New Applications of Heteroarylzinc Nucleophiles

By

James Robert Colombe

A.B. Chemistry
Harvard College (2010)

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the
Massachusetts Institute of Technology

September 2015

Signature of Author: Signature redacted
Department of Chemistry
August 25, 2015

Certified by: Signature redacted
Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Accepted by: Signature redacted
Robert W. Field
Haslam and Dewey Professor of Chemistry
Chairman, Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Signature redacted

Professor Mohammad Movassaghi: ___ _____
Thesis Committee Chair

Signature redacted

Professor Stephen L. Buchwald: _____ _____
Thesis Supervisor

Signature redacted

Professor Jeremiah A. Johnson: _ _____

New Applications of Heteroarylzinc Nucleophiles

By

James Robert Colombe

Submitted to the Department of Chemistry on August 28, 2015
in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy
in Organic Chemistry at the Massachusetts Institute of Technology

Abstract

This thesis describes the development and application of chemical methodologies for the use of 2-pyridyl and other aryl and heteroaryl organometallic nucleophiles. Aiming for a practical and effective alternative to 2-pyridylboron reagents, a solid 2-pyridylzinc compound was prepared and is described in Chapter 1. Chapter 2 details a new approach to the synthesis of sulfonamides using aryl and heteroaryl organozinc nucleophiles. Chapter 3 describes ongoing collaborative efforts to discover new malaria therapeutics where the synthetic method developed in Chapter 2 facilitated access to targeted compounds.

Chapter 1. The Synthesis of a Solid, Air-Stable 2-Pyridylzinc Reagent and its Use in Negishi Cross-Coupling Reactions.

As an alternative to unstable or unreliable 2-pyridylboron reagents, a solid, air-stable 2-pyridylzinc reagent was developed. Using 1,4-dioxane as an additive enabled a 2-pyridylzinc concentrate as a free-flowing solid that was not deliquescent. The reagent can be manipulated in air and is a competent nucleophile in Negishi cross-coupling reactions. The reagent can also be stored in paraffin wax capsules for significant added stability.

Chapter 2. Synthesis of Heteroaryl Sulfonamides from Organozinc Reagents and 2,4,6-Trichlorophenyl Chlorosulfate.

A method for the preparation of aryl and heteroaryl sulfonamides using 2,4,6-trichlorophenyl chlorosulfate (TCPC) is described. The reaction of 2-pyridylzinc reagents with TCPC resulted in 2,4,6-trichlorophenyl (TCP) pyridine-2-sulfonates, and the parent pyridine-2-sulfonate was shown to react with amines. Less electron-rich aryl- and heteroarylzinc reagents reacted with TCPC to afford sulfonyl chlorides that were converted *in situ* to sulfonamides.

Chapter 3. Structure-Activity Relationship Studies on Selective Inhibitors of *Plasmodium Falciparum* Growth.

Two classes of compounds that selectively inhibit *P. Falciparum* were identified by the Lindquist Lab at MIT through the MLPCN compound library and high-throughput screening facilities at the Broad Institute. Using the sulfonamide synthesis methodology described in Chapter 2 and other approaches, analogs of these compounds were prepared and tested using a yeast assay in collaboration with the Lindquist lab at MIT and a *P. falciparum* assay in collaboration with the Wirth lab at the Harvard T.H. Chan School of Public Health.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgements

This thesis is dedicated to my mother, who died of cancer on May 28, 2012.

Preface

This thesis has been adapted from the following published articles co-written by the author:

Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. Synthesis of Solid 2-Pyridylzinc Reagents and Their Application in Negishi Reactions. *Org. Lett.* **2013**, *15*, 5754-5757.

Colombe, J. R.; Debergh, J. R.; Buchwald, S. L. Synthesis of Heteroaryl Sulfonamides from Organozinc Reagents and 2,4,6-Trichlorophenyl Chlorosulfate. *Org. Lett.* **2015**, *17*, 3170-3173.

Sather, A. C.; Lee, H. G.; Colombe, J. R.; Zhang, A.; Buchwald, S. L. Dosage Delivery of Sensitive Reagents Enables Glove-Box-Free Synthesis. *Nature* **2015**, *524*, 208-211.

Respective Contributions

This thesis contains work that is the result of collaborative efforts between the author and colleagues at MIT, Harvard, and Ludwig-Maximilians-Universität München. The specific contributions of the author and the collaborators are detailed below.

The solid 2-pyridylzinc chloride dioxanate studies in Chapter 1 were done in parallel with studies on solid 2-pyridylzinc pivalates in the Knochel group at Ludwig-Maximilians-Universität München in München, Germany. Although the two groups communicated regularly, the dioxanate work was separate from the pivalate work and was performed solely by the author. The pivalate work in the joint publication was performed solely by Dr. Sebastian Bernhardt and Dr. Christos Stathakis.

The wax encapsulation work was done in collaboration with Dr. Aaron Sather, Dr. Hong Geun Lee, and Annie Zhang, an MIT undergraduate. Drs. Sather and Lee invented the capsules, and the author applied this technique to the solid 2-pyridylzinc dioxanate. Other experiments in the joint publication on palladium-catalyzed nucleophillic fluorination and amination were performed by Dr. Aaron Sather, Dr. Hong Geun Lee, and Annie Zhang.

The work in Chapter 2 was a collaborative effort between Dr. John Robb Debergh and the author. Dr. Debergh performed initial experiments for this project.

The work in Chapter 3 is part of an ongoing collaborative effort between Dr. Lauren Pepper, Dr. Catherine McLellan, Dr. Luke Whitesell, Professor Susan Lindquist, Dr. Amanda Lukens, Professor Dyann Wirth, and the author. Dr. Pepper designed the project, including the yeast assay and high-throughput screen, and collected data from the yeast assay. Dr. Lukens collected data from the parasite assay. Dr. McLellan is currently continuing the project, performing further biological experiments. Except for the lead compounds from the MLPCN screen, the author designed and prepared the compounds described in this chapter.

Table of Contents

Introduction

Wöhler's 1828 synthesis of urea[1] is a landmark in chemistry, demonstrating that organic and biological molecules could in fact be prepared in a laboratory and marking the beginning of the modern history of organic synthesis.[2] In the spirit of Wöhler, the synthetic community has been and is still today driven to push the limits of preparative chemistry by devising elegant routes to increasingly complex molecules.[3] Besides academic interest in new structures, new modes of reactivity, and deep understandings of ubiquitous or useful chemistry, there are also powerful economic forces behind this trend. Modern pharmaceutical chemists – the major consumers of the research described in this thesis and the research that is generally performed in the Buchwald laboratory – constantly demand innovation in synthetic methodology, not only to increase the overall yield of desired organic transformations and add to the list of bond-forming processes in the synthetic repertoire, but also to increase the user-friendliness of these protocols. Drug discovery is extremely expensive ($800[4] to $1200 million[5] per drug), and the ability to prepare target molecules quickly and easily is an essential part of streamlining the process.[6] More than just a cost consideration at the corporate level, the efficiency and user-friendliness of reaction setups and product purifications directly affect the daily experience and productivity of practicing industrial chemists,[7] impacting decisions about which targets are prepared and which are not.

---

[1] Wöhler, F. *Annalen der Physik und Chemie* **1828**, *88*, 253–256.
[2] Nicolaou, K. C.; Sorensen, E. J. Introduction: Constructing the Molecules of Nature. *Classics in Total Synthesis*. VCH Publishers, Inc.: New York, NY, 1996; 2-17.
[3] Li, J.; Eastgate, M. D. *Org. Biomol. Chem.* **2015**, *13*, 7164-7176.
[4] DiMasi, J. A.; Hansen, R. W.; Grabowski, H. G. *J. Health Econ.* **2003**, *22*, 151-185.
[5] Adams, C. P.; Brantner, V. V. *Health Econ.* **2010**, *19*, 130–141.
[6] MacCoss, M.; Baillie, T. A. *Science* **2004**, *303*, 1810-1813.
[7] Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451-3479.

A central component of the modern user-friendly reaction arsenal is palladium-catalyzed cross-coupling methodology. Recognized with the 2010 Nobel Prize in chemistry, cross-coupling reactions and the biaryl compounds they typically form now appear frequently in medicinal chemistry and drug molecules. Among the most popular of these transformations is the Suzuki-Miyaura[8] reaction, which has broad substrate scope and can be conducted under mild reaction conditions. The impact of convenience, generality, and synthetic utility is by no means insignificant. One study found that Suzuki couplings account for approximately 40% of carbon-carbon bond-forming reactions performed by pharmaceutical chemists.[7] This same analysis found that Negishi reactions[9] made up ≤1.3% of those reactions. While Negishi couplings can be extremely effective and also operate under mild reaction conditions, the formation, storage, and use of the pyrophoric organozinc reagent solutions or oils required for these reactions are much less convenient than the air-stable, solid boronic acids used in Suzuki reactions. Roughley and Jordan go so far as to say, when discussing carbon-carbon bond-forming reactions in medicinal chemistry, that "alternative Pd-catalyzed processes are generally only employed when issues of stability or reactivity prevent a successful outcome in a Suzuki reaction."[7] Another key factor promoting the use of boronic acids is the perception that the compounds are reasonably safe, an idea that has only recently come under scrutiny in the synthetic organic community.[10]

---

[8] Suzuki, A. Cross-coupling Reactions of Organoboron Compounds with Organic Halides. In *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J.; WILEY-VCH Verlag GmbH: D-69469 Weinheim (Federal Republic of Germany), 1998; 49-97.

[9] Negishi, E.-i.; Liu, F. Palladium- or Nickel-catalyzed Cross-coupling with Organometals Containing Zinc, Magnesium, Aluminium, and Zirconium. In *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J.; WILEY-VCH Verlag GmbH: D-69469 Weinheim (Federal Republic of Germany), 1998; 1-47.

[10] Hansen, M. M.; Jolly, R. A.; Linder, R. J. *Org. Process Res. Dev.* **2015**, Article ASAP, 10.1021/acs.oprd.5b00150

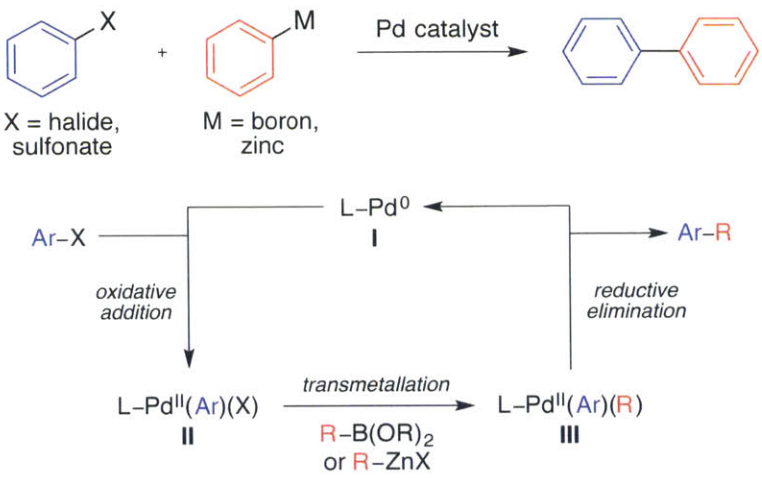


Figure 1a. General mechanism for Suzuki-Miyaura and Negishi coupling reactions.

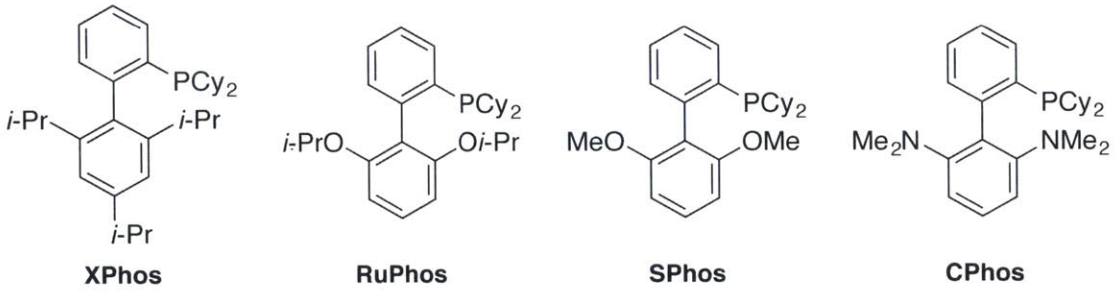


Figure 1b. Bulky biaryl phosphine ligands used in Suzuki-Miyaura and Negishi coupling reactions.

Suzuki and Negishi reactions operate under similar mechanisms (Figure 1a). A ligated Pd(0) species **I** undergoes oxidative addition with an aryl electrophile (typically an aryl halide or sulfonate) to provide electrophilic Pd(II) species **II**. This species reacts with an organometallic nucleophile (a boronic acid or boronate in the case of Suzuki reactions, and an organozinc reagent in the case of Negishi reactions), forming transmetallation complex **III**. To complete the catalytic cycle, **III** undergoes reductive elimination to furnish the product and reform species **I**.

Bulky biaryl phosphine ligands developed in the Buchwald lab have been successful as supporting ligands in Suzuki[11] and Negishi coupling reactions, and have a number of important

[11] Martin, R. M.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

structural features contributing to that success (Figure 1b). The ligands are very bulky and electron-rich. The electron-rich character of the corresponding ligated palladium species **I** facilitates oxidative addition. At the same time, the bulky ligand substituents – both the large alkyl groups directly attached to the phosphine and the "lower ring," which is itself often fitted with bulky alkyl groups – increase the rate of reductive elimination. Importantly, the steric features of the biaryl phosphine ligands favor monoligated LPd(0) complexes over more highly coordinated species. The low-coordinate complexes have relatively low electron counts and are thus highly reactive.[12] The monoligated species are also relatively less sterically encumbered, increasing the rate of reaction with aryl electrophiles for oxidative addition compared with more highly coordinated complexes. With these combined features, the catalysts derived from the bulky biaryl phosphine ligands are capable of room temperature oxidative addition of aryl chlorides and the reductive elimination of carbon-fluorine bonds from Pd(II),[13] among other impressive feats.

In the early 2000's, catalysts based on SPhos were to shown to have unprecedented activity and substrate scope in the Suzuki reaction.[14] Then, in 2010, the Buchwald group disclosed a breakthrough cross-coupling precatalyst (Figure 2a).[15] The 2-aminobiphenyl-derived palladacycle precatalyst[16,17] based on XPhos was able to facilitate the coupling of challenging halide and triflate electrophiles with unstable fluorinated and heterocyclic boronic acid nucleophiles under very mild conditions. The precatalyst exploits an acidic arylamine

---

[12] Vilar, R.; Christmann, U. *Angew. Chem. Int. Ed.* **2005**, *44*, 366-374.
[13] Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Buchwald, S. L. *Science* **2009**, *325*, 1661-1664.
[14] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.
[15] Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.
[16] Studies leading up to the 2-aminobiphenyl-derived palladacycle precatalysts: Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687.
[17] Further studies on the 2-aminobiphenyl-derived palladacycle precatalysts: (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916-920. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876-2879. (c) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161-4166.

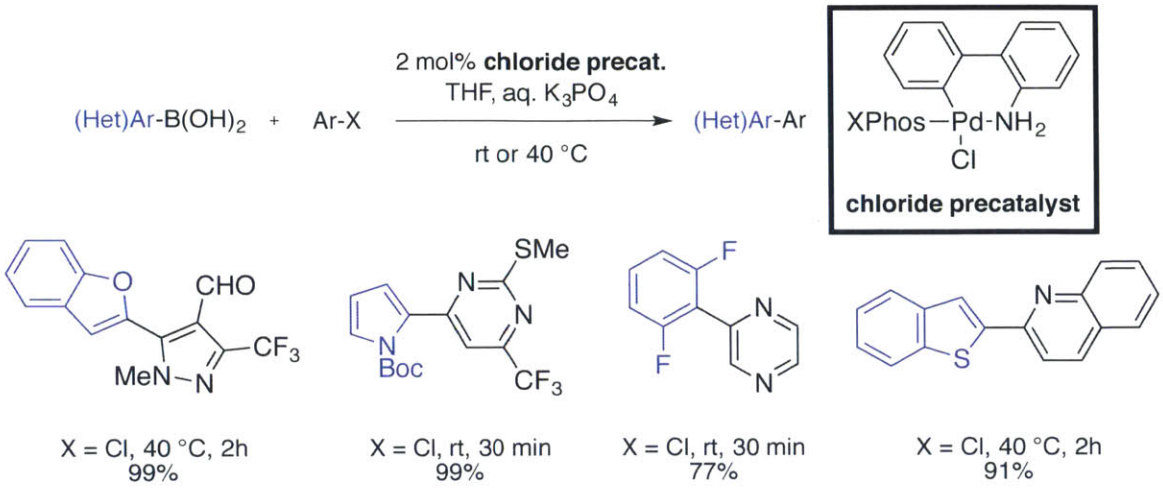


Figure 2a. Suzuki-Miyaura coupling of heteroaryl boronic acids enabled by chloride palladacycle precatalyst.

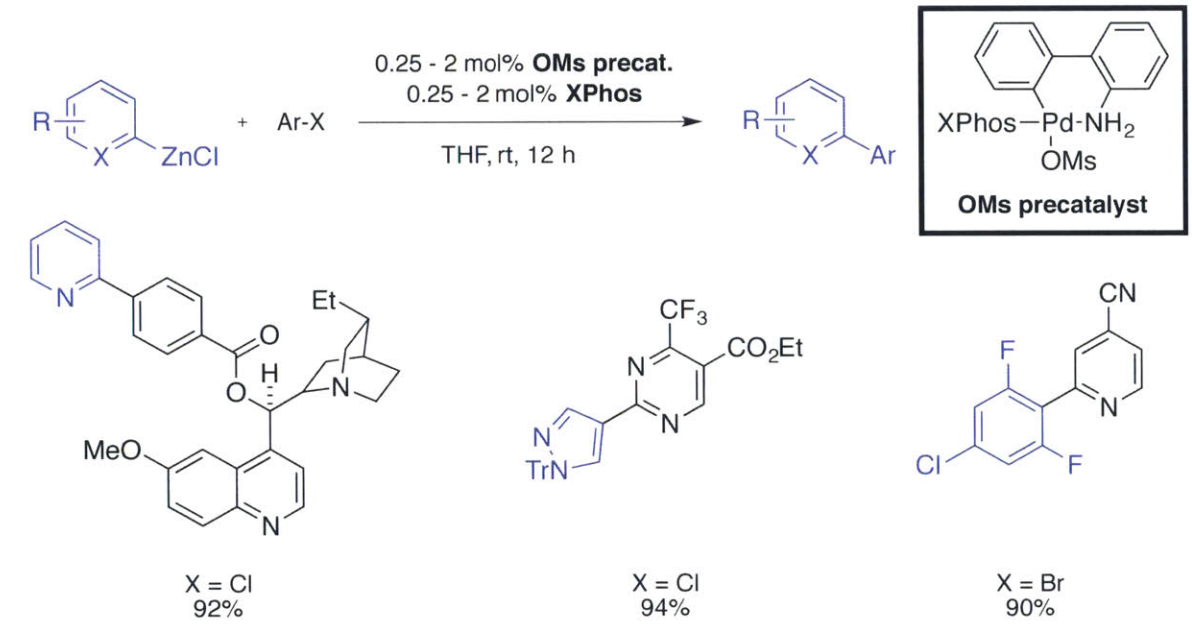


Figure 2b. Negishi coupling of heteroarylzinc nucleophiles enabled by methanesulfonate palladacycle precatalyst.

palladacycle that is rapidly deprotonated under the basic conditions required for Suzuki-Miyaura coupling, cleanly releasing LPd(0) and carbazole as a (usually) innocuous byproduct through reductive elimination of the resultant palladium amido. Like the biaryl phosphines themselves,[18] the precatalysts are easy to handle, air stable solids. Except for some unprotected nitrogen

[18] Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096-5101.

heterocycles, where SPhos offered better results,[19] subsequent reports from the Buchwald lab have found XPhos-based catalyst systems to be optimal in a variety of Suzuki-Miyaura coupling reactions.[20]

While RuPhos was shown to be excellent supporting ligand for Negishi reactions in a 2004 report,[21] XPhos has since been revealed to provide a more general supporting ligand using the same precatalyst strategy as previously reported for Suzuki couplings, with RuPhos only required in specific cases (Figure 2b).[22] No extra base is required for precatalyst activation, as the organozinc nucleophiles are sufficiently basic to deprotonate the acidic precatalyst. The catalyst system coupled many interesting heterocyclic nucleophiles and electrophiles, including 2-pyridylzinc nucleophiles.

For Negishi reactions with alkylzinc[23] and allylzinc[24] nucleophiles, CPhos-derived ligands have been the most effective. The CPhos catalyst systems were uniquely successful in avoiding undesired regioisomeric products resulting from either β–hydride elimination for secondary alkyl organozinc reagents or 1,3-migration for allylzinc nucleophiles. In the alkyl cases, the selectivity has been attributed to faster reductive elimination compared to β–hydride elimination due to the electron-withdrawing nature of the dimethylamino groups, which are not co-planar with the aromatic ring.[23b] These problems are not faced by aryl-aryl cross-couplings, and CPhos was not pursued in the Negishi coupling studies described in this thesis.

---

[19] Düfert, M. A.; Billingsley, K. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 12877-12885.
[20] (a) Noël, T.; Kuhn, S.; Musacchio, A. J.; Jensen, K. F.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5943-5946. (b) Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 10665-10669. (c) Oberli, M. A.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 4606-4609.
[21] Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028-13032.
[22] Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 615-619.
[23] (a) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532-7533. (b) Yang, Y.; Niedermann, K.; Han, C.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4638-4641.
[24] Yang, Y.; Mustard, T. J. L.; Cheong, P. H.-Y.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 14098-14102.

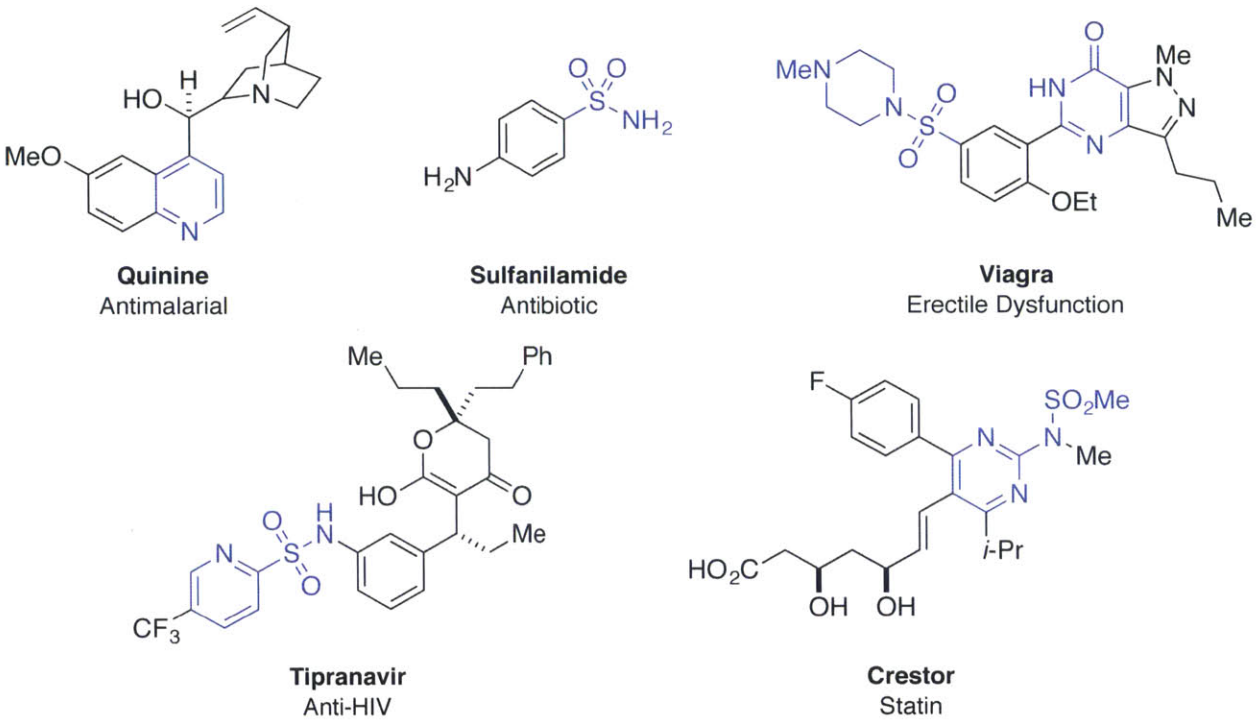


Figure 3. Pharmaceticals containing pyridine and sulfonamide functional groups.

The importance of heteroatom-containing molecules in organic chemistry and beyond is difficult to overstate. Heteroatoms and heterocycles can dramatically change the polarity of organic structures and confer Lewis basic, Lewis acidic, and hydrogen bond donating and accepting properties. Making up one of the most fundamental organic frameworks, pyridine appears in important natural and synthetic pharmaceuticals from quinine to modern drugs like Viagra,[25] Tipranavir,[26] and Crestor[27] (Figure 3). Sulfonamides are another foundational organic functional group and also appear in many important drug molecules. Sulfonamides are an important part of the history of medicinal chemistry, sulfanilamide being one of the first widely

[25] Goldstein, I.; Lue, T. F.; Padma-Nathan, H.; Rosen, R. C.; Steers, W. D.; Wicker, P. A. *N. Engl. J. Med.* **1998**, *338*, 1397-1404.
[26] Romines, K. R. Discovery and Development of Tipranavir. In *Antiviral Drugs: From Basic Discovery through Clinical Trials*; Kazmierski, W. M.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2011; 47-57.
[27] Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437-444.

available synthetic antibacterial drugs.[28] For all these reasons and more, much of the current research in reaction development, including palladium-catalyzed cross-coupling chemistry, is oriented towards heterocycle synthesis and conditions and reagents that either tolerate heterocyclic functional groups or making efficient use of the innate reactivity of heterocycles.

In the following chapters, this thesis will describe efforts to develop user-friendly synthetic methods for the installation of pyridyl and sulfonyl functional groups onto pharmaceutically relevant structurs. Chapter 1 details studies on a new solid and air-stable 2-pyridylzinc chloride reagent. Chapter 2 describes the synthesis of aryl and heteroaryl sulfonamides using organozinc nucleophiles and a chlorosulfate electrophile. Finally, chapter 3 describes structure-activity relationship studies on potential malaria therapeutics in collaboration with the Lindquist lab at MIT, studies that were partly facilitated by the method developed in chapter 2.

[28] Trefouel, J.; Trefouel, J.; Nitti, F.; Bovet, D. *C. R. Soc. Bio.* **1935**, *120*, 756-758.

Chapter I

The Synthesis of a Solid, Air-Stable 2-Pyridylzinc Reagent and its Use in Negishi Cross-Coupling Reactions

1.1 Introduction

The 2-pyridyl group is a structural component of a variety of biologically active compounds,[1] functional materials,[2] and ligands in metal-mediated reactions.[3] While Suzuki-Miyaura coupling with heteroaryl boronates is a convenient and popular method for the installation of heteroaryls,[4] coupling of 2-pyridyl boronates[5] is plagued by reagent instability[6] and has been slow to develop. The best strategy for this problem has been the employment of 2-pyridyl MIDA[5d] and pinacol[5e-g] boronates, but a method with milder conditions and broader substrate scope remains highly desirable. Alternatives to cross-coupling have not yet fully replaced the traditional methodology, as methods for the addition of radicals and other carbon nucleophiles to electron-deficient heterocycles are often not regioselective and also have limited substrate scope.[7]

---

[1] (a) Ohori, M.; Kinoshita, T.; Okubo, M.; Sato, K.; Yamazaki, A.; Arakawa, A.; Nishimura, S.; Inamura, N.; Nakajima, H.; Neya, M.; Miyake, H.; Fujii, T. *Biochem. Biophys. Res. Commun.* **2005**, *336*, 357– 363. (b) Rao, K. V.; Cullen, W. *Antibiot. Annu.* **1959**, *7*, 950-953. (c) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987-3992. (d) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482-17485.

[2] (a) (a) Whittell, G. R.; Manners, I. *Adv. Mater.* **2007**, *19*, 3439-3468. (b) Wild, A.; Winter, A.; Schlütter, F.; Schubert, U. S. *Chem. Soc. Rev.* **2011**, *40*, 1459-1511. (c) Glasson, C. R. K.; Lindoy, L. F.; Meehan, G. V. *Coord. Chem. Rev.* **2008**, *252*, 940-963.

[3] (a) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456-17458. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. (c) Izawa, Y.; Zheng, C.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3672-3675. (d) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129-3170.

[4] Kinzel, T.; Zhang, Y.; Buchwald. S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

[5] (a) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973-980. (b) Ren, W.; Li, J.; Zou, D.; Wu, Y. *Tetrahedron* **2012**, *68*, 1351-1358. (c) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695–4698. (d) Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 2667-2672. (e) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345-347. (f) Crowley, B. M.; Potteiger, C. M.; Deng, J. Z.; Prier, C. K.; Paone, D. V.; Burgey, C. S. *Tetrahedron Lett.* **2011**, *52*, 5055-5059. (g) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381-384. (h) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928-931. (i) Sakashita, S.; Takizawa, M.; Sugai, J.; Ito, H.; Yamamoto, Y. *Org. Lett.* **2013**, *15*, 4308-4311.

[6] Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664-674.

[7] (a) Seiple, I. B.; Su, S.; Rodriguez, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194-13196. (b) Kazzouli, S. E.; Koubachi, J.; Brahmi, N. E.; Guillaumet, G. *RSC Adv.* **2015**, *5*, 15292-15327.

In contrast, 2-pyridylzinc reagents are excellent nucleophiles in cross-coupling processes and their reactions often proceed at room temperature.[8] Although these reagents are more basic than the corresponding boronates, their use avoids the troublesome protodeboronation issues commonly observed with 2-heteroarylboronates. This chapter describes a strategy to obtain solid, air-stable 2-pyridylzinc reagents, with the goal of uniting the operational simplicity of boronates and the reliability of 2-pyridylzinc halides. The author worked in parallel with the Knochel group at Ludwig-Maximilians-Universität München, who applied the organozinc pivalate approach[9] to provide 2-pyridylzinc reagents that are free-flowing solids. The 2-pyridylzinc pivalates were indefinitely stable when stored under an inert atmosphere and comparable in reactivity to organozinc halides in Negishi reactions. The Knochel work was published alongside the work described in this chapter, but was not carried out by the author, and the coauthors from that publication did not carry out any of the work described in this chapter.

While the Knochel group changed the arylzinc counterion to control the form and stability of the reagent, this work was based on the hypothesis that the addition of a neutral ligand for zinc could provide a 2-pyridylzinc halide complex that was protected from ambient moisture and/or less basic or hygroscopic. In some ways, this approach is analogous to Burke's MIDA boronate methodology. The study resulted in solid reagents that are stable in air for roughly one day and are competent nucleophiles in cross-coupling reactions.

---

[8] (a) Coleridge, B. M.; Bello, C. S.; Ellenberger, D. H.; Leitner, A. *Tetrahedron Lett.* **2010**, *51*, 357-359. (b) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564–565. (c) Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, *75*, 8330–8332 and references therein. (d) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **2009**, *50*, 5329–5331. (e) Kim, S.-H.; Rieke, R. D. *Tetrahedron* **2010**, *66*, 3135–3146. (f) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **2010**, *51*, 2657-2659. (g) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 615-619.

[9] (a) Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9205-9209. (b) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9428-9432. (c) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15*, 1302-1305. (d) Manolikakes, S. M.; Ellwart, M.; Stathakis, C. I.; Knochel, P. *Chem. Eur. J.* **2014**, *38*, 12289–12297. (e) Hernán-Gómez, A.; Herd, E.; Hevia, E.; Kennedy, A. R.; Knochel, P.; Koszinowski, K.; Manolikakes, S. M.; Mulvey, R. E.; Schnegelsberg, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 2706-2710.

There is significant precedent for the use of a ligand to enhance the stability of an organozinc species. Charette recently prepared a series of bipyridyl-ligated zinc carbenoids that were greatly stabilized towards ambient atmosphere and reactive for up to eight months.[10] An early example is from Sheverdina, who crystallized a variety of alkyl- and arylorganozinc compounds as the corresponding 1,4-dioxane complexes.[11] Subsequently, Noltes prepared a variety of ligated organozinc compounds that "seem[ed] to be less sensitive towards hydrolysis" than the unligated compounds.[12]

1.2 Results and Discussion

1.2.1 Development and Negishi Coupling of 2-Pyridylzinc Chloride Dioxanate

A series of ligands were added to a solution of 2-pyridylzinc chloride prepared from 2-bromopyridine **1** by sequential magnesium-halogen exchange and transmetalation with zinc chloride (Table 1).[8c] The resulting mixture was then concentrated under reduced pressure and the material was aged and then titrated[13] to determine air stability. With no ligand, a sticky orange solid was obtained[14] that was titrated to give a reference point for the complexes prepared with additives (Table 1, entry 1). All of the ligated compounds were obtained as non-deliquescent solids and were easily manipulated. A variety of potentially chelating ligands were studied

---

[10] Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, É. *J. Am. Chem. Soc.* **2000**, *122*, 4508-4509.

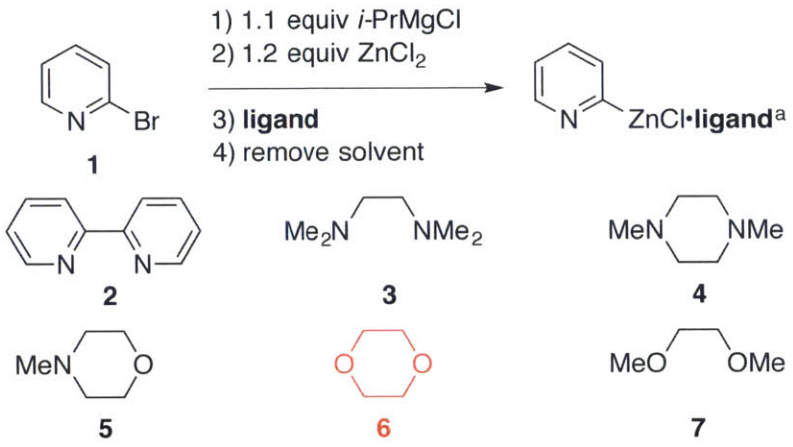
[11] (a) Sheverdina, N. I.; Abramova, L. V.; Kocheskov, K. A. *Dokl. Akad. Nauk SSSR* **1959**, *124*, 602-605. (b) Sheverdina, N. I.; Abramova, L. V.; Kocheskov, K. A. *Dokl. Akad. Nauk SSSR* **1959**, *128*, 320-322. (c) Sheverdina, N. I.; Abramova, L. V.; Kocheskov, K. A. *Dokl. Akad. Nauk SSSR* **1960**, *134*, 853-855.

[12] (a) Noltes, J. G.; Van Den Hurk, J. W. G. *J. Organomet. Chem.* **1964**, *1*, 377-383. (b) Noltes, J. G.; Van Den Hurk, J. W. G. *J. Organomet. Chem.* **1965**, *3*, 222-228.

[13] Yield of the reaction was determined by titration of a solution of the solid material with iodine. See: Krasovskiy, A.; Knochel, P.; *Synthesis* **2006**, *5*, 890-891.

[14] The "ligandless" example could have been the tetrahydrofuran (solvent) complex of the 2-pyridylzinc species.

(Table 1, entries 2-7), but only the complexes formed with 2.3 equivalents 1,4-dioxane (**6**)[15] and 1,2-dimethoxyethane (**7**) were markedly more stable than the mixture without an added ligand[14] (Table 1, entries 8 and 11), with the dimethoxyethane complex roughly half as stable as the dioxanate.



entry	ligand	equiv	yield[b]	% remaining after 1 hour[c]	% remaining after 1 day[c]
1	**no ligand**	-	-	48%	<10%
2	**2**	1.2	42%	53%	~18%
3	**2**	2.3	92%	~17%	<10%
4	**3**	1.2	86%	51%	<10%
5	**4**	1.2	81%	67%	<10%
6	**5**	1.2	100%	69%	~16%
7	**5**	2.3	80%	22%	<10%
8	**6**	2.3	65%	96%	66%
9	**6**	1.2	66%	85%	~14%
10	**6**	5.0	62%	100%	63%
11	**7**	2.3	78%	87%	34%

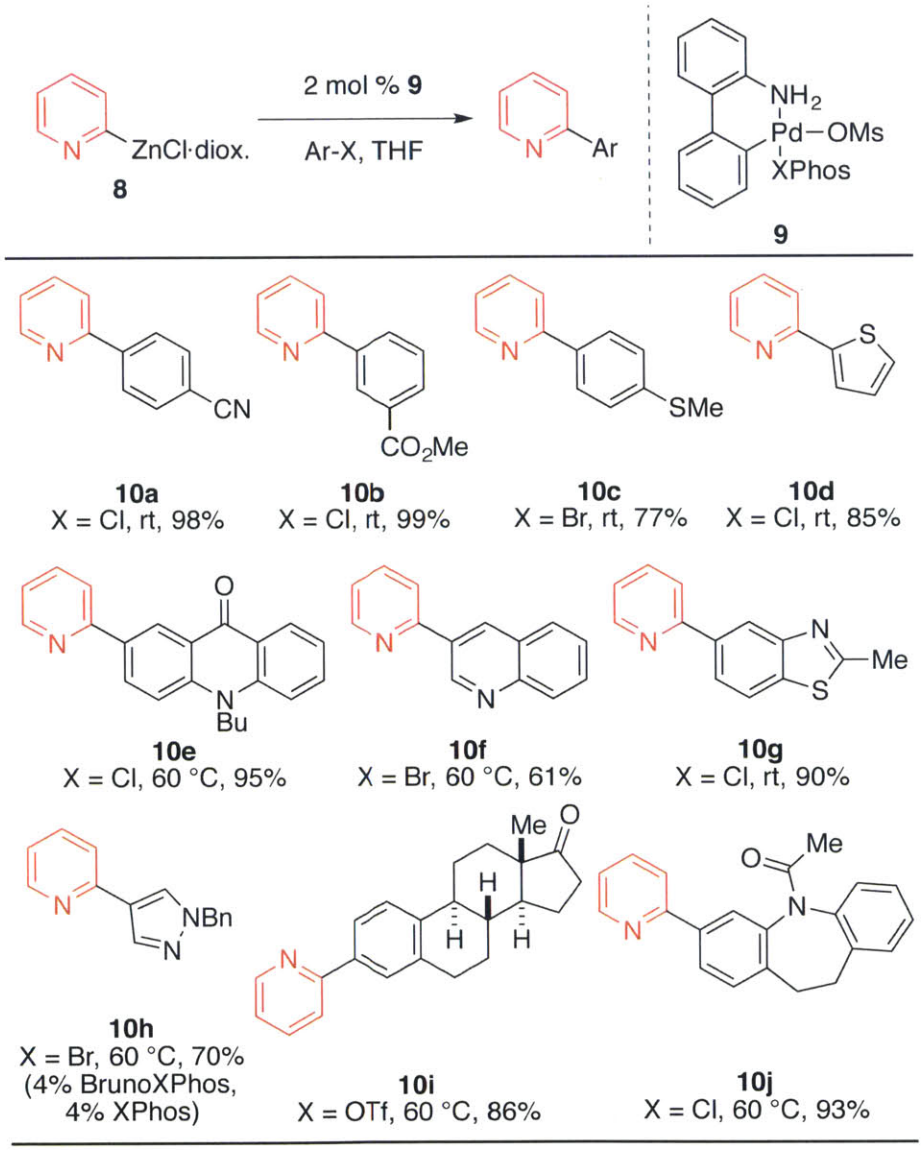
[a]Complexed $MgCl_2$ and $ZnCl_2$ omitted for clarity. [b]By titration with iodine. [c]By titration with iodine after aging with air.

Table 1. Evaluation of potentially stabilizing ligands.

The dioxanate complex **8** was an effective nucleophile under recently developed Negishi cross-coupling conditions (see Scheme 1).[8g] Simple electron-poor and electron-rich

[15] The optimized procedure for the preparation of the dioxanate reagent was performed with 30 millimoles of 2-bromopyridine. No larger scales were attempted. The average yield over seven preparations at 30 millimole scale was 58% (47%-70%).

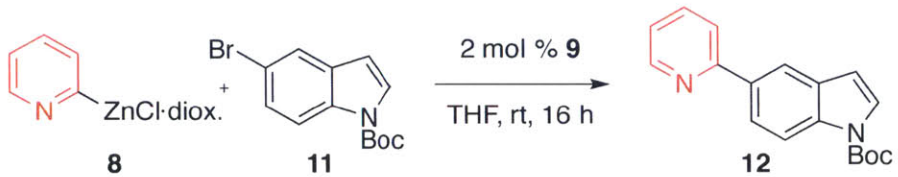
haloaromatics (Scheme 3, **10a**, **10b**, and **10c**) as well as the triflate of estrone (**10i**) could be coupled in good yields. Moreover, reagent **8** could also be coupled with more challenging, heterocycle-containing aryl- (**10e**, **10g**, **10j**) and heteroaryl- (**10d**, **10f**, **10h**) bromides and chlorides in moderate to excellent yields (61-95%).



Reaction conditions: **8** (1.3 mmol), Ar-X (1.0 mmol), **9** (2 mol%), THF (4 mL), temp., 16 h; isolated yields, average of two runs.

Scheme 1. Negishi Coupling with Dioxanate Reagent.

Reagent **8** should be titrated to determine its concentration for use after long-term storage. However, decomposition products do not interfere with the reagent's efficacy. Three different samples – one stored in a glovebox for 30 days, another stored in the glovebox for 30 days and then in air for 24 hours, and a third stored in a vacuum desiccator for 40 days – all gave virtually identical yields of cross-coupled product (see Table 2). While the aged samples have lower concentrations of active zinc nucleophile and are presumably admixed with unreactive material, these decomposition products have no effect on the cross-coupling reaction in terms of yield.



8 1.3 equiv *aged reagent* **11** **12**

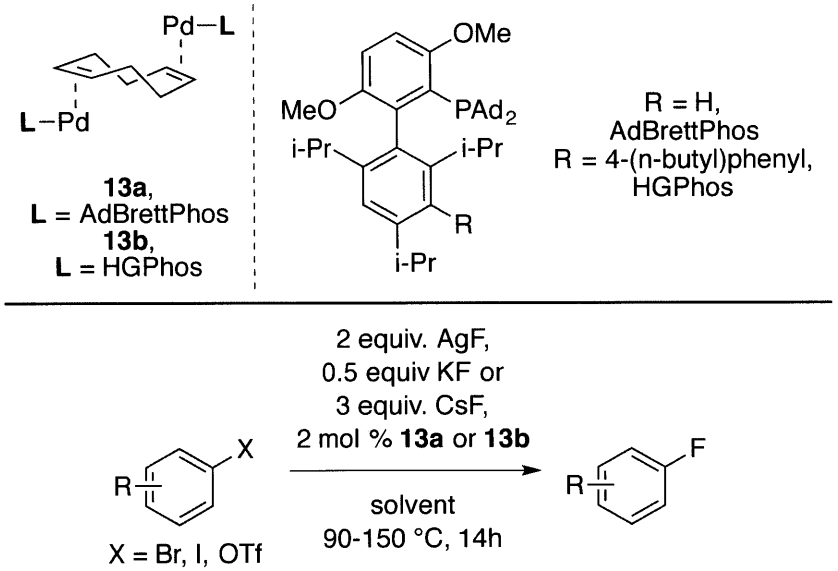
entry	aging	original concn (mol/g)[a]	aged concn (mol/g)[b]	yield[c]
1	glovebox, 30 days	0.93	0.80	98%
2	glovebox, 30 days then 1 day on bench	0.93	0.60	94%
3	40 days, vacuum desiccator	1.13	0.73	91%

[a]By titration with iodine. [b]By titration with iodine after aging as described. [c]Isolated yield based on 1 mmol aryl bromide **11** and 1.3 mmol aged solid organozinc reagent **8** - mass of solid oragnozinc reagent mixture used depended on concentration of active zinc reagent in aged mixture by titration with iodine.

Table 2. Reaction of partially decomposed reagents.

1.2.2 Negishi Cross-Coupling of 2-Pyridylzinc Chloride Dioxanate Encapsulated in Paraffin Wax

Many transition metal-catalyzed reactions require the use of sensitive precatalysts and reagents, often calling for complex or unusual techniques and limiting the application of these reactions by non-experts. While 2-pyridylzinc dioxanate **8** can be easily handled in air to be weighed out for individual reactions, the moisture-sensitivity of the reagent is still a significant drawback, especially when the reagent is compared to the boronic acids used in typical Suzuki reactions. At roughly the same time as the author developed reagent **8**, other members of the Buchwald lab discovered a new palladium precatalyst **13** that was effective for the palladium-catalyzed nucleophillic fluorination of many challenging heterocycles (Scheme 2).[16] However, the fluoride salts necessary for the reaction were extremely hygroscopic, and Pd(0) reagent **13** was air sensitive, thus requiring a glove box for reaction setup. Similarly, palladium-catalyzed C-



Scheme 2. Palladium-catalyzed fluorination of aryl electrophiles with precatalyst 13.

[16] (a) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 5602-5605. (b) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792-3795.

N couplings often require moisture-sensitive bases like sodium *tert*-butoxide[17] and cesium carbonate,[18] reagents that are best stored for long periods under inert atmospheres or rigorously dried before use.

To address these issues, paraffin wax was proposed as a medium to protect such reagents from atmospheric moisture and oxygen. Paraffin wax was already known for its ability to stabilize moisture-sensitive potassium hydride[19] and a Grubbs ruthenium-based olefin methathesis catalyst[20] in wax dispersions. However, initial investigations by Dr. Sather and Dr. Lee showed that Taber's dispersion approach was not suitable for the fluorination precatalysts and reagents. Potassium hydride has a similar density to molten paraffin and can be relied on to form an even dispersion, but the more dense precatalyst **13** and required fluoride salts sank when mixed with molten paraffin, resulting in a visible gradient in the solid and a variable concentration throughout the material. There was also fear that the heating required (the wax used melts at 58-62 °C) to form such a dispersion could decompose the precatalyst. Thus, it was impossible to form an effective multicomponent fluorination wax dispersion containing fluoride salts and **13**. Even if a uniform dispersion were achieved, hygroscopic reagents at the surface of the dispersion would be exposed to the atmosphere, and even small amounts of water can dramatically affect the outcome of catalytic fluorinations. Furthermore, a dispersion containing multiple reagents for C-N and Negishi couplings would be impossible, as the acidic methanesulfonate precatalysts and required bases would almost certainly react in the molten paraffin.

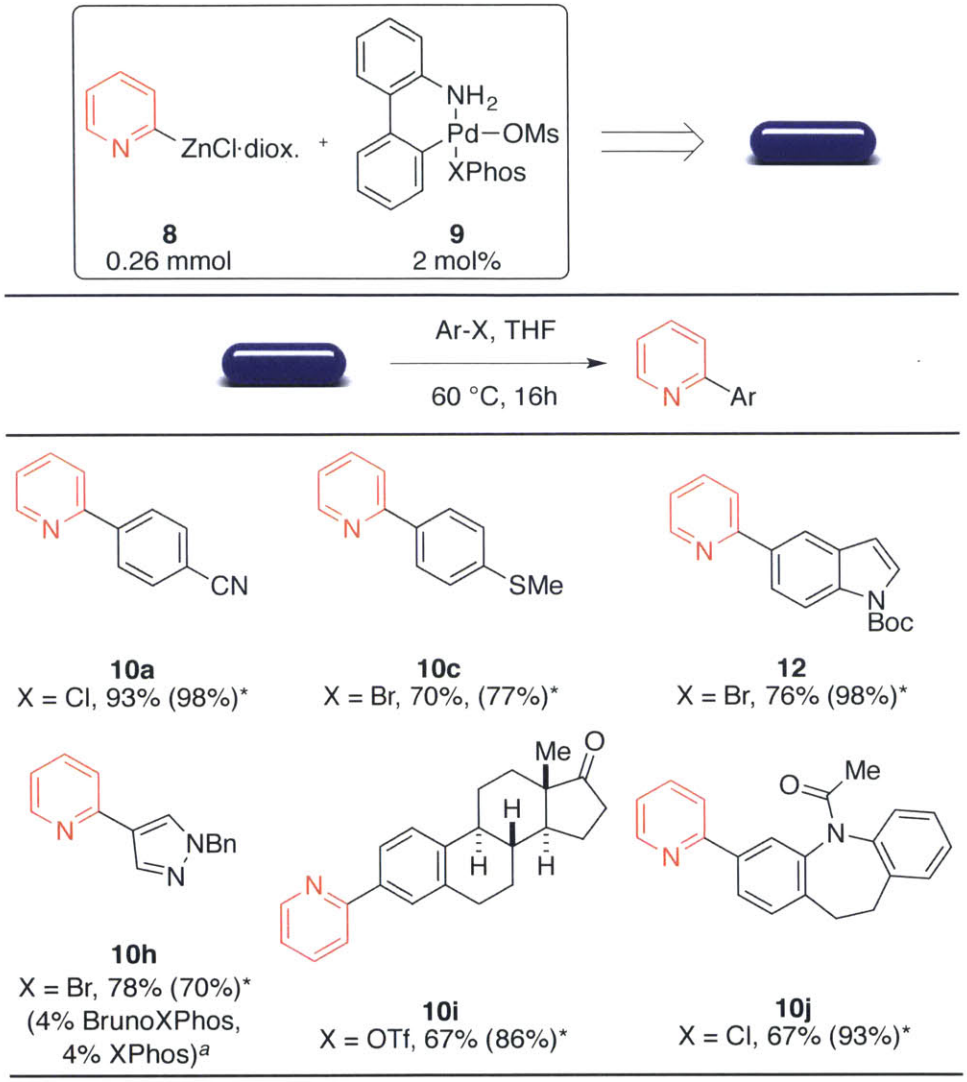
---

[17] Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914-15917.
[18] McGowan, M. A.; McAvoy, C. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 3800-3803.
[19] Taber, D. F.; Nelson, C. G. *J. Org. Chem.* **2006**, *71*, 8973-8974.
[20] Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2003**, *68*, 6047-6048.

Paraffin wax capsules were proposed as an alternative to wax dispersions. Rather than suspend reagents in molten paraffin, reagents could be loaded into a paraffin shell that would later be sealed. Using this method, complex mixtures of solid reagents could be easily prepared, unless those reagents reacted quickly at the interface of the solids. To test this strategy, capsules in a nitrogen-filled glove box were loaded with solid 2-pyridylzinc chloride dioxanate **8**, sealed with a hot spatula, and stored on the bench in air for a specified period of time.[21] Periodically, the capsules were brought back into the glove box, opened, and the contents titrated as in the previous section. Remarkably, the material was found to maintain its titre for up to one year, compared with only 66% of the original titre remaining when **8** is stored on the bench in air without encapsulation for 24 h.

The efficiency of 2-pyridyl Negishi coupling capsules containing both **8** and a catalytic amount of precatalyst **9** was then explored (Scheme 3). These capsules were prepared in the same way as the single-component capsules, except two solids were added before melting the capsule shut. Using electrophiles already shown in Scheme 1, successful Negishi couplings were achieved by adding the capsules to a reaction setup along with aryl halide and THF and heating the mixture overnight. Useful yields were obtained in all cases, with the previously reported yield (without wax encapsulation) indicated in parentheses. The multicomponent capsules were aged for as long as two months with no observed loss in potency, suggesting that the strongly basic organozinc reagent and the acidic precatalyst do not quench one another at an appreciable rate inside the capsule.

[21] This strategy was also effective for the storage of C-F and C-N bond-forming reagents. That work was not performed by the author, and is not discussed in detail in this thesis.



Reaction conditions: Capsule (contains **8** (0.26 mmol) and **9** (2 mol%)), Ar-X (0.2 mmol), THF (1 mL), 60 °C, 16 h; isolated yields, average of two runs. *Yield as previously reported for comparison. [a]2 mol% **9** and 4 mol% XPhos used in addition to the precatalyst contained in the capsule.

Scheme 3. Negishi coupling with dioxanate reagent stored in wax capsules with the methanesulfonate precatalyst.

1.3 Conclusions

In summary, the addition of excess 1,4-dioxane has been shown to be an effective method for the preparation of a solid 2-pyridylzinc chloride nucleophilic reagent that is sufficiently air-stable to be handled on the bench and a viable alternative to 2-pyridyl boronates in cross-coupling reactions. This strategy should be applicable to other organozinc compounds. Paraffin wax

capsules were developed that enable the long-term bench storage of the reagent. The wax capsules could be loaded with both the nucleophile and methanesulfonate precatalyst, greatly simplifying the setup of Negishi reactions. These advances may eventually increase the proportion of Negishi coupling reactions used by discovery chemists for carbon–carbon bond formation. The capsules should expand the use of a range of difficult to handle reagents, from strong bases and strong acids to sensitive organometallic complexes.

1.4 Experimental

General Information

All reactions were carried out under an argon atmosphere in flame-dried or oven-dried glassware unless otherwise specified. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Commercial materials were used without additional purification unless otherwise specified. The part number for the oven-dried culture tubes used in section 1.2.1 was Fisher 20 x 150 mm tubes (Cat. No. 1495937C); for plastic screw top caps, CLOSURE OT S/T 18-400TH 8 (Cat. No. 033407G); and for septa that fit into the screw cap tops, Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10 (Cat. No. 03394B). The part number for the oven-dried culture tubes used in section 1.2.2 was Fisher 16 x 125 mm tubes (Cat. No. 1495925C); for plastic screw top caps, Closure OT S/T 15-425TH 8 (Cat. No. 033407E); and for septa that fit into the screw cap tops, Thermo Scientific SPTA PTFE/SIL F/15-425 10 (Cat. No. 03394A).

Reagents: Tetrahydrofuran (THF) was purchased from J. T. Baker in CYCLE-TAINER™ containers and then vigorously purged with argon for one hour and passed through two activated alumina columns or purchase from Sigma-Aldrich in Sure/Seal™ bottles. Triethylamine was purchased from J. T. Baker. Zinc chloride (ultra dry, 99.99%) was purchased from Alfa Aesar. Isopropylmagnesium chloride (2.0 M in tetrahydrofuran), estrone, 4-bromo-*N*-benzylpyrazole, 3-bromoquinoline, methyl 3-chlorobenzoate, 4-chlorobenzonitrile were purchased from Sigma-Aldrich. Di-*tert*-butyl dicarbonate, trifluoromethanesulfonic anhydride, and 2-bromopyridine were purchased from Oakwood Chemical. 5-Bromoindole and 2-chlorothiophene were purchased from Acros Organics. Triethylamine was purchased from J. T. Baker. 4-Dimethylaminopyridine was purchased from Avocado Research Chemicals. 4-Bromothioanisole was purchased from Alfa Aesar. 10-Butyl-2-chloroacridin-9(10H)-one, 5-acetyl-3-chloro-10,11-dihydrodibenzo[b,f]azepine, and 5-methyl-2-chlorobenzothiazole were

purchased from TCI. *N*-Boc-5-bromoindole and 3-(Trifluoromethanesulfonyl)estrone prepared according to literature procedures.[21] Precatalyst **9** was prepared according to the literature procedure.[22]

Analytical Data: Compounds were characterized by melting point, ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, elemental analysis, mass spectrometry, and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were obtained on Varian 500 MHz instruments at ambient temperature. Chemical shifts for ^{1}H- and ^{13}C-NMR were reported in parts per million (ppm) relative to solvent signals ($CDCl_3$: 7.26 for ^{1}H-NMR and 77.16 for ^{13}C-NMR; CD_3OD: 3.31 for ^{1}H-NMR and 49.00 for ^{13}C-NMR; $(CD_3)_2SO$: 2.50 for ^{1}H-NMR and 39.52 for ^{13}C-NMR). Multiplicities were abbreviated in the following ways: "s" for singlet; "bs" for broad singlet; "d" for doublet; "t" for triplet; "q" for quartet; "h" for heptet; and "m" for multiplet. All IR spectra were taken on a Thermo Scientific – Nicolet iS5 spectrometer (iD5 ATR – diamond). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High resolution mass spectrometry data was collected on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points were measured on a Stanford Research Sytems EZ-Melt MPA120 automated melting point system. Column chromatography was performed using Silacycle 230-400 mesh silica gel or a Biotage SP4 apparatus with pre-packed silica cartridges. Chemical yields refer to isolated yields of compounds analyzed by elemental analysis or high-resolution mass spectrometry.

Note on Aging in Air: "In air" refers to the air-conditioned laboratory environments of the Buchwald group. These environments varied from 22-23 °C and 30-40% humidity over the course of our studies.

---

[21] Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662-1663.
[22] Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916-920.

Synthesis and Air Stability of Ligated 2-Pyridylzinc Chlorides

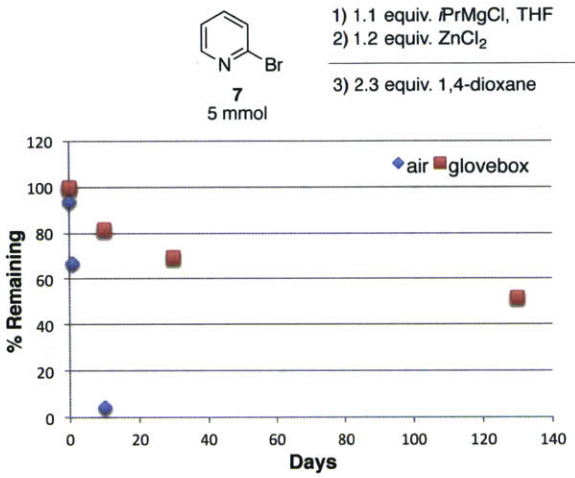
General Procedure for Table 1 (GPT1): Synthesis, Titration, and Air-Stability of Ligated 2-Pyridylzinc Chloride Reagents

A 50 mL round-bottom flask equipped with magnetic stir bar and rubber septum was flamed dry under vacuum and evacuated and backfilled with argon (the evacuation/backfilling process was repeated a total of three times). The entire set-up (flask filled with argon, stir bar, and septum) was weighed. Isopropylmagnesium chloride solution (1.7 mL, 2.0 M in THF, 3.3 mmol) was added via syringe. Next, the flask was submerged in an ice/water bath, and then 2-bromopyridine (290 μL, 3.0 mmol) was added dropwise via syringe. The ice bath was removed, and the mixture was stirred for 4 h at ambient temperature (during this time, the mixture may become heterogeneous). The mixture was then resubmerged in an ice/water bath. The flask was charged with 3.6 mL dry THF and then 3.6 mL zinc chloride solution (1.0 M in THF, 3.6 mmol) via syringe, then the ice bath was again removed. After stirring for 2 h the appropriate ligand was added either via syringe (for liquid reagents) or by briefly removing the rubber septum (for solid reagents). The mixture was stirred for 16 h, and then the solvent was removed in vacuo. The reagent was dried under vacuum for 24 h, and then the pre-weighed set-up with reagent was weighed again. The set-up was then taken into a nitrogen-filled glovebox. Inside the glovebox, 50 mg of the material so obtained was transferred into each of three oven-dried culture tubes with magnetic stir bars and then the tubes were sealed with Teflon septa and screw caps. 300 mg of material was then transferred into each of two vials, one marked "one hour" and a second marked "24 hours," which were both sealed with a Kimwipe and rubber band. All of these tubes and vials were removed at the same time from the glovebox. The vials were allowed to stand open and exposed to air for the indicated times while the culture tubes were evacuated and backfilled with argon (the evacuation/backfilling process was repeated a total of three times). The tubes were then charged with 4 mL THF, and then the mixture was titrated with a solution of iodine (1.0 M I_2, 0.5 M LiCl in THF). The initial concentration of organozinc reagent in the solid was determined by calculating the average of the

three titres. This concentration and the mass of the material (calculated from the difference between the mass of the reaction set-up before the reaction and after the removal of solvent for 24 h) were used to calculate the yield of the reaction. The titration process was repeated in exactly the same way for the "one hour" and "24 hours" samples after the appropriate amount of time had elapsed, except that after the samples were aged the material was weighed into oven-dried culture tubes with magnetic stir bars in air, not in the glovebox. The "one hour" and "24 hours" titres were compared with the original value to determine the percentage decay in air of the reagent over those time periods.

Supplementary Titration Data: Long Term Air-Stability of 2-Pyridylzinc Chloride Dioxanate

The synthesis and titration of 2-pyridylzinc chloride dioxanate was perfomed as in GPT2 from 5 mmol 2-bromopyridine, except additional samples for titrations after aging for 10 days, 30 days, and 130 days in both the glovebox and air were prepared and titrated. After 130 days in the glovebox, 51% of the original titre remained in the sample (see below).



time	% remaining[a] (air)	% remaining[a] (glovebox)
1h	96%	ND
1d	66%	ND
10d	<5%	82%
30d	ND	70%
130d	ND	51%

[a] By titration with I_2/LiCl THF solution.

Large Scale Synthesis of 2-Pyridylzinc Chloride Dioxanate 8

A 200 mL round-bottom flask with magnetic stir bar and rubber septum was flame-dried under vacuum and evacuated and back-filled with argon (the evacuation/backfilling process was repeated a total of three times). The entire set up (flask filled with argon, stir bar, and septum) was weighed, and then charged with isopropylmagnesium chloride solution (16.5 mL, 2.0 M in THF, 33 mmol, 1.1 equivalents). The flask was submerged in an ice bath, and 2-bromopyridine (2.9 mL, 30 mmol, 1.0 equivalents) was added dropwise via syringe. The ice bath was removed, and the mixture was stirred for four hours (the mixture may become heterogeneous during this time). Meanwhile, in a nitrogen-filled glovebox, a 100 mL round bottom flask with magnetic stirring bar that had been flamed dry under vacuum before being brought into the box was charged with anhydrous zinc chloride (4.9 g, 36 mmol, 1.2 equivalents). This flask was removed from the glovebox, evacuated and back-filled with argon (the evacuation/backfilling process was repeated a total of three times), and then charged with 60 mL THF. The mixture was stirred until the zinc chloride was fully dissolved. The flask that contained the 2-pyridylmagnesium chloride solution was again submerged in an ice bath, and the zinc chloride solution was transferred into it via cannula. The zinc chloride flask was rinsed with an additional 12 mL of THF to capture any remaining zinc chloride and then also transferred via cannula to the 2-pyridylmagnesium chloride solution. The ice bath was removed, and the mixture was stirred for two hours. 1,4-Dioxane (5.9 mL, 69 mmol, 2.3 equivalents) was added via syringe, and the solvent was removed under reduced pressure. After most of the solvent had been removed and solid material had been obtained, the material was quickly broken up into small pieces/powder and scraped off of the sides of the flask under argon with a large spatula. The material was then dried under reduced pressure for 24 h. The set up was weighed again (with the flask still under argon) and brought into a nitrogen-filled glovebox. Inside the glovebox 50 mg solid organozinc material was then weighed into each of three oven-dried culture tubes with magnetic stir bars and then the tubes were sealed with Teflon septa and screw caps, removed from the glovebox, evacuated and backfilled with argon (the evacuation/backfilling process was repeated a

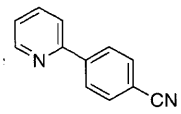
total of three times), and charged with 4 mL THF. The resulting mixtures were then titrated with a solution of iodine (1.0 M I_2, 0.5 M LiCl in THF). The initial concentration of organozinc reagent in the solid was determined by calculating the average of the three titres. This concentration and the mass of the material formed (calculated from the difference between the mass of the reaction set-up before the reaction and after the removal of solvent for 24 hours) gave the yield of the reaction. Average yield based on seven experiments: 58% (range: 47%- 70%).

General Procedure for Scheme 1 (GPS1): Negishi Couplings with 2-Pyridylzinc Chloride Dioxanate

To a flame-dried culture tube with Teflon septum and screw cap and *two magnetic stir bars* (as the reagent is largely insoluble in THF, two stir bars may help with stirring so as to avoid settling of the solids at the bottom of the vessel, depending on the scale of the cross-coupling reaction and the sizes and shapes of the vessel and stir bars) was added catalyst **9** (2-4 mol% palladium), aryl halide or triflate (1.0 mmol, for solid aryl halides or triflates), and **8** (1.3 mmol, amount depended on concentration of active zinc reagent). All solids were weighed in air on the bench. The tube was evacuated and back-filled with argon (the evacuation/backfilling process was repeated a total of three times), and then charged with aryl halide or triflate via syringe (for liquid aryl halides or triflates). THF was added via syringe. The punctured septum was replaced with a new septum. The reaction mixture was then stirred for 16 hours at either room temperature or 60 °C. After stirring for 16 h, the tube was allowed to cool to room temperature if appropriate, and then charged with 10 mL water and 10 mL ethyl acetate by opening the screw cap. The mixture was poured into a separatory funnel and the aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The mixture was filtered and concentrated under reduced pressure. The crude mixture was then purified by chromatography.

Nucleophile **8** was stored in a nitrogen-filled glovebox between uses in cross coupling reactions.

4-(pyridin-2-yl)benzonitrile (10a)[23]



According to **GPS1**, **8** (1.4 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 4-chlorobenzonitrile (138 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-40% ethyl acetate/hexanes) to provide **10a** (first run: 179 mg, 99%; second run: 174 mg, 97%) as a yellow solid.

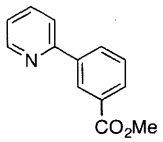
M.p. (°C): 62 – 68.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.65 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.13 – 8.09 (m, 2H), 7.91 – 7.88 (m, 2H), 7.81 – 7.77 (m, 2H), 7.39 (td, *J* = 4.9, 3.5 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 156.41, 150.78, 144.54, 138.93, 133.66, 128.71, 124.79, 122.76, 119.56, 113.50.

Elemental Analysis: Anal. calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.47. Found: C, 79.39; H, 4.60.

methyl 3-(pyridin-2-yl)benzoate (10b)[24]



According to **GPS1**, **8** (1.3 g, 1.3 mmol), **9** (17 mg, 2 mol%), and methyl 3-chlorobenzoate (139 µL, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-60% ethyl acetate/hexanes) to provide **10b** (first run: 211 mg, 99%; second run: 213 mg, 100%) as a light yellow solid.

M.p. (°C): 51 – 53.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.63 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 8.59 (td, *J* = 1.9, 0.6 Hz, 1H), 8.17 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 8.06 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.94 – 7.83 (m, 2H), 7.59 (td, *J* = 7.8, 0.6 Hz, 1H), 7.38 (ddd, *J* = 7.0, 4.9, 1.6 Hz, 1H), 3.93 (s, 3H).

---

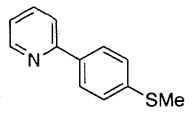
[23] Kim. S.-H.; Rieke, R. D. *Tetrahedron* **2010**, *66*, 3135-3146.

[24] Molander, G. A.; Trice, S. L. J.; Kennedy, S. M. *J. Org. Chem.* **2012**, *77*, 8678-8688.

^{13}C NMR (126 MHz, Methanol-d_4): δ 168.00, 157.31, 150.43, 140.60, 138.80, 132.39, 131.82, 130.89, 130.03, 128.92, 124.07, 122.27, 52.70.

Elemental Analysis: Anal. calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20. Found: C, 73.24; H, 5.41.

2-(4-(methylthio)phenyl)pyridine (10c)[25]



According to **GPS1**, **8** (1.3 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 4-bromothioanisole (138 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-60% ethyl acetate/hexanes) to provide **10c** (first run: 151 mg, 75%; second run: 156 mg, 78%) as a yellow solid.

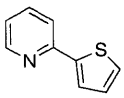
M.p. (°C): 59 – 60.

^{1}H-NMR (500 MHz, Methanol-d_4): δ 8.56 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.87 – 7.75 (m, 4H), 7.35 – 7.27 (m, 3H), 2.49 (s, 3H).

^{13}C NMR (126 MHz, Methanol-d_4): δ 158.12, 150.16, 141.84, 138.73, 136.60, 128.34, 127.08, 123.40, 121.96, 15.18.

Elemental Analysis: Anal. calcd. for $C_{12}H_{11}NS$: C, 71.60; H, 5.51. Found: C, 71.60; H, 5.63.

2-(thiophen-2-yl)pyridine (10d)[26]



According to **GPS1**, **8** (1.6 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 2-chlorothiophene (92 μL, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-60% ethyl acetate/hexanes) to provide **10d** (first run: 125 mg, 78%; second run: 147 mg, 91%) as a light tan solid.

M.p. (°C): 58 – 62.

---

[25] Harrak, Y.; Casula, G.; Basset, J.; Rosell, G.; Plescia, S.; Raffa, D.; Cusimano, M. G.; Pouplana, R.; Pujol, M. D. *J. Med. Chem.* **2010**, *53*, 6560-6571.

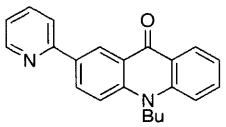
[26] Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, *75*, 8330-8332.

^{1}H-NMR (500 MHz, Methanol-d_4): δ 8.44 (dt, *J* = 4.9, 1.4 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.65 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.48 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.21 (td, *J* = 5.0, 3.4 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.7 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-d_4): δ 153.74, 150.09, 145.19, 138.53, 129.15, 128.74, 126.31, 123.29, 120.45.

Elemental Analysis: Anal. Calcd. for C_9H_7NS: C, 67.05; H, 4.38. Found: C, 67.20; H, 4.56.

10-butyl-2-(pyridin-2-yl)acridin-9(10*H*)-one (10e)



According to **GPS1**, **8** (1.5 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 10-butyl-2-chloroacridin-9(10*H*)-one (286 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-80% ethyl acetate/dichloromethane) to provide **10e** (first run: 307 mg, 93%; second run: 319 mg, 97%) as a bright yellow solid.

M.p. (°C): 143 – 145.

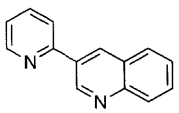
^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.04 (d, *J* = 2.4 Hz, 1H), 8.67 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 8.58 – 8.50 (m, 2H), 7.92 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.68 (ddd, *J* = 8.7, 6.9, 1.8 Hz, 1H), 7.54 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.26 (ddd, *J* = 8.1, 6.6, 0.9 Hz, 1H), 7.21 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 4.34 – 4.28 (m, 2H), 1.93 – 1.84 (m, 2H), 1.56 (h, *J* = 7.4 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 177.92, 156.04, 149.54, 142.15, 141.63, 136.99, 133.98, 132.56, 132.10, 128.03, 125.67, 122.60, 122.27, 122.07, 121.49, 120.38, 115.40, 114.78, 46.07, 29.30, 20.24, 13.95.

IR (neat, cm^{-1}): 2964, 2926, 2870, 2226, 1631, 1591, 1498, 1482, 1368,1259, 1060, 695, 817, 586.

HRMS ($C_{22}H_{20}N_2O$): Calcd. $[M+H]^+$: 329.1648. Found: 329.1644.

3-(pyridin-2-yl)quinoline (10f)[3]



According to **GPS1**, **8** (1.35 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 3-bromoquinoline (136 µL, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by chromatography using a Biotage instrument (100 g SNAP column, 0-80% ethyl acetate/dichloromethane) to provide **10f** (first run: 130 mg, 63%; second run: 122 mg, 59%) as a pale yellow solid.

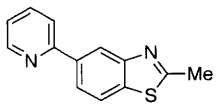
M.p. (°C): 100 – 101.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 9.42 (d, *J* = 2.2 Hz, 1H), 8.78 (d, *J* = 2.1 Hz, 1H), 8.66 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.99 (dddd, *J* = 12.8, 11.7, 8.4, 1.1 Hz, 3H), 7.90 (td, *J* = 7.7, 1.8 Hz, 1H), 7.75 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.38 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H).

^{13}C-NMR (126 MHz, CDCl$_3$): δ 155.31, 150.75, 149.88, 148.34, 138.77, 135.57, 132.89, 131.57, 129.79, 129.06, 128.84, 128.43, 124.31, 122.39.

Elemental Analysis: Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89. Found: C, 81.23; H, 4.77.

2-methyl-5-(pyridin-2-yl)benzo[*d*]thiazole (10g)[6]



According to **GPS1**, **8** (1.4 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 5-chloro-2-methylbenzothiazole (184 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by preparative HPLC (Agilent Prep-C18 21.2 x 150 mm, 5 µm, 65% acetonitrile/35% water) to provide **10g** (first run: 199 mg, 88%; second run: 206 mg, 91%) as a light yellow solid.

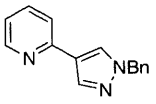
M.p. (°C): 101 – 102.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.63 (dt, *J* = 4.9, 1.5 Hz, 1H), 8.43 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.01 – 7.96 (m, 2H), 7.94 – 7.88 (m, 2H), 7.37 (ddd, *J* = 6.4, 4.9, 2.3 Hz, 1H), 2.84 (s, 3H).

^{13}C-NMR (126 MHz, CDCl$_3$): δ 170.71, 158.05, 154.57, 150.40, 138.90, 138.86, 137.47, 124.95, 123.84, 122.97, 122.51, 121.14, 19.78.

Elemental Analysis: Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H 4.45. Found: C, 68.82; H, 4.56.

2-(1-benzyl-1*H*-pyrazol-4-yl)pyridine (10h)



According to **GPS1**, **8** (1.4 g, 1.3 mmol), **22** (35 mg, 4 mol%), XPhos (20 mg, 4 mol%), and 1-benzyl-4-bromopyrazole (237 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-100% ethyl acetate/dichloromethane) to provide **10h** (first run: 175 mg, 74%; second run: 154 mg, 66%) as a yellow solid.

M.p. (°C): 78 – 80.

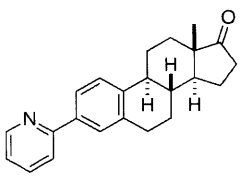
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.42 (ddd, *J* = 5.0, 1.9, 1.0 Hz, 1H), 8.19 (d, *J* = 0.7 Hz, 1H), 8.05 (d, *J* = 0.8 Hz, 1H), 7.72 (td, *J* = 7.7, 1.8 Hz, 1H), 7.60 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.36 – 7.24 (m, 5H), 7.16 (ddd, *J* = 7.4, 5.0, 1.1 Hz, 1H), 5.34 (s, 2H).

^{13}C-NMR (126 MHz, Methanol-d$_4$): δ 152.82, 149.98, 138.81, 138.76, 137.87, 130.23, 129.81, 129.12, 128.75, 124.45, 122.71, 121.46, 56.80.

IR (neat, cm^{-1}): 3011, 1595, 1552, 1427, 1366, 1231, 1157, 992, 960, 851, 703, 694, 635.

Elemental Analysis: Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57. Found: C, 76.43; H, 5.52.

(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(pyridin-2-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (10i)



According to **GPS1**, **8** (1.35 g, 1.3 mmol), **9** (17 mg, 2 mol%), and estrone triflate (402 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-80% ethyl acetate/hexanes) to provide **10i** (first run: 298 mg, 90%; second run: 272 mg, 82%) as a white solid.

M.p. (°C): 167 – 171.

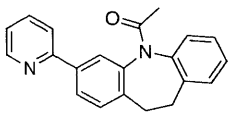
^{1}H-NMR (500 MHz, CDCl$_3$): δ 8.67 (dt, *J* = 4.9, 1.4 Hz, 1H), 7.79 – 7.68 (m, 4H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.19 (ddd, *J* = 6.6, 4.8, 2.2 Hz, 1H), 3.06 – 2.92 (m, 2H), 2.54 – 2.42 (m, 2H), 2.33 (td, *J* = 11.0, 4.2 Hz, 1H), 2.18 – 1.93 (m, 4H), 1.68 – 1.41 (m, 6H), 0.91 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 157.29, 149.56, 140.85, 137.04, 136.83, 136.80, 127.49, 125.84, 124.22, 121.97, 120.42, 50.55, 48.03, 44.49, 38.13, 35.92 , 31.64, 29.55, 26.55, 25.76, 21.65, 13.92.

IR (neat, cm^{-1}): 2924, 2857, 1726, 1586, 1462, 1440, 1255, 1007, 910, 743, 621.

HRMS ($C_{23}H_{25}NO$): Calcd. $[M+H]^+$: 332.2009. Found: 332.2011.

1-(3-(pyridin-2-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethan-1-one (10j)



According to **GPS1**, **8** (**1**.4 g, 1.3 mmol), **9** (17 mg, 2 mol%), and 5-acetyl-3-chloro-10,11-dihydrodibenzo[*b*,*f*]azepine (272 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography (silica gel, 0-60% ethyl acetate/hexanes plus 1% methanol) to provide **10j** (first run: 311 mg, 99%; second run: 270 mg, 86%) as a light tan solid. Peaks doubled in spectra due to amide rotamers.[27]

M.p. (°C): 159-161.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.69 – 8.61 (m, 1H), 8.06 – 7.96 (m, 1H), 7.91 – 7.78 (m, 1H), 7.76 – 7.63 (m, 2H), 7.45 – 7.10 (m, 6H), 3.49 – 3.30 (m, 1H), 2.94 – 2.76 (m, 2H), 2.11 – 1.98 (m, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.60, 156.41, 155.86, 149.71, 149.46, 143.14, 142.63, 140.23, 138.79, 138.25, 137.55, 136.94, 136.75, 135.34, 134.46, 131.19, 130.62, 130.30, 129.79, 128.83, 128.62, 127.77, 127.56, 127.41, 127.25, 126.64, 126.08, 125.75, 122.50, 122.12, 120.54, 120.29, 77.42, 31.01, 30.96, 30.12, 30.07, 22.91, 22.81.

IR (neat, cm^{-1}): 3070, 2921, 1666, 1561, 1368, 1325, 1312, 818, 850, 783, 770, 651.

HRMS-ESI ($C_{21}H_{18}N_2O$): Calcd. $[M+H]^+$: 315.1492. Found: 315.1492.

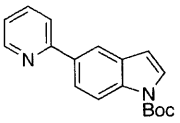
---

[27] Related compounds are known to feature multiple amide rotamers in ^{1}H- and ^{13}C-NMR spectra. See: Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.

Procedure for Scheme 4: Cross-Coupling Reactivity of Aged Reagent

Synthesis and titration of 2-pyridylzinc chloride dioxanate perfomed as in the above large scale procedure. Three portions of fresh reagent were taken: (1) one stored for 30 days in the glovebox; (2) one stored for 30 days in the glovebox, and then 1 day in air; and (3) one stored in a vacuum desiccator for 40 days. After the appropriate amount of time, the reagents were titrated with iodine as above and then subjected to cross-coupling conditions (see below) with *N*-boc-5-bromoindole. The amount of nucleophile **8** used was based on the aged titration value in g/mmol. Yields are isolated yields after purification by column chromatography.

***tert*-butyl 5-(pyridin-2-yl)-1*H*-indole-1-carboxylate (12)[26]**



According to **GPS1**, **8** (1.3 mmol: 1.6 g for sample aged for 30 days in glovebox; 2.17 g for sample aged for 30 days in glovebox and then one day in air; 1.8 g for sample aged for 40 days in vacuum desiccator), **9** (17 mg, 2 mol%), and *N*-boc-5-bromoindole (**11**, 296 mg, 1 mmol) were dissolved in THF (4 mL) and the mixture was stirred for 16 h at room temperature. The crude material was purified by chromatography using a Biotage instrument (50 g SNAP column, 0-30% ethyl acetate/hexanes) to provide **12** (30 days in glovebox: 290 mg, 98%; 30 days in glovebox plus 1 day in air: 278 mg, 94%; 40 days in vacuum desiccator: 269 mg, 91%) as a white solid.

M.p. (°C): 85 – 86.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.60 – 8.56 (m, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.10 (dt, J = 1.9, 0.9 Hz, 1H), 7.88 – 7.81 (m, 3H), 7.64 (d, J = 3.6 Hz, 1H), 7.31 (dddd, J = 6.1, 4.9, 2.5, 1.2 Hz, 1H), 6.68 (dt, J = 3.8, 1.0 Hz, 1H), 1.67 (s, 9H).

^{13}C-NMR (126 MHz, CDCl$_3$): δ 159.17, 150.75, 150.03, 138.70, 136.96, 135.04, 132.36, 127.69, 124.38, 123.13, 122.49, 120.79, 116.19, 108.76, 85.05, 28.33.

Elemental Analysis: Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16. Found: C, 73.55; H, 6.23.

Preparation of Paraffin Wax Capsules

Paraffin wax (mp 58-62 °C) was placed in a beaker with a stir bar and heated to 62 °C with stirring open to the air. Once molten, the volume of the molten colorless wax was approximately 300 mL. A room temperature glass rod (25.5 cm in length, 0.5 cm in diameter) was then repeatedly dipped into the molten wax (to a depth of 3.5 cm) 6-8 times to develop a wax coating on the glass rod (Figure S1).

Figure S1. Coating a glass rod with molten paraffin wax (left and middle). Glass rod coated with paraffin wax (right).

The coated rod was allowed to cool to room temperature and the wax coating was removed from the glass rod to provide a hollow paraffin wax shell. Cracks develop in the wax shell upon removing from the glass rod. To repair the cracks, the hollow paraffin shell was dipped into the molten wax mixture three times (Figure S2).

