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Beyond Conventional Routes: Mechanochemical Transformations in Organic Synthesis for Sustainable Chemistry

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(Catone)

Summary

This thesis is aimed at providing a novel perspective about the contribution of mechanochemistry in the process chemistry's panorama. Leafing through the chapters of the present dissertation, one will delve into some information about historical background of organic chemistry and its interaction with this contemporary enabling technology and process sustainability. This will serve as the necessary background for introducing the course I navigated in assembling my thesis, which was directed towards the demonstration and subsequent integration of diverse molecular architectures and multi-step processes within mechanochemistry, with some recalls to industrial scalability.

The synthesis of indoles constituted the first step for building molecular complexity, while formamides, isocyanides and sulfonamides served as the direct nexus to process chemistry and sustainable synthetic plans. Lastly, the investigation of catalytic hydrogenation through ball milling paved the way to laboratory and potential industrial scale-up assessment.

1. Introduction

Amid widespread disinterest, mixed in the crowd, organic chemists quietly enjoy the process of creating, with their own hands, molecular architectures in an attempt to contribute to meeting the challenges posed by modern science and technology.

Obsessed with the improvement of chemical synthesis, they keep gaining ground on nature, daily fighting inch by inch, with the ultimate goal of disclosing and enabling practical solutions to the main issues that afflict society. There is everything in between, from enhancing the efficiency of half-forgotten reactions to increasing the sustainability of the vital industrial productions. It is, therefore, no surprise that the relentless activity in the laboratories worldwide combines classical chemical knowledge with the new paradigm of green chemistry. The impacts, especially on pharmaceutical and medicinal chemistry, more receptive to innovation, are starting to show.

The empirical character of operations that shines through the endless succession of dissolutions, transformations, purifications, distillations, crystallizations and analyses must not be misleading. It is the extreme difficulty of mastering the art of constructing substances that requires the researcher to let himself be led by a subtle mix of sound knowledge and unbound intuition. Organic chemistry is one of the spearheads of hard sciences and his followers cannot but believe in the famous Galileo Galilei's statement from *Il Saggiatore* that "[The universe] … is written in mathematical language, and the letters are triangles, circles and other geometrical figures, without which means it is humanly

impossible to comprehend a single word" and in similar ones that came later. Beneath the surface of tangible reality, mathematics seems to rule undisputed and even the most naïve is aware of its astounding capability to express physical laws. However, the scenery changes rapidly as chemistry is approached and the existence itself of the broad interdisciplinary areas of physical chemistry and chemical physics is an important sign of the increasing complexity. Such is the degree of complexity of chemical systems, not to mention biochemical and biological ones, that rigorous equations leave room to equally rigorous empiricism, always anchored to science by the same, unifying thread.

In fact, it is experimental evidence to pave the way to the advance of knowledge. Albeit with all the issues this involves, chemistry is unequivocally committed to the experimental investigation of the processes governing the transformation of matter and organic chemistry occupies a position of privilege in this respect. Mistress and maid at the same time, it permeates many diverse research areas including material science and chemical engineering.

The scope of organic chemists goes beyond the *design* of new, possibly intricate, reactions with exoteric substrates. It addresses the limitations of current methods and tackle reactivity issues. Sustainability is inherently part of the challenge, putting pressure on the opening of novel routes to fine chemicals and the development of enabling technologies.

1.1. *Historical Background: The Birth of Organic Chemistry*

Although many recipes and practices can be dated back at least to Paracelsus and his alchemical knowledge,[1] the birth of organic chemistry is usually credited to Berzelius, who identified it, in 1807, with the study of compounds derived from living organisms.[2] The synthesis of urea using inorganic reagents conducted by Wöhler made such definition obsolete quite soon.[3] He correctly claimed that "the philosophy of chemistry will draw the conclusion from this work that the production of all organic materials in our laboratories must be considered not only likely but certain, in as much as they no longer belong to the organism. […] Of course, we do not yet know the ways to reach this goal, because we do not know the precursors from which these compounds are generated, but we shall get to know them". It ushered organic chemistry in the multifaceted era of the scientific inquiry into carbon-based compounds, according to the definition proposed by Kekulé in 1861.[4]

Organic chemistry flourished during the so-called Second Industrial Revolution, which covered the late XIX century and early XX century and resulted in the complete metamorphosis of manufacturing and automation. Marked by the achievements of visionary minds like those of James Watt, Henry Ford, and Thomas Edison, the period eventually witnessed a reshaping of industrial

production with consequence that are still under our eyes. With lights and shadows, organic chemistry relentlessly sailed through the unfolding currents of such period, always as an active participant, never as a mere spectator. Traditionally, the Kolbe's synthesis of acetic acid in 1847,[5] the Pasteur's discovery of the stereochemical forms of tartaric acid in 1849,[6] the Silliman's invention of the petroleum cracking process in 1855,[7] and Kekulé's first description of aromatic compounds in 1865 stand as the pioneering findings.[8] Further contributions include the Baeyer's discovery of indigo dye in 1865,[9] the van't Hoff and Le Bel's empirical exploration of chirality in 1873,[10] the Tsvet's development of chromatography in 1903,[11] and the Thomson's elucidation of the mass spectrometry principles in 1913.[12]

Collectively, the advances mentioned above marked a revolutionary period together with several others that also inspired the present thesis. For instance, the catalytic hydrogenation of organic compounds, established in 1863,[13] determined a significant step forward organic synthesis. Similarly, the Fischer's indole synthesis in 1883 addressed subsequent work on the preparation of heterocycles.[14] Along the same line, the discovery of sulfonamides in 1932 revealed new strategies for the development of antibiotics[15] and the Ugi synthesis of isocyanides in 1965 provided useful building blocks for multicomponent reactions.[16]

Despite the intense investigation devoted to these methods in the last 100 years, they still hold considerable potential. The full exploitation of such potential mostly relies upon a suitable re-visitation of the methods based on the innovative tools made available by technology in the meantime, an almost perfect playground for enabling technologies.

1.2. *Mechanochemistry: The Force Behind Transformation.*

History quickly propels us into the times when the looming onset of the Cold War takes centre stage. The technological strides witnessed in the 1800s and the tumultuous backdrop of the two World Wars in the first half of the XX century give rise to apprehensions regarding a possible nuclear conflict. The urgency of war efforts prompted scientists to channel their expertise into research with military application, mostly concerning materials science.

The 1950s are a watershed moment in history. The scientific community begins to disengage from the influences of war, restoring its independence. Based on Ostwald's seminal work,[17] the systematic exploration of different energy sources to enhance chemical reactivity takes off. While the thermal activation of reactions keeps its central position, photochemistry and electrochemistry attract interest

from organic chemists.[18] The use of mechanical energy to activate chemical reactions remains temporarily in the background.[19]

And yet, the application of mechanical forces to activate physical and chemical transformations has ancient roots,[19] clearly proved by the first written testimony of the past on science, a small fragment by Theophrastus of Eresus (De Lapidibus, 315 B.C.) that survived centuries. Nonetheless, mechanochemistry remained a relatively unexplored field until the 1800s. Following the first investigations by Faraday and Carey Lea,[19] it was in the second half of the XX century that the interest in mechanical processing grows. In the 1950s, the studies focused on inorganic systems.[20] Subsequently, research groups expressly dedicated to mechanochemistry are established in the Soviet Union and Eastern Europe. The discovery of mechanical alloying at the end of the 1960s[21] and the consequent emphasis laid on the fabrication of innovative materials determined a further expansion of the field.[22] Nowadays, mechanochemistry has reached also organic[23] and pharmaceutical chemistry,[24] becoming one of the top ten emerging technologies with the potential to change our world (IUPAC, 2019).[25]

Mechanochemistry has gained significant attention for its unique ability to harness mechanical energy to promote chemical reactions.[26] This innovative approach typically takes advantage of ball mills and extruders to effectively applying mechanical forces to the chemical substances. Ball mills, in particular, are the most widespread equipment in research laboratories, with a working principle based on the transfer of mechanical energy powders during impacts involving the milling tools.[27]

The application of ball milling to organic synthesis is relatively new, but it shows great promise to beneficially impact organic and pharmaceutical chemistry offering greener alternatives to traditional methods through the reduction, or the elimination, of the solvent phases.[28]

1.3. *Green Chemistry: Embracing a Sustainable Perspective*

At the dawn of the 1990s, the rising concern fuelled by the environmental repercussions of the industrial revolution, prompted a critical examination of many scientific and technologic fields, including traditional chemical synthesis.[29]

Green Chemistry emerged as a new philosophy in response to environmental issues, and evolved into a paramount discipline influencing scientific and industrial practices.[30] The term *Green Chemistry* was coined by Paul Anastas and John Warner in their seminal work, entitled "Green

Chemistry: Theory and Practice" and published in 1998, that provides a roadmap for sustainable and environmentally friendly practices in the field.[31]

The evolution of this pioneering approach in chemistry can be delineated into various phases, each characterized by significant strides in methodology, technological innovation, and a growing consciousness regarding environmental responsibility.[32]

In the initial phase, the primary objective was to comprehend and minimize the ecological footprint of chemical manufacturing and processes. This period was marked by rigorous research to discover and implement alternative, less harmful solvents, design more efficient catalysts, and optimize reaction conditions to be more environmentally benign. The goal was to mitigate the adverse effects of chemical processes on the environment and improve the safety and efficiency of these processes.[32]

As the discipline evolved, there was a noticeable shift towards a more collaborative and integrated approach. Interactions and partnerships among academic institutions, industry leaders, and regulatory agencies began to flourish.[33] This collaborative environment was crucial in driving the field forward, as it facilitated sharing knowledge, resources, and best practices. The synergy between these entities ensured that the principles of green chemistry were not confined to research labs but were translated into practical, industrial applications, leading to the development of more sustainable products and processes.[34]

Simultaneously, there was a concerted effort to institutionalize *Green Chemistry*. Universities and research institutions established specialized research centers and academic programs focused exclusively on this field. These centers became hubs for innovation, offering interdisciplinary research and education platforms. The curriculum was designed to impart knowledge about the principles and practices of green chemistry and instill a sense of responsibility toward sustainable development. This educational aspect was pivotal in cultivating a new generation of chemists and professionals well-versed in green chemistry principles and committed to its ethos.[35]

This development phase was also characterized by an increasing awareness and acceptance of *Green Chemistry* principles in the broader cultural context. As public awareness about environmental issues grew, there was a corresponding increase in the demand for greener products and processes. This cultural shift played a significant role in accelerating the adoption of *Green Chemistry* principles in industry.

The 12 principles of *Green Chemistry* serve as a guiding framework for designing and implementing sustainable chemical processes. These principles encapsulate the essence of *Green Chemistry*, emphasizing the need for efficiency, safety, and minimal environmental impact.

The impact of Green Chemistry extends beyond the laboratory, influencing industrial practices, policies, and societal attitudes towards sustainability. Its adoption has resulted in developing more sustainable materials, processes, and products across diverse sectors, including pharmaceuticals, materials science, and agriculture. With the rise of enabling technologies, these basilar principles are efficiently integrated within the chemical processes.[36]

1.4. *Target of this Thesis: A Design for Process Chemistry*

The present thesis walked me through all aspects and topics mentioned so far. It forced me to delve into a profound exploration of a selection of organic chemical reactions, viewed through the lens of sustainability and with the ultimate goal of examining how the potential of mechanochemistry can be best exploited in organic chemistry.

It has been claimed that mechanochemistry can result in a paradigm shift, replacing traditional methodologies with solutions able to overcome the intrinsic limits of classical chemical synthesis. This is why I have methodically dissected individual reactions, setting the stage for a broader, more comprehensive discussion of their strengths and weaknesses and a suitable comparison of old and new. The different parts of this thesis are intended to eventually form a full mosaic where individual tiles find their own place.

With the present thesis, I make an attempt to gain insight into mechanochemical transformations without losing sight of the wealth of refined knowledge we have of conventional chemical processes. Mechanochemistry can well be not merely an ancillary field, but a pivotal one, but we cannot deny that finding for it the right place in already existing, perfectly coded chemical processes is also a terrible challenge. In the end, this thesis endeavours to highlight the multifaceted nature of applications that mechanochemistry can have in the synthesis and production of organic compounds while fostering sustainability and propelling organic chemistry into new, uncharted territories.

2. Solid State Fischer's Indole Synthesis

In the canvas of modern synthetic chemistry, the exploration of molecular complexity serves as a linchpin in constructing sophisticated drug scaffolds and bioactive molecular frameworks.[37] The field of heterocyclic chemistry, particularly the synthesis of indoles, exemplifies this pursuit.[38] Indoles, with their ubiquity in natural products and medicinal compounds, demonstrate chemists' ingenuity in mimicking and manipulating nature's complexity.[39] The well-known Fischer indole synthesis, a stalwart in the chemist's anthology for over a century, epitomizes this versatility.[14] It offers a robust pathway to an array of complex indole structures, underpinning numerous pharmaceutical applications.[40]

Traditionally, the Fischer indolisation, mainly for constructing the indole nucleus, has relied on acetic acid as a dual solvent and acid catalyst, necessitating temperatures exceeding 200 °C.[41] This conventional approach, while effective, is marred by the tendency for undesirable side reactions and the ensuing necessity for solvent removal, posing challenges to both efficiency and environmental sustainability.

In this context, the paradigm shifts towards mechanochemistry, aligning with the tenets of green chemistry, heralds a new era of synthetic methodology.[42] Mechanochemistry, eschewing the need for solvents, offers an elegant solution to these challenges.[43] By facilitating reactions at room temperature and circumventing the use of traditional solvents, it minimizes side reactions and aligns with the imperative for environmental sustainability. This approach dovetails with the broader purpose of accessing complex molecular structures in a more sustainable manner.[44]

The implications of such a mechanochemical approach are profound, especially in total synthesis and multi-step drug synthesis.[45] By leveraging the solvent-free nature of mechanochemistry, chemists can now orchestrate the assembly of intricate molecular architectures with greater precision and minimal environmental impact. This innovative strategy unlocks a new dimension of molecular complexity, paving the way for the synthesis of next-generation pharmaceuticals through more sustainable and efficient means.[46]

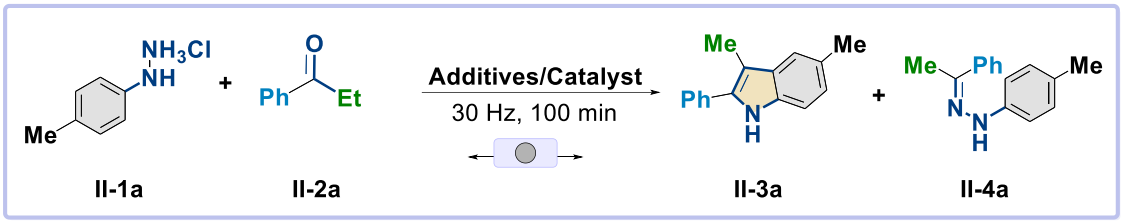
Thus, in this chapter, the exploration of mechanochemistry represents a technical advancement and embodies a philosophical alignment toward sustainable practices in pursuing sophisticated molecular architectures. Therefore, the transition to mechanochemical methods marks a significant stride in our ongoing quest to responsibly and sustainably mimic nature's complexity in the laboratory.[47]

2.1. Results: Optimization – Scope for Indoles and Indolines

Initiated by the demand for environmentally friendly and efficient procedures, the present investigation[48] focused on the mechanochemical Fischer synthesis. Using *p*-Tolylhydrazine hydrochloride **II-1a** and propiophenone **II-2a** as model substrates, the conditions were optimized for indole- and indoline-based template preparation, employing a solid grinding auxiliary/adsorbent due to the predominantly liquid nature of aldehydes and ketones. Silica gel, chosen for its success in mechanosynthesis, exhibited enhanced acidity, facilitating the subsequent acid-catalyzed Fischer reaction, and despite initial challenges in promoting the desired indolisation, adding $NaHSO_4$ increased acidity and improved indole yield, emphasizing the critical role of operating acidity in mechanochemical hydrazone-indole conversion. Attempts to enhance yield by adjusting the ratio of sulfate acid salt to silica gel proved counterproductive. Introducing solvents or $NaHSO_4$ without silica gel did not yield significant improvements, indicating a synergistic effect of the two components. Exploring alternative solid acids such as tetrabutylammonium bisulfate, *p*-toluensulfonic acid (PTSA), and tartaric acid resulted in modest efficiency. Imidazole, acting as a mild base, was employed to scavenge hydrochloric acid to address the inefficiency in phenylhydrazone formation. While influential in phenylhydrazone formation, Imidazole hindered the [3 + 3] rearrangement to the indole ring. Subsequent fine-tuning involved a two-step process, where PTSA was introduced in the second step. However, only limited amounts of the desired indole **II-3a** were obtained, indicating a competing path possibly involving *N–N* phenylhydrazine bond cleavage. Further investigations explored binary mixtures of hydrogen bond acceptors and donors under mechanochemical conditions. The oxalic acid (OA) and dimethylurea (DMU) mixture demonstrated notable efficiency, with OA contributing acidity to promote the Fischer reaction and DMU enhancing the conversion rate without significantly impacting process selectivity. Preliminary mechanochemical studies utilized an excess of DMU and OA as solid components, emphasizing their role in the process. The process efficiency showed a slight increase by transitioning from 2 (Ø = 8 mm) to 20 (Ø = 3 mm) zirconia balls while maintaining the overall final weight unchanged (m_{tot}: 6.5 g, Table 1, entry 8). Under these conditions, the mechanochemical Fischer indole synthesis yielded a 56% yield of the desired indole **II-3a** after 100 minutes of milling (Table 1, entry 8). Extending the reaction time to 250 minutes did not significantly improve yields (Table 1, entry 9), but altering the ratio of DMU and OA enhanced selectivity (99 : 1, Table 1, entry 10). Reduction in the auxiliary grinding mixture and longer milling times further improved conversion without compromising selectivity (Table 1, entries 11 and 12).

Including a small amount of solvent (η = 0.1, μL mg^{-1}) under liquid-assisted grinding conditions, especially using acetic acid, provided indole **II-3a** with improved and comparable yields (Table 1, entries 14–16). Acetic acid, chosen for its efficacy, cost-effectiveness, and environmental impact, could be easily removed during the final purification step. The mechanochemical protocol demonstrated its green character by allowing the recovery of indole **II-3a** through filtration without employing any organic solvents during trituration with water.

Table 1. Screening of reaction conditions for the mechanochemical Fischer indole synthesis.



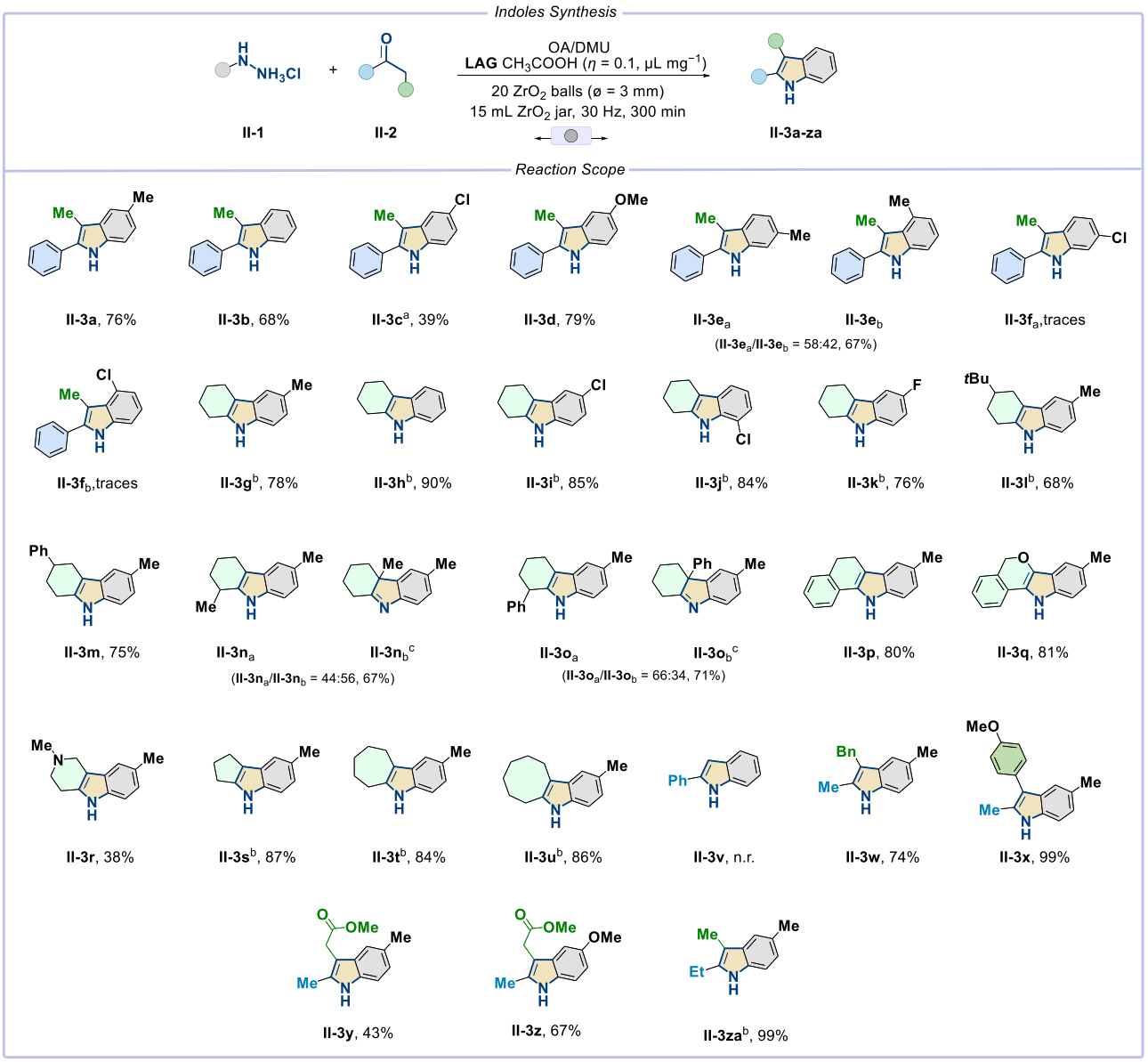
Entry[a]	Catalysts (mmol)	3a (%)[b]	Ratio (%)[b] of 3a:4a
1	PTSA (1.5)	36	99:1
2	Oxalic acid (1.5)	32	99:1
3	Tartaric acid (1.5)	6	1:99
4	Imidazole (1)	-	1:99
5[c]	PTSA/imidazole (2:1)	25	78:22
6	DMU/PTSA (7:3)	43	77:23
7	DMU/OA (7:3)	40	71:29
8[d]	DMU/OA (7:3)	56	69:31
9[d,e]	DMU/OA (7:3)	50	73:27
10[d,e]	DMU/OA (3:7)	58	99:1
11[d]	DMU/OA (1.5:3.5)	60	99:1
12[d,e]	DMU/OA (1.5:3.5)	68	99:1
13[d,e]	DMU/OA (1.5:3.5), MeOH (η = 0.1 μL mg^{-1})	55	99:1
14[d,e]	**DMU/OA (1.5:3.5), CH_3COOH (η = 0.1 μL mg^{-1})**	**76**	**99:1**
15 [d,e]	DMU/OA (1.5:3.5), 3-pentanol (η = 0.1 μL mg^{-1})	77	99:1
16 [d,e]	DMU/OA (1.5:3.5), DMF (η = 0.1 μL mg^{-1})	79	99:1

[a] **II-1a** (158.6 mg, 1.0 mmol), **II-2a** (147.6 mg, 1.1 mmol), and catalysts were ball-milled in a 15 mL ZrO_2 milling jar with 2 milling balls (f = 8 mm, 6.5 g overall) of the same material. [b] Determined by GC-MS. [c] **II-1a** (158.6 mg, 1.0 mmol), **II-2a** (147.6 mg, 1.1 mmol) and imidazole (68.1 mg, 1.0 mmol) were milled for 60 minutes, afterward PTSA (344.4 mg, 2.0 mmol) was added, and the mixture was ball-milled for additional 100 minutes. [d] The jar was loaded with ZrO_2 balls (20, f = 3 mm, m_{tot} = 6.5 g). [e] The mixture was ball milled for 300 minutes

Expanding the reaction scope, various phenylhydrazines **II-1a-II-1i** and ketones **II-2a–II-2q** were employed, confirming the generality and efficiency of the mechanochemical protocol. The results aligned with the general trends observed for Fischer indole synthesis in solution, reflecting the influence of steric and electronic factors on substituent groups (Scheme 1).

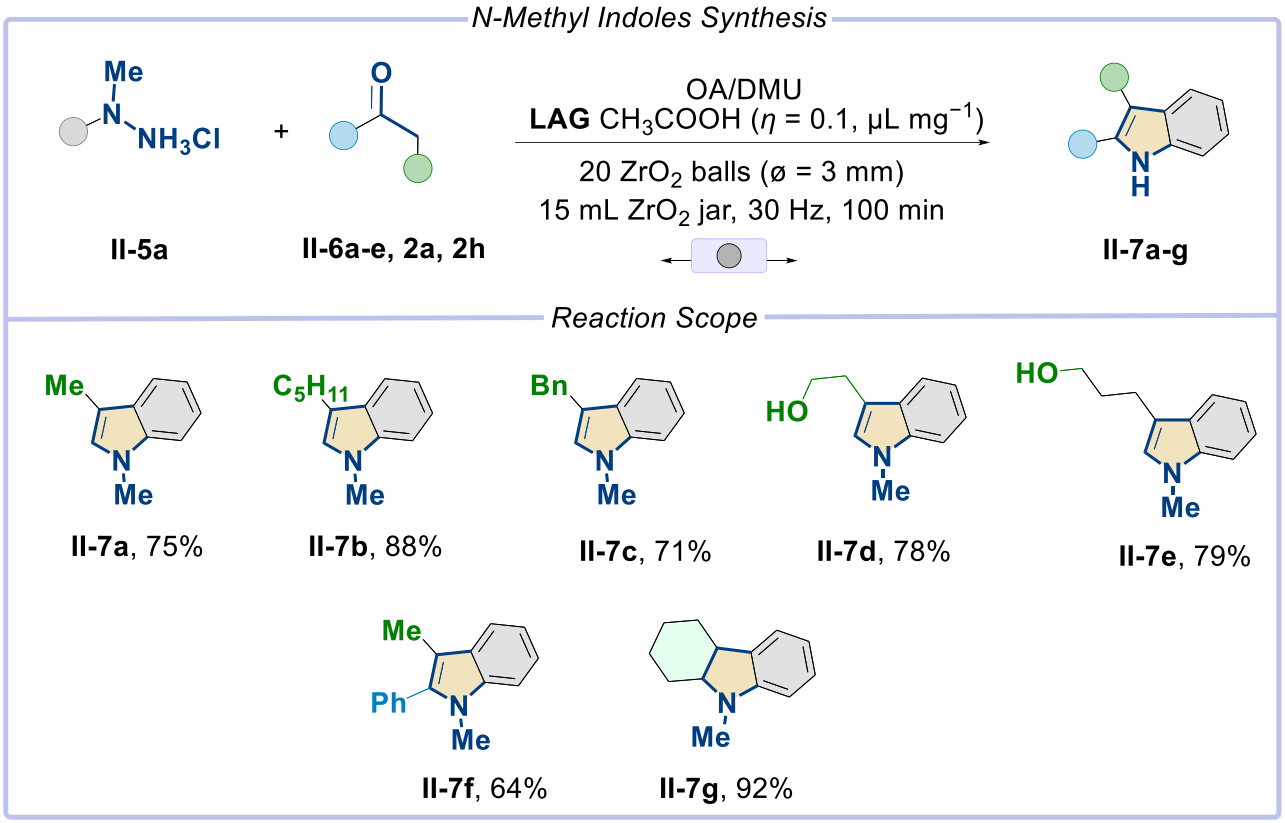
Examining structure–reactivity relationships, the impact of substituents on phenylhydrazines and ketones was explored. While 4-methyl- and phenylhydrazine provided comparable amounts of indoles **II-3a** and **II-3b**, the introduction of a para-chlorine substituent on the phenylhydrazine ring negatively affected the reaction outcome (Scheme 1, indole **II-3c**). Conversely, 4-methoxy phenylhydrazine with propiophenone exhibited a more favourable reaction, providing the corresponding indole in 79% yield (Scheme 1, indole **II-3d**). Investigation of meta-substituted phenylhydrazines revealed modest regioselectivity for indole **II-3e$_a$** (**II-3e$_a$**/**II-3e$_b$**: 58/42, Scheme 1), while resulted in only traces for indole **II-3f$_a$**/**II-3f$_b$**.

Expanding the synthesis to tetrahydrocarbazole products using cyclic aliphatic ketones resulted in high yields and purity of compounds **II-3g** and **II-3h**. Halogen-substituents on the aromatic ring (**II-3i-II-3k**, as well as bulky or pendant groups on the cyclohexanone ring (**II-3l-II-3o**), were well-tolerated. Similarly, more complex architectures present in compounds **II-3p** and **II-3q**, heterocycles (**II-3r**), carbocycles (**II-3s-II-3u**) showcased the versatility of the Fischer indole synthesis under the optimized mechanochemical conditions (Scheme 1). Lastly, different decorations on the indole ring further expanded the substrate scope (compounds **II-3v-II-3za**, Scheme 1).



Scheme 1. Reaction scope for mechanochemical Fischer's indole synthesis. Reaction conditions: **II-1** (1 mmol), **II-2** (1.1 mmol), oxalic acid (3.5 mmol), di-methylurea (1.5 mmol) and acetic acid (η = 0.1 μLmg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (Ø = 3 mm, m_{tot} 6.5 g) of the same material for the given time. If not otherwise stated, the yields refer to the isolated compounds. The reaction mixture was ball-milled for 400 minutes. [b] The reaction mixture was ball milled for 100 minutes. [c] Isomer ratio determined after reduction, assuming a completed conversion of indolenine into the corresponding indoline. The abbreviation n.r. = no results.

Additionally, the mechanochemical protocol successfully produced indoles from aldehydes, albeit encountering challenges with propionaldehyde, 3-phenyl-propionaldehyde, and heptanal. However, using 1-methyl-1-phenylhydrazine **II-5a** addressed these challenges, allowing for the synthesis of **II-7a-II-7g** indole products (Scheme 2).

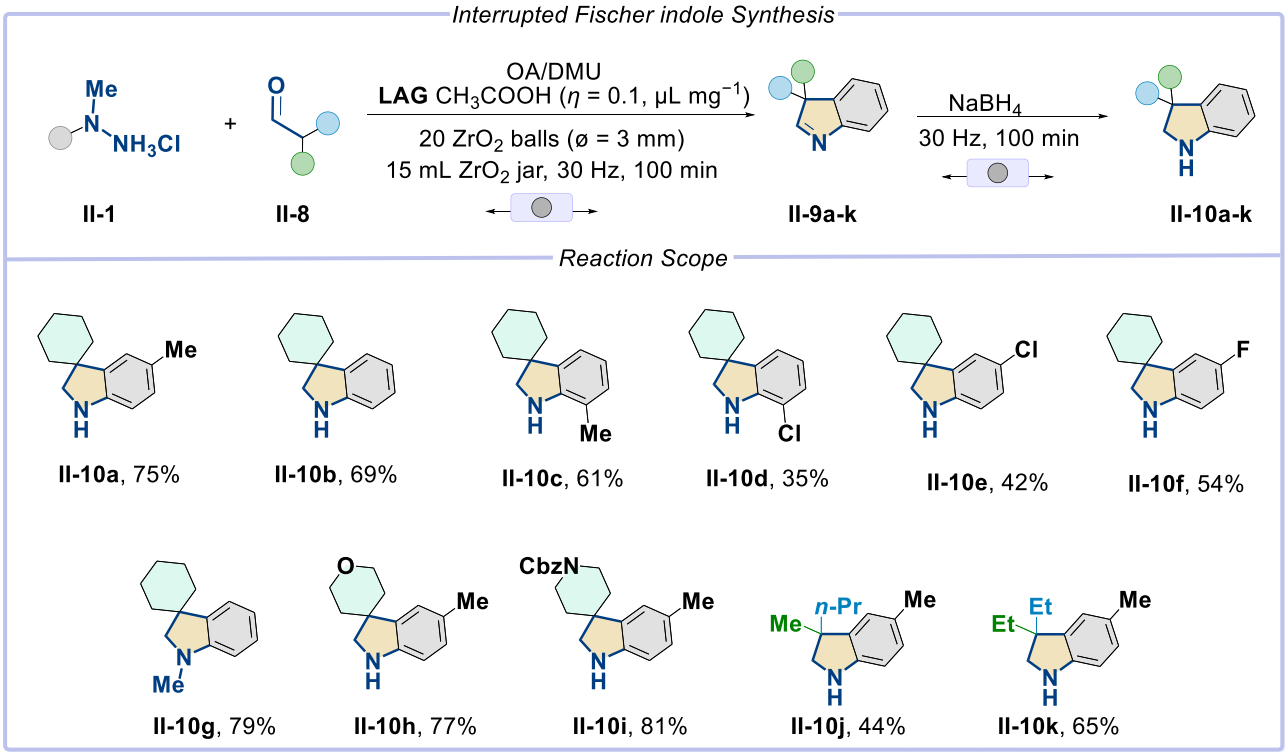


Scheme 2. Reaction scope of mechanochemical Fischer indole synthesis using N-methylphenylhydrazine. Reaction conditions: **II-5a** (1.0 mmol), **II-6** or **II-2** (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid ($\eta = 0.1$ μL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (Ø = 3 mm, m_{tot} = 6.5 g) of the same material for the given time. If not otherwise stated, the yields refer to the isolated compounds.

The feasibility of interrupted Fischer indolisation followed by in situ reduction was demonstrated successfully. Using commercially available arylhydrazine hydrochlorides, in situ reactions afforded free hydrazine derivatives without preliminary acid–base treatments. The selectivity of the desired indolenine over the 1,2-migration product was achieved under the developed conditions.

Efforts to reduce the C=N double bond in the indolenine core using Pd catalyst and ammonium formate or $NaBH(OAc)_3$ yielded unsatisfactory results. However, employing 4 equivalents of $NaBH_4$ provided excellent results, and halving the reducing agent amount maintained complete conversion toward the desired product **II-10a** (Scheme 3). Including 3-pentanol as a liquid assistant of grinding (LAG, η = 0.1 μL mg^{-1}) enables the reduction with only 1.5 equivalents of sodium borohydride, testing out the versatility of the approach.

The reaction scope was studied for various 2-disubstituted aldehydes, demonstrating the strategy's effectiveness in obtaining indoline derivatives. The methodology proved successful with halogen-functionalized phenylhydrazine substrates and 1-methyl-1-phenylhydrazine (compounds **II-10a-II-10g**, Scheme 3). Additionally, heteroatom-containing aldehyde derivatives showed good tolerance (**II-10h** and **II-10i**, Scheme 3) and aliphatic compounds (**II-10j** and **II-10k**, Scheme 3).



Scheme 3. The reaction scope of mechanochemical interrupted Fischer indole synthesis. Reaction conditions: **II-5a** (1.0 mmol), **II-8** (1.1 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol), and acetic acid (η = 0.1 µL mg^{-1}) were ball-milled in a 15 mL ZrO_2 milling jar with 20 milling balls (Ø = 3 mm, m_{tot} = 6.5 g) of the same material for the given time. Afterwards, the jar was opened, and the sodium borohydride (2.0 mmol) was added to the resulting reaction mixture that was further ball-milled for 60 minutes. If not otherwise stated, the yields refer to the isolated compounds.

2.2. *Discussion: A Step Towards Sustainability and Process Chemistry*

The mechanochemical Fischer indole synthesis, as elucidated in the results section, emerges as a groundbreaking avenue in process chemistry, notably in contrast to the conventional solution-based methodologies. This innovative approach signifies an exemplary shift toward a greener, more sustainable chemical synthesis, and its exploration underscores the unique attributes and challenges inherent in mechanochemistry.

Traditionally, Fischer indole synthesis necessitates using solvents, external heating, and intricate purification procedures. However, the mechanochemical model diverges from these conventions, featuring a solvent-free process that not only adheres to the fundamental principles of *Green Chemistry* but also introduces a distinct difference from the continuous nature of solution-phase operations. The green metrics evaluation (please refer to section 5.1) emphasized the sustainability and environmental benefits of the mechanochemical promoted Fischer and interrupted Fischer processes, showcasing advantages in terms of E-factor and Eco scale values. An exemplary facet of this novel approach lies in its ability to operate at ambient temperatures, unlike the conventional methods that frequently mandate external heating. This accentuates operational safety and aligns

intimately with the energy efficiency principles intrinsic to *Green Chemistry*. By avoiding external heat input, the sustainability of the process is enhanced, and thermally sensitive compounds are preserved from degradation. Moreover, replacing liquid acids with solid grinding agents – precisely the combination of oxalic acid (OA) and dimethylurea (DMU) – plays a pivotal role in assessing the greenness of such reactions. This strategic shift simplifies the downstream purification steps and advocates for waste reduction and minimized chemical dispersion in the environment. At the same time, the possibility of recycling these solid grinding components further accentuates the sustainable attributes of the mechanochemical process.

In other words, the mechanochemical Fischer indole synthesis represents a discrete methodological advancement and serves as a "catalyst" for evolving a unified process chemistry tailored for mechanochemical endeavours. With this specific mechanochemical protocol, a chemist can rely on a robust synthesis to build more complex molecules under solvent-free conditions.

3. Multistep Syntheses: Sustainable Process Chemistry

This chapter dwells on the synthesis of formamides/isonitriles and sulfonyl chlorides/sulfonamides, compounds of remarkable biological and pharmaceutical importance, among many other potential applications. [49,50]

Isonitriles are crucial in the Ugi reaction,[16,51] a cornerstone in drug discovery, highlighting their significance in synthesizing diverse bioactive molecules.[52] Notably, isocyanides can be obtained through Ugi synthesis, which involves the dehydration of formamides.[53] However, the traditional synthesis of such compounds typically necessitates large amounts of solvents and harsh conditions, a practice at odds with the principles of *Green Chemistry*. On the other hand, sulfonamides are crucial moieties for synthesizing and developing antibiotics, diuretics, anti-cancer drugs, and many other classes of pharmaceuticals.[54] They can be synthesized by sulfonyl chlorides using traditional solution-based methods, implying large volumes of toxic solvents and chemicals.[55]

Implementing multi-step syntheses in organic chemistry, especially within mechanochemistry, presents a troubling dichotomy between the traditional solvent-based methods and the emerging solvent-free approach. The paradox especially conflicts with the pursuit of mechanochemical syntheses, which promise reduced toxicity and environmental impact due to their solvent-free nature.[56] In an ideal scenario, the entire synthetic pathway, including the formation of precursors (formamides and sulfonyl chlorides), should adhere to the green chemistry ethos, minimizing the use of hazardous solvents and energy-intensive processes (reduced-pressure distillation, purification methods, and so forth). Yet, the reliance on solvent-based methods for precursors synthesis undermines the environmental sustainability of the overall process.[57]

This contradiction beckons a strategic re-evaluation of the synthetic route. The challenge, therefore, is to develop a cohesive and environmentally benign approach, beginning from the very first synthetic step. Embracing mechanochemistry for the entire synthetic sequence of isonitriles and sulfonamides, including the formamide and sulfonyl chloride precursors, not only aligns with *Green Chemistry* principles but also paves the way for a new paradigm in process chemistry. Such an approach would signify a substantial stride towards truly sustainable chemical synthesis, marrying the ecological benefits of mechanochemistry with the versatility and biological significance of isonitriles and sulfonamides.[58] The key, thus, lies in the innovative adaptation of multi-step syntheses in a solvent-free environment, a goal that promises to reshape the landscape of green synthetic chemistry.

3.1 Results: Optimization – Scope for Formamides/Isocyanides

The study[59] commenced by investigating the mechanochemical reactions using ZrO_2 vessels, milling aniline **III-2a,** and *N*-formyl saccharin. Initial conditions (1 mmol each) at 30 Hz for 15 min yielded a 23% of compound **III-3a**, increasing to 52% at 30 min. The best results were obtained when extending the reaction time to 60 minutes without any additive, resulting in the complete conversion of aniline **III-2a** into the desired formamide **III-3a**.

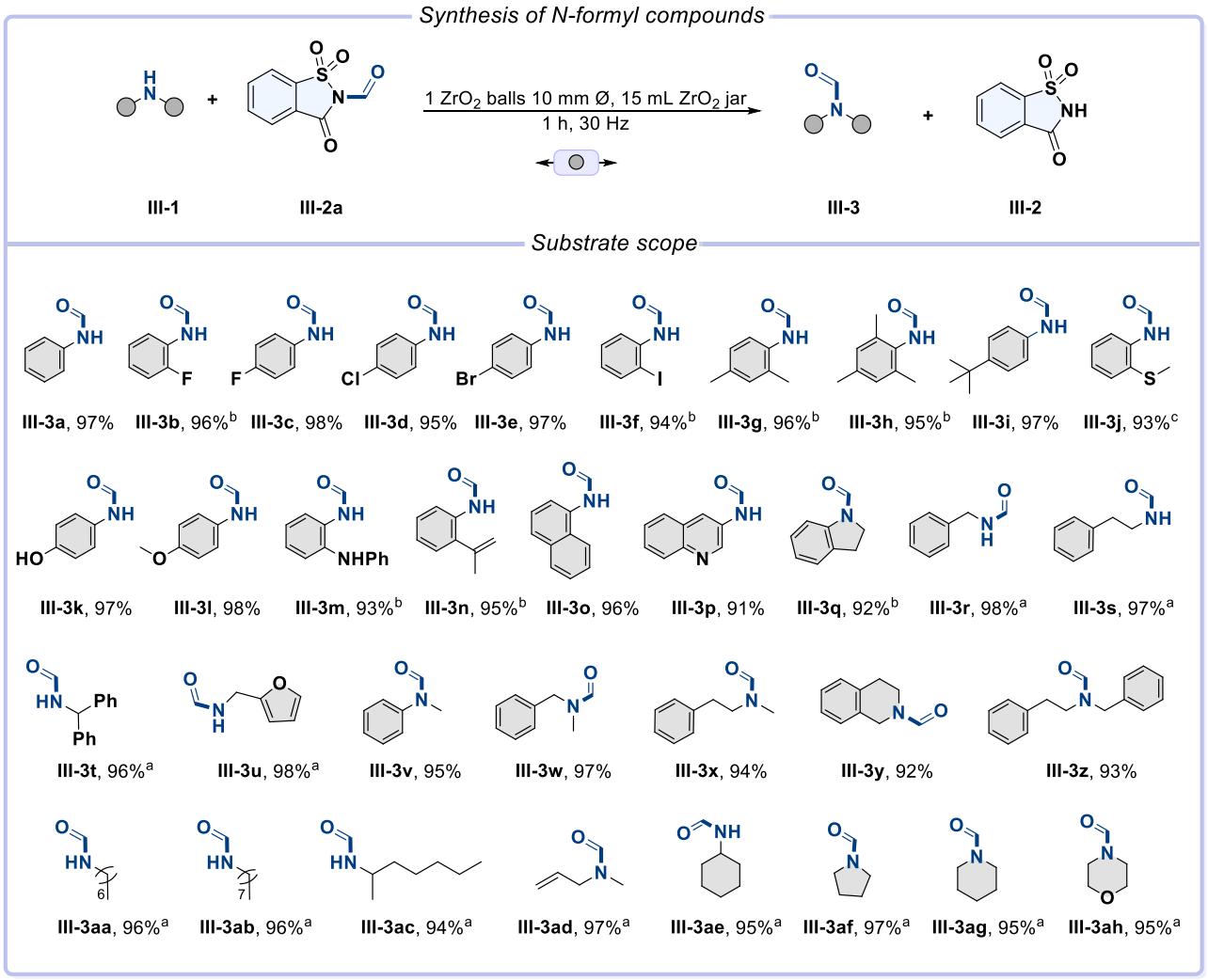
Several bases were investigated to explore the influence of other parameters to achieve complete conversion by decreasing the reaction time. Testing different carbonates (Na, K, Cs) in both anhydrous and moist forms alongside the reaction in a jar, simultaneous grinding, and subsequent recovery with ethyl acetate revealed no beneficial effects on shortening reaction time. Metal oxides and various solid or liquid organic bases, including imidazole, *N*-methylimidazole, and potassium *tert*-butylate, failed to improve conversion yields. Stainless-steel jars and balls of different materials also showed no dramatic effects.

Upon establishing that the nature of the base was almost irrelevant, attention shifted to stoichiometry. However, the results remained unsatisfactory even with varied starting material/base ratios, up to 1:3. Liquid Assisted Grinding (LAG) conditions with THF and CPME were explored, testing different η values ranging from 0.1 to 0.5 μL/mg. Nevertheless, small amounts of solvent did not enhance reactivity under the experimental conditions. Then, the best conditions were established as follows: aniline **III-2a** and N-formyl saccharin (ratio 1:1.1) milled inside a ZrO_2 vessel with 1 ZrO_2 milling ball (Φ = 10 mm) for 60 minutes. Adding a stoichiometric amount of non-anhydrous $NaHCO_3$ at the end of the reaction, followed by grinding the resulting reaction crude for an additional 10 minutes, not only afforded the formamide **III-3a** in high yields and purities but also allowed for the exclusive recovery of **III-3a** due to the poor solubility of the solid saccharin salt in AcOEt.

Examining aromatic and secondary benzylic amines, the study observed varying conversion times based on the nucleophilicity of the amines. Primary and secondary aliphatic and aromatic amines achieved complete conversion within 1 hour, showcasing a prompt reactivity (compounds **III-3a**, **III-3c**-**III-3e**, **III-3i**, **III-3k**, **III-3l**, **III-3o**, **III-1p**, **III-1v–III-1z**, Scheme 4). In contrast, more hindered substrates such as ortho-substituted anilines and the heteroaromatic indoline required an extended reaction time of 2 hours (compounds **III-3b**, **III-3i**, **III-3g**, **III-3m**, **III-3n, III-3q**, **III-3v-III-3z,** Scheme 4) witnessing the influence of each substrate's chemical features on the mechanochemical process (in line with Hammett's parameters). Lastly, primary benzylamines and primary and secondary aliphatic amines were obtained in only 30 minutes in high yields (compounds **III-3r-III-**

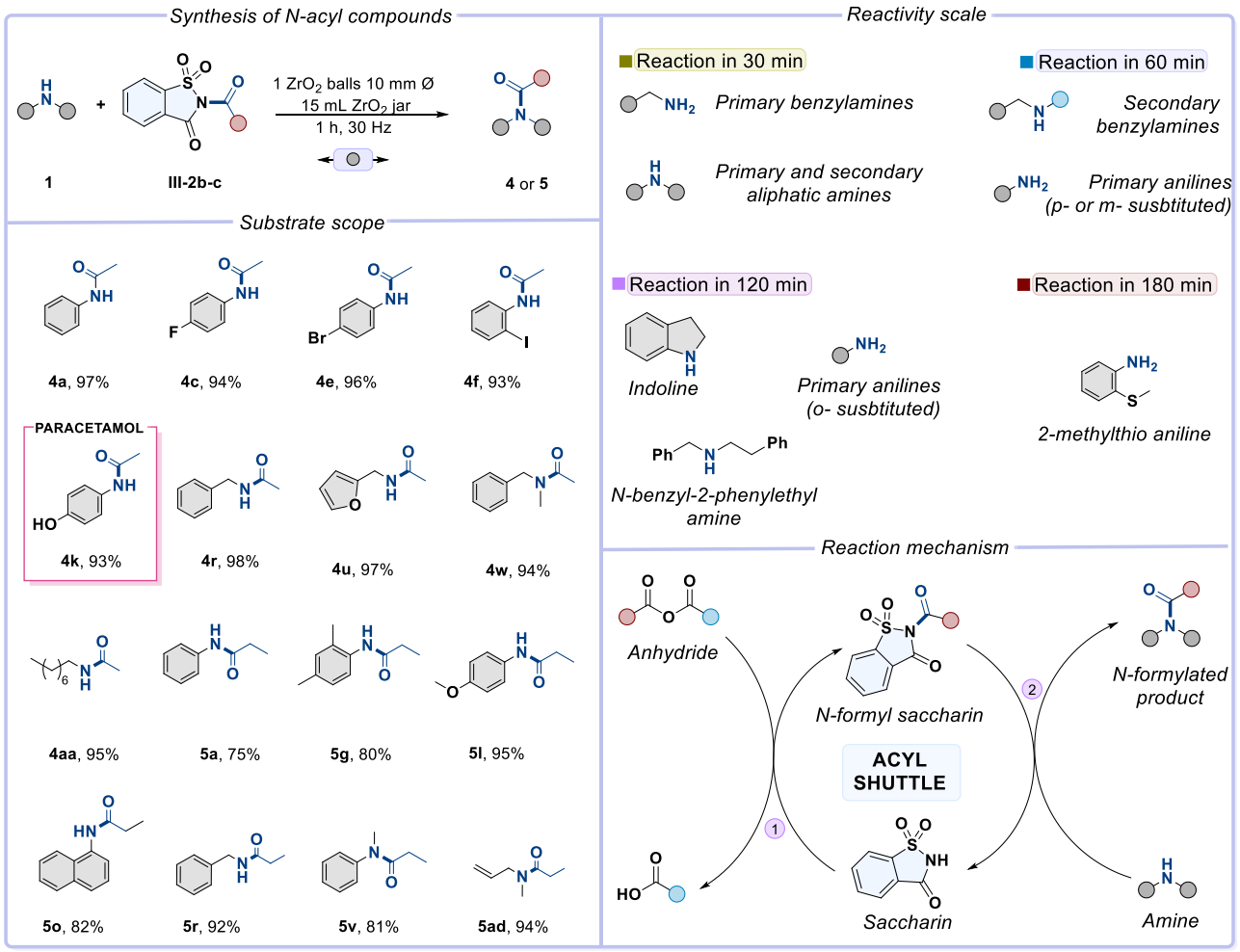
3u, **III-3aa-III-3ah**, Scheme 4). Only for 2-methylthio aniline was a 3h reaction time necessary for a complete conversion (compound **III-3j**, Scheme 4).

