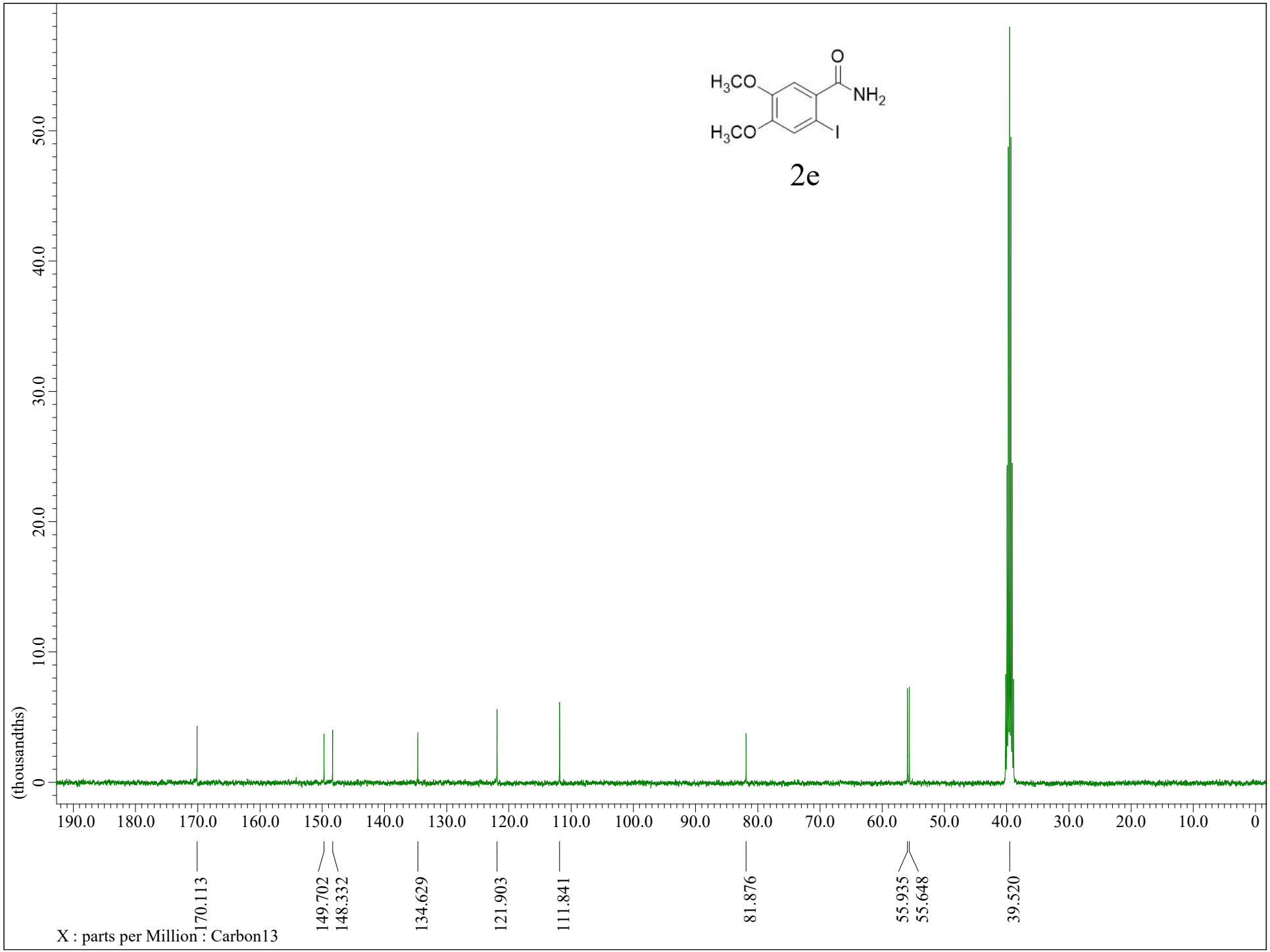

O2N
O
NH2
Br
2c
1.98
0.78
1.00
0.80
abundance
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.182
8.175
8.169
8.162
8.147
8.140
8.121
7.977
7.956
7.857
3.339
2.500
X : parts per Million : 1H

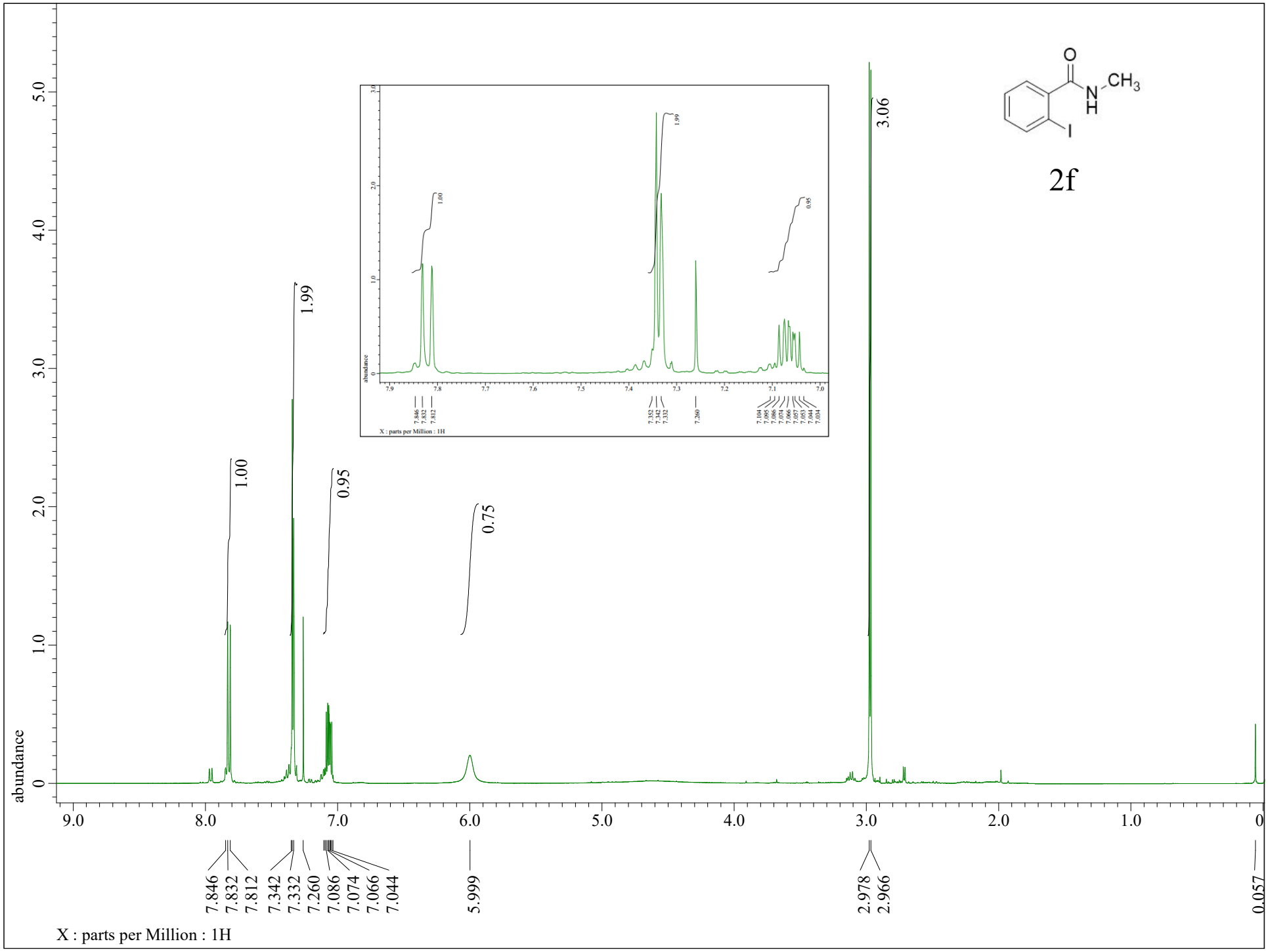

O
O2N
NH2
Br
2c
(thousandths)
60.0
50.0
40.0
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.654
147.013
140.851
135.034
126.985
125.595
123.554
X : parts per Million : Carbon13


O
NH2
N
Br
2d
abundance
1.00
0.79
1.03
0.74
0.96
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.458
8.453
8.446
8.442
8.056
7.909
7.904
7.891
7.886
7.780
7.494
7.482
7.475
7.463
X : parts per Million : 1H

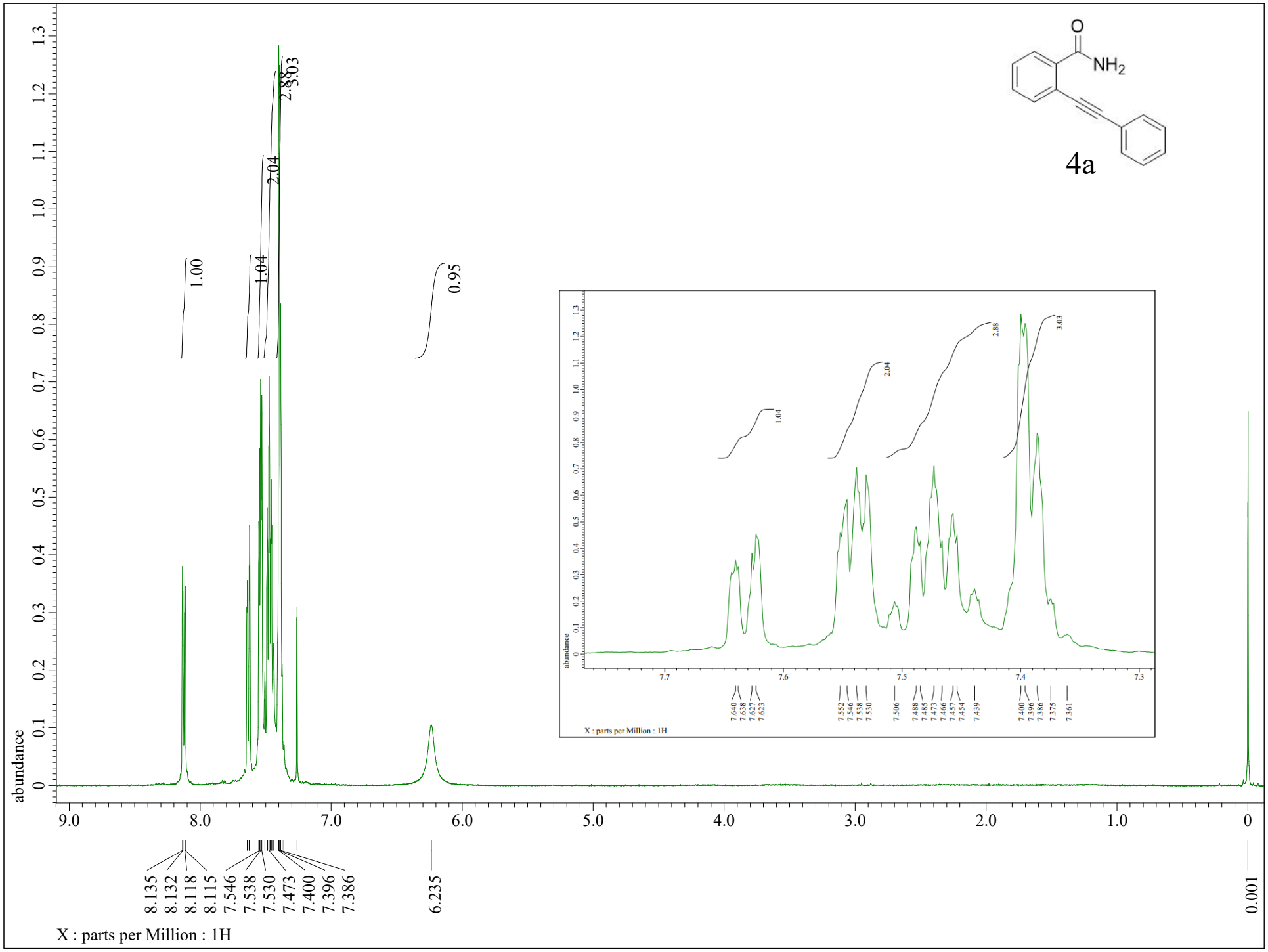
O
NH2
N
Br
2d
(thousandths)
25.0
23.0
21.0
19.0
17.0
15.0
13.0
11.0
9.0
7.0
5.0
3.0
1.0
-1.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.424
150.539
146.792
138.341
133.904
123.545
40.223
40.012
39.811
39.600
39.600
39.600
X : parts per Million : Carbon13


2e
abundance
X : parts per Million : Proton
0.92
0.88
1.04
1.00
7.677
7.394
7.282
6.961
3.758
3.751
3.330
2.490

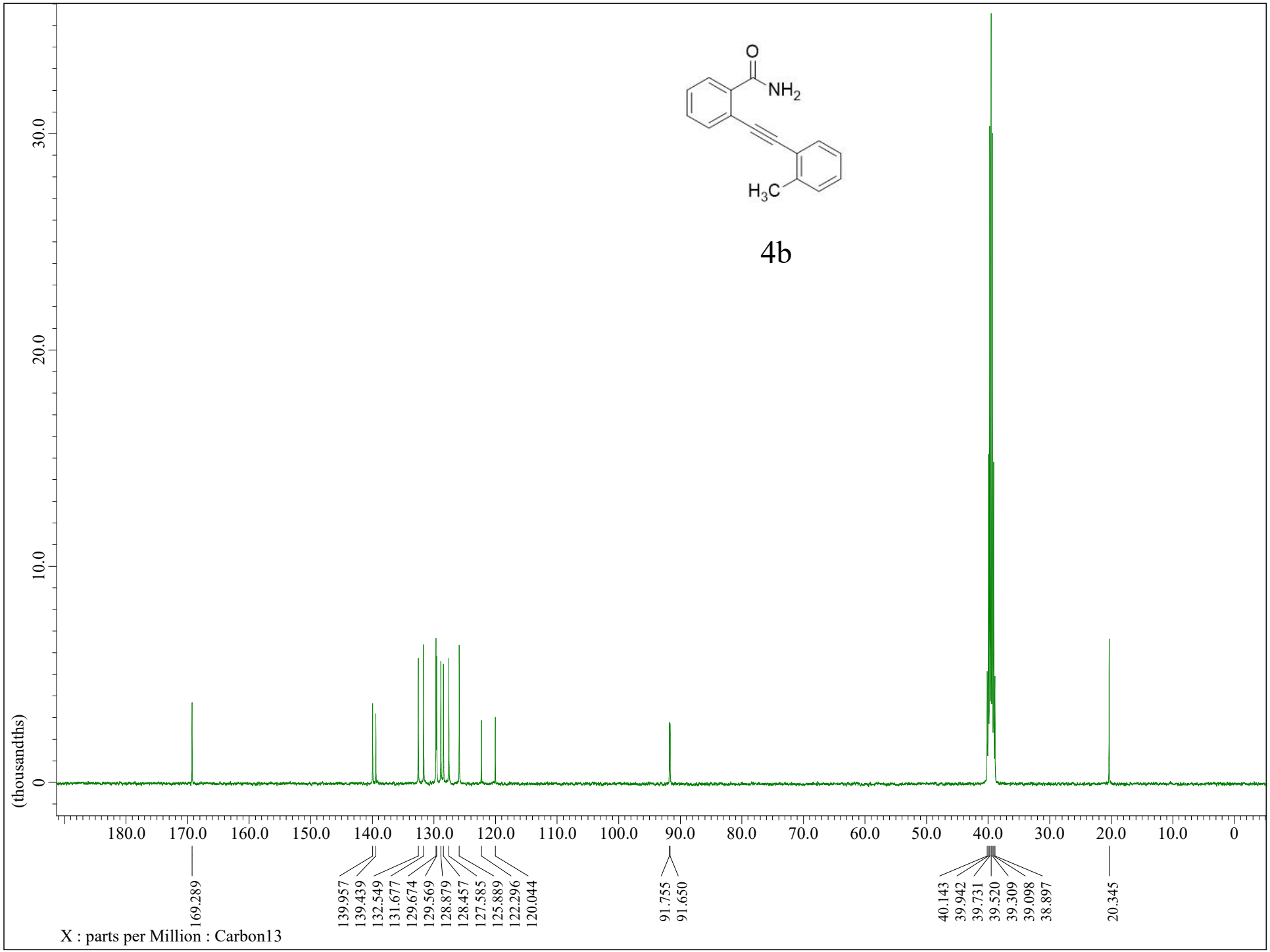

O
H3CO
NH2
H3CO
I
2e
(thousandths)
50.0
40.0
30.0
20.0
10.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
170.113
149.702
148.332
134.629
121.903
111.841
81.876
55.935
55.648
39.520
X : parts per Million : Carbon13


