AURONE: DERIVATIZATION, REACTION METHODOLOGY DEVELOPMENT, AND ITS UTILIZATION AS A FLUOROPHORE FOR DEVELOPING A FLUOROGENIC PROBE FOR SENSING HYDROGEN SULFIDE

By

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I dedicate this research to my parents, Til Prasad Kafle and Dhan Kumari Kafle, and my son Aayush Kafle.

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ABSTRACT

Aurones, a sub-class of the flavonoids with proven therapeutic importance, also exist in variously glycosylated forms. Although a large number of glycosylated aurone derivatives have been isolated from plant sources, no syntheses have been reported yet. Inspired from this gap, here we report the first synthesis of peracetylated glycosyl derivatives of synthetic aurones. The direct *O*-glycosylation was achieved by reacting 6-hydroxy aurones with 2, 3, 4, 6-tetra-*O*-acetyl-*α*-D glucopyranosyl bromide in the presence of a phase transfer catalyst tetrabutylammonium bromide (TBAB). The successful synthesis of aurone glycosides (33 examples) in 60-92% yield will benefit the synthesis of combinatorial libraries of glycosylated aurones for their biological study and comparison with non-glycosylated aurones.

Similarly, in an attempt to prepare azido-substituted aurones via a copper-catalyzed azidation, the reaction failed to afford the desired product but instead resulted in an unusual triazole formation reaction. Further efforts noted that copper was not required for this reaction but simply thermal treatment with sodium azide in a polar aprotic solvent. A wide range of substitution patterns was tolerated in this reaction to afford the interesting salicyl-substituted triazoles in modest to excellent yield. While the mechanism is not yet clear, a simple elimination/cyclization pathway seems unlikely given the failure of the reaction on the corresponding thioaurones, which feature an even better thiol leaving group. Regardless, the potential utility of these easily accessible, multifunctional compounds should engender further interest and applications.

Besides derivatizing aurone scaffolds for combinatorial library synthesis and developing a reaction protocol for the synthesis of a unique and unexplored salicyl-substituted triazoles scaffold, we utilized the aurone scaffold to develop a fluorescent probe for hydrogen sulfide detection in biological as well as environmental situations. While many methods are currently available, the most sensitive and biologically applicable ones are fluorescent-based. In general, these fluorescent probes are based upon large, high-molecular-weight, and well-characterized fluorescent scaffolds that are synthetically demanding to prepare and difficult to tune and modify. We have developed a new system based upon a synthetically simple aurone scaffold that features good sensitivity, selectivity for hydrogen sulfide, and has potential for application in a variety of contexts.

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LIST OF ABBREVIATIONS AND SYMBOLS

ATP	Adenosine triphosphate
$BF_3.Et_2O$	Boron trifluoride diethyl etherate
CDK	Cyclin-dependent kinase
CTAB	Cetyl trimethylammonium bromide
DBU	Diazabicycloundecene
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
ESI	Electrospray ionization
HEPES	Hydroxyethyl piperazineethanesulfonic acid
HRMS	High-resolution mass spectrometry
MeCN	Acetonitrile
mM	Millimolar
nM	Nanomolar
NMR	Nuclear magnetic resonance
PBS	Phosphate buffer saline
PCT	Phase transfer catalyst
TBAB	Tetra-n-butylammonium bromide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TNFα	Tumor necrosis factor alpha

CHAPTER I

INTRODUCTION

1. Natural products

Natural products are a large and diverse groups of substances produced by living organisms, including plants, animals, bacteria, and fungi. Unlike primary metabolites (nucleic acids, amino acids, sugars, and fatty acids), which are the essential elements for the growth and development of living beings, secondary metabolites are non-essential compounds produced via primary metabolism.[1] With the emergence of chemical ecology, the majority of these enormous numbers (> 200,000) of structurally diverse natural products have been proven to be vital components for the regulation of interactions between the organisms.

Among the various roles of these natural products, they are well known for their unique pharmacological or biological activities, which has been the basis for modern drug discovery. They have been used to cure a wide spectrum of diseases from ancient times.[2] More than 80% of the drug molecules were either natural products or their synthetic analogs in the post-genomic era before the high-throughput screening technique was developed.[3] This dependency on the utilization of the natural products and their novel structure for drug discovery is still alive and crucial. For instance, over the last seven decades (1940-2014) 49% of the total small molecules approved for cancer-related

treatment were either natural products or their direct derivatives.[4] Besides medicinal purposes, the utility of natural products and their derivatives extends to food additives in the form of spices and herbs as well as antimicrobials and antioxidants. As a whole, natural products are in almost every facet of our lives. They are classified into various types, including alkaloids, terpenoids, and flavonoids. Among them, flavonoids have significant importance in terms of their therapeutic as well as coloring properties.

2. Flavonoids

Flavonoids are low molecular weight phenolic natural products distributed in the plant kingdom especially in higher plants.[5, 6] Besides their primary function of imparting colors to flowers and fruits they are reported for defense against pathogen invasion, photoprotection from UV radiation, attract insects for pollination, growth, and development of seedlings, and interact with soil microbes.[7-9] Additionally, they also function as a signaling molecule for various receptors including purinergic receptors (P_2X and P_2Y).[10]

Structurally, flavonoids contain the C6-C3-C6 framework, commonly referred to as phenylbenzopyran. Based on the abundance in nature, they are broadly divided into major and minor flavonoids. Major flavonoids are widely distributed in nature. Depending on the position of the attachment of the phenyl ring to the benzopyrano moiety, major flavonoids are further classified into flavonoids (2-phenylbenzopyrans), isoflavonoids (3-phenylbenzopyrans), and neoflavonoids (4-phenylbenzopyrans). The further classification with corresponding examples is shown below (Figure 1).

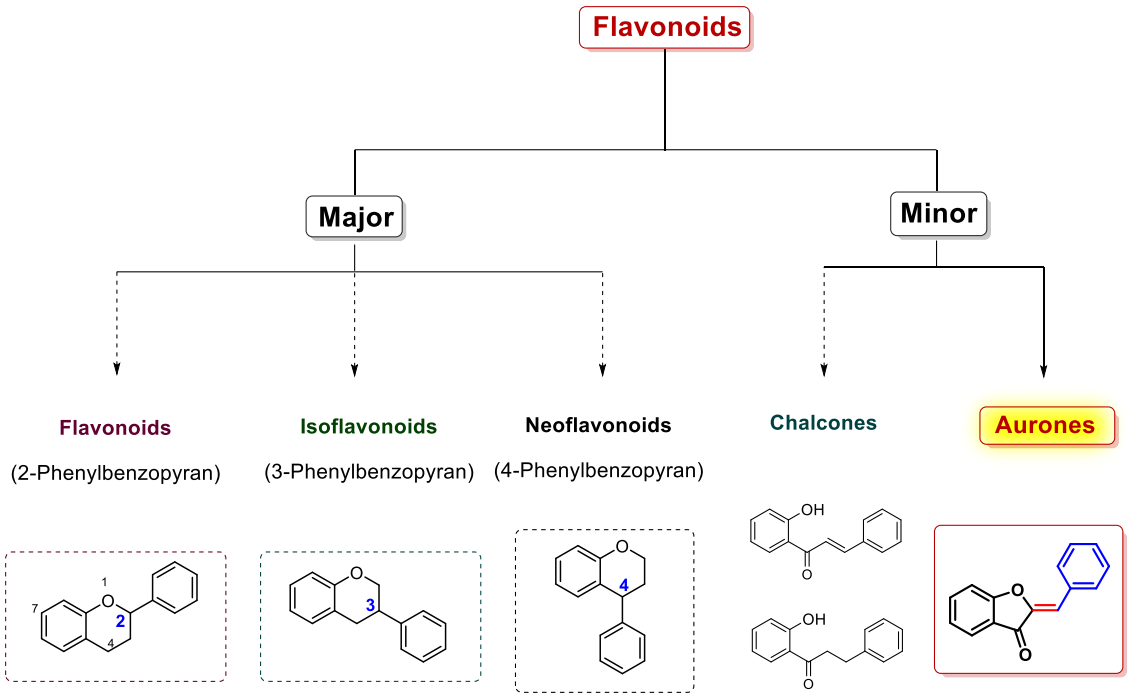


Figure 1: Classification of Flavonoids

Flavonoids, especially the major flavonoids, have been well explored and studied for their broad range of biological activities. Apart from the well-known antioxidative property, they have exhibited anticancer, anti-inflammatory, and antimicrobial activities. [11] Unlike major flavonoids, minor flavonoid chalcones and aurones, have very limited abundance in nature. This group of compounds includes 2′-hydroxychalcones, dihydro-(2′-hydroxy)chalcones, 2′-hydroxy-*retro*-chalcone, aurones (2-benzylidenecoumaranone), and auronols (Figure 2). We are particularly interested in the minor flavonoid Aurone family.

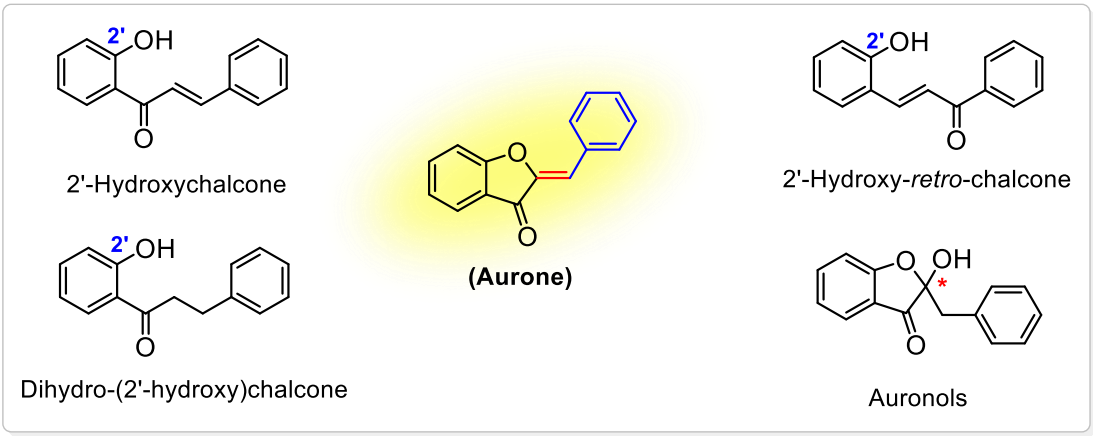


Figure 2: Minor Flavonoids

2.1. Aurones

Aurones are tricyclic structural isomers of well-known flavonoids. They are primarily responsible for imparting bright yellow color to flowers, such as for snapdragon and cosmos.[9, 12] Structurally, aurones contain a benzofuranone ring connected to a phenyl ring by an exocyclic carbon-carbon double bond forming a stable (Z) isomer (Figure 3).[13-16]

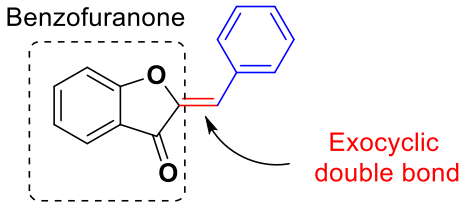


Figure 3: Structure of Aurone

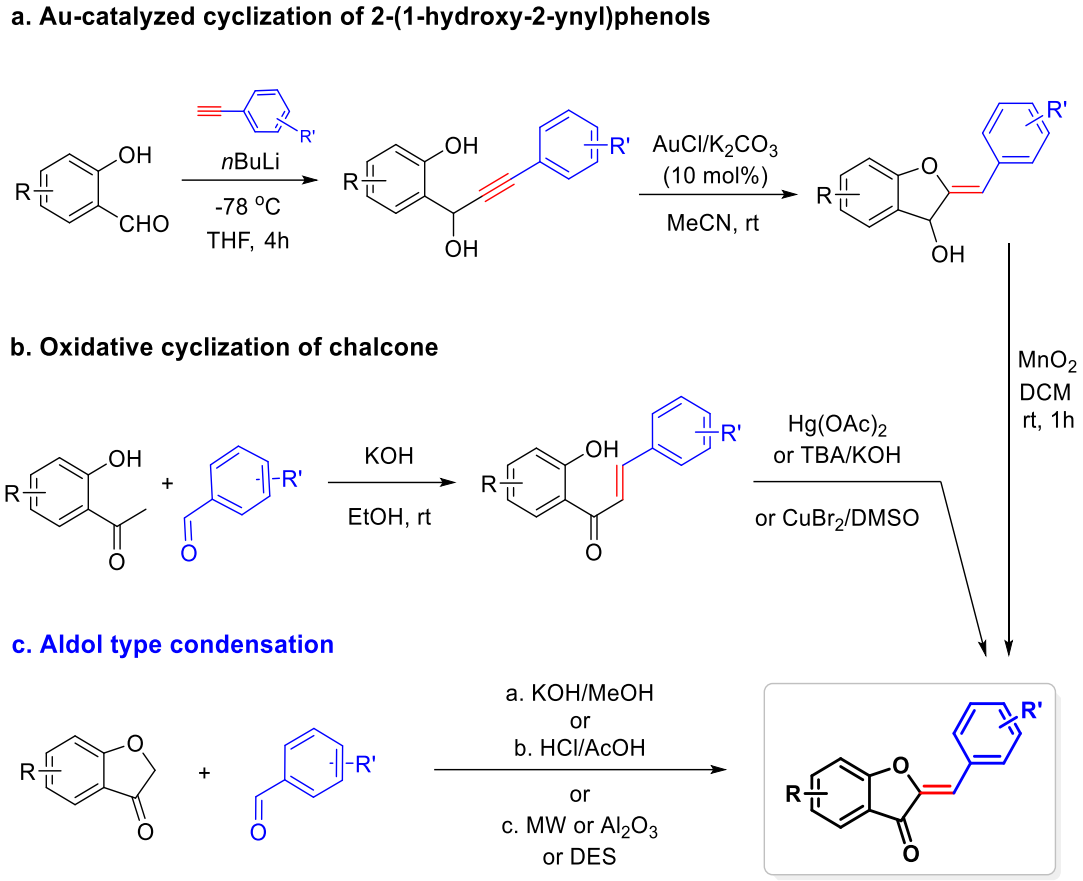
Although chalcones are known for various biological activities, their fate of undergoing easy cyclization to flavones makes them less advantageous over comparatively

stable aurones.[17] Despite their limited presence in nature, aurones have gained remarkable attention in the field of drug discovery. Inspired by their wide range of biological properties including antimicrobial, antimalarial, anti-inflammatory, and antioxidant properties, several semi-synthetic and synthetic aurone analogs have been explored in the last two decades which has further widened the therapeutic utility of the aurone scaffold.[18-27]

There are three general methods employed for the synthesis of aurones. (Scheme 1) The first strategy reported in 2008 incorporates a convenient three-step synthesis of aurones via gold-catalyzed cyclization of 2-(1-hydroxy-2-ynyl)phenols obtained by alkynylation of ortho salicylaldehyde.[28] (Scheme 1a) The next one mimics the biosynthetic route by involving oxidative cyclization of previously synthesized 2′-hydroxychalcones under various conditions.[29-33] (Scheme 1b) The most popular and versatile method for the aurone synthesis is an aldol type condensation of a benzofuranone with an aromatic aldehyde.[26, 34-39] (Scheme 1c) This strategy can be performed under acidic, basic, neutral, as well as solvent-free microwave conditions, although accommodation of certain labile functional groups under acidic and basic conditions can be limited.[34, 39, 40] In such cases, neutral-alumina mediated method and a reaction employing a deep eutectic solvent are useful strategies.[38, 41]

The alumina-mediated condensation method is limited in the case of hydroxylated aurone synthesis because of the decrease in the catalytic activity of alumina due to the possible interaction of alumina with the free hydroxyl group in the benzofuranone ring. An acidic condensation of hydroxy benzofuranone with an aldehyde in glacial acetic acid in the presence of few drops of concentrated hydrochloric is preferred in such cases (Scheme

1c).[39] Easy commercial availability of various benzofuranones has further increased the relevancy of this condensation method for the synthesis of variously substituted aurones.



Scheme 1: Synthesis of Aurones

There has been a continuous effort, particularly from academia, in the synthesis of structurally diverse combinatorial aurone libraries in search of hits against both metabolic and infective diseases. Various *in vitro* and *in vivo* studies have revealed a useful inhibitory role of aurones in several situations, including enzyme or protein specific interactions with topoisomerase, cyclin-dependent kinase (CDK), tubulin polymerization, ATP-binding

cassette, and tumor necrosis factor-alpha (TNFα). [10, 14, 42-46] This clearly shows their therapeutic efficacy in the cancer area.

At the same time, aurones have been noticed for their probing potential. In a study of aurones as possible small-molecule fluorescent probes, Shanker *et al*. explored both, UV-Vis absorption as well as fluorescence characteristics of a series of aurones.[47] As expected, they found that the presence of an amino group, especially at 4′-position of B ring, imparts a significant red-shift to the absorption maxima (Figure 4). They were also able to show the preferential binding of molecules **3** and **4** to protein and DNA, revealing their probing potential.

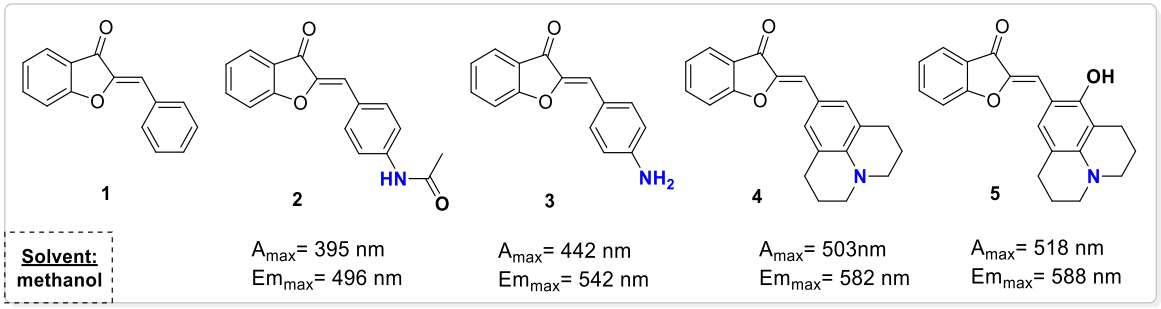


Figure 4: Absorption and Emission Maxima of Aurones in Methanol.

Based on these facts, we envisioned aurones as a tunable fluorophore for the development of azide reduction-based fluorescent probes for the detection of hydrogen sulfide (H_2S) in living systems. This dissertation incorporates the three publications that employed aurone scaffolds for library synthesis, new methodology development, and design and synthesis of a fluorogenic probe for the detection of a biological and

environmental analyte H_2S as represented in Figure 5. More detailed background information is provided in each chapter.

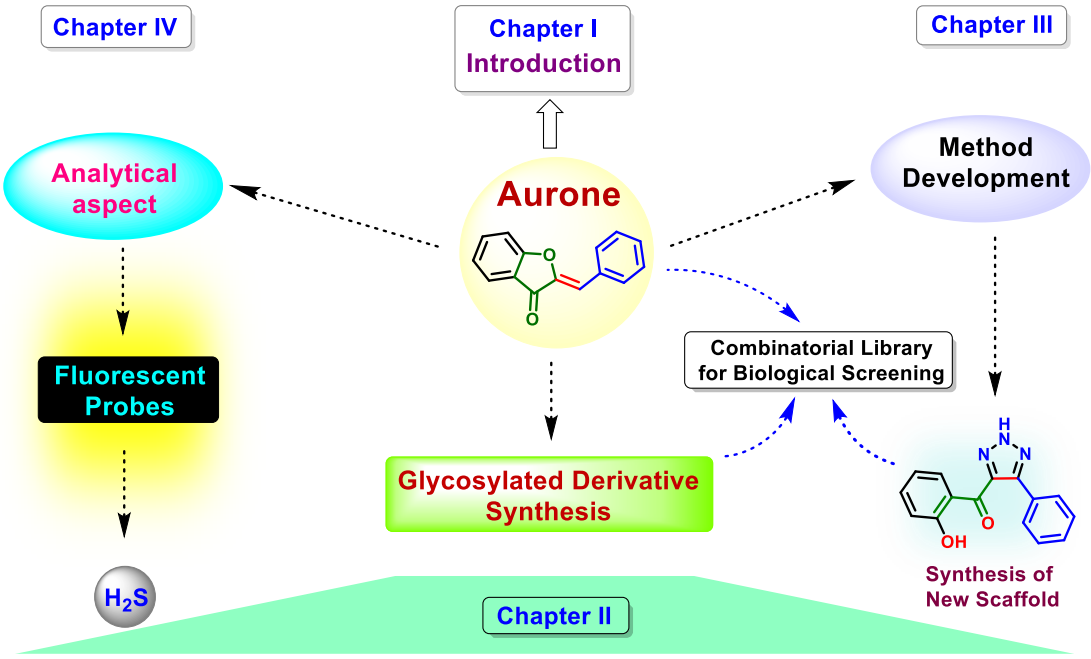
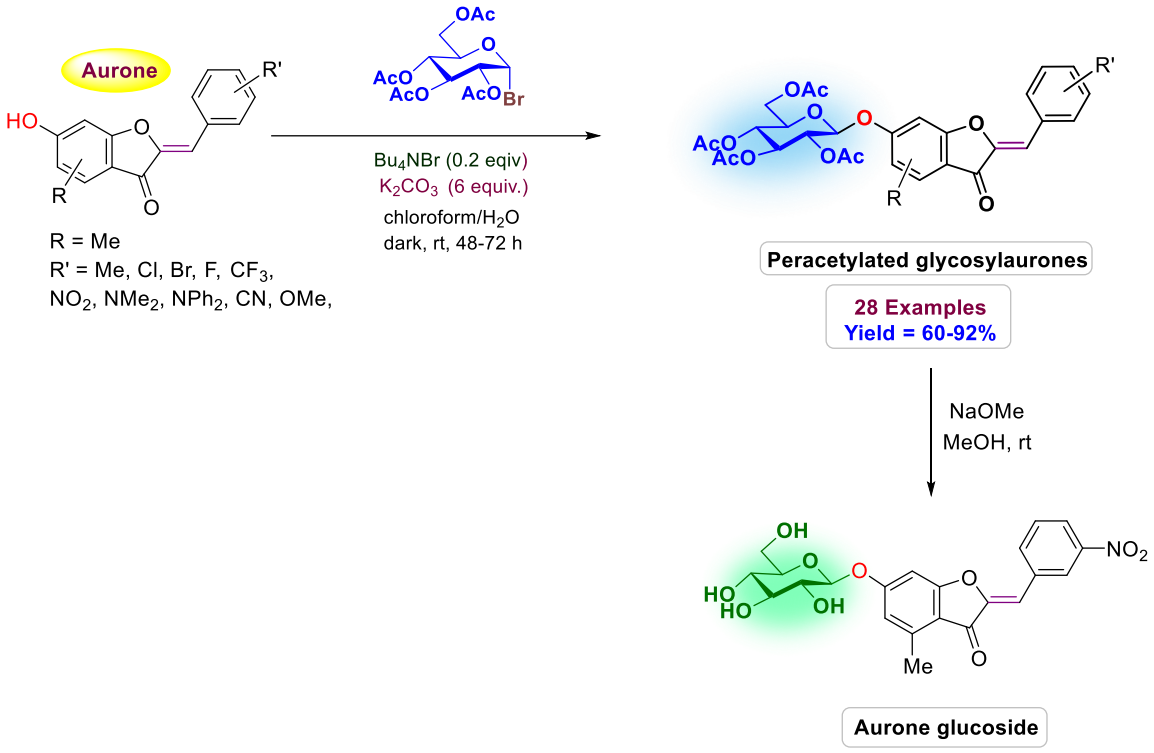


Figure 5: Graphical Representation of Dissertation

Chapter II describes the first synthesis of aurone glycosides. Among various derivatives, glycosides are one of the interesting categories to study in terms of biological activities. As evident from many glycosylated drug molecules, including antibiotics vancomycin, gentamycin, and streptomycin, glycosylation has been reported to improve the activity as well as pharmacokinetics parameters of the molecules.[48] Although numerous glycosylated aurones have been isolated from plant sources, their non-enzymatic synthesis has not been reported yet. This chapter discusses the first synthesis of peracetylated

glucosyl derivatives of synthetic aurones, which is published in *Tetrahedron* **2020**, *76*, 131525. (Scheme 2)

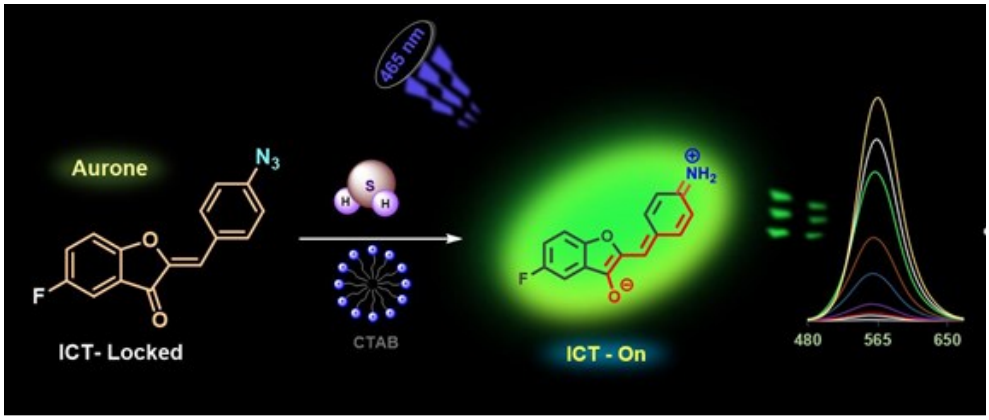


Scheme 2: Graphical Abstract for Chapter II

Chapter III details how an effort on direct functionalization of halogen-containing aurones with an azido group surprisingly led to an unusual synthesis of triazole scaffold.[44] This work has been published in *Synthesis* 2020, ***52***, 2337-2346. This simple and easy metal-free reaction protocol exhibited a wide range of substitution pattern tolerance in affording the interesting salicyl-substituted triazoles in modest to excellent yield in a short time (~ 30 minutes). (Scheme 3)

Scheme 3: Graphical Abstract for Chapter III

Despite the known coloring property of aurones, typically the aminoaurones, they have been hardly studied and utilized as a fluorophore scaffold. Chapter IV discusses how we rationally designed and synthesized a turn-on fluorogenic probes using an aurone scaffold as a fluorophore for the selective detection of hydrogen sulfide. (Scheme 4) The findings of this research are published in *RSC Advances* 2020, ***10***, 45180-45188.



Scheme 4: Graphical Abstract for Chapter IV

3. References

1. Springob, K.; Kutchan, T. M. Introduction to the Different Classes of Natural Products. In *Plant-derived Natural Products;* Osbourn, A. E., Lanzotti, V. Ed.; Springer Science: New York, 2009; pp 3-50.
2. Harvey, A. L. *Drug Discov. Today* **2008,** *13*, 894-901.
3. Sneader, W. *Drug Prototypes and Their Exploitation*, 1st ed.; John Wiley and Sons, Chichester, 1996; p 800.
4. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016,** *79* , 629-661.
5. Martens, S.; Mithofer, A. *Phytochemistry* **2005,** *66*, 2399-2407.
6. Boucherle, B.; Peuchmaur, M.; Boumendjel, A.; Haudecoeur, R. *Phytochemistry* **2017,** *142*, 92-111.
7. Spaink, H. P. *Annu. Rev. Phytopathol.* **1995,** *33*, 345-368.
8. Koes, R. E.; Quattrocchio, F.; Mol, J. N. M. *BioEssays,* **1994,** *16*, 123-132.
9. Ono, E.; Fukuchi-Mizutani, M.; Nakamura, N.; Fukui, Y.; Yonekura-Sakakibara, K.; Yamaguchi, M.; Nakayama, T.; Tanaka, T.; Kusumi, T.; Tanaka, Y. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** *103*, 11075-11080.
10. Jacobson, K. A.; Moro, S.; Manthey, J. A.; West, P. L.; Ji, X. D. Interactions of Flavones and Other Phytochemicals with Adenosine Receptors. In *Flavonoids in Cell Function.* Buslig, B. S.; Manthey, J. A. Ed.; Springer: Boston, **2002**; pp 163-171.
11. Panche, A. N.; Diwan, A. D.; Chandra, S. R. *J. Nutr. Sci.* **2016,** *5*, E47.
12. Nakayama, T.; Yonekura-Sakakibara, K.; Sato, T.; Kikuchi, S.; Fukui, Y.; Fukuchi-Mizutani, M.; Ueda, T.; Nakao, M.; Tanaka, Y.; Kusumi, T.; Nishino, T. *Science* **2000,** *290*, 1163-1166.
13. Haudecoeur, R.; Boumendjel, A. *Curr. Med. Chem.* **2012,** *19*, 2861-2875.
14. Boumendjel, A. *Curr. Med. Chem.* **2003,** *10*, 2621-2630.
15. Atta Ur, R.; Choudhary, M. I.; Hayat, S.; Khan, A. M.; Ahmed, A. *Chem. Pharm. Bull.* **2001,** *49*, 105-107.

16. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985,** *107*, 3902-3909.
17. Alsayari, A.; Muhsinah, A. B.; Hassan, M. Z.; Ahsan, M. J.; Alshehri, J. A.; Begum, N. *Eur. J. Med. Chem.* **2019,** *166*, 417-431.
18. Bandgar, B. R.; Patil, S. A.; Korbad, B. L.; Biradar, S. C.; Nile, S. N.; Khobragade, C. N. *Eur. J. Med. Chem.* **2010,** *45*, 3223-3227.
19. Thomas, M. G.; Lawson, C.; Allanson, N. M.; Leslie, B. W.; Bottomley, J. R.; McBride, A.; Olusanya, O. A. *Bioorg. Med. Chem. Lett.* **2003,** *13*, 423-426.
20. Hadj-Esfandiari, N.; Navidpour, L.; Shadnia, H.; Amini, M.; Samadi, N.; Faramarzi, M. A.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 6354-6363.
21. Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlotsky, J. M.; Boumendjel, A. *J. Med. Chem.* **2011,** *54*, 5395-5402.
22. Shin, S. Y.; Shin, M. C.; Shin, J. S.; Lee, K. T.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 4520-4523.
23. Venkateswarlu, S.; Panchagnula, G. K.; Gottumukkala, A. L.; Subbaraju, G. V., *Tetrahedron* **2007,** *63*, 6909-6914.
24. Detsi, A.; Majdalani, M.; Kontogiorgis, C. A.; Hadjipavlou-Litina, D.; Kefalas, P. *Bioorg. Med. Chem.* **2009,** *17*, 8073-8085.
25. Cheng, H. M.; Zhang, L. W.; Liu, Y. X.; Chen, S. P.; Cheng, H.; Lu, X.; Zheng, Z. X.; Zhou, G. C. *Eur. J. Med. Chem.* **2010,** *45*, 5950-5957.
26. Sim, H. M.; Lee, C. Y.; Ee, P. L. R.; Go, M. L. *Eur. J. Pharm. Sci.* **2008,** *35*, 293-306.
27. Sim, H. M.; Loh, K. Y.; Yeo, W. K.; Lee, C. Y.; Go, M. L. *ChemMedChem.* **2011,** *6*, 713-724.
28. Harkat, H.; Blanc, A.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2008,** *73*, 1620-1623.
29. Sekizaki, H. *Bull. Chem. Soc. Jpn.* **1988,** *61*, 1407-1409.
30. Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001,** *42*, 8907-8909.
31. Thakkar, K.; Cushman, M. *Tetrahedron Lett.* **1994,** *35*, 6441-6444.

32. Thakkar, K.; Cushman, M. *J. Org. Chem.,* **1995,** *60*, 6499-6510.
33. Agrawal, N. N.; Soni, P. A. *Indian J. Chem.* **2006,** *45B*, 1301-1303.
34. Okombi, S.; Rival, D.; Bonnet, S.; Mariotte, A. M.; Perrier, E.; Boumendjel, A. *J. Med. Chem.,* **2006,** *49*, 329-333.
35. Morimoto, M.; Fukumoto, H.; Nozoe, T.; Hagiwara, A.; Komai, K. *J. Agric. Food Chem.* **2007,** *55*, 700-705.
36. Sheng, R.; Xu, Y.; Hu, C. Q.; Zhang, J.; Lin, X.; Li, J. Y.; Yang, B.; He, Q. J.; Hu, Y. Z. *Eur. J. Med. Chem.* **2009,** *44*, 7-17.
37. Hadjeri, M.; Beney, C.; Boumendjel, A. *Curr. Org. Chem.* **2003,** *7*, 679-689.
38. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992,** *33*, 5937-5940.
39. Geissman, A. T.; Harborne, J. B. *J. Am. Chem. Soc.* **1955,** *77*, 4622-4624.
40. Villemin, D.; Martin, B.; Bar, N. *Molecules* **1998,** *3*, 88-93.
41. Hawkins, I.; Handy, S. T. *Tetrahedron* **2013,** *69*, 9200-9204.
42. Choi, S.U.; Ryu, S.Y.; Yoon, S.K.; Jung, N.P.; Park, S.H.; Kim, K.H.; Choi, E.J.; Lee, C.O. *Anticancer Res.*, **1999**, *19*, 5229-5533.
43. Park, H.S; Nelson, D.E.; Taylor, Z.E.; Hayes, J.B.; Cunningham, K.D.; Arivett, B.A.; Ghosh, R. Wolf, L.C.; Taylor, K.M.; Farone, M.B.; Handy, S.T.; Farone, A.L. *Int. Immunopharm.* **2017**, *43*, 116-128.
44. Lawrence, N.J.; Rennison, D.; McGown, A.T.; Hadfield, J.A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3759-3763.
45. Schoepfer, J.; Fretz, H.; Chaudhari, B.; Muller, L.; Seeber, E.; Meijer, L.; Lozach, O.; Vangrevelinghe, E.; Furet, P. *J. Med. Chem.* **2002**, *45*, 1741-1747.
46. Sui, G.; Li, T.; Zhang, B.; Wang, R.; Hao, H.; Zhou, W. *Bioorg. Med. Chem.* **2021**, *29*, 115895.
47. Shanker, N.; Dilek, O.; Mukherjee, K.; McGee, D. W.; Bane, S. L. *J. Fluoresc.* **2011,** *21*, 2173-2184.
48. Kren, V.; Martinkova, L. *Curr. Med. Chem.* **2001,** *8*, 1303-1328.

CHAPTER - II

THE FIRST SYNTHESIS OF PERACETYL GLYCOSYL AURONE DERIVATIVES AND AURONE GLUCOSIDES

1. Introduction

Aurones, a minor sub-class of flavonoid family, are naturally occurring pigments. They are primarily responsible for imparting bright yellow color to flowers and fruits.[1] Mainly found in eudicots and advanced monocots such as *Cyperaceae*, aurones are one of the less explored sub-families of the flavonoids.[2, 3] Besides their primary role in plants, as a secondary metabolite, they are found to exhibit several useful biological activities against both metabolic and infective diseases. Both natural, as well as synthetic analogs, are reported to possess a broad spectrum of bioactivity, including antimicrobial, antiviral, anti-inflammatory, antioxidant, and anticancer properties.[4-8] As a result, they are emerging as a potential therapeutic heterocyclic scaffold for the design and development of pharmaceuticals.

Unlike other flavonoids, aurones contain a benzofuranone ring connected to a phenyl ring by an exocyclic double bond-forming the thermodynamically more stable (Z) isomer.[4, 5, 9] Despite their limited skeletal variation, aurones are found to maintain their structural diversity through different substitution patterns, mostly hydroxylation, methoxylation, and glycosylation.[2] At the same time, the development of a significant

number of synthetic strategies has tremendously contributed to structural diversification of the aurone scaffold, providing access to various different types of aurone derivatives for application in drug discovery.[8, 10-14]

Aurones are biosynthesized in plants via oxidative cyclization followed by rearrangement of, typically, 2′ and 4′-hydroxylated chalcones in the presence of *aureusidin synthase*. During this process, a chalcone is glycosylated in the cytoplasm, which eventually converts into an aurone-glucoside. [15, 16] Although various types of glycosylated aurone derivatives have been isolated from plant sources (Figure 6)[2], they lack variation in the substitution pattern, and there is only a single report of their synthesis. This paper by Tronina used an enzymatic reaction catalyzed by fungal strains to prepare two glycosylated aurones in modest yield with reaction times of several days.[17]

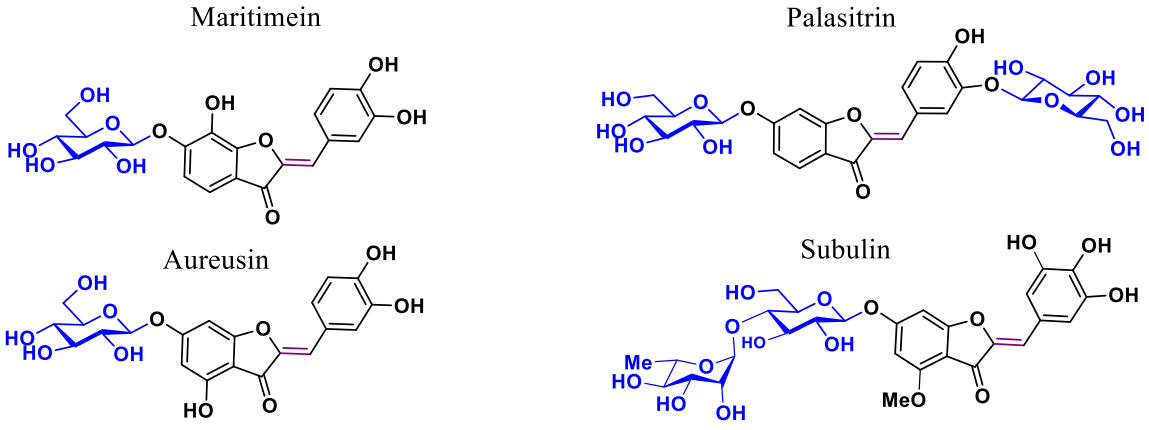


Figure 6: Structures of Some Aurone Glucoside Derivatives Found in Various Plants

Given the general importance of carbohydrate moieties in biological activity, recognition, and transport, the ability to readily access glycosylated aurones via a direct

and simple method would be of considerable value. Among N-, O-, and C-glycosylations, O-glycosylation is very common in nature, which involves an attachment of carbohydrate with another molecule. The formation of a glycosidic bond usually takes place in the presence of a promotor by nucleophilic substitution of a leaving group at the anomeric carbon of a glycosyl donor. Different direct activation-based O-glycosylation methods, as summarized in Figure 7, have been developed based on the types of glycosyl donors and promotors employed in the reaction.[18, 19]

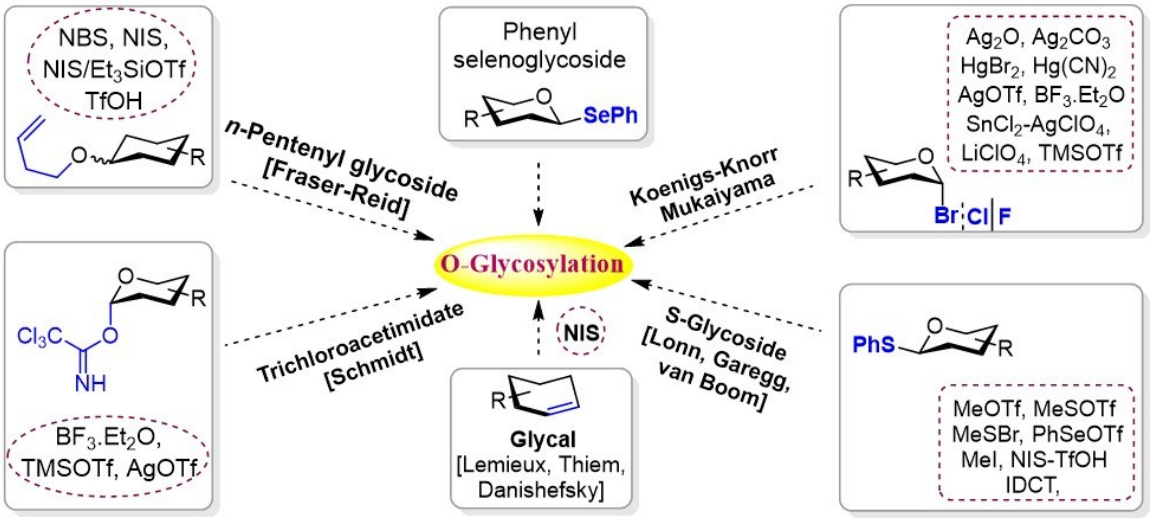


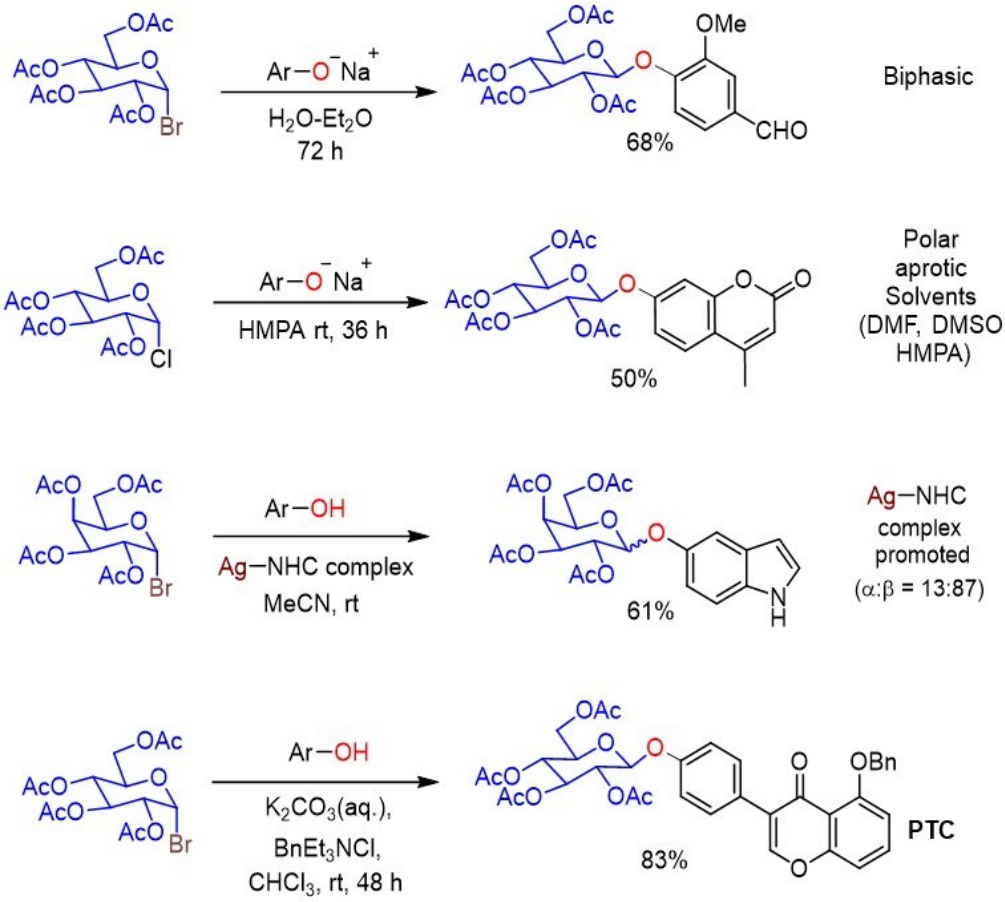
Figure 7: Methods of O-glycosylation

Glycosylation itself is challenging in that even a subtle change in electronic and/or steric factors often requires extensive optimization of the reaction conditions.[18e] The Lewis acid promoted methods (Figure 7), including the Fischer glycosylation, were developed mostly for alcohols and, more typically, for oligosaccharide synthesis. In comparison, the glycosylation of less nucleophilic phenols has received relatively little attention. [19, 20]

An electron-deficient phenol, such as those found in aurones, is even more challenging, and in reported examples typically requires acidic conditions employing glycosyl anomeric acetate and chloroacetimidate donors in the presence of the Lewis acid $BF_3.Et_2O$, which in most cases generates side reactions. [19, 20] In contrast, the basic medium proves to be advantageous, particularly for phenols as it cut off the side reactions triggered by the Lewis acid promotors. Alongside, generation of more stable and less basic phenolate ion in the basic medium greatly discourage 1, 2-elimination in donor molecule as well as drive the reaction via S_N2 pathway providing better stereochemical control of the product.[19]

In this context, the Michael protocol developed back in 1879, is one of the effective and most utilized methods for O-glycosylation of phenols.[21] Among various synthetic protocols that include the use of various types of glycosyl donors such as acetate, esters, trichloroacetimidates, and thioglycosides, Michael type protocols utilize glycosyl halides.[20] Glycosyl bromides, particularly the thermodynamically favored α-anomers, have been the frontrunner as they are more reactive than the chlorides and relatively more stable than the iodides. Influenced by their anomeric stereochemistry, the O-glycosylation generally results in *β*-glycosidic linkage irrespective of the solvent effect.[19, 20]

This method has evolved with variations in the types of solvent and catalysts employed (Scheme 5).[22] Particularly, the use of quaternary ammonium salts as a phase transfer catalyst (PTC) in a biphasic reaction condition has received significant attention for aromatic O-glycosylation. Tetrabutylammonium bromide (TBAB) is one of the most commonly employed PTC among other quaternary salts, particularly with glycosyl bromide donors. It helps to transport the water-soluble anionic reactants, in this case the aurone phenolate, into the organic phase.

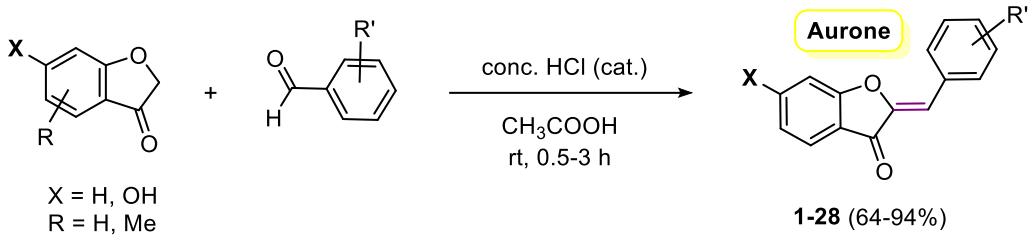


Scheme 5: Variations in Michael Glycosylation

Both synthetic and natural aurones have been studied for their possible biological importance.[5-8] Despite the proven therapeutic potential, their carbohydrate derivatives, including the isolated ones, have not been explored well. Inspired from this gap herein, we report the first synthesis of 2, 3, 4, 6-tetra-*O*-acetyl-*β*-D-glucosyl derivatives of previously synthesized variously substituted aurones using 2,3,4,6-tetra-*O*-acetyl-*α*-D glucopyranosyl bromide as a glycosyl donor.

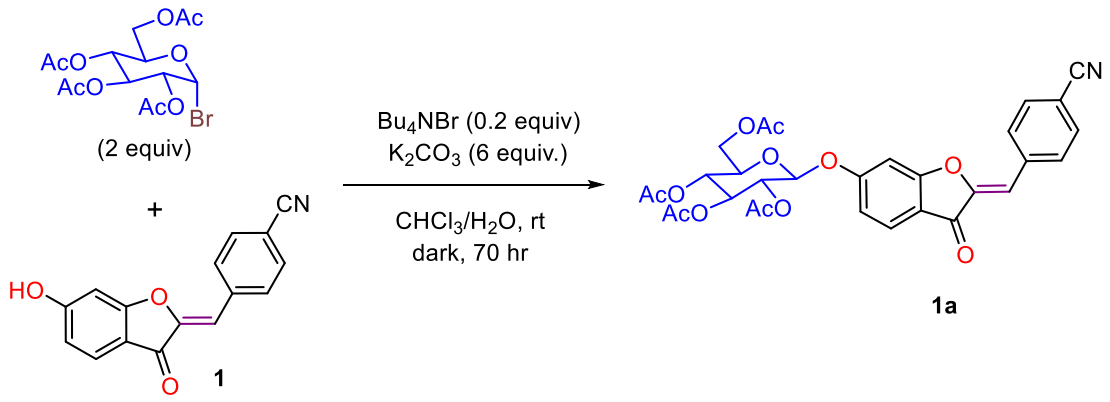
2. Results and Discussion

To access a library of glycosylated aurones, first, we synthesized various hydroxy-substituted aurones via an acid-catalyzed Knoevenagel type condensation of a benzofuranone with an aldehyde in glacial acetic acid medium. (Scheme 6)



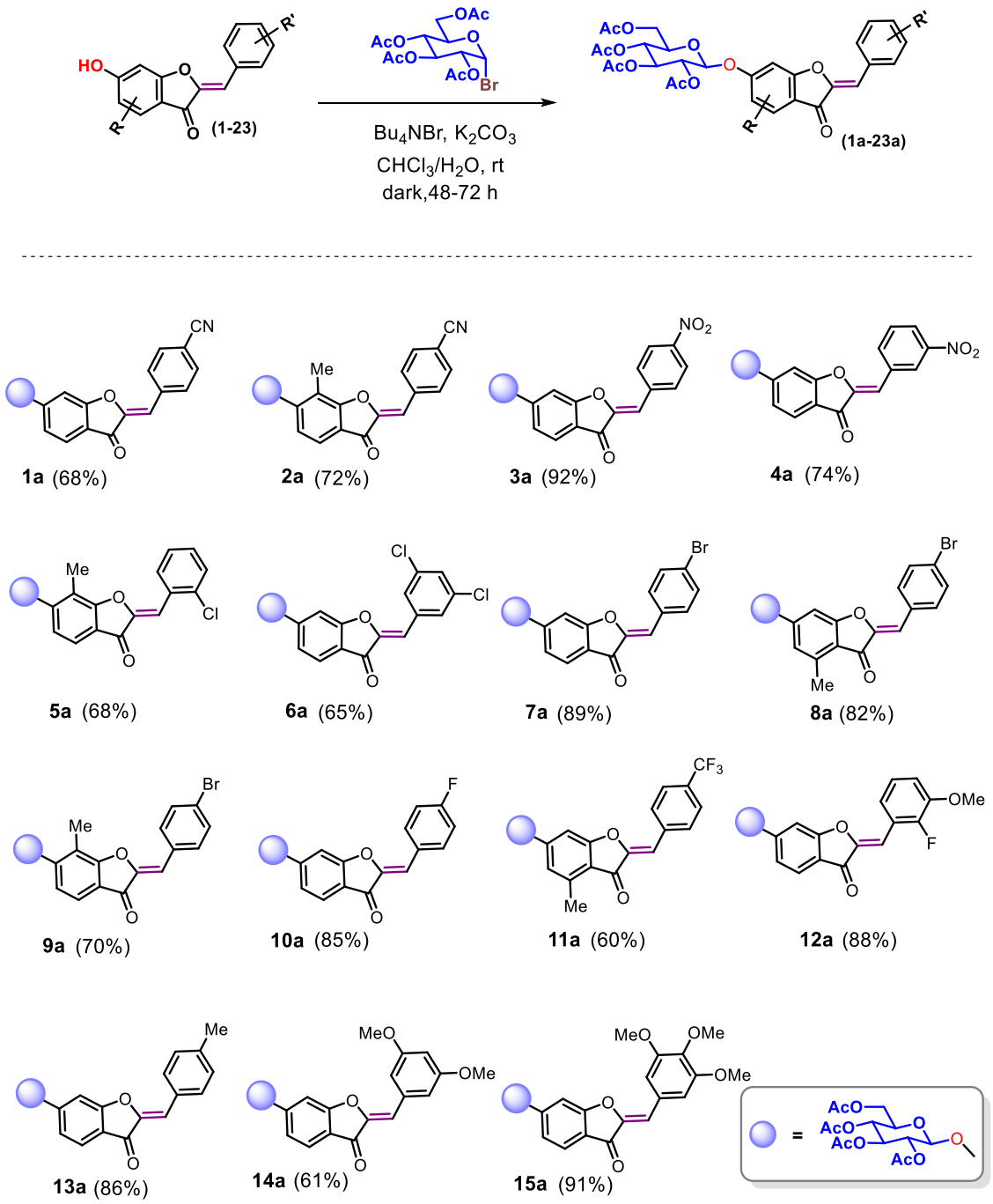
Scheme 6: Synthesis of Aurones

The reaction generally results in the precipitation of the desired product, which can simply be filtered avoiding the necessity of chromatographic separation. The ease of separation, as well as the relatively fast reaction, allowed us to access the desired number of hydroxyaurones and their analogs in a short time for further glycosylation. With the initial subsequent failures to glycosylate aurone **1** with the glycosyl bromide (acetobromo-α-D-glucose) under Koenigs-Knorr (using Ag_2O) and original Michael conditions (employing 1M NaOH) we utilized tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in a biphasic basic medium of chloroform and 5% aqueous Na_2CO_3. The reaction successfully resulted in 68% of the corresponding *β*-glycoside (**1a**) utilizing an excess of glycosyl donor to maintain its concentration, as it readily undergoes hydrolysis in an aqueous medium. (Scheme 7)

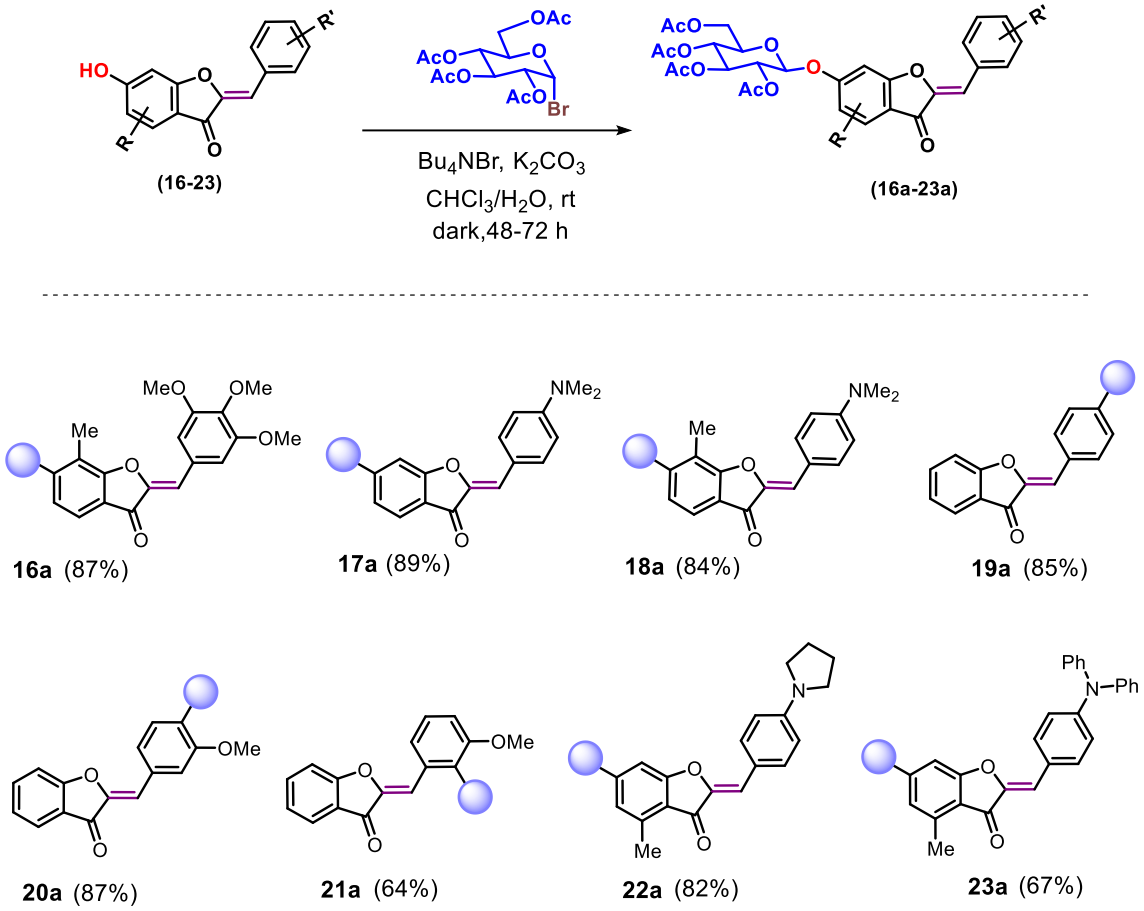


Scheme 7: Glycosylation of Aurone

Both electron-withdrawing and electron-donating groups in the phenyl moiety of the aurone molecule were tolerated well, yielding 61-92% of the corresponding peracetylated- *β*-D-glycosyl aurones. (Scheme 8) As expected, the stereochemistry of the anomeric carbon of the donor changed, creating β-glycosidic linkage with the aglycon (hydroxyaurone) in accordance with the likelihood of the reaction proceeding via S_N2 mechanism in the basic medium. The β-stereochemistry of the glycosidic linkage is established from the magnitude of coupling constant ($J_{1,2}$), with values 7-9 Hz observed for the anomeric hydrogens of the synthesized compounds in contrast to the J-values of 2-4 Hz for α-anomers.[23] While the alkene geometry of aurones is generally observed to be the thermodynamically favored Z geometry, this was also confirmed by the highly characteristic chemical shift of the exocyclic alkene proton signal in the as a singlet below 6.9 ppm, while the E isomer would have a signal above 6.95 ppm.[24]

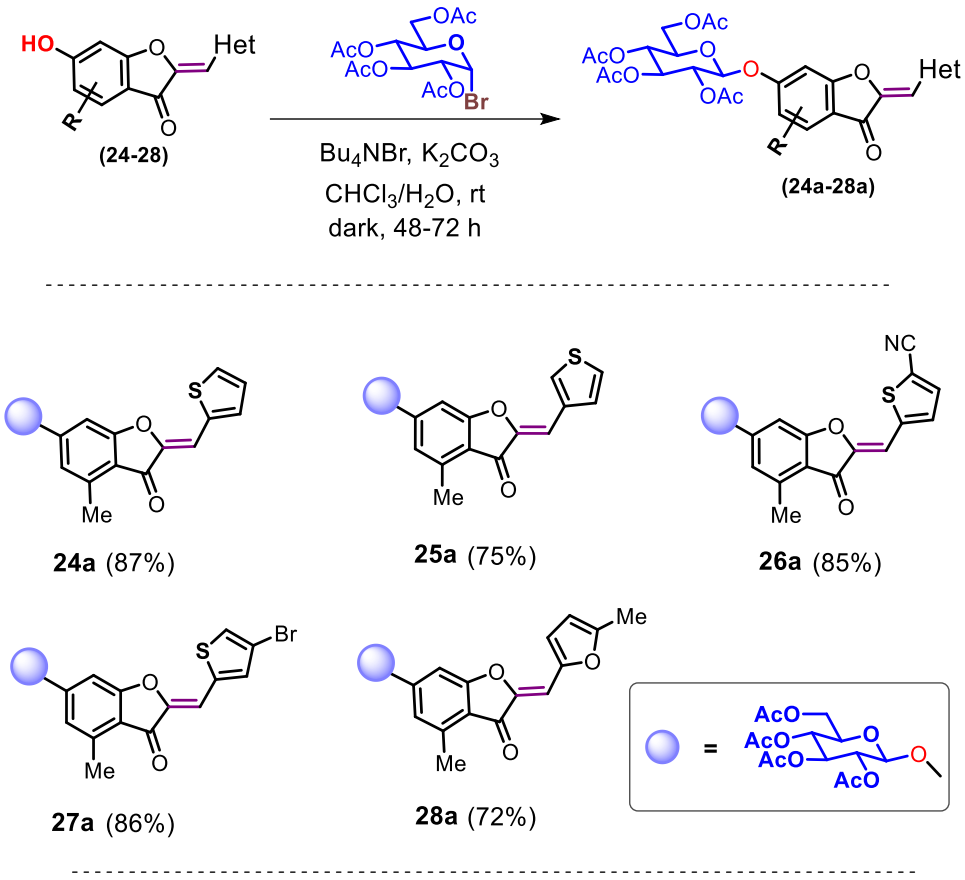


Scheme 8: Glycosylation of Aurone Analogs



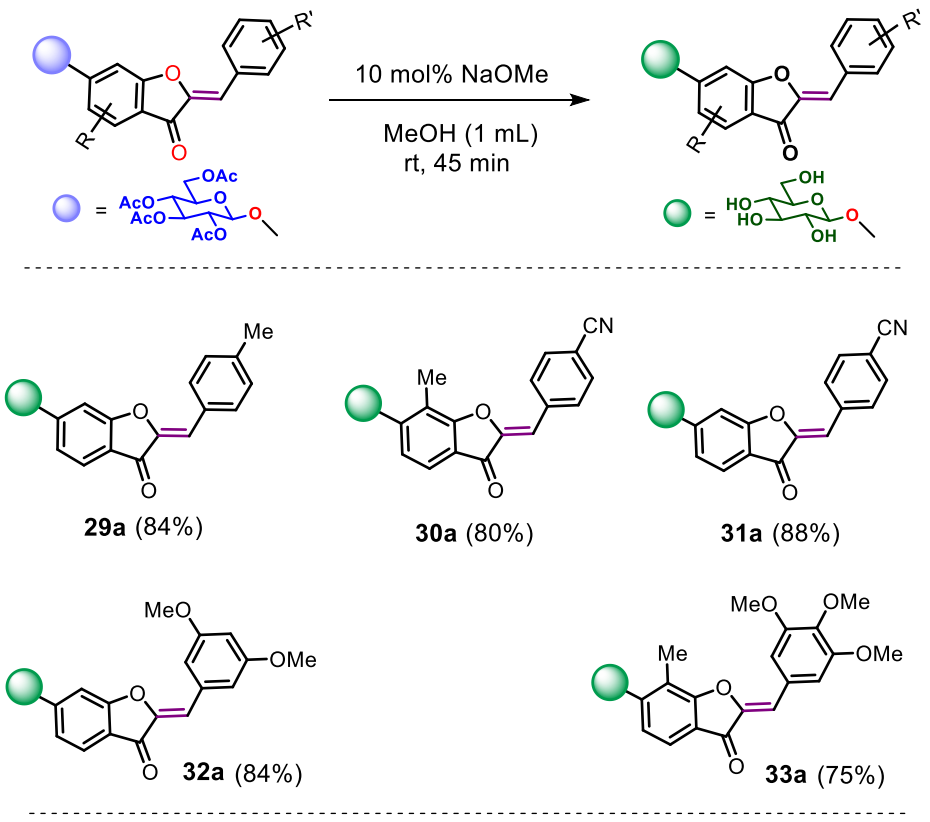
Scheme 8 (cont.): Glycosylation of Aurone Analogs

Similarly, reactions with aurone analogs containing different heterocyclic moieties attached to the exocyclic double bond also afforded good yield reflecting the generality of the reaction. (Scheme 9)



Scheme 9: Glycosylation of Aurone Analogs Containing Heterocyclic Moiety

Since naturally occurring glycosylated aurones exist mostly as glucosides, we took some of the peracetylted glycosyl aurone derivatives and subjected them to deacetylation using sodium methoxide to get the corresponding aurones glucosides in good (> 72%) yield. (Scheme 10)



Scheme 10: Deacetylation of Glycosylated Aurones

3. Conclusion

In conclusion, we report the first convenient and efficient *O*-glycosylation of variously substituted synthetic hydroxyaurones and their analogs with 2, 3, 4, 6-tetra-*O*-acetyl-*α*-D glucopyranosyl bromide using a readily available phase transfer catalyst tetrabutylammonium bromide (TBAB) in a basic medium. This will eventually provide us with an opportunity to access synthetically diverse glycosides and glucoside of aurones

and their analogs for further biological screening against both metabolic and infective diseases.

4. Experimental

General Information. All the reactions were done under an air atmosphere. ^{1}H and ^{13}C NMR of all the compounds were recorded on JEOL AS (500 and 300 MHz) NMR instrument, and chemical shifts were recorded in ppm. All the chemical shifts were recorded taking $CDCl_3$, DMSO, methanol, or acetone as a standard reference.[25] The following conventions are used for multiplicities: s, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet; *tt*, triplet of triplet; *dt*, doublet of triplet; *ddd*, doublet of doublet of doublet; *br*, broad. Cary 630 FT-IR (Agilent Technologies was used to collect IR spectra. All extracts were concentrated under reduced pressure using a Buchi Rotary Evaporator. During purification and identification of compounds, Thin Layer Chromatography (TLC) was performed on silica-coated TLC plates and monitored by short wavelength (254 nm) UV light. Products were purified by silica gel column chromatography. ACS grade reagents were employed during the experiments.

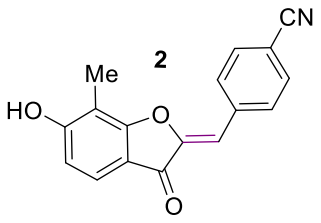
4.1. General procedure: Synthesis of aurones

All the aurones utilized for the glycosylation were synthesized based on the literature.[10] 0.57 mmol of benzofuranone was dissolved in 5 mL of glacial acetic acid in a 3-dram glass vial containing a magnetic stir bar in it. To this solution, 1.1 equivalent of aldehyde and 3 drops (0.1 mL) of concentrated HCl were added and stirred at room temperature for 30 min to 4 hours. In most cases, reaction resulted in the precipitation of the desired product

indicating completion of the reaction. After the reaction was completed, it was poured into ice-cold DI water. The precipitate obtained was filtered and washed multiple times with DI water and air-dried. Thus obtained aurones were characterized and directly used for the glycosylation reaction. For some of the aurones which did not precipitate out efficiently, the water diluted reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate.

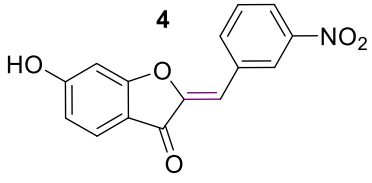
4.1.1. Characterization data for aurones

Among 28 aurones 1, 3, 7, 10, 13, 14, 15, 16, 17, 19, 20, and 21 were characterized by comparing ^{1}H and ^{13}C NMR with those reported in the literature.[10, 26-33]

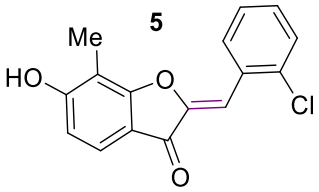


(Z)-4-((6-hydroxy-7-methyl-3-oxobenzofuran-2(3H) ylidene) methyl) benzonitrile (2):

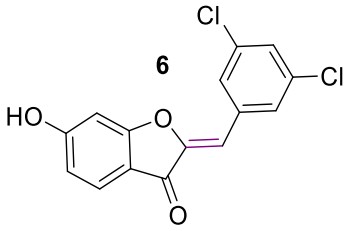
Yield: 144 mg (91%); yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 2.22 (s, 3H).



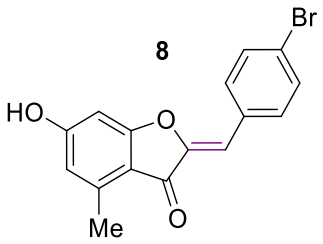
(Z)-6-hydroxy-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (4): Yield: 136 mg (84%); yellow solid. ^{1}H NMR (300 MHz, DMSO-D6) δ 11.35 (s, 1H), 8.79 – 8.74 (m, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.25 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.70 – 7.62 (m, 1H), 6.98 (s, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1H).



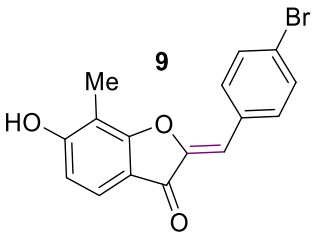
(Z)-2-(2-chlorobenzylidene)-6-hydroxy-7-methylbenzofuran-3(2H)-one(5): Yield: 124 mg (77%); light orange solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.20 (s, 1H), 8.32 (s, 1H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.47-7.43 (m, 1H), 6.96 (s, 1H), 6.79 (t, *J* = 7.0 Hz, 1H), 2.20 (s, 3H).



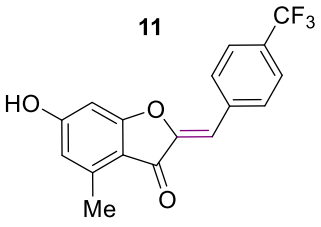
(Z)-2-(3,5-dichlorobenzylidene)-6-hydroxybenzofuran-3(2H)-one(6): Yield: 145 mg (83%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.36 (s, 1H), 7.97 (s, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 6.84 (s, 1H), 6.80 (s, 1H), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1H).



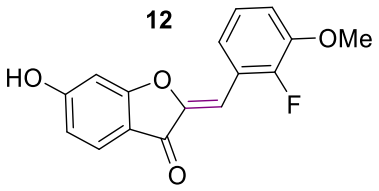
(Z)-2-(4-bromobenzylidene)-6-hydroxy-4-methylbenzofuran-3(2H)-one(8): Yield: 147 mg (78%); coral solid. ^{1}H NMR (300 MHz, DMSO-D6) δ 11.13 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 6.71 (s, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 6.49 (dd, *J* = 2.1, 0.9 Hz, 1H), 2.50 (s, 3H, overlapped with the DMSO signal). ^{1}HNMR using Methanol-D_3 has been included as an inset.



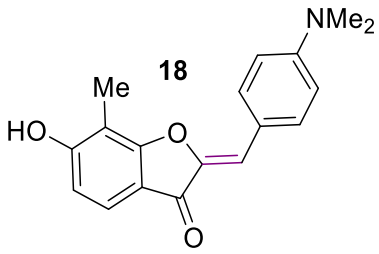
(Z)-2-(4-bromobenzylidene)-6-hydroxy-7-methylbenzofuran-3(2H)-one (9): Yield: 182 mg (96%); yellow solid. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.79 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 2.21 (s, 3H).



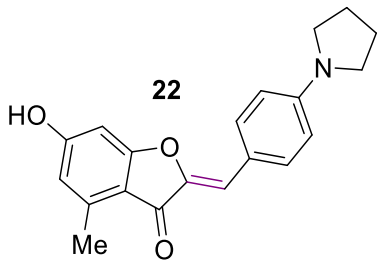
(Z)-6-hydroxy-4-methyl-2-(4-(trifluoromethyl)benzylidene)benzofuran-3(2H)-one (11): Yield: 50 mg (68%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.19 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 6.5 (t, J = 1.5 Hz, 1H), 2.51 (s, 3H).



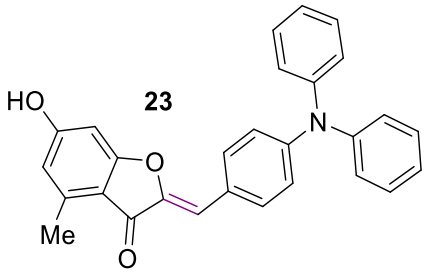
(Z)-2-(2-fluoro-3-methoxybenzylidene)-6-hydroxybenzofuran-3(2H)-one(12): Yield: 131 mg (80%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.32 (s, 1H), 7.78 – 7.73 (m, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.30-7.25 (m, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.77 (s, 1H), 6.73 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.88 (s, 3H).



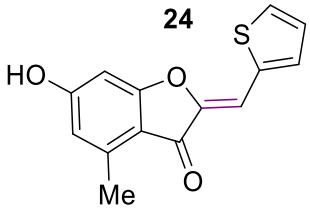
(Z)-2-(4-(dimethylamino)benzylidene)-6-hydroxy-7-methylbenzofuran-3(2H)-one (18): Yield: 155 mg (92%); red solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 10.87 (s, 1H), 7.82 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.71 (s, 1H), 3.01 (s, 6H), 2.22 (s, 3H).



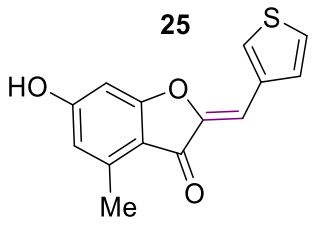
(Z)-6-hydroxy-4-methyl-2-(4-(pyrrolidin-1-yl)benzylidene)benzofuran-3(2H)-one (22): Yield: 40 mg (22%); dark brown solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.77 (d, *J* = 9.0 Hz, 2H), 6.64-6.62 (m, 3H), 6.58 (d, *J* = 2.0 Hz, 1H), 6.46 – 6.43 (m, 1H), 3.32 (t, *J* = 6.5 Hz, 4H), 1.98 (t, *J* = 6.5 Hz, 4H).



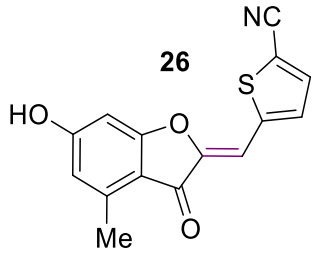
(Z)-2-(4-(diphenylamino)benzylidene)-6-hydroxy-4-methylbenzofuran-3(2H)-one (23): Crude; yield: 118 mg (49%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 10.98 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 5H), 7.12 (d, *J* = 7.5 Hz, 5H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.64 (s, 1H), 6.55 (s, 1H), 6.46 (s, 1H), 2.50 (s, 3H, overlapped with DMSO).



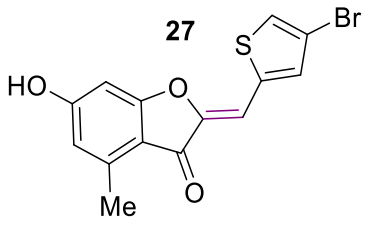
(Z)-6-hydroxy-4-methyl-2-(thiophen-2-ylmethylene)benzofuran-3(2H)-one (24): Yield: 116 mg (79%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.06 (s, 1H), 7.87 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.66 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.21 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.11 (s, 1H), 6.57 (d, *J* = 1.5 Hz, 1H), 6.48 t = 1.5 Hz, 1H), 2.5 (s, 3H, overlapped with DMSO).



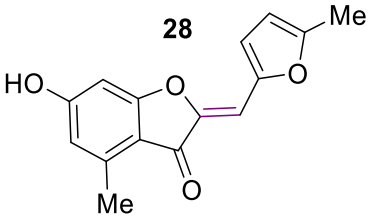
(Z)-6-hydroxy-4-methyl-2-(thiophen-3-ylmethylene)benzofuran-3(2H)-one (25): Yield: 133mg (90%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.05 (s, H), 8.14 (dd, *J* = 3.0, 1.0 Hz, 1H), 7.69 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.66 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.83 (s, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.48 – 6.45 (m, 1H), 2.50 (s, 3H, overlapped with DMSO peak). ^{1}H NMR (300 MHz, MeOD) δ 7.98 – 7.95 (m, 1H), 7.62 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.53 – 7.49 (m, 1H), 6.79 (s, 1H), 6.54 – 6.51 (m, 1H), 6.44 (dd, *J* = 2.0, 1.0 Hz, 1H), 2.55 (s, 3H).



(Z)-5-((6-hydroxy-4-methyl-3-oxobenzofuran-2(3H)ylidene)methyl)thiophene-2-carbonitrile (26): Yield: 110mg (68%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.00 (d, *J* = 4.0 Hz, 1H), 7.73 (d, *J* = 4.0 Hz, 1H), 7.20 (s, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 2.49 (s, 3H).



(Z)-2-((4-bromothiophen-2-yl)methylene)-6-hydroxy-4-methylbenzofuran-3(2H)-one (27): Yield: 151mg (84%); yellow solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.29 (s, 1H), 7.99 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.16 (s, 1H), 6.77 (s, 1H), 6.73 (d, *J* = 8.5 Hz, 1H).



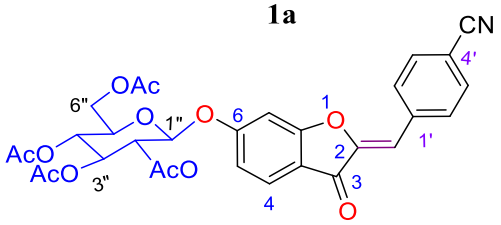
(Z)-6-hydroxy-4-methyl-2-((5-methylfuran-2-yl)methylene)benzofuran-3(2H)-one (28): Yield: 129mg (88%); light orange solid. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.01 (s, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.57 (s, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.47 – 6.45 (m, 1H), 6.37 (d, *J* = 3.0 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H).

4.2. General procedure: Glycosylation of aurones

In a 6-dram glass vial aurone (50 mg, 0.186 mmol) and glycosyl donor peracetylglycosyl bromide (153.3 mg, 2 equiv.) were dissolved in 4 mL chloroform. After stirring for 5 minutes, tetrabutylammonium bromide (TBAB) (13.29 mg, 0.2 equiv.) and potassium carbonate (154.23 mg, 6 equiv.) solution (3 mL in DI water) were added. The reaction vial was then wrapped with an Al-foil as the glycosyl donor is light sensitive. The reaction mixture was then stirred for the next 72 hours at room temperature. The reaction was monitored by thin-layer chromatography followed by p-anisaldehyde staining [(ethanol: conc. H_2SO_4: p-anisaldehyde (10:1:1 by volume)]. After the completion of the reaction, the mixture was transferred to a 50 mL centrifuge tube, diluted with distilled water, and extracted with dichloromethane (DCM). The organic layer was concentrated *in vacuo*. The crude thus obtained was purified by flash column chromatography using a mixture of hexane and ethyl acetate.

4.2.1. Characterization data for glycosylated aurones

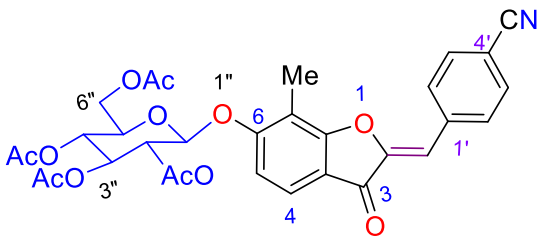
1a



[(Z)-2-(4'-cyanobenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (1a): Reaction mixture of aurone **1** (0.26 mmol, 68.4 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the

presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Yield: 106 mg, 68%; yellow solid, mp 239-240 ^{o}C. ^{1}H NMR (500 MHz, DMSO-D6) δ = 8.12 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.99 (s, 1H), 6.91 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.76 (s, 1H), 5.40 (t, *J* = 9.6 Hz, 1H), 5.15 (dd, *J* = 9.7, 8.0 Hz, 1H), 5.05 (t, *J* = 9.8 Hz, 1H), 4.41 – 4.33 (m, 1H), 4.18 (ddd, *J* = 14.9, 12.5, 4.2 Hz, 1H), 2.05 (s, 1H), 2.03 (s, 2H), 1.99 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.78, 170.48, 170.27, 169.48, 169.28, 167.99, 164.15, 148.86, 136.75, 132.55, 131.51, 126.48, 118.61, 116.43, 113.72, 112.70, 109.81, 100.49, 98.24, 72.56, 72.50, 70.98, 68.10, 61.97, 20.76, 20.70. IR (neat) 2231, 1754, 1709, 1607, 1445, 1372, 1238, 1218, 1086, 1065, 1035, 910, 886, 829 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{28}NO_{12}$, 594.1612, found 594.1604.

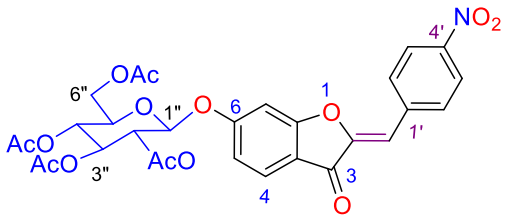
2a



[(Z)-2-(4'-cyanobenzylidene)-7-methylbenzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (2a): Reaction mixture of aurone **2** (0.26 mmol, 72 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield:

112 mg, 72%; yellow solid, mp 226-228 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.97 (s, 1H), 5.74 (d, *J* = 7.9 Hz, 1H), 5.47 (t, *J* = 9.6 Hz, 1H), 5.24 – 5.16 (m, 1H), 5.05 (t, *J* = 9.7 Hz, 1H), 4.34 (d, *J* = 7.4 Hz, 1H), 4.23 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.11 (d, *J* = 10.6 Hz, 1H), 2.19 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.63, 170.57, 170.27, 169.51, 169.24, 166.00, 161.92, 149.02, 136.98, 132.63, 131.50, 123.38, 118.67, 116.16, 112.69, 112.57, 110.62, 109.51, 98.67, 72.47, 72.44, 70.92, 68.21, 61.91, 20.79, 20.73, 8.15. IR (neat) 2959, 2926, 2229, 1750, 1706, 1657, 1603, 1369, 1208, 1037, 910, 875, 775, 685 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{31}H_{30}NO_{12}$, 608.1768, found 608.1775.

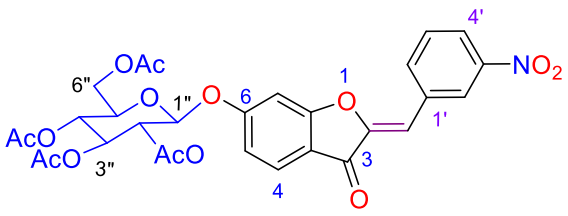
3a



[(Z)-2-(4'-nitrobenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside](3a): Reaction mixture of aurone **3** (0.26 mmol, 74 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 147.5 mg, 92%; yellow solid, mp 218-221 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.04 (s, 1H),

5.84 (d, J = 7.9 Hz, 1H), 5.42 (t, J = 9.6 Hz, 1H), 5.15 (dd, J = 9.7, 8.0 Hz, 1H), 5.05 (t, J = 9.8 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.21 (dd, J = 12.3, 5.8 Hz, 1H), 4.15 (dd, J = 12.3, 2.3 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.71, 170.47, 170.25, 169.47, 169.28, 168.03, 164.20, 149.05, 147.68, 138.64, 131.74, 126.50, 124.05, 116.31, 113.80, 109.17, 100.48, 98.20, 72.53, 72.48, 70.96, 68.08, 61.95, 20.75, 20.68. IR (neat) 2956, 2928, 1752, 1711, 1611, 1594, 1516, 1445, 1341, 1212, 1084, 1045, 910, 864, 852, 773 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{28}NO_{14}$, 614.1510, found 614.1502.

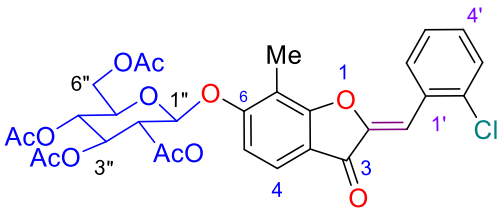
4a



[(Z)-2-(3'-nitrobenzylidene)benzofuran-3(2H)-one]- [(2", 3", 4", 6"-tetra-O-acetyl)-6-O-ß-D-glucopyranoside](4a): Reaction mixture of aurone **4** (0.26 mmol, 74 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 118 mg, 74%; yellow solid, mp 218-221 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.79 (s, 1H), 8.37 (d, J = 7.7 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.79 (dd, J = 8.0, 6.2 Hz, 2H), 7.21 (s, 1H), 7.09 (s, 1H), 5.86 (d, J = 7.9 Hz, 1H), 5.41 (t, J = 9.5 Hz, 1H), 5.15 (t, J = 8.8 Hz, 1H), 5.05 (t, J = 9.7 Hz, 1H), 4.38 (d, J = 7.2 Hz, 1H), 4.19 (m, 2H), 2.04 (s, 9H), 1.99 (s,

3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.72, 170.57, 170.25, 169.50, 169.30, 168.05, 164.18, 148.75, 148.63, 136.80, 133.97, 129.92, 126.42, 125.41, 124.10, 116.41, 113.91, 109.36, 100.34, 98.16, 72.60, 72.55, 71.01, 68.14, 62.01, 20.71, 20.70. IR (neat) 2962, 2924, 1747, 1709, 1665, 1613, 1527, 1447, 1352, 1236, 1220, 1037, 914, 905, 773, 739, 681 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{28}NO_{14}$, 614.1510, found 614.1513.

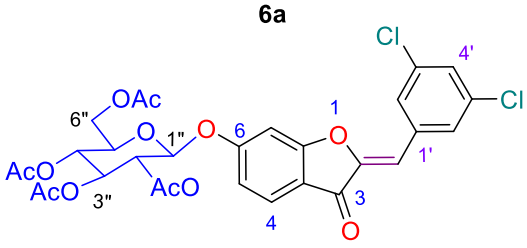
5a



[(Z)-2-(2'-chlorobenzylidene)-7-methylbenzofuran-3(2H)-one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β -D-glucopyranoside] (5a): Reaction mixture of aurone **5** (0.26 mmol, 74.5 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 109 mg, 68%; yellow solid, mp 195-197 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.31 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.62 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.47 (td, *J* = 7.8, 1.6 Hz, 1H), 7.07 – 7.01 (m, 2H), 5.74 (d, *J* = 7.9 Hz, 1H), 5.47 (t, *J* = 9.6 Hz, 1H), 5.19 (dd, *J* = 9.8, 8.0 Hz, 1H), 5.05 (t, *J* = 9.7 Hz, 1H), 4.35 (ddd, *J* = 9.9, 5.6, 2.3 Hz, 1H), 4.23 (dd, *J* = 12.3, 5.7 Hz, 1H), 4.11 (dd, *J* = 12.2, 2.1 Hz, 1H), 2.16 (s, 3H), 2.06 (s, 3H), 2.03 (d, *J* = 3.9 Hz, 5H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.68, 170.57, 170.23, 169.51, 169.25, 165.85, 161.59, 148.39, 135.95, 132.09,

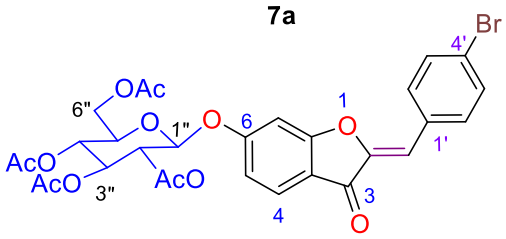
130.60, 130.50, 130.11, 127.21, 123.19, 116.49, 112.54, 110.35, 107.41, 98.70, 72.47, 72.40, 70.91, 68.23, 61.92, 20.76, 20.70, 8.05. IR (neat) 2961, 2935, 1737, 1709, 1657, 1607, 1426, 1378, 1214, 1035, 914, 782, 758 732 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{30}ClO_{12}$, 617.1426, found 624.1433.

6a



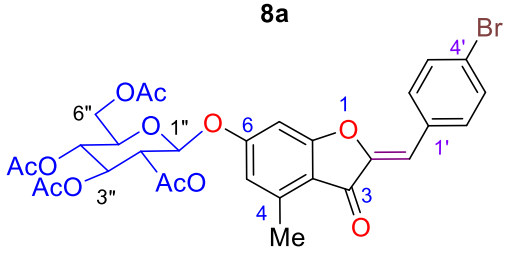
[(Z)-2-(3',5'-dichlorobenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl) -6-O-β-D-glucopyranoside] (6a): Reaction mixture of aurone **6** (0.26 mmol, 79.8mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 30% ethylacetate in hexane. Yield: 124.5 mg, 65%; yellow solid, mp 109-110 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.99 (d, *J* = 1.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.71 (t, *J* = 1.5 Hz, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 1.5 Hz, 2H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.38 (t, *J* = 9.5 Hz, 1H), 5.15 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.42 – 4.36 (m, 1H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.46, 170.45, 170.15, 169.43, 169.19, 167.83, 164.02, 148.32, 135.33, 134.99, 129.32, 128.99, 126.19, 116.23, 113.89, 109.05, 100.09, 98.09, 72.51, 72.45, 70.89, 68.13, 62.03, 20.80, 20.60. IR (neat) 1749, 1709, 1611, 1447, 1369, 1216, 1035,

961, 907, 674 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{27}Cl_2O_{12}$, 637.0880, found 637.0887.



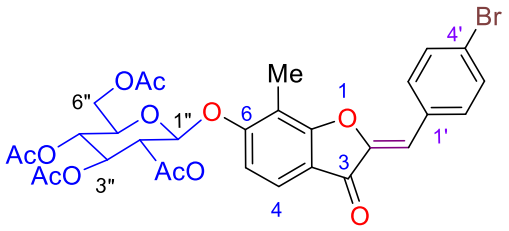
[(Z)-2-(4'-bromobenzylidene)benzofuran-3(2H)-one]- [(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β -D-glucopyranoside](7a): Reaction mixture of aurone **7** (0.26 mmol, 82 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 149.5 mg, 89%; yellow solid, mp 224-226 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.20 (s, 1H), 6.90 (s, br, 2H), 5.82 (d, *J* = 7.5 Hz, 1H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 12.5, 4.9 Hz, 1H), 5.05 (t, *J* = 9.5 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.18 (m, 2H), 2.03 (s, 9H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.94, 170.51, 170.27, 169.49, 169.30, 167.78, 163.88, 147.78, 132.75, 132.24, 131.19, 126.24, 124.41, 116.83, 113.51, 111.38, 100.37, 98.32, 72.56, 71.02, 68.19, 62.03, 20.77, 20.70. IR (neat) 3097, 3067, 2957, 1739, 1706, 1654, 1611, 1490, 1378, 1348, 1225, 1134, 1106, 1073, 1050, 1037,821 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{28}BrO_{12}$, 647.0764, found 647.0759.

8a

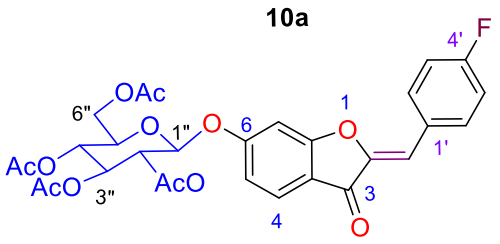


[(Z)-2-(4'-bromobenzylidene)-4-methybenzofuran-3(2H)one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β -D-glucopyranoside] (8a)*:* Reaction mixture of aurone **8** (0.26 mmol, 86 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 138 mg, 82%; yellow solid, mp 99-102 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.82 (s, 1H), 6.69 (dd, *J* = 1.8, 0.9 Hz, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 5.39 (t, *J* = 9.6 Hz, 1H), 5.12 (dd, *J* = 9.6, 7.8 Hz, 1H), 5.03 (t, *J* = 9.6 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.22 – 4.13 (m, 2H), 2.55 (s, 3H), 2.05 (s, 3H), 2.03 (s, 6H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.58, 170.50, 170.26, 169.50, 169.30, 168.02, 163.19, 147.95, 142.00, 132.60, 132.14, 131.37, 124.05, 115.17, 114.40, 110.25, 98.19, 97.54, 72.58, 72.51, 71.03, 68.25, 62.10, 20.76, 20.73, 20.69, 18.15. IR (neat) 2957, 1747, 1704, 1667, 1596, 1488, 1367, 1214, 1171, 1138, 1037, 1013, 909, 821, 732 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{30}BrO_{12}$, 661.0920, found 661.0923.

9a

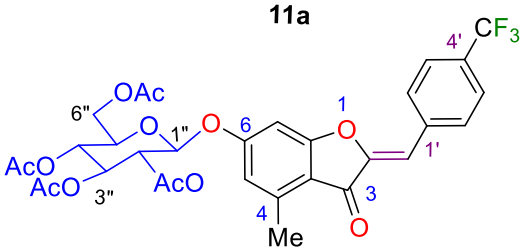


[(Z)-2-(4'-bromobenzylidene)-7-methybenzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (9a): Reaction mixture of aurone **8** (0.26 mmol, 86 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 30% ethylacetate in hexane. Yield: 120.5 mg, 70%; yellow solid, mp 218-219 ºC. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 3H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 5.73 (d, *J* = 7.9 Hz, 1H), 5.47 (t, *J* = 9.6 Hz, 1H), 5.26 – 5.14 (m, 1H), 5.05 (t, *J* = 9.7 Hz, 1H), 4.34 (d, *J* = 9.9 Hz, 1H), 4.23 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.11 (d, *J* = 11.7 Hz, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.81, 170.59, 170.28, 169.52, 169.26, 165.84, 161.62, 147.95, 132.78, 132.34, 131.42, 124.30, 123.13, 116.59, 112.60, 111.11, 110.41, 98.78, 72.52, 72.47, 70.97, 68.28, 61.96, 20.79, 20.74, 8.11. IR (neat) 2957, 2263, 1745, 1706, 1657, 1605, 1490, 1371, 1223, 1041, 1013, 918, 905, 888, 823, 734 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{30}BrO_{12}$, 661.0920, found 661.0918.



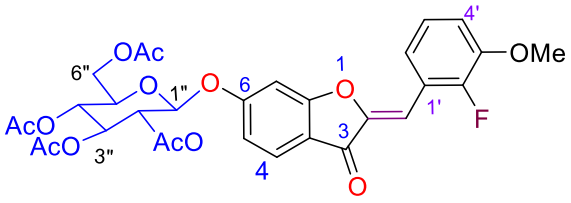
[(Z)-2-(4'-fluorobenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside](10a): Reaction mixture of aurone **10** (0.26 mmol, 67 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 130 mg, 85%; off-white solid, mp 191-194 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.04 (dd, *J* = 9.0, 6.0 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.37 (t, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.95 (s, 1H), 6.90 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.81 (d, *J* = 7.5 Hz, 1H), 5.41 (t, *J* = 10.0 Hz, 1H), 5.15 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.05 (t, *J* = 10.0 Hz, 1H), 4.37 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H), 4.20 (dd, *J* = 12.5, 6.0 Hz, 1H), 4.15 (dd, *J* = 12.5, 2.5 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 183.01, 170.53, 170.29, 169.50, 169.31, 167.77, 164.51, 163.80, 163.5 (d, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 147.21, 133.5 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 133.46, 128.58 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 126.21, 116.96, 116.31 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 113.42, 111.62, 100.34, 98.34, 72.57, 71.01, 68.18, 62.02, 20.77, 20.71. IR (neat) 2950, 1745 1706, 1657, 1600, 1449, 1369, 1216, 1071 1033, 892, 830, 702, 685 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{28}FO_{12}$, 587.1565, found 587.1560.

11a



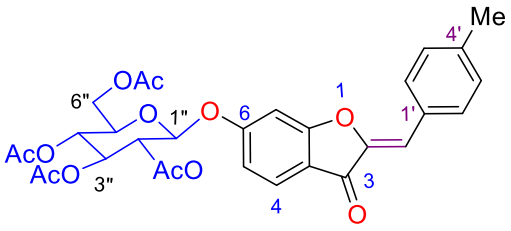
[(Z)-4-methyl-2-(4'-(trifluoromethyl)benzylidene)benzofuran-3(2H)-one]-[(2",3",4", 6"-tetra-O-acetyl)]-6-O-β-D-glucopyranoside (11a): Reaction mixture of aurone **11** (0.13 mmol, 42 mg) and glycosyl donor (0.26 mmol,107 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 8.6 mg), potassium carbonate (6 equiv., 106.5 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 51 mg, 60%; off-white solid, mp 201-203 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 6.92 (s, 1H), 6.72 (s, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 10.0 Hz, 1H), 5.13 (dd, *J* = 10.0, 8.0 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.38 – 4.33 (m, 1H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.15 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.56 (s, 3H), 2.05 (s, 3H), 2.03 (s, 6H), 1.98 (s, 3H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 183.65, 170.55, 170.31, 169.53, 169.35, 168.28, 163.40, 148.70, 142.25, 135.93, 131.27 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 125.74, 123.9 (q, $^{1}J_{C\text{-}F}$ = 272.2 Hz), 115.02, 114.55, 109.51, 98.18, 97.63, 72.57, 72.55, 71.04, 68.22, 62.10, 20.78, 20.75, 20.72, 18.22. IR (neat) 2941, 1749, 1708, 1598, 1326, 1216, 1123, 1052, 1035, 1020, 910, 702, 687 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{31}H_{30}F_3O_{12}$, 651.1689, found 651.1684.

12a



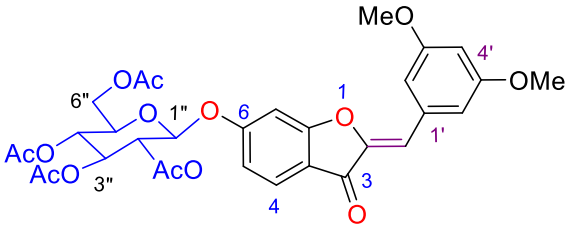
[(Z)-2-(2'-fluoro-3'-methoxybenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"- tetra-O-acetyl)-6-O-β -D-glucopyranoside] (12a): Reaction mixture of aurone **12** (0.26 mmol, 74 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition . Eluent 40% ethyl acetate in hexane. Yield: 141 mg, 88%; off-white solid, mp 220-222 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.79 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.33 – 7.26 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.85 (s, 1H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.15 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.88 (s, 3H), 2.04 (s, 3H), 2.03 (d, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.77, 170.54, 170.25, 169.49, 169.31, 167.83, 163.87, 151.58 (d, $^{1}J_{C\text{-}F}$ = 254.8 Hz), 147.91 (d, $^{2}J_{C\text{-}F}$ = 10.6 Hz, , 126.25, 124.09 (d, $^{4}J_{C\text{-}F}$ = 4.1 Hz) , 122.71, ,121.17 (d, $^{2}J_{C\text{-}F}$ = 9.2 Hz , 116.78, 114.72, 113.49, 103.81 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz 100.33, 98.34, 72.56, 72.53, 70.97, 68.19, 62.02, 56.43, 20.75, 20.69. IR (neat) 2969, 1747, 1737, 1708, 1657, 1613, 1449, 1253, 1223, 1132, 1087, 1035, 842, 834, 782,722 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{29}FO_{13}$, 616.1592, found 616.1587.

13a



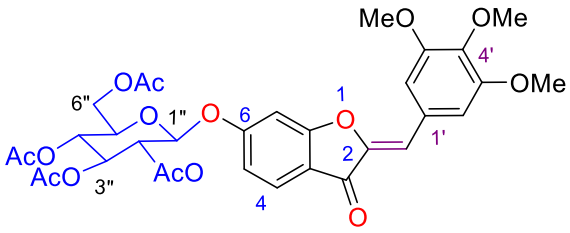
[(Z)-2-(4'-methylbenzylidene)benzofuran-3(2H)-one]-[(2", 3", 4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside](13a): Reaction mixture of aurone **13** (0.26 mmol, 66 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethylacetate in hexane. Yield: 129 mg, 86%; off-white solid, mp 210-211°C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.5 Hz, 2H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 10.0, 8.0 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.20 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.16 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.37 (s, 3H), 2.07 – 2.03 (m, 9H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D6) δ 181.84, 169.95, 169.64, 169.38, 169.13, 167.16, 163.41, 146.64, 140.28, 131.30, 129.71, 129.10, 125.89, 115.91, 113.49, 111.91, 99.85, 96.50, 71.87, 71.22, 70.45, 67.91, 61.68, 21.18, 20.46, 20.44, 20.35, 20.31. IR (neat) 2957, 2918, 1737, 1700, 1652, 1607, 1596, 1443, 1378, 1348, 1246, 1052 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{31}O_{12}$, 583.1816, found 583.1810.

14a



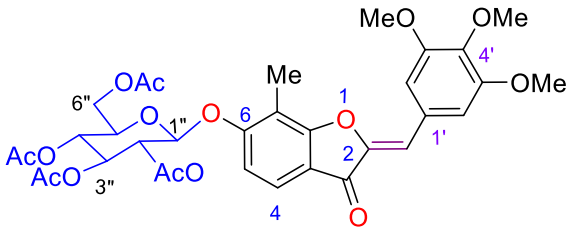
[(Z)-2-(3',5'-dimethoxybenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (14a): Reaction mixture of aurone **14** (0.26 mmol, 79 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 50% ethyl acetate in hexane. Yield: 100 mg, 61%; off-white solid, mp 192-193 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 2H), 6.90 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.83 (s, 1H), 6.63 (t, *J* = 2.0 Hz, 1H), 5.83 (d, *J* = 8.0 Hz, 1H), 5.39 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 10.0, 8.0 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.19 (dd, *J* = 12.5, 6.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.80 (s, 6H), 2.03 (s, 9H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D6) δ 181.94, 169.98, 169.64, 169.38, 169.13, 167.28, 163.53, 160.66, 147.20, 133.40, 126.01, 115.73, 113.39, 111.63, 109.49, 101.70, 99.98, 96.35, 71.86, 71.21, 70.41, 67.91, 61.68, 55.41, 20.48, 20.43, 20.36, 20.31. IR (neat) 2950, 2922, 2853, 1749, 1739, 1704, 1657, 1607, 1590, 1449, 1367, 1318, 1249, 1223, 1091, 1974, 843, 776 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{31}H_{33}O_{14}$, 629.1870, found 629.1875.

15a



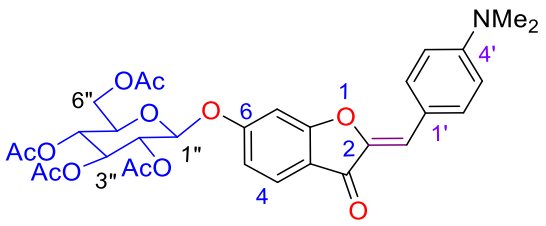
[(Z)-2-(3', 4', 5'-trimethoxybenzylidene)benzofuran-3(2H)-one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β -D-glucopyranoside] (15a): Reaction mixture of aurone **15** (0.26 mmol, 85 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 50% ethyl acetate in hexane. Yield: 156 mg, 91%; yellow solid, mp 113-116 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.79 (d, *J* = 8.6 Hz, 1H), 7.35 (s, 2H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.87 (s, 1H), 5.86 (d, *J* = 8.0 Hz, 1H), 5.42 (t, *J* = 9.6 Hz, 1H), 5.14 (dd, *J* = 9.7, 7.9 Hz, 1H), 5.05 (t, *J* = 9.7 Hz, 1H), 4.36 (ddd, *J* = 10.1, 5.7, 2.5 Hz, 1H), 4.21 (dd, *J* = 12.4, 5.7 Hz, 1H), 4.11 (dd, *J* = 12.4, 2.3 Hz, 1H), 3.86 (s, 6H), 3.74 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.85, 170.50, 170.20, 169.44, 169.30, 167.41, 163.54, 153.37, 146.99, 140.18, 127.57, 126.11, 117.04, 113.09, 112.63, 109.05, 100.66, 98.06, 72.46, 72.34, 71.00, 68.17, 61.92, 61.05, 56.35, 20.70, 20.64. IR (neat) 1754, 1732, 1652, 1605, 1506, 1447, 1423, 1372, 1350, 1339, 1240, 1214, 1074, 1035, 843, 910, 691 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{32}H_{35}O_{15}$, 659.1976, found 659.1971.

16a



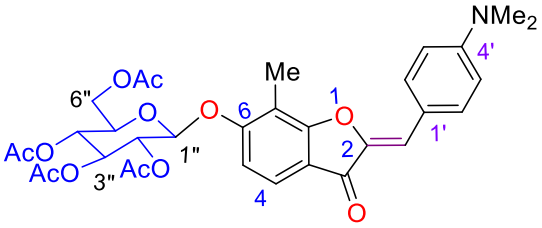
[(Z)-7-methyl-2-(3',4',5'-trimethoxybenzylidene)benzofuran-3(2H)-one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (16a): Reaction mixture of aurone **16** (0.26 mmol, 89 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 50% ethyl acetate in hexane. Yield: 150.7 mg, 87% yellow solid, mp 127-130 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.69 (d, *J* = 8.5 Hz, 1H), 7.39 (s, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.87 (s, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.47 (t, *J* = 9.5 Hz, 1H), 5.19 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.05 (t, *J* = 9.5 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.23 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.11 (d, *J* = 10.0 Hz, 1H), 3.86 (s, 6H), 3.73 (s, 3H), 2.17 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.62, 170.56, 170.23, 169.50, 169.25, 165.53, 161.32, 153.33, 147.27, 139.84, 127.82, 123.04, 116.68, 112.80, 112.09, 110.13, 108.68, 98.66, 72.44, 72.39, 70.93, 68.24, 61.92, 61.09, 56.07, 20.75, 20.68, 7.90. IR (neat) 2942, 2844, 1752, 1730, 1655, 1611, 1506, 1426, 1214, 1037, 910, 775 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{33}H_{37}O_{15}$, 673.2133, found 673.2135.

17a

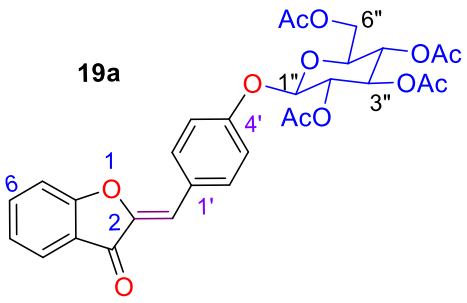


[(Z)-2-(4'-(dimethylamino)benzylidene)benzofuran-3(2H)one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (17a): Reaction mixture of aurone **17** (0.26 mmol, 73 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 141 mg, 89%; orange solid, mp 140-142 ^{o}C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.82 (d, *J* = 9.0 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.83 (s, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 5.79 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 10.0 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.21 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.16 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.02 (s, 6H), 2.06 (s, 3H), 2.04 (d, 6H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D6) δ 180.86, 169.96, 169.65, 169.38, 169.14, 166.17, 162.74, 151.33, 144.71, 133.29, 125.40, 118.81, 116.65, 114.04, 113.09, 111.94, 99.73, 96.59, 71.88, 71.17, 70.50, 67.94, 61.67, 20.45, 20.35, 20.32. IR (neat) 2920, 2117, 1747, 1698, 1644, 1588, 1527, 1369, 1222, 1037, 951, 814, 732 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{31}H_{34}NO_{12}$, 612.2081, found 612.2077.

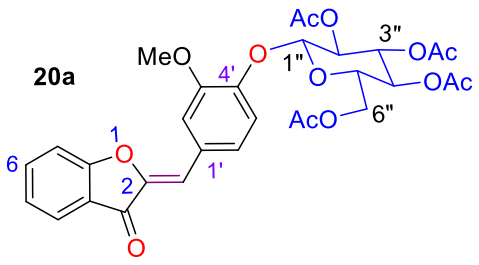
18a



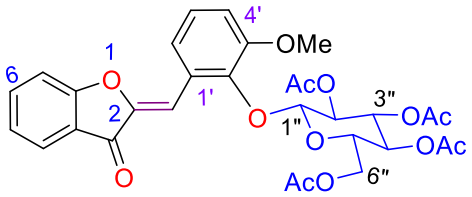
[(Z)-2-(4'-(dimethylamino)benzylidene)-7-methylbenzofuran-3(2H)-one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β-D-glycopyranoside] (18a): Reaction mixture of aurone **18** (0.26 mmol, 77 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 137 mg, 84%; red solid, mp 107-109 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.85 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 3H), 5.70 (d, *J* = 8.0 Hz, 1H), 5.47 (t, *J* = 9.5 Hz, 1H), 5.18 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.36 – 4.30 (m, 1H), 4.23 (dd, *J* = 12.5, 5.6 Hz, 1H), 4.11 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.03 (s, 6H), 2.19 (s, 3H), 2.06 (s, 3H), 2.03 (d, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.25, 170.59, 170.23, 169.52, 169.29, 164.97, 160.72, 151.30, 145.77, 133.58, 122.49, 120.09, 117.54, 114.73, 112.26, 112.06, 109.96, 98.91, 72.57, 72.31, 70.98, 68.30, 61.95, 40.14, 20.76, 20.72, 8.07. IR (neat) 2926, 2861, 1749, 1581, 1527, 1428, 1367, 1212, 1113, 1035, 815, 778, 685 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{32}H_{36}NO_{12}$, 626.2238, found 626.2241.



[(Z)-2-benzylidenebenzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-4'-O-β-D-glycopyranoside] (19a): Reaction mixture of aurone **19** (0.26 mmol, 62 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 125.7 mg, 85%; yellow solid, mp 77-79 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.83 – 7.79 (m, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.98 (s, 1H), 5.71 (d, *J* = 8.0 Hz, 1H), 5.43 (t, *J* = 9.5 Hz, 1H), 5.10 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.03 (t, *J* = 9.5 Hz, 1H), 4.30 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 4.22 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.10 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 6H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.74, 170.67, 170.34, 169.50, 169.40, 166.06, 157.86, 146.44, 136.94, 133.32, 127.59, 124.76, 123.58, 121.80, 117.18, 112.99, 112.51, 98.54, 72.71, 72.25, 71.15, 68.25, 61.95, 20.80, 20.73. IR (near) 1745, 1706, 1600, 1510, 1369, 1210, 1035, 888, 758, 702 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{29}O_{12}$, 569.1659, found 569.1664.

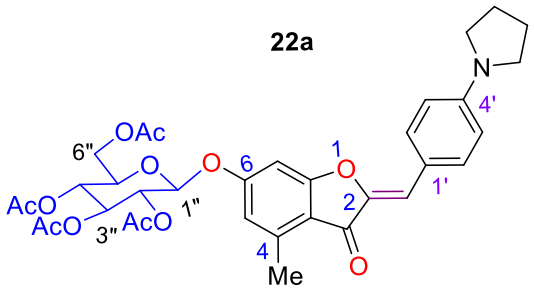


[(Z)-2-(3'-methoxybenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-4'-O-β-D-glucopyranoside](20a): Reaction mixture of aurone **20** (0.26 mmol, 70 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 136 mg, 87%; yellow solid, mp 78-79 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.81 (d = 7.0 Hz, 2H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.96 (s, 1H), 5.54 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.09 (dd, *J* = 10.0, 8.0 Hz, 1H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.23 (dt, *J* = 9.0, 6.0 Hz, 2H), 4.10 (t, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.71, 170.73, 170.41, 169.54, 169.47, 166.06, 150.68, 147.62, 146.57, 136.97, 128.88, 125.30, 124.82, 123.68, 121.78, 119.51, 115.40, 113.00, 112.79, 100.33, 72.60, 72.23, 71.21, 68.40, 61.97, 56.25, 20.85, 20.78, 20.73. IR (neat) 2924, 1745, 1648, 1600, 1514, 1369, 1216, 1067, 1035, 884, 758, 702 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{31}O_{13}$, 599.1796, found 599.1800.

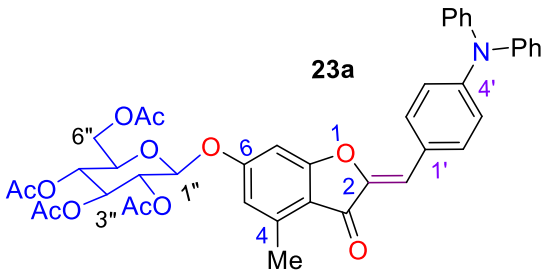


21a

[(Z)-2-(3'-methoxybenzylidene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-2'-O-β-D-glucopyranoside] (21a): Reaction mixture of aurone **21** (0.26 mmol, 69.5 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 98.5 mg, 64%; yellow solid, mp 105-107 ºC. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.64 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.44 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.19 (m, 2H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.40 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.31 (t, *J* =9.5 Hz, 1H), 5.25 (t, *J* = 9.5 Hz, 1H), 5.05 (d, *J* = 7.5 Hz, 1H), 4.11 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.03(dd, *J* = 12.0, 2.5 Hz, 1H), 3.88 (s, 3H), 3.59. (ddd, *J* = 9.8, 4.0, 2.6 Hz, 1H), 2.14 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.49, 170.95, 170.58, 169.64, 169.44, 166.11, 152.16, 147.33, 144.64, 136.81, 128.40, 125.66, 124.79, 123.49, 121.86, 113.85, 112.91, 108.00, 101.58, 72.88, 71.80, 71.71, 68.48, 61.58, 56.05, 20.85, 20.79, 20.70, 20.57. IR (neat) 3613, 2952, 1745, 1704, 1652, 1603, 1462, 1367, 1218, 1190, 1035, 886, 761, 737, 702 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{30}H_{31}O_{13}$, 599.1796, found 599.1893.

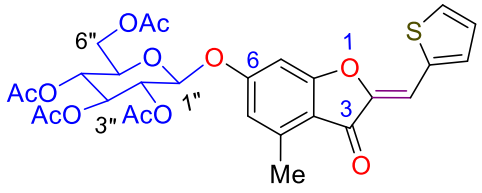


[(Z)-4-methyl-2-(4'-(pyrrolidin-1-yl)benzylidene)benzofuran-3(2H)-one]-[(2",3",4", 6"-tetra-O-acetyl)-6-O-β-D-glucopyrano side (22a): Reaction mixture of aurone **22** (0.093 mmol, 30 mg) and glycosyl donor (0.187 mmol, 76.8 mg) in 2.5 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 6.2 mg), potassium carbonate (6 equiv., 77 mg) and 1.5 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 50 mg, 82%; red solid, mp 113-116 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.80 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 1.6 Hz, 1H), 6.74 (s, 1H), 6.63 (d, *J* = 9.0 Hz, 3H), 5.76 (d, *J* = 8.0 Hz, 1H), 5.39 (t, *J* = 9.5 Hz, 1H), 5.12 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.03 (t, *J* = 10.0 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.23 – 4.11 (m, 2H), 3.36-3.33 (m, 4H, overlapped with H_2O signal) 2.56 (s, 3H), 2.06 (s, 3H), 2.03 (d, 6H), 1.98 (s, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.28, 170.66, 170.31, 169.54, 169.39, 167.11, 162.37, 148.87, 145.65, 141.28, 133.57, 119.56, 116.23, 114.30, 113.84, 111.96, 98.41, 97.40, 72.71, 72.44, 71.10, 68.38, 62.16, 47.66, 25.57, 20.83, 20.76, 20.72, 18.13. IR (neat)) 2959, 2928, 2855, 1747, 1581, 1525, 1378, 1346, 1214, 1171, 1138, 1037, 815, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{34}H_{38}NO_{12}$, 652.2394, found 652.2395.

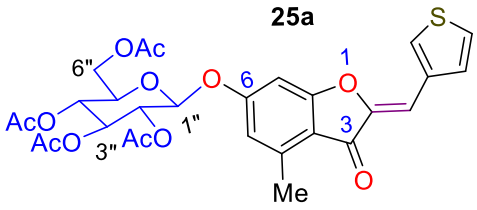


[(Z)-2-(4'-(diphenylamino)benzylidene)-4-methylbenzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside] (23a): Reaction mixture of aurone **23** (0.26 mmol, 109 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 129 mg, 67%; orange- yellow solid, mp 103-105 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.83 (d, *J* = 9.0 Hz, 2H), 7.38 (dd, *J* = 11.0, 5.0 Hz, 4H), 7.20 – 7.10 (m, 6H), 6.97 – 6.90 (m, 3H), 6.75 (s, 1H), 6.67 (d, *J* = 1.0 Hz, 1H), 5.75 (d, *J* =8.0 Hz, 1H), 5.39 (t, *J* = 9.5 Hz, 1H), 5.11 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.34 – 4.30 (m, 1H), 4.19-4.11 (m, 2H), 2.55 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.52, 170.22, 169.44, 169.28, 167.50, 162.68, 149.31, 146.72, 141.47, 132.60, 129.56, 125.61, 125.22, 124.28, 121.33, 114.15, 112.21, 98.20, 97.32, 72.59, 72.39, 70.96, 68.20, 62.04, 20.70, 20.66, 18.10. IR (neat) 1749, 1695, 1650, 1587, 1510, 1492, 1214, 1138, 1035, 907, 758, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{42}H_{40}NO_{12}$, 750.2550, found 750.2547.

24a

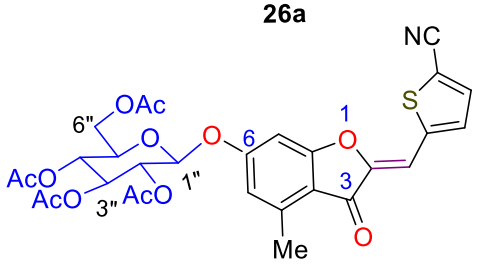


[(Z)-4-methyl-2-(thiophen-2-ylmethylene)benzofuran-3(2H)-one]-[(2", 3", 4", 6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside (24a): Reaction mixture of aurone **24** (0.26 mmol, 67 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 143 mg, 87%; yellow solid, mp 93-94 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.94 (d, *J* = 5.0 Hz, 1H), 7.71 (d, *J* = 3.5 Hz, 1H), 7.23 (dd, *J* = 4.0, 3.0 Hz, 2H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.71 – 6.67 (m, 1H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.39 (t, *J* = 9.5 Hz, 1H), 5.13 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.41 – 4.34 (m, 1H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.14 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.55 (s, 3H), 2.06 (s, 3H), 2.03 (s, 6H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.85, 170.52, 170.18, 169.45, 169.26, 167.48, 162.87, 146.07, 141.59, 135.48, 132.67, 131.16, 127.97, 115.74, 114.29, 105.63, 98.02, 97.36, 72.53, 72.37, 70.95, 68.24, 62.06, 20.82, 20.67, 20.62, 18.01. IR (neat) 2956, 1749, 1698, 1650, 1605, 1423, 1367, 1216, 1171, 1134, 1037, 909 717, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{28}H_{29}SO_{12}$, 589.2550, found 589.1385.



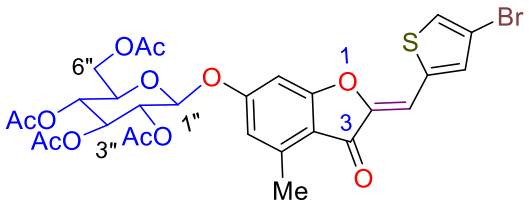
[(Z)-4-methyl-2-(thiophen-3'-ylmethylene)benzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside (25a): Reaction mixture of aurone **25** (0.26 mmol, 67 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 115 mg, 75%; yellow solid, mp 94-96 ºC. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.20 – 8.15 (m, 1H), 7.73 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.68 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.94 (s, 1H), 6.68 (d, *J* = 1.0 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.12 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.41 – 4.29 (m, 1H), 4.26 – 4.09 (m, 2H), 2.55 (s, 3H), 2.03 (d, 9H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.63, 170.53, 170.25, 169.48, 169.31, 167.74, 162.97, 146.94, 141.74, 133.82, 129.86, 129.13, 126.32, 115.65, 114.13, 105.91, 98.13, 97.41, 72.56, 72.41, 70.98, 68.20, 62.05, 20.76, 20.71, 20.67, 18.10. IR (neat) 2956, 1747, 1700, 1652, 1601, 1369, 1212, 1171, 1130, 1035, 909, 791, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{28}H_{29}SO_{12}$, 589.1380, found 589.1379.

26a



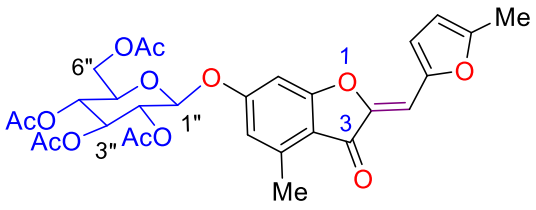
[(Z)-2-((5'-cyanothiophen-2'-yl)methylene)-4-methylbenzofuran-3(2H)-2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glucopyrano side] (26a): Reaction mixture of aurone **26** (0.26 mmol, 74 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Yield: 135 mg, 85%; yellow solid, mp 139-140 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 8.02 (d, *J* = 4.0 Hz, 1H), 7.76 (d, *J* = 4.0 Hz, 1H), 7.31 (s, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 1.0 Hz, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.13 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.37 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H), 4.17 (m, 2H), 2.54 (s, 3H), 2.05 (s, 3H), 2.03 (d, 6H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.26, 170.39, 170.13, 169.42, 169.20, 167.65, 163.39, 147.81, 142.08, 137.42, 131.32, 115.09, 114.85, 113.95, 112.82, 102.85, 97.93, 97.49, 72.42, 70.88, 68.09, 62.02, 20.78, 20.63, 20.59, 18.01. IR (neat) 2218, 1745, 1704, 1655, 1596, 1439, 1369, 1214, 1173, 1134, 1033, 909, 810, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{28}NSO_{12}$, 614.1332, found 614.1330.

27a



[(Z)-2-((4'-bromothiophen-2'-yl)methylene)-4-methylbenzofuran-3(2H)-one]-[(2",3",4",6"-tetra-O-acetyl)-6-O-β-D-glycopyranoside (27a): Reaction mixture of aurone **27** (0.26 mmol, 84 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 30% ethyl acetate in hexane. Yield: 146 mg, 86%; yellow solid, mp 139-140 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.08 – 8.01 (m, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.27 (s, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.43 – 4.32 (m, 1H), 4.24 – 4.09 (m, 2H), 2.05 (s, 3H), 2.03 (s, 6H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, CHLOROFORM-D) δ 182.01, 170.52, 170.21, 169.47, 169.26, 167.31, 163.79, 146.59, 136.38, 134.20, 128.03, 126.06, 117.08, 113.65, 111.41, 104.83, 100.22, 98.17, 72.49, 70.95, 68.17, 62.02, 20.84, 20.66, 20.63. IR (neat) 3093, 1745, 1650, 1605, 1447, 1411, 1371, 1216, 1035, 910, 875, 732, 696 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{28}H_{27}BrSO_{12}$, 667.0485, found 667.0489.

28a



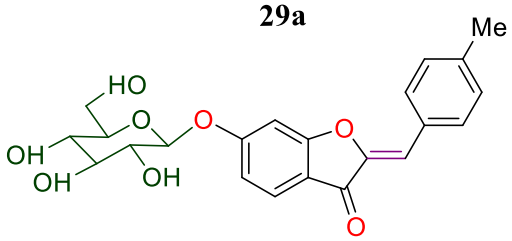
[(Z)-4-methyl-2-((5'-methylfuran-2'yl)methylene)benzofuran-3(2H)-one]-[(2",3",4", 6"-tetra-O-acetyl)-6-O-β-D-glucopyranoside (28a): Reaction mixture of aurone **28** (0.26 mmol, 67 mg) and glycosyl donor (0.52 mmol, 214 mg) in 4 mL chloroform was stirred for 48 hours in the presence of TBAB (0.2 equiv., 17.12 mg), potassium carbonate (6 equiv., 213 mg) and 3 mL DI water under the standard condition. Eluent 40% ethyl acetate in hexane. Yield: 109 mg, 72%; yellow solid, mp 83-85 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.07 (d, *J* = 3.0 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.70 (s, 1H), 6.67 (d, *J* = 1.0 Hz, 1H), 6.41 (d, *J* = 3.0 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.39 (t, *J* = 9.5 Hz, 1H), 5.12 (dd, *J* = 9.5, 8.0 Hz, 1H), 5.03 (t, *J* = 10.0 Hz, 1H), 4.38 – 4.33 (m, 1H), 4.19 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.16 – 4.11 (m, 1H), 2.54 (s, 3H), 2.39 (s, 3H), 2.04 (s, 3H), 2.03 (d, 6H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.04, 170.59, 170.26, 169.50, 169.34, 167.41, 162.75, 156.07, 147.39, 145.12, 141.49, 118.48, 115.86, 114.09, 109.88, 100.91, 98.18, 97.48, 72.60, 72.41, 71.01, 68.27, 62.08, 20.79, 20.72, 20.68, 18.07, 14.13. IR (neat) 1747, 1695, 1648, 1600, 1521, 1369, 1210, 1171, 1132, 1033, 909, 791, 698 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{29}H_{31}SO_{13}$, 687.1765, found 687.1767.

4.3. Deacetylation of peracetyl glycosyl aurones

In a 1-dram glass vial, 0.1 mmol of peracetylated glycosyl aurone was dissolved in 1 mL MeOH. To this solution, 10 mol% of NaOMe was added (5M in MeOH) and stirred at room temperature for 45 minutes. After the completion of the reaction, the solvent was vacuum off and subjected to flash column chromatography. The crude was eluted with ethyl acetate, followed by 5-7% MeOH in DCM.

4.3.1. Characterization data for glucosides

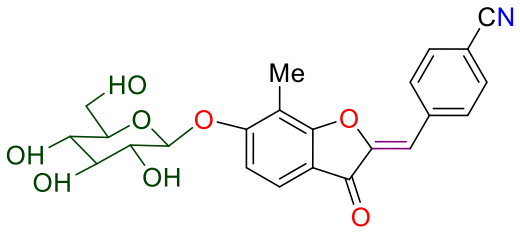
29a



[(Z)-2-(4-methylbenzylidene)benzofuran-3(2H)-one]-6-O-β-D-glucopyranoside (29a): 0.051 mmol (30 mg) **13a** was stirred in 1 mL MeOH in the presence of 10 mol% NaOMe (5M in MeOH) for 2h under standard condition. Eluent 5% MeOH in DCM. Yield: 18 mg, 18 mg, 84%; off-white solid, mp 158-160 ^{o}C. ^{1}H NMR (500 MHz, Acetone-d6) δ 7.88 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.16 (s, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.76 (s, 1H), 5.25 (d, J = 7.5 Hz, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.76 – 3.70 (m, 1H), 3.67 (s, 1H), 3.58-3.53 (m, 2H), 3.52-3.47 (m, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, METHANOL-D4) δ 184.74, 169.53, 166.95, 148.62, 141.98, 132.69, 130.73,

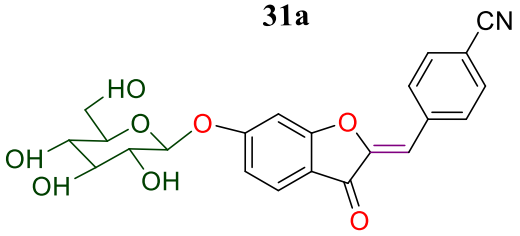
126.56, 116.88, 114.99, 113.95, 101.68, 100.84, 78.43, 77.82, 74.70, 71.21, 62.45, 21.59. HRMS (ESI): [M + H], calcd for $C_{22}H_{23}O_{18}$, 415.1393, found 415.1397.

30a



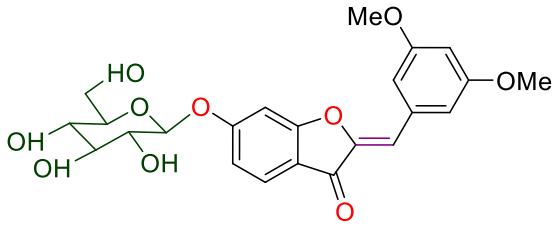
[(Z)-2-(4'-cyanobenzylidene)-7-methylbenzofuran-3(2H)-one]-6-O-β-D-glucopyrano side] (30a): 0.051 mmol (31 mg) **2a** was stirred in 1 mL MeOH in the presence of 10 mol% NaOMe (5M in MeOH) for 2h under standard condition. Eluent 5% MeOH in DCM. Yield: 18.3 mg, 80%; off-white solid, mp 230-233 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.93 (s, 1H), 5.59 (s, 1H, -OH), 5.45 (s, 1H, -OH), 5.31 (s, 1H, -OH), 5.08 (d, *J* = 7.0 Hz, 1H), 4.67 (s, 1H, -OH), 3.69 (d, *J* = 11.0 Hz, 1H), 3.54 – 3.45 (m, 2H), 3.42 (m, Hz, 2H), 3.22 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D6) δ 182.53, 165.24, 162.92, 148.65, 136.89, 132.80, 131.52, 123.05, 118.73, 114.25, 111.34, 111.00, 110.90, 108.58, 100.35, 77.28, 76.39, 73.24, 69.48, 60.54, 7.94. IR (neat) 3313, 2924, 2227, 1693, 1654, 1600, 1428, 1397, 1264, 1102, 1080, 1043, 991, 778, 681 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{23}H_{22}NO_8$, 440.1345, found 440.1339.

31a



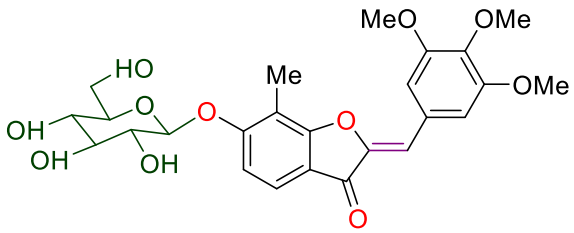
[Z)-2-(4'-cyanobenzylidene)benzofuran-3(2H)-one]-6-O-β-D-glucopyranoside (31a): 0.051 mmol (30.5 mg) **1a** was stirred in 1 mL MeOH in the presence of 10 mol% NaOMe (5M in MeOH) for 2h under standard condition. Eluent 5% MeOH in DCM. Yield: 20 mg, 88%; off-white solid, mp 188-190 °C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.13 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.98 – 6.90 (m, 2H), 5.62 (s, 1H, -OH), 5.52 (s, 1H, -OH), 5.35 (s, 1H, -OH), 5.18 (d, *J* = 7.0 Hz, 1H), 4.69 (s, 1H, -OH), 3.71 (d, *J* = 9.0 Hz, 1H), 3.49 (d, *J* = 8.0 Hz, 2H), 3.29 (d, *J* = 6.0 Hz, 2H), 3.23 – 3.12 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D6) δ 181.87, 167.85, 165.39, 148.54, 136.72, 132.75, 131.46, 125.83, 118.68, 114.45, 114.05, 111.47, 108.83, 99.82, 99.66, 77.22, 76.38, 73.12, 69.48, 60.60. IR (neat) 3395, 3326, 2918, 2240, 1704, 1657, 1613, 1600, 1354, 1264, 1080, 1011, 903, 834, 683 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{22}H_{20}NO_8$, 426.1189, found 426.1186.

32a



[(Z)-2-(3',5'-dimethoxybenzylidene)benzofuran-3(2H)-one]-6-O-β-D-glucopyranoside (32a): 0.051 mmol, (32 mg) **14a** was stirred in 1 mL MeOH in the presence of 10 mol% NaOMe (5M in MeOH) for 2h under standard condition. Eluent 5% MeOH in DCM. Yield: 20 mg, 63%; yellow solid, mp 174-177 °C. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.72 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 2H), 6.92 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.81 (s, 1H), 6.63 (t, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 3.0 Hz, 1H, OH), 5.17 (d, *J* = 7.0 Hz, 2H, OH and anomeric), 5.11 (d, *J* = 5.0 Hz, 1H, OH), 4.63 (t, *J* = 5.5 Hz, 1H, OH), 3.81 (s, 6H), 3.71 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.53 – 3.43 (m, 2H), 3.37-3.35 (m, 1H), 3.30-3.28 (m, 2H), 3.18 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D6) δ 182.01, 167.68, 165.20, 160.71, 147.40, 133.58, 125.69, 114.84, 113.92, 111.35, 109.38, 101.89, 99.91, 99.80, 77.28, 76.49, 73.18, 69.65, 60.70, 55.45. IR (neat) 3604, 3348, 2931, 2885, 2851, 1702, 1654, 1615, 1596, 1445, 1428, 1357, 1346, 1279, 1166, 1089, 1074, 1063, 1039, 853, 685 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{23}H_{25}O_{10}$, 461.1448, found 461.1451.

33a



[(Z)-7-methyl-2-(3',4',5'-trimethoxybenzylidene)benzofuran-3(2H)-one]-6-O-β-D-gluco pyranoside (33a): 0.051 mmol (34 mg) **16a** was stirred in 1 mL MeOH in the presence of 10 mol% NaOMe (5M in MeOH) for 2h under standard condition. Eluent 7% MeOH in DCM. Yield: 17 mg, 75%; yellow solid, mp 190-192 ºC. ^{1}H NMR (300 MHz, DMSO-D6) (signals are highly overlapped) δ 7.61 (d, J = 8.5 Hz, 2H), 7.40 (s, 4H), 7.07 (d, J = 8.5 Hz, 2H), 6.85 (s, 2H), 5.53 (s, 1H, OH), 5.23 (s, 1H, OH), 5.05 (d, J = 7.0 Hz, 1H), 4.64 (s, 1H, OH), 3.87 (s, 6H), 3.74 (s, 3H), 3.68 (m, 1H), 3.49 (dd, J = 5.0, 3.0 Hz, 4H), 3.41 (m, 1H), 3.20 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D6) δ 182.32, 164.84, 162.47, 152.95, 146.78, 139.10, 127.53, 122.68, 114.69, 111.51, 110.91, 108.77, 100.54, 77.25, 76.40, 73.23, 69.51, 60.56, 60.21, 55.80, 7.58. IR (neat) 3339, 2931, 1641, 1605, 1587, 1505, 1423, 1352, 1259, 1123, 1099, 1076, 1043, 992, 776 cm^{-1}. HRMS (ESI): [M + H], calcd for $C_{25}H_{29}O_{11}$, 505.1710, found 505.1713.

5. References

1. Ono, E.; Fukuchi-Mizutani, M.; Nakamura, N.; Fukui, Y.; Yonekura-Sakakibara, K.; Yamaguchi, M.; Nakayama, T.; Tanaka, T.; Kusumi, T.; Tanaka, Y., Proc. *Natl. Acad. Sci. U. S. A.* **2006,** *103*, 11075-11080.
2. Boucherle, B.; Peuchmaur, M.; Boumendjel, A.; Haudecoeur, R. *Phytochemistry,* **2017**, *142*, 92-111.
3. Bohm, B. A. The Minor Flavonoids. In *The Flavonoids: Advances in Research*; Harborne, J. B.; Mabry, T. J., Ed.; Springer: Boston, 1988; pp 313-416.
4. Haudecoeur, R.; Boumendjel, A. *Curr. Med. Chemistry* **2012,** *19*, 2861-2875.
5. Boumendjel, A. *Curr. Med. Chem.* **2003,** *10*, 2621-2630.
6. Bandgar, B. R.; Patil, S. A.; Korbad, B. L.; Biradar, S. C.; Nile, S. N.; Khobragade, C. N. *Eur. J. Med. Chem.* **2010,** *45*, 3223-3227.
7. Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A.; Brillet, R.; Belle, C.; Nicolle, E.; Pallier, C.; Pawlotsky, J. M.; Boumendjel, A. *J. Med. Chem.* **2011,** *54*, 5395-5402.
8. Zwergel, C.; Gaascht, F.; Diederich, M.; Kirsch, G. *Nat. Prod. Commun*, **2012**, 7, 389-394.
9. Atta Ur, R.; Choudhary, M. I.; Hayat, S.; Khan, A. M.; Ahmed, A., *Chem. Pharma. Bull.* **2001,** *49*, 105-107.
10. Geissman, A. T.; Harborne, J. B. *J. Am. Chem. Soc.* **1955,** *77*, 4622-4624.
11. Thakkar, K.; Cushman, M. *Tetrahedron Lett.* **1994,** *35*, 6441-6444.
12. Harkat, H.; Blanc, A.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2008,** *73*, 1620-1623.
13. Hadjeri, M.; Beney, C.; Boumendjel, A. *Curr. Org. Chem.* **2003,** *7*, 679-689.
14. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992,** *33*, 5937-5940.
15. Nakayama, T. *J. Biosci. Bioeng.* **2002,** *94*, 487-491.
16. Nakayama, T.; Yonekura-Sakakibara, K.; Sato, T.; Kikuchi, S.; Fukui, Y.; Fukuchi-Mizutani, M.; Ueda, T.; Nakao, M.; Tanaka, Y.; Kusumi, T.; Nishino, T. *Science* **2000,** *290*, 1163-1166.

17. Tronina, T.; Strugala, P.; Poplonski, J.; Wloch, A.; Sordon, S.; Bartmanska, A.; Huszcza, E. *Molecules*, **2017**, *22*, 1230.
18. (a) Fischer, E. *Chem. Ber.,* **1893**, *26*, 2400-2412; (b) Fischer, E. *Chem. Ber.* **1895,** *28*, 1145-1167; (c) Fischer, E.; Beesch, L. *Chem. Ber.* **1894,** *27*, 2478-2486; (d) E. Fischer, E.; Beesch, L. *Chem. Ber.* **1896**, *29*, 2927-2931; (e) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957-981; (f) Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155-173; (g) Schmidt, R. R.; Castro-Palomino, J. C.; Retz, O. *Pure Appl. Chem,* **1999**, *71*, 729-744; h) Kafle, A.; Liu, J.; Cui, L. *Can. J. Chem.* **2016**, *94*, 894-901.
19. Jensen, K. J. *J. Chem. Soc., Perkin Trans*. *1*, **2002**, 2219–2233.
20. Jacobsson, M.; Malmberg, J.; Ellervik, U. *Carbohydr. Res.* **2006**, *341,* 1266–1281.
21. Michael, A. *Am. Chem. J.* **1879,** *1*, 305-312.
22. a) Fischer, E.; Raske, K. *Chem. Ber.* **1909**, *42*, 1465-1476; (b) Courtin-Duchateau, M.-C.; Veyriéres, A. *Carbohydr. Res.* **1978**, *65*, 23; (c) Talisman, I. J.; Kumar, V.; Deschamps, J. R.; Frisch, M.; Malhotra, S. V. *Carbohydr. Res.* **2011**, *346*, 2337-2341; (d) Jung, S.-H.; Cho, S.-H.; Dang, T. H.; Lee, J.-H.; Ju, J.-H.; Kim, M.-K.; Lee, S.-H.; Ryu, J.-C.; Kim, Y. *Eur. J. Med. Chem.* **2003**, *38,* 537–545; (e) Kroger, L.; Thiem, J. J. *Carbohydr. Chem*. **2003**, *22*, 9-23.
23. Bubb, W. A. *Concept. Magn. Reson. A* **2003**, *19A*, 1-19.
24. Hastings, J. S.; Heller, G.H. *J. Chem. Soc. Perkins Trans. 1.* **1972**, 2128-2132.
25. Gottlieb, H. E.; Lotlyr V. *J. Org. Chem.* **1997**, 62, 7512-7515.
26. Lee, C-Y.; Chew, E-H.; Go, M-L. *Eur. J. Med. Chem*. **2010**, *45*, 2957-2971.
27. Siah, M.; Farzaei, M. H.; Ashrafi-Kooshk, M. R.; Adibi, H.; Arab, S. S.; Rashidi, M. R.; Khodarahmi, R. *Bioorg. Chem.* **2016**, *64*, 74-84.
28. Stubblefield, J.; Taylor, Z. E.; Handy, S.; Farone, M.; McClelland, E.; Sutton, C.; Farone, A.; Park, H.; Araujo, D. *PCT Int. Appl.* **2017**, WO 2017180644 A1.
29. Bao, Y-T.; Zhang, M.; Li, T.; Xiao, H-F.; Zhao, T.; Xu, X-H.; Yang, L-Q. *J. Heterocycl. Chem.*, **2016**, *53*, 637-642.
30. Lee, Y. H.; Shin, M. C.; Yun, Y. D.; Shin, S. Y.; Kim, J. M.; Seo, J. M.; Kim, N-J.; Ryu, J. H.; Lee, Y. S *Bioorg. Med. Chem*. **2015**, *23*, 231-240.

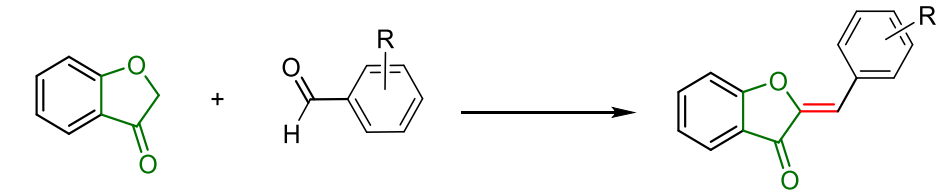
31. Popova, A. V.; Bondarenko, S. P.; Podobii, E. V.; Frasinyuk, M. S.; Vinogradova, V. I. *Chem. Nat. Compd.* **2017**, *53*, 708-713.
32. Liew, K-F.; Chan, K-L.; Lee, C-Y. *Eur. J. Med. Chem.* **2015**, *94*, 195-210.
33. Wang, S.; Xu, L.; Lu, Y-T.; Liu, Y-F.; Han, B.; Liu, T.; Tang, J.; Li, J.; Wu, J.; Li, J-Y.; Yu, L-F.; Yang, F. *Eur. J. Med. Chem.* **2017**, *130*, 195-2098.

CHAPTER - III

AN UNUSUAL TRIAZOLE SYNTHESIS FROM AURONES

1. Introduction

Aurones are an interesting minor sub-family of the flavonoid family of natural products.[1] Although known for some time, they have received comparatively little interest until fairly recently. Even this current interest has been fairly limited in terms of its diversity. In part, this situation is the result of most efforts being determined by the synthetic approach employed to access the aurone framework. In virtually all cases, this approach is the Knoevenagel-type condensation of a benzofuranone with an aromatic aldehyde.[2] (Scheme 11)



benzofuranone aromatic aldehyde aurone

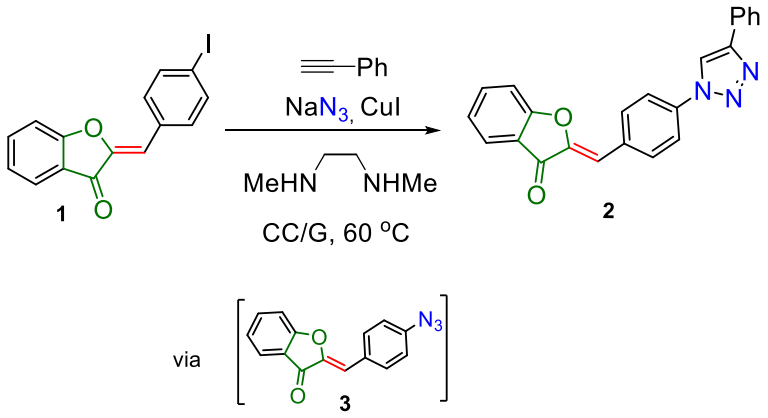
Scheme 11: Condensation Routes to Aurones

While it is true that there are many commercially available aldehydes as well as a number of commercially available benzofuranones, we were interested in potentially combining our recently reported azidation/click reaction of aryl halides to further diversify

and functionalize halogen-containing aurones.[3] In this way, even greater structural diversity could be accessed without the need to synthesize a new aldehyde for each new aurone.

In addition, this same azidation chemistry in the absence of an alkyne should afford the unknown 4-azidoaurone. This compound or similar azidoaurones are expected to be suitable substrates for photoaffinity labeling via nitrene generation and thus find application in studies to better understand the interaction of these compound with biological systems.[4]

With these twin goals in mind, iodoaurone **1** was selected as a substrate for an *in situ* azidation/click reaction. Initial attempts did result in the consumption of the iodoaurone, but failed to afford any of the anticipated triazole **2**. (Scheme 12)

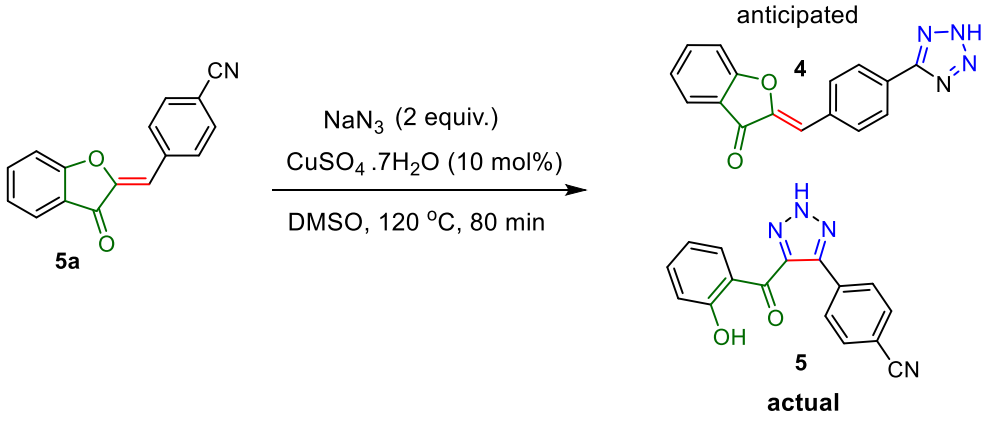


Scheme 12: Azidation /Click Attempt

In an effort to understand the failure of this transformation, iodoaurone **1** was simply subjected to our standard azidation conditions but without the alkyne (sodium azide,

catalytic copper (I) iodide and *N*, *N*'-dimethylethylenediamine in choline chloride/ glycerol). Again, this consumed the starting material but failed to afford any azide **3**. Further variations in solvent, catalyst, and temperature likewise only resulted in conversion to a new unknown product that did not contain an azide. However, the product featured most of the anticipated spectral features of an aurone except for the very characteristic enone *β*-proton.

After several other failed attempts, new attempts were made to react cyanoaurone **5a** with sodium azide to form the corresponding tetrazole **4**. (Scheme 13) Again, the reaction failed to afford the anticipated tetrazole but did result in the consumption of the starting material and the formation of a new polar product that showed considerable similarity to that obtained from the reactions with iodoaurone **1**.



Scheme 13: New Triazole Formation

This product could be isolated as a solid that could be crystalized to afford crystals suitable for x-ray diffraction analysis.[5] (Figure 8) This analysis confirmed that the product was indeed not a tetrazole, but actually triazole **5**.

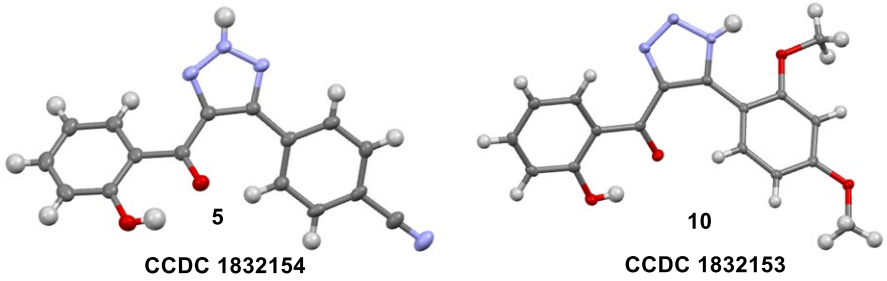


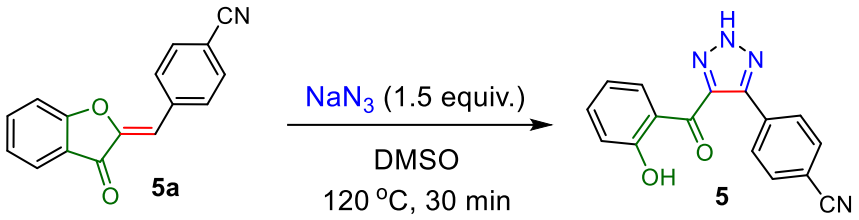
Figure 8: Crystal Structure of New Triazoles

2. Results and discussions

With this structural confirmation, reexamination of the products from the reaction with iodoaurone **1** proved to have similarly afforded these unique triazole products. Further optimization of this transformation was conducted using cyanoaurone **5a**. (Scheme 14)

Using sodium azide in DMSO without any catalyst also afforded the triazole product **5**. Further attempts at the optimization of this transformation noted that polar aprotic solvents were suitable for this reaction, affording modest to good yields of the triazole after short reaction times at moderate temperatures (120 °C). Decreasing the temperature resulted in slower conversion to the azide, with the reaction at 100 °C requiring 3 hours and one at 80 °C requiring 6 hours. Further reduction in temperature resulted in a very sluggish and unclean reaction. Less polar solvents (THF and dioxane) were not

effective, while a protic solvent (EtOH) was slower, but did afford the product in a reduced yield.



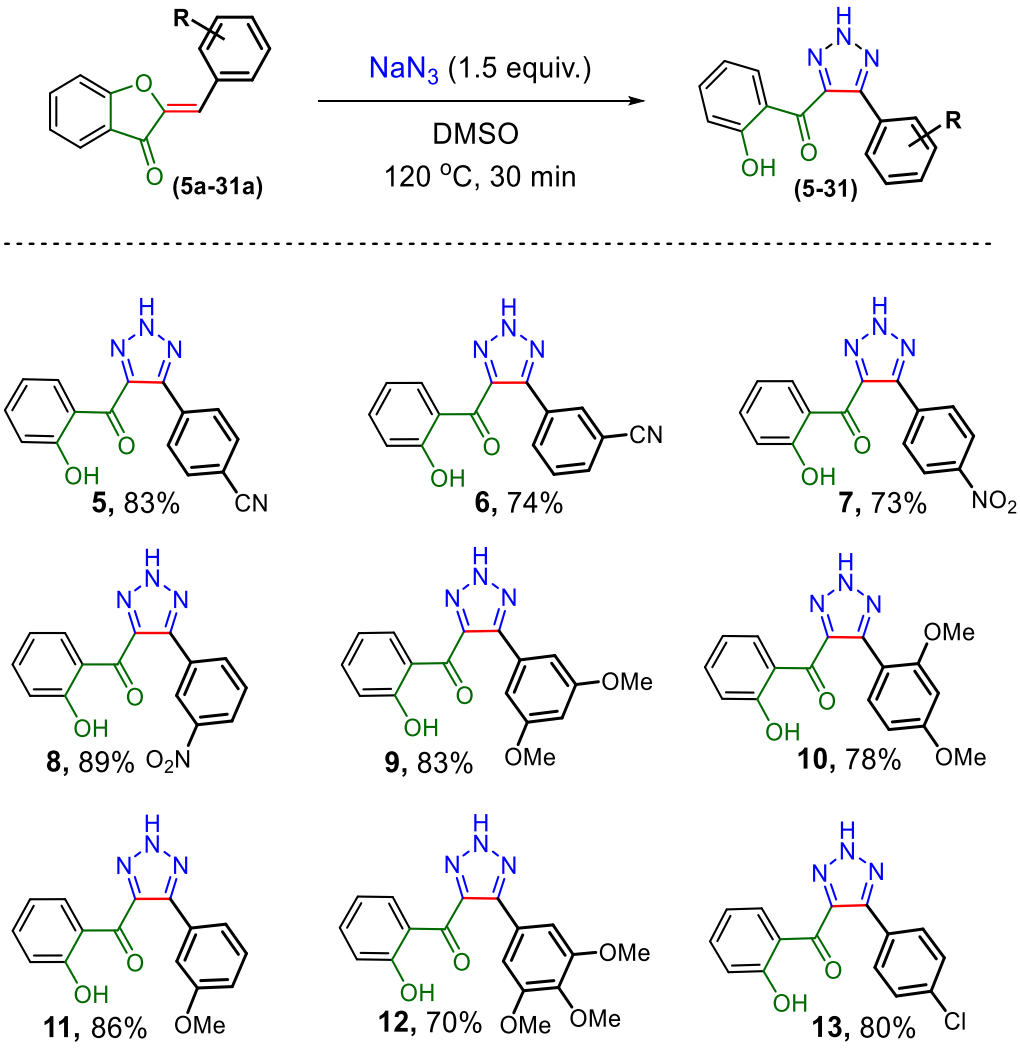
Entry	Condition Modification	Time	Yield[a] (%)
1	$CuSO_4$. $7H_2O$, 140 °C	80 min	100 (75)
2	**None**	**30 min**	**100 (83)**
3	80 °C	6 hr	100 (ND)
4	100 °C	3 hr	100 (ND)
5	DMF, 105 °C	30 min	100 (86)
6	Dioxane, 105 °C	15 hr	NR
7	THF, 65 °C	24 hr	NR
8	EtOH (95%), 105 °C	15 hr	75 (ND)
9	Glacial Acetic Acid, 120 °C	12 hr	NR

[a] Conversion yield by ^1H NMR. Values in parentheses is isolated yield ND = not determined, NR = no reaction, DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofurane

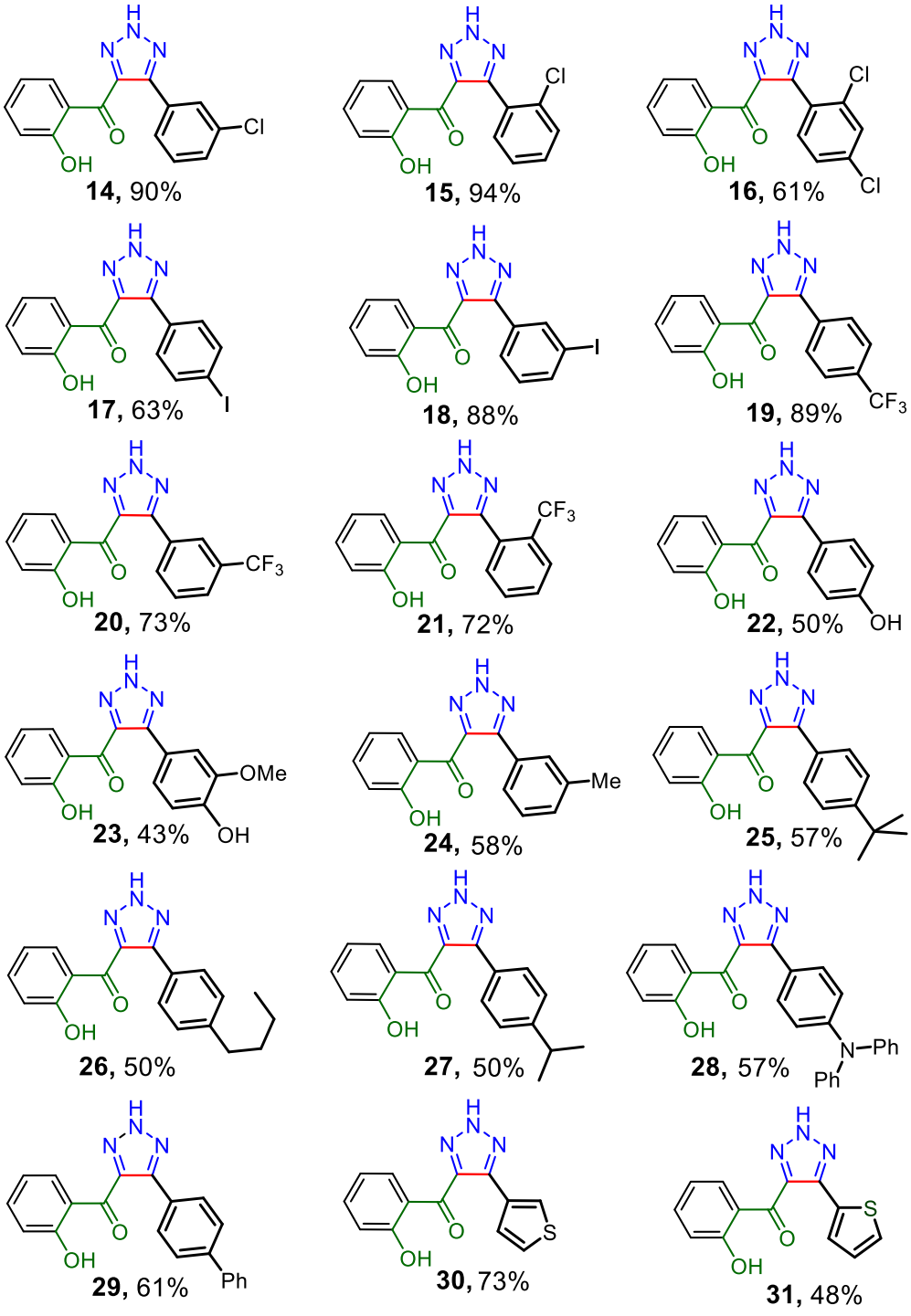
Scheme 14: Reaction Condition Study

While the results in Scheme 14 might appear to indicate that DMF was the best solvent, further examples did not demonstrate this to be a consistent result. Further, one major challenge with this chemistry was product isolation. The triazole products are relatively polar and frequently do not afford good recovery following chromatography. DMSO could be removed much more readily from the reactions than DMF and was used in all subsequent examples.

In examining the scope of the reaction, variations of the aryl group proved to be well tolerated. (Scheme 15) While the isolated yields varied from near 50% to just under 90%, there was no clear trend in terms of electronics or location of substitution on the aryl ring.



Scheme 15: Aryl Variations

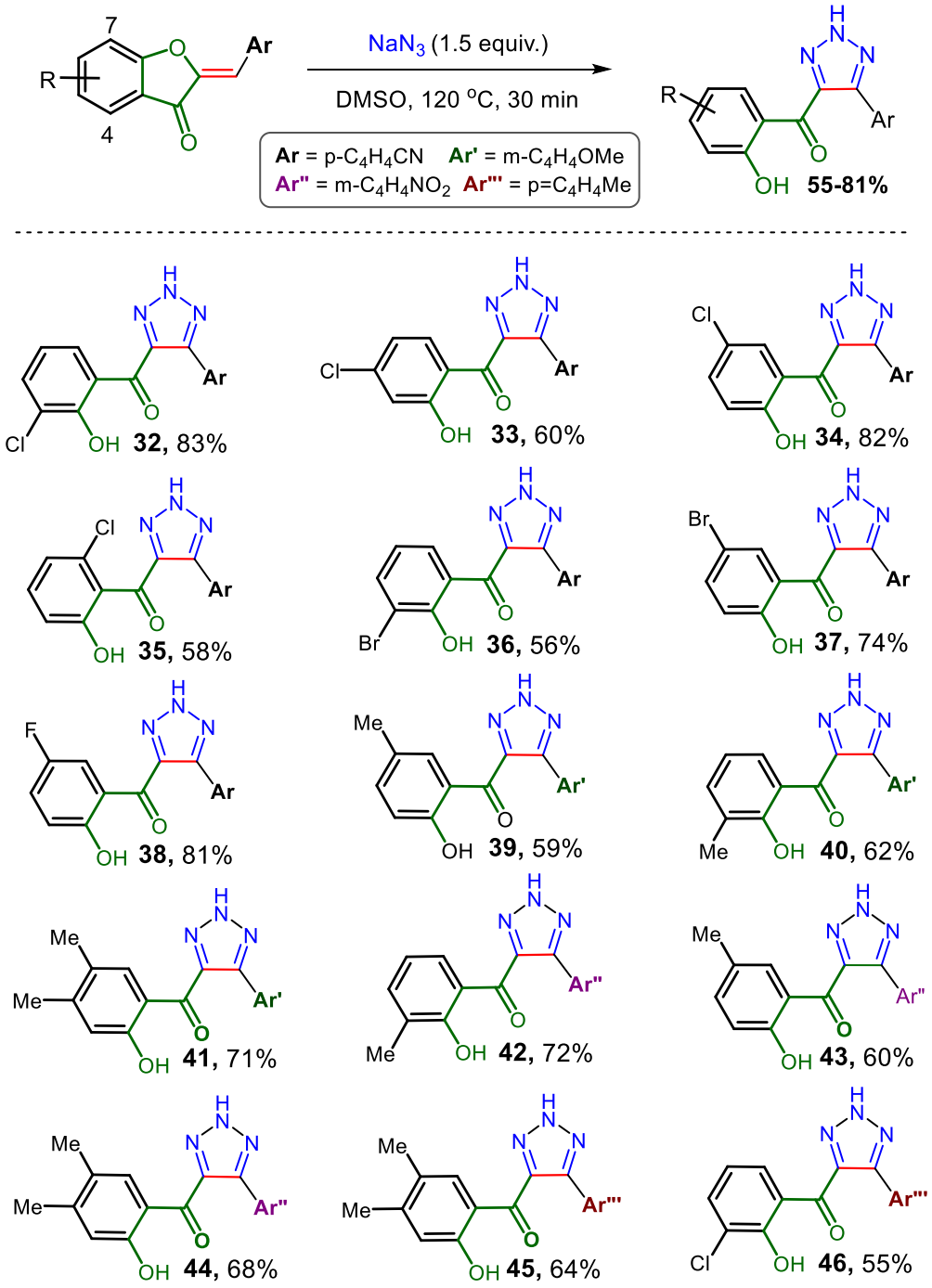


Scheme 15 (cont): Aryl Variations

Electron withdrawing groups afforded high yields, as did methyl ethers. Most halogens were similarly efficient. Curiously, free hydroxyl groups and alkyl groups tended to afford the lowest yields. In the case of free hydroxyl groups, this is likely due to their highly polar nature, making isolation and purification difficult. It is worth noting that NMR analysis of the crude reaction mixtures showed clean conversion to the product, with only small amounts (< 10%) of starting material or unidentified by-products as well as residual solvent. Further, mass balance was near quantitative, demonstrating that the yield challenge is clearly in the purification step. Two heteroaromatics that were explored afforded similar yields.

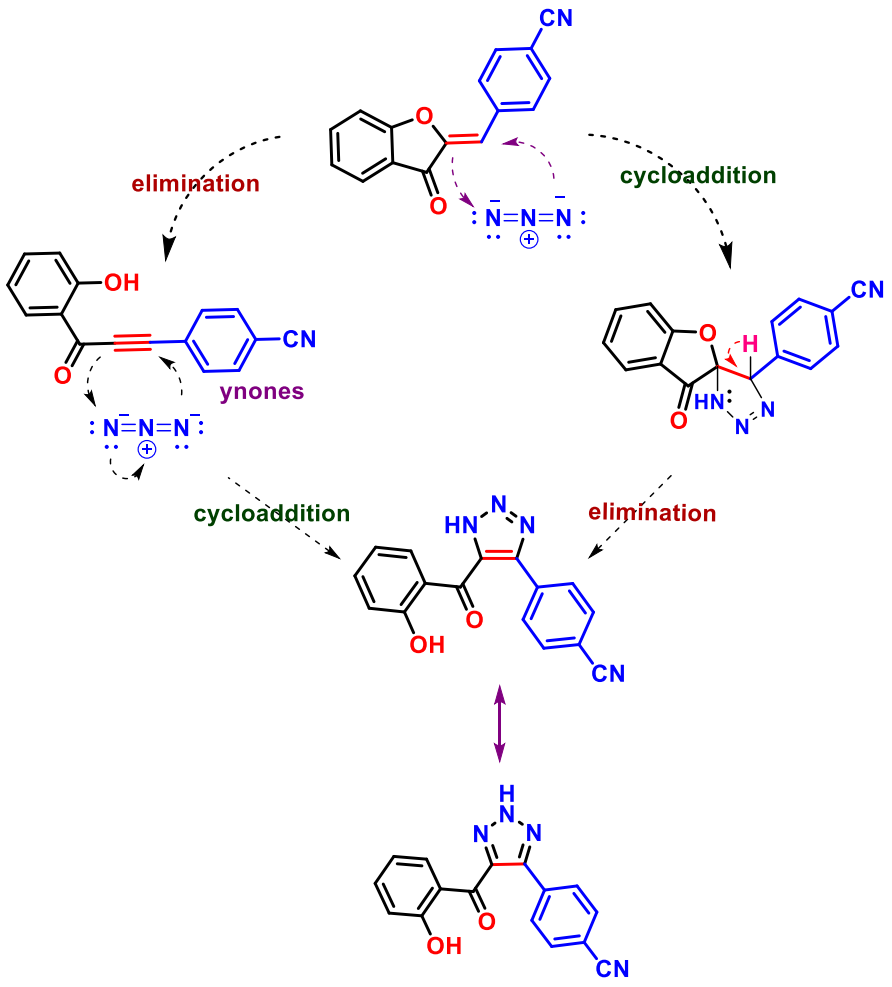
In probing the utility of the reaction with respect to the benzofuranone portion, it proved to be equally general. (Scheme 16) Halogens were tolerated at all positions as were methyl groups at all 3 positions that were tested. Yields ranged from 55-81%.

Additional peaks observed, which were particularly evident in the ^{13}C-NMR of some triazoles, suggested the presence of tautomeric mixtures that depend on the concentration and type of solvent used. Tautomerism has been reported as a common phenomenon in 1,2,3-triazoles,[6] which in our case, was further evidenced in the crystal structures of triazoles **5** and **10** which feature the N2 and N1 tautomers respectively. (Figure 1) This tautomerization is evident from the hybridization and bond lengths indicated in the crystal structures and the inferred location of hydrogen atoms.



Scheme 16: Benzofuranone Variations

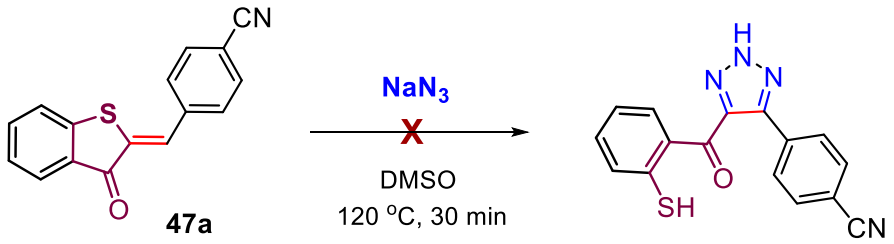
With respect to the reaction mechanism, it is unclear at this point whether some form of Michael addition/elimination/cyclization sequence, a cycloaddition/elimination sequence, or an elimination to an intermediate ynone followed by cycloaddition is occurring as proposed in scheme 17. From the literature, the closest transformation was reported a number of years ago by Bognar and co-workers on the conversion of dibromochalcones with sodium azide in DMF into a number of different compounds, including a triazole.[7]. Even in this case, the mechanism is unclear, and a number of



Scheme 17: Plausible Mechanism for Triazole Formation

possible pathways are proposed. Ring opening of aurones using methyl isocyanoacetate has been reported recently by Shao and co-workers for which a more complicated cyclization/ring-opening pathway has been proposed.[8] But, this reaction also requires a base catalyst and proceeds best in protic solvents. Additionally, Msadek and co-workers have reported the ring-opening synthesis of pyrazoles from aurones by reaction with aryldiazomethanes under mild thermal conditions. They propose that this reaction occurs via cycloaddition followed by elimination to afford the aromatic pyrazole, but no mechanistic evidence is provided.[9]

At the same time, ynones are known to readily undergo reaction with sodium azide to afford triazoles, making the elimination/cycloaddition pathway appear to be the simplest mechanistic explanation.[10] Unfortunately, attempts to observe an ynone intermediate have not been successful, and reactions under the same reaction conditions using thioaurone **47a** afforded only recovered starting material even though it would be expected that elimination of the better thiol-leaving group would be more facile and thus afford better yields of the triazole product. (Scheme 18) Additionally, attempts to induce elimination using DBU in DMSO at temperatures up to 120 °C for up to 12 hours have resulted only in recovery of the starting aurone, as has thermal treatment of the aurone in the absence of sodium azide. All of this evidence lends more support for a cycloaddition/elimination pathway.



Scheme 18: Thioaurone Attempt

3. Conclusion

In conclusion, we have observed an unusual ring-opening triazole formation by the reaction of aurones with sodium azide. The product triazoles feature two clear sites for alkylation chemistry, as well as a great opportunity for modification at many sites in the ring system. Given this potential and their ease of access, it is anticipated that they could prove to be new, unexplored scaffolds for further development.

4. Experimental

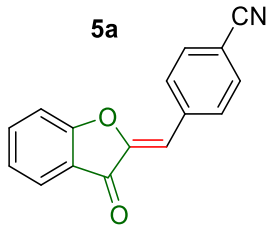
General Information: All the reactions were done under an air atmosphere. ^{1}H and ^{13}C NMR of all the compounds were recorded on JEOL AS (500 and 300 MHz) NMR instrument, and chemical shifts were recorded in ppm. All the chemical shifts were recorded taking $CDCl_3$ or DMSO or acetone-D as a standard reference.[11] The following conventions are used for multiplicities: s, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet; *tt*, triplet of triplet; *dt*, doublet of triplet; *ddd*, doublet of doublet of doublet; *br*, broad. Cary 630 FT-IR (Agilent Technologies) was used to collect IR spectra. All mass spectra were acquired on a Waters Synapt HDMS QToF with Ion Mobility. All

extracts were concentrated under reduced pressure using a Buchi Rotary Evaporator. During purification and identification of compounds, Thin Layer Chromatography (TLC) was performed on silica-coated TLC plates and monitored by short wavelength (254 nm) UV light. Products were purified by silica gel column chromatography. ACS grade reagents were employed during the experiments.

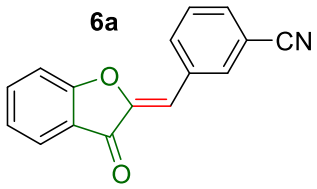
4.1. General procedure: Synthesis of aurones

All the aurones (**5a-46a**) utilized for the triazole formation were synthesized based on the literature.[12] 0.57 mmol of benzofuranone was dissolved in 5 mL of glacial acetic acid in a 3-dram glass vial containing a magnetic stir bar. To this solution, 0.63 (1.1 equivalent) of aldehyde and 3 drops (0.2 mL) of concentrated HCl were added and stirred at room temperature for 30 min to 6 hours. In most cases, reaction resulted in a precipitate normally after 30 min indicating the completion of the reaction. After the reaction was complete, it was poured into ice-cold DI water. The precipitate obtained was filtered, and the residue was washed multiple times with water and allowed to air dry. No further purification was required. For some of the aurones which did not precipitate out efficiently, the water diluted reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. Among the synthesized aurones, **5a-10a, 12a-17a, 19a-29a**, and **31a** are known compounds and were characterized by comparing ^{1}H and ^{13}C NMR with those reported in the literature.[13]

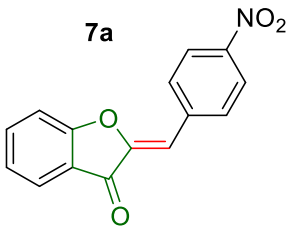
4.1.1. Characterization data for known aurones



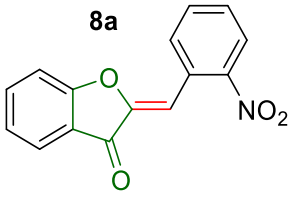
(Z)-4-((3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (5a)[13a]: Yield: 84% (119 mg); yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.70 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 6.83 (s, 1H).



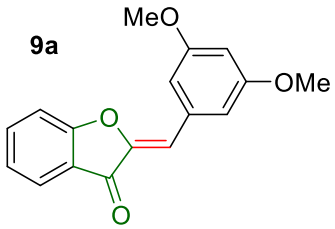
(Z)-3-((3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (6a)[13b]: Yield: 87% (123 mg); yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.02 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.81 (s, 1H).



