AMERICAN UNIVERSITY OF BEIRUT

SYNTHESIS OF NOVEL HETEROCYCLIC COMPOUNDS: ISOINDOLINONE, CINNOLINE AND BENZOTRIAZINE DERIVATIVES

by
FATAT BILAL EL DHAIBI

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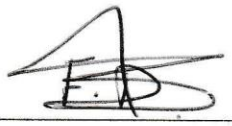

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I owe a deep sense of gratitude to Prof. Ahmad EL Douhaibi for pointing and leading me toward the organic field two years ago, for his constant encouragement and for his continuous believing in me which played a brilliant role in my academic accomplishments in chemistry.

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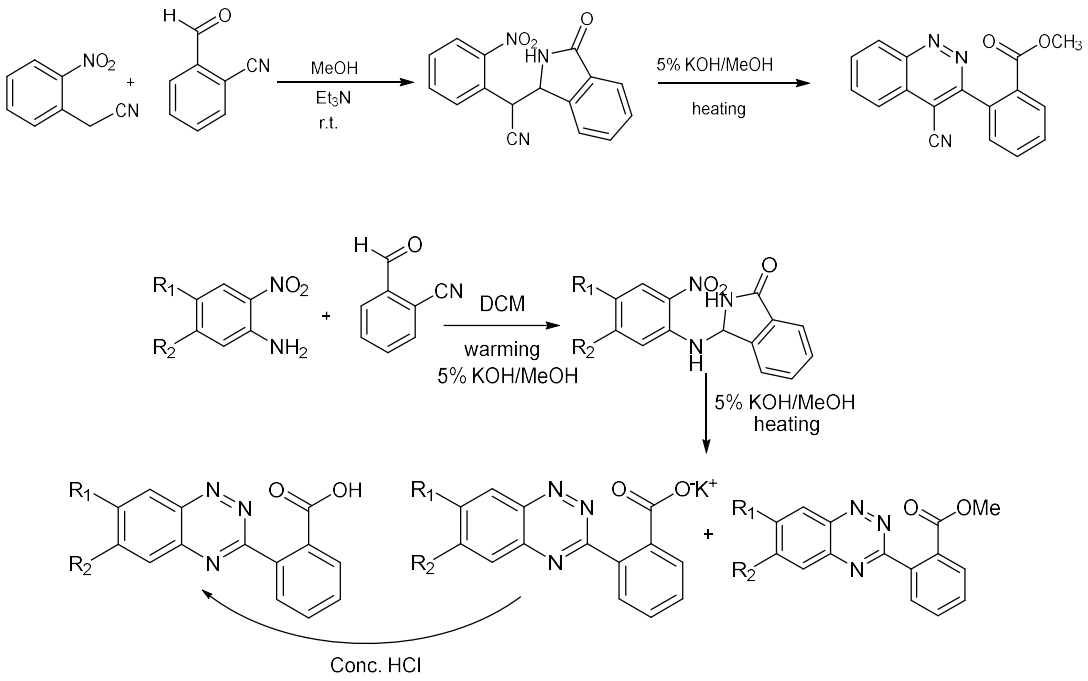
Last but not least, I would like to express my very special and gratefulness to my beloved family. To my superhero, my father Bilal. To my queen, my mother Fatima. To my sisters and brothers. Thank you for always being there for me. Thank you for supporting me during this journey although the difficult situation our country is passing through. Thank you for never giving up on me and helping me finding my way. To my parents: without you, I will not be there today and couldn't achieve my goals. May God bless you and protect you.

ABSTRACT
OF THE THESIS OF

Fatat Bilal EL Dhaibi for Master of Science
Major: Chemistry

Title: Synthesis of Novel Heterocyclic Compounds: Isoindolinone, Cinnoline and Benzotriazine Derivatives

Heterocyclic chemistry of organic compounds made an important progress in the last century. α-phentriazine, also known as benzo-fused analogs or 1,2,4-benzotriazine and cinnoline constitute an important class of the biological active compounds. Due to their wide range of applications in the biological, medicinal, pharmaceutical and therapeutic fields (acting as: anti-tumor, anti-inflammatory, anti-analgesic and anti-malarial drugs) as well as their electronic and photonic properties, and despite all the monumental effort made to enhance the synthesis of these novels, a robust, economic and green synthetic methodology that increase the yield and generate a bulk amount of the desired product is needed. Thus, we worked on developing and accessing an easy and time consumed process yielding our target products 1,2,4-benzotriazines and cinnoline. The aim of our project is to synthesize a series of 1,2,4-benzotriazine derivatives and cinnoline compounds via the intermediate solid isoindolinone.



R^1	R^2
H	H
CH_3	H
CH_3	CH_3
OCH_3	H
H	OCH_3
Cl	H
Cl	Cl
CF_3	H

Indeed, 27 compounds (both the ester and acid products) were synthesized in two steps reactions each. Whereby, after each step, all the structures of the stated compounds were isolated as yellow solid products, and characterized by spectroscopic analysis: IR, ^{1}H NMR, ^{13}C NMR, DEPT.135, UV-visible and melting points. The molecular weight was determined by high resolution mass spectroscopy (HR-MS). Moreover, the X-ray structure of the product: methyl 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl)benzoate was resolved by Dr. James Fettinger and Distinguished Professor Mark Kurth, from the Chemistry Department of the University of California, Davis CA, USA.

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ABBREVIATIONS

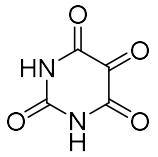
˚C	Degree Celsius
CH_3CN	Acetonitrile
$CDCl_3$	Deuterated chloroform
^{13}C-NMR	^{13}C Carbon nuclear magnetic resonance
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
dq	Doublet of quartet
eq	Equivalent(s)
EtOH	Ethanol
EtoAc	Ethyl acetate
FTIR	Fourier transfer infrared
g	Gram(s)
h	Hour(s)
HR-MS	High resolution- Mass spectroscopy
^{1}H-NMR	Proton nuclear magnetic resonance
m	Multiplet
mg	Milligram(s)
mL	Milliliter(s)
mmol	Millimole(s)
m.p.	Melting point
MeOH	Methanol
MHz	Mega Hertz
NMR	Nuclear magnetic resonance
ppm	Parts per million
ppb	Parts per billion
rt	Room temperature
t	Triplet (1:2:1)
s	Singlet
TLC	Thin layer chromatography
UV-Vis	Ultraviolet-Visible

For my number one supporters…
For my father Bilal and my mother Fatima…
I dedicate my thesis!

CHAPTER I

INTRODUCTION

Synthesis of heterocyclic compounds was firstly performed at the early 1800s.[1,2] It is the chemistry studying the compounds holding heteroatoms such oxygen (O), nitrogen (N) and sulfur (S) as members of their ring, in addition to the carbon skeleton.[1, 3] The first heterocyclic molecule isolated was "alloxan'' **(1)** from uric acid in 1818 by Brugnatelli.[4] In 1832, Dobereiner treated the starch with sulfuric acid, it resulted in "furfural'' **(2).**[5] Friedlander modified the synthesize and isolation procedure of an indigo dye **(3)** in 1906.[1]



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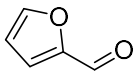

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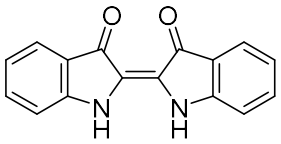
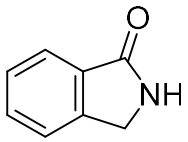


3

Heterocyclic compounds are of a great interest due to their wide range of applications in the pharmaceutical and agrochemical fields,[2, 6] in addition to being efficient sanitizers, antioxidants and corrosion inhibitors.[7]

Three main classes of heterochemical compounds showed an increase in their usage in organic chemistry in the past few years.[7, 8] This introduction will cover the chemistry of isoindolinone **(4)** cinnoline **(5)** and 1,2,4-benzotriazine **(6).** They are relatively stable aromatics heterocycles systems that can be synthesized through multiple synthetic step reactions.



Isoindolinone

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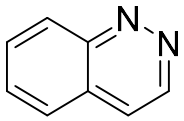

Cinnoline

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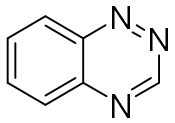
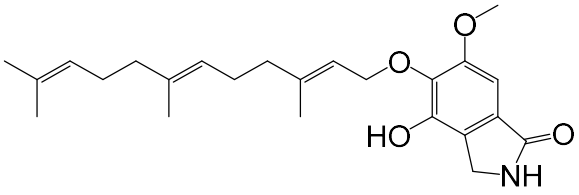


1,2,4-Benzotriazine

6

A. Isoindolinone

Isoindolinone also known as benzo-fused pyrrolidin-2-one compound showed a widespread and increasing interest over the past few decades.[9] This is because of its skeleton holding the core structure of a large number of bioactive natural products such as aspernidine A **(7)** acting as anti-virus H_1N_1,[10] pestalachloride A **(8)**[10] and lennoxamine **(9)**.[11] Others, are isolated from marine sources, as example: Aspochalasin A (**10)** (Gram-positive bacterial Inhibitions) and Aspochalasin B (**11)** (anti-biotic and cytotoxic towards human leukemic HL-60 cells).[12] Some synthetic isoindolinone products like pazinaclone **(12)**[10, 13] and pagoclone **(13)**[10, 14] expressed drug activity toward the treatment of diseases.



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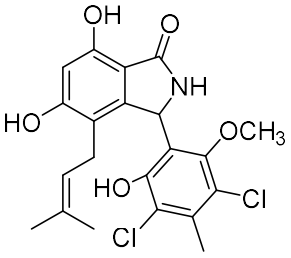

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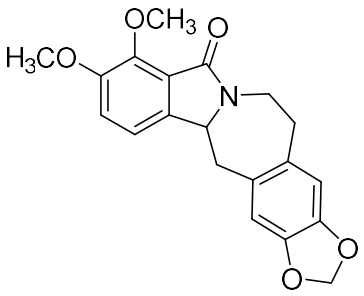

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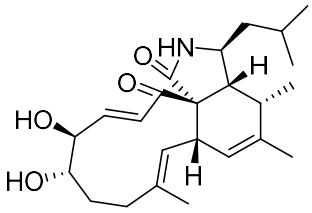

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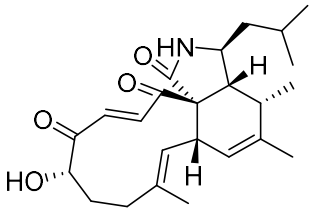

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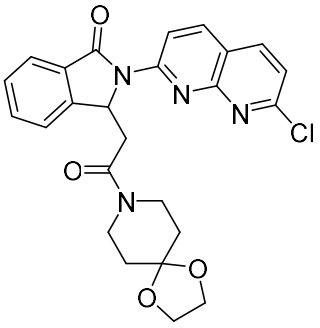

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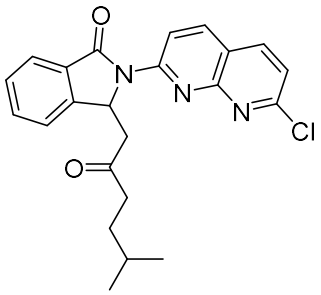
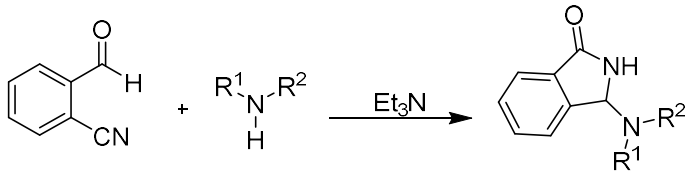


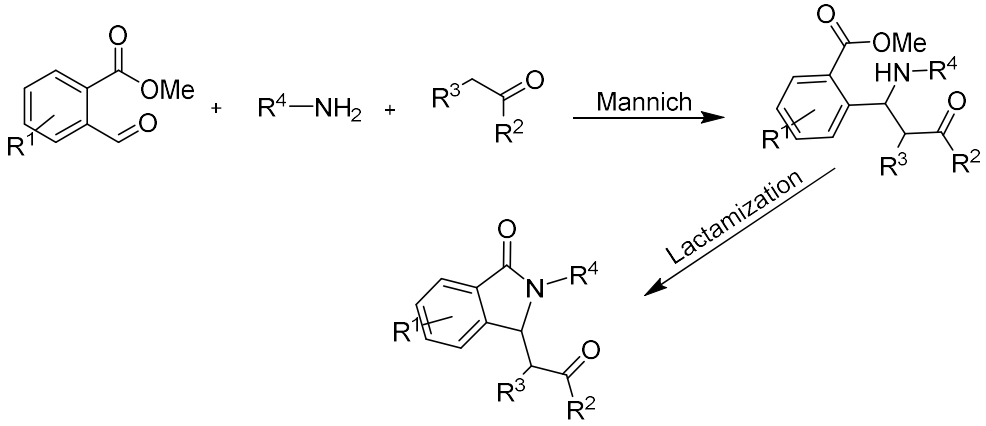
13

Although the synthesis of 3-(*N*- substituted amino) isoindolin-1-one began a century ago,[9] chemists manage to develop some notable reactions in this area. Researchers R. Sato, T. Senzaki, T. Goto and M. Saito synthesized the isoindolinone from 2-cyanobenzaldehyde and amine through a nucleophilic addition reaction in 1984 (Scheme 1).[15]



Scheme 1: Synthesis of isoindolinone by Sato *et al.*[15]

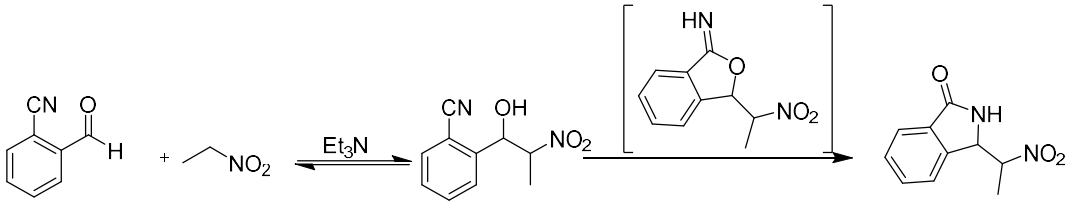
Duan *et al*. described a synthetic procedure via the cornerstone coupling reaction of synthetic organic chemistry of nitrogenous compounds: Mannich reaction described after the chemist Mannich in 1912 followed by a lactamization step as described in Scheme 2.[16] This reaction is a nucleophilic addition of a primary or secondary amine to a carbonyl functional group, followed by a dehydration to yield a Schiff base. This latter will be the electrophile, and will react in an electrophilic addition with the compound having an acidic proton to become an enol in the second step. Mannich reaction can be considered to be a condensation reaction.



Scheme 2: Synthesis of Isoindolinone via a Mannich-lactamization cascade reaction.[16]

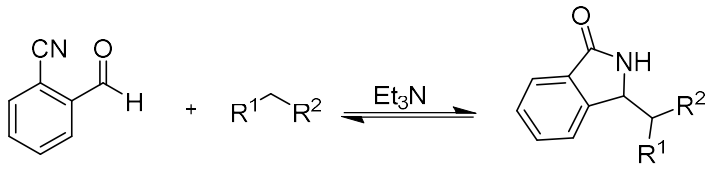
Another important reaction has been described by Ramström et al. (Angelin, M.; Rahm, M.; Fischer, A.; Brinck, T.; Ramstrom) in 2008: the tandem Nitro-aldol/Cyclization reaction.[14] The research group succeed in demonstrating that this

reaction occurs via a tandem aldol addition/cyclization/rearrangement and finalized by the aza-Micheal mechanism (Scheme 3).[17-19]



Scheme 3: Synthesis of 3-nitrosubstituted isoindolinone via Ramström mechanism.[14, 17]

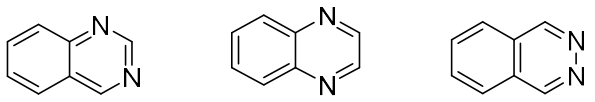
Three years later, Massa's group (Di Mola, A.; Palombi, L.; Massa) derived the Ramström mechanism to cover the 1,3-dicarbonyl compounds (Scheme 4).[14, 20]



Scheme 4: Massa *et al.* reaction.[14]

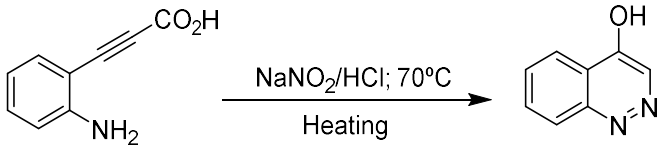
B. Cinnoline

Cinnoline **(5)** also known as benzo [c]-1,2-diaazine, belong to the diazanaphthalene family as 1,2-diazanaphtalene.[21] It consists of isomers of general formula $C_8H_6N_2$ that only differ by the position of the two nitrogen atoms in the cycle. As example: quinazoline (**14)** quinoxaline (**15)** and phtalazine **(16).**[21]



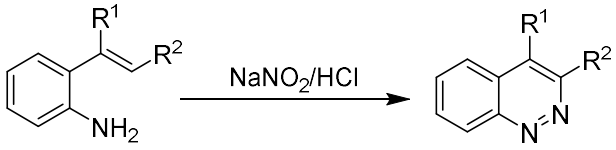
14 **15** **16**

Cinnoline was first synthesized by Von Richter in 1883 through the reaction shown in Scheme 5.[22]



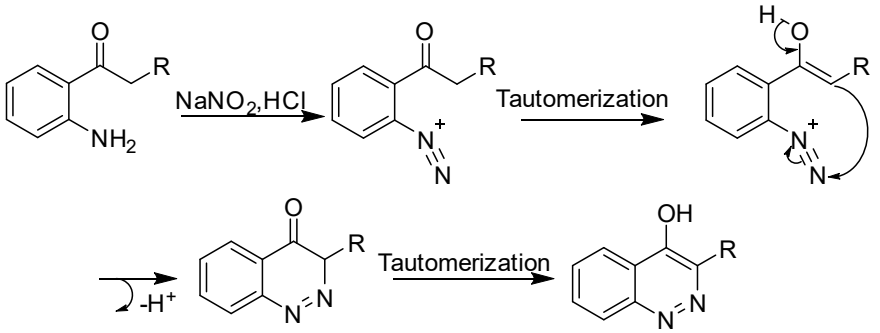
Scheme 5: Von Richter reaction.[22]

One year later, in 1884, a classic organic reaction: Widman-Stoermer reaction was reported and extended in 1909 by Stoermer *et al*. (Scheme 6).[23]



Scheme 6: Stoermer *et al*. reaction.[23]

After a short interval of time, Borsche-Koelsch cinnoline synthesis reaction had been invoked by Borsche in 1941 [24] and Koelsch in 1943 (Scheme7).[25]



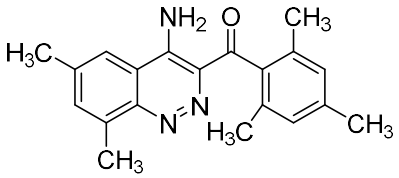
Scheme 7: Borsche-Koelsch reaction.[25]

Due to the wide range of applications of cinnoline in medicinal field, as their incredible biological properties and the structure activity relationship,[26, 27] researcher's interest in studying and improving the derivatives of these compounds have been through a noteworthy progress. It is important to mention that cinnoline and its derivatives are artificial molecules and cannot be found in nature.[21]

Old studies showed that cinnoline itself is cytotoxic and has an antibacterial effect toward Escherichia Coli **(**Figure.1).[21]

Figure 1: Escherichia Coli Bacteria

Cinnoline Compounds were reported as anticancer drug like (4-amino-6,8-dimethylcinnolin-3-yl)(mesityl)methanone **(17)**. Others, showed activity toward the central nervous system for treating neurological disorders: 4-amino-8-butyl-*N*-(cyclopropylmethyl)cinnoline-3-carboxamide **(18).**[21]



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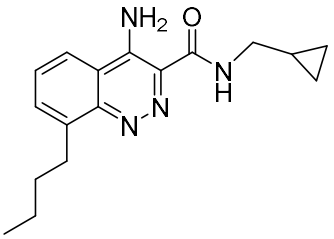

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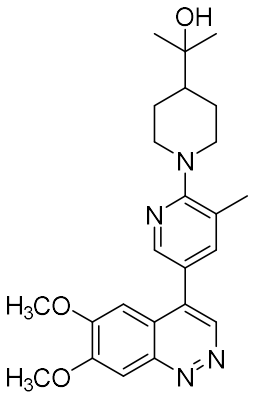
2-(1-(5-(6,7-Dimethoxycinnolin-4-yl)-3-methylpyridin-2-yl)piperidin-4-yl)propan-2-ol **(19)** and (1-(5-(6,7-dimethoxycinnolin-4-yl)-3-methylpyridin-2-yl)piperidin-4-yl)(pyridin-3-yl)methanol **(20)** are used for the treatment of schizophrenia (mental disorder disease) as phosphodiesterase10A (PDE10A) inhibitor.[20]



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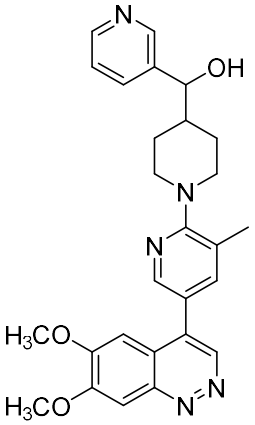

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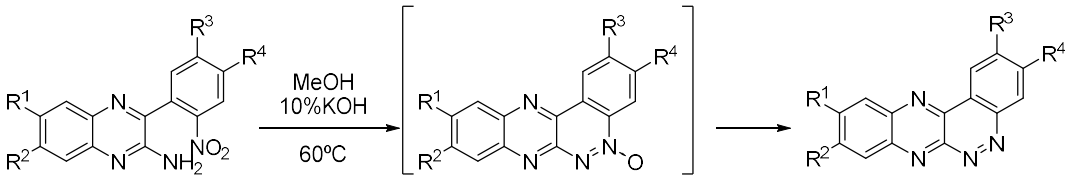
Multiples of quinaxolinocinnoline derivatives were synthesized by Mr. Tharallah Shocker and Costas and Bonnie Issidorides Professor Makhluf J.Haddadin in 2010 (Scheme 8).[28, 29]

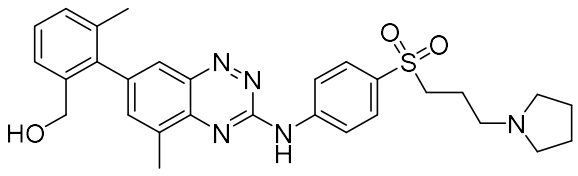


Scheme 8: Synthesis of cinnoline by T.Shocker and M.J. Haddadin.[29]

C. 1,2,4-Benzotriazine

Benzotriazine represents a vital class of nitrogen-containing compounds. The interest in these heterocycles is growing specially in the medical field.[30] Statistics reported that these compounds are among the top ten selling drugs in the world.[31] Two isomers of benzotriazine exist in nature. In fact, 1,2,4-benzotriazines are more abundant than 1,2,3 isomers.[32] Despite that the synthesis of the first *N*-fused benzotriazine was performed by Bischler at the end of the 19th century,[33] organic chemists continue on developing new reactions and methods for preparing and making of these novels.

Like isoindolinone and cinnoline; benzotriazine showed numerous biological activities in the medical and pharmaceutical domains, most importantly, their activities toward tumor.[33-35] Anticancer behavior of 1,2,4-Benzotriazine was recalled by Cascioferro *et.al*.[36] 3-Amino-1,2,4-benzotriazine derivatives **(21), (22)** are anti-tumor compounds. [34, 35]



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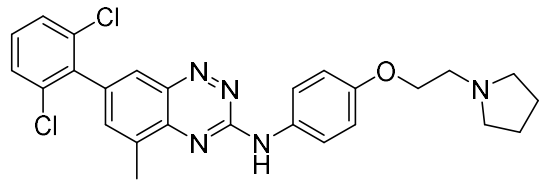
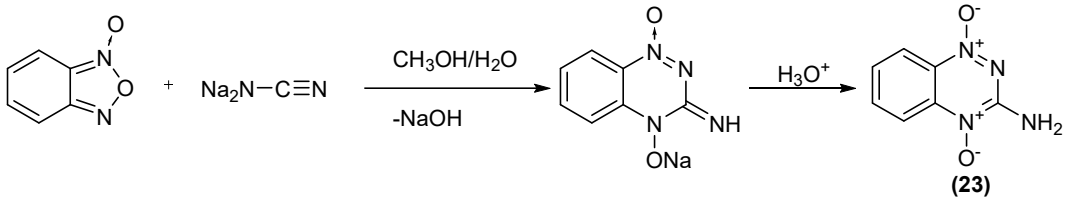


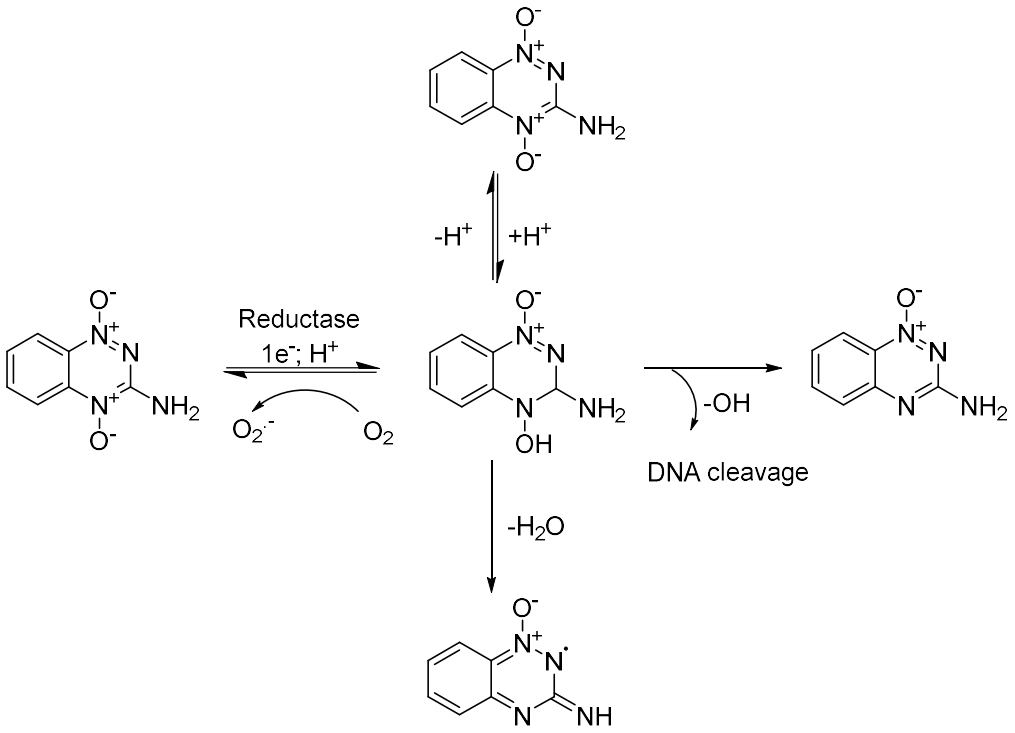
22

Tirapazamine (TPZ) known as 3-amino-1,2,4-benzotriazine 1,4-dioxide **(23)** which can be synthesized through the Beirut reaction (Scheme 9),[37, 38] was the first drug that demonstrated a high efficacy in selective potentiation of cisplatin in randomized phase III trials with non-small cell lung cancer.[39, 40] It is also known to be active toward head, neck, and gynecological cancer.[40]



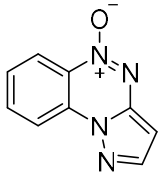
Scheme 9: Synthesis of Tirapazamine through Beirut reaction.[38]

The mechanism of tirapazamine action is explained in Scheme 10.[30] At low concentration of oxygen, TPZ is converted into a toxic radical. In hypoxic region, the tumor cells which are resistant to the radiotherapy and anticancer drugs, have been treated by a combination of TPZ with conventional anticancer. In this case, tirapazamine is known to be a bio-reductive drug.[41]



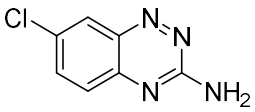
Scheme 10: Presumed Tirapazamine mechanism.[30]

In addition, Ciciani's research group reported that analogues of pyrazole[5,1-c][1,2,4] benzotriazine *N*-oxide **(24)** act as cytotoxic agent in hypoxic and normoxic conditions.[41]



24

The 1,2,4-Benzotriazines also act as antimicrobial,[42, 43] Kinase inhibitor,[41] anti-malarial **(25), (26)**[44, 45] and anti-inflammatory **(27)**,[46] antibacterial agents.[44] Some could be found to act as dyes.[41]



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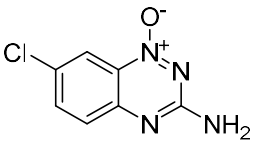

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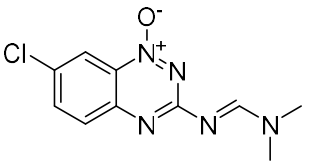


27

Taking into consideration the wide range applications and pharmaceutical potential of these novel compounds, the synthesis of these compounds have progressed noticeably year after year, however, it was important to develop synthetic techniques economical and highly efficient.

CHAPTER II

RESULTS AND DISCUSSION

Taking into consideration the significant importance of the novels isoindolinone, cinnoline and 1,2,4-benzotriazine systems summarized in the introduction, we have been working on synthesizing these compounds while assessing and modifying the reaction conditions. We succeed in isolating the essential entity in our work: Isoindolinone as pure yellow solid compounds. All the NMR spectra of the isoindolinones are obtained as expected. The preparation of the isoindolinones intermediate are done through a nucleophilic addition mechanism in basic conditions.[15, 19] Two different mechanisms were envisaged to synthesize the isoindolinone compounds.

A. Synthesis of 2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile

The synthesis of 3-substituted isoindolin-1-one **31** was done through a nucleophilic addition reaction followed by a cyclization and a rearrangement process. (Figure 2)[17]

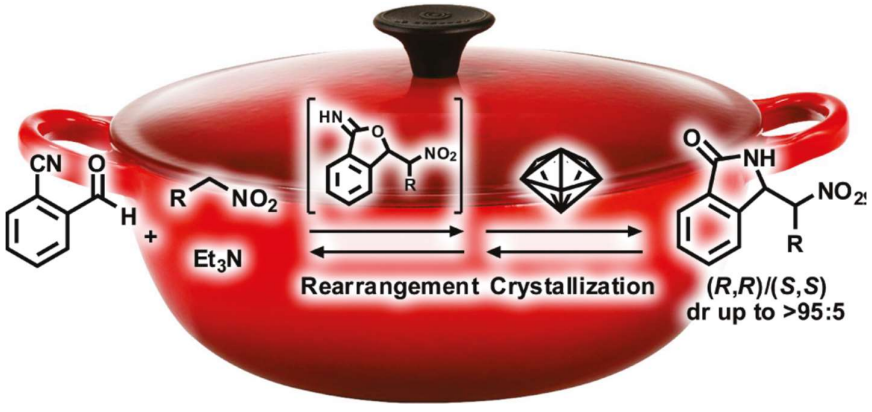
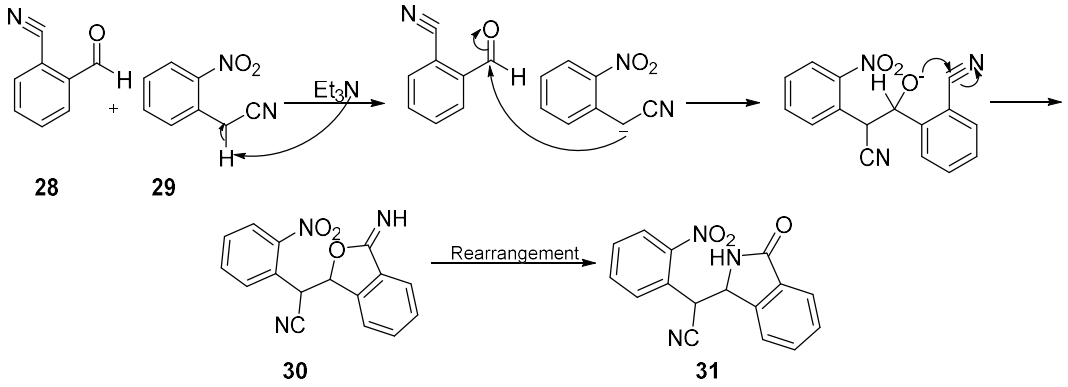


Figure 2: Isoindolinone synthesize via Ramström reaction.[17]

One mmol equivalent of 2-(2-nitrophenyl) acetonitrile **(29)** was added to 1.2 mmol equivalent of 2-cyanobenzaldehyde **(28)** in 3 mL of methanol in the presence of 0.4 mL of triethylamine Et_3N at room temperature for 2 minutes. Et_3N is mandatory for the initiation of the reaction. It is the source for the generation of the nucleophilic species by abstracting the acidic proton at the α-position of the nitrile group, yielding the attack on the carbonyl function of the cyanobenzaldehyde. Intermediate **30** was then formed (Scheme 11). Using strong bases such as HO^- may lead to some undesired side reactions. The amount of the solvent used should be minimized to improve the yield of the reaction. Replacing methanol by ethyl acetate or chlorinated organic solvents prevent the reaction from proceeding.



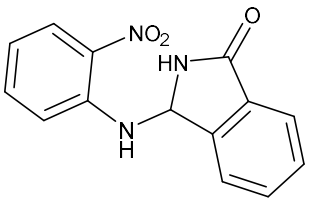
Scheme 11: Synthesis of isoindolinone **31** through carbonyl addition mechanism.

According to the literature, the strong peak at 1703 cm^{-1} indicated the formation of the isoindolinone ring compared to the carbonyl function of 2-cyanobenzaldehyde **(29)** that showed at 1693 cm^{-1}.[15] CN stretching was observed in the IR spectrum as well as the nitro group at 1532 and 1358 cm^{-1}. Since it is an asymmetric molecule holding two chiral carbon centers, it was expected to get 4 stereoisomers of the product,[17] however, NMR spectrum of the product indicates only one compound.

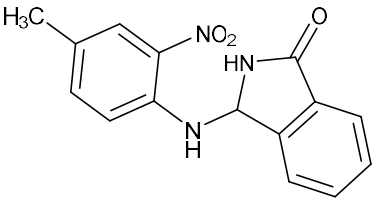
The ^{1}H NMR spectrum results in eight aromatic protons which is compatible with the number of benzylic protons of the predicted product. A broad N-H peak shows at 7.48 ppm, and two neighboring hydrogen of the chiral centers coupling together at 5.22 and 5.51 ppm. ^{13}C NMR of the compound shows sixteen carbons in total. The carbon of the nitrile group showed at 116 ppm. This isoindolinone is isolated as pure white powder solid by suction filtration, and it is sensitive to the light, it became a dark brown solid. This might be explained by the reaction of the oxygen, of nitro group, with the benzylic proton of the cyano group. This reaction holds well with 2-nitrobenzaldehyde yielding 2-nitrosobenzoic acid, and many other reactions.

B. Synthesis of 3-(*N*-substituted amino) isoindolin-1-ones

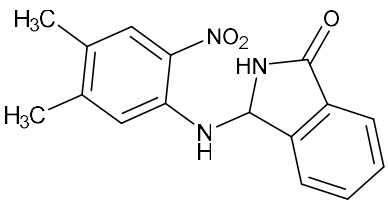
As part A, all the prepared isoindolinones were characterized by ^{1}H NMR,^{13}C NMR, ^{13}C NMR DEPT 135, FTIR and HR-MS. Melting points of the prepared compounds were also recorded.



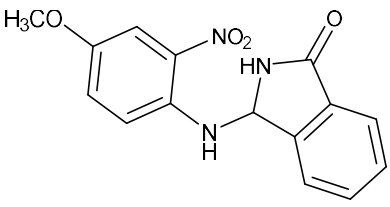
34a



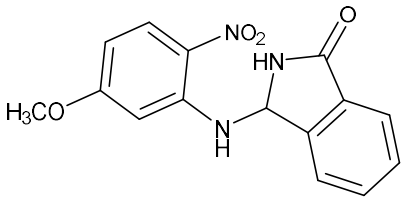
34b



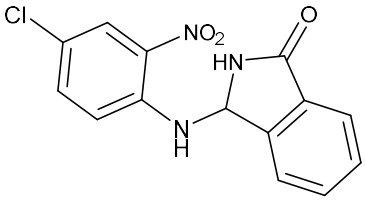
34c



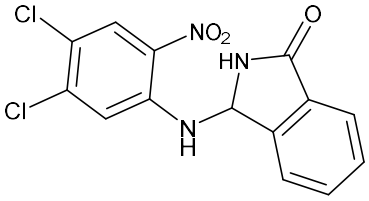
34d



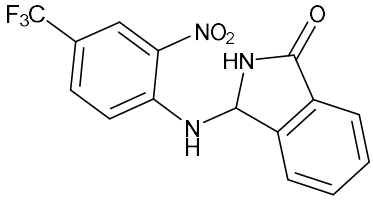
34e



34f

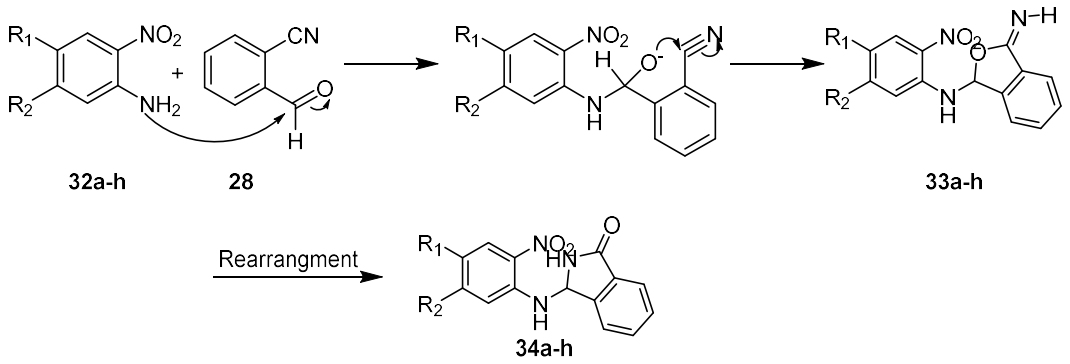


34g



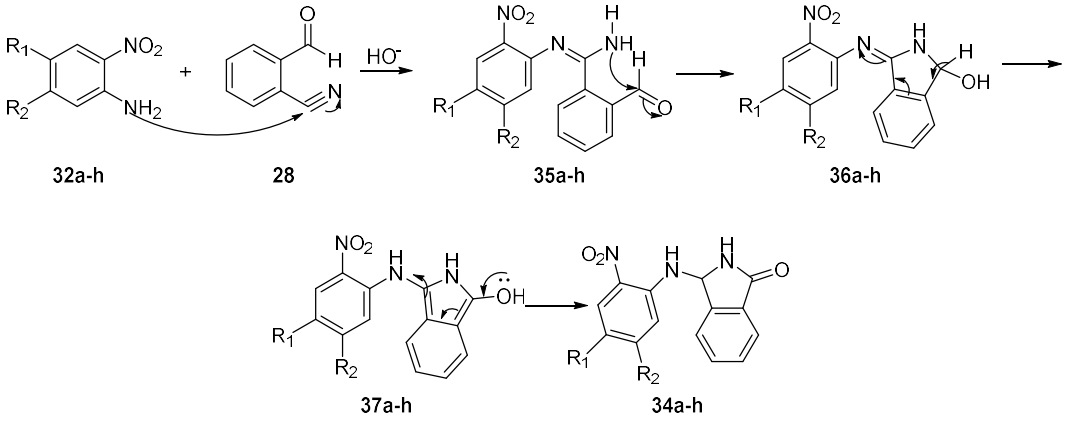
34h

Isoindolinones **34a-h** were synthesized through a nucleophilic addition reaction between the aldehyde of the 2-cyanobenzaldehyde **(28)** and the amine function of the 2-nitroaniline derivatives **32a-h.** Two possible mechanisms may exist for this synthesis of the isoindolinones series products. The first is as reported in the literature, the cyclization of the formyl and cyano group in 2-cyanobenzaldehyde with the amines nucleophile.[15] The lone pair of the nitrogen attacked the carbonyl entity. The latter will then attack the cyano group and form the first cyclic intermediate product **33a-h**. A simple rearrangement occurs to give the lactam isoindolinone (Scheme 12).



Scheme 12: Synthesis of isoindolinone **34a-h** through carbonyl addition reaction.

However, based on the results we got in the lab, we suggest a second mechanism more compatible with our observations. The attack is occurring directly on the cyano instead of the aldehyde entity. This is explained by the formation of the red colored intermediate **36a-h** that appears for a while accompanied by the release of the heat just before the formation of the paste product (Scheme 13). Both mechanisms result in a single pure stable product.

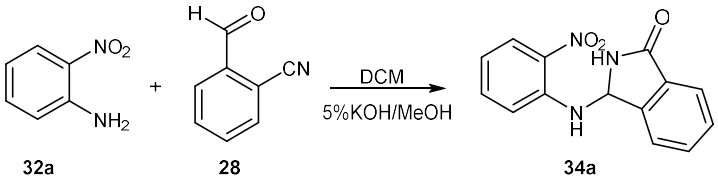


Scheme 13: Synthesis of isoindolinone **34a-h** through nitrile addition mechanism.

The reactions of 2-cyanobenzaldehyde with 2-nitroaniline derivatives are warmed for 1 minutes to dissolve the starting material in 1 mL of dichloromethane (DCM) and then cooled down to room temperature. Hence, 0.3 mL of 5% KOH in MeOH is added while stirring. An exothermic reaction accompanied with a red color

intermediate formed instantly and disappeared just before the formation of the paste (isoindolinone product). Reactions did not proceed when replacing the KOH by Et_3N, which means that the strong base HO^- is the key requisite that drive these difficult reactions to completion. The amount of the base added should be monitored, if HO^- is added in excess, it decreased the yield of the target product. Although, these reactions are of high yield, however it is slightly dependent on whether the substituent is an electron withdrawing or electron donating (releasing) and on its position. The amount of the solvent used should be minimized in order to improve the yield and decrease the solubility of the desired product in the solvent. The carbonyl function of the isoindolinone rings was detected by IR at around 1700-1715 cm^{-1}, almost at the same range (1720 cm^{-1}) as determined by R. Sato, T. Senzaki, T. Goto and M. Saito.[15]

1. Synthesis of 3-((nitrophenyl) amino) isoindolin-1-one (34a)

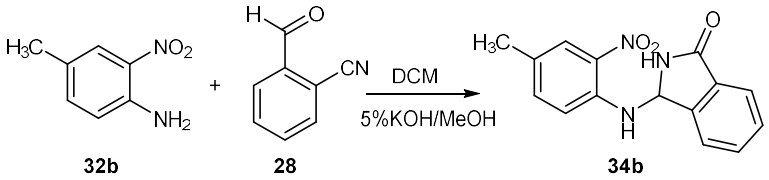


32a 28 34a

A yellow product **34a** is obtained from the reaction of 2-nitroaniline **(32a)** (1 mmol) and 2-cyanobenzaldehyde **(28)** (2.5 mmol) in 1 mL DCM. It yields a 79% product comparing to the same reaction in 1 mL DMF (46%). The IR spectrum showed the carbonyl C=O peak at 1714 cm^{-1} as strong, marking the presence of the isoindolinone function. ^1H NMR showed the isoindolinone NH proton as singlet at 9.28 ppm. ^{13}C NMR showed a peak at 169 ppm corresponding to the C=O, and 14 carbons in

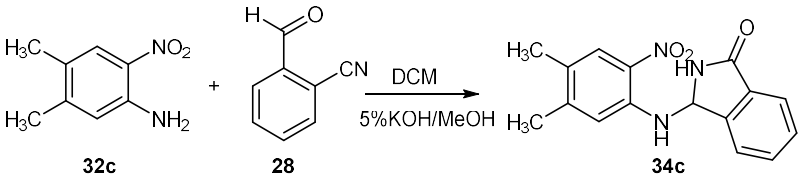
total. Finally, the ^{13}C NMR DEPT 135 resulted in nine peaks corresponding to nine different CH groups.

2. Synthesis of 3-((4-methyl-2-nitrophenyl) amino) isoindolin-1-one (34b)



The compound 3-((4-methyl-2-nitrophenyl) amino) isoindolin-1-one **34b** is a yellow product obtained from the reaction of 4-methyl-2-nitroaniline **(32b)** (1 mmol) and 2-cyanobenzaldehyde **(28)** (2.5 mmol) in 1 mL DCM. It yields a 70% product. This same reaction has only 54% in DMF product. The IR spectrum C=O peak at 1709 cm^{-1} is very strong, and confirms the presence of the carbonyl function of the isoindolinone. ^{1}H NMR showed the singlet isoindolinone proton NH at 9.26 ppm, and three C-H singlet protons of the methyl group are at 2.26 ppm. The total number of carbons in ^{13}C spectrum are 15 corresponding to the desired product. The 169 ppm peak correspond to the C=O. Methyl carbon appeared at 19 ppm. ^{13}C NMR DEPT 135 resulted in nine peaks corresponding to nine different CH groups.

3. Synthesis of 3-((4.5-dimethyl-2-nitrophenyl) amino) isoindolin-1-one (34c)



Reacting 4.5-dimethyl-2-nitroaniline (**32c)** and 2-cyanobenzaldehyde (**28)** in 1 mL DCM will yield a dark yellow product: 3-((4.5-dimethyl-2-nitrophenyl) amino) isoindolin-1-one **(34c).** The reaction is first tried in DCM by varying the amount of starting materials. The results are shown in Table 1.

Table 1: The experimental yields of **34c** as a factor of the number of mole equivalent in DCM.

Equivalents of **28** 2-cyanobenzaldehyde (mmol)	Equivalents of **32c** 4,5-dimethyl-2-nitroaniline (mmol)	% yield of **34c**
1.0	1.2	9
1.0	1.5	24
1.0	1.8	29
1.0	2.0	53
1.0	2.2	66
1.0	2.5	77
1.0	3.0	60

4,5-Dimethyl-2-nitroaniline and 2-cyanobenzaldehyde 1:2.5 ratio was selected after comparing the yields. In order to study the effect of the solvent, the same reaction was performed in 5 different solvents: DCM, ethyl acetate (EtOAc), methanol (MeOH), chloroform ($CHCl_3$) and dimethylformamide (DMF). Results are shown in Table 2.

Table 2: The experimental yields of **34c** as a factor of solvent.

Solvent	Equivalents of **28** (mmol)	Equivalents of **32c** (mmol)	% Yield of **34c**
DCM	1.0	2.5	76
EtOAc	1.0	2.5	39
MeOH	1.0	2.5	36
$CHCl_3$	1.0	2.5	42
DMF	1.0	2.5	65

While it was expected theoretically to get higher yield in DMF than DCM, the experimental results showed the contrary. And thus the best solvent for our reactions was DCM. However, to highlight the amount of the solvent used, three same reactions were initiated in three different volume of DCM; 1,5 and 10 mL. Results are shown in Table 3.

Table 3: The experimental yields of **34c** vs volume of DCM.

Volume of DCM (ml)	Equivalents of **28** (mmol)	Equivalents of **32c** (mmol)	% yield of **34c**
1	1.0	2.5	78
3	1.0	2.5	62
5	1.0	2.5	48

As the volume of the solvent increases, the solubility of the product increases and the yield of the reaction decreases. Finally, to spot the importance of the amount of the base used, three different concentrations of KOH/MeOH were added to the same reaction condition, (Table 4).

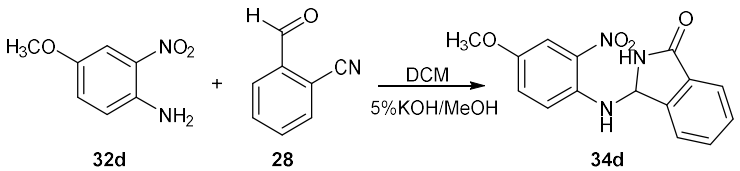
Table 4: The experimental yields of **34c** vs KOH concentration.

KOH/MeOH %	Equivalents of **28** (mmol)	Equivalents of **32c** (mmol)	% Yield of **34c**
2.5	1.0	2.5	37
5	1.0	2.5	77
10	1.0	2.5	38

Increasing or decreasing the concentration of the KOH in methanol solution decreased the yield of the product. Replacing KOH by Et_3N stopped the reaction from proceeding and thus spotting the importance of the amount of KOH.

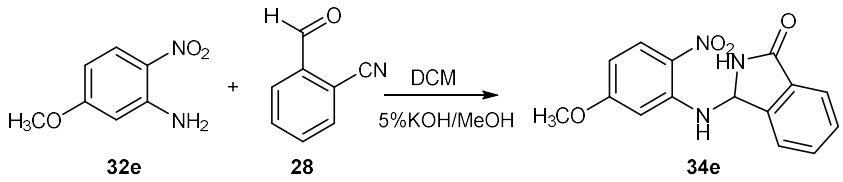
A yield of 77% was the maximum yield obtained in optimal conditions of the reaction in DCM while only 65% was isolated in DMF. Very strong peak appear in the IR spectrum at 1707 cm^{-1} due to the C=O bond. Singlet isoindolinone NH proton is observed at 9.31 ppm while the six singlets C-H protons of the two methyl groups are at 2.19 and 2.26 ppm respectively in the ^{1}H NMR spectrum. 16 carbons are shown in the ^{13}C MNR corresponding to the total number of carbon in the desired product. The peaks at 169 ppm corresponds to the carbonyl group. The peaks at 18 and 20 ppm correspond to the two methyl groups at 4 and 5 positions. The ^{13}C NMR DEPT 135 resulted in nine peaks corresponding to nine different CH groups.

4. Synthesis of 3-((4-methoxy-2-nitrophenyl) amino) isoindolin-1-one (34d)



The orange, 3-((4-methoxy-2-nitrophenyl) amino) isoindolin-1-one **(34d)** product is the result of reacting 4-methoxy-2-nitroaniline **(32d)** (1 mmol) with the 2-cyanobenzaldehyde (**28)** (2.5 mmol) in 1 ml DCM. The yield of this reaction was 81% which was more than 55% when using DMF. The C=O peak was observed at 1707 cm^{-1} in the IR spectrum. Singlet isoindolinone NH proton shift is obtained at 9.24 ppm in the ^{1}H NMR spectrum. The three hydrogens of the methoxy group para to the amine appears at 3.77 ppm as singlets. The ^{13}C NMR DEPT 135 spectrum showed nine carbon peaks corresponding to nine different CH group. Adding to that, ^{13}C NMR approved the number of carbons in the compound to be 15, where the C=O shown at 169 ppm and the methoxy carbon at 56 ppm.

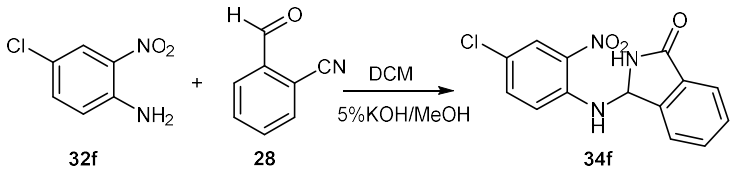
5. Synthesis of 3-((5-methoxy-2-nitrophenyl) amino) isoindolin-1-one (34e)



Similarly, to **34d**, the yellow pale product **34e**, is obtained from the reaction of 5-methoxy-2-nitroaniline (**32e)** (2.5 mmol) with 2-cyanobenzaldehyde (**28)** (1 mmol) in 1 mL of DCM. It has a greater yield 89% while it only shows 61 % in DMF. The C=O peak is strong and is observed at 1708 cm^{-1} in the IR spectrum. In the ^{1}H NMR spectrum, the isoindolinone NH proton is obtained at 9.36 ppm as singlet. The three hydrogens of the methoxy group para to the nitro group are singlets and appear at 3.83 ppm. The ^{13}C NMR DEPT 135 spectrum showed nine carbon peaks corresponding to nine different CH groups. And finally, the ^{13}C NMR showed the C=O peak at 169 ppm

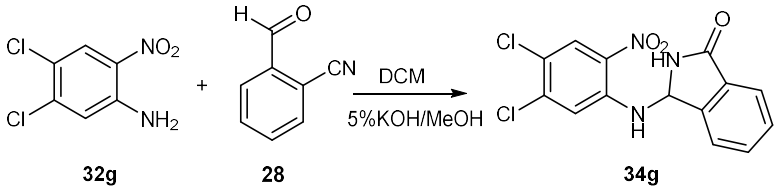
and the methoxy carbon at 56 ppm. It also confirmed the total number of carbons in the compound to be 15.

6. Synthesis of 3-((4-chloro-2-nitrophenyl) amino) isoindolin-1-one (34f)



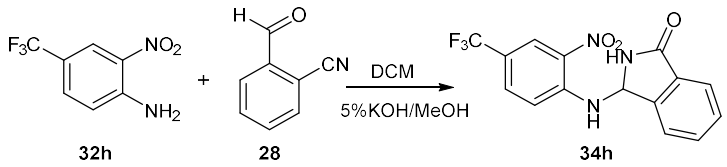
Likewise, **34b, 34c** and **34f** products are also yellow colored solid. They were produced from the reaction of 4-chloro-2-nitroaniline (**32f)** (1 mmol) and 2-cyanobenzaldehyde (**28)** (2.5 mmol equivalent) in 1 mL DCM. The yield of this latter reaction is 79% while only 52% in DMF. The carbonyl C=O group is strong and is detected at 1708 cm^{-1} in the IR spectra. In the ^{1}H NMR, the isoindolinone NH singlet proton appears at 9.25 ppm. 14 carbons were present in the ^{13}C NMR spectrum where the carbonyl carbon shown at 169 ppm. And finally, the ^{13}C NMR DEPT 135 resulted in eight peaks corresponding to eight different CH groups.

7. Synthesis of 3-((4.5-dichloro-2-nitrophenyl) amino) isoindolin-1-one (34g)



Compound 3-((4.5-dichloro-2-nitrophenyl) amino) isoindolin-1-one (**34g)** is yellow as well. It results in 87% from the reaction of 4.5-dichloro-2-nitroaniline (**32g)** (1 mmol) and 2-cyanobenzaldehyde (**28)** (2.5 mmol) in 1 mL DCM while the yield was 60% in DMF. The strong C=O peak appears at 1713 cm^{-1} in the IR spectrum. ^{1}H NMR spectrum showed the NH singlet proton at 9.32 ppm and 9 protons in total. The carbonyl carbon shows at 169.32 ppm, and a total of 14 carbons are detected in the ^{13}C NMR. Seven peaks corresponding to seven different CH groups are present in the ^{13}C NMR DEPT 135 as expected.

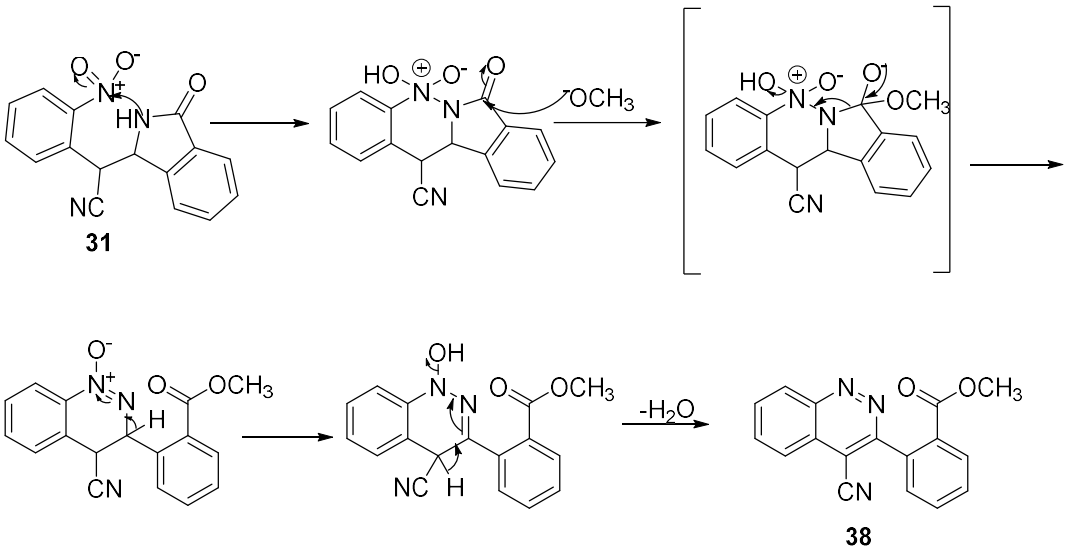
8. Synthesis of 3-((2-nitro-4-(trifluoromethyl) phenyl) amino) isoindolin-1-one (34h)



The last product in this series reaction is the 3-((2-nitro-4-(trifluoromethyl) phenyl) amino) isoindolin-1-one **34h.** It is a light yellow solid product of the reaction between 2-nitro-4-(trifluoromethyl) aniline (**32h)** (1 mmol) and 2-cyanobenzaldehyde (**28)** (2.5 mmol) in 1 mL DCM. The yield of this reaction is low compared to the remaining derivatives. It is only 38% in DCM and 10% in DMF. The IR result showed the carbonyl C=O peak at 1709 cm^{-1}. ^{1}H NMR shows the singlet NH isoindolinone proton at 9.28 ppm. The C=O appeared at 169 ppm in the ^{13}C NMR spectrum. ^{13}C NMR DEPT 135 resulted in nine peaks corresponding to nine different CH groups.

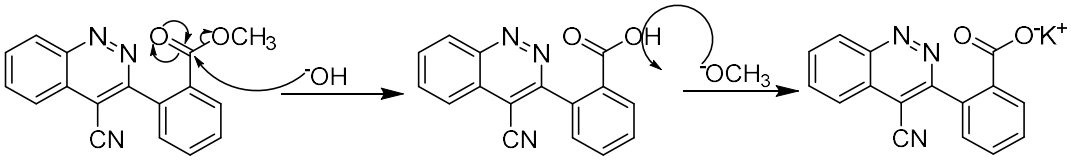
C. Synthesis of Cinnoline

Cinnoline is the result of heating 2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile **31** in basic solution of 5% KOH in MeOH at 65 ºC. It was expected to get the cinnoline ester product: methyl 2-(4-cyanocinnolin-3-yl) benzoate **38**. However, TLC showed the presence of two products; the second is much more polar than the first. After acidifying the solution with HCl, we were able to identify both products. The corresponded carboxylic acid: 2-(4-cyanocinnolin-3-yl) benzoic acid (**39)** of the cinnoline ester is the co-product of the reaction. Upon heating the reaction, the ester is being formed through the decomposition of the isoindolinone according to the mechanism illustrated in Scheme 14.



Scheme 14: Synthesis of cinnoline ester **38** through the formation from isoindolinone.

This ester **(38)** is hydrolyzed to the carboxylate salt of the acid: potassium 2-(4-cyanocinnolin-3-yl) benzoate **(39)** (Scheme 15)



Scheme 15: Hydrolysis of the cinnoline ester **38**.

Heating the reaction for 15 min was enough to isolate the crude ester with traces of acid. But keeping heating for longer time causes the ester to hydrolyze faster and thus increasing the yield of the acid and lowering the one of the ester. Results are shown in Table 5.

Table 5: The isolated % yields of the Cinnoline ester and acid products.

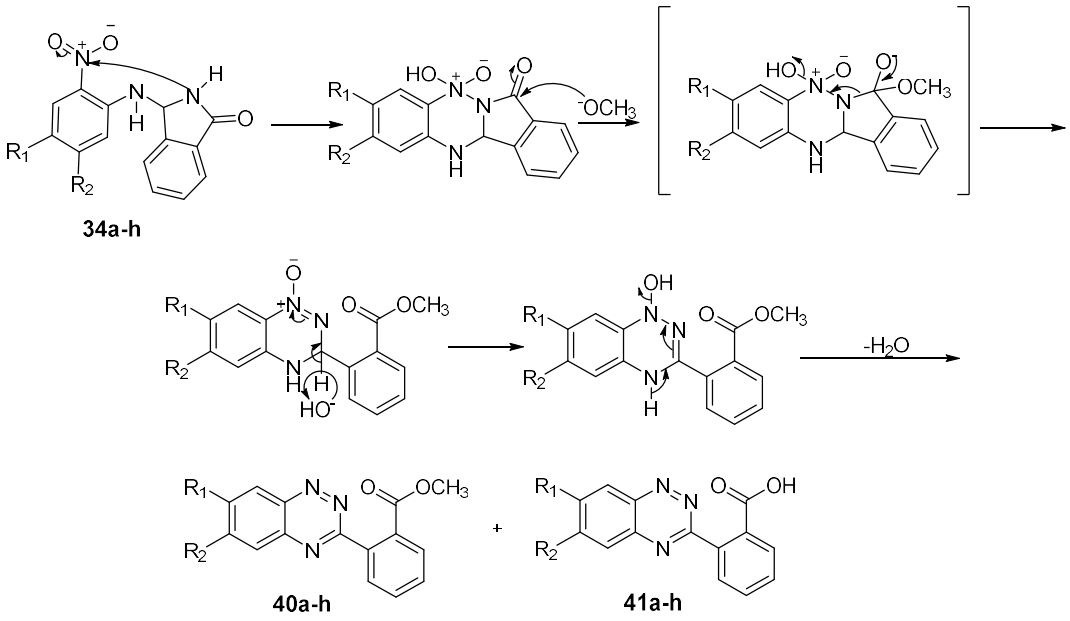
Heating time	% Yield of **38**	% Yield of **39**	Combined % yield of **38** and **39**
15 min	82	15	97
30 min	60	34	94
1 h	17	76	93

The reaction is extracted by water the by EtOAc. The ester is isolated and EtOAc is dried by anhydrous magnesium sulfate, then evaporated under vacuum to yield a yellow solid. The aqueous layer is acidified by concentrated HCl, until the product solidified and then the flask was placed in ice bath. Both products were filtered and recrystallized from methanol. They precipitate as yellow crystals. Characterization by ^{1}H NMR and ^{13}C NMR confirm the suggested structures of **38** & **39**. Three methoxy protons appear as singlet at 3.70 ppm and the carbon appears at 52.40 ppm in ^{13}C NMR.

The CN ^{13}C carbon appears at 106.84 ppm for the ester and at 106.99 ppm for the acid. The carbonyl C=O strong peak is detected at 1716 cm^{-1} for the ester while it appears at 1681 cm^{-1} for the acid in the IR spectrum.

D. Synthesis of 1,2,4-Benzotriazine

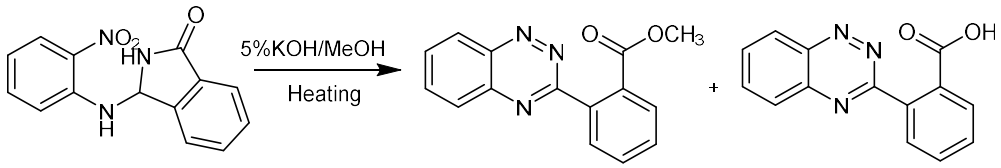
Same as cinnoline, 1,2,4-benzotriazine derivatives are obtained through the dissociation of isoindolinone intermediates **34a-h**. This latter is being heated in 10 mL of methanol basic solution: 5% KOH in MeOH between 60 and 65 ºC. Ester and acid derivatives of benzotriazines were obtained as co-products. The reaction mechanism is illustrated in Scheme 16. Increasing the heating temperature or applying a reflux system, accelerate the rate of the ester hydrolysis and in some cases it ensures a total hydrolysis and thus obtaining the acid alone.



Scheme 16: Synthesis of 1,2,4-benzotriazine **40a-h** & **41a-h** through the destruction of isoindolinone **34a-h**.

All the benzotriazine products were characterized by ^{1}H NMR, ^{13}C NMR, ^{13}C NMR DEPT 135 FTIR and HR-MS. Melting points of these solids were recorded as well.

1. Synthesis of methyl 2-(benzo[e][1,2,4]triazin-3-yl)benzoate (40a) and 2-(benzo[e][1,2,4]triazine-3-yl)benzoic acid (41a)



34a **40a** **41a**

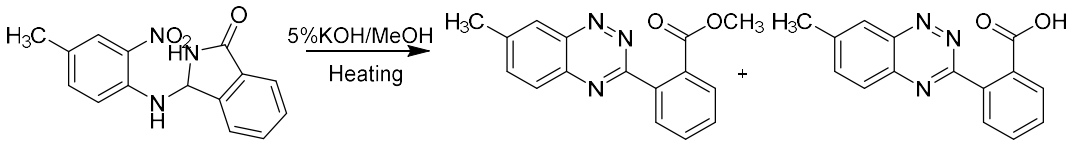
A 0.1 g of 3-((nitrophenyl) amino) isoindolin-1-one **34a** was heated in 10 mL of basic solution of 5% KOH in MeOH for 15 min, 30 min and 1 hour. The solution color changes from red color at 15 min to an orange clear solution after 1 hour of heating. The ester was recrystallized from ethanol however, the acid from methanol. In general, carboxylic acids are more polar then esters and thus required a more polar solvent for the crystallization process. The obtained products are yellow crystals isolated by suction filtration. The % yields are presented in Table 6. As the heating proceeds, the yield of the ester decreases and that of the acid increases. In total, the reaction has a very high yield.

Table 6: Isolated % yield of **40a** and **41a**

Heating duration	Solution color	% yield of **40a**	% yield of **41a**	Combined % yield of **40a** and **41a**
15 min	red	61	25	86
30 min	dark orange	45	51	96
1 hour	orange	27	66	93

The carbonyl functional group of the ester was detected at 1735 cm^{-1}, however, it shows at 1705 cm^{-1} for the acid in the IR spectra. The ^{13}C NMR spectrum shows fifteen carbons in total for the ester and fourteen for the acid. The C=O peaks show at 169.04 and 172.83 ppm for the ester and the acid, respectively. Both products show nine and eight carbons in the ^{13}C NMR DEPT 135, same as expected. The three methoxy protons of the ester **40a** are detected at 3.73 ppm as singlet and the total number of hydrogens is as predicted theoretically for compounds **40a** and **41a**.

2. Synthesis of methyl 2-(7-methylbenzo[e][1,2,4]triazin-3-yl)benzoate (40b) and 2-(7-methylbenzo[e][1,2,4]triazin-3-yl)benzoic acid (41b)



34b **40b** **41b**

Upon heating, the solution color was red after 15 min, then it turned orange after 30 min of heating and became yellow after 1 hour of heats. The yield of this reaction was little bit lower compared to the non-substituted isoindolinone. Both products were

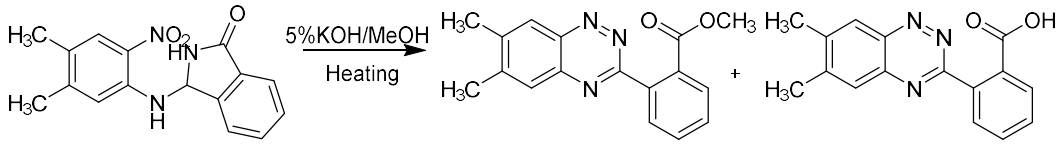
purified by recrystallization; compound **40b** in ethanol and **41b** in methanol. This latter was obtained as yellow powder and the ester was collected as orange crystals. Results are shown in Table 7.

Table 7: Isolated % yield of **40b** and **41b**

Heating duration	Solution color	% yield of **40b**	% yield of **41b**	Combined % yield of **40b** and **41b**
15 min	red	43	21	64
30 min	orange	20	61	81
1 hour	yellow	21	63	81

The ^{1}H and ^{13}C NMR spectra of compounds **40b** and **41b** result in thirteen and eleven protons, sixteen and fifteen carbons in total, including three singlet protons at 2.69 and 2.67 ppm respectively corresponding to the methyl groups for the ester and the acid on the benzo ring. In addition, the three methoxy singlet protons show at 3.72 ppm for the ester. The carbonyl is detected at 169.17 and 171.60 ppm for **40b** and **41b** respectively while the methyl ^{13}C carbons show at 22.05 and 22.06 ppm respectively and the methoxy carbon appears at 52.26 ppm. Nine carbons are positive in the ^{13}C NMR DEPT 135 for the ester and eight signals appear for the acid. The IR spectrum of the ester shows the carbonyl strong peak at 1727 cm^{-1}, however, the acid group shows at 1690 cm^{-1}.

3. *Synthesis of methyl 2-(6,7-dimethylbenzo[e][1,2,4]triazin-3-yl)benzoate (40c) and 2-(6,7-dimethylbenzo[e][1,2,4]triazin-3-yl)benzoic acid (41c)*



34c **40c** **41c**

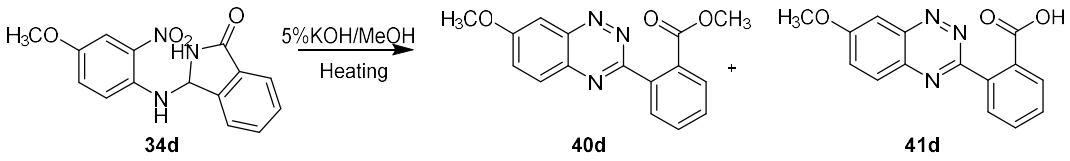
Once adding the basic solution to the isoindolinone **34c**, the color turned brown. After initiating the heating, the solution turned into dark brown at 15 min, it become black after 30 min and returned back to brown after 1 hour. TLC of the ester showed many impurities, and thus, purification by recrystallization was not efficient. Column chromatography was used to purify the crude product. However, the acid recrystallizes in methanol. Both compounds were collected as yellow powder. Similarly, to the previous reaction, the yield was low compared to the non-substituted benzotriazines. The percentage yields are provided below in Table 8.

Table 8: Isolated % yield of **40c** and **41c**

Heating duration	Solution color	% yield of **40c**	% yield of **41c**	Combined % yield of **40c** and **40c**
15 min	dark brown	48	34	82
30 min	black	35	38	73
1 hour	brown	27	39	66

Structures of **40c** and **41c** were confirmed by their spectroscopic data. The ^{1}H NMR showed fifteen and thirteen protons where six of each are singlet at 2.56 and 2.58 ppm representing the dimethyl functional group. In addition, the three methoxy singlet protons of the ester were also detected at 3.71 ppm. Furthermore, seventeen and sixteen carbons were detected in ^{13}C NMR, where C=O carbons appear at 169.30 and 170.87 ppm for **40c** and **41c,** respectively. Dimethyl carbons CH_3 were evident at 20.56 and 21.11 ppm. Nine and eight peaks were detected in the ^{13}C NMR DEPT 135 which is consistent with the number of positive carbons. Finally, the IR spectrum showed some characteristic peaks among them are the carbonyl C=O at 1723 cm^{-1} for **40c** and 1706 cm^{-1} for **41c**.

4. Synthesis of methyl 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl)benzoate (40d) and 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl)benzoic acid (41d)



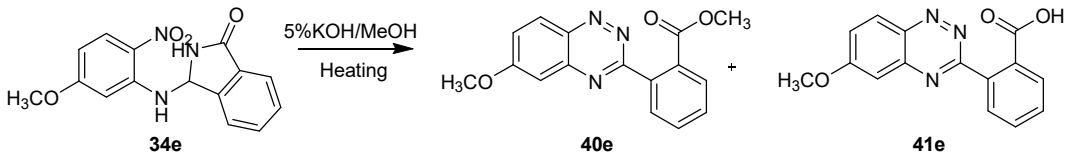
Likewise, the previous reactions, upon heating the percentage yield of the ester decreases and that of the acid increases. The overall yield decreases as well and this is due to the by-products or by-reactions occurring when heating for longer time. The color of the solution is orange and it became lighter upon the reaction. **40d** is recrystallized in ethanol and isolated as yellow fine crystals while **41d** in methanol and obtained as yellow powder. Results are shown in Table 9.

Table 9: Isolated % yield of **40d** and **41d**

Heating duration	Solution color	% yield of **40d**	% yield of **41d**	Combined % yield of **40d** and **41d**
15 min	dark orange	54	42	96
30 min	orange	35	53	88
1 hour	light orange	17	62	79

Structures of the two products were confirmed by ^{1}H MNR, ^{13}C NMR, ^{13}C NMR DEPT 135 and IR spectroscopy. Carbonyl C=O strong peaks appear at 1726 and 1705 $cm^{-1}$for **40d** & **41d** in the IR spectrum, respectively. Three methoxy protons of the ester were detected at 3.75 ppm as a singlet in the ^{1}H NMR spectrum. In addition to the methoxy protons of the derivative appearing as singlet at 4.09 ppm for the ester and 4.05 ppm for the acid. In this case, the acid protons appeared as well as a broad weak peak at 12.88 ppm. The ^{13}C NMR showed sixteen and fifteen carbons including the C=O at 169.24 and 169.55 ppm for **40d** and **41d**, OCH_3 of the ester at 52.25 ppm and methoxy derivative carbon at 56.23 and 56.92 ppm. In addition to nine and eight peaks in the ^{13}C NMR DEPT 135. Structure of **40d** was also proved by X-Ray crystallography.

5. *Synthesis of methyl 2-(6-methoxybenzo[e][1,2,4]triazin-3-yl)benzoate (40e) and 2-(6-methoxybenzo[e][1,2,4]triazin-3-yl)benzoic acid (41e)*



34e **40e** **41e**

Similarly, the ester hydrolyzed to give the acid, 2-(6-methoxybenzo[e][1,2,4] triazin-3-yl)benzoic acid upon heating. At the moment of adding the base 5% KOH in MeOH, the color turned to brown and it became lighter until 30 minutes and yellow after 1 hour. **40e** was purified by column chromatography and was collected as oily sticky brown solid while the acid recrystallized in methanol and was isolated as light yellow crystals. Reaction yields were very high and are shown in Table 10.

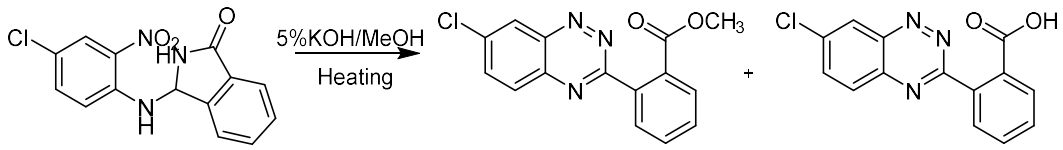
Table 10: Isolated % yield of **40e** and **41e**

Heating duration	Solution color	% yield of **40e**	% yield of **41e**	Combined % yield of **40e** and **41e**
15 min	brown	47	45	92
30 min	light brown	8	86	94
1 hour	orange	5	92	97

The ^{1}H NMR showed three methoxy protons at 3.725 ppm as singlet corresponding to the ester functional group. In addition to the six singlets methoxy

protons of the derivative group at 4.03 and 4.05 ppm for **40e** and **41e**. Moreover, the carboxylic OH proton appeared as a weak broad singlet peak at 12.90 ppm. Sixteen and fifteen carbons were detected in the ^{13}C NMR among them the carbonyl C=O carbons at 169.13 and 168.30 ppm, and the methoxy carbons at 52.28 and 56.33ppm for the ester, 56.12 ppm for the acid. The ^{13}C NMR DEPT 135 confirmed the total number of positive carbon to be nine and eight for **40e** and **41e** respectively. Finally, the IR spectrum displayed the C=O strong peaks at 1724 cm^{-1} for the ester, and 1717 cm^{-1} for the acid.

6. *Synthesis of methyl 2-(7-chlorobenzo[e][1,2,4]triazin-3-yl)benzoate (40f) and 2-(7-chlorobenzo[e][1,2,4]triazin-3-yl)benzoic acid (41f)*



34f **40f** **41f**

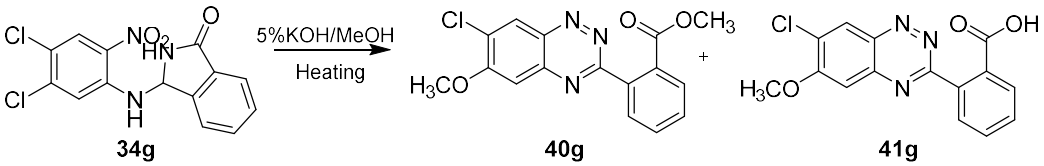
The synthesis of **40f** and **41f** was done using the same method as mentioned previously. At 15 min, the solution color was brown, it clears up to become orange at the end of the reaction. Both the acid and ester were purified by recrystallization in ethanol and methanol. Product **40f** was collected as light orange crystals while product **41f** was a yellow powder. This reaction is of high yield distributed between the ester and the acid and represented as following (Table 11).

Table 11: Isolated % yield of **40f** and **41f**

Heating duration	Solution color	% yield of **40f**	% yield of **41f**	Combined % yield of **40f** and **41f**
15 min	brown	78	19	97
30 min	dark orange	75	22	97
1 hour	orange	29	60	89

IR analysis of these compounds showed the essential characteristic peaks of the carbonyl C=O at 1729 and 1704 cm^{-1} for **40f** and **41f,** respectively. Three singlet protons appeared at 3.73 ppm corresponding to the methoxy group of the ester. The remaining ^{1}H NMR results are consistent with the expected spectra of the compounds. The ^{13}C NMR spectrum, showed fifteen and fourteen total carbons, the exact number of carbons in the molecules. Carbonyl carbons appeared at 168.87 ppm for **40f** and 172.14 ppm for **41f**, OCH_3 carbon of the ester appeared at 52.34 ppm. Eight and seven carbons are shown in the ^{13}C NMR DEPT 135.

7. Synthesis of methyl 2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl)benzoate (40g) and 2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl)benzoic acid (41g)



Isoindolinone **34g** was treated in a basic solution of 5% KOH in MeOH. Once adding this latter, the yellow solid **34g** become brown and dissolve directly in the solution. The color was transformed into orange and then yellow at the end of the reaction. The products were isolated and were purified both by recrystallization in methanol, and were obtained as light orange and yellow powder solids. The % yields are shown in Table 12.

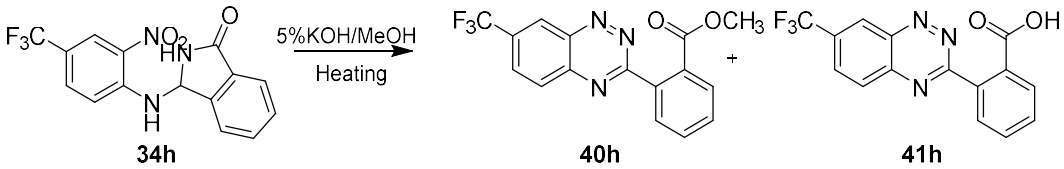
Table 12: Isolated % yield of **40g** and **41g**

Heating duration	Solution color	% yield of **40g**	% yield of **41g**	Combined % yield of **40g** and **41g**
15 min	brown	78	17	95
30 min	orange	42	48	90
1 hour	yellow	16	70	86

The C=O carbonyl carbons of the two products were observed at 1727 and 1705 cm^{-1} in the IR spectrum. However, the ^{1}H and ^{13}C NMR results were not compatible with the expected structures. Yet, six unexpected methoxy protons appear as singlets at 4.13 and 4.03 ppm and two OCH_3 carbons at 57.25 and 57.23 ppm in addition to the predicted peaks as well the aromatic protons of the desired products. This results can

only be explained by the hydrolysis and substitution of one chlorine group by CH_3O^-. In fact, HR-MS peaks are consistent with the structures **40g** and **41g**.

8. Synthesis of methyl 2-(7-(trifluoromethyl)benzo[e][1,2,4]triazin-3-yl)benzoate (40h) and 2-(7-(trifluoromethyl)benzo[e][1,2,4]triazin-3-yl)benzoic acid (41h)



Finally, the last two products were synthesized in the same way in 5% of KOH in MeOH. The solution color turned from orange at 15 min to yellow after 1 hour. Product **40h** was purified by column chromatography and was obtained as oily sticky yellow solid while the acid was recrystallized in methanol and isolated as yellow powder. The yield of the above reaction was high and represented in Table 13.

Table 13: Isolated % yield of **40h** and **41h**

Heating duration	Solution color	% yield of **40h**	% yield of **41h**	Combined % yield of **40h** and **41h**
15 min	orange	67	29	96
30 min	yellow	44	51	95
1 hour	yellow	29	62	91

The structures were confirmed by their spectroscopic data, where the IR strong carbonyl C=O peaks appeared at 1731 and 1722 cm^{-1} for **40h** and **41h**, respectively. The ^{1}H NMR results revealed the same number of the expected protons, among them the methoxy singlet protons at 3.74 ppm. The ^{13}C NMR showed sixteen and fifteen carbons, the OCH_3 carbon shifted at 52.40 ppm and that of the carbonyl at 168.69 and 171.77 ppm for **40h** and **41h**, respectively. Nine and eight positive carbons appeared in the ^{13}C NMR DEPT 135.

E. Effect of the substituent groups in isoindolinones and 1,2,4-benzotriazine

In order to study the effect of the substituent groups on the isoindolinone and 1,2,4-benzotriazine products, multiple derivatives have been used where some are electron donating and releasing groups by resonance such CH_3O while others are electron withdrawing like CF_3.

^{1}H NMR spots a slight shift in the position of the N-H proton para to the substituent and the amide N-H proton of isoindolinones (Figures 3,4 and 5).