Building on the success of the formylation reaction, which is valid for synthesizing isocyanides, the methodology was also expanded to general acylating systems. The study synthesized *N*-acetyl and *N*-propionyl saccharin-activating agents, showcasing the versatility of the mechanochemical approach in the context of acyl transfer processes. This extension led to the mechanosynthesis of acetamides **III-4a-III-4aa** and propionamides **III-5a-III-5ad** in yields from good to excellent, demonstrating the method's feasibility across a range of substrates.



Scheme 4. Mechanosynthesis of aryl, alkyl and heterocyclic formamides. [a] 30 minutes of reaction time; [b] 120 min of reaction time; [c]180 min of reaction time. Yields refer to pure isolated compounds.

A significant outcome of this extension was the successful synthesis of paracetamol **III-4k**, identified as an Active Pharmaceutical Ingredient (API) of considerable interest. This accomplishment not only underscored the broad applicability of the methodology but also highlighted its potential in synthesizing pharmaceutically relevant compounds.



Scheme 5. Mechanosynthesis of aryl, alkyl and heterocyclic acylamides (on the left).The different reaction times depending on the nature of the substrate (top right). Plausible reaction mechanism (down right).

Based on the previously established protocol, the aim was to produce isocyanides from primary formamides using anhydrides as dehydrating agents, focusing on acetic, trifluoroacetic, and isotonic anhydrides.[60] Initial attempts with acetic and trifluoroacetic anhydrides, milled with *N*-benzylformamide **III-3r** and triethylamine or *N*-methylimidazole as bases, provided satisfactory results, albeit the overly liquid texture of the reaction mixture. Solid isatoic anhydride, though of interest, yielded unsatisfactory outcomes.

Exploration shifted to traditional coupling reagents, specifically carbodiimides (DIC and DCC) and CDI. Despite the theoretical advantage of generating thermodynamically stable products, they showed no improvement over acetic anhydride. CDI, activated in an acid environment, necessitated $NaHSO_4$, which was ruled out due to isocyanide sensitivity to acids. *p*-Tosylimidazole faced similar challenges, requiring acid activation. Turning to DIC and DCC compounds in stoichiometric quantities with 1 equivalent of triethylamine (NEt_3), only traces of the desired product were obtained.

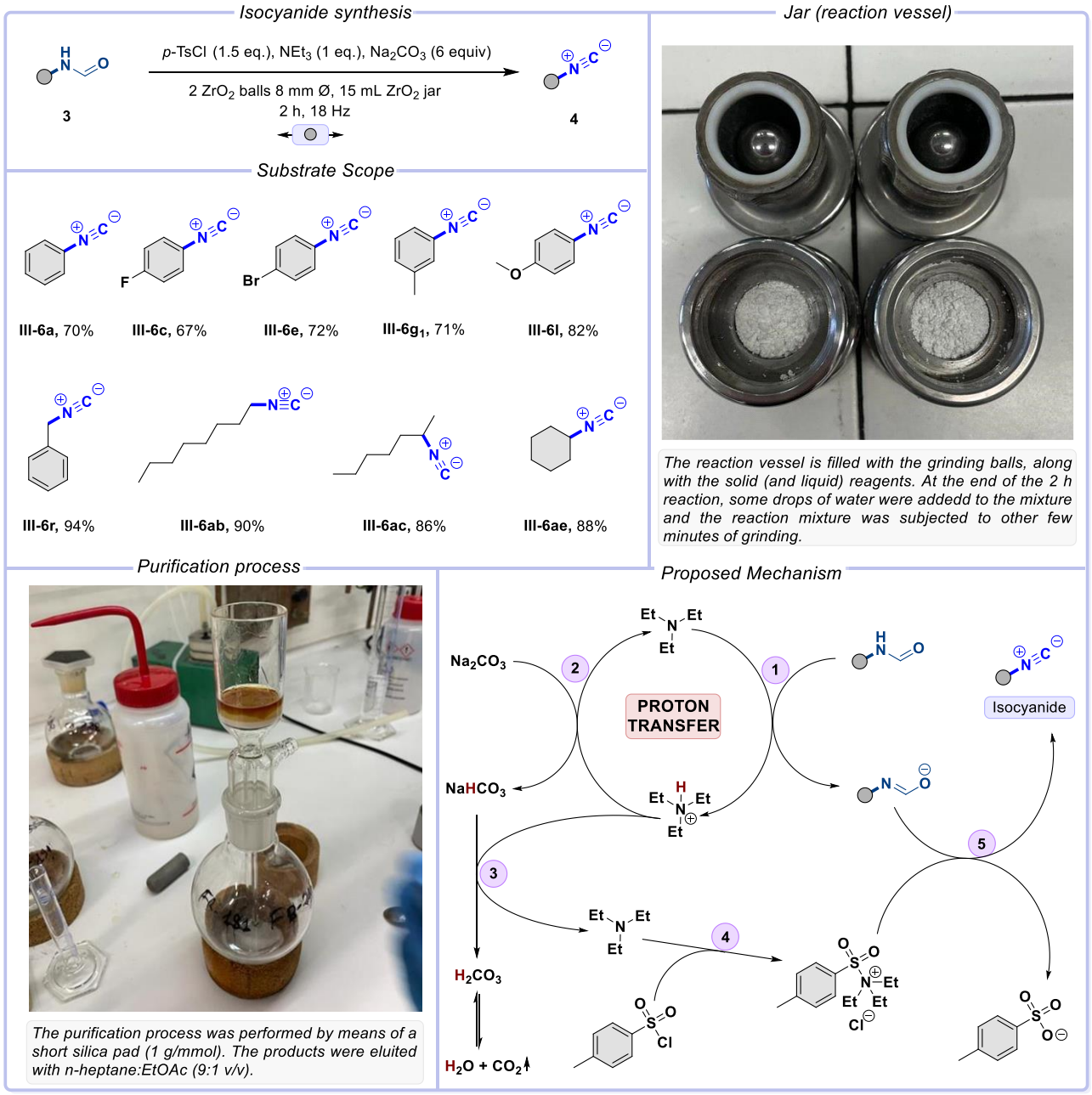
When combined with a basic milieu, tosyl chloride emerged as the most suitable agent for synthesizing isocyanides. The best results were achieved with the association of triethylamine, *p*-tosyl chloride, and **III-3r**, prompting further optimization efforts.

Optimization involved a 1:2:7 ratio of formamide **III-3r**, *p*-tosyl chloride, and triethylamine, with the addition of 400 mg of NaCl as a grinding auxiliary at 36 Hz for 0.5 h. Substituting triethylamine with solid inorganic bases or organic bases did not match its effectiveness. Surprisingly, the combination of 1 equivalent of triethylamine and 6 equivalents of sodium carbonate demonstrated reasonable conversion rates at 36 Hz after 1 h (70% yield). Refining parameters such as frequency and reaction time led to total conversion after 1 h at 18 Hz.

Applying this method to aromatic substrates showcased varying yields (compounds **III-6a-III-6l**, scheme 6), with the maximum at 82% for **III-6e**. A nearly complete conversion into isocyanides was obtained for aliphatic compounds **III-6r-III-6ae**, with high to excellent yields (scheme 6). The diverse electronic distribution between aliphatic and aromatic formamides, especially the impact of electron-withdrawing (EWG) or electron-donating groups (EDG), slightly contributed to these differences.

The post-reaction process involved adding 0.5 water equivalents for a 15-minute grinding step to hydrolyse excess p-tosyl chloride. The mixture was recovered as a solid, shredded in n-heptane, and filtered with a short silica pad to enhance isocyanide purity.

The proposed reaction mechanism involves triethylamine activating formamide tautomerism through an acid–base reaction. The triethylammonium salt produced can regenerate triethylamine through Na_2CO_3 action, facilitating proton transfer and forming $NaHCO_3$. Releasing H_2O maintains the basicity required for deprotonating the regenerated ammonium species, contributing to the overall isocyanide synthesis (Scheme 6).



Scheme 6. The scope of isocyanide synthesis using aliphatic and aromatic primary formamides. Reaction conditions: formamide (1.0 mmol), p-TsCl (1.5 mmol), triethylamine (1.0 mmol), dry Na2CO3 (6.0 mmol), 1 h, zirconia jar (15 mL), 2 balls (⍰ = 8 mm), 18 Hz. Proposed reaction mechanism (down right).

3.2 *Results: Optimization – Scope for Sulfonyl Chlorides/Sulfonamides*

The investigation[61] commenced with diphenyl disulfide **III-7a** as the model substrate and sodium hypochlorite pentahydrate for preparing phenyl sulfonyl chloride **III-8a**. Specific conditions, including a vibrating mill at 30 Hz and zirconia jars, initially yielded minimal product (Table 2, entries 1-3), with 12% conversion at prolonged times (Table 2, entry 3). Calcium hypochlorite and trichloroisocyanuric acid were ineffective (Table 2, entries 4-6), and disulfide oxidated intermediates

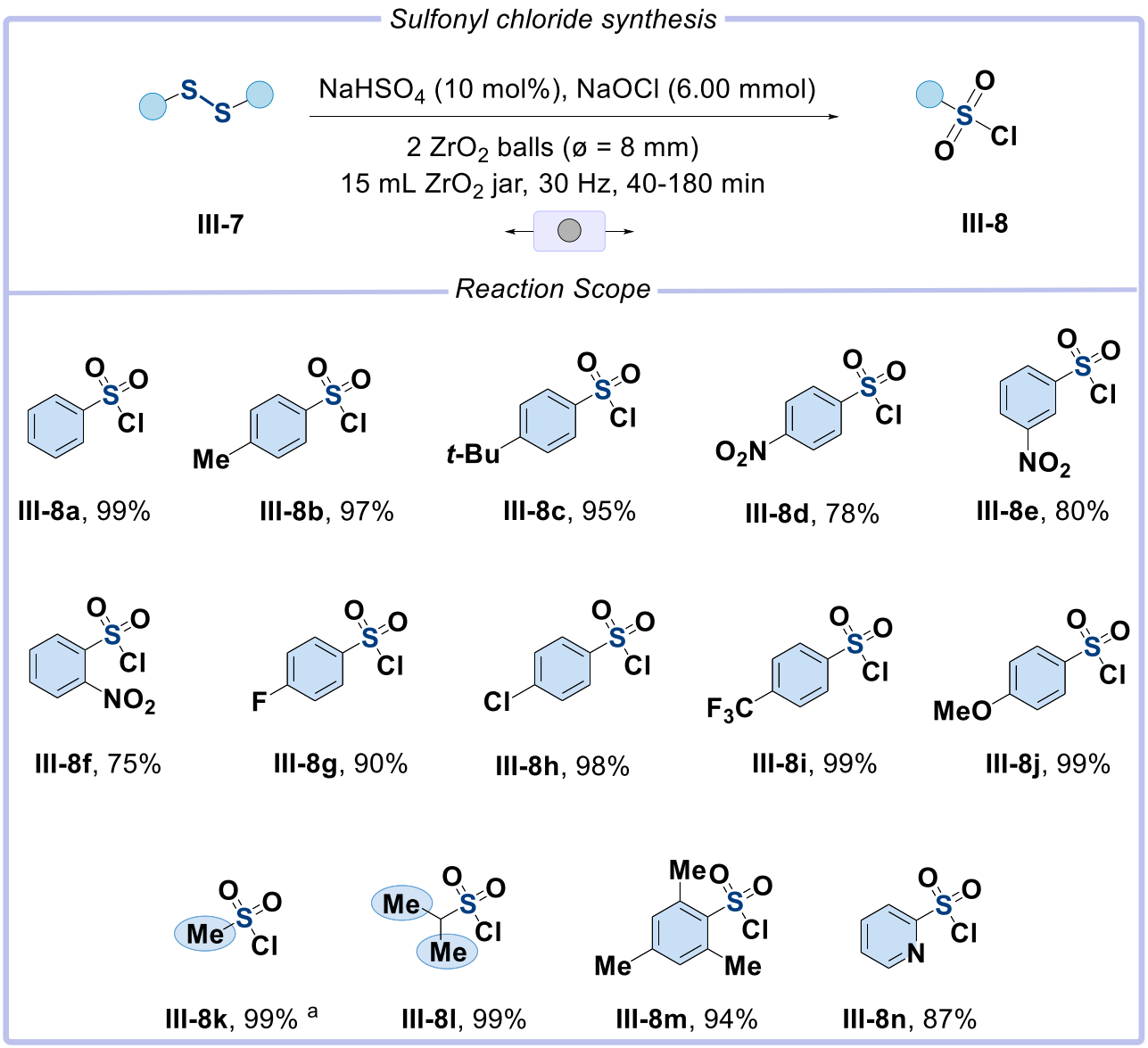
were detected. Adding $NaHSO_4$ as a solid inorganic acid catalyst significantly improved the yield, achieving > 99% conversion under optimized conditions (Table 2, entry 8). Upon adding acid, HCl release occurred, followed by regeneration in the early stages. Atmospheric CO_2 participation in the oxidative chlorination mechanochemical process was proposed. Other agents (TCIA and $Ca(OCl)_2$) provided lower yields, emphasizing the pivotal role of $NaOCl*5H_2O$. Optimized conditions facilitated the mechanochemical reaction of differently substituted disulfides **III-7a-III-7n** with $NaOCl*5H_2O$ and $NaHSO_4$, yielding sulfonyl chloride **III-8a-III-8n** in near quantitative isolation (Scheme 7).

Table 2. Reaction optimization for the sulfonyl chloride synthesis screening several chlorinating agents and acid additives under different conditions.

Entry	Chlorinating agent	Additive	Time	Conversion[a]
1	NaOCl (6 mmol)	-	20 min	traces
2	NaOCl (6 mmol)	-	40 min	9%
3	NaOCl (6 mmol)	-	60 min	12%
4	$Ca(OCl)_2$ (3 mmol)	-	20 min	n.d
5	$Ca(OCl)_2$ (3 mmol)	-	40 min	traces
6	TCIA (6 mmol)	-	40 min	23%
7	NaOCl (6 mmol)	$NaHSO_4$ (5 mmol%)	40 min	43%
8	**NaOCl (6 mmol)**	**$NaHSO_4$ (10 mmol%)**	**40 min**	**> 99%**
9	$Ca(OCl)_2$ (3 mmol)	$NaHSO_4$ (5 mmol%)	40 min	36%
10	$Ca(OCl)_2$ (3 mmol)	$NaHSO_4$ (10 mmol%)	40 min	74%
11	TCIA (6 mmol)	$NaHSO_4$ (10 mmol%)	40 min	48%

Mechanochemical conditions for this screening: disulfide **1a** (1 mmol) was placed in a 15 mL zirconia jar equipped with two zirconia balls (ϕ = 8.00 mm, $mass_{tot}$ = 3.22 g) at a frequency of 30 Hz. Conversion was detected by GC-MS analysis.

The exploration encompasses a broad substrate scope, showcasing mechanochemistry's versatility in synthesizing sulfonyl chlorides. Aliphatic disulfides (**III-7f-III-7i**) yielded sulfonyl chlorides **III-8f-III-8i**, demonstrating near-complete conversion with very high to excellent yields (Scheme 7). Aromatic starting compounds (**III-7a-III-7e**) exhibited varied reactivity, resulting in sulfonyl chlorides **III-8a-III-8e** with a maximum yield of 82%. Electron-rich disulfides (**III-7b-III-7c**, **III-7j**, and **III-7m**) showed excellent reactivity, achieving complete conversion in 40 minutes and yielding sulfonyl chlorides **III-8b-III-8c**, **III-8j**, and **III-8m** with high efficiency (90-99%, Scheme 7). Halogenated disulfides (**III-7g-III-7h**) demonstrated high conversion rates, producing sulfonyl chlorides **III-7g-III-7h** with excellent yields (90-99%, Scheme 7). Aliphatic disulfides (**III-7k-III-7l**) and heterocyclic disulfides (**III-7n**) led to excellent yields, ranging from 90% to 99% (Scheme 7)

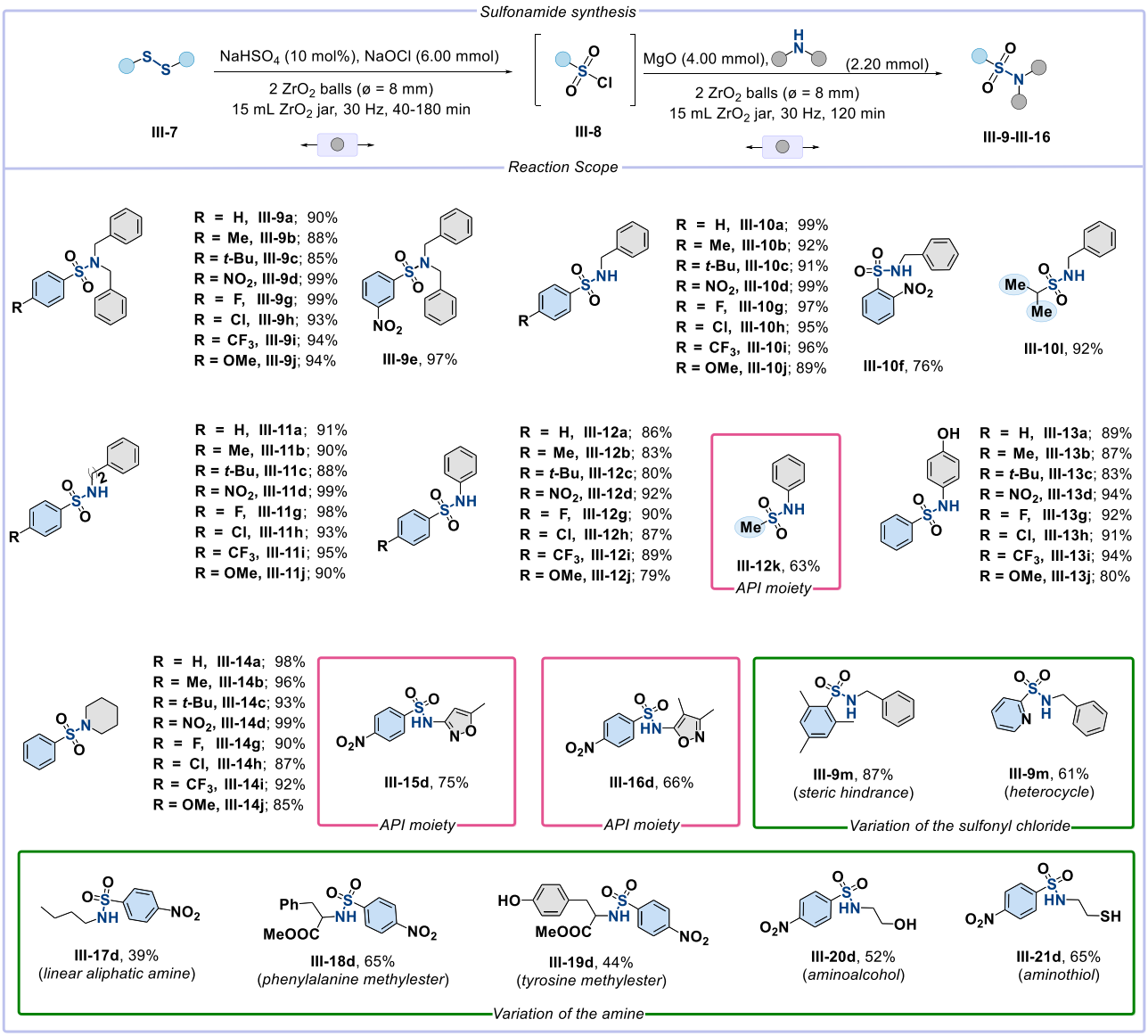


Scheme 7. The scope for the synthesis of sulfonyl chlorides. General reaction conditions: NaHSO4 (10 mol%) was placed into a 15 mL zirconia jar equipped with two zirconia balls (ϕ = 8.00 mm, masstot = 3.22 g), followed by disulfide 1a-l (1 mmol) and then NaOCl*5H2O (6 mmol); the reaction was then conducted at a frequency of 30 Hz for a time ranging from 40 to 180 min. If not

otherwise noted, yields refer to isolated compounds. [a] Yields refers to ^{1}H-NMR calculated due to the high volatility of the product (trimethoxy benzene used as an internal standard).

In the second stage, namely the mechanochemical reaction of sulfonyl chlorides with dibenzyl amine **III-9**, different bases were screened, with magnesium oxide (MgO) emerging as a suitable choice, preventing hydrolysis and maintaining eco-friendliness. Stoichiometric optimization established a 4:1 ratio of MgO to dibenzyl amine, leading to a 90% isolated yield of sulfonamide **III-9a** (Scheme 8). One-pot, two-step procedures were successfully executed, affirming the feasibility of the proposed mechanochemical process.

The scope was validated with a diverse set of disulfides **III-7a-III-7n** and amines **III-9-III-16**, resulting in 61 sulfonamides with good to excellent yields (Scheme 8). Compatibility was demonstrated with multi-functional groups, hydroxy residues, and amines bearing various functionalities.



Scheme 8. One-pot, two-step sulfonamide synthesis, including aromatic, aliphatic, secondary, and cyclic amines. Mechanochemical reaction conditions: disulfide 1a-j (1.00 mmol), NaHSO4 (10 mol%), and NaOCl*5H2O (6.00 mmol) were added and placed in a 15 mL jar equipped with two zirconia balls (Φ = 8.00 mm, masstot = 3.22 g). The reaction was then carried out for 40-180 min at 30 Hz. At the end of the reaction, the vessel was opened, and amine 3-8 (1.10 equiv.) and MgO (4 mmol) were eventually added to the resulting mixture. The second step was then performed for 120 min at a frequency of 30 Hz. Yields refer to isolated compounds.

Notably, a potential pathway for synthesizing the NSAID nimesulide was outlined. On top of this, despite initial challenges in synthesizing pharmaceuticals (**III-15d** and **III-16d**), the approach's eco-sustainability and reduced toxicity were effectively demonstrated. Liquid Assisted Grinding (LAG) addressed issues, utilizing N-methyl imidazole as a solvent alternative. Green metrics calculations underscored the environmentally friendly nature of the methodology and its contribution to eco-sustainability, particularly in comparison to traditional solution-based protocols.

3.3 Discussion: Multi-step and Telescopic Syntheses for Convenient Scaffolds Manufacturing

The strengths of the isocyanide methodology were emphasized by its solvent-free and straightforward nature, suggesting its suitability for industrial scale-up. The ability to convert the saccharin by-product into a non-toxic sodium salt provided an eco-friendly insight to the entire process. Notably, the recovery of residual saccharinate salt as a solid at the end of each reaction showcased a practical and efficient recyclability assessment of the methodology, contributing to its overall attractiveness in sustainable synthesis.

This innovative approach, exemplified in the sequential synthesis of formamides and isonitriles, underscores the importance of starting with simple reaction models to understand the general features of a mechanochemical protocol. This foundational knowledge enables the expansion of these concepts to more complex molecular structures. In the case of formamides, a step-wise approach with an intermediate purification step highlighted the adaptability of the methodology to diverse molecular architectures while maintaining the principles of *Green Chemistry*. The purification of formamides using environmentally benign solvents like ethyl acetate, followed by solvent recovery and recycling, exemplifies a sustainable model in chemical process design.

Conversely, the synthesis of sulfonyl chlorides and their subsequent transformation into sulfonamides, following a telescopic approach, demonstrates the efficiency of conducting multiple synthetic steps in a single reactor without any intermediate purifications. This strategy effectively reduces the overall reaction time, labour, and potential waste, signifying a leap toward more sustainable and efficient process chemistry. The final purification involving a simple wash with citric

acid aligns with eco-friendly practices and simplifies the process, enhancing its practicality for industrial applications.

While slightly differing in their approach, both methodologies converge on the principle of performing sequential syntheses using mechanochemistry. This solvent-free technique, applied consistently throughout the synthetic sequence, circumvents the paradoxes often encountered in traditional multistep syntheses through mechanochemical conditions, such as using solvents in one step counteracting the sustainable benefits achieved in another. By employing mechanochemistry from start to finish, these protocols contribute to a novel perspective for sustainable synthesis, challenging conventional methodologies and demonstrating the feasibility of complex, sequential syntheses in a green and efficient manner.

The cumulative impact of this work lies in its demonstration of a scalable, solvent-free, and eco-friendly approach to sophisticated molecular synthesis. This paradigm shift in process chemistry enhances the sustainability of chemical manufacturing and paves the way for future innovations in green synthesis, opening new avenues for environmentally conscious industrial applications.

4. Catalytic Hydrogenation as Model Reaction for Process Investigation

In organic synthesis, catalytic hydrogenation stands as a cornerstone, essential for building diverse molecules.[62] This process, critical in forming pharmaceuticals, agrochemicals, and materials, epitomizes the fusion of efficiency and versatility.[63] The move towards a deeper understanding of the kinetics in mechanochemical reactions, particularly in hydrogenation reactions, opens a new horizon in scalable and manageable chemical processes, both academically and industrially.[64]

As reported in this chapter, developing a novel mechanochemical route for synthesizing and harnessing diboron compounds explains this advancement.[65] Abandoning dichloromethane, a volatile organic compound fraught with environmental and operator hazards,[66] this new method employs a solvent-free approach, simply mixing reagents inside a stainless-steel jar. This adaptation aligns with the principles of *Green Chemistry* and underscores the significance of optimizing reaction conditions to enhance yields. The observed reaction sensitivity to mechanical deformation highlights the intricate relationship between reaction conditions and product formation, an essential aspect of reaction kinetics in mechanochemistry.[67]

The use of the synthesized diboron compound in reducing aldehydes and ketones further accentuates the versatility of this methodology. The need of mechanical deformation for effective reaction progression, as demonstrated by the stark contrast in yields with and without a milling ball, underscores the importance of understanding the mechanistic aspects of mechanochemical processes.

Furthermore, the fulcrum of the methodology involves catalytic hydrogenation of unsaturated substrates, using a combination of diboron compounds and palladium on carbon, showcasing the adaptability of mechanochemistry in synthesizing a diverse array of chemical structures.

This chapter, therefore, not only presents a series of optimized mechanochemical protocols for synthesizing several molecules but also serves as a witness to the potential of mechanochemistry in developing a sustainable industrial scale-up. By prioritizing efficiency, and scalability, the research encapsulated in this section paves the way for a new era of green and sustainable chemical manufacturing, challenging traditional paradigms and setting a precedent for future innovations in the field.

4.1 Results: Optimization – Scope for a Model Reductive Process

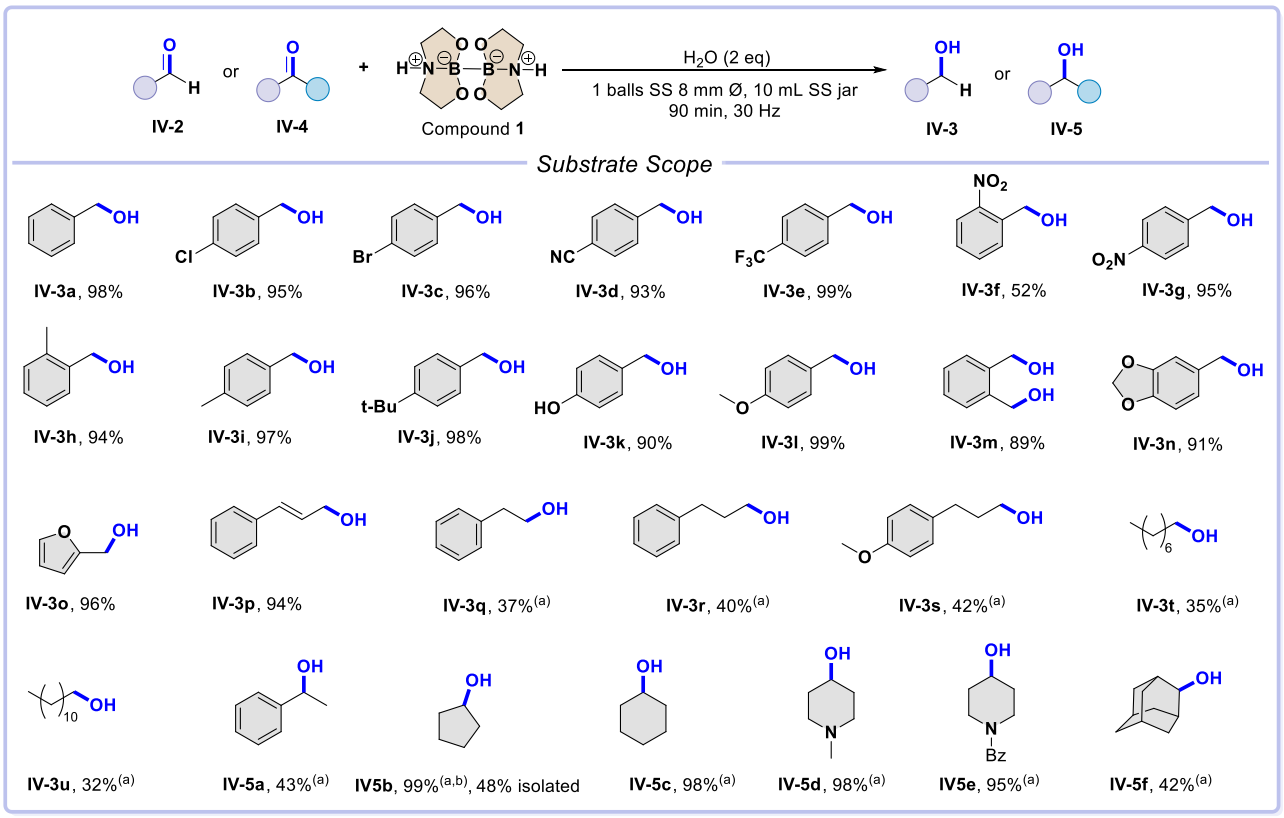
The literature outlines the preparation of diboron compound **IV-1** using diethanolamine and tetrahydroxydiboron in dichloromethane (10 mL/mmol).[68] However, due to the environmental and operator hazards of this volatile organic compound (VOC), we developed a new synthetic route employing a mechanochemical approach.[69] This involves mixing diethanolamine (2 mmol) and tetrahydroxydiborane (1 mmol) without solvent. Optimal results were obtained with solvent-free conditions in a 10 mL SS jar with one SS ball (8 mm φ, 2.09 g mass) at 30 Hz for 20 minutes, yielding diboron compound **IV-1** at 85% (Entry 4, Table 3). Varying reaction time and frequency impacted yields (Table 3), indicating the significance of mechanical deformation. The compound was further tested to reduce aldehydes and ketones, with benzaldehyde **IV-2a** as the model substrate. Ball milling benzaldehyde **IV-2a** (1 mmol), diboron compound **IV-1** (2 mmol), and H_2O (2 mmol) in a 10 mL SS jar with one SS ball (8 mm φ, 2.09 g mass) at 30 Hz for 90 min resulted in a 98% yield of benzyl alcohol **IV-3a**. Notably, shaking the jar without balls only yielded 8% of the desired product **IV-3a**, highlighting the necessity of mechanical deformation for correct reaction occurrence.

Table 3. Screening of reaction conditions for the reduction of carbonyl compounds.

Entry	Time	Frequency	Material	Balls	Yield[b]
1	5 min	30 Hz	SS	1 (8 mm)	7%
2	10 min	30 Hz	SS	1 (8 mm)	23%
3	15 min	30 Hz	SS	1 (8 mm)	67%
4	20 min	30 Hz	SS	1 (8 mm)	84%
5	20 min	30 Hz	SS	5 (4 mm)	34%
6	20 min	25 Hz	SS	1 (8 mm)	79%
7	20 min	30 Hz	ZrO_2	1 (8 mm)	83%
8	20 min	30 Hz	Ertalyte®	1 (8 mm)[a]	81%
9	20 min	30 Hz	SS	none	5%

Optimization screening for the diboron compound **1** synthesis. Reaction stoichiometry: diethanolamine (2 mmol) and tetrahydroxydiboron (1 mmol), 10 mL jar. If not otherwise stated, the material of the balls employed was the same as the one composing the jar. [a] ZrO_2 ball. [b] Yields refer to isolated products.

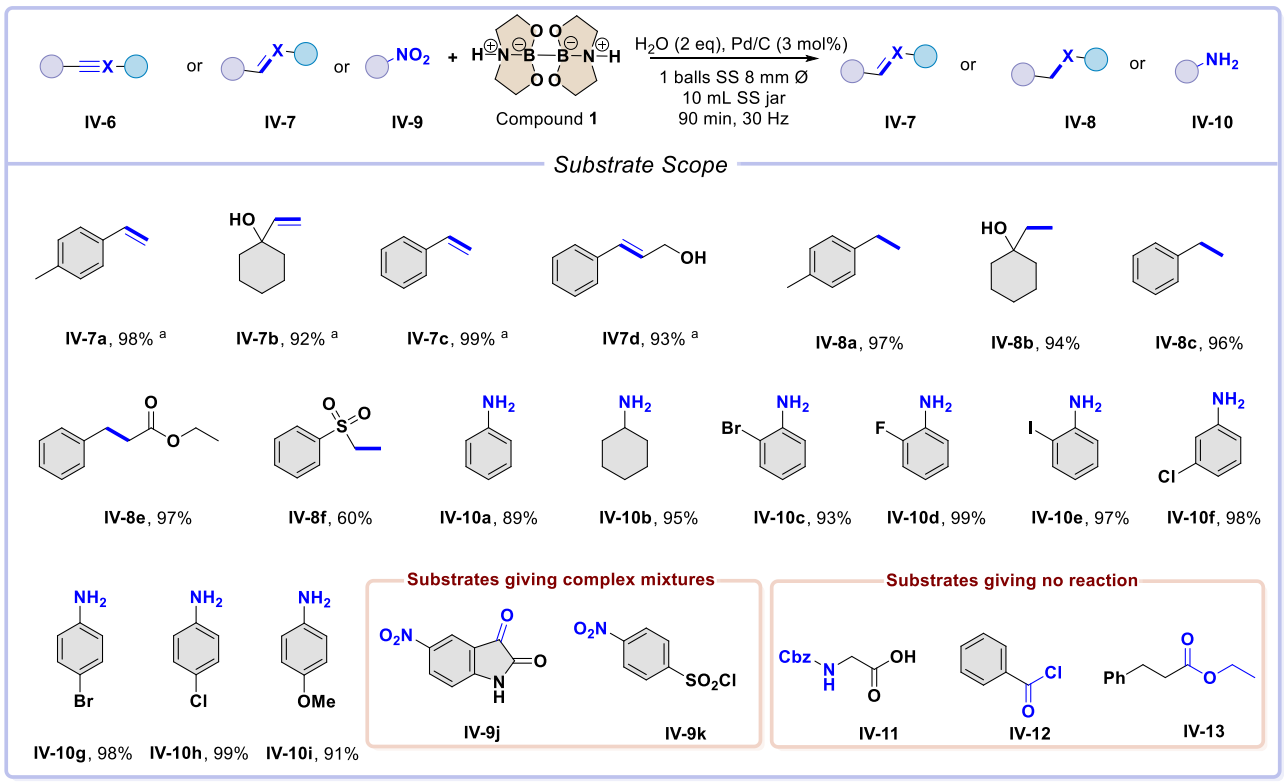
The reaction displayed similar trends for benzaldehydes **IV-2be** and **IV-2g-IV-2n**, achieving excellent yields for corresponding alcohols (Scheme 9). Alcohols **IV-3b-IV-3e** yielded 93-99% yields, while alcohols **IV-3g-IV-3n** exhibited 89-99% yields. However, decreased yields for compound **IV-3f** (52%) can be attributed to steric hindrance from the nitro moiety. Heterocyclic and conjugated aldehydes **IV-2o-IV-2p** yielded excellent alcohols **IV-3o-IV-3p** (96% and 94%, respectively). Conversely, aliphatic aldehydes or ketones required one equivalent of LiCl to enhance the reaction rate. For example, ketones **IV-4a-IV-4f** produced alcohols **IV-5a-IV-5f** with yields of 78-99% (Scheme 9). LiCl's dual role in promoting carbonyl activation as a Lewis acid and forming more robust reducing species near lithium borohydride reactivity is noteworthy.



Scheme 9. The reaction scope for the reduction of aldehyde and ketones. Typical procedure: carbonyl compound (1 mmol), compound **1** (2 mmol), and H_2O (2 mmol) were placed inside a 10 mL SS jar with one ball of the same material (Ø = 8 mm, 2.09 g). The reaction was conducted for 90 min at room temperature, 30 Hz, and under ball milling conditions. Yields refer to isolated products if not otherwise stated. [a] LiCl (1 mmol) was used as an additive. [b] The yield was calculated by GC-MS analysis.

Having optimized carbonyl reduction, we focused on catalytic hydrogenation of unsaturated substrates, using alkyne **IV-6a** as the model. In a 10 mL SS jar, we mixed 4-methyl phenylacetylene **IV-6a** (1 mmol), diboron compound **IV-1** (2 mmol), Pd/C (3 mol%), and H_2O (2 mmol), ball-milling at 30 Hz for 90 minutes. Gratifyingly, we obtained alkane **IV-8a** with a 97% yield, confirming complete reduction. These optimized conditions were applied to alkynes (**IV-6ac**) and alkenes (**IV-7a-IV-7f**), yielding corresponding alkanes **IV-8a-IV-8c** and **IV-8e-IV-8f** (60-97% yield). Synthesizing alkenes **IV-7a-IV-7d** from the corresponding alkyne presented challenges, but using a

smaller ball (2mm φ, 0.3 g mass) improved the yield of alkene **IV-7a** to 89%. Experiments shaking the jar without grinding media resulted in complete alkene conversion. Our reported protocol selectively interrupts reduction at the semi-hydrogenation stage, demonstrating impressive yields of corresponding alkenes (92-99%). Expanding reactions to nitro derivatives **IV-9a-IV-9i** under modified conditions using three mmol of diboron compound **IV-1** yielded anilines **IV-10a-IV-10i** with outstanding yields (Scheme 10, 89-99% isolated yields). Some screened compounds resulted in complex mixtures (compounds **IV-9j** and **IV-9k**), while others did not react (substrates **IV-11**, **IV-12**, and **IV-13**) under specified Scheme 10 conditions.



Scheme 10. The reaction scope for the catalytic hydrogenation of alkanes, alkenes, and nitro compounds. Typical procedure: alkyne, alkene, or nitro compound (1 mmol), compound **1** (2 mmol), Pd/C (3 mol%), and H_2O (2 mmol) were placed inside a 10 mL SS jar with one ball of the same material (Ø = 8 mm, 2.09 g). The reaction was conducted for 90 min at room temperature, 30 Hz, and under ball milling conditions. See paper for the specific reaction conditions. [a] The yield calculated by GC-MS analysis.

4.2 Discussion: The Relationship Between Physical State, Reaction Rate, and Interface Area in Catalytic Hydrogenation

The investigation extends these findings by offering a more nuanced understanding of the kinetic behaviours and the impact of the physical state of reactants in hydrogenation reactions.

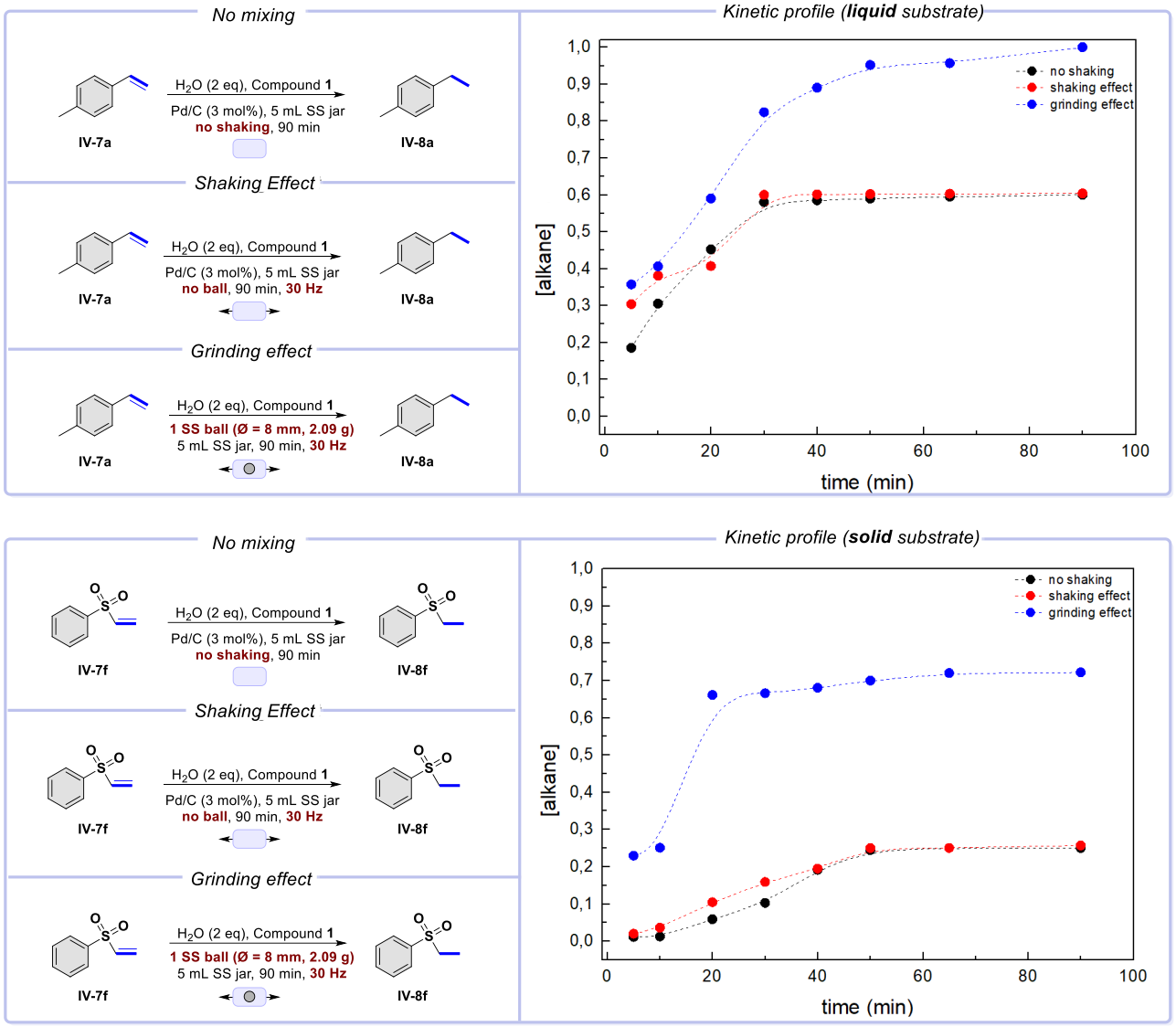
It was meticulously examined the hydrogenation of a liquid alkene **IV-7a** and observed an intriguing phenomenon. Under static conditions, without the application of external mechanical forces, the liquid alkene demonstrated a remarkable 60% conversion rate. This finding is pivotal as it underscores the inherent ability of liquid reagents to interact effectively with hydrogen gas. The

molecular mobility and fluidity in the liquid state facilitate enhanced absorption and diffusion of hydrogen, leading to substantial reaction progress even in the absence of mechanical agitation. Such behaviour aligns with the control experiment performed under shaking conditions without any milling tool, corroborating these findings. The addition of a grinding media, namely one stainless steel ball, simply accelerates the reaction kinetics, as evidence in the plot in Scheme 11.

In stark contrast, the experiments with a solid alkene **IV-7f** revealed a vastly different kinetic profile. The hydrogenation of solid alkenes under static conditions resulted in a considerably lower conversion rate. This discrepancy highlights a fundamental aspect of mechanochemistry: the critical role of physical state in dictating reaction efficiency. Solid reagents, with their limited molecular mobility and surface exposure, exhibit a diminished capacity to absorb and diffuse hydrogen gas within the bulk. Consequently, their interaction with hydrogen is primarily confined to the surface regions, leaving the bulk of the material largely unreacted.

The necessity of mechanical impact in altering the crystalline structure of solid reagents and enhancing its surface area becomes evident here. The introduction of a milling ball into the reaction mixture marked an increase in conversion rate. This enhancement can be attributed to the mechanical deformation caused by the milling ball, which not only disrupts the crystalline structure but also significantly increases the interface area between the chemical species. The grinding action exposes new surfaces of the solid alkene, creating additional active sites for hydrogen interaction. This mechanistic insight is crucial in understanding the differential behaviour of solid reagents in mechanochemical hydrogenation. It highlights the profound impact of mechanical forces in modifying the physical properties of solids, thereby facilitating more effective chemical reactions.

By elucidating these aspects, this chapter addresses the industrial scalability of mechanochemical reactions. Indeed, providing a clear demonstration of how the physical state of reagents influence their reactivity and susceptibility to mechanochemical processes, a process chemist can efficiently control an increased scale for industry. The distinct responses of liquid and solid reagents to hydrogen gas and mechanical forces underscore the complexity and versatility of mechanochemistry. This chapter not only offers optimized protocols for various molecular syntheses but also sheds light on some fundamental principles governing the interaction between physical state, mechanical deformation, and chemical reactivity. As such, it paves the way for future advancements in green and sustainable chemical manufacturing, challenging conventional methods and setting new benchmarks for industrial scalability and efficiency.

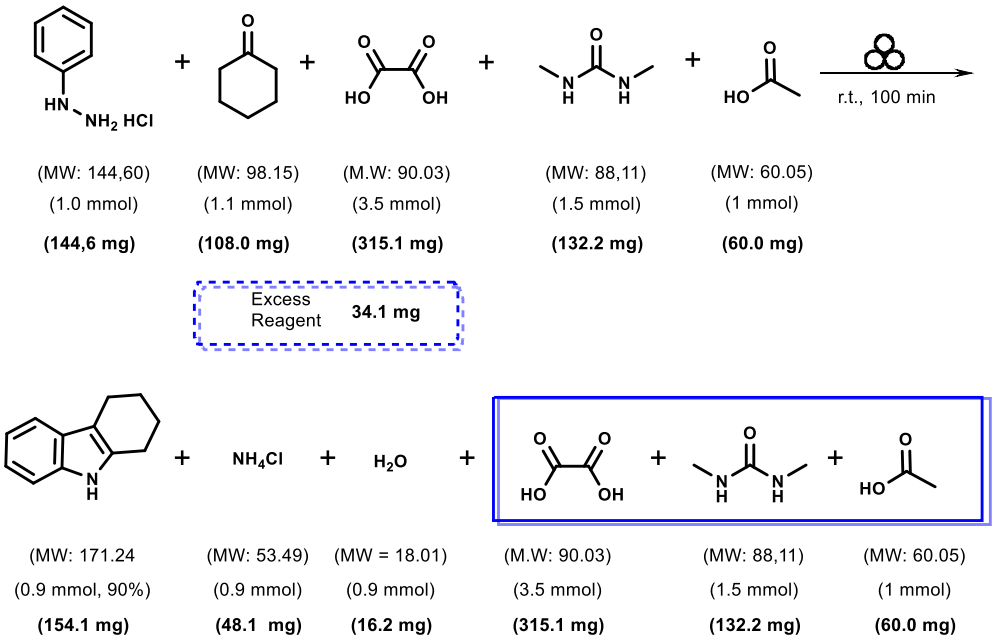


Scheme 11. The control experiments and kinetics for liquid (above) and solid (below) starting materials. Typical procedure: solid or liquid alkene (0.3 mmol), compound **1** (0.6 mmol), Pd/C (3 mol%), and H_2O (2 mmol) were placed inside a 5 mL SS jar. Whenever a ball was used, 1 SS ball (Ø = 8 mm, 2.09 g) was placed inside the reaction vessel. The conversion was calculated by GC-MS analysis

5. Green Chemistry Metrics

The present chapter include all the green chemistry assessments and metrics for the previously discussed topics, each divided by the corresponding chapter. Within this, there will be the Green Chemistry features in terms of Environmental factor (*E*-factor), Eco-scale assessment, and, where needed, atom economy and mass efficiency.