2f
abundance
X : parts per Million : 1H
1.00
1.99
0.95
0.75
3.06
7.846
7.832
7.812
7.342
7.332
7.260
7.086
7.074
7.066
7.044
5.999
2.978
2.966
0.057

2g


O
NH2
4a
1.00
1.04
2.04
2.88
3.03
0.95
abundance
X : parts per Million : 1H
8.135
8.132
8.118
8.115
7.546
7.538
7.530
7.473
7.400
7.396
7.386
6.235
0.001
7.640
7.638
7.627
7.623
7.552
7.546
7.538
7.530
7.506
7.488
7.485
7.473
7.466
7.457
7.454
7.439
7.400
7.396
7.386
7.375
7.361

O
NH2
H3C
4b
3.07
1.93
2.08
0.98
0.96
1.04
3.00
abundance
0
0.1
0.2
0.3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.822
7.587
7.583
7.565
7.521
7.504
7.499
7.454
7.448
7.443
7.435
7.430
7.425
7.411
7.407
7.284
7.274
3.330
2.466
2.438
X : parts per Million : Proton

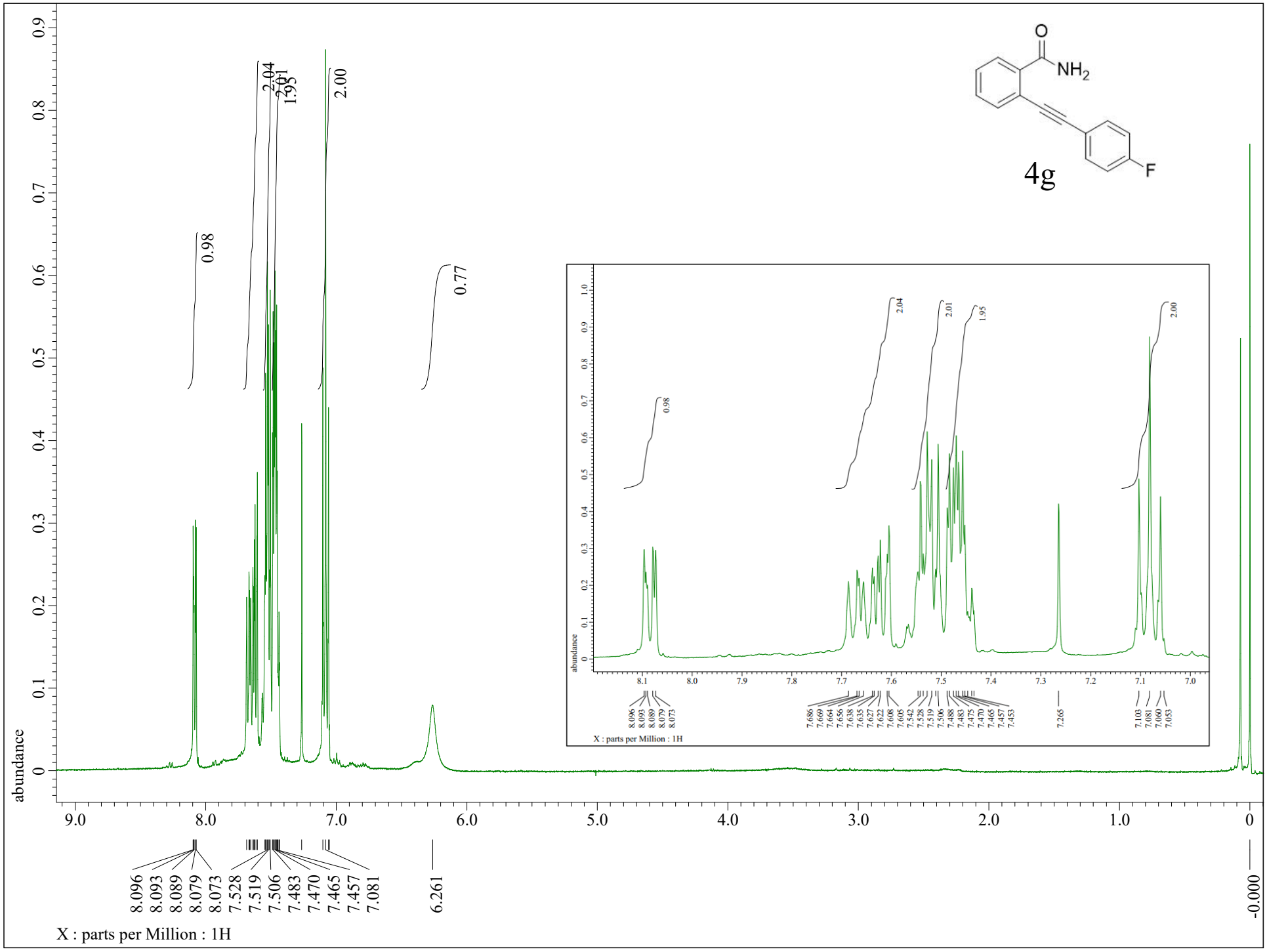

O
NH2
H3C
4b
(thousandths)
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
169.289
139.957
139.439
132.549
131.677
129.674
129.569
128.879
128.457
127.585
125.889
122.296
120.044
91.755
91.650
40.143
39.942
39.731
39.520
39.309
39.098
38.897
20.345
X : parts per Million : Carbon13

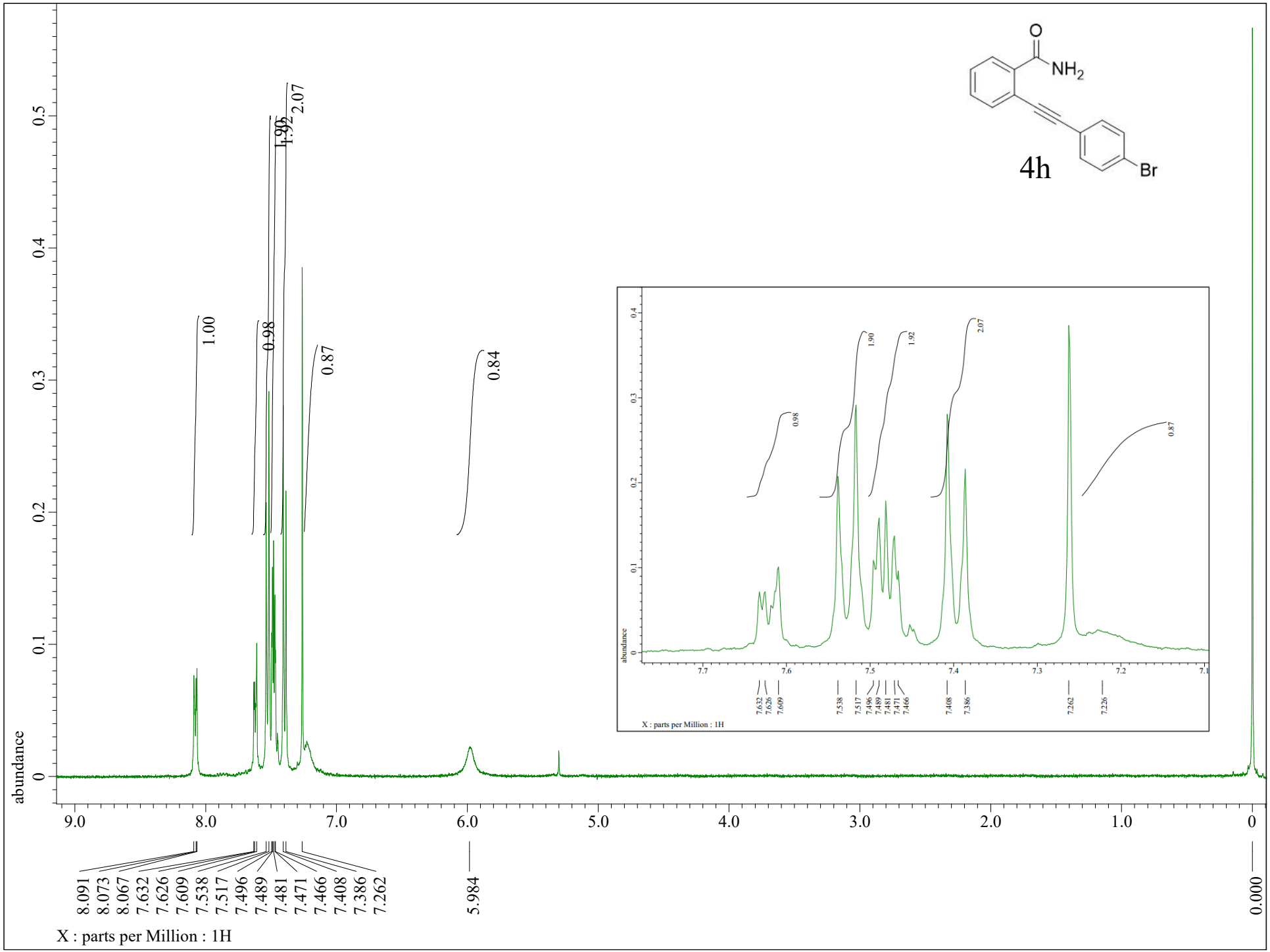
3.0
2.0
1.0
0
abundance
1.00
0.99
2.81
1.96
0.86
0.81
0.81
3.02
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.142
8.124
7.613
7.483
7.470
7.451
7.360
7.337
7.277
6.204
2.373
0.003
X : parts per Million : 1H
O
NH2
CH3
4c

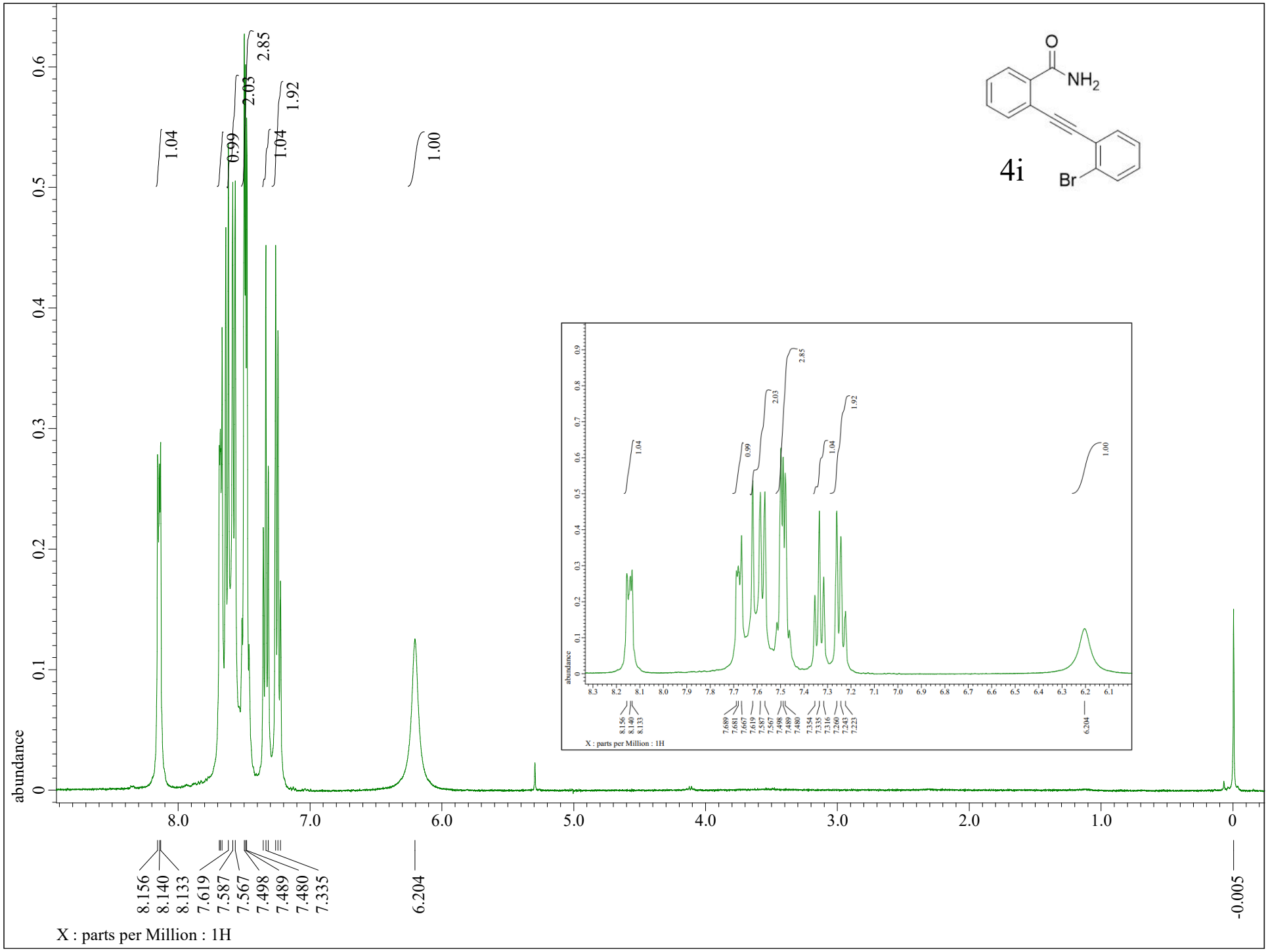
4d
O
NH2
CH3
abundance
X : parts per Million : 1H
8.134
8.131
8.116
8.111
7.471
7.458
7.454
7.435
7.416
7.199
7.179
6.284
2.385
-0.004
1.00
1.07
4.86
1.99
0.79
2.97

4e
abundance
X : parts per Million : 1H
1.00
1.90
4.09
0.89
2.05
3.06
8.081
8.062
8.058
7.580
7.577
7.559
7.455
7.449
7.433
7.426
7.403
7.384
7.380
6.874
6.852
3.792
-0.014

4f
NH2
N(CH3)2
abundance
X : parts per Million : 1H
1.00
0.75
1.02
4.08
2.19
0.88
6.07
8.170
8.150
7.757
7.598
7.580
7.451
7.433
7.419
7.408
7.402
7.399
7.395
7.386
7.260
6.677
6.656
6.084
3.011
0.072
0.000