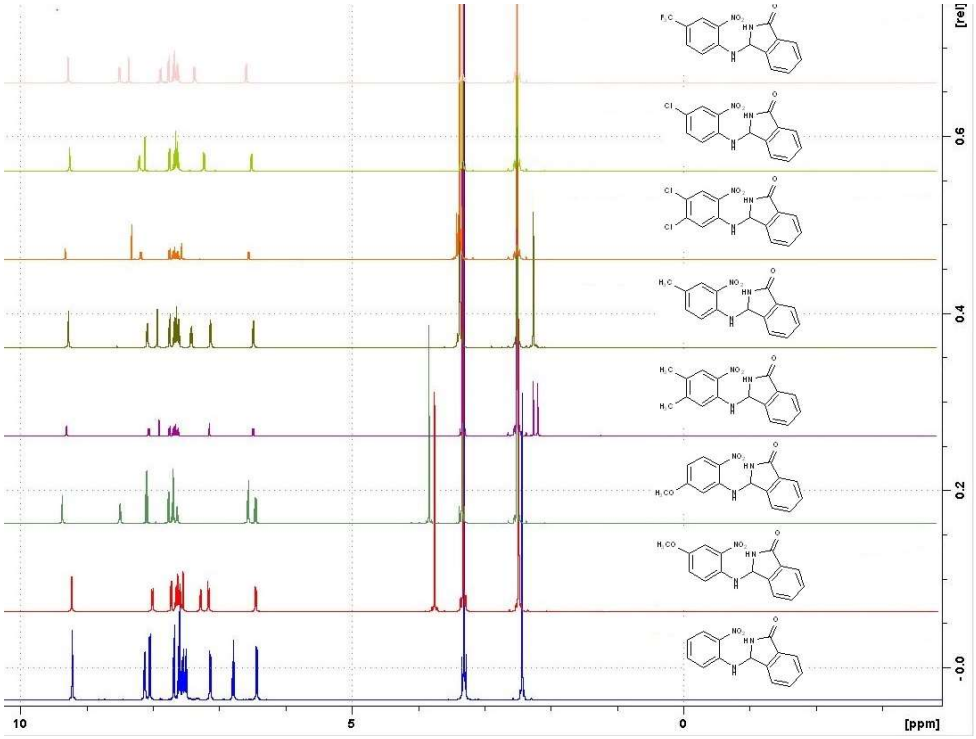


Figure 3: ^{1}H NMR of isoindolinones **34a-h**

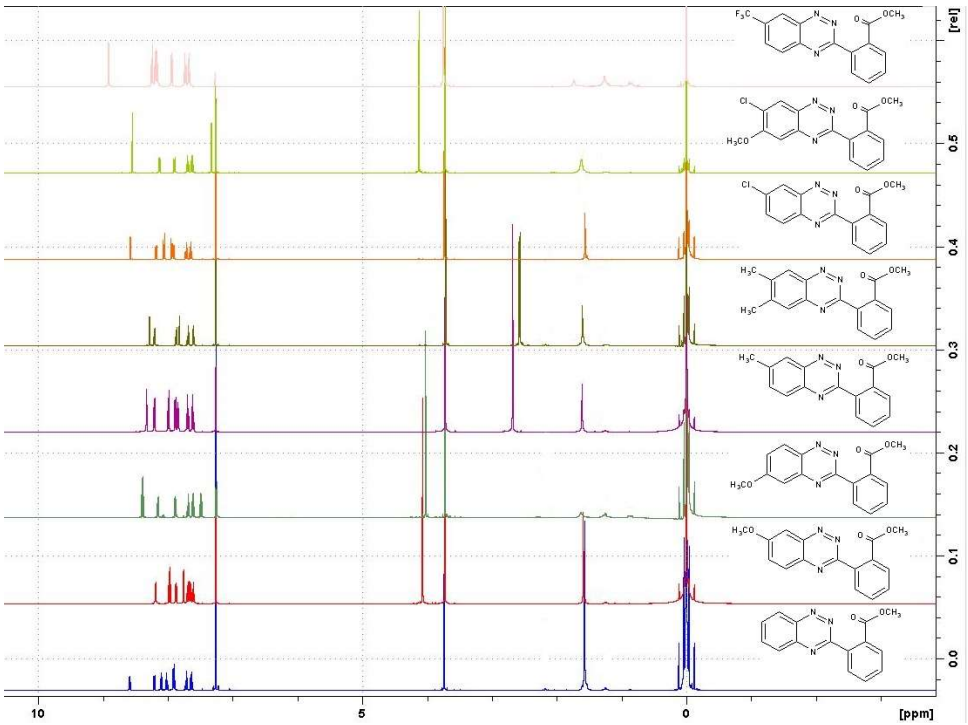


Figure 4: ^{1}H NMR of ester benzotriazines **40a-h**

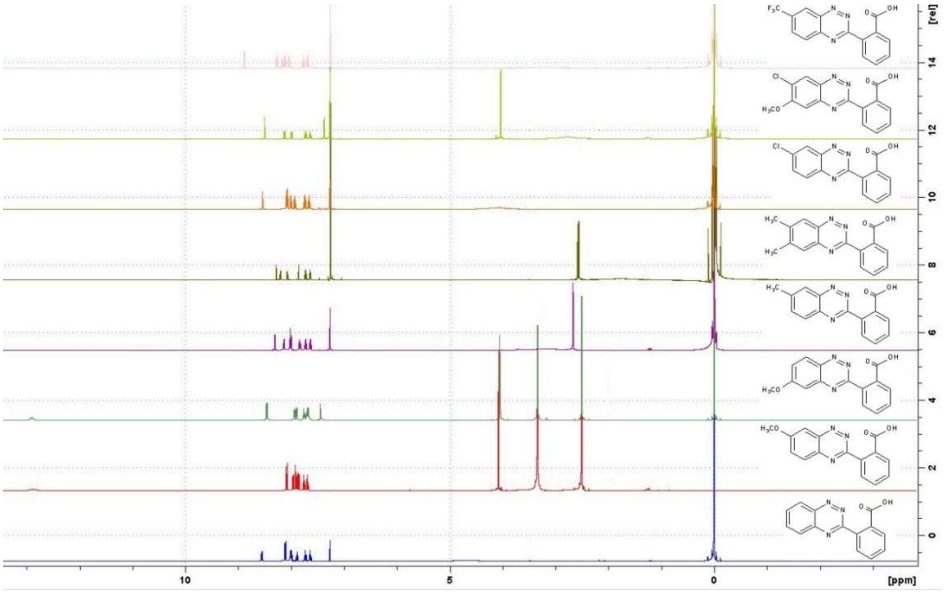


Figure 5: ^{1}H NMR of acid benzotriazine **41a-h**

Ultra-Violet spectroscopy spots the shift of the maximum absorption affected by the derivative. As known, the electron releasing group (OCH_3) results in a bathochromic (red) shift to the right. The wavelength is higher compared to the non-substituted compound. And the inverse is observed in the case of electron withdrawing group (CF_3), shift toward lower wavelength; an hypsochromic (blue) shift (Figures 6,7 and 8).

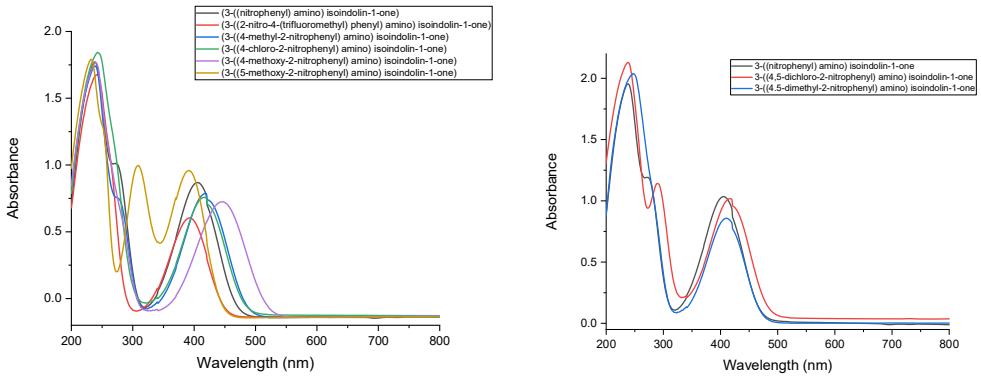


Figure 6: UV-Vis spectrum of isoindolinones **34a-h**

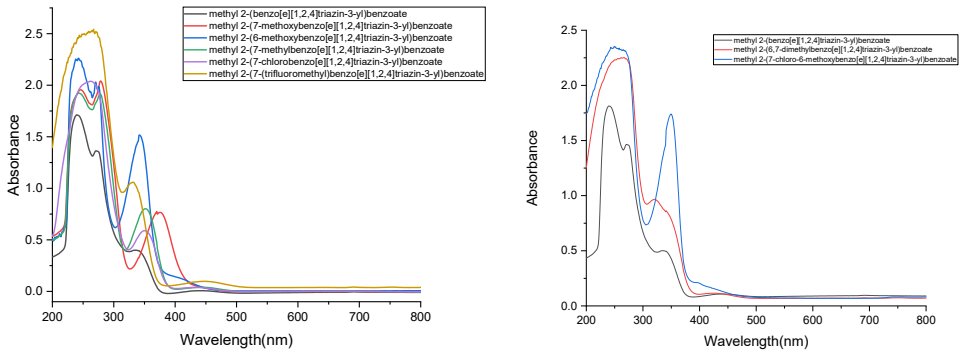


Figure 7: UV-Vis spectrum of ester benzotriazine **40a-h**

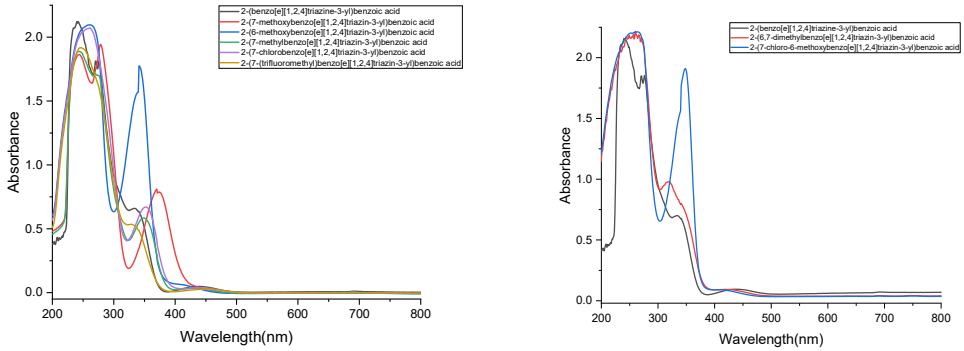


Figure 8: UV-Vis spectrum of acid benzotriazine **41a-h**

CHAPTER III

CONCLUSION

A total of 27 compounds were successfully synthesized, identified and characterized by ^{1}H NMR, ^{13}C NMR, ^{13}C NMR DEPT 135, FT-IR, HR-MS and UV-Visible spectroscopy. The melting point of all products have been recorded. The synthesized products are new and not known in the literature. In addition, we report the reason of hydrolysis of one chlorine group in the case of presumed 4.5-dichloro isoindolinone.

The synthesis was done through a new, concise, efficient and low cost reactions, yielding fairly yields of the products.

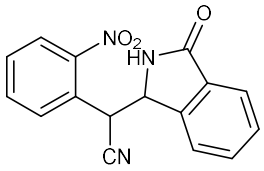
Since most of heterocyclic compounds showed some biological activities as mention previously in the introduction, the series of the novel products achieved should be tested towards anomaly cells, wishing they might show positive results.

CHAPTER IV

EXPERIMENTAL

Melting points were determined by the digital melting point apparatus: DigiMelt and they were uncorrected. ^{1}H MNR, ^{13}C NMR and Dept 135 spectra were determined in $CDCl_3$ or DMSO-d_6 using a Bruker AM 500 NMR spectrometer. Chemical shifts were recorded in ppm (δ). Infra-red spectra were collected using thermos-scientific iD_3 ATR for Nicolet iS5 FT-IR spectrometer. IR bands are reported as wavenumbers (cm^{-1}). High resolution mass spectroscopy (HR-MS) spectra were recorded using SCIEX X500R HPLC/QTOF Mass Spectrometry. Thin layer chromatography (TLC) was performed on TLC silica gel 60 F_{254} (used directly as received). Starting material needed were commercially available.

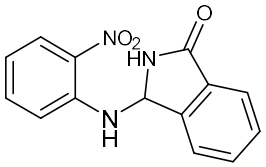
2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile 31:



Product 2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile **31:** o-cyanobenzaldehyde (0.32 g; 2.50 mmol) and 2-(2-nitrophenyl) acetonitrile (0.13 g; 0.99 mmol) were dissolved in 3 mL of MeOH. A volume of 0.5 mL of Et_3N was added while stirring the mixture at room temperature. After 2 min, a white precipitate appears. The product was filtrated by suction and was washed with cold ethanol (0.21g, 79%). Melting point: 203-204 ºC.

^{1}H NMR (500 MHz, DMSO-d_6): δ 5.22 (d, J = 2.5 Hz, 1H), 5.51 (d, J = 3 Hz, 1H), 7.48 (s, 1H), 7.60-7.67 (m, 2H), 7.72-7.75 (m, 3H), 7.85 (d, J = 7.5 Hz, 1H), 7.89 (dd, J = 7.5, 1.5 Hz, 1H), 8.25 (d, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 171.11, 147.38, 143.27, 135.03, 133.07, 132.09, 131.42, 130.58, 129.94, 127.34, 126.39, 124.33, 122.89, 116.04, 58.38, 40.23 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 135.03, 133.07, 131.42, 130.58, 129.94, 126.39, 124.33, 122.89, 58.38, 40.24; FTIR (cm^{-1}): 2361 (m), 2343 (w), 1703 (s), 1615 (w), 1532 (s),1470 (m), 1348 (s), 1306 (w), 1138 (m), 858 (m), 758 (m), 721 (s), 703 (s); *m/z* calculated for $C_{16}H_{11}N_3O_3$ $[M+H]^+$ 294.08732, found 294.0874, $[M+Na]^+$ calc. 316.06926, found 316.0693, $[M+K]^+$ calc. 332.0432, found 332.0418.

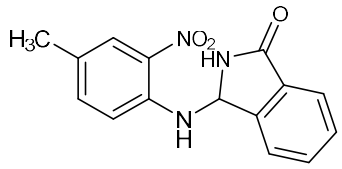
3-((nitrophenyl) amino) isoindolin-1-one 34a:



The 3-((nitrophenyl)amino) isoindolin-1-one **34a**: o-cyanobenzaldehyde (0.32 g; 2.50mmol) and 2-nitroaniline (0.13 g; 0.99 mmol) were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5%KOH in MeOH solution was added. The solution color turned red and heat was released just before a yellow paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.21g; 79%). Melting point: 235-236 ºC.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.51(d, J = 8 Hz, 1H), 6.85-6.88 (m, 1H), 7.21 (d, J= 8.5 Hz, 1H), 7.56-7.60 (m,1H), 7.62 (dt, J = 7.0, 1.5 Hz, 1H), 7.65-7.67 (m, 1H), 7.69 (dt, J = 7.0, 1.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 8.12 (dd, J = 8.5, 1.5 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.34, 145.03, 143.66, 136.91, 133.16, 133.05, 132.81, 130.19, 126.76, 123.95, 123.53, 117.82, 116.12, 64.35 ppm; ^{13}C NMR DEPT 135 (126 MHz, DMSO-d_6): δ 136.91, 133.05, 130.20, 126.76, 123.95, 123.53, 117.82, 116.13, 64.35; FTIR (cm^{-1}): 1714 (s),1619 (m), 1577 (m), 1498 (m), 1470 (w), 1446 (m), 1409 (w), 1346 (m), 1262 (m), 1228 (m), 1138 (w), 1122 (m), 1069 (w), 869 (w), 738 (s), 696 (w); *m/z* calculated for $C_{14}H_{11}N_3O_3$ $[M+H]^+$ 270.08732, found 270.1003, $[M+Na]^+$ calc. 292.06926, found 292.0696, $[M+K]^+$ calc. 308.0432, found 308.0528.

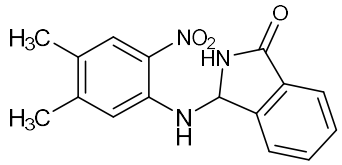
3-((4-methyl-2-nitrophenyl) amino) isoindolin-1-one 34b:



Product 3-((4-methyl-2-nitrophenyl)amino) isoindolin-1-one **34b**: o-cyanobenzaldehyde (0.32 g; 2.45 mmol) and 4-methyl-2-nitroaniline (0.15 g; 1 mmol) were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was added. The solution color turned red and heat was released just before a dark yellow paste formed. The

product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.20g; 70%). Melting point: 209-210 ºC. ^{1}H NMR (500MHz, DMSO-d_6): δ 2.26 (s, 3H), 6.48 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 9.0, 2.0 Hz 1H), 7.61 (dt, J = 7.5, 1.0 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.68 (dt, J = 7.5, 1.0 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.93 (d, J = 1.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.32, 145.14, 141.79, 138.15, 133.01, 132.88, 132.81, 130.14, 127.12, 125.84, 123.90, 123.50, 116.23, 64.49, 19.91 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 138.16, 133.01, 130.14, 127.12, 125.84, 123.90, 123.50, 116.23, 64.49, 19.91; FTIR (cm^{-1}): 1710 (s), 1633 (w), 1567 (w), 1524 (m), 1470 (w), 1443 (w), 1409 (w), 1348 (m), 1316 (w), 1273 (m), 1237 (w), 1206 (m), 1156 (w), 1124 (w), 1063 (w), 924 (w), 792 (w), 762 (m), 741 (m), 706(m); *m/z* calculated for $C_{15}H_{13}N_3O_3$ $[M+H]^+$ 284.10297, found 284.1037, $[M+Na]^+$ calc. 306.08491, found 306.0855, $[M+K]^+$ calc. 322.05885, found 322.0588.

3-((4.5-dimethyl-2-nitrophenyl) amino) isoindolin-1-one 34c:

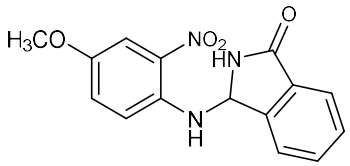


The 3-((4.5-dimethyl-2-nitrophenyl)amino) isoindolin-1-one **34c**: o-cyanobenzaldehyde (0.32 g; 2.49 mmol) and 4.5-dimethyl-2-nitroaniline (0.16 g; 0.99 mmol) were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was

added. The solution color turned red and heat was released just before a yellow paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.23g; 77%). Melting point: 256-258 ºC.

^{1}H NMR (500MHz, DMSO-d_6): δ 2.20 (s, 3H), 2.26 (s, 3H), 6.49 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.62 (dt, J = 7.5, 1.0 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.70 (dt, J = 7.5, 1.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.91 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.34, 147.88, 145.14, 142.21, 133.07, 132.76, 130.86, 130.21, 126.75, 126.06, 123.93, 123.48, 116.54, 64.27, 20.65, 18.56 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 133.07, 130.21, 126.06, 123.93, 123.93, 123.48, 116.54, 64.27, 20.65, 18.56; FTIR (cm^{-1}): 1707 (s), 1632 (w), 1569 (w), 1508 (m), 1471 (w), 1446 (w), 1409 (w), 1330 (w), 1279 (m), 1248 (m), 1210 (w), 1119 (m), 1054 (w), 846 (w), 733 (m); *m/z* calculated for $C_{16}H_{15}N_3O_3$ $[M+H]^+$ 298.11862, found 298.1318, $[M+Na]^+$ calc. 320.10056, found 320.1008, $[M+K]^+$ calc. 336.0745, found 336.0748.

3-((4-methoxy-2-nitrophenyl) amino) isoindolin-1-one 34d:

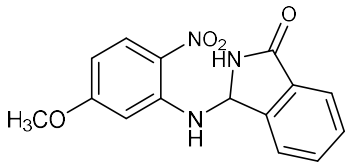


The product 3-((4-methoxy-2-nitrophenyl)amino) isoindolin-1-one **34d**: o-cyanobenzaldehyde (0.32 g; 2.49 mmol) and 4-methoxy-2-nitroaniline (0.16 g; 1.00 mmol) were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then

cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was added. The solution color turned red and heat was released just before an orange paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was orange powder (0.25g; 83%). Melting point: 208-209 ºC.

^{1}H NMR (500MHz, DMSO-d_6): δ 3.77 (s, 3H), 6.47 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 9.5 Hz, 1H), 7.30 (dd, J = 9.5, 3.0 Hz, 1H), 7.57 (d, J = 3 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.27, 150.88, 145.19, 138.94, 133.01, 132.82, 132.73, 130.15, 126.66, 123.91, 123.51, 117.86, 107.76, 64.74, 56.21 ppm; ^{13}C NMR DEPT 135 (126 MHz, DMSO-d_6): δ 133.01, 130.15, 126.66, 123.91, 123.51, 117.86, 107.76, 64.74, 56.21; FTIR (cm^{-1}): 1707 (s), 1576 (w), 1526 (m), 1509 (w) 1416 (w), 1343 (w), 1237 (m), 1206 (w), 1058 (m), 1037 (m), 741 (m); *m/z* calculated for $C_{15}H_{13}N_3O_4$ $[M+H]^+$ 300.09788, found 300.0993, $[M+Na]^+$ calc. 322.07983, found 322.0805, $[M+K]^+$ calc. 338.05376, found 338,0540.

3-((5-methoxy-2-nitrophenyl) amino) isoindolin-1-one 34e:

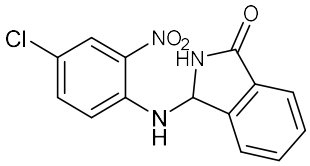


Product 3-((5-methoxy-2-nitrophenyl)amino) isoindolin-1-one **34e**: o-cyanobenzaldehyde (0.32 g; 2.5 mmol) and 5-methoxy-2-nitroaniline (0.16g; 1 mmol) were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation

of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution is added. The solution color turned red and heat was released just before a brown paste formed. The product was collected by suction filtration, washed with water and cold methanol. The solid was pale yellow powder (0.27g; 90%). Melting point: 257-258 ºC.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 3.83 (s, 3H), 6.45 (dd, *J* = 9.5, 2.5 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 2H), 7.63 (dt, *J* = 7.0, 1.5 Hz, 1H), 7.70 (dd, *J* = 6.5, 1.0 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 9.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ 169.35, 165.94, 146.29, 144.85, 133.16, 132.77, 130.28, 129.10, 127.09, 123.98, 123.55, 107.24, 97.70, 64.17, 56.46 ppm; ^{13}C NMR DEPT 135 (126 MHz, DMSO-*d*$_6$): δ 133.16, 130.28, 129.10, 123.98, 123.55, 107.24, 97.70, 64.18, 56.46; FTIR (cm^{-1}): 1709 (s), 1615 (m), 1584 (m), 1499 (m), 1421 (m), 1365 (w), 1313 (w), 1236 (s), 1122 (m), 1088 (w), 1071 (m), 845 (s), 785 (m), 735 (m); *m/z* calculated for $C_{15}H_{13}N_3O_4$ $[M+H]^+$ 300.09788, found 300.1072, $[M+Na]^+$ calc. 322.07983, found 322.0800, $[M+K]^+$ calc. 338.05376, found 338,0541.

3-((4-chloro-2-nitrophenyl) amino) isoindolin-1-one 34f:

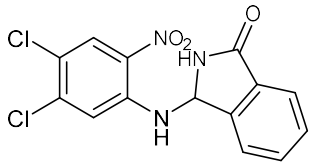


Product 3-((4-Chloro-2-nitrophenyl) amino) isoindolin-1-one **34f**: o-cyanobenzaldehyde (0.32g; 2.50 mmol) and 4-chloro-2-nitroaniline (0.17g; 1.00 mmol)

were dissolved in 1 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was added. The solution color turned red and heat was released just before a yellow paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.24g; 79%). Melting point: 235- 237 ºC.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.51 (d, J = 8 Hz, 1H), 7.23 (d, J = 9.5 Hz, 1H), 7.61 (dd, J = 7.0, 1.0 Hz, 1H), 7.63 (t, J = 2.5 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.68 (dt, J = 7.5, 1.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.29, 144.80, 142.53, 136.46, 133.33, 133.04, 132.84, 130.22, 125.63, 123.96, 123.54, 120.96, 118.18, 64.46 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 136.46, 133.04, 130.22, 125.63, 123.96, 123.54, 118.18, 64.46; FTIR (cm^{-1}): 1708 (s), 1615 (w), 1564 (w), 1520 (m), 1501 (m), 1442 (w), 1409 (m), 1345 (m), 1298 (w), 1265 (s), 1210 (w), 1155 (m), 1123 (w), 1057 (w), 893 (m), 818 (m), 729 (m), 704 (m); *m/z* calculated for $C_{14}H_{10}ClN_3O_3$ $[M+H]^+$ 304.04835, found 304.1496, $[M+Na]^+$ calc. 326.03029, found 326.0305, $[M+K]^+$ calc. 342.00423, found 342.0034.

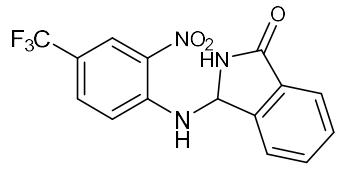
3-((4,5-dichloro-2-nitrophenyl) amino) isoindolin-1-one 34g:



Product 3-((4,5-dichloro-2-nitrophenyl)amino) isoindolin-1-one **34g**: o-cyanobenzaldehyde (0.32 g; 2.50 mmol) and 4.5-dichloro-2-nitroaniline (0.21 g; 1.00 mmol) were dissolved in 1.0 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was added. The solution color turned dark red and heat was released just before a yellow paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.30g; 87%). Melting point: 257-258 ºC.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 6.56(d, J = 8.5 Hz, 1H), 7.57 (s, 1H), 7.63 (dt, J = 7.5, 1.0 Hz, 1H), 7.66 (d, J = 7 Hz, 1H), 7.70 (dt, J = 7.5, 1.0 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ 169.32, 144.50, 142.82, 139.66, 133.06, 132.79, 132.33, 130.31, 127.79, 124.06, 123.50, 119.11, 117.65, 64.33 ppm; DEPT 135 (126 MHz, DMSO-*d*$_6$): δ 133.09, 130.31, 127.79, 124.06, 123.50, 117.65, 64.33; FTIR (cm^{-1}): 1713 (s), 1615 (m), 1553 (m), 1469 (s), 1331 (w), 1276 (m), 1260 (s), 1218 (m), 1072 (m), 756 (s), 633 (s); *m/z* calculated for $C_{14}H_9Cl_2N_3O_3$ $[M+H]^+$ 338.00937, found 338.0095, $[M+Na]^+$ calc. 359.99132, found 359.9914, $[M+K]^+$ calc. 375.96525, found 375.9636.

3-((2-nitro-4-(trifluoromethyl) phenyl) amino) isoindolin-1-one 34h:

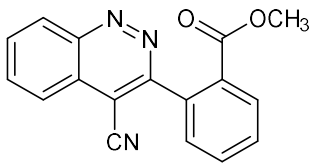


Product 3-((2-nitro-4-(trifluoromethyl)phenyl)amino) isoindolin-1-one **34h**: o-cyanobenzaldehyde (0.32 g; 2.50 mmol) and 2-nitro-4-(trifluoromethyl) aniline (0.21 g; 0.99 mmol) were dissolved in 1.0 mL of DCM. The mixture was warmed to ensure total dissolvation of all the starting materials for 1 minute. The reaction mixture was then cooled down to room temperature and 0.4 mL of 5% KOH in MeOH solution was added. The solution color turned red and heat was released just before a brown paste formed. The product was collected by suction filtration, washed with water and cold methanol. The collected solid was yellow powder (0.13g; 39%). Melting point: 208-210 ºC.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.59 (d, J = 8 Hz, 1H), 7.37 (d, J = 9.5 Hz, 1H), 7.63 (dt, J = 7.5, 1.5 Hz, 1H), 7.66 (d, J = 6.5 Hz, 1H), 7.69 (dt, J = 7.5, 1.0 Hz, H), 7.76 (d, J = 7.5 Hz, 1H), 7.88 (dd, J = 9.0, 2.0 Hz, 1H), 8.37 (d, J = 1.5 Hz, 1H), 8.50 (d, J = 8.5 Hz, 1H), 9.28 (s, 1H);^{13}C NMR (126 MHz, DMSO-d_6): δ 169.35, 145.76, 144.55, 133.07, 132.84, 132.43, 130.28, 125.17, 124.47, 124.43, 124.00, 123.58, 117.59, 117.36, 64.32 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 133.07, 132.43, 130.28, 124.47, 124.43, 124.00, 123.58, 117.36, 64.32; FTIR (cm^{-1}): 1709 (s), 1635 (m), 1571 (w), 1534 (m), 1469 (w), 1446 (w), 1426 (w), 1335 (s), 1303 (w), 1271 (m), 1238 (w), 1211 (w), 1159 (m), 1111 (s), 1089 (w), 1064 (w), 914 (w), 763 (w), 744 (m), 715 (m);

m/z calculated for $C_{15}H_{10}F_3N_3O_3$ $[M+H]^+$ 338.0747, found 338.0761, $[M+Na]^+$ calc. 360.0567, found 360.0571, $[M+K]^+$ calc. 376.0306, found 376.0296.

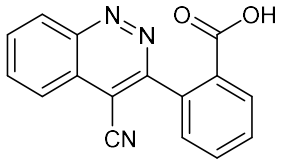
Methyl 2-(4-cyanocinnolin-3-yl) benzoate 38:



Methyl 2-(4-cyanocinnolin-3-yl) benzoate **38**: 2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile (0.10 g; 0.36 mmol) was dissolved in 10 mL of 5%KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned brown. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of ethanol and filtrated by vacuum. Yellow crystals were isolated ($6.2x10^{-2}$ g, 60%). Melting point: 143-145 ºC.

^1H NMR (500 MHz, $CDCl_3$): δ 3.70 (s, 3H), 7.66-7.71 (m, 2H), 7.77 (dt, J = 7.5, 1.0 Hz, 1H), 8.00-8.02 (m, 2H), 8.21-8.23 (m, 2H), 8.72-8.74 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.67, 156.64, 148.74, 136.69, 134.13, 132.47, 131.77, 131.45, 131.09, 130.47, 130.30, 124.23, 123.87, 114.04, 106.84, 52.40 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 134.13, 132.47, 131.77, 131.45, 131.09, 130.96, 130.30, 124.23, 52.41;FTIR (cm^{-1}): 1716 (s), 1564 (w), 1434 (w), 1294 (w), 1272 (s), 1128 (m), 1084 (m), 1064 (w), 1048 (w), 1030 (m), 772 (s), 771 (m); *m/z* calculated for $C_{17}H_{11}N_3O_2$ $[M+H]^+$ 290.0924, found 290.0921, $[M+Na]^+$ calc. 312.07435, found 312.0741, $[M+K]^+$ calc. 328.04828, found 328.0484.

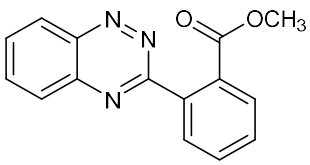
2-(4-cyanocinnolin-3-yl) benzoic acid 39:



Product 2-(4-cyanocinnolin-3-yl) benzoic acid **39:** 2-(2-nitrophenyl)-2-(3-oxoisoindolin-1-yl) acetonitrile (0.10 g; 0.36 mmol) was dissolved in 10 mL of 5%KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned brown. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl. The crude precipitate was filtrated using a Buchner funnel. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained ($3.3x10^{-2}$ g, 34%). Melting point: 205-206 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dt, J = 8.0, 0.5 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.78 (dt, J = 7.25, 1.0 Hz, 1H), 8.00-8.02 (m, 2H), 8.19-8.22 (m, 1H), 8.24 (d, J = 8 Hz, 1H), 8.71-8.72 (m, 1H);^{13}C NMR (126 MHz, $CDCl_3$): δ 169.46, 156.45, 148.70, 136.91, 134.17, 133.02, 131.84, 131.78, 131.57, 130.89, 130.35, 129.63, 124.24, 123.95, 113.95, 106.99 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 134.18, 133.03, 131.85, 131.79, 131.57, 130.89, 130.36, 124.25; FTIR (cm^{-1}): 1700 (w), 1684 (s), 1679 (s), 1673 (s), 1662 (s), 1279 (m), 1148 (w),1136 (w), 727 (s); *m/z* calculated for $C_{16}H_9N_3O_2$ $[M+H]^+$ 276.07675, found 276.0766, $[M+Na]^+$ calc. 298.0587, found 298.0587, $[M+K]^+$ calc. 314.03263, found 314.0241.

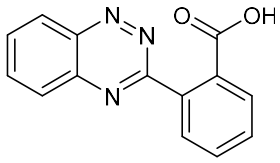
Methyl 2-(benzo[*e*][1,2,4]triazin-3-yl) benzoate 40a:



Methyl 2-(benzo[*e*][1,2,4]triazin-3-yl) benzoate **40a:** 3-((nitrophenyl)amino) isoindolin-1-one(0.10 g; 0.38 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of ethanol and filtrated by vacuum. Yellow crystals were obtained ($4.6x10^{-2}$ g, 45%). Melting point: 144-145 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73(s, 3H), 7.64 (dt, J = 7.5, 1.5 Hz, 1H), 7.71 (dt, J = 7.5, 1.5 Hz, 1H), 7.89-7.92 (m,2H), 8.00-8.03 (m, 1H), 8.11 (qd, J=8.5, 0.5Hz, 1H), 8.21 (dd, J = 7.5, 1.0 Hz, 1H), 8.59 (qd, J = 8.5, 0.5 Hz, 1H);^{13}C NMR (126 MHz, $CDCl_3$): δ 169.04, 161.41, 145.94, 140.61, 136.44, 135.68, 132.83, 131.38, 130.89, 130.69, 130.27, 129.68, 129.68, 128.99, 52.31 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 135.68, 131.38, 130.89, 130.70, 130.27, 129.68, 129.68, 128.99, 52.31 ;FTIR (cm^{-1}): 2923 (w), 1735 (s), 1683 (m), 1625 (w), 1604 (w), 1572 (w), 1524 (m), 1509 (w), 1260 (w), 1096 (w), 867 (w), 778 (m), 743 (m), 705 (s); *m/z* calculated for $C_{15}H_{11}N_3O_2$ $[M+H]^+$ 266.0924, found 266.0926, $[M+Na]^+$ calc. 288.07435, found 288.0743, $[M+K]^+$ calc. 304.04828, found 304.0485.

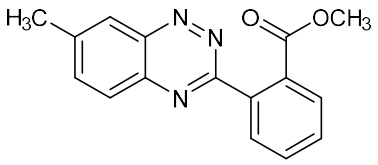
2-(benzo[e][1,2,4]triazine-3-yl) benzoic acid 41a:



Product 2-(benzo[e][1,2,4]triazine-3-yl) benzoic acid **41a:** 3-((nitrophenyl)amino) isoindolin-1-one (0.10 g; 0.38 mmol) were dissolved in 10 mL of 5%KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained ($4.86x10^{-2}$ g, 51%). Melting point: 180-181 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dt, J = 7.5, 1.0 Hz, 1H), 7.73 (dt, J = 7.5, 1.0 Hz, 1H), 7.86-7.89 (m, 1H), 7.97-8.01 (m, 2H), 8.10 (d, J = 8.5 Hz, 2H), 8.54 (dd, J = 8.5, 0.5Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.25, 161.55, 145.85, 140.60, 136.97, 135.83, 131.99, 131.77, 131.15, 130.83, 130.43, 130.19, 129.56, 128.97 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 135.83, 131.99, 131.15, 130.83, 130.43, 130.19, 129.55, 128.96 ; FTIR (cm^{-1}): 2928 (w), 1705 (s), 1489 (w), 1451 (w), 1391 (w), 1238 (s) 1120 (m), 1015 (m), 1003 (m), 806 (m), 775 (s), 762 (s), 726 (s), 631 (m); *m/z* calculated for $C_{14}H_9N_3O_2$ $[M+H]^+$ 252.07675, found 252.0767, $[M+Na]^+$ calc. 274.0587, found 274.0587, $[M+K]^+$ calc. 290.03263, found 290.0243.

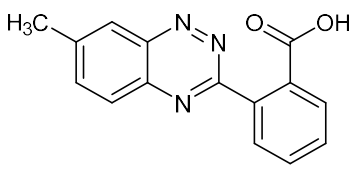
Methyl 2-(7-methylbenzo[e][1,2,4]triazin-3-yl) benzoate 40b:



Methyl 2-(7-methylbenzo[e][1,2,4]triazin-3-yl) benzoate **40b:** 3-((4-methyl-2-nitrophenyl)amino) isoindolin-1-one (0.10 g, 0.36 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned dark orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of ethanol and filtrated by vacuum. Light orange crystals were obtained ($2.0x10^{-2}$ g, 20%). Melting point: 143-144 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (s, 3H), 3.72 (s, 3H), 7.62 (dt, J = 7.5, 1.0Hz, 1H), 7.70 (dt, J = 7.5, 1.5 Hz, 1H), 7.84 (dd, J = 8.5, 2.0 Hz, 1H), 7.88 (dd, J = 8.0, 1.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 8.20 (dd, J = 8.0, 1.0 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.17, 160.95, 145.98, 141.65, 139.33, 138.29, 136.49, 132.82, 131.29, 130.77, 130.10, 129.61, 128.45, 127.88, 52.26, 22.05 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 138.29, 131.29, 130.77, 130.10, 129.60, 128.45, 127.88, 52.26, 22.05; FTIR (cm^{-1}): 1727 (s), 1558 (m), 1501 (m), 1431 (m), 1417 (m), 1318 (m), 1287 (s), 1249 (m), 1119 (m), 1087 (m), 827 (m), 734 (s); *m/z* calculated for $C_{16}H_{13}N_3O_2$ $[M+H]^+$ 280.10805, found 280.1078, $[M+Na]^+$ calc. 302.0900, found 302.0898, $[M+K]^+$ calc. 318.06393, found 318.0640.

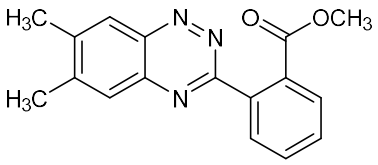
2-(7-methylbenzo[e][1,2,4]triazin-3-yl) benzoic acid 41b:



Product 2-(7-methylbenzo[e][1,2,4]triazin-3-yl) benzoic acid **41b:** 3-((4-methyl-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.36 mmol) was dissolved in 10 mL of 5%KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned dark orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were collected ($5.83x10^{-2}$ g, 61%). Melting point: 195-197 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.97 (s, 3H), 7.63 (dt, J = 7.5, 0.5 Hz, 1H), 7.73 (dt, J = 7.5, 1.5 Hz, 1H), 7.83 (dd, J = 8.5, 1.5 Hz, 1H), 8.01 (t, J = 9.0 Hz, 2H), 8.13 (dd, J = 7.5, 0.5 Hz, 1H), 8.30 (d, J = 0.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.60, 161.04, 145.93, 141.91, 139.33, 138.54, 136.92, 131.96, 161.67, 131.16, 130.56, 130.10, 128.40, 127.78, 22.06 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 138.54, 131.96, 131.16, 130.56, 130.10, 128.40, 127.78, 22.07; FTIR (cm^{-1}): 1690 (m), 1653 (w), 1263 (m), 1007 (w), 836 (m), 761 (m), 710 (w), 672 (w); *m/z* calculated for $C_{15}H_{11}N_3O_2$ $[M+H]^+$ 266.0924, found 266.0925, $[M+Na]^+$ calc. 288.07435, found 288.0744, $[M+K]^+$ calc. 304.04828, found 304.0413.

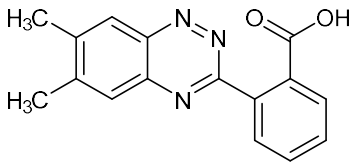
Methyl 2-(6,7-dimethylbenzo[e][1,2,4]triazin-3-yl) benzoate 40c:



Methyl 2-(6,7-dimethylbenzo[e][1,2,4]triazine-3-yl) benzoate **40c**: 3-((4.5-dimethyl-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned dark brown-black. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product ws purified by column chromatography (hexane/ethyl acetate 90:10). Yellow powder was collected ($4.8x10^{-2}$ g, 48%). Melting point: 150-151 ºC.

^1H NMR (500 MHz, $CDCl_3$): δ 2.56 (s, 3H), 2.58 (s, 3H), 3.71 (s, 3H), 7.60 (dt, J = 7.6, 1.5 Hz, 1H) 7.68 (dt, J = 7.5, 1.5 Hz, 1H), 7.82 (s, 1H), 7.87 (dd, J = 7.7, 1.0 Hz, 1H), 8.20 (dd, J = 8.0, 1.0 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.30, 160.93, 147.74, 145.40, 141.94, 139.90, 136.62, 132.83, 131.22, 130.71, 129.99, 129.53, 128.05, 127.45, 52.26, 21.11, 20.55 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.22, 130.71, 129.99, 129.52, 128.04, 127.45, 52.26, 21.11, 20.55; FTIR (cm^{-1}): 2923 (m), 1723 (s), 1456 (w), 1377 (w), 1331 (w), 1286 (m), 1249 (w), 1114 (m), 1089 (m), 1049 (m), 1023 (w), 999 (w), 862 (w), 771 (m), 719 (s), 706 (w);*m/z* calculated for $C_{17}H_{15}N_3O_2$ $[M+H]^+$ 294.1237, found 294.1234, $[M+Na]^+$ calc. 316.10565, found 316.1056, $[M+K]^+$ calc. 332.07958, found 322.0797.

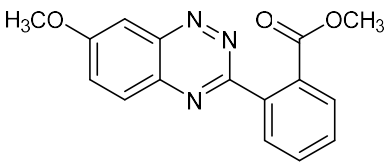
2-(6,7-dimethylbenzo[e][1,2,4]triazin-3-yl) benzoic acid 41c:



Product 2-(6,7-dimethylbenzo[e][1,2,4]triazin-3-yl) benzoic acid **41c**: 3-((4.5-dimethyl-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned dark brown-black. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow powder was collected ($3.2x10^{-2}$ g, 34%). Melting point: 214-215 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.56 (s, 3H), 2.58 (s, 3H), 7.64 (dt, J = 7.6, 1.0 Hz, 1H), 7.73 (dt, J = 7.6, 1.5 Hz, 1H), 7.85 (s, 1H), 8.07 (dd, J = 7.5, 1.0 Hz, 1H), 8.20 (dd, J = 7.5, 1.0 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.87, 160.94, 148.27, 145.37, 142.36, 139.81, 136.76, 131.90, 131.77, 131.25, 130.82, 130.10, 127.96, 127.33, 21.11, 20.57 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.89, 131.25, 130.82, 130.09, 127.95, 127.32, 21.11, 20.57; FTIR (cm^{-1}): 2925 (w), 1706 (s), 1653 (w), 1468 (w), 1442 (w), 1332 (w), 1260 (w), 1220 (m), 1126 (m), 1020 (w), 997 (w), 870 (m), 794 (m), 771 (s), 754 (w), 724 (s), 668 (s), 634 (m); *m/z* calculated for $C_{16}H_{13}N_3O_2$ $[M+H]^+$ 280.10805, found 280.1078, $[M+Na]^+$ calc. 302.0900, found 302.0899, $[M+K]^+$ calc. 318.06393, found 318.0602.

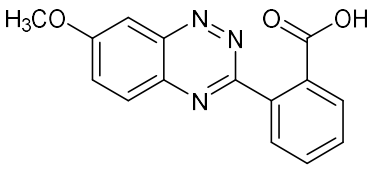
Methyl 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate 40d:



Methyl 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate **40d:** 3-((4-methoxy-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of ethanol and filtrated by vacuum. Orange crystals were collected ($5.41x10^{-2}$ g, 54%). Melting point: 150-151 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H), 4.09 (s, 3H), 7.63 (dt, J = 7.5, 1.0 Hz, 1H), 7.67 (dd, J = 9.5, 2.5, 1H), 7.71 (dt, J = 7.5, 1.5, 1H), 7.78 (d, J = 2.5 Hz, 1H), 7.90 (dd, J = 7.5, 1.0 Hz, 1H), 7.99 (d, J = 9.5 Hz, 1H), 8.21 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.24, 161.03, 160.36, 147.33, 137.72, 136.50, 132.70, 131.27, 130.62, 130.35, 129.99, 129.94, 129.58, 105.05, 56.23, 52.25 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.27, 130.62, 130.35, 129.99, 129.94, 129.58, 56.23, 52.25; FTIR (cm^{-1}): 1726 (s), 1618 (w), 1506 (w), 1426 (s), 1290 (m), 1254 (w), 1199 (s), 1171 (w), 1089 (s), 1015 (m), 838 (s), 776 (m), 763 (s), 737 (m), 696 (m), 604 (s); *m/z* calculated for $C_{16}H_{13}N_3O_3$ $[M+H]^+$ 296.1029, found 296.1027, $[M+Na]^+$ calc. 318.0850, found 318.0848, $[M+K]^+$ calc. 334.0589, found 334.0588.

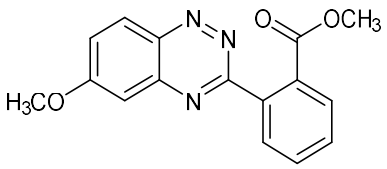
2-(7-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid 41d:



Product 2-(7-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid **41d:** 3-((4-methoxy-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate s performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained ($4.00x10^{-2}$ g, 42%). Melting point: 230-231 ºC.

^{1}H NMR (500 MHz, DMSO-d_6): δ 4.05 (s, 3H), 7.69 (dt, J = 7.5, 1.0 Hz,1H), 7.76 (dt, J = 7.5, 1.5 Hz, 1H), 7.85 (dd, J = 9.0, 2.5 Hz, 1H), 7.89 (dd, J = 7.5, 1.0 Hz, 1H), 7.92 (d, J = 2.5 Hz, 1H), 7.96 (dd, J = 7.5, 1.0 Hz, 1H), 8.08 (d, J = 9.5 Hz, 1H), 12.88 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 169.55, 161.32, 161.06, 147.27, 137.31, 137.10, 133.85, 131.69, 131.05, 131.02, 130.40, 130.35, 129.78, 105.46, 56.92 ppm; DEPT 135 (126 MHz, DMSO-d_6): δ 131.70, 131.05, 131.02, 130.40, 130.35, 129.78, 105.46, 56.92; FTIR (cm^{-1}): 1705 (s), 1620 (w), 1501 (m), 1432 (m), 1288 (w), 1228 (s), 1204 (s), 1178 (w), 1117 (m), 1042 (m), 1015 (s), 850 (s), 773 (s), 723 (m), 668 (m); *m/z* calculated for $C_{15}H_{11}N_3O_3$ $[M+H]^+$ 282.0867, found 282.0870, $[M+Na]^+$ calc. 304.0692, found 304.0692, $[M+K]^+$ calc. 320.0432, found 320.0368.

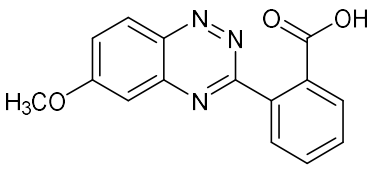
Methyl 2-(6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate 40e:



Methyl 2-(6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate **40e:** 3-((5-methoxy-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned light brown. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 60:40). Oily sticky solid was obtained ($4.8x10^{-2}$ g, 47%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (s, 3H), 4.03 (s, 3H), 7.24 (d, J = 2.5 Hz, 1H), 7.49 (dd, J = 10.0, 2.5 Hz, 1H), 7.61 (dt, J = 7.5, 1.5 Hz, 1H), 7.69 (dt, J = 7.5, 1.0 Hz, 1H), 7.89 (dd, J = 7.5, 1.0 Hz, 1H), 8.15 (dd, J = 7.5, 1.0 Hz, 1H), 8.39 (d, J = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.13, 165.18, 161.70, 143.67, 143.52, 136.79, 132.75, 131.29, 130.95, 130.72, 130.07, 129.61, 125.33, 104.56, 56.33, 52.28 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.29, 130.95, 130.72, 130.07, 129.61, 125.33, 104.56, 56.33, 52.28; FTIR (cm^{-1}): 1724 (s), 1615 (s), 1510 (w), 1468 (s), 1432 (w), 1410 (s), 1318 (w), 1291 (m), 1241 (w), 1219 (s), 1180 (w), 1113 (m), 1088 (m), 1048 (w), 1013 (m), 836 (m), 770 (m), 728 (s), 708 (m); *m/z* calculated for $C_{16}H_{13}N_3O_3$ $[M+H]^+$ 296.10297, found 296.1027, $[M+Na]^+$ calc. 318.0849, found 318.0850, $[M+K]^+$ calc. 334.0588, found 334.0590.

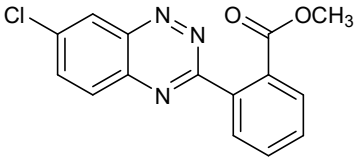
2-(6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid 41e:



Product 2-(6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid **41e**: 3-((5-methoxy-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 15 min. The color of the solution turned light brown. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained ($4.3x10^{-2}$ g, 45%). Melting point: 212-213 ºC.

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 4.05 (s, 3H), 7.44 (d, J = 2.5 Hz, 1H), 7.66-7.71 (m, 2H), 7.75 (dt, J = 7.5, 1.5 Hz, 1H), 7.89 (dd, J = 7.5, 1.0 Hz, 1H), 7.93 (dd, J = 7.5, 1.0 Hz, 1H), 8.46 (d, J = 9.5 Hz, 1H), 12.90 (s, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$): δ ;168.30, 164.38, 161.36, 142.39, 142.23, 136.30, 132.88, 130.52, 129.94, 129.94, 129.35, 128.67, 124.91, 104.27, 56.12 ppm; DEPT 135 (126 MHz, DMSO-*d*$_6$): δ 130.52, 129.94, 129.94, 129.36, 128.67, 124.91, 104.27, 56.12; FTIR (cm^{-1}): 1717 (s), 1615 (s), 1469 (s), 1319 (w), 1221 (m), 1179 (w), 1116 (m), 1089 (w), 1013 (m), 837 (m), 769 (m), 726 (m); *m/z* calculated for $C_{15}H_{11}N_3O_2$ $[M+H]^+$ 282.08732, found 282.0872, $[M+Na]^+$ calc. 304.06926, found 304.0694, $[M+K]^+$ calc. 320.0432, found 320.0400.

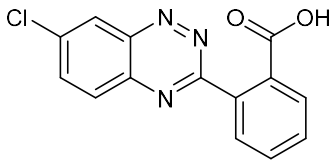
Methyl 2-(7-chlorobenzo[e][1,2,4]triazin-3-yl) benzoate 40f:



Methyl 2-(7-chlorobenzo[e][1,2,4]triazin-3-yl) benzoate **40f :** 3-((4-Chloro-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned dark orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of ethanol and filtrated by vacuum. Orange crystals were obtained (0.82 mg, 78%). Melting point:113-114 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 3H), 7.65 (dt, J = 7.5, 1.5 Hz, 1H), 7.72 (dt, J = 7.5, 1.5 Hz, 1H), 7.91 (dd, J = 7.5, 1.0 Hz, 1H), 7.94 (dd, J = 9.0, 2.5 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.18 (dd, J = 7.5, 1.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H);^{13}C NMR (126 MHz, $CDCl_3$): δ 168.87, 161.62, 145.76, 139.24, 136.89, 136.56, 136.09, 132.79, 131.44, 130.88, 130.53, 130.48, 129.77, 128.25, 52.34 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 136.90, 131.44, 130.88, 130.53, 130.48, 129.77, 128.25, 52.34; FTIR (cm^{-1}): 1729 (s), 1689 (w), 1506 (m), 1413 (m), 1288 (s), 1118 (m), 1084 (m), 1043 (w), 1011 (m), 902 (m), 849 (m), 839 (m), 774 (m), 741 (m), 721 (s), 705 (m); *m/z* calculated for $C_{15}H_{10}ClN_3O_2$ $[M+H]^+$ 300.05343, found 300.0534, $[M+Na]^+$ calc. 322.03537, found 322.0351, $[M+K]^+$ calc. 338.00931, found 338.0094.

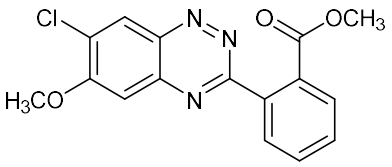
2-(7-chlorobenzo[e][1,2,4]triazin-3-yl) benzoic acid 41f:



Product 2-(7-chlorobenzo[e][1,2,4]triazin-3-yl) benzoic acid **41f:** 3-((4-Chloro-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.34 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned dark orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were collected (0.19 mg, 19%). Melting point: 176-178 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dt, J = 7.5, 1.0 Hz, 1H), 7.74 (dt, J = 7.5, 1.0 Hz, 1H), 7.92 (dd, J = 9.0, 2.0 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 8.04-8.09 (m, 2H), 8.53 (d, J = 2.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.14, 161.77, 145.70, 139.24, 137.01, 136.74, 136.70, 132.09, 131.63, 131.10, 130.56, 130.43, 130.38, 128.10 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 137.01, 132.09, 131.10, 130.56, 130.43, 130.38, 128.11; FTIR (cm^{-1}): 1704 (s), 1488 (w), 1431 (w), 1417 (w), 1224 (s), 1206 (m), 1117 (m), 1043 (m), 1019 (m), 1006 (m), 847 (s), 804 (w), 772 (s), 720 (m), 668 (s), 652 (m), 647 (m), 636 (m); *m/z* calculated for $C_{14}H_8ClN_3O_2$ $[M+H]^+$ 286.03778, found 286.0378, $[M+Na]^+$ calc. 308.01972, found 308.0198, $[M+K]^+$ calc. 323.99366, found 323.0094.

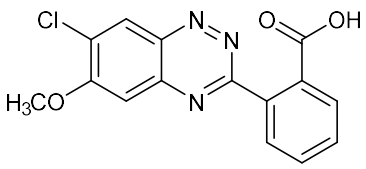
Methyl 2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate 40g:



Methyl 2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoate **40g**: 3-((4,5-dichloro-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.31 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained (0.42 mg, 42%). Melting point:164-166 ºC.

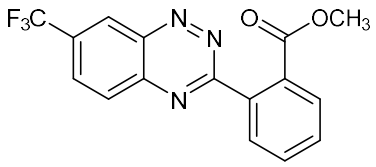
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (s, 3H), 4.13 (s, 3H), 7.33 (s, 1H), 7.62 (dt, J = 7.6, 1.5 Hz, 1H), 7.69 (dt, J = 7.6, 1.5 Hz, 1H), 7.90 (dd, J = 8.0, 1.0 Hz, 1H), 8.13 (dd, J = 8.0, 1.0 Hz, 1H), 8.55 (s,1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.99, 161.78, 160.67, 142.73, 142.12, 136.49, 132.69, 131.37, 130.70, 130.25, 130.20, 129.87, 129.70, 105.74, 57.25, 52.32 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.37, 130.70, 130.25, 129.87, 129.70, 105.74, 57.25, 52.33; FTIR (cm^{-1}): 1727 (s), 1695 (w), 1602 (w), 1474 (m), 1410 (m), 1282 (m), 1242 (w), 1226 (m), 1116 (w), 1089 (m), 1040 (m), 1023 (w), 999 (w), 880 (w), 841 (m), 732 (s); *m/z* calculated for $C_{16}H_{12}ClN_3O_3$ $[M+H]^+$ 330.0640, found 330.0637, $[M+Na]^+$ calc. 352.04594, found 352.0459, $[M+K]^+$ calc. 368.01988, found 368.0198.

2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid 41g:



Product 2-(7-chloro-6-methoxybenzo[e][1,2,4]triazin-3-yl) benzoic acid **41g**: 3-((4,5-dichloro-2-nitrophenyl) amino) isoindolin-1-one (0.10 g, 0.31 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl. The crude precipitate was filtrated using a Buchner funnel. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were obtained (0.46 mg, 48%). Melting point: 215-216 ºC.
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03 (s, 3H), 7.37 (s, 1H), 7.63(dt, J = 7.6, 1.0 Hz, 1H), 7.72 (dt, J = 7.6, 1.5 Hz, 1H), 7.98 (dd, J = 7.5, 1.0 Hz, 1H), 8.11 (dd, J = 8.0, 1.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.88, 161.63, 160.82, 142.71, 142.11, 136.68, 131.91, 131.86, 131.03, 130.49, 130.42, 130.29, 129.71, 105.79, 57.23 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 131.92, 131.03, 130.42, 130.29, 129.71, 105.76, 57.23; FTIR (cm^{-1}): 1705 (s), 1598 (w), 1474 (s), 1413 (s), 1264 (m), 1244 (s), 1225 (m), 1123 (w), 1041 (m), 1021 (m), 997 (m), 768 (s); *m/z* calculated for $C_{15}H_{10}ClN_3O_3$ $[M+H]^+$ 316.04835, found 316.0483 $[M+Na]^+$ calc. 338.03029, found 338.0305, $[M+K]^+$ calc. 354.00423, found 353.9991.

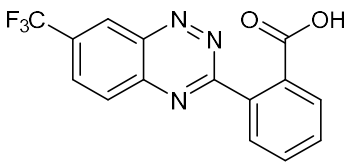
Methyl 2-(7-(trifluoromethyl)benzo[e][1,2,4]triazin-3-yl) benzoate 40h:



Methyl 2-(7-(trifluoromethyl)benzo[e][1,2,4]triazin-3-yl) benzoate **40h**: 3-((2-nitro-4-(trifluoromethyl) phenyl) amino) isoindolin-1-one (0.10 g, 0.31 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The organic layer was then dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 90:10). Yellow oily sticky solid was obtained (0.44 mg, 44%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (s, 3H), 7.67 (t, J = 8 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H), 8.16 (dd, J = 8.75, 2.0 Hz, 1H), 8.18 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 9 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.69, 162.71, 144.65, 141.56, 135.91, 132.87, 132.22, 131.56, 131.06, 130.81, 130.72, 129.88, 127.92, 124.10, 121.93, 52.40 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 132.87, 132.22, 131.56, 131.06, 130.81, 130.72, 129.89, 127.92, 52.40; FTIR (cm^{-1}): 1731 (s), 1684 (m), 1561 (m), 1421 (m), 1322 (s), 1186 (m), 1149 (m), 1122 (s), 1092 (m), 1056 (m), 772 (m), 745 (m), 708 (s), 614 (s); *m/z* calculated for $C_{16}H_{10}F_3N_3O_2$ $[M+H]^+$ 334.07979, found 334.0796, $[M+Na]^+$ calc. 356.06173, found 356.0614, $[M+K]^+$ calc. 372.03567, found 372.0358.

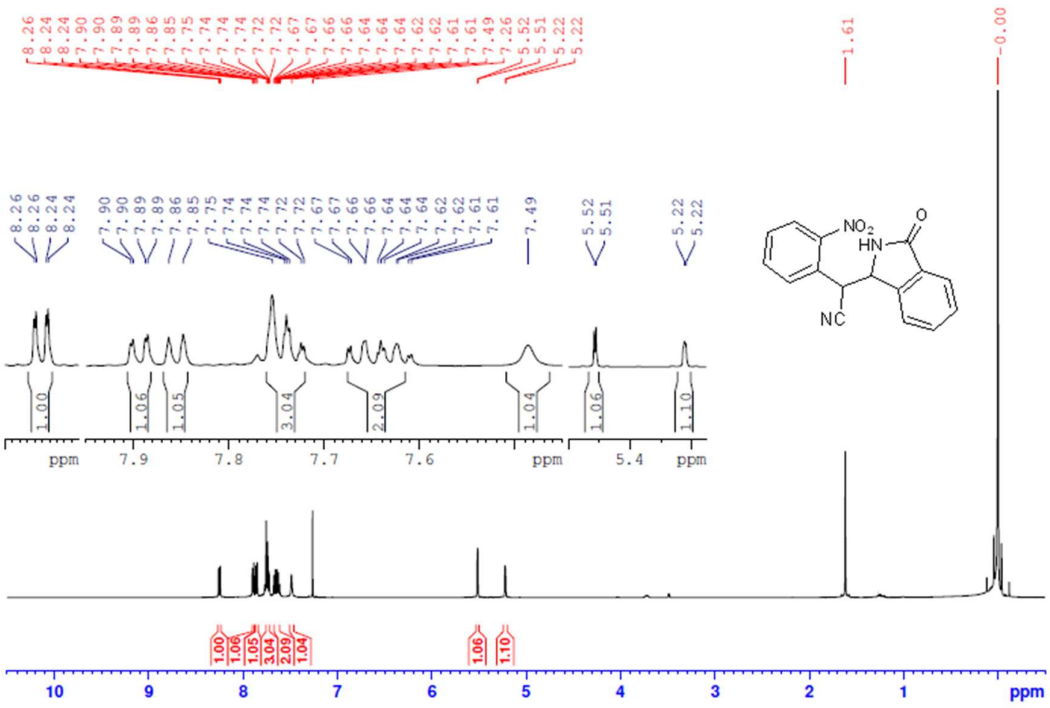
2-(7-(trifluoromethyl)benzo[e][1,2,4]triazin-3-yl) benzoic acid 41h:



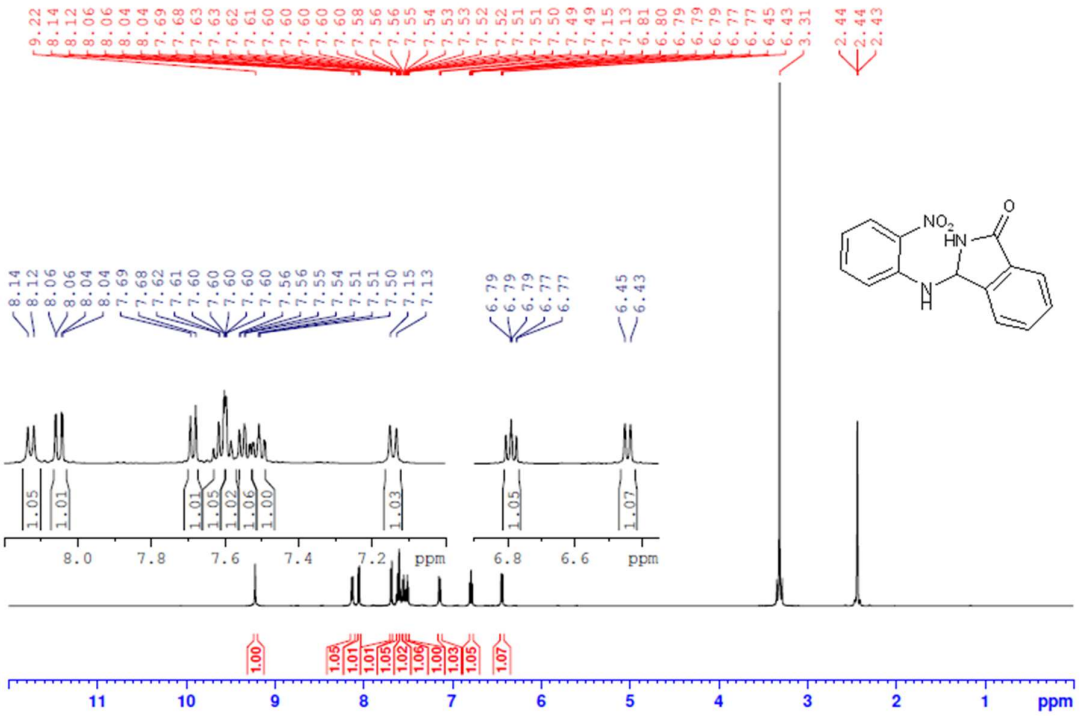
2-(7-(trifluoromethyl) benzo[e][1,2,4]triazin-3-yl) benzoic acid **41h:** 3-((2-nitro-4-(trifluoromethyl) phenyl) amino) isoindolin-1-one (0.10 g, 0.31 mmol) was dissolved in 10 mL of 5% KOH in MeOH. The mixture was heated for 30 min. The color of the solution turned orange. Reaction was stopped by adding few mL of water and extraction by ethyl acetate was performed. The aqueous layer was then acidified with concentrated HCl and extracted again by ethyl acetate. The latter was dried by anhydrous $MgSO_4$ and solvent was evaporated under reduced pressure. The product was recrystallized in 2 mL of methanol and filtrated by vacuum. Yellow crystals were collected (0.49 mg, 51%). Melting point: 161-162 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (t, J = 7.5 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 8.16 (dd, J = 9.0, 1.5 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.77, 162.80, 144.67, 141.55,136.61, 132.35, 132.27, 131.50, 131.30, 131.16, 130.76, 130.71, 130.53, 127.87, 127.84 ppm; DEPT 135 (126 MHz, $CDCl_3$): δ 132.28, 131.32, 131.18, 130.77, 130.71, 130.54, 127.87; FTIR (cm^{-1}): 1722 (m), 1423 (w), 1323 (s), 1235 (m), 1188 (m), 1155 (w), 1123 (s), 1057 (w), 1009 (w), 847 (m), 771 (m), 730 (m), 654 (m); *m/z* calculated for $C_{15}H_8F_3N_3O_2$ $[M+H]^+$ 320.06414, found 320.0643, $[M+Na]^+$ calc. 342.04608, found 342.0463, $[M+K]^+$ calc. 358.02002, found 358.0122.

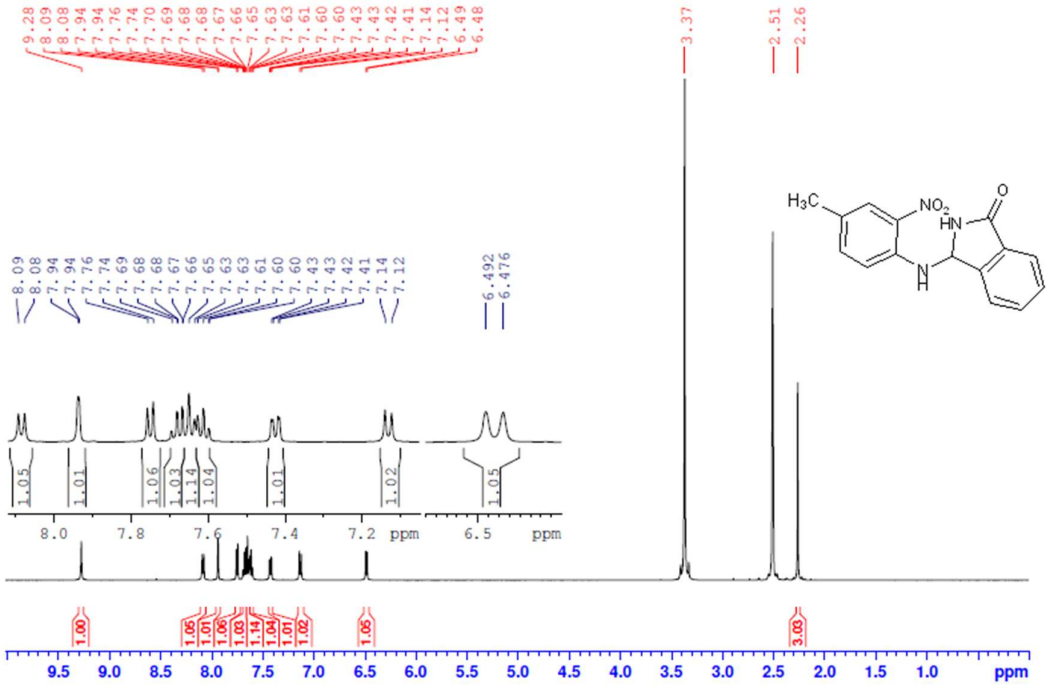
APPENDIX A ^{1}H NMR SPECTROSCOPY



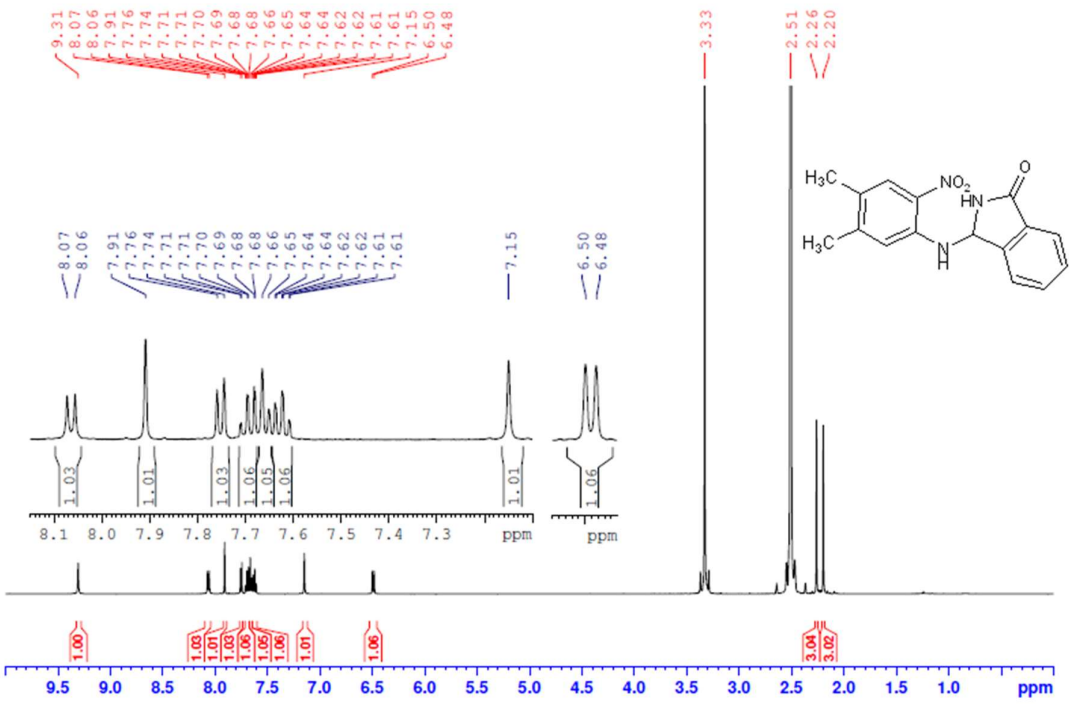
^{1}H-NMR of **31** in $CDCl_3$ at room temperature.



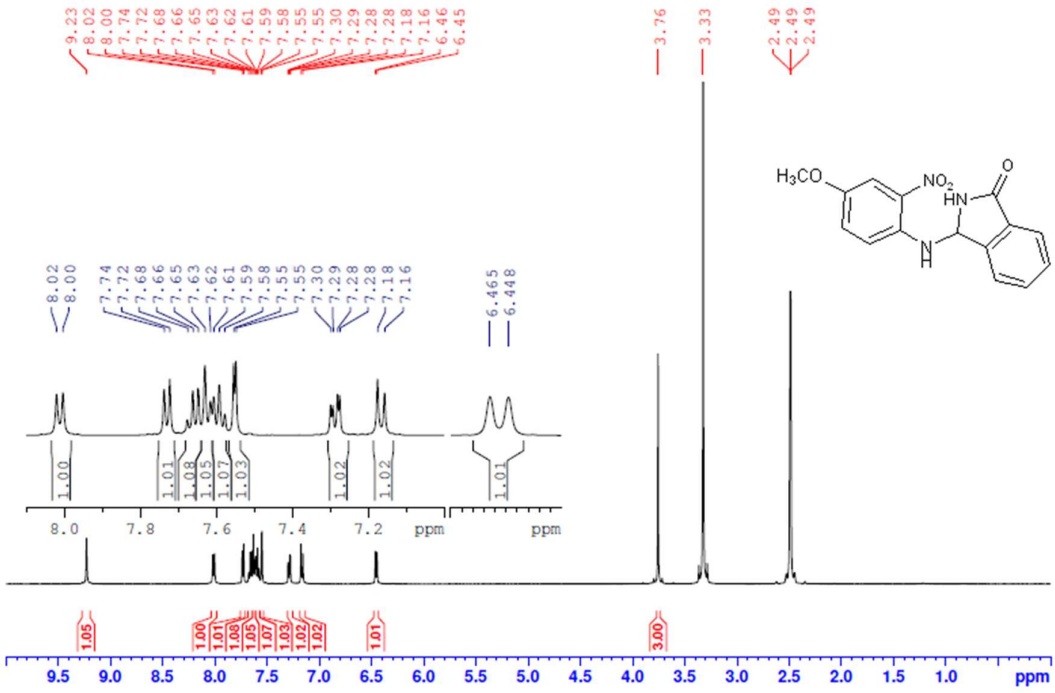
^{1}H-NMR of **34a** in DMSO-*d6* at room temperature.



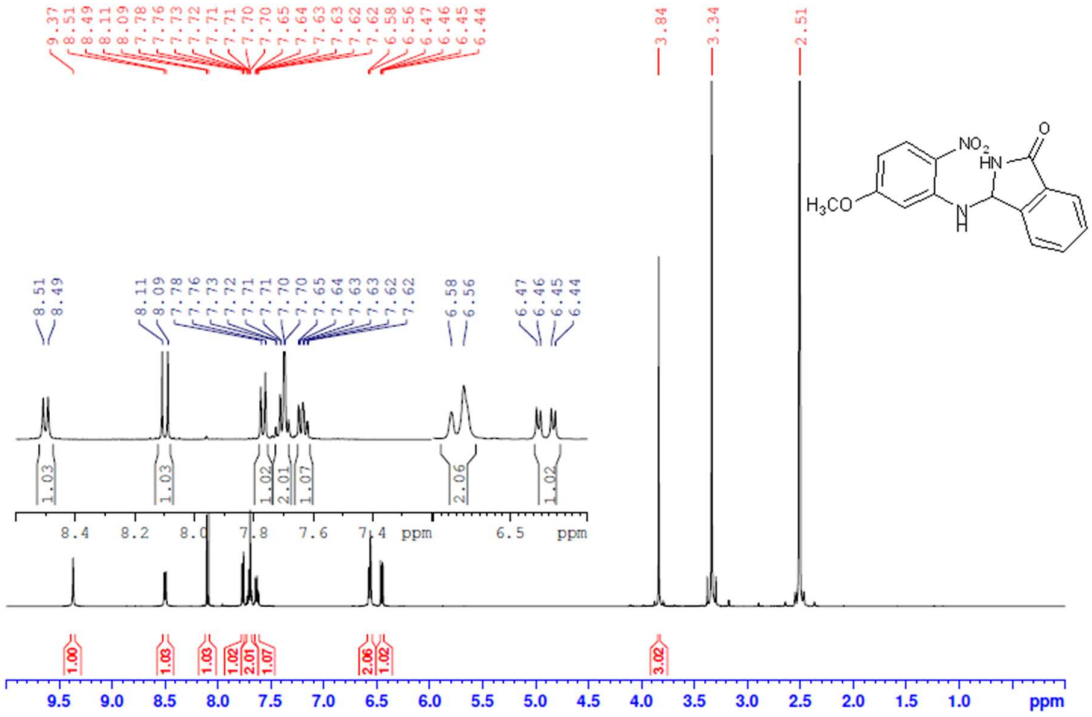
^{1}H-NMR of **34b** in DMSO-*d6* at room temperature.



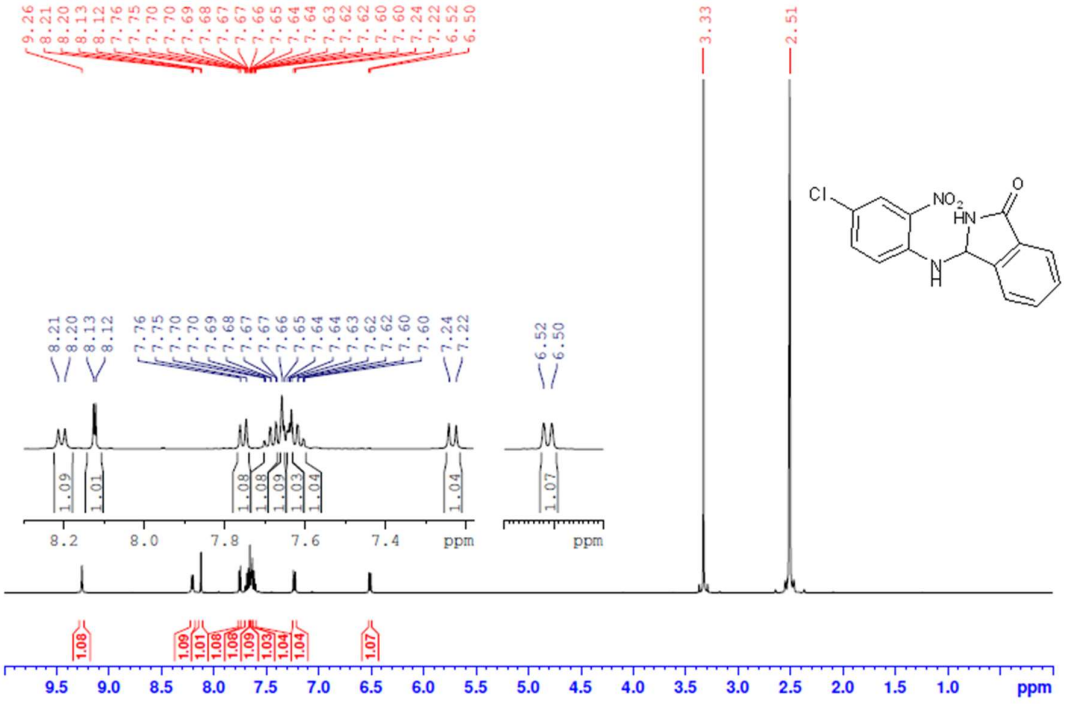
^{1}H-NMR of **34c** in DMSO-*d6* at room temperature.



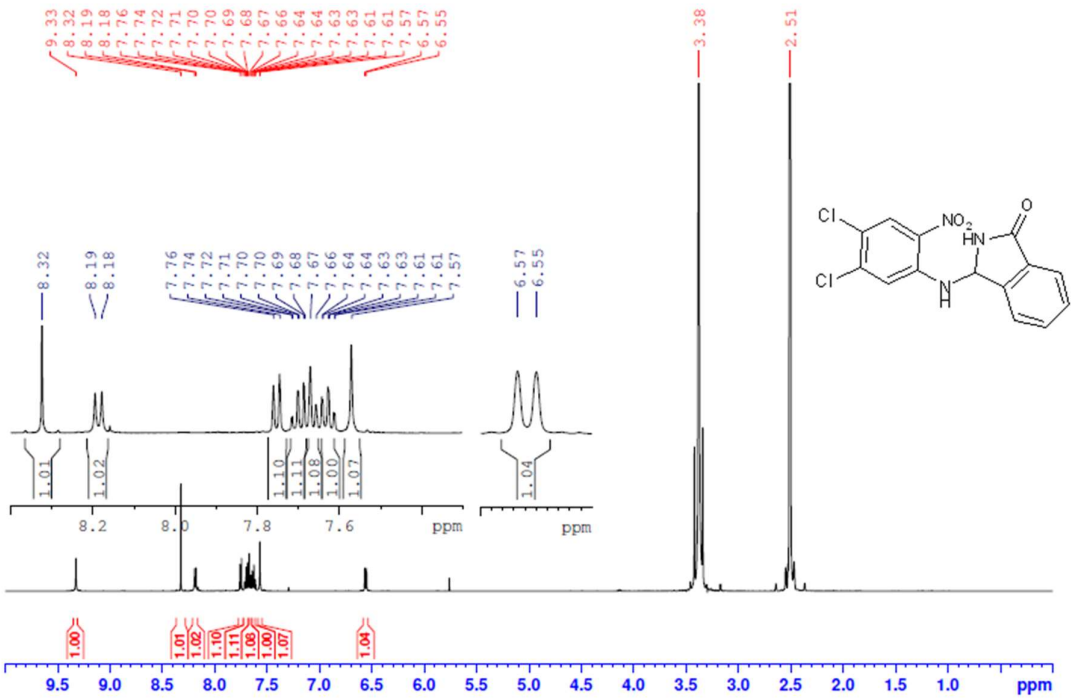
^{1}H-NMR of **34d** in DMSO-*d6* at room temperature.



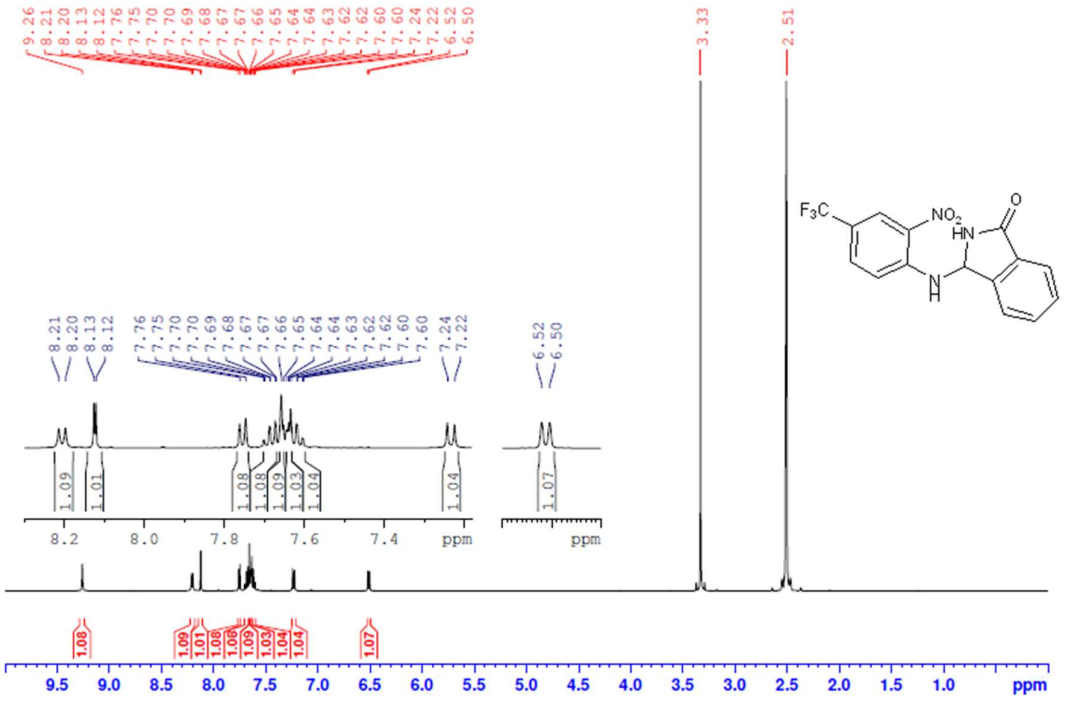
^{1}H-NMR of **34e** in DMSO-*d6* at room temperature.



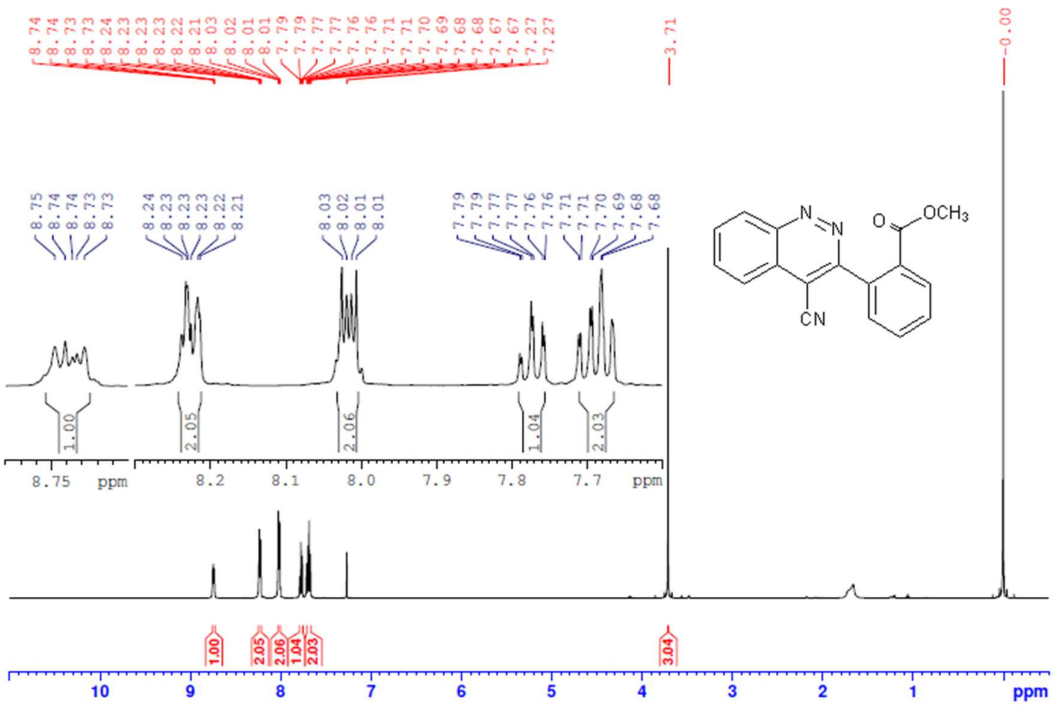
^{1}H-NMR of **34f** in DMSO-*d6* at room temperature.



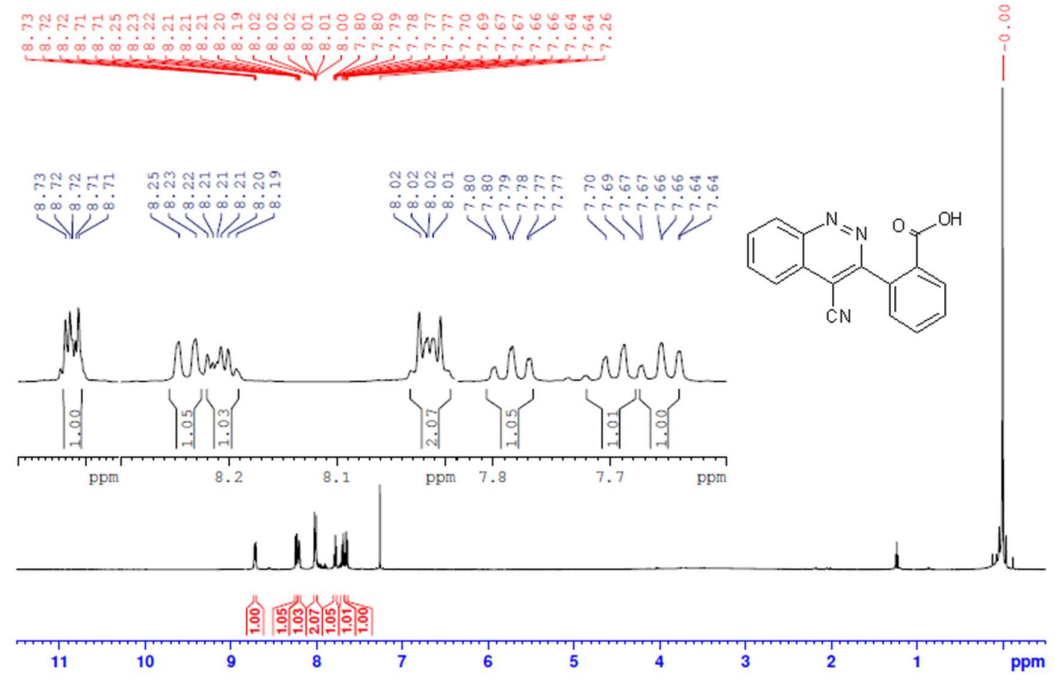
^{1}H-NMR of **34g** in DMSO-*d6* at room temperature.