5.1 Green Metrics and Assessments for Chapter II



$$\text{Enviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(34.1 + 48.1 + 16.2 + 315.1 + 132.2 + 60.0)\ \text{mg}}{154.1\ \text{mg}} = \frac{605.7\ \text{mg}}{154.1\ \text{mg}} = \mathbf{3.9}$$

Work-up: 6000 mg of H_2O **or** 5400 mg EtOAc and 1500 mg silica

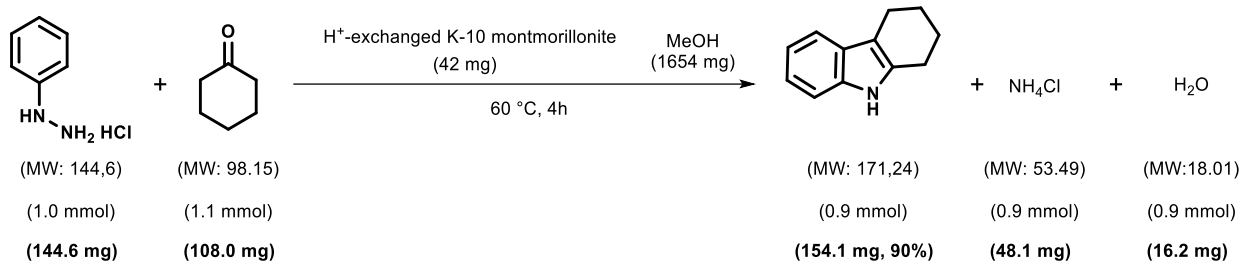
$$\textit{E} \text{ (after purification, aqueous work-up)} = \frac{(6000\ \text{mg} + 606\ \text{mg})}{154.1\ \text{mg}} = \frac{6606\ \text{mg}}{154.1\ \text{mg}} = \mathbf{42.9}$$

$$\textit{E} \text{ (after purification, silica filtration work-up)} = \frac{6900\ \text{mg} + 606\ \text{mg})}{154.1\ \text{mg}} = \frac{7506\ \text{mg}}{154.1\ \text{mg}} = \mathbf{48.7}$$

Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2$. HCl	144.60	0.1446	1.0	1.0
Cyclohexanone	$C_6H_{10}O$	98.15	0.1080	1.1	1.1
Dimethyl urea	$C_3H_8N_2O$	88.11	0.1322	1.5	1.5
Oxalic acid	$C_2H_2O_4$	90.03	0.3150	3.5	3.5
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1.0	1.0
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
1,2,3,4-Tetrahydrocarbazole	$C_{12}H_{13}N$	171.24	0.1545	0.9	90%

Entry	Parameters	Penalty Points
1	Yield (90%)	-5
2	Price/availability	-8
3	Safety	-10
4	Technical set-up (Unconventional activation technique)	-2
5	Room temperature (< 24h)	-1
6	Work-up and purification	0
	EcoScale Score	**74**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



Work-up: DCM (5532 mg), brine (5000 mg).

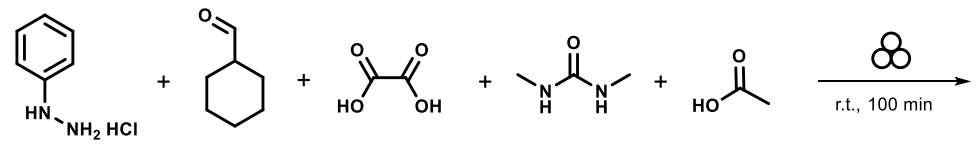
$$\text{Enviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(34.1 + 48.1 + 16.2 + 1654)\ \text{mg}}{154.1\ \text{mg}} = \frac{1784.5\ \text{mg}}{154.1\ \text{mg}} = \mathbf{11.4}$$

$$\textit{E}\ \text{(after purification, solvent work-up)} = \frac{(10532 + 1784)\ \text{mg}}{154.1\ \text{mg}} = \frac{12316\ \text{mg}}{154.1\ \text{mg}} = \mathbf{79.9}$$

Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2 \cdot HCl$	144.60	0.1446	1.0	1.0
Cyclohexanone	$C_6H_{10}O$	98.15	0.1079	1.1	1.1
Montmorillonite KSF			0.0420		
Methanol	CH_4O	32.04	1.6400	51.3	51.3
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
1,2,3,4-Tetrahydrocarbazole	$C_{12}H_{13}N$	171.24	0.1545	0.9	90%

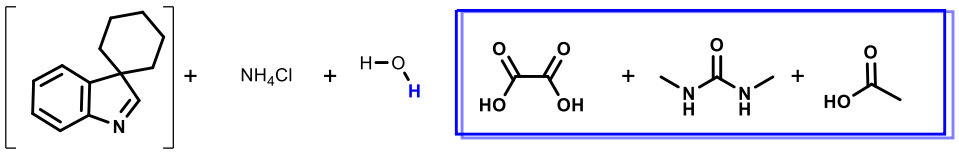
Entry	Parameters	Penalty Points
1	Yield (90%)	-5
2	Price/availability	-5
3	Safety	-20
4	Technical set-up (Common set-up)	0
5	Temperature/time (Heating, > 1h)	-3
6	Work-up and purification (liquid-liquid extraction or washing)	-3
	EcoScale Score	**64**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



(MW: 144,60) (1.0 mmol) **(144.6 mg)** | (MW: 112.2) (1.1 mmol) **(123.4 mg)** | (M.W: 90.03) (3.5 mmol) **(315.1 mg)** | (MW: 88,11) (1.5 mmol) **(132.2 mg)** | (MW: 60.05) (1 mmol) **(60.0 mg)**

Excess Reagent : **75.4 mg**

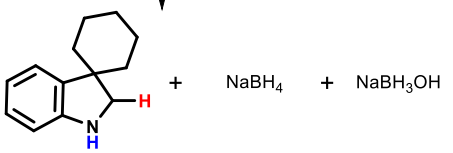


(MW: 185.27)

(MW: 53.49) 0.75 mmol **(40.1 mg)** | MW: 18.01) 0.75 mmol **(13.5 mg)** | (M.W: 90.03) (3.5 mmol) **(315.1 mg)** | (MW: 88,11) (1.5 mmol) **(132.2 mg)** | (MW: 60.05) (1 mmol) **(60.0 mg)**

Overall Isolated yield[a] = 75%

$NaBH_4$ (MW: 37.83) (2.0 mmol) **(75.7 mg)**



(MW: 187.29) (0.75 mmol) **(140.5 mg, 75%)** | (MW: 37.83) 1.25 mmol **(47.3 mg)** | (MW: 53.84) 0.75 mmol **(40.4 mg)**

[a]Last step assumed quantitative

Enviromental factor (***E***) = $\frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(75.4 + 40.1 + 13.5 + 315.1 + 132.2 + 60.0 + 47.3 + 26.9)\ mg}{140.5\ mg} = \frac{710.5\ mg}{140.5\ mg} =$ **5.0**

Work-up: H_2O (6000 mg), EtOAc (5400 mg), silica (4000 mg), hexane (10400 mg), EtOAc (3600 mg)

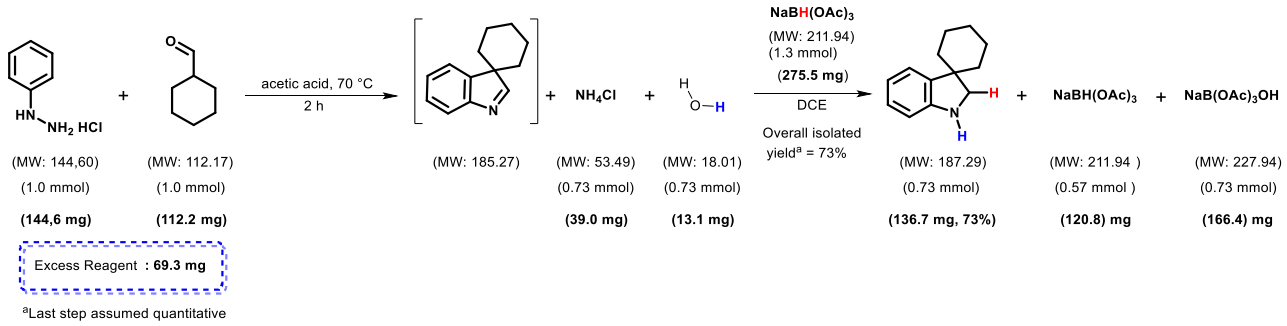
E (after purification: liquid-liquid extraction, filtration on silica plug) = $\frac{(6000\ mg + 5400 + 4000 + 10400 + 3600 + 710)\ mg}{140.5\ mg} = \frac{30110\ mg}{140.5\ mg} =$ **214.3**

Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2$. HCl	144.60	0.1446	1.1	1.1
Cyclohexanecarboxaldehyde	$C_7H_{12}O$	112.17	0.1122	1.1	1.1
Dimethyl urea	$C_3H_8N_2O$	88.11	0.1322	1.5	1.5
Oxalic acid	$C_2H_2O_4$	90.03	0.3150	3.5	3.5
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1.0	1.0
Sodium borohydride	H_4BNa	37.83	0.0940	2.5	2.5

Product	MF	MW	g	mmol	Yield
Spiro[cyclohexane-1,3'-indoline]	$C_{13}H_{17}N$	187,14	0.140	0.75	75%

Entry	Parameters	Penalty Points
1	Yield (75%)	-12
2	Price/availability	0
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-2
5	Temperature/time (r.t, > 1h)	0
6	Work-up and purification (liquid-liquid extraction, classical chromatography	-13
	EcoScale Score	**52.5**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



Solvent 1st step: acetic acid = 3.33 mL (3.500 mg)

Solvent 2nd step: 1,2-dichloroethane = 3.33 mL (4.162 mg)

$$\text{Enviromental factor } (E) = \frac{\textit{mass of total waste}}{\textit{mass of desired product}} = \frac{(69.3 + 39.0 + 120.8 + 166.4 + 3500 + 4162)\ \text{mg}}{136.7\ \text{mg}} = \frac{8057.5\ \text{mg}}{136.7\ \text{mg}} = \mathbf{58.9}$$

Work-up: H_2O (6000 mg), Na_2CO_3 (600 mg), EtOAc (5400 mg), silica (4000 mg), hexane (10400 mg), EtOAc (3600 mg)

$$\textbf{\textit{E}} \text{ (after purification, aqueous work-up)} = \frac{(6000 + 600 + 5400 + 4000 + 10400 + 3600 + 8057)\ \text{mg}}{136.7\ \text{mg}} = \frac{38057\ \text{mg}}{136.7\ \text{mg}} = \mathbf{278.4}$$

Reagents	MF	MW	g	mmol	Equiv.
Phenylhydrazine hydrochloride	$C_6H_8N_2$ .HCl	144.60	0.1446	1	1
Cyclohexanecarboxaldehyde	$C_7H_{12}O$	112.17	0.112172	1.1	1.1
Acetic acid	$C_2H_4O_2$	60.05	0.0600	1	1
1,2-Dichloroethane	$C_2H_4Cl_2$	98.96	4.162	42	139
Sodium borohydride	H_4BNa	37.83	0.094	58	192
Product	**MF**	**MW**	**g**	**mmol**	**Yield**
spiro[cyclohexane-1,3'-indoline]	$C_{13}H_{17}N$	187,14	0.138	0.74	74%

Entry	Parameters	Penalty Points
1	Yield (75%)	-13
2	Price/availability	0
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (heating, > 1h, cooling to 0 °C)	-7
6	Work-up and purification (liquid-liquid extraction, classical chromatography	-13
	EcoScale Score	**45**

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

5.2 *Green Metrics and Assessments for Chapter III*

Excess Reagents	21,12 mg (*N*-Formylsaccharin)
Work-up Base	84,01 mg ($NaHCO_3$)
Work-up Solvent	3600 mg (4 mL EtOAc)

$$\textbf{A}\text{tom }\textbf{E}\text{conomy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{149{,}19}{121{,}18 + 211{,}19} \times 100 = 45\%$$

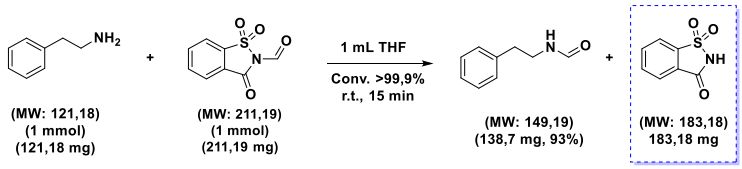
$$\textbf{E}\text{nvironmental }\textbf{F}\text{actor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{183{,}18 + 21{,}12 + 3600{,}00 + 84{,}01}{144{,}7} = 26{,}9$$

$$\textbf{R}\text{eaction }\textbf{M}\text{ass }\textbf{E}\text{fficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{144{,}7}{121{,}2 + 232{,}3} \times 100 = 41\%$$

Reagents	MF	MW	G	mmol	Equiv.
Phenetylamine	$C_8H_{11}N$	121.18	0.1212	1.00	1.00
N-Formylsaccharin	$C_8H_5NO_4S$	211.19	0.2323	1.10	1.10
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Formamide, *N*-(2-phenylethyl)-	$C_9H_{11}NO$	149.19	0.1447	0.97	97%

Entry	Parameters	Penalty Points
1	Yield (97%)	-1.5
2	Price/availability	-5
3	Safety	0
4	Technical set-up (Common set-up)	0
5	Temperature/time (r.t.; < 1 h)	0
6	Work-up and purification (adding a solvent)	0
	Eco-Scale Score	93.5

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



Excess Reagents	-
Work-up Base	955 mg ($NaHCO_3$)
Work-up Solvent	890 mg (THF 1 mL) 39900 mg (DCM 30 mL) 10000 mg (H_2O)

$$\textbf{A}\text{tom }\textbf{E}\text{conomy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{149{,}19}{121{,}18 + 211{,}19} \times 100 = 45\%$$

$$\textbf{E}\text{nvironmental }\textbf{F}\text{actor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{183{,}2 + 955{,}0 + 890{,}0 + 39900{,}0 + 10000{,}0}{138{,}7} = 374{,}4$$

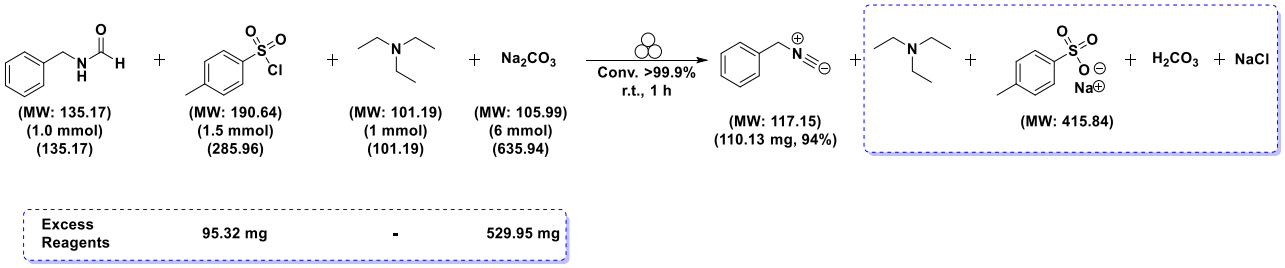
$$\textbf{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100$$

$$\textbf{RME} = \frac{138{,}7}{121{,}18 + 211{,}19} \times 100 = 42\%$$

Reagents	MF	MW	G	mmol	Equiv.
Phenetylamine	$C_8H_{11}N$	121.18	0.1212	1.00	1.00
N-Formylsaccharin	$C_8H_5NO_4S$	211.19	0.2112	1.00	1.00
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Formamide, *N*-(2-phenylethyl)-	$C_9H_{11}NO$	149.19	0.1387	0.93	93%

Entry	Parameters	Penalty Points
1	Yield (93%)	-3.5
2	Price/availability	-3
3	Safety	0
4	Technical set-up (Common set-up)	0
5	Temperature/time (r.t.; < 1 h)	0
6	Work-up and purification (adding a solvent, liquid-liquid extraction or washing)	-3
	Eco-Scale Score	90.5

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



$$\textbf{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{117{,}15}{532{,}99} \times 100 = 22\%$$

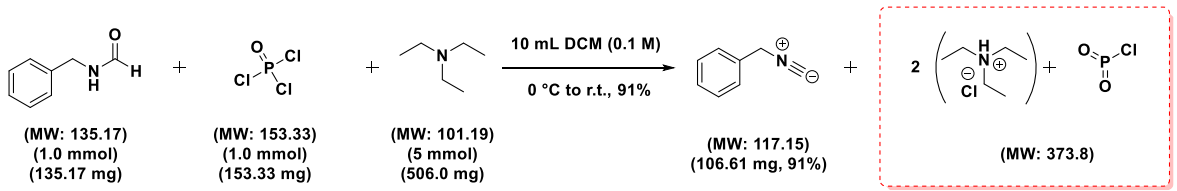
$$\textbf{E}\text{nvironmental }\textbf{F}\text{actor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{194{,}18 + 95{,}32 + 58.44 + 101{,}19 + 529{,}95 + 62.03}{110{,}13} = 9{,}5$$

$$\textbf{R}\text{eaction }\textbf{M}\text{ass }\textbf{E}\text{fficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{110{,}1}{135{,}2 + 286{,}0 + 101{,}2 + 635{,}9} \times 100 = 9{,}5\%$$

Reagents	MF	MW	G	mmol	Equiv.
N-Benzylformamide	C8H9NO	135.16	0.1352	1	1
p-Toluenesulfonyl chloride	C7H7ClO2S	190.64	0.2860	1.5	1.5
Triethylamine	C6H15N	101.19	0.1012	1	1
Sodium carbonate	CNa2O3	105.99	0.6360	6	6
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Benzyl isocyanide	C8H7N	117.15	0.1102	0.94	94%

Entry	Parameters	Penalty Points
1	Yield (94%)	-3
2	Price/availability	-5
3	Safety	-10
4	Technical set-up (Common set-up)	0
5	Temperature/time (r.t.; < 24 h)	-1
6	Work-up and purification	0
	EcoScale Score	81

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



$$\textbf{A}\text{tom }\textbf{E}\text{conomy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{117{,}15}{389{,}68} \times 100 = 30\%$$

$$\textbf{E}\text{nvironmental }\textbf{F}\text{actor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{303.6 + 13300{,}0 + 373.8}{106{,}6} = 131.1$$

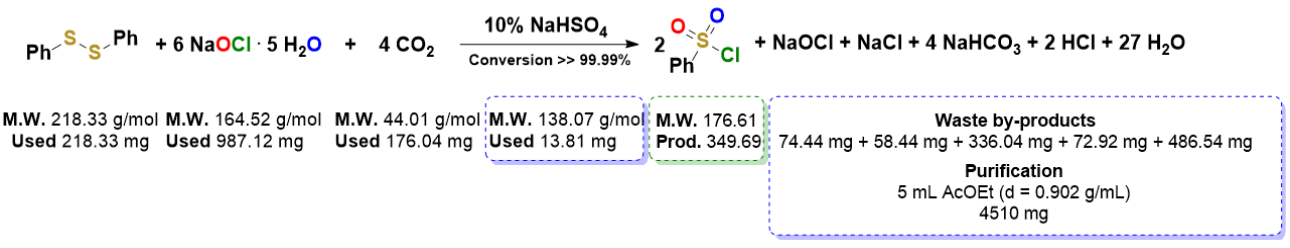
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100$$

$$\textbf{RMS} = \frac{106{,}61}{135{,}16+505{,}96+153{,}33} \times 100 = 13{,}42\%$$

Reagents	MF	MW	G	mmol	Equiv.
N-Benzylformamide	C8H9NO	135.16	0.1352	1	1
Phosphorus oxychloride	Cl3OP	153.33	0.15333	1	1
Triethylamine	C6H15N	101.19	0.5060	5	5
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Benzyl isocyanide	C8H7N	117.15	0.1066	0.91	91%

Entry	Parameters	Penalty Points
1	Yield (91%)	-4
2	Price/availability	-5
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-2
5	Temperature/time (Cooling to 0 °C)	-4
6	Work-up and purification (Classical chromatography)	-10
	EcoScale Score	55

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{353.22}{372.20+18.02+88.02+218.33} \times 100 = 51.00\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{13.81+74.44+58.44+336.04+72.92+486.54+4510.00}{349.69} = 15.88$$

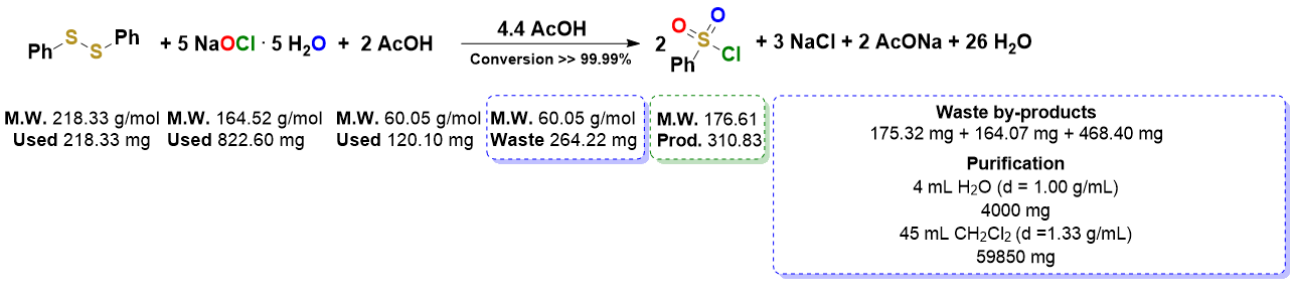
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{349.69}{218.33 + 987.12 + 176.04 + 13.81} \times 100 = 25.00\ \%$$

It is worth pointing out that we considered in our E-Factor calculations the amount of solvent used for the recovery of the product. If this value is neglected (due to the reusability of the solvent after distillation under reduced pressure), the E-Factor of our procedure should be:

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{13.81 + 74.44 + 58.44 + 336.04 + 72.92 + 486.54 + \sout{(1510.00)}}{349.69} = 2.98$$

Reagents	MF	MW	G	mmol	Equiv.
Phenyl disulfide	C12H10S2	218.33	0.21833	1	1
Hypochlorite salts	H10O6ClNa	164.52	0.9871	6	6
Sodium bisulfate	HNaO4S	120.06	0.012	0.1	0.1
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Benzenesulfonyl chloride	C6H5ClO2S	176.62	0.3532	1.99	99%

Entry	Parameters	Penalty Points
1	Yield (99%)	-0.5
2	Price/availability	-3
3	Safety	-5
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (Cooling to 0 °C)	0
6	Work-up and purification (Classical chromatography)	0
	EcoScale Score	91.5



$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{353.22}{218.33 + 329.04 + 60.05} \times 100 = 58\%$$

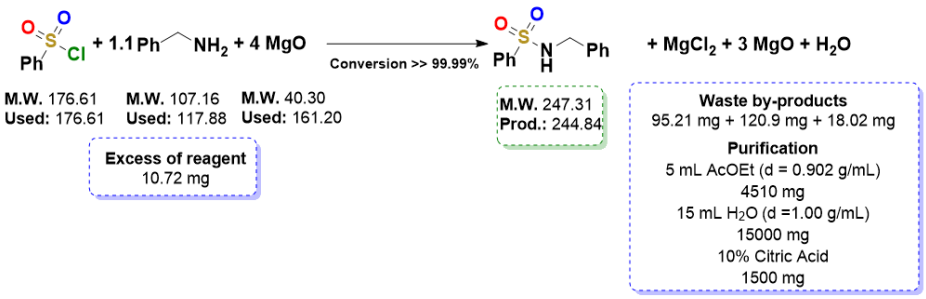
$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{264.22 + 175.32 + 164.07 + 468.40 + 4000 + 59850}{310.83} = 208.87$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{310.83}{218.33 + 822.60 + 120.10 + 264.22} \times 100 = 21.80\ \%$$

Reagents	MF	MW	G	mmol	Equiv.
Phenyl disulfide	C12H10S2	218.33	0.21833	1	1
Hypochlorite salts	H10O6ClNa	164.52	0.8225	5	5
Acetic Acid	C2H4O2	120.06	0.3843	6.4	6.4
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Benzenesulfonyl chloride	C6H5ClO2S	176.62	0.3532	1.76	88%

Entry	Parameters	Penalty Points
1	Yield (88%)	-6
2	Price/availability	-3
3	Safety	-5
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (Cooling to 0 °C)	0
6	Work-up and purification (Classical chromatography)	-3
	EcoScale Score	83

http://ecoscale.cheminfo.org/calculator



$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{247.31}{176.61 + 107.16 + 40.30} \times 100 = 76\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{95.21 + 120.9 + 18.02 + 4510 + 15000 + 1500 + 10.72}{244.84} = 86.81$$

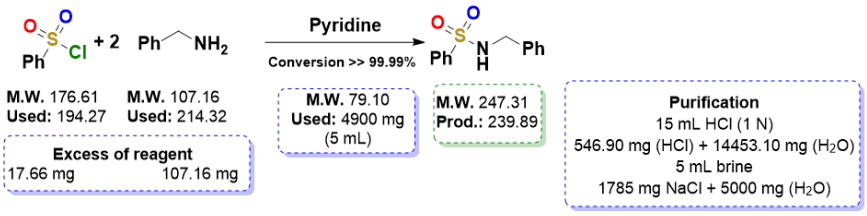
$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{244.84}{176.61 + 117.88 + 161.20} \times 100 = 53.7\ \%$$

It is worth pointing out that we considered in our E-Factor calculations the amount of solvent used for the recovery of the product, and both the solvent and the acid mass for the purification washes. If the value for all of this is neglected (due to the reusability of the solvent after distillation under reduced pressure), the E-Factor of our procedure should be:

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{95.21 + 120.9 + 18.02 \ \cancel{(+ 4510 + 15000 + 1500)} + 10.72}{244.84} = 1.00$$

Reagents	MF	MW	G	mmol	Equiv.
Benzenesulfonyl chloride	C6H5ClO2S	176.62	0.17662	1	1
Benzylamine	C7H9N	107.16	0.1179	1.1	1.1
Magnesium Oxide	MgO	40.30	0.1612	4	4
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
N-(phenylmethylbenzenesulfonamide	C13H13NO2S	247.31	0.4946	1.99	99%

Entry	Parameters	Penalty Points
1	Yield (99%)	-0.5
2	Price/availability	0
3	Safety	0
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (Cooling to 0 °C)	-1
6	Work-up and purification (Classical chromatography)	-3
	EcoScale Score	95.5



$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{247.31}{176.61 + 107.16 + 79.10} \times 100 = 68.2\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{17.66 + 107.16 + 4900 + 546.90 + 14453.10 + 1785 + 5000}{239.89} = 111.76$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{239.89}{194.27 + 214.32 + 4900} \times 100 = 4.5\ \%$$

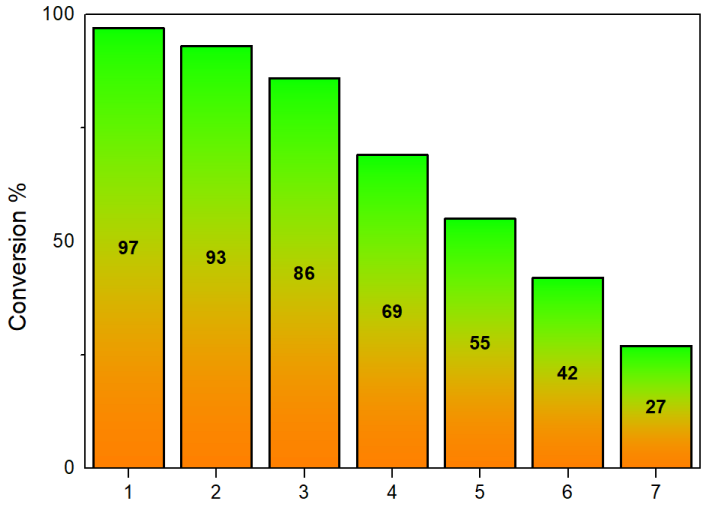
Reagents	MF	MW	G	mmol	Equiv.
Benzenesulfonyl chloride	C6H5ClO2S	176.62	0.17662	1	1
Benzylamine	C7H9N	107.16	0.2143	2	2

Pyridine	C5H5N	79.10	4.89	61.82	61.82
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
N-(phenylmethylbenzenesulfonamide	C13H13NO2S	247.31	0.4946	1.99	97%

Entry	Parameters	Penalty Points
1	Yield (97%)	-1.5
2	Price/availability	0
3	Safety	-5
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (Cooling to 0 °C)	-5
6	Work-up and purification (Classical chromatography)	-13
	EcoScale Score	75.5

Please note: Since not enough information are provided on the amount of sodium sulfate, silica and solvents used for the separation, they have been neglected in calculations for the purification process. Since neither the amount of hydrochloric acid solution was given, we considered a minimum 5 mL of HCl 1 N (3x5 mL = 15 mL) and a minimum of 5 mL of brine (solubility of NaCl in water: 358 g/L).

5.3 *Green Metrics and Assessments for Chapter IV*



MW: 176.21	MW: 227.86	MW: 18.02	MW: 178.23	MW: 243.86
1.0 mmol	2.0 mmol	2.0 mmol	0.97 mmol	1.0 mmol
176.21 mg	445.72 mg	36,04 mg	172.90 mg	243.86 mg

Excess and wastes

-	227.86 mg 1.0 mmol	18.02 mg 1.0 mmol	3.19 mg 3 mmol%	Ethyl Acetate (10 mL) d = 0.902 g/mL 11090 mg *(recycled after evaporation)*

$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{178.23}{425.28} \times 100 = 41.91\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{227.86 + 18.02 + 3.19 + 11090}{172.90} = 65.58$$

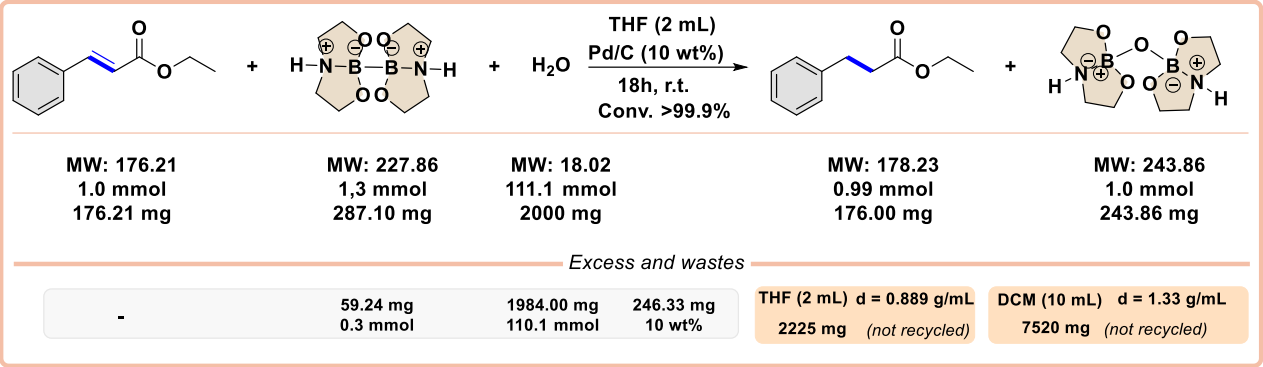
$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{227.86 + 18.02 + 3.19}{172.90} = 1.44$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{172.90}{176.21 + 445.72 + 36.04 + 3.19} \times 100 = 26.15\%$$

Reagents	MF	MW	G	mmol	Equiv.
Ethyl trans-cinnamate	C11H12O2	176.21	0.17621	1	1
(2,2'-Bi(1,3,6,2-dioxazaborocane))	C8H18B2N2O4	107.16	0.2143	2	2
H2O	H2O	18.02	0.036	0.036	0.036
Palladium on activated carbon	Pd	106.42	0.032	0.03	0.03
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Ethyl 3-phenylpropionate	C11H14O2	178.23	0.1729	0.97	97%

Entry	Parameters	Penalty Points
1	Yield (97%)	-1
2	Price/availability	-15
3	Safety	-15
4	Technical set-up (Unconventional activation technique)	0
5	Temperature/time (Cooling to 0 °C)	-1
6	Work-up and purification (Classical chromatography)	0
	EcoScale Score	68

[a]Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator



$$\text{Atom Economy} = \frac{\text{Mass of desired useful product}}{\text{Total Mass of all reactants}} \times 100 = \frac{178.23}{425.28} \times 100 = 41.91\%$$

$$\text{Environmental Factor} = \frac{\text{Mass of total waste}}{\text{Mass of desired product}} = \frac{59.24 + 1984.00 + 246.33 + 2225.00 + 7520.00}{176.00} = 69.60$$

$$\text{Reaction Mass Efficiency} = \frac{\text{actual mass of desired product}}{\text{mass of reactants}} \times 100 = \frac{172.90}{176.21 + 287.10 + 2000.00 + 246.3} \times 100 = 6.38\%$$

Reagents	MF	MW	G	mmol	Equiv.
Ethyl trans-cinnamate	C11H12O2	176.21	0.17621	0.5	1
(2,2'-Bi(1,3,6,2-dioxazaborocane))	C8H18B2N2O4	107.16	0.2143	0.63	1.26
H2O	H2O	18.02	2	110.99	221.98
Palladium on activated carbon	Pd	106.42	0.4	3.76	7.52
Tetrahydrofuran	C4H8O	72.11	1.76	24.41	48.82
Product	**MF**	**MW**	**G**	**mmol**	**Yield**
Ethyl 3-phenylpropionate	C11H14O2	178.23	0.1729	0.97	88%

Entry	Parameters	Penalty Points
1	Yield (88%)	-1
2	Price/availability	-23
3	Safety	-20
4	Technical set-up (Unconventional activation technique)	-5
5	Temperature/time (Cooling to 0 °C)	-1
6	Work-up and purification (Classical chromatography)	-3
	EcoScale Score	47

Values calculated using the eco scale calculator software available at the link: http://ecoscale.cheminfo.org/calculator

6. Conclusions

This dissertation showcases a series of careful studies on the mechanochemistry of organic molecules, each exploring the reactivity of distinct families of compounds while offering a contribution to the development of efficient synthetic routes.

The renown Fischer's method for producing indoles has been redesigned to enable the synthesis of heterocycles in the solid state and isocyanides and sulfonamides have been prepared according to suitably optimized multi-step processes. Similarly, innovative strategies have been identified for the synthesis of paracetamol using N-acetylsaccharin, the obtainment of precursors for sulfisoxazole and sulfamethoxazole, and the preparation of key analogues and intermediates for the production of high-value drugs such as fentanyl analogues and nimesulide scaffolds.

In all these case studies, mechanochemistry has proven itself a good alternative to classical solution chemistry, providing a viable access to molecular complexity. Seemingly, it also imparted the overall chemical transformations with a green footprint. In this respect, green chemistry metrics has undeniably pointed out the benefits of using mechanical activation, at least on the laboratory scale and restricted to laboratory practices. This bodes well for the future implementation of mechanochemical processing steps in the large-scale production of fine chemicals aimed at enhancing the sustainability and environmental friendliness of chemical industry.

Beyond the details of single reactions, the body of experimental findings concerning the use of mechanical forces as an external forcing to assist the chemical transformation of organic molecules strengthens the impression that mechanochemistry can significantly expand the achievements of organic chemistry. From simple yields to kinetic evidence, from simple reactions to catalytic ones, everything seems to point towards a beneficial effect of mechanical processing.

However, research has still to meet significant challenges and the journey is far from over. This dissertation has simply highlighted the efficacy of various mechanochemical processes in tailoring a greener chemical synthesis for a few specific organic compounds. Hopefully, it represents a significant stride towards the development of innovative synthetic routes, setting the stage for impactful advancements in the broader field of organic synthesis.

7. Experimental

7.1 Materials and Methods

Commercially available reagents were purchased from Acros, Aldrich, Alfa-Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealedTM bottles over molecular sieves. Flash column chromatography was performed with Eco-ChromeMP Silica gel 60A, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. An 8000M Mixer/Mill®, ball milling apparatus was used for all reactions. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 25 °C and are calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, d scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, d=7.27 ppm or DMSO-d_6 d=2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, brs = broad singlet), coupling constant (*J*) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, d scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, d=77.0 ppm or DMSO-d_6 d=39.5 ppm). Deuterated NMR solvents were obtained from Aldrich. High-resolution mass spectra (HR-MS) were recorded using an Electrospray Ionization (ESI) spectrometer. Infrared (IR) spectra were recorded on a NICOLET 5700 FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). The IR spectra have been recorded with 64 scans, 0.8 cm^{-1} resolution and within a range of 4000 to 400 cm^{-1}. Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrected. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Yields refer to pure isolated materials.

7.2 Syntheses and Characterizations of Compounds in Chapter II

Synthesis of Indoles

Aldehyde or ketone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 µl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (Φ = 3 mm, $mass_{tot}$ 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in a shaker mill until the complete disappearance of the starting material was observed by TLC (heptane/EtOAc: 9/1) and GC-MS analysis on an aliquot of crude. After completing the reaction, the resulting solid was triturated with water (2x3 mL), filtered through a filter paper, and dried in vacuo, affording the desired indole product. ^{1}H-NMR and ^{13}C spectrometry confirmed its structure. Alternatively, the solid mixture was triturated with EtOAc (2x3 mL), the resulting solution filtered through a short silica plug, and the filtrate dried in vacuo to give the indole product. Where necessary, further purification can be achieved by column chromatography (n-hexane:EtOAc 9:1 v/v).

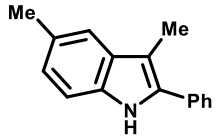
Synthesis of Indolines

Aldehyde or ketone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 µl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (Φ = 3 mm, mass$_{tot}$ 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in a shaker mill until the complete disappearance of the starting material was observed by TLC (heptane/EtOAc: 9:1 v/v) and GC-MS analysis on an aliquot of crude. At the end of this time, sodium borohydride (2.0 mmol) was added to the resulting reaction mixture and further ball-milled for 60 minutes at 30 Hz. Upon completion of the ball-milling process, the jar's content was treated with water (2x3 mL) and EtOAc (2x3mL). Next, the resulting organic layers were combined, filtered through a short silica plug, and dried in vacuo to give the corresponding indoline.

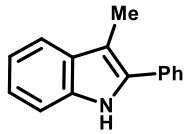
Additive-recycling Experiments in the Preparation of Indole

Propiophenone (1.1 mmol), phenylhydrazine hydrochloride (1.0 mmol), oxalic acid (3.5 mmol), dimethylurea (1.5 mmol) and acetic acid (η = 0.1 µl mg^{-1}) were loaded into a zirconium dioxide grinding jar (15 mL) equipped with 20 balls (Φ = 3 mm, mass$_{tot}$ 6.5g) of the same material. The jar was sealed and shaken at a frequency of 30 Hz in a shaker mill until for 300 minutes. After completing the reaction, the resulting solid was triturated with water (2x3 mL), filtered through a filter paper, and dried in vacuo, affording the desired indole product. The wash waters were collected and evaporated under reduced pressure. The recovered solid additive containing oxalic acid and dimethyl urea was dried under vacuum for several hours and then reused for the next cycle with a fresh charge of reagents. Cycle 1: 76%, Cycle 2: 74%, Cycle 3: 73 %, Cycle 4: 70%.

3,5-Dimethyl-2-phenyl-1*H*-indole (II-3a).

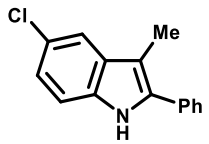


Orange solid, 168 mg, 76% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.63 – 7.60 (m, 2H), 7.55 – 7.50 (m, 2H), 7.48 (m, 1H), 7.44 – 7.40 (tt, *J* = 8.2, 1.7 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.58 (s, 3H), 2.52 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.30, 134.29, 133.6, 130.4, 128.85 (2C), 128.80, 127.8 (2C), 127.3, 124.0, 118.8, 110.5, 108.3, 21.7, 9.8. All spectral data are consistent with previously published findings.

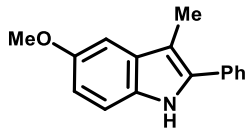


3-Methyl-2-phenyl-1*H*-indole (II-3b). Yellow oil, 140 mg, 68% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.59 – 7.55 (m, 3H), 7.49 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.6, 134.3,

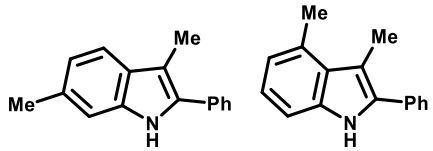
133.0, 131.3, 129.0 (2C), 127.9 (2C), 127.8, 125.4, 122.6, 118.7, 111.8, 108.6, 9.7. All spectral data are consistent with previously published findings.



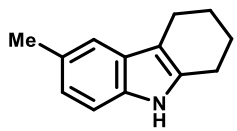
5-Chloro-3-methyl-2-phenyl-1*H*-indole (II-3c). Yellow solid, 94 mg, 39% yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.60-7.55 (m, 3H), 7.51-7.46 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.6 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.6, 134.3, 133.0, 131.3, 129.0 (2C), 127.9 (2C), 127.8, 125.4, 122.6, 118.7, 111.8, 108.6, 9.7. HRMS (ESI): 242.0731m/z calcd for $C_{15}H_{13}ClN$: $[M+H]^+$. Found:242.0735.



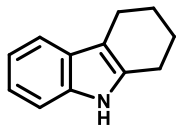
5-Methoxy-3-methyl-2-phenyl-1H-indole (II-3d). White solid, 187 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.62 – 7.55 (m, 2H), 7.49-7.47 (m, 2H), 7.38 (tt, *J* = 8.2, 1.6 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.93 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.2, 135.1, 133.5, 131.2, 130.5, 128.9 (2C), 127.8, 127.4 (2C), 112.5, 111.6, 108.6, 101.0, 56.1, 9.9. All spectral data are consistent with previously published findings.



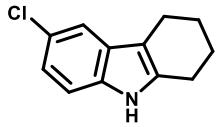
3,6-Dimethyl-2-phenyl-1*H*-indole + 3,4-dimethyl-2-phenyl-1*H*-indole (II-3e$_a$ + II-3e$_b$). Non-separable regioisomers (58:42). White solid, 148 mg, 67% overall yield (**3e$_a$ + 3e$_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.88 (s, 1H), 7.59 – 7.55 (m, 2H), 7.55 – 7.52 (m, 2H), 7.47 (td, *J* = 7.8, 3.8 Hz, 5H), 7.39 – 7.32 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.16 (dt, *J* = 1.7, 0.9 Hz, 1H), 7.06 (dd, *J* = 8.1, 7.1 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.85 (dt, *J* = 7.2, 1.0 Hz, 1H), 2.78 (s, 3H), 2.62 (s, 3H), 2.48 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.4, 136.3, 134.5, 133.7, 133.6, 133.5, 132.3, 131.6, 128.9, 128.8, 128.6, 128.3, 128.1, 127.7, 127.5, 127.2, 122.4, 121.4, 121.4, 118.8, 110.8, 109.6, 108.8, 108.7, 21.9, 20.6, 12.5, 9.9. All spectral data are consistent with previously published findings.



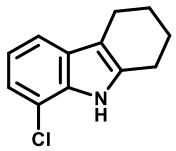
6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-3g). Yellow solid**,** 144 mg, 78 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 7.29 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.72 (t, *J* = 6.0 Hz, 4H), 2.48 (s, 3H), 1.97 – 1.85 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.4, 134.1, 128.3, 128.2, 122.5, 117.7, 110.1, 109.8, 23.5, 23.4 (2C), 21.6, 21.1 All spectral data are consistent with previously published findings.



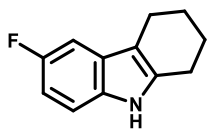
2,3,4,9-Tetrahydro-1*H*-carbazole (II-3h). Yellow solid, 200 mg, 81 % yield**. ^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.59 (br s, 1H), 7.32 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.23 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.91 (td, *J* = 7.7, 7.0, 1.2 Hz, 1H), 2.72 – 2.67 (m, 2H), 2.63 – 2.59 (m, 2H), 1.86 – 1.77 (m, 4H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.6, 134.3, 127.3, 120.0, 117.9, 117.0, 110.5, 108.0, 23.0, 22.9, 22.8, 20.6. All spectral data are consistent with previously published findings.



6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole (II-3i). Brown solid, 174 mg, 85 % yield. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.82 (br s, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.96 (dd, *J* = 8.5, 2.1 Hz, 1H), 2.69 (m, 2H), 2.60 – 2.56 (m, 2H), 1.84 – 1.74 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.9, 134.1, 129.1, 124.9, 121.2, 117.5, 111.3, 110.2, 23.4, 23.3, 23.2, 20.9. All spectral data are consistent with previously published findings.

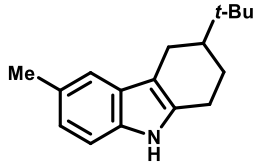


8-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole (II-3j). Brown solid, 172 mg, 84 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 2.85 – 2.72 (m, 4H), 2.01 – 1.89 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.0, 132.9, 129.5, 120.4, 119.9, 116.5, 115.9, 111.4, 23.3, 23.23, 23.16, 21.1. All spectral data are consistent with previously published findings.

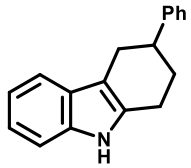


6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (II-3k). Yellow solid, 143 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.18-7.13 (m, 2H), 6.89 (dt, *J* = 9.1, 2.6 Hz, 1H), 2.74 – 2.67 (m, 4H), 1.96 – 1.88 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.8 (d, *J* = 233.4 Hz), 136.4, 132.2, 128.3

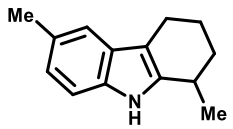
(d, = 9.8 Hz), 110.8 (d, *J* = 9.8 Hz), 110.5 (d, *J* = 4.3 Hz), 108.8 (d, *J* = 26.0 Hz), 102.9 (d, *J* = 23.3 Hz), 23.4, 23.3, 23.2, 20.9. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -126.32. All spectral data are consistent with previously published findings.



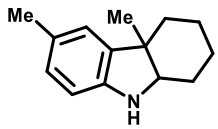
3-(*tert*-Butyl)-6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-3l). White solid, 163 mg, 68% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.28 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.85 – 2.80 (m, 1H), 2.76 – 2.71 (m, 2H), 2.46 (s, 3H), 2.43 – 2.36 (m, 1H), 2.13 – 2.08 (m, 1H), 1.59 – 1.49 (m, 2H), 1.02 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.5, 134.4, 128.4, 128.3, 122.5, 117.6, 110.2, 110.1, 45.6, 32.8, 27.7 (3C), 24.9, 24.3, 22.4, 21.6. All spectral data are consistent with previously published findings.



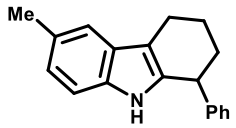
3-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-3m). White solid, 185 mg, 75% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.23 (m, 4H), 7.20 – 7.15 (m, 2H), 7.08 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 3.04-2.95 (m, 2H), 2.80 – 2.71 (m, 2H), 2.70 – 2.61 (m, 1H), 2.16 – 2.08 (m, 1H), 2.08 – 1.98 (m, 1H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.8, 136.1, 133.7, 128.6 (2C), 127.6, 127.1 (2C), 126.3, 121.2, 119.3, 117.8, 110.6, 110.1, 41.2, 30.4, 29.4, 23.4. All spectral data are consistent with previously published findings.



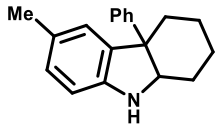
1,6-Dimethyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-3n$_a$). Pale brown solid, 134 mg, 67 % overall yield (**3n$_a$**+**3n$_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.29 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.00 – 2.95 (m, 1H), 2.76 – 2.66 (m, 2H), 2. 49 (s, 3H), 2.10 – 1.99 (m, 2H), 1.83-1.76 (m, 1H), 1.59 – 1.52 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.9, 134.1, 128.4, 128.1, 122.6, 117.9, 110.2, 109.4, 32.5, 28.9, 22.1, 21.6, 21.3, 20.4. HRMS (ESI): 200,1434 m/z calcd for: $C_{14}H_{18}N$ $[M+H]^+$. Found 200.1436.



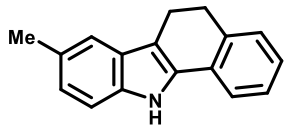
6-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (II-10n$_b$). Yellow oil, 134 mg, **3n$_a$+3n$_b$** 67 % overall yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 – 6.85 (m, 2H), 6.65 – 6.61 (m, 1H), 3.48 (br s, 1H), 3.42 (t, *J* = 4.5 Hz, 1H), 2.32 (s, 3H), 1.75 – 1.60 (m, 4H), 1.51 – 1.39 (m, 4H), 1.33 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.2, 139.8, 128.1, 127.4, 122.4, 110.2, 66.2, 42.9, 35.1, 27.7, 23.7, 21.6, 21.3, 21.1. HRMS (ESI): 202.1590 m/z calcd for $C_{14}H_{20}N$: $[M+H]^+$. Found: 202.1588.