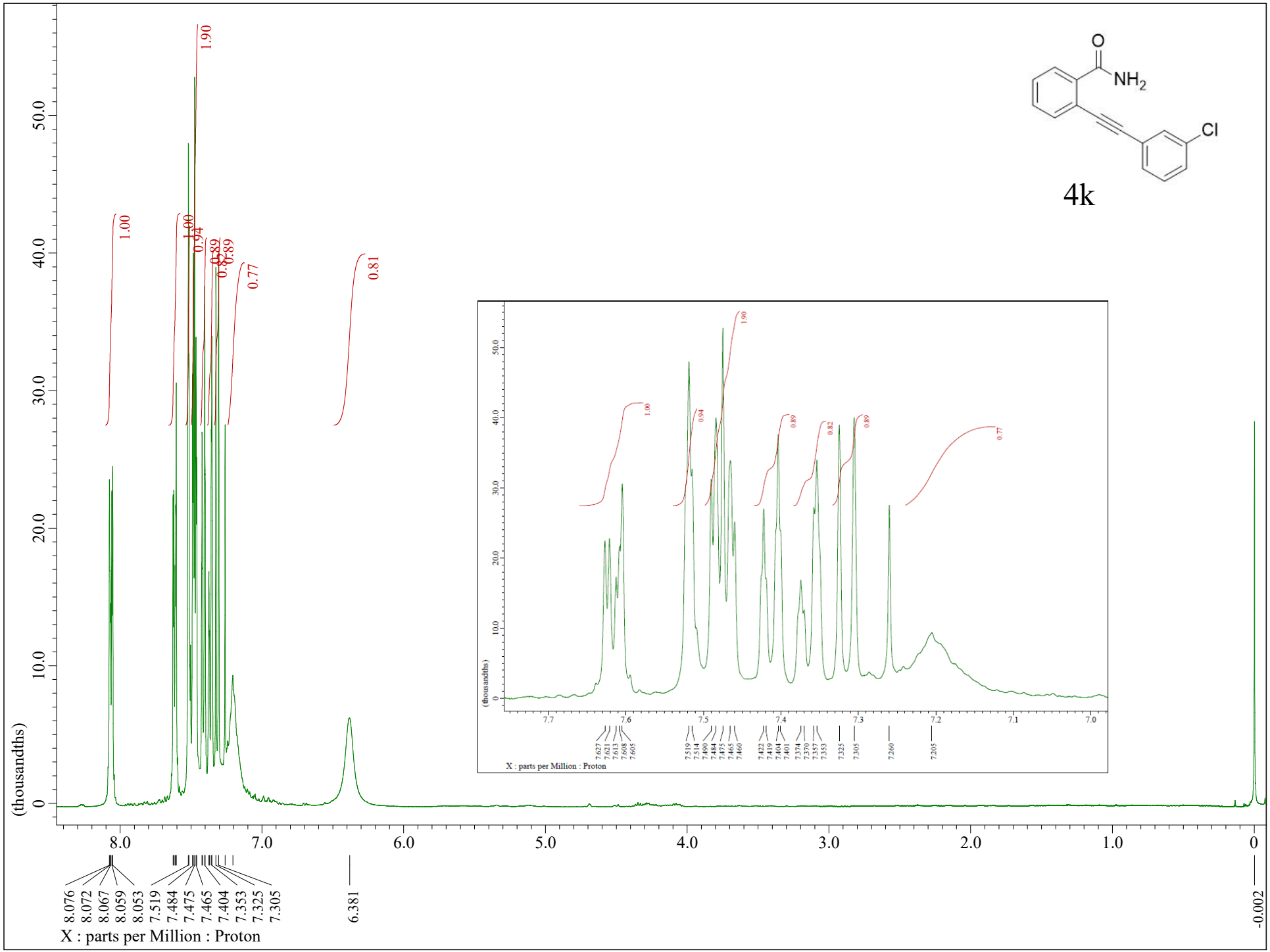

O
NH2
F
4g
abundance
X : parts per Million : 1H
0.98
2.04
2.01
1.95
2.00
0.77
8.096
8.093
8.089
8.079
8.073
7.528
7.519
7.506
7.483
7.470
7.465
7.457
7.081
6.261
7.686
7.669
7.664
7.656
7.638
7.635
7.627
7.622
7.608
7.605
7.542
7.528
7.519
7.506
7.488
7.483
7.475
7.470
7.465
7.457
7.453
7.265
7.103
7.081
7.060
7.053


O
NH2
Br
4h
1.00
0.98
1.90
1.92
2.07
0.87
0.84
abundance
X : parts per Million : 1H
8.091
8.073
8.067
7.632
7.626
7.609
7.538
7.517
7.496
7.489
7.481
7.471
7.466
7.408
7.386
7.262
5.984
0.000


4i
NH2
O
Br
abundance
X : parts per Million : 1H
1.04
0.99
2.03
2.85
1.92
1.04
1.00
8.156
8.140
8.133
7.619
7.587
7.567
7.498
7.489
7.480
7.335
6.204
-0.005

4j
abundance
X : parts per Million : 1H
0.87
1.03
1.96
0.99
0.96
1.00
0.97
7.700
7.601
7.581
7.565
7.560
7.545
7.541
7.301
7.283
7.222
7.206
7.203
7.043
6.565
3.944
3.935
0.073
-0.028

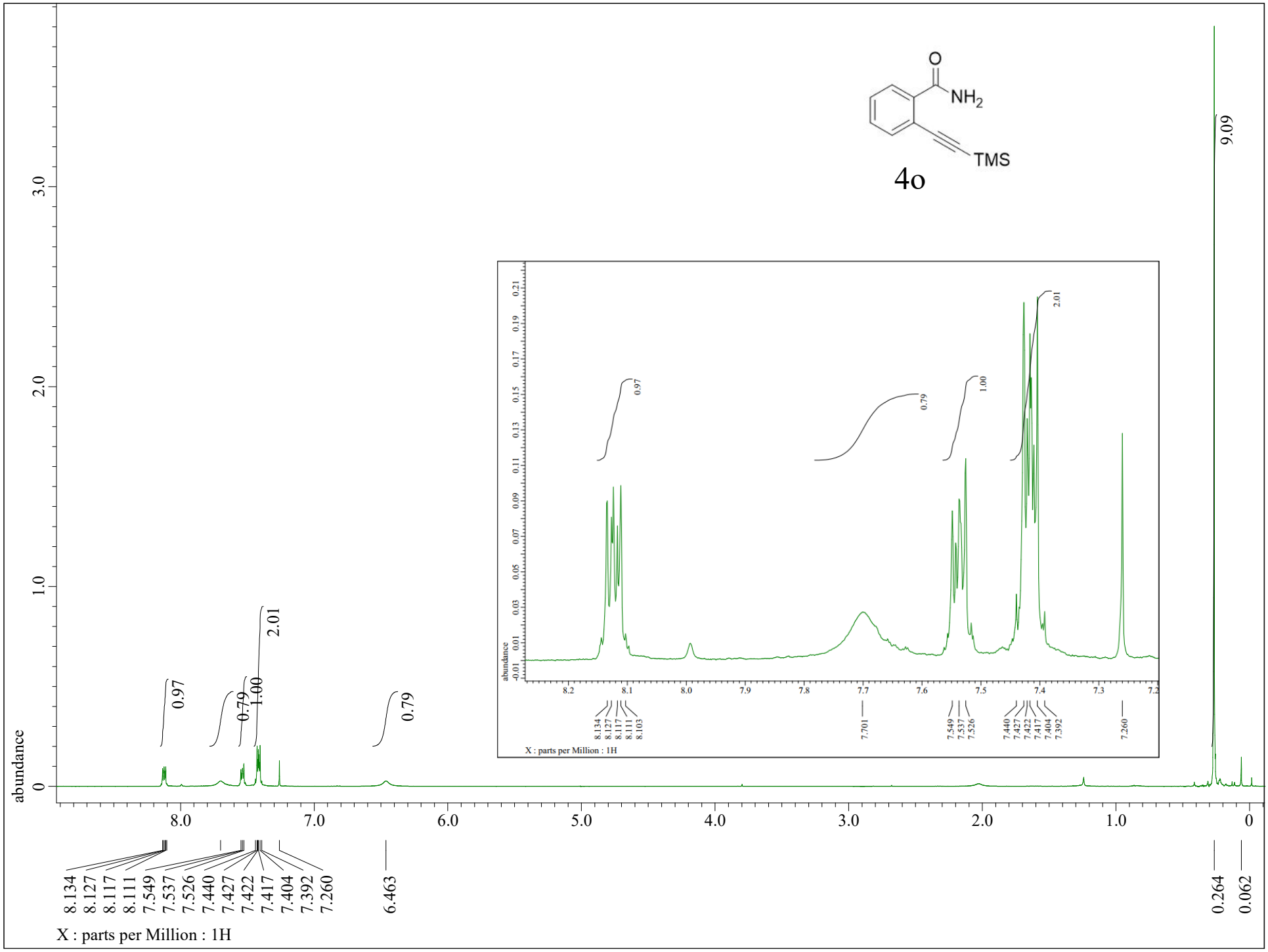
4j
abundance
X : parts per Million : 13C
167.550
150.988
149.530
133.464
132.491
130.089
127.257
124.930
124.349
115.348
115.310
112.860
112.574
93.314
91.969
77.324
77.000
76.685
56.081


O
NH2
Cl
4k
(thousandths)
X : parts per Million : Proton
8.076
8.072
8.067
8.059
8.053
7.519
7.484
7.475
7.465
7.404
7.353
7.325
7.305
6.381
-0.002

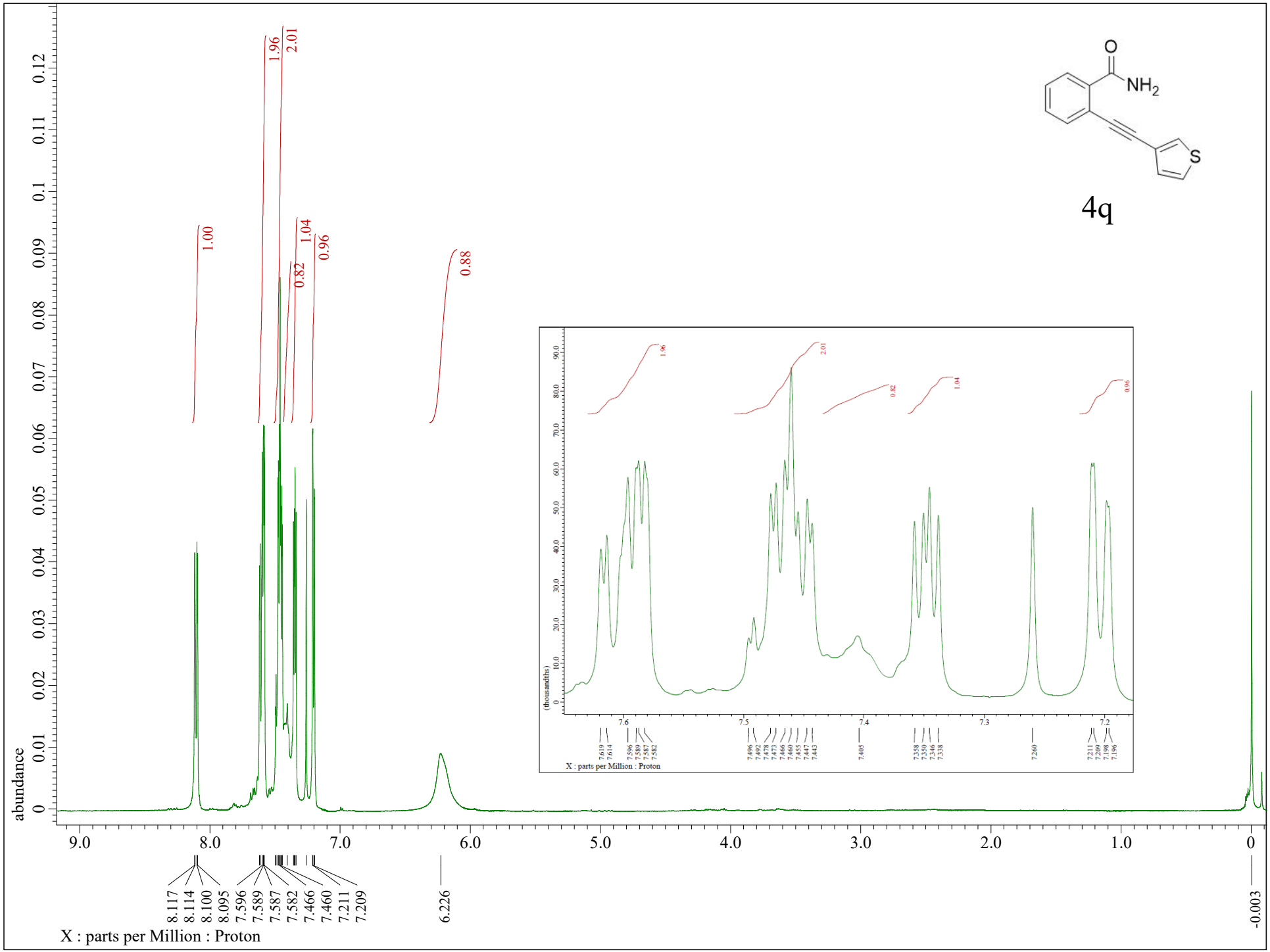
O
NH2
C6H13
41
abundance
X : parts per Million : 1H
1.00
0.90
0.91
1.94
0.82
2.04
2.08
1.99
3.99
3.08
8.138
8.133
8.130
8.120
8.115
7.705
7.481
7.420
7.416
7.404
7.392
6.170
2.504
2.487
2.469
1.636
1.617
1.339
1.330
1.322
1.313
0.923
0.906
0.889
-0.000

O
NH2
4m
abundance
X : parts per Million : 1H
0.92
0.91
1.00
1.87
0.92
0.92
1.86
1.85
1.88
3.63
8.131
8.113
8.107
7.741
7.471
7.400
7.395
7.389
7.377
6.433
2.692
2.683
2.669
2.660
2.649
2.636
2.626
1.893
1.749
1.743
1.735
1.560
1.554
1.529
1.385
1.363
1.344
-0.009

4n
abundance
X : parts per Million : 1H
1.00
0.78
0.96
2.02
0.94
1.04
1.93
1.97
4.07
8.132
8.113
8.109
7.494
7.427
7.424
7.410
7.395
6.574
6.281
6.271
6.267
6.261
2.231
2.210
2.191
2.185
2.176
2.170
2.160
2.155
1.710
1.700
1.685
1.641
1.628
1.622
1.614
0.000


O
NH2
TMS
4o
abundance
X : parts per Million : 1H
8.134
8.127
8.117
8.111
7.549
7.537
7.526
7.440
7.427
7.422
7.417
7.404
7.392
7.260
6.463
0.264
0.062
9.09
0.97
0.79
1.00
2.01
0.79

4p
abundance
X : parts per Million : 1H
8.084
8.078
8.076
8.070
8.065
8.060
7.582
7.476
7.471
7.463
7.454
7.448
7.260
6.306
3.522
-0.007
0.97
0.99
2.06
0.74
0.79
1.00


4q
abundance
X : parts per Million : Proton
1.00
1.96
2.01
0.82
1.04
0.96
0.88
8.117
8.114
8.100
8.095
7.596
7.589
7.587
7.582
7.466
7.460
7.211
7.209
6.226
-0.003

MeO
MeO
O
NH2
Ph
4r
abundance
X : parts per Million : 1H
7.734
7.548
7.542
7.533
7.526
7.524
7.461
7.403
7.400
7.396
7.388
7.386
7.268
7.051
6.118
3.975
3.962
0.000
1.00
1.04
1.95
0.95
2.08
0.84
0.77
2.90

F
O
NH2

4s

abundance
1.00
0.82
2.10
3.86
1.17
0.81
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-0.000
7.845
7.638
7.624
7.617
7.604
7.539
7.535
7.527
7.523
7.515
7.404
7.399
7.389
7.386
7.260
7.196
7.189
X : parts per Million : 1H

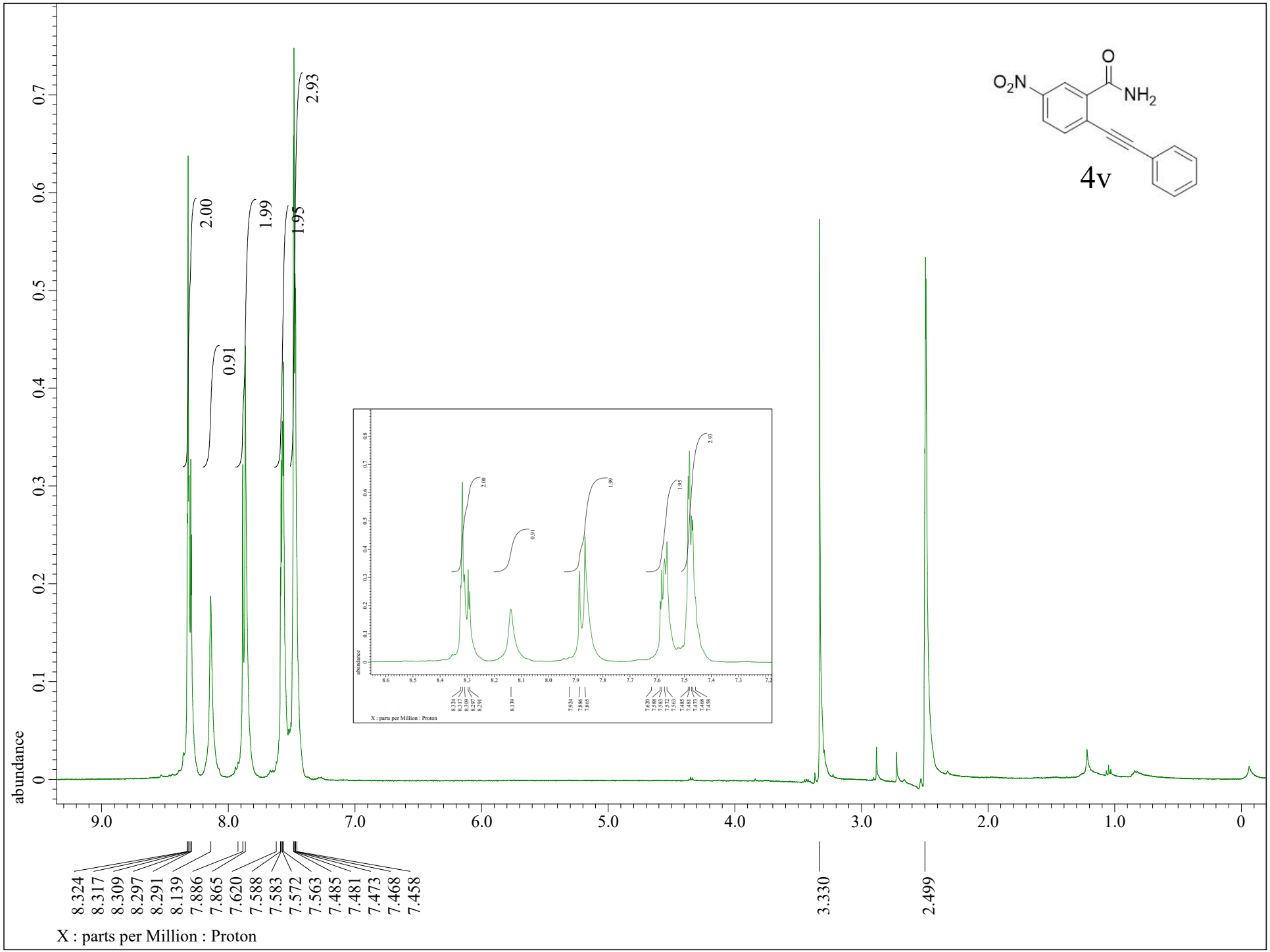
4s
abundance
X : parts per Million : 13C
166.892
163.727
137.011
135.552
131.500
129.335
128.639
121.755
117.741
117.322
116.244
95.631
86.630
77.324
77.000
76.685