Figure S2. Hollow wax shell with cracks after removal from the glass rod (left). Hollow wax shell with the cracks repaired by dipping into molten wax (middle). Top view of a finished hollow wax shell (right).

This process was repeated until the desired amount of hollow paraffin shells were obtained. Small wax cylinders were prepared by filling the underside of a rubber septum (VWR – Cat. No. 89097-538) with molten wax (Figure S3). Once cool, the wax cylinder was removed and trimmed with a razor blade to provide a wax cylinder (4 mm diameter and 3 mm height).

Figure S3. Filling the underside of a septum with a molten wax to create a wax cylinder (left). Wax cylinder once removed from the septa and trimmed to size (right).

The hollow shells, wax cylinders, and reagents were brought into a nitrogen filled glove box. The hollow wax shells were then charged with the desired reagents and catalysts. Capsules were prepared for either (1) cross-coupling or (2) aging and titration of the solid 2-pyridylzinc reagent, differing only in the reagents the capsules contained. For cross-coupling reactions, the capsules were charged with 2-pyridylzinc chloride dioxanate (260 mg, 0.26 mmol, 1.3 equiv) and **XPhos Pd G3** (3.5 mg, 0.0040 mmol, 2.0 mol %). The average mass of wax contained in the capsules was 0.918 g. For aging and titration, the capsules charged with 2-pyridylzinc chloride dioxanate (250 mg, 0.25 mmol). To seal the capsules, a wax cylinder was added into the filled capsules and packed into the capsule. The excess wax was trimmed using a metal spatula that was warmed on a hot plate and the open end of the capsule was then melted shut. Once sealed, the capsules were removed from the glove box and the sealed end of the capsule was dipped into the molten wax to secure the seal (Figure S4). The capsules were stored in a glass jar on a laboratory bench open to air.

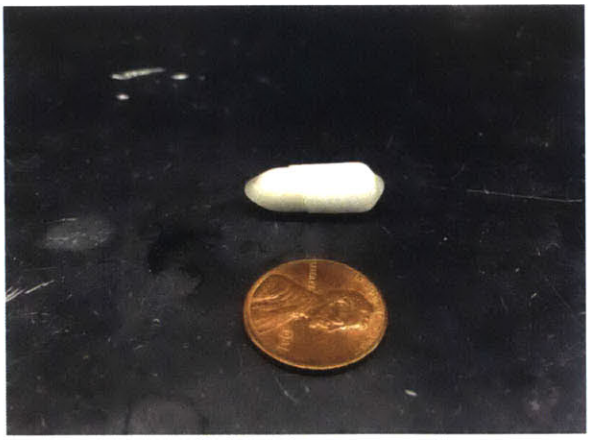


Figure S4. A finished wax capsule.

Aging and Titration of Solid 2-Pyridylzinc Chloride Dioxanate Stored in Wax Capsules

Wax capsules were stored in a glass jar on a laboratory bench open to air. At specific time intervals, one capsule was brought into a nitrogen-filled glove box and opened by cutting with a metal spatula. Three oven-dried reaction tubes (Fisher 13 x 100 mm tubes – Cat. No. 1495925A) containing magnetic stir bars were charged with 50 mg each of the contents of the capsule. The tubes were sealed with a septum and screw cap (Thermo Scientific ASM PHN CAP w/PTFE/SIL – Cat. No. 03378316), removed from the glove box, and evacuated and back-filled with argon (this process was repeated a total of three times). The tubes were each charged with 4 mL THF and the mixtures were stirred at room temperature. Under a positive pressure of argon, the mixtures were titrated by addition of an I_2/LiCl solution until the color of the I_2 persisted.[12] No significant decomposition of the solid organozinc reagent was observed after storage of the capsules for up to one year in air (see table **S5** for titration data).

8

stored in wax capsule

entry	aging	concentration (g/mmol)[a]
1	none - before encapsulation	1.0[b]
2	benchtop, one year	1.0[b]

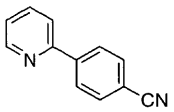
[a]Determined by titration with I_2/LiCl. Average of three titrations. [b]Error ±0.16 g/mmol.

Table S1. Titration of 2-pyridylzinc dioxanate in wax capsules stored on a lab bench in air.

General Procedure for Scheme 3 (GPS3): Negishi Couplings with 2-Pyridylzinc Chloride Dioxanate and Pd Precatalyst Stored in Wax Capsules

An oven-dried reaction tube equipped with a magnetic stir bar was charged with a wax capsule containing 2-pyridylzinc chloride dioxanate **8** (260 mg, 0.26 mmol, 1.3 equiv) and **9** (3.5 mg, 0.0040 mmol, 2.0 mol %), followed by the solid aryl halide or triflate (0.20 mmol). The reaction tube was fitted with a Teflon septum and plastic screw cap. The tube was evacuated and backfilled with argon via a needle (this procedure was repeated a total of three times). Aryl electrophiles that are liquid were added via syringe/needle after purging with argon. THF (1 mL) was added via syringe/needle, the punctured septum was replaced with a new septum, and the tube was placed in an oil bath preheated to 60 °C with magnetic stirring for 16 h. The tube was then removed and allowed to cool to room temperature before being charged with methanol (10 mL). The wax is largely insoluble in methanol, and the mixture was gently heated with a heat gun to homogenize. The mixture was allowed to cool to room temperature with vigorous stirring, and the wax formed small chunks and particulates that were removed by filtration through a short plug of Celite eluting methanol (100 mL). The filtrate was concentrated and again and filtered through a Celite or cotton plug with methanol 1-2 more times to remove residual wax. The material was than adsorbed onto silica gel and purified by flash column chromatography. The compounds described in Scheme 3 were consistent with the previous spectral data from Scheme 1.

4-(pyridin-2-yl)benzonitrile (10a)



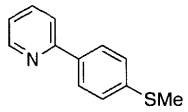
According to **GPS3**, a wax capsule and 4-chlorobenzonitrile (28 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography (silica gel, 0-80% ethyl acetate/hexanes) to provide **10a** (first run: 33 mg, 92%; second run: 34 mg, 93%) as a yellow solid.

M.p. (°C): 98 – 100. (Lit. 98 – 99[28])

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.77 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 8.16-8.13 (m, 2H), 7.91 (td, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.80-7.77 (m, 2H), 7.40 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.72, 149.23, 142.28, 138.40, 132.81, 127.82, 123.79, 121.67, 118.76, 113.09.

2-(4-(methylthio)phenyl)pyridine (10c)



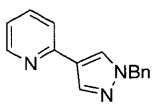
According to **GPS3**, a wax capsule and and 4-bromothioanisole (41 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography (silica gel, 0-60% ethyl acetate/hexanes) to provide **10c** (first run: 27 mg, 68%; second run: 29 mg, 72%) as a yellow solid.

M.p. (°C): 58 – 60.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.69-8.64 (m, 1H), 7.95-7.90 (m, 2H), 7.75-7.67 (m, 2H), 7.36-7.31 (m, 2H), 7.20 (ddd, *J* = 7.2, 4.8, 1.4 Hz, 1H), 2.52 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.91, 149.77, 139.92, 136.85, 136.14, 127.28, 126.48, 122.05, 120.18, 15.65.

2-(1-benzyl-1*H*-pyrazol-4-yl)pyridine (10h)



According to **GPS3**, a wax capsule, **9** (3.5 mg, 2 mol%), XPhos (4 mg, 4 mol%), and 1-benzyl-4-bromopyrazole (48 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography

[28] Cohen, T.; Deets, G. L. *J. Org. Chem.* **1972**, *37*, 55–58.

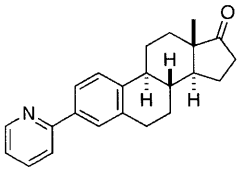
(silica gel, 0-99% ethyl acetate/hexanes plus 1% methanol throughout) to provide **10h** (first run: 36 mg, 75%; second run: 38 mg, 81%) as a yellow solid.

M.p. (°C): 75 – 79.

^{1}H-NMR (500 MHz, Methanol-d_4): δ 8.45 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 8.23 (d, *J* = 0.8 Hz, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.79 (td, *J* = 7.8, 1.8 Hz, 1H), 7.67 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.38-7.27 (m, 5H), 7.22 (ddd, *J* = 7.5, 5.0, 1.2 Hz, 1H), 5.39 (s, 2H).

^{13}C-NMR (126 MHz, Methanol-d_4): δ 152.86, 149.95, 138.93, 138.84, 137.92, 130.32, 129.84, 129.16, 128.77, 124.42, 122.79, 121.58, 56.85.

(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(pyridin-2-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (10i)



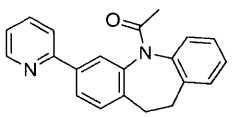
According to **GPS3**, a wax capsule and and estrone triflate (81 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography (silica gel, 0-100% ethyl acetate/hexanes) to provide **10i** (first run: 46 mg, 69%; second run: 42 mg, 65%) as a white solid.

M.p. (°C): 172 – 175.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.71 (dt, *J* = 4.9, 1.3 Hz, 1H), 7.83-7.71 (m, 4H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.29-7.24 (m, 1H), 3.09-2.93 (m, 2H), 2.56-2.44 (m, 3H), 2.36 (td, *J* = 11.0, 4.1 Hz, 1H), 2.21-2.02 (m, 3H), 1.99 (dt, *J* = 12.7, 3.0 Hz, 1H), 1.70-1.44 (m, 6H), 0.93 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 220.96, 157.04, 149.01, 141.38, 137.68, 137.32, 136.03, 127.68, 126.04, 124.39, 122.23, 120.88, 50.66, 48.10, 44.61, 38.19, 35.99, 31.72, 29.59, 26.60, 25.82, 21.73, 13.99.

1-(3-(pyridin-2-yl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethan-1-one (10j)



According to **GPS3**, a wax capsule and 5-acetyl-3-chloro-10,11-dihydrodibenzo[*b*,*f*]azepine (55 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column

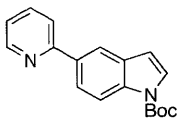
chromatography (silica gel, 0-99% ethyl acetate/hexanes plus 1% methanol throughout) to provide **10j** (first run: 44 mg, 69%; second run: 41 mg, 65%) as a light tan solid.

M.p. (°C): 150-152.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.98 (s, 1H), 7.87 (d, J = 7.3 Hz, 1H), 7.81-7.65 (m, 2H), 7.45-7.10 (m, 5H), 3.49-3.32 (m, 2H), 2.86 (dtt, J = 13.8, 8.8, 4.9 Hz, 2H), 2.07 (d, J = 22.3 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 170.94, 170.83, 156.65, 156.06, 149.86, 149.65, 148.68, 143.21, 142.68, 140.24, 140.04, 138.38, 137.64, 137.14, 135.51, 134.55, 131.31, 130.72, 130.42, 129.88, 128.94, 128.78, 127.93, 127.69, 127.55, 127.50, 126.83, 126.75, 126.23, 126.01, 125.20, 122.64, 122.36, 121.03, 120.53, 31.11, 31.04, 30.23, 30.14, 23.00, 22.89. Peaks doubled in spectra due to amide rotamers.[29]

***tert*-butyl 5-(pyridin-2-yl)-1*H*-indole-1-carboxylate (12)**



According to **GPS3**, a wax capsule and *N*-boc-5-bromoindole (**11**, 60 mg, 0.2 mmol) were dissolved in THF (1 mL) and the mixture was stirred for 16 h at 60 °C. The crude material was purified by flash column chromatography (silica gel, 0-1000% ethyl acetate/hexanes) to provide **12** (first run: 47 mg, 90%; second run: 43 mg, 72%) as a yellow oil.

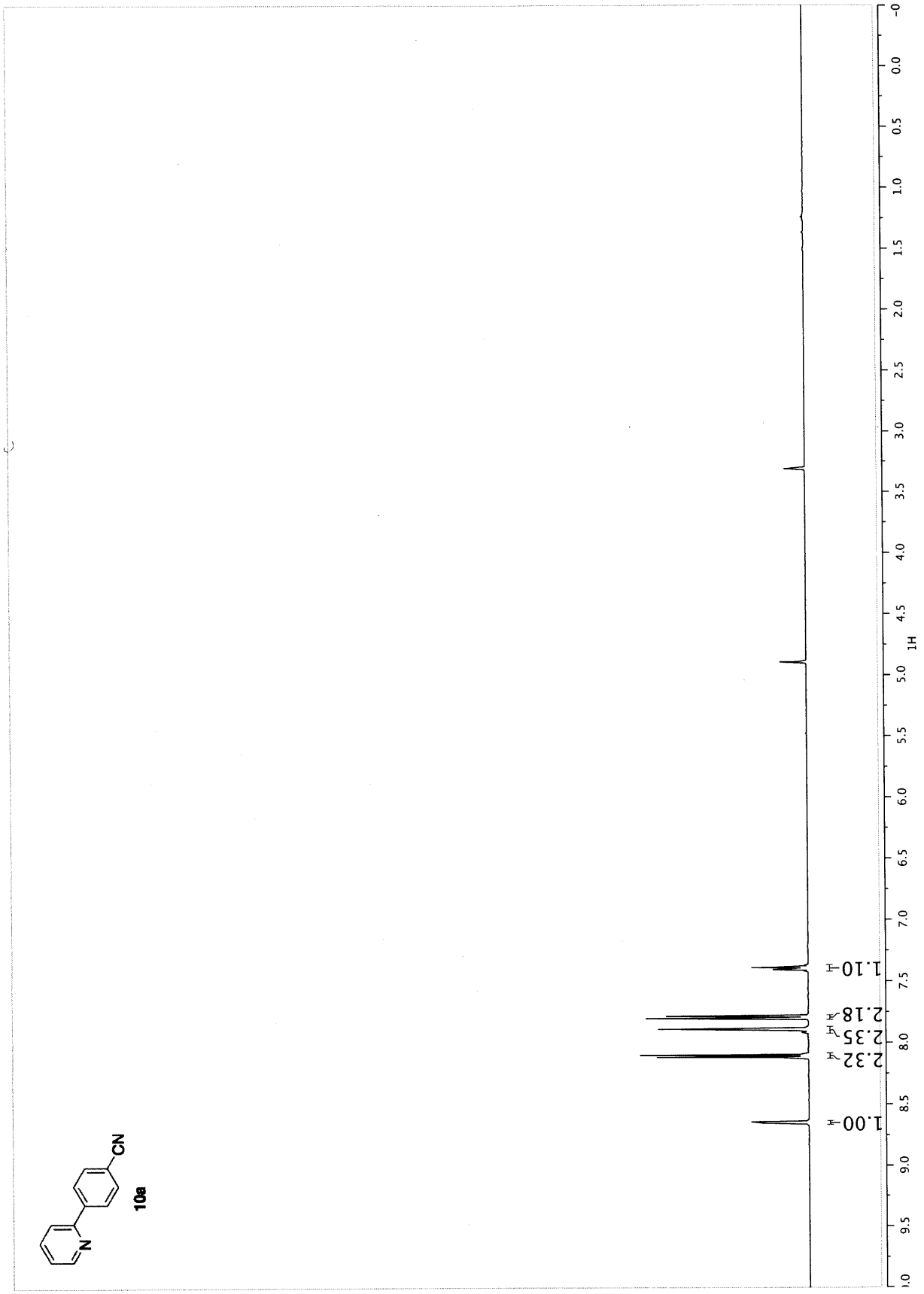
^{1}H-NMR (500 MHz, Methanol-d_4): δ 8.70 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 8.25-8.19 (m, 2H), 7.96 (dd, J = 8.7, 1.8 Hz, 1H), 7.80-7.71 (m, 2H), 7.64-7.61 (m, 1H), 7.21 (ddd, J = 7.2, 4.8, 1.3 Hz, 1H), 6.66-6.63 (m, 1H), 1.69 (s, 9H).

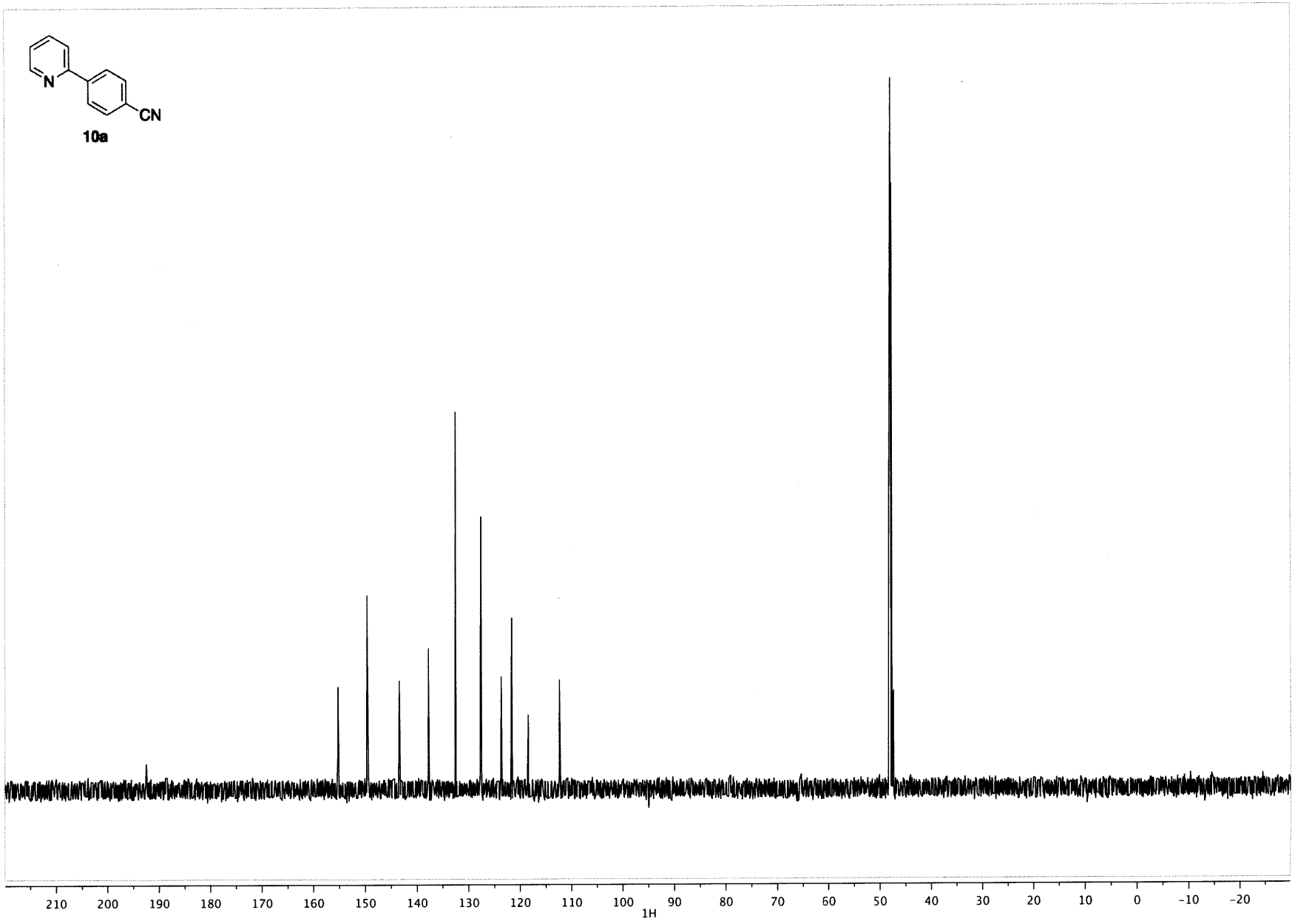
^{13}C-NMR (126 MHz, $CDCl_3$): δ 157.88, 149.76, 149.59, 136.95, 135.83, 134.10, 131.18, 126.71, 123.41, 121.78, 120.68, 119.73, 115.42, 107.89, 83.97, 28.32.

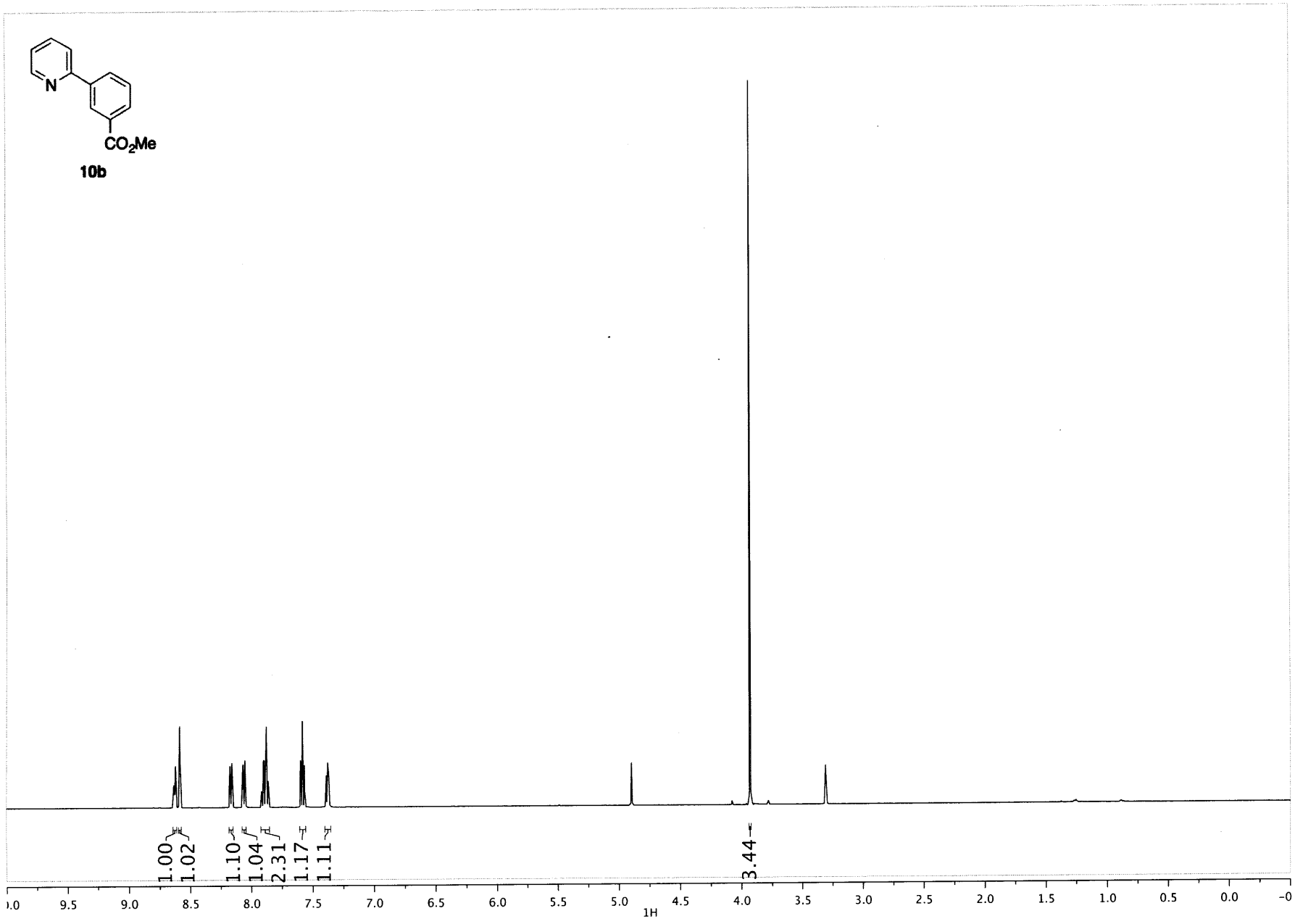
---

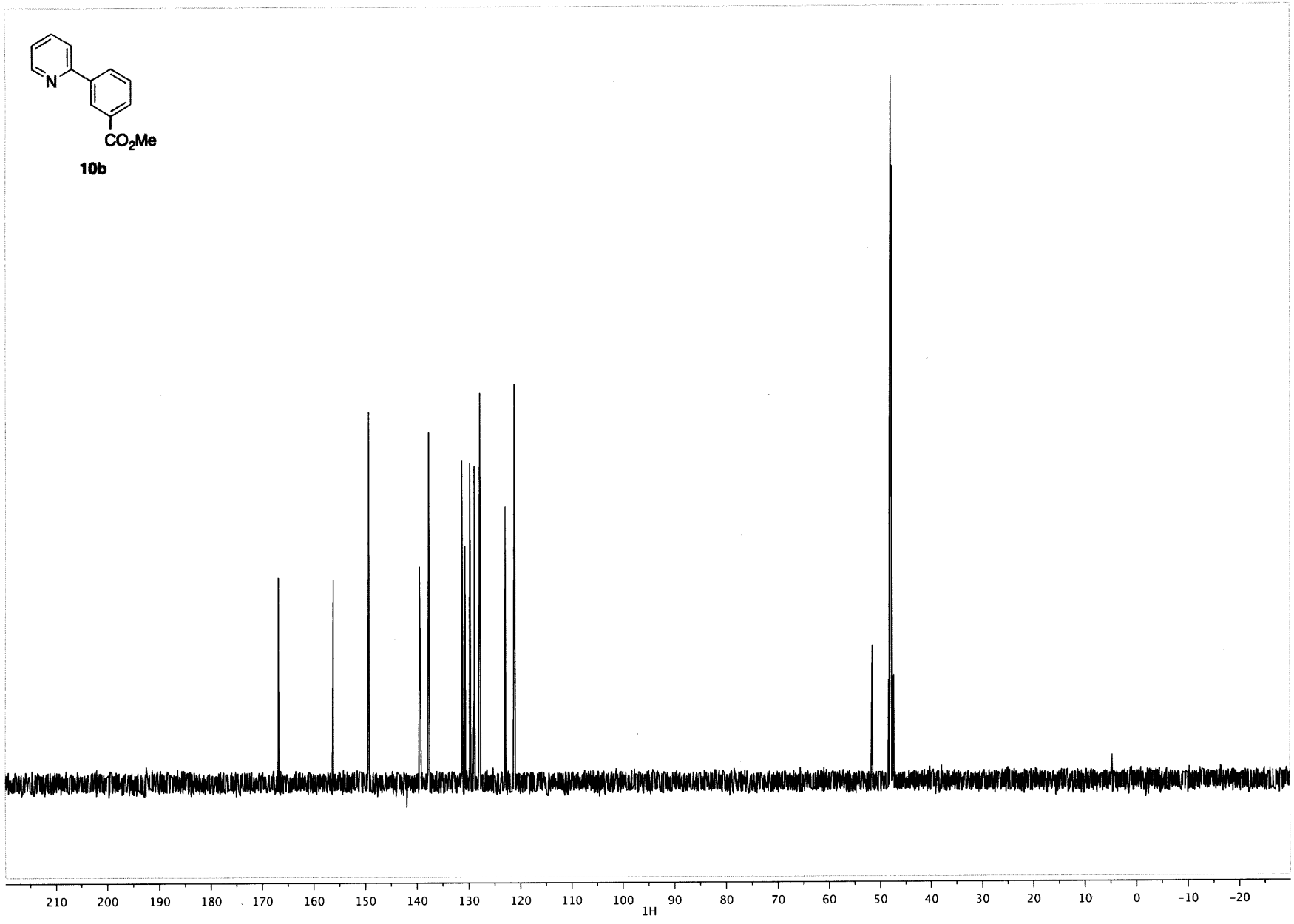
[29] Related compounds are known to feature multiple amide rotamers in ^{1}H- and ^{13}C-NMR spectra. See: Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

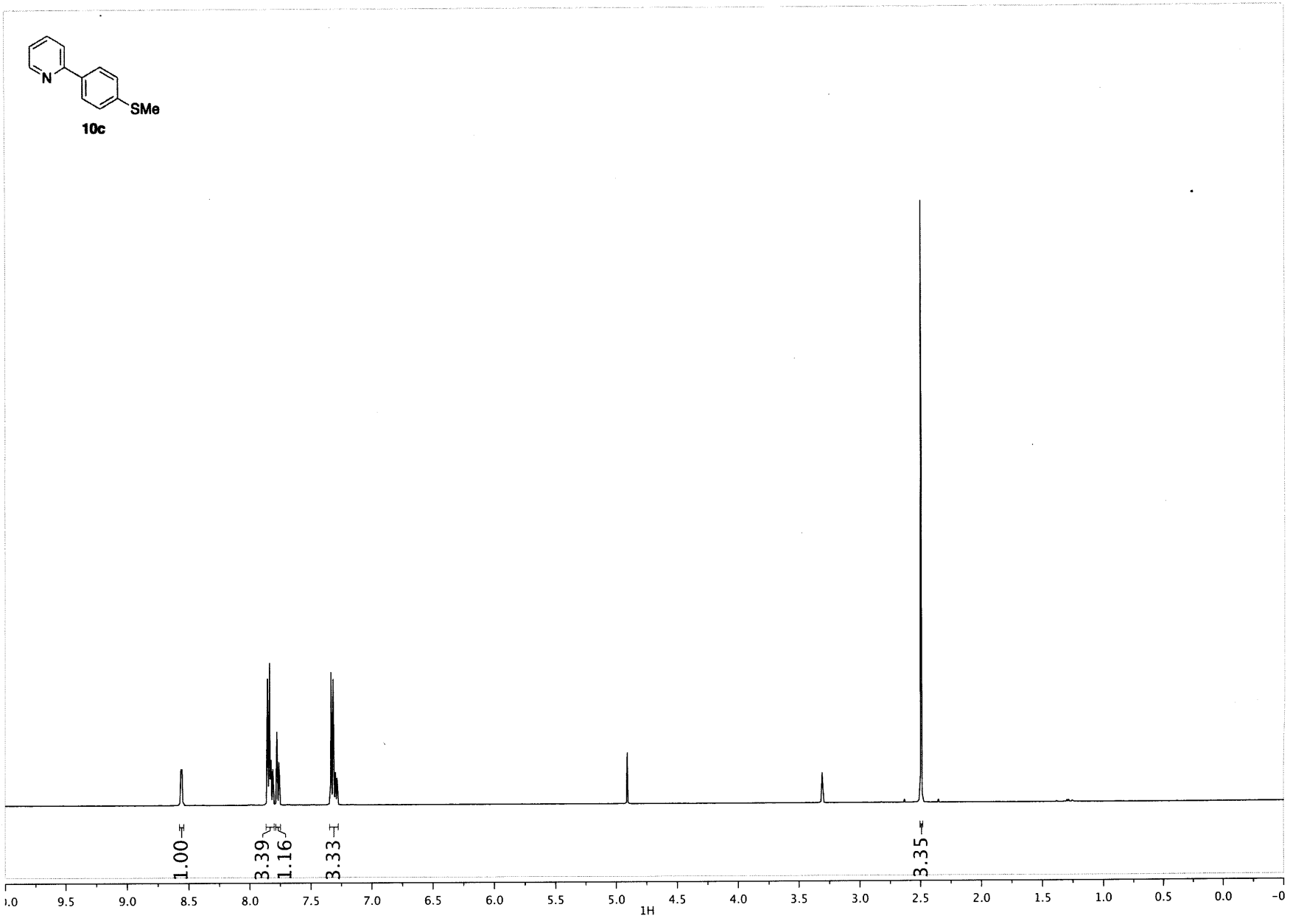
NMR Spectra

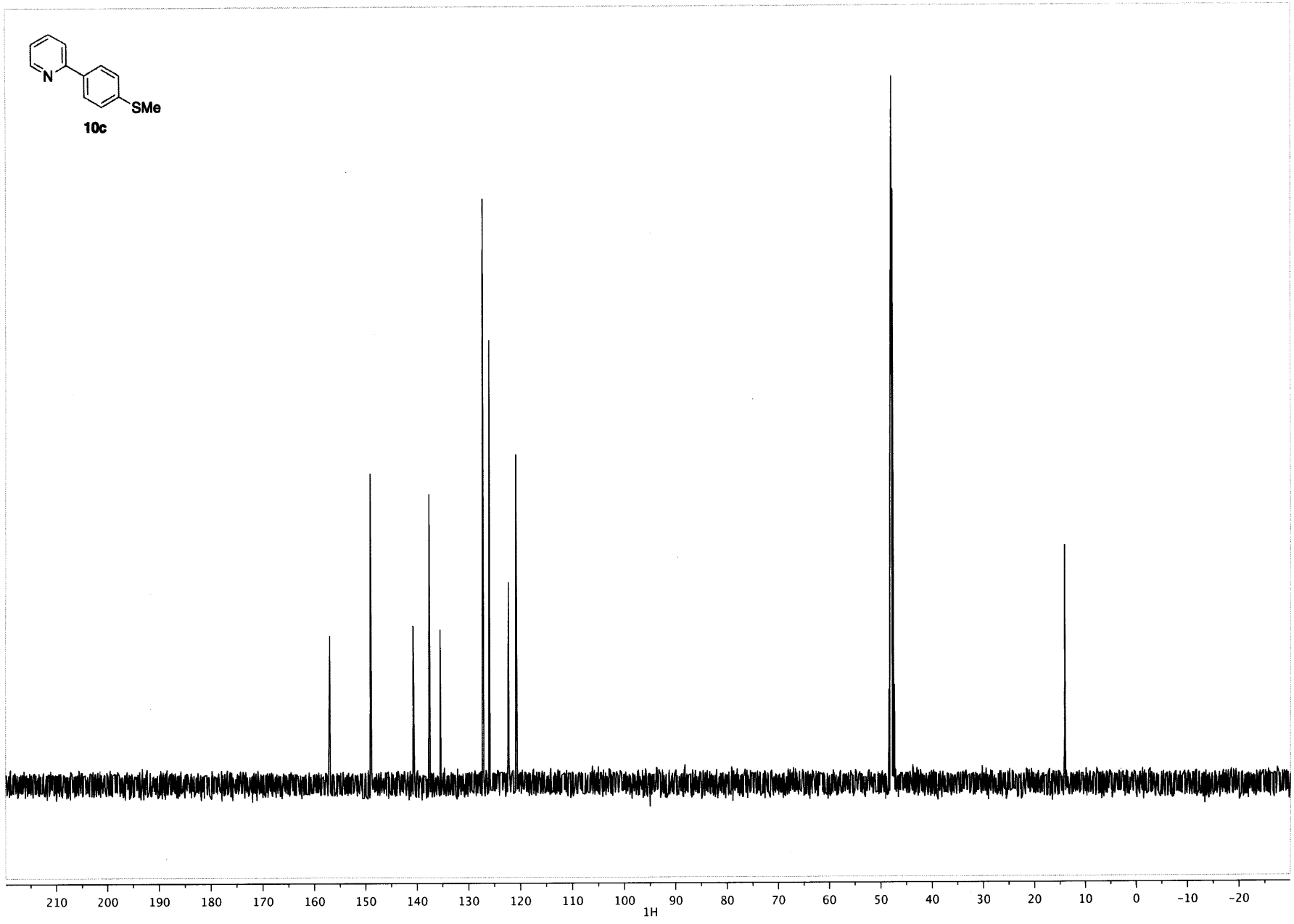



N
CN
10a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

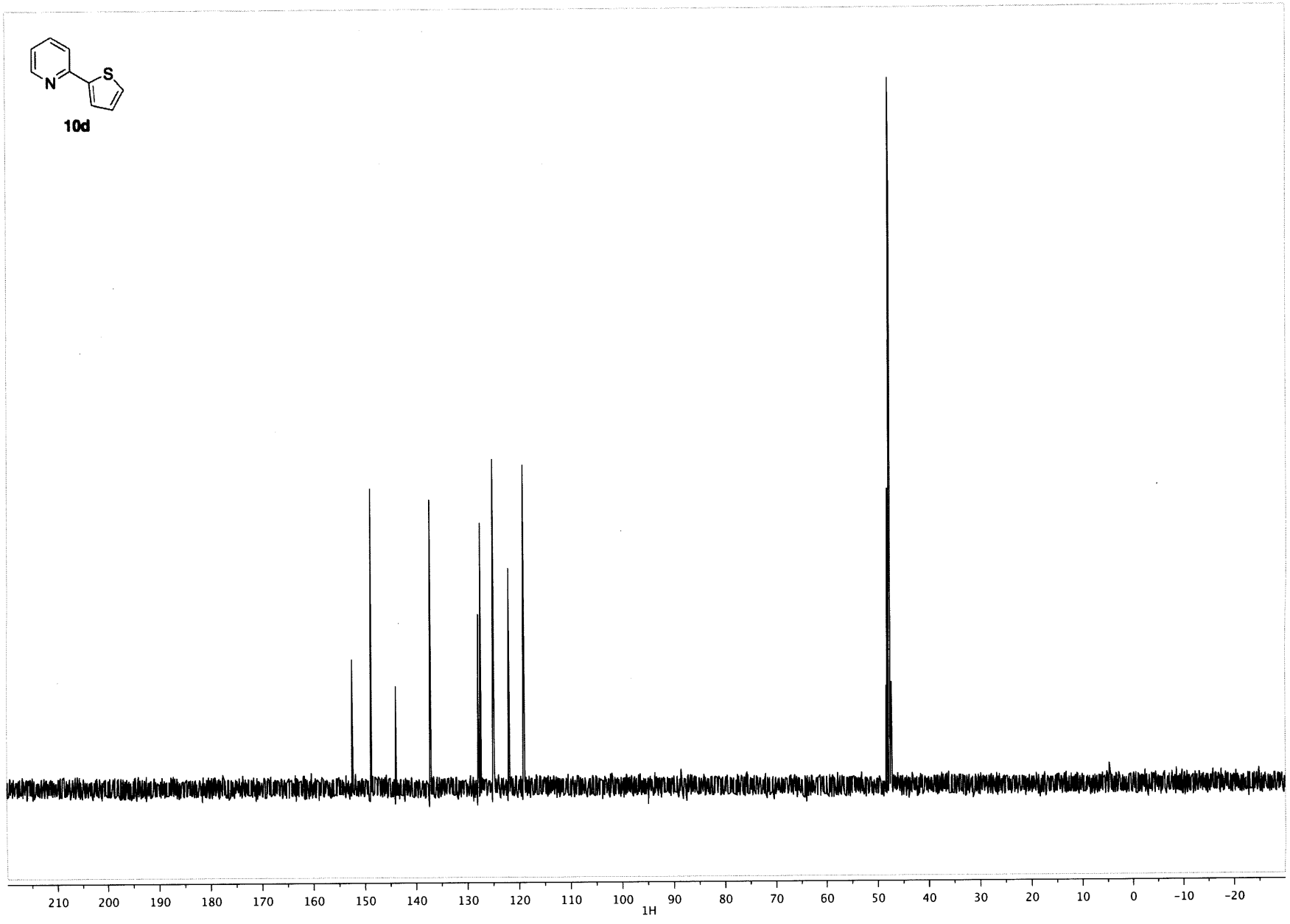

N
CO2Me
10b
1.00
1.02
1.10
1.04
2.31
1.17
1.11
3.44
1H

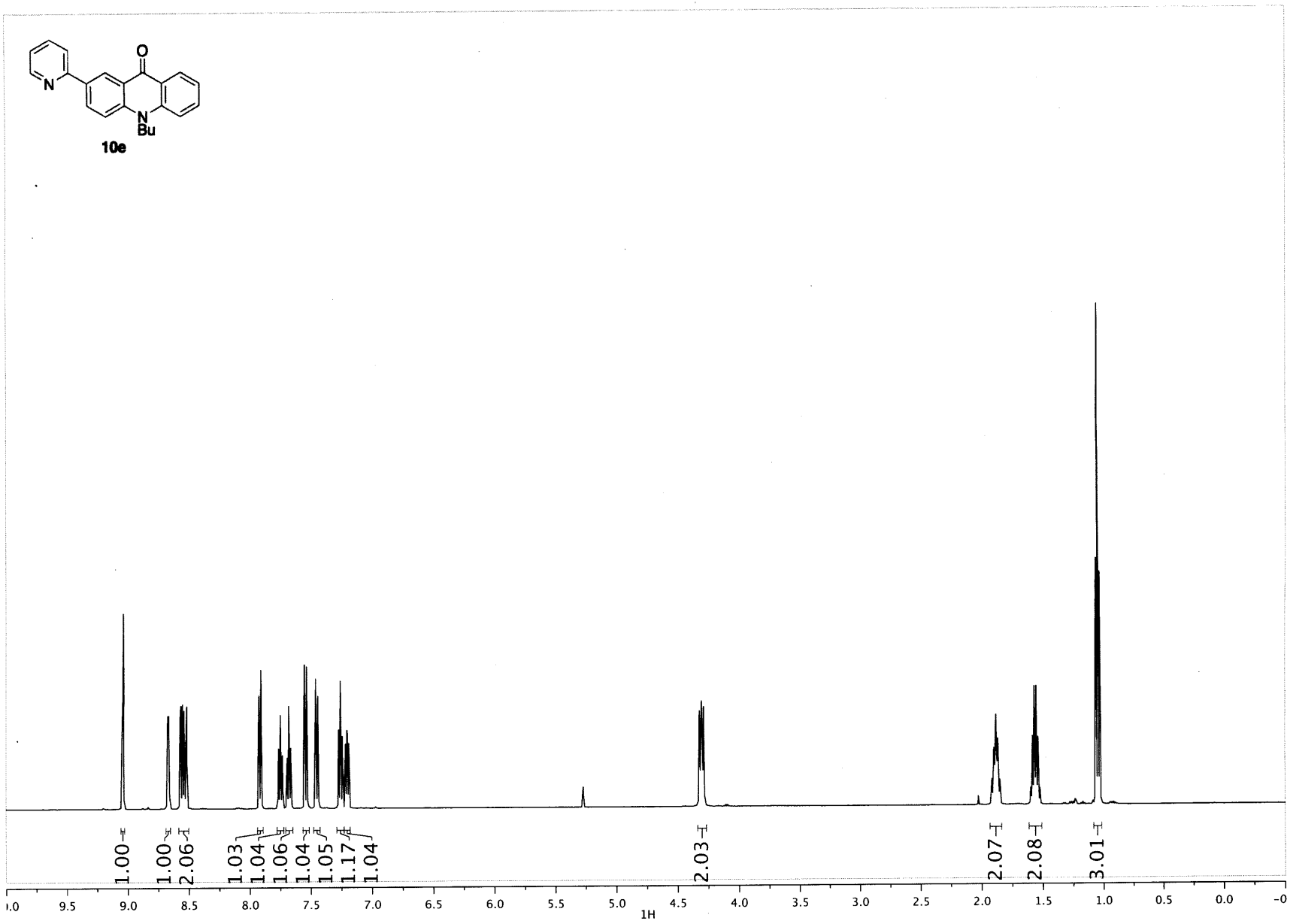

N
CO2Me
10b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

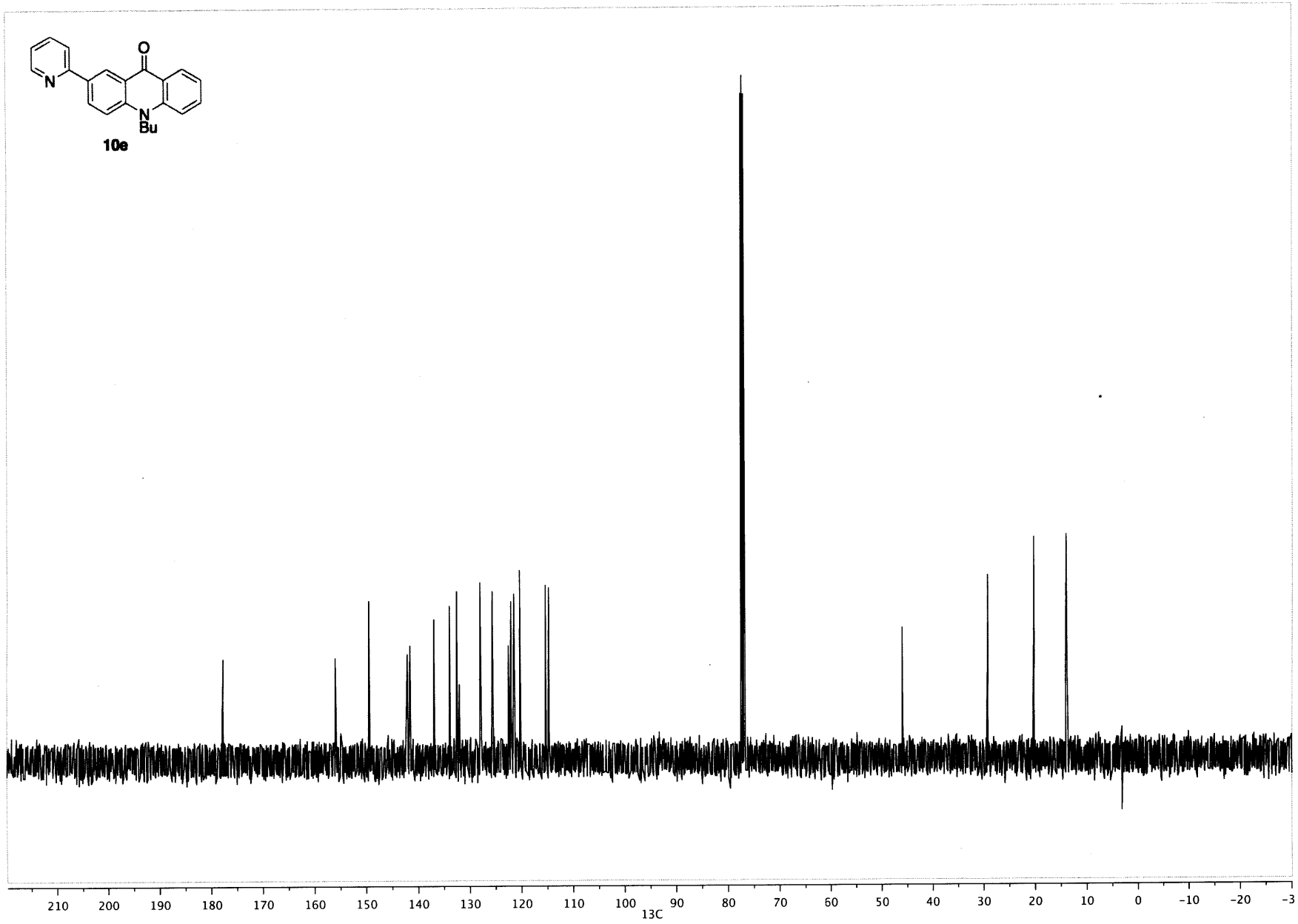

N
SMe
10c
1.00
3.39
1.16
3.33
3.35
1H

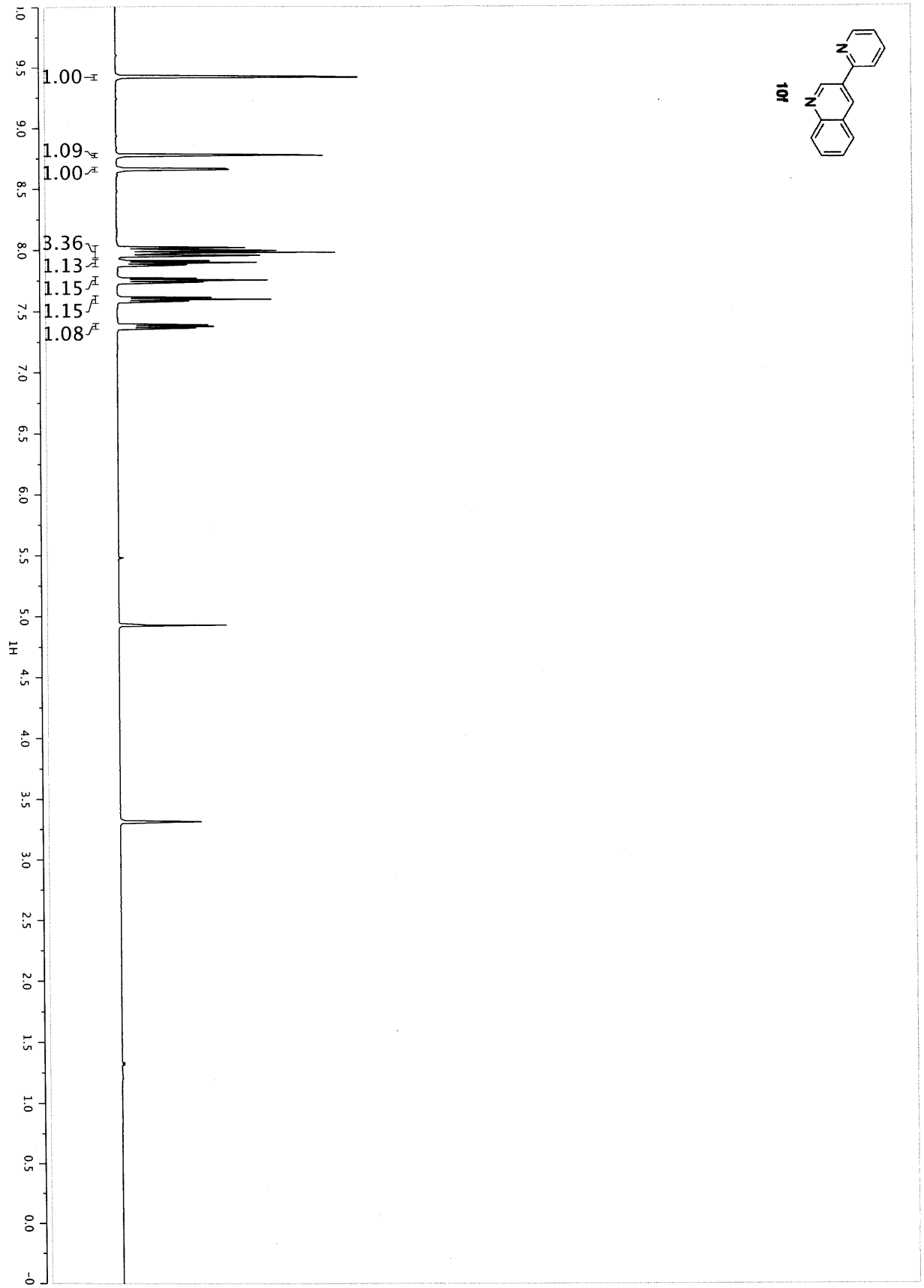

N
SMe
10c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

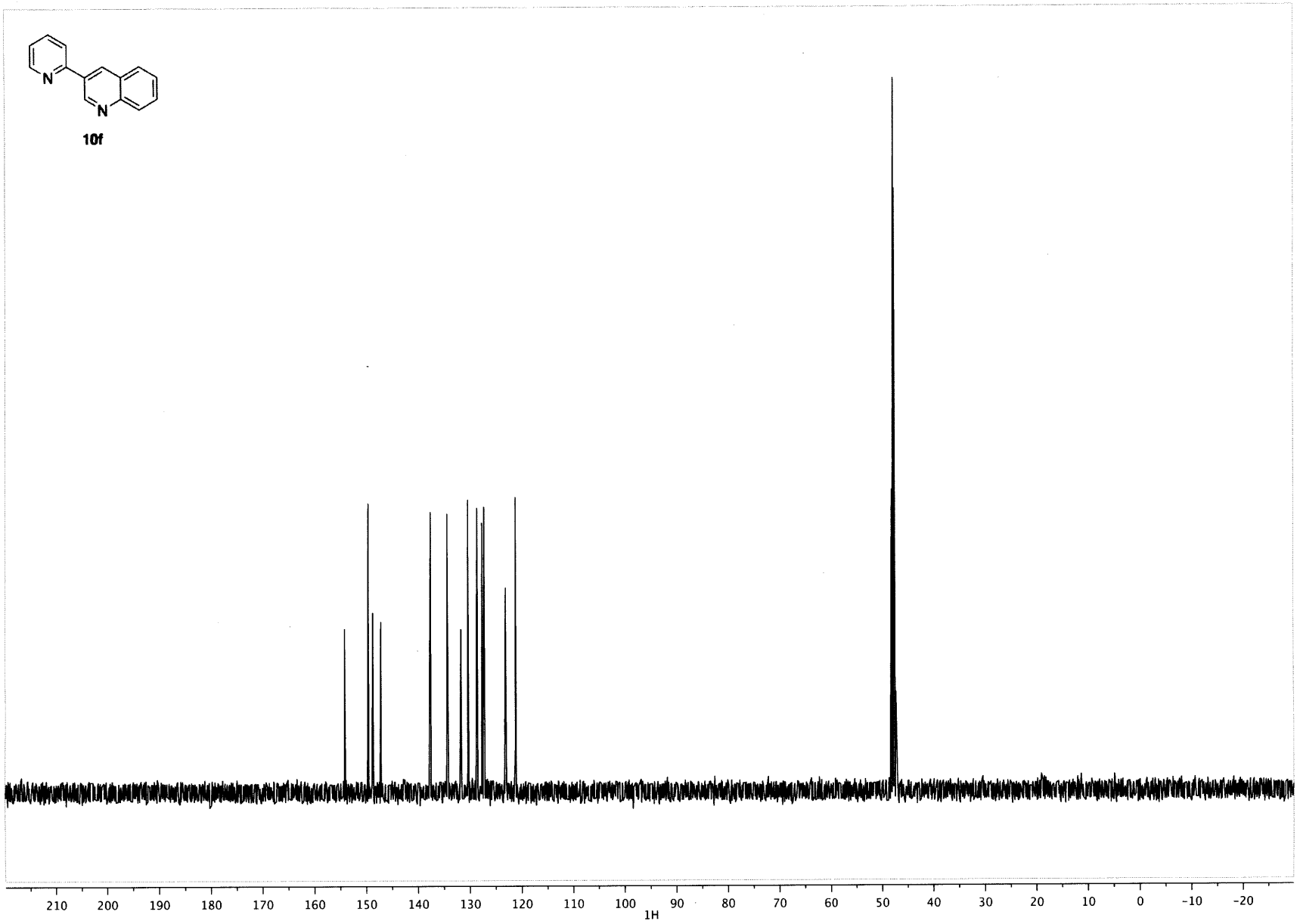
N
S
10d
1.00
2.09
1.04
0.98
1.04
1.02
1H

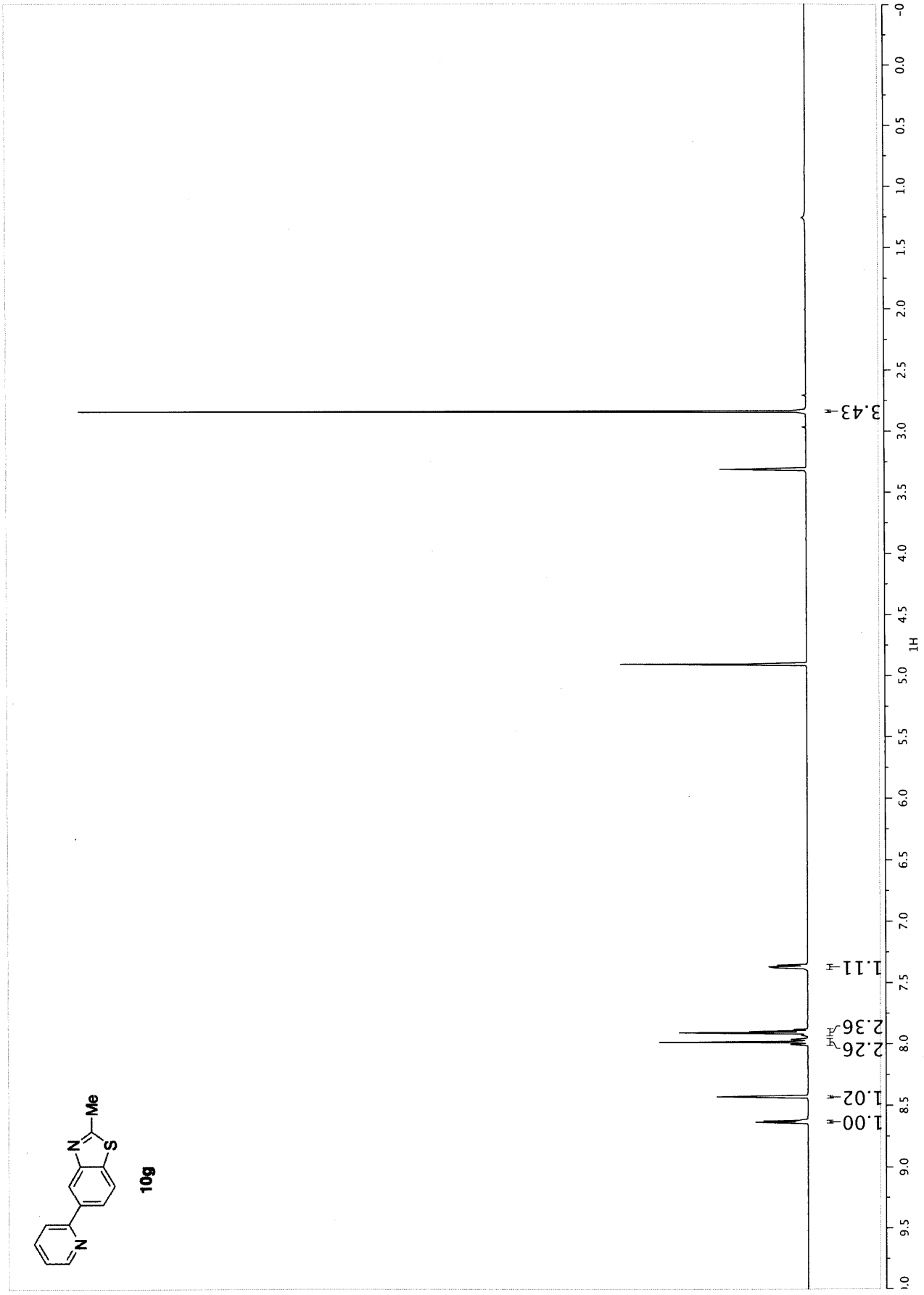

N
S
10d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

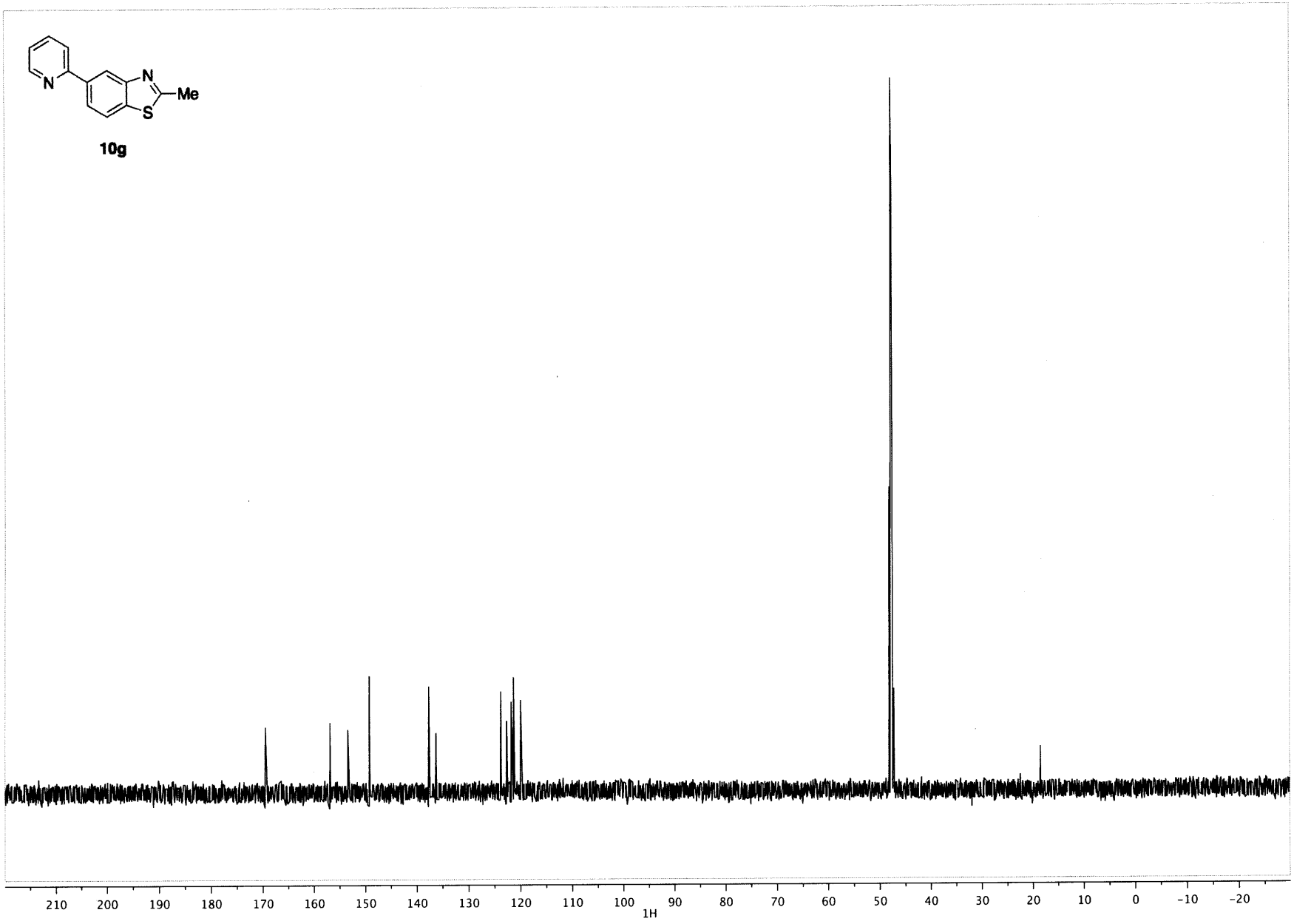

O
N
N
Bu
10e
1.00
1.00
2.06
1.03
1.04
1.06
1.04
1.05
1.17
1.04
2.03
2.07
2.08
3.01
1H


O
N
N
Bu
10e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
13C

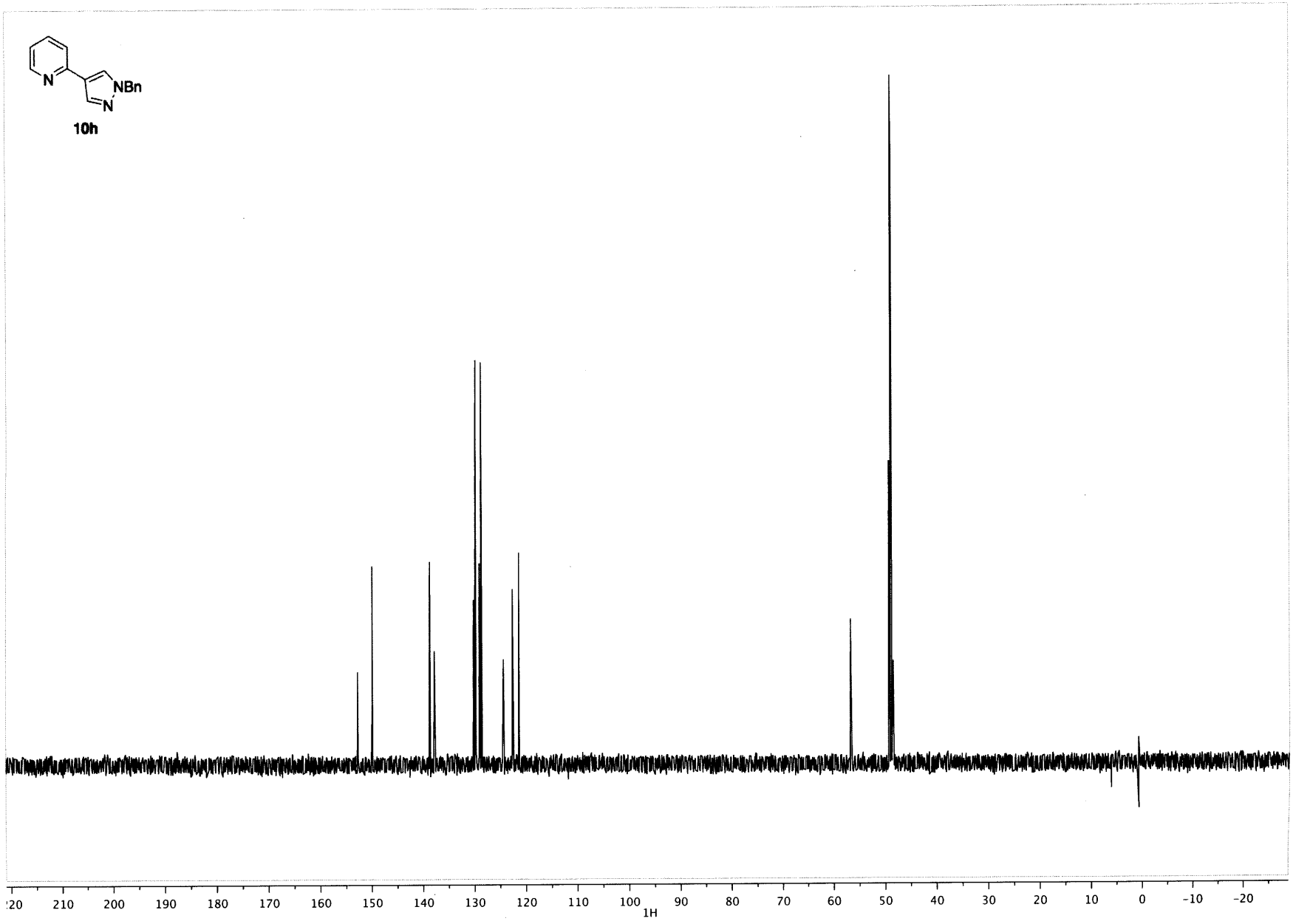

1.00
1.09
1.00
3.36
1.13
1.15
1.15
1.08
1H
10f


10f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

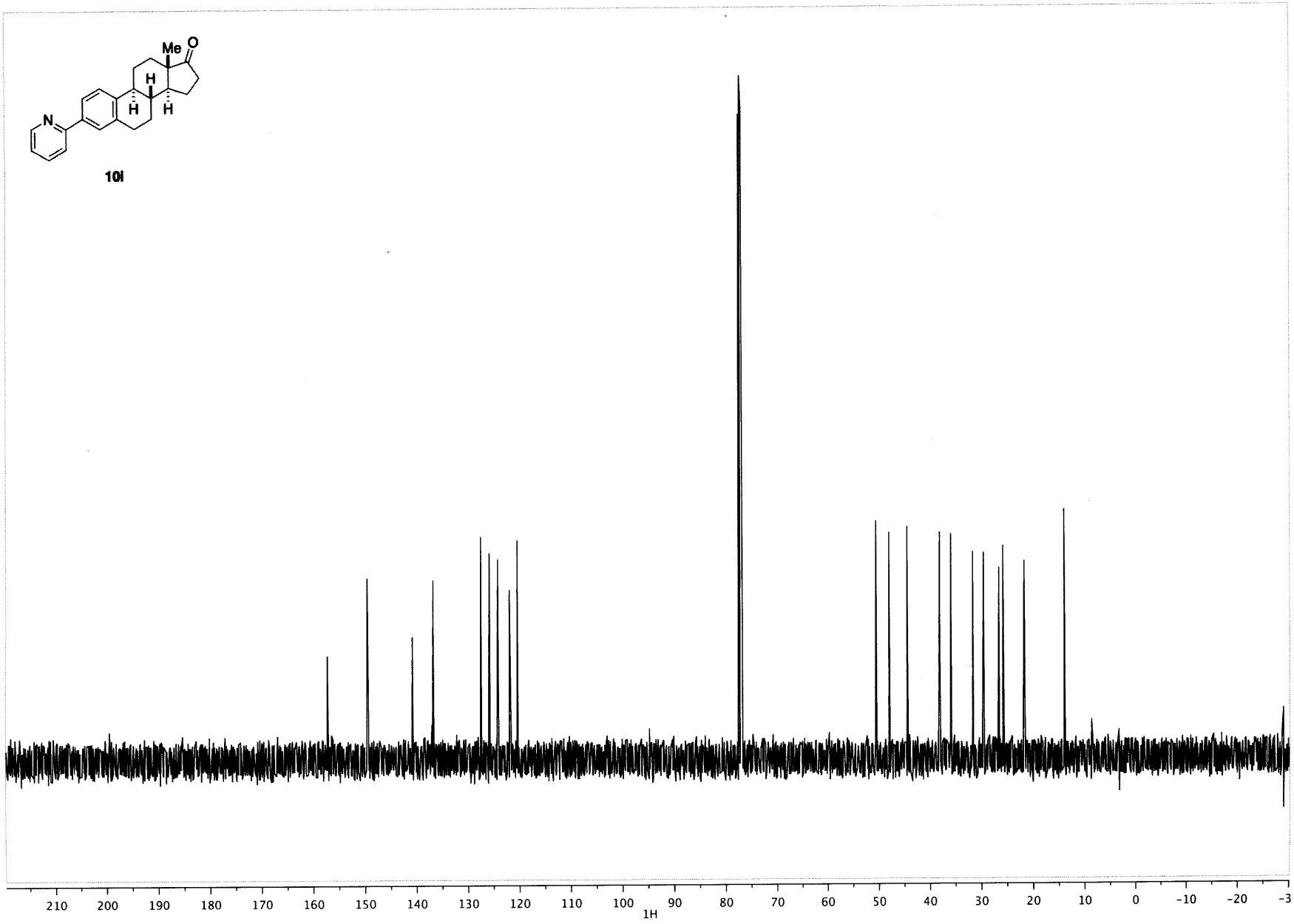

Me
N
S
N
10g
3.43
1.11
2.36
2.26
1.02
1.00
1H

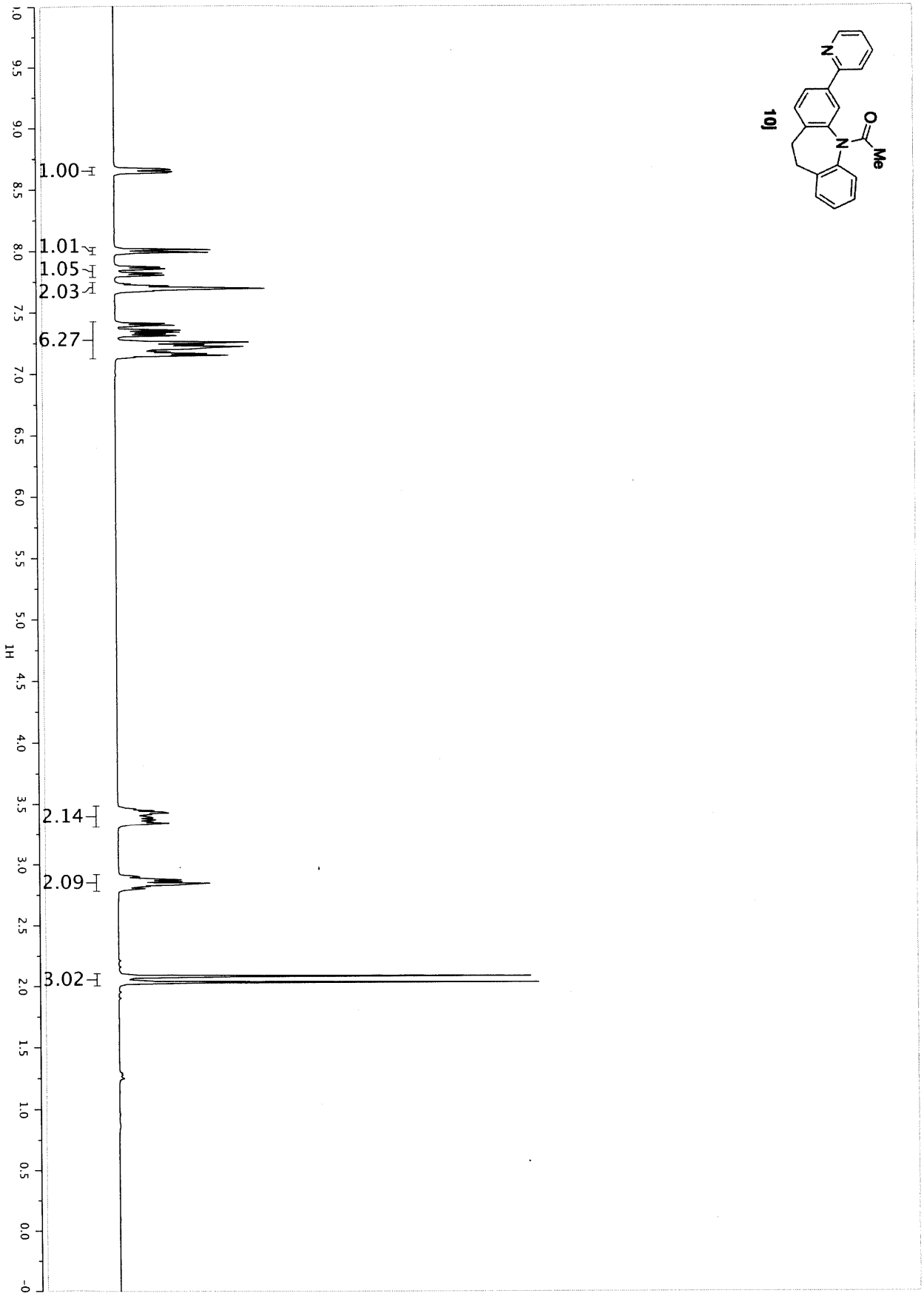

N
N
Me
S
10g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

N
NBn
N
10h
1.00
1.01
0.99
1.04
1.04
5.10
1.04
2.04
1H

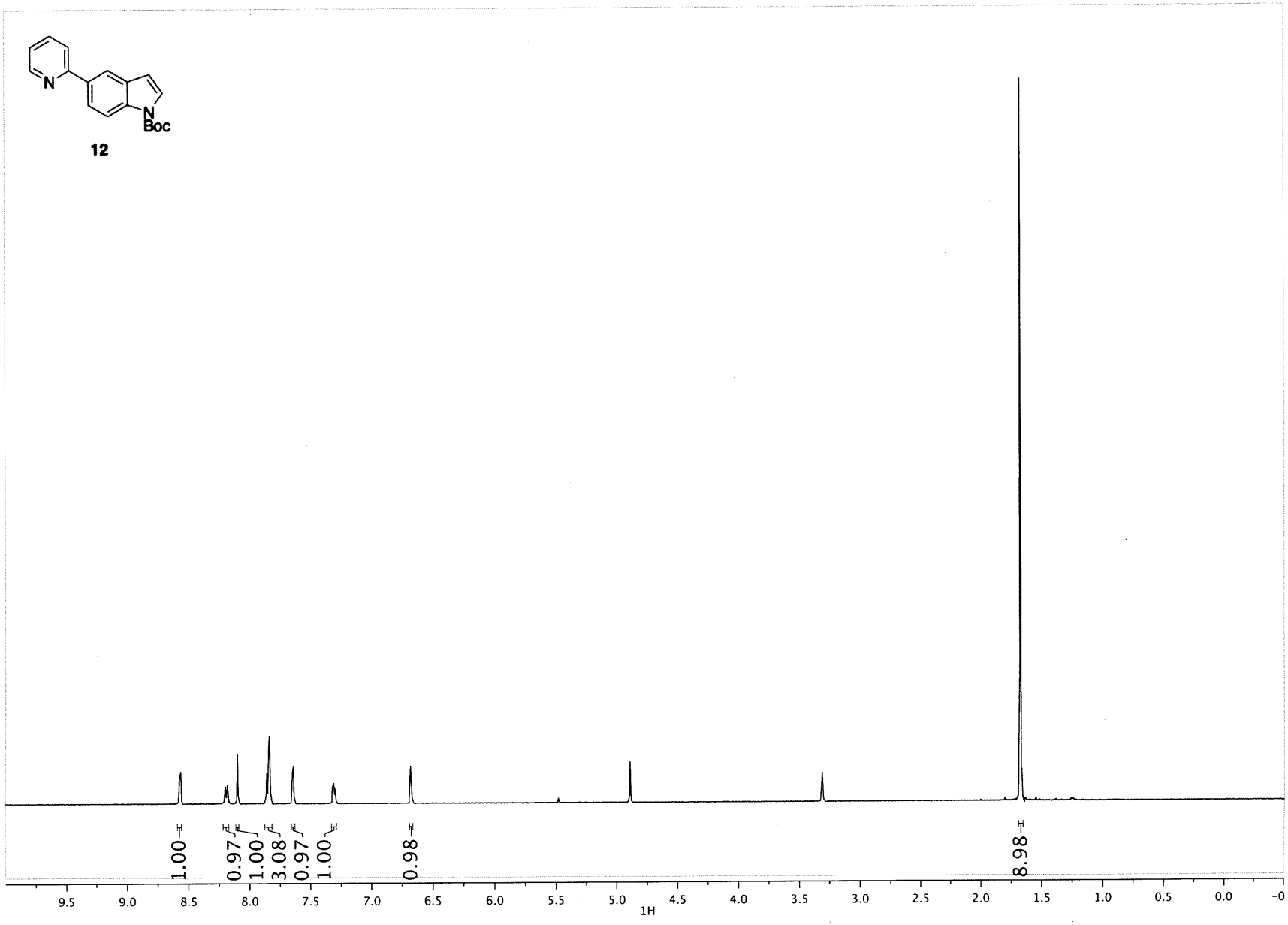

N
NBn
N
10h
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

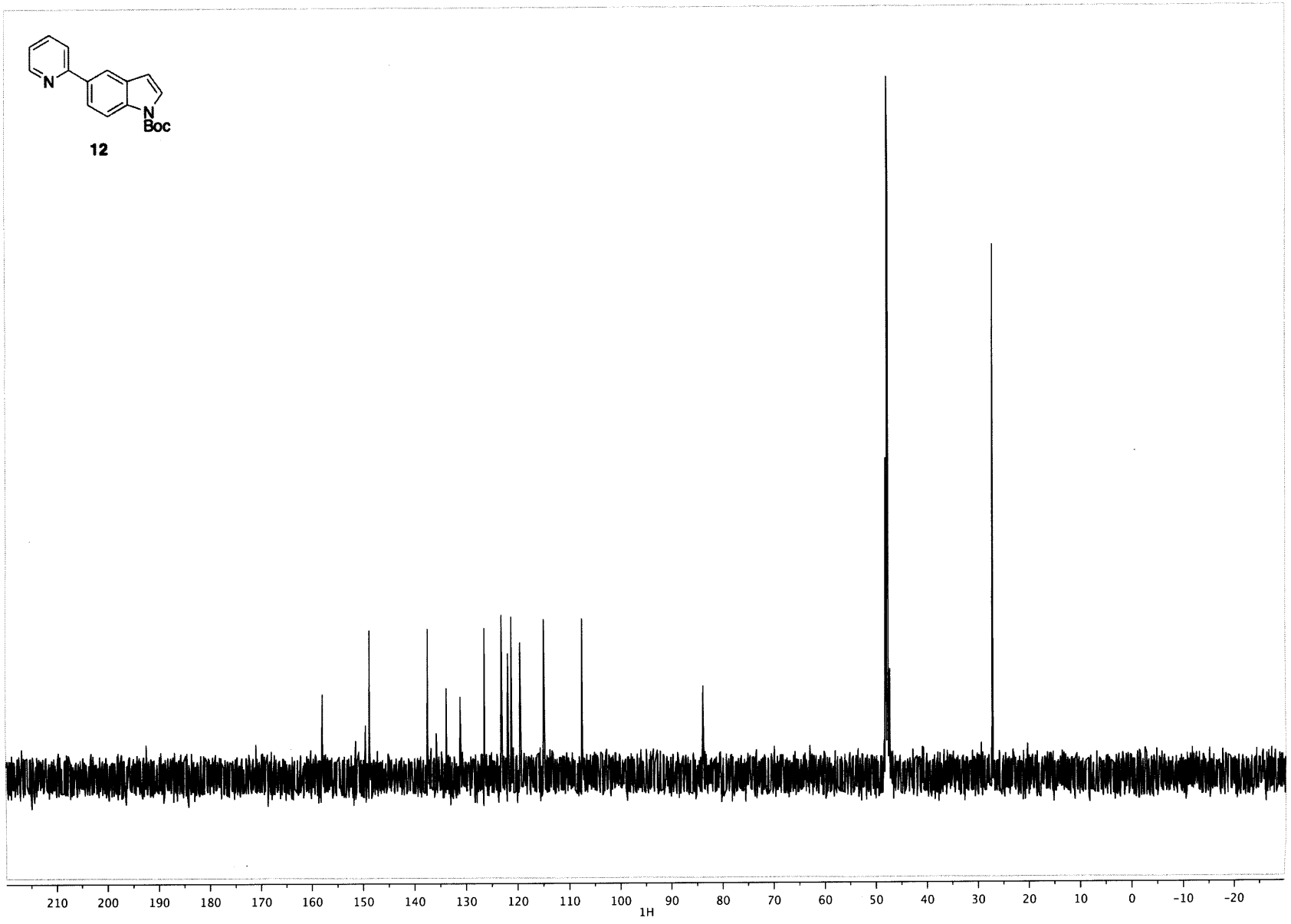
10i


Me
O
H
H
H
N
10i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H


1.00
1.01
1.05
2.03
6.27
2.14
2.09
3.02
1H
10j
N
N
O
Me

Me
O
N
N
10j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H


N
N
Boc
12
1.00
0.97
1.00
3.08
0.97
1.00
0.98
8.98
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
1H


N
N
Boc
12
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

Chapter II

Synthesis of Heteroaryl Sulfonamides from Organozinc Reagents and 2,4,6-Trichlorophenyl Chlorosulfate

2.1 Introduction

Heterocyclic sulfonamides are a historically significant and still common feature in successful pharmaceuticals and biologically active molecules.[1] Yet many examples of their most straightforward synthetic precursors, heterocyclic sulfonyl chlorides, are challenging to synthesize and/or notoriously unstable. Developing an efficient, modular, and general route to

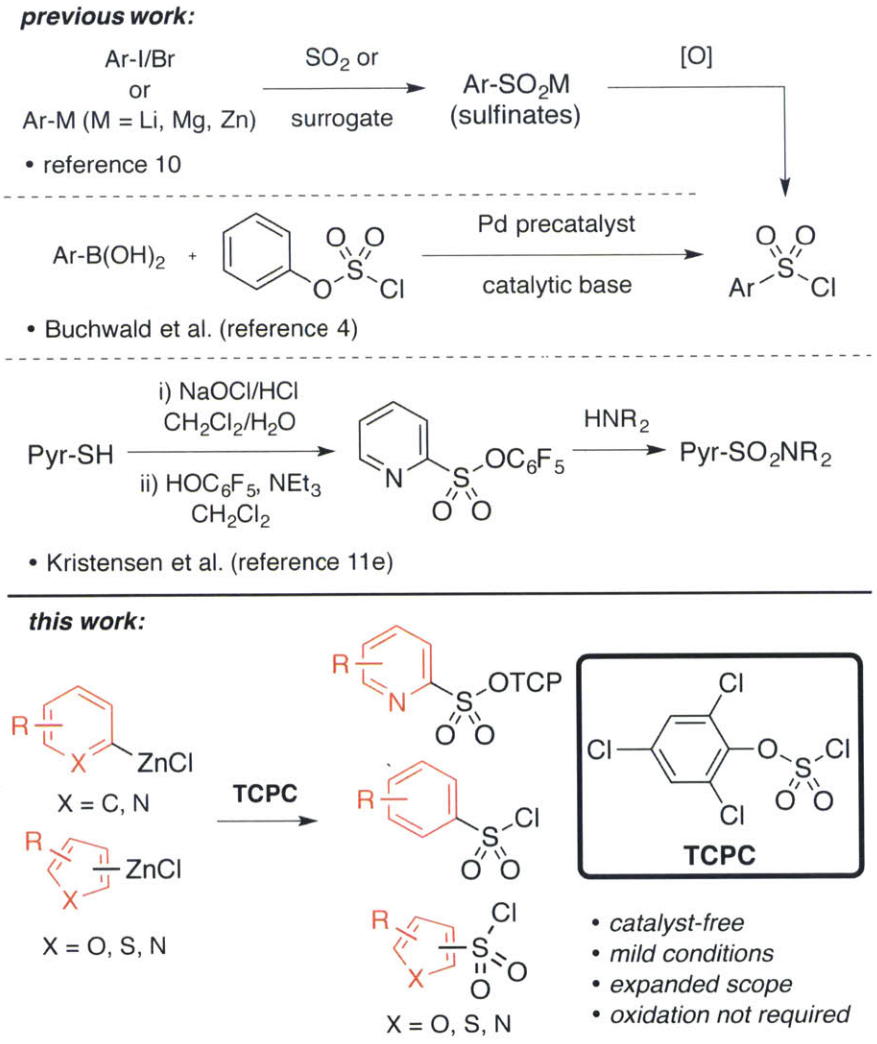


Figure 1. Synthesis of aryl and heteroaryl sulfonyl chlorides and sulfonate esters with 2,4,6-trichlorophenyl chlorosulfate (TCPC).