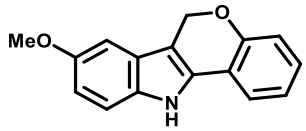
6-Methyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-3o$_a$). Pale brown solid, 186 mg, 71 % overall yield (**3o$_a$+3o$_b$**). Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.17 – 7.12 (m, 2H), 7.07 – 7.03 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 1H), 2.75 – 2.68 (m, 2H), 2.37 (s, 3H), 2.21 – 2.13 (m, 1H), 1.95 – 1.86 (m, 1H), 1.84 – 1.68 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.5, 135.7, 134.3, 128.7 (2C), 128.4 (2C), 128.4, 127. 9, 126.8, 122.9, 118.0, 111.4, 110.4, 41.6, 34.2, 22.0, 21.6, 21.2. HRMS (ESI): 262.1590 m/z calcd for: $C_{19}H_{20}N$ $[M+H]^+$. Found 262.1594



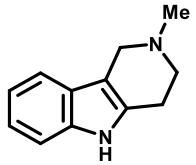
6-Methyl-4a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (II-10o$_b$). Pale brown solid**,** 186 mg, 71 % overall yield (**3o$_a$+3o$_b$**). **^{1}H NMR** (600 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, CDCl3) δ 7.40 – 7.36 (m, 2H), 7.32 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.24 – 7.20 (m, 1H), 6.92 – 6.89 (m, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 4.10 (t, *J* = 5.1 Hz, 1H), 2.26 (s, 3H), 2.23 – 2.17 (m, 1H), 2.03 – 1.95 (m, 1H), 1.77 – 1.68 (m, 2H), 1.65 – 1.42 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.4, 146.4, 137.8, 128.5, 128.1, 127.9, 127.8, 126.1, 124.5, 110.6, 67.0, 52.1, 33.7, 28.4, 22.5, 21.2, 21.1. HRMS (ESI): 264.1747 m/z calcd for $C_{19}H_{22}N$: $[M+H]^+$. Found 264.1753.



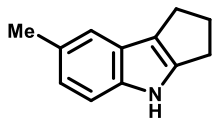
8-Methyl-6,11-dihydro-5*H*-benzo[a]carbazole (II-3p). White solid, 175 mg, 80% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.34 (s, 1H), 7.29 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.07-3.02 (m, 2H), 2.97 – 2.92 (m, 2H), 2.46 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.6, 135.5, 133.3, 129.3, 129.2, 128.6, 127.8, 126.73, 126.72, 124.1, 119.8, 118.6, 112.4, 110.9, 29.7, 21.6, 19.8. All spectral data are consistent with previously published findings.



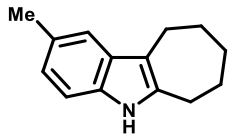
8-Methoxy-6,11-dihydrochromeno[4,3-*b*]indole (II-3q). White solid**,** 203 mg, 81% yield. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 11.47 (br s, 1H), 7.56 (dd, J = 7.6, 1.6 Hz, 1H), 7.29 (d, J = 8.7 Hz, 1H), 7.14 (dt, J = 7.6, 1.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.90 (dd, J = 8.1, 1.1 Hz, 1H), 6.76 (dd, J = 8.7, 2.4 Hz, 1H), 5.55 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 153.7, 153.3, 132.4, 128.4, 125.5, 124.6, 121.3, 121.2, 117.9, 116.3, 112.1, 112.0, 104.8, 100.0, 65.0, 55.3. HRMS (ESI): 252.1019 m/z calcd for: $C_{16}H_{14}NO_2$ $[M+H]^+$. Found 252.1018.



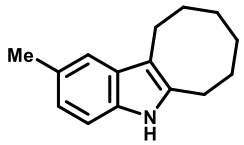
2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (II-3r). Yellow solid, 70.7 mg, 38% yield. Purified on a column chromatography after basic treatment. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.74 (br s, 1H), 7.30 (dd, J = 7.7, 1.2 Hz, 1H), 7.25 (dd, J = 8.0, 1.0 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.94 – 6.90 (m, 1H), 3.51 (s, 2H), 2.80 – 2.77 (m, 2H), 2.71 (t, J = 5.7 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 135.9, 132.4, 125.5, 120.1, 118.2, 116.9, 110.7, 107.1, 52.1, 51.4, 45.6, 23.5. All spectral data are consistent with previously published findings.



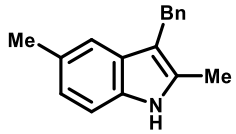
7-Methyl-1,2,3,4-tetrahydrocyclopenta[b]indole (II-3s). Yellow oil, 149 mg, 87% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.24 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.2, 1.7 Hz, 1H), 2.87 – 2.79 (m, 4H), 2.57 – 2.50 (m, 2H), 2.44 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.0, 139.4, 128.8, 125.1, 122.0, 119.5, 118.5, 111.0, 28.8, 26.0, 24.5, 21.6. HRMS (ESI): 172.1121 m/z calcd for $C_{12}H_{14}N$: $[M+H]^+$. Found 172.1121



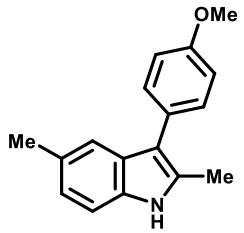
2-Methyl-5,6,7,8,9,10-Hexahydrocyclohepta[b]indole (II-3t). Yellow solid, 167 mg, 84% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (br s, 1H), 7.26 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.92 (dd, J = 8.1, 1.6 Hz, 1H), 2.78-2.62 (m, 4H), 2.45 (s, 3H), 1.91-1.88 (m, 2H), 1.80 – 1.75 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.7, 132.7, 129.6, 128.3, 122.2, 117.5, 113.4, 110.0, 32.0, 29.7, 28.9, 27.7, 24.8, 21.7. HRMS (ESI): 200.1434 m/z calcd for: $C_{14}H_{18}N$ $[M+H]^+$. Found: 200.1431.



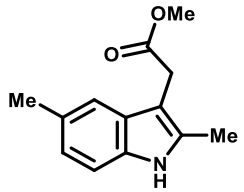
2-Methyl-6,7,8,9,10,11-hexahydro-5*H*-cycloocta[b]indole (II-3u). Colourless oil, 183 mg, 86%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.32 – 7.29 (m, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.1, 1.6 Hz, 1H), 2.89 – 2.80 (m, 4H), 2.48 (s, 3H), 1.75 (dt, *J* = 12.5, 6.2 Hz, 4H), 1.52 – 1.42 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.9, 133.5, 129.9, 128.1, 122.2, 117.6, 111.3, 110.1, 29.8, 29.7, 26.2, 26.05, 26.00, 22.3, 21.7. HRMS (ESI): 214.1590 m/z calcd for: $C_{15}H_{20}N$ $[M+H]^+$. Found 214.1592.



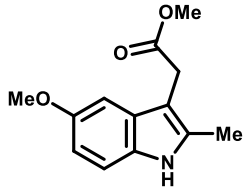
3-benzyl-2,5-dimethyl-1*H*-indole (II-3v). White solid**,** 174 mg**,** 74% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.26 – 7.13 (m, 7H), 6.93 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.05 (s, 2H), 2.39 (s, 3H), 2.36 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.9, 133.7, 131.9, 129.3, 128.5 (2C), 128.4 (2C), 128.3, 125.7, 122.6, 118.2, 110.2, 109.9, 30.1, 21.6, 12.0. HRMS (ESI): 236.1434 m/z calcd for: $C_{17}H_{18}N$ $[M+H]^+$. Found 236.1435.



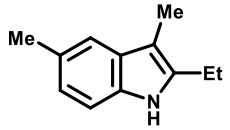
3-(4-Methoxyphenyl)-2,5-dimethyl-1*H*-indole (II-3x). White solid, 249 mg, 99% yield**. ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.53 – 7.49 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 3.94 (s, 3H), 2.53 (s, 3H), 2.46 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.8, 133.6, 131.3 (2C), 130.6, 129.1, 128.3, 128.1, 122.9, 118.5, 114.1 (2C), 113.6, 110.1, 55.4, 21.6, 12.4. HRMS (ESI): 252.1383 m/z calcd for $C_{17}H_{18}NO$: $[M+H]^+$. Found: 252.1385.



Methyl 2-(2,5-dimethyl-1*H*-indol-3-yl)acetate (II-3y). White solid, 93 mg, 43% yield. Purified on a column chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.31 (s, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.6 Hz, 1H), 3.69-3.65 (m, 5H), 2.45 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 133.5, 132.9, 128.9, 128.8, 122.8, 117.9, 110.1, 104.1, 52.0, 30.3, 21.7, 11.8. HRMS (ESI): 218,1176 m/z calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$. Found 218.1178.

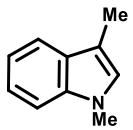


Methyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (II-3z). White solid, 156 mg, 67% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.87 (s, 3H), 3.69-3.65 (m, 5H), 2.31 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.8, 154.1, 133.8, 130.3, 128.9, 111.1, 110.9, 104.2, 100.5, 56.0, 51.9, 30.3, 11.7. All spectral data are consistent with previously published findings.[11,12]

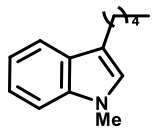


2-Ethyl-3,5-dimethyl-1*H*-indole (II-3za). White solid 171 mg, 99 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.30 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.6 Hz, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.49 (s, 3H), 2.24 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.8, 133.5, 129.8, 128.3, 122.5, 118.0, 110.0, 105.8, 21.6, 19.5, 14.1, 8.4. HRMS (ESI): 174.1277 m/z calcd for: $C_{12}H_{16}N$ $[M+H]^+$. Found 174.1273.

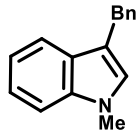
Spectral data for indole II-7a-II-7g



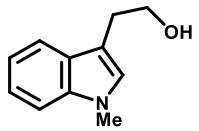
1,3-Dimethyl-1*H*-indole (II-7a). Colorless oil, 109 mg, 75%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.25 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.20 (ddd, *J* =7.4, 6.9, 1.1 Hz, 1H), 7.10 (td, *J* = 7.4, 6.9, 1.1 Hz, 1H), 6.78 (s, 1H), 3.69 (s, 3H), 2.31 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.1, 128.8, 126.6, 121.5, 119.0, 118.6, 110.2, 109.1, 32.6, 9.6. All spectral data are consistent with previously published findings.



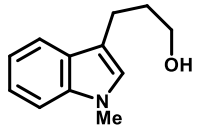
1-Methyl-3-pentyl-1*H*-indole (II-7b) Colourless oil, 177 mg, 88 %. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.27 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.09 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.81 (s, 1H), 3.72 (s, 3H), 2.73 (t, *J* = 7.0 Hz, 2H), 1.70 (quint, *J* = 7.0 Hz, 2H), 1.41 – 1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.2, 128.2, 126.1, 121.5, 119.2, 118.5, 115.8, 109.2, 32.6, 32.0, 30.3, 25.2, 22.7, 14.2. HRMS (ESI): 202.1590 m/z calcd for: $C_{14}H_{20}N$ $[M+H]^+$. Found Chemical Formula: $C_{14}H_{21}N$ Exact Mass: 202.1588.



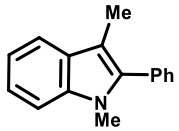
3-Benzyl-1-methyl-1*H*-indole (II-7c) Colourless oil, 157 mg, 71 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.26 – 7.20 (m, 5H), 7.19 – 7.13 (m, 2H), 7.04 (ddt, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.66 (s, 1H), 4.06 (s, 2H), 3.59 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.5, 137.3, 128.8, 128.4, 128.0, 127.2, 125.9, 121.7, 119.9, 119.3, 118.9, 114.9, 114.3, 109.2, 32.6, 31.6. All spectral data are consistent with previously published findings.



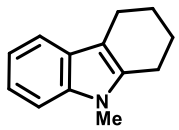
2-(1-Methyl-1*H*-indol-3-yl)ethan-1-ol (II-7d). Colourless oil, 138 mg, 78% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (td, *J* = 7.9, 1.1 Hz, 1H), 7.27 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.20 (dt *J* = 8.2, 1.1 Hz, 1H), 7.08 (td, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.89 (s, 1H), 3.85 (t, *J* = 6.4Hz, 2H), 3.71 (s, 3H), 2.98 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.3, 128.0, 127.4, 121.8, 119.03, 119.00, 110.8, 109.4, 62.9, 32.7, 28.8. All spectral data are consistent with previously published findings.



3-(1-Methyl-1*H*-indol-3-yl)propan-1-ol (II-7e). Colourless oil, 149 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.9, 1.0 Hz, 1H), 7.27 (td, *J* = 8.2, 0.9 Hz, 1H), 7.21 (dt, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.09 (dt, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.82 (s, 1H), 3.71 (s, 3H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 1.95 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.2, 128.0, 126.3, 121.6, 119.1, 118.7, 114.5, 109.3, 62.7, 33.3, 32.6, 21.4. All spectral data are consistent with previously published findings.

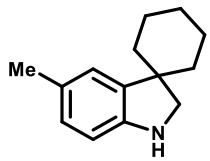


1,3-Dimethyl-2-phenyl-1*H*-indole (II-7f). Yellow oil, 142 mg, 64 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.29-7.26 (m, 3H), 7.19 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.13 (dt, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.03 (dt, *J* = 7.9, 6.9, 1.0 Hz, 1H), 3.47 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.8, 137.4, 132.3, 130.8 (2C), 128.6, 128.4 (2C), 127.9, 121.9, 119.2, 118.9, 109.4, 108.7, 31.0, 9.5. All spectral data are consistent with previously published findings.

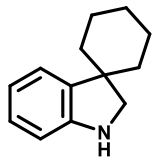


9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (II-7g). Yellow oil**,** 170 mg, 92 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.18 (t, 1H), 7.11 (t, 1H), 3.60 (s, 3H), 2.78– 2.71 (m, 4H), 2.00 – 1.87 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.8, 135.8, 127.3, 120.6, 118.7, 117.8, 109.3, 108.5, 29.0, 23.36, 23.38 , 22.2, 21.2. All spectral data are consistent with previously published findings.

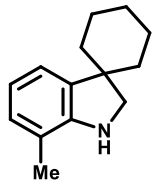
Spectral data for indoline II-10a-II-10k



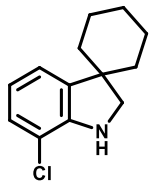
5'-Methylspiro[cyclohexane-1,3'-indoline] (II-10a). Pale yellow solid, 151 mg, 75 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 3.64 (br s, 1H), 3.43 (s, 2H), 2.28 (s, 3H), 1.71-1.66 (m, 5H), 1.61-1.56 (m, 2H), 1.45 – 1.29 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.2, 139.3, 128.9, 128.0, 123.5, 110.5, 57.0, 46.3, 36.5, 25.9, 23.4, 21.1. All spectral data are consistent with previously published findings.



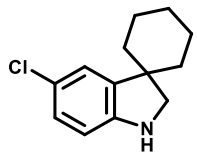
Spiro[cyclohexane-1,3'-indoline] (II-10b). Yellow oil, 129 mg, 69% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 – 7.02 (m, 2H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 3.47 (s, 2H), 1.79 – 1.69 (m, 5H), 1.65 – 1.57 (m, 2H), 1.43 – 1.28 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.7, 139.2, 127.7, 122.8, 120.1, 111.0, 56.6, 46.3, 36.6 (2C), 25.9, 23.3 (2C). All spectral data are consistent with previously published findings.



7'-Methylspiro[cyclohexane-1,3'-indoline] (II-10c). Yellow solid**,** 123 mg, 61% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.94 (d, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 3.47 (s, 2H), 2.17 (s, 3H), 1.77-1.71 (m, 6H), 1.62 – 1.57 (m, 2H), 1.42 – 1.31 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.3, 138.3, 128.6, 120.2, 119.8, 119.5, 56.8, 46.6, 36.7 (2C), 25.9, 23.3 (2C), 16.9. HRMS (ESI): 202,1590 m/z calcd for $C_{14}H_{20}N$: $[M+H]^+$. Found: 202.1593.

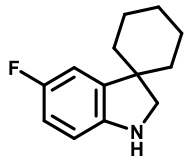


7'-Chlorospiro[cyclohexane-1,3'-indoline] (II-10d). Orange solid**,** 78 mg, 35% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 3.50 (s, 2H), 1.79 – 1.76 (m, 2H), 1.74 – 1.71 (m, 3H), 1.58 (dt, *J* = 12.7, 3.1 Hz, 2H), 1.43 – 1.35 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.3, 140.0, 127.2, 120.9, 119.4, 115.0, 56.7, 47.5, 36.6 (2C), 25.8, 23.1 (2C). HRMS (ESI): 222.1044 m/z calcd for: $C_{13}H_{17}ClN$ $[M+H]^+$. Found 222.1045.

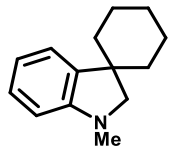


5'-Chlorospiro[cyclohexane-1,3'-indoline] (II-10e). Yellow solid, 93 mg, 42% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.99-6.95 (m, 2H), 6.56 (d, *J* = 8.2 Hz, 1H), 3.69 (br s, 1H), 3.44 (s, 2H), 1.74– 1.70

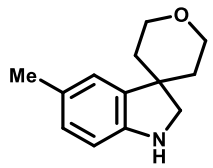
(m, 5H), 1.57 – 1.52 (m, 2H), 1.41 – 1.31 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.6, 140.7, 127.3, 123.7, 123.1, 110.8, 57.1, 46.6, 36.5 (2C), 25.8, 23.2 (2C). HRMS (ESI): 222.1044 10 m/z calcd for: $C_{13}H_{17}ClN$ $[M+H]^+$. Found 222.1044.



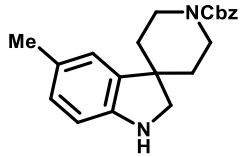
5'-Fluorospiro[cyclohexane-1,3'-indoline] (II-10f). Yellow oil, 111 mg, 54% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.72 (dt, *J* = 8.7, 2.7 Hz, 1H), 6.56 (dd, *J* = 8.7, 4.3 Hz, 1H), 3.75 (br s, 1H), 3.44 (s, 2H), 1.76 – 1.69 (m, 5H), 1.57 – 1.51 (m, 2H), 1.43-1.29 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.5 (d, *J* = 235 Hz, 1C), 145.9, 140.7 (d, *J* = 7.1 Hz, 1C), 113.5 (d, *J* = 23.5, 1C), 110.4 (d, *J* = 8.2 Hz, 1C), 110.2 (d, *J* = 23.7 Hz, 1C), 57.4, 46.7, 36.4 (2C), 25.8, 23.2 (2C). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -125.71. HRMS (ESI): 206.1340 m/z calcd for: $C_{13}H_{17}FN$ $[M+H]^+$. Found 206,1340.



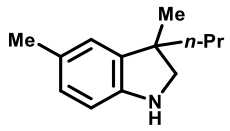
1'-Methylspiro[cyclohexane-1,3'-indoline] (II-10g). Colourless oil, 159 mg, 79% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.73 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.22 (s, 2H), 2.80 (s, 3H),1.80- 1.72 (m, 5H), 1.65-1.58 (m, 2H), 1.50 – 1.36 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.3, 139.3, 127.7, 122.2, 117.8, 107.3, 65.7, 44.8, 36.4 (2C), 36.1, 26.0, 23.4 (2C). All spectral data are consistent with previously published findings.



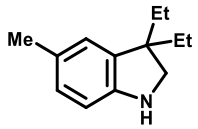
5-Methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (II-10h). White solid, 156 mg, 77% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.7 Hz, 1H), 6.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 4.01-3.97 (m, 2H), 3.58 (dt, *J* = 12.0, 2.2 Hz, 2H), 3.53 (s, 2H), 2.30 (s, 3H), 2.02-1.96 (m, 2H), 1.69-1.63 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.2, 136.9, 128.3, 128.3, 123.4, 109.9, 65.2 (2C) , 56.8, 43.8, 36.4 (2C), 21.0. HRMS (ESI): 204.1383 m/z calcd for: $C_{13}H_{18}NO$ $[M+H]^+$. Found 204.1381.



Benzyl 5-methylspiro[indoline-3,4'-piperidine]-1'-carboxylate (II-10i). White solid, 272 mg, 81% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 4H), 7.35 (dd, *J* = 6.2, 2.7 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.19 (s, 2H), 4.19-4.09 (m, 2H), 3.51 (br s, 1H), 3.43 (s, 2H) , 3.05-2.93 (m, 2H), 2.29 (s, 3H), 1.89 – 1.69 (m, 4H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.4, 148.1, 136.9, 136.5, 128.6, 128.4 (2C), 128.3, 128.1, 128.0 (2C), 123.4, 109.9, 67.2, 56.2, 44.5 (2C), 41.4 (2C), 35.4, 21.0. HRMS (ESI): 337.1911 m/z calcd for: $C_{21}H_{25}N_2O_2$ $[M+H]^+$. Found 337.1914.



3-Ethyl-3,5-dimethylindoline (II-10j). Yellow oil, 83 mg, 44% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.88 – 6.82 (m, 2H), 6.62 (d, *J* = 7.7 Hz, 1H), 3.41 (d, *J* = 9.0 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 2.28 (s, 3H), 1.65 – 1.52 (m, 2H), 1.43 – 1.32 (m, 2H), 1.29 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.4, 138.4, 128.8, 127.8, 123.5, 110.4, 59.6, 45.4, 25.7, 21.1, 18.1, 14.8. HRMS (ESI): 190.1590 m/z calcd for: $C_{13}H_{20}N$ $[M+H]^+$. Found: 190.1587.



3,3-Diethyl-5-methylindoline (II-10k). Yellow oil, 123 mg, 65 % yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.80 (br s, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.38 (s, 2H), 2.28 (s, 3H), 1.76 – 1.58 (m, 4H), 0.83 (t, *J* = 7.5 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.8, 136.8, 129.6, 128.0, 124.5, 111.1, 56.8, 49.6, 30.6 (2C), 21.2, 8.9 (2C). HRMS (ESI): 190.1590 m/z calcd for: $C_{13}H_{20}N$ $[M+H]^+$. Found 190.1587.

7.3 Syntheses and Characterizations of Compounds in Chapter III

General procedure for N-acetylsaccharin synthesis

A 10 mL microwave vessel equipped with one stirring magnet was filled with saccharin **III-2** (1.0 mmol) and acetic anhydride (1.0 mL, 10.5 eq.). The vessel was then closed, and the reaction was conducted for 240 min at 100 °C and 200 W (power max). At the end of the reaction, the solid was washed with a saturated aqueous $KHCO_3$ solution and filtered on paper to purify the reaction mixture. Lastly, the white solid was let air dry to afford the pure compound **III-2b**.

General procedure for N-propionylsaccharin synthesis

A 10 mL microwave vessel equipped with one stirring magnet was filled with saccharin **III-2** (1.0 mmol) and propionic anhydride (1.5 mL, 11.8 eq.). The vessel was then closed, and the reaction was conducted for 300 min at 100 °C and 200 W (power max). At the end of the reaction, the solid was washed with a saturated aqueous $KHCO_3$ solution and filtered on paper to purify the reaction mixture. Lastly, the white solid was let air dry to afford the pure compound **III-2c**.

General Procedure For N-formamides Synthesis from Primary and Secondary Amines

A 15 mL zirconium dioxide jar equipped with one milling ball of the same material (10 mm diameter) was filled with amine **III-1a-III-1ah** (1.0 mmol) and **III-2a** (1.1 mmol). The vessel was then closed and the mechanochemical reaction was conducted ranging from 30 to 180 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with 1 equiv. of wet $NaHCO_3$ (it is prepared by adding 2 mmol of H_2O for mmol of dry $NaHCO_3$) for purifying the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (4 mL) and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the pure formamide **III-3a-III-3ah**.

General Procedure For N-acetamides Synthesis from Primary and Secondary Amines

A 15 mL zirconium dioxide jar equipped with one milling ball of the same material (10 mm diameter) was filled with amine **III-1a, III-1c, III-1e, III-1e, III-1k, III-1r, III-1u, III-1w, III-1aa** (1.0 mmol) and **III-2b** (1.1 mmol). The vessel was then closed and the mechanochemical reaction was conducted ranging from 60 to 180 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with 1 equiv. of wet $NaHCO_3$ (it is prepared by adding 2 mmol of H_2O for mmol of dry $NaHCO_3$) for purifying the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (4 mL) and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the pure acetamide **III-4a, III-4c, III-4e, III-4e, III-4k, III-4r, III-4u, III-4w, III-4aa**.

General Procedure For N-propionamide Synthesis from Primary and Secondary Amines

A 15 mL zirconium dioxide jar equipped with one milling ball of the same material (10 mm diameter) was filled with amine **III-1a, III-1g, III-1l, III-1o, III-1r, III-1v, III-1ad** (1.0 mmol), and **III-2c** (1.1 mmol). The vessel was then closed, and the mechanochemical reaction was conducted for 120 min at a frequency of 30 Hz. At the end of the reaction, an additional 10 min grinding was made with 1 equiv. of wet $NaHCO_3$ (it is prepared by adding 2 mmol of H_2O for mmol of dry $NaHCO_3$) for purifying the reaction mixture. The crude was then recovered as a solid in a beaker, dissolved in EtOAc (4 mL) and washed with a citric acid solution (5% p/p) dried on Na_2SO_4, when necessary. Lastly, the crude was filtered on paper, and the solvent was removed under reduced pressure to afford the pure propionamide **III-5a, III-5g, III-5l, III-5o, III-5r, III-5v, III-5ad**

General procedure for isocyanide synthesis

A 20 mL zirconium oxide jar equipped with two milling ball of the same material (8 mm diameter) was filled with formamide **III-1a, III-1c, III-1g$_1$**, **III-1l**, **III-1r**, **III-1ab**, **III-1ac**, **III-1ae** (1 mmol), p-tosyl chloride (1.5 mmol), triethylamine (1 mmol) and Na_2CO_3 (6 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 60 min at a frequency of 18 Hz. At the

end of the reaction, additional 15 min grinding with H_2O (0.5 eq.) was performed. After this step, the crude was recovered as a solid in a beaker and dissolved in heptane (10 mL). A short silica pad (1 g) was required for a further purification. Lastly, the organic layer was dried over Na_2SO_4 and the solvent was removed under pressure to afford the pure isocyanide compound **III-6a, III-6c, III-6g$_1$**, **III-6l**, **III-6r**, **III-6ab**, **III-6ac**, **III-6ae**.

General procedure for isocyanide gram scale synthesis

A 35 mL zirconium oxide jar equipped with three milling balls of the same material (10 mm diameter) was filled with formamide **III-1a, III-1c, III-1g$_1$**, **III-1l**, **III-1r**, **III-1ab**, **III-1ac**, **III-1ae** (5 mmol), p-tosyl chloride (7.5 mmol), triethylamine (5 mmol) and Na_2CO_3 (30 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 60 min at a frequency of 18 Hz. At the end of the reaction, additional 15 min grinding with H_2O (0.5 eq.) was performed. After this step, the crude was recovered as a solid in a beaker and dissolved in heptane (50 mL). A short silica pad (5 g) was required for a further purification. Lastly, the organic layer was dried over Na_2SO_4 and the solvent was removed under pressure to afford the pure isocyanide compound **III-6a, III-6c, III-6g$_1$**, **III-6l**, **III-6r**, **III-6ab**, **III-6ac**, **III-6ae.**

General procedure for the preparation of sulfonyl chloride

A 15 mL zirconium oxide jar equipped with two balls of the same material (Φ = 8 mm, $mass_{tot}$ = 3.22 g) was charged with $NaHSO_4$ (10 mol%, 0.1 mmol), followed by disulfide (**III-7a-III-7n**) (1.0 mmol) and NaOCl*5 H_2O (6 mmol). (*Attention!* It is crucial to add the reagents in the written order for the success of the reaction since a variable loss of gas could affect the yields). The jar was then closed, and the mechanochemical reaction was conducted for 40 minutes at a frequency of 30 Hz. At the end of the reaction, the crude was recovered with 5 mL of AcOEt, filtered and concentrated under reduced pressure to afford the desired product **III-8a-III-8n**. For the synthesis of **III-7h**, the amount of NaOCl*5H_2O had to be raised up to 7 mmol. For the synthesis of **III-7d-III-7f** and **III-7i** the reaction time raised up to 180 min, and a short silica pad (Hexane/AcOEt: 3/7) was required for further purification.

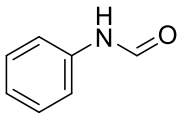
General procedure for the preparation of sulfonamides

A 15 mL zirconium oxide jar equipped with two balls of the same material (Φ = 8 mm, $mass_{tot}$ = 3.22 g) was charged with sulfonyl chloride **III-8a- III-8n** (1 mmol), amine **9-21** (1.1 mmol) and MgO (4 mmol) The jar was then closed, and the reaction was conducted for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude was recovered with AcOEt (5 ml) from the jar and filtered. The filtrate was washed with an aqueous solution of citric acid 3x5 mL (10% w/w), to obtain the desired sulfonamide product **III-9- III-21**. In some cases, a further extraction with AcOEt of the aqueous phase was required to improve the yields. A short silica pad (Hexane/AcOEt: 3/7) was required for compound **III-12k**. For the synthesis of sulfonamides **III-15d** and **III-16d**, *N*-methyl imidazole was added as LAG (η = 0.6 $\mu L\ mg^{-1}$) and the reaction was conducted for 180 min.

General one pot procedure for the preparation of sulfonamides

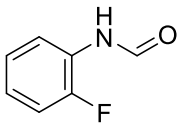
A 15 mL zirconium oxide jar equipped with two balls of the same material (Φ = 8 mm, $mass_{tot}$ = 3.22 g) was charged with $NaHSO_4$ (10 mol%, 0.1 mmol), followed by disulfide (**III-7a- III-7n**) (1.0 mmol) and $NaOCl*5H_2O$ (6 mmol). (*Attention!* It is crucial to add the reagents in the written order for the success of the reaction since a variable loss of gas could affect the yields). The jar was then closed and the mechanochemical reaction was conducted for 40 min at a frequency of 30 Hz (for the synthesis of **III-8h**, the amount of $NaOCl*5\ H_2O$ had to be raised up to 7 mmol. For the synthesis of **III-8d- III-8f** and **III-8i** the reaction time raised up to 180 min). At the end of the first step, the jar was opened and the amine **9-21** (2.2 mmol) and MgO (4 mmol) were added to the mixture. The jar was then closed, and the reaction was conducted for 90-120 min at a milling frequency of 30 Hz. Once the second step was ended, the crude was recovered from the jar with 10 mL of AcOEt and filtered. The filtrate was washed with an aqueous solution of citric acid 3x5 mL (10% w/w), to obtain the desired sulfonamide product **III-9- III-21**. In some cases, a further extraction with AcOEt of the aqueous phase was required to improve the yields. A short silica pad (Hexane/ AcOEt: 3/7) was required for compound **III-12k**. For the synthesis of sulfonamides **III-15d** and **III-16d**, *N*-methyl imidazole was added as LAG ($\eta = 0.6\ \mu L\ mg^{-1}$) and the reaction was conducted for 180 min.

N-phenyl formamide (**III-3a**)



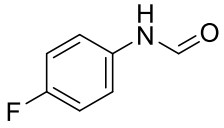
Colorless solid (117.5 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 53/47)** δ = 8.70 (d, J = 11.3 Hz, 0.53H), 8.38 (s, 0.47H), 8.21 – 7.32 (m, 1H), 7.55 – 7.54 (m, 1H), 7.38 – 7.32 (m, 2H), 7.21 – 7.13 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.7, 159.1, 137.0, 136.8, 129.9, 129.3, 125.5, 125.0, 120.1, 119.0. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-fluorophenyl) formamide (**III-3b**)



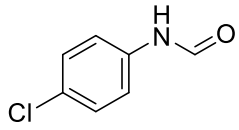
Yellowish liquid (133.5 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 68/32)** δ = 8.69 (dd, J^1 = 11.3 Hz, J^2 = 1.5 Hz, 0.68H), 8.47 (s, 0.32H), 8.34 – 7.23 (m, 1H), 7.65 – 7.54 (m, 1H), 7.17 – 7.06 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.0, 158.9, 154.1, 153.2, 151.5, 126.2, 126.1, 125.6, 125.5, 125.1, 125.0, 124.9, 124.8, 124.7, 122.3, 119.6, 116.6, 116.5, 115.1, 115.0. **IR (FTIR):** 3217, 3074, 1694, 1672, 1618, 1529, 1457, 1413, 1287, 1100, 1037, 748, 698, 635, 519. **HRMS:** calculated for $C_7H_6FNO+Na^+$: 162.0331 [M+Na]$^+$; found: 162.0329.

N-(4-fluorophenyl) formamide (**III-3c**)



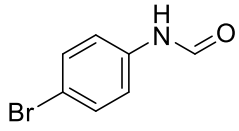
Yellowish solid (136.3 mg, 0.98 mmol, 98%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 43/57)** δ = 8.57 (d, J = 11.2 Hz, 0.43H), 8.36 – 8.35 (s, 0.57H), 8.17 – 7.37 (m, 1H), 7.52 – 7.49 (dd, 1H), 7.07 – 7.01 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 162.9, 161.4, 160.6, 159.8, 159.0, 159.0, 133.0, 122.0, 121.9, 121.5, 121.4, 116.8, 116.7, 116.0, 115.9. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-chlorophenyl) formamide (**III-3d**)



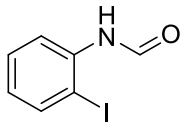
Grey solid (147.8 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 41/59)** δ= 8.65 (d, J = 11.3 Hz, 0.41H), 8.49 (s, 0.59H), 8.08 (s, 1H), 7.51 – 7.02 (m, 2H), 7.34 – 7.26 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 162.4, 159.0, 135.5, 135.4, 131.0, 130.1, 130.0, 129.3, 121.3, 120.3. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-bromophenyl) formamide **(III-3e**)



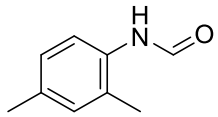
Yellowish liquid (194.0 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 40/60)** δ = 8.65 (d, J = 11.0 Hz, 0.40H), 8.39 – 8.38 (s, 0.60H), 7.85 – 7.22 (m, 1H), 7.49 –6.96 (m, 4H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.1, 158.9, 136.0, 133.0, 132.3, 121.6, 120.6, 118.5, 117.7. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-iodophenyl) formamide (**III-3f**)



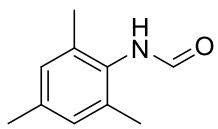
Yellowish liquid (232.2 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 38/62)** δ = 8.65 (d, J = 11.2 Hz, 0.38H), 8.48 (s, 0.62H), 8.28 – 6.86 (m, 2H), 7.85 – 7.78 (m, 1H), 7.59 – 7.51 (m, 1H), 7.37 – 7.34 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.1, 159.1, 159.0, 140.1, 139.1, 137.9, 137.4, 129.8, 129.5, 127.2, 126.5, 122.5, 122.4, 119.5, 90.9, 89.4. **IR (FTIR):** 3222, 3017, 2919, 2901, 1655, 1583, 1570, 1521, 1431, 1391, 1279, 1150, 1016,882, 743, 694. **HRMS:** calculated for $C_7H_6INO+Na^+$: 269.9392 [M+Na]$^+$; found: 269.9392.

N-(2,4-dimethyl) phenyl formamide (**III-3g**)



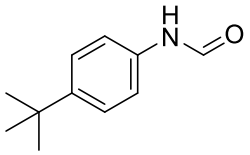
Black solid (143.2 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 63/37)** δ = 8.47 (d, J = 11.4 Hz, 0.63 H), 8.42 (s, 0.37 H), 7.72 – 7.02 (m, 3H) 7.34 – 6.94 (m, 1H), 2.31 – 2.30 (d, 3H), 2.25 (d, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 163.3, 159.1, 136.2, 135.5, 132.4, 132.0, 131.4, 129.9, 128.9, 127.8, 127.5, 123.4, 121.3, 21.0, 20.9, 17.9, 17.8. **IR (FTIR):** 3279, 3021, 2962, 2910, 1675, 1580, 1513, 1434, 1264, 743, 671, 593. **HRMS:** calculated for $C_9H_{11}NO+Na^+$: 172.0738 [M+Na]$^+$; found: 172.0735.

N-mesityl formamide (**III-3h**)



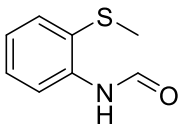
Brown solid (155.0 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 50/50)** δ = 8.40 (s, 0.45 H), 8.05 (d, J = 12.0 Hz, 0.45 H), 6.93 – 6.91 (d, 2H), 6.81 – 6.75 (bs, 1H), 2.34 – 2.22 (m, 9H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 165.1, 159.6, 158.7, 139.0, 137.8, 137.6, 135.4, 135.2, 133.9, 131.7, 130.5, 129.9, 129.5, 129.4, 129.1, 129.0, 21.1, 21.0, 18.8, 18.7, 18.6. **IR (FTIR):** 3282, 3024, 2967, 2900, 1680, 1582, 1513, 1434, 1261, 743, 671, 639. **HRMS:** calculated for $C_{10}H_{13}NO+Na^+$: 186.0895 [M+Na]$^+$; found: 186.0894. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-(*tert*-butyl) phenyl) formamide (**III-3i**)



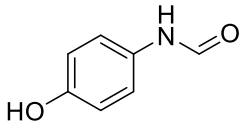
Brownish solid (171.9 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 54/46)** δ= 8.64 (d, J= 11.1 Hz, 0.54H), 8.65 – 8.63 (d, 0.54H), 8.37 – 8.36 (s, 0.46H), 7.71 – 7.18 (m, 1H), 7.46 – 7.35 (m, 3H), 7.03 – 7.01 (m, 1H), 1.32 – 1.31 (d, 9H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 162.6, 158.9, 148.8, 148.1, 134.3, 134.1, 126.8, 126.1, 119.9, 119.1, 34.7, 34.6, 31.6, 31.5. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-(methylthio) phenyl) formamide (**III-3j**)



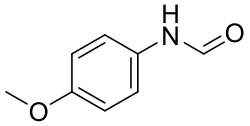
Black oil (155.5 mg, 0.93 mmol, 93%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 34/66)** δ = 8.69 (d, J = 11.2 Hz, 0.34H), 8.50 (s, 0.66H), 8.42 – 8.18 (bs, 1H), 8.33 – 7.08 (m, 4H), 2.38 (d, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 162.1, 159.3, 137.3, 136.2, 132.9, 131.6, 128.8, 128.3, 128.0, 125.8, 125.5, 124.9, 121.2, 118.5, 18.9, 17.7. **IR (FTIR):** 3293, 3069, 2994, 2922, 1672, 1582, 1515, 1430, 1296, 743, 671, 635, 533. **HRMS:** calculated for $C_8H_9NOS+Na^+$: 190.0303 [M+Na]$^+$; found: 190.0302. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-hydroxyphenyl) formamide (**III-3k**)



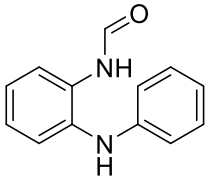
White solid (133.0 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, DMSO-d_6, mixture of rotamers *trans/cis:* 35/65)** δ= 9.88 – 9.82 (m, 1H), 9.26 – 9.22 (m, 1H), 8.50 (d, J = 11.3 Hz, 0.35H), 8.16 (s, 0.65H), 8.10 – 6.69 (m, 2H), 7.38 – 6.97 (m, 2H). **^{13}C NMR (151 MHz, DMSO-d_6, mixture of rotamers)** δ= 162.4, 159.3, 159.1, 159.0, 122.8, 122.0, 121.2, 120.4. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-methoxyphenyl) formamide (**III-3l**)



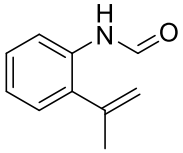
Brownish solid (148.2 mg, 0.98 mmol, 98%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 49/51)** δ= 8.50 (d, J = 11.2 Hz, 0.49H), 8.33 (s, 0.51H), 7.63 – 7.13 (m, 1H), 7.45 – 7.44 (m, 1H), 7.04 – 7.02 (m, 1H), 6.90 – 6.86 (m, 2H), 3.81 – 3.79 (d, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 163.0, 158.9, 157.9, 156.9, 130.0, 129.6, 122.0, 121.9, 115.1, 114.4, 55.7, 55.6. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-(phenylamino) phenyl) formamide (**III-3m**)



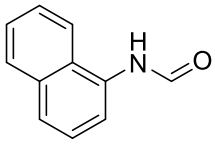
Dark purple oil (197.3 mg, 0.93 mmol, 93%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers)** δ= 9.37 (bs, 1H), 8.28 (s, 1H), 7.98 – 7.72 (m, 1H), 7.60 – 7.48 (m, 6H), 7.39 – 7.34 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 142.8, 142.2, 136.1, 133.7, 133.4, 130.3, 128.5, 124.3, 124.2, 123.4, 120.3, 110.8. **IR (FTIR):** 3300, 3063, 3044, 2897, 1713, 1642, 1579, 1460, 1237, 1180, 1078, 1013, 899. **HRMS:** calculated for $C_{11}H_9NO+Na^+$: 194.0582 [M+Na]$^+$; found: 194.0586.

N-(2-(prop-1-en-2-yl) phenyl) formamide (**III-3n**)



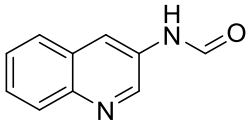
Orangish solid (153.1 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 50/50)** δ= 8.69 (d, J = 11.4 Hz, 0.50H), 8.41 – 8.40 (s, 0.50H), 8.33 – 7.09 (m, 4H), 7.62 (bs, 1H), 5.41 – 5.36 (m, 1H), 5.04 – 5.00 (m, 1H), 2.08 – 2.05 (d, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 162.4, 162.3, 159.1, 142.6, 142.1, 134.9, 134.7, 134.0, 133.8, 133.5, 133.2, 133.1, 133.0, 132.6, 129.1, 128.7, 128.3, 128.1, 128.0, 127.9, 126.7, 125.2, 125.0, 124.4, 123.8, 122.4, 121.4, 121.0, 120.5, 118.5, 117.6, 117.2, 24.6, 24.2. **IR (FTIR):** 3280, 3075, 2972, 2892, 1690, 1668, 1579, 1516, 1445, 1297, 1279, 909, 729. **HRMS:** calculated for $C_{10}H_{11}NO+Na^+$: 184.0738 $[M+Na]^+$; found: 184.0737. The spectroscopic data closely match the ones previously reported in the literature.

N-(naphthalen-1-yl) formamide (**III-3o**)



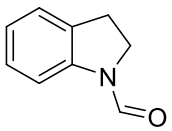
Pink solid (164.4 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 100/0)** δ = 8.61 (d, J = 11.3 Hz, 1H), 8.18 (bs, 1H), 8.04 – 7.32 (m, 7H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 163.9, 159.6, 134.4, 134.2, 132.1, 129.0, 128.8, 127.9, 127.3, 127.2, 127.0, 126.8, 126.7, 126.4, 126.3, 125.9, 125.7, 121.3, 121.0, 120.4, 119.4. **IR (FTIR):** 3221, 2985, 2891, 1654, 1600, 1533, 1506, 1502, 1390, 1270, 1149, 1011, 921, 769. **HRMS:** calculated for $C_{11}H_9NO+Na^+$: 194.0582 $[M+Na]^+$; found: 194.0586.

N-(quinolin-3-yl) formamide (**III-3p**)



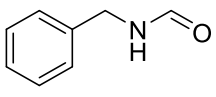
Pale-yellow solid (165.3 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 20/80)** δ= 10.61 – 10.43 (m, 1H), 8.90 (d, J = 10.8 Hz, 0.20H), 8.85 – 8.84 (s, 0.80H), 8.75 – 8.63 (m, 1H), 8.40 – 8.06 (m, 1H), 7.90 – 7.78 (m, 2H), 7.58 – 7.48 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 163.0, 160.6, 144.7, 144.4, 144.2, 143.7, 132.2, 131.9, 128.7, 128.6, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 122.4, 120.0. **IR (FTIR):** 3200, 3025, 2877, 1649, 1538, 1493, 1444, 1381, 1238, 1024, 926, 752, 702, 609. **HRMS:** calculated for $C_{10}H_9N_2O+H^+$: 173.0715 $[M+H]^+$; found: 173.0713.

Indoline-1-carbaldehyde (**III-3q**)



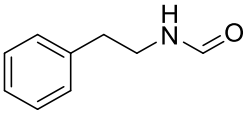
Brownish solid (135.4 mg, 0.92 mmol, 92%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *endo/eso:* 19/81)** δ= 8.91 (s, 0.19H), 8.49 (s, 0.81H), 8.09 – 6.99 (m, 4H), 4.09 – 4.02 (m, 2H), 3.18 – 3.11 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 159.4, 157.6, 141.2, 141.0, 134.8, 134.0, 132.1, 131.9, 127.6, 127.5, 126.0, 125.1, 124.8, 124.6, 124.3, 120.9, 116.6, 109.4, 47.0, 44.6, 27.7, 27.1. **IR (FTIR):** 2962, 2931, 2895, 2855, 1640, 1591, 1488, 1413, 1368, 1337, 1287, 1220, 1176, 1033, 743. **HRMS:** calculated for $C_9H_9NO+Na^+$: 170.0582 $[M+Na]^+$; found: 170.0578. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl formamide (**III-3r**)



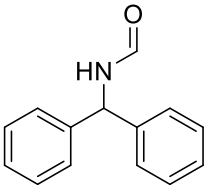
White solid (132.5 mg, 0.98 mmol, 98%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 23/77)** δ= 8.29 (s, 0.77H), 8.22 (d, J = 12.0 Hz, 0.23H), 7.38 – 7.26 (m, 5H), 5.77 (bs, 1H), 4.51-4.43 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 164.7, 161.1, 137.7, 129.1, 129.0, 128.1, 128.0, 127.9, 127.1, 45.8, 42.4. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-phenylethyl) formamide (**III-3s**)



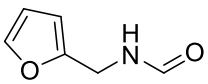
Brownish oil (144.7 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 17/83)** δ = 7.99 (s, 0.83H), 7.76 (d, J = 12.0 Hz, 0.83H), 7.28 – 7.10 (m, 5H), 6.13 – 6.00 (m, 1H), 3.49 – 3.36 (m, 2H), 2.78 – 2.73 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 164.6, 161.6, 161.5, 138.6, 138.5, 137.6, 128.7, 128.6, 128.5, 128.4, 126.6, 126.3, 43.1, 39.1, 37.4, 35.3. The spectroscopic data closely match the ones previously reported in the literature.

N-benzhydrylformamide (**III-3t**)



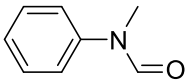
Pale-yellow solid (202.8 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 17/83)** δ = 8.19 (s, 0.83H), 8.14 (d, J = 12.1 Hz, 0.17H), 7.35 – 7.20 (m, 10H), 6.52 – 6.43 (m, 1H), 6.30 – 5.71 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 164.5, 160.4, 145.3, 145.0, 141.1, 141.0, 129.1, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.1, 127.0, 60.03, 59.8, 55.8. **IR (FTIR):** 3119, 2967, 2913, 1801, 1770, 1721, 1502, 1435, 1368, 1301, 1176, 1042, 805, 586. **HRMS:** calculated for $C_{14}H_{13}NO+Na^+$: 234.0895 [M+Na]$^+$; found: 234.0894. The spectroscopic data closely match the ones previously reported in the literature.

N-(furan-2-ylmethyl) formamide (**III-3u**)



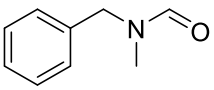
Brownish oil (122.6 mg, 0.98 mmol, 98%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 15/85)** δ = 8.15 – 8.14 (s, 0.85H), 8.10 (d, J = 11.9 Hz, 0.15H), 7.35 – 7.31 (m, 1H), 6.51 (bs, 1H), 6.31 – 6.20 (m, 2H), 4.43 – 4.32 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 165.0, 161.3, 150.7, 142.9, 142.4, 110.6, 110.6, 107.7, 107.6, 39.0, 35.1. The spectroscopic data closely match the ones previously reported in the literature.

N-methyl-*N*-phenylformamide (**III-3v**)



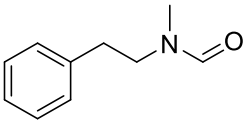
White solid (128.4 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers)** δ = 8.48 (s, 0.95H), 8.36 (s, 0.05H), 7.41 (t, J = 6Hz, 2H), 7.27 (t, J = 6Hz, 1H), 7.18 (d, J = 6Hz, 2H), 3.35 – 3.32 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.4,162.2, 142.2, 140.2, 129.7, 129.1, 126.4, 126.3, 123.6, 122.4, 36.9, 32.1. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl-*N*-methylformamide (**III-3w**)



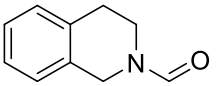
Yellowish oil (144.7 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers)** δ = 8.27 (s, 0.58H), 8.14 (s, 0.42H), 7.36 – 7.19 (m, 5H), 4.51 – 4.38 (m, 2H), 2.83 – 2.77 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.7, 162.6, 136.0, 135.7, 128.8, 128.6, 128.2, 128.0, 127.6, 127.4, 53.4, 47.7, 34.0, 29.4. The spectroscopic data closely match the ones previously reported in the literature.

N-methyl-*N*-phenethylformamide (**III-3x**)



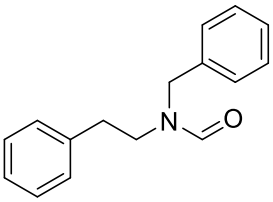
Yellowish oil (153.4 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers)** δ = 7.98 (s, 0.37H), 7.77 (s, 0.63H), 7.30 – 7.12 (m, 5H), 3.56 – 3.43 (m, 2H), 2.87 – 2.80 (m, 5H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.6, 162.4, 138.5, 137.7, 128.8, 128.7, 128.6, 128.5, 126.7, 126.4, 51.1, 45.9, 34.9, 34.7, 33.1, 29.6. The spectroscopic data closely match the ones previously reported in the literature.