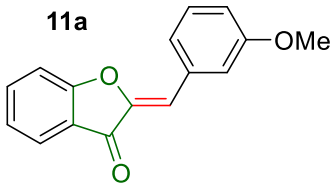
(Z)-2-(4-nitrobenzylidene)benzofuran-3(2H)-one (7a)[13a]: Yield: 88% (134 mg); orange solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.84 (ddd, *J* = 7.5, 1.4, 0.5 Hz, 1H), 7.72 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.30 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.88 (s, 1H).



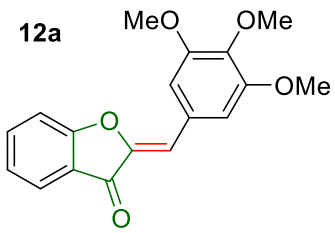
(Z)-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (8a)[13a]: Yield: 81% (123 mg); yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.24 (ddd, *J* = 8.4, 2.2, 1.0 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H).



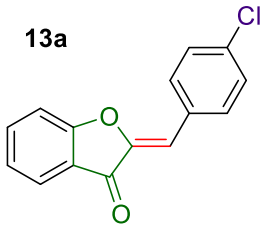
(Z)-2-(3,5-dimethoxybenzylidene)benzofuran-3(2H)-one (9a)[13c]: Yield: 70% (112 mg); greenish yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.10 (d, J = 2.1 Hz, 2H), 6.82 (s, 1H), 6.54 (t, *J* = 2.4 Hz, 1H).



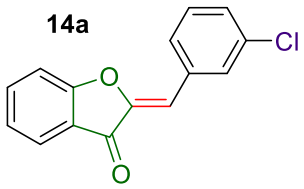
(Z)-2-(3-methoxybenzylidene)benzofuran-3(2H)-one (11a)[13c]: Yield: 83% (119 mg); yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.5, 1.5 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.97 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 6.87 (s, 1H), 3.89 (s, 3H).



(Z)-2-(3,4,5-trimethoxybenzylidene)benzofuran-3(2H)-one (12a)[13a,13c]: Yield: 82% (146 mg); bright yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.32 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.20 (s, 2H), 6.83 (s, 1H), 3.95 (s, 6H), 3.93 (s, 3H).

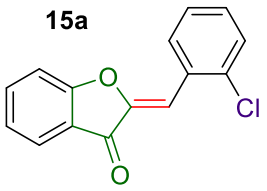


(Z)-2-(4-chlorobenzylidene)benzofuran-3(2H)-one (13a)[13d]: Yield: 80% (117 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.82 (ddd, *J* = 7.5, 1.5, 0.9 Hz, 1H), 7.76 (ddd, *J* = 8.4, 7.5, 1.5 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.23 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.84 (s, 1H).



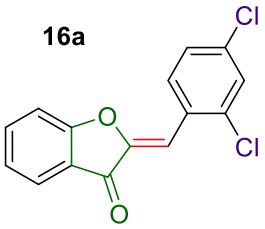
(Z)-2-(3-chlorobenzylidene)benzofuran-3(2H)-one (14a)[13c]: Yield: 50.6% (73 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.82(ddd, *J* = 7.5, 1.2, 0.6 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.69 (ddd, *J* = 8.8, 7.5, 1.5 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.81 (s, 1H).

15a



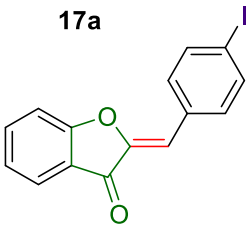
(Z)-2-(2-chlorobenzylidene)benzofuran-3(2H)-one (15a)[13d]: Yield: 82.7% (121 mg), yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.37 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H).

16a



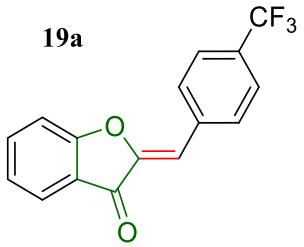
(Z)-2-(2,4-dichlorobenzylidene)benzofuran-3(2H)-one (16a)[13e]: Yield: 72% (119 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.6 Hz, 1H), 7.83 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.37 (ddd, *J* = 8.6, 1.5, 0.6 Hz, 1H), 7.33 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.27 (s, 1H), 7.27 – 7.22 (m, 1H).

17a



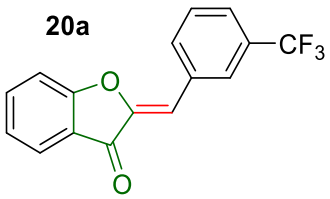
(Z)-2-(4-iodobenzylidene)benzofuran-3(2H)-one (17a)[13f]: Yield: 64.5% (128 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 3H), 7.71 – 7.66 (m, 1H, overlapped with the next signal), 7.64 (d, *J* = 8.7 Hz, 2H), 7.34 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.28 – 7.20 (t, *J* = 6.6 Hz, 1H), 6.80 (s, 1H).

19a

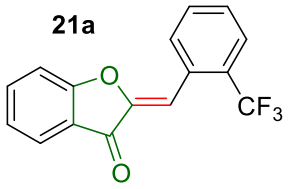


(Z)-2-(4-(trifluoromethyl)benzylidene)benzofuran-3(2H)-one (19a)[13d, 13f]: Yield: 71% (118 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.83 (ddd, *J* = 7.5, 1.4, 0.6 Hz, 1H), 7.73-7.67 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.23 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H).

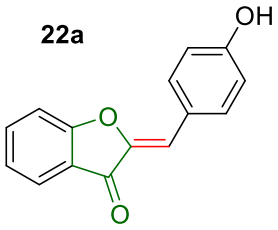
20a



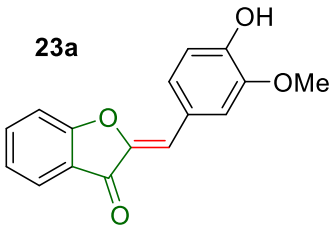
(Z)-2-(3-(trifluoromethyl)benzylidene)benzofuran-3(2H)-one(20a) [13d, 13f]: Yield: 83% (138 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.82 (ddd, *J* = 7.5, 1.2, 0.6 Hz, 1H), 7.72-7.56 (m, Hz, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 6.88 (s, 1H).



(Z)-2-(2-(trifluoromethyl)benzylidene)benzofuran-3(2H)-one (21a)[13d, 13f]: Yield: 30% (45 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.8 Hz, 1H), 7.84 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.32 (dt, *J* = 8.4, 0.6 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.20 (q, *J* = 1.8 Hz, 1H).

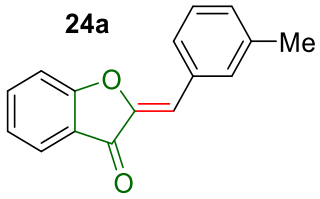


(Z)-2-(4-hydroxybenzylidene)benzofuran-3(2H)-one (22a)[13d]: Yield: 87% (118 mg), yellow solid; ^{1}H NMR (500 MHz, DMSO-D6) δ 10.24 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.92-6.90 (m, 3H).



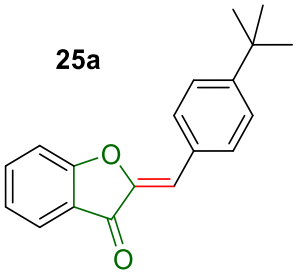
(Z)-2-(4-hydroxy-3-methoxybenzylidene)benzofuran-3(2H)-one(23a)[13c]: Yield: 71.3% (109 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 1H), 7.65 (ddd, *J* = 8.4, 7.5, 1.2 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 4.00 (s, 3H).

24a

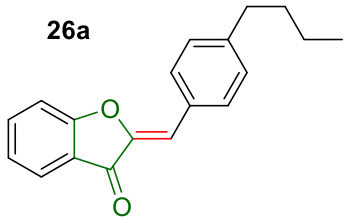


(Z)-2-(3-methylbenzylidene)benzofuran-3(2H)-one (24a)[13g]: Yield: 34% (46 mg), yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.68 – 7.65 (m, 1H), 7.39 – 7.34 (m, 2H), 7.25 – 7.20 (m, 2H), 6.88 (s, 1H), 2.43 (s, 3H).

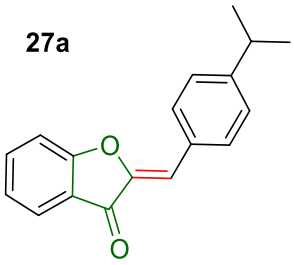
25a



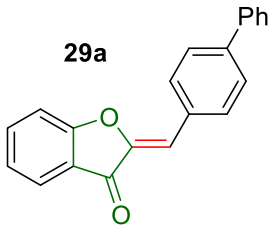
(Z)-2-(4-(tert-butyl)benzylidene)benzofuran-3(2H)-one (25a)[13h]: Crude yield: 94.5 % (150 mg, impure), brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 8.4, 0.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 1.36 (s, 9H).



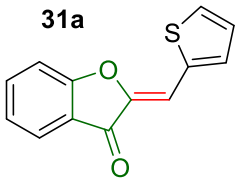
(Z)-2-(4-(butyl)benzylidene)benzofuran-3(2H)-one (26a)[13i]: Crude yield: 97 % (154 mg, impure), brown liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 6.6 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.92 (s, 1H), 2.69 – 2.64 (m, 2H), 1.63 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.37 (m, 2H), 0.94 (td, *J* = 7.2, 1.5 Hz, 3H).



(Z)-2-(4-(isopropyl)benzylidene)benzofuran-3(2H)-one (27a)[13j]: Crude yield: 93 % (140 mg, impure), brown liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.69 – 7.63 (m, 1H), 7.33 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 3.25 – 2.81 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 6H).

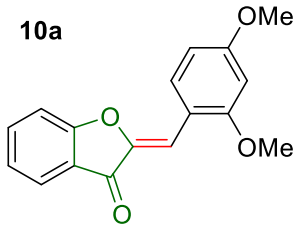


(Z)-2-(4-phenyl)benzylidene)benzofuran-3(2H)-one (29a)[13a, 13d] Crude yield: 84 % (143 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.62 (m, 3H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.38 (m, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.95 (s, 1H).

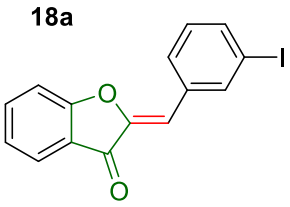


(Z)-2-(thiophen-2-ylmethylene)benzofuran-3(2H)-one (31a)[13a]**:** Crude yield: 57.6 % (75 mg), yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.63 – 7.60 (m, 1H), 7.56 (d, *J* = 3.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 7.16 (dd, *J* = 5.1, 3.7 Hz, 1H).

4.1.2. Characterization data for new aurones

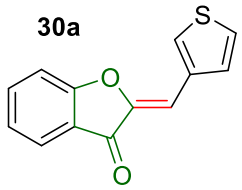


(Z)-2-(2,4-dimethoxybenzylidene)benzofuran-3(2H)-one (10a): Yield: 84% (135 mg); greenish yellow solid, mp 168-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.0 Hz, 1H), 7.8 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 184.5, 165.7, 162.9, 160.6, 146.0, 136.3, 133.5, 124.6, 123.2, 122.3, 114.6, 112.9, 107.9, 105.8, 98.1, 55.7, 55.6. IR (neat) 2929, 1701, 1645, 1589, 1459, 1271, 1183, 1094, 1028, 883 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{17}H_{15}O_4$, 283.0971, found 283.0973.

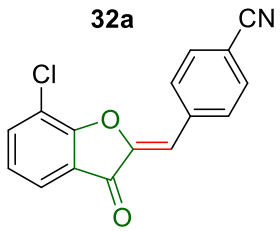


(Z)-2-(3-iodobenzylidene)benzofuran-3(2H)-one (18a): Yield: 72% (143 mg); off-white solid, mp 128-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.82 (dd, J = 8.0, 1.0, 1H), 7.74 – 7.71 (m, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.76

(s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 166.3, 147.4, 139.9, 138.7, 137.3, 134.5, 130.7, 130.6, 124.9, 123.9, 121.5, 113.2, 111.1, 94.8. IR (neat) 3054, 1709, 1649, 1600, 1459, 1302, 1190, 1067, 883, 749 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{15}H_{10}IO_2$, 248.9726, found 248.9723.



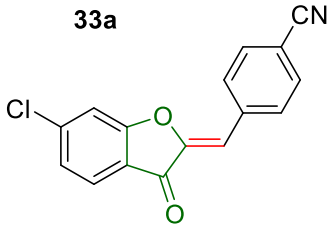
(Z)-2-(thiophen-3-ylmethylene)benzofuran-3(2H)-one (30a): Yield: 82% (107 mg); yellow solid, mp 99-101 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 3.0 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.64 (d, J = 5.0 Hz, 1H), 7.41 (dd, J = 5.0, 3.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 166.0, 146.3, 136.9, 133.9, 130.5, 129.4, 126.5, 124.7, 123.5, 122.2, 113.0, 107.3. IR (neat) 3091, 1705, 1647, 1601, 1595, 1459, 1299, 1187, 1092, 868, 751 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{13}H_9O_2S$, 229.8350, found 229.8349.



(Z)-4-((7-chloro-3-oxobenzofuran-2(3H)ylidene)methyl)benzonitrile(32a) Yield: 89% (143 mg); pink solid, mp 226-228 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz,

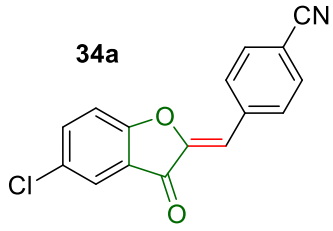
2H), 7.76 (d, J = 8.5 Hz, 2H), 7.73 (dd, J = 7.5, 1.0 Hz, 1H), 7.70 (dd, J = 8.0, 1.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 6.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 161.9, 147.9, 137.2, 136.4, 132.7, 131.9, 124.9, 123.3, 123.1, 118.9, 118.5, 113.2, 111.6. IR (neat) 3036, 2225, 1715, 1657, 1601, 1477, 1434, 1289, 1138, 890 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9ClNO_2$, 282.0323, found 282.0324.

33a

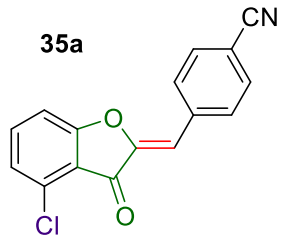


(Z)-4-((6-chloro-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (33a) Yield: 90 % (145 mg); light pink solid, mp 242-244 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 2H), 7.78 – 7.71 (m, 3H), 7.40 (d, J = 1.8 Hz, 1H), 7.26 (dd, J = 8.1, 1.5 Hz, 1H), 6.85 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 166.5, 148.3, 143.8, 136.5, 132.7, 131.7, 125.8, 125.2, 119.9, 118.6, 113.9, 113.0, 110.9. IR (neat) 3093, 2227, 1708, 1654, 1609, 1428, 1343, 1136, 873, 817 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9ClNO_2$, 282.0323, found 282.0326.

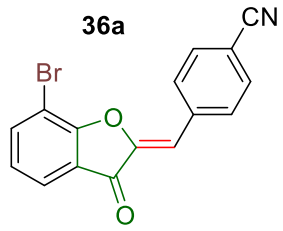
34a



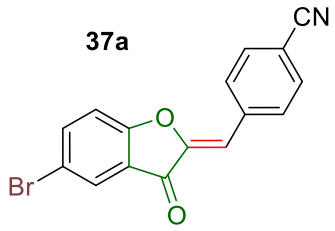
(Z)-4-((5-chloro-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (34a) Yield: 89 % (142 mg); yellow solid, mp 220-223 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.26 (s, 1H), 6.86 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 164.6, 148.3, 137.4, 136.5, 132.7, 131.8, 130.0, 124.7, 122.5, 118.6, 114.5, 113.1, 111.1. IR (neat) 3065, 2228, 1712, 1651, 1587, 1459, 1261, 1179, 1116, 833, 808 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9ClNO_2$, 282.0323, found 282.0321.



(Z)-4-((4-chloro-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (35a) Yield: 92 % (148 mg); light yellow solid, mp 248-250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.22 (dd, *J* = 7.9, 0.6 Hz, 1H), 6.86 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8, 166.8, 147.8, 137.62, 136.6, 133.0, 132.6, 131.7, 125.5, 118.8, 118.6, 113.0, 111.5, 110.7. IR (neat) 3041, 2221, 1716, 1649, 1597, 1472, 1252, 1161, 971, 829, 792 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9ClNO_2$, 282.0323, found 282.0325.

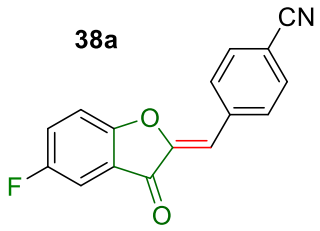


(Z)-4-((7-bromo-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (36a) Yield: 89 % (165 mg); light pink solid, mp 234-237 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.86 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.81 – 7.74 (m, 3H), 7.18 (t, J = 7.8 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.8, 163.3, 147.9, 140.1, 136.4, 132.7, 131.9, 125.4, 123.9, 122.9, 118.5, 113.2, 111.5, 106.3. IR (neat) 2223, 1712, 1653, 1599, 1426, 1272, 1129, 971, 833, 752 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9BrNO_2$, 325.9817, found 325.9815.

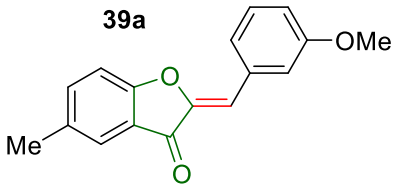


***(Z)-4-((5-bromo-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (37a)*:** Yield: 70 % (130 mg); orange solid, mp 205-207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.2, 164.9, 148.1, 140.1, 136.4, 132.6, 131.8, 127.7, 122.9, 118.5, 117.1, 114.8, 113.1, 111.2. IR (neat) 3063, 2227,

1712, 1653, 1595, 1457, 1177, 1116, 833, 807 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9BrNO_2$, 325.9817, found 325.9814.

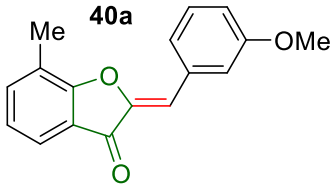


***(Z)-4-((5-fluoro-3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (38a)*:** Yield: 88 % (133 mg); yellow solid, mp 208-211 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.50 – 7.45 (m, 1H), 7.42 (dd, J = 8.4, 2.7 Hz, 1H), 7.34 (dd, J = 8.7, 3.6 Hz, 1H) 6.85 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 162.4, 159.25 (d, $^1J_{C\text{-}F}$ = 245.8 Hz), 148.8, 136.6, 132.6, 131.7, 125.0 (d, $^2J_{C\text{-}F}$ = 26.1 Hz), 122.0 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 118.6, 114.4 (d, J = 7.8 Hz), 113.0, 110.96, 110.7 (d, $^2J_{C\text{-}F}$ = 24.5 Hz). IR (neat) 3069, 2219, 1712, 1656, 1608, 1479, 1261, 1192, 1090, 905, 820 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_9FNO_2$, 266.0618, found 266.0621.

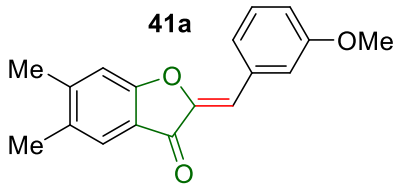


***(Z)-2-(3-methoxybenzylidene)-5-methylbenzofuran-3(2H)-on (39a)*:** Yield: 50 % (83 mg); yellow solid, mp 152-154 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, (br) 1H), 7.50 (s, 1H), 7.49 – 7.45 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 6.98 – 6.94

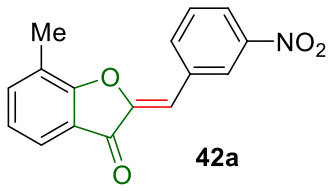
(m, 1H), 6.84 (s, 1H), 3.88 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 164.8, 159.9, 147.5, 138.2, 133.7, 133.4, 129.9, 124.4, 124.4, 121.6, 116.6, 115.8, 112.7, 112.6, 55.5, 20.9. IR (neat) 2920, 1697, 1649, 1484, 1269, 1164, 905, 816, 780 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{17}H_{15}O_3$, 267.1022, found 267.1024.



***(Z)-2-(3-methoxybenzylidene)-7-methylbenzofuran-3(2H)-one (40a)*:** Purified by column chromatography (eluent - 10% EA : hexane). Yield: 50 % (76 mg); yellow solid, mp 126-128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.43 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.82 (s, 1H), 3.85 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 164.9, 159.9, 147.2, 137.8, 133.8, 129.9, 124.4, 123.5, 122.9, 122.0, 121.2, 116.3, 115.9, 112.7, 55.3, 14.3. IR (neat) 3011, 1693, 1646, 1600, 1493, 1456, 1264, 1201, 1131, 1041, 807, 758,cm^{-1}. HRMS (EI): [M+H], calcd for $C_{17}H_{15}O_3$, 267.1022, found 267.1025.

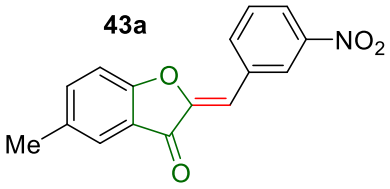


***(Z)-2-(3-methoxybenzylidene)-5,6-dimethylbenzofuran-3(2H)-one(41a)*:** Purified by column chromatography (eluent - 10% EA : hexane) Yield: 45 % (80 mg); orange solid, mp 133-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.48 – 7.44 (m, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 6.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.79 (s, 1H), 3.87 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 165.4, 159.9, 148.1, 147.7, 133.9, 132.5, 129.9, 124.6, 124.3, 119.5, 116.4, 115.7, 113.5, 112.2, 55.4, 21.6, 19.5. IR (neat) 2922, 1696, 1655, 1613, 1467, 1387, 1195, 1127, 907, 851, 780cm^{-1}. HRMS (EI): [M+H], calcd for $C_{18}H_{17}O_3$, 281.1178, found 281.1177.

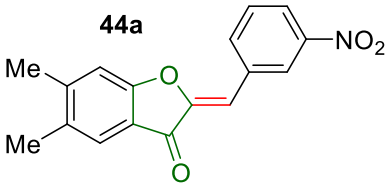


42a

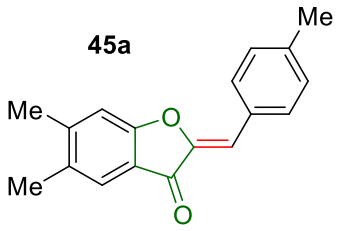
***(Z)-7-methyl-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (42a)*:** Yield: 92 % (147 mg); orange solid, mp 230-233 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (t, *J* = 1.8 Hz, 1H), 8.24 (ddd, *J* = 8.0, 2.1, 0.9 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* =7.8 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 165.1, 148.9, 148.4, 138.5, 136.8, 134.4, 129.9, 125.8, 124.1, 123.9, 123.3, 122.3, 120.8, 109.4, 14.3. IR (neat) 3073, 1703, 1653, 1597, 1528, 1343, 1192, 1138, 930, 766 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_{12}NO_4$, 282.0767, found 282.0764.



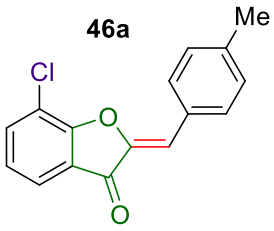
(Z)-5-methyl-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (43a): Yield: 92 % (147 mg); orange solid, mp 176-179 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (t, *J* = 1.9 Hz, 1H), 8.23 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.55 – 7.49 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 164.9, 148.8, 148.5, 138.8, 136.8, 134.3, 134.0, 129.9, 125.6, 124.6, 124.0, 121.2, 112.8, 109.4, 20.9. IR (neat) 2968, 1712, 1660, 1489, 1203, 1162, 799 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_{12}NO_4$, 282.0767, found 282.0767.



***(Z)-5,6-dimethyl-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (44a*)**:* Yield: 74 % (138 mg); yellow solid, mp 227-230 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (t, *J* = 1.8 Hz, 1H), 8.22 (ddd, *J* = 8.4, 2.2, 1.0 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.56 (s, 1H), 7.20 (s, 1H), 6.83 (s, 1H), 2.42 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3, 165.6, 148.9, 148.8, 136.7, 134.4, 133.1, 129.8, 125.5, 124.8, 123.8, 119.1, 113.7, 108.8, 21.7, 19.6. IR (neat) 2926, 1703, 1658, 1613, 1524, 1459, 1341, 1131, 799 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{17}H_{14}NO_4$, 296.0924, found 296.0928.

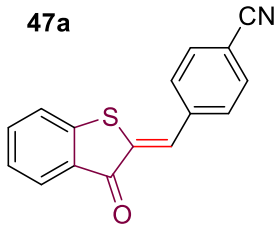


(Z)-5,6-dimethyl-2-(4-methylbenzylidene)benzofuran-3(2H)-one (45a): Yield: 63 % (95 mg); yellow solid, mp 154-157 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 2H), 6.83 (s, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 165.3, 147.9, 147.2, 140.3, 132.3, 131.5, 129.9, 129.8, 124.5, 119.7, 113.5, 112.7, 21.7, 21.6, 19.6. IR (neat) 2922, 1697, 1647, 1589, 1466, 1194, 1157, 1121, 1023, 816 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{18}H_{17}O_2$, 265.1229, found 265.1232.



(Z)-7-chloro-2-(4-methylbenzylidene)benzofuran-3(2H)-one (46a): Yield: 65 % (101 mg); yellow solid, mp 124-126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 161.6, 146.3, 141.3, 136.4, 132.1, 130.0, 129.2, 124.2, 123.7, 122.9, 118.7, 115.2, 21.8. IR (neat) 2922,

1705, 1643, 1599, 1479, 1194, 1176, 1138, 969, 887 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_{12}ClO_2$, 271.0524, found 271.0522.



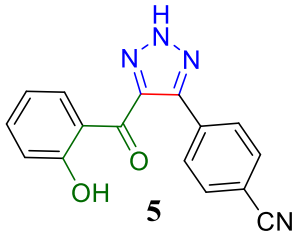
(Z)-4-((3-oxobenzo[b]thiophen-2(3H)-ylidene)methyl)benzonitrile (47a): Following the general procedure benzo[*b*]thiophen-3(*2H*)-one (53 mg, 0.35 mmol) and 4-formylbenzonitrile (50 mg, 0.38 mmol) were dissolved in 5 mL glacial acetic and stirred at room temperature for 1 hour in the presence of 3 drops of conc. HCl. Yield: 65 % (101 mg); brown solid, mp 188-190 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.0 Hz, 1H), 7.89 (s, 1H), 7.80 – 7.74 (m, 4H), 7.65 – 7.61 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 145.58, 138.7, 136.1, 133.7, 132.8, 131.1, 130.5, 129.9, 127.5, 126.3, 124.2, 118.5, 112.9. IR (neat) 3069, 2227, 1682, 1599, 1586, 1194, 1449, 1280, 1049, 833, 734 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_{10}NOS$, 264.0484, found 264.0485.

4.2. General procedure for the synthesis of triazoles

In a 3-dram glass vial, aurone (1 equivalent) and sodium azide (1.5 equivalent) were combined and dissolved in 1.5 mL of regular DMSO. The reaction mixture was then stirred for 30 minutes at 120 ºC in a sand bath. The reaction mixture immediately changed its color to dark brown. The reaction was monitored by thin-layer chromatography. After 30

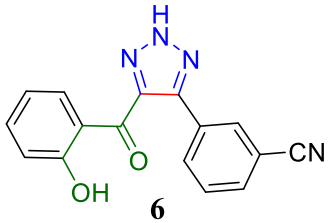
minutes, the mixture was transferred to a 50 mL centrifuge tube, diluted with distilled water, and extracted with ethyl acetate multiple times. To remove residual DMSO, the organic fraction was then washed with DI water, followed by brine. The organic fraction was concentrated in vacuo, and the crude material was further purified by flash column chromatography using mixtures of hexane and ethyl acetate (20-50% ethyl acetate: hexane) to obtain the desired triazole.

4.2.1. Characterization data for triazoles (5-46)



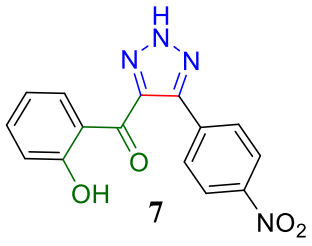
5

4-(5-(2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl)benzonitrile (5): From aurone **5a** (215 mg, 0.87 mmol); No chromatographic separation was needed. Yield: 83% (241 mg); yellow solid, mp 162-164 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.29 – 8.20 (m, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.62 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 7.04 (dd, J = 8.5, 0.9 Hz, 1H), 6.98 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ 193.4, 164.3, 138.1, 135.5, 134.9, 133.1, 133.0, 130.2, 130.1, 120.5, 119.9, 119.0, 118.8, 113.4 (peaks for another tautomer were also observed). IR (neat) 3160, 2997, 2924, 2238, 1737, 1628, 1469, 1432, 1264, 1233, 1153, 991, 920, 747 cm^{-1}.HRMS (EI): [M+H], calcd for $C_{16}H_{11}N_4O_2$, 291.0882, found 291.0885.



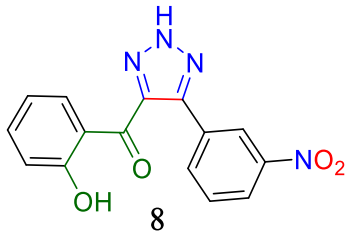
6

3-(5-(2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl)benzonitrile (6): From aurone **6a** (94 mg, 0.38 mmol); Yield: 74% (82 mg); eluent = 40% ethyl acetate : hexane, yellow solid, mp 159-161 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.31 (d, J = 7.5 Hz, 1H), 8.24 (s, 1H), 8.13 (dd, J = 8.0, 1.5 Hz, 1H), 7.88-7.85 (m, 1H), 7.70 (dd, J = 10.0, 6.0 Hz, 1H), 7.61 (ddd, J = 10.0, 6.0, 1.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.98 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ 193.1, 164.3, 138.0, 134.9, 133.9, 133.4, 132.2, 132.9, 132.5, 131.8, 130.6, 120.5, 119.9, 118.9, 118.7, 113.4 (peaks for another tautomer were also observed). IR (neat) 3306, 3073, 2924, 2231, 1628, 1600, 1475, 1315, 1145, 1119, 924, 760, 732 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{16}H_{11}N_4O_2$, 291.0882, found 291.0879.



7

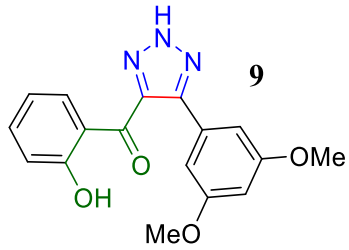
***(2-hydroxyphenyl)(5-(4-nitrophenyl)-2H-1,2,3-triazol-4-yl)methanone (7)*:** From aurone **7a** (80 mg, 0.30 mmol); Yield: 73% (68 mg); eluent = 40% ethyl acetate : hexane, yellow solid, mp 200-202 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.34 (d, J = 9.0 Hz, 2H), 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 8.10 (d, J = 9.0 Hz, 2H), 7.63 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.99 (ddd, J = 8.5, 7.5, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 193.4, 164.3, 149.0, 138.2, 136.8, 134.9, 130.6, 130.5, 124.4, 120.5, 119.9, 118.8 (peaks for another tautomer were also observed). IR (neat) 3471, 2903, 1596, 1467, 1438, 1207, 1162, 1149, 1041, 929, 834, 754 cm^{-1}. HRMS (EI): [M+H], calcd for $C_{15}H_{11}N_4O_4$, 311.0780, found 311.0781.



8

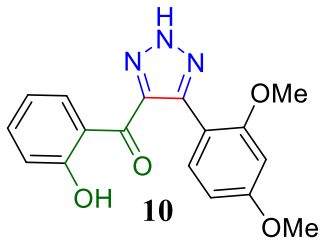
(2-Hydroxyphenyl)[5-(3-nitrophenyl)-2H-1,2,3-triazol-4-yl]methanone(8):From aurone **8a** (101.5 mg, 0.38 mmol); eluent: 50% EtOAc/hexane; yield: 105 mg (89%); yellow solid; mp 157–158 °C. ^{1}H NMR (500 MHz, acetone-d6): δ = 8.72 (br s, 1 H), 8.32 (t, J = 7.5 Hz, 2 H), 8.27 (d, J = 8.5 Hz, 1 H), 7.79 (t, J = 8.0 Hz, 1 H), 7.62 (t, J = 8.0 Hz, 1 H), 7.04 (d, J = 8.5 Hz, 1 H), 6.99 (t, J = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 193.2, 164.3, 149.2, 138.1, 134.9, 132.2, 130.7, 124.6, 124.4, 124.2, 124.0, 120.5, 119.9, 118.8 (peaks for another tautomer were also observed). IR (neat): 3110, 2903, 1628, 1534, 1482,

1350, 1253, 1153, 1100, 925, 817, 747 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{15}H_{11}N_4O_4$: 311.0780; found: 311.0783.



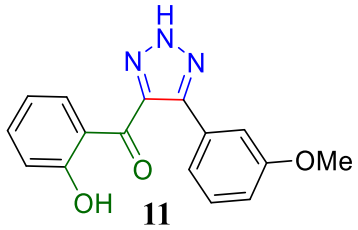
9

[5-(3,5-Dimethoxyphenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone(9): From aurone **9a** (107.3 mg, 0.38 mmol); eluent: 50% EtOAc/hexane; yield: 103 mg (83%); waxy solid; mp 79–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.99 (s, 1 H), 7.99 (d, *J* = 6.0 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 6.82 (s, 2 H), 6.49 (d, *J* = 2.5 Hz, 1 H), 3.74 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 163.6, 160.9, 137.4, 133.8, 119.6, 119.3, 118.3, 106.7, 102.1, 55.6. IR (neat): 3478, 3070, 2905, 2838, 1600, 1596, 1469, 1439, 1289, 1248, 1151, 1069, 752, 678 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{17}H_{16}N_3O_4$: 326.1141; found: 326.1138.



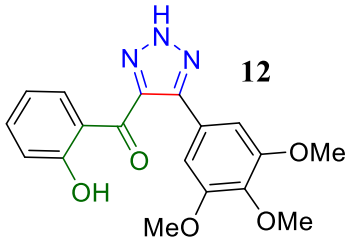
10

(2-Hydroxyphenyl)[5-(3-methoxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (10): From aurone **10a** (96 mg, 0.38 mmol); eluent: 50% EtOAc/hexane; yield: 96 mg (78%); yellow solid; mp 94-96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.03 (s, 1 H), 8.05 (d, *J* = 5.0 Hz, 1 H), 7.51 (ddd, *J* = 8.5, 3.0, 1.5 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.27 (overlapped with residual $CHCl_3$ in the solvent, 1 H) 7.23 (d, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 6.87 (t, *J* = 8.0 Hz, 1 H), 3.79 (s, 3 H). ^{13}C NMR (125 MHz, CDCl3): δ = 192.3, 163.5, 159.6, 140.7, 137.3, 133.8, 129.9, 128.6, 121.0, 119.5, 119.3, 118.3, 115.8, 114.1, 55.4. IR (neat): 3078, 2959, 2907, 1628, 1598, 1585, 1484, 1441, 1225, 1150, 1033, 1009, 752 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{14}N_4O_3$: 296.1035; found: 296.1038.

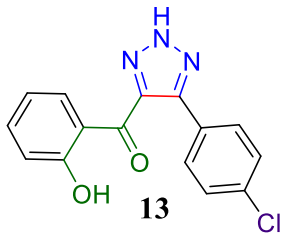


11

[5-(2,4-Dimethoxyphenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (11): From aurone **11a** (107.3 mg, 0.38 mmol); eluent: 50% EtOAc/hexane; yield: 96 mg (86%); yellow solid; mp 194-195 °C. ^{1}H NMR (300 MHz, DMSO-*d*6): δ = 11.55 (s, 1 H), 7.8 (br s, 1 H), 7.46 (dd, *J* = 18.6, 7.5 Hz, 2 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.1 Hz, 1 H), 6.53 (s, 1 H), 3.79 (s, 3 H), 3.43 (s, 3H). ^{13}C NMR (75 MHz, acetone-*d*6): δ = 194.5, 164.1, 163.3, 158.3, 137.4, 134.6, 131.8, 120.6, 119.7, 118.5, 106.4, 99.2, 55.8, 55.3. IR (neat): 3237, 1624, 1581, 1499, 1458, 1441, 1210, 1032, 925, 819, 756 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{17}H_{16}N_3O_4$: 326.1141; found: 326.1143.

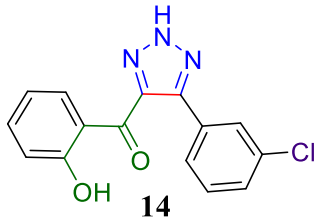


(2-Hydroxyphenyl)[5-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (12): From aurone **12a** (62.5 mg, 0.20 mmol); eluent: 50% EtOAc/hexane; yield: 50 mg (70%); yellow solid; mp 211–213 °C. ^{1}H NMR (500 MHz, DMSO-*d*6): δ = 7.77 (s, 1 H), 7.52–7.42 (m, 1 H), 7.10 (s, 2 H), 6.93 (m, 2 H), 3.77 (m, 6 H), 3.69 (m, 3 H). ^{13}C NMR (125 MHz, DMSO-*d*6): δ = 190.7, 159.3, 152.7, 138.3, 134.9, 131.9, 123.5, 118.9, 117.2, 106.1, 60.1, 55.9. IR (neat): 2957, 2928, 1631, 1596, 1482, 1441, 1248, 1132, 983, 935, 760 cm–1. HRMS (EI): *m*/*z* [M + H] calcd for $C_{18}H_{18}N_3O_5$: 356.1247; found: 356.1246.



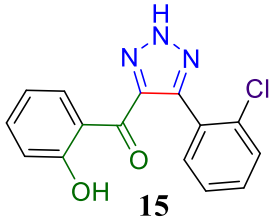
[5-(4-Chlorophenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (13): From aurone **13a** (97.5 mg, 0.38 mmol); eluent: 40% EtOAc/hexane; yield: 91 mg (80%); yellow solid; mp 147–149 °C. ^{1}H NMR (300 MHz, acetone-*d*6): δ = 12.03 (br s, 1 H), 8.28 (d, *J* = 9.0 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.59 (ddd, *J* = 8.5, 4.5, 0.7 Hz, 1 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 6.96 (dd, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz,

acetone-*d*6): δ = 193.5, 164.3, 137.9, 135.6, 134.9, 131.1, 130.9, 129.4, 129.3, 120.5, 119.8, 118.7 (peaks for another tautomer were also observed). IR (neat): 3150, 2913, 2825 (br), 1626, 1596, 1443, 1259, 1318, 1259, 1222, 1154, 1099, 924, 791 cm–1. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}ClN_3O_2$: 300.0540; found: 300.0545.



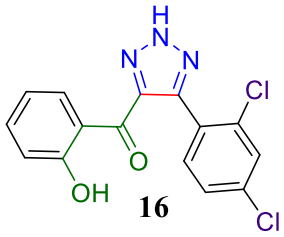
14

[5-(3-Chlorophenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (14): From aurone **14a** (97.5 mg, 0.38 mmol); eluent: 30% EtOAc/hexane; yield: 103 mg (90%); waxy solid; mp 67-69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.98 (s, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 1.5 Hz, 1 H), 7.57–7.49 (m, 2 H), 7.40–7.29 (m, 1 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.87 (t, *J* = 7.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 163.6, 141.1, 137.6, 134.8, 133.7, 129.9, 128.7, 126.9, 119.4, 118.5 (peaks for another tautomer were also observed). IR (neat): 3161 (br), 2920, 1626, 1598, 1445, 1255, 1153, 925, 754, 680 cm–1. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}ClN_3O_2$: 300.0540; found: 300.0541.



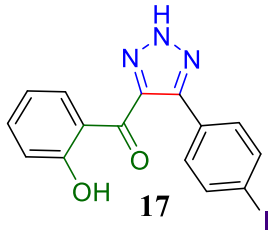
15

[5-(2-Chlorophenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (15): From aurone **15a** (97.5 mg, 0.38 mmol); eluent: 40% EtOAc/hexane; yield: 107 mg (94%); yellow solid; mp 102–105 °C. IR (neat): 3460, 3091, 2812, 1601, 1473, 1452, 1249, 1153, 1037, 992, 752 cm–1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.91 (s, 1 H), 8.36 (br s, 1 H), 7.56–7.54 (m, 1 H), 7.51 (d, *J* = 7.0 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.44–7.38 (m, 2 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.93 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 163.6, 137.2, 133.5, 133.4, 131.5, 131.1, 130.1, 127.2, 119.3, 119.1, 118.3. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}ClN_3O_2$: 300.0540; found: 300.0538.



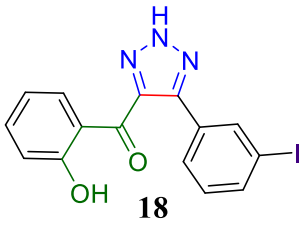
16

[5-(2,4-Dichlorophenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone 16: From aurone **16a** (128 mg, 0.44 mmol); eluent: 30% EtOAc/hexane; yield: 90 mg (61%); yellow waxy solid; mp 62–64 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.88 (s, 1 H), 8.35 (br s, 1 H), 7.56–7.52 (m, 1 H), 7.51–7.49 (m, 2 H), 7.39 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 6.94 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.8, 163.7, 137.3, 136.5, 134.2, 133.4, 132.3, 129.9, 127.6, 119.3, 119.0, 118.4. IR (neat): 3132, 2909, 1626, 1601, 1447, 1248, 1151, 922, 618 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{10}Cl_2N_3O_2$: 334.0150; found: 334.0151.



17

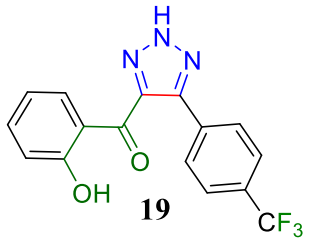
[(2-Hydroxyphenyl)[5-(4-iodophenyl)-2H-1,2,3-triazol-4-yl]methanone (17): From aurone **17a** (250.7 mg, 0.72 mmol); eluent: 30% EtOAc/hexane; yield: 177 mg (63%); yellow solid; mp 161–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.98 (s, 1 H), 8.08 (br s, 1 H), 7.78 (d, *J* = 8.5 Hz, 1 H), 7.55 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1 H), 7.06 (dd, *J* = 8.5, 1.0 Hz, 1 H), 6.91 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.1, 163.58, 138.0, 137.6, 133.7, 130.3, 119.5, 119.4, 118.6, 96.5. IR (neat): 3132, 2909, 1626, 1601, 1447, 1248, 1151, 922, 618 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}IN_3O_2$: 391.9896; found: 391.9896.



18

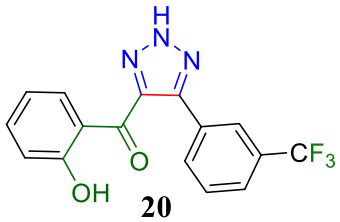
[(2-Hydroxyphenyl)[5-(3-iodophenyl)-2H-1,2,3-triazol-4-yl]methanone(18):From aurone **18a** (212.4 mg, 0.61 mmol); eluent: 30% EtOAc/hexane; yield: 209 mg (88%); waxy solid; mp 60–61 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.27 (d, *J* = 8.0 Hz, 1 H), 8.21 (t, *J* = 1.5 Hz, 1 H), 7.83 (t, *J* = 7.5 Hz, 2 H), 7.62 (t, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 8.0

Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.5, 192.1, 163.6, 145.5, 141.1, 138.5, 137.3, 133.8, 130.2, 128.0, 119.5, 119.3, 118.4, 94.3. IR (neat): 2887, 3060 (br), 2920, 1628, 1443, 1257, 1218, 1153, 1009, 924, 752 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}IN_3O_2$: 391.9896; found: 391.9898.



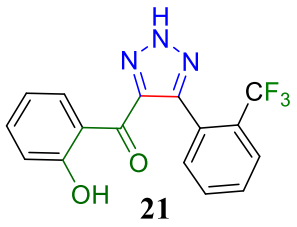
19

[(2-Hydroxyphenyl){5-[4-(trifluoromethyl)phenyl]-2H-1,2,3-triazol-4-yl}methanone (19): From aurone **19a** (98.7 mg, 0.34 mmol), no chromatographic separation was needed; yield: 101 mg (89%); yellow solid; mp 127–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.96 (s, 1 H), 8.07 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 2 H), 7.70 (d, J = 8.0 Hz, 2 H), 7.56 (ddd, J = 8.5, 7.5, 1.5 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 6.92 (t, J = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.1, 163.7, 146.2, 141.3, 137.8, 133.6, 131.8 (q, $^2J_{C,F}$ = 30 Hz), 129.1, 127.4 (q, $^1J_{C,F}$ = 240 Hz), 125.7 (q, $^3J_{C,F}$ = 4.5 Hz), 119.5, 119.4, 118.6 (peaks for another tautomer were also observed). IR (neat): 3226, 2828, 1626, 1607, 1479, 1450, 1432, 1322, 1158, 1110, 920, 845 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{11}F_3N_3O_2$: 334.0803; found: 334.0800.



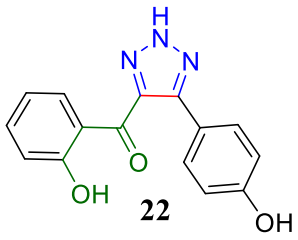
20

[(2-Hydroxyphenyl){5-[3-(trifluoromethyl)phenyl]-2H-1,2,3-triazol-4-yl}methanone (20): From aurone **20a** (119 mg, 0.41 mmol); eluent: 30% EtOAc/hexane; yield: 99 mg (73%); mp 113–115 °C.1H NMR (300 MHz, $CDCl_3$): δ = 11.97 (s, 1 H), 8.07 (d, *J* = 9.0 Hz, 2 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 7.4 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 2 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 6.89 (t, *J* = 7.7 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.9, 163.6, 141.1, 137.7, 133.6, 132.1, 131.2 (q, 2*J*C,F = 32.5 Hz), 129.3, 129.1, 126.4 (q, $^3J_{C,F}$ = 2.5 Hz), 125.6 (q, $^3J_{C,F}$ = 3.75 Hz), 123.8 (q, $^1J_{C,F}$ = 270 Hz), 119.4, 119.3, 118.3. IR (neat): 3226, 2828, 1626, 1607, 1479, 1432, 1322, 1110, 920, 758 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{11}F_3N_3O_2$: 334.0803; found: 334.0801.



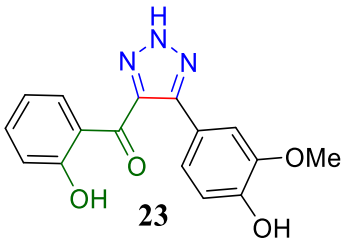
21

[(2-Hydroxyphenyl){5-[2-(trifluoromethyl)phenyl]-2H-1,2,3-triazol-4-yl}methanone (21): From aurone **21a** (41 mg, 0.14 mmol); eluent: 30% EtOAc/hexane; yield: 36 mg (72%); yellow solid; mp 147–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.90 (s, 1 H), 8.48 (d, *J* = 7.5 Hz, 1 H), 7.77 (d, *J* = 7.5 Hz, 1 H), 7.61 (td, *J* = 15.0, 7.3 Hz, 2 H), 7.53–7.46 (m, 2 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 6.93 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.3, 163.6, 143.3, 137.1, 133.61, 132.3, 131.8, 129.9, 129.3 (q, $^2J_{C,F}$ = 30 Hz), 127.5, 126.5 (q, $^3J_{C,F}$ = 5 Hz), 123.7 (q, $^1J_{C,F}$ = 272.5 Hz), 120.4, 119.3, 118.3. IR (neat): 3084, 2855, 1629, 1574, 1439, 1328, 1253, 1076, 973, 758 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{11}F_3N_3O_2$: 334.0803; found: 334.0804.



22

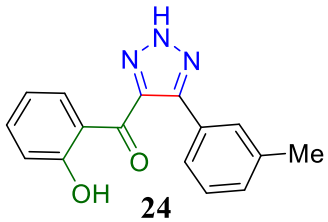
[(2-Hydroxyphenyl)[5-(4-hydroxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (22): From aurone **22a** (100 mg, 0.42 mmol); eluent: 50% EtOAc/hexane; yield: 59 mg (50%); yellow solid; mp 130–132 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.26 (d, J = 6.0 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 2 H), 7.56–7.50 (m, 1 H), 6.98 (d, J = 8.5 Hz, 1 H), 6.92–6.87 (m, 3 H) (peaks for another tautomer were also observed). ^{13}C NMR (125 MHz, acetone-d_6): δ = 193.8, 164.3, 159.5, 137.6, 135.0, 131.0, 130.8, 120.7, 119.7, 118.6, 116.3, 116.0 (peaks for another tautomer were also observed). IR (neat): 3131, 2961, 1615, 1592, 1434, 1223, 922, 748 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}N_3O_3$: 282.0878; found: 282.0875.



23

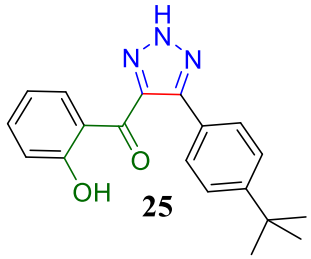
[5-(4-Hydroxy-3-methoxyphenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (23): From aurone **23a** (110 mg, 0.41 mmol); eluent: 50% EtOAc/hexane; yield: 55 mg (43%); yellow solid; mp 186–187 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 12.08 (s, 1 H), 8.26 (s, 1 H), 7.60 (ddd, J = 8.5, 7.5, 1.5 Hz, 1 H), 7.46 (d, J = 1.5 Hz, 1 H), 7.30 (dd, J = 8.0, 2.0 Hz, 1 H), 7.02 (d, J = 8.5 Hz, 1 H), 6.96 (t, J = 8.0 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 1

H), 3.87 (s, 3 H) (peaks for another tautomer were also observed). ^{13}C NMR (125 MHz, acetone-d_6): δ = 194.0, 164.3, 148.9, 148.3, 137.7, 135.1, 122.9, 120.9, 119.8, 118.7, 116.0, 113.1, 56.3 (peaks for other tautomers were also observed). IR (neat): 3181, 2939, 1628, 1594, 1486, 1445, 1214, 927, 789 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{16}H_{14}N_3O_4$: 312.0984; found: 312.0981.



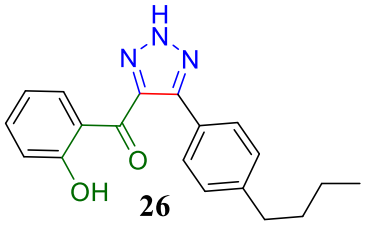
24

[(2-Hydroxyphenyl)[5-(m-tolyl)-2H-1,2,3-triazol-4-yl]methanone (24): From aurone **24a** (45 mg, 0.19 mmol); eluent: 30% EtOAc/hexane; yield: 31 mg (58%); waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.05 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.53–7.46 (m, 2 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.86 (t, *J* = 7.5 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 163.7, 141.1, 138.7, 137.3, 133.9, 130.8, 129.3, 128.8, 127.6, 125.9, 119.7, 119.3, 118.4, 77.4, 77.2, 76.9, 21.5. IR (neat): 3134, 2918, 1626, 1445, 1309, 1257, 1151, 925, 754 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{16}H_{14}N_3O_2$: 280.1086; found: 280.1084.



25

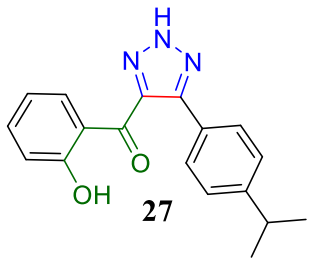
{5-[4-(tert-Butyl)phenyl]-2H-1,2,3-triazol-4-yl}(2-hydroxyphenyl)methanone (25): From aurone **25a** (142 mg, 0.51 mmol); eluent: 20% EtOAc/hexane; yield: 93 mg (57%); yellow solid; mp 138–139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.07 (s, 1 H), 8.14 (s, 1 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.50 (t, *J* = 7.8 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 7.04 (d, *J* = 8.5 Hz, 1 H), 6.86 (t, *J* = 7.6 Hz, 1 H), 1.32 (s, 9 H) (COSY, HMQC, HMBC spectra are provided in the Supporting Information). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 163.7, 153.4, 137.2, 133.9, 128.4, 125.9, 119.7, 119.3, 118.4, 34.9, 31.3. IR (neat): 3272, 2969, 1628, 1452, 1328, 1205, 998, 922, 756 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{19}H_{20}N_3O_2$: 322.1555; found: 322.1556.



26

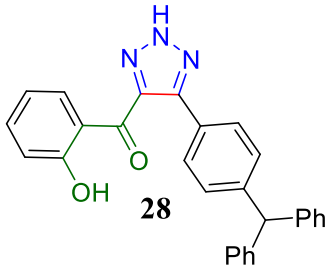
[5-(4-Butylphenyl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (26): From aurone **26a** (147.5 mg, 0.53 mmol); eluent: 20% EtOAc/hexane; yield: 85 mg (50%); brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.08 (s, 1 H), 8.16 (s, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.26 (d, *J* = 0.7 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.90

(t, J = 7.5 Hz, 1 H), 2.65 (t, J = 7.5 Hz, 2 H), 1.62 (dt, J = 13.0, 7.5 Hz, 2 H), 1.37 (dq, J = 14.5, 7.5 Hz, 2 H), 0.93 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 163.6, 145.2, 140.7, 137.2, 133.9, 128.9, 128.6, 119.7, 119.2, 118.3, 35.6, 33.4, 22.5, 14.0. IR (neat): 3105, 2928, 1628, 1469, 1253, 1151, 922, 756 cm^{-1}. HRMS (EI): m/z [M + H] calcd for $C_{19}H_{20}N_3O_2$: 322.1555; found: 322.1554.



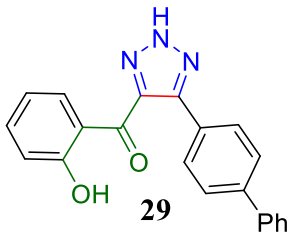
27

[(2-Hydroxyphenyl)[5-(4-isopropylphenyl)-2H-1,2,3-triazol-4-yl]methanone (27): From aurone **27a** (129.5 mg, 0.49 mmol); eluent: 20% EtOAc/hexane; yield: 75 mg (50%); yellow solid; mp 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.06 (s, 1 H), 8.12 (d, J = 7.5 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.49 (t, J = 7.5 Hz, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.24 (d, J = 1.0 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 6.84 (t, J = 7.5 Hz, 1 H), 3.12–2.81 (m, 1 H), 1.24 (d, J = 7.0 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 163.7, 151.1, 140.8, 137.2, 133.9, 128.7, 127.1, 119.7, 119.2, 118.4, 34.1, 23.8. IR (neat): 3250, 2961, 1618, 1488, 1452, 1244, 1210, 1162, 998, 924, 761 cm^{-1}. HRMS (EI): m/z [M + H] calcd for $C_{18}H_{18}N_3O_2$: 308.1399; found: 308.1401.



28

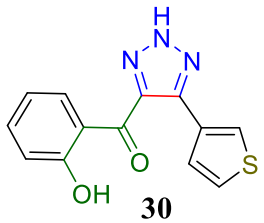
[{5-[4-(Diphenylamino)phenyl]-2H-1,2,3-triazol-4-yl}(2-hydroxyphenyl)methanone (28): From aurone **28a** (210 mg, 0.54 mmol); eluent: 30% EtOAc/hexane; yield: 133 mg (57%); orange solid; mp 88–90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.07 (s, 1 H), 8.13 (s, 1 H), 7.55 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.26 (t, *J* = 7.0 Hz, 4 H), 7.10 (d, *J* = 8.0 Hz, 4 H), 7.06 (t, *J* = 7.5 Hz, 2 H), 7.04–6.99 (m, 3 H), 6.81 (t, *J* = 7.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 163.7, 149.6, 147.0, 137.2, 133.9, 129.6, 125.5, 124.1, 121.7, 119.7, 119.2, 118.4. IR (neat): 3159, 2922, 1600, 1590, 1486, 1447, 1253, 1151, 920, 821, 754, 696 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{27}H_{21}N_4O_2$: 433.1664; found: 433.1665.



29

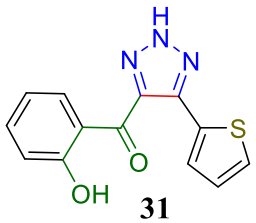
[5-([1,1'-Biphenyl]-4-yl)-2H-1,2,3-triazol-4-yl](2-hydroxyphenyl)methanone (29): From aurone **29a** (137 mg, 0.46 mmol); eluent: 20% EtOAc/hexane; yield: 94 mg (61%); yellow solid; mp 165–166 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.06 (s, 1 H), 8.15 (d, *J* = 6.5 Hz, 1 H), 7.78 (d, *J* = 8.5 Hz, 2 H), 7.65 (d, *J* = 8.5 Hz, 2 H), 7.61–7.59 (m, 2 H), 7.54–

7.50 (m, 1 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.38 (ddd, J = 7.5, 4.0, 1.5 Hz, 1 H), 7.05 (dd, J = 8.0, 1.0 Hz, 1 H), 6.90–6.87 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.8, 192.3, 163.7, 142.7, 140.9, 140.0, 137.4, 133.9, 129.1, 129.0, 127.9, 127.5, 127.2, 119.6, 119.3, 118.4. IR (neat): 3071, 2920, 1628, 1596, 1475, 1445, 1259, 1223, 1156, 924, 735 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{21}H_{16}N_3O_2$: 342.1242; found: 342.1238.



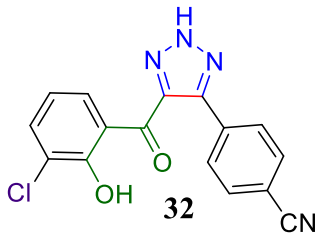
30

[(2-Hydroxyphenyl)[5-(thiophen-3-yl)-2H-1,2,3-triazol-4-yl]methanone (30): From aurone **30a** (89 mg, 0.39 mmol); eluent: 20% EtOAc/hexane;yield: 77 mg (73%); yellow solid; mp 125–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.11 (s, 1 H), 8.17 (d, J = 8.0 Hz, 1 H), 8.07 (d, J = 2.0 Hz, 1 H), 7.52 (dd, J = 12.0, 6.0 Hz, 2 H), 7.38 (dd, J = 5.0, 3.0 Hz, 1 H), 7.05 (d, J = 8.0 Hz, 1 H), 6.89 (t, J = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.0, 163.7, 140.8, 137.3, 133.9, 127.6, 127.3, 126.6, 119.7, 119.3, 118.5. IR (neat): 2883, 2922, 1628, 1600, 1445, 1309, 1255, 1108, 931, 732 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{13}H_{10}N_3O_2S$: 272.0493; found: 272.0491.



31

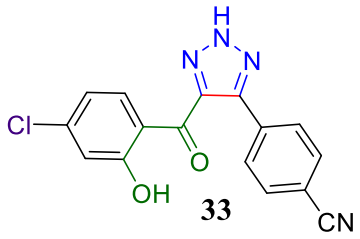
[(2-Hydroxyphenyl)[5-(thiophen-2-yl)-2H-1,2,3-triazol-4-yl]methanone (31): From aurone **31a** (105 mg, 0.46 mmol); eluent: 30% EtOAc/hexane; yield: 60 mg (48%); yellow solid; mp 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 7.5 Hz, 1 H), 7.80 (dd, *J* = 4.0, 1.0 Hz, 1 H), 7.54 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1 H), 7.45 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.12 (dd, *J* = 5.0, 3.5 Hz, 1 H), 7.08–7.05 (dd, *J* = 8.5, 1.0 Hz, 1 H), 6.92 (t, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 163.8, 140.5, 137.3, 133.8, 129.5, 128.4, 127.9, 119.7, 119.3, 118.5. IR (neat): 3080, 2928, 1626, 1596, 1467, 1443, 1255, 1161, 985, 912, 752 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{13}H_{10}N_3O_2S$: 272.0493; found: 272.0490.



32

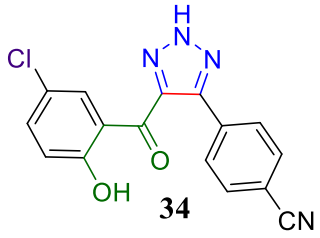
4-[5-(3-Chloro-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (32): From aurone **32a** (113 mg, 0.40 mmol); eluent: 50% EtOAc/hexane; yield: 108 mg (83%); yellow solid; mp 182–183 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 8.33 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.05 (d, *J* = 8.7 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H), 7.76 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.03 (t, *J* =

8.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 192.9, 170.9, 159.7, 148.1, 142.1, 141.6, 137.7, 135.4, 134.6, 133.7, 133.1, 133.0, 130.3, 130.2, 122.8, 121.6, 120.2, 118.9, 113.5, 113.3 (tautomers). IR (neat): 3170, 2922, 2231, 1624, 1430, 1261, 1143, 951, 737 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{10}ClN_4O_2$: 325.0492; found: 325.0493.



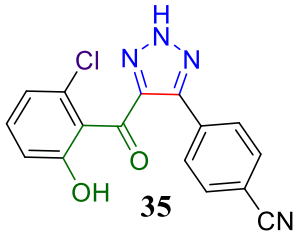
33

4-[5-(4-Chloro-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (33): From aurone **33a** (113 mg, 0.40 mmol); eluent: 50% EtOAc/hexane; yield: 78 mg (60%); yellow solid; mp 200–201 °C. 1H NMR (300 MHz, acetone-*d*6): δ = 8.37 (d, *J* = 8.7 Hz, 1 H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 2.1 Hz, 1 H), 7.03 (dd, *J* = 8.7, 2.1 Hz, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ = 192.25, 164.91, 143.09, 138.15, 136.38, 134.69, 133.12, 133.05, 130.40, 130.29, 130.23, 120.45, 119.96, 119.36, 119.02, 118.57, 113.56 (tautomers). IR (neat): 3203, 2922, 2237, 1596, 1469, 1292, 1128, 935, 782 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{10}ClN_4O_2$: 325.0492; found: 325.0495.



34

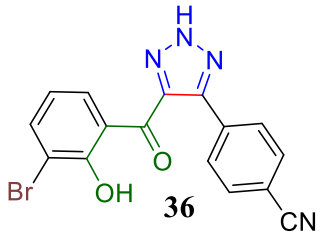
4-[5-(5-Chloro-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (34): From aurone **34a** (113 mg, 0.40 mmol); eluent: 50% EtOAc/hexane; yield: 106 mg (82%); yellow solid; mp 212–214 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.42 (d, J = 2.0 Hz, 1 H), 8.05 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 8.5 Hz, 2 H), 7.62 (dd, J = 9.0, 2.5 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 190.9, 161.9, 141.4, 136.6, 133.9, 132.9, 132.3, 129.7, 129.6, 123.3, 120.6, 119.9, 118.2, 112.8. IR (neat): 3155, 2995, 2922, 2237, 1737, 1628, 1467, 1257, 1158, 937, 827, 737 cm^{-1}. HRMS (EI): m/z [M + H] calcd for $C_{16}H_{10}ClN_4O_2$: 325.0492; found: 325.0490.



35

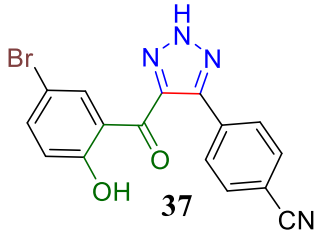
4-[5-(2-Chloro-6-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (35): From aurone **35a** (113 mg, 0.40 mmol); eluent: 50% EtOAc/hexane; yield: 75 mg (58%); yellow solid; mp 177–179 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 8.23 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 6.9 Hz, 1 H), 7.29 (t, J = 8.1 Hz, 1 H), 6.96 (dd, J = 13.2, 8.2 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 187.2, 155.7, 145.5, 134.1, 132.2, 131.3, 130.8, 129.7, 129.6, 127.9,

120.3, 118.3 114.6, 112.2 (tautomers). IR (neat): 3177, 2924, 2235, 1672, 1588, 1287, 1140, 905, 780 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{10}ClN_4O_2$: 325.0492; found: 325.0494.



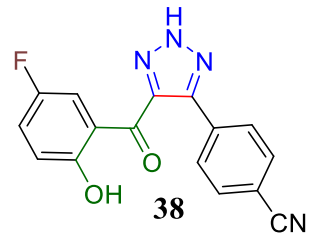
36

4-[5-(3-Bromo-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (36): From aurone **36a** (130 mg, 0.40 mmol); eluent: 50% EtOAc/hexane; yield: 83 mg (56%); yellow solid; mp 217–218 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.38 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.93–7.86 (m, 3H), 6.97 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 206.3, 192.9, 160.5, 148.1, 142.0, 141.5, 140.9, 135.4, 134.5, 133.1, 133.1, 130.4, 130.3, 121.5, 120.8, 118.9, 113.5, 113.3, 111.9 (tautomers). IR (neat): 3287, 2231, 1622, 1564, 1426, 1330, 1223, 1138, 996, 765 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{10}BrN_4O_2$: 368.9987; found: 368.9989.



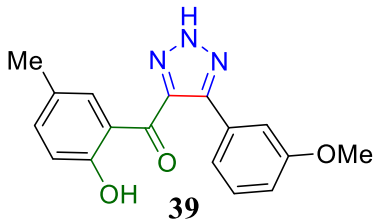
37

4-[5-(5-Bromo-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (37): From aurone **37a** (98 mg, 0.30 mmol), no chromatographic separation was needed; yield: 82 mg (74%); yellow solid; mp 240–243 °C. ^{1}H NMR (300 MHz, acetone-*d*6): δ = 8.55 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ = 191.6, 163.1, 140.2, 136.7, 133.0, 130.5, 121.9, 121.10, 119.03, 113.52, 110.94. IR (neat): 3162, 2922, 2238, 1626, 1467, 1231, 1158, 991, 726 cm^{-1}. HRMS (EI): *m*/*z* [M + H], calcd for $C_{16}H_{10}BrN_4O_2$: 368.9987; found: 368.9984.



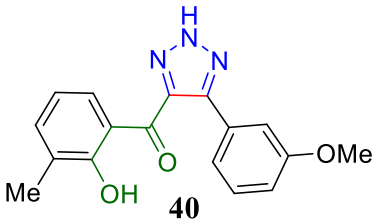
38

4-[5-(5-Fluoro-2-hydroxybenzoyl)-2H-1,2,3-triazol-4-yl]benzonitrile (38): From aurone **38a** (106 mg, 0.40 mmol); no chromatographic separation was needed; yield: 100 mg (81%); yellow solid; mp 220–223 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.16 (dd, *J* = 10.0, 3.5 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 2 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 7.47–7.43 (m, 1 H), 7.06 (dd, *J* = 9.0, 4.5 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 191.8, 160.6, 155.6 (d, $^{1}J_{C,F}$ = 235 Hz), 148.3, 141.7, 135.5, 134.7, 133.1, 125.3 (d, $^{2}J_{C,F}$ = 25 Hz), 120.3 (d, $^{3}J_{C,F}$ = 7.5 Hz), 120.1 (d, $^{3}J_{C,F}$ = 7.5 Hz), 119.4 (d, $^{2}J_{C,F}$ = 25 Hz), 119.0, 113.6, 113.3. IR (neat): 3153, 2995, 2922, 2240, 1611, 1469, 1430, 1244, 1141, 991, 789 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{10}FN_4O_2$: 309.0788; found: 309.0791.



39

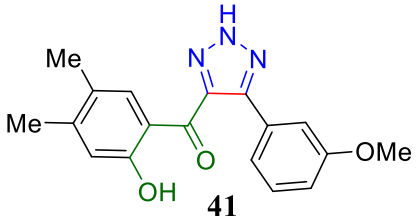
(2-Hydroxy-5-methylphenyl)[5-(3-methoxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (39): From aurone **39a** (77 mg, 0.29 mmol); eluent: 50% EtOAc/hexane; yield: 55 mg (59%); yellow solid; mp 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.85 (s, 1H), 7.77 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.97–6.91 (m, 2H), 3.80 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, CDCl3): δ = 161.7, 159.8, 138.6, 133.3, 130.0, 128.5, 121.0, 119.3, 118.2, 115.8, 114.0, 55.5, 20.6. IR (neat): 3466, 3347, 2667, 1605, 1585, 1477, 1261, 1033, 955, 830, 795 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{17}H_{16}N_3O_3$: 310.1191; found: 310.1187.



40

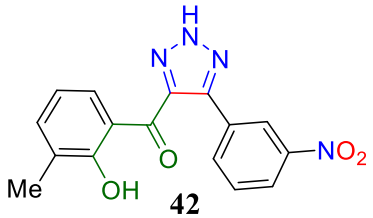
(2-Hydroxy-3-methylphenyl)[5-(3-methoxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (40): From aurone **40a** (133 mg, 0.50 mmol); eluent: 30% EtOAc/hexane; yield: 96 mg (62%); yellow solid; mp 77–80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.30 (s, 1 H), 7.82 (d, *J* = 6.0 Hz, 1 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.28 (s, 1 H), 7.23 (d, *J* = 7.6 Hz, 1 H), 6.96 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.77 (t, *J* = 8.0 Hz, 1 H), 3.80 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (125 MHz, CDCl3): δ = 192.8, 162.1, 159.8, 138.2, 131.4, 129.9,

127.4, 120.9, 118.9, 118.6, 115.8, 113.9, 55.5, 15.7. IR (neat): 3470, 2890, 1605, 1425, 1259, 1041, 849, 756 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{17}H_{16}N_3O_3$: 310.1191; found: 310.1189.



41

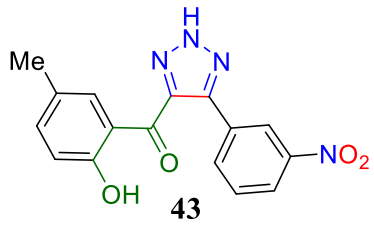
(2-Hydroxy-4,5-dimethylphenyl)[5-(3-methoxyphenyl)-2H-1,2,3-triazol-4-yl]methanone (41): From aurone **41a** (118 mg, 0.38 mmol); eluent: 50% EtOAc/hexane; yield: 87 mg (71%); waxy solid; mp 75–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.91 (s, 1H), 7.68 (s, 1H), 7.32–7.25 (m, 2H, 7.22 (d, *J* = 7.4 Hz, 1 H), 6.94 (dd, *J* = 5.8, 4.7 Hz, 1H), 6.83 (s, 1H), 3.78 (s, 3 H), 2.25 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.9, 162.1, 159.8, 148.5, 141.1, 133.6, 129.9, 127.8, 120.9, 118.9, 117.6, 115.8, 113.9, 55.5, 20.8, 18.9. IR (neat): 3458, 2920, 1639, 1579, 1451, 1264, 1246, 1030, 901, 700 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{18}H_{18}N_3O_3$: 324.1348; found: 324.1350.



42

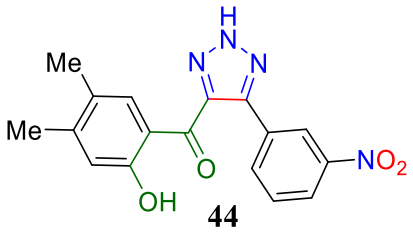
(2-Hydroxy-3-methylphenyl)[5-(3-nitrophenyl)-2H-1,2,3-triazol-4-yl]methanone (42): From aurone **42a** (120 mg, 0.43 mmol); eluent: 30% EtOAc/hexane, yield: 101 mg (72%);

yellow solid; mp 170–171 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.72–8.70 (m, 1 H), 8.35–8.30 (m, 1 H), 8.26 (d, J = 7.5 Hz, 1 H), 8.12 (t, J = 7.0 Hz, 1 H), 7.80 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 7.5 Hz, 1 H), 6.89 (t, J = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 193.7, 162.9, 149.2, 138.9, 135.1, 132.7, 132.3, 130.8, 130.7, 127.7, 124.6, 124.4, 124.1, 123.9, 119.7, 119.4, 15.5. IR (neat): 3200, 2922, 1605, 1540, 1426, 1356, 1268, 1074, 968, 737 cm^{-1}. HRMS (EI): m/z [M + H] calcd for $C_{16}H_{13}N_4O_4$: 325.0937; found: 325.0941.



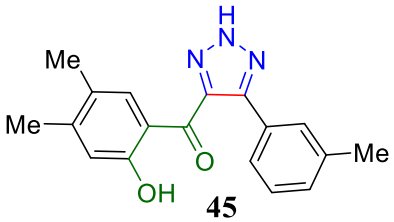
43

(2-Hydroxy-5-methylphenyl)[5-(3-nitrophenyl)-2H-1,2,3-triazol-4-yl]methanone (43): From aurone **43a** (130 mg, 0.46 mmol); eluent: 30% EtOAc/hexane; yield: 90 mg (60%); yellow solid; mp 152–153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.77 (s, 1H), 8.69 (t, J = 2.0 Hz, 1H), 8.30–8.27 (m, 1H), 8.12–8.09 (m, 1H), 7.85 (s, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.5, 2.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 193.1, 162.3, 149.1, 139.1, 135.6, 134.5, 134.4, 132.2, 130.7, 130.62, 128.95, 124.49, 124.06, 120.16, 118.57, 20.41 (tautomeric mixture). HRMS (EI): m/z [M + H], calcd for $C_{16}H_{13}N_4O_4$: 325.0937; found: 325.0936.



44

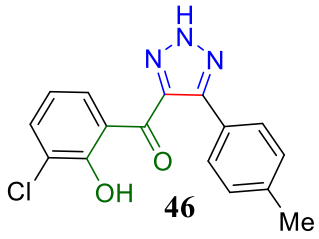
(2-Hydroxy-4,5-dimethylphenyl)[5-(3-nitrophenyl)-2H-1,2,3-triazol-4-yl]methanone (44): From aurone **44a** (121 mg, 0.41 mmol); eluent: 40% EtOAc/hexane; yield: 92 mg (68%); yellow solid; mp 155–157 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.84 (s, 1H), 8.68 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.2, 162.3, 149.0, 148.4, 134.7, 133.3, 130.9, 129.7, 128.0, 124.1, 123.8, 119.1, 117.4, 20.8, 19.0. IR (neat): 3330, 3185, 1639, 1534, 1352, 1268, 991, 735 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C^{17}H_{15}N_4O_4$: 339.1093; found: 339.1089.



45

(2-Hydroxy-4,5-dimethylphenyl)[5-(p-tolyl)-2H-1,2,3-triazol-4-yl]methanone(45): From aurone **45a** (80 mg, 0.30 mmol); eluent: 30% EtOAc/hexane; yield: 59 mg (64%); yellow solid; mp 129–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.96 (s, 1 H), 7.78 (s, 1 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.80 (s, 1 H), 2.33 (s, 3 H), 2.23 (s, 3 H), 2.05 (s, 3 H) (tautomeric peaks observed). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 162.0,

148.2, 140.0, 133.7, 129.5, 128.5, 127.7, 126.5, 118.8, 117.6, 21.5, 20.7, 18.8 (tautomeric peaks observed). HRMS (EI): *m*/*z* [M + H] calcd for $C_{18}H_{18}N_3O_2$: 308.1399; found: 308.1401.



46

(3-Chloro-2-hydroxyphenyl)[5-(p-tolyl)-2H-1,2,3-triazol-4-yl]methanone (46): From aurone **46a** (97 mg, 0.36 mmol); eluent: 20% EtOAc/hexane; yield: 63 mg (55%); yellow solid; mp 107–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.63 (s, 1 H), 8.22 (s, 1 H), 7.63 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.26 (dd, *J* = 8.5, 0.5 Hz, 1 H), 6.88 (t, *J* = 8.0 Hz, 1 H), 2.41 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 159.2, 140.7, 137.0, 132.49, 129.7, 128.6, 122.8, 120.5, 119.3, 21.6. IR (neat): 2998, 1624, 1598, 1430, 1264, 1147, 1007, 955, 737 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{16}H_{13}ClN_3O_2$: 314.0696; found: 314.0700.

5. References

1. Popova, A. V.; Bondarenko, S. P.; Frasinyuk, M. S. *J. Heterocycl. Chem.* **2019**, *55*, 285-299.
2. Kumar, G. G.; Vinod, K. *Res. J. Chem. Environ.* **2014**, *18*, 73.
3. Kafle, A.; Handy, S. T. *Tetrahedron* **2017**, *73*, 7024-7029.

4. Wilson, R. M.; Voskresenska, V. Nitrenium Ions and Related Species in Photoaffinity Labeling. In *Nitrenes and Nitrenium Ions*; Falvey, D. E.; Gudmundsdottir, A. D., Ed.; Wiley: Hoboken, **2013**; pp 77–115.
5. CCDC 1832154 and 1832153 contain the supplementary crystallographic data for compounds **5** and **10**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
6. Albert, A.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1903-1905.
7. Patonay, T.; Bognar, R.; Litkei, G. *Tetrahedron* **1984**, *40*, 2555-2562.
8. Wang, Z-P.; He, Y.; Saho, P-L. *Org. Biomol. Chem.* **2018**, *16*, 5422-5426.
9. Haouas, A.; Hamadi, N. B.; Nsira, A.; Msadek, M. *J. Chem. Res.* **2013**, 435-437.
10. Li, J.; Zhang, Y.; Wang, D.; Wang, W.; Gao, T.; Wang, L.; Li, J.; Huang, G.; Chen, B. *Synlett* **2010**, 1617-1622.
11. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.
12. Geissman, A. T.; Harborne, J. B. *J. Am. Chem. Soc.* **1955**, *77*, 4622-4624.
13. (a) Hawkins, I.; Handy, S. T. *Tetrahedron* **2013**, *69*, 9200-9204. (b) Sim, H. M.; Loh, K. Y.; Yeo, W. K.; Lee, C. Y.; Go, M. L. *ChemMedChem*. **2011**, *6*, 713-724. (c) Morimoto, M.; Fukumoto, H.; Nozoe, T.; Hagiwara, A.; Komai, K. *J. Agric. Food Chem.* **2007**, *55*, 700−705. (d) Kadayat, T. M.; Banskota, S.; Gurung, P.; Bist, G.; Thapa M. T. B,; Shrestha, A.; Kim, J-A.; Lee, E-S. *Eur. J. Med. Chem*. **2017**, *137*, 575-597. (e) Carrasco, M. P.; Newton, A. S.; Gonçalves, L.; Góis, A.; Marta, M.; Gut, J.; Nogueira, F.; Hänscheid, T.; Guedes, R. C.; dos Santos, D. J. V. A.; Rosenthal, P. J.; Moreira, R. *Eur. J. Med. Chem.* **2014**, *80*, 523-534. (f) Taylor, K. M.; Taylor, Z. E.; Handy, S. T. *Tetrahedron Lett.* **2017**, *58*, 240-241. (g) Weng, Y.; Chen, Q.; Su, W. *J. Org. Chem.* **2014**, *79*, 4218-4224. (h) Liu, J.; Liu, M.; Yue, Y.; Zhang, N.; Zhang, Y.; Zhuo, K. *Tetrahedron Lett.* **2013**, 54, 1802-1807. (i) Haudecoeur, R.; Ahmed-Belkacem, A.; Yi, W.; Fortune, A.; Brillet, R.; Belle C.; Nicolle, E.; Pallier, C.; Pawlotsky, J-M.; Boumendjel, A. *J. Med. Chem.* **2011**, *54*, 5395-402. (j) Stubblefield, J.; Taylor, Z. E.; Handy, S.; Farone, M.; McClelland, E.; Sutton, C.; Farone, A.; Park, H.; Araujo, D. *PCT Int. Appl.* WO 2017180644 A1 Oct 19, 2017.

CHAPTER - IV

HYDROGEN SULFIDE SENSING USING AN AURONE-BASED SCAFFOLD

1. Introduction

The detection of hydrogen sulfide has been an important goal for some time.[1-5] From an environmental perspective, hydrogen sulfide is a noxious and toxic by-product of various industrial processes, particularly the Kraft pulping process.[6] From a biological perspective, hydrogen sulfide has increasingly been recognized as a critical signaling molecule akin to nitric oxide and carbon monoxide that can be diagnostic for a range of pathological conditions,[7] including kidney disease,[8] Down syndrome,[9] and cirrhosis of the liver.[10] This recognition, combined with the desire to understand better the role and localization/transport of hydrogen sulfide, has gained considerable attention these days. Although most of the reports suggest the normal physiological blood concentration of hydrogen sulfide is in the range of 10-100 μM, some other studies label this range to vary over a 10^5-fold range.[11-16]

The complicated sample preparation steps and their incompatibility with living cells and tissues limit currently available methods. The rapid fluctuation of H_2S concentration in living cells and tissues further limits the applicability of these methods for the fast, accurate, and real-time detection of H_2S. In relevance to these limitations, a

fluorescence-based method is emerging as a powerful tool for both qualitative and quantitative detection of H_2S. Since fluorescent probes are easy to use and afford real-time analysis without destroying the cells, they have appeared as the frontrunner resulted in the development of several probes for live-cell imaging.[17]

Mechanistically, a fluorescent probe can be either turn-on or turn-off. A turn-on strategy works by converting a non-fluorescent or weakly fluorescent molecular probe into an intensely fluorescent species in the presence of a particular analyte or target. Turn-on probes, when triggered by a chemical reaction, transduce signals by converting the molecular recognition phenomenon into an intense fluorescence signal. A turn-off probe works in just the opposite fashion. (Figure 9) In general, turn-on probes can effectively detect analytes at low concentration and greatly minimize the background signals.[18]

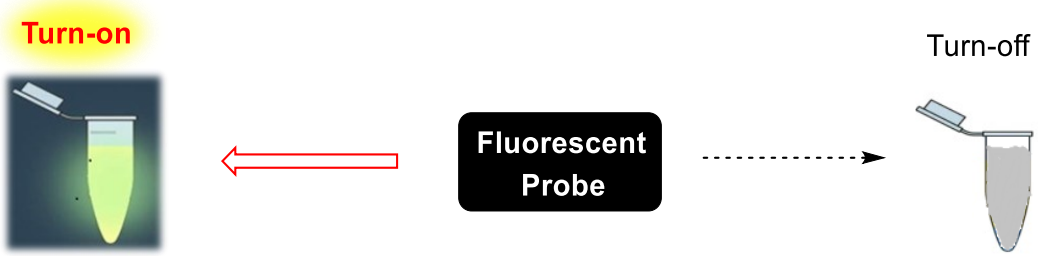


Figure 9: Working Principle of a Fluorescent Probe

The development of H_2S detecting fluorescent probes utilizes specific irreversible chemical reactions. Several different approaches have been developed, including the

reduction of nitro and azido groups,[19-29] the chelation with copper (II) complexes,[30-32] nucleophilic thiolysis,[33-47] and conjugate additions and cyclizations.[47-52] (Figure 10)

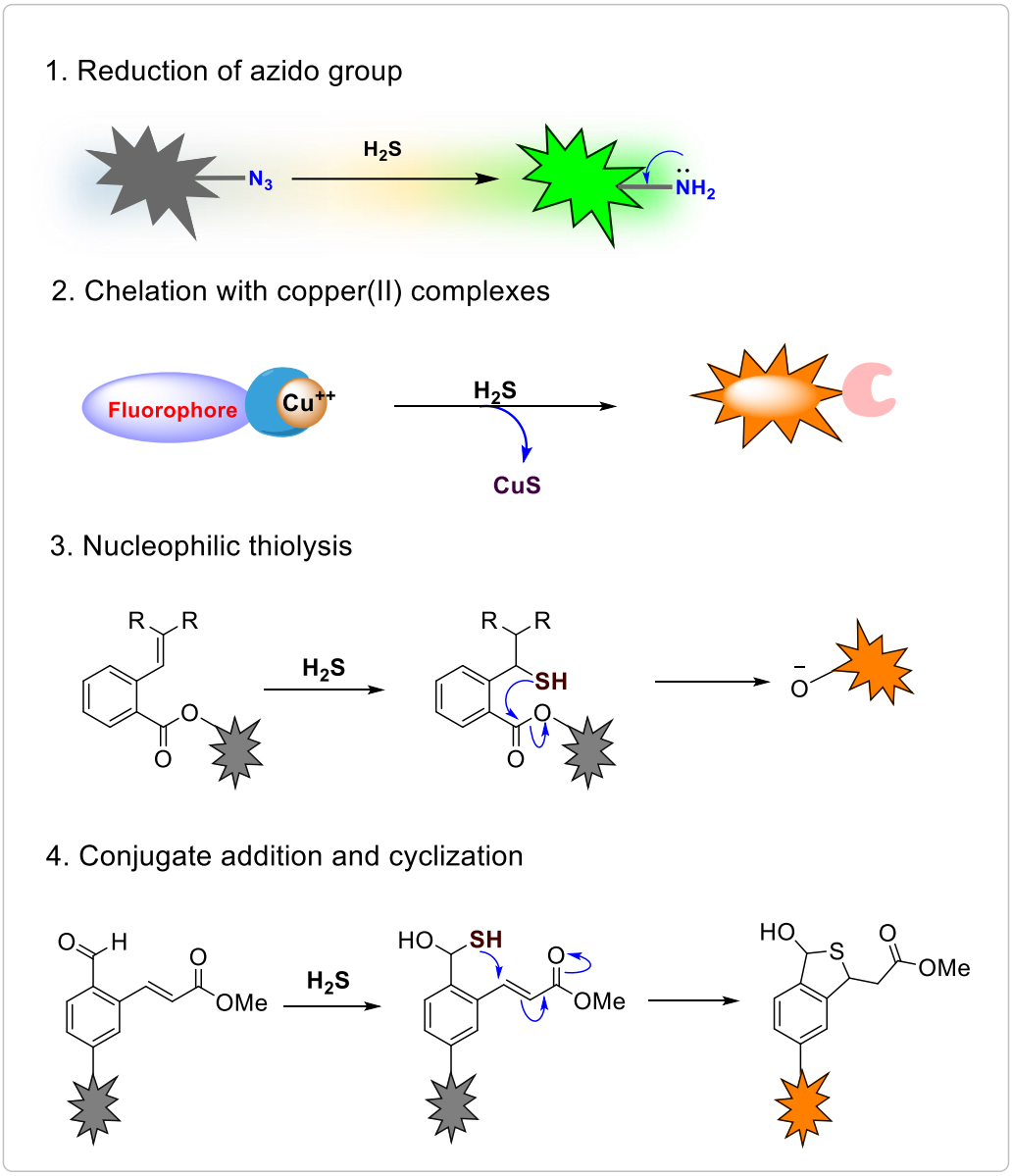


Figure 10: Probe Design Strategies

The reduction of azido groups is the most commonly utilized strategy among others. For all of these approaches, one key consideration is avoiding reaction with other common sulfur-containing compounds, particularly glutathione and cysteine. A second concern with existing probes is that they are mostly based upon common bulky scaffolds, including fluorescein, xanthene, and rhodamine, which have inherent limitations in terms of cell permeability and solubility in the cellular environment.[53, 54] Additionally, these molecules often require more lengthy synthetic sequences for their preparation, and significant effort is required to modify their intrinsic spectral range.

To address this situation, we envisioned using the aurone system as an alternative fluorescent scaffold. Aurones are a small family of natural products primarily responsible for the golden pigmentation present in plants with yellow flowers such as dahlias, snapdragons, and cosmos.[55-57] Due to their unusual exocyclic alkene, they absorb at longer wavelengths compared to the more common flavones. At the same time, this ring system is easy to synthesis in a variety of ways, particularly the acid or base-catalyzed condensation of an aldehyde and a benzofuranone.[58-61] Indeed, this condensation can even be performed under effectively neutral conditions, rendering it highly functional group compatible as well as generally high yielding.

Aurones have been reported to be fluorescent, with the first significant study reported by Bane and co-workers.[53] Since this report on the fluorescent properties of a series of amino-substituted aurones, a few other studies have explored variations of the benzofuranone portion either experimentally or computationally.[62-64] Nonetheless, application of aurone fluorescence has been virtually unexplored. To date, only two reports have appeared in the literature. (Figure 11)

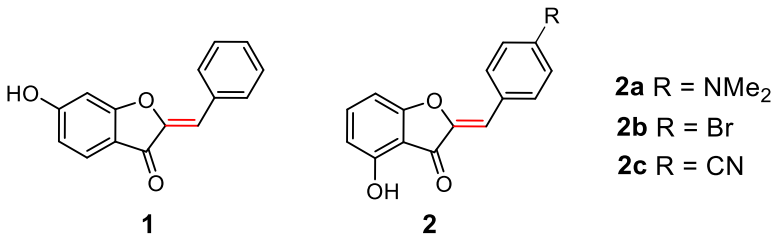


Figure 11: Aurone-based Fluorescent Probes

In the first, hydroxyaurone **1** was reported as a selective sensor for mercury (II) in aqueous solution as well as living cells.[65] It exhibited high selectivity and a linear decrease in fluorescence intensity in the presence of low micromolar concentrations of mercury (II) salts. An earlier report noted that 4-hydroxyaurones **2** exhibited changes in their UV and fluorescence spectra in the presence of cyanide anion.[66] p-Bromo-substituted compound **2b** was particularly interesting as it showed a dramatic increase in emission upon irradiation at 469 nm in acetonitrile in the presence of cyanide anion as well as a visual color change. This observation is attributed to the hydrogen bonding between the cyanide anion and the hydroxy (-OH) group of the probe. Other anions did not induce a similar change. As a result, aurones certainly have the potential to be fluorescent sensors.

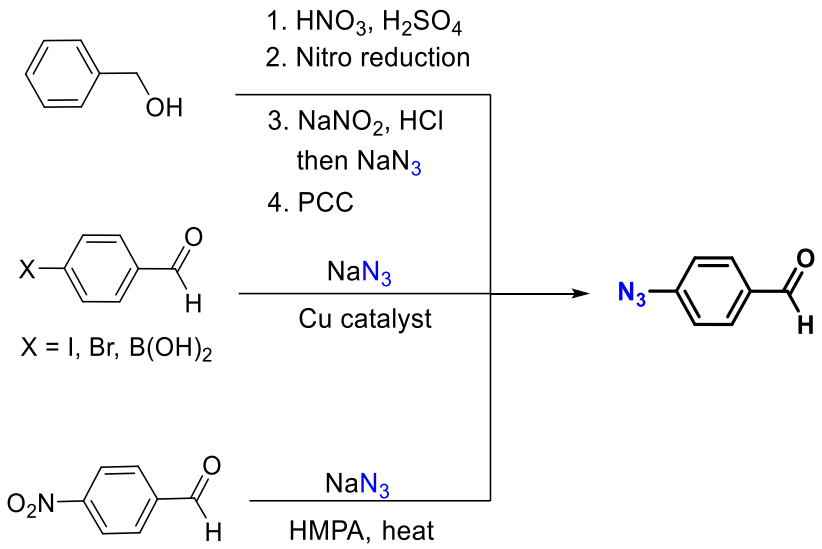
With this in mind, we envisioned utilizing an aurone scaffold to develop an azide-reduction based turn-on fluorescent probe, which in the presence of H_2S, undergoes reduction to the corresponding amine accompanied by a significant shift in the absorption and emission spectrum. For this purpose, we explored 4′-azidodoaurone **6a** as a simple model probe, which ultimately on appropriate optimization led us to the rationally designed H_2S selective probe **6g**. (Scheme 21)

2. Results and Discussion

2.1. Probe Design

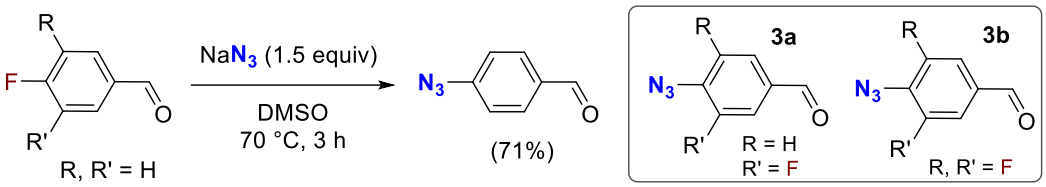
As attempts to install azides on halogenated aurones proved ineffective, we turned our attention to first installing the azide on an aryl aldehyde and then condensing this aldehyde to afford the azido-aurone. A search of the literature regarding the synthesis of azide-substituted benzaldehydes revealed an interesting situation. While para-azidobenzaldehyde and related compounds are well known, they are most accessed via relatively lengthy procedures (particularly when considering the simplicity of such compounds).

Thus, the vast majority of publications that employ this compound prepare it via a 3-4 step pathway involving the nitration of benzyl alcohol, reduction of the nitro group to an aniline, diazonium ion formation and displacement with sodium azide, and then oxidation of the alcohol to an aldehyde.[67] (Scheme 19) While this chemistry is simple to perform and generally high-yielding, it is still a much longer sequence than one would expect. The primary alternative method has been a copper-catalyzed azidation of aryl bromides,[68, 69] iodides,[70] or boronic acids,[71-75,] which in our attempts were ineffective. Direct, metal-free S_NAr reactions have been limited to either nitro group displacement (most typically in toxic HMPA),[76-79] or a single patent report of fluoride displacement in DMSO.[80]



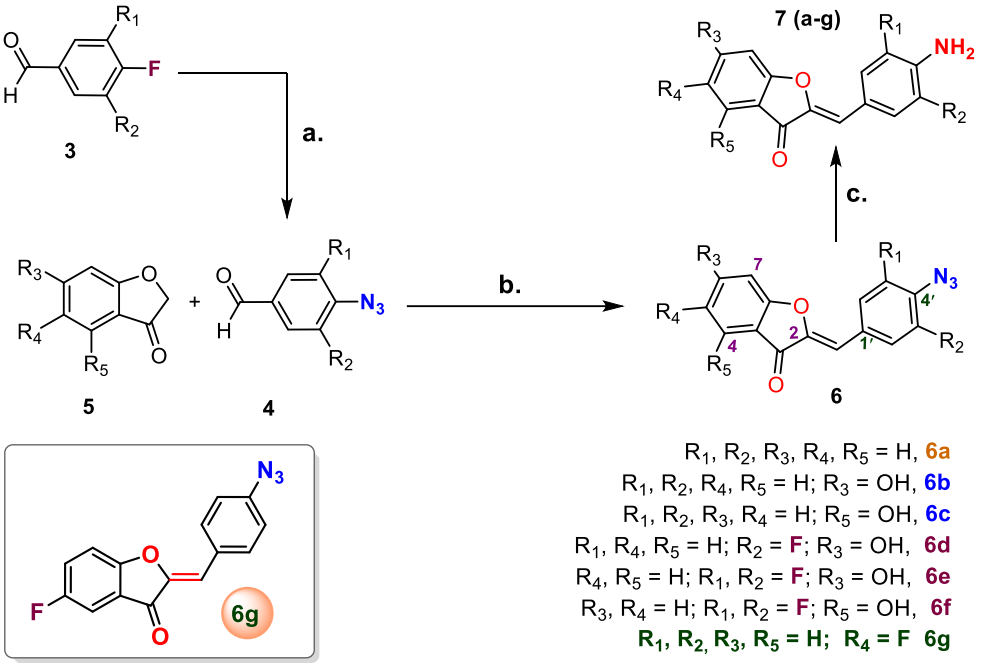
Scheme 19: General Synthetic Approaches to Azidoaldehydes

With the patent report as an only available example, we put an effort to access azidobenzaldehydes quickly and inexpensively from fluorobenzaldehydes and establish the generality of the protocol. The reaction of para-fluorobenzaldehyde with sodium azide in DMSO at 70 °C for 3 hours completely consumed the starting material and afforded the desired azide in 71% yield. (Scheme 20). Under this reaction condition, a series of fluoroaldehydes were treated with sodium azide. As expected for an S_NAr type reaction, fluoro groups ortho or para to the aldehyde reacted smoothly, while fluoro groups at meta did not react.[81] This selectivity was important to prepare fluoroazidobenzaldehydes such as **3a** and **3b** (Scheme 20) which are useful building blocks for hydrogen sulfide sensors, due to their increased reaction rates of reduction.[82]



Scheme 20: Azidobenzaldehyde Synthesis Using DMSO as Solvent

All the fluorescent probe candidates **6a-6g** were synthesized as outlined in Scheme 21. The reaction involved Knoevenagel-type condensation of a benzofuranone **5** with a 4-azidobenzaldehyde derivative **4** under acidic reaction conditions.[61]



Scheme 21: Aurone-based Probe Synthesis. *a) 1.5 equiv. NaN_3, DMSO, 70-90 °C, 2-5 h b)1.1 equiv. 4, glacial acetic acid, 3 drops conc. HCl, rt, 3h c) 4 equiv. NaHS, 2 mL MeCN or acetone, few drops DI water, 30 min.*

Since the reaction product generally precipitates out in the cold water, the products were separated simply by filtration. As depicted in Scheme 3, the 4-azidoaldehydes were prepared by direct azidation of the corresponding 4-fluorobenzaldehydes with NaN_3 in DMSO.[81] The 4′-azidoaurone derivatives **6(a-g)** were further reduced by NaHS to give the corresponding amines **7**.

Based on the fact that highly water-soluble H_2S predominantly (>75%) exists as HS^- under physiological conditions, NaHS was utilized as the source of H_2S for this study.[83] Although the model probe **6a** (100 μM) was found to react efficiently (~7 min) with 5 equivalent of NaHS in a 1:1 or higher ratio of DMSO in phosphate buffer saline (PBS) medium, its utility was significantly limited in a highly aqueous medium (< 1% DMSO) as the probe precipitates out below 20% DMSO or MeCN in PBS. Additionally, increasing the aqueous fraction of the solvent was accompanied by a significant decrease in the fluorescence intensity of the corresponding amine. Nevertheless, this observation provided proof of concept for the utility of an aurone scaffold for hydrogen sulfide detection.

To improve solubility with increasing ratios of water to DMSO, we introduced a hydroxyl (-OH) group at C-6 or C-4 of the benzofuranone moiety of the model probe **6a** to give respective aurones **6b** and **6c** respectively. As expected, this rendered them highly soluble in predominantly aqueous media (as low as 5% DMSO in PBS). Unfortunately, it also resulted in significant spectral overlap limiting the selective excitation of the starting azides and/or the corresponding amine products. (Figure 12)

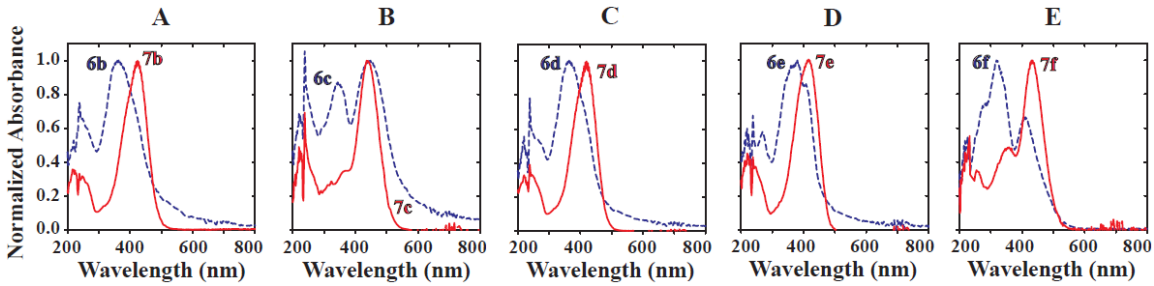


Figure 12: UV-visible Spectra Illustrating Spectral Overlap. *Samples (50 µM) were prepared in 5% DMSO in PBS (v/v) for the study.*

Next, leaving the hydroxyl group intact to the benzofuranone moiety, the effects of a substitution in phenyl ring on the reactivity and electronic properties of the probe molecule were explored. As suggested by Henthorn and Pluth in their mechanistic study of H_2S-mediated reduction of aryl azides, the introduction of fluorine was reported to result in roughly a 2.2-fold rate increase for each fluorine substitution.[84-87] Utilizing this same strategy, we synthesized both mono- and di-fluoro substituted hydroxylated candidates **6d-6f**. Despite their outstanding aqueous solubility, all of them resulted in highly overlapped absorption spectra with their corresponding amines **7d-7f**, similar to that observed with **6b** and **6c** (devoid of fluorine). The result was that there was still no excitation window available for the selective excitation of the reactant or the product to monitor the reaction. (Figure 12) This situation can be attributed to the electron-donating effect of the hydroxyl group making the carbonyl group less electron-deficient, which in overall results a reduction in the resonance mediated electron donation from the amine.

Since phenyl ring functionalization of aurones encountered spectral overlap of azido and amino compounds, we decided to introduce fluorine in the benzofuranone moiety. This should increase the electrophilicity of the carbonyl carbon, which in turn will

efficiently pull the electron via resonance from the amino group. This should impart significant differences in the electronic properties of the compounds, thereby improving the spectral separation. The impact of the fluorine functional group on the rate of azide reduction was less clear. As an initial test, **6g** and its corresponding amine **7g** were synthesized. Interestingly, the introduction of fluorine (F) at C-5 of benzofuranone moiety not only solved the problem with spectral overlap but also afforded considerable solubility to the probe in predominantly aqueous media (as low as 0.5% DMSO in PBS buffer) and without the need for any hydroxyl group. This ultimately provided us with the desired turn-on fluorescent probe **6g** for the detection of H_2S.

2.2. Spectral Characterization of 6g and 7g

To evaluate its utility as a fluorescent probe, the excitation and emission properties of probe **6g** (reactant) and corresponding amine **7g** (product) were characterized under varied solvent conditions. Figures 13A-13B present excitation and emissions spectra collected with either molecule in the presence of 0.5, 50, 90, or 100 % v/v DMSO and phosphate-buffered saline (PBS) solution. All **6g** excitation spectra recorded in DMSO/PBS mixtures exhibit two distinct excitation modes that are not significantly dependent on DMSO/PBS ratio (Figure 13A). Excitation maxima are observed at 346/394 nm, 362/414 nm, 346/402 nm, and 350/406 nm for conditions of 0.5, 50, 90, or 100 % v/v DMSO, respectively (dashed lines in Figure 13A).

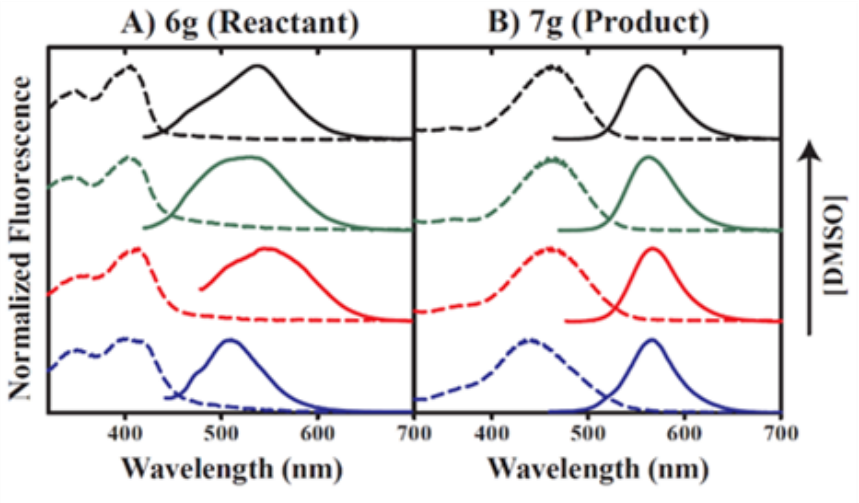


Figure 13: Evaluation of Chromophore DMSO-Sensitivity. *A-B) Normalized excitation and emission spectra are represented from bottom to top of the frame in order of ascending [DMSO]. All spectra are colored blue, red, green, or black to indicate 0.5 % v/v, 50 % v/v, 90 % v/v, or 100 % v/v DMSO, respectively. Excitation and emissions spectra are represented as either dashed or solid lines, respectively. Peak maxima are discussed in-text. Panel (A) and (B) represent spectral data corresponding to reactant* ***6g*** *or product* ***7g****, respectively.*

Emission spectra of **6g** indicate solvent sensitivity when excited at 405 nm where maximum fluorescence is observed for 0.5 % DMSO/99.5 % PBS conditions at 510 nm (solid lines in Figure 13A). This contrasts with the red-shifted **6g** emission maxima of 545, 531, and 539 nm for 50 %, 90 %, and 100 % v/v DMSO conditions, respectively. In comparison, maximal **7g** absorption occurs at 442 nm in the presence of 0.5 % DMSO, whereas absorption maxima equal to 458, 462, and 462 are observed for conditions including 50, 90, and 100 % v/v DMSO, respectively (Figure 13B). However, maximal

emissions occur at 566, 566, 563, and 561 nm for 0.5, 50, 90, and 100 % v/v DMSO, respectively, thereby indicating minimal solvent sensitivity for product species fluorescence. Comparison of the spectra in Figures 13A-13B indicates that excitation of **6g**/**7g** mixtures using wavelengths in the 440-460 nm range may allow for selective observation of product emission.

Inspection of raw **7g** fluorescence intensities as a function of increasing DMSO concentration suggests that an aqueous environment may contribute to quenched product emission. Our data indicate a 33-fold increase in fluorescence intensity for conditions including 90 % versus 0.5 % v/v DMSO. Thus, the use of **6g** as a fluorescent sulfide probe may be limited in biological applications under these conditions. In this context, cationic surfactant cetyltrimethylammonium bromide (CTAB) has been utilized in the literature to enhance both the rate of the reaction and the intensity of the fluorescence (Figure 14).[88-89] Based on this precedent, we successfully employed CTAB to enhance the reactivity of probe **6g** in highly aqueous medium (0.5% DMSO in PBS).

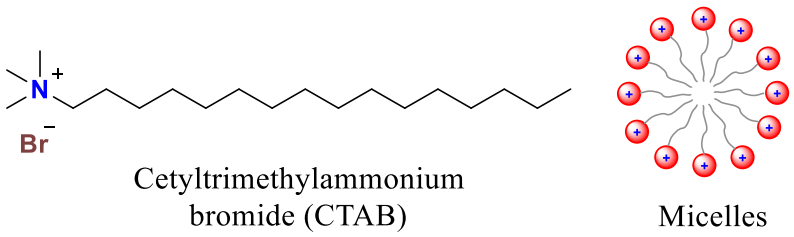


Figure 14: Structure of CTAB

Figure 15 indicates that the inclusion of 1 mM CTAB in 0.5 % v/v DMSO does not impact **6g** excitation properties (dashed lines in Figure 15A), but instead promotes a red-

shift in the apparent emission maximum from 510 nm to 550 nm in the absence versus presence of CTAB, respectively. In contrast, **7g** excitation properties in 0.5 % v/v DMSO are perturbed by the inclusion of CTAB such that maximal absorption shifts from 442 nm to 462 nm in the absence versus presence of surfactant, respectively (Figure 15B). However, it reveals no impact of CTAB on the wavelength of maximum emission.

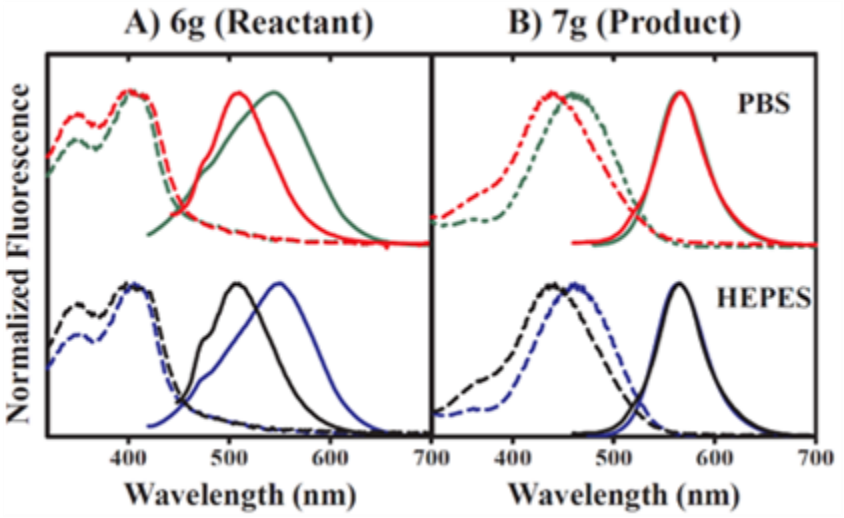


Figure 15: CTAB Influences Product Emissions Properties. *Normalized excitation/ emission spectra are presented in the presence of 0.5 % v/v DMSO and varied buffer components. Excitation and emission spectra are represented by dashed or solid lines, respectively. Spectra corresponding to conditions including PBS buffer without or with 1 mM CTAB are colored red or green, respectively (top panel). Spectra corresponding to conditions including HEPES buffer without or with 1 mM CTAB are colored black or blue, respectively (bottom panel). Peak maxima are discussed in-text. Panel (A) and (B) represent spectral data corresponding to reactant* ***6g*** *or product* ***7g,*** *respectively.*

Furthermore, raw **7g** fluorescence intensities are observed to increase 42-fold for 0.5 % v/v DMSO conditions, including CTAB versus conditions that do not. Our data also indicate that these trends occur independent of buffer components included in the aqueous fraction since the inclusion of PBS or HEPES buffers yield identical results. The data presented in Figures 15A-15B collectively suggest that **7g** may be utilized in aqueous solution as a fluorescent probe under conditions that include CTAB.

2.3. Effect of pH on Spectral Properties of 6g and 7g

The effect of pH on **6g** and **7g** spectral properties was also examined. Excitation and emission spectra were collected in PBS buffer previously pH adjusted to pH = 3.0, 4.8, 7.5, 9.2, and 11 in the absence and presence of CTAB as described above. Figures 16A-16B illustrate that **6g** experiences an altered Stokes shift that depends on whether CTAB is included. In the absence of CTAB, we note excitation and emission maxima occur at 424 and 500 nm, respectively, at pH = 3.0. A similar observation is made when the pH is adjusted to 4.8, where excitation and emission maxima occur at 426 and 502 nm, respectively. At pH = 3.0 and 4.8, the Stokes shift is calculated as 76 nm. However, at pH 7.5 and above, we observe a blue-shift, where excitation maxima are observed at 400 nm when determined at pH = 7.5, 9.2, and 11.0. Corresponding emission maxima were observed at 527, 528, and 528 nm for pH = 7.5, 9.2, and 11.0, respectively. The calculated Stokes shift for pH $\geq$ 7.5 is ~128 nm. In contrast, when CTAB is included, no effect of pH is observed such that maximal excitation is observed at 404 nm independent of pH. Emission maxima are observed at wavelengths that increase with increasing pH such that maxima are observed at 511 (Stokes shift = 107 nm), 527 (Stokes shift = 123 nm), 547

(Stokes shift = 143 nm), 547, and 550 (Stokes shift = 146 nm) nm for pH = 3.0, 4.8, 7.5, 9.2, and 11.0, respectively. In contrast **7g** exhibits pH-independent excitation maxima at 440 and 460 nm when CTAB is absent or present, respectively. The emission maximum for **7g** is observed at 565 nm independent of pH, yielding a Stokes shift equal to 125 or 105 depending on the absence or presence of CTAB, respectively. Taken together, we note **7g** spectral properties to be largely independent of solution pH. However, we do note an increase in raw emission intensities for **7g** when CTAB is included, where mild fluorophore quenching is observed at pH below 4.8. At pH ≥ 4.8, emission intensities are observed to be independent of pH.

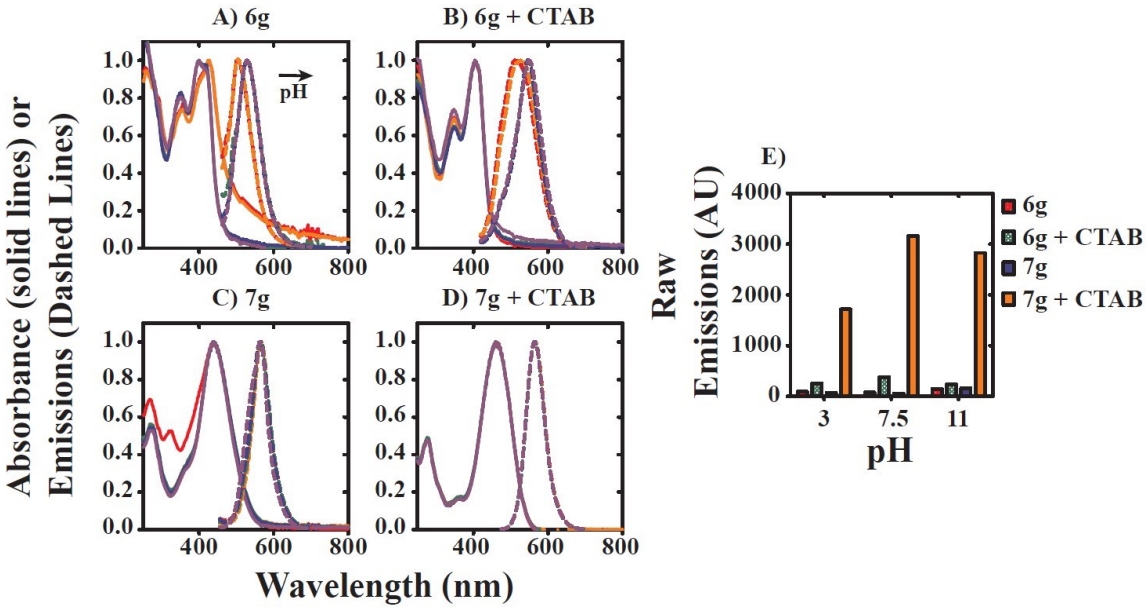


Figure 16: Effects of pH on 6g/7g Spectral Properties. *Excitation spectra collected in 0.5 % DMSO/PBS buffer with pH adjusted to 3.0, 4.8, 7.5, 9.2, and 11.0 are represented as solid red, orange, green, blue, and purple lines, respectively. Corresponding emission*

spectra collected at pH = 3.0, 4.8, 7.5, 9.2, and 11.0 are represented as dashed red, orange, green, blue, and purple lines, respectively. Excitation/emission spectra were collected for (A) ***6g*** *in the absence of CTAB, (B)* ***6g*** *in the presence of 1 mM CTAB, (C)* ***7g*** *in the absence of CTAB, and (D)* ***7g*** *in the presence of 1 mM CTAB.* ***6g*** *emission spectra were collected using excitation wavelengths of 425, 425, 405, 405, and 405 nm for conditions with pH = 3.0, 4.8, 7.5, 9.2, and 11.0, respectively, in the absence of CTAB. In the presence of CTAB,* ***6g*** *emission spectra were collected using an excitation wavelength equal to 405 nm at all pH values.* ***7g*** *emission spectra were generated using excitation wavelengths equal to 440 or 460 nm depending on whether 1 mM CTAB was absent or present, respectively. (E) Raw emission intensities plotted for* ***6g*** *without CTAB (red bars),* ***6g*** *with 1 mM CTAB (green bars),* ***7g*** *without CTAB (purple bars), and* ***7g*** *with 1 mM CTAB (orange bars) as a function of pH.*

2.4. Dynamic Range Study

The use of any fluorescent probe requires knowledge of the dynamic range under specific working conditions. As such, we next determined the useful working range of **7g** in conditions including either increased DMSO concentrations or 0.5 % v/v DMSO/1 mM CTAB. Knowledge of dynamic range under these separate conditions allows for both biological and non-aqueous applications. (Figure 17A)

Figure 17A demonstrates that the titration of [**7**g] in 0.5 % v/v DMSO, 99.5 % v/v PBS, and 1 mM CTAB with excitation at 465 nm yield emission spectra with maxima observed at ~565 nm. A secondary plot of maximum fluorescence intensity versus [**7g**] clearly reveals non-linear behavior for concentrations exceeding 20 μM (Figure 17B). Our

data also indicate that fluorescence intensities can be reliably estimated for [**7g**] as low as 1 µM based on spectra signal-to-noise ratio and deviation from linearity. Thus, the useful dynamic range for **7g** in the presence of 0.5 % v/v DMSO, 99.5 % PBS, and 1 mM CTAB spans from 1 µM to 20 µM.

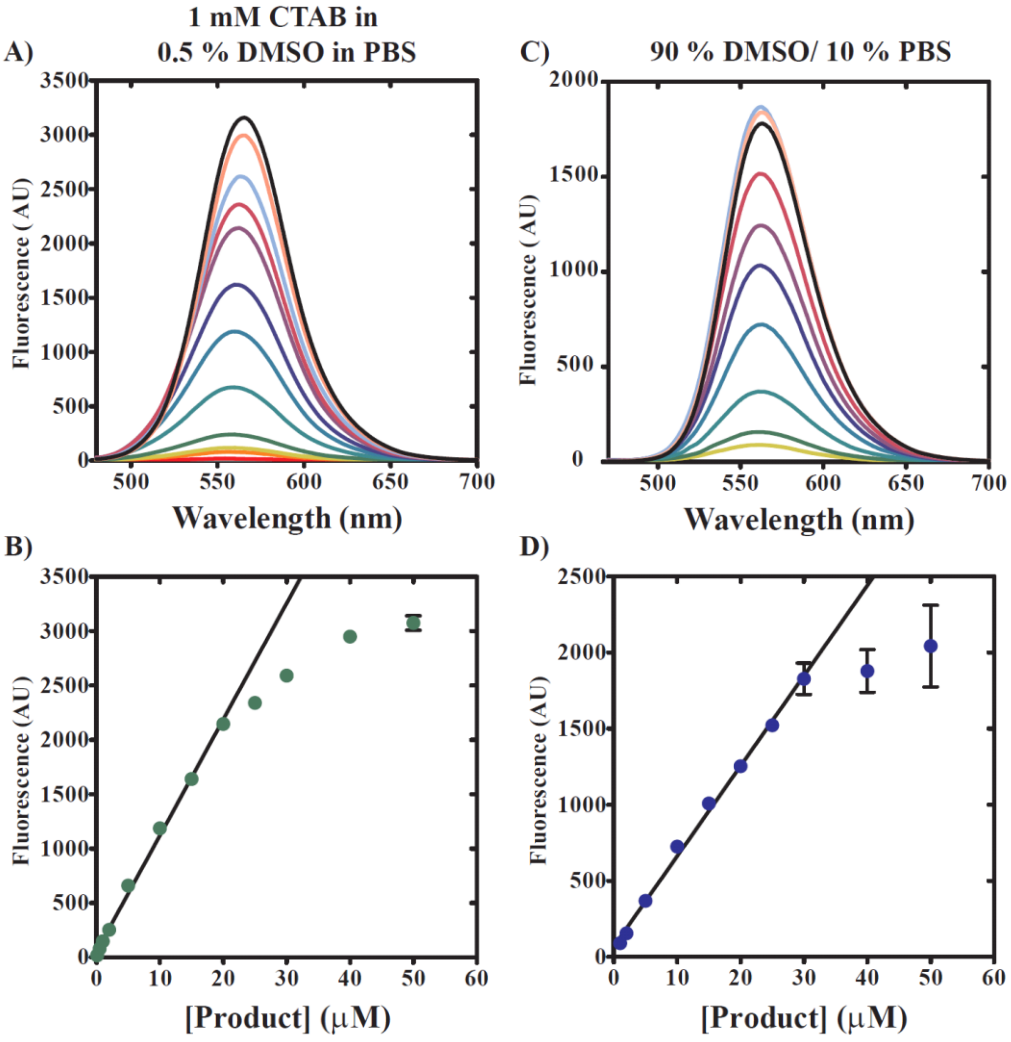


Figure 17: Determination of Product 7g Range of Detection. *Product **7g** was titrated separately into conditions including either 1 mM CTAB and 0.5 % v/v DMSO in PBS (A-*

*B) or 90 % v/v DMSO/10 % v/v PBS buffer (c-d). Emissions spectra are represented as solid lines (A, C). Signal intensity observed at 560 nm plotted as a function of [7**g**] reveals linear range of detection (B, D). All data points represent average values determined from at least three independent experiments. Error bars indicate ± standard deviation. Solid lines are the result of Linear Least Squares (LLS) fits. For conditions with 1 mM CTAB and 0.5 % v/v DMSO in PBS (B), LLS fit yields estimates of slope and y-intercept equal to 50 ± 24 (AU) and 107 ± 3 AU μM, respectively. For conditions with 90 % v/v DMSO/10 % v/v PBS buffer (D), LLS fit yields estimates of slope and y-intercept equal to 68 ± 24 (AU) and 60 ± 1 AU μM, respectively.*

Figures 17C and D reveal a similar trend when measurements are made under conditions including 90 % v/v DMSO and 10 % v/v PBS solution. However, elevated DMSO concentrations appear to increase the useful linear concentration range such that non-linearity is observed for [**7g**] greater than 30 μM. We note the observation of decreased reproducibility when **7g** concentrations are utilized that exceed 25 μM in 90 % v/v DMSO/10 % v/v PBS as indicated by increased standard deviation on mean fluorescence intensities presented in Figure 17D.

2.5. Reaction Kinetics and Solvent Studies

Quantification of sulfide concentration in any sample using "turn-on" fluorescent sensing requires knowledge of kinetic rates of reaction under varied solution conditions. Rate profiles describing the reduction of azide reactant to amine product were performed by the incubation of 20 μM **6g** with 100 μM NaHS in either 0.5 % v/v DMSO/99.5 % PBS/1 mM CTAB or 90 % v/v DMSO/10 % v/v PBS solvent systems at 25 ºC. Samples

were excited at 465 nm, and emission spectra spanning from 480 to 700 nm were collected at 2-minute intervals. Figures 18 demonstrate a time-dependent increase in fluorescence intensity for both conditions.

Figure 18C shows a plot of maximum fluorescence intensity as a function of time for aqueous reaction conditions, including 0.5 % v/v DMSO/99.5 % v/v PBS in the presence or absence of 1 mM CTAB. In the presence of 1 mM CTAB, reaction completion is achieved within approximately one hour (blue spheres, Figure 18C). In contrast, no reaction is observed in the absence of CTAB (green spheres, Figure 18C). By comparison, reactions performed in 90 % v/v DMSO/10 % v/v PBS are observed to reach completion within 20 minutes (green spheres, Figure 18D). Nonlinear least squares (NLLS) analysis of the data shown in Figure 18C estimates the apparent rate constant, amplitude, and y-intercept as 0.078 ± 0.002 min^{-1}, 842 ± 8 AU, and 149 ± 7 AU, respectively. In comparison, NLLS analysis of reaction data collected in 90 % v/v DMSO/10 % v/v PBS (Figure 18D) estimates the apparent rate constant, amplitude, and y-intercept as 0.28 ± 0.02 min^{-1}, 284 ± 7 AU, and 249 ± 6 AU, respectively. These data collectively indicate that reactions performed in a polar aprotic environment occur with increased reaction rates relative to those performed in aqueous conditions.

NLLS analyses of data presented in Figures 18C and D yield estimates of the y-intercept as nonzero values. Reference to Figure 14 illustrates that excitation at 465 nm of a mixture of **6g** and **7g** may yield an apparent fluorescence intensity that contains contributions from both reactant and product. Moreover, no product could be present at time zero. Therefore, we interpret the observation of a nonzero y-intercept to reflect the contribution of reactant emission to the overall observed signal.

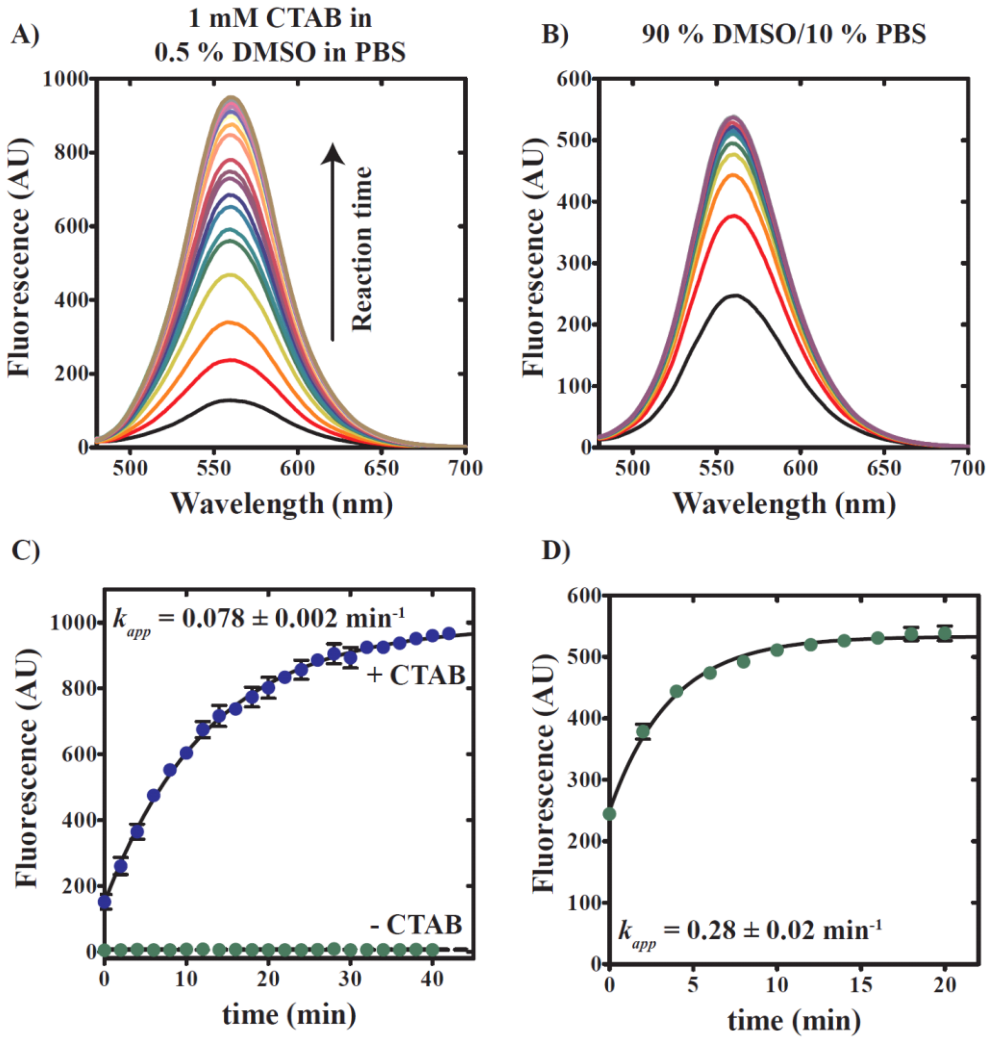


Figure 18: Compound 6g Reaction Rate Constant is Dependent on Solvent Condition. *Reaction profiles describing the reduction of azide reactant to amine product by the incubation of compound* ***6g*** *with 100 µM NaHS in the presence of either 0.5 % v/v DMSO in PBS +/- 1 mM CTAB (A) or 90 % v/v DMSO/10 % v/v PBS buffer (B). Emissions spectra are represented as solid lines and reveal increasing signal intensity as a function of reaction time (A-B). All data points represent average values determined from at least*

three independent experiments. Error bars indicate ± standard deviation. Solid lines are the result of Nonlinear Least Squares (NLLS) fits with rate constants indicated.

To determine whether contaminating reactant emission leads to errors in our estimation of reaction rate, we performed a series of reactions using independent excitation wavelengths wherein 20 µM **6g** was incubated with 100 µM NaHS in 0.5 % v/v DMSO/99.5 % PBS/1 mM CTAB. Samples were excited at 465, 480, and 500 nm with spectra collected at 2-minute intervals as described above. (Figure 19)

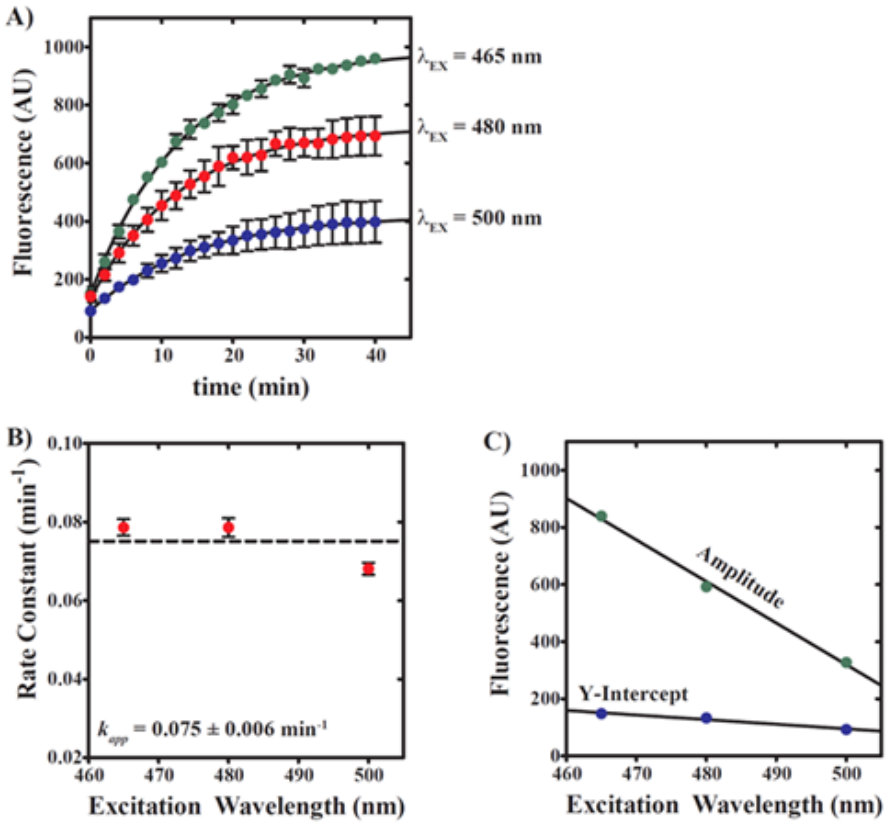


Figure 19: Compound 6g Reaction Rate Constant is Independent of Excitation Wavelength. *A) Kinetic time courses were collected using excitation wavelengths equal to 465 (green*

spheres), 480 (red spheres), and 500 nm (blue spheres). Reactions were performed by incubating 20 μM ***6g*** *with 100 μM NaHS in 1 mM CTAB and 0.5 % v/v DMSO in PBS. Reaction progress was monitored by fluorescence intensity observed at 560 nm. Solid lines are the result of Nonlinear Least Squares (NLLS) fits to a single-exponential function. B) First-order rate constants plotted as a function of excitation wavelength with average apparent rate constant indicated. C) Estimates of amplitude (green spheres) and Y-intercept (blue spheres) describing time courses in Figure 19a obtained from NLLS analyses. Solid lines are the result of LLS fits with slopes equal to -14.6 ± 0.9 and -1.6 ± 0.3 AU* nm^{-1}*, respectively. All data points represent average values determined from at least three independent experiments. Error bars indicate ± standard deviation.*

Fluorescence time courses are presented in Figure 19A, which qualitatively demonstrates a decrease in apparent amplitude and y-intercept with increasing excitation wavelength. Figure 19B predicts no significant dependence in the apparent rate constant describing product formation on excitation wavelength. NLLS analyses of the data presented in Figure 19A yield estimates of the rate constant that fluctuate about a mean value equal to 0.075 ± 0.006 min^{-1}.

In addition, the apparent amplitude and Y-intercept are observed to linearly decrease as excitation wavelength is increased, which is an observation consistent with the excitation of sample at non-maximal excitation wavelengths for both reactant and product (Figure 19C). Given that the Y-intercept represents signal derived at time zero prior to any product formation, we interpret the observation of a Y-intercept that decreases with increasing excitation wavelength to suggest that longer excitation wavelengths favor

decreased background signal associated with reactant emission. Taken together, the data presented in Figure 19 collectively indicate that reactant contribution to overall apparent fluorescence signal does not interfere in the estimation of reaction rate constants.

Moreover, knowledge of the dependence of time course y-intercept on excitation wavelength allows for baseline correction to remove reactant signal contributions, thereby allowing for conversion of fluorescence intensity values into concentration units. By subtracting baseline emissions from subsequent time points, the resulting emission values can be readily converted into concentration units if a standard curve relating product concentration to emission value is available. Figure 20 highlights this ability for time courses collected in the presence of 1 mM CTAB in 0.5 % DMSO in PBS or 90 % DMSO/10 % PBS. Though the estimated rate constants are unaltered, Figure 20 now readily allows for estimation of hydrogen sulfide concentration in real-time.

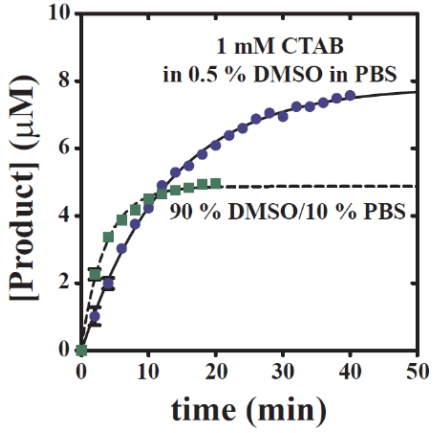


Figure 20: All time courses can be converted into plots of [Product] versus time. *Blue spheres represent conditions including 1 mM CTAB, 0.5 % DMSO in PBS (Condition A).*

Green squares represent conditions including 90 % DMSO and 10 % PBS (Condition B). The solid line represents the results of a NLLS fit with A, kapp, and b estimated as 7.9 ± 0.1, 0.08 ± 0.002, and -0.03 ± 0.07, respectively. The dashed line represents the results of a NLLS fit with A, kapp, and b estimated as 4.8 ± 0.1, 0.28 ± 0.02, and 0.1 ± 0.1, respectively. Error bars indicate ± standard deviation.

2.6. Selectivity for Sulfide Studies

Any use of **6g** as a molecular probe will require knowledge of its reaction specificity. To evaluate reaction specificity, a series of fluorescence time courses were collected using the same methodology as described above. In place of sodium hydrogen sulfide (NaHS), three potential sulfide-donors were employed: L-cysteine, reduced glutathione, and 2-mercaptoethanol.

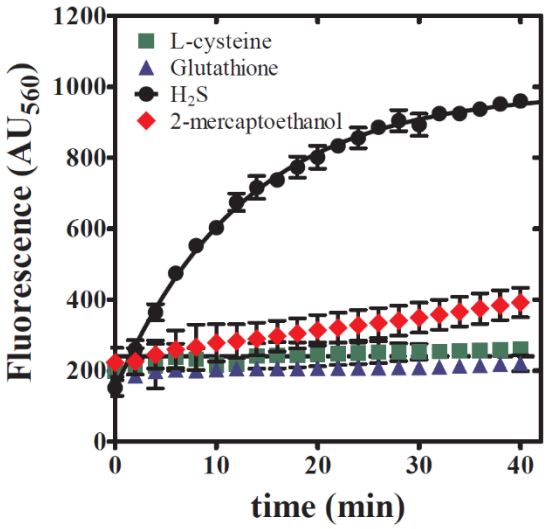


Figure 21: Compound 6g Displays Chemical Reactivity that is Selective for Sulfide. *Kinetic time courses were collected using an excitation wavelength equal to 465 nm.*

Reactions were performed by incubating 20 μM ***6g*** *with 100 μM sulfide-donor in 1 mM CTAB and 0.5 % v/v DMSO in PBS. Sulfide-donors examined include L-cysteine (green squares), glutathione (blue triangles), NaHS (black circles), and 2-mercaptoethanol (red diamonds). Reaction progress was monitored by fluorescence intensity observed at 560 nm. Solid lines are the result of Nonlinear Least Squares (NLLS) fits to a single-exponential function. All data points represent average values determined from at least three independent experiments. Error bars indicate ± standard deviation.*

All emission spectra reflect the reaction of 100 μM sulfide-donor with 20 μM **6g** in 0.5 % v/v DMSO, 99.5 % v/v PBS, and 1 mM CTAB. As expected, highly nucleophilic NaHS yields the observation of significant product emission at λ_{EM} = 560 nm (Figure 21). In contrast, the inclusion of less nucleophilic either L-cysteine or reduced glutathione yielded no observed product formation. Figure 21 illustrates that a mild increase in emission was observed when 2-mercaptoethanol was utilized as a sulfide-donor. However, 2-mercaptoethanol reactivity with **6g** is apparently slow on the time scale associated with NaHS: **6g** reaction. Taken together, we conclude that **6g** chemical reactivity is selective for free sulfide.

2.7. Sensing Mechanism

In this study the turn-on probe **6g**, in the presence of HS^- undergoes an irreversible chemical transformation to amine **7g** thereby transducing signals by converting the molecular recognition phenomenon into an intense fluorescence signal.

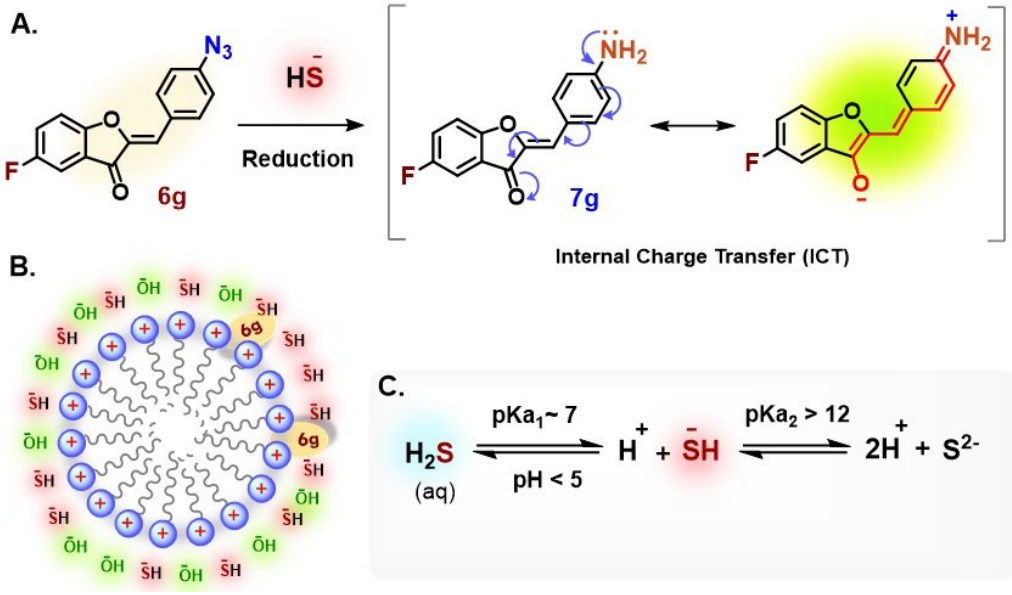


Figure 22: Sensing Mechanism of **6g**. A) *Reaction scheme showing the reduction of azide (-N_3) to the corresponding amine. The resonance responsible for the fluorescence is depicted in parenthesis. B) Schematic representation of CTAB micelle and its role in recruiting and changing the local concentration of 6g and HS^-. C) Reaction scheme representing the dissociation of H_2S in aqueous medium.*

Based on the mechanistic study by Henthorn and Pluth, this reaction is suggested to proceed via nucleophilic attack of hydrosulfide ion (HS^-) to the terminal electrophilic nitrogen of azido group forming an azidothiol intermediate species which on subsequent HS^- intermolecular attack is converted to the respective amine **7g**.[86] The amine subsequently undergoes a spontaneous internal charge transfer (ICT) via resonance to its corresponding highly fluorescent zwitterionic form as depicted in Figure 22A. The presence of CTAB may further stabilize the charged species via electrostatic interactions. This consequently leads to the stabilization of the high quantum yield state resulting in an

enhanced emission intensity as evident in Figures 18A, C, Appendix B. It has been suggested that CTAB works by changing the local concentration of the reactants and the pH value of the reaction mixture. The CTAB micelles increase the local concentration of anions, including OH^- and HS^- around it (Figure 22B), which increases the local pH of the solution. This in turn decreases the $[H_2S]/[HS^-]$ ratio thereby contributing an overall higher HS^- concentration around the micelles.[88] The effect of pH on dissociation of H_2S in an aqueous medium is summarized in Figure 22C.[83] At lower pH (~ 3) the fluorescence intensity of the product is expected to decrease due to protonation of the amine which shuts down the ICT process (Figure 16E). This is apparent from Appendix B which clearly demonstrates how the emission intensity of the product **7g** is affected by the pH although uv-absorption remains unaffected. In this overall phenomenon, CTAB micelles serve as a scaffold to recruit HS^- and probe **6g** in the vicinity of each other localizing within the micelles, thereby significantly increasing the reaction rate (Figure 18A and C) along with fluorescent intensities.

3. Conclusions

In short, an aurone-based sensor for hydrogen sulfide has been developed that exhibits good sensitivity and selectivity. Further, the development of this probe molecule has demonstrated the strength of the aurone framework in terms of the ease with which new compounds can be prepared to modify the reactivity and physical properties (solubility in this case) to fit the demands of various sensing applications. Based on these results, future optimized compounds can be designed and prepared for a wide range of environmental as well as biological applications. Given the ease and flexibility in the

synthesis of the aurone framework, many additional sensing applications can be envisioned, particularly applying the lessons learned in this project. Efforts to this end are underway and will be reported in due course.

4. Experimental

4.1. Materials and methods

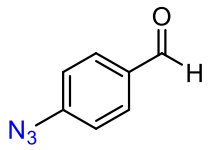
ACS grade chemicals and solvents used for the synthesis were directly employed without further purification. All the reactions were done under an air atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AS (500 and 300 MHz) NMR instrument and chemical shifts were recorded in ppm with reference to the tetramethylsilane (TMS) chloroform-*d* or DMSO-d_6.[90] The following conventions are used for multiplicities: s, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet; *dt*, doublet of triplet; *ddd*, doublet of doublet of doublet; *br*, broad. Cary 630 FT-IR (Agilent Technologies) was used to collect IR spectra. Fluorescence spectra were collected using F-4500 fluorescence spectrophotometer (Hitachi, Japan) with the slit width for excitation and emission set at 5 nm and photomultiplier voltage set at 700v. Alongside, HP-8452A Diode Array Spectrophotometer (Agilent Technologies Inc.) was used to record UV-visible absorption spectra. The reaction was monitored by Thin Layer Chromatography (TLC) on aluminum supported silica-coated plates (Sorbent Technologies, Inc.). All extracts were concentrated under reduced pressure using a Buchi Rotary Evaporator. During purification and identification of compounds, Thin Layer Chromatography (TLC) was performed on aluminum supported Silica coated plates (Sorbent Technologies, Inc.) and monitored by

short wavelength (254 nm) UV light. Products were purified by flash silica gel (32-63u) column chromatography.

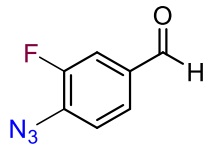
4.2. Synthesis of 4′-azido benzaldehyde derivatives

In a 3-dram glass vial containing a magnetic stir bar, 1.0 mmol of fluorinated aromatic aldehyde and 1.5 mmol (1.5 equivalent) of sodium azide (NaN_3) were dissolved in 2 mL of dimethylsulfoxide (DMSO) and heated for 2-3 h at 70-90 ºC (70 ºC for multi-fluorosubstituted) in a sand bath. After the completion of the reaction, it was diluted with DI water and extracted with ethyl acetate (×4). To remove residual DMSO, the organic fraction was further washed with DI water and brine, followed by drying over anhydrous $MgSO_4$. The organic fraction was concentrated in vacuo and purified by flash column chromatography using 2-10% ethyl acetate: hexane mixture to obtain the desired 4′-azido benzaldehydes.

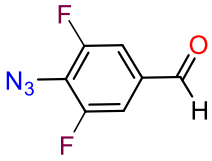
4.2.1. Characterization data for 4′-azido benzaldehydes



4-Azidobenzaldehyde (4a, 4b, 4c, 4g)[91]: Yield: 105 mg (71%); brown oil, eluted with 2% EA : hexane, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 146.41, 133.4, 131.7, 119.6. IR (neat) 2832, 2113, 1689, 1599, 1506, 1283, 784 cm^{-1}.



4-Azido-3-fluorobenzaldehyde (4d)[92]: Yield: 132 mg (80%); yellow soild, eluted with 2% EA : hexane; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (d, J = 1.9 Hz, 1H), 7.67-7.65 (m, 1H), 7.62 (dd, J = 10.5, 1.5 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, CHLOROFORM-D) δ 189.6, 155.5 (d, $^{1}J_{C\text{-}F}$ = 252.7 Hz), 134.5 (d, $^{3}J_{C\text{-}F}$ = 11.5 Hz), 134.2 (d, $^{4}J_{C\text{-}F}$ = 4.9 Hz), 127.2, 121.5, 116.8 (d, $^{2}J_{C\text{-}F}$ = 19.5 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ -123.8. IR (neat) 2858, 2125, 1689, 1588, 1480, 1372, 1197, 881, 817, 795 cm^{-1}.

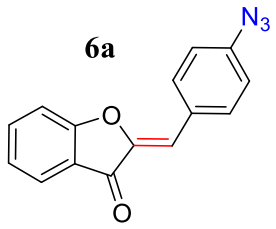


***4-Azido-3,5-difluorobenzaldehyde (4e, 4f)[93]*:** Yield: 151 mg (82%); yellow solid, eluted with 5% EA : hexane; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (t, J = 2.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 155.8 (dd, J = 254, 4.0 Hz), 132.6 (t, J = 6.3 Hz), 124.0 (t, J = 14.0 Hz), 113.1 (dd, J = 18, 6.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ -120.0. IR (neat) 2819, 2115, 1698, 1574, 1500, 1336, 1040, 859 cm^{-1}.

4.3. Synthesis of aurones (6a-6g)

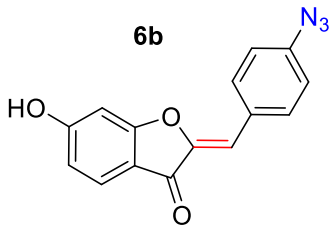
All the aurones **6a-6g** were synthesized based on the literature.[61] In a 3-dram glass vial, benzofuranone (1 equivalent) was dissolved in 5 mL of glacial acetic acid containing a magnetic stir bar. To this solution 4′-azidobenzaldehyde (1.5 equivalent) and 2-3 drops (0.2 mL) of concentrated HCl were added and stirred at room temperature for up to 3 hours. In most cases, reaction resulted in a precipitate usually after 30 min indicating the completion of the reaction. After the reaction was complete, it was poured into ice-cold DI water. The precipitate obtained was filtered, and the residue was washed multiple times with water and allowed to air dry. No further purification was required. For some of the aurones which did not precipitate out efficiently, the water diluted reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate and purified by flash column chromatography.

4.3.1. Characterization data for aurones 6a-6g

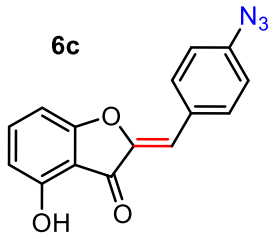


(Z)-2-(4-azidobenzylidene)benzofuran-3(2H)-one (6a): Reaction scale (1.80 mmol), Yield: 70% (331 mg); yellow solid, mp 128-129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 1H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 184.7, 166.1, 146.8, 141.6, 137.0, 133.2, 129.3, 124.8, 123.7, 121.8, 119.7, 113.0, 112.2. IR (neat) 2121, 1704, 1655, 1596, 1508, 1302, 1186, 1108, 829, 750 cm^{-1}.

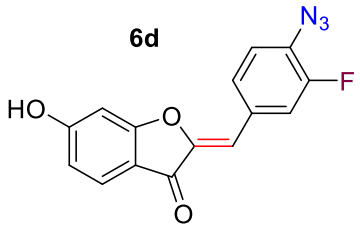


(Z)-2-(4-azidobenzylidene)-6-hydroxybenzofuran-3(2H)-one (6b): Reaction scale (0.114 mmol), Yield: 94% (25.4 mg); faint orange red solid, mp 194-196 °C.^{1}H NMR (500 MHz, DMSO-D6) δ 11.23 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (s, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-D6) δ 181.2, 167.8, 166.5, 147.1, 140.5, 132.7, 128.9, 125.9, 119.6, 113.0, 112.8, 109.5, 98.6. IR (neat) 3074-2600 (br), 2117, 1681, 1577, 1506, 1458, 1294, 1112, 825 cm^{-1}.

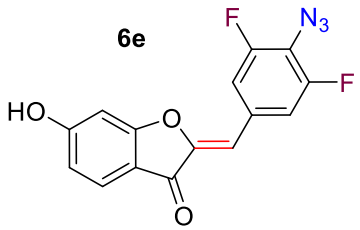


(Z)-2-(4-azidobenzylidene)-4-hydroxybenzofuran-3(2H)-one (6c): Reaction scale (0.30 mmol), Yield: 90% (75 mg); red solid, mp 179-181 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ

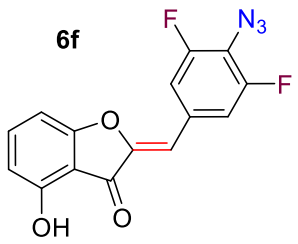
11.16 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.0 Hz, 1H), 6.77 (s, 1H), 6.64 (d, J = 8.5 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-D6) δ 181.2, 165.9, 157.2, 146.31, 140.5, 138.7, 132.7, 129.1, 119.7, 110.7, 109.2, 109.1, 102.4. IR (neat) 3283, 2125, 2028, 1693, 1652, 1592, 1458, 1316, 1134, 769 cm^{-1}.



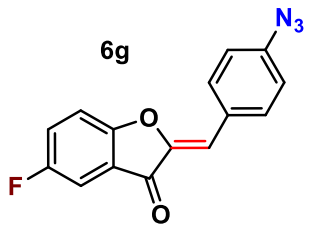
(Z)-2-(4-azido-3-fluorobenzylidene)-6-hydroxybenzofuran-3(2H)-one(6d): Reaction scale (0.27 mmol), Yield: 76% (61 mg); red solid, mp 186 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.24 (s, 1H), 7.80 (d, J = 12.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 8.6 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 6.73 (s, 1H), 6.71 (dd, J = 8.3, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-D6) δ 153.5 (d, $^{1}J_{C\text{-}F}$ = 247.3 Hz), 130.3 (d, $^{2}J_{C\text{-}F}$ = 7.5 Hz), 128.3 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 118.30 (d, $^{2}J_{C\text{-}F}$ = 20.1 Hz), 108.43 (d, $^{3}J_{C\text{-}F}$ = 2.4 Hz). IR (neat) 3074-2653 (br), 2136, 2106, 1685, 1573, 1462, 1298, 1119, 851 cm^{-1}.



(Z)-2-(4-azido-3,5-difluorobenzylidene)-6-hydroxybenzofuran-3(2H)-one (6e): Reaction scale (0.33 mmol), Yield: 76% (79.3 mg); yellow solid, mp 260 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.30 (s, 1H), 7.72 (d, *J* = 9.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-D6) δ 181.0, 167.9, 166.8, 154.7 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 148.0, 129.6 (t, $^{2}J_{C\text{-}F}$ = 10.1 Hz), 125.9, 114.3 (d, $^{2}J_{C\text{-}F}$ = 19.6 Hz), 113.2, 112.3, 107.3, 98.8. IR (neat) 3078, 2117, 1685, 1577, 1506, 1458, 1279, 1138, 1112, 1045, 832 cm^{-1}.



(Z)-2-(4-azido-3,5-difluorobenzylidene)-4-hydroxybenzofuran-3(2H)-one (6f): Reaction scale (0.36 mmol), Yield: 70% (80 mg); yellow solid, mp 160-170 ºC. ^{1}H NMR (300 MHz, DMSO-D6) δ 11.27 (s, 1H), 7.75 (d, *J* = 10.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-D6) δ 180.9, 165.8, 157.2, 154.9 (d, $^{1}J_{C\text{-}F}$ = 245.9, 4.6 Hz), 147.2, 138.9, 129.68 (t, $^{3}J_{C\text{-}F}$ = 9.8 Hz), 117.32 (t, $^{2}J_{C\text{-}F}$ = 14.0 Hz), 114.22 (dd, $^{2}J_{C\text{-}F}$ = 19.2, 4.7 Hz), 111.0, 108.6, 106.8, 102.5. IR (neat) 3379, 2121, 1696, 1607, 1495, 1339, 1305, 1179, 1041, 799 cm^{-1}.

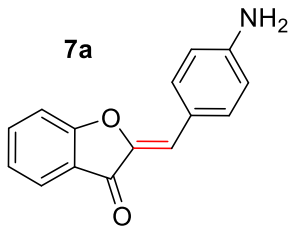


(Z)-2-(4-azidobenzylidene)-5-fluorobenzofuran-3(2H)-one (6g): Reaction scale (0.40 mmol), Yield: 80% (90 mg); yellow solid, mp 137-138 ºC. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.45 (dd, *J* = 7.0, 3.0 Hz, 1H), 7.38 (td, *J* = 8.5, 3.0 Hz, 1H), 7.29 (dd, *J* = 9.0, 3.5 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.85 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 162.1, 159.02 (d, $^{1}J_{C\text{-}F}$ = 244.7 Hz), 147.4, 141.9, 133.3, 129.0, 124.4 (d, $^{2}J_{C\text{-}F}$ = 26.1 Hz), 122.5 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 119.7, 114.21 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 113.08, 110.36 (d, $^{2}J_{C\text{-}F}$ = 24.3 Hz). IR (neat) 2128, 1707, 1655, 1598, 1484, 1305, 1268, 1190, 892, 832.

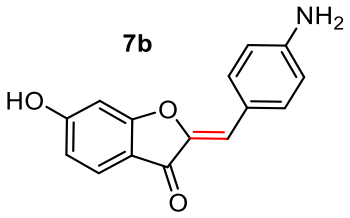
4.4. Synthesis of amino aurones (7a-7g)

For the synthesis of the corresponding amines (7a-7g) of the probe candidates, 1 equivalent of the aurone **(6a-6g)** was mixed with an excess of NaHS (4 equivalent) in a 1-dram glass vial containing a magnetic stir bar. To the mixture, 1.5 mL of MeCN with few drops of DI H_2O was added and stirred for 30 minutes (acetone can also be used as a solvent). The solution turned bright red in about 5 minutes. Once the reaction was complete based on the TLC, the mixture was concentrated under vacuum and subjected to flash column chromatography.

4.4.1. Characterization data for amino aurones 7a-7g

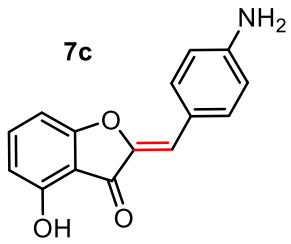


(Z)-2-(4-aminobenzylidene)benzofuran-3(2H)-one (7a): Reaction scale (0.114 mmol), Yield: 94% (25.4 mg); orange red solid, mp 173-175 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.61 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.87 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 2H), 4.09 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 165.6, 148.7, 145.4, 136.3, 133.9, 124.5, 123.2, 122.5, 122.3, 115.1, 114.8, 112.9. IR (neat) 3439, 3312, 3216, 1683, 1577, 1518, 1488, 1302, 1182, 1100, 832, 754 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{15}H_{12}NO_2$ 238.0868, found 238.0871.

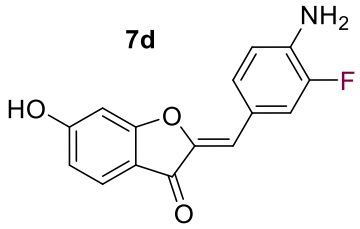


(Z)-2-(4-aminobenzylidene)-6-hydroxybenzofuran-3(2H)-one (7b): Reaction scale (0.11 mmol), Yield: 92% (25.6 mg); orange red solid, mp > 260 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 11.00 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 3H), 5.94 (s, 2H). ^{13}C NMR (125 MHz, DMSO-D6) δ 180.7, 166.9, 165.6, 151.1, 144.5, 133.3, 125.3, 119.0, 113.8, 113.6,

112.9, 112.5, 98.4. IR (neat) 3461, 3361, 3300-2500 (br), 1666, 1629, 1551, 1454, 1287, 1108, 821 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{15}H_{12}NO_3$ 254.0817, found 254.0813.

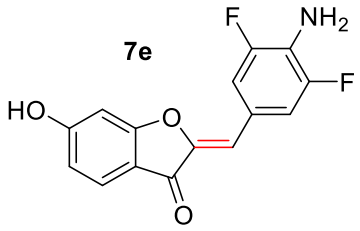


(*Z*)-2-(4-aminobenzylidene)-4-hydroxybenzofuran-3(*2H*)-one (7c): Reaction scale (24 mg, 0.083 mmol), Yield: 92% (20 mg); red solid, mp >260 ºC. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.54 (d, *J* = 8.5 Hz, 2H), 6.99 (dd, *J* = 8.5, 7.5 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 2H), 6.25 (s, 1H), 5.86 (d, *J* = 9.0 Hz, 1H), 5.79 (d, *J* = 7.5 Hz, 1H), 5.63 (s, 2H). ^{13}C NMR (75 MHz, DMSO-D6) δ 182.1, 173.9, 165.9, 149.7, 145.9, 136.4, 131.9, 120.4, 117.7, 113.8, 110.7, 107.5, 89.3. IR (neat) 3394-3275 (br), 1674, 1592, 1561, 1477, 1376, 1235, 1127, 1004, 803 cm^{-1}. HRMS (EI): *m/z* [M + H] calcd for $C_{15}H_{12}NO_3$ 254.0817, found 254.0819.

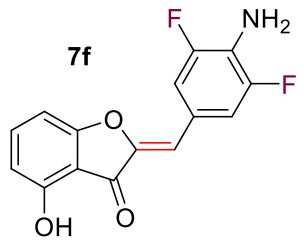


(Z)-2-(4-amino-3-fluorobenzylidene)-6-hydroxybenzofuran-3(2H)-one(7d): Reaction scale (21.5 mg, 0.069 mmol), Yield: 98% (18.4 mg); orange solid, mp >260 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.64 (d, *J* = 12.0 Hz, 1H), 7.58 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.50 (d,

J = 8.0 Hz, 1H), 6.86 – 6.76 (m, 2H), 6.69 (s, 1H), 5.96 (s, 2H). ^{13}C NMR (125 MHz, DMSO-D6) δ 180.8, 167.2, 166.0, 149.8 (d, $^{1}J_{C\text{-}F}$ = 237.2 Hz), 145.3, 138.9 (d, $^{2}J_{C\text{-}F}$ = 12.8 Hz), 129.1, 125.5, 119.5 (d, $^{3}J_{C\text{-}F}$ = 7.0 Hz, 117.25 (d, $^{2}J_{C\text{-}F}$ = 18.8 Hz), 115.7, 113.2, 112.8, 111.5, 98.5. IR (neat) 3478, 3372, 3041-2586 (br), 1674, 1566, 1521, 1454, 1294, 1112, 999 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}FNO_3$ 272.07230, found 272.07228.

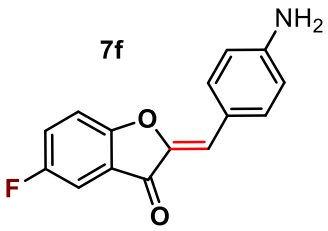


(Z)-2-(4-amino-3,5-difluorobenzylidene)-6-hydroxybenzofuran-3(2H)-one(7e):Reaction scale (31 mg, 0.098 mmol), Yield: 80% (22.7 mg); orange solid, mp >260 ºC. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.62 – 7.49 (m, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.00 (s, 1H). ^{13}C NMR (75 MHz, DMSO-D6) δ 180.9, 167.4, 150.4 (dd, $J_{C\text{-}F}$ = 238.8, 10.0 Hz), 146.0, 128.0 (t, $J_{C\text{-}F}$ = 16.5 Hz), 125.7, 117.85 (t, $J_{C\text{-}F}$ = 9.1 Hz), 113.95 (dd, $J_{C\text{-}F}$ = 13.3, 8.4 Hz), 113.0, 110.4, 98.7. IR (neat) 3469, 3368, 1678, 1581, 1532, 1454, 1324, 1287, 1115, 821, 769 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}FNO_3$ 272.07230, found 272.08226.



(Z)-2-(4-amino-3,5-difluorobenzylidene)-4-hydroxybenzofuran-3(2H)-one(7f):

Reaction scale (13 mg, 0.041 mmol), Yield: 84% (10 mg); red solid, mp 222-225 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.44 (dd, *J* = 8.0, 2.1 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.33 (s, 1H), 6.00 (d, *J* = 8.0 Hz, 2H), 5.74 (s, 2H). ^{13}C NMR (125 MHz, DMSO-D6) δ 181.2, 165.8, 150.6 (dd, $^{1}J_{C\text{-}F}$ = 238.4, 9.8 Hz), 147.5 (t, $J_{C\text{-}F}$ = 10.4), 136.6, 126.3 (t, $^{2}J_{C\text{-}F}$ = 11.2 Hz), 119.5, 112.7 (d, $^{2}J_{C\text{-}F}$ = 16.7 Hz), 109.9, 104.9, 104.8, 104.7. IR (neat) 3346, 1689, 1596, 1566, 1566, 1480, 1354, 1235, 1115, 1000, 803 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{10}F_2NO_3$ 290.06288, found 290.06290.



(Z)-2-(4-aminobenzylidene)-5-fluorobenzofuran-3(2H)-one (7g): Reaction scale (18 mg, 0.064 mmol), Yield: 73% (12 mg); red solid, mp 178-180 ºC. ^{1}H NMR (500 MHz, DMSO-D6) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.65 – 7.58 (m, 2H), 7.57 (dd, *J* = 7.0, 2.4 Hz, 1H), 6.88 (s, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.16 (s, 2H). ^{13}C NMR (76 MHz, DMSO-D6) δ 181.64,

160.5, 158.18 (d, $^{1}J_{C\text{-}F}$ = 240.9 Hz), 152.1, 144.3, 134.2, 123.7 (d, $^{2}J_{C\text{-}F}$ = 26.0 Hz), 122.6 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 118.7, 116.2, 114.72 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 113.9, 109.48 (d, $^{2}J_{C\text{-}F}$ = 24.2 Hz). IR (neat) 3420, 3320, 3216, 1689, 1633, 1562, 1514, 1480, 1272, 1156, 817, 762 cm^{-1}. HRMS (EI): *m*/*z* [M + H] calcd for $C_{15}H_{11}FNO_2$ 256.0774, observed 256.0071.

4.5. Sample preparation method for spectroscopic measurement

Stock solutions (10, 5, and 1mM) of the probe candidates (**6a-6g**) and their respective amines were prepared in DMSO. Similarly, the stock solutions of NaHS (10, 5 and 1 mM), cetyltrimethylammonium bromide (CTAB) (5 and 1 mM), and various biologically relevant sulfide sources L-cysteine, reduced glutathione, and 2-mercaptoethanol (5 and 1 mM) were prepared in phosphate-buffered saline (PBS) (1X, pH = 7.4, without Ca and Mg). The detailed sample preparation procedure for the experiments is incorporated in the supporting information. All UV-visible absorption and emission spectra were collected in various concentrations of DMSO (0.5, 5, 50, and 100%) and/or MeCN in PBS -buffer (1X, pH = 7.4, without Ca and Mg) in 3 mL and 1.5 mL cuvettes respectively, in the presence and absence of 1mM CTAB. The detection limit was determined using different concentrations of **7g** (0.1-50 μM) in different solvent systems (biological and non-aqueous). Limits of detection were defined based on linearity and signal-to-noise ratios for the upper and lower limits, respectively. All emission intensities used to determine detection limits were derived from triplicate experimental measurements. Rate profiles of the reduction reaction as well as the selectivity study of the probe were performed by the incubation of 20 μM **6g** with 100 μM H_2S source (NaHS) in either 0.5 % v/v DMSO in PBS/1 mM CTAB (biological) or 90 % v/v DMSO/10 % v/v PBS (non-aqueous) solvent

systems. The reactions were excited at 465 nm and emission spectra spanning from 480 to 700 nm were collected at 2-minute intervals. All Nonlinear Least Squares (NLLS) analyses were performed using a single-exponential function given as:

$$Y = A(1 - e^{-kapp*t}) + b$$

,where A, k_{app}, t, and b represent the time course amplitude, apparent rate constant, time, and the y-intercept, respectively. All kinetic data were measured in triplicate to allow for statistical comparisons.

4.5.1. UV-visible absorption and emission spectra

The 10 mM stock solution of all the 4'-azidoaurones **6a-g** and corresponding amines **7a-g** were prepared in DMSO. Unless otherwise stated 1X, pH = 7.4 PBS was used for the preparation of samples. All the UV-absorption and emission spectra were collected using a 50 μM solution of the compounds in different solvent systems (90% DMSO/10% PBS, 5% DMSO in PBS, and 0.5% DMSO in PBS) in the presence or absence of CTAB.

Sample preparation for UV-Vis absorption

a) 50 μM solution of **6g** and **7g** in 0.5% DMSO in PBS

   15 μL 10 mM stock solution of **6g** or **7g** in DMSO was diluted with 2985 μL of PBS (1x pH = 7.4) in a 3 mL cuvette.

b) 50 μM solution of **6g** and **7g** in 5% DMSO in PBS

   150 μL 1.0 mM stock solution of **6g** or **7g** in DMSO was diluted with 2850 μL of PBS (1x pH = 7.4) in a 3 mL cuvette.

c) 50 μM solution of **6g** and **7g** in 90% DMSO in PBS

150 µL 1.0 mM stock solution of **6g** or **7g** in DMSO was diluted with 2550 µL DMSO and 300 PBS (1x pH = 7.4) in a 3 mL cuvette.

d) 50 µM solution of **6g** v **7g** in 0.5% DMSO in PBS and 1mM CTAB (in PBS)

To a 15 µL 10 mM **6g** and **7g**, 600 µL of CTAB (5 mM stock solution in PBS) and 2385 µL of PBS in a 3 mL cuvette.

Similarly, for collecting the emission spectra the 50 µM solutions of **6g** and **7g** in a 1.5 mL cuvette were excited at their respective absorption maxima (λmax) obtained for the specific solvent condition e.g., **6g** and **7g** were excited at 405 and 460 nm respectively in 0.5% v/v DMSO in PBS with 1mM CTAB.

4.5.2. Effect of pH on spectral properties of 6g and 7g

The effect of pH on the absorption and fluorescence behavior of probe **6g** and the corresponding amine **7g** in the presence or absence of 1 mM CTAB was studied. This study was done in 0.5% v/v DMSO in PBS (1X) solvent. For the study, five different PBS (1X) solutions of pH = 3, 4.8, 7.5, 9.15, and 11 were prepared by adjusting pH using a pH meter. Five different 10 mM stock solution of CTAB (pH = 3, 4.8, 7.5, 9.15, and 11) were prepared using the corresponding PBS (1X, pH = 3, 4.8, 7.5, 9.15, and 11) solutions. The UV-Vis absorption spectra of **6g** and **7g** were collected with and without the inclusion of 1mM CTAB in 0.5% v/v DMSO in PBS (1X) of the specific pH as described above.

Sample preparation (example)

1. 50 µM solution of **6g** and **7g** in 0.5% DMSO in PBS (pH = 3) with 1mM CTAB

To a 15 µL 10 mM stock solution of **6g** and **7g**, 600 µL of CTAB (5 mM stock solution in PBS, pH =3) and 2385 µL of PBS (pH = 3) were mixed in a 3 mL cuvette and excited at the corresponding λmax to collect the emission spectra.

Similarly, the emission spectra of **6g** and **7g** at specific pH were collected by preparing and exciting their 50 µM solution in a 1.5 mL cuvette at their corresponding absorption maxima (λmax)**.**

4.5.3. Determination of detection limit

Using the stock solutions of **7g** the emission spectra of its various concentrations (0.1 - 50 µM) were collected in either 0.5% v/v DMSO in PBS/ 1 mM CTAB or 90% v/v DMSO/ 10% v/v PBS (IX, pH 7.4) solvent systems. Each solution of **7g** (0.1, 0.5, 1, 2, 5, 10, 15, 20, 25, 30, 40 and 50 µM) prepared in a particular solvent system in a 1.5 mL cuvette was excited at the 465 nm. For each concentration, at least three independent trials were performed. The corresponding emission intensity observed at 560 nm was then plotted as a function of [**7g**] to obtain the linear range of detection. This generated the calibration curve for each solvent condition revealing the useful working range of **7g**.