[1] (a) Drews, J. *Science* **2000**, *287*, 1960-1964. (b) Chrusciel, R. A.; Strohbach, J. W. *Curr. Top. Med. Chem.* **2004**, *4*, 1097-1114. (c) Malawska, B. *Curr. Top. Med. Chem.* **2005**, *5*, 69-85. (d) Olson, R. E.; Albright, C. F. *Curr. Top. Med. Chem.* **2008**, *8*, 17-33. (e) Sun, D.; Wang, M.; Wang, Z. *Curr. Top. Med. Chem.* **2011**, *11*, 1464-1475.

sulfonyl chlorides or synthetic equivalents without using toxic, inconvenient reagents such as chlorine gas or sulfuryl chloride is an important unsolved synthetic problem, especially from a discovery chemistry perspective.[2] Toward this end, our laboratory recently described a palladium-mediated synthesis of sulfonyl chlorides using phenyl chlorosulfate[3] and a variety of commercially available arylboronic acids (Figure 1).[4] The sulfonyl chloride products could be either isolated or reacted with amines to make sulfonamides in a one-pot procedure. However, 3-thienylboronic acid and dibenzofuran-4-boronic acid were the only heteroaryl nucleophiles for which this method could be employed. This inefficiency was due either to the protodeboronation of the heteroarylboronic acid nucleophiles[5] or the thermal instability of electron-deficient heteroar-yl sulfonyl chloride products, which in many cases readily decompose at room temperature to the corresponding chlorohet-eroarene and sulfur dioxide.[6]

Many other researchers have contributed to the synthesis of sulfonamides in recent years. Explored by the groups of Willis[7] and Wu,[8] an approach to sulfonamides using 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) and a Pd catalyst has been successful with some heterocycles. However, these protocols are mostly limited to iodoarenes and exclusively access N-aminosulfonamide products. Wu recently described the reaction of aryldiazonium tetrafluoroborates with DABSO to form sulfonamides, but no heterocyclic

---

[2] Wright, S. W.; Hallstrom, K. N. *J. Org. Chem.* **2005**, *71*, 1080-1084 and references therein.

[3] Buncel, E. *Chem. Rev.* **1970**, *70*, 323-337.

[4] DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10638–10641.

[5] (a) Lennox, A. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664-674. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469-483.

[6] Kwart, H.; Body, R. W. *J. Org. Chem.* **1965**, *30*, 1188-1195 and references therein.

[7] (a) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372-16373. (b) Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayter, B. R.; Willis, M. C. *Org. Biomol. Chem.* **2012**, *10*, 4007-4014.

[8] Li, W.; Li, H.; Langer, P.; Beller, M.; Wu, X.-F. *Eur. J. Org. Chem.* **2014**, 3101-3103.

examples were reported, and this reaction too was limited *N*-amino products.[9] A useful approach targets the more stable sulfinate functional group, which can be oxidized to form sulfonyl chlorides (Figure 1).[10] Organolithium,[10c] organo-magnesium,[10b,c,h,i] and organozinc[10g] reagents can be reacted with SO_2 or SO_2-surrogates like DABSO to form sulfinates directly, or aryl halides can be converted to sulfinates in the presence of an SO_2-surrogate and a Pd catalyst. However, relatively few heterocyclic sulfonamides have been prepared using either of these sulfinate strategies. Notably, sulfinates must be oxidized to form sulfonyl chlorides, and so methods that access them require an oxidation step to reach sulfonamide products. Although examples have been reported of aryl sulfonate esters as shelf-stable alternatives to thermally unstable heterocyclic sulfonyl chlorides, these compounds are still prepared by using the unstable sulfonyl chlorides in question (Figure 1).[11]

With the challenge of preparing heterocyclic sulfonamides still remaining, we aimed to increase the scope of our previous chemistry. In this chapter, we describe the preparation of aryl and heteroaryl sulfonamides using 2,4,6-trichlorophenyl chlorosulfate (TCPC)[12] and aryl- and

---

[9] Zheng, D.; An, Y.; Li, Z.; Wu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2451-2454.

[10] (a) For a recent review on sulfinates in organic synthesis: Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. *Org. Biomol. Chem.* **2014**, *12*, 9743-9759. (b) Woolven, H.; Gonzalez-Rodriguez, C.; Marco, I.; Thompson, A.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876-4878. (c) Deeming, A.; Russell, C. J.; Willis, M. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1168 –1171. (d) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10204-10208. (e) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 4404-4407. (f) Shavnya, A.; Coffey, S. B.; Smith. A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226-6229. (g) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154-157. (h) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. *J. Org. Chem.* **2003**, *68*, 8274–8276. (i) Chen, C. C.; Waser, J. *Org. Lett.* **2015**, *17*, 736–739.

[11] (a) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549-2551. (b) Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 1024-1025. (c) Caddick, S.; Wilden, J. D.; Judd, D. B. *Chem. Commun.* **2005**, 2727-2728. (d) Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem. Commun.* **2007**, 1074-1076. (e) Bornhold, J.; Fjære, K. W.; Felding, J.; Kristensen, J. L. *Tetrahedron* **2009**, *65*, 9280-9284.

[12] The reagent 2,4,6-trichlorophenyl chlorosulfate (TCPC) has made few appearances in the literature. See: (a) Takiura, K.; Honda, S. *Yakugaku Zasshi* **1967**, *87*, 1248-1255. (b) Doucet-Baudry, G.; *C. R. Seances Acad. Sci, Ser. C.* **1968**, *267*, 1057-1059. (c) Hedayatullah, M.; Leveque, J. C.; Denivell, L. *C. R. Seances Acad. Sci, Ser. C.* **1972**, *274*, 1937-1940.

heteroarylzinc reagents. Upon reaction with organozinc reagents, this electrophile generates intermediates at the sulfonyl chloride oxidation state that can be directly coupled with amines.

Substituting organozinc reagents for boronic acids has been a powerful and general strategy for enabling cross-coupling reactions of heteroaryl carbon nucleophiles,[13] and the same strategy was proposed for the synthesis of sulfonyl chlorides. This tactic, as in previous endeavors, was in part meant to circumvent the aforementioned protodeboronation problems associated with the corresponding Suzuki-Miyaura coupling reactions of heteroaryl boronates.[14] Additionally, initial experiments revealed that organozinc reagents react with arylchlorosulfates directly, without a transition metal catalyst (Scheme 1).[15]

2.2 Results and Discussion

In preliminary investigations, two modes of reactivity were observed. Allowing 2-pyridylzinc bromide **1** to react with TCPC afforded a 75% yield of 2,4,6-trichlorophenyl (TCP) pyridine-2-sulfonate **4a**. This product suggests a change of leaving group preference for TCPC when reacting with the 2-pyridylzinc reagent compared to what we observed in the Pd-catalyzed reaction with arylboronic acids and phenyl chlorosulfate[4] and to the reactivity of aryl chlorosulfates in general.[3] We believe that such a change is unlikely, and propose that although 2,4,6-trichlorophenoxide **3** leaves upon attack of TCPC by the organozinc reagent, an equivalent of the liberated phenoxide subsequently traps the highly reactive pyridine-2-sulfonyl chloride **2**.[16]

---

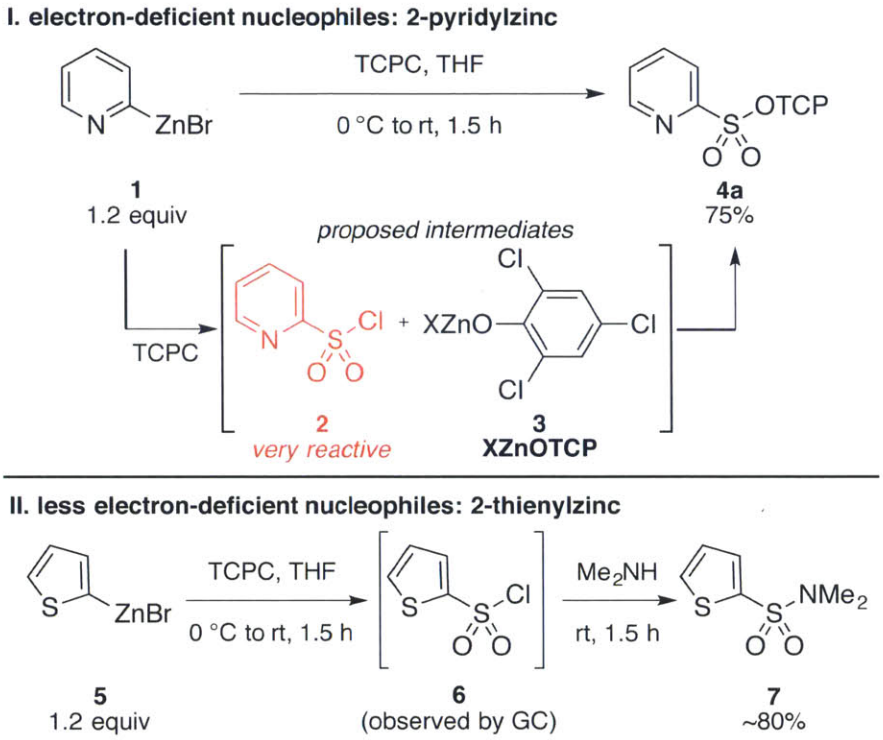
[13] (a) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 615-619. (b) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013**, *15*, 5754-5757.

[14] Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.

[15] The more reactive nucleophile 2-pyridylmagnesium chloride afforded only 11% of the desired sulfonate ester **4a** upon treatment with TCPC at -78 °C. Under the same reaction conditions, 2-pyridyllithium also resulted in a low (<10%) yield of **4a**.

[16] Kristensen has reported that pyridine-2-sufonyl chloride **2** can react with pentafluorophenol in the presense of triethylamine to form pentafluorophenyl pyridine-2-sulfonate in 76% yield. See reference 11e above.

This proposed mechanism is consistent with the known reactivity of both aryl chlorosulfates and the electrophile **2**.

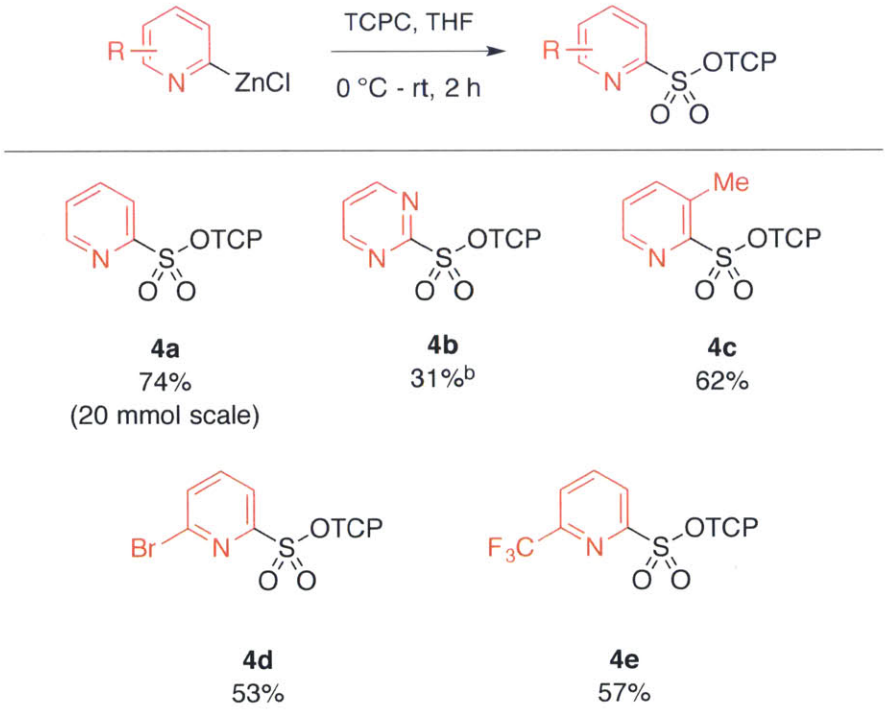


Scheme 1. TCPC exhibits two modes of reactivity.

In contrast, combining TCPC and 2-thienylzinc bromide **5** resulted in thiophene-2-sulfonyl chloride **6** (observed by GC), which was treated in situ with excess dimethylamine to afford sulfonamide **7**. This further substantiates the proposed mechanism of preferential displacement of 2,4,6-trichlorophenoxide over the chloride. Sulfonyl chloride **6** is more stable than **2**, and was not observed to react with the phenoxide under these conditions.

Formation of **4a** was surprising but quite advantageous. While pyridine-2-sulfonyl chloride 2 is very unstable, the TCP esters could be stored at room temperature for months without significant decomposition and were isolated by flash chroma-tography on silica gel. We chose TCPC over phenyl chlorosulfate for this work because TCP sulfonates are more reactive electrophiles than phenyl sulfonates. Caddick has shown that perfluorophenyl and TCP

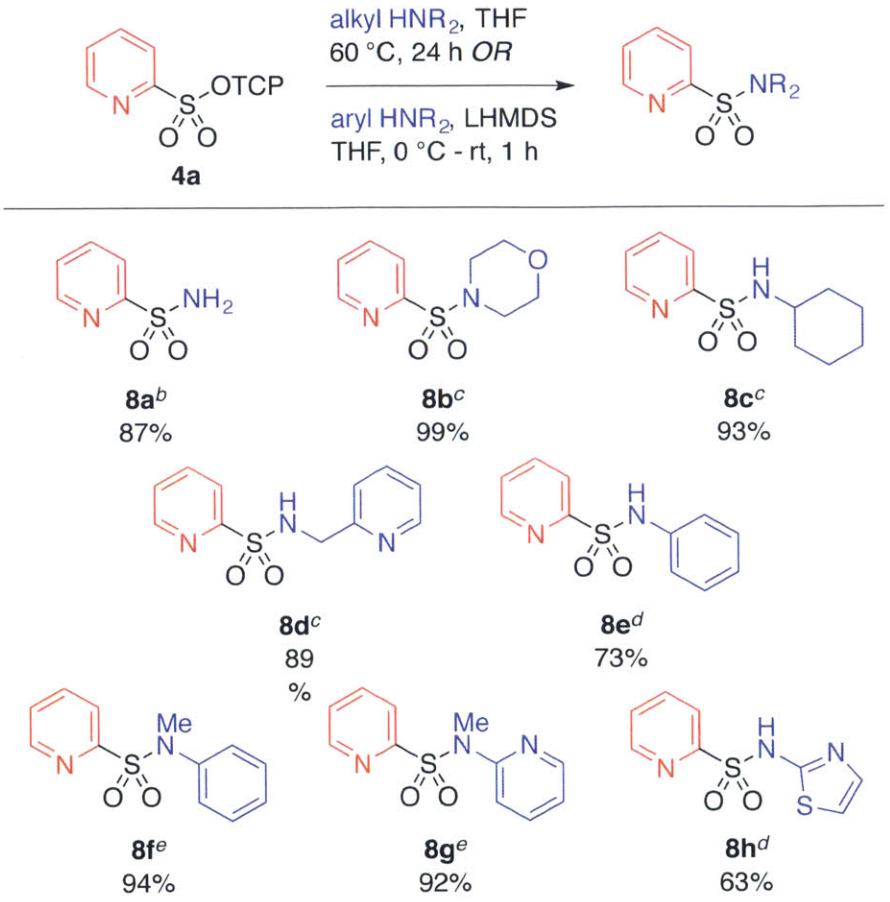
sulfonates are solid, stable, and sufficiently reactive electrophiles that can be used as sulfonyl chloride surrogates.[11a-d] While Caddick's methods were only extended to a few heteroaryl sulfonyl electrophiles, Kristensen further demonstrated that perfluorophenyl sulfonates of elec-tron-deficient heteroarenes were stable alternatives to the cor-responding unstable sulfonyl chlorides.[11e] However, perfluorophenyl chlorosulfate decomposed when we attempted to purify it by silica gel chromatography, and was not pursued in light of our success with TCPC.



[a]Reaction conditions: HetArBr (1.0 mmol), *n*-BuLi (1.0 mmol), $ZnCl_2$ (1.0 mmol), TCPC (1.0 mmol). Isolated yields are an average of two runs. [b]Reaction conditions: 2-Iodopyrimidine (1.0 mmol), *i*-PrMgCl•LiCl (1.0 mmol), $ZnCl_2$ (1.0 mmol), TCPC (1.0 mmol).

Scheme 2. Synthesis of 2,4,6-trichlorophenyl pyridine-2-sulfonates from 2-pyridylzinc reagents and TCPC.

We were able to generate a series of TCP pyridine-2-sulfonates (Scheme 2), with minimal optimization required to determine the described reaction conditions. A 1:1 ratio of organozinc reagent to TCPC afforded satisfactory yields of the desired esters. The parent substrate, **4a**, was prepared on a 20 mmol scale with no additional difficulty. Several substituted pyridines were



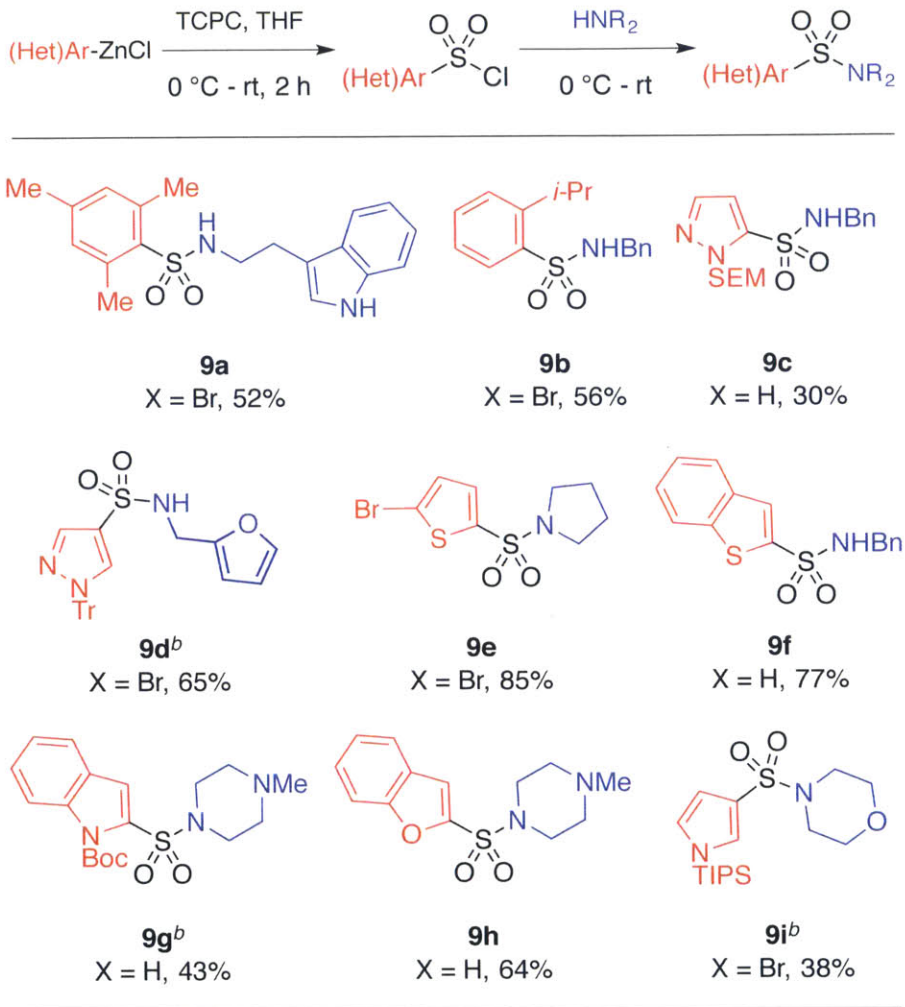
[a]Isolated yields are an average of two runs. [b]Reaction conditions: **4a** (1.0 mmol), 56% aqueous NH_4OH (2 mL), 1 h. [c]Reaction conditions: **4a** (1.0 mmol), amine (2.0 mmol). [d]Reaction conditions: **4a** (1.0 mmol), amine (2.0 mmol), LHMDS (2.0 mmol). [e]Reaction conditions: **4a** (1.0 mmol), amine (1.2 mmol), LHMDS (1.2 mmol).

Scheme 3. Preparation of pyridine-2-sulfonamides.

used, all isolated as solids that were stable in air on the lab bench (**4b-e**). While our laboratory and others have generally found that magnesium-halogen exchange is preferable to lithium-halogen exchange when preparing 2-pyridylzinc for Negishi cross-coupling reactions,[13,17] 2-pyridylzinc mixtures prepared from Grignard reagents consistently afforded lower yields of the sulfonate ester when reacted with TCPC. This is seen in the yield of **4b**, where the only

[17] Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, *75*, 8330-8332.

successful method for preparing the 2-pyrimidinylzinc reagent was by use of magnesium-iodine exchange.



[a]Reaction conditions: (Het)Ar-H/Br (1.0 mmol), *n*-BuLi (1.0 mmol), $ZnCl_2$ (1.0 mmol), TCPC (1.0 mmol), amine (2.0 mmol). Isolated yields are an average of two runs. [b]Same as general procedure, except TCPC was added at -78 °C with subsequent warming to rt overnight.

Scheme 4. Preparation of (hetero)aryl sulfonamides with organozinc reagents and TCPC via sulfonyl chlorides.

To demonstrate the utility of TCP pyridine-2-sulfonates, 4a was converted to N-alkyl and -aryl sulfonamides in good yields (Scheme 3). The ester is not as reactive as pyridine-2-sulfonyl chloride, and while this imparts the benefit of bench stability, more vigorous conditions are required to react this electrophile with amines. Heating to 60 °C was sufficient for ammonia and

alkylamines (8a-d), but strong base (LHMDS) was required for *N*-aryl- and *N*-heteroarylamines (**8e-h**).

We then showed that the scope of TCPC with less electron-deficient aryl- and heteroarylzinc reagents is quite broad (Scheme 4). Of note, sterically encumbered arylzinc reagents represent suitable nucleophiles for the sulfonylation reaction (**9a-b**). Sulfonamides attached at the 2- and 3-positions of pyrazole were both prepared in useful yields (**9c-d**), as well as two thiophene-based sulfonamides (**9e-f**). Lastly, three examples of electron-rich 5-membered heterocycles were converted to sulfonamides (**9g-i**).

2.3 Conclusions

The underexplored reagent TCPC has been shown to facilitate a new and convenient way to prepare aryl and heteroaryl sulfonyl chlorides. No transition metal catalyst is required for the reaction, and using organozinc reagents enabled the functionalization of heterocycles. A broad range of amines and electron-rich (hetero)arylzinc reagents were suitable coupling partners, enabling the rapid synthesis of a diverse set of sulfonamides. TCPC also allowed for the preparation of TCP pyridine-2-sulfonates, bench stable alternatives to pyridine-2-sulfonyl chlorides that are still reactive with both alkyl- and arylamines. For both classes of heterocycles, these protocols take advantage of the modularity of the sulfonamide functional group when generating molecular diversity. This modularity and the operationally simplicity of the procedures described herein suggest that TCPC may serve as a useful and practical reagent in drug discovery or medicinal chemistry efforts.

2.4 Experimental

General Information

All reactions were carried out under an argon atmosphere in flame-dried or oven-dried glassware unless otherwise specified. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Commercial materials were used without additional purification unless otherwise specified. The part number for the oven-dried culture tubes used was Fisher 20 x 150 mm tubes (Cat. No. 1495937C); for plastic screw top caps, CLOSURE OT S/T 18-400TH 14 (Cat. No. 033407G); and for septa that fit into the screw cap tops, Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10 (Cat. No. 03394B).

Reagents: Tetrahydrofuran (THF) was purchased from J. T. Baker in CYCLE-TAINER™ containers and then vigorously purged with argon for one hour and passed through two activated alumina columns. Triethylamine was purchased from J. T. Baker. Zinc chloride solution (1.9M in 2-methyl tetrahydrofuran), *n*-butyl lithium solution (2.5M in hexanes), isopropylmagnesium chloride lithium chloride complex solution (1.3 M in THF) (Turbo Grignard), 2-pyridylzinc bromide solution (0.5M in THF), 2-thienylzinc bromide solution (0.5M in THF), lithium bis(trimethylsilyl)amide (LHMDS) solution (1.0 M in THF), aniline, sulfuryl chloride, 2,6-dibromopyridine, morpholine, benzylamine, *N*-methylaniline, 2-aminothiazole, 2,4,6-trichlorophenol, thianaphthene, 2,4,6-trimethylbromobenzene, 2,3-benzofuran, *tert*-butyl 1*H*-indole-1-carboxylate, hexanes, ethyl acetate (EtOAc), dichloromethane, and methanol (MeOH) were purchased from Sigma Aldrich. 2,5-Dibromothiophene, 2-bromo-6-(trifluoromethyl)pyridine, and 4-bromopyrazole were purchased from Oakwood Chemical. 2-Bromopyridine was purchased from Oakwood Chemical and distilled over calcium hydride under reduced pressure and stored under an argon atmosphere prior to use. 2-Bromo-3-methylpyridine was purchased from Acros. Cyclohexylamine and 1-bromo-2-isopropylbenzene were purchased from Alfa Aesar. 2-Aminomethylpyridine was purchased from Avocado. Ammonium hydroxide solution was purchased from Macron Fine Chemicals. $CDCl_3$, CD_3OD, and $(CD_3)_2SO$ were purchased from

Cambridge Isotope Laboratories. 2-Iodopyrimidine,[18] 4-bromo-1-trityl-1*H*-pyrazole,[19] 1-(triisopropylsilyl)-1H-pyrrole,[20] and 3-bromo-1-(triisopropylsilyl)-1*H*-pyrrole[21] were prepared according to literature procedures.

Analytical Data: Compounds were characterized by melting point, ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, elemental analysis, mass spectrometry, and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were obtained on Varian 500 MHz instruments at ambient temperature. Chemical shifts for ^{1}H- and ^{13}C-NMR were reported in parts per million (ppm) relative to solvent signals ($CDCl_3$: 7.26 for ^{1}H-NMR and 77.16 for ^{13}C-NMR; CD_3OD: 3.31 for ^{1}H-NMR and 49.00 for ^{13}C-NMR; $(CD_3)_2SO$: 2.50 for ^{1}H-NMR and 39.52 for ^{13}C-NMR). Multiplicities were abbreviated in the following ways: "s" for singlet; "bs" for broad singlet; "d" for doublet; "t" for triplet; "q" for quartet; "h" for heptet; and "m" for multiplet. All IR spectra were taken on a Thermo Scientific – Nicolet iS5 spectrometer (iD5 ATR – diamond). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High resolution mass spectrometry data was collected on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points were measured on a Stanford Research Sytems EZ-Melt MPA120 automated melting point system. Column chromatography was performed using a Biotage SP4 apparatus with pre-packed silica cartridges. Chemical yields refer to isolated yields of compounds analyzed by elemental analysis or high-resolution mass spectrometry.

---

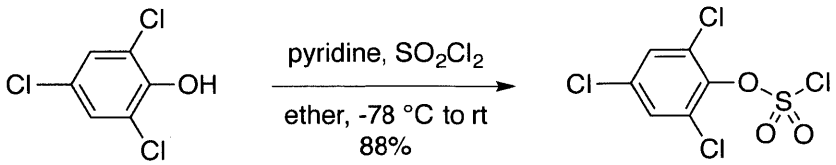
[18] Vlád, G.; Horváth, I. T. *J. Org. Chem.* **2002**, *67*, 6550-6552.

[19] Cheung, C. W.; Surry, D. S.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3734-3737.

[20] Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446-4456.

[21] Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653-1656.

Preparation of 2,4,6-Trichlorophenylchlorosulfate (TCPC)



50 mmol **TCPC**

(The following procedure was directly adapted from the previously reported synthesis of phenylchlorosulfate.[22]) 2,4,6-trichlorophenol (10g, 50 mmol, 1 equiv.) was added to an oven-dried 500 mL round bottom flask with large magnetic stir bar. The flask was fitted with a rubber septum and then was evacuated and back-filled with argon (the purging procedure was repeated a total of three times). The flask was charged with ether (200 mL) and pyridine (4.1 mL, 50 mmol, 1 equiv.). The flask was put into a -78 °C (dry ice/acetone) bath with magnetic stirring. Upon cooling, solids formed in the mixture. The mixture was then charged with sulfuryl chloride (4.2 mL, 50 mmol, 1 equiv.) in small portions over 10 min. The mixture was allowed to warm overnight with magnetic stirring. The mixture was then filtered through a plug of celite with ether (300 mL), concentrated, adsorbed onto silica gel, and purified by silica gel chromatography with a Biotage instrument (100g SNAP column, 0 – 5% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford 2,4,6-trichlorophenyl chlorosulfate (TCPC) as a colorless oil (13.057g, 88%). The compound is thermally sensitive, and should be stored in a freezer. Extended heating during isolation, such as with a ≥25 °C water bath used with a rotary evaporator when concentrating either the crude, filtered reaction mixture or after chromatography, will result in slight decomposition and the formation of a yellow or orange oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.8, 134.9, 130.6, 129.7.

Elemental Analysis: Anal. calcd. for $C_6H_2Cl_4O_3S$: C, 24.35; H, 0.68. Found: C, 24.60; H, 0.65.

IR (neat, cm^{-1}): 1738, 1564, 1421, 1218, 1191, 1131, 883, 858, 802, 739, 667, 604.

---

[5] DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *15*, 10638-10641.

General Procedures (Schemes 2-4)

General Procedure A: Preparation of 2,4,6-trichlorophenyl pyridine-2-sulfonates (Scheme 2)

An oven-dried culture tube (Fisher 20 x 150 mm tubes; Cat. No. 1495937C) with a Teflon septum (Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10; Cat. No. 03394B) and screw cap (CLOSURE OT S/T 18-400TH 14; Cat. No. 033407G) and magnetic stir bar was charged with solid 2-bromopyridine analog. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid compounds were added after purging with argon). THF was added (2 mL/mmol bromopyridine), and the tube was put in an acetone/dry ice bath with magnetic stirring and argon inlet. *n*-Butyllithium solution (2.5M in hexanes, 1 equiv.) was added dropwise via syringe over 5 min and the mixture was stirred in the cold bath for an additional 15 min. Zinc chloride solution (1.9M in 2-methyltetrahydrofuran, 1 equiv.) was added dropwise via syringe over 5 min. (Care must be taken to add *n*-butyllithium and zinc chloride solutions slowly, as the exotherm that results from too rapid of an addition of either reagent decomposes the sensitive 2-pyridyllithium species.) The tube was then removed from the cold bath and the mixture stirred at room temperature for the remainder of 1 h. The tube was placed in an ice/water bath and TCPC (1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The tube was removed from the ice/water bath and the mixture was diluted with ethyl acetate (10 mL), water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure B: Preparation of 2-pyridyl sulfonamides from 2,4,6-trichlorophenyl pyridine-2-sulfonate (4a) and alkylamines (Scheme 3)

An oven-dried culture tube with a Teflon septum and screw cap (all the same part numbers as in General Procedure A) and magnetic stir bar was charged with 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a**. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times). THF was added (3 ml/mmol ester), then amine for liquid amines or aqueous ammonium hydroxide. The punctured septum was replaced with a new septum, and the tube was put in a 60 °C oil bath with magnetic stirring for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure C: Preparation of 2-pyridyl sulfonamides from 2,4,6-trichlorophenyl pyridine-2-sulfonate (4a) and arylamines (Scheme 3)

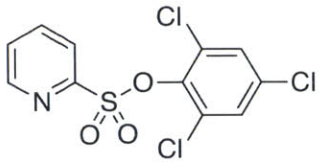
An oven-dried culture tube with a Teflon septum and screw cap (all the same part numbers as in General Procedure A) and magnetic stir bar was charged with 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (1 equiv.) and solid arylamine (1.2 or 2 equiv.). The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid arylamines were added after purging with argon). THF was added (2 ml/mmol ester), and then the tube was put in an ice/water bath with magnetic stirring. LHMDS solution (1.2 or 2 equiv., same as arylamine) was added dropwise over 5 min. After the remainder of an hour, with the ice/water bath being allowed to warm naturally, the mixture was diluted with MeOH (10 mL). The mixture was concentrated under reduced pressure, adsorbed onto the silica gel, and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure D: Preparation of aryl and heteroaryl sulfonamides (Scheme 4)

An oven-dried culture tube with a Teflon septum and screw cap and magnetic stir bar (all the same part numbers as in General Procedure A) was charged with solid aryl or heteroaryl bromide or heteroarene. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid compounds were added after purging with argon). THF was added (2 ml/mmol bromide or heteroarene), and the tube was put in an acetone/dry ice bath with magnetic stirring and argon inlet. *n*-Butyllithium solution (400 μL, 2.5M in hexanes, 1 mmol, 1 equiv.) was added dropwise via needle/syringe over 5 min and the mixture was stirred in the cold bath for the remainder of 1 h. Zinc chloride solution (530 μL, 1.9M in 2-methyltetrahydrofuran, 1 mmol, 1 equiv.) was added dropwise via needle/syringe over 5 min. (Care must be taken to add *n*-butyllithium and zinc chloride solutions slowly, as the exotherm that results from too rapid of an addition of either reagent may decompose the aryllithium species.) The tube was then removed from the cold bath and the mixture stirred at room temperature for the remainder of 1 h. The tube was placed in an ice/water bath and TCPC (175 μL, 1 mmol, 1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The ice/water bath was refreshed and then the appropriate amine (2 mmol, 2 equiv.) was added dropwise via needle/syringe to the reaction mixture. After one hour the ice/water bath was removed and the mixture was stirred until the reaction was complete as determined by analytical thin-layer chromatography (TLC), typically an additional 1 h. The mixture was diluted with ethyl acetate (10 mL) water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

Preparation and Characterization of Compounds in Scheme 2

2,4,6-Trichlorophenyl pyridine-2-sulfonate (4a)



4a

According to General Procedure A, 2-bromopyridine (1.9 mL, 20 mmol) was reacted sequentially with *n*-butyllithium solution (8 mL, 2.5 M in hexanes, 20 mmol), $ZnCl_2$ solution (10.6 mL, 1.9 M in 2-MeTHF, 20 mmol), and TCPC (3.5 mL, 20 mmol). Diverging from the general procedure, a flame-dried 200 mL round-bottom flask with rubber septum was substituted for the culture tube. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 100 g SNAP column, 0 – 60% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4a** as an off-white solid (first run: 5.04 g, 74%; second run: 5.02 g, 74%). See Figure S1 (below) for a picture of the material on a piece of weighing paper.

M.p. (°C): 92 – 99.

^{1}H-NMR (500 MHz, Chloroform-d): δ 8.80 (ddt, J = 4.7, 1.7, 0.8 Hz, 1H), 8.09 (dq, J = 7.9, 0.9 Hz, 1H), 8.01 (tdd, J = 7.8, 1.8, 0.7 Hz, 1H), 7.65 (ddt, J = 7.6, 4.7, 0.9 Hz, 1H), 7.33 (d, J = 0.7 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 154.6, 150.6, 142.4, 138.5, 133.2, 130.75, 129.3, 128.6, 123.9.

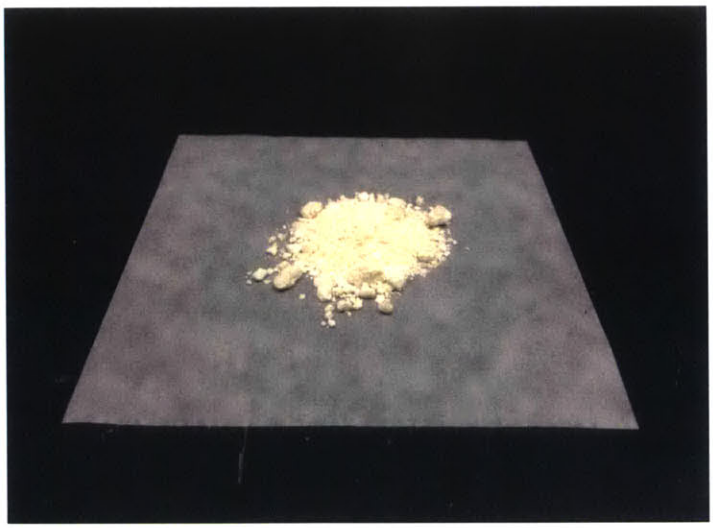
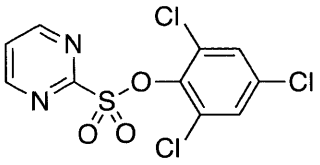


Figure S1. 2,4,6-Trichlorophenyl pyridine-2-sulfonate **4a**

Elemental Analysis: Anal. calcd. for $C_{11}H_6Cl_3NO_3S$: C, 39.02; H, 1.79. Found: C, 38.96; H, 1.93.

IR (neat, cm^{-1}): 1738, 1561, 1442, 1380, 1259.50, 1227, 1189, 1113, 1089, 993, 858, 778, 739, 649.

2,4,6-Trichlorophenyl pyrimidine-2-sulfonate (4b)



4b

The following Grignard synthesis protocol was adapted from a literature procedure.[23] An oven-dried culture tube with magnetic stir bar and screw cap with teflon septum (same part numbers as in General Procedure A) was charged 2-iodopyrimidine (206 mg, 1.0 mmol). The tube was evacuated and back-filled with argon (this procedure was repeated a total of three times). THF (3 mL) was added, and the tube was put in an ice water bath with magnetic stirring. Isopropylmagnesium chloride lithium chloride complex (Turbo Grignard) solution (770 µL, 1.3 M in THF, 1.0 mmol) was added dropwise via needle/syringe over 5 min. The mixture was stirred for 1 h with the tube in the ice/water bath. $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol) was then added dropwise over 5 min via needle/syringe, and the mixture was stirred at rt for 15 min. The tube was placed in an ice/water bath and TCPC (1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The tube was removed from the ice/water bath and the mixture was diluted with ethyl acetate (10 mL), water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 60% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4b** as a white solid (first run: 97.4 mg, 29%; second run: 107 mg, 32%).

M.p. (°C): 120 – 123.

^{1}H-NMR (500 MHz, DMSO-d6): δ 9.19 (d, J = 5.0 Hz, 1H), 8.06 – 7.98 (m, 2H), 7.88 (s, 2H).

^{13}C NMR (126 MHz, DMSO-d6): δ 161.8, 159.9, 141.8, 132.9, 129.6, 129.5, 126.1.

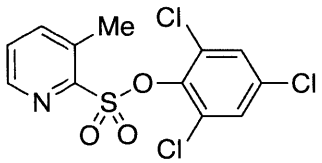
Elemental Analysis: Anal. calcd. for $C_{10}H_5Cl_3N_2O_3S$: C, 35.37; H, 1.48. Found: C, 35.46; H, 1.65.

---

[23] Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528-5531.

IR (neat, cm^{-1}): 3072, 1738, 1585, 1442, 1380, 1233, 1212, 1152, 1134, 989, 897, 874, 859, 824, 794, 739, 660, 604.

2,4,6-Trichlorophenyl 3-methylpyridine-2-sulfonate (4c)



4c

According to General Procedure A, 2-bromo-3-methylpyridine (120 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), and TCPC (175 μL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 100 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4c** as white solid (first run: 241 mg, 68%; second run: 196.5 mg, 56%).

M.p. (°C): 118 – 120.

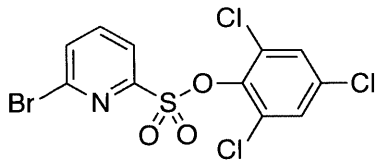
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.55 (ddd, J = 4.6, 1.5, 0.7 Hz, 1H), 7.80 (ddt, J = 7.8, 1.6, 0.7 Hz, 1H), 7.52 (dd, J = 7.7, 4.5 Hz, 1H), 7.32 (s, 2H), 2.80 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 153.4, 146.9, 142.6, 141.6, 135.1, 133.1, 130.8, 129.2, 128.4, 19.6.

Elemental Analysis: Anal. calcd. for $C_{12}H_8Cl_3NO_3S$: C, 40.88; H, 2.29. Found: C, 40.77; H, 2.44.

IR (neat, cm^{-1}): 1738, 1566, 1443, 1420, 1385, 1225, 1200, 1167, 1134, 986, 875, 858, 801, 771, 738, 724, 663, 650, 608, 585.

2,4,6-Trichlorophenyl 6-bromopyridine-2-sulfonate (4d)



4d

According to General Procedure A, 2,6-dibromopyridine (240 mg, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), and TCPC (175 μL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4d** as a white solid (first run: 236.8 mg, 57%; second run: 204 mg, 49%).

M.p. (°C): 149 – 152.

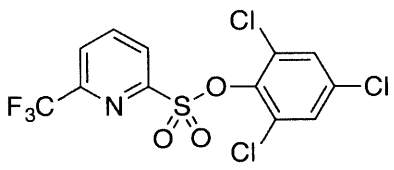
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.06 (dt, J = 7.4, 1.1 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.38 – 7.35 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 154.6, 142.8, 142.4, 140.2, 133.5, 133.4, 130.7, 129.4, 122.7.

Elemental Analysis: Anal. calcd. for $C_{11}H_5Cl_3NO_3S$: C, 31.65; H, 1.21. Found: C, 31.88; H, 1.35.

IR (neat, cm^{-1}): 2970, 1740, 1365, 1217.

2,4,6-Trichlorophenyl 6-(trifluoromethyl)pyridine-2-sulfonate (4e)



4e

According to General Procedure B, 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 20 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), and TCPC (175 μL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4e** as a tan solid (first run: 236.7 mg, 58%; second run: 226 mg, 56%).

M.p. (°C): 110 – 113.

^{1}H-NMR (500 MHz, Chloroform-d): δ 8.33 – 8.29 (m, 1H), 8.26 (tt, J = 7.8, 0.6 Hz, 1H), 8.03 (dt, J = 7.8, 0.7 Hz, 1H), 7.36 (d, J = 0.6 Hz, 2H).

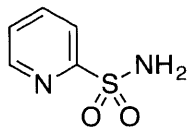
^{13}C NMR (126 MHz, Chloroform-d): δ 154.9, 149.7, 149.4, 149.1, 148.8, 142.4, 140.6, 133.6, 130.6, 129.4, 126.4, 126.4, 125.2, 125.2, 125.2, 125.1, 121.6, 119.4.

Elemental Analysis: Anal. calcd. for $C_{12}H_5Cl_3F_3NO_3S$: C, 35.45; H, 1.24. Found: C, 35.72; H, 1.45.

IR (neat, cm^{-1}): 1739, 1561, 1444, 1404, 1330, 1220, 1191, 1142, 1106, 995, 881, 865, 834, 792, 741, 727, 672, 648, 597.

Preparation and Characterization of Compounds in Scheme 3

Pyridine-2-sulfonamide (8a)



8a

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with 56% ammonium hydroxide (14.5 M, 2 mL, 29 mmol). Diverging from the general procedure, only 2 mL THF were used, and the reaction mixture was stirred in a 60 °C oil bath for only 1 h. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 5% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8a** as a white solid (first run: 145.7 mg, 92%; second run: 128.6 mg, 81%).

M.p. (°C): 144 – 147.

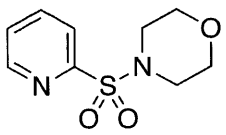
^{1}H-NMR (500 MHz, Methanol-d4): δ 8.68 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.10 – 7.95 (m, 2H), 7.60 (ddd, J = 7.2, 4.7, 1.5 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-d4): δ 160.9, 150.8, 139.7, 127.9, 122.0.

Elemental Analysis: Anal. calcd. for $C_5H_6N_2O_2S$: C, 37.97; H, 3.82. Found: C, 38.13; H, 3.82.

IR (neat, cm^{-1}): 2487, 2263, 1738, 1582, 1428, 1335, 1290, 1186, 1162, 1151, 1109, 1088, 1043, 998, 865, 836, 785, 734, 607.

4-(Pyridin-2-ylsulfonyl)morpholine (8b)



8b

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with morpholine (175 μL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8b** as a white solid (first run: 225 mg, 98%; second run: 228.5 mg, quant.).

M.p. (°C): 70 – 73.

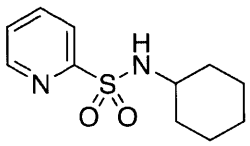
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.78 – 8.63 (m, 1H), 7.97 – 7.85 (m, 2H), 7.51 (ddd, J = 5.6, 4.7, 3.4 Hz, 1H), 3.78 – 3.66 (m, 4H), 3.35 – 3.24 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-d): δ 156.0, 150.2, 138.1, 126.9, 123.3, 66.5, 46.7.

Elemental Analysis: Anal. calcd. for $C_9H_{12}N_2O_3S$: C, 47.36; H, 5.30. Found: C, 47.38; H, 5.19.

IR (neat, cm^{-1}): 1738, 1344, 1258, 1217, 1176, 1114, 1088, 1071, 946, 796, 760, 706, 612.

***N*-Cyclohexylpyridine-2-sulfonamide (8c)**



8c

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with cyclohexylamine (230 μL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8c** as a white solid (first run: 222.4 mg, 93%; second run: 198.1 mg, 82%).

M.p. (°C): 91 – 93.

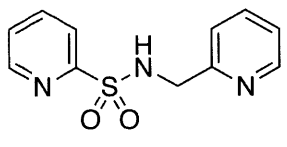
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.01 (dt, J = 7.9, 1.1 Hz, 1H), 7.90 (td, J = 7.7, 1.7 Hz, 1H), 7.48 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 5.27 (d, J = 7.5 Hz, 1H), 3.22 (dddd, J = 9.8, 7.6, 5.9, 3.9 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.66 – 1.54 (m, 2H), 1.51 – 1.42 (m, 1H), 1.28 – 0.99 (m, 5H).

^{13}C NMR (126 MHz, Chloroform-d): δ 158.6, 150.1, 138.1, 126.6, 122.0, 53.3, 33.9, 25.2, 24.7.

Elemental Analysis: Anal. calcd. for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71. Found: C, 54.93; H, 6.58.

IR (neat, cm^{-1}): 2933, 1738, 1583, 1448, 1427, 1365, 1329, 1217, 1173, 1127, 1082, 996, 888, 780, 737, 623.

***N*-(Pyridin-2-ylmethyl)pyridine-2-sulfonamide (8d)**



8d

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with pyridin-2-ylmethanamine (206 μL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8d** as a slightly-greenish brown solid (first run: 210 mg, 84%; second run: 235.2 mg, 94%).

M.p. (°C): 123 – 126.

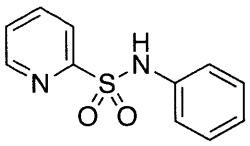
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.60 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.39 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.94 (dt, J = 7.9, 1.1 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.11 (ddd, J = 7.7, 4.9, 1.1 Hz, 1H), 7.08 – 7.03 (m, 1H), 4.44 (d, J = 6.4 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 157.7, 155.6, 150.1, 149.0, 138.0, 136.9, 126.5, 122.61, 122.2, 122.1, 48.2.

Elemental Analysis: Anal. calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45. Found: C, 53.26; H, 4.46.

IR (neat, cm^{-1}): 1739, 1596, 158, 1482, 1430, 1365, 1329, 1217, 1170, 1114, 1088, 993, 828.

***N*-Phenylpyridine-2-sulfonamide (8e)**[24]



8e

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with aniline (185 μL, 2 mmol) and LHMDS solution (2 mL, 1.0 M, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8e** as a white solid (first run: 183 mg, 78%; second run: 158.4 mg, 68%).

M.p. (°C): 172 – 175. (Lit. 170 – 172.)

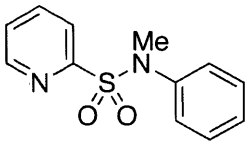
^{1}H-NMR (500 MHz, Methanol-d4): δ 8.65 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.54 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.22 – 7.11 (m, 4H), 7.06 – 7.00 (m, 1H).

^{13}C NMR (126 MHz, Methanol-d4): δ 158.1, 151.1, 139.5, 138.6, 130.0, 128.3, 125.8, 124.0, 122.5.

Elemental Analysis: Anal. calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30. Found: C, 56.38; H, 4.43.

[24] *N*-Phenylpyridine-2-sulfonamide has been previously reported and characterized: García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927-10931.

***N*-methyl-*N*-phenylpyridine-2-sulfonamide (8f)**[25]



8f

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with *N*-methylaniline (130 μL, 1.2 mmol) and LHMDS solution (1.2 mL, 1.0 M, 1.2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8f** as a dark yellow solid (first run: 239.1 mg, 96%; second run: 227.3 mg, 92%).

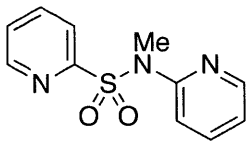
M.p. (°C): 92 – 95. (Lit. 100 – 102.)

^{1}H-NMR (500 MHz, Chloroform-d): δ 8.73 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 7.78 (td, J = 7.8, 1.7 Hz, 1H), 7.67 (dt, J = 7.9, 1.0 Hz, 1H), 7.47 (ddd, J = 7.7, 4.7, 1.2 Hz, 1H), 7.28 – 7.14 (m, 5H), 3.47 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 156.7, 150.0, 141.2, 137.8, 129.1, 127.5, 127.0, 126.8, 123.2, 40.0.

Elemental Analysis: Anal. calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 57.76; H, 4.92.

***N*-methyl-*N*-(pyridin-2-yl)pyridine-2-sulfonamide (8g)**



8g

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with *N*-methylpyridin-2-amine (125 μL, 1.2 mmol) and LHMDS solution (1.2 mL, 1.0 M, 1.2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% EtOAc/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8g** as an orange solid (first run: 224.6, 90%; second run: 234.3 mg, 94%).

M.p. (°C): 71 – 73.

^{1}H-NMR (500 MHz, Chloroform-d): δ 8.56 (dt, J = 4.7, 1.3 Hz, 1H), 8.17 (ddt, J = 4.8, 1.7, 0.8 Hz,

[25] *N*-Methyl-*N*-phenylpyridine-2-sulfonamide has been previously reported and characterized: García-Rubia, A.'; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927-10931.

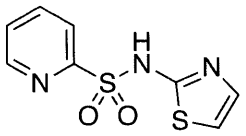
1H), 7.82 – 7.76 (m, 2H), 7.62 – 7.53 (m, 2H), 7.42 – 7.36 (m, 1H), 7.01 – 6.95 (m, 1H), 3.42 (s, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 156.0, 153.4, 150.0, 147.7, 137.8, 137.6, 126.9, 122.8, 120.6, 118.9, 36.2.

Elemental Analysis: Anal. calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45. Found: C, 52.70; H, 4.47.

IR (neat, cm^{-1}): 1738, 1573, 1471, 1429, 1365, 1345, 1311, 1229, 1217, 1172, 1159, 1087, 1067, 986, 895, 779, 771, 748, 736, 709, 624, 593.

***N*-(thiazol-2-yl)pyridine-2-sulfonamide (8h)**



8h

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with 2-aminothiazole (201 mg, 2 mmol) and LHMDS solution (2 mL, 1.0 M, 2 mmol). Diverging from the general procedure, the crude product was loaded onto a short silica plug that had been pre-flushed with dichloromethane. The plug was flushed with 100 mL dichloromethane, collected as a first fraction, and then 100 mL methanol, collected as a second fraction. The methanol fraction was concentrated and the concentrate was recrystallized from methanol, filtered, washed with cold methanol, and dried to afford **8h** as a red-brown solid (first run: 154.3 mg, 64%; second run: 135.9 mg, 61%).

Decomposition point (°C): 170.

^{1}H-NMR (500 MHz, DMSO-d6): δ 8.63 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.02 (td, J = 7.7, 1.8 Hz, 1H), 7.94 (dt, J = 7.9, 1.1 Hz, 1H), 7.58 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 6.87 (d, J = 4.6 Hz, 1H).

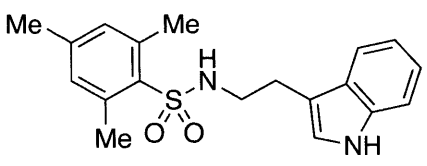
^{13}C NMR (126 MHz, DMSO-d6): δ 170.3, 159.0, 150.0, 138.4, 126.7, 124.2, 120.8, 108.8.

Elemental Analysis: Anal. calcd. for $C_8H_7N_3O_2S_2$: C, 39.82; H, 2.92. Found: C, 39.53; H, 3.00.

IR (neat, cm^{-1}): 1738, 1495, 1428, 1365, 1299, 1217, 1162, 11512, 1112, 929, 851, 739, 725, 629, 620, 592.

Preparation and Characterization of Compounds in Scheme 4

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2,4,6-trimethylbenzenesulfonamide (9a)**



9a

According to General Procedure D, 2-bromo-1,3,5-trimethylbenzene (153 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and tryptamine (321 mg, 2 mmol). Diverging from the general procedure, tryptamine was added as a solid directly to the sulfonyl chloride solution by quickly removing the cap of the reaction vessel rather than via needle/syringe. The mixture was allowed to stir for 24 h after the addition of tryptamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **9a** as a tan solid (first run: 170 mg, 50%; second run: 183.2 mg, 54%).

M.p. (°C): 136 – 138.

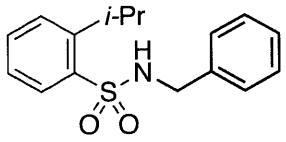
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.35 – 8.29 (bs, 1H), 7.39 – 7.34 (m, 2H), 7.20 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H), 7.05 (ddd, J = 7.8, 7.0, 0.9 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.86 (s, 2H), 4.65 (t, J = 6.1 Hz, 1H), 3.23 (q, J = 6.5 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.49 (s, 6H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 142.1, 138.9, 136.5, 133.1, 131.9, 126.8, 122.8, 122.1, 119.3, 118.3, 111.5, 111.2, 42.5, 25.2, 22.7, 20.9.

IR (neat, cm^{-1}): 3398, 3294, 1460, 1320, 1297, 1154, 1082, 1061, 1010, 851, 818, 746, 740, 654.

HRMS ($C_{19}H_{22}N_2O_2S$): Calcd. $[M+H]^+$: 343.1475. Found: 343.1475.

***N*-Benzyl-2-isopropylbenzenesulfonamide (9b)**



9b

According to General Procedure D, 1-bromo-2-isopropylbenzene (153 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and benzylamine (220 μL, 2 mmol). The mixture was allowed to stir for 18 h after the addition of

benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **9b** as a white solid (first run: 173.1 mg, 60%; second run: 151.5 mg, 52%).

M.p. (°C): 109 – 110.

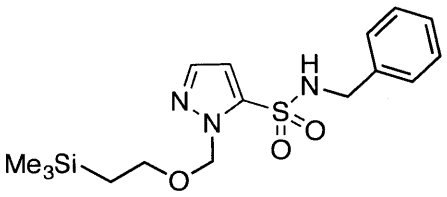
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.99 (dd, J = 8.0, 1.4 Hz, 1H), 7.55 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.50 (dd, J = 7.9, 1.4 Hz, 1H), 7.32 – 7.24 (m, 4H), 7.19 – 7.16 (m, 2H), 4.74 (t, J = 6.2 Hz, 1H), 4.14 (d, J = 6.1 Hz, 2H), 3.81 (hept, J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-d): δ 148.6, 136.9, 136.4, 133.3, 129.6, 128.9, 128.1, 128.1, 128.1, 126.0, 47.5, 29.6, 24.2.

Elemental Analysis: Anal. calcd. for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62. Found: C, 66.45; H, 6.45.

IR (neat, cm^{-1}): 3304, 1495, 1438, 1420, 1364, 1316, 1153, 1118, 1082, 1068, 1055, 1027, 825, 761, 729, 695, 688, 597, 573, 563.

***N*-Benzyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-sulfonamide (9c)**



9c

According to General Procedure D, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (130 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and benzylamine (220 μL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 40% EtOAc/hexanes gradient, visualized on TLC plate with $KMnO_4$ stain) to afford **9c** as a clear oil (first run: 114.7 mg, 31%; second run: 106.9 mg, 29%).

^{1}H-NMR (500 MHz, Chloroform-d): δ 7.50 (d, J = 1.9 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.21 – 7.17 (m, 2H), 6.87 (d, J = 1.9 Hz, 1H), 5.69 (s, 2H), 5.43 (t, J = 6.1 Hz, 1H), 4.08 (d, J = 6.1 Hz, 2H), 3.45 – 3.41 (m, 2H), 0.64 – 0.60 (m, 2H), -0.09 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d): δ 138.8, 138.1, 135.7, 128.8, 128.2, 127.9, 113.1, 79.5, 67.2,

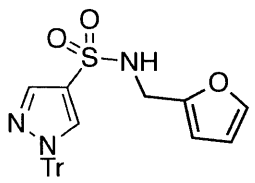
47.9, 17.8, -1.5.

Elemental Analysis: Anal. calcd. for $C_{16}H_{25}N_3O_3SSi$: C, 52.29; H, 6.86. Found: C, 52.54; H, 6.96.

HRMS ($C_{16}H_{25}N_3O_3SSi$): Calcd. $[M+H]^+$: 368.1459. Found: 368.1465.

IR (neat, cm^{-1}): 1738, 1347, 1249, 1160, 1075, 834, 749, 697, 616.

***N*-(Furan-2-ylmethyl)-1-trityl-1*H*-pyrazole-4-sulfonamide (9d)**



9d

According to General Procedure D, 4-bromo-1-trityl-1*H*-pyrazole (390 mg, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and furfurylamine (180 μL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (13 h) and then the mixture was stirred at rt for an additional 0.5 h before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of furfurylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate by anisaldehyde stain) to afford **9d** as an orange-brown solid (first run: 291.7 mg, 62%; second run: 315 mg, 67%).

M.p. (°C): 175 – 180.

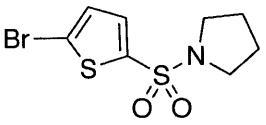
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.84 (dd, J = 0.4 Hz, 1H), 7.78 (dd, J = 0.8, 0.3 Hz, 1H), 7.38 – 7.30 (m, 9H), 7.24 (dt, J = 1.9, 0.5 Hz, 1H), 7.11 – 7.07 (m, 6H), 6.22 (dd, J = 3.2, 1.9 Hz, 1H), 6.12 (dd, J = 3.2, 0.8 Hz, 1H), 4.73 (t, J = 6.0 Hz, 1H), 4.26 – 4.22 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 149.6, 142.5, 142.0, 138.6, 134.0, 130.0, 128.3, 128.0, 121.1, 110.5, 108.3, 80.0, 40.0.

IR (neat, cm^{-1}): 1445, 1319, 1151, 1104, 869, 745, 700, 640.

HRMS ($C_8H_9N_3O_3S$ – loss of CPh_3 group): Calcd. $[M+H]^+$: 228.0437. Found: 228.0456.

1-((5-Bromothiophen-2-yl)sulfonyl)pyrrolidine (9e)



9e

According to General Procedure D, 2,5-dibromothiophene (113 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and pyrrolidine (170 μL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of pyrrolidine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate with UV lamp) to afford **9e** as a slightly orange solid (first run: 255.5 mg, 86%; second run: 245.7 mg, 83%).

M.p. (°C): 67 – 69.

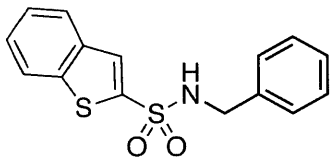
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.30 (dd, J = 4.0, 0.6 Hz, 1H), 7.13 – 7.04 (m, 1H), 3.30 – 3.18 (m, 4H), 1.80 – 1.76 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-d): δ 138.1, 132.4, 130.8, 119.5, 48.5, 25.6.

HRMS ($C_8H_{10}BrNO_2S_2$): Calcd. $[M+H]^+$: 295.9409. Found: 295.9401.

IR (neat, cm^{-1}): 1406, 1337, 1209, 1062, 1017, 1006, 805, 753, 667.

***N*-Benzylbenzo[*b*]thiophene-2-sulfonamide (9f)**



9f

According to General Procedure D, benzo[*b*]thiophene (120 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and benzylamine (220 μL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate with UV lamp) to afford **9f** as a pink solid (first run: 238 mg, 78%; second run: 228.8 mg, 75%).

M.p. (°C): 118 – 119.

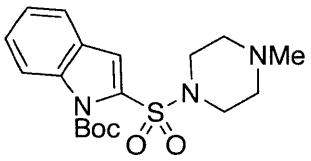
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.90 – 7.85 (m, 3H), 7.53 – 7.45 (m, 2H), 7.31 – 7.23 (m, 5H), 4.87 (t, J = 6.1 Hz, 1H), 4.27 (d, J = 6.1 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 141.8, 140.8, 137.7, 135.9, 129.7, 128.8, 128.1, 128.0, 127.4, 125.8, 125.6, 122.8, 47.6.

HRMS ($C_{15}H_{13}NO_2S_2$): Calcd. $[M+NH_4]^+$: 321.0726. Found: 321.0737.

IR (neat, cm^{-1}): 3259, 1425, 1333, 1148, 1039, 1022, 1002, 746, 695, 596, 556.

***Tert*-butyl 2-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indole-1-carboxylate (9g)**



9g

According to General Procedure D, *tert*-butyl 1*H*-indole-1-carboxylate (203 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and 1-methylpiperazine (222 μL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (14 h) and then the mixture was stirred at rt for an additional 0.5 h before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of 1-methylpiperazine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 5% MeOH/dichloromethane gradient, visualized on TLC plate with UV lamp) to afford **9g** as a brown solid (first run: 179 mg, 47%; second run: 147.7 mg, 39%).

M.p. (°C): 151 – 154.

^{1}H-NMR (500 MHz, Chloroform-d): δ 8.13 (dt, J = 8.6, 0.8 Hz, 1H), 7.61 (dt, J = 7.9, 1.0 Hz, 1H), 7.45 (ddt, J = 8.2, 7.4, 0.9 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.10 (d, J = 0.8 Hz, 1H), 3.58 – 3.51 (m, 4H), 2.53 (t, J = 4.9 Hz, 4H), 2.36 (s, 3H), 1.73 (d, J = 0.6 Hz, 9H).

^{13}C NMR (126 MHz, Chloroform-d): δ 148.5, 137.5, 135.7, 127.5, 126.0, 123.6, 122.3, 115.8, 115.0, 86.1, 55.0, 46.3, 46.1, 28.1.

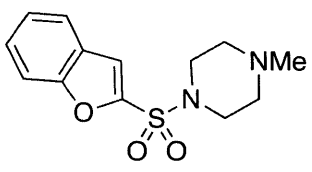
Elemental Analysis: Anal. calcd. for $C_{18}H_{25}N_3O_4S$: C, 56.97; H, 6.64. Found: C, 56.71; H, 6.55.

HRMS ($C_{18}H_{25}N_3O_2S$): Calcd. $[M+NH_4]^+$: 380.1639. Found: 380.1624.

IR (neat, cm^{-1}): 2784, 1737, 1446, 1357, 1336, 1318, 1285, 1257, 1217, 1140, 1098, 1068, 844, 821,

753, 717, 619, 588.

1-(Benzofuran-2-ylsulfonyl)-4-methylpiperazine (9h)



9h

According to General Procedure D, benzofuran (110 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and 1-methylpiperazine (222 μL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of 1-methylpiperazine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **9h** as a tan solid (first run: 187.5 mg, 67%; second run: 170 mg, 61%).

M.p. (°C): 86 – 91.

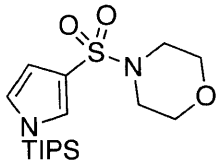
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.67 (dt, J = 7.8, 1.0 Hz, 1H), 7.53 (dt, J = 8.4, 0.9 Hz, 1H), 7.45 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.36 (t, J = 0.8 Hz, 1H), 7.33 (tt, J = 7.2, 0.8 Hz, 1H), 3.32 (t, J = 4.9 Hz, 4H), 2.50 (t, J = 5.1 Hz, 4H), 2.28 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 155.9, 148.3, 127.8, 125.8, 124.3, 122.9, 113.3, 112.3, 54.1, 45.9, 45.8.

Elemental Analysis: Anal. calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75. Found: C, 55.42; H, 5.66.

IR (neat, cm^{-1}): 1144, 1360, 1282, 1236, 1181, 1150, 950, 925, 866, 793, 782, 737, 725, 645, 620.

4-((1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl)sulfonyl)morpholine (9i)



9i

According to General Procedure A, 3-bromo-1-(triisopropylsilyl)-1*H*-pyrrole (270 μL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 μL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 μL, 1.9 M, 1 mmol), TCPC (175 μL, 1 mmol), and morpholine (175 μL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (14 h) and then the mixture was stirred at rt for an additional 0.5 h

before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of morpholine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate with $KMnO_4$ stain) to afford **9i** as a brown solid (first run: 155.8 mg, 42%; second run: 122.9 mg, 31%).

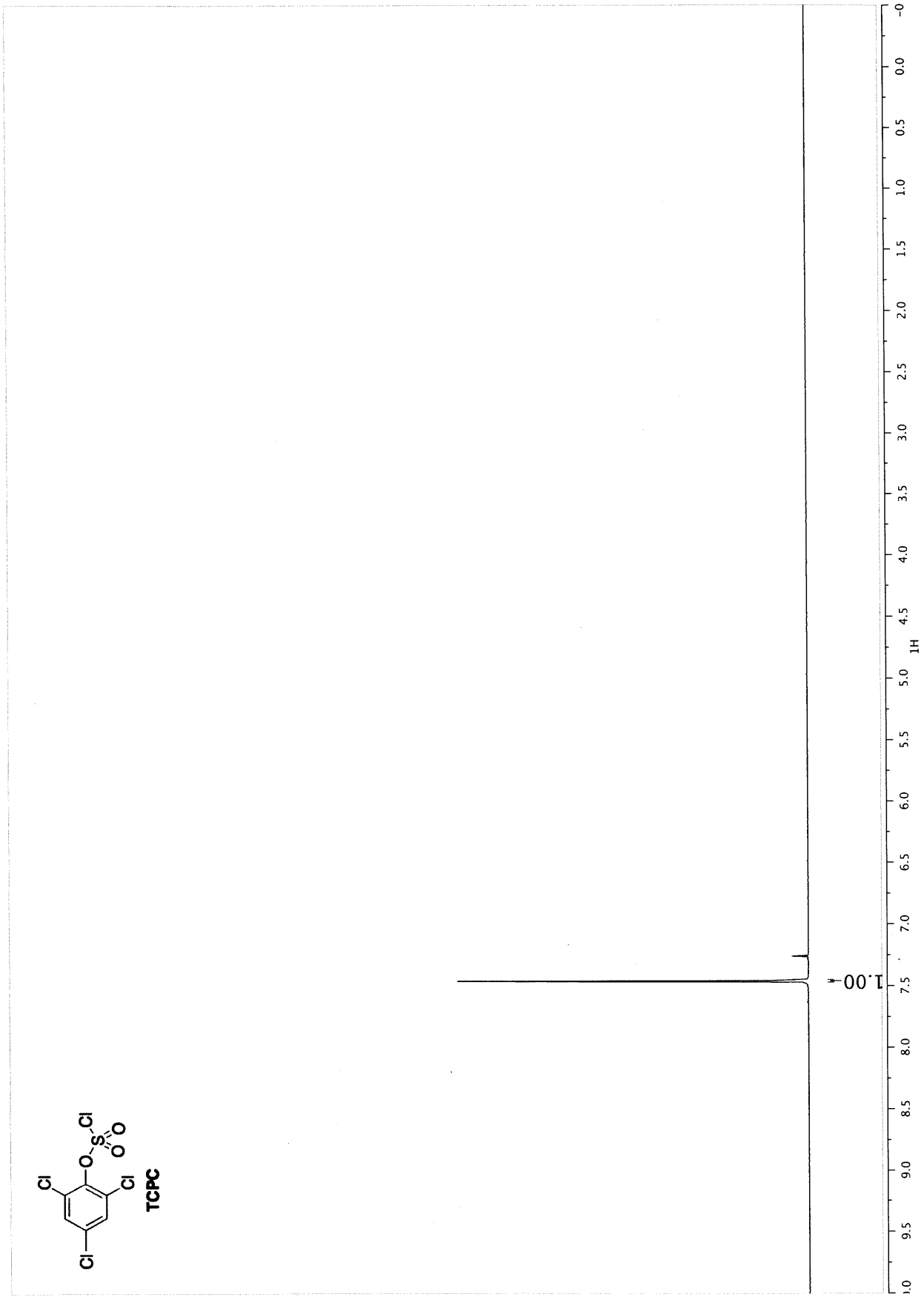
M.p. (°C): 74 – 79.

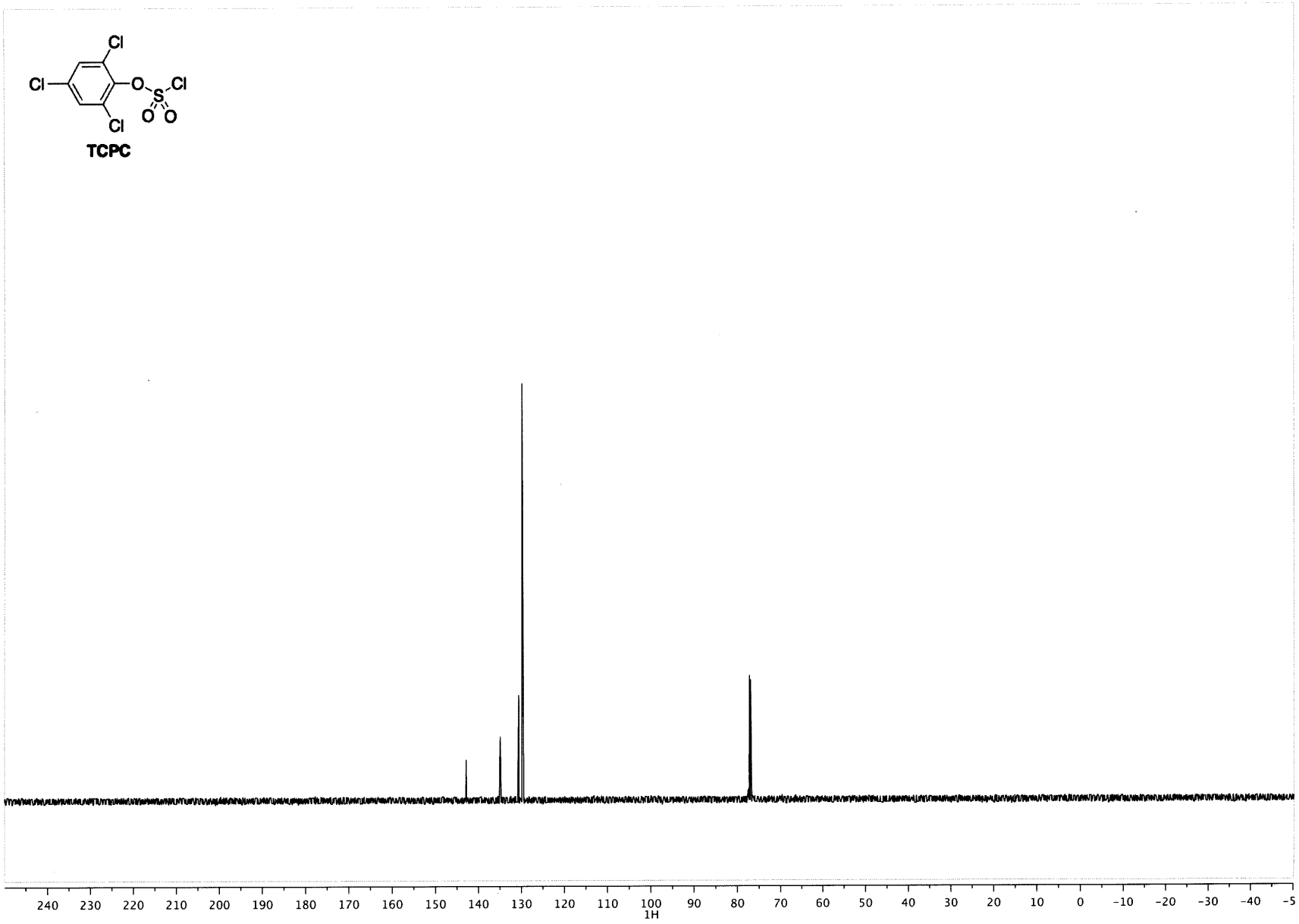
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.21 (dd, J = 2.2, 1.4 Hz, 1H), 6.80 (dd, J = 2.9, 2.2 Hz, 1H), 6.51 (dd, J = 2.9, 1.4 Hz, 1H), 3.78 – 3.75 (m, 4H), 2.99 – 2.95 (m, 4H), 1.47 (h, J = 7.5 Hz, 3H), 1.10 (d, J = 7.5 Hz, 18H).

^{13}C NMR (126 MHz, Chloroform-d): δ 128.7, 126.1, 119.3, 110.6, 66.4, 46.2, 17.8, 11.7.

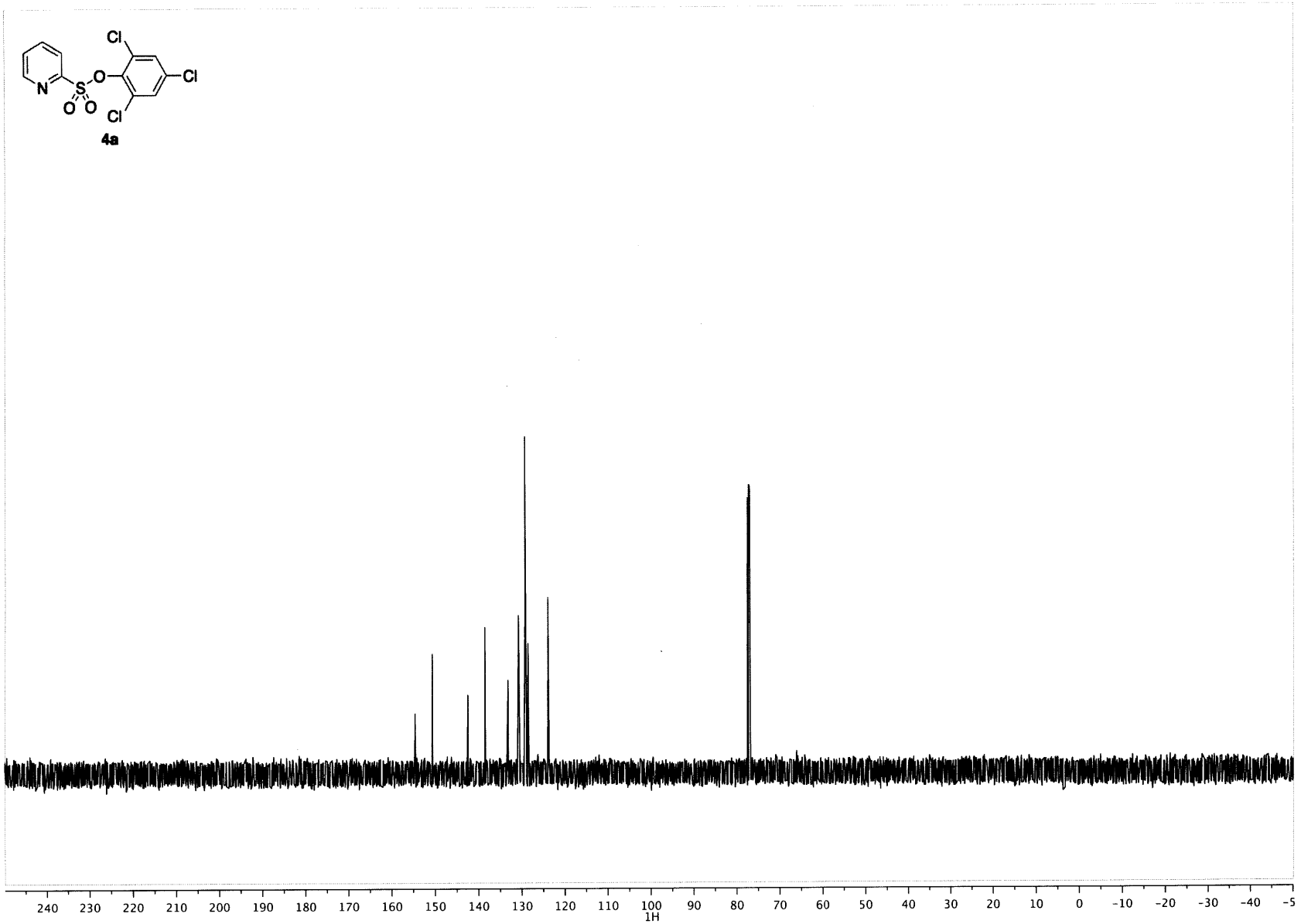
Elemental Analysis: Anal. calcd. for $C_{17}H_{32}N_2O_3SSi$: C, 54.80; H, 8.66. Found: C, 54.50; H, 8.50.

IR (neat, cm^{-1}): 2948, 2863, 1509, 1455, 1339, 1326, 1292, 1260, 1147, 1118, 1090, 1070, 1021, 994, 949, 935, 882, 848, 695, 653, 614.