3,4-dihydroisoquinoline-2(1H)-carbaldehyde (**III-3y**)



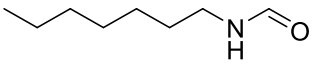
Yellow oil (148.3 mg, 0.92 mmol, 92%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *endo/eso:* 63/37)** δ = 8.23 (s, 0.63 H), 8.18 (s, 0.37H), 7.21 – 7.08 (m, 4H), 4.67 –4.52 (m, 2H), 3.78 – 3.62 (m, 2H), 2.90 – 2.85 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 161.8, 161.2, 134.5, 133.6, 132.3, 131.8, 129.2, 129.0, 127.2, 126.8, 126.7, 126.6, 125.9, 47.4, 43.3, 42.4, 38.1, 29.8, 28.0. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl-*N*-phenethylformamide (**III-3z**)



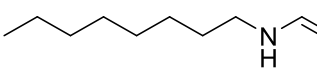
Orange oil (222.5 mg, 0.93 mmol, 93%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers 50/50)** δ = 8.26 (s, 0.50H), 7.77 (s, 0.50H), 7.87 – 7.06 (m, 10H), 4.54 – 4.22 (m, 2H), 3.45 – 3.23 (m, 2H), 3.06 – 2.75 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 166.7, 163.2, 163.1, 142.3, 138.7, 137.8, 136.5, 136.3, 135.9, 133.4, 133.3, 133.2, 131.2, 130.6, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.7, 127.0, 126.8, 126.5, 124.2, 120.6, 52.0, 51.3, 48.5, 48.3, 45.6, 44.0, 35.1, 33.5, 32.3. **IR (FTIR):** 3069, 3029, 2931, 1663, 1578, 1457, 1430, 1283, 1149, 1118, 953, 747, 698, 600. **HRMS:** calculated for $C_6H_{17}NO+H^+$: 240.1388 $[M+H]^+$; found: 240.1389.

N-heptylformamide (**III-3aa**)



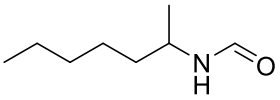
Yellowish oil (137.5 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 21/79)** δ = 8.10 (s, 0.79H), 7.96 (d, J = 12.0 Hz, 0.21), 6.38 – 6.18 (m, 1H), 3.23 – 3.13 (m, 2H), 1.49 – 1.44 (m, 2H), 1.28 – 1.24 (m, 8H), 0.84 – 0.82 (t, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ= 165.0, 161.6, 42.0, 40.1, 38.2, 31.8, 31.7, 31.5, 31.2, 29.5, 28.9, 28.8, 28.7, 26.8, 26.5, 26.4, 22.7, 22.6, 22.5, 14.2, 14.1, 14.0. The spectroscopic data closely match the ones previously reported in the literature.

N-octyl formamide (**III-3ab**)



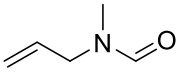
Yellowish oil (150.9 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 27/73)** δ= 8.14 (s, 0.73H), 8.02 (d, J = 12.0 Hz, 0.27H), 5.70 (s, 1H), 3.29 – 3.17 (m, 2H), 1.53 – 1.23 (m, 12H), 0.88 – 0.85 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 164.7, 161.3, 41.9, 38.3, 31.9, 31.8, 31.4, 29.6, 29.4, 29.3, 29.2, 29.1, 27.0, 26.0, 22.7, 22.6, 14.2. The spectroscopic data closely match the ones previously reported in the literature.

(±)-*N*-(heptan-2-yl) formamide (**III-3ac**)



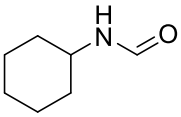
Yellowish oil (134.6 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 28/72)** δ = 8.13 (s, 0.28H), 8.08 – 8.06 (m, J = 12.1 Hz, 0.72H), 5.30 – 5.29 (m, 1H), 4.08 – 3.47 (m, 1H), 1.46 – 1.15 (m, 11H), 0.90 – 0.87 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 160.6, 48.5, 44.3, 38.0, 37.0, 31.8, 31.6, 25.7, 22.8, 22.7, 22.6, 21.1, 14.1, 14.0. **IR (FTIR):** 3271,3062, 2963, 2932, 2861, 1655, 1588, 1530, 1463, 1382, 1275, 1244, 1150, 1123, 819, 699.

N-allyl-*N*-methylformamide (**III-3ad**)



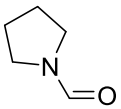
Yellowish oil (96.1 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 10/90)** δ = 8.06 (s, 0.90H), 7.68 (d, *J* = 12.0 Hz, 0.10H), 5.77 – 5.67 (m, 1H), 5.25 – 5.16 (m, 2H), 3.94 – 3.81 (m, 2H), 2.89 – 2.82 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 162.9, 162.4, 133.0, 132.0, 118.6, 118.2, 52.1, 46.8, 34.1, 29.6. **IR (FTIR):** 3100, 2949, 2913, 1761, 1631, 1493, 1457, 1359, 1296, 1238, 1162, 1042, 792, 752, 680. **HRMS:** calculated for $C_5H_9NO+Na^+$: 122.0582 [*M*+Na]$^+$; found: 122.0582.

N-cyclohexylformamide (**III-3ae**)



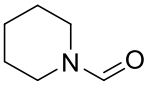
Pinkish solid (120.8 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers *trans/cis:* 32/68)** δ = 8.11 (d, *J* = 12.1 Hz, 0.32H), 8.09 (s, 0.68H), 5.75 – 5.54 (m, 1H), 3.88 – 3.27 (m, 1H), 1.94 – 1.13 (m, 10H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 163.6, 160.4, 51.1, 47.2, 34.8, 33.2, 25.6, 25.2, 24.9, 24.8. The spectroscopic data closely match the ones previously reported in the literature.

Pyrrolidine-1-carbaldehyde (**III-3af**)



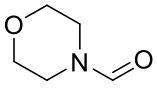
Yellowish oil (96.1 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 8.24 – 8.08 (m, 1H), 3.49 – 3.40 (m, 4H), 1.92 – 1.88 (m, 4H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 161.0, 46.2, 43.3, 25.0, 24.4. The spectroscopic data closely match the ones previously reported in the literature.

Piperidine-1-carbaldehyde (**III-3ag**)



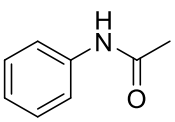
Brownish oil (107.5 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.97 (s, 1H), 3.46 – 3.27 (m, 4H), 1.67 – 1.50 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 160.9, 46.9, 40.7, 26.7, 25.2, 24.8. The spectroscopic data closely match the ones previously reported in the literature.

Morpholine-4-carbaldehyde (**III-3ah**)



Brownish oil (109.3 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 8.06 (s, 1H), 3.70 – 3.65 (m, 4H), 3.58 – 3.57 (t, 2H), 3.40 – 3.39 (t, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 161.0, 67.4, 66.6, 46.0, 40.8. The spectroscopic data closely match the ones previously reported in the literature.

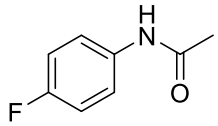
N-phenylacetamide (**III-4a**)



White solid (131.0 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.57 (bs, 1H), 7.51 – 7.49 (d, 2H), 7.32 – 7.29 (t, 2H), 7.11 – 7.08 (t, 1H), 2.16 (s, 3H). **^{13}C**

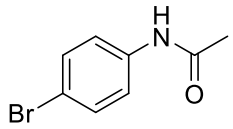
NMR (151 MHz, $CDCl_3$) δ = 168.7, 138.1, 129.1, 124.4, 120.1, 24.7. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-fluorophenyl) acetamide (**III-4c**)



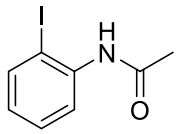
White solid (144.0 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.44 (dt, 3H), 7.00 (t, 2H), 2.16 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 168.5, 160.3, 158.7, 134.1, 134.0, 122.0, 121.9, 115.8, 115.7, 24.5. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-bromophenyl) acetamide (**III-4e**)



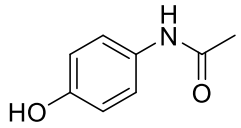
White solid (205.5 mg, 0.96 mmol, 96%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 8.09 – 7.41 (m, 4H), 7.18 (bs, 1H), 2.17 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 168.3, 132.1, 121.5, 29.9, 24.8. The spectroscopic data closely match the ones previously reported in the literature.

N-(2-iodophenyl) acetamide (**III-4f**)



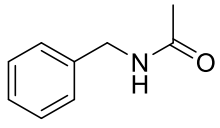
White solid (242.8 mg, 0.93 mmol, 93%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers)** δ = 8.18 – 7.10 (m, 1H), 7.77 – 7.61 (m, 1H), 7.44 (bs, 1H), 7.34 – 6.44 (m, 1H), 6.85 – 6.72 (m, 1H), 4.09 – 2.23 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 168.4, 146.9, 139.1, 138.9, 138.3, 129.5, 129.4, 126.1, 122.3, 120.0, 114.8, 90.2, 84.3, 29.8, 24.9. **IR (FTIR):** 3364, 2976, 2922, 1765, 1613, 1502, 1439, 1363, 1301, 1265, 1180, 1042, 1002, 752. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-hydroxyphenyl) acetamide (**III-4k**)



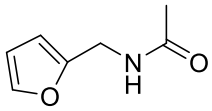
White solid (140.5 mg, 0.93 mmol, 93%). **^{1}H NMR (600 MHz, DMSO-d_6)** δ = 9.60 (s, 1H), 9.12 (s, 1H), 7.30 – 7.28 (d, 2H), 6.64 – 6.62 (d, 2H), 1.93 (s, 3H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ = 167.5, 153.2, 131.0, 120.8, 115.0, 23.7. The spectroscopic data closely match the ones previously reported in the literature.

N-benzylacetamide (**III-4r**)



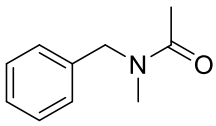
White solid (146.2 mg, 0.98 mmol, 98%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.35 – 7.32 (m, 2H), 7.29 – 7.26 (m, 3H), 5.80 (bs, 1H), 4.43 – 4.42 (d, 2H), 2.02 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 170.0, 138.4, 128.9, 128.0, 127.7, 43.9, 23.4. The spectroscopic data closely match the ones previously reported in the literature.

N-(furan-2-ylmethyl) acetamide (**III-4u**)



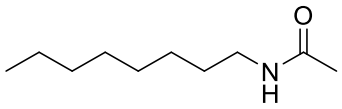
Colorless solid (135.0 mg, 0.97 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.34 (dd, 1H), 6.31 – 6.30 (dd, 1H), 6.22 – 6.21 (m, 1H), 5.92 (s, 1H), 4.41 (d, 2H), 1.99 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 170.0, 151.4, 142.3, 110.6, 107.6, 36.7, 23.3. **IR (FTIR):** 3275, 3078, 1636, 1551, 1497, 1435, 1368, 1287, 1252, 1149, 1064, 1024, 810, 752, 725. **HRMS:** calculated for $C_7H_9NO_2$+H^+: 140.0712 [*M*+H]$^+$; found: 140.0708. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl-*N*-methylacetamide (**III-4w**)



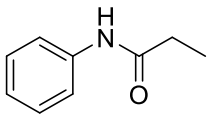
White solid (153.4 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers 55/45)** δ = 7.42 – 7.08 (m, 5H), 4.64 – 4.48 (m, 2H), 3.06 – 2.82 (m, 3H), 2.18 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 171.5, 171.2, 129.1, 128.7, 128.2, 128.0, 127.5, 126.4, 54.4, 50.8, 35.7, 34.0, 21.9, 21.5. The spectroscopic data closely match the ones previously reported in the literature.

N-octylacetamide (**III-4aa**)



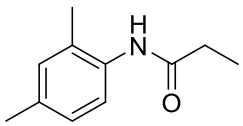
Yellow oil (162.7 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 5.71 (bs, 1H), 3.21 – 3.18 (m, 2H), 1.95 (s, 3H), 1.49 – 1.44 (m, 2H), 1.30 – 1.23 (m, 10H), 0.86 – 0.84 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 170.3, 39.8, 31.9, 29.7, 29.4, 29.3, 27.0, 23.4, 22.7, 14.2. **IR (FTIR):** 3285, 3084, 2959, 2928, 2856, 1650, 1556, 1467, 1440, 1373, 1293, 1145, 726, 605. The spectroscopic data closely match the ones previously reported in the literature.

N-phenylpropionamide (**III-5a**)



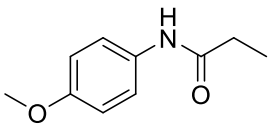
White solid (111.8 mg, 0.75 mmol, 75%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 8.00 (bs, 1H), 7.52 – 7.51 (d, 2H), 7.28 – 7.25 (t, 2H), 7.08 – 7.05 (t, 1H), 2.37 – 2.34 (q, 2H), 1.21 – 1.18 (t, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 172.8, 138.2, 128.9, 124.2, 120.2, 30.7, 9.8. The spectroscopic data closely match the ones previously reported in the literature.

N-(2,4-dimethylphenyl) propionamide (**III-5g**)



White solid (141.8 mg, 0.80 mmol, 80%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers 86/14)** δ = 7.57 – 6.98 (m, 4H), 3.08 – 2.38 (m, 2H), 2.28 (s, 3H), 2.20 (s, 3H), 1.28 – 1.24 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers)** δ = 172.2, 157.8, 136.5, 135.1, 135.0, 133.2, 131.2, 129.7, 127.3, 126.4, 123.8, 121.3, 32.0, 30.6, 21.0, 17.8, 10.1, 7.7. **IR (FTIR):** 3271, 2968, 2919, 2861, 1650, 1525, 1431, 1364, 1270, 1212, 815, 699. The spectroscopic data closely match the ones previously reported in the literature.

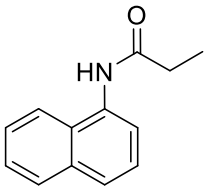
N-(4-methoxyphenyl) propionamide (**III-5l**)



Brownish solid (170.2 mg, 0.95 mmol, 95%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers 87/13)** δ = 7.78 (bs, 1H), 7.40 – 7.38 (dd, 2H), 6.80 – 6.78 (dd, 2H), 3.75 – 3.74 (d, 3H), 3.06 – 2.30 (m, 2H), 1.26 – 1.17 (m, 1H).

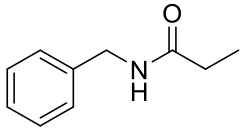
^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers) δ = 172.5, 172.2, 156.3, 136.6 135.0, 131.3, 126.3, 122.0, 121.2, 114.1, 55.5, 31.9, 30.4, 9.9, 7.6. **IR (FTIR):** 3312, 3008, 2981, 2941, 2843, 1641, 1597, 1538, 1516, 1463, 1248, 1177, 1034, 824, 681, 525. The spectroscopic data closely match the ones previously reported in the literature.

N-(naphthalen-1-yl) propionamide (**III-5o**)



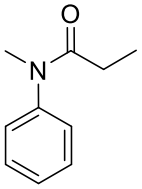
Pink solid (163.4 mg, 0.82 mmol, 82%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.84 – 7.38 (m, 8H), 2.46 (m, 2H), 1.27 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 173.0, 134.2, 132.5, 128.7, 127.6, 126.2, 126.0, 125.9, 125.7, 121.4, 121.0, 30.5, 10.0. **IR (FTIR):** 3263, 3066, 2977, 2936, 2883, 1655, 1538, 1498, 1275, 1248, 1217, 931, 801, 766, 717. The spectroscopic data closely match the ones previously reported in the literature.

N-benzylpropionamide (**III-5r**)



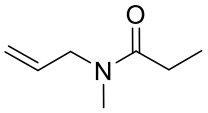
Colourless solid (150.1 mg, 0.92 mmol, 92%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.33 – 7.25 (m, 5H), 6.07 (bs, 1H), 4.43 – 4.42 (d, 2H), 2.28 – 2.24 (q, 2H), 1.19 – 1.16 (t, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 174.3, 138.3, 128.8, 127.9, 127.6, 43.7, 29.7, 10.0. The spectroscopic data closely match the ones previously reported in the literature.

N-methyl-*N*-phenylpropionamide (**III-5v**)



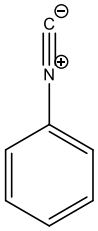
Orange oil (132.4 mg, 0.81 mmol, 81%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.42 – 7.19 (m, 5H), 3.27 (s, 3H), 2.09 (m, 2H), 1.05 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 174.1, 173.6, 144.1, 130.1, 129.7, 129.0, 127.7, 127.2, 122.8, 37.3, 27.4, 20.8, 9.6. **IR (FTIR):** 3490, 3062, 2981, 2945, 2875, 1659, 1592, 1494, 1378, 1279, 1123, 1092, 1038, 775, 708. The spectroscopic data closely match the ones previously reported in the literature.

N-allyl-*N*-methylpropionamide (**III-5ad**)



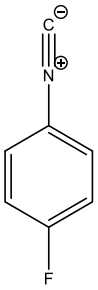
Colourless solid (119.4 mg, 0.94 mmol, 94%). **^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers 50/50**) δ = 5.73 – 5.64 (m, 1H), 5.14 – 5.04 (m, 2H), 3.93 – 3.82 (m, 2H), 2.87 – 2.85 (d, 3H), 2.30 – 2.23 (m, 2H), 1.09 – 1.05 (dt, 3H). **^{13}C NMR (151 MHz, $CDCl_3$, mixture of rotamers**) δ = 174.0, 173.5, 133.2, 132.6, 117.0, 116.4, 52.05, 49.9, 34.5, 33.6, 26.7, 26.0, 9.5, 9.2. **IR (FTIR):** 3307, 3070, 2928, 1726, 1646, 1588, 1458, 1360, 1333, 1230, 1150, 1114, 967, 676. **HRMS:** calculated for $C_7H_{13}NO+Na^+$: 150.0895 $[M+Na]^+$; found:150.0890. The spectroscopic data closely match the ones previously reported in the literature.

Isocyanobenzene **III-6a**



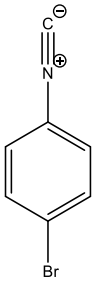
Yellowish oil (72.2 mg, 0.7 mmol, 70%). R_f = 0.60 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.40-7.36 (m, 5H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 164.1, 129.6, 129.5, 126.6. The spectroscopic data closely match the ones previously reported in the literature.

1-Fluoro-4-isocyanobenzene **III-6c**



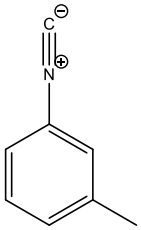
Brownish solid (81.1 mg, 0.67 mmol, 67%). **R_f** = 0.64 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.38-7.36 (d, *J* = 8.5 Hz, 2H), 7.32-7.31 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 165.8, 135.5, 129.9, 127.8, 125.3, 125.2, 125.1. The spectroscopic data closely match the ones previously reported in the literature.

1-Bromo-4-isocyanobenzene **III-6e**



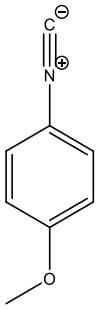
Yellowish solid (131.0 mg, 0.72 mmol, 72%). **R_f** = 0.61 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.55 – 7.53 (m, 2H), 7.26-7.25 (d, *J* = 2.1 Hz, 2H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 132.9, 128.0, 123.6. The spectroscopic data closely match the ones previously reported in the literature.

1-Isocyano-3-methylbenzene **III-6g$_1$**



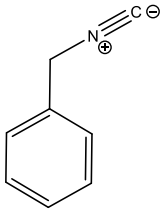
Brown oil (83.2 mg, 0.71 mmol, 71%). **R_f** = 0.57 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.27 – 7.25 (m, 1H), 7.21 – 7.17 (m, 3H), 2.36 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 163.7, 139.8, 130.3, 129.3, 127.0, 123.6, 21.2.

1-isocyano-4-methoxybenzene **III-6l**



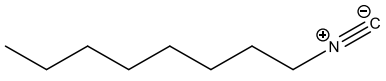
Yellow solid (109.2 mg, 0.82 mmol, 82%). **R_f** = 0.45 (*n*-exane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, CDCl3):** δ = 7.31 (d, 2H), 6.93 – 6.83 (m, 2H), 3.82 (s, 3H). **^{13}C NMR (151 MHz, CDCl3):** δ = 160.0, 127.9, 114.7, 55.7. The spectroscopic data closely match the ones previously reported in the literature.

Benzyl isocyanide **III-6r**



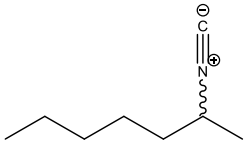
Brown oil (110.2 mg, 0.94 mmol, 94%). **R_f** = 0.55 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 3H), 4.65 (t, J = 2.3 Hz, 2H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 157.8, 132.35, 129.00, 128.44, 126.62, 45.6. The spectroscopic data closely match the ones previously reported in the literature.

1-Isocyanooctane **III-6ab**



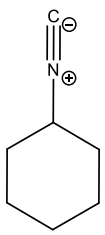
Colourless oil (125.3 mg, 0.9 mmol, 90%). **R_f** = 0.53 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 3.37 (ddt, 2H), 1.67 (dddd, 2H), 1.43 (td, 2H), 1.35 – 1.21 (m, 8H), 0.89 (t, 3H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 155.7, 41.8, 41.7, 41.6, 31.8, 29.3, 29.2, 28.8, 26.5, 22.7, 14.2. The spectroscopic data closely match the ones previously reported in the literature.

2-Isocyanoheptane **III-6ac**



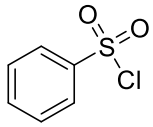
Yellow oil (107,6 mg, 0.86 mmol, 86%). **R_f** = 0.50 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 3.62-3.58 (m, 1H), 1.70-1.69 (m, 2H), 1.36-1.34 (m, 6H), 0.91-0.88 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 154.2, 50.4, 36.9, 31.3, 25.5, 22.6, 21.8, 14.1.

Isocyanocyclohexane **III-6ae**



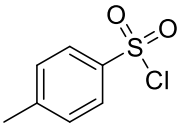
Yellowish oil (96.1 mg, 0.88 mmol, 88%). **R_f** = 0.60 (*n*-heptane:EtOAc 9:1 v/v). **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 3.61-3.58 (tt, J = 8.2, 3.4 Hz, 1H), 1.90 – 1.86 (m, 2H), 1.77 – 1.64 (m, 4H), 1.49-1.34 (m, 4H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ = 154.1, 52.0, 51.9, 51.8, 32.8, 25.1, 22.9. The spectroscopic data closely match the ones previously reported in the literature.

Benzenesulphonyl chloride **III-8a**



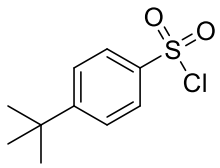
Yellowish oil (349.69 mg, 0.99 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.06 – 8.04 (m, 2H), 7.77 – 7.74 (m, 1H), 7.65 – 7.62 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 144.6, 135.4, 129.8, 127.1. The spectroscopic data closely match the ones previously reported in the literature.

4-(Methyl)benzenesulphonyl chloride **III-8b**



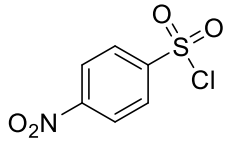
White solid. (369.84 mg, 0.97 mmol, 97%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92-7.90 (d, *J* = 8.3 Hz, 2H), 7.41-7.40 (d, *J* = 8.3 Hz, 2H), 2.49 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.0, 141.8, 130.4, 127.1, 21.9. **M.P.:** 69-71 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(*tert*-Butyl)benzenesulphonyl chloride **III-8c**



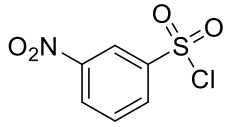
White solid. (442.17 mg, 0.95 mmol, 95%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.97 – 7.95 (m, 2H), 7.63 – 7.61 (m, 2H), 1.37 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 159.8, 141.7, 127.1, 126.8, 35.7, 31.1. **M.P.:** 80-82 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(Nitro)benzenesulphonyl chloride **III-8d**



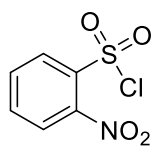
Yellow solid. (345.71 mg, 0.78 mmol, 78%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.49 – 8.47 (m, 2H), 8.27 – 8.26 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.5, 148.8, 128.7, 125.2. **M.P.**: 78 °C. The spectroscopic data closely match the ones previously reported in the literature.

3-(Nitro)benzenesulphonyl chloride **III-8e**



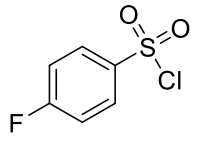
Yellow solid. (354.58 mg, 0.80 mmol, 80%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.88-8.86 (t, *J* = 2.0 Hz, 1H), 8.62-8.60 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 8.39-8.37 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H), 7.93-7.90 (t, *J* = 8.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.5, 145.6, 132.4, 131.5, 129.7, 122.5. **M.P.:** 60-62 °C. The spectroscopic data closely match the ones previously reported in the literature.

2-(Nitro)benzenesulphonyl chloride **III-8f**



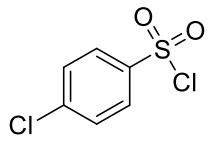
Yellow solid. (332.42 mg, 0.75 mmol, 75%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.93 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.86 – 7.84 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.2, 136.6, 136.2, 133.0, 130.6, 125.4. **M.P.:** 65-67 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(Fluoro)benzenesulphonyl chloride **III-8g**



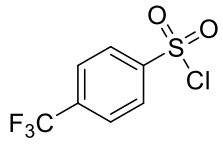
White solid. (350.28 mg, 0.90 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.10 – 8.07 (m, 2H), 7.32 – 7.29 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.4 (d, $J_{C\text{-}F}$ = 260.6 Hz), 140.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.1 (d, $J_{C\text{-}F}$ = 10.1 Hz), 117.1 (d, $J_{C\text{-}F}$ = 23.2 Hz). **M.P.:** 30-31 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(Chloro)benzenesulphonyl chloride **III-8h**



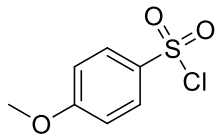
White solid. (405.24 mg, 0.98 mmol, 98%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.00 – 7.98 (m, 2H), 7.62 – 7.59 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.8, 142.4, 130.2, 128.6. **M.P.:** 54-56 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(Trifluoromethyl)benzenesulphonyl chloride **III-8i**



White solid. (484.33 mg, 0.99 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.20 – 8.19 (m, 2H), 7.92 – 7.91 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.3, 137.0 (q, $J_{C\text{-}F}$ = 33.3 Hz), 136.7, 127.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 121.9 (q, $J_{C\text{-}F}$ = 273.7 Hz). **M.P.:** 31-33 °C. The spectroscopic data closely match the ones previously reported in the literature.

4-(Methoxy)benzenesulphonyl chloride **III-8j**

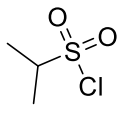


White solid. (409.15 mg, 0.99 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 2H), 7.06 – 7.04 (m, 2H), 3.92 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.0, 136.3, 129.7, 114.9, 56.1. **M.P.:** 40-41 °C. The spectroscopic data closely match the ones previously reported in the literature.

Dimethylsolfonyl chloride **III-8k**

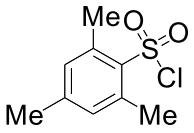
Colourless oil. (GC-MS conversion: 99%).

2-Isopropylsolfonyl chloride **III-8l**



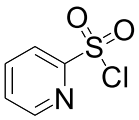
White solid. (282.35 mg, 0.99 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.80 – 3.70 (hept, J = 6.7 Hz, 1H), 1.61 – 1.58 (dd, J = 6.7, 1.1 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 67.5, 17.4. The spectroscopic data closely match the ones previously reported in the literature.

2,4,6-Trimethylbenzenesulfonyl chloride **III-8m**



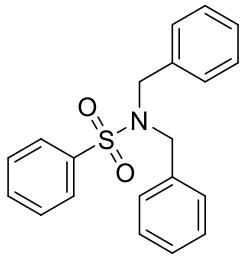
Pale yellow solid. (411,12 mg, 0.94 mmol, 94%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.03 (s, 2H), 2.73 (s, 6H), 2.35 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.6, 140.1, 139.6, 132.4, 23.0, 21.3. **M.P.:** 58 °C

Pyridine-2-sulfonyl chloride **III-8n**



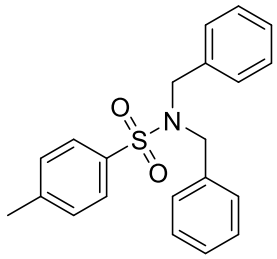
Viscous yellow oil. (310,13 mg, 0.87 mmol, 87%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.81 (d, *J* = 4.7 Hz, 1H), 8.12 – 8.03 (m, 2H), 7.72 – 7.66 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 150.8, 139.2, 129.3, 122.0.

N,N-dibenzyl-benzenesulfonamide **III-9a**



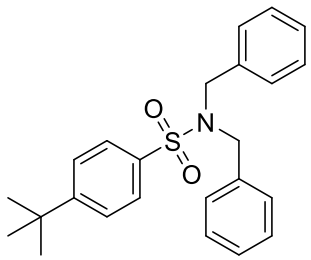
White solid (607.40 mg, 1.8 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.87 – 7.85 (m, 2H), 7.59 – 7.58 (m, 1H), 7.53 – 7.50 (m, 2H), 7.22 – 7.21 (m, 6H), 7.05 – 7.04 (m, 4H), 4.34 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 141.0, 135.7, 132.6, 129.3, 129.2, 128.7, 128.6, 127.8, 50.6. **M.P.:** 74-76 °C. The spectroscopic data closely match the ones previously reported in the literature.

N,N-Dibenzyl-4-(methyl)benzenesulfonamide **III-9b**



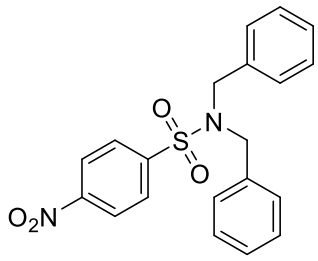
White solid (618.57 mg, 1.76 mmol, 88%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.76 – 7.75 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.23 – 7.22 (m, 6H), 7.08 – 7.06 (dd, *J* = 6.5, 3.1 Hz, 4H), 4.33 (s, 4H), 2.45 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 143.4, 137.8, 135.8, 128.7, 128.6, 128.4, 127.8, 127.7, 50.7, 21.6. **M.P.:** 75-77 °C. The spectroscopic data closely match the ones previously reported in the literature.

N,N-Dibenzyl-4-(tert-buthyl)benzenesulfonamide **III-9c**



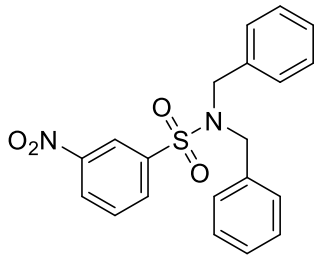
White solid (669.04 mg, 1.70 mmol, 85%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 2H), 7.52 – 7.50 (m, 2H), 7.22 – 7.18 (m, 6H), 7.04 – 7.01 (m, 4H), 4.33 (s, 4H), 1.37 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.5, 137.9, 135.9, 128.7, 128.5, 127.8, 127.2, 126.2, 50.6, 35.3, 31.3. **M.P.:** 79-81 °C

N,N-Dibenzyl-4-(nitro)benzenesulfonamide **III-9d**



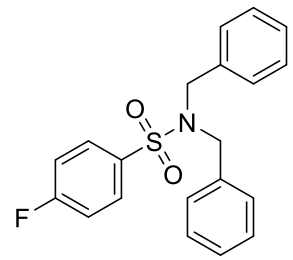
Brown solid (757.21 mg, 1.98 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.29 – 8.27 (m, 2H), 7.92 – 7.91 (m, 2H), 7.26 – 7.25 (m, 6H), 7.10 – 7.08 (m, 4H), 4.35 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.8, 146.8, 134.9, 128.7, 128.6, 128.3, 128.1, 124.2, 50.8. **M.P.:** 126 – 127 °C. The spectroscopic data closely match the ones previously reported in the literature.

N,N-Dibenzyl-3-(nitro)benzenesulfonamide **III-9e**



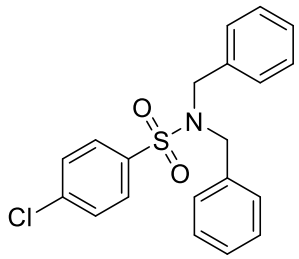
Brown solid (741.91 mg, 1.94 mmol, 97%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.55 – 8.52 (t, J = 2.0 Hz, 1H), 8.38 – 8.37 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 8.07 – 8.06 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.67 – 7.64 (t, J = 8.0 Hz, 1H), 7.28 – 7.26 (m, 6H), 7.15 – 7.13 (m, 4H), 4.44 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.3, 143.3, 135.0, 132.6, 130.4, 128.8, 128.7, 128.3, 126.9, 122.4, 51.0. **M.P.:** 105-106°C

N,N-Dibenzyl-4-(fluoro)benzenesulfonamide **III-9g**



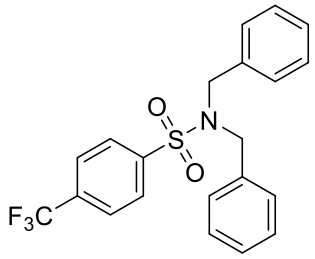
White solid (703.75 mg, 1.98 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.84 – 7.81 (m, 2H), 7.26 – 7.22 (m, 6H), 7.18 – 7.14 (m, 2H), 7.07 – 7.06 (m, 4H), 4.34 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 165.1 (d, $J_{C\text{-}F}$ = 255.2 Hz), 137.1, 137.0, 135.5, 130.0 (d, $J_{C\text{-}F}$ = 15.1 Hz), 128.7, 127.9, 116.4 (d, $J_{C\text{-}F}$ = 30.2 Hz), 50.6. **M.P.:** 89-90 °C. The spectroscopic data closely match the ones previously reported in the literature.

N,N-dibenzyl-4-(chloro)benzenesulfonamide **III-9h**



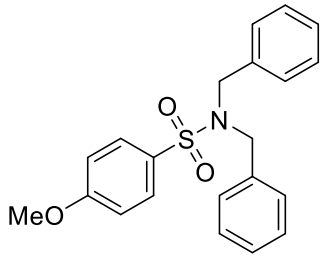
White solid (691.70 mg, 1.86 mmol, 93%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 2H), 7.46 – 7.45 (m, 2H), 7.26 – 7.23 (m, 6H), 7.07 – 7.06 (m, 4H), 4.33 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.2, 138.8, 135.3, 129.3, 128.7, 128.6, 128.5, 127.9, 50.6. **M.P.:** 92 °C. The spectroscopic data closely match the ones previously reported in the literature.

N,N-Dibenzyl-4-(trifluoromethyl)benzenesulfonamide **III-9i**



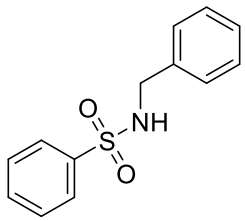
White solid (762.23 mg, 1.88 mmol, 94%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.90 – 7.89 (d, *J* = 8.1 Hz, 2H), 7.72 – 7.71 (d, *J* = 8.1 Hz, 2H), 7.24 – 7.20 (dd, *J* = 5.1, 2.0 Hz, 6H), 7.07 – 7.05 (m, 4H), 4.37 (s, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.6, 135.2, 134.2 (q, J_{C-F} = 287 Hz), 128.3 (q, J_{C-F} = 136 Hz), 126.3, 126.1, 126.0, 124.3, 122.5, 50.8. **M.P.:** 91 - 92 °C

N,N-Dibenzyl-4-(methoxy)benzenesulfonamide **III-9j**



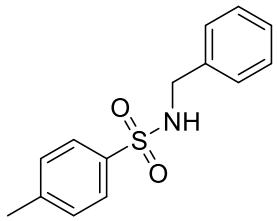
White solid (609.98 mg, 1.66 mmol, 94%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 – 7.78 (m, 2H), 7.26 – 7.21 (m, 6H), 7.07 – 7.06 (m, 4H), 6.98 – 6.96 (m, 2H), 4.31 (s, 4H), 3.89 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9, 135.9, 132.6, 129.5, 128.7, 128.5, 127.9, 114.4, 55.8, 50.6. **M.P.:** 63-65 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-benzenesulfonamide **III-10a**



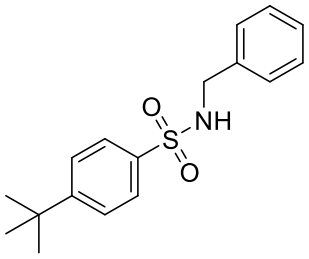
White solid (489.68 mg, 1.98 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 2H), 7.56 – 7.54 (m, 1H), 7.53 – 7.51 (m, 2H), 7.50 – 7.47 (m, 3H), 7.46 – 7.45 (m, 2H), 5.23 – 5.21 (t, *J* = 6.3 Hz, 1H), 4.11 – 4.10 (d, *J* = 6.3 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 140.0, 136.4, 132.7, 129.2, 128.7, 127.9, 127.8, 127.1, 47.3. **M.P.:** 85-86 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl-4-(methyl)benzenesulfonamide **III-10b**



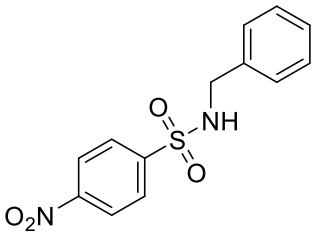
White solid (480.87 mg, 1.84 mmol, 92%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 – 7.77 (m, 2H), 7.34 – 7.32 (m, 3H), 7.30 – 7.29 (m, 2H), 7.28 – 7.27 (m, 2H), 4.63 – 4.61 (s, 1H), 4.15 – 4.14 (d, *J* = 5.9 Hz, 2H), 2.46 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.7, 137.0, 136.4, 129.9, 128.8, 128.1, 128.0, 127.4, 47.5, 21.7. **M.P.:** 112 – 113 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-4-(*tert*-buthyl)benzenesulfonamide **III-10c**



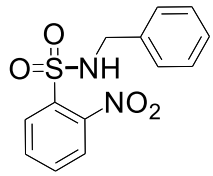
White solid (552.22 mg, 1.82 mmol, 91%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 2H), 7.54 – 7.52 (m, 2H), 7.30 – 7.29 (m, 3H), 7.28 – 7.26 (m, 2H), 4.63 (s, 1H), 4.18 – 4.17 (d, J = 4.8 Hz, 2H), 1.37 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.7, 137.0, 136.4, 128.8, 128.0, 127.9, 127.1, 126.3, 47.5, 35.3, 31.2. **M.P.:** 110 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-benzyl-4-(nitro)benzenesulfonamide **III-10d**



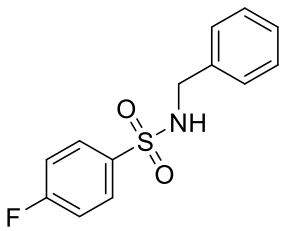
Brown solid (578.77 mg, 1.98 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.31 – 8.30 (m, 2H), 8.00 – 7.99 (m, 2H), 7.27 – 7.26 (m, 3H), 7.18 – 7.16 (m, 2H), 4.97 (t, J = 6.0 Hz, 1H), 4.24 – 4.23 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.1, 146.2, 135.6, 129.0, 128.5, 128.4, 128.0, 124.5, 47.6. **M.P.:** 124-126 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-2-nitrobenzenesulfonamide **III-10f**



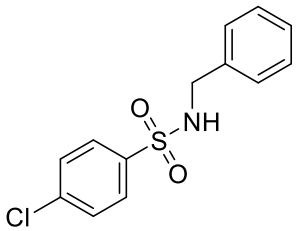
Brown solid (444.31 mg, 1.52 mmol, 76%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 – 8.03 (dd, J = 7.7, 1.6 Hz, 1 H), 7.86 – 7.84 (dd, J = 7.7, 1.6 Hz, 1 H), 7.68 – 7.65 (dd, J = 7.7, 1.6 Hz, 2 H), 7.25–7.18 (m, 5 H), 5.72 (t, J = 6.0 Hz, 1 H), 4.32 (d, J = 6.0 Hz, 2 H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 147.6, 135.9, 134.1, 133.6, 133.4, 129.8, 128.9, 127.7, 127.6, 125.2, 47.7. **M.P.:** 43-44 °C.

N-Benzyl-4-(fluoro)benzenesulfonamide **III-10g**



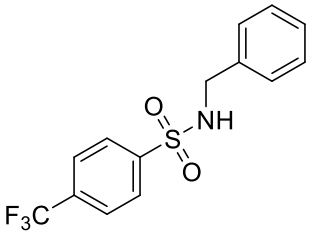
White solid (514.68 mg, 1.94 mmol, 97%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 – 7.86 (m, 2H), 7.28 – 7.26 (m, 3H), 7.19 – 7.16 (m, 4H), 4.74 – 4.72 (t, J = 6.1 Hz, 1H), 4.17 – 4.16 (d, J = 6.1 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.3 (d, $J_{C\text{-}F}$ = 256.7 Hz), 136.1, 130.0, 129.9 (d, $J_{C\text{-}F}$ = 15.1 Hz), 128.1 (d, $J_{C\text{-}F}$ = 30.2 Hz), 127.9, 116.5, 116.4, 47.5. **M.P.:** 99 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-4-(chloro)benzenesulfonamide **III-10h**



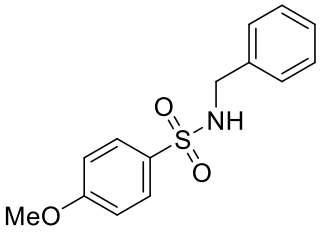
White solid (535.33 mg, 1.90 mmol, 95%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 – 7.77 (m, 2H), 7.47 – 7.46 (m, 2H), 7.28 – 7.26 (m, 3H), 7.19 – 7.17 (m, 2H), 4.76 (m, 1H), 4.16 – 4.15 (d, J = 6.2 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.2, 138.6, 135.9, 129.4, 128.8, 128.6, 128.1, 127.9, 47.3. **M.P.:** 108-109 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-4-(trifluoromethyl)benzenesulfonamide **III-10i**



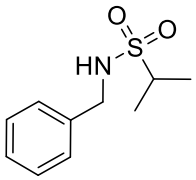
White solid (605.40 mg, 1.92 mmol, 96%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 – 7.95 (m, 2H), 7.76 – 7.74 (m, 2H), 7.29 – 7.25 (m, 3H), 7.18 – 7.16 (m, 2H), 4.79 – 4.77 (t, J = 6.0 Hz, 1H), 4.21 – 4.20 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.9, 135.8, 134.6 (q, J_{C-F} = 35.0 Hz), 128.9, 128.4, 128.0, 127.7, 126.3 (q, J_{C-F} = 135.9 Hz), 124.3, 47.6. **M.P.:** 121 - 122 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-4-(methoxy)benzenesulfonamide **III-10j**



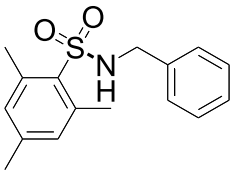
White solid (605.40 mg, 1.78 mmol, 89%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.81 (m, 2H), 7.30 – 7.21 (m, 3H), 7.20 – 7.19 (m, 2H), 6.99 – 6.97 (m, 2H), 4.57 – 4.56 (t, J = 6.3 Hz, 1H), 4.13 – 4.12 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.1, 136.4, 131.6, 129.5, 128.9, 128.1, 128.0, 114.5, 55.9, 47.4. **M.P.:** 108-109 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzylpropane-2-sulfonamide **III-10l**



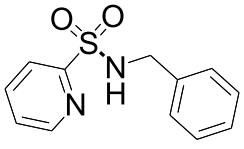
White solid (392.47 mg, 1.84 mmol, 92%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 5H), 4.82 (s, 1H), 4.21 (s, 2H), 3.01 – 2.94 (p, J = 6.8 Hz, 1H), 1.25 – 1.24 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 137.5, 128.8, 128.0, 127.9, 53.9, 47.5, 16.6. **M.P.:** 98-100 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Benzyl-2,4,6-trimethylbenzenesulfonamide **III-10m**



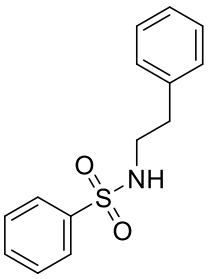
White solid (504.02 mg, 1.74 mmol, 87%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 3H), 7.19 – 7.18 (m, 2H), 6.97 (s, 2H), 4.84 (t, J = 6.4 Hz, 1H), 4.08 (d, J = 6.4 Hz, 2H), 2.65 (s, 6H), 2.33 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.4, 139.3, 136.52, 132.1, 128.7, 128.0, 127.9, 46.9, 23.0, 21.0. **M.P.:** 98-100 °C.

N-Benzylpyridine-2-sulfonamide **III-10n**



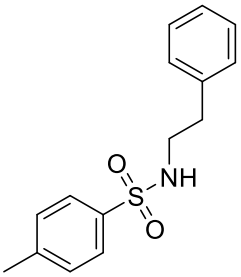
White solid (504.02 mg, 1.74 mmol, 61%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.67 – 8.66 (m, 1H), 7.99 – 7.98 (d, J = 7.8 Hz, 1H), 7.90 – 7.88 (t, J = 7.8 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.27 (s, 2H), 7.26 – 7.24 (m, 3H), 5.21 (bs, 1H), 4.27 (s, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.7, 150.2, 138.1, 136.4, 128.8, 128.1, 127.5, 126.8, 122.4, 48.0. **M.P.:** 99 °C.