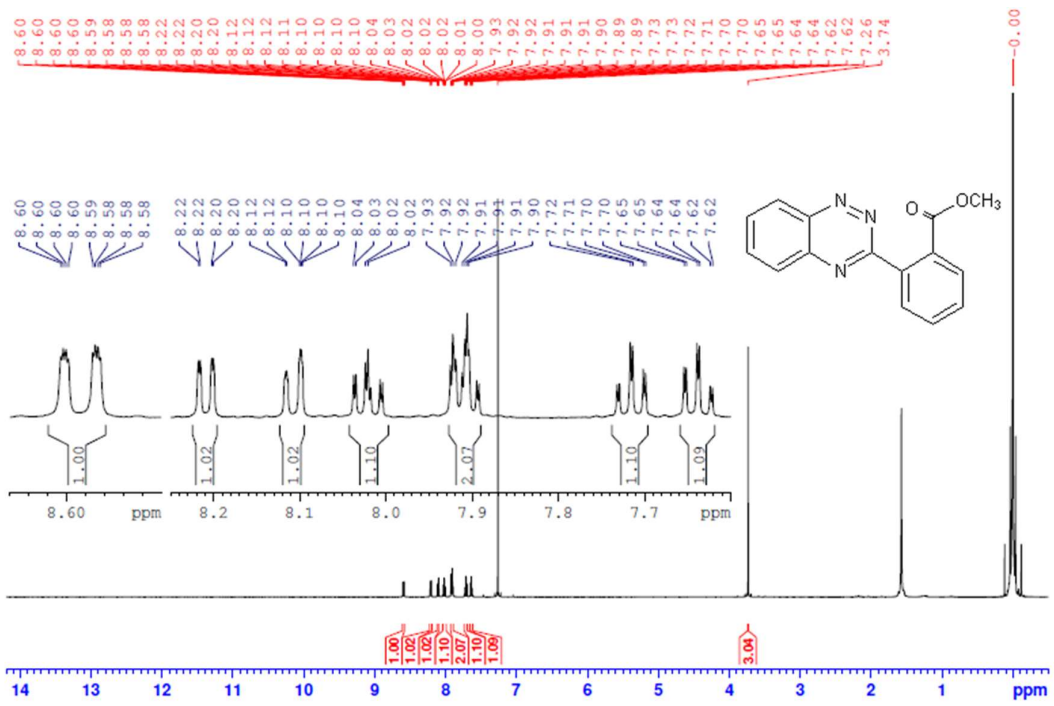
^{1}H-NMR of **34h** in DMSO-*d6* at room temperature.



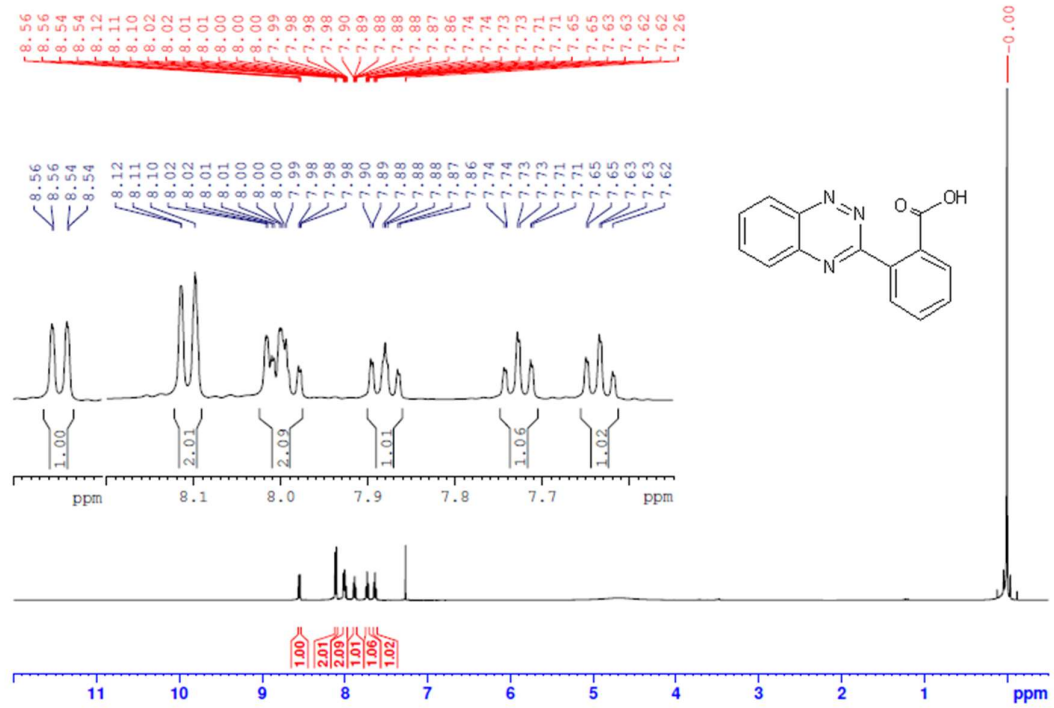
^{1}H-NMR of **38** in $CDCl_3$ at room temperature.



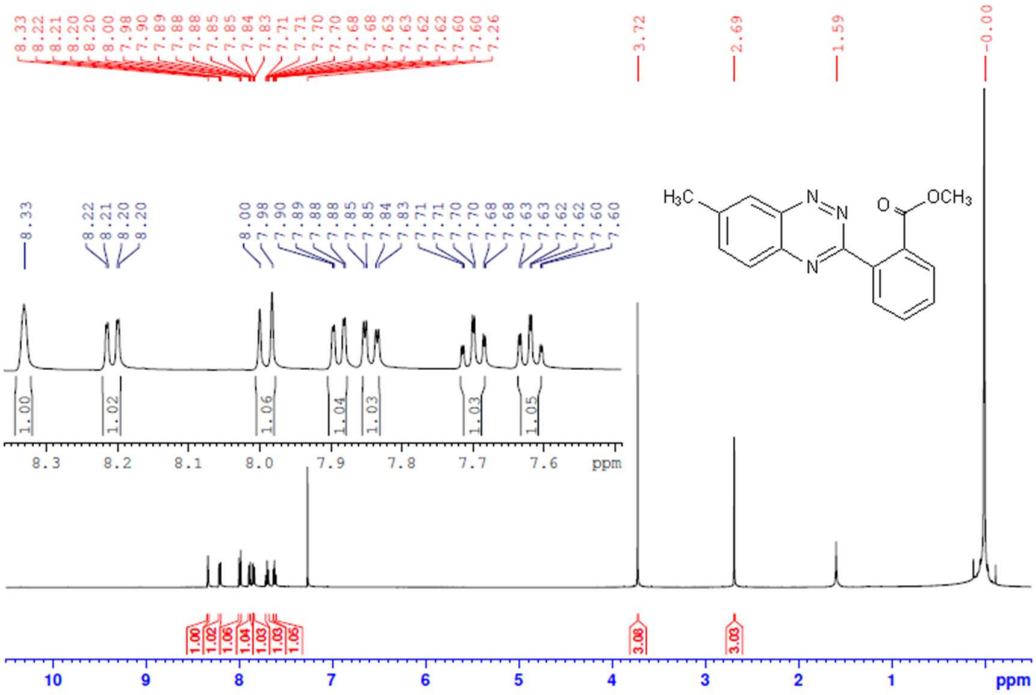
^{1}H-NMR of **39** in $CDCl_3$ at room temperature.



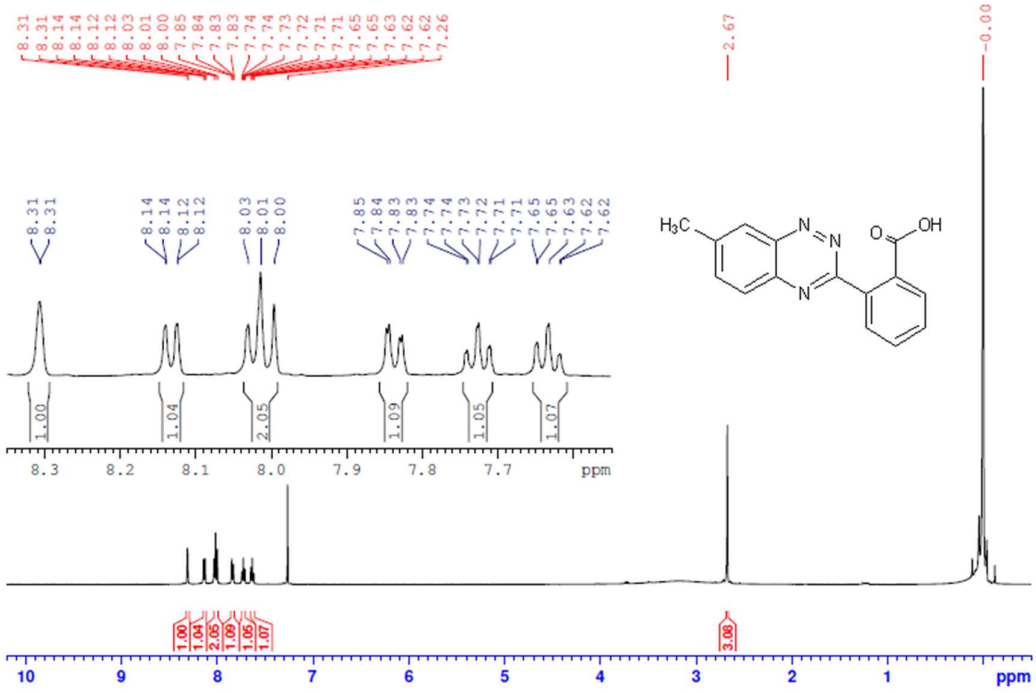
^{1}H-NMR of **40a** in $CDCl_3$ at room temperature.



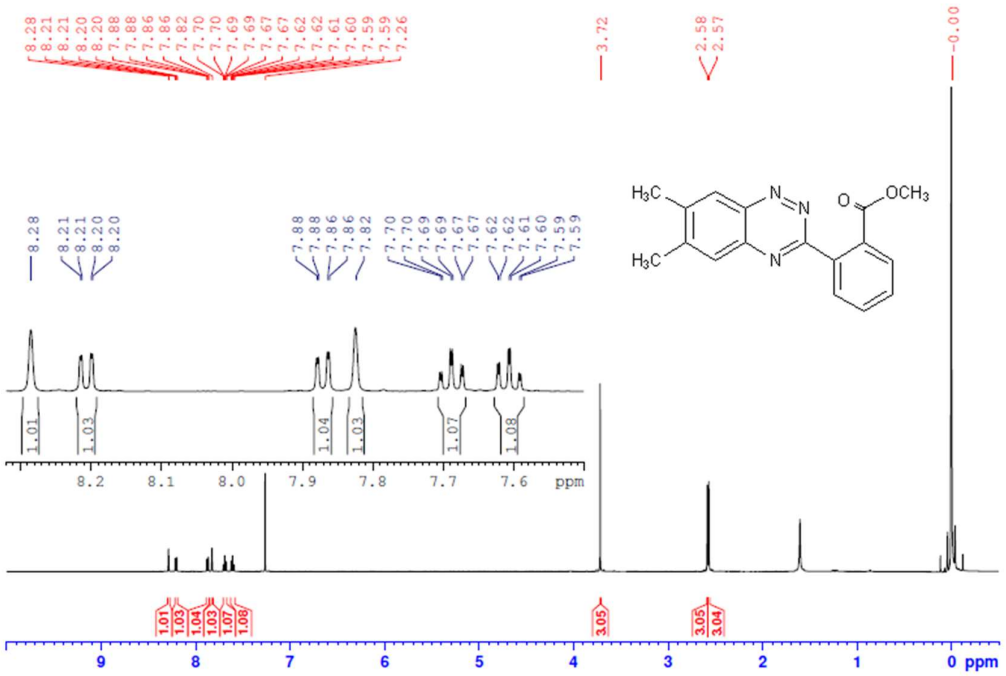
^{1}H-NMR of **41a** in $CDCl_3$ at room temperature.



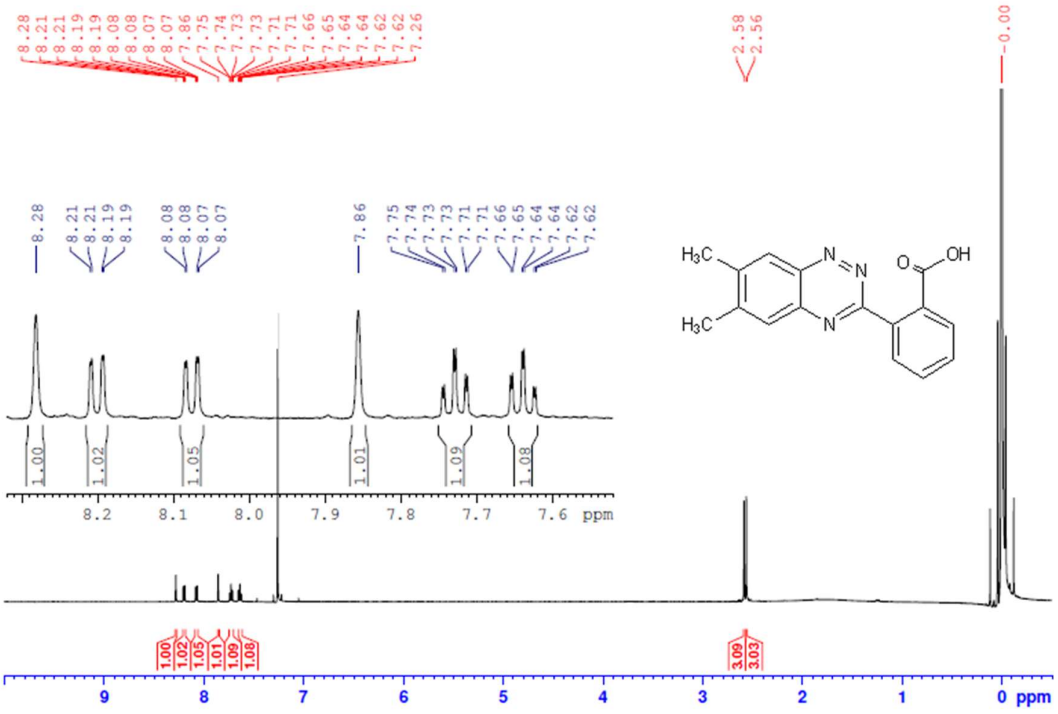
^{1}H-NMR of **40b** in $CDCl_3$ at room temperature.



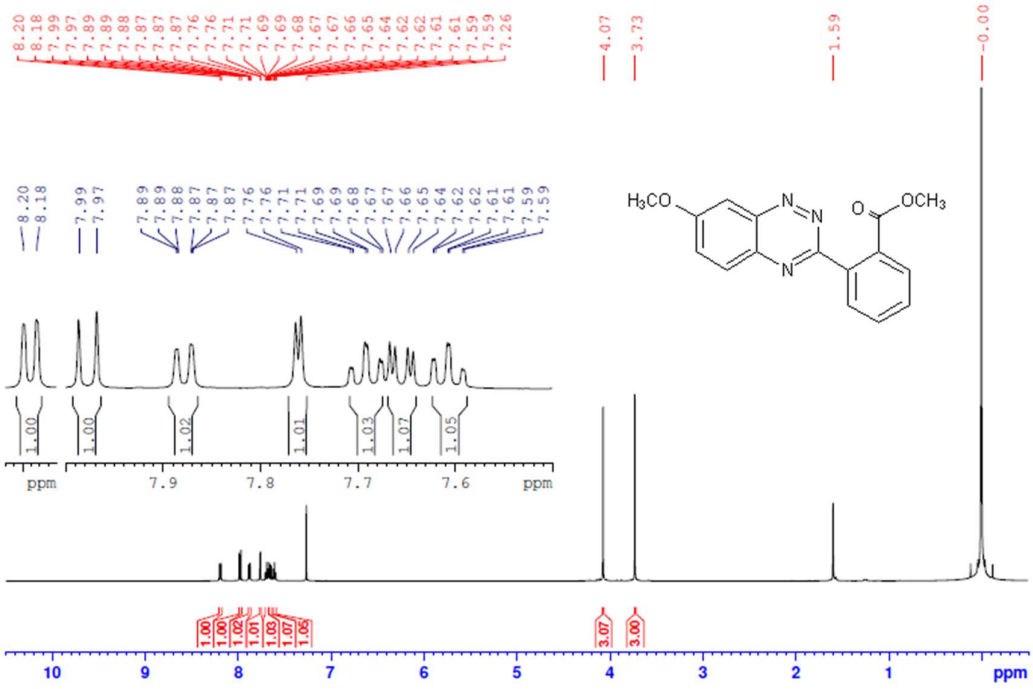
^{1}H-NMR of **41b** in $CDCl_3$ at room temperature.



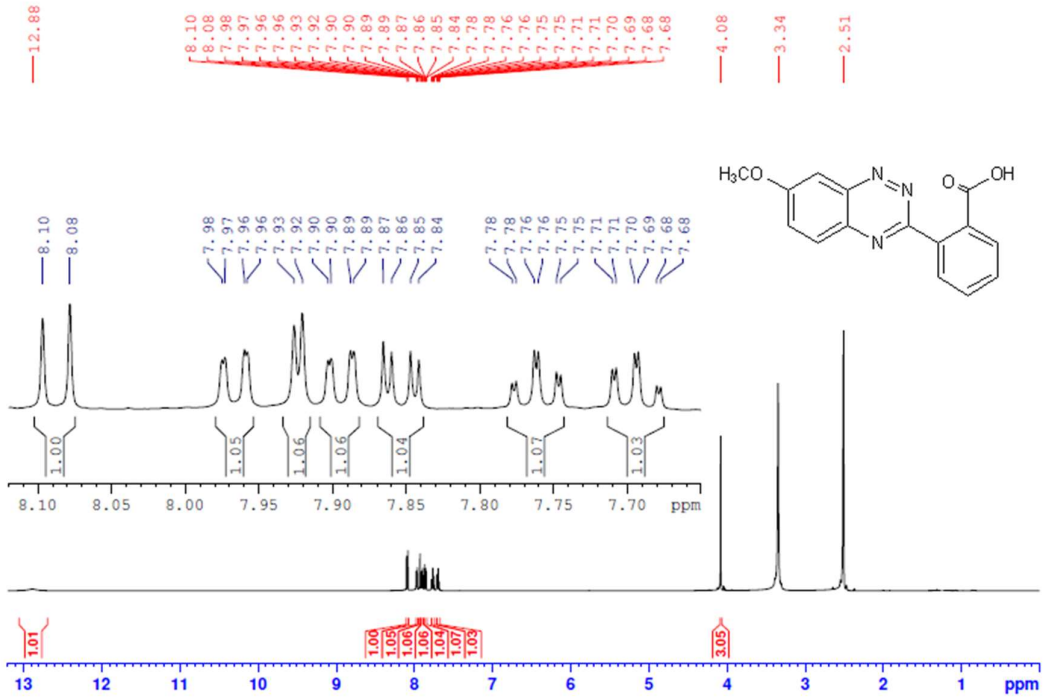
^{1}H-NMR of **40c** in $CDCl_3$ at room temperature.



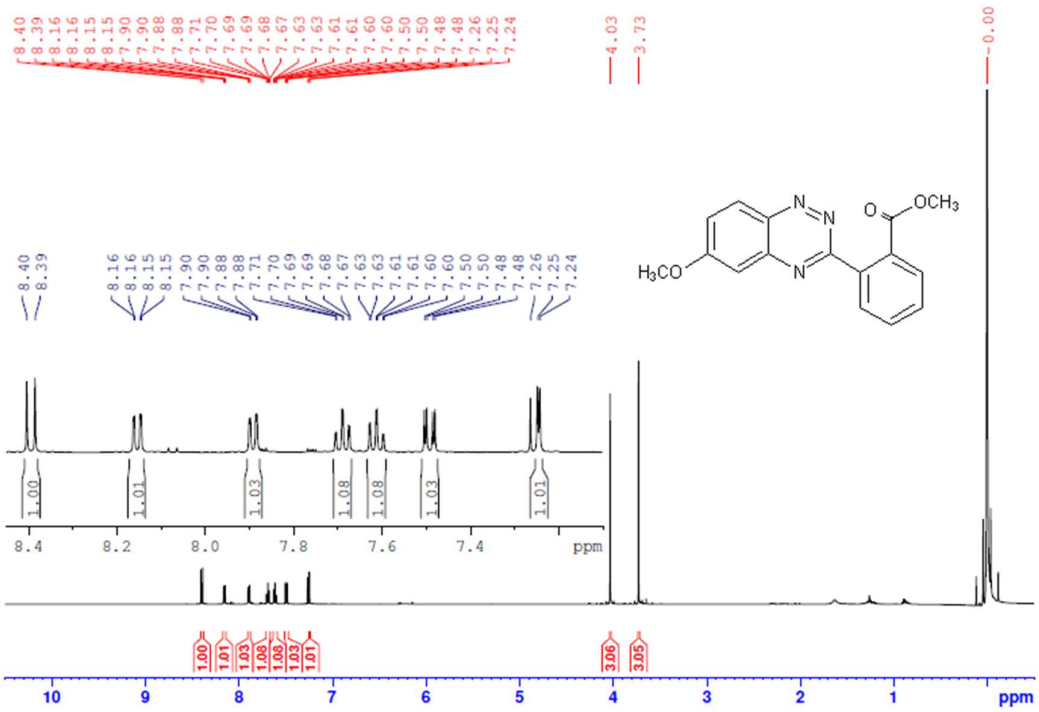
^{1}H-NMR of **41c** in $CDCl_3$ at room temperature.



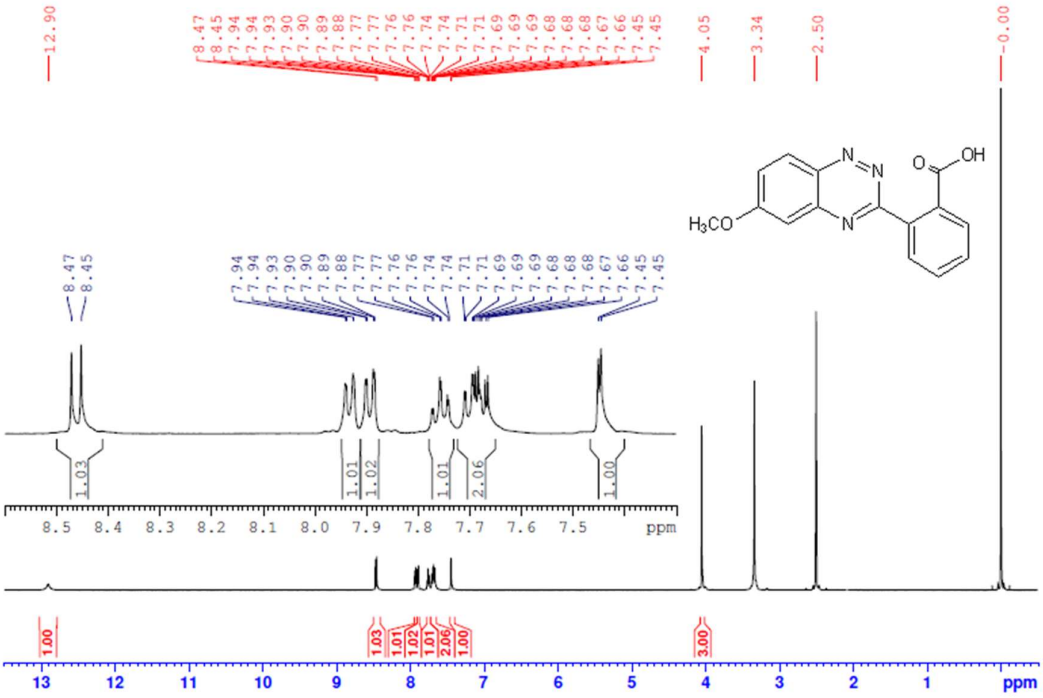
^{1}H-NMR of **40d** in $CDCl_3$ at room temperature.



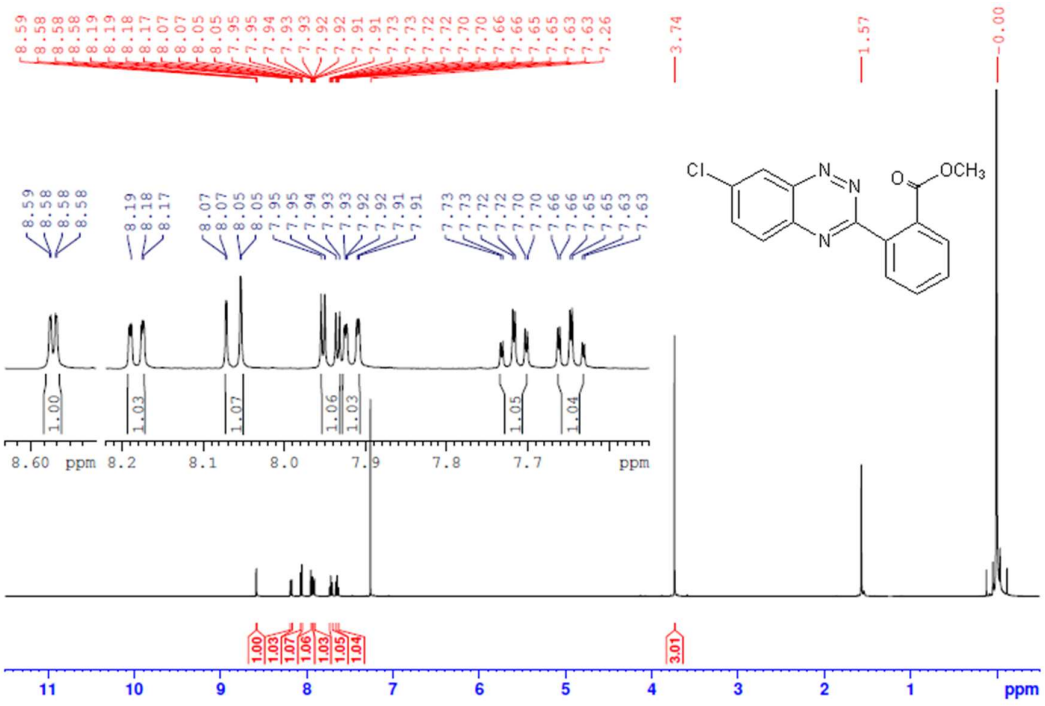
^{1}H-NMR of **41d** in DMSO-*d6* at room temperature.



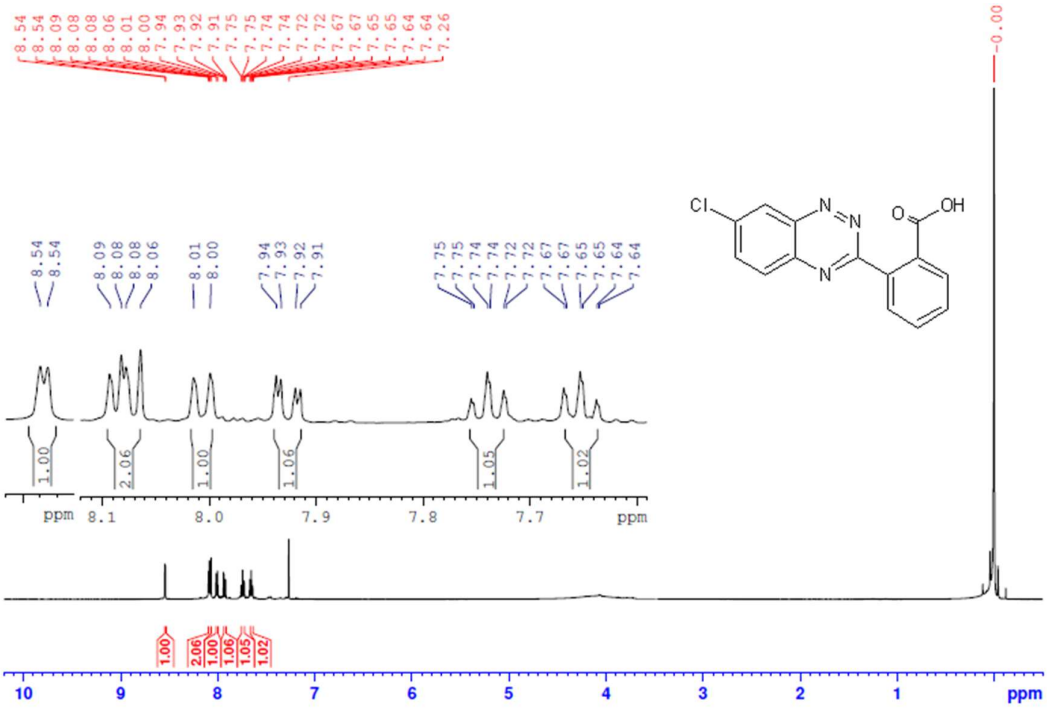
^{1}H-NMR of **40e** in $CDCl_3$ at room temperature.



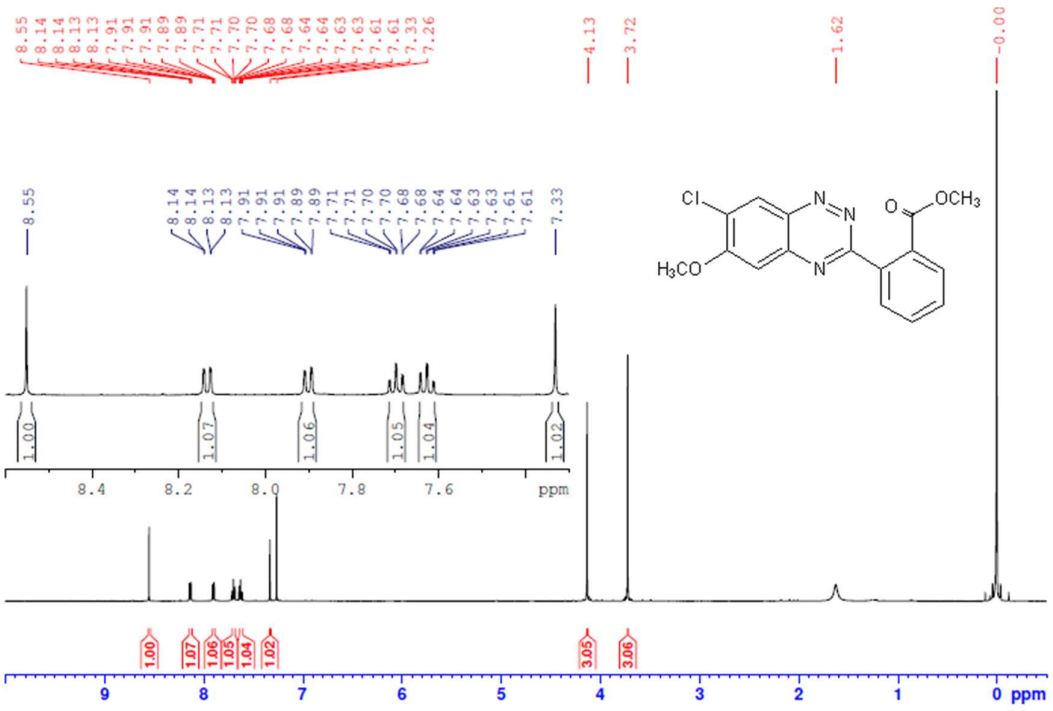
^{1}H-NMR of **41e** in DMSO-*d6* at room temperature.



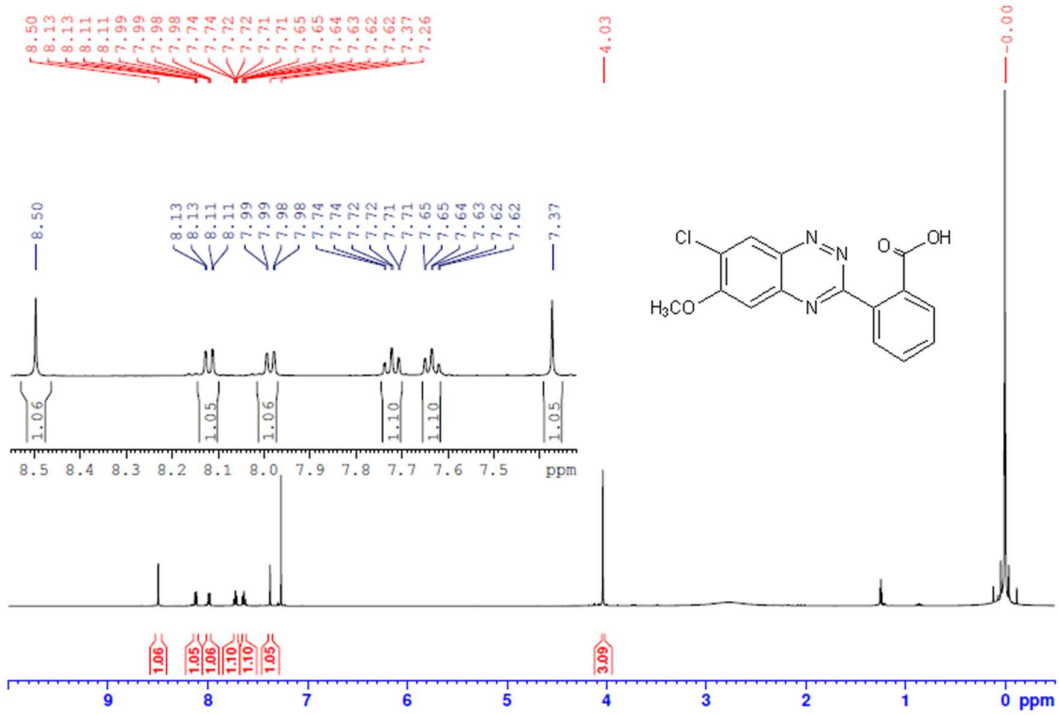
^{1}H-NMR of **40f** in $CDCl_3$ at room temperature.



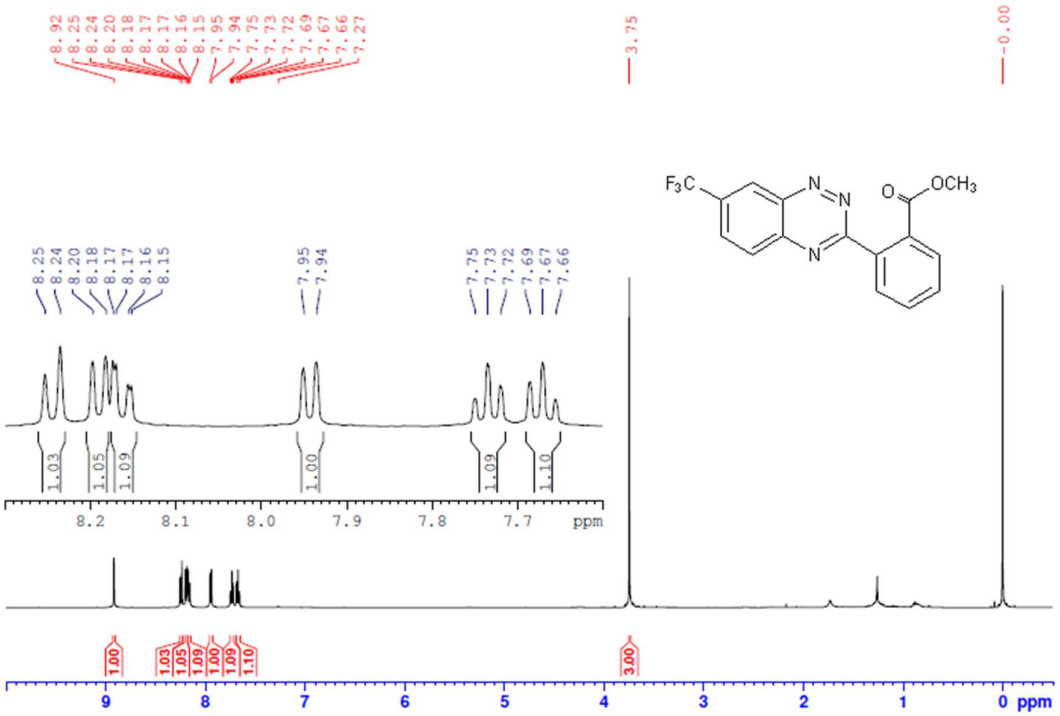
^{1}H-NMR of **41f** in $CDCl_3$ at room temperature.



^{1}H-NMR of **40g** in $CDCl_3$ at room temperature.



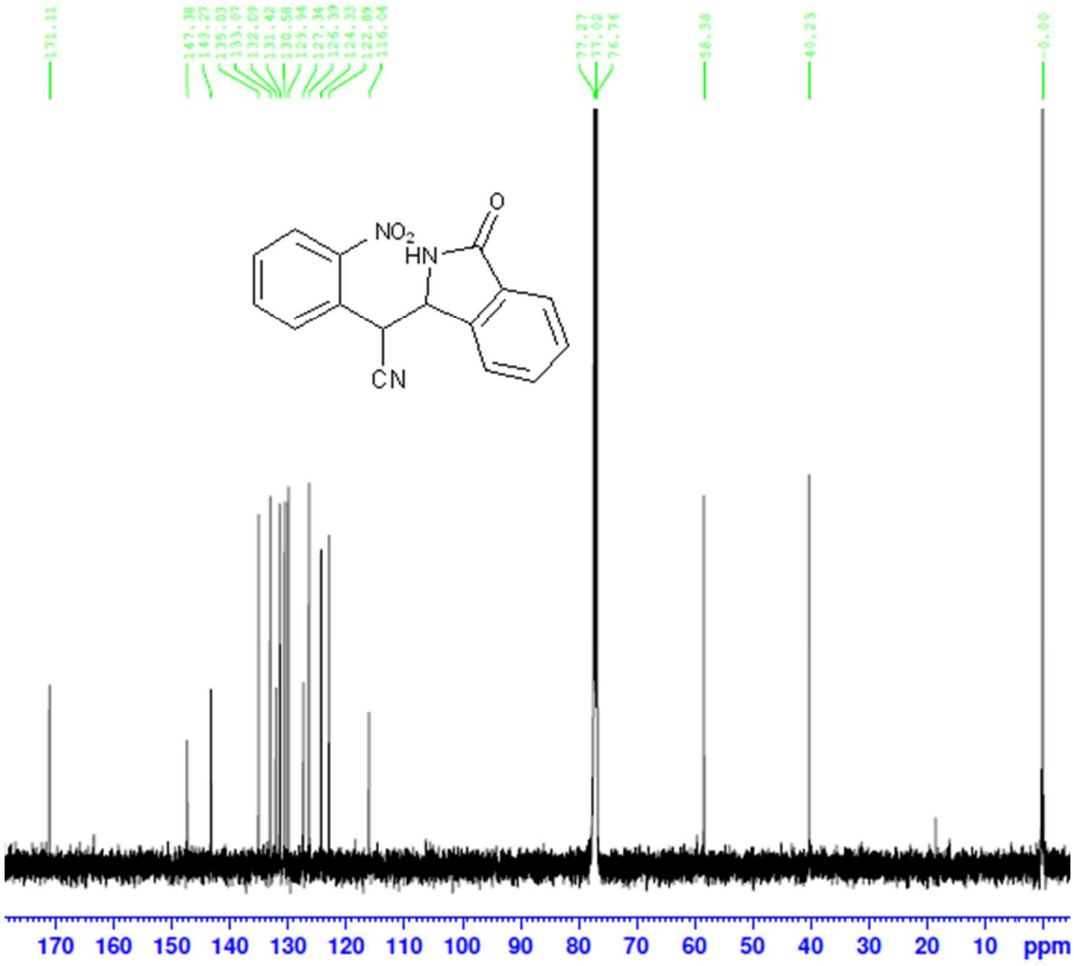
^{1}H-NMR of **41g** in $CDCl_3$ at room temperature.



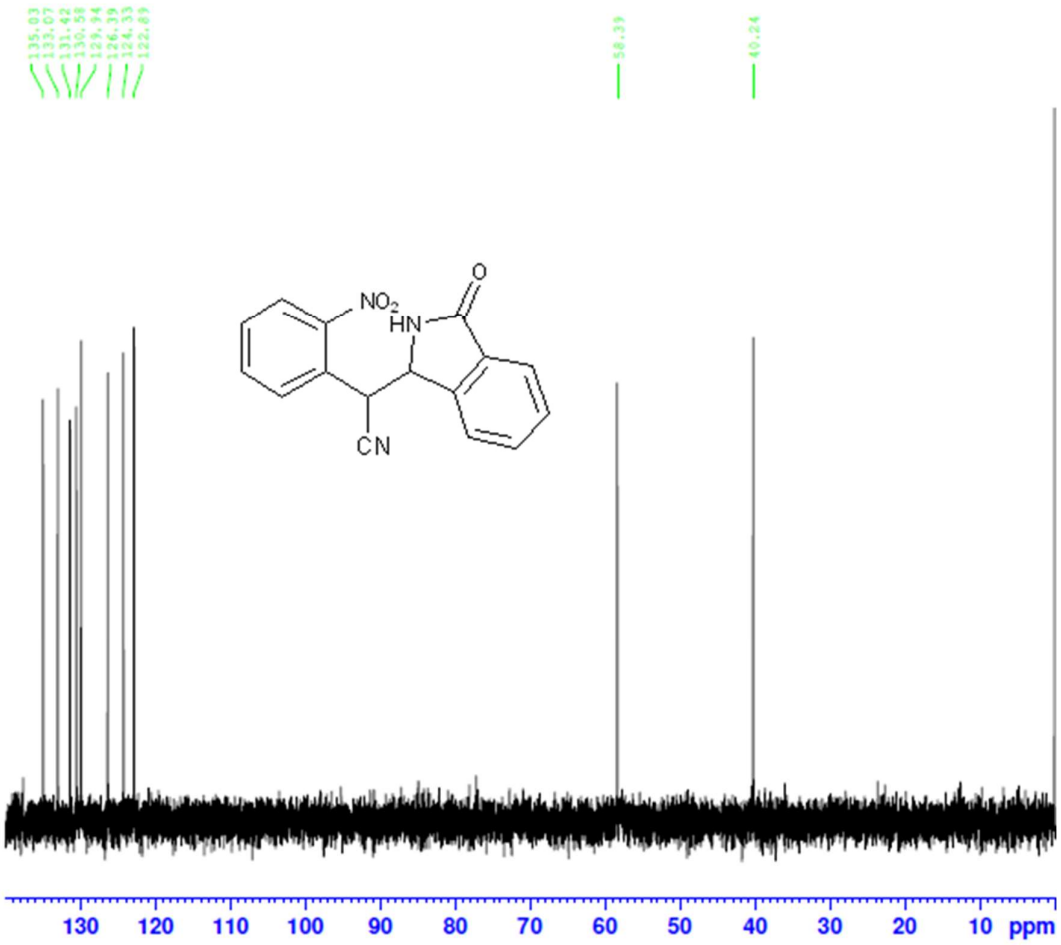
^{1}H-NMR of **40h** in $CDCl_3$ at room temperature.

^{1}H-NMR of **41h** in $CDCl_3$ at room temperature.

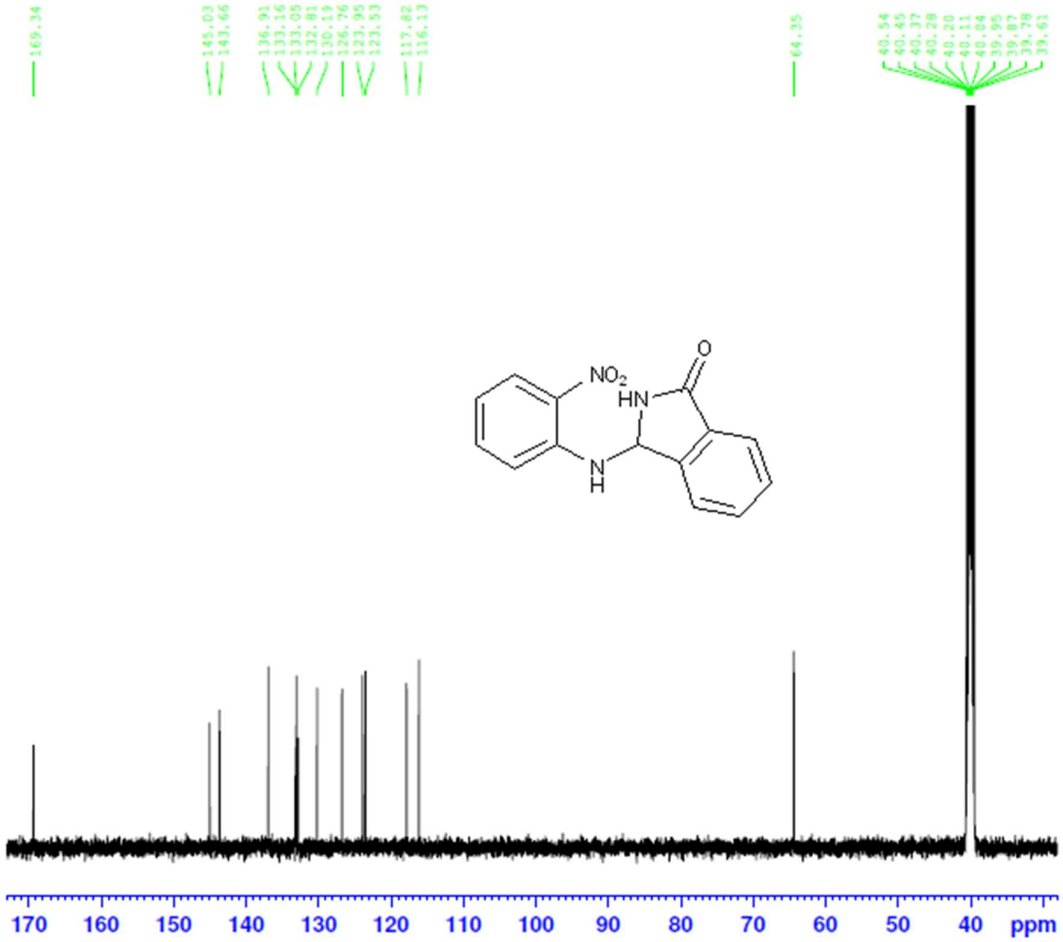
APPENDIX B ^{13}C NMR AND ^{13}C NMR DEPT 135:



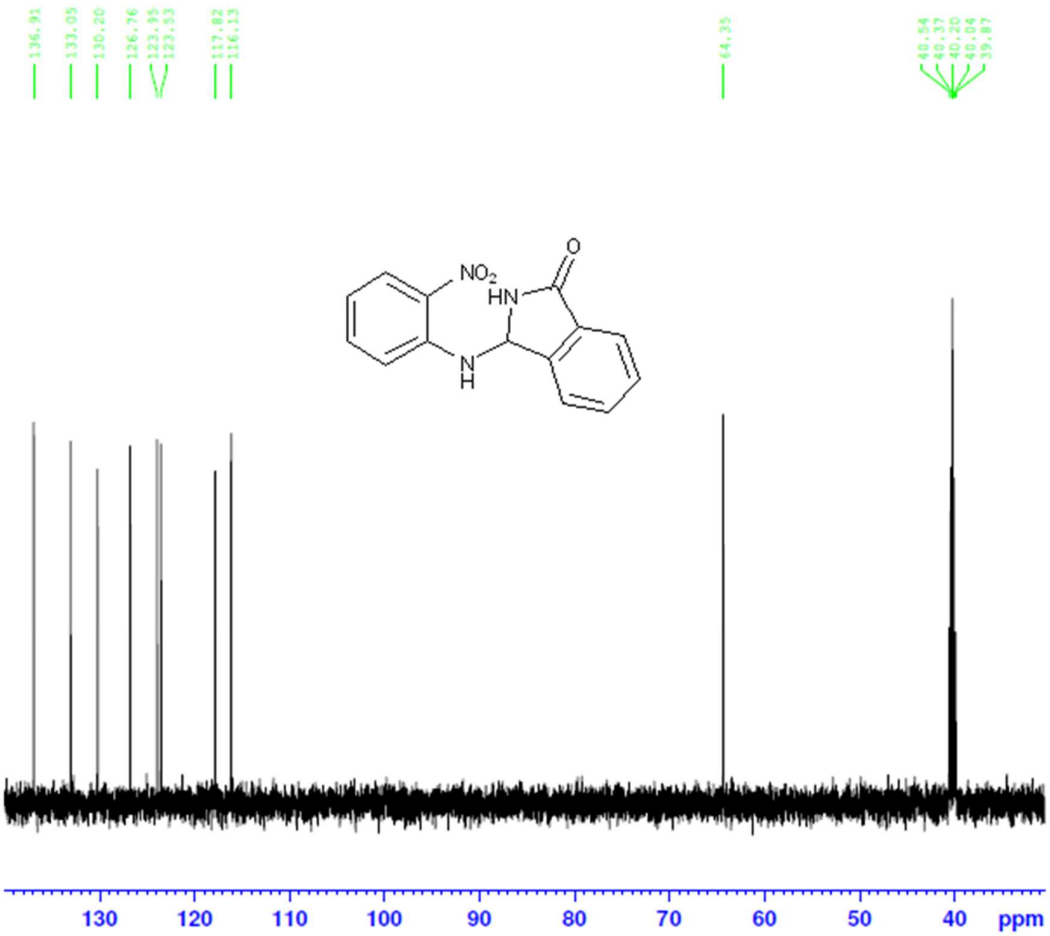
^{13}C-NMR of **31** in $CDCl_3$ at room temperature.



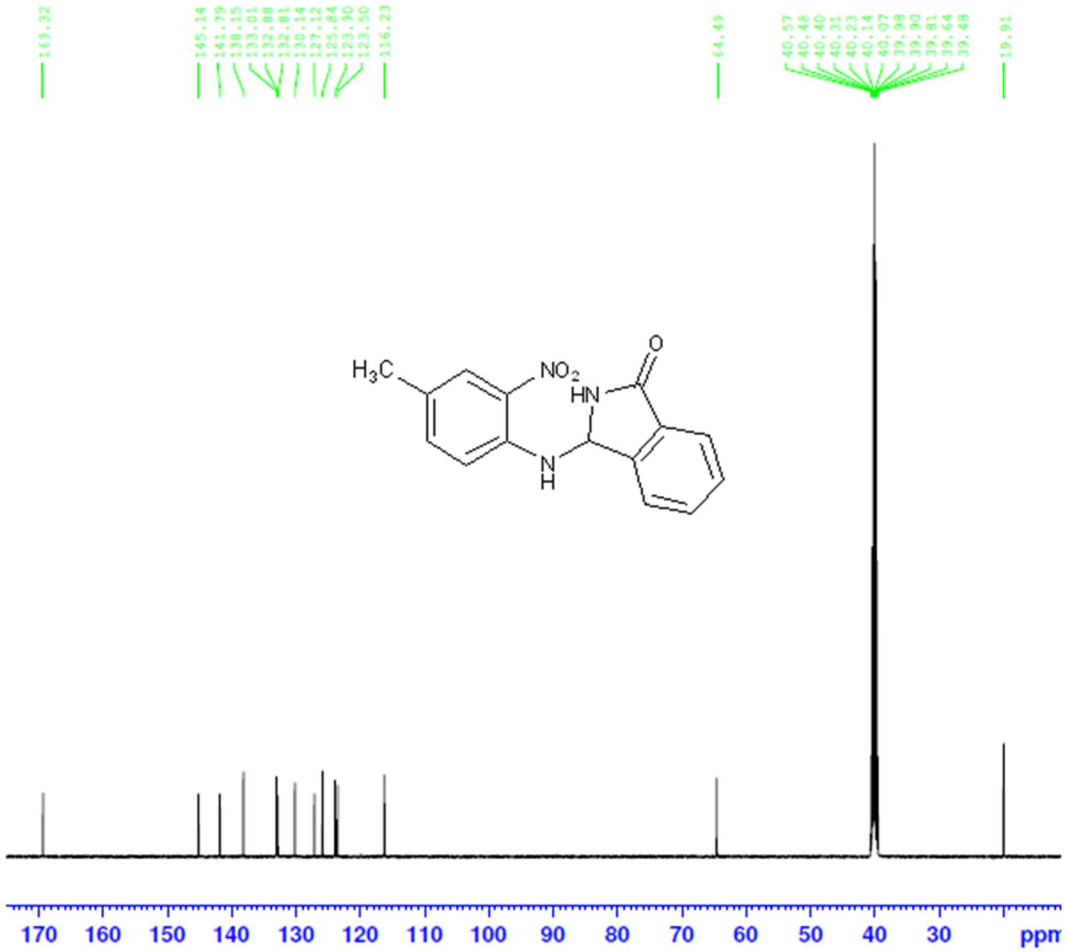
^{13}C DEPT 135-NMR of **31** in $CDCl_3$ at room temperature.



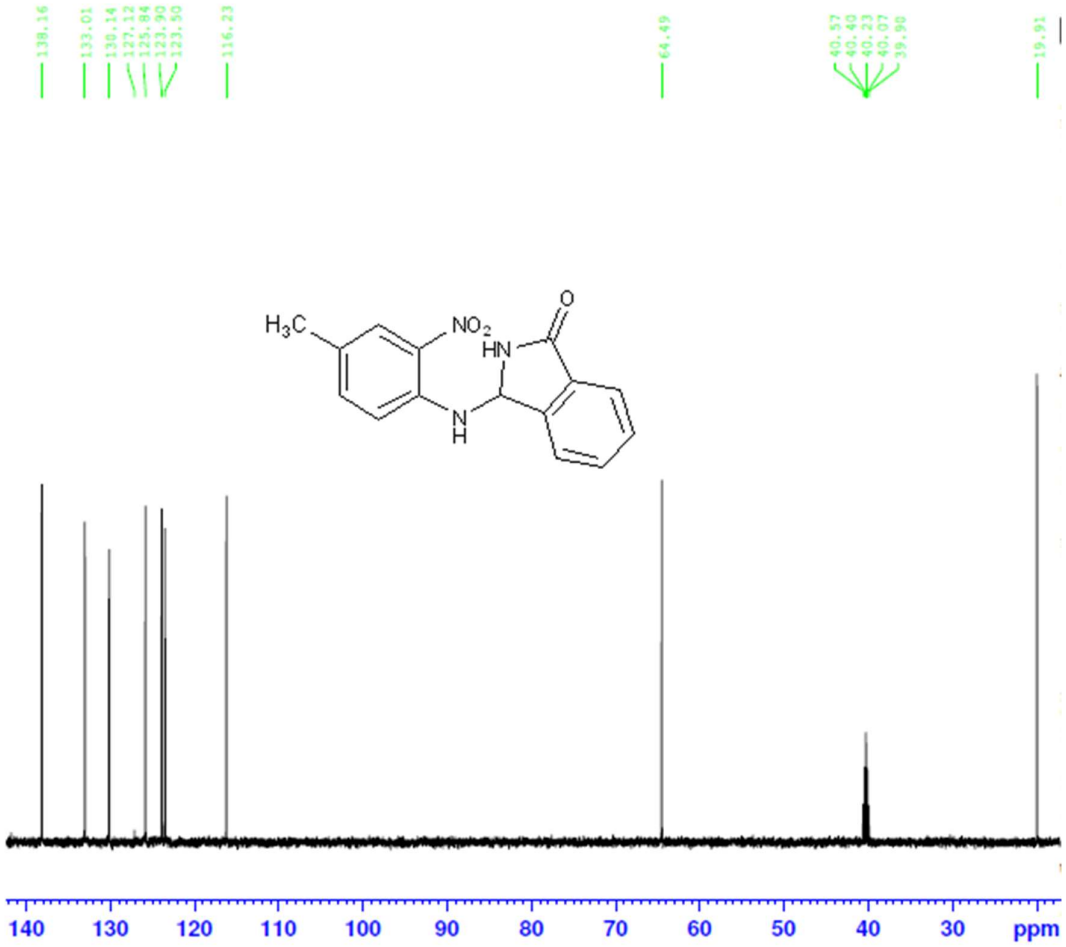
^{13}C-NMR of **34a** in DMSO-*d6* at room temperature.



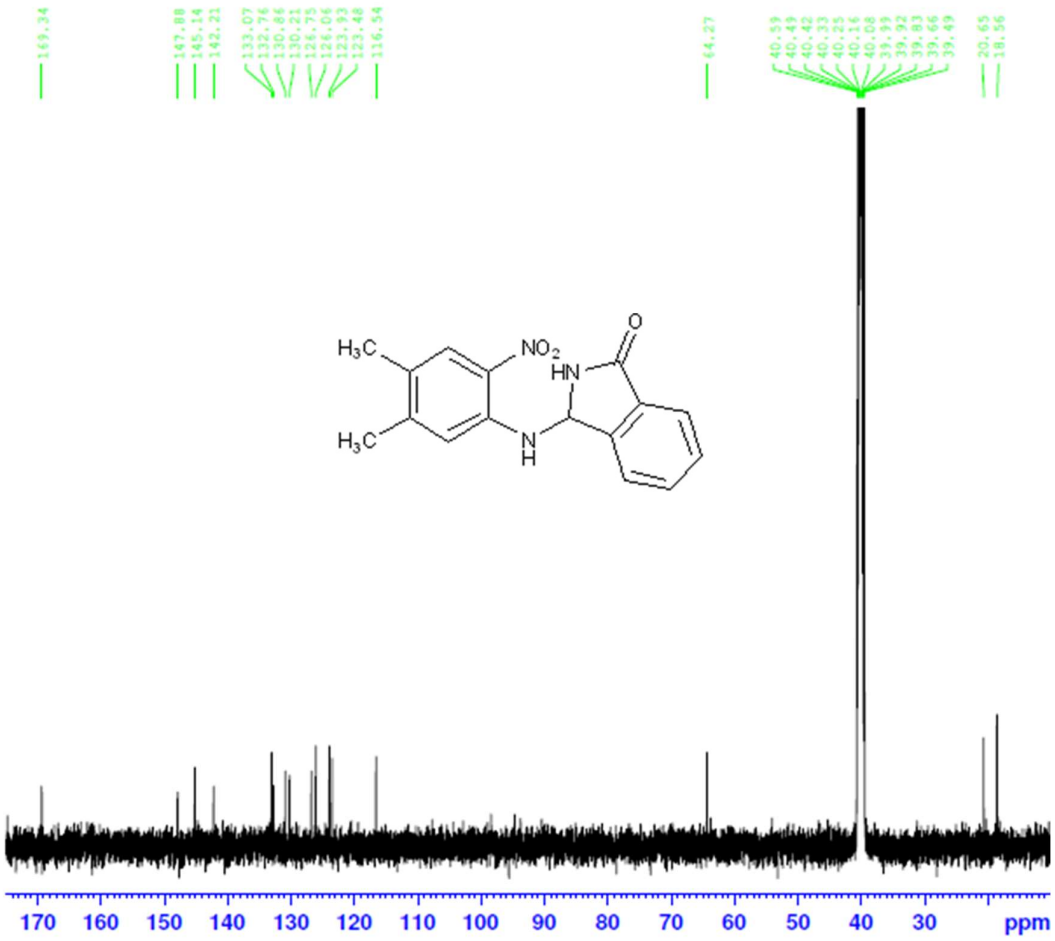
^{13}C DEPT 135-NMR of **34a** in DMSO-*d6* at room temperature.



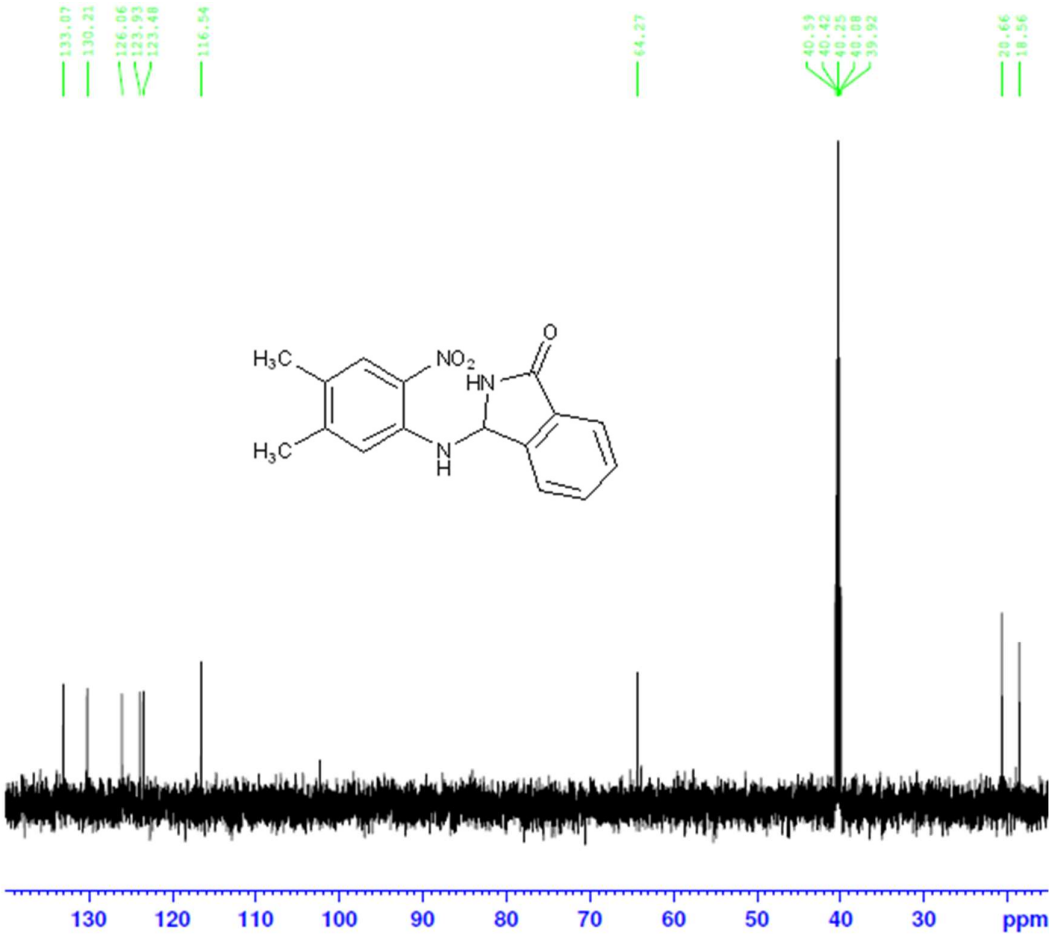
^{13}C-NMR of **34b** in DMSO-*d6* at room temperature.



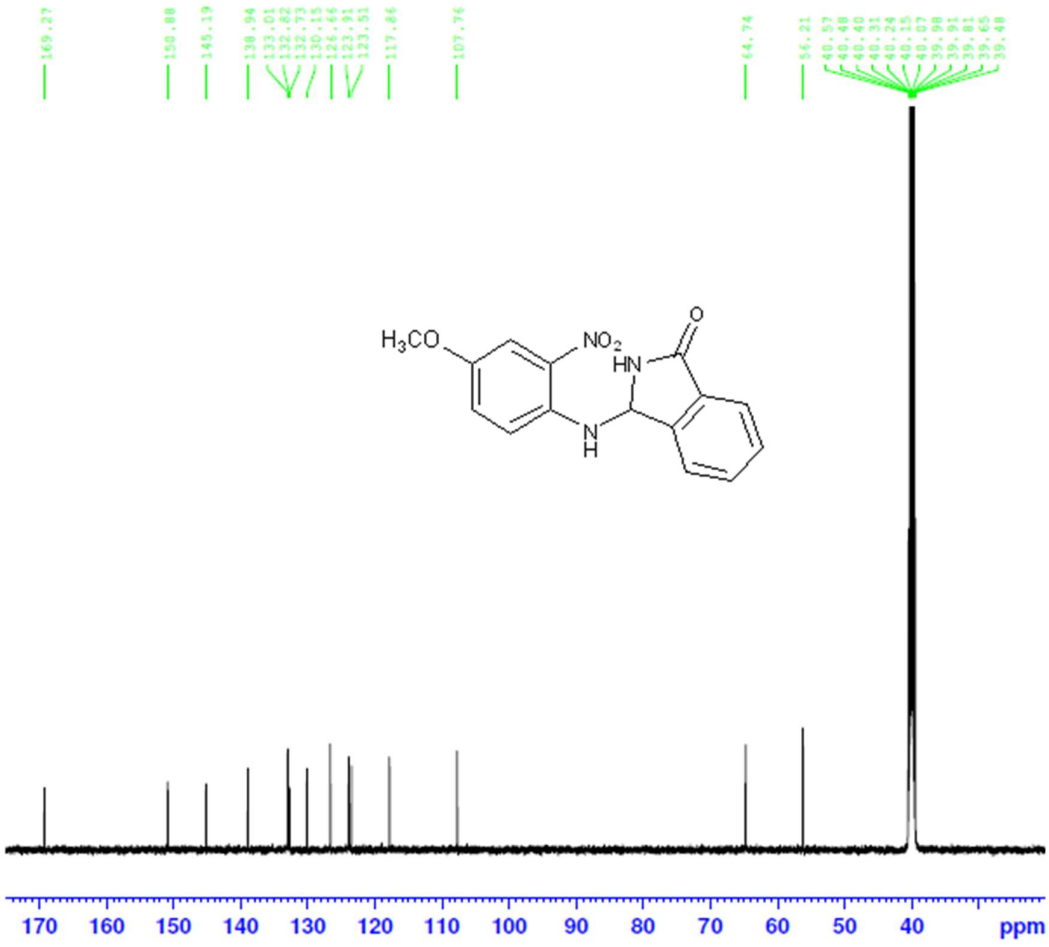
^{13}C DEPT 135-NMR of **34b** in DMSO-*d6* at room temperature.



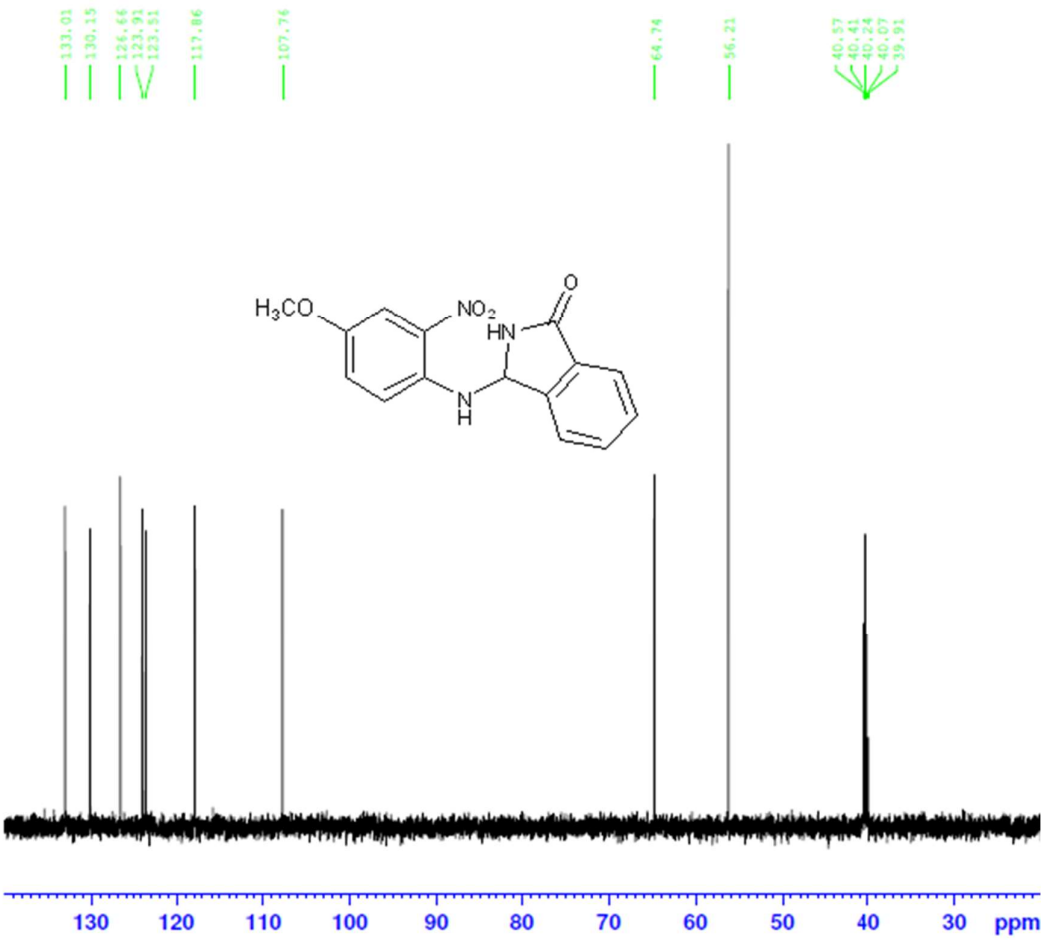
^{13}C-NMR of **34c** in DMSO-*d6* at room temperature.



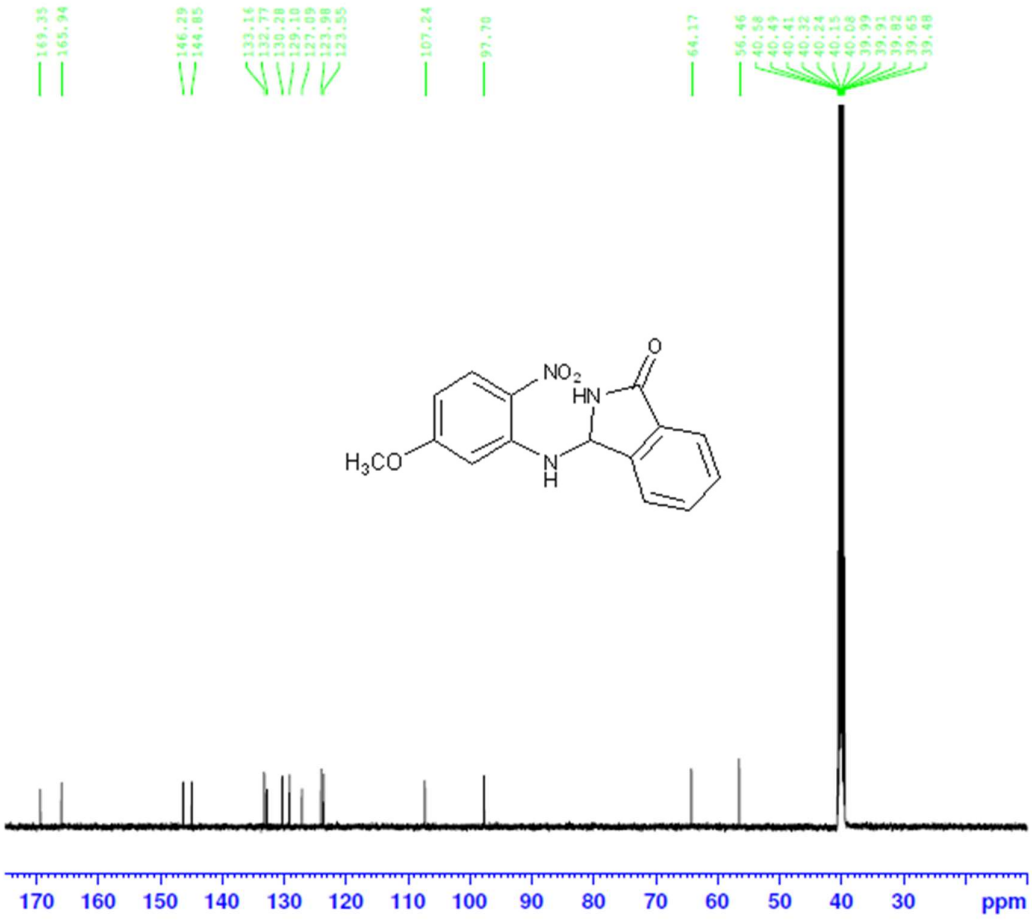
^{13}C DEPT 135-NMR of **34a** in DMSO-*d6* at room temperature.



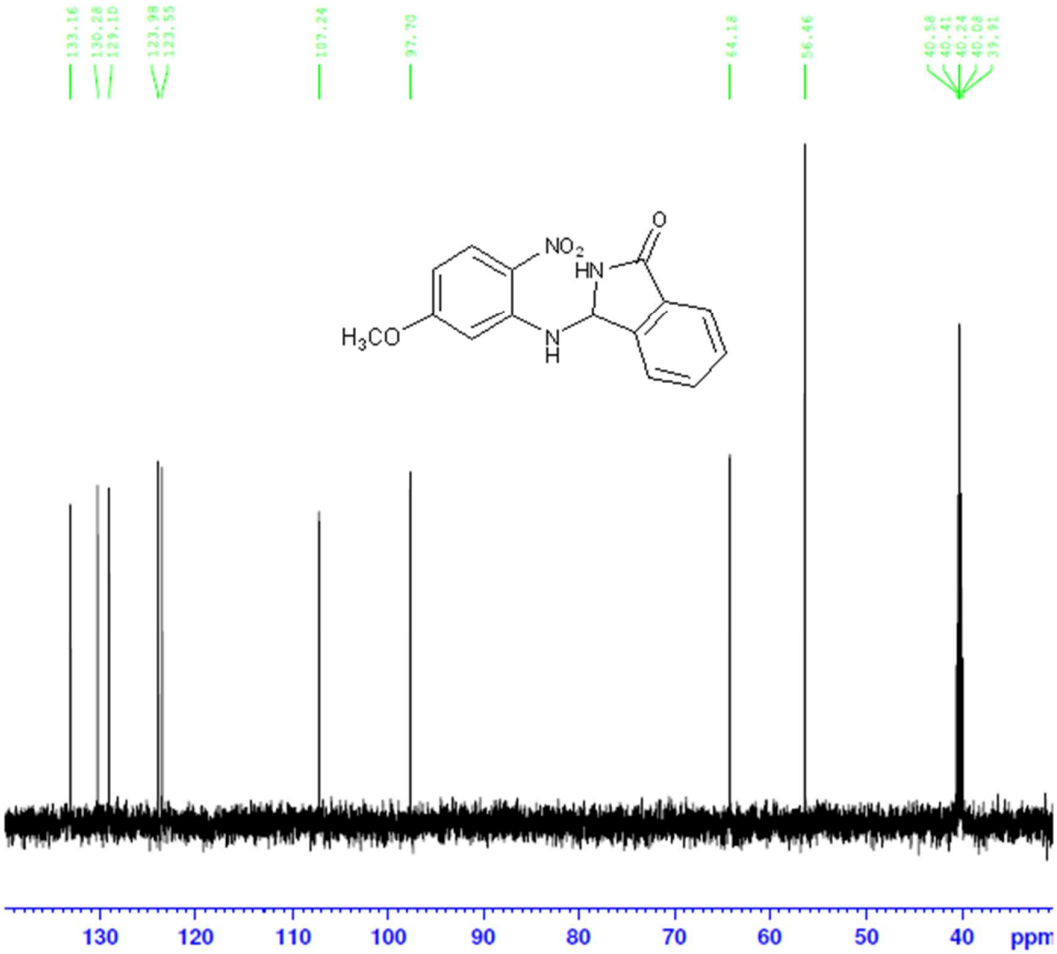
^{13}C-NMR of **34d** in DMSO-*d6* at room temperature.



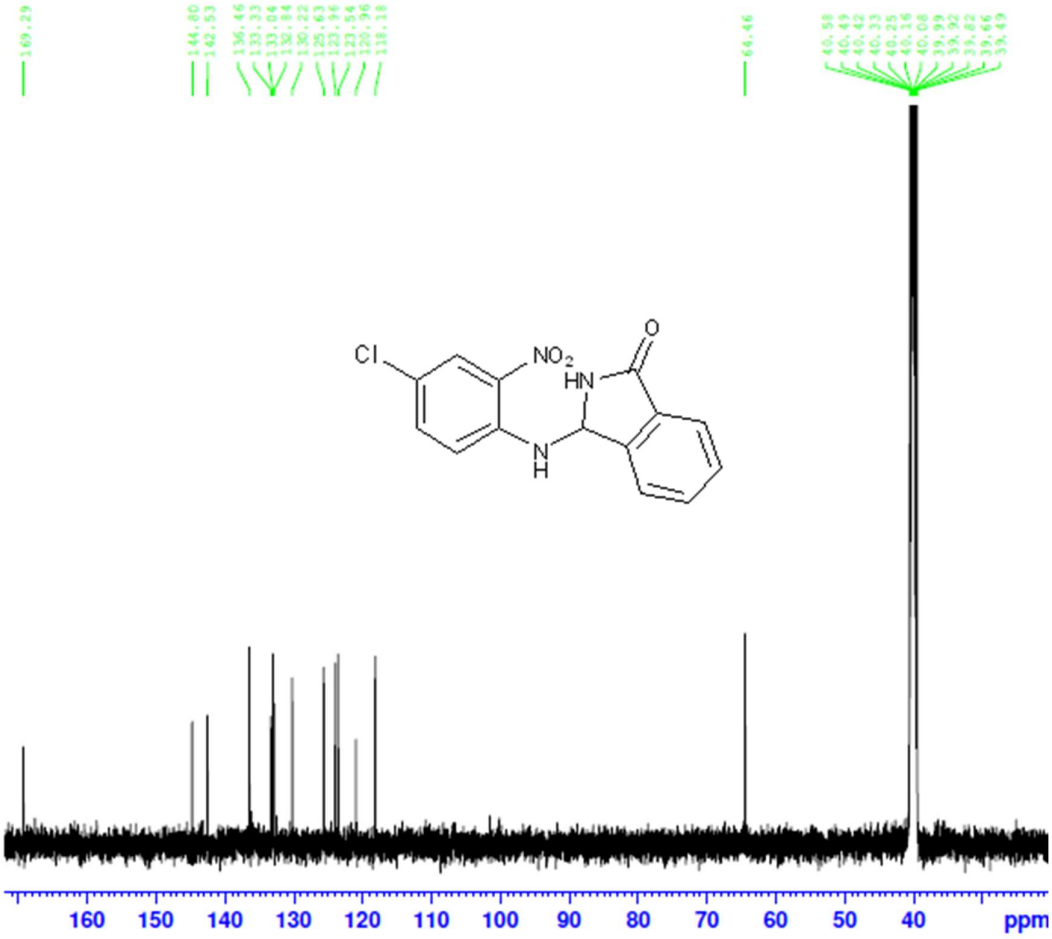
^{13}C DEPT 135-NMR of **34d** in DMSO-*d6* at room temperature.



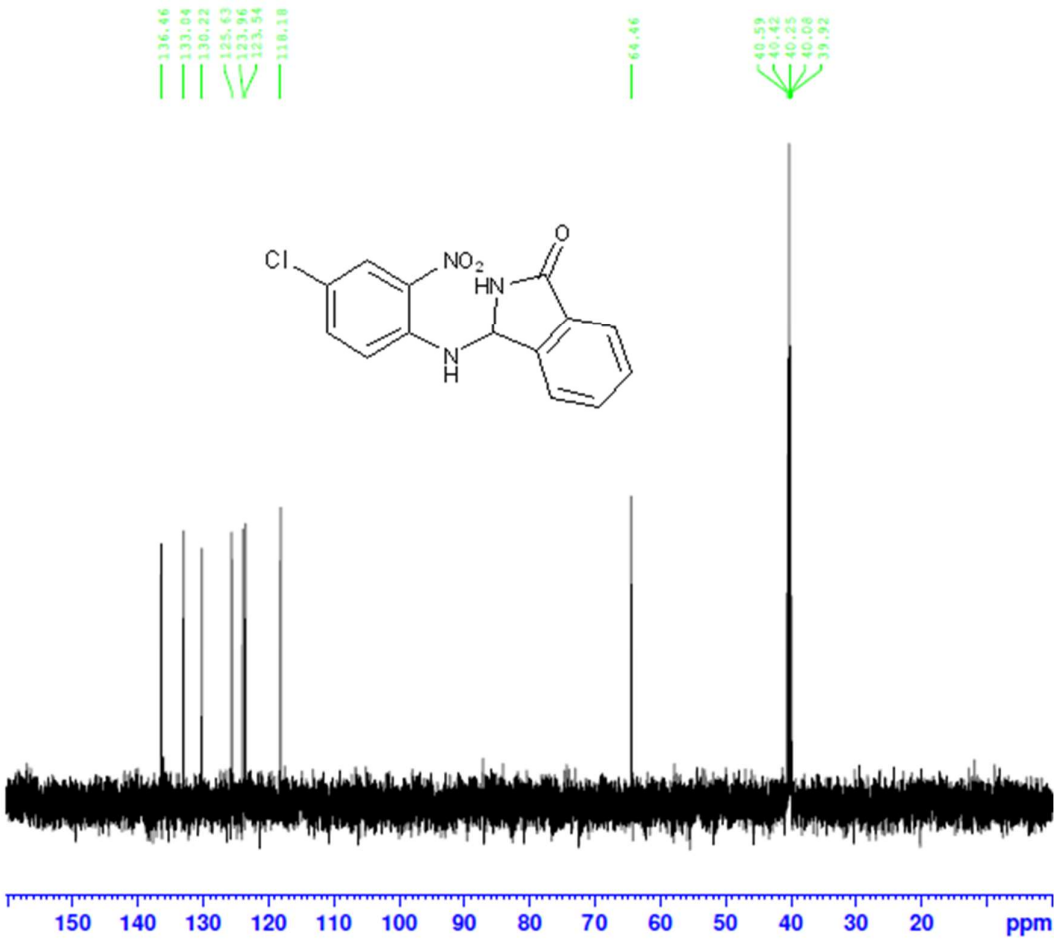
^{13}C-NMR of **34e** in DMSO-*d6* at room temperature.



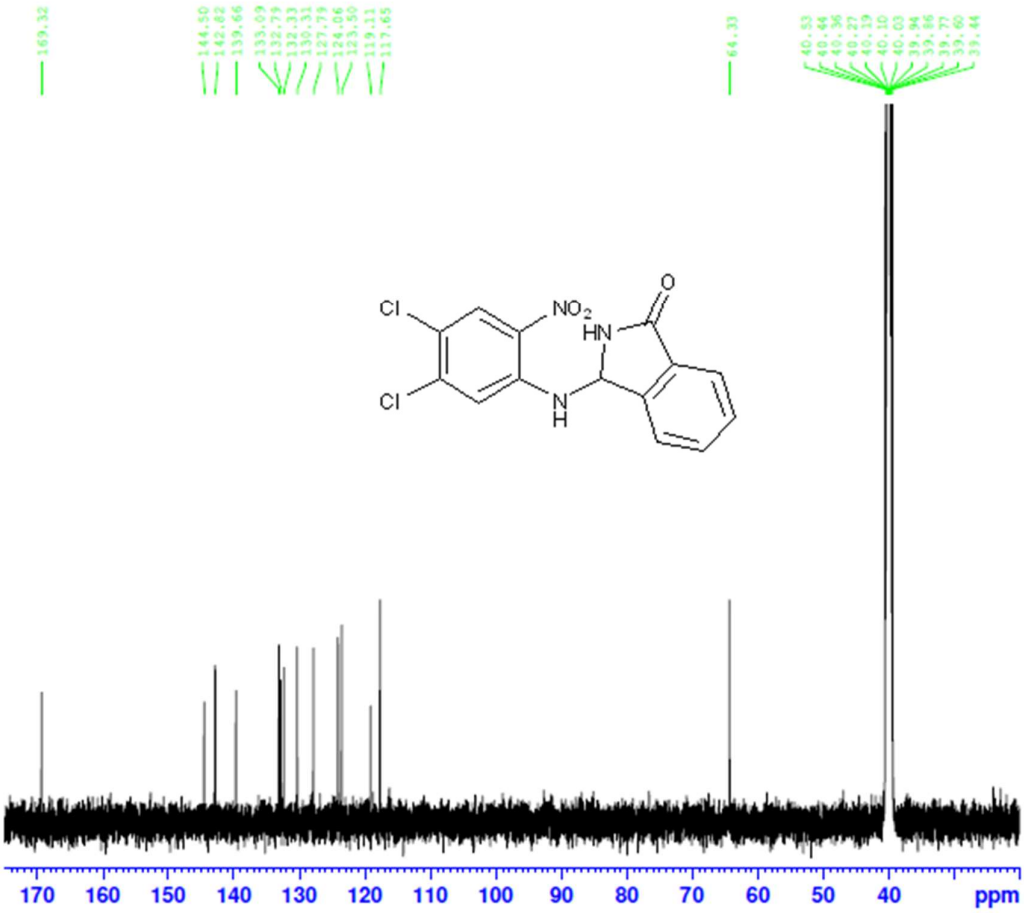
^{13}C DEPT 135-NMR of **34e** in DMSO-*d6* at room temperature.