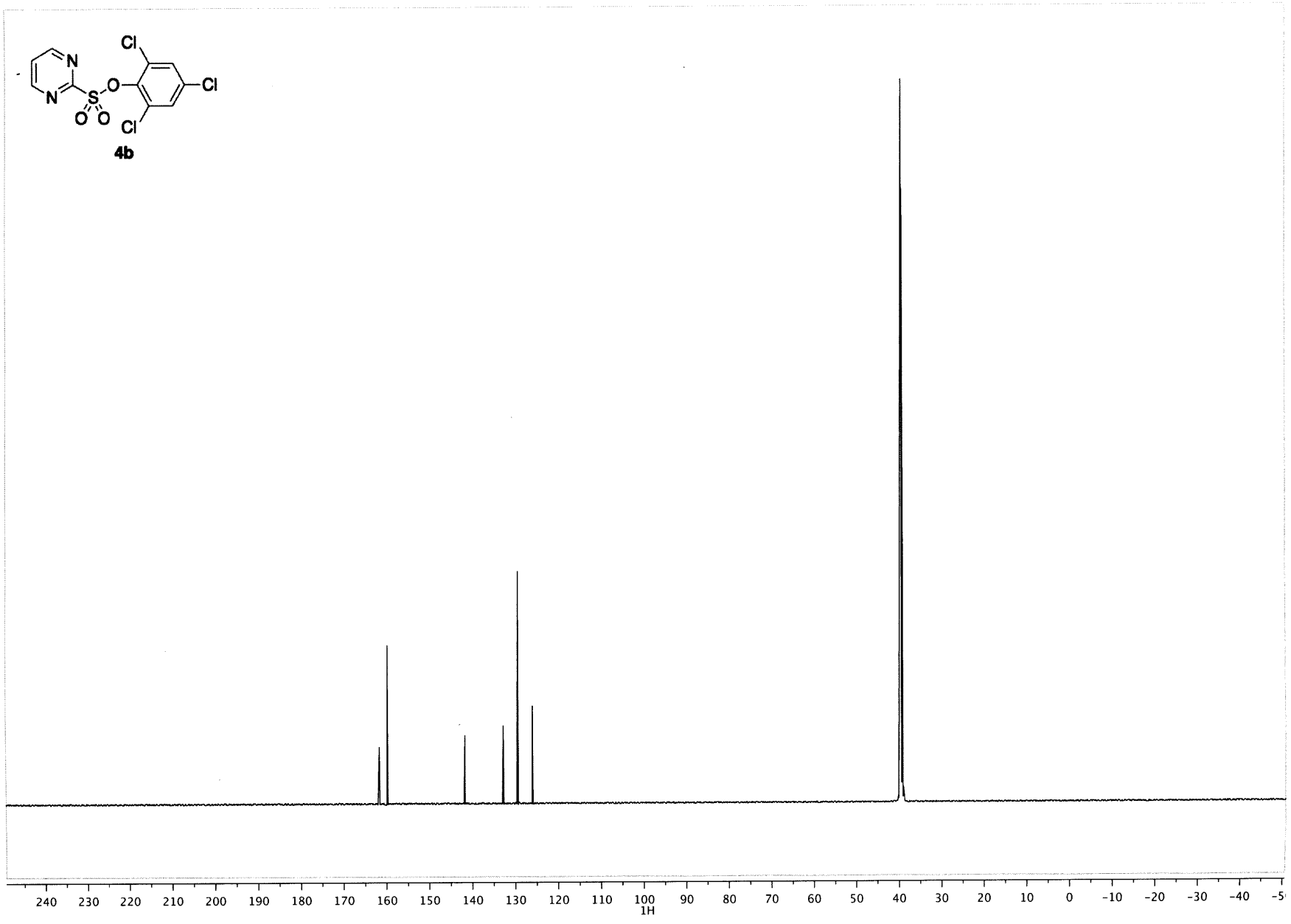

1.00
1H
TCPC

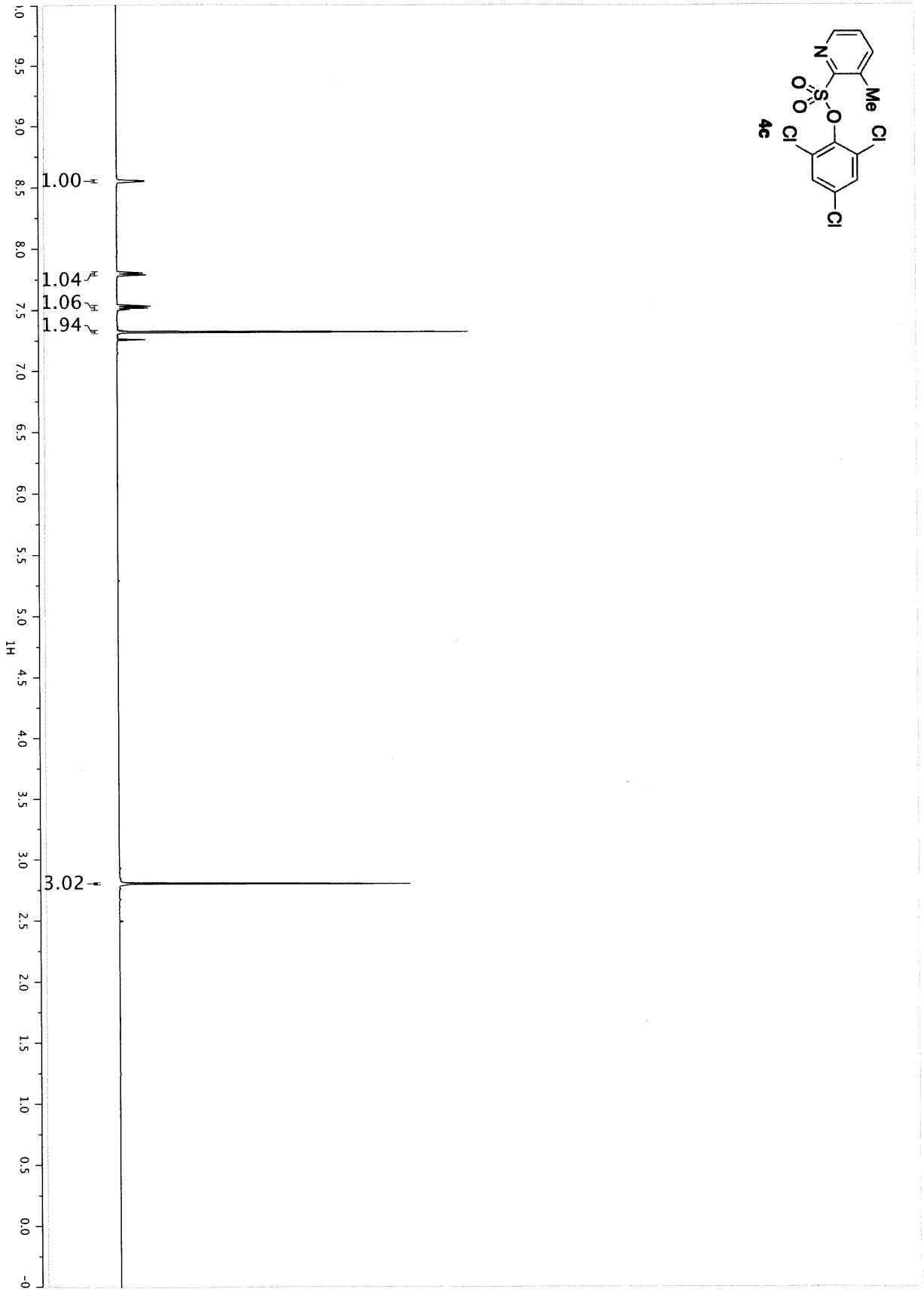

Cl
Cl
O
S
Cl
O
O
Cl
TCPC
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

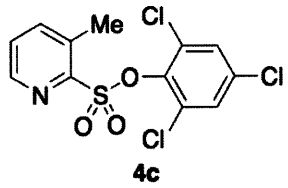
Cl
Cl
Cl
N
S
O
O
O
4a
1.00
1.01
1.08
1.06
1.85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


Cl
Cl
Cl
N
S
O
O
O
4a
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

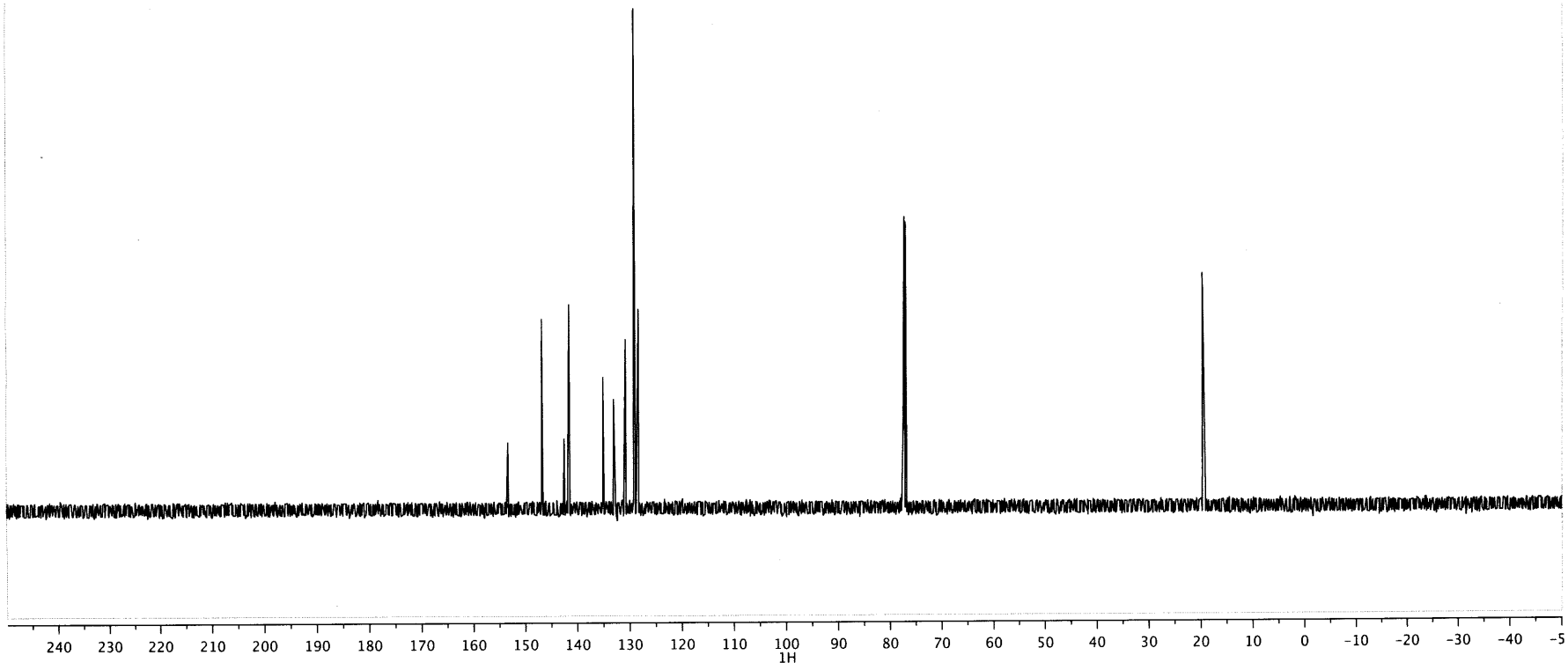
Cl
N
N
S
O
Cl
O
O
Cl
4b
1.82
1.00
1.60
1H

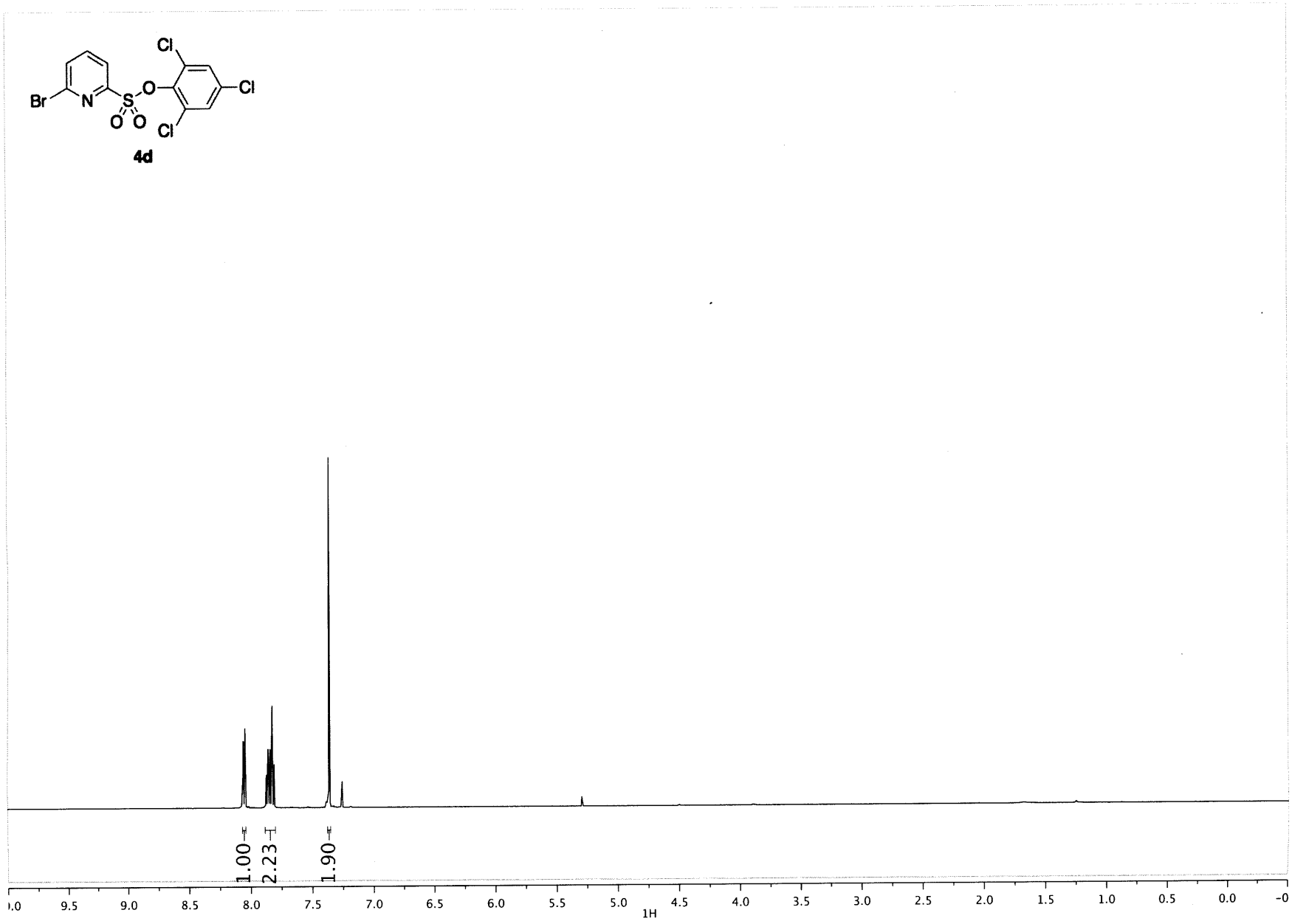

Cl
N
N
S
O
O
O
Cl
Cl
4b
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H

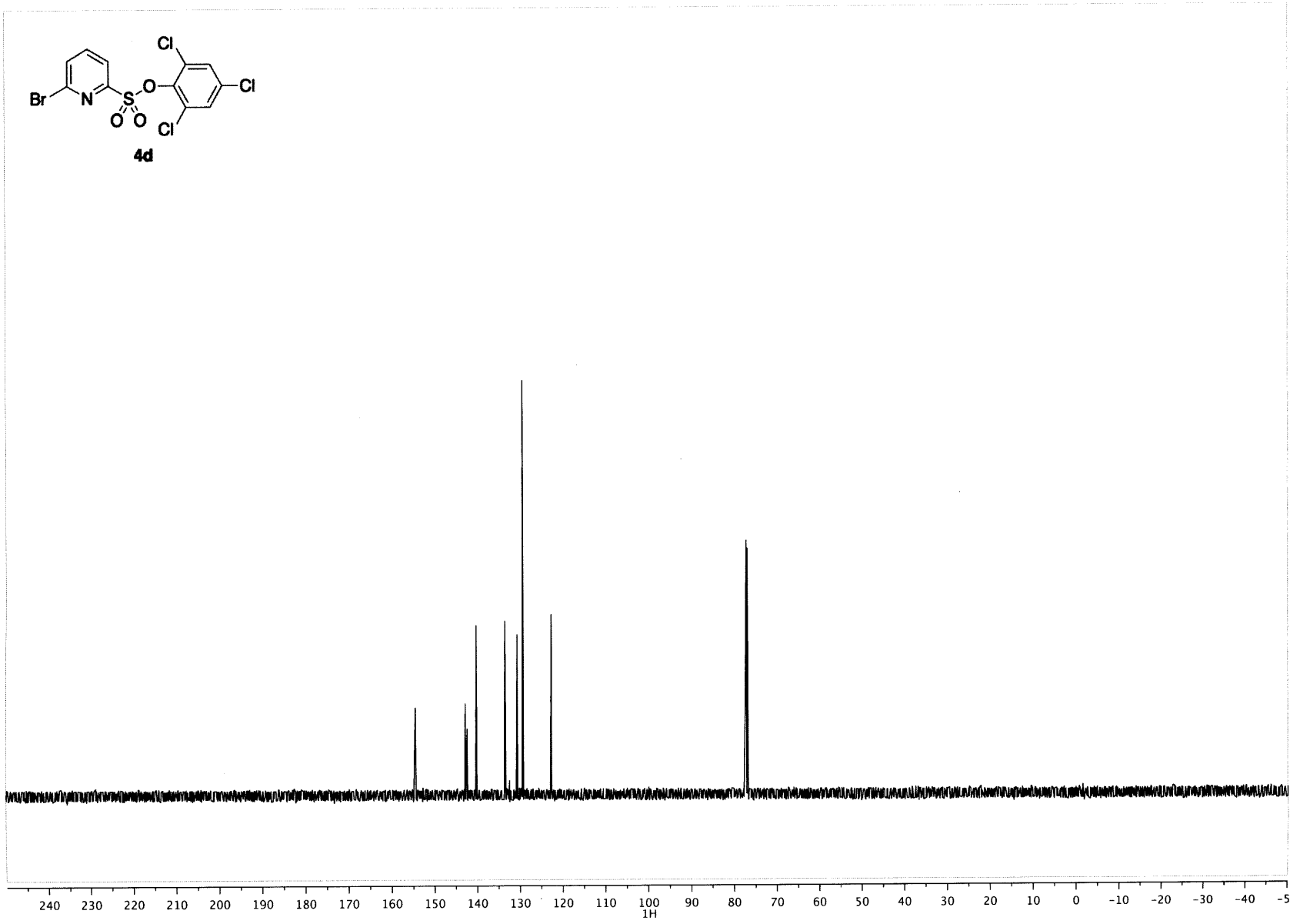

1.00
1.04
1.06
1.94
3.02
1H
4c
Me
Cl
Cl
Cl
N
S
O
O
O

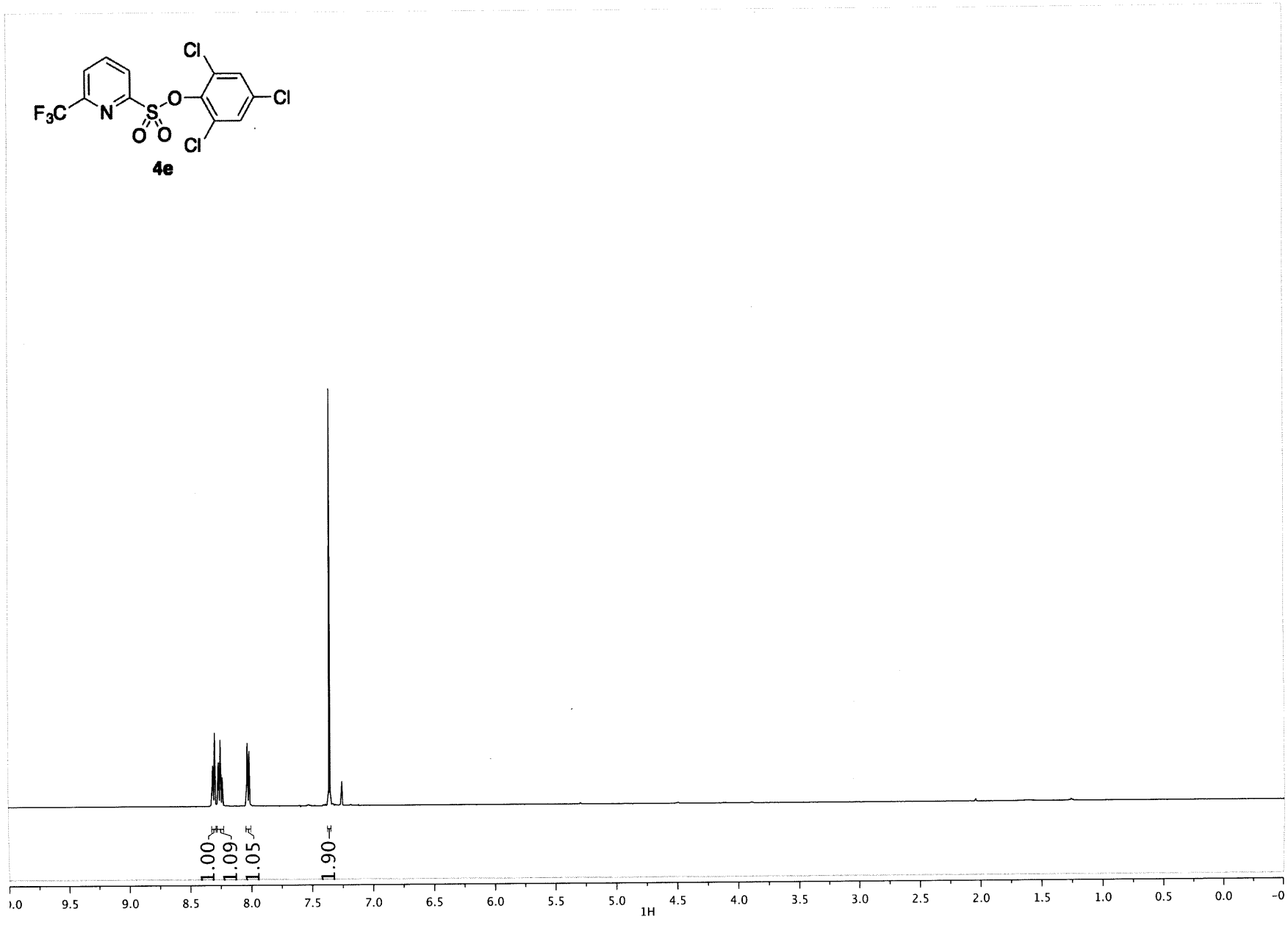

Me
Cl
N
S
O
O
O
Cl
Cl

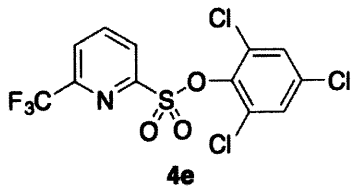
4c


240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

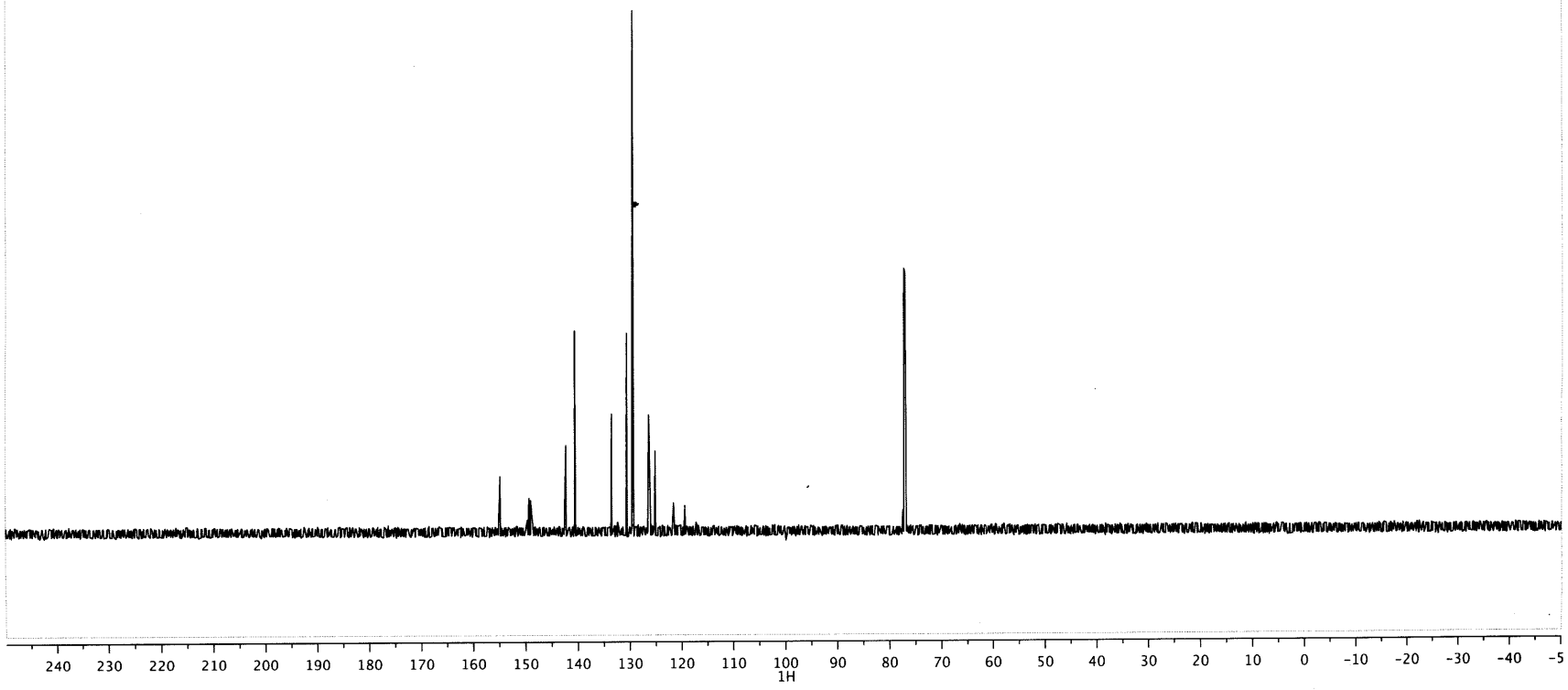

Br
N
S
O
O
O
Cl
Cl
Cl
4d
1.00
2.23
1.90
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H

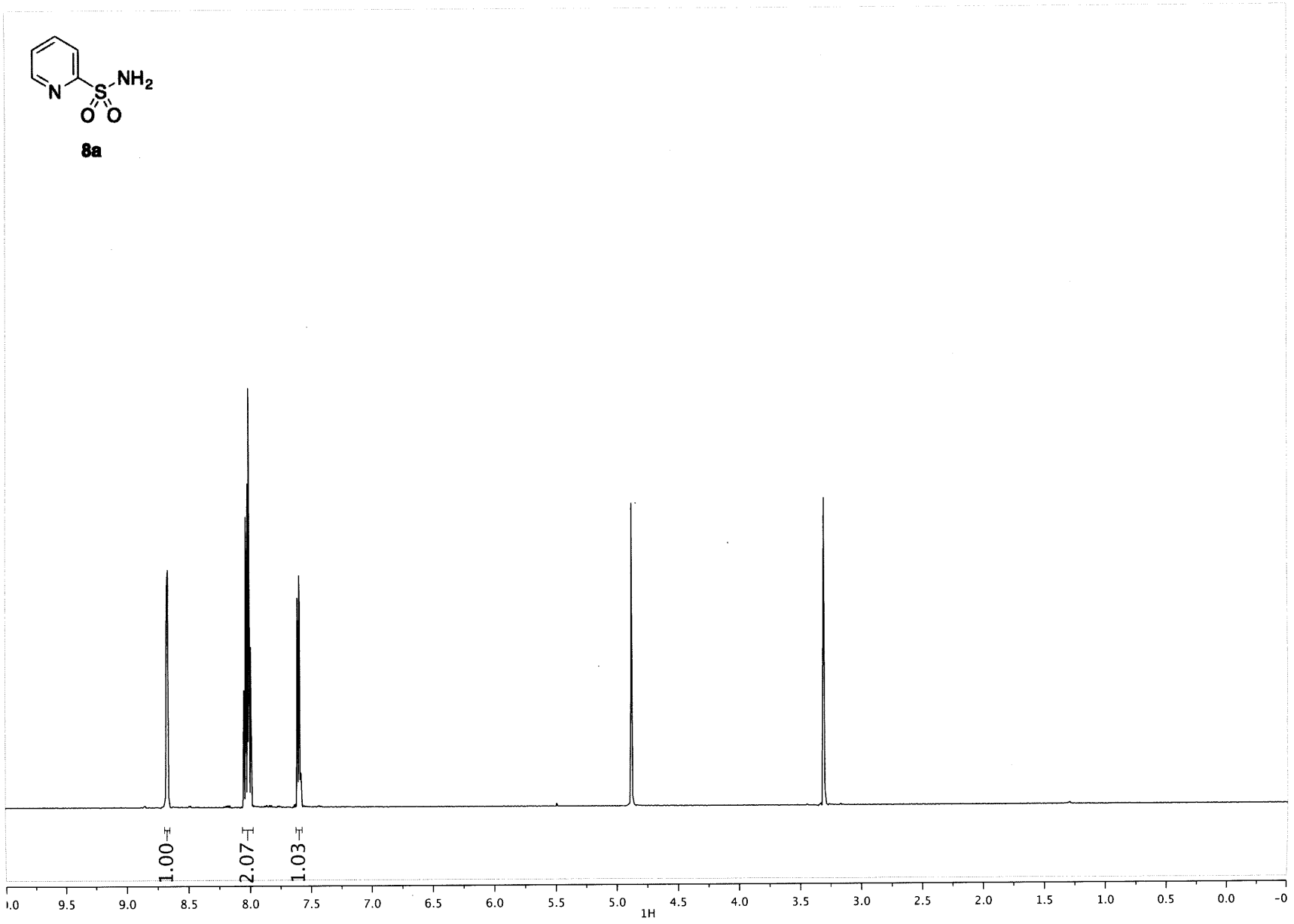

Cl
Br
N
S
O
O
O
Cl
Cl
4d
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

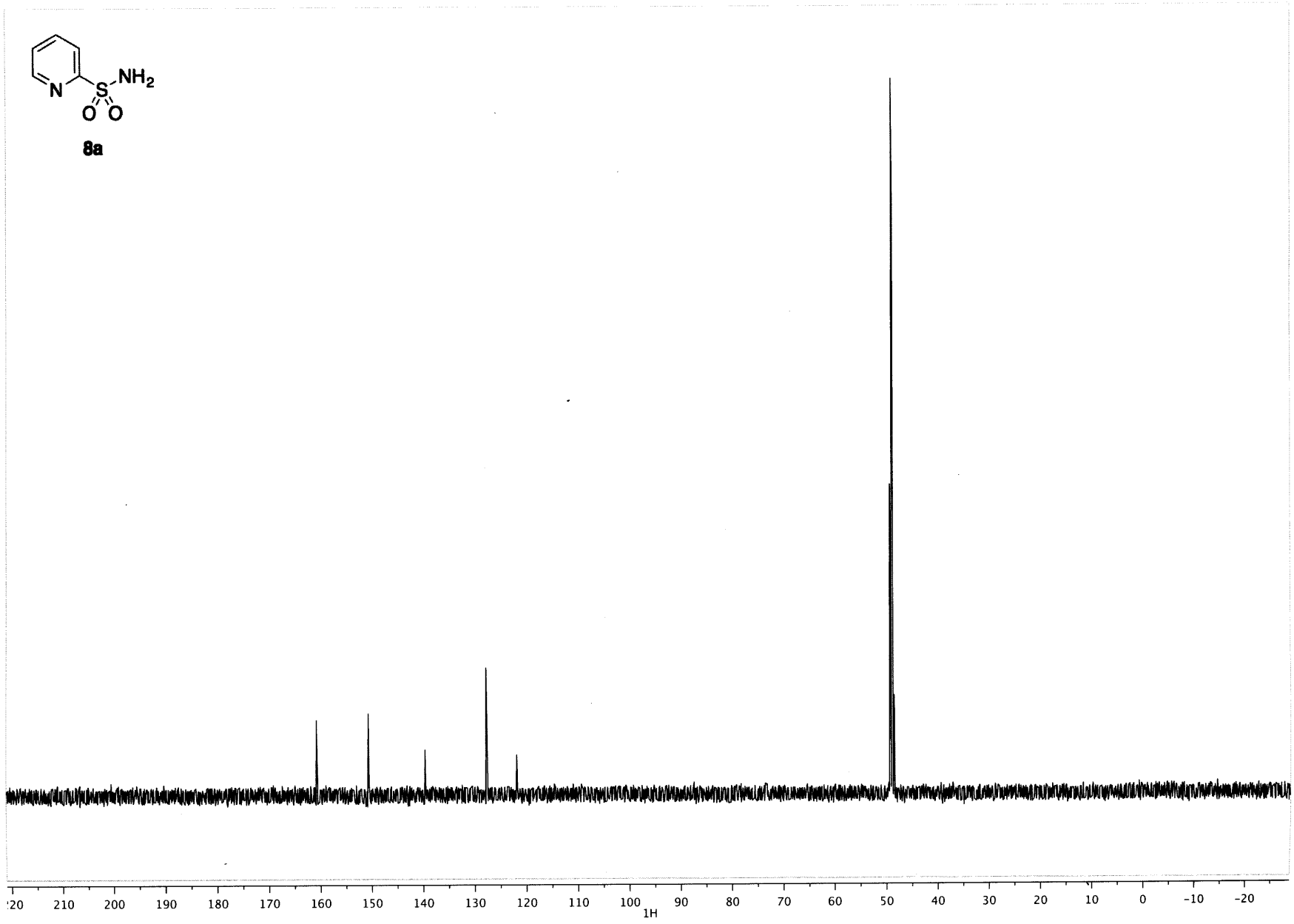

Cl
Cl
Cl
F3C
N
S
O
O
O
4e
1.00
1.09
1.05
1.90
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