N-Phenylethyl-benzenesulfonamide **III-11a**



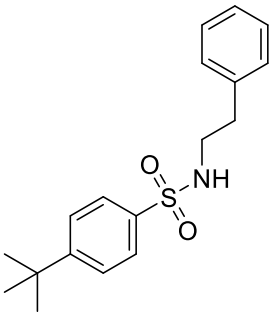
White solid (475.64 mg, 1.82 mmol, 91%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 2H), 7.59 – 7.56 (m, 1H), 7.52 – 7.49 (m, 2H), 7.29 – 7.22 (m, 2H), 7.08 – 7.07 (m, 3H), 4.33 (s, 1H), 3.26 – 3.23 (q, *J* = 6.7 Hz, 2H), 2.78 – 2.76 (t, *J* = 6.7 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 140.1, 137.7, 132.8, 129.3, 128.9, 128.8, 127.2, 127.0, 44.3, 36.0. **M.P.:** 63-66 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(methyl)benzenesulfonamide **III-11b**



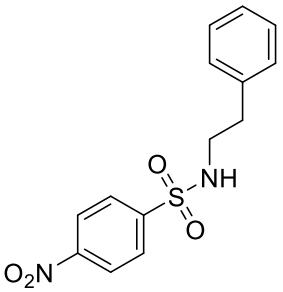
White solid (495.67 mg, 1.80 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 – 7.69 (d, *J* = 7.9 Hz, 2H), 7.27 – 7.25 (d, *J* = 7.9 Hz, 4H), 7.23 – 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 – 7.06 (d, *J* = 7.3 Hz, 2H), 4.88 (d, *J* = 6.8 Hz, 1H), 3.19 – 3.18 (q, *J* = 6.8 Hz, 2H), 2.75 – 2.74 (t, *J* = 6.8 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.4, 137.9, 137.0, 129.8, 128.8, 128.7, 127.1, 126.7, 44.3, 35.9, 21.5. **M.P.:** 63-66 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(tert-buthyl)benzenesulfonamide **III-11c**



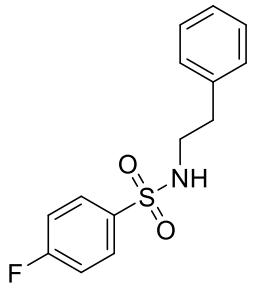
White solid (558.71 mg, 1.76 mmol, 88%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 – 7.72 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.48 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.25 (d, *J* = 7.3 Hz, 2H), 7.24 – 7.20 (t, *J* = 7.3 Hz, 1H), 7.08 – 7.07 (m, 1H), 4.72 – 4.71 (t, *J* = 6.2 Hz, 2H), 3.23 – 3.20 (q, *J* = 6.8 Hz, 2H), 2.78 – 2.76 (t, *J* = 6.8 Hz, 2H), 1.34 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.5, 137.9, 136.9, 128.8, 128.7, 127.0, 126.8, 126.1, 44.3, 35.9, 35.2, 31.2. **M.P.:** 112 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(nitro)benzenesulfonamide **III-11d**



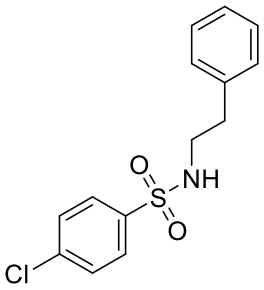
Brown solid (606.55 mg, 1.76 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 2H), 7.95 – 7.93 (m, 2H), 7.25 – 7.24 (m, 3H), 7.23 – 7.18 (m, 2H), 5.14 – 5.12 (t, *J* = 6.0 Hz, 1H), 3.30 – 3.27 (q, *J* = 6.7 Hz, 2H), 2.80 – 2.78 (t, *J* = 6.9 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.0, 145.8, 137.4, 128.8, 128.7, 128.3, 127.0, 124.4, 44.4, 35.9. **M.P.**: 95°C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(fluoro)benzenesulfonamide **III-11g**



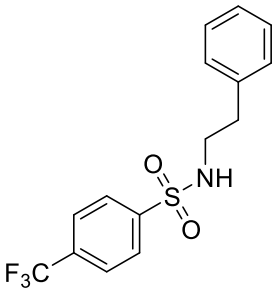
White solid (547.49 mg, 1.96 mmol, 98%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 2H), 7.27 – 7.26 (m, 3H), 7.16 – 7.13 (t, J = 8.5 Hz, 2H), 7.09 – 7.07 (m, 2H), 4.80 (s, 1H), 3.23 – 3.21 (t, J = 7.0 Hz, 2H), 2.78 – 2.76 (t, J = 7.0 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.1 (d, $J_{C\text{-}F}$ = 135.9 Hz), 137.7, 136.1, 129.8 (d, $J_{C\text{-}F}$ = 271.8 Hz), 128.9, 128.8, 126.9, 116.5 (d, $J_{C\text{-}F}$ = 15.1 Hz), 44.3, 35.9. **M.P.:** 81-83 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(chloro)benzenesulfonamide **III-11h**



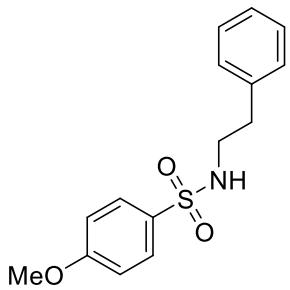
White solid (550.20 mg, 1.86 mmol, 93%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 – 7.71 (m, 2H), 7.42 – 7.40 (m, 2H), 7.24 – 7.20 (m, 2H), 7.19 – 7.18 (m, 1H), 7.07 – 7.05 (m, 2H), 5.14 – 5.13 (t, J = 6.3 Hz, 1H), 3.21 – 3.17 (q, J = 6.7 Hz, 2H), 2.76 – 2.74 (t, J = 6.9 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.0, 138.4, 137.9, 129.4, 128.7, 128.5, 126.8, 44.4, 44.3 35.8. **M.P.:** 101 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(trifluoromethyl)benzenesulfonamide **III-11i**



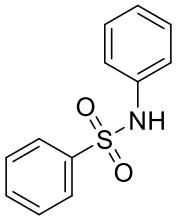
White solid (625.75 mg, 1.90 mmol, 95%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 – 7.89 (m, 2H), 7.74 – 7.73 (d, J = 8.3 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.08 – 7.06 (m, 3H), 4.70 – 4.69 (t, J = 5.9 Hz, 1H), 3.29 – 3.25 (q, J = 6.5 Hz, 2H), 2.79 – 2.78 (t, J = 6.9 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.6, 137.3, 134.3 (q, $J_{C\text{-}F}$ = 30.2 Hz), 128.8 (d, $J_{C\text{-}F}$ = 15.1 Hz), 127.5, 126.4, 126.3, 126.2, 123.3 (q, $J_{C\text{-}F}$ = 135.9 Hz), 44.3, 35.8. **M.P.:** 93-94 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenylethyl-4-(methoxy)benzenesulfonamide **(5j)**



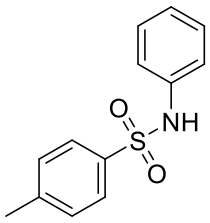
White solid (524.47 mg, 1.80 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 2H), 7.26 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 7.08 – 7.07 (m, 2H), 6.94 – 6.93 (m, 2H), 4.79 – 4.77 (t, J = 6.2 Hz, 1H), 3.84 (s, 3H), 3.19 – 3.16 (t, J = 7.1 Hz,, 2H), 2.76 – 2.74 (t, J = 7.1 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9, 137.9, 131.3, 129.2, 128.8, 128.7, 126.7, 114.3, 55.7, 44.3, 35.8. **M.P.:** 52-53 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(Phenyl)benzenesulfonamide **III-12a**



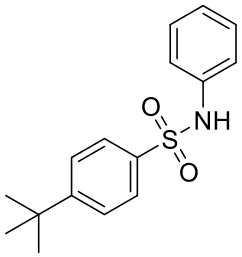
White solid (396.59 mg, 1.72 mmol, 86%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 2H), 7.44 – 7.43 (m, 2H), 7.42 – 7.40 (m, 2H), 7.33 – 7.30 (m, 2H), 7.14 – 7.10 (m, 2H), 7.03 – 6.98 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.0, 136.6, 133.1, 129.3, 129.1, 127.3, 125.4, 121.7. **M.P.:** 110 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(methyl)benzenesulfonamide **III-12b**



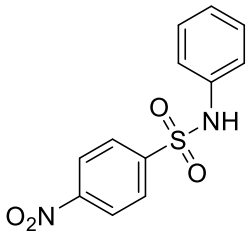
White solid (410.54 mg, 1.66 mmol, 83%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 – 7.70 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.22 – 7.19 (d, *J* = 7.9 Hz, 4H), 7.12 – 7.06 (m, 3H), 2.35 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.9, 136.8, 136.1, 129.7, 129.3, 127.4, 125.2, 121.4, 21.6. **M.P.:** 103 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(*tert*-buthyl)benzenesulfonamide **III-12c**



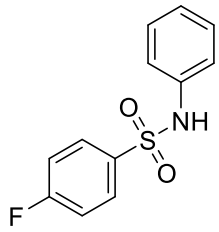
White solid (460.02 mg, 1.60 mmol, 80%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 – 7.76 (m, 2H), 7.47 – 7.42 (m, 3H), 7.24 – 7.21 (m, 2H), 7.14 – 7.07 (m, 2H), 1.29 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.9, 136.9, 136.2, 129.4, 127.2, 126.2, 125.1, 121.3, 35.2, 31.1. **M.P.:** 118-119 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(nitro)benzenesulfonamide **III-12d**



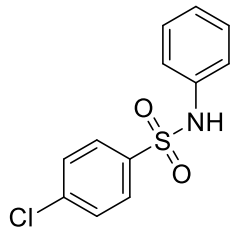
Brown solid (512.04 mg, 1.84 mmol, 92%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.29 – 8.26 (m, 2H), 7.94 – 7.92 (m, 2H), 7.29 – 7.26 (m, 2H), 7.20 – 7.18 (m, 1H), 7.09 – 7.07 (m, 2H), 6.80 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.4, 144.8, 135.4, 129.8, 128.7, 126.7, 124.4, 122.6. **M.P.:** 135-136 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl 4-(fluoro)benzenesulfonamide **III-12g**



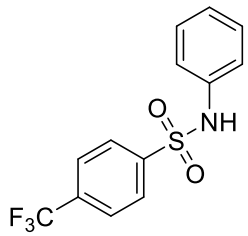
White solid (452.30 mg, 1.80 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 2H), 7.26 – 7.23 (m, 2H), 7.14 – 7.07 (m, 5H), 7.03 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.1 (d, $J_{C\text{-}F}$ = 252.5 Hz), 136.3, 135.0 (d, $J_{C\text{-}F}$ = 328.9 Hz), 130.3, 129.9, 125.6, 121.8, 116.2 (d, $J_{C\text{-}F}$ = 22.9 Hz). **M.P.:** 109-111 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(chloro)benzenesulfonamide **III-12h**



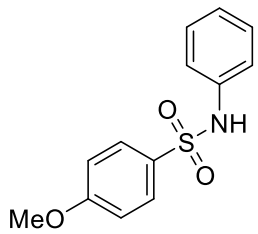
White solid (465.85 mg, 1.74 mmol, 87%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 – 7.71 (m, 2H), 7.40 – 7.38 (m, 2H), 7.26 – 7.23 (m, 2H), 7.14 (m, 1H), 7.13 – 7.08 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.7, 137.5, 136.2, 129.6, 129.5, 128.8, 125.9, 122.0. **M.P.:** 103-105 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(trifluoromethyl)benzenesulfonamide **III-12i**



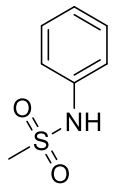
White solid (536.28 mg, 1.78 mmol, 89%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.90 – 7.89 (d, J = 8.2 Hz, 2H), 7.71 – 7.70 (d, J = 8.2 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.18 – 7.15 (m, 1H), 7.10 – 7.07 (m, 2H), 6.95 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.7, 135.8, 133.5 (q, $J_{C\text{-}F}$ = 32.9 Hz), 127.8, 126.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2, 122.4, 122.3 (d, $J_{C\text{-}F}$ = 272.1 Hz), 121.5. **M.P.:** 121-123 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Phenyl-4-(methoxy)benzenesulfonamide **III-12j**



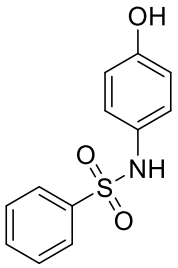
White solid (416.03 mg, 1.58 mmol, 79%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 – 7.71 (m, 2H), 7.26 – 7.21 (m, 2H), 7.11 – 7.07 (m, 3H), 6.94 – 6.93 (m, 1H), 6.89 – 6.87 (m, 2H), 3.82 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.1, 136.8, 130.5, 129.5, 129.3, 125.1, 121.4, 114.2, 55.6. **M.P.:** 108-109 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-phenyl-methanesulfonamide **III-12k**



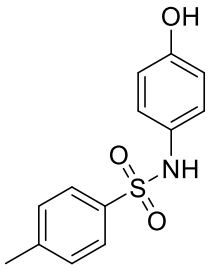
White solid (215.73 mg, 1.26 mmol, 63%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.36 (m, 2H), 7.35 – 7.34 (m, 2H), 7.33 (s, 1H), 3.02 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.9, 129.9, 125.6, 120.9, 39.4. **M.P.:** 98-100 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-benzenesulfonamide **III-13a**



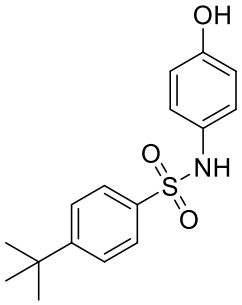
Brown solid (443.72 mg, 1.78 mmol, 89%). **^{1}H NMR** (600 MHz, DMSO) δ 9.71 (s, 1H), 9.30 (s, 1H), 7.66 – 7.64 (m, 2H), 7.60 – 7.57 (m, 1H), 7.53 – 7.50 (m, 2H), 6.83 – 6.81 (m, 2H), 6.60 – 6.58 (m, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 155.6, 139.9, 133.5, 129.8, 129.1, 127.5, 125.2, 116.4. **M.P.:** 155-156 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(methyl)benzenesulfonamide **III-13b**



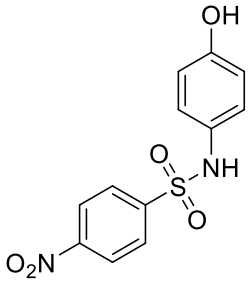
Brown solid (458.16 mg, 1.74 mmol, 87%). **^{1}H NMR** (600 MHz, DMSO) δ 9.65 (s, 1H), 7.56 – 7.54 (m, 2H), 7.30 – 7.28 (m, 2H), 6.87 – 6.85 (m, 2H), 6.63 – 6.60 (m, 2H), 2.30 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 154.9, 142.9, 136.8, 129.5, 128.7, 126.8, 124.0, 115.6, 21.0. **M.P.:** 148-150 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(*tert*-buthyl)benzenesulfonamide **III-13c**



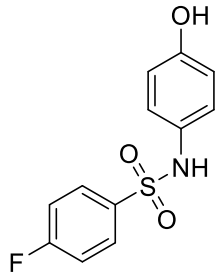
Brown solid (506.95 mg, 1.66 mmol, 83%). **^{1}H NMR** (600 MHz, DMSO) δ 9.72 (s, 1H), 7.62 – 7.60 (m, 2H), 7.54 – 7.52 (m, 2H), 6.88 – 6.87 (m, 2H), 6.62 – 6.60 (m, 2H), 1.25 (s, 9H). **^{13}C NMR** (151 MHz, DMSO) δ 172.0, 155.5, 154.7, 137.0, 128.7, 126.6, 126.2, 115.6, 34.8, 30.8. **M.P.:** 159-161 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(nitro)benzenesulfonamide **III-13d**



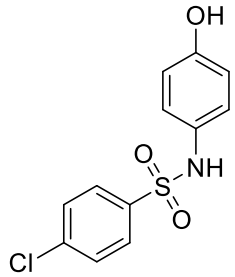
Brown solid (553.25 mg, 1.88 mmol, 94%). **^{1}H NMR** (600 MHz, DMSO) δ 10.04 (s, 1H), 9.38 (s, 1H), 8.36 – 8.34 (m, 2H), 7.89 – 7.87 (m, 2H), 6.84 – 6.82 (m, 2H), 6.63 – 6.60 (m, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 155.6, 150.0, 145.2, 128.6, 127.7, 125.1, 124.7, 116.0. **M.P.:** 186 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(fluoro)benzenesulfonamide **III-13g**



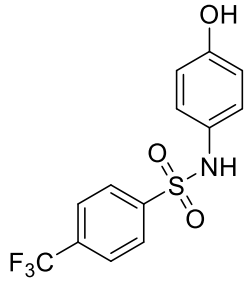
Brown solid (491.78 mg, 1.84 mmol, 92%). **^{1}H NMR** (600 MHz, DMSO) δ 9.72 (s, 1H), 9.33 (s, 1H), 7.70 – 7.68 (m, 2H), 7.38 – 7.35 (m, 2H), 6.83 – 6.81 (m, 2H), 6.62 – 6.59 (m, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 164.0 (d, J_{C-F} = 135.9 Hz), 155.1, 135.9, 130.2 (d, J_{C-F} = 30.2 Hz), 128.7, 124.4, 116.7 (d, J_{C-F} = 15.1 Hz), 116.0. **M.P.:** 171-172 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(chloro)benzenesulfonamide **III-13h**



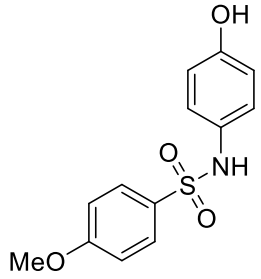
Brown solid (516.39 mg, 1.82 mmol, 91%). **^{1}H NMR** (600 MHz, DMSO) δ 10.50 (s, 1H), 7.79 – 7.71 (m, 2H), 7.70 – 7.63 (m, 2H), 7.05 – 7.04 (m, 2H), 6.95 – 6.93 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.1, 133.6, 129.9, 129.6, 129.5, 128.7, 123.4, 122.9. **M.P.:** 178 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-Hydroxyphenyl)-4-(trifluoromethyl)benzenesulfonamide **III-13i**



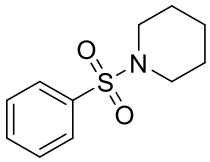
Brown solid (596.49 mg, 1.88 mmol, 94%). **^{1}H NMR** (600 MHz, DMSO) δ 9.96 (s, 1H), 9.38 (s, 1H), 7.93 – 7.92 (d, J = 8.3 Hz, 2H), 7.86 – 7.84 (d, J = 8.3 Hz, 2H), 6.85 – 6.83 (m, 2H), 6.63 – 6.61 (m, 2H). **^{13}C NMR** (151 MHz, DMSO) δ 155.3, 143.4, (q, J_{C-F} = 30.2 Hz), 132.0, 127.8, 127.7, 126.4, 126.3, 124.4 (q, J_{C-F} = 135.9 Hz), 115.7. **M.P.:** 181-182 °C.

N-(4-Hydroxyphenyl)-4-(methoxy)benzenesulfonamide **III-13j**



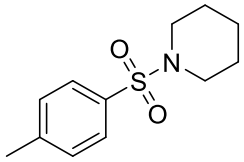
Brown solid (446.90 mg, 1.60 mmol, 80%).**^{1}H NMR** (600 MHz, DMSO): δ 9.56 (s, 1H), 7.58 – 7.57 (m, 2H), 7.03 – 7.02 (m, 2H), 6.84 – 6.82 (m, 2H), 6.60 – 6.59 (m, 2H), 3.79 (s, 3H). **^{13}C NMR** (151 MHz, DMSO): δ 172.0, 162.2, 154.7, 131.2, 128.7, 123.9, 115.5, 114.1, 55.6. **M.P.:** 185 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-phenylsulfonylpiperidine **III-14a**



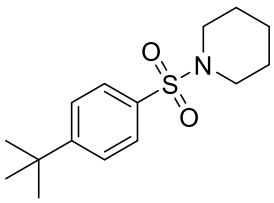
White solid (441.61 mg, 1.96 mmol, 98%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 2H), 7.60 – 7.57 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.51 (t, *J* = 7.5 Hz, 2H), 2.99 – 2.97 (t, *J* = 5.7 Hz, 4H), 1.65 – 1.61 (p, *J* = 5.7 Hz, 4H), 1.43 – 1.39 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.5, 132.7, 129.0, 127.8, 47.1, 25.3, 23.6. **M.P.**: 95-97 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-(Methyl)phenylsulfonyl) piperidine **III-14b**



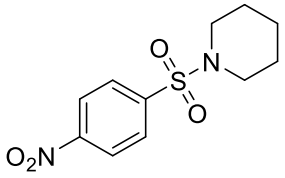
White solid (469.51 mg, 1.96 mmol, 96%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 – 7.63 (m, 2H), 7.32 – 7.31 (m, 2H), 2.98 – 2.96 (m, 4H), 2.43 (s, 3H), 1.65 – 1.62 (m, 4H), 1.42 – 1.40 (qd, *J* = 7.1, 4.7 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.4, 133.5, 129.7, 127.9, 47.1, 25.3, 23.7, 21.7. **M.P.:** 97-99 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-(*tert*-Butyl)phenylsulfonyl) piperidine **III-14c**



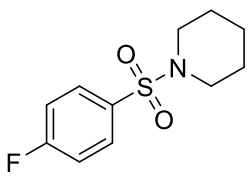
White solid (523.43 mg, 1.86 mmol, 93%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 2H), 7.52 – 7.51 (m, 2H), 3.00 – 2.98 (m, 4H), 1.66 – 1.63 (m, 4H), 1.44 – 1.40 (m, 2H), 1.34 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.3, 133.5, 127.7, 126.0, 47.1, 35.3, 31.3, 25.4, 23.7. **M.P.:** 129 – 130 °C. The spectroscopic data closely match the ones previously reported in the literature.

N -(4-(Nitro)phenylsulfonyl) piperidine **III-14d**



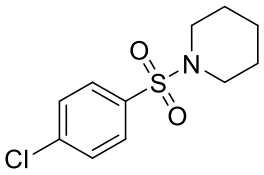
Pale-yellow solid (523.43 mg, 1.98 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.38 – 8.37 (m, 2H), 7.95 – 7.93 (m, 2H), 3.07 – 3.05 (m, 4H), 1.68 – 1.64 (m, 4H), 1.48 – 1.44 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.0, 142.9, 128.9, 124.4, 47.1, 25.3, 23.5. **M.P.:** 168-170 °C. The spectroscopic data closely match the ones previously reported in the literature.

N -(4-(Fluoro)phenylsulfonyl) piperidine **III-14g**



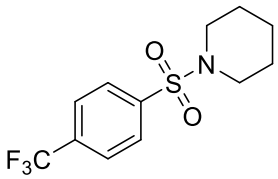
White solid (437.94 mg, 1.80 mmol, 90%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 2H), 7.22 – 7.19 (m, 2H), 3.00 – 2.98 (m, 4H), 1.67 – 1.63 (p, *J* = 5.8 Hz, 4H), 1.45 – 1.41 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.3 (d, J_{C-F} = 135.9 Hz), 130.5, 130.4, 116.2 (d, J_{C-F} = 15.1 Hz), 47.1, 25.3, 23.6. **M.P.:** 76–77 °C. The spectroscopic data closely match the ones previously reported in the literature.

N -(4-(Chloro)phenylsulfonyl) piperidine **III-14h**



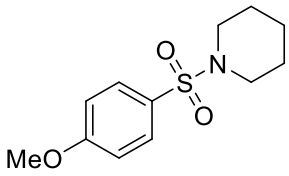
White solid (450.73 mg, 1.74 mmol, 87%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 – 7.68 (m, 2H), 7.51 – 7.49 (m, 2H), 3.00 – 2.98 (t, *J* = 5.5 Hz, 4H), 1.67 – 1.63 (q, *J* = 5.5 Hz, 4H), 1.46 – 1.42 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.1, 135.0, 129.3, 129.1, 46.9, 25.2, 23.5. **M.P.:** 92-93 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-(Trifluoromethyl)phenylsulfonyl) piperidine **III-14i**



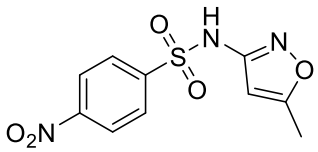
White solid (539.67 mg, 1.84 mmol, 92%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.89 – 7.88 (d, *J* = 8.3 Hz, 2H), 7.81 – 7.79 (d, *J* = 8.3 Hz, 2H), 3.03 – 3.01 (t, *J* = 5.5 Hz, 4H), 1.68 – 1.64 (p, *J* = 5.8 Hz, 4H), 1.47 – 1.43 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.2, 140.3, 134.3 (q $J_{C\text{-}F}$ = 32.9 Hz) , 126.2 (q $J_{C\text{-}F}$ = 15.1 Hz), 122.4, 46.9, 25.2, 23.4. **M.P.:** 95–96 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(4-(Methoxy)phenylsulfonyl) piperidine **III-14j**



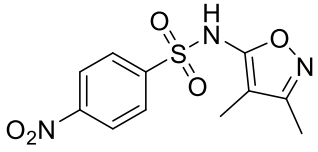
White solid (434.06 mg, 1.7 mmol, 85%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.64 – 7.62 (m, 2H), 6.95 – 6.94 (m, 2H), 3.82 (s, 3H), 2.91 – 2.89 (m, 4H), 1.60 – 1.56 (m, 4H), 1.37 – 1.34 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 162.9, 129.7, 127.8, 114.1, 55.6, 46.9, 25.1, 23.5. **M.P.:** 105-108 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(5-Methylisoxazol-3-yl)-4-(nitro)benzenesulfonamide **III-15d**



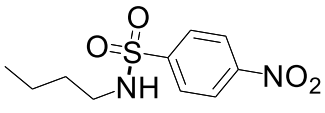
Orange solid (424.89 mg, 1.50 mmol, 75%). **^{1}H NMR** (600 MHz, DMSO) δ 8.44 – 8.43 (m, 2H), 8.13 – 8.11 (m, 2H), 2.31 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 171.2, 157.5, 150.6, 145.1, 128.9, 125.3, 96.0, 12.5. **M.P.:** 194-195 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-(3,4-dimethylisoxazol-5-yl)-4-(nitro)benzenesulfonamide **III-16d**



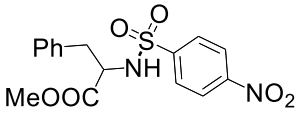
Orange solid (392.42 mg, 1.32 mmol, 66%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.33 – 8.32 (d, *J* = 8.7 Hz, 2H), 8.02 – 8.01 (d, *J* = 8.7 Hz, 2H), 4.15 (s, 1H), 2.19 (s, 3H), 1.93 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 164.6, 162.3, 154.7, 150.5, 145.8, 128.7, 124.6, 11.0, 6.8. **M.P.:** 205-207 °C. The spectroscopic data closely match the ones previously reported in the literature.

N-Butyl-4-nitrobenzenesulfonamide **III-17d**



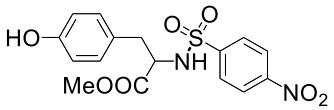
White solid (201.24 mg, 0.78 mmol, 39%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 4.55 (bs, 1H), 3.03 (q, *J* = 6.9 Hz, 2H), 1.47 (t, *J* = 7.5 Hz, 2H), 1.31 (p, *J* = 7.5 Hz, 2H), 0.89 – 0.85 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.2, 146.2, 128.4, 124.5, 43.3, 31.8, 19.8, 13.6. **M.P.:** 75 °C.

Methyl ((4-nitrophenyl)sulfonyl)phenylalaninate **III-18d**



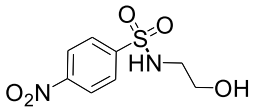
White solid (473.68 mg, 1.30 mmol, 65%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 – 8.22 (m, 2H), 7.90 – 7.84 (m, 2H), 7.35 – 7.31 (m, 1H), 7.26 (m, 2H), 7.10 (m, 2H), 5.59 (d, *J* = 9.3 Hz, 1H), 4.30 (q, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 3.19 – 2.98 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.3, 150.1, 145.7, 128.9, 128.7, 128.3, 127.6, 125.2, 124.3, 57.3, 52.9, 39.3. **M.P.:** 153-155°C.

Methyl ((4-nitrophenyl)sulfonyl)tyrosinate **III-19d**



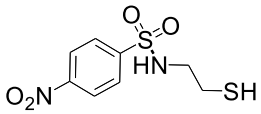
White solid (334.73 mg, 0.88 mmol, 44%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.38 – 8.32 (m, 2H), 8.05 – 7.97 (m, 2H), 7.17 – 7.06 (m, 2H), 6.96 – 6.88 (m, 2H), 4.18 (bs, 1H), 3.74 (s, 3H), 3.15 – 2.99 (m, 2H), 2.96 – 2.79 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.9, 155.6, 134.9, 131.1, 130.8, 130.1, 129.9, 128.3, 128.2, 56.9, 55.4, 38.6. **M.P.:** 169 °C.

N-(2-Hydroxyethyl)-4-nitrobenzenesulfonamide **III-20d**



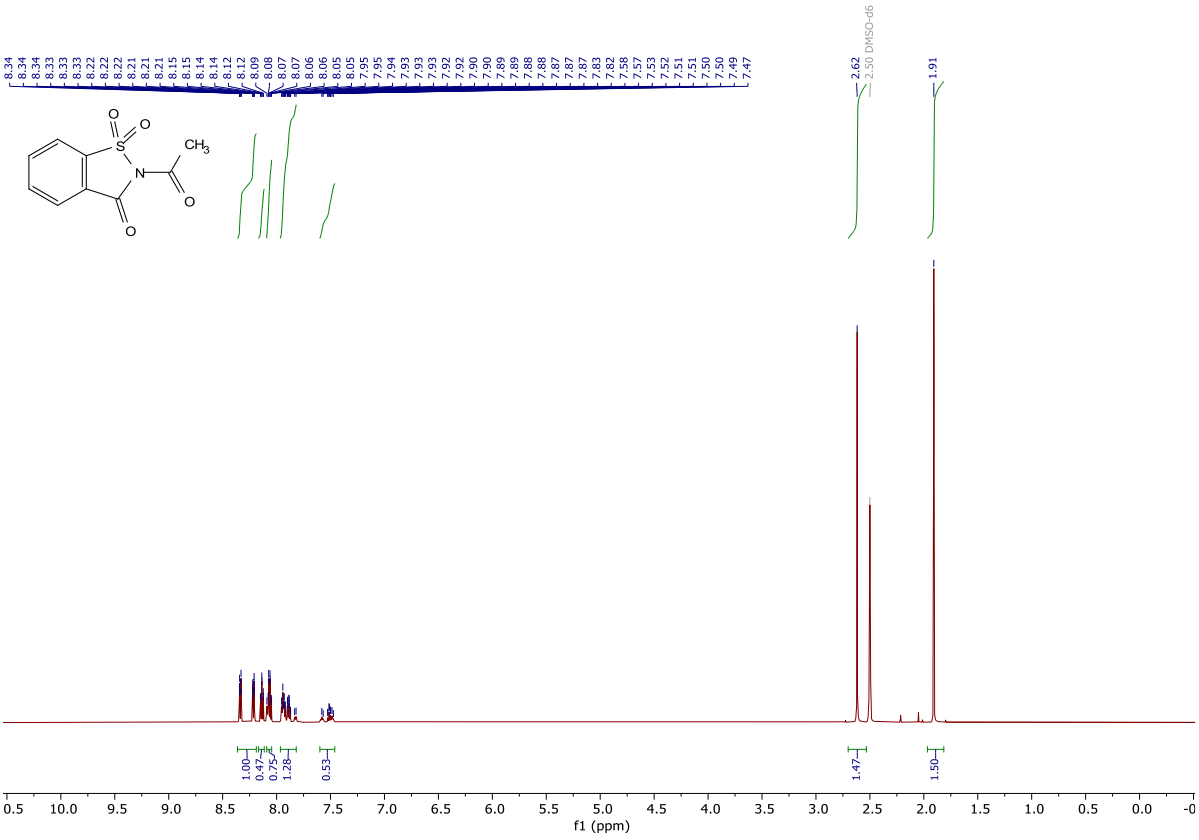
White solid (256,09 mg, 1.04 mmol, 52%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.3 Hz, 2H), 8.07 (d, *J* = 8.3 Hz, 2H), 5.11 (bs, 1H), 3.74 (t, *J* = 5.2 Hz, 2H), 3.19 (q, *J* = 5.2 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 156.6, 146.0, 128.5, 124.6, 61.3, 45.3. **M.P.:** 124 °C.

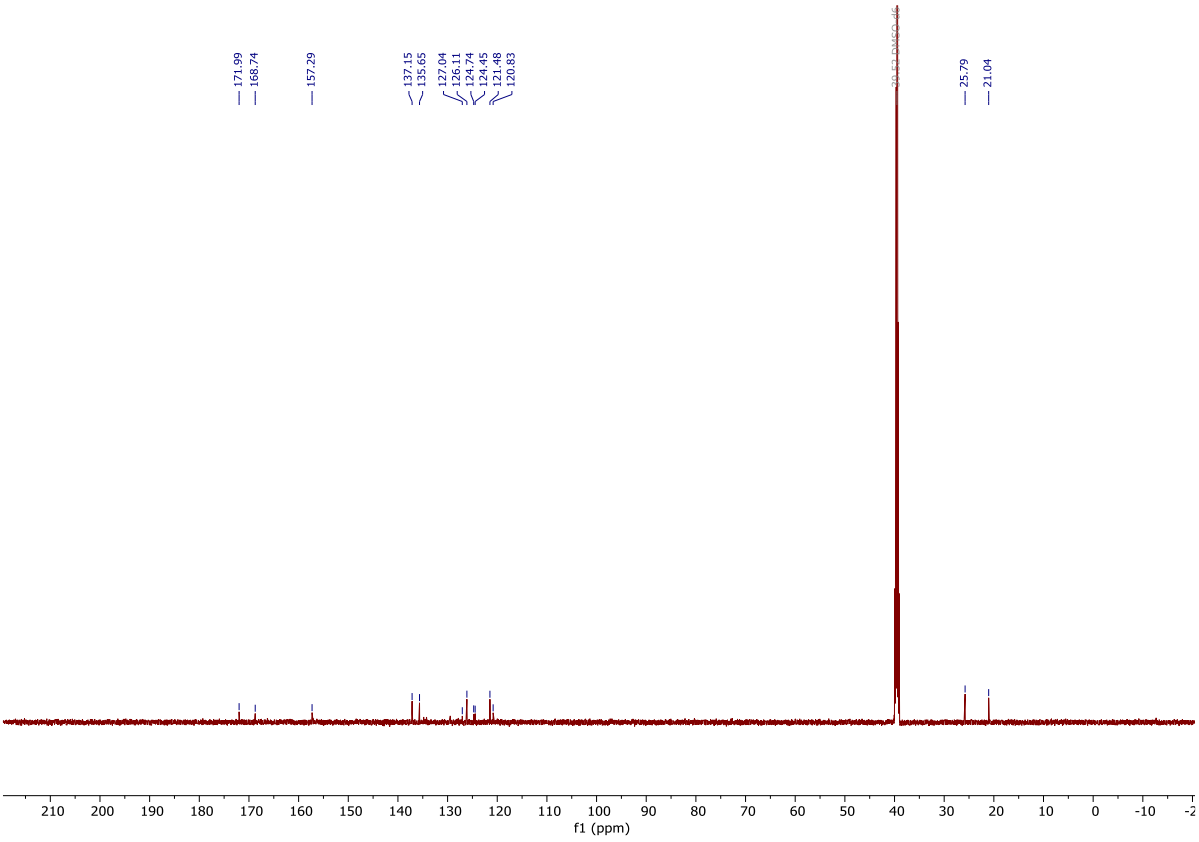
N-(2-mercaptoethyl)-4-nitrobenzenesulfonamide **III-21d**

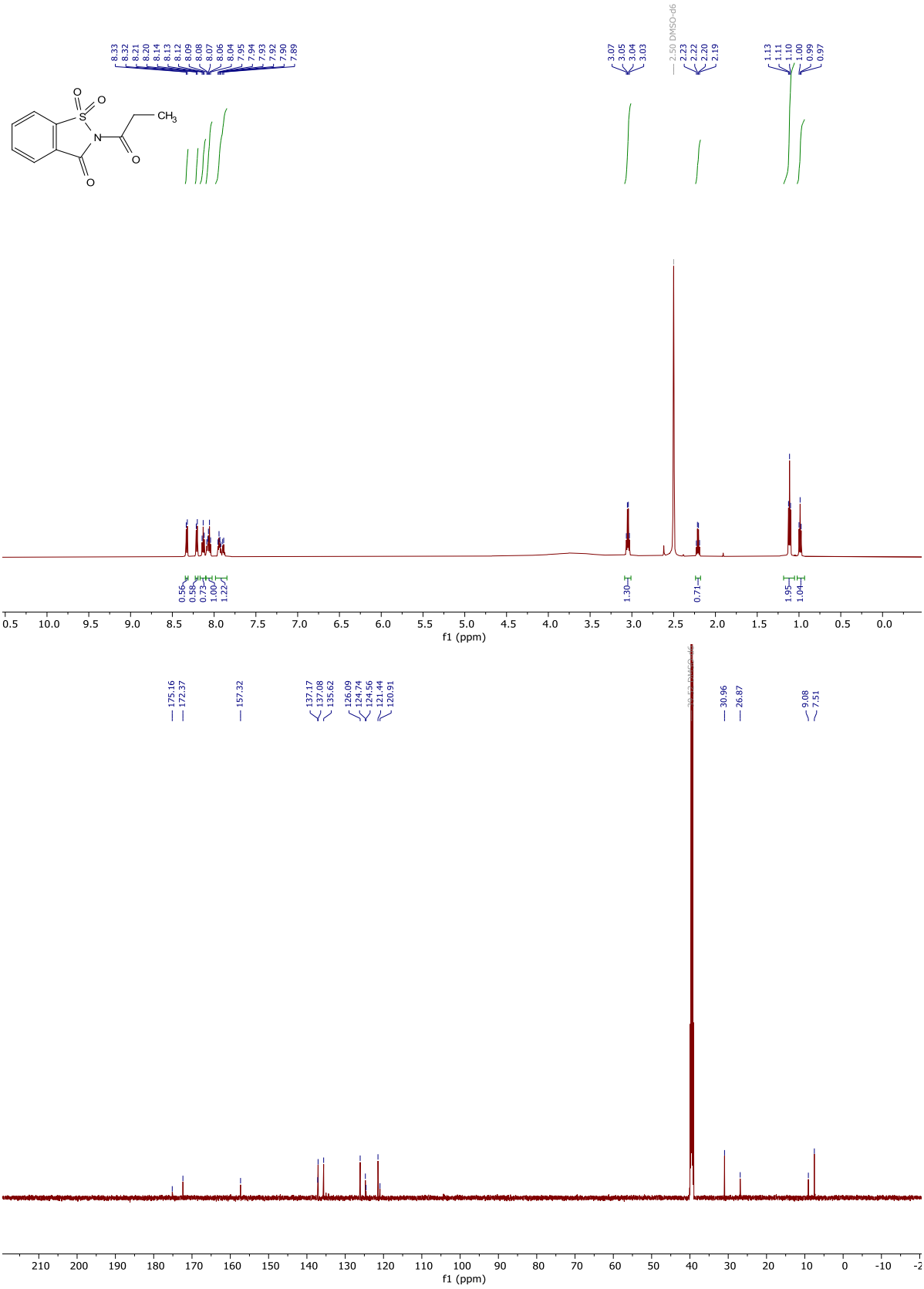


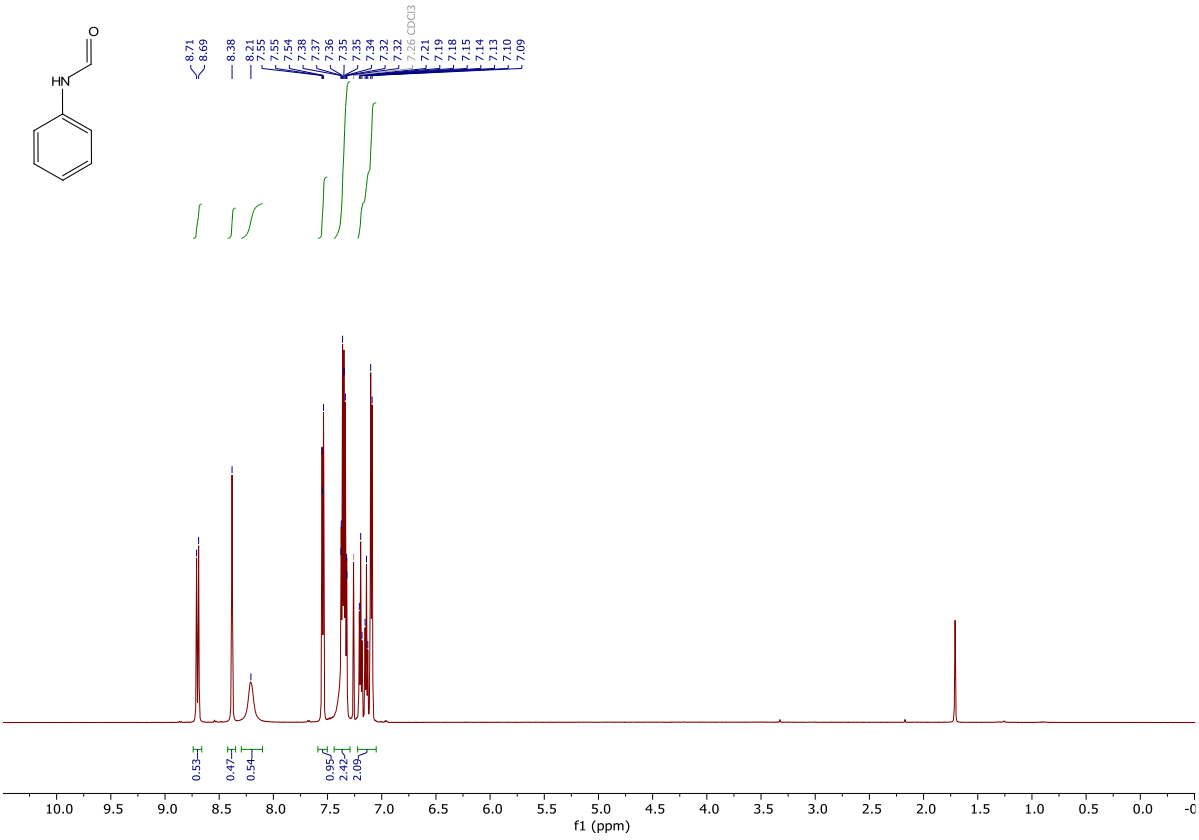
White solid (341.00 mg, 1.30 mmol, 65%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.44 – 8.32 (m, 2H), 8.13 – 8.04 (m, 2H), 3.34 (m, 2H), 3.03 (m, 1H), 2.83 – 2.73 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 150.4, 145.8, 128.5, 124.7, 41.9, 38.3. **M.P.:** 131-133 °C

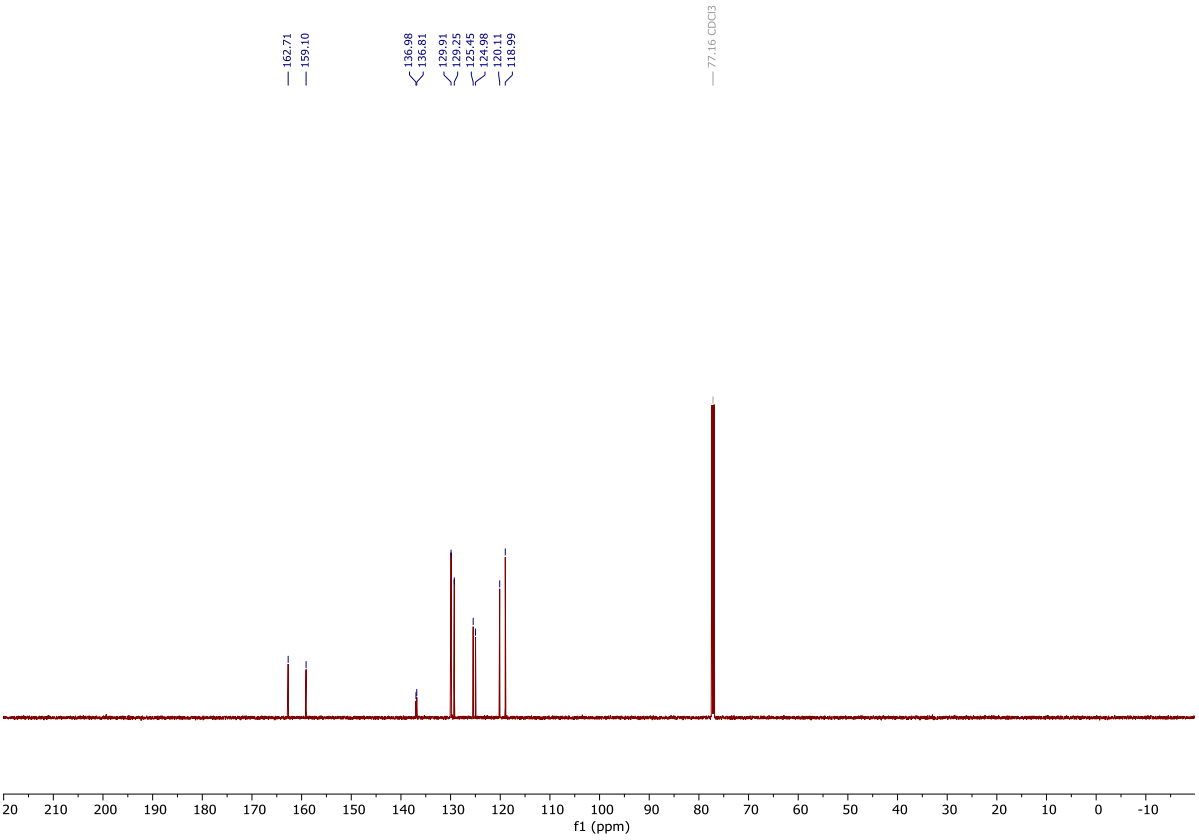
Ed. n: A selection of NMR spectra is reported below for simpleness; however the entire collection of spectra is available in the related article.