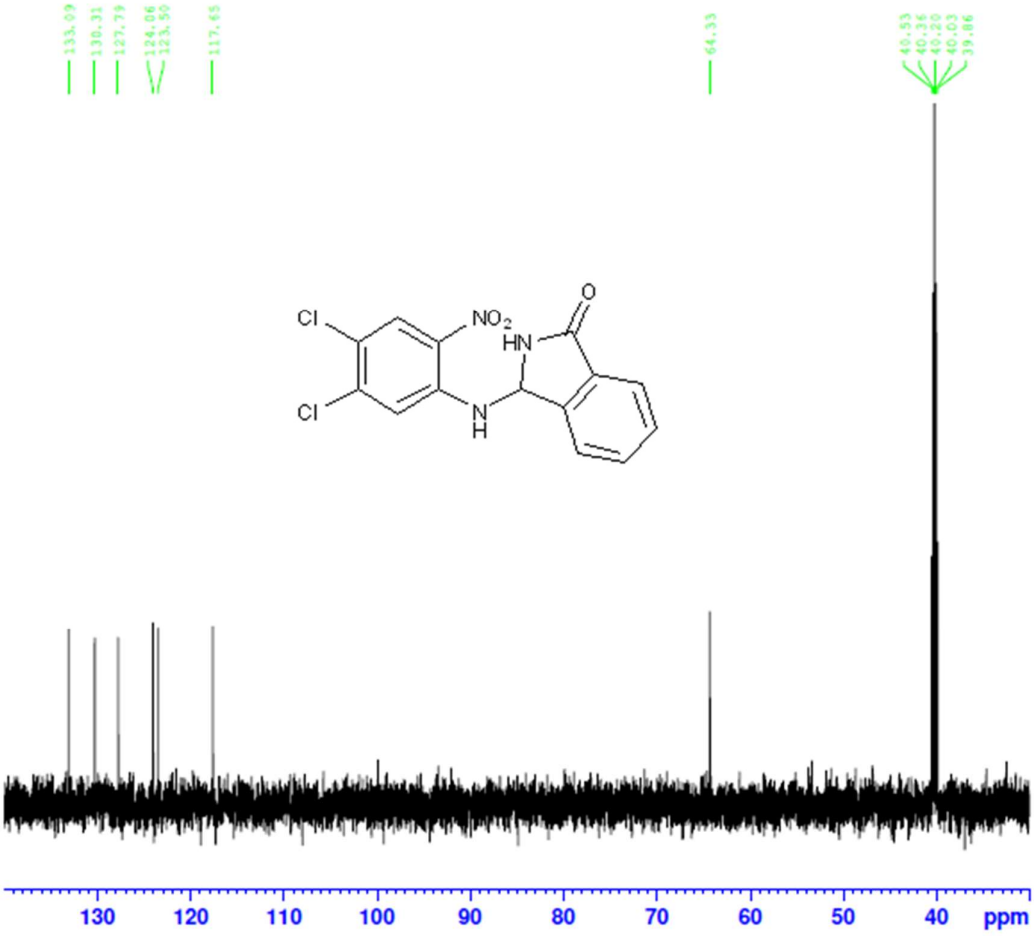
^{13}C-NMR of **34f** in DMSO-*d6* at room temperature.



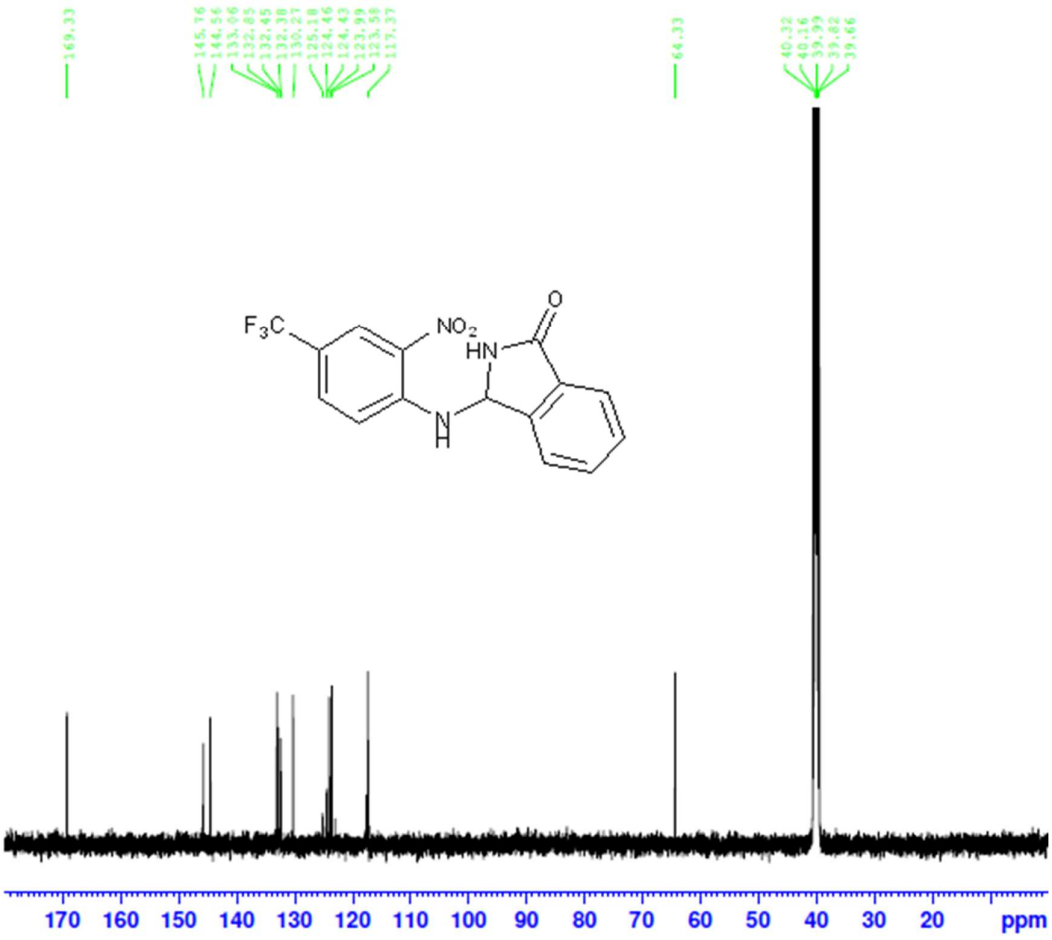
^{13}C DEPT 135-NMR of **34f** in DMSO-*d6* at room temperature.



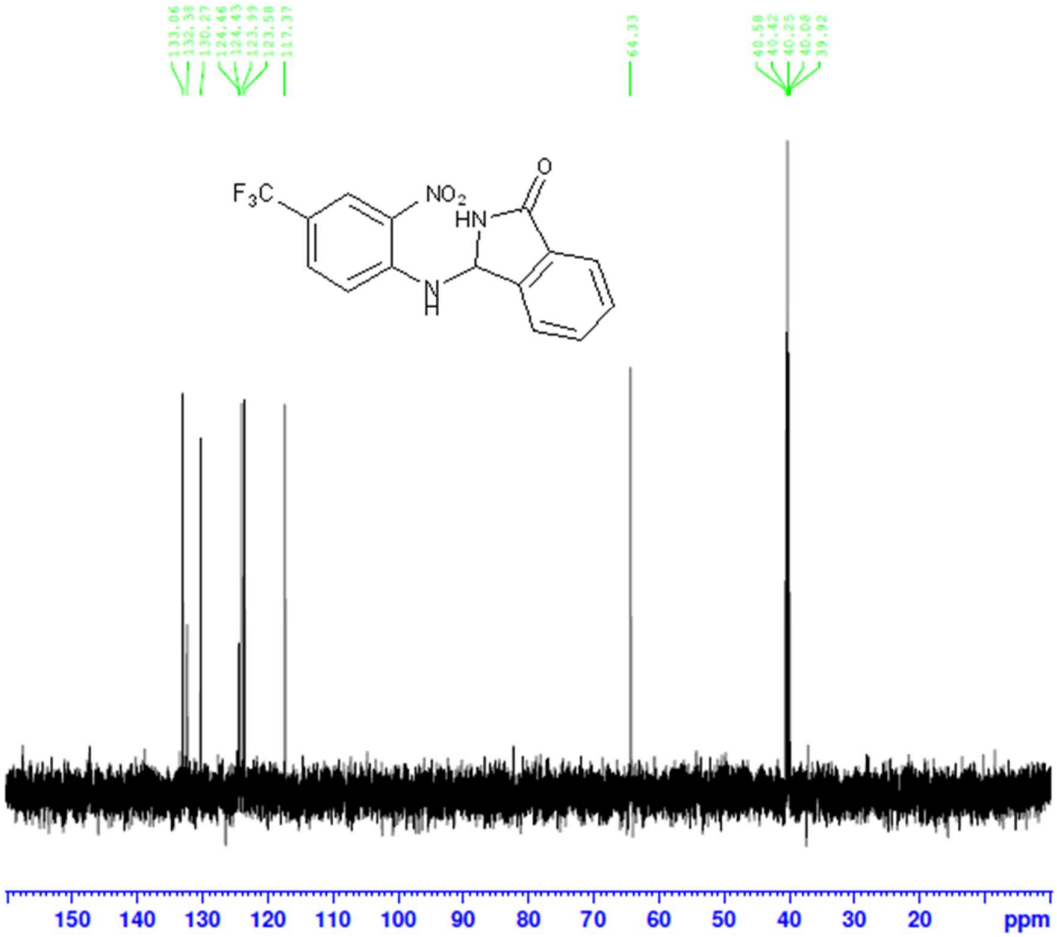
^{13}C-NMR of **34g** in DMSO-*d6* at room temperature.



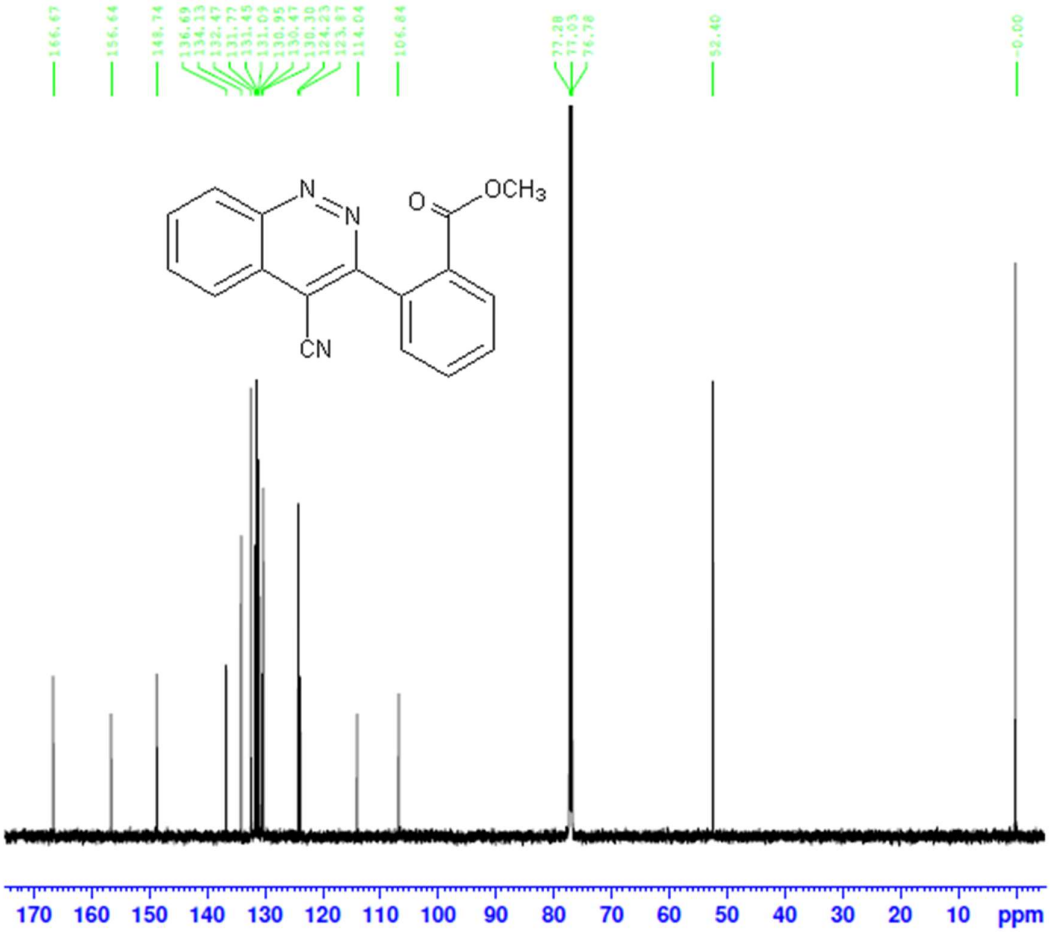
^{13}C DEPT 135-NMR of **34g** in DMSO-*d6* at room temperature.



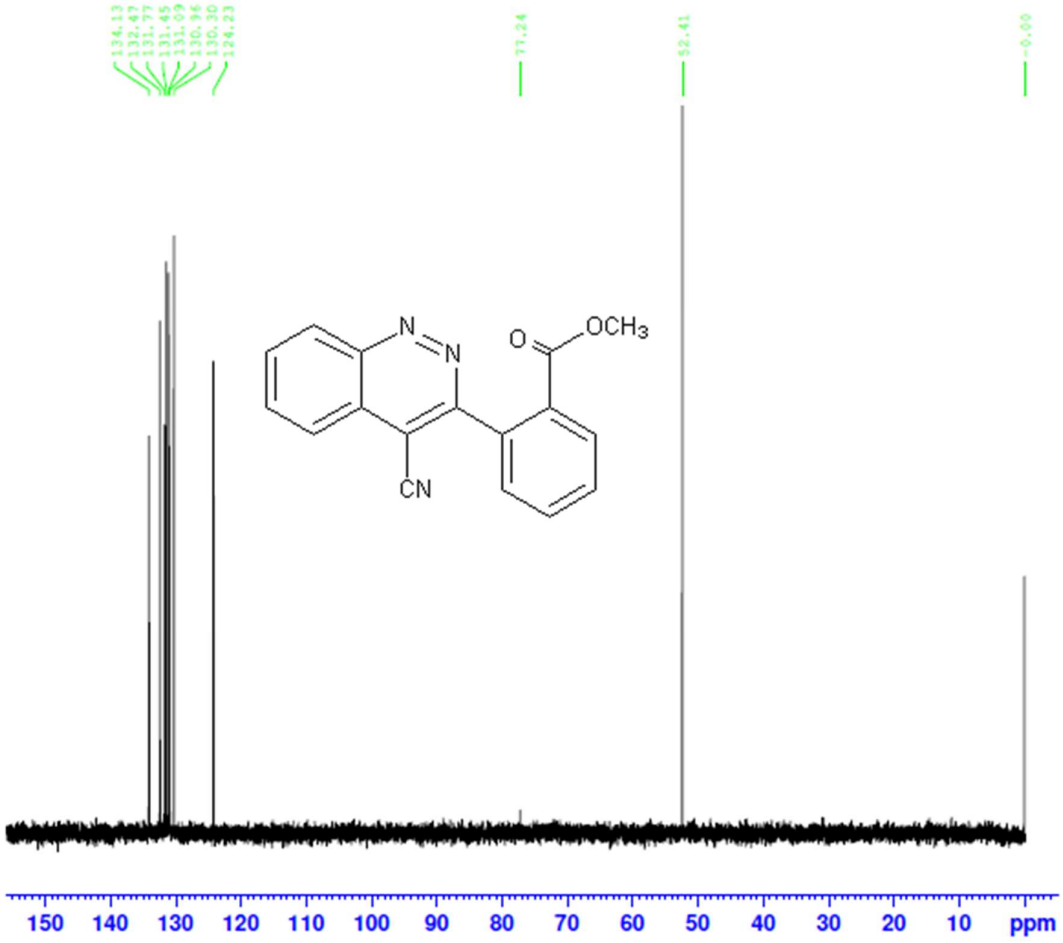
^{13}C-NMR of **34h** in DMSO-*d6* at room temperature.



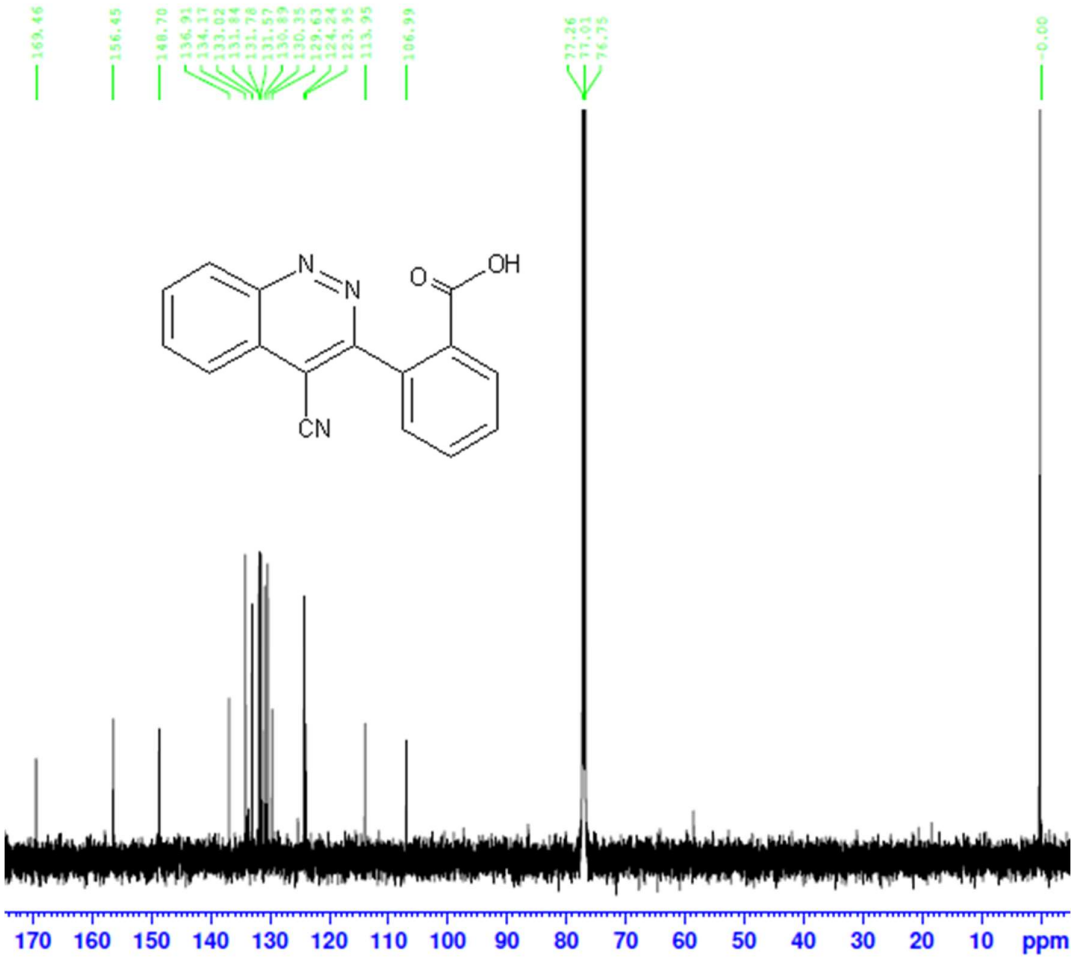
^{13}C DEPT 135-NMR of **34h** in DMSO-*d6* at room temperature.



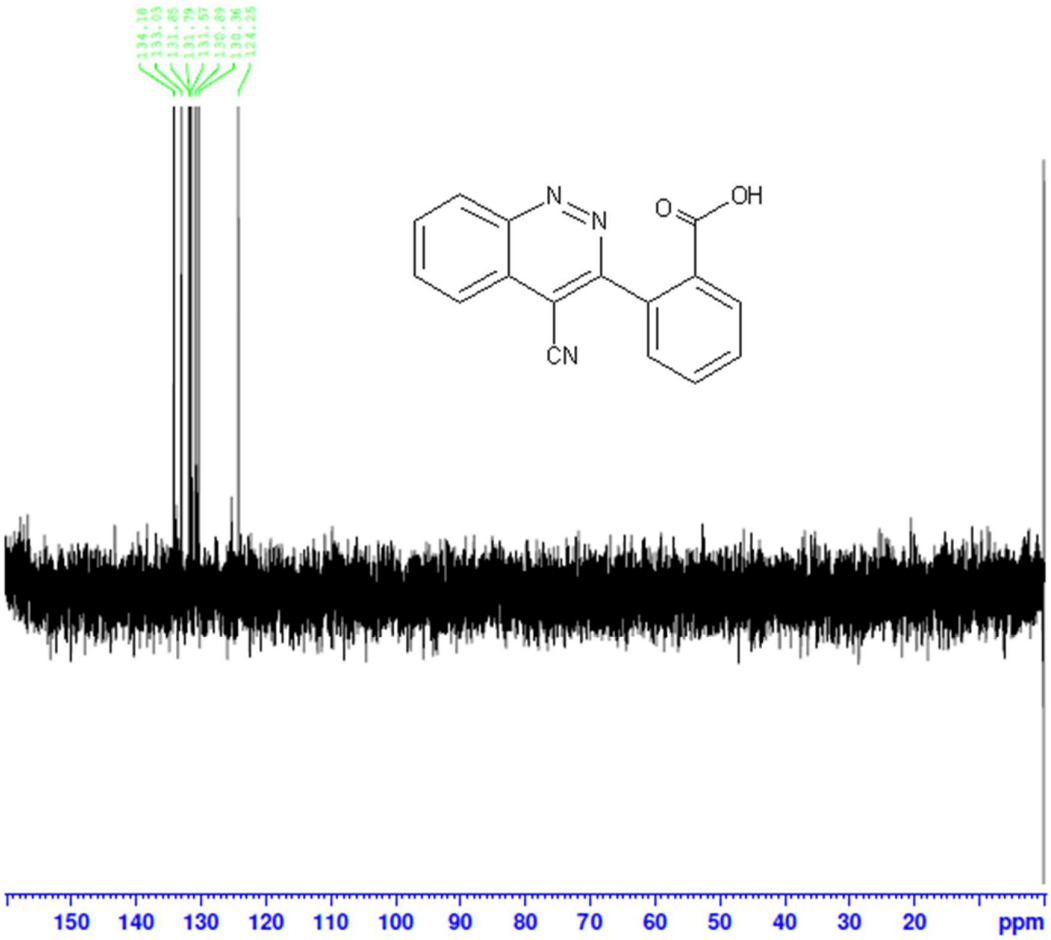
^{13}C-NMR of **38** in $CDCl_3$ at room temperature.



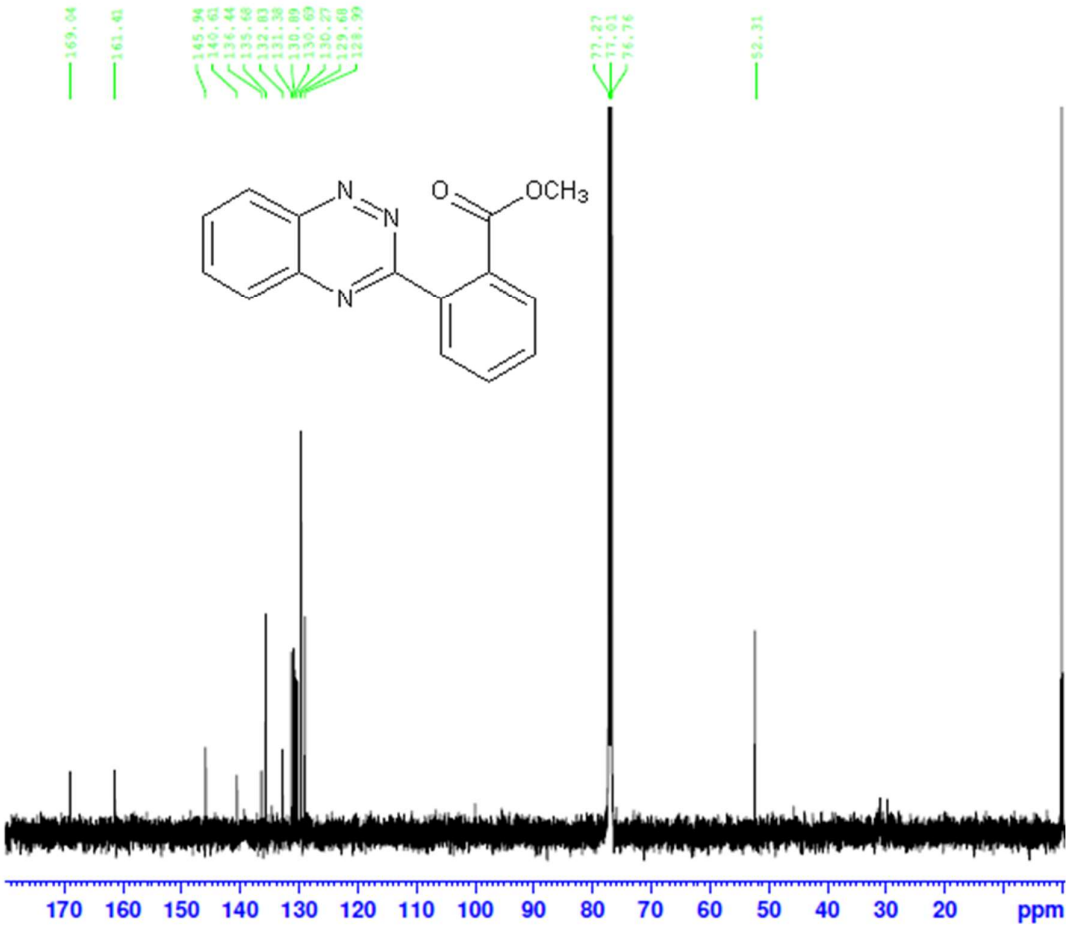
^{13}C DEPT 135-NMR of **38** in $CDCl_3$ at room temperature.



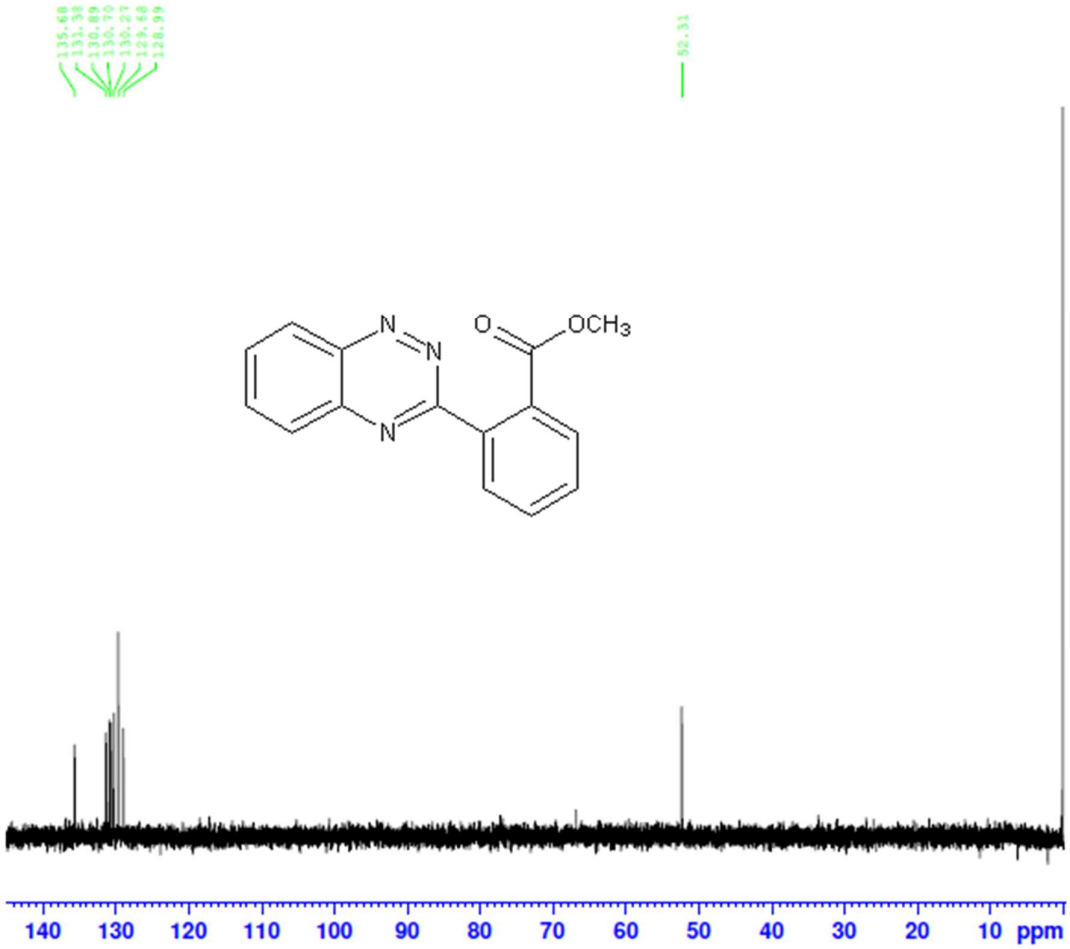
^{13}C-NMR of **39** in $CDCl_3$ at room temperature.



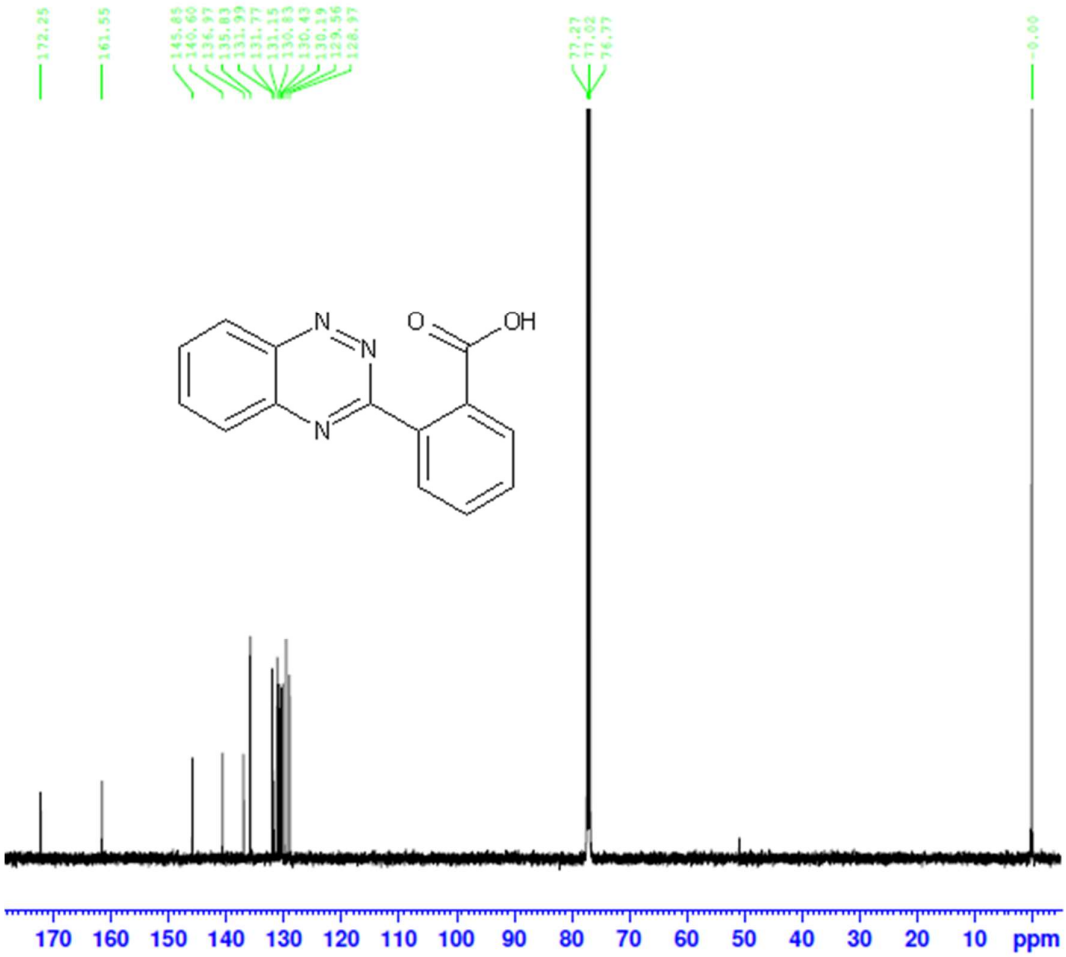
^{13}C DEPT 135-NMR of **39** in $CDCl_3$ at room temperature.



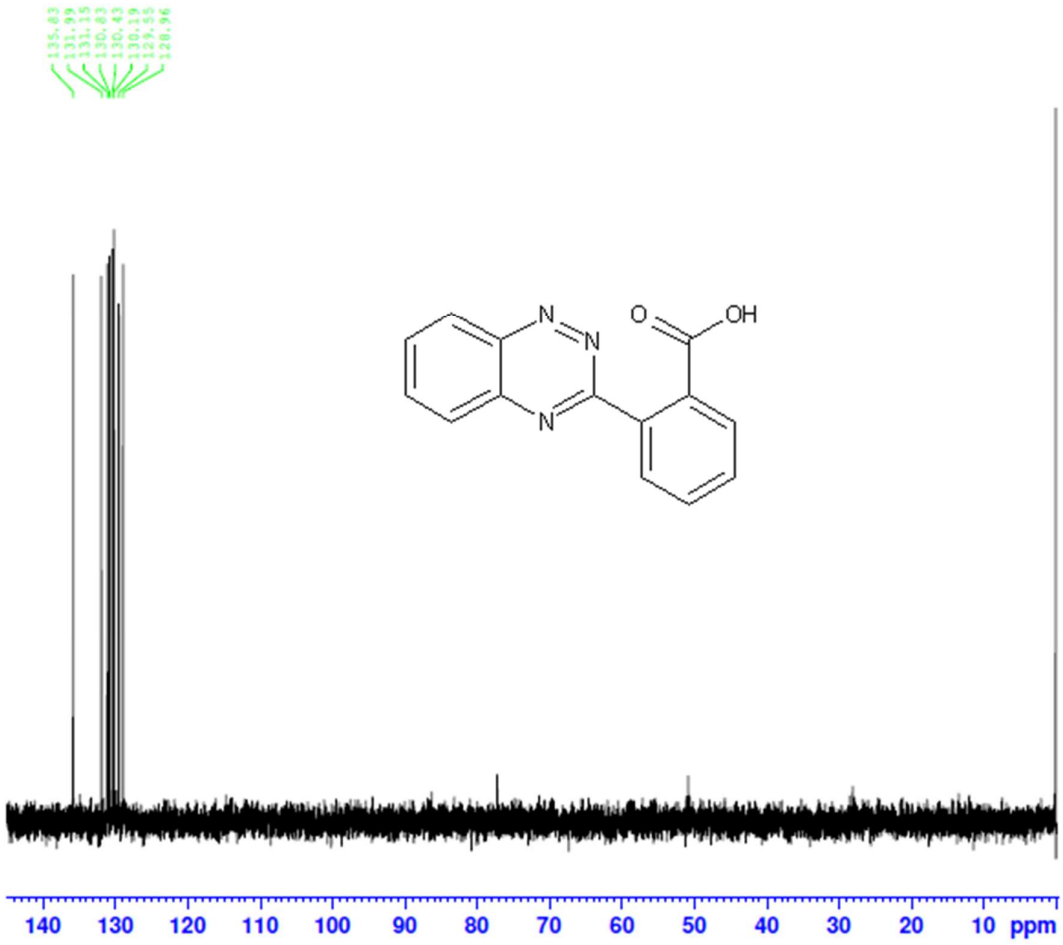
^{13}C-NMR of **40a** in $CDCl_3$ at room temperature.



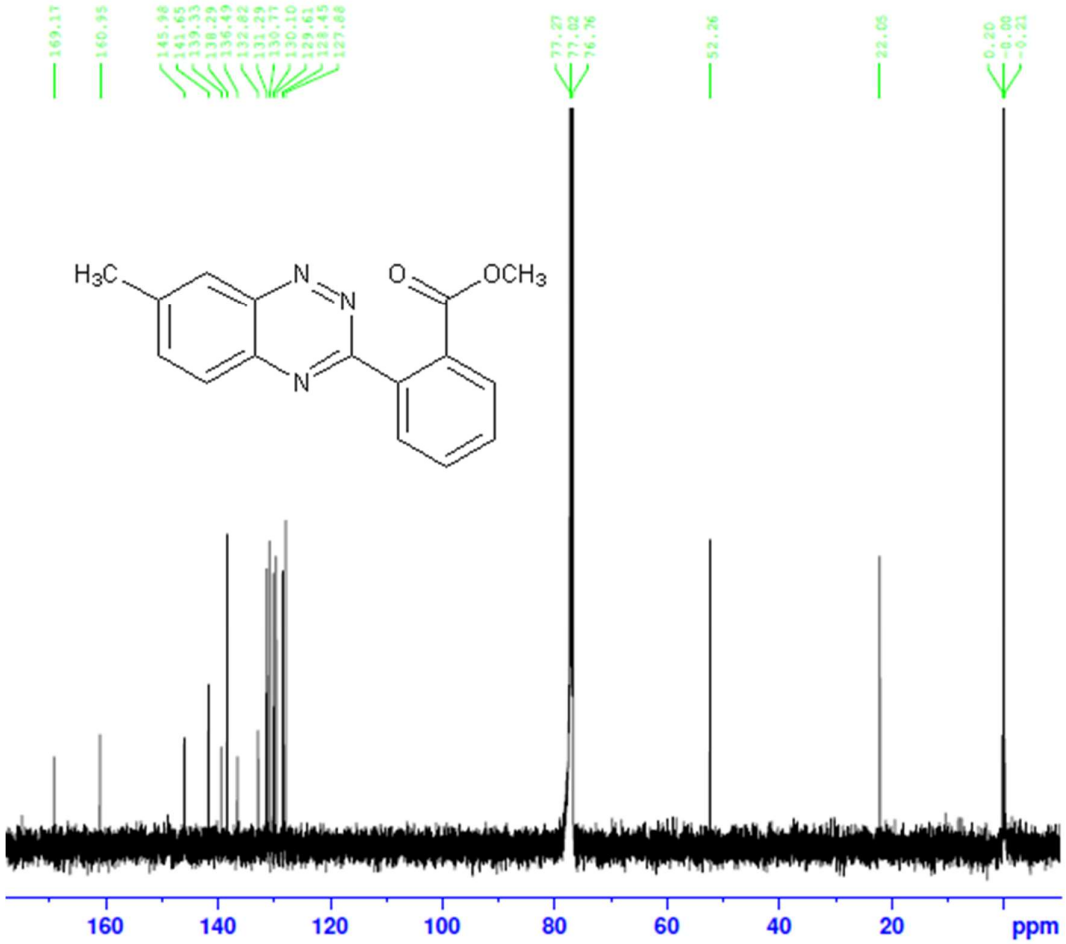
^{13}C DEPT 135-NMR of **40a** in $CDCl_3$ at room temperature.



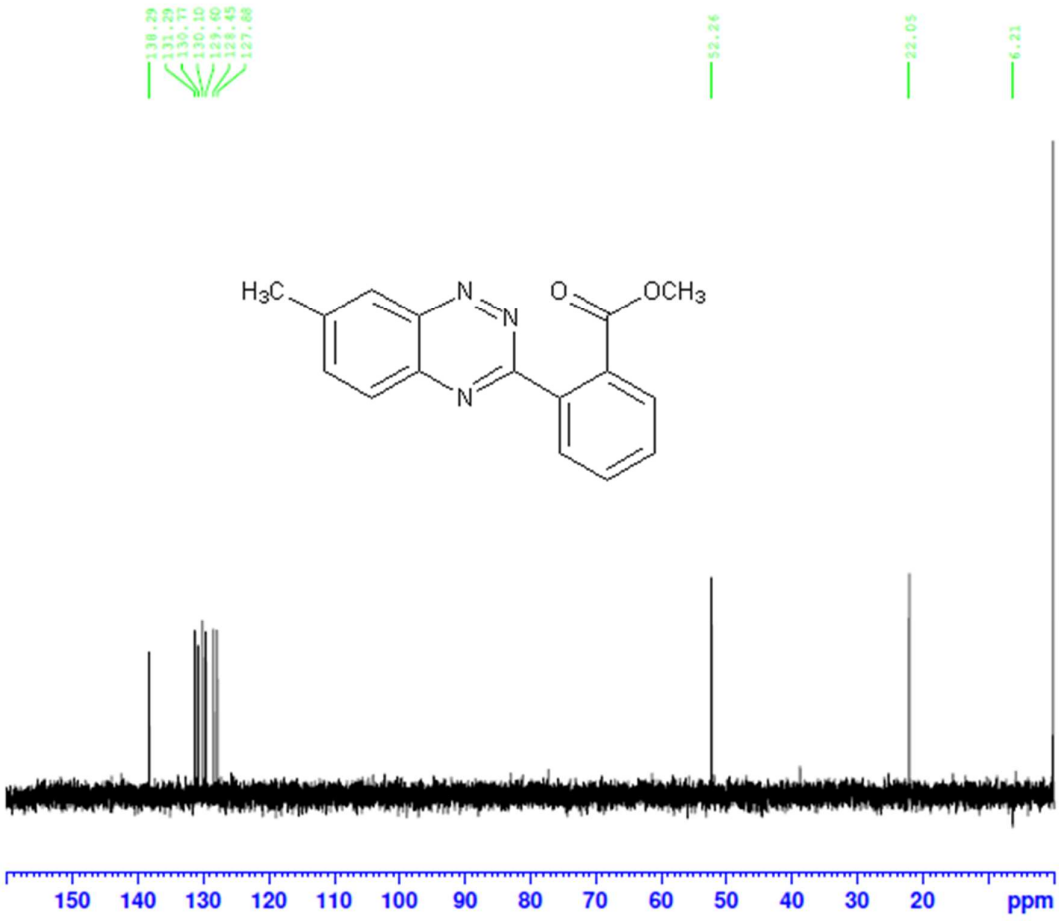
^{13}C-NMR of **41a** in $CDCl_3$ at room temperature.



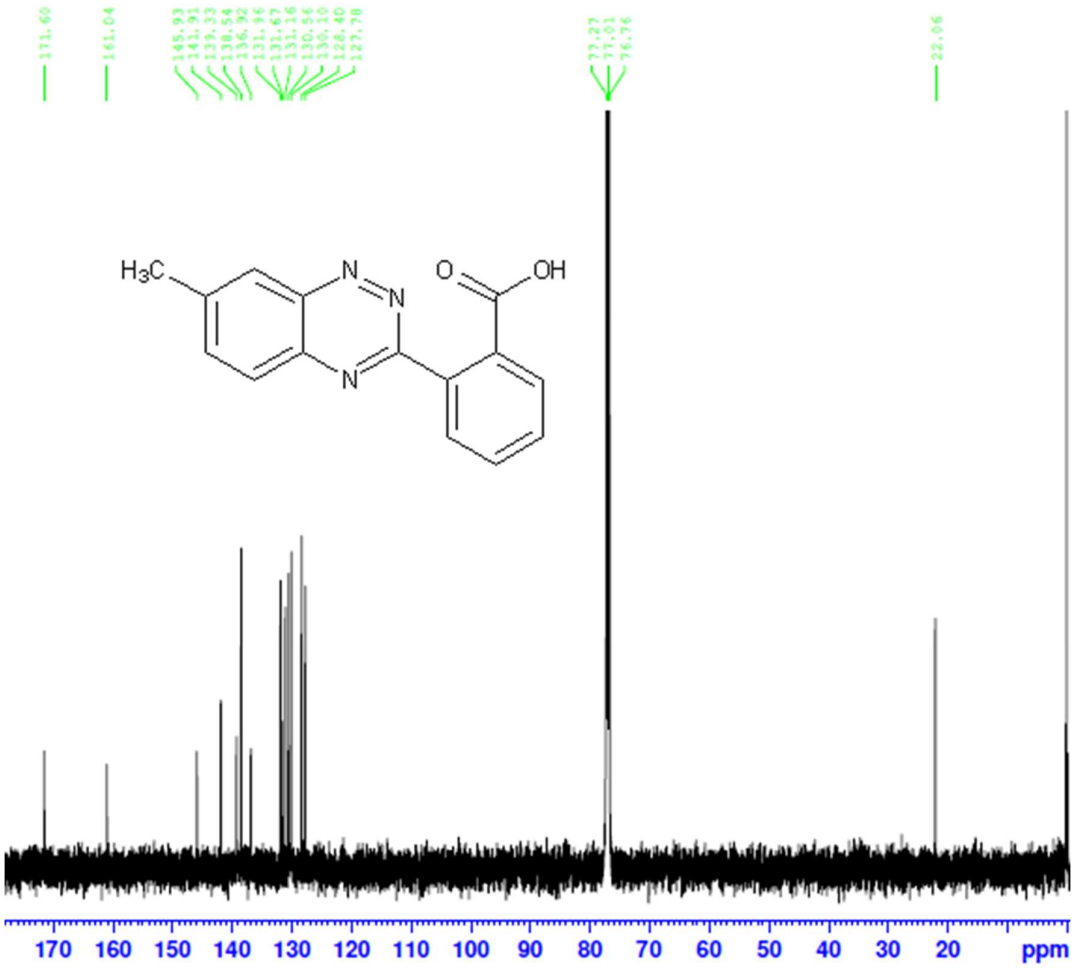
^{13}C DEPT 135-NMR of **41a** in $CDCl_3$ at room temperature.



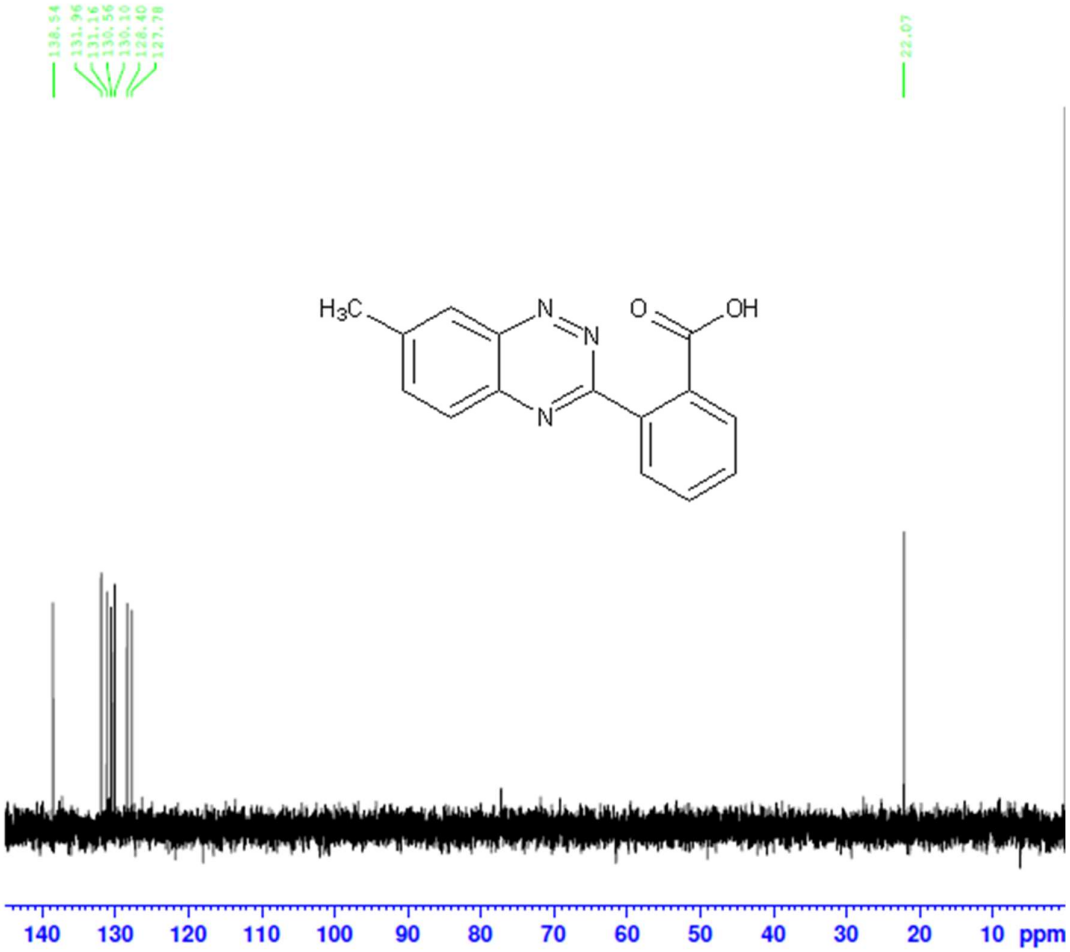
^{13}C-NMR of **40b** in $CDCl_3$ at room temperature.



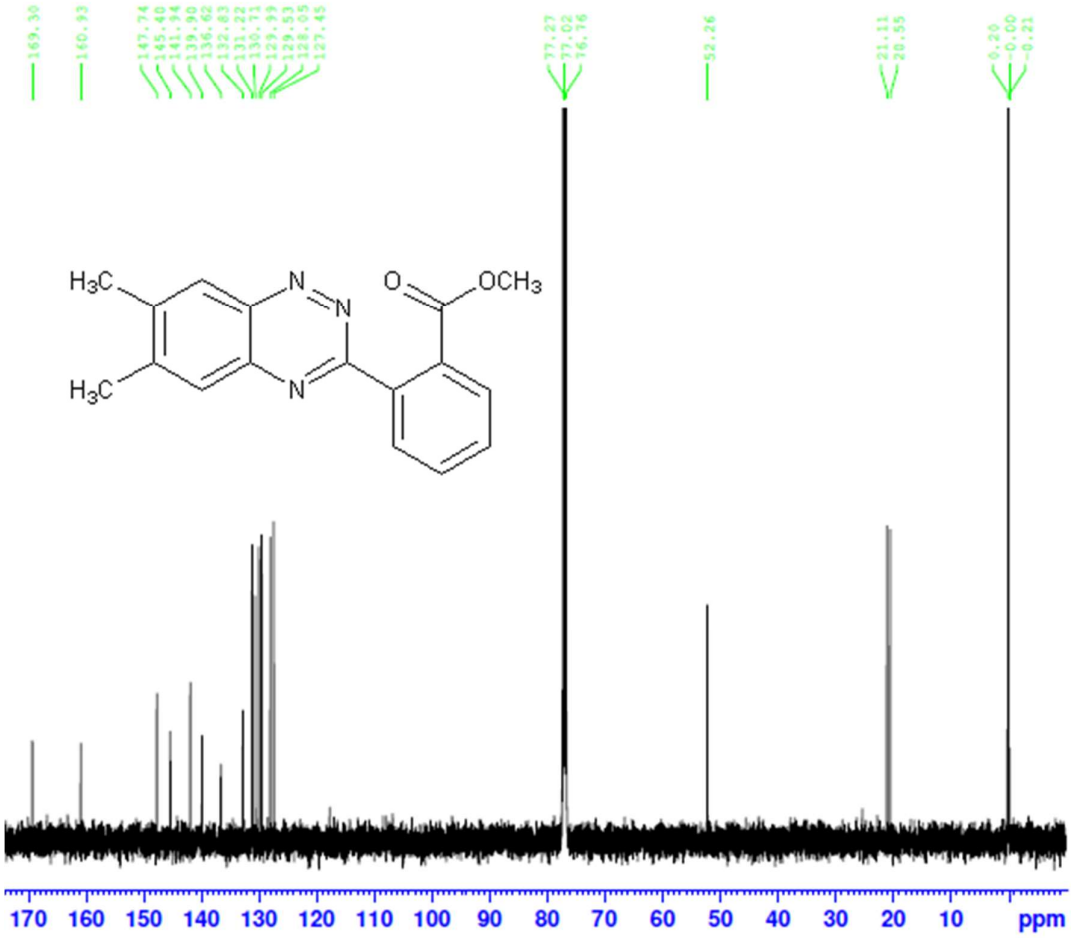
^{13}C DEPT 135-NMR of **40b** in $CDCl_3$ at room temperature.



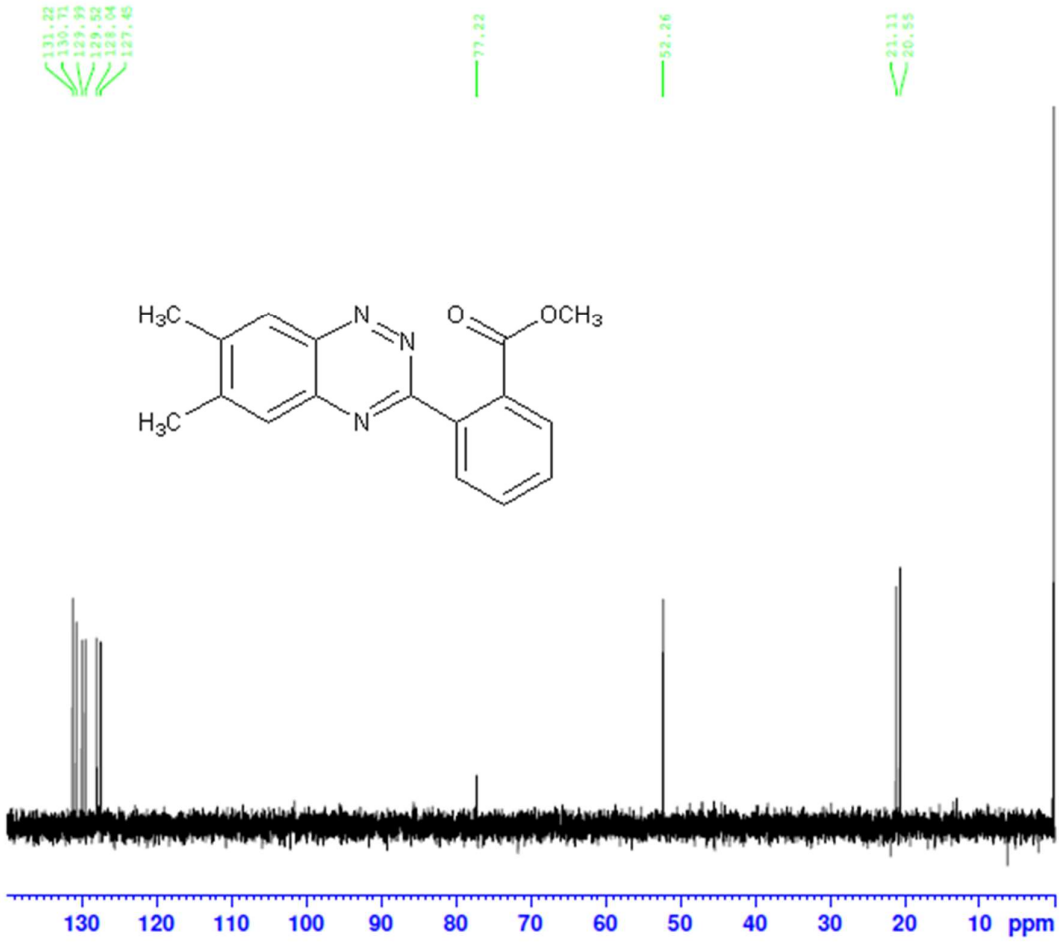
^{13}C-NMR of **41b** in $CDCl_3$ at room temperature.



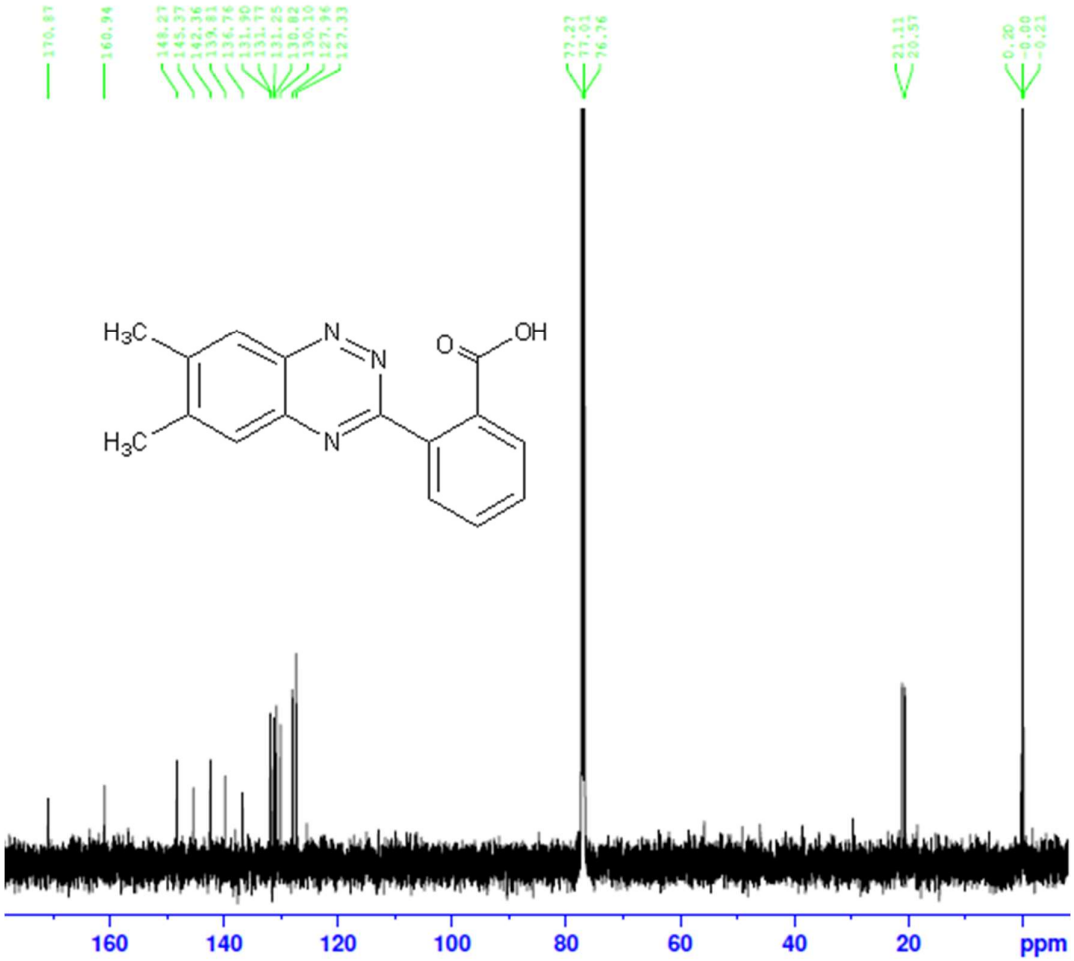
^{13}C DEPT 135-NMR of **41b** in $CDCl_3$ at room temperature.



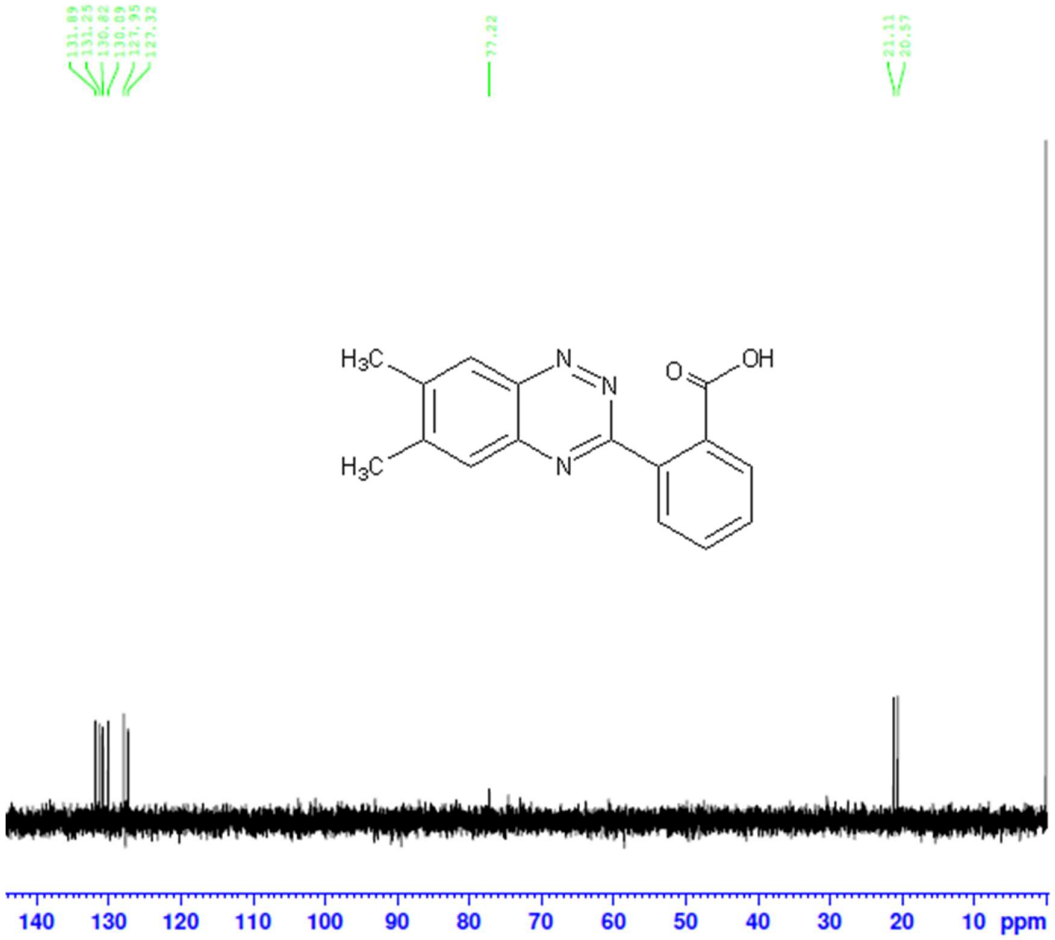
^{13}C-NMR of **40c** in $CDCl_3$ at room temperature.



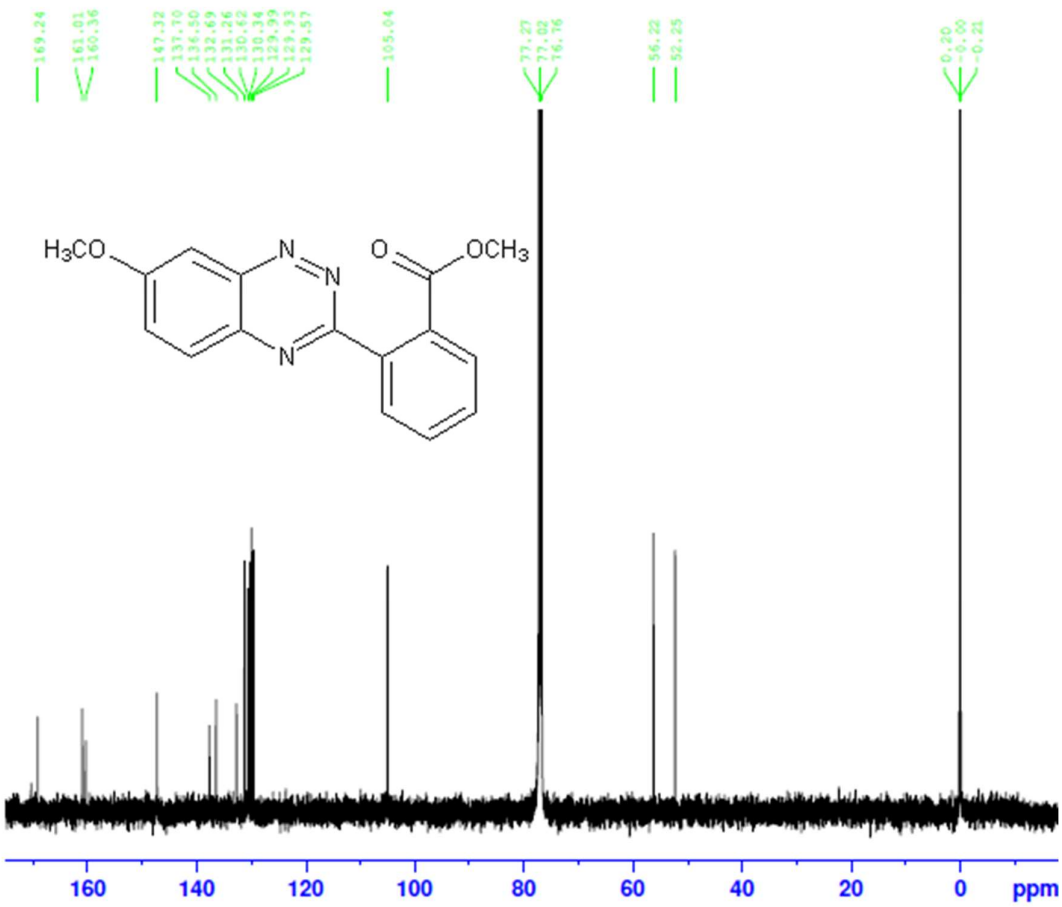
^{13}C DEPT 135-NMR of **40c** in $CDCl_3$ at room temperature.



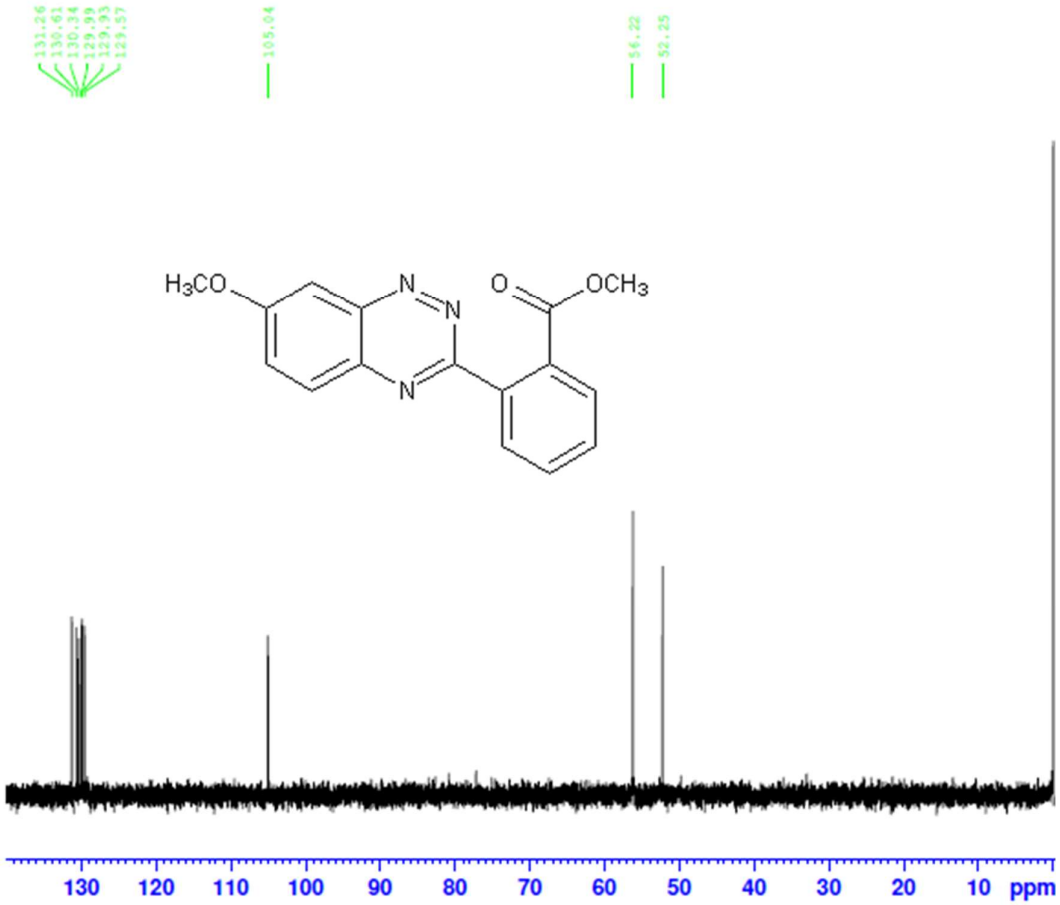
^{13}C-NMR of **41c** in $CDCl_3$ at room temperature.



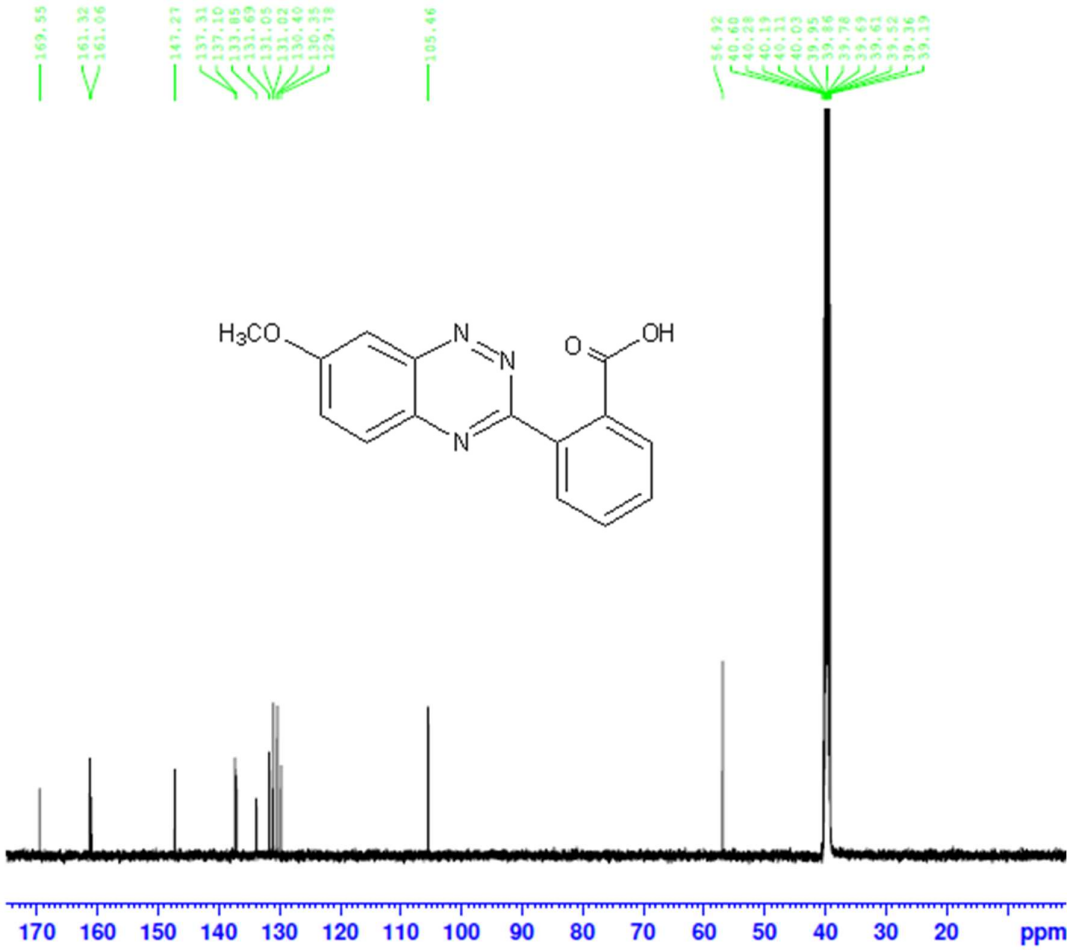
^{13}C DEPT 135-NMR of **41c** in $CDCl_3$ at room temperature.



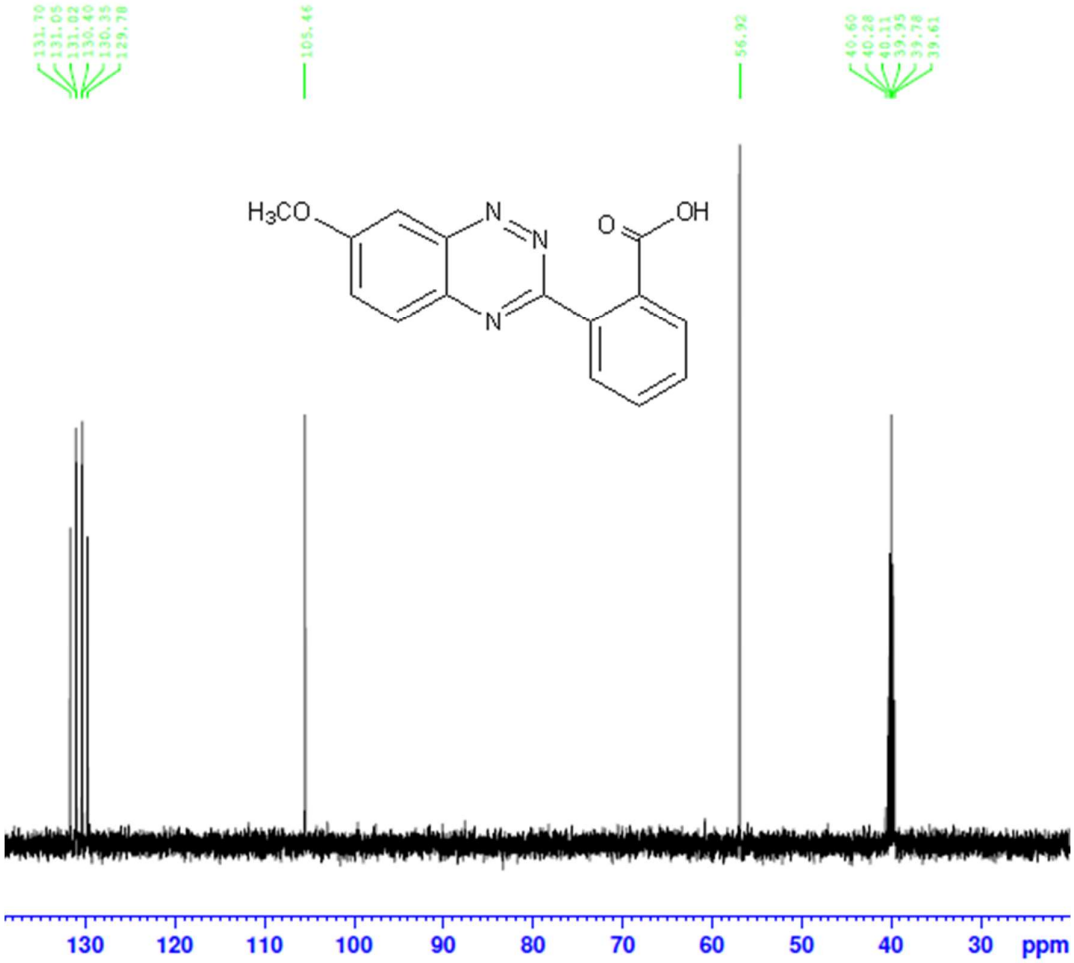
^{13}C-NMR of **40d** in $CDCl_3$ at room temperature.



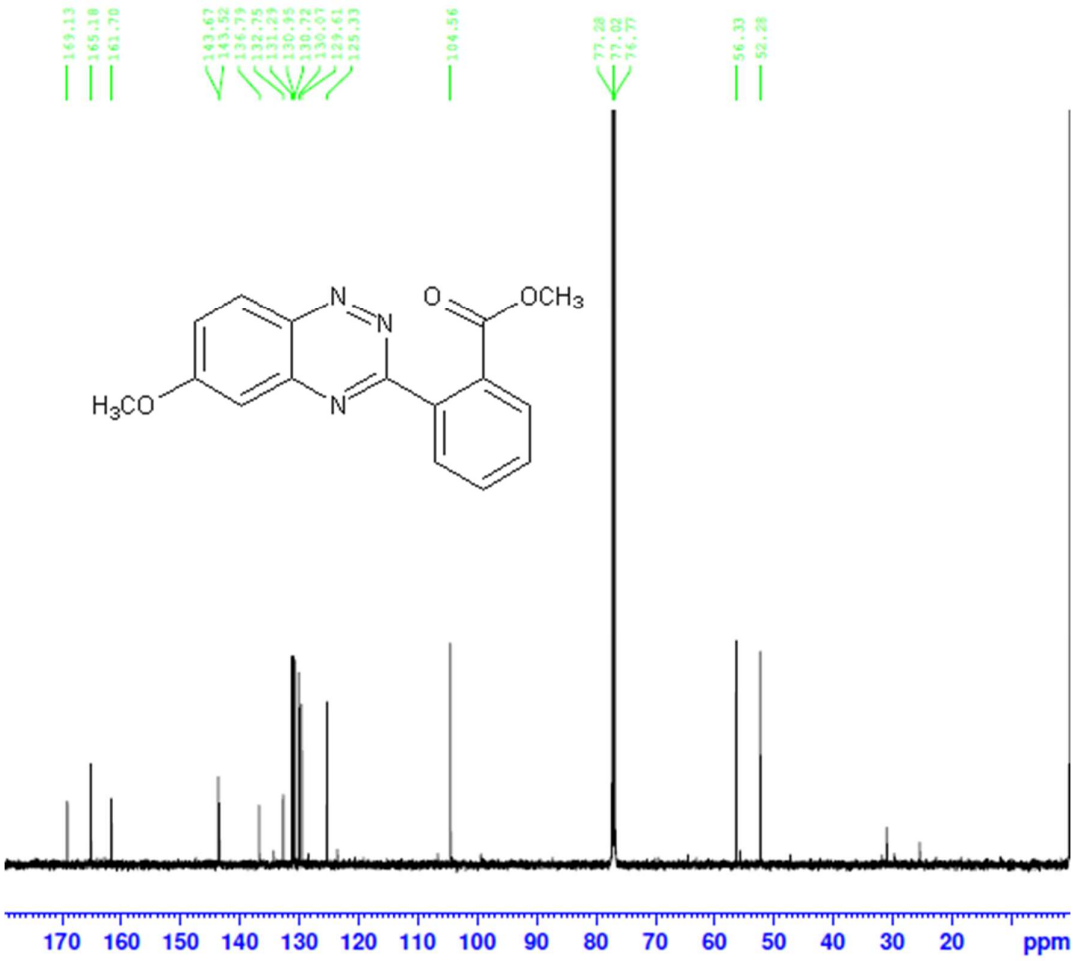
^{13}C DEPT 135-NMR of **40d** in $CDCl_3$ at room temperature.



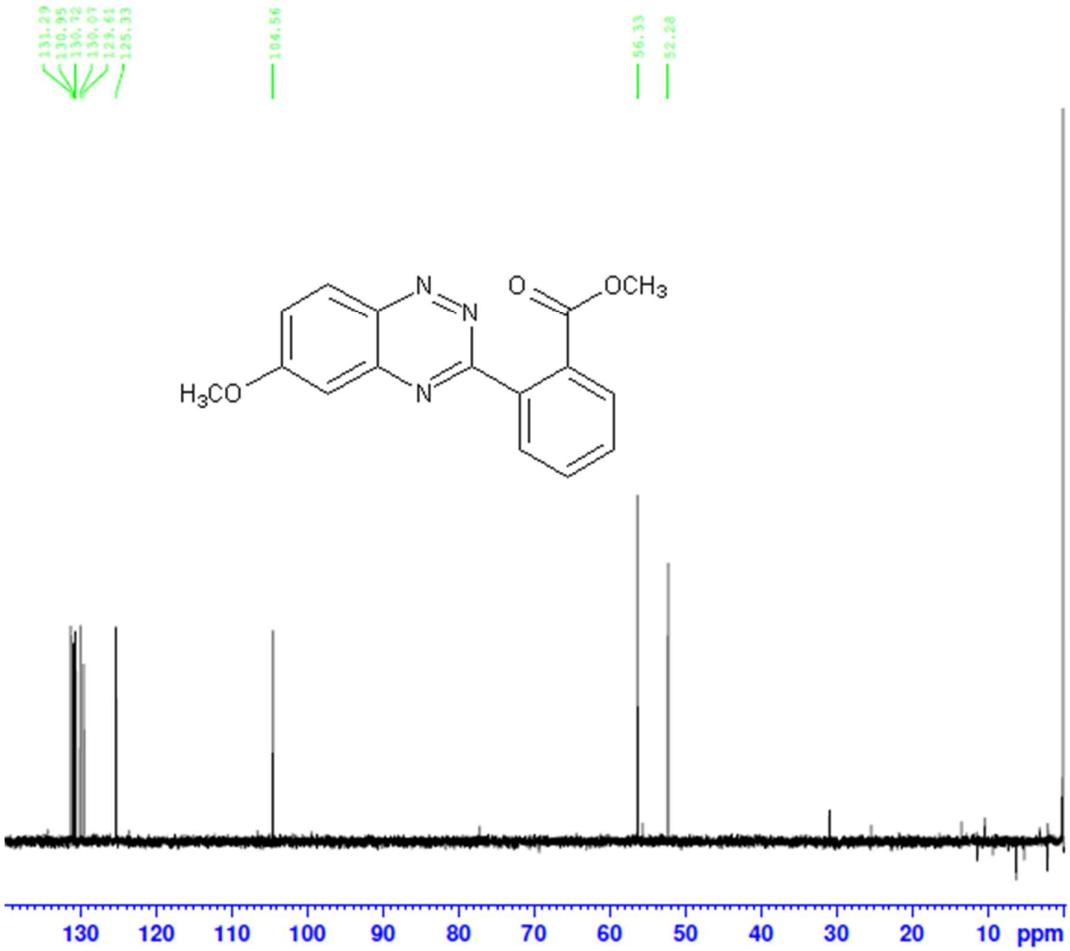
^{13}C-NMR of **41d** in DMSO-*d6* at room temperature.