Cl
F3C
N
S
O
O
O
Cl
Cl

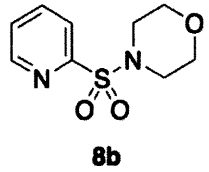
4e


240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H


NH2
N
S
O O
8a
1.00
2.07
1.03
1H

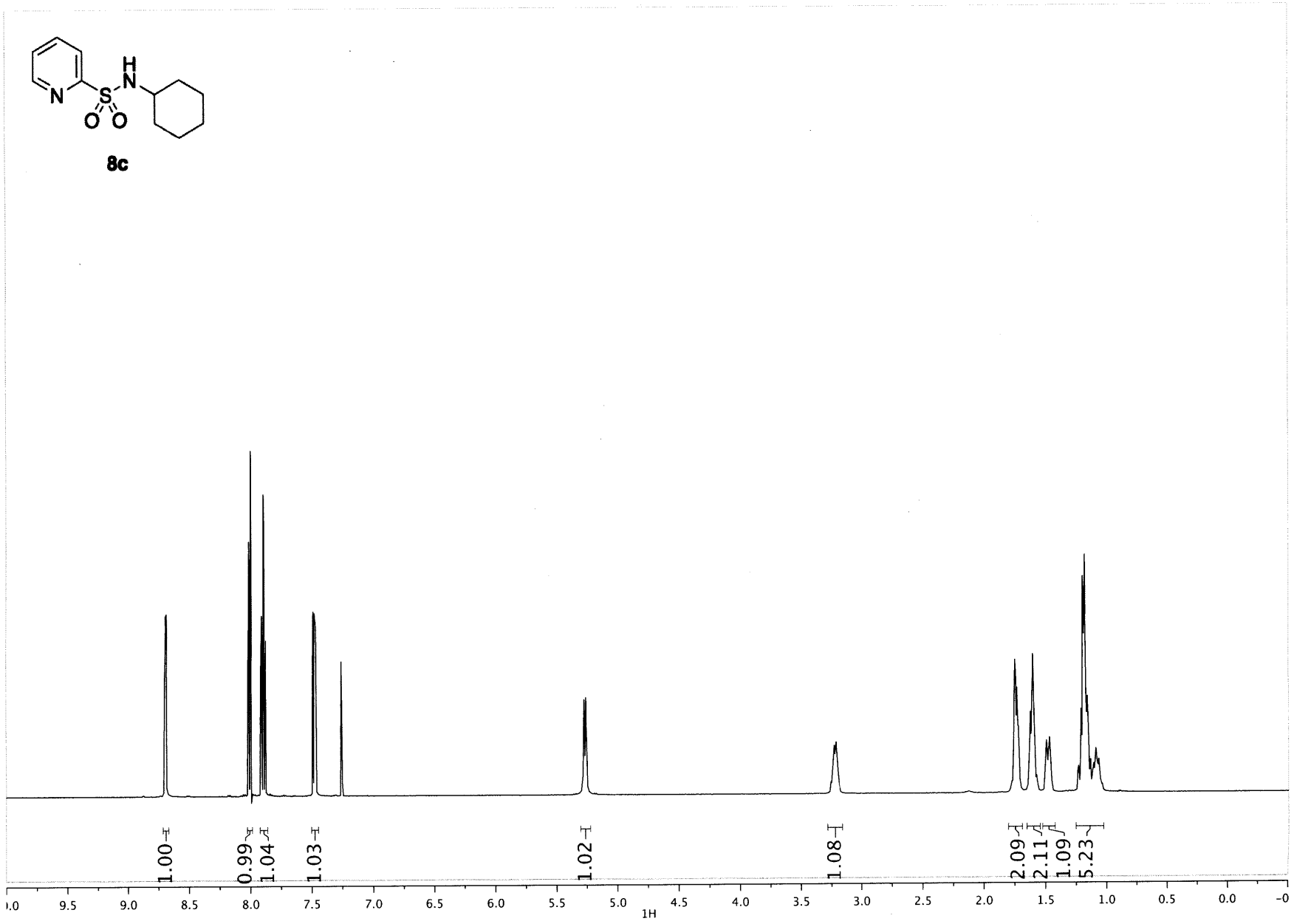

NH2
N
S
O O
8a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
1H

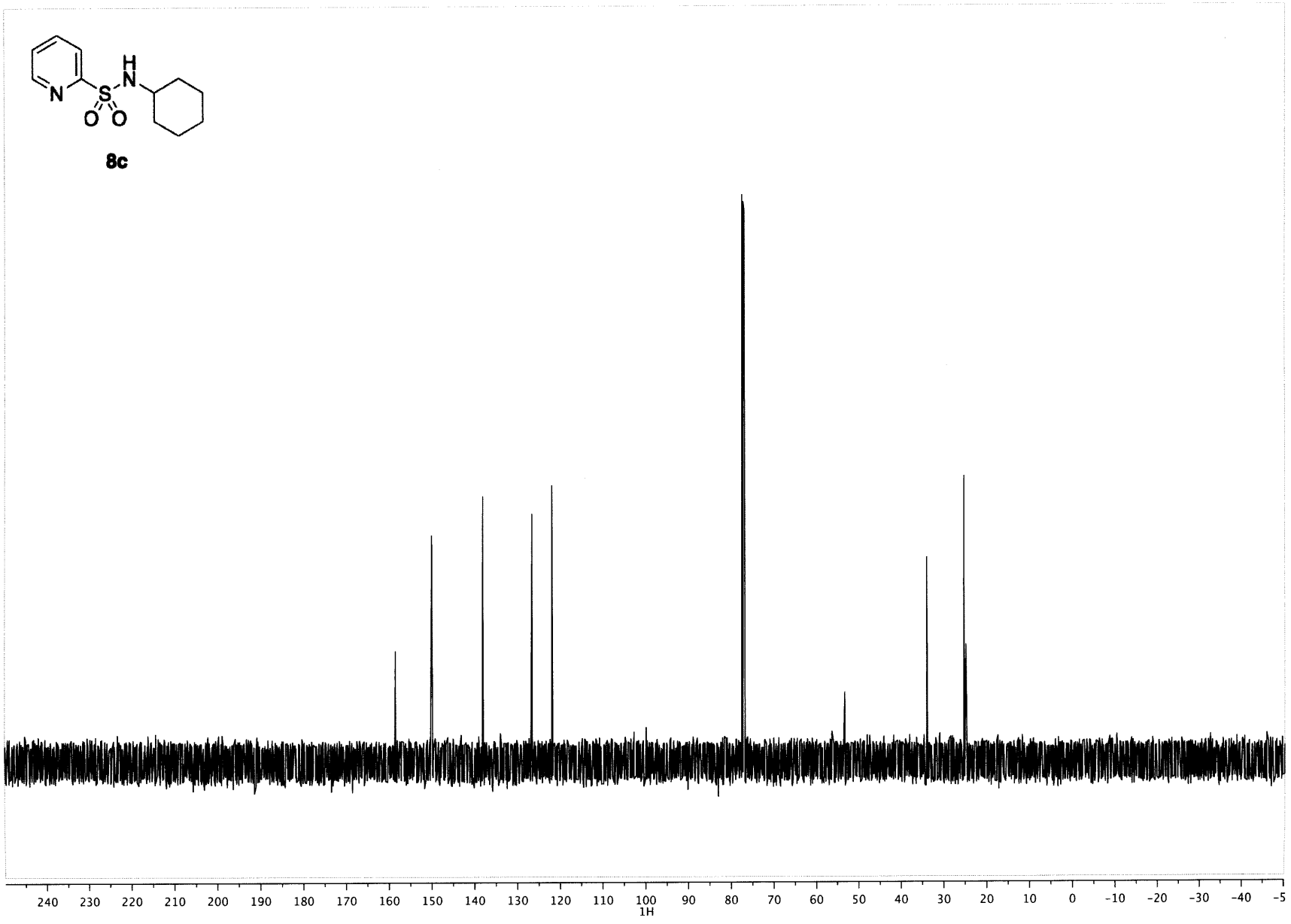
8b
1.00
2.09
1.07
4.15
4.13
1H

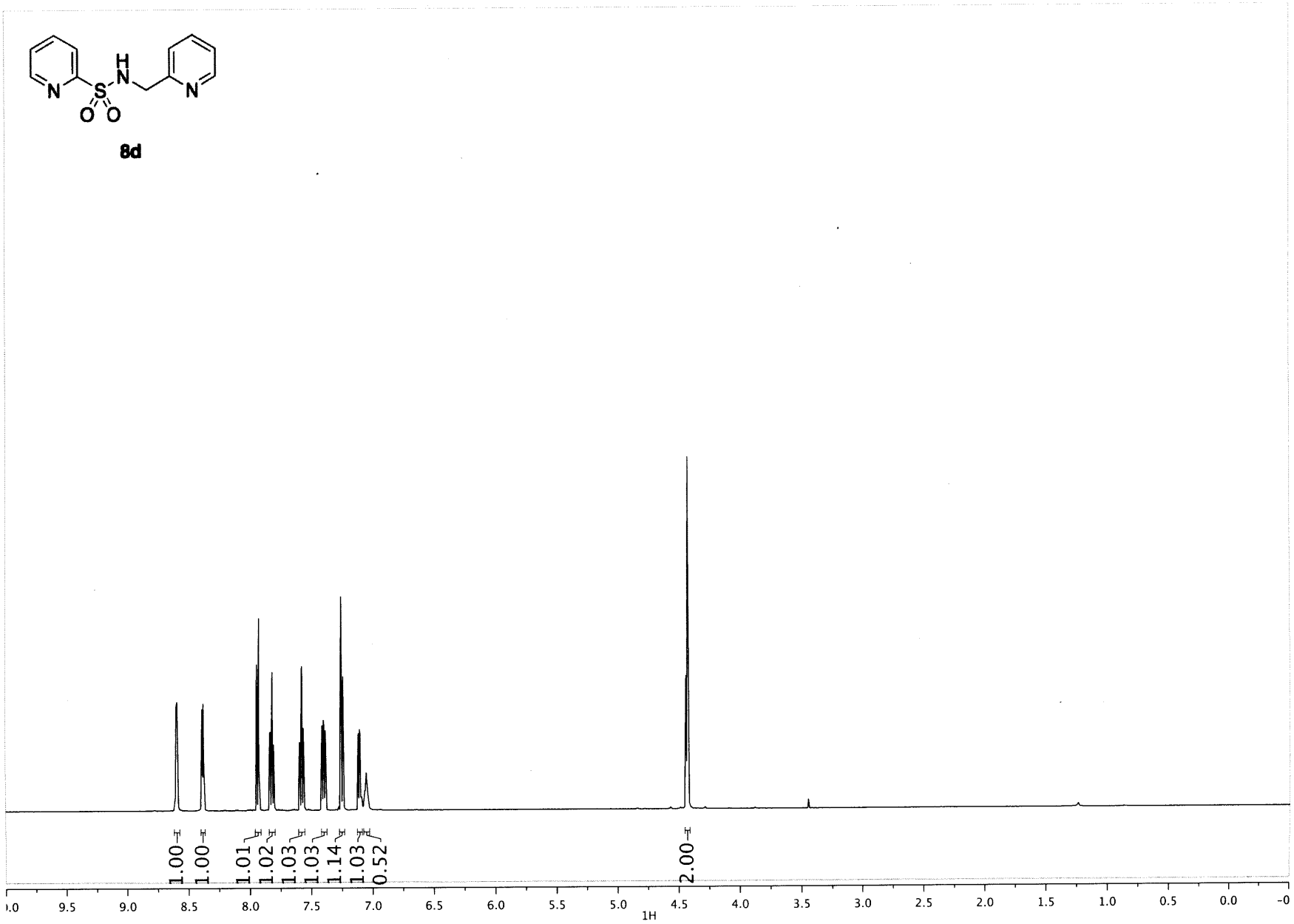

N
S
N
O
O
O

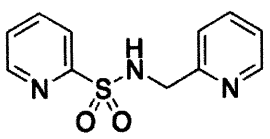
8b

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

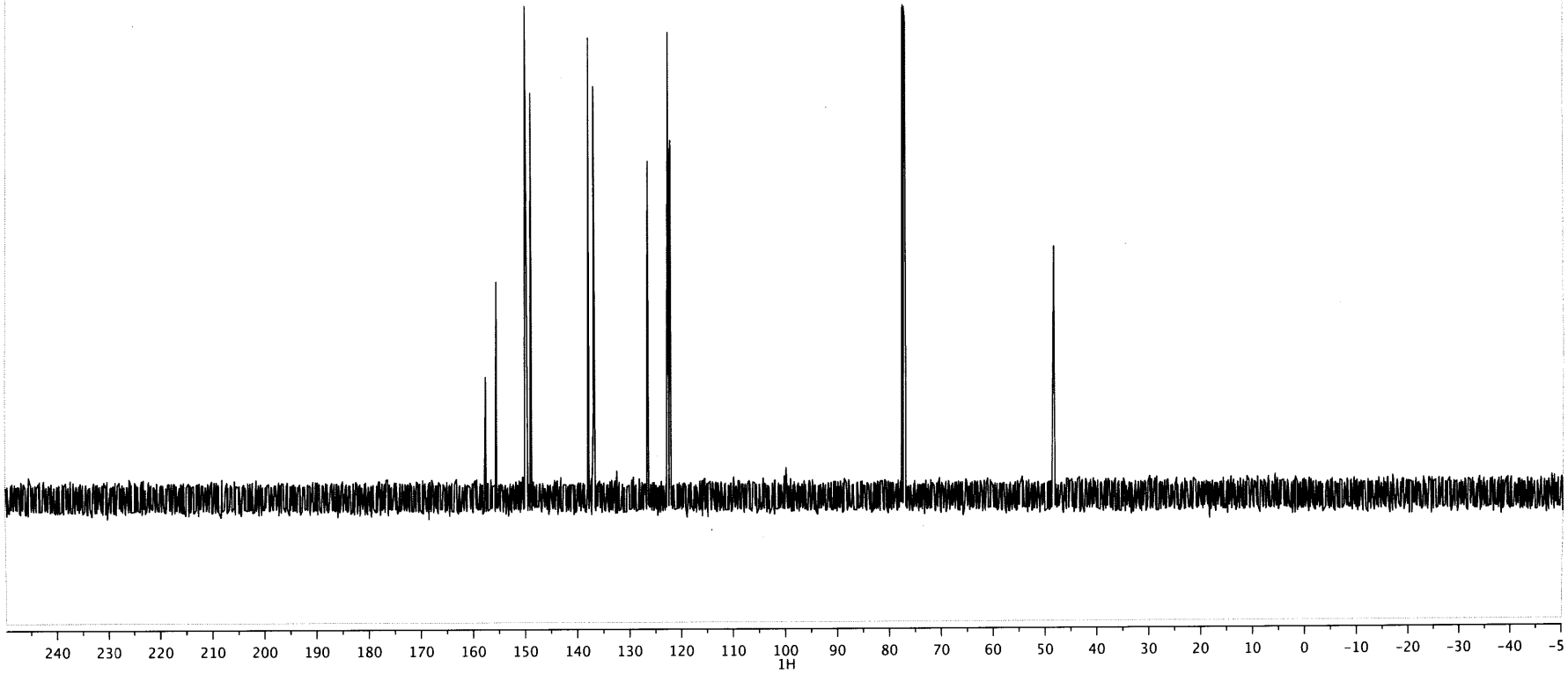

8c
1.00
0.99
1.04
1.03
1.02
1.08
2.09
2.11
1.09
5.23
1H


8c
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

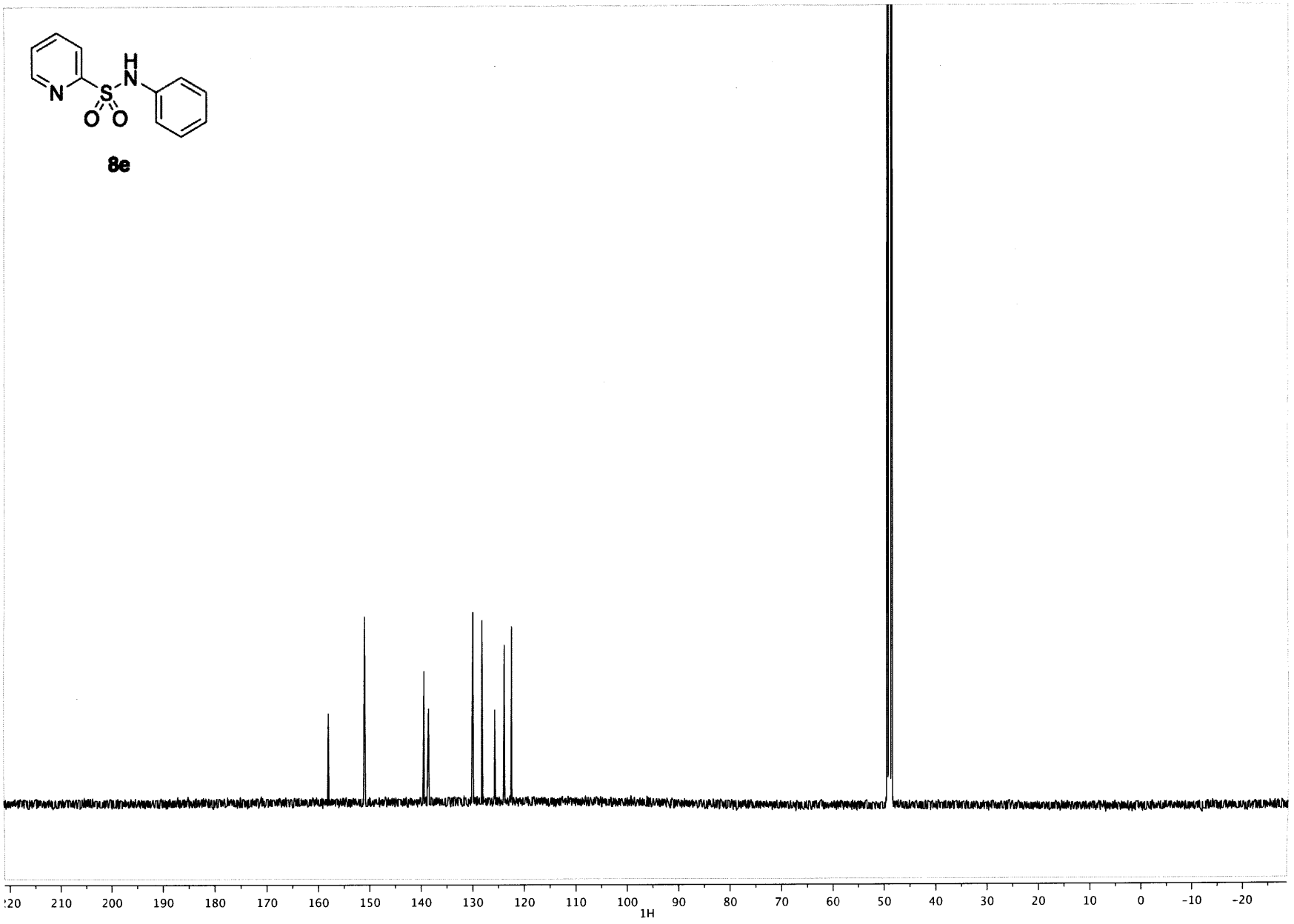

8d
1.00
1.00
1.01
1.02
1.03
1.03
1.14
1.03
0.52
2.00
1H

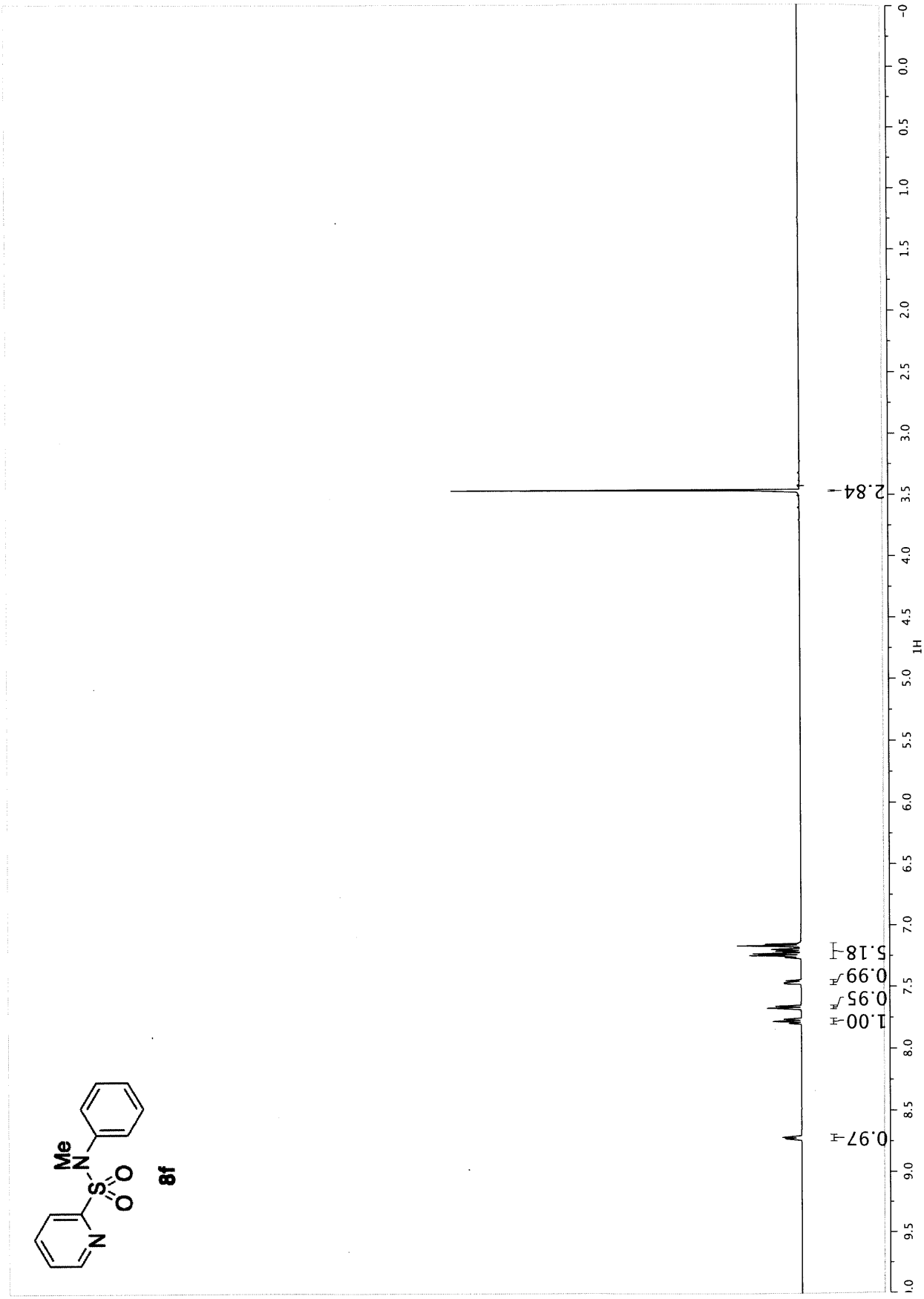


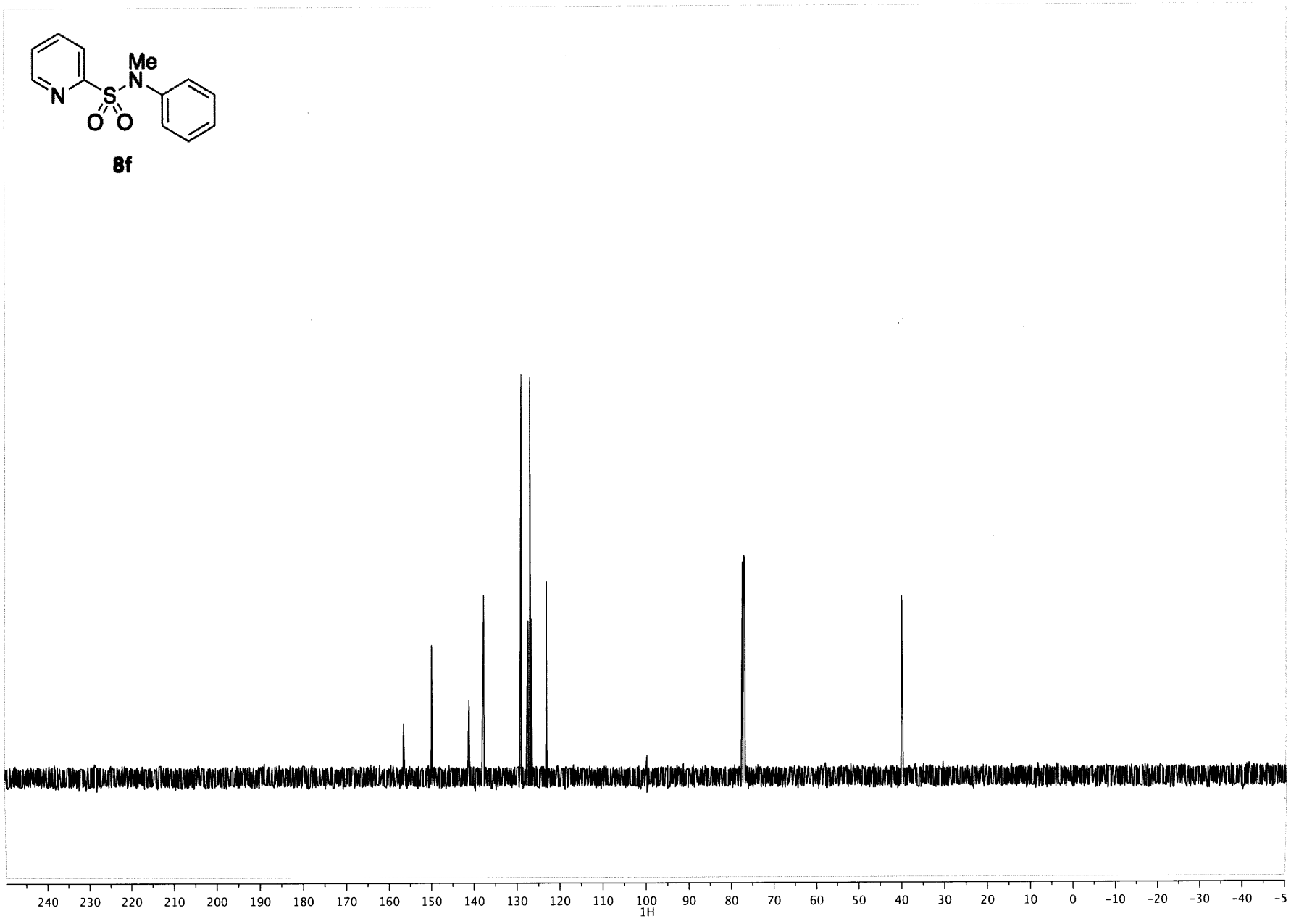
8d

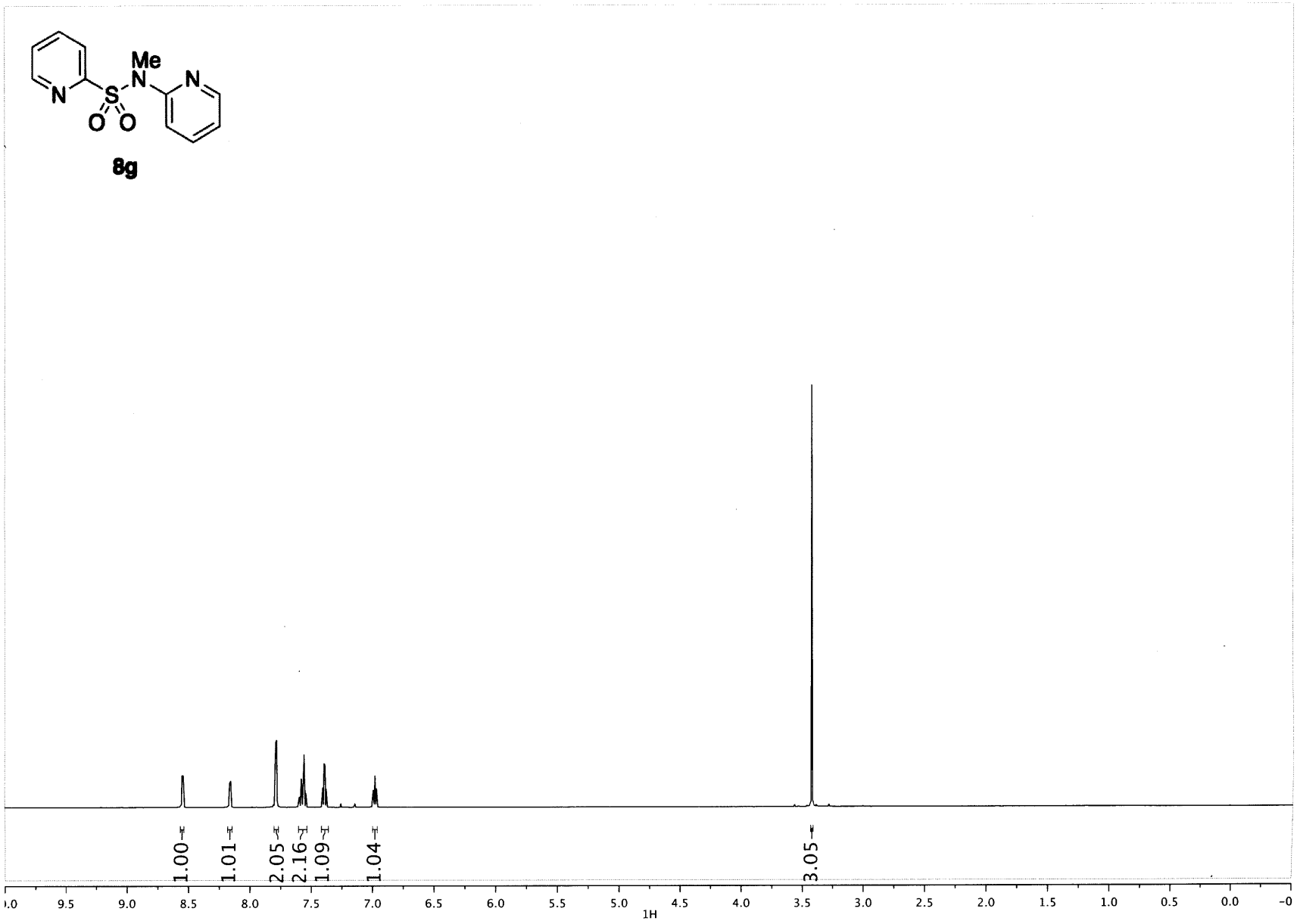

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

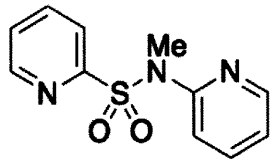
8e
1.00
2.06
1.02
4.11
1.03
1H


8e
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
1H

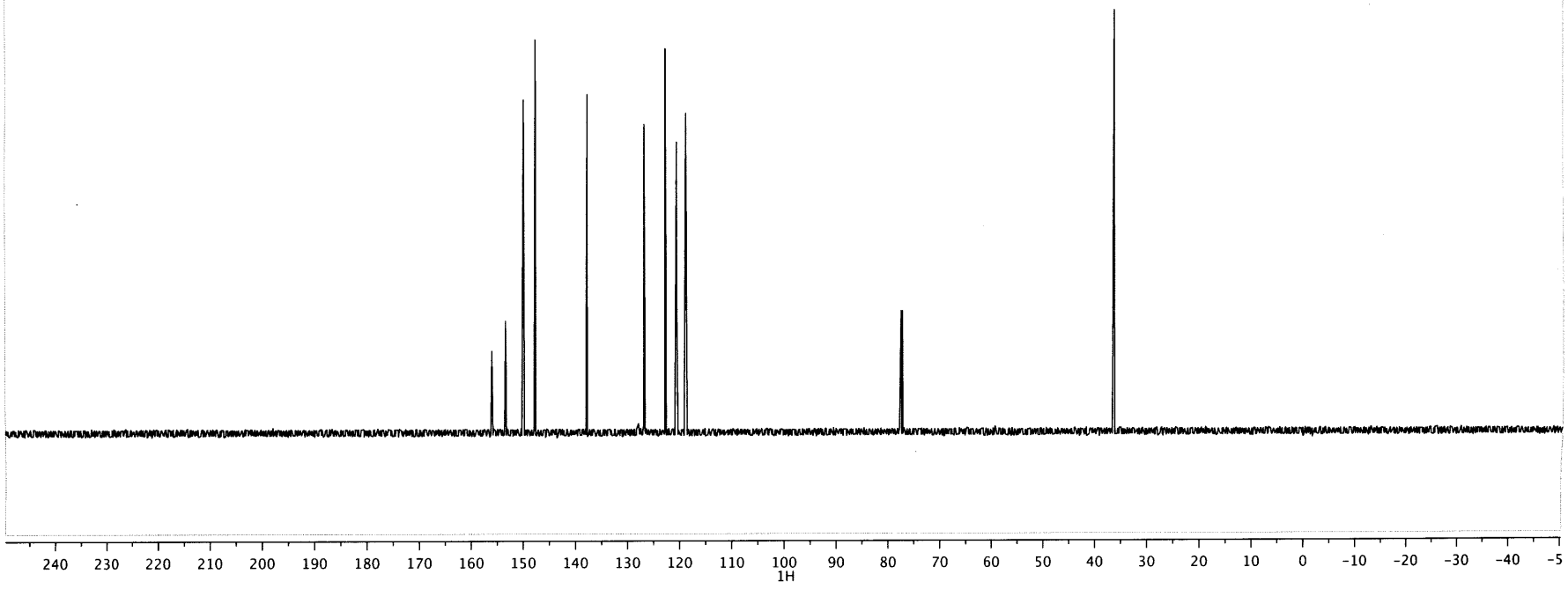

Me
N
S
O
O
N
8f
2.84
0.97
1.00
0.95
0.99
5.18
1H

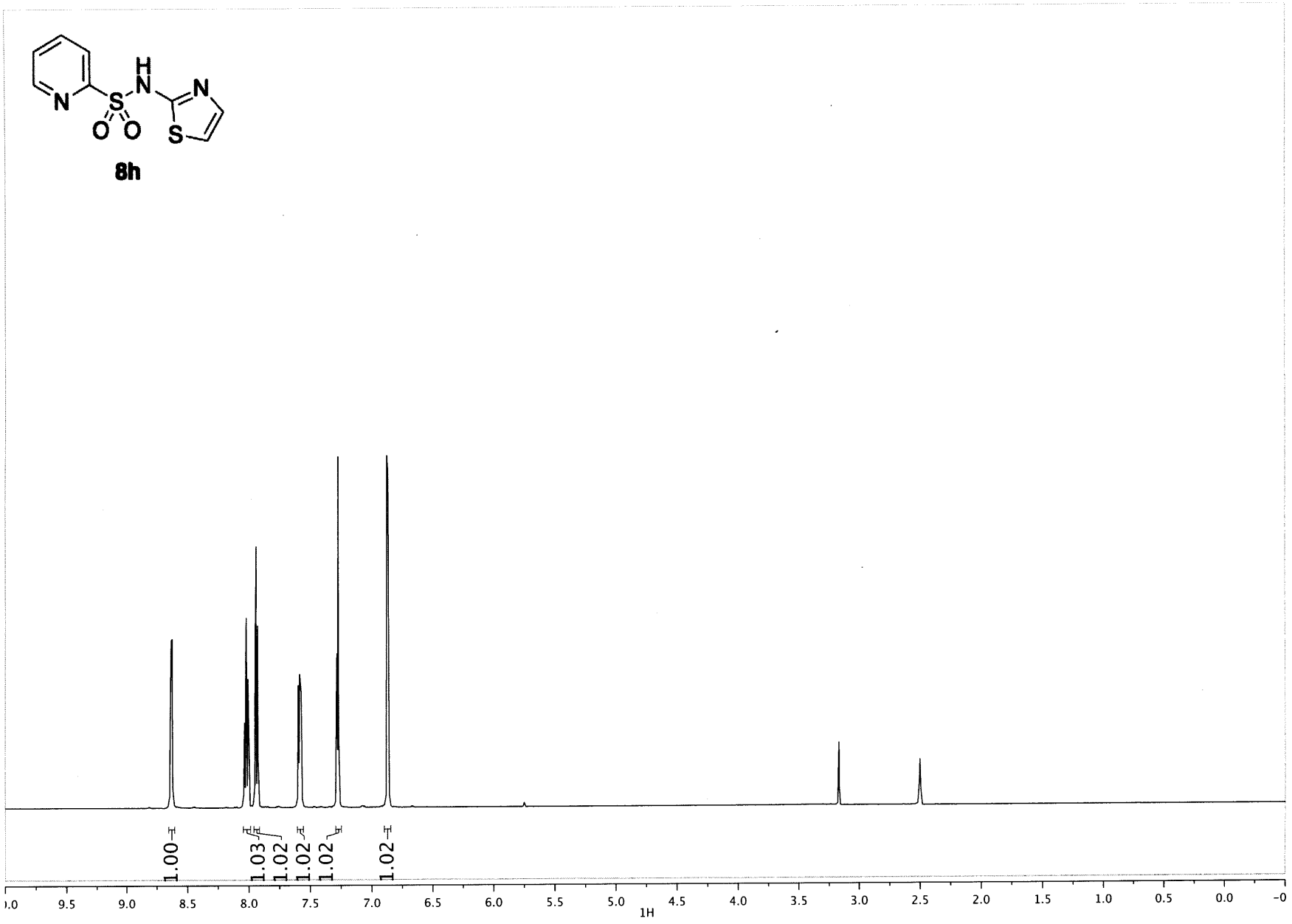

Me
N
S
N
O O
8f
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

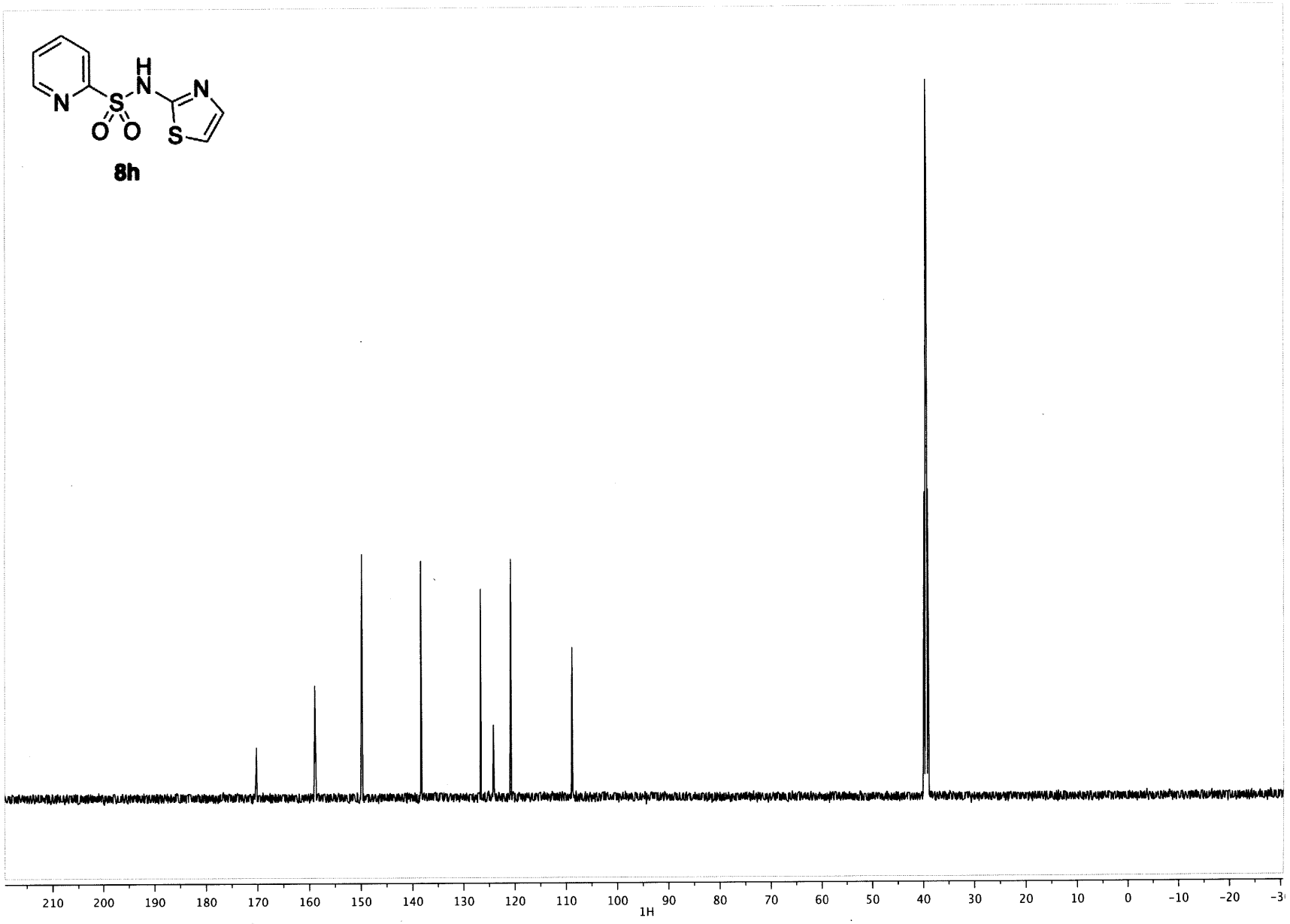

Me
N
S
O
O
N
N
8g
1.00
1.01
2.05
2.16
1.09
1.04
3.05
1H

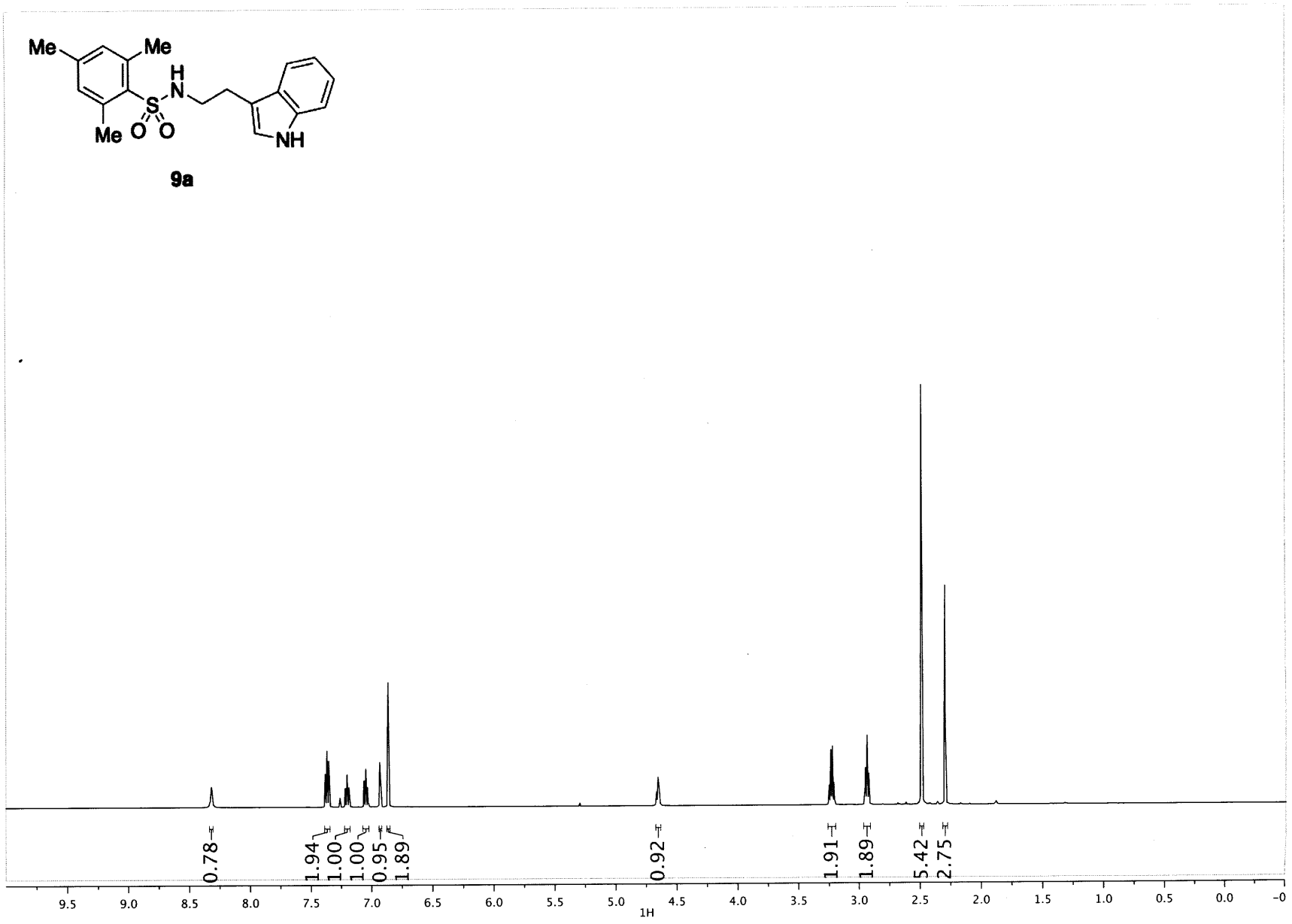

Me
N
N
S
O
O
N

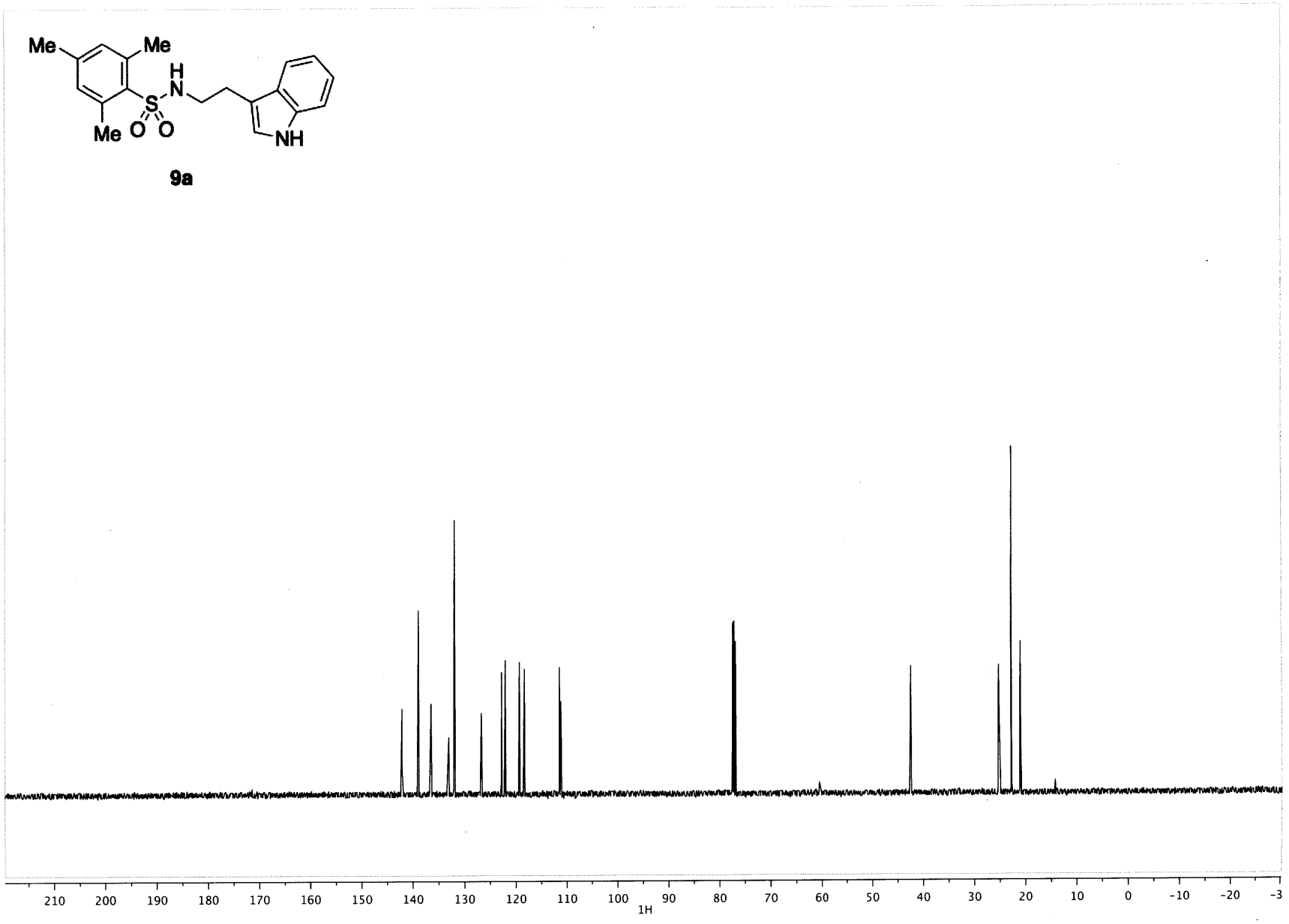
8g


240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

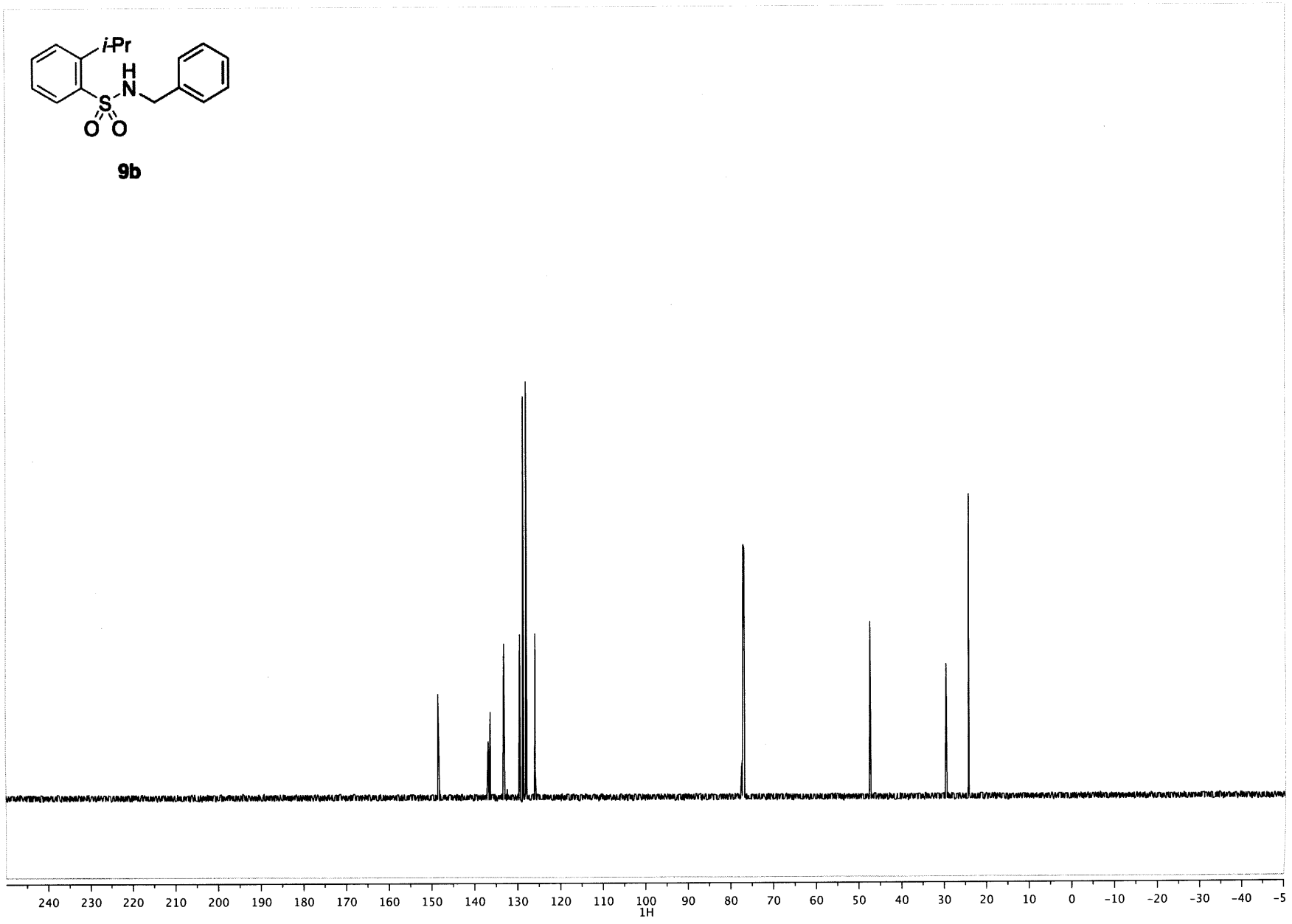

8h
1.00
1.03
1.02
1.02
1.02
1.02
1H

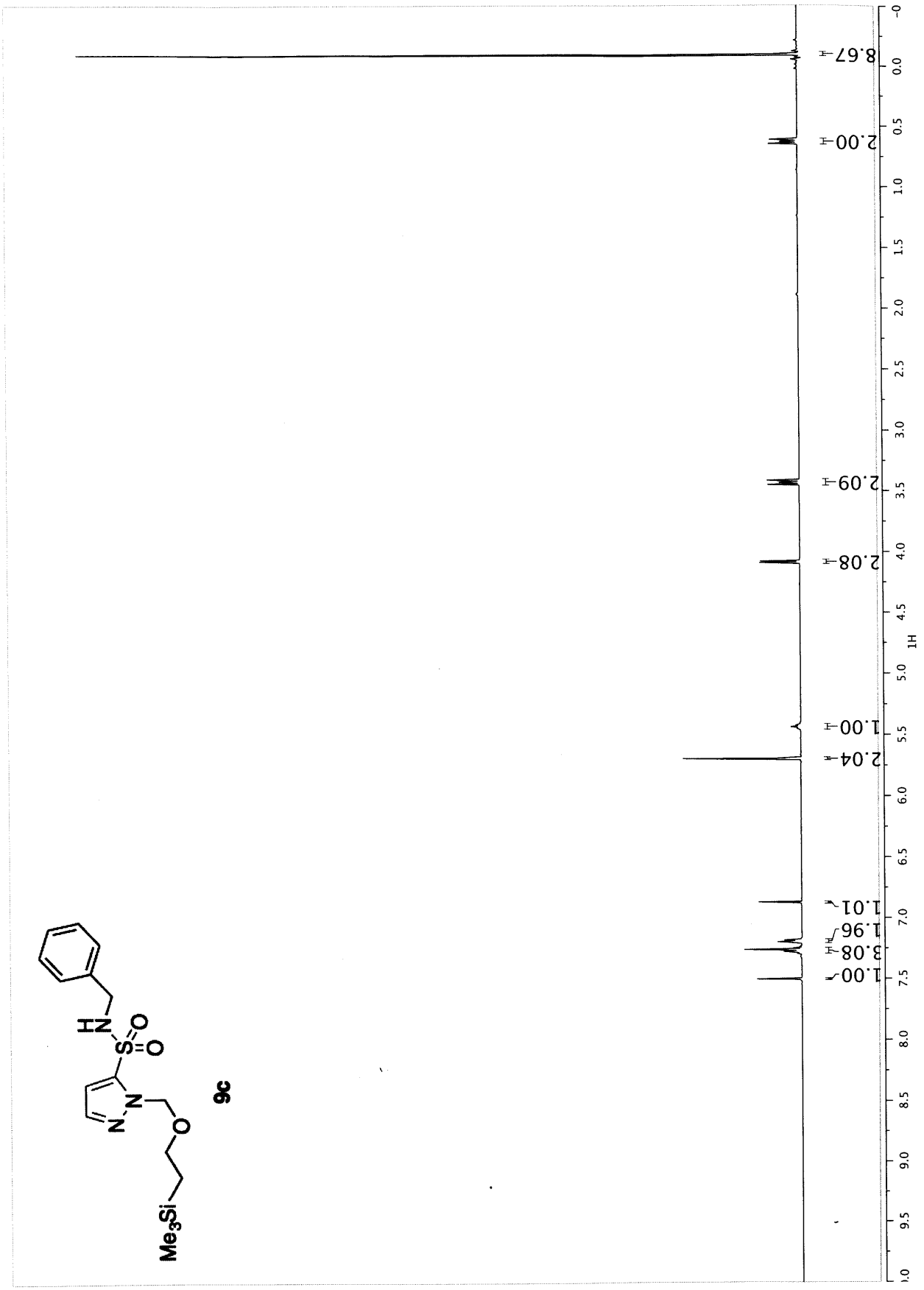

8h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

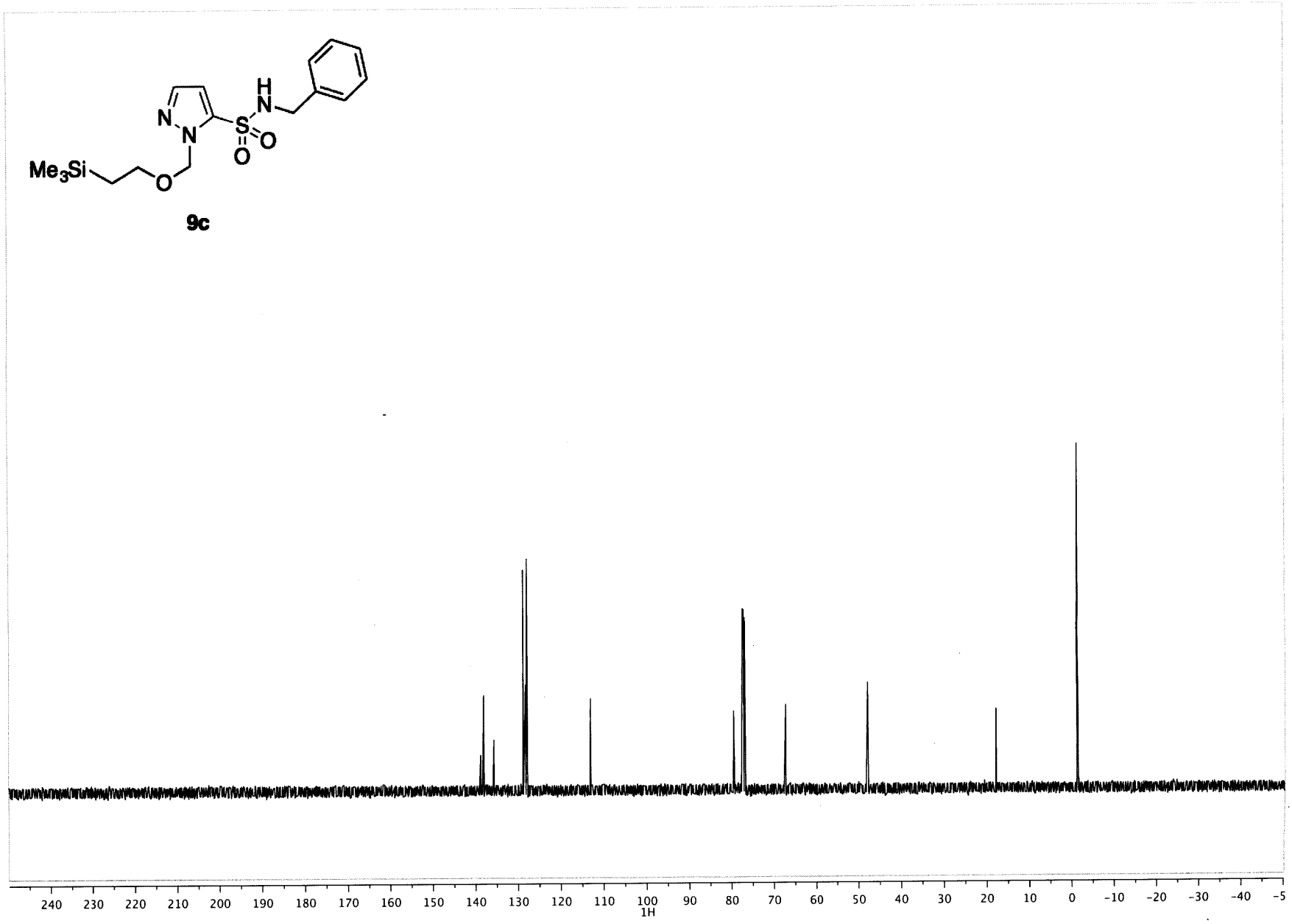

Me
Me
H
N
S
O
O
Me
NH
9a
0.78
1.94
1.00
1.00
0.95
1.89
0.92
1.91
1.89
5.42
2.75
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
1H


Me
Me
H
N
S
O
O
Me
NH
9a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H

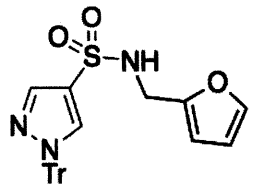
i-Pr
H
N
S
O
O
9b
1.00
1.05
1.03
4.37
1.91
0.97
2.08
1.13
6.07
1H


i-Pr
H
N
S
O O
9b
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

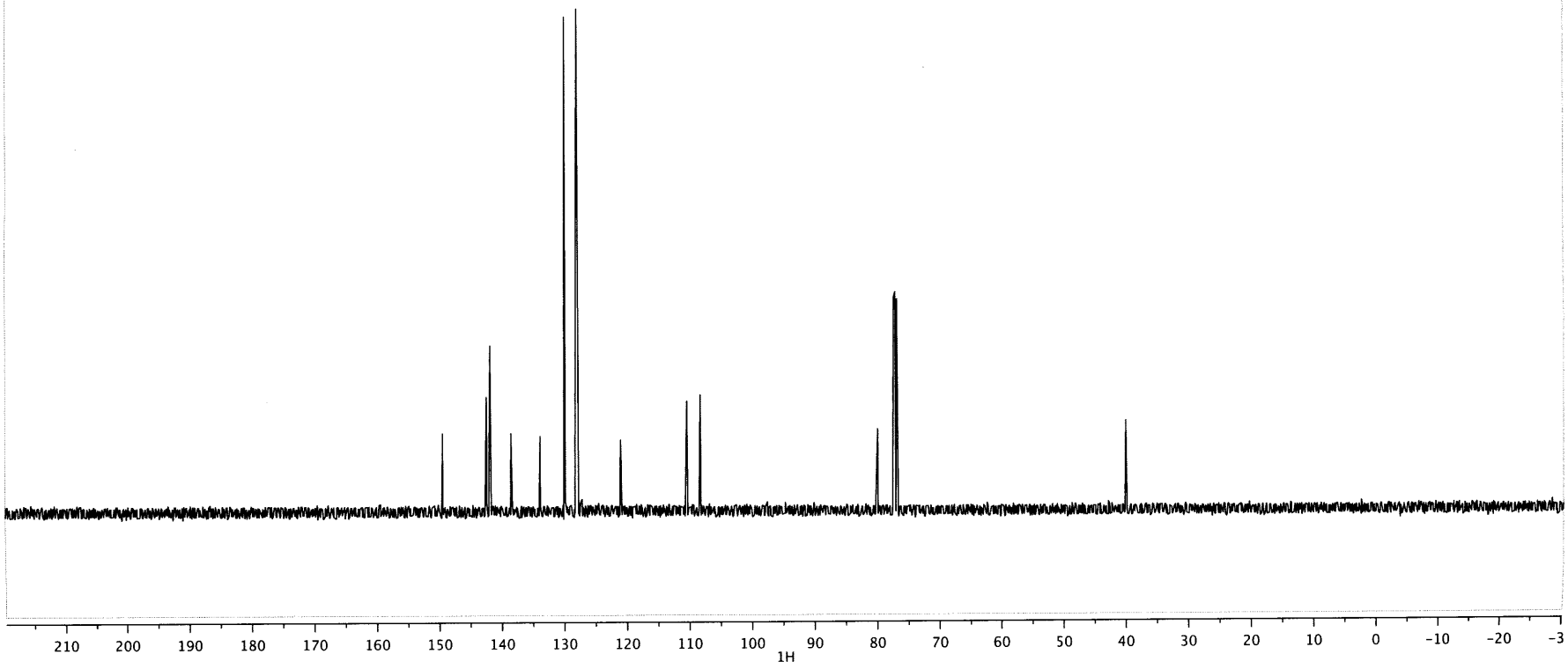

8.67
2.00
2.09
2.08
1.00
2.04
1.01
1.96
3.08
1.00
1H
Me3Si
9c

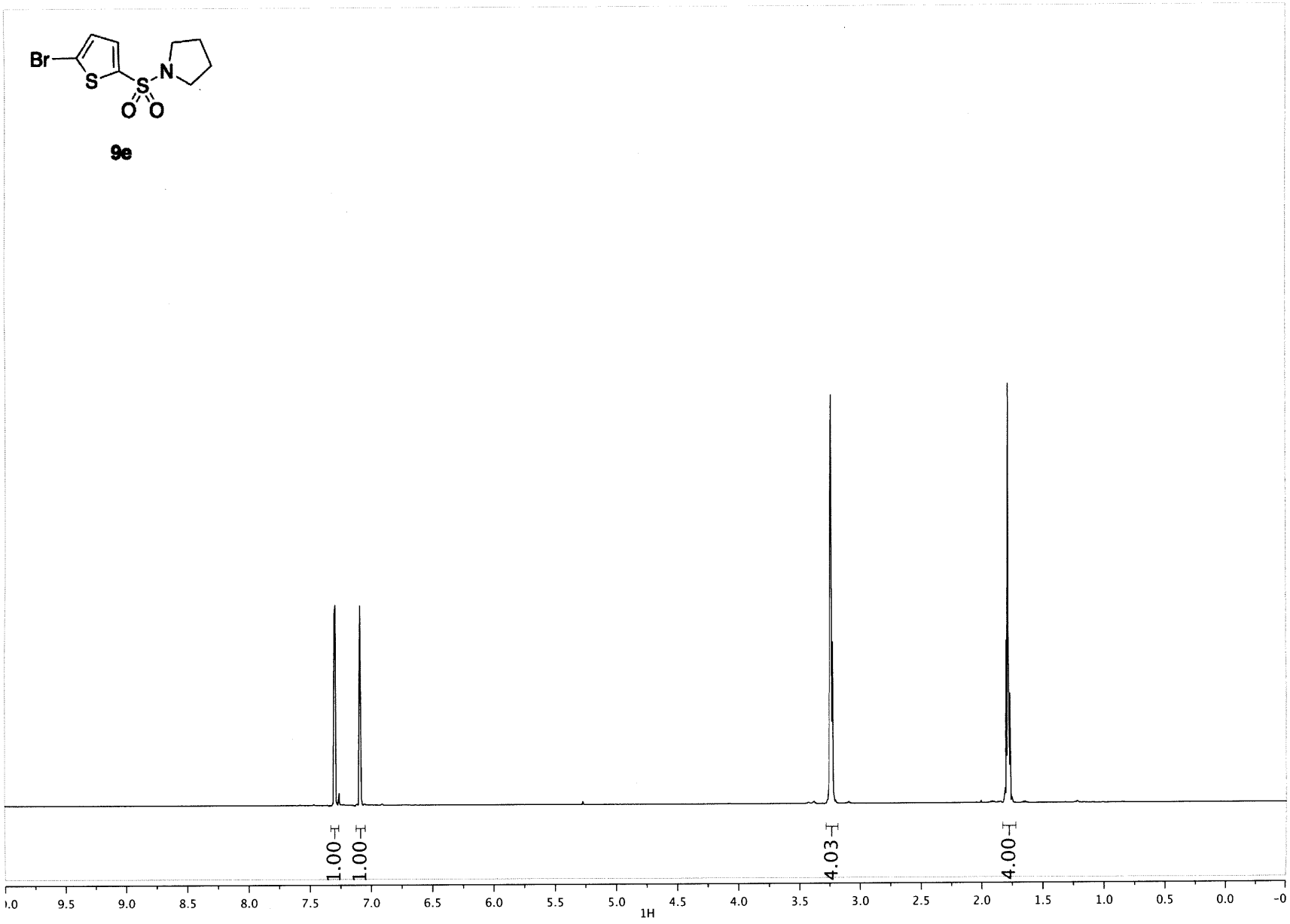

Me3Si
O
N
N
S
O
O
H
N
9c
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

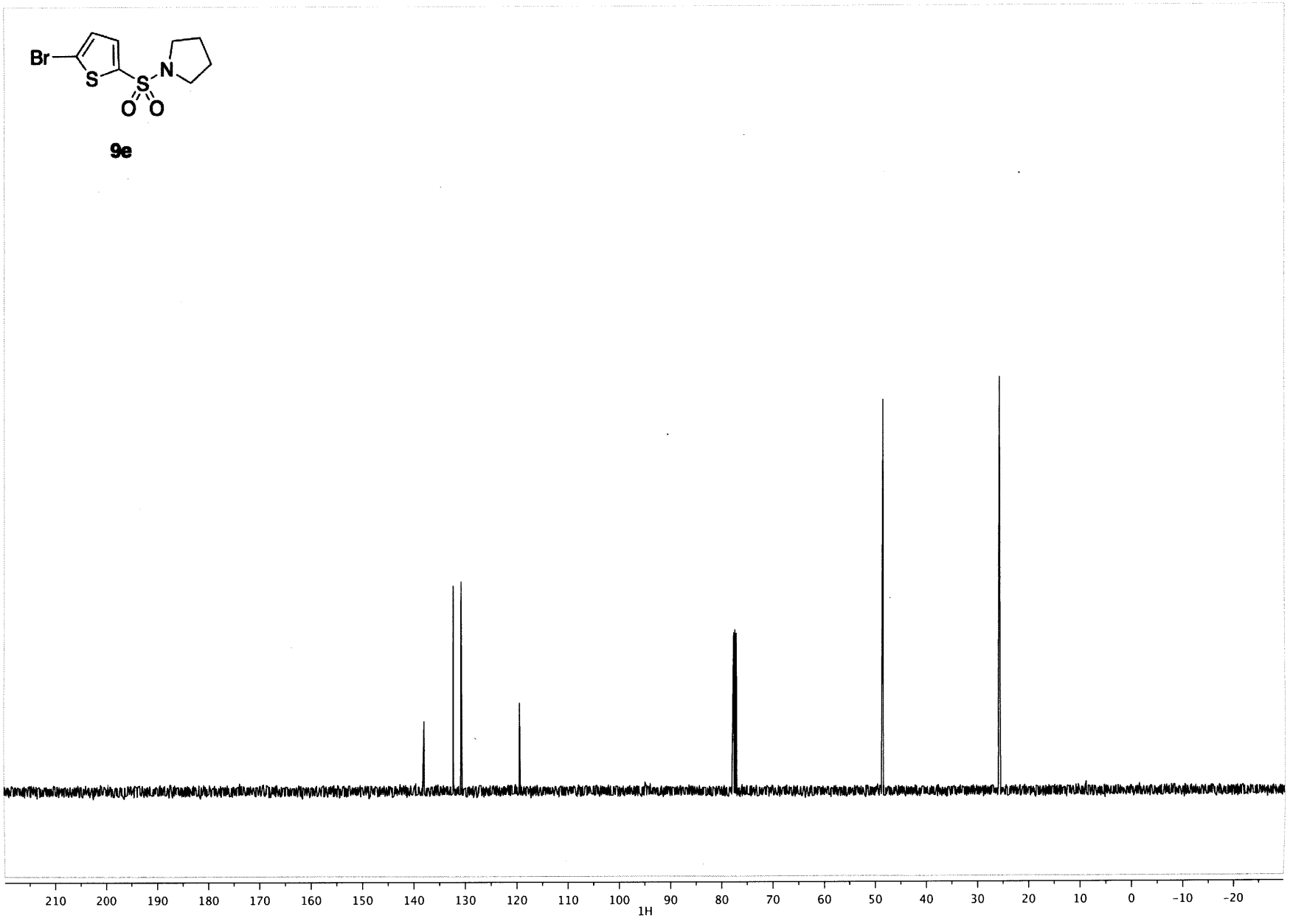
O
O
S
NH
O
N
N
Tr
9d
1.00
1.02
9.83
0.99
6.30
1.03
1.03
0.95
2.05
1H


O
O
S
NH
O
N
N
Tr

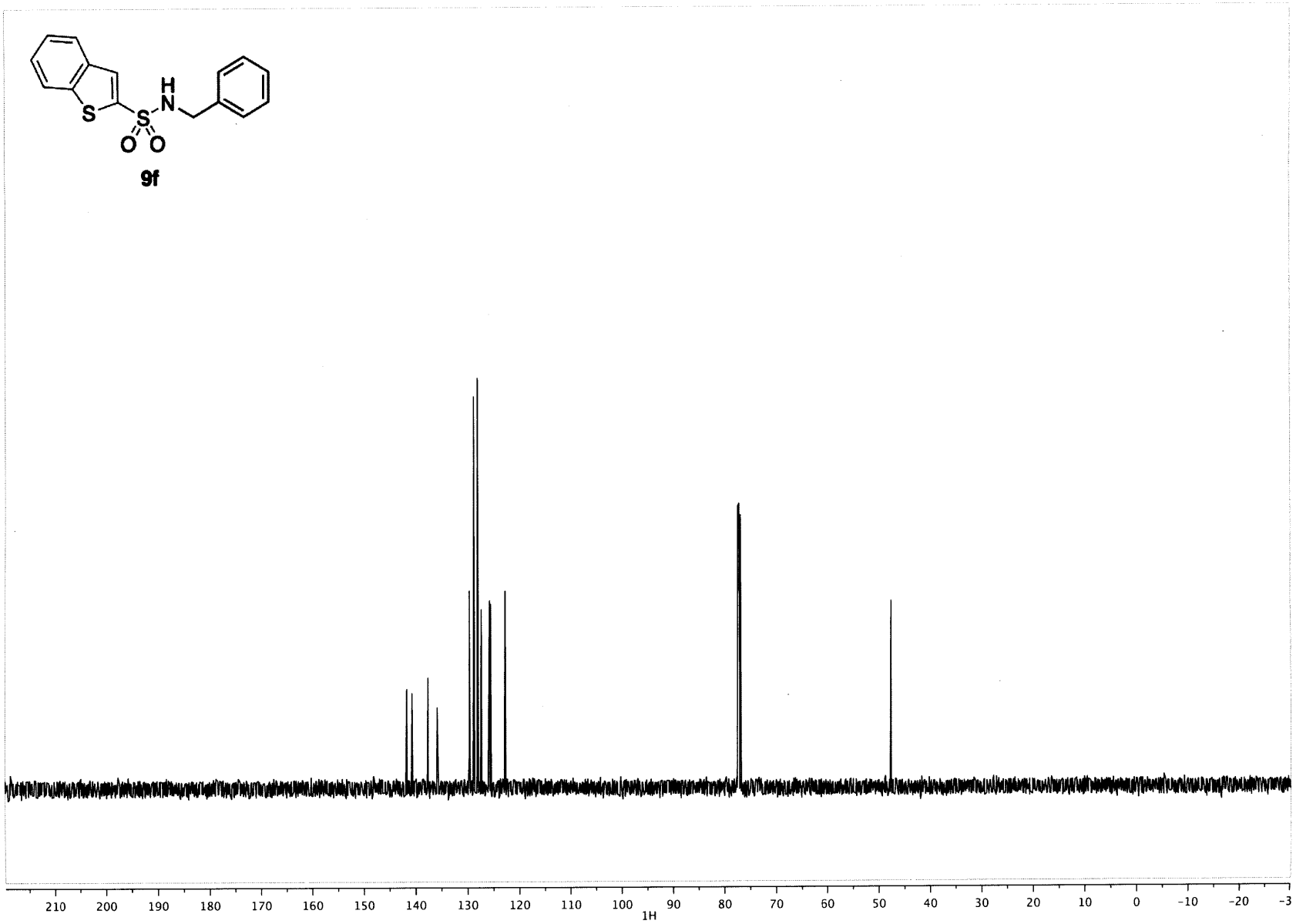
9d


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H


Br
S
S
N
O
O
9e
1.00
1.00
4.03
4.00
1H


Br
S
S
N
O
O
9e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

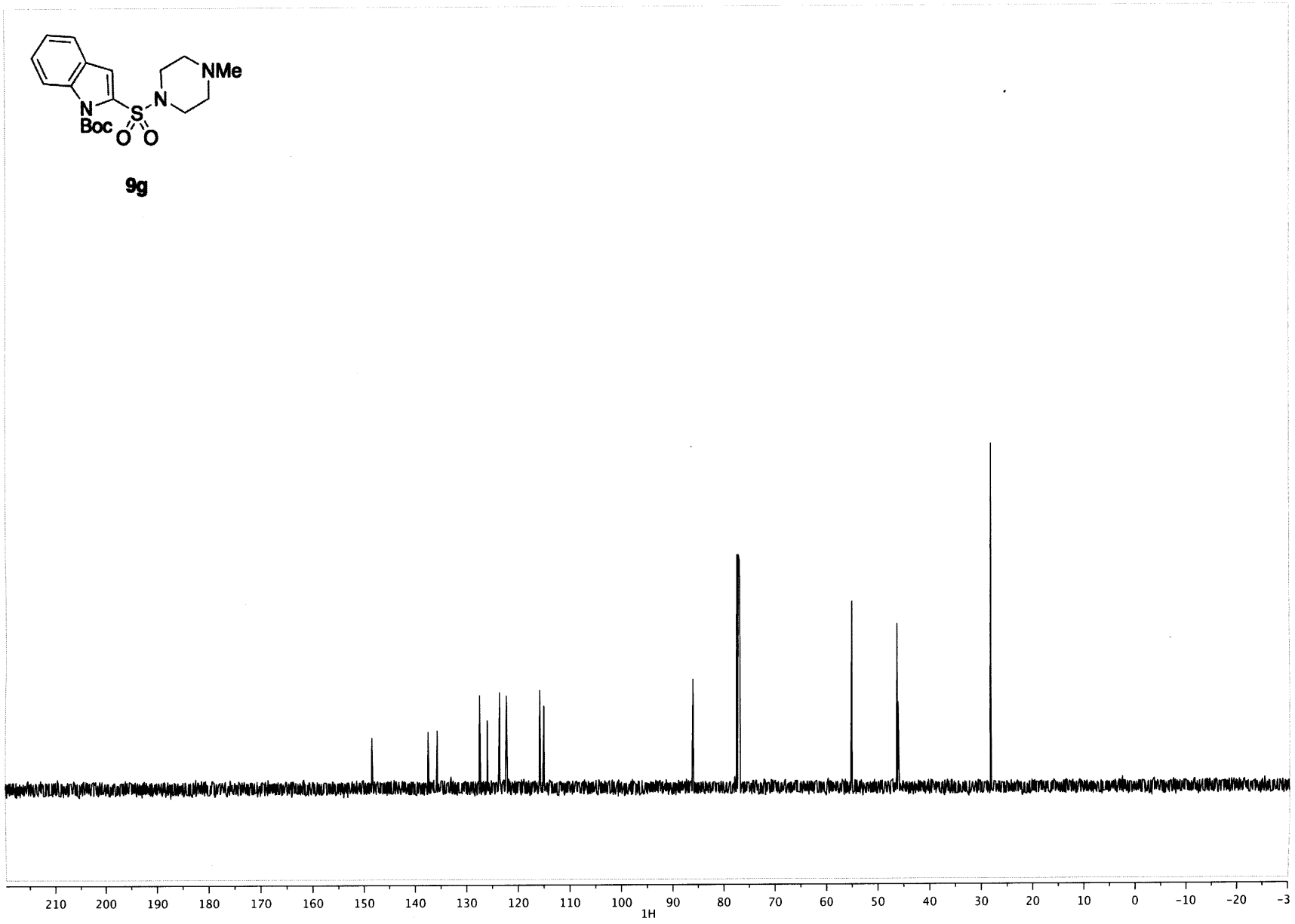
9f
2.91
2.02
5.48
1.00
2.03
1H

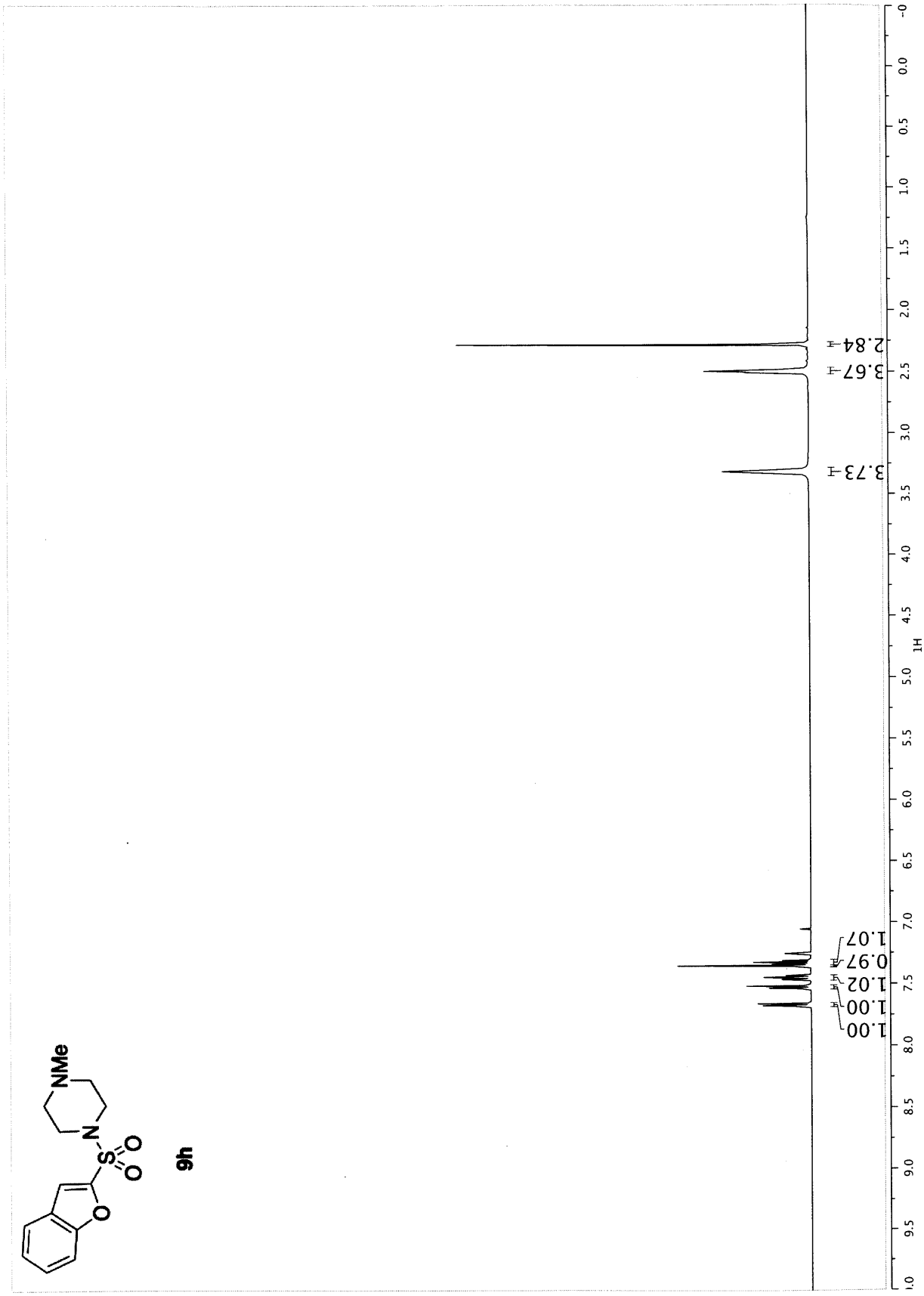

9f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H

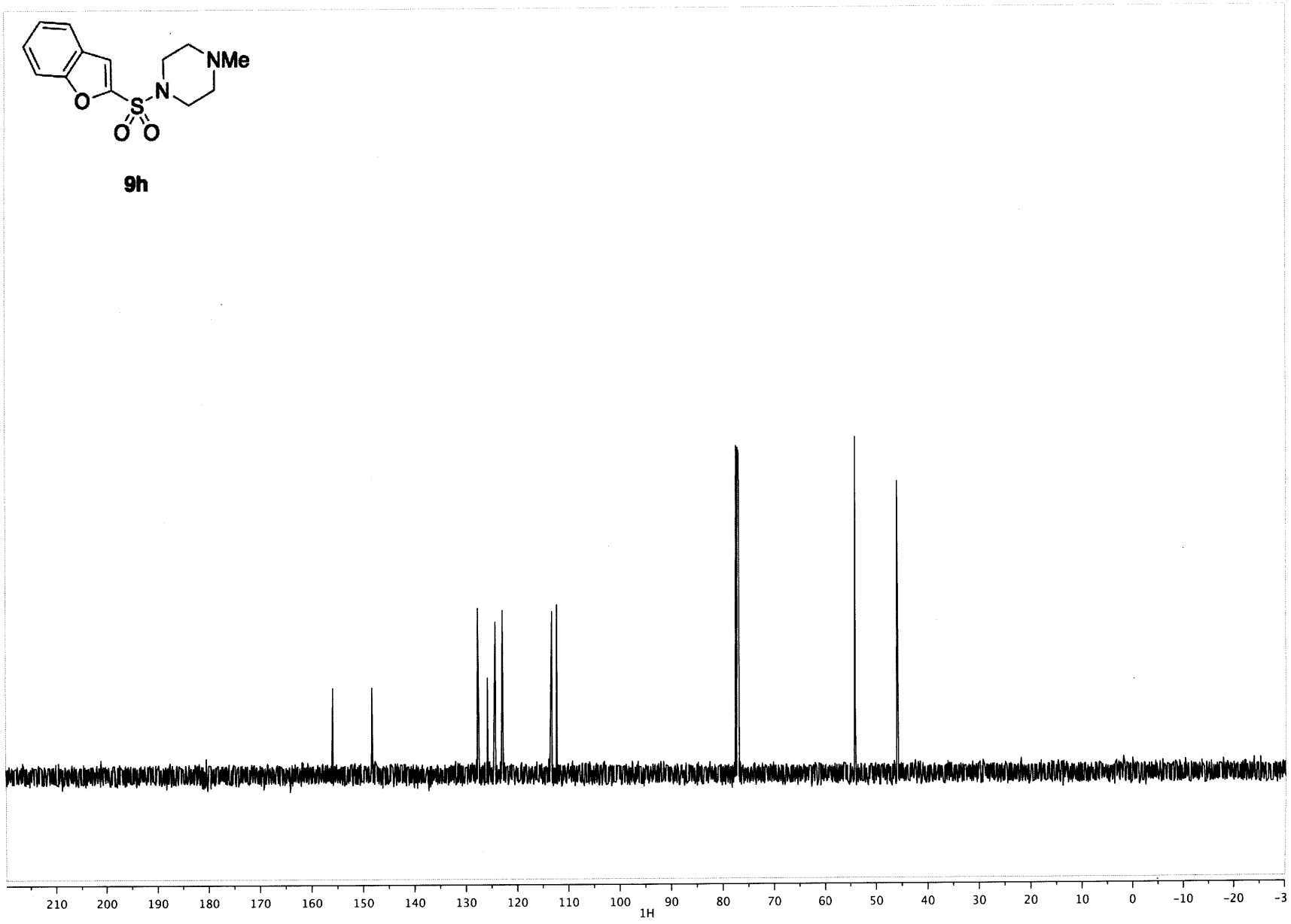
NMe
N
S
N
Boc
O
O

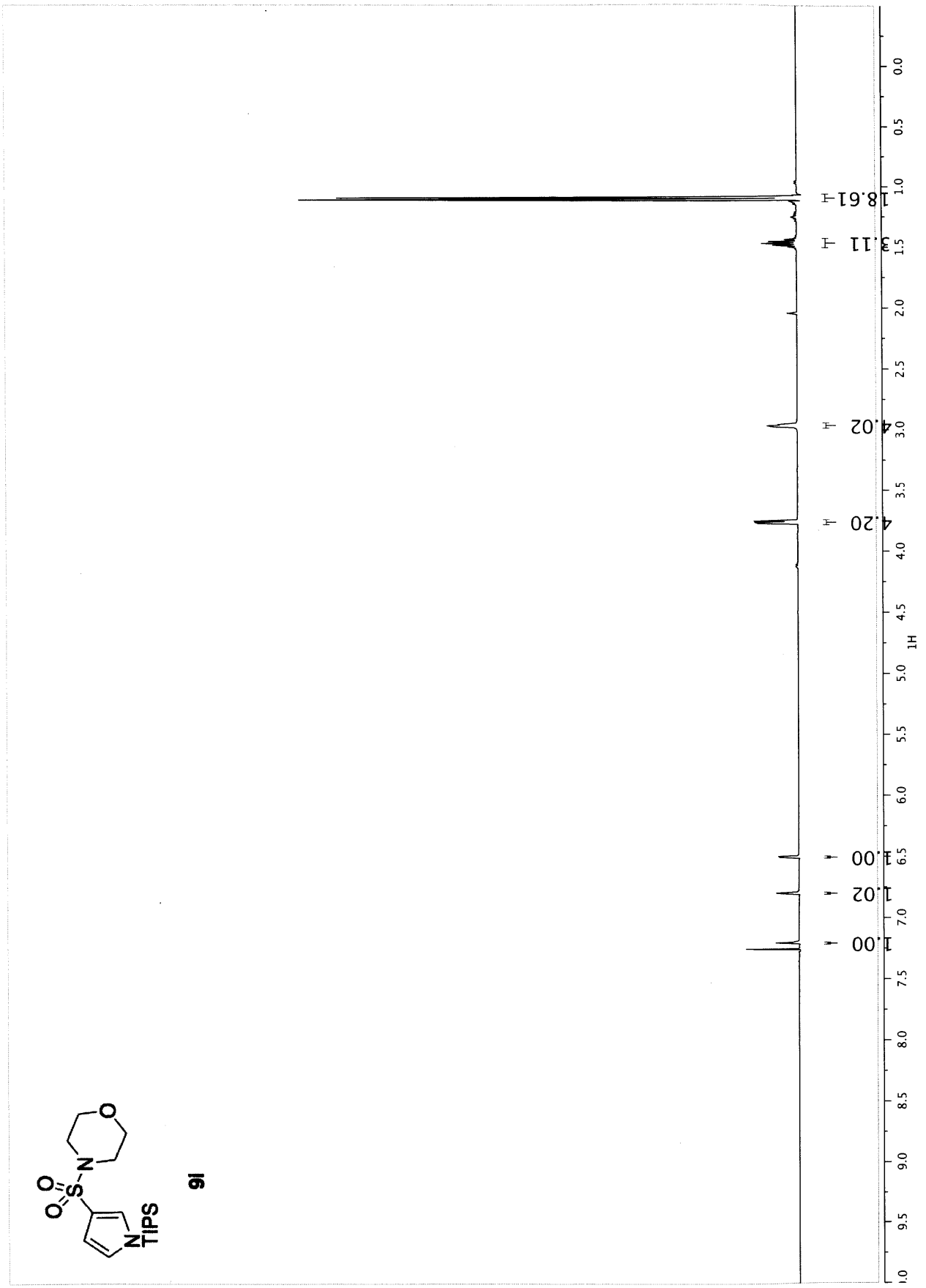
9g

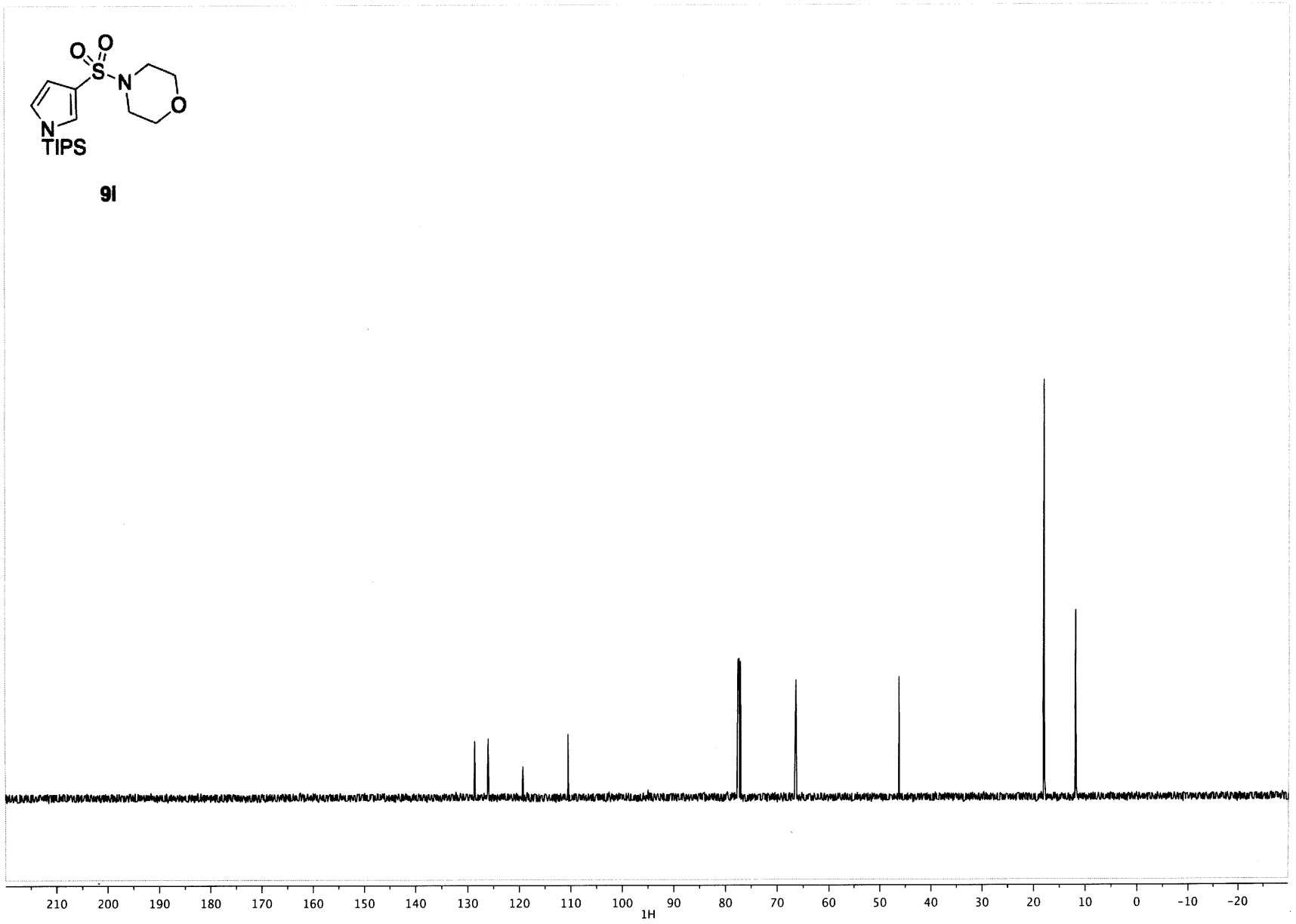
1.00
1.04
1.12
1.25
1.02
4.23
4.23
3.31
9.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


NMe
N
S
N
Boc
O
O
9g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H


NMe
N
S
O
O
O
9h
1.00
1.00
1.02
0.97
1.07
3.73
3.67
2.84
1H


NMe
N
S
O
O
O
9h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H


16
TIPS
18.61
3.11
4.02
4.20
1.00
1.02
1.00
1H


O
O
S
N
O
N
TIPS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

9l

Chapter III

Structure-Activity Relationship Studies on Selective Inhibitors of *P. Falciparum* Growth

3.1 Introduction

Malaria, a disease caused by parasites of the genus *Plasmodium*, is one of the greatest public health problems facing the world today. There were an estimated 198 million cases of malaria and 584,000 deaths due to malaria in 2013.[1] The disease disproportionately affects economically disadvantaged areas, with 90% of malaria deaths in Africa and 78% of deaths in children under five years old. *P. falciparum* is the most prevalent species in Africa and the most deadly malaria parasite, causing the vast majority of malaria deaths. Malaria death tolls have decreased substantially over the last several years, with significant progress made in the management of the *Anopheles* mosquito vector and in the availability of preventative treatments and artemisinin-based combination therapies (ACTs), the best available medication. However, only $2.7 billion was available in 2013 to combat malaria worldwide, compared with the estimated $5.1 billion needed in that period to effectively control and eventually eradicate the parasite. At the same time, artemisinin-resistant strains are emerging in Southeast Asia, and the effects of such strains spreading throughout the regions with endemic malaria would be devastating. As a result, the discovery and synthesis of antimalarial compounds is an important and active area of research.[2]

Heat shock protein 90 (Hsp90) is an essential chaperone that is highly conserved among eukaryotes.[3] Hsp90 regulates protein folding, "buffer[ing] proteostasis against environmental stress" by preventing protein misfolding, aggregation, or degradation.[3b] Hsp90 has many co-chaperones and even more clients (the proteins that are helped to fold), and is involved in signal transduction, protein trafficking, muscle contraction, and other processes in addition to its

---

[1] World Health Organization. *World Malaria Report 2014*; WHO Press: 20 Avenue Appia, 1211 Geneva 27, Switzerland, 2014.

[2] (a) Read, K. D.; Ian H. Gilbert, I. H. et al. *Nature* **2015**, *522*, 315-320. (b) Daub, M. E.; Prudhomme, J.; Roch, K. L.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912-4915. (c) Li, H.; Tsu, C.; Blackburn, C.; Li, G.; Hales, P.; Dick, L.; Bogyo, M. *J. Am. Chem. Soc.* **2014**, *136*, 13562-13565. (d) Hu, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2014**, *136*, 5287-5290.

[3] (a) Pearl, L. H.; Prodromou, C. *Annu. Rev. Biochem.* **2006**, *75*, 271-294. (b) Taipale, M.; Jarosz, D. F.; Lindquist, S. *Nat. Rev. Mol. Cell Bio.* **2010**, *11*, 515-528.

namesake heat shock response. The protein consists of three sections: a carboxy-terminal domain (CTD), which facilitates formation of the active dimeric complex; a middle domain, which plays a role in binding clients; and, the most conserved portion of Hsp90, the amino-terminal domain (NTD), where Hsp90 binds ATP.[4]

Hsp90 has been shown to be key to the growth of *P. falciparum* in human blood cells.[5] Tatu and coworkers demonstrated that geldanamycin, a known Hsp90 inhibitor (Figure 1),[6] inhibited parasite growth (LD_{50} = 200 nM), particularly affecting the ring to trophozite transition. Tatu further validated *P. falciparum* Hsp90 (*Pf*Hsp90) as a malaria drug target by showing that geldanamycin binds the protein with considerable affinity, that it selectively inhibited the ATPase activity of *Pf*Hsp90 over human Hsp90 (*Hs*Hsp90), and that tanespimycin (17-(allylamino)-17-demethoxygeldanamycin)[7] both inhibited parasite growth and increased survival in a mouse model of malaria.

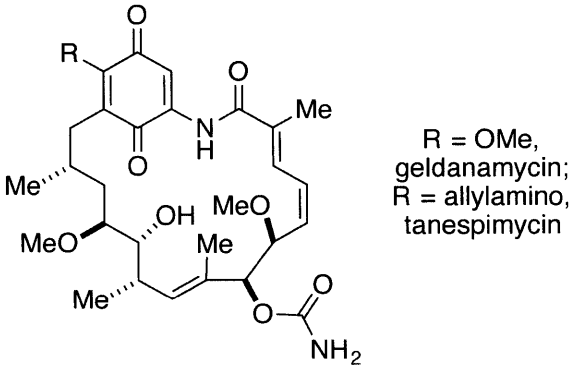


Figure 1. Geldanamycin and tanespimycin.

The Lindquist lab at the Whitehead Institute and MIT has a long-standing interest in Hsp90. With expertise in protein misfolding and significant contributions in related areas such as

---

[4] Prodromou, C.; Roe, S. M.; O'Brien, R.; Ladbury, J. E.; Piper, P. W.; Pearl, L. H. *Cell* **1997**, *90*, 65-75.
[5] Banumathy, G.; Singh, V.; Pavithra, S. R.; Tatu, U. *J. Biol. Chem.* **2003**, *278*, 18336-18345.
[6] (a) DeBoer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442-447. (b) Whitesell, L.; Mimnaugh, E. G.; De Costa, B.; Myers, C. E.; Neckers, L. M. *Proc. Natl. Acad. Sci.* **1994**, *91*, 8324-8328.
[7] (a) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; Moyer, J. D.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; O'Brien, A. T.; Morin, M. L.; Foster, B. A.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. r.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3806-3812. (b) Schnur, R. C.; Corman, M. L.; Gallaschun, R. J.; Cooper, B. A.; Dee, M. F.; Doty, J. L.; Muzzi, M. L.; DiOrio, C. I.; Barbacci, E. G.; Miller, P. E.; Pollack, V. A.; Savage, D. M.; Sloan, D. E.; Pustilnik, L. R.; Moyer, J. D.; Moyer, M. P. *J. Med. Chem.* **1995**, *38*, 3813-3820.

neurodegenerative disease,[8] prions,[9] and fungal infections,[10] the Lindquist group has made several important advances in the study of Hsp90.[11] Beyond applied research in specific disease areas, the lab has made fundamental biological contributions. Professor Lindquist and coworkers have shown that Hsp90's chaperone activity can mask genetic variation, allowing organisms to build up mutations corresponding to phenotypic variations that only manifest in stress situations where the Hsp90 buffer is overcome. Hsp90 is thus described as a "capacitor" of evolution, storing silent phenotypic diversity until environmental pressures release the reserved variations.

The Lindquist lab looked to leverage their Hsp90 expertise in an effort to cure malaria. Knowing that Hsp90 was essential for the parasite, research was undertaken to find a drug that targeted *Pf*Hsp90. Because Hsp90 is highly conserved and important for human biology, it is of critical importance that any drug that targets *Pf*Hsp90 be selective for the parasite protein over the human homolog. This could be challenging, as the two proteins have significant sequence homology and have been shown to be very similar by X-ray crystallography.[12]

A yeast assay was developed with this specific problem in mind (Figure 2). The assay relied on two strains of yeast. Both had been genetically engineered from the yeast strain W303a,[13] with both copies of the yeast Hsp90 removed (yHsp82 and yHsc82) and exogenous Hsp90 genes added. One strain expressed *Pf*Hsp90, and the other *Hs*Hsp90 (Figure 2a).[14] These strains could

---

[8] Narayan, P.; Ehsani, S.; Lindquist, S. *Nat. Chem. Bio.* **2014**, *10*, 911-920.
[9] Shorter, J.; Lindquist, S. *Nat. Rev. Genet.* **2005**, *6*, 435-450.
[10] Cowen, L.; Singh, S. D.; Köhler, J. R.; Collins, C.; Zaas, A. K.; Schell, W. A.; Aziz, H.; Mylonakis, E.; Perfect, J. R.; Whitesell, L.; Lindquist, S. *Proc. Natl. Acad. Sci* **2009**, *106*, 2818-2823.
[11] (a) Rutherford, S. L.; Lindquist, S. *Nature* **1998**, *396*, 336-342. (b) Jarosz, D. F.; Lindquist, S. *Science* **2010**, *330*, 1820-1824. (c) Rohner, N.; Jarosz, D. F.; Kowalko, J. E.; Yoshiawa, M.; Jeffery, W. R.; Borwsky, R. L.; Lindquist, S.; Tabin, C. J. *Nat. Rev. Cancer* **2005**, *5*, 761-772.
[12] Corbett, K. D.; Berger, J. M. *Proteins* **2010**, *78*, 2738-2744.
[13] Veal, E. A.; Ross, S. J.; Malakasi, P.; Peacock, E.; Morgan, B. A. *J. Biol. Chem.* **2003**, *278*, 30896-30904.
[14] Scroggins, B. T.; Robzyk, K.; Wang, D.; Marcu, M. G.; Tsutsumi, S.; Beebe, K.; Cotter, R. J.; Felts, S.; Toft, D.; Kartniz, L.; Rosen, N.; Neckers, L. *Mol. Cell* **2007**, *25*, 151-159.

then be tested against drug candidates, with the relative and absolute growth inhibitions indicative of the potency and selectivity of the tested compounds (Figure 2b).

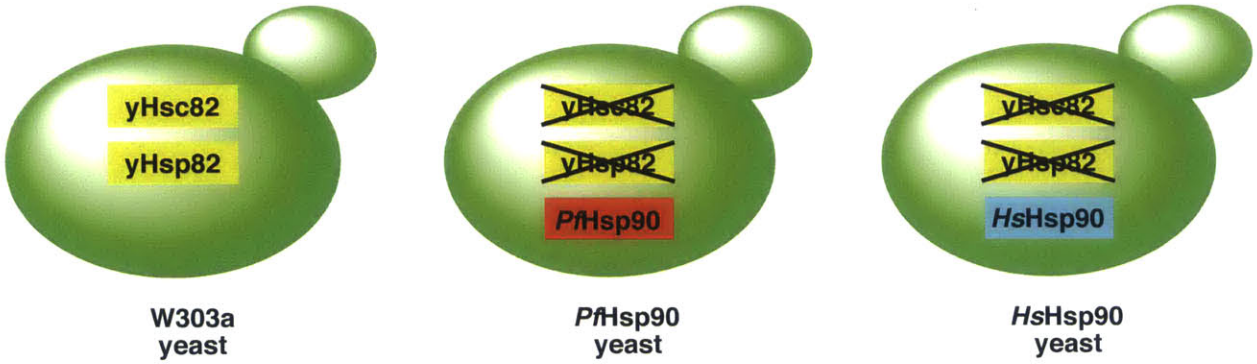


Figure 2a. Genetically engineered yeast with *Pf*Hsp90 and *Hs*Hsp90.

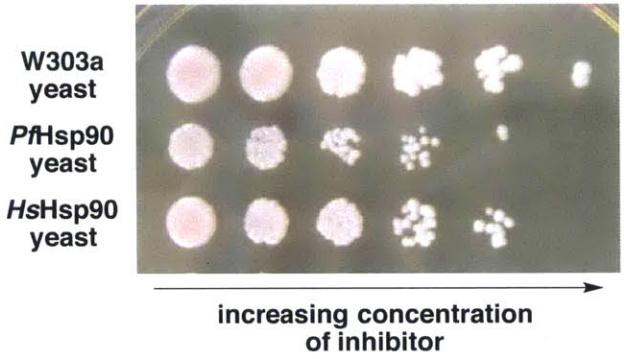


Figure 2b. Selective inhibition of *Pf*Hsp90 strain in compound assay.

Yeast is an effective model system for targeting such a highly conserved and diversely functional eukaryotic protein as Hsp90. Phenotypic assays have been proposed to be more successful in drug discovery when compared to target-based approaches.[15] An effective antimalarial could potentially affect any of the hundreds of interactions in which *Pf*Hsp90 is involved, and the two strains provide a clear and simple test for selectivity. Any discrepancies between efficacy in the yeast model system and efficacy against *P. falciparum* can be resolved by using an assay for growth inhibition of blood-stage malaria parasite. In this assay, performed

[15] Swinney, D. C.; Anthony, J. *Nat. Rev. Drug Discov.* **2011**, *10*, 507-519.

in the Wirth lab at the Harvard T. H. Chan School of Public Health,[16] both the multidrug resistant parasite strain Dd2 and an Hsp90 mutant strain of Dd2 (referred to as D88Y in the figures) with increased resistance to Hsp90 inhibitors were used.

The yeast assay was used in collaboration with the NIH's Molecular Libraries Probe Production Centers Network (MLPCN) program at the Broad Institute. Broad scientists used the assay to screen over 300,000 compounds from the MLPCN library. Compounds were first screened for potency of inhibition of the *Pf*Hsp90 yeast strain, then selectivity for that strain over the *Hs*Hsp90, and finally potency against actual blood-stage *P. falciparum*. Four promising compounds emerged (Figure 2). **SA1-3** all contained sulfonamides (SA meaning sulfonamide), but **SA2** and **SA3** were considerably less selective and potent than **SA1**. **CA1** featured an entirely different structure: an amide with a chromene connected to the carbonyl and a 4-chlorobenzyl group bound to the amine (CA meaning chromene amide). This compound was less potent than **SA1**, but more selective. Because of these differences between the SA and CA scaffolds, structure-activity relationship (SAR) studies of both **SA1** and **CA1** were pursued.

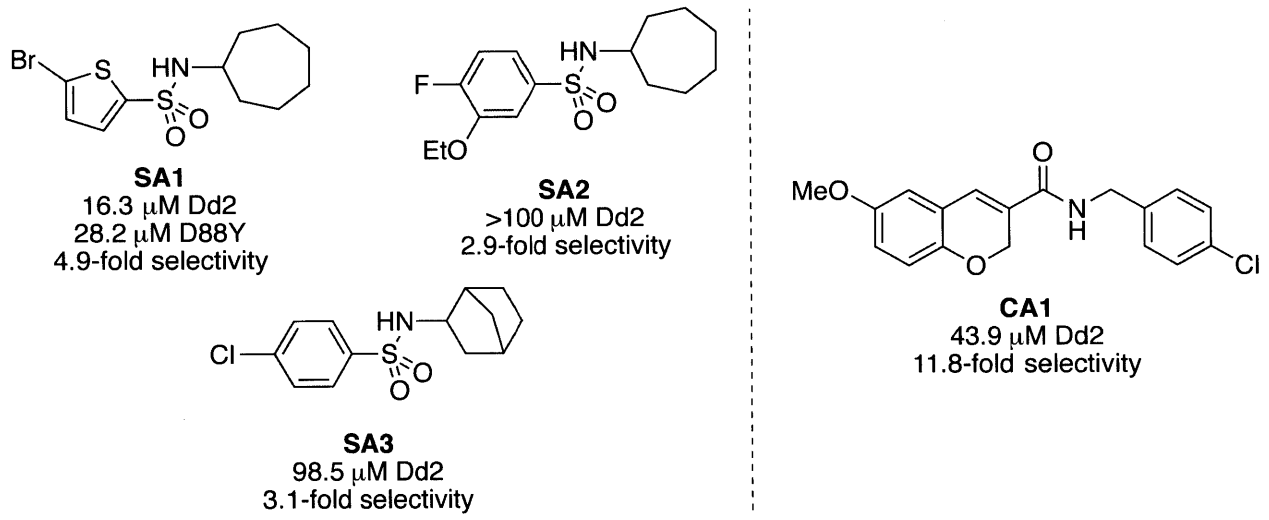


Figure 3. SA and CA compounds from the MLPCN high-throughput screen.

[16] Baniecki, M. L.; Wirth, D.; Clardy, J. *Antimicrob. Agents Ch.* **2007**, *51*, 716-723.

The SAR of the **SA1** and **CA1** scaffolds would be explored through analog synthesis (Figure 4). **SA1** featured a thiophene (aryl/heteroaryl) connected to a cycloheptyl sulfonamide (cycloalkyl group and sulfonamide linker). These three components would be modified by varying sulfonyl chloride electrophiles and amine nucleophiles in sulfonamide coupling reactions, as well as by replacing the sulfonamide linker with a carbonyl. **CA1** had a 2H-chromene (bicyclic aromatic) with a benzyl amide in the 3-position (aryl group and amide linker). SAR for this series would be based on variation of amine nucleophiles and carboxylic acid electrophiles.

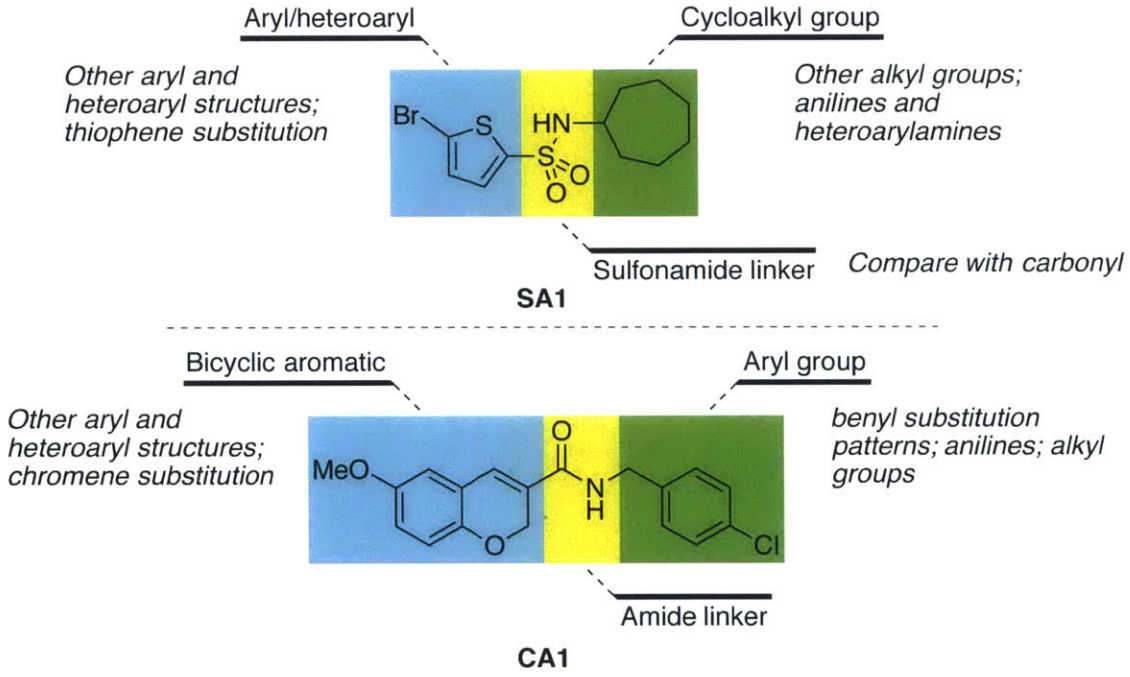


Figure 4. Planned modifications of SA and CA compounds.

3.2 Results and Discussion

3.2.1 General Routes to SA and CA Analogs

Analogs of the SA and CA compounds could easily be prepared through amide and sulfonamide coupling reactions (Figure 5). For the SA series, commercially available sulfonyl chlorides or sulfonyl chlorides synthesized using the method described in chapter 2[17] could be reacted with amines. The TCPC method was extremely convenient, expanding the substrate scope to aryl and heteroaryl halides and heteroarenes as well as sulfonyl chlorides. For both the SA and CA series, amides were prepared from the corresponding carboxylic acids, which were converted to acid chlorides by treatment with Vilsmeier reagent generated *in situ* from oxalyl chloride and catalytic dimethylformamide (DMF). New 2H-chromene scaffolds were prepared

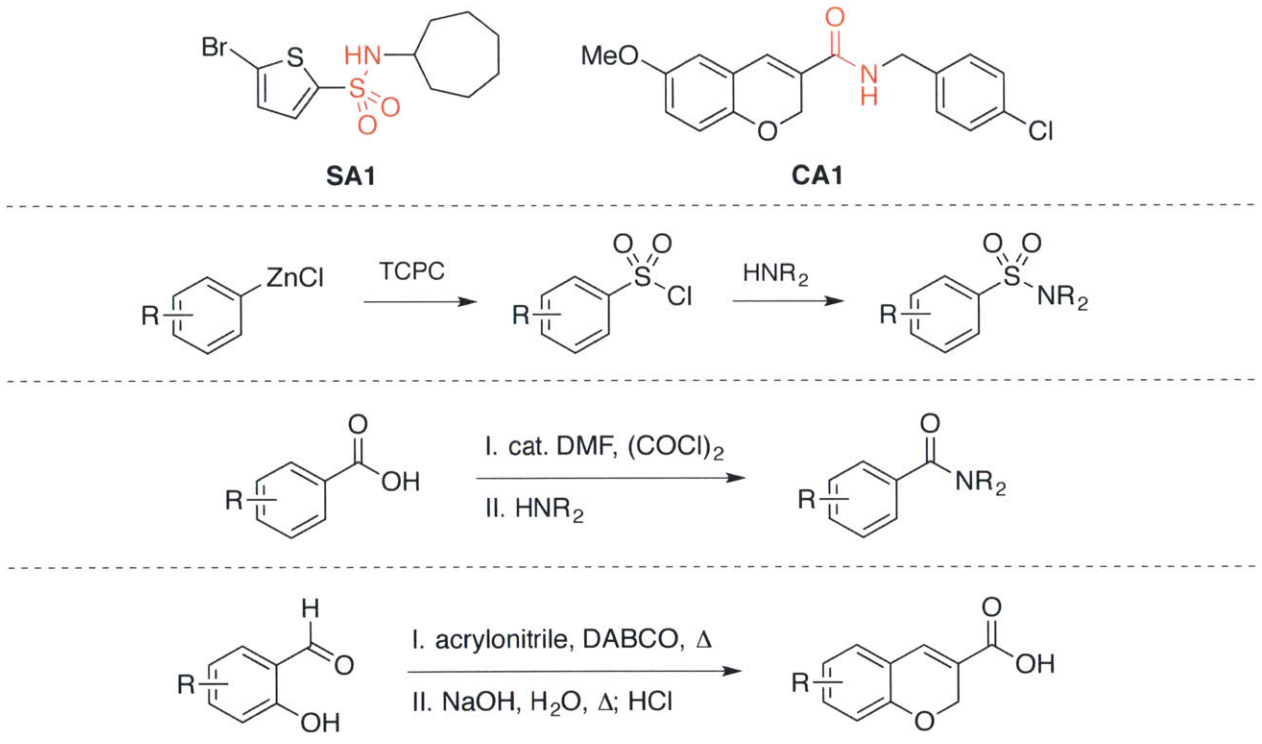


Figure 5. General synthetic routes to SA and CA analogs.

[17] Colombe, J. R.; Debergh, J. R.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 3170-3173.

from salicylic acids.[18] Cyclization with acrylonitrile in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and subsequent saponification of the vinyl nitrile product afforded the desired acid, which could then be converted to the amide as described above.

[16] (a) Pave, G.; Chalard, P.; Viaud-Massuard, M.-C.; Troin, Y.; Guillaumet, G. *Synthesis* **2004**, *1*, 121-127. (b) Beliaev, A.; Wahon, J.; Russo, D. *Org. Process Res. Dev.* **2012**, *16*, 704-709.

3.2.2 SAR Studies on SA and CA Compounds

Modification of the cycloalkyl group of **SA1** was explored (Figure 4). Switching to a tertiary morpholine amide (**SA4**) resulted in a complete loss of selectivity in the yeast model system and activity in the parasite assay (LD_{50} > 100 μM). The same was true for switching to an *N*-phenylsulfonamide (**SA5**). A neopentyl sulfonamide (**SA6**) retained some potency against the blood-stage parasite, but was not selective. Switching to the 4-chlorobenzyl (**SA7**) or exo-nobornyl (**SA8**) amine substituents of **CA1** and **SA3** was deleterious, but some activity was retained. Replacing the cycloheptyl group with a heterocycle (**SA9**) resulted in a loss of activity against the parasite. Overall, the activity was quite sensitive to changes in the cycloalkyl group, with the only active analogs of this series (**SA6**, **SA8**) also bearing large alkyl groups on a secondary sulfonamide.

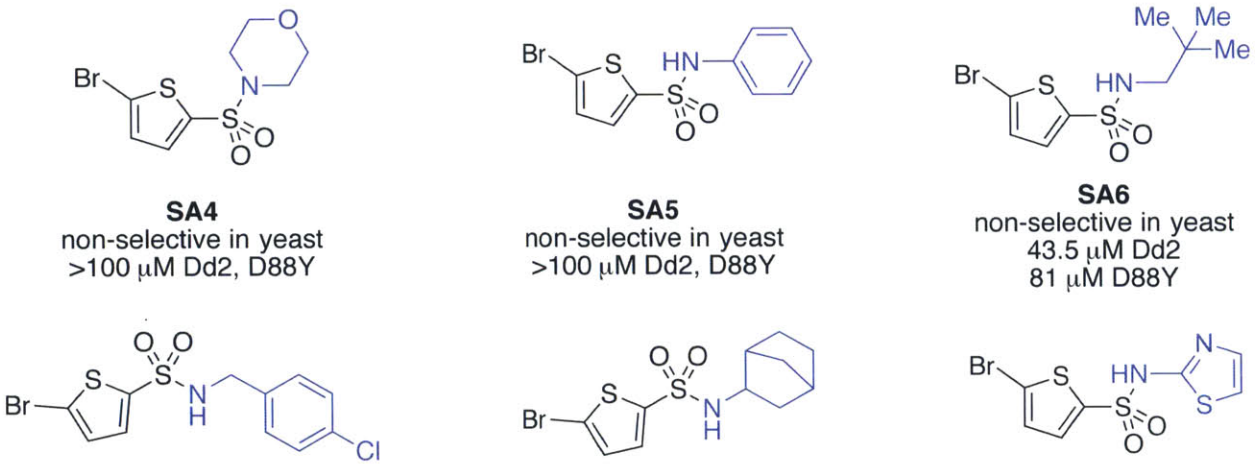
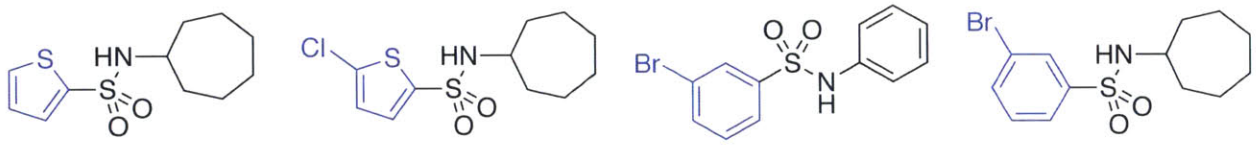


Figure 6. Modification of SA1 amide substituent.

The halogen substituent on the thiophene core was essential to selectivity in the engineered yeast (Figure 7). Removal of the bromide gave a nonselective compound (**SA10**), but

replacement of the bromide with a chloride (**SA11**) resulted in a compound with a very similar profile. Analog **SA12** was discovered to be selective and to have an LD_{50} of 71.2 μM against blood-stage *P. falciparum*. This compound was prepared previously in the Buchwald lab in a study on the synthesis of sulfonyl chlorides from boronic acids using palladium catalysis,[19] and was screened against the yeast assay along with the other sulfonamide substrates from that paper. Among those compounds, only **SA12** showed promising activity. While this is perhaps surprising, the results highlight the structural similarity of **SA12** to **SA1**. Indeed, replacing the **SA12** phenyl group with a cycloheptyl ring (**SA13**) resulted in a compound with potency closer to that of **SA1**.



SA10
non-selective in yeast
parasite EC_{50} ND

SA11
selective in yeast
14.4 μM Dd2
18.5 D88Y

SA12
selective in yeast
71.2 μM Dd2
39.9 μM D88Y

SA13
selective in yeast
33.6 μM Dd2
42.2 D88Y

Figure 7. Modification of SA1 thiophene core.

It was discovered that the sulfonamide linker of the SA series could be replaced with a carbonyl without substantial loss of potency (**SA14**) (Figure 8). In light of the assay data from **SA14** and **SA13**, several benzamide derivatives were prepared (**SA15-17**). None of these alternative halogenation patterns were tolerated, and neither were more ambitious changes to the thiophene core using an amide linker (**SA18-20**).

Removal and substitution of the 6-methoxy group of **CA1** was not tolerated (Figure 9). Both removal (**CA2**) and switching to a bromide (**CA3**) resulted in losses of potency. However, this represents a very limited exploration of substituted chromene analogs, and further SAR studies

[19] Debergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10638-10641.

may examine both different substitution at the 6-position and substitution at other positions on the chromene rings.

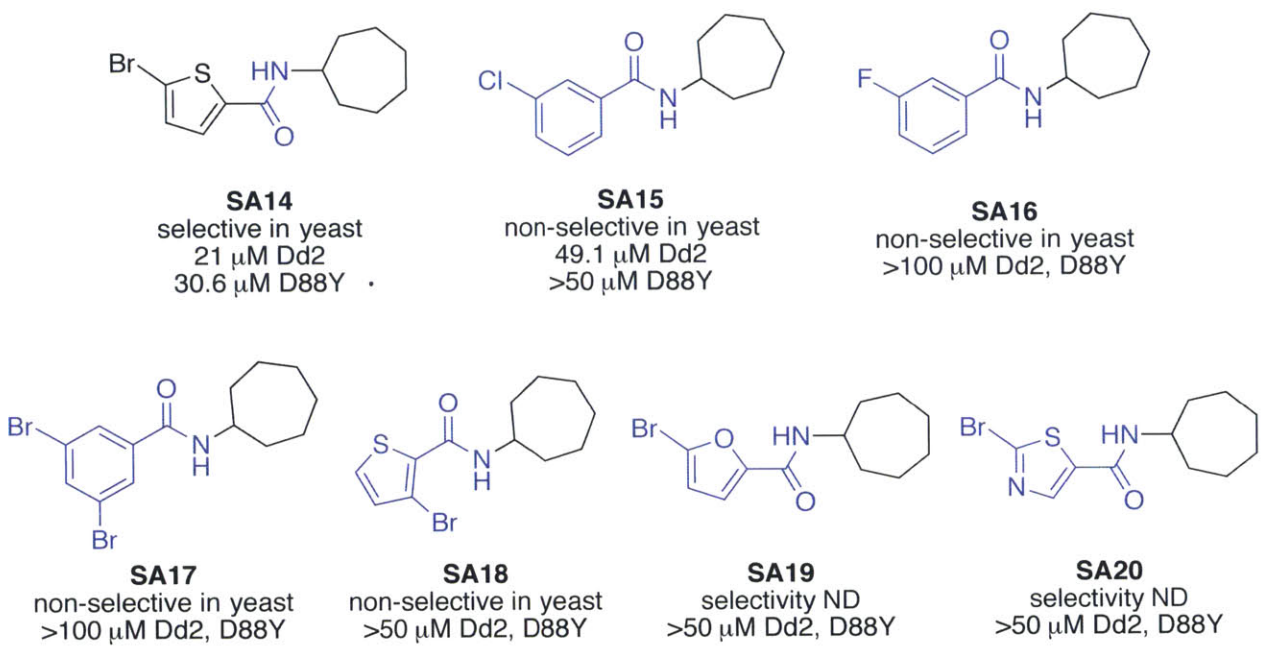


Figure 8. Modification of SA1 sulfonamide linker and thiophene core.

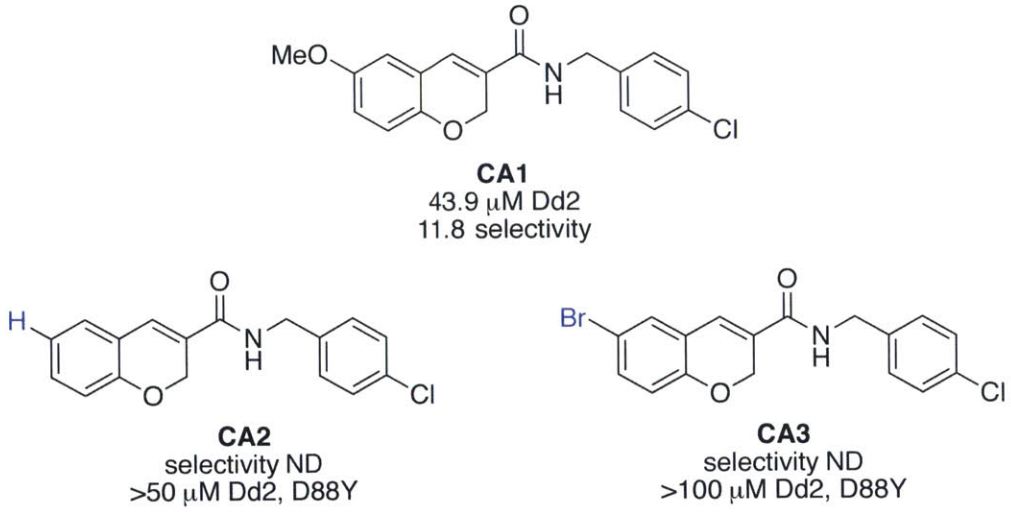


Figure 9. Modification of CA1 chromene substituent.

Notably, only aniline-derived **CA4** and **CA5** showed promising selectivity and potency among the CA analogs prepared with different aryl groups attached to the amide nitrogen (Figure 10). Seemingly similar benzyl **CA1** analogs (**CA6-8**) lost all potency, as did a homologated chlorophenyl analog (**CA9**). Using a cycloheptyl group, which was optimal for **SA1**, led to a loss of activity (**CA10**), further suggesting that **SA1** and **CA1** are separate compound classes in terms of their molecular mechanisms of action.