Sample preparation in 0.5% DMSO in PBS (1X, pH = 7.4) with 1mM CTAB)

a) 0.1 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

   In a cuvette containing 3.0 µL of **7g** (50 µM stock in DMSO), 4.5 µL DMSO, 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL, 1X, pH = 7.4)

b) 0.5 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 7.5 µL of **7g** (100 µM stock in DMSO), 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

c) 1.0 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 7.5 µL of **7g** (200 µM stock in DMSO), 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

d) 2.0 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 3.0 µL of **7g** (1 mM stock in DMSO), 4.5 µL DMSO, 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

e) 5.0 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 7.5 µL of **7g** (1 mM stock in DMSO), 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

f) 10 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 3.0 µL of **7g** (5 mM stock in DMSO), 4.5 µL DMSO, 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

g) 15 µM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 4.5 µL of **7g** (5 mM stock in DMSO), 3.0 µL DMSO, 300 µL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 µL with PBS (1192.5 µL)

h) 20 μM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 3.0 μL of **7g** (10 mM stock in DMSO), 4.5 μL DMSO, 300 μL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 μL with PBS (1192.5 μL)

i) 25 μM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 7.5 μL of **7g** (5 mM stock in DMSO), 300 μL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 μL with PBS (1192.5 μL).

j) 30 μM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 4.5 μL of **7g** (10 mM stock in DMSO), 3.0 μL DMSO, 300 μL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 μL with PBS (1192.5 μL).

k) 40 μM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 6.0 μL of **7g** (10 mM stock in DMSO), 1.5 μL DMSO, 300 μL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 μL with PBS (1192.5 μL)

l) 50 μM **7g** in 0.5% DMSO in PBS with 1mM CTAB

In a cuvette containing 7.5 μL of **7g** (10 mM stock in DMSO), 300 μL CTAB (5 mM in PBS) were added and diluted to the final volume of 1500 μL with PBS (1192.5 μL).

4.5.4. Reaction kinetics study

The time course reaction kinetics for the reduction of the azide (**6g**) to amine (**7g**) was performed by incubating 20 μM **6g** with 100 μM NaHS in either 0.5% v/v DMSO in PBS (1X, pH = 7.4) +/- 1 mM CTAB or 90% v/v DMSO/10% v/v PBS (1X, pH = 7.4) solvent systems. Samples were excited at 465 nm and emission spectra spanning from 480 to 700 nm were collected at 2-minute intervals.

Sample preparation (solvent system 0.5% v/v DMSO in PBS (1X, pH = 7.4)/1 mM CTAB):

In a cuvette, 3.0 μL of **6g** (10 mM stock in DMSO) was added followed by 4.5 μL DMSO, 300 μL CTAB (5 mM in PBS), and 1042.5 μL PBS (1X, pH = 7.4). To this solution, 150 μL of NaHS (1 mM stock solution in PBS) was mixed and placed in the fluorescence spectrophotometer to monitor the progress of the reaction by exciting the sample at 465 nm. The emission spectra corresponding to the amine were collected every 2-minutes for 60 minutes. At least 3 trials were performed for each experiment. For the reaction that employed 90% v/v DMSO/10% v/v PBS (1X, pH = 7.4) solvent system, the emission spectra were collected every 2-minutes for 30 minutes

4.5.5. Selectivity study

To evaluate the reaction specificity, a series of fluorescence time courses were collected using the same methodology as described for the kinetics study. In place of NaHS, three potential sulfide-donors were substituted: L-cysteine, reduced glutathione, and 2-mercaptoethanol. All emission spectra reflect the reaction of 100 μM sulfide-donor with 20 μM **6g** in 0.5 % v/v DMSO, 99.5 % v/v PBS, and 1 mM CTAB. At least 3 trials were performed for each experiment.

5. References

1. Guo, Z.; Chen, G.; Zeng, G.; Li, Z.; Chen, A.; Wang, J.; Jiang, J. *Analyst* **2015**, *140*, 1772-1786.
2. Li, J.; Yin, C.; Huo, F. *RSC Adv.* **2015**, *5*, 2191-2206.
3. Yu, F.; Han, X.; Chen, L. *Chem. Commun.* **2014**, *50*, 12234-12249.
4. Lin, V. S.; Lippert, A. R.; Chang, C. J. *Meth. Enzym*. **2015**, *554*, 63-80.
5. Peng, B.; Xian, M. *Meth. Enzym.* **2015**, *554*, 47-62.
6. Rubright, S. L. M.; Pearce, L. L.; Peterson, J. *Nitric Oxide,* **2017**, *71*, 1-13.
7. Kolluru, G. K.; Shen, X.; Bir, S. C.; Kevil, C. G. *Nitric Oxide,* **2013**, 35, 5−20.
8. A. F. Perna and D. Ingrosso, Nepthrol., Dial., *Transplant.* **2012**, *27*, 486-493.
9. Kamoun, P.; Belardinelli, M-C.; Chabli, A.; Lallouchi, K.; Chadefaux-Vekemans, B. *Am. J. Med. Genet. Part A,* **2003**, *116*, 310-311.
10. Fiorucci, S.; Antonelli, E.; Mencarelli, A.; Orlandi, S.; Renga, B.; Rizzo, G.; Distrutti, E.; Shah, V.; Morelli, A. *Heptaology*, **2005**, *42*, 539-548.
11. Hyspler, R.; Ticha, A.; Indrova, M.; Zadak, Z.; Hysplerova, L.; Gasparic, J.; Churacek, J. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2002**, *770*, 255-259.
12. Chen, Y. H.; Yao, W. Z.; Geng, B.; Ding, Y. L.; Lu, M.; Zhao, M. W.; Tang, C. S. *Chest* **2005**, *128*, 3205-3211.
13. Li, L.; Bhatia, M.; Zhu, Y. Z.; Zhu, Y. C.; Ramnath, R. D.; Wang, Z. J.; Anuar, F. B. M.; Whiteman, M.; Salto-Tellez, M.; Moore, P. K. *FASEB J.* **2005**, *19*, 1196-1198.
14. Goodwin, L. R.; Francom, D.; Dieken, F. P.; Taylor, J. D.; Warenycia, M. W.; Reiffenstein, R. J.; Dowling, G. *J. Anal. Toxicol.* **1989**, *13*, 105-109.
15. Savage, J. C.; Gould, D. H. *J. Chromatogr. B. Biomed. Sci. Appl.* **1990**, *526*, 540-545.
16. Liu, C. R.; Peng, B.; Li, S.; Park, C. M.; Whorton, A. R.; Xian, M. *Org. Lett.* **2012**, *14*, 2184-2187.
17. For a recent example, see: Chen, Y.; Shang, X.; Li, C.; Xue, Z.; Chen, H.; Wu, H.; Wang, T. *Sci. Rep.* **2018**, *8*, 16159.

18. Jun, M. E.; Roya, B.; Ahn, K. H. *Chem. Commun.* **2011**, *47*, 7583-7601.
19. Bae, S. K.; Heo, H.; Choi, D. J.; Sen, D.; Joe, E-H.; Cho, B. R.; Kim, H. M. *J. Am. Chem. Soc.* **2013**, *135*, 9915-9923.
20. Bailey, T. S.; Pluth, M. D. *J. Am. Chem. Soc.* **2013,** *135*, 16697-16704.
21. Katla, J.; Kanvah, S. *Photochem. Photobiol. Sci.* **2018**, *17*, 42-50.
22. Zeng, Y-S.; Gao, R-C.; Wu, T-W.; Cho, C.; Tan, K-T. *Bioconjugate Chem.* **2016**, *27*, 1872-1879.
23. Choi, S-A.; Park, C. S.; Kwon, O. S.; Giong, H-K.; Lee, J-S.; Ha, T. H.; Lee, C-S. *Sci. Rep.* **2016**, *6*, 26203.
24. Guo, Y.; Zeng, T.; Shi, G.; Cai, Y.; Xie, R. *RSC Adv.* **2014**, *4*, 33626-33628.
25. Xiang, K.; Liu, Y.; Li, C.; Tian, B.; Tong, T.; Zhang, J. *Dyes Pigments* **2015**, *123*, 78-84.
26. Jiang, Y.; Wu, Q.; Chang, X. *Talanta* **2014**, *121*, 122-126.
27. Wang, R.; Yu, F.; Chen, L.; Chen, H.; Wang, L.; Zhang, W. *Chem. Commun.* **2012**, *48*, 11757-11759.
28. Peng, H.; Cheng, Y.; Dai, C.; King, A. L.; Predmore, B. L.; Lefer, D. J.; Wang, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 9672-9675.
29. Ozdemir, T.; Sozmen, F.; Mamur, S.; Tekinay, T.; Akkaya, E. U. *Chem. Commun.* **2014**, *50*, 5455-5457.
30. Qu, X.; Li, C.; Chen, H.; Mack, J.; Guo, Z.; Shen, Z. *Chem. Commun.* **2013**, *49*, 7510-7512.
31. Hou, F.; Huang, L.; Xi, P.; Cheng, J.; Zhao, X.; Xie, G.; Shi, Y.; Cheng, F.; Yao, X.; Bai. D.; Zeng, Z. *Inorg. Chem.* **2012**, *51*, 2454-2460.
32. Abd-Elaal, A. A.; Tawfik, S. M.; Lee, Y-I. *J. Mol. Liq.* **2017**, *247*, 35-42.
33. Zhang, W.; Chen, X. *Biosens. Bioelectron.* **2017**, *48*, 96-100.
34. Cao, X.; Lin, W.; Zheng, K.; He, L. *Chem. Commun.* **2012**, *48*, 10529-10531.
35. Maity, D.; Raj, A.; Samanta, P. K.; Karthigeyan, D. T.; Mundu, K.; Pati, S. K.; Govindaraju, T. *RSC Adv.* **2014**, *4*, 11147-11151.
36. Das, S.; Sahoo, P. *Sensor Actuat. B-Chem*. **2019**, *291*, 287-292.

37. Chen, Y.; Shang, X.; Li, C.; Xue, Z.; Chen, H.; Wu, H.; Wang, T. *Sci. Rep*. **2018**, *8*, 1-9.
38. Wang, Y.; Yang, L.; Wei, X-R.; Sun, R.; Xu, Y-J.; Ge, J-F. *Anal. Meth.* **2018**, *10*, 5291-5296.
39. Asaithambi, G.; Periasamy, V. J. *Photochem. Photobio. A*, **2019**, *369*, 97-105.
40. Wang, H.; Wu, X.; Yang, S.; Tian, H.; Liu, Y.; Sun, B. *Dyes Pigments* **2019**, *160*, 757-764.
41. Wang, H.; Wang, J.; Yang, S.; Tian, H.; Liu, Y.; Sun, B. *Food Chem.* **2018**, *257*, 150-154.
42. Cui, J.; Zhang, T.; Sun, Y-Q.; Li, D-P.; Liu, J-T.; Zhao, B-X. *Sensors Actuat. B-Chem.* **2016**, *232*, 705-711.
43. Peng, B.; Chen, W.; Liu, C.; Rosser, E. W.; Pacheco, A.; Zhao, Y.; Aguilar, H. C.; Xian, M. *Chem. Euro. J.* **2014**, *20*, 1010-1016.
44. Maity, D.; Raj, A.; Samanta, P. K.; Karthigeyan, D.; Kundu, T. K.; Pati, S. K.; Govindaraju, T. *RSC Adv.* **2014**, *4*, 11147-11151.
45. Chao, J.; Xu, M.; Zhang, Y.; Huo, F.; Liu, Y.; Wang, X.; Yin, C. *Spectrochim. Acta A*, **2019**, *214*, 227-232.
46. Zhang, H.; Chen, J.; Xiong, H.; Zhang, Y.; Chen, W.; Sheng, J.; Song, X. *Org. Biomol. Chem.* **2019**, *17*, 1436-1441.
47. Li, J-B.; Wang, Q.; Liu, H-W.; Yuan, L.; Zhang, X-B. *Chem. Commun.* **2019**, *55* 4487-4490.
48. Chen, F.; Han, D.; Liu, Wang, H S.; Li, K-B.; Zhang, S.; Shi, W. *Analyst,* **2018**, *143*, 440-448.
49. Shang, X.; Li, J.; Feng, Y.; Chen, H.; Guo, W.; Zhang, J.; Wang, T.; Xu, X. *Front. Chem.* **2018**, *6*, 202/1-202/8.
50. Patra, S. K.; Sheet, S. K.; Sen, B.; Aguan, K.; Roy, D. R.; Khatua, S. *J. Org. Chem.* **2017**, *82*, 10234-10246.
51. Qian, Y.; Yang, B.; Shen, Y.; Du, Q.; Lin, L.; Lin, J.; Zhu, H. *Sensors Actuat. B-Chem.* **2013**, *182*, 498-503.

52. Hou, X.; Guo, X.; Luo, Z.; Zhao, H.; Chen, B.; Zhao, J.; Wang, J. *Anal. Meth.* **2014**, *6*, 3223-3226.
53. Shanker, N.; Dilek, O.; Mukherjee, K.; McGee, D. W.; Bane, S. L. *J. Fluoresc.* **2011**, *21*, 2173-2184.
54. Choi, H. Y.; Veal, D. A.; Karuso, P. *J. Fluoresc.* **2006**, *16*, 475-482.
55. Haudecoeur, R.; Boumendjel, A. *Curr. Med. Chem.* **2012**, *19*, 2861-2875
56. Zwergel, C.; Gaascht, F.; Valente, S.; Diederich, M.; Bagrel, D.; Kirsch, G. *Nat. Prod. Commun.* **2012**, *7*, 389-394
57. Popova, A. V.; Bondarenko, S. P.; Frasinyuk, M. S. *Chem. Hetero. Comp.* **2019**, *55*, 285-299.
58. Lee, C.; Chew, E.; Go, M. *Eur. J. Med. Chem*. **2010**, *45*, 2957-2971.
59. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937-5940
60. Hawkins, I.; Handy, S. T. Tetrahedron **2013**, *69*, 9200-9204.
61. Geissman, A. T.; Harborne, J. B. *J. Am. Chem. Soc.* **1955**, *77*, 4622-4624.
62. Xue, Y.; Dou, Y.; An, L.; Zheng, Y.; Liu, Y.; *RSC Adv.* **2016**, *6*, 7002-7010.
63. Espinosa-Bustos, C.; Coretes-Arriagada, D.; Soto-Arriaza, M. A.; Robinson-Duggon, J.; Pizarro, N.; Cabrera, A. R.; Ruentealba, D.; Salas, C.O. *Photochem. Photobiol. Sci.* **2017**, *16*, 1268-1276.
64. Munoz-Becerra, K.; Villegas-Escobar, N.; Zuniga-Loyola, C.; Cortes-Arriagada, D.; Toro-Labbe, A. *Mol. Phys.* **2019**, *117*, 1451-1458.
65. Zhang, M.; Bao, Y-T.; Yang, W.; Xiao, H-F.; Han, Z-X.; Wu, X.; Yang. L. *J. Heterocycl. Chem.* **2018**, *55*, 1130-1135.
66. Chen, H.; Sun, Y.; Zhou, C.; Cao, D.; Liu, Z.; Ma, L. *Spectrochim. Acta A*, **2013**, *11*, 389-393.
67. For a recent reference using this approach, see: Yue, Y.; Huo, F.; Yue, P.; Meng, X.; Salamanca, J.C.; Escobedo, J.O.; Strongin, R.M.; Yin, C. *Anal. Chem.* **2018**, *90*, 7018-7024.
68. de Miguel, G.; Wielopolski, M.; Schuster, D.I.; Fasio, M.A.; Lee, O.P.; Haley, C.K.; Ortiz, A.L.; Echegoyen, L.; Clark, T.; Guldi, D.M. *J. Am. Chem. Soc.* **2011**, *133*, 13036-13054.

69. Fazio, M.A.; Lee, O.P.; Schuster, D.I. *Org. Lett.* **2008**, *10*, 4979-4982.
70. Mukherjee, S.; Robinson, C.A.; Howe, A.G.; Mazor, T.; Wood, P.A.; Urgaonkar, S.; Hebert, A.M.; RayChaudhuri, D.; Shaw, J.T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6651-6655.
71. Ozdemir, T.; Sozmen, F.; Mamur, S.; Tekinay, T.; Engin, U. *Chem. Commun.* **2014**, 5455-5457.
72. Roy, S.R.; Sau, S.C.; Mandal, S.K. *J. Org. Chem.* **2014**, *79*, 9150-9160.
73. Wu, X.; Sun, X.; Guo, Z.; Tang, J.; Shen, T.; James, T.D.; Tian, H.; Zhu, W. *J. Am. Chem. Soc.* **2014**, *136*, 3579-3588.
74. Yang, H.; Li, Y.; Jiang, M.; Wangm J.; Fu, H. *Chem. Eur. J.* **2011**, *17*, 5652-5660.
75. Grimes, K.D.; Gupte, A.; Aldrich, C.C. *Synthesis* **2010**, 1441-1448.
76. Su, C; Liu, X. *Asian J. Chem.* **2014**, *26*, 5301-5304.
77. Herner, A.; Nikic, I.; Kallay, M.; Lemke, E.A.; Kele, P. *Org. Biomol. Chem*. **2013**, *11*, 3297-3306.
78. Duval, R.; Kolb, S.; Braud, E.; Genest, D.; Garbay, C. *J. Comb. Chem.* **2009**, *11*, 947-950.
79. Ursuegui, S.; Recher, M.; Krezel, W.; Wagner, A. *Nat. Comm.* **2017**, 15242.
80. Timpe, H-J.; Muller, U. US 20020090566, **2002**.
81. Kafle, A.; Yossef, S.; Handy, S. T. *Tetrahedron Lett.* **2020**, *61*, 151899.
82. Lord, S.J.; Lee, H.D.; Samuel, R.; Weber, R.; Liu, N.; Conley, N.R.; Thompson, M.A.; Twieg, R.J.; Moerner, W.E. *J. Phys. Chem. B*, 2010, 114, 14157-14167.
83. Li, Q.; Lancaster, J. R. *Nitric Oxide,* **2013**, *35*, 21-34.
84. Zhu, Z.; LI, Y.; Wei, C.; Wen, X.; Xi, Z. *Chem. Asian J.* 2016, 11, 68-71.
85. Wei, C.; Wang, R.; Wei, L.; Li, Z.; Xi, Z.; Yi, L. *Chem. Asian J.* **2014**, *9*, 3586-3592.
86. Zhang, J.; Gao, Y.; Kang, X.; Zhu, Z.; Wang, Z.; Xi, Z.; Yi, L. *Org. Biomol. Chem.* **2017**, *15*, 4212-4217.
87. Henthorn, H. A.; Pluth, M. D. *J. Am. Chem. Soc.* **2015**, *137*, 15330-15336.
88. Tian, H.; Qian, J.; Bai, H.; Sun, Q.; Zhang, L.; Zhang, W. *Anal. Chim. Acta,* **2013**, 768, 136-142.
89. Zhang, J.; Guo, W. *Chem. Commun*., **2014**, *50*, 4214-4217.

90. Gottlieb, H. E.; Lotlyr, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.
91. Herner, A.; Nikić, I.; Kállay, M.; Lemkeb E. A.; Kele, P. *Org. Biomol. Chem*. *2013*, 11, 3297-3306.
92. Lord, S. J.; Lee, H-L. D.; Samuel, R.; Weber, R.; Liu, N.; Conley, N. R.; Thompson, M. A.; Twieg, R. J.; Moerner, W. E. *J. Phys. Chem. B*, **2010**, *114*, 14157–14167.
93. Gagnon, T.; Fillion, D.; Lefebvre, M-R.; Escher, E. *J. Recept. Sig. Transd.* **2006**, 26, 435–451.

CHAPTER – V

CONCLUSIONS

Aurones are secondary metabolites found in various flowering plants. As a secondary metabolite, they are well documented to exhibit a wide range of biological activity against infective diseases, including bacteria, viruses, and various parasites, consequently making the aurone structure a potential therapeutic scaffold. Among several types of aurone derivatives, information on glycosylated analogs is limited. Although various glycosylated aurone derivatives have been isolated from plant sources, there is no report on their syntheses. Since glycosylation in many drug molecules, e.g., vancomycin, gentamycin, and streptomycin, has been found to help to improve their activity, as well as their pharmacokinetic parameters, developing efficient reaction protocols for their easy access is essential.[1]

To address this omission, we reported the first synthesis of peracetylated aurone analogs as discussed in chapter II. This research provided an efficient and convenient O-glycosylation of hydroxyaurones with acetobromo-α-D-glucose donor. The reaction in the presence of phase transfer catalyst TBAB, under mild basic condition, is found to tolerate different electron-withdrawing and donating groups yielding the desired glycosylated products in good to excellent (60-92%) yield. This will eventually provide us with an opportunity to access synthetically diverse glycosides and glucoside of aurones and their analogs for further biological screening against various pathological conditions.

Concurrently, the diversification of the aurone skeleton led us to the synthesis of a unique and unexplored triazole scaffold, as discussed in chapter III. To achieve even greater structural diversity without the need for the synthesis of new aldehydes, halogen (iodo-) containing aurones were subjected to a direct azidation reaction with sodium azide in the presence of CuI. These same azidoaurones were also expected to be a stable substrate for photoaffinity labeling to understand the interaction of these compounds with biological systems. Unfortunately, the reactions failed to afford the desired azide substituted product. Instead, it resulted in an unknown and relatively polar compound with most of the anticipated structural features of the aurone substrate. Since the NMR analysis was inconclusive, the structure of the compound was confirmed by X-ray diffraction analysis to be a salicyl-substituted triazole. This provided a convenient and straightforward thermal mediated reaction protocol to synthesize a unique triazole scaffold using aurones and sodium azide in a short time (~ 30 min). Further, the synthesis of 42 different salicyl-substituted triazoles proves the generality of this reaction. Although the reaction mechanism is not clear yet, the ease of access and the presence of multiple modification sites make this new and unexplored scaffold appealing for further interest and applications.

In another project, discussed in chapter IV, we utilized the aurone scaffold as a fluorophore to develop a fluorogenic probe for the detection of hydrogen sulfide (H_2S). H_2S is recognized as a third gaseous signaling molecule (gasotransmitter) following carbon monoxide (CO) and nitric oxide (NO). This endogenously generated H_2S, primarily from cysteine and homocysteine, has been identified to regulate a wide range of biological processes, while an abnormal level of H_2S has been implicated in various pathological conditions. As a result, the importance of understanding the biological role of H_2S has

gained considerable attention. Cellular incompatibility limits currently available methods for the selective detection of H_2S. In relevance to these limitations, fluorescence-based approaches are emerging as a powerful tool for both qualitative and quantitative detection of H_2S as they are easy to use and afford real-time analysis without causing cell damage.

In this context, despite their promising fluorescence characteristics, minor flavonoid aurones have not been explored well as a potential fluorophore scaffold, and particularly for H_2S detection, no fluorescent probe utilizing the aurone scaffold has been reported so far. Inspired by this gap, we envisioned and successfully used the aurone scaffold as a tunable fluorophore to develop an azide reduction-based fluorescent probe for the detection of H_2S in living and aqueous systems. In this research, a rationally designed turn-on fluorescent probe ***(****Z)-2-(4-azidobenzylidene)-5-fluorobenzofuran-3(2H)-one* is demonstrated to react effectively with NaHS in the presence of cationic surfactant cetyltrimethylammonium bromide (CTAB), resulting in the formation of the corresponding amine accompanied by both a color change and ~42-fold enhancement in the raw fluorescence intensities with a detection limit as low as 1 μM. Furthermore, the probe displayed excellent selectivity for HS^- over cysteine, glutathione, and 2-mercaptoethanol revealing its applicability for quantitative detection of H_2S in both living systems and the environment. Given the ease and flexibility in synthesizing the aurone framework, many additional sensing applications can be envisioned, particularly applying the lessons learned in this project.

In conclusion, these projects have expanded the potential of the aurone system for both application to the treatment of pathological conditions and its potential for probing or

sensing various biological processes. Further exploration and expansion of these areas can be readily imagined and will serve as the basis of considerable future work.

References

1. Křen, V.; Řezanka, T. *FEMS Microbiol. Rev.,* 2008, ***32***, 858-889.

APPENDICES

APPENDIX – A

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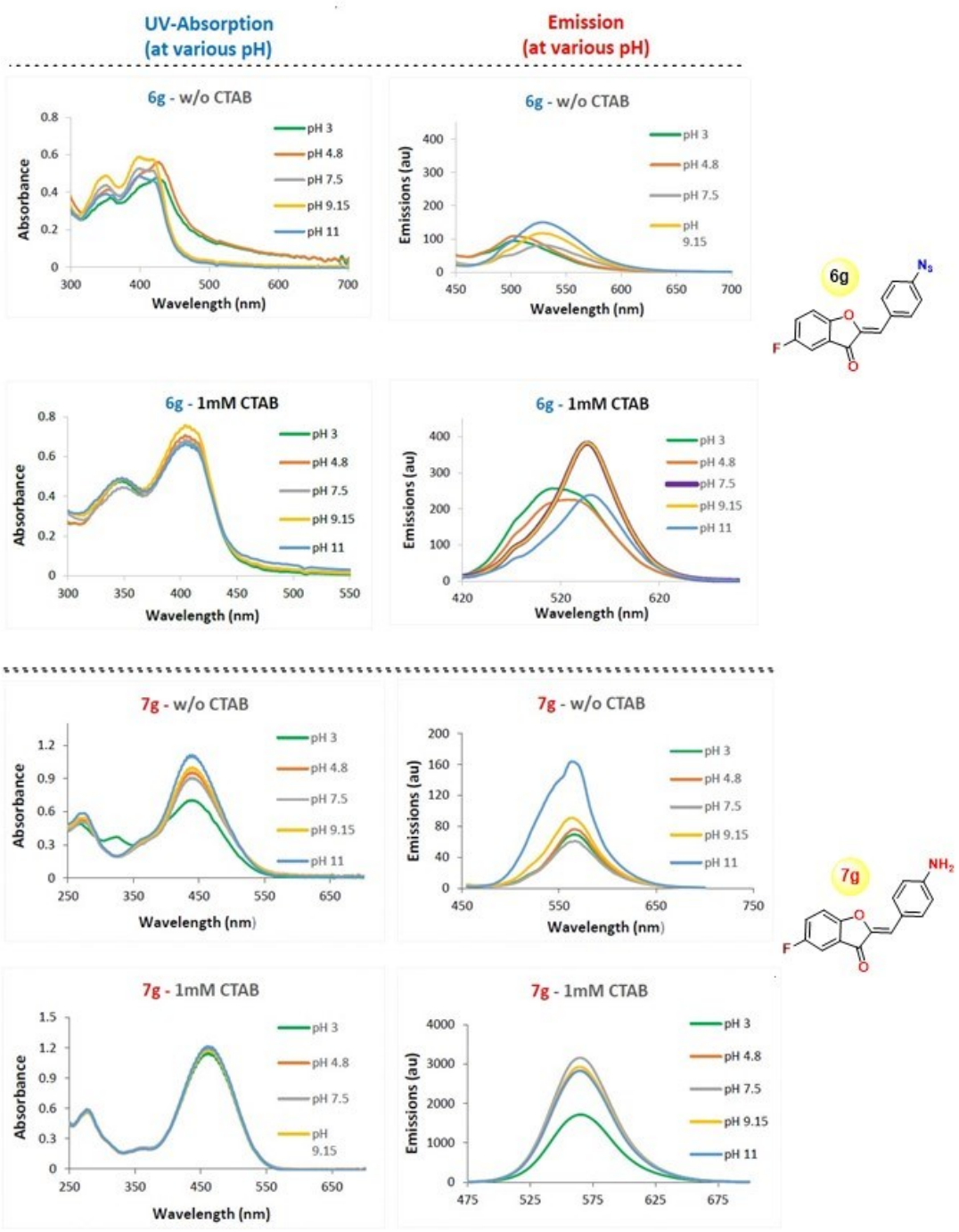
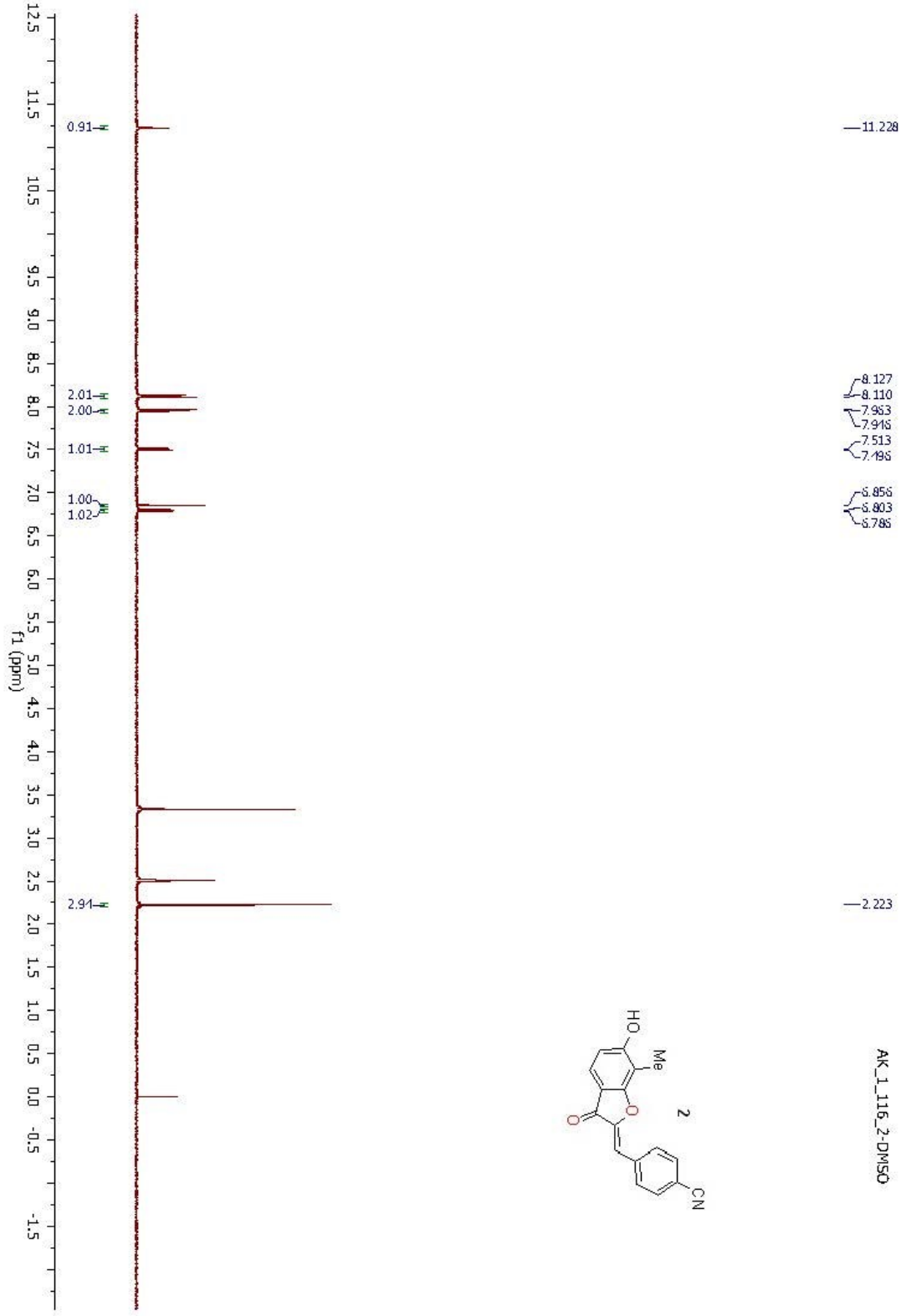
APPENDIX - B

Effect of pH on 6g/7g Absorption and Emission Properties - Chapter IV



APPENDIX - C

NMR Spectra - Chapter I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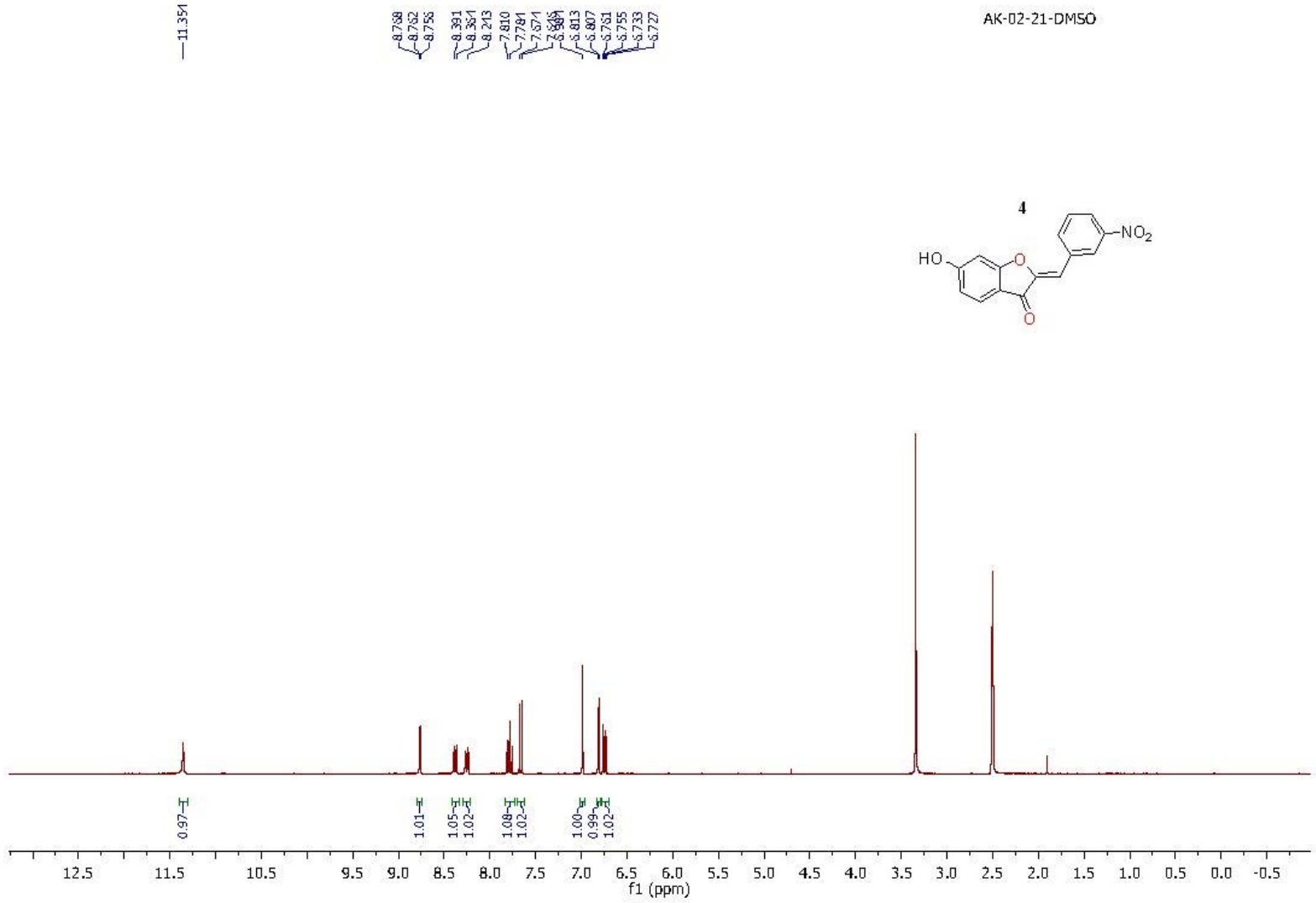
8.127
8.110
7.963
7.946
7.513
7.496
6.856
6.803
6.786
2.223
0.91
2.01
2.00
1.01
1.00
1.02
2.94
f1 (ppm)
HO
Me
O
O
CN
2
AK_1_116_2-DMSO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5.761
5.755
5.733
5.727
AK-02-21-DMSO
4
HO
O
O
NO2
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1.01
1.05
1.02
1.08
1.02
1.00
0.99
1.02
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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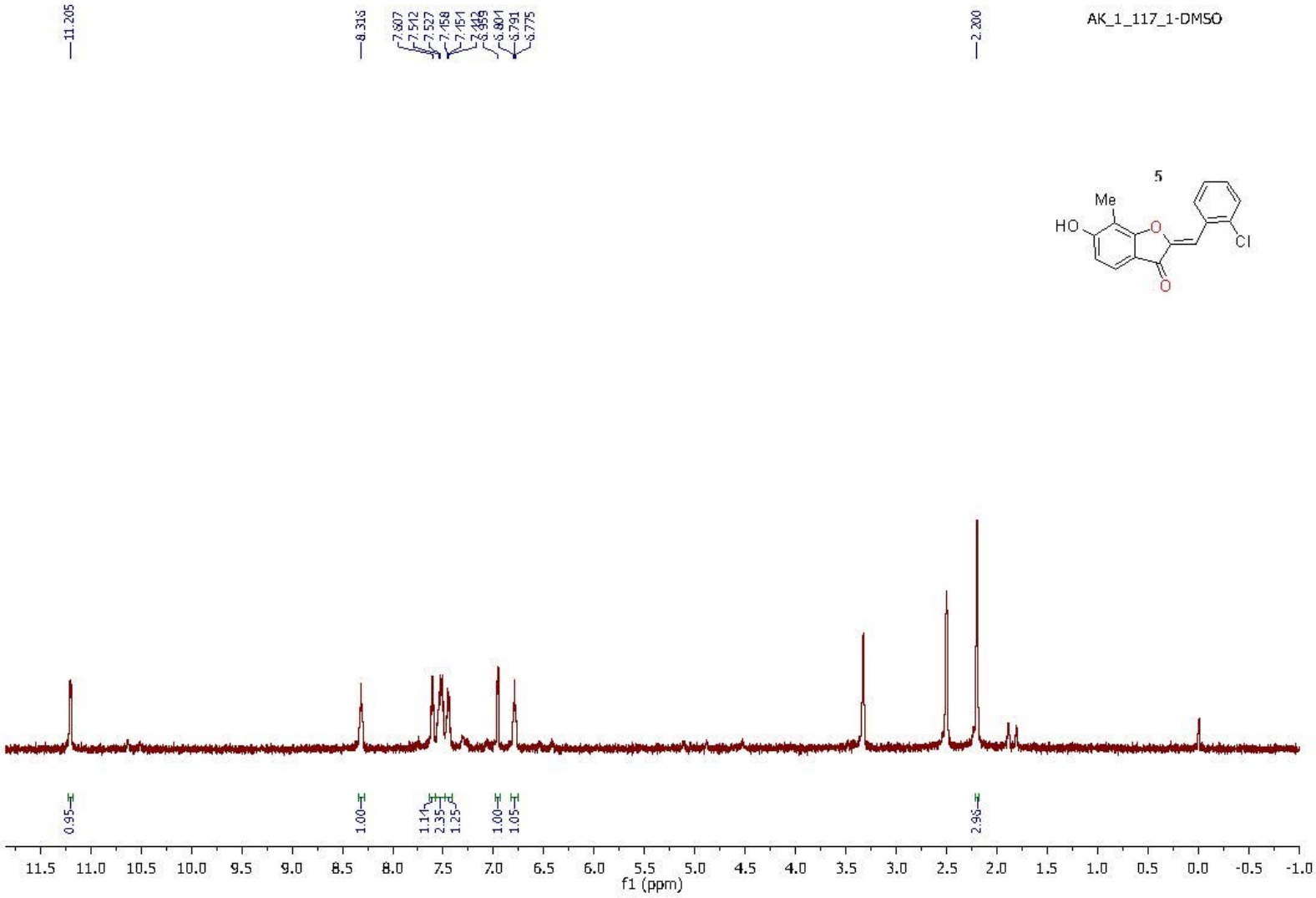
1.0
0.5
0.0
-0.5
f1 (ppm)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5.775
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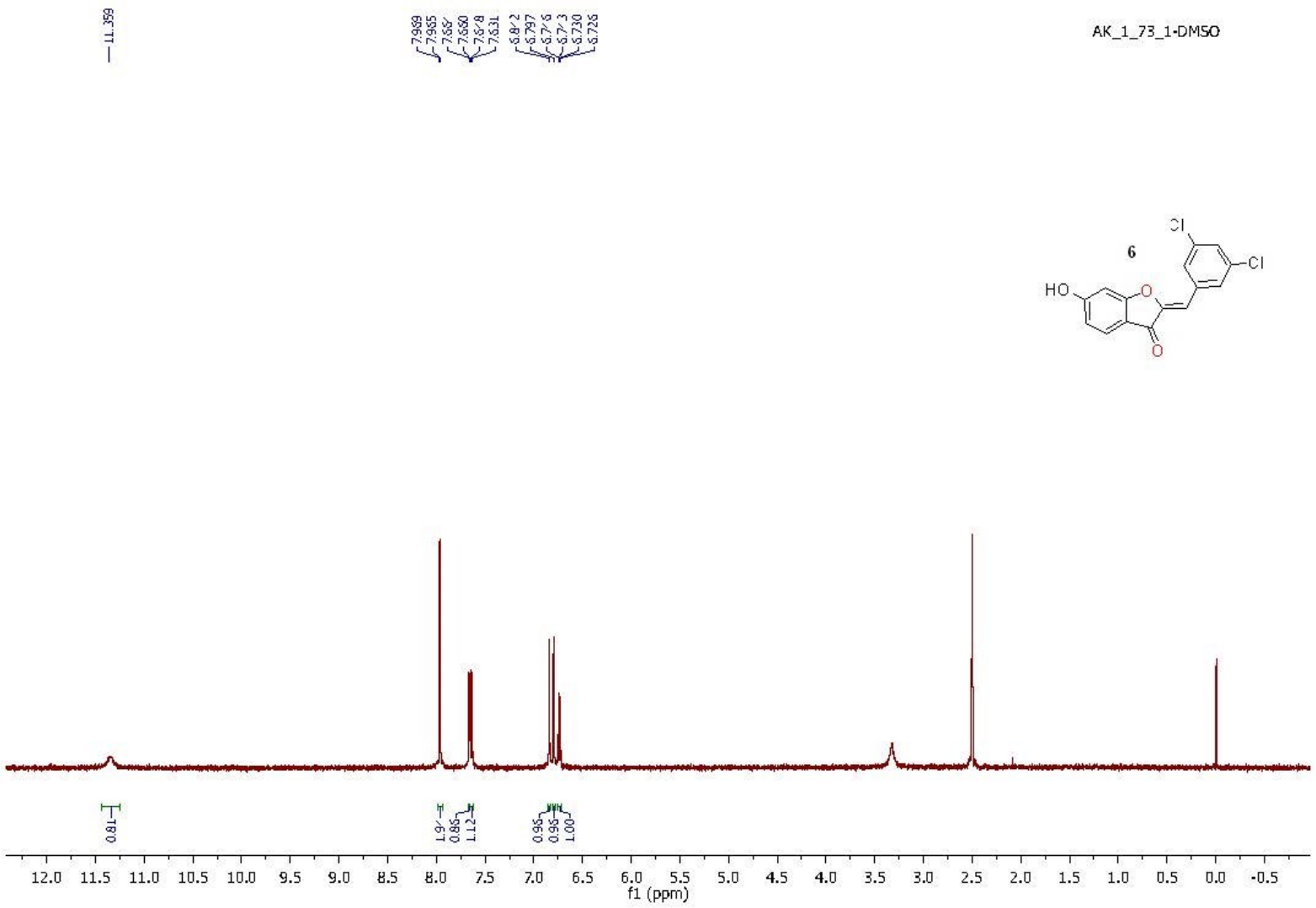
5
Me
HO
O
Cl
O
0.95
1.00
1.14
2.35
1.25
1.00
1.05
2.96
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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7.985
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6.776
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6.730
6.725
AK_1_73_1-DMSO
6
Cl
Cl
HO
O
O
0.810
1.912
0.985
1.112
0.965
0.935
1.000
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

AK-02-20-DMSO
11.133
7.888
7.859
7.697
7.688
6.707
6.606
6.599
6.491
6.489
6.485
6.482
HO
Me
O
O
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8
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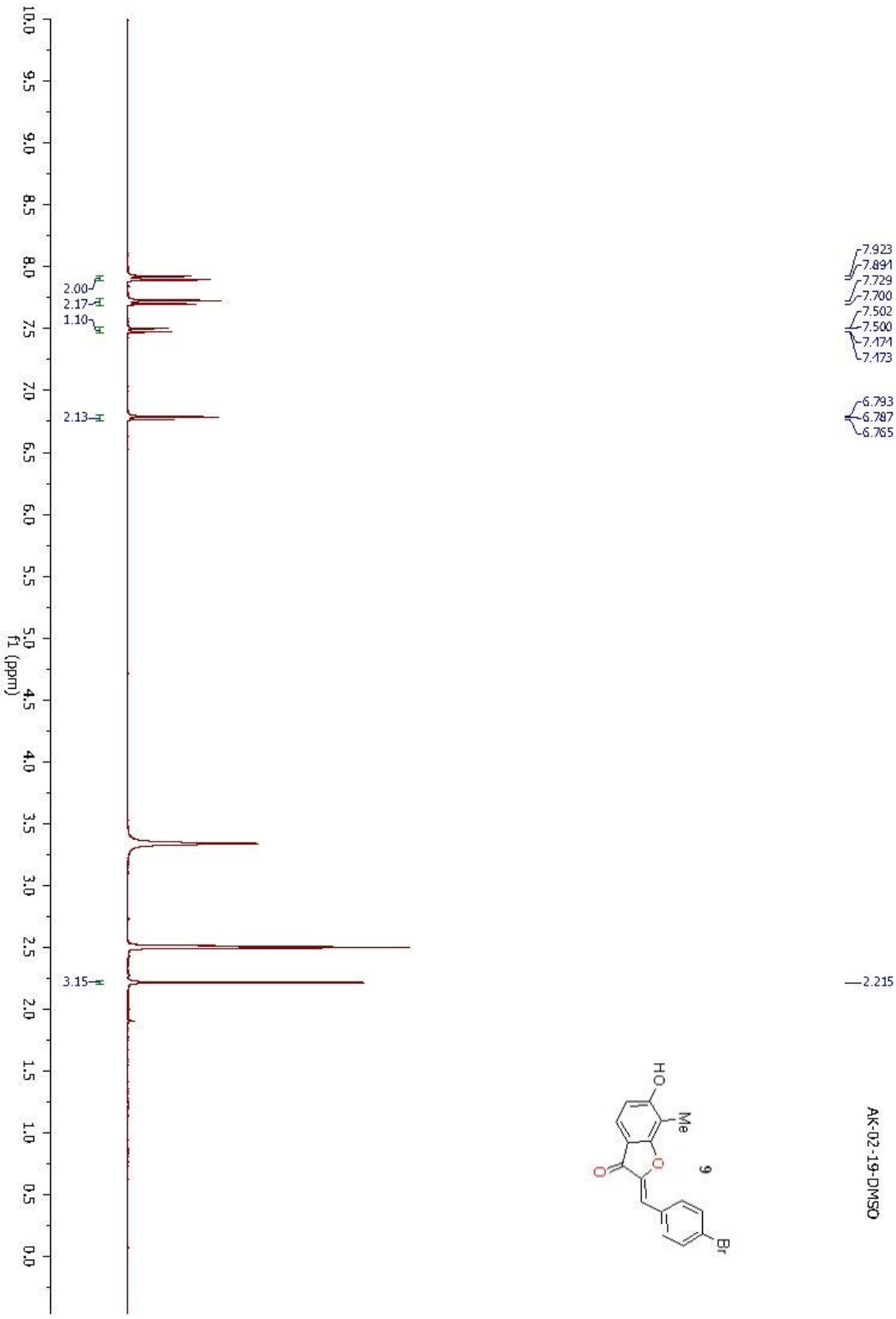
Me-signal
overlapped
with solvent
f1 (ppm)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6.5
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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2.00
2.17
1.10
2.13
3.15
7.923
7.891
7.729
7.700
7.502
7.500
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6.765
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O
O
Br
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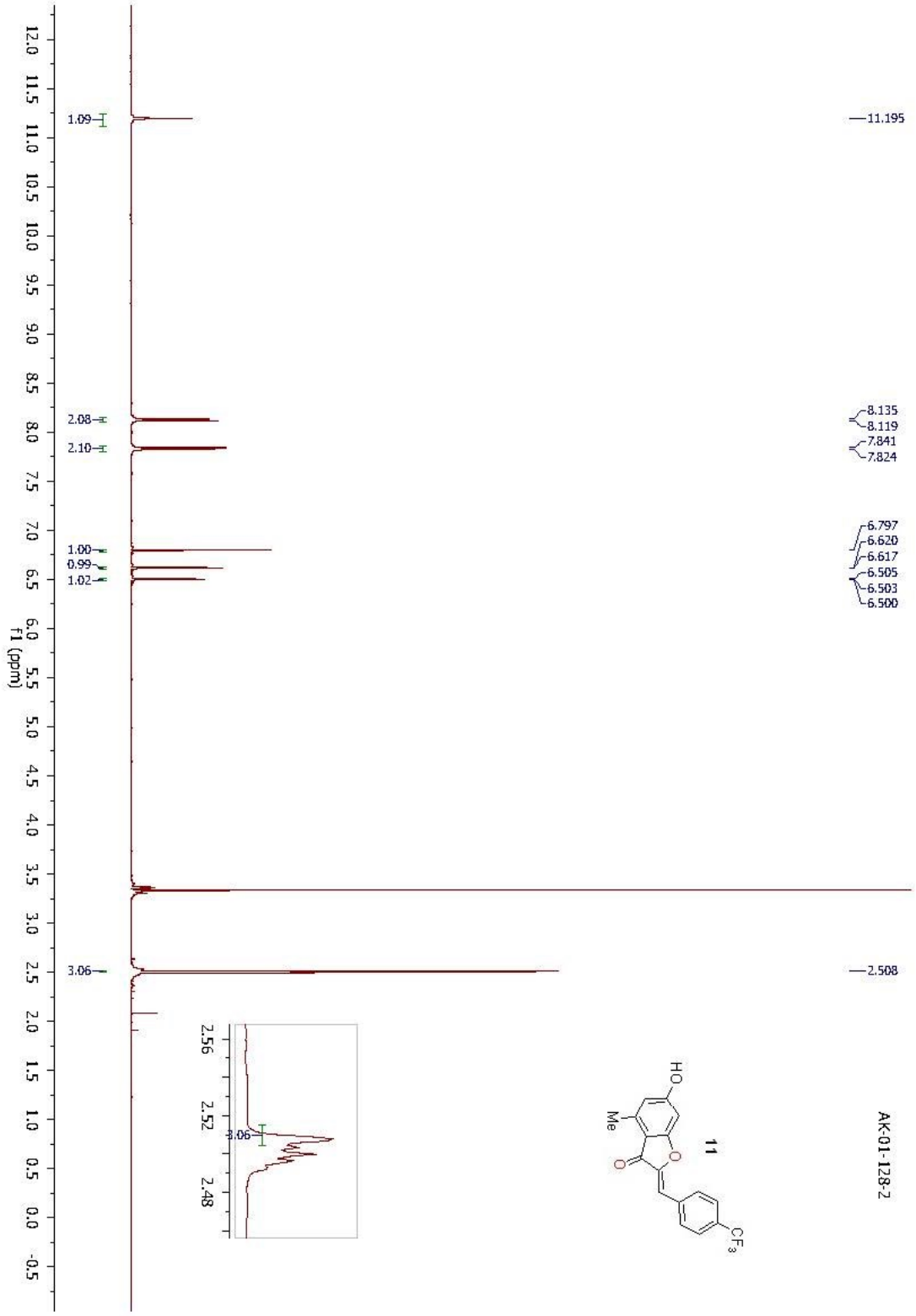
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1.09
2.08
2.10
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1.02
3.06
f1 (ppm)
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Me
O
O
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11
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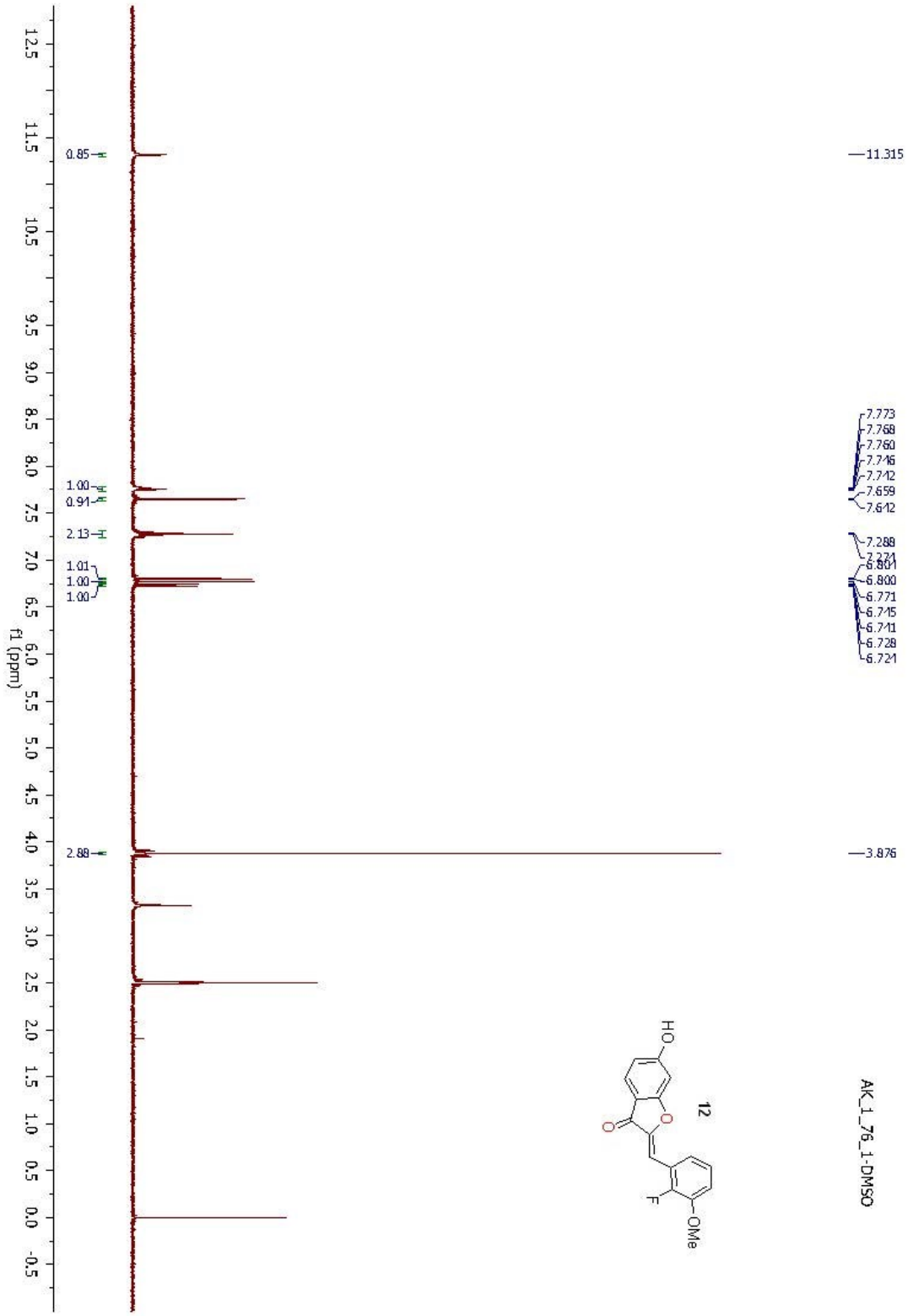
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7.742
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6.745
6.741
6.728
6.721
3.876
0.85
1.00
0.91
2.13
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O
O
F
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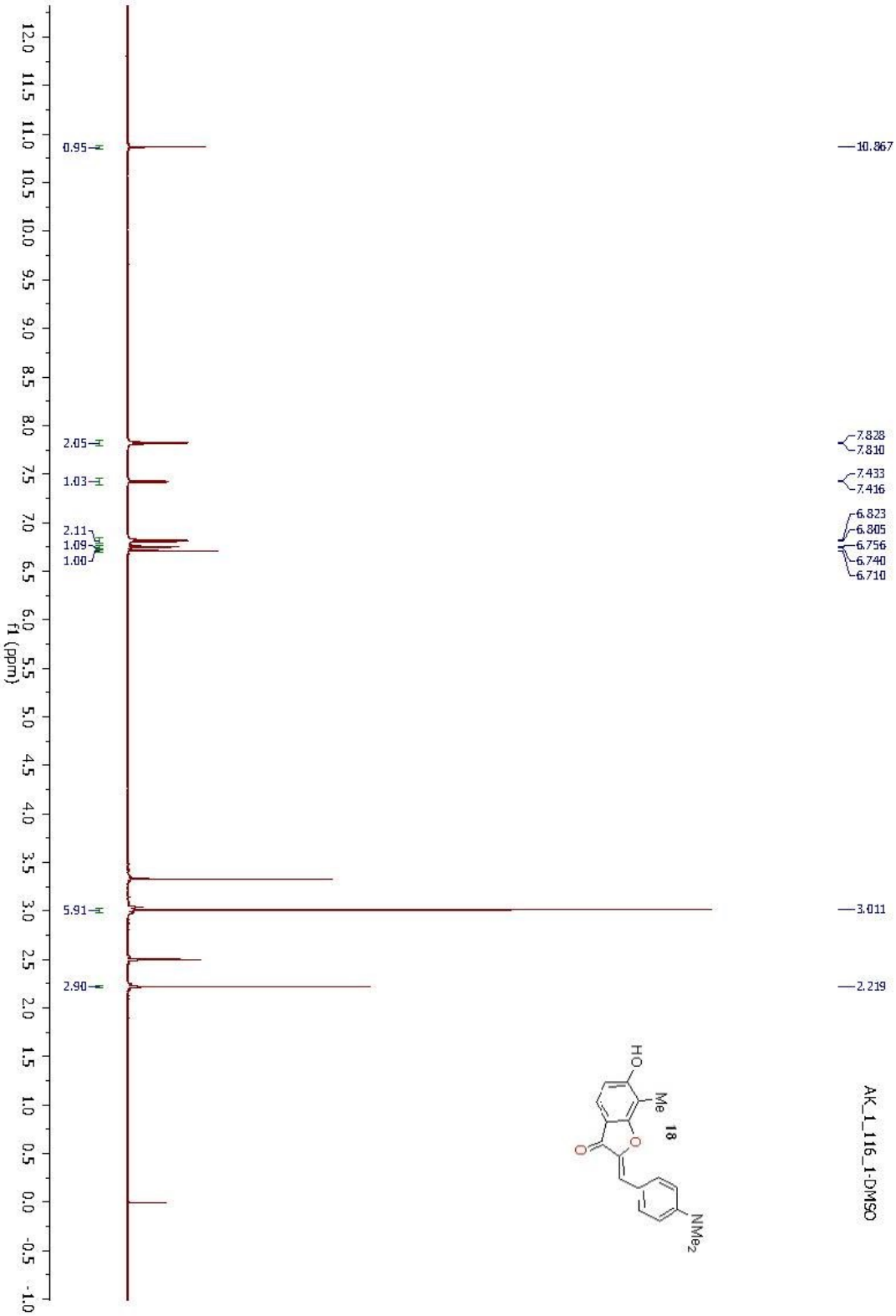
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f1 (ppm)
0.95
2.05
1.03
2.11
1.09
1.00
5.91
2.90
10.867
7.828
7.810
7.433
7.416
6.823
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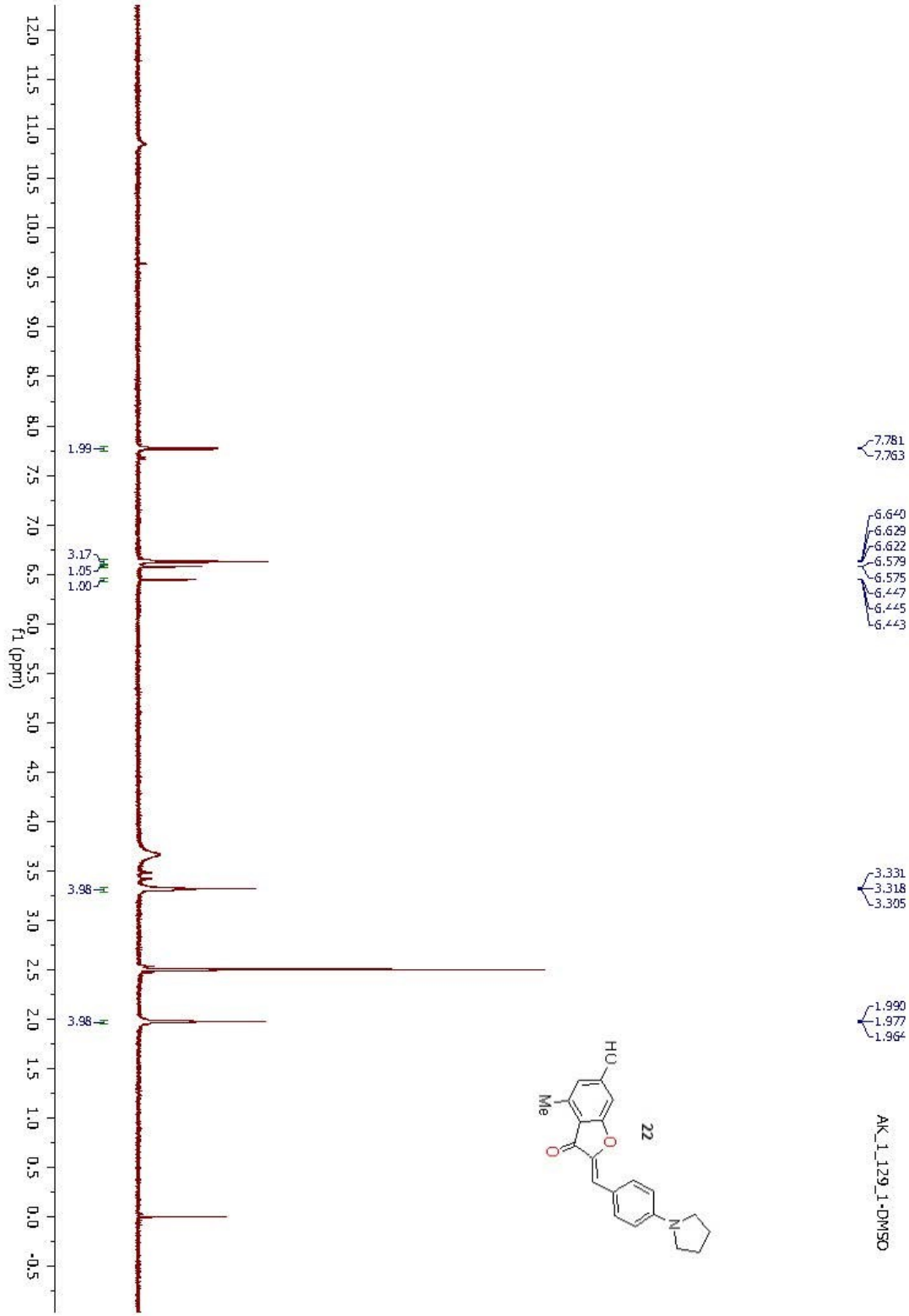
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f1 (ppm)
1.99
3.17
1.05
1.00
3.98
3.98
7.781
7.763
6.640
6.629
6.622
6.579
6.575
6.447
6.445
6.443
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Me
O
O
N
22
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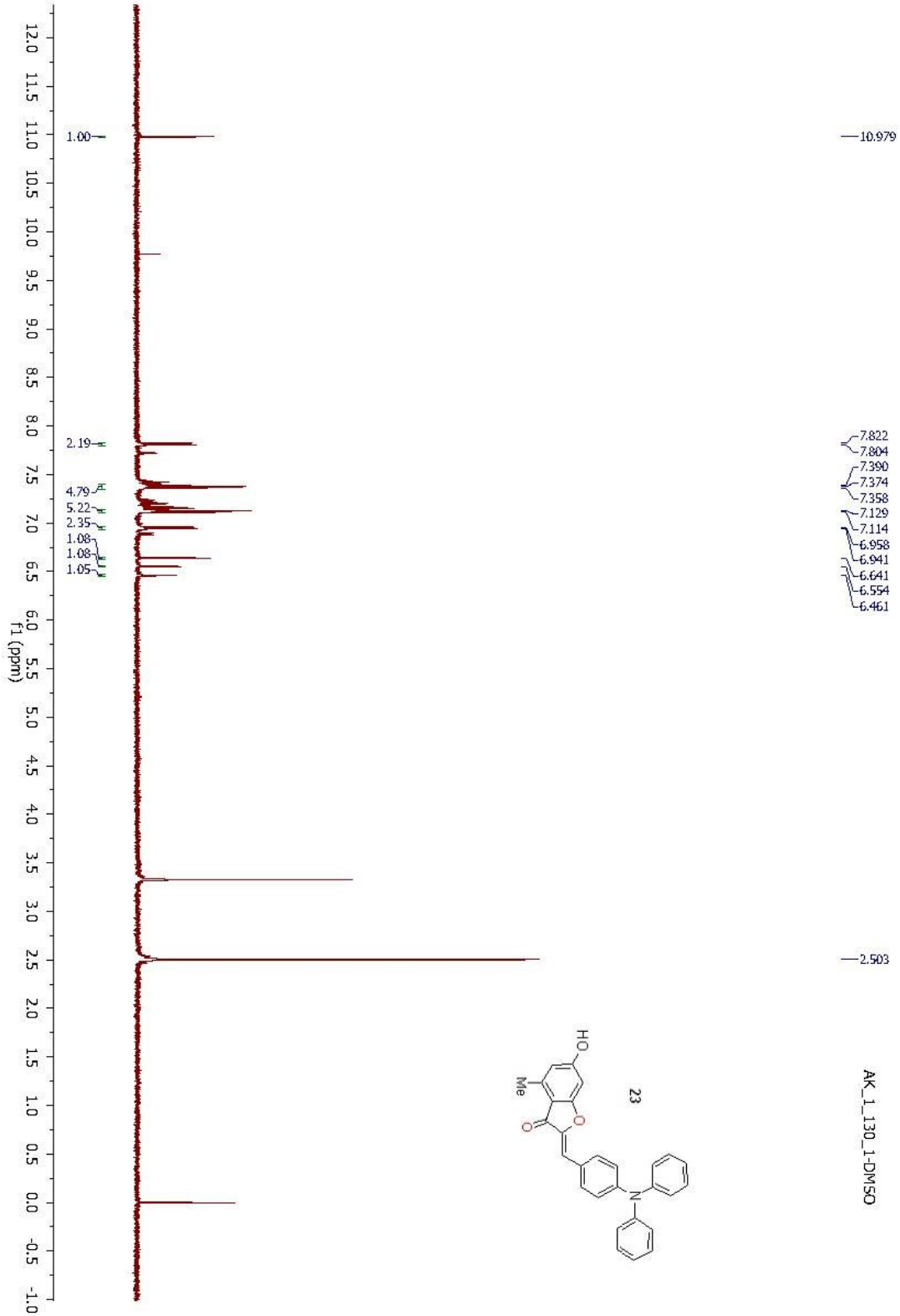
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7.114
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6.554
6.461
2.503
1.00
2.19
4.79
5.22
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1.08
1.05
f1 (ppm)
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Me
O
O
N
23
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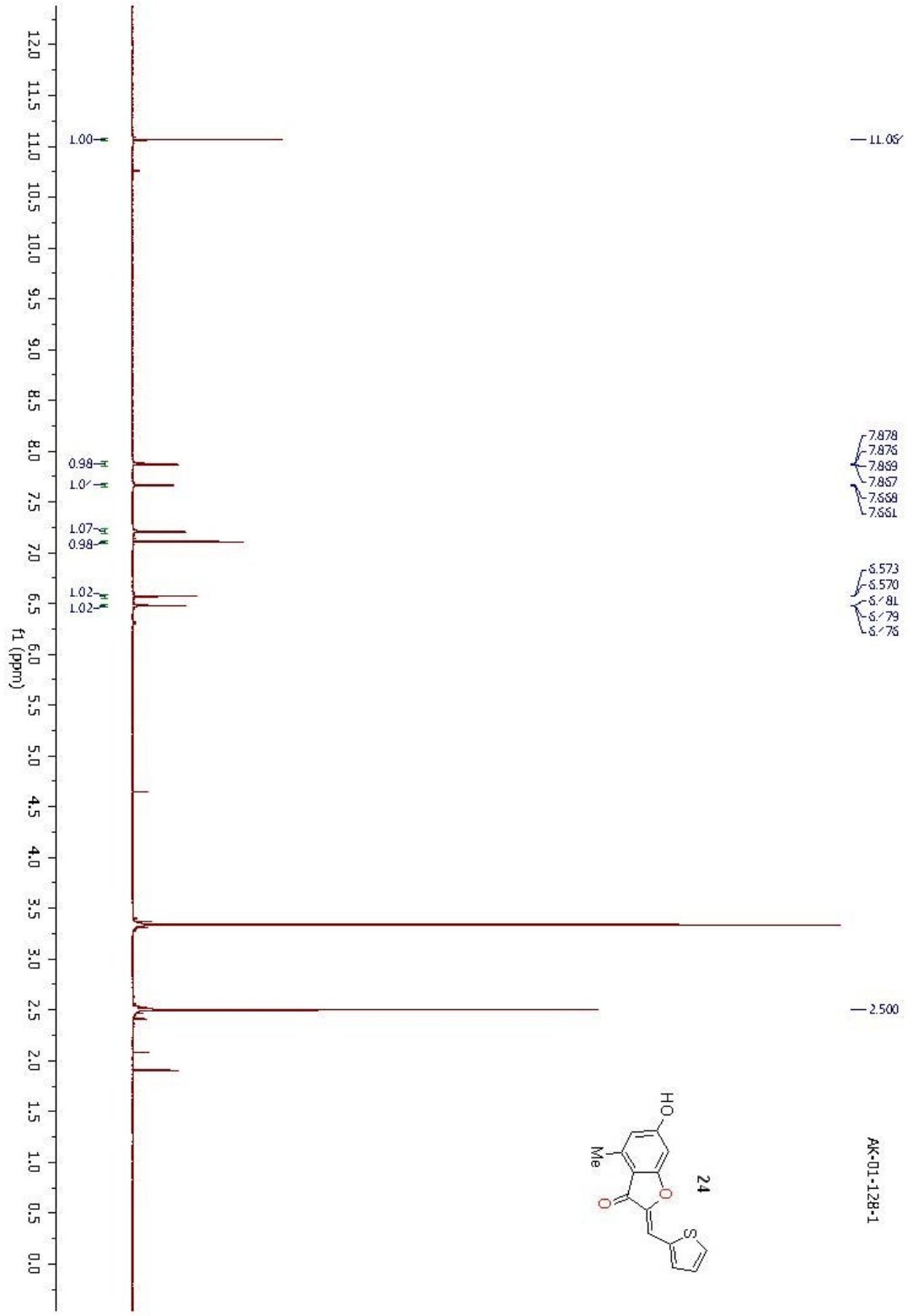
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7.857
7.658
7.651
6.573
6.570
6.481
6.479
6.476
2.500
HO
Me
O
O
S
24
AK-01-128-1

AK-01-126-2
25
HO
Me
O
O
S
Me-peak
(overlapped)
f1 (ppm)
1.00
0.97
1.07
1.09
1.00
1.03
1.05
3.62
11.051
8.179
8.177
8.173
8.171
7.688
7.682
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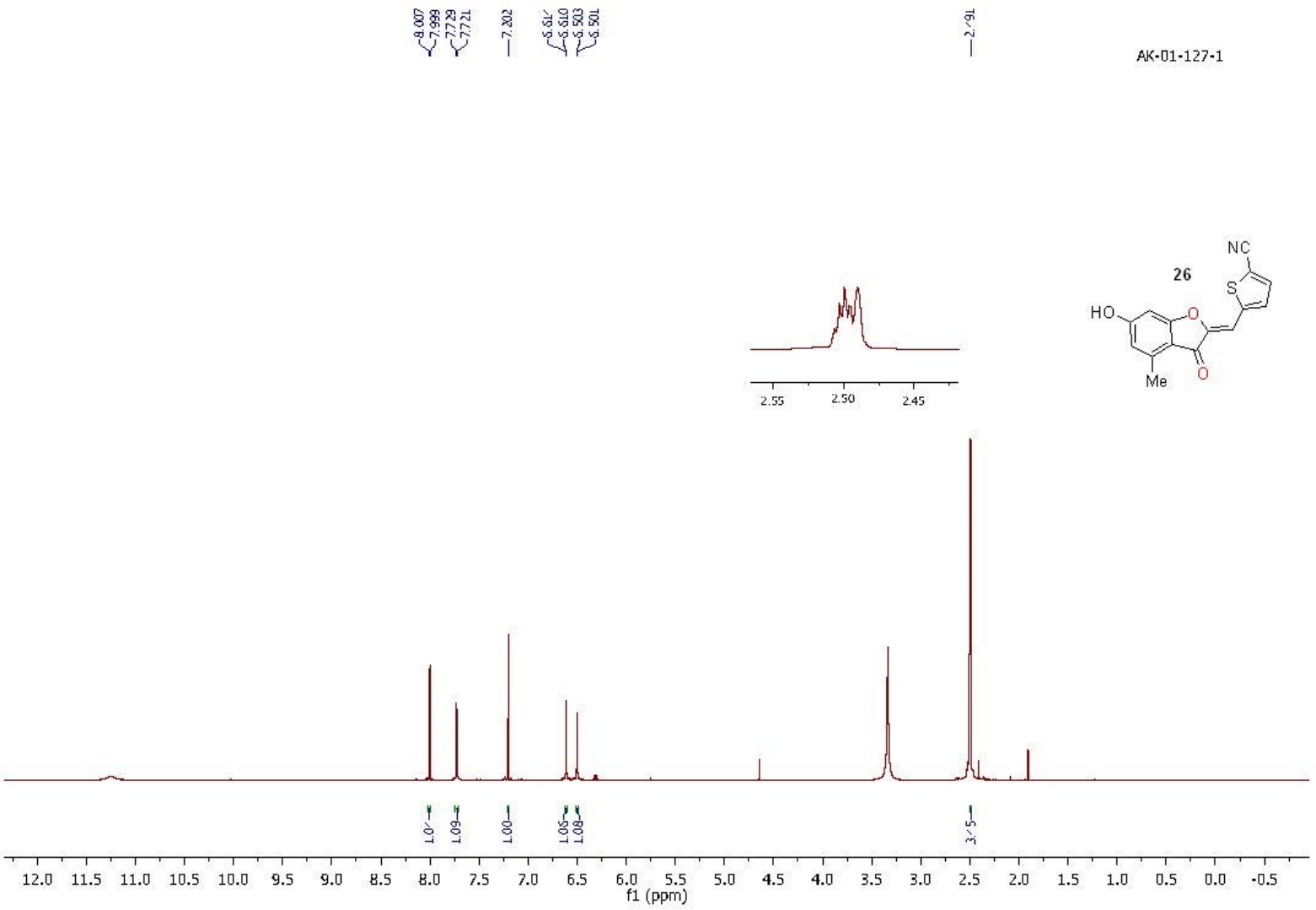
6.771
6.768
2.500
1.003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7.721
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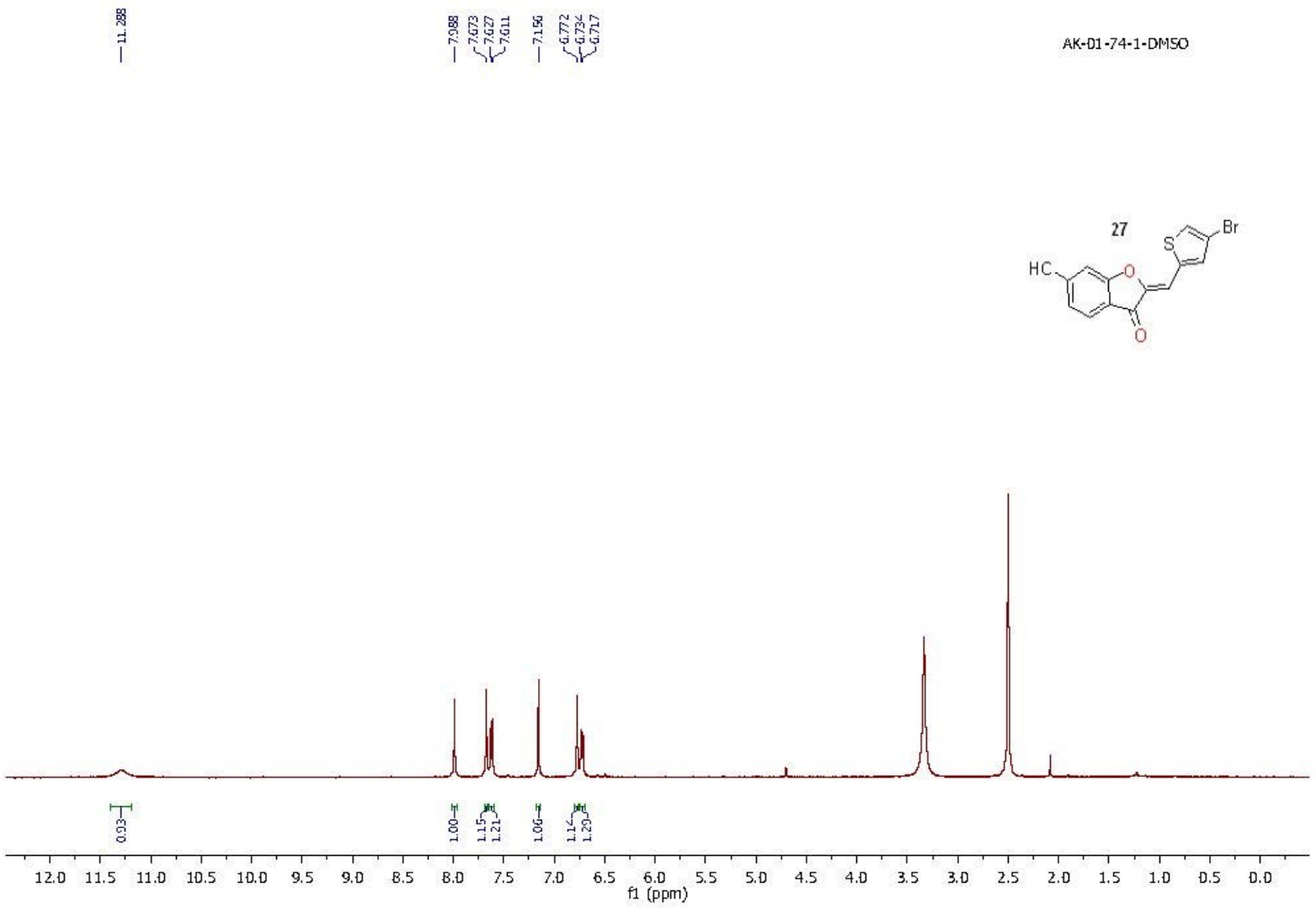
6.517
6.510
6.503
6.501
2.491
AK-01-127-1
26
NC
S
HO
O
O
Me
2.55
2.50
2.45
1.07
1.09
1.00
1.05
1.08
3.45
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


11.288
7.988
7.673
7.627
7.611
7.156
6.772
6.734
6.717
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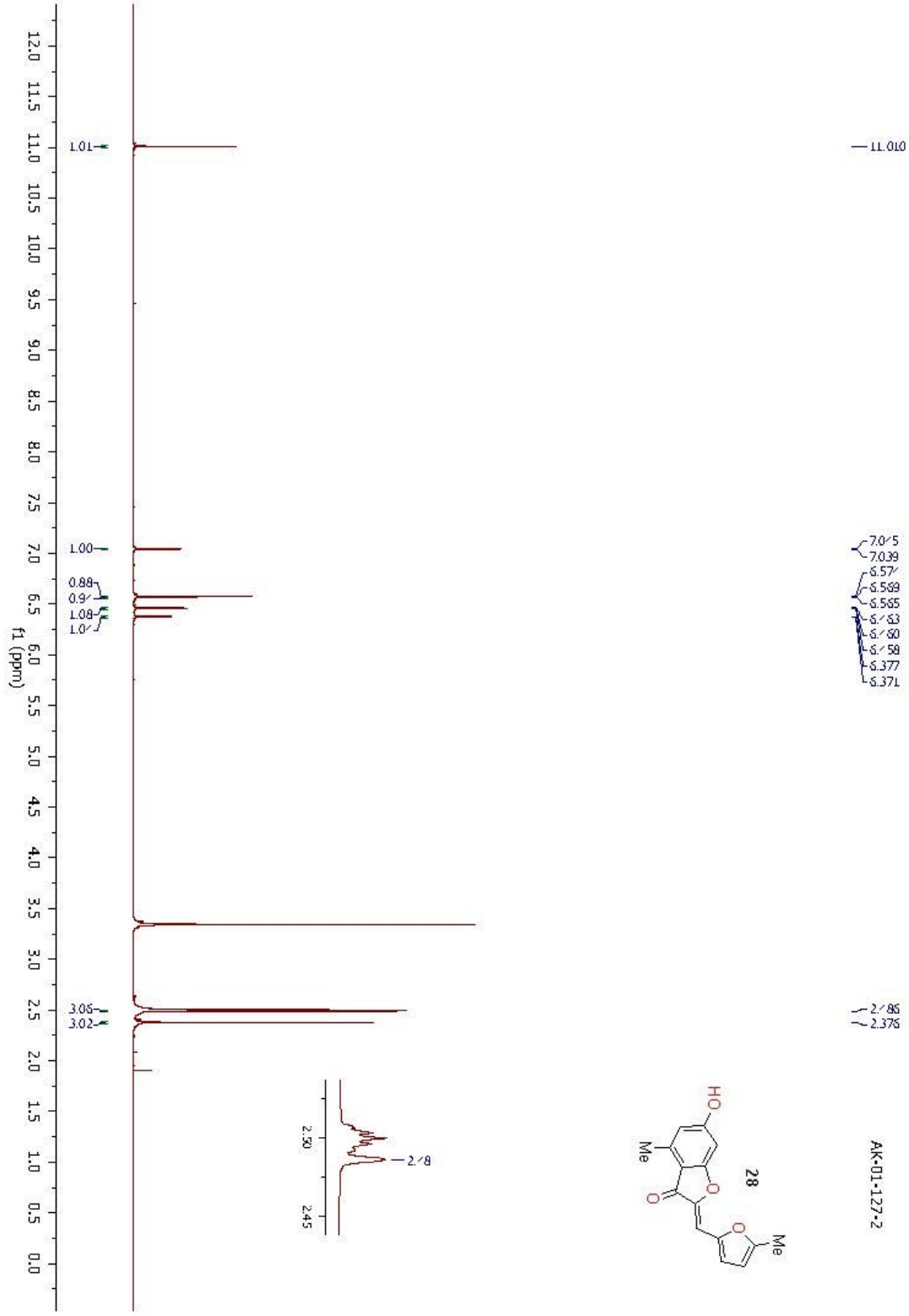
27
Br
S
HC
O
O
0.93
1.00
1.15
1.21
1.06
1.14
1.29
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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6.560
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6.371
2.886
2.378
2.878
1.01
1.00
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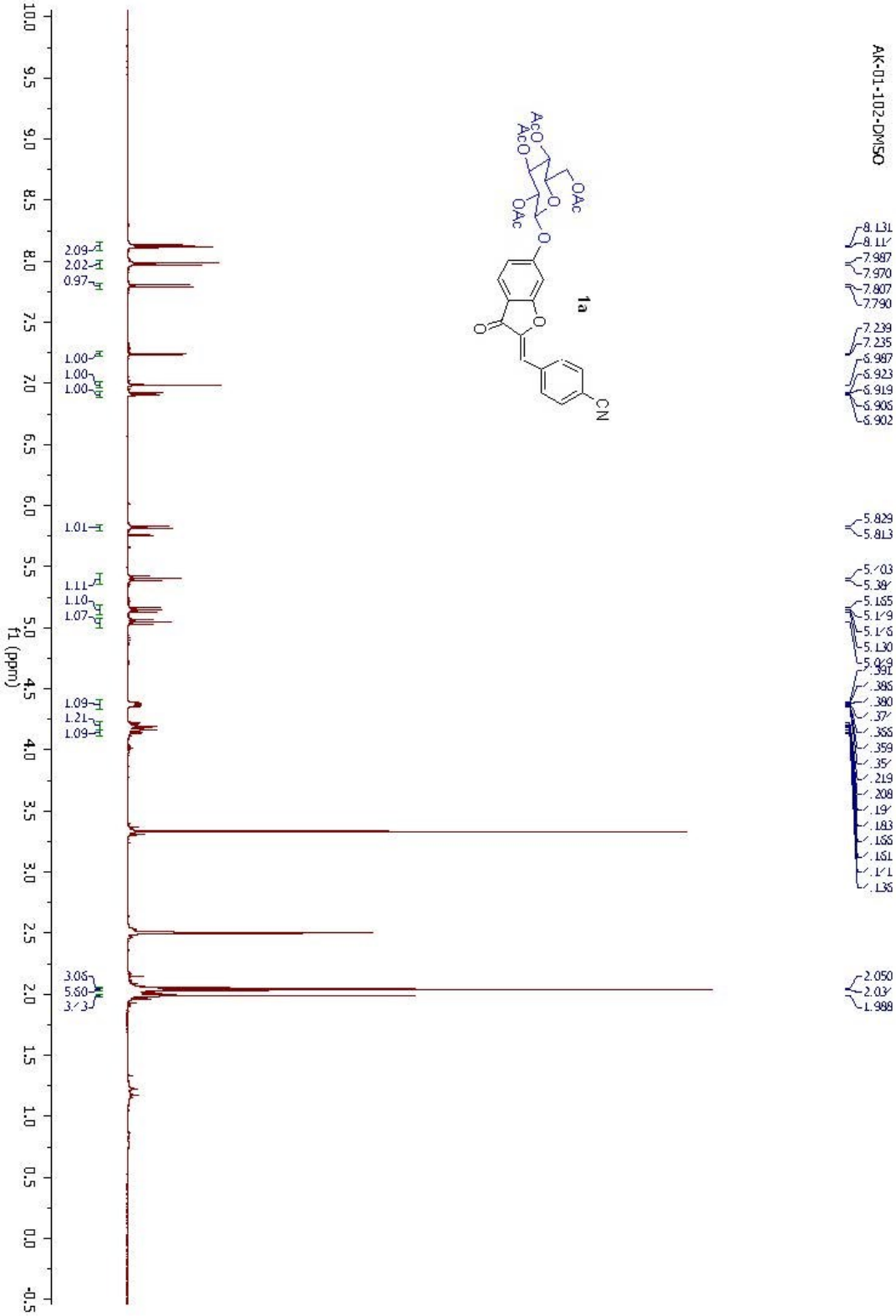
1.08
1.07
3.06
3.02
f1 (ppm)

Peracetyl Glycosylated Aurone Derivatives

(1a-33a)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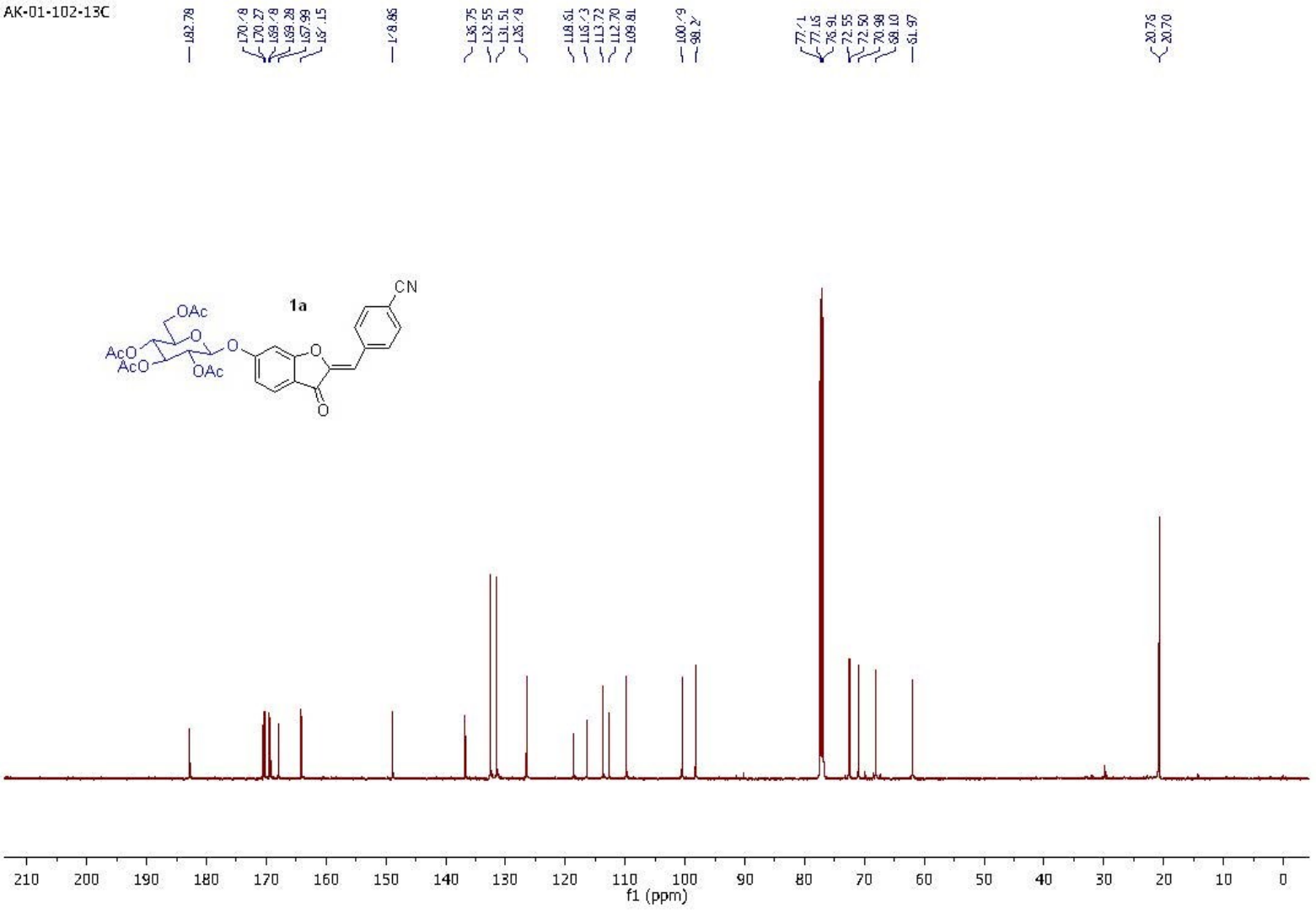
1a
f1 (ppm)

AK-01-102-13C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167.99
167.15
148.86
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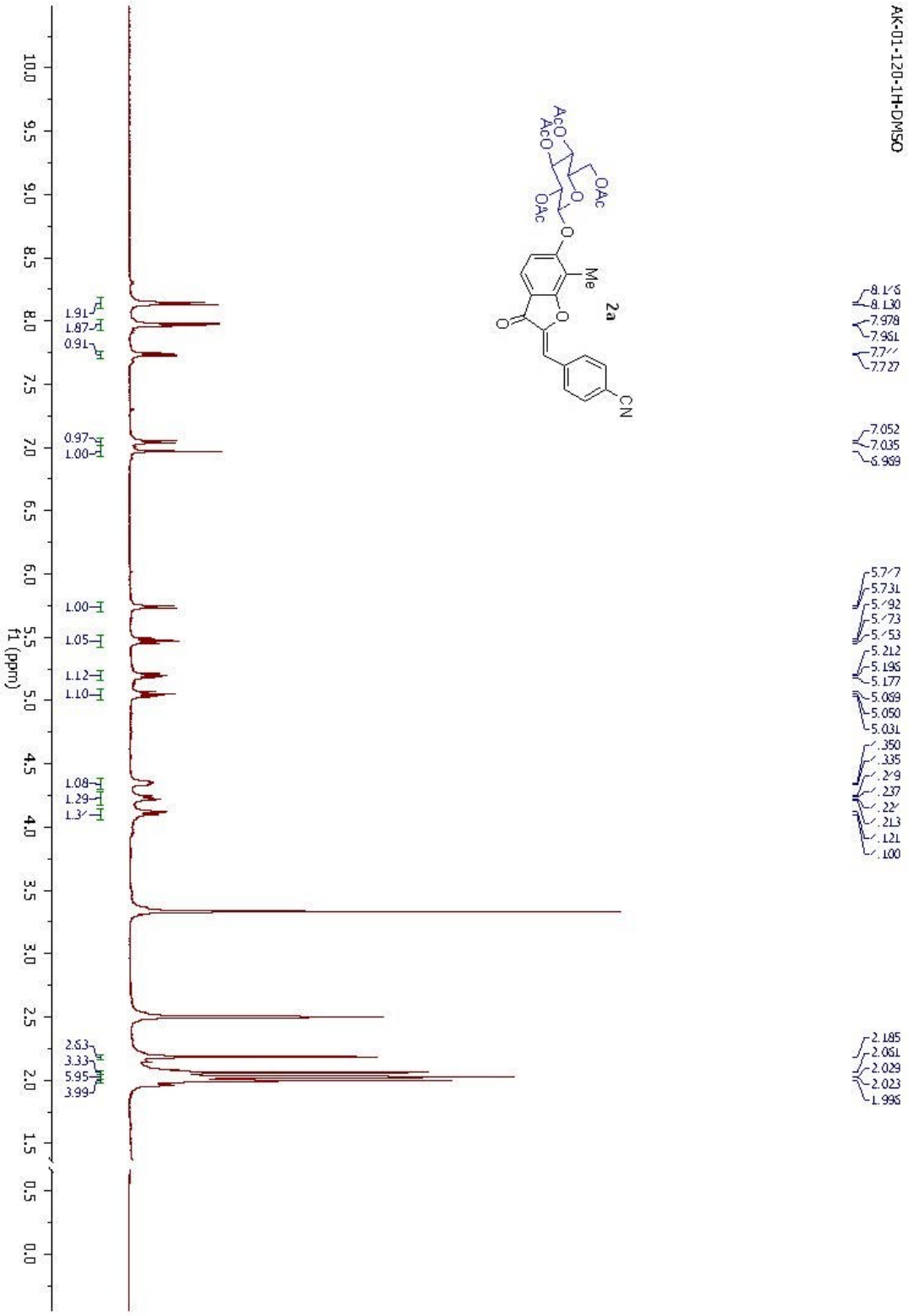
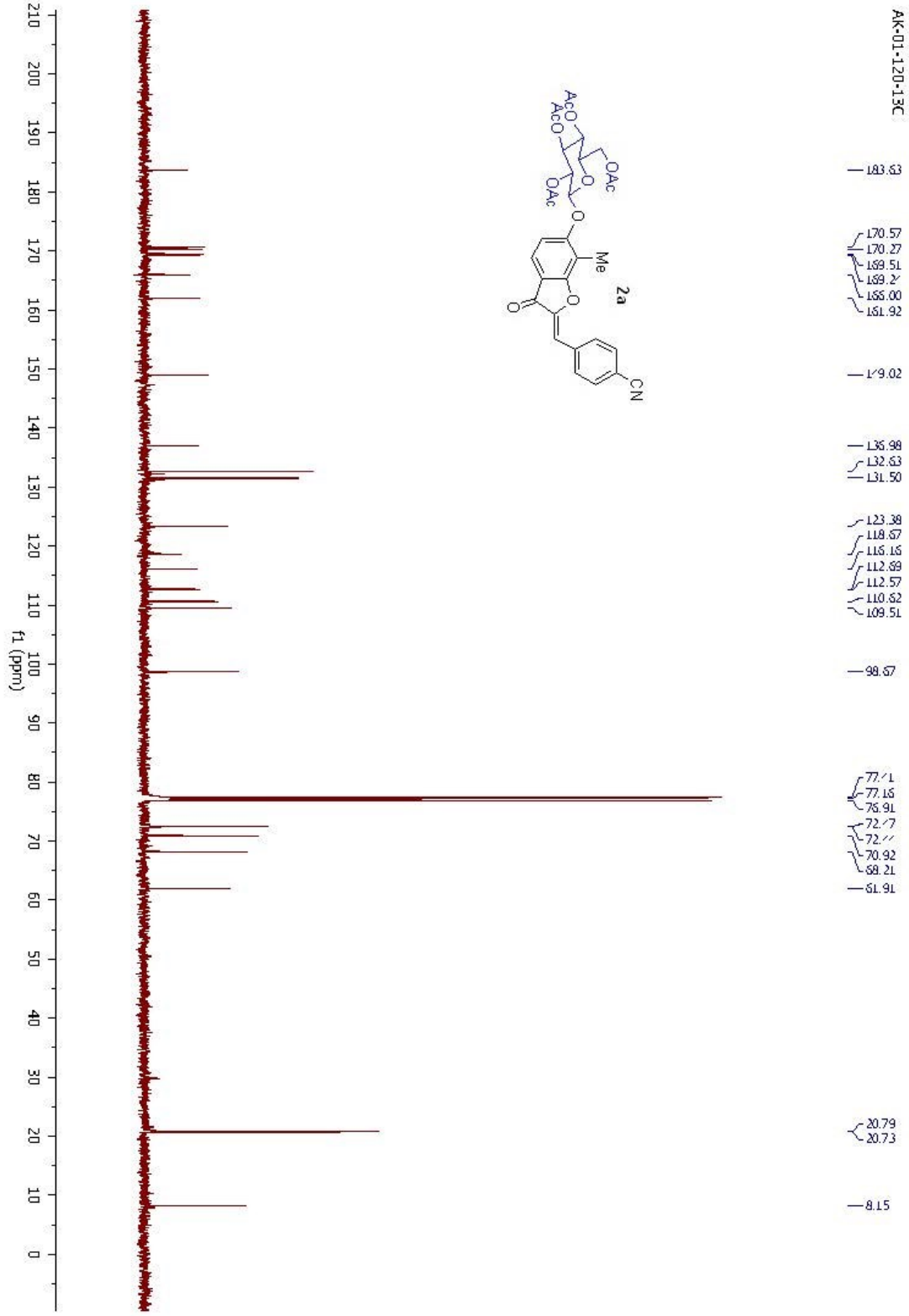
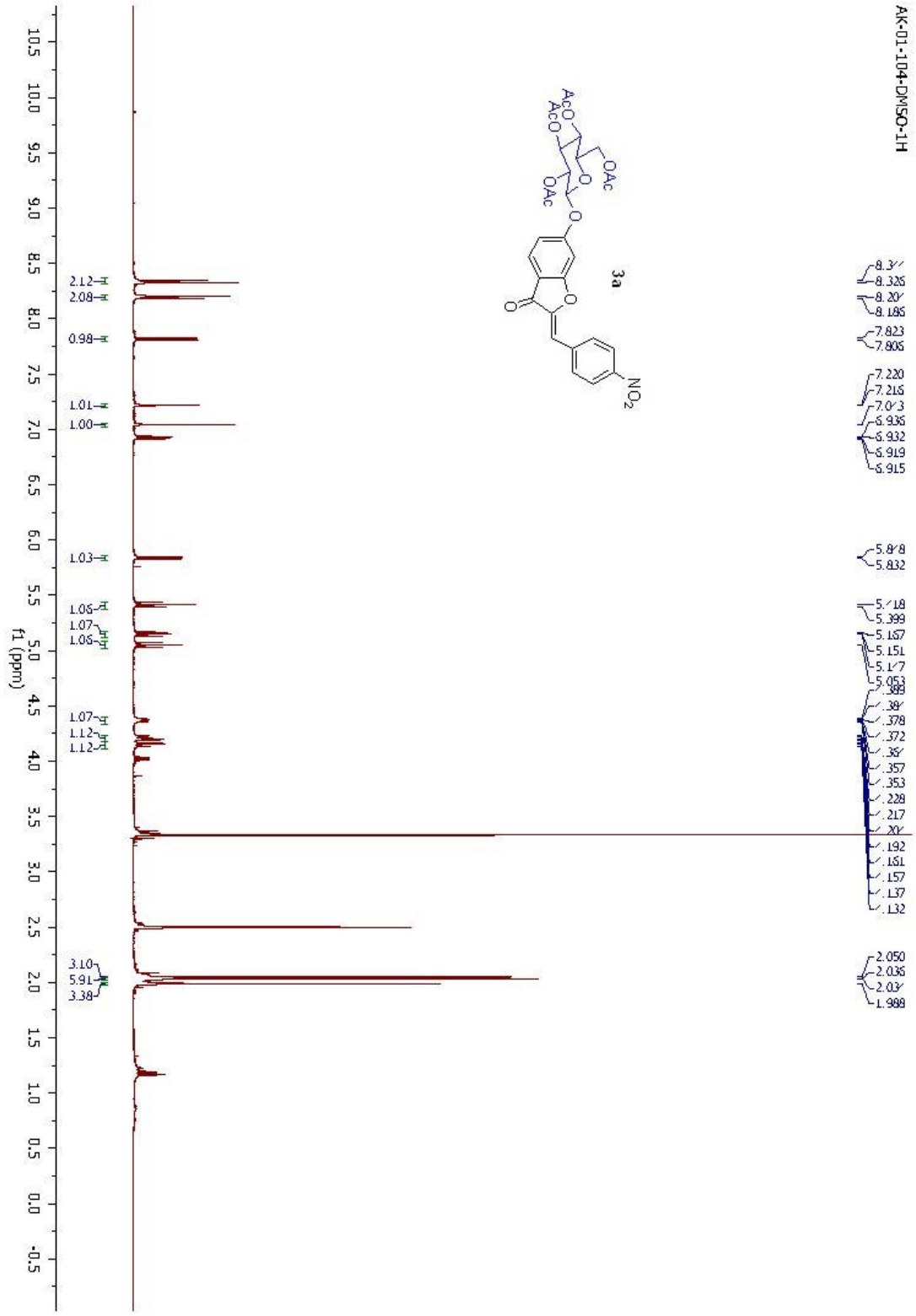
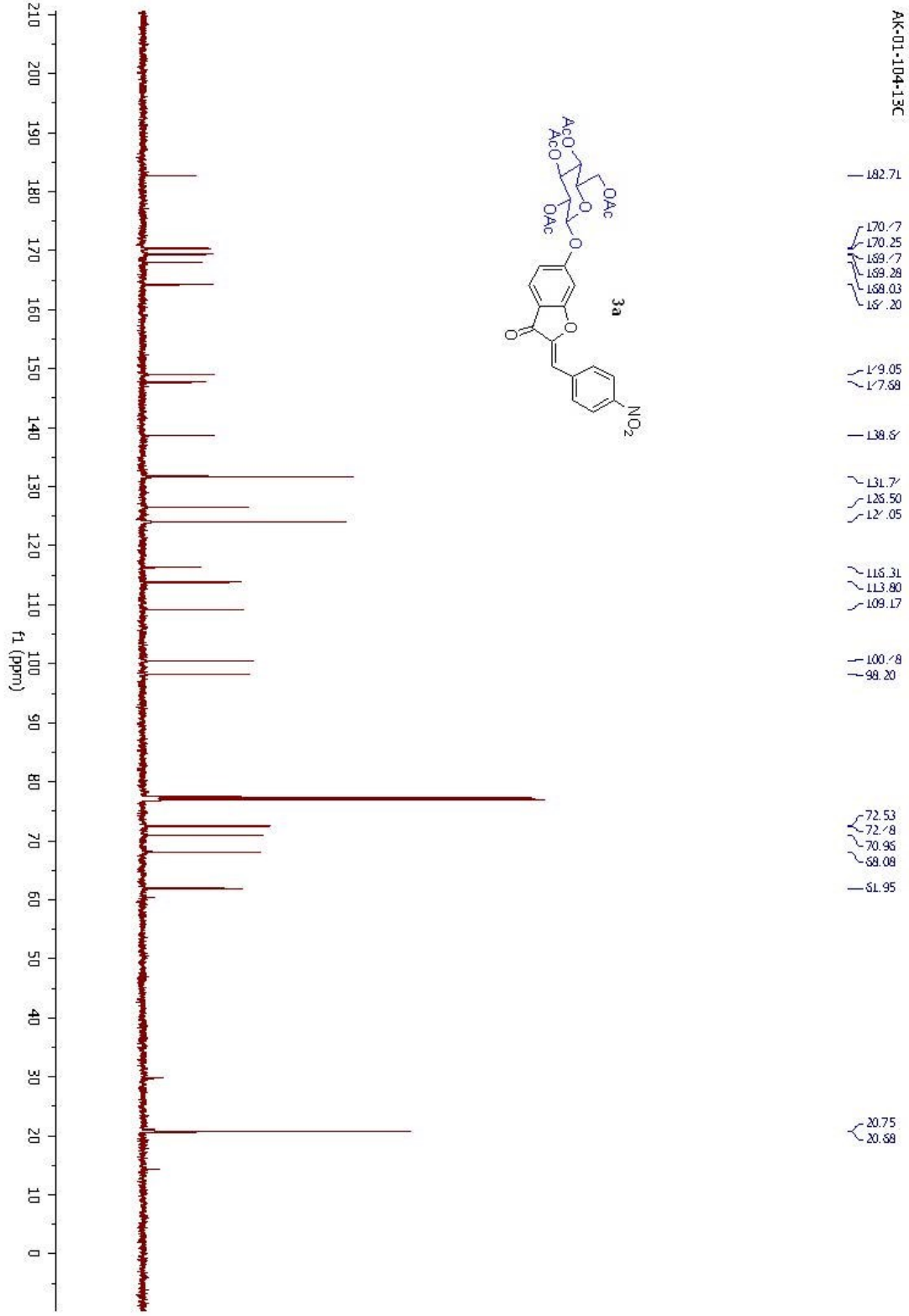
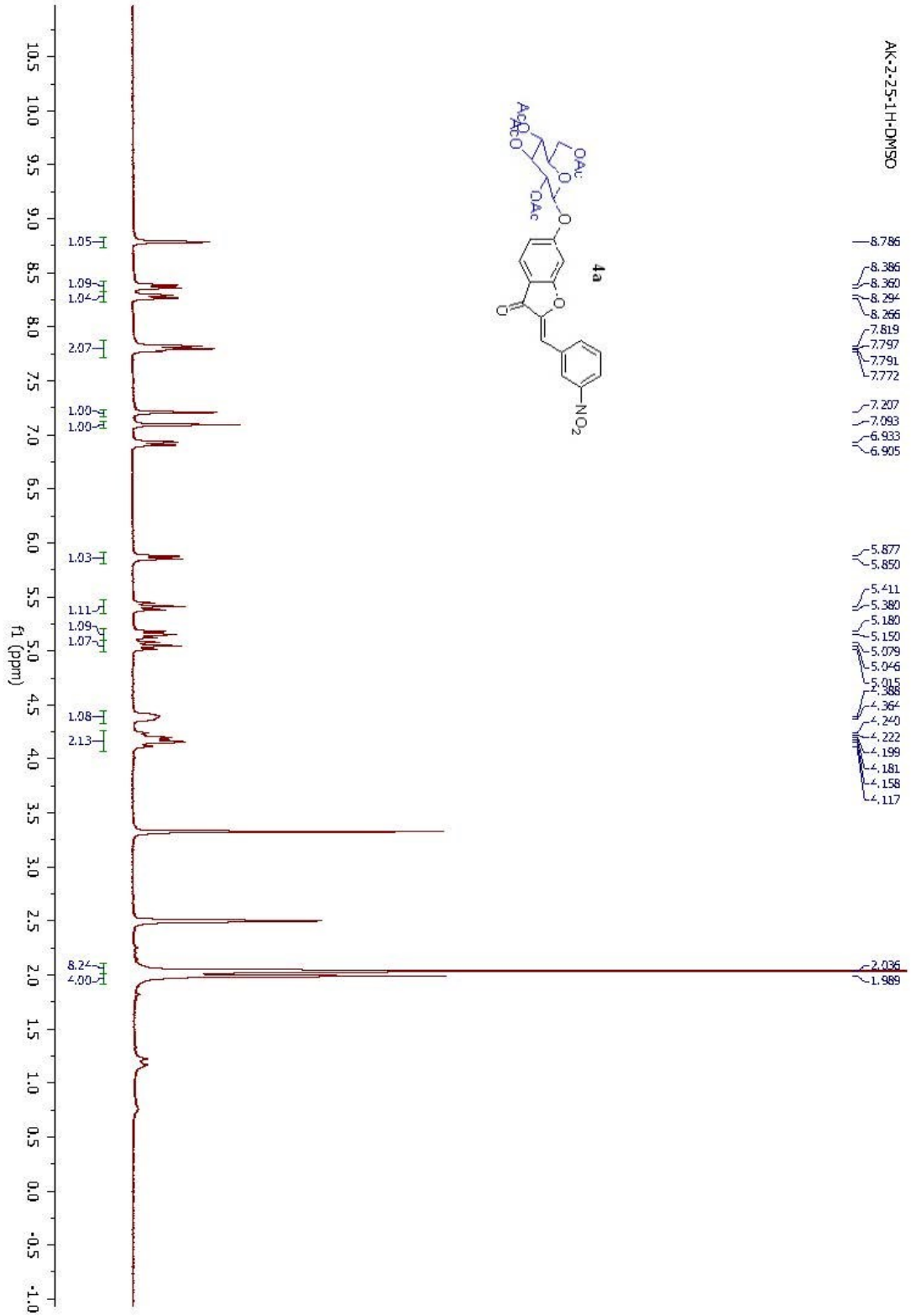
132.55
131.51
125.78
118.61
116.23
113.72
112.70
109.81
100.79
98.27
77.21
77.16
76.91
72.55
72.50
70.98
68.10
61.97
20.76
20.70
1a
CN
OAc
AcO
AcO
OAc
O
O
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

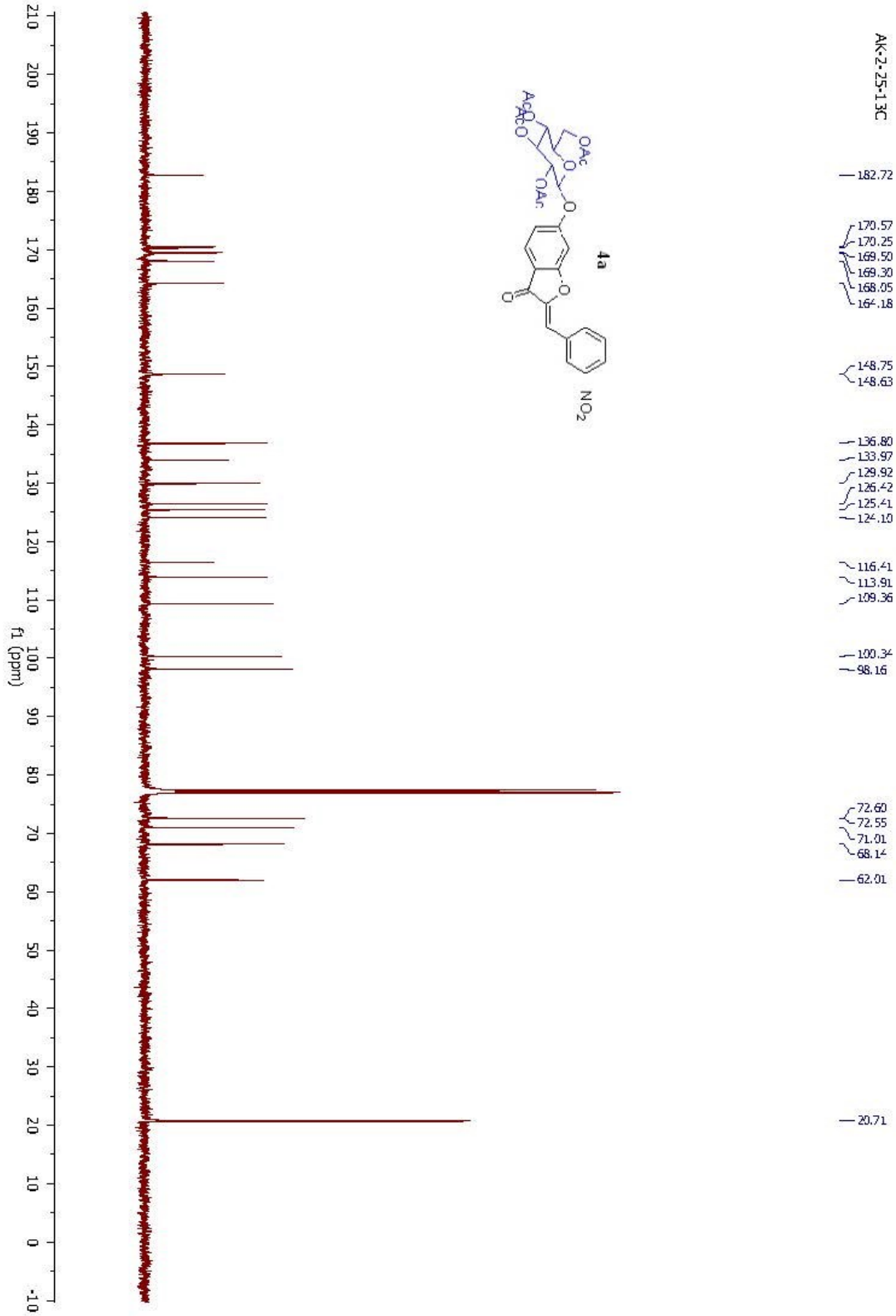

AK-01-120-1H-DMSO
2a
Me
CN
OAc
AcO
AcO
OAc
f1 (ppm)

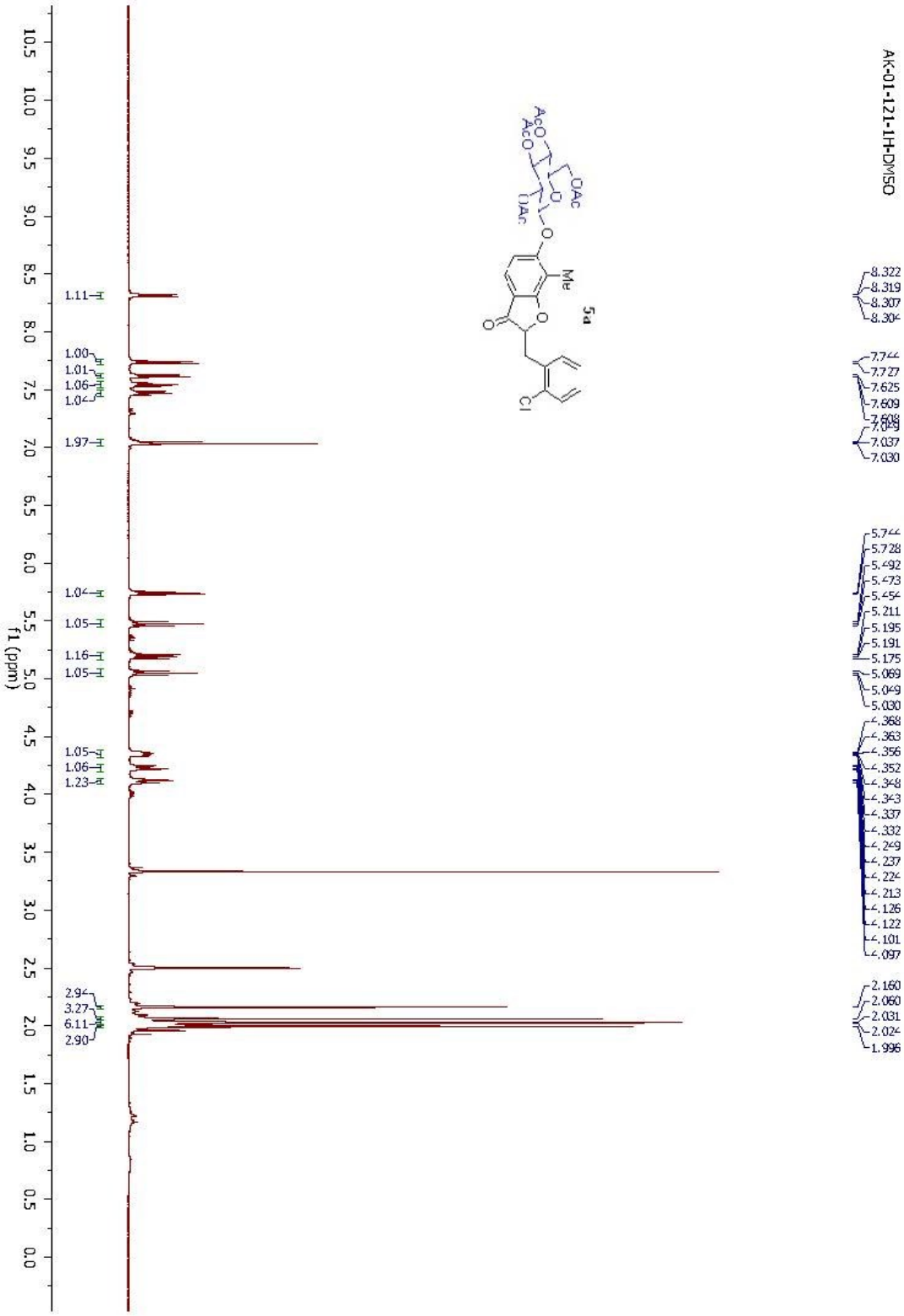

AK-01-120-13C
183.63
170.57
170.27
169.51
169.27
155.00
151.92
149.02
136.98
132.63
131.50
123.38
118.67
116.16
112.69
112.57
110.62
109.51
98.67
77.41
77.16
76.91
72.47
72.11
70.92
68.21
61.91
20.79
20.73
8.15
Me
2a
CN
f1 (ppm)

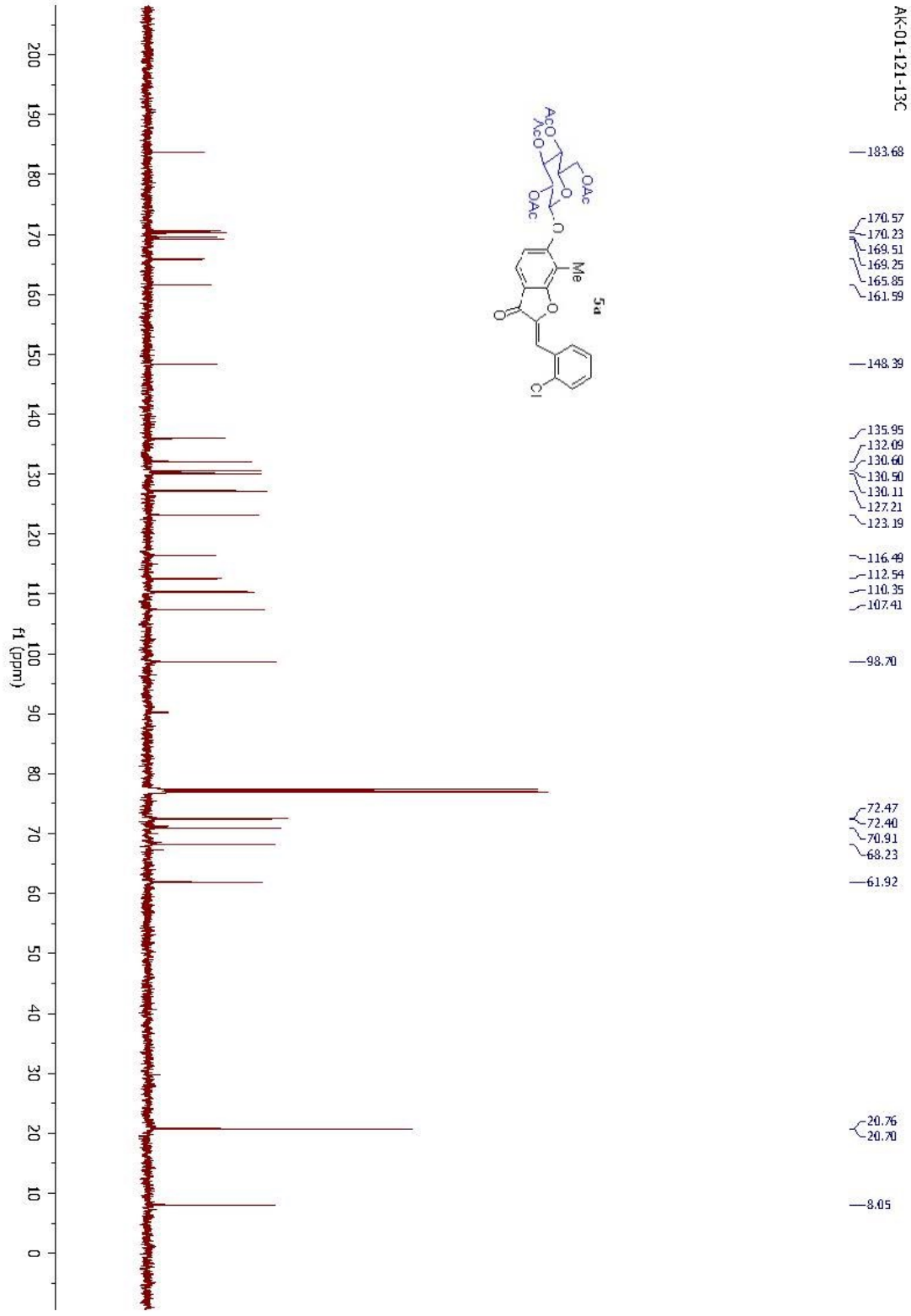

AK-01-1104-DMSO-1H
3a
f1 (ppm)

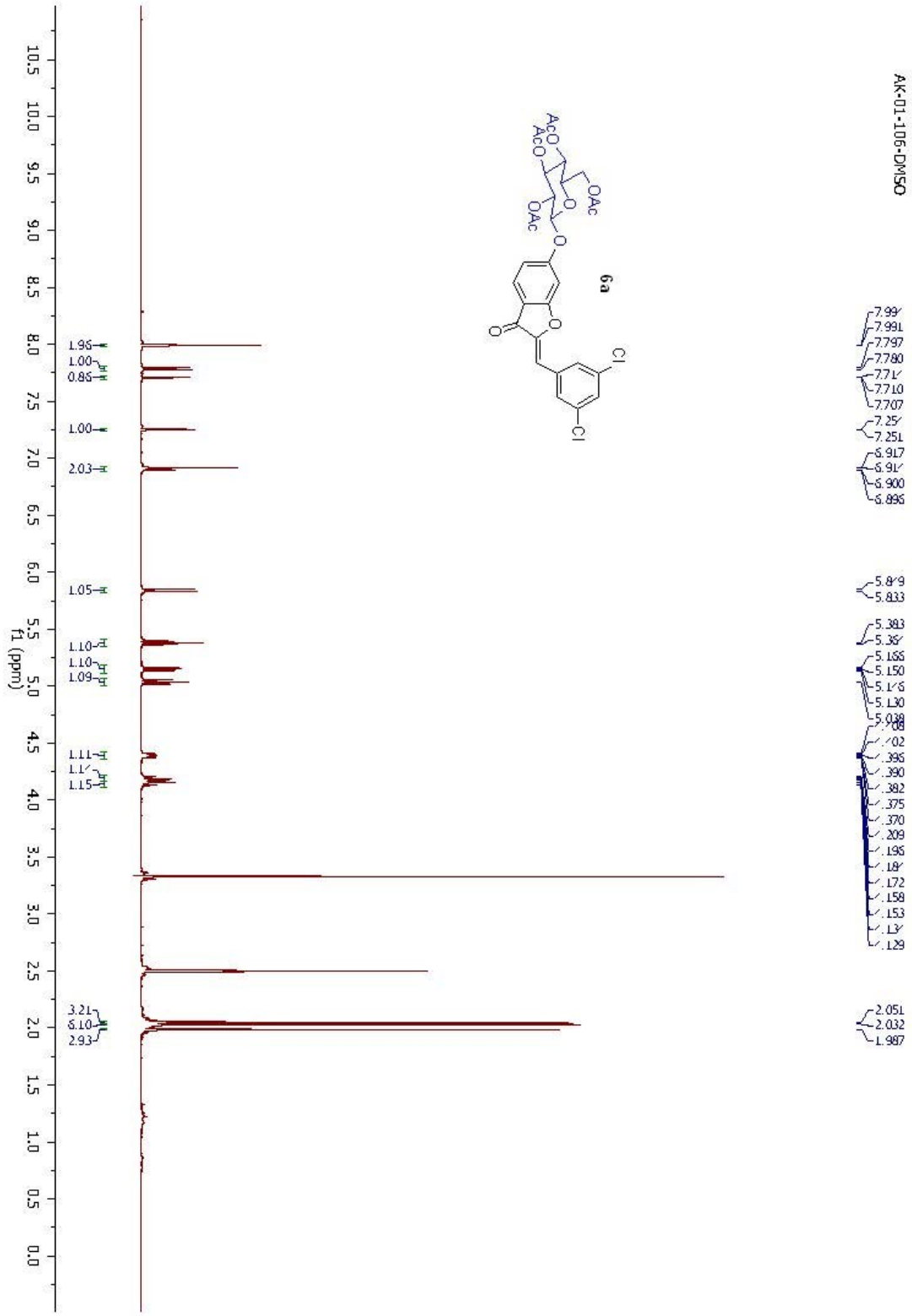

AK-01-104-13C
182.71
170.77
170.25
169.77
169.28
168.03
167.20
149.05
147.68
138.67
131.77
126.50
122.05
116.31
113.80
109.17
100.78
98.20
72.53
72.18
70.96
68.08
61.95
20.75
20.68
3a
f1 (ppm)


AK-2-25-1H-DMSO
4a
8.786
8.386
8.360
8.294
8.266
7.819
7.797
7.791
7.772
7.207
7.093
6.933
6.905
5.877
5.850
5.411
5.380
5.180
5.150
5.079
5.046
5.015
4.388
4.364
4.240
4.222
4.199
4.181
4.158
4.117
2.036
1.989
1.05
1.09
1.04
2.07
1.00
1.00
1.03
1.11
1.09
1.07
1.08
2.13
8.24
4.00
f1 (ppm)

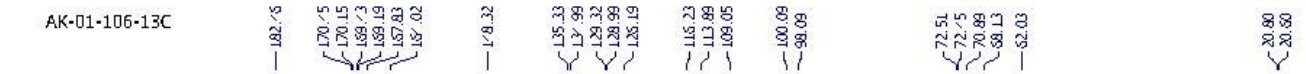

AK-2-25-13C
182.72
170.57
170.25
169.50
169.30
168.05
164.18
148.75
148.63
136.80
133.97
129.92
126.42
125.41
124.10
116.41
113.91
109.36
100.34
98.16
72.60
72.55
71.01
68.14
62.01
20.71
4a
f1 (ppm)

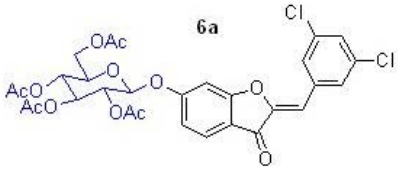

AK-01-121-1H-DMSO
f1 (ppm)
5a
8.322
8.319
8.307
8.304
7.727
7.625
7.609
7.037
7.030
5.728
5.492
5.473
5.211
5.195
5.191
5.175
5.069
5.049
5.030
4.368
4.363
4.356
4.352
4.348
4.343
4.337
4.332
4.249
4.237
4.224
4.213
4.126
4.122
4.101
4.097
2.160
2.060
2.031
2.024
1.996
1.11
1.00
1.01
1.06
1.07
1.97
1.07
1.05
1.16
1.05
1.05
1.06
1.23
2.94
3.27
6.11
2.90

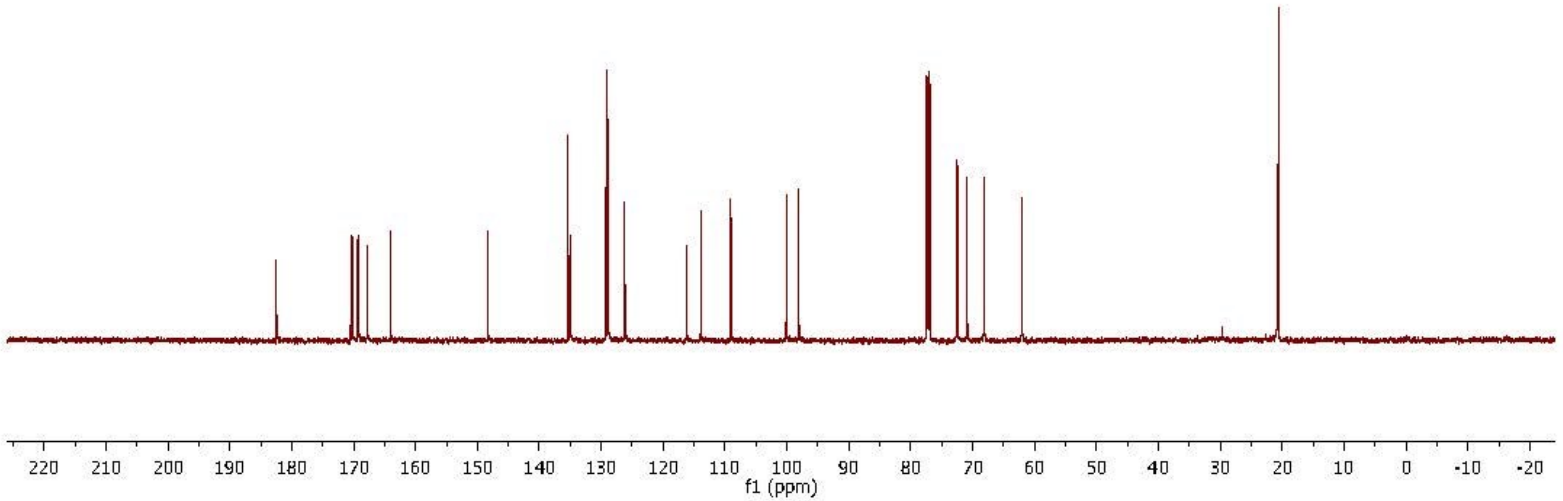

AK-01-121-13C
183.68
170.57
170.23
169.51
169.25
165.85
161.59
148.39
135.95
132.09
130.60
130.50
130.11
127.21
123.19
116.49
112.54
110.35
107.41
98.70
72.47
72.40
70.91
68.23
61.92
20.76
20.70
8.05
f1 (ppm)
Me
5a

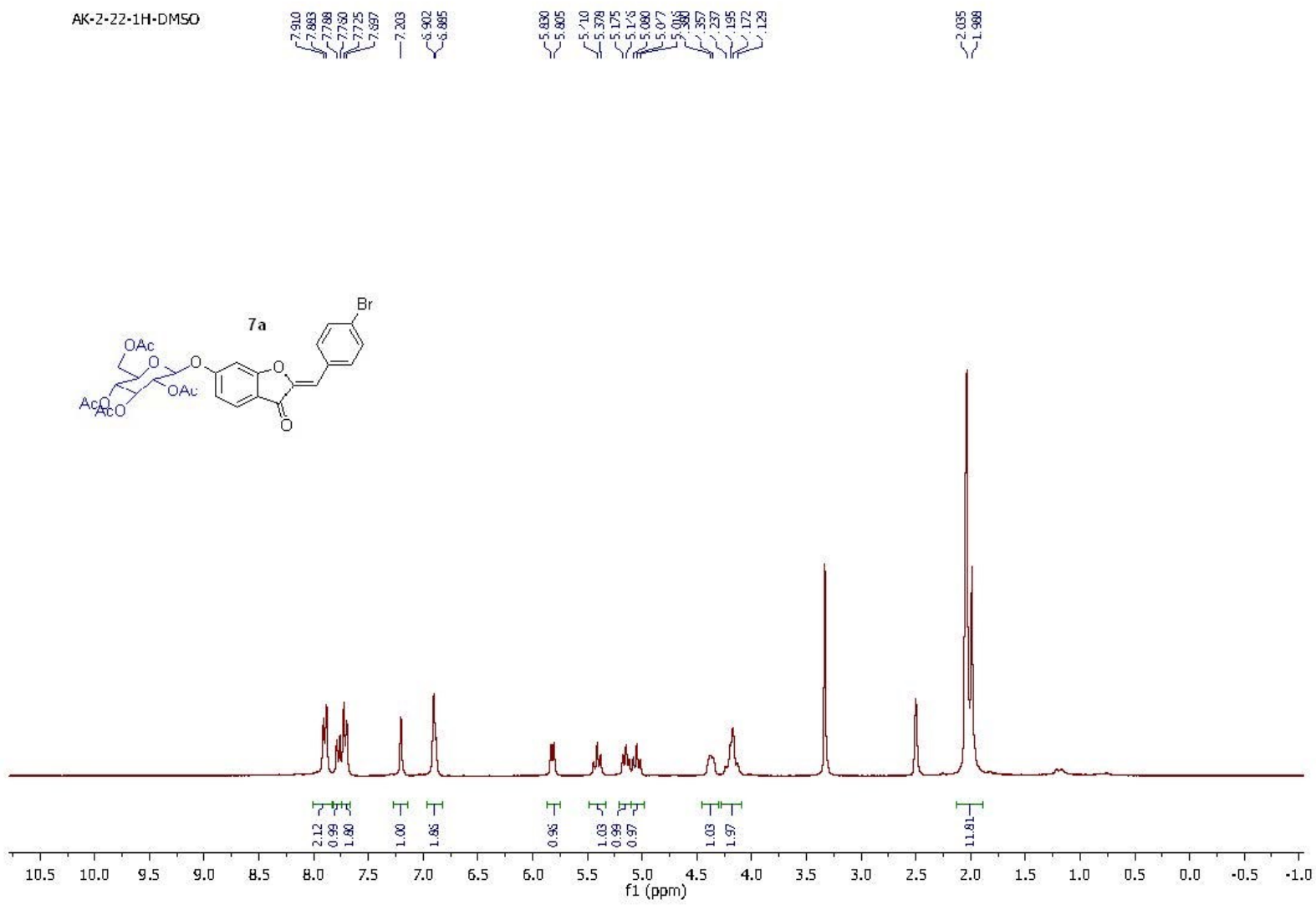

AK-01-106-DMSO
6a
f1 (ppm)

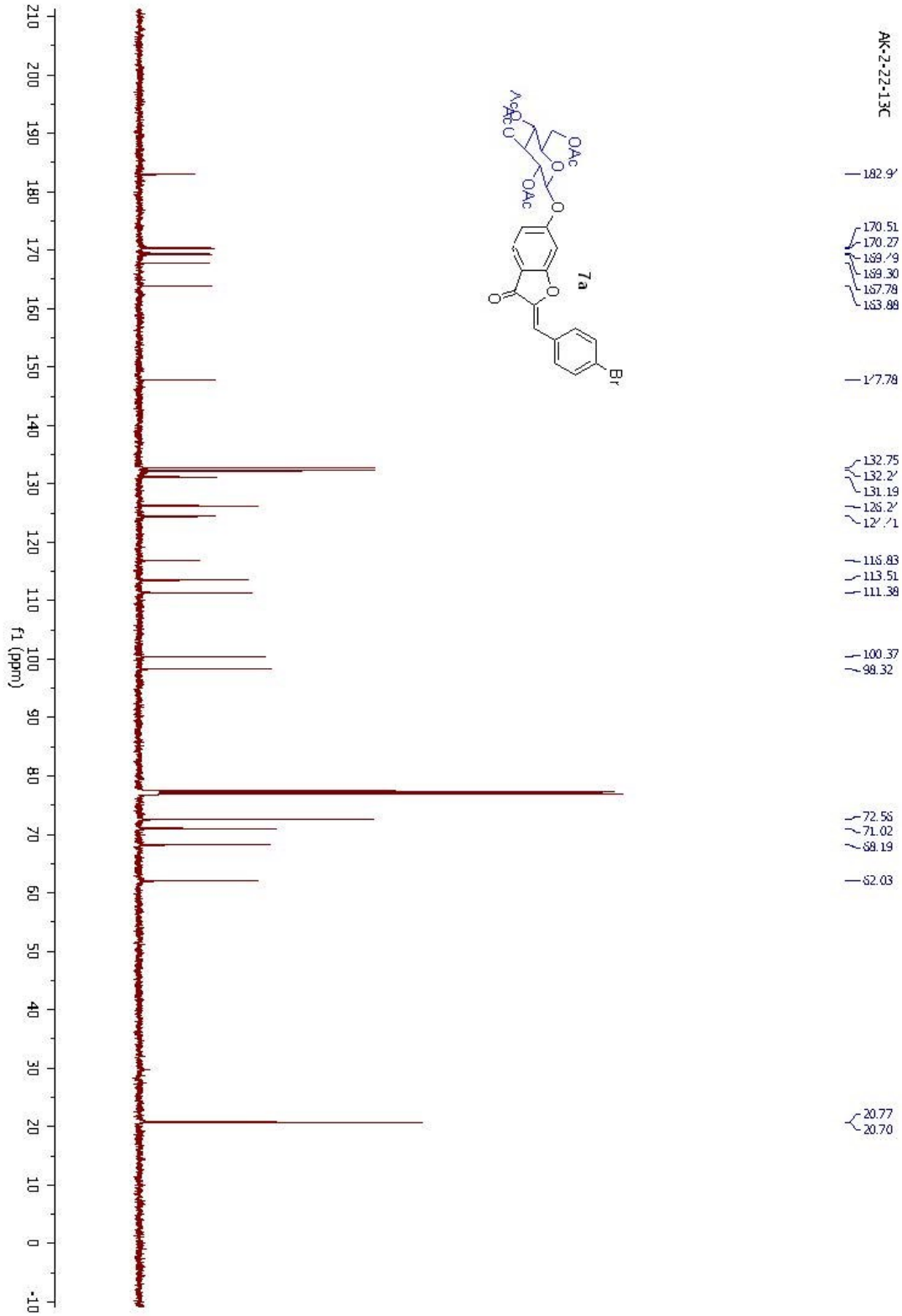
AK-01-106-13C

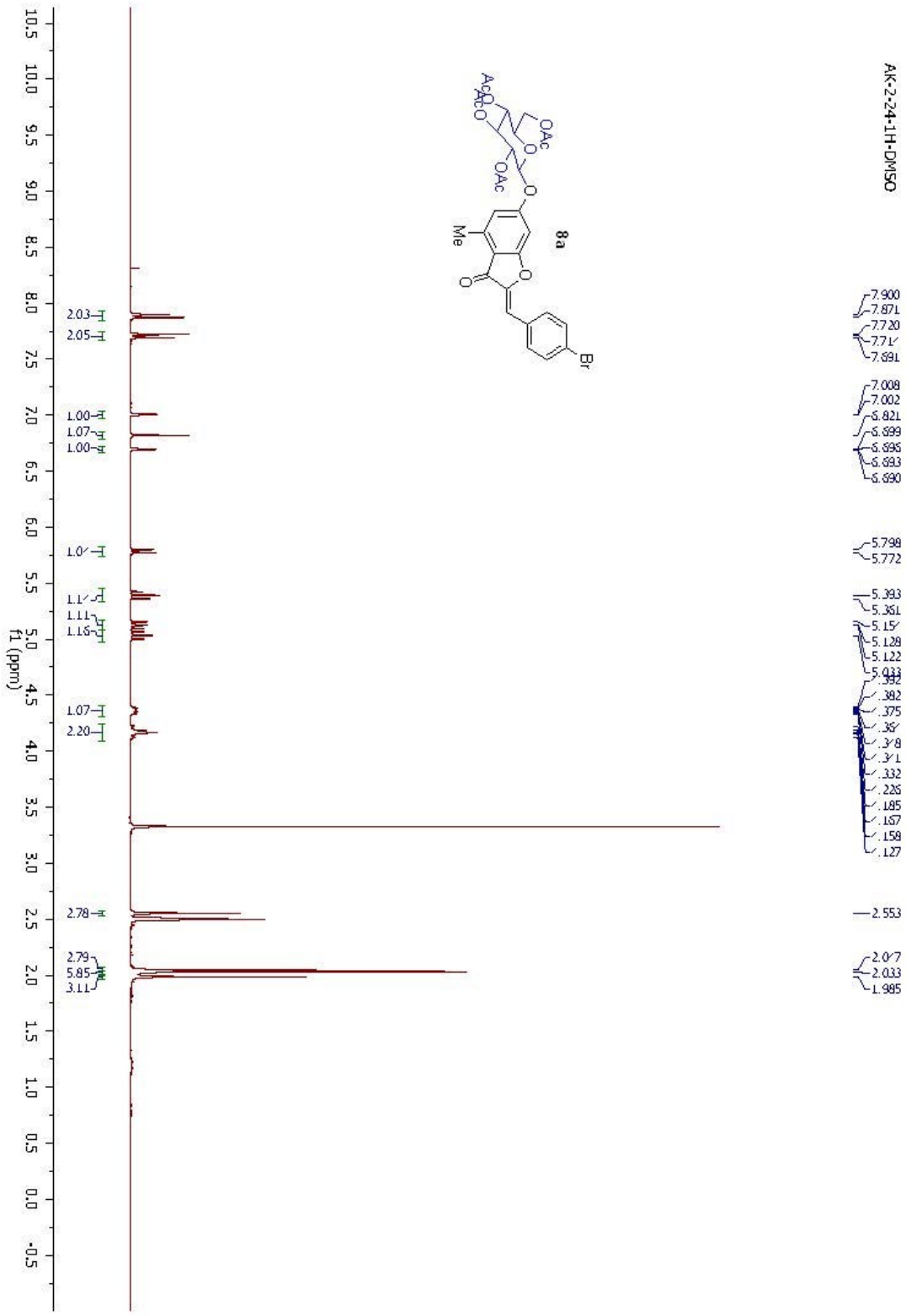

182.76
170.75
170.15
169.73
169.19
157.83
107.02
148.32
135.33
129.99
129.32
128.99
125.19
116.23
113.89
109.05
100.09
98.09
72.51
72.45
70.89
68.13
62.03
20.80
20.50

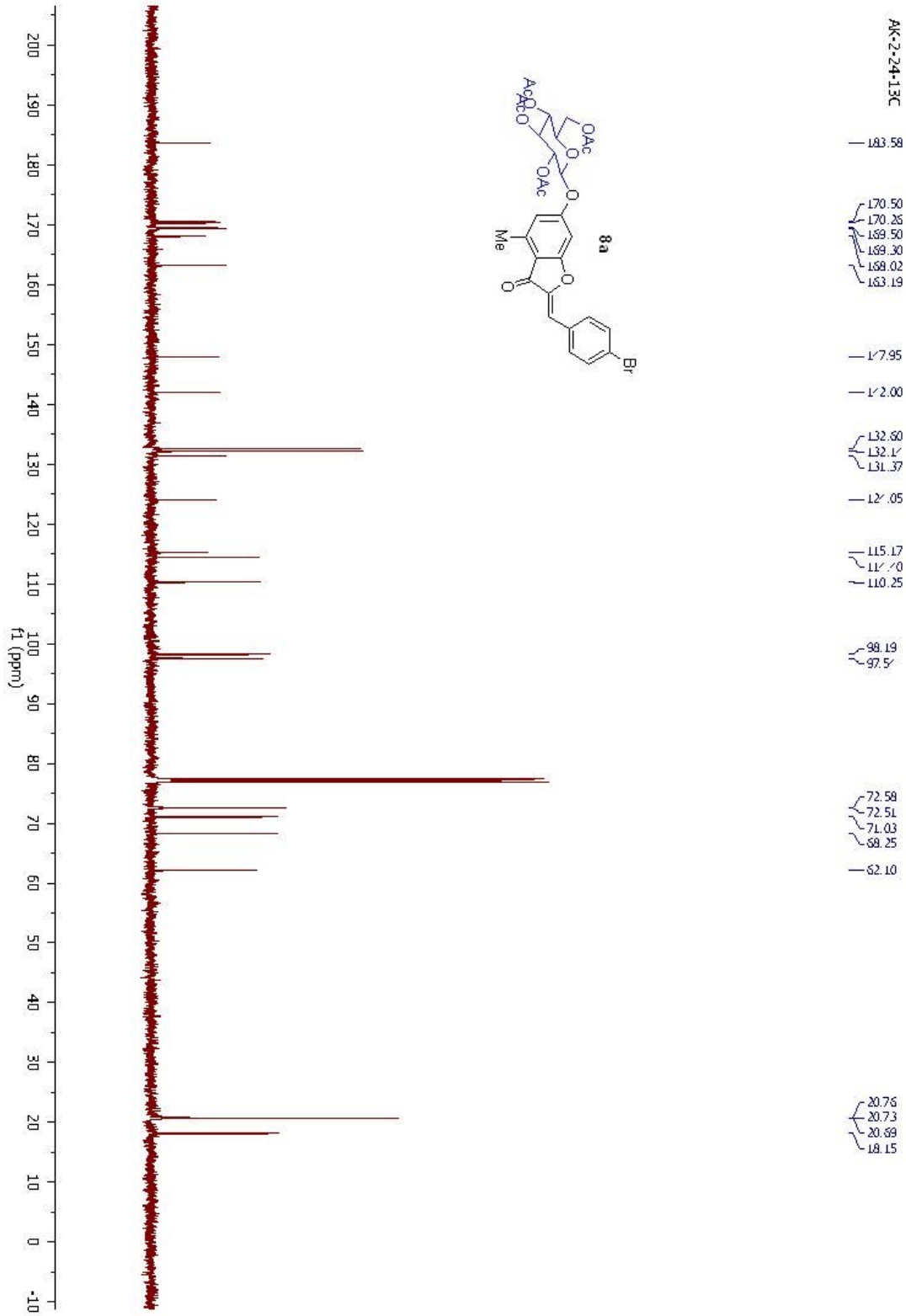

6a
OAc
AcO
AcO
OAc
O
O
O
Cl
Cl
O

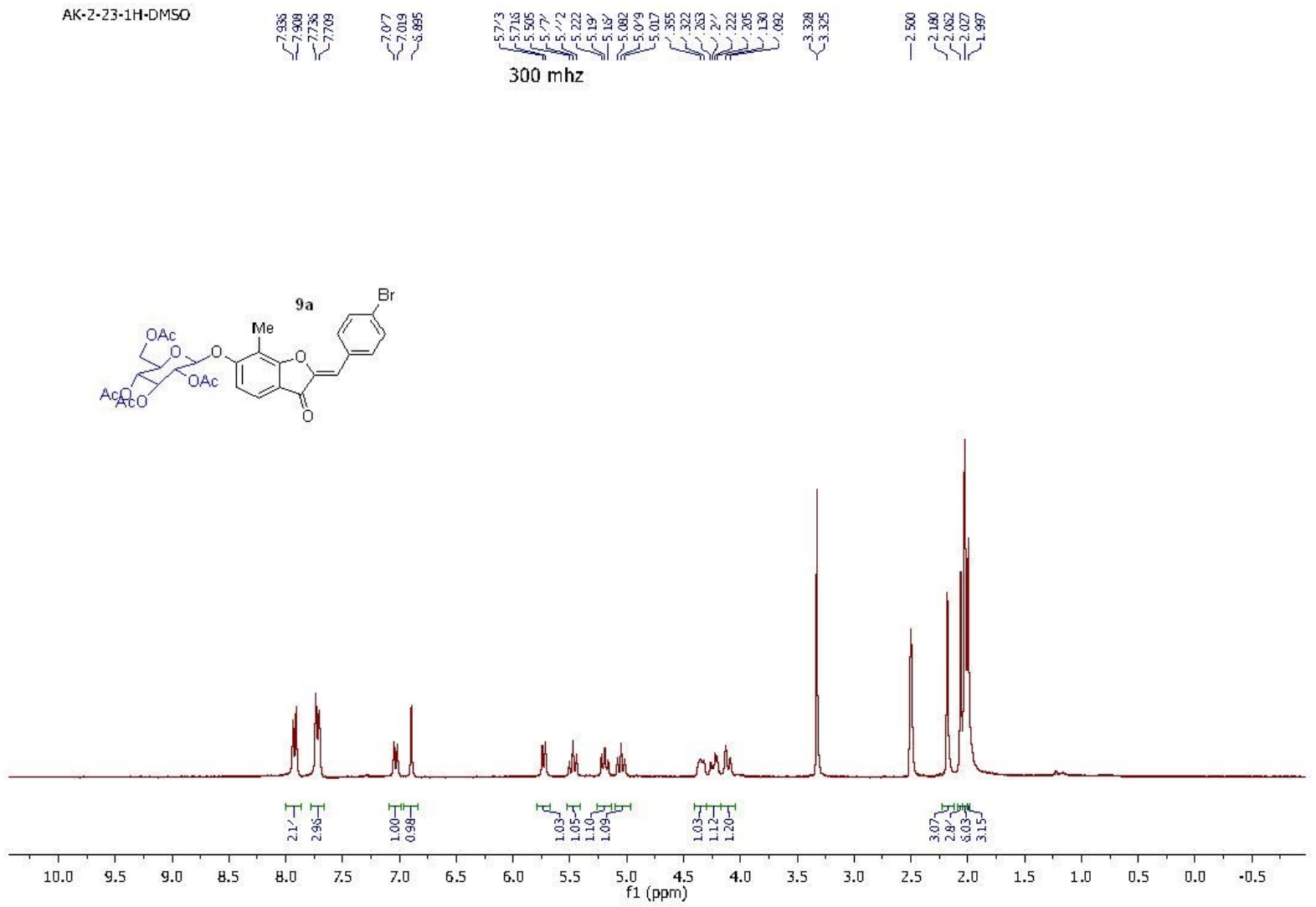

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

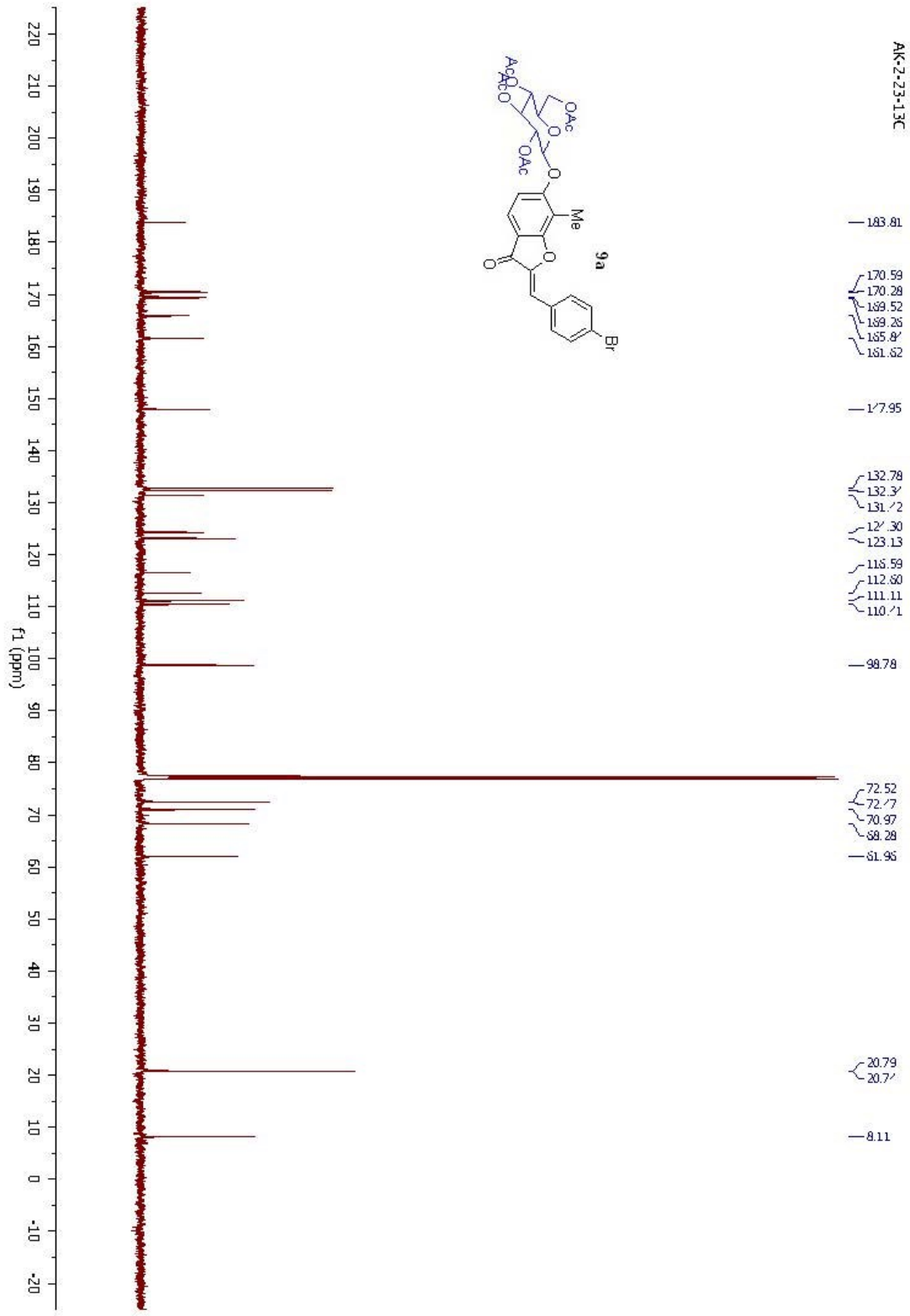

AK-Z-22-1H-DMSO
7a
Br
OAc
AcO
AcO
OAc
O
f1 (ppm)

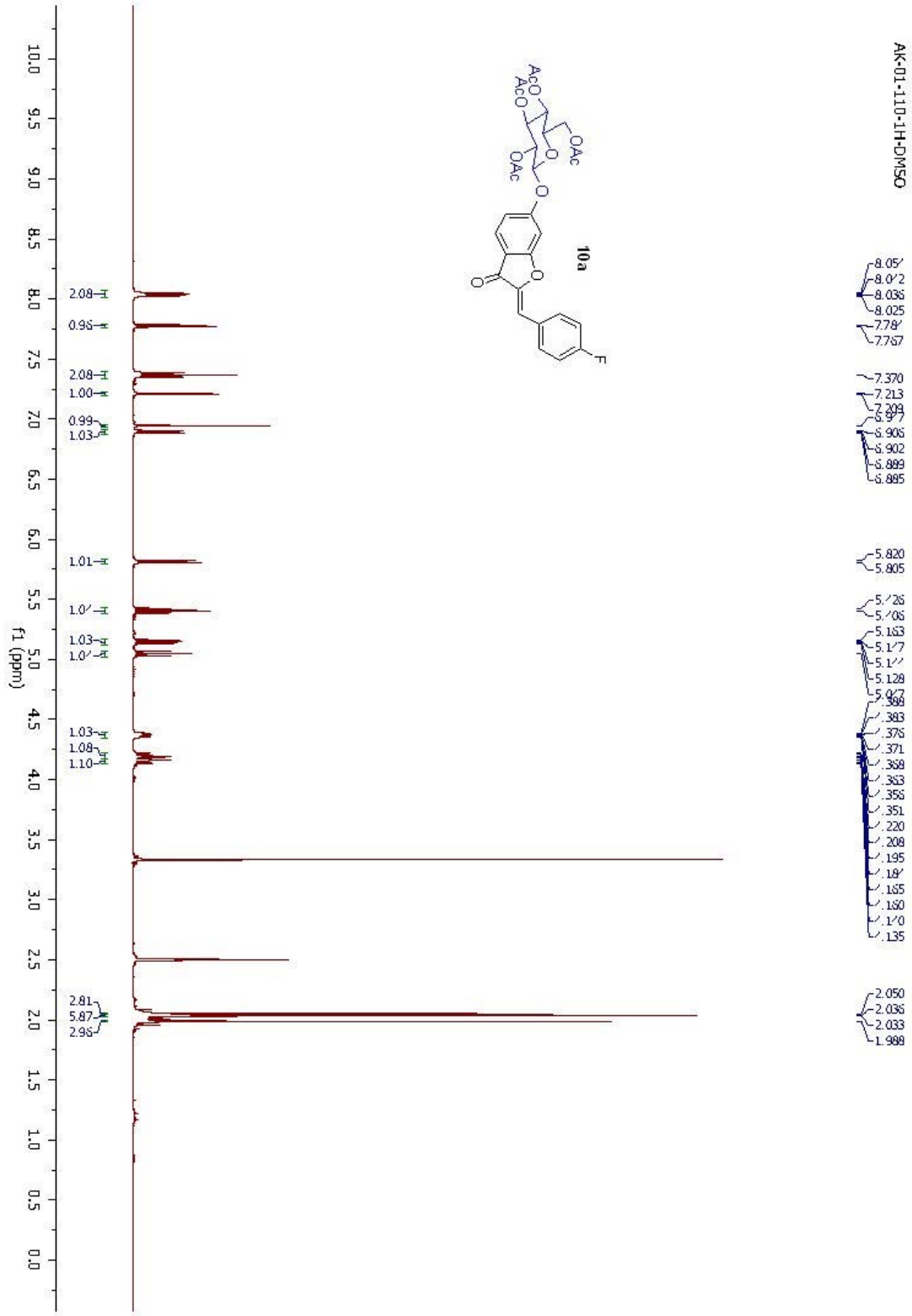

AK-2-22-13C
182.97
170.51
170.27
169.79
169.30
167.78
163.88
147.78
132.75
132.27
131.19
126.27
122.71
116.83
113.51
111.39
100.37
98.32
72.56
71.02
68.19
62.03
20.77
20.70
7a
Br
f1 (ppm)

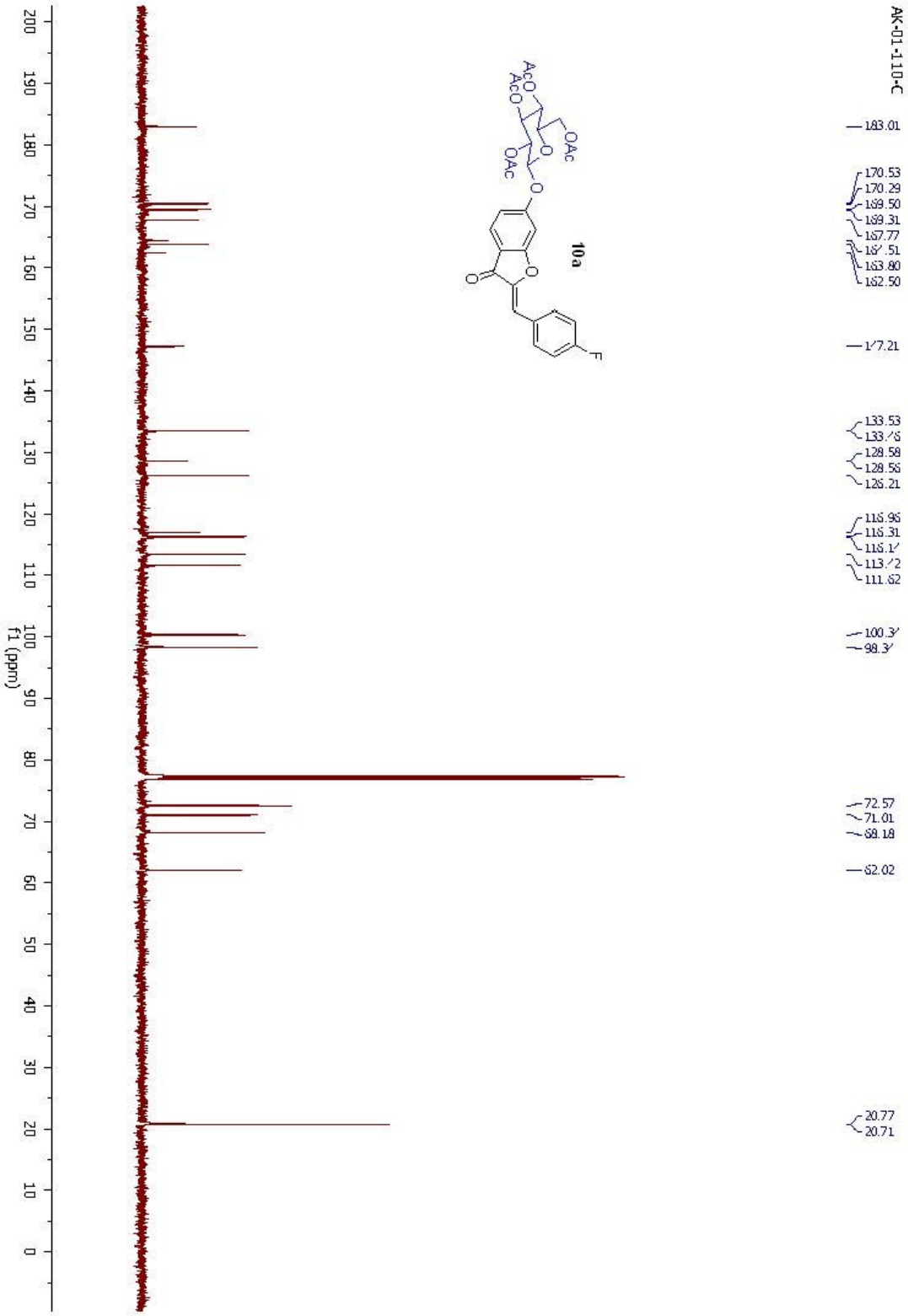

AK-2-24-1H-DMSO
8a
Me
Br
OAc
AcO
AcO
OAc
O
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.03
2.05
1.00
1.07
1.00
1.07
1.11
1.11
1.16
1.07
2.20
2.78
2.79
5.85
3.11
7.900
7.871
7.720
7.714
7.691
7.008
7.002
6.821
6.699
6.696
6.693
6.690
5.798
5.772
5.393
5.361
5.154
5.128
5.122
5.033
.392
.382
.375
.367
.348
.341
.332
.226
.185
.167
.158
.127
2.553
2.077
2.033
1.985

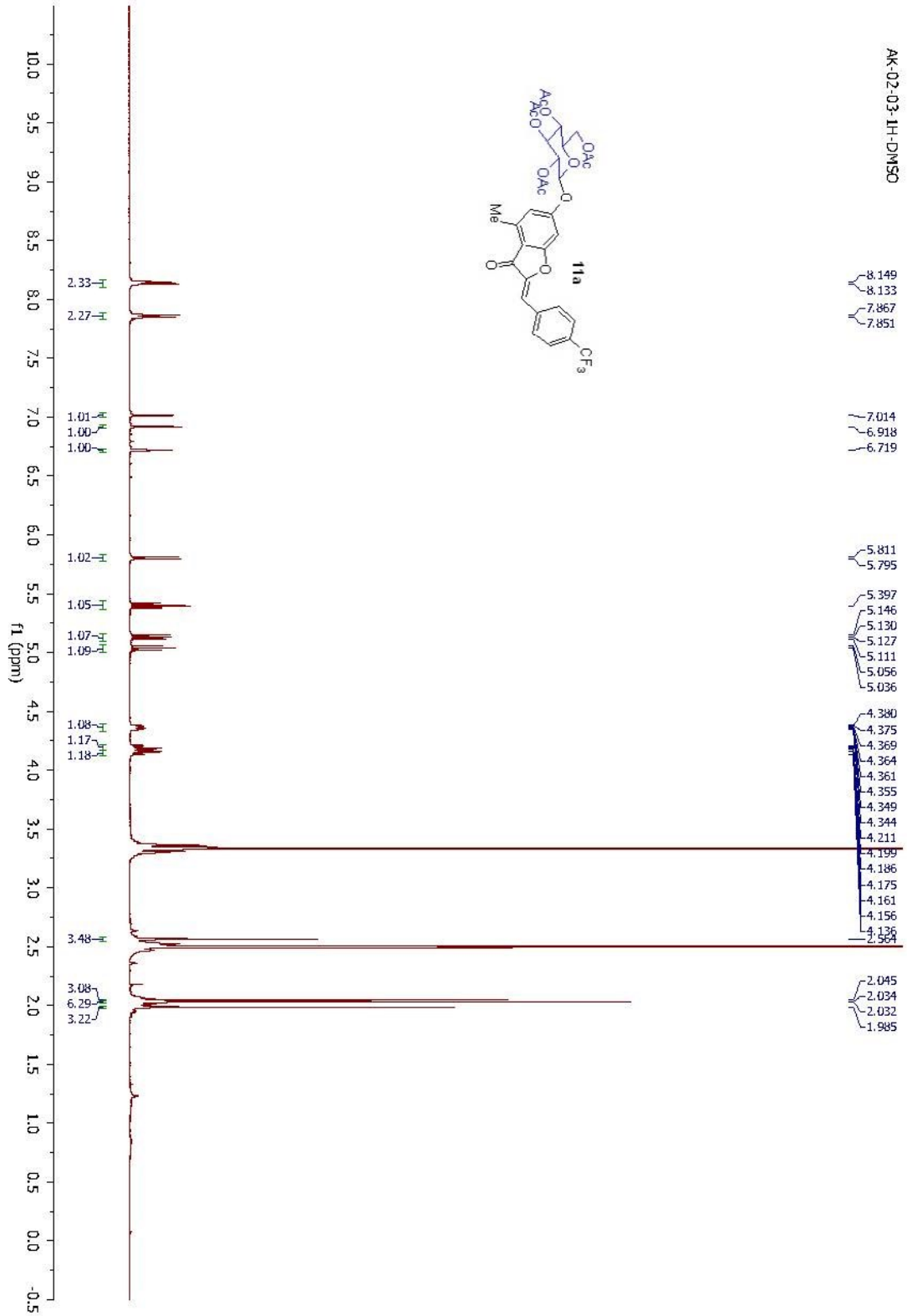

AK-2-24-13C
183.58
170.50
170.26
169.50
169.30
168.02
163.19
147.95
142.00
132.60
132.17
131.37
127.05
115.17
111.70
110.25
98.19
97.57
72.58
72.51
71.03
68.25
62.10
20.76
20.73
20.69
18.15
8a
Me
Br
f1 (ppm)

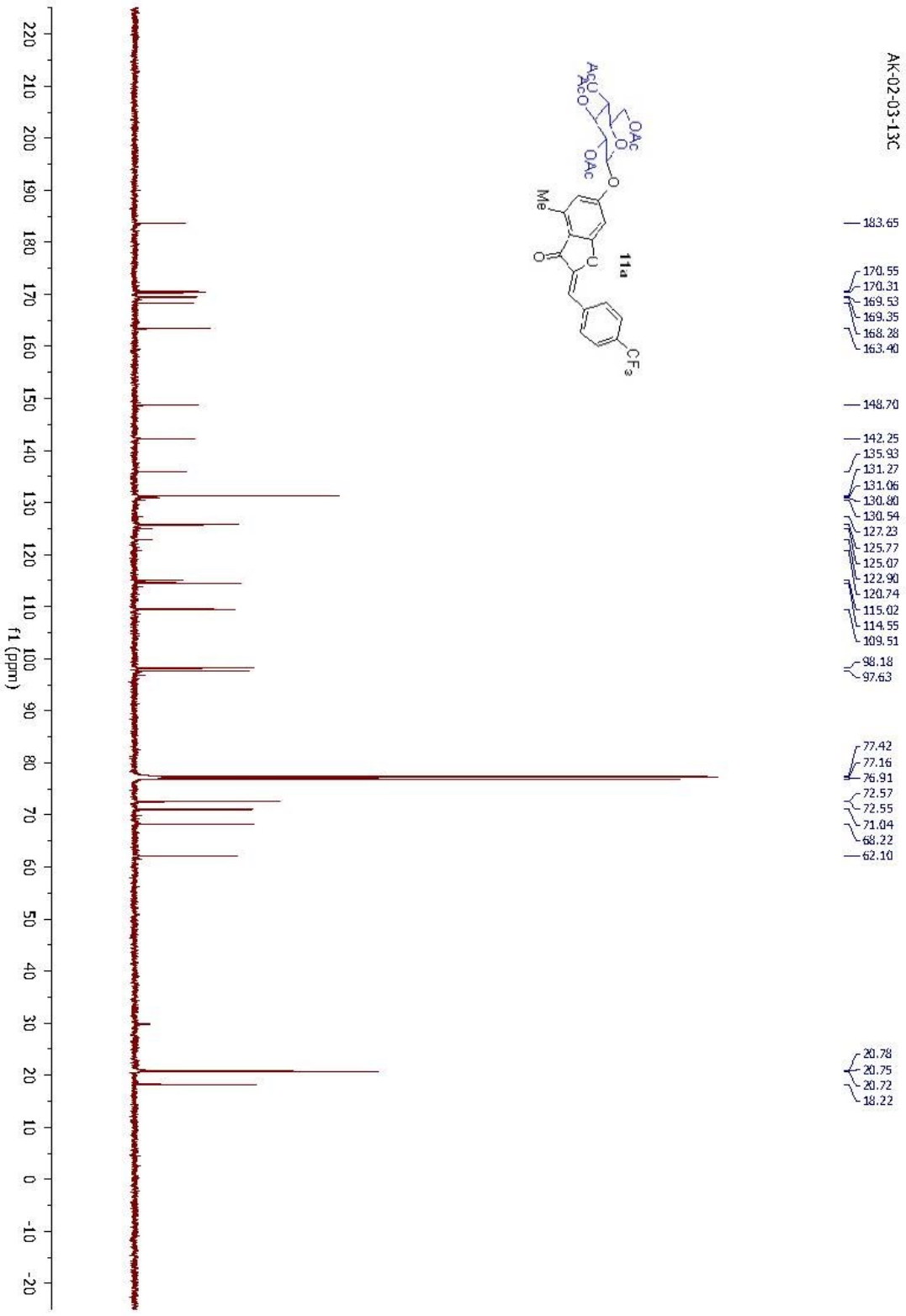

AK-2-23-1H-DMSO
300 mhz
9a
Br
Me
OAc
OAc
AcO
AcO
O
f1 (ppm)


AK-2-23-13C
183.81
170.59
170.28
169.52
169.26
165.89
161.62
147.95
132.78
132.34
131.72
127.30
123.13
116.59
112.60
111.11
110.71
98.78
72.52
72.17
70.97
68.28
61.96
20.79
20.71
8.11
Me
OAc
OAc
OAc
Br
9a
f1 (ppm)

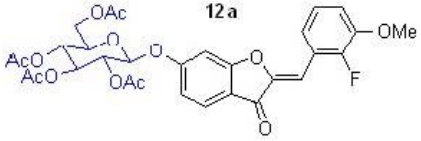

AK-01-110-1H-DMSO
10a
f1 (ppm)