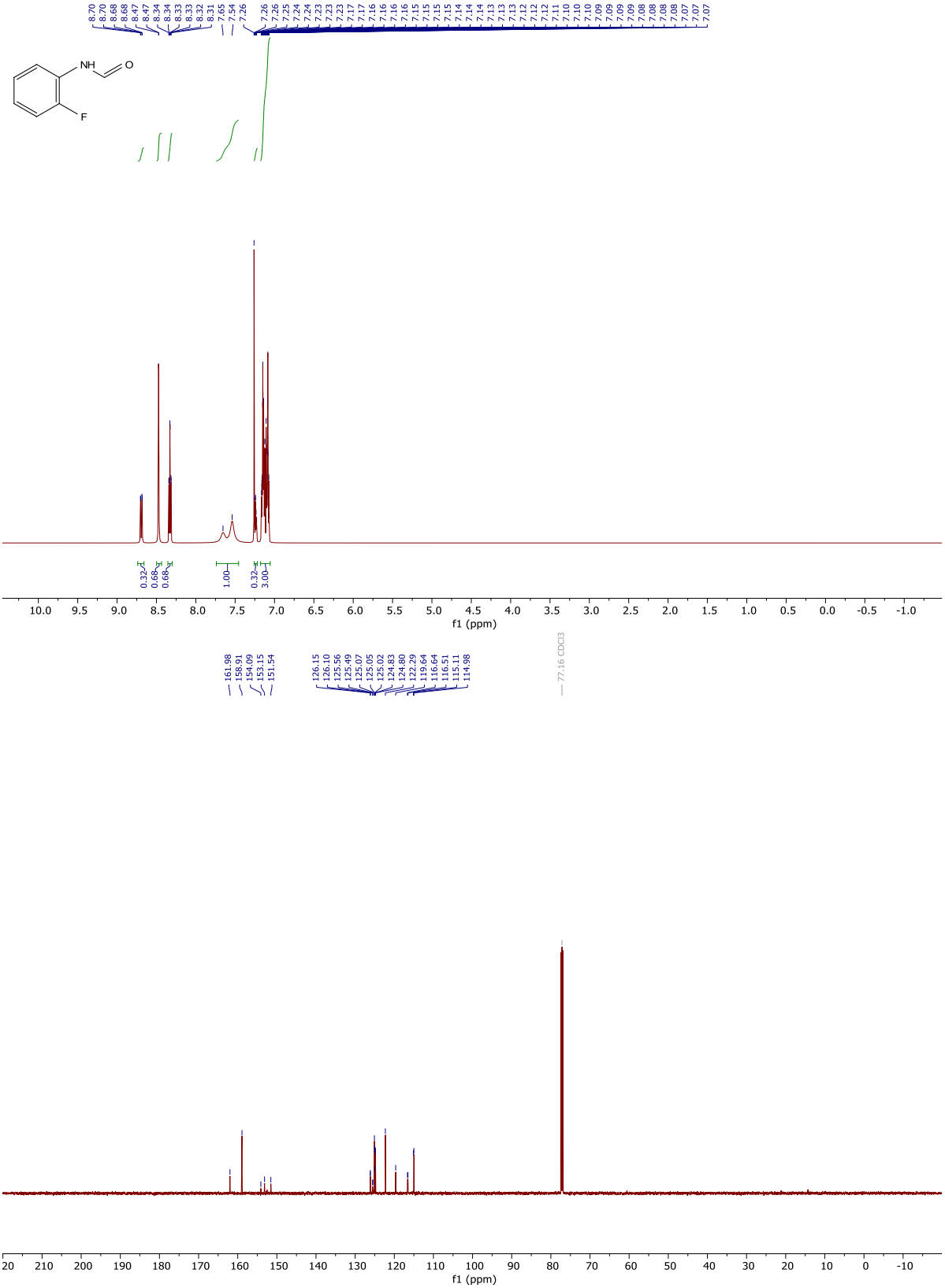

8.34 8.34 8.34 8.33 8.33 8.33 8.22 8.22 8.22 8.21 8.21 8.21 8.15 8.15 8.14 8.14 8.12 8.12 8.09 8.08 8.07 8.07 8.06 8.06 8.05 8.05 7.95 7.95 7.94 7.93 7.93 7.93 7.92 7.92 7.90 7.90 7.89 7.89 7.88 7.88 7.87 7.87 7.87 7.83 7.82 7.58 7.57 7.53 7.52 7.51 7.51 7.50 7.50 7.49 7.47
2.62
2.50 DMSO-d6
1.91
O
O
S
N
CH3
O
O
O
1.00
0.47
0.75
1.28
0.53
1.47
1.50
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

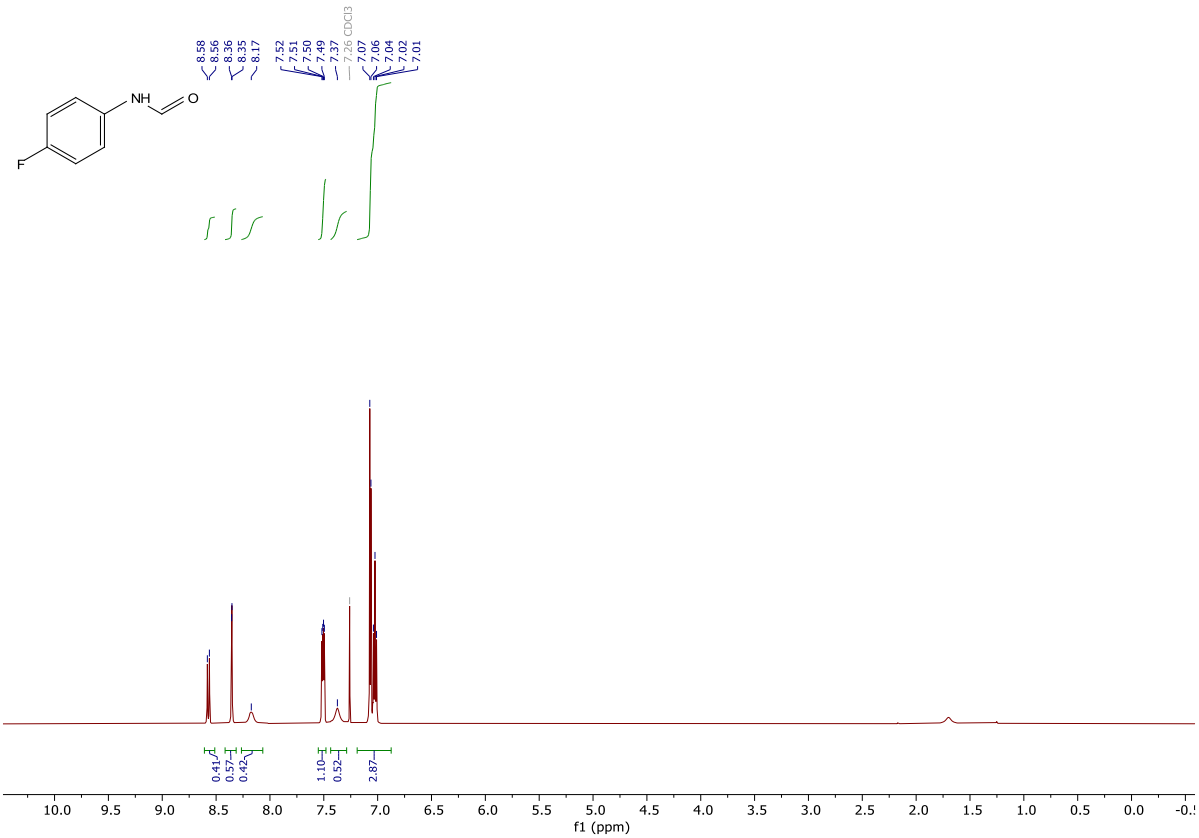

171.99
168.74
157.29
137.15
135.65
127.04
126.11
124.74
124.45
121.48
120.83
39.52 DMSO-d6
25.79
21.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)

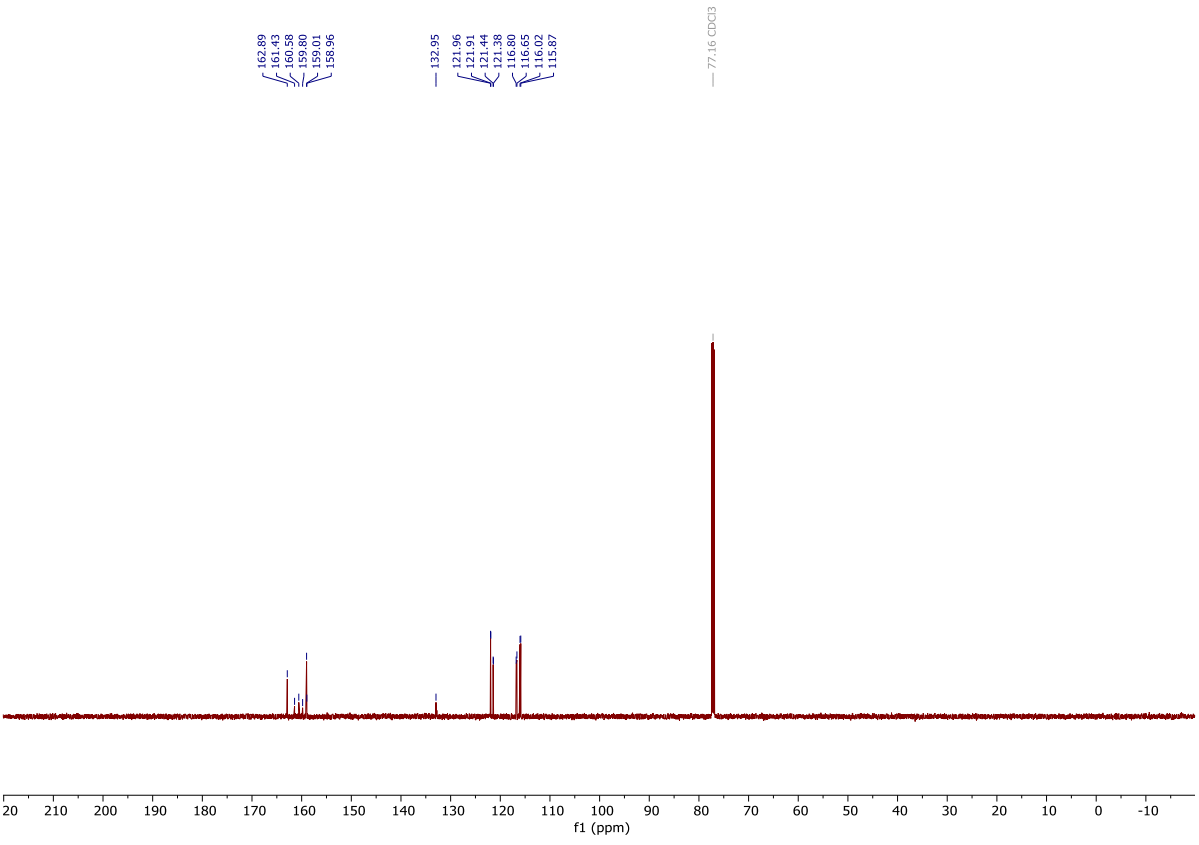

8.33
8.32
8.21
8.20
8.14
8.13
8.12
8.09
8.08
8.07
8.06
8.04
7.95
7.94
7.93
7.92
7.90
7.89
3.07
3.05
3.04
3.03
2.50 DMSO-d6
2.23
2.22
2.20
2.19
1.13
1.11
1.10
1.00
0.99
0.97
O
O
S
N
CH3
O
O
0.56
0.58
0.73
1.00
1.22
1.30
0.71
1.95
1.04
f1 (ppm)
175.16
172.37
157.32
137.17
137.08
135.62
126.09
124.74
124.56
121.44
120.91
30.96
26.87
9.08
7.51
f1 (ppm)

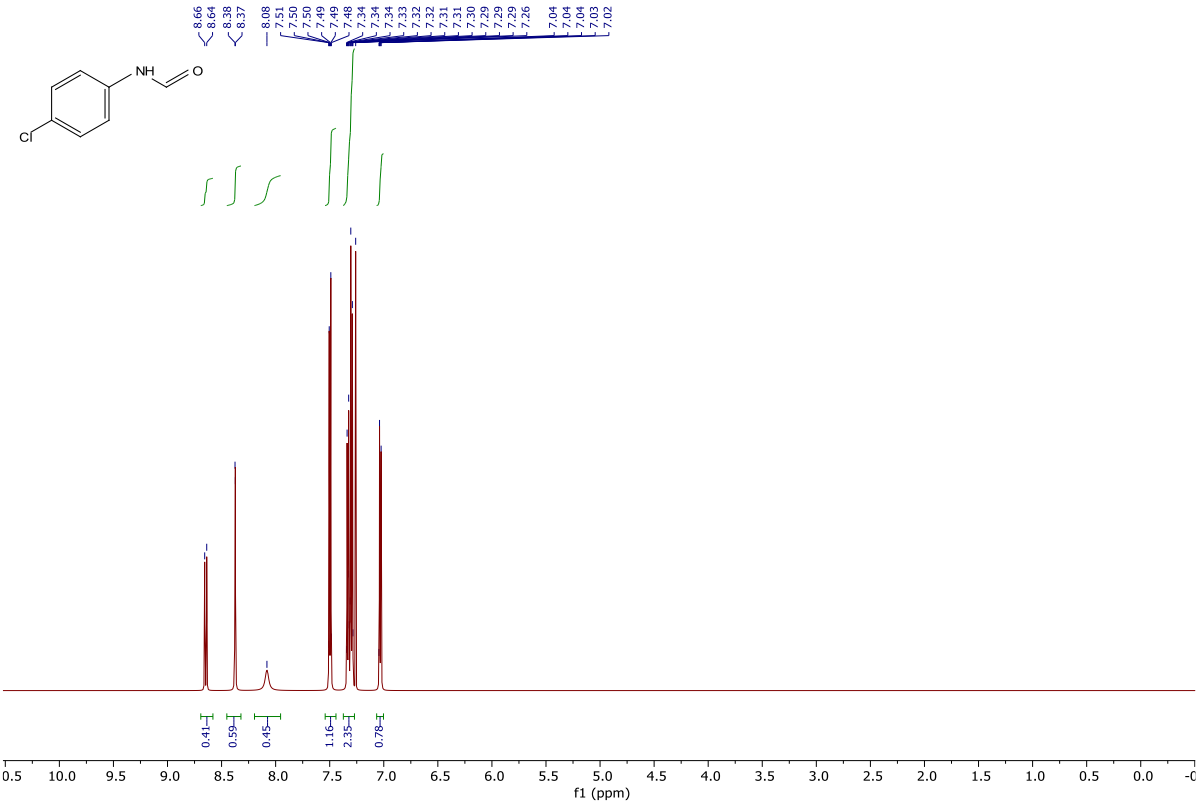

O
HN
8.71
8.69
8.38
8.21
7.55
7.55
7.54
7.38
7.37
7.36
7.35
7.35
7.34
7.32
7.32
7.26 CDCl3
7.21
7.19
7.18
7.15
7.14
7.13
7.10
7.09
0.53
0.47
0.54
0.95
2.42
2.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

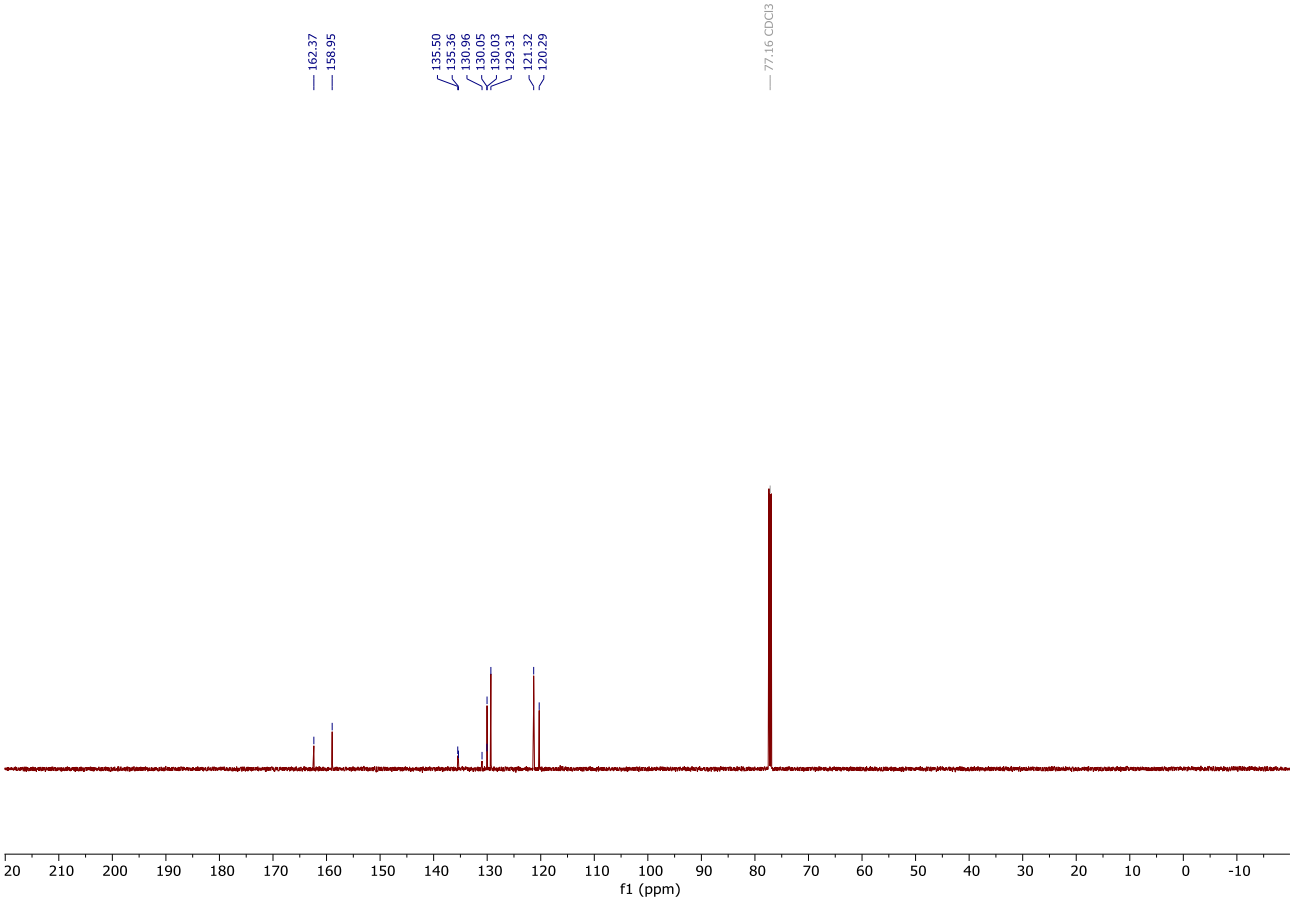

162.71
159.10
136.98
136.81
129.91
129.25
125.45
124.98
120.11
118.99
77.16 CDCl3
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

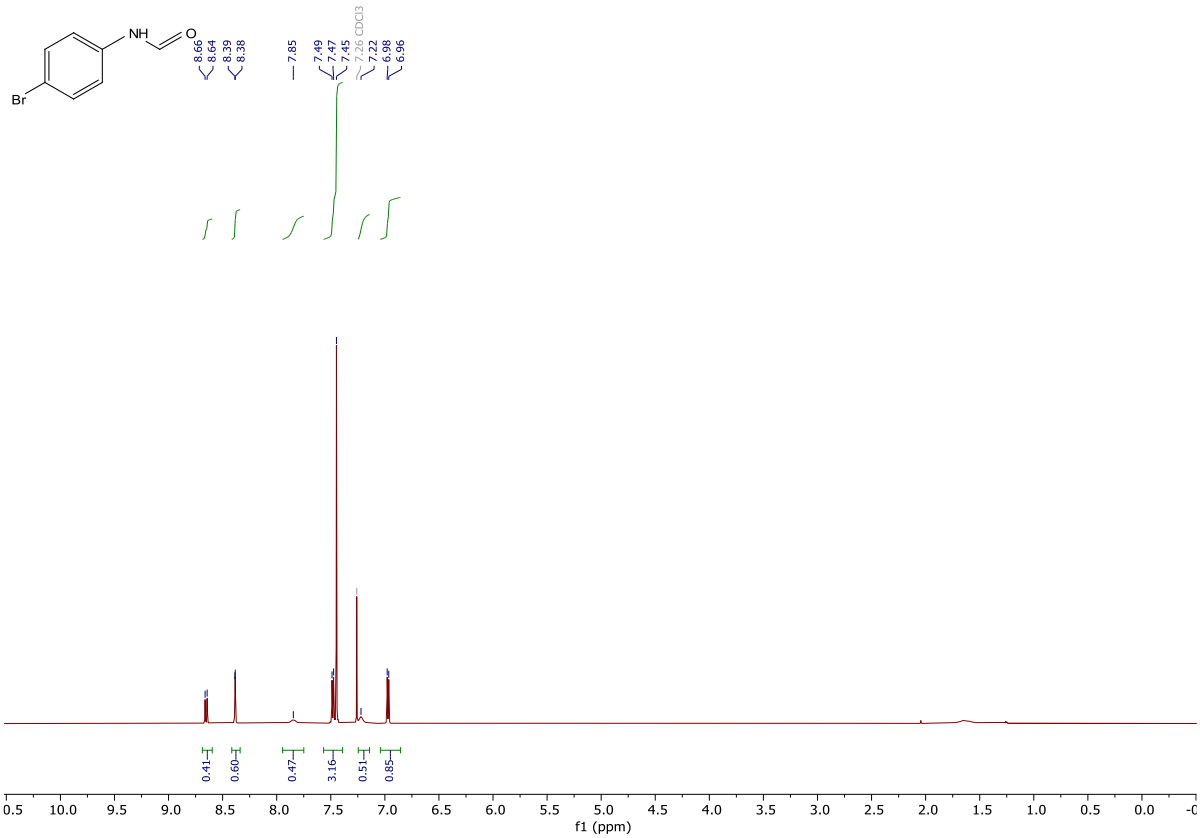

8.70
8.68
8.47
8.34
8.33
8.32
8.31
7.65
7.54
7.26
7.25
7.24
7.23
7.17
7.16
7.15
7.14
7.13
7.12
7.11
7.10
7.09
7.08
7.07
NH
O
F
0.32
0.68
0.68
1.00
0.32
3.00
f1 (ppm)
161.98
158.91
154.09
153.15
151.54
126.15
126.10
125.56
125.49
125.07
125.05
125.02
124.83
124.80
122.29
119.64
116.64
116.51
115.11
114.98
77.16 CDCl3
f1 (ppm)

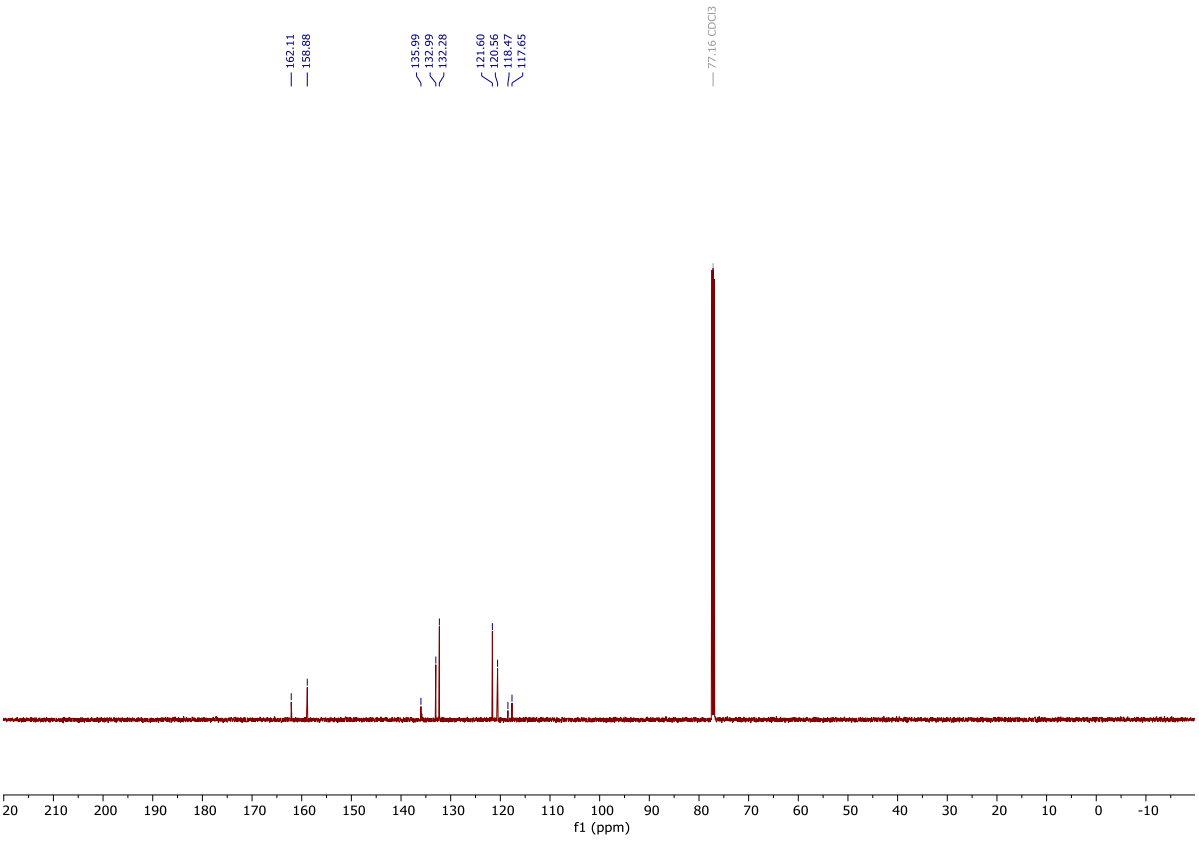

8.58
8.56
8.36
8.35
8.17
7.52
7.51
7.50
7.49
7.37
7.26 CDCl3
7.07
7.06
7.04
7.02
7.01
NH
O
F
0.41
0.57
0.42
1.10
0.52
2.87
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

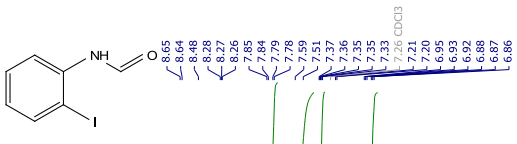

162.89
161.43
160.58
159.80
159.01
158.96
132.95
121.96
121.91
121.44
121.38
116.80
116.65
116.02
115.87
77.16 CDCl3
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

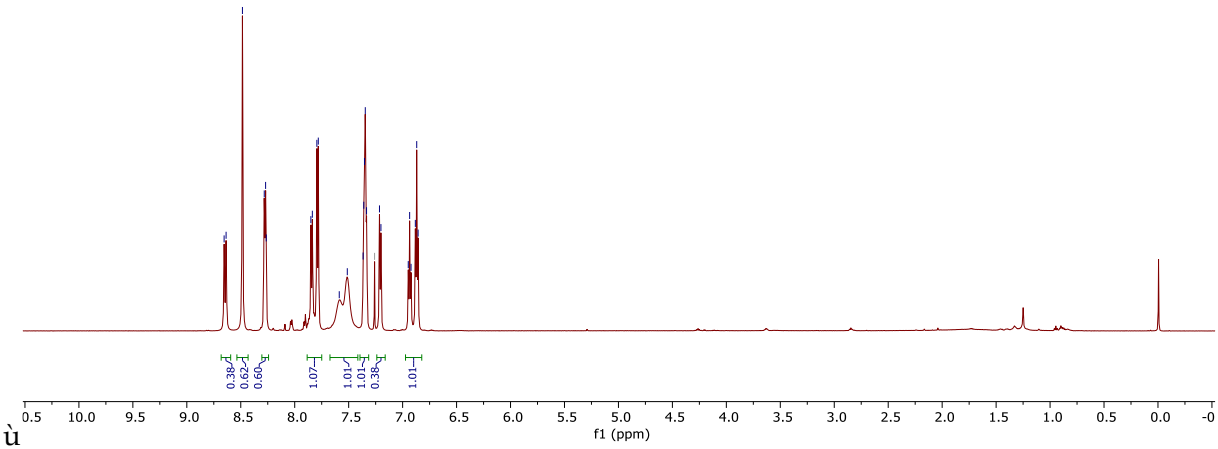

8.66
8.64
8.38
8.37
8.08
7.51
7.50
7.50
7.49
7.49
7.48
7.34
7.34
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.29
7.29
7.26
7.04
7.04
7.04
7.03
7.02
NH
O
Cl
0.41
0.59
0.45
1.16
2.35
0.78
f1 (ppm)


162.37
158.95
135.50
135.36
130.96
130.05
130.03
129.31
121.32
120.29
77.16 CDCl3
f1 (ppm)


NH
O
Br
8.66
8.64
8.39
8.38
7.85
7.49
7.47
7.45
7.26 CDCl3
7.22
6.98
6.96
0.41
0.60
0.47
3.16
0.51
0.85
f1 (ppm)

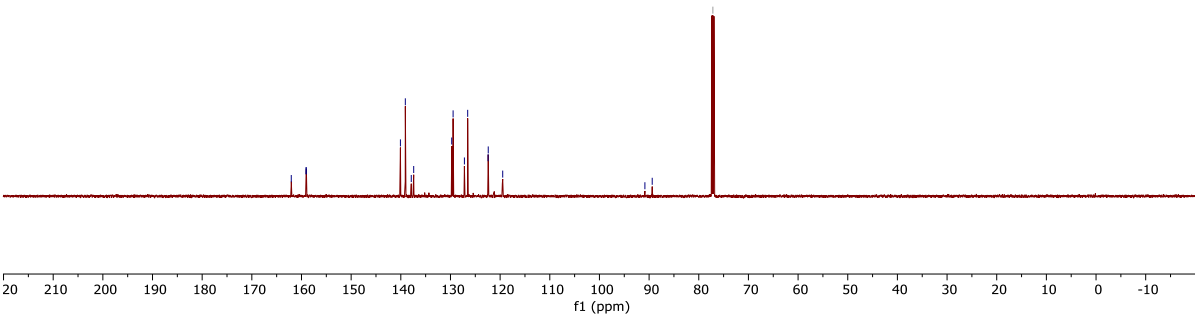

162.11
158.88
135.99
132.99
132.28
121.60
120.56
118.47
117.65
77.16 CDCl3
f1 (ppm)

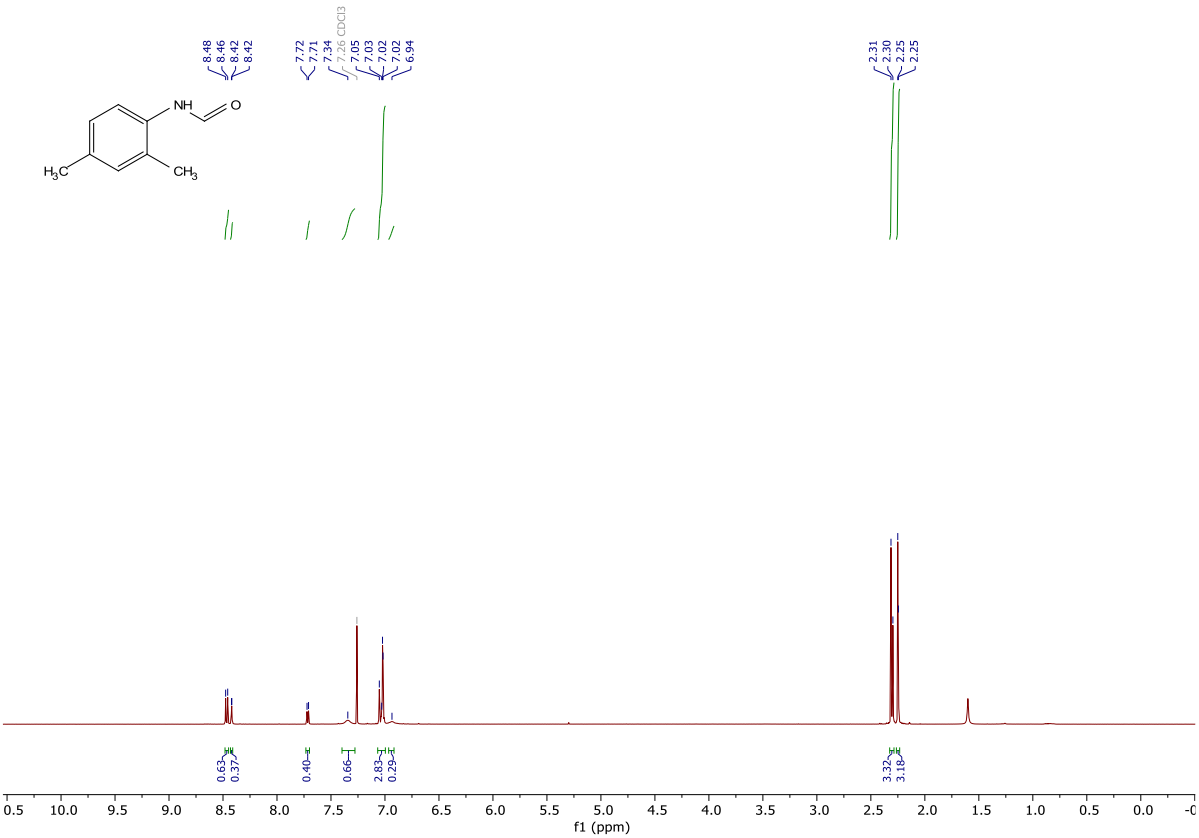

NH
O
I
8.65
8.64
8.48
8.28
8.27
8.26
7.85
7.84
7.79
7.78
7.59
7.51
7.37
7.36
7.35
7.33
7.26 CDCl3
7.21
7.20
6.95
6.93
6.92
6.88
6.87
6.86

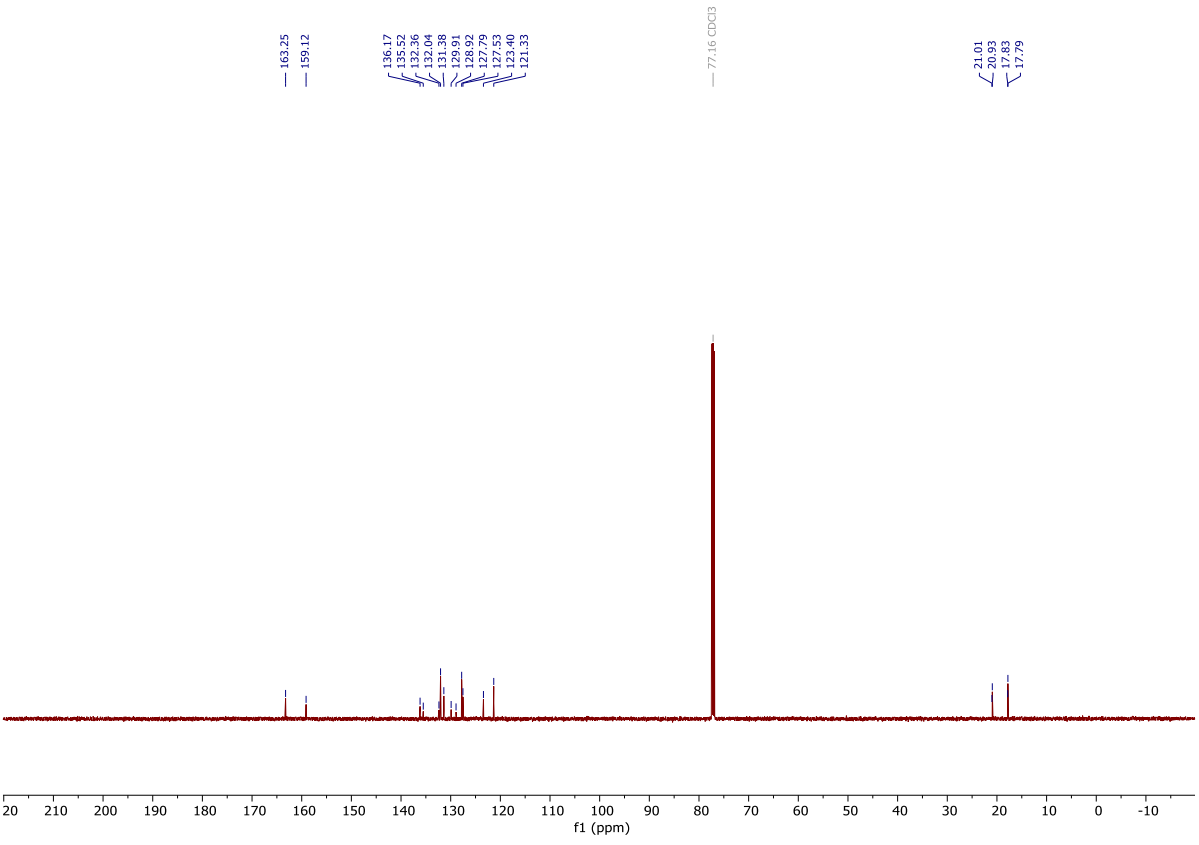

0.38
0.62
0.60
1.07
1.01
1.01
0.38
1.01
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

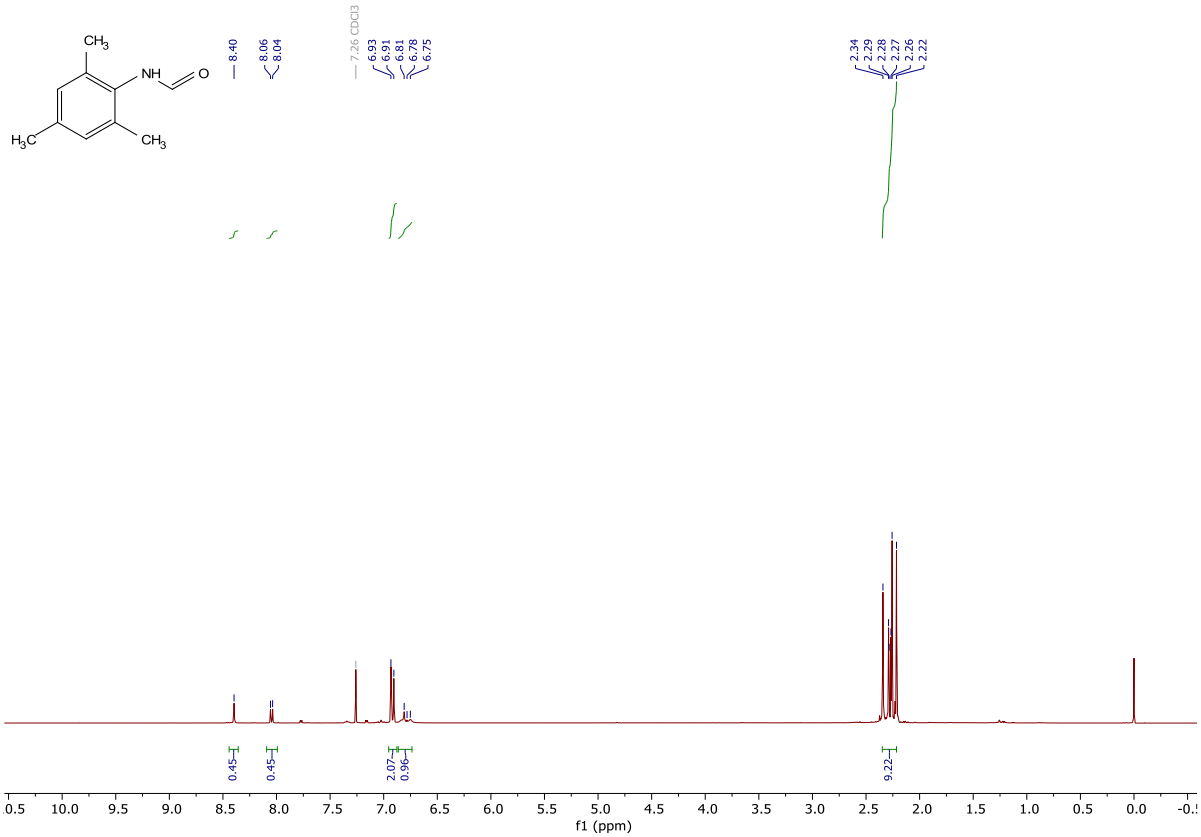
ù

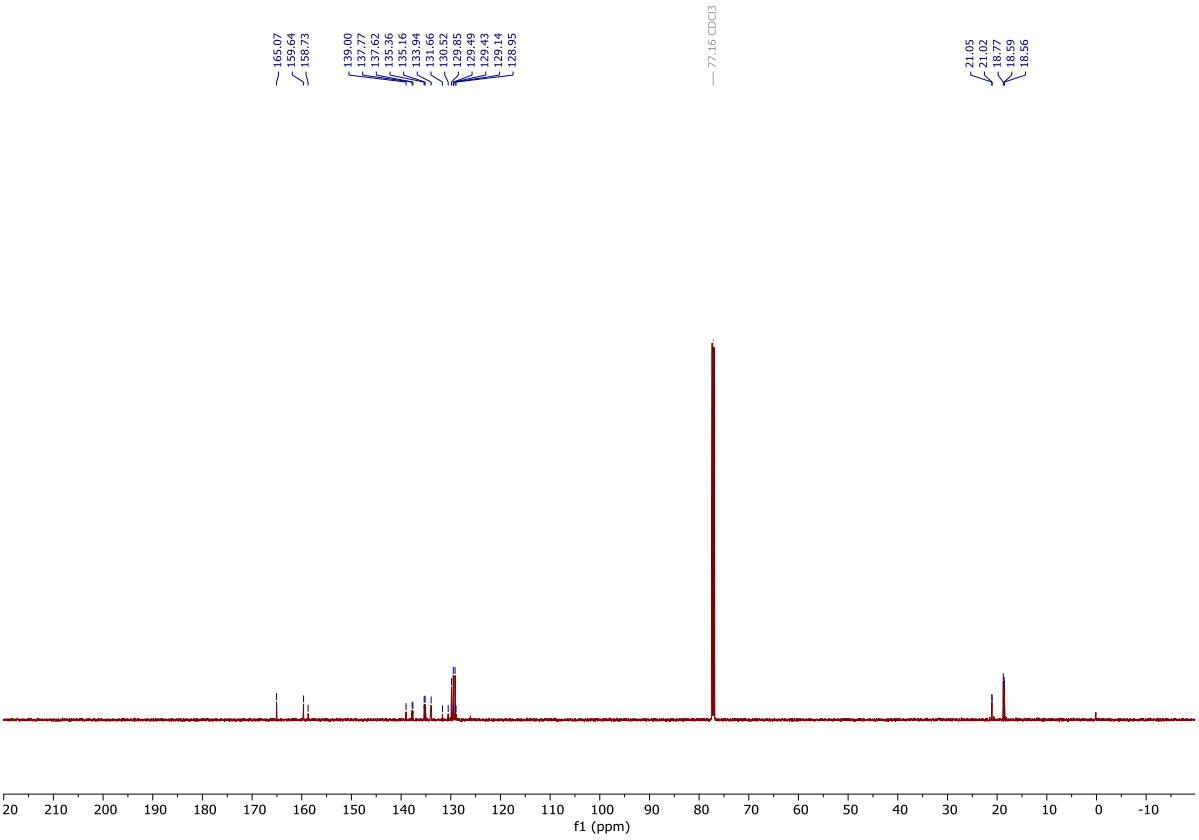

162.06
159.08
159.04
140.08
139.09
137.89
137.41
129.75
129.47
127.19
126.53
122.42
122.39
119.48
90.85
89.37
77.16 CDCl3

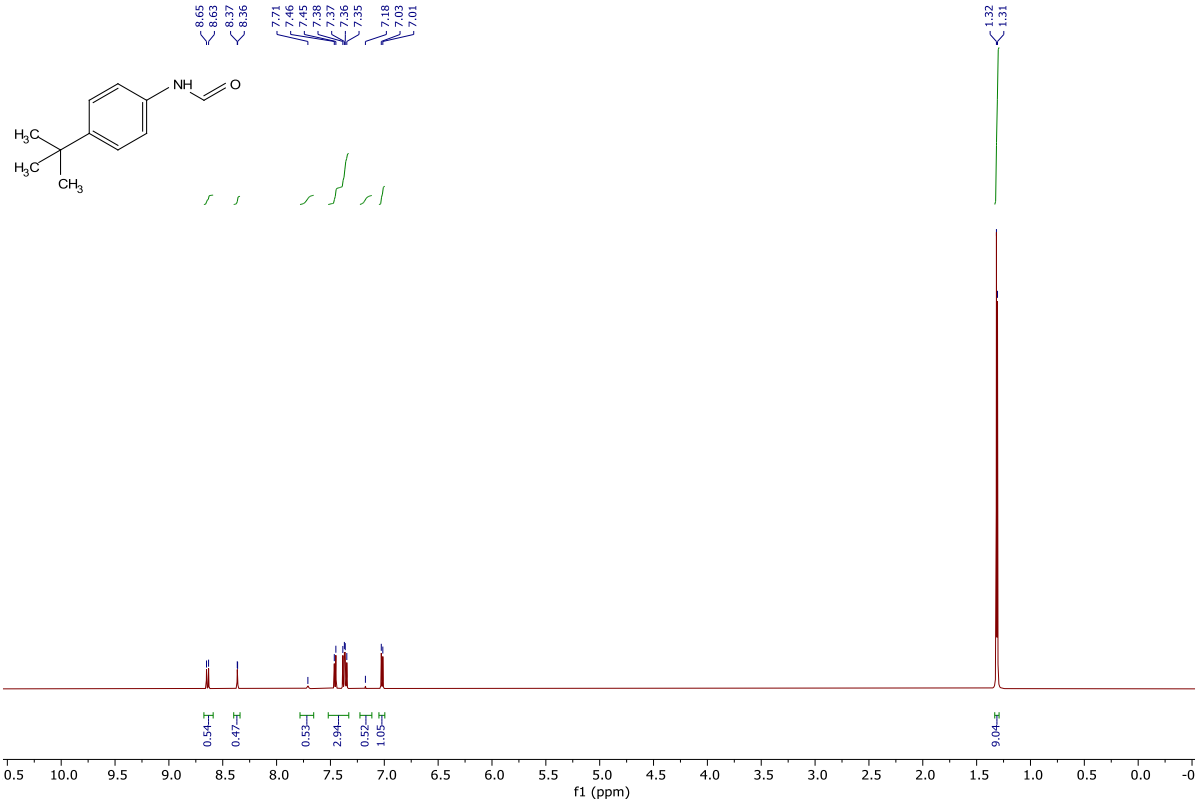

20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.48
8.46
8.42
8.42
7.72
7.71
7.34
7.26 CDCl3
7.05
7.03
7.02
7.02
6.94
2.31
2.30
2.25
2.25
NH
O
H3C
CH3
0.63
0.37
0.40
0.66
2.83
0.29
3.32
3.18
f1 (ppm)


163.25
159.12
136.17
135.52
132.36
132.04
131.38
129.91
128.92
127.79
127.53
123.40
121.33
77.16 CDCl3
21.01
20.93
17.83
17.79
f1 (ppm)


CH3
NH
O
H3C
CH3
8.40
8.06
8.04
7.26 CDCl3
6.93
6.91
6.81
6.78
6.75
2.34
2.29
2.28
2.27
2.26
2.22
0.45
0.45
2.07
0.96
9.22
f1 (ppm)