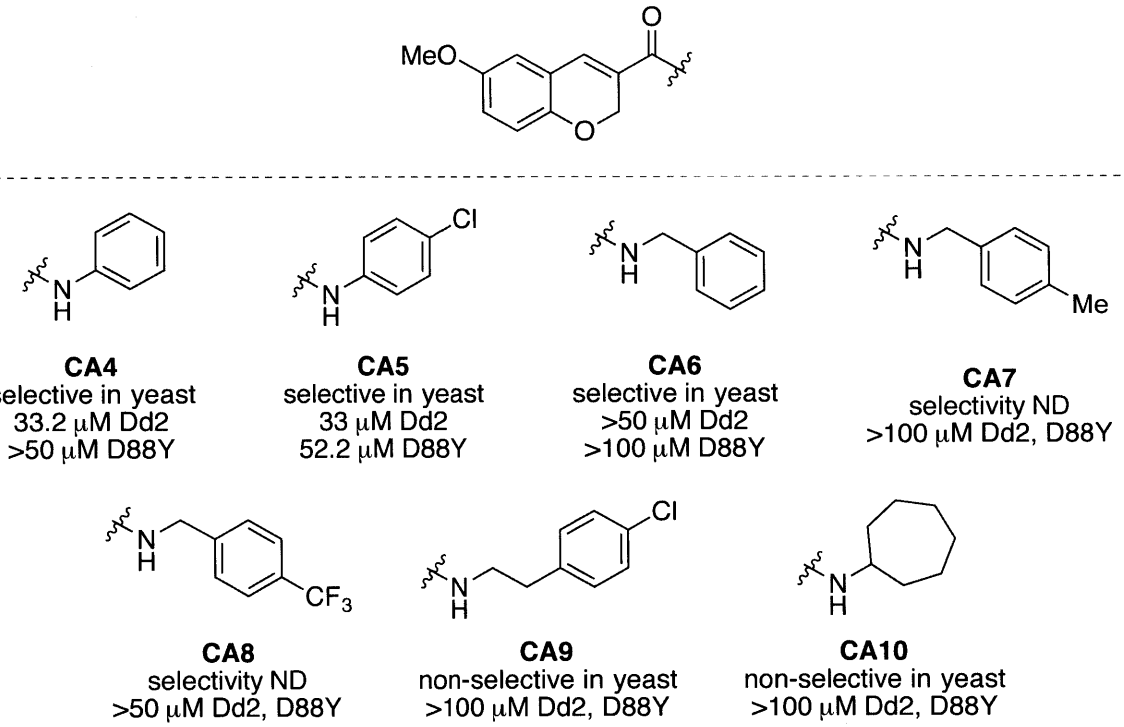


Figure 10. Modification of CA1 amide substitution.

Quinoline-based analog **CA11** was prepared based on the hypothesis that the Lewis basic lone pair of the 2H-chromene oxygen in **CA1** was important for activity (Figure 11). This compound featured similar potency against the parasite, as did other amine analogs of the quinoline amide (**CA12-13**). However, the nicotinic acid derivative **CA14** and the differently substituted quinoline **CA15** lost potency against the blood-stage parasite.

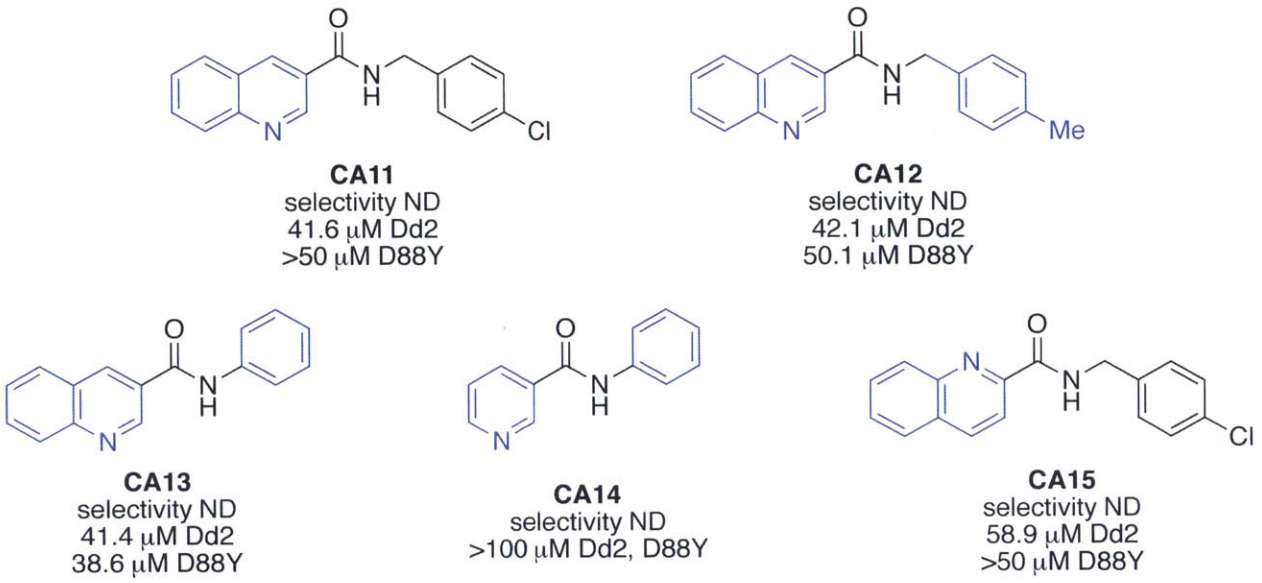


Figure 11. Modification of CA1 chromene core.

3.3 Conclusions

In summary, new compounds from the MLPCN library were identified as potential malaria therapeutics. A yeast assay was developed to identify compounds that selectively target *Pf*Hsp90 (or a client or co-chaperone) over *Hs*Hsp90, with the results supported by a second assay using blood-stage *P. falciparum*. A slightly improved chlorothiophene analog was discovered (**SA11**), suggesting that substitution of the thiophene core of **SA1** may be a promising avenue for further synthetic efforts. An active amide analog and a benzene analog were also found, expanding the scope of compounds that could be examined in the SA series. In the CA series, more active *N*-phenyl amides were identified, as well as a new quinoline-based series. Further SAR studies on both the SA and CA series are necessary to develop more potent and selective compounds based on the results described in this chapter.

3.4 Experimental

General Information

All reactions were carried out under an argon atmosphere in flame-dried or oven-dried glassware unless otherwise specified. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Commercial materials were used without additional purification unless otherwise specified. The part number for the oven-dried culture tubes used was Fisher 20 x 150 mm tubes (Cat. No. 1495937C); for plastic screw top caps, CLOSURE OT S/T 18-400TH 14 (Cat. No. 033407G); and for septa that fit into the screw cap tops, Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10 (Cat. No. 03394B).

Reagents: Tetrahydrofuran (THF) was purchased from J. T. Baker in CYCLE-TAINER™ containers and then vigorously purged with argon for one hour and passed through two activated alumina columns. Triethylamine was purchased from J. T. Baker. Zinc chloride solution (1.9M in 2-methyl tetrahydrofuran), *n*-butyl lithium (2.5M in hexanes), aniline, 5-bromo-thiophene-2-sulfonyl chloride, 2-bromo-5-chlorothiophene, 2-aminothiazole, benzylamine, salicylaldehyde, acrylonitrile, 5-bromo-2-thiophenecarboxylic acid, morpholine, 4-chloroaniline, dimethylformamide, 4-(dimethylamino)pyridine (DMAP), exo-2-aminonorbornane, 3-chlorobenzoic acid, 3-fluorobenzoic acid, 3-bromothiophene-2-carboxylic acid, 2-(4-chlorophenyl)ethylamine, and 4-methylbenzylamine were purchased from Sigma Aldrich. 2,5-Dibromothiophene, 3-bromobenzenesulfonyl chloride, 2-bromothiophene, 5-bromosalicylaldehyde, neopentylamine, 3,5-dibromobenzoic acid, and 2-bromo-5-thiazolecarboxylic acid were purchased from Oakwood Chemical. Cycloheptylamine, cyclohexylamine, 4-chlorobenzylamine, 5-bromo-2-furoic acid, and 2-hydroxy-5-methoxybenzaldehyde were purchased from Alfa Aesar. Nicotinic acid and quinaldic acid were purchased from Acros Organics. Quinoline-3-carboxylic acid was purchased from COMBI-BLOCKS. 4-(trifluoromethyl)benzylamine was purchased from Matrix Scientific. 2*H*-chromene-3-carboxylic acid, 6-methoxy-2*H*-chromene-3-carboxylic acid,

and 6-bromo-2*H*-chromene-3-carboxylic acid[18] were prepared according to a known procedure from the corresponding salicylaldehydes in two steps.[16] The reagent 2,4,6-trichlorophenylchlorosulfate (TCPC) was prepared according to the literature procedure.[15] The sample of 3-bromo-*N*-phenylbenzenesulfonamide (**SA12**) used in this study was the same sample that was reported in a previous study.[17]

Analytical Data: Compounds were characterized by melting point, ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, elemental analysis, mass spectrometry, and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were obtained on Varian 500 MHz instruments at ambient temperature. Chemical shifts for ^{1}H- and ^{13}C-NMR were reported in parts per million (ppm) relative to solvent signals ($CDCl_3$: 7.26 for ^{1}H-NMR and 77.16 for ^{13}C-NMR; CD_3OD: 3.31 for ^{1}H-NMR and 49.00 for ^{13}C-NMR; $(CD_3)_2SO$: 2.50 for ^{1}H-NMR and 39.52 for ^{13}C-NMR). Multiplicities were abbreviated in the following ways: "s" for singlet; "bs" for broad singlet; "d" for doublet; "t" for triplet; "q" for quartet; "h" for heptet; and "m" for multiplet. All IR spectra were taken on a Thermo Scientific – Nicolet iS5 spectrometer (iD5 ATR – diamond). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High resolution mass spectrometry data was collected on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points were measured on a Stanford Research Sytems EZ-Melt MPA120 automated melting point system. Column chromatography was performed using Silacycle 230-400 mesh silica gel or a Biotage SP4 apparatus with pre-packed silica cartridges. Chemical yields refer to isolated yields of compounds analyzed by elemental analysis or high-resolution mass spectrometry.

[18] Johnson, T. O.; Hua, Y.; Luu, H. T.; Brown, E. L.; Chan, F.; Chu, S. S.; Dragovich, P. S.; Eastman, B. W.; Ferre, R. A.; Fuhrman, S. A.; Hendrickson, T. F.; Maldonado, F. C.; Matthews, D. A.; Meador, J. W.; Patick, A. K.; Reich, S. H.;

General Procedure A: Preparation of sulfonamides starting with direct lithiation or lithium-halogen exchange

An oven-dried culture tube with a Teflon septum and screw cap and magnetic stir bar (see General Information for part numbers) was charged with solid aryl or heteroaryl bromide or heteroarene. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid compounds were added after purging with argon). THF was added (2 mL/mmol bromide or heteroarene), and the tube was placed in an acetone/dry ice bath with magnetic stirring and argon inlet. n-Butyllithium solution (2.5M in hexanes, 1 equiv.) was added dropwise via needle/syringe over 5 min and the mixture was stirred in the cold bath for the remainder of 1 h. Zinc chloride solution (1.9M in 2-methyltetrahydrofuran, 1 equiv.) was added dropwise via needle/syringe over 5 min. (Care must be taken to add n-butyllithium and zinc chloride solutions slowly, as the exotherm that results from too rapid of an addition of either reagent may decompose the aryllithium species.) The tube was then removed from the cold bath and the mixture stirred at room temperature for the remainder of 1 h. The tube was placed in an ice/water bath and TCPC (175 μL, 1 mmol, 1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The ice/water bath was refreshed and then the appropriate amine (2 equiv.) was added dropwise via needle/syringe to the reaction mixture. After one hour the ice/water bath was removed and the mixture was stirred until the reaction was complete as determined by analytical thin-layer chromatography (TLC), typically an additional 1 h. The mixture was diluted with ethyl acetate (10 mL) water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument using an eluent gradient of ethyl acetate/hexanes or methanol/dicholoromethane.

General Procedure B: Preparation of sulfonamides from sulfonyl chlorides

An oven-dried culture tube with Teflon septum and screw cap and magnetic stir bar was charged with sulfonyl chloride (see General Information for part numbers). The tube was then evacuated and back-filled with argon (this process was repeated a total of three times, and was done before the addition of sulfonyl chloride for liquid sulfonyl chlorides). Dichloromethane (DCM) was added (4 mL/mmol sulfonyl chloride), and the tube was put in an ice/water bath with magnetic stirring. Liquid alkyl amine (2 equiv.) or aryl amine and pyridine were added dropwise via syringe (or, for solid amines, by removing the cap and adding the solid directly) and the mixture was stirred at room temperature until the reaction was complete as determined by analytical thin-layer chromatography. The mixture was diluted with DCM and water. The layers were separated and the aqueous layer was washed another two times with DCM. The collected organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by column chromatography with a Biotage instrument using an eluent gradient of ethyl acetate/hexanes or methanol/dicholoromethane.

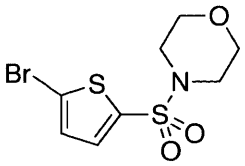
General Procedure C: Preparation of amides from carboxylic acids

An oven-dried culture tube with Teflon septum and screw cap and magnetic stir bar was charged with carboxylic acid (see General Information for part numbers). The tube was then evacuated and back-filled with argon (this process was repeated a total of three times). DCM (5 mL/mmol acid) and oxalyl chloride (1.0 equiv) were added, and the tube was put in an ice/water bath with magnetic stirring. Dimethylformamide (DMF, 10 μL) was added and then the ice bath was removed. The mixture was stirred for 1 h at room temperature **(WARNING: use a vented system – gas begins to evolve from the mixture immediately after addition of DMF)**. The amine and, for aryl amines, base and DMAP (10 mol%), were added, and then the mixture was stirred until reaction was complete as determined by analytical thin-layer chromatography. The mixture was diluted with DCM and water. The layers were separated and the aqueous layer was washed another two times with DCM. The collected organic layers

were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by column chromatography using an eluent gradient of ethyl acetate/hexanes or methanol/dicholoromethane.

Synthesis and Characterization of SA Compounds

4-((5-bromothiophen-2-yl)sulfonyl)morpholine (SA4)



SA4

According to General Procedure A, 2,5-dibromothiophene (57 μL, 0.5 mmol), TCPC (90 μL, 0.5 mmol), and morpholine (90 μL, 1 mmol) were allowed to react to prepare **SA4** as a white solid (122.6 mg, 79%).

M.p. (°C): 109 – 112.

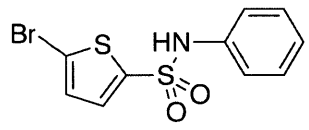
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.30 (d, *J* = 4.0 Hz, 2H), 7.15 (d, *J* = 4.0 Hz, 1H), 3.80-3.77 (m, 4H), 3.08-3.04 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-d): δ 136.3, 133.0, 131.0, 120.5, 66.1, 46.0.

IR (neat, cm^{-1}): 3091, 3080, 2981, 2858, 1512, 1346, 1158, 943, 739.

Elemental Analysis: Anal. calcd. for $C_8H_{10}BrN_2O_3S_2$: C, 30.78; H, 3.23. Found: C, 30.96; H, 3.10.

5-bromo-*N*-phenylthiophene-2-sulfonamide (SA5)



SA5

According to General Procedure B, 5-bromothiophene-2-sulfonyl chloride (131 mg, 0.5 mmol), pyridine (140 μL, 1.5 mmol), and aniline (140 μL, 1.5 mmol) were allowed to react to prepare **SA5** as a white solid (28 mg, 18%).

M.p. (°C): 92 – 94.

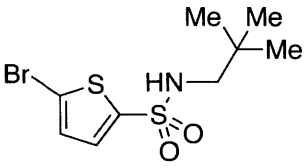
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.34 – 7.29 (m, 2H), 7.24 (d, J = 4.1 Hz, 1H), 7.19 (ddt, J = 7.9, 6.9, 1.2 Hz, 1H), 7.16 – 7.13 (m, 2H), 6.97 (d, J = 4.1 Hz, 1H), 6.88 (bs, 1H).

^{13}C NMR (126 MHz, Chloroform-d): δ 140.2, 135.8, 133.2, 130.5, 129.7, 126.3, 122.2, 120.7.

IR (neat, cm^{-1}): 3523, 1336, 1154, 1085, 1023, 895, 611.

HRMS ($C_{10}H_8NO_2S_2$): Calcd. $[M+NH_4]^+$: 336.9502. Found: 336.9522.

5-bromo-*N*-neopentylthiophene-2-sulfonamide (SA6)



SA6

According to General Procedure A, 2,5-dibromothiophene (57 µL, 0.5 mmol), TCPC (90 µL, 0.5 mmol), and cycloheptylamine (130 µL, 1 mmol) were allowed to react to prepare **SA7** as a white solid (69.4 mg, 44%).

M.p. (°C): 119 – 121.

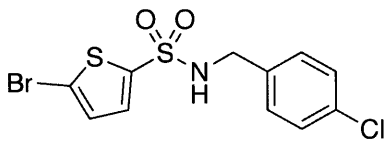
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.35 (d, J = 3.9 Hz, 1H), 7.06 (d, J = 4.0 Hz, 1H), 4.87 (t, J = 6.7 Hz, 1H), 2.76 (d, J = 6.7 Hz, 2H), 0.91 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d): δ 142.0, 132.1, 130.5, 119.7, 55.0, 31.5, 27.1.

IR (neat, cm^{-1}): 3272, 2957, 1326, 1156, 1056, 1033, 818, 667.

Elemental Analysis: Anal. calcd. for $C_9H_{14}NO_2S_2$: C, 34.62; H, 4.52. Found: C, 34.61; H, 4.42.

5-bromo-*N*-(4-chlorobenzyl)thiophene-2-sulfonamide (SA7)



SA7

According to General Procedure A, 2,5-dibromothiophene (60 µL, 0.5 mmol), TCPC (90 µL, 0.5 mmol), and 4-chlorobenzylamine (130 µL, 1 mmol) were allowed to react to afford **SA7** as a white solid (98 mg, 54%).

M.p. (°C): 102 – 104.

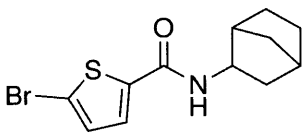
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.30 (d, J = 4.0 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.19 – 7.15 (m, 2H), 7.03 (d, J = 4.0 Hz, 1H), 5.26 (t, J = 6.2 Hz, 1H), 4.16 (d, J = 6.2 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 141.5, 134.4, 134.1, 132.6, 130.5, 129.4, 129.0, 120.3, 46.9.

IR (neat, cm^{-1}): 3251, 1735, 1493, 1424, 1399, 1349, 1326, 1203, 1152, 1096, 1080, 1055, 1015, 967, 916, 817, 803, 669, 607, 577, 563.

Elemental Analysis: Anal. calcd. for $C_{11}H_9BrClNO_2S_2$: C, 36.03; H, 2.47. Found: C, 36.28; H, 2.59.

_N_-(bicyclo[2.2.1]heptan-2-yl)-5-bromothiophene-2-sulfonamide (SA8)



SA8

According to General Procedure C, 5-bromo-2-thiophenecarboxylic acid (105 mg, 0.5 mmol) and exo-2-aminonorbornane (130 μL, 1 mmol) were allowed to react to afford **SA8** as a white solid (84 mg, 61%).

M.p. (°C): 160 – 161.

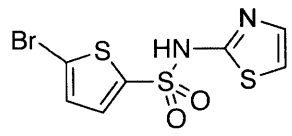
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.19 (d, J = 3.9 Hz, 1H), 7.01 (d, J = 4.0 Hz, 1H), 5.75 (d, J = 7.1 Hz, 1H), 3.89 – 3.81 (m, 1H), 2.31 (m, 2H), 1.86 (ddd, J = 13.2, 8.0, 2.4 Hz, 1H), 1.60 – 1.42 (m, 2H), 1.35 (dq, J = 10.3, 2.0 Hz, 1H), 1.32 – 1.20 (m, 3H), 1.15 (tdd, J = 9.6, 4.6, 2.3 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d): δ 160.7, 141.5, 131.2, 128.3, 118.2, 54.1, 43.1, 41.2, 36.5, 36.4, 28.8, 27.2.

IR (neat, cm^{-1}): 3290, 2955, 2868, 1611, 1547, 1520, 1421, 1322, 1312, 1222, 1156, 1127, 973, 805, 747, 651.

Elemental Analysis: Anal. calcd. for $C_{12}H_{14}BrNOS$: C, 48.01; H, 4.7. Found: C, 48.29; H, 4.84.

5-bromo-_N_-(thiazol-2-yl)thiophene-2-sulfonamide (SA9)



SA9

According to General Procedure B, 5-bromothiophene-2-sulfonyl chloride (131 mg, 0.5 mmol), triethylamine(140 μL, 1 mmol), and 2-aminothiazole (101 μL, 1.0 mmol) were allowed to react to prepare **SA9** as a red-brown solid (76.3 mg, 24%).

Decomposition temperature (°C): 200.

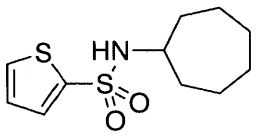
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.38 (d, *J* = 4.0 Hz, 1H), 7.17 (d, *J* = 4.6 Hz, 1H), 7.11 (d, *J* = 4.0 Hz, 1H), 6.80 (d, *J* = 4.6 Hz, 1H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 171.5, 145.7, 132.0, 131.4, 125.4, 119.0, 110.2.

IR (neat, cm^{-1}): 2981, 1524, 1302, 1134, 1033, 858, 797.

HRMS ($C_7H_5N_2O_2S_3$): Calcd. $[M+H]^+$: 326.8749. Found: 326.8765.

_N_-cycloheptylthiophene-2-sulfonamide (SA10)



SA10

According to General Procedure A, thiophene (80 μL, 1 mmol), TCPC (180 μL, 1 mmol), and cycloheptylamine (260 μL, 2 mmol) were allowed to react to prepare **SA10** as a white solid (48 mg, 18%).

M.p. (°C): 58 – 60.

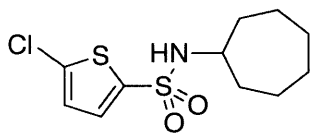
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.61 (dd, J = 3.7, 1.3 Hz, 1H), 7.56 (dt, J = 5.0, 0.9 Hz, 1H), 7.09 – 7.05 (m, 1H), 4.86 (d, J = 7.0 Hz, 1H), 3.42 (ddq, J = 12.8, 8.5, 4.5 Hz, 1H), 1.81 (ddd, J = 12.8, 8.5, 4.5 Hz, 2H), 1.59 – 1.32 (m, 7H).

^{13}C NMR (126 MHz, Chloroform-d): δ 142.4, 131.9, 131.6, 127.4, 55.4, 35.9, 28.0, 23.6.

IR (neat, cm^{-1}): 3260, 3106, 2923, 2851, 1438, 1405, 1326, 1144, 1014, 854, 734, 667.

HRMS ($C_{11}H_{17}NO_2S_2$): Calcd. $[M+H]^+$: 260.0773. Found: 260.0777.

5-chloro-_N_-cycloheptylthiophene-2-sulfonamide (SA11)



SA11

According to General Procedure A, 2-bromo-5-chlorothiophene (55 μL, 0.5 mmol), TCPC (90 μL, 0.5 mmol), and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **SA11** as a clear, colorless oil (106 mg, 72%).

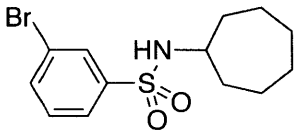
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.39 (d, J = 4.0 Hz, 1H), 6.91 (d, J = 4.0 Hz, 1H), 4.51 (bs, 1H), 3.43 (ddq, J = 13.0, 8.7, 4.5 Hz, 1H), 1.91-1.79 (m, 2H), 1.62-1.35 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 140.4, 136.9, 131.3, 126.8, 55.5, 36.0, 28.0, 23.6.

IR (neat, cm^{-1}): 3277, 2923, 1411, 1331, 1152, 1000, 800, 674.

Elemental Analysis: Anal. calcd. for $C_{11}H_{16}ClNO_2S_2$: C, 44.97; H, 5.49. Found: 45.52; 5.39.

3-bromo-*N*-cycloheptylbenzenesulfonamide (SA13)



SA13

According to General Procedure B, 3-bromobenzenesulfonyl chloride (72 μL, 0.5 mmol) and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **SA13** as a clear, colorless oil (160.3 mg, 97%).

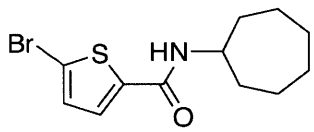
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.03 (t, *J* = 1.7 Hz, 1H), 7.84-7.78 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 5.23-4.94 (m, 1H), 3.35 (dh, *J* = 8.5, 4.3 Hz, 1H), 1.80-1.70 (m, 2H), 1.56-1.40 (m, 8H), 1.38-1.29 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 143.2, 135.5, 130.7, 129.9, 125.5, 123.0, 55.1, 35.9, 28.0, 23.5.

IR (neat, cm^{-1}): 3729, 2923, 2860, 1569, 1460, 1321, 1154, 1000, 785, 679, 668.

Elemental Analysis: Anal. calcd. for $C_{13}H_{18}BrNO_2S$: C, 46.99; H, 5.46. Found: C, 47.26; H, 5.38.

5-bromo-*N*-cycloheptylthiophene-2-carboxamide (SA14)



SA14

According to General Procedure C, 5-bromo-2-thiophenecarboxylic acid (207 mg, 1 mmol) and cycloheptylamine (260 μL, 2 mmol) were allowed to react to afford **SA14** as a white solid (216 mg, 64%).

M.p. (°C): 150 – 153.

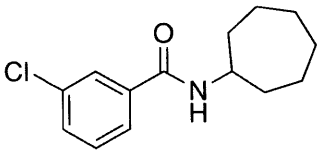
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.24 (d, J = 3.9 Hz, 1H), 6.98 (d, J = 3.9 Hz, 1H), 6.21 (d, J = 8.1 Hz, 1H), 4.04 (qd, J = 9.5, 8.8, 4.7 Hz, 1H), 1.96 (ddd, J = 10.3, 6.8, 4.3 Hz, 2H), 1.68 – 1.42 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 159.9, 141.2, 130.6, 127.7, 117.5, 51.2, 35.1, 28.0, 24.2.

IR (neat, cm^{-1}): 3296, 3086, 2924, 2854, 1721, 1549, 1316, 1293, 1178, 972, 813, 667.

HRMS ($C_{12}H_{16}BrNOS$): Calcd. $[M+H]^+$: 304.0196. Found: 304.0181.

3-chloro-*N*-cycloheptylbenzamide (SA15)



SA15

According to General Procedure C, 3-chlorobenzoic acid (157 mg, 1 mmol) and cycloheptylamine (260 μL, 2 mmol) were allowed to react to prepare **SA15** as a white solid (71 mg, 28%).

M.p. (°C): 118 – 120.

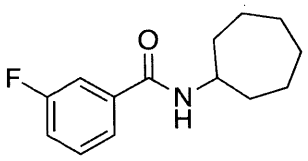
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.71 (t, J = 1.9 Hz, 1H), 7.61 (dt, J = 7.7, 1.4 Hz, 1H), 7.45 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.03 (d, J = 8.1 Hz, 1H), 4.14 (tp, J = 9.1, 4.5 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.74 – 1.46 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.2, 137.1, 134.8, 131.4, 130.0, 127.3, 125.1, 51.3, 35.3, 28.2, 24.3.

IR (neat, cm^{-1}): 3324, 2927, 2854, 1629, 1570, 1537, 1448, 1347, 1319, 1292, 1263, 1080, 1049, 899, 805, 757, 710, 682, 650.

Elemental Analysis: Anal. calcd. for $C_{14}H_{18}ClNO$: C, 66.79; H, 7.21. Found: C, 66.61; H, 7.13.

_N_-cycloheptyl-3-fluorobenzamide (SA16)



SA16

According to General Procedure C, 3-chlorobenzoic acid (157 mg, 1 mmol) and cycloheptylamine (260 µL, 2 mmol) were allowed to react to prepare **SA16** as a white solid (71 mg, 28%).

M.p. (°C): 116 – 118.

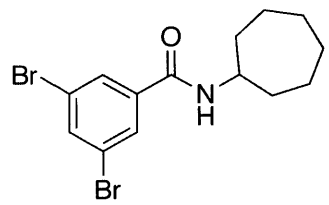
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.51 – 7.44 (m, 2H), 7.37 (td, J = 7.9, 5.4 Hz, 1H), 7.16 (td, J = 8.3, 2.6 Hz, 1H), 6.11 (d, J = 7.6 Hz, 1H), 4.13 (tp, J = 8.4, 4.5 Hz, 1H), 2.02 (m, 2H), 1.72 – 1.46 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.19 (d, J = 2.4 Hz), 162.84 (d, J = 247.5 Hz), 137.53 (d, J = 6.6 Hz), 130.26 (d, J = 7.8 Hz), 122.38 (d, J = 3.1 Hz), 118.30 (d, J = 21.3 Hz), 114.40 (d, J = 22.8 Hz), 51.21, 35.24, 28.14, 24.25.

IR (neat, cm^{-1}): 3245,·2924, 1740, 1626, 1582, 1555, 1481, 1326, 1225, 938, 888, 796, 708.

Elemental Analysis: Anal. calcd. for $C_{14}H_{18}FNO$: C, 71.46; H, 7.71. Found: C, 71.31; H, 7.75.

3,5-dibromo-_N_-cycloheptylbenzamide (SA17)



SA17

According to General Procedure C, 3,5-dibromobenzoic acid (280 mg, 1 mmol) and cycloheptylamine (260 µL, 2 mmol) were allowed to react to prepare **SA17** as a white solid (233 mg, 62%).

M.p. (°C): 174 – 177.

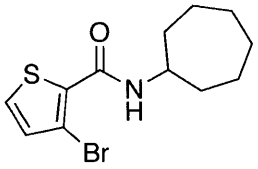
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.78 (d, J = 1.8 Hz, 2H), 7.75 (t, J = 1.8 Hz, 1H), 6.12 (d, J = 8.0 Hz, 1H), 4.09 (tt, J = 8.3, 4.2 Hz, 1H), 2.01 (m, 2H), 1.72 – 1.47 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 163.71, 138.54, 136.64, 128.99, 123.30, 51.52, 35.21, 28.14, 24.23.

IR (neat, cm^{-1}): 3296.1, 2929.7, 2855.2, 1634.6, 1538.6, 1444.3, 1407.9, 1317.7, 1264.8, 1054.4, 864.8, 740.0, 686.7.

Elemental Analysis: Anal. calcd. for $C_{14}H_{17}Br_2NO$: C, 44.83; H, 4.57. Found: C, 45.05; H, 4.55.

3-bromo-*N*-cycloheptylthiophene-2-carboxamide (SA18)



SA18

According to General Procedure C, 3-bromothiophene-2-carboxylic acid (105 mg, 0.5 mmol) and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **SA18** as a white solid (84 mg, 61%).

M.p. (°C): 102 – 104.

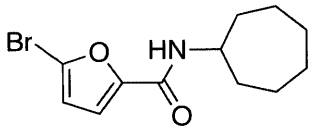
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.41 (d, J = 5.2 Hz, 1H), 7.06 – 7.01 (m, 1H), 7.00 (d, J = 5.2 Hz, 1H), 4.17 (qt, J = 8.4, 4.2 Hz, 1H), 2.00 (ddd, J = 11.9, 7.3, 3.7 Hz, 2H), 1.71 – 1.48 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 159.3, 135.6, 132.0, 129.9, 108.1, 51.0, 34.9, 28.1, 24.1.

IR (neat, cm^{-1}): 3290, 2925, 2854, 1735, 1609, 1538, 1502, 1423, 1350, 1320, 1261, 878, 797, 756, 725, 677, 661, 603.

Elemental Analysis: Anal. calcd. for $C_{12}H_{16}BrNOS$: C, 47.69; H, 5.34. Found: C, 47.94; H, 5.42.

5-bromo-*N*-cycloheptylfuran-2-carboxamide (SA19)



SA19

According to General Procedure C, 5-bromo-2-furoic acid (95 mg, 0.5 mmol) and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **SA19** as a white solid (85 mg, 59%).

M.p. (°C): 138 – 140.

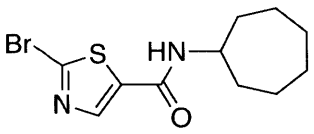
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.07 (d, *J* = 3.5 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 3.99 (ddd, *J* = 14.2, 9.8, 4.3 Hz, 1H), 1.96-1.87 (m, 2H), 1.76-1.47 (m, 10H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 158.4, 151.0, 126.2, 117.3, 115.1, 52.2, 35.7, 29.0, 25.5.

IR (neat, cm^{-1}): 3249, 2981, 2923, 2843, 1629, 1594, 1526, 1475, 1454, 1326, 1201, 1053, 792, 700.

Elemental Analysis: Anal. calcd. for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64. Found: C, 50.24; H, 5.55.

2-bromo-*N*-cycloheptylthiazole-5-carboxamide (SA20)



SA20

According to General Procedure C, 2-bromo-5-thiazolecarboxylic acid (105 mg, 0.5 mmol) and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **SA20** as a white solid (89 mg, 59%).

M.p. (°C): 142 – 143.

^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 8.51 (d, J = 7.4 Hz, 1H), 8.10 (s, 1H), 4.04 – 3.92 (m, 1H), 1.95 (ddd, J = 13.5, 6.9, 3.4 Hz, 2H), 1.81 – 1.41 (m, 10H).

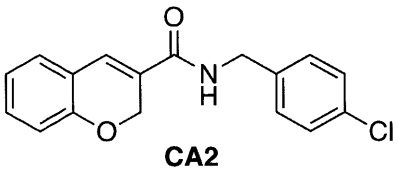
^{13}C NMR (126 MHz, Methanol-d$_4$): δ 160.3, 160.2, 156.3, 156.3, 143.8, 142.6, 139.4, 139.4, 53.0, 52.89, 35.7, 35.7, 29.1, 25.4. (Spectral complexity due to amide rotamers.)

IR (neat, cm^{-1}): 3311, 3080, 2920, 2852, 1615, 1553, 1506, 1461, 1447, 1364, 1349, 1339, 1323, 1295, 1231, 1181, 1161, 1136, 1120, 1057, 883, 845, 870, 828, 807, 791, 753, 725, 647.

HRMS ($C_{11}H_{15}N_2OS$): Calcd. $[M+H]^+$: 305.0147. Found: 305.0161.

Synthesis and Characterization of CA Compounds

***N*-(4-chlorobenzyl)-2*H*-chromene-3-carboxamide (CA2)**



CA2

According to General Procedure C, 2*H*-chromene-3-carboxylic acid (90 mg, 0.5 mmol) and 4-chlorobenzylamine (130 μL, 1 mmol) were allowed to react to prepare **CA2** as a white solid (117.6 mg, 78%).

M.p. (°C): 137 – 140.

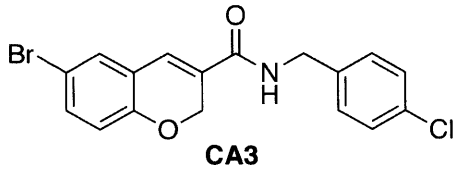
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.34 – 7.29 (m, 4H), 7.23 – 7.19 (m, 2H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.94 (d, *J* = 1.4 Hz, 2H), 4.45 (s, 2H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 167.5, 156.2, 139.0, 133.9, 132.4, 130.2, 129.6, 129.6, 129.4, 129.4, 127.5, 122.9, 122.6, 116.9, 65.7, 43.4.

IR (neat, cm^{-1}): 3294, 2967, 2865, 2843, 1646, 1538, 1249, 1054, 905, 752, 680, 655.

Elemental Analysis: Anal. calcd. for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71. Found: C, 67.86; H, 4.63.

6-bromo-*N*-(4-chlorobenzyl)-2*H*-chromene-3-carboxamide (CA3)



CA3

According to General Procedure C, 6-bromo-2*H*-chromene-3-carboxylic acid (127 mg, 0.5 mmol) and 4-chlorobenzylamine (130 μL, 1 mmol) were allowed to react to prepare **CA3** as a white solid (100.4 mg, 53%).

M.p. (°C): 170 – 175.

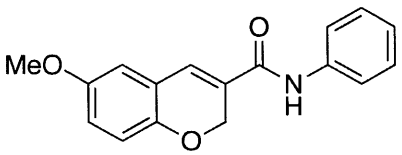
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.36 – 7.29 (m, 6H), 7.15 (q, *J* = 1.3 Hz, 1H), 6.78 – 6.74 (m, 1H), 4.97 (d, *J* = 1.4 Hz, 2H), 4.45 (s, 2H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 167.1, 155.2, 138.9, 134.7, 134.0, 131.8, 130.2, 129.6, 129.0, 127.9, 124.6, 118.8, 114.6, 65.9, 43.5.

IR (neat, cm^{-1}): 3266, 2981, 2865, 2843, 2358, 1649, 1532, 1479, 1360, 1283, 1212, 1054, 811.

Elemental Analysis: Anal. calcd. for $C_{17}H_{13}BrClNO_2$: C, 53.92; H, 3.46. Found: C, 53.90; H, 3.45.

6-methoxy-*N*-phenyl-2*H*-chromene-3-carboxamide (CA4)



CA4

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (103 mg, 0.5 mmol) and aniline (140 µL, 1.5 mmol) were allowed to react to prepare **CA4** as a caramel solid (126.5 mg, 90%). Amide coupling assisted with triethylamine (250 µL, 2 mmol) and DMAP (10 mg, 0.08 mmol).

M.p. (°C): 118 – 120.

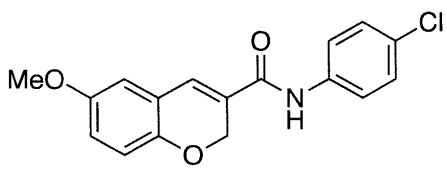
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.64-7.60 (m, 2H), 7.35-7.29 (m, 3H), 7.11 (ddt, *J* = 8.6, 7.3, 1.1 Hz, 1H), 6.83-6.75 (m, 3H), 4.92 (d, *J* = 1.3 Hz, 2H), 3.75 (s, 3H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 166.1, 156.0, 150.1, 139.6, 129.9, 129.8, 128.9, 125.5, 123.2, 122.0, 118.0, 117.6, 114.0, 100.5, 65.7, 56.4.

IR (neat, cm^{-1}): 3311, 2967, 2865, 2843, 1655, 1625, 1595 1529, 1444, 1317, 1054, 824, 686.

Elemental Analysis: Anal. calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37. Found: C, 72.31; H, 5.46.

***N*-(4-chlorophenyl)-6-methoxy-2*H*-chromene-3-carboxamide (CA5)**



CA5

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (100 mg, 0.49 mmol) and 4-chloroaniline (96 mg, 0.75 mmol) were allowed to react to prepare **CA5** as a yellow solid (128.6 mg, 83%). Amide coupling assisted with triethylamine (140 µL, 1 mmol) and DMAP (10 mg, 0.08 mmol).

M.p. (°C): 136 – 139.

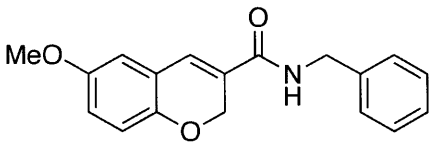
^{1}H-NMR (500 MHz, 1:1 Methanol-d$_4$:Chloroform-d): δ 7.57-7.54 (m, 2H), 7.27-7.22 (m, 3H), 6.77 (d, *J* = 1.8 Hz, 2H), 6.70 (t, *J* = 1.7 Hz, 1H), 4.94 (d, *J* = 1.4 Hz, 2H), 4.40-4.35 (m, 1H), 3.75 (s, 3H).

^{13}C NMR (126 MHz, 1:1 Methanol-d$_4$:Chloroform-d): δ 164.9, 154.7, 149.1, 137.1, 129.6, 129.2, 129.06, 127.8, 122.3, 122.2, 117.2, 116.9, 113.5, 65.0, 56.0.

IR (neat, cm^{-1}): 3291, 2975, 2834, 1653, 1533, 1488, 1423, 1321, 1239, 1203, 1093, 1009, 763.

HRMS ($C_{17}H_{14}N_2OS$): Calcd. $[M+H]^+$: 316.0735. Found: 316.0744.

***N*-benzyl-6-methoxy-2*H*-chromene-3-carboxamide (CA6)**



CA6

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (103 mg, 0.5 mmol) and benzylamine (110 μL, 1 mmol) were allowed to react to prepare **CA6** as a yellow solid (90.8 mg, 61%).

M.p. (°C): 99 – 100.

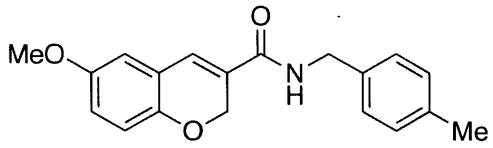
^{1}H-NMR (500 MHz, Methanol-d$_4$): δ 7.32 (m, 4H), 7.27 – 7.22 (m, 1H), 7.18 (m, 1H), 6.81 – 6.73 (m, 3H), 4.90 – 4.86 (m, 2H), 4.48 (s, 2H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, Methanol-d$_4$): δ 167.5, 156, 150.0, 140.1, 129.5, 129.4, 128.5, 128.5, 128.2, 123.3, 117.9, 117.5, 113.9, 65.7, 56.1, 44.1.

IR (neat, cm^{-1}): 3294, 2973, 2863, 2843, 1645, 1613, 1489, 1255, 1053, 753, 701.

Elemental Analysis: Anal. calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 73.00; H, 5.95.

6-methoxy-*N*-(4-methylbenzyl)-2*H*-chromene-3-carboxamide (CA7)



CA7

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (42 mg, 0.2 mmol) and 4-methylbenzylamine (51 μL, 0.4 mmol) were allowed to react to prepare **CA7** as a yellow solid (90.8 mg, 61%).

M.p. (°C): 132 – 135.

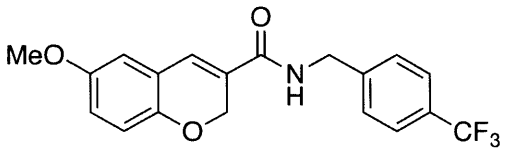
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.25 – 7.21 (m, 2H), 7.20 – 7.16 (m, 2H), 6.92 (s, 1H), 6.82 – 6.74 (m, 2H), 6.62 (t, J = 3.3 Hz, 1H), 6.03 (s, 1H), 5.02-4.91 (m, 2H), 4.54-4.46 (m, 2H), 3.80-3.71 (m, 3H), 2.36 (d, J = 3.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.0, 154.4, 148.8, 137.7, 135.0, 129.6, 128.2, 127.8, 127.2, 121.7, 116.8, 116.8, 113.0, 65.2, 55.9, 43.7, 21.3.

IR (neat, cm^{-1}): 3324, 2981, 2863, 2843, 1645, 1611, 1491, 1255, 1054, 822, 653.

Elemental Analysis: Anal. calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19. Found: C, 73.15; H, 6.26.

6-methoxy-*N*-(4-(trifluoromethyl)benzyl)-2H-chromene-3-carboxamide (CA8)



CA8

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (42 mg, 0.2 mmol) and 4-(trifluoromethyl)benzylamine (60 μL, 0.4 mmol) were allowed to react to prepare **CA8** as a yellow solid (50 mg, 69%).

M.p. (°C): 112 – 115.

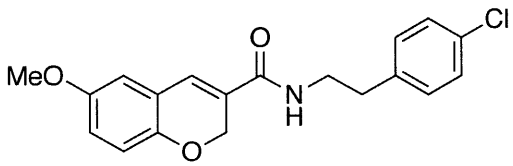
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.58 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.97 (s, 1H), 6.81 – 6.75 (m, 2H), 6.60 (d, J = 2.6 Hz, 1H), 6.46 (t, J = 5.6 Hz, 1H), 4.94 (d, J = 1.3 Hz, 2H), 4.57 (d, J = 6.0 Hz, 2H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.32, 154.46, 148.83, 142.23 (t, J = 1.3 Hz), 129.99 (q, J = 32.4 Hz), 128.08, 127.78, 127.30, 125.81 (q, J = 3.8 Hz), 125.23, 123.07, 121.56, 113.01, 64.92, 55.86, 43.24.

IR (neat, cm^{-1}): 3282, 1735, 1646, 1604, 1548, 1490, 1434, 1322, 1278, 1157, 1121, 1066, 1051, 1020, 911, 849, 814, 760, 711, 633.

Elemental Analysis: Anal. calcd. for $C_{19}H_{16}F_3NO_3$: C, 62.81; H, 4.44. Found: C, 62.54; H, 4.40.

6-methoxy-*N*-(4-(trifluoromethyl)benzyl)-2H-chromene-3-carboxamide (CA9)



CA9

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (42 mg, 0.2 mmol) and 2-(4-chlorophenyl)ethylamine (60 μL, 0.4 mmol) were allowed to react to prepare **CA9** as a slightly yellow solid (51 mg, 74%).

M.p. (°C): 151 – 153.

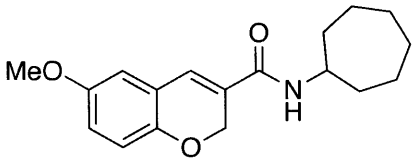
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.30 – 7.27 (m, 2H), 7.15 – 7.12 (m, 2H), 6.82 (s, 1H), 6.79 – 6.74 (m, 2H), 6.60 (dd, J = 2.6, 0.7 Hz, 1H), 5.96 (t, J = 6.1 Hz, 1H), 4.90 (d, J = 1.4 Hz, 2H), 3.75 (s, 3H), 3.58 (td, J = 7.0, 5.9 Hz, 2H), 2.85 (t, J = 7.0 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.3, 154.4, 148.8, 137.3, 132.6, 130.2, 128.9, 127.8, 127.2, 121.7, 116.8, 113.0, 65.0, 55.9, 40.8, 35.2.

IR (neat, cm^{-1}): 3296, 1737, 1647, 1602, 15789, 1549, 1431, 1365, 1336, 1302, 1273, 40, 1211, 1163, 1089, 1045, 1014, 909, 868, 839, 805, 711, 690, 668.

Elemental Analysis: Anal. calcd. for $C_{19}H_{16}F_3NO_3$: C, 66.38; H, 5.28. Found: C, 66.19; H, 5.30.

***N*-cycloheptyl-6-methoxy-2*H*-chromene-3-carboxamide (CA10)**



CA10

According to General Procedure C, 6-methoxy-2*H*-chromene-3-carboxylic acid (103 mg, 0.5 mmol) and cycloheptylamine (130 μL, 1 mmol) were allowed to react to prepare **CA10** as a slightly yellow solid (60.4 mg, 40%).

M.p. (°C): 141 – 144.

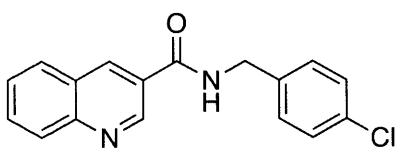
^{1}H-NMR (500 MHz, Chloroform-d): δ 6.87 (d, J = 1.3 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.63 (d, J = 2.8 Hz, 1H), 5.84 (d, J = 8.0 Hz, 1H), 4.92 (d, J = 1.3 Hz, 2H), 4.07 – 4.00 (m, 1H), 3.75 (s, 3H), 1.97 (dq, J = 13.3, 4.3 Hz, 2H), 1.68 – 1.44 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-d): δ 164.1, 154.4, 148.7, 128.5, 126.5, 121.8, 116.7, 116.5, 112.9, 65.1, 55.9, 50.7, 35.3, 28.1, 24.3.

IR (neat, cm^{-1}): 3680, 3250, 2936, 2863, 2843, 2355, 1640, 1600, 1489, 1239, 1210, 1053, 829, 702, 677.

Elemental Analysis: Anal. calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.24; H, 7.68.

***N*-(4-chlorobenzyl)quinoline-3-carboxamide (CA11)**



CA11

According to General Procedure C, quinoline-3-carboxylic acid (87 mg, 0.5 mmol) and 4-chlorobenzylamine (130 μL, 1 mmol) were allowed to react to prepare **CA11** as a white solid (88 mg, 59%).

M.p. (°C): 178 – 181.

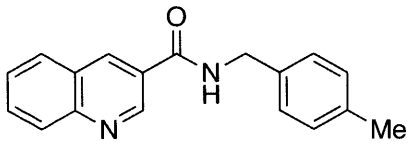
^{1}H-NMR (500 MHz, Methanol-d_4): δ 9.26 (d, *J* = 2.2 Hz, 1H), 8.81 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.08 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.06-8.03 (m, 1H), 7.88 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41-7.37 (m, 2H), 7.37-7.32 (m, 2H), 4.62 (s, 2H).

^{13}C NMR (126 MHz, Methanol-d_4): δ 167.8, 149.7, 149.7, 138.8, 137.7, 134.1, 133.0, 130.3, 129.7, 129.2, 129.0, 128.5, 128.5, 44.0.

IR (neat, cm^{-1}): 3249, 2981, 2934, 2864, 2843, 1660, 1501, 1300, 1004, 841, 744.

Elemental Analysis: Anal. calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42. Found: C, 68.62; H, 4.44.

***N*-(4-methylbenzyl)quinoline-3-carboxamide (CA12)**



CA12

According to General Procedure C, quinoline-3-carboxylic acid (87 mg, 0.5 mmol) and 4-methylbenzylamine (130 μL, 1 mmol) were allowed to react to prepare **CA12** as a white solid (46.3 mg, 34%).

M.p. (°C): 158 – 159.

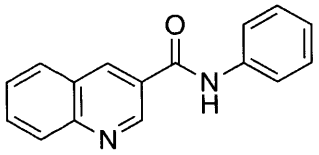
^{1}H-NMR (500 MHz, Chloroform-d): δ 9.26 (d, J = 2.2 Hz, 1H), 8.57 (dd, J = 2.3, 0.8 Hz, 1H), 8.08 (dq, J = 8.5, 0.9 Hz, 1H), 7.80 (dd, J = 8.0, 1.4 Hz, 1H), 7.75 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.03 (t, J = 4.7 Hz, 1H), 4.63 (d, J = 5.6 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d): δ 165.6, 149.2, 148.3, 137.6, 135.8, 134.9, 131.3, 129.6, 129.3, 128.8, 128.1, 127.6, 127.0, 127.0, 44.2, 21.2.

IR (neat, cm^{-1}): 3254, 3061, 1719, 1658, 1621, 1599, 1541, 1501, 1431, 1382, 1300, 1250, 1235, 1202, 1134, 1108, 966, 841, 816, 783, 765, 691, 636.

HRMS ($C_{18}H_{16}N_2O$): Calcd. $[M+H]^+$: 277.1335. Found: 277.1344.

***N*-phenylquinoline-3-carboxamide (CA13)**[19]



CA13

According to General Procedure C, quinoline-3-carboxylic acid (87 mg, 0.5 mmol), aniline (100 μL, 1 mmol), DMAP (12 mg, 0.1 mmol), and triethylamine (140 μL, 1 mmol) were allowed to react to prepare **CA13** as an off-white solid (65.5 mg, 53%).

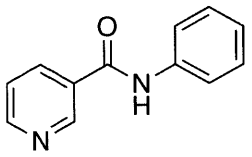
M.p. (°C): 220 – 222. (Lit. 212.)

^{1}H-NMR (500 MHz, Dimethyl sulfoxide-d_6): δ 9.36 (d, J = 2.3 Hz, 1H), 8.96 (d, J = 2.1 Hz, 1H), 8.16 (ddd, J = 8.5, 1.3, 0.6 Hz, 1H), 8.12 (dt, J = 8.4, 0.8 Hz, 1H), 7.90 (dddd, J = 8.5, 6.9, 1.5, 0.5 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.73 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.17 – 7.12 (m, 1H).

^{13}C NMR (126 MHz, Dimethyl sulfoxide-d_6): δ 164.1, 149.1, 148.5, 139.0, 136.0, 131.4, 129.2, 128.8, 128.8, 1277, 127.5, 126.5, 124.0, 120.4.

Elemental Analysis: Anal. calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87. Found: C, 77.14; H, 5.01.

***N*-phenylnicotinamide (CA14)**[20]



CA14

According to General Procedure C, nicotinic acid (62 mg, 0.5 mmol), aniline (100 μL, 1 mmol), DMAP (12 mg, 0.1 mmol), and triethylamine (140 μL, 1 mmol) were allowed to react to prepare **CA14** as a golden-yellow solid (88 mg, 59%).

M.p. (°C): 119 – 120. (Lit. 119 – 120.)

^{1}H-NMR (500 MHz, Chloroform-d): δ 9.04 (s, 1H), 8.68 (d, J = 3.8 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.15 (t, J = 7.4 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d): δ 164.3, 152.3, 148.0, 137.7, 135.6, 131.0, 129.2, 125.1, 123.8, 120.8.

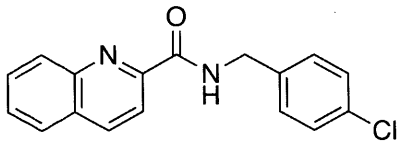
Elemental Analysis: Anal. calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09. Found: C, 72.45; H, 5.22.

---

[19] *N*-Phenylquinoline-3-carboxamide has been previously reported and characterized: Taylor, E. C.; Eckroth, D. R.; Bartulin, J. *J. Org. Chem.* **1967**, *32*, 1899-1900.

[20] *N*-Phenylnicotinamide has been previously reported and characterized: Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8460-8463.

***N*-(4-chlorobenzyl)quinoline-2-carboxamide (CA15)**



CA15

According to General Procedure C, quinaldic acid (87 mg, 0.5 mmol) and 4-chlorobenzylamine (130 µL, 1 mmol) were allowed to react to prepare **CA15** as an off-white solid (98.5 mg, 66%).

M.p. (°C): 118 – 119.

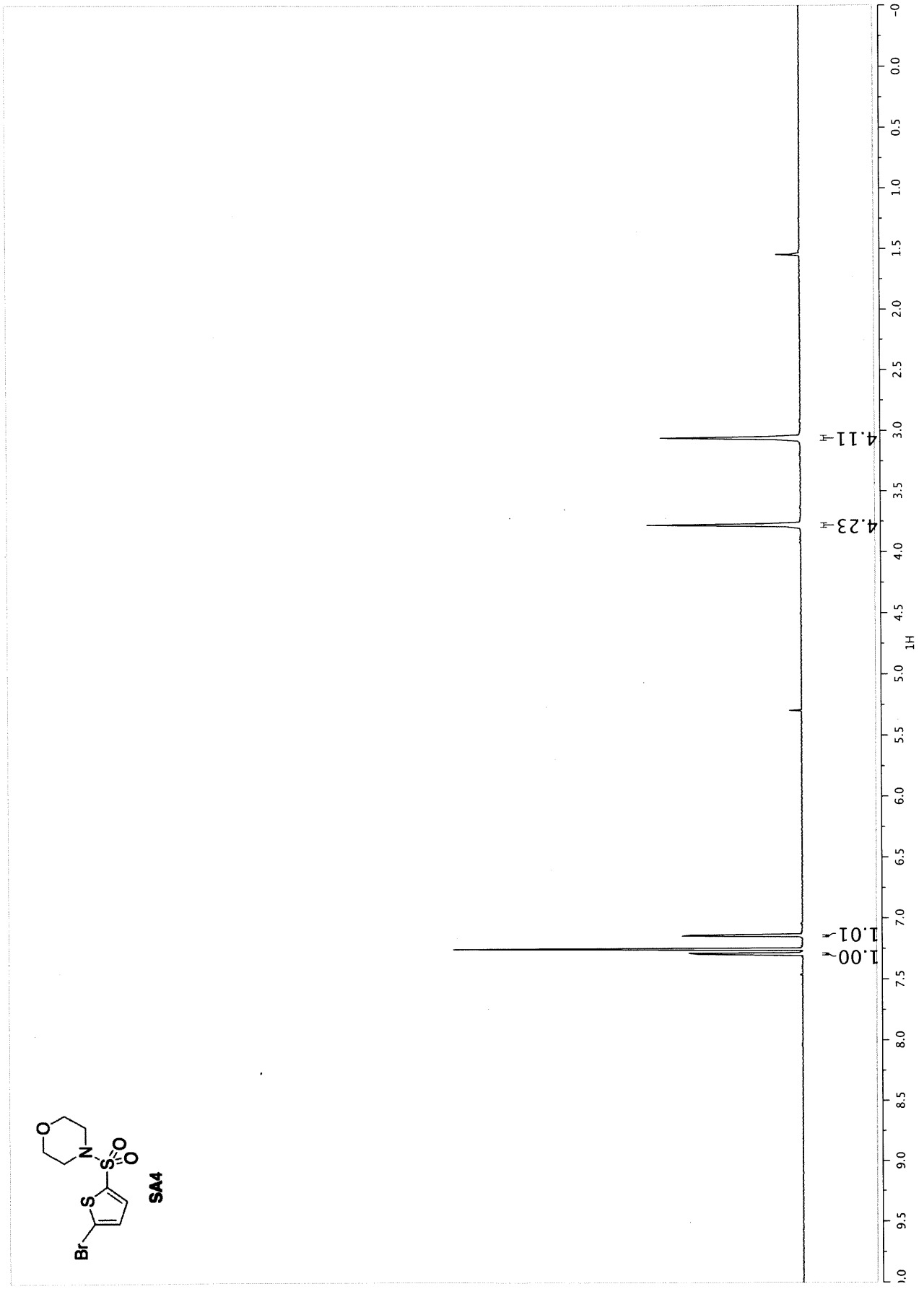
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.64 (bs, 1H), 8.36 – 8.31 (m, 2H), 8.08 (ddt, J = 8.5, 1.3, 0.7 Hz, 1H), 7.89 (ddd, J = 8.2, 1.5, 0.7 Hz, 1H), 7.76 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.62 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.37 – 7.30 (m, 4H), 4.70 (d, J = 6.2 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 164.7, 149.6, 146.6, 137.7, 137.0, 133.4, 130.3, 129.8, 129.5, 129.3, 129.0, 128.1, 127.9, 119.0, 43.0.

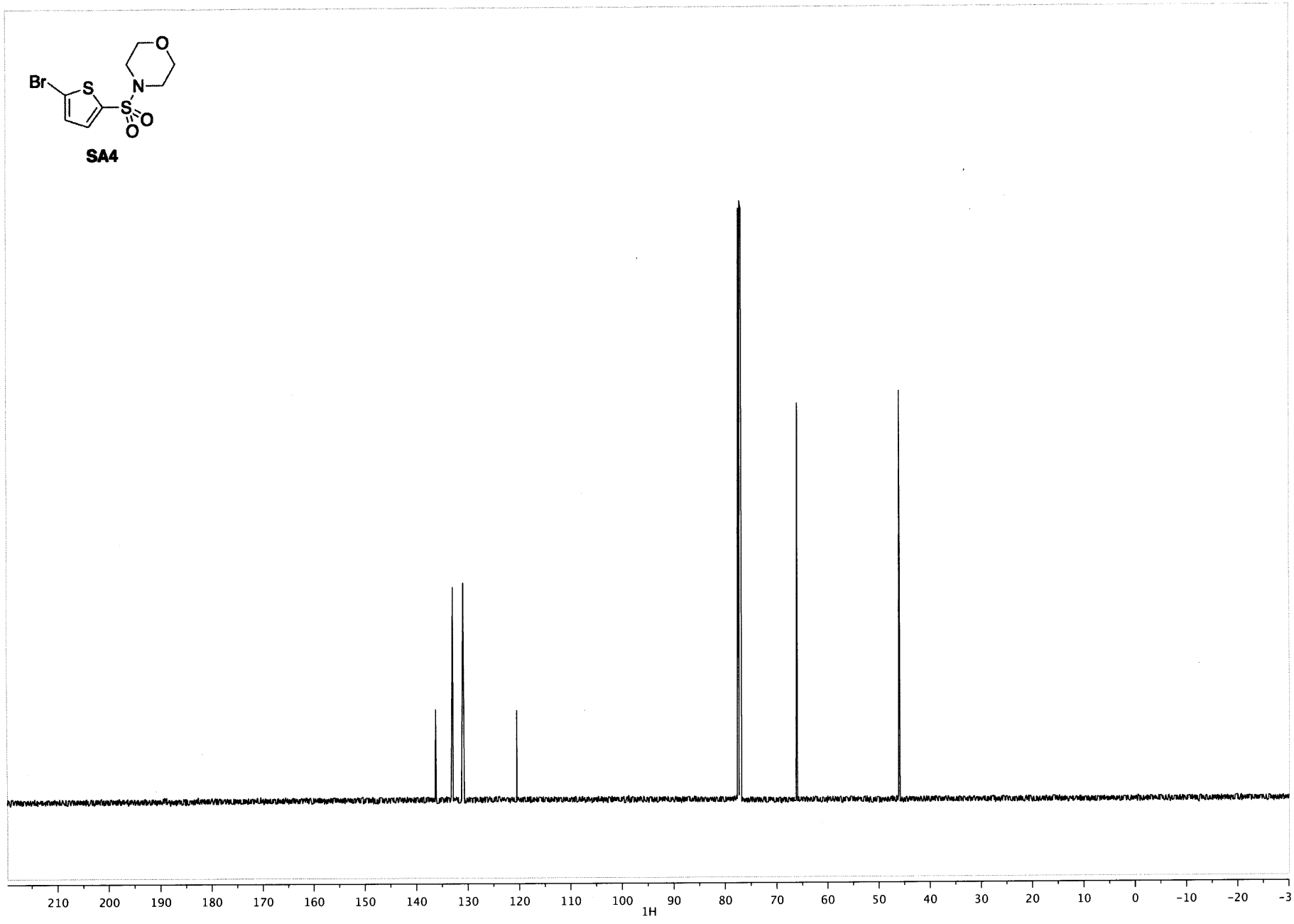
IR (neat, cm^{-1}): 3334, 1647, 1560, 1532, 1488, 1450, 1426, 1411, 1293, 1164, 1104, 1093, 1019, 983, 945, 850, 809, 774, 744, 721, 657, 625.

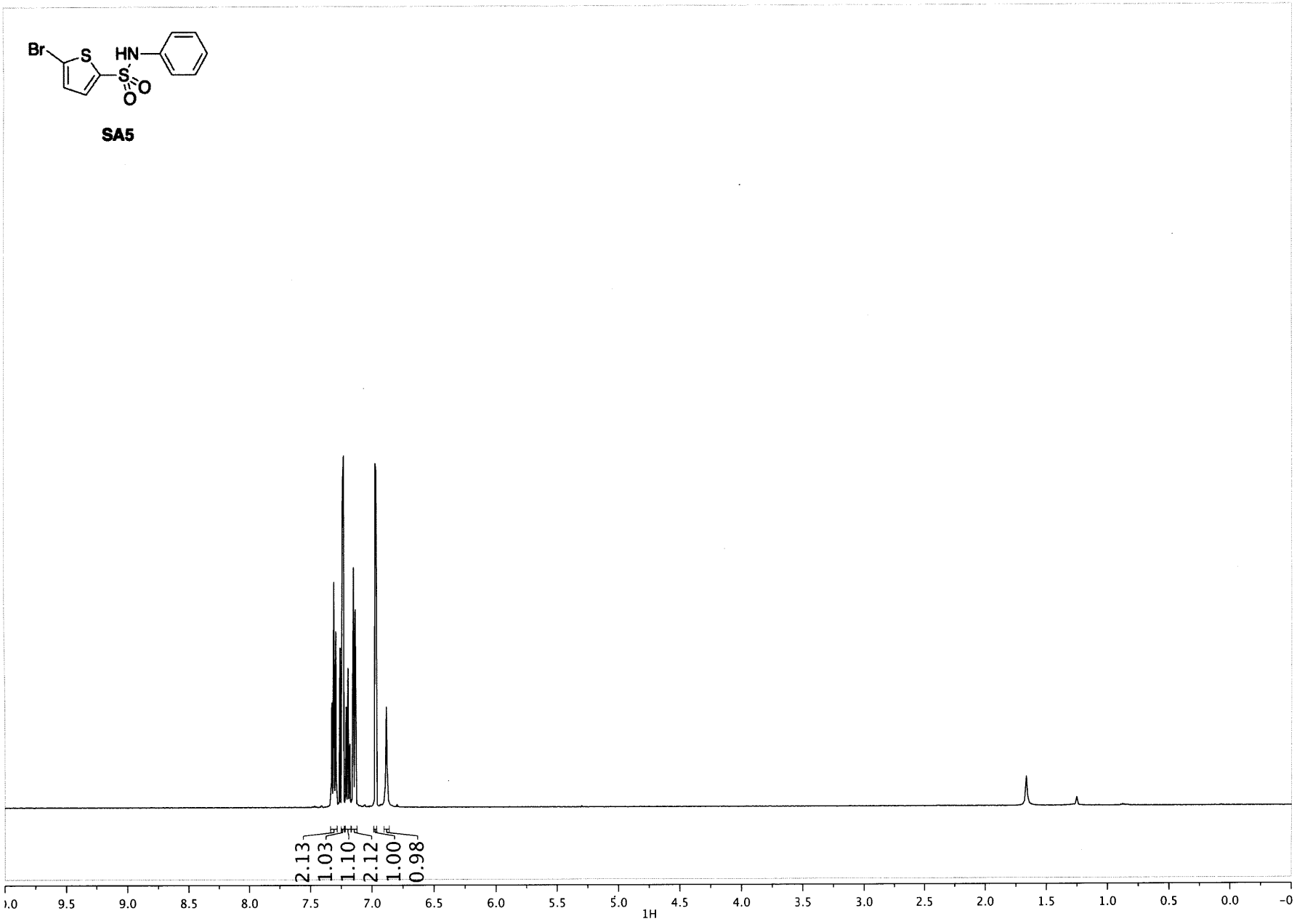
HRMS ($C_{17}H_{13}ClN_2O$): Calcd. $[M+H]^+$: 297.0789. Found: 297.0790.