4t
F
O
NH2
CH3
abundance
X : parts per Million : 1H
1.00
1.91
2.01
2.84
0.77
3.03
7.876
7.869
7.852
7.845
7.621
7.607
7.600
7.586
7.425
7.404
7.260
7.204
7.184
7.165
6.315
2.388
-0.001

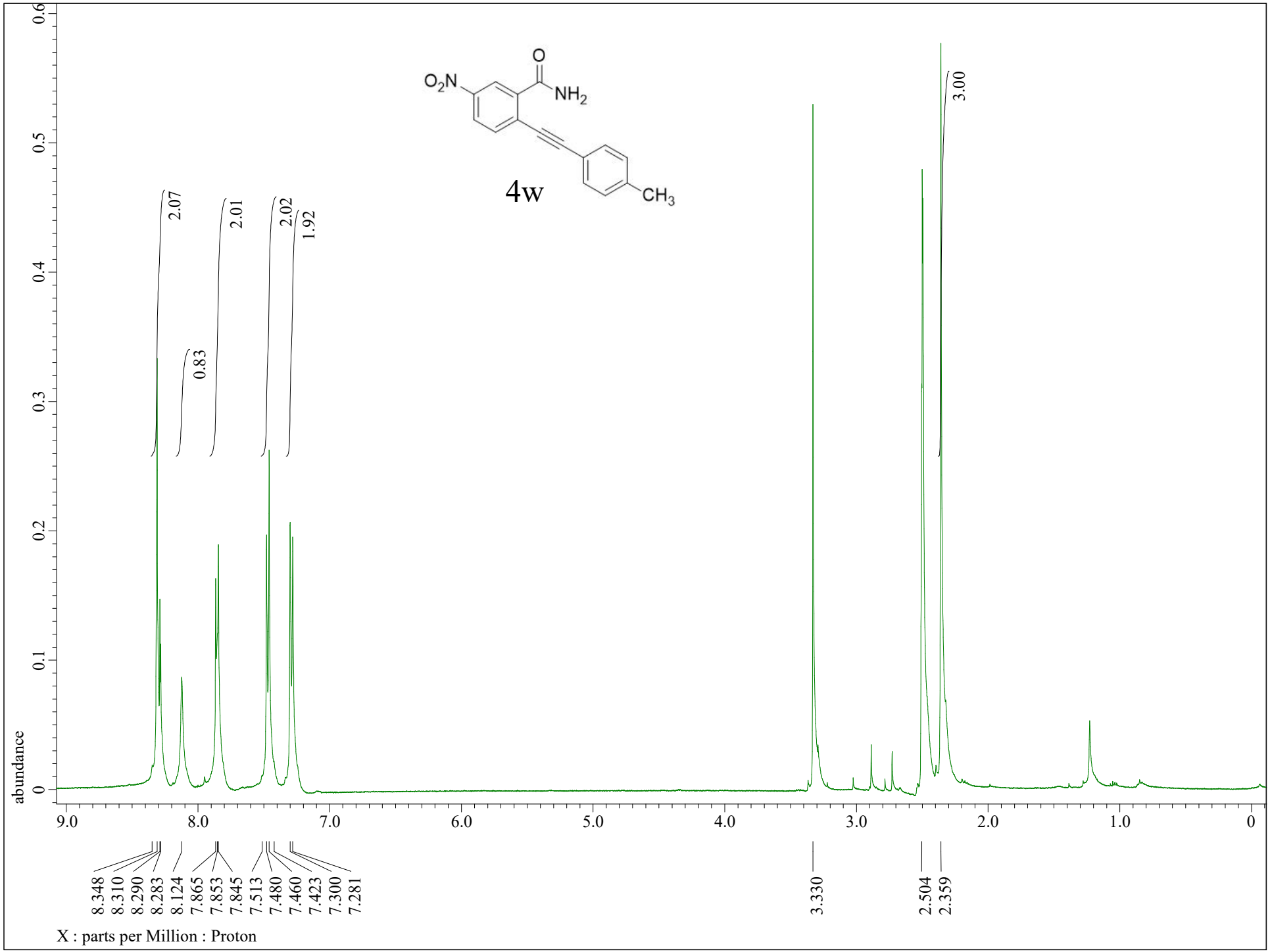
F
O
NH2
4t
CH3
(thousandths)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
166.761
163.609
139.709
135.541
135.464
131.382
129.389
118.656
117.631
117.391
116.500
95.945
86.084
77.316
77.000
76.674
21.564
X : parts per Million : Carbon13

4u
abundance
X : parts per Million : Proton
0.81
1.00
0.99
1.98
1.95
0.89
7.806
7.803
7.798
7.795
7.638
7.630
7.625
7.622
7.617
7.600
7.360
7.336
7.313
7.187
7.183
7.174
7.172
3.330
2.471

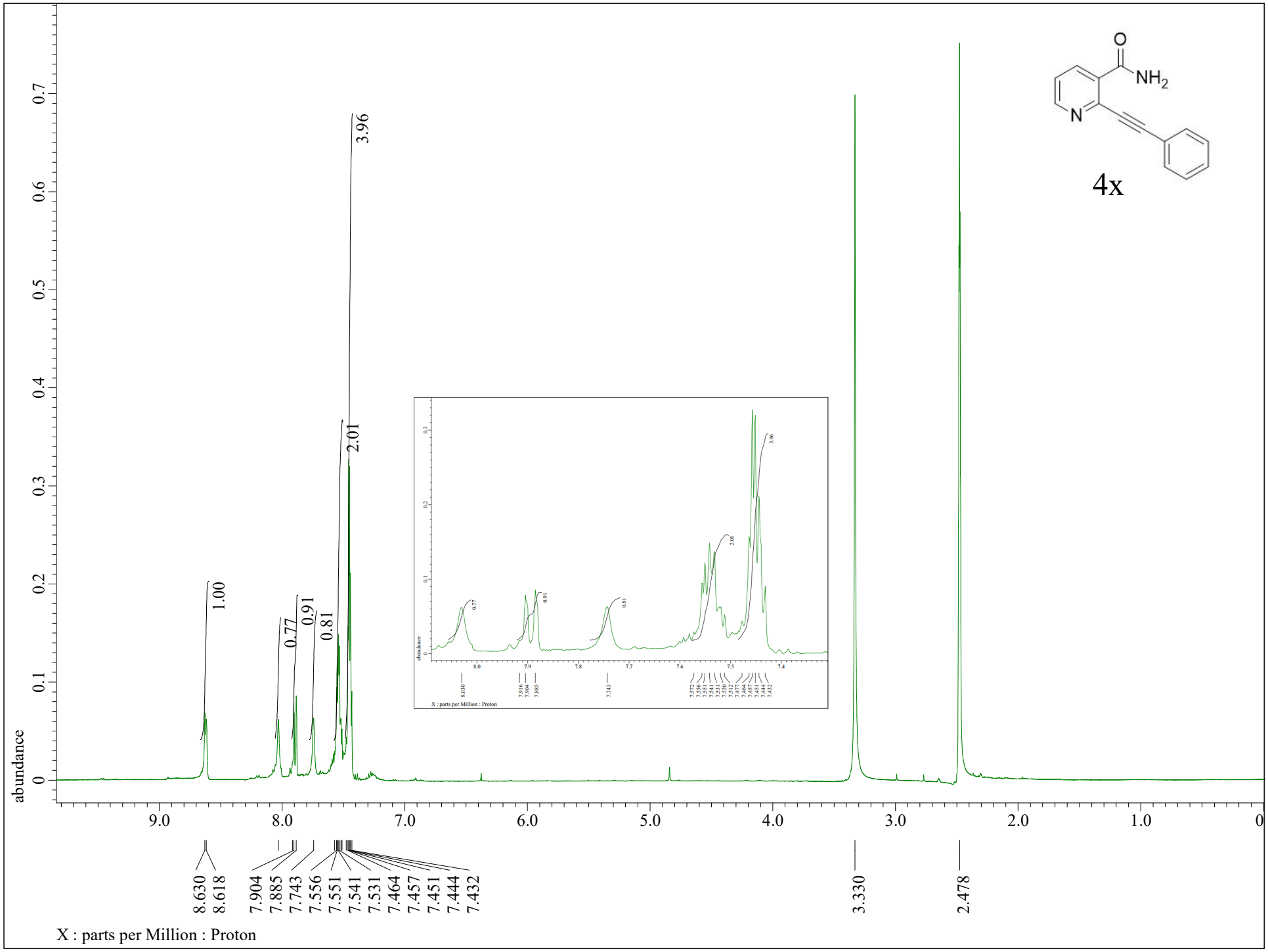
O
F
NH2
S
4u
(thousandths)
50.0
40.0
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.747
162.543
141.672
134.935
134.849
129.971
129.531
127.058
121.242
117.044
115.013
88.009
86.265
39.520
X : parts per Million : Carbon13


4v
abundance
X : parts per Million : Proton
2.00
0.91
1.99
1.95
2.93
8.324
8.317
8.309
8.297
8.291
8.139
7.886
7.865
7.620
7.588
7.583
7.572
7.563
7.485
7.481
7.473
7.468
7.458
3.330
2.499

O2N
O
NH2
4v
(thousandths)
50.0
40.0
30.0
20.0
10.0
0
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
167.530
146.840
141.110
134.469
132.160
130.310
129.419
127.090
124.896
123.104
122.069
98.055
87.274
X : parts per Million : Carbon13


4w
O2N
NH2
O
CH3
2.07
0.83
2.01
2.02
1.92
3.00
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.348
8.310
8.290
8.283
8.124
7.865
7.853
7.845
7.513
7.480
7.460
7.423
7.300
7.281
3.330
2.504
2.359
X : parts per Million : Proton

O2N
O
NH2
CH3
4w
(thousandths)
19.0
18.0
17.0
16.0
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.645
146.745
140.899
140.334
134.095
131.958
130.042
127.311
124.551
122.558
118.543
98.428
86.402
21.498
X : parts per Million : Carbon13

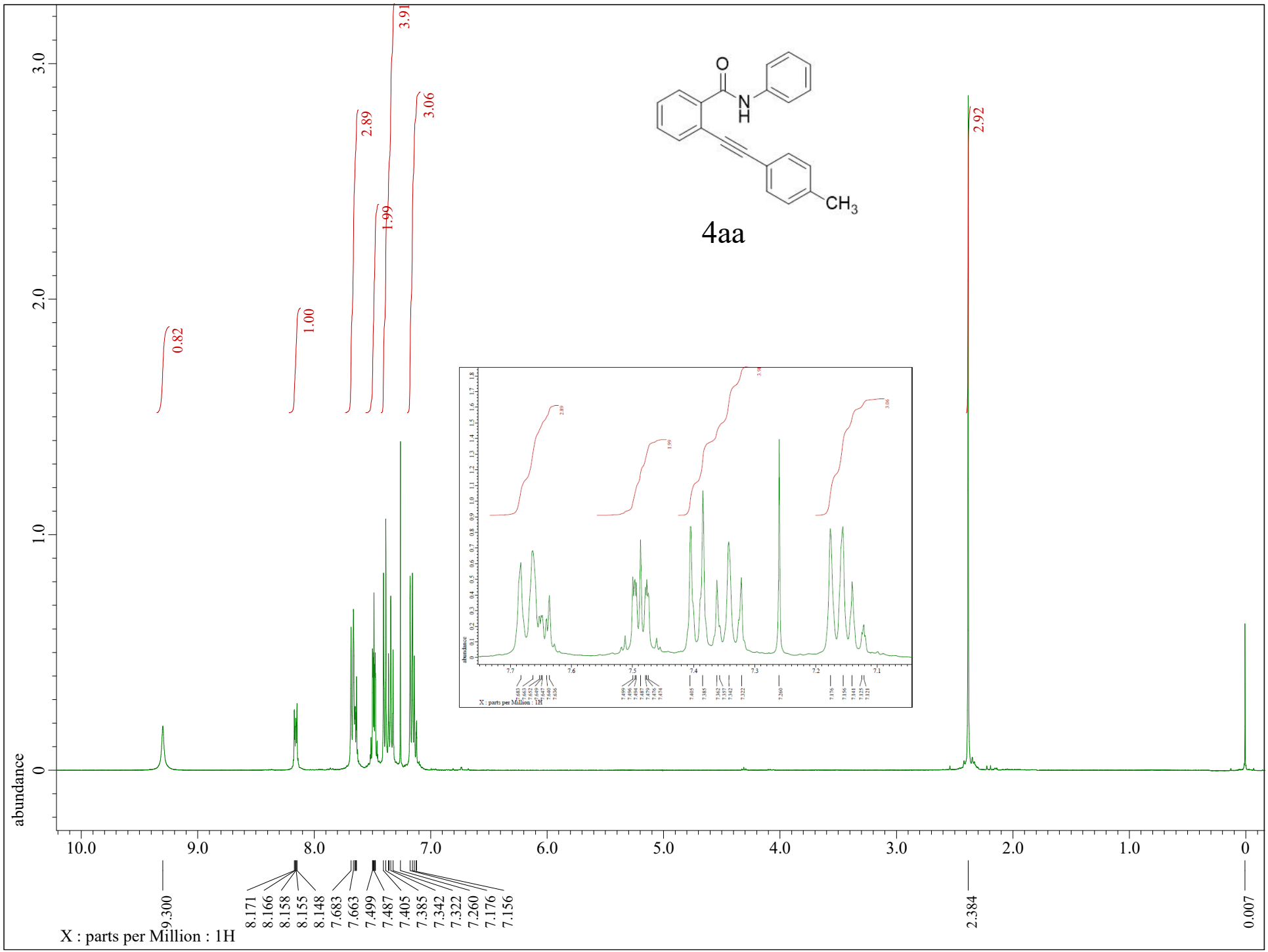

O
NH2
N
4x
abundance
1.00
0.77
0.91
0.81
2.01
3.96
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.630
8.618
7.904
7.885
7.743
7.556
7.551
7.541
7.531
7.464
7.457
7.451
7.444
7.432
3.330
2.478
X : parts per Million : Proton

O
NH2
N
4x
(thousandths)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.034
150.546
139.008
136.066
135.434
131.610
129.569
128.889
123.139
121.606
91.583
87.807
39.520
X : parts per Million : Carbon13