AK-01-110-C
183.01
170.53
170.29
169.50
169.31
167.77
167.51
163.80
162.50
147.21
133.53
133.45
128.58
128.56
126.21
116.96
116.31
116.17
113.72
111.62
100.37
98.37
72.57
71.01
68.18
62.02
20.77
20.71
10a
f1 (ppm)

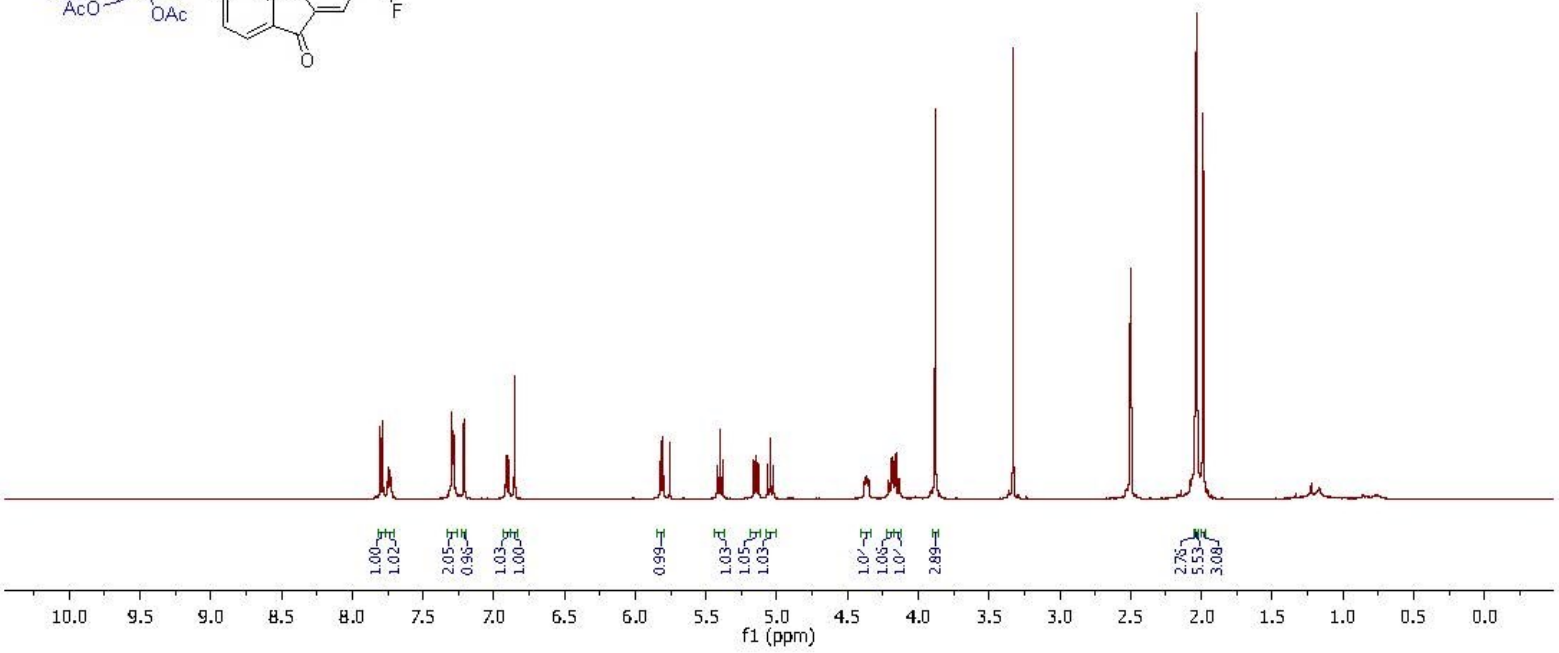

AK-02-03-1H-DMSO
11a
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
2.33
2.27
1.01
1.00
1.00
1.02
1.05
1.07
1.09
1.08
1.17
1.18
3.48
3.08
6.29
3.22
8.149
8.133
7.867
7.851
7.014
6.918
6.719
5.811
5.795
5.397
5.146
5.130
5.127
5.111
5.056
5.036
4.380
4.375
4.369
4.364
4.361
4.355
4.349
4.344
4.211
4.199
4.186
4.175
4.161
4.156
4.126
2.364
2.045
2.034
2.032
1.985

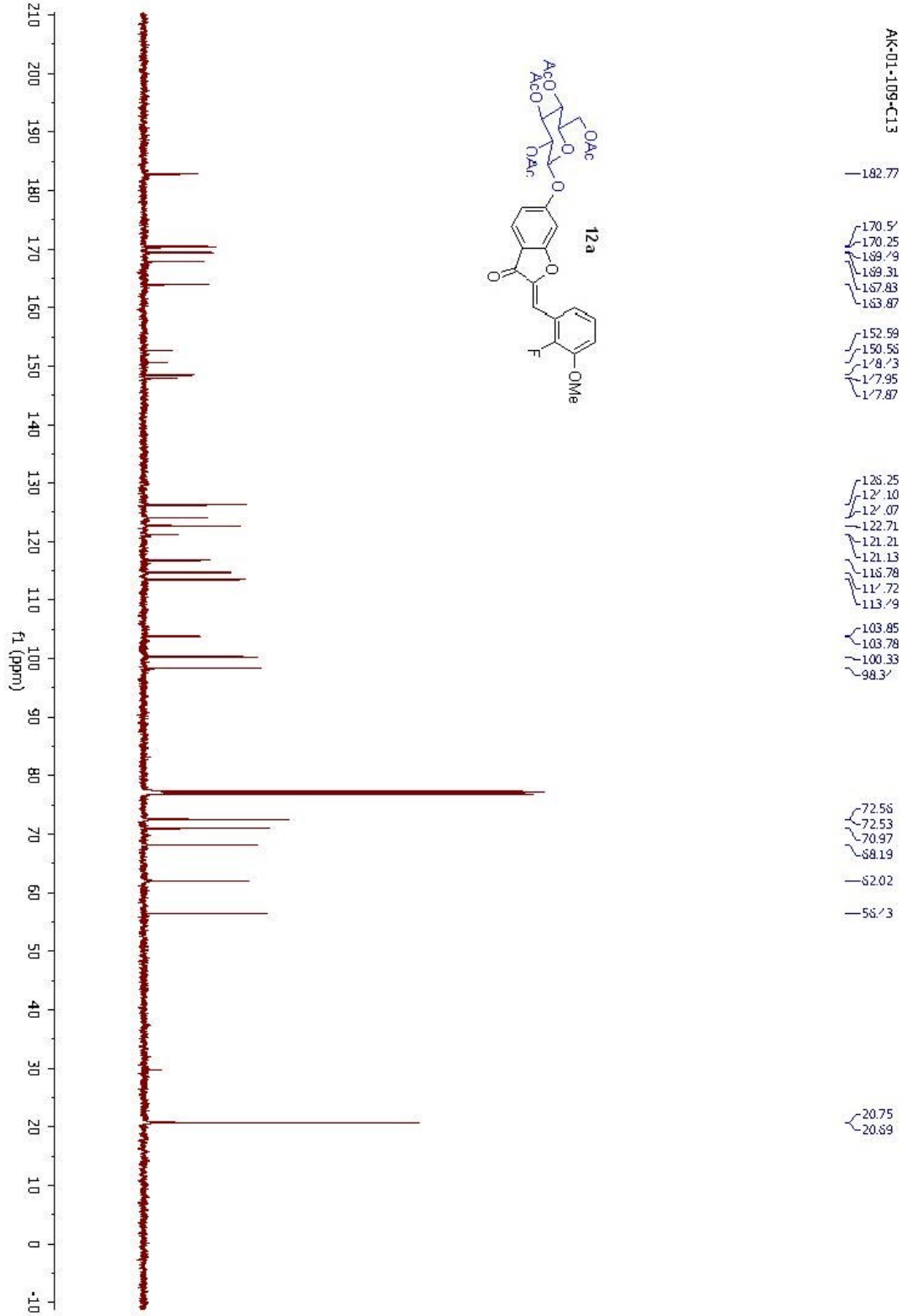

AK-02-03-13C
11a
Me
OAc
OAc
OAc
AcO
AcO
CF3
183.65
170.55
170.31
169.53
169.35
168.28
163.40
148.70
142.25
135.93
131.27
131.06
130.80
130.54
127.23
125.77
125.07
122.90
120.74
115.02
114.55
109.51
98.18
97.63
77.42
77.16
76.91
72.57
72.55
71.04
68.22
62.10
20.78
20.75
20.72
18.22
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

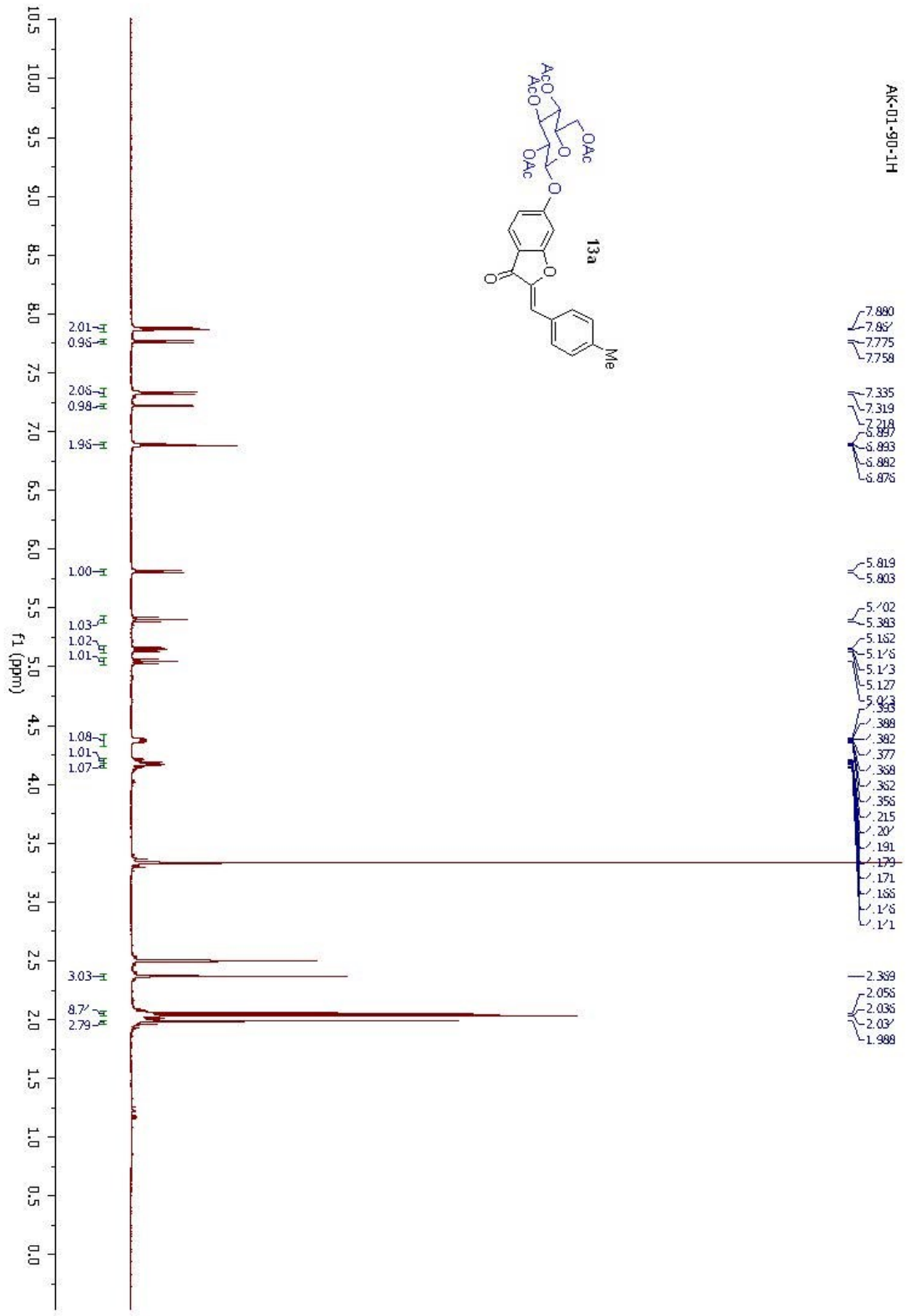
AK-01-109-DMSO

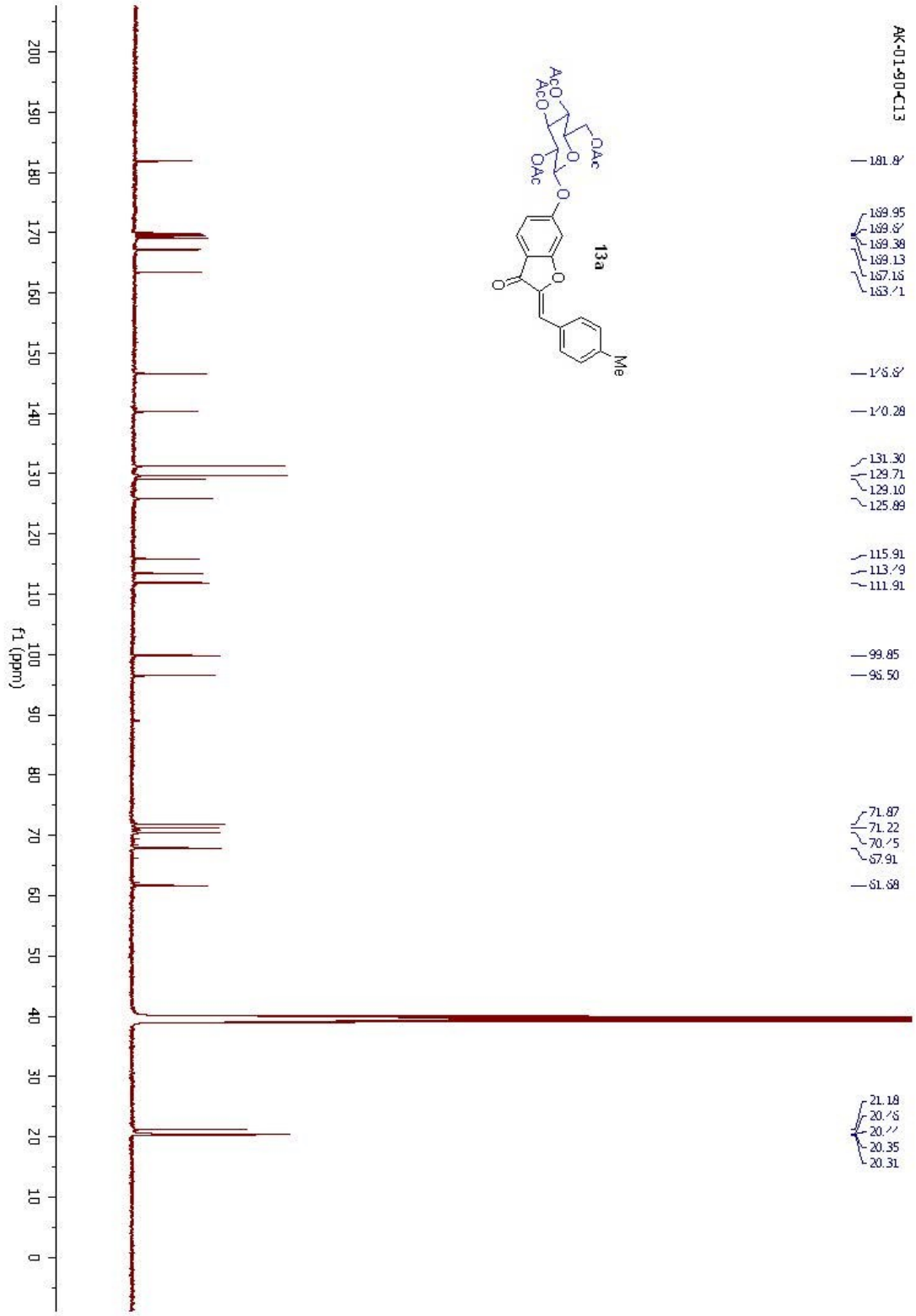


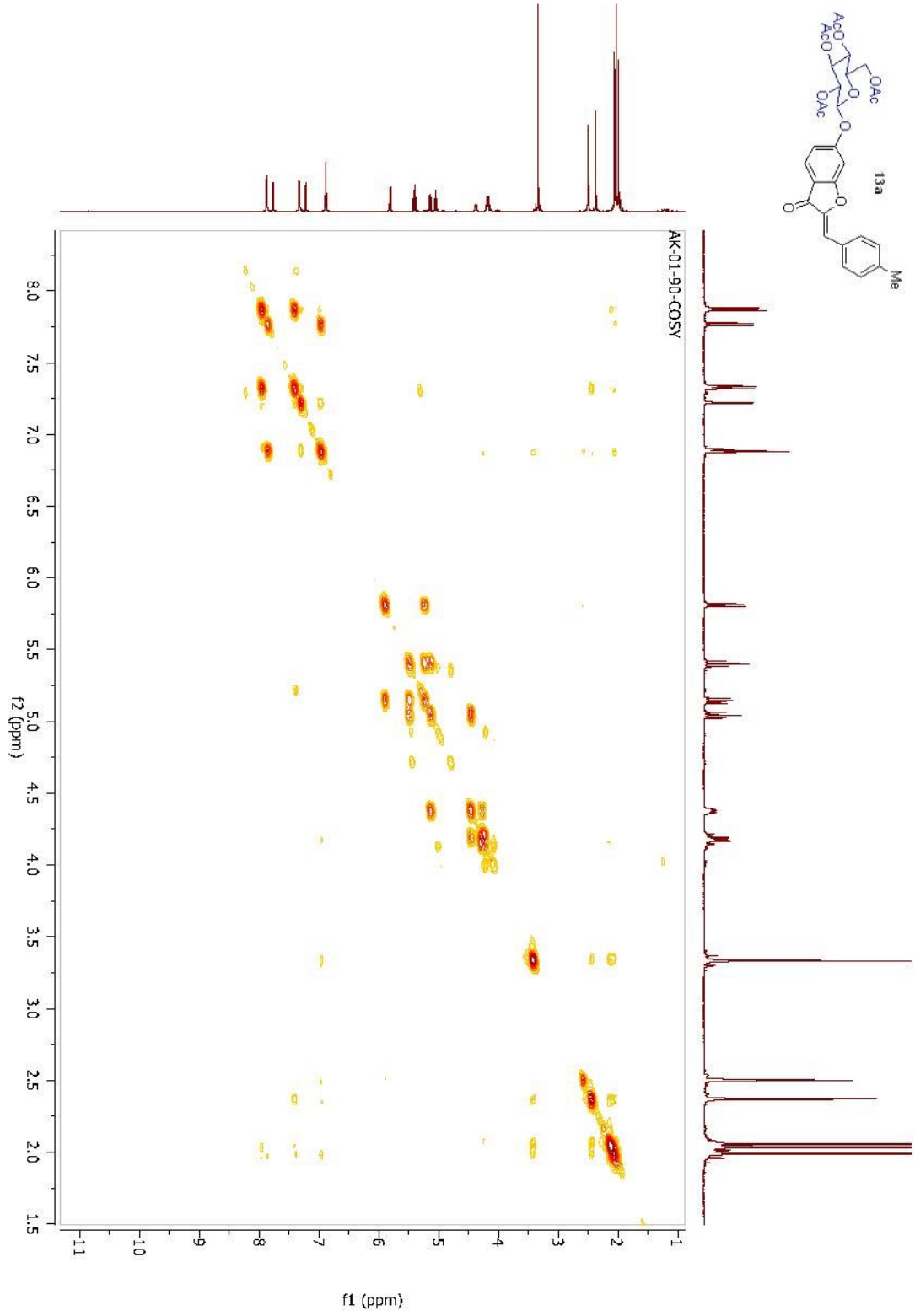
12 a

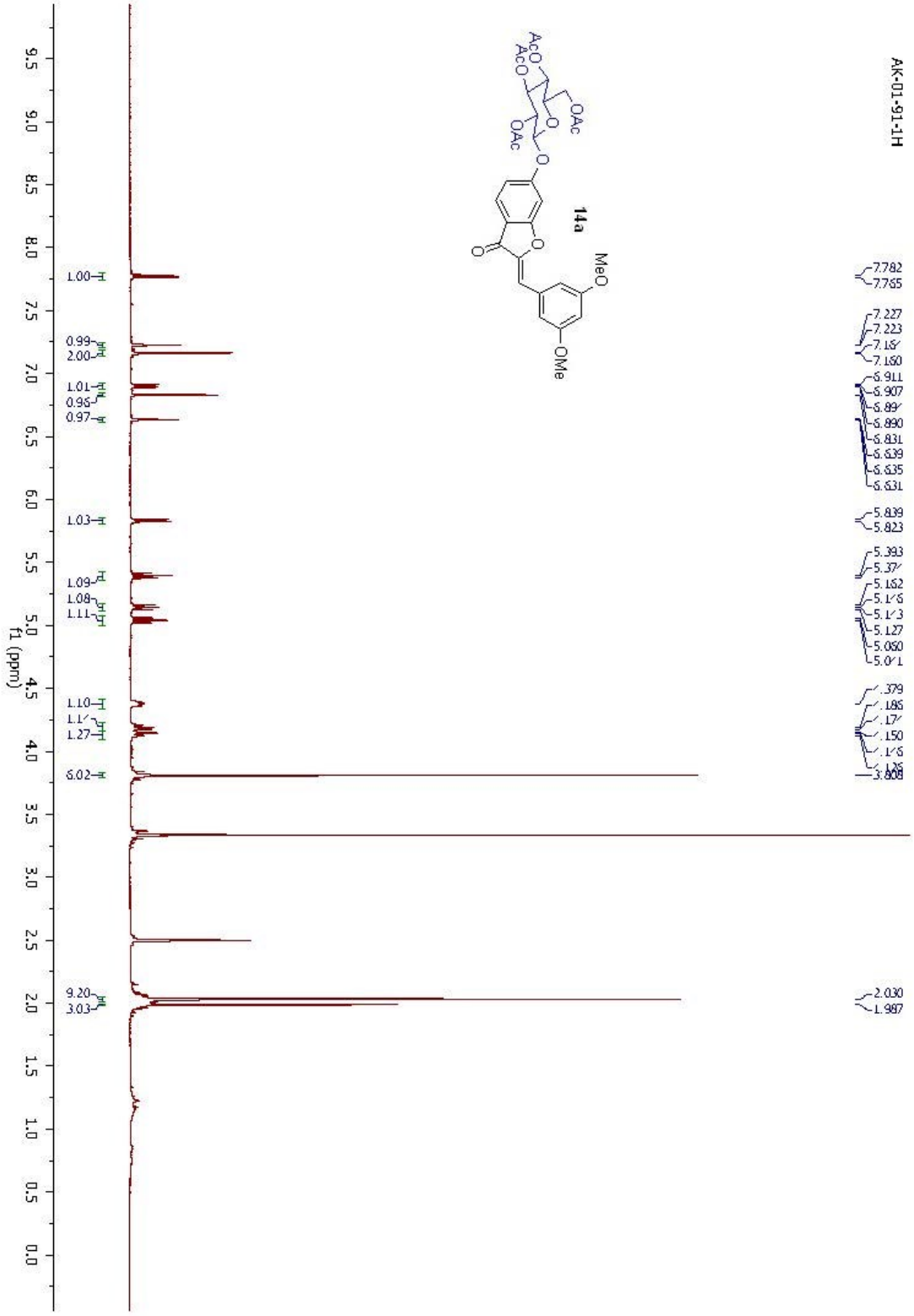


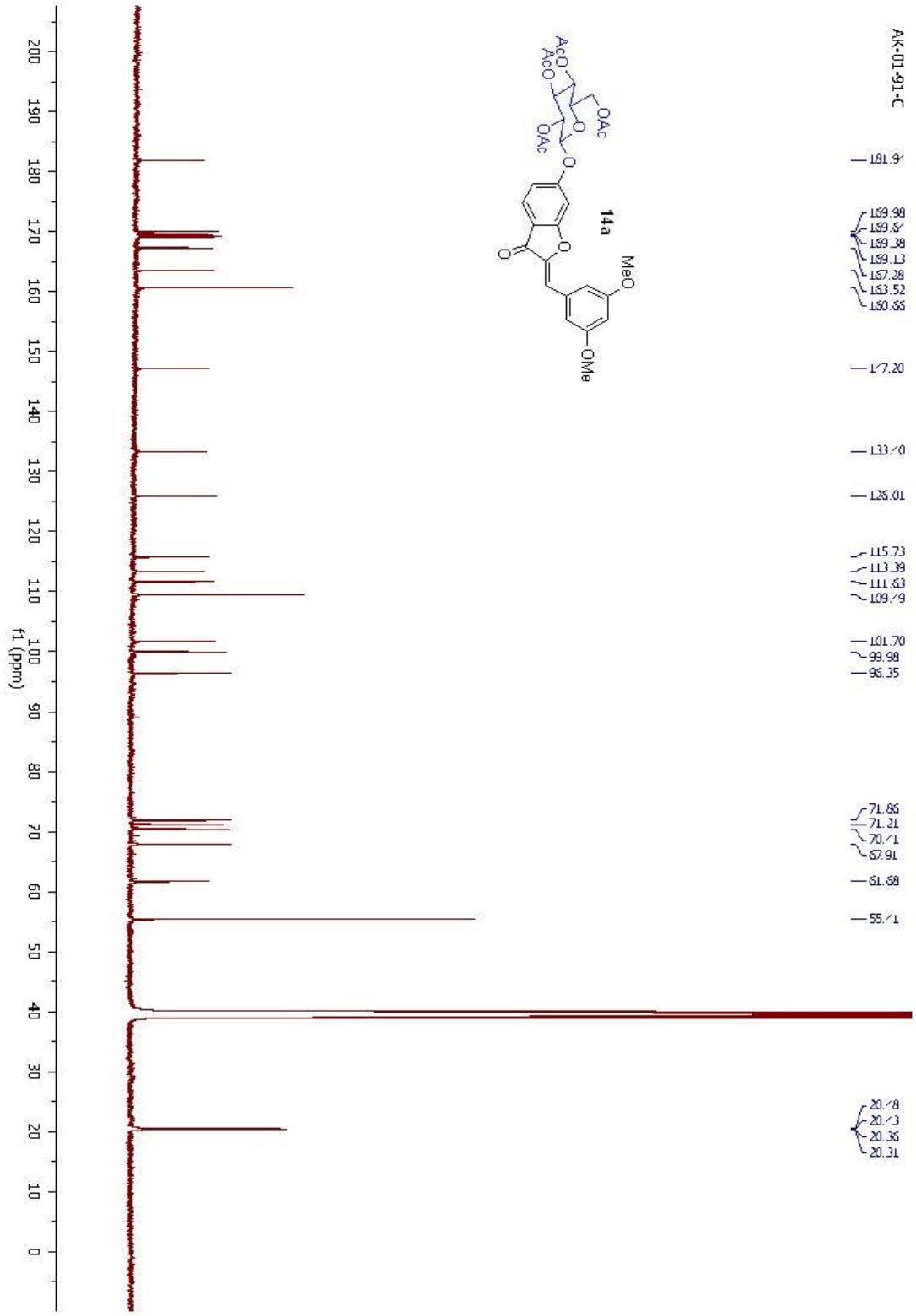

AK-01-109-C13
182.77
170.57
170.25
169.79
169.31
167.83
163.87
152.59
150.56
148.73
147.95
147.87
126.25
124.10
124.07
122.71
121.21
121.13
116.78
114.72
113.79
103.85
103.78
100.33
98.37
72.56
72.53
70.97
68.19
62.02
56.73
20.75
20.69
12a
AcO
AcO
OAc
OAc
O
O
O
F
OMe
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

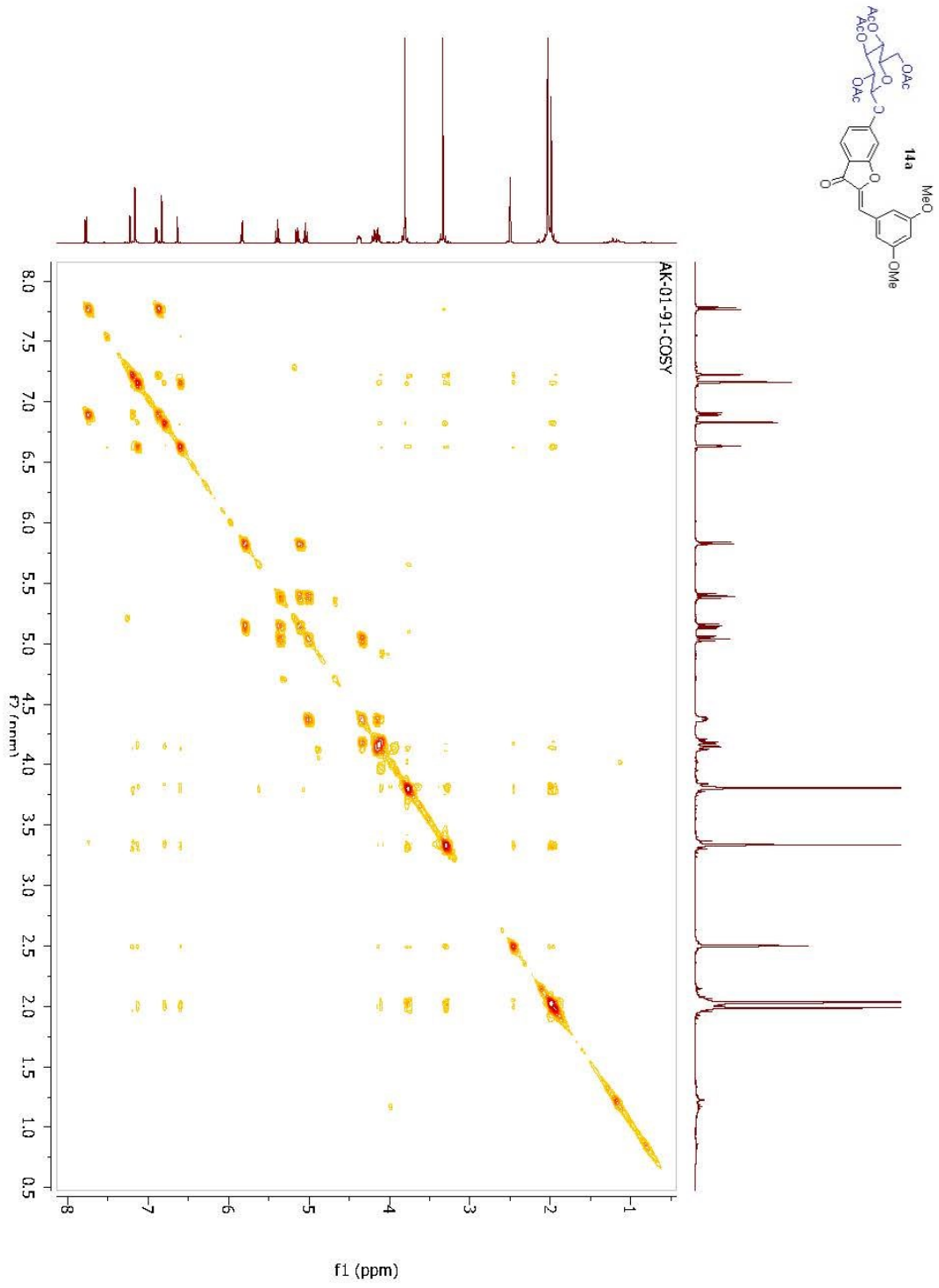

AK-01-90-1H
13a
AcO
AcO
OAc
OAc
O
O
O
O
Me
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.01
0.96
2.05
0.98
1.96
1.00
1.03
1.02
1.01
1.08
1.01
1.07
3.03
8.77
2.79
7.880
7.867
7.775
7.758
7.335
7.319
7.218
6.897
6.893
6.882
6.876
5.819
5.803
5.702
5.383
5.162
5.148
5.143
5.127
5.023
2.369
2.056
2.036
2.037
1.988

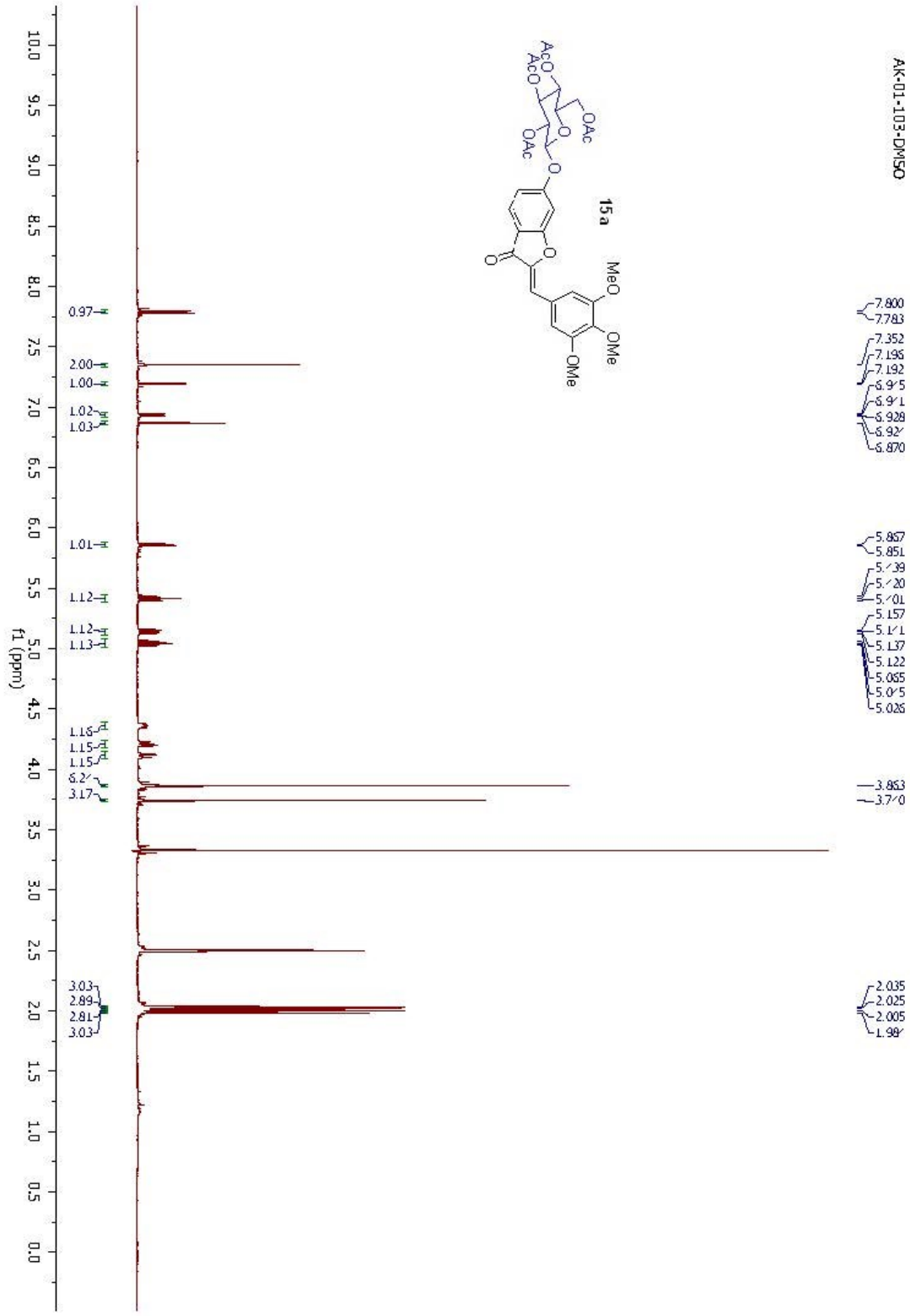

AK-01-90-C13
181.87
169.95
169.87
169.38
169.13
157.15
153.71
145.87
140.28
131.30
129.71
129.10
125.89
115.91
113.79
111.91
99.85
96.50
71.87
71.22
70.75
67.91
61.58
21.18
20.78
20.77
20.35
20.31
13a
Me
f1 (ppm)

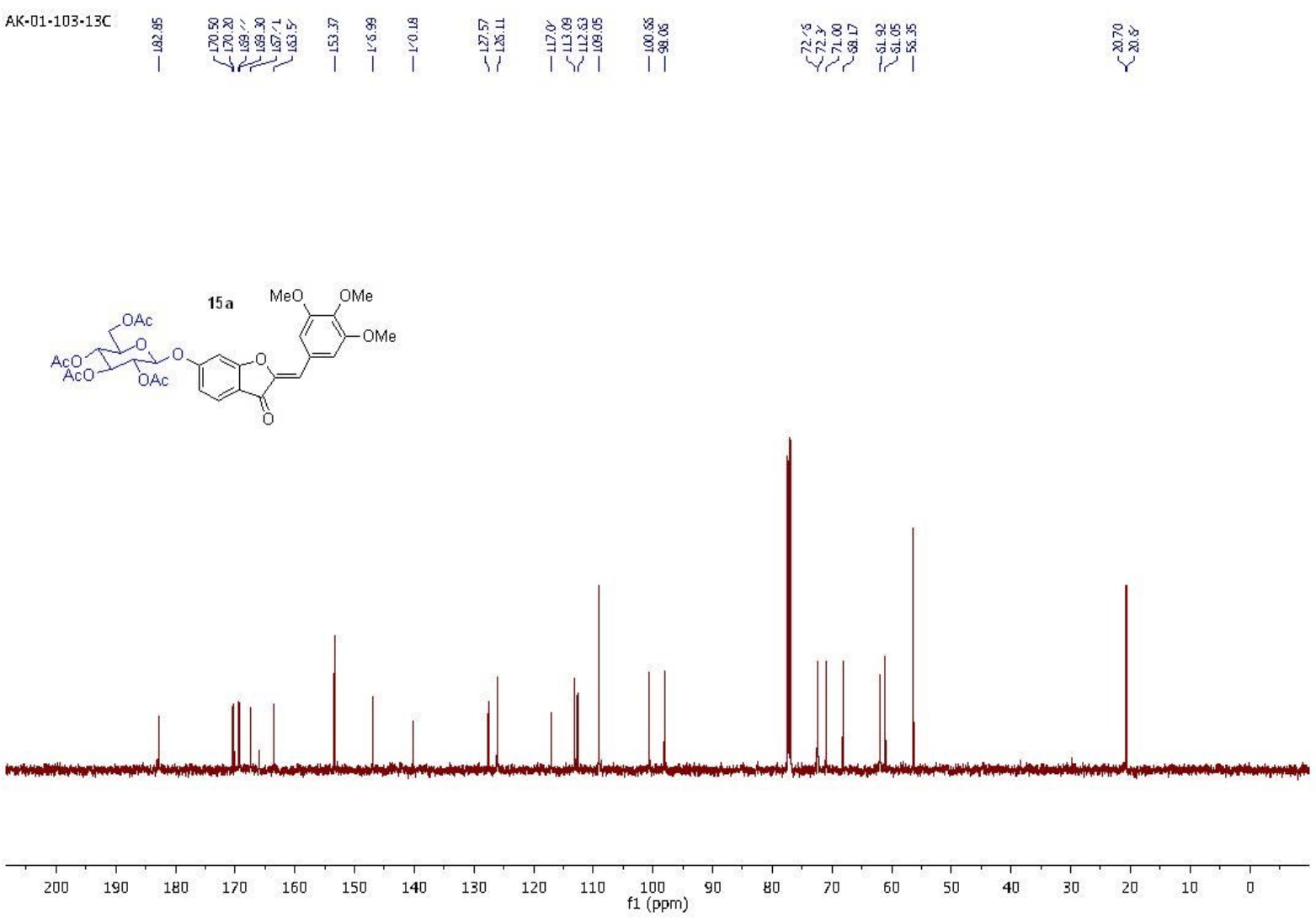

AK-01-90-COSY
13a
Me
f2 (ppm)
f1 (ppm)

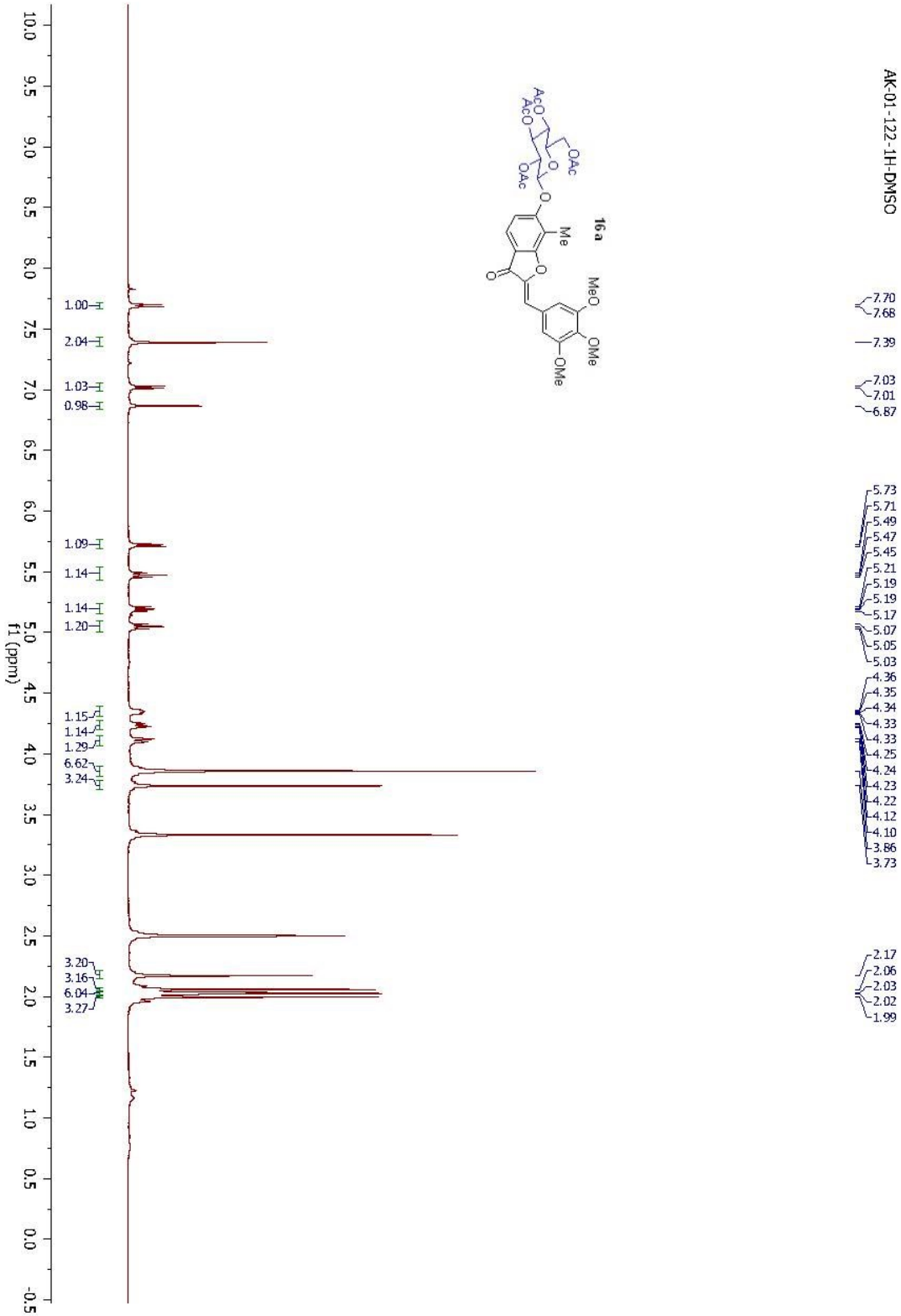

AK-01-91-1H
14a
MeO
OMe
AcO
OAc
f1 (ppm)

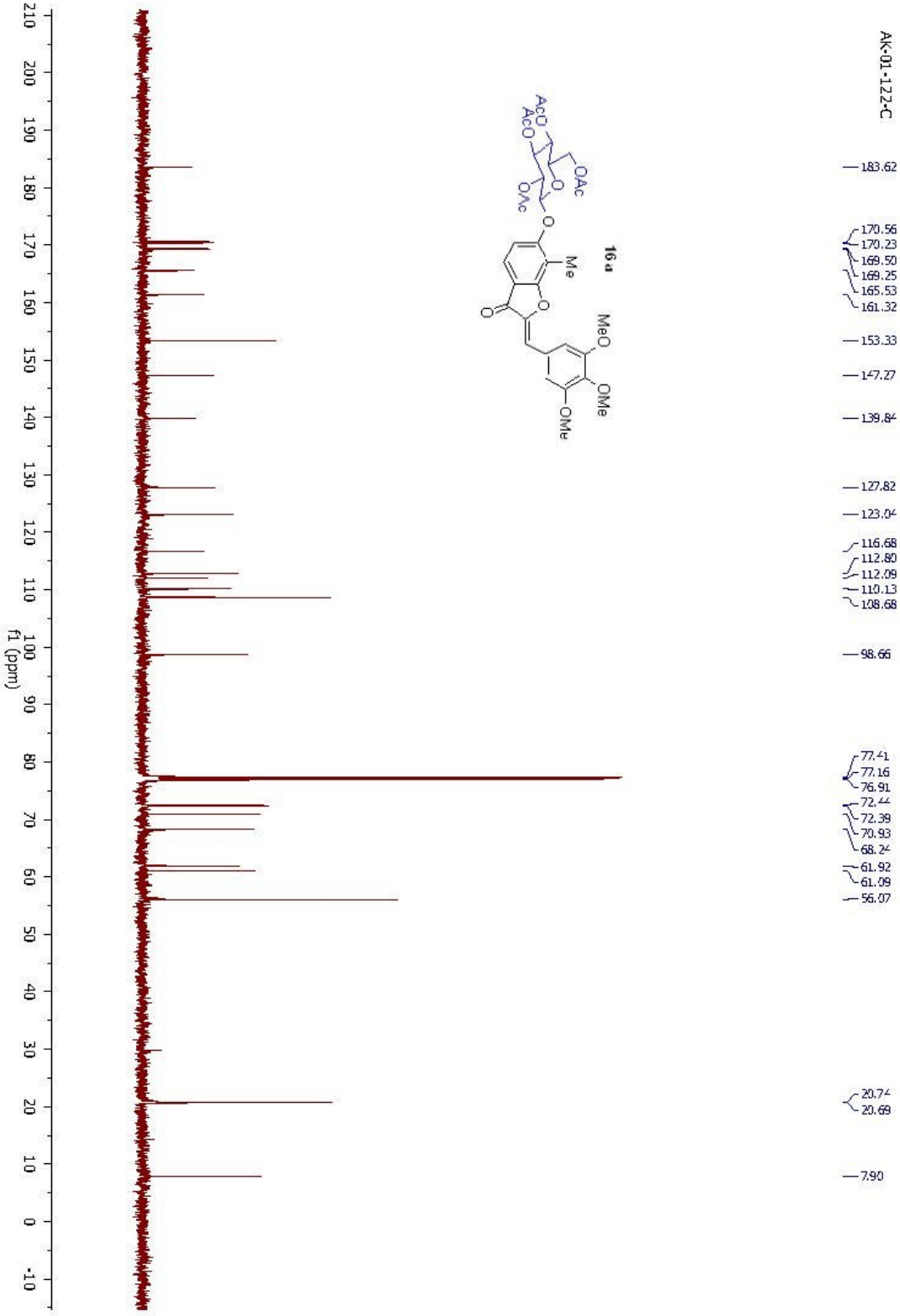

AK-01-91-C
181.97
169.98
169.67
169.38
169.13
167.28
163.52
160.65
147.20
133.70
126.01
115.73
113.39
111.63
109.79
101.70
99.98
96.35
71.86
71.21
70.71
67.91
61.68
55.71
20.78
20.73
20.36
20.31
14a
MeO
OMe
OAc
AcO
AcO
OAc
O
O
O
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


AK-01-91-COSY
f1 (ppm)
f2 (ppm)
14a
AcO
AcO
AcO
OAc
OAc
OAc
O
O
O
O
MeO
OMe

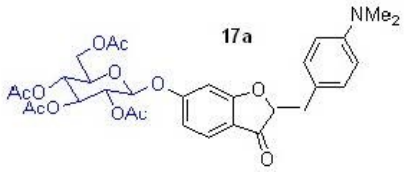

AK-01-103-DMSO
15a
MeO
OMe
OMe
OAc
OAc
OAc
AcO
AcO
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.97
2.00
1.00
1.02
1.03
1.01
1.12
1.12
1.13
1.15
1.15
1.15
6.27
3.17
3.03
2.89
2.81
3.03
7.800
7.783
7.352
7.196
7.192
6.945
6.941
6.928
6.924
6.870
5.857
5.851
5.439
5.420
5.401
5.157
5.141
5.137
5.122
5.065
5.045
5.026
3.853
3.740
2.035
2.025
2.005
1.984

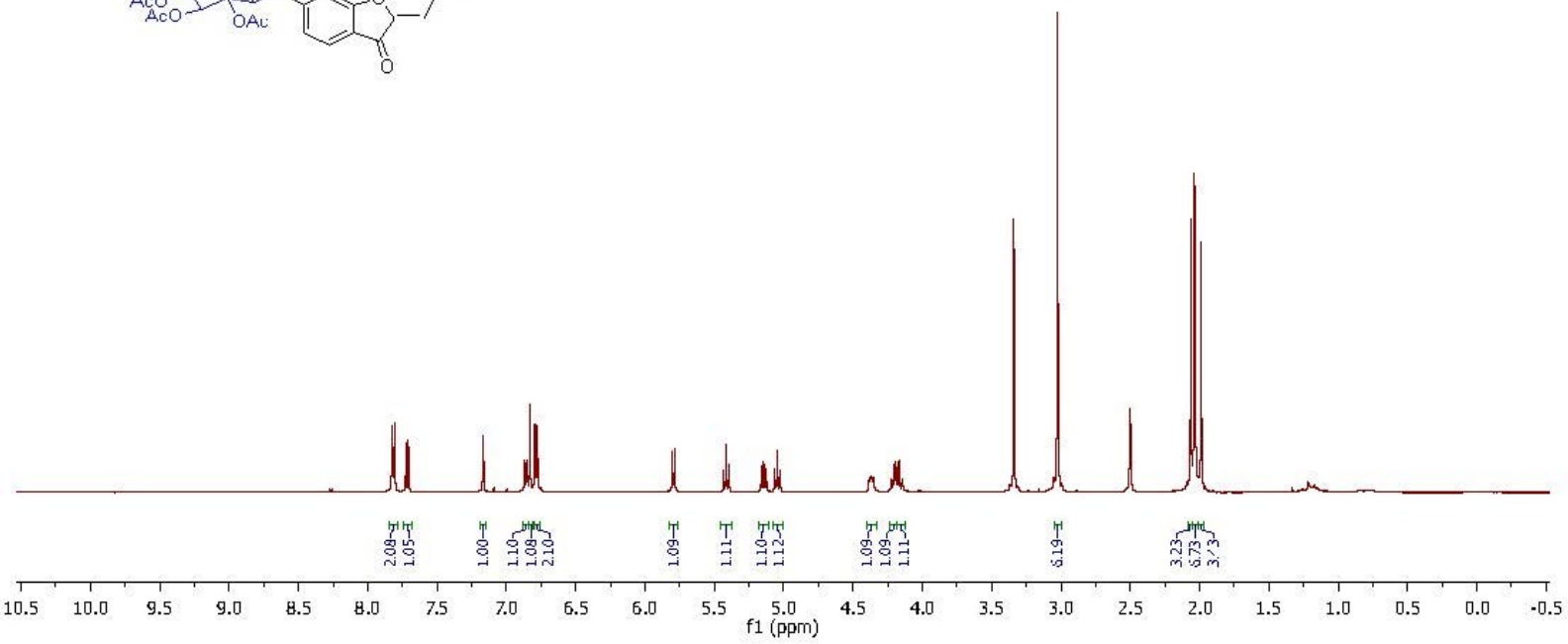

AK-01-103-13C
182.85
170.50
170.20
169.77
169.30
157.71
153.37
145.99
140.18
127.57
125.11
117.07
113.09
112.53
109.05
100.56
98.05
72.45
72.39
71.00
68.17
61.92
61.05
56.35
20.70
20.67
15a
MeO
OMe
OMe
OAc
AcO
AcO
OAc
O
O
O
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

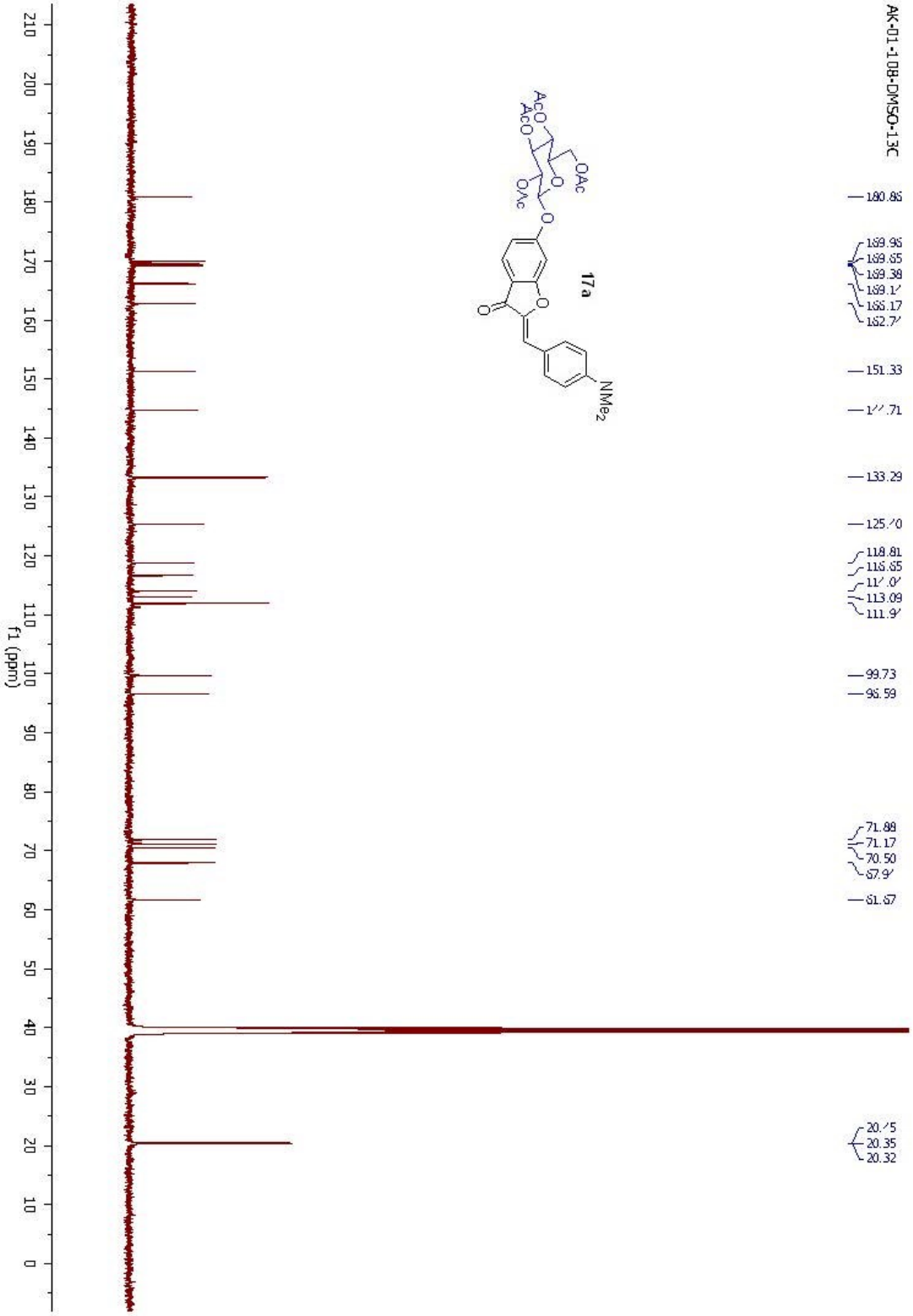

AK-01-122-1H-DMSO
16a
f1 (ppm)
1.00
2.04
1.03
0.98
1.09
1.14
1.14
1.20
1.15
1.14
1.29
6.62
3.24
3.20
3.16
6.04
3.27
7.70
7.68
7.39
7.03
7.01
6.87
5.73
5.71
5.49
5.47
5.45
5.21
5.19
5.19
5.17
5.07
5.05
5.03
4.36
4.35
4.34
4.33
4.33
4.25
4.24
4.23
4.22
4.12
4.10
3.86
3.73
2.17
2.06
2.03
2.02
1.99

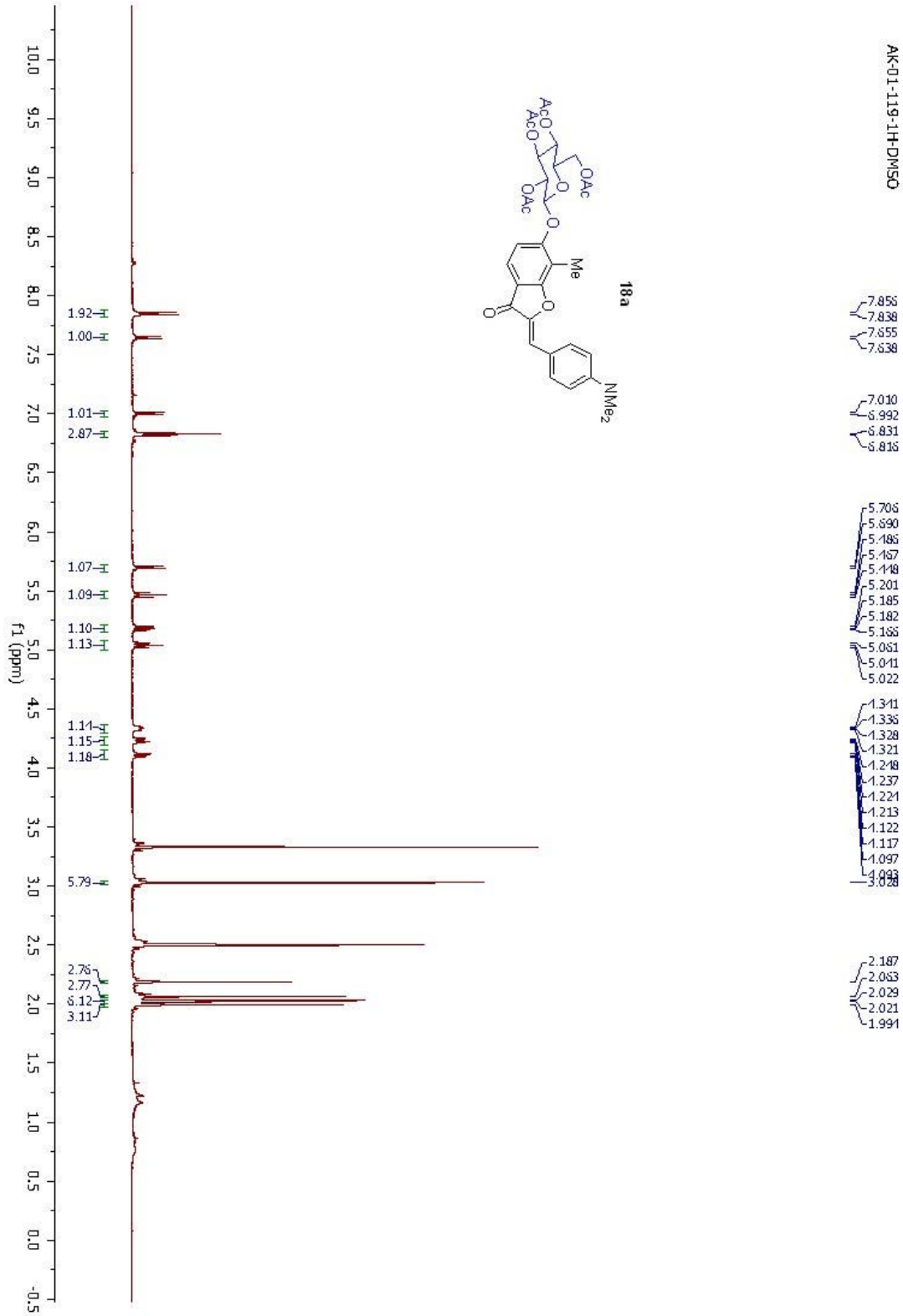

AK-01-122-C
183.62
170.56
170.23
169.50
169.25
165.53
161.32
153.33
147.27
139.84
127.82
123.04
116.68
112.80
112.09
110.13
108.68
98.66
77.41
77.16
76.91
72.44
72.39
70.93
68.24
61.92
61.09
56.07
20.74
20.69
7.90
16a
Me
MeO
OMe
OMe
AcO
AcO
OAc
OAc
f1 (ppm)

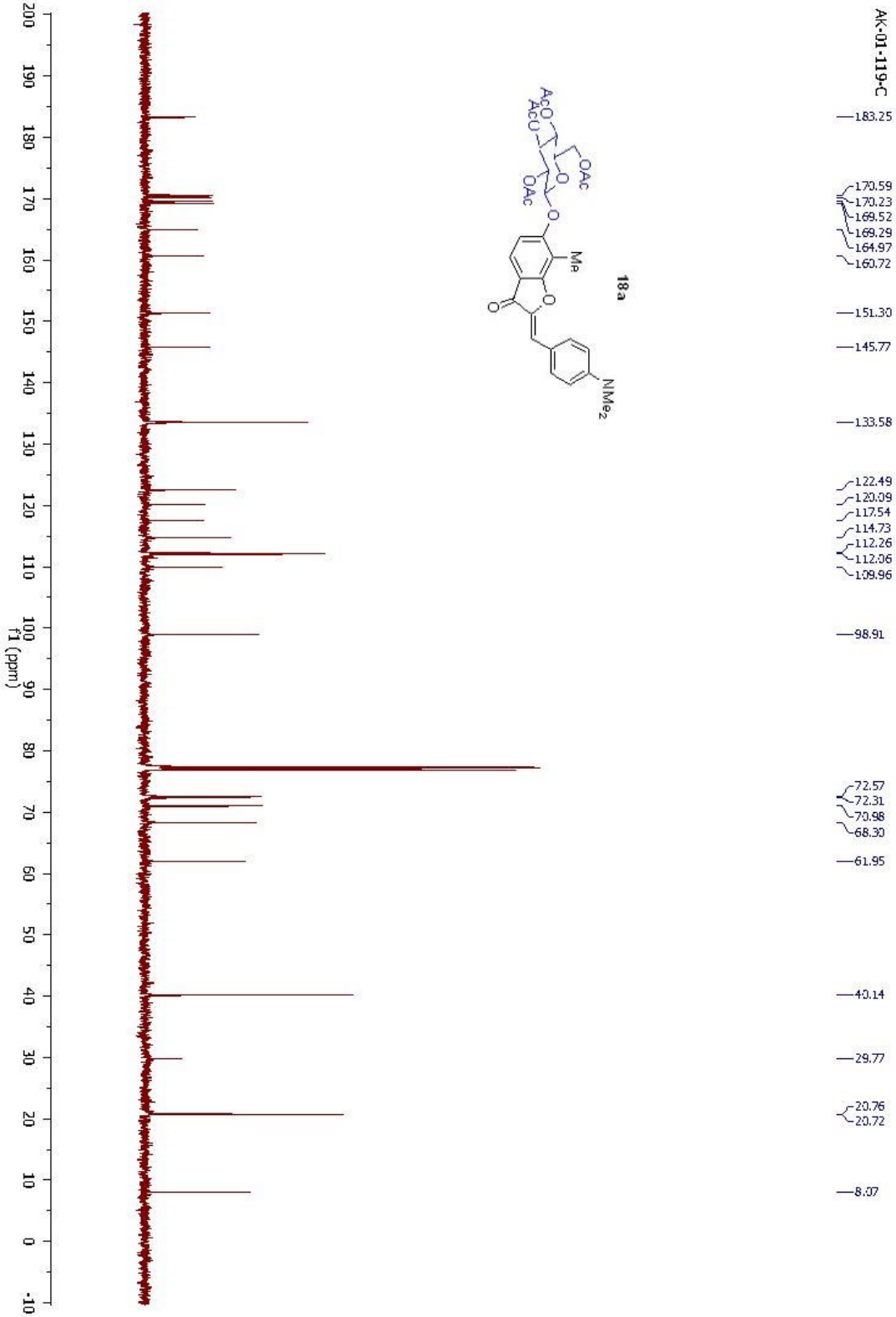
AK-01-108-dmso-1H

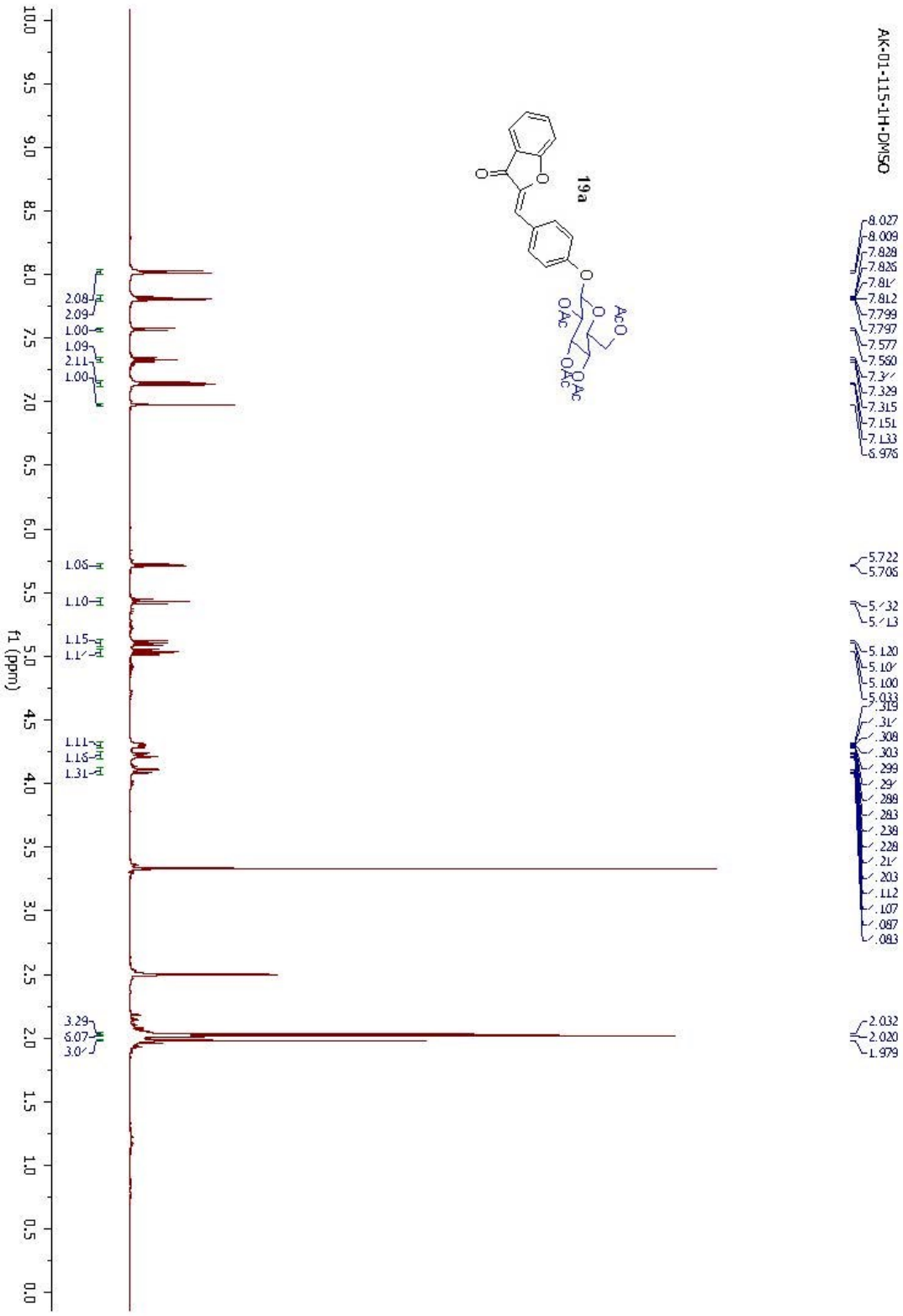


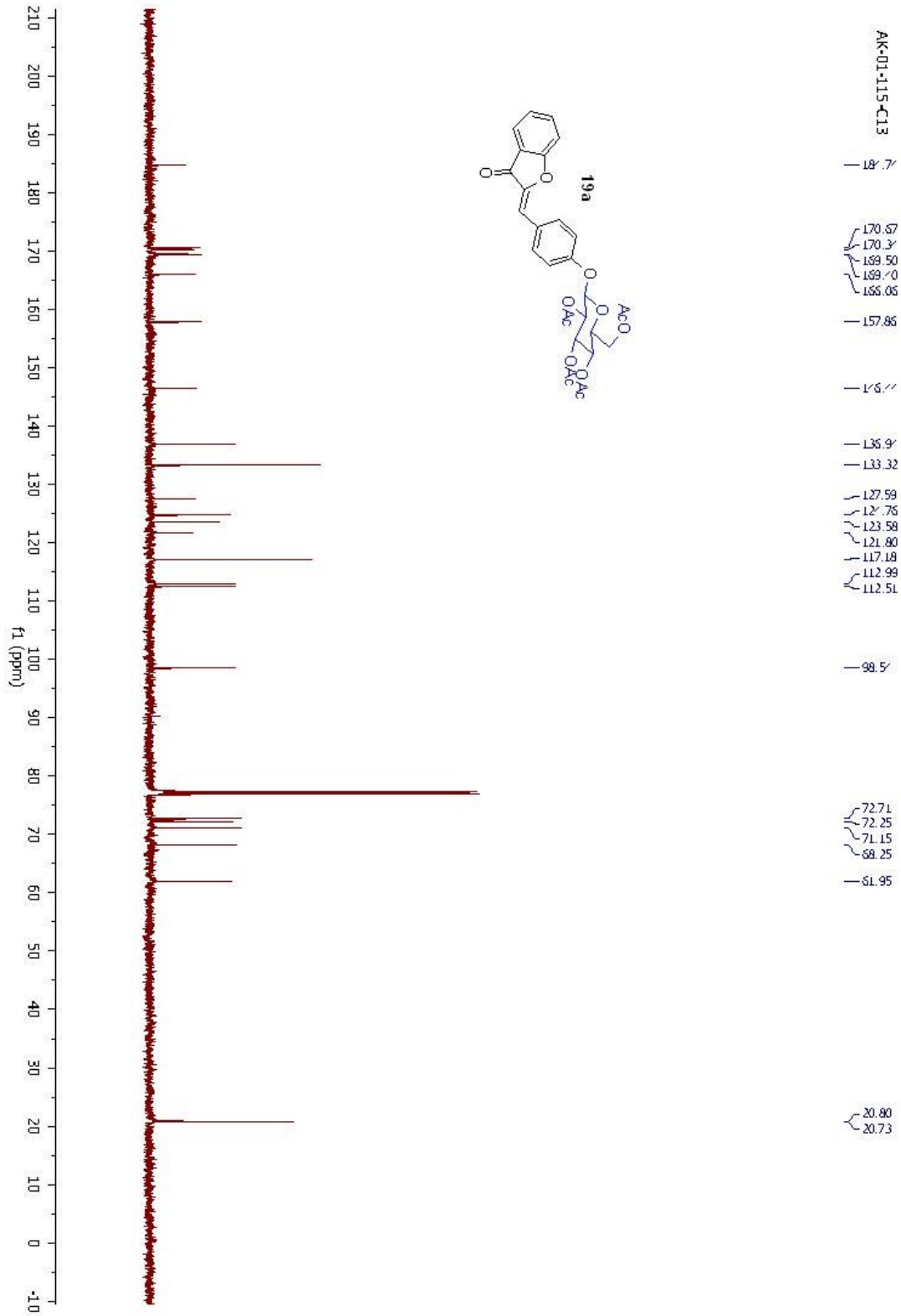


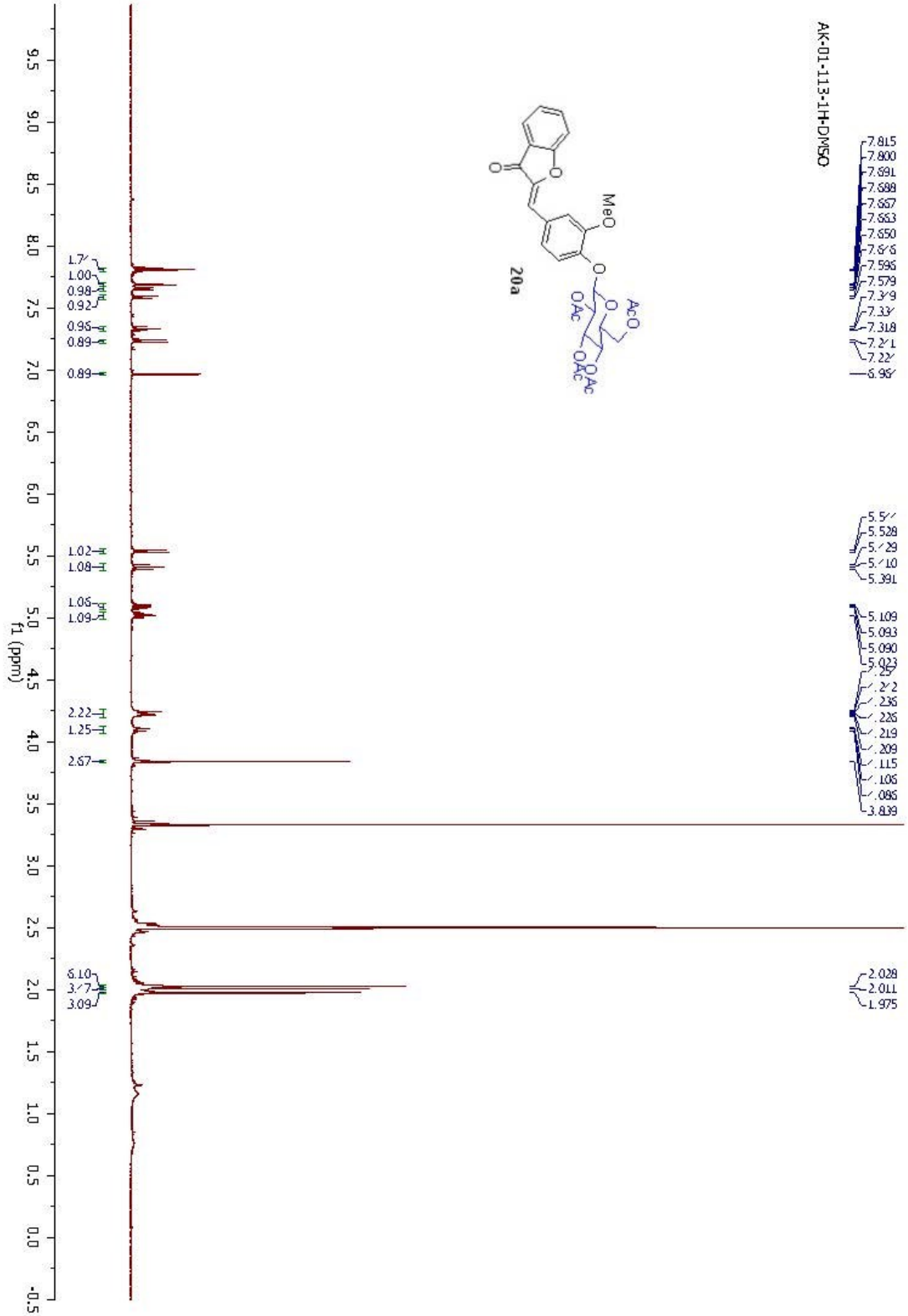

AK-01-108-DMSO-13C
180.86
169.96
169.65
169.38
169.17
166.17
162.77
151.33
147.71
133.29
125.70
118.81
116.65
114.04
113.09
111.97
99.73
96.59
71.88
71.17
70.50
67.94
61.67
20.75
20.35
20.32
17a
NMe2
f1 (ppm)

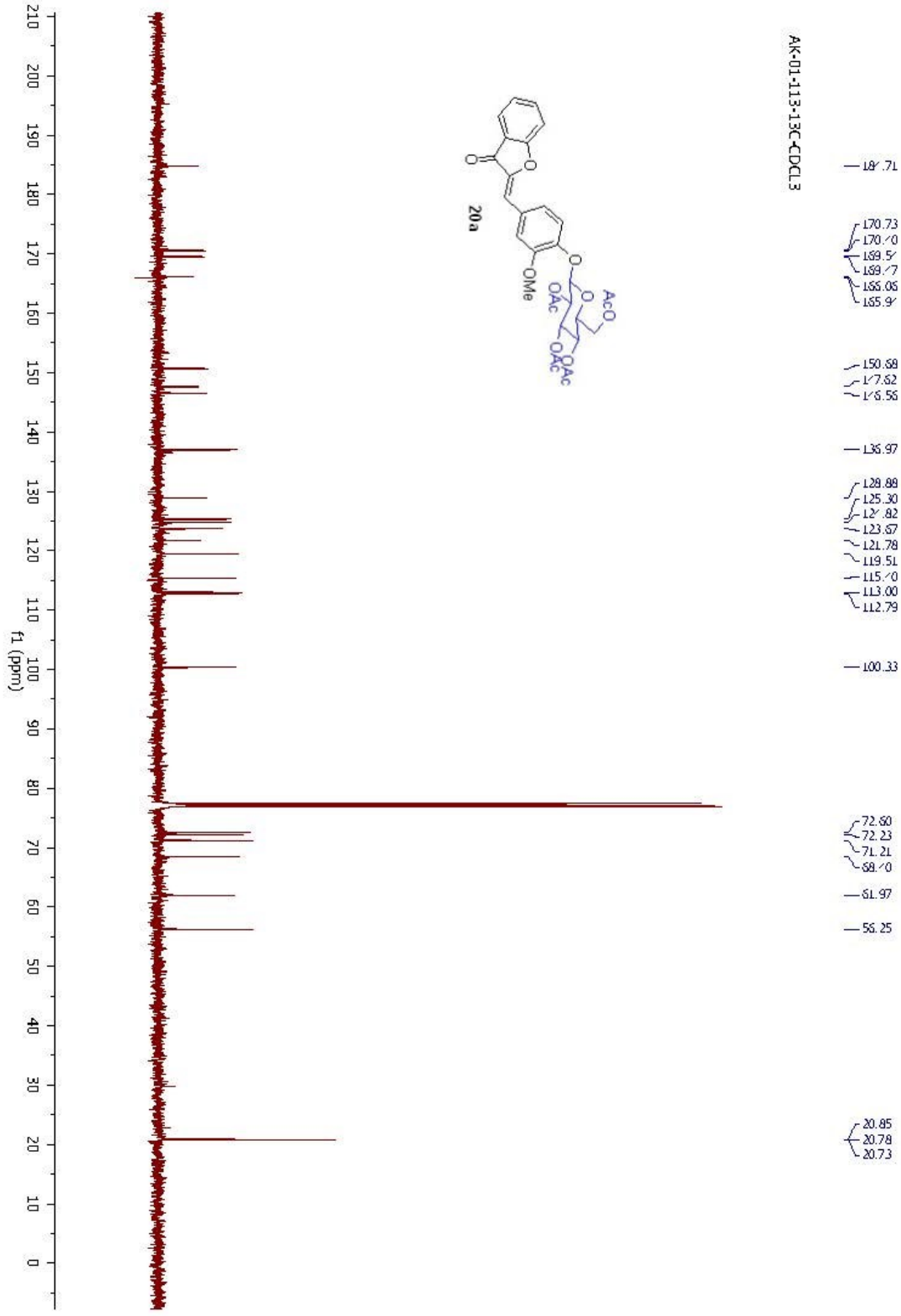

AK-01-119-1H-DMSO
18a
Me
NMe2
AcO
AcO
OAc
OAc
O
O
O
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.92
1.00
1.01
2.87
1.07
1.09
1.10
1.13
1.14
1.15
1.18
5.79
2.76
2.77
6.12
3.11
7.856
7.838
7.655
7.638
7.010
6.992
6.831
6.816
5.706
5.690
5.486
5.467
5.448
5.201
5.185
5.182
5.166
5.061
5.041
5.022
1.341
1.336
1.328
1.321
1.248
1.237
1.221
1.213
1.122
1.117
1.097
3.028
2.187
2.063
2.029
2.021
1.991

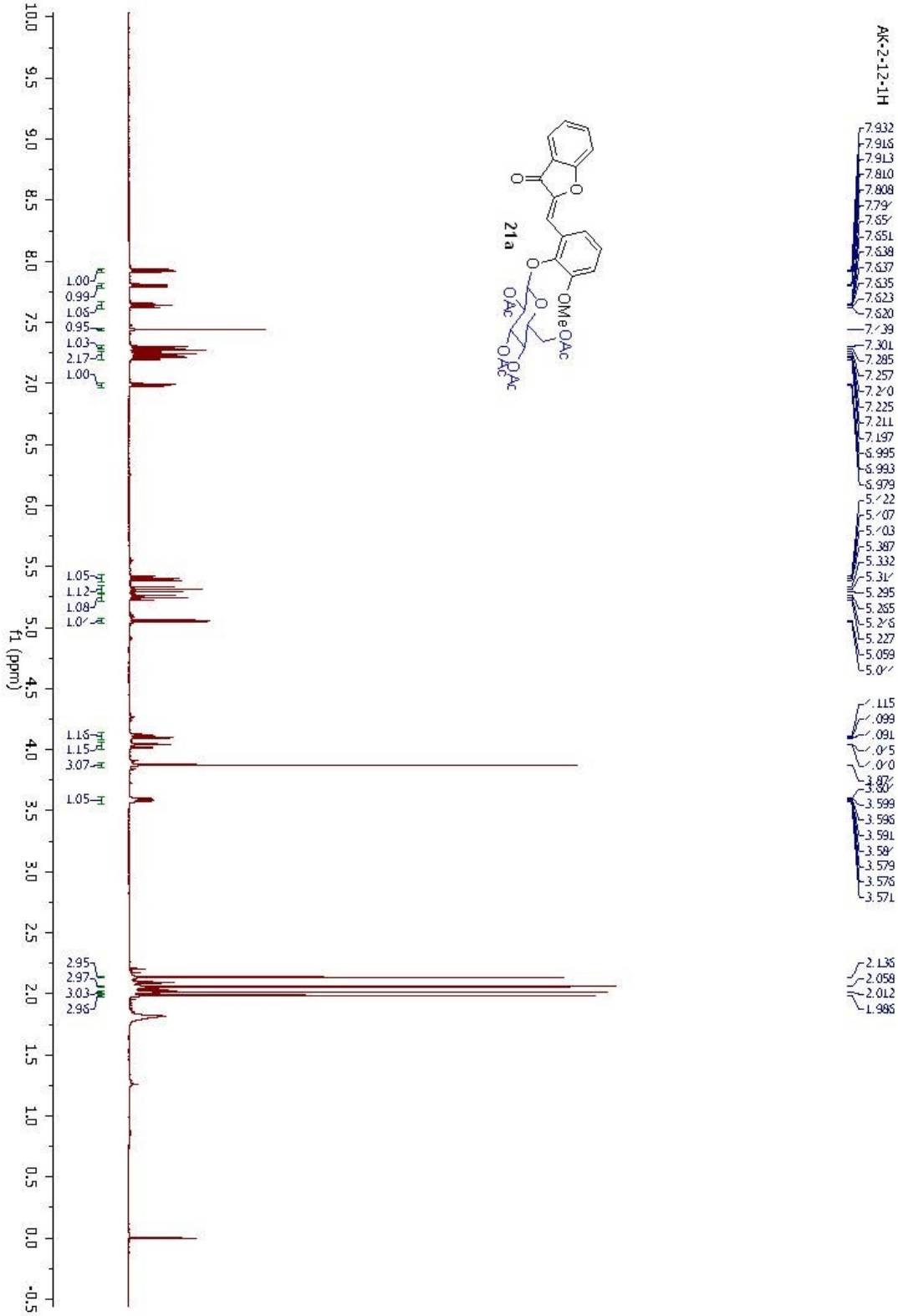

Ak-01-119-C
183.25
170.59
170.23
169.52
169.29
164.97
160.72
151.30
145.77
133.58
122.49
120.09
117.54
114.73
112.26
112.06
109.96
98.91
72.57
72.31
70.98
68.30
61.95
40.14
29.77
20.76
20.72
8.07
18a
f1 (ppm)

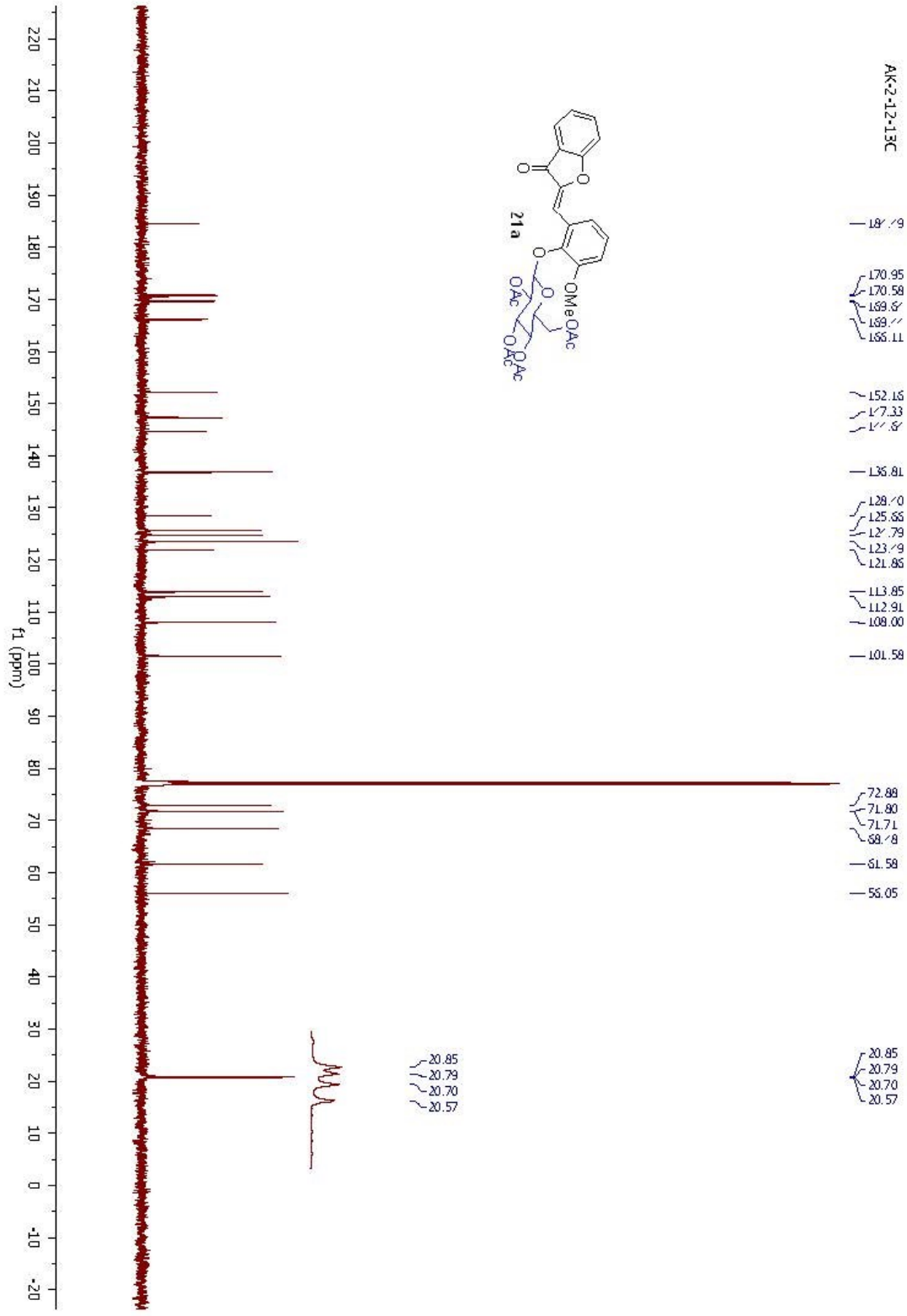

AK-01-115-1H-DMSO
19a
f1 (ppm)

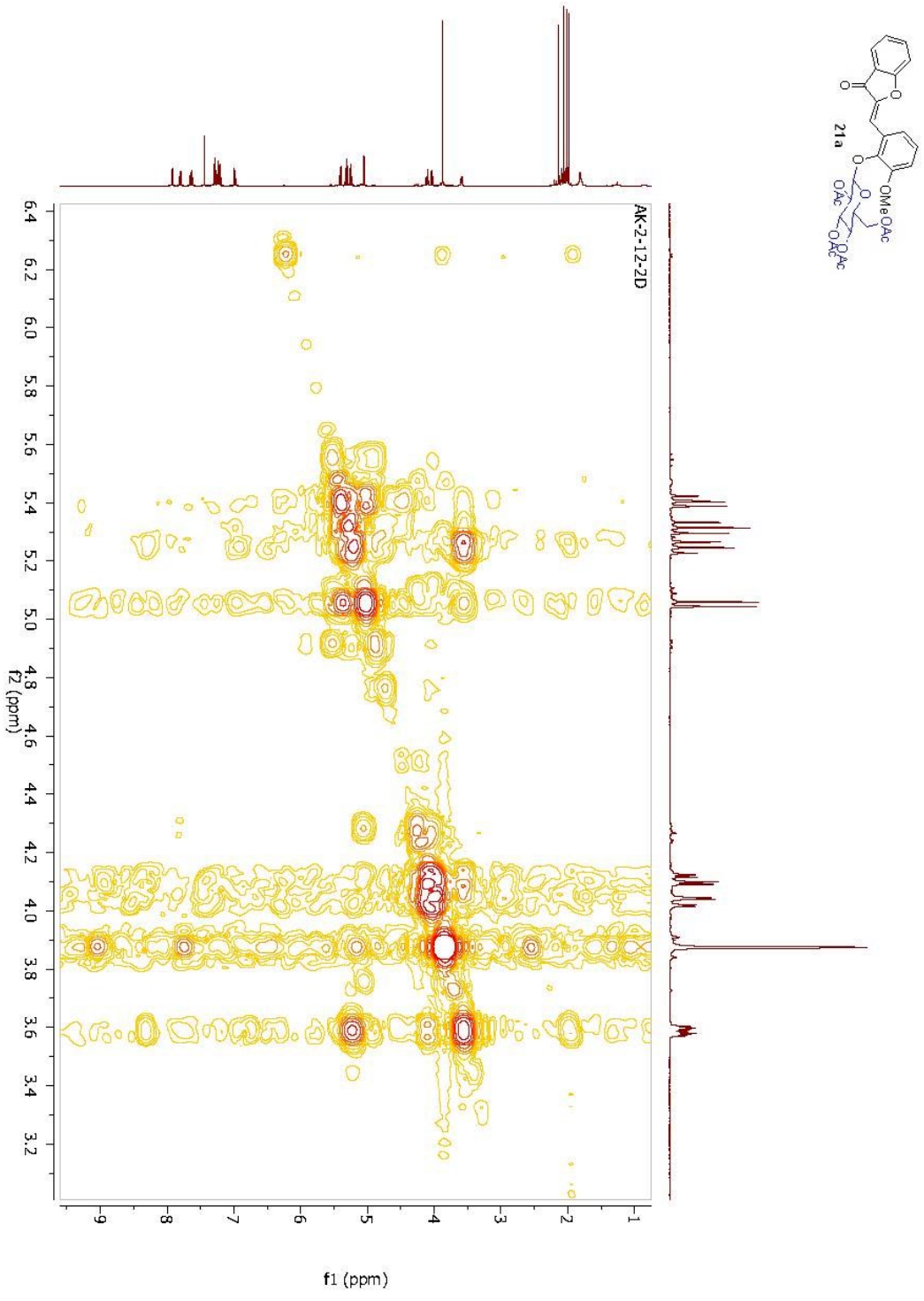

AK-01-115-C13
19a
AcO
OAc
OAc
OAc
OAc
168.77
170.67
170.34
169.50
169.10
166.06
157.86
136.94
133.32
127.59
124.76
123.58
121.80
117.18
112.99
112.51
98.54
72.71
72.25
71.15
68.25
61.95
20.80
20.73
f1 (ppm)

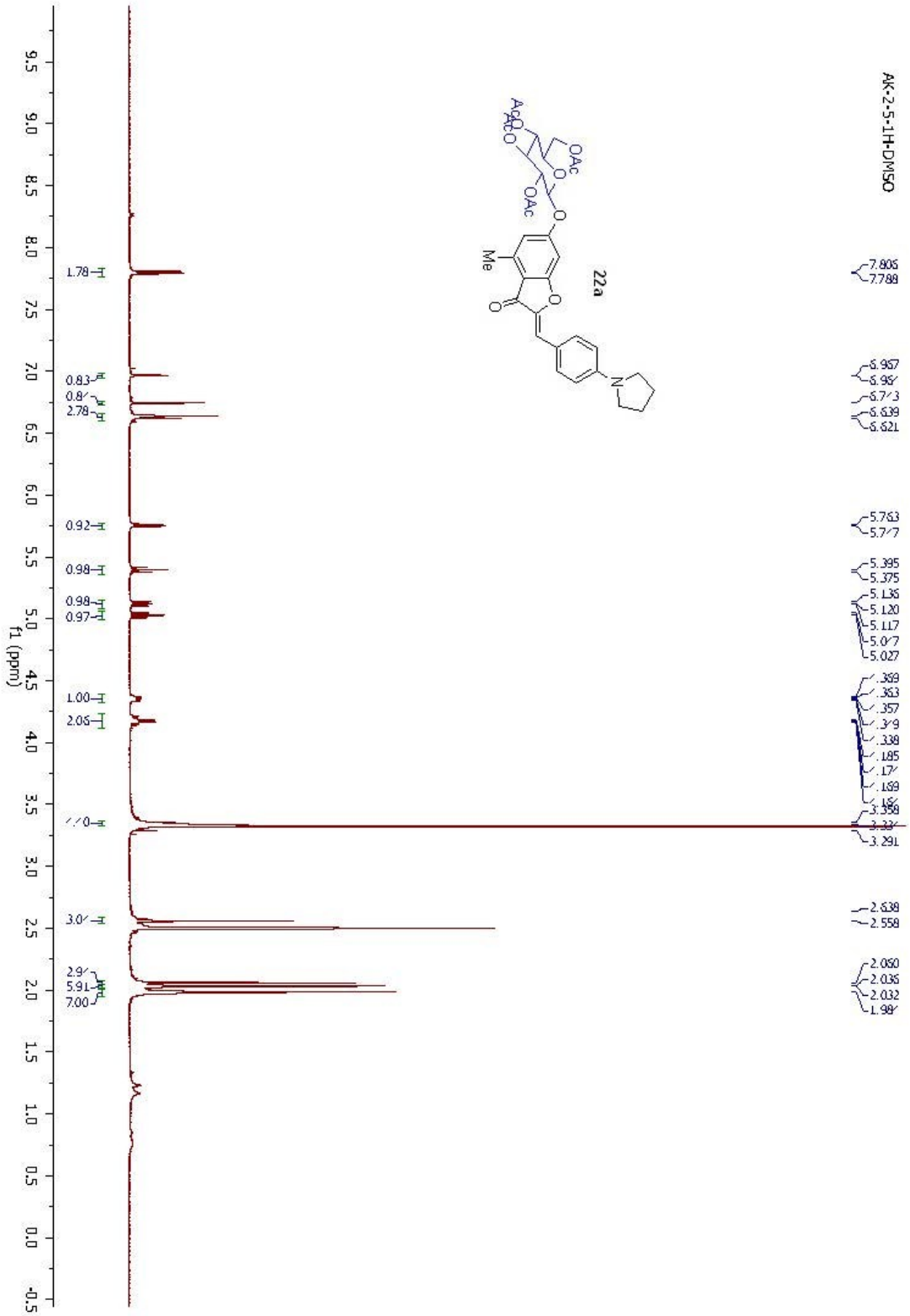

AK-01-113-1H-DMSO
20a
MeO
AcO
OAc
OAc
OAc
f1 (ppm)

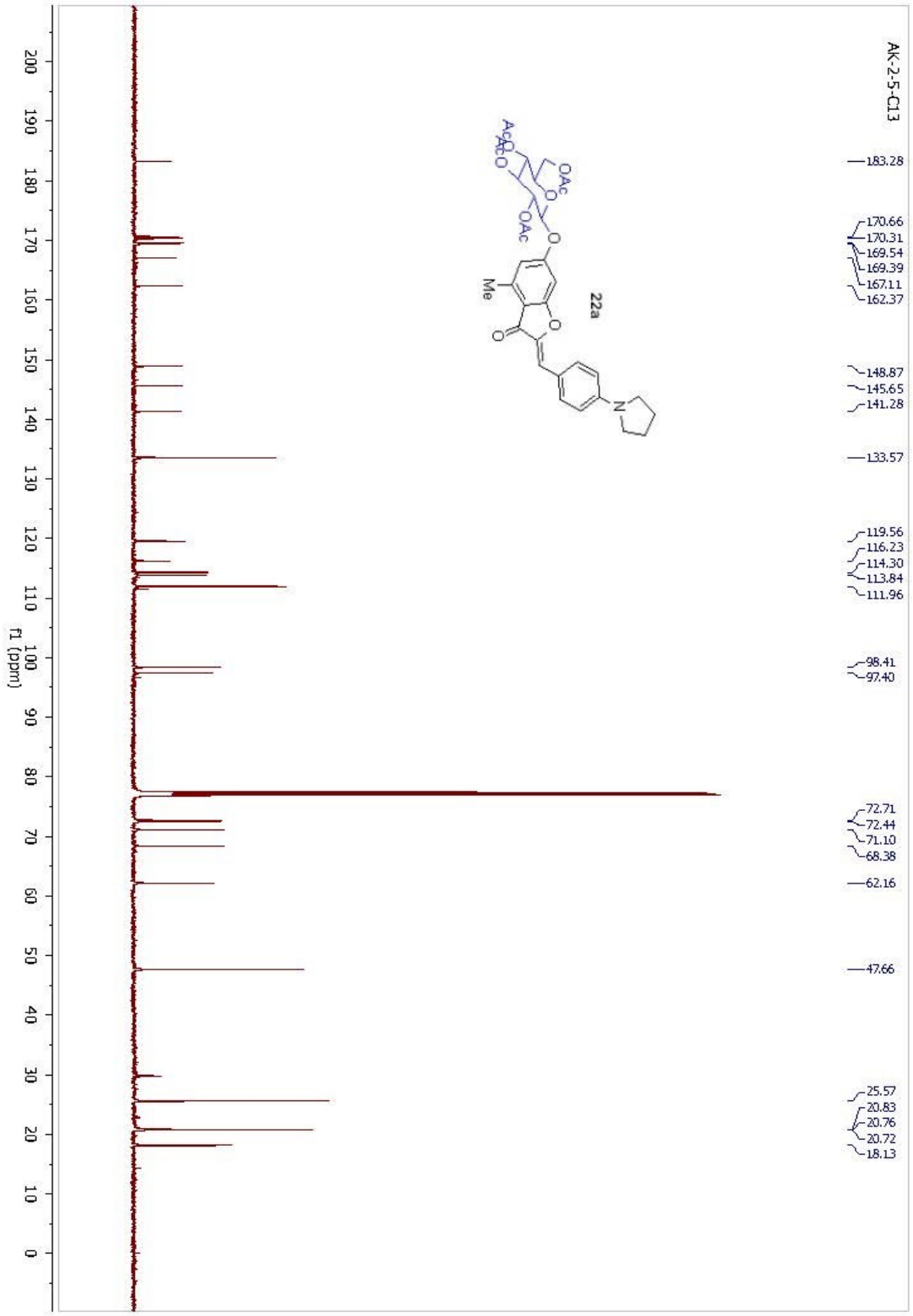

AK-01-113-13C-CDCL3
20a
OMe
OAc
OAc
OAc
AcO
O
O
O
O
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
187.71
170.73
170.70
169.57
169.47
155.05
155.97
150.68
147.62
146.56
136.97
128.88
125.30
124.82
123.67
121.78
119.51
115.70
113.00
112.79
100.33
72.60
72.23
71.21
68.70
61.97
56.25
20.85
20.78
20.73

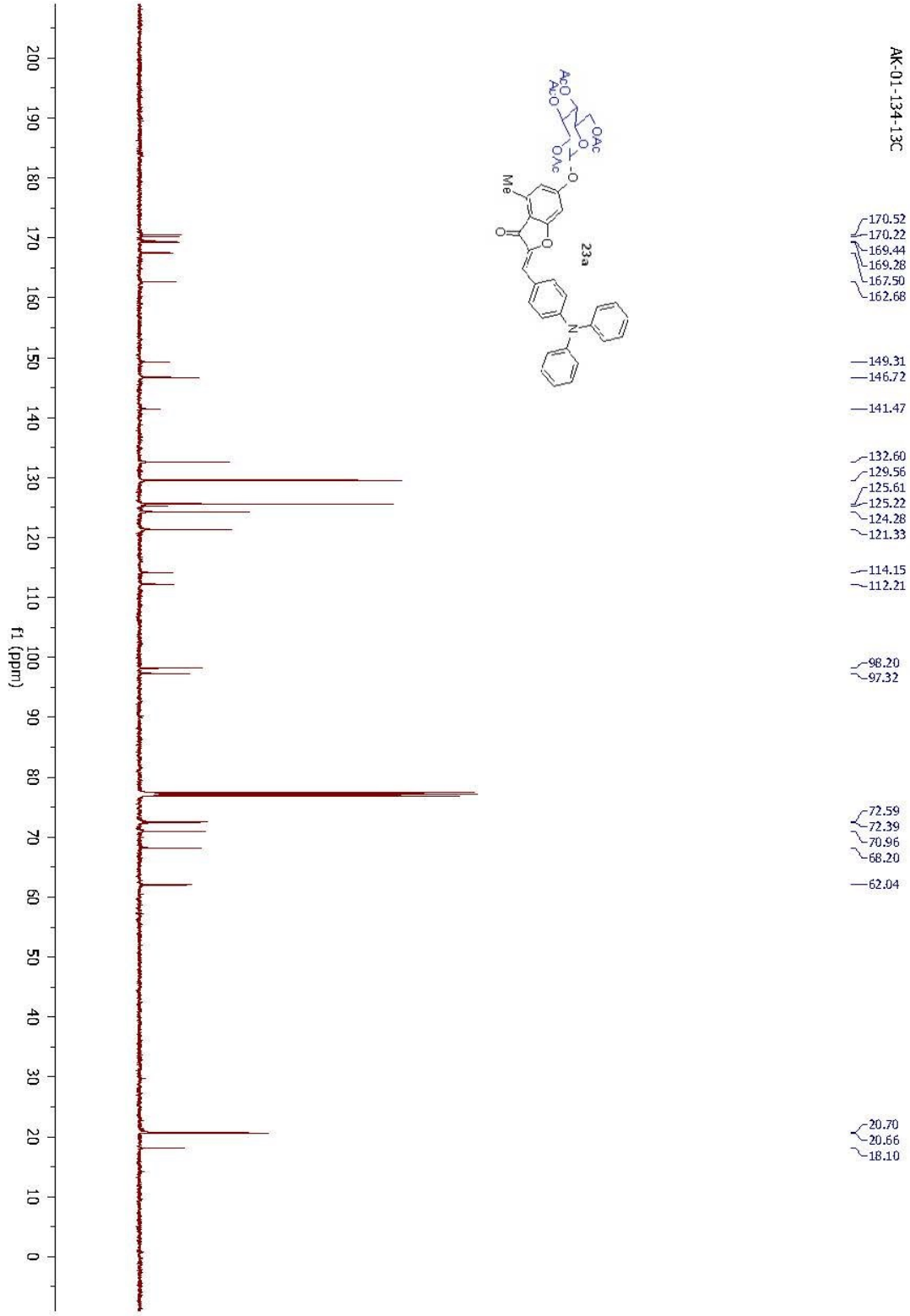

AK-2-12-1H
21a
OMeOAc
OAc
OAc
OAc
f1 (ppm)

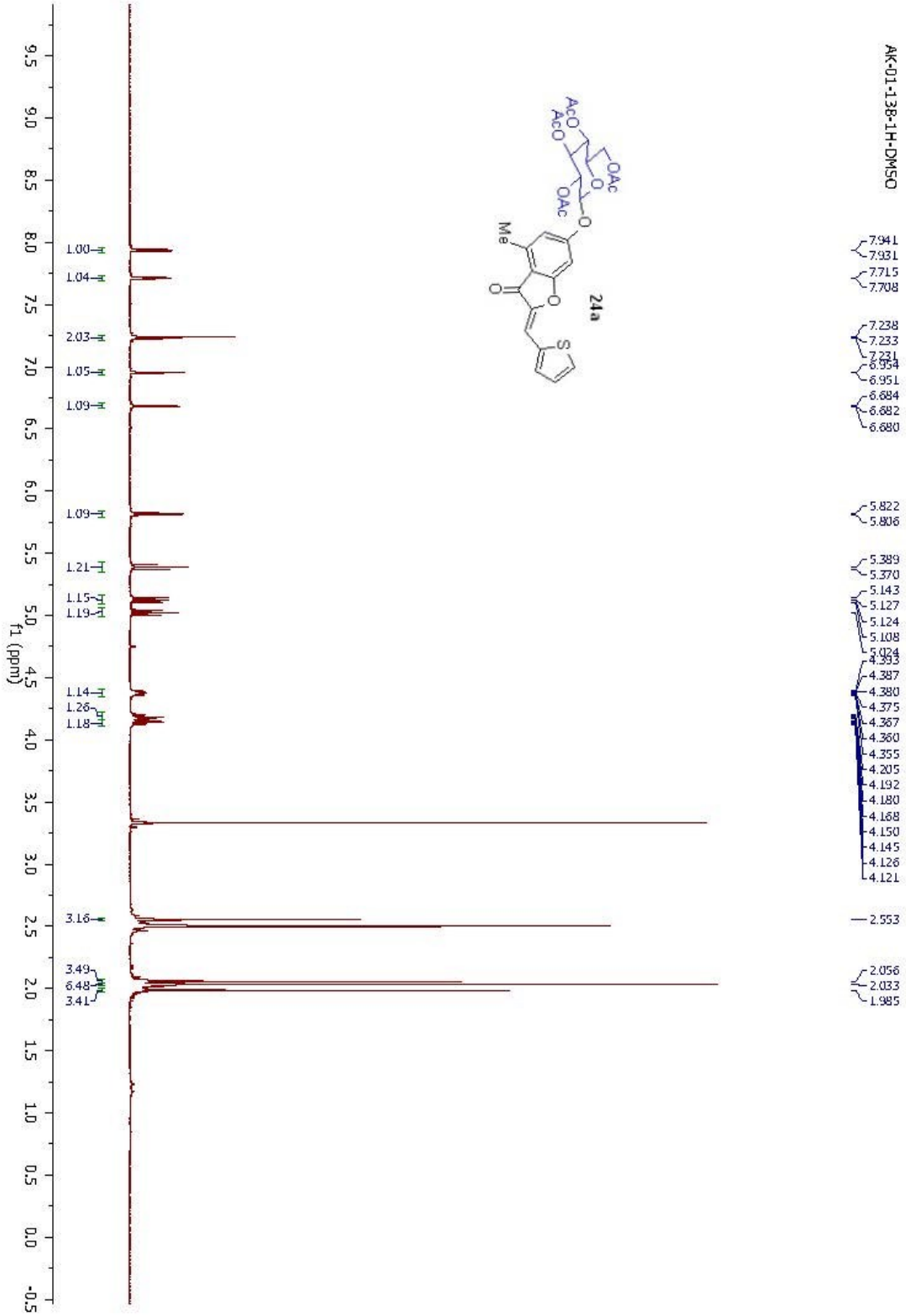

AK-2-12-13C
21a
OMe
OAc
OAc
OAc
OAc
170.95
170.58
169.87
169.77
155.11
152.16
147.33
137.87
136.81
128.70
125.55
123.79
123.79
121.86
113.85
112.91
109.00
101.58
72.88
71.80
71.71
69.78
61.58
56.05
20.85
20.79
20.70
20.57
20.85
20.79
20.70
20.57
f1 (ppm)

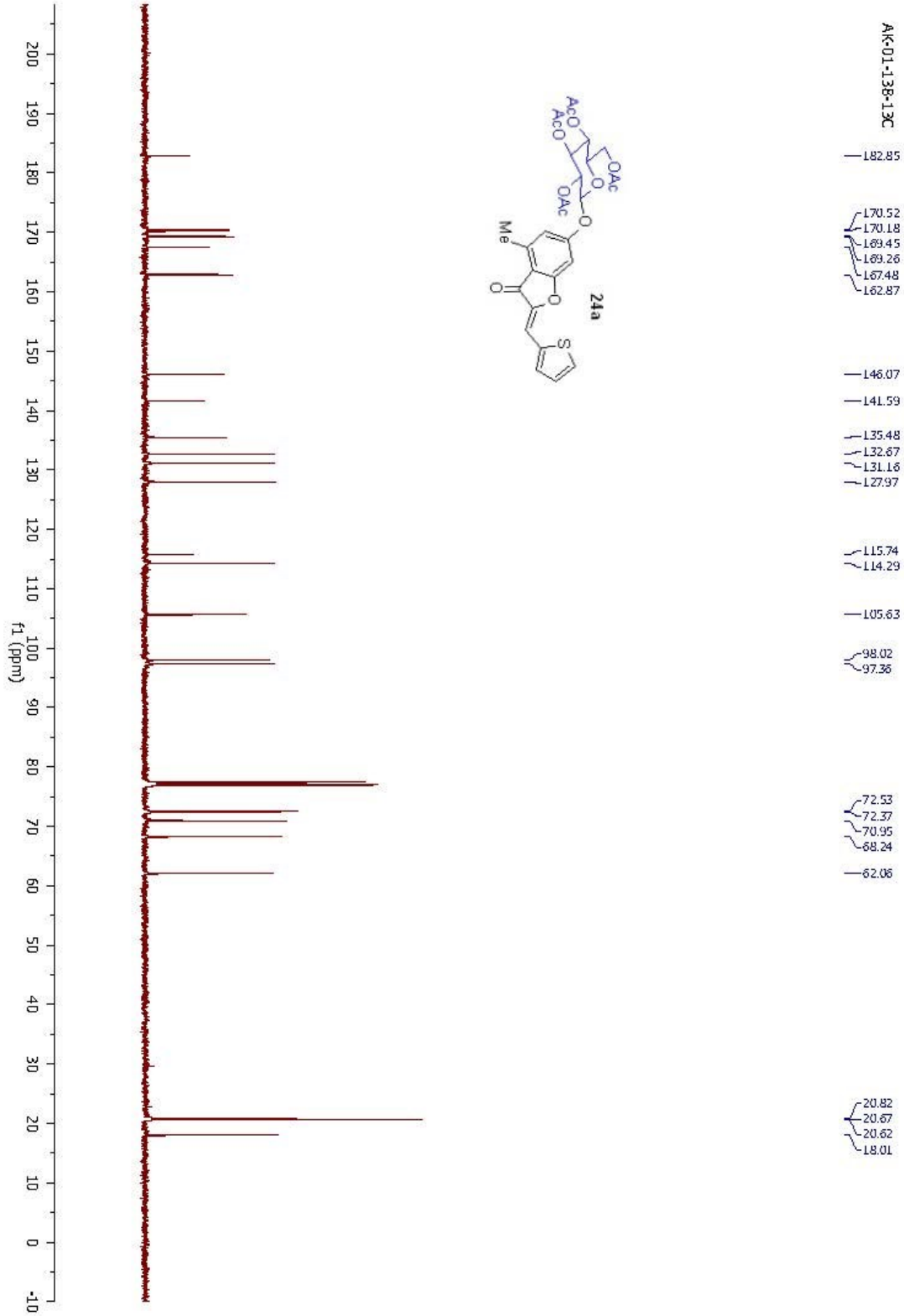

AK-2-12-2D
21a
f2 (ppm)
f1 (ppm)

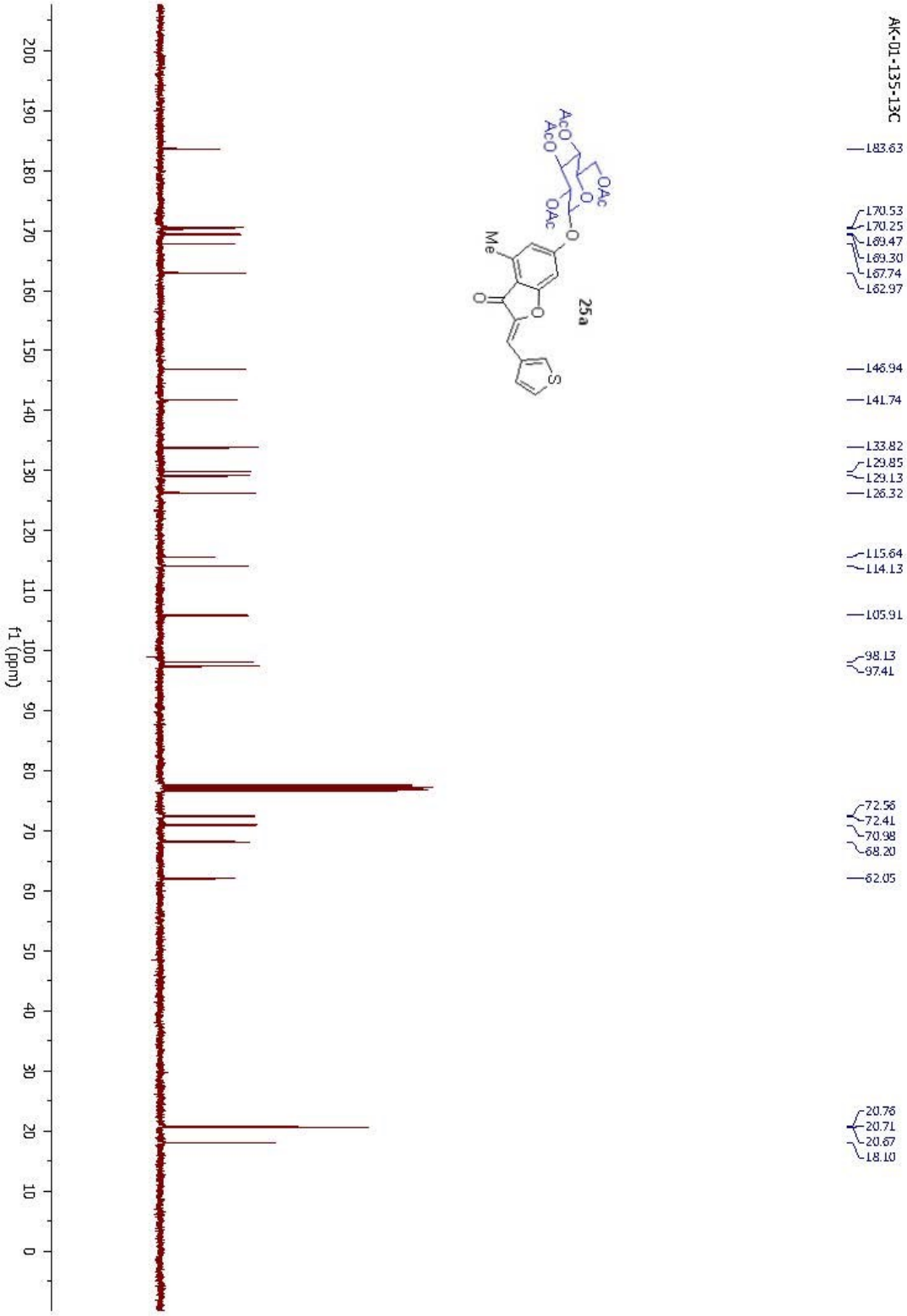

AK-2-5-1H-DMSO
22a
Me
OAc
AcO
f1 (ppm)

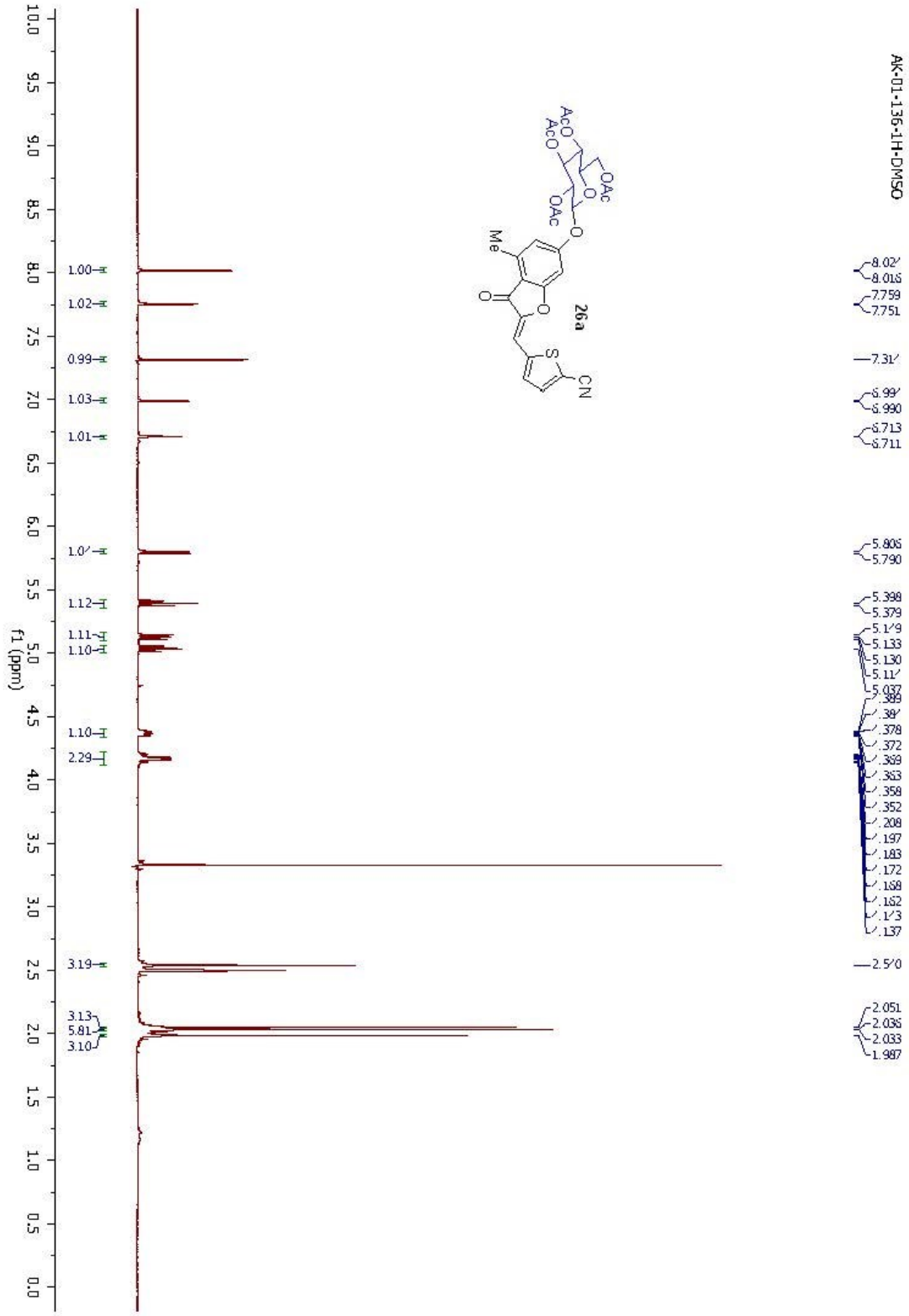

AK-2-5-C13
183.28
170.66
170.31
169.54
169.39
167.11
162.37
148.87
145.65
141.28
133.57
119.56
116.23
114.30
113.84
111.96
98.41
97.40
72.71
72.44
71.10
68.38
62.16
47.66
25.57
20.83
20.76
20.72
18.13
22a
Me
OAc
AcO
AcO
O
N
f1 (ppm)

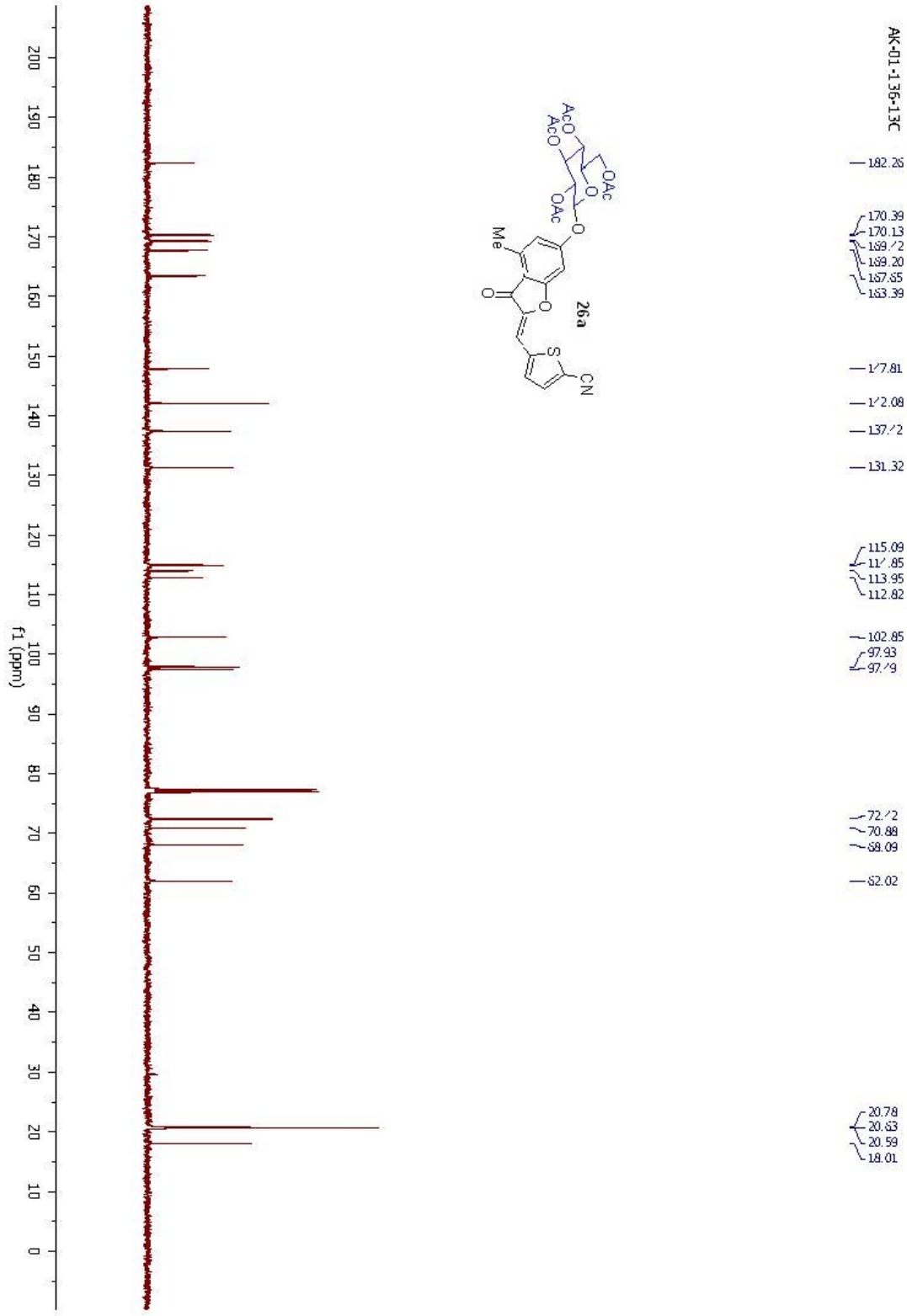

AK-01-134-13C
170.52
170.22
169.44
169.28
167.50
162.68
149.31
146.72
141.47
132.60
129.56
125.61
125.22
124.28
121.33
114.15
112.21
98.20
97.32
72.59
72.39
70.96
68.20
62.04
20.70
20.66
18.10
f1 (ppm)
23a
Me
OAc
AcO
AcO
OAc

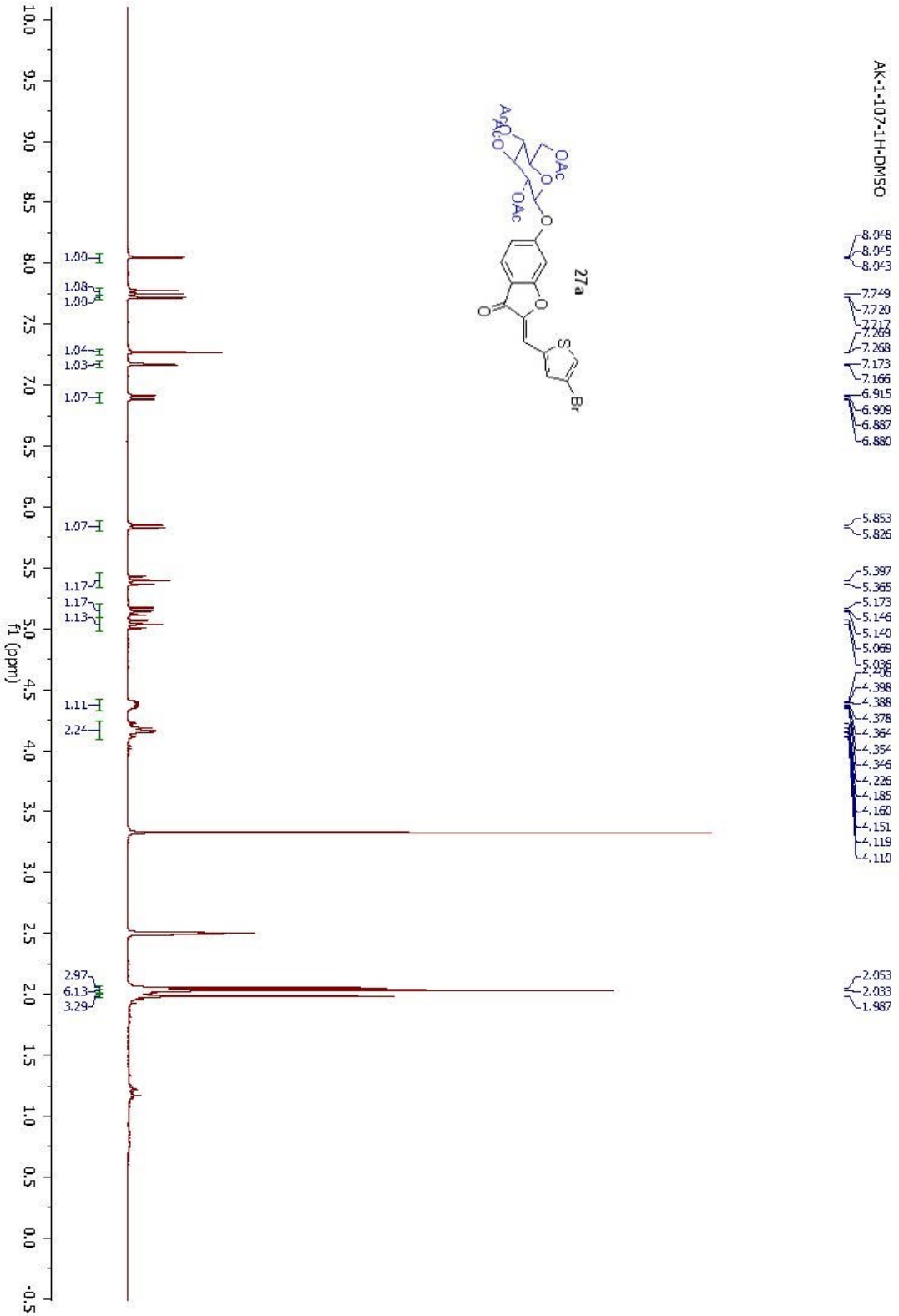

AK-01-138-1H-DMSO
24a
Me
AcO
AcO
OAc
OAc
O
O
O
O
S
f1 (ppm)
1.00
1.04
2.03
1.05
1.09
1.09
1.21
1.15
1.19
1.14
1.26
1.18
3.16
3.49
6.48
3.41
7.941
7.931
7.715
7.708
7.238
7.233
7.231
6.954
6.951
6.684
6.682
6.680
5.822
5.806
5.389
5.370
5.143
5.127
5.124
5.108
5.024
4.393
4.387
4.380
4.375
4.367
4.360
4.355
4.205
4.192
4.180
4.168
4.150
4.145
4.126
4.121
2.553
2.056
2.033
1.985

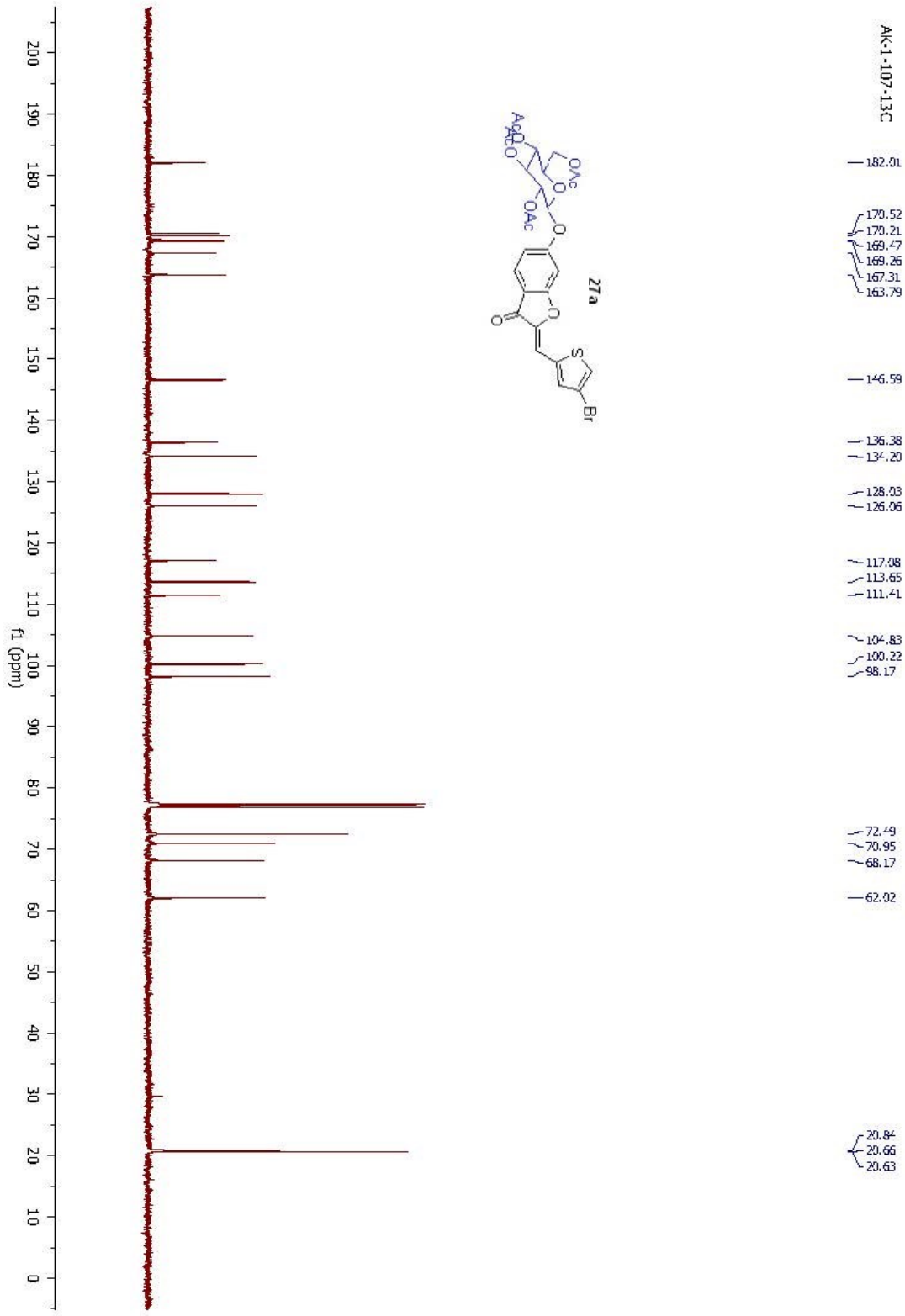

AK-01-138-13C
182.85
170.52
170.18
169.45
169.26
167.48
162.87
146.07
141.59
135.48
132.67
131.16
127.97
115.74
114.29
105.63
98.02
97.36
72.53
72.37
70.95
68.24
62.06
20.82
20.67
20.62
18.01
f1 (ppm)
24a

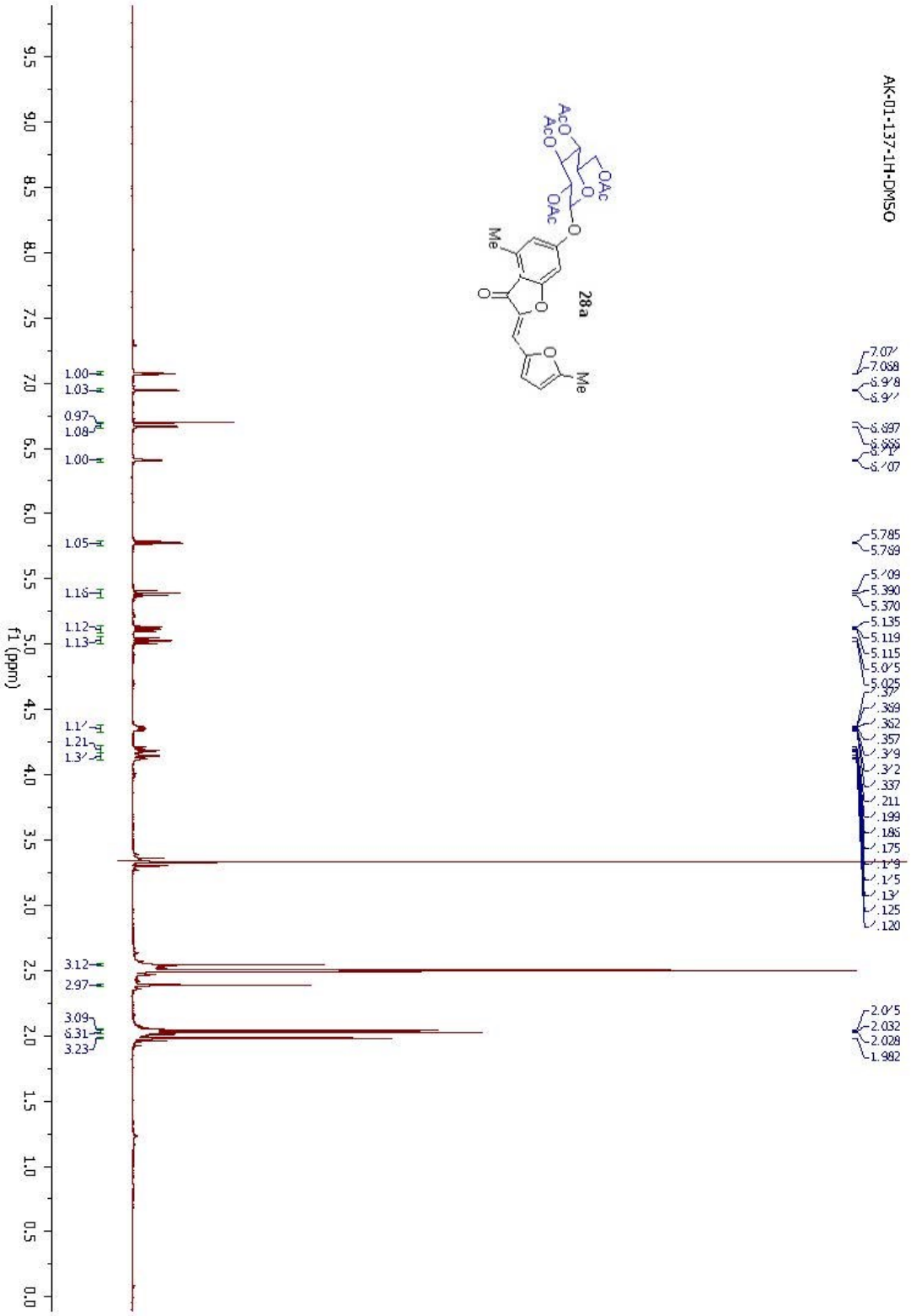

AK-01-135-13C
183.63
170.53
170.25
169.47
169.30
167.74
162.97
146.94
141.74
133.82
129.85
129.13
126.32
115.64
114.13
105.91
98.13
97.41
72.56
72.41
70.98
68.20
62.05
20.76
20.71
20.67
18.10
AcO
AcO
AcO
OAc
OAc
O
Me
O
O
S
25a
f1 (ppm)

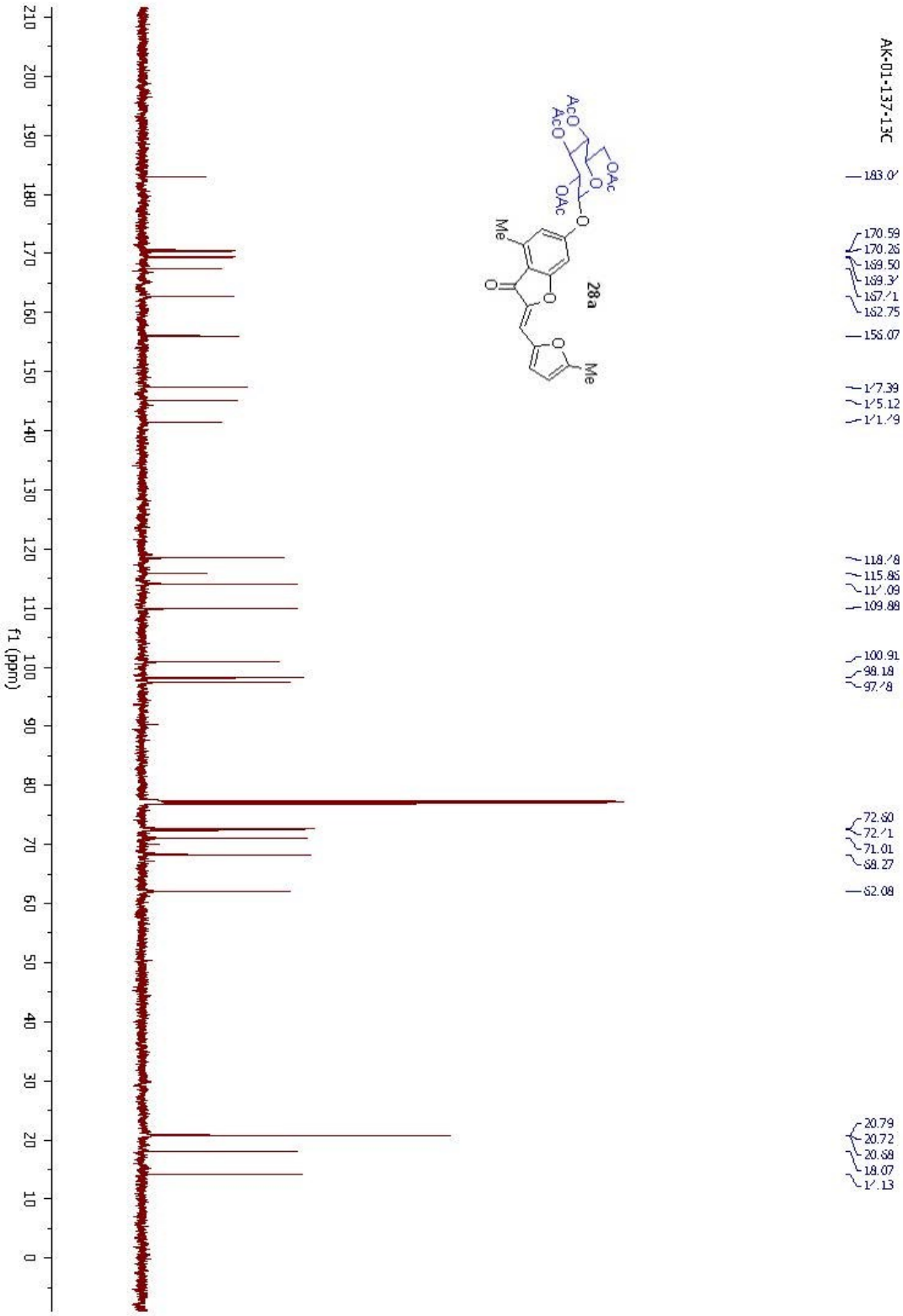

AK-01-136-1H-DMSO
26a
f1 (ppm)

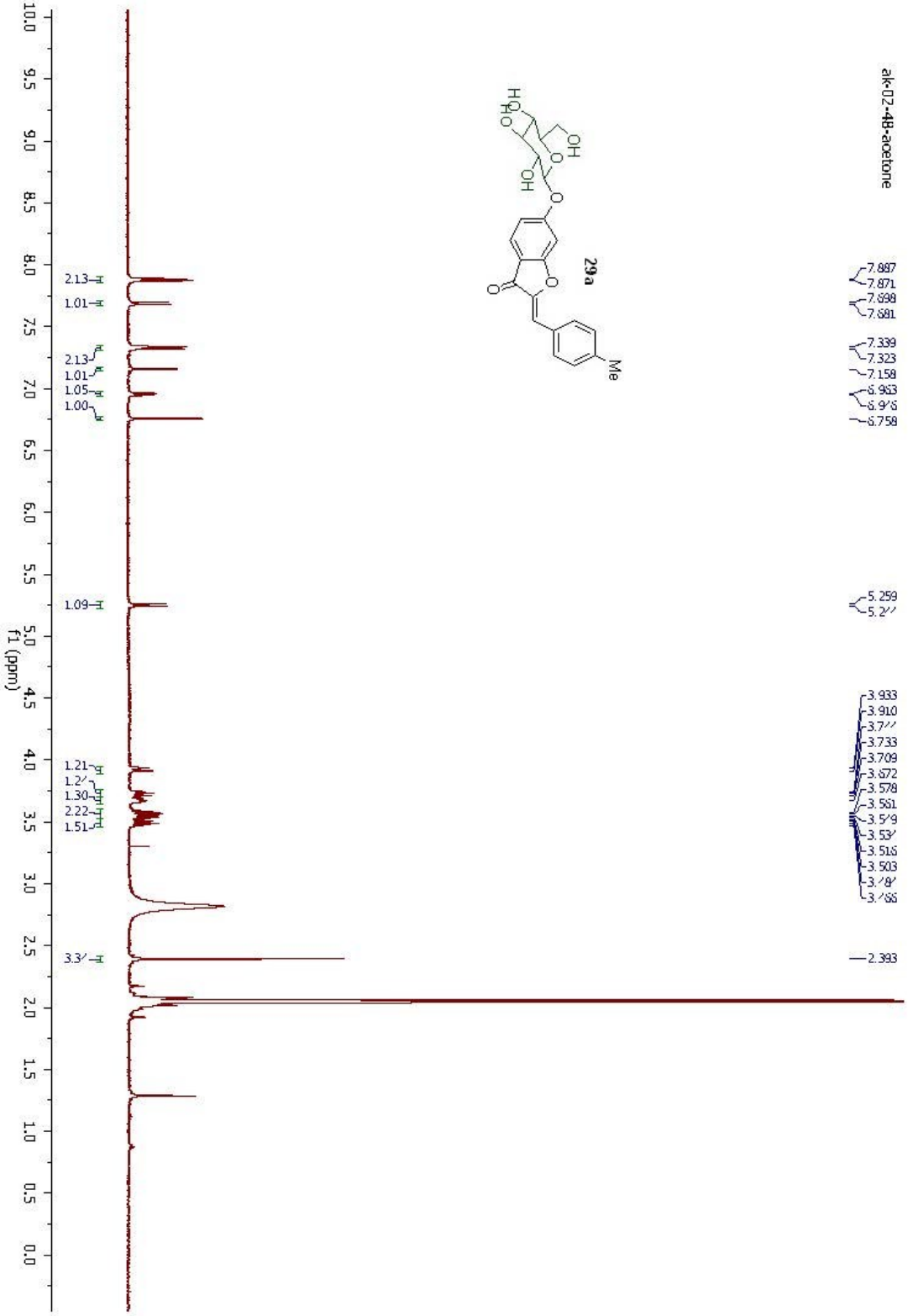

AK-01-136-13C
182.26
170.39
170.13
169.72
169.20
167.85
163.39
147.81
142.08
137.72
131.32
115.09
114.85
113.95
112.82
102.85
97.93
97.79
72.72
70.88
68.09
62.02
20.78
20.63
20.59
18.01
26a
Me
O
O
S
CN
AcO
AcO
AcO
OAc
OAc
f1 (ppm)

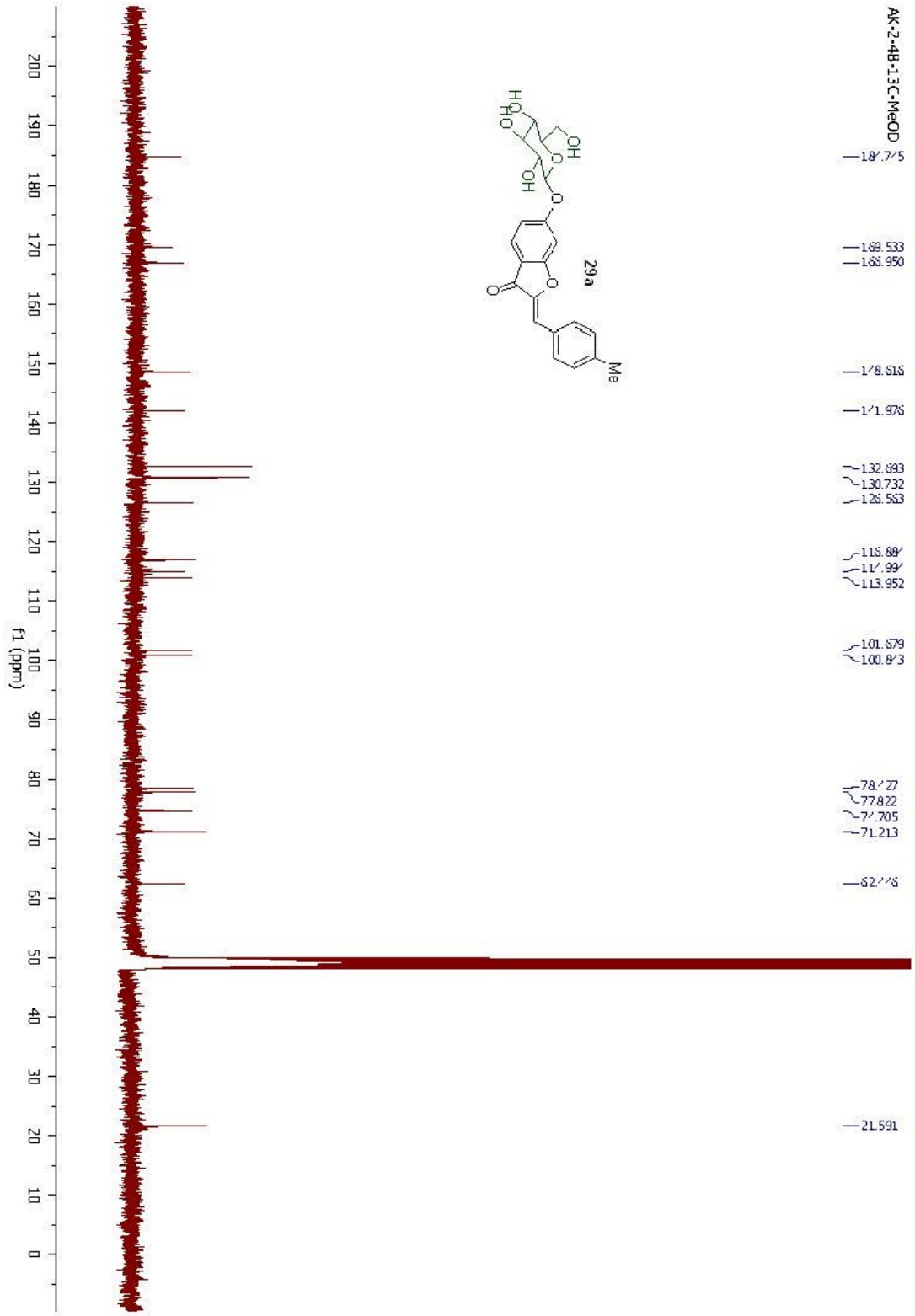

AK-1-107-1H-DMSO
27a
f1 (ppm)

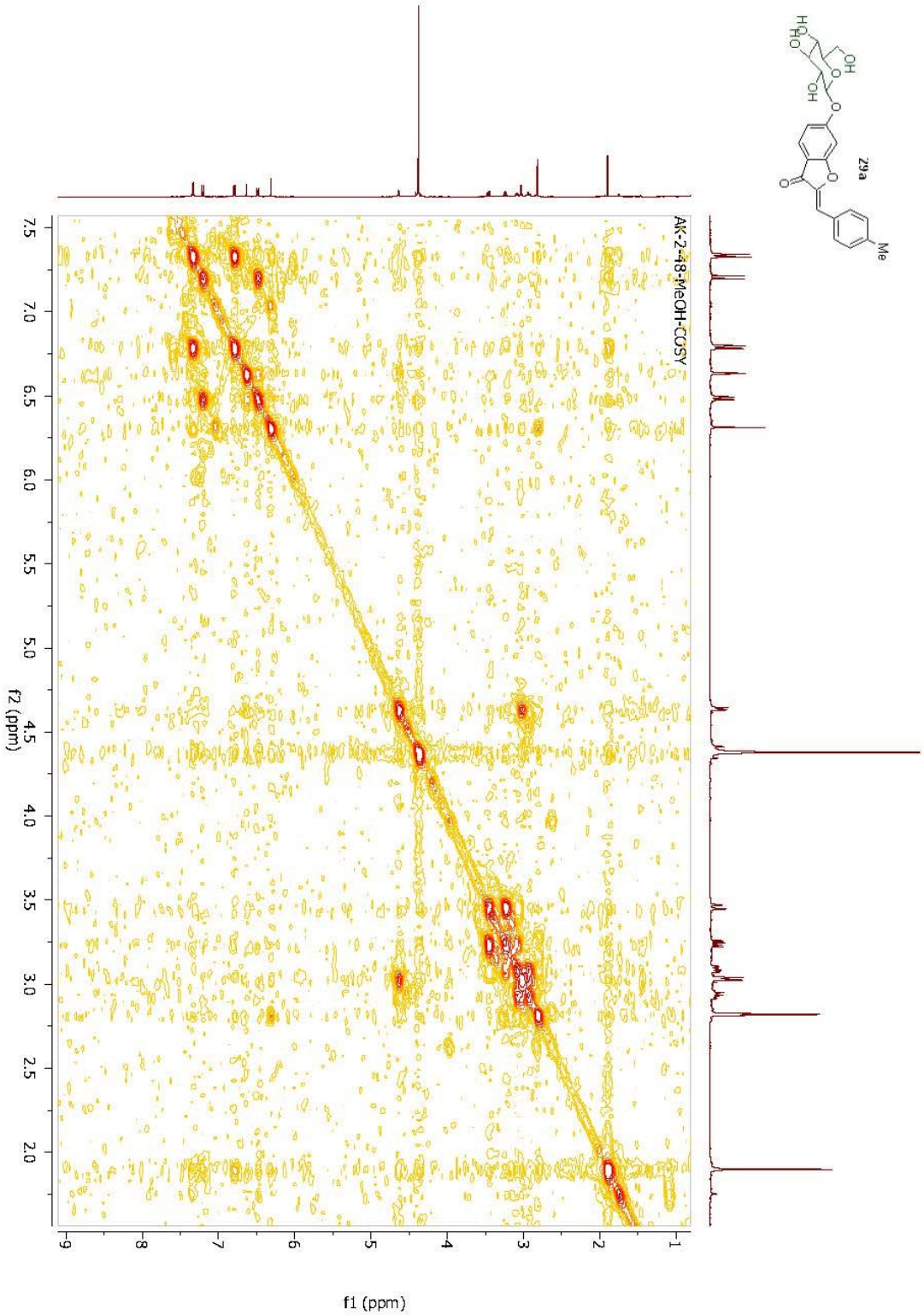

AK-1-107-13C
182.01
170.52
170.21
169.47
169.26
167.31
163.79
146.59
136.38
134.20
128.03
126.06
117.08
113.65
111.41
104.83
100.22
98.17
72.49
70.95
68.17
62.02
20.84
20.66
20.63
27a
f1 (ppm)

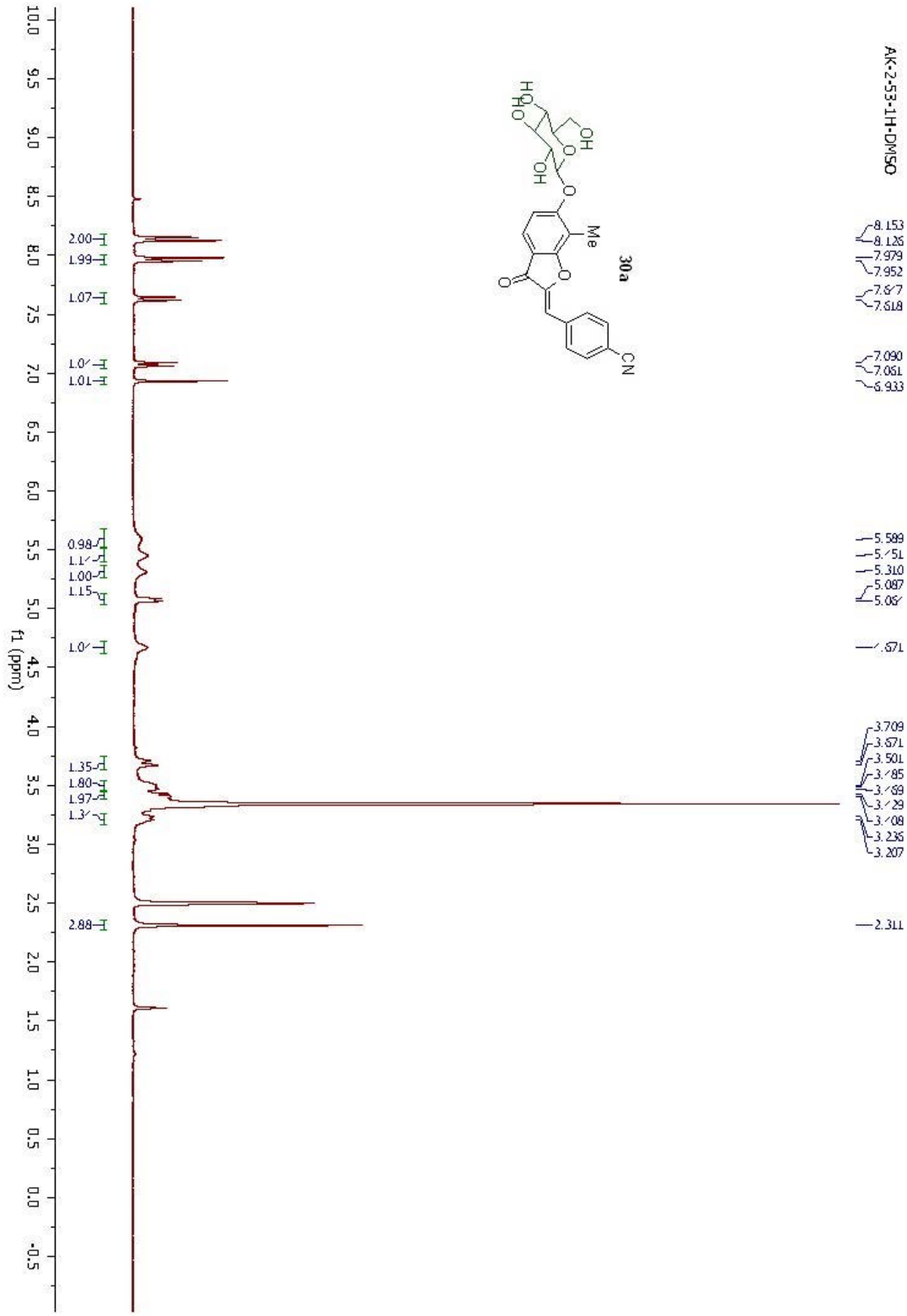

AK-01-137-1H-DMSO
28a
Me
Me
AcO
AcO
AcO
OAc
OAc
OAc
O
O
O
O
f1 (ppm)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
1.03
0.97
1.08
1.00
1.05
1.16
1.12
1.13
1.17
1.21
1.37
3.12
2.97
3.09
6.31
3.23
7.07
7.058
6.978
6.971
6.697
6.686
6.671
6.607
5.785
5.769
5.709
5.390
5.370
5.135
5.119
5.115
5.075
5.025
.377
.369
.362
.357
.349
.342
.337
.211
.199
.186
.175
.149
.145
.137
.125
.120
2.075
2.032
2.028
1.982

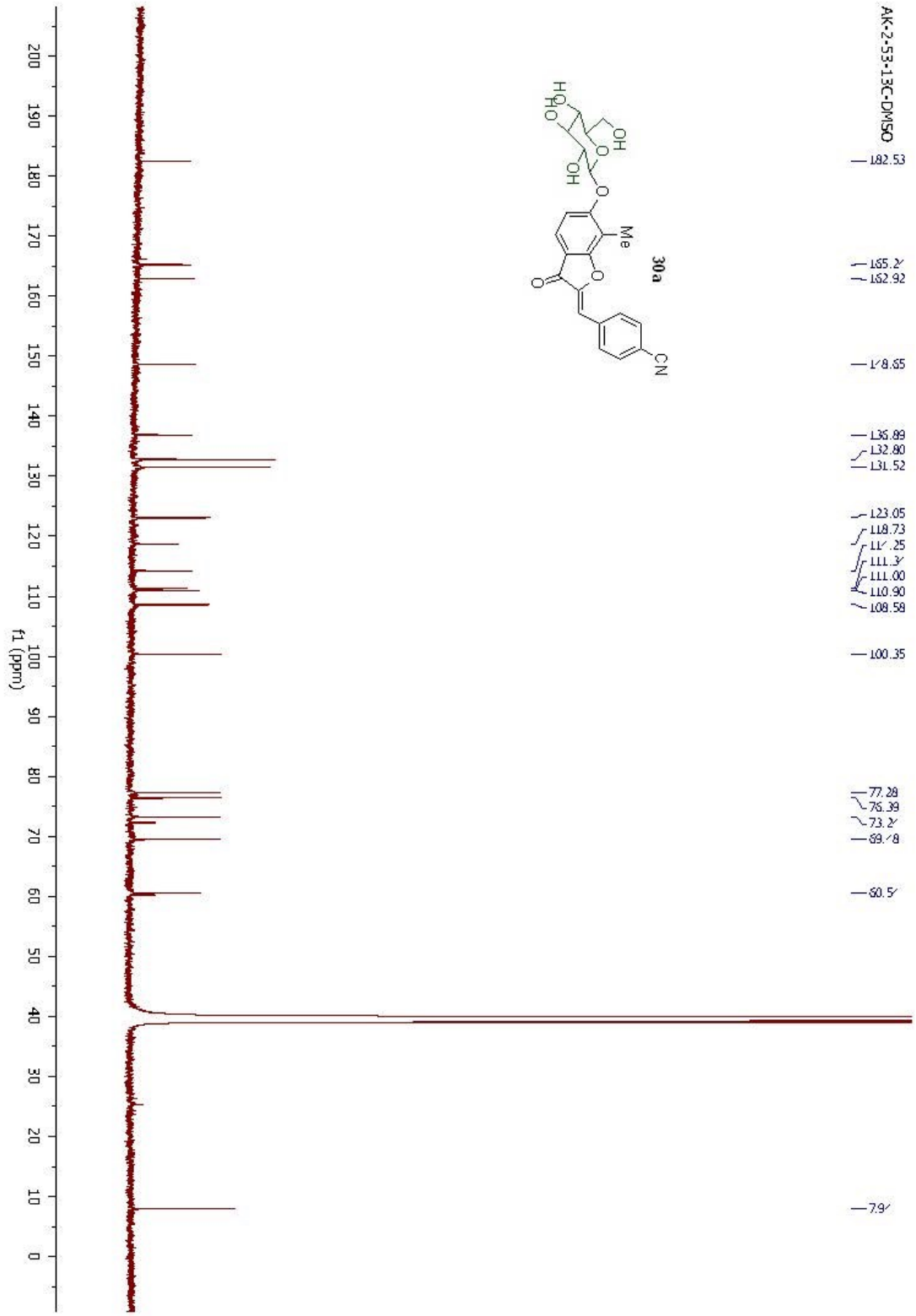

AK-01-137-13C
183.07
170.59
170.26
169.50
169.37
167.71
162.75
156.07
147.39
145.12
141.79
118.78
115.85
111.09
109.88
100.91
98.18
97.78
72.80
72.71
71.01
68.27
62.08
20.79
20.72
20.68
18.07
17.13
28a
Me
Me
AcO
AcO
OAc
OAc
OAc
O
O
O
O
O
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

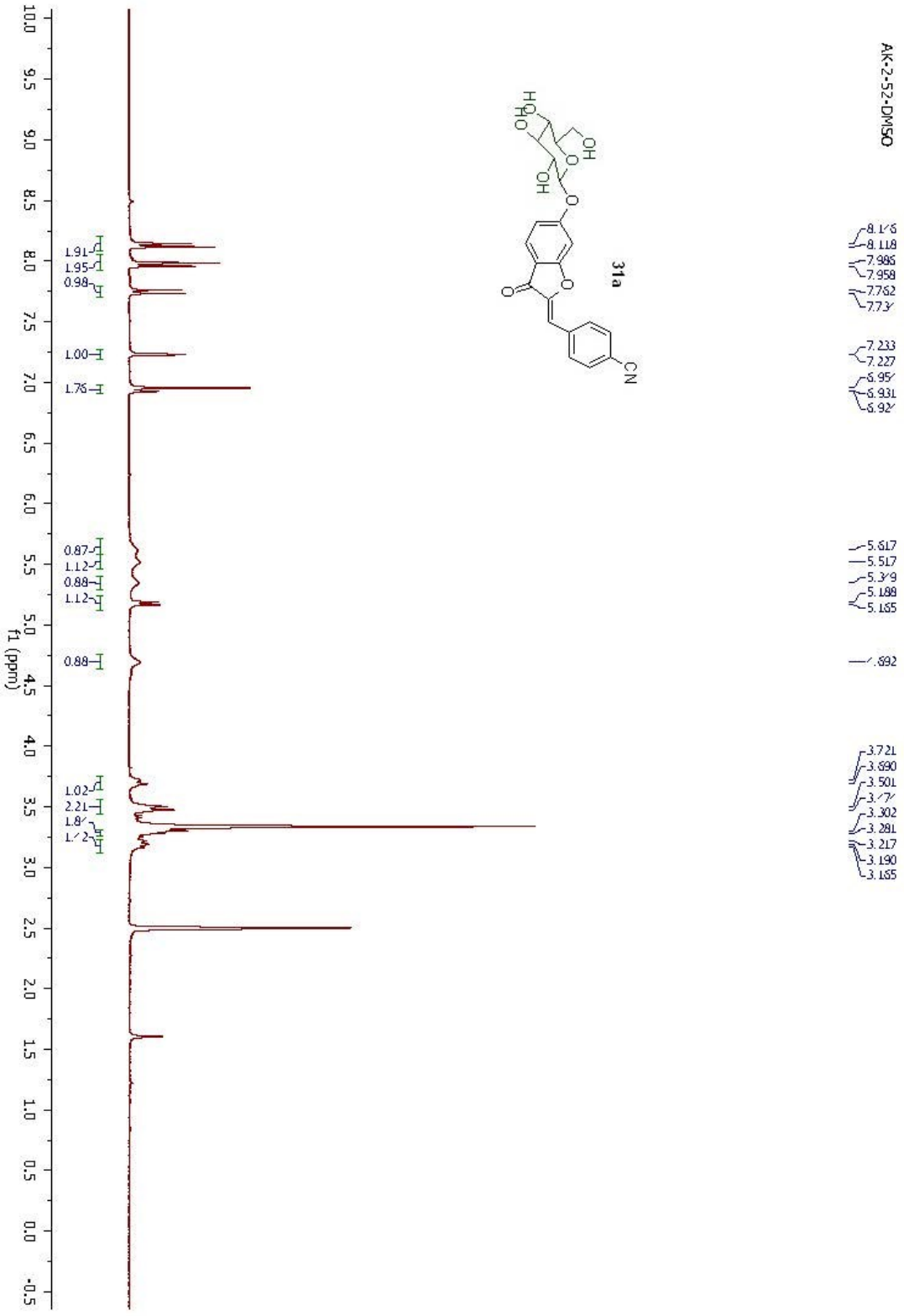

ak-02-48-acetone
29a
Me
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.13
1.01
2.13
1.01
1.05
1.00
1.09
1.21
1.30
2.22
1.51
3.3
7.887
7.871
7.598
7.581
7.339
7.323
7.158
6.963
6.758
5.259
3.933
3.910
3.733
3.709
3.572
3.578
3.561
3.539
3.516
3.503
2.393

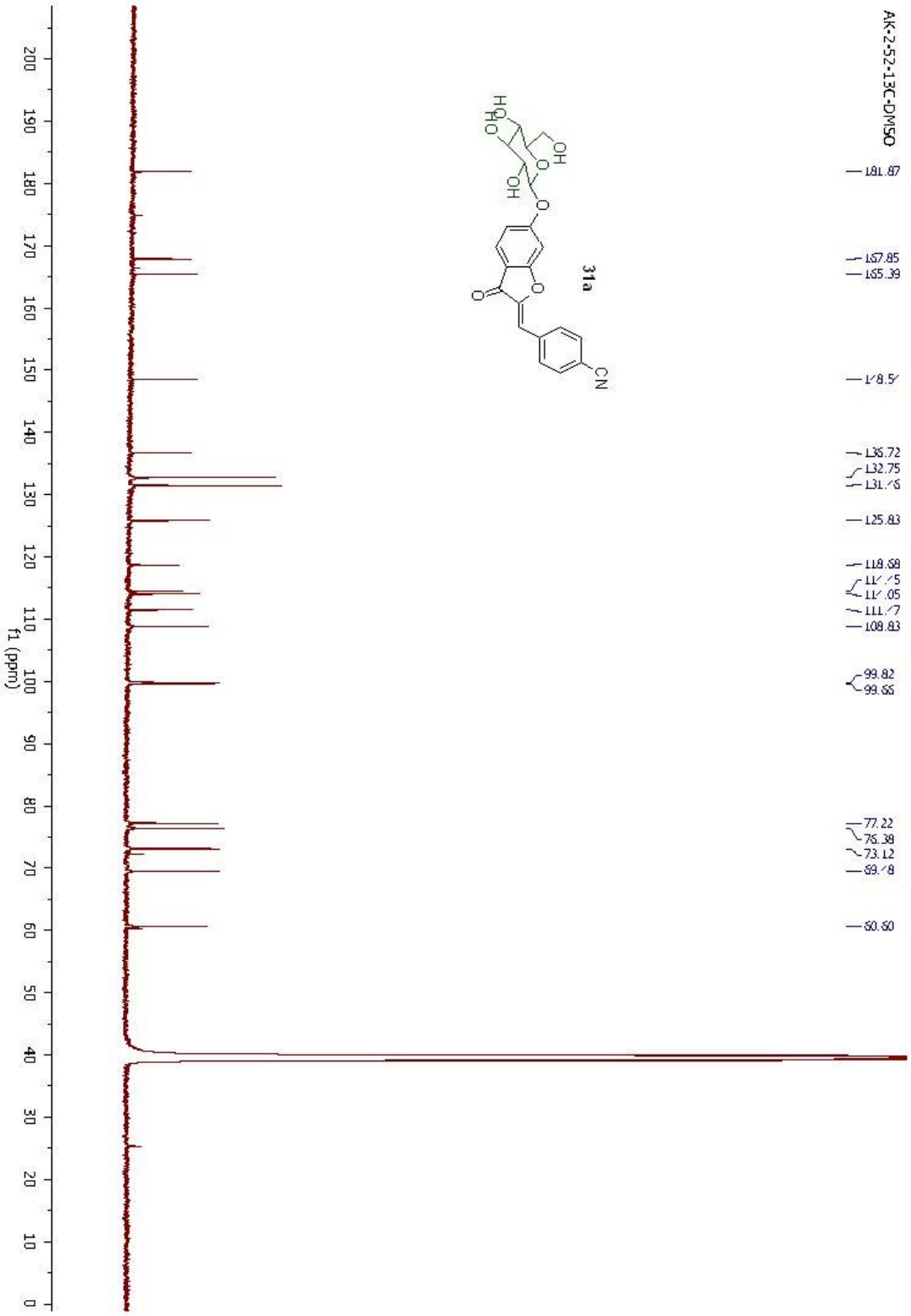

AK-2-4B-13C-MeOD
189.775
169.533
166.950
148.616
141.976
132.693
130.732
126.563
116.897
114.997
113.952
101.679
100.893
78.427
77.822
77.705
71.213
62.778
21.591
29a
Me
f1 (ppm)