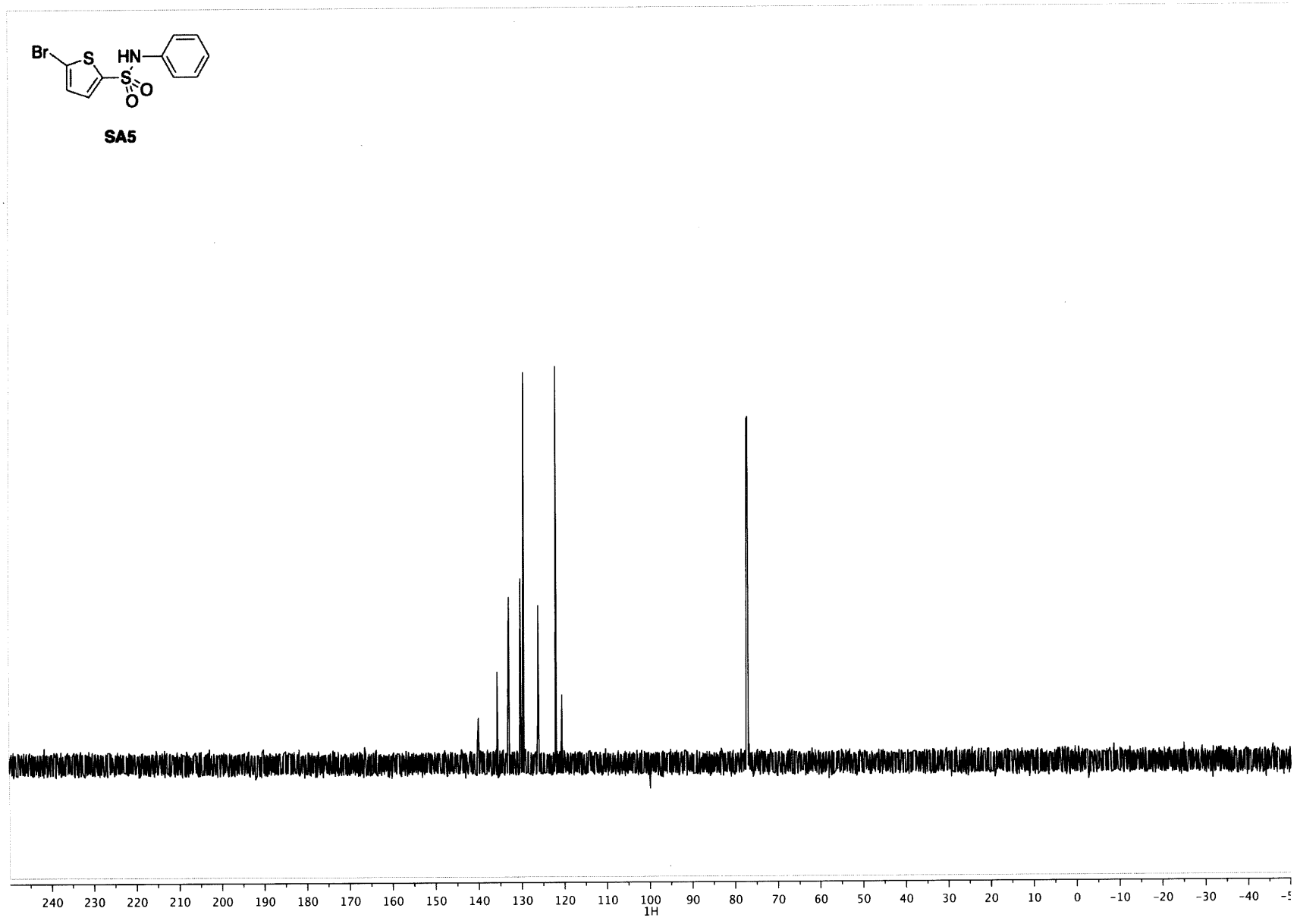
NMR Spectra

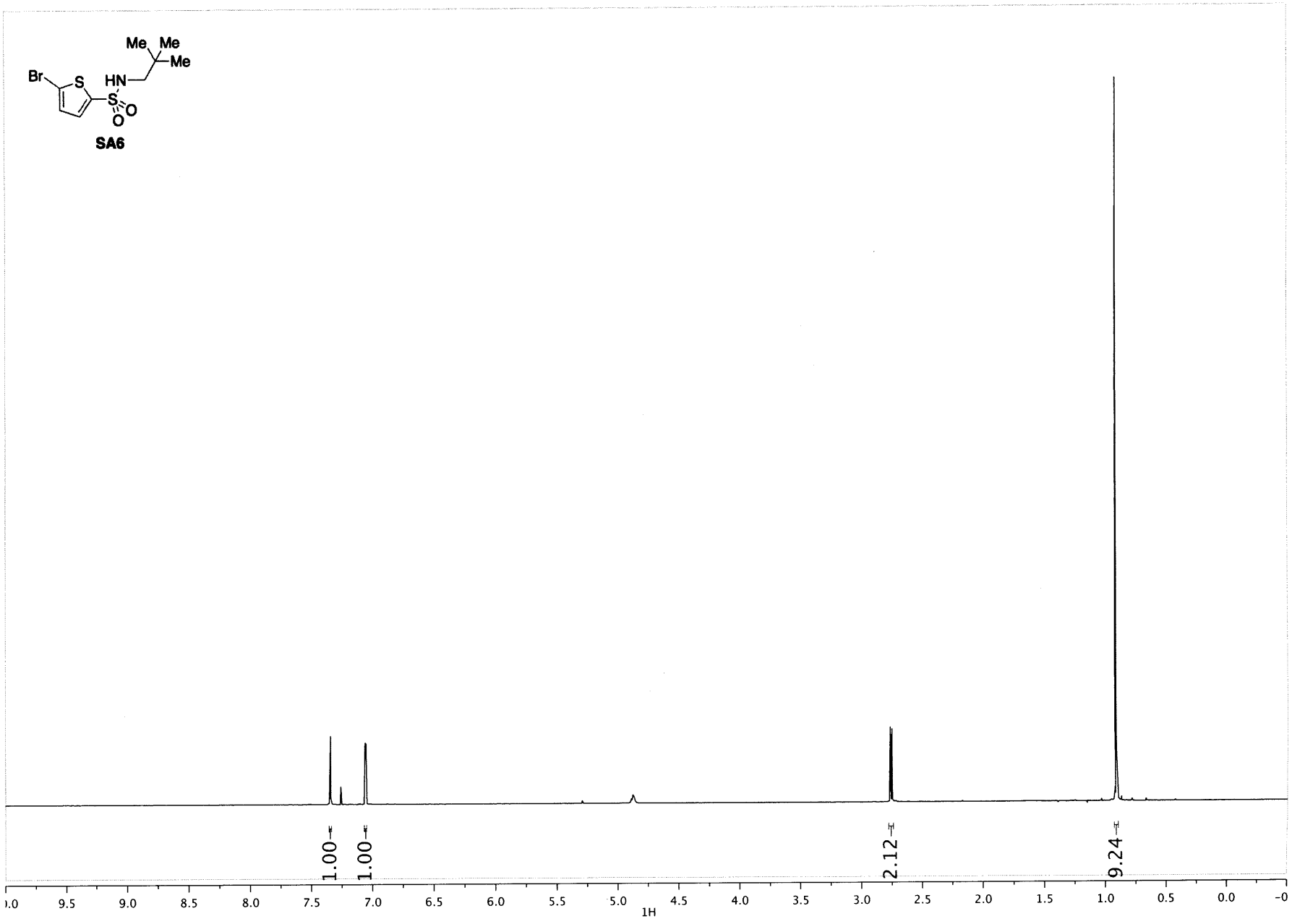


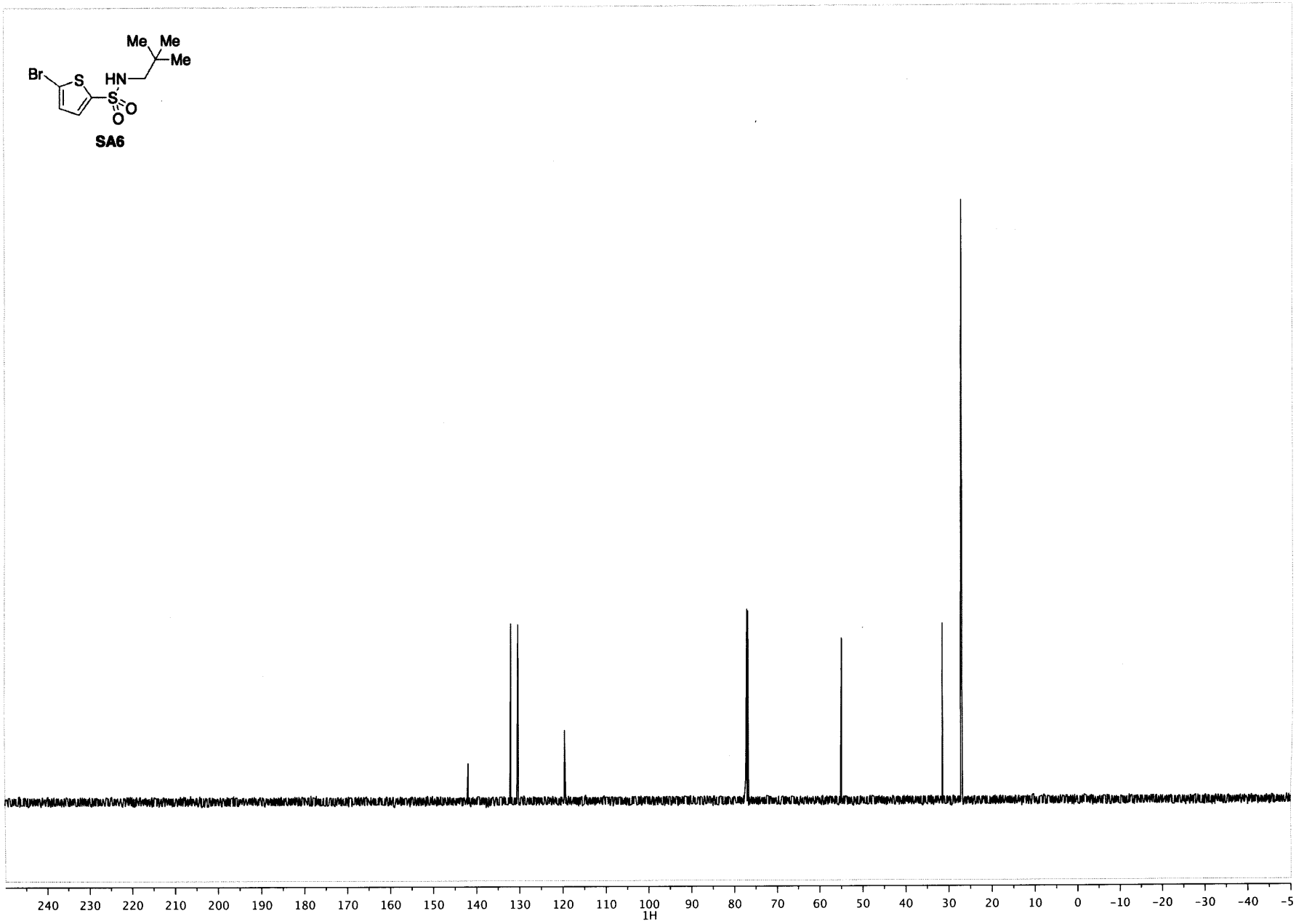
SA4

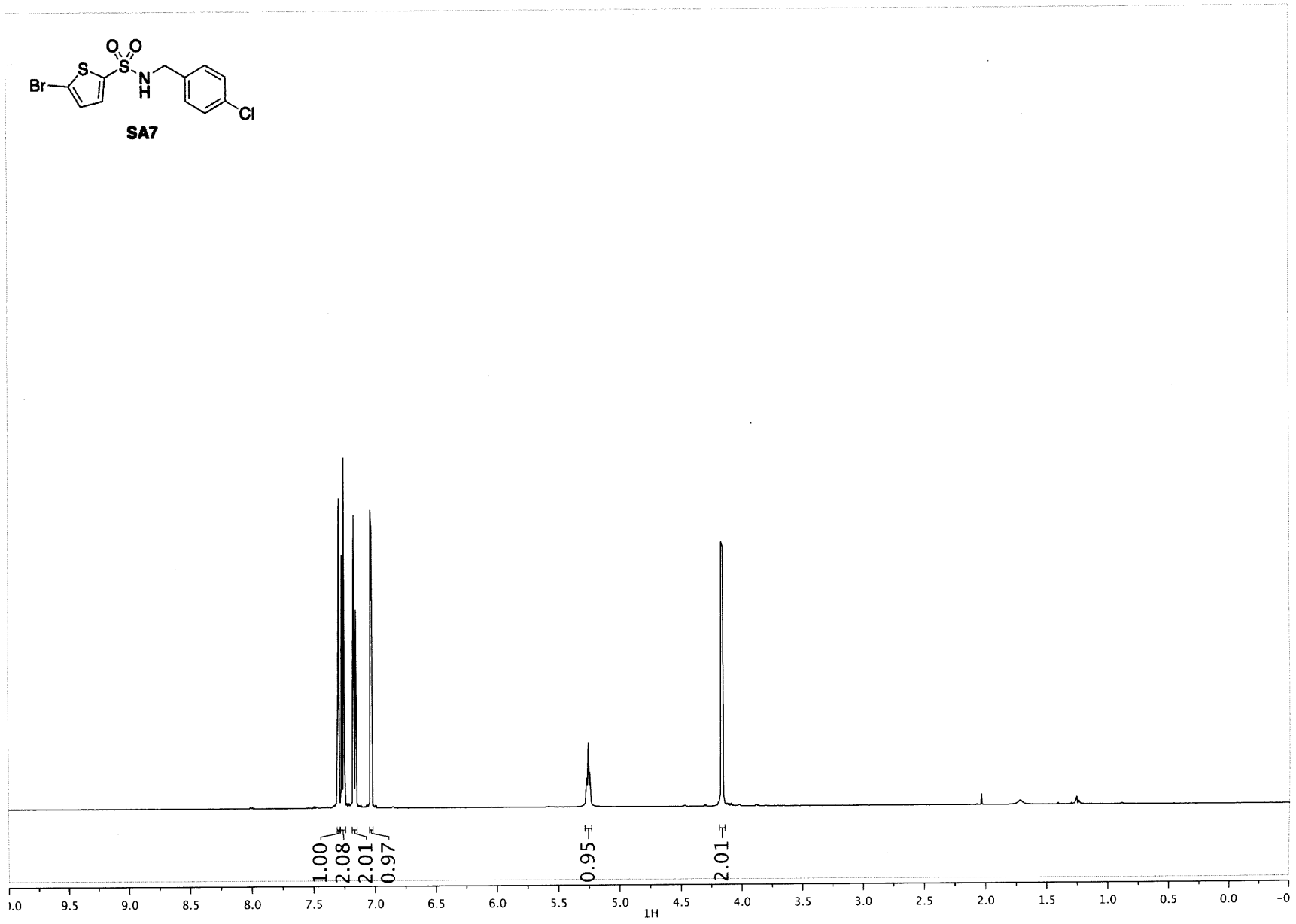

Br
S
N
O
S
O
O
SA4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H

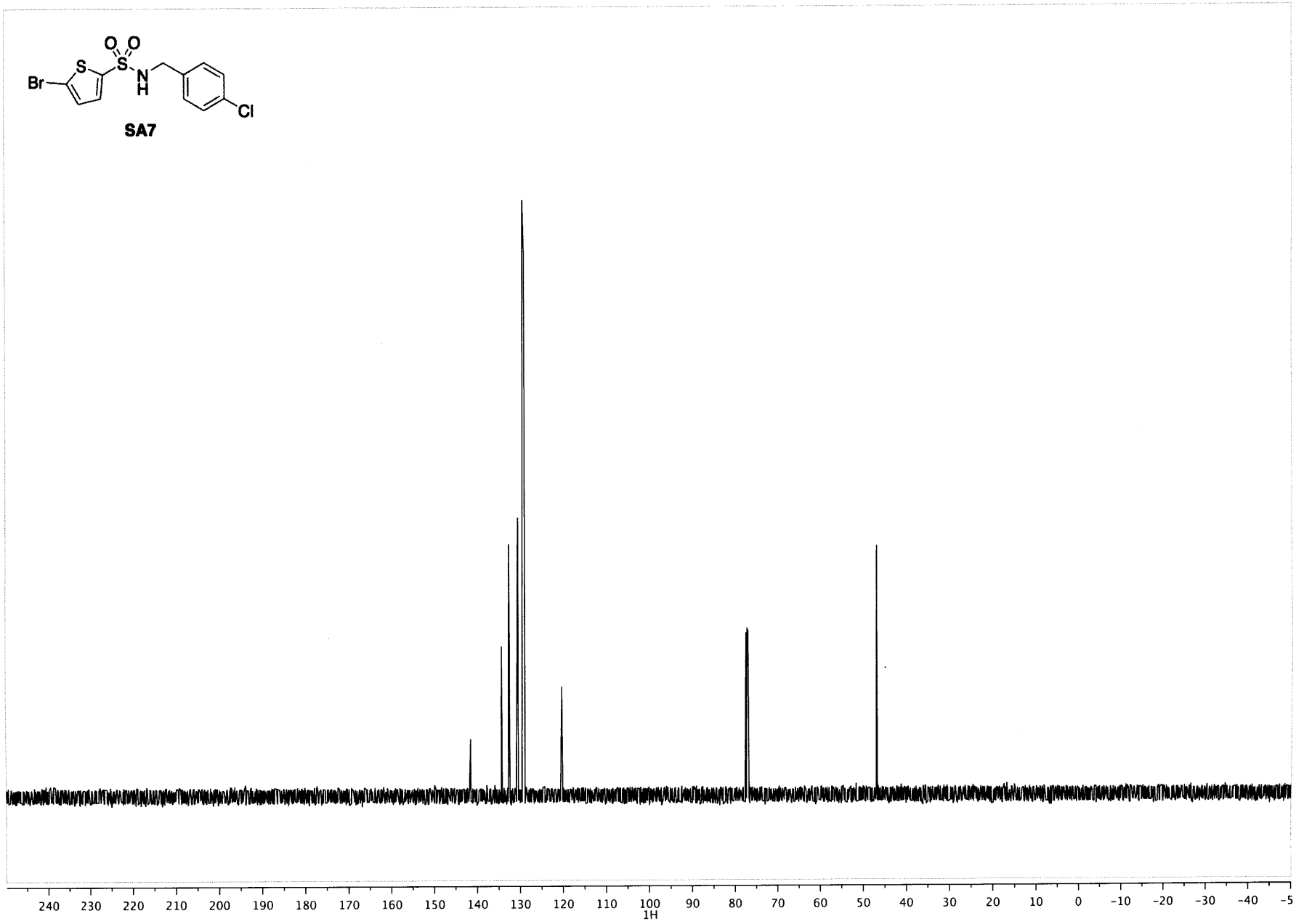

Br
S
HN
S
O
O
SA5
2.13
1.03
1.10
2.12
1.00
0.98
1H

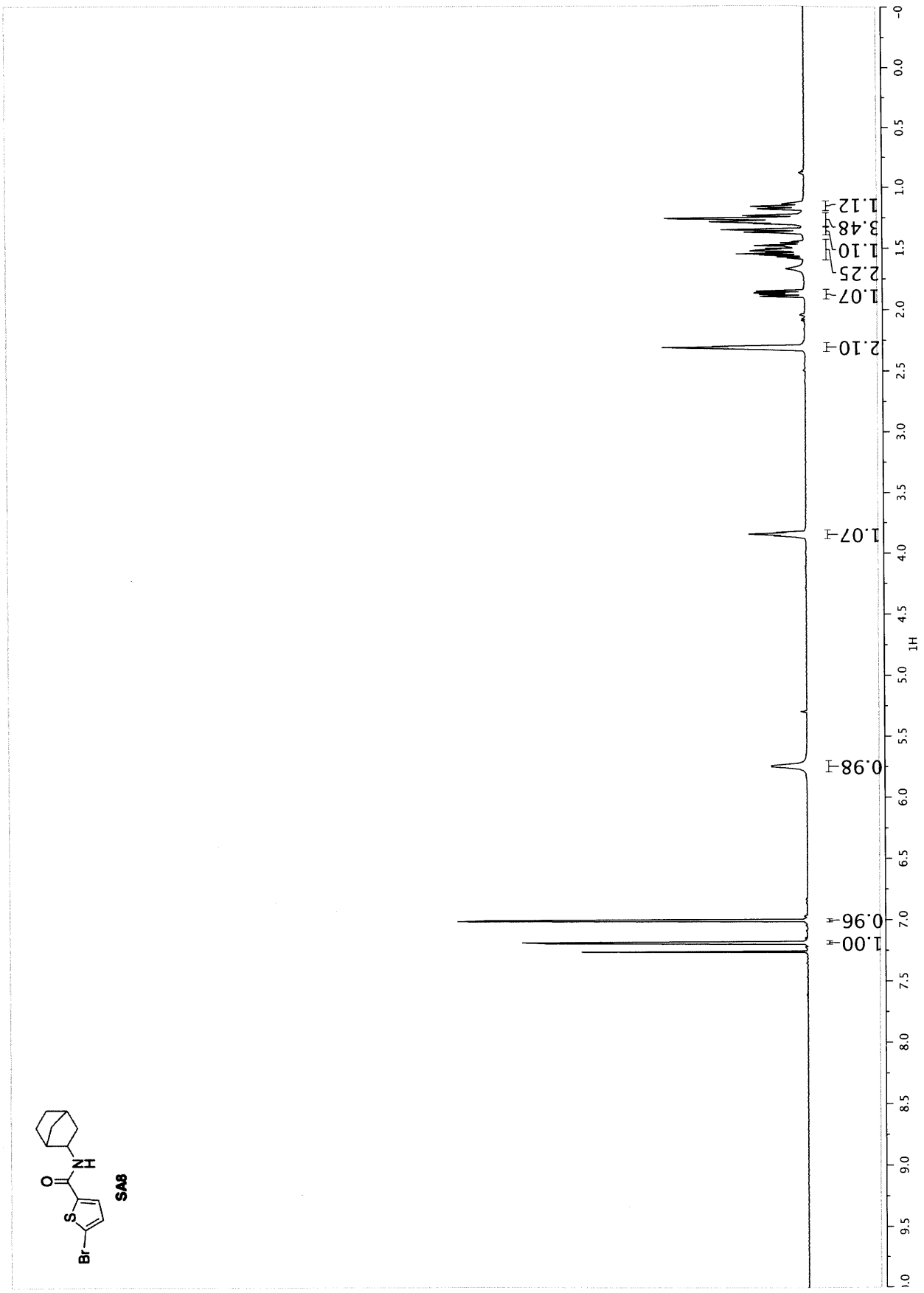

Br
S
HN
S
O
O
SA5
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H

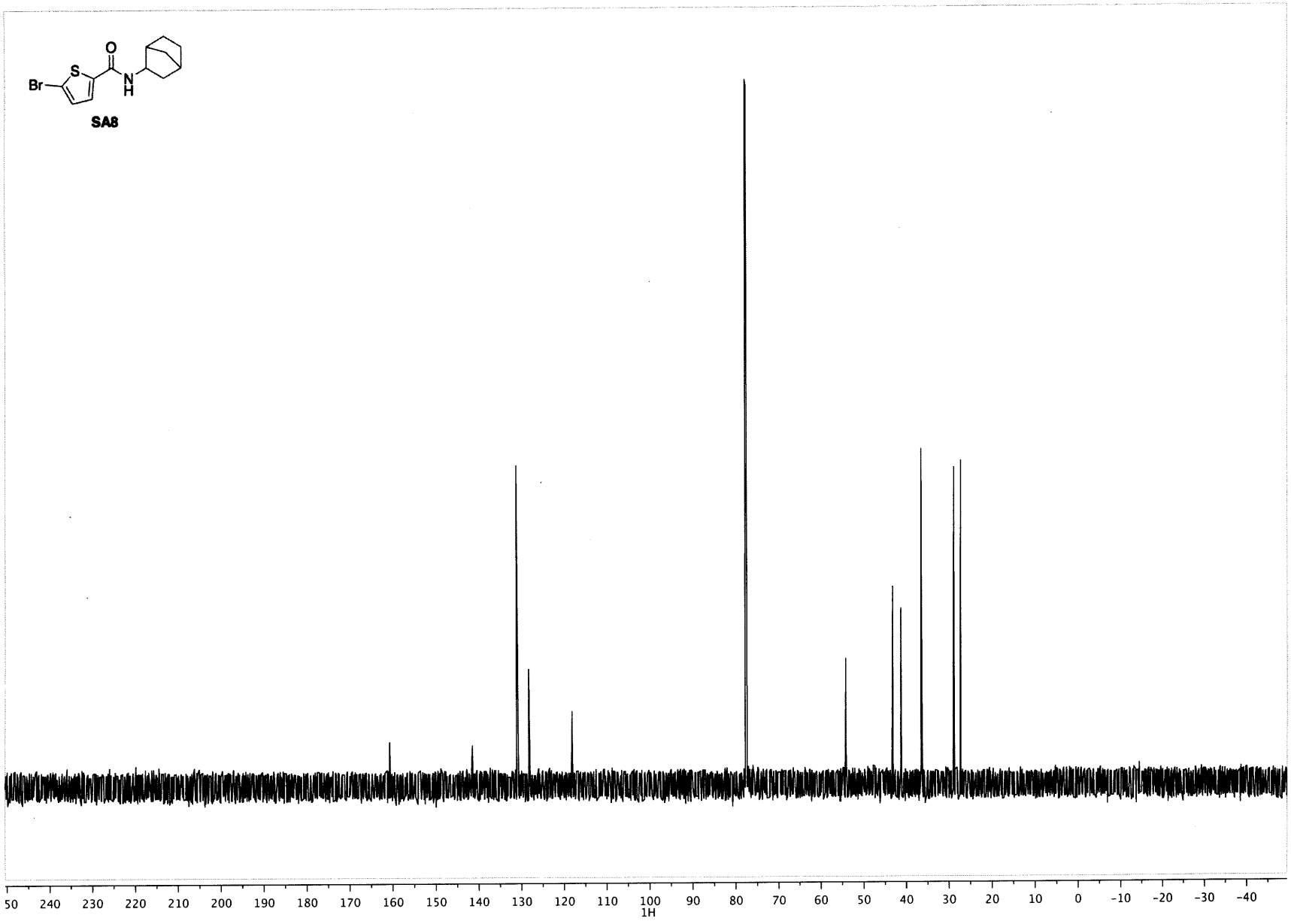

Me
Me
Me
Br
S
HN
S
O
O
SA6
1.00
1.00
2.12
9.24
1H

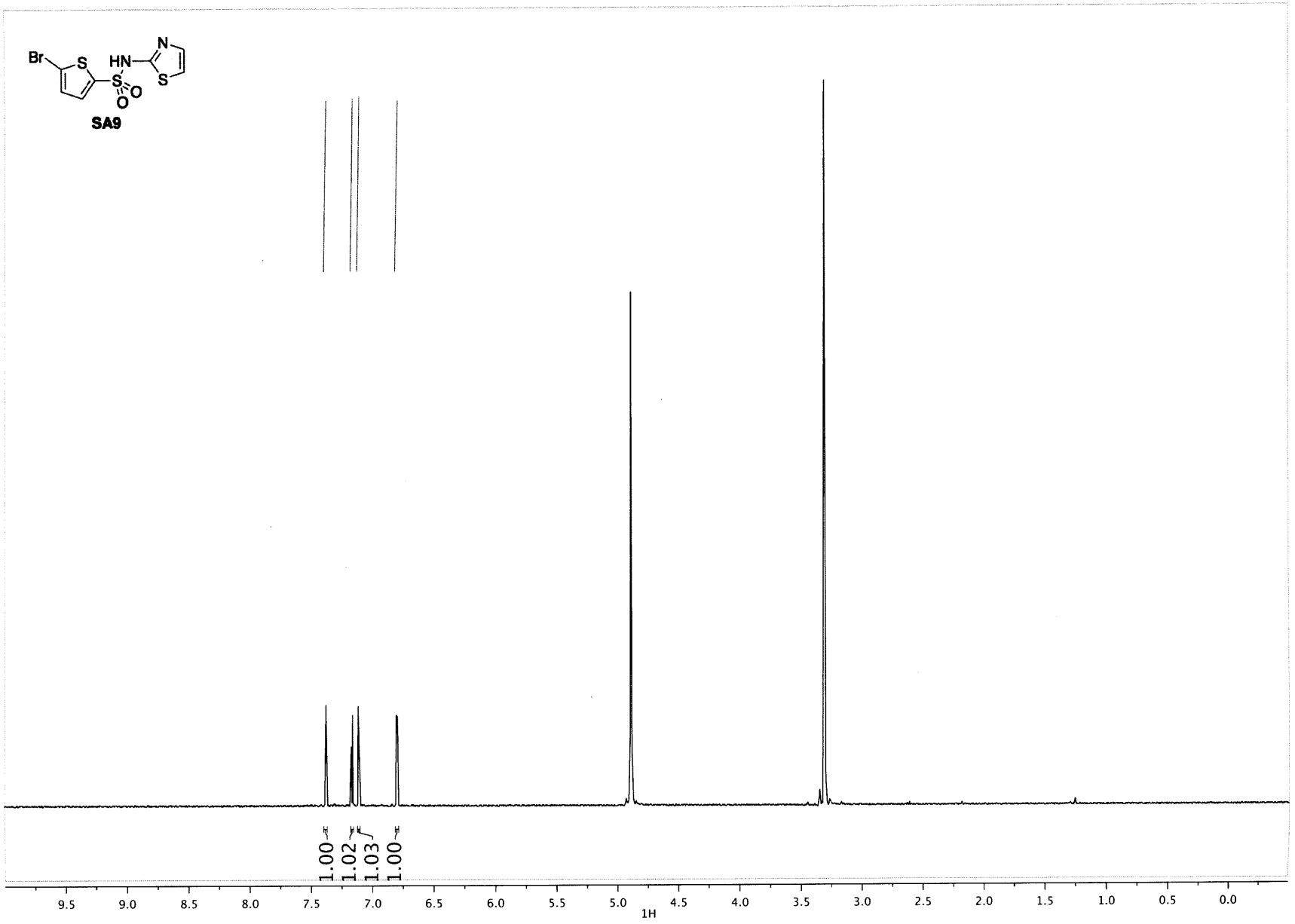

Me Me
Me
Br
S
HN
S
O
O
SA6
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

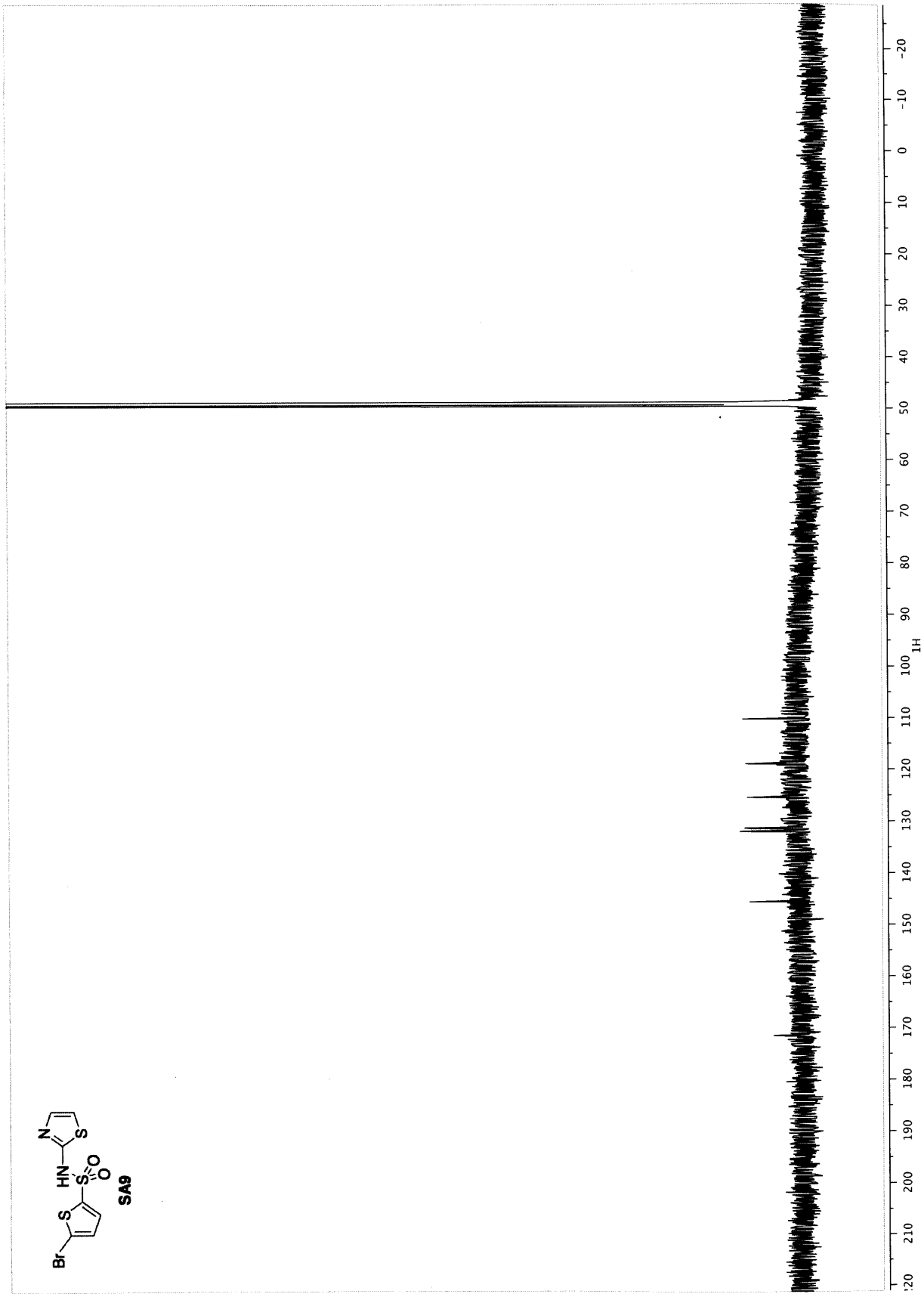

Br
S
O
O
S
N
H
Cl
SA7
1.00
2.08
2.01
0.97
0.95
2.01
1H


Br
S
O
O
S
N
H
Cl
SA7
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

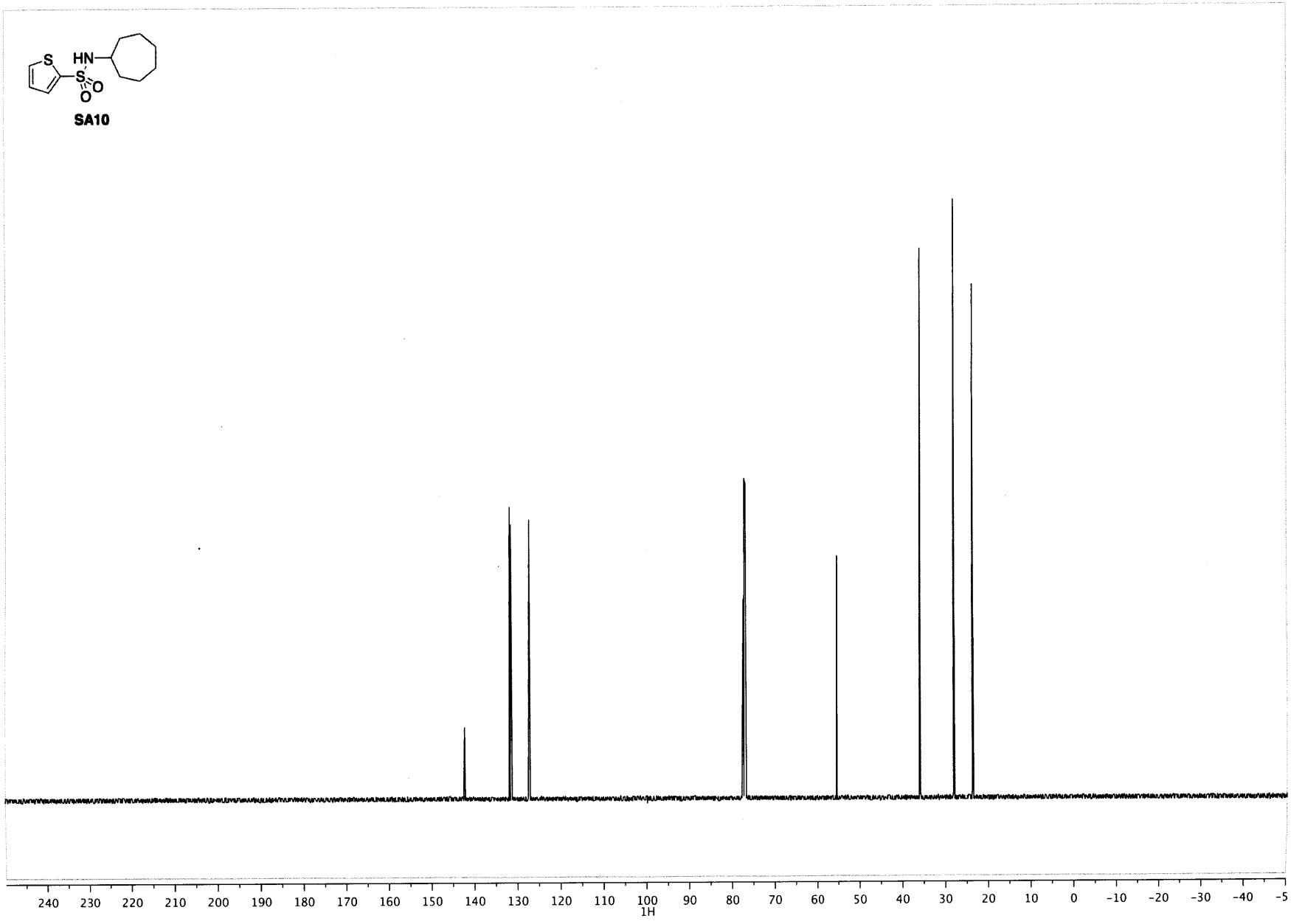

SA8
1.00
0.96
0.98
1.07
2.10
1.07
2.25
1.10
3.48
1.12
1H

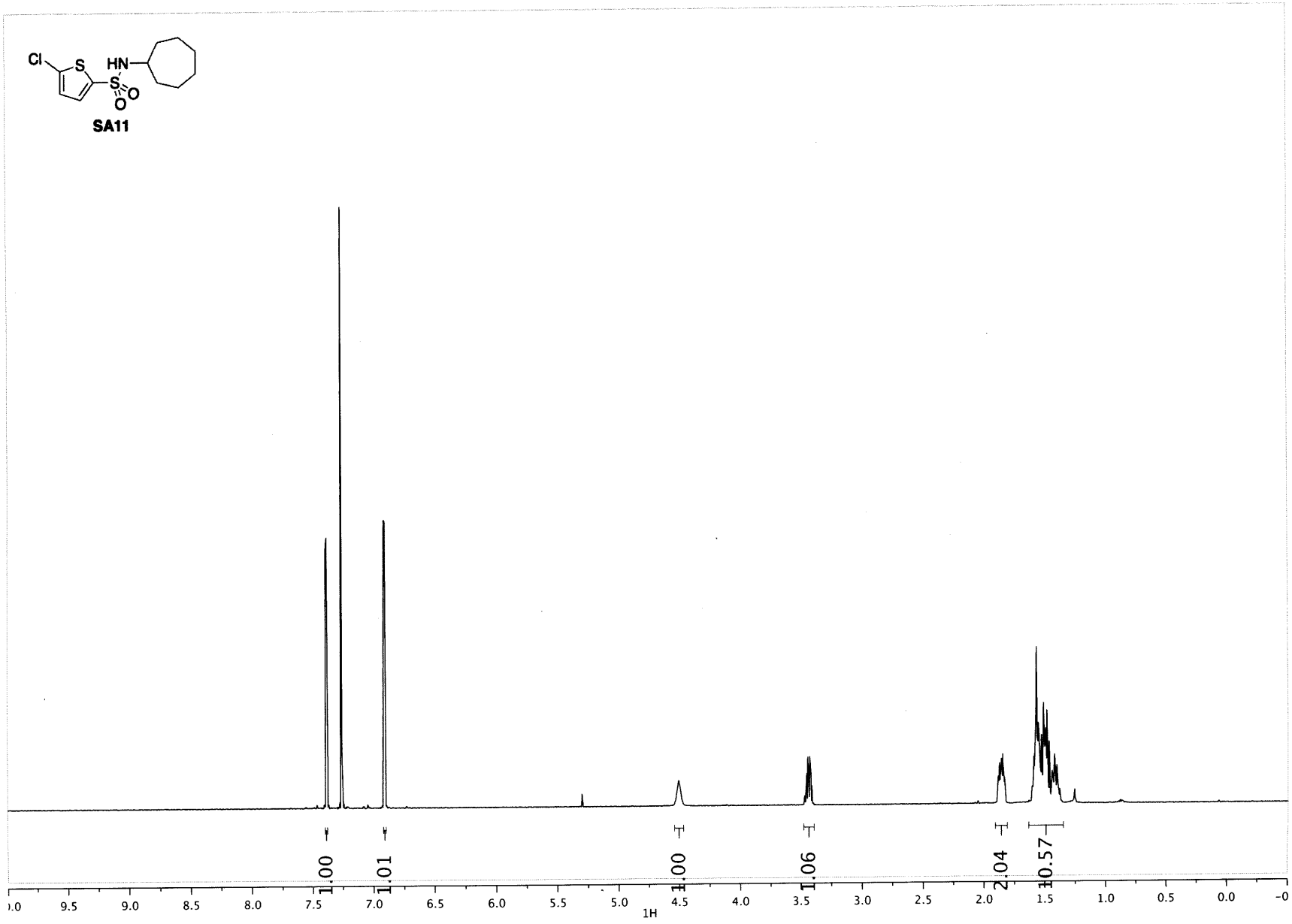

O
S
N
H
Br
SA8
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H

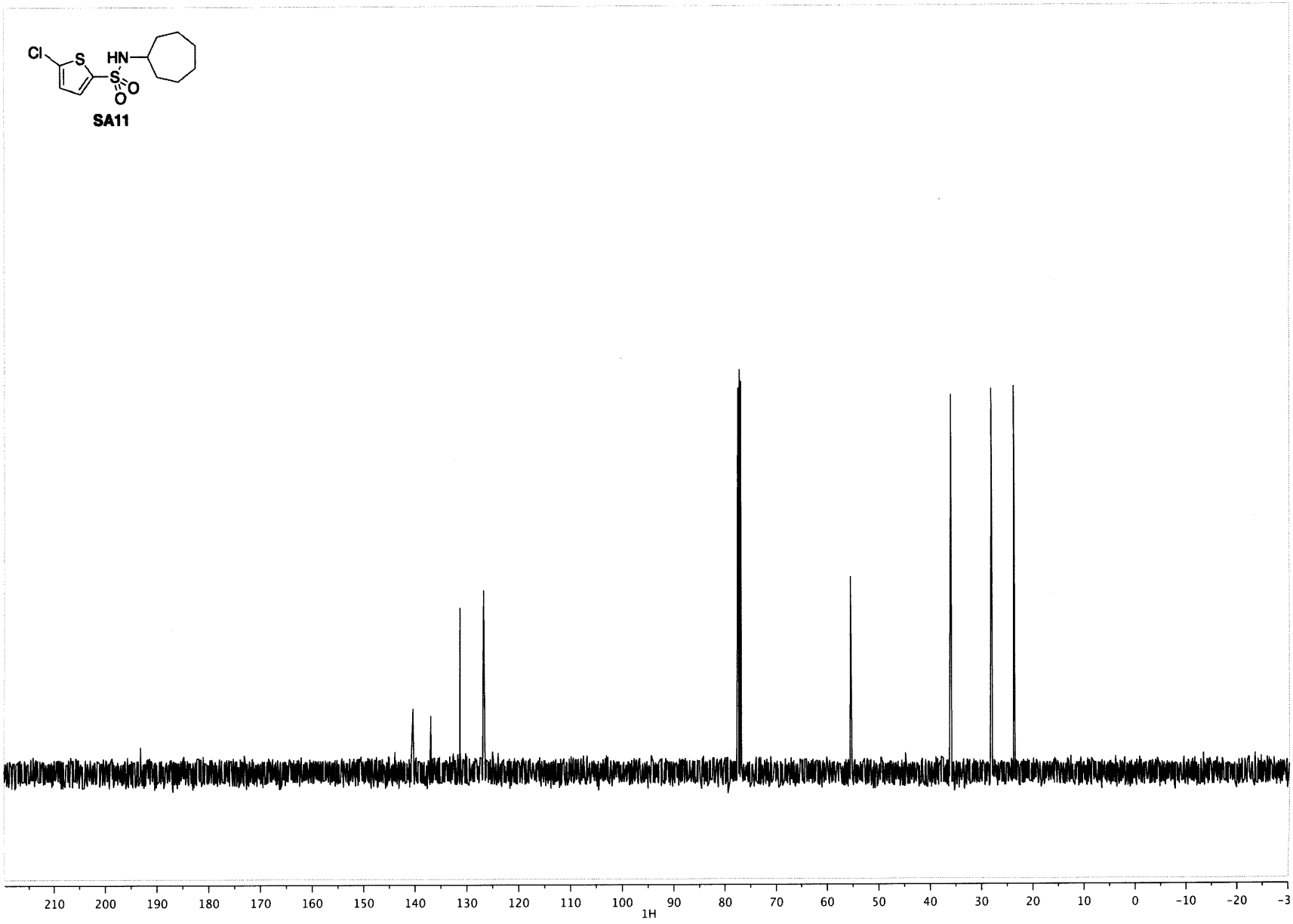

Br
S
HN
N
S
S
O
O
SA9
1.00
1.02
1.03
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H

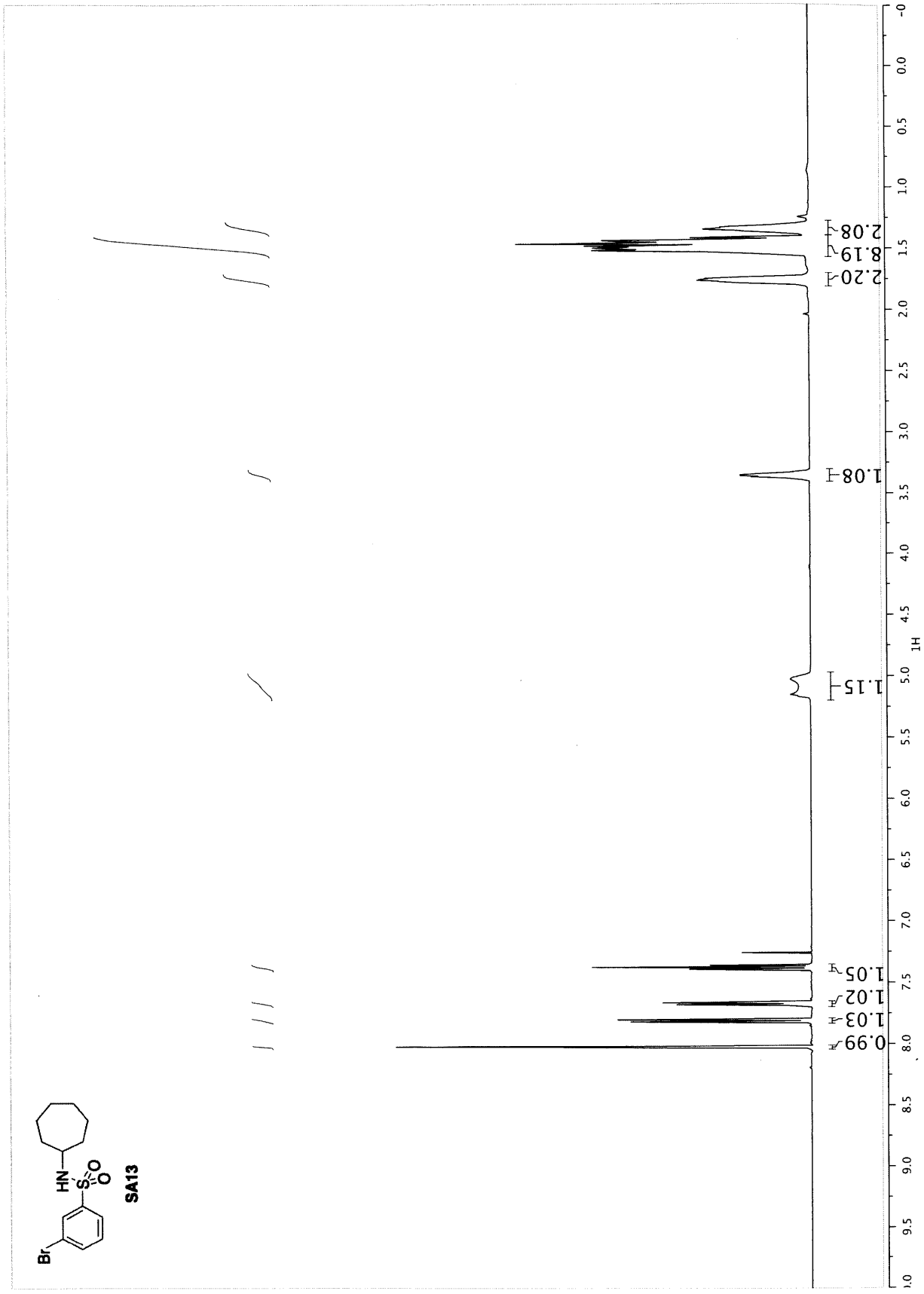

SA9
1H

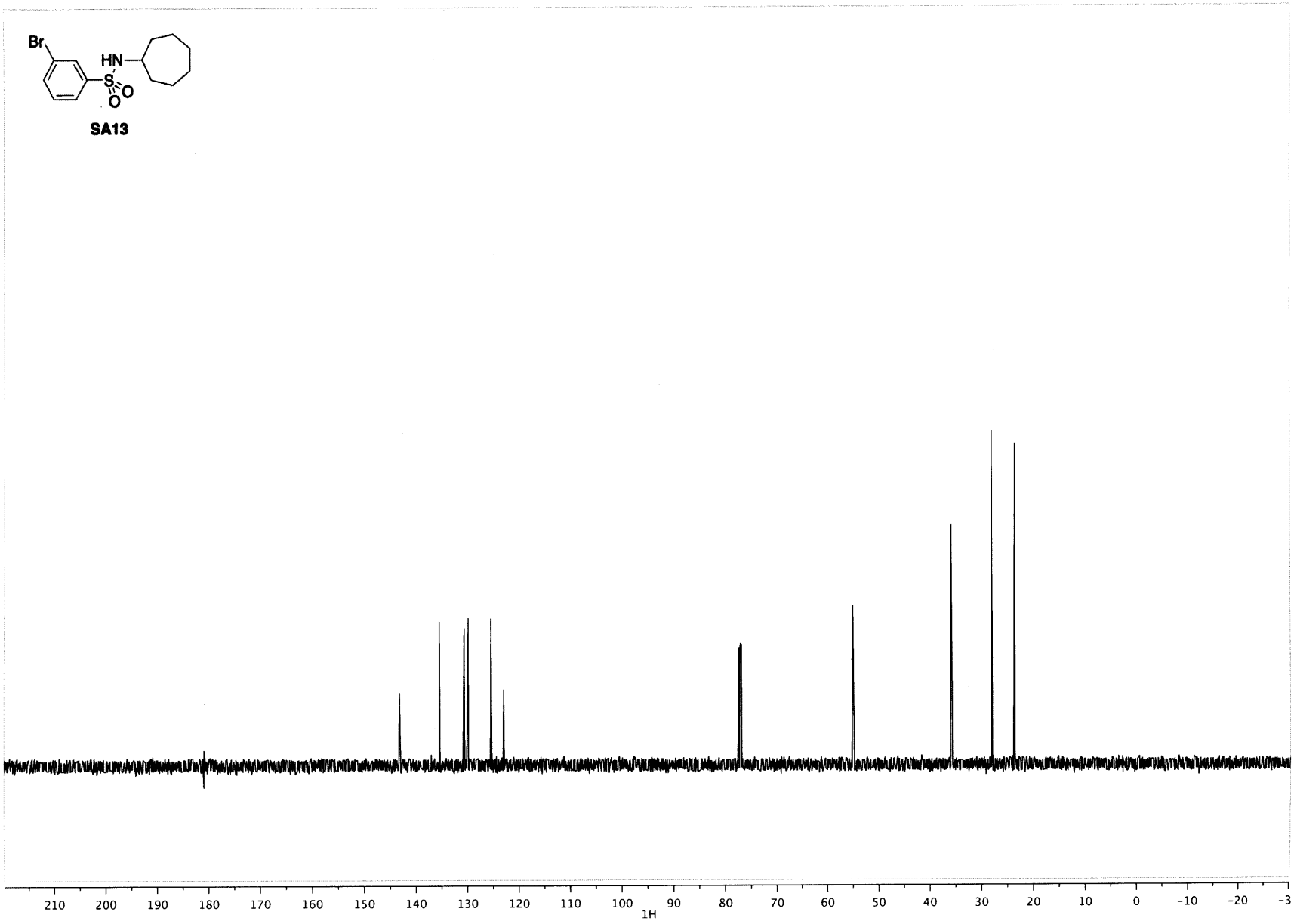
SA10
1.00
2.03
1.00
1.00
1.05
1.04
1.04
1.94
9.47
1H


S
HN
S
O
O
SA10
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

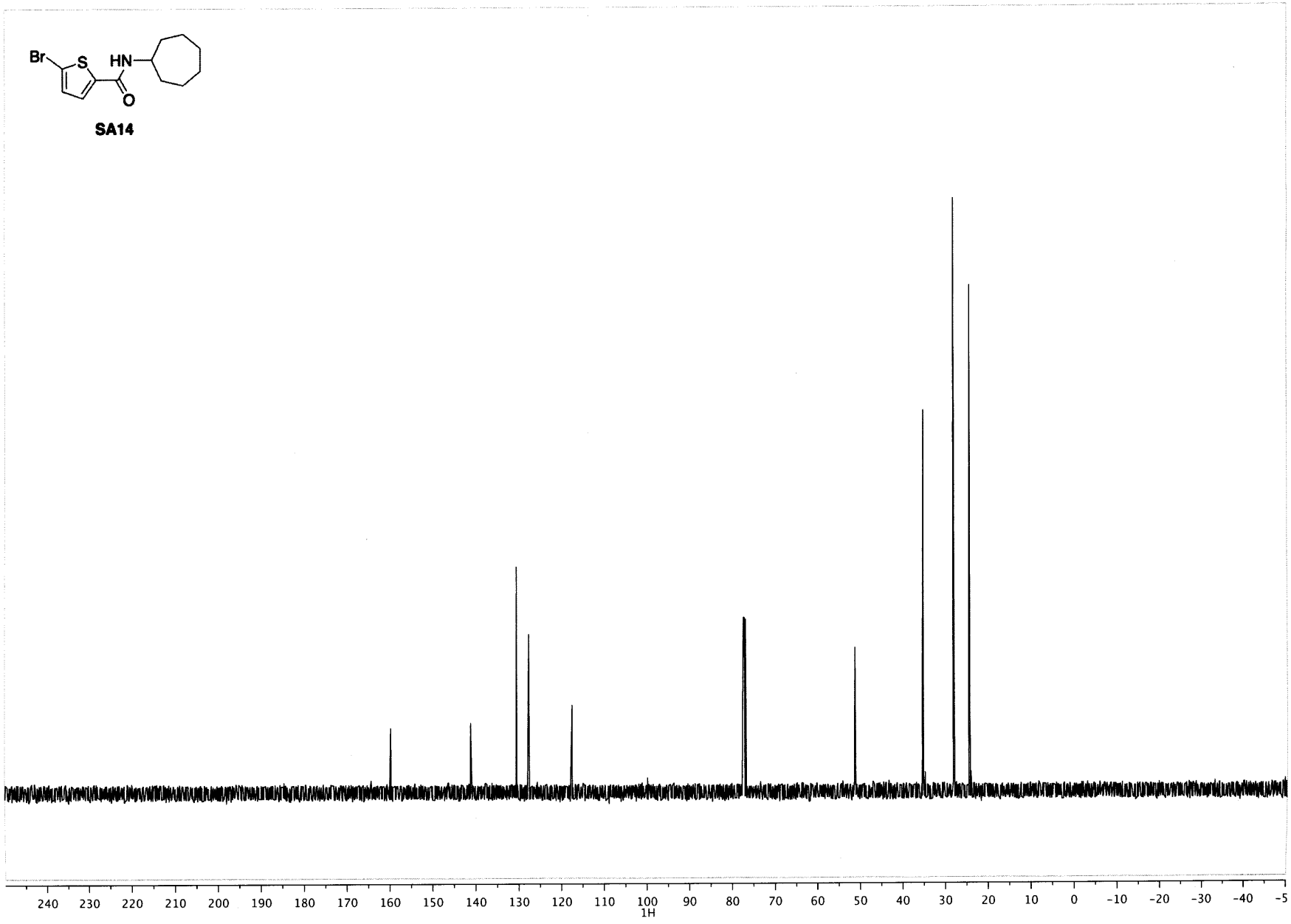

Cl
S
HN
S
O
O
SA11
1.00
1.01
1.00
1.06
2.04
10.57
1H


Cl
S
HN
S
O
O
SA11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H

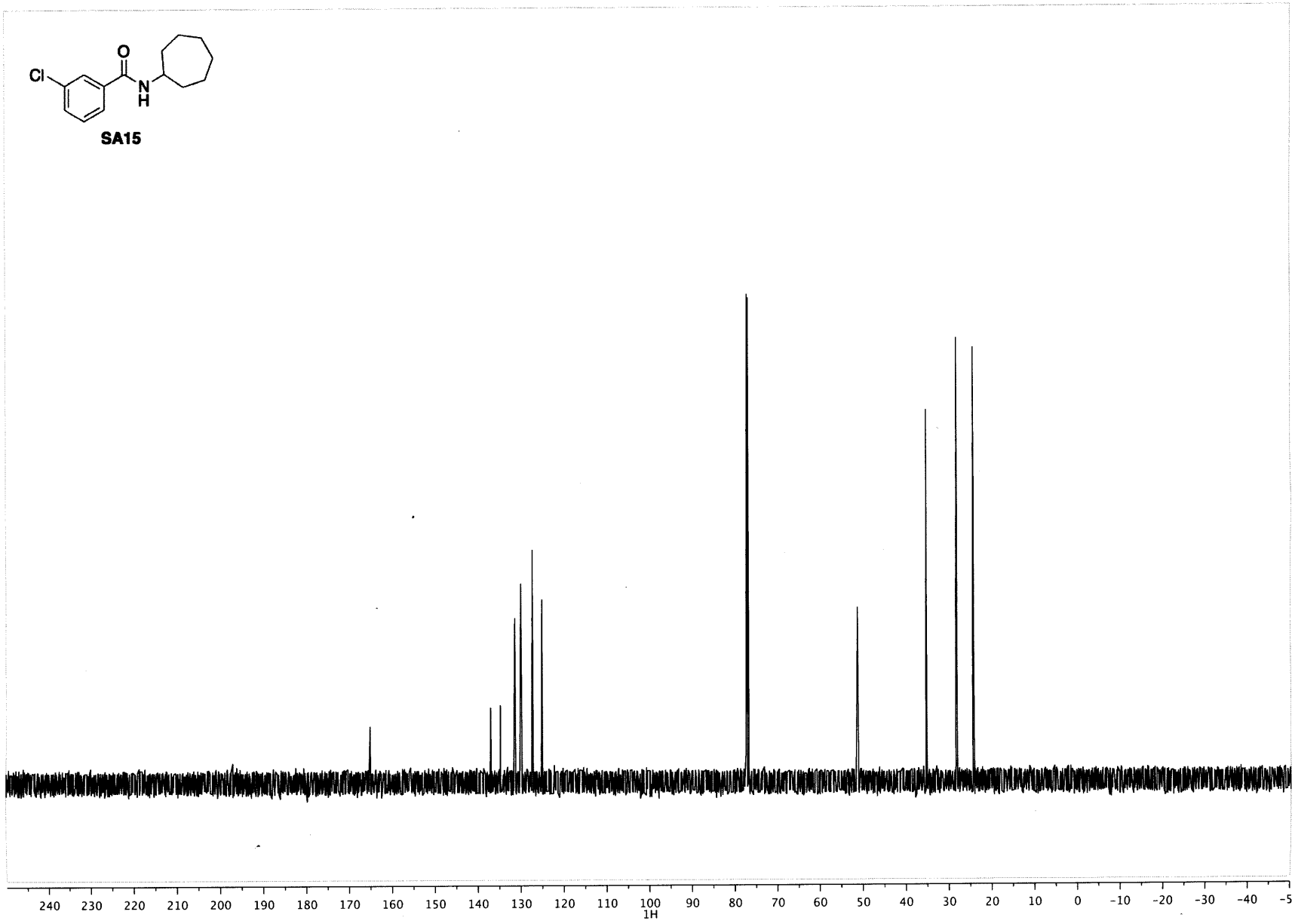

SA13
Br
HN
S
O
O
0.99
1.03
1.02
1.05
1.15
1.08
2.20
8.19
2.08
1H


Br
HN
S
O
O
SA13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-3
1H

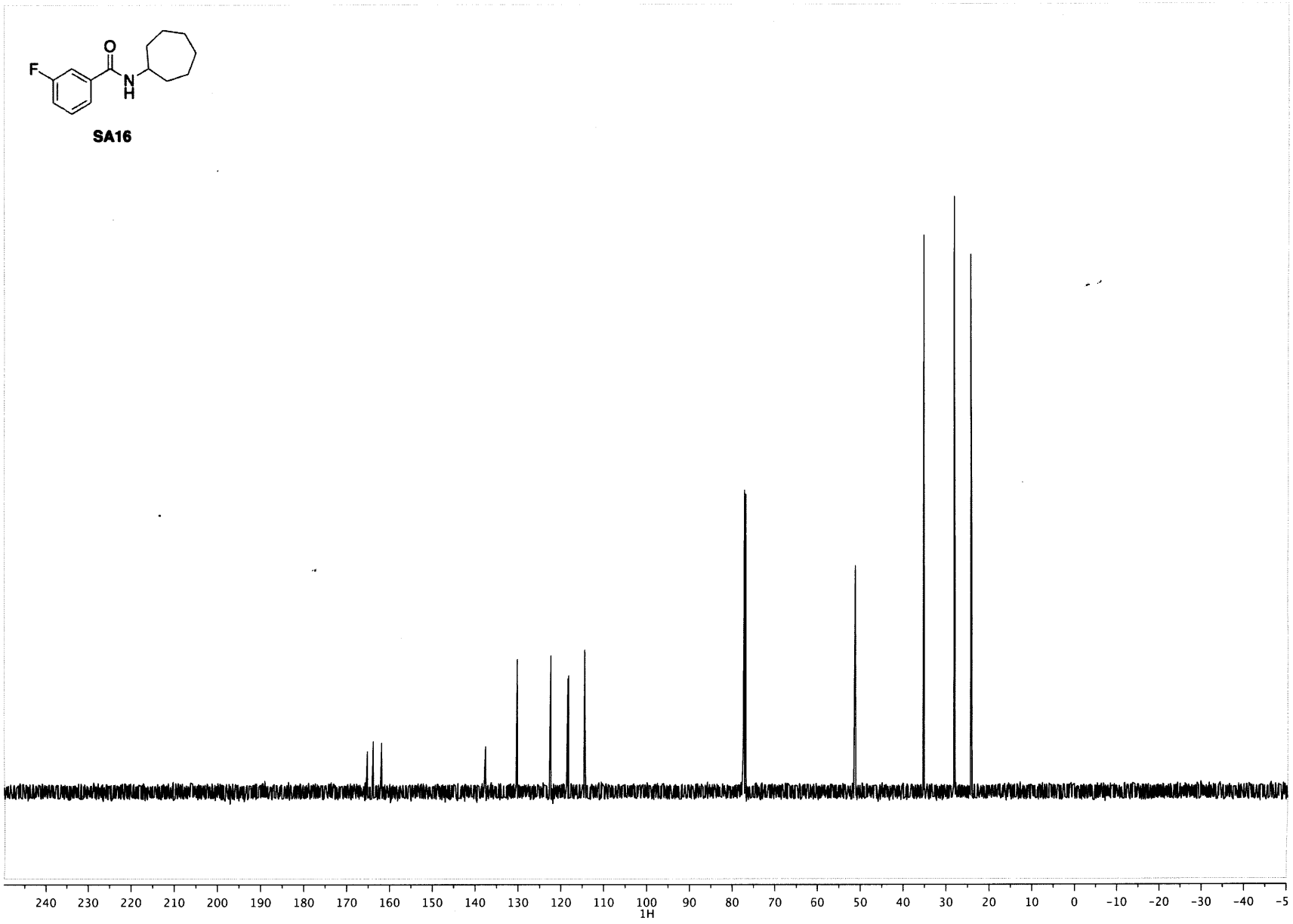
Br
S
HN
O
SA14
1.00
1.03
0.86
1.13
2.15
11.84
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


Br
S
HN
O
SA14
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

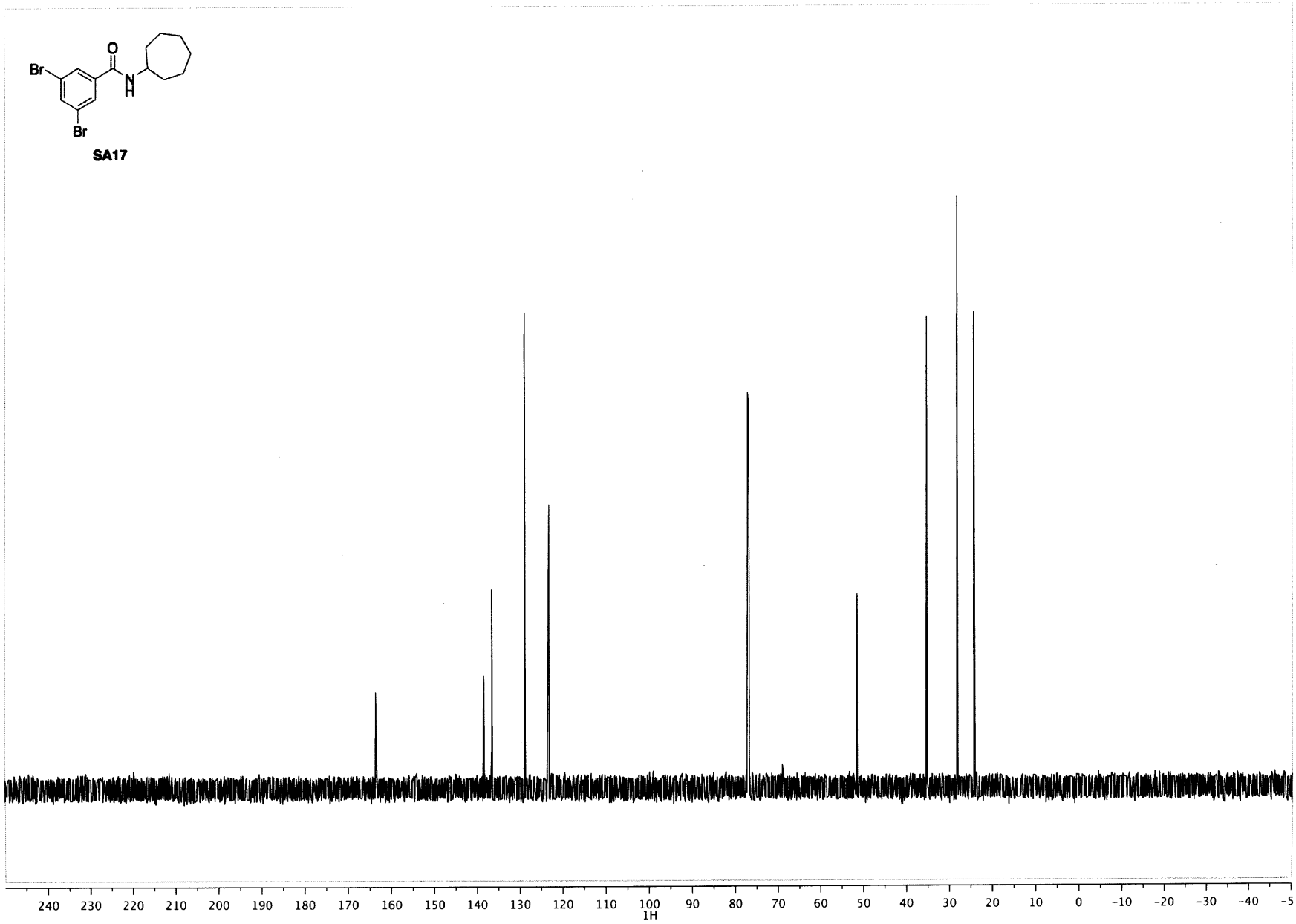
Cl
O
N
H
SA15
1.00
1.07
1.05
1.11
1.07
1.18
2.31
1.42
1H

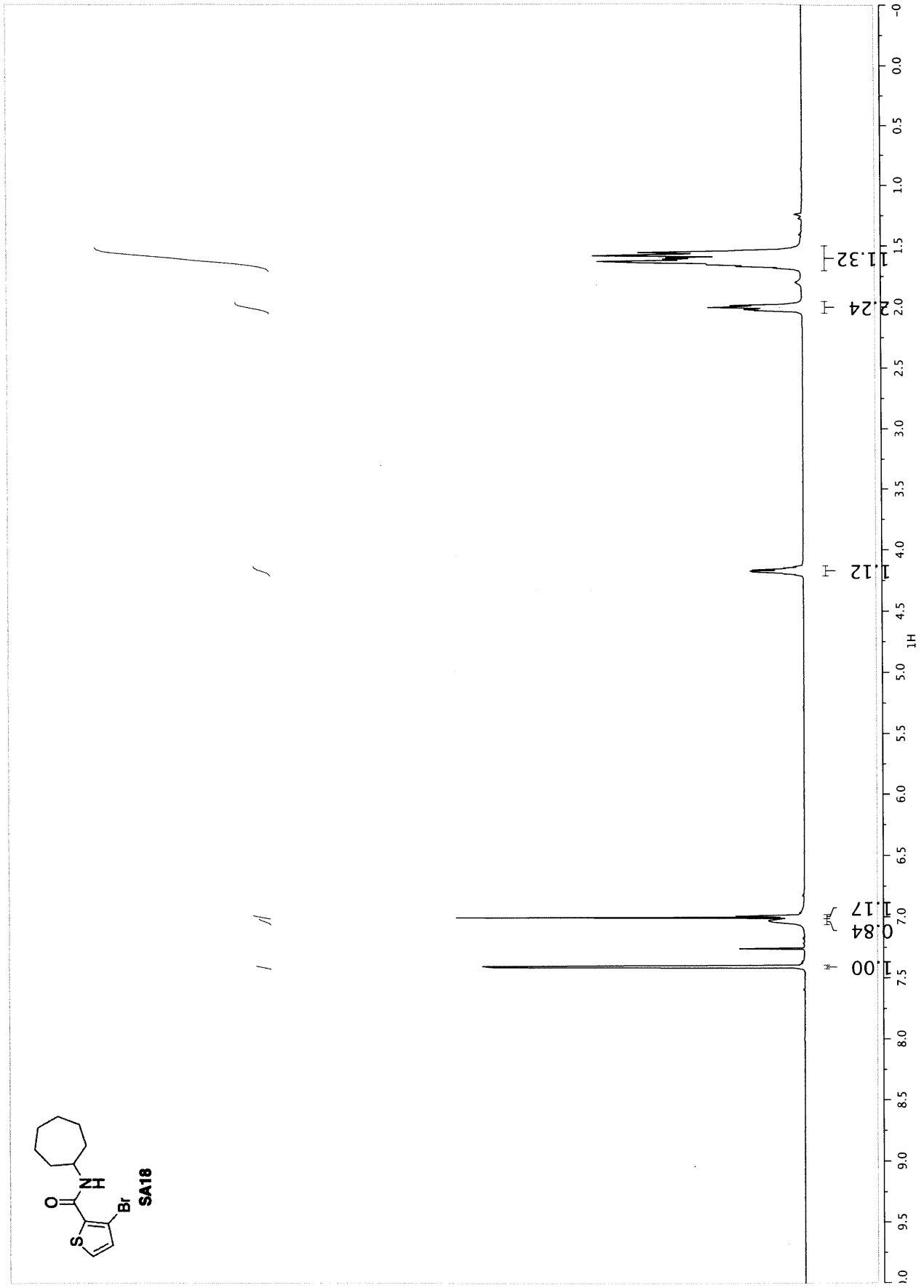

Cl
O
N
H
SA15
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

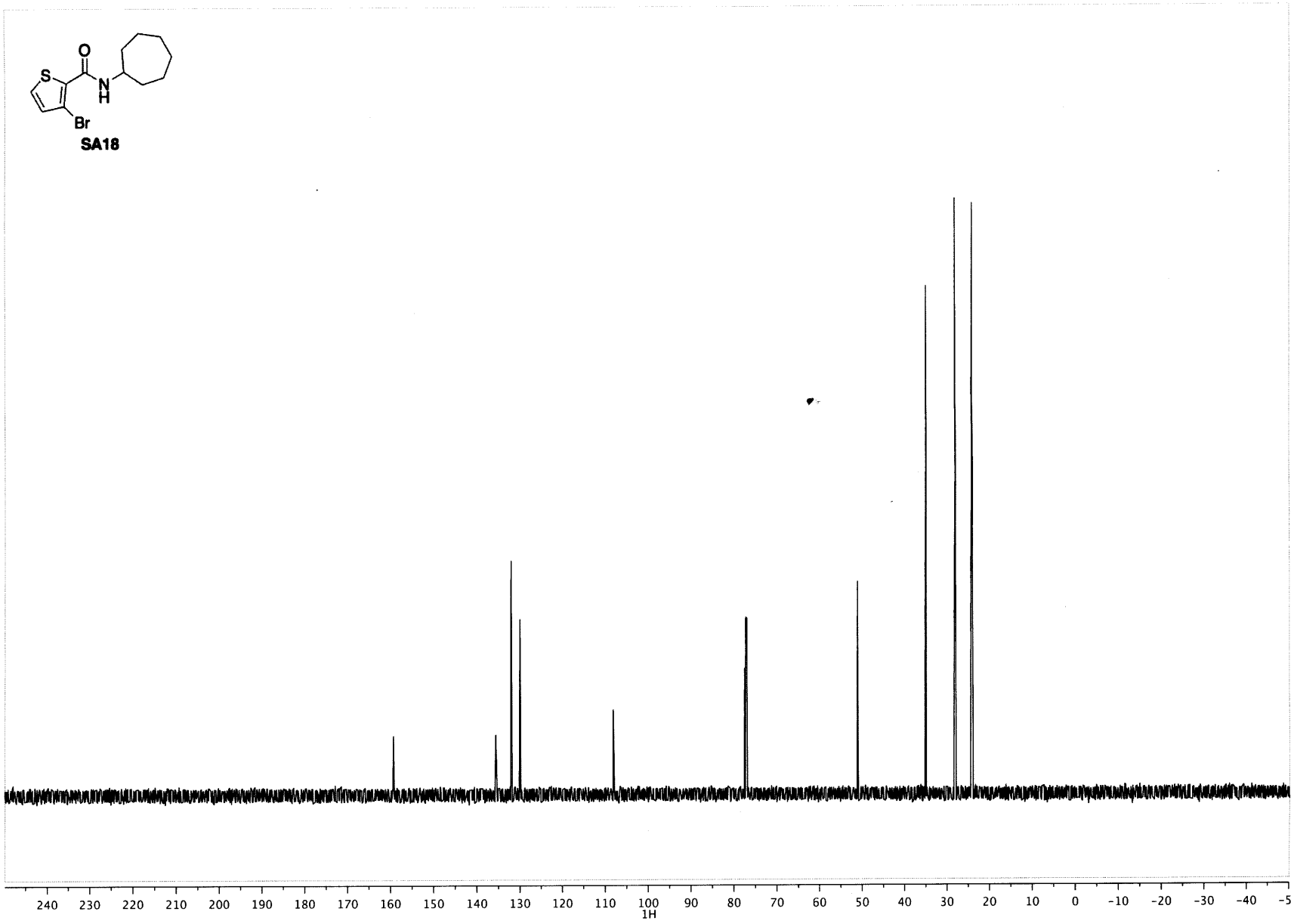
F
O
N
H
SA16
2.00
1.04
1.00
1.02
1.08
2.12
10.57
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H

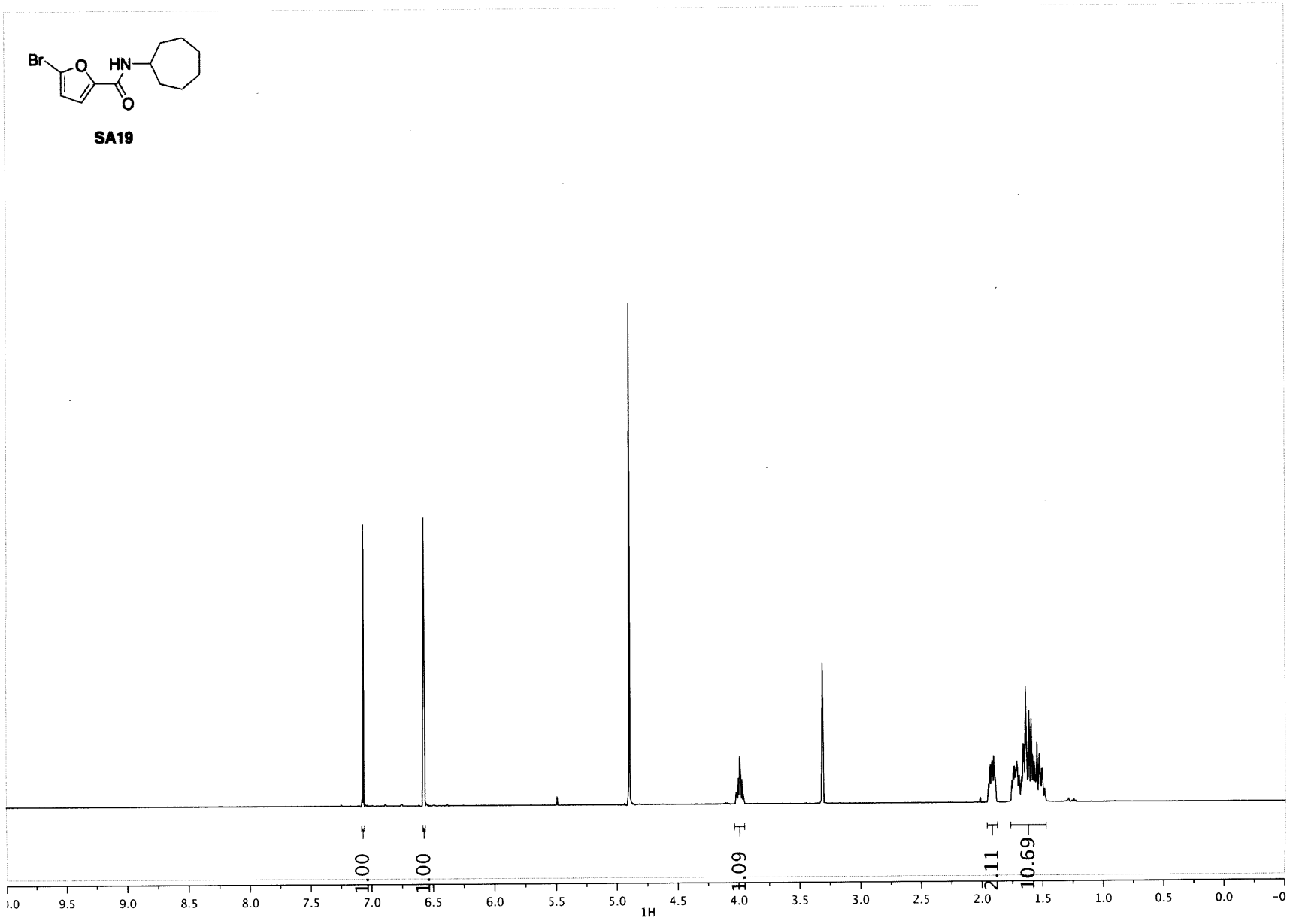

F
O
N
H
SA16
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

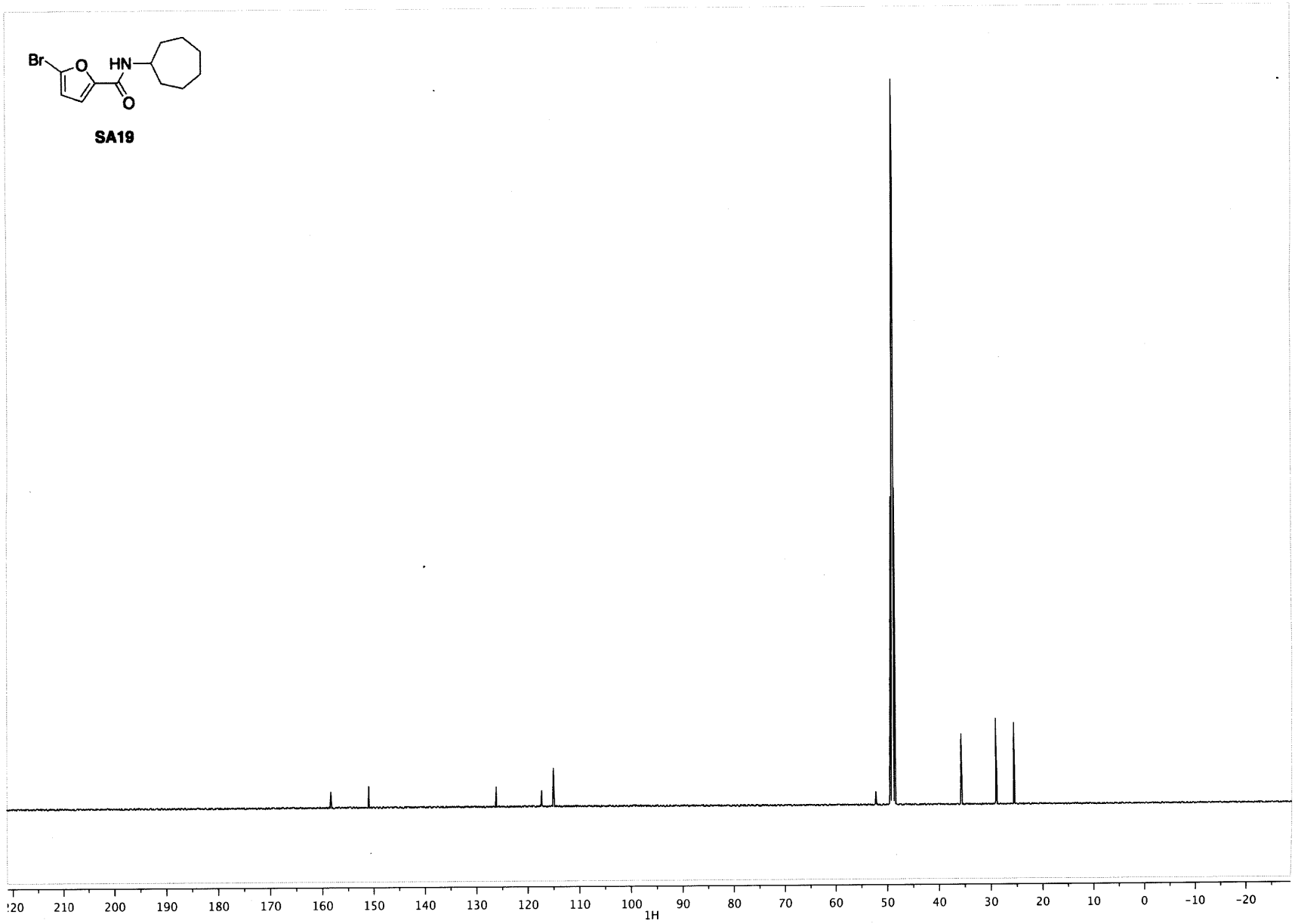
Br
O
N
H
Br
SA17
2.12
1.00
1.06
1.19
2.31
1.56
1H