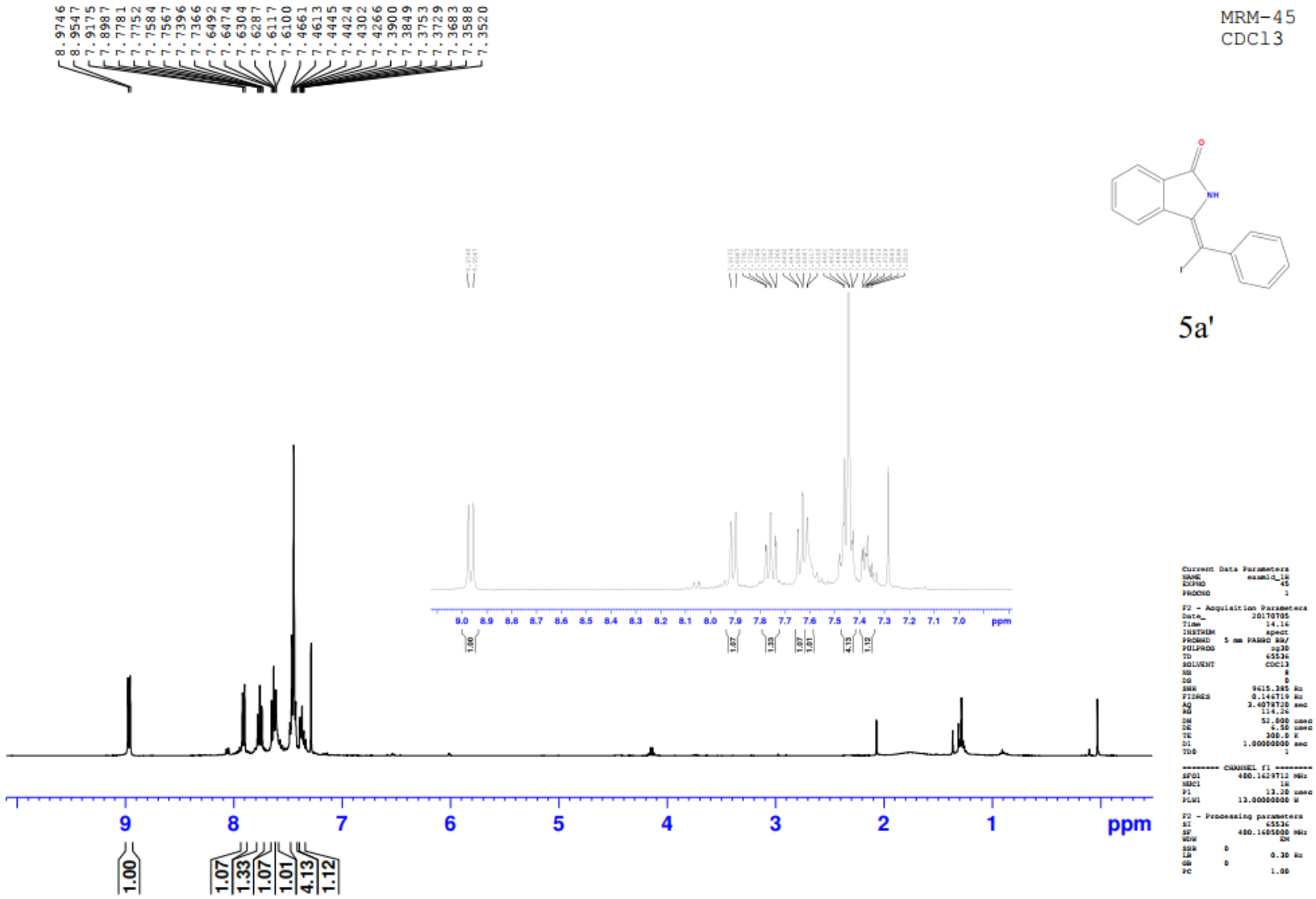
O
NH2
N
C6H13
4y
40.0
30.0
20.0
10.0
0
(thousandths)
1.00
1.03
0.85
1.02
0.97
2.03
2.01
1.99
3.98
3.08
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.654
8.649
8.642
8.638
8.425
8.421
8.405
8.401
7.745
7.356
7.344
7.336
7.324
6.517
2.540
2.522
2.504
1.414
1.313
1.302
1.295
1.287
1.278
0.893
0.878
0.861
0.056
X : parts per Million : Proton

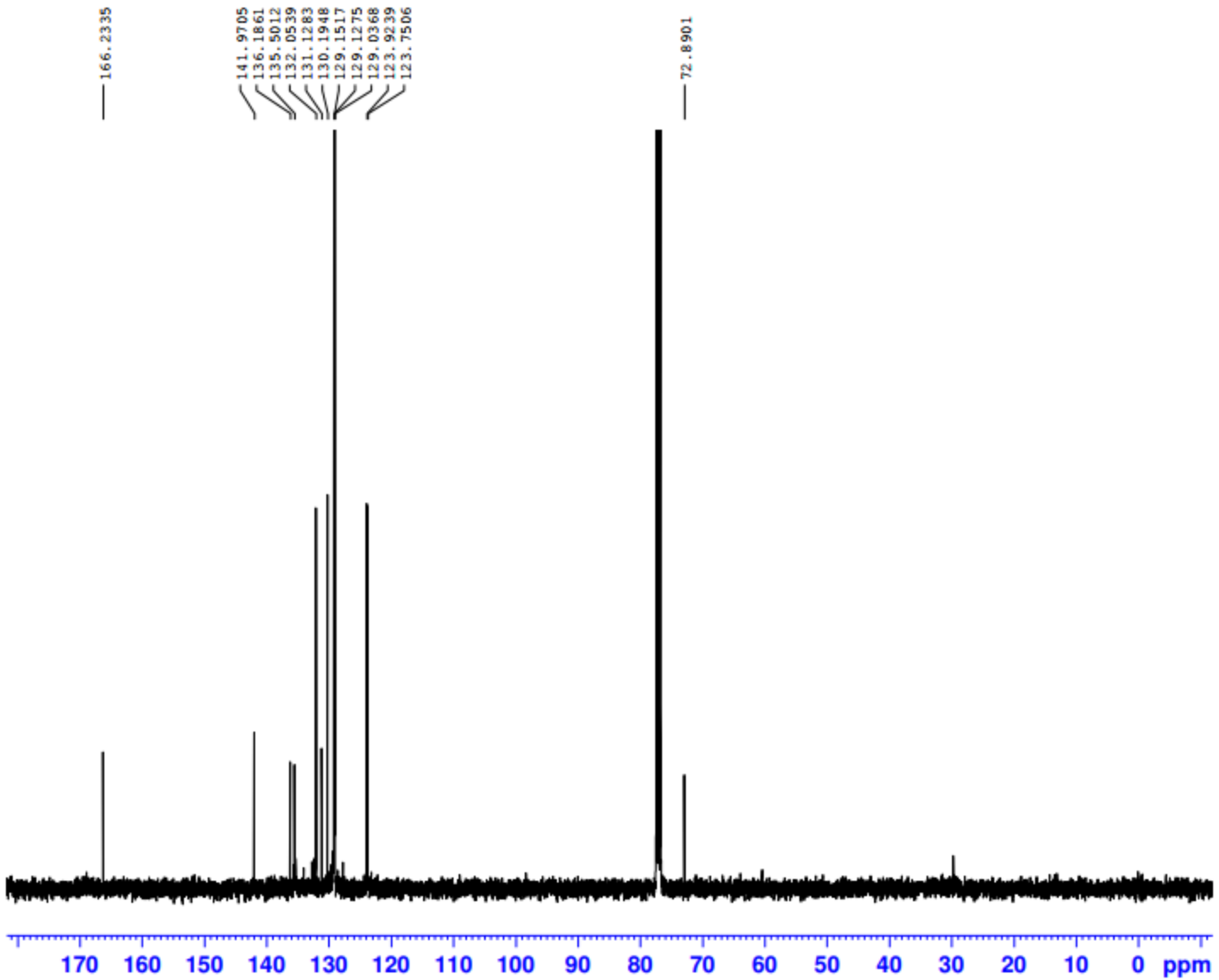
O
NH2
N
C6H13
4y
(thousandths)
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
166.617
151.875
139.952
138.313
130.319
122.738
98.173
79.665
77.316
77.000
76.684
31.214
28.713
27.994
22.444
19.559
13.990
X : parts per Million : Carbon13

4z
abundance
X : parts per Million : 1H
0.94
1.00
0.86
2.09
2.06
2.92
3.00
8.025
8.019
8.013
8.002
7.519
7.510
7.501
7.432
7.425
7.420
7.408
7.394
7.387
7.378
3.069
3.057
-0.005

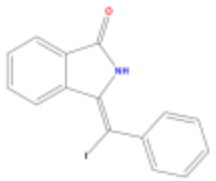

4aa
abundance
X : parts per Million : 1H
0.82
1.00
2.89
1.99
3.91
3.06
2.92
9.300
8.171
8.166
8.158
8.155
8.148
7.683
7.663
7.499
7.487
7.405
7.385
7.342
7.322
7.260
7.176
7.156
2.384
0.007

O
NH
I
Ph
5a
abundance
X : parts per Million : 1H
1.09
0.76
6.09
0.94
1.00
7.795
7.775
7.458
7.451
7.449
7.441
7.432
7.430
7.413
7.411
7.260
7.242
6.519
6.498
0.078
0.069
-0.002


8.9746
8.9547
7.9175
7.8987
7.7781
7.7752
7.7584
7.7567
7.7396
7.7366
7.6492
7.6474
7.6304
7.6287
7.6117
7.6100
7.4661
7.4613
7.4445
7.4424
7.4302
7.4266
7.3900
7.3849
7.3753
7.3729
7.3683
7.3588
7.3520
MRM-45
CDC13
NH
5a'
9.0 8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 ppm
1.00
1.07
1.33
1.07
1.01
4.13
1.12
9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME example_1H
EXPNO 45
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170705
Time 14.14
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 0
SWH 9615.385 Hz
FIDRES 0.146719 Hz
AQ 3.4078720 sec
RG 114.24
DW 52.000 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1429712 MHz
NUC1 1H
P1 13.20 usec
PLW1 13.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



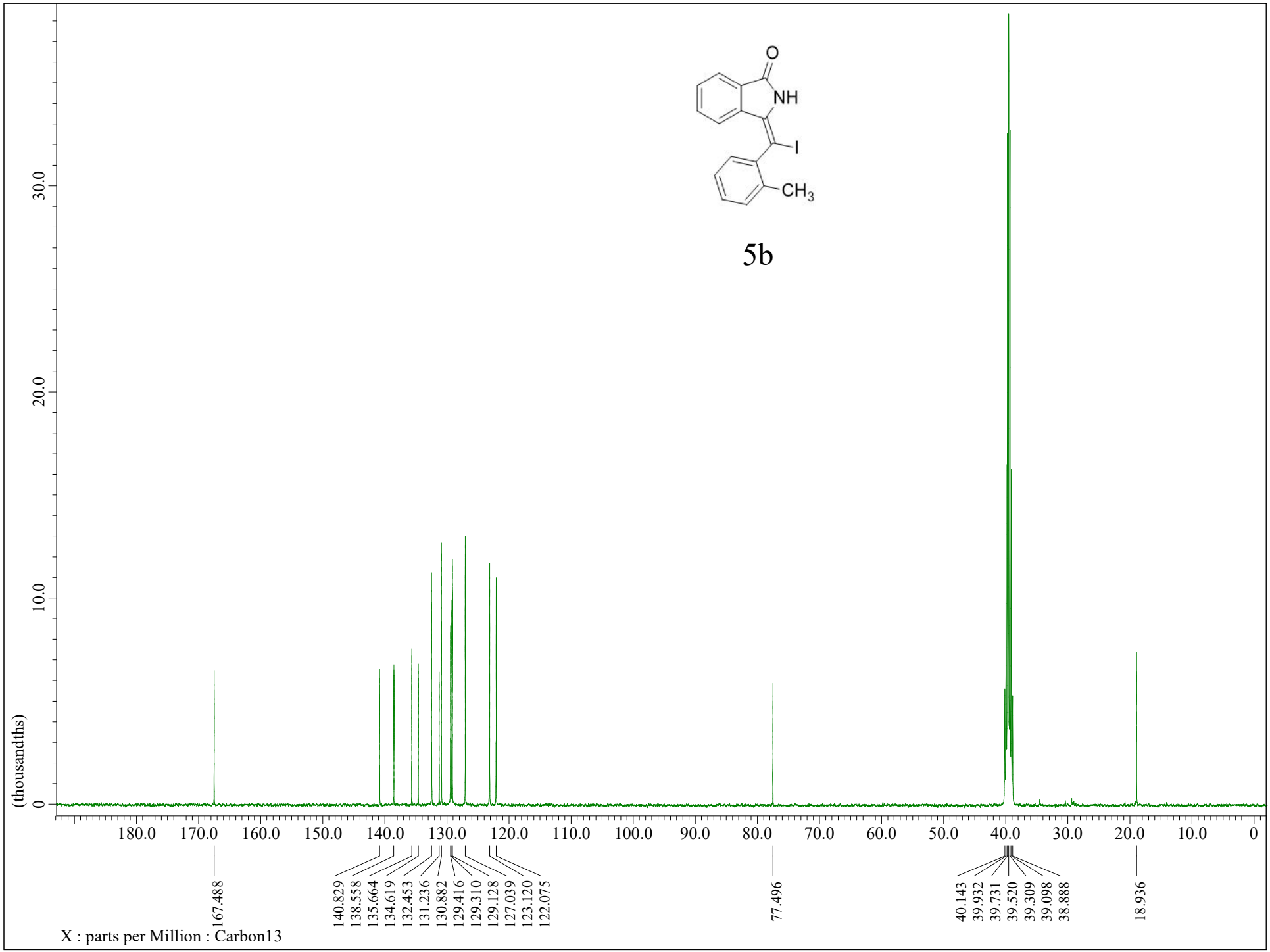
MRM-45
CDC13



5a'

```
Current Data Parameters
NAME                  examld_13C
EXPNO                         45
PROCNO                         1

F2 - Acquisition Parameters
Date_               20170707
Time                      2.00
INSTRM                   spect
PROBHD     5 mm PABBO BB/
PULPROG                zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                          512
DS                            0
SWH                 24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                       201.48
DW                       20.800 usec
DE                        6.50 usec
TE                       300.0 K
D1                  2.00000000 sec
D11                 0.03000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1               100.6304993 MHz
NUC1                       13C
P1                        9.90 usec
PLW1               53.00000000 W

======== CHANNEL f2 ========
SFO2               400.1621006 MHz
NUC2                       1H
CPDPRG[2                waltz16
PCPD2                    90.00 usec
PLW2               13.00000000 W
PLW12               0.27963999 W
PLW13               0.22651000 W

F2 - Processing parameters
SI                        32768
SF                 100.6204380 MHz
WDW                          EM
SSB                0
LB                        1.00 Hz
GB                 0
PC                        1.40
```

O
NH
I
CH3
5b
abundance
0.87
0.96
1.03
1.09
3.80
1.00
2.35
10.277
7.674
7.655
7.436
7.434
7.354
7.351
7.342
7.339
7.332
7.302
7.283
7.243
7.227
6.028
6.008
3.330
2.478
2.109
X : parts per Million : Proton


O
NH
I
CH3
5b
(thousandths)
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.488
140.829
138.558
135.664
134.619
132.453
131.236
130.882
129.416
129.310
129.128
127.039
123.120
122.075
77.496
40.143
39.932
39.731
39.520
39.309
39.098
38.888
18.936
X : parts per Million : Carbon13

O
NH
I
CH3
5c
2.05
1.04
1.02
4.07
1.11
3.04
abundance
X : parts per Million : 1H
7.781
7.762
7.416
7.399
7.331
7.312
7.260
7.250
7.243
7.233
7.222
7.216
6.537
6.518
2.378
-0.013