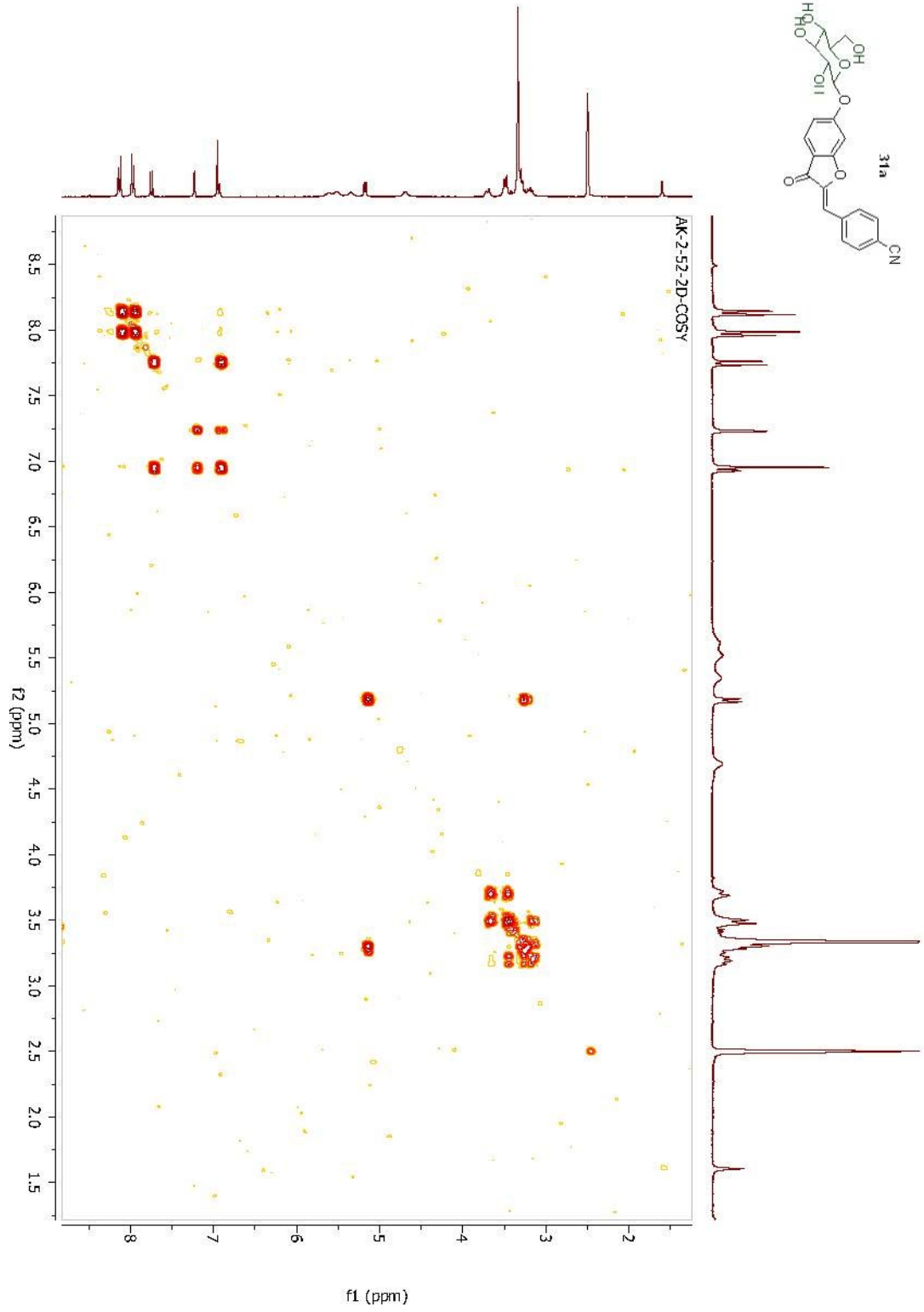

AK-2-48-MeOH-COSY
f2 (ppm)
f1 (ppm)
29a
Me

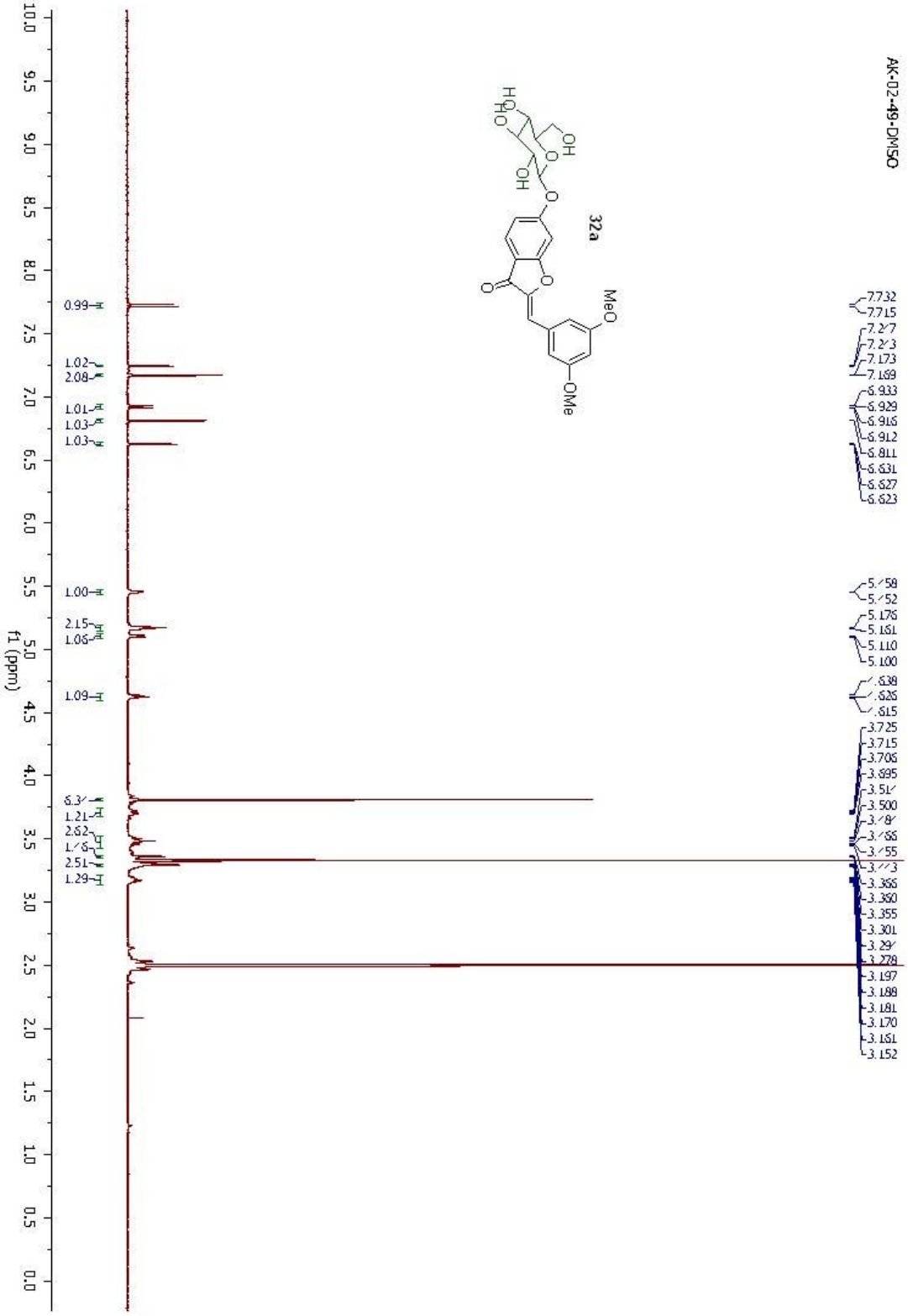

AK-2-53-1H-DMSO
30a
Me
CN
OH
OH
HO
HO
8.153
8.126
7.979
7.952
7.677
7.618
7.090
7.061
6.933
5.589
5.451
5.310
5.087
5.069
3.709
3.671
3.501
3.485
3.469
3.429
3.408
3.236
3.207
2.311
2.00
1.99
1.07
1.01
0.98
1.00
1.15
1.35
1.80
1.97
2.88
f1 (ppm)

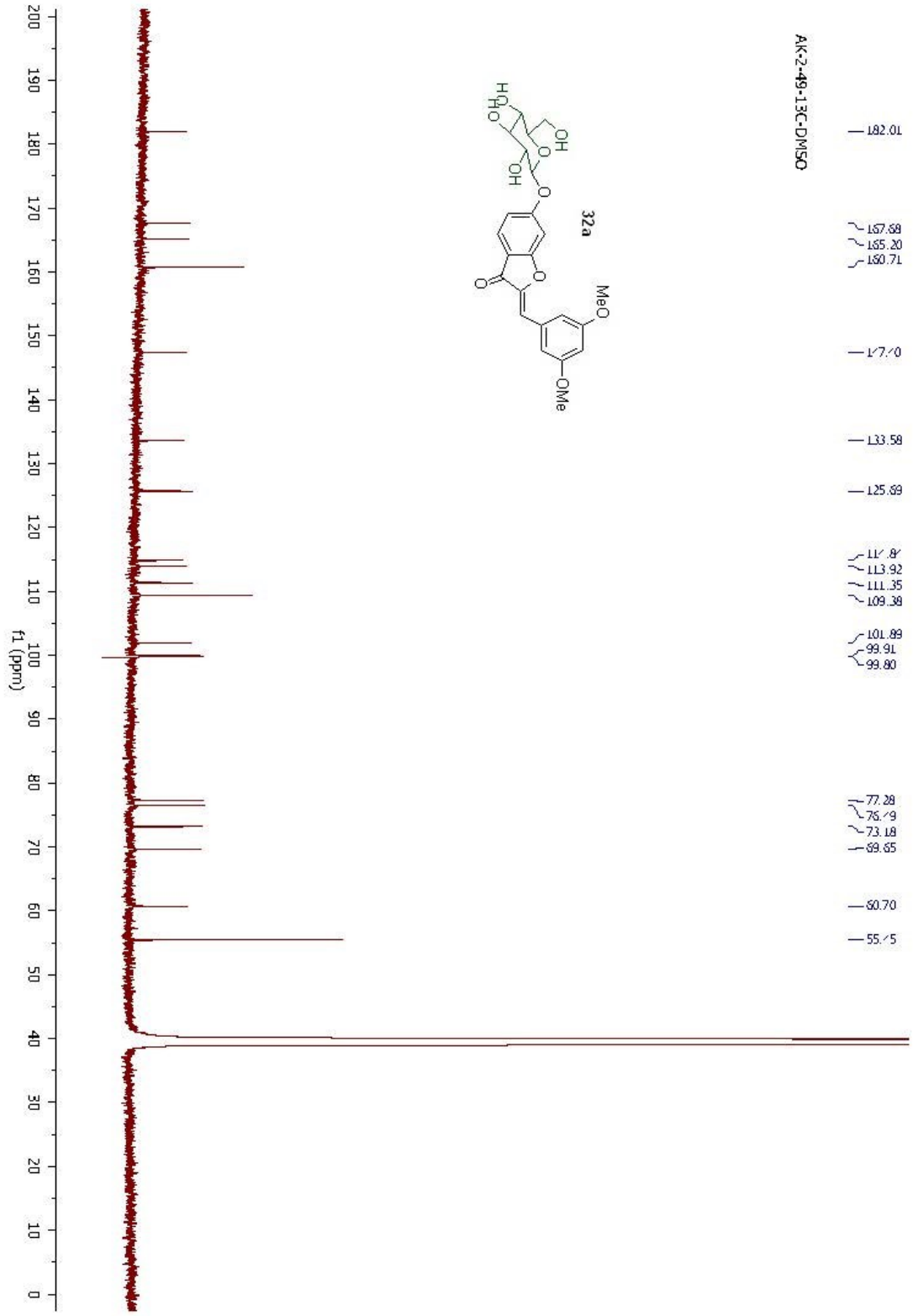

AK-2-53-13C-DMSO
182.53
165.27
162.92
148.65
136.89
132.80
131.52
123.05
118.73
117.25
111.37
111.00
110.90
108.58
100.35
77.28
76.39
73.27
69.78
60.57
39.79
30a
Me
CN
OH
HO
HO
O
f1 (ppm)

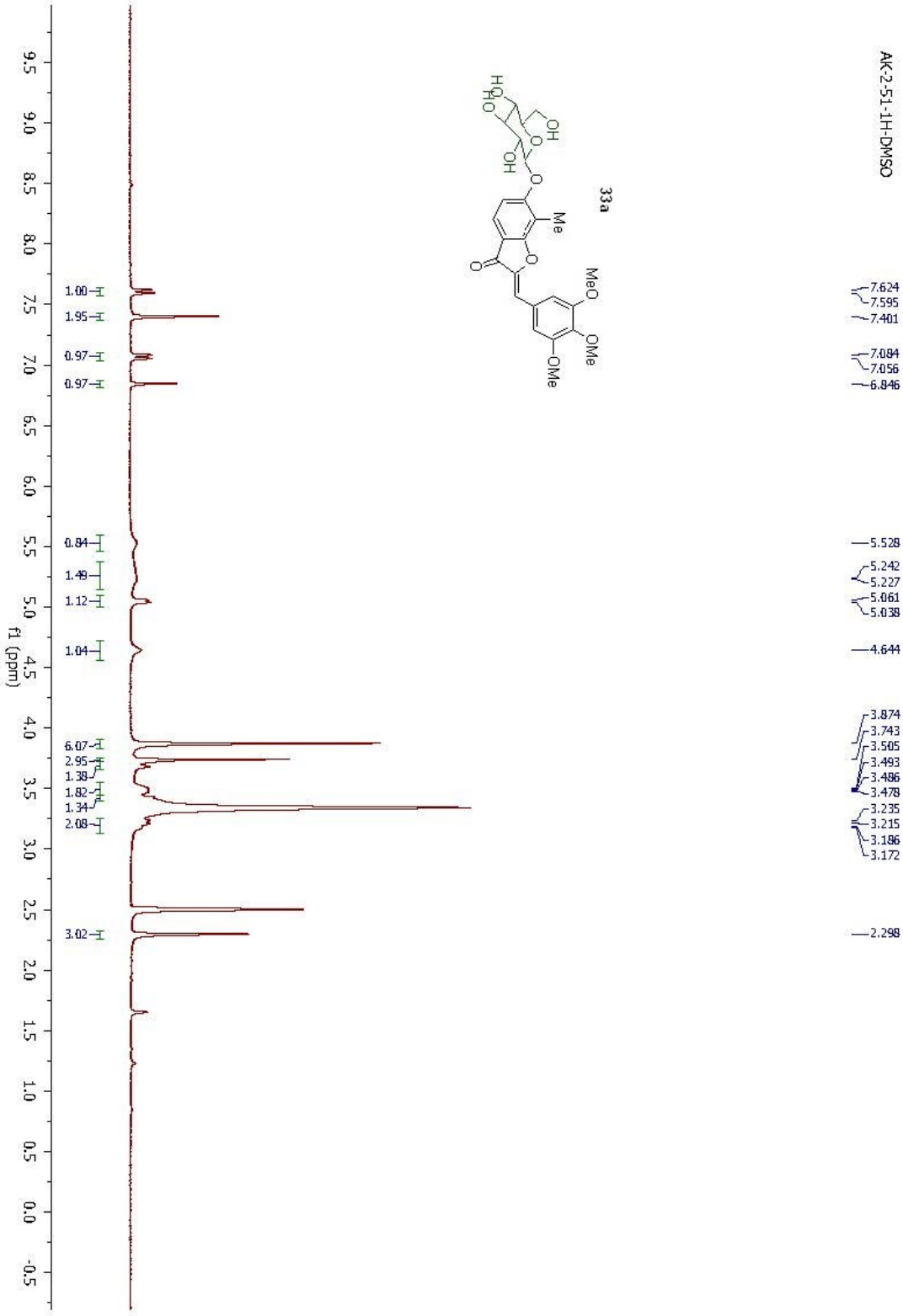

AK-2-52-DMSO
31a
f1 (ppm)

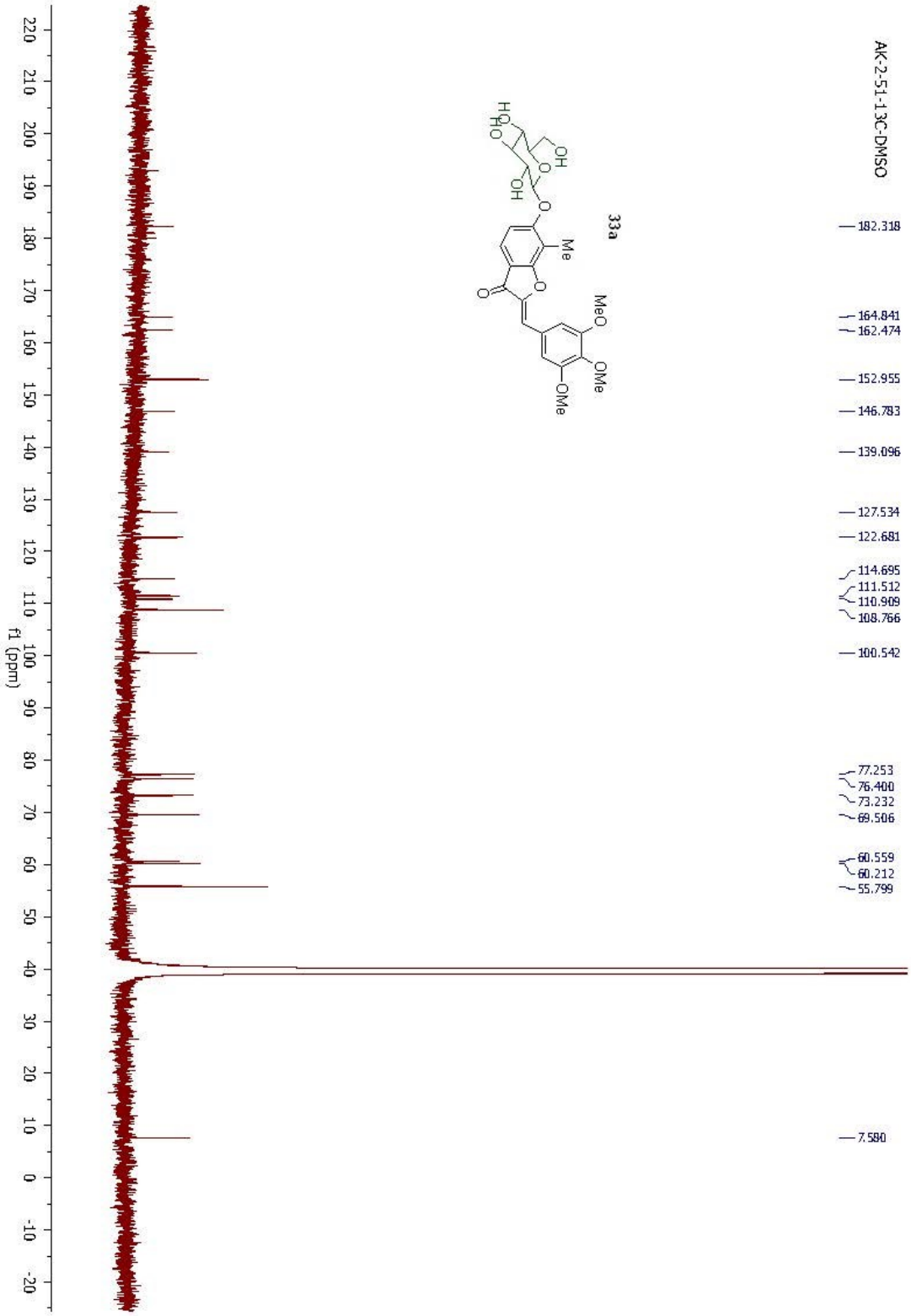

AK-2-52-13C-DMSO
181.87
167.85
165.39
148.57
136.72
132.75
131.76
125.83
118.68
117.75
117.05
111.77
108.83
99.82
99.65
77.22
76.38
73.12
69.78
60.60
31a
f1 (ppm)


AK-2-52-2D-COSY
f2 (ppm)
f1 (ppm)
31a


AK-02-49-DMSO
32a
MeO
OMe
OH
HO
HO
OH
O
f1 (ppm)


AK-2-49-13C-DMSO
182.01
157.68
155.20
150.71
147.70
133.58
125.69
117.87
113.92
111.35
109.38
101.89
99.91
99.80
77.28
76.79
73.18
69.65
60.70
55.75
32a
MeO
OMe
OH
OH
HO
HO
f1 (ppm)

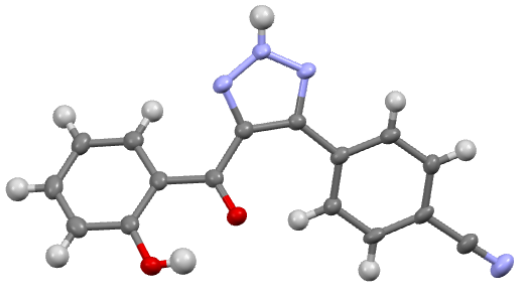

AK-2-51-1H-DMSO
33a
7.624
7.595
7.401
7.084
7.056
6.846
5.528
5.242
5.227
5.061
5.038
4.644
3.874
3.743
3.505
3.493
3.486
3.478
3.235
3.215
3.186
3.172
2.298
1.00
1.95
0.97
0.97
0.84
1.49
1.12
1.04
6.07
2.95
1.38
1.82
1.34
2.08
3.02
f1 (ppm)


AK-2-51-13C-DMSO
182.318
164.841
162.474
152.955
146.783
139.096
127.534
122.681
114.695
111.512
110.909
108.766
100.542
77.253
76.400
73.232
69.506
60.559
60.212
55.799
7.580
33a
f1 (ppm)

APPENDIX – D

X-ray crystallographic data – Chapter II

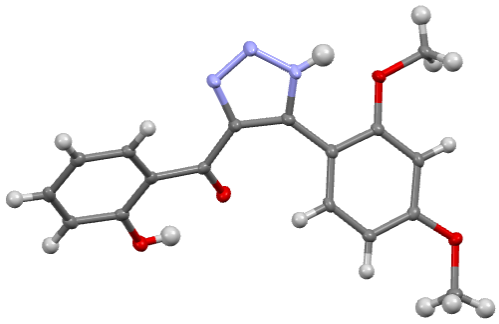
Compound 5 (CCDC : 1832154)



Chemical formula	$C_{16}H_{10}N_4O_2$	
Chemical name	4-[5-(2-hydroxybenzoyl)-*2H*-triazol-4-yl]benzonitrile	
Formula weight	290.28	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal size	0.074 × 0.07 × 0.06 mm^3	
Crystal color:	yellow	
Crystal system	orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 20.4270 (5)Å	α = 90
	b = 3.76320 (1)Å	β = 90
	c = 20.4678 (4) Å,	γ = 90
Volume	1573.38(6) $Å^3$	
Z	4	

Dx, g, cm^{-3}	1.225
Absorption coefficient (Mu)	0.698 mm^{-1}
F(000)	600
Diffractometer	Rigaku SuperNova
Radiation type	CuK\α
Diffraction source type	SuperNova (Cu) X-ray source
Diffraction source	'micro-focus sealed X-ray tube'
Theta (max)	67.954
Index ranges (h, k, lmax)	24, 4, 24
Unique reflections (Nref)	2824
wR2 (reflections)	0.0856 (2824)
R (reflections)	0.0333 (2650)
Absorption correction (Tmin, Tmax)	0.947, 1.000
Absorption correction	GAUSSIAN
Structure solution program	SHELXT (Sheldrick 2015)
Structure refinement program	SHELXL (Sheldrick, 2015)
Data / restraints / parameters	2824 / 1 / 205
Goodness-of-fit	1.022
Δ/σ_{max}	0.001
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0658P)^2]$ where $P=(F_o^2+2F_c^2)/3$
Data completeness	1.938

Compound 10 (CCDC : 1832154)

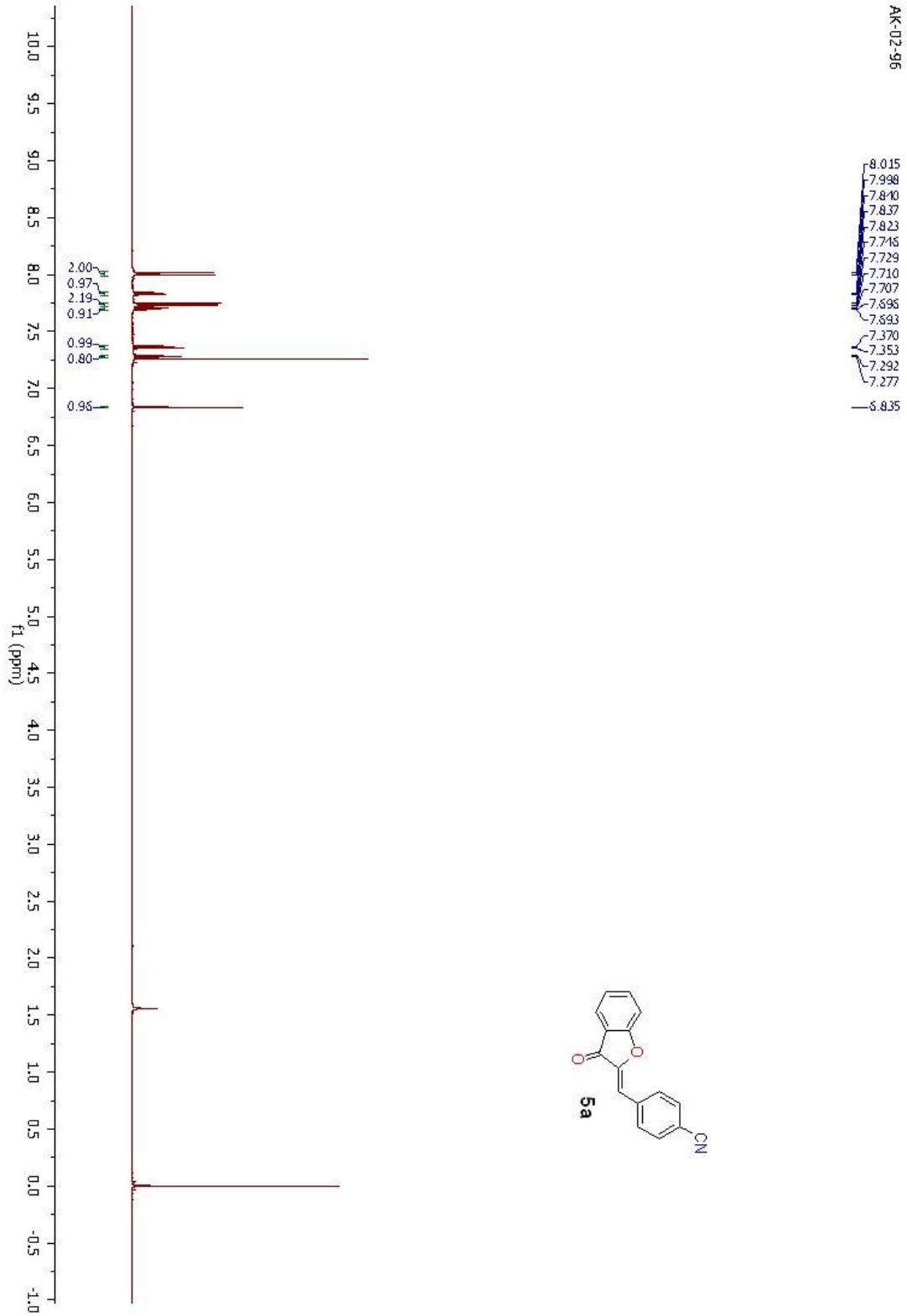


Chemical formula	$C_{17}H_{15}N_3O_4$	
Chemical name	[5-(2,4-dimethoxyphenyl)-1H-triazol-4-yl]-(2-hydroxyphenyl)methanone	
Formula weight	325.32	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal size	0.057 × 0.04 × 0.02 mm^3	
Crystal color:	yellow	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 3.89210 (10)Å	α = 90
	b = 12.2806 (2)Å	β = 90.19
	c = 30.0412 (4) Å,	γ = 90
Volume	1434.84(5) $Å^3$	
Z	1	
Dx, g, cm^{-3}	1.506	
Absorption coefficient (Mu)	0.912 mm^{-1}	
F(000)	680	
Diffractometer	Rigaku SuperNova	
Radiation type	CuK\α	

Diffraction source type	SuperNova (Cu) X-ray source
Diffraction source	'micro-focus sealed X-ray tube'
Theta (max)	68.201
Index ranges (h, k, lmax)	4, 14, 36
Unique reflections (Nref)	3111
wR2 (reflections)	0.1032 (3111)
R (reflections)	0.0393 (2631)
Absorption correction (Tmin, Tmax)	0.821, 1.000
Absorption correction	MULTI-SCAN
Structure solution program	SHELXT (Sheldrick 2015)
Structure refinement program	SHELXL (Sheldrick, 2015)
Restraints / parameters	0 / 225
Goodness-of-fit	1.046
Δ/σ_{max}	0.001
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0658P)^2+2.3363P]$ where $P=(F_o^2+2F_c^2)/3$
Data completeness	1.178
Refine special details	'Refined as a 2-component twin.,Twin'

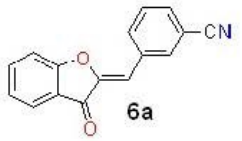
NMR Spectra - Chapter II

Known aurones
(5a-10a, 12a-17a, 19a-29a, 31a)

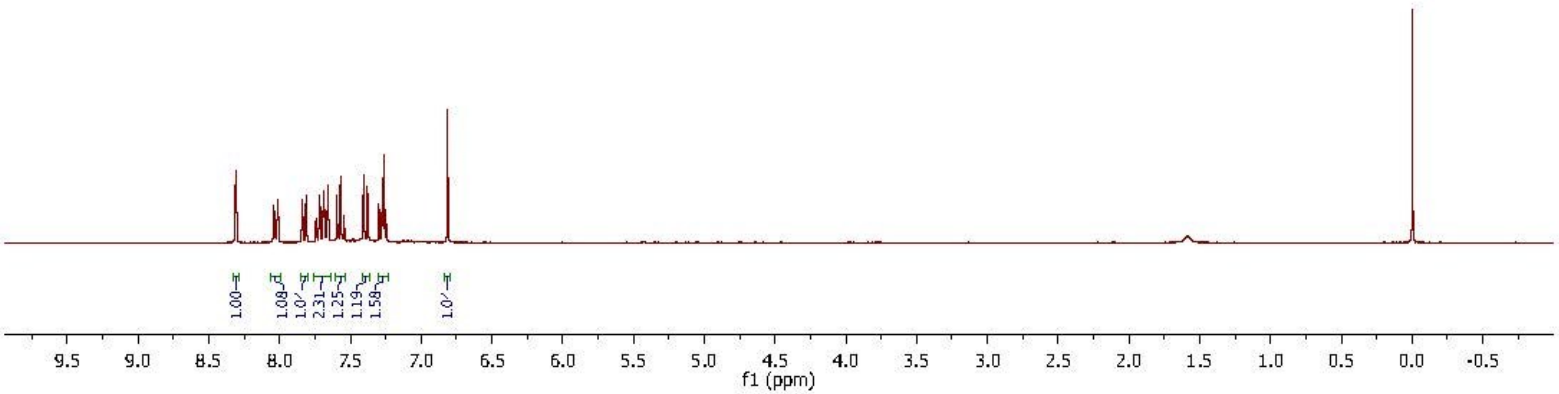

AK-02-96
8.015
7.998
7.840
7.837
7.823
7.746
7.729
7.710
7.707
7.696
7.693
7.370
7.353
7.292
7.277
6.835
2.00
0.97
2.19
0.91
0.99
0.80
0.96
f1 (ppm)
5a
O
O
CN

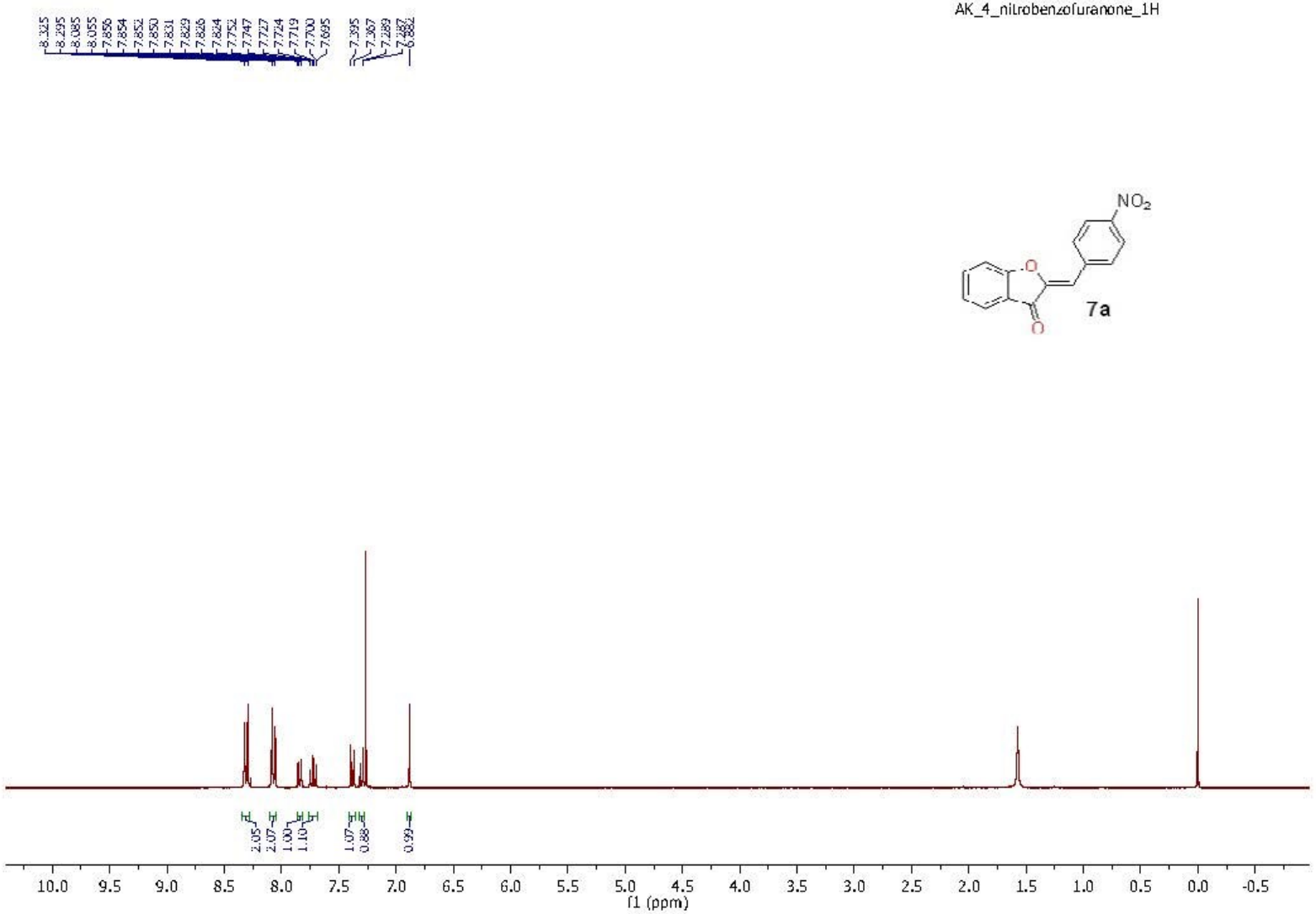
AK_2_126_1H

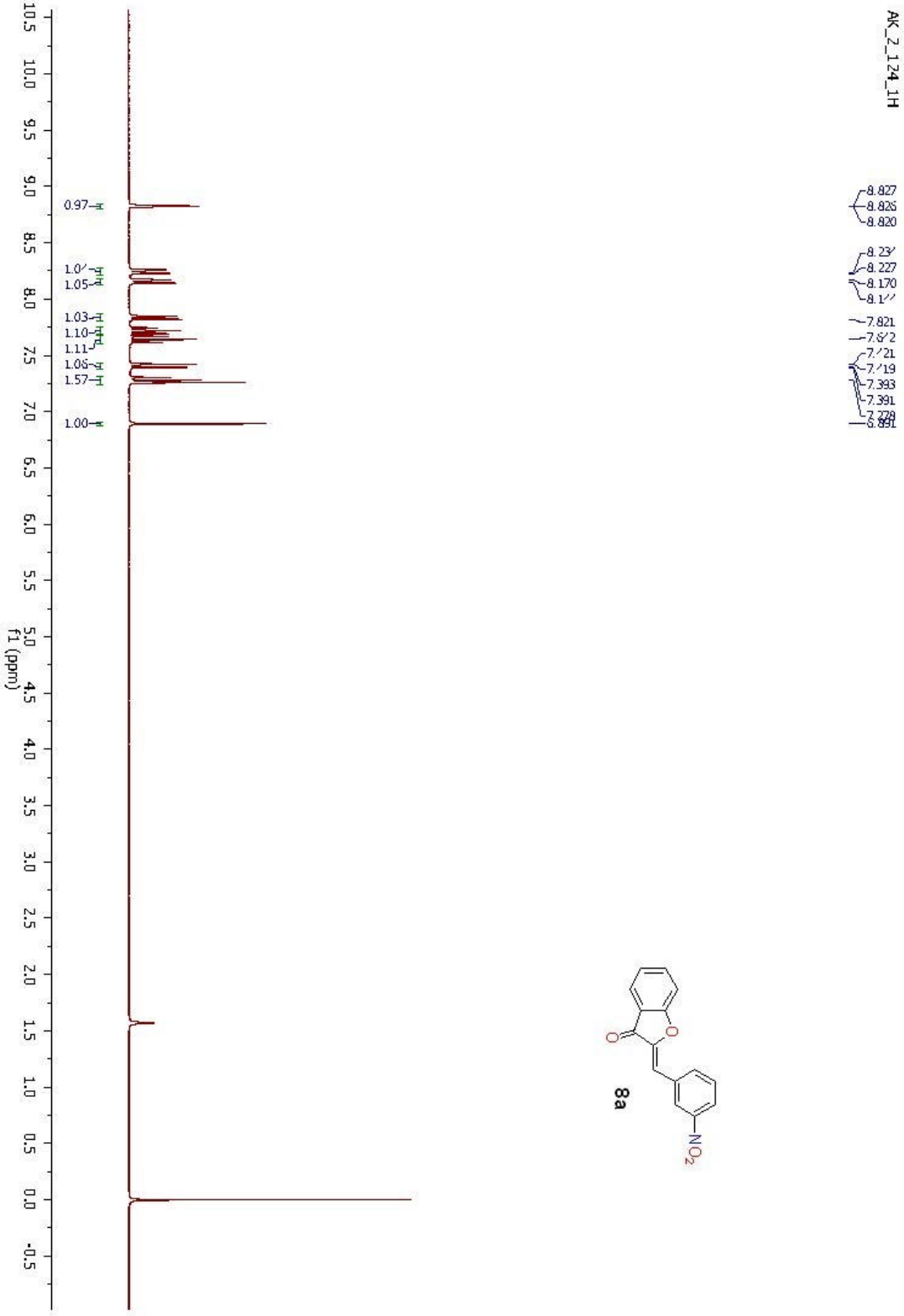

8.310
7.813
7.710
7.690
7.687
7.650
7.596
7.570
7.408
7.390
7.273

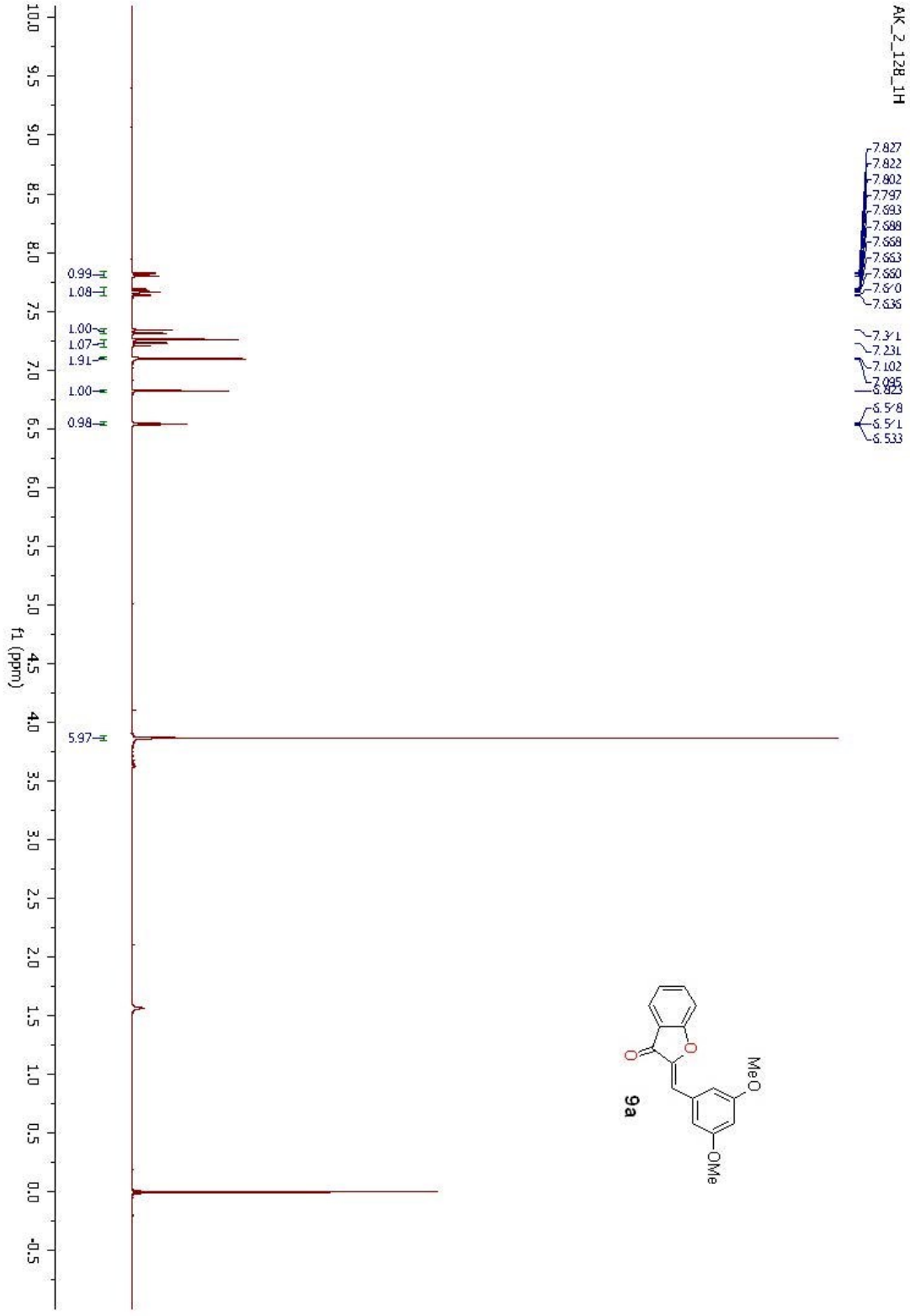

CN
O
O

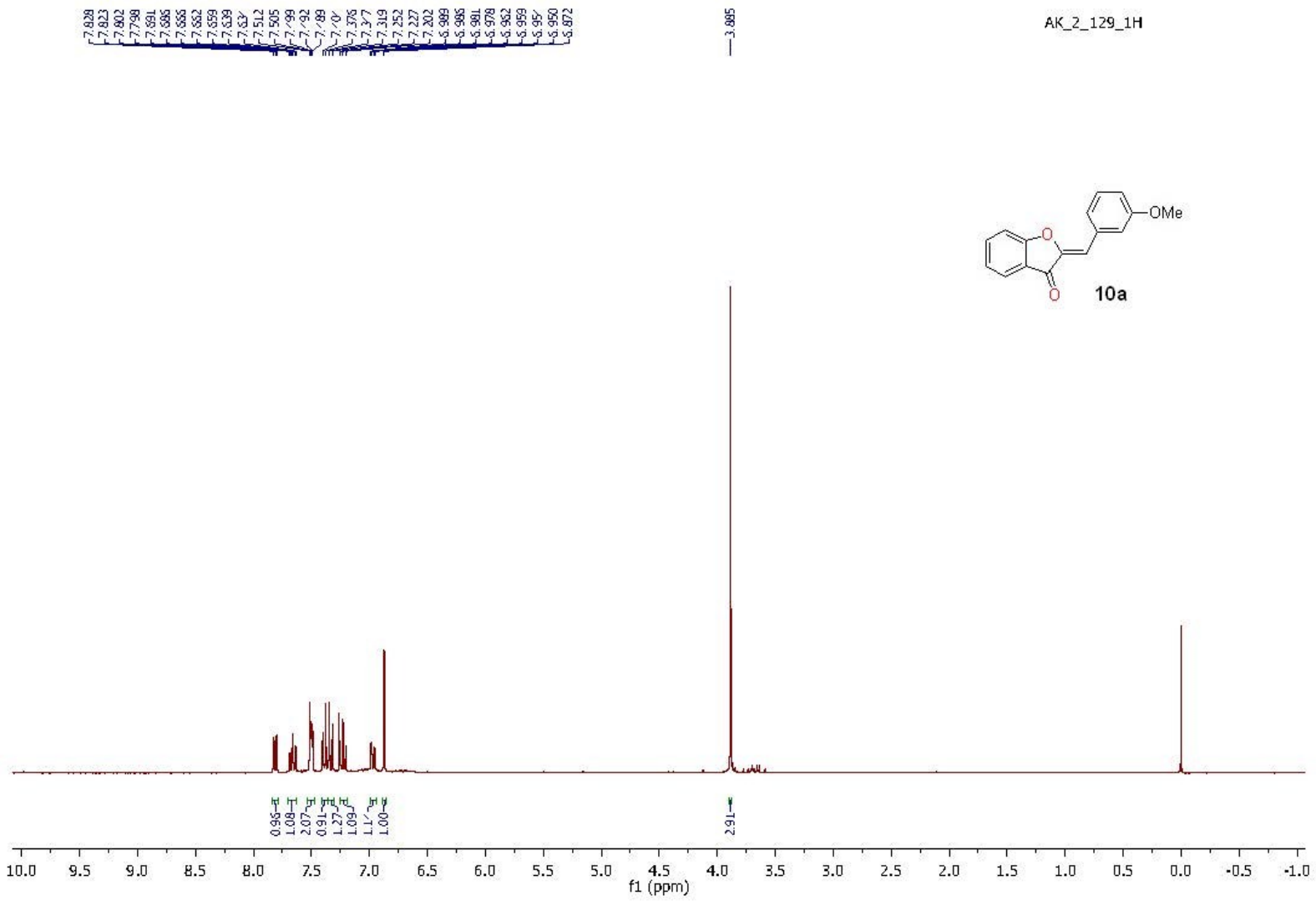
6a

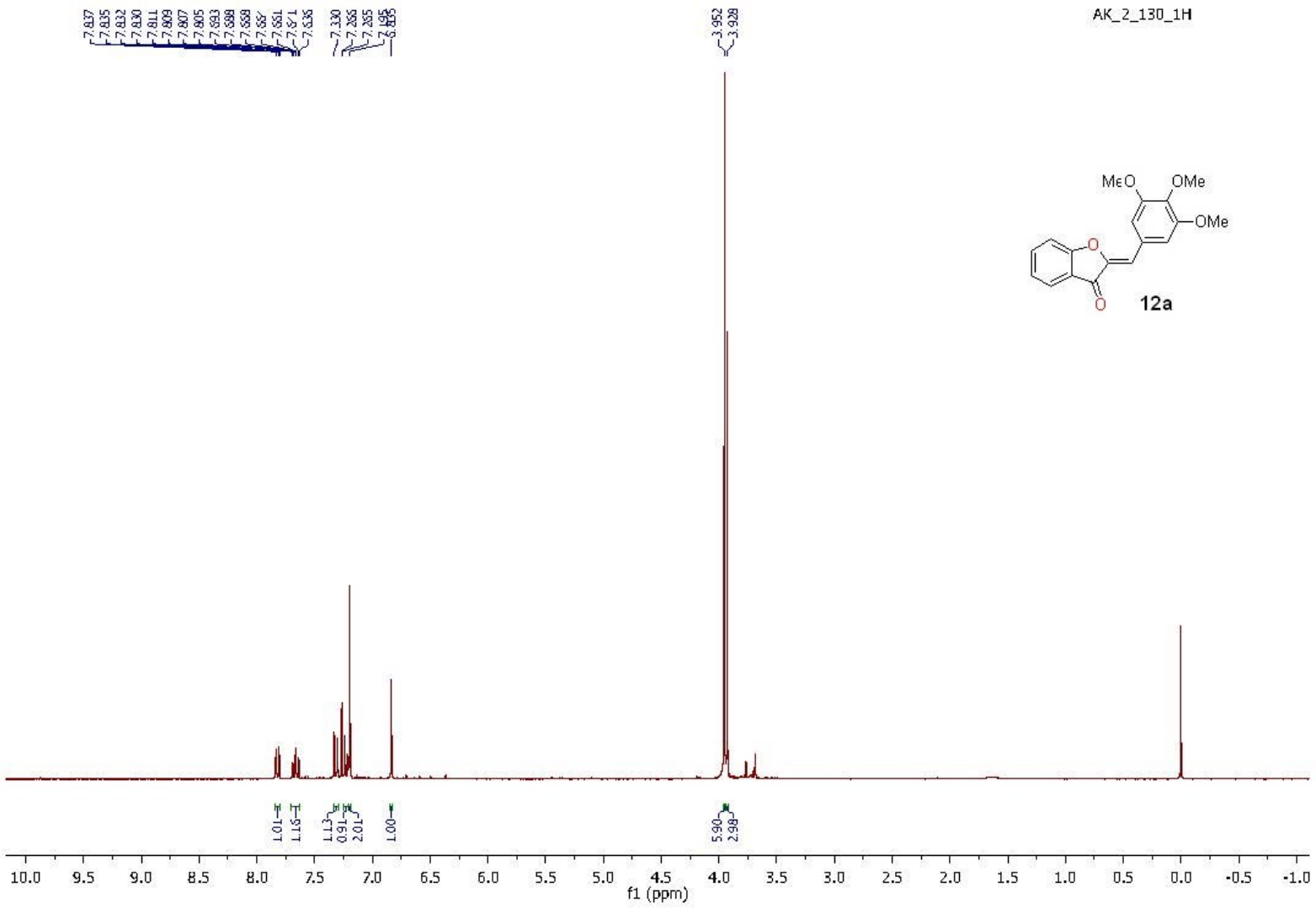

1.00
1.08
1.07
2.31
1.25
1.19
1.58
1.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


AK_4_nitrobenzofuranone_1H
8.325
8.295
8.085
8.055
7.856
7.854
7.852
7.850
7.831
7.829
7.826
7.824
7.752
7.747
7.727
7.724
7.719
7.700
7.695
7.395
7.367
7.289
7.287
6.882
NO2
O
O
7a
2.05
2.07
1.00
1.10
1.07
0.88
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

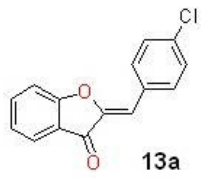

AK_Z_124_1H
8.827
8.826
8.820
8.237
8.227
8.170
8.167
7.821
7.812
7.721
7.719
7.393
7.391
7.278
6.891
0.97
1.07
1.05
1.03
1.10
1.11
1.08
1.57
1.00
f1 (ppm)
8a
O
O
NO2


AK_2_128_1H
7.827
7.822
7.802
7.797
7.693
7.688
7.658
7.653
7.650
7.570
7.636
7.371
7.231
7.102
7.095
6.823
6.578
6.571
6.533
0.99
1.08
1.00
1.07
1.91
1.00
0.98
5.97
f1 (ppm)
MeO
OMe
9a

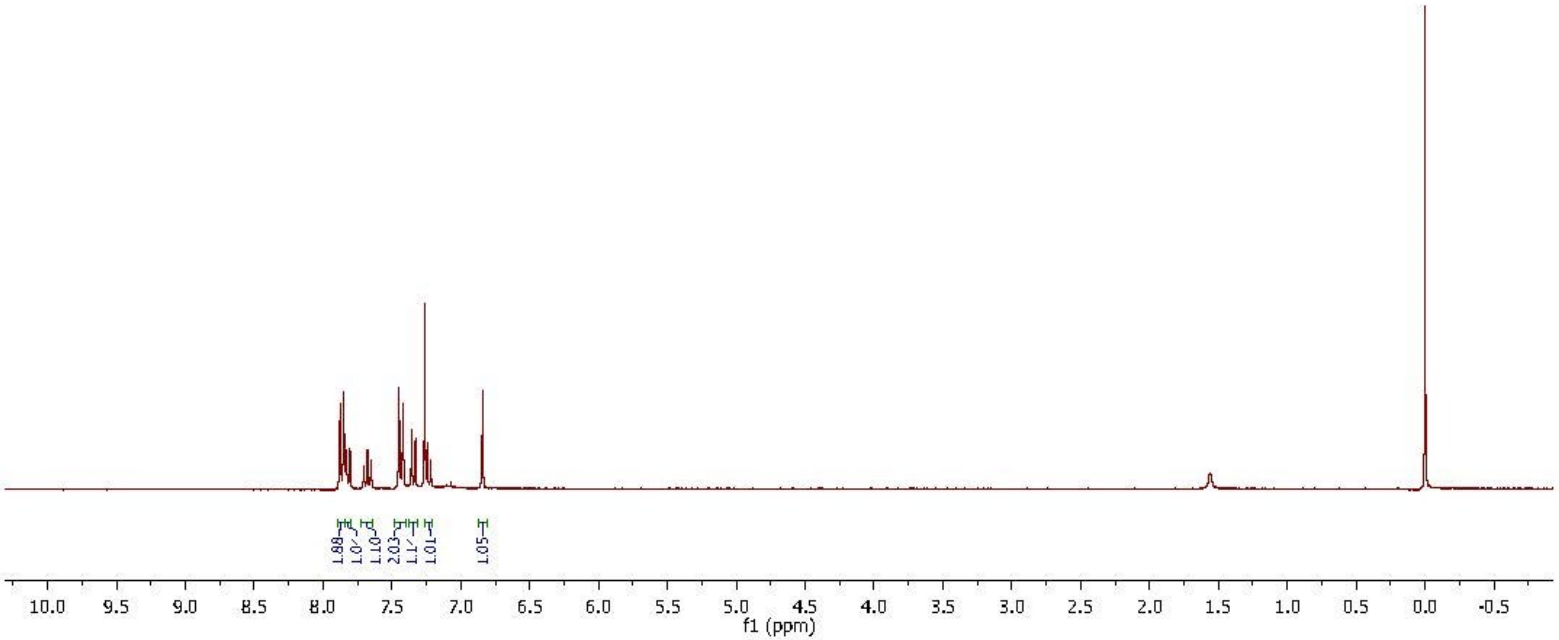

AK_2_129_1H
OMe
O
O
10a
f1 (ppm)

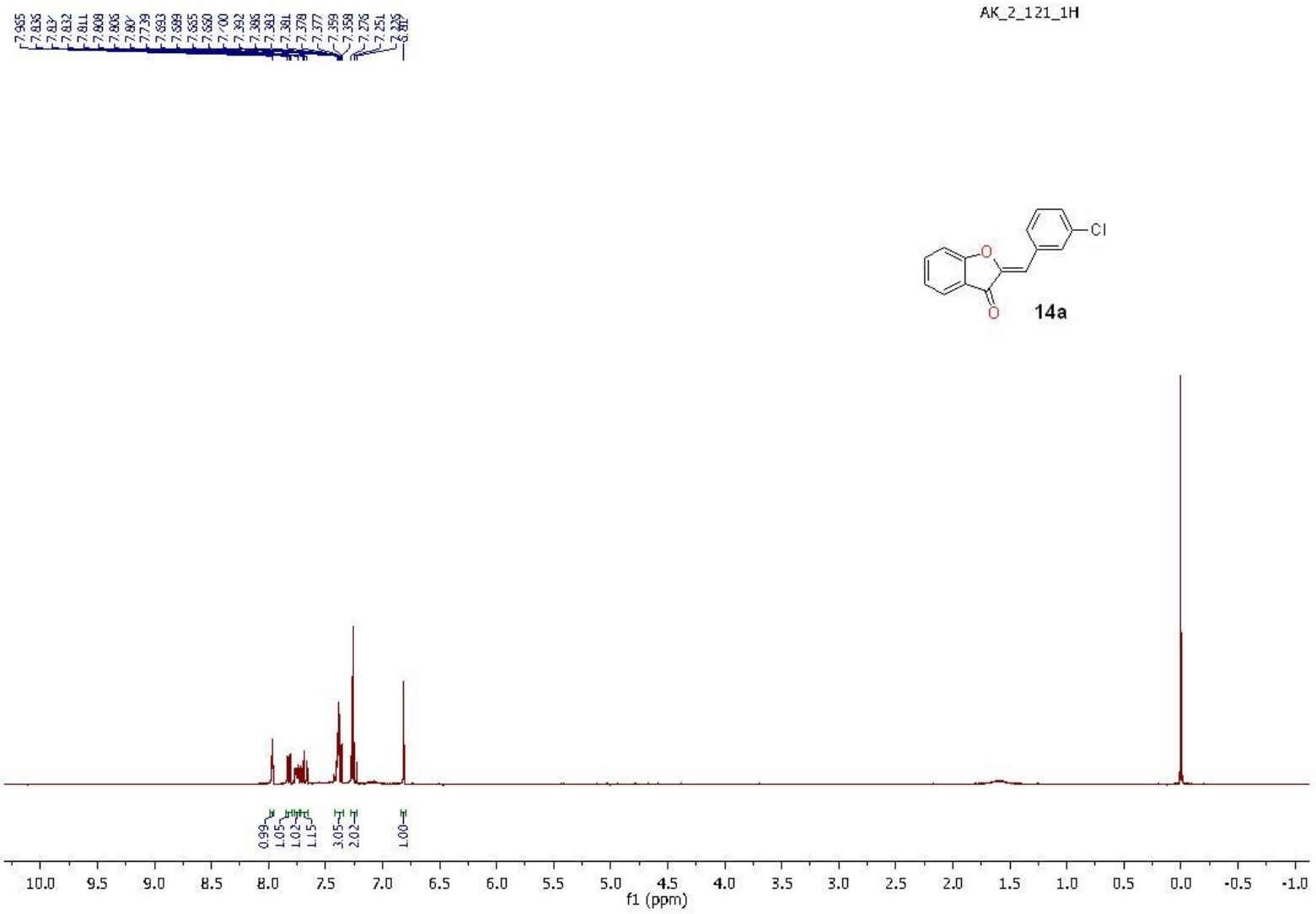

AK_2_130_1H
MeO
OMe
OMe
O
O
12a
f1 (ppm)

AK_2_120_1H

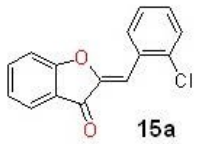


13a

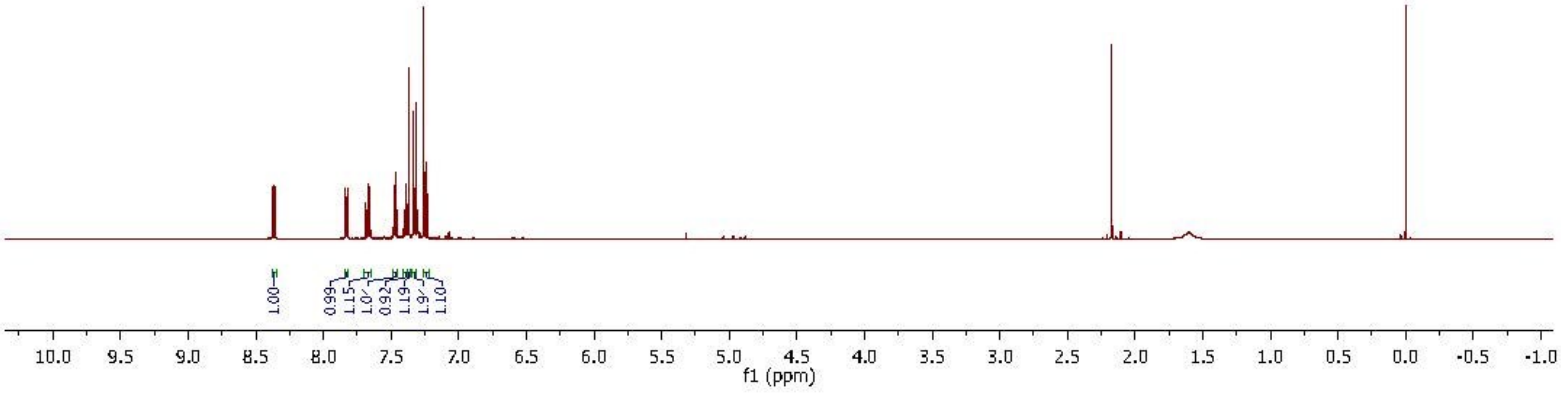



AK_2_121_1H
7.965
7.836
7.817
7.812
7.811
7.808
7.805
7.800
7.739
7.693
7.689
7.555
7.550
7.700
7.392
7.385
7.383
7.381
7.378
7.377
7.359
7.358
7.276
7.251
Cl
O
O
14a
0.99
1.05
1.02
1.15
3.05
2.02
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

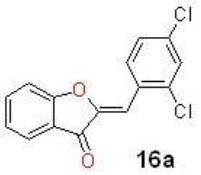
AK_2_147_2_1H



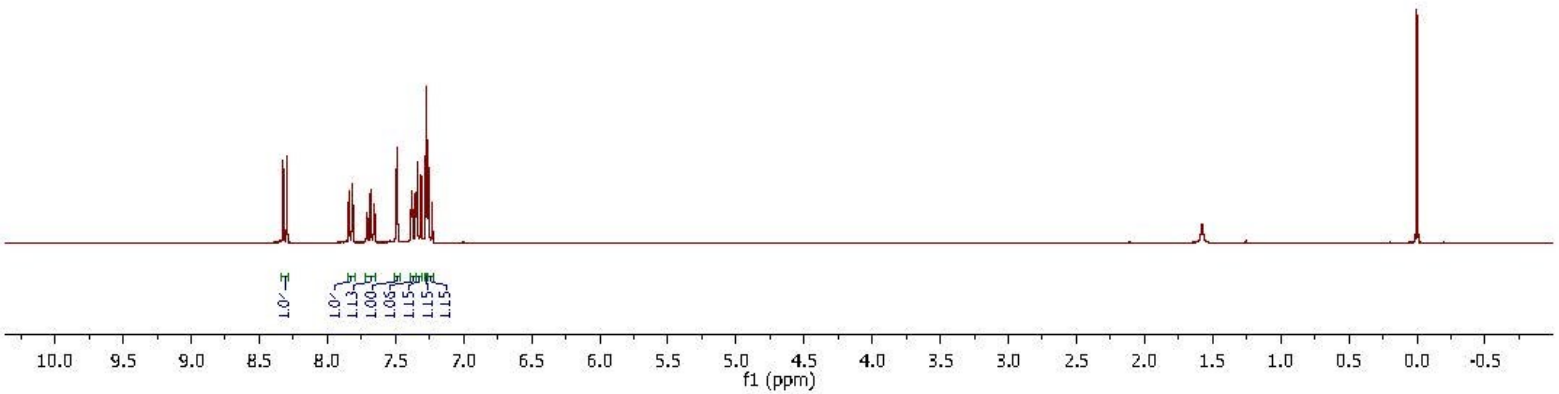
15a



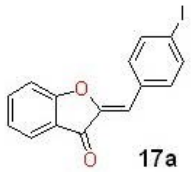
AK_3_25_1_1H



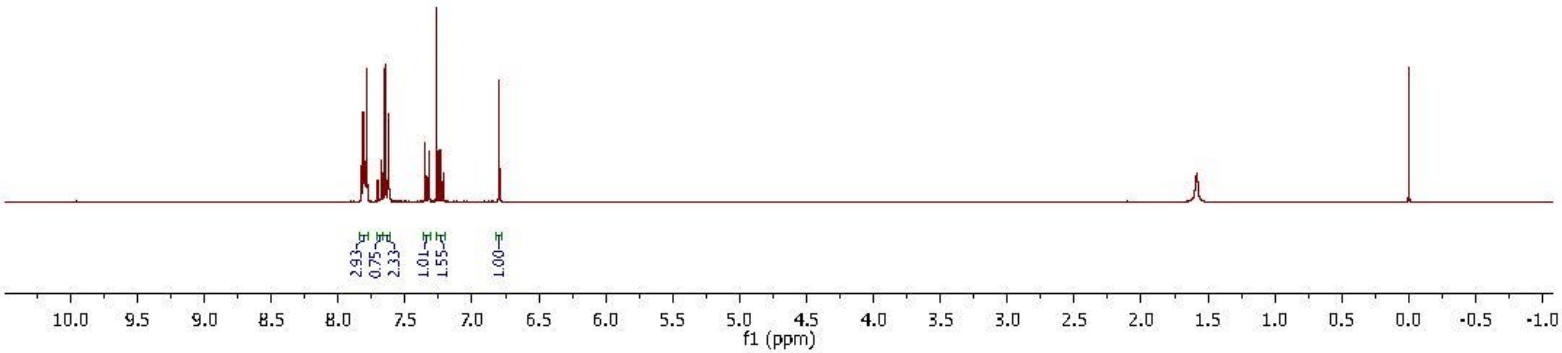
16a

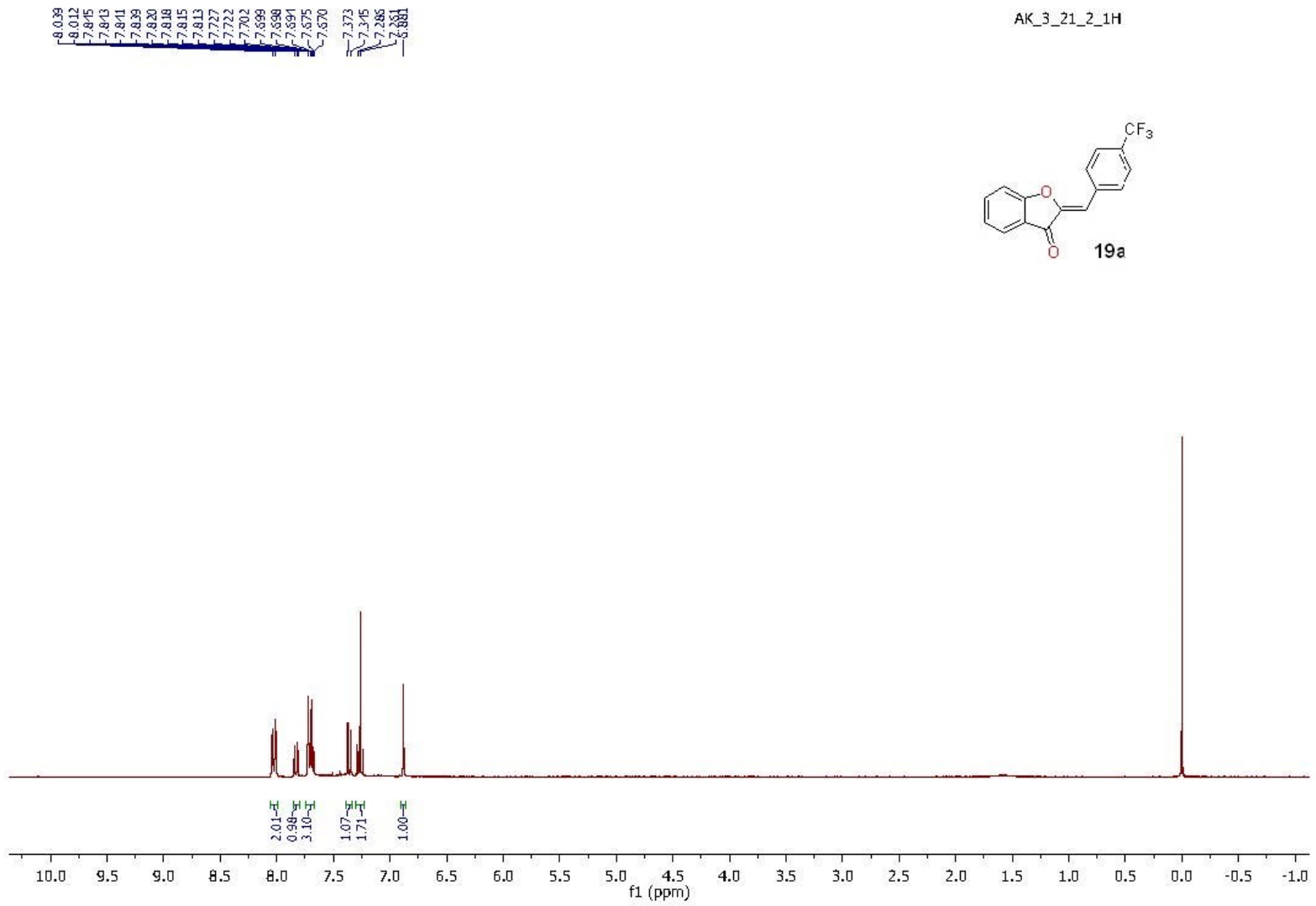


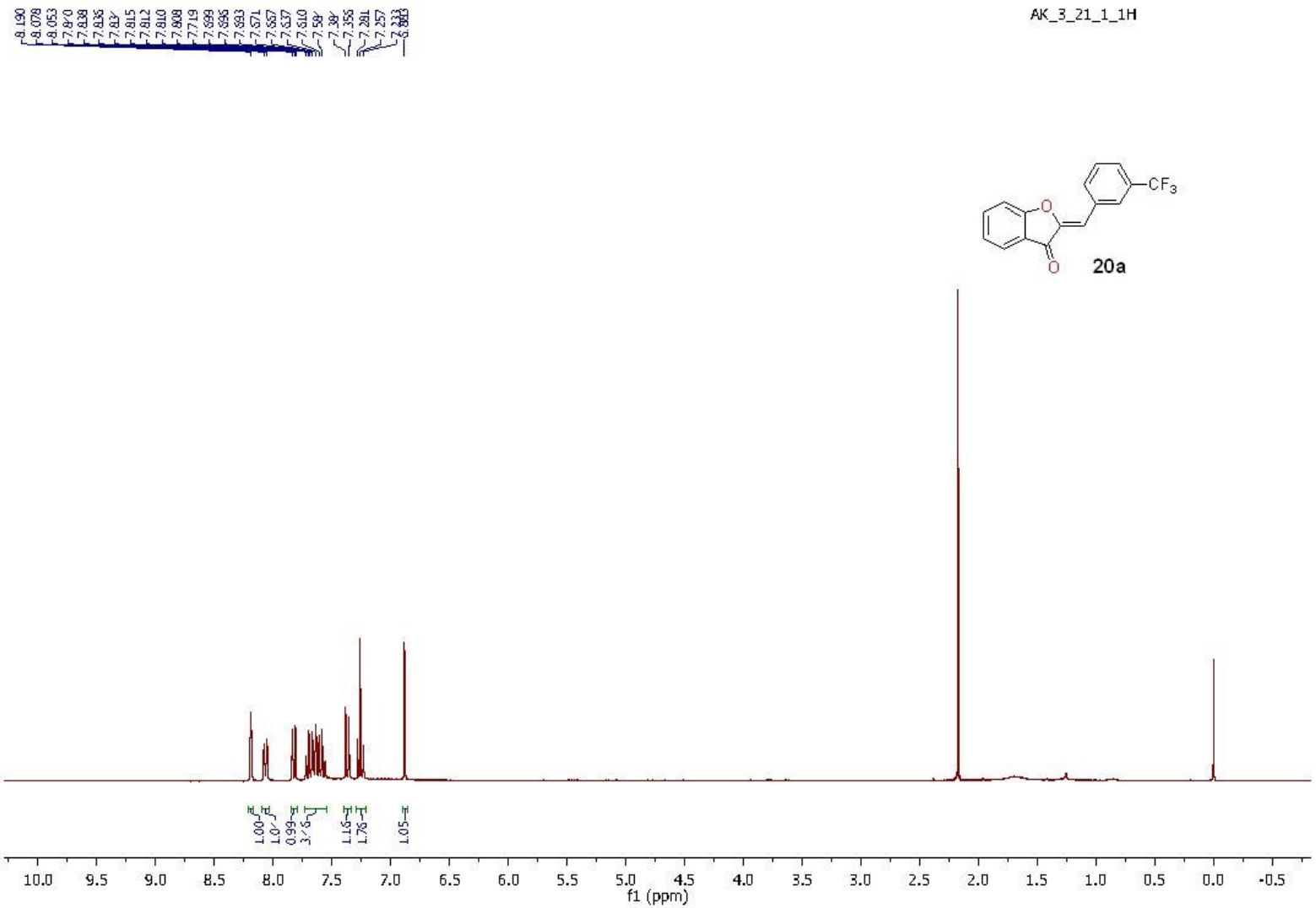
AK_1_111_1_1H



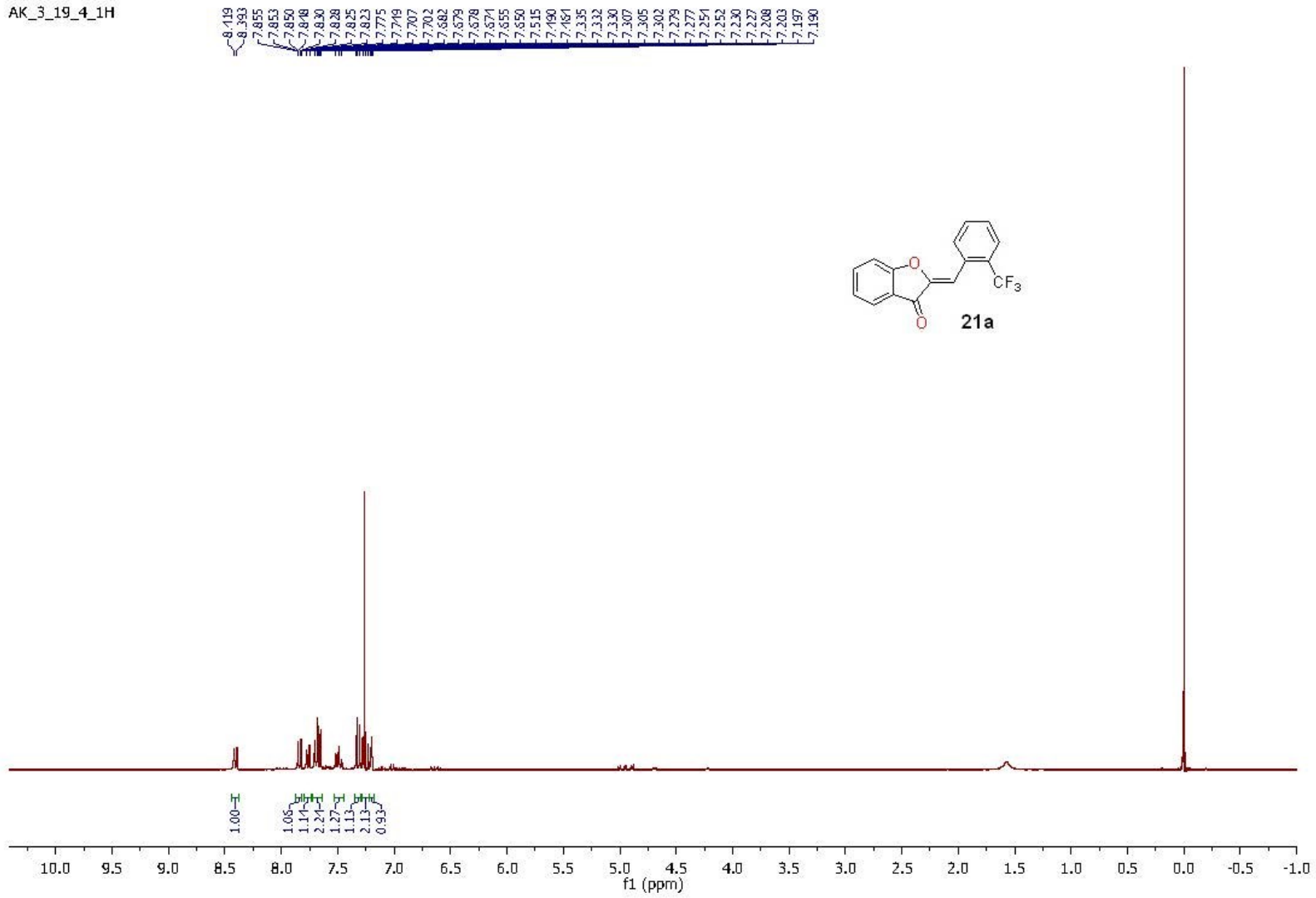
17a

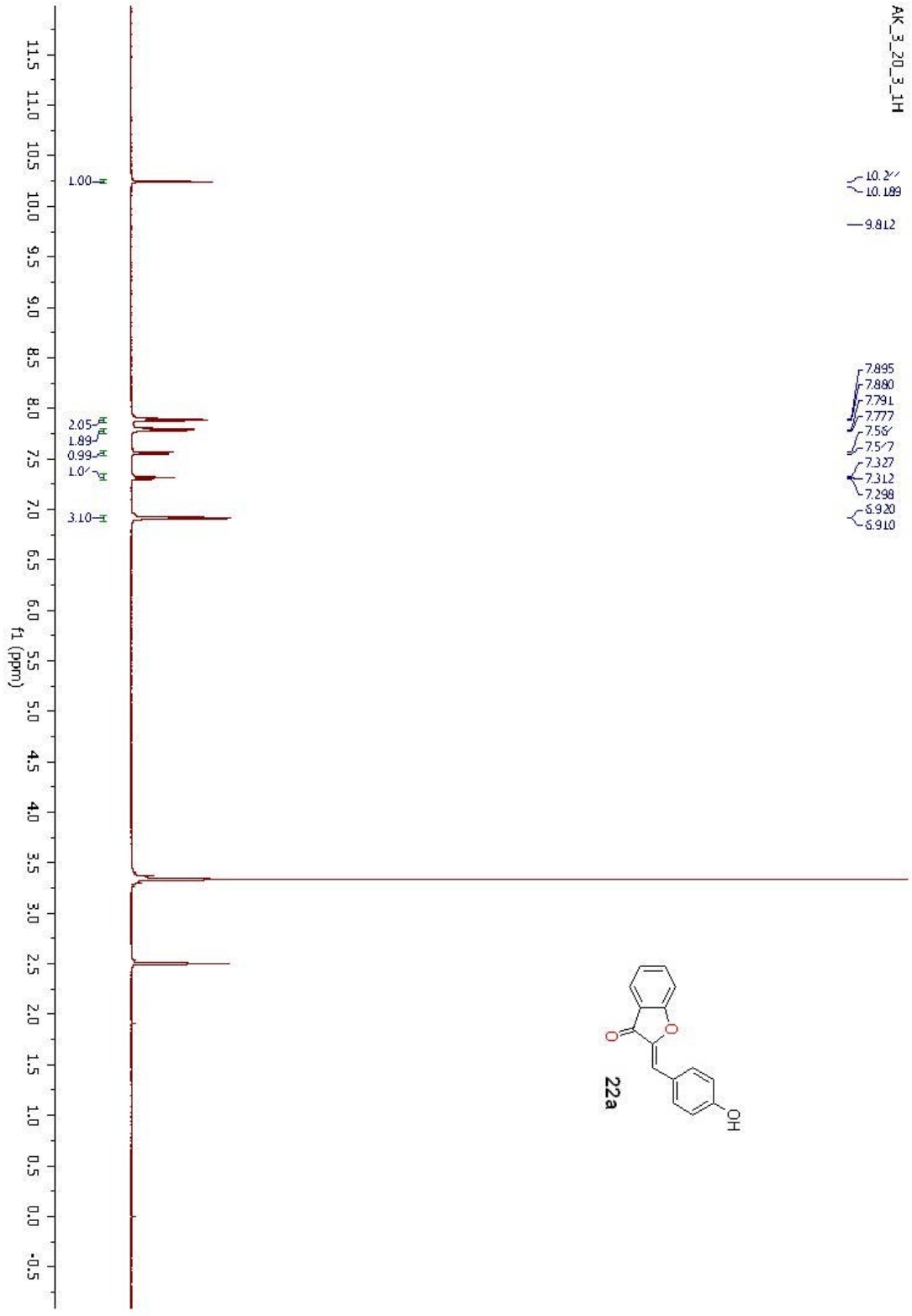



AK_3_21_2_1H
CF3
O
O
19a
8.039
8.012
7.845
7.843
7.841
7.839
7.820
7.818
7.815
7.813
7.727
7.722
7.702
7.699
7.698
7.691
7.675
7.670
7.373
7.345
7.286
2.01
0.98
3.10
1.07
1.71
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


AK_3_21_1_1H
20a
f1 (ppm)

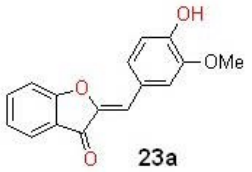
AK_3_19_4_1H


8.419
8.393
7.855
7.853
7.850
7.848
7.830
7.828
7.825
7.823
7.775
7.749
7.707
7.702
7.682
7.679
7.678
7.671
7.655
7.650
7.515
7.490
7.484
7.335
7.332
7.330
7.307
7.305
7.302
7.279
7.277
7.251
7.252
7.230
7.227
7.208
7.203
7.197
7.190
O
CF3
O
21a
1.00
1.05
1.14
2.24
1.27
1.13
2.13
0.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

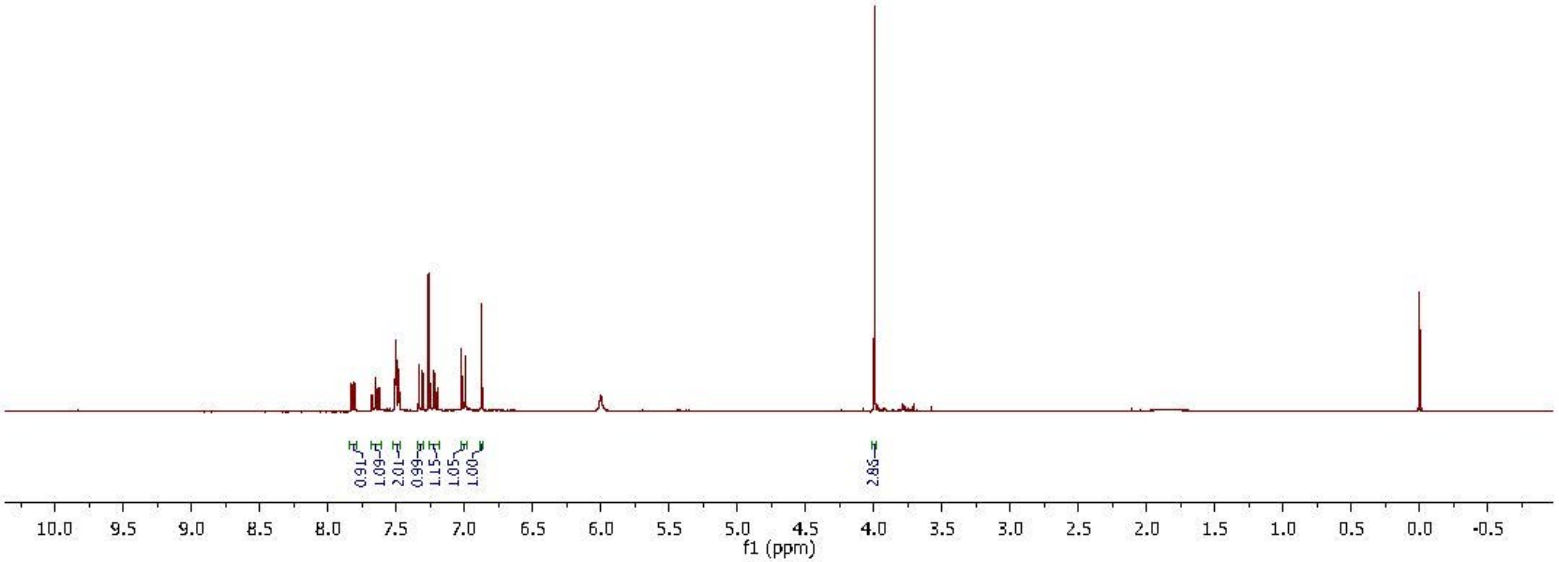

AK_3_20_3_1H
10.2
10.189
9.812
7.895
7.880
7.791
7.777
7.558
7.547
7.327
7.312
7.298
6.920
6.910
1.00
2.05
1.89
0.99
1.07
3.10
f1 (ppm)
22a
OH

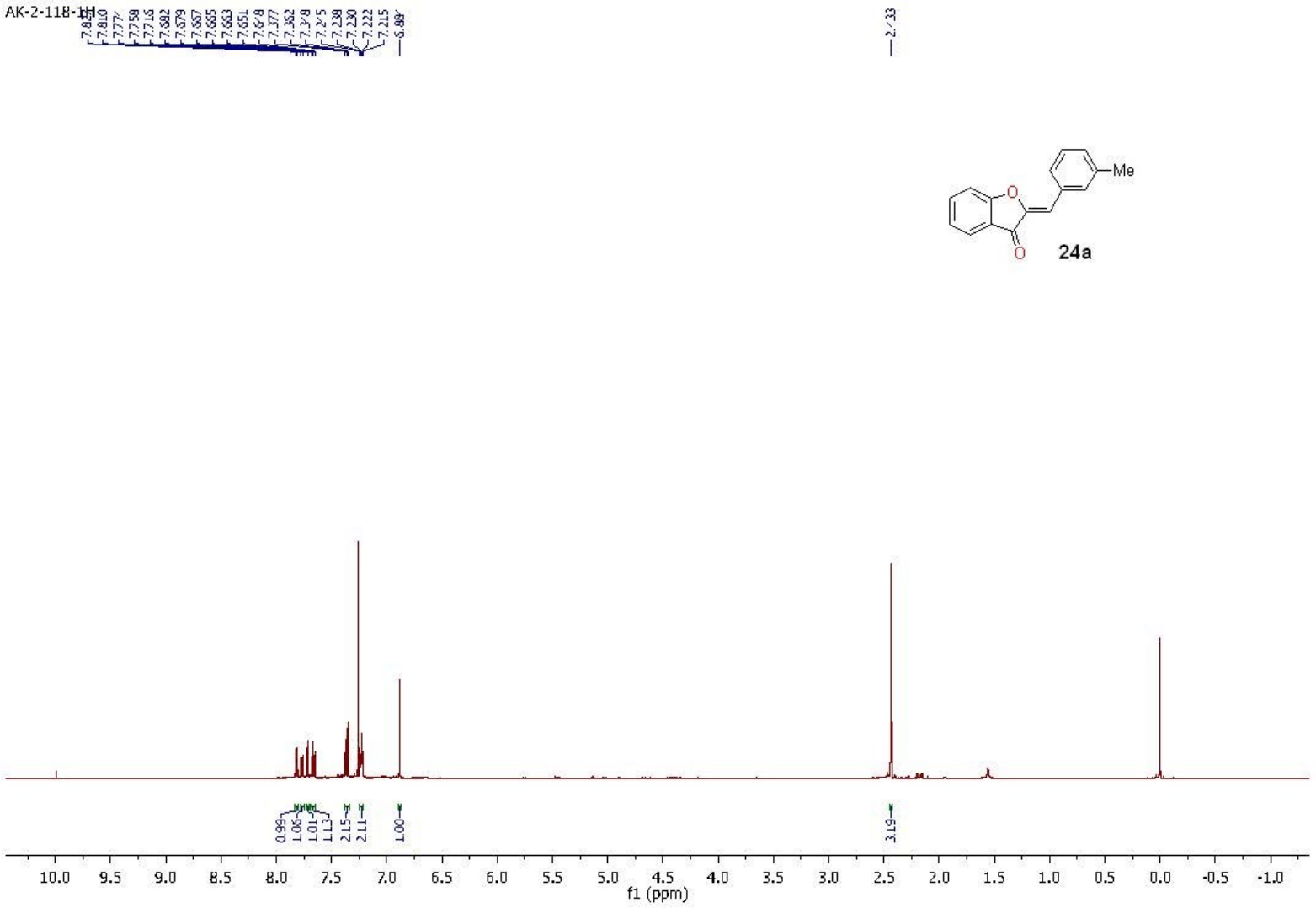
AK_1_85_1H

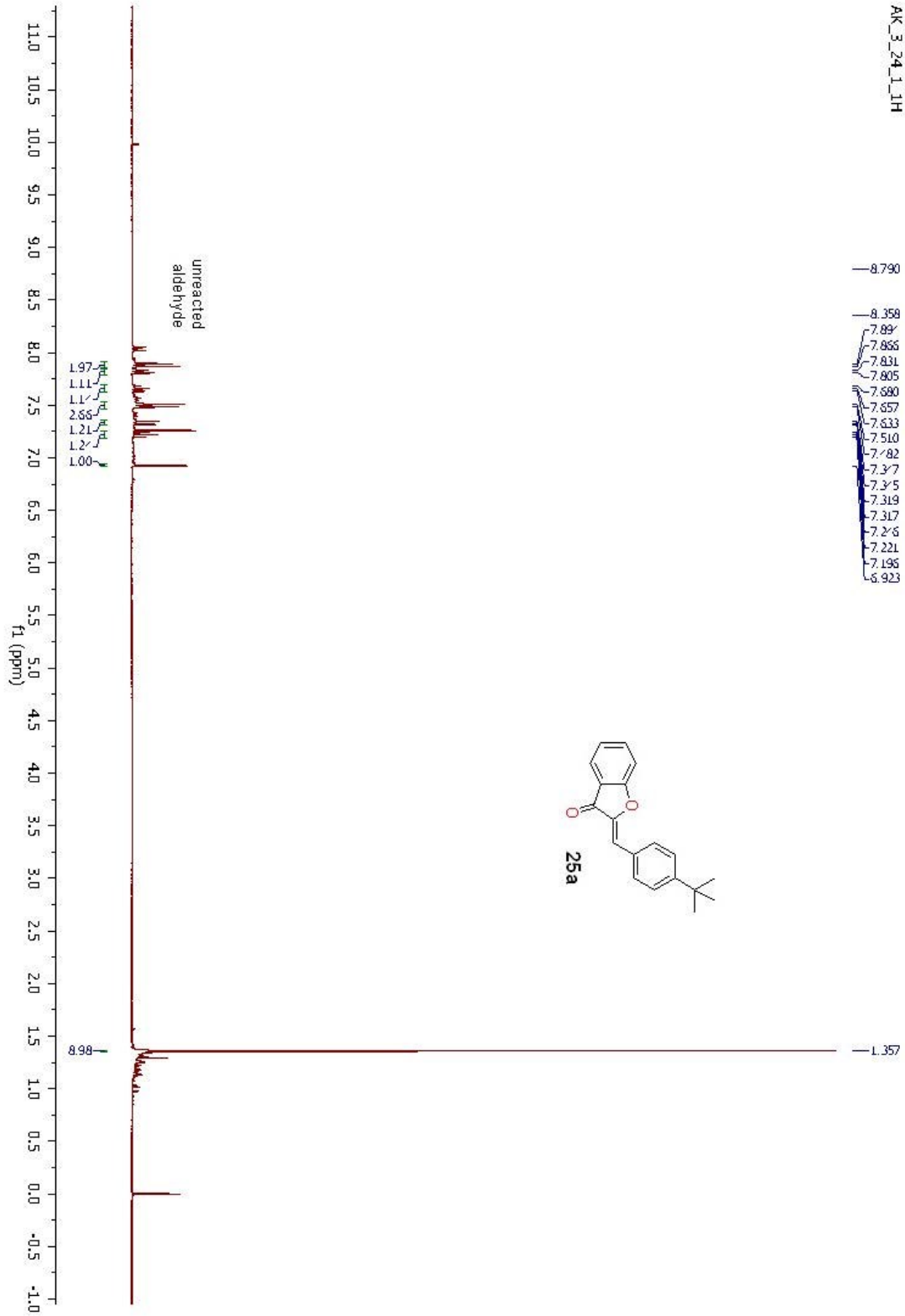

7.831
7.828
7.826
7.805
7.803
7.801
7.677
7.673
7.653
7.649
7.645
7.625
7.620
7.512
7.502
7.496
7.482
7.476
7.333
7.305
7.276
7.221
7.195
7.019
6.990
6.872
3.995

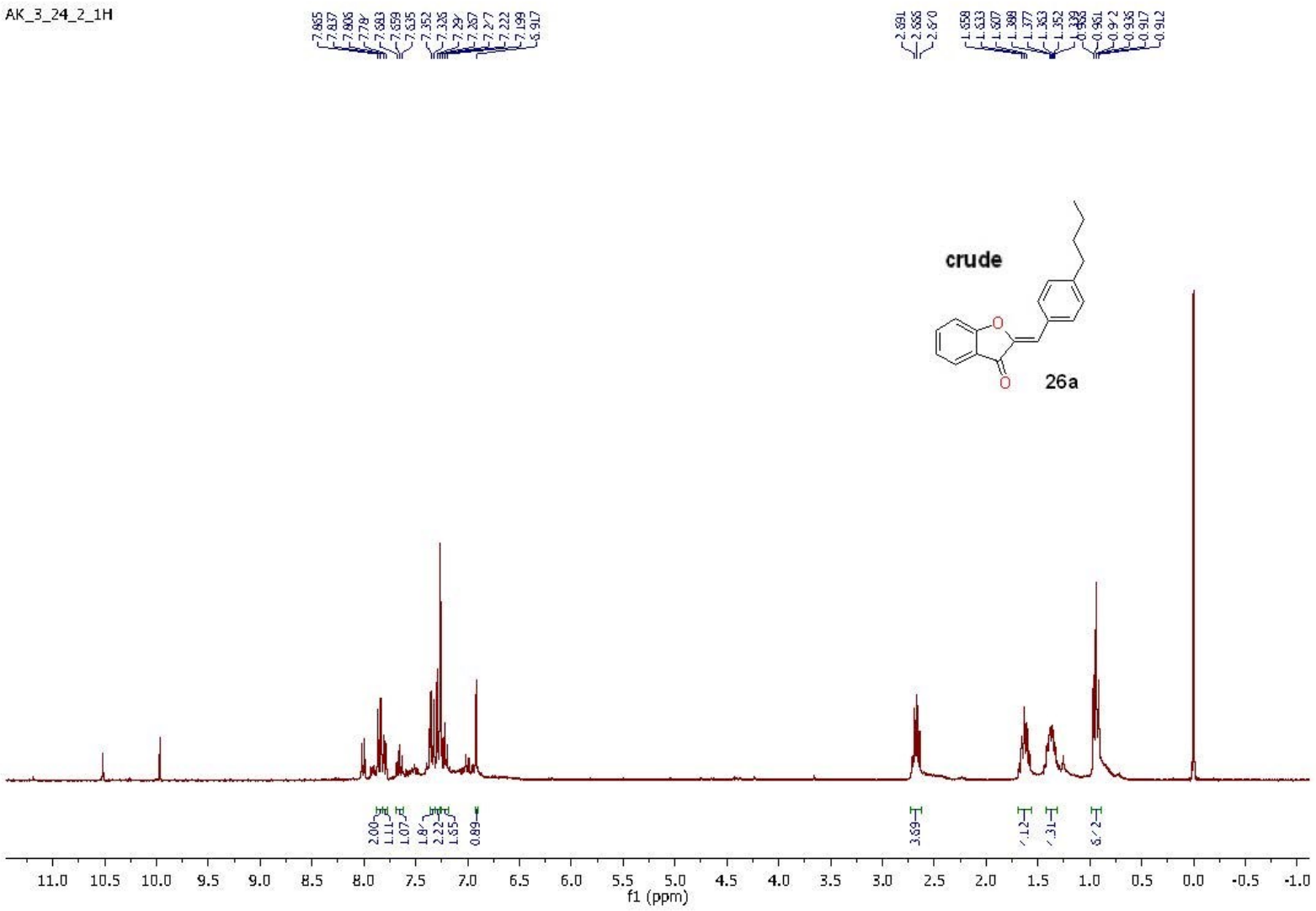

OH
OMe
O
O

23a

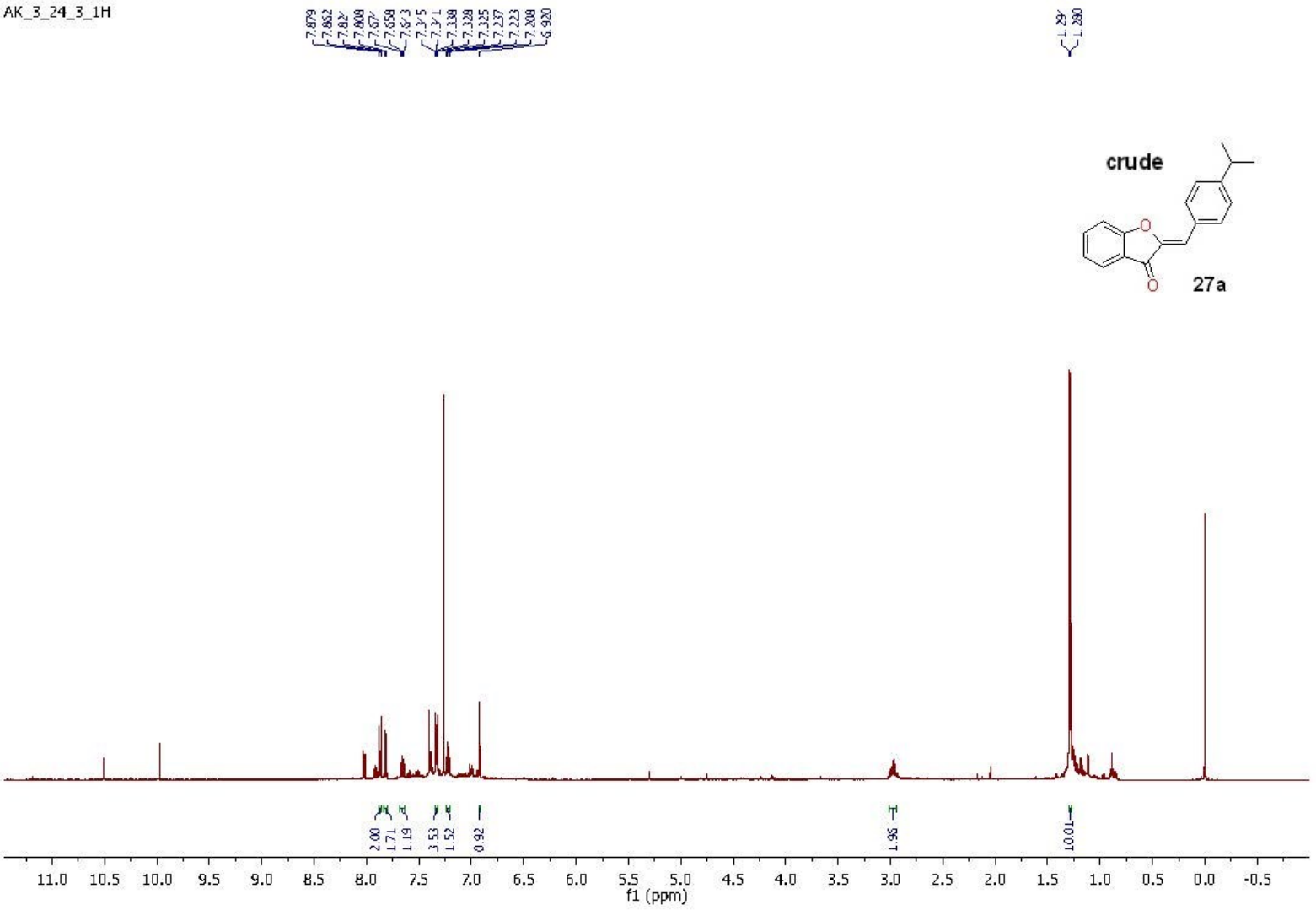

0.91
1.09
2.01
0.99
1.15
1.05
1.00
2.86
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


AK-2-118-1H
Me
O
O
24a
0.99
1.05
1.01
1.13
2.15
2.11
1.00
3.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


AK_3_24_1_1H
unreacted
aldehyde
8.790
8.358
7.897
7.886
7.831
7.805
7.690
7.657
7.633
7.510
7.482
7.397
7.375
7.319
7.317
7.276
7.221
7.196
6.923
1.357
8.98
1.97
1.11
1.17
2.66
1.21
1.27
1.00
25a
f1 (ppm)

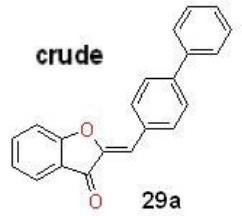

AK_3_24_2_1H
crude
26a
f1 (ppm)

AK_3_24_3_1H

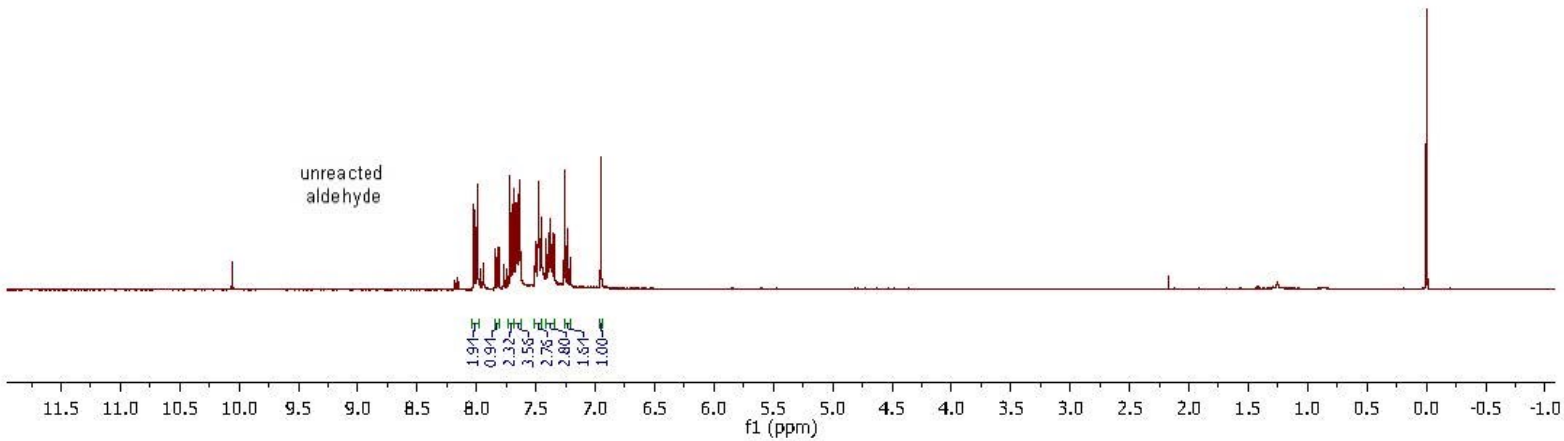

7.879
7.862
7.827
7.808
7.657
7.650
7.643
7.345
7.341
7.338
7.328
7.325
7.237
7.223
7.208
6.920
1.297
1.280
crude
O
O
27a
2.00
1.71
1.19
3.53
1.52
0.92
1.95
10.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

AK_3_24_4_1H

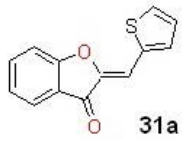
crude



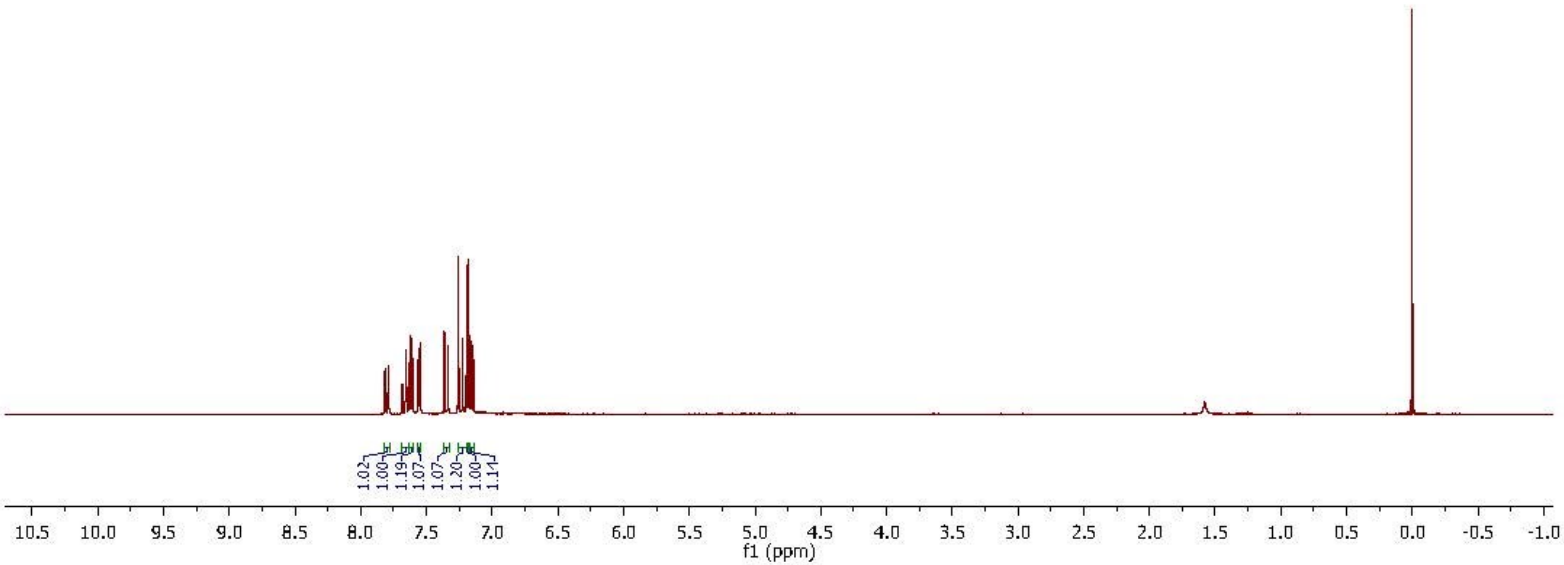
29a



AK_3_25_4_1H

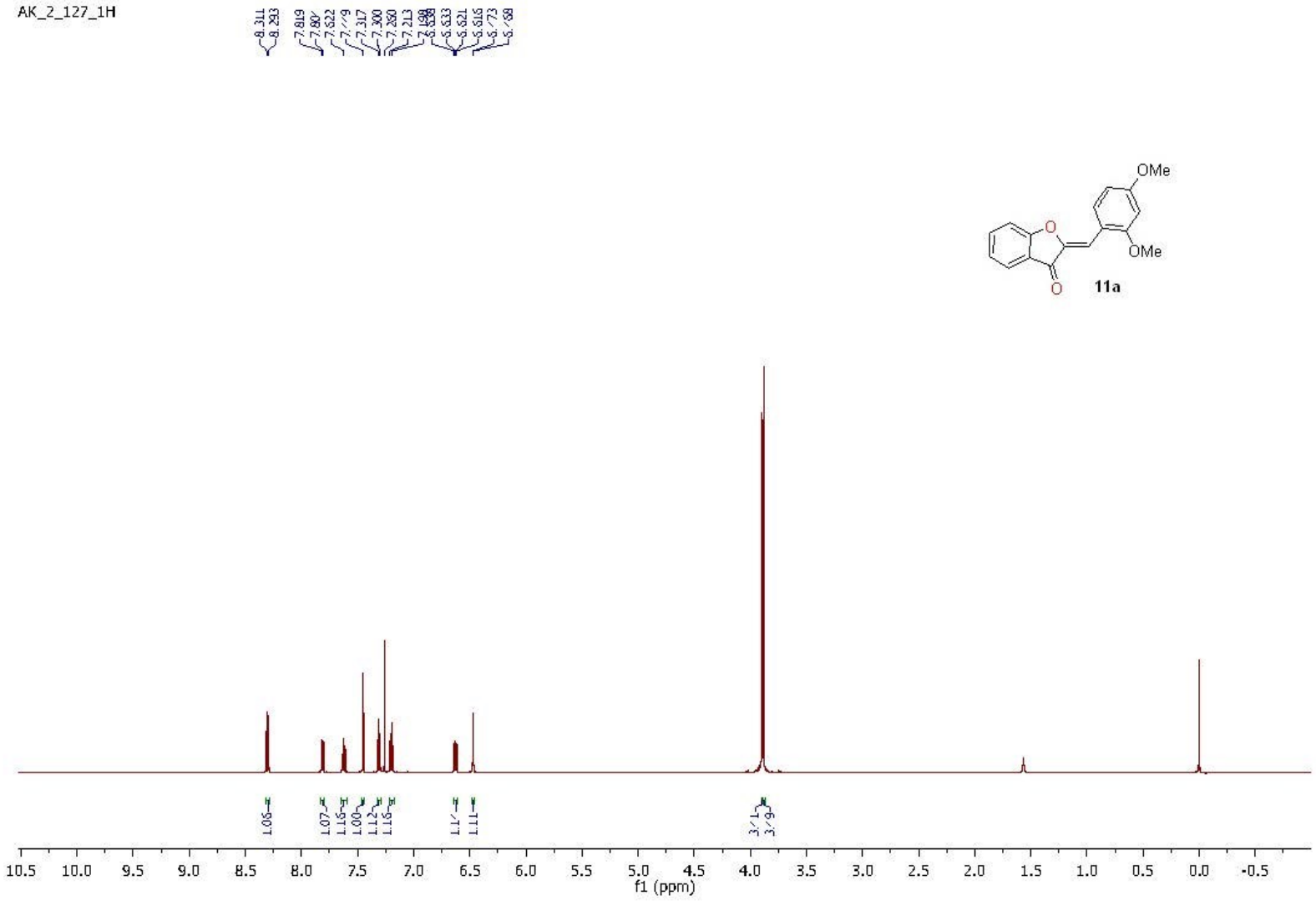


31a

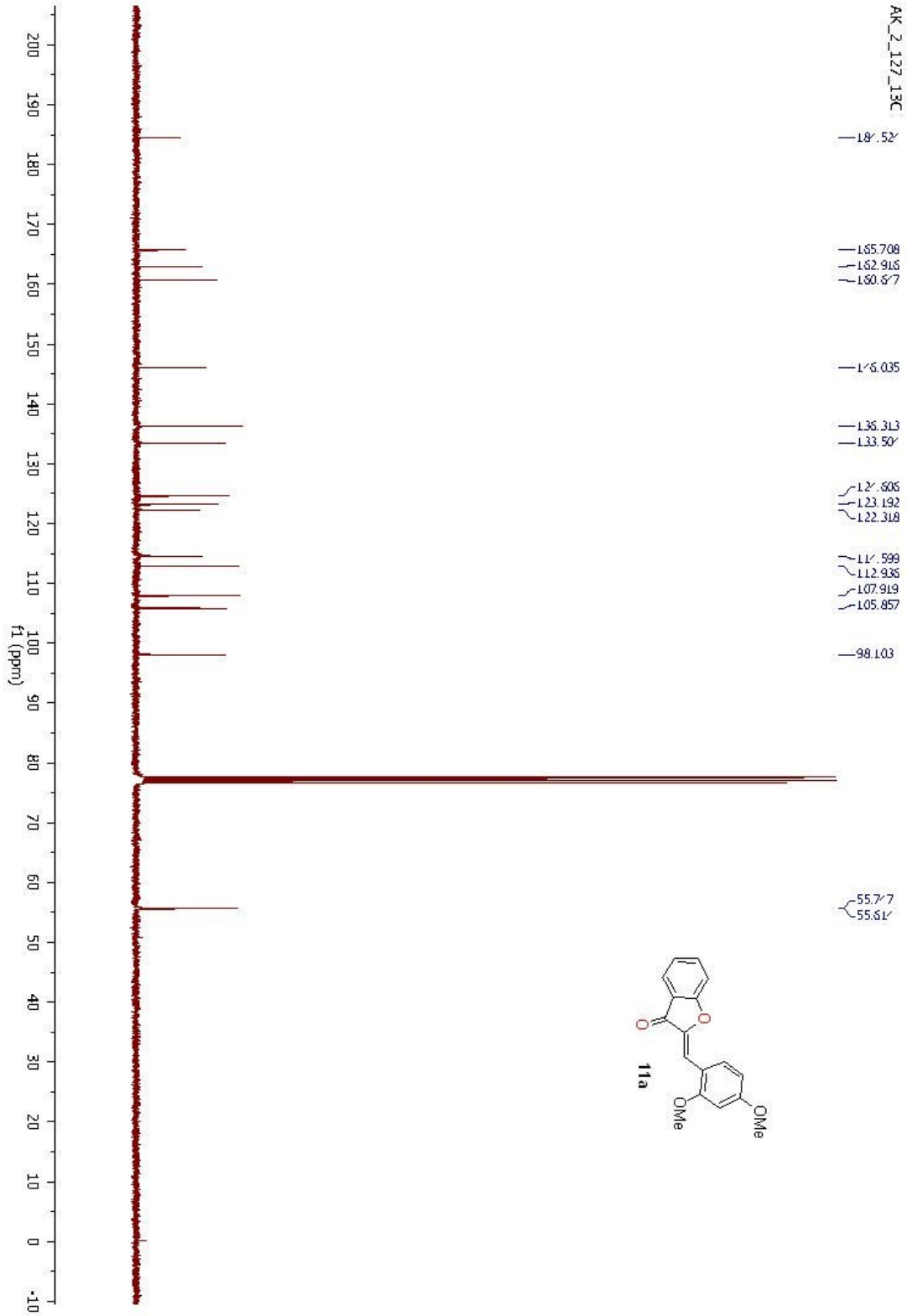


New aurones
(11a, 18a, 30a, 32a-47a)

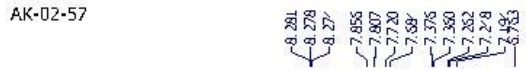
AK_2_127_1H

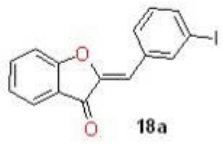


11a

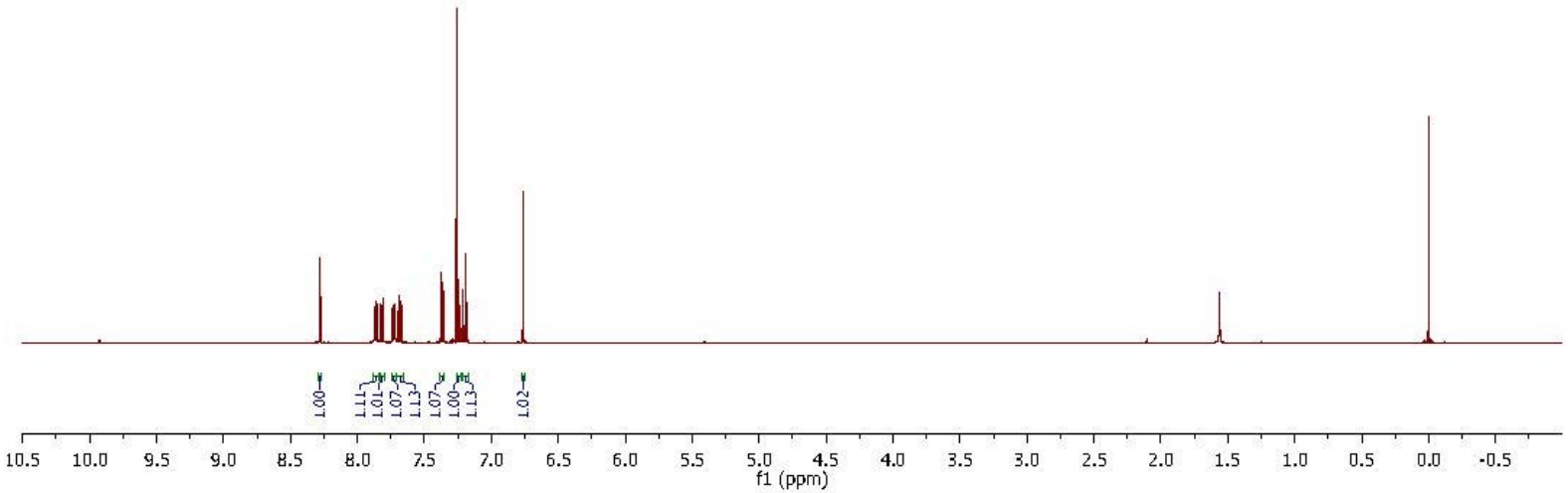

AK_2_127_13C
184.52
165.708
162.916
160.677
146.035
136.313
133.507
124.606
123.192
122.318
114.599
112.936
107.919
105.857
98.103
55.777
55.617
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
O
O
OMe
OMe
11a

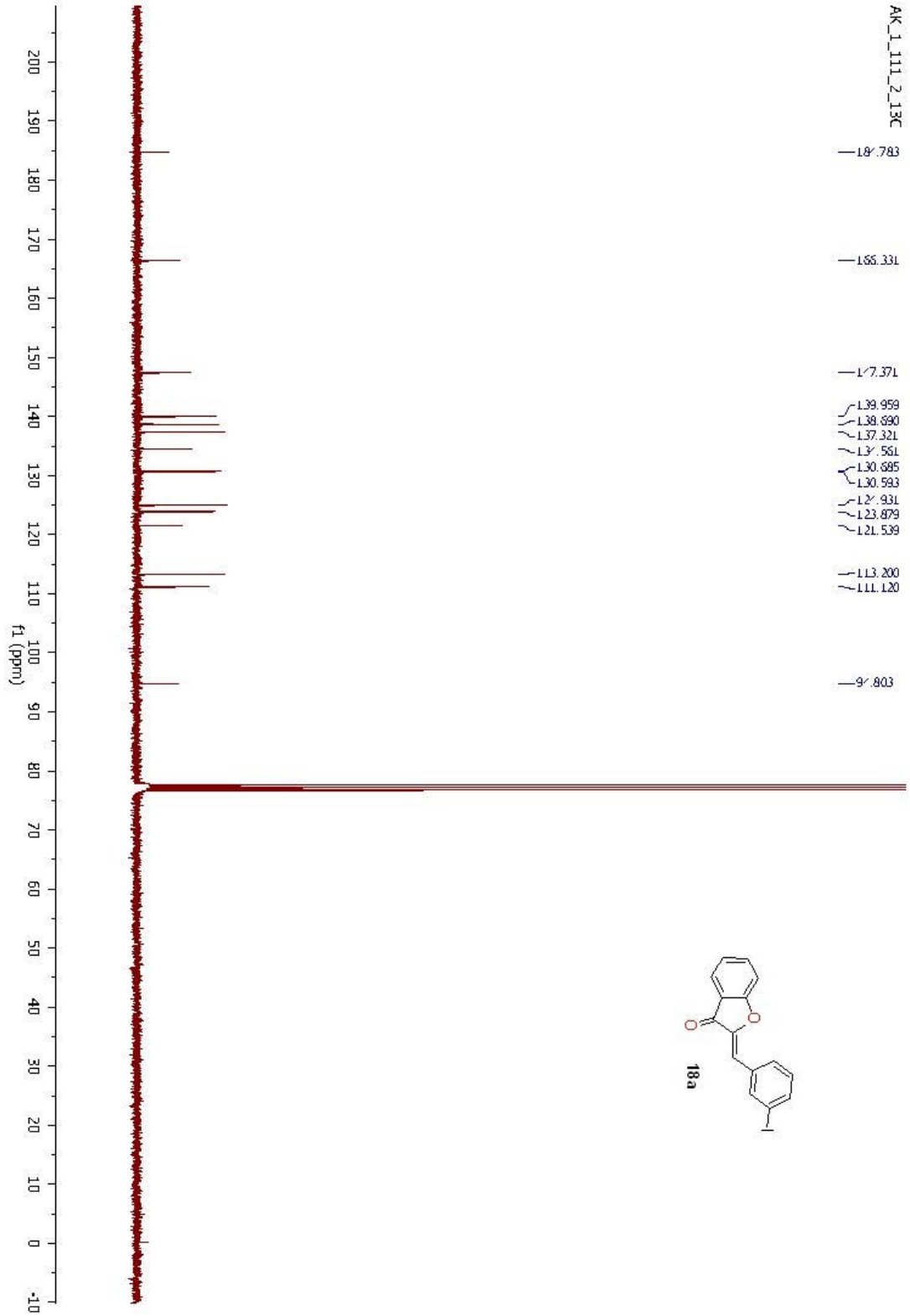
AK-02-57


8.281
8.278
8.277
7.855
7.807
7.720
7.589
7.375
7.360
7.262
7.248
7.143
7.143

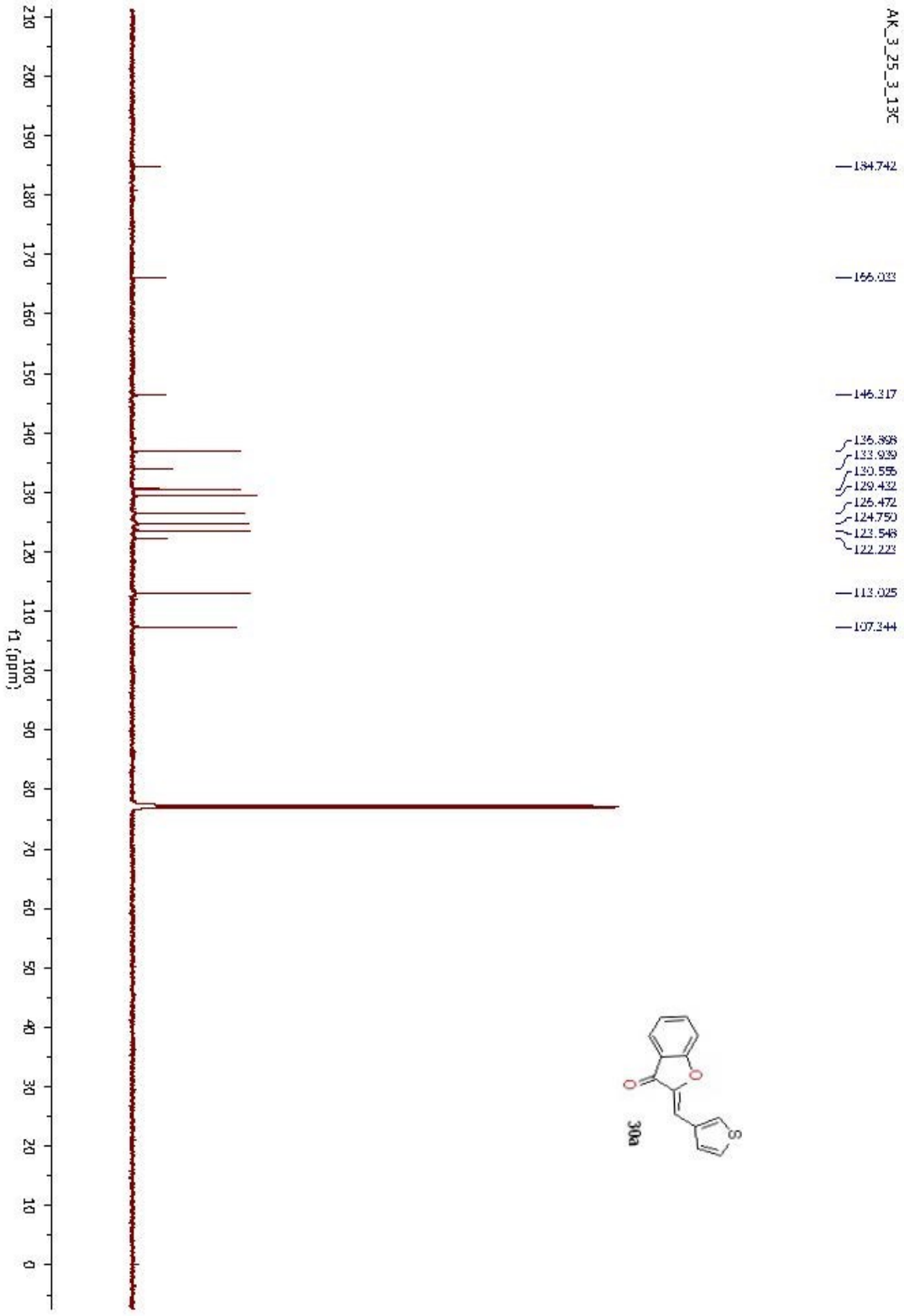

O
I
O

18a


1.00
1.11
1.01
1.07
1.13
1.07
1.00
1.13
1.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

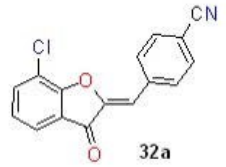

AK_1_111_2_13C
184.783
165.331
147.371
139.959
138.690
137.321
134.561
130.685
130.593
124.931
123.879
121.539
113.200
111.120
94.803
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
18a

AK_3_25_3_1H
7.935
7.929
7.814
7.799
7.671
7.657
7.655
7.641
7.632
7.418
7.412
7.408
7.402
7.227
7.211
7.238
7.223
7.208
6.985
0.82
0.85
0.75
1.14
0.95
0.98
1.00
0.82
f1 (ppm)
30a

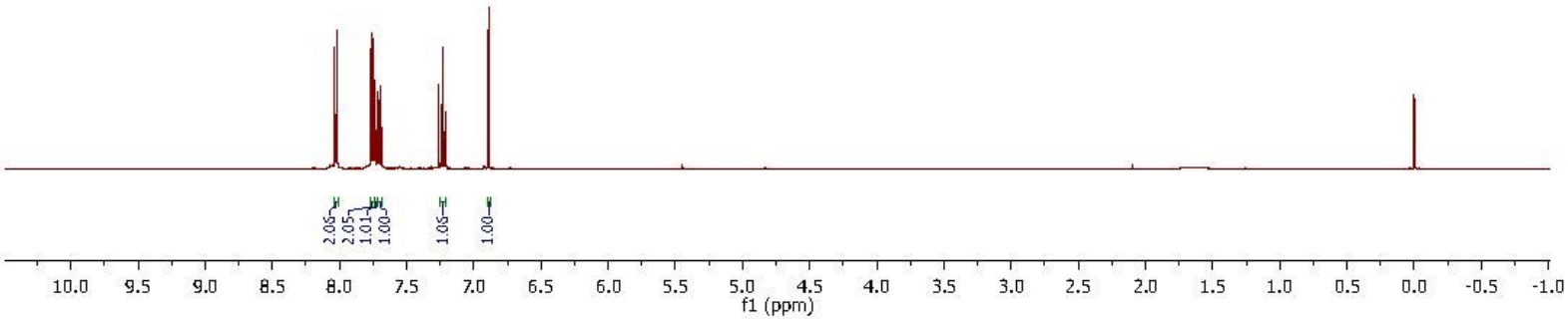

AK_3_25_3_13C
184.742
166.033
146.317
136.898
133.939
130.556
129.432
126.472
124.750
123.548
122.223
113.025
107.244
f1 (ppm)
30a

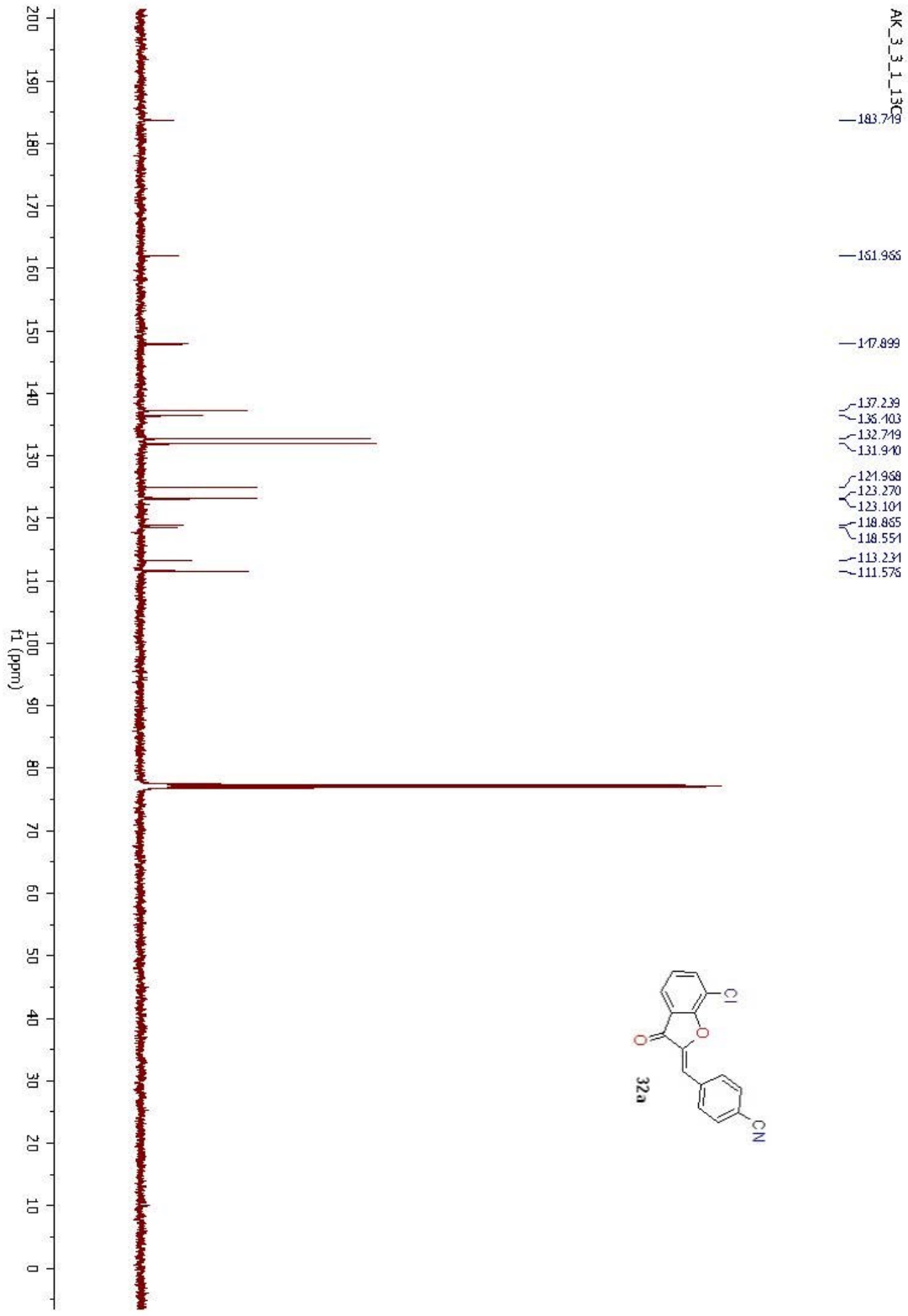
AK_3_3_1_1H


8.038
8.021
7.761
7.747
7.735
7.733
7.721
7.718
7.708
7.706
7.692
7.690
7.261
7.242

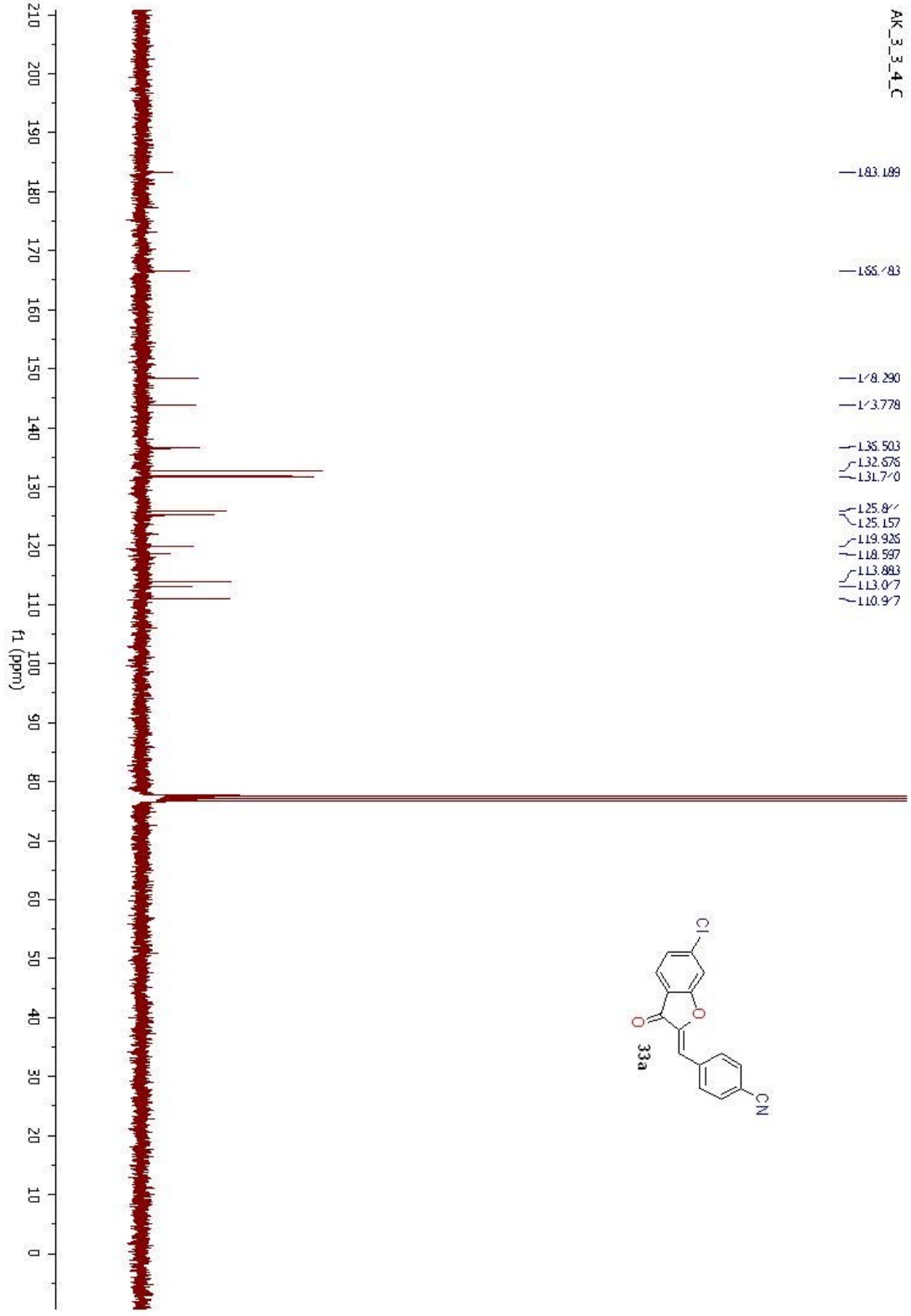

CN
Cl
O
O

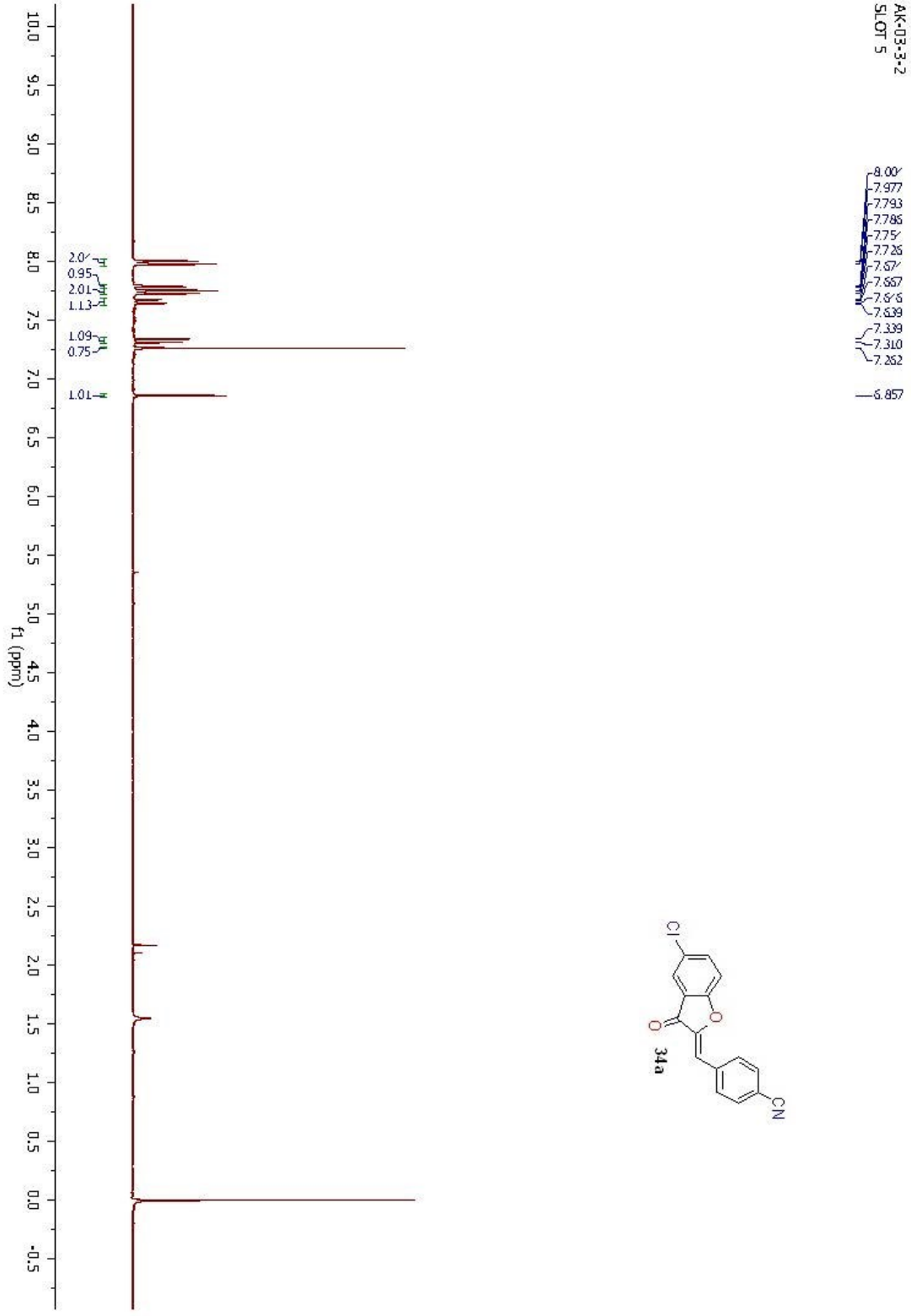
32a

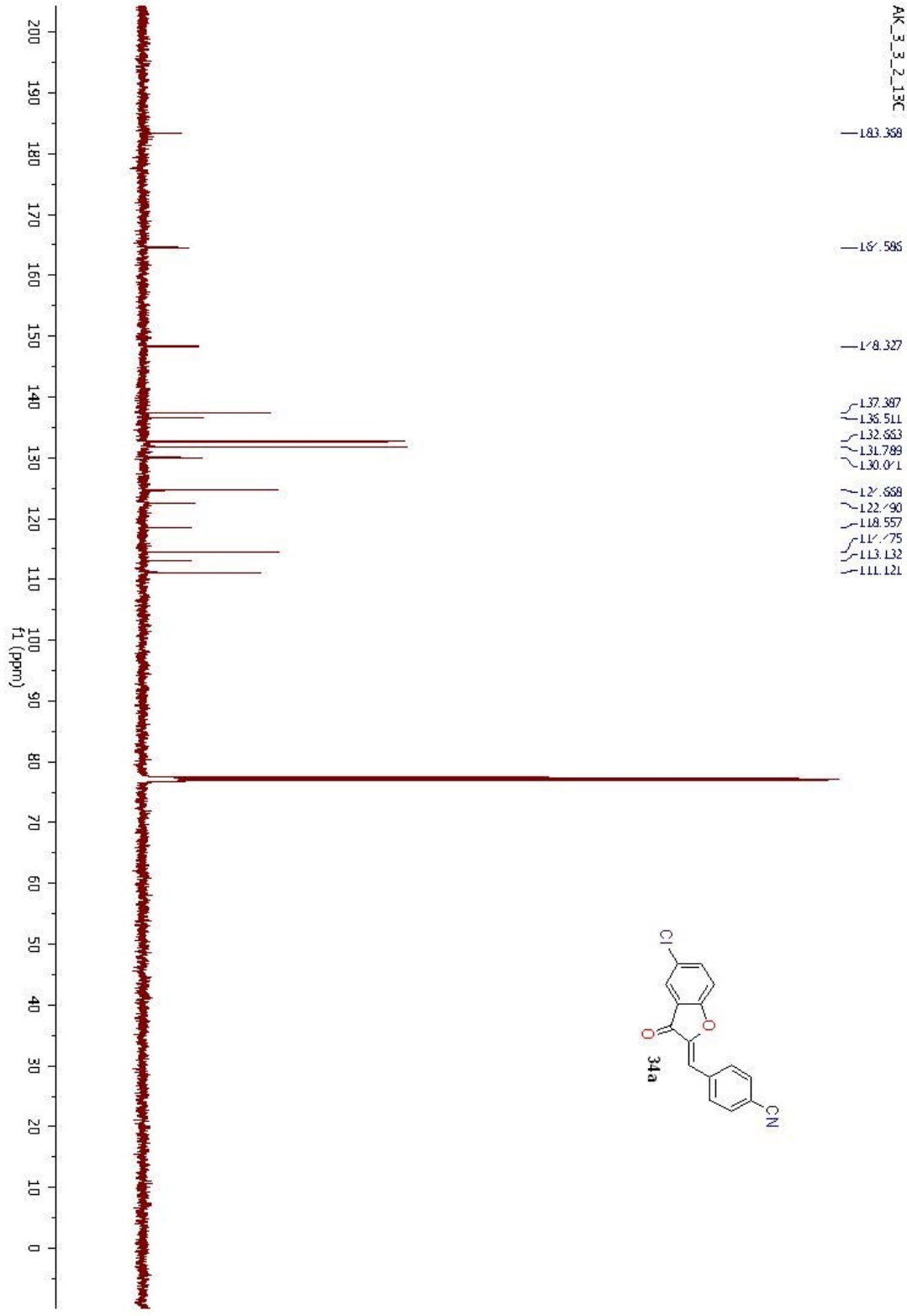

2.05
2.05
1.01
1.00
1.05
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


AK_3_3_1_13C
183.719
161.966
147.899
137.239
136.103
132.749
131.940
124.968
123.270
123.104
118.865
118.554
113.231
111.576
f1 (ppm)
Cl
O
O
CN
32a

AK-03-34
9.612
7.994
7.966
7.775
7.772
7.756
7.748
7.717
7.727
7.706
7.700
7.278
7.273
6.852
2.08
3.12
1.00
2.16
1.00
f1 (ppm)
33a
Cl
O
O
CN


AK_3_3_4_C
183.189
165.783
148.290
143.778
136.503
132.576
131.760
125.897
125.157
119.926
118.597
113.883
113.067
110.967
f1 (ppm)
Cl
O
O
CN
33a


AK-03-3-2
SLOT 5
8.00
7.977
7.793
7.785
7.775
7.726
7.657
7.647
7.636
7.639
7.339
7.310
7.262
6.857
2.0
0.95
2.01
1.13
1.09
0.75
1.01
f1 (ppm)
Cl
O
O
34a
CN

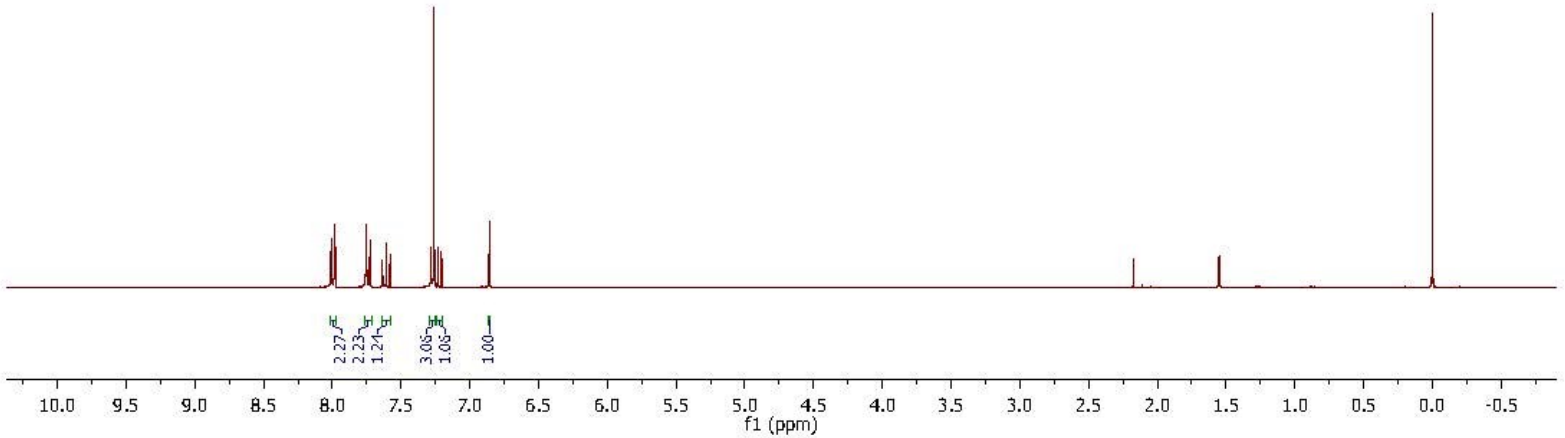

AK_3_3_2_13C
183.358
167.586
148.327
137.387
136.511
132.663
131.789
130.071
122.490
118.557
113.132
111.121
f1 (ppm)
34a
Cl
O
CN

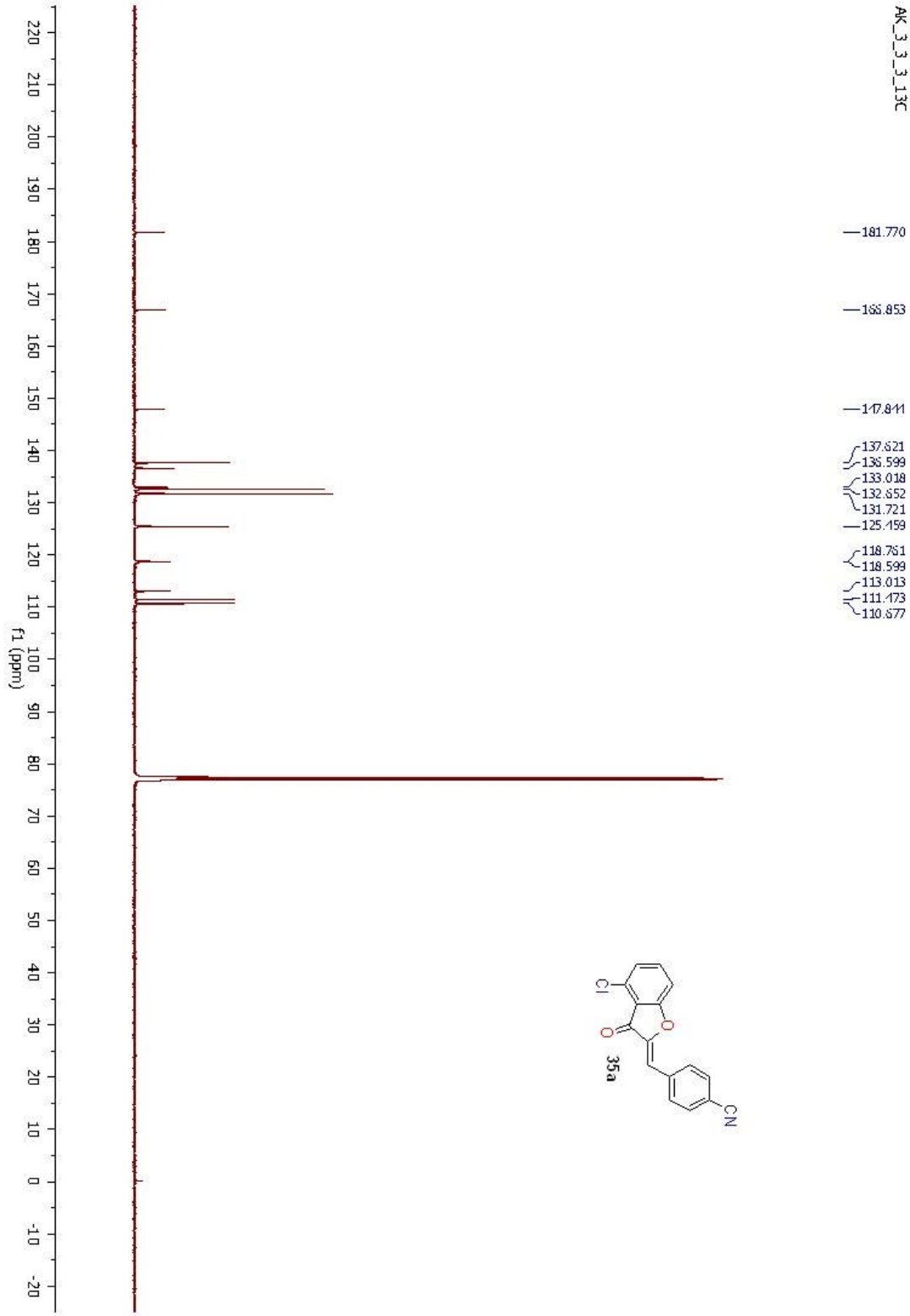
AK-03-3-3

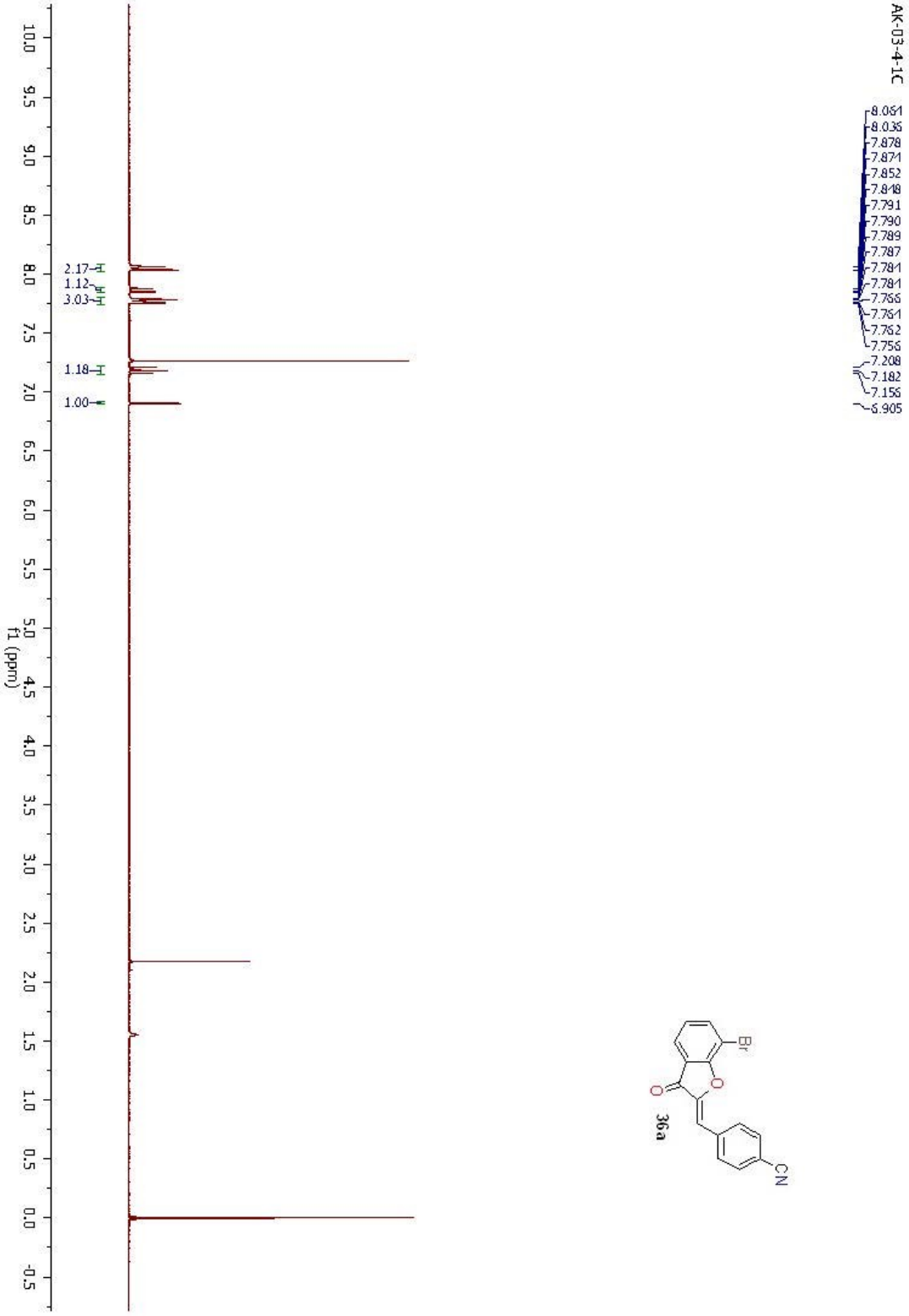

8.009
7.980
7.751
7.726
7.635
7.608
7.581
7.282
7.280

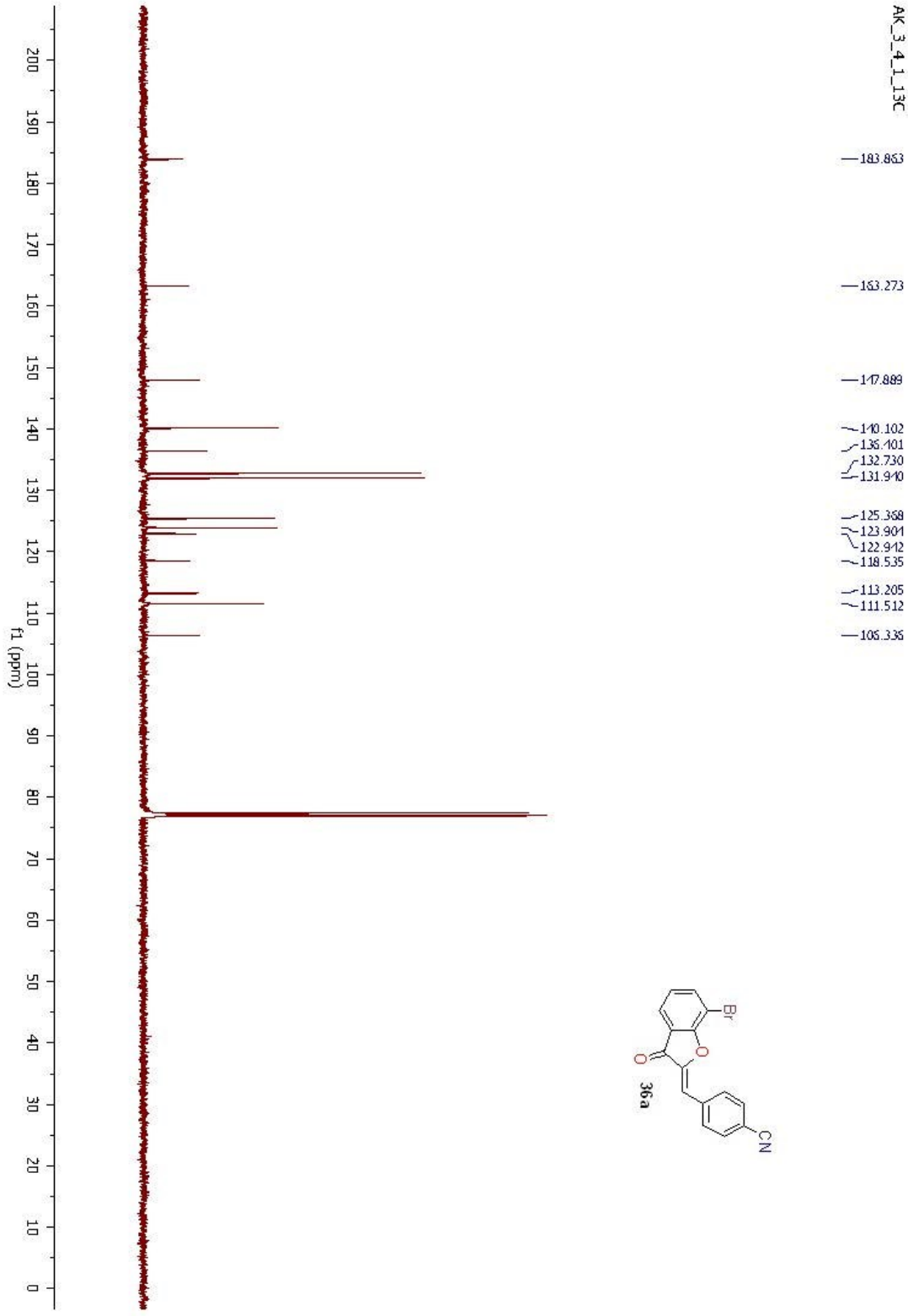

CN
O
O
Cl

35a


2.27
2.23
1.24
3.08
1.06
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

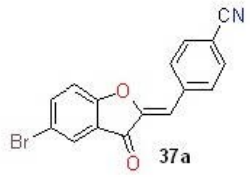

AK_3_3_3_13C
181.770
166.853
147.841
137.621
136.599
133.018
132.652
131.721
125.459
118.761
118.599
113.013
111.473
110.677
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Cl
O
O
CN
35a


AK-03-4-1C
8.061
8.036
7.878
7.871
7.852
7.848
7.791
7.790
7.789
7.787
7.784
7.781
7.766
7.764
7.762
7.756
7.208
7.182
7.156
6.905
2.17
1.12
3.03
1.18
1.00
f1 (ppm)
Br
O
O
CN
36a

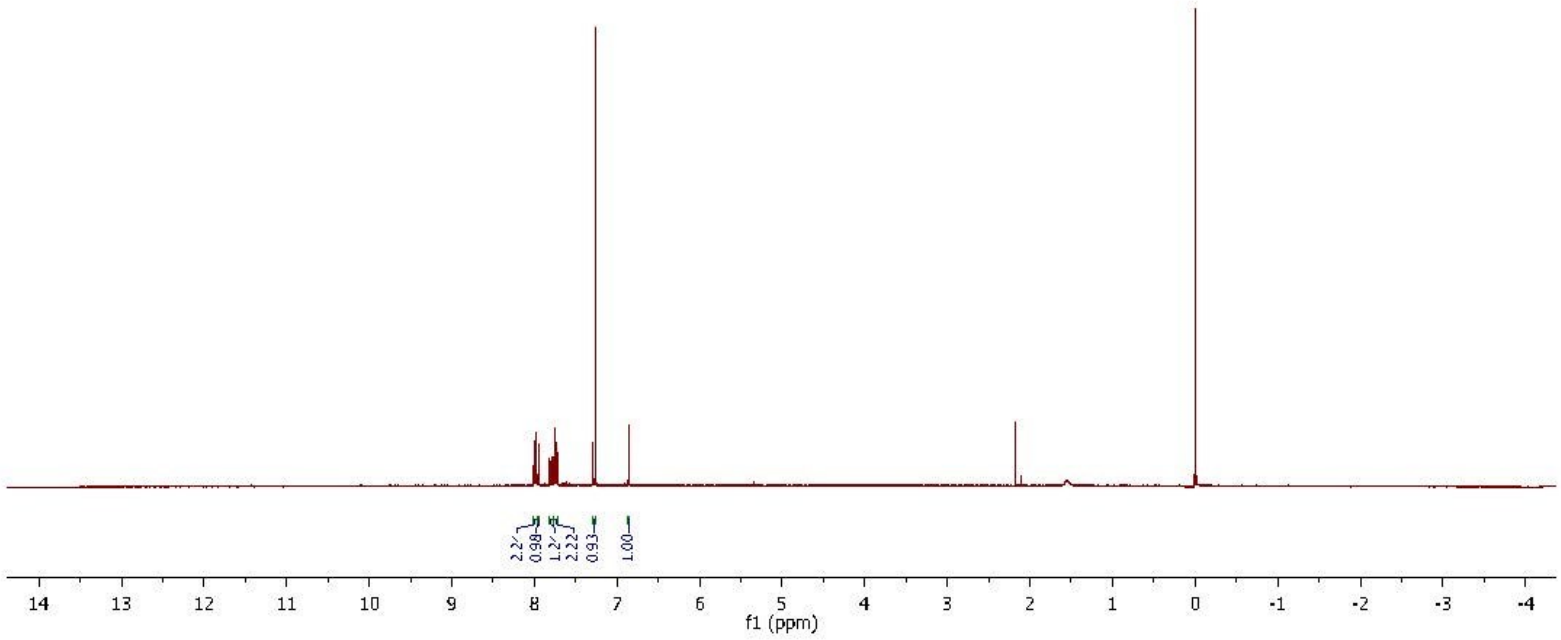

AK_3_4_1_13C
183.863
163.273
147.889
140.102
135.401
132.730
131.940
125.368
123.904
122.942
118.535
113.205
111.512
105.336
f1 (ppm)
Br
O
O
CN
36a

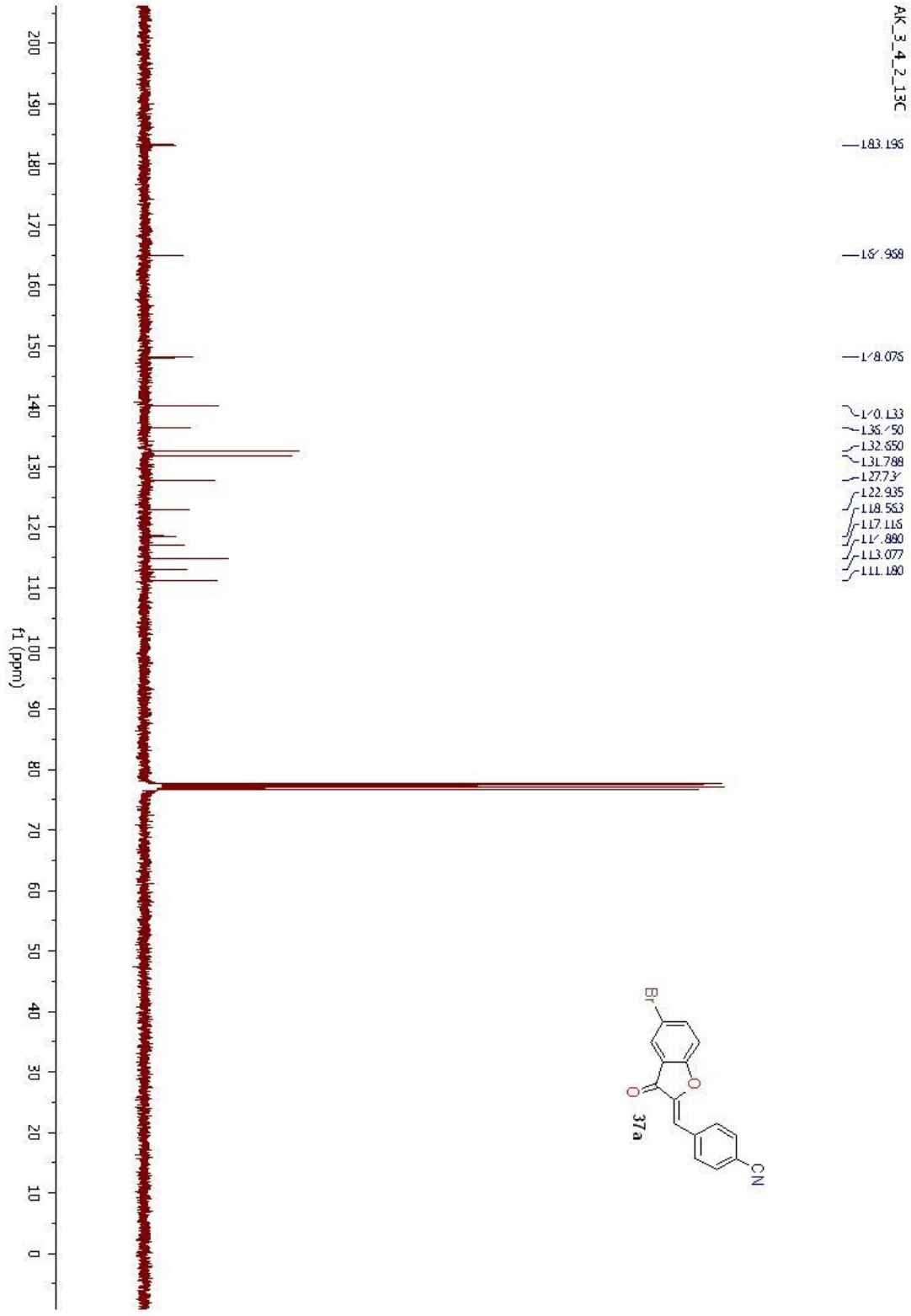
AK-03-4-2B


8.000
7.976
7.949
7.942
7.817
7.806
7.785
7.777
7.759
7.728
7.290
7.262
6.859


CN
O
Br
O

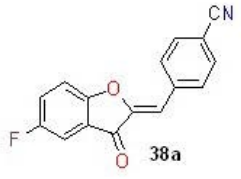
37a


2.24
0.98
1.24
2.22
0.93
1.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

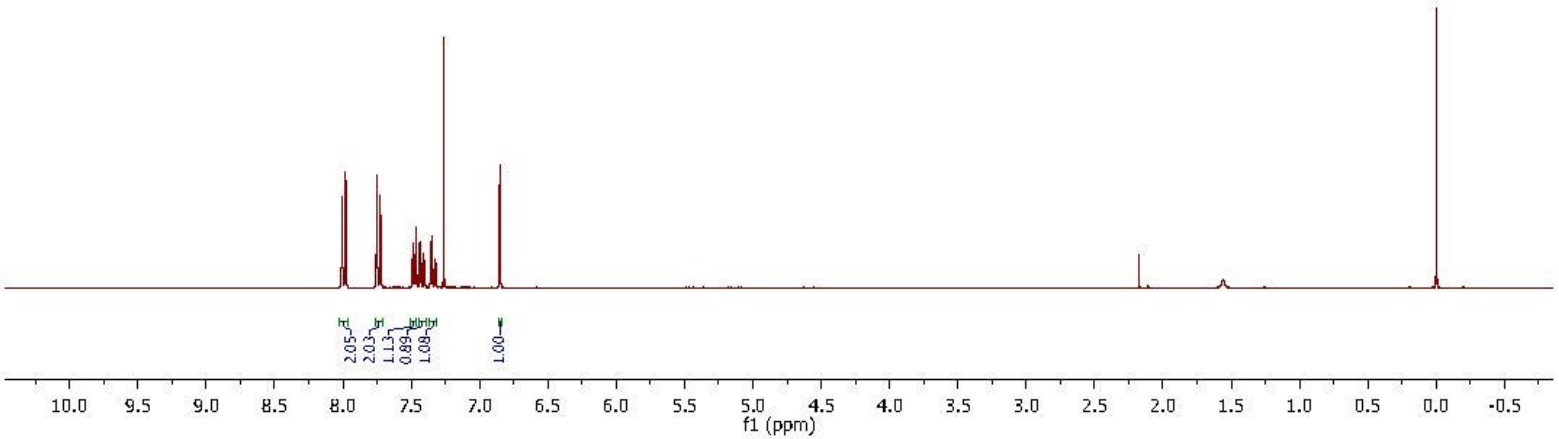

AK_3_4_2_13C
183.196
158.958
148.076
140.133
136.450
132.650
131.788
127.737
122.935
118.563
117.116
114.890
113.077
111.180
f1 (ppm)
Br
O
O
37a
CN