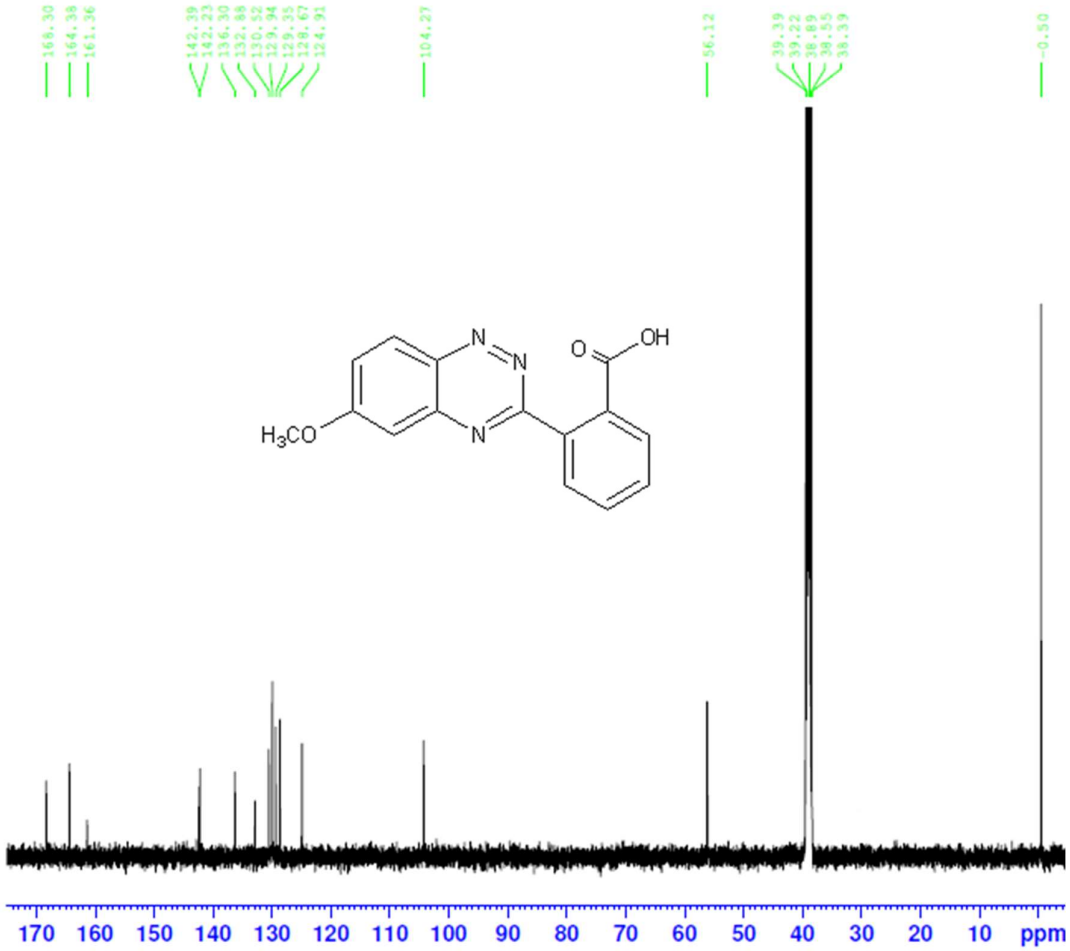
^{13}C DEPT 135-NMR of **41d** in DMSO-*d6* at room temperature.



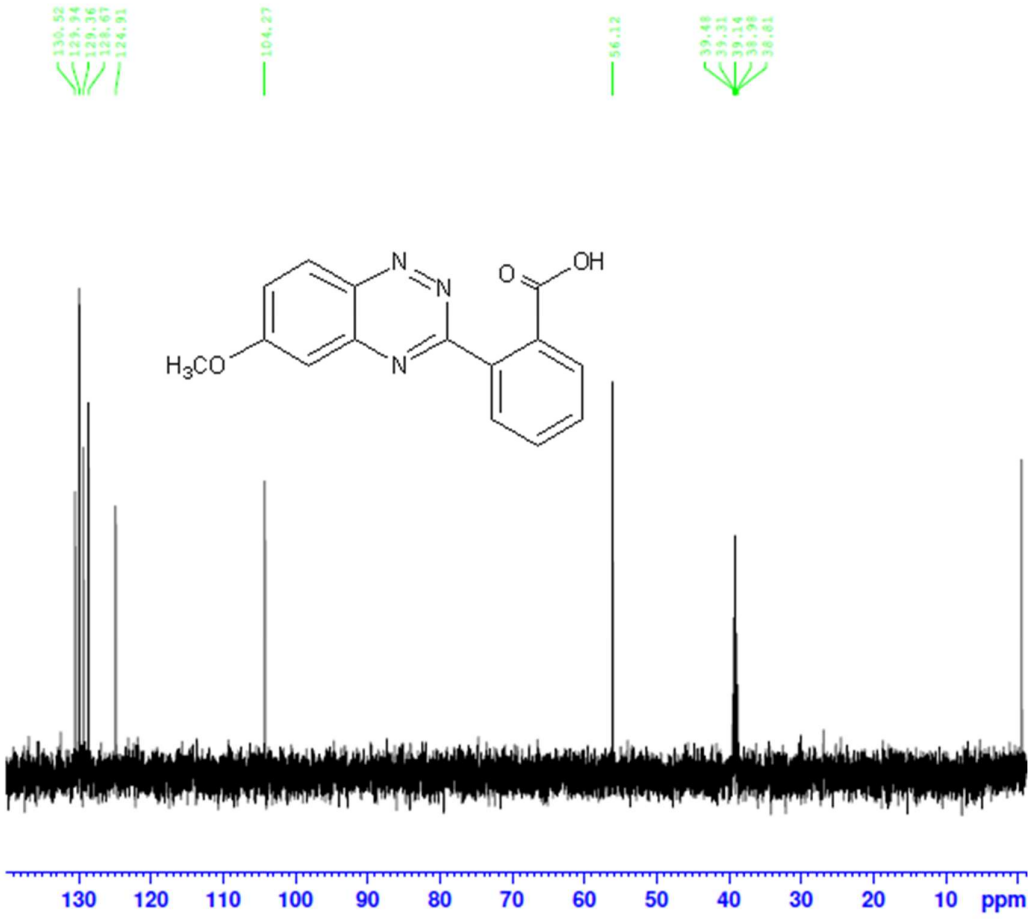
^{13}C-NMR of **40e** in $CDCl_3$ at room temperature.



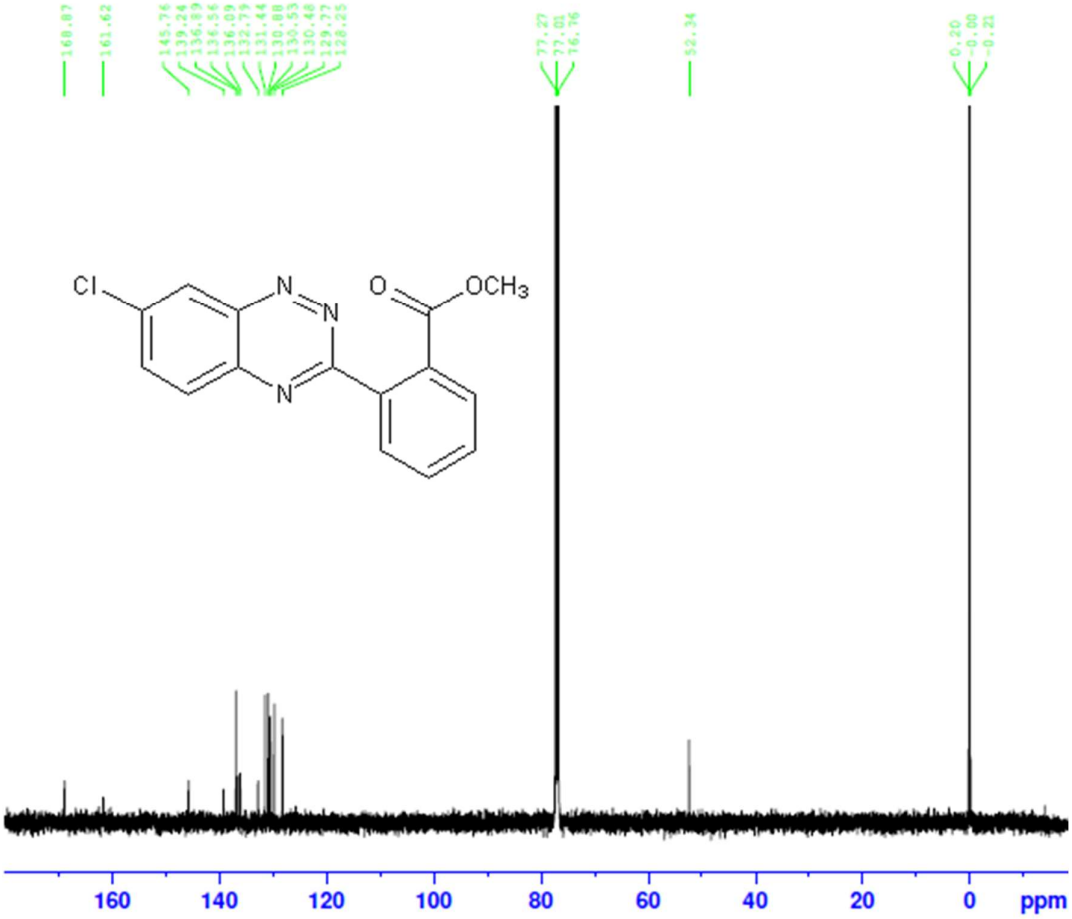
^{13}C DEPT 135-NMR of **40e** in $CDCl_3$ at room temperature.



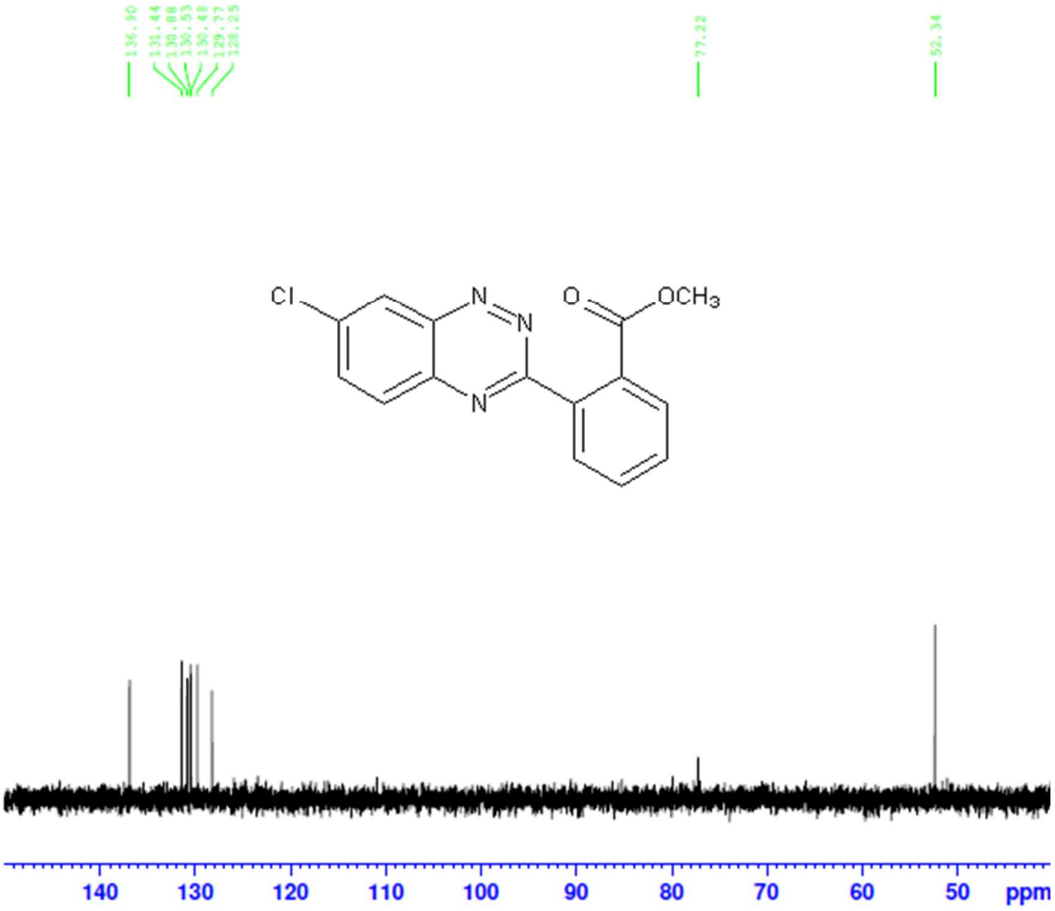
^{13}C-NMR of **41e** in DMSO-*d6* at room temperature.



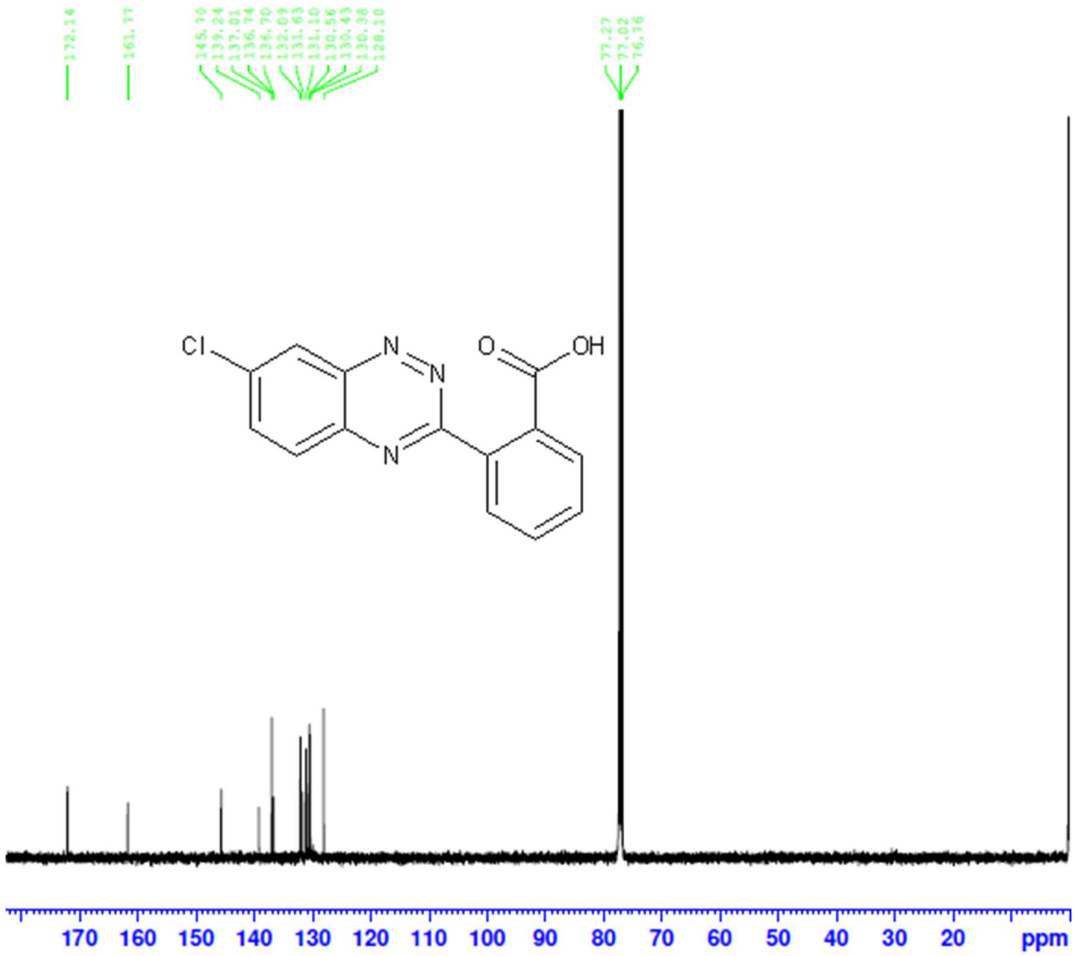
^{13}C DEPT 135-NMR of **41e** in DMSO-*d6* at room temperature.



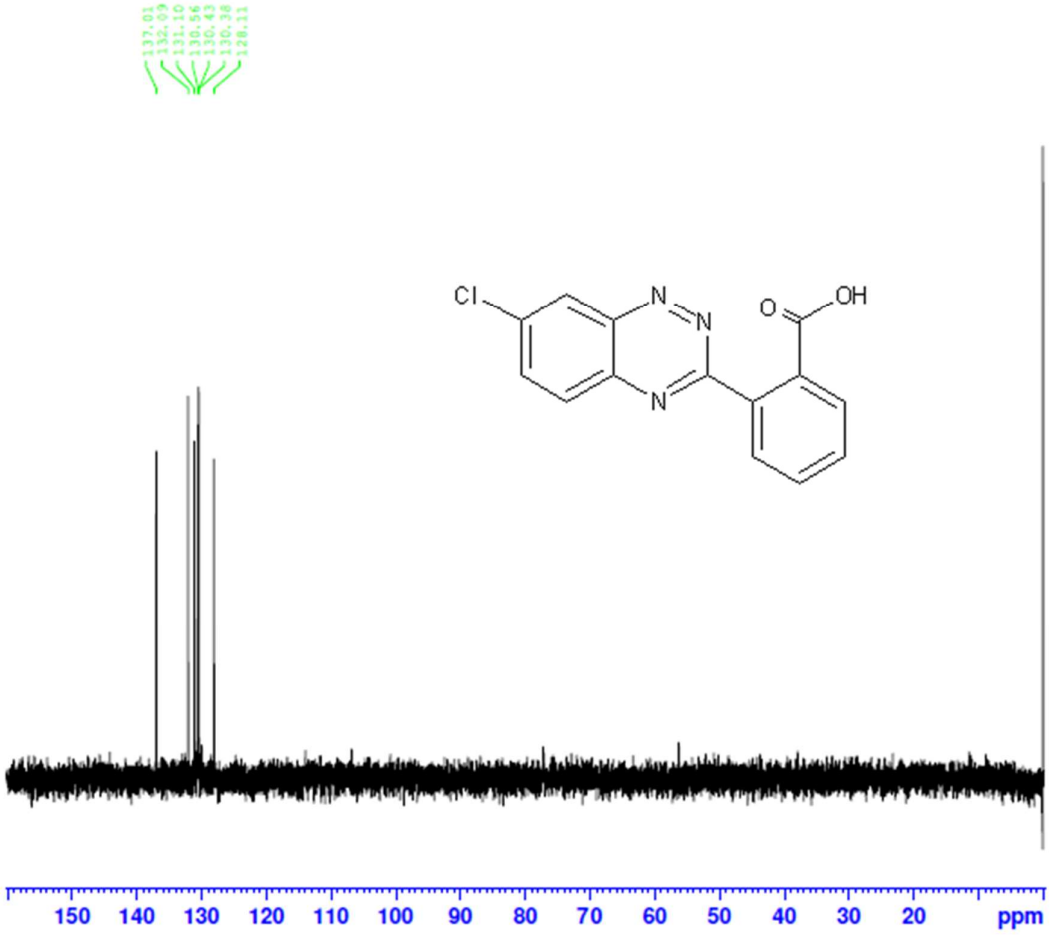
^{13}C -NMR of **40f** in $CDCl_3$ at room temperature.



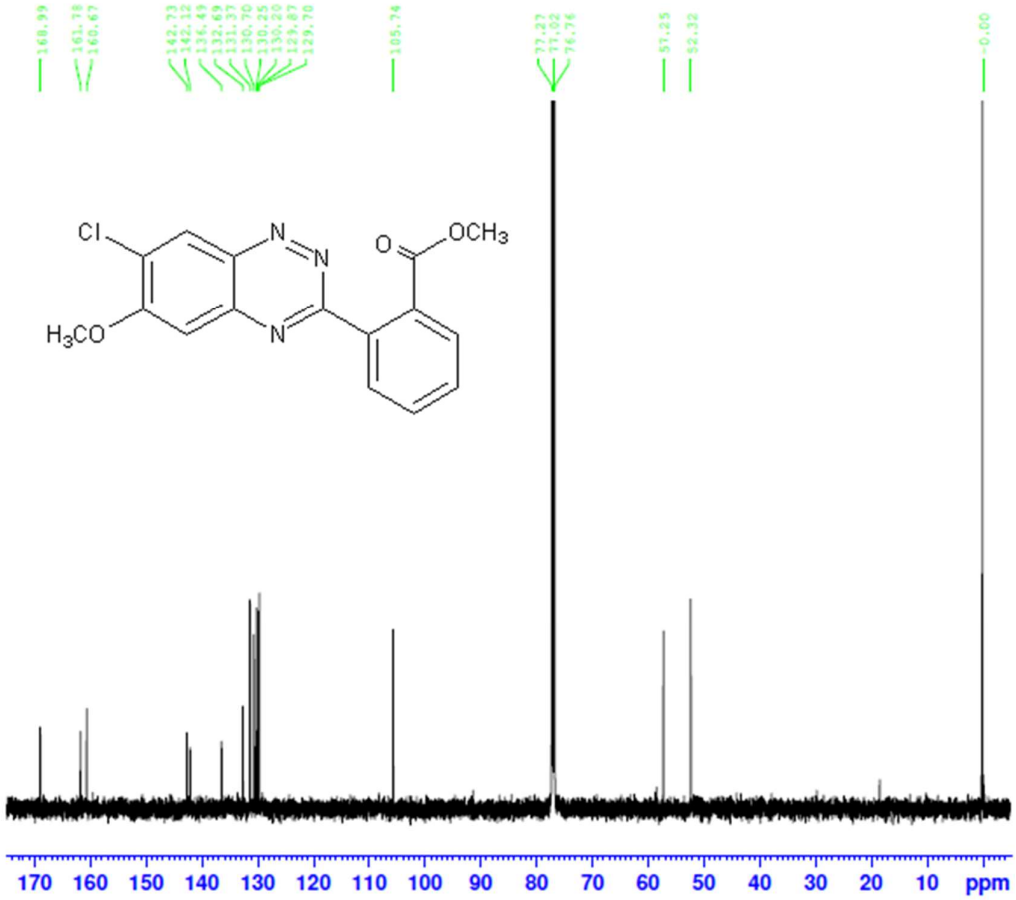
^{13}C DEPT 135-NMR of **40f** in $CDCl_3$ at room temperature.



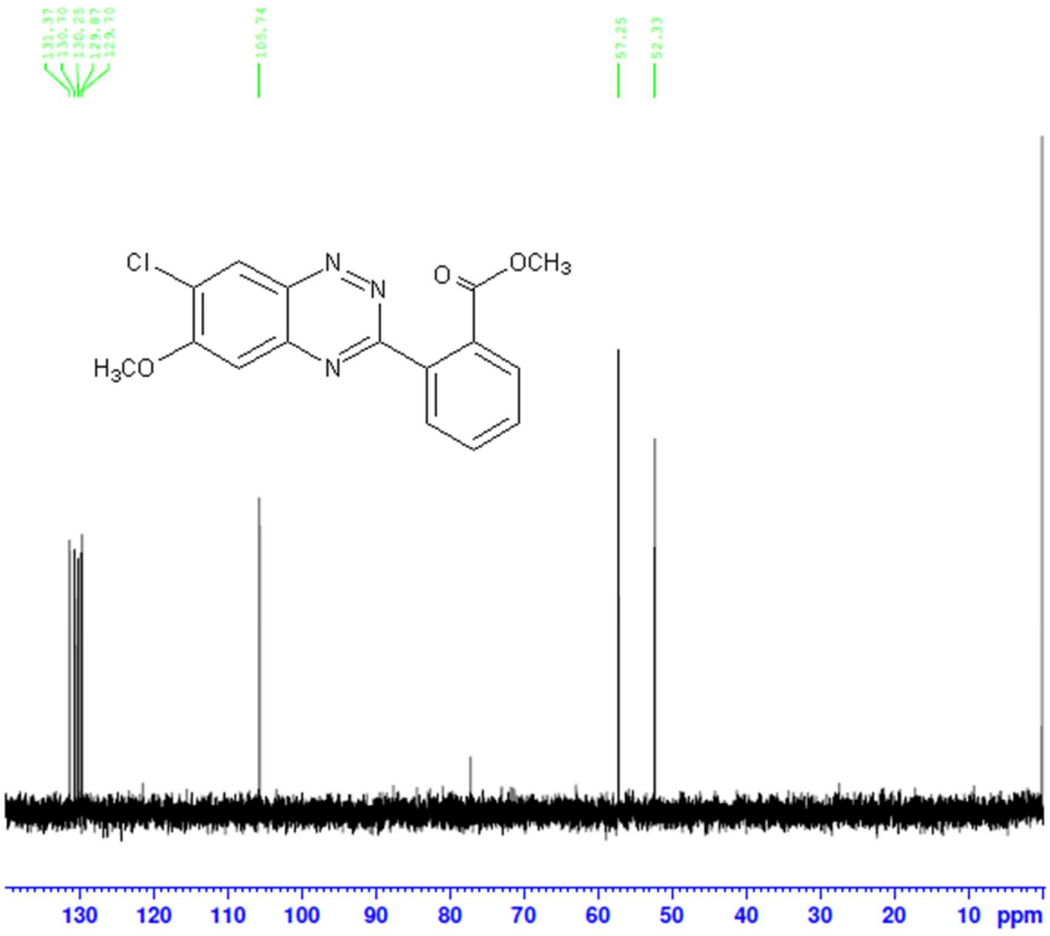
^{13}C -NMR of **41f** in $CDCl_3$ at room temperature.



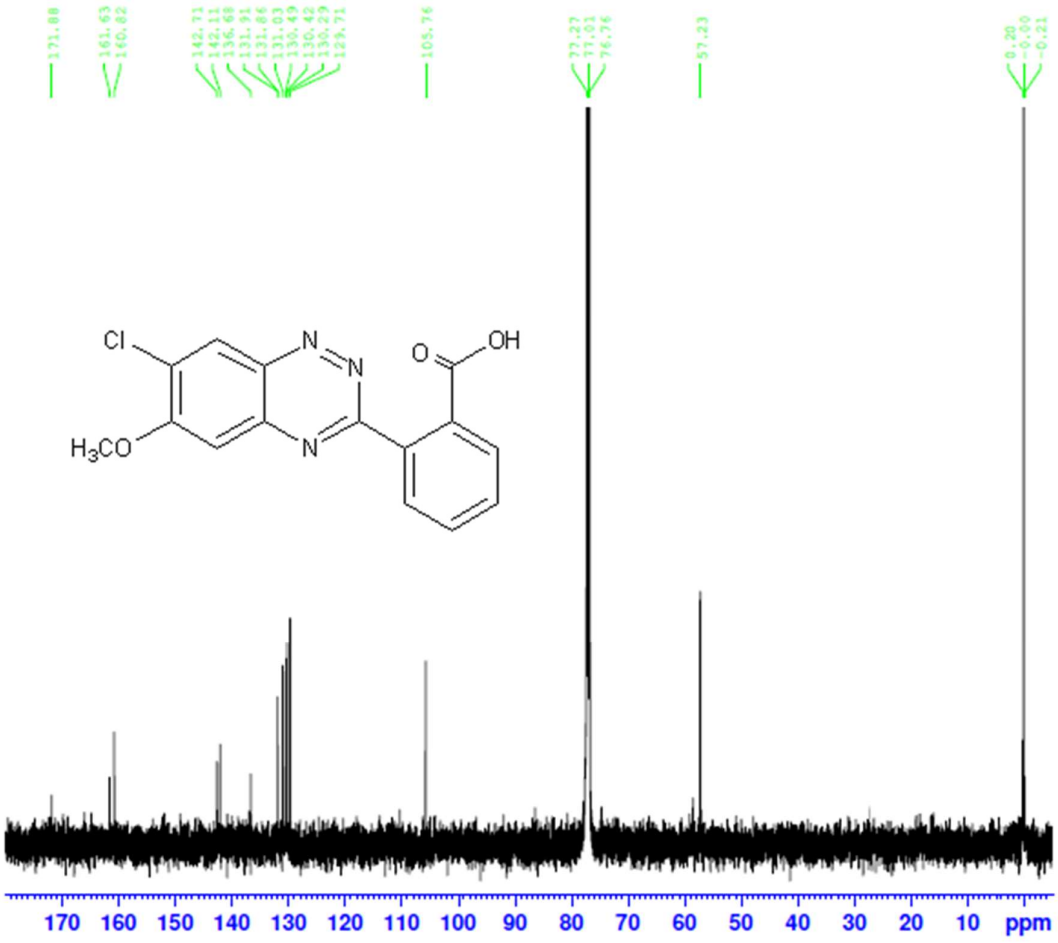
^{13}C DEPT 135-NMR of **41f** in $CDCl_3$ at room temperature.



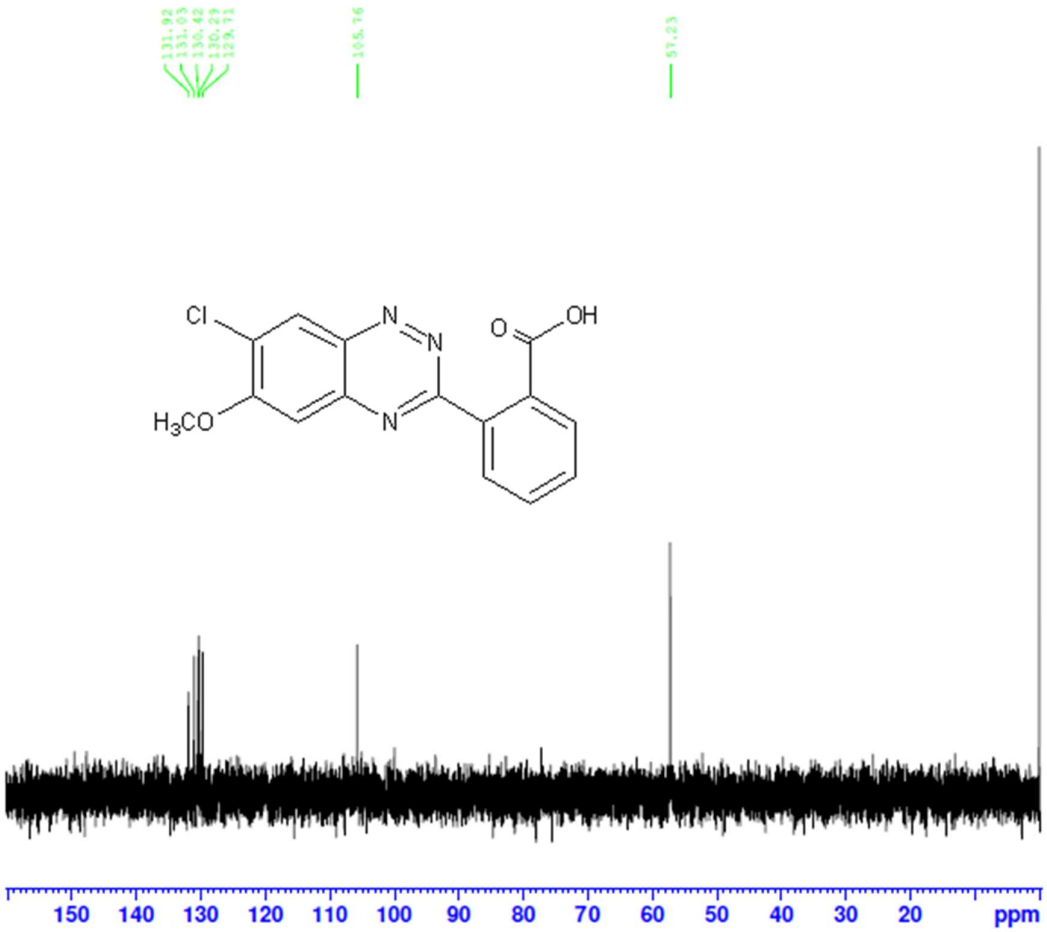
^{13}C-NMR of **40g** in $CDCl_3$ at room temperature.



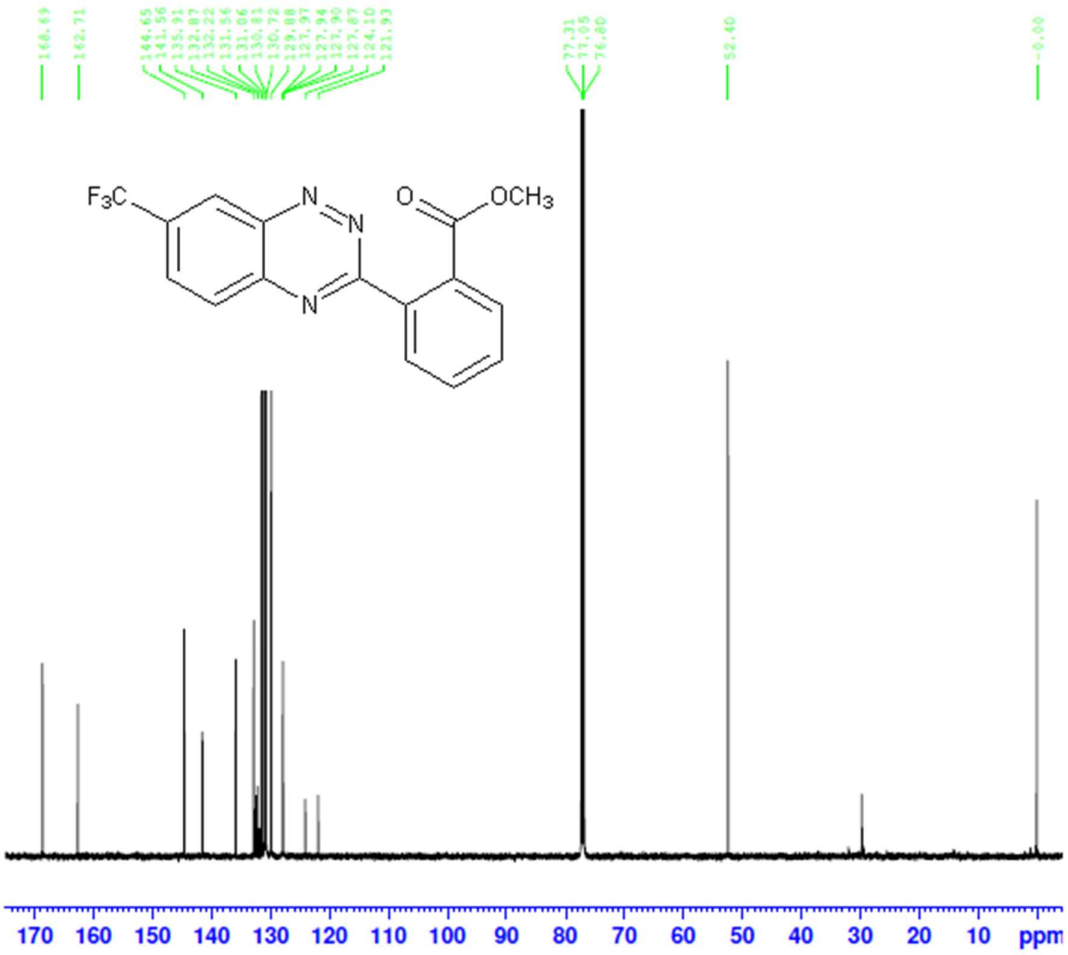
^{13}C DEPT 135-NMR of **40g** in $CDCl_3$ at room temperature.



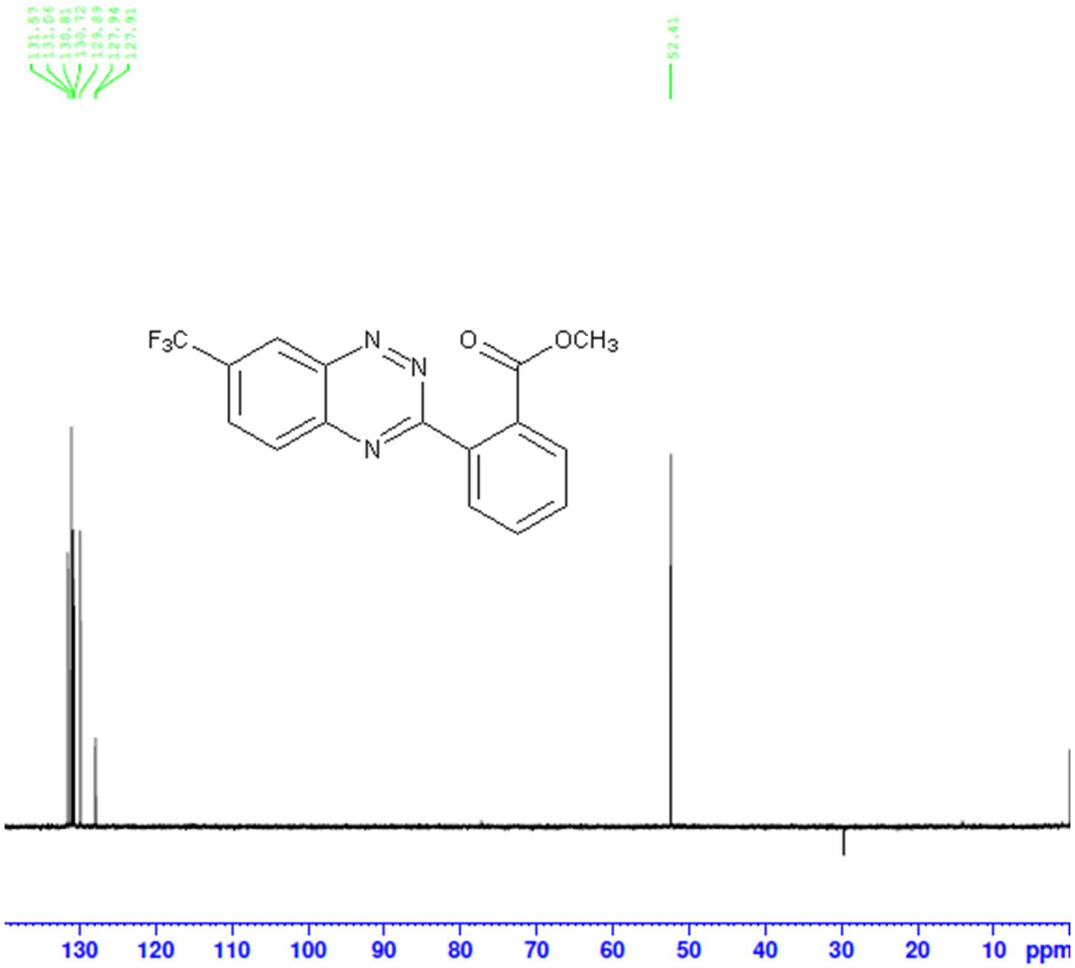
^{13}C-NMR of **41g** in $CDCl_3$ at room temperature.



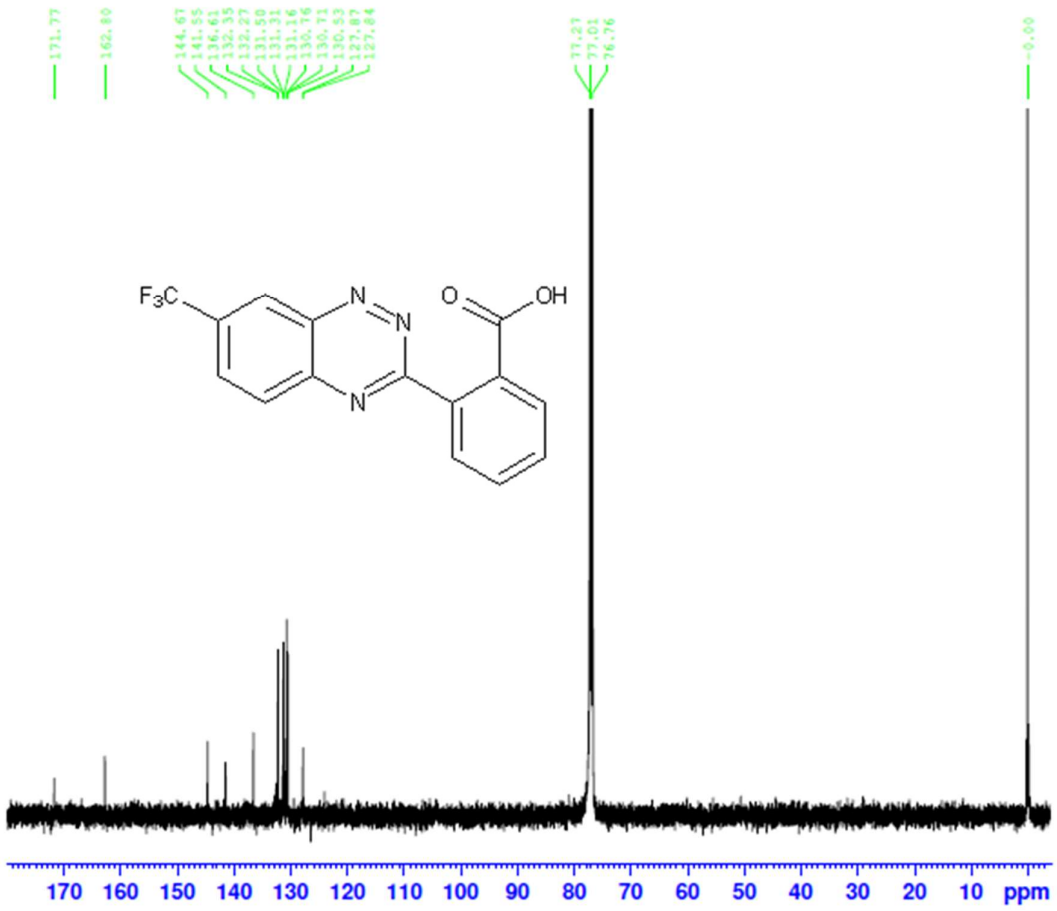
^{13}C DEPT 135-NMR of **41g** in $CDCl_3$ at room temperature.



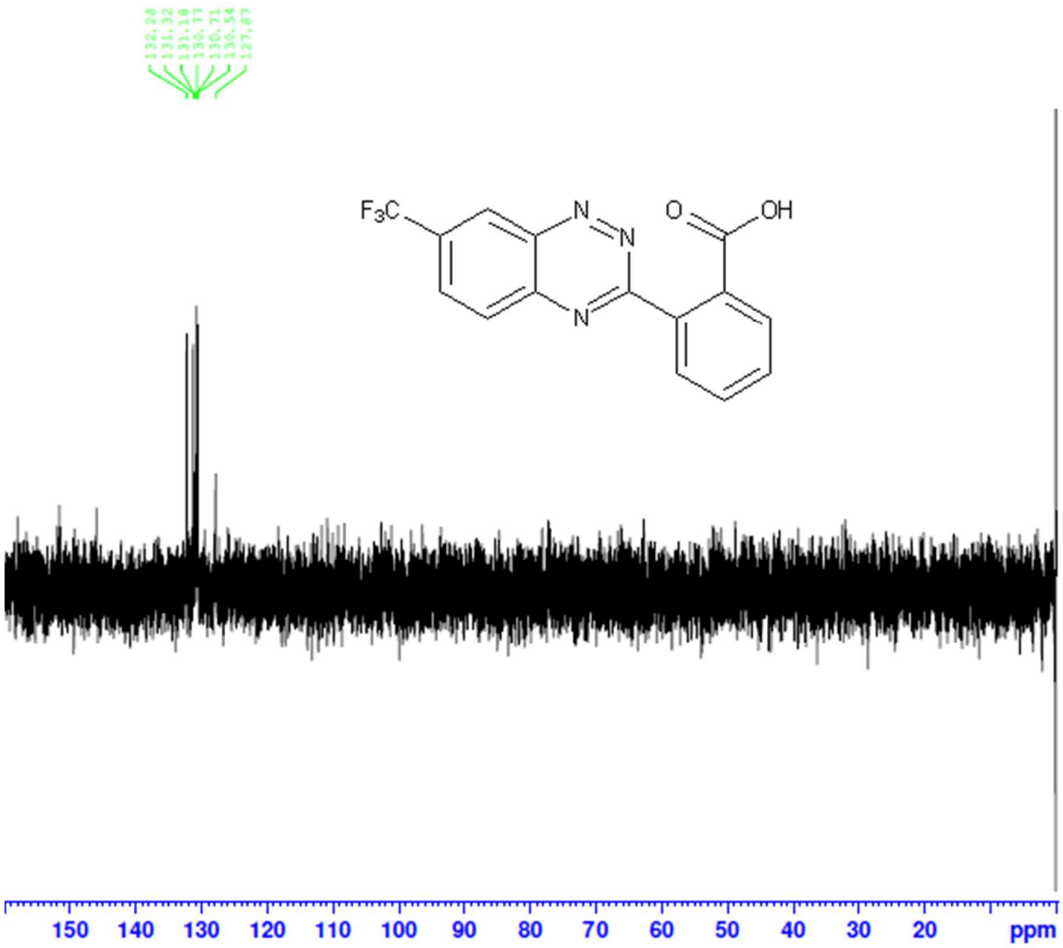
^{13}C-NMR of **40h** in $CDCl_3$ at room temperature.



^{13}C DEPT 135-NMR of **40h** in $CDCl_3$ at room temperature.

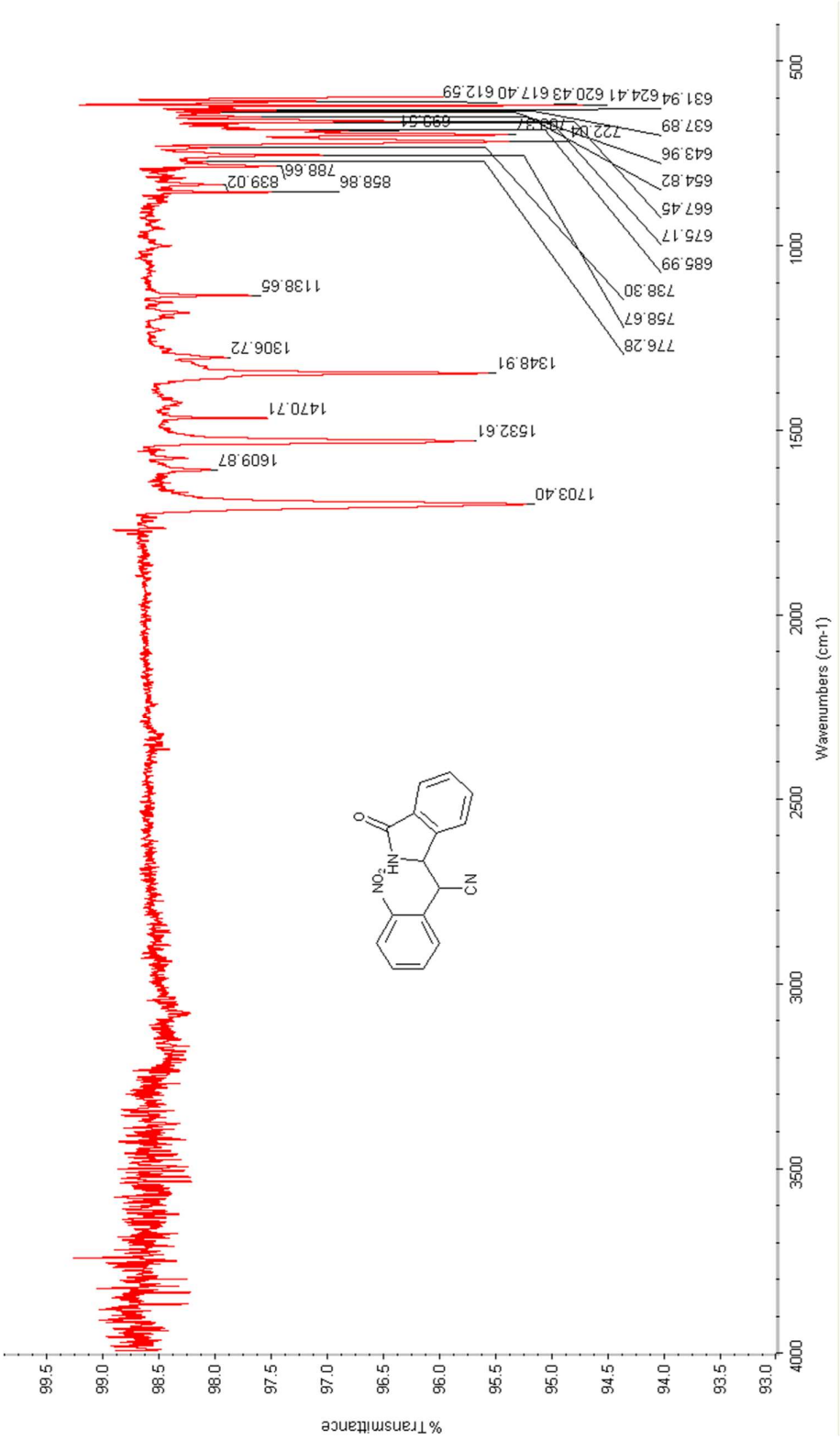


^{13}C-NMR of **41h** in $CDCl_3$ at room temperature.

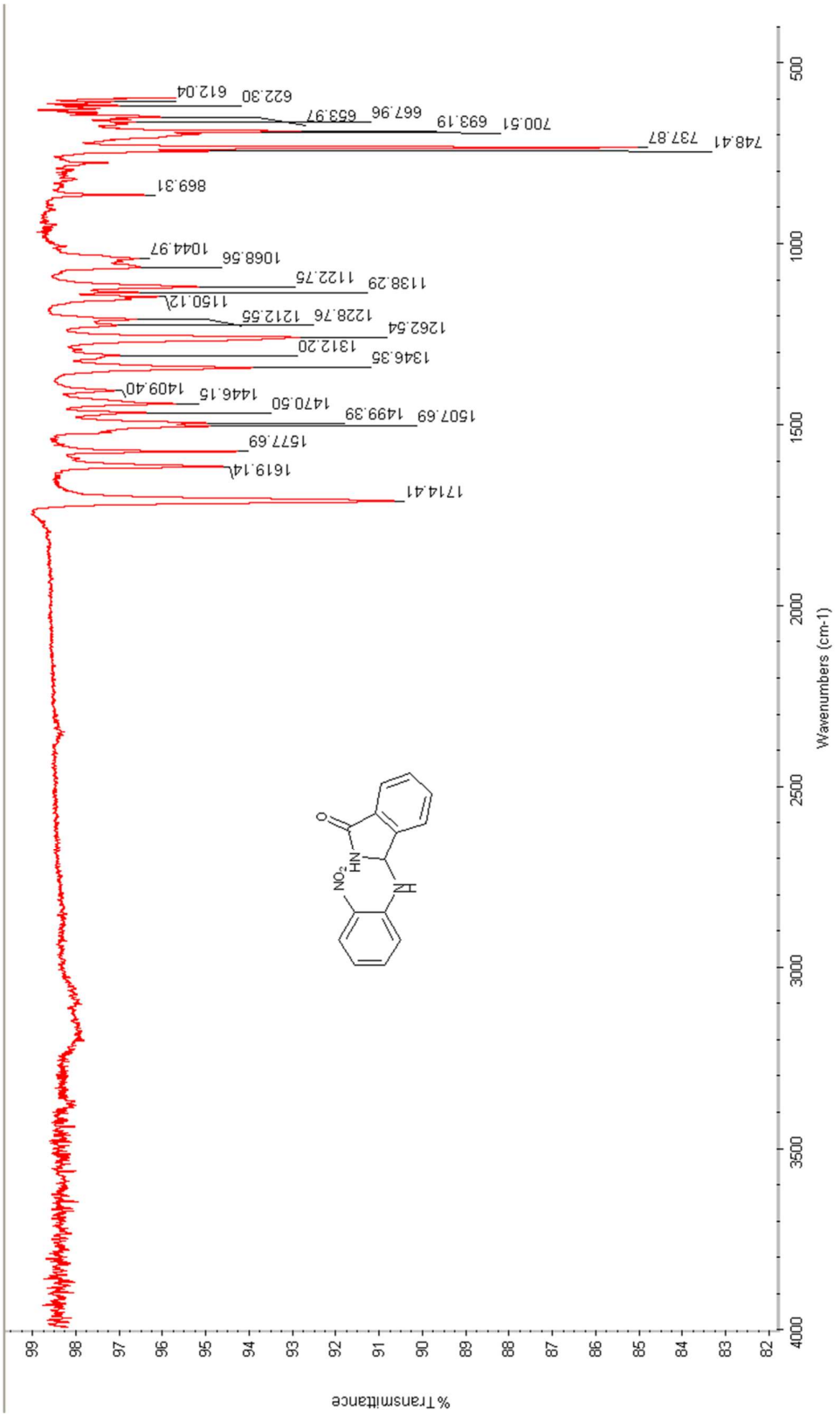


^{13}C DEPT 135-NMR of **41h** in $CDCl_3$ at room temperature.

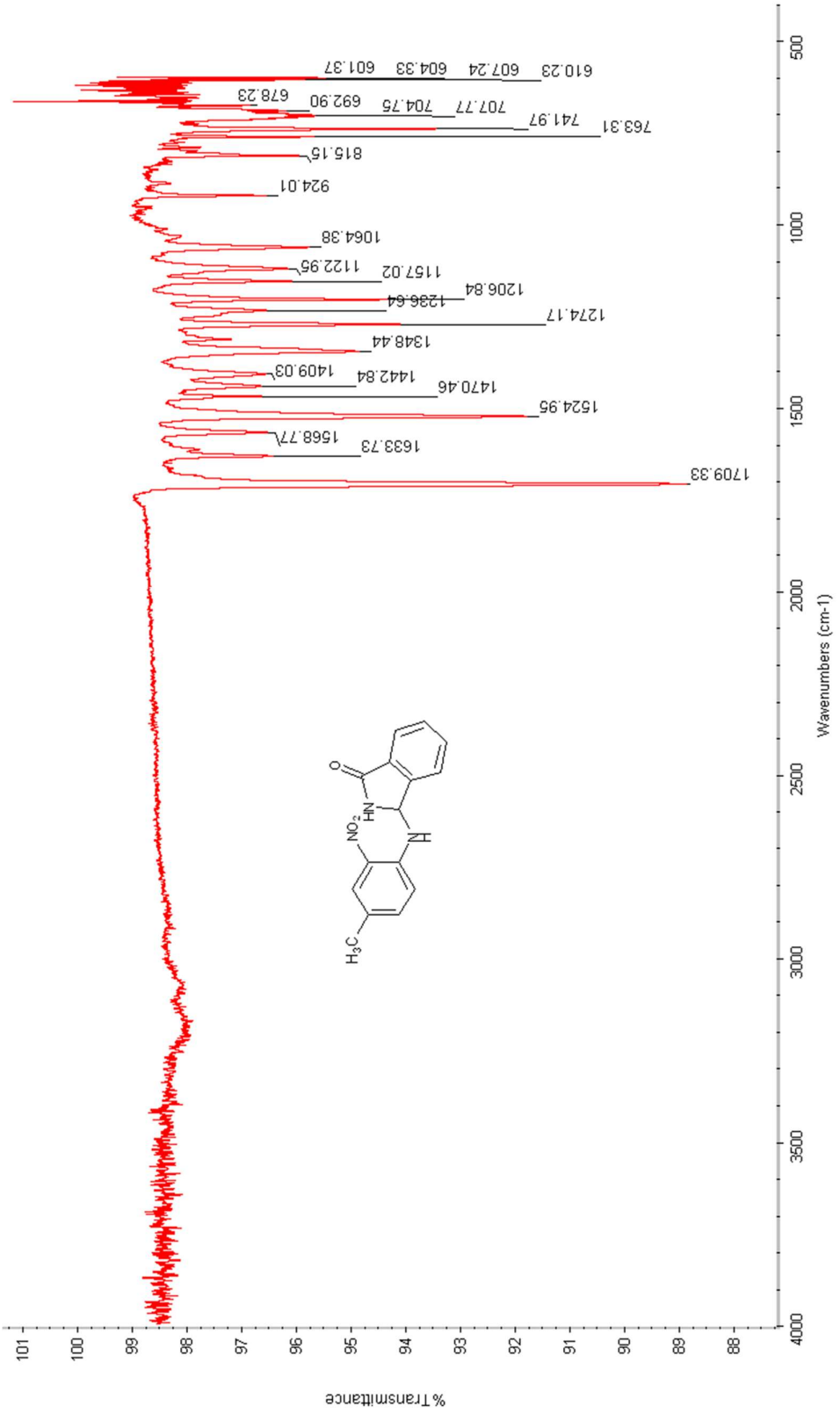
APPENDIX C IR SPECTRUM



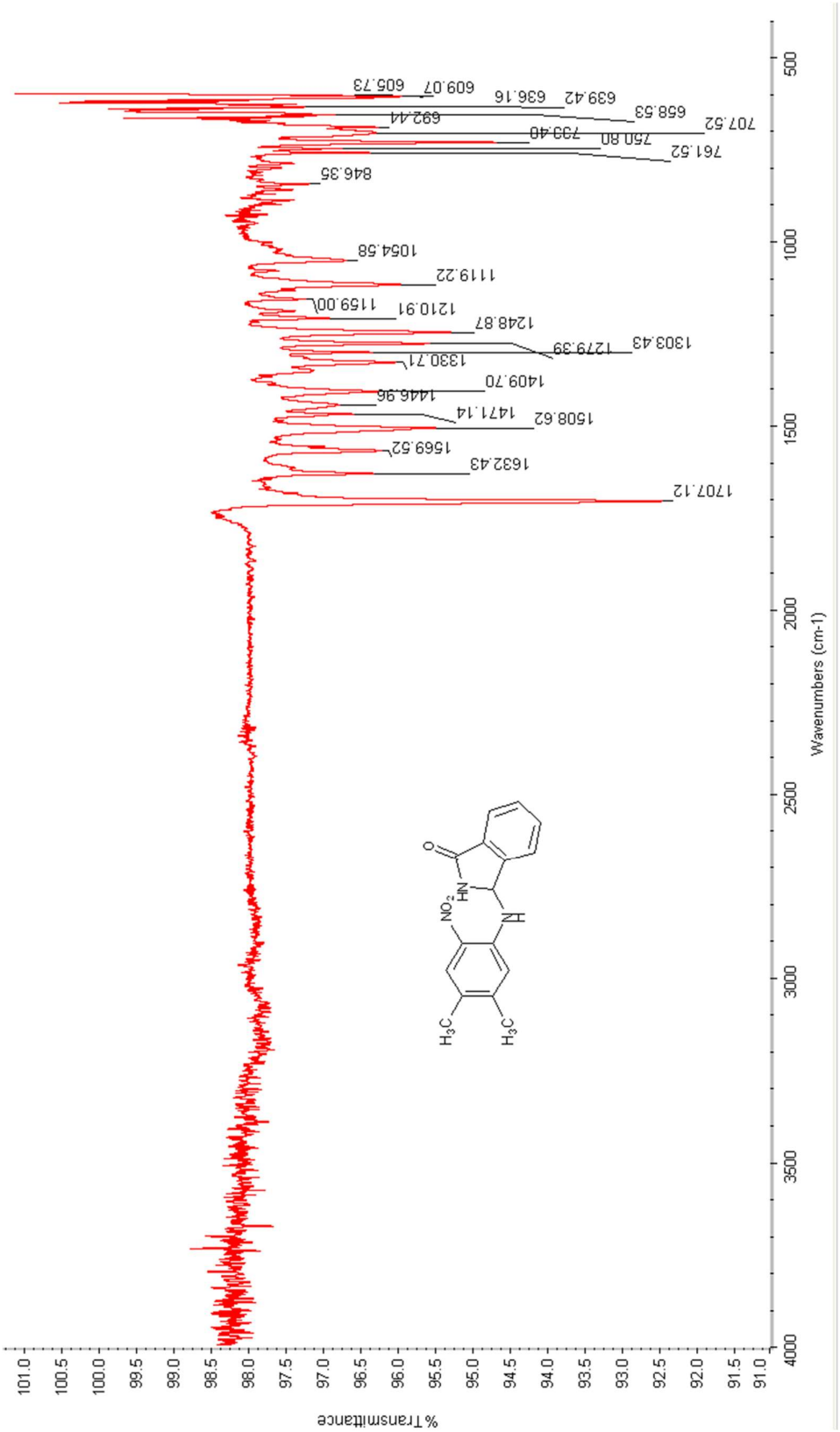
IR of **31**


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
84
83
82
622.30
612.04
700.51
698.19
667.96
653.97
748.41
737.87
869.31
1068.56
1044.97
1138.29
1122.75
1150.12
1228.76
1212.55
1262.54
1346.35
1312.20
1507.69
1499.39
1470.50
1446.15
1409.40
1577.69
1619.14
1714.41
O
HN
NO2
N
H

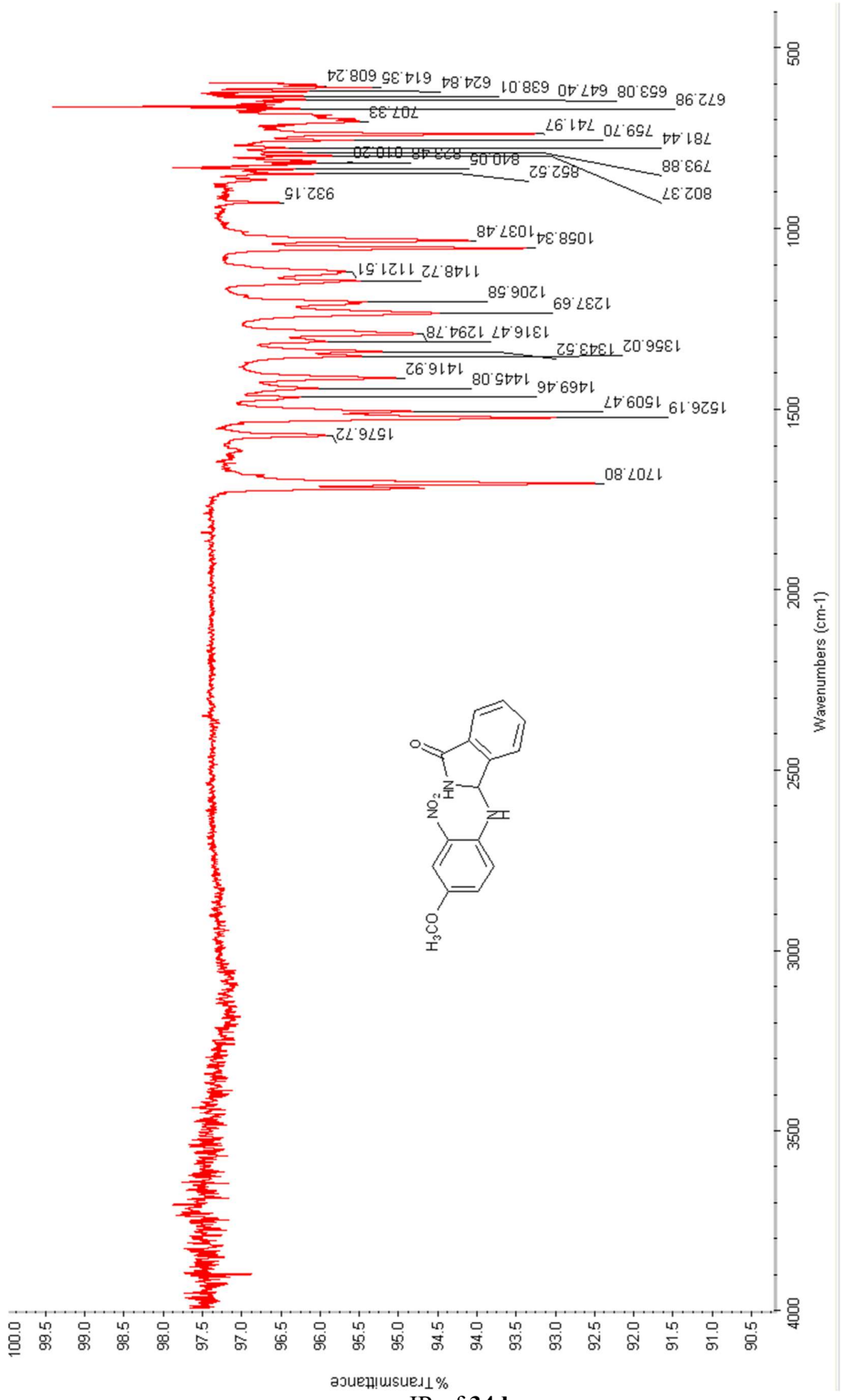
IR of **34a**


610.23
607.24
604.33
601.37
678.23
692.90
704.75
707.77
741.97
763.31
815.15
924.01
1064.38
1122.95
1157.02
1206.84
1236.64
1274.17
1348.44
1409.03
1442.84
1470.46
1524.95
1568.77
1633.73
1709.33
O
HN
NO2
H
H3C
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
101
100
99
98
97
96
95
94
93
92
91
90
89
88
%Transmittance

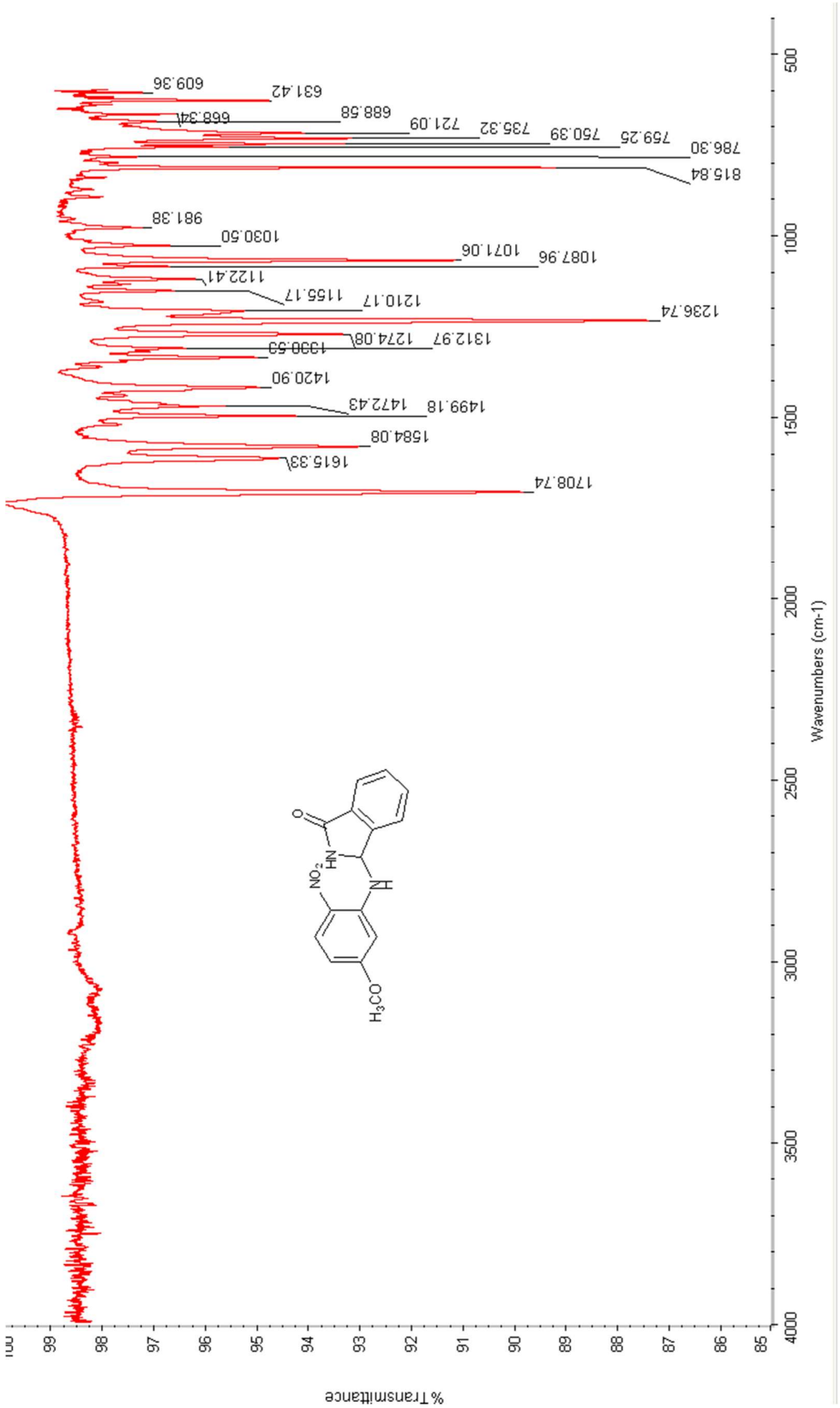
IR of **34b**


%Transmittance
Wavenumbers (cm-1)
605.73
609.07
636.16
639.42
658.53
692.44
707.52
739.40
750.80
761.52
846.35
1054.58
1119.22
1159.00
1210.91
1248.87
1279.39
1303.43
1330.71
1409.70
1446.96
1471.14
1508.62
1569.52
1632.43
1707.12
O
HN
NO2
N
H3C
H3C

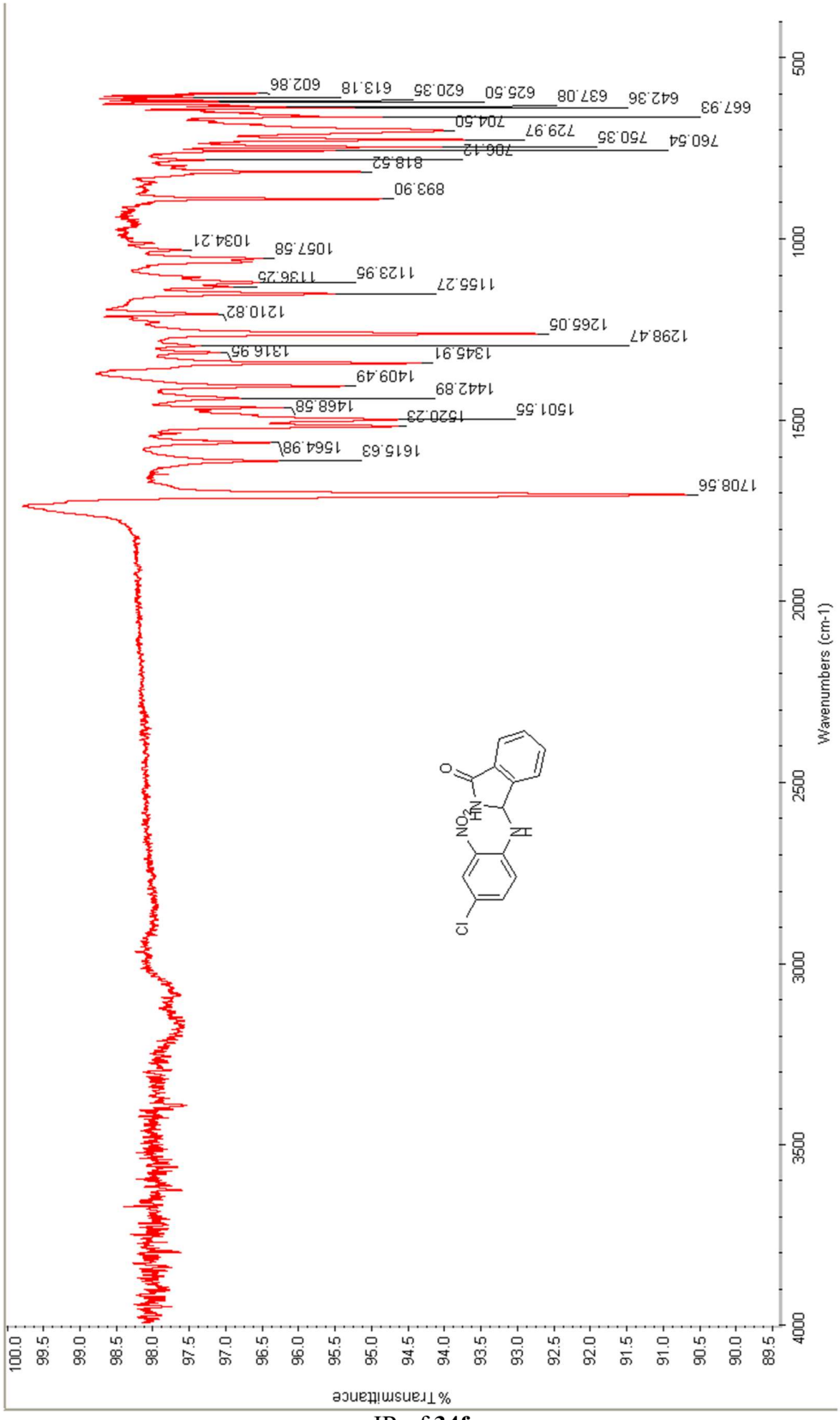
IR of **34c**


672.98
653.08
647.40
638.01
624.84
614.35
608.24
707.33
781.44
759.70
741.97
793.88
840.05
823.48
810.20
802.37
852.52
932.15
1058.34
1037.48
1148.72
1121.51
1237.69
1206.58
1356.02
1343.52
1316.47
1294.78
1526.19
1509.47
1469.46
1445.08
1416.92
1576.72
1707.80
O
HN
NH
NO2
H3CO
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.5
94.0
93.5
93.0
92.5
92.0
91.5
91.0
90.5
%Transmittance
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

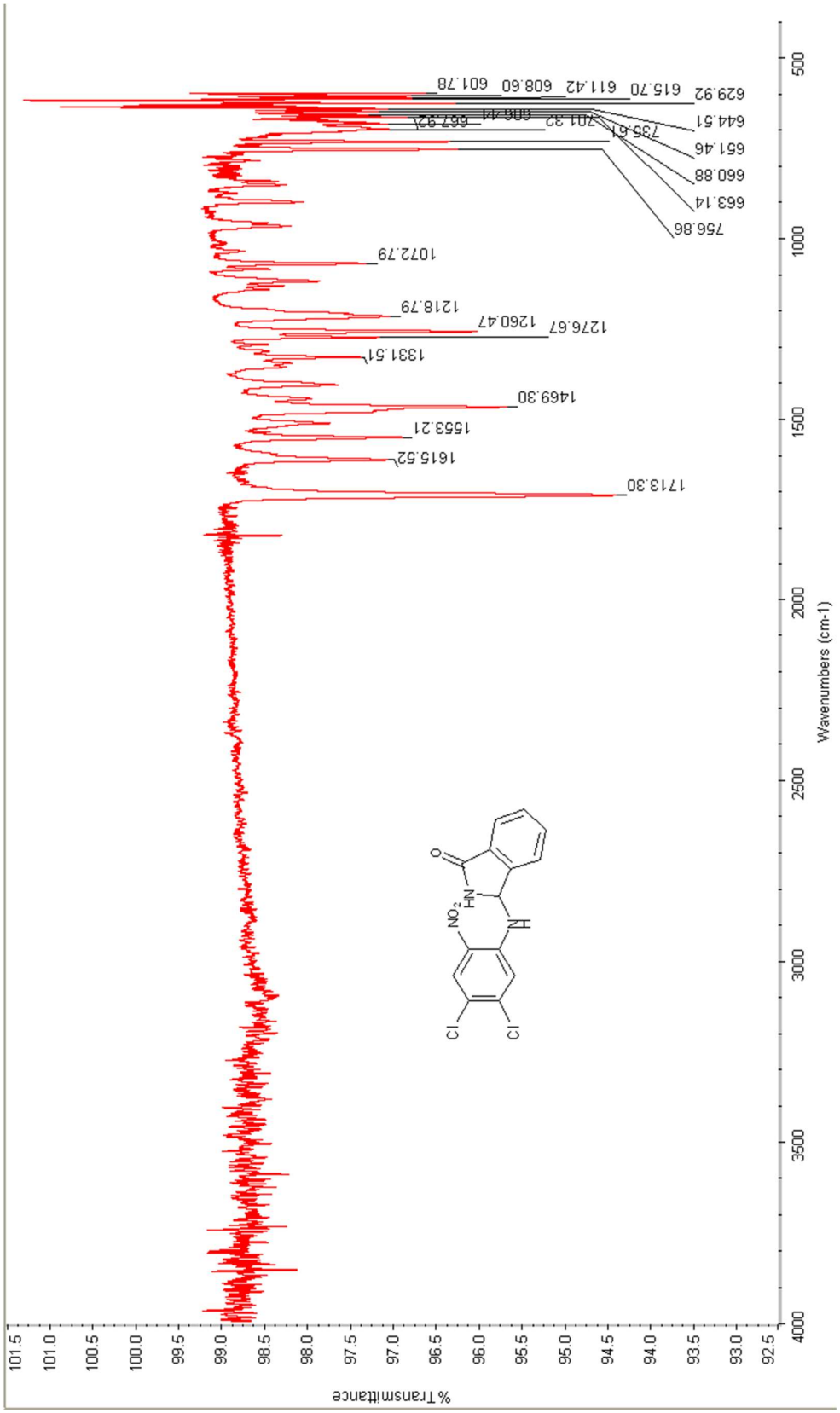
IR of **34d**


609.36
631.42
668.34
688.58
721.09
735.32
750.39
759.25
786.30
815.84
981.38
1030.50
1071.06
1087.96
1122.41
1155.17
1210.17
1236.74
1274.08
1312.97
1330.53
1420.90
1472.43
1499.18
1584.08
1615.33
1708.74
%Transmittance
Wavenumbers (cm-1)

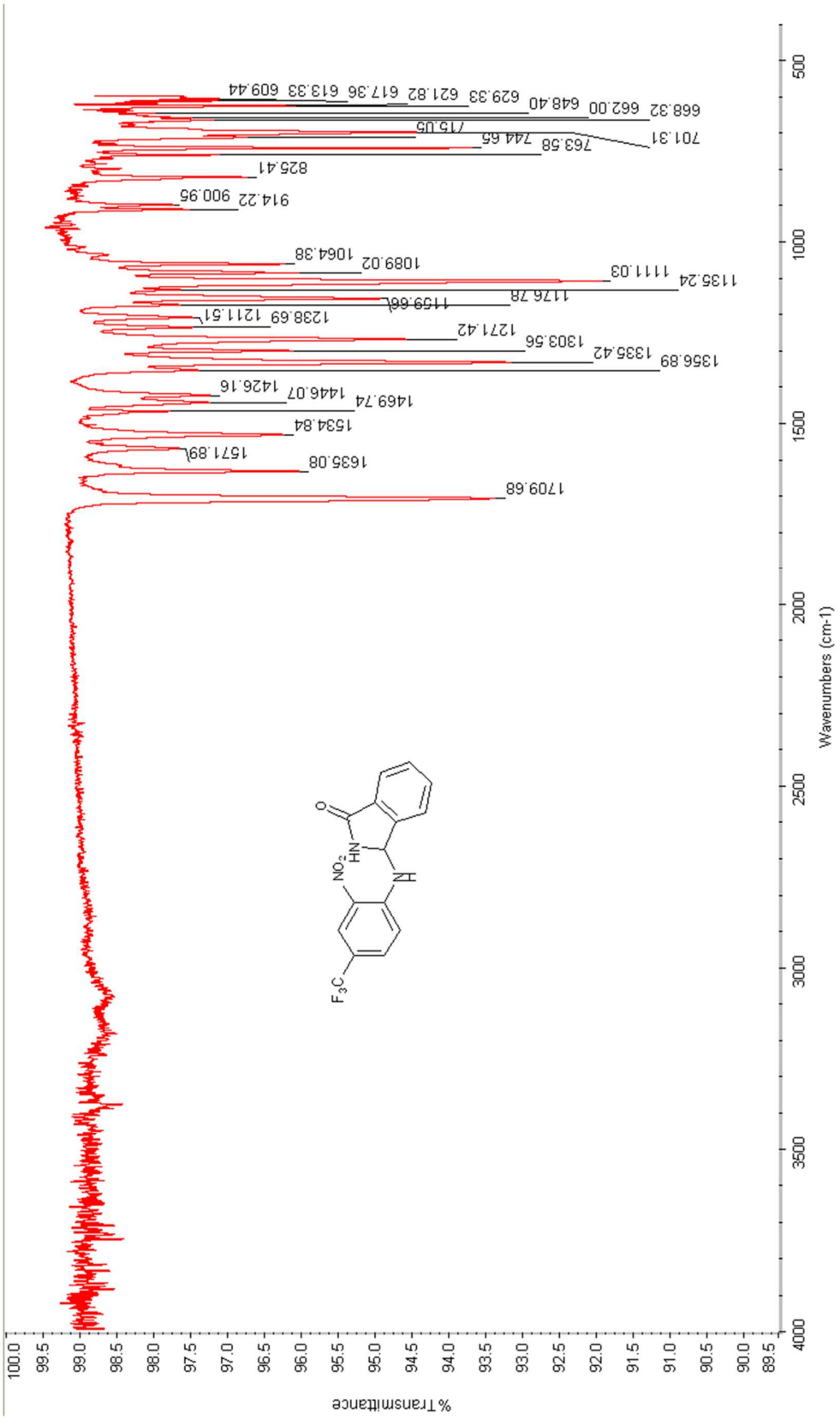
IR of **34e**


%Transmittance
Wavenumbers (cm-1)
1708.56
1615.63
1564.98
1520.23
1501.55
1468.58
1442.89
1409.49
1345.91
1316.95
1298.47
1265.05
1210.82
1155.27
1123.95
1136.25
1057.58
1034.21
893.90
818.52
706.12
760.54
750.35
729.97
704.50
667.93
642.36
637.08
625.50
620.35
613.18
602.86

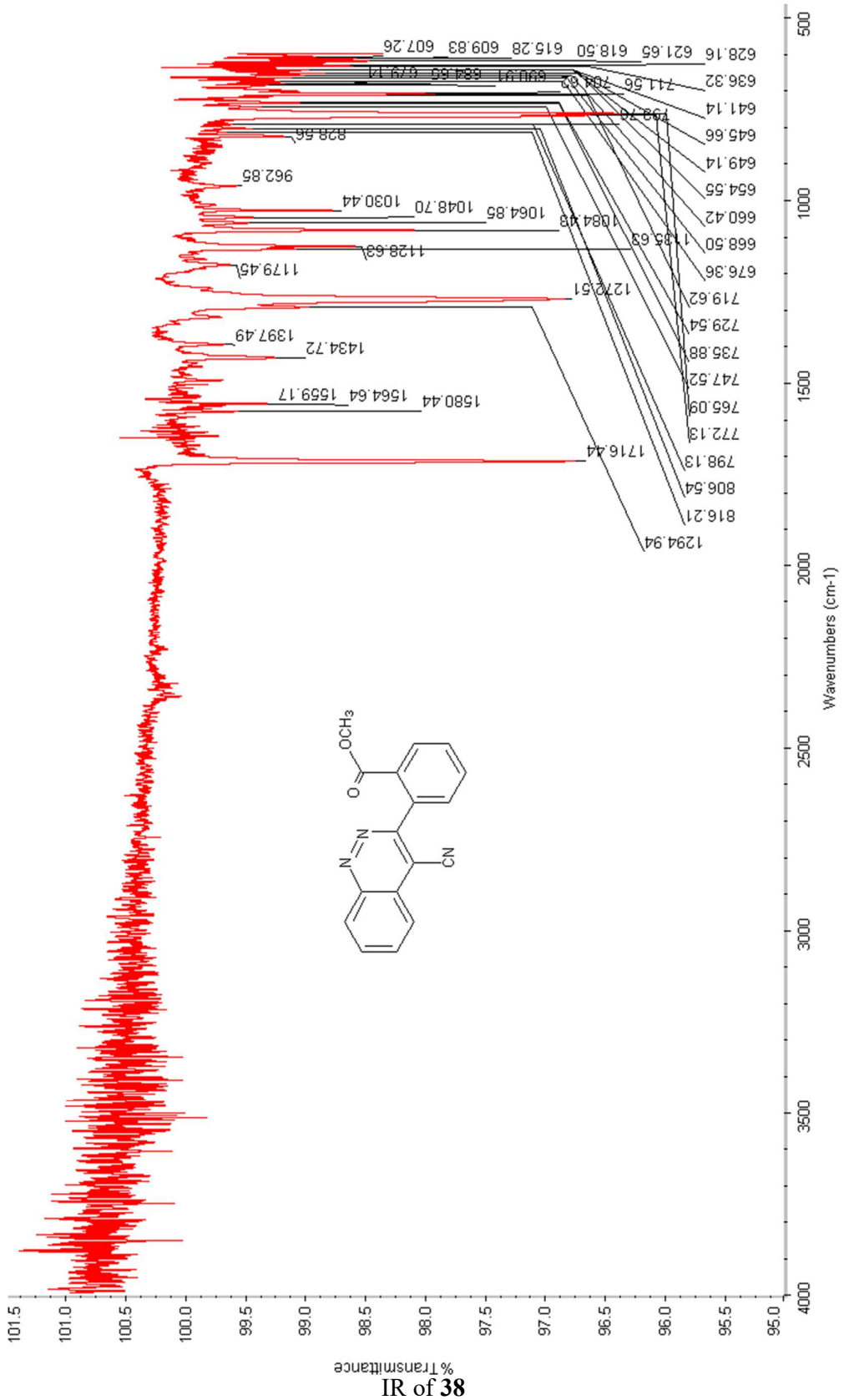
IR of **34f**


629.92
615.70
611.42
608.60
601.78
644.51
606.41
667.92
701.32
735.61
651.46
660.88
663.14
756.86
1072.79
1218.79
1260.47
1276.67
1331.51
1469.30
1553.21
1615.52
1713.30
Cl
Cl
NO2
HN
NH
O
%Transmittance
Wavenumbers (cm-1)