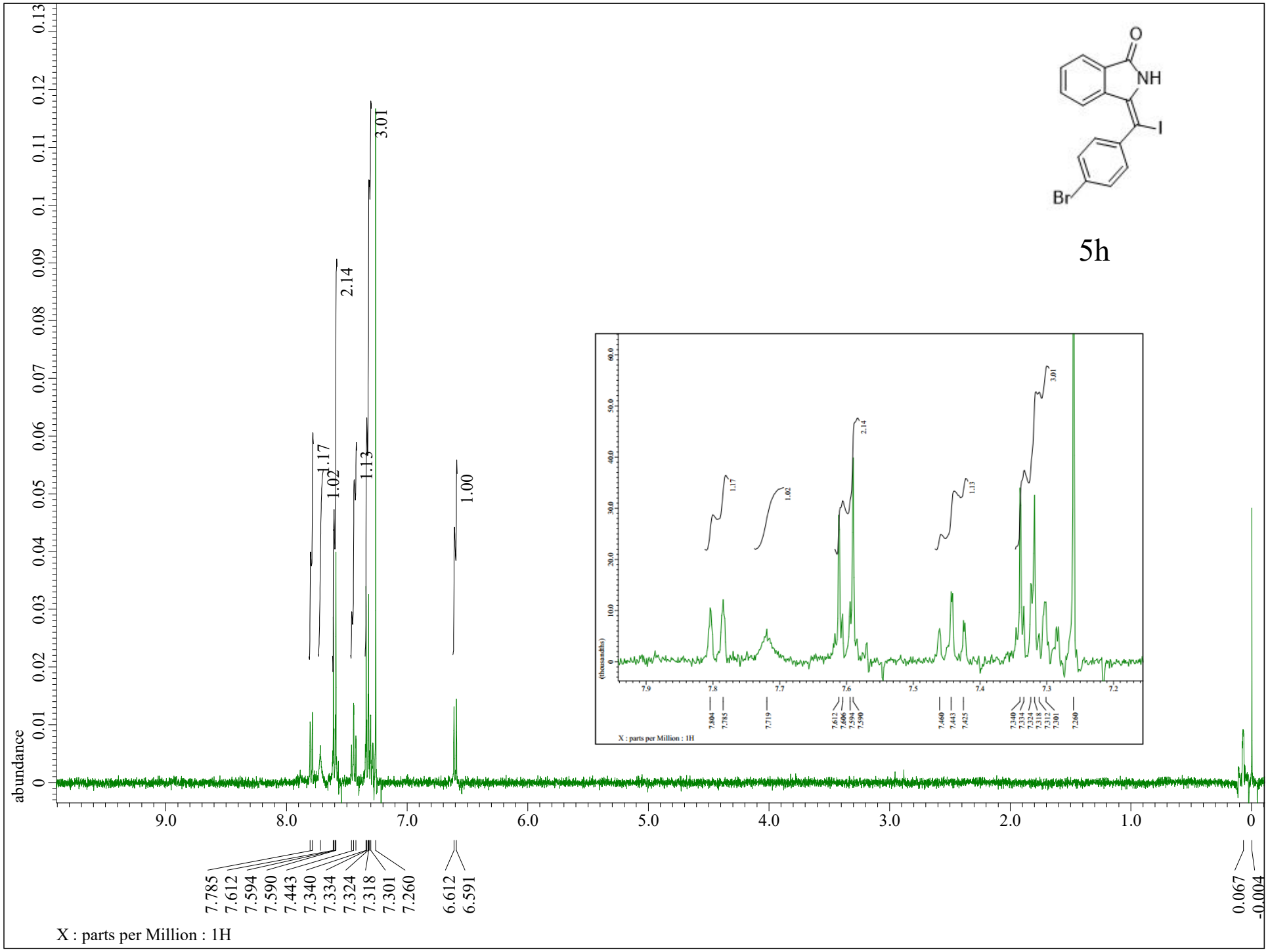
O
NH
I
H3C
5d
abundance
X : parts per Million : 1H
3.92
2.14
3.00
1.05
0.76
1.09
1.06
7.803
7.783
7.422
7.404
7.355
7.334
7.292
7.279
7.274
7.260
7.254
7.251
6.614
6.594
2.457
0.077
-0.016

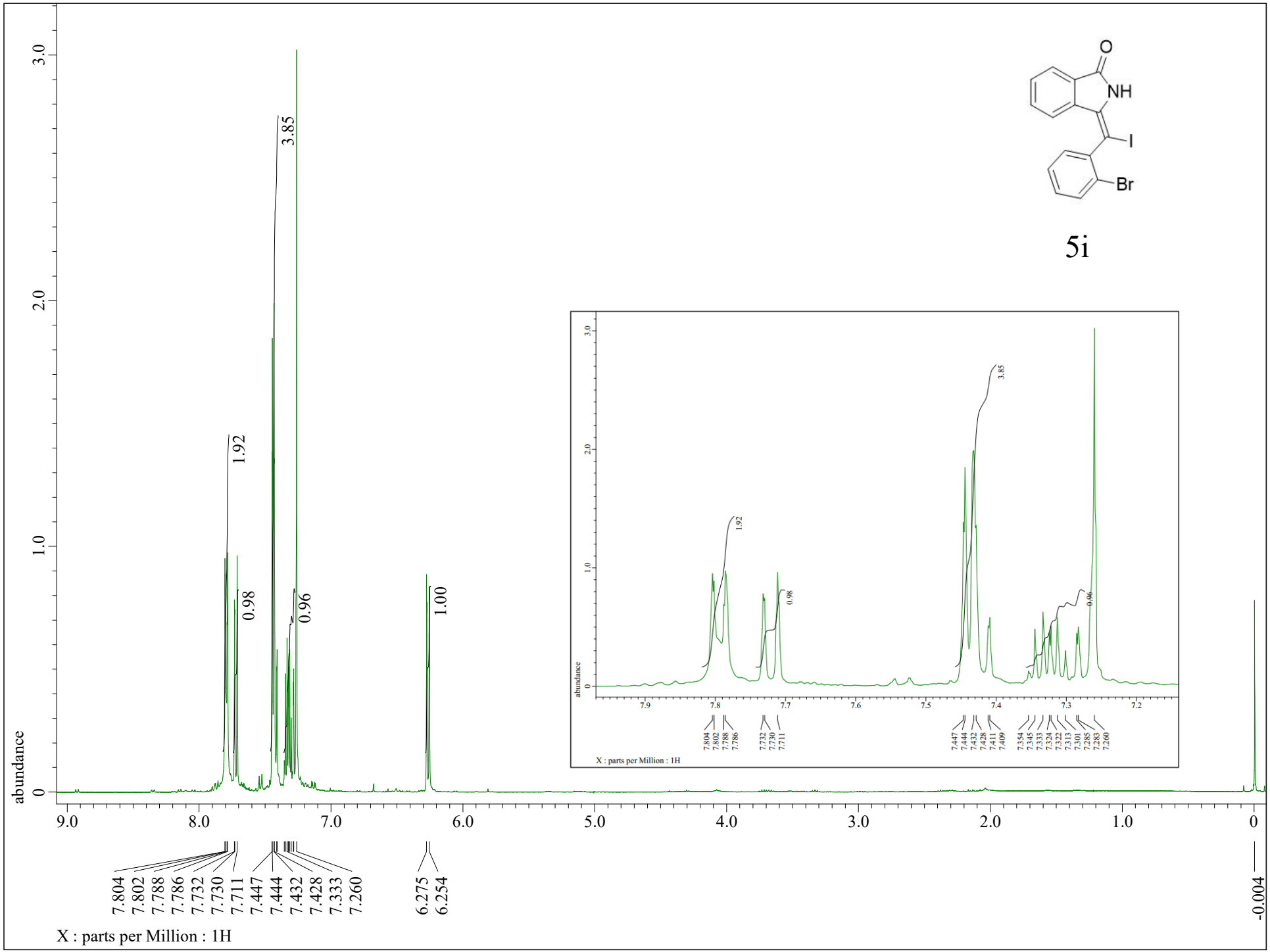
O
NH
I
H3CO
5e
abundance
X : parts per Million : 1H
1.04
0.70
2.78
1.08
2.10
1.00
3.08
7.760
7.741
7.678
7.403
7.384
7.365
7.354
7.333
7.260
7.241
7.229
7.222
6.951
6.930
6.598
6.579
3.859
0.039

abundance
X : parts per Million : 1H
0.94
1.09
1.04
1.00
0.95
2.63
1.15
6.00
9.347
8.352
8.329
7.990
7.970
7.755
7.733
7.712
7.505
7.488
7.467
7.409
7.387
7.260
6.761
6.738
3.035
0.074
-0.000
O
NH
I
(H3C)2N

5f

O
NH
I
F
5g
2.03
3.04
3.01
1.00
abundance
X : parts per Million : 1H
7.800
7.780
7.449
7.436
7.428
7.419
7.415
7.260
7.178
7.173
7.156
7.135
6.537
6.518
0.069
-0.006


O
NH
I
Br
5h
abundance
1.17
1.02
2.14
1.13
3.01
1.00
7.785
7.612
7.594
7.590
7.443
7.340
7.334
7.324
7.318
7.301
7.260
6.612
6.591
0.067
-0.004
X : parts per Million : 1H


O
NH
I
Br
5i
abundance
X : parts per Million : 1H
1.92
0.98
3.85
0.96
1.00
7.804
7.802
7.788
7.786
7.732
7.730
7.711
7.447
7.444
7.432
7.428
7.333
7.260
6.275
6.254
-0.004

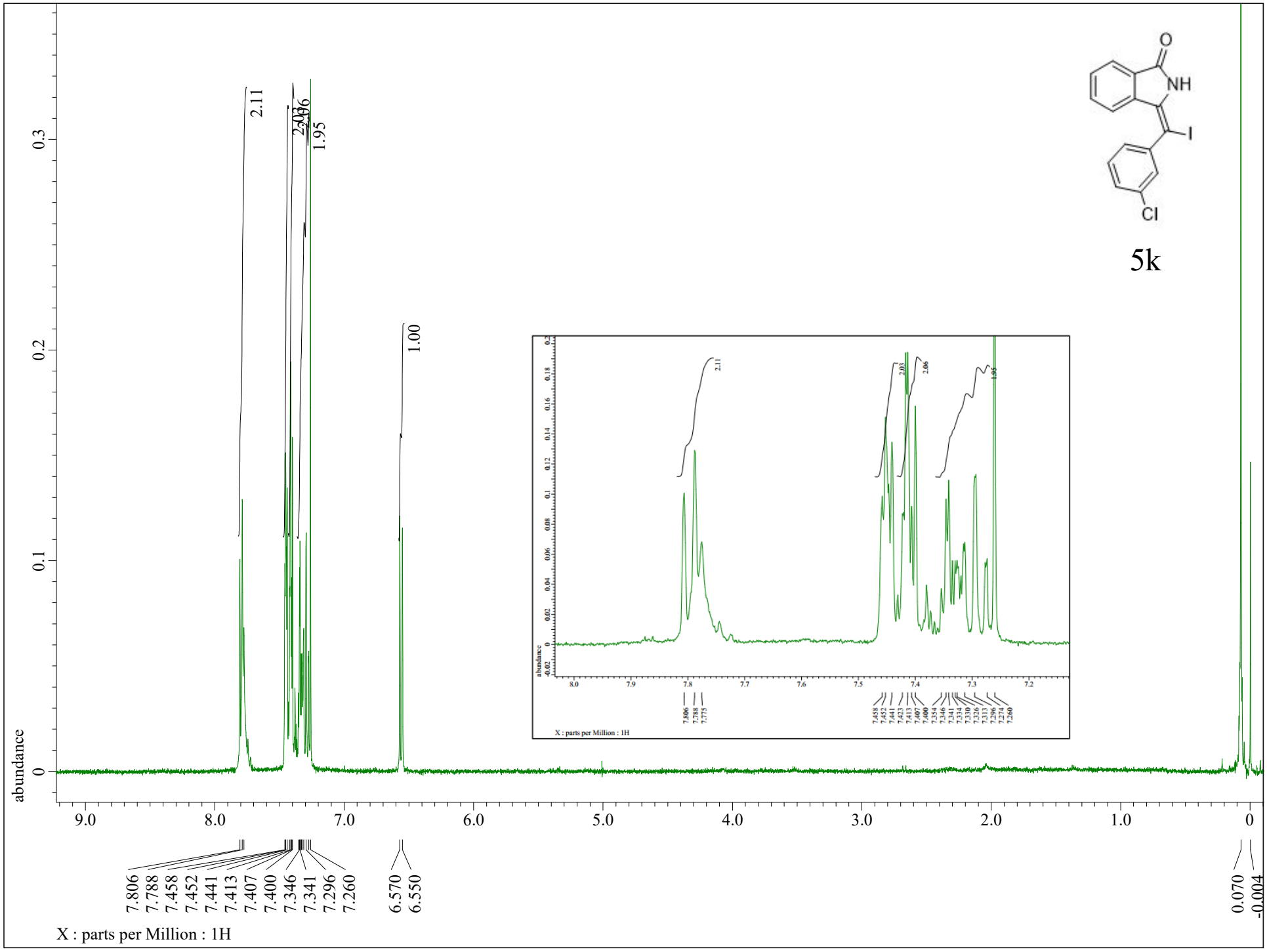
O
NH
I
Br

5i

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.292
140.491
138.822
134.293
133.817
132.606
131.605
131.328
130.832
129.536
128.410
124.187
123.910
122.737
77.324
77.210
77.000
76.685
76.314
0.990
X : parts per Million : 13C

5j
abundance
X : parts per Million : Proton
10.321
7.677
7.674
7.657
7.612
7.593
7.590
7.418
7.416
7.398
7.193
6.604
3.917
3.851
3.330
2.482
0.86
0.93
1.99
0.93
1.05
1.00
2.93
2.92
H3CO
H3CO
O
NH
I
Br

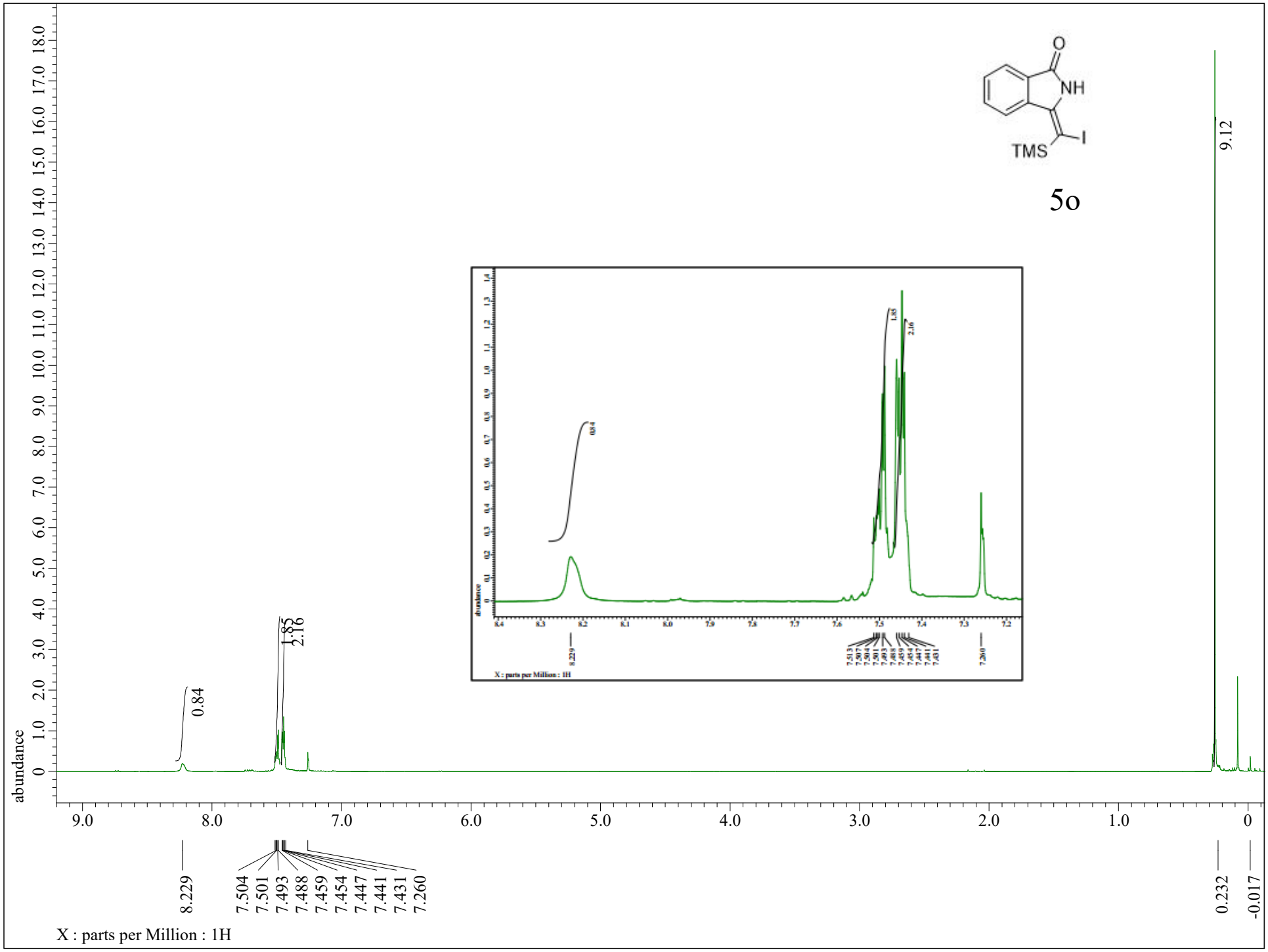
O
H3CO
NH
H3CO
I
Br
5j
(thousandths)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
169.050
153.056
150.852
135.146
134.801
132.540
131.610
131.390
128.831
127.969
123.388
121.462
104.271
103.159
72.063
56.251
55.878
39.520
X : parts per Million : Carbon13