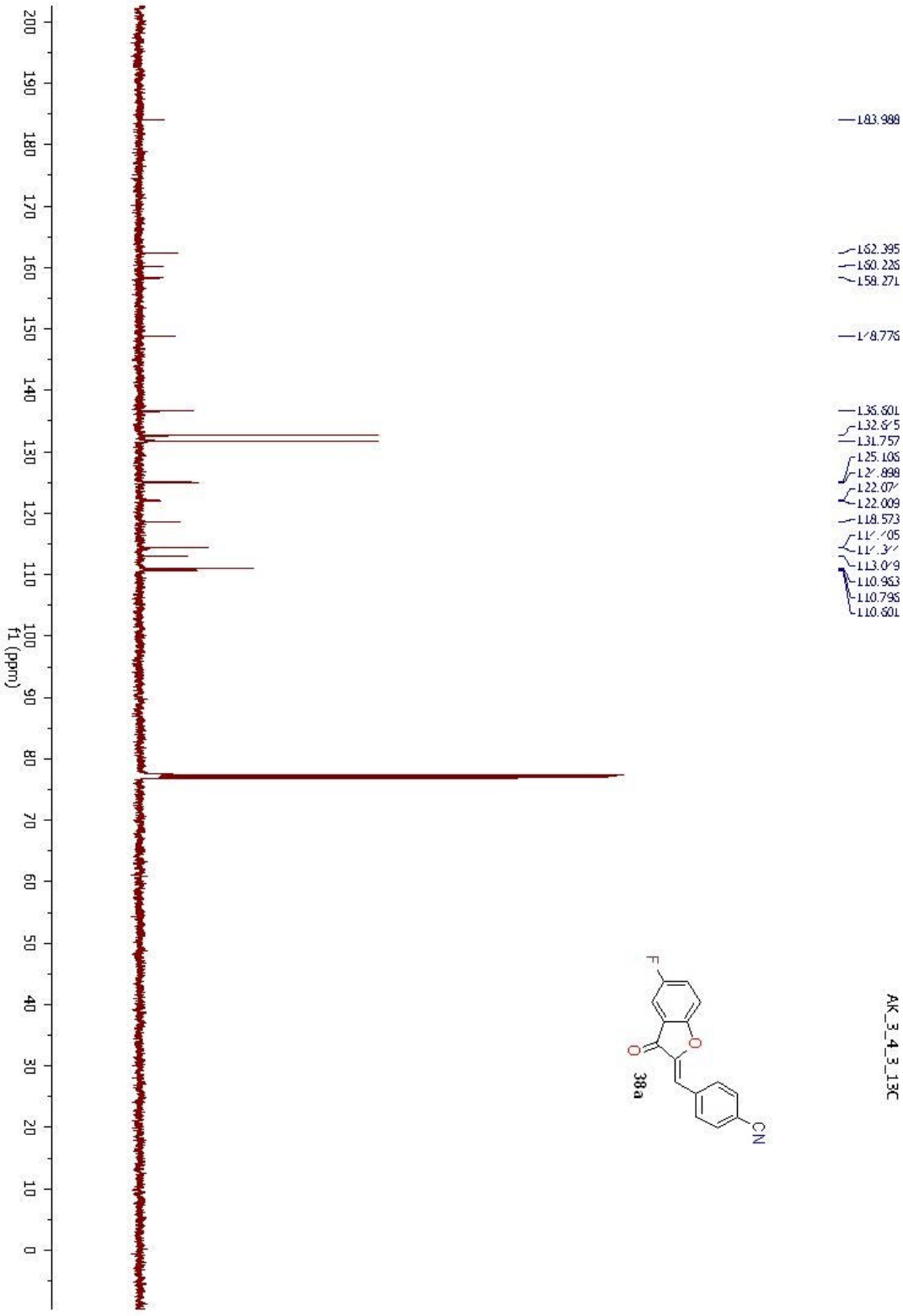
AK-03-4-3

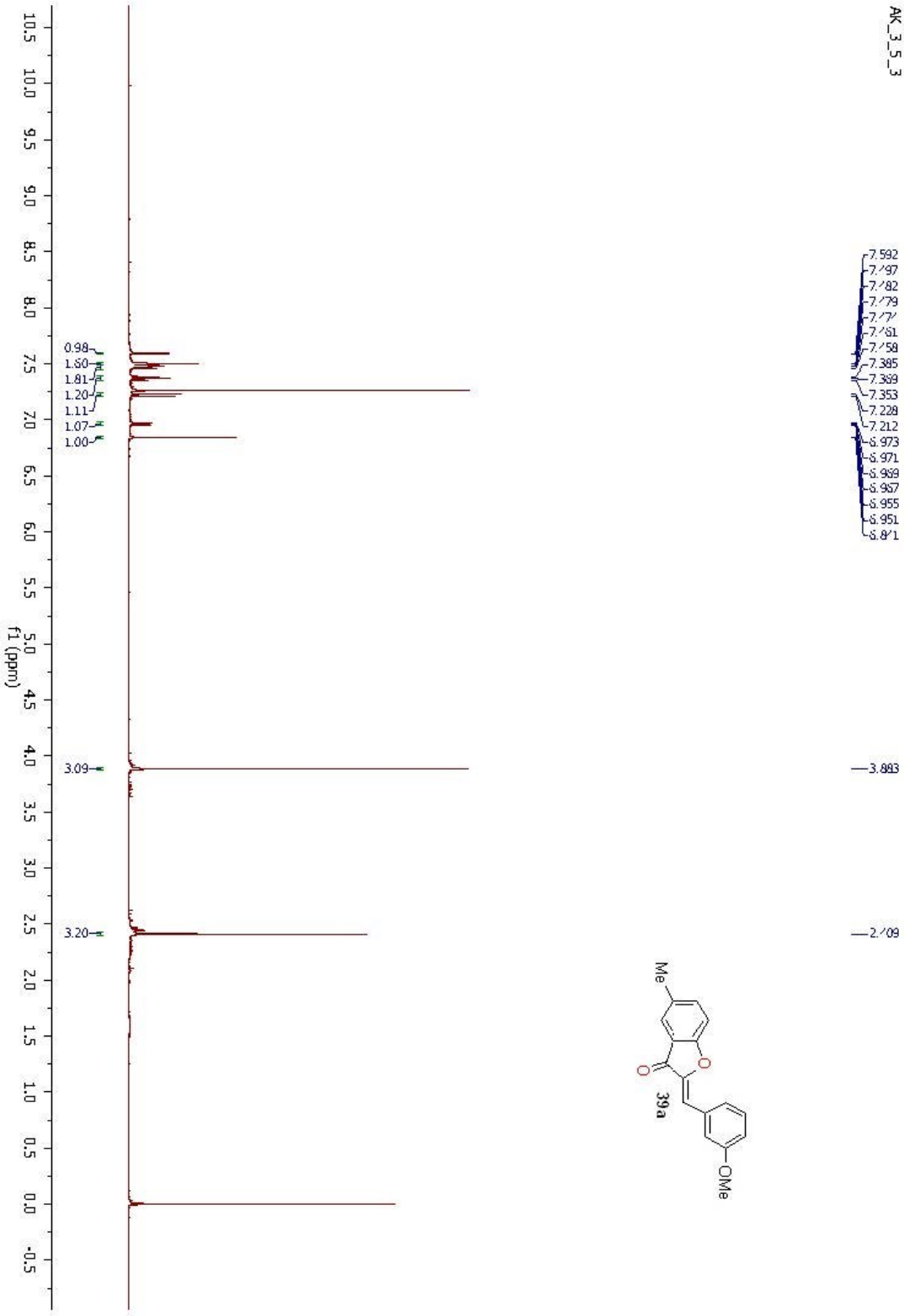

8.008
7.980
7.775
7.735
7.705
7.687
7.677
7.657
7.645
7.637
7.628
7.610
7.600
7.359
7.347
7.330
7.317
6.852

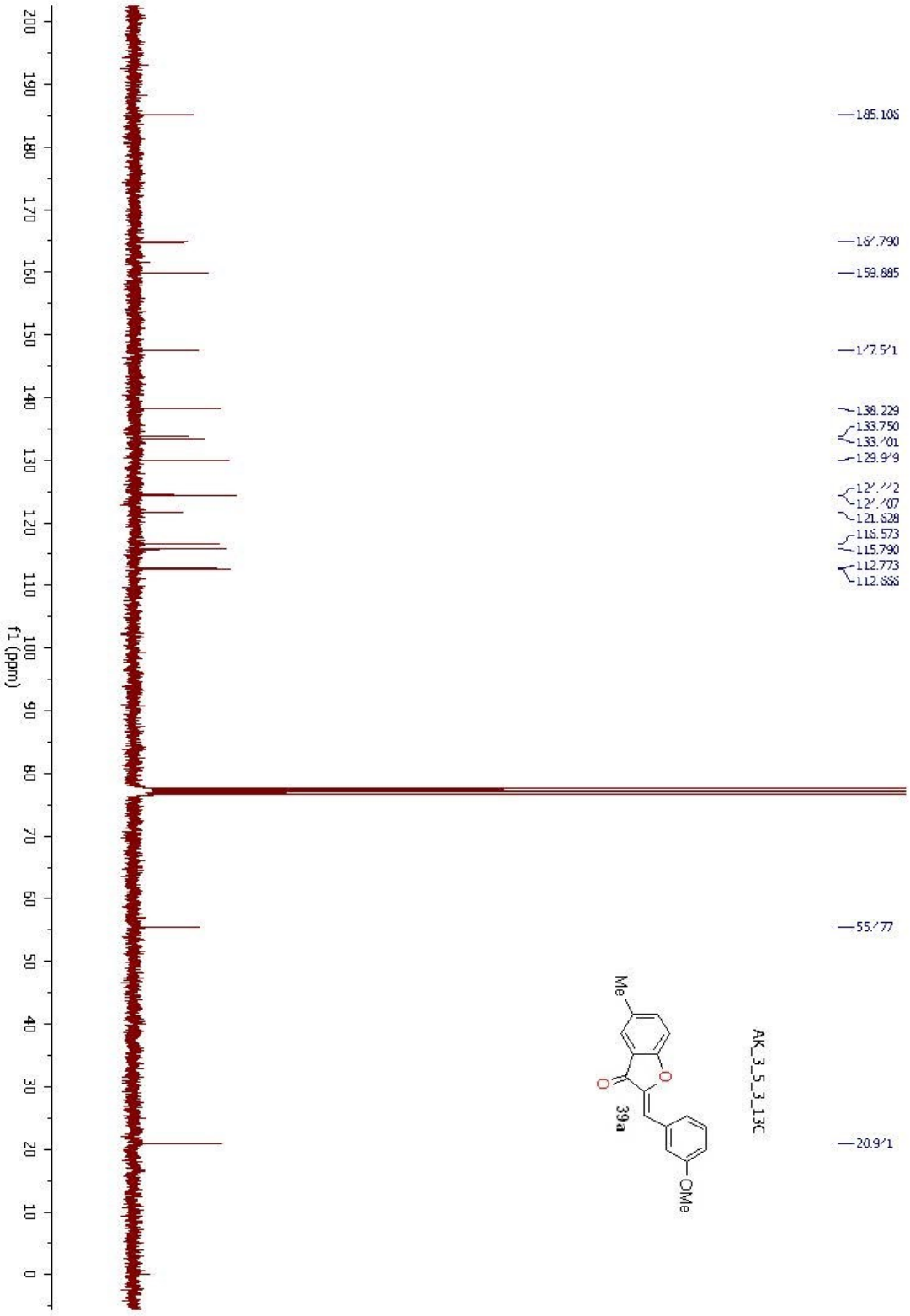

CN
O
F
O

38a


2.05
2.03
1.13
0.89
1.08
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

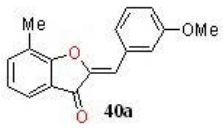

183.988
162.395
160.226
158.271
148.776
136.601
132.675
131.757
125.105
122.079
122.009
118.573
113.079
110.963
110.795
110.601
f1 (ppm)
38a
AK_3_4_3_13C


AK_3_5_3
7.592
7.497
7.482
7.479
7.477
7.461
7.458
7.385
7.369
7.353
7.228
7.212
6.973
6.971
6.969
6.967
6.955
6.951
6.871
3.883
2.709
0.98
1.60
1.81
1.20
1.11
1.07
1.00
3.09
3.20
f1 (ppm)
Me
O
O
OMe
39a

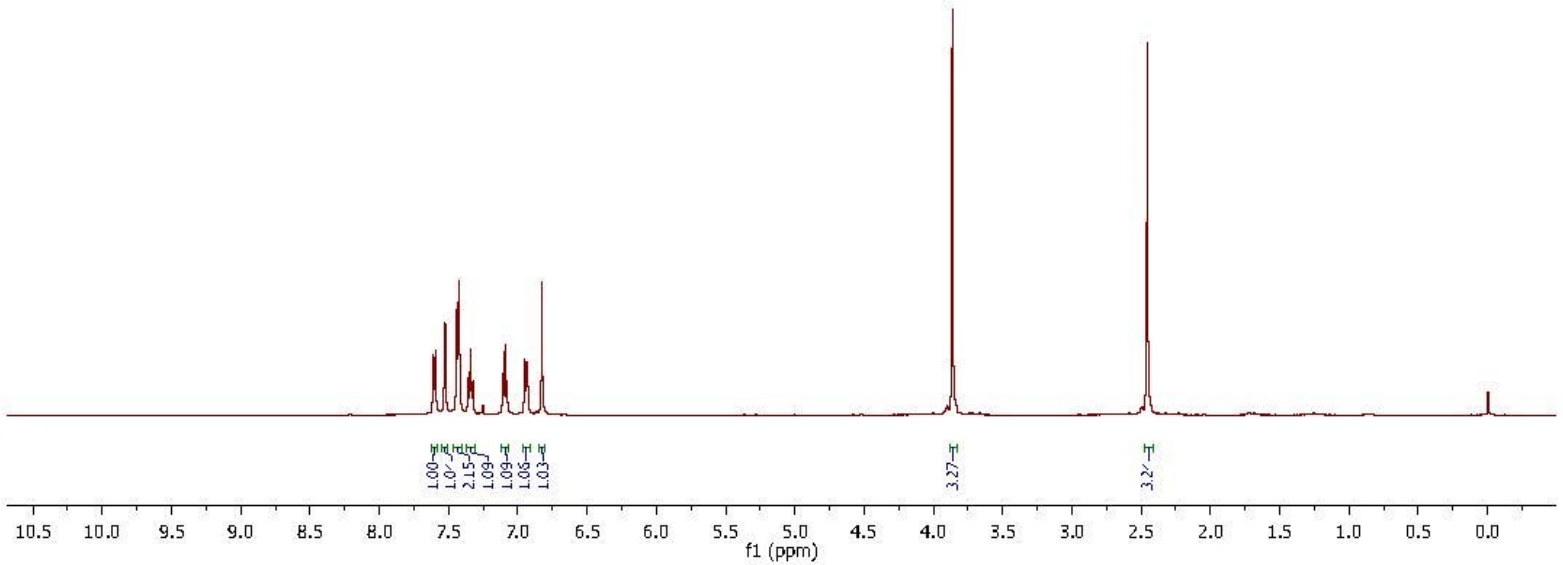

185.105
159.885
138.229
133.750
129.979
121.628
116.573
115.790
112.773
55.477
20.971
Me
OMe
O
O
39a
AK_3_5_3_13C
f1 (ppm)

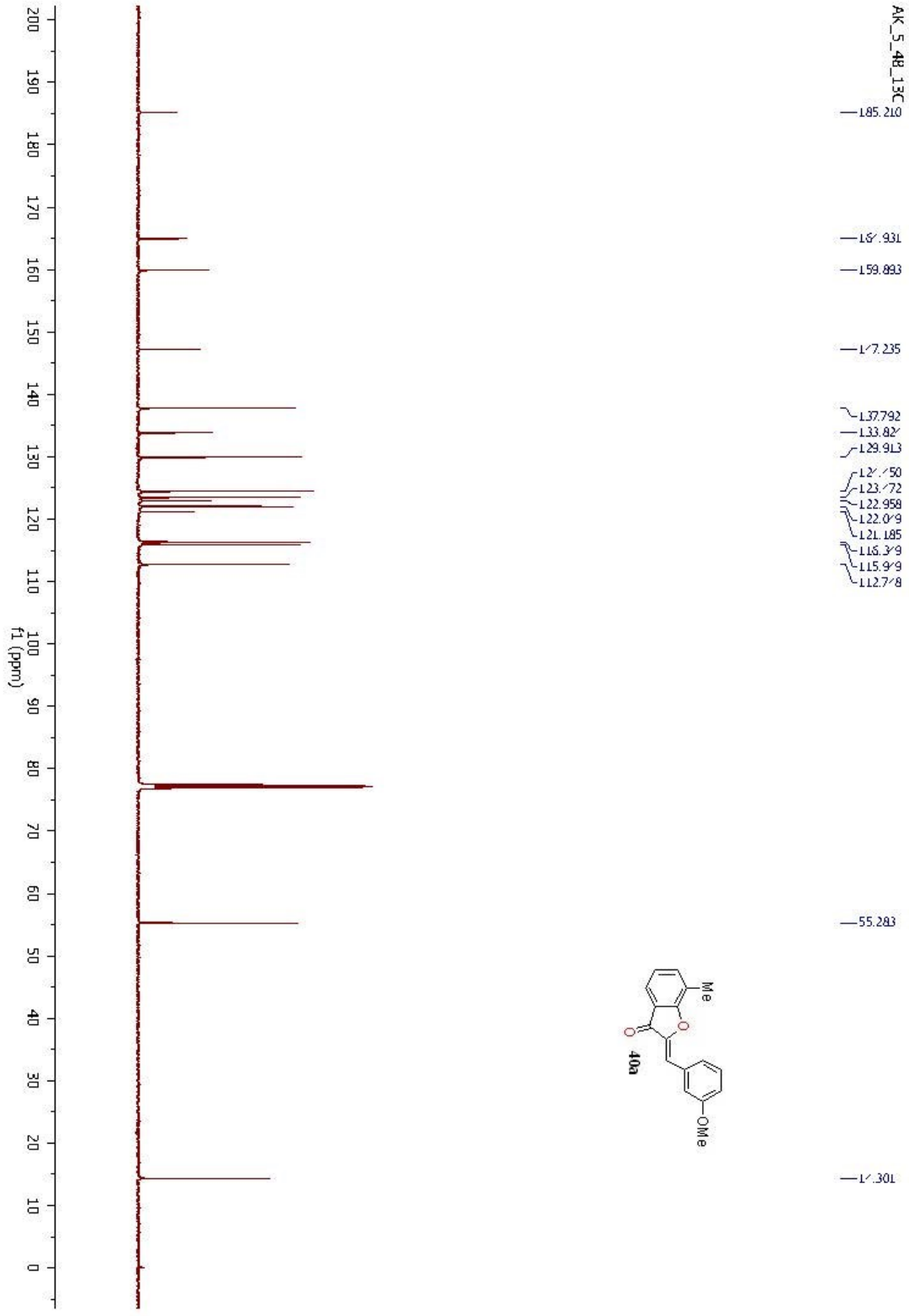
AK_5_48_1H

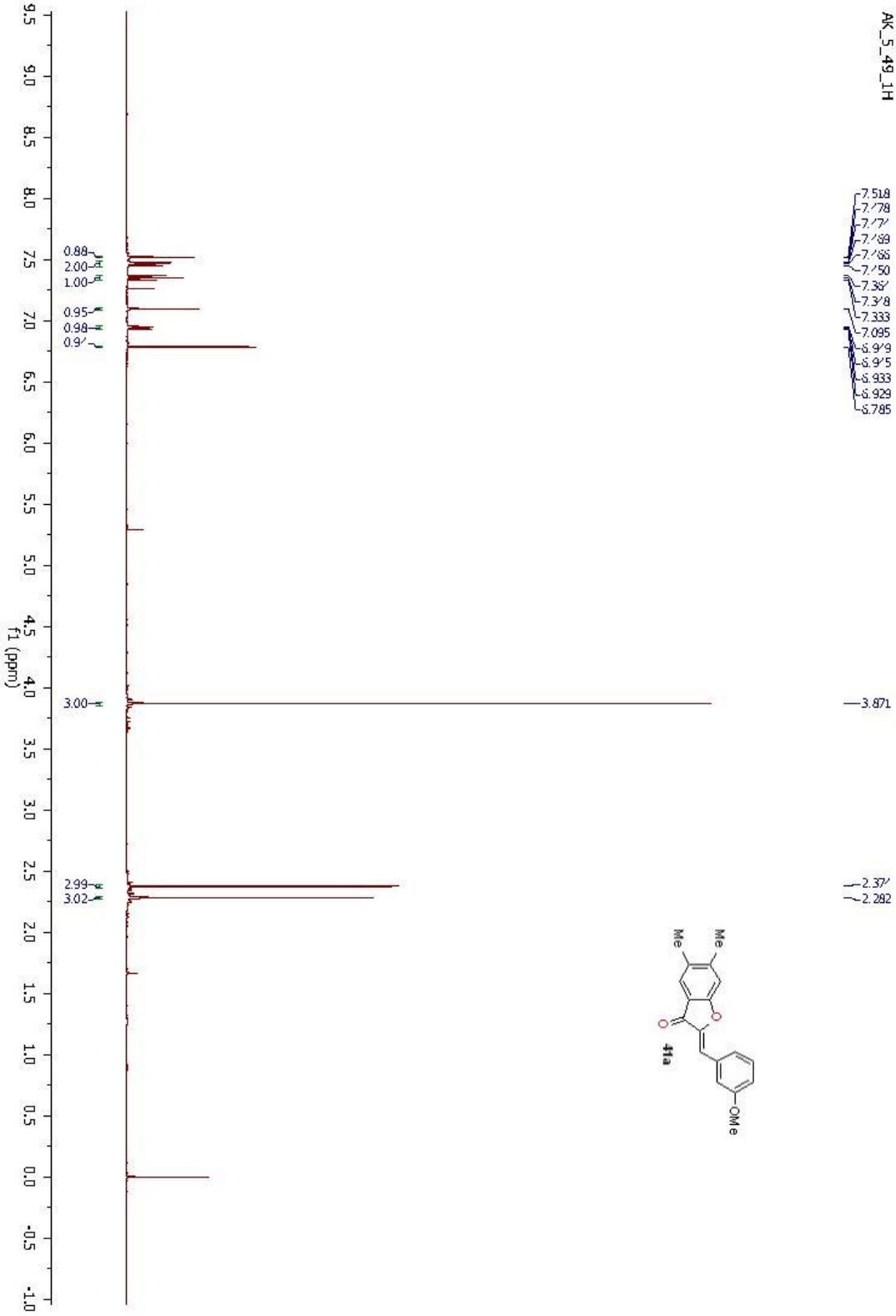

7.609
7.599
7.527
7.520
7.139
7.122
7.357
7.338
7.322
7.105
7.091
7.076
6.978
6.932
6.825

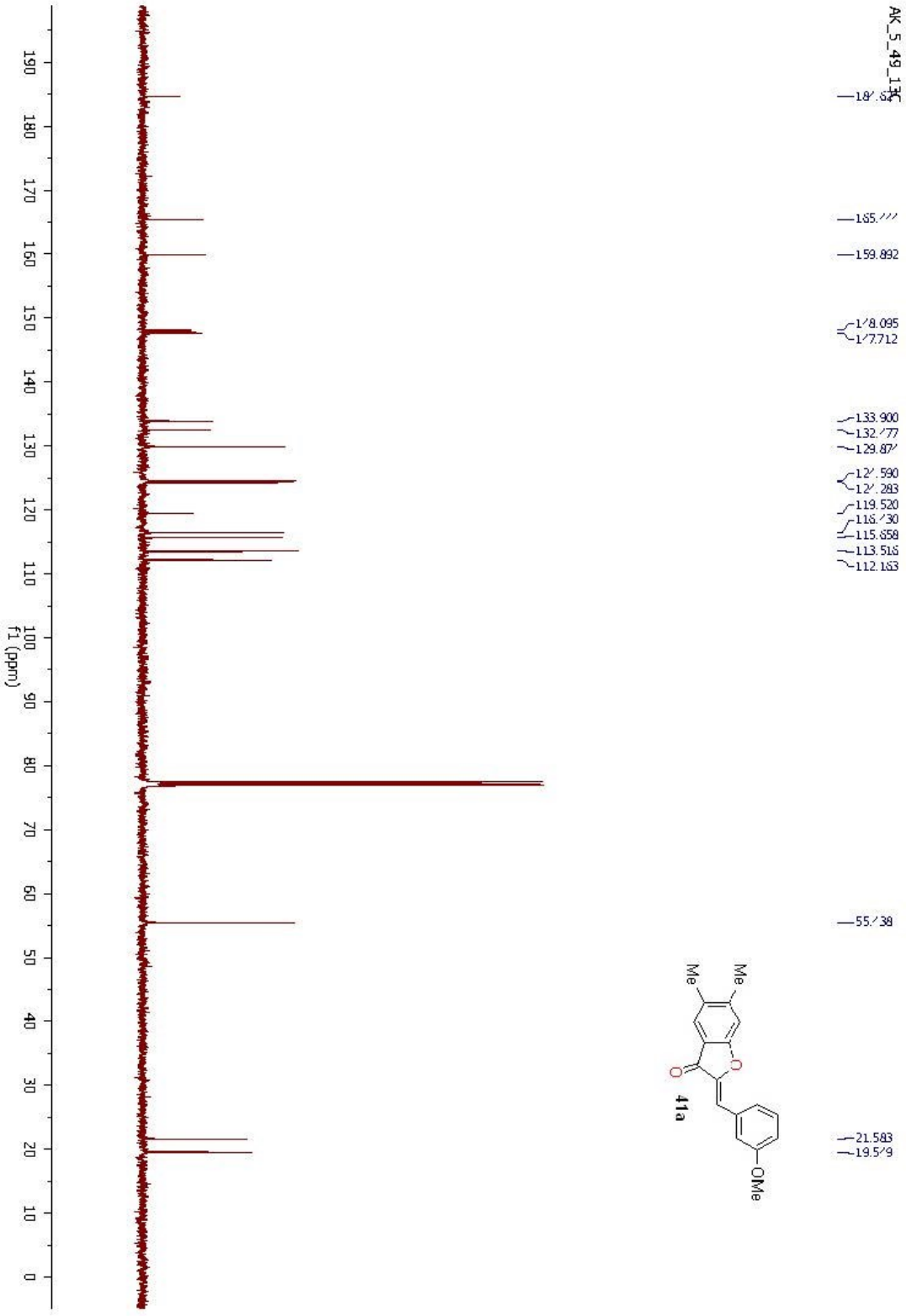

Me
O
OMe
O

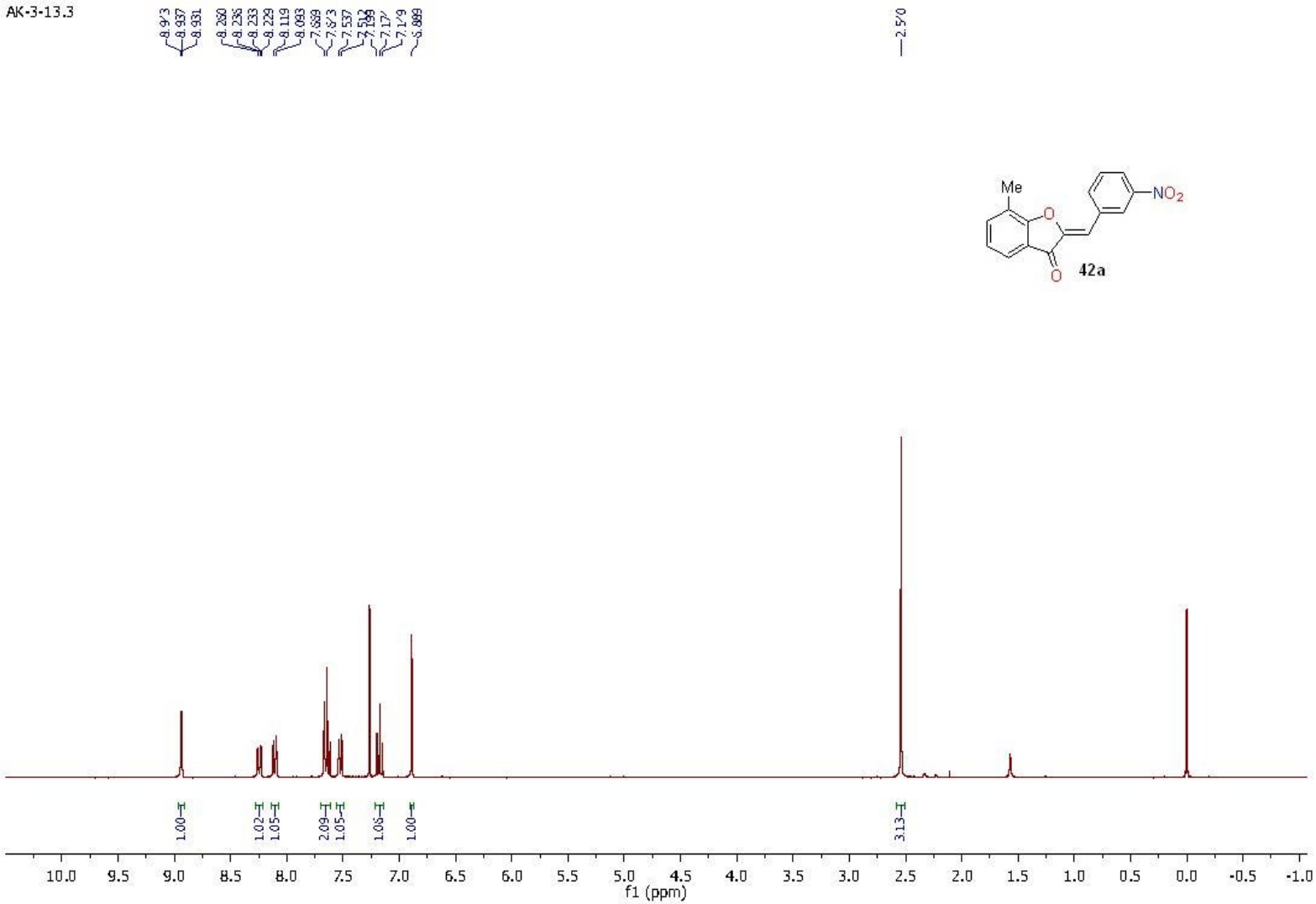
40a

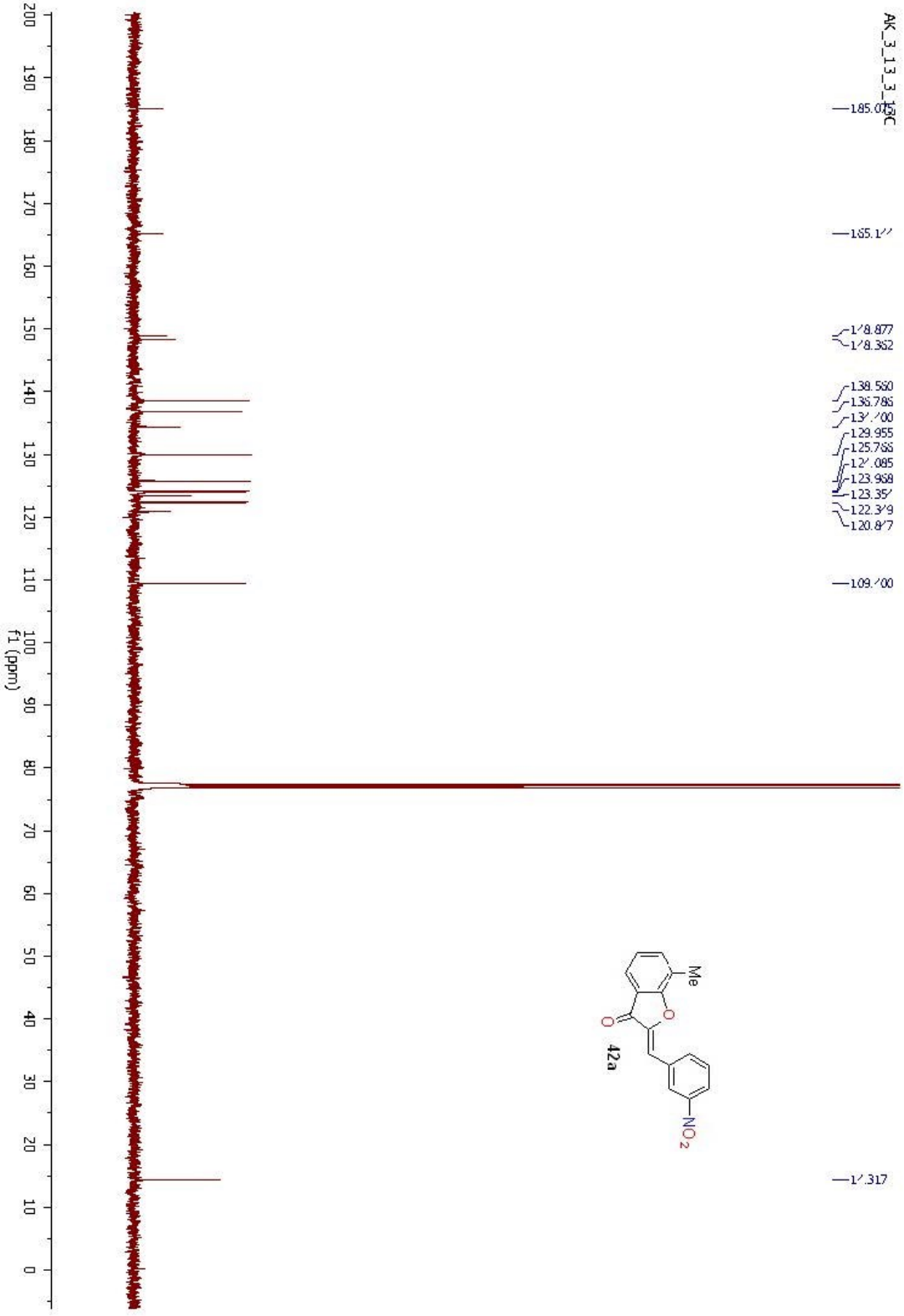

1.00
1.07
2.15
1.09
1.09
1.08
1.03
3.27
3.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

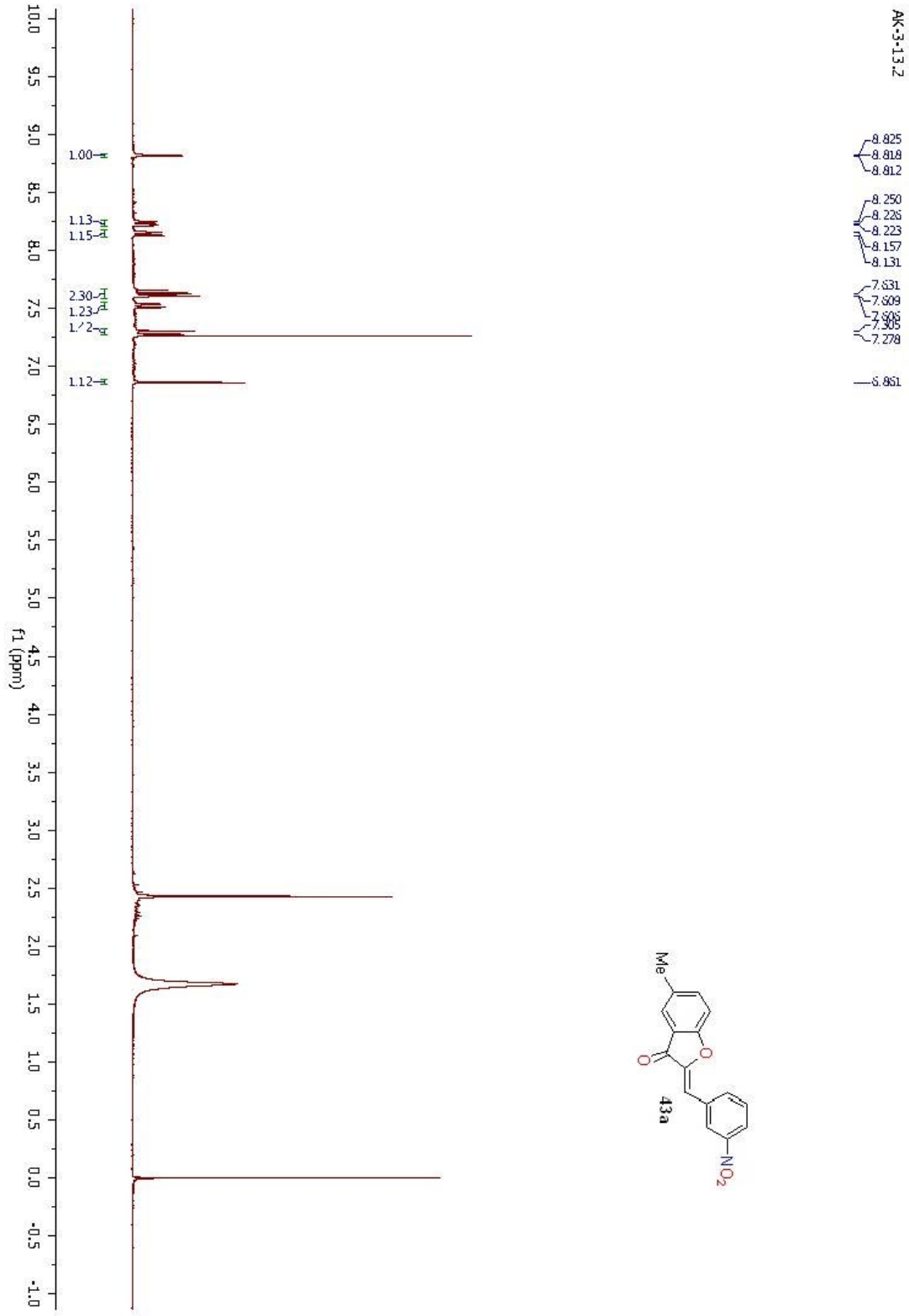

AK_5_4B_13C
185.210
167.931
159.893
147.235
137.792
133.827
129.913
127.750
123.772
122.958
122.079
121.185
116.379
115.979
112.778
55.283
17.301
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Me
O
O
OMe
40a

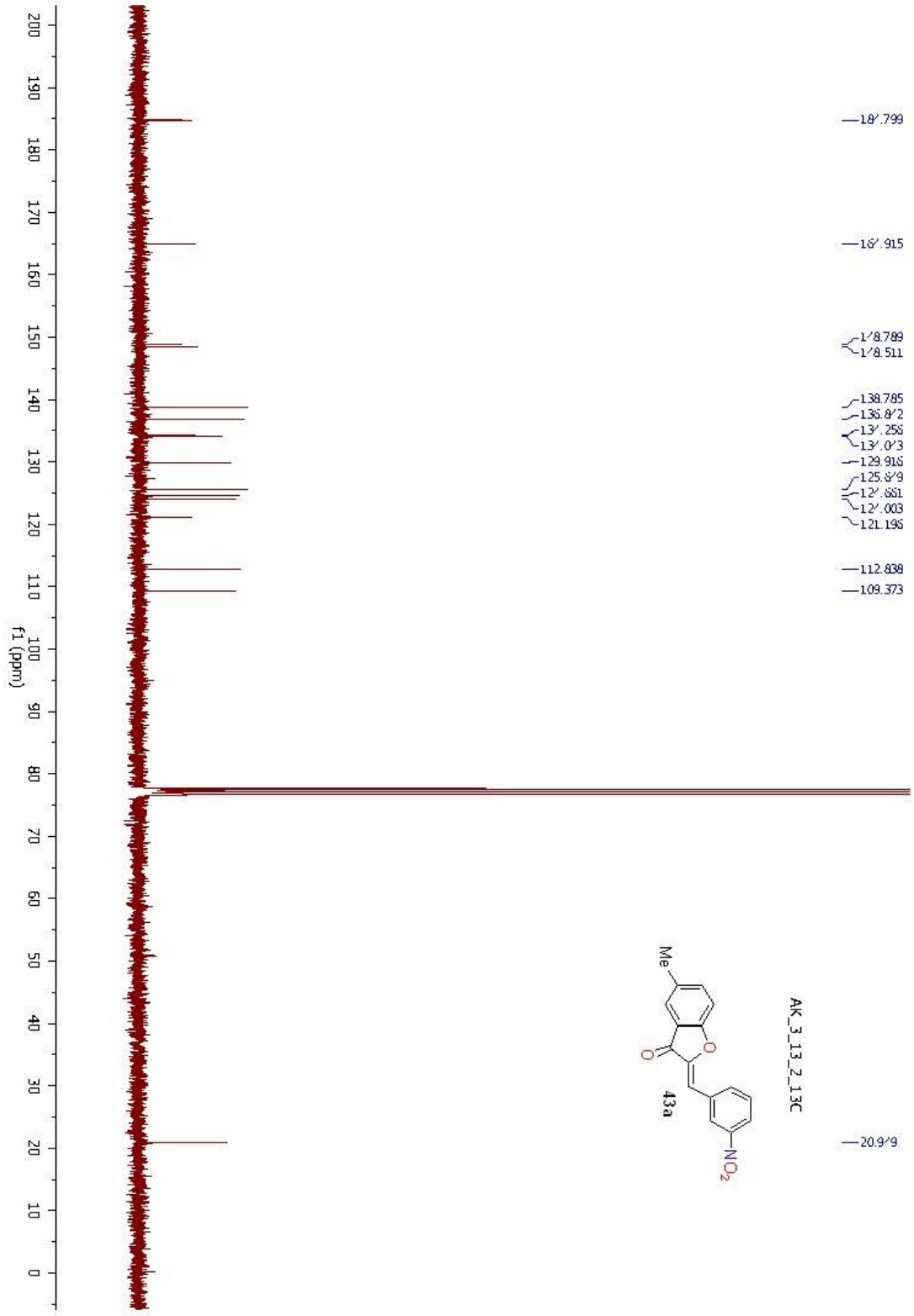

AK_5_49_1H
7.518
7.478
7.477
7.469
7.466
7.450
7.387
7.378
7.333
7.095
6.979
6.975
6.933
6.929
6.785
3.871
2.377
2.282
0.88
2.00
1.00
0.95
0.98
0.97
3.00
2.99
3.02
f1 (ppm)
Me
Me
OMe
4ia

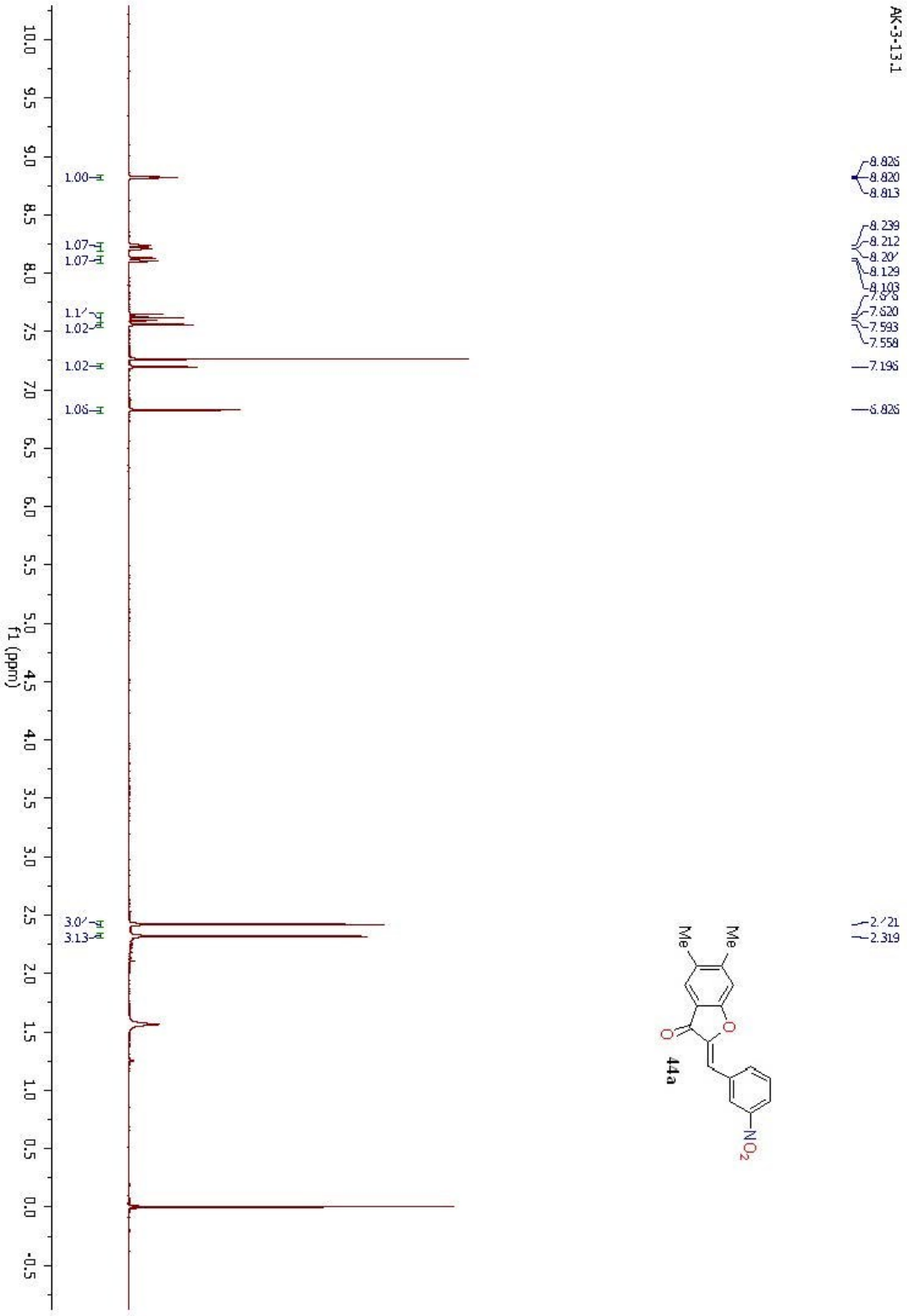

AK_5_49_13C
184.624
165.777
159.892
148.095
147.712
133.900
132.777
129.877
124.590
124.283
119.520
116.730
115.658
113.516
112.163
55.738
21.583
19.579
f1 (ppm)
Me
Me
O
O
O
41a
OMe

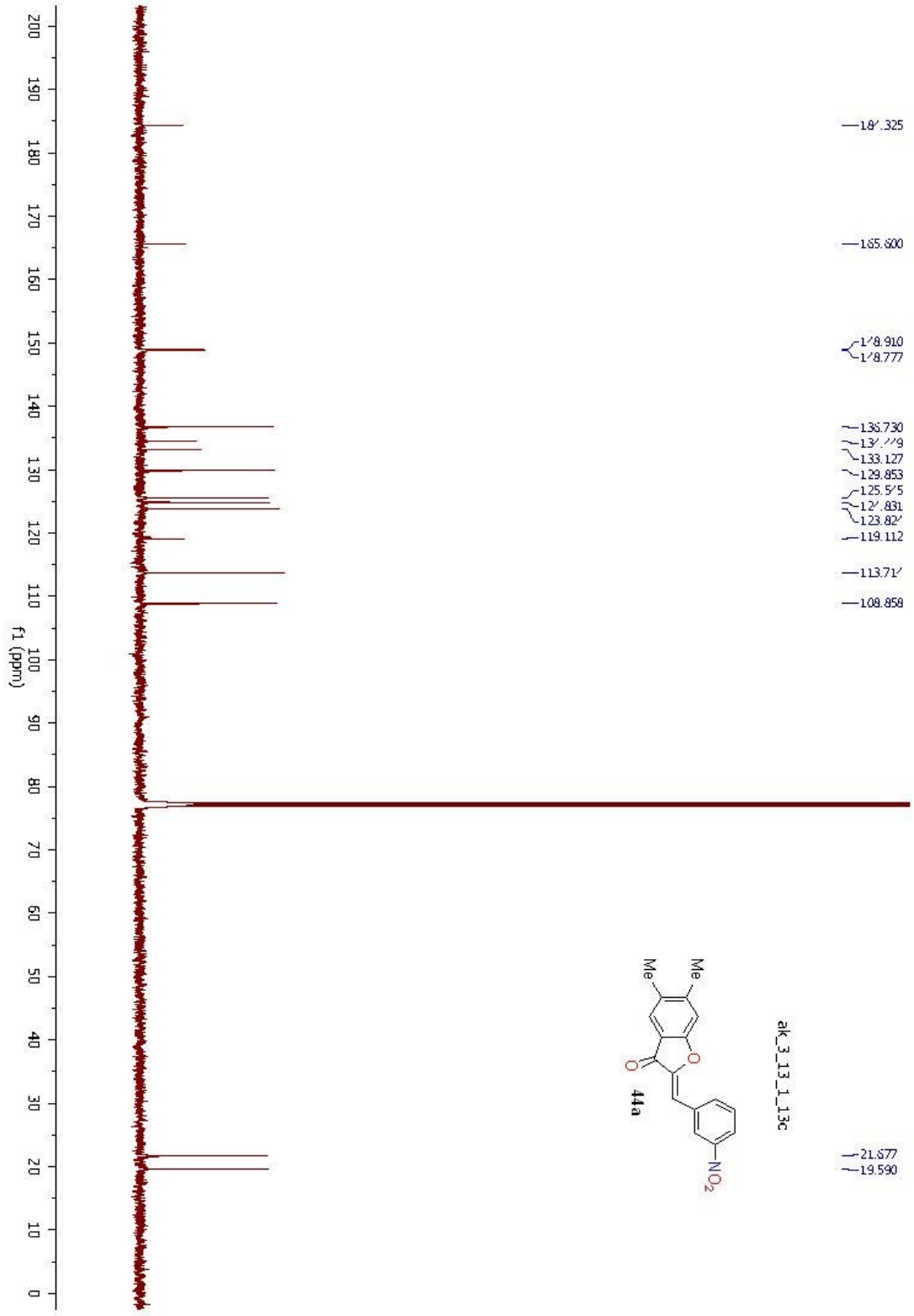

AK-3-13.3
8.973
8.937
8.931
8.260
8.236
8.233
8.229
8.119
8.093
7.689
7.673
7.537
7.513
7.199
7.177
7.179
6.889
2.570
Me
O
NO2
O
42a
1.00
1.02
1.05
2.09
1.05
1.06
1.00
3.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


AK_3_13_3_13C
185.07
165.17
148.877
148.362
138.560
136.786
134.700
129.955
125.786
124.085
123.958
123.357
122.379
120.847
109.700
17.317
f1 (ppm)
Me
O
O
42a
NO2

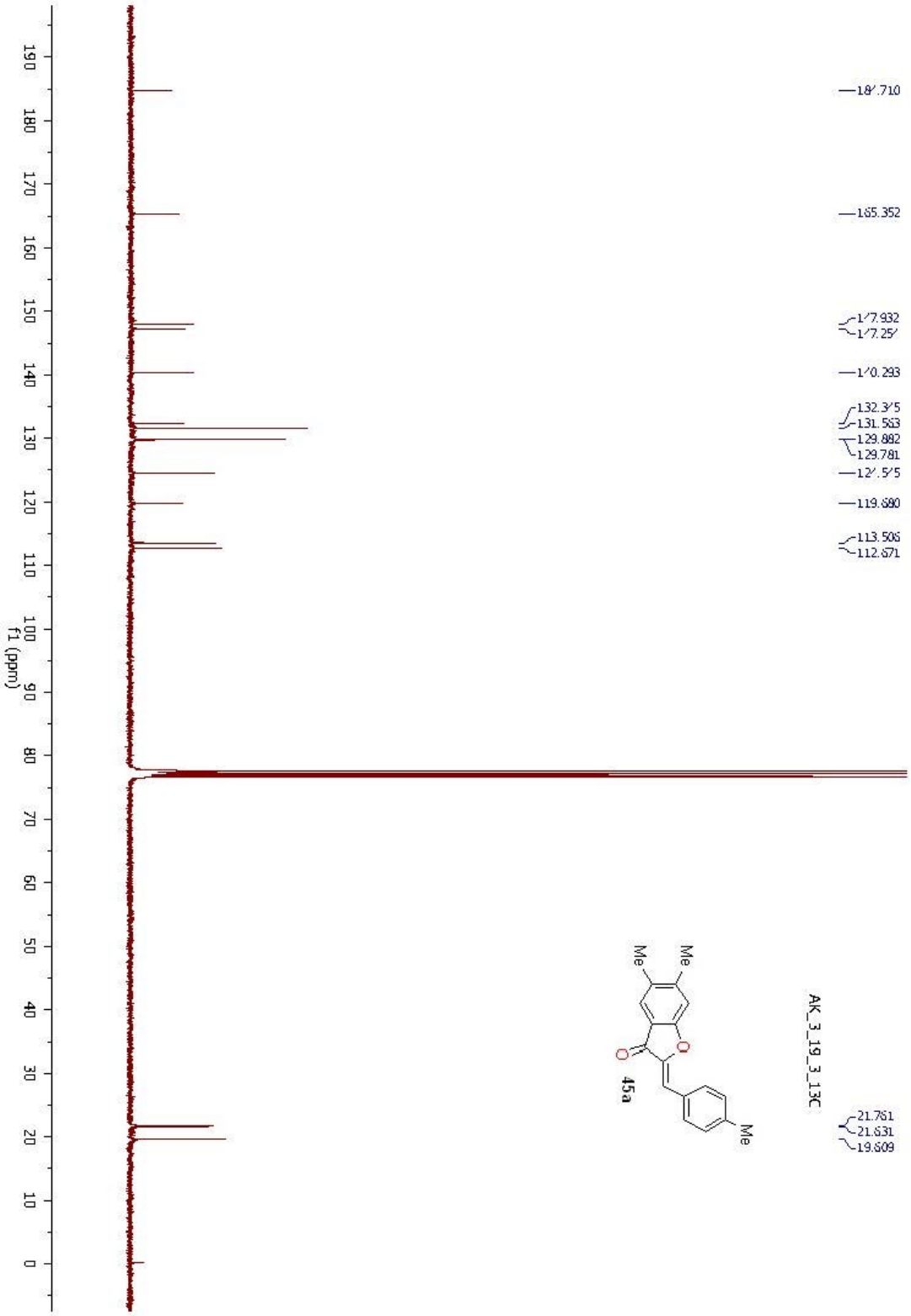

AK-3-13.2
8.825
8.818
8.812
8.250
8.226
8.223
8.157
8.131
7.631
7.609
7.505
7.278
6.861
1.00
1.13
1.15
2.30
1.23
1.12
f1 (ppm)
Me
O
O
43a
NO2


AK_3_13_2_13C
43a
Me
O
O
NO2
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
18.799
18.915
18.789
18.511
138.785
136.872
13.256
13.073
129.916
125.879
12.651
12.003
121.196
112.838
109.373
20.979

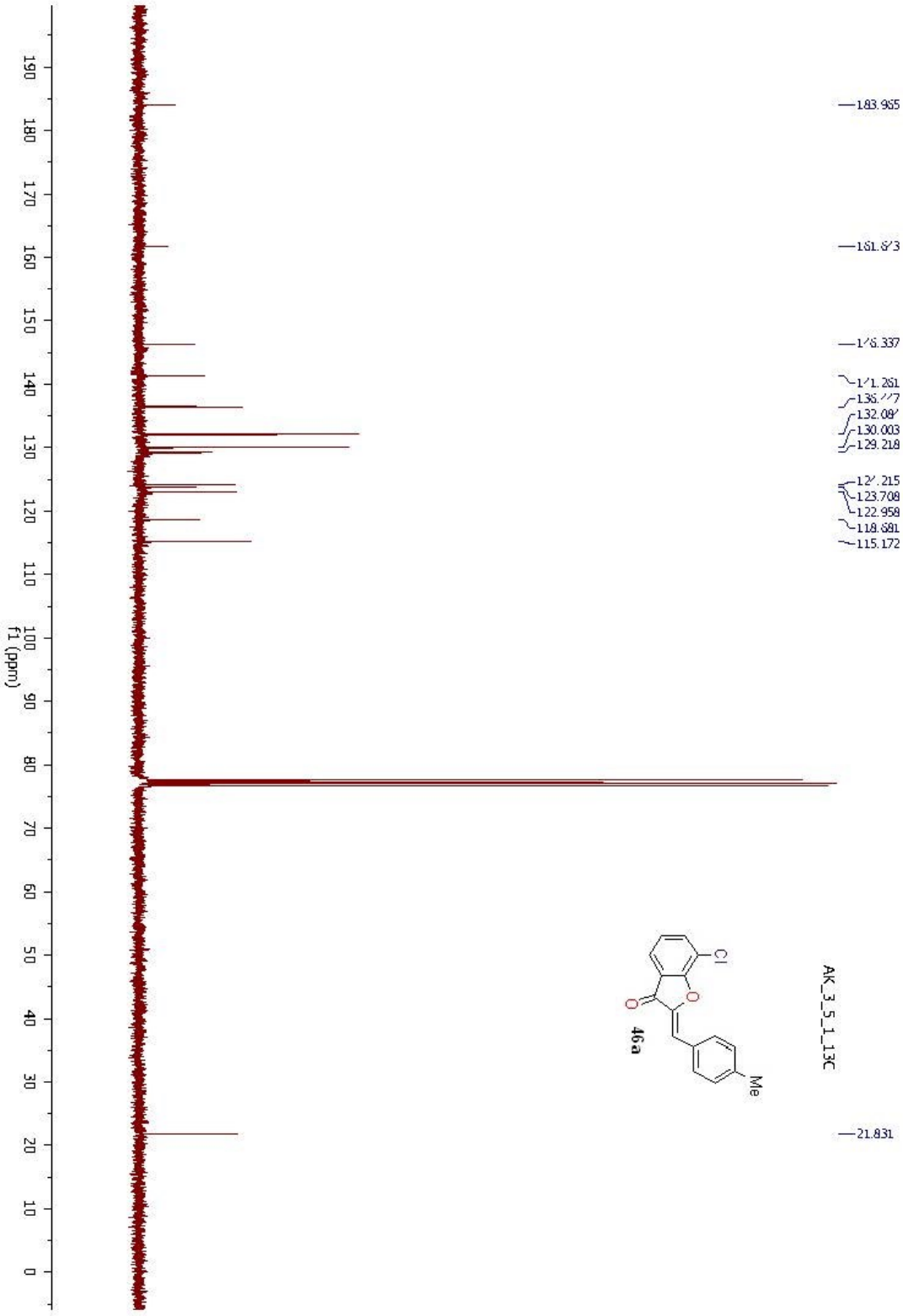

AK-3-13.1
8.826
8.820
8.813
8.239
8.212
8.207
8.129
8.103
7.678
7.620
7.593
7.558
7.196
6.826
2.721
2.319
1.00
1.07
1.07
1.17
1.02
1.02
1.08
3.07
3.13
f1 (ppm)
Me
Me
O
O
NO2
44a


ak_3_13_1_13c
44a
Me
Me
O
O
NO2
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
184.325
165.600
148.910
148.777
136.730
134.779
133.127
129.853
125.575
124.831
123.827
119.112
113.717
108.858
21.677
19.590

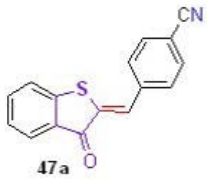
AK-3-19.3
7.820
7.792
7.572
7.270
7.243
7.128
6.832
2.405
2.393
2.300
2.05
1.00
3.61
1.09
1.00
2.68
3.08
2.98
f1 (ppm)
Me
Me
O
O
Me
45a


f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
184.710
165.352
147.932
147.257
140.293
132.375
131.563
129.882
129.781
125.575
119.680
113.506
112.671
21.761
21.631
19.609
AK_3_19_3_13C
Me
Me
Me
O
O
45a

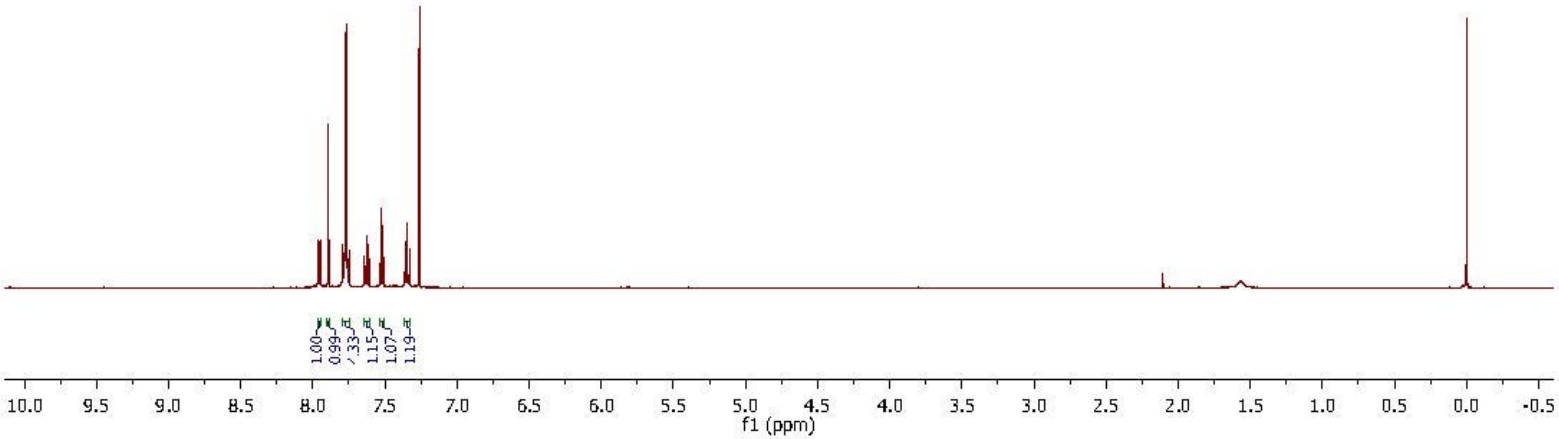
AK_3_5_1
7.878
7.852
7.726
7.710
7.687
7.679
7.309
7.293
7.193
7.177
7.152
6.957
2.723
1.99
1.00
1.02
2.28
1.10
1.01
3.17
f1 (ppm)
Cl
O
O
Me
46a

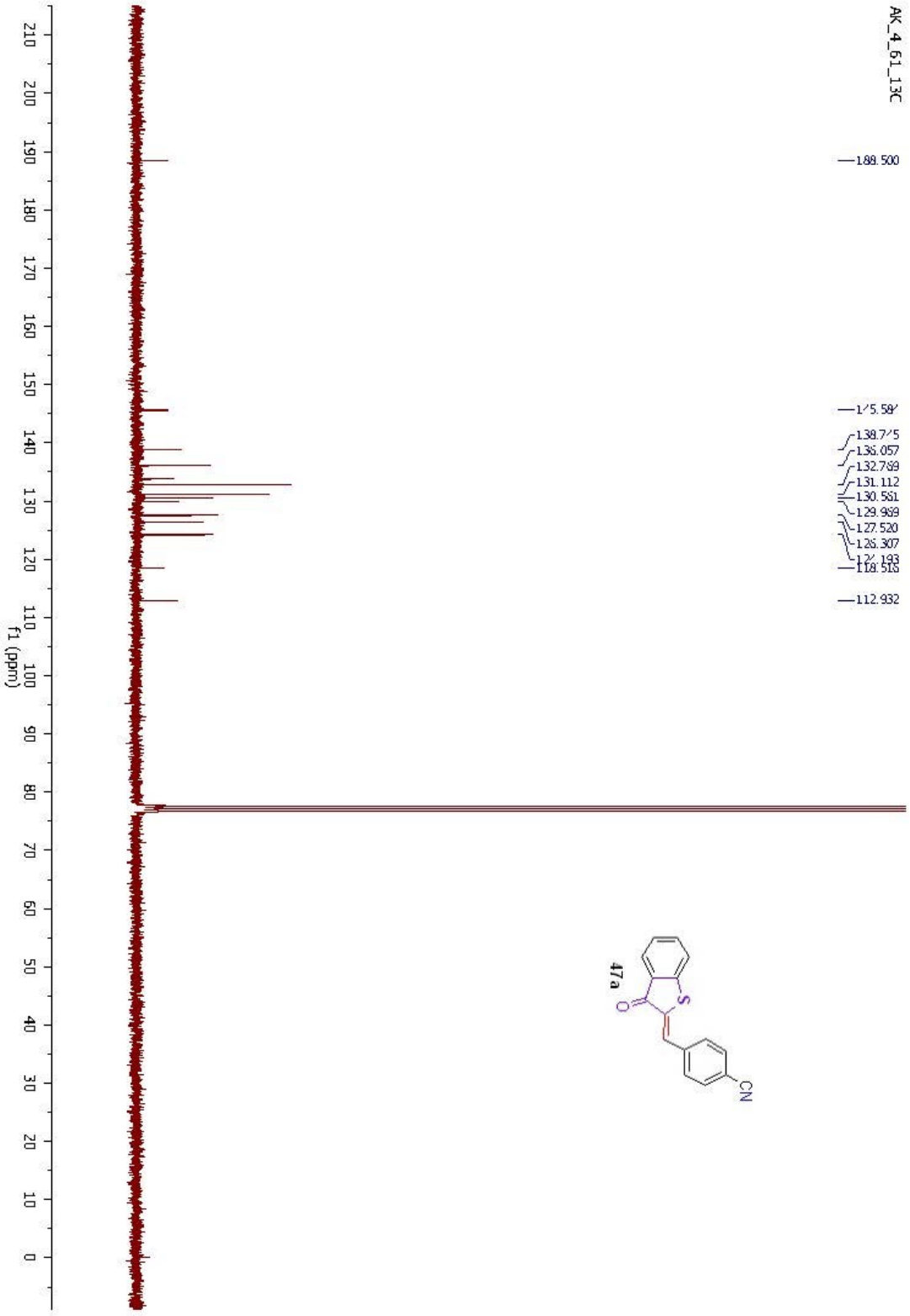

183.965
161.873
146.337
141.261
136.277
132.097
130.003
129.218
124.215
123.709
122.958
118.581
115.172
21.831
f1 (ppm)
Cl
O
O
Me
46a
AK_3_5_1_13C

AK_4_61_thio



47a

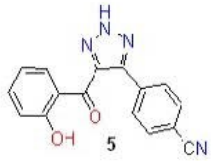


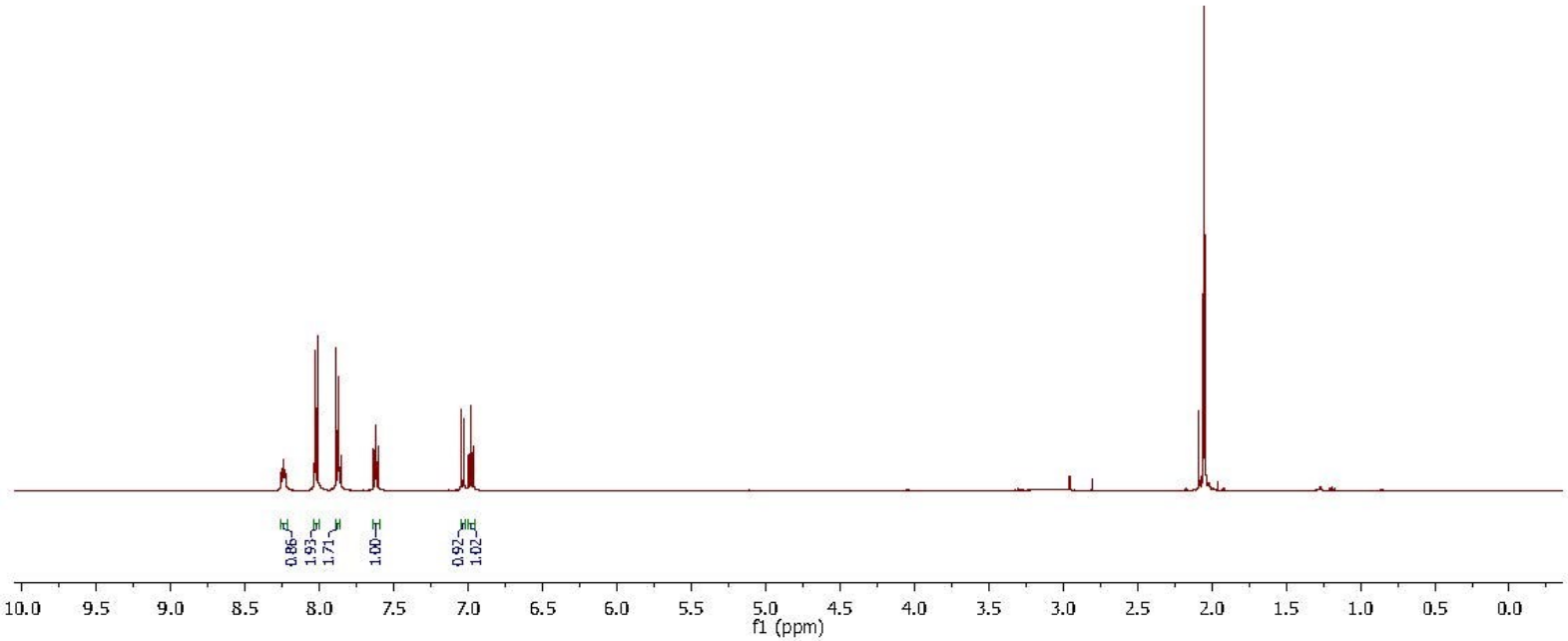

AK_4_61_13C
188.500
145.587
138.775
136.057
132.789
131.112
130.561
129.969
127.520
126.307
124.193
118.510
112.932
f1 (ppm)
47a
O
S
CN

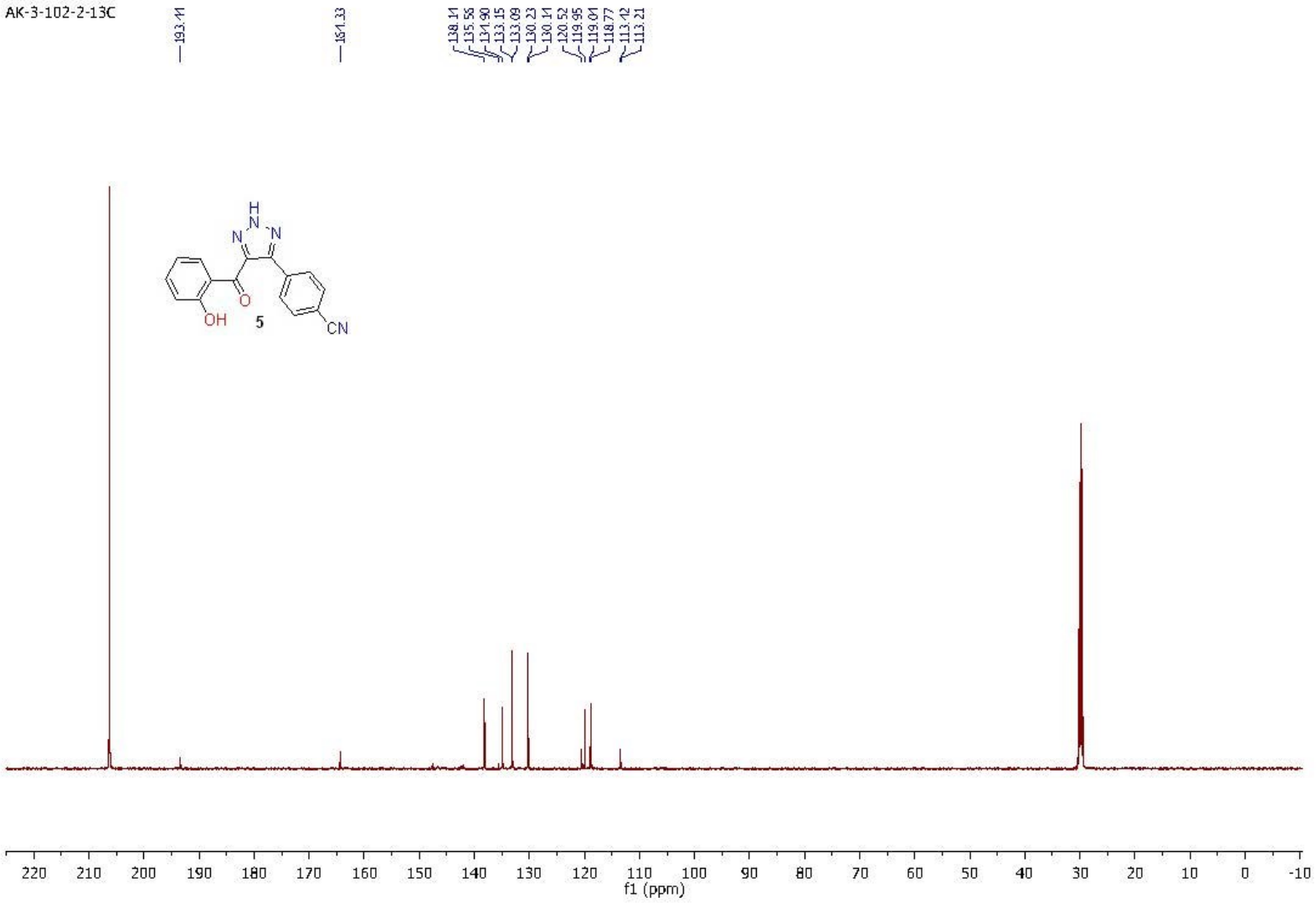
Triazoles

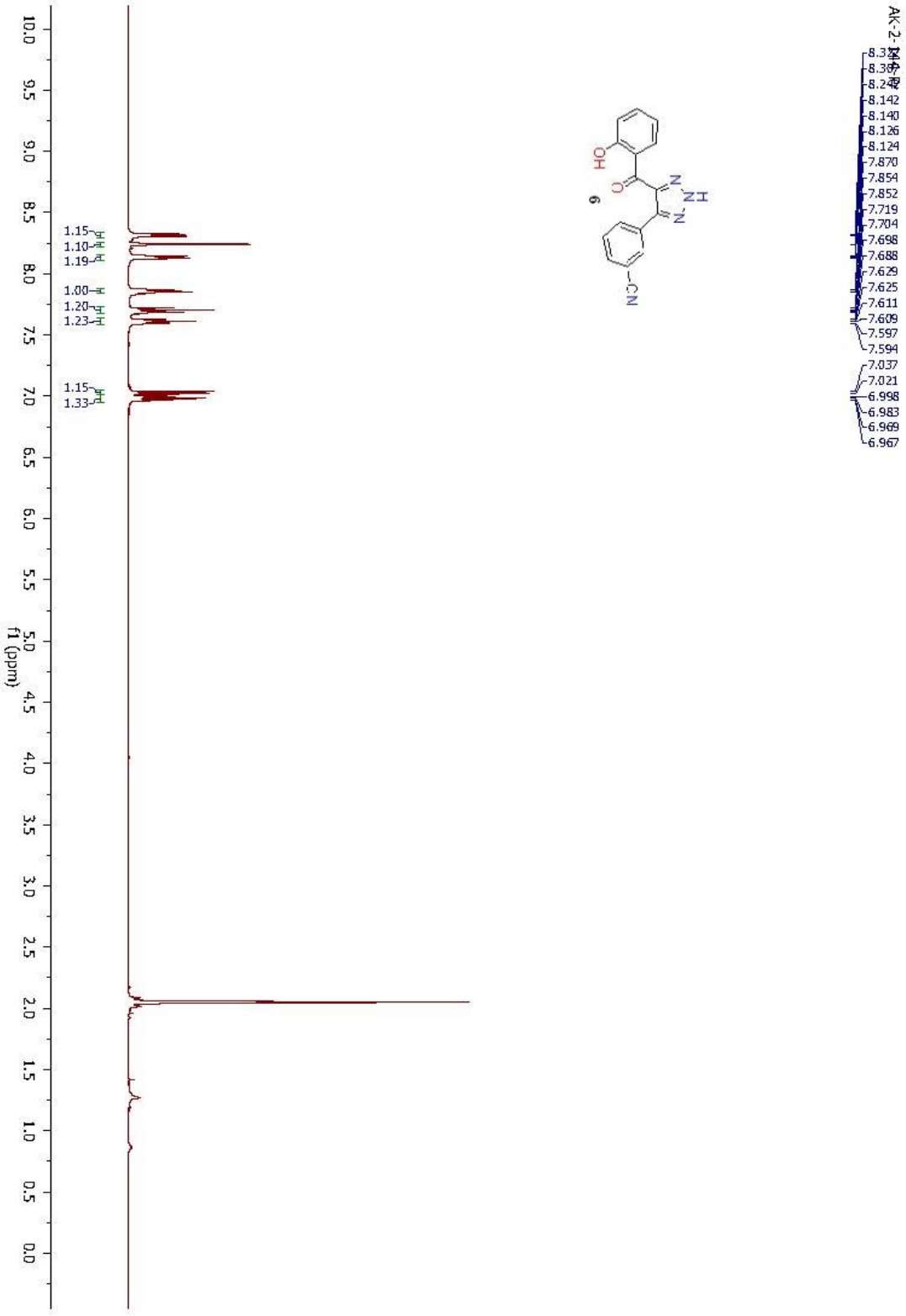

8.26
8.26
8.24
8.24
8.23
8.03
8.01
7.89
7.87
7.64
7.63
7.62
7.62
7.62
7.61
7.60
7.05
7.05
7.03
7.03
7.00
6.99
6.98
6.98
6.98
6.97
6.96

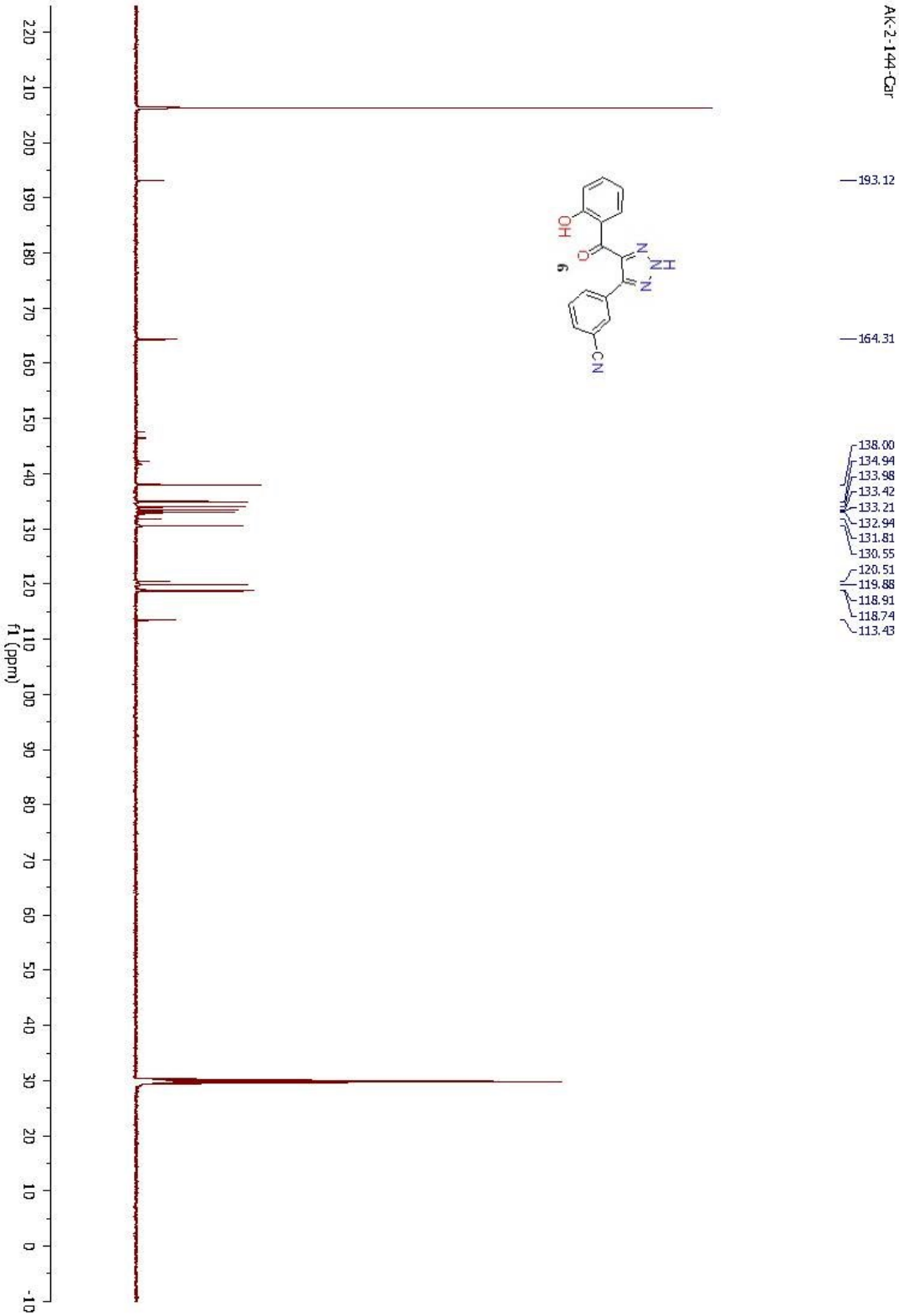
AK-3-102-2-1H


H
N
N
N
O
OH
5
CN


0.86
1.93
1.71
1.00
0.92
1.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AK-3-102-2-13C
193.11
164.33
138.14
135.56
134.90
133.15
133.09
130.23
130.14
120.52
119.95
119.04
118.77
113.42
113.21
H
N
N
N
O
OH
5
CN
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.15
1.10
1.19
1.00
1.20
1.23
1.15
1.33
HO
O
N
N
H
N
C
N
6
Ak-2-
8.142
8.140
8.126
8.124
7.870
7.854
7.852
7.719
7.704
7.698
7.688
7.629
7.625
7.611
7.609
7.597
7.594
7.037
7.021
6.998
6.983
6.969
6.967

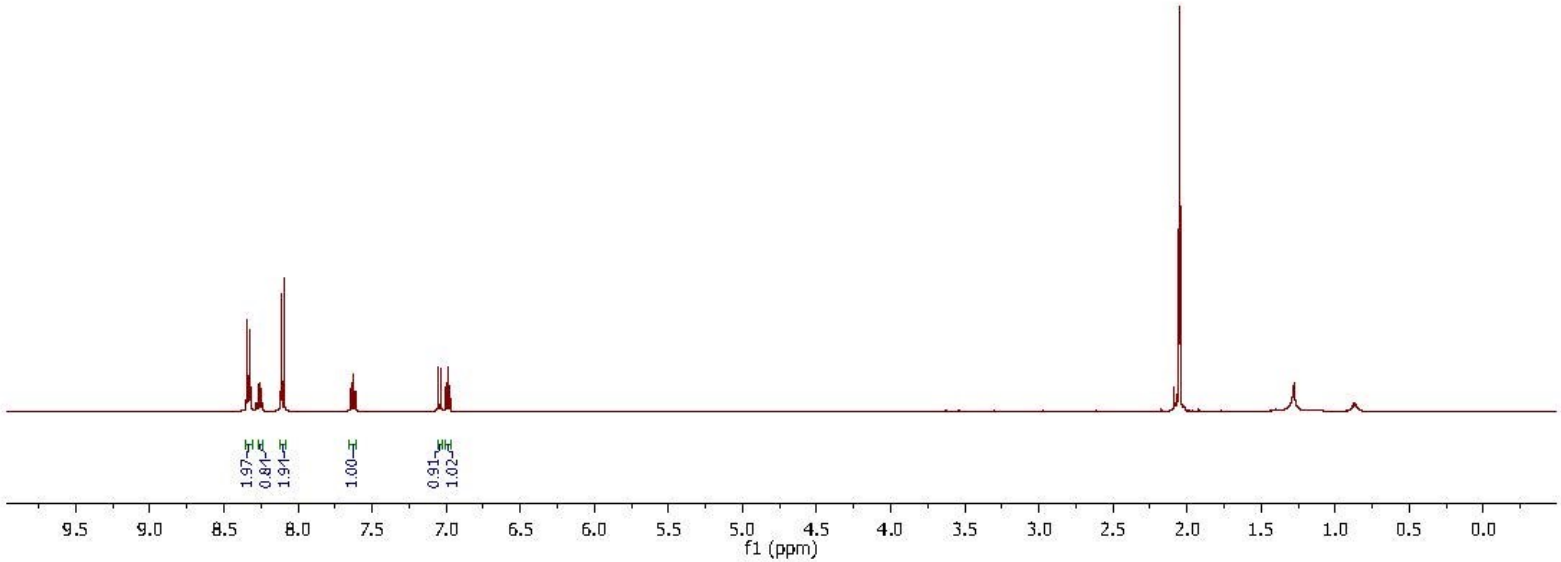

AK-2-144-Car
193.12
164.31
138.00
134.94
133.98
133.42
133.21
132.94
131.81
130.55
120.51
119.88
118.91
118.74
113.43
HO
O
N
NH
N
CN
9
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

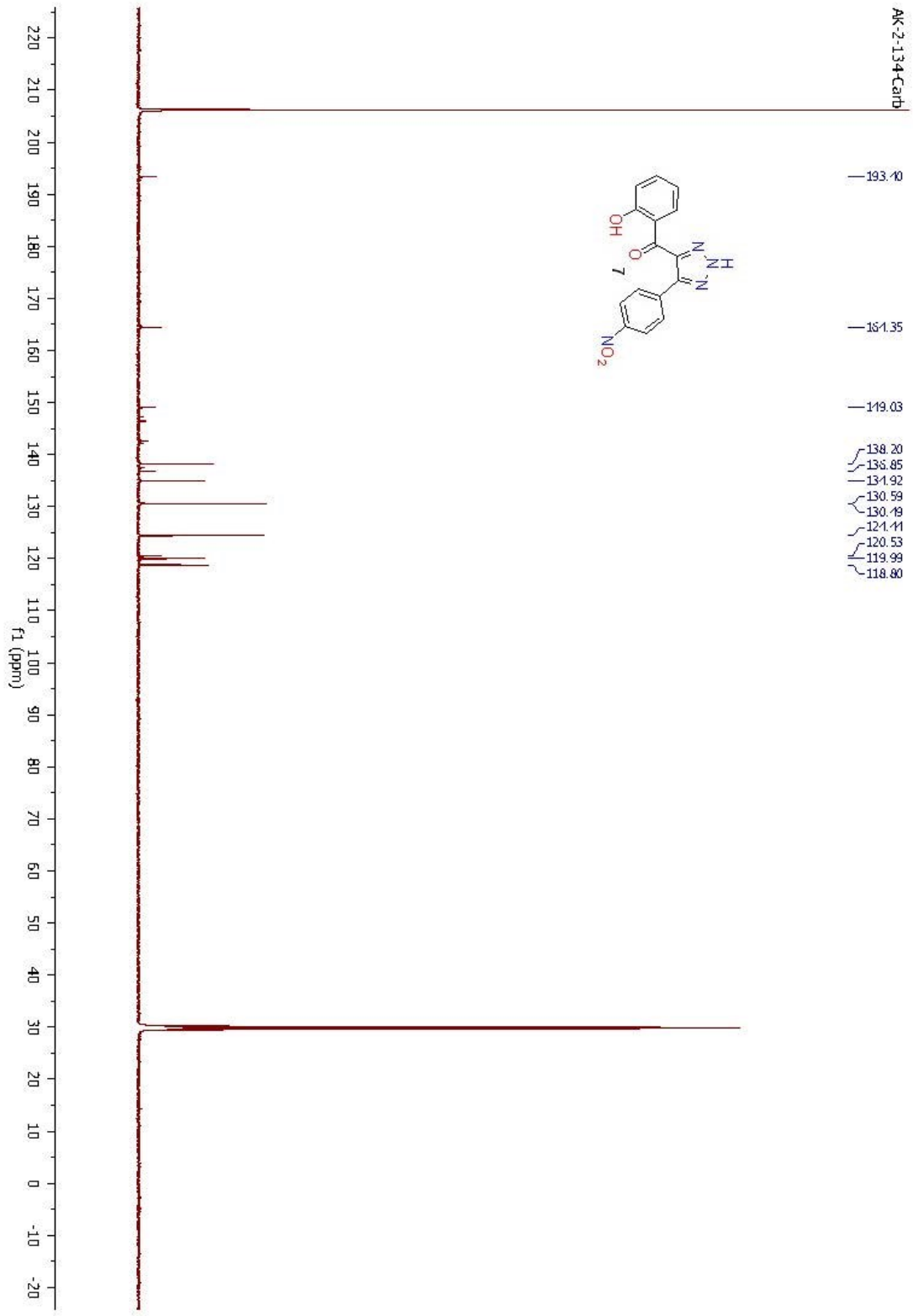
AK-2-134-Pr

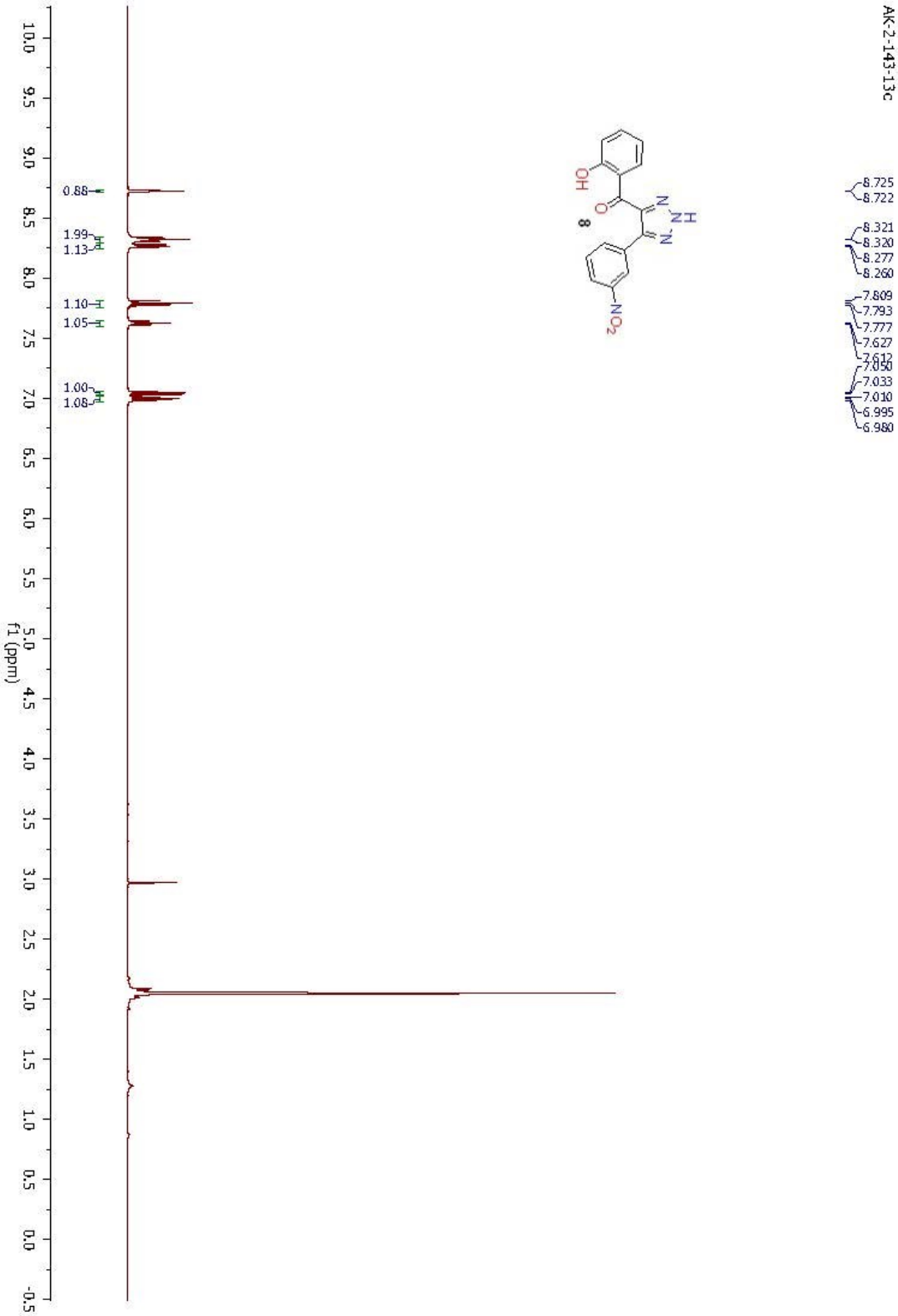

8.346
8.328
8.265
8.262
8.249
8.246
8.113
8.095
7.647
7.632
7.630
7.053
7.036
7.005
6.990
6.971

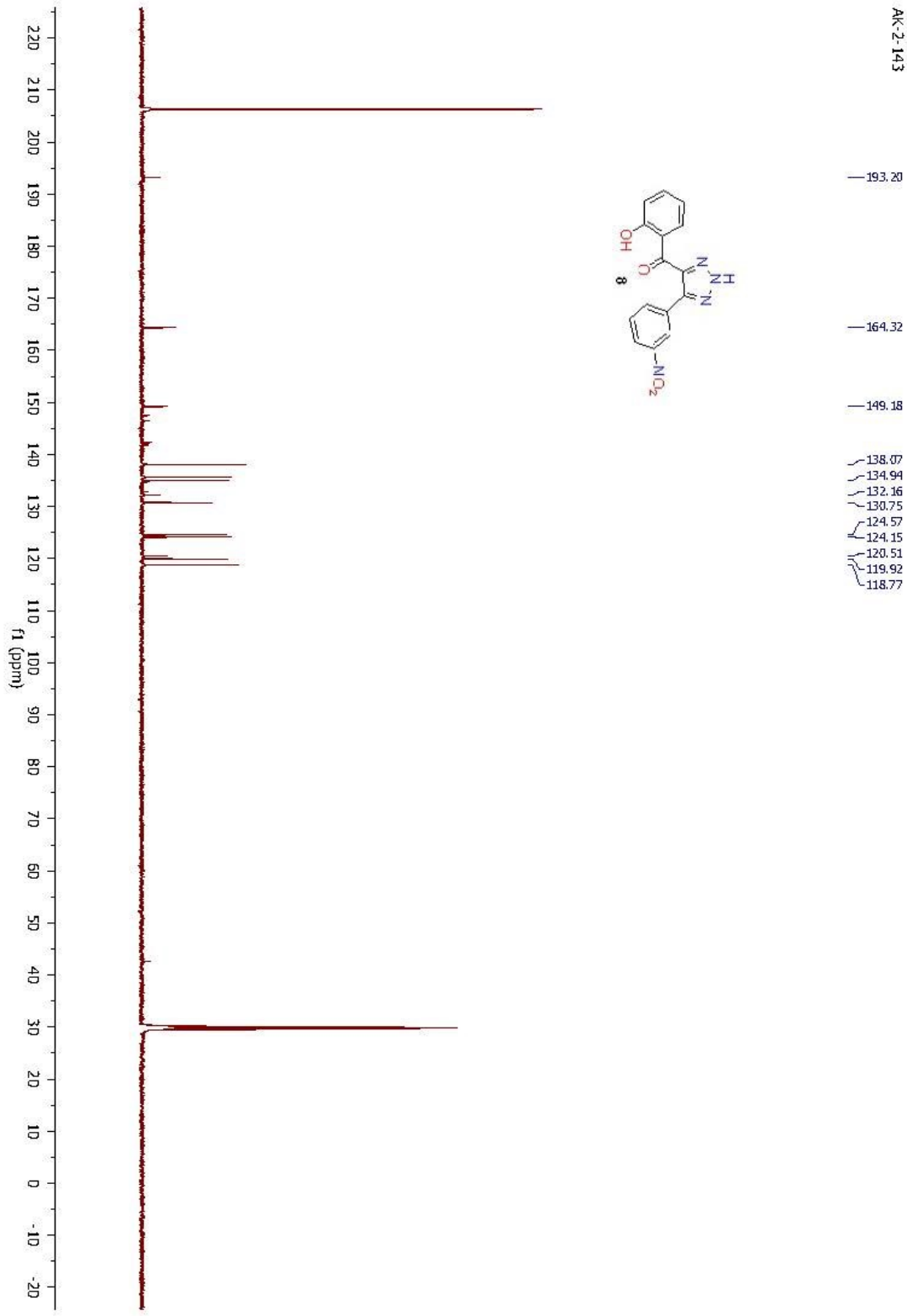

H
N
N
N
O
OH
NO2

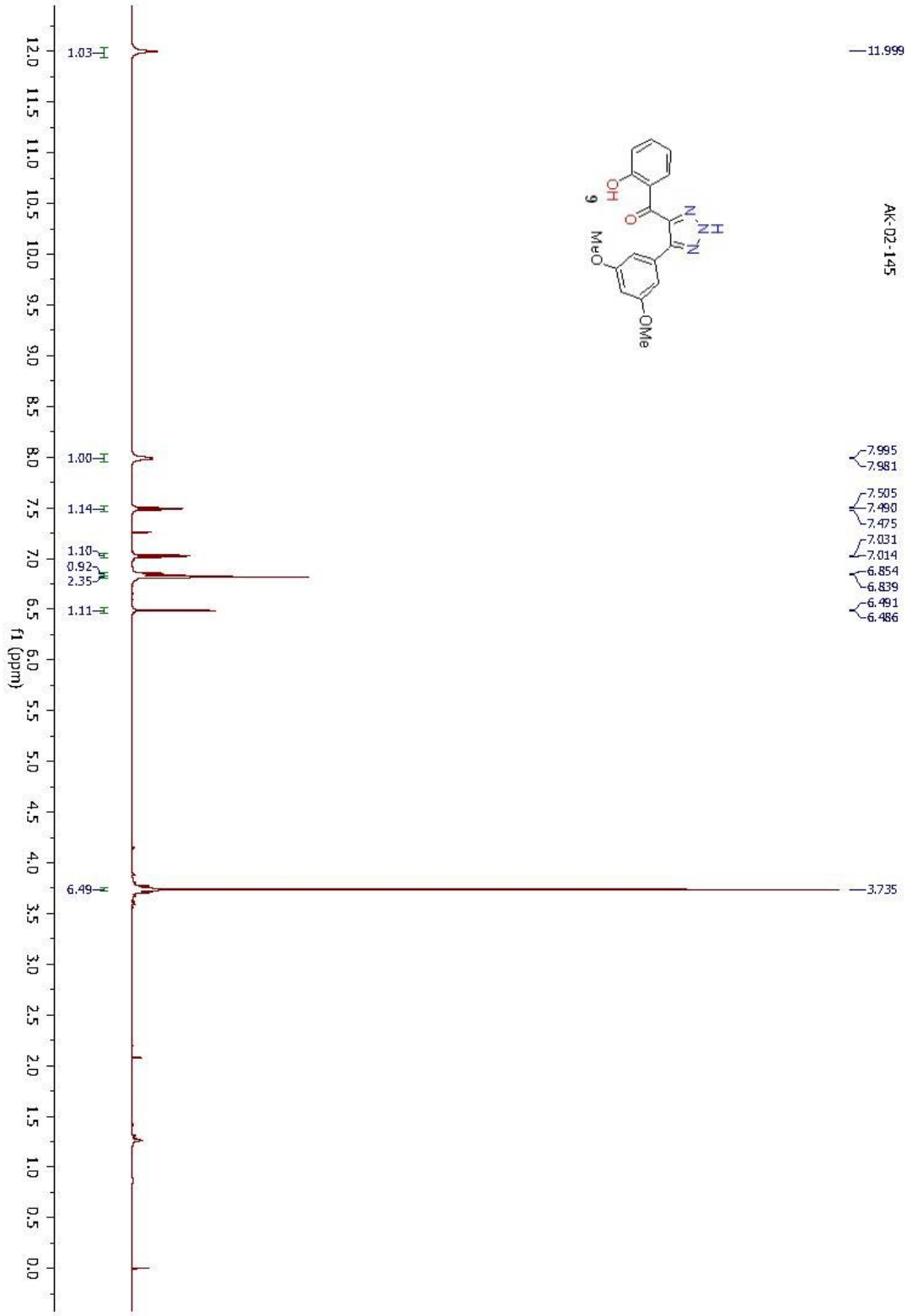
7

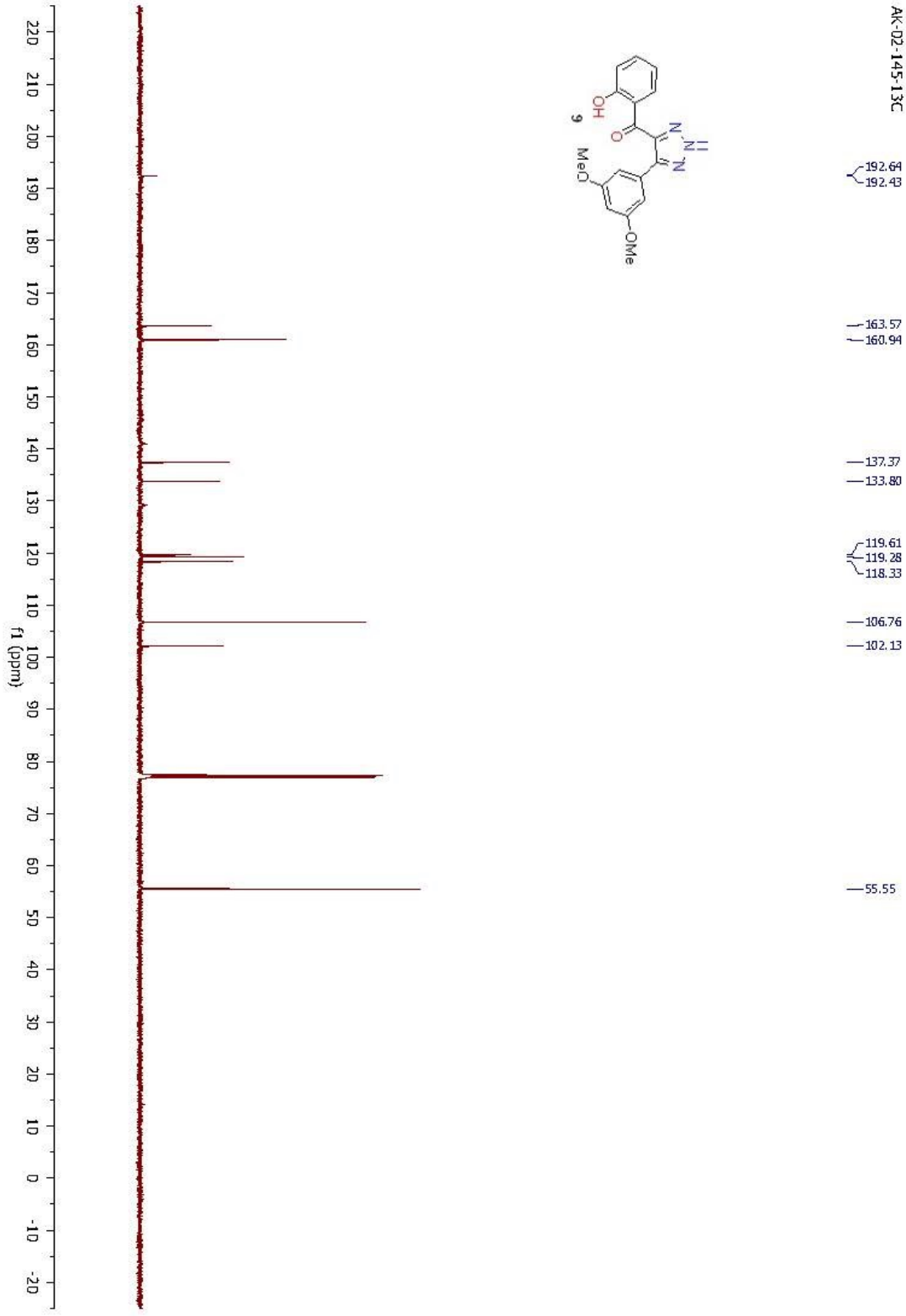

1.97
0.84
1.94
1.00
0.91
1.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

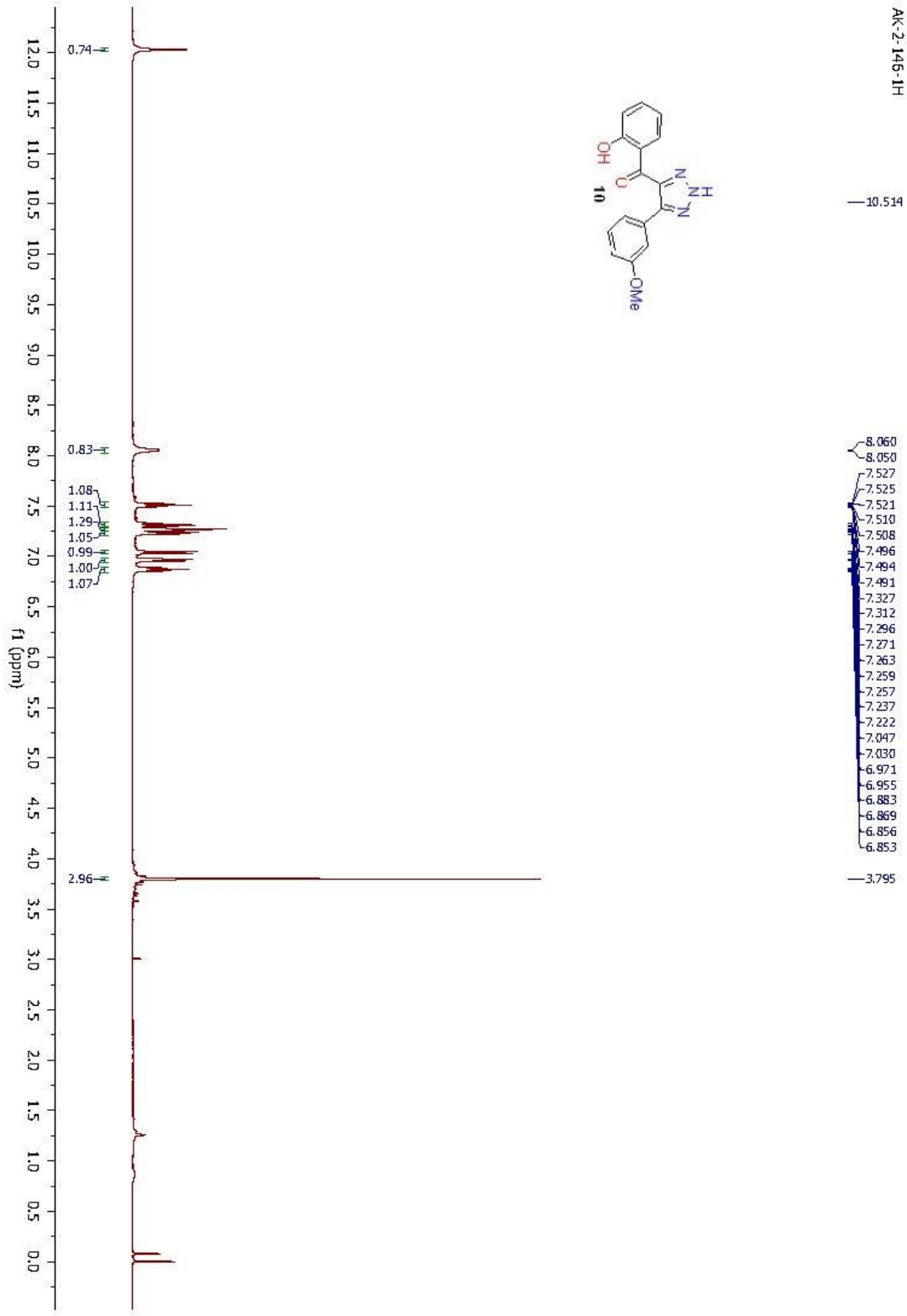

AK-2-134-Carb
193.40
164.35
149.03
138.20
136.85
134.92
130.59
130.49
124.44
120.53
119.99
118.80
OH
O
7
NO2
f1 (ppm)

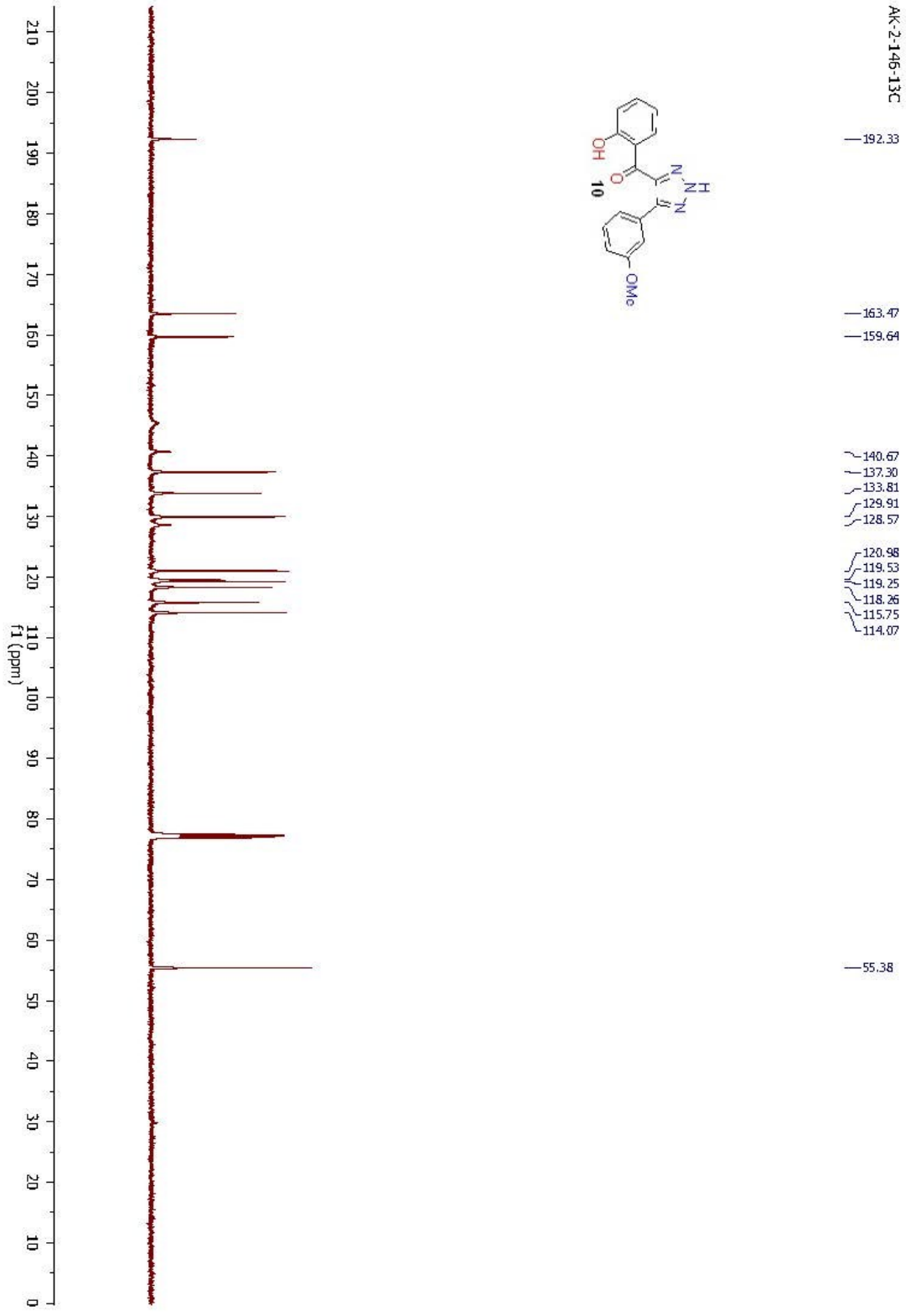

AK-2-143-13c
8.725
8.722
8.321
8.320
8.277
8.260
7.809
7.793
7.777
7.627
7.612
7.050
7.033
7.010
6.995
6.980
0.88
1.99
1.13
1.10
1.05
1.00
1.08
f1 (ppm)

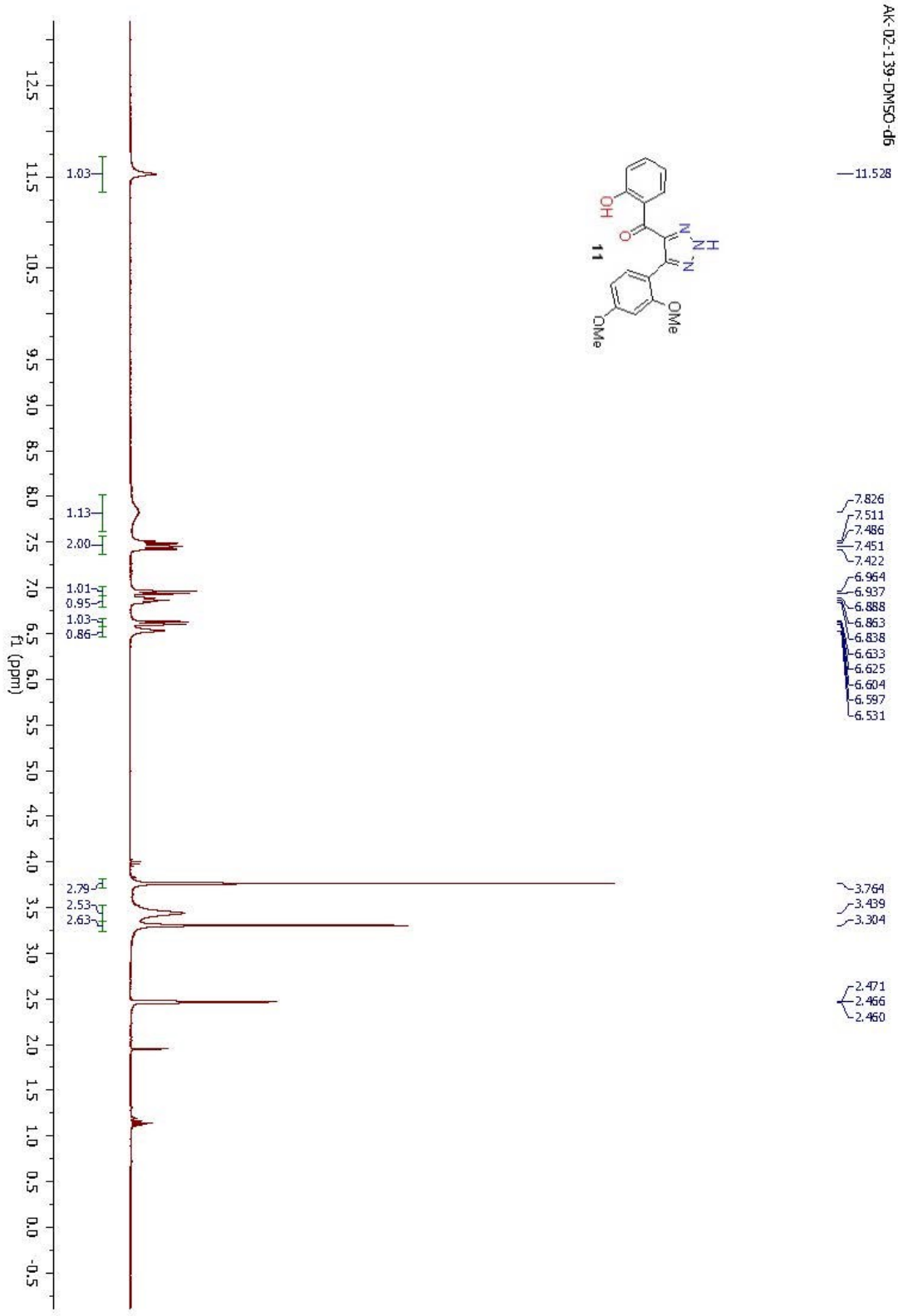

AK-2-143
193.20
164.32
149.18
138.07
134.94
132.16
130.75
124.57
124.15
120.51
119.92
118.77
8
f1 (ppm)

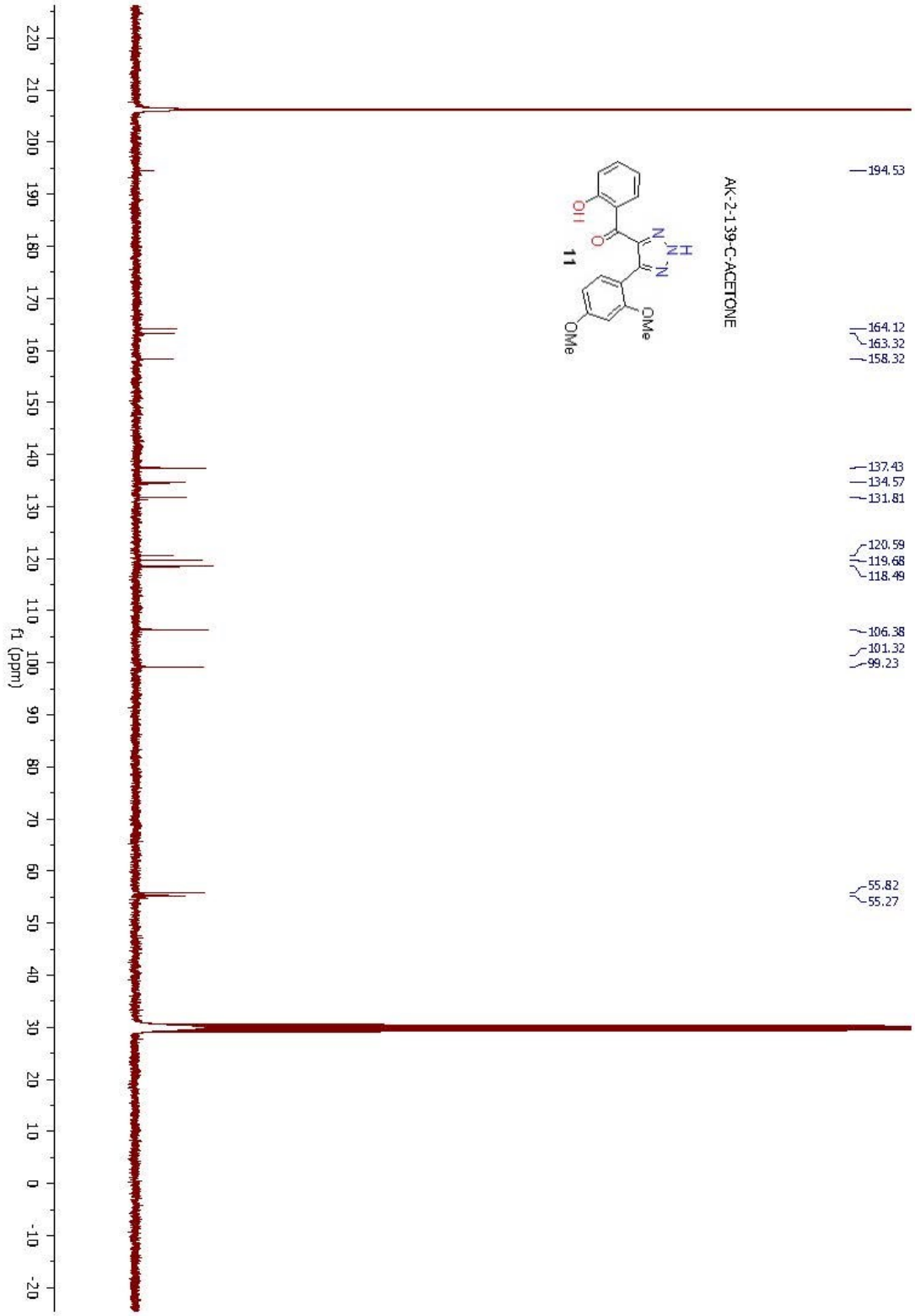

11.999
7.995
7.981
7.505
7.490
7.475
7.031
7.014
6.854
6.839
6.491
6.486
3.735
1.03
1.00
1.14
1.10
0.92
2.35
1.11
6.49
f1 (ppm)
AK-02-145
6
OMe
OMe
HO
O
N
N
N
H

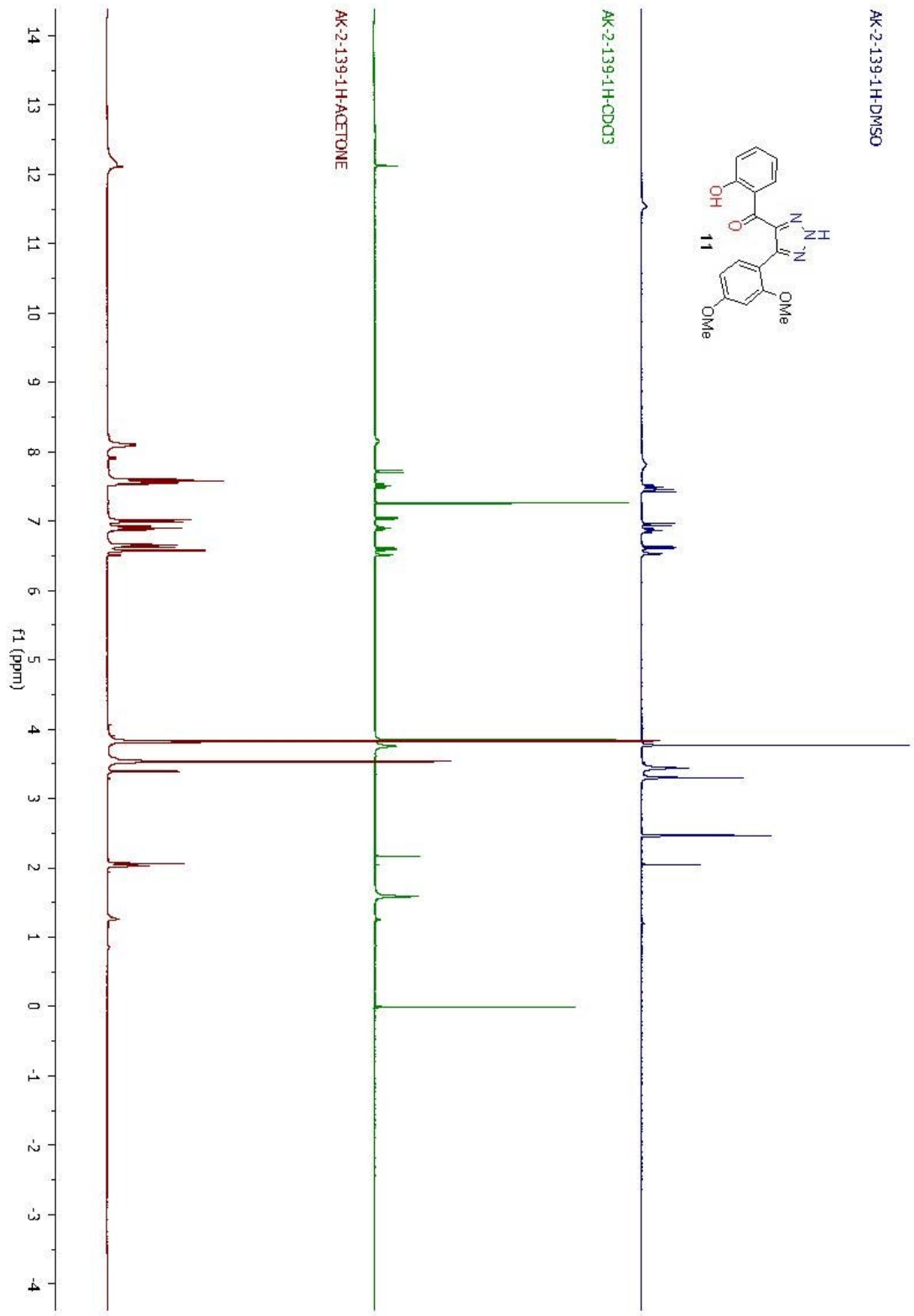

Ak-02-145-13C
192.64
192.43
163.57
160.94
137.37
133.80
119.61
119.28
118.33
106.76
102.13
55.55
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
OH
O
N
N
N
MeO
OMe
9


AK-2-146-1H
10
OH
O
N
N
H
OMe
10.514
8.060
8.050
7.527
7.525
7.521
7.510
7.508
7.496
7.494
7.491
7.327
7.312
7.296
7.271
7.263
7.259
7.257
7.237
7.222
7.047
7.030
6.971
6.955
6.883
6.869
6.856
6.853
3.795
0.74
0.83
1.08
1.11
1.29
1.05
0.99
1.00
1.07
2.96
f1 (ppm)

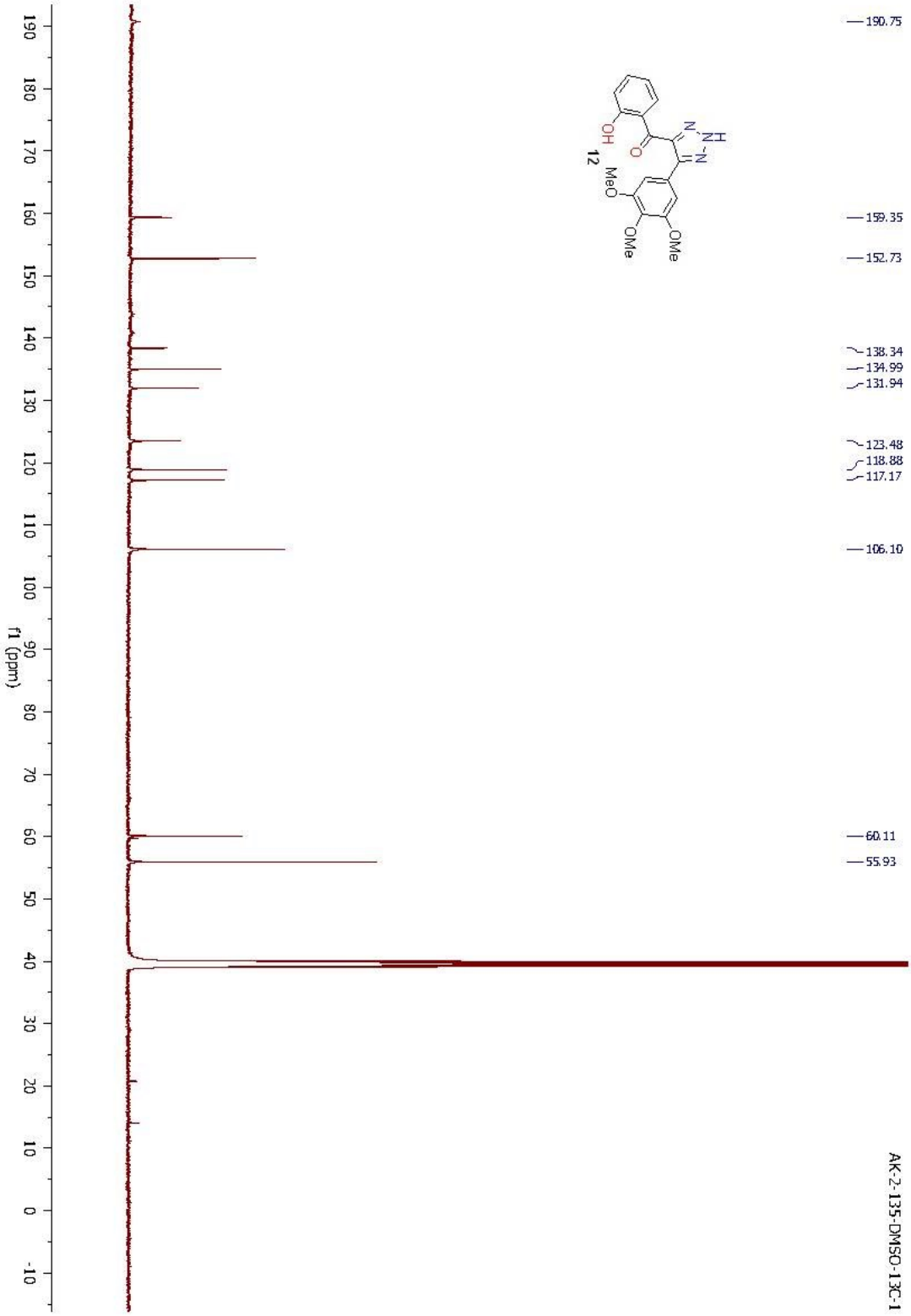

AK-2-146-13C
192.33
163.47
159.64
140.67
137.30
133.81
129.91
128.57
120.98
119.53
119.25
118.26
115.75
114.07
55.38
OH
O
N
N
H
N
OMe
10
f1 (ppm)

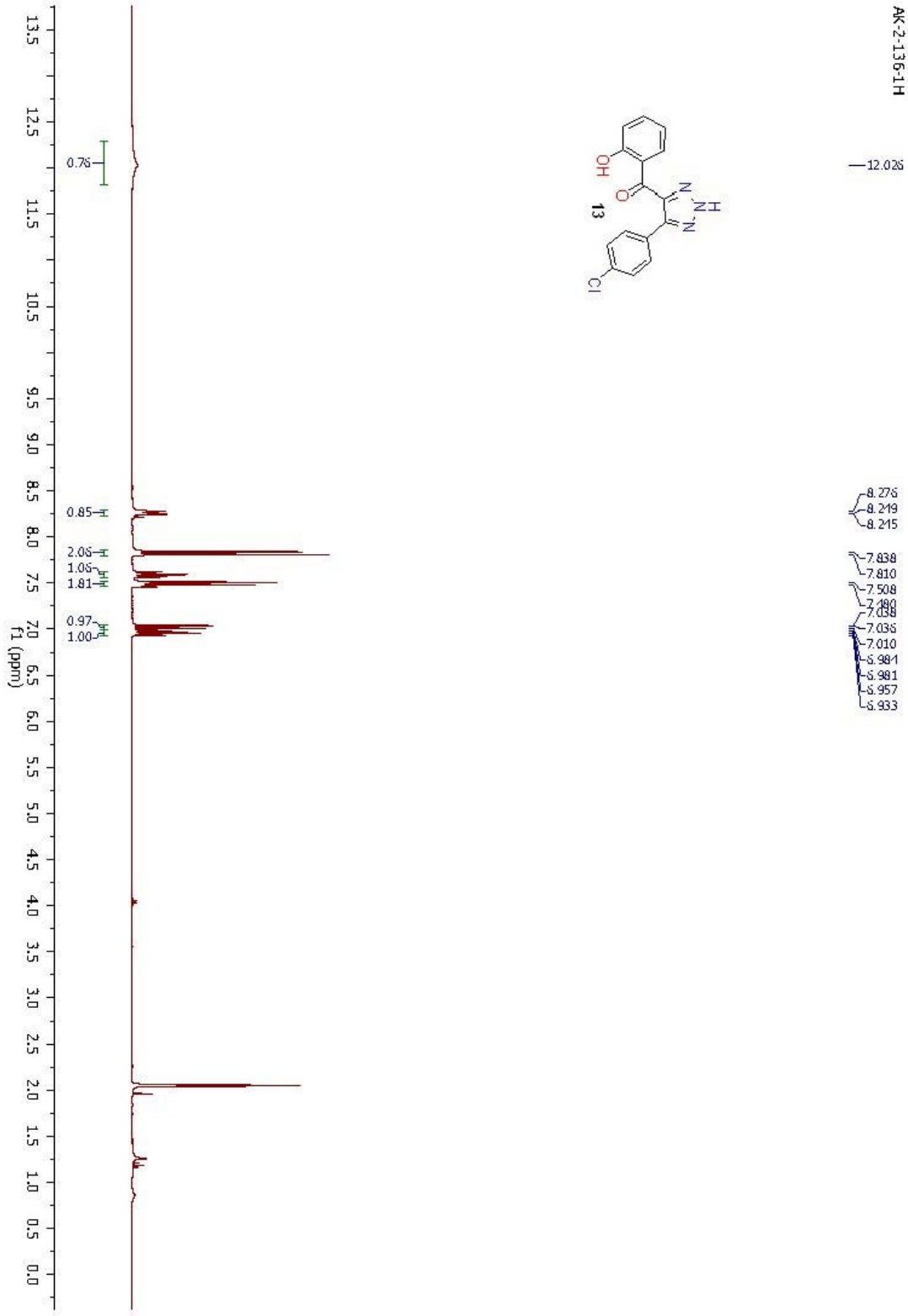

AK-02-139-DMSO-d6
11.528
7.826
7.511
7.486
7.451
7.422
6.964
6.937
6.888
6.863
6.838
6.633
6.625
6.604
6.597
6.531
3.764
3.439
3.304
2.471
2.466
2.460
1.03
1.13
2.00
1.01
0.95
1.03
0.86
2.79
2.53
2.63
f1 (ppm)
OH
O
N
N
H
N
OMe
OMe
11

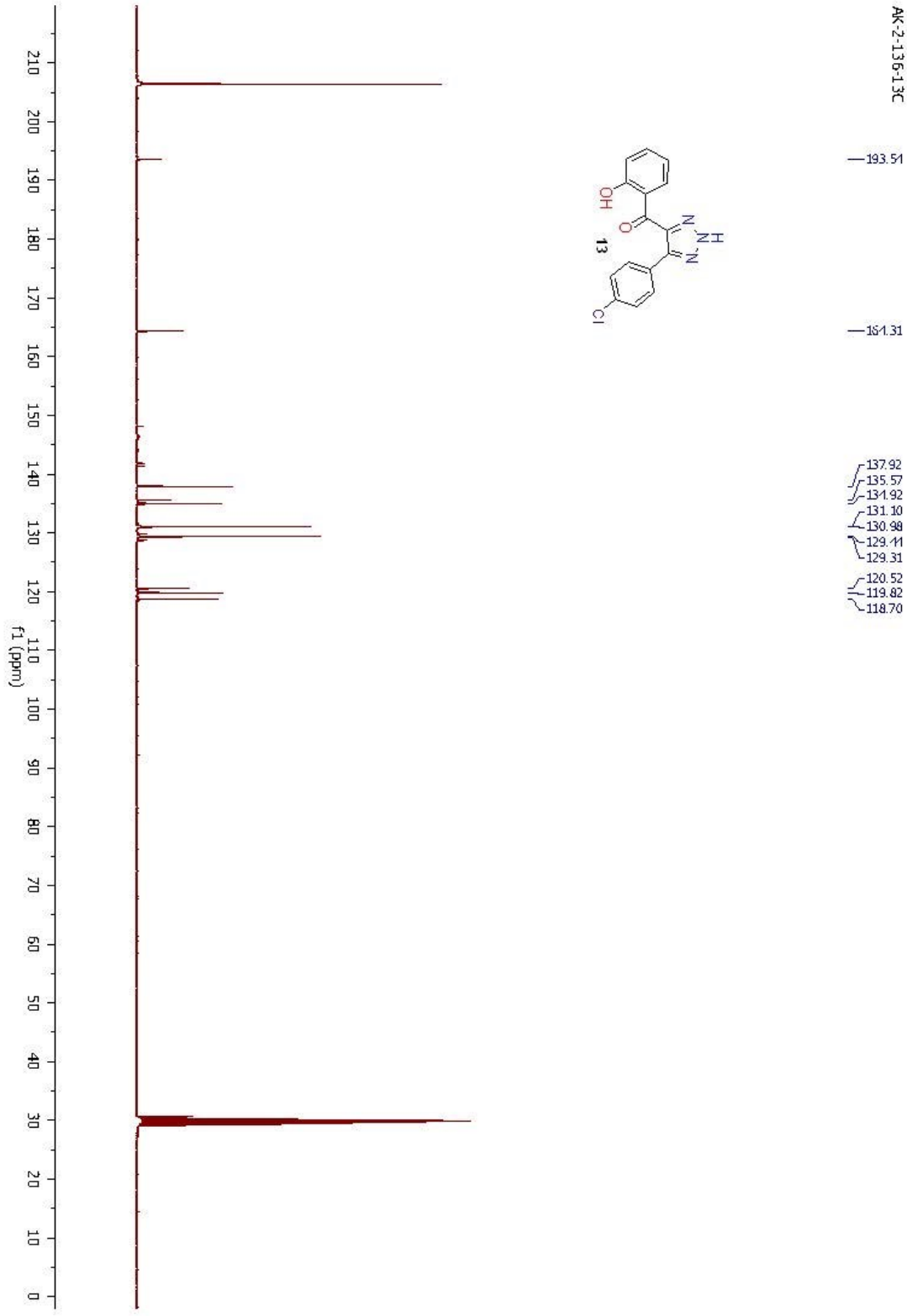

AK-2-139-C-ACETONE
11
OH
O
N
N
H
N
OMe
OMe
194.53
164.12
163.32
158.32
137.43
134.57
131.81
120.59
119.68
118.49
106.38
101.32
99.23
55.82
55.27
f1 (ppm)


AK-2-139-1H-DMSO
AK-2-139-1H-CDCl3
AK-2-139-1H-ACETONE
OH
O
H
N
N
N
OMe
OMe
11
f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4

AK-2-135-1H-DMSO

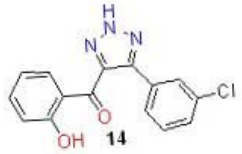

190.75
159.35
152.73
138.34
134.99
131.94
123.48
118.88
117.17
106.10
60.11
55.93
f1 (ppm)
AK-2-135-DMSO-13C-1
12


AK-2-136-1H
12.026
8.278
8.249
8.245
7.838
7.810
7.508
7.480
7.038
7.036
7.010
6.984
6.981
6.957
6.933
OH
O
N
N
H
N
Cl
13
0.76
0.85
2.06
1.06
1.81
0.97
1.00
f1 (ppm)

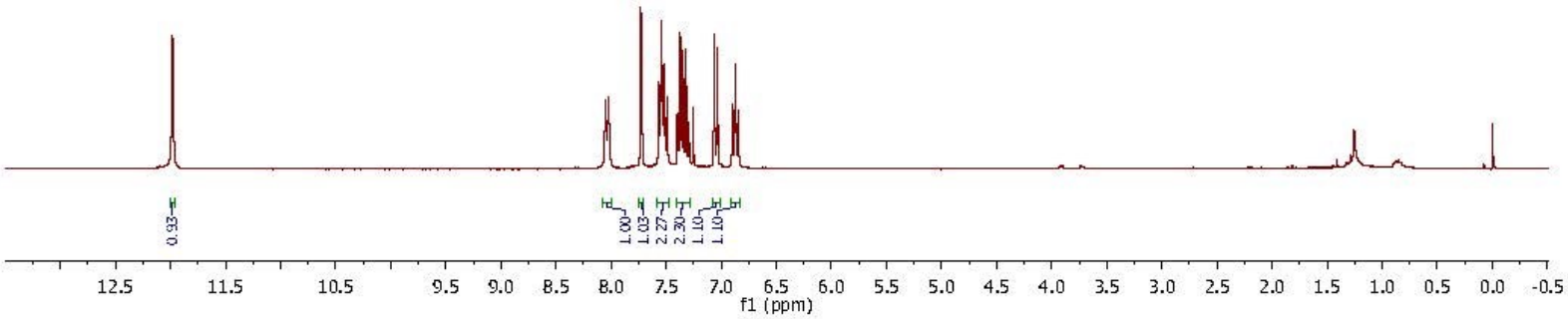

AK-2-136-13C
193.54
164.31
137.92
135.57
134.92
131.10
130.98
129.41
129.31
120.52
119.82
118.70
OH
O
N
N
H
Cl
13
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

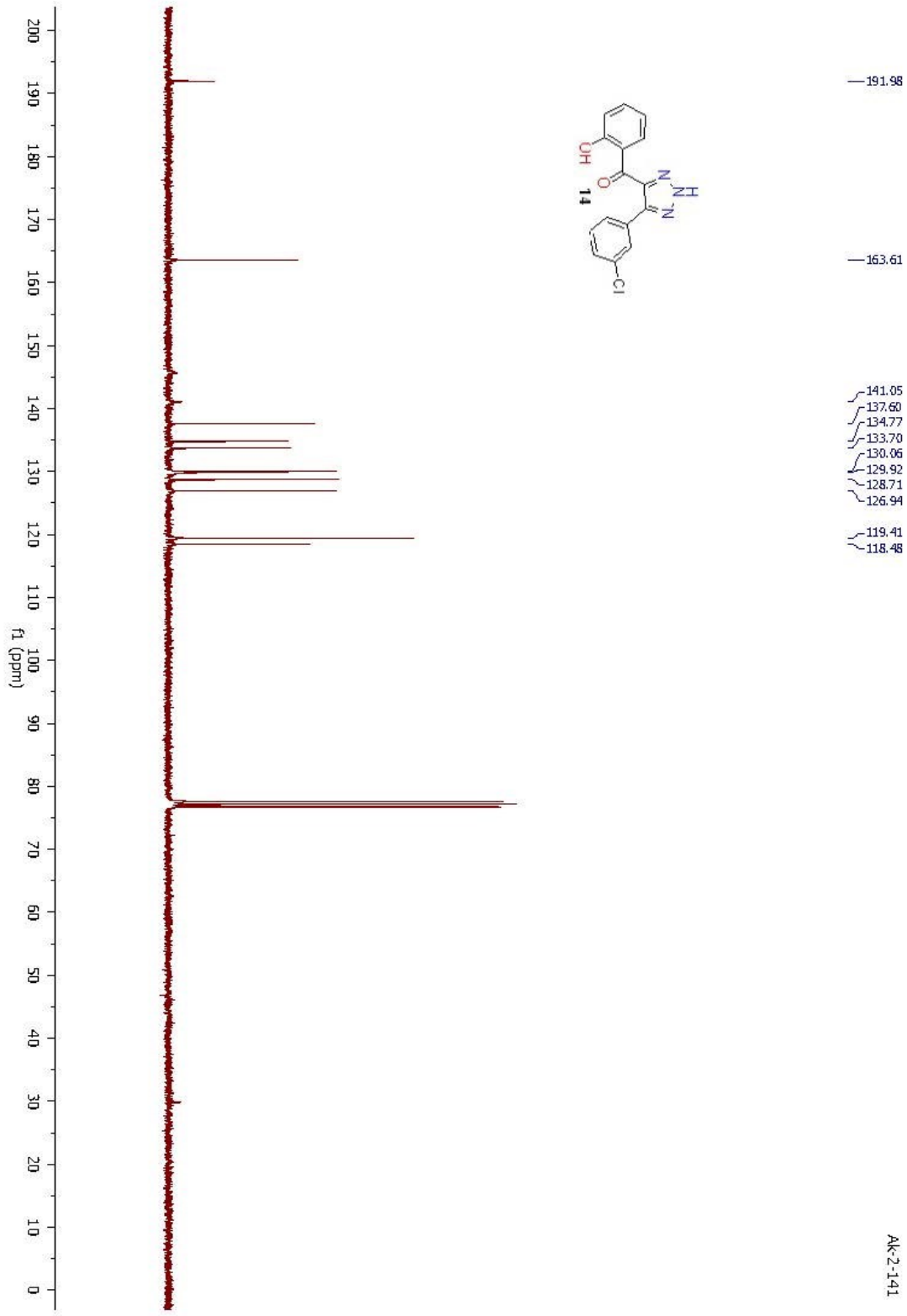
AK-2-141

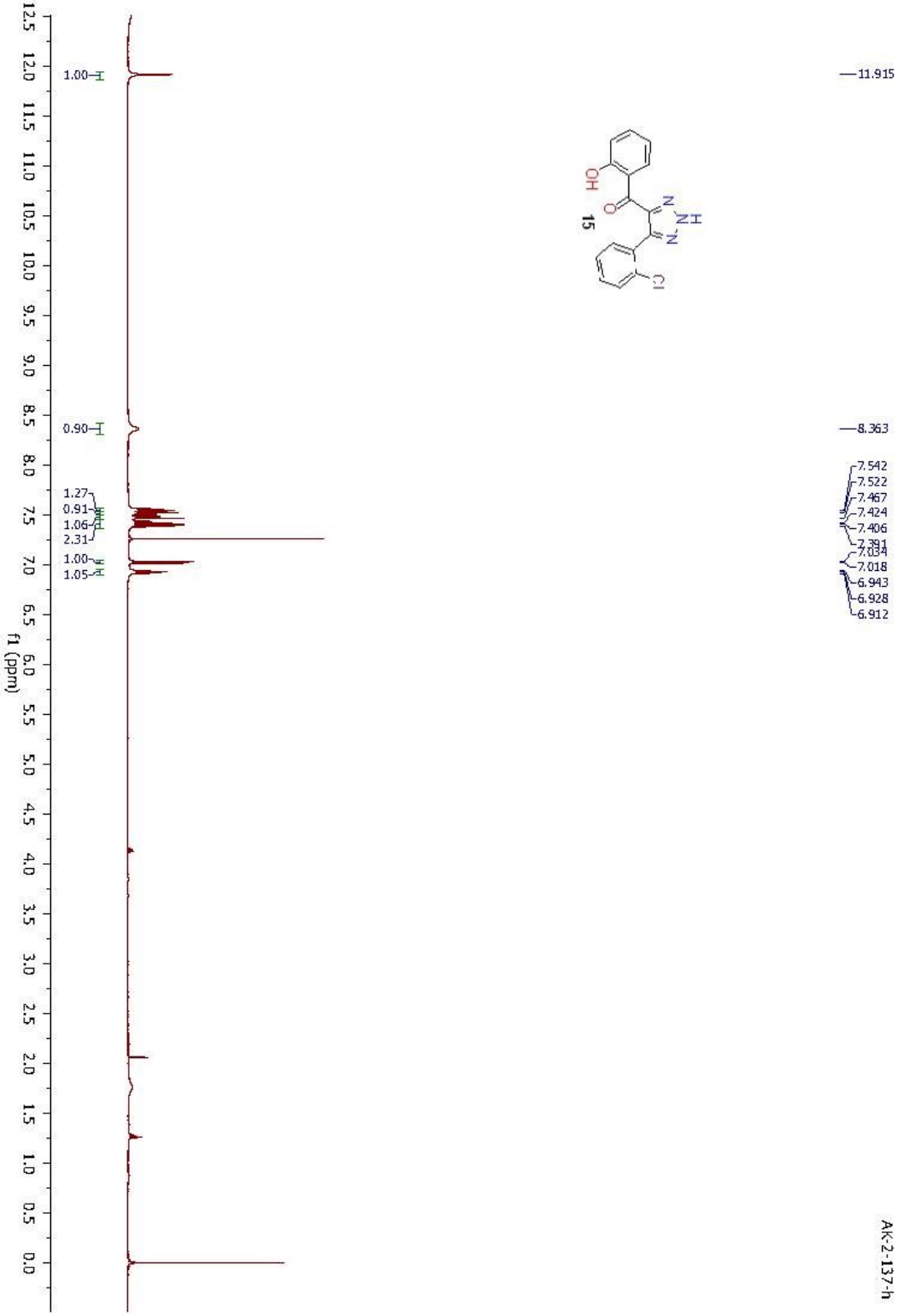

11.981
8.049
8.023
7.729
7.724
7.567
7.562
7.543
7.538
7.521
7.516
7.497
7.492
7.399
7.394
7.372
7.347
7.322
7.295
7.063
7.035
6.838
6.872
6.847


H
N
N
N
O
OH
Cl

14

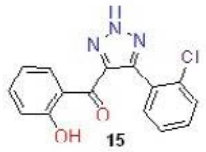

0.93
1.00
1.03
2.27
2.30
1.10
1.10
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


191.98
163.61
141.05
137.60
134.77
133.70
130.06
129.92
128.71
126.94
119.41
118.48
OH
O
N
N
H
N
Cl
14
f1 (ppm)
Ak-2-141

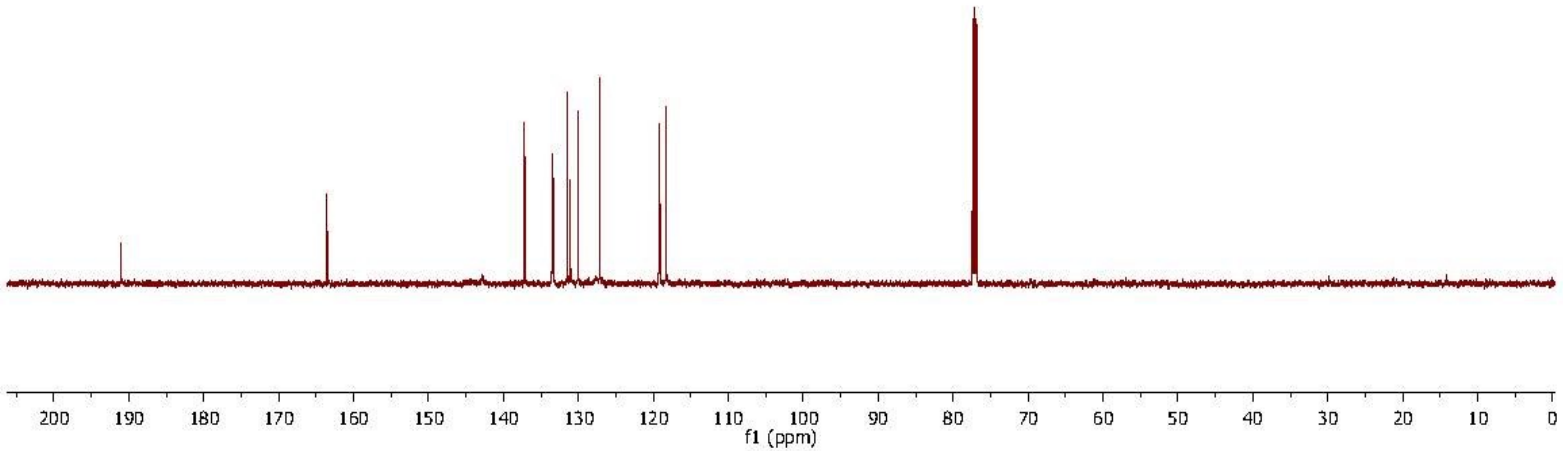

11.915
8.363
7.542
7.522
7.467
7.424
7.406
7.391
7.034
7.018
6.943
6.928
6.912
1.00
0.90
1.27
0.91
1.06
2.31
1.00
1.05
f1 (ppm)
15
AK-2-137-h

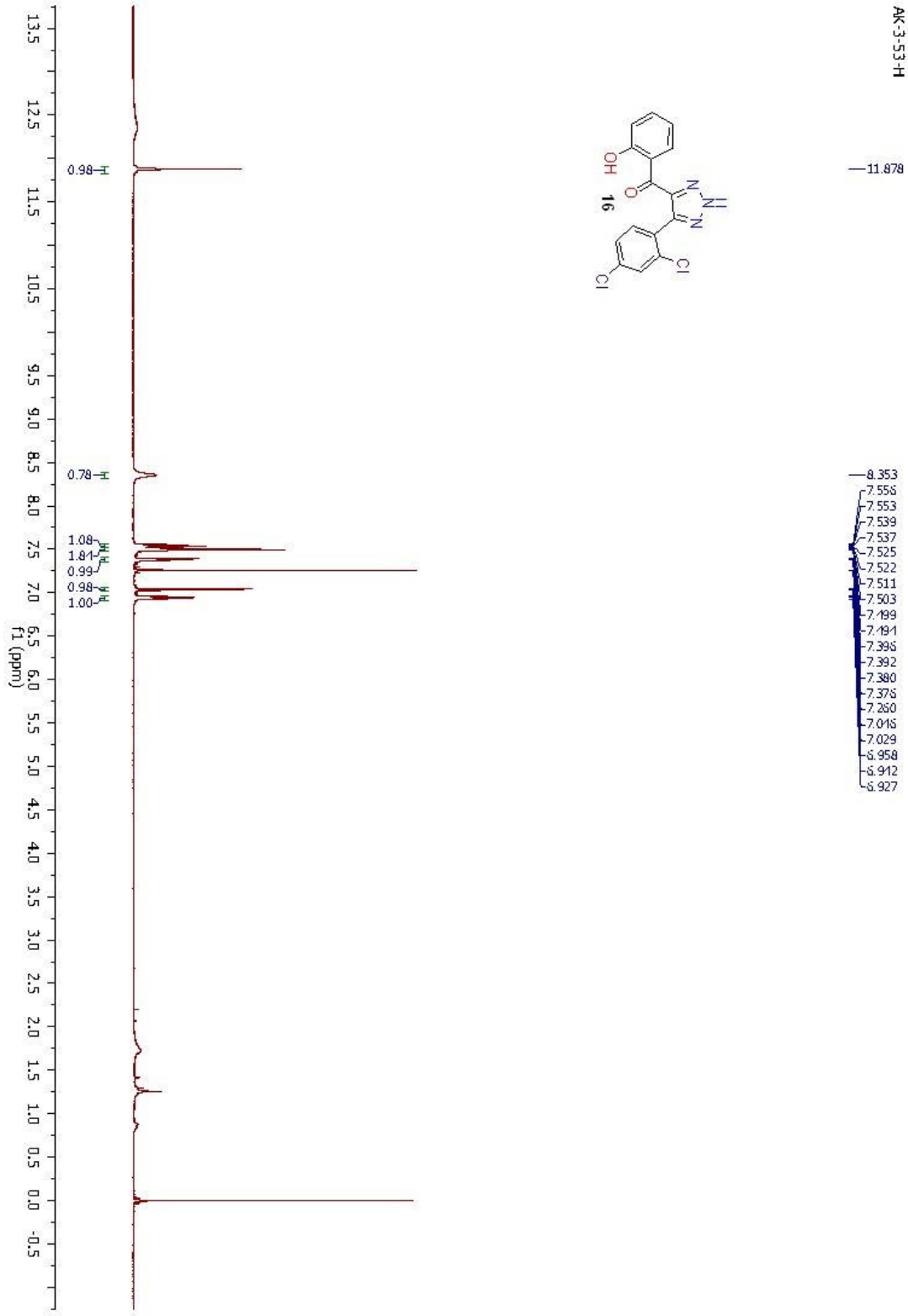
AK-2-137-c

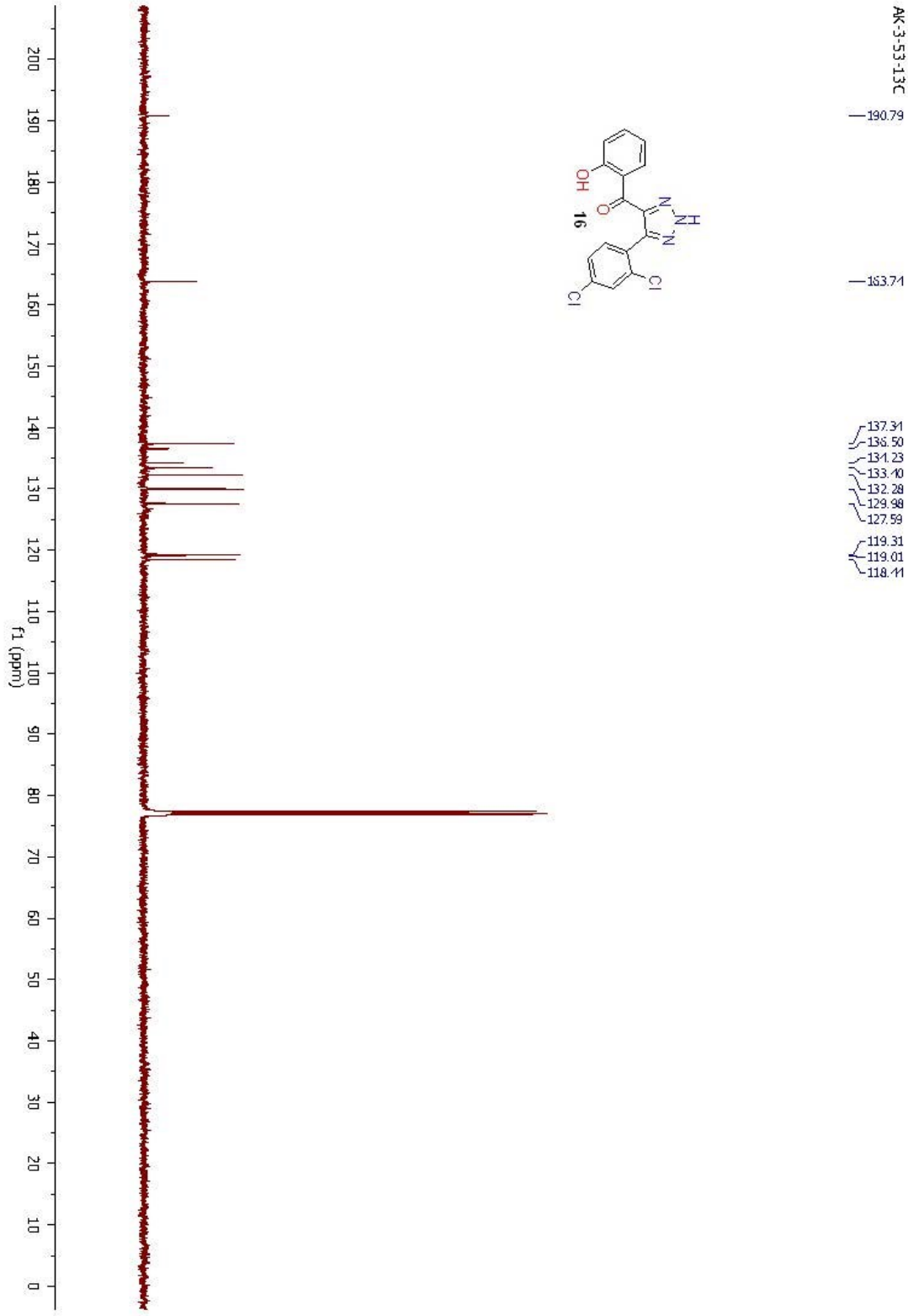
191.06
163.55
137.19
133.52
133.39
131.48
131.10
130.06
127.17
119.27
119.14
118.31

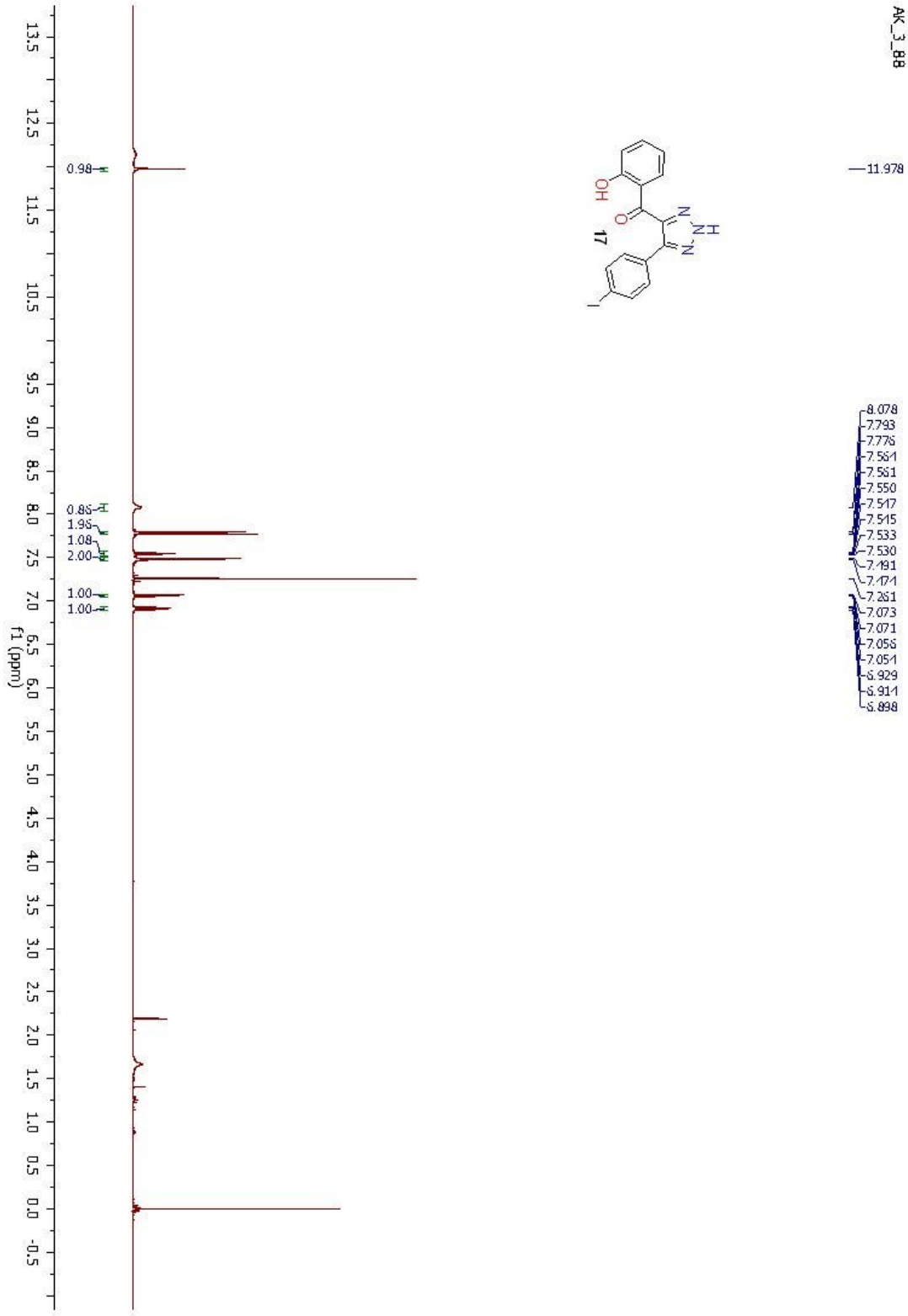


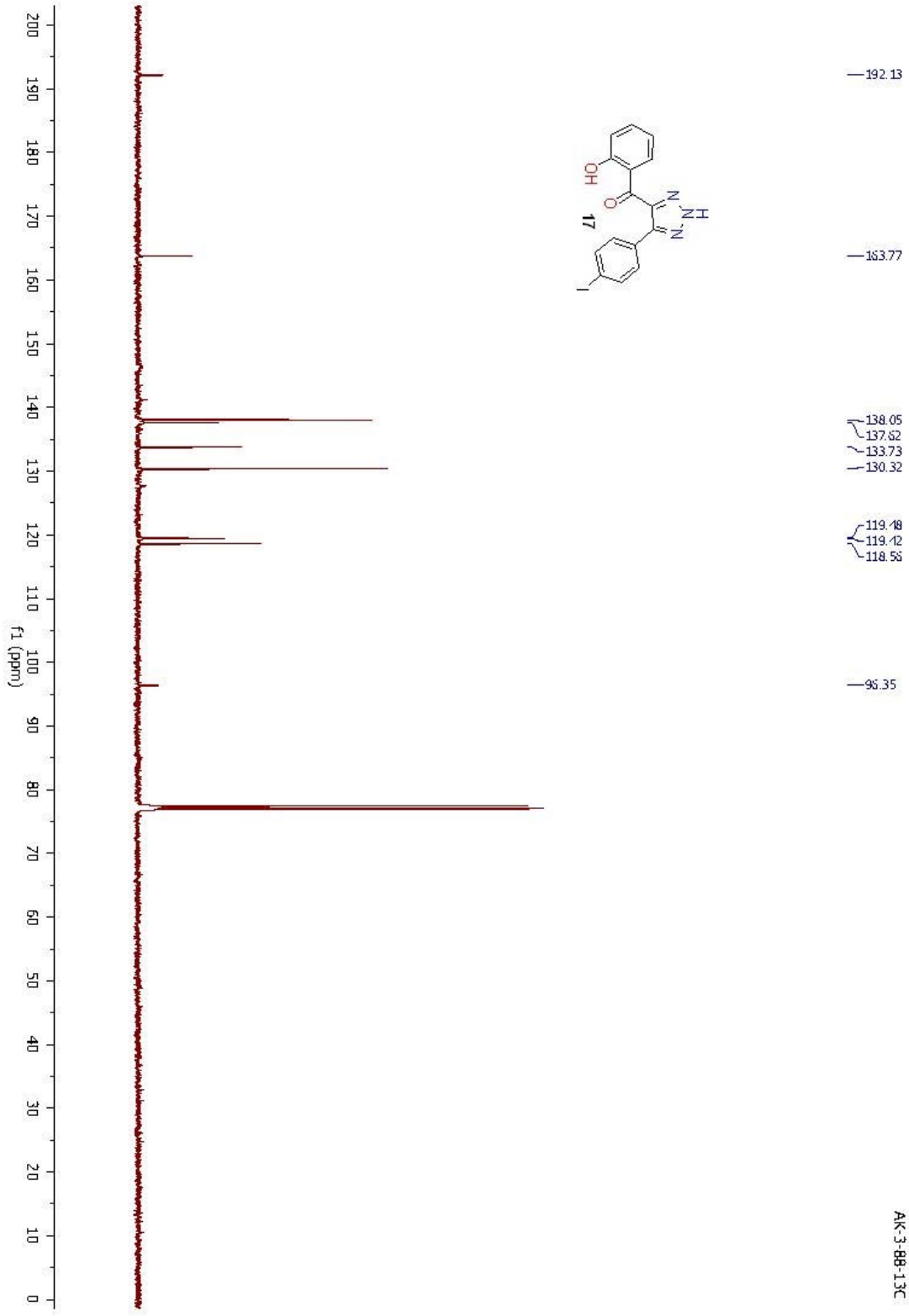
15

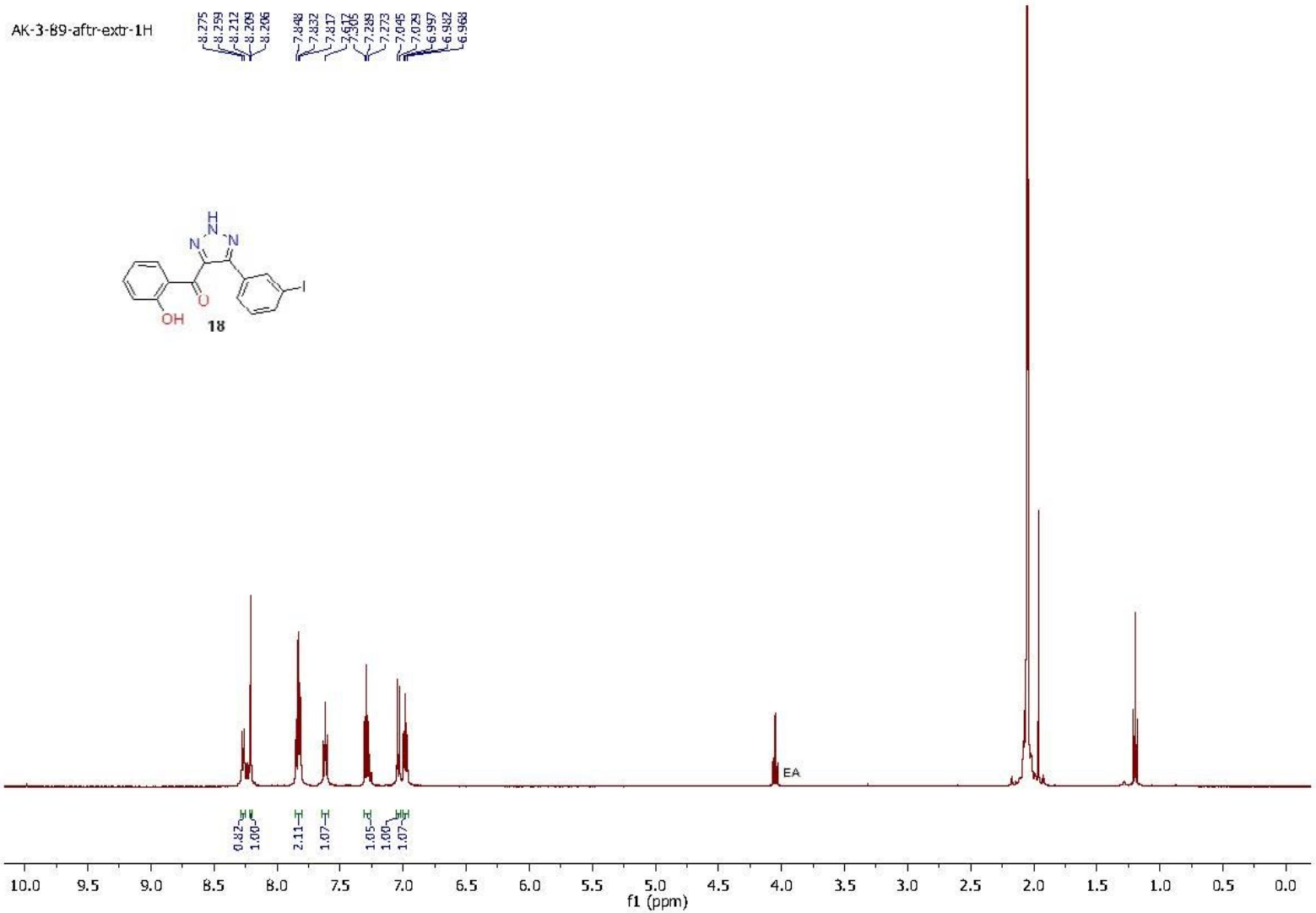


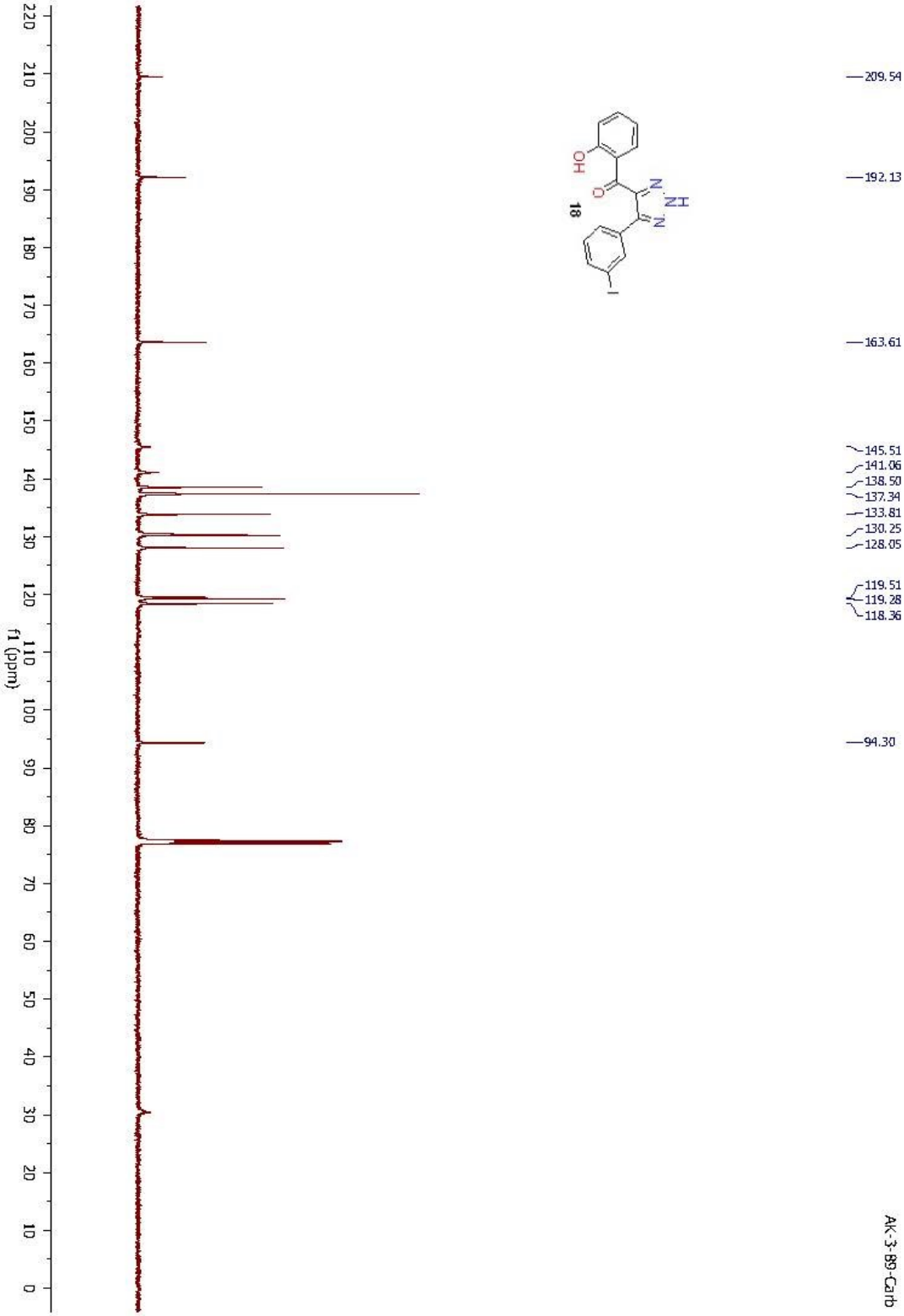

AK-3-53-H
11.878
8.353
7.556
7.553
7.539
7.537
7.525
7.522
7.511
7.503
7.499
7.491
7.396
7.392
7.380
7.376
7.260
7.046
7.029
6.958
6.912
6.927
16
OH
O
N
N
N
Cl
Cl
0.98
0.78
1.08
1.84
0.99
0.98
1.00
f1 (ppm)