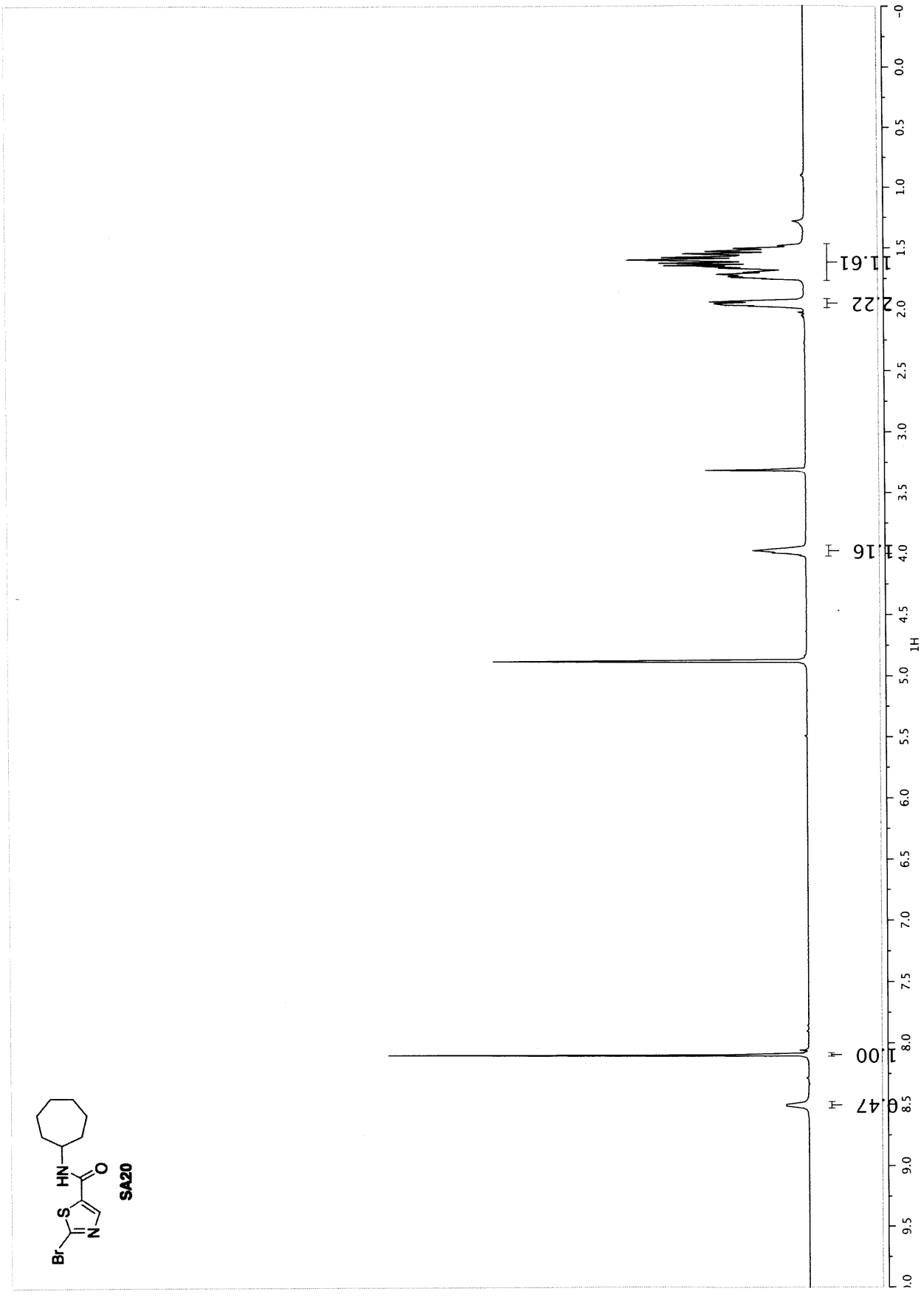

Br
O
N
H
Br
SA17
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

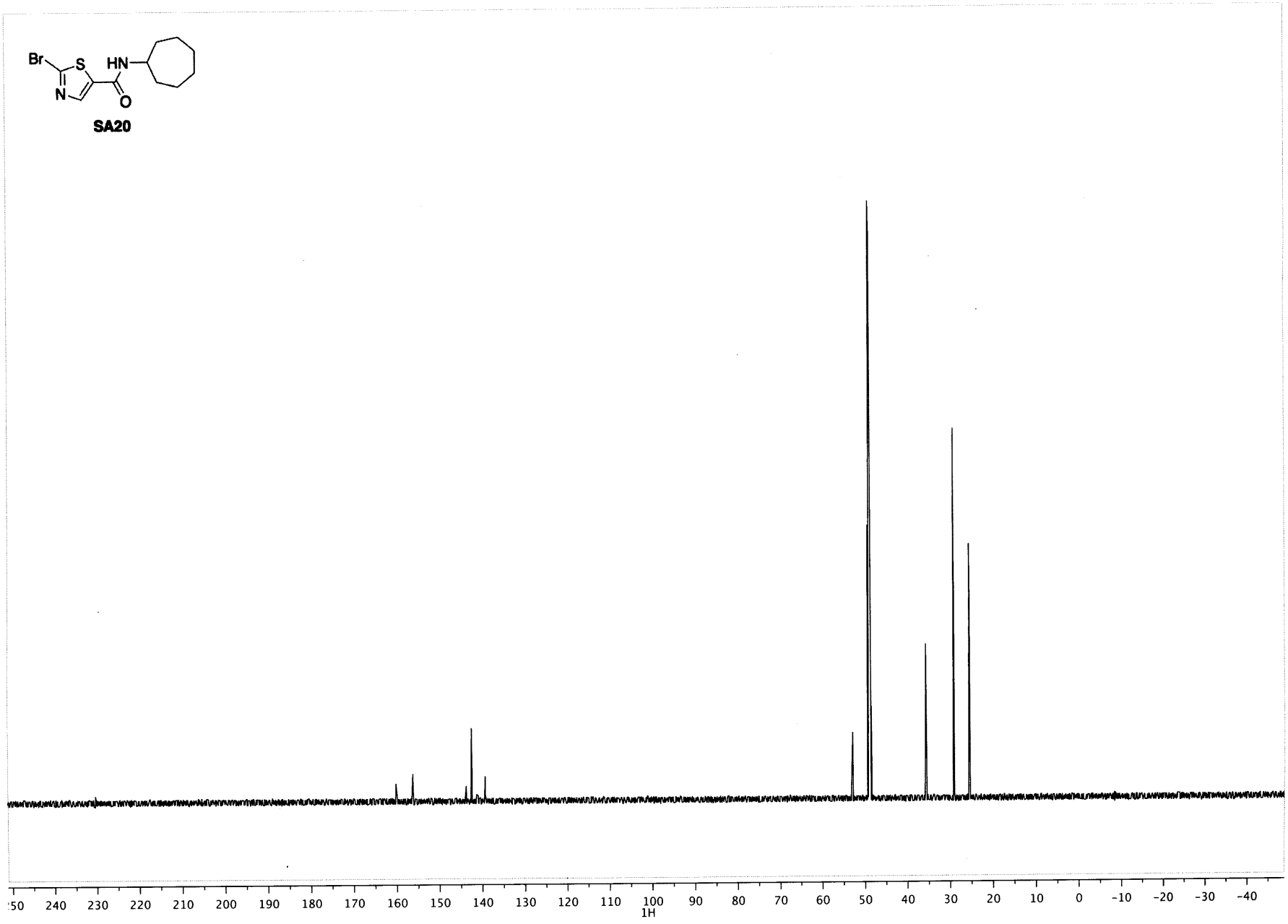

1.32
2.24
1.12
1.17
0.84
1.00
1H
SA18

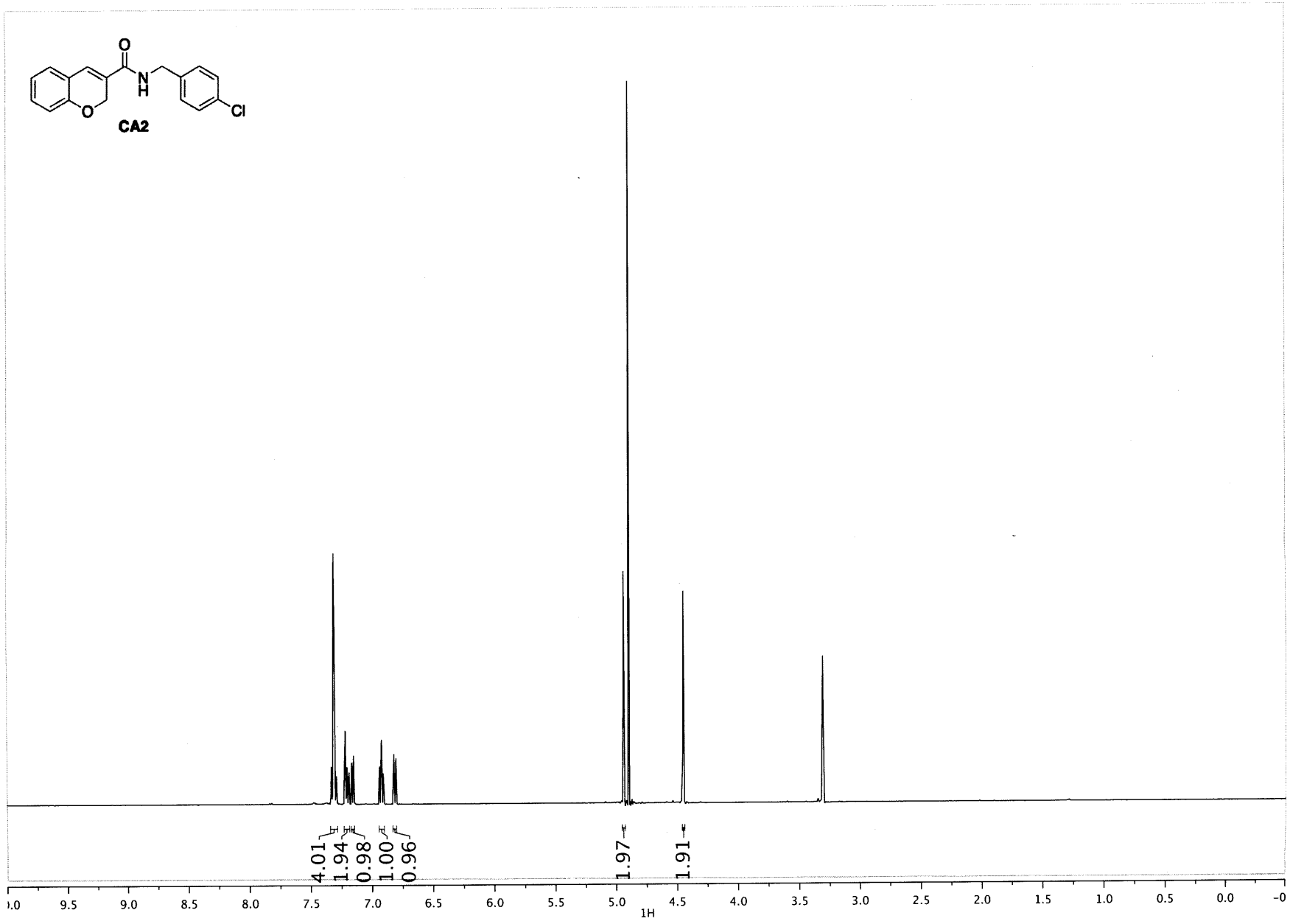

O
S
N
H
Br
SA18
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

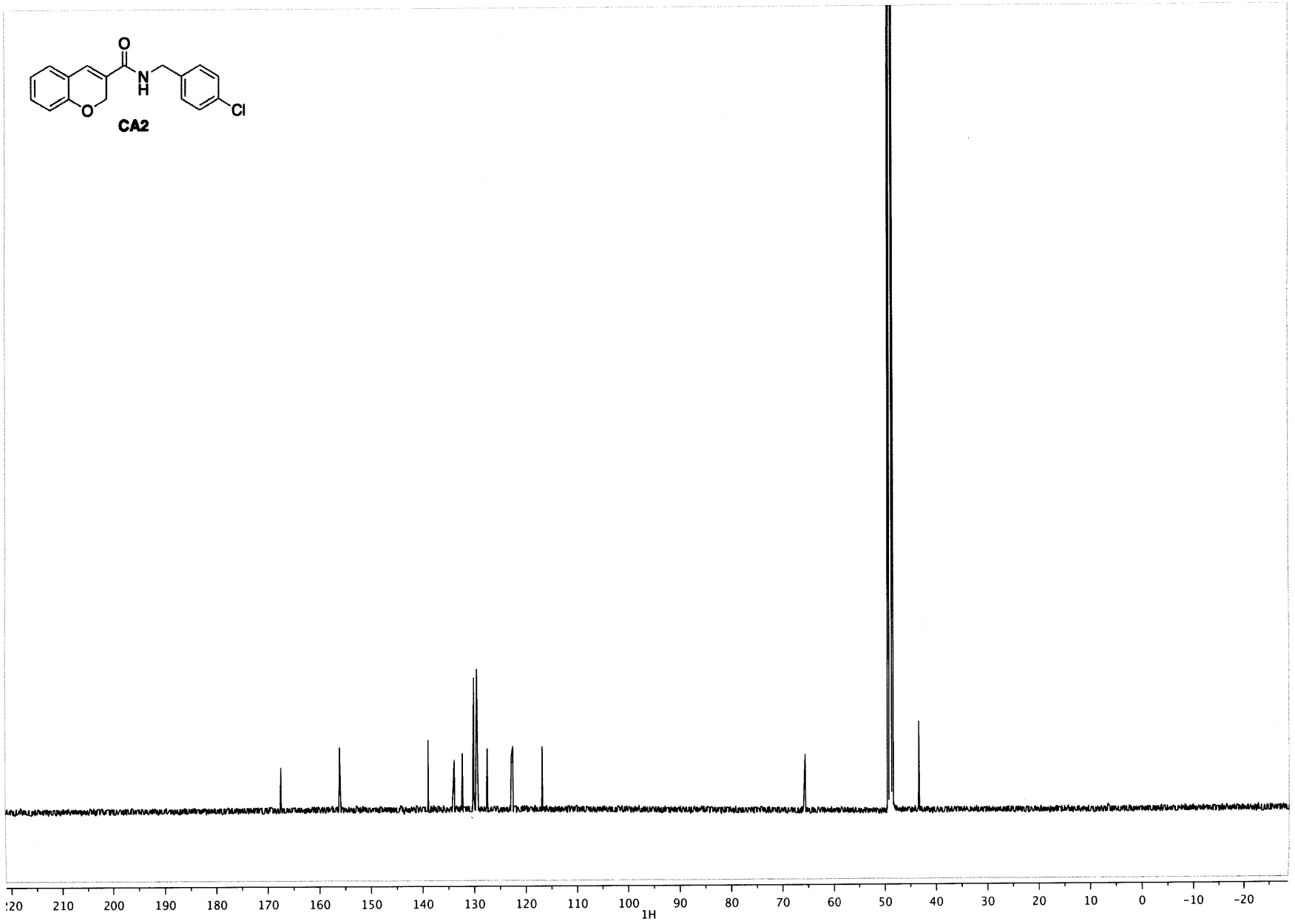

Br
O
HN
O
SA19
1.00
1.00
1.09
2.11
10.69
1H

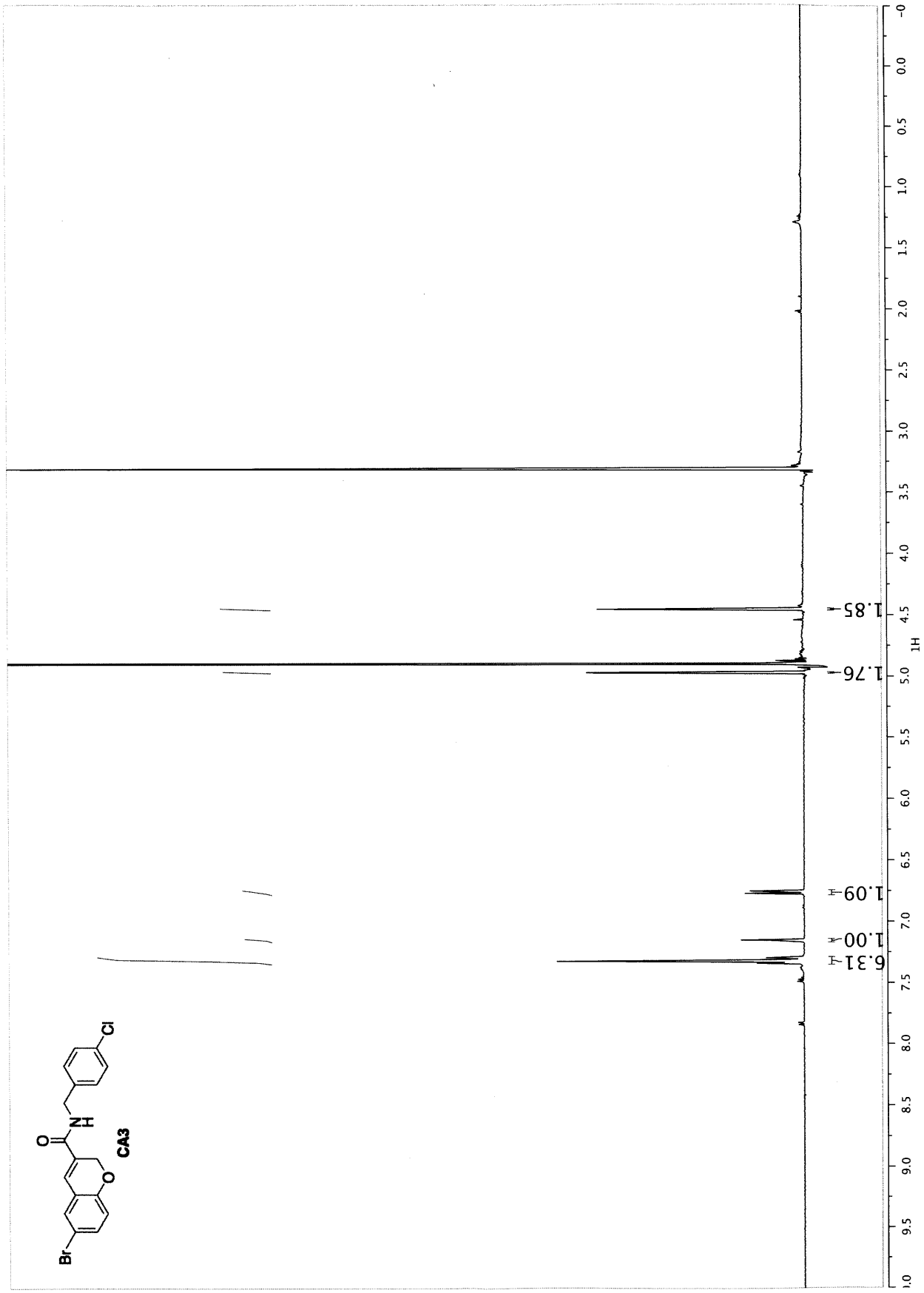

Br
O
HN
O
SA19
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
1H

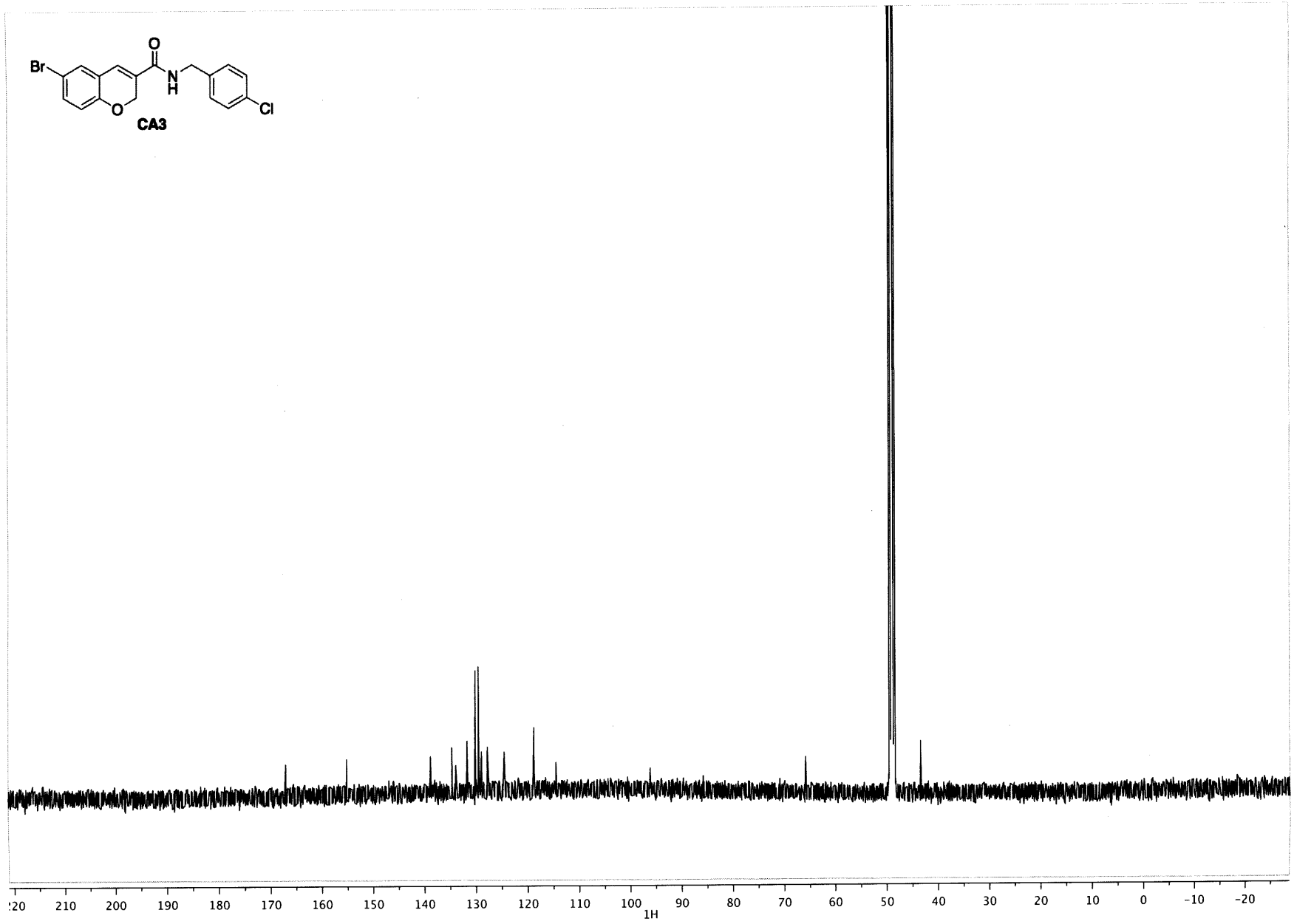

SA20
0.47
1.00
1.16
2.22
11.61
1H


Br
S
HN
N
O
SA20
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H

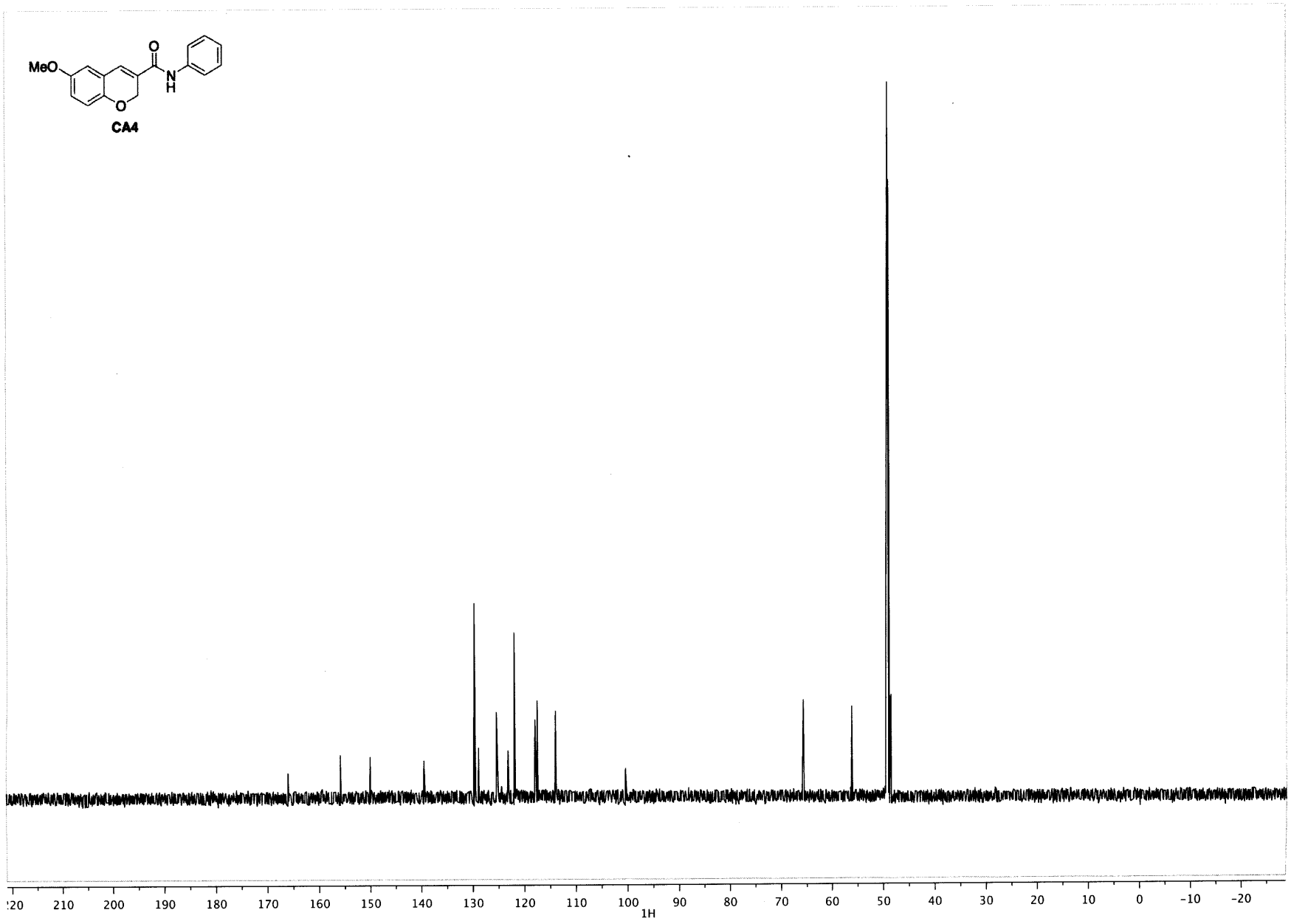

O
N
H
O
Cl
CA2
4.01
1.94
0.98
1.00
0.96
1.97
1.91
1H

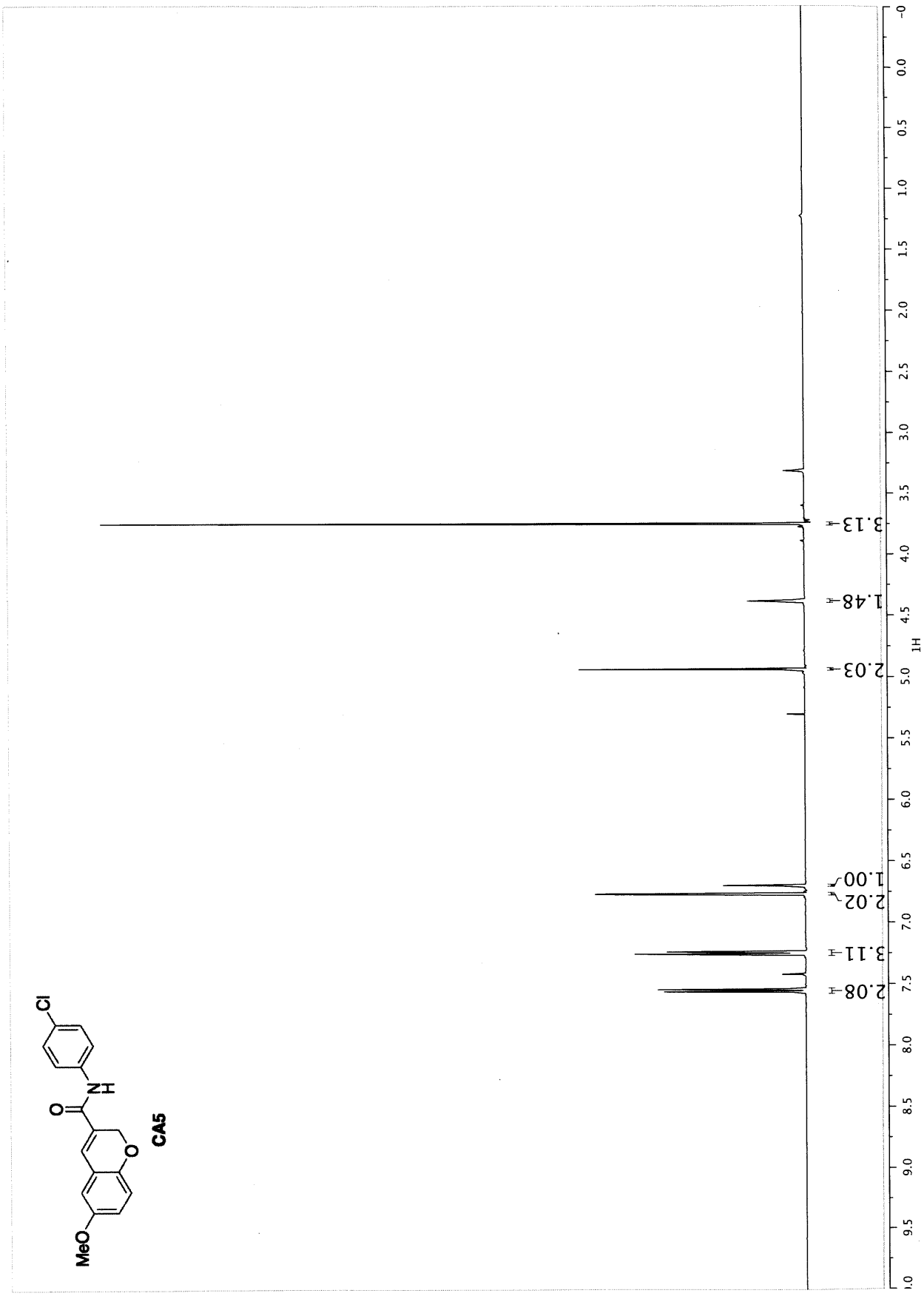

O
N
H
O
Cl
CA2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

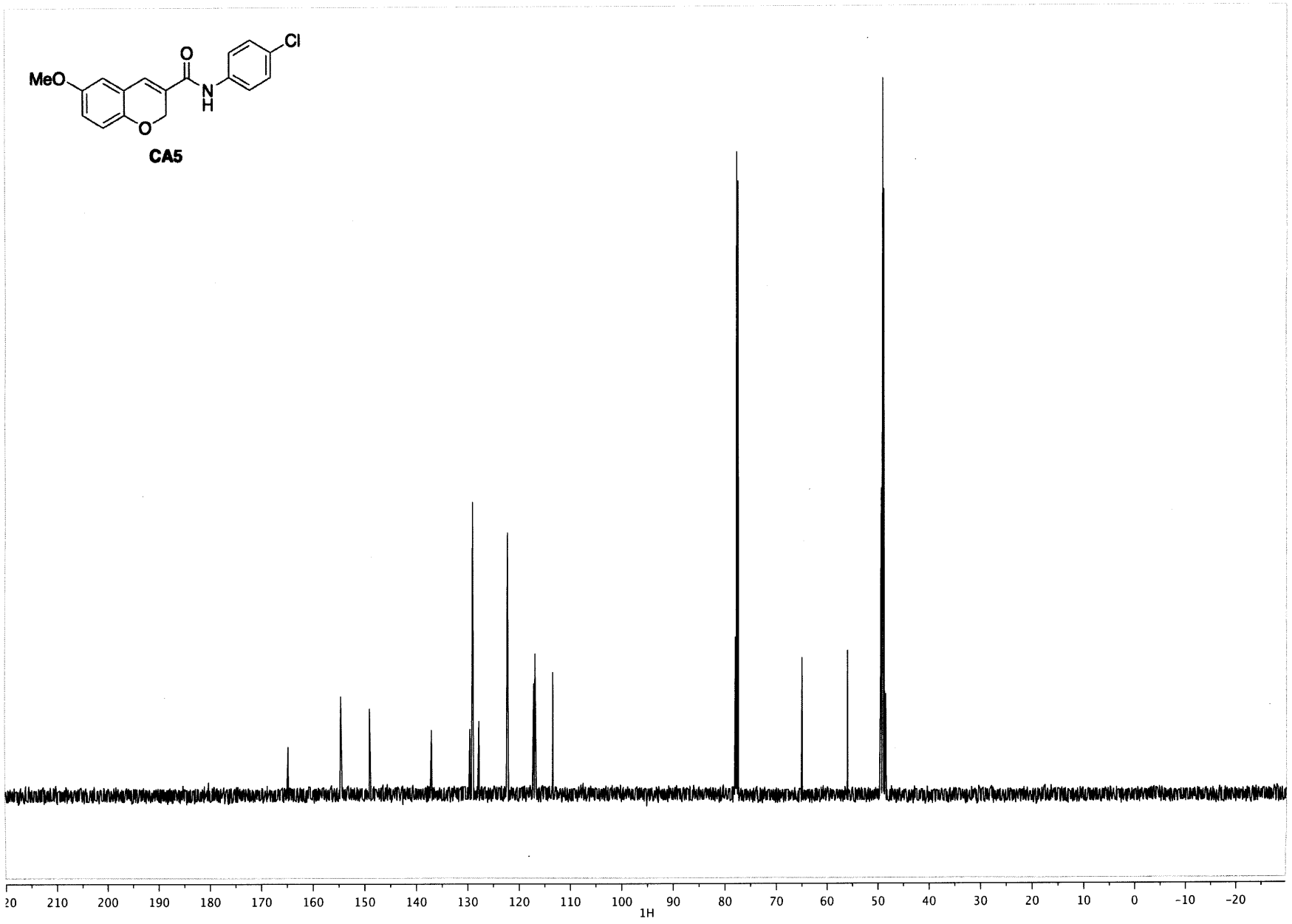

1.85
1.76
1.09
1.00
6.31
1H
CA3
O
N
H
O
Cl
Br


Br
O
N
H
O
Cl
CA3
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
1H

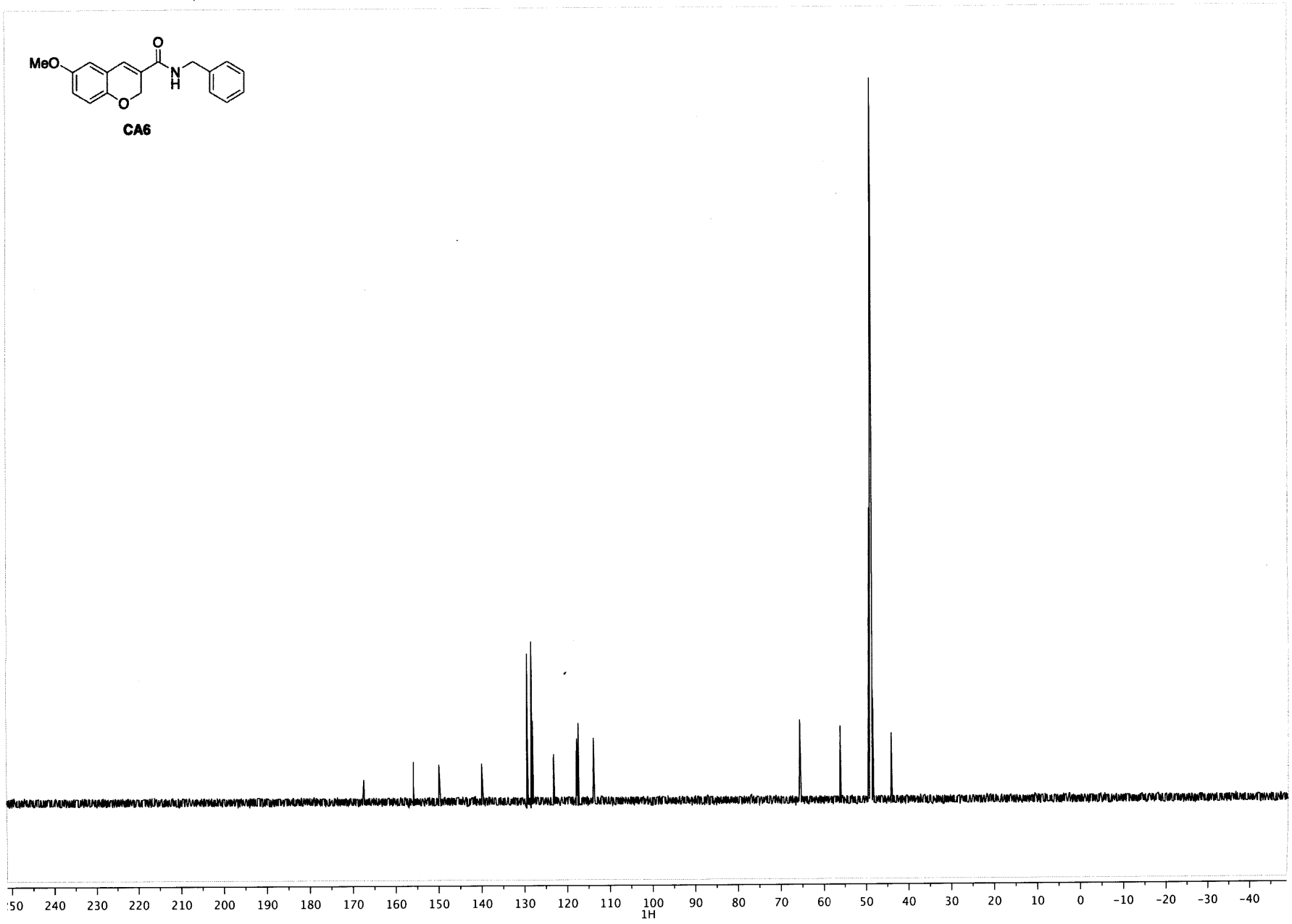
MeO
O
N
H
O
CA4
1.97
3.03
1.00
2.99
2.02
2.99
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


MeO
O
N
H
O
CA4
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
1H

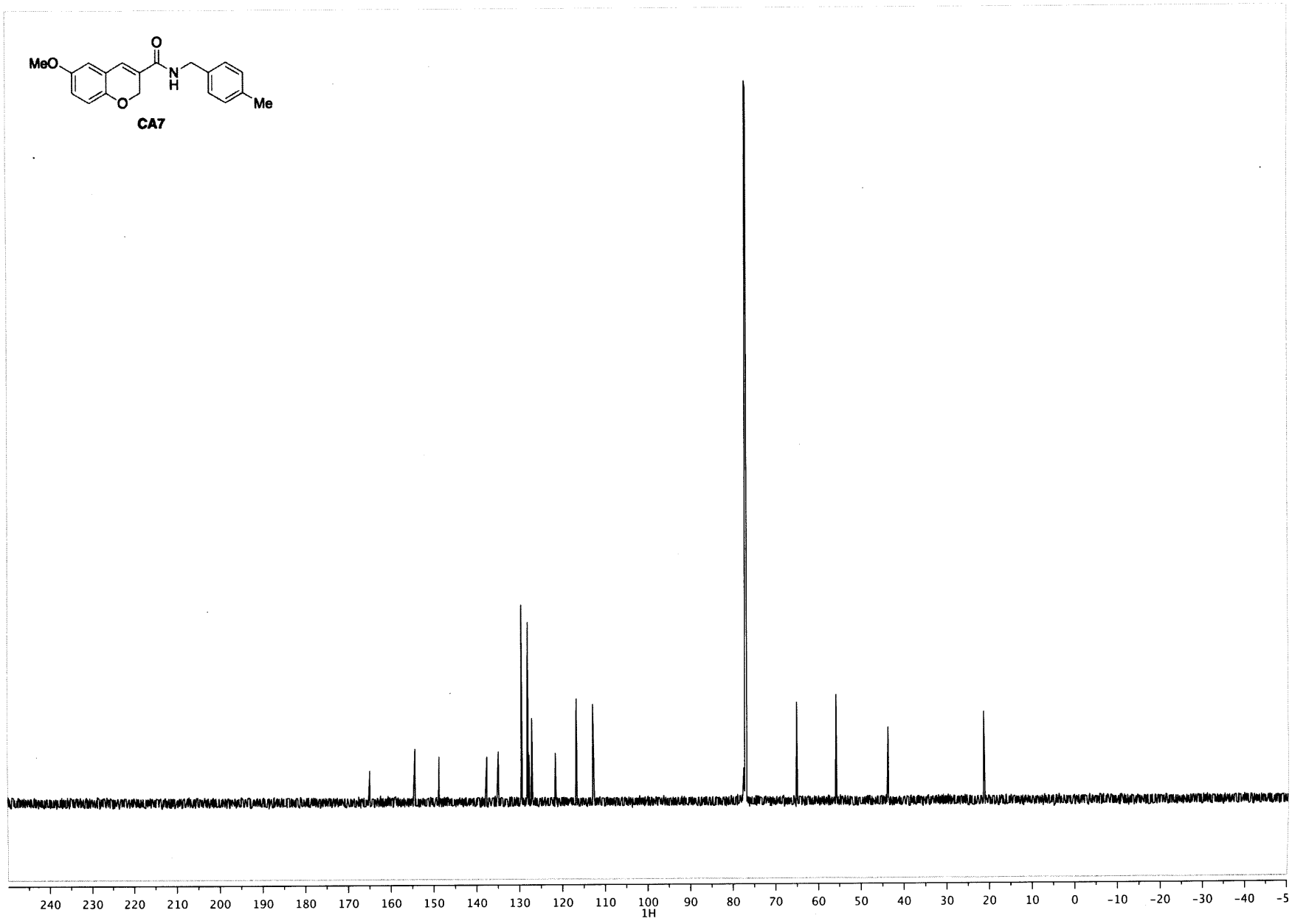

Cl
N
H
O
O
MeO
CA5
3.13
1.48
2.03
1.00
2.02
3.11
2.08
1H


MeO
O
N
H
Cl
O
CA5
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
1H

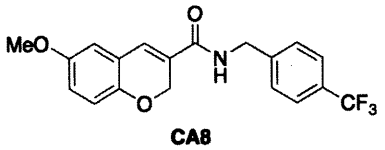
MeO
O
N
H
O
CA6
4.21
1.10
1.00
3.21
2.15
2.07
3.10
1H


MeO
O
N
H
O
CA6
50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H

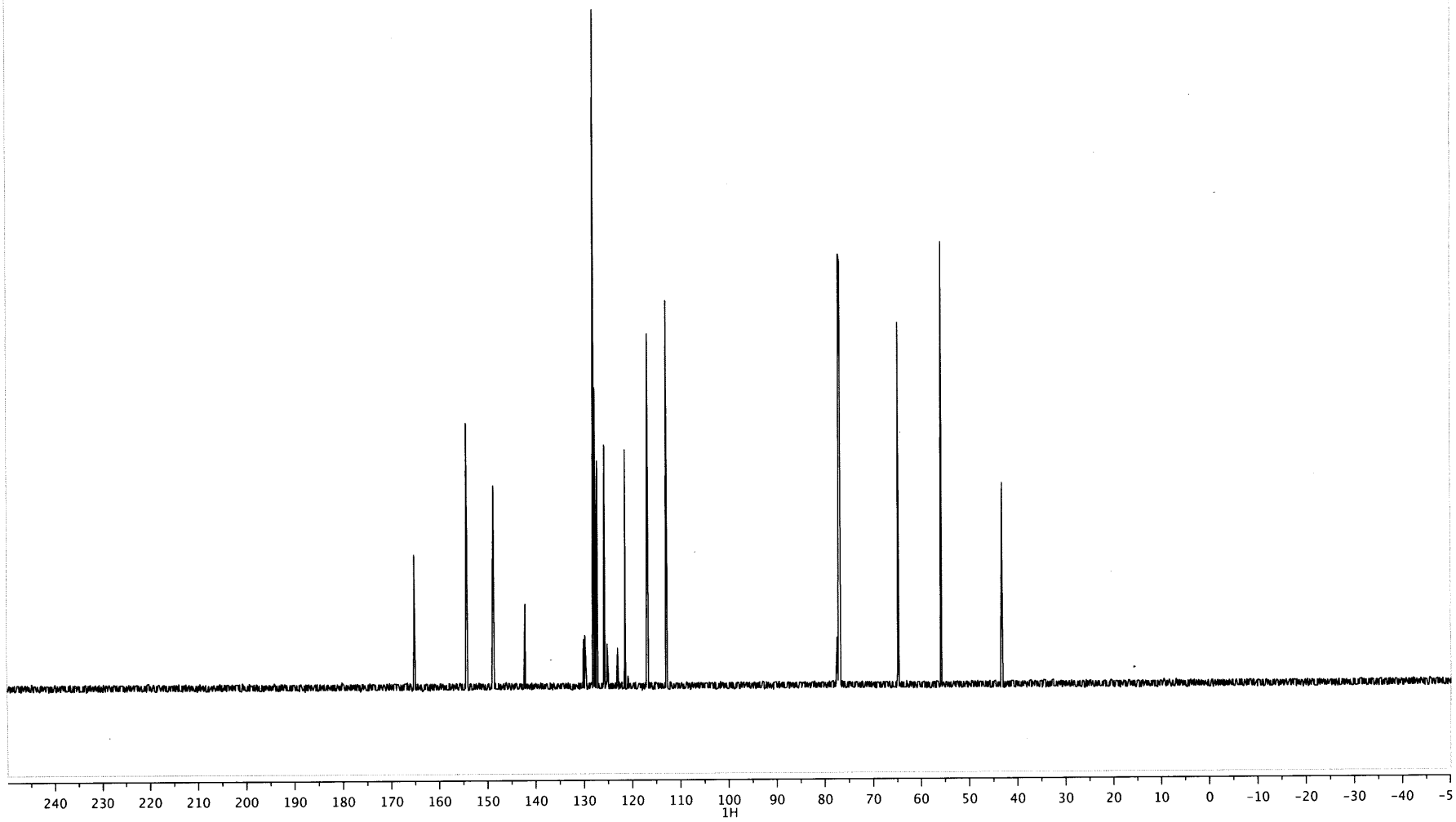
MeO
O
N
H
Me
O
CA7
2.31
2.22
1.00
2.11
1.02
0.86
2.09
2.10
3.22
3.12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
1H

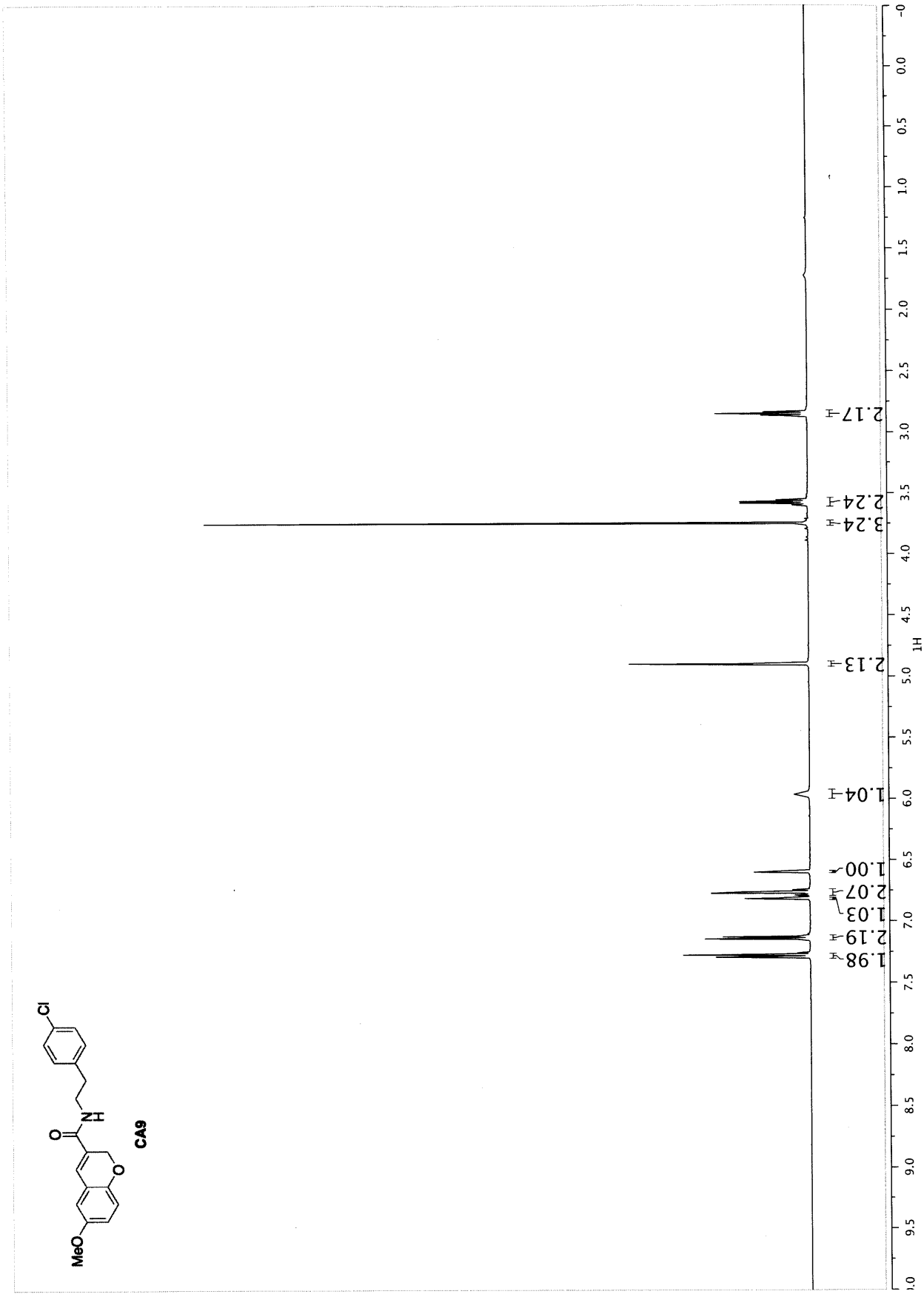

MeO
O
N
H
O
Me
CA7
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

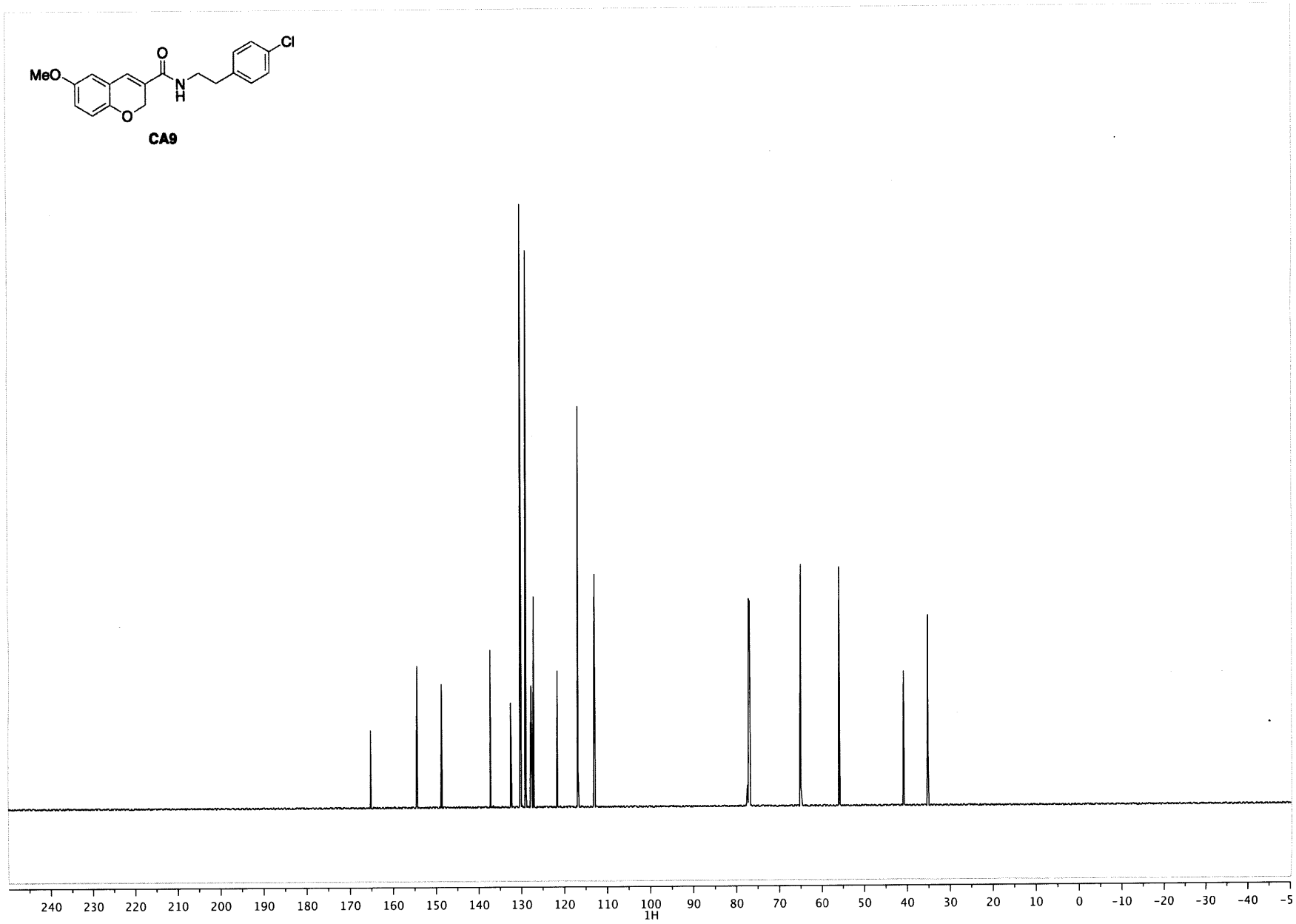
MeO
O
N
H
O
CF3
CA8
2.13
2.11
1.00
2.15
1.05
1.01
2.07
2.09
3.16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H


MeO
O
N
H
O
CF3

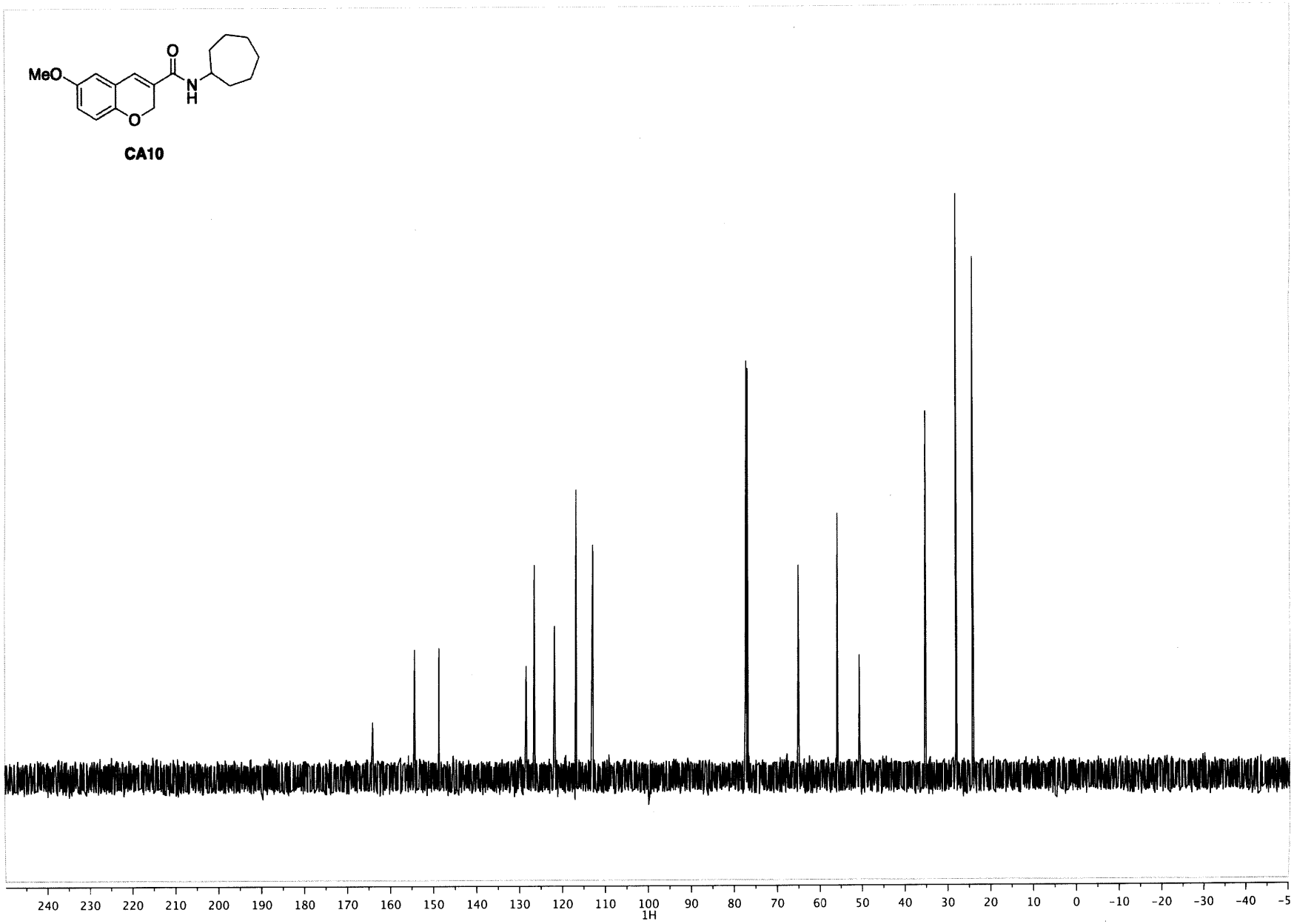
CA8

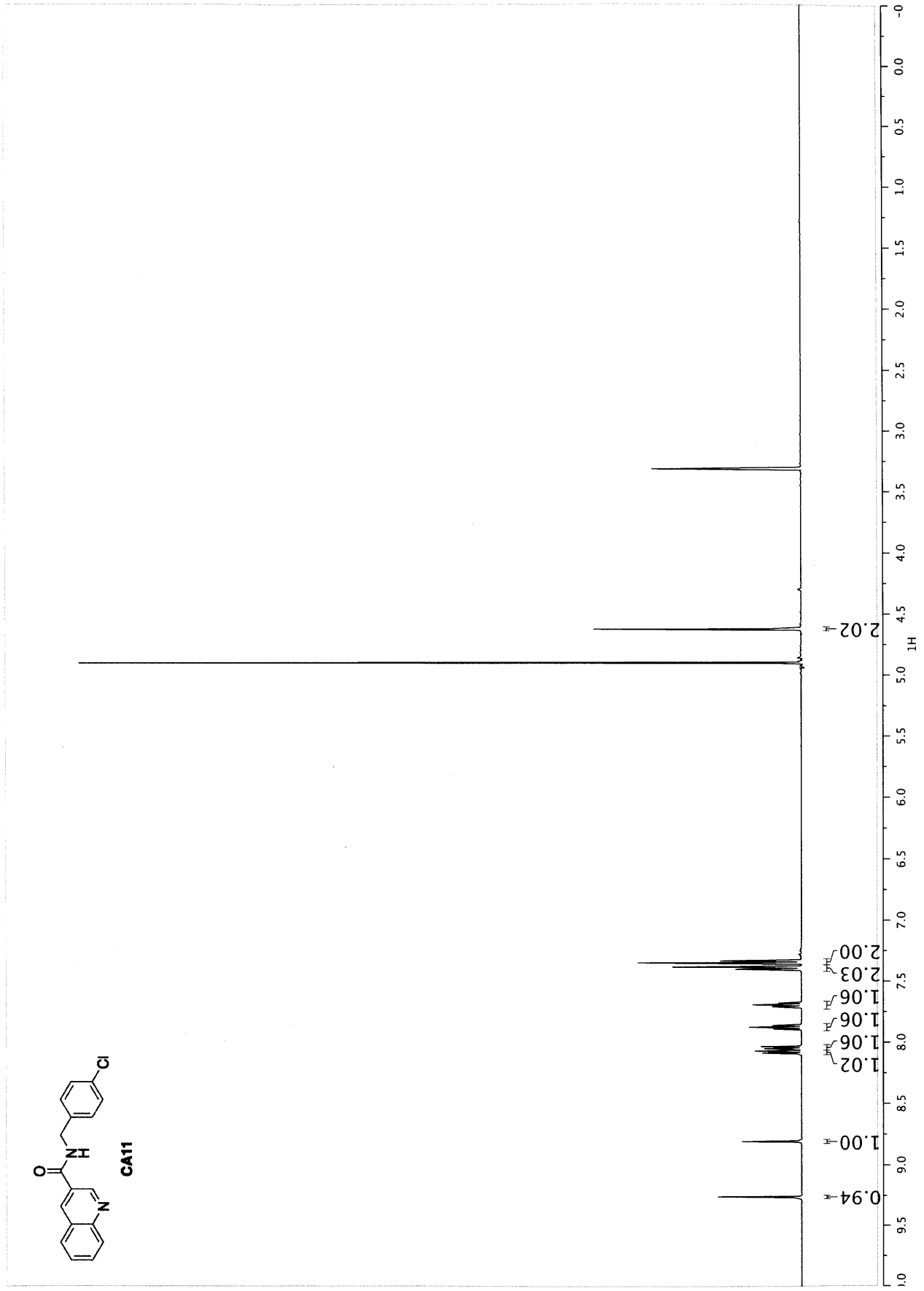

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

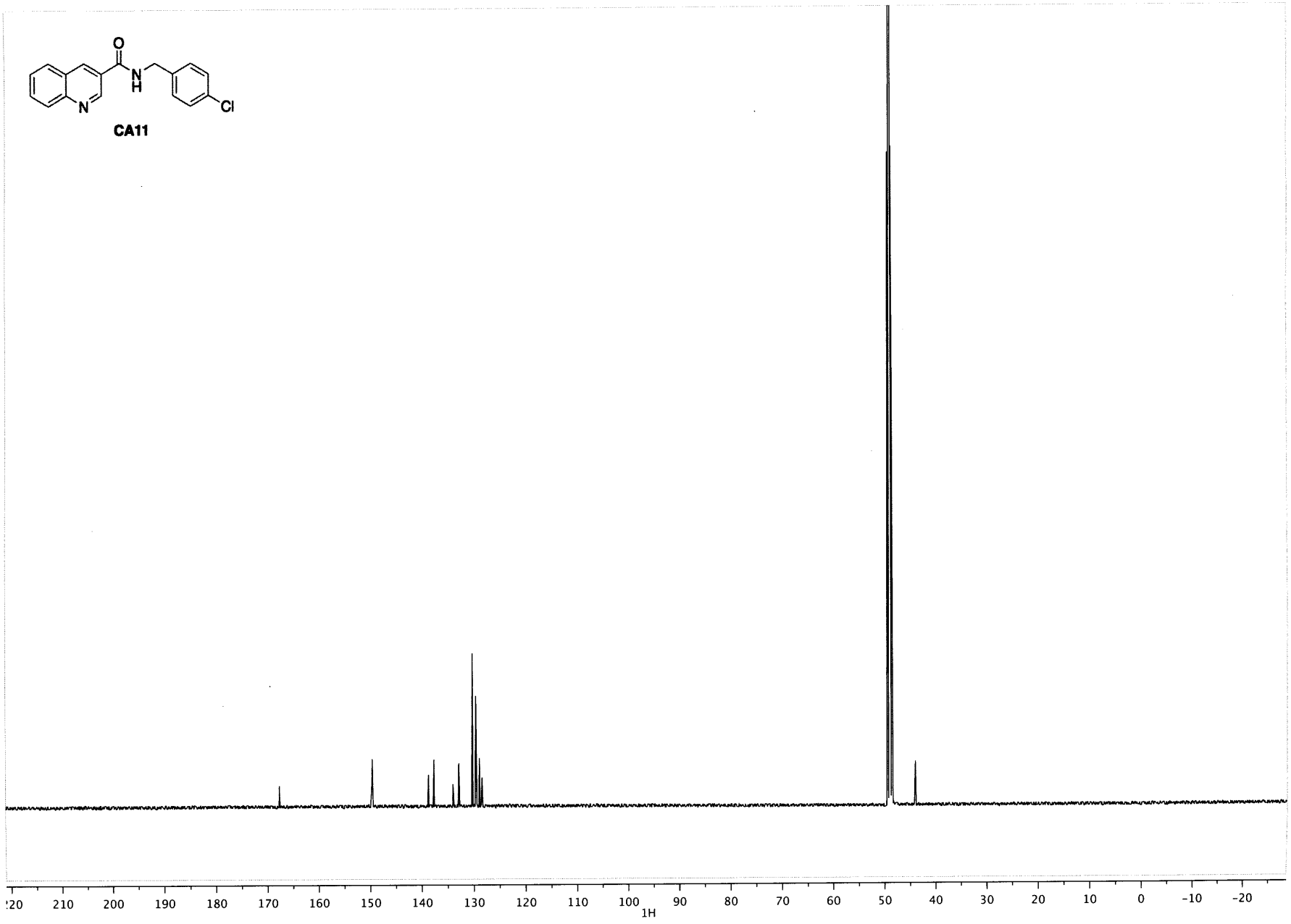

Cl
NH
O
O
MeO
CA9
1.98
2.19
1.03
2.07
1.00
1.04
2.13
3.24
2.24
2.17
1H

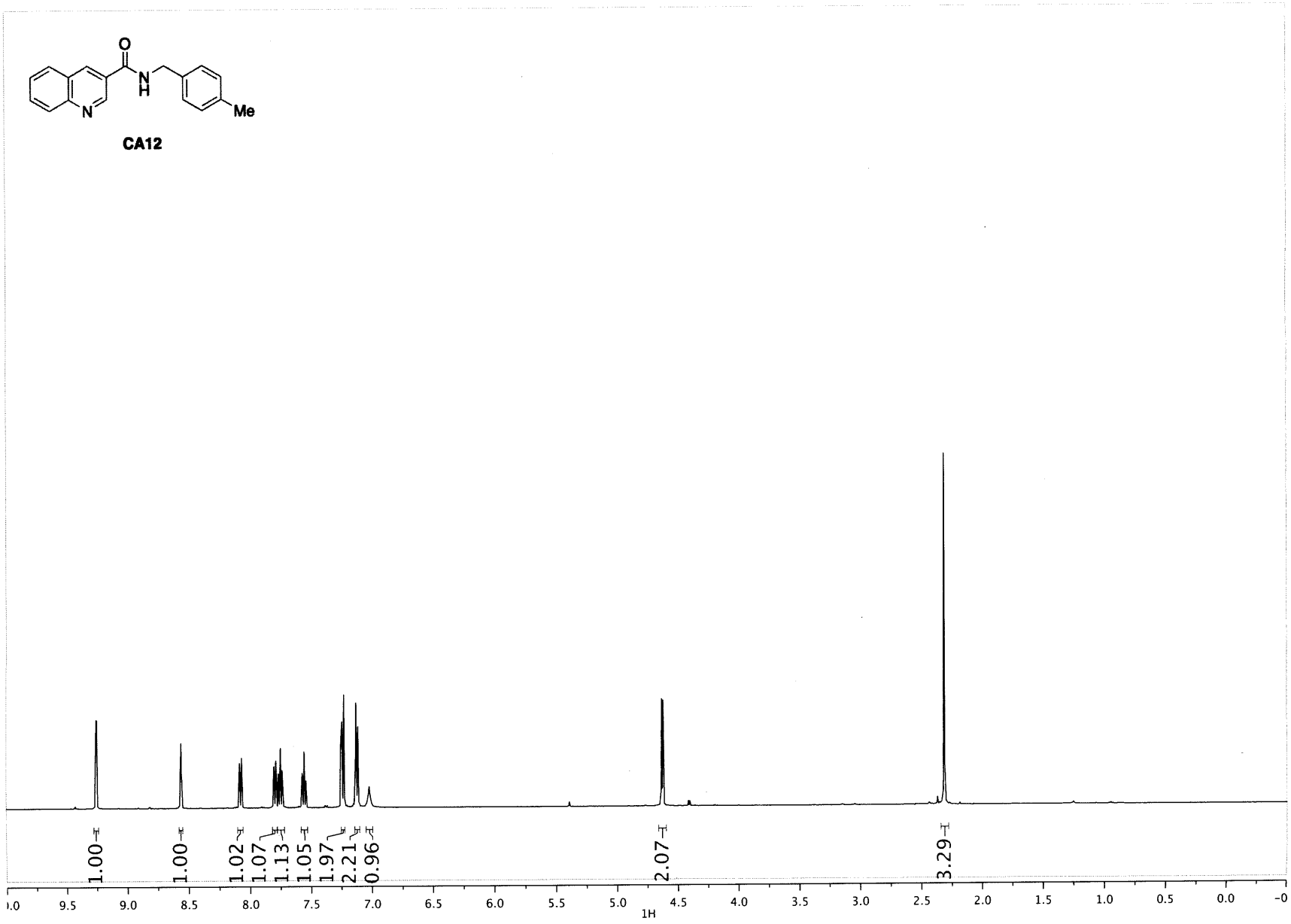

MeO
O
N
H
O
Cl
CA9
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

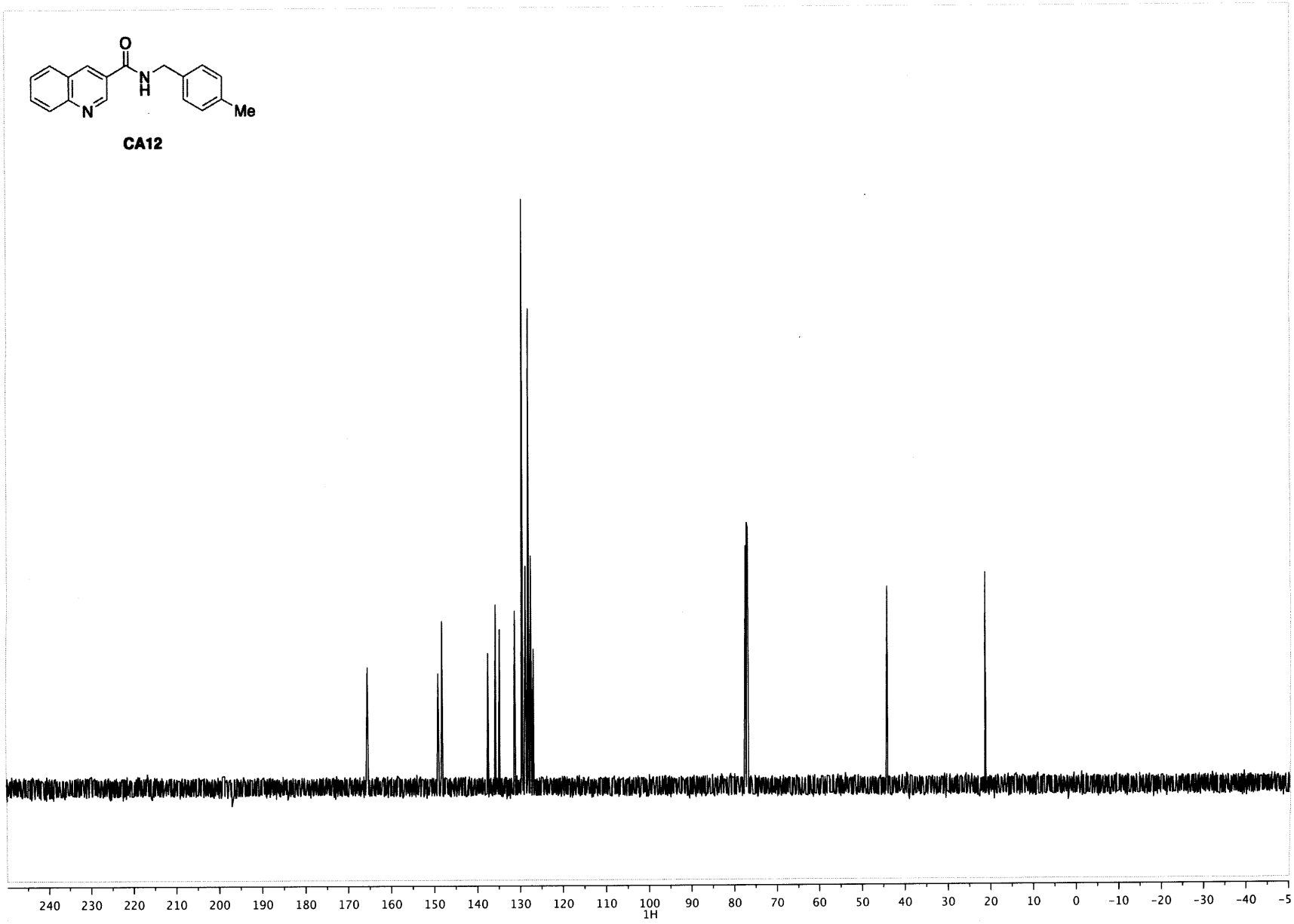
MeO
O
N
H
O
CA10
1.05
2.12
1.00
0.68
2.05
1.12
3.24
2.17
1.51
1H

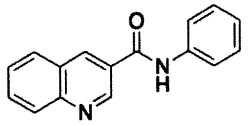

MeO
O
N
H
O
CA10
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H


CA11
0.94
1.00
1.02
1.06
1.06
1.06
2.03
2.00
2.02
1H

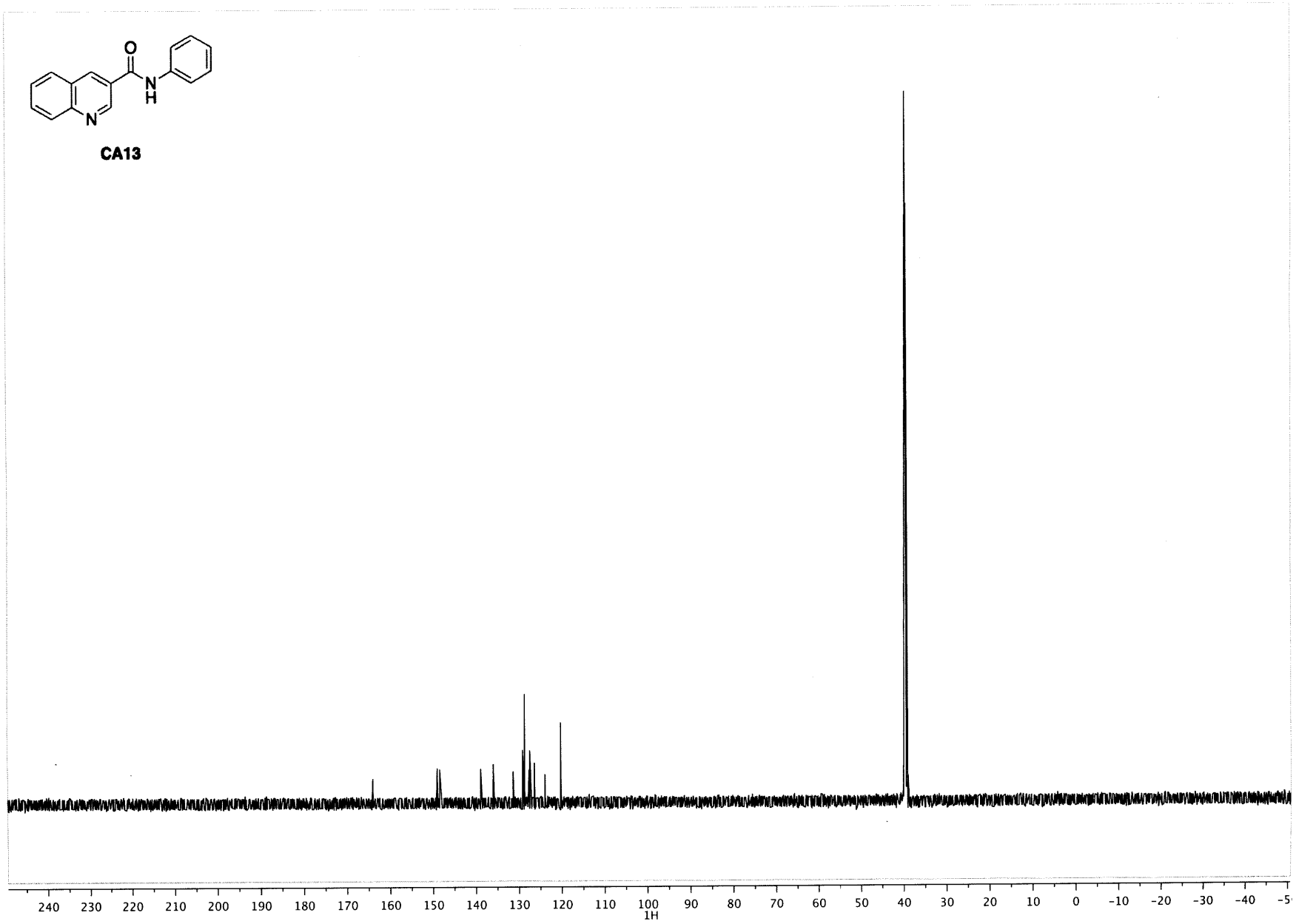

O
N
H
N
Cl
CA11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
1H

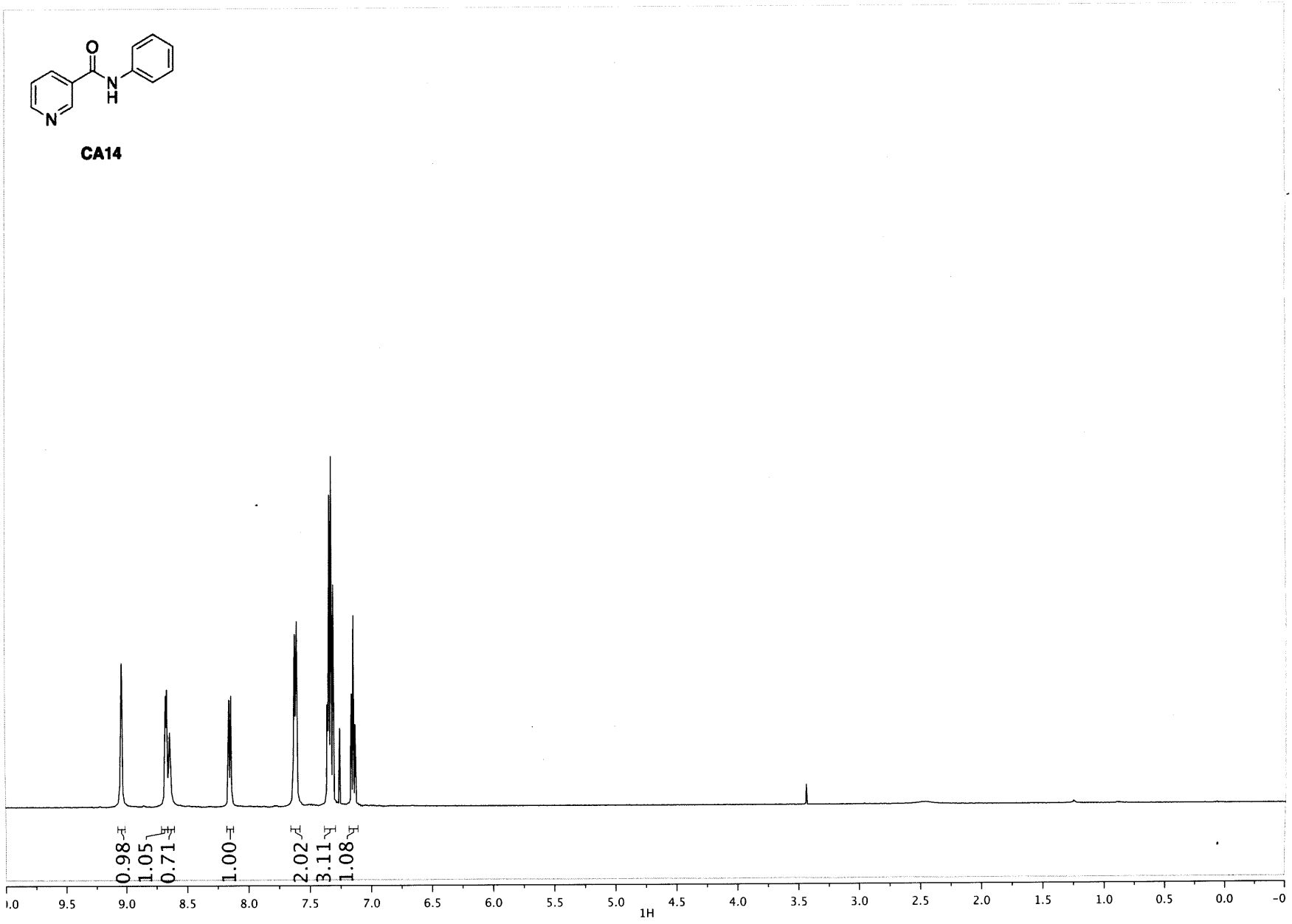

O
N
H
N
Me
CA12
1.00
1.00
1.02
1.07
1.13
1.05
1.97
2.21
0.96
2.07
3.29
1H

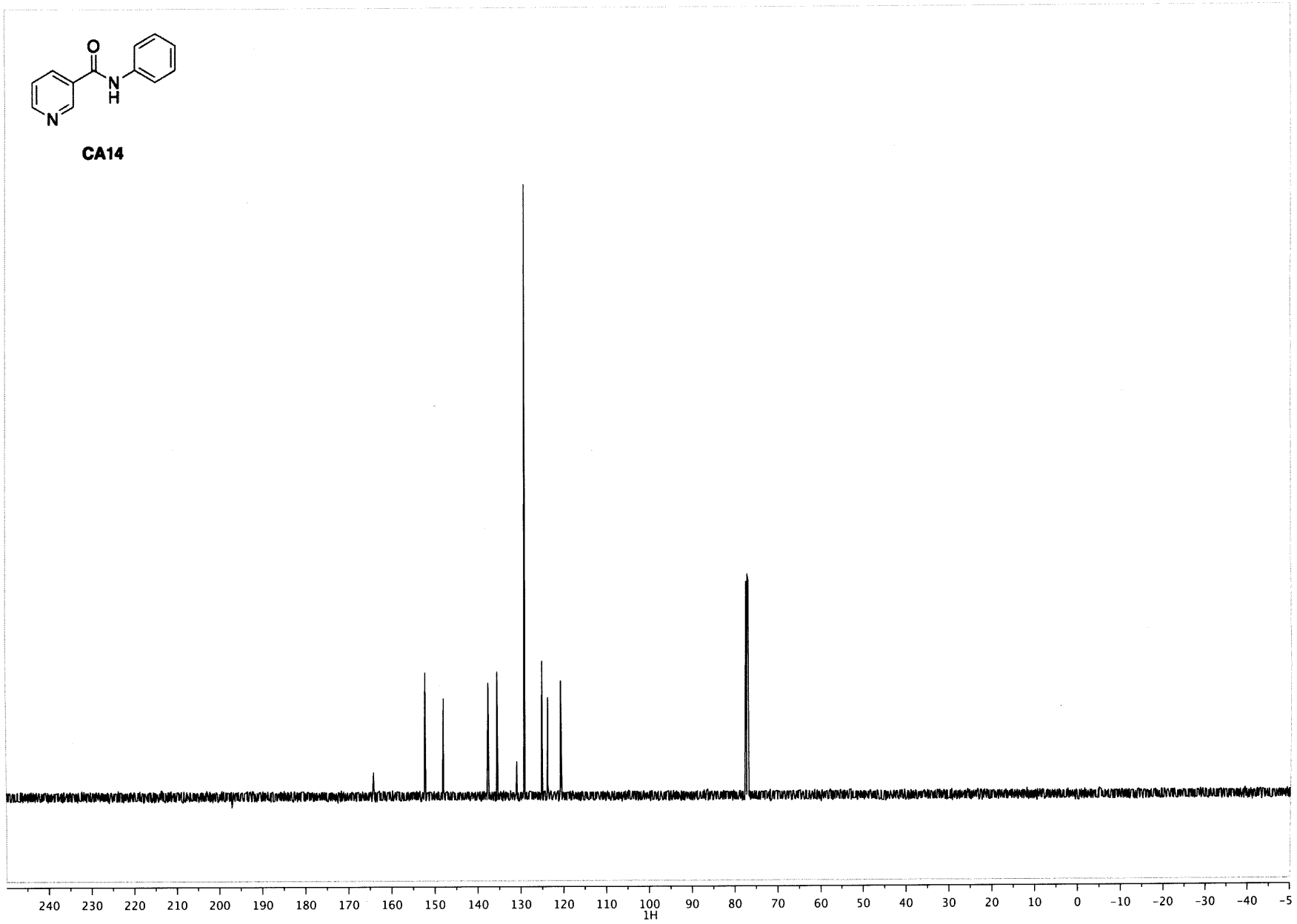

O
N
H
N
Me
CA12
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H

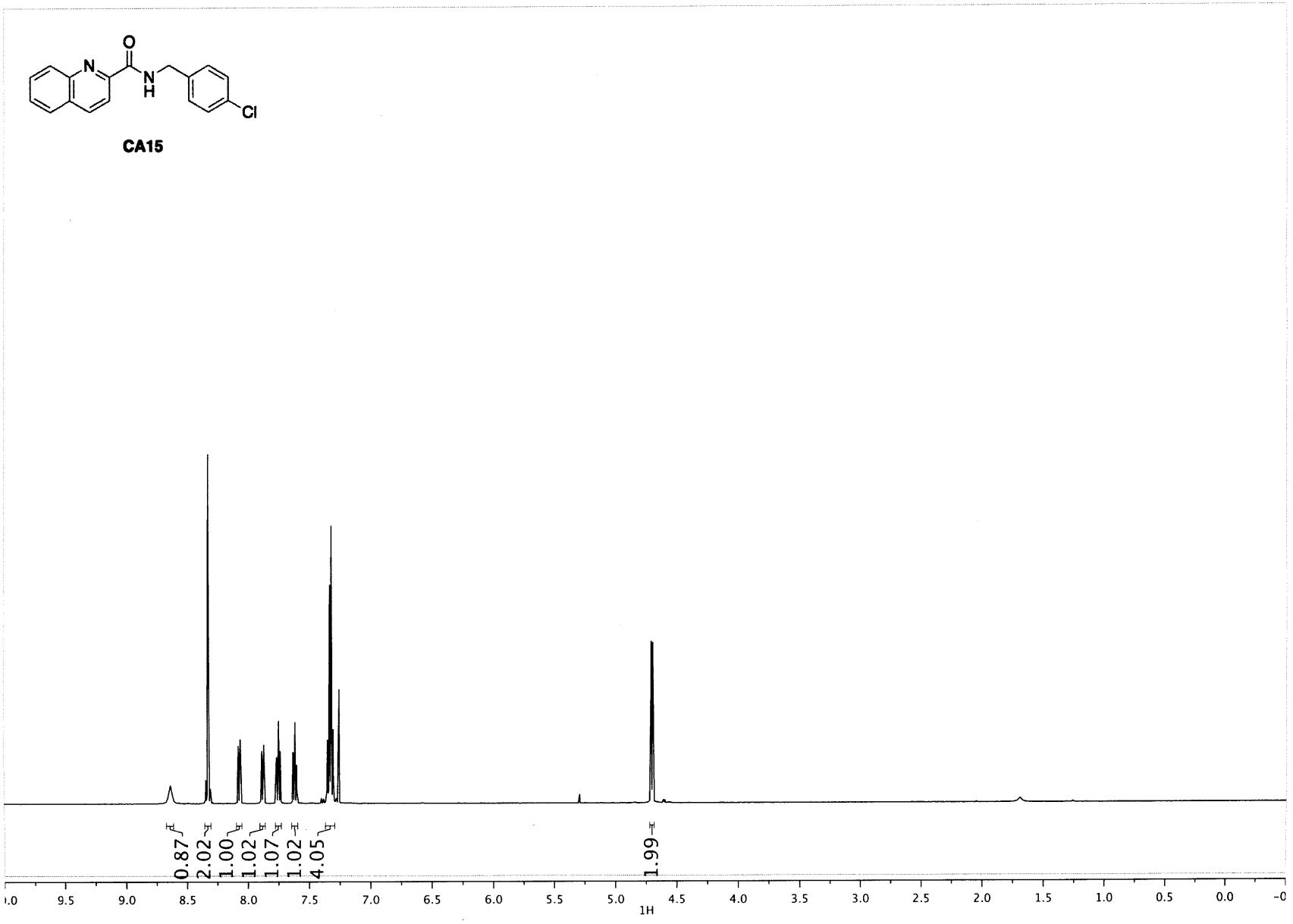


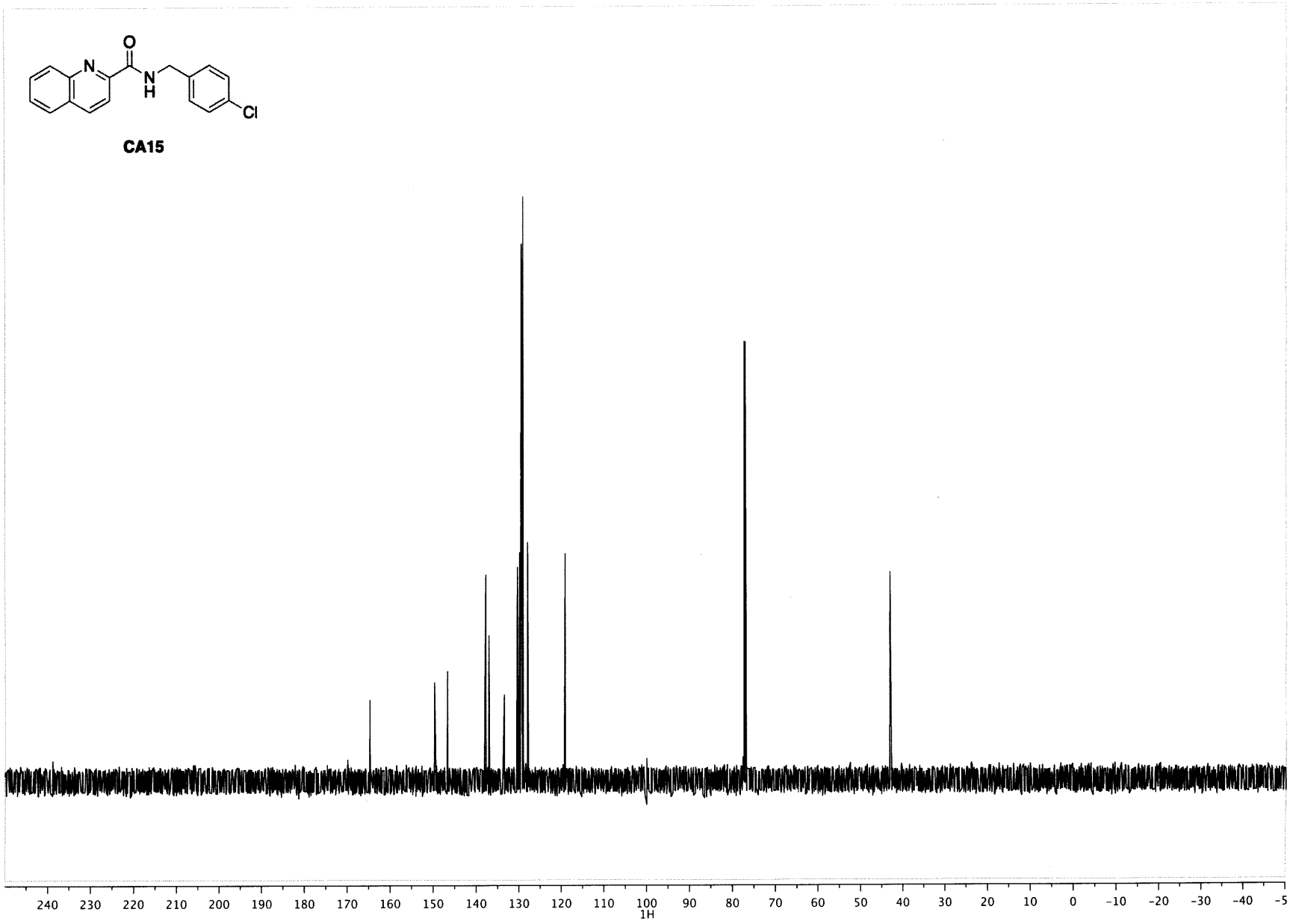
CA13


O
N
H
N
CA13
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
1H


O
N
H
N
CA14
0.98
1.05
0.71
1.00
2.02
3.11
1.08
1H


O
N
H
N
CA14
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H


O
N
H
Cl
CA15
0.87
2.02
1.00
1.02
1.07
1.02
4.05
1.99
1H


O
N
H
N
Cl
CA15
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
1H