O
NH
I
Cl
5k
2.11
2.03
2.06
1.95
1.00
abundance
X : parts per Million : 1H
7.806
7.788
7.458
7.452
7.441
7.413
7.407
7.400
7.346
7.341
7.296
7.260
6.570
6.550
0.070
-0.004

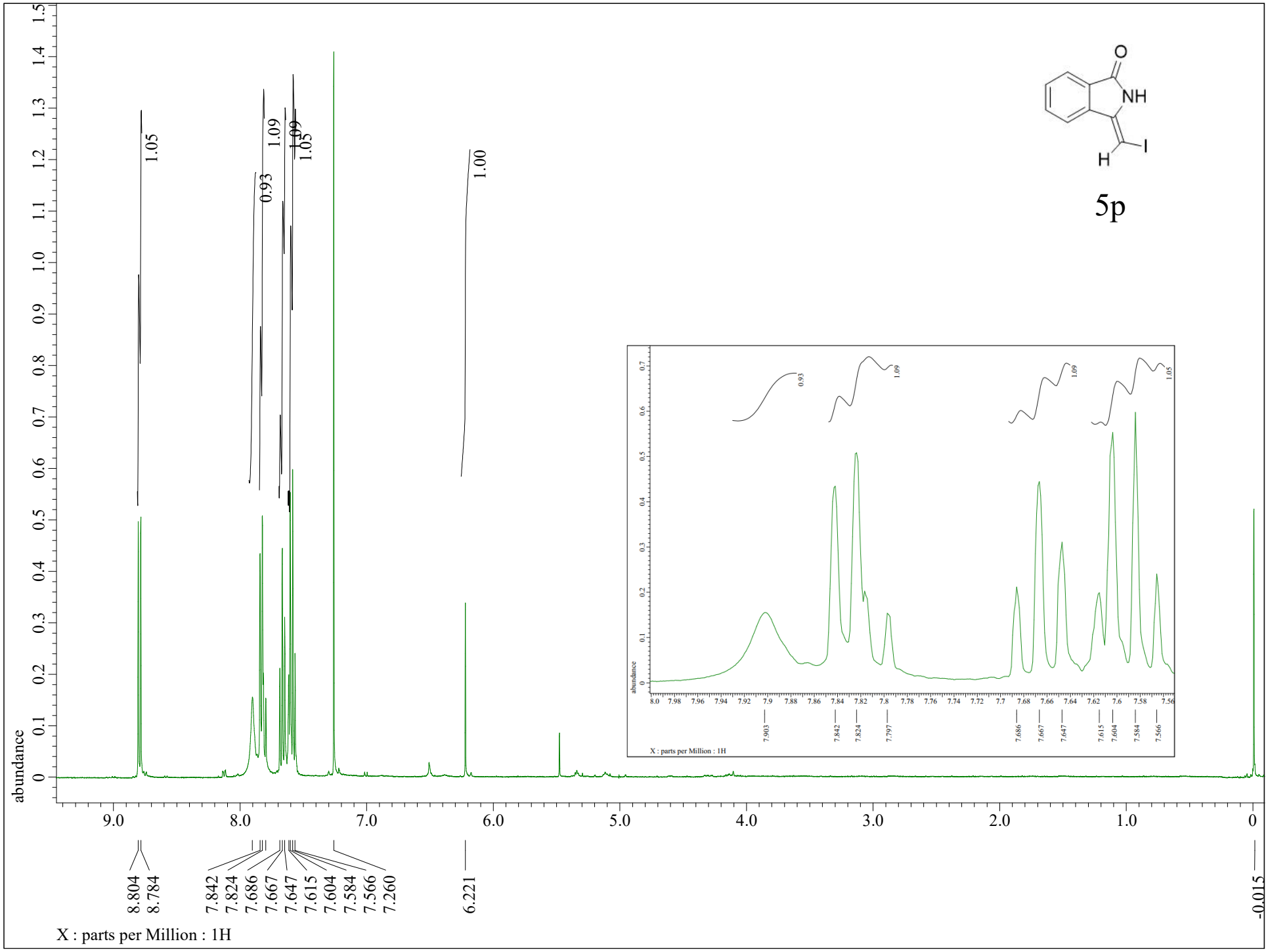
O
NH
I
C6H13
51
abundance
X : parts per Million : 1H
7.849
7.830
7.796
7.775
7.616
7.614
7.597
7.543
7.526
7.260
1.747
1.728
1.708
1.689
1.670
1.344
1.333
1.328
0.916
0.899
0.892
0.881
-0.006
1.11
1.09
0.88
1.00
0.95
2.25
2.17
6.04
3.00

O
NH
I
5m
3.05
1.13
1.11
1.00
3.92
2.06
2.09
2.09
abundance
X : parts per Million : 1H
7.851
7.832
7.820
7.800
7.624
7.606
7.548
7.528
7.510
7.260
2.764
2.746
2.738
2.720
1.889
1.882
1.742
1.719
1.521
1.507
1.483
1.479
1.242
0.066
-0.012

O
NH
I
5n
0.82
1.04
0.99
0.93
1.04
1.00
2.00
2.05
1.95
2.18
abundance
0.3
0.2
0.1
0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
10.435
8.354
8.336
7.929
7.908
7.740
7.722
7.512
7.493
7.474
7.260
5.970
5.966
5.961
5.952
2.348
2.329
2.267
2.260
2.252
2.245
1.856
1.846
1.842
1.769
1.763
1.754
0.070
-0.002
X : parts per Million : 1H


O
NH
I
TMS
5o
9.12
0.84
1.85
2.16
abundance
X : parts per Million : 1H
8.229
7.504
7.501
7.493
7.488
7.459
7.454
7.447
7.441
7.431
7.260
0.232
-0.017

O
NH
I
TMS
5o
abundance
0.4
0.3
0.2
0.1
0
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
167.331
140.033
135.485
135.161
132.224
131.023
123.967
123.920
77.629
77.515
77.315
77.000
71.851
0.247
X : parts per Million : 13C

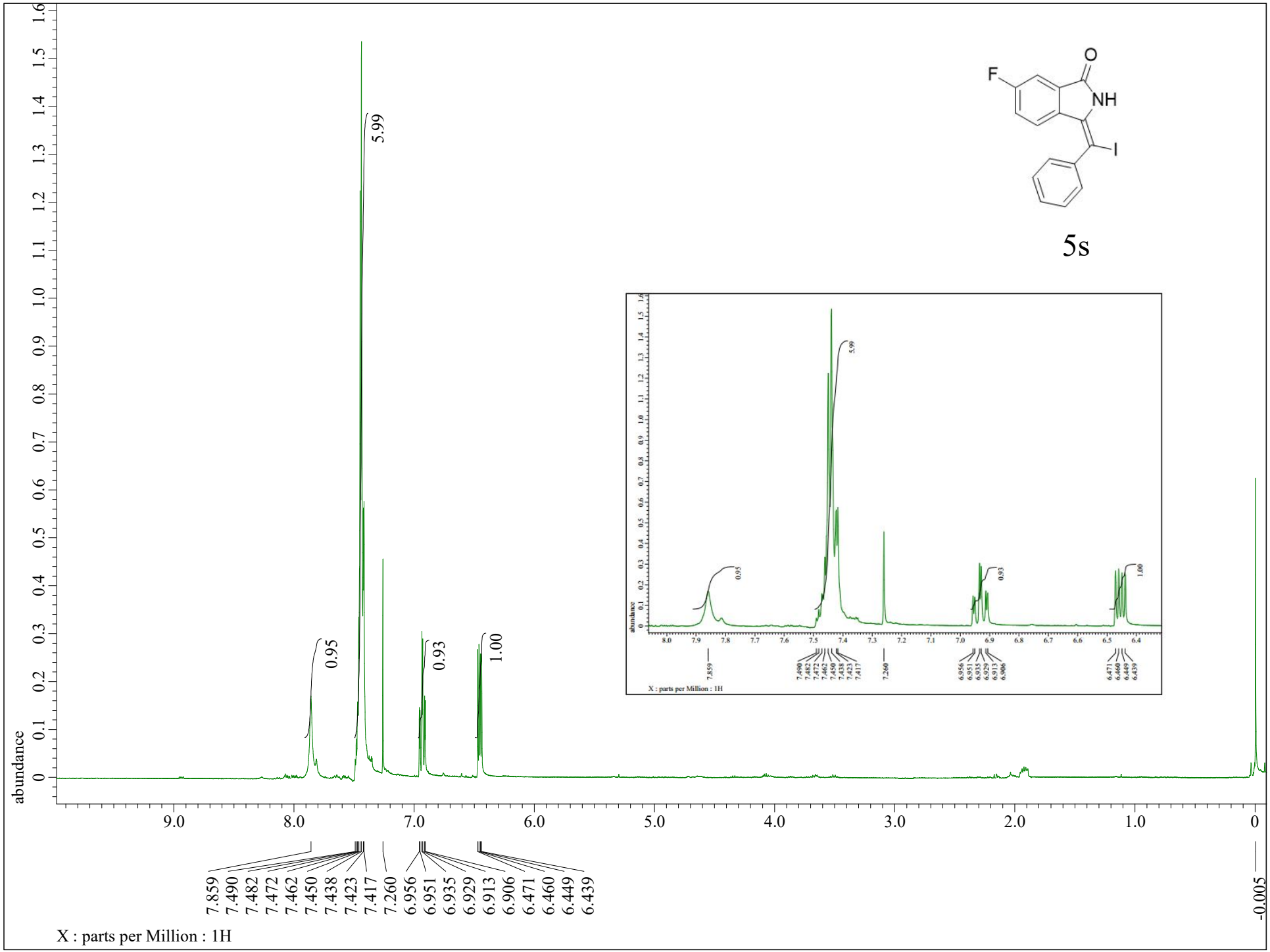

5p
abundance
X : parts per Million : 1H
1.05
0.93
1.09
1.09
1.05
1.00
8.804
8.784
7.842
7.824
7.686
7.667
7.647
7.615
7.604
7.584
7.566
7.260
6.221
-0.015

5q

O
H3CO
NH
H3CO
I

5r

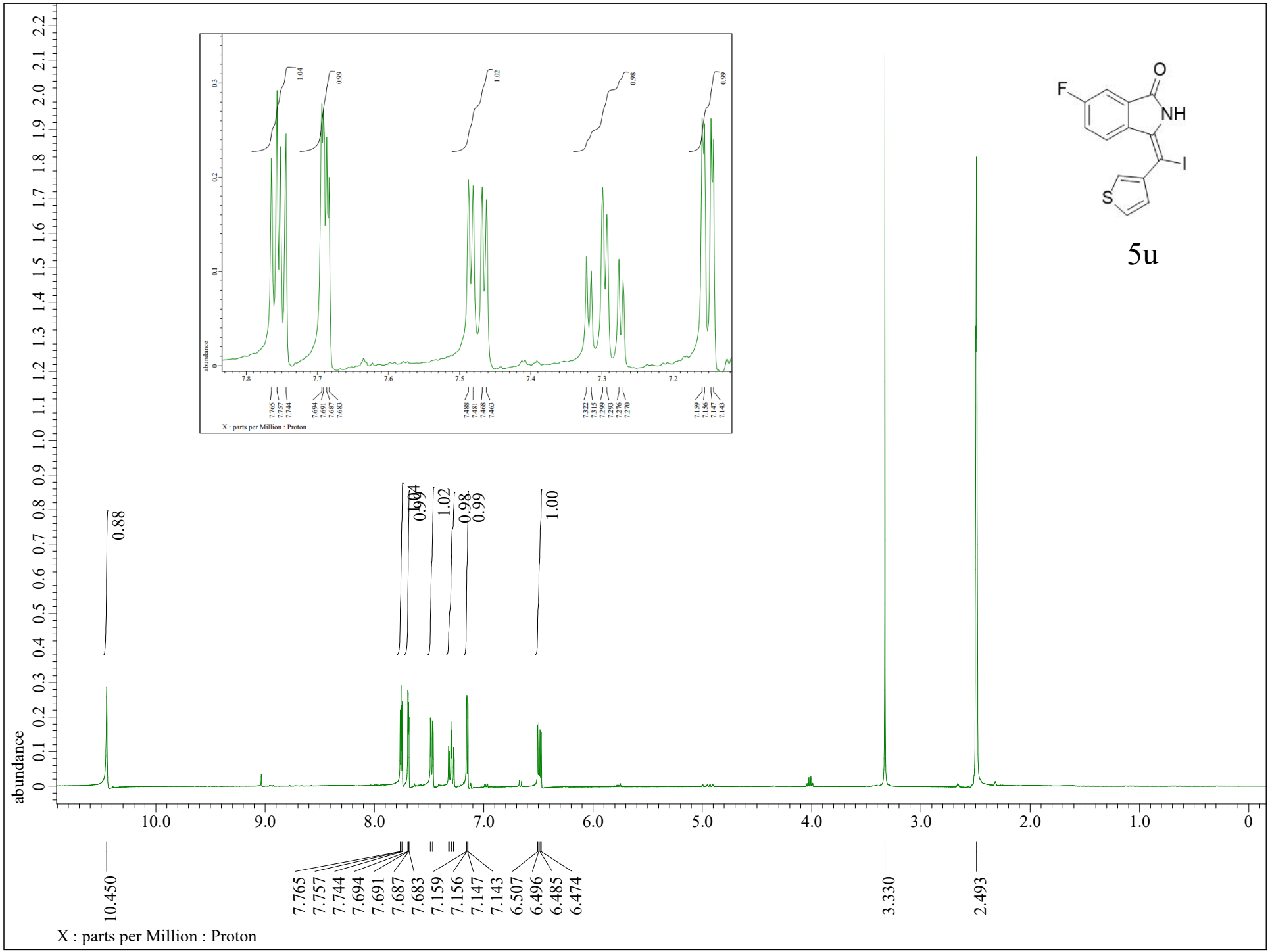
abundance
X : parts per Million : 1H
0.83
4.01
1.01
0.94
1.00
3.11
3.16
7.792
7.475
7.464
7.438
7.427
7.417
7.405
7.394
7.260
7.180
5.874
3.896
3.391
-0.006


O
F
NH
I
5s
abundance
5.99
0.95
0.93
1.00
7.859
7.490
7.482
7.472
7.462
7.450
7.438
7.423
7.417
7.260
6.956
6.951
6.935
6.929
6.913
6.906
6.471
6.460
6.449
6.439
X : parts per Million : 1H