AK-3-53-13C
190.79
163.74
137.31
136.50
134.23
133.40
132.28
129.98
127.59
119.31
119.01
118.41
16
HO
O
N
N
H
N
Cl
Cl
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

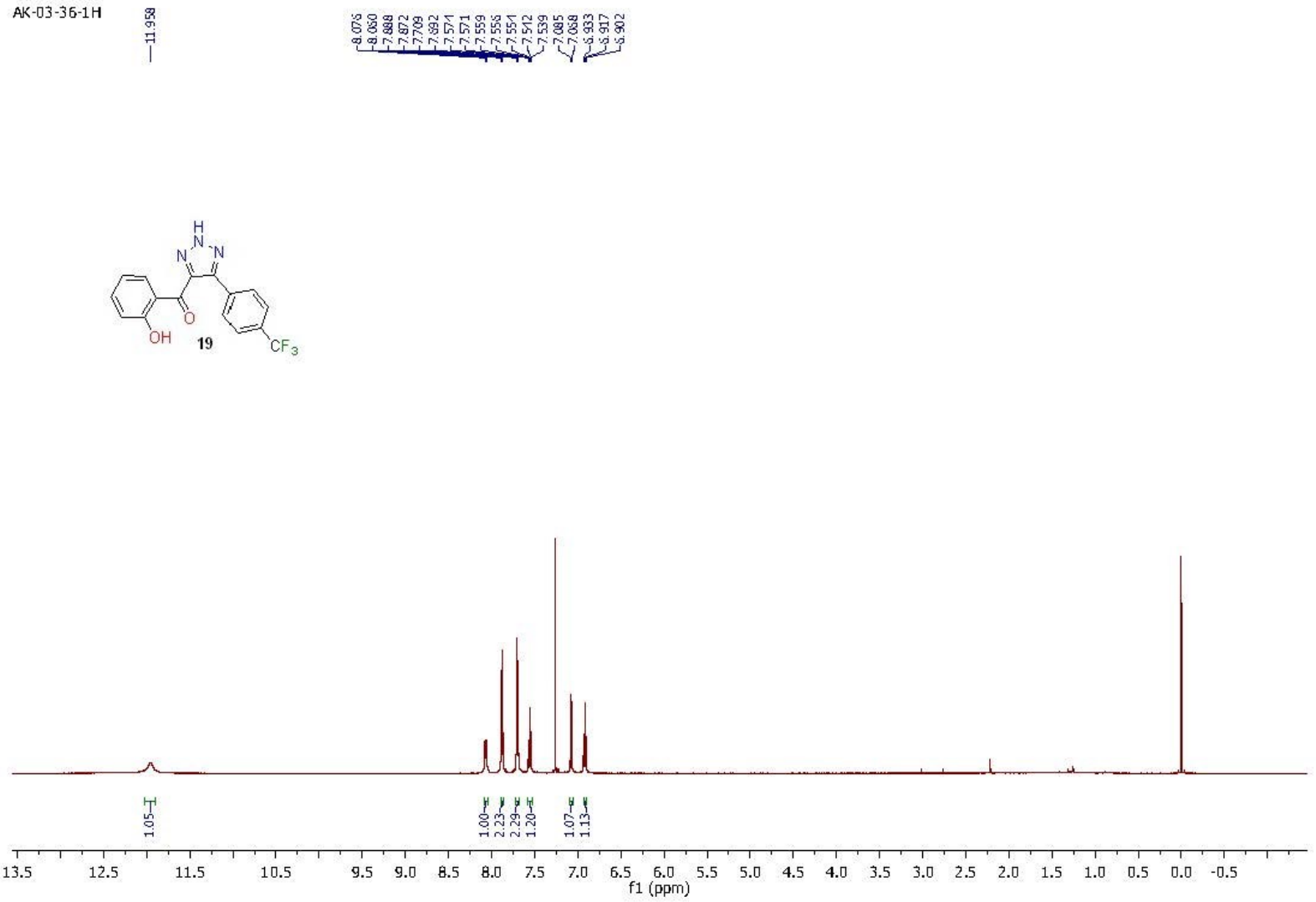

AK_3_88
11.978
8.078
7.793
7.776
7.564
7.561
7.550
7.547
7.545
7.533
7.530
7.491
7.474
7.261
7.073
7.071
7.056
7.054
6.929
6.914
6.898
0.98
0.86
1.96
1.08
2.00
1.00
1.00
f1 (ppm)
17

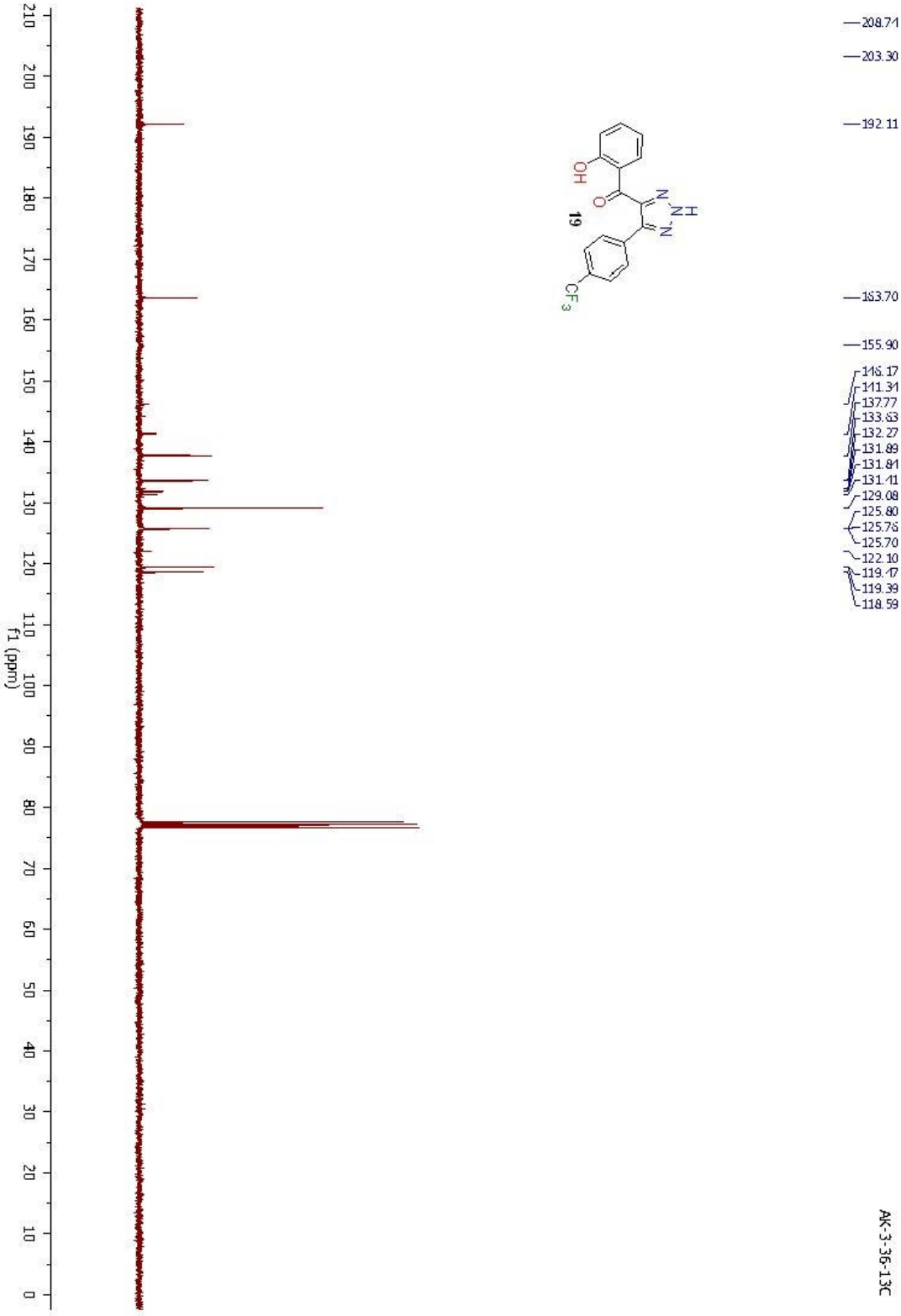

192.13
163.77
138.05
137.62
133.73
130.32
119.48
119.42
118.56
96.35
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
HO
O
N
N
H
17
I
AK-3-BB-13C


AK-3-89-aftr-extr-1H
8.275
8.259
8.212
8.209
8.206
7.848
7.832
7.817
7.617
7.605
7.289
7.273
7.045
7.029
6.997
6.982
6.968
H
N
N
N
O
OH
I
18
EA
0.82
1.00
2.11
1.07
1.05
1.00
1.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

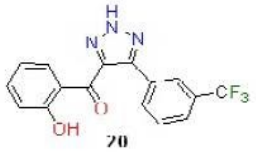

209.54
192.13
163.61
145.51
141.06
138.50
137.34
133.81
130.25
128.05
119.51
119.28
118.36
94.30
f1 (ppm)
18
AK-3-89-Carb

AK-03-36-1H

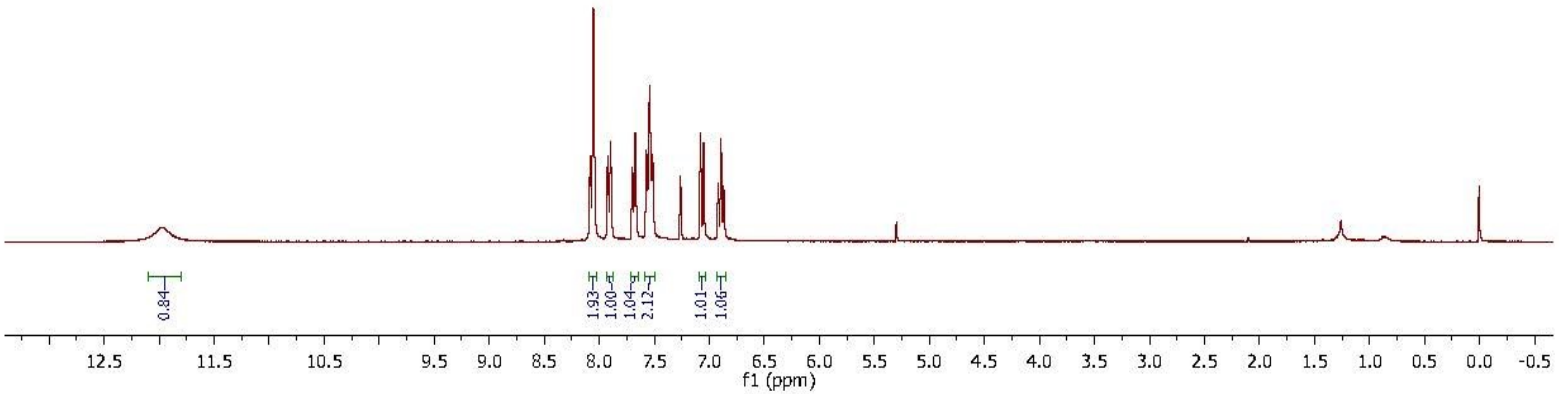

11.958
8.076
8.060
7.888
7.872
7.709
7.692
7.574
7.571
7.559
7.555
7.551
7.512
7.539
7.085
7.068
6.933
6.917
6.902
OH
19
CF3
1.05
1.00
2.23
2.29
1.20
1.07
1.13
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

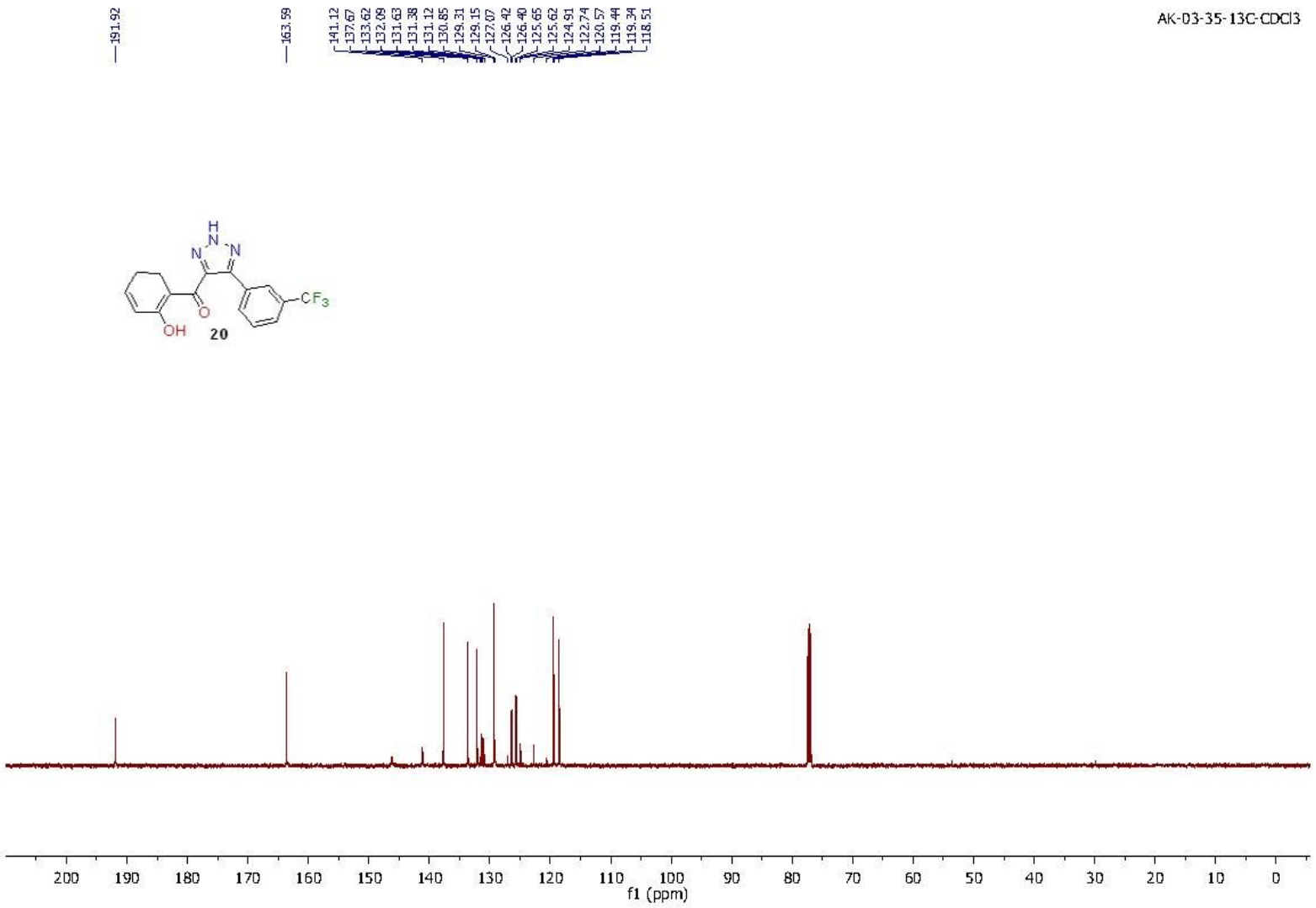

208.74
203.30
192.11
163.70
155.90
146.17
141.34
137.77
133.63
132.27
131.89
131.84
131.41
129.08
125.80
125.76
125.70
122.10
119.47
119.39
118.59
OH
O
N
N
H
19
CF3
f1 (ppm)
AK-3-36-13C

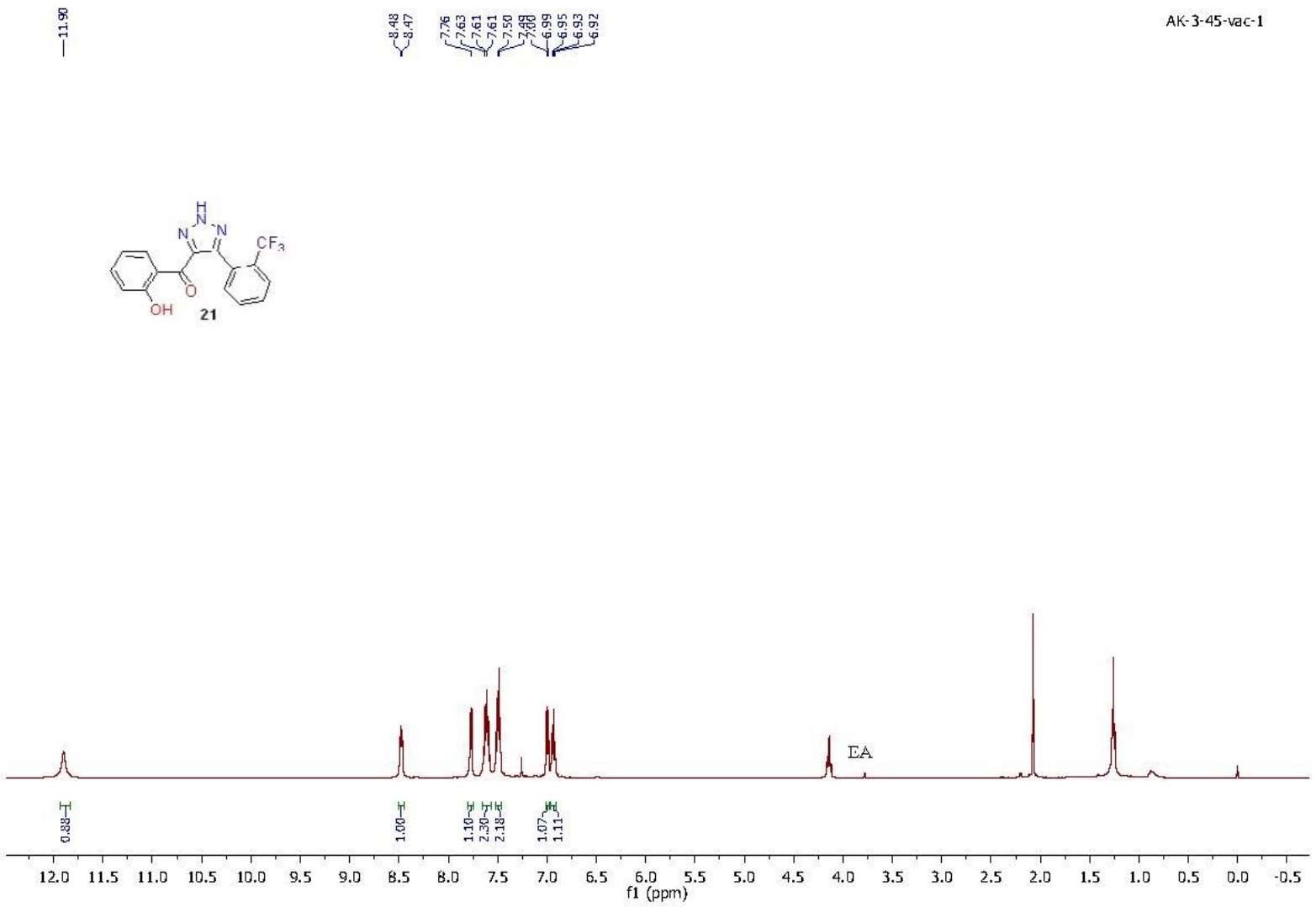
AK-3-35

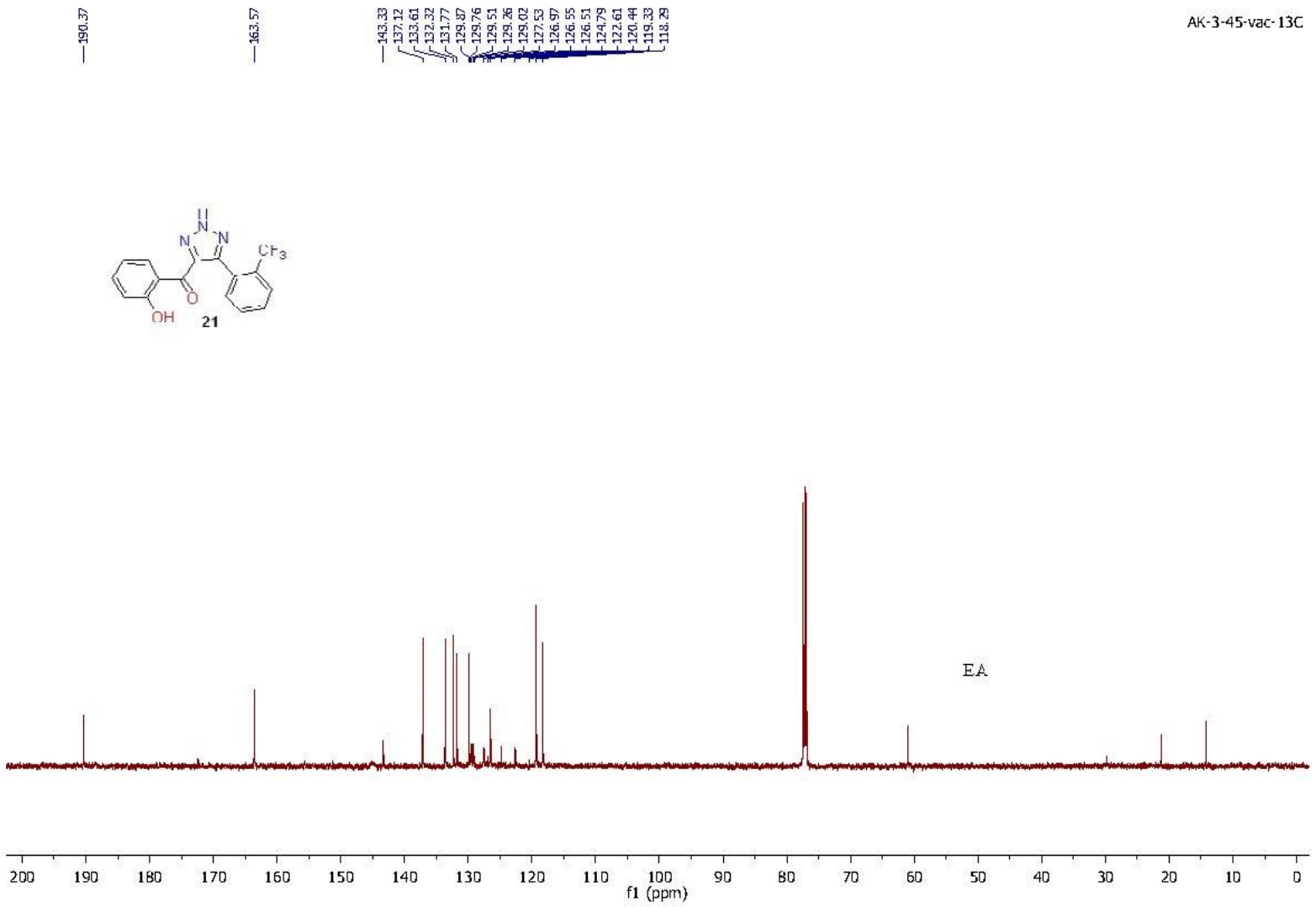

H
N
N
N
O
OH
CF3

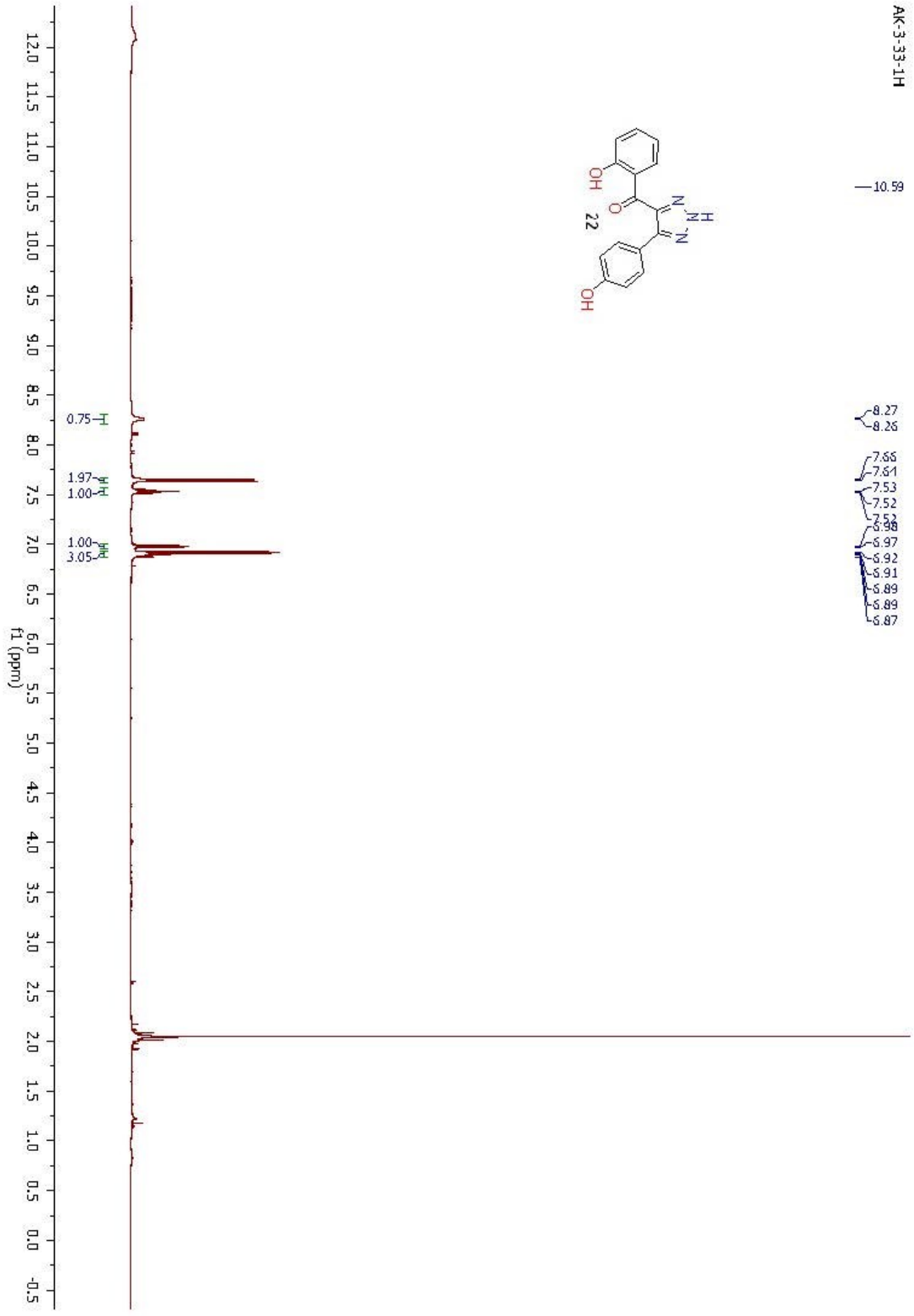
20

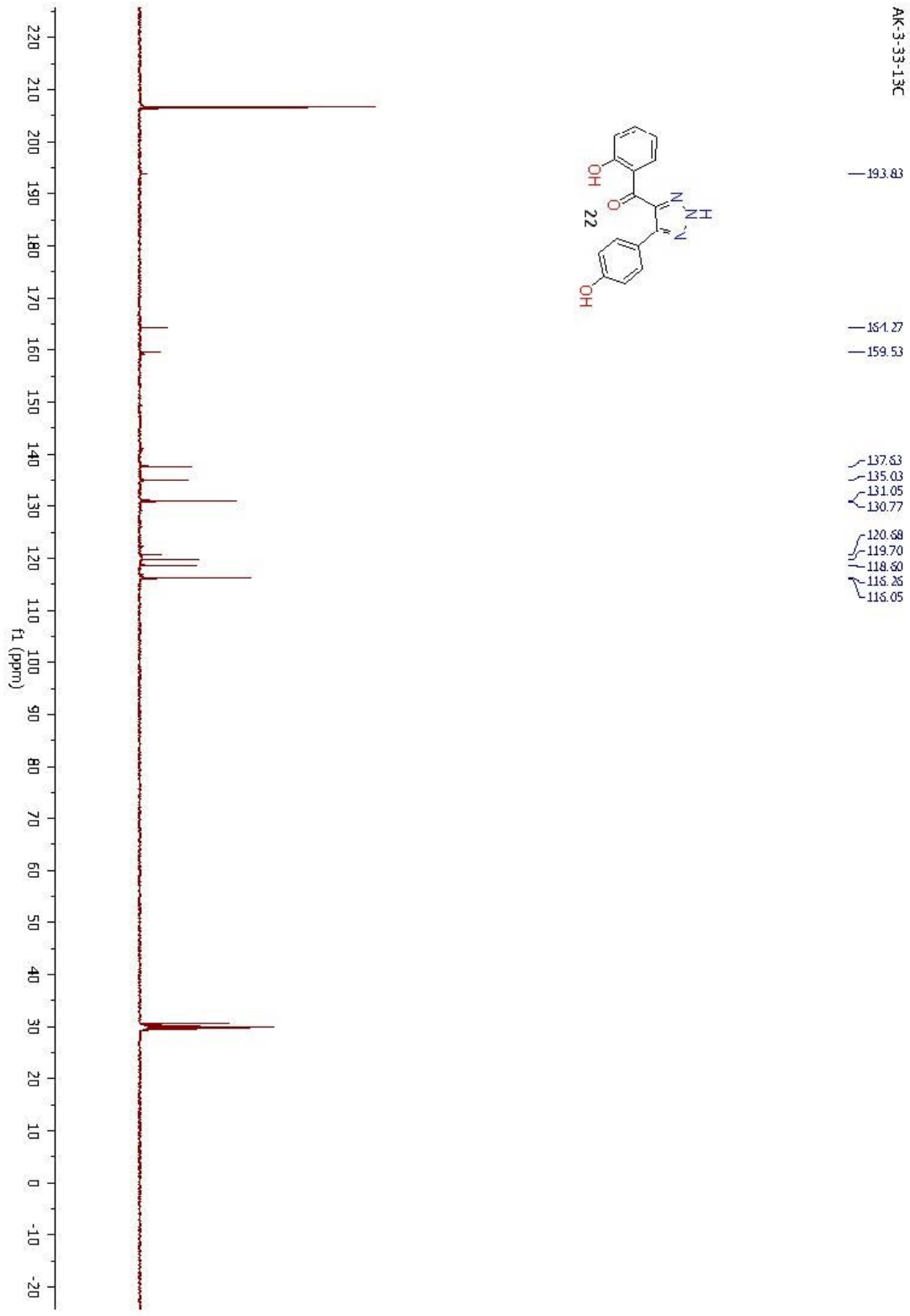

11.973
8.084
8.054
7.922
7.897
7.698
7.674
7.565
7.542
7.513
7.078
7.050
6.916
6.893
6.865
0.84
1.93
1.00
1.04
2.12
1.01
1.06
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

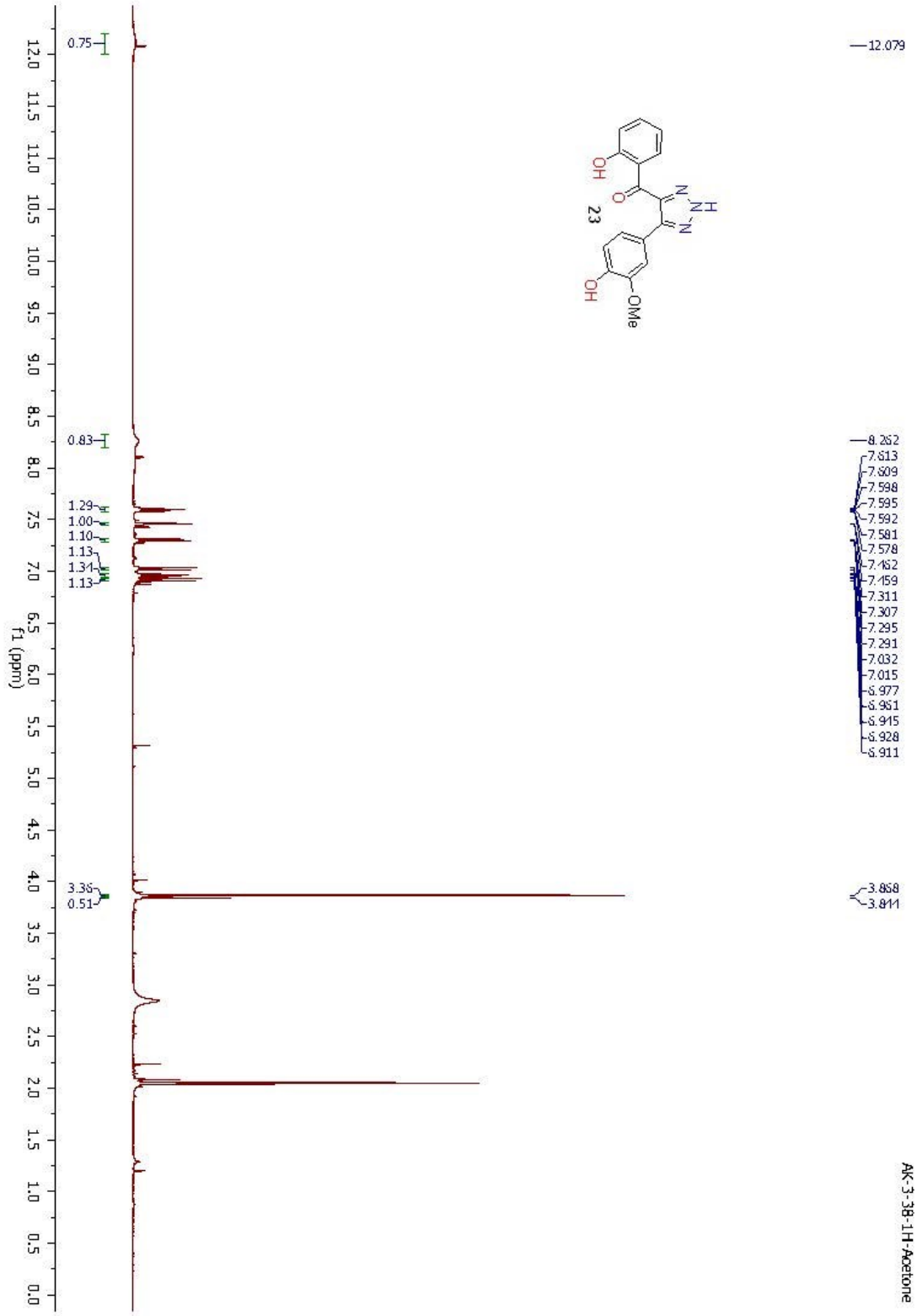

191.92
163.59
141.12
137.67
133.62
132.09
131.63
131.38
131.12
130.85
129.31
129.15
127.07
126.42
126.40
125.65
125.62
124.91
122.74
120.57
119.44
119.34
118.51
AK-03-35-13C-CDCl3
H
N
N
N
O
OH
CF3
20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

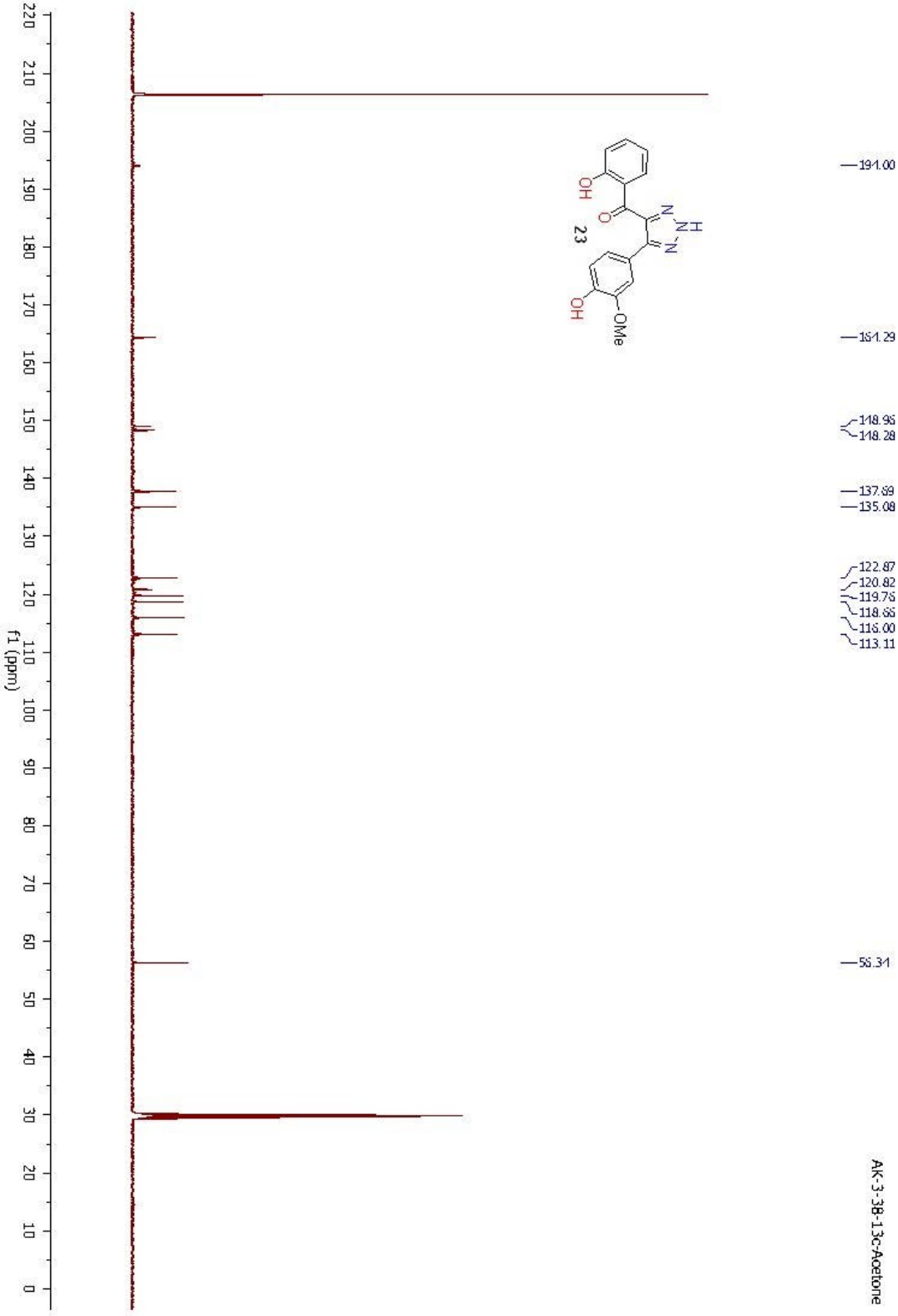

11.90
8.48
8.47
7.76
7.63
7.61
7.61
7.50
7.48
7.00
6.99
6.95
6.93
6.92
AK-3-45-vac-1
CF3
OH
21
EA
0.88
1.00
1.10
2.30
2.18
1.07
1.11
f1 (ppm)

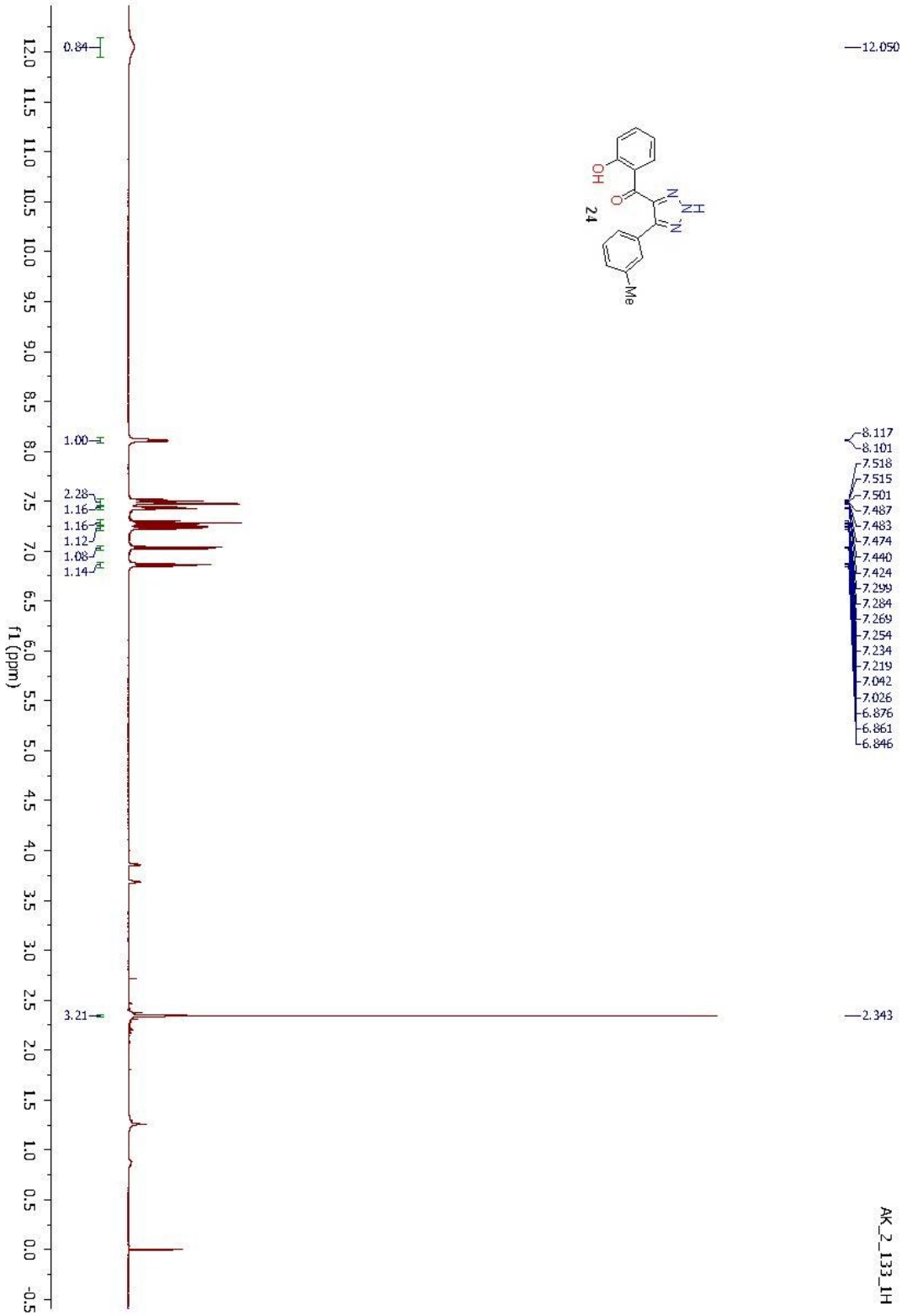

190.37
163.57
143.33
137.12
133.61
132.32
131.77
129.87
129.76
129.51
129.26
129.02
127.53
126.97
126.55
126.51
124.79
122.61
120.44
119.33
118.29
AK-3-45-vac-13C
CF3
OH
O
21
EA
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

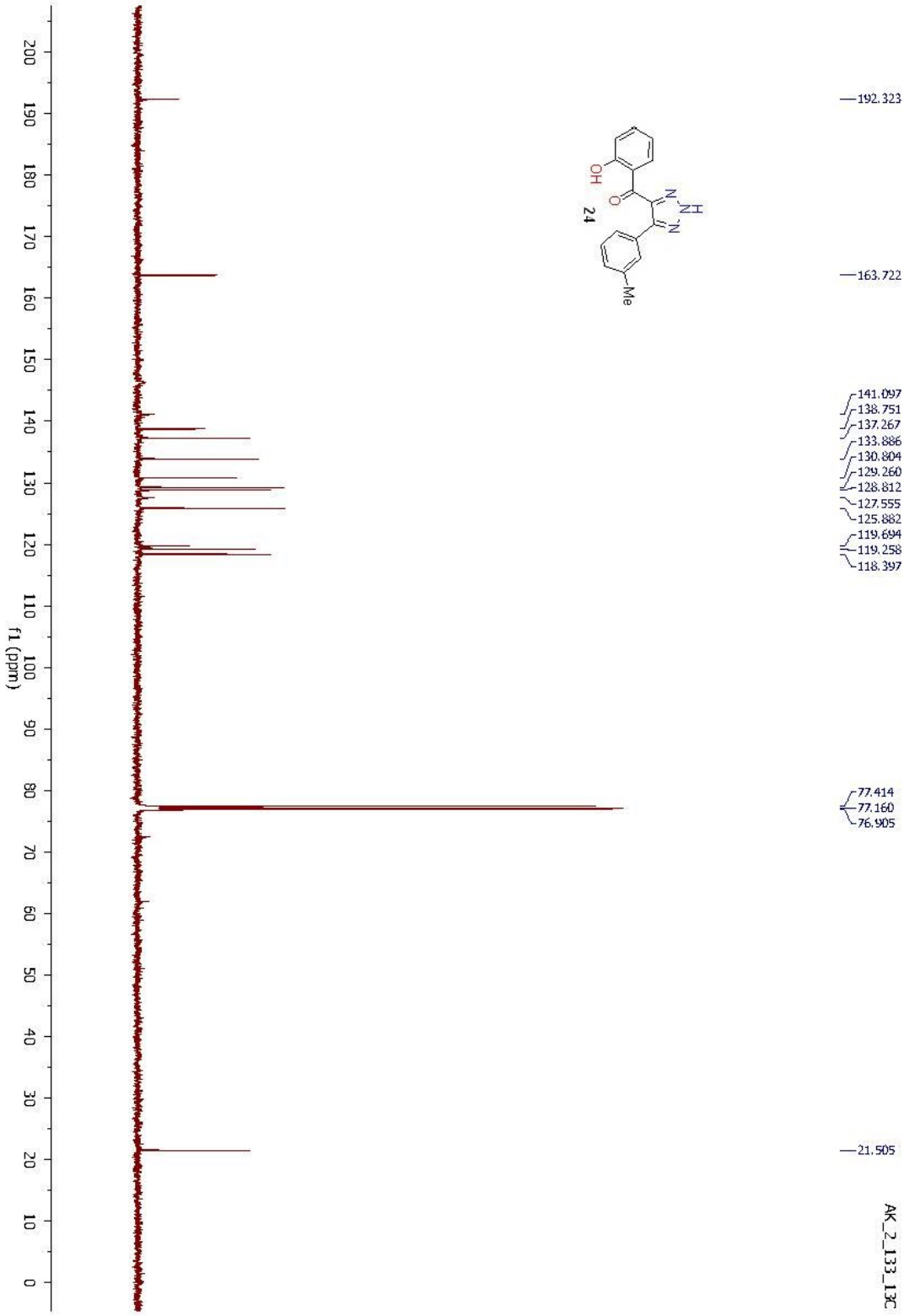

AK-3-33-1H
10.59
8.27
8.26
7.66
7.64
7.53
7.52
6.98
6.97
6.92
6.91
6.89
6.89
6.87
0.75
1.97
1.00
1.00
3.05
22
f1 (ppm)

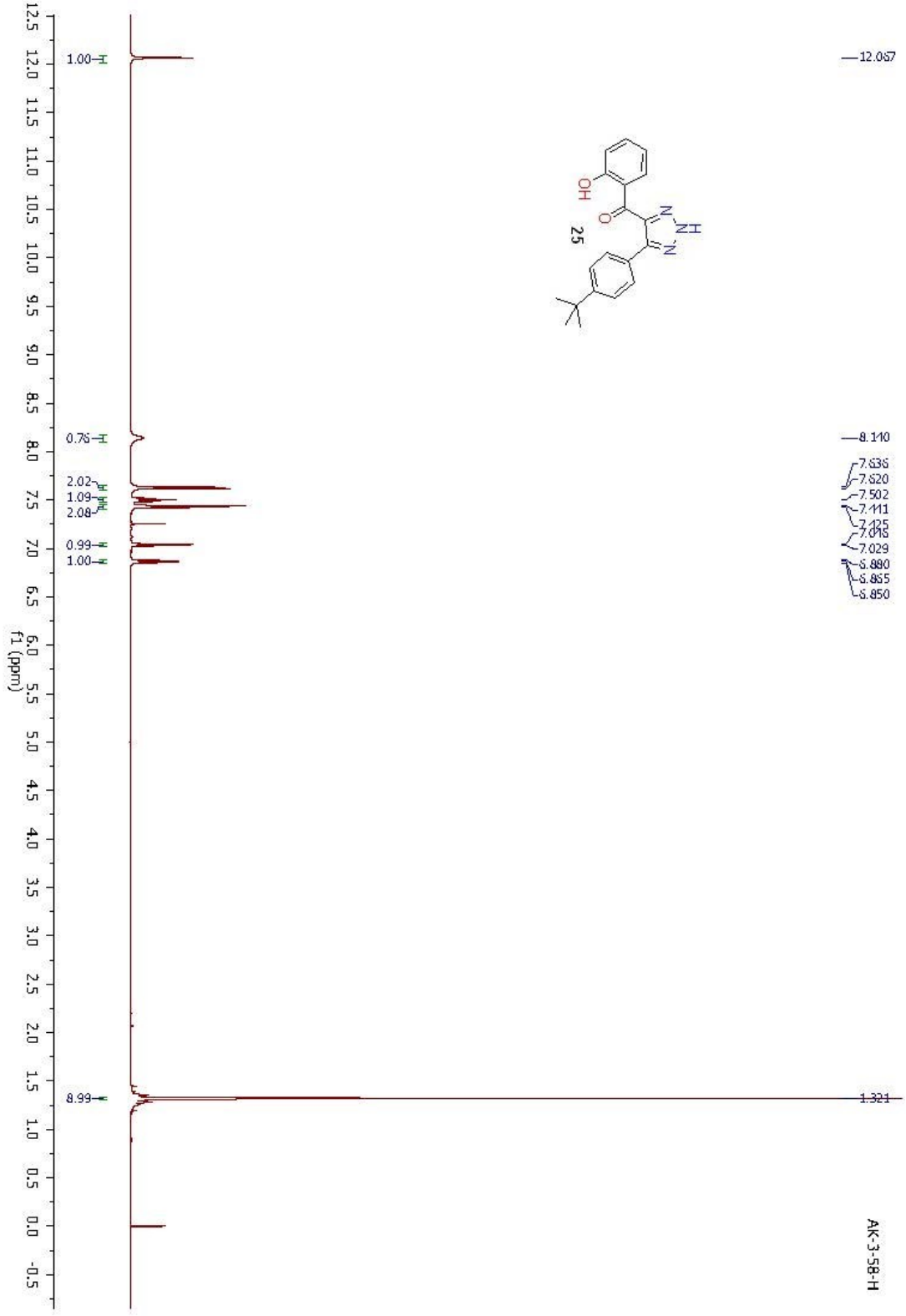

AK-3-33-13C
193.83
164.27
159.53
137.63
135.03
131.05
130.77
120.68
119.70
118.60
116.26
116.05
OH
O
N
N
H
N
OH
22
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

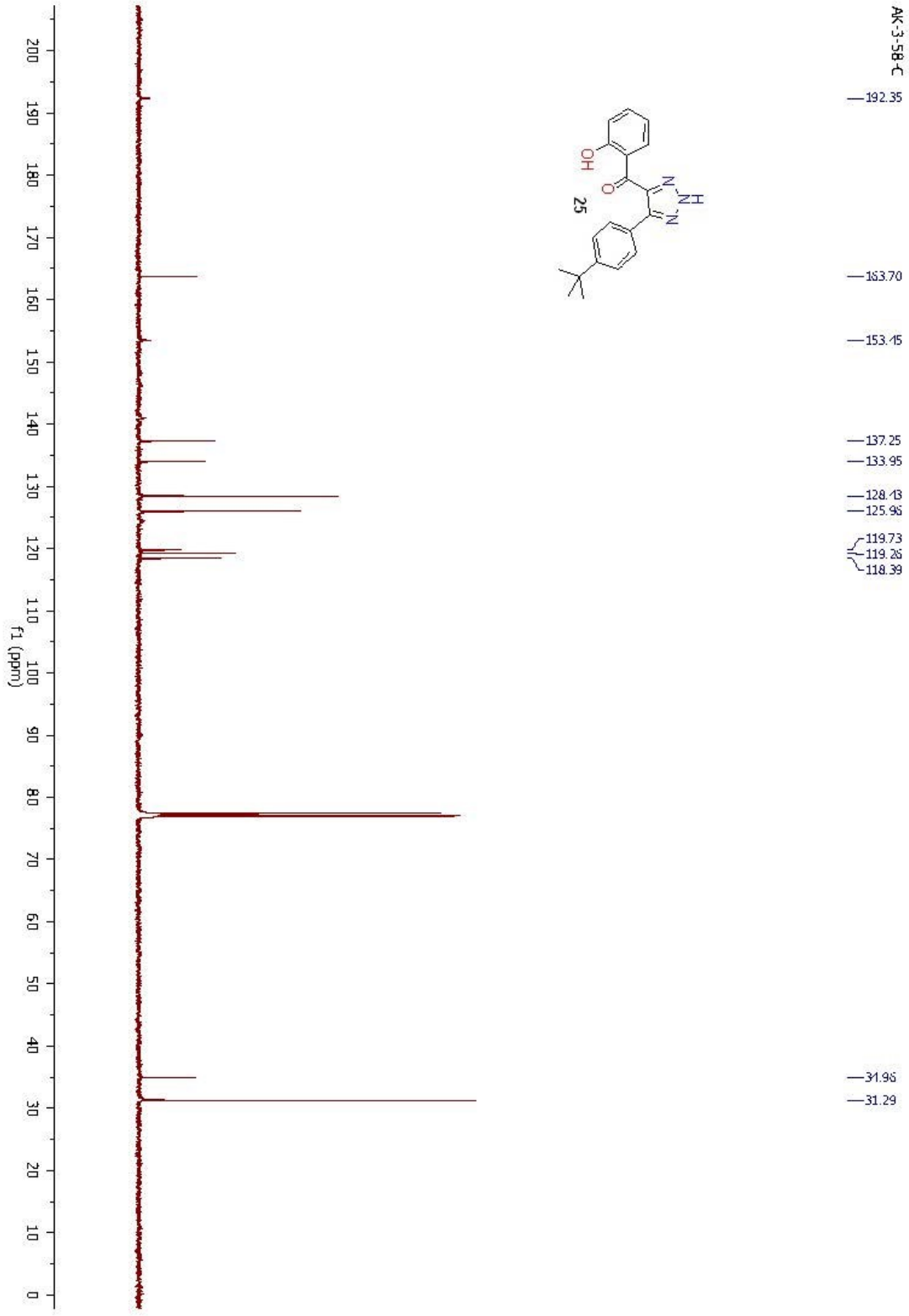

23
OH
O
N
N
H
OH
OMe
12.079
8.262
7.613
7.609
7.598
7.595
7.592
7.581
7.578
7.462
7.459
7.311
7.307
7.295
7.291
7.032
7.015
6.977
6.961
6.945
6.928
6.911
3.858
3.841
0.75
0.83
1.29
1.00
1.10
1.13
1.34
1.13
3.36
0.51
f1 (ppm)
AK-3-38-1H-Acetone

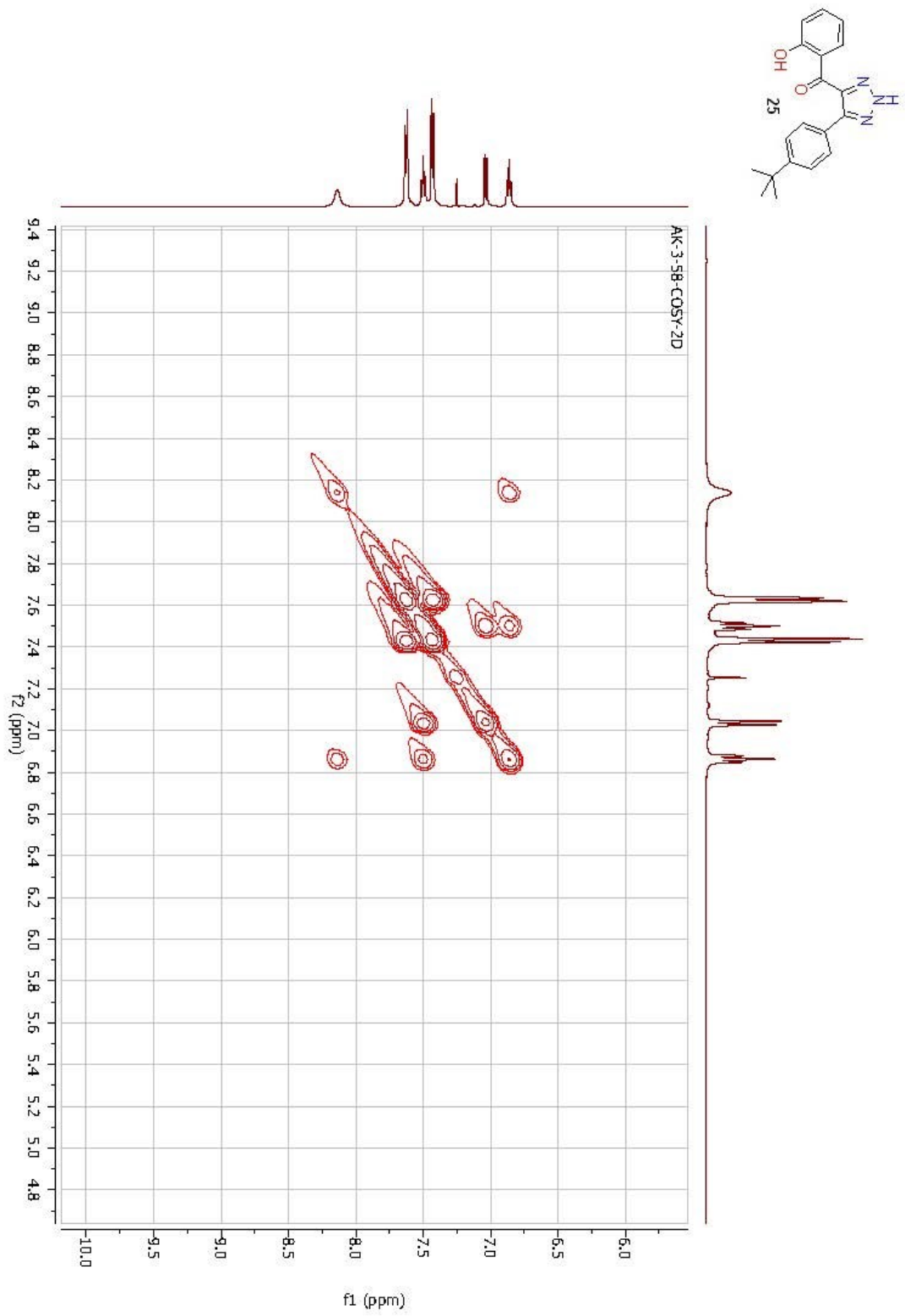

23
OH
O
N
N
H
OH
OMe
194.00
164.29
148.96
148.28
137.89
135.08
122.87
120.82
119.76
118.86
116.00
113.11
56.34
f1 (ppm)
AK-3-38-13c-Acetone

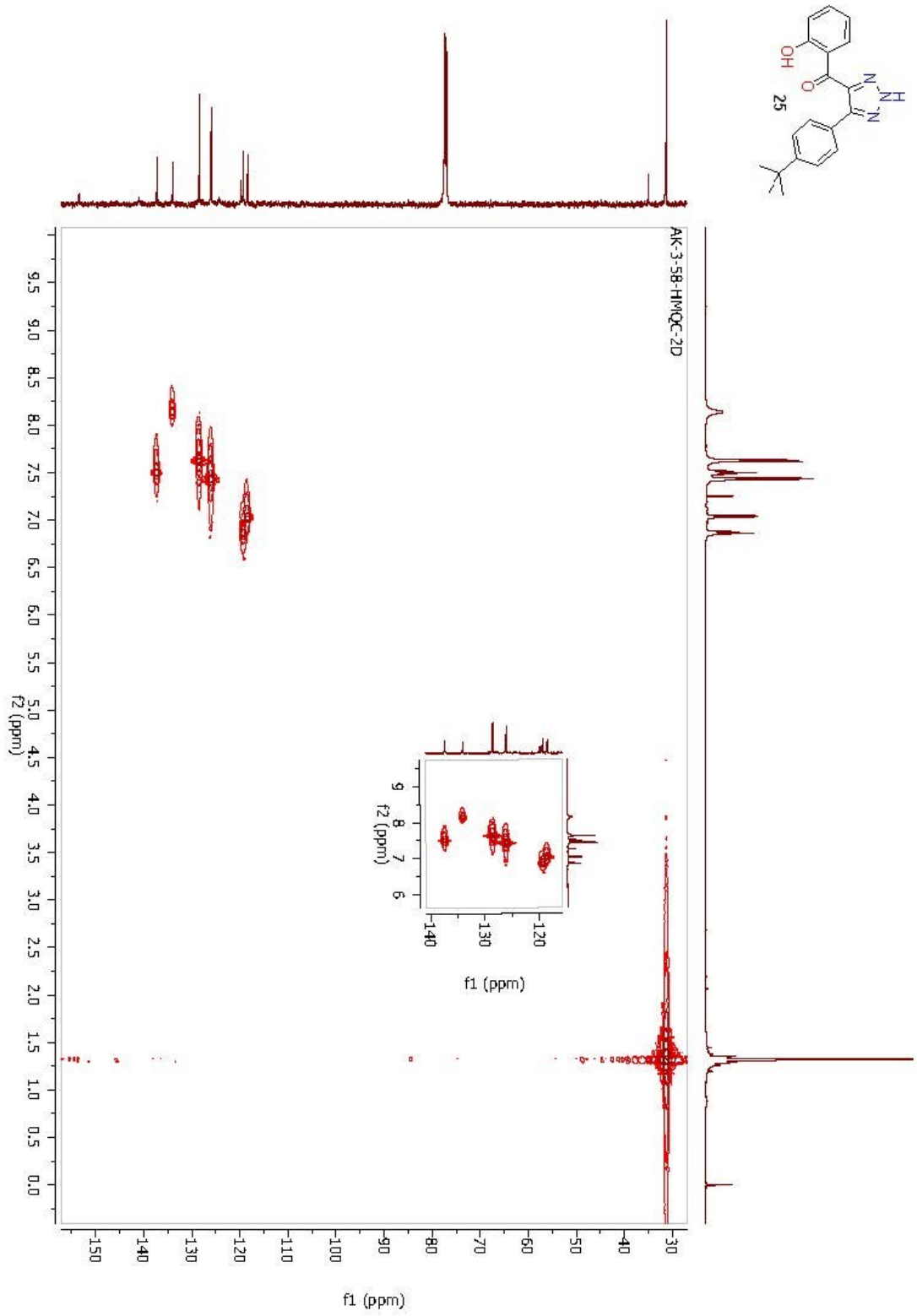

12.050
8.117
8.101
7.518
7.515
7.501
7.487
7.483
7.474
7.440
7.424
7.299
7.284
7.269
7.254
7.234
7.219
7.042
7.026
6.876
6.861
6.846
2.343
0.84
1.00
2.28
1.16
1.16
1.12
1.08
1.14
3.21
f1 (ppm)
OH
O
N
N
H
Me
24
AK_2_133_1H

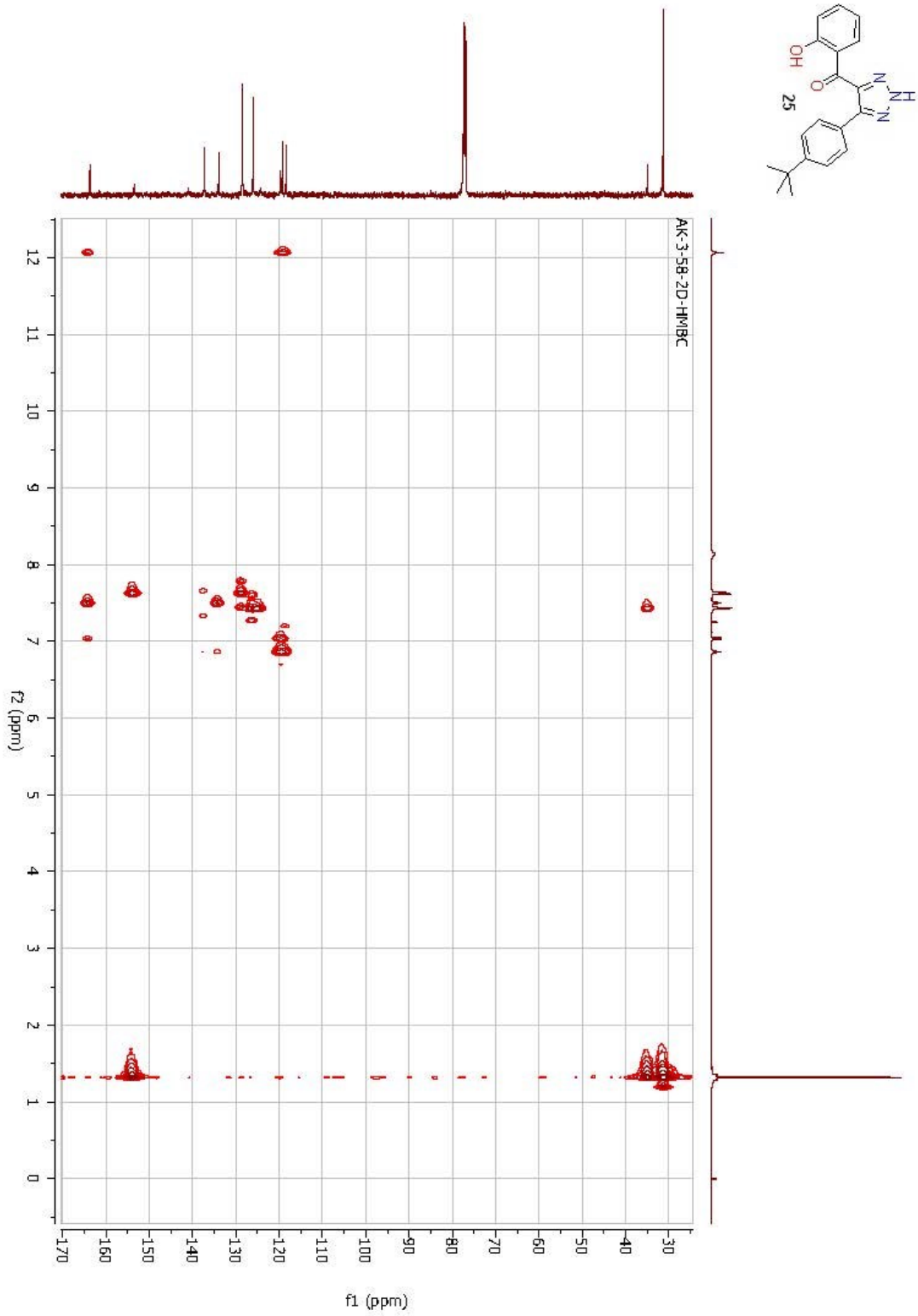

192.323
163.722
141.097
138.751
137.267
133.886
130.804
129.260
128.812
127.555
125.882
119.694
119.258
118.397
77.414
77.160
76.905
21.505
f1 (ppm)
AK_2_133_13C
24
OH
O
N
NH
N
Me

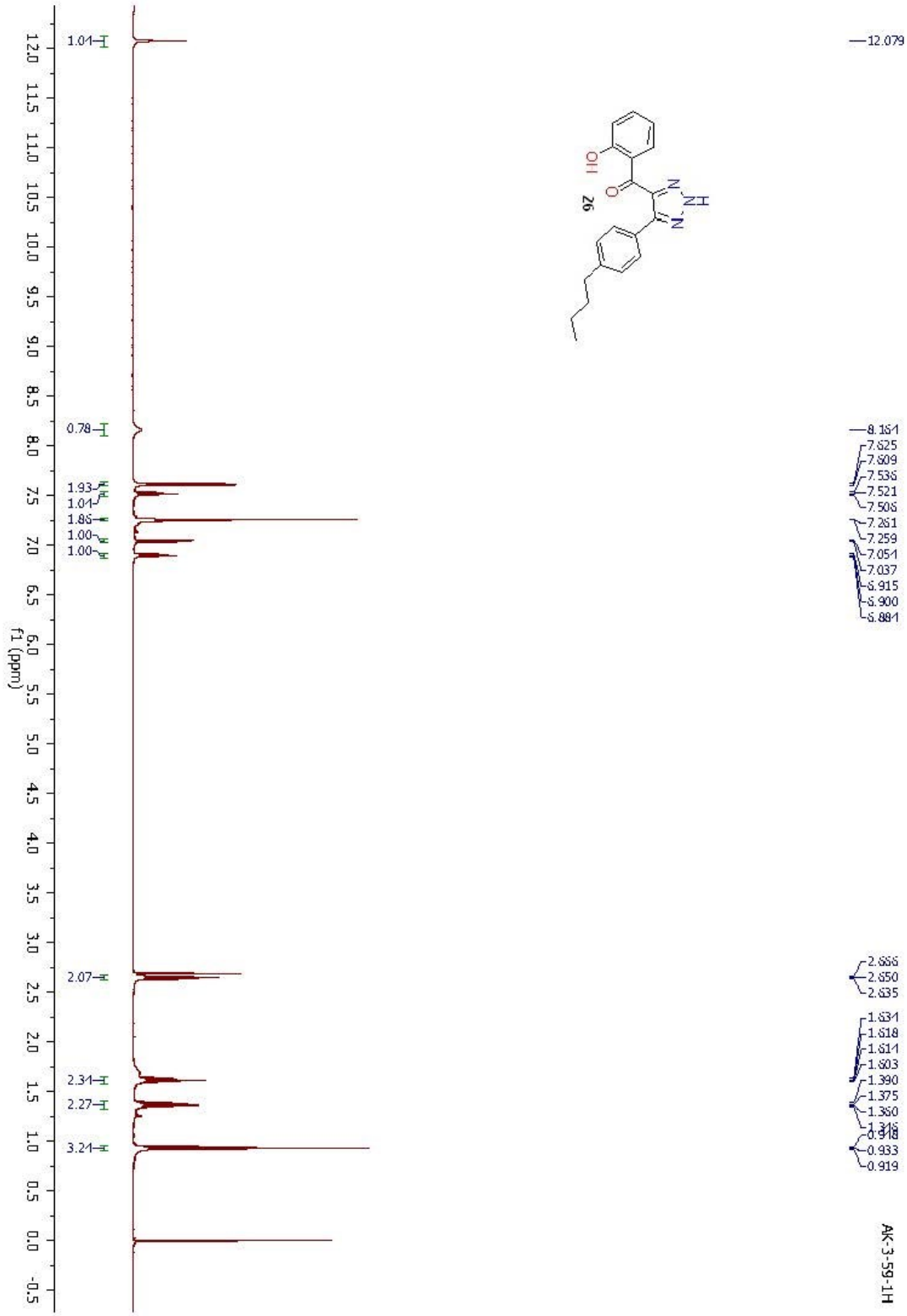

12.067
8.140
7.636
7.620
7.502
7.111
7.025
7.018
7.029
6.880
6.855
6.850
1.321
1.00
0.76
2.02
1.09
2.08
0.99
1.00
8.99
25
OH
O
N
NH
N
f1 (ppm)
AK-3-58-H

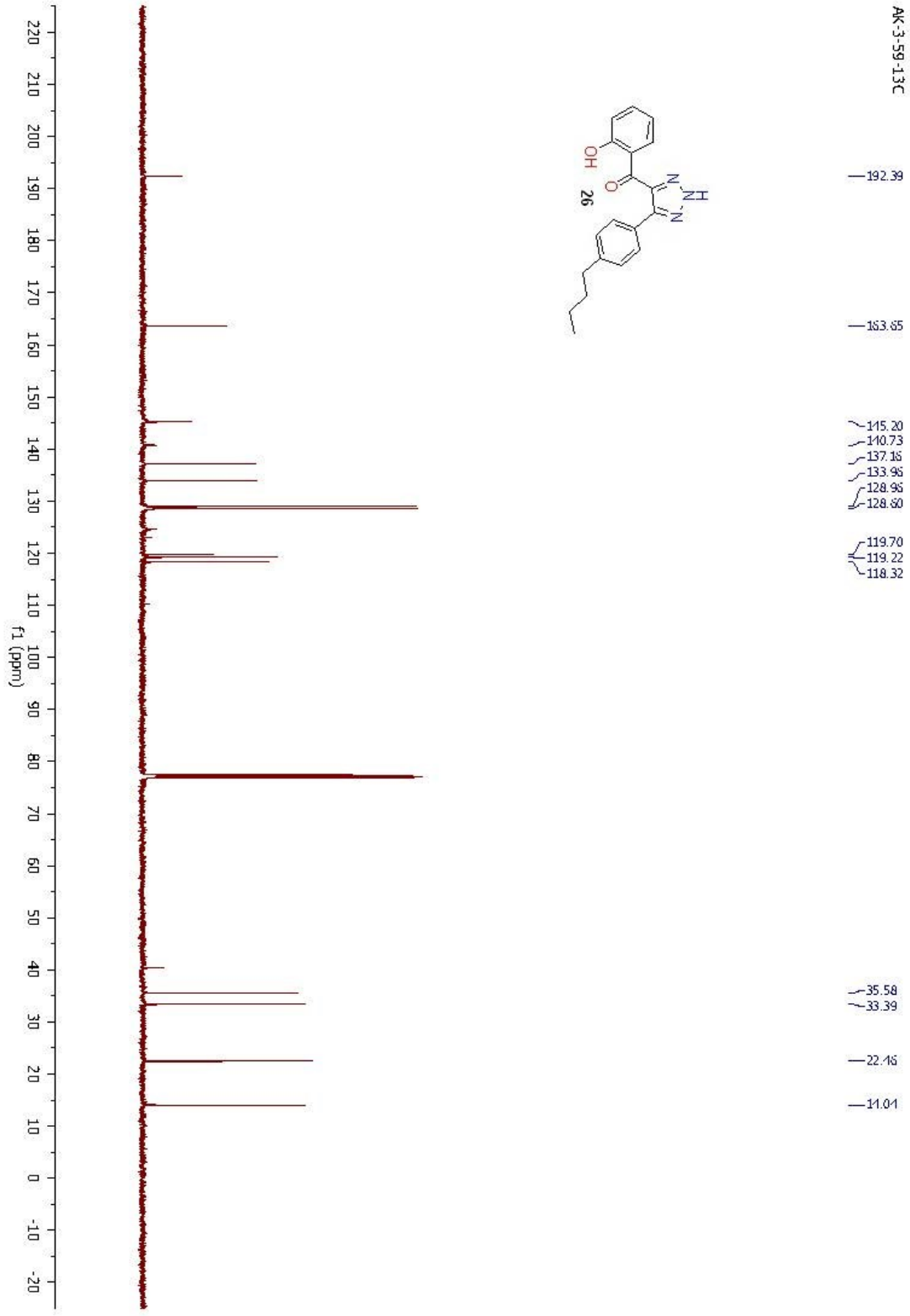

AK-3-58-C
192.35
163.70
153.15
137.25
133.95
128.43
125.96
119.73
119.26
118.39
31.96
31.29
25
OH
O
N
N
H
N
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

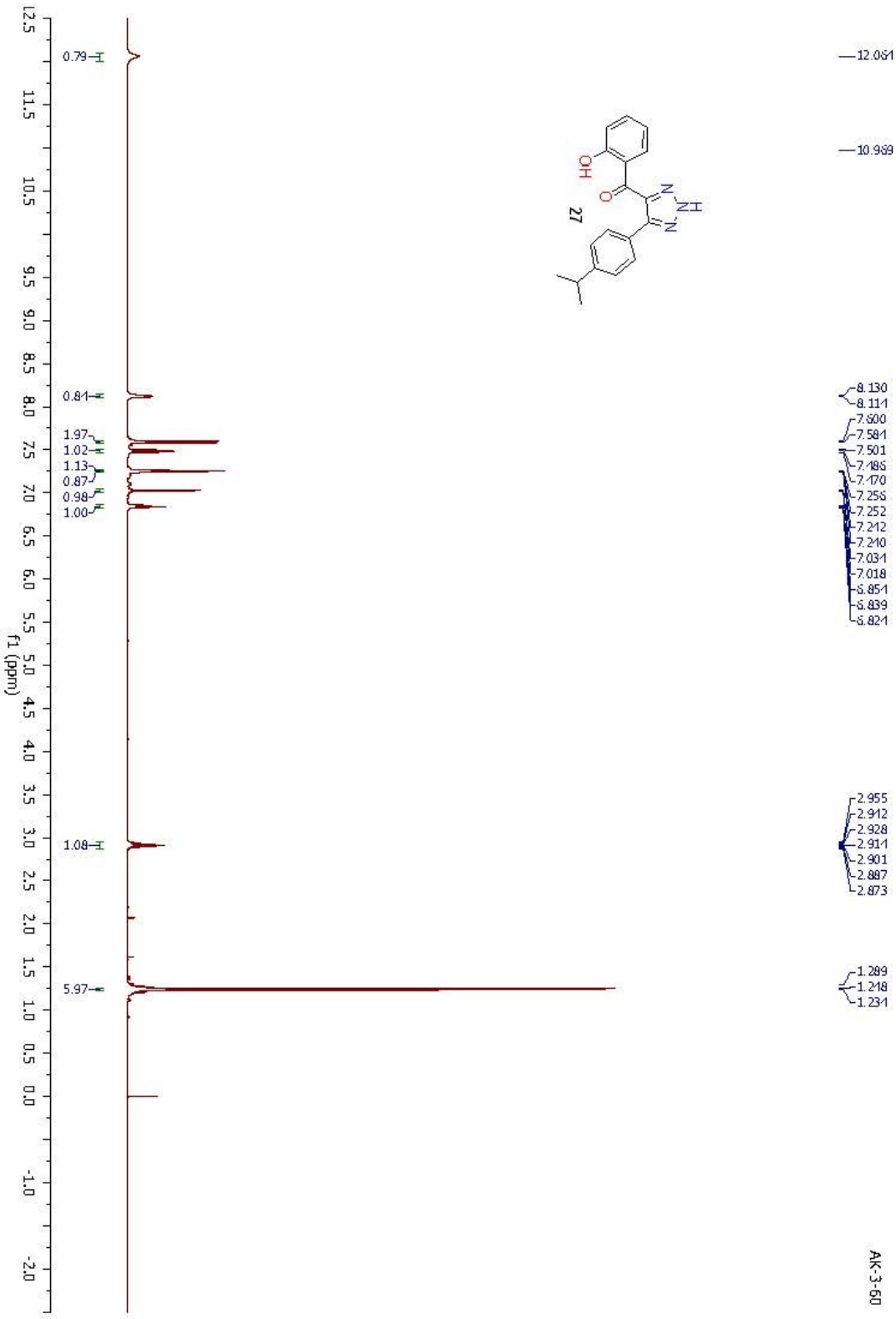

AK-3-58-COSY-2D
f2 (ppm)
f1 (ppm)
25

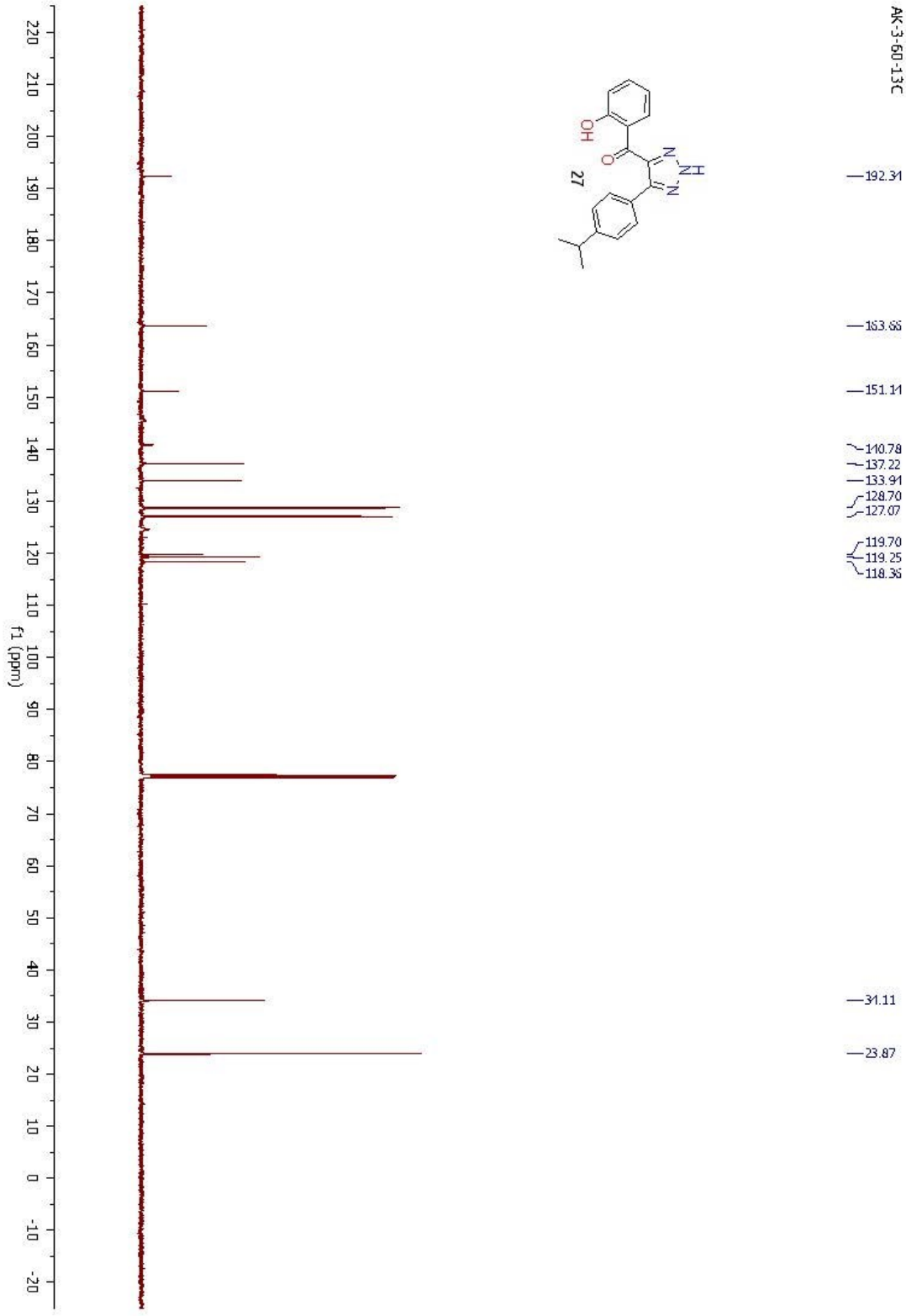

AK-3-58-HMQC-2D
f2 (ppm)
f1 (ppm)
OH
O
N
N
H
N
25

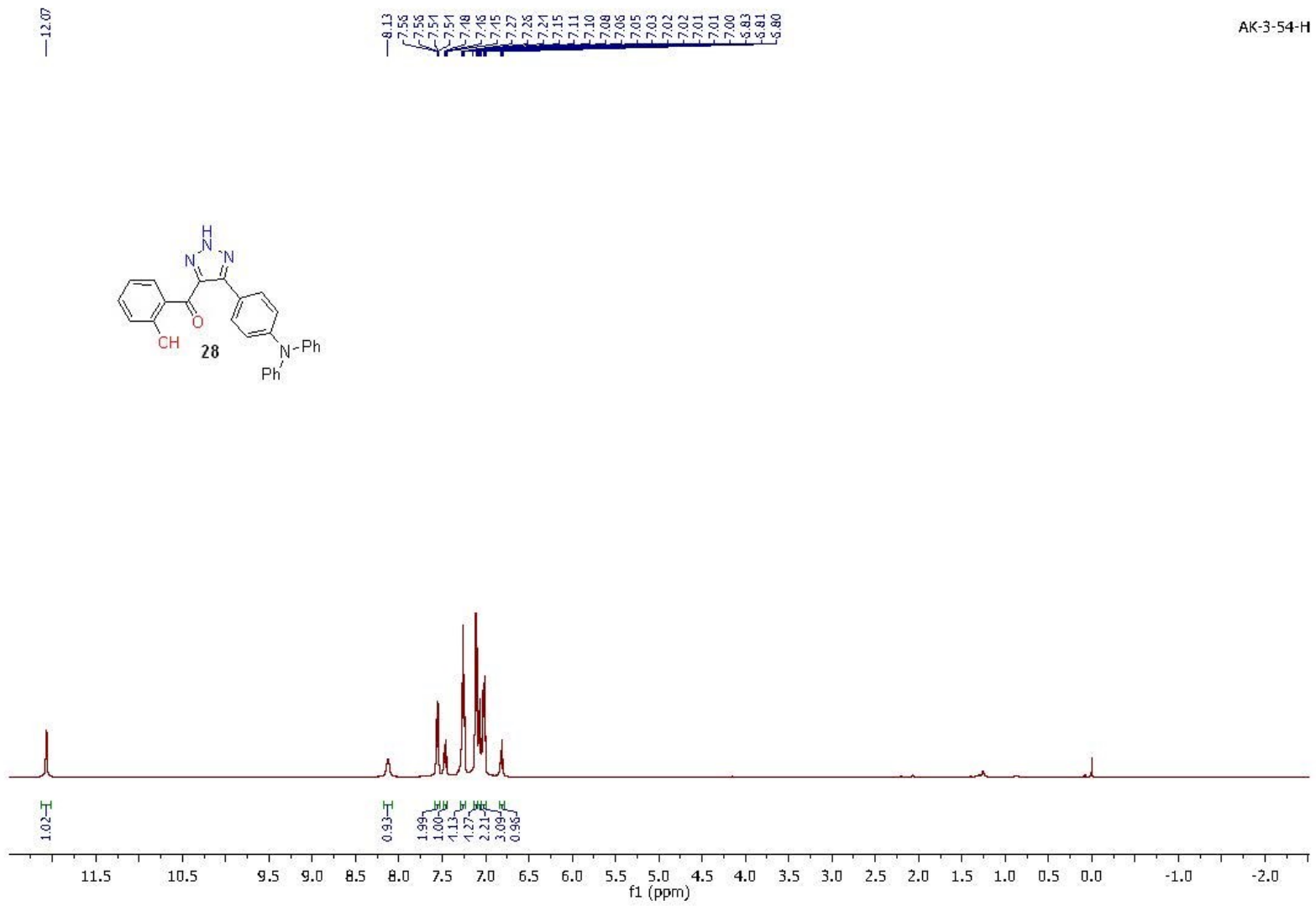

AK-3-58-2D-HMBC
f2 (ppm)
f1 (ppm)
25
OH
O
N
N
H
N

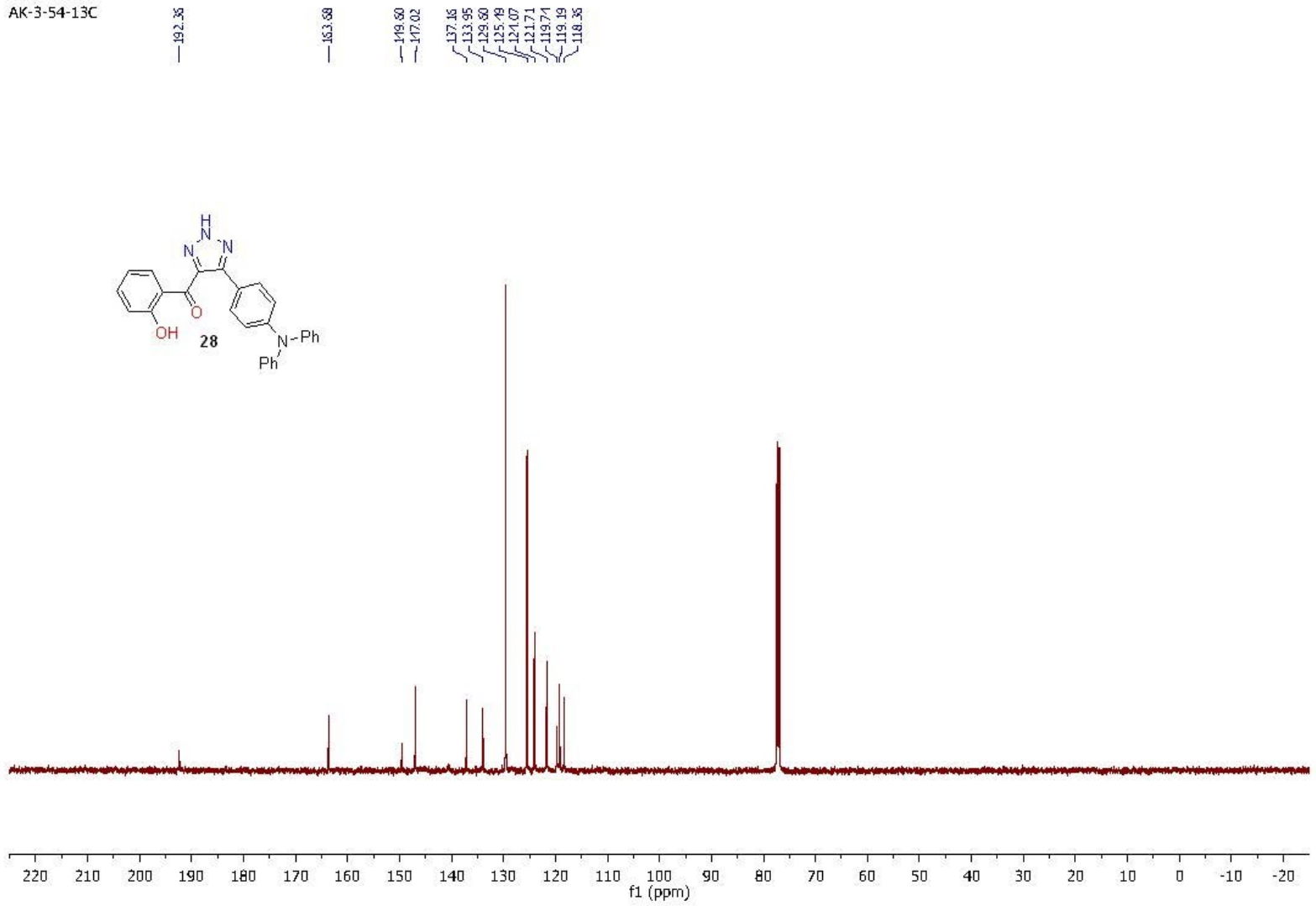

12.079
8.164
7.625
7.609
7.536
7.521
7.506
7.261
7.259
7.054
7.037
6.915
6.900
6.884
2.656
2.650
2.635
1.634
1.618
1.611
1.603
1.390
1.375
1.360
0.948
0.933
0.919
1.04
0.78
1.93
1.04
1.86
1.00
1.00
2.07
2.34
2.27
3.24
f1 (ppm)
OH
O
N
NH
N
26
AK-3-59-1H

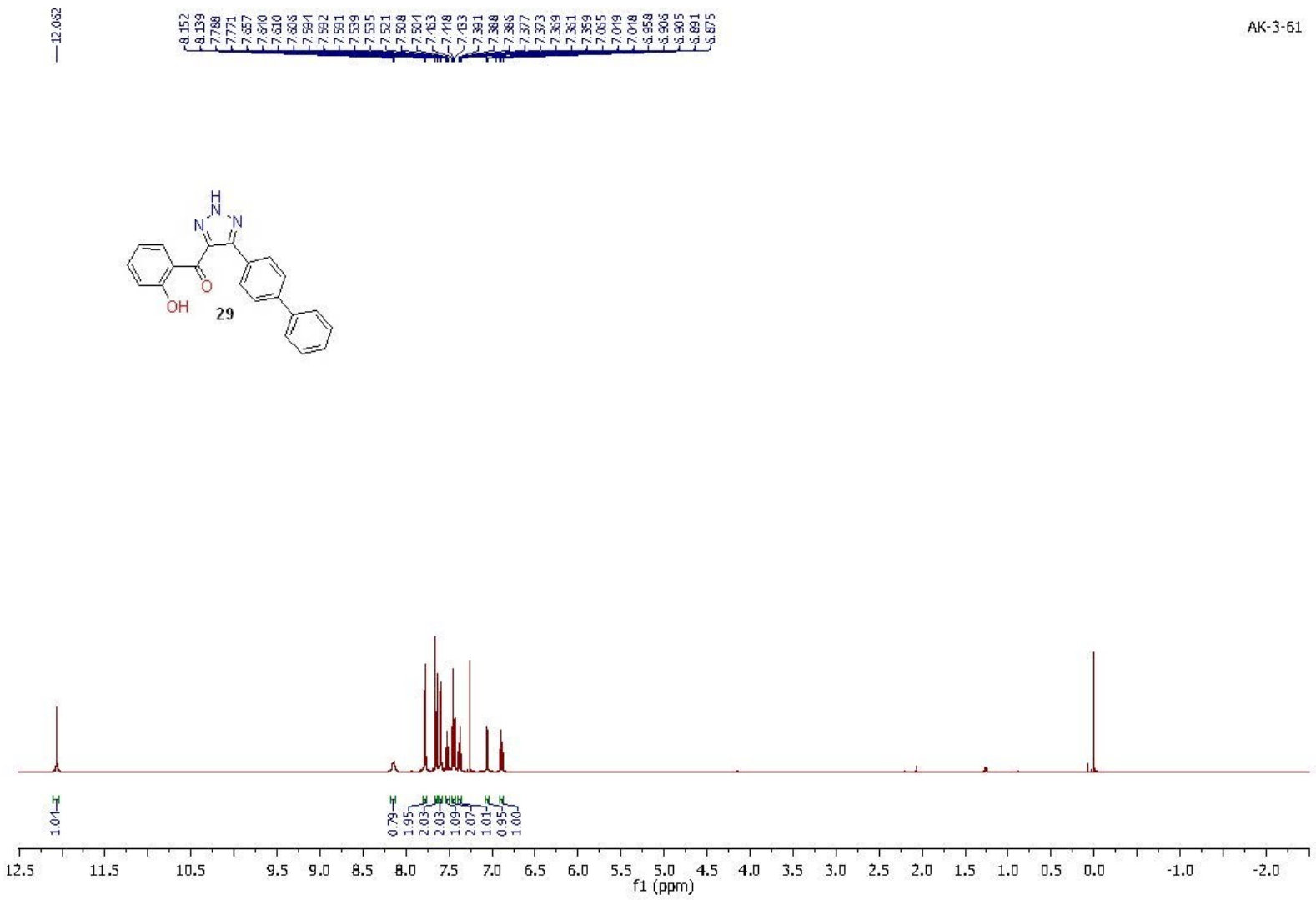

AK-3-59-13C
192.39
163.65
145.20
140.73
137.16
133.96
128.96
128.60
119.70
119.22
118.32
35.58
33.39
22.46
14.04
OH
O
HN
N
N
26
f1 (ppm)

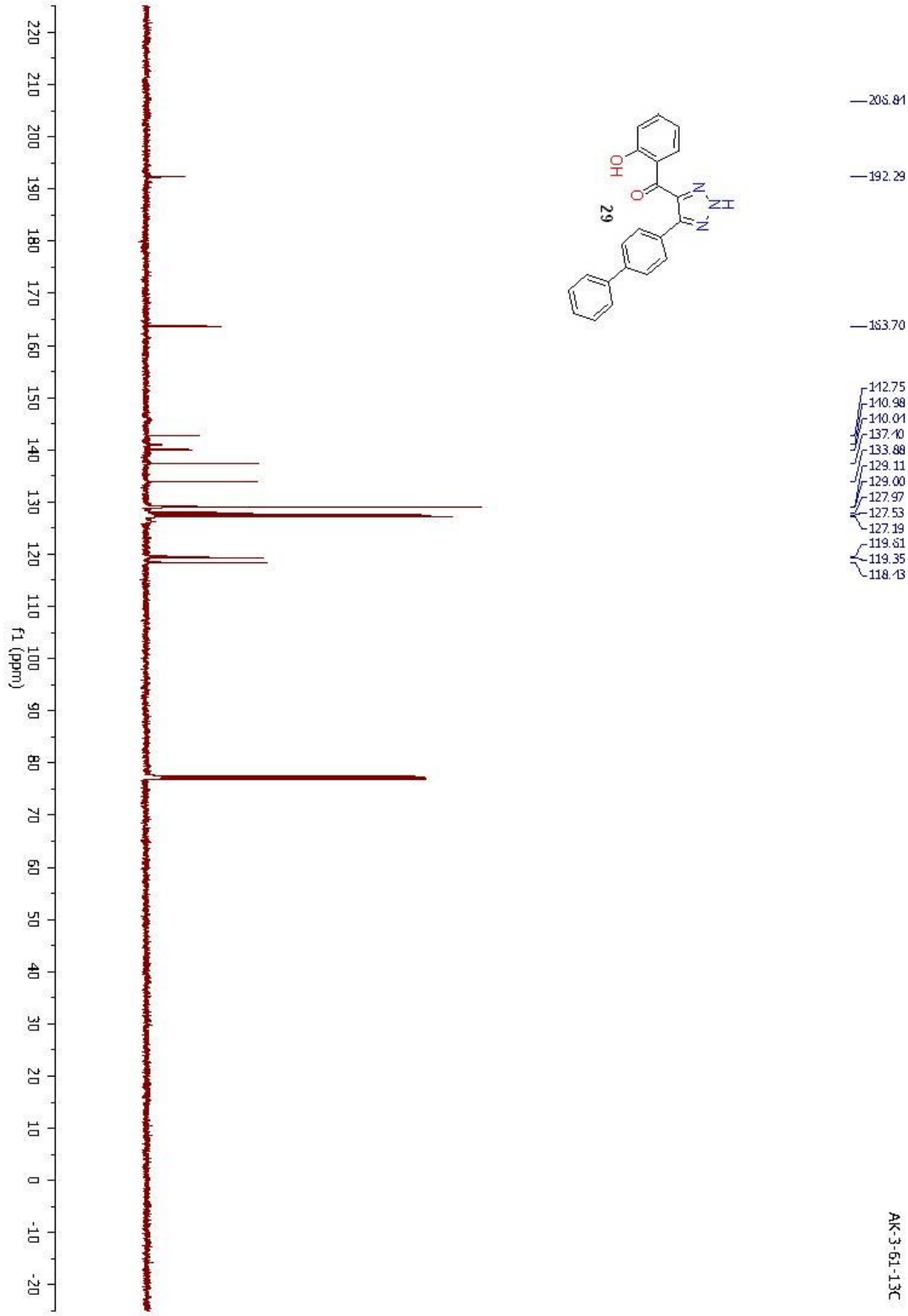

12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.0
-2.0
f1 (ppm)
0.79
0.84
1.97
1.02
1.13
0.87
0.98
1.00
1.08
5.97
12.061
10.989
8.130
8.114
7.600
7.584
7.501
7.486
7.470
7.256
7.252
7.242
7.240
7.034
7.018
6.854
6.839
6.824
2.955
2.942
2.928
2.914
2.901
2.887
2.873
1.289
1.248
1.234
OH
O
N
HN
N
27
AK-3-60

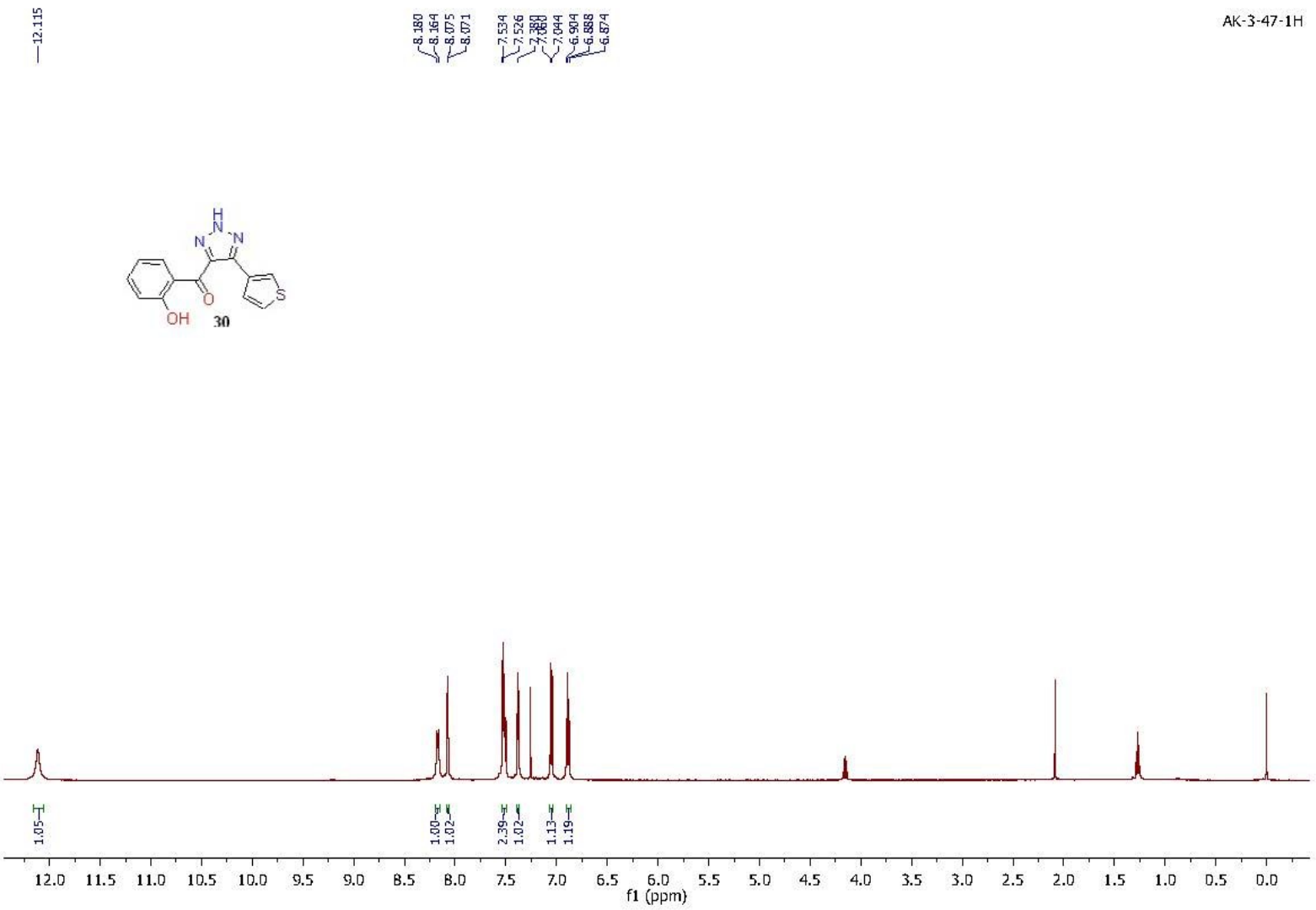

AK-3-60-13C
192.34
163.68
151.14
140.78
137.22
133.94
128.70
127.07
119.70
119.25
118.36
34.11
23.87
27
OH
O
N
NH
N
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

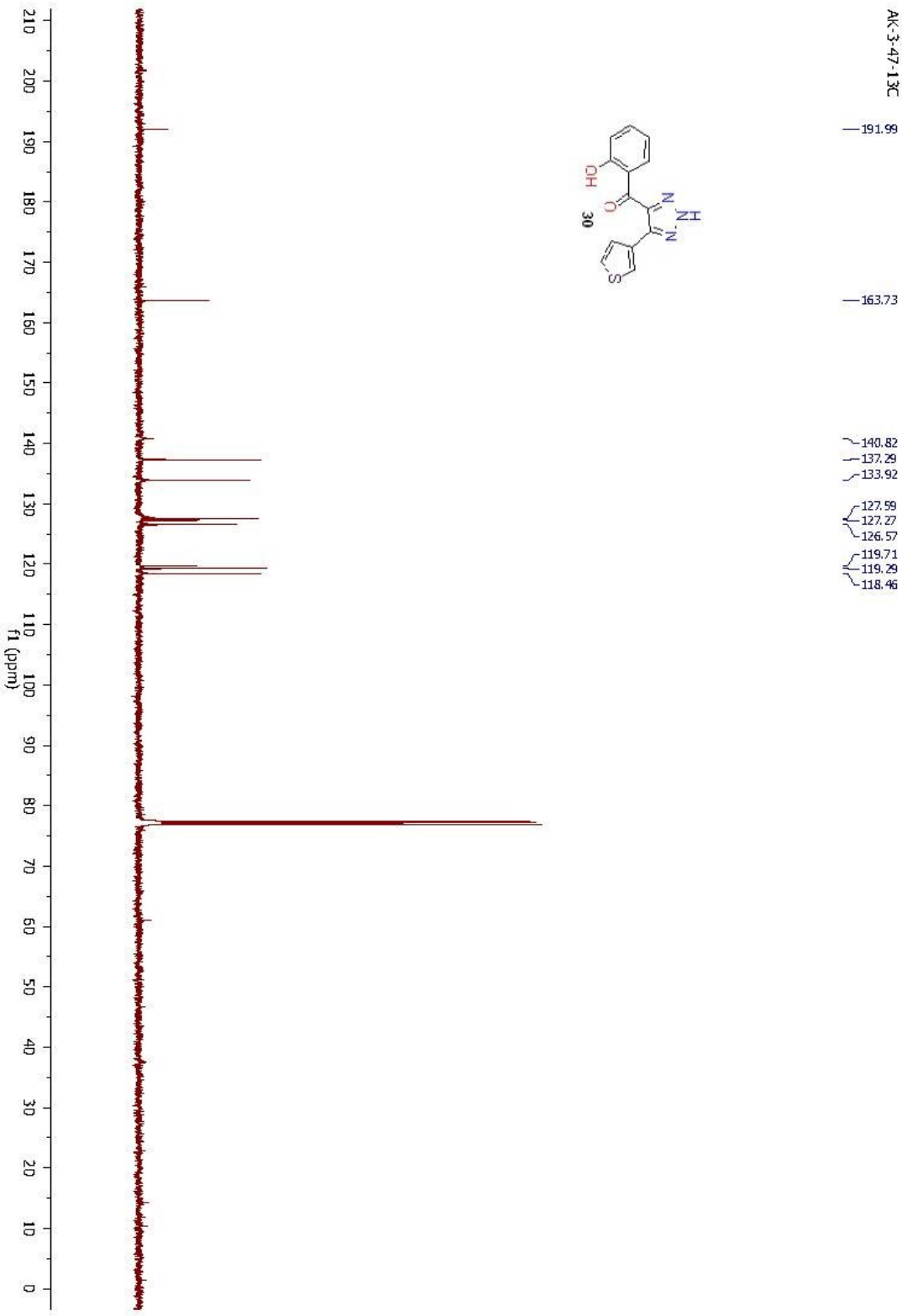

12.07
8.13
7.56
7.55
7.54
7.51
7.48
7.46
7.45
7.27
7.26
7.21
7.15
7.11
7.10
7.08
7.06
7.05
7.03
7.02
7.02
7.01
7.01
7.00
6.83
6.81
6.80
AK-3-54-H
H
N
N
N
O
CH
28
N-Ph
Ph
1.02
0.93
1.99
1.00
1.13
1.27
2.21
3.09
0.96
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.0
-2.0
f1 (ppm)


AK-3-54-13C
192.36
163.68
149.60
147.02
137.16
133.95
129.60
125.49
124.07
121.71
119.74
119.19
118.36
28
OH
O
N-Ph
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


12.052
8.152
8.139
7.788
7.771
7.657
7.610
7.606
7.591
7.592
7.591
7.539
7.535
7.521
7.508
7.504
7.463
7.418
7.433
7.391
7.388
7.386
7.377
7.373
7.369
7.361
7.359
7.065
7.049
7.048
6.958
6.906
6.905
6.891
6.875
AK-3-61
OH
29
1.04
0.79
1.95
2.03
2.03
1.09
2.07
1.01
0.95
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.0
-2.0
f1 (ppm)

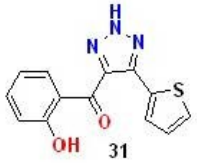

208.84
192.29
163.70
142.75
140.98
140.04
137.40
133.88
129.11
129.00
127.97
127.53
127.19
119.61
119.35
118.43
OH
O
N
NH
N
29
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
AK-3-61-13C


12.115
8.180
8.164
8.075
8.071
7.534
7.526
7.388
7.044
6.904
6.888
6.874
AK-3-47-1H
OH
30
1.05
1.00
1.02
2.39
1.02
1.13
1.19
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

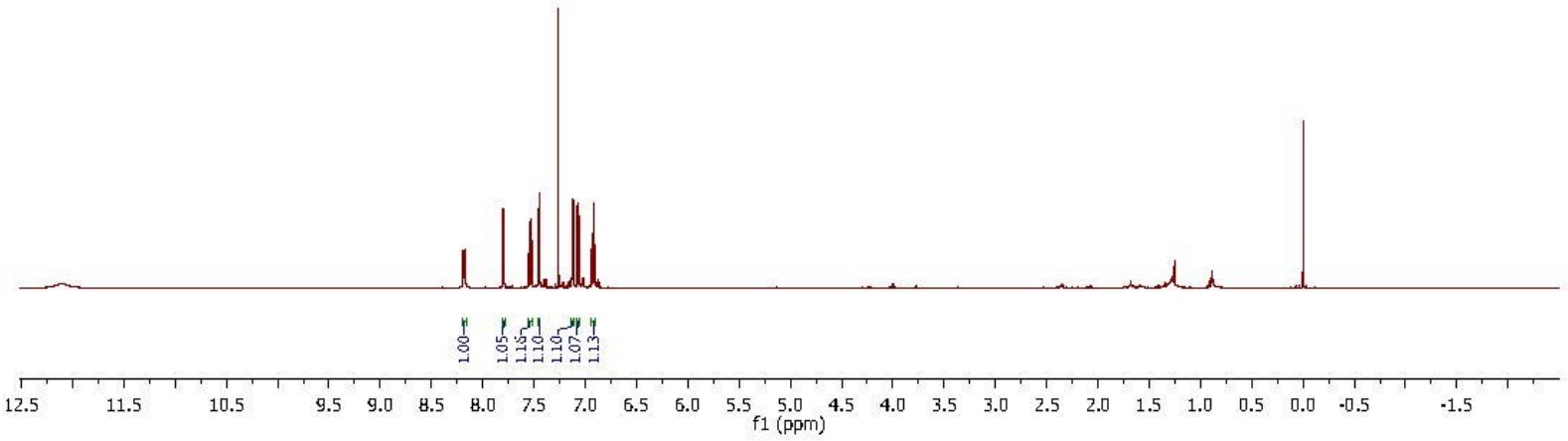

AK-3-47-13C
191.99
163.73
140.82
137.29
133.92
127.59
127.27
126.57
119.71
119.29
118.46
f1 (ppm)
30

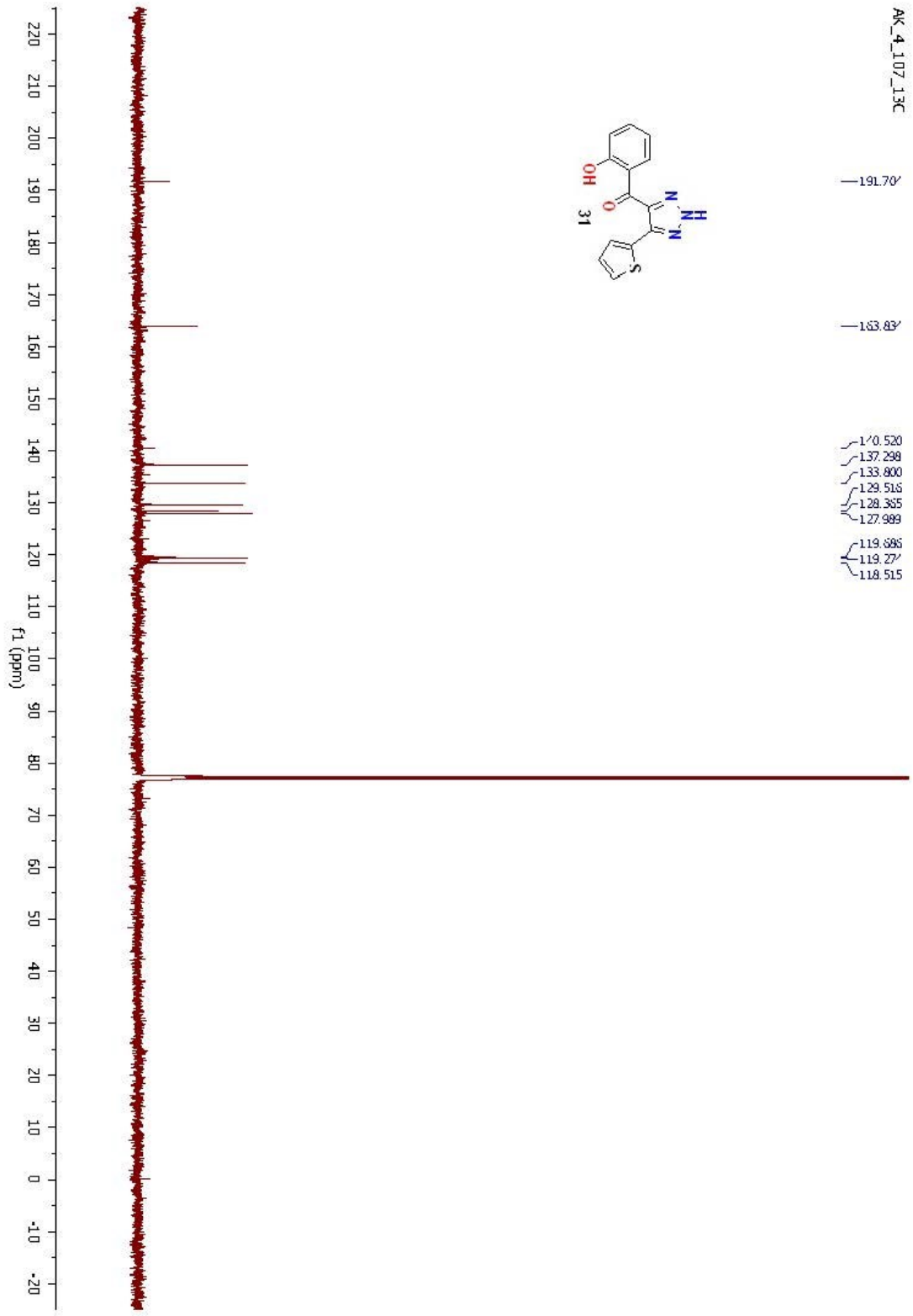
AK_4_107

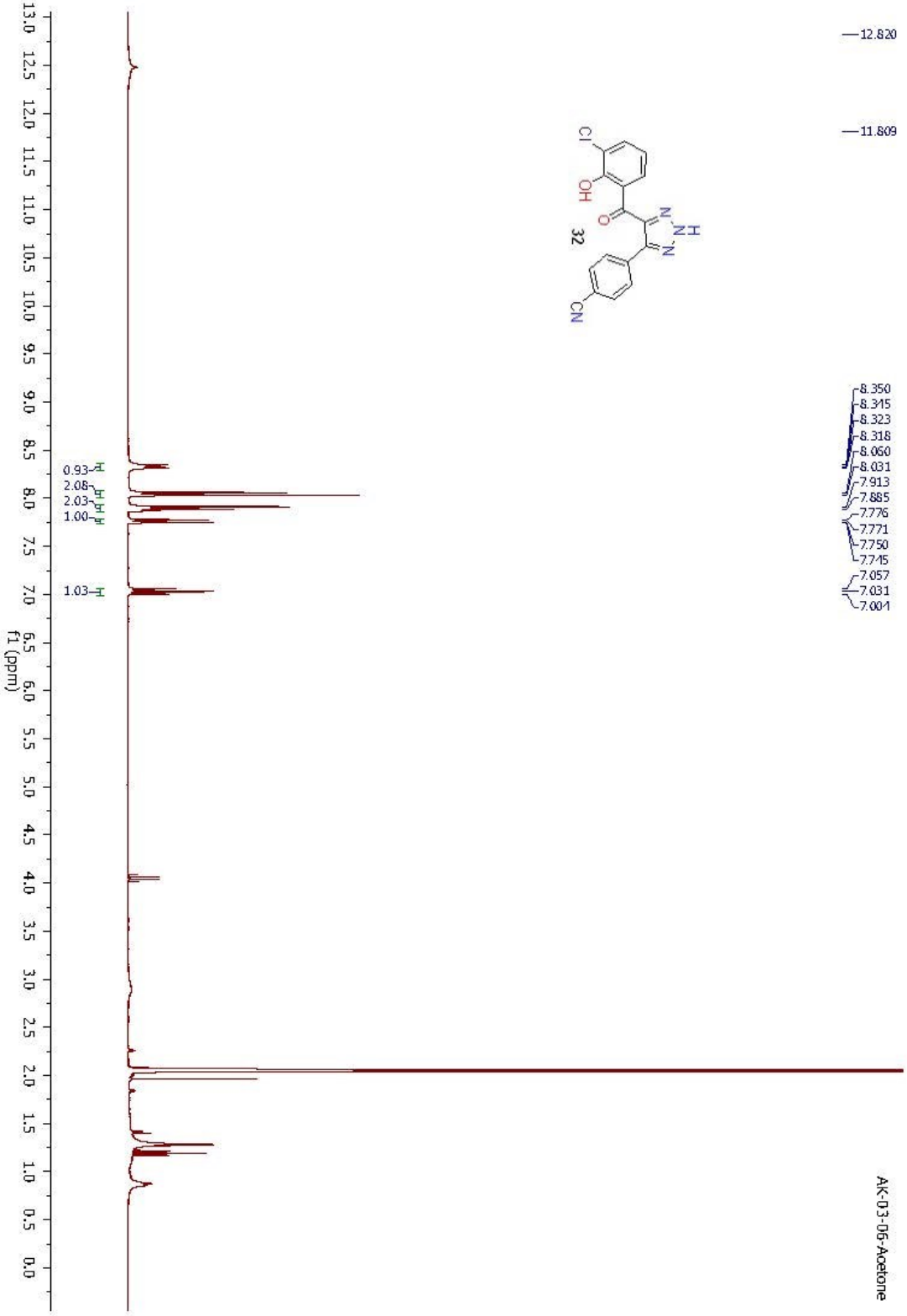

8.190
8.177
7.803
7.801
7.795
7.794
7.553
7.550
7.539
7.536
7.533
7.522
7.519
7.759
7.757
7.129
7.122
7.119
7.112
7.076
7.059
6.937
6.922
6.908

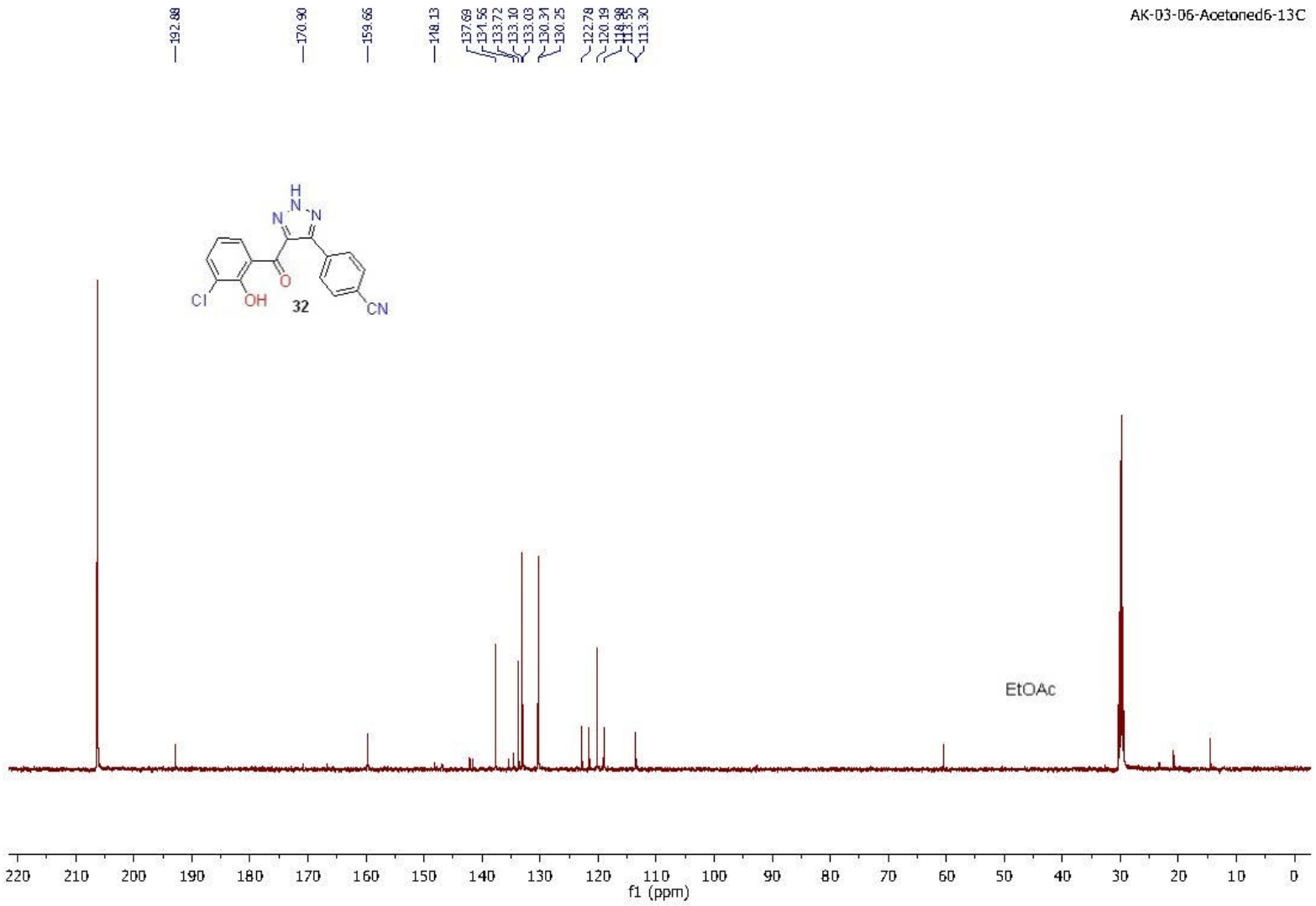

H
N
N
N
S
O
OH

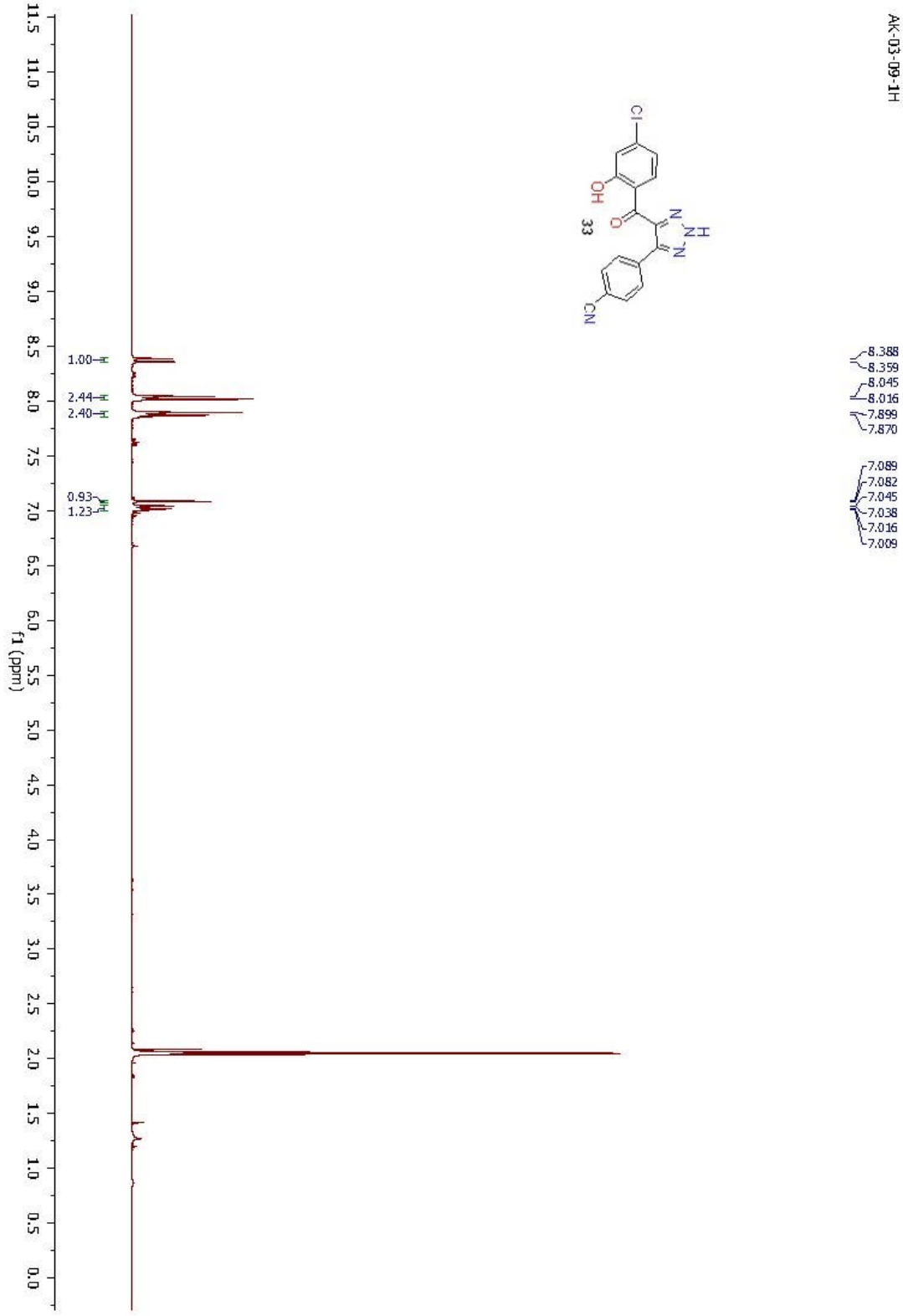
31

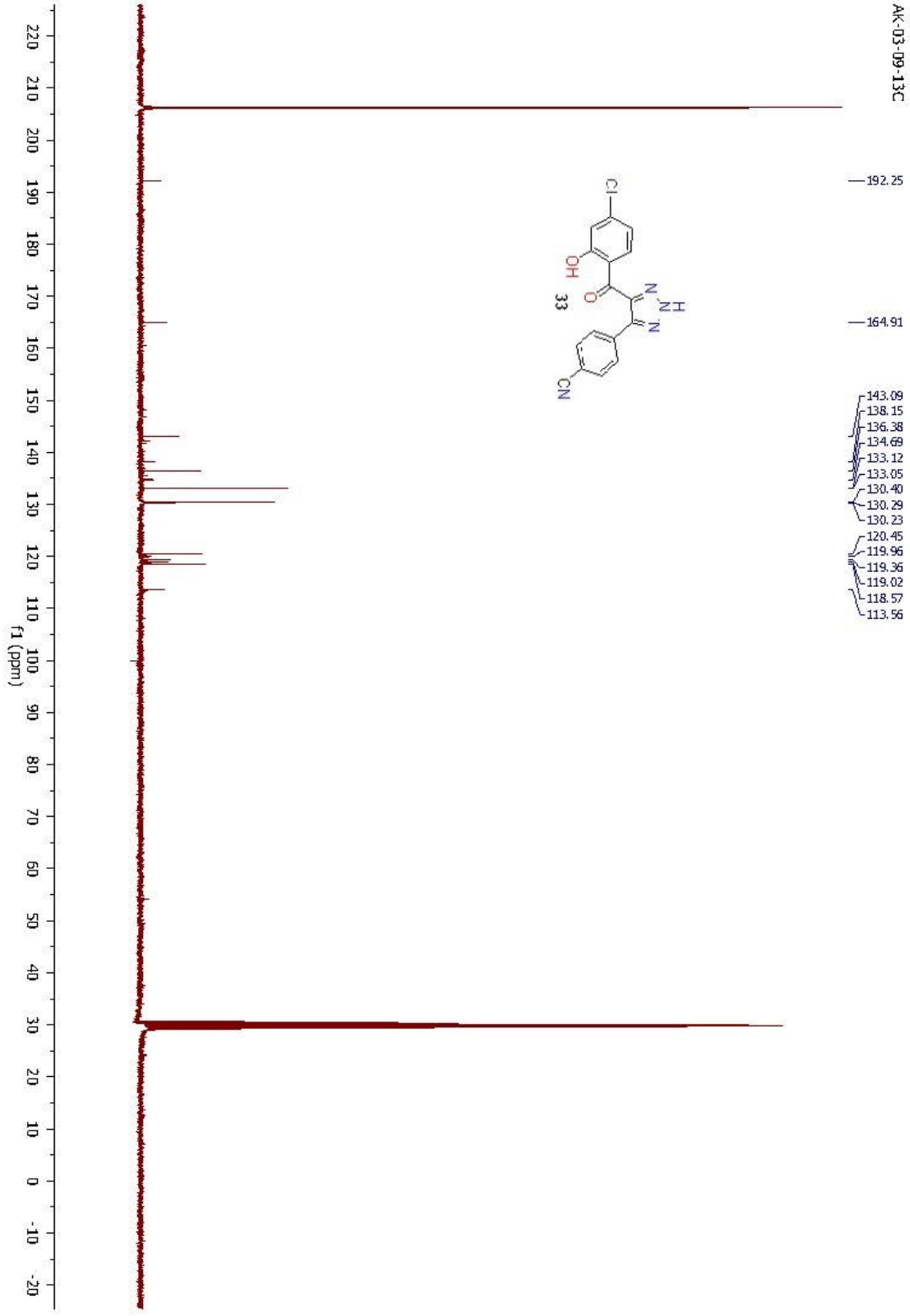

1.00
1.05
1.16
1.10
1.10
1.07
1.13
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)

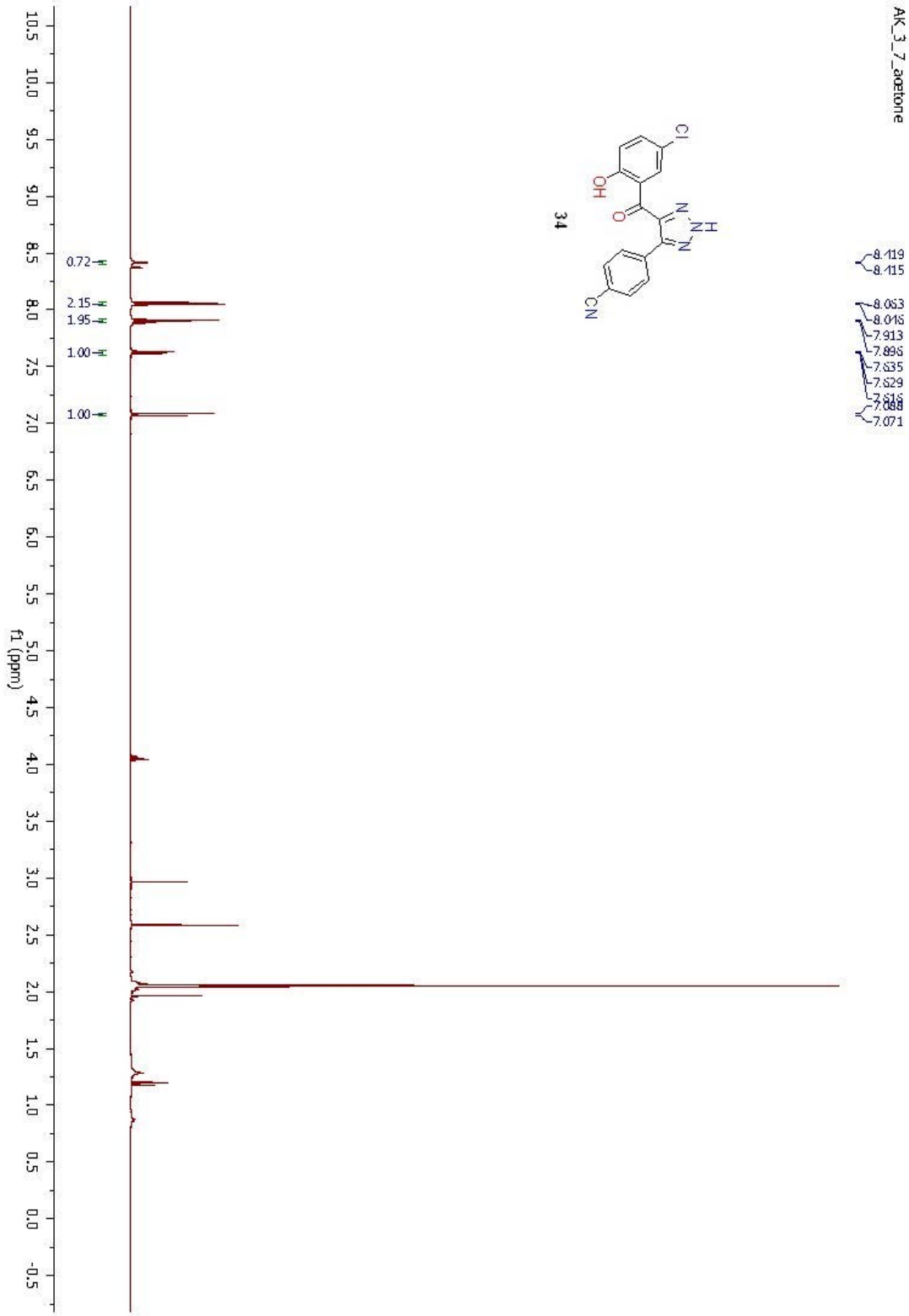

AK_4_107_13C
191.707
163.837
140.520
137.298
133.800
129.516
128.365
127.989
119.586
119.277
118.515
OH
O
N
NH
N
S
31
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

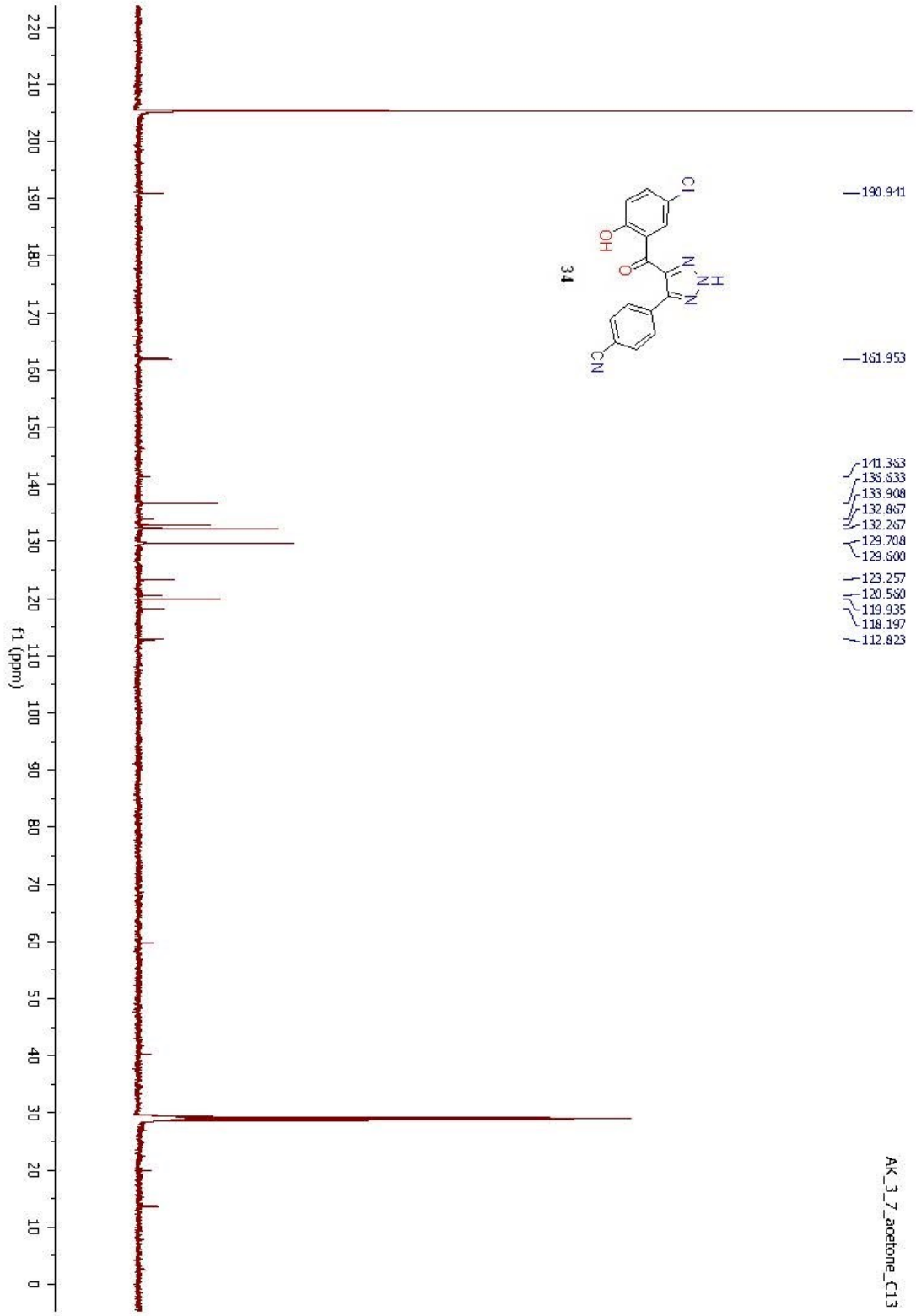

12.820
11.809
8.350
8.345
8.323
8.318
8.060
8.031
7.913
7.885
7.776
7.771
7.750
7.745
7.057
7.031
7.004
0.93
2.08
2.03
1.00
1.03
32
Cl
OH
O
N
NH
N
CN
f1 (ppm)
AK-03-06-Acetone

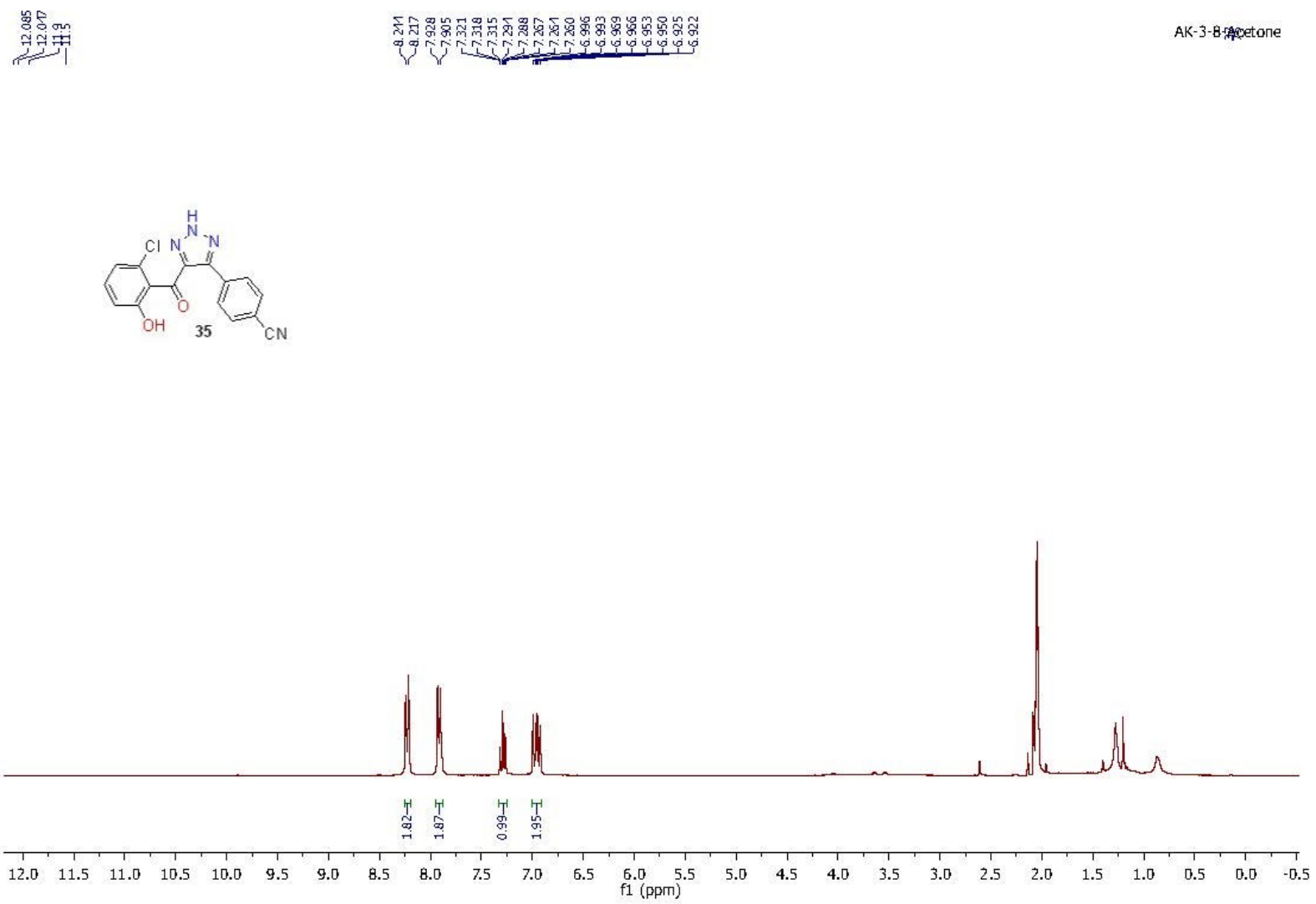

192.88
170.90
159.66
148.13
137.69
134.56
133.72
133.10
133.03
130.34
130.25
122.78
120.19
113.30
AK-03-06-Acetoned6-13C
H
N
N
N
O
Cl
OH
32
CN
EtOAc
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

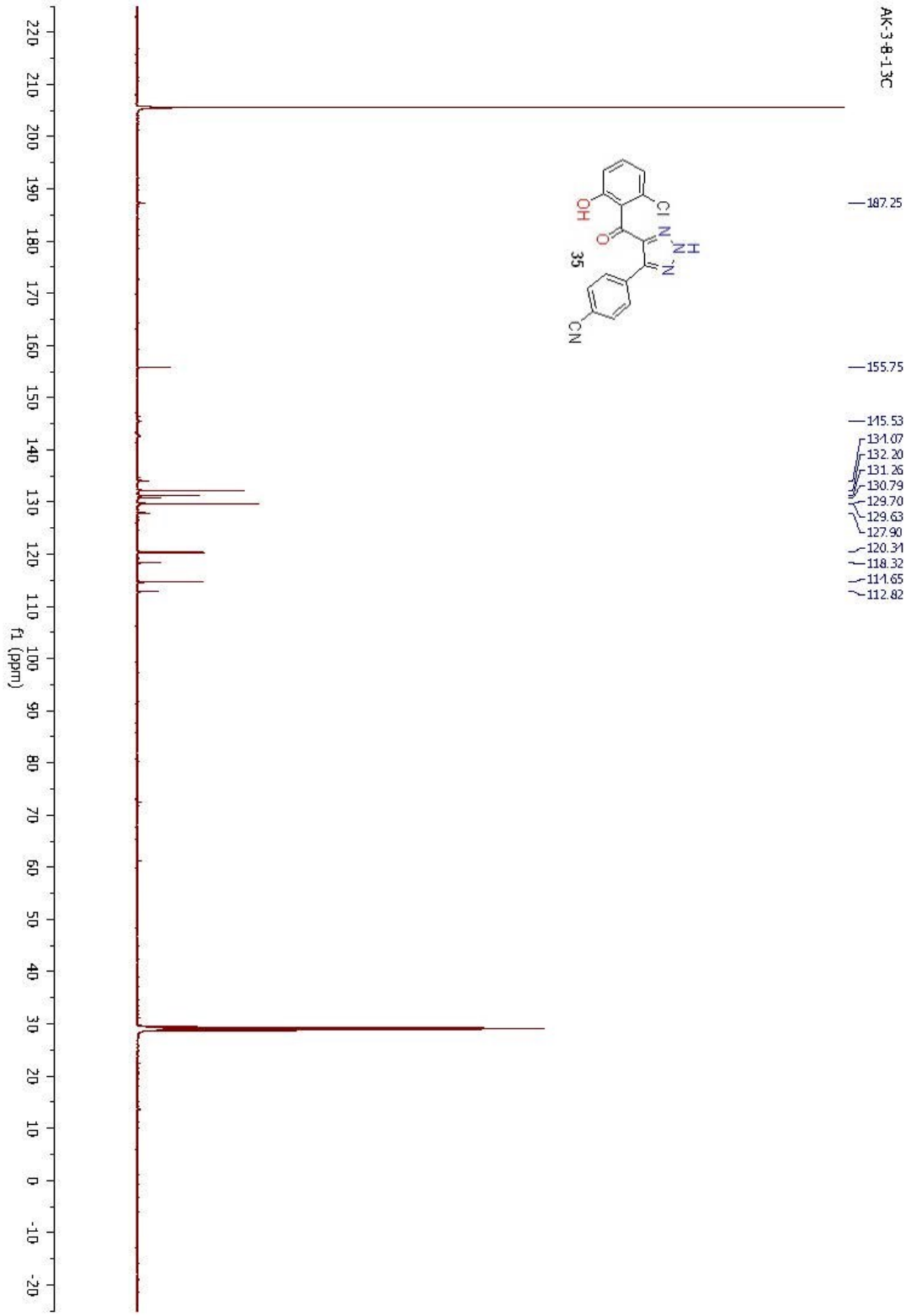

AK-03-09-1H
8.388
8.359
8.045
8.016
7.899
7.870
7.089
7.082
7.045
7.038
7.016
7.009
1.00
2.44
2.40
0.93
1.23
f1 (ppm)
33
Cl
OH
O
N
N
H
N
CN

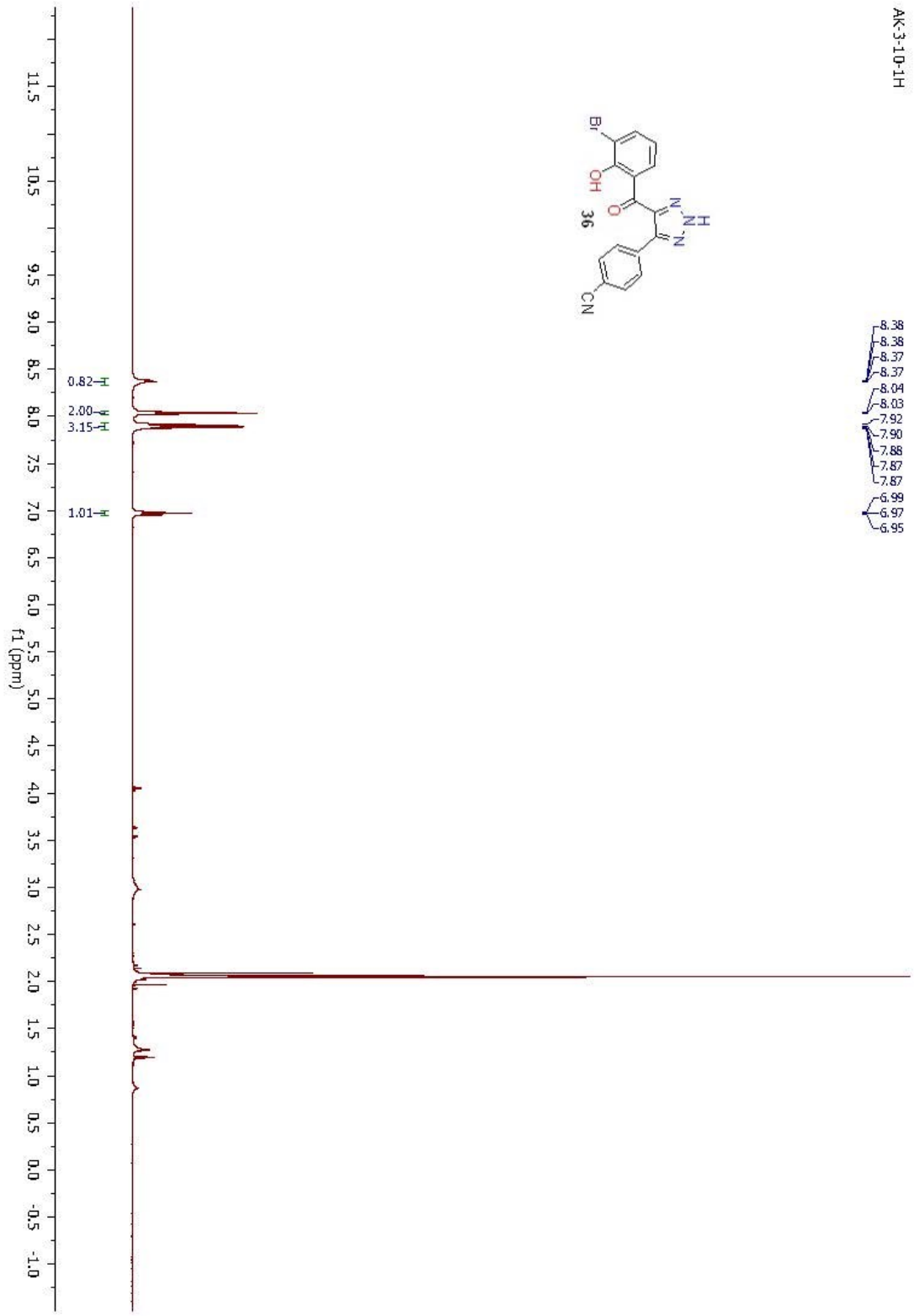

AK-03-09-13C
192.25
164.91
143.09
138.15
136.38
134.69
133.12
133.05
130.40
130.29
130.23
120.45
119.96
119.36
119.02
118.57
113.56
Cl
OH
O
N
N
H
N
CN
33
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

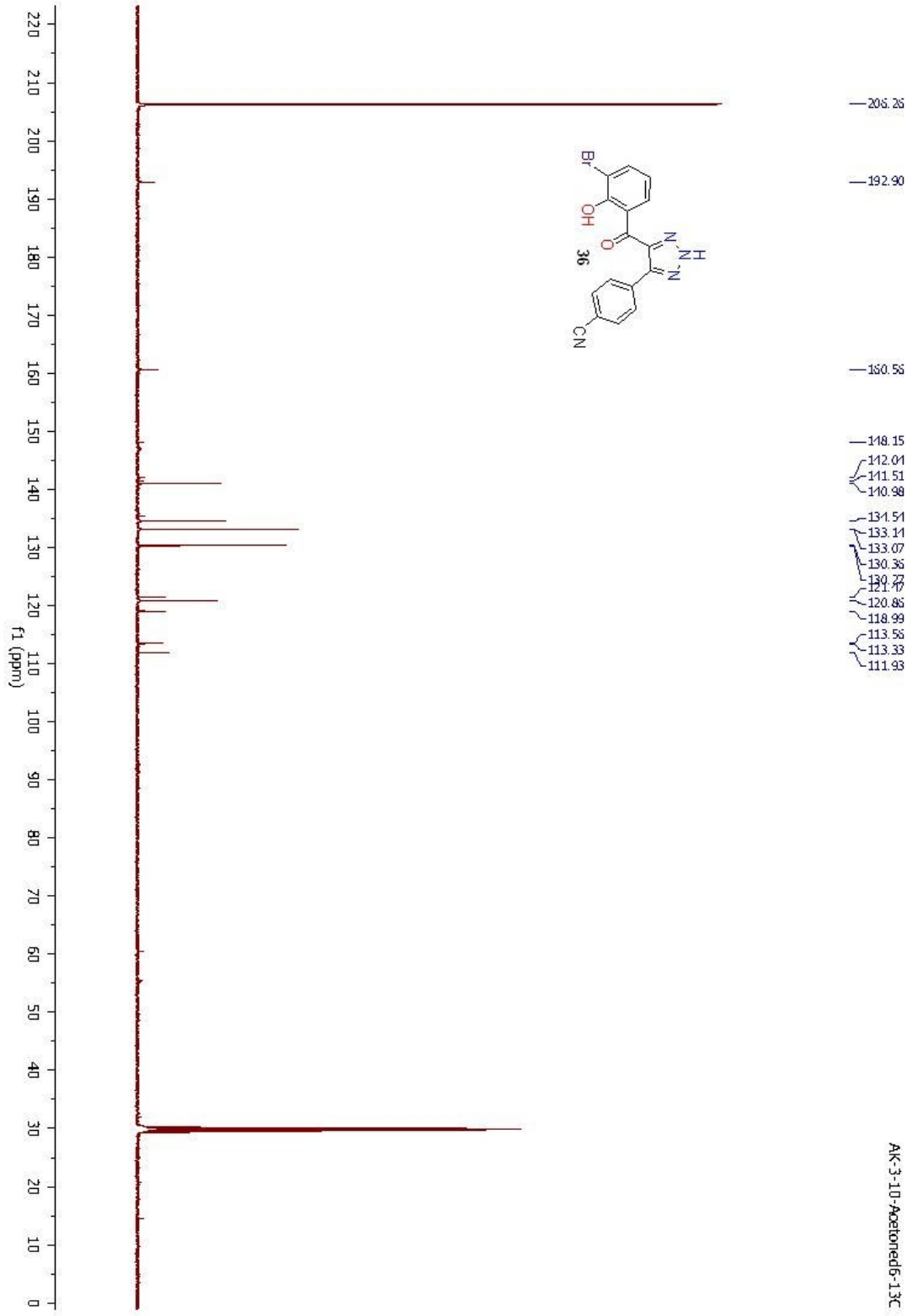

AK_3_7_acetone
34
Cl
OH
O
N
N
H
N
CN
8.119
8.115
8.063
8.046
7.913
7.896
7.635
7.629
7.071
0.72
2.15
1.95
1.00
1.00
f1 (ppm)

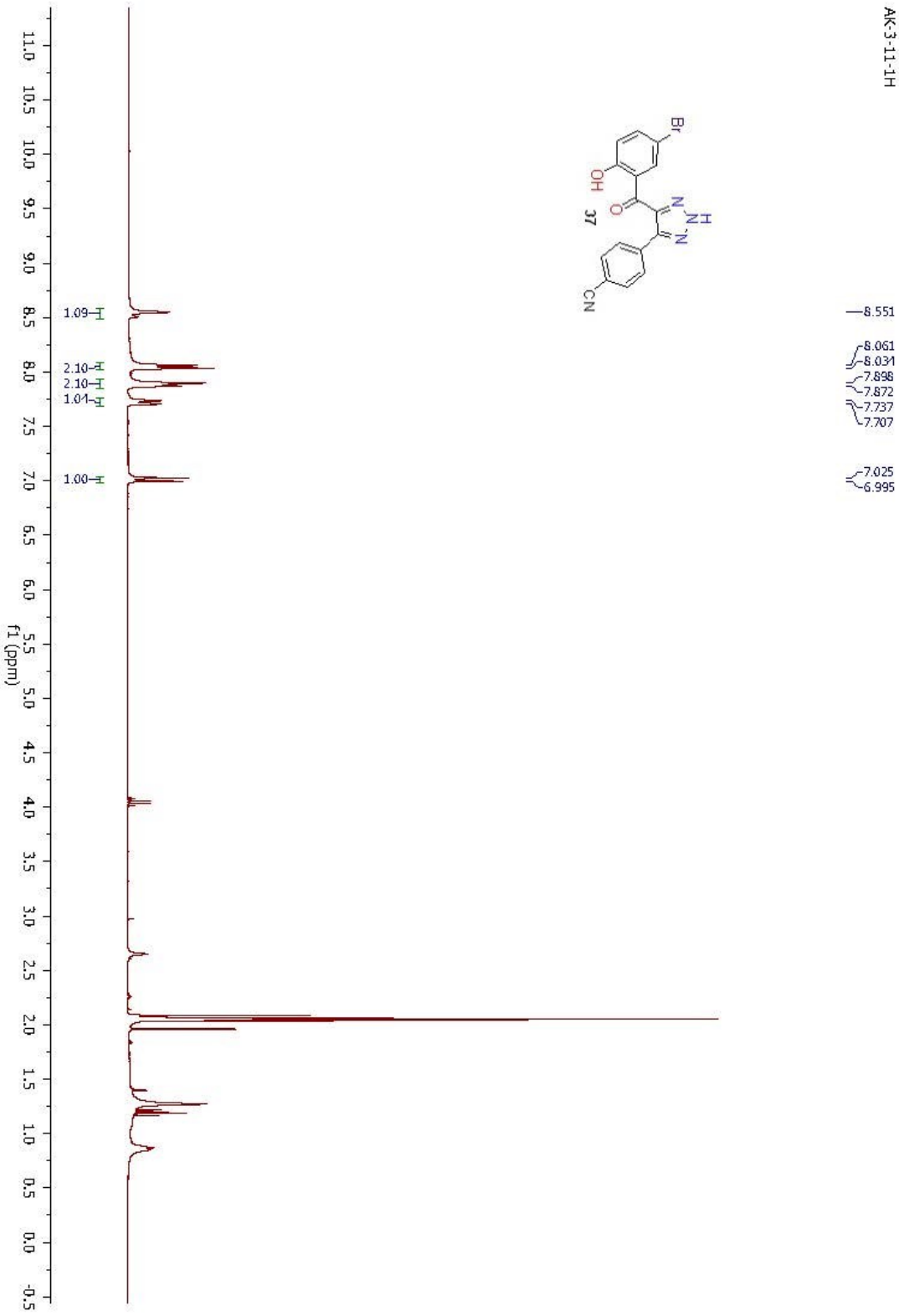

190.941
161.953
141.363
136.833
133.908
132.867
132.267
129.708
129.600
123.257
120.560
119.935
118.197
112.823
34
f1 (ppm)
AK_3_7_acetone_C13

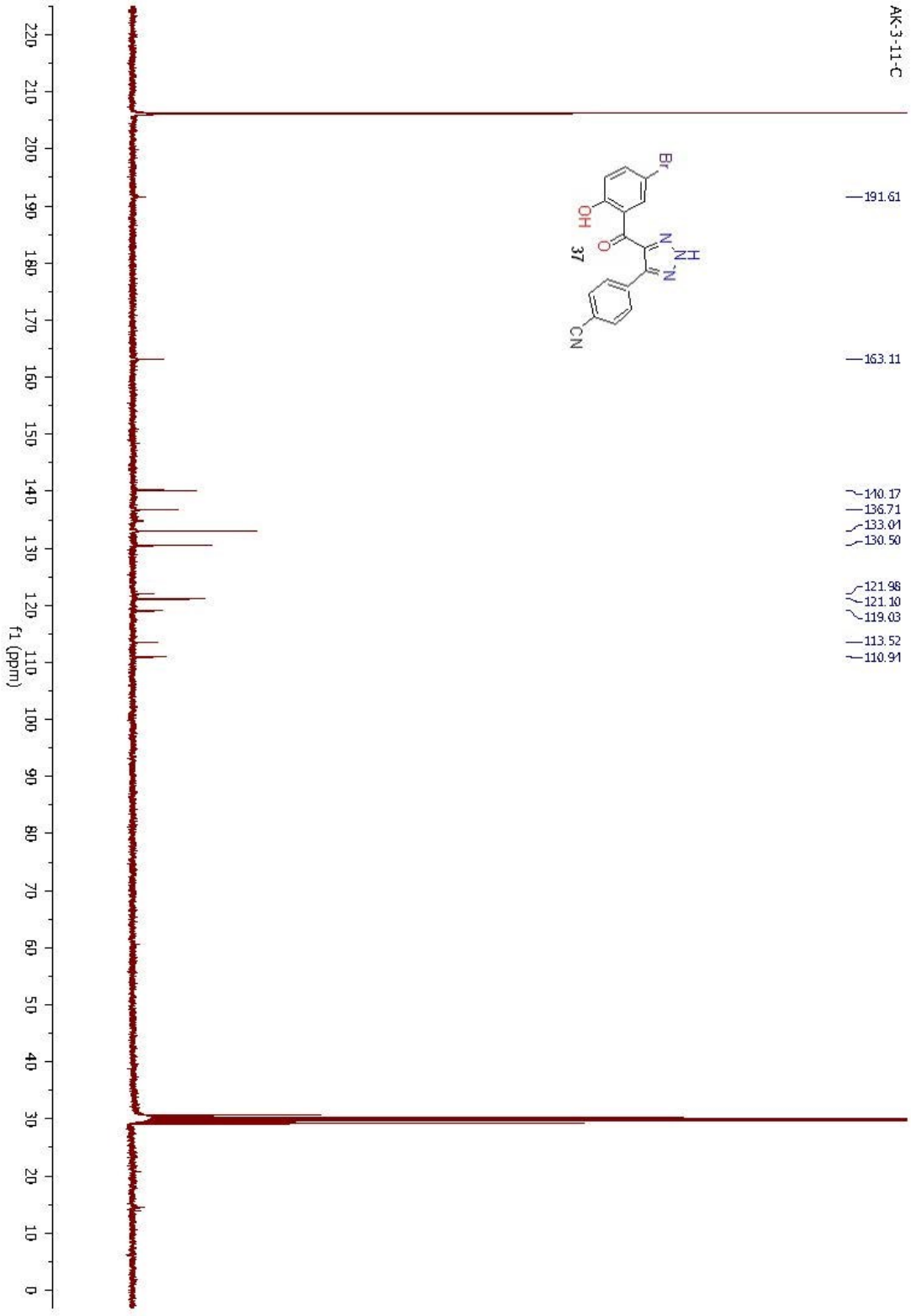

12.085
12.047
11.9
11.5
8.241
8.217
7.928
7.905
7.321
7.318
7.315
7.291
7.288
7.267
7.261
7.260
6.996
6.993
6.969
6.966
6.953
6.950
6.925
6.922
AK-3-B-Acetone
Cl
N
H
N
N
O
OH
35
CN
1.82
1.87
0.99
1.95
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

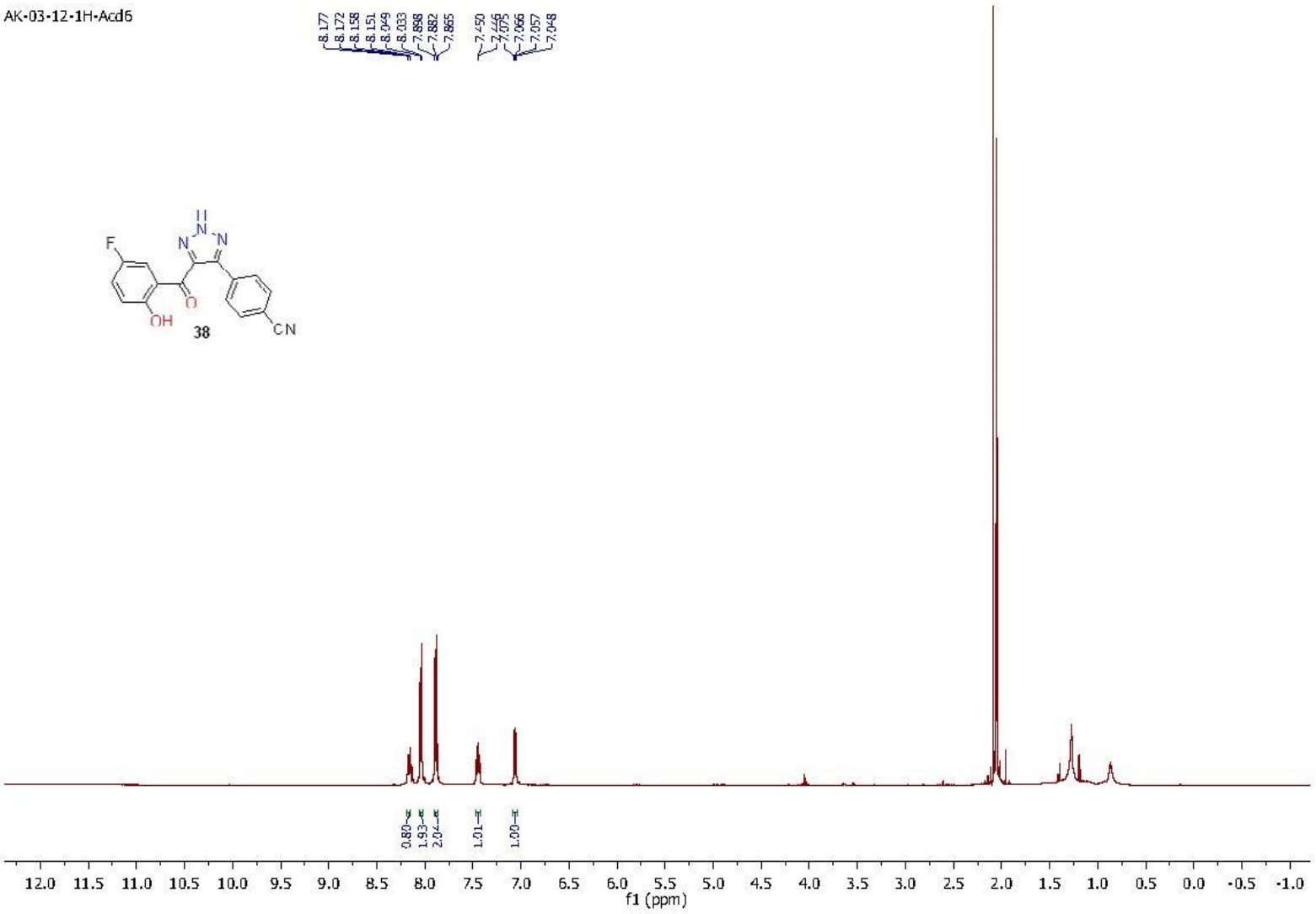

AK-3-B-13C
187.25
155.75
145.53
134.07
132.20
131.26
130.79
129.70
129.63
127.90
120.34
118.32
114.65
112.82
35
f1 (ppm)