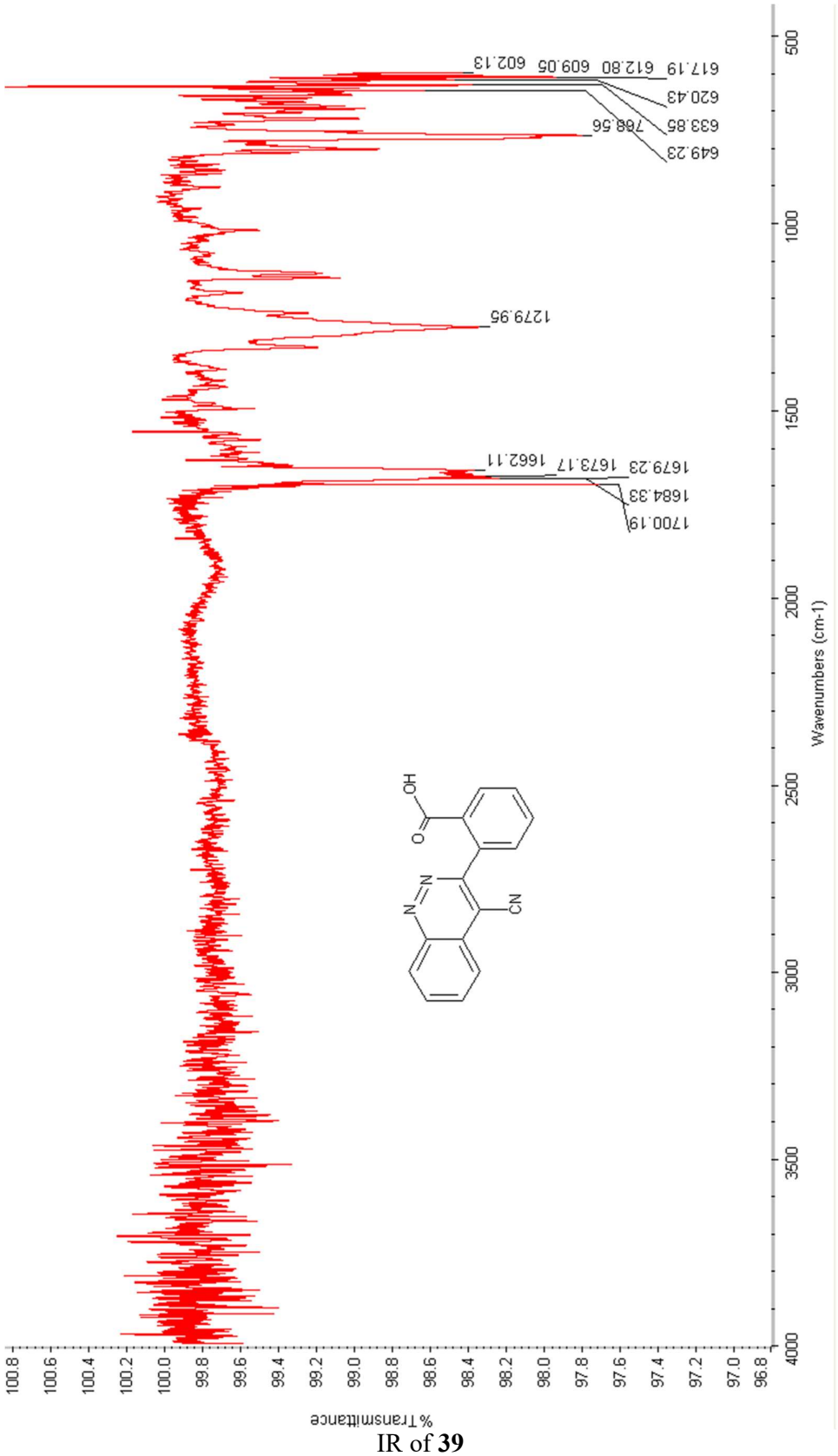
IR of **34g**


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.5
94.0
93.5
93.0
92.5
92.0
91.5
91.0
90.5
90.0
89.5
1709.68
1635.08
1571.89
1534.84
1469.74
1446.07
1426.16
1356.89
1335.42
1303.56
1271.42
1238.69
1211.51
1176.78
1159.66
1135.24
1111.03
1089.02
1064.38
914.22
900.95
825.41
763.58
744.65
715.05
701.31
668.32
662.00
648.40
629.33
621.82
617.36
613.33
609.44
O
HN
NH
NO2
F3C

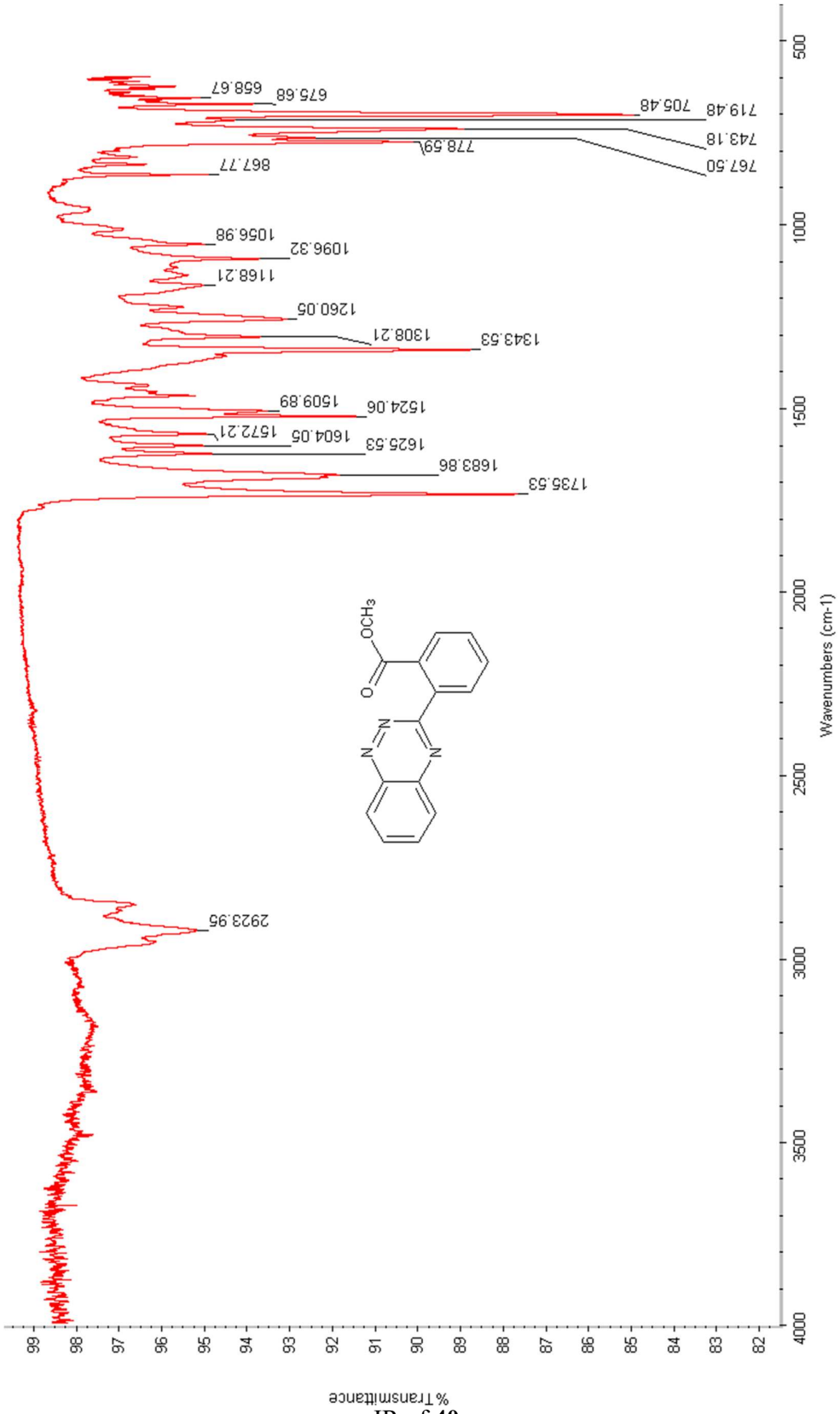
IR of **34h**


628.16
636.32
641.14
645.66
649.14
654.55
660.42
668.50
676.36
719.62
729.54
735.88
747.52
765.09
772.13
798.13
806.54
816.21
1294.94
1716.44
1580.44
1564.64
1559.17
1434.72
1397.49
1272.51
1179.45
1128.63
1084.48
1064.85
1048.70
1030.44
962.85
828.66
798.76
711.56
704.62
OCH3
O
N
N
CN
Wavenumbers (cm-1)
%Transmittance

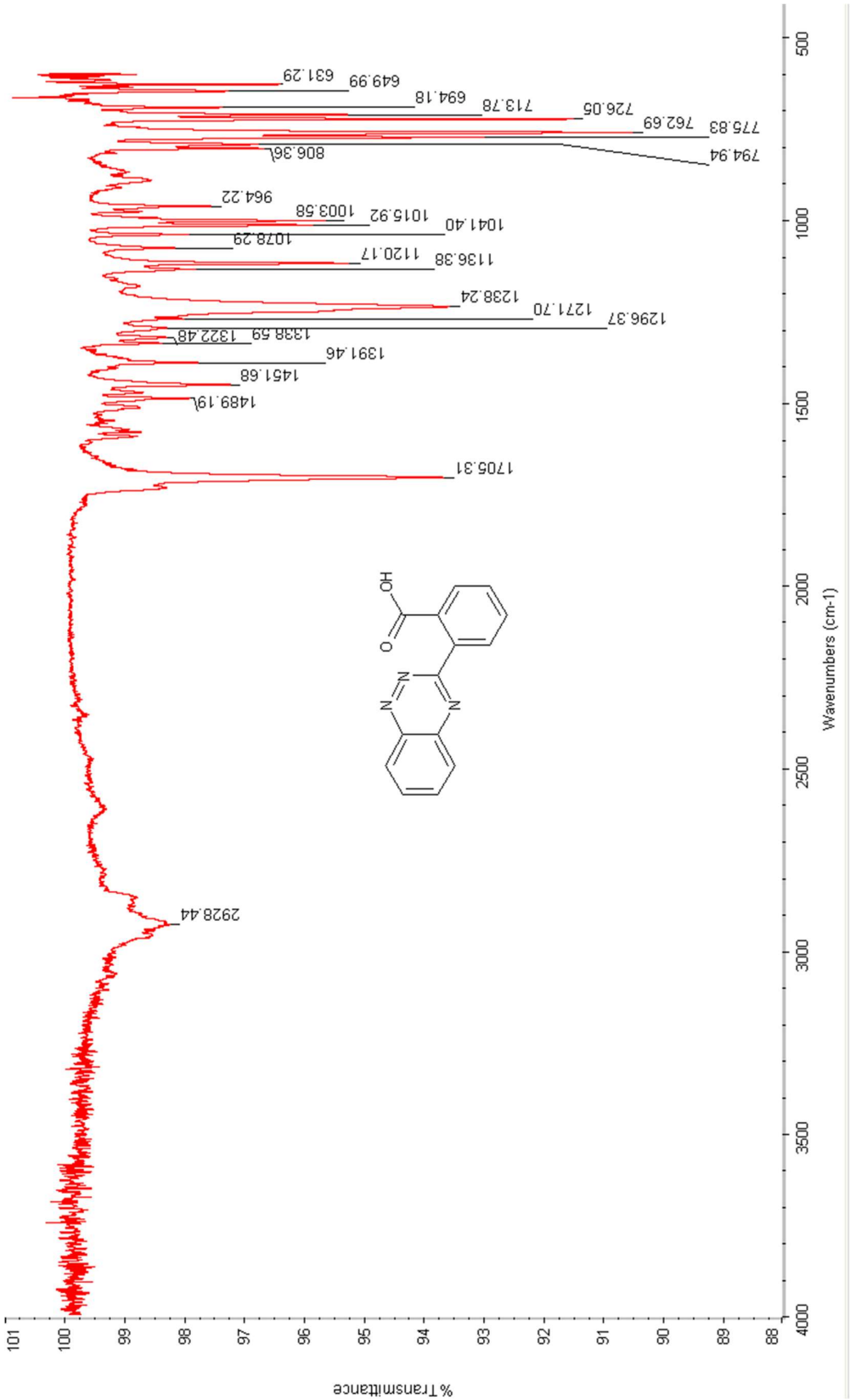
IR of **38**


617.19
612.80
609.05
602.13
620.43
633.85
708.56
649.23
1279.95
1679.23
1673.17
1662.11
1684.33
1700.19
%Transmittance
Wavenumbers (cm-1)
OH
O
N
N
CN

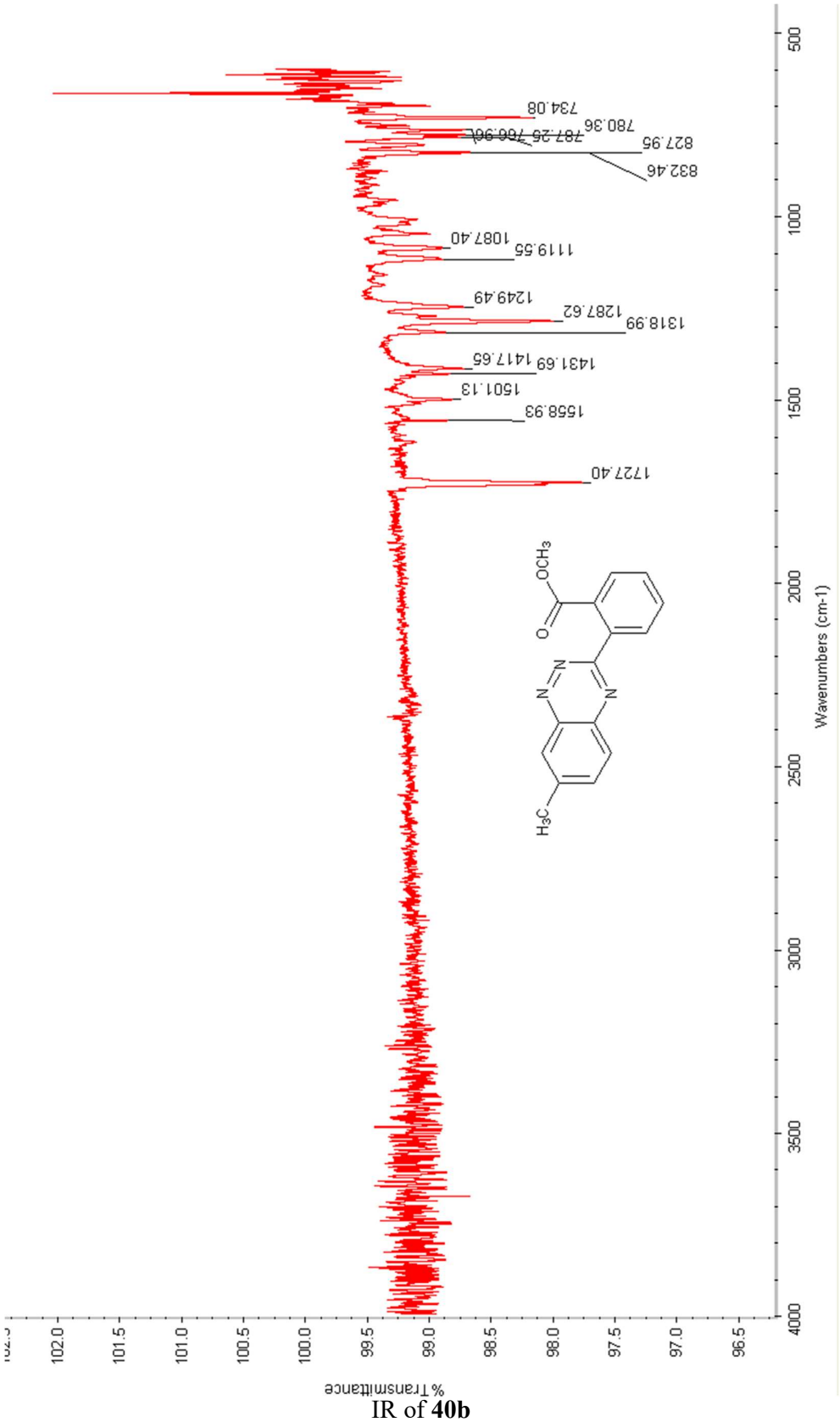
IR of **39**


2923.95
1735.53
1683.86
1625.53
1604.05
1572.21
1524.06
1509.89
1343.53
1308.21
1260.05
1168.21
1096.32
1056.98
867.77
778.59
767.50
743.18
719.48
705.48
675.68
658.67
OCH3
O
N
N
N
N
%Transmittance
Wavenumbers (cm-1)

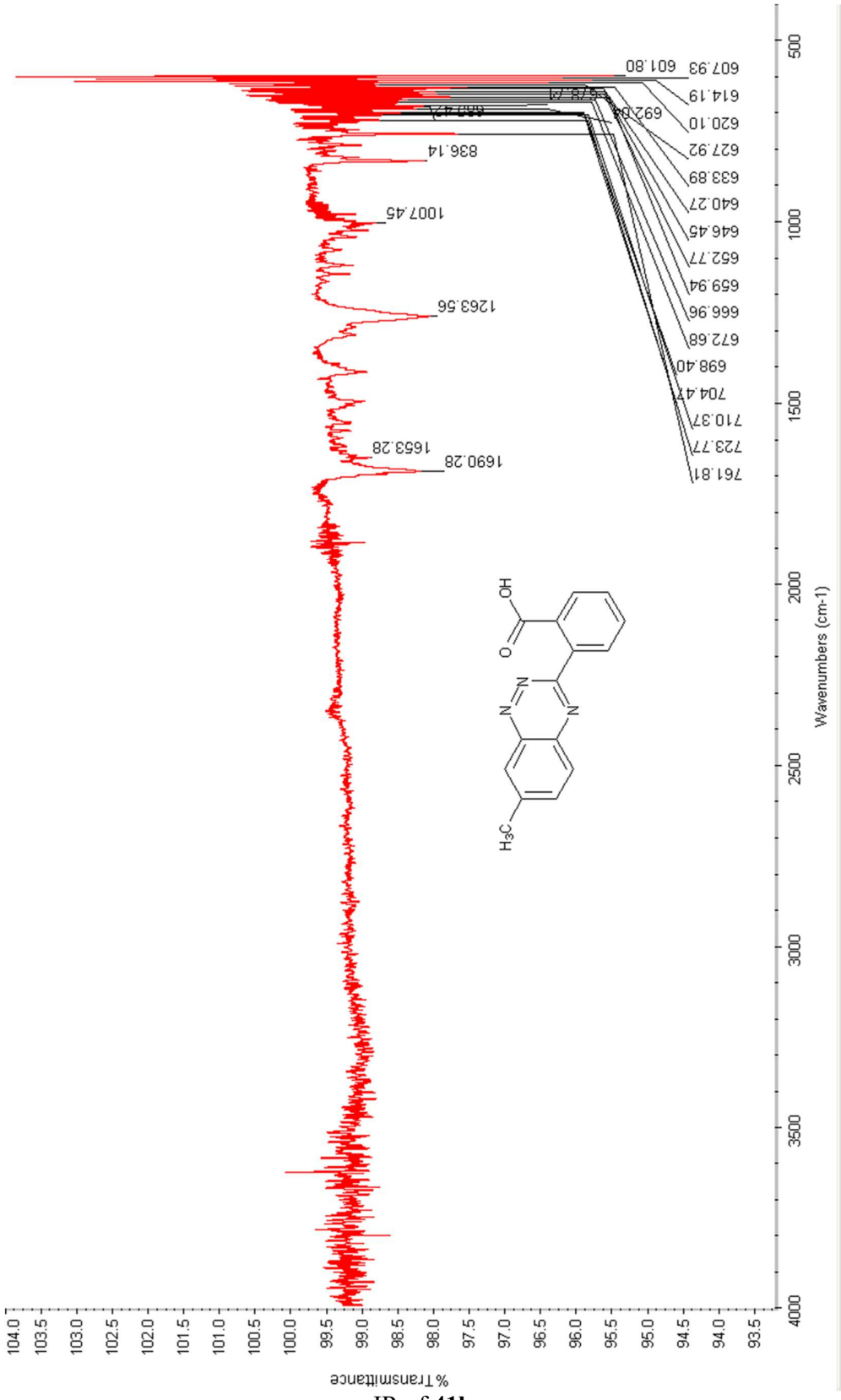
IR of **40a**


631.29
649.99
694.18
713.78
726.05
762.69
775.83
794.94
806.36
964.22
1003.58
1015.92
1041.40
1078.29
1120.17
1136.38
1238.24
1271.70
1296.37
1322.48
1338.59
1391.46
1451.68
1489.19
1705.31
2928.44
HO
O
N
N
N
%Transmittance
Wavenumbers (cm-1)

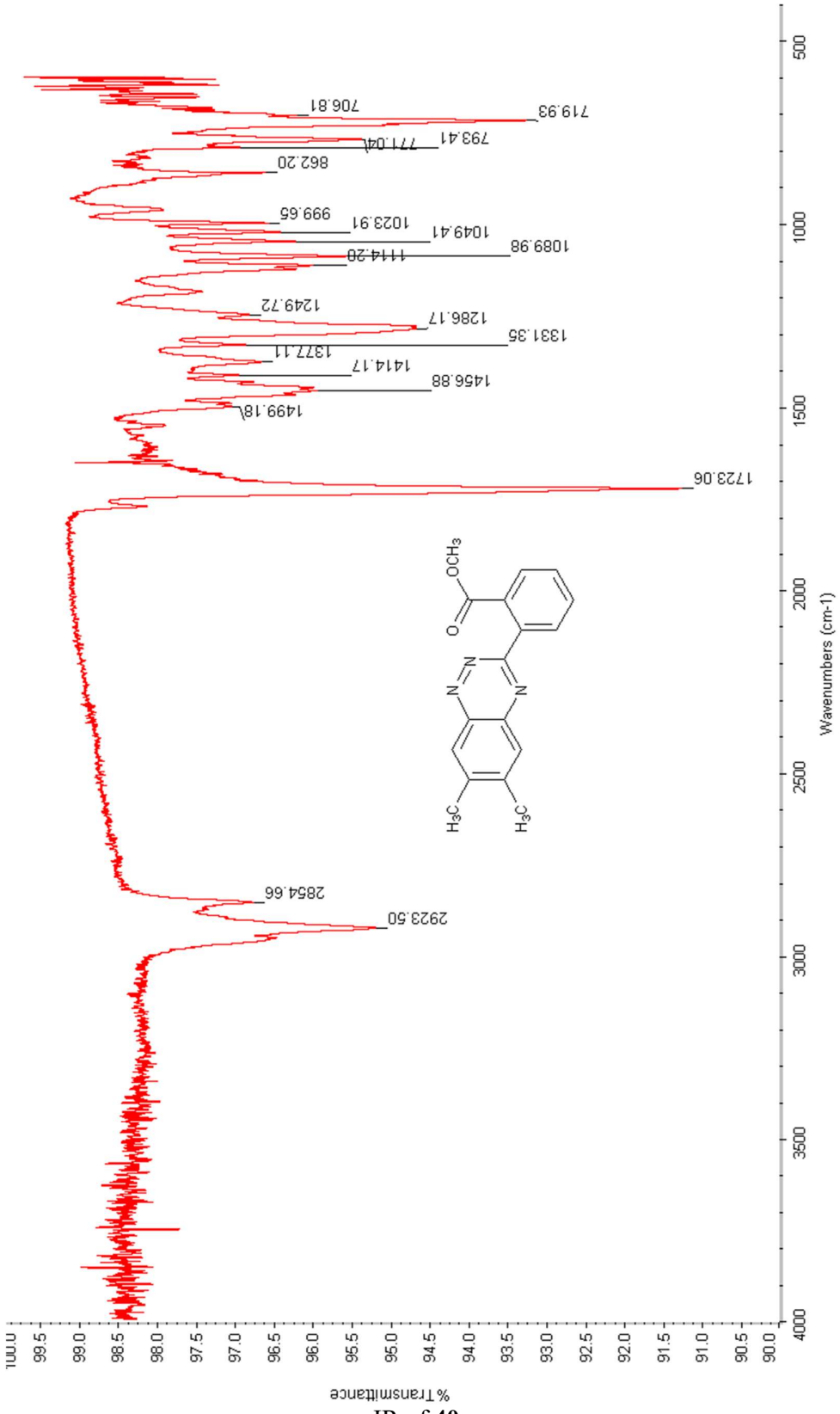
IR of **41a**


734.08
780.36
787.25
827.95
832.46
1087.40
1119.55
1249.49
1287.62
1318.99
1417.65
1431.69
1501.13
1558.93
1727.40
OCH3
O
N
N
N
H3C
Wavenumbers (cm-1)
%Transmittance

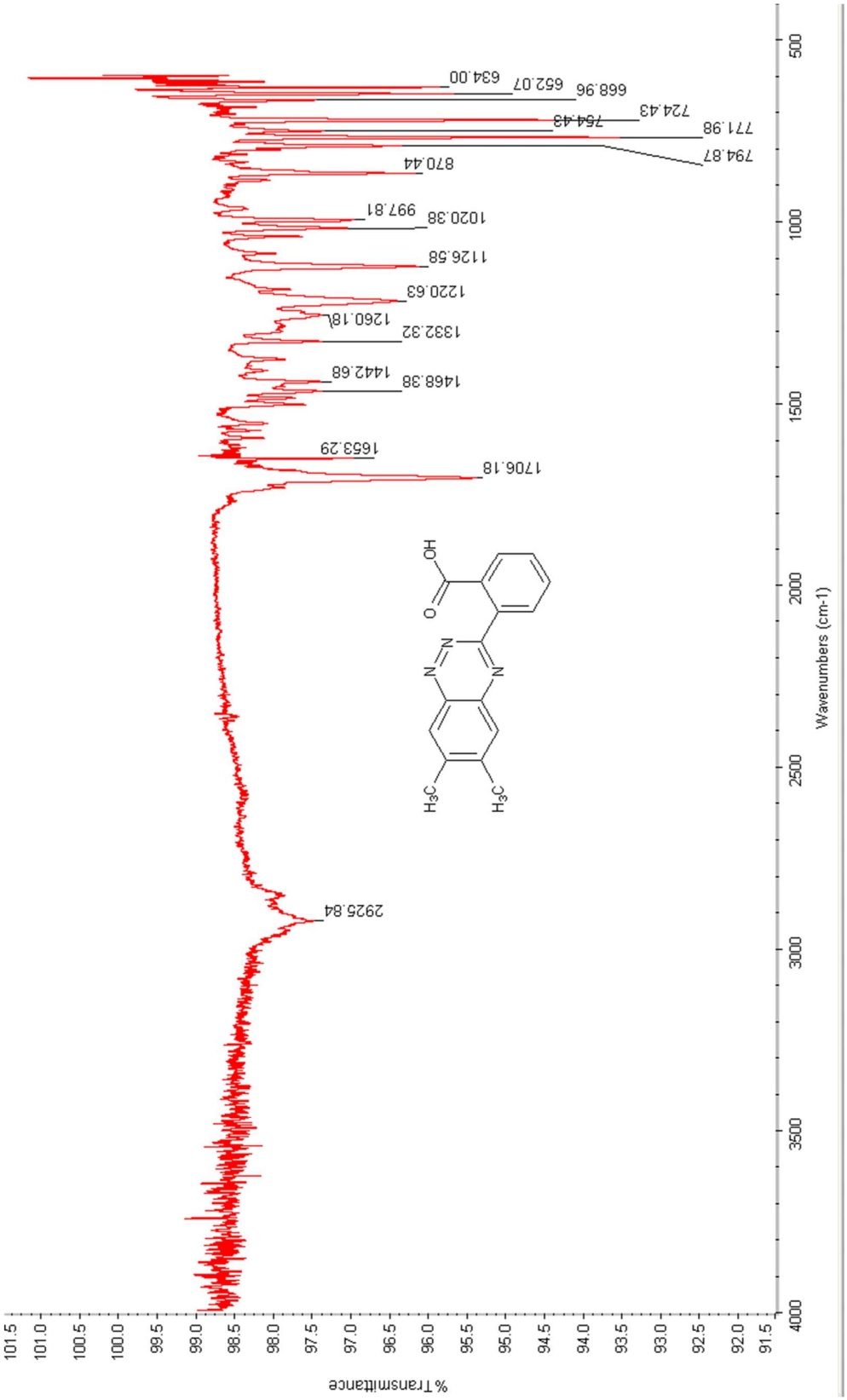
IR of **40b**


%Transmittance
Wavenumbers (cm-1)
761.81
723.77
710.37
704.47
698.40
672.68
666.96
659.94
652.77
646.45
640.27
633.89
627.92
620.10
614.19
607.93
601.80
836.14
1007.45
1263.56
1653.28
1690.28
OH
O
N
N
N
H3C

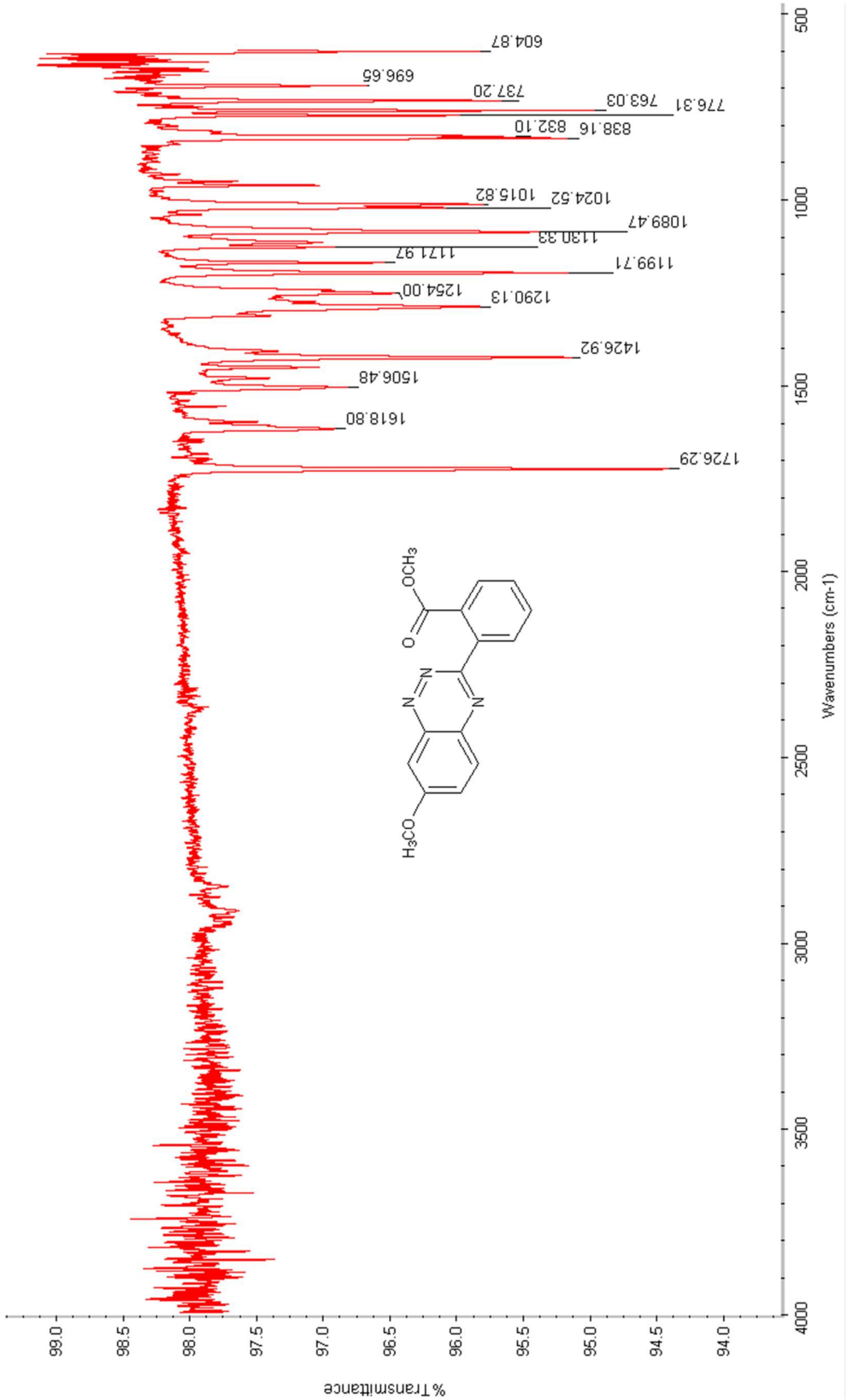
IR of **41b**


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
2923.50
2854.66
1723.06
1499.18
1456.88
1414.17
1377.11
1331.35
1286.17
1249.72
1114.20
1089.98
1049.41
1023.91
999.65
862.20
793.41
771.04
719.93
706.81
OCH3
O
N
N
H3C
H3C

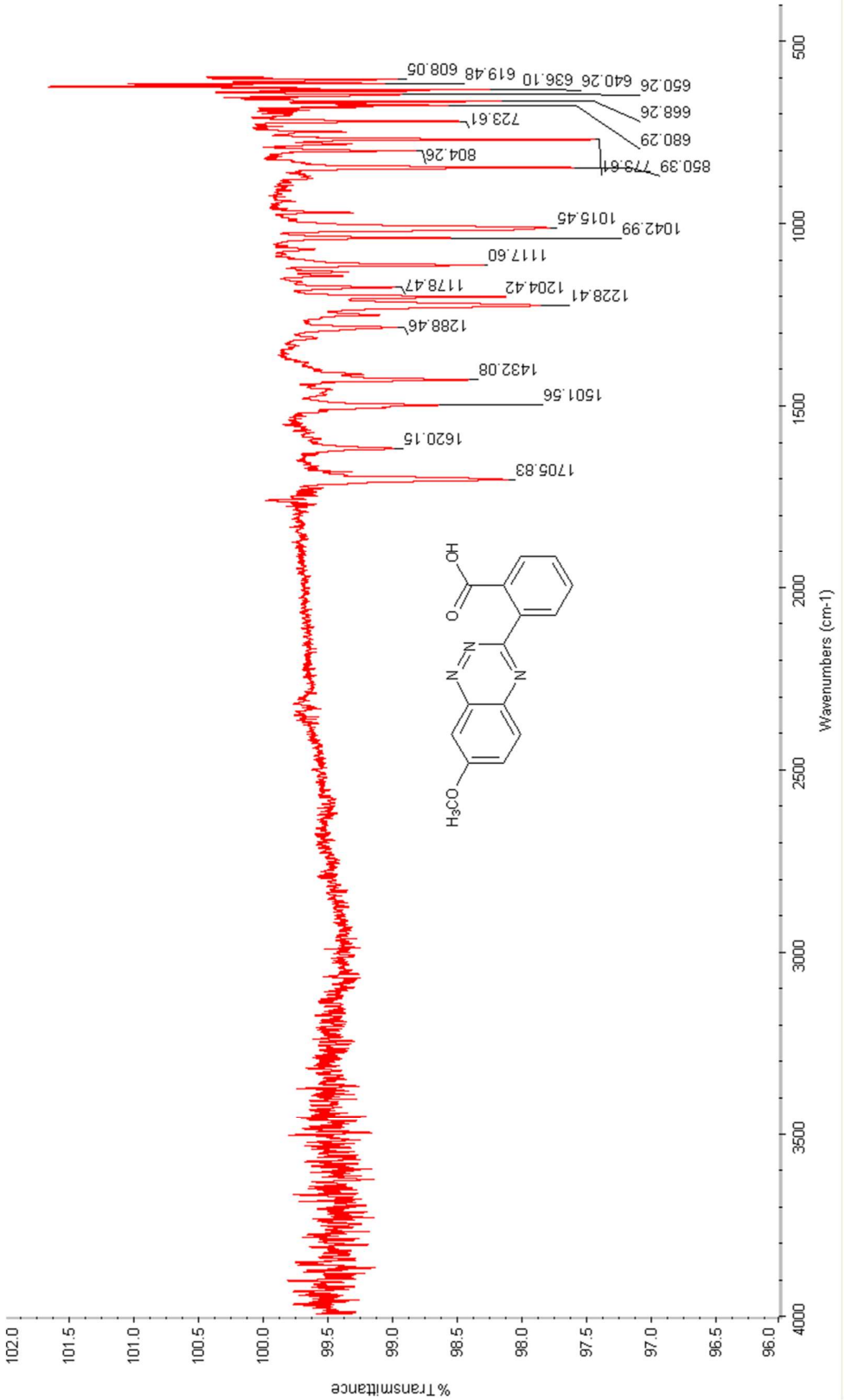
IR of **40c**


2925.84
1706.18
1653.29
1468.38
1442.68
1332.32
1260.18
1220.63
1126.58
1020.38
997.81
870.44
794.87
771.98
754.43
724.43
668.96
652.07
634.00
%Transmittance
Wavenumbers (cm-1)
OH
O
N
N
N
N
H3C
H3C

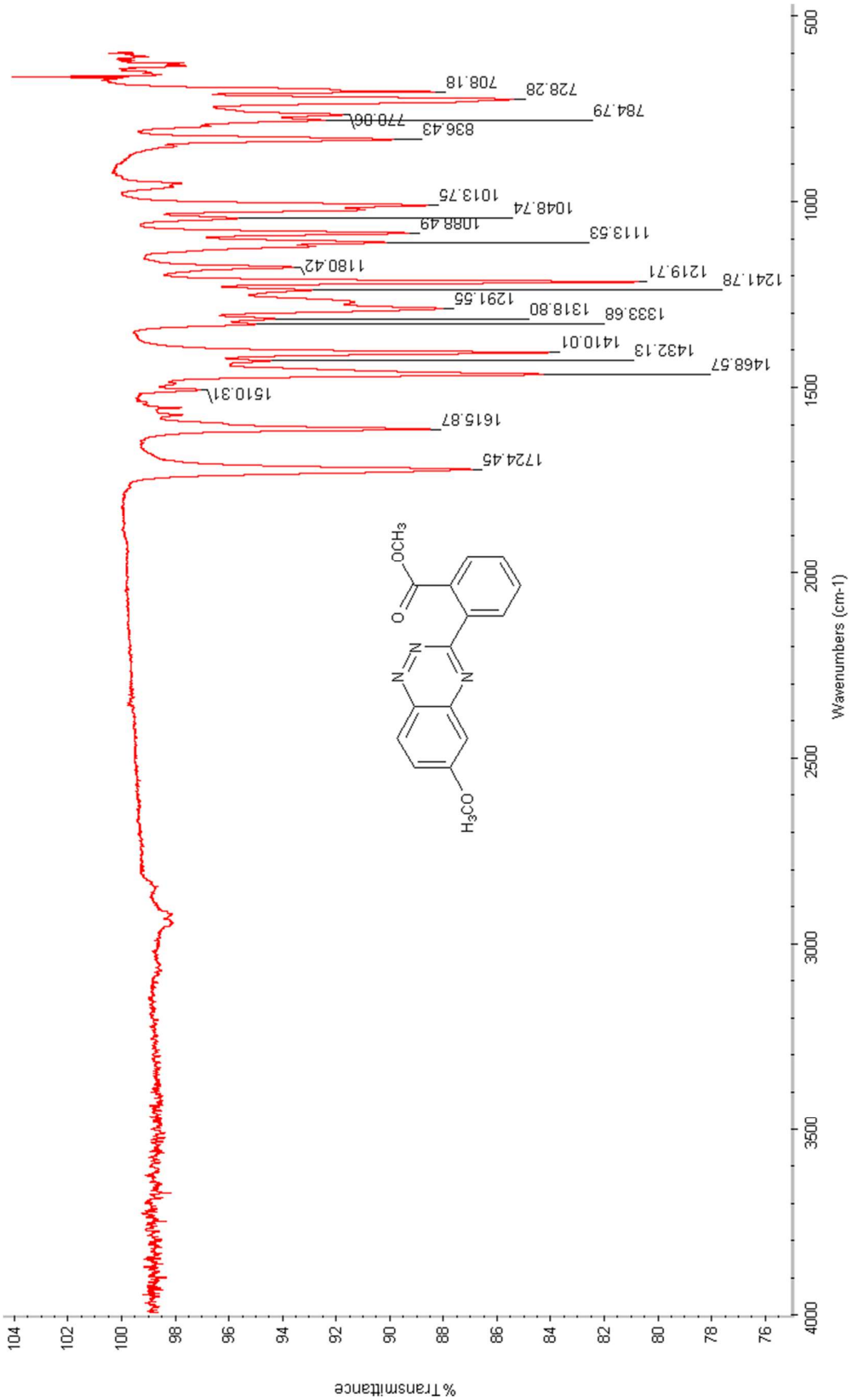
IR of **41c**


604.87
696.65
737.20
763.03
776.31
832.10
838.16
1015.82
1024.52
1089.47
1130.33
1171.97
1199.71
1254.00
1290.13
1426.92
1506.48
1618.80
1726.29
OCH3
O
N
N
N
H3CO
%Transmittance
Wavenumbers (cm-1)

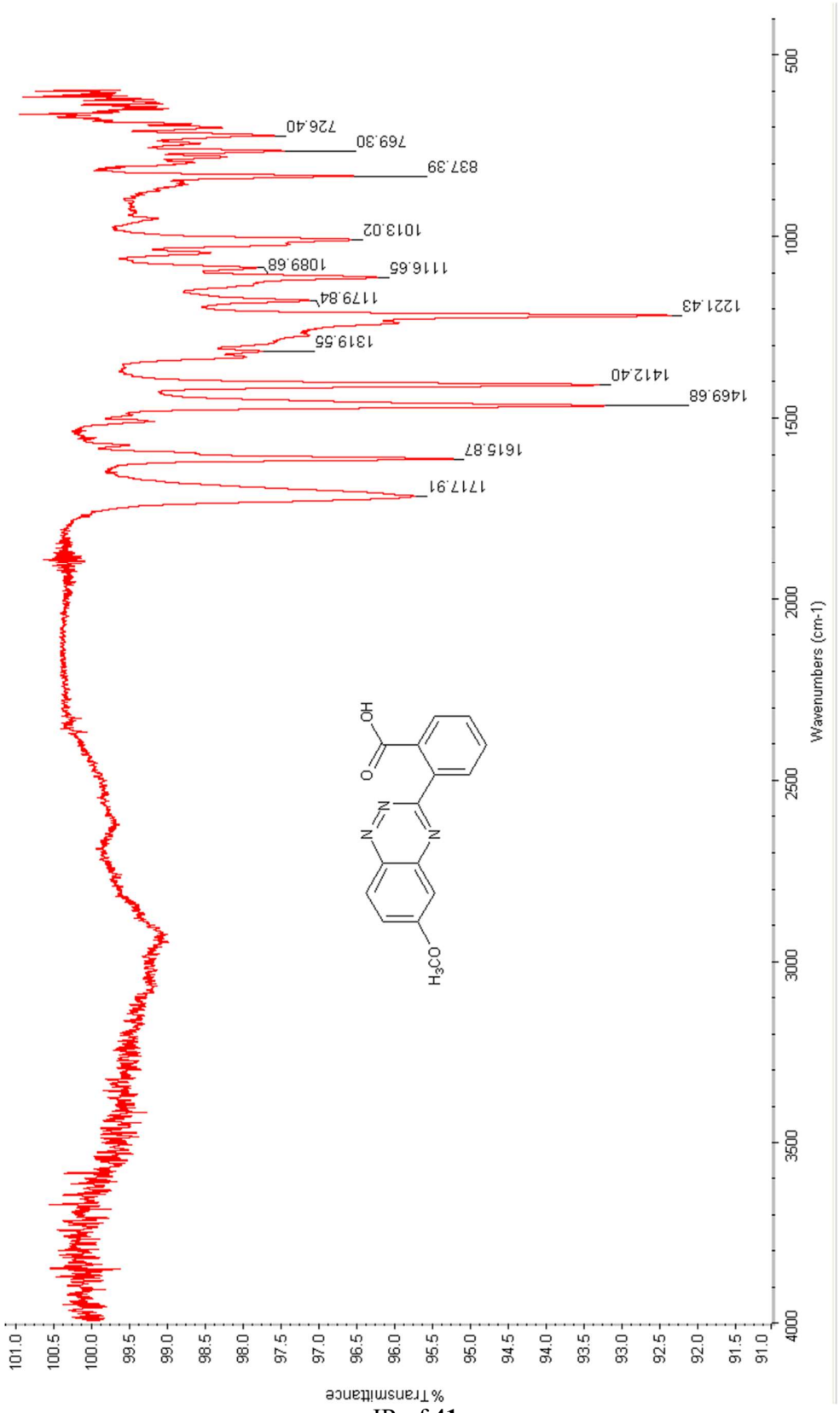
IR of **40d**


%Transmittance
Wavenumbers (cm-1)
650.26
640.26
636.10
619.48
608.05
668.26
723.61
680.29
804.26
850.39
773.61
1042.99
1015.45
1117.60
1228.41
1204.42
1178.47
1288.46
1432.08
1501.56
1620.15
1705.83
OH
O
N
N
N
H3CO

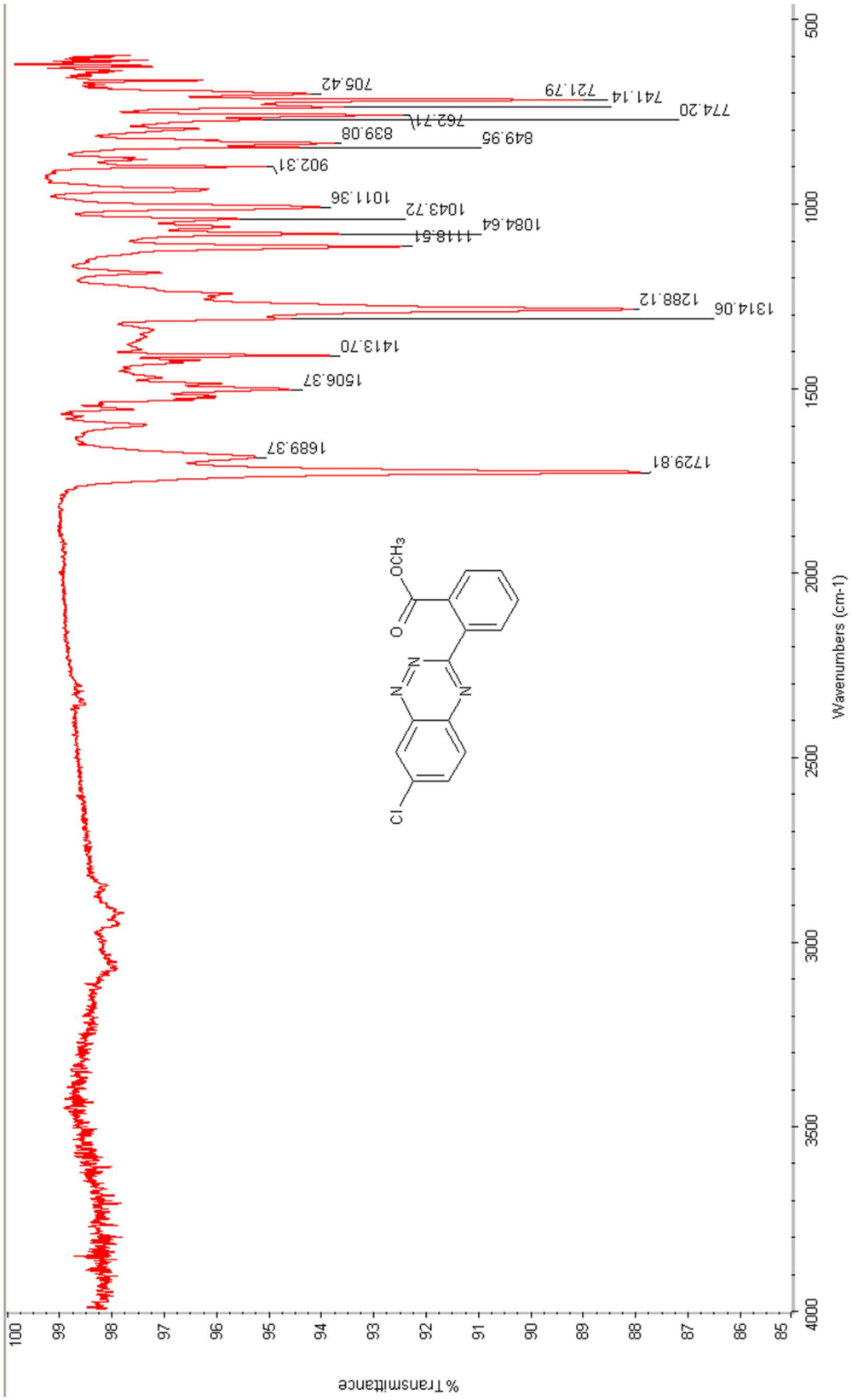
IR of **41d**


%Transmittance
Wavenumbers (cm-1)
OCH3
O
N
N
N
H3CO
1724.45
1615.87
1510.31
1468.57
1432.13
1410.01
1333.68
1318.80
1291.55
1241.78
1219.71
1180.42
1113.53
1088.49
1048.74
1013.75
836.43
770.06
784.79
728.28
708.18

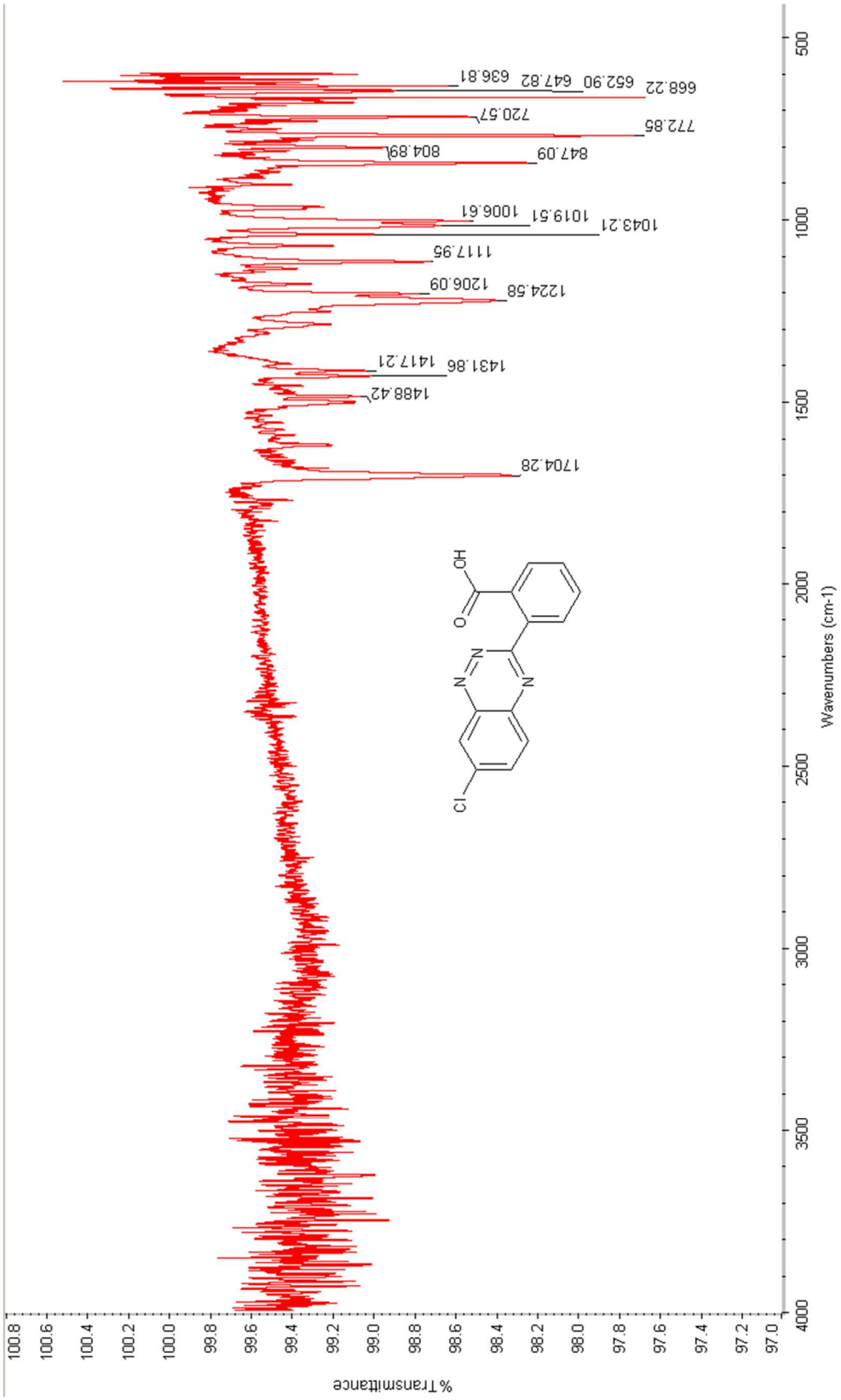
IR of **40e**


%Transmittance
Wavenumbers (cm-1)
726.40
769.30
837.39
1013.02
1089.68
1116.65
1179.84
1221.43
1319.55
1412.40
1469.68
1615.87
1717.91
OH
O
N
N
N
H3CO

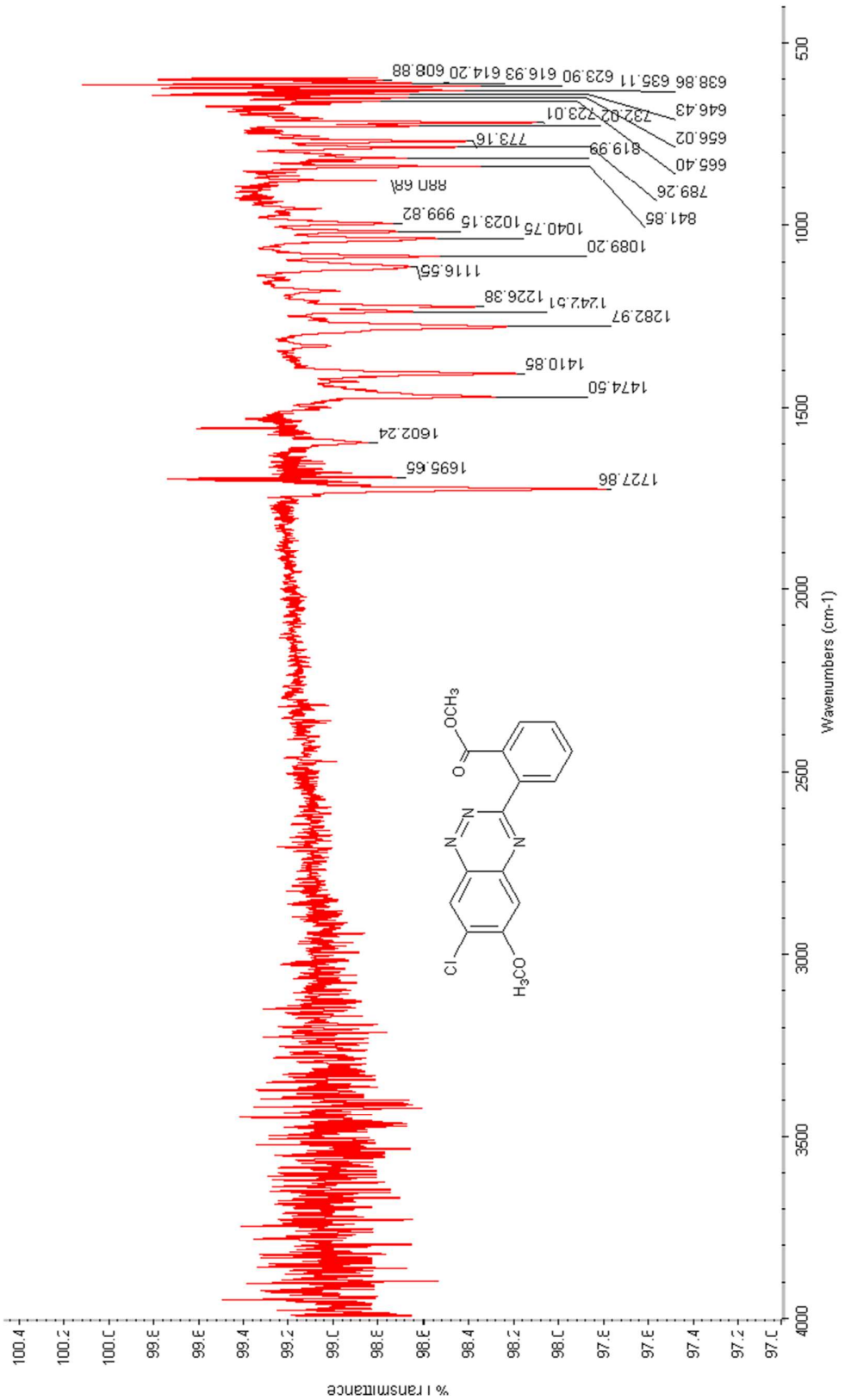
IR of **41e**


%Transmittance
Wavenumbers (cm-1)
705.42
721.79
741.14
774.20
762.71
839.08
849.95
902.31
1011.36
1043.72
1084.64
1118.61
1288.12
1314.06
1413.70
1506.37
1689.37
1729.81
OCH3
O
N
N
N
Cl

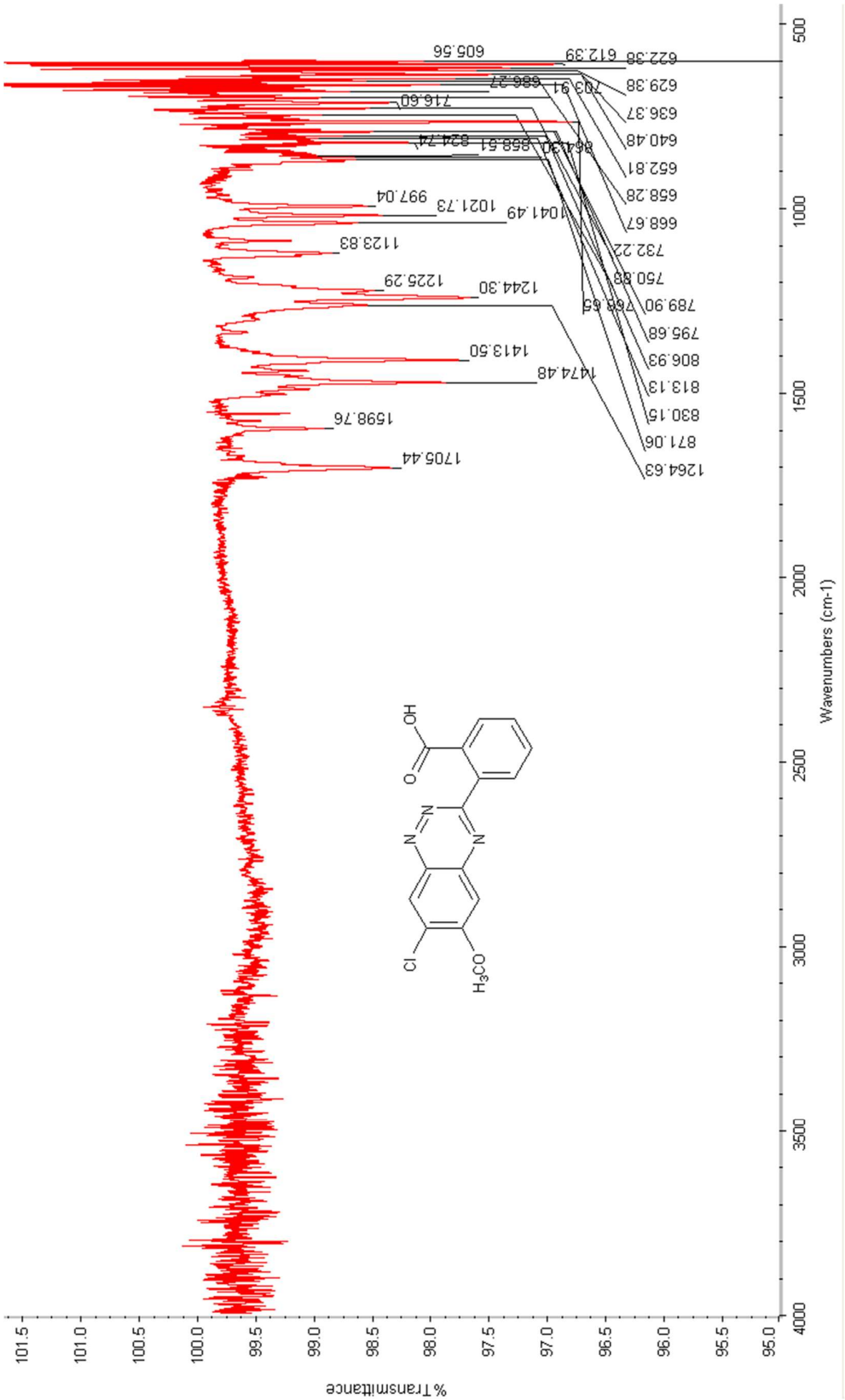
IR of **40f**


668.22
652.90
647.82
636.81
772.85
720.57
847.09
804.89
1043.21
1019.51
1006.61
1117.95
1224.58
1206.09
1431.86
1417.21
1488.42
1704.28
OH
O
N
N
N
Cl
%Transmittance
Wavenumbers (cm-1)
100.8
100.6
100.4
100.2
100.0
99.8
99.6
99.4
99.2
99.0
98.8
98.6
98.4
98.2
98.0
97.8
97.6
97.4
97.2
97.0
4000
3500
3000
2500
2000
1500
1000
500

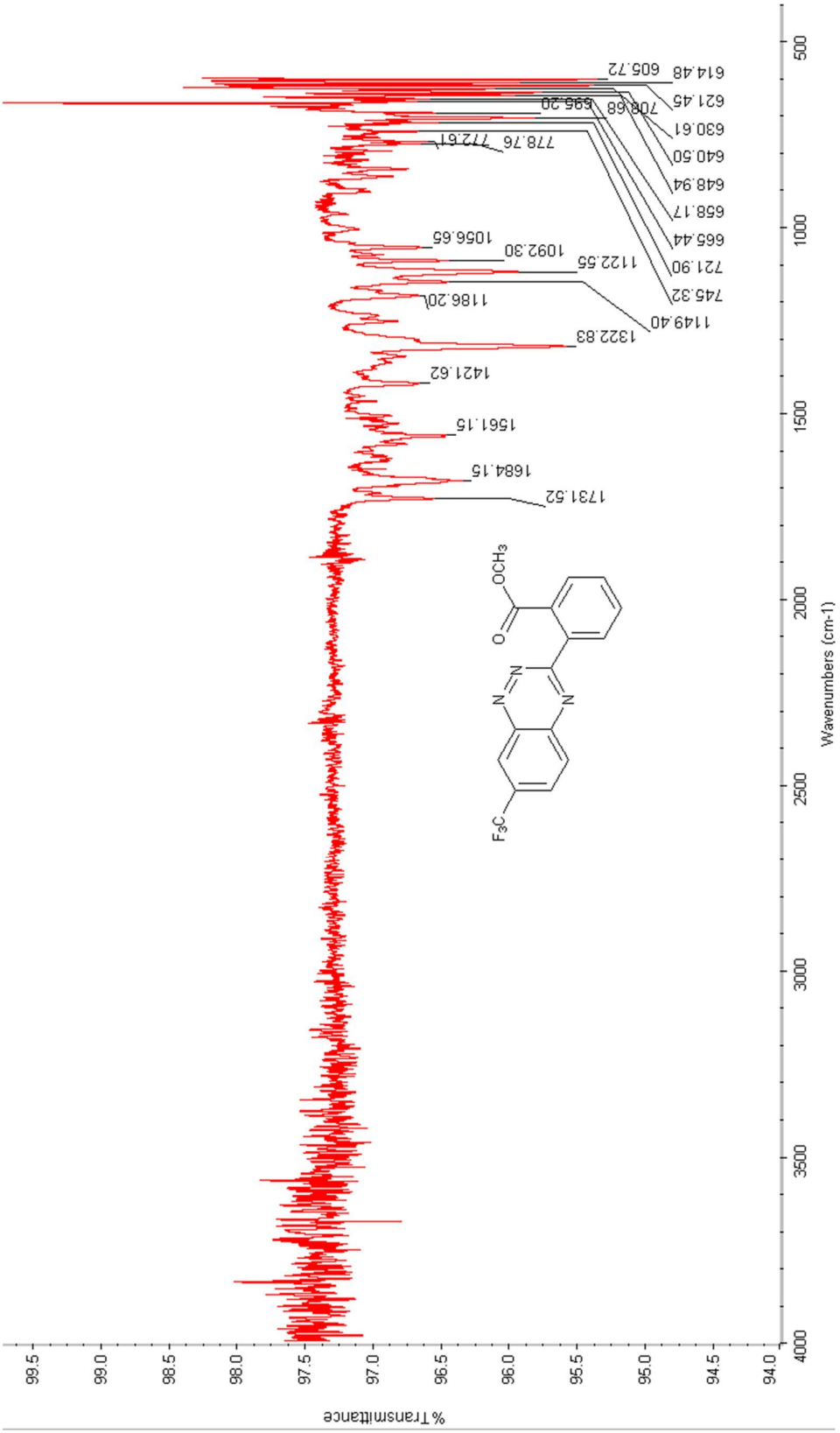
IR of **41f**


% Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
1727.86
1695.65
1602.24
1474.50
1410.85
1282.97
1242.51
1226.38
1116.55
1089.20
1040.75
1023.15
999.82
841.85
789.26
665.40
656.02
646.43
638.86
635.11
623.90
616.93
614.20
608.88
819.99
773.16
732.02
723.01
OCH3
O
N
N
Cl
H3CO

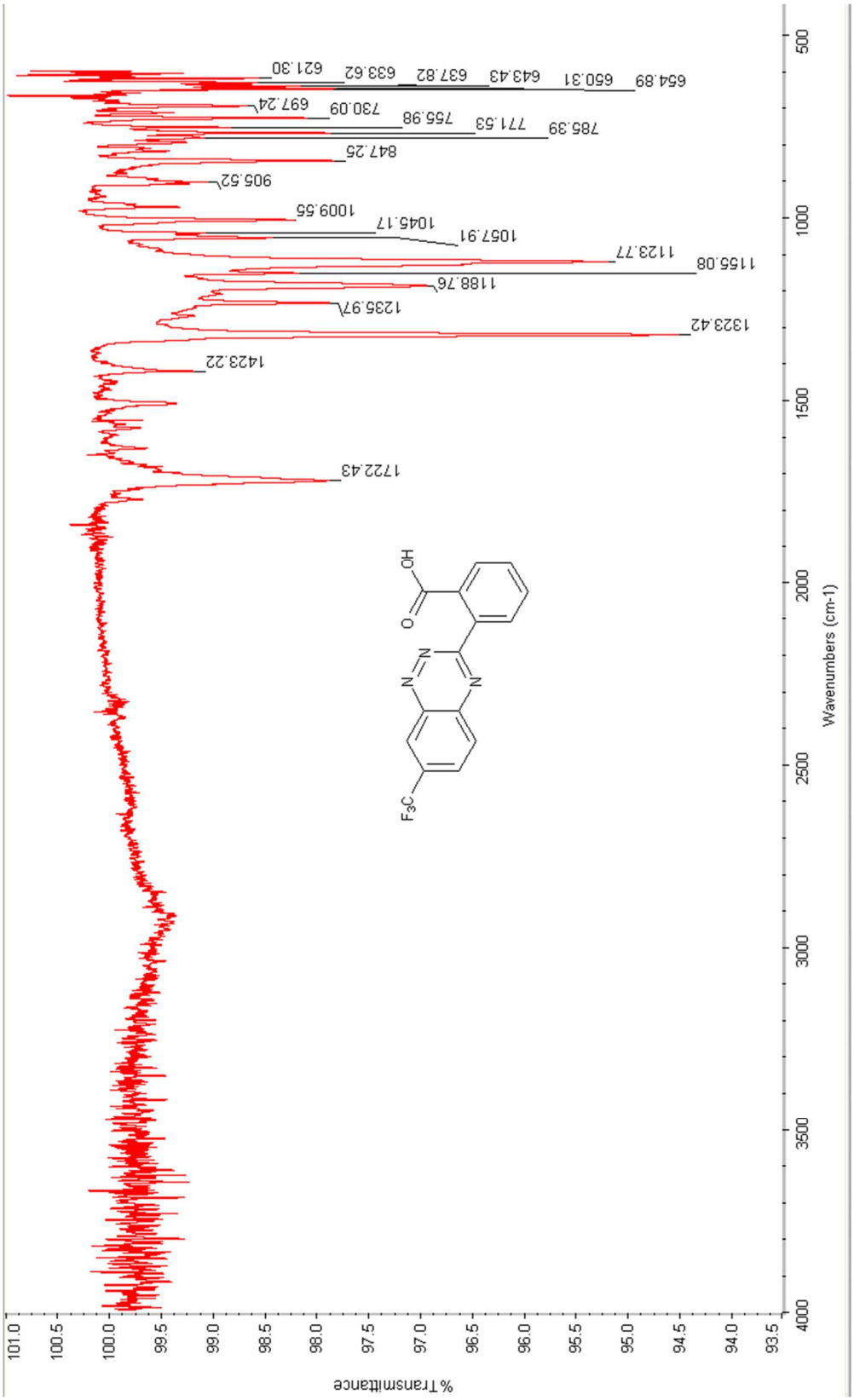
IR of **40g**


%Transmittance
Wavenumbers (cm-1)
605.56
612.39
622.38
629.38
636.37
640.48
652.81
658.28
668.67
732.22
750.88
766.63
789.90
795.68
806.93
813.13
830.15
871.06
1264.63
1705.44
1598.76
1474.48
1413.50
1244.30
1225.29
1123.83
1041.49
1021.73
997.04
716.60
703.91
686.27
858.51
824.74
OH
O
N
N
N
Cl
H3CO

IR of **41g**

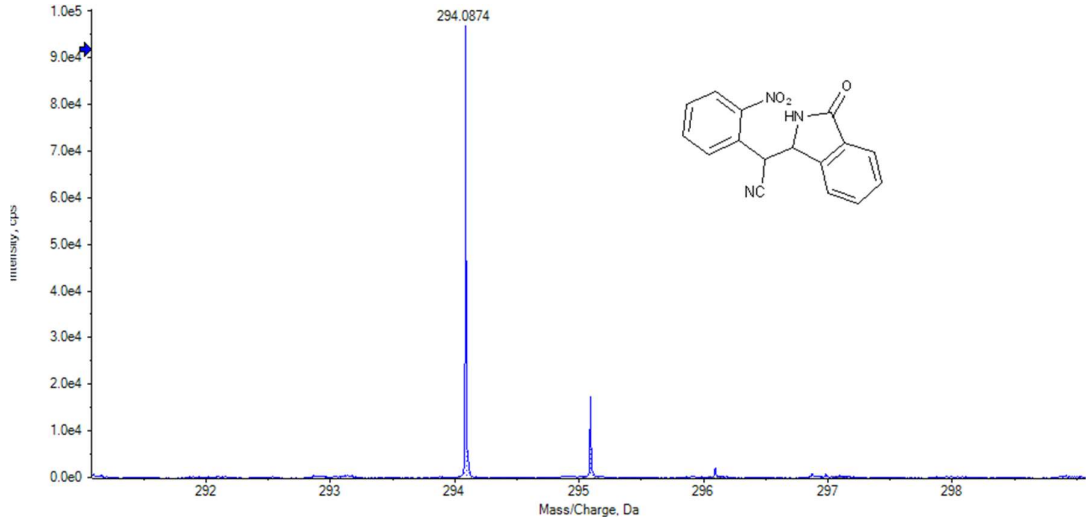

614.48
605.72
621.45
708.68
696.20
630.61
778.76
772.61
640.50
648.94
658.17
665.44
721.90
745.32
1149.40
1186.20
1122.55
1092.30
1056.65
1322.83
1421.62
1561.15
1684.15
1731.52
OCH3
O
N
N
N
F3C
% Transmittance
Wavenumbers (cm-1)

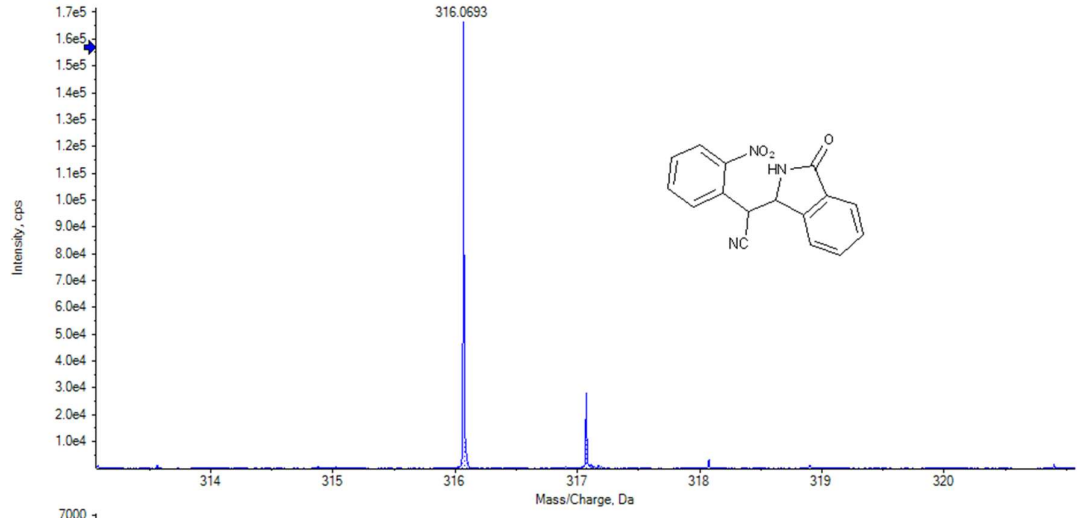
IR of **40h**

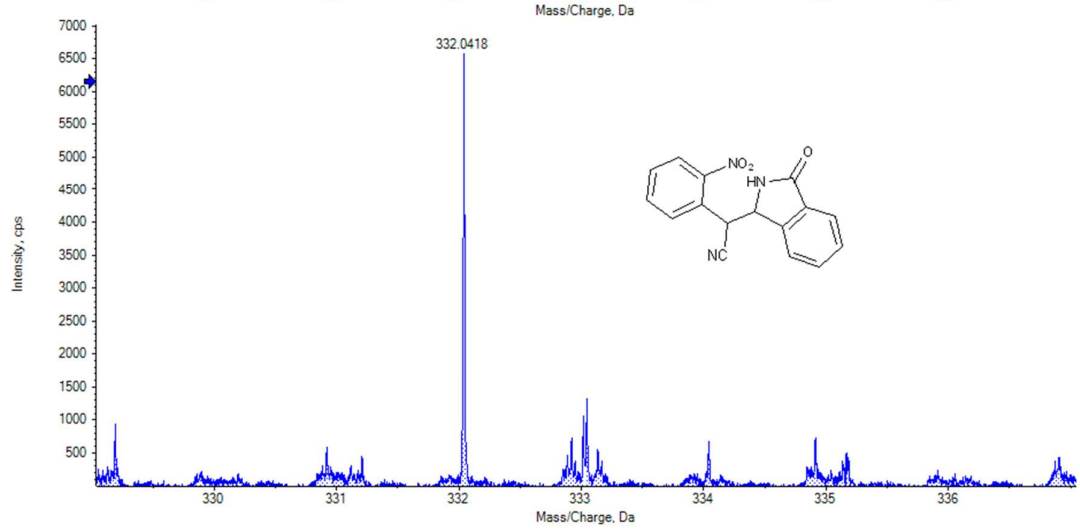

654.89
650.31
643.43
637.82
633.62
621.30
785.39
771.53
755.98
730.09
697.24
847.25
905.52
1009.55
1045.17
1057.91
1123.77
1155.08
1188.76
1235.97
1323.42
1423.22
1722.43
OH
O
N
N
F3C
%Transmittance
Wavenumbers (cm-1)

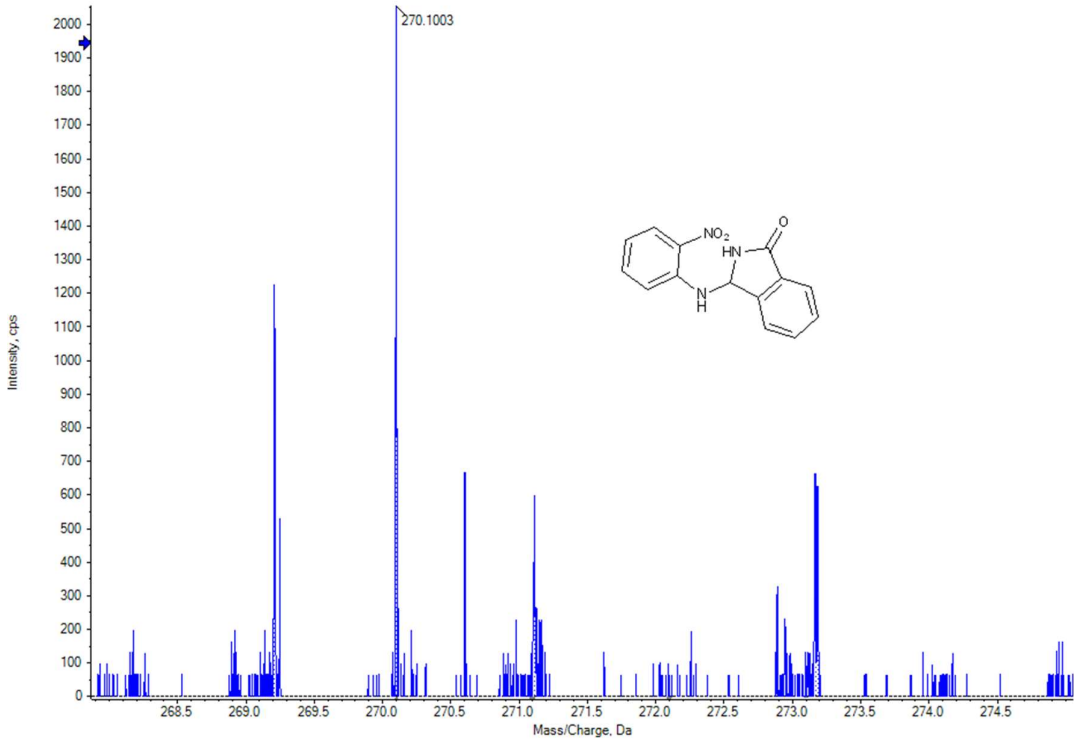
IR of **41h**

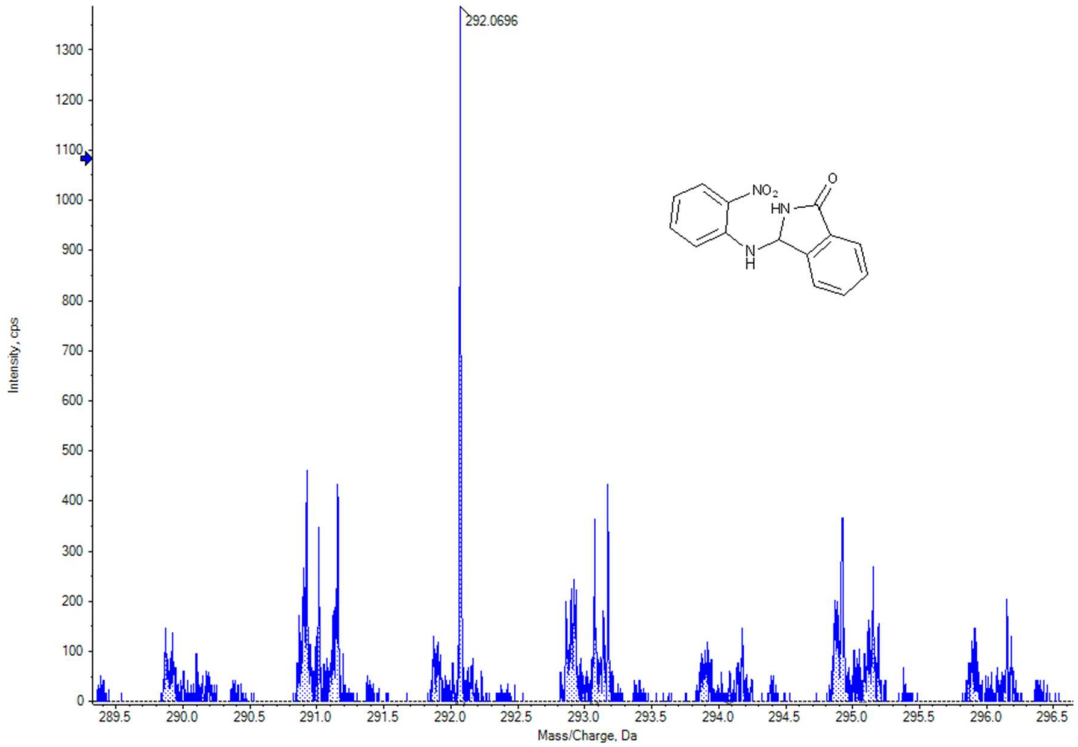
APPENDIX D HR-MS SPECTROSCOPY:

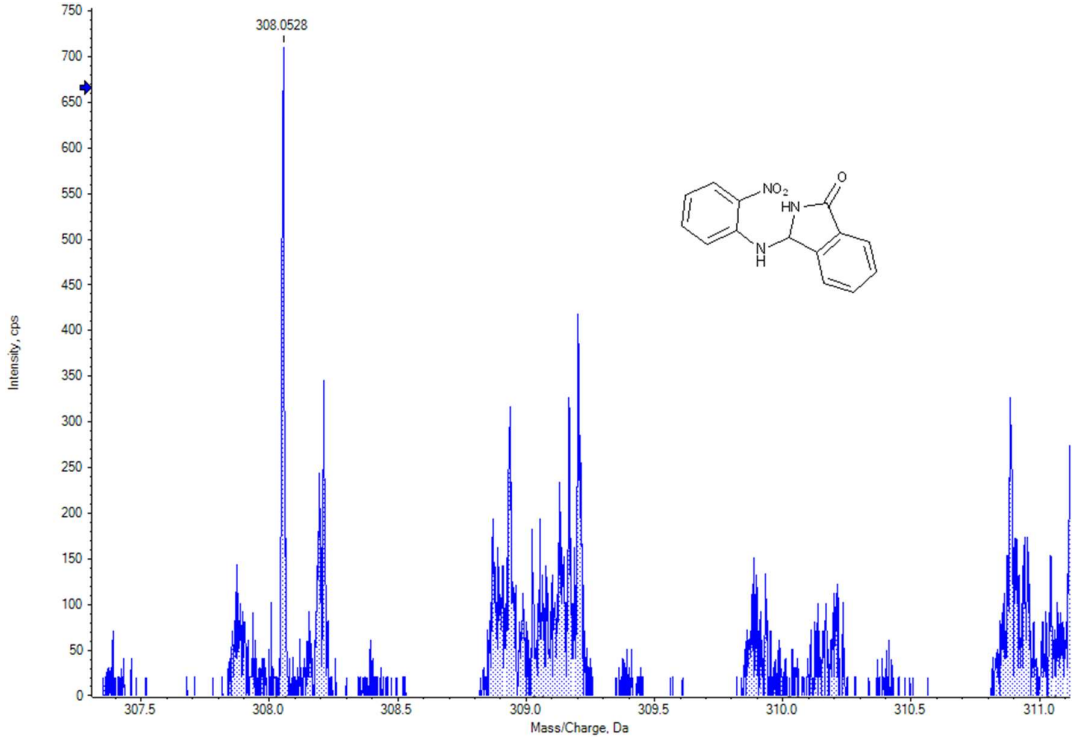


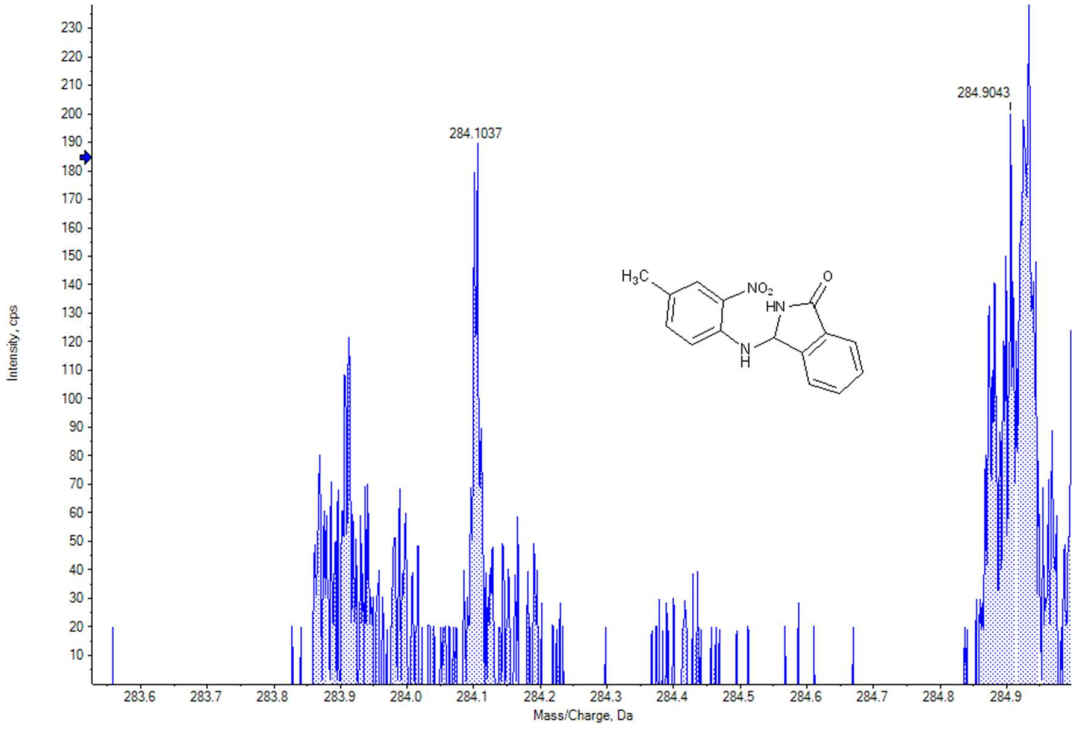


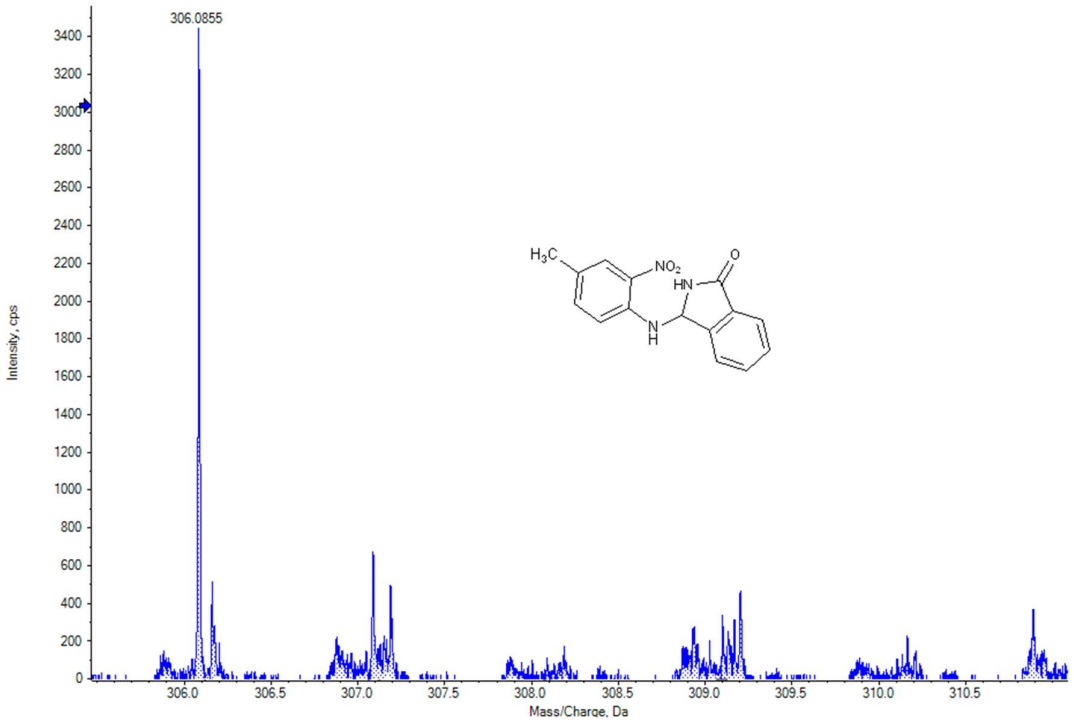


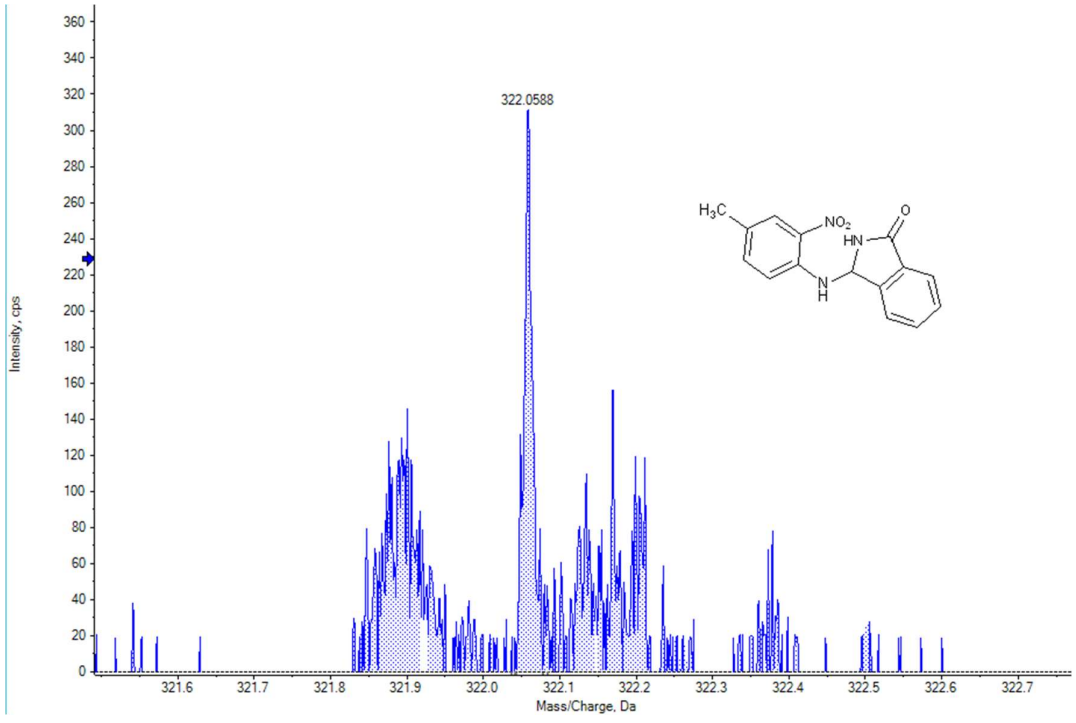

270.1003
Intensity, cps
Mass/Charge, Da
NO2
HN
O
N
H

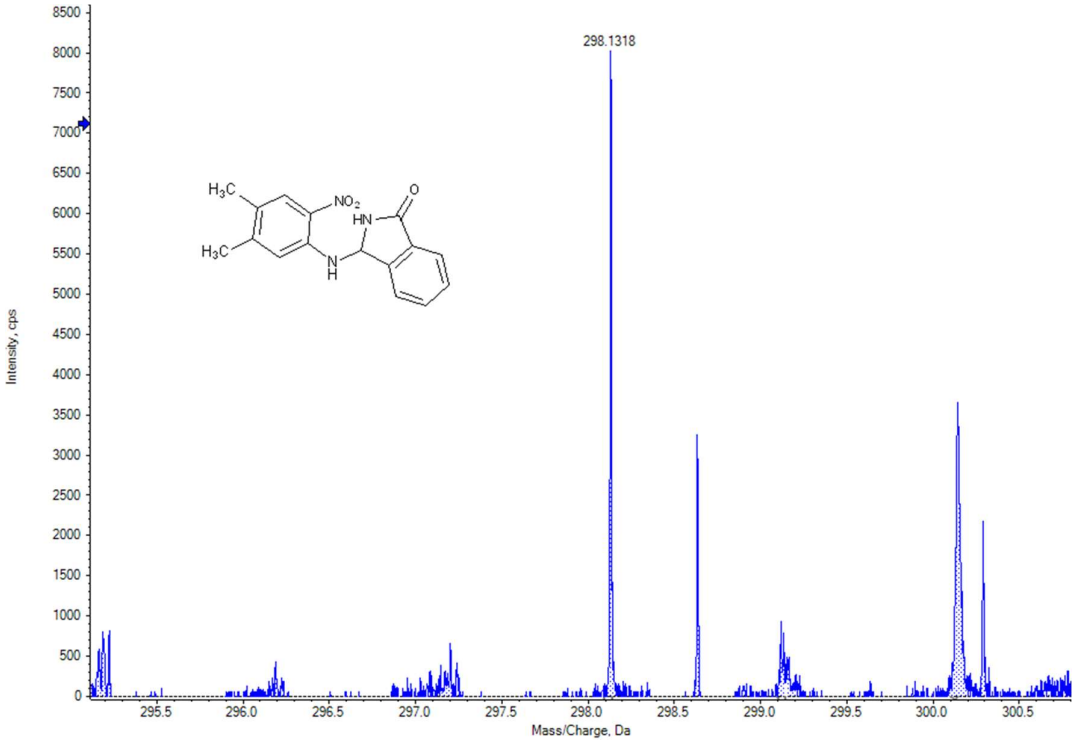

292.0696
Intensity, cps
Mass/Charge, Da
NO2
HN
O
N
H

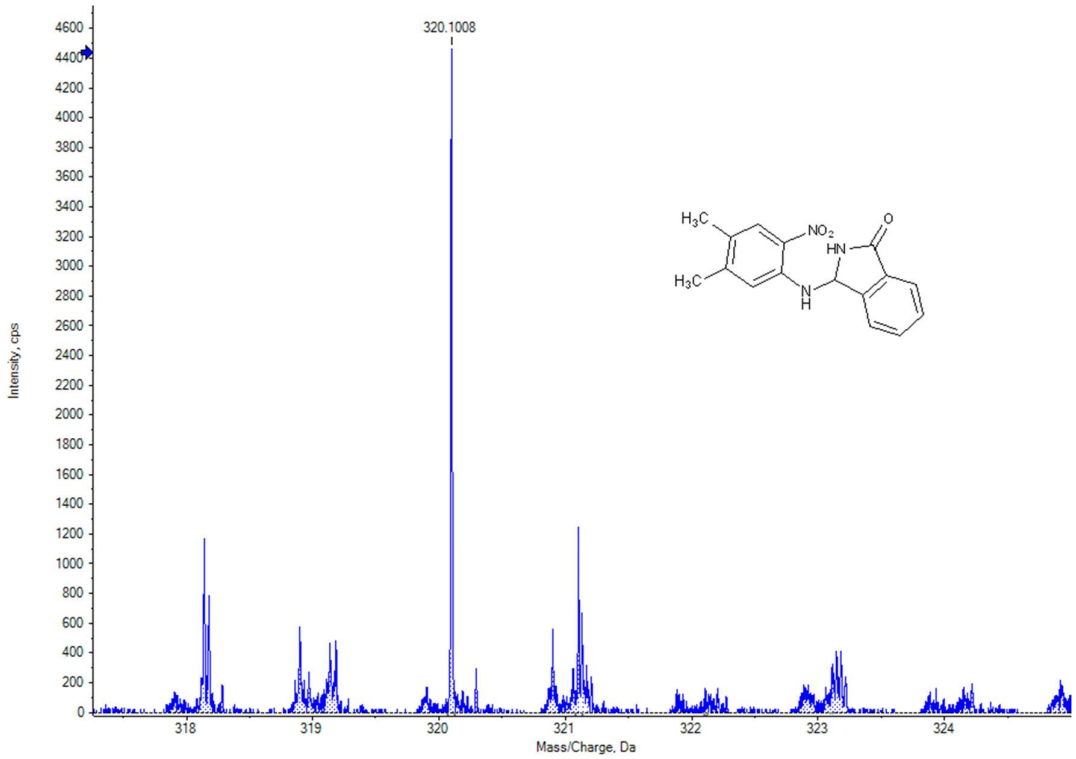

308.0528
Intensity, cps
Mass/Charge, Da
NO2
HN
O
N
H

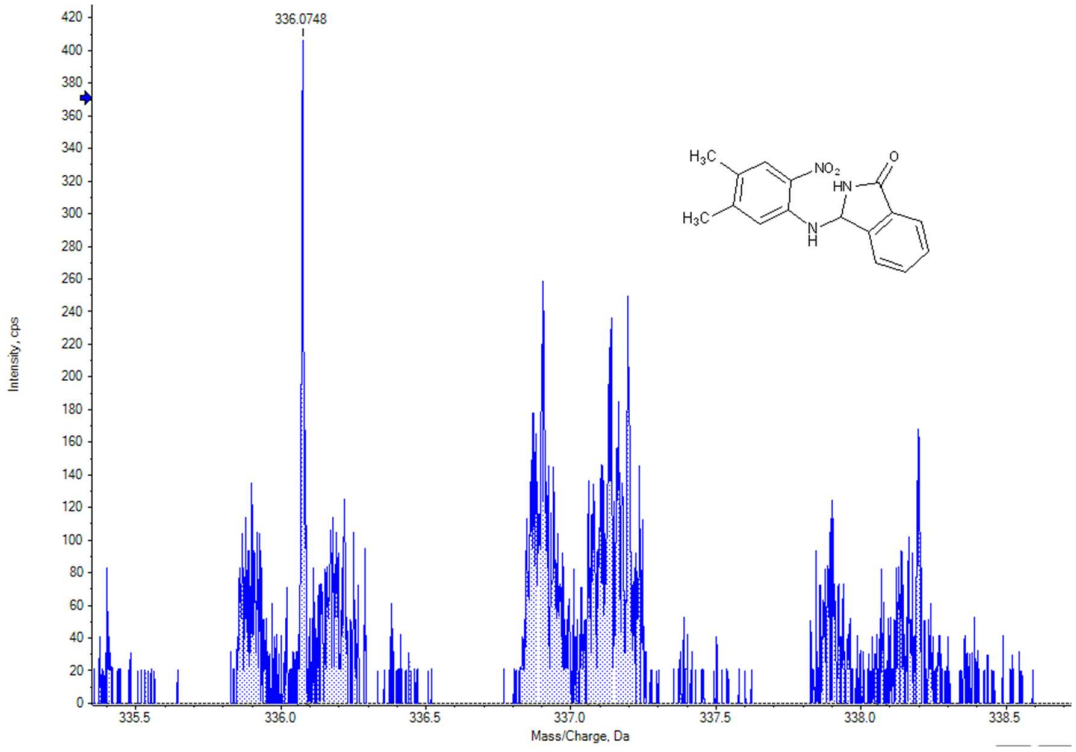

284.1037
284.9043
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
N
H

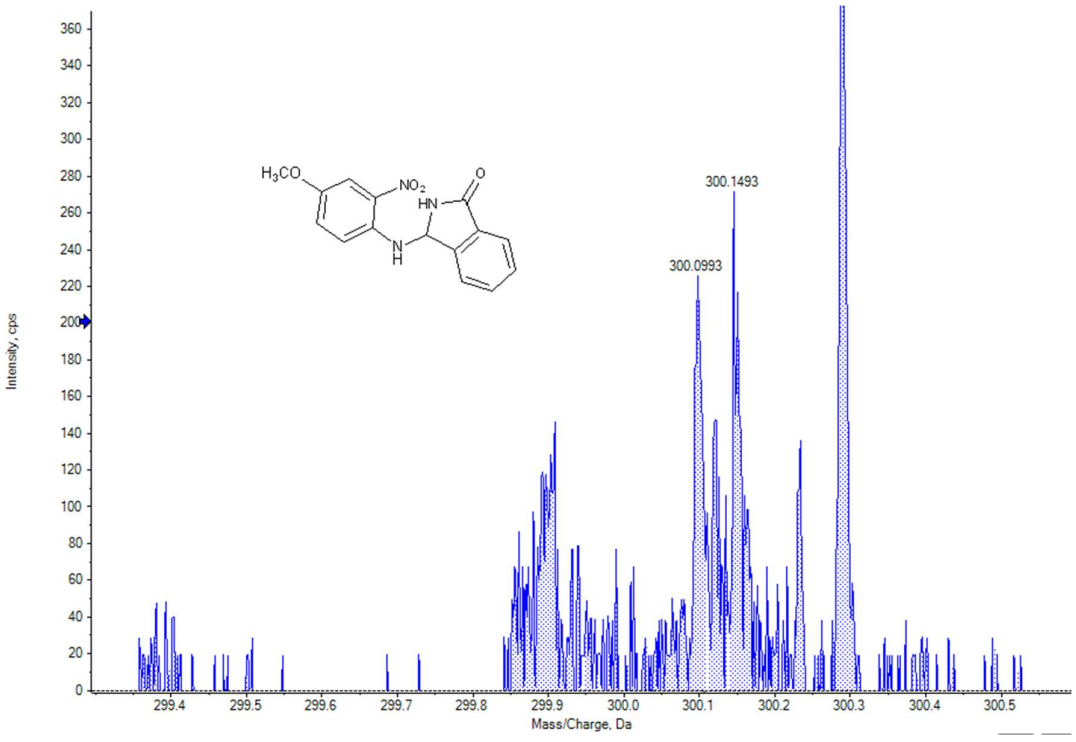

306.0855
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
N
H

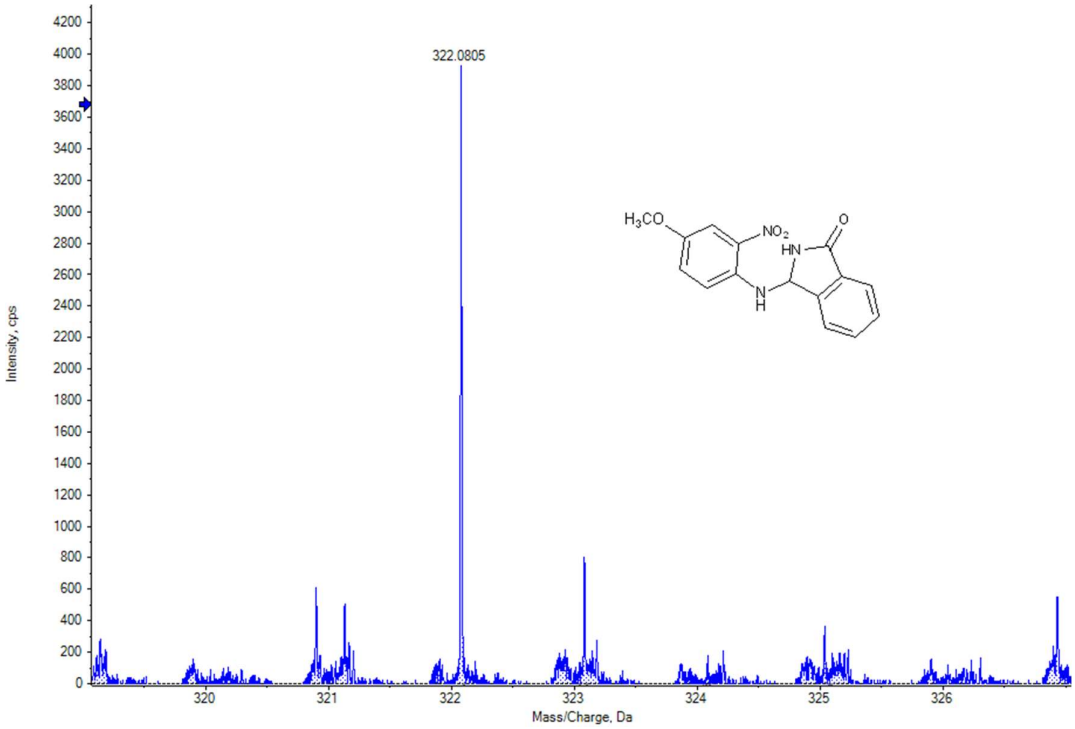

322.0588
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
N
H

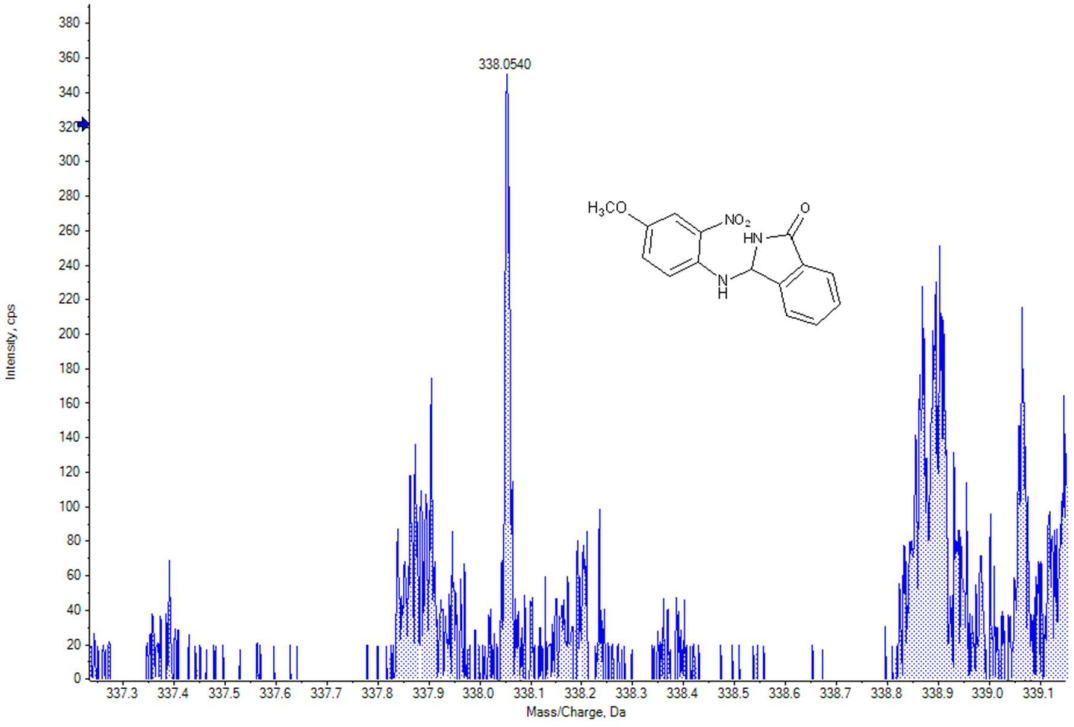

298.1318
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
H3C
N
H

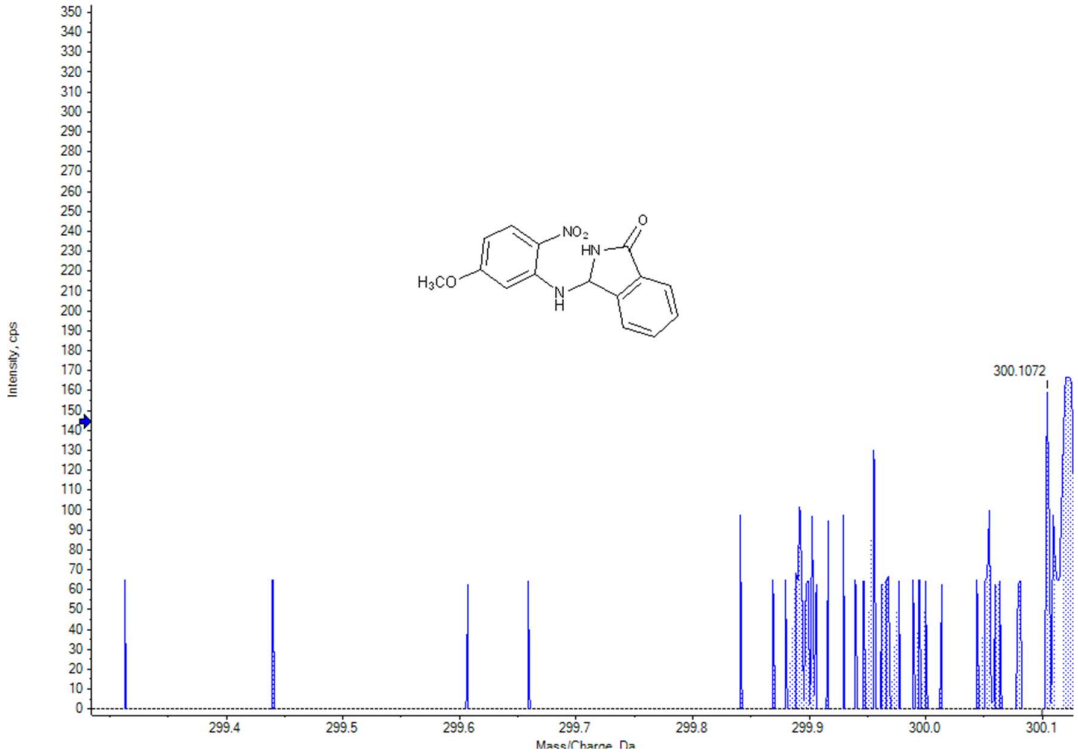

320.1008
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
H3C
N
H

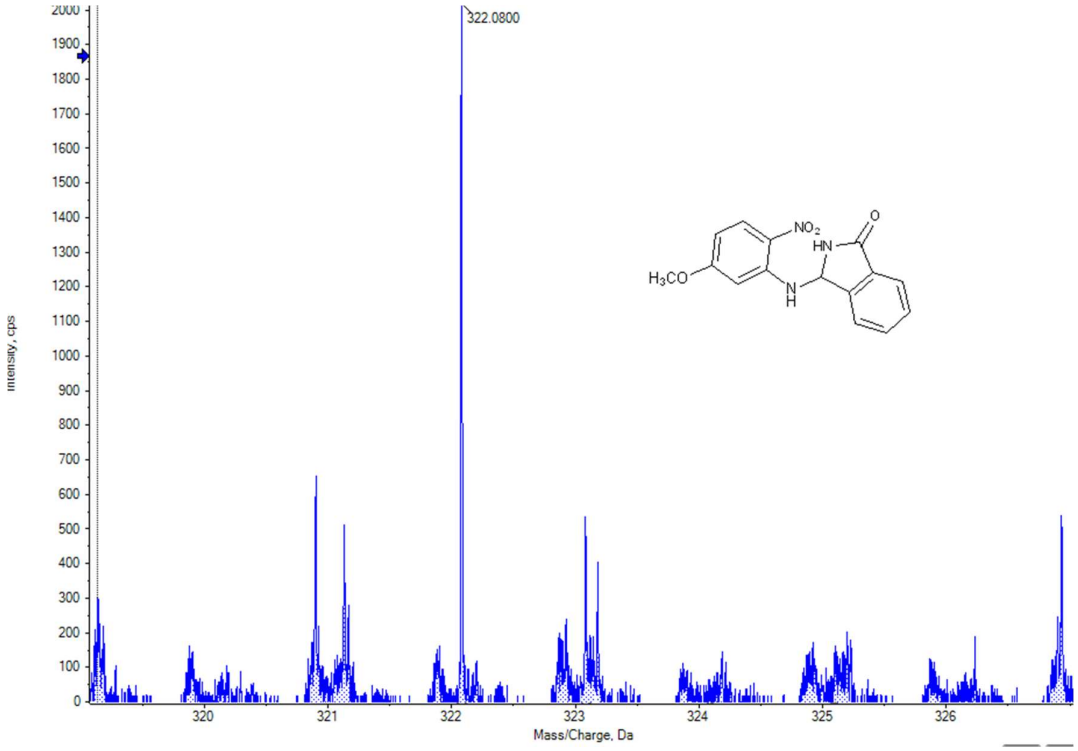

336.0748
Intensity, cps
Mass/Charge, Da
H3C
NO2
HN
O
H3C
N
H

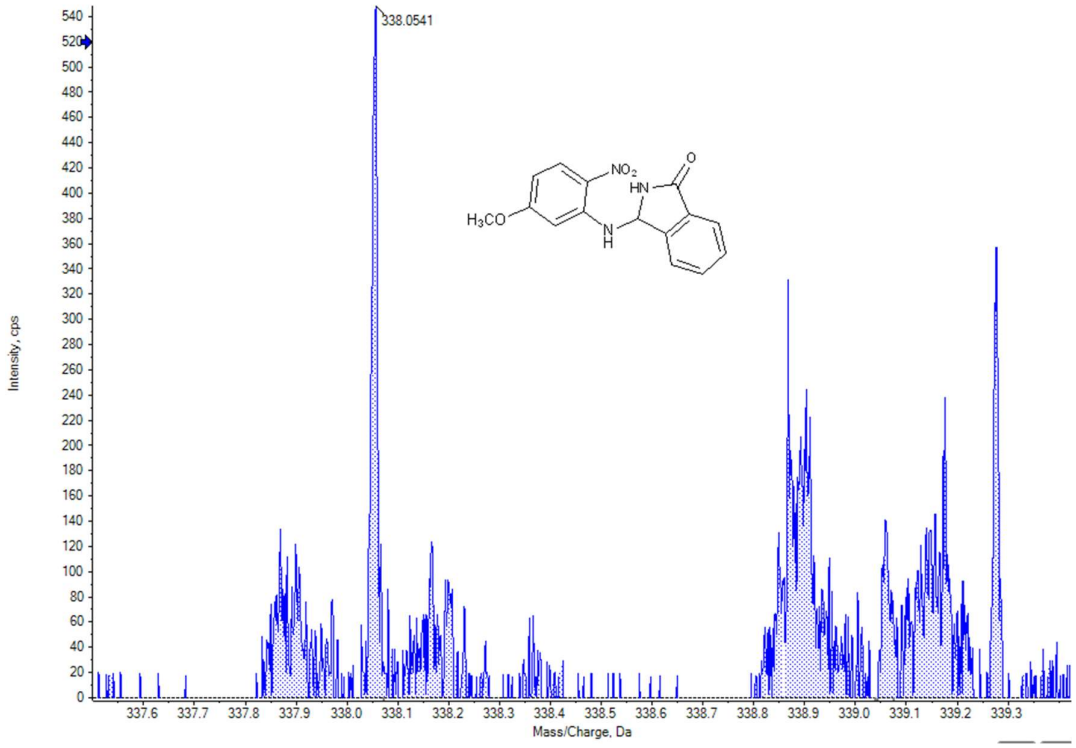

300.1493
300.0993
Intensity, cps
Mass/Charge, Da
H3CO
NO2
HN
O
N
H

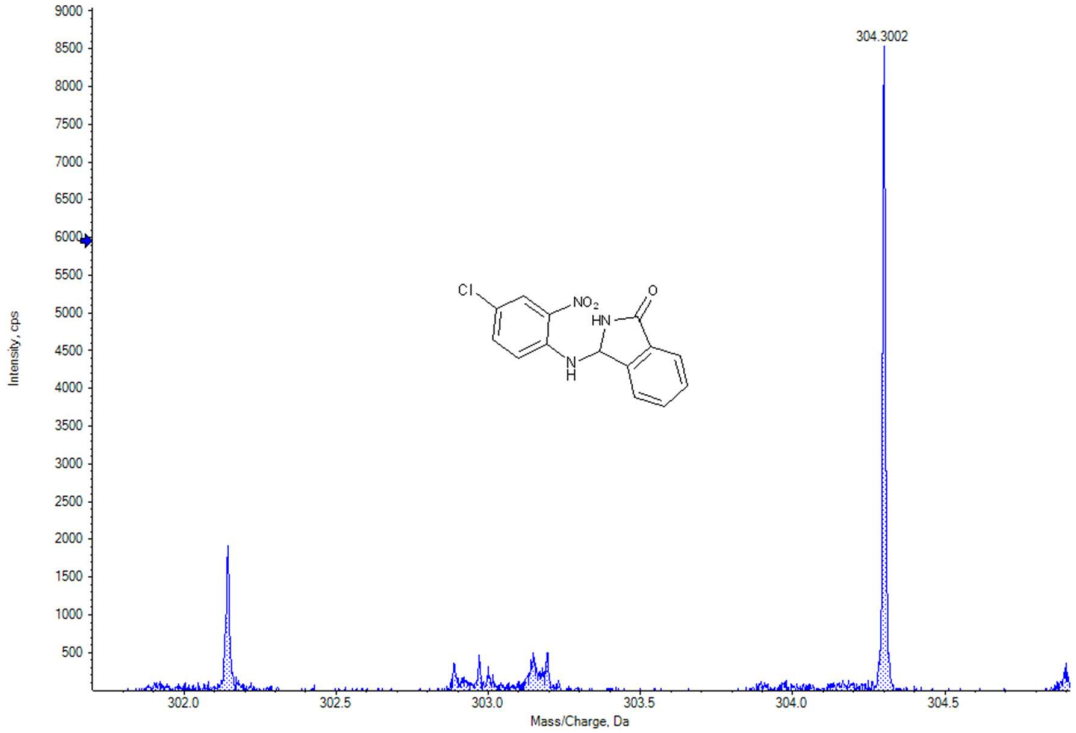

322.0805
Intensity, cps
Mass/Charge, Da
H3CO
NO2
HN
O
N
H

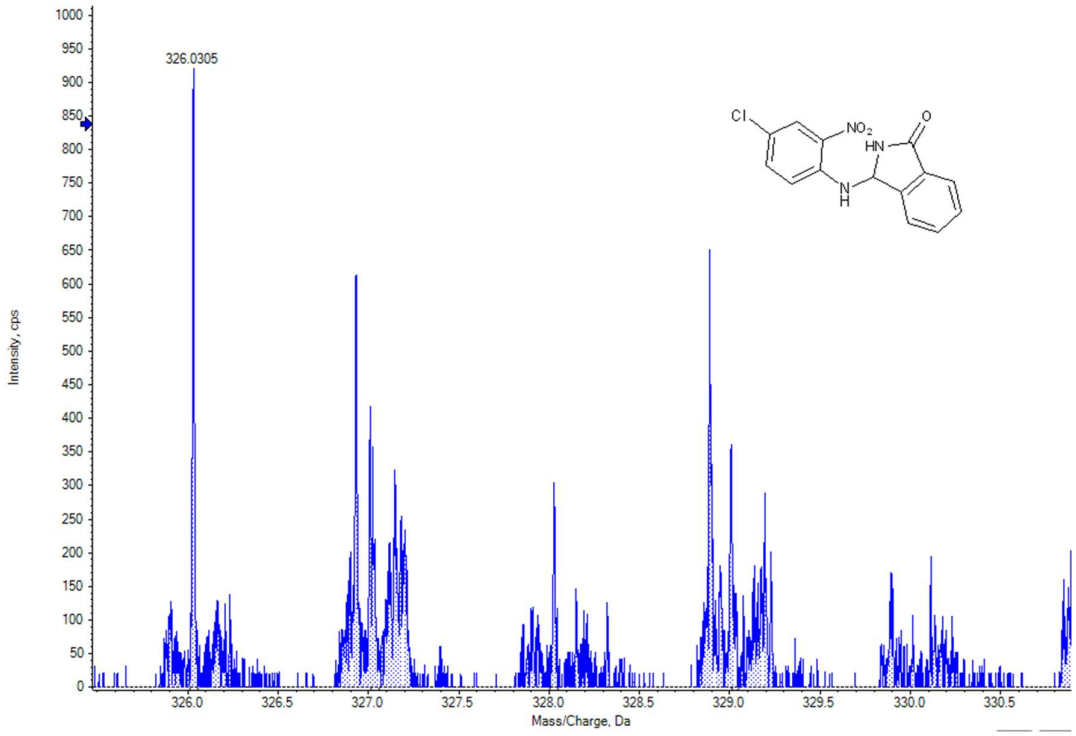

338.0540
Intensity, cps
Mass/Charge, Da
H3CO
NO2
HN
O
N
H

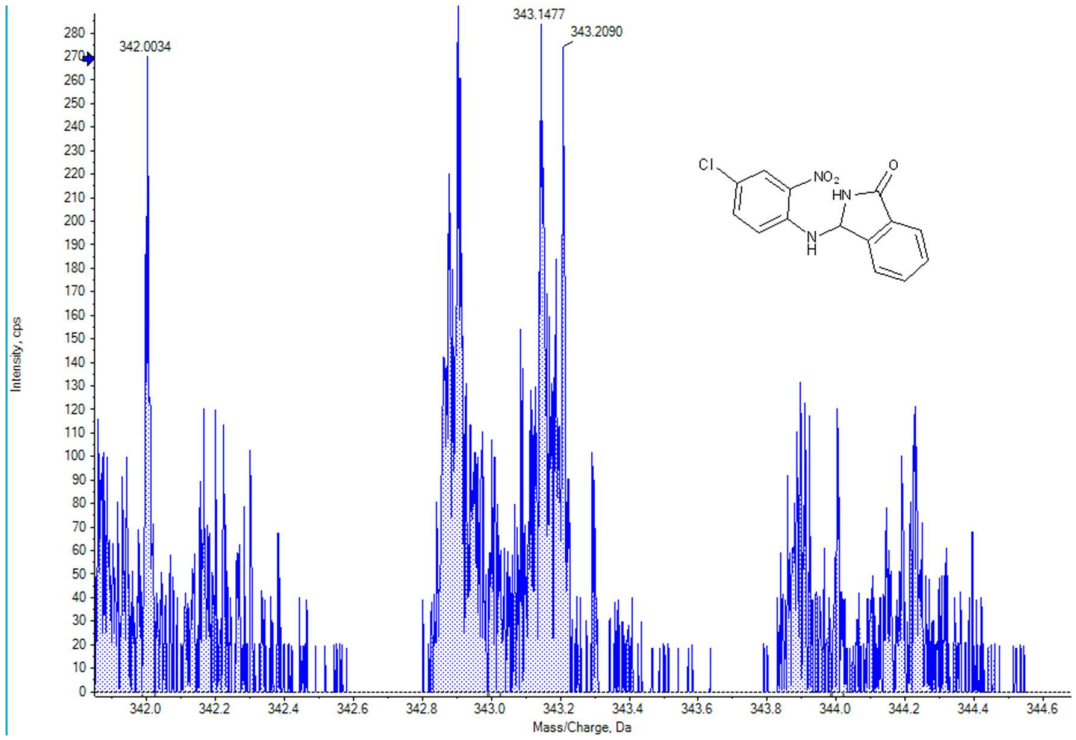

Intensity, cps
300.1072
Mass/Charge, Da

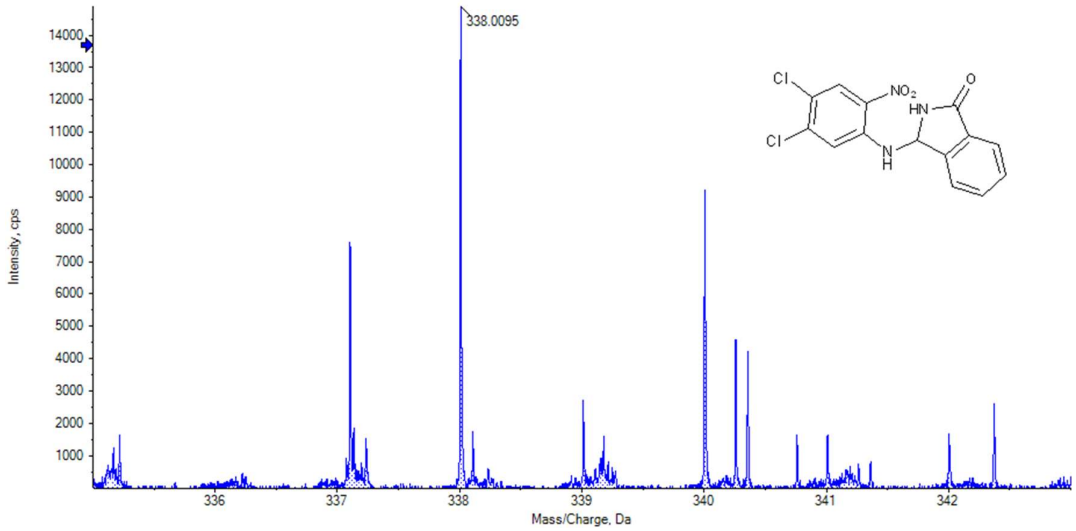

Intensity, cps
322.0800
Mass/Charge, Da

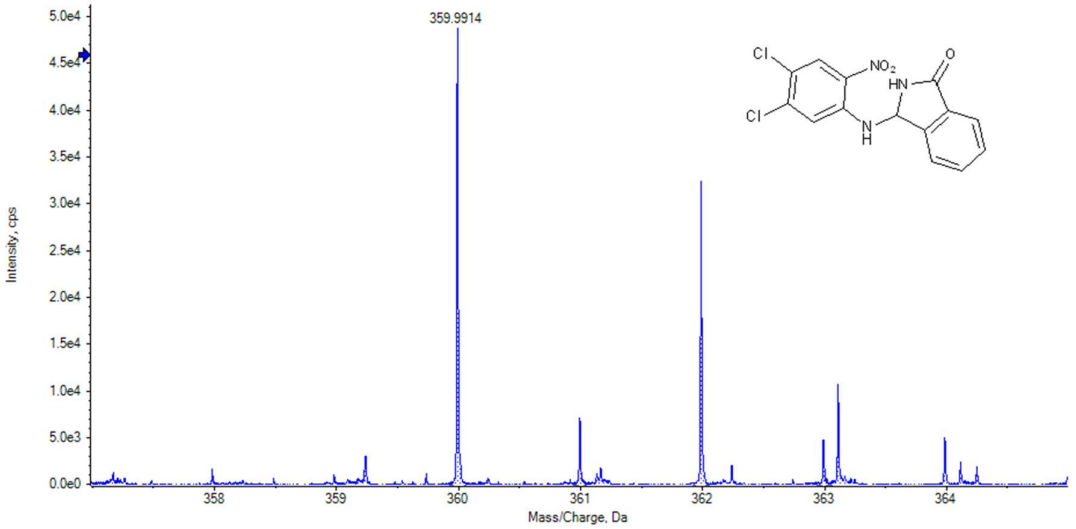

338.0541
Intensity, cps
Mass/Charge, Da
NO2
HN
O
H3CO
N
H

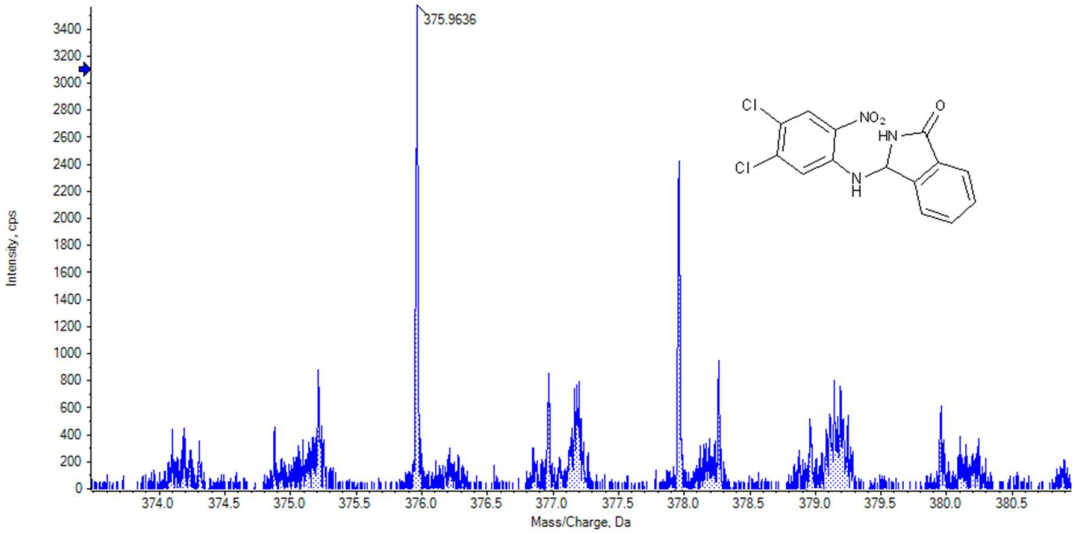

304.3002
Intensity, cps
Mass/Charge, Da
Cl
NO2
HN
O
N
H

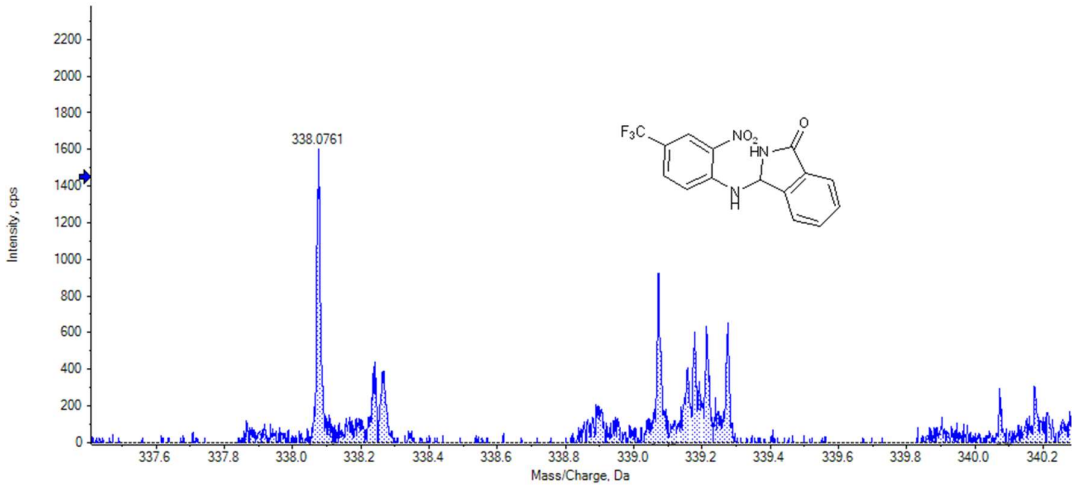

326.0305
Intensity, cps
Mass/Charge, Da
Cl
NO2
HN
O
N
H

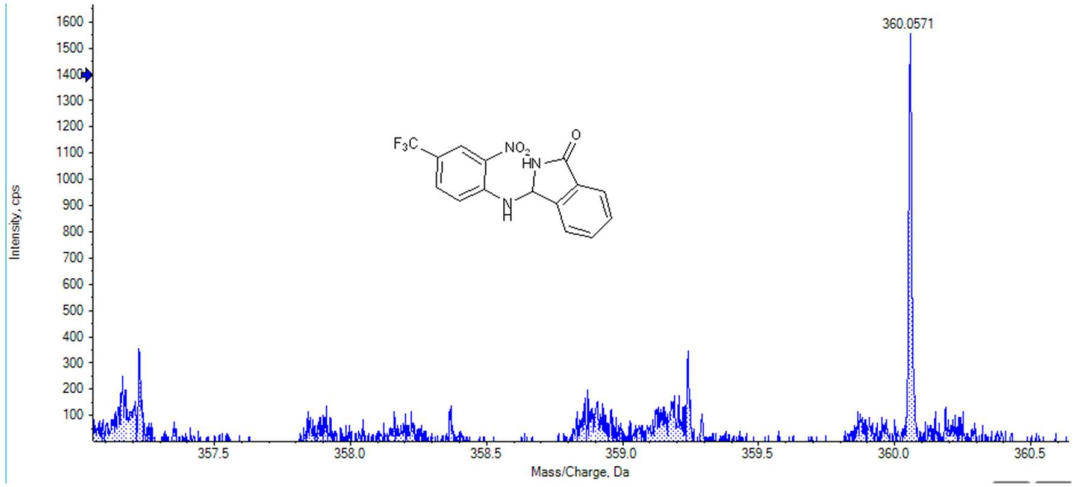

342.0034
343.1477
343.2090
Intensity, cps
Mass/Charge, Da
Cl
NO2
HN
O
N
H

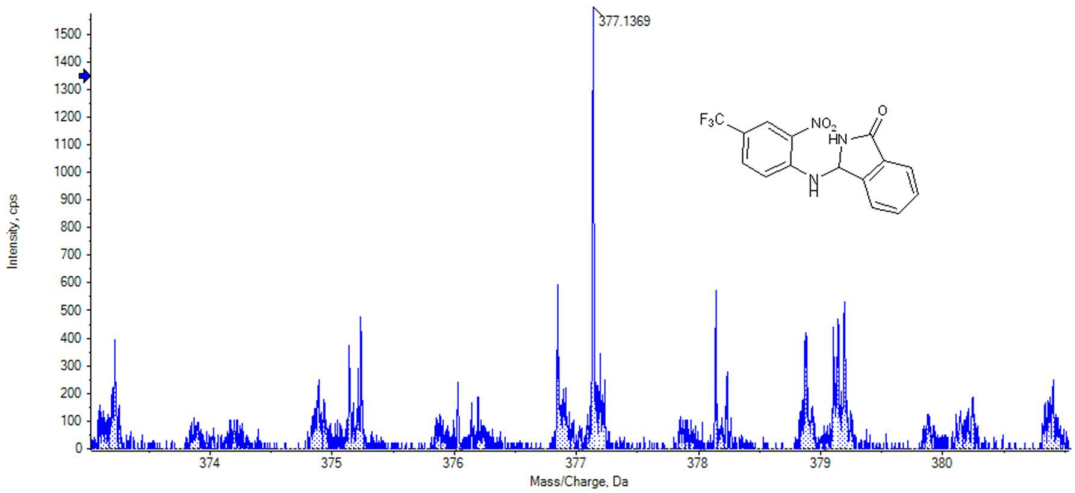

338.0095
Intensity, cps
Mass/Charge, Da
Cl
Cl
NO2
HN
O
N
H

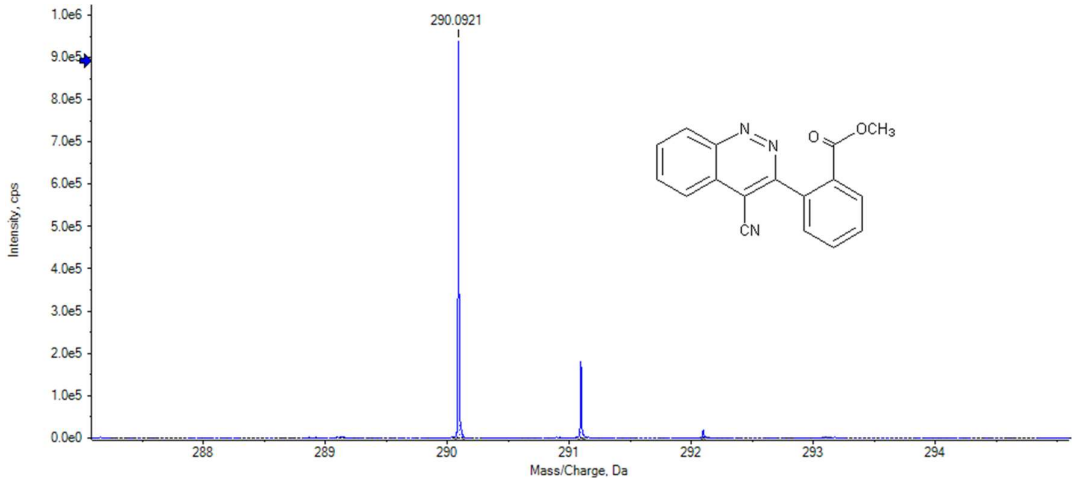

359.9914
Intensity, cps
Mass/Charge, Da
Cl
Cl
NO2
HN
O
N
H

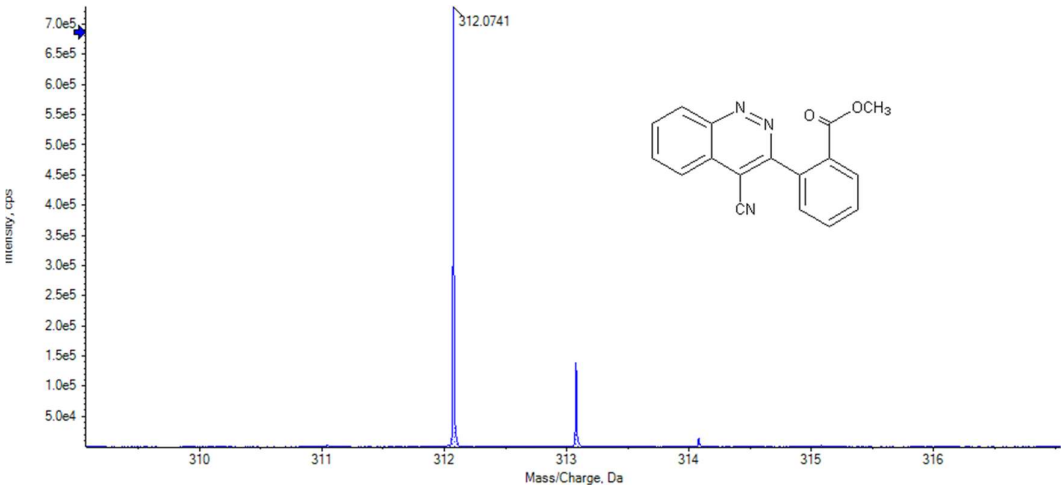

375.9636
Intensity, cps
Mass/Charge, Da
Cl
Cl
NO2
HN
O
N
H

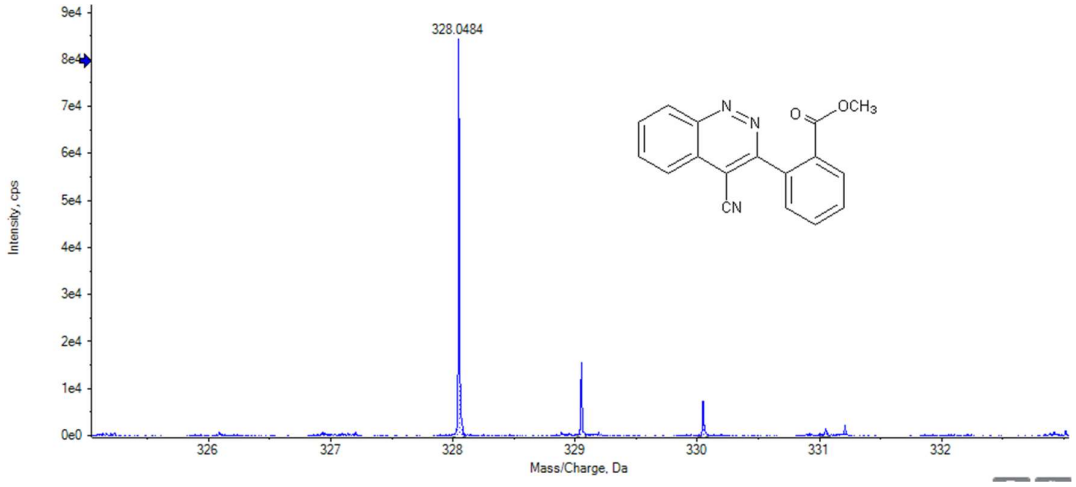

338.0761
Intensity, cps
Mass/Charge, Da

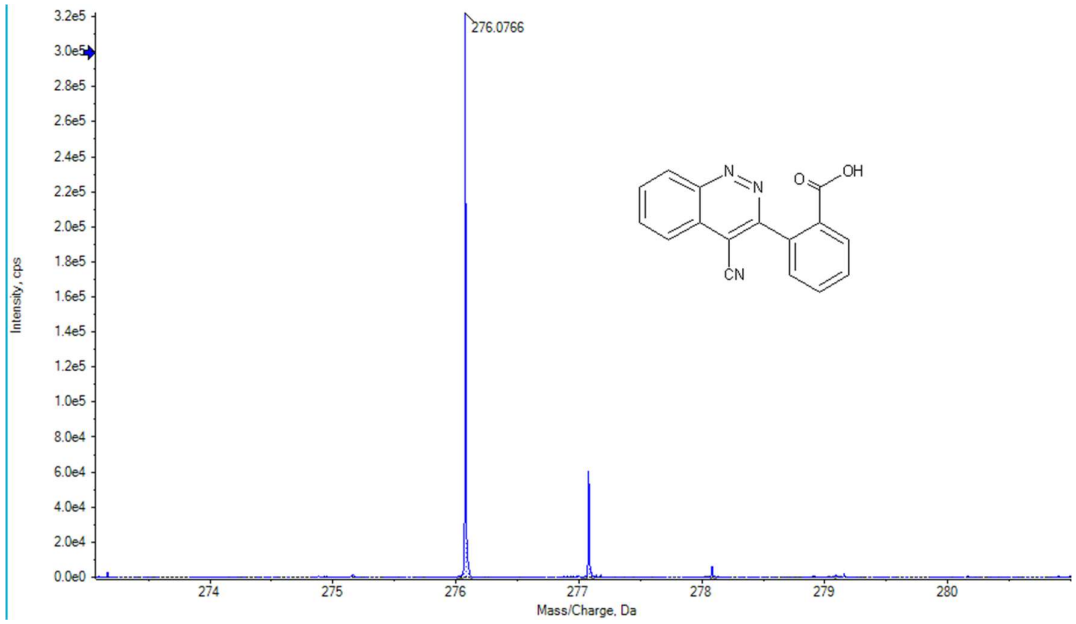

360.0571
Intensity, cps
Mass/Charge, Da

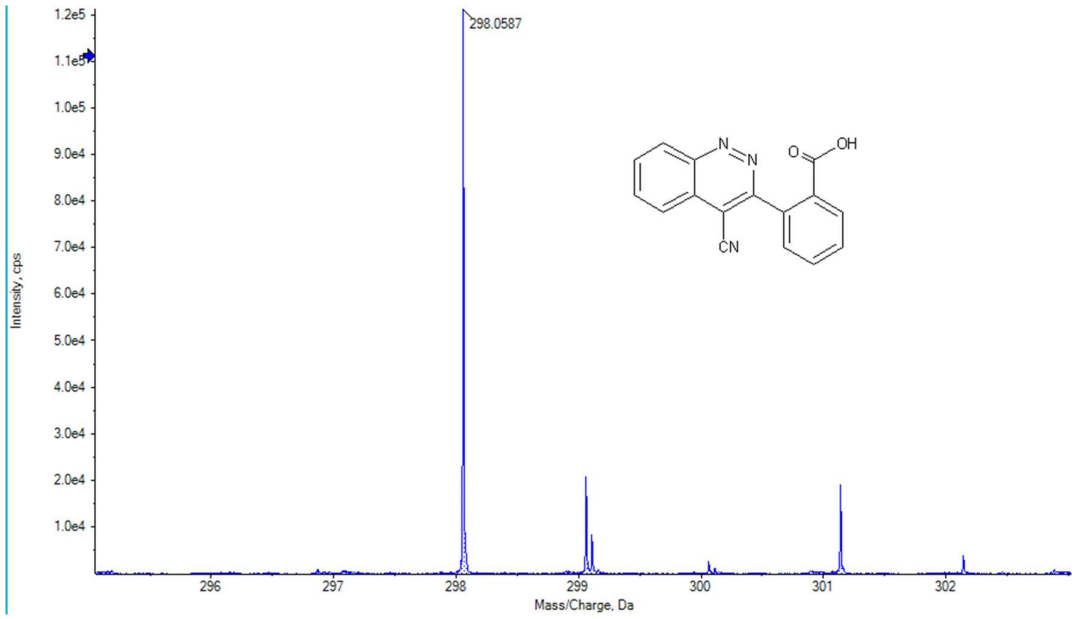

377.1369
Intensity, cps
Mass/Charge, Da

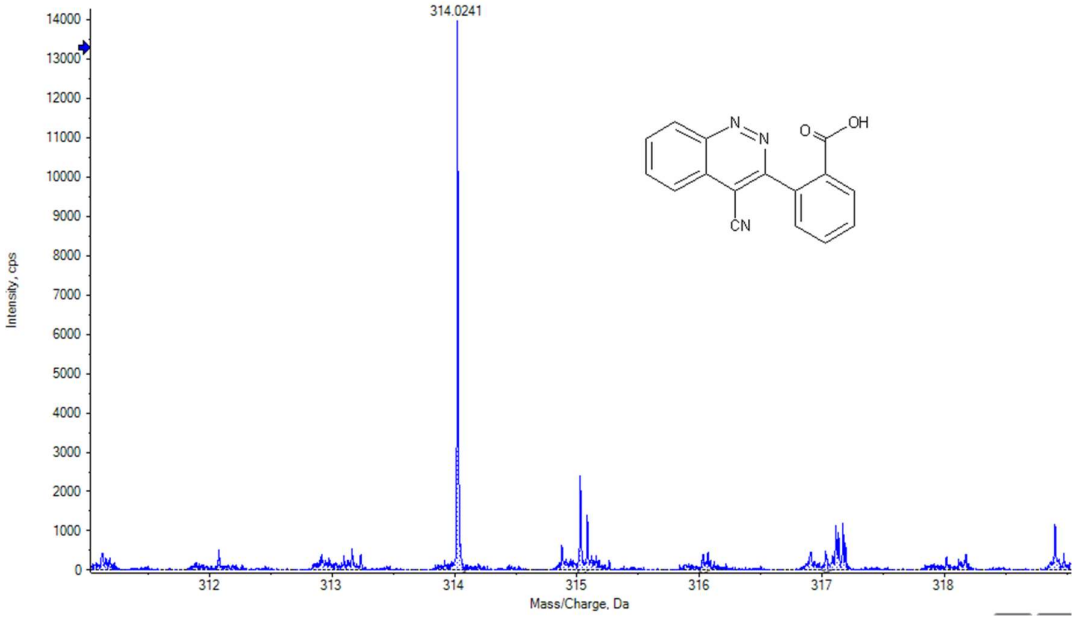

290.0921
Intensity, cps
Mass/Charge, Da
N
N
O
OCH3
CN

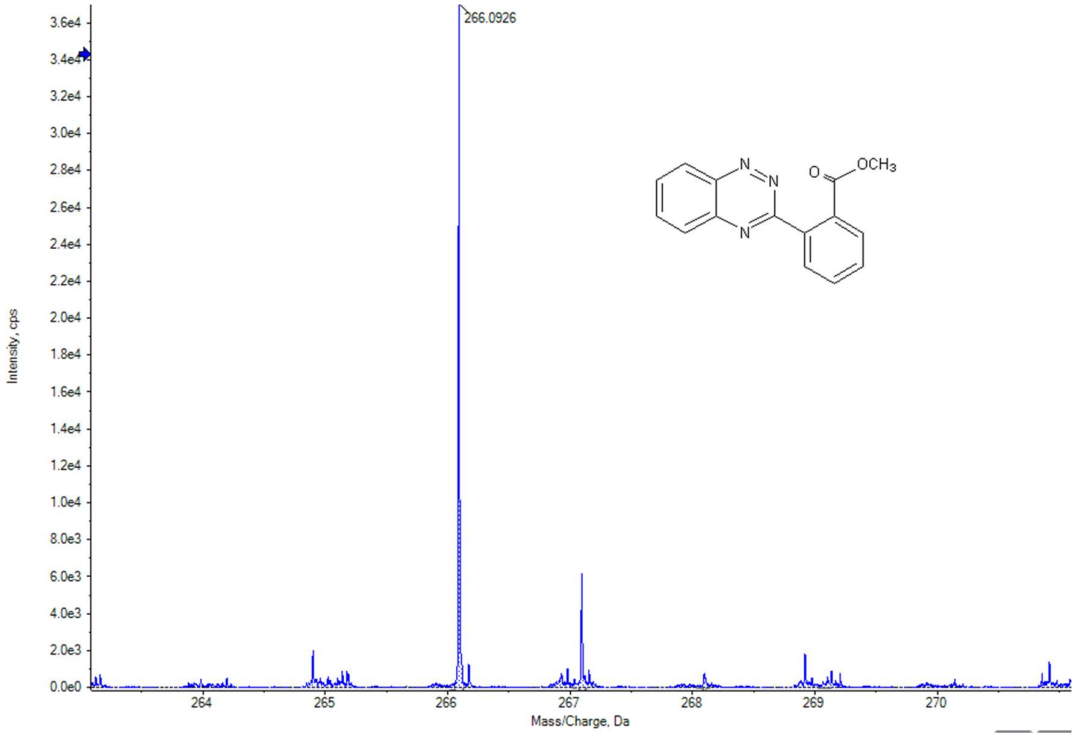

312.0741
Intensity, cps
Mass/Charge, Da
N
N
O
OCH3
CN

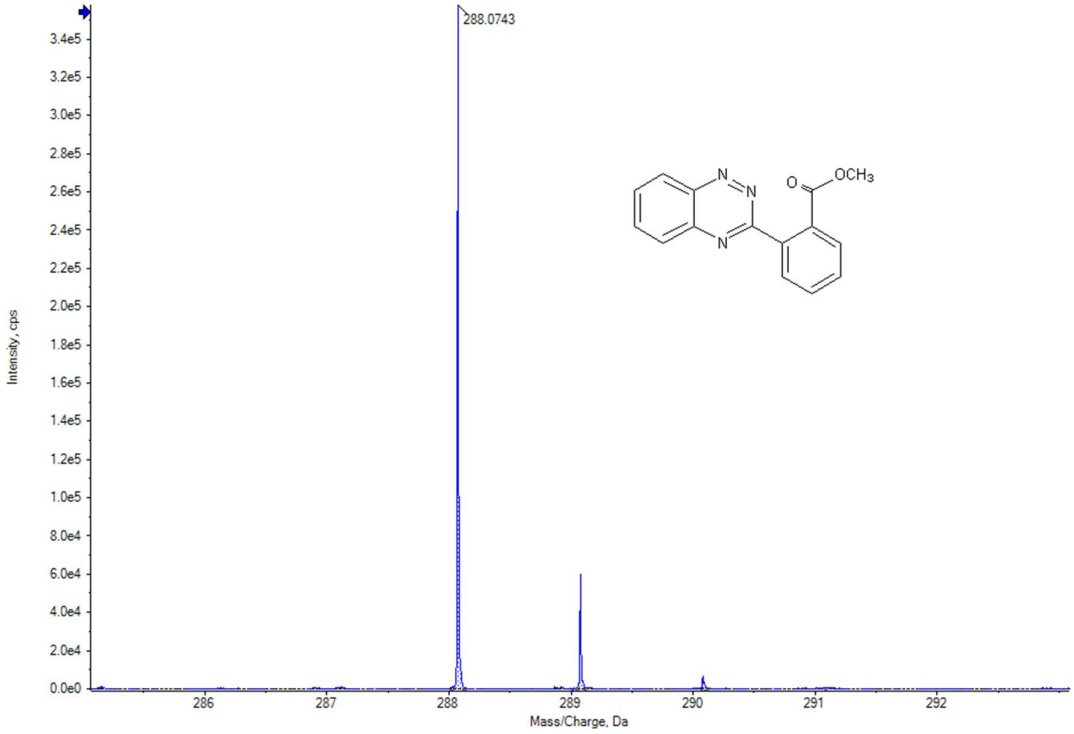

328.0484
Intensity, cps
Mass/Charge, Da
N
N
O
OCH3
CN

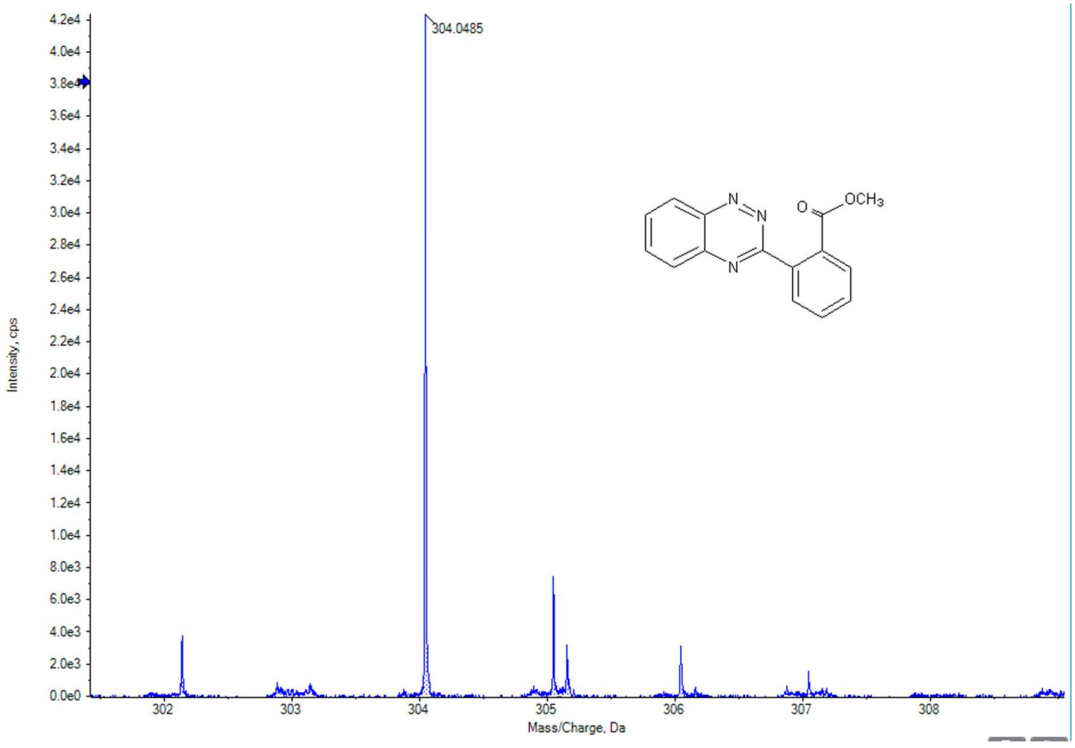

276.0766
Intensity, cps
Mass/Charge, Da
N
N
O
OH
CN

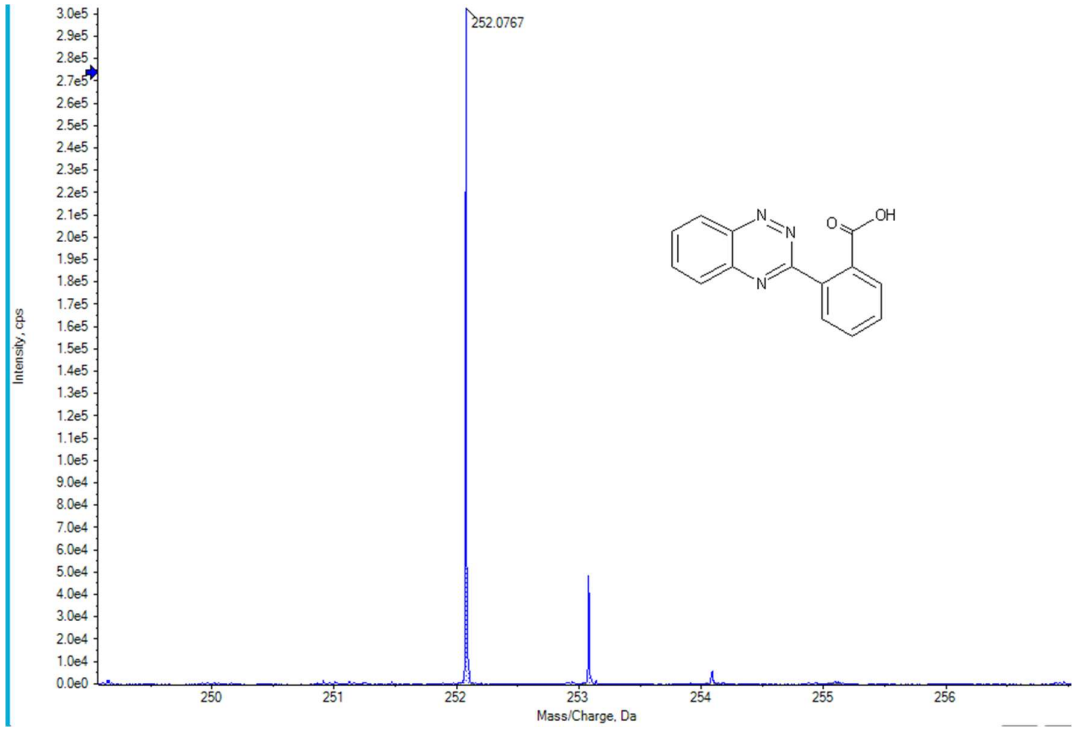

298.0587
Intensity, cps
Mass/Charge, Da
N
N
O
OH
CN


314.0241
Intensity, cps
Mass/Charge, Da
N
N
O
OH
CN

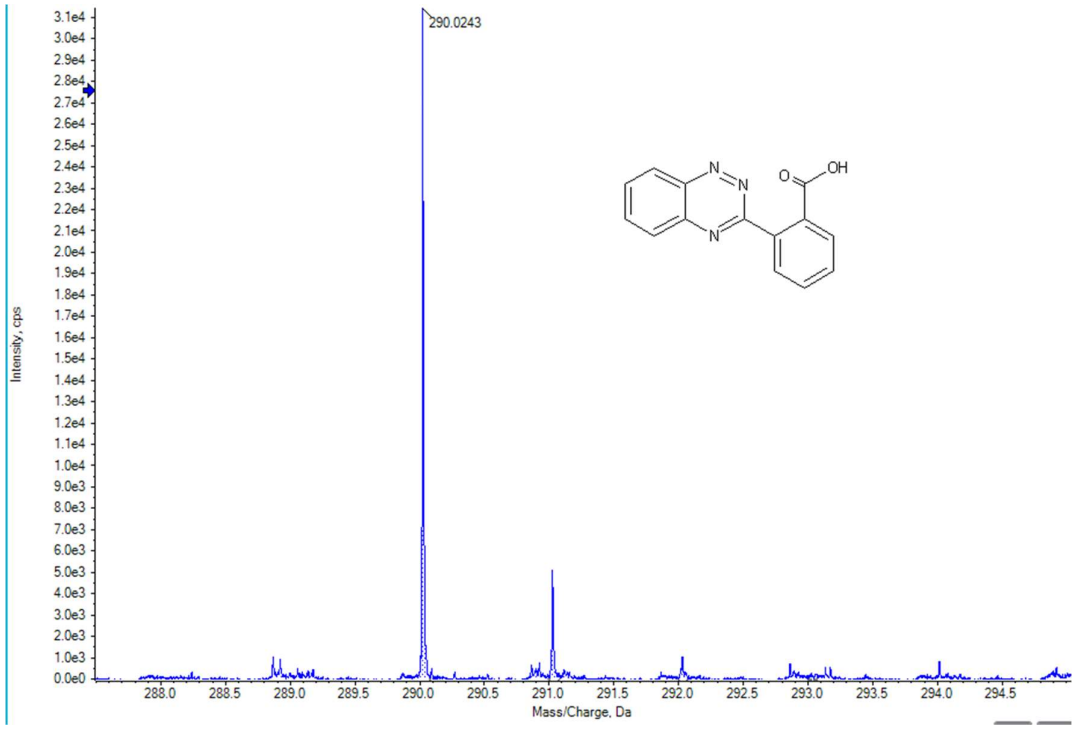

266.0926
Intensity, cps
Mass/Charge, Da
N
N
N
O
OCH3

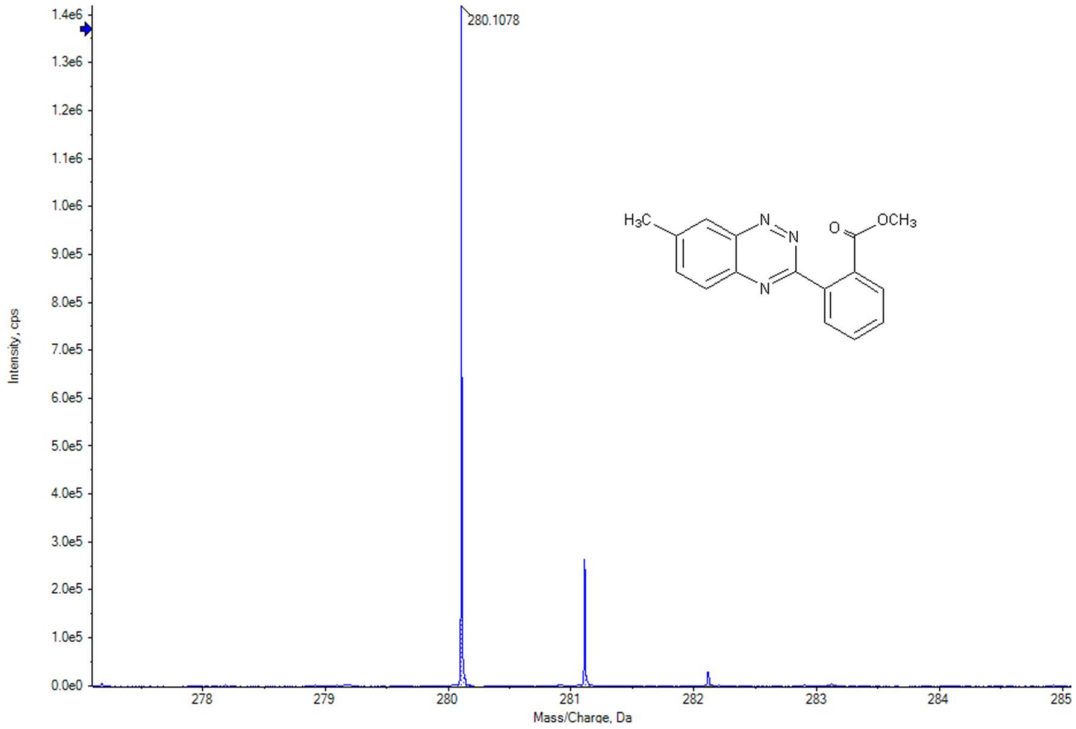

288.0743
Intensity, cps
Mass/Charge, Da
OCH3


304.0485
Intensity, cps
Mass/Charge, Da
OCH3

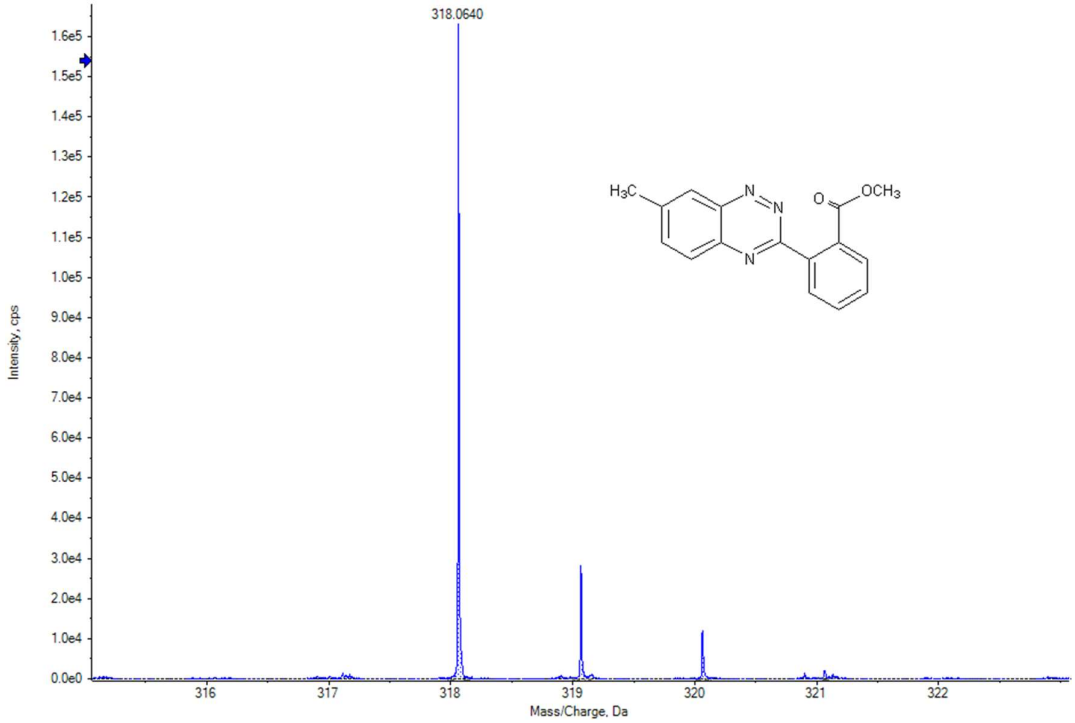

252.0767
Intensity, cps
Mass/Charge, Da
OH
O
N
N
N

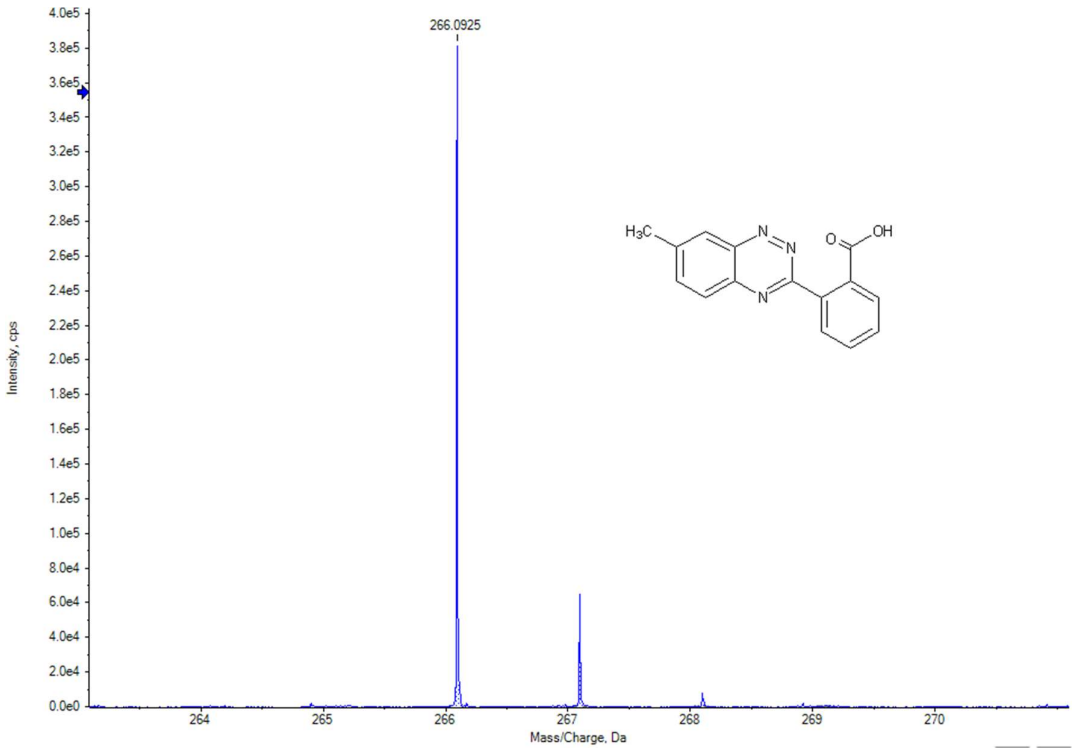

274.0587
Intensity, cps
Mass/Charge, Da
OH
O
N
N
N


290.0243
Intensity, cps
Mass/Charge, Da
OH
O
N
N
N

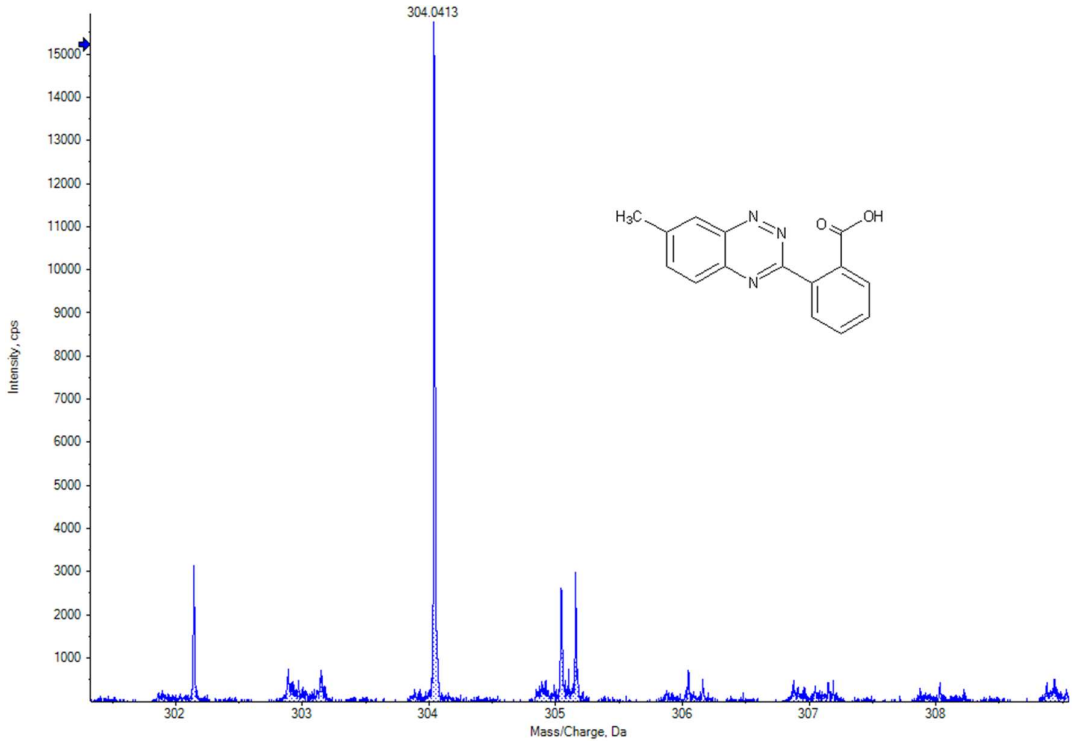

280.1078
Intensity, cps
Mass/Charge, Da
H3C
OCH3
O
N
N
N

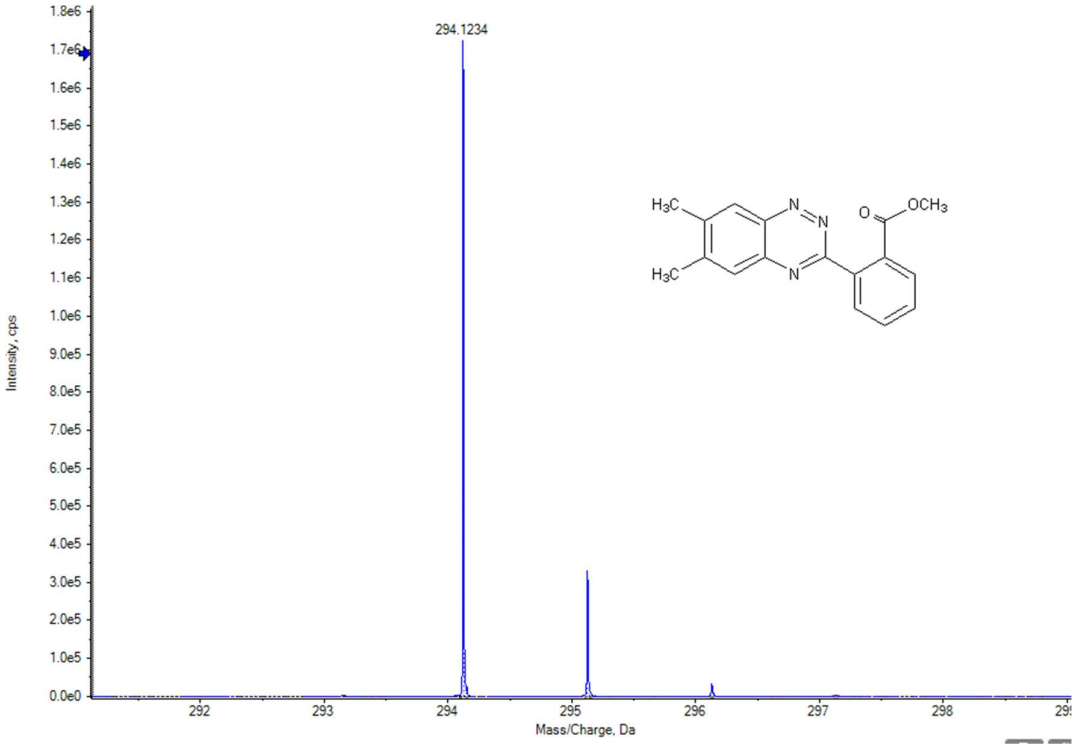

302.0898
Intensity, cps
Mass/Charge, Da
H3C
N
N
N
O
OCH3

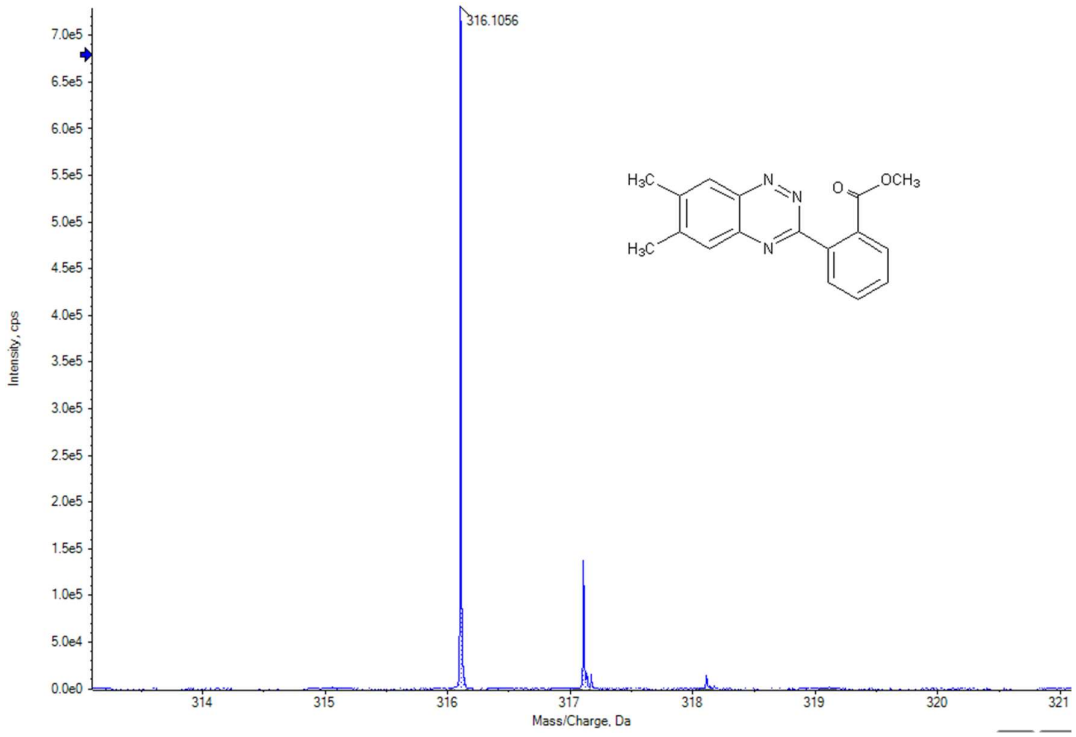

318.0640
Intensity, cps
Mass/Charge, Da
H3C
N
N
N
O
OCH3

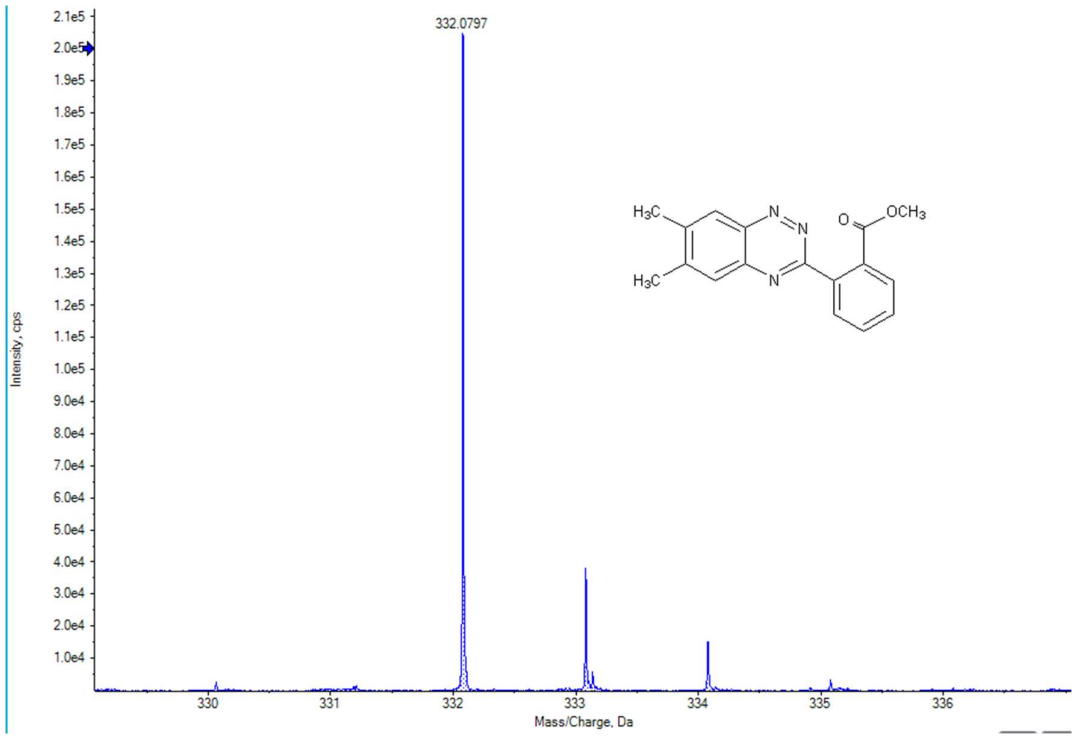

266.0925
Intensity, cps
Mass/Charge, Da
H3C
N
N
N
O
OH

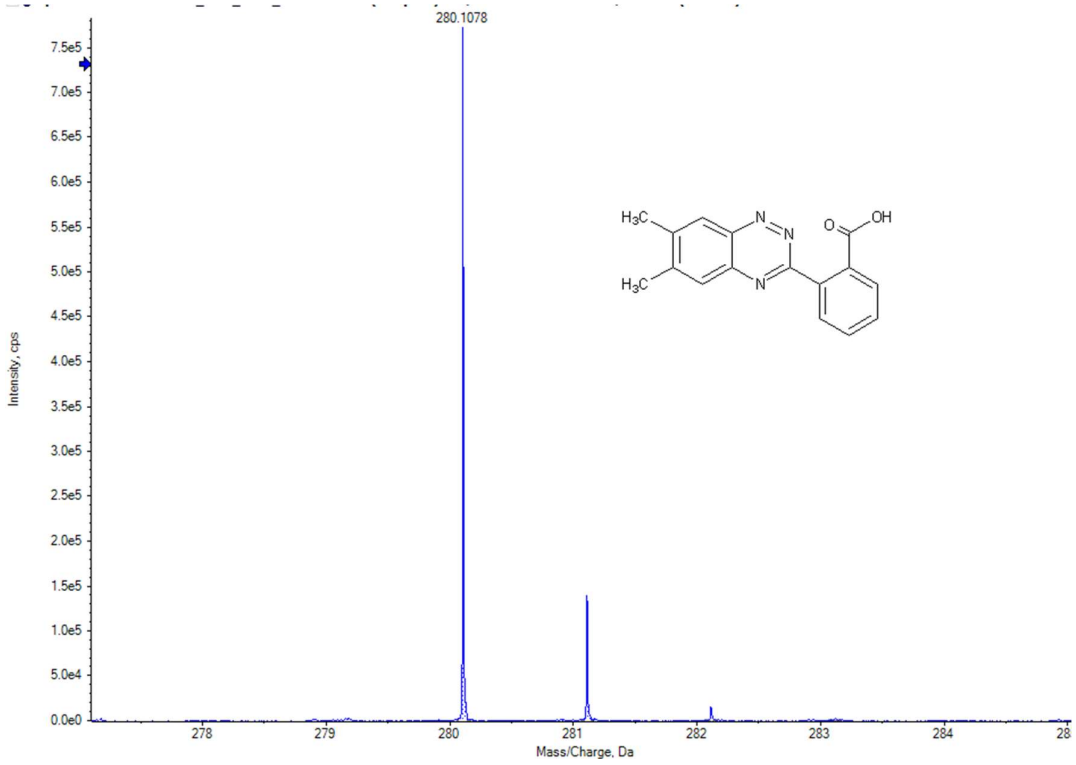

288.0744
Intensity, cps
Mass/Charge, Da
H3C
N
N
N
O
OH

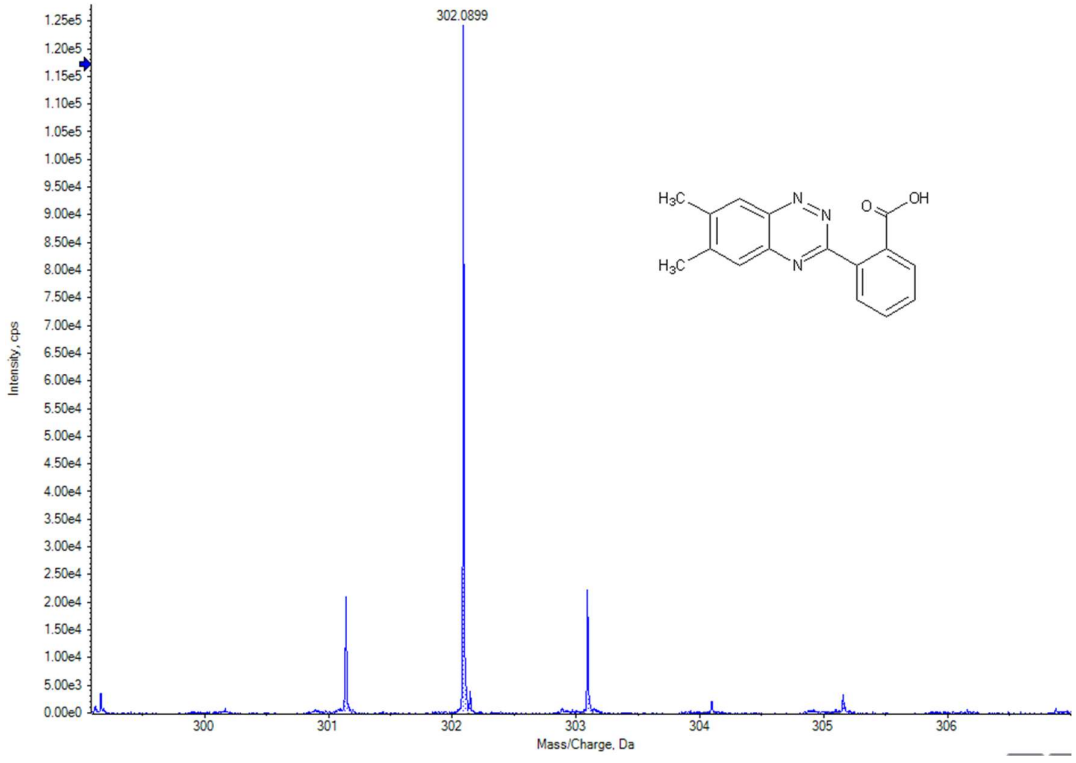