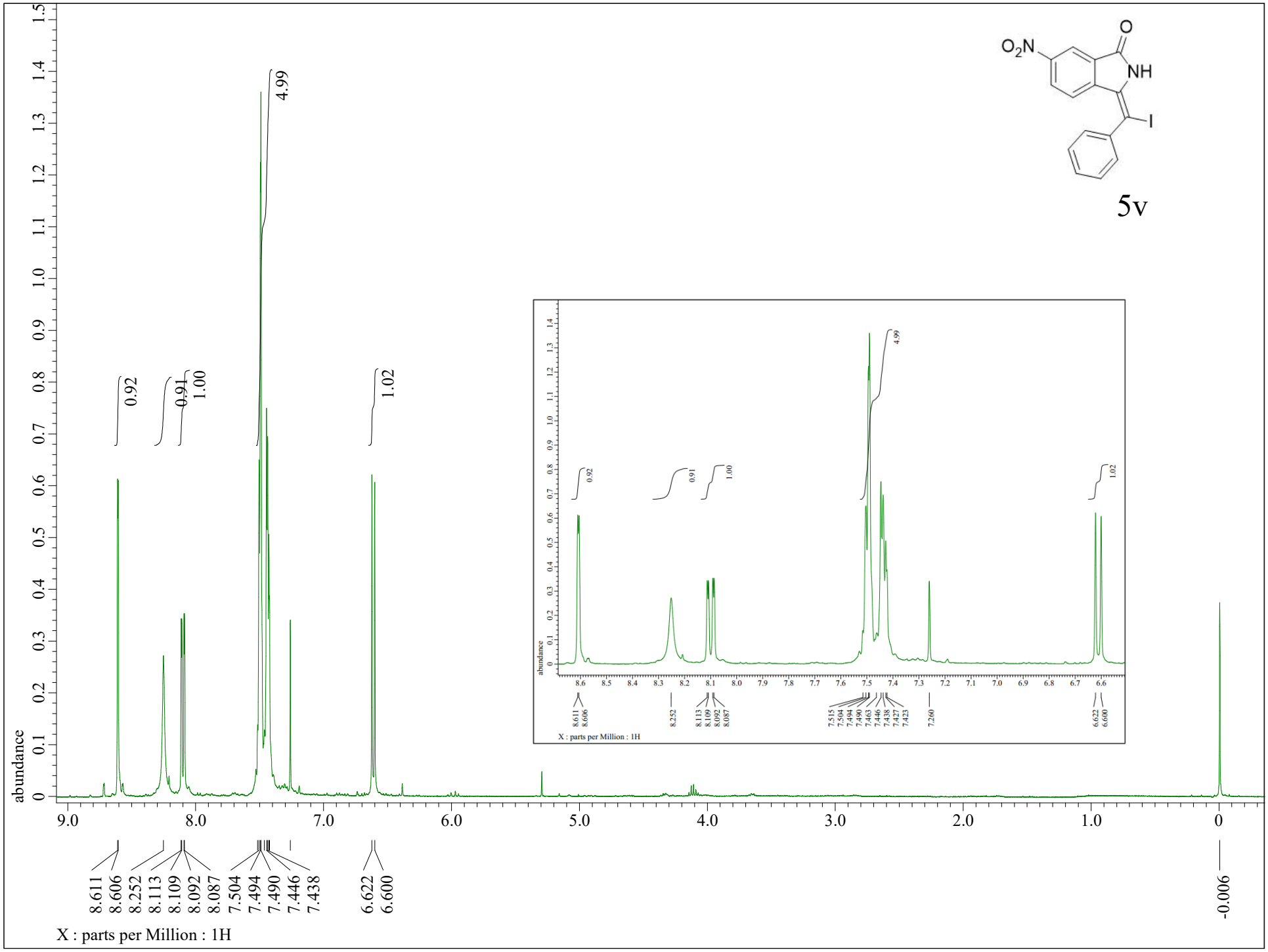
O
F
NH
I
5s
abundance
0
0.1
0.2
0.3
0.4
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
166.091
164.241
140.739
136.829
134.084
133.998
130.422
129.459
129.221
125.226
119.953
119.724
78.583
77.315
77.000
76.676
X : parts per Million : 13C

F
O
NH
I
H3C
5t
3.09
3.00
1.94
0.80
0.96
1.02
1.01
(thousandths)
X : parts per Million : Proton
7.729
7.438
7.432
7.420
7.414
7.331
7.316
7.311
7.271
7.261
7.251
6.978
6.972
6.956
6.950
6.934
6.928
6.562
6.550
6.540
6.529
2.445
0.000

O
F
NH
I
H3C
5t
abundance
0
0.1
0.2
0.3
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
166.129
164.213
139.652
137.840
136.601
133.950
130.470
129.907
129.326
125.207
119.925
119.696
79.288
77.315
77.000
76.676
24.655
X : parts per Million : 13C


O
F
NH
I
S
5u
abundance
X : parts per Million : Proton
10.450
7.765
7.757
7.744
7.694
7.691
7.687
7.683
7.159
7.156
7.147
7.143
6.507
6.496
6.485
6.474
3.330
2.493
0.88
1.04
0.99
1.02
0.98
0.99
1.00

F
O
NH
I
S
5u
(thousandths)
X : parts per Million : Carbon13
166.290
163.626
141.720
138.318
133.642
130.978
128.275
127.815
125.908
124.816
120.015
109.781
72.063
39.520


O2N
O
NH
I
5v
abundance
X : parts per Million : 1H
0.92
0.91
1.00
4.99
1.02
8.611
8.606
8.252
8.113
8.109
8.092
8.087
7.504
7.494
7.490
7.446
7.438
6.622
6.600
-0.006

O2N
O
NH
I
5v
(thousandths)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
165.085
147.998
140.399
138.349
136.662
133.097
130.098
129.437
129.149
127.070
124.243
119.423
84.216
77.316
77.000
76.684
X : parts per Million : Carbon13

5w
abundance
X : parts per Million : 1H
0.91
1.94
4.11
1.00
3.06
8.608
8.604
8.135
8.131
8.113
8.108
7.334
7.314
7.302
7.282
7.260
6.714
6.692
2.465
-0.005

5w

(thousandths)

166.140
148.010
139.644
139.423
137.967
132.926
130.416
129.783
129.400
127.675
124.541
118.696
79.704
21.527

X : parts per Million : Carbon13

O
NH
N
I

5x

abundance
0.76
1.00
0.99
0.97
4.93
9.958
9.055
9.048
9.044
8.580
8.576
8.560
8.556
7.570
7.564
7.551
7.543
7.535
7.526
7.475
7.464
7.456
7.444
7.260
-0.005
X : parts per Million : 1H

5x

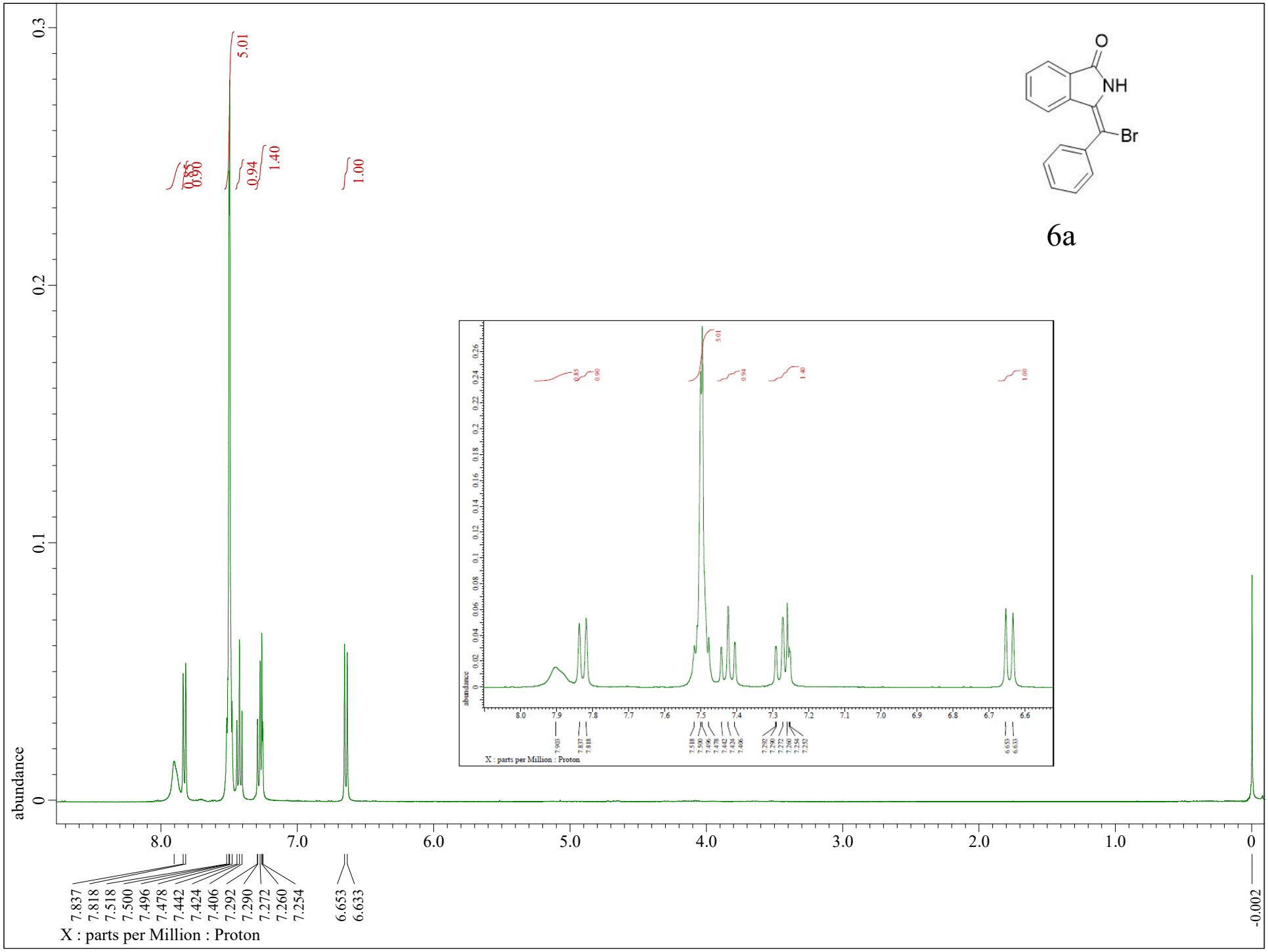
(thousandths)

X : parts per Million : Carbon13

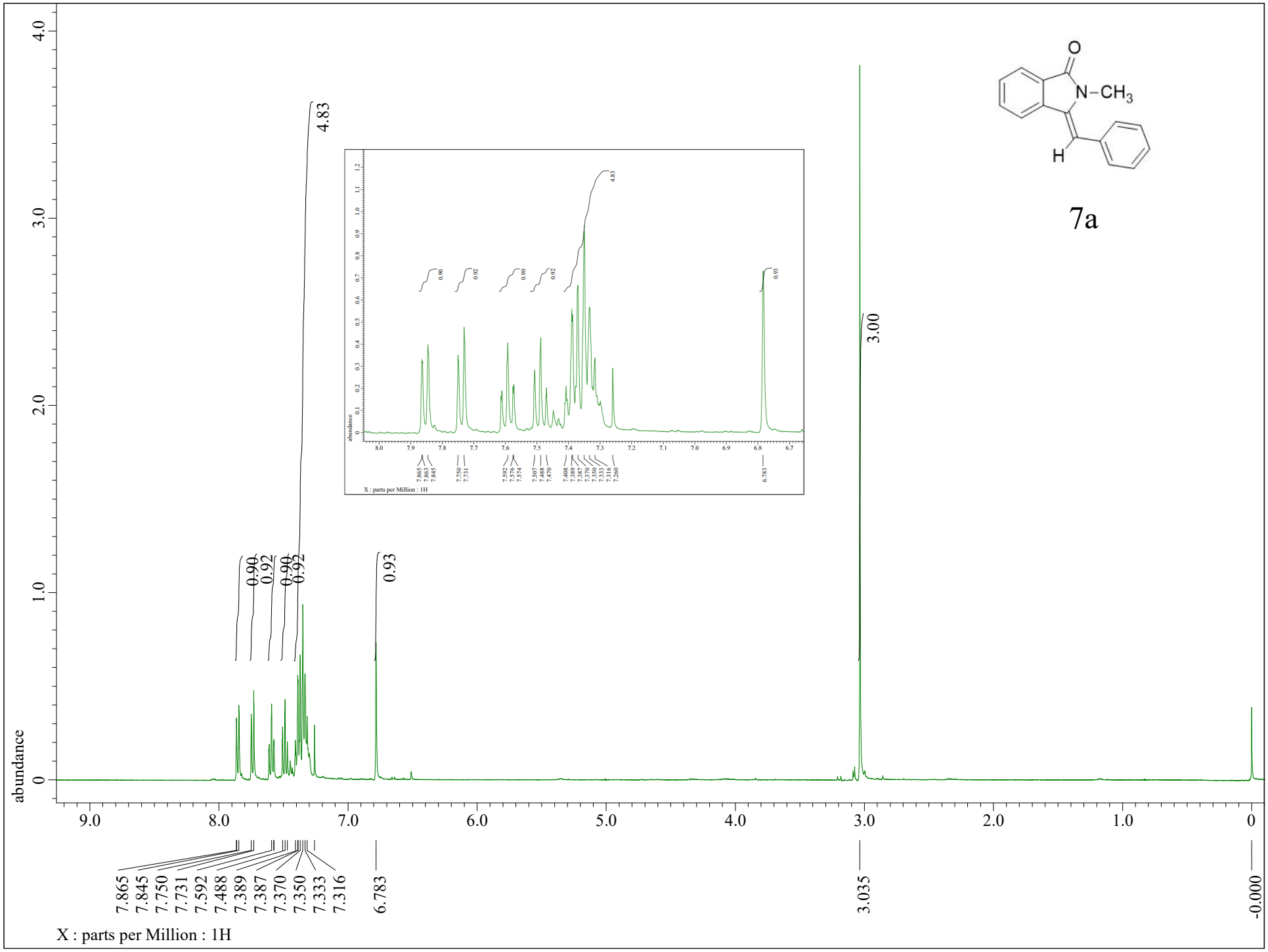
161.872
155.270
152.452
147.719
137.580
135.577
129.511
128.199
122.593
120.494
79.221
39.520

O
NH
N
I
C6H13
5y
(thousandths)
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
0.86
1.00
1.06
1.05
1.89
1.92
2.03
4.12
3.09
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
11.718
9.023
9.018
9.011
9.007
8.615
8.611
8.595
8.591
7.431
7.419
7.411
7.400
7.260
1.509
1.491
1.373
1.364
1.356
1.350
1.333
1.279
1.249
1.236
0.918
0.900
0.883
0.066
X : parts per Million : Proton

O
NH
N
I
C6H13
5y
(thousandths)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
164.096
155.383
153.275
148.281
136.128
121.569
119.824
79.597
77.316
77.000
76.684
38.709
31.415
28.914
28.329
22.521
14.058
X : parts per Million : Carbon13


O
NH
Br
6a
5.01
1.40
0.94
1.00
0.85
0.90
abundance
X : parts per Million : Proton
7.837
7.818
7.518
7.500
7.496
7.478
7.442
7.424
7.406
7.292
7.290
7.272
7.260
7.254
6.653
6.633

O
NH
Br
6a
(thousandths)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.238
137.481
135.095
133.485
132.210
130.993
130.112
129.805
129.278
129.124
123.815
122.761
103.719
77.316
77.000
76.684
X : parts per Million : Carbon13


O
N–CH3
H
7a
4.83
3.00
0.90
0.92
0.90
0.92
0.93
abundance
X : parts per Million : 1H
7.865
7.845
7.750
7.731
7.592
7.488
7.389
7.387
7.370
7.350
7.333
7.316
6.783
3.035
-0.000

O
N–CH3
H
7a
(thousandths)
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.898
137.994
136.125
134.698
131.727
129.513
128.948
128.459
128.066
127.424
123.141
119.202
106.496
77.316
77.000
76.684
30.485
X : parts per Million : Carbon13

O
N
H
CH3
7b
4.88
3.87
3.00
1.00
0.96
0.95
0.97
0.96
abundance
X : parts per Million : 1H
7.960
7.940
7.860
7.841
7.685
7.666
7.647
7.554
7.536
7.518
7.260
7.113
7.110
7.101
7.093
7.082
6.809
6.762
6.740
6.735
6.714
2.193
0.009

O
N
H
CH3

7b

abundance
0
0.1
0.2
0.3
0.4
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
167.960
136.486
135.971
133.693
132.329
130.527
129.030
128.925
127.896
127.676
127.238
127.076
126.780
123.824
119.267
107.949
77.324
77.000
76.685
21.118
X : parts per Million : 13C

8a

O
NH

8a

30.0
20.0
10.0
0
(thousandths)
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
168.916
135.604
134.990
134.243
131.799
129.442
129.279
129.010
128.665
127.736
126.902
125.330
123.586
123.414
105.502
39.520
X : parts per Million : Carbon13

H3CO
H3CO
O
NH
8b
abundance
X : parts per Million : Proton
10.840
9.121
9.117
9.102
9.098
7.958
7.954
7.938
7.935
7.853
7.600
7.594
7.586
7.582
7.568
7.547
7.543
7.134
4.040
4.024
3.330
2.487
0.76
1.07
1.06
1.03
2.02
0.97
3.09
3.10

H3CO
H3CO
O
NH
8b
30.0
20.0
10.0
0
(thousandths)
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
168.465
154.272
150.410
135.163
134.885
129.183
127.544
126.902
125.972
125.464
123.318
121.612
119.916
109.930
104.668
59.971
56.971
39.520
X : parts per Million : Carbon13