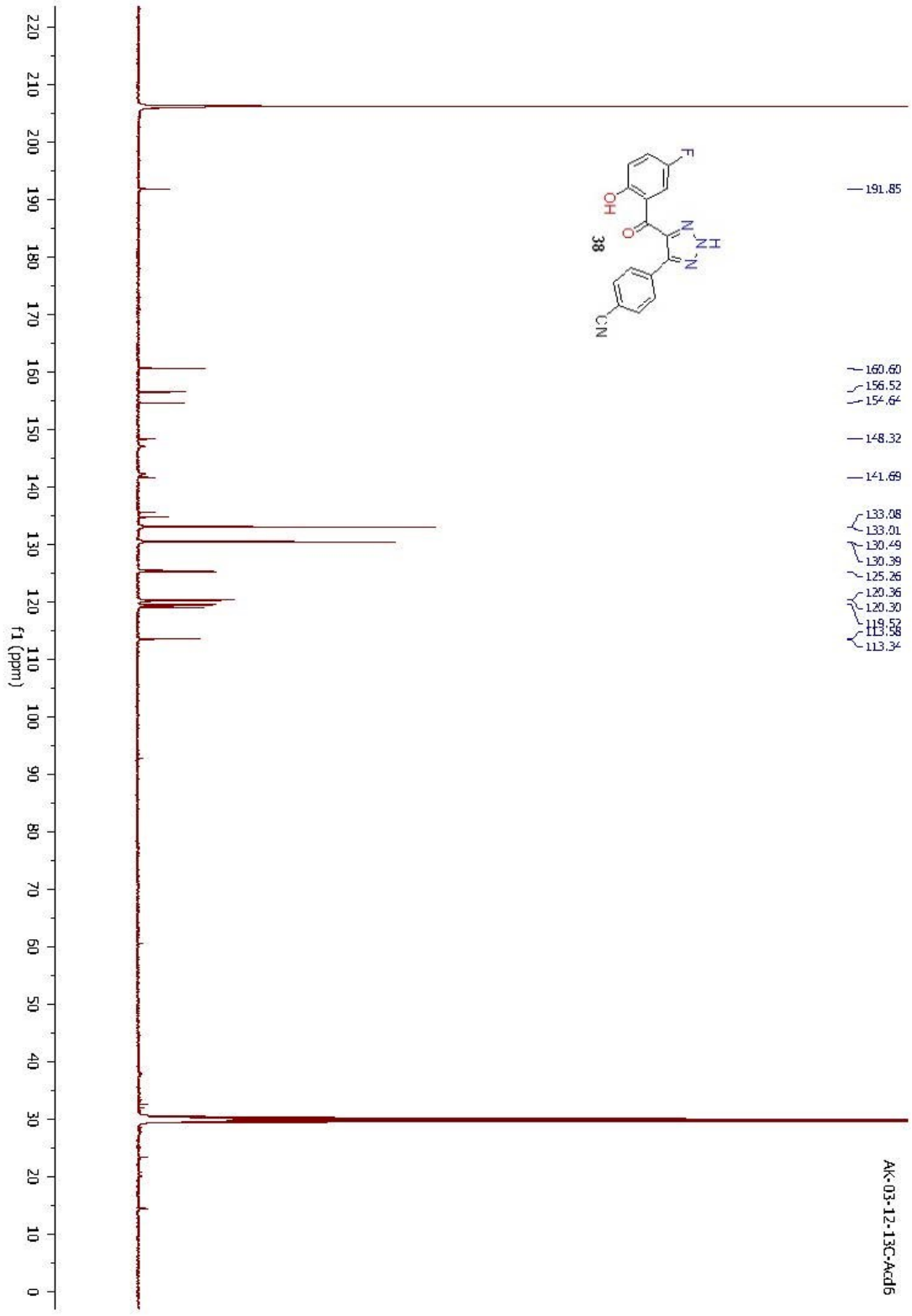

AK-3-10-1H
8.38
8.38
8.37
8.37
8.04
8.03
7.92
7.90
7.88
7.87
7.87
6.99
6.97
6.95
0.82
2.00
3.15
1.01
f1 (ppm)
36

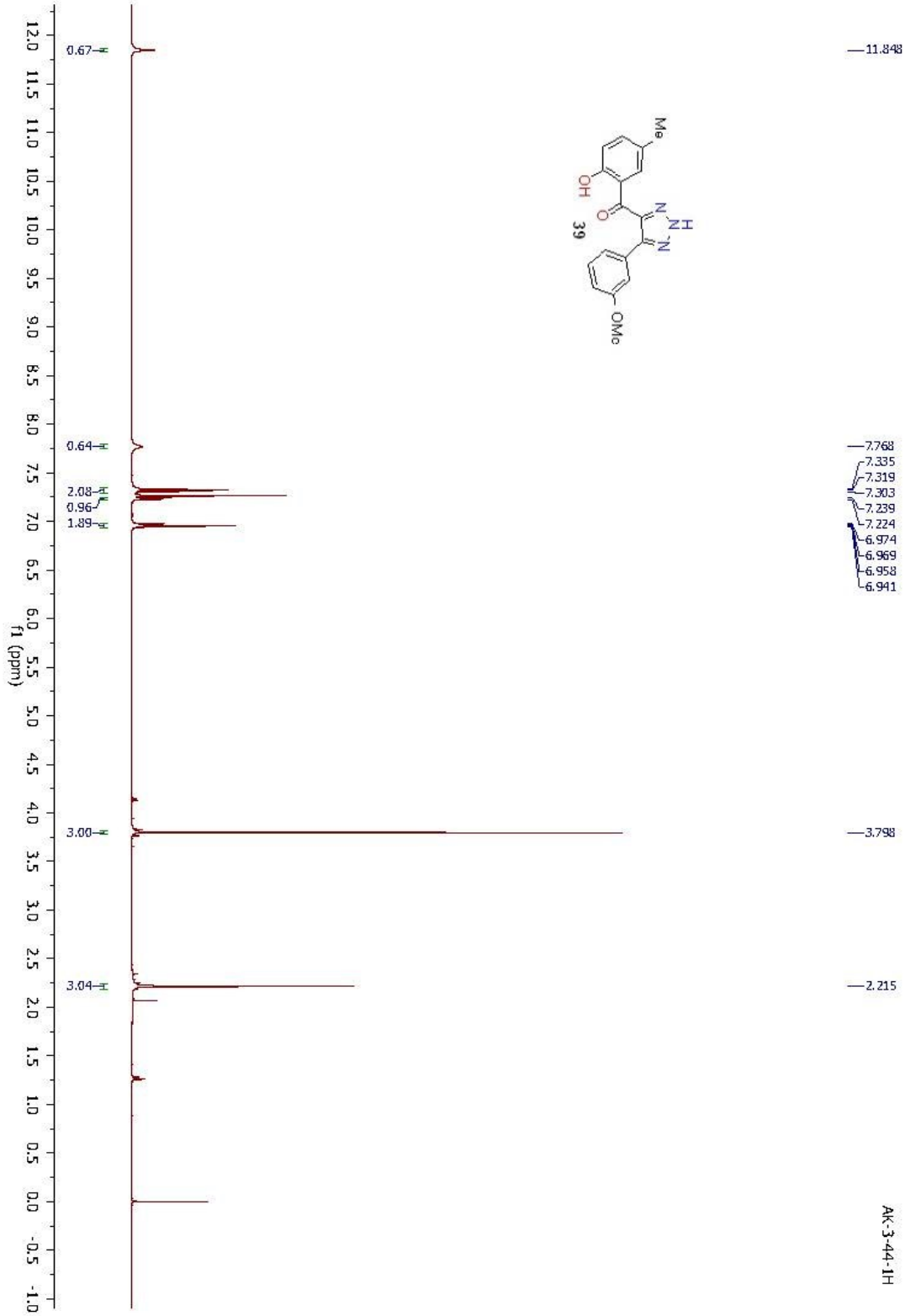

206.26
192.90
160.56
148.15
142.04
141.51
140.98
134.54
133.14
133.07
130.36
130.27
121.47
120.86
118.99
113.56
113.33
111.93
Br
OH
O
N
N
H
N
CN
36
f1 (ppm)
AK-3-10-Acetoned6-13C

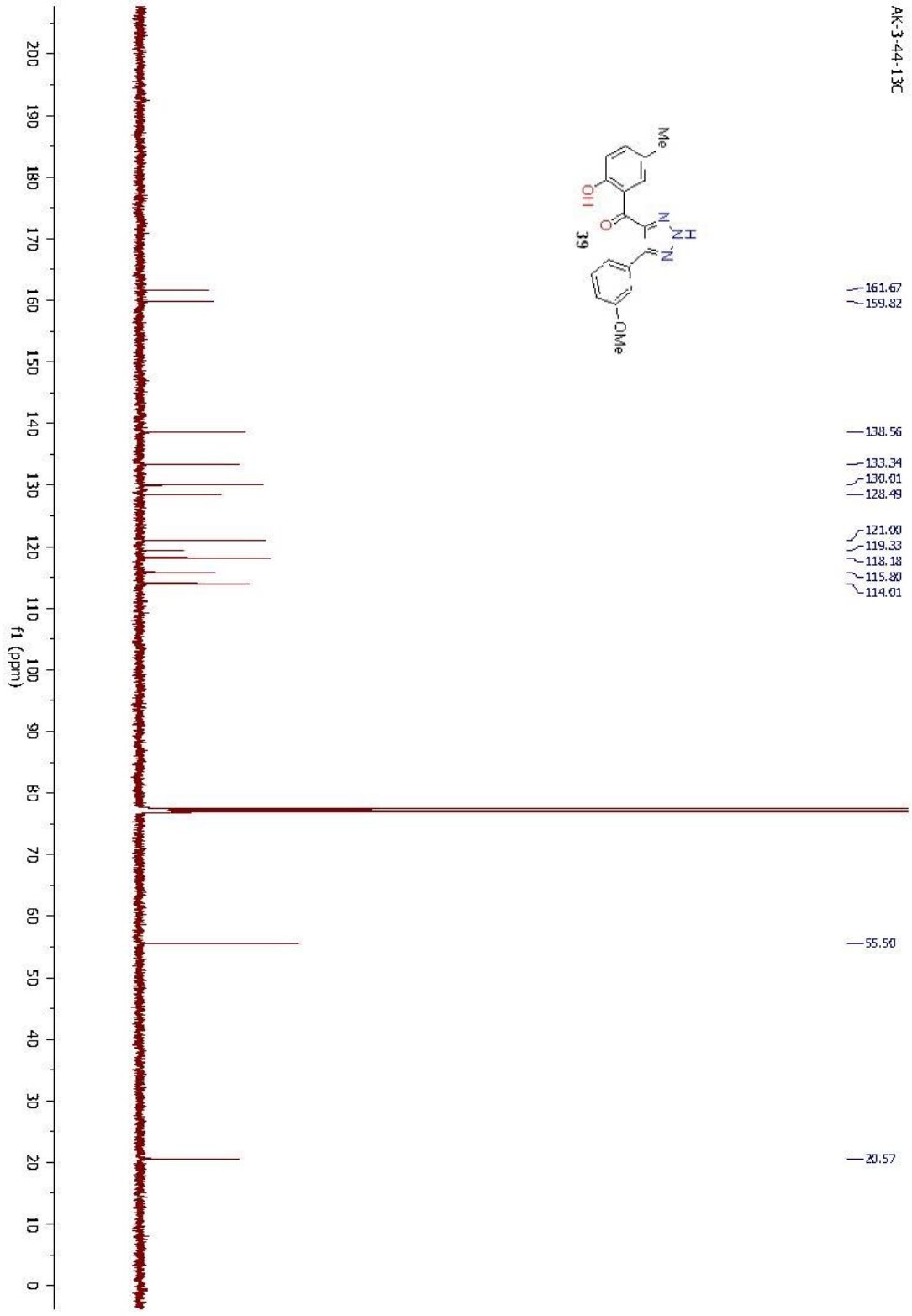

AK-3-11-1H
8.551
8.061
8.034
7.898
7.872
7.737
7.707
7.025
6.995
1.09
2.10
2.10
1.04
1.00
f1 (ppm)
37

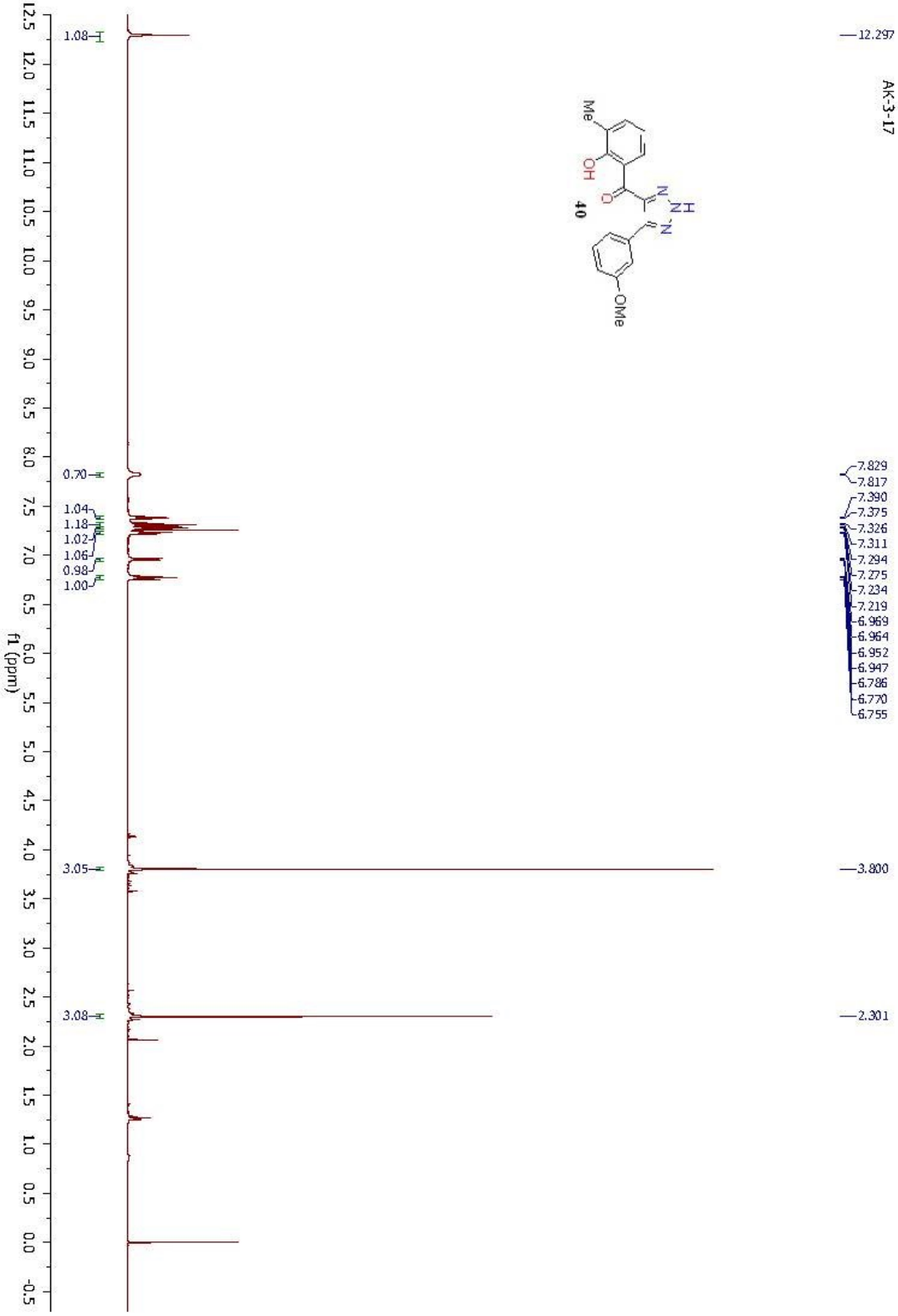

AK-3-11-C
191.61
163.11
140.17
136.71
133.04
130.50
121.98
121.10
119.03
113.52
110.94
Br
OH
O
N
N
H
N
CN
37
f1 (ppm)

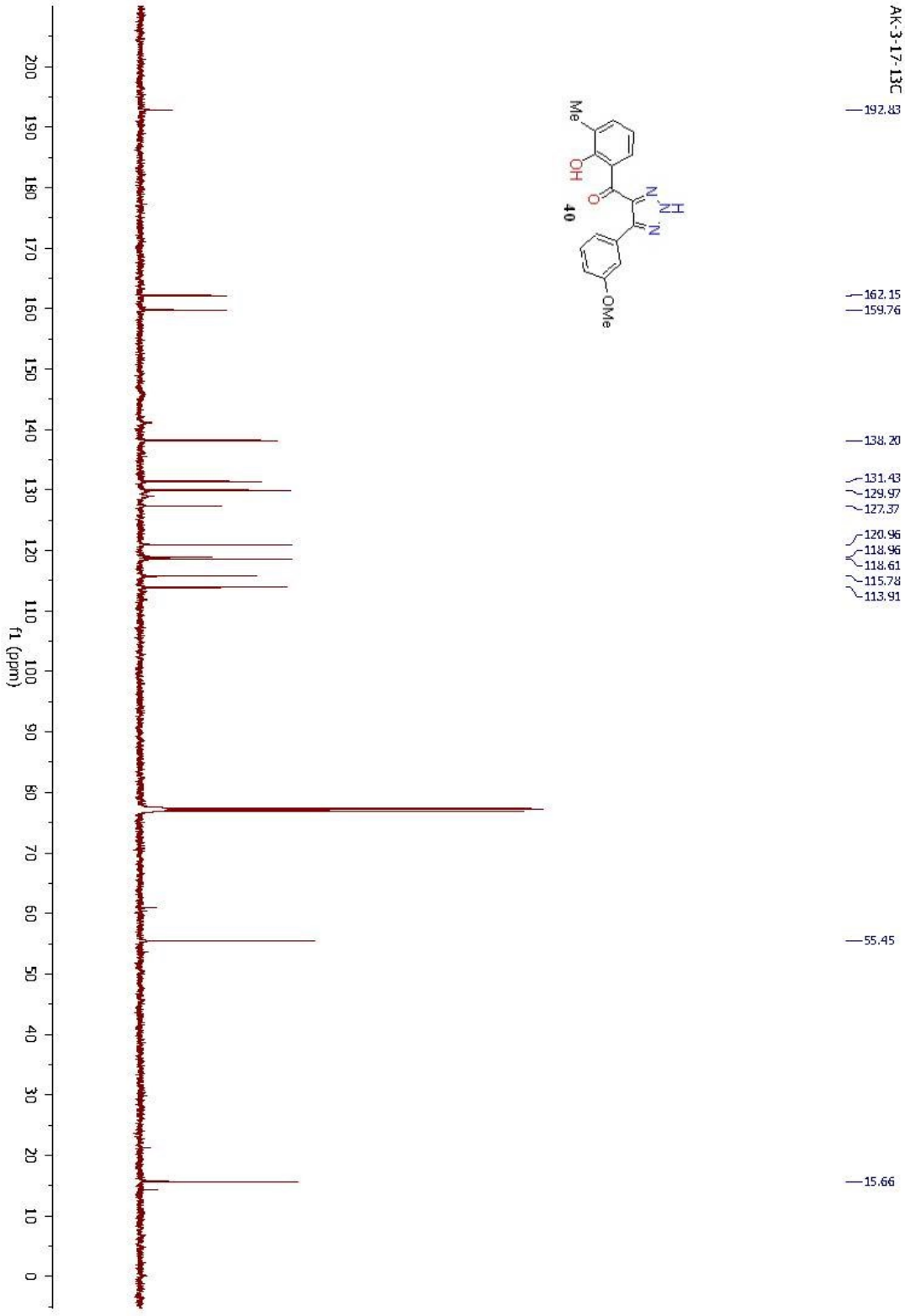

AK-03-12-1H-Acd6
8.177
8.172
8.158
8.151
8.049
8.033
7.898
7.882
7.865
7.450
7.446
7.075
7.066
7.057
7.048
F
N
N
N
H
O
OH
CN
38
0.80
1.93
2.04
1.01
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

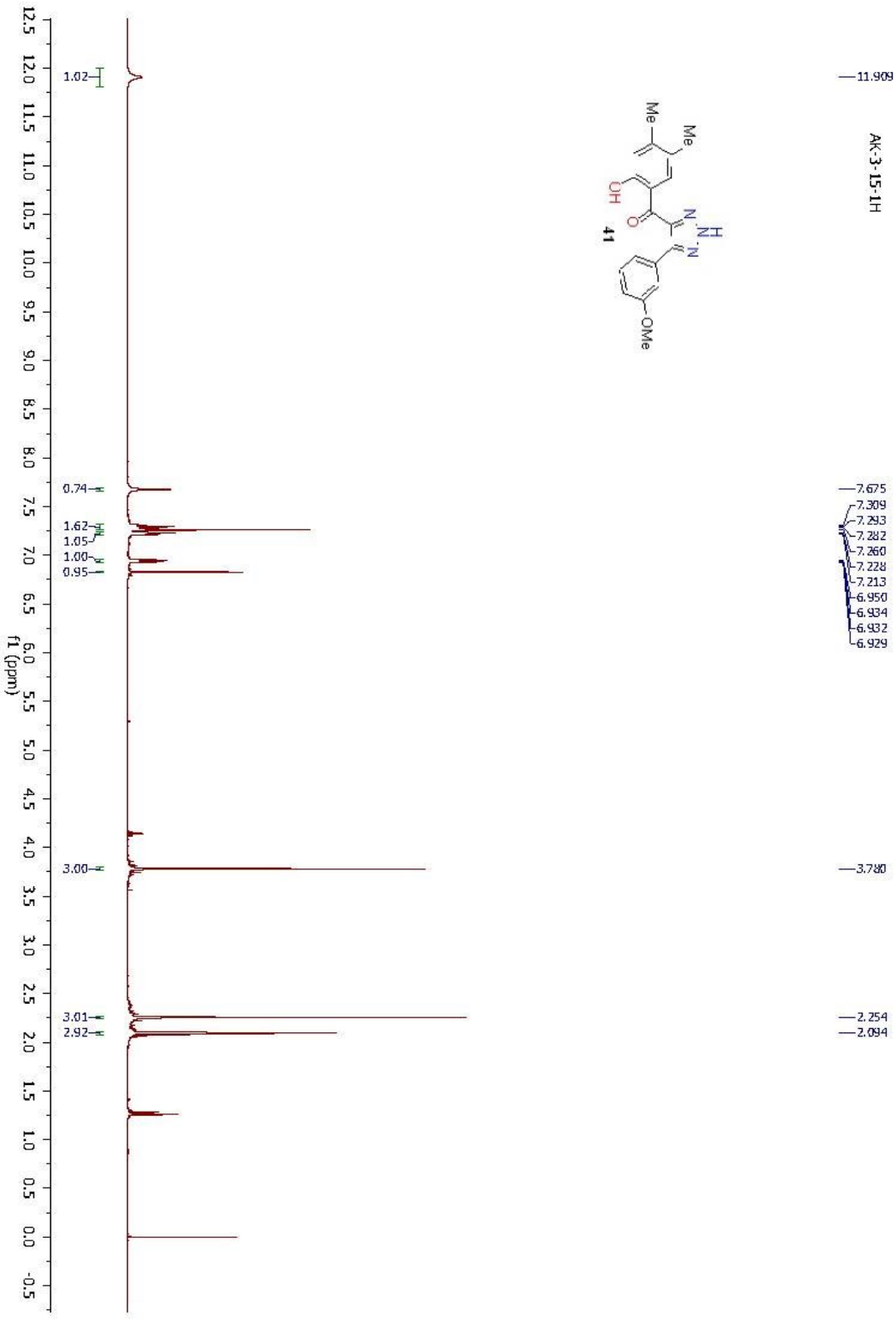

191.85
160.60
156.52
154.64
148.32
141.69
133.08
133.01
130.49
130.39
125.26
120.36
120.30
119.52
113.58
113.34
38
F
HO
O
N
N
H
N
CN
f1 (ppm)
AK-03-12-13C-Acd6

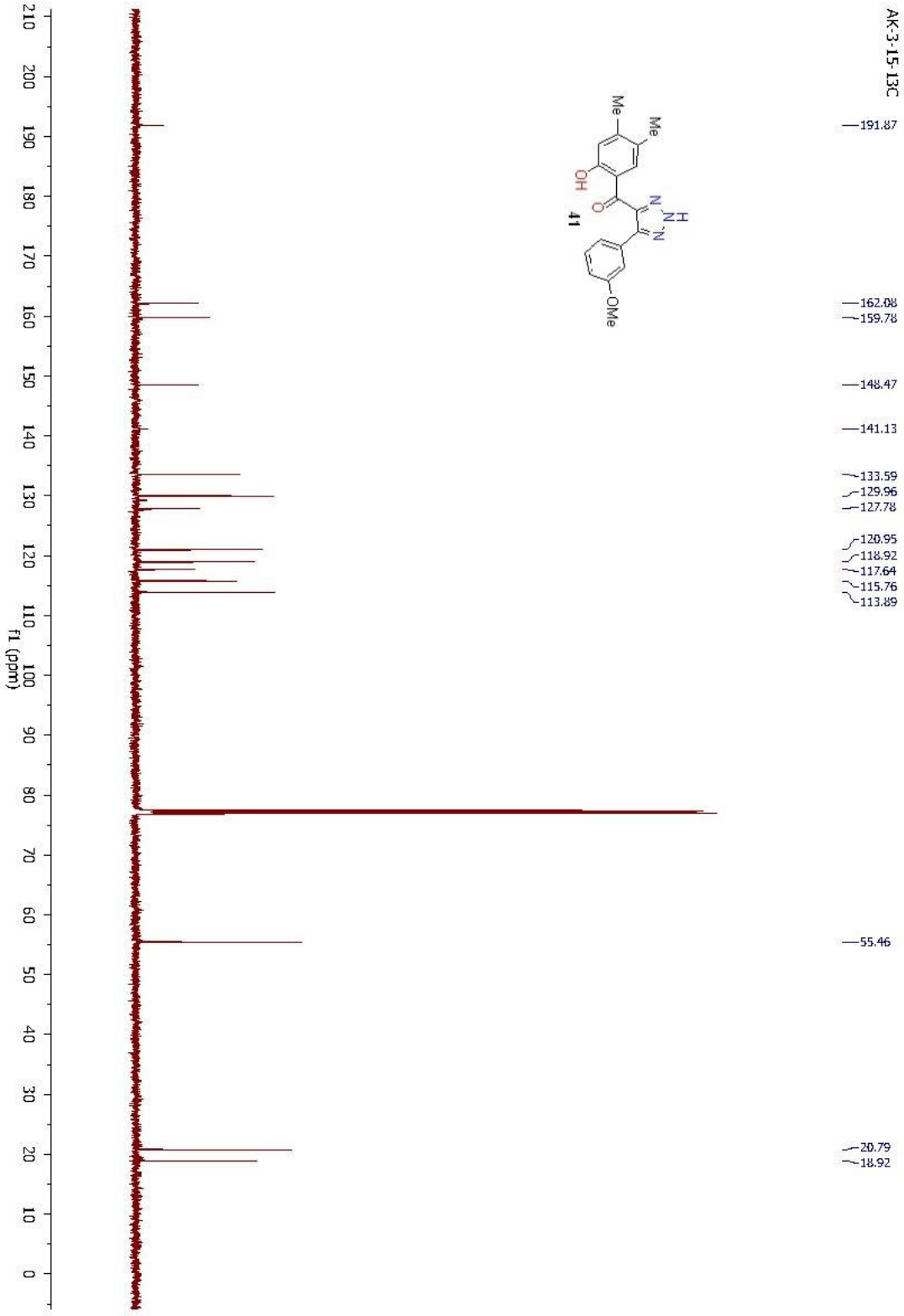

0.67
0.64
2.08
0.96
1.89
3.00
3.04
f1 (ppm)
11.848
7.768
7.335
7.319
7.303
7.239
7.224
6.974
6.969
6.958
6.941
3.798
2.215
Me
OH
O
N
NH
N
OMe
39
AK-3-44-1H

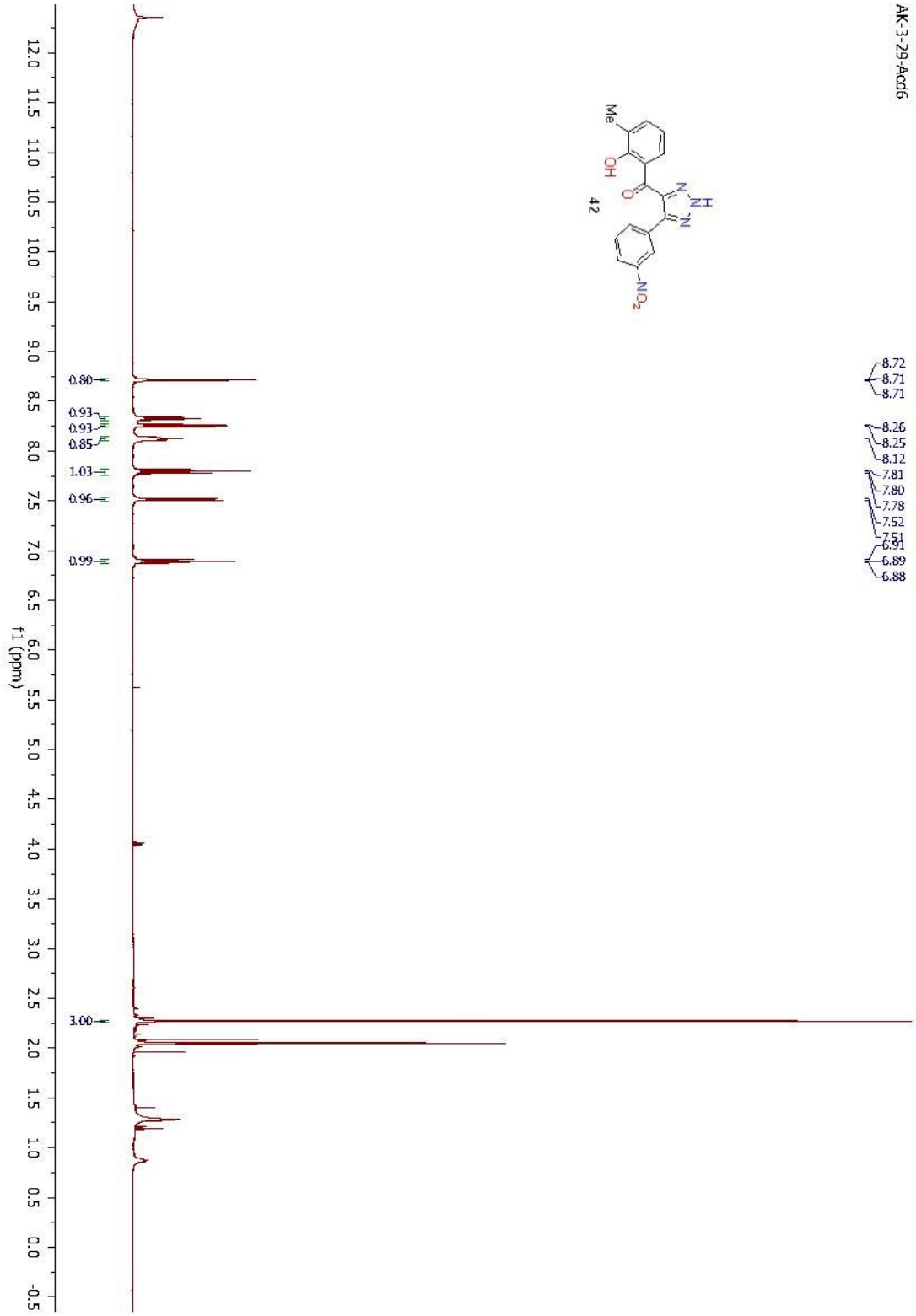

Ak-3-44-13C
Me
OH
O
N
NH
N
OMe
39
161.67
159.82
138.56
133.34
130.01
128.49
121.00
119.33
118.18
115.80
114.01
55.50
20.57
f1 (ppm)

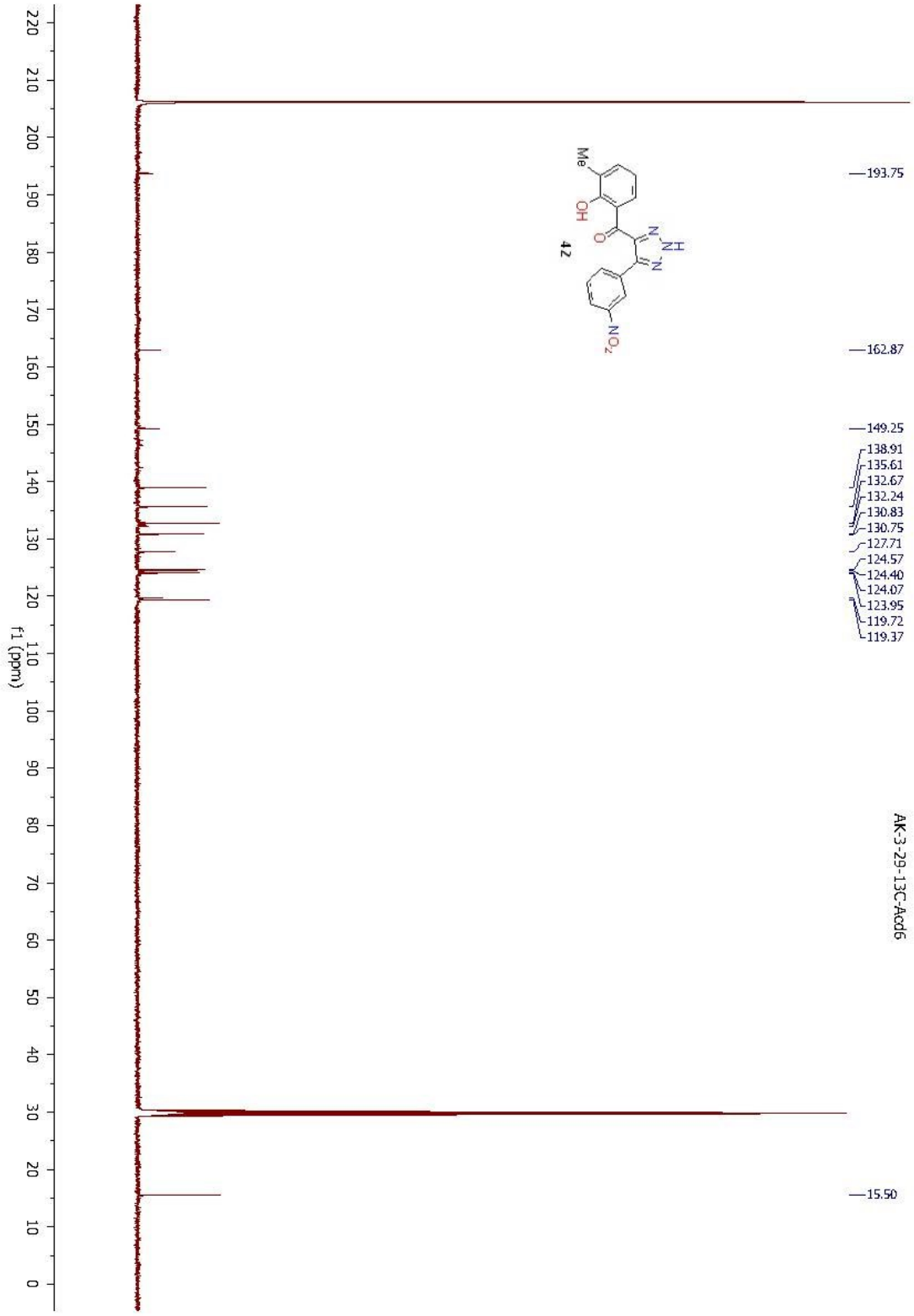

AK-3-17
40
Me
OH
O
N
NH
N
OMe
12.297
7.829
7.817
7.390
7.375
7.326
7.311
7.294
7.275
7.234
7.219
6.969
6.964
6.952
6.947
6.786
6.770
6.755
3.800
2.301
1.08
0.70
1.04
1.18
1.02
1.06
0.98
1.00
3.05
3.08
f1 (ppm)

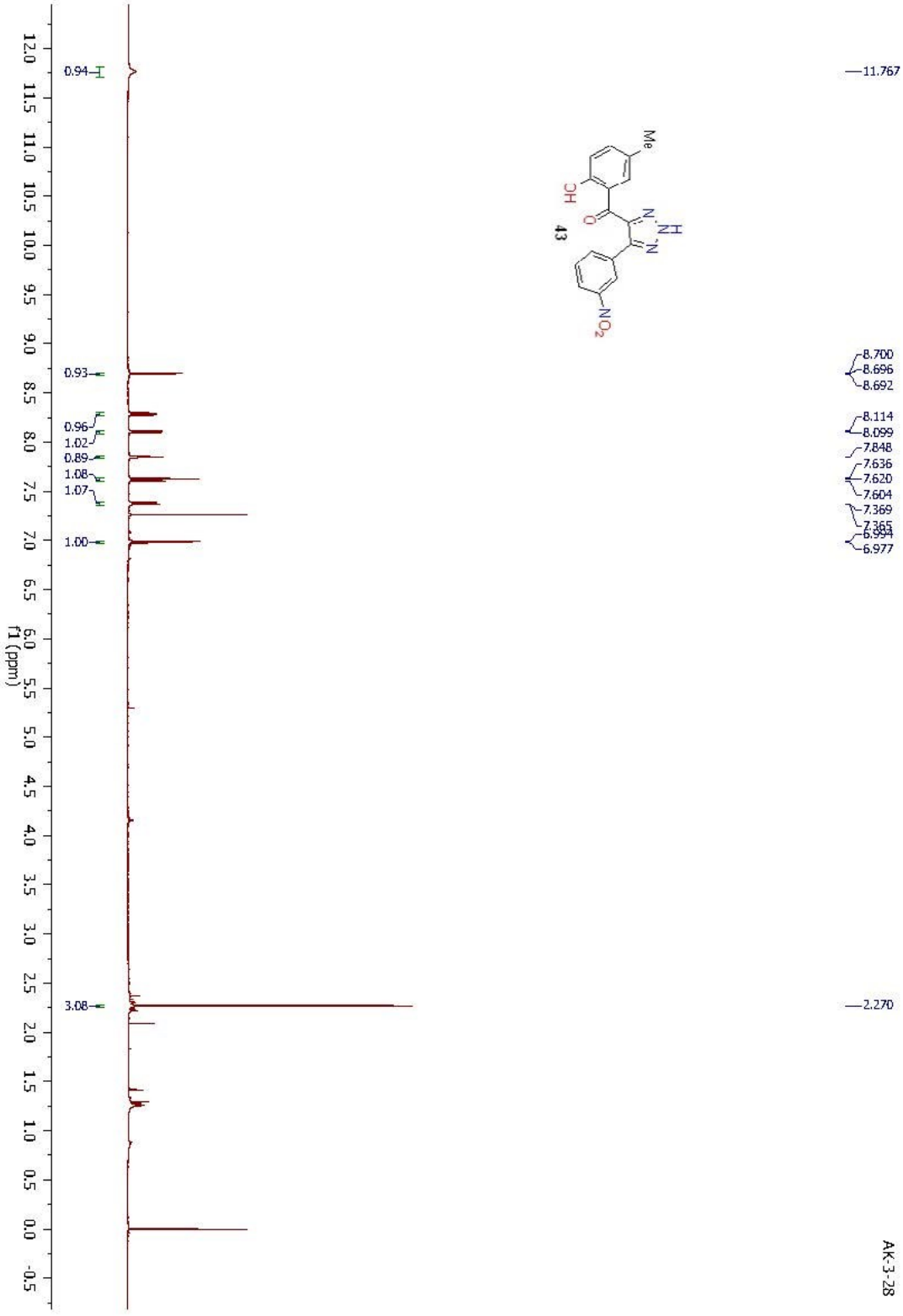

AK-3-17-13C
192.83
162.15
159.76
138.20
131.43
129.97
127.37
120.96
118.96
118.61
115.78
113.91
55.45
15.66
f1 (ppm)
Me
OH
O
N
N
H
N
OMe
40

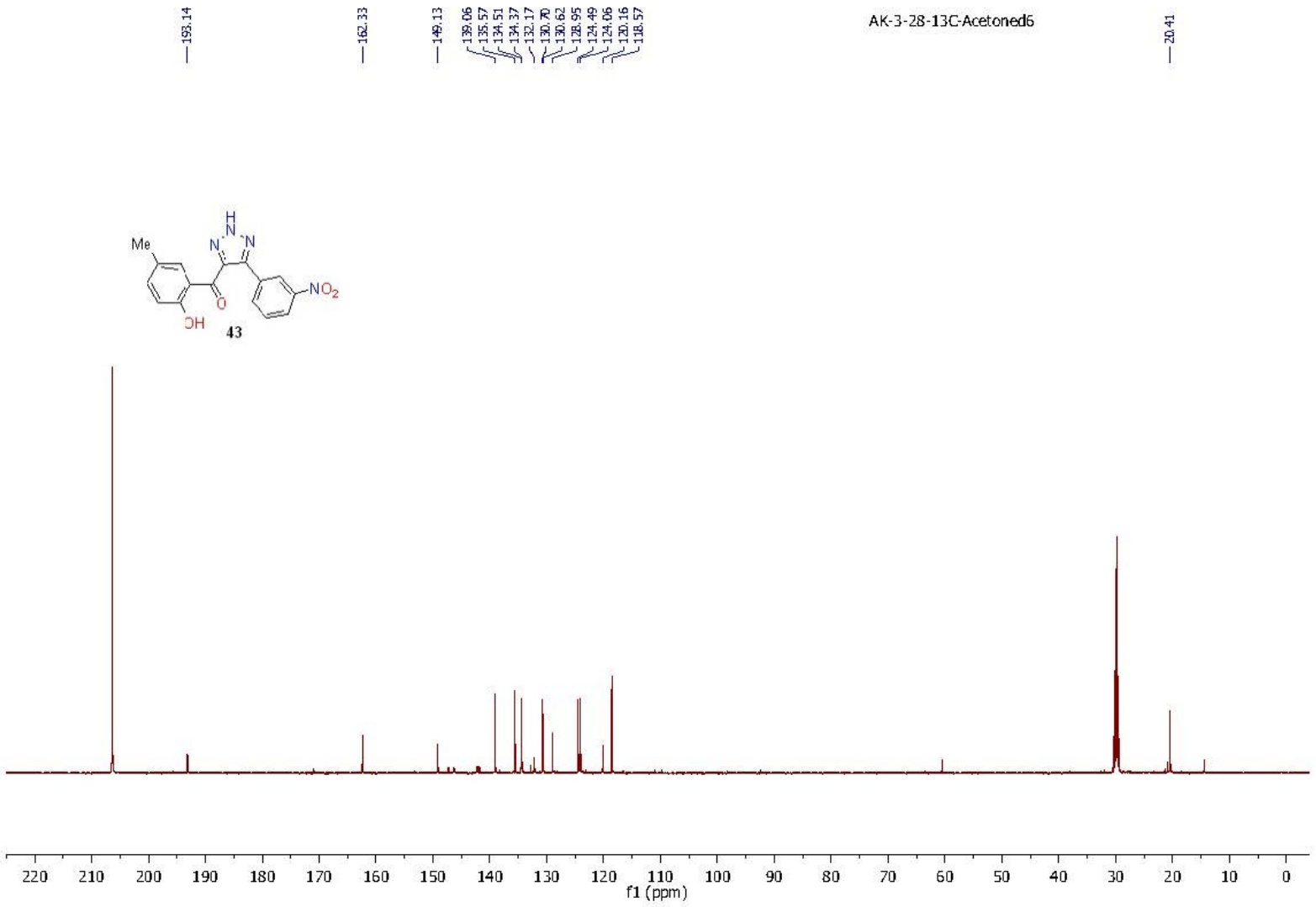

AK-3-15-1H
11.909
7.675
7.309
7.293
7.282
7.260
7.228
7.213
6.950
6.934
6.932
6.929
3.780
2.254
2.094
1.02
0.74
1.62
1.05
1.00
0.95
3.00
3.01
2.92
f1 (ppm)
Me
Me
OH
O
N
NH
N
OMe
41

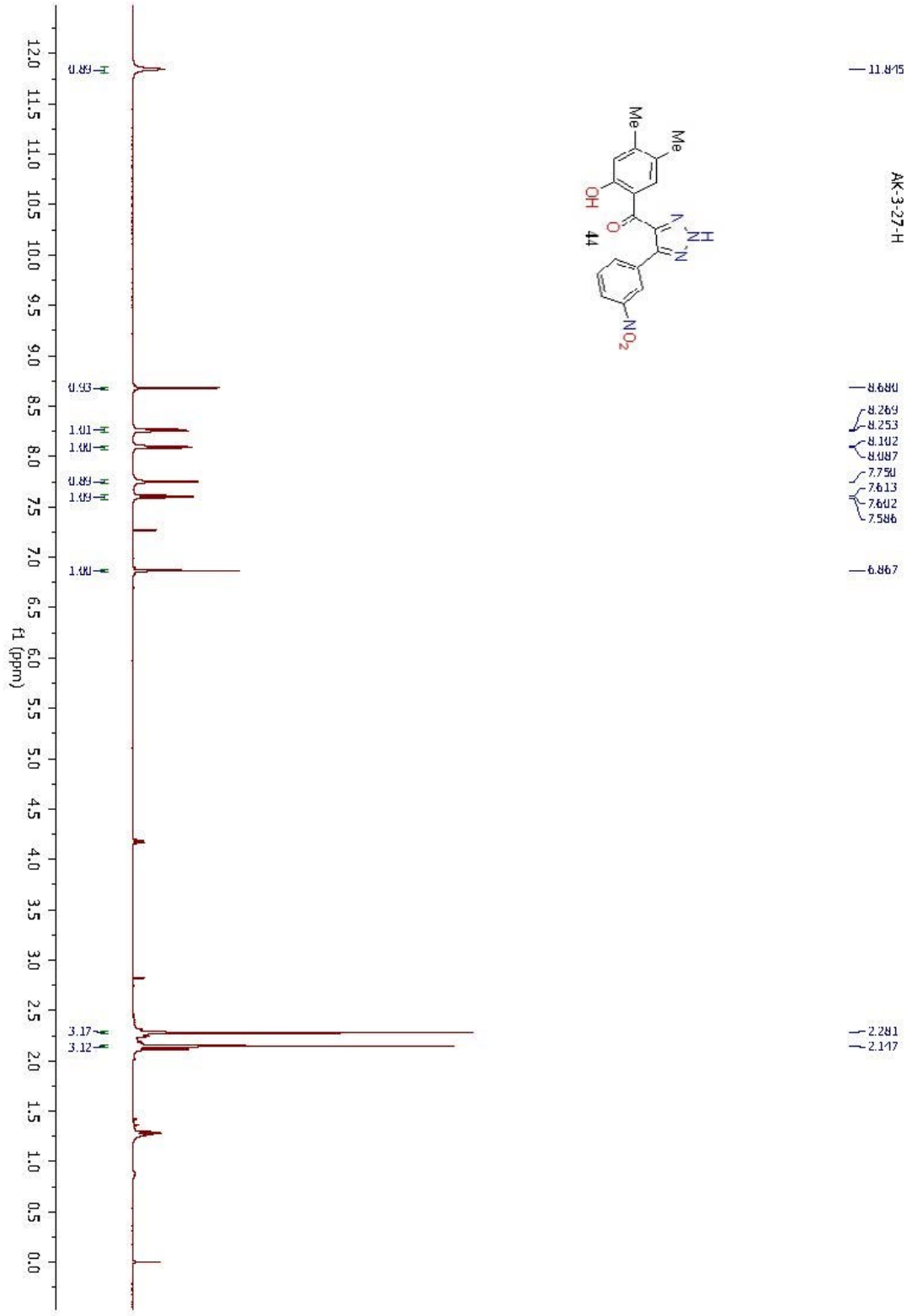

AK-3-15-13C
191.87
162.08
159.78
148.47
141.13
133.59
129.96
127.78
120.95
118.92
117.64
115.76
113.89
55.46
20.79
18.92
Me
Me
OH
O
N
NH
N
OMe
41
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

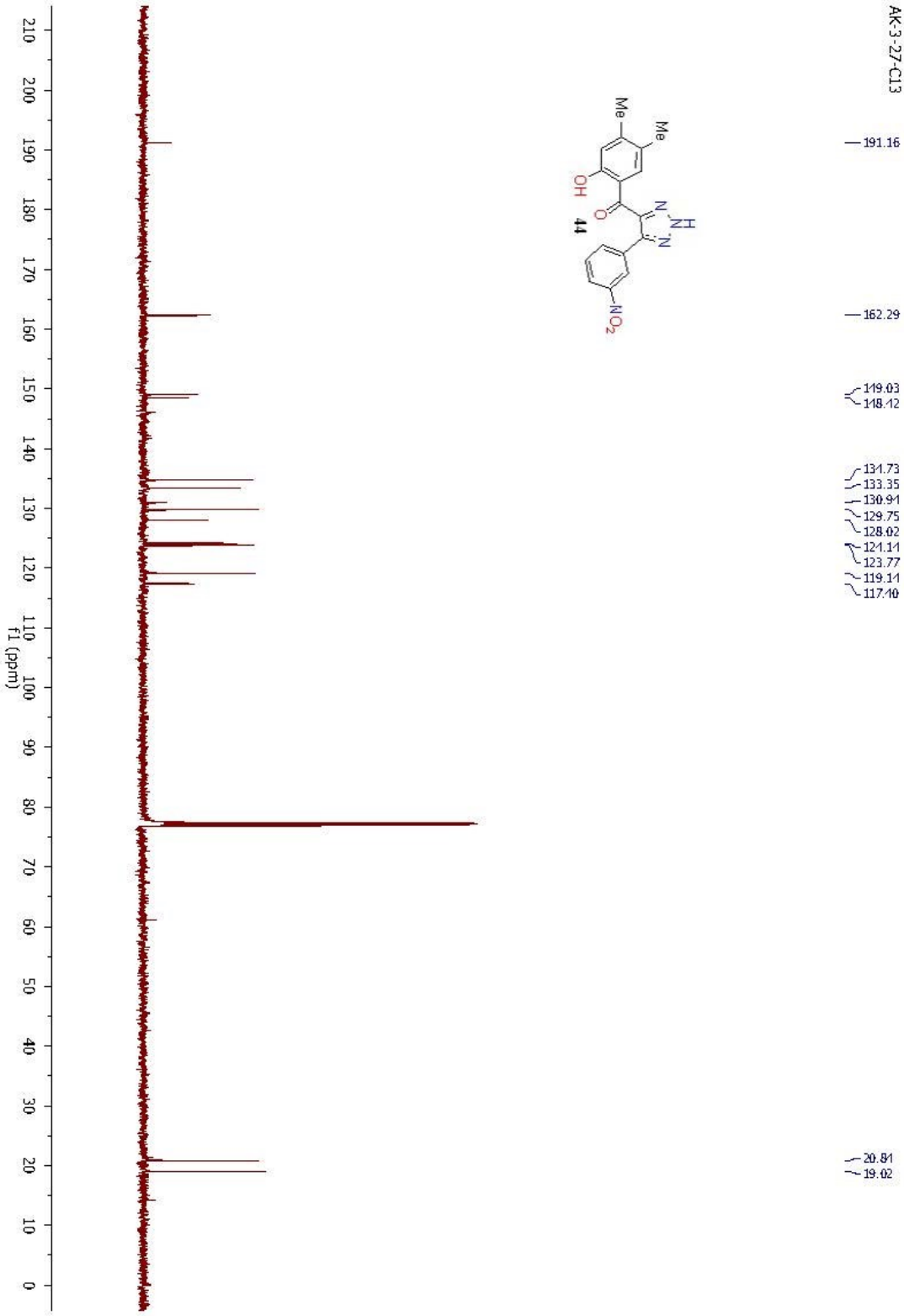

AK-3-29-Acd6
Me
OH
O
N
N
H
N
NO2
42
8.72
8.71
8.71
8.26
8.25
8.12
7.81
7.80
7.78
7.52
7.51
6.91
6.89
6.88
0.80
0.93
0.93
0.85
1.03
0.96
0.99
3.00
f1 (ppm)

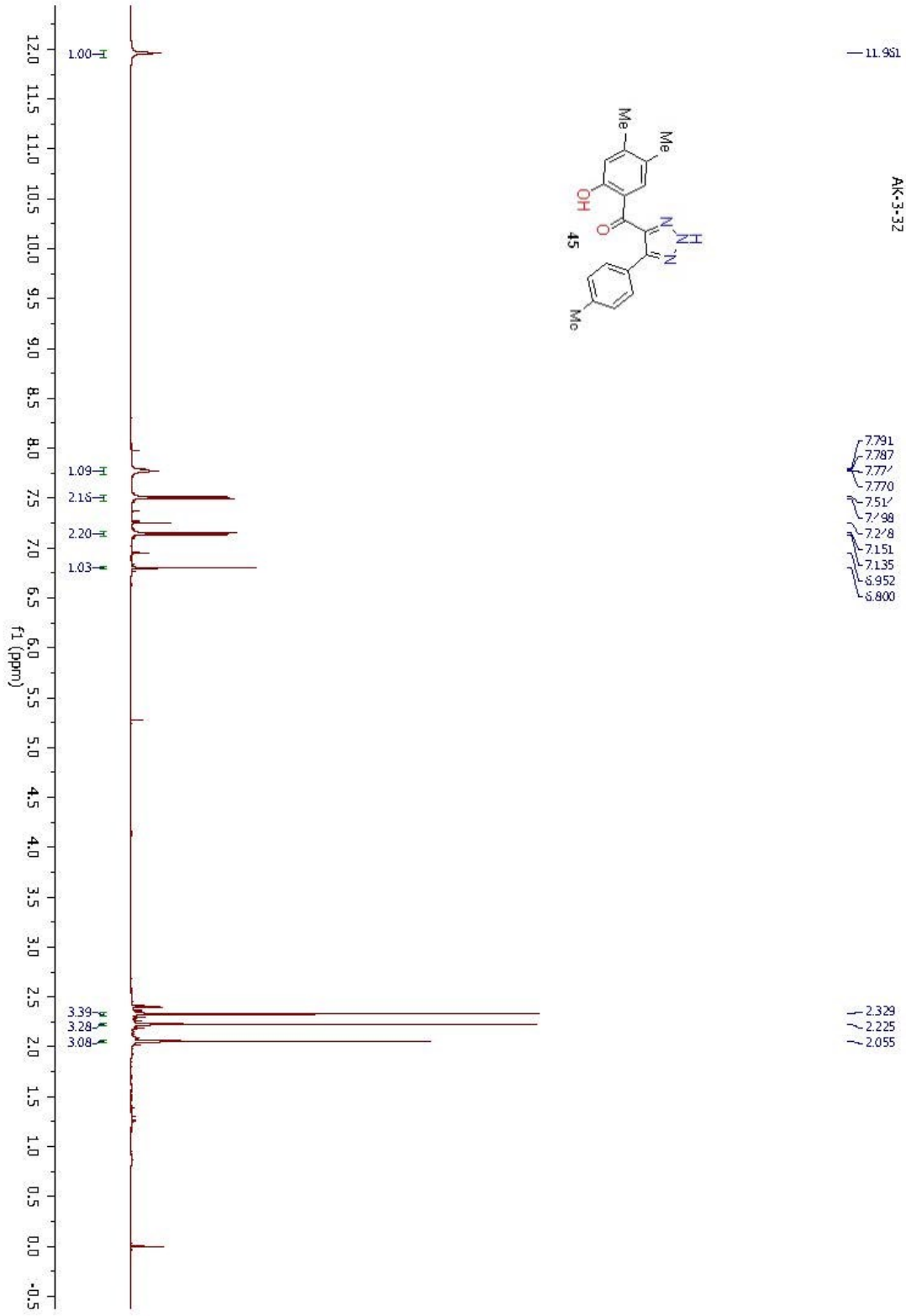

193.75
162.87
149.25
138.91
135.61
132.67
132.24
130.83
130.75
127.71
124.57
124.40
124.07
123.95
119.72
119.37
15.50
Me
OH
O
HN
NO2
4z
f1 (ppm)
AK-3-29-13C-Acd6

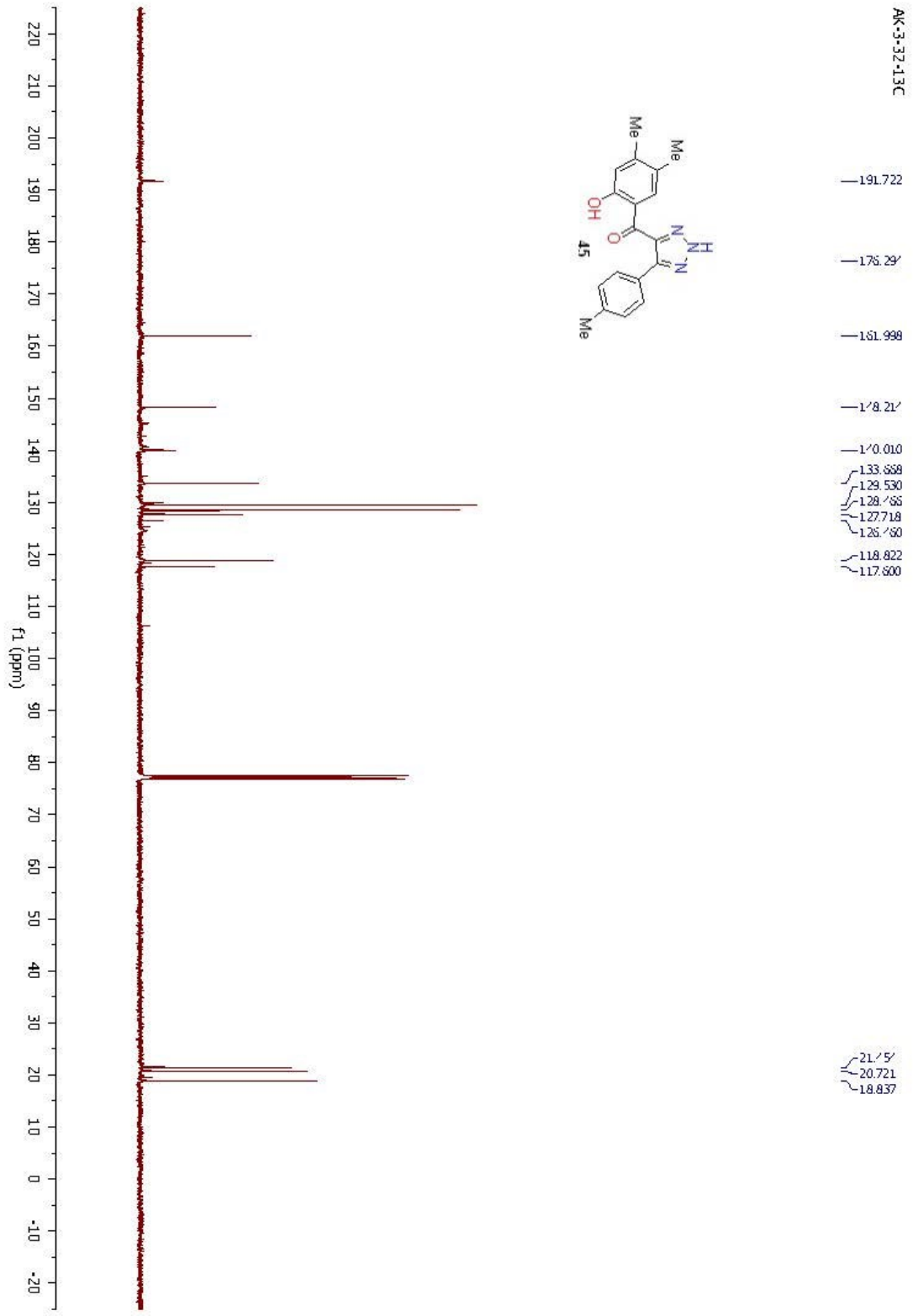

11.767
8.700
8.696
8.692
8.114
8.099
7.848
7.636
7.620
7.604
7.369
7.365
6.994
6.977
2.270
0.94
0.93
0.96
1.02
0.89
1.08
1.07
1.00
3.08
f1 (ppm)
AK-3-28
43
Me
OH
O
NH
N
NO2

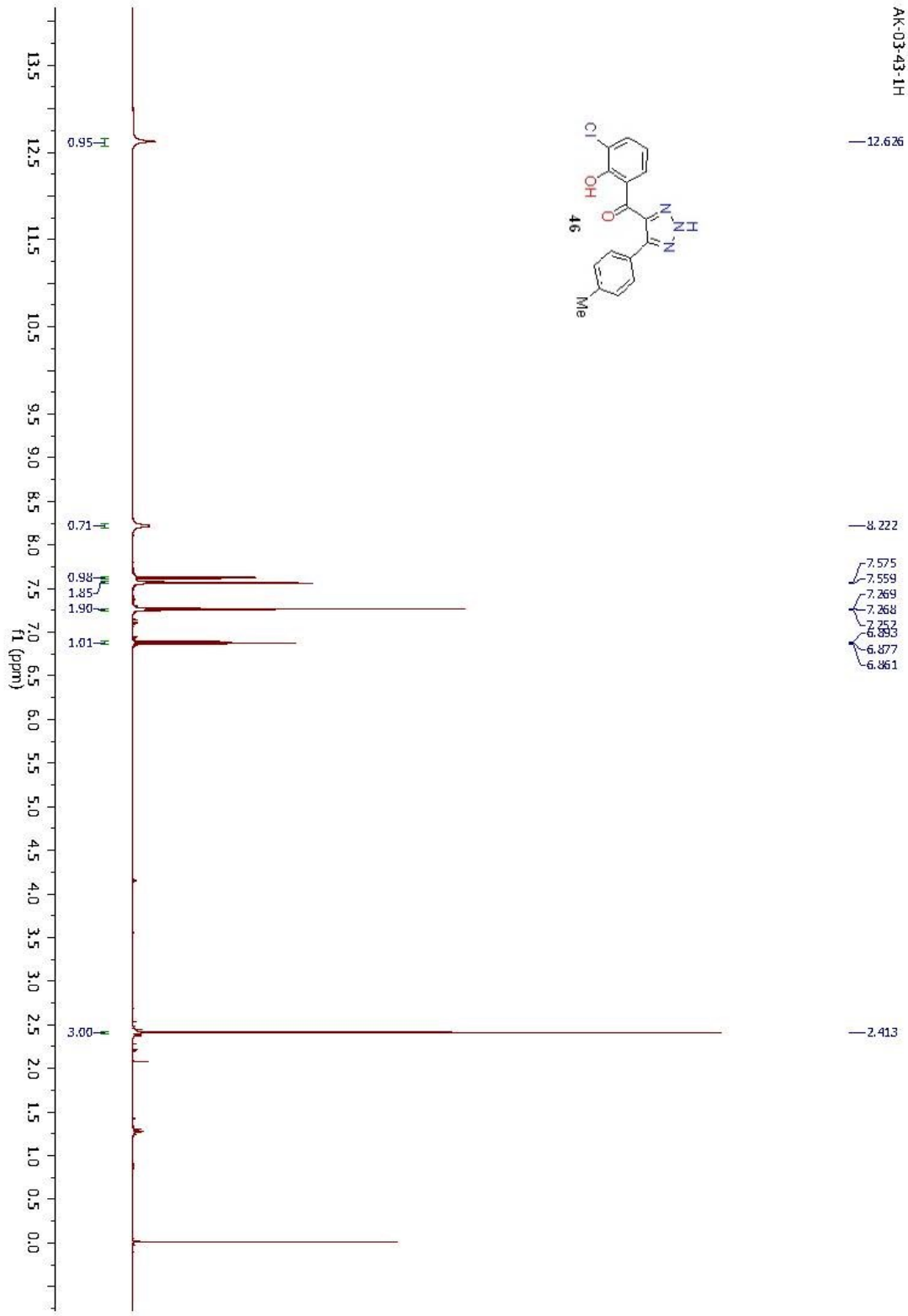

193.14
162.33
149.13
139.06
135.57
134.51
134.37
132.17
130.70
130.62
128.95
124.49
124.06
120.16
118.57
AK-3-28-13C-Acetoned6
20.41
Me
OH
O
NO2
43
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

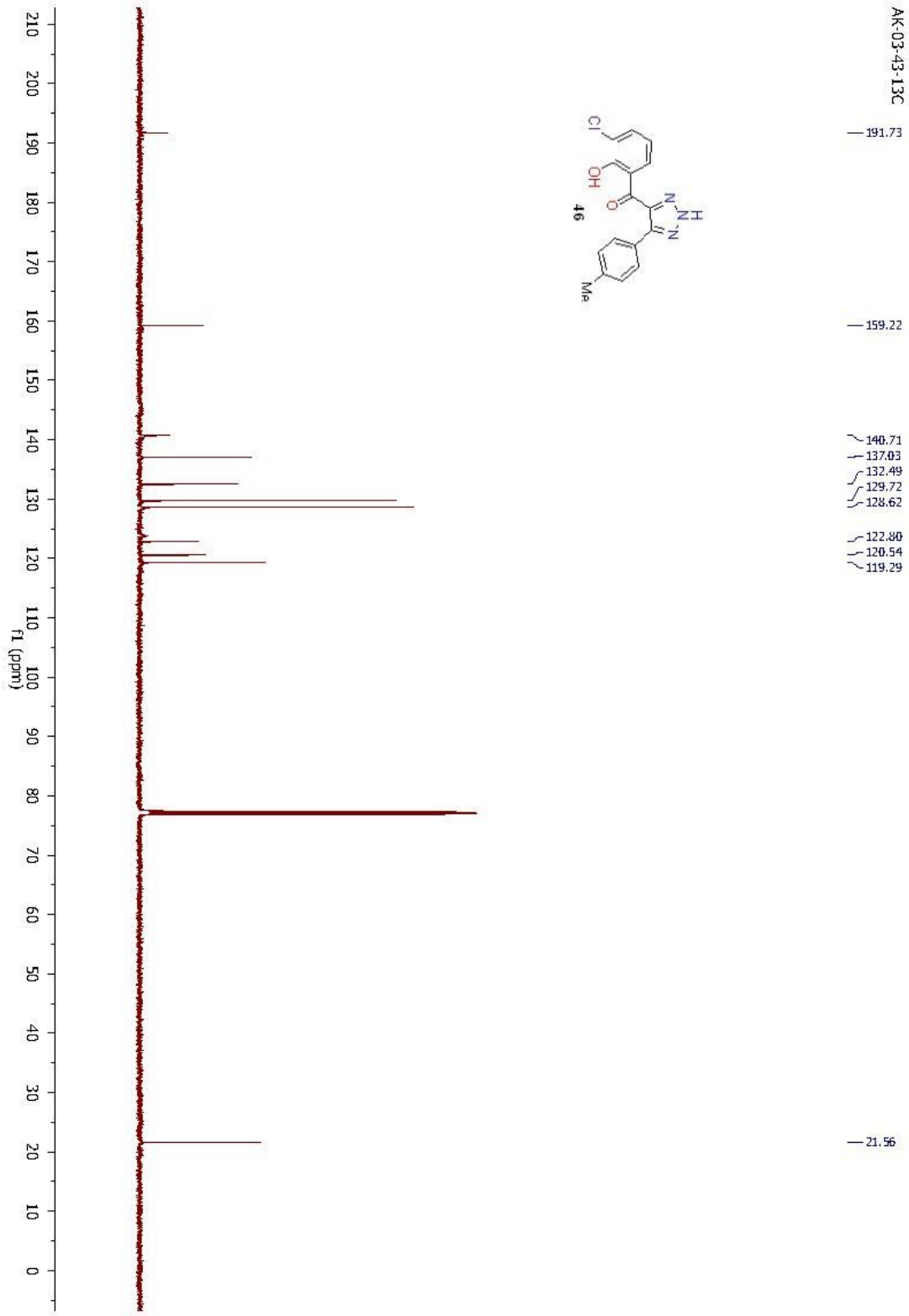

AK-3-27-H
11.845
8.680
8.269
8.253
8.102
8.087
7.750
7.613
7.602
7.586
6.867
2.281
2.147
0.89
0.93
1.01
1.00
0.89
1.09
1.00
3.17
3.12
Me
Me
OH
O
H
N
N
NO2
44
f1 (ppm)


AK-3-27-C13
191.16
162.29
149.03
148.12
134.73
133.35
130.91
129.75
128.02
124.14
123.77
119.14
117.40
20.84
19.02
Me
Me
OH
O
N
N
H
N
44
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


AK-3-32
45
11.961
7.791
7.787
7.777
7.770
7.517
7.498
7.228
7.151
7.135
6.952
6.800
2.329
2.225
2.055
1.00
1.09
2.16
2.20
1.03
3.39
3.28
3.08
f1 (ppm)


AK-3-32-13C
191.722
176.297
161.998
148.217
140.010
133.668
129.530
128.766
127.718
126.760
118.822
117.600
21.759
20.721
18.837
Me
Me
OH
O
N
N
H
N
45
Me
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20


AK-03-43-1H
12.626
8.222
7.575
7.559
7.269
7.268
7.252
6.893
6.877
6.861
2.413
0.95
0.71
0.98
1.85
1.90
1.01
3.00
f1 (ppm)
46
Cl
OH
O
N
N
H
N
Me

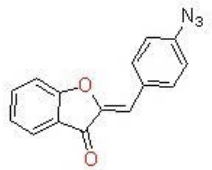

AK-03-43-13C
191.73
159.22
140.71
137.03
132.49
129.72
128.62
122.80
120.54
119.29
21.56
f1 (ppm)
Cl
OH
O
N
NH
N
Me
4g

APPENDIX - E

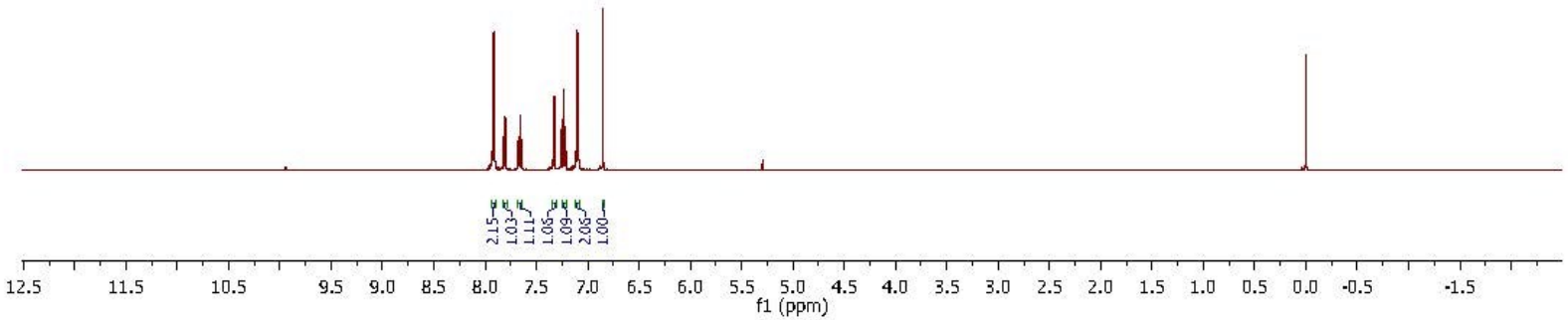
NMR Spectra - Chapter IV

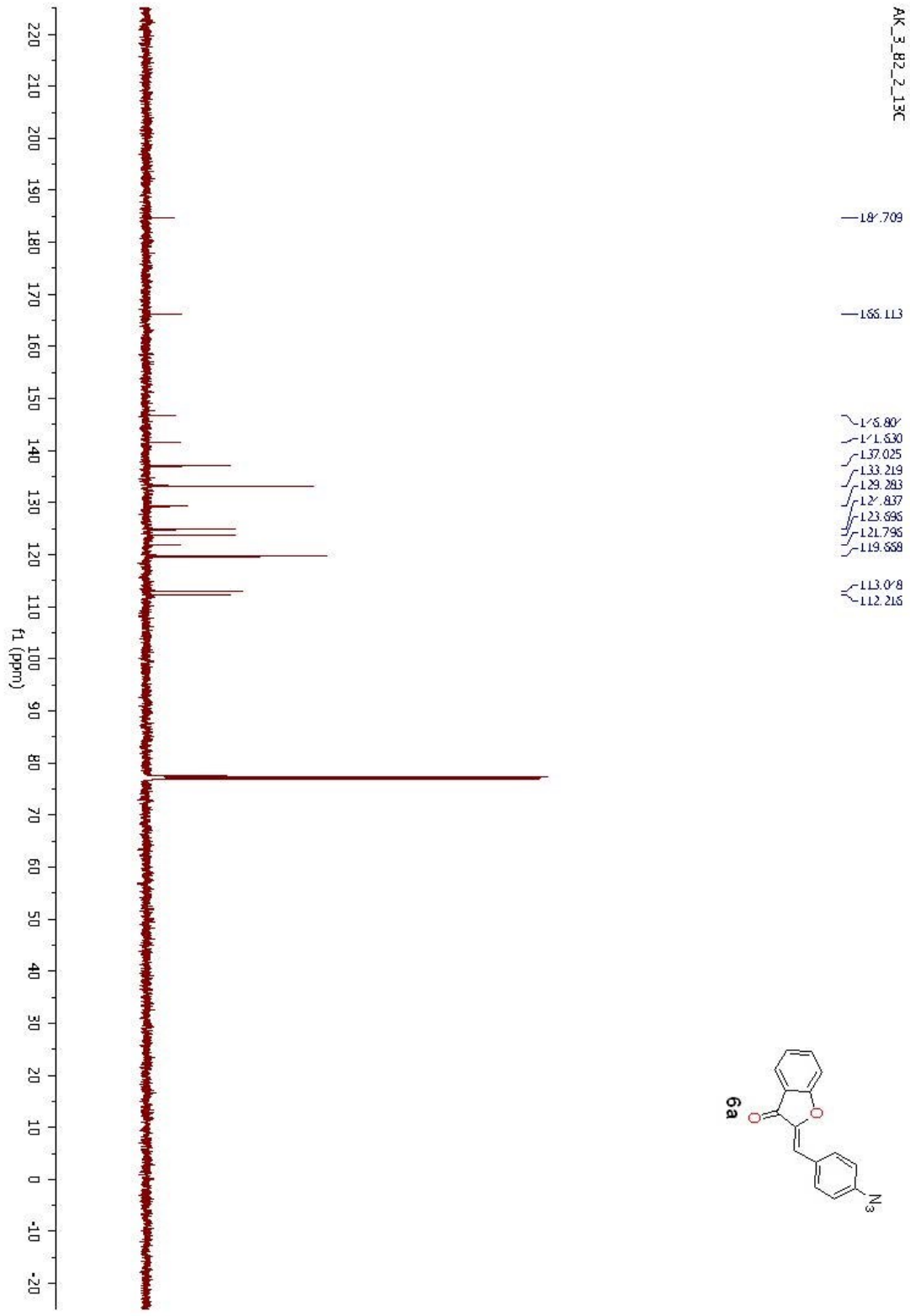
AK_3_82_2_1H


7.926
7.909
7.815
7.801
7.677
7.550
7.335
7.319
7.109
7.092
6.851

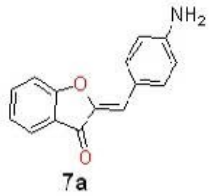

N3
O
O

6a

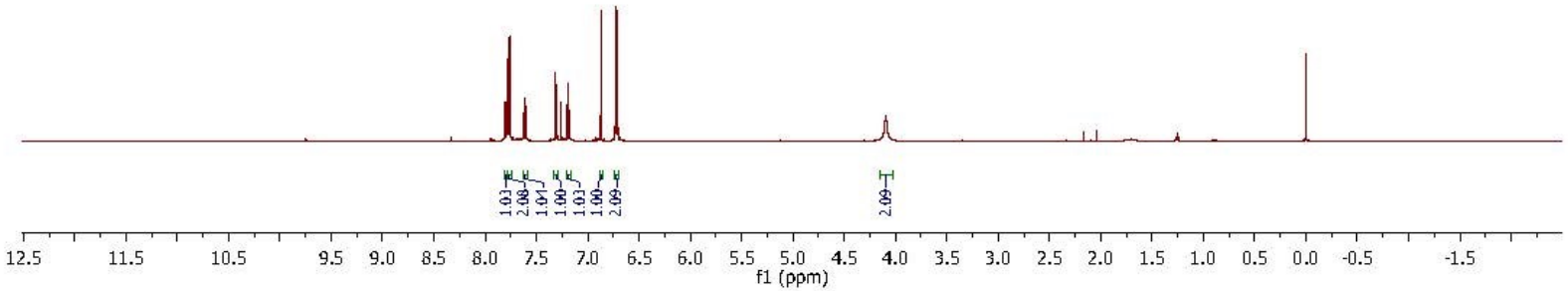

2.15
1.03
1.11
1.05
1.09
2.08
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)

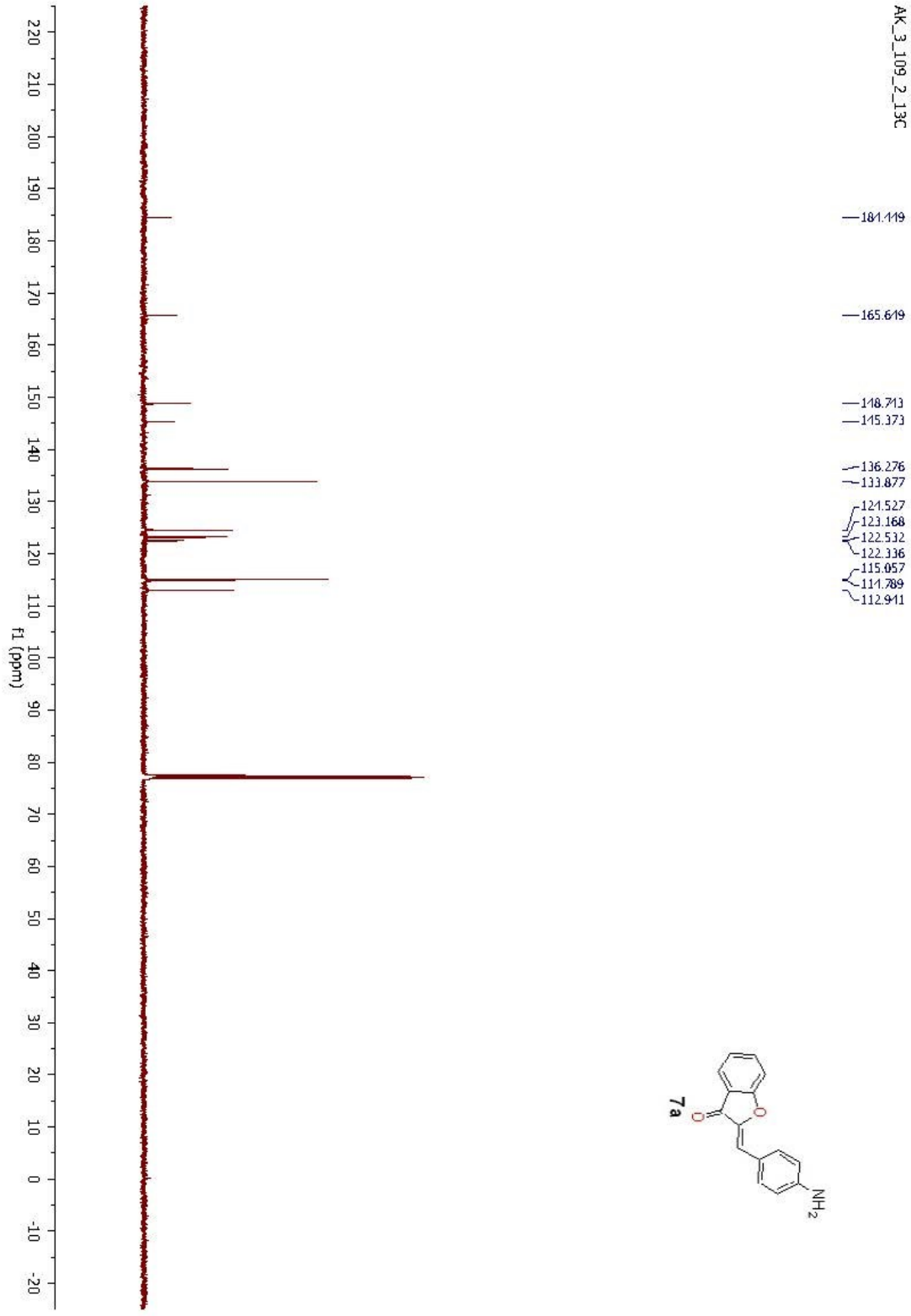

AK_3_82_2_13C
184.709
166.113
146.806
141.630
137.025
133.219
129.283
124.837
123.695
121.795
119.658
113.078
112.216
6a
O
O
N3
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

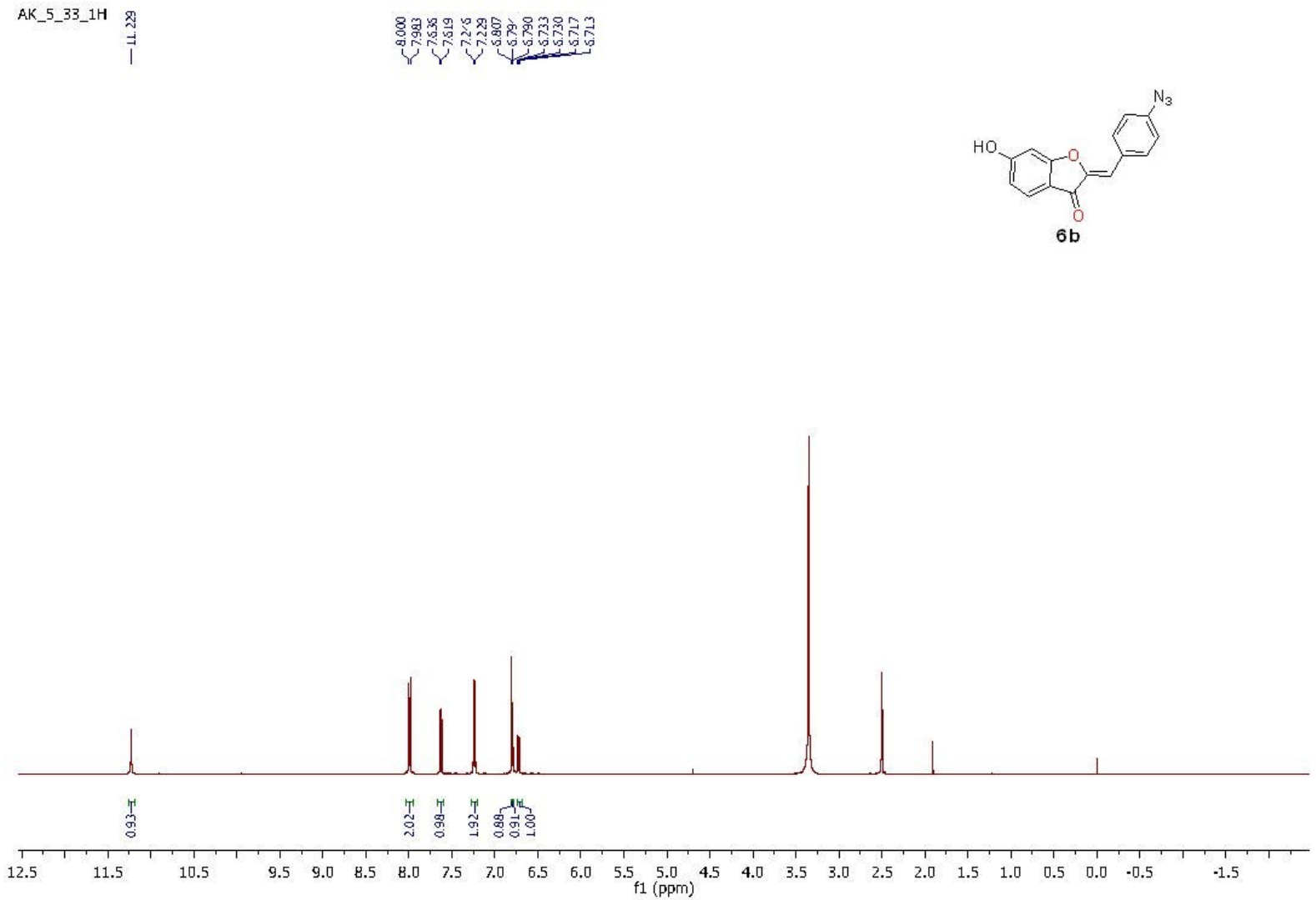
AK_3_109_2_1H

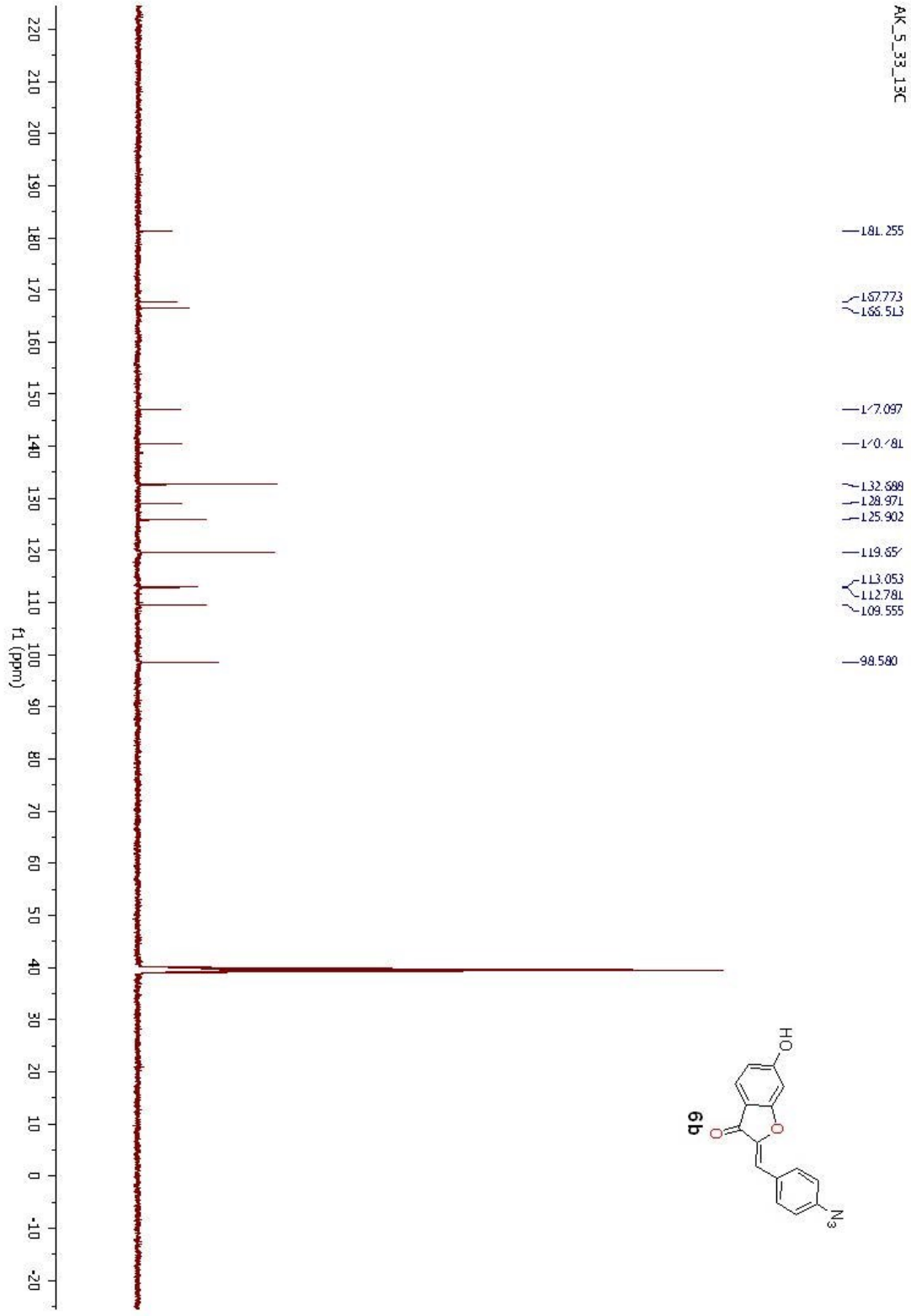


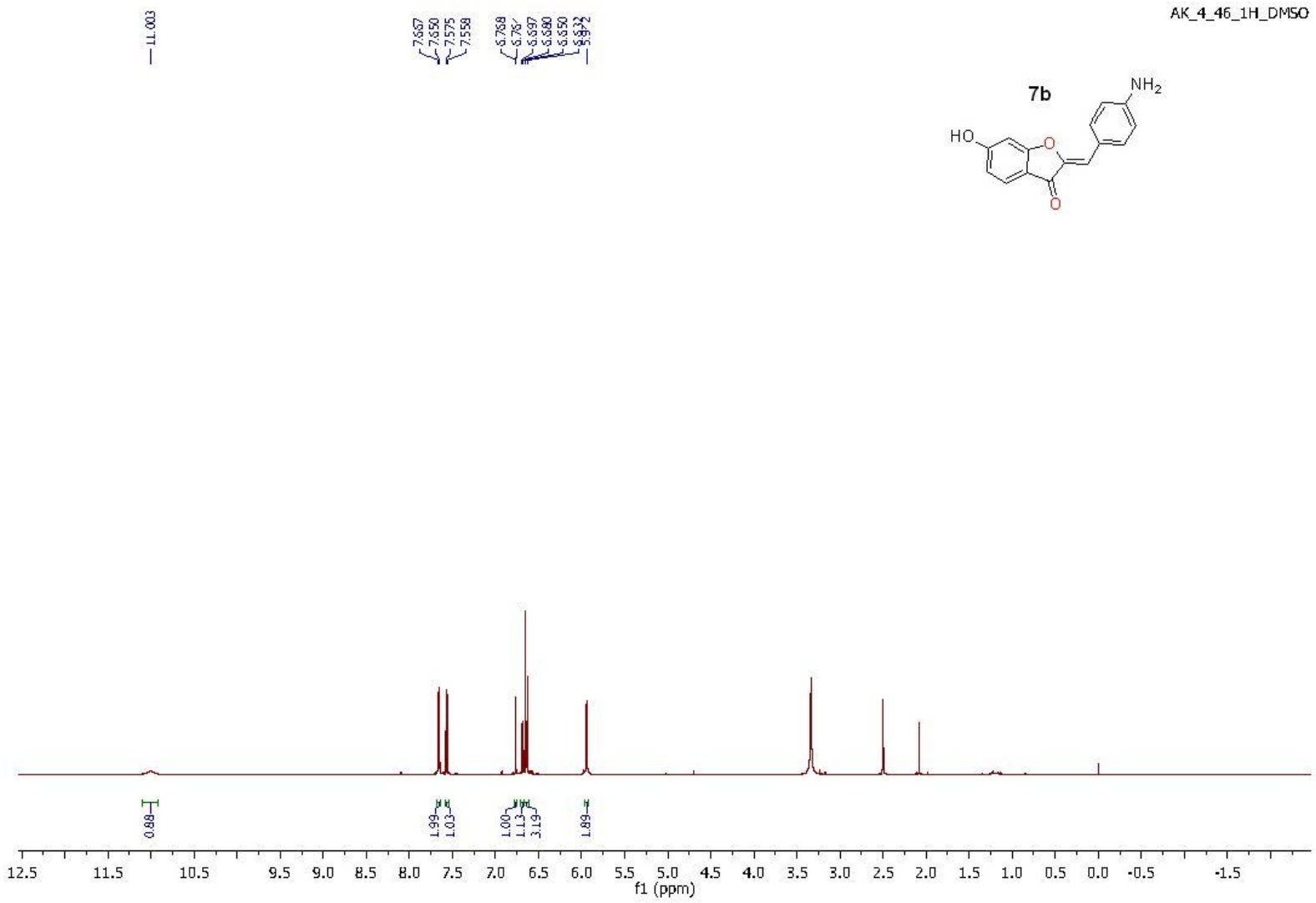
7a

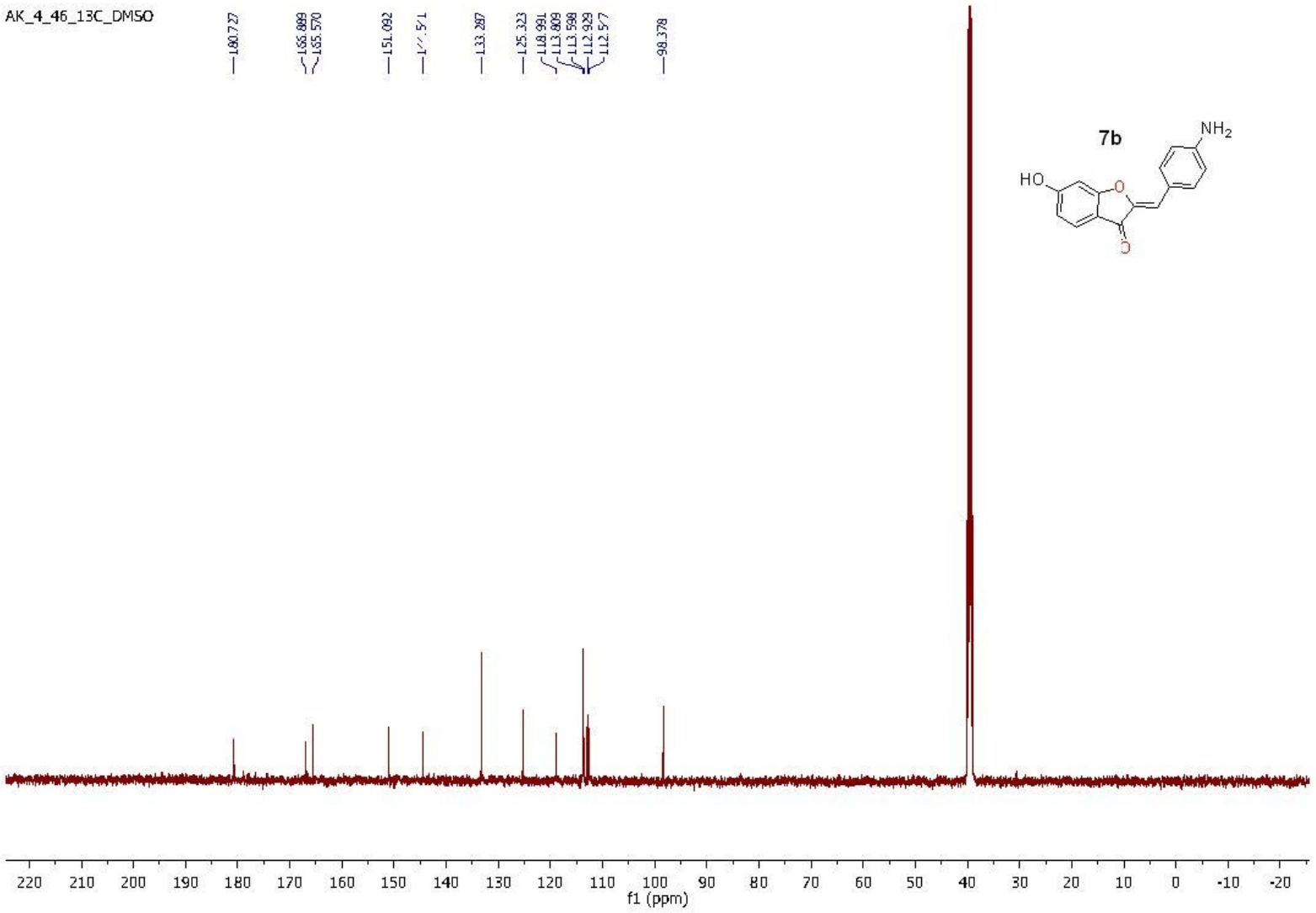


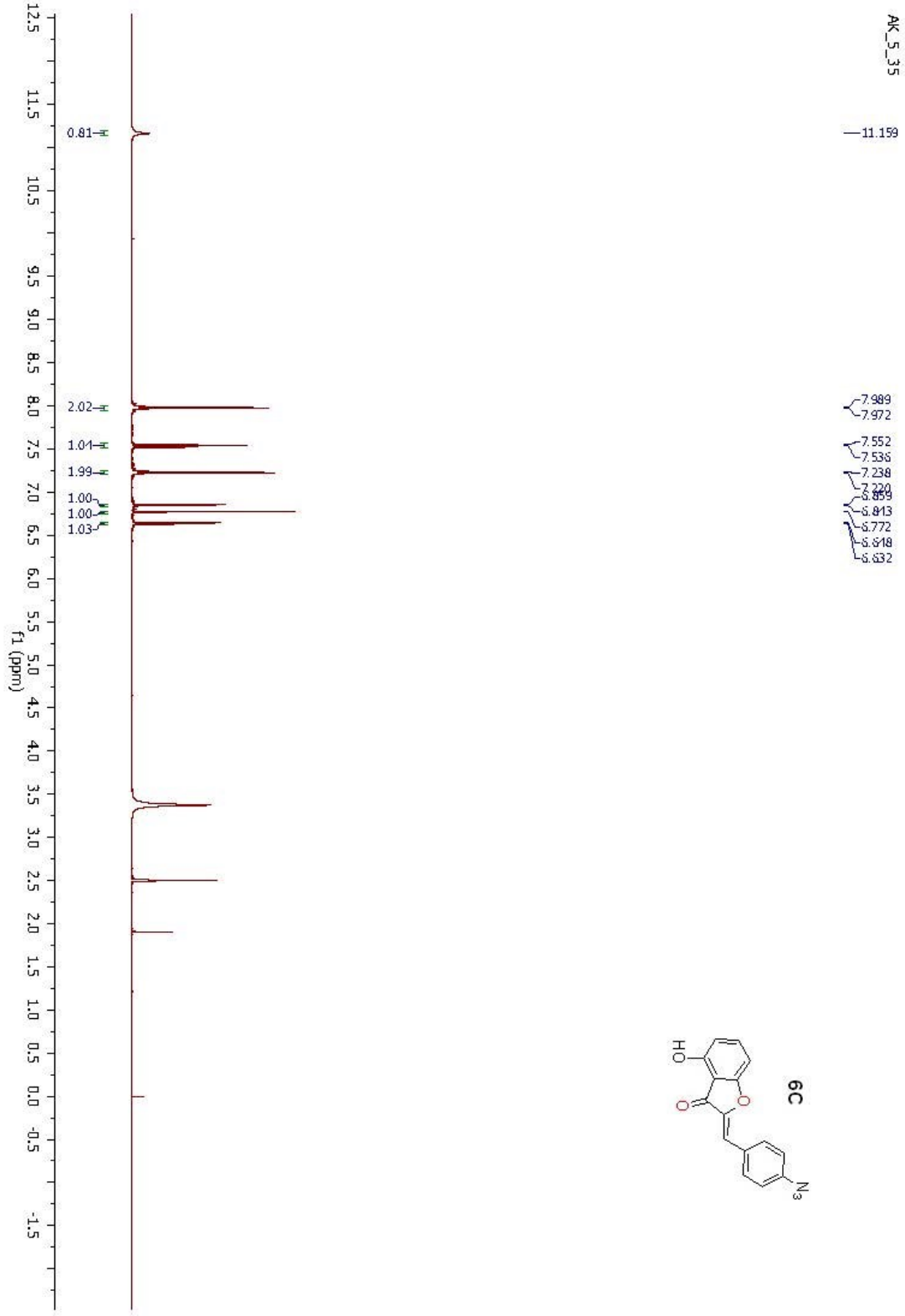

AK_3_109_2_13C
184.119
165.619
148.713
145.373
136.276
133.877
124.527
123.168
122.532
122.336
115.057
114.789
112.941
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
7a
O
O
NH2

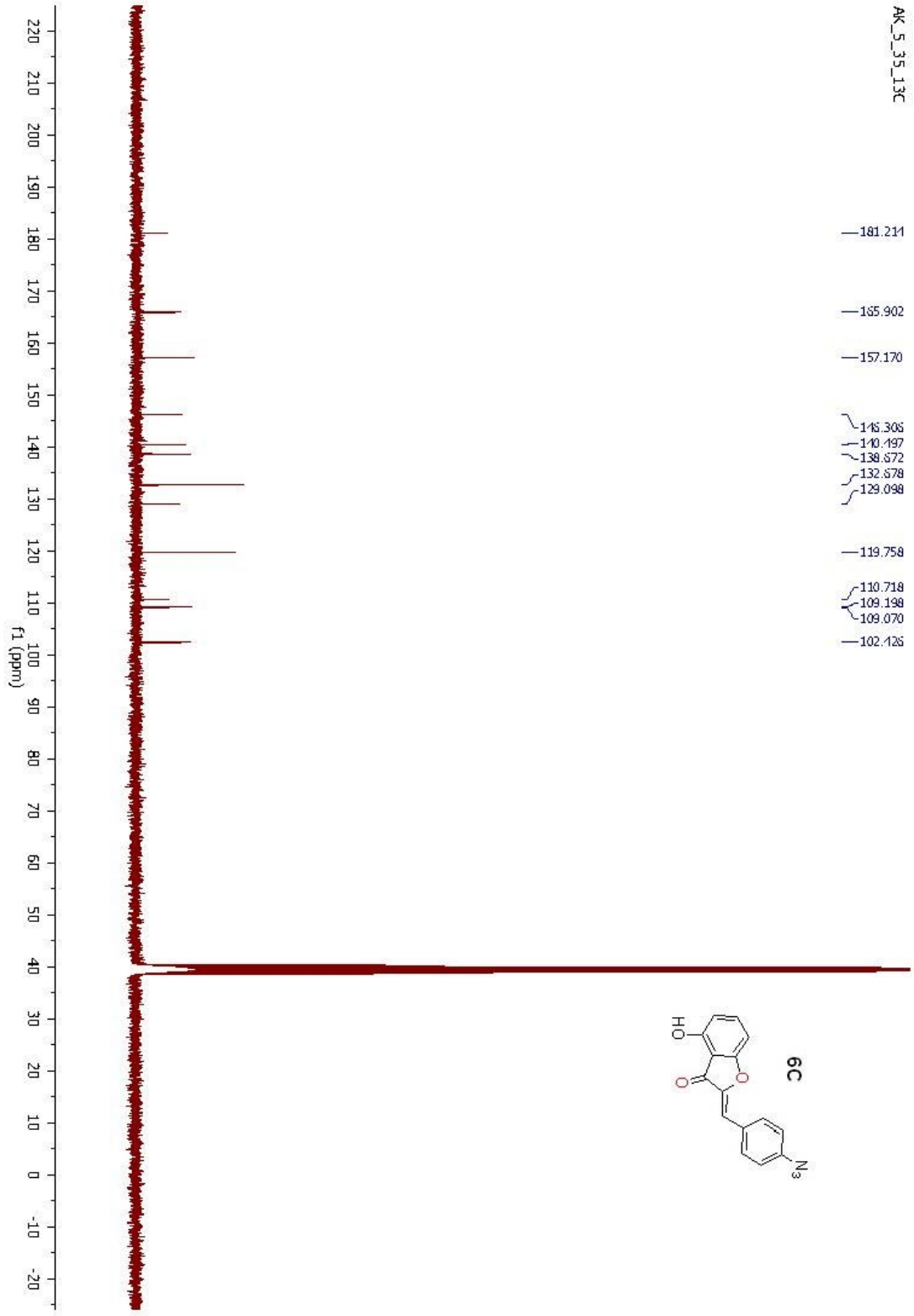

AK_5_33_1H
11.229
8.000
7.983
7.636
7.619
7.245
7.229
6.807
5.797
5.790
5.733
5.730
5.717
5.713
HO
O
O
N3
6b
0.93
2.02
0.98
1.92
0.88
0.91
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)

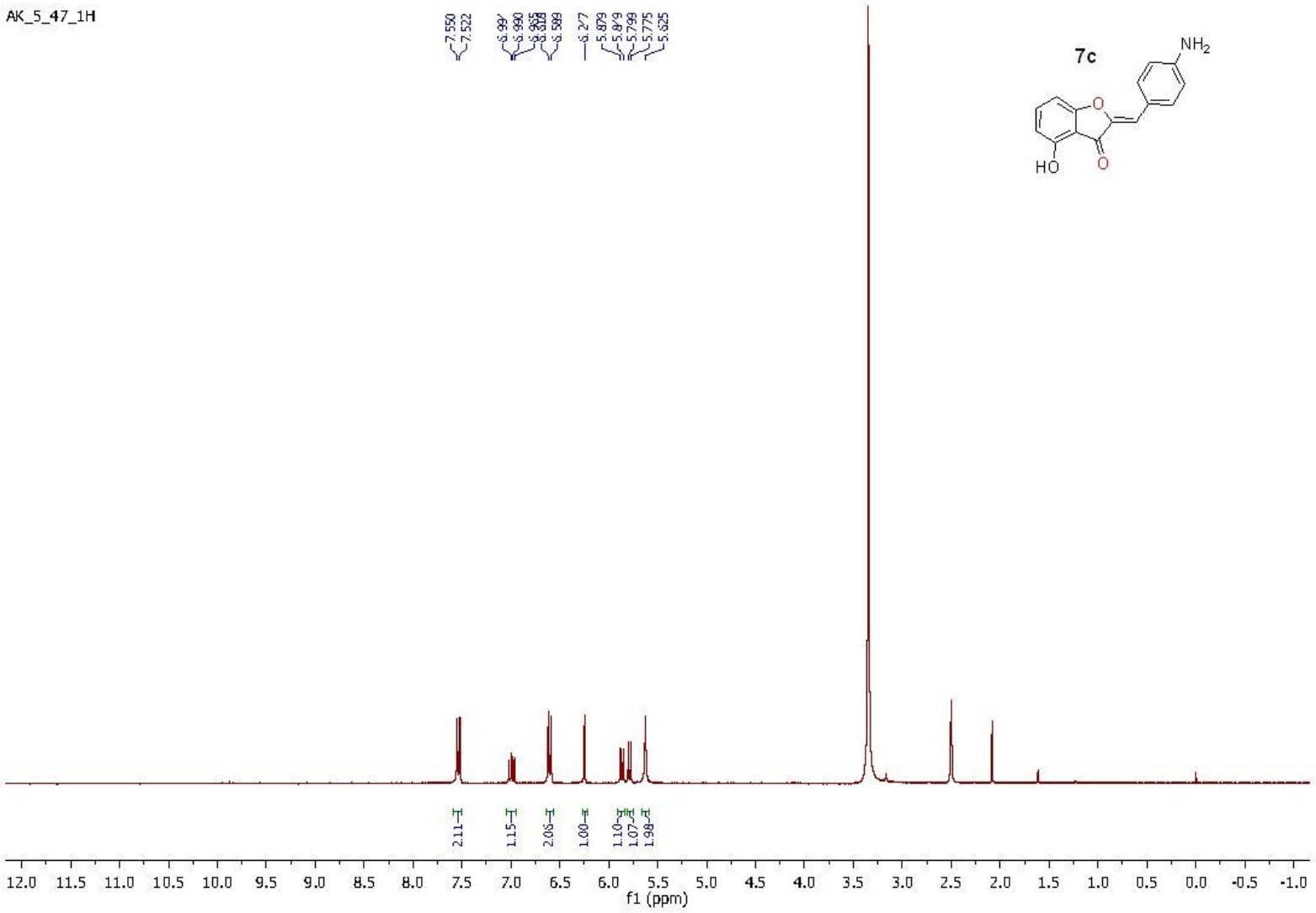

AK_5_33_13C
181.255
167.773
166.513
147.097
140.781
132.588
128.971
125.902
119.657
113.053
112.781
109.555
98.580
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
HO
O
O
N3
6b

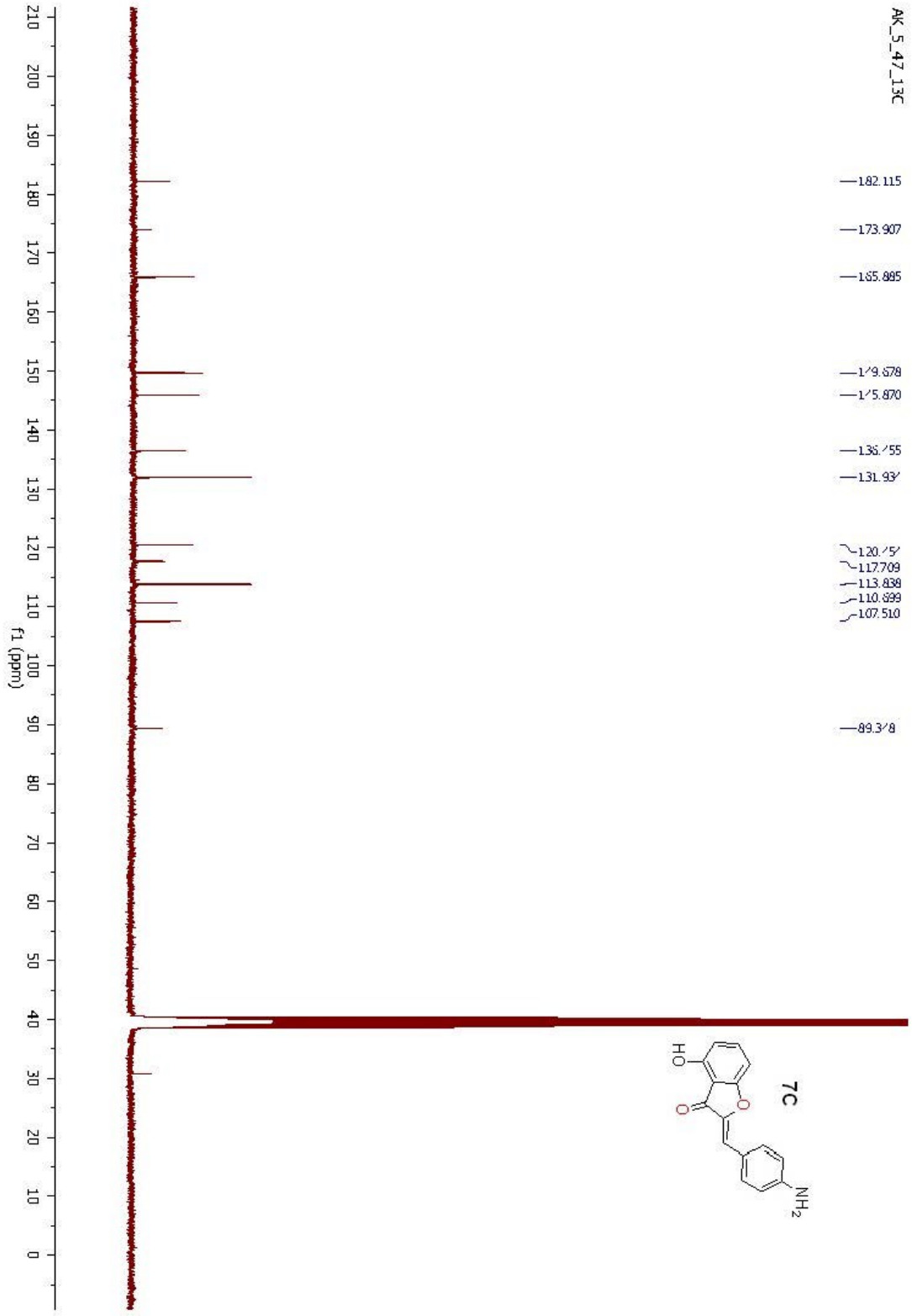

AK_4_46_1H_DMSO
11.003
7.667
7.650
7.575
7.559
6.768
5.787
5.697
5.680
5.650
5.633
5.622
7b
NH2
HO
O
O
0.88
1.99
1.03
1.00
1.13
3.19
1.89
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)


AK_4_46_13C_DMSO
180.727
165.889
165.570
151.092
133.287
125.323
118.991
113.809
113.598
112.929
112.577
98.378
7b
NH2
HO
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

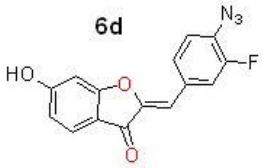

AK_5_35
11.159
7.989
7.972
7.552
7.536
7.238
7.220
6.859
6.843
6.772
6.618
6.632
0.81
2.02
1.01
1.99
1.00
1.00
1.03
f1 (ppm)
HO
O
O
N3
6C

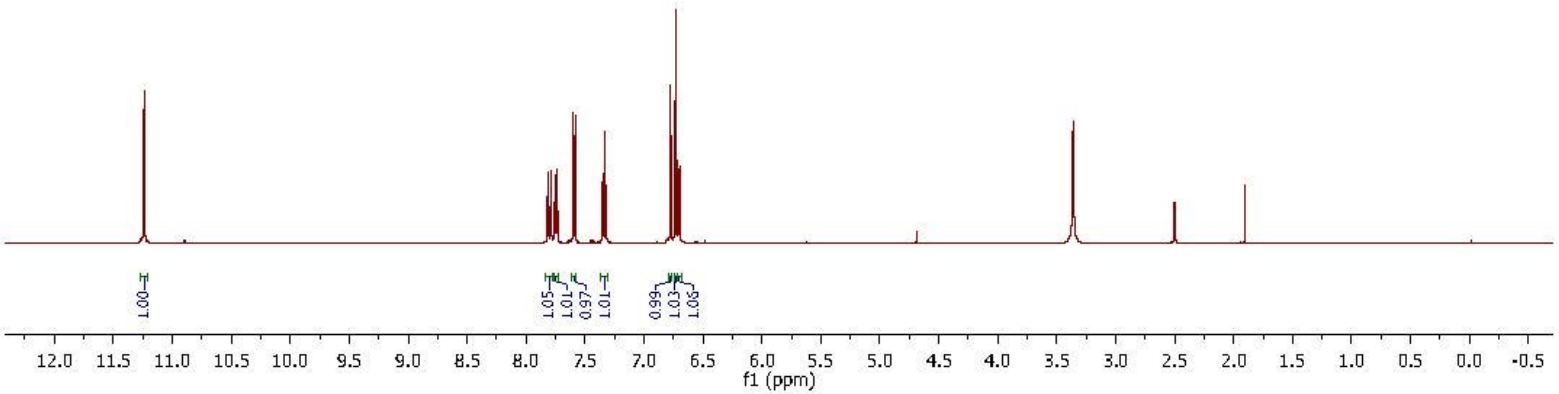

AK_5_35_13C
181.214
165.902
157.170
146.306
140.497
138.672
132.578
129.098
119.758
110.718
109.198
109.070
102.426
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
HO
O
O
N3
6C

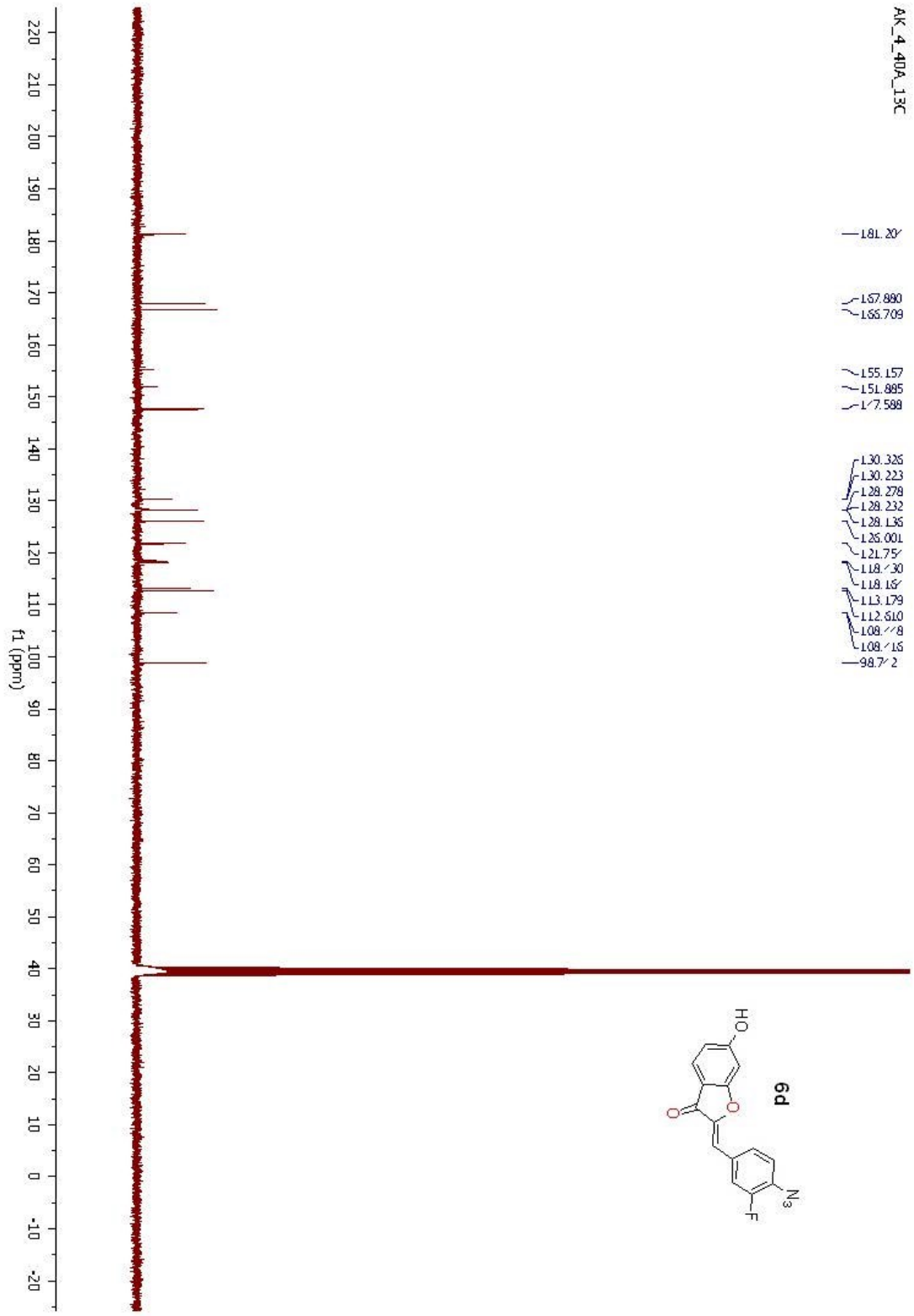

AK_5_47_1H
7.550
7.522
6.997
6.990
6.509
6.277
5.879
5.879
5.799
5.775
5.625
7c
NH2
O
HO
O
2.11
1.15
2.06
1.00
1.10
1.07
1.98
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


AK_5_47_13C
182.115
173.907
165.885
149.678
145.870
136.755
131.937
120.725
117.709
113.838
110.899
107.510
89.378
f1 (ppm)
HO
O
O
NH2
7C

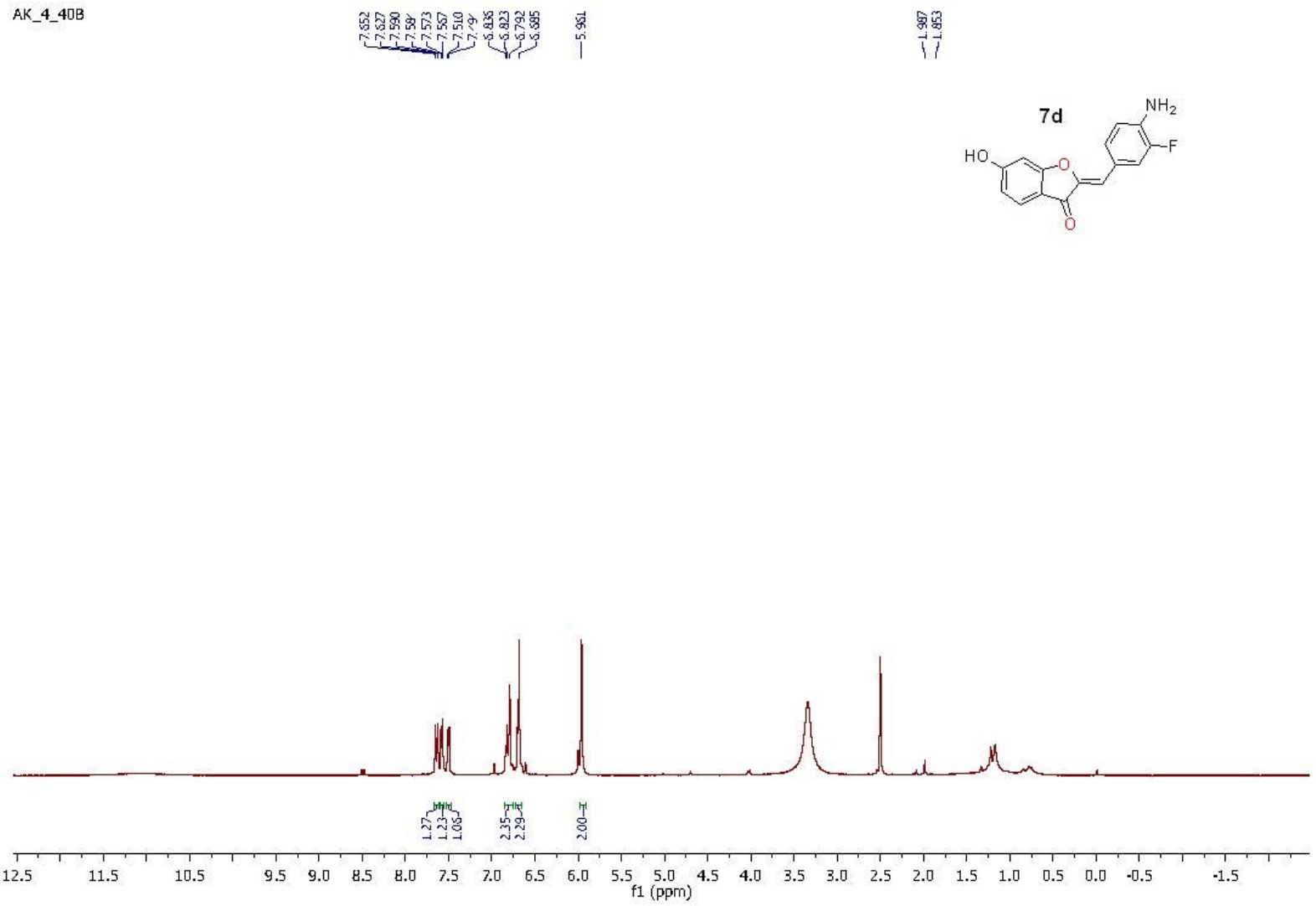
AK_4_40A

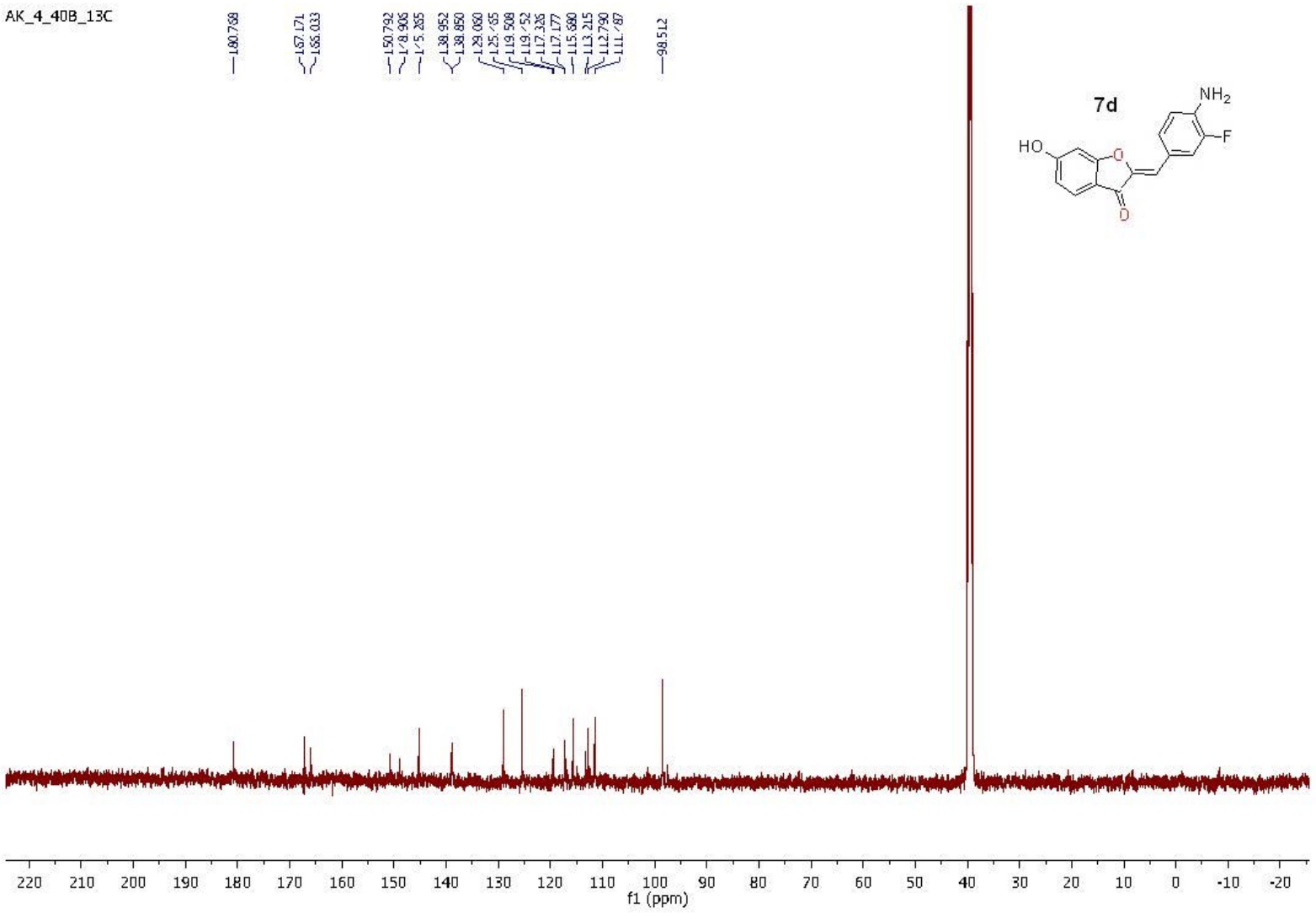

6d
HO
O
O
N3
F

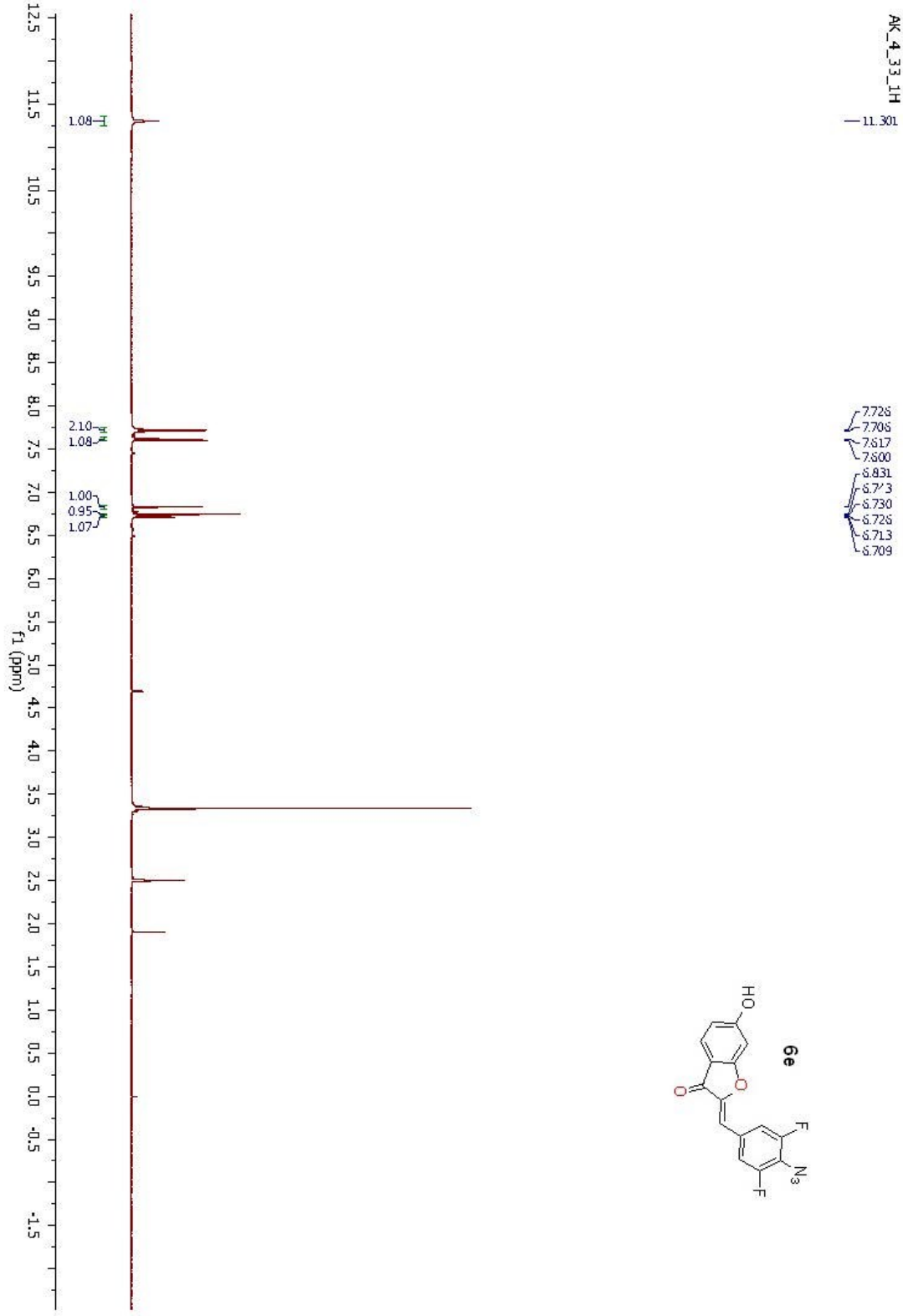

1.00
1.05
1.01
0.97
1.01
0.99
1.03
1.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

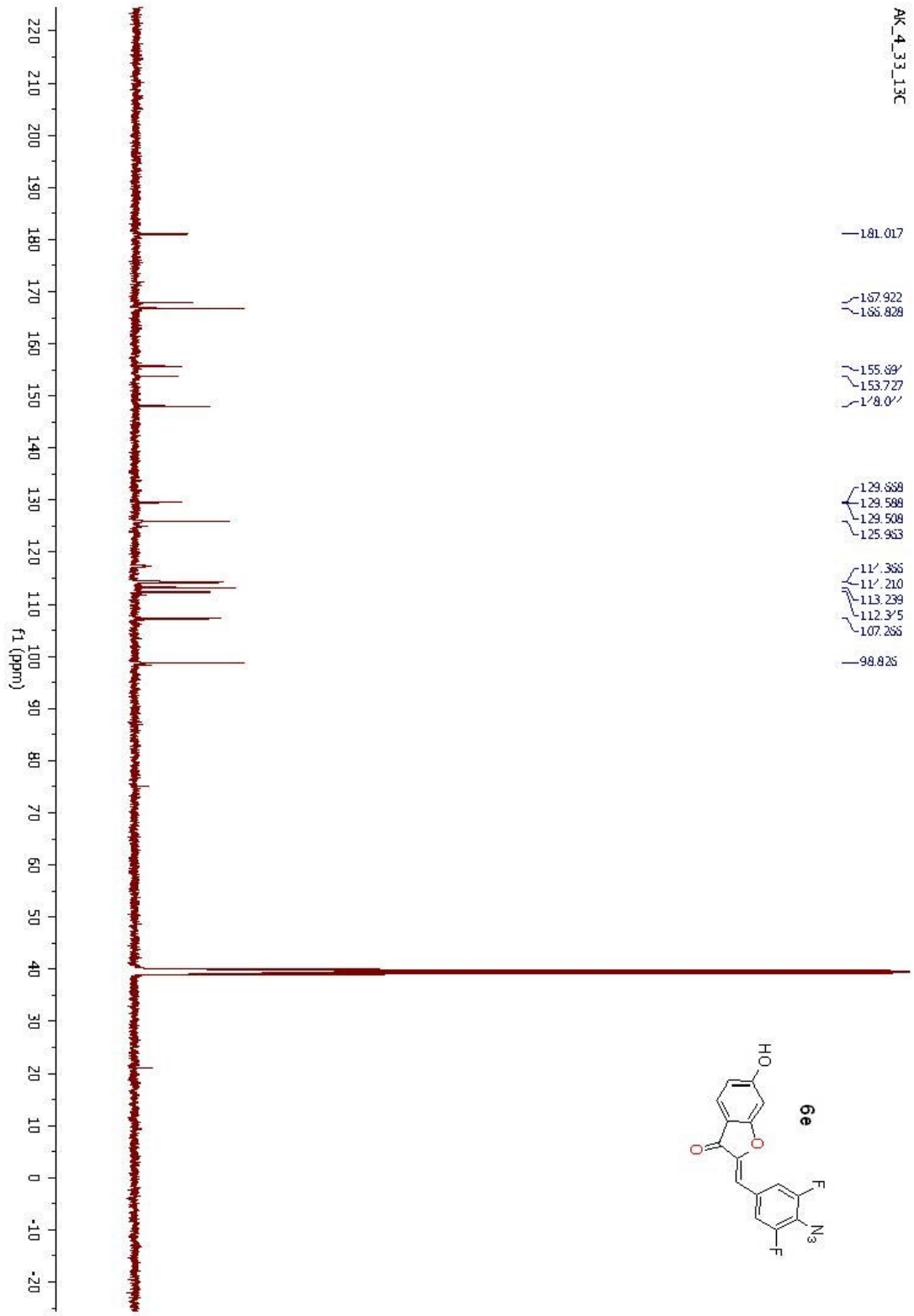

AK_4_40A_13C
181.20
167.880
166.709
155.157
151.895
147.589
130.326
130.223
128.278
128.232
128.136
126.001
121.757
118.730
118.167
113.179
112.510
109.778
109.716
98.772
HO
O
O
F
N3
6d
f1 (ppm)

AK_4_40B


7.652
7.627
7.590
7.587
7.573
7.557
7.510
7.479
6.836
6.823
6.792
6.685
5.961
1.997
1.853
7d
NH2
F
HO
O
O
1.27
1.23
1.06
2.35
2.29
2.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)


AK_4_40B_13C
180.759
157.171
155.033
150.792
148.906
145.265
138.952
138.850
129.060
125.455
119.508
119.452
117.326
117.177
115.680
113.215
112.790
111.487
98.512
7d
NH2
F
HO
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


AK_4_33_1H
11.301
7.726
7.706
7.617
7.600
6.831
6.713
6.730
6.726
6.713
6.709
1.08
2.10
1.08
1.00
0.95
1.07
f1 (ppm)
HO
O
O
F
N3
F
6e


AK_4_33_13C
181.017
167.922
166.828
155.697
153.727
148.077
129.868
129.588
129.508
125.963
117.365
117.210
113.239
112.375
107.285
98.826
f1 (ppm)
6e

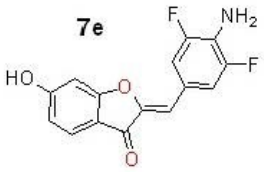
AK_5_39

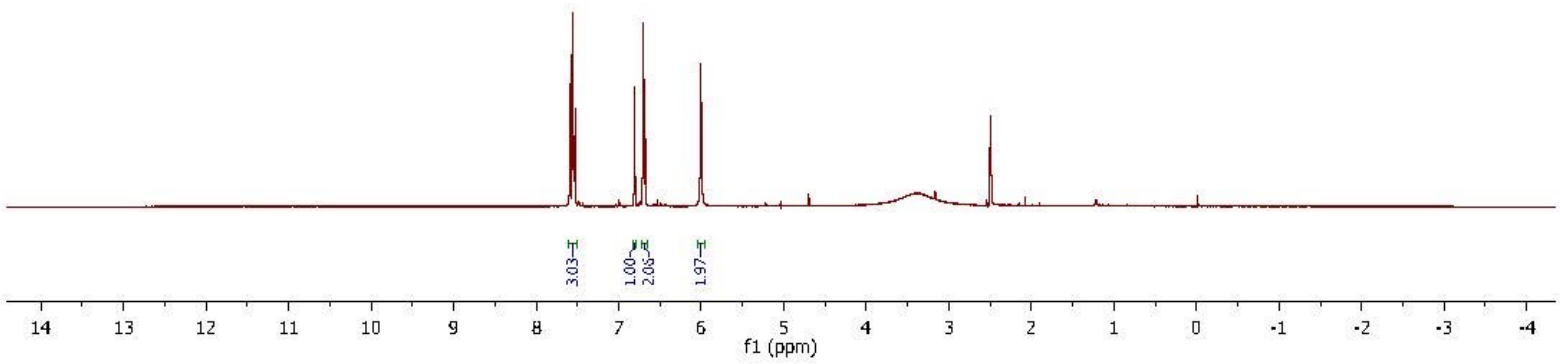
11.375

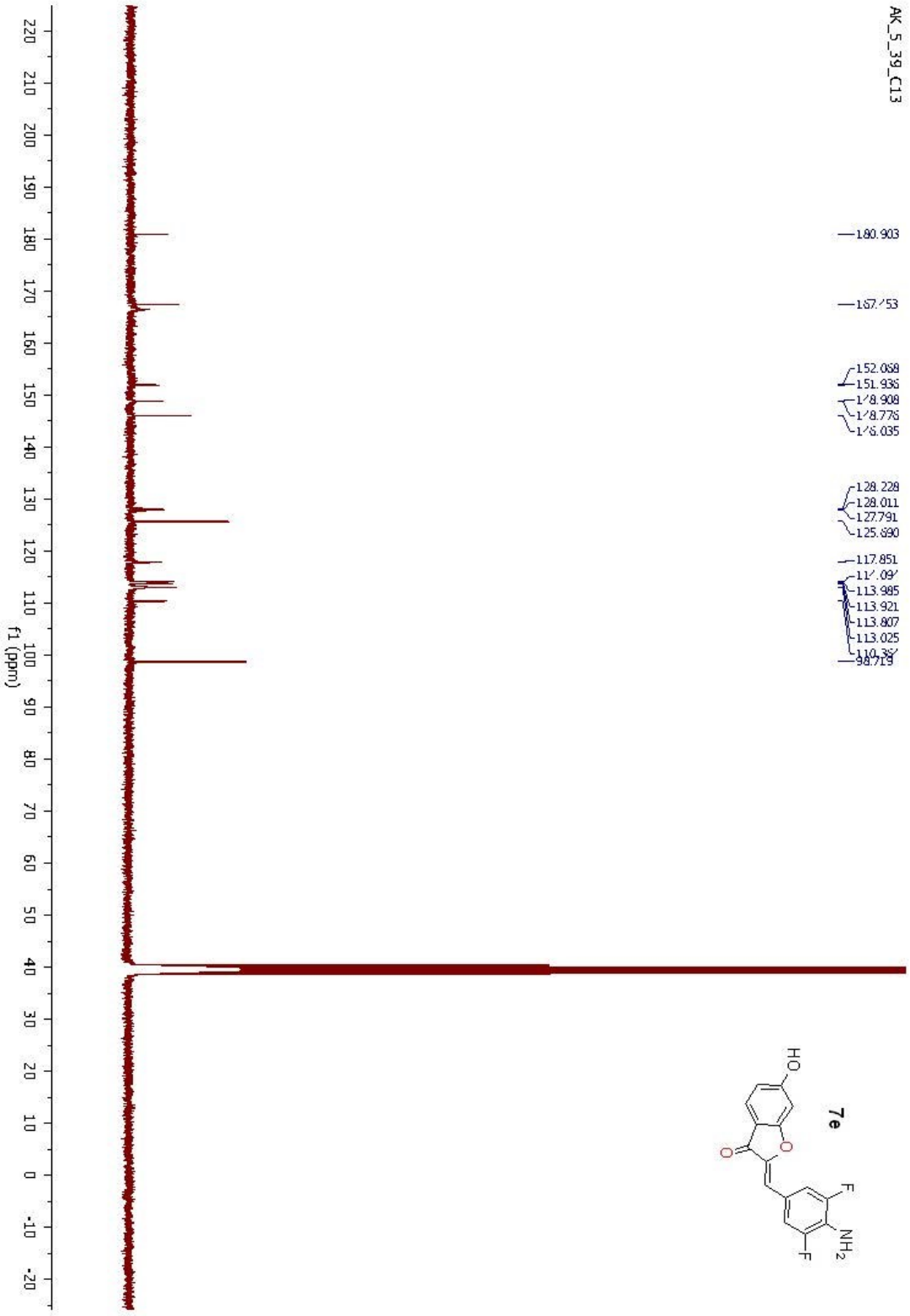
7.593
7.587
7.555
7.536
7.528

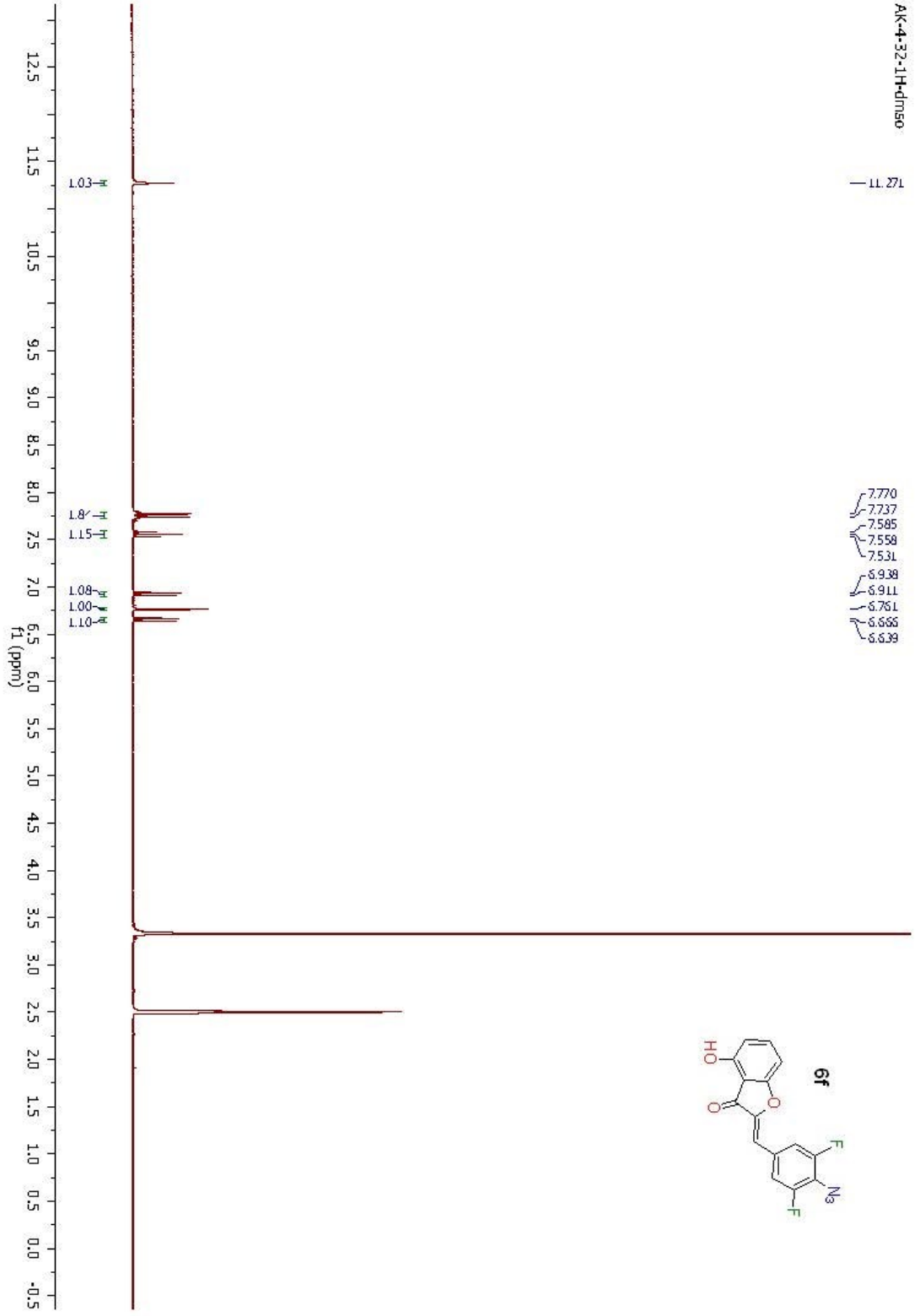
6.811
6.805
5.710

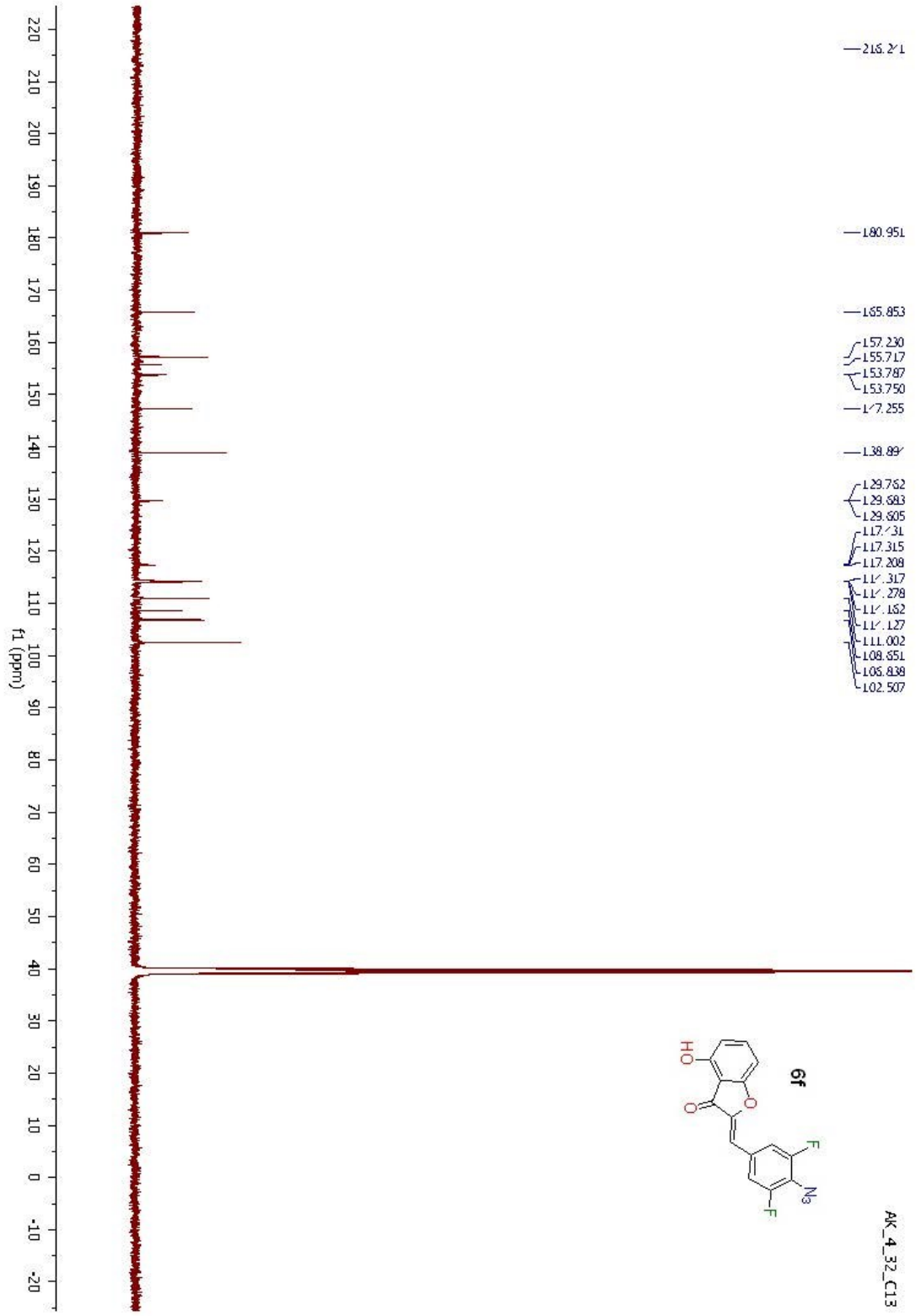
7e



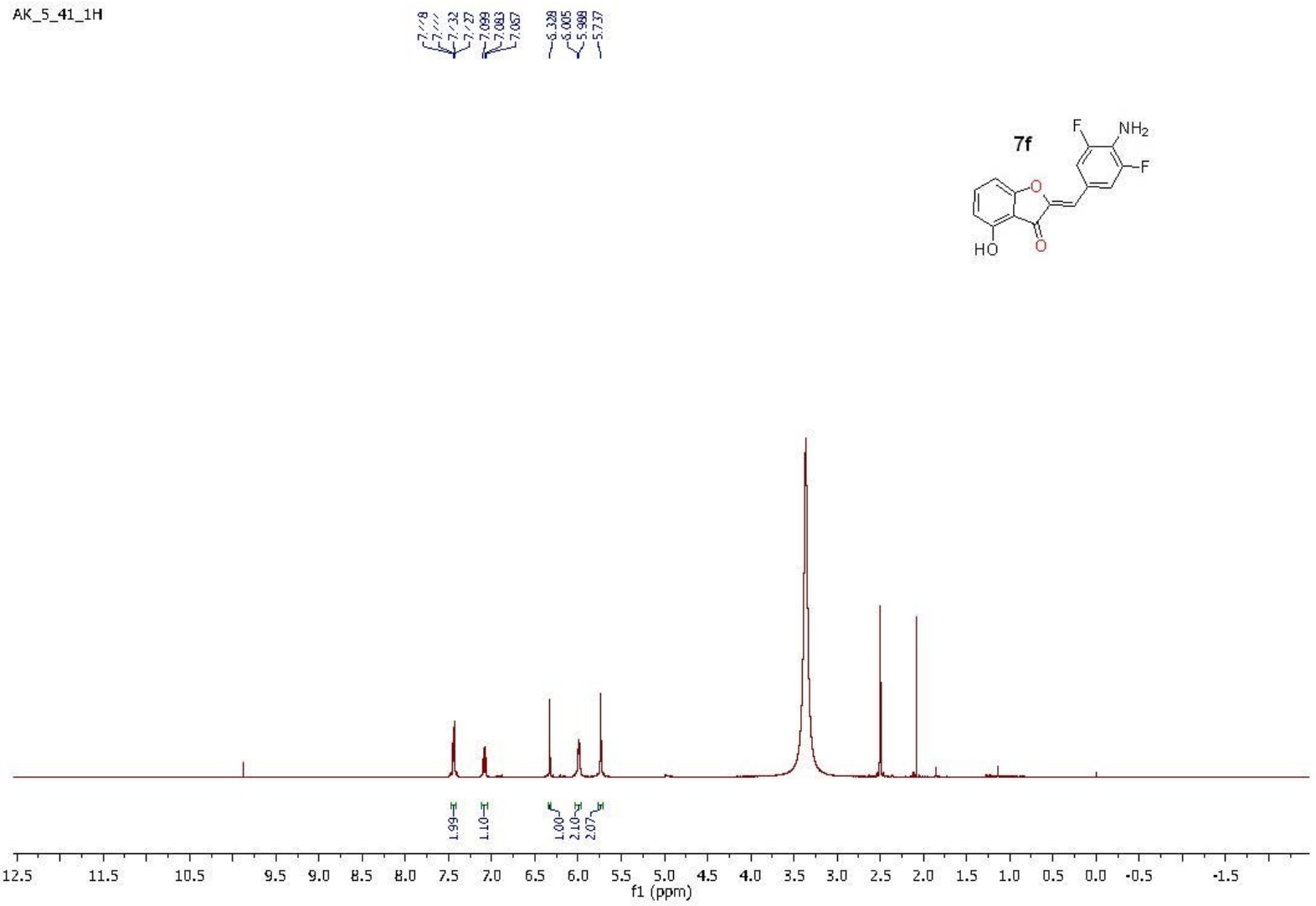


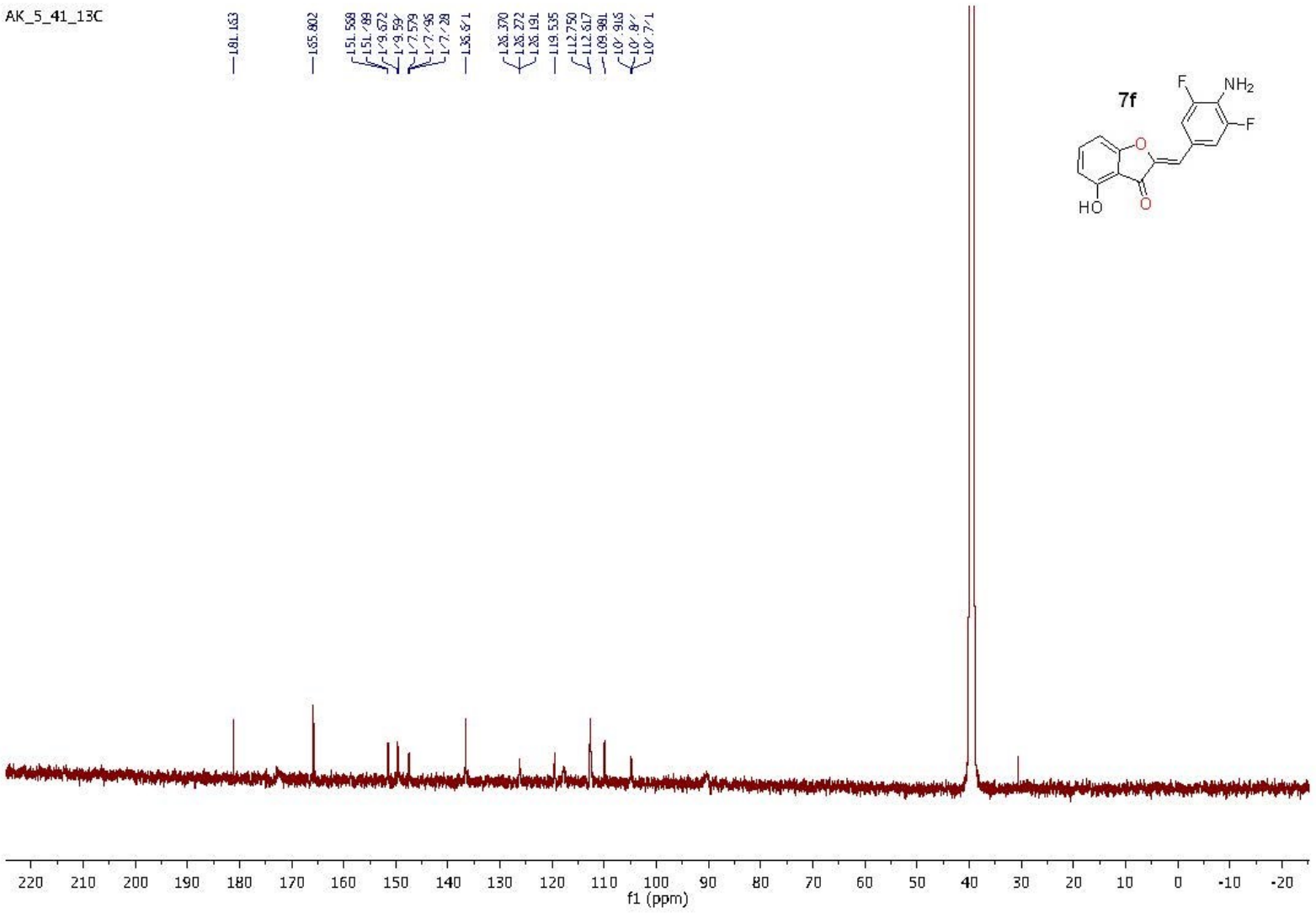

AK_5_39_C13
180.903
167.753
152.058
151.936
148.908
148.776
146.035
128.228
128.011
127.791
125.690
117.851
113.985
113.921
113.807
113.025
98.719
f1 (ppm)
7e


AK-4-32-1H-dmso
11.271
7.770
7.737
7.585
7.558
7.531
6.938
6.911
6.761
6.666
6.639
1.03
1.87
1.15
1.08
1.00
1.10
f1 (ppm)
HO
O
O
F
N3
F
6f


216.271
180.951
165.853
157.230
155.717
153.787
153.750
147.255
138.897
129.762
129.583
129.605
117.431
117.315
117.208
117.317
117.278
117.152
117.127
111.002
108.651
106.838
102.507
f1 (ppm)
6f
AK_4_32_C13

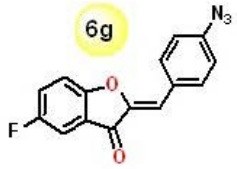
AK_5_41_1H

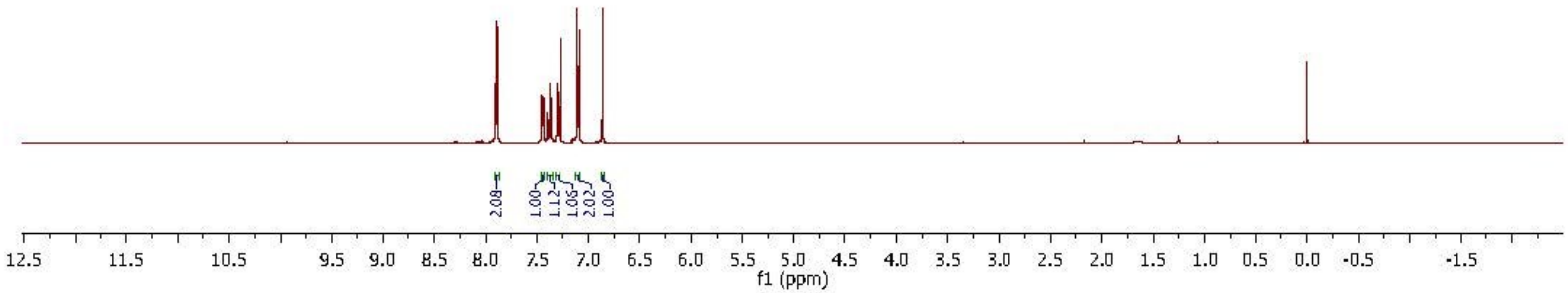

7.718
7.717
7.732
7.727
7.099
7.083
7.057
6.328
6.005
5.988
5.737
7f
F
NH2
F
O
HO
O
1.99
1.10
1.00
2.10
2.07
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)

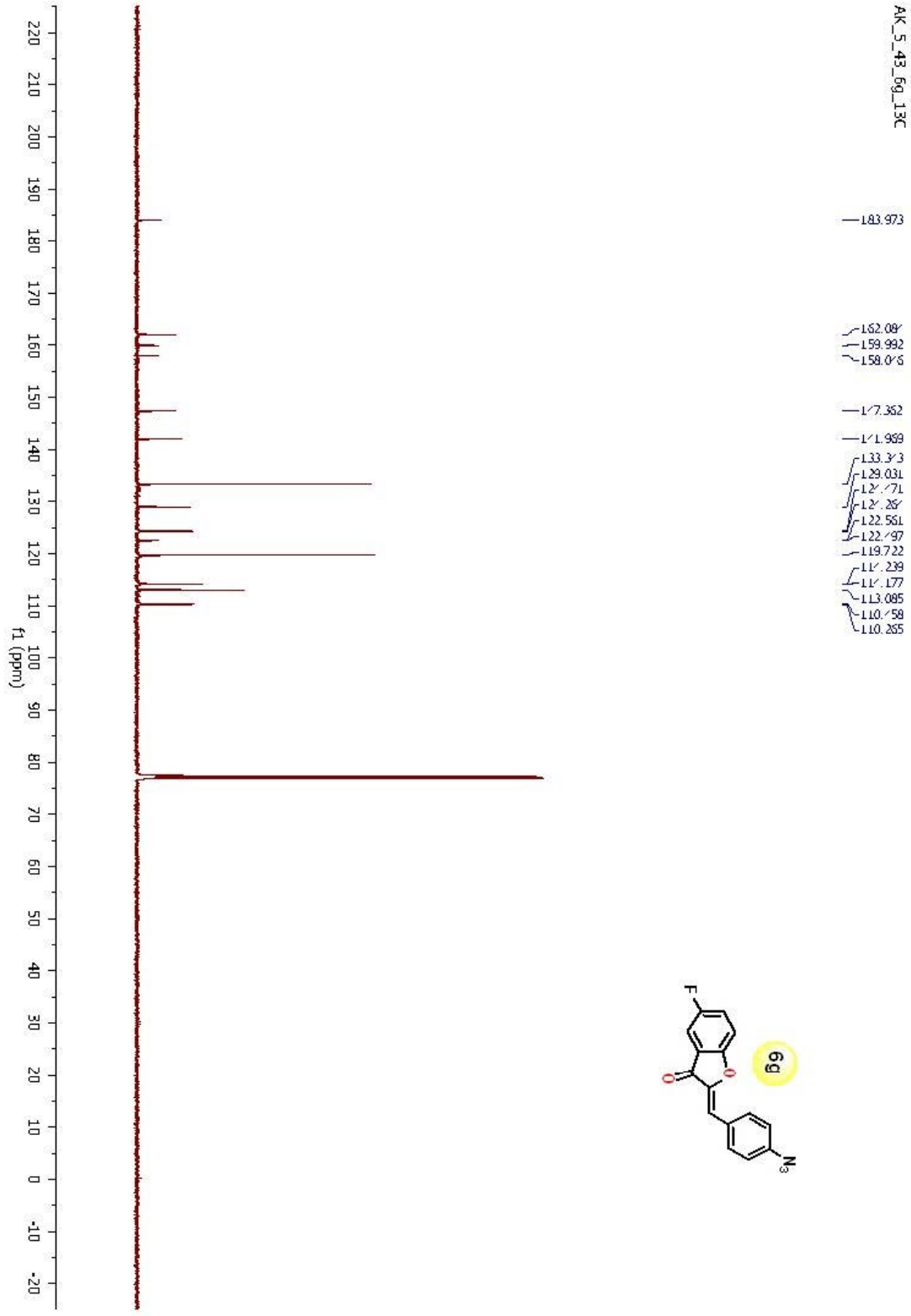

AK_5_41_13C
181.153
155.802
151.569
151.489
149.672
149.597
147.579
147.496
147.428
136.671
125.370
125.272
125.191
119.535
112.750
112.617
109.981
109.916
109.847
109.771
7f
F
NH2
F
O
HO
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

AK_5_43_6g_1H

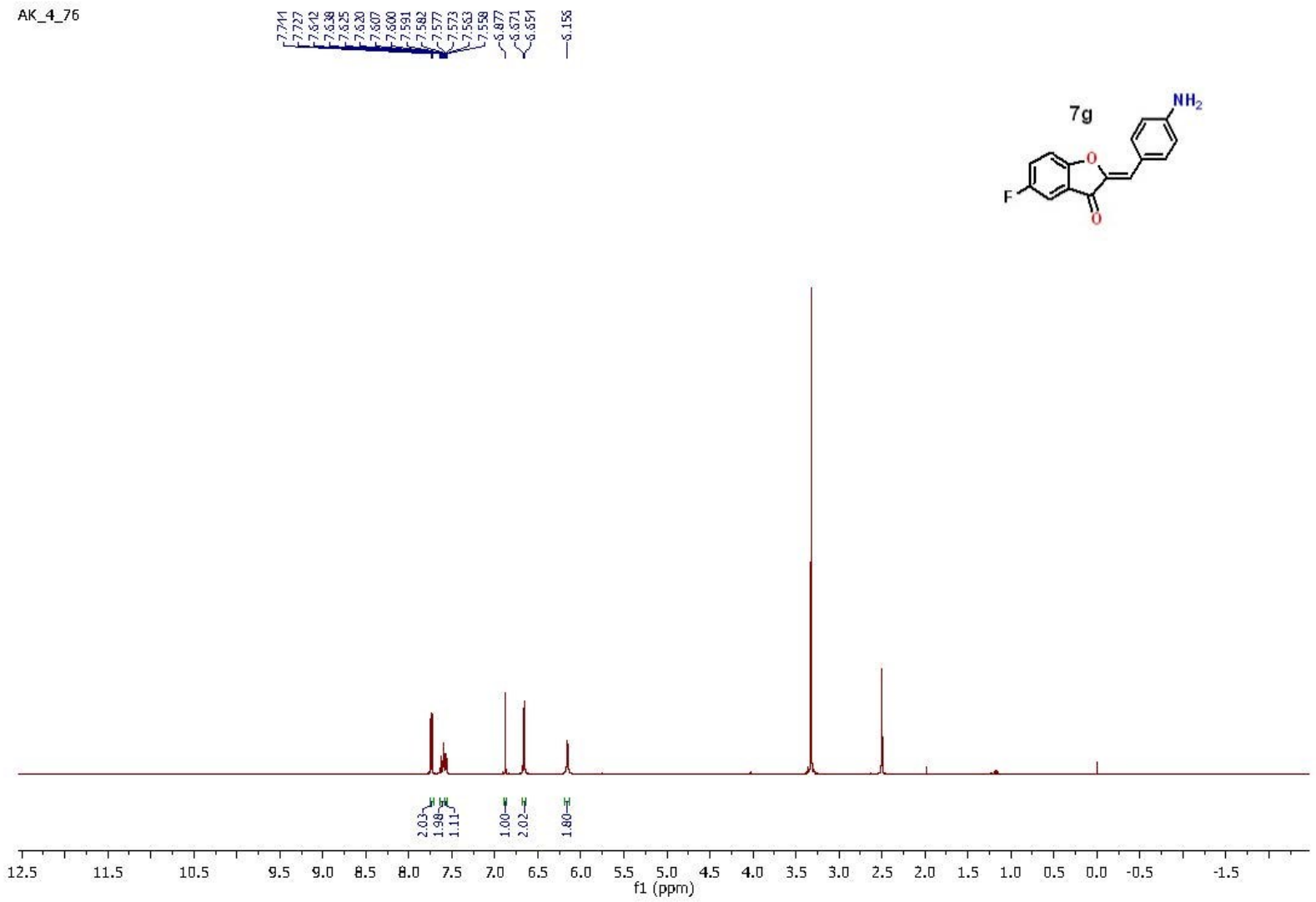

7.902
7.885
7.755
7.751
7.737
7.399
7.393
7.382
7.376
7.359
7.307
7.300
7.289
7.282
7.107
7.087
6.855

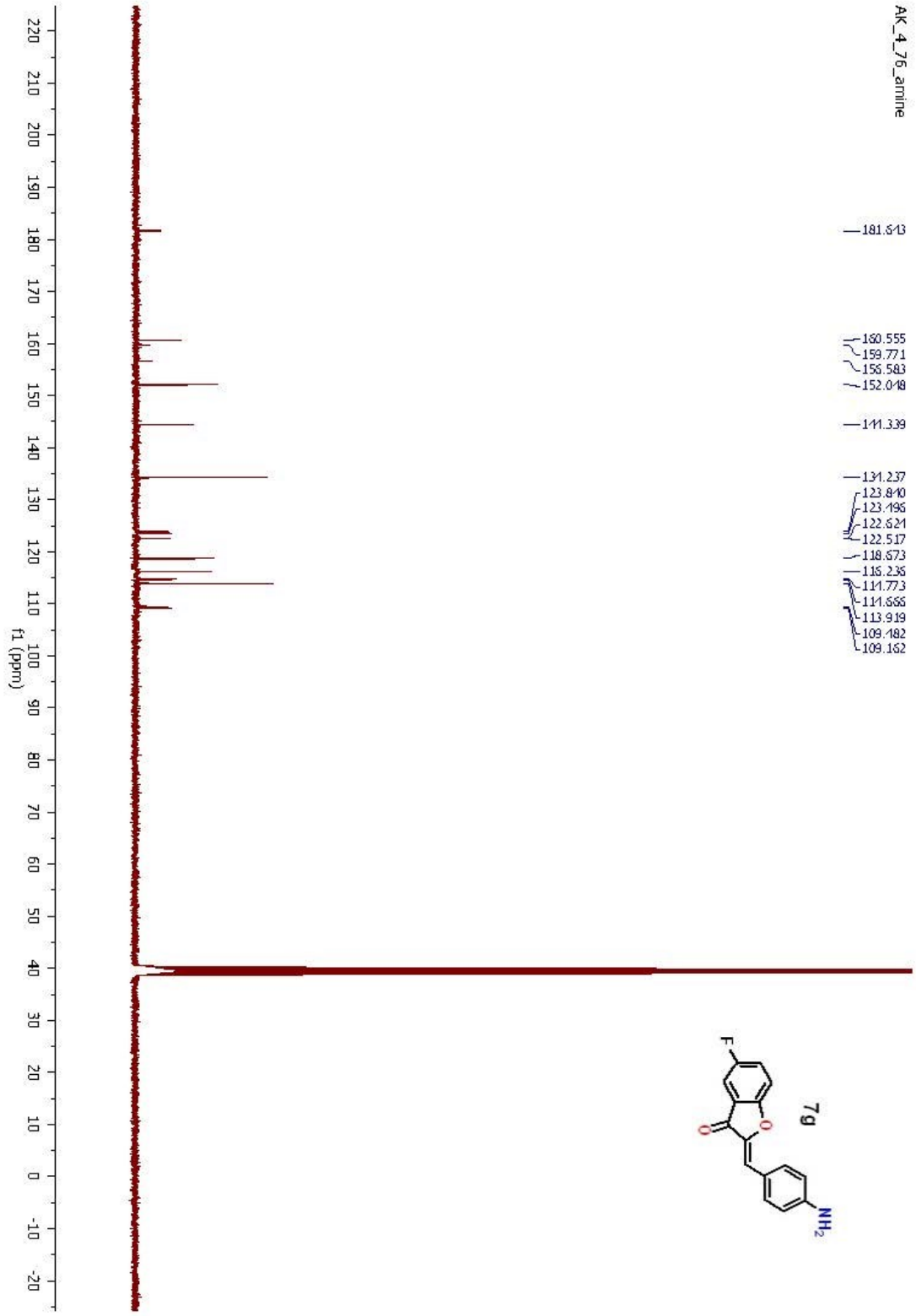

6g
N3
O
F
O


2.08
1.00
1.12
1.05
2.02
1.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)


AK_5_43_6g_13C
183.973
162.09
159.992
158.076
147.352
141.959
133.373
129.031
127.471
127.265
122.561
122.497
119.722
117.239
117.177
113.085
110.758
110.265
6g
F
O
O
N3
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

AK_4_76


7.741
7.727
7.642
7.638
7.625
7.620
7.607
7.600
7.591
7.582
7.577
7.573
7.563
7.558
6.677
6.671
6.654
6.156
7g
NH2
O
F
O
2.03
1.98
1.11
1.00
2.02
1.80
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.5
f1 (ppm)


AK_4_76_amine
181.643
160.555
159.771
156.583
152.048
141.339
131.237
123.840
123.496
122.624
122.517
118.573
116.236
114.773
114.566
113.919
109.482
109.162
7g
F
O
O
NH2
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20