304.0413
Intensity, cps
Mass/Charge, Da
H3C
N
N
N
O
OH

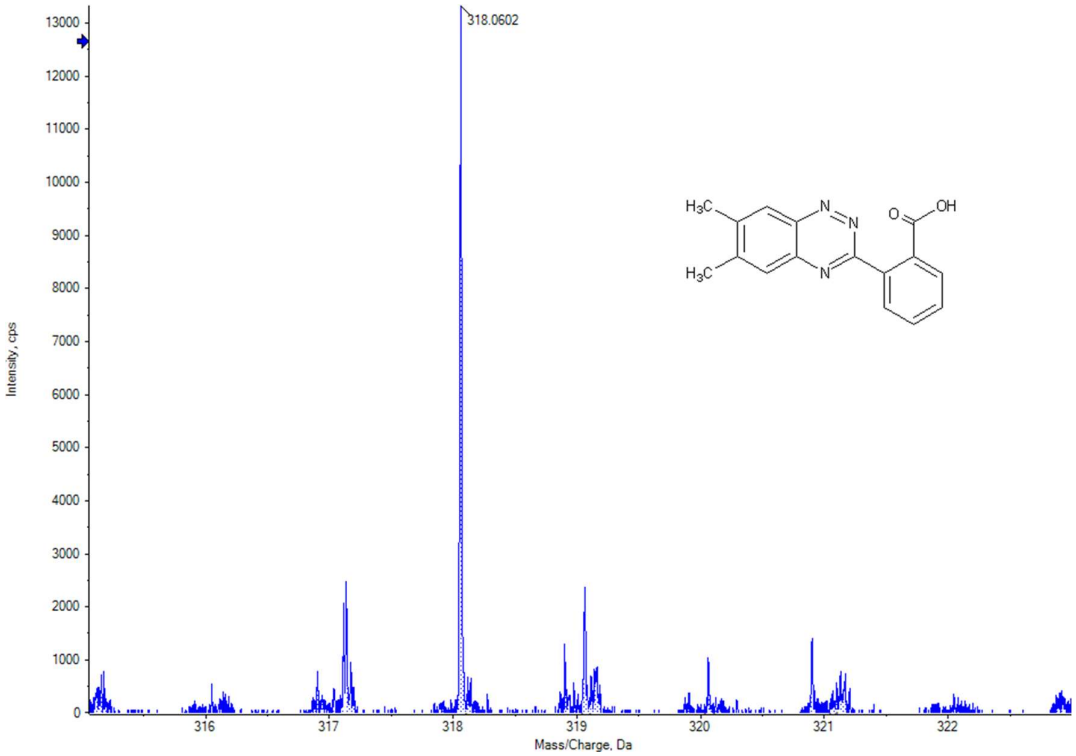

294.1234
Intensity, cps
Mass/Charge, Da
H3C
H3C
N
N
N
O
OCH3


316.1056
Intensity, cps
Mass/Charge, Da
H3C
H3C
N
N
N
O
OCH3


332.0797
Intensity, cps
Mass/Charge, Da
H3C
H3C
N
N
N
O
OCH3

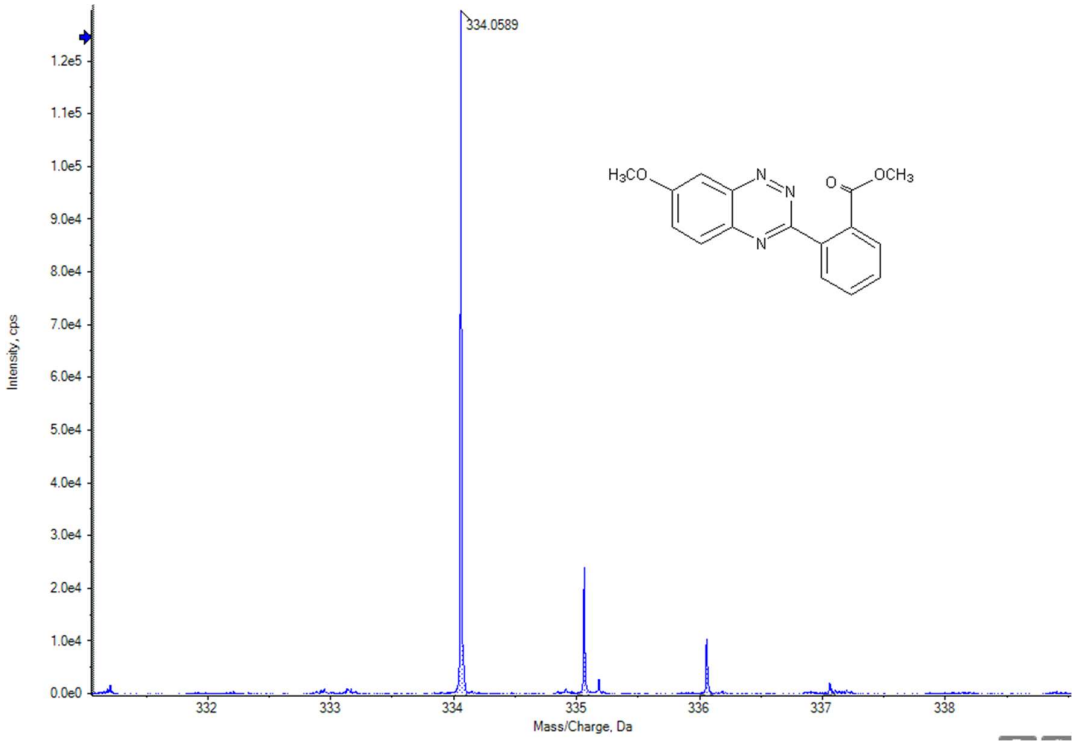

280.1078
Intensity, cps
Mass/Charge, Da
H3C
H3C
N
N
N
O
OH


302.0899
Intensity, cps
Mass/Charge, Da
H3C
H3C
N
N
N
O
OH

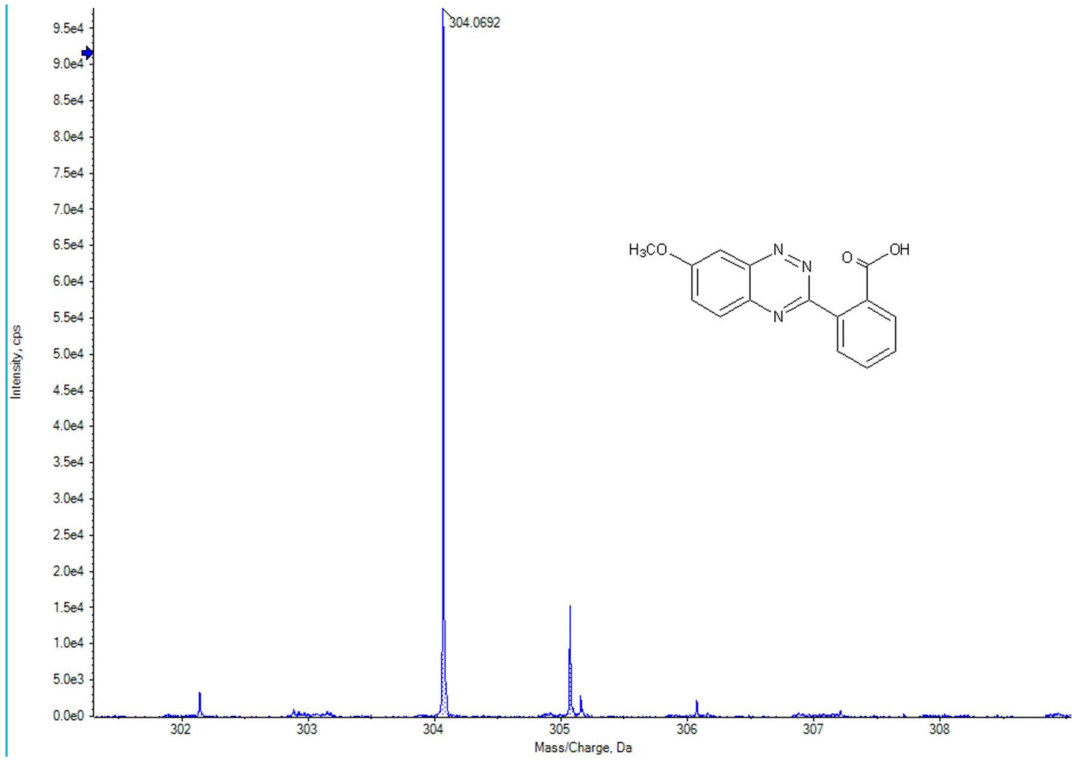

318.0602
Intensity, cps
Mass/Charge, Da
H3C
CH3
N
N
N
O
OH

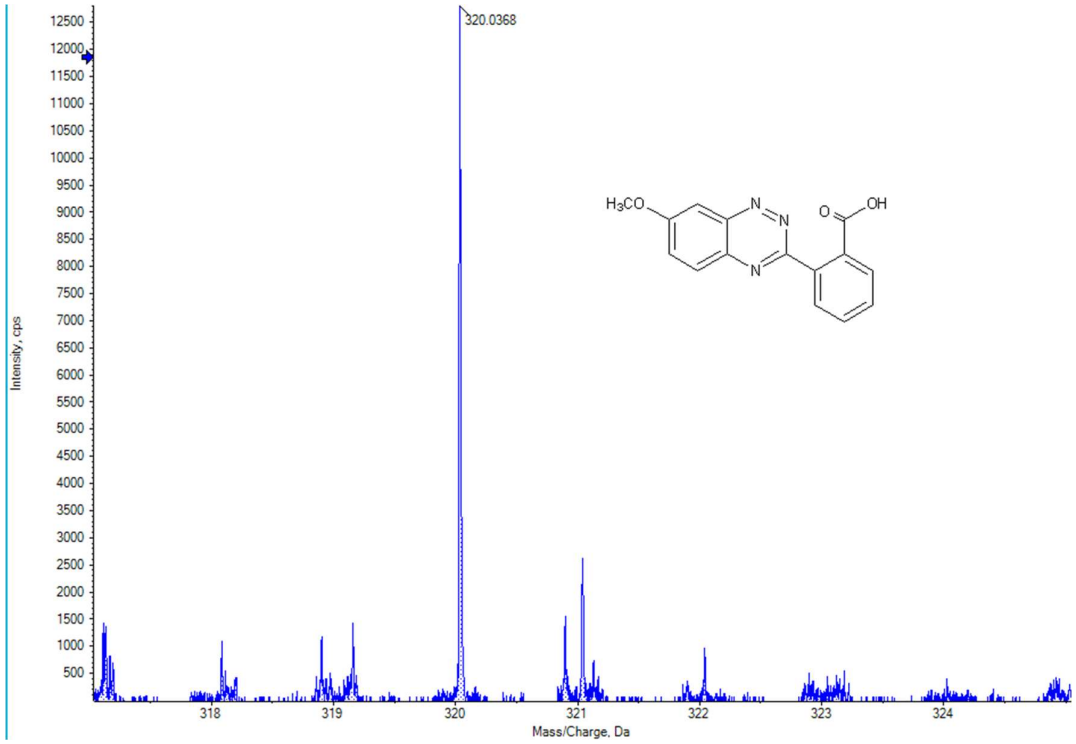

296.1027
Intensity, cps
Mass/Charge, Da
H3CO
N
N
N
O
OCH3

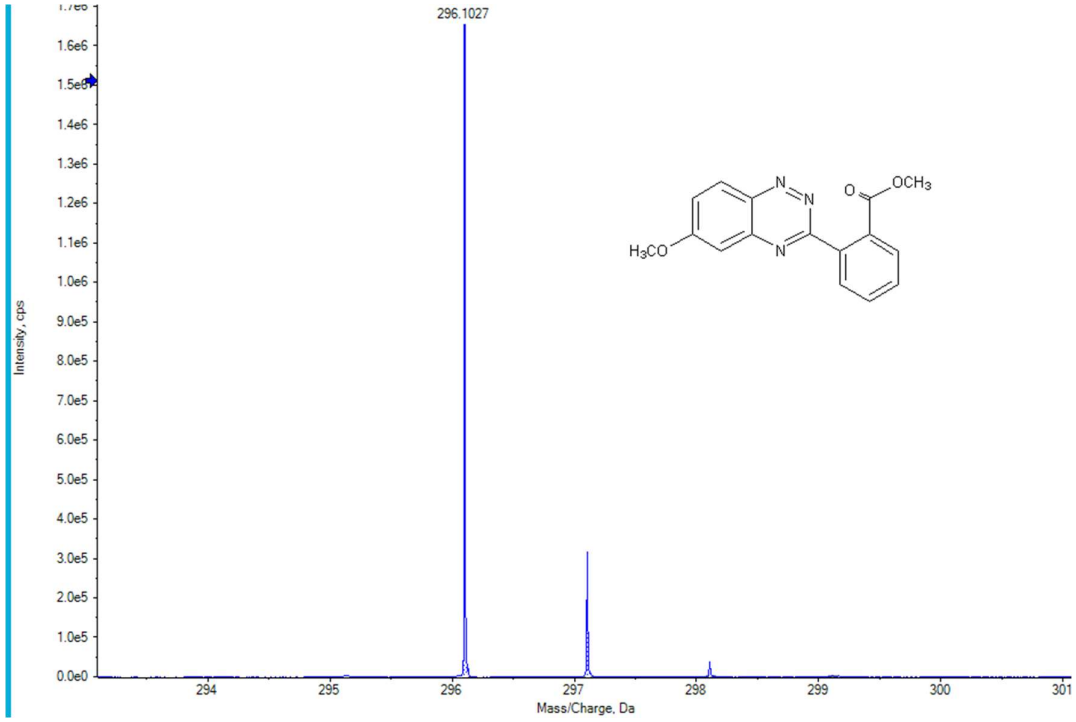

318.0848
Intensity, cps
Mass/Charge, Da
H3CO
OCH3
O
N
N
N


334.0589
Intensity, cps
Mass/Charge, Da
H3CO
OCH3
O
N
N
N

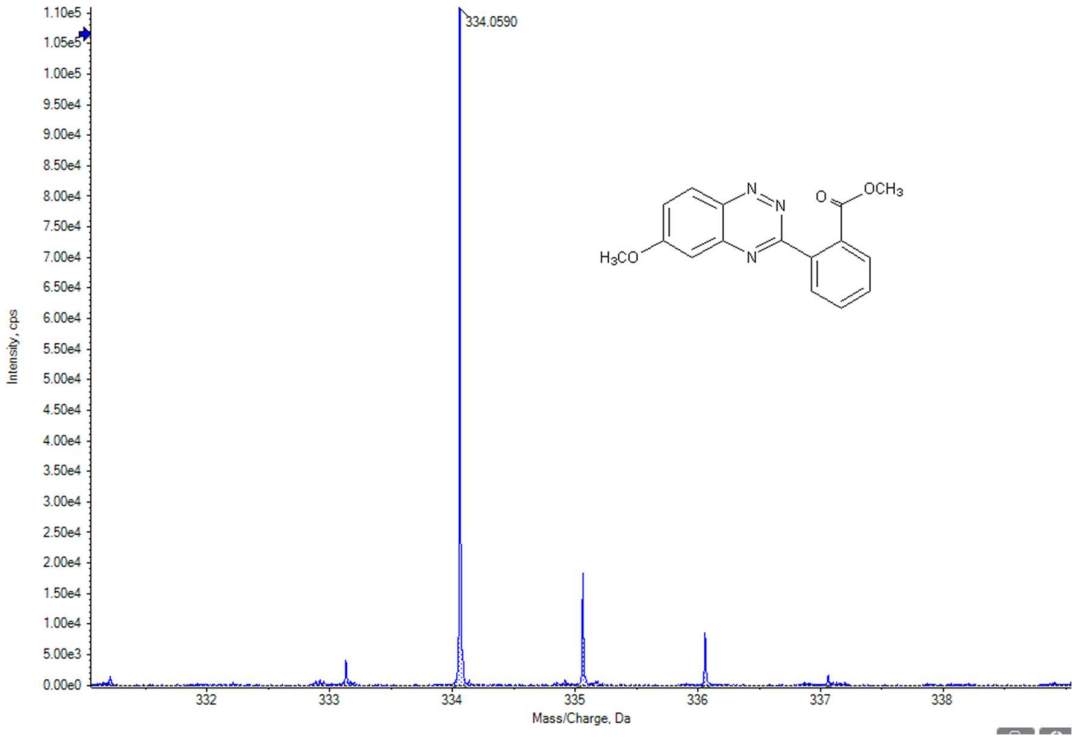

282.0873
Intensity, cps
Mass/Charge, Da
H3CO
OH
O
N
N
N

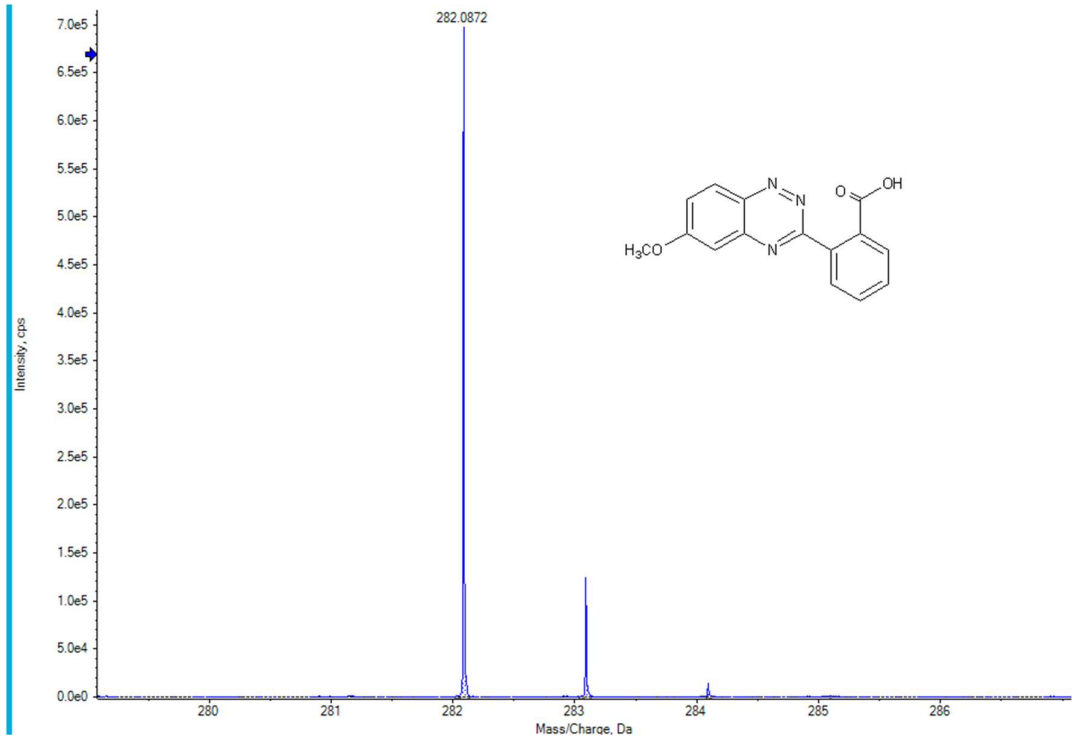

304.0692
Intensity, cps
Mass/Charge, Da
H3CO
OH
O
N
N
N

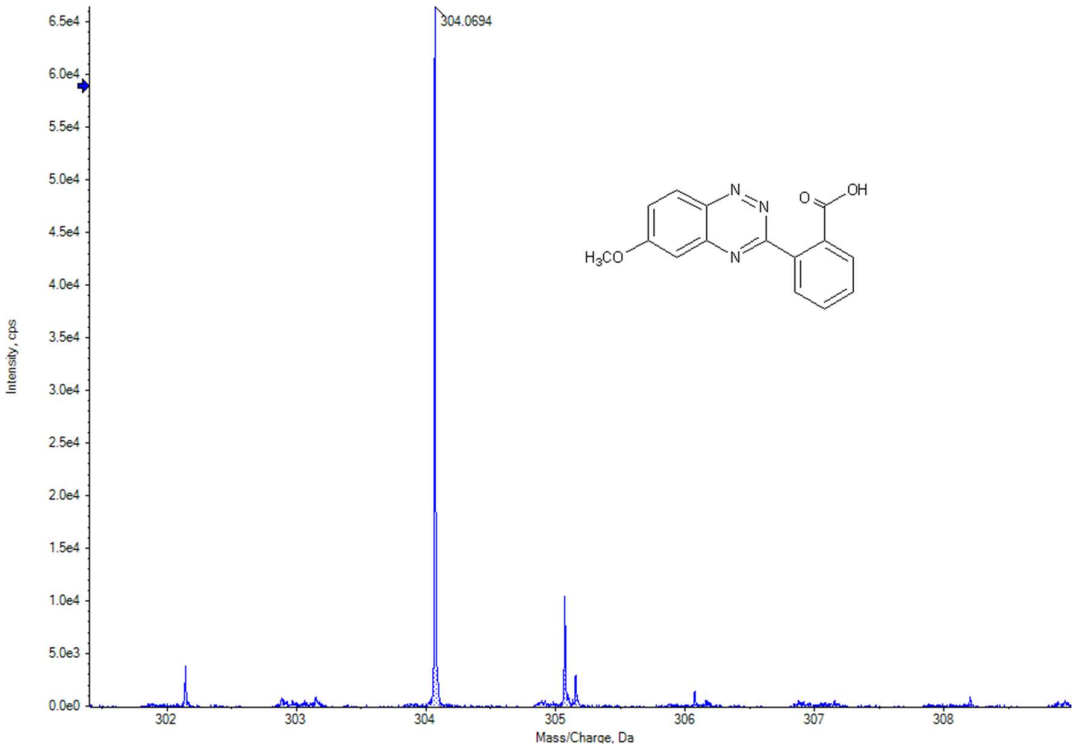

320.0368
Intensity, cps
Mass/Charge, Da
H3CO
OH
O
N
N
N

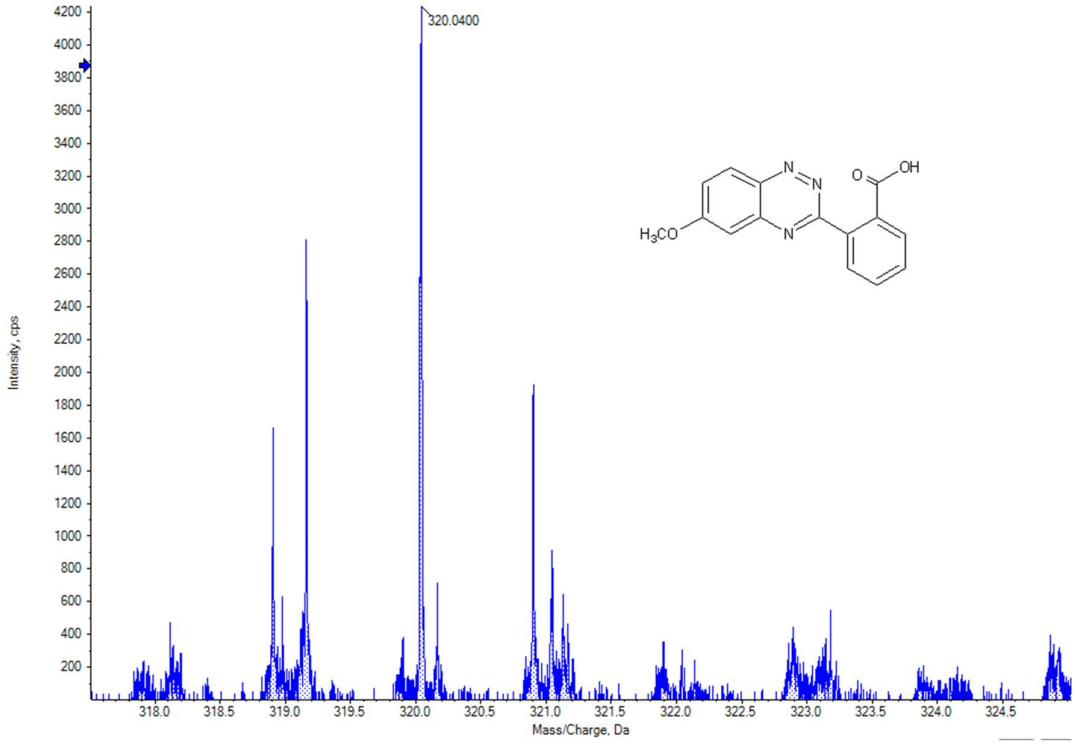

296.1027
Intensity, cps
Mass/Charge, Da
H3CO
OCH3
O
N
N
N

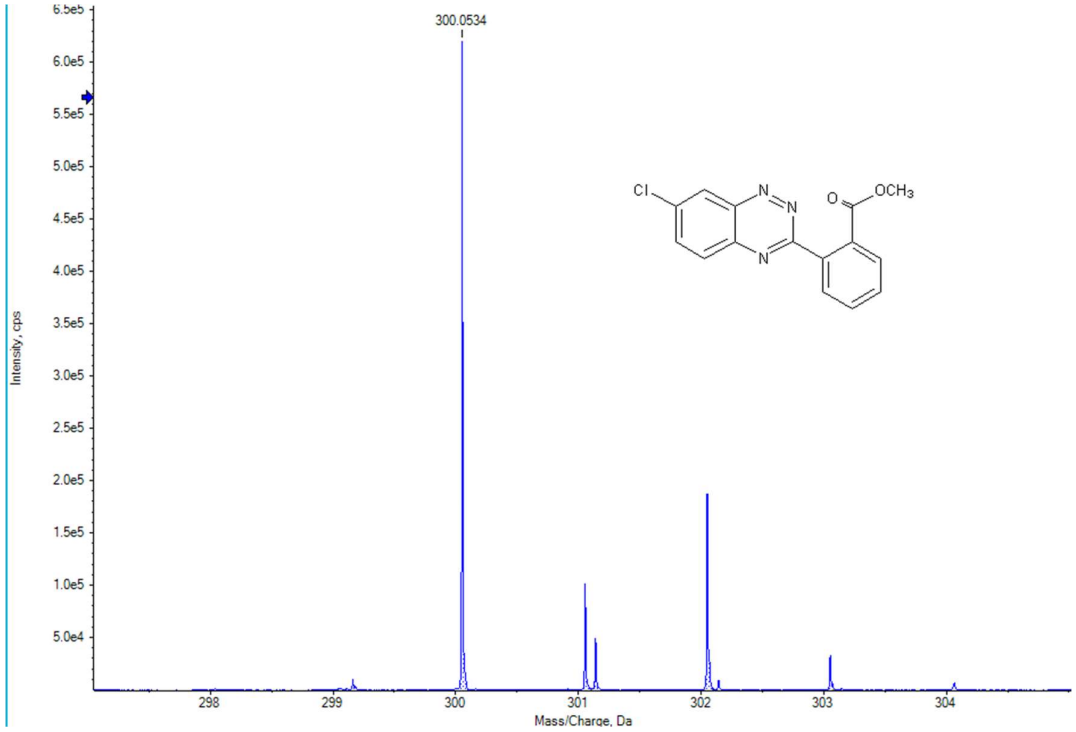

318.0850
Intensity, cps
Mass/Charge, Da
H3CO
OCH3

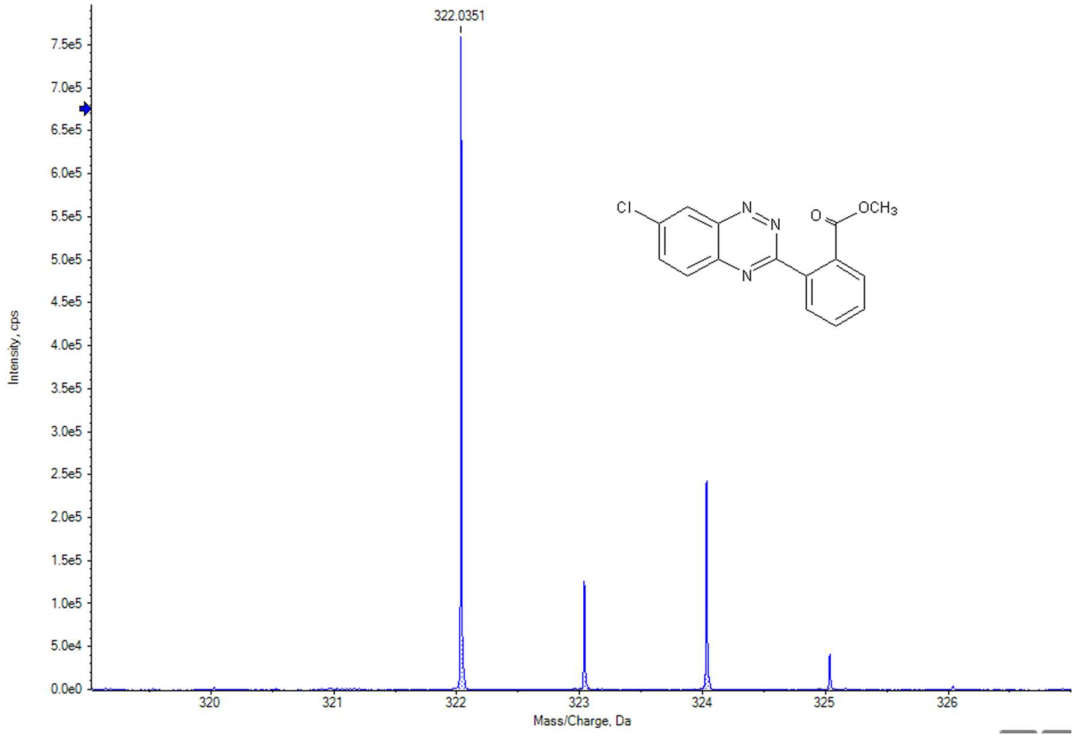

334.0590
Intensity, cps
Mass/Charge, Da
H3CO
OCH3

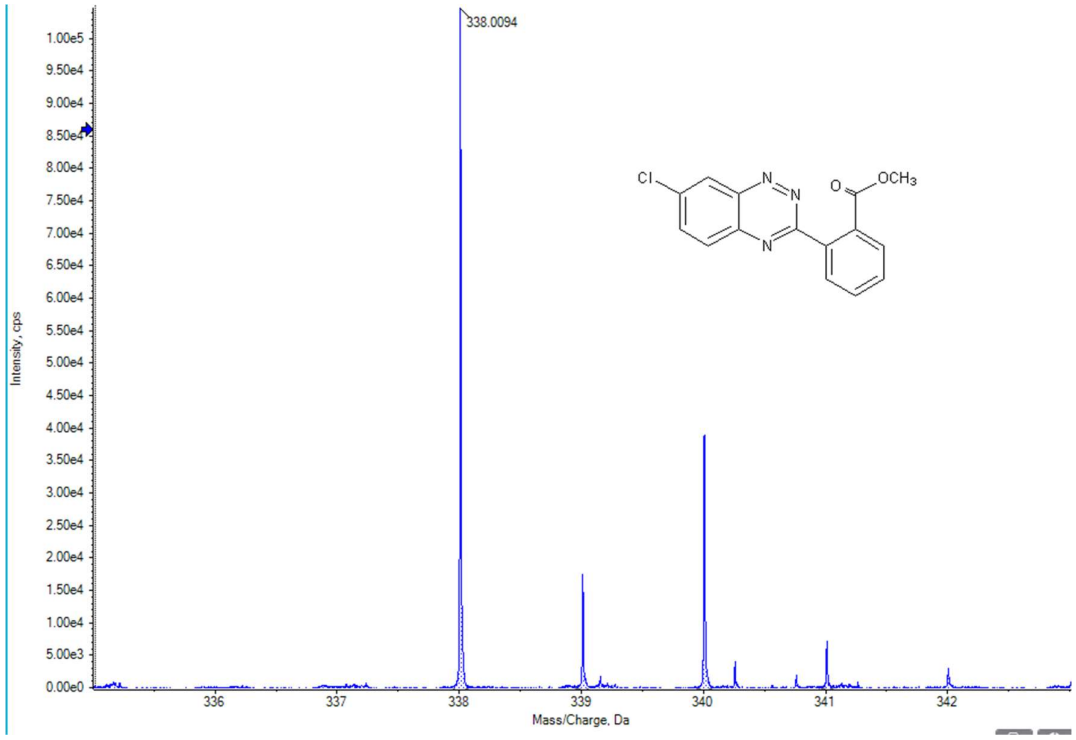

282.0872
Intensity, cps
Mass/Charge, Da
7.0e5
6.5e5
6.0e5
5.5e5
5.0e5
4.5e5
4.0e5
3.5e5
3.0e5
2.5e5
2.0e5
1.5e5
1.0e5
5.0e4
0.0e0
280
281
282
283
284
285
286
N
N
N
O
OH
H3CO

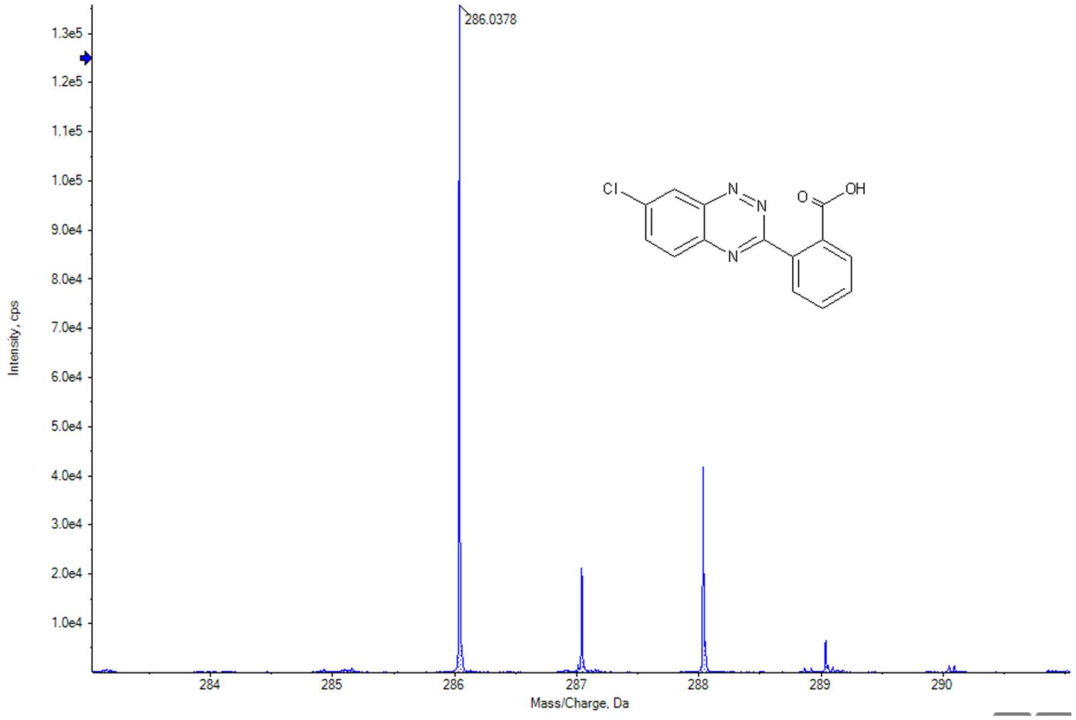

304.0694
Intensity, cps
Mass/Charge, Da
6.5e4
6.0e4
5.5e4
5.0e4
4.5e4
4.0e4
3.5e4
3.0e4
2.5e4
2.0e4
1.5e4
1.0e4
5.0e3
0.0e0
302
303
304
305
306
307
308
N
N
N
O
OH
H3CO

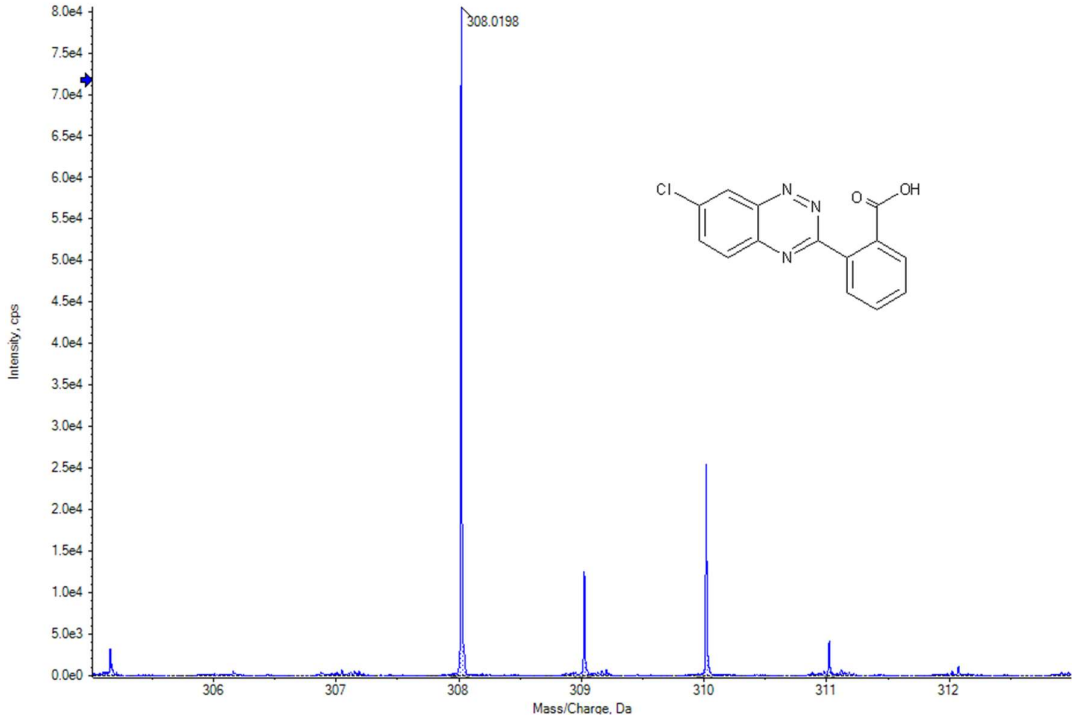

320.0400
Intensity, cps
Mass/Charge, Da
H3CO
OH
O
N
N
N

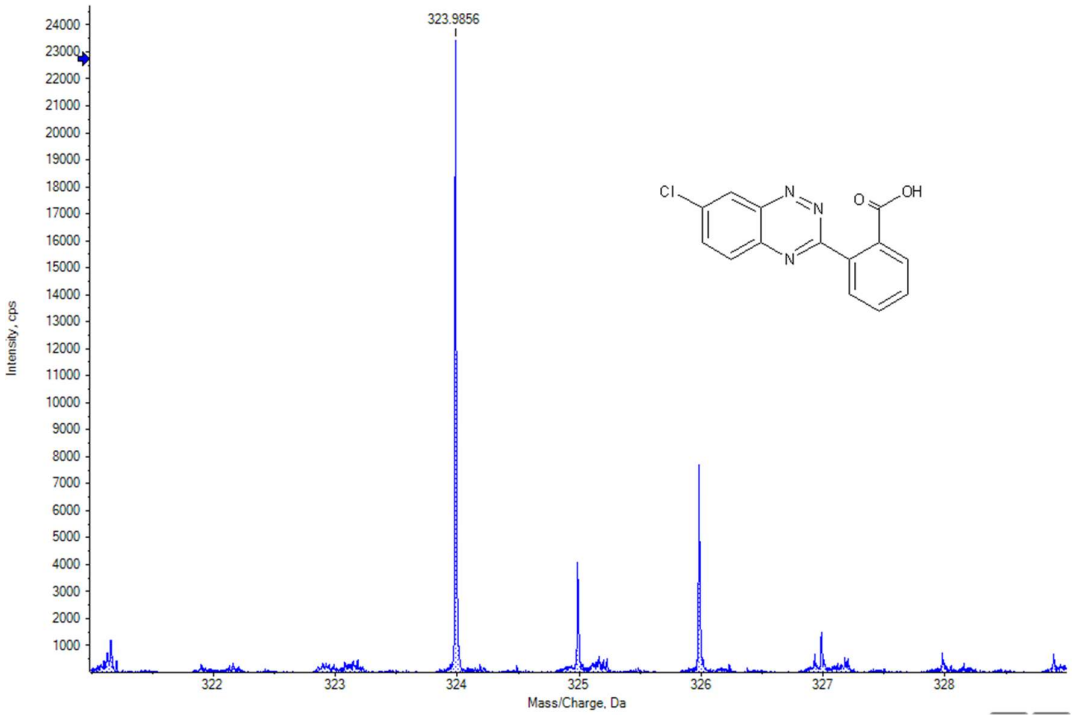

300.0534
Intensity, cps
Mass/Charge, Da
Cl
OCH3
O
N
N
N

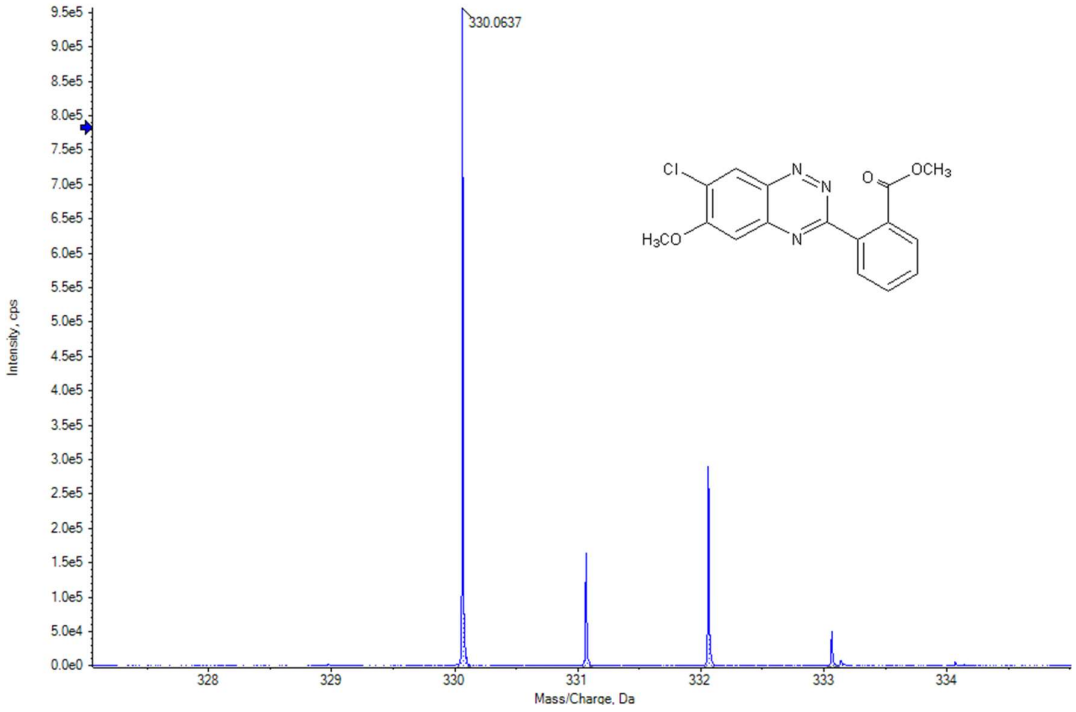

322.0351
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OCH3


338.0094
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OCH3

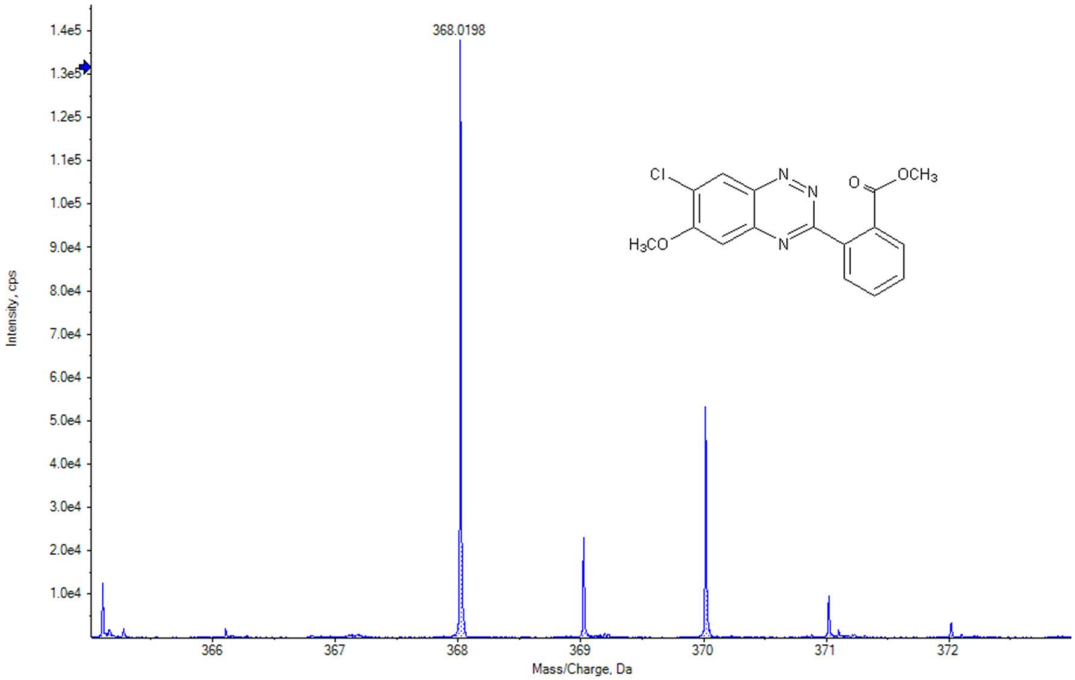

286.0378
Intensity, cps
1.3e5
1.2e5
1.1e5
1.0e5
9.0e4
8.0e4
7.0e4
6.0e4
5.0e4
4.0e4
3.0e4
2.0e4
1.0e4
284
285
286
287
288
289
290
Mass/Charge, Da
Cl
N
N
N
O
OH

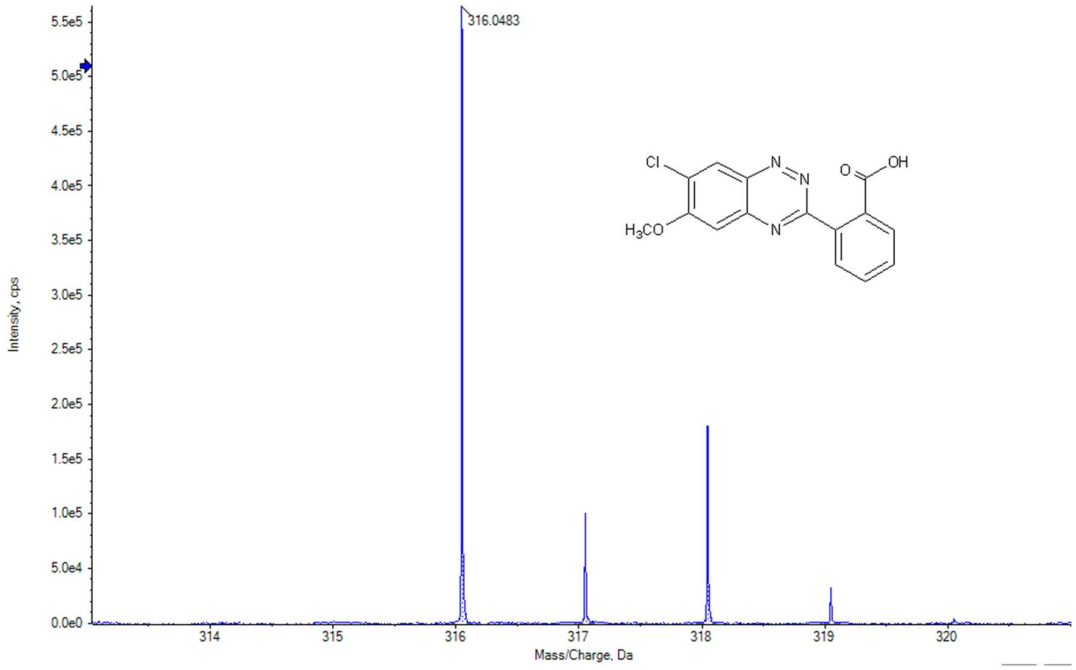

308.0198
Intensity, cps
8.0e4
7.5e4
7.0e4
6.5e4
6.0e4
5.5e4
5.0e4
4.5e4
4.0e4
3.5e4
3.0e4
2.5e4
2.0e4
1.5e4
1.0e4
5.0e3
0.0e0
306
307
308
309
310
311
312
Mass/Charge, Da
Cl
N
N
N
O
OH

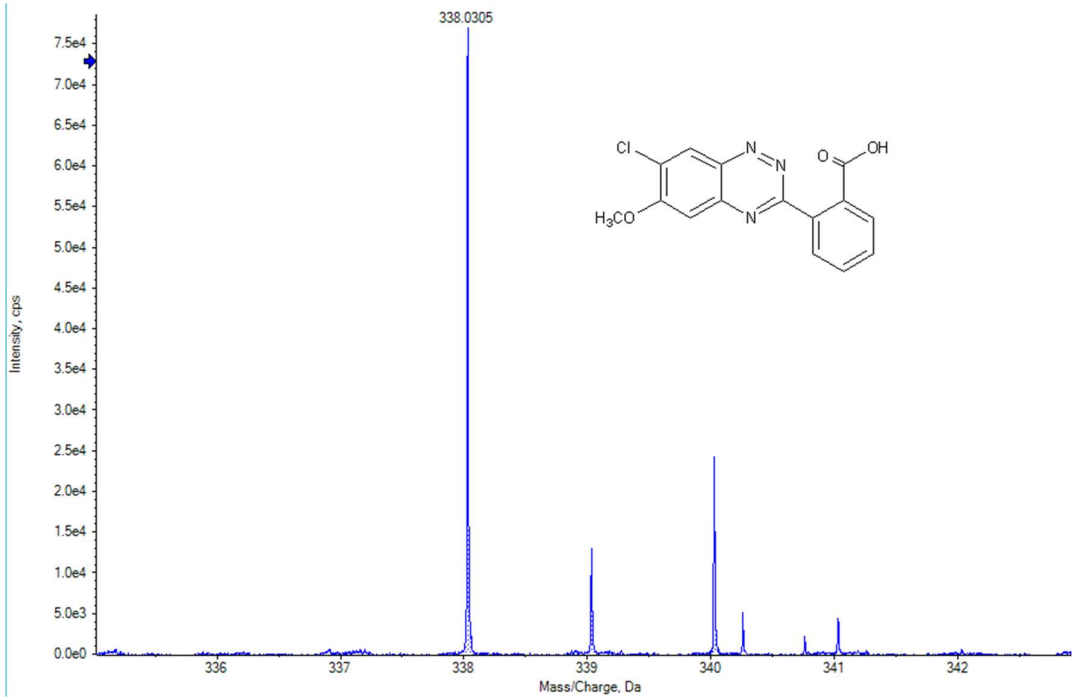

323.9856
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OH

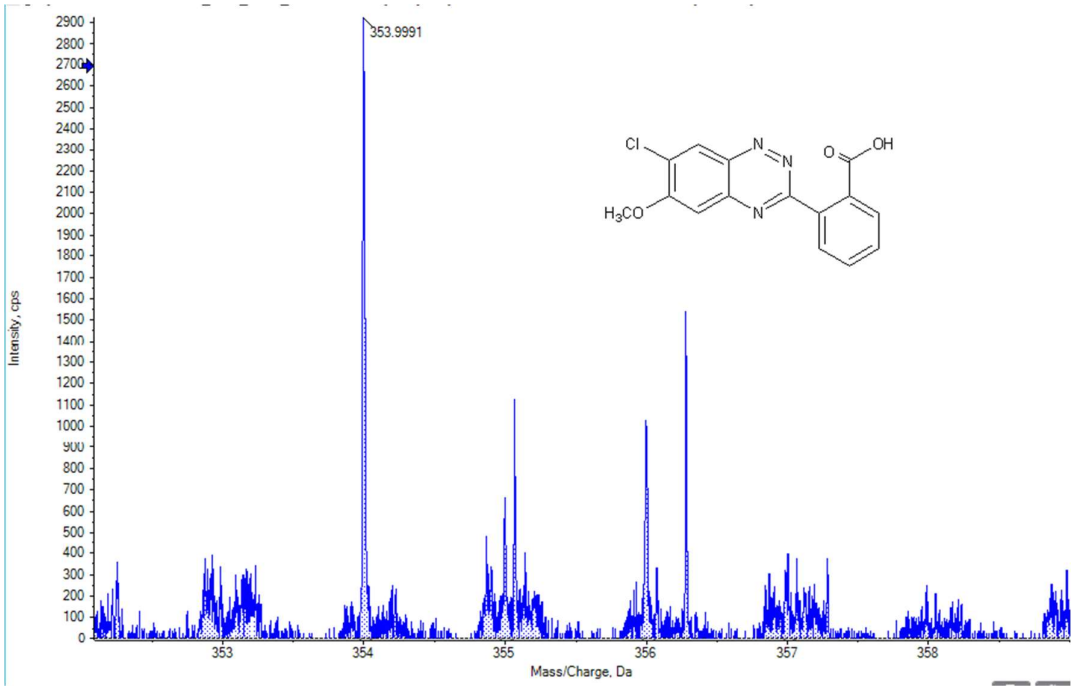

330.0637
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OCH3
H3CO

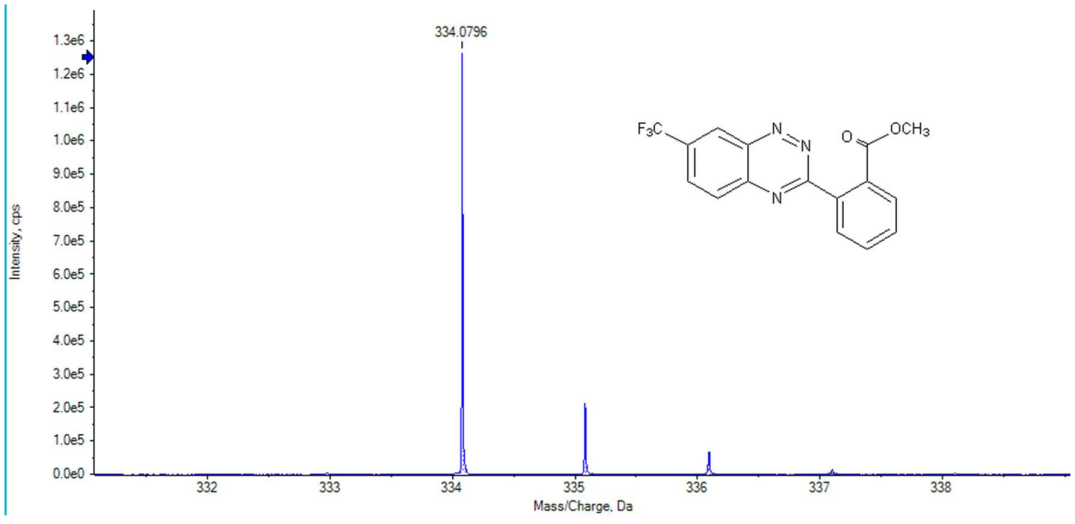

352.0459
Intensity, cps
Mass/Charge, Da
Cl
N
N
O
OCH3
H3CO
N


368.0198
Intensity, cps
Mass/Charge, Da
Cl
N
N
O
OCH3
H3CO
N

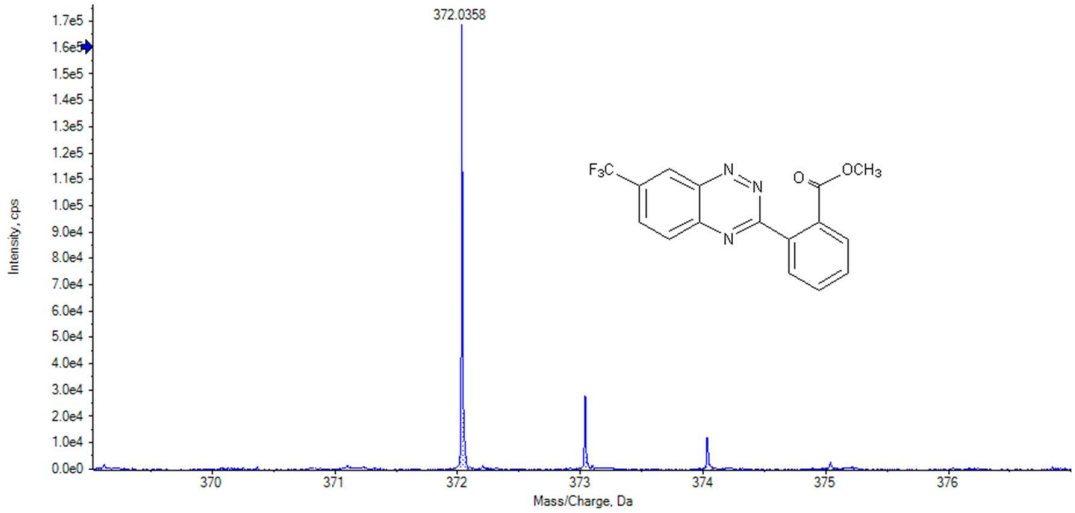

316.0483
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OH
H3CO

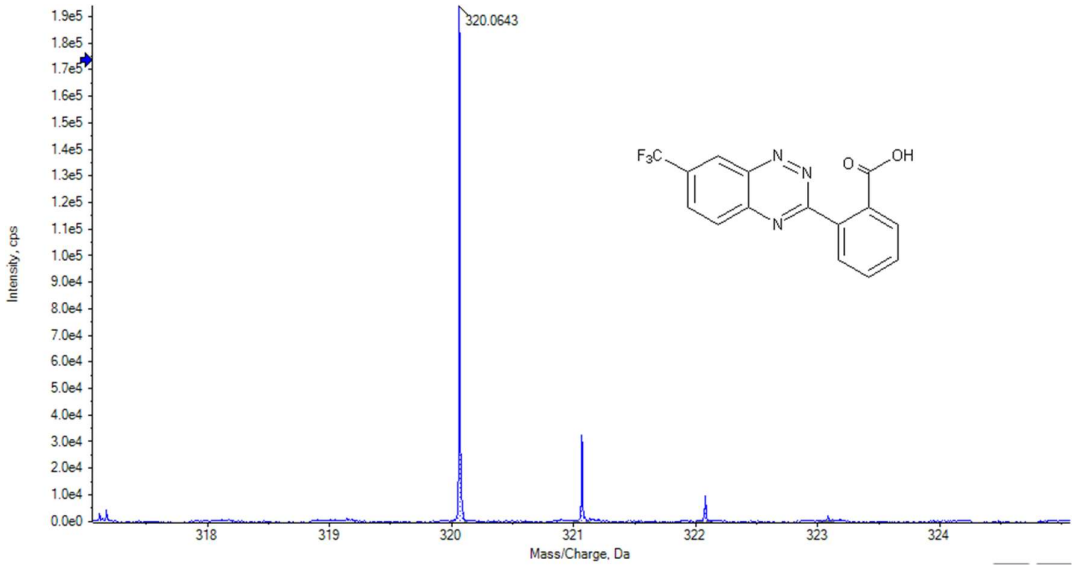

338.0305
Intensity, cps
Mass/Charge, Da
Cl
N
N
N
O
OH
H3CO

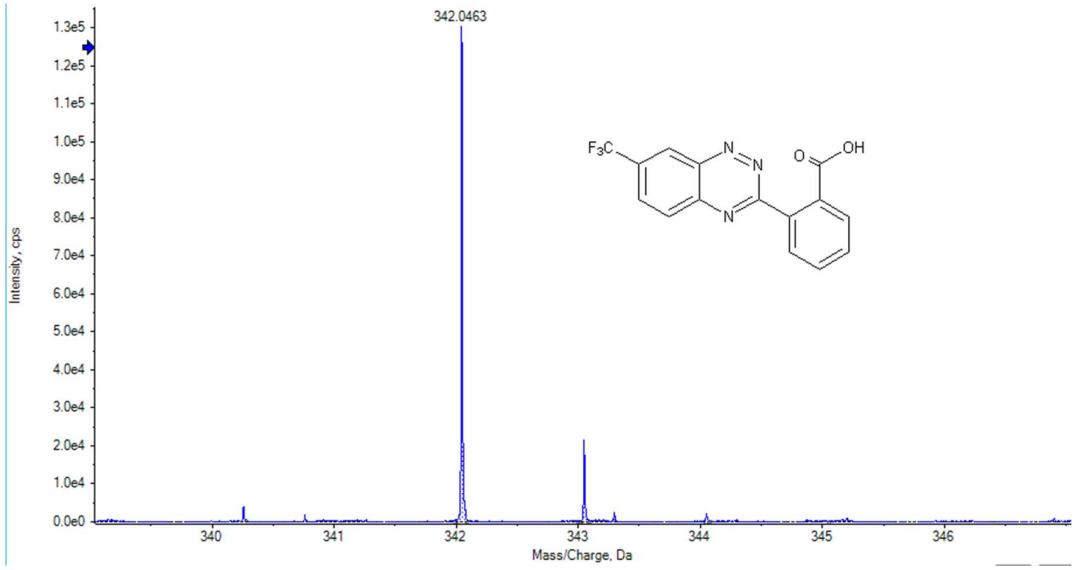

353.9991
Intensity, cps
Mass/Charge, Da
Cl
N
N
O
OH
H3CO
N

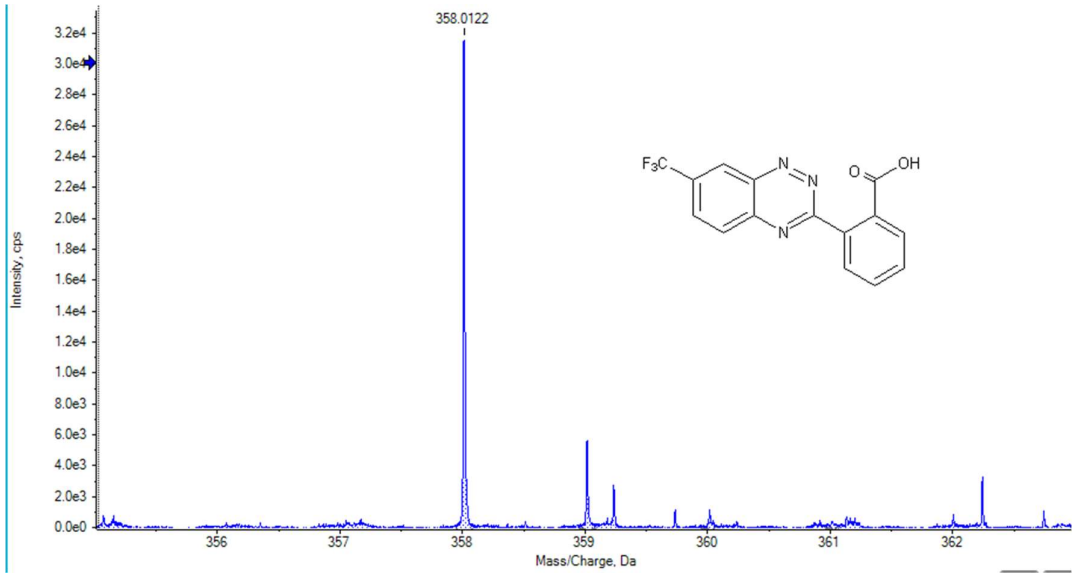

334.0796
Intensity, cps
Mass/Charge, Da
F3C
N
N
O
OCH3
N


356.0614
Intensity, cps
Mass/Charge, Da
F3C
OCH3
O
N
N
N

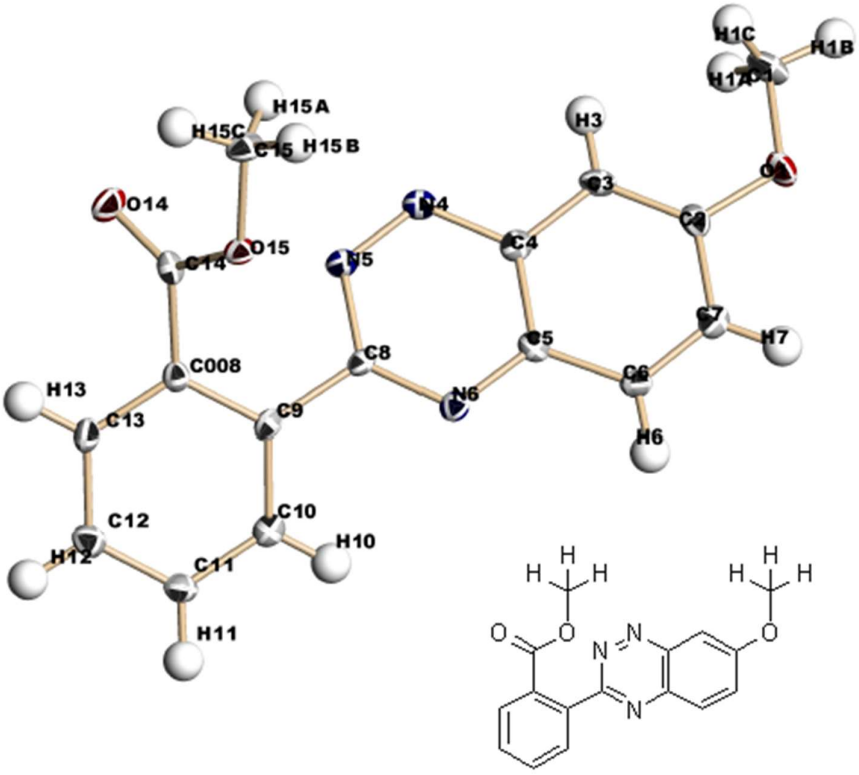

372.0358
Intensity, cps
Mass/Charge, Da
F3C
OCH3
O
N
N
N

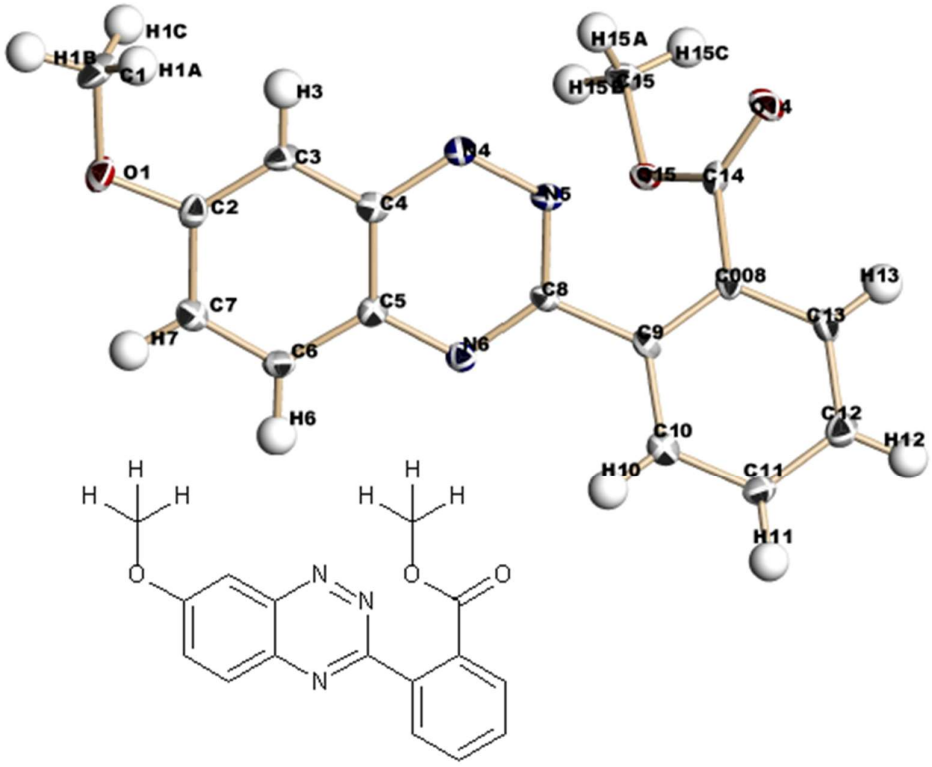

320.0643
Intensity, cps
Mass/Charge, Da
F3C
OH
O
N
N
N


342.0463
Intensity, cps
Mass/Charge, Da
F3C
N
N
N
O
OH


358.0122
Intensity, cps
Mass/Charge, Da
F3C
N
N
N
O
OH

APPENDIX E X-RAY CRYSTALLOGRAPHY OF 40D:




H1C
H1B
C1
H1A
H3
O1
C3
C2
C4
N4
N5
H15A
H15C
H15B
C15
O14
C14
C008
H13
C13
C7
C5
C8
C9
H7
C6
N6
H6
C12
C10
H12
H10
C11
H11
H
H
H
O
N
N
N
H
H
H
O
O

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