165.07
159.64
158.73
139.00
137.77
137.62
135.36
135.16
133.94
131.66
130.52
129.85
129.49
129.43
129.14
128.95
77.16 CDCl3
21.05
21.02
18.77
18.59
18.56
f1 (ppm)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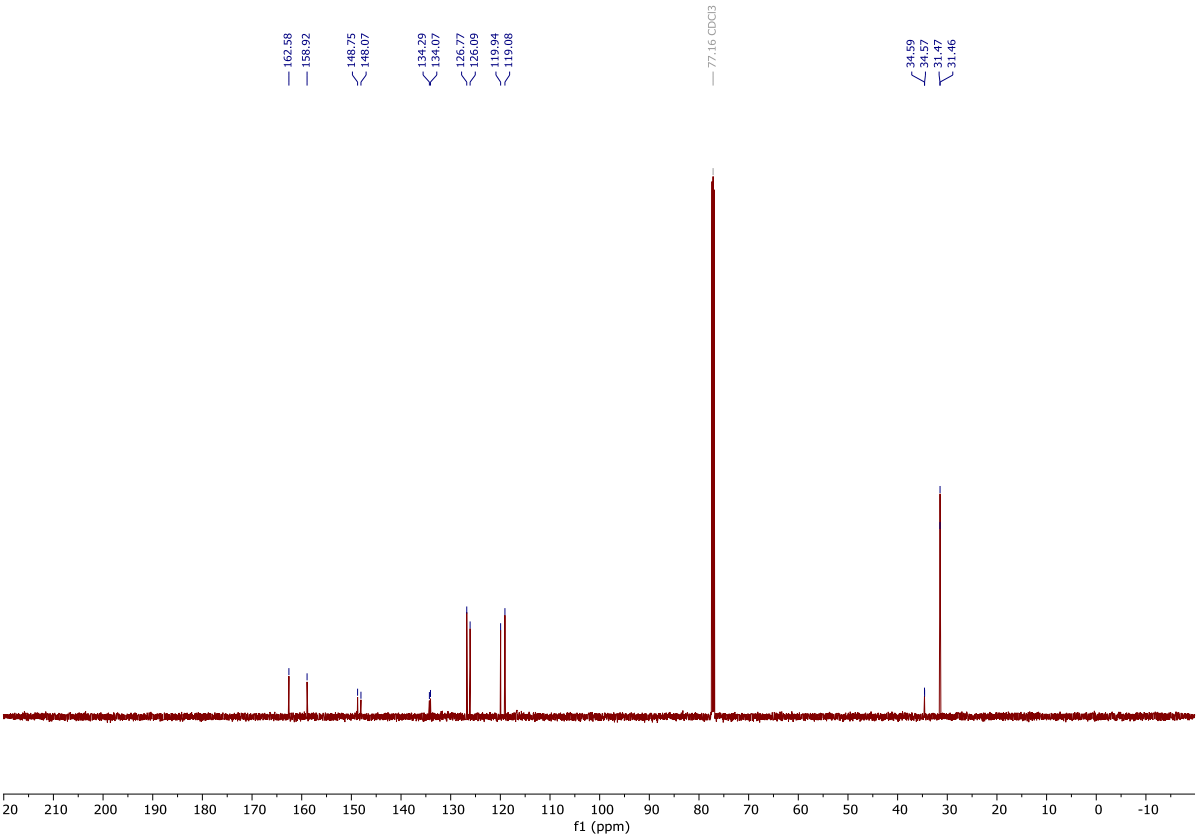
7.46
7.45
7.38
7.37
7.36
7.35
7.18
7.03
7.01
1.32
1.31
NH
O
H3C
H3C
CH3
0.54
0.47
0.53
2.94
0.52
1.05
9.04
f1 (ppm)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148.75
148.07
134.29
134.07
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126.09
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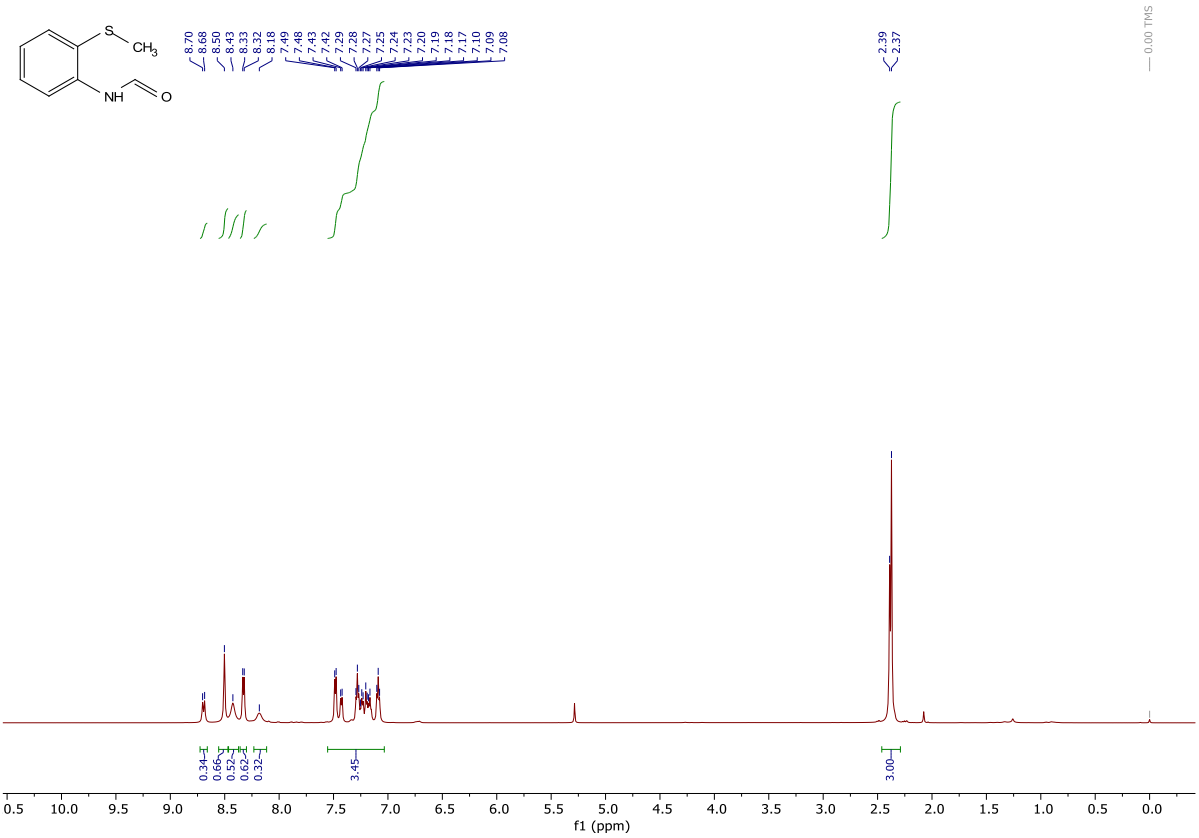
119.08
77.16 CDCl3
34.59
34.57
31.47
31.46
f1 (ppm)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CH3
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O
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8.32
8.18
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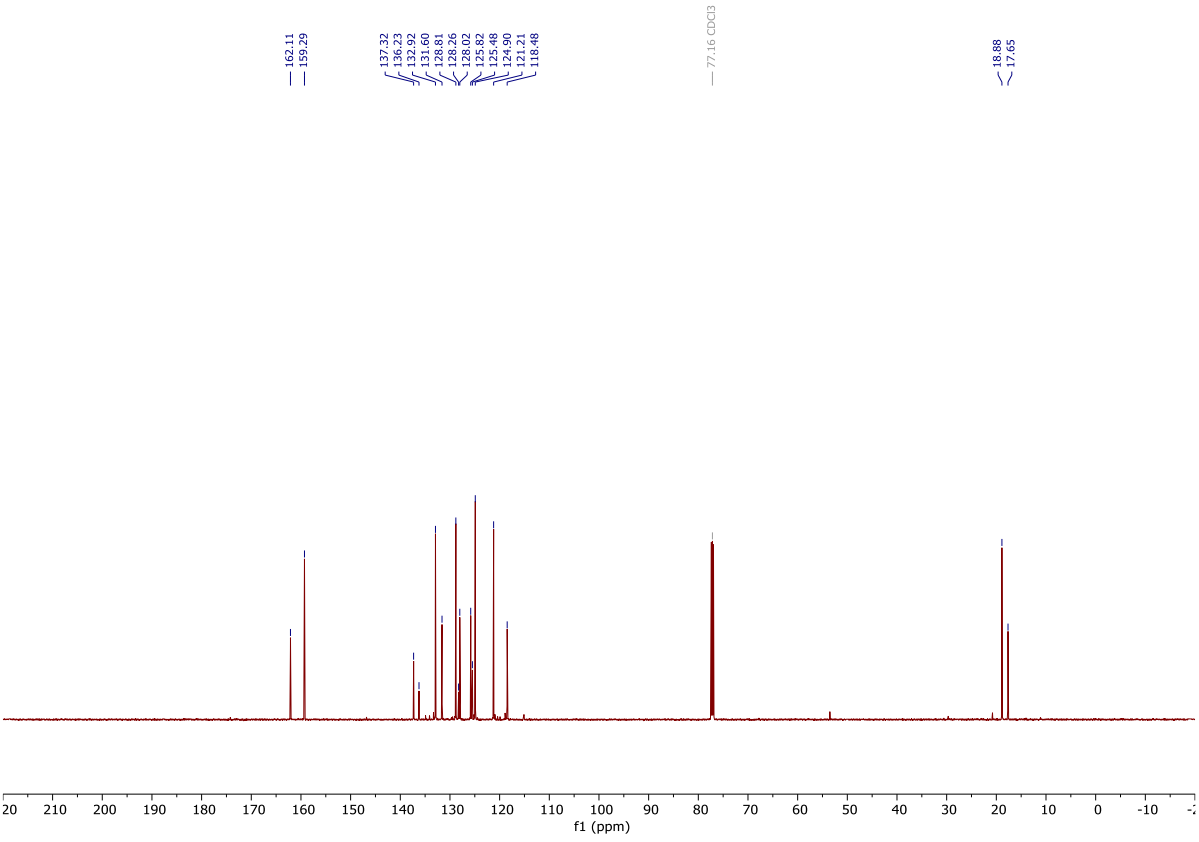
7.48
7.43
7.42
7.29
7.28
7.27
7.25
7.24
7.23
7.20
7.19
7.18
7.17
7.10
7.09
7.08
2.39
2.37
0.00 TMS
0.34
0.66
0.52
0.62
0.32
3.45
3.00
f1 (ppm)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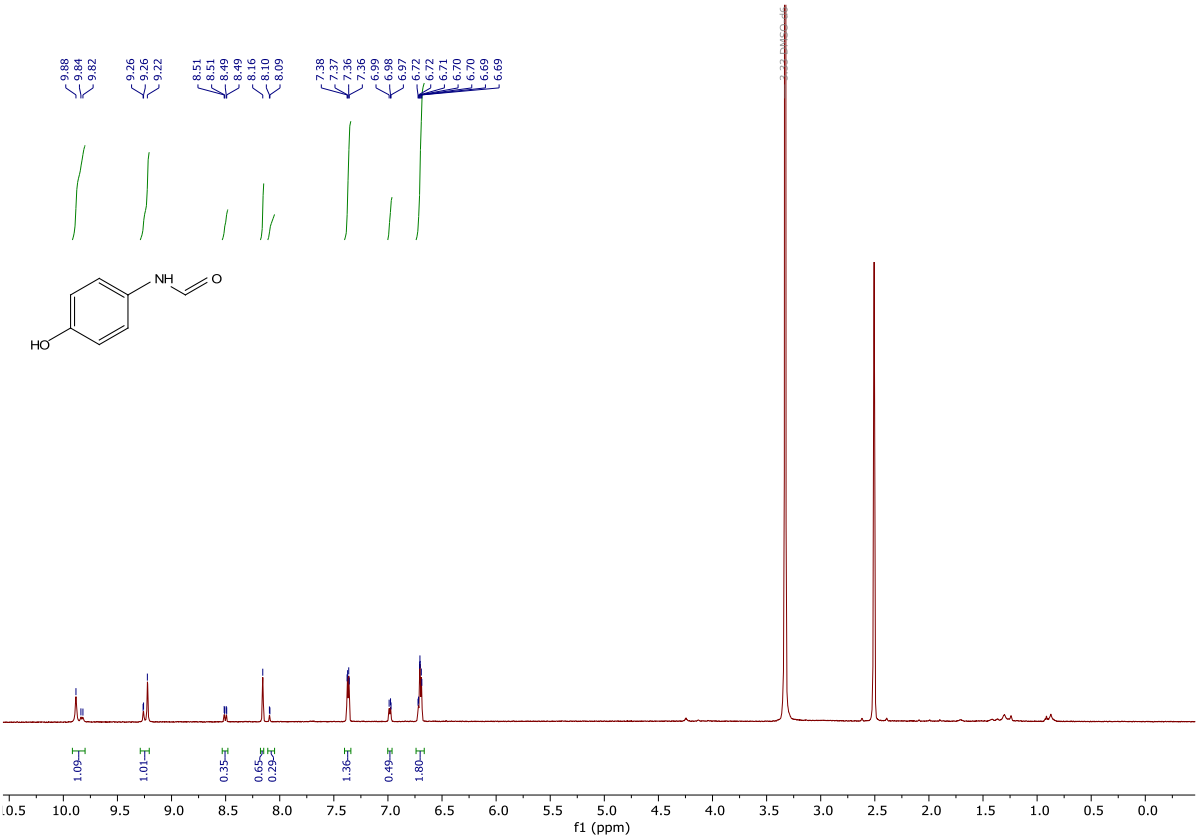
136.23
132.92
131.60
128.81
128.26
128.02
125.82
125.48
124.90
121.21
118.48
77.16 CDCl3
18.88
17.65
f1 (ppm)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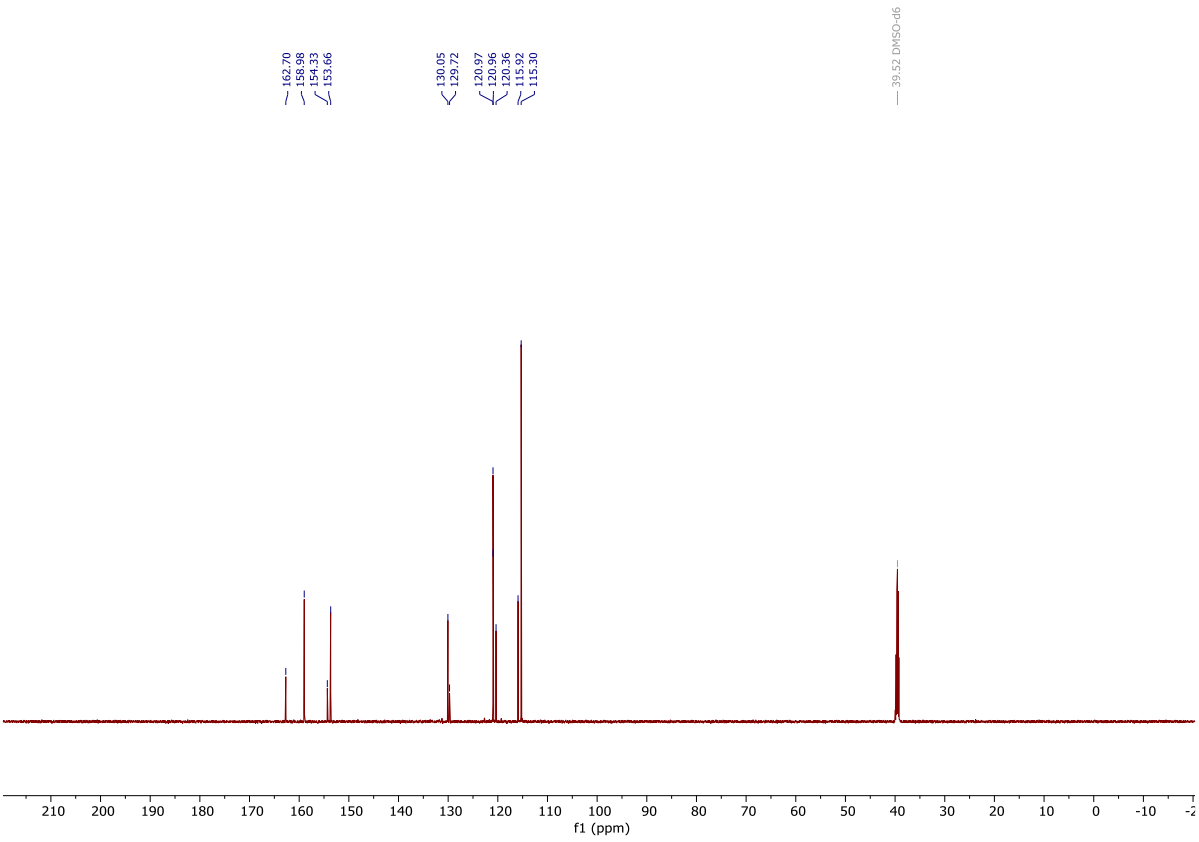
9.84
9.82
9.26
9.26
9.22
8.51
8.51
8.49
8.49
8.16
8.10
8.09
7.38
7.37
7.36
7.36
6.99
6.98
6.97
6.72
6.72
6.71
6.70
6.70
6.69
6.69
2.32 DMSO-d6
NH
O
HO
1.09
1.01
0.35
0.65
0.29
1.36
0.49
1.80
f1 (ppm)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158.98
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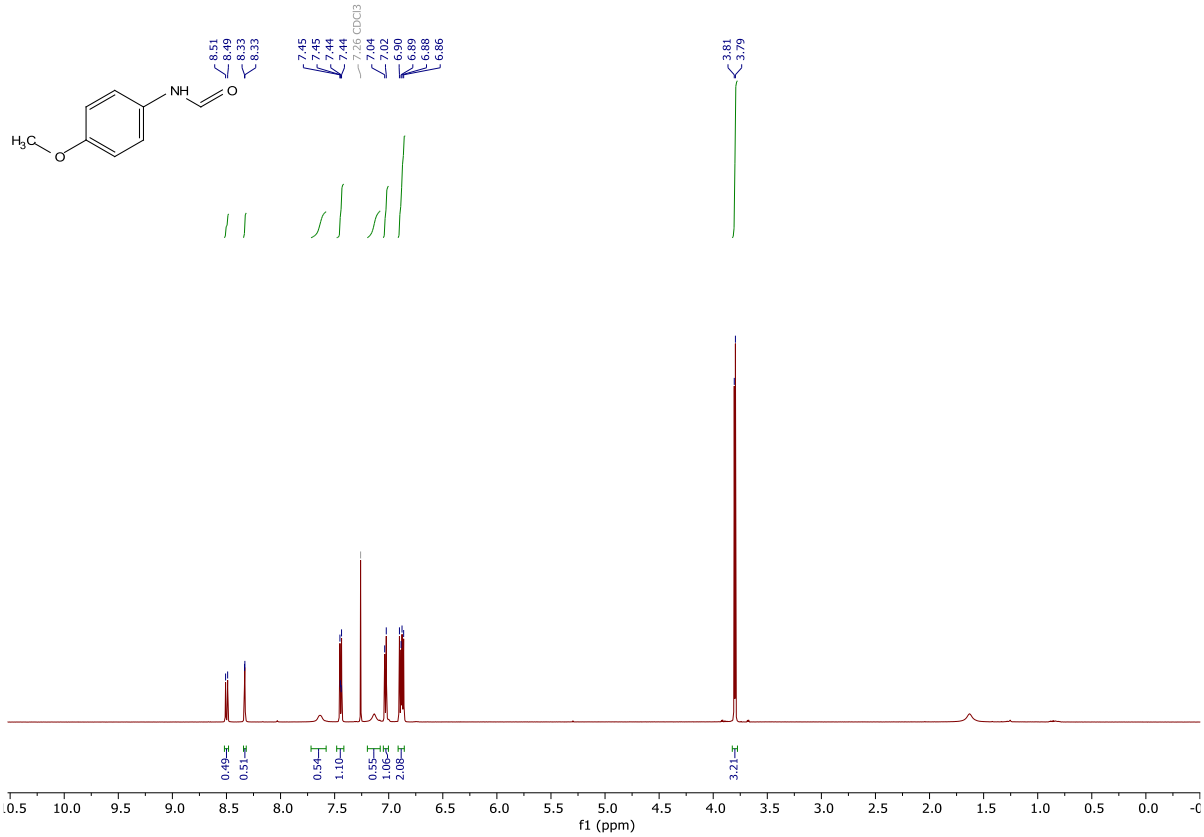
153.66
130.05
129.72
120.97
120.96
120.36
115.92
115.30
39.52 DMSO-d6
f1 (ppm)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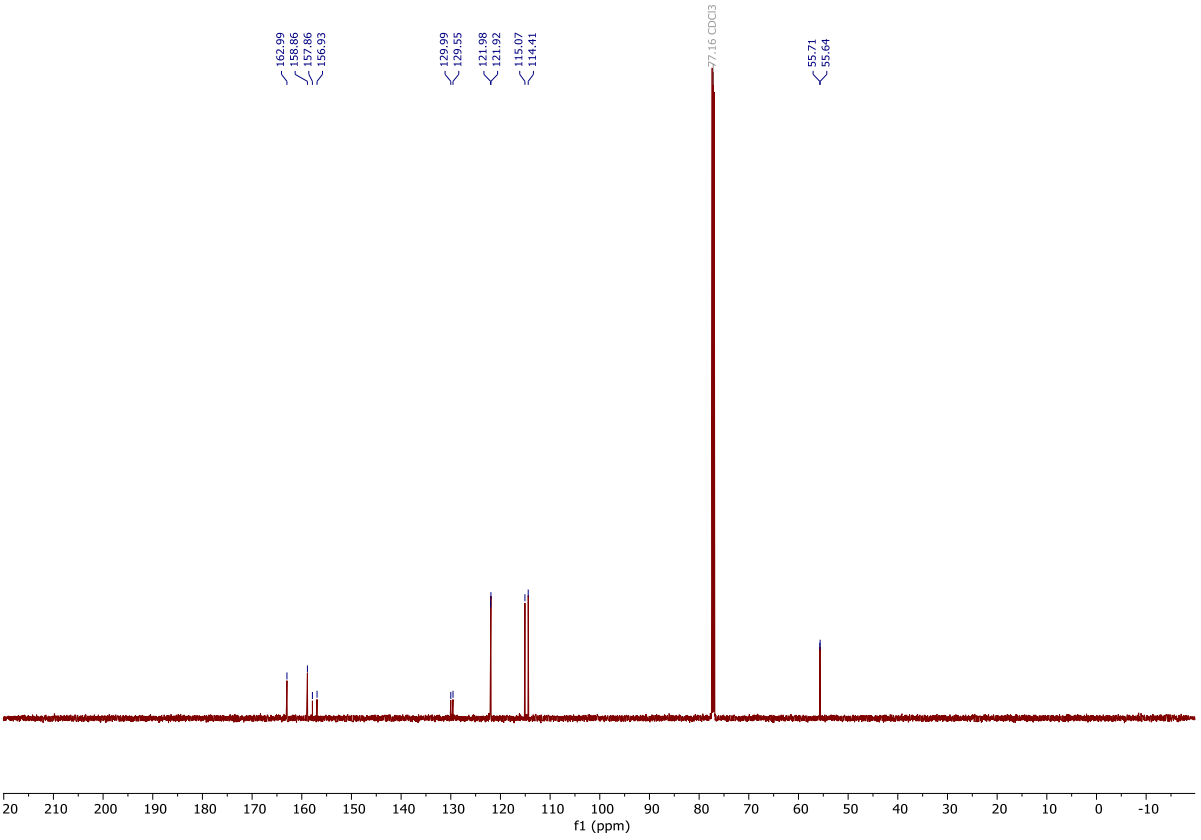
8.49
8.33
8.33
7.45
7.45
7.44
7.44
7.26 CDCl3
7.04
7.02
6.90
6.89
6.88
6.86
3.81
3.79
NH
O
H3C
O
0.49
0.51
0.54
1.10
0.55
1.06
2.08
3.21
f1 (ppm)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157.86
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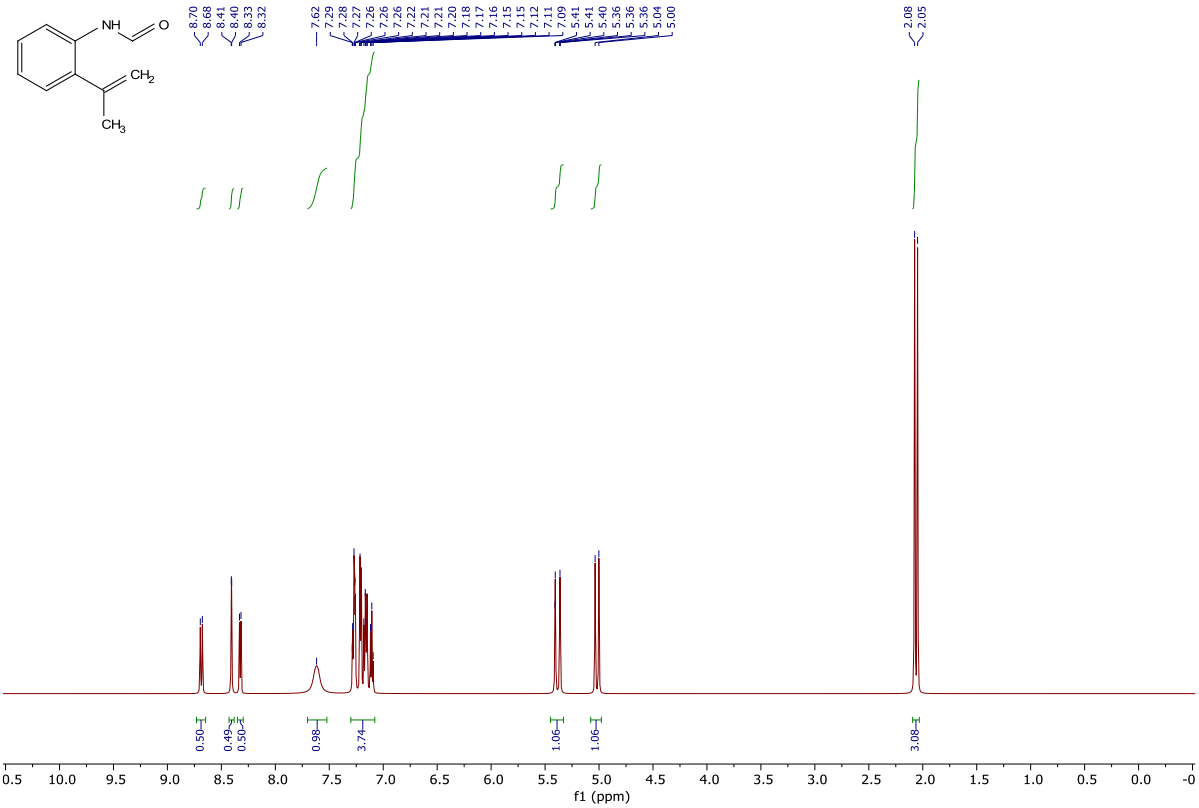
129.99
129.55
121.98
121.92
115.07
114.41
77.16 CDCl3
55.71
55.64
f1 (ppm)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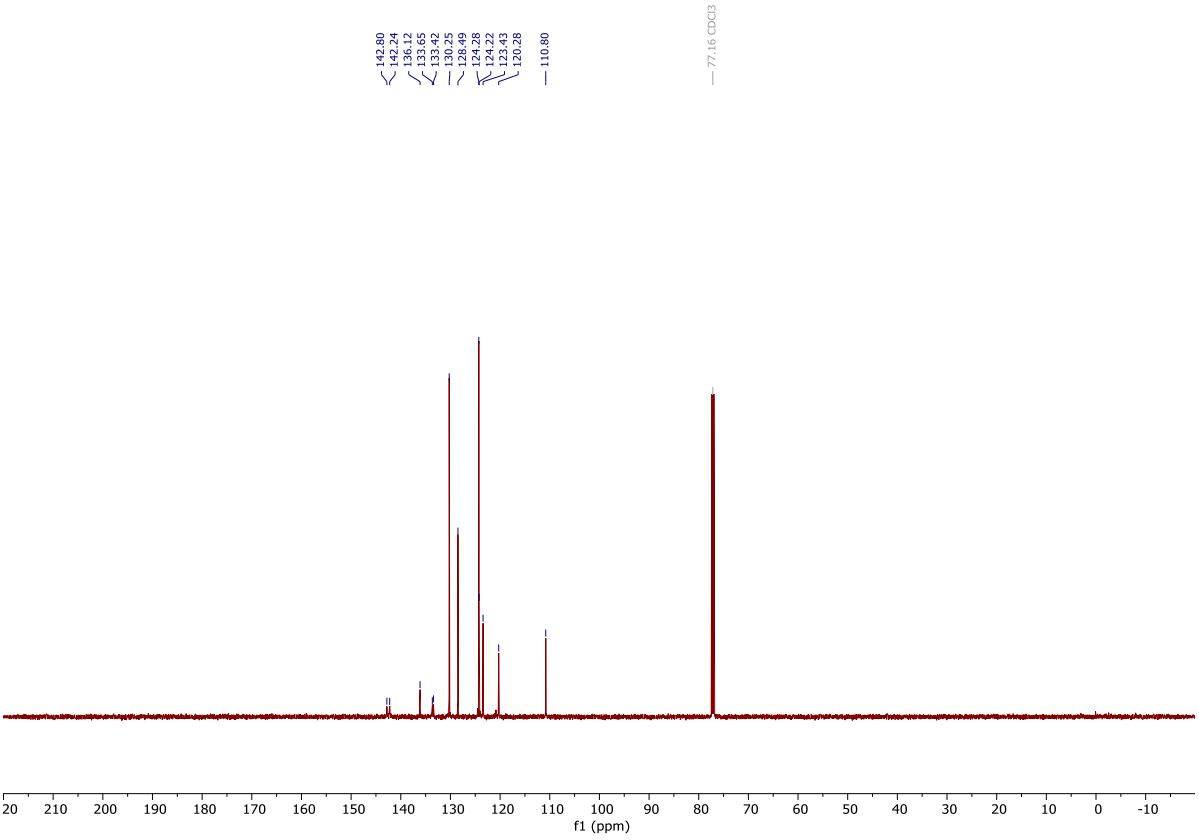
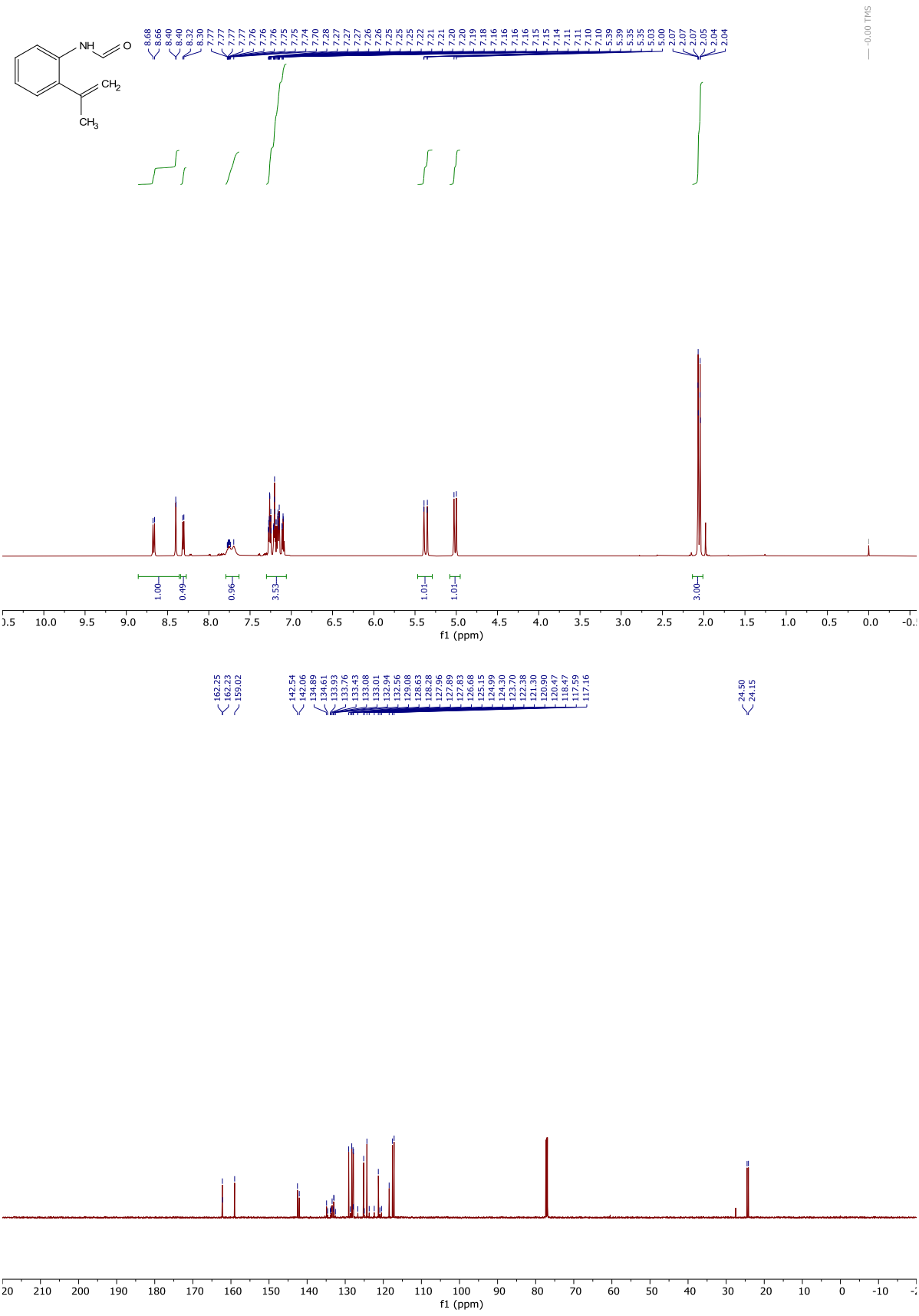
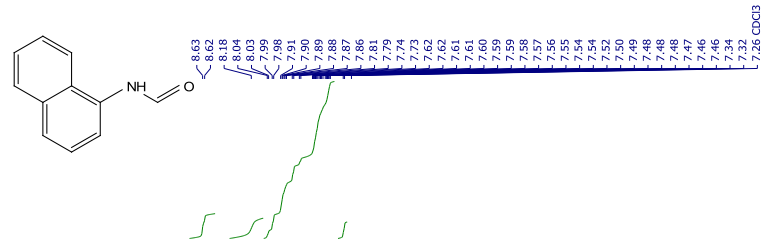
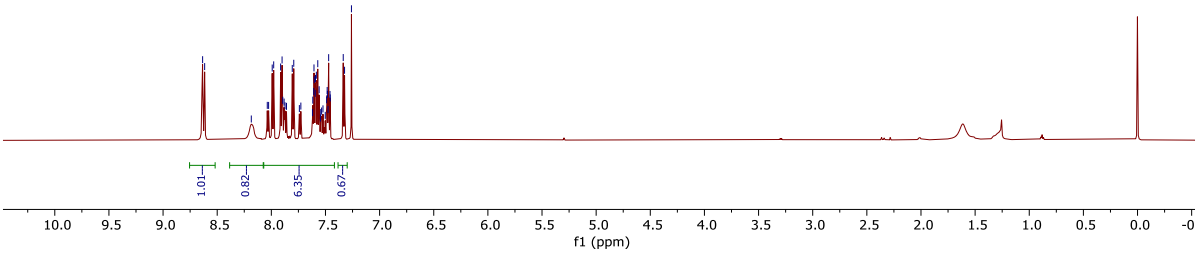
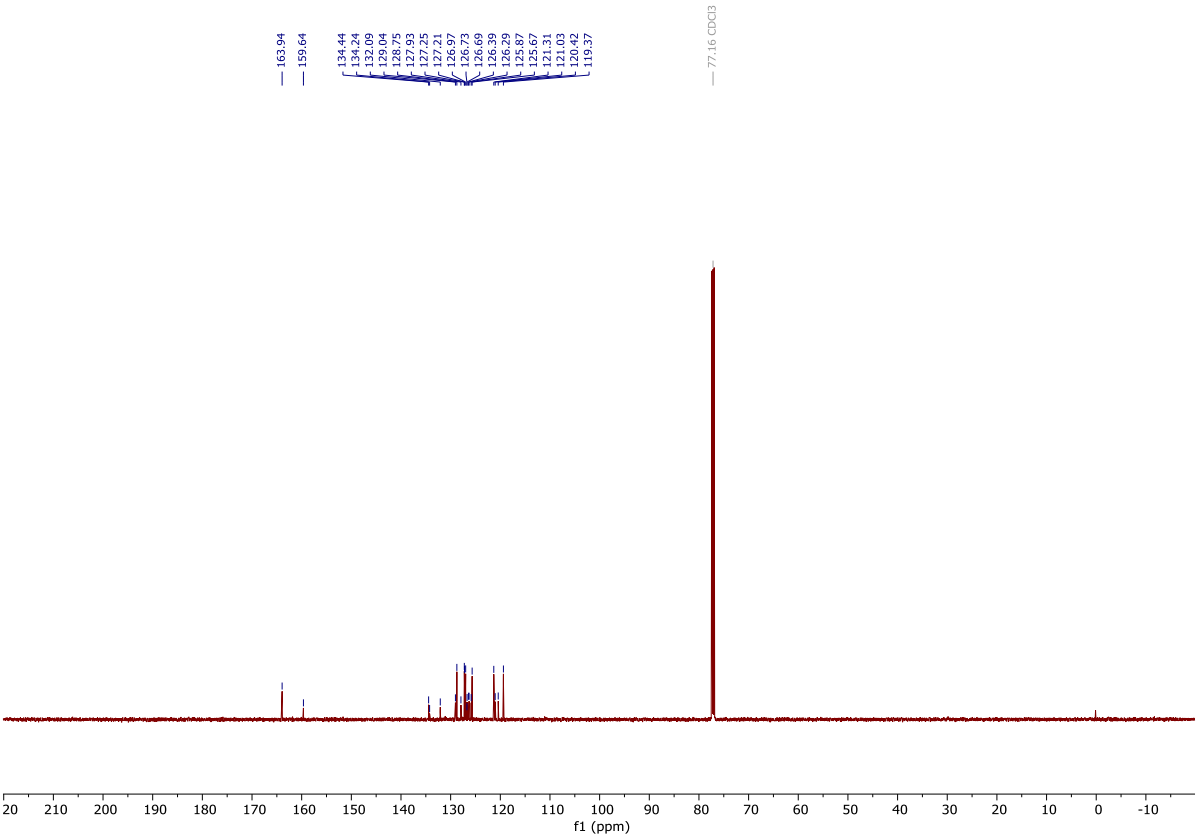
O
CH2
CH3
8.70
8.68
8.41
8.40
8.33
8.32
7.62
7.29
7.28
7.27
7.26
7.26
7.26
7.22
7.21
7.21
7.20
7.18
7.17
7.16
7.15
7.15
7.12
7.11
7.09
5.41
5.41
5.40
5.36
5.36
5.36
5.04
5.00
2.08
2.05
0.50
0.49
0.50
0.98
3.74
1.06
1.06
3.08
f1 (ppm)


142.80
142.24
136.12
133.65
133.42
130.25
128.49
124.28
124.22
123.43
120.28
110.80
77.16 CDCl3
f1 (ppm)


NH
O
CH2
CH3
f1 (ppm)
f1 (ppm)


NH
O
8.63
8.62
8.18
8.04
8.03
7.99
7.98
7.91
7.90
7.89
7.88
7.87
7.86
7.81
7.79
7.74
7.73
7.62
7.62
7.61
7.61
7.60
7.59
7.59
7.58
7.57
7.56
7.55
7.54
7.54
7.52
7.50
7.49
7.48
7.48
7.48
7.47
7.46
7.46
7.34
7.32
7.26 CDCl3


1.01
0.82
6.35
0.67
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)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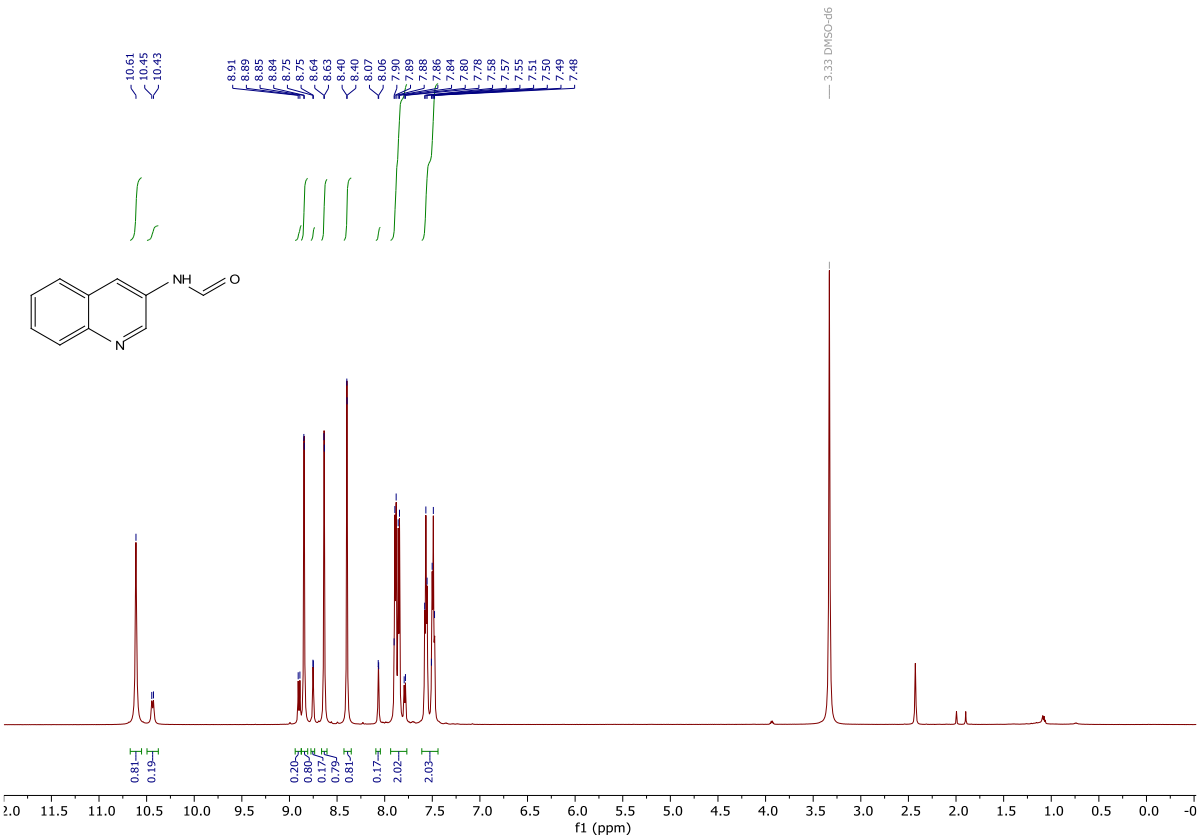
134.24
132.09
129.04
128.75
127.93
127.25
127.21
126.97
126.73
126.69
126.39
126.29
125.87
125.67
121.31
121.03
120.42
119.37
77.16 CDCl3
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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10.45
10.43
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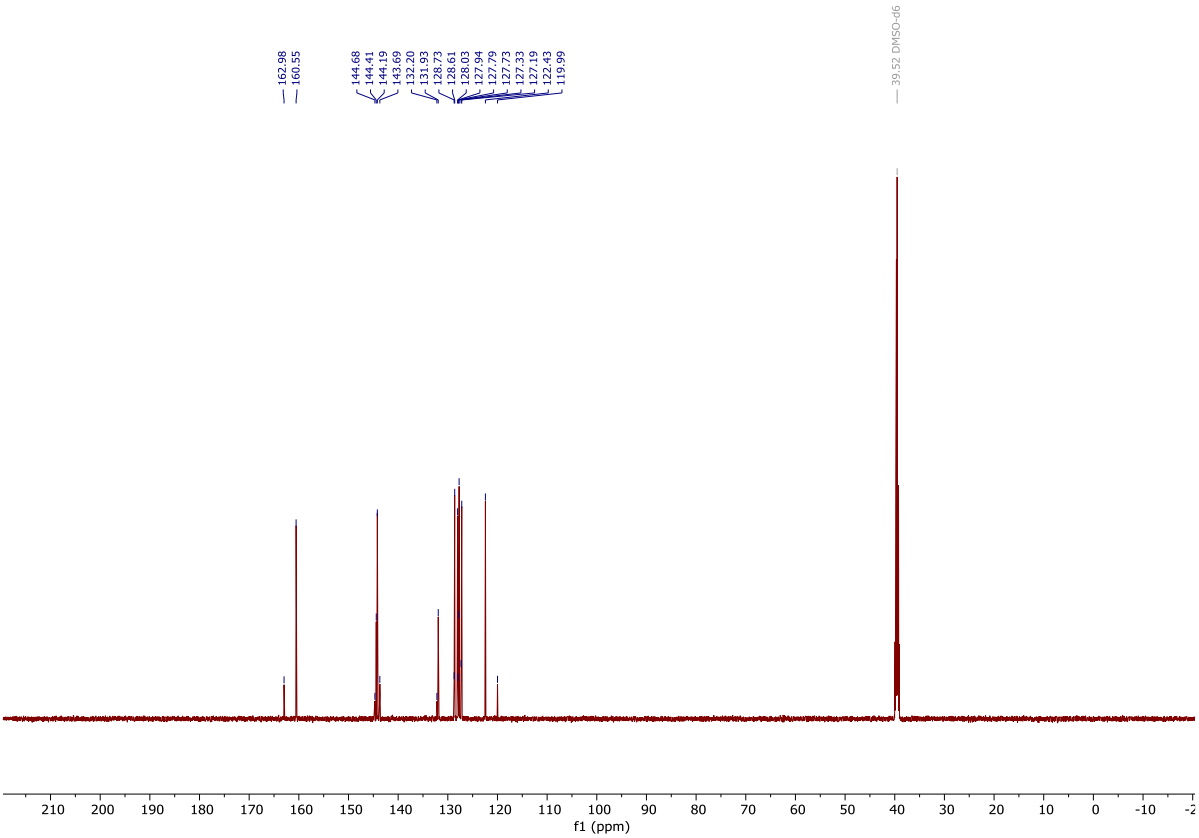
8.85
8.84
8.75
8.75
8.64
8.63
8.40
8.40
8.07
8.06
7.90
7.89
7.88
7.86
7.84
7.80
7.78
7.58
7.57
7.55
7.51
7.50
7.49
7.48
3.33 DMSO-d6
NH
O
N
0.81
0.19
0.20
0.80
0.17
0.79
0.81
0.17
2.02
2.03
f1 (ppm)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160.55
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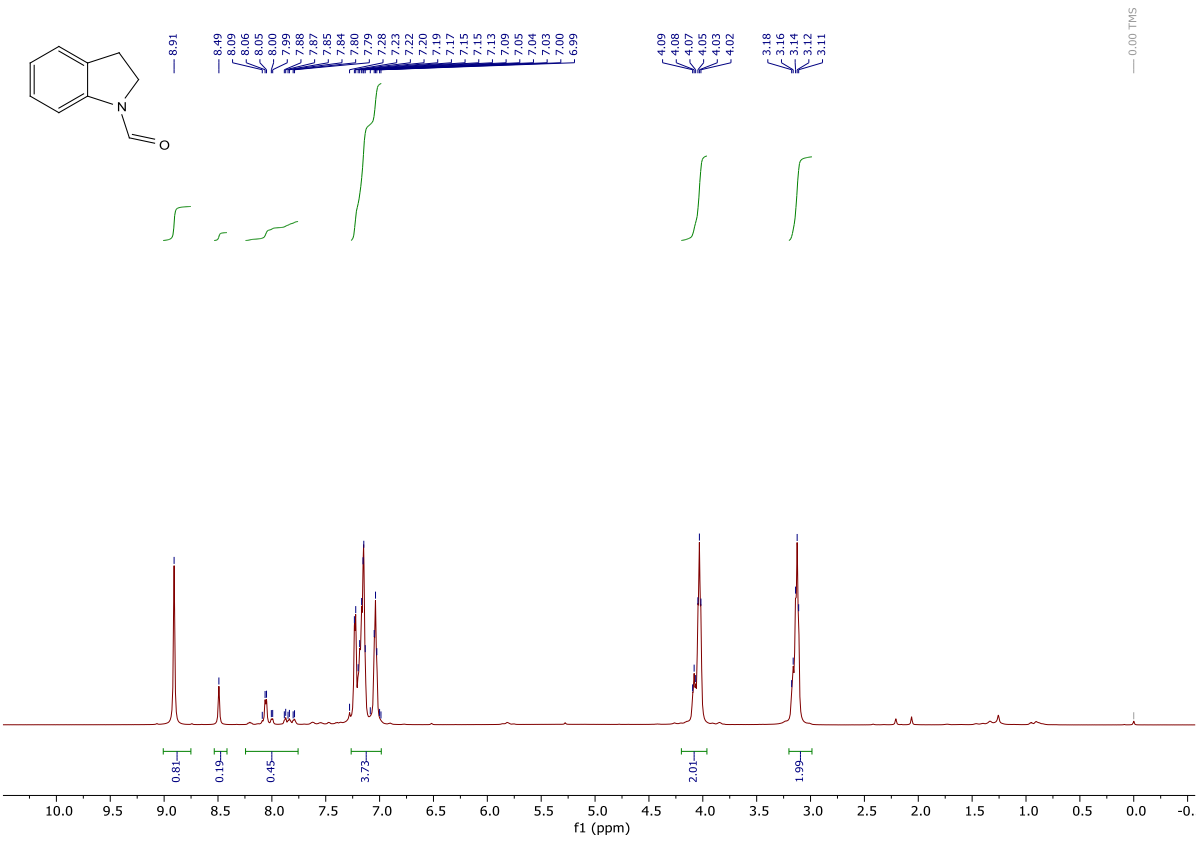
144.19
143.69
132.20
131.93
128.73
128.61
128.03
127.94
127.79
127.73
127.33
127.19
122.43
119.99
39.52 DMSO-d6
f1 (ppm)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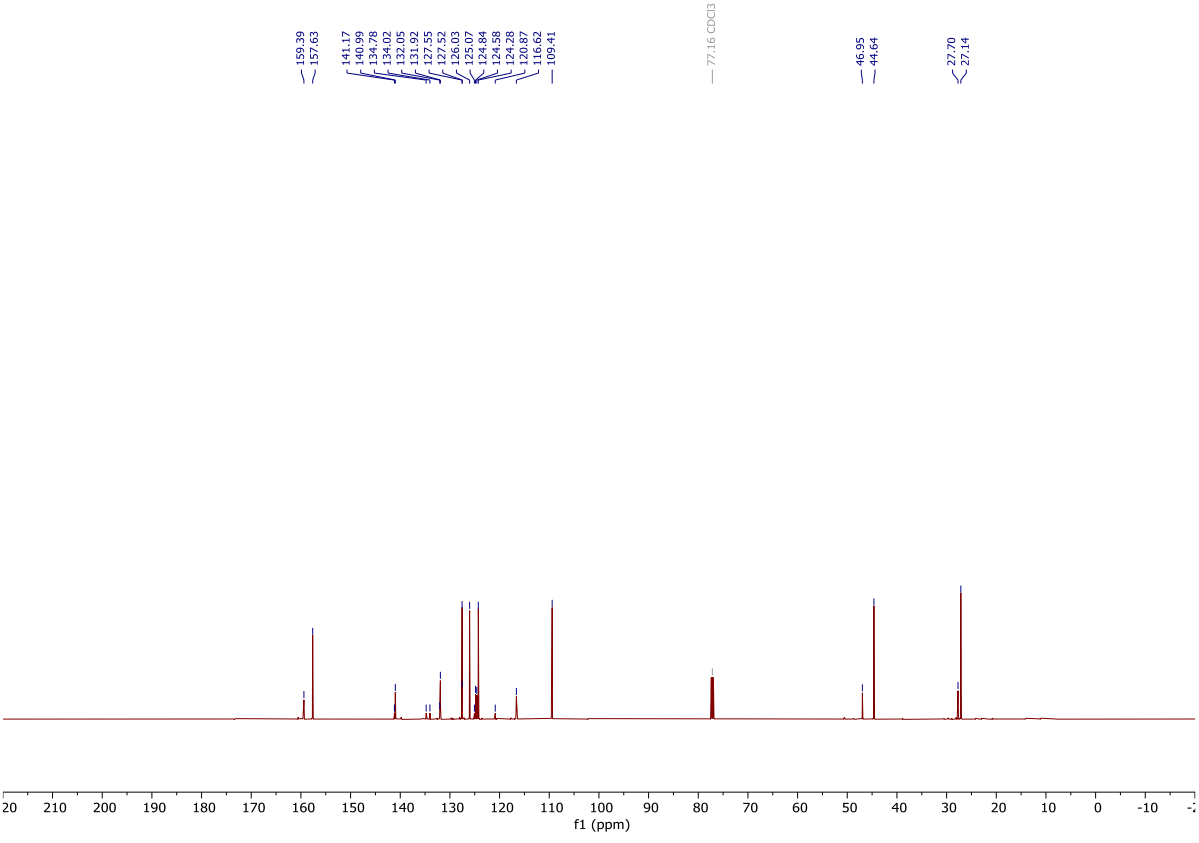
8.09
8.06
8.05
8.00
7.99
7.88
7.87
7.85
7.84
7.80
7.79
7.28
7.23
7.22
7.20
7.19
7.17
7.15
7.15
7.13
7.09
7.05
7.04
7.03
7.00
6.99
4.09
4.08
4.07
4.05
4.03
4.02
3.18
3.16
3.14
3.12
3.11
0.00 TMS
0.81
0.19
0.45
3.73
2.01
1.99
f1 (ppm)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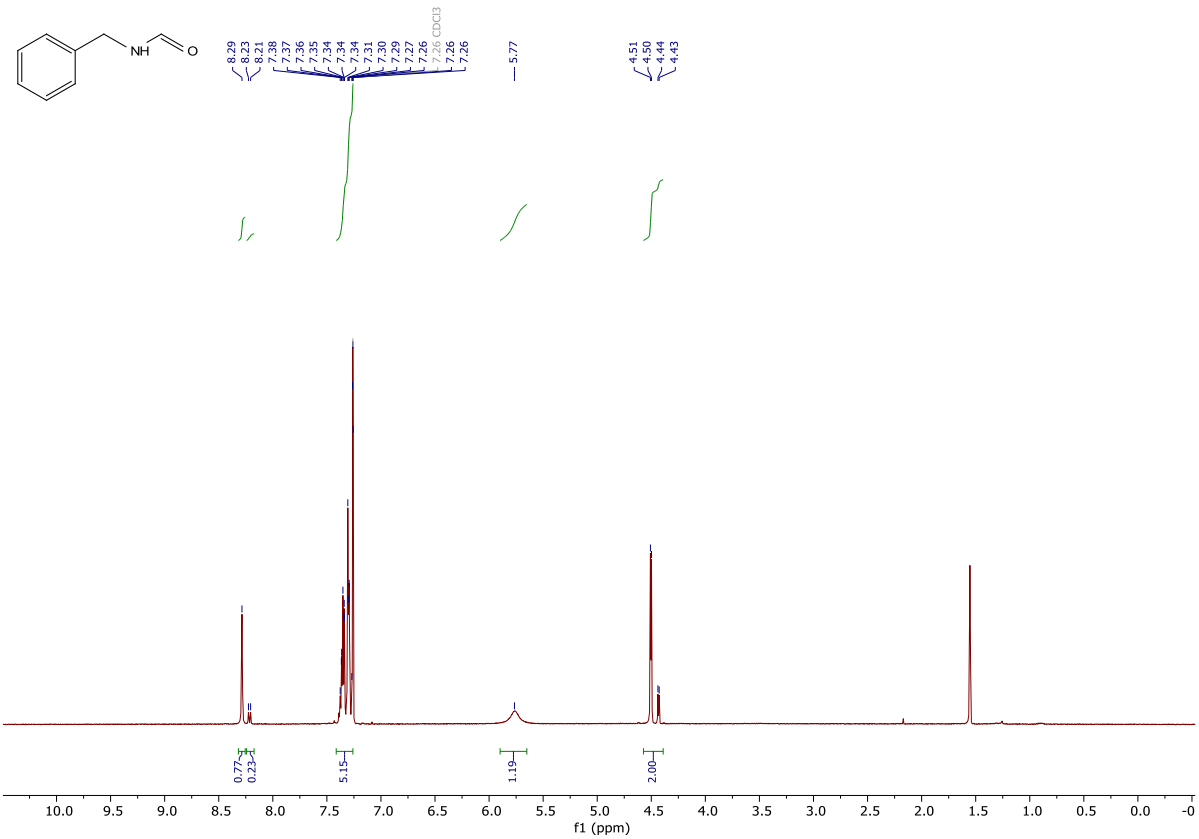
157.63
141.17
140.99
134.78
134.02
132.05
131.92
127.55
127.52
126.03
125.07
124.84
124.58
124.28
120.87
116.62
109.41
77.16 CDCl3
46.95
44.64
27.70
27.14
f1 (ppm)


NH
O
8.29
8.23
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7.37
7.36
7.35
7.34
7.34
7.34
7.31
7.30
7.29
7.27
7.26
7.26 CDCl3
7.26
7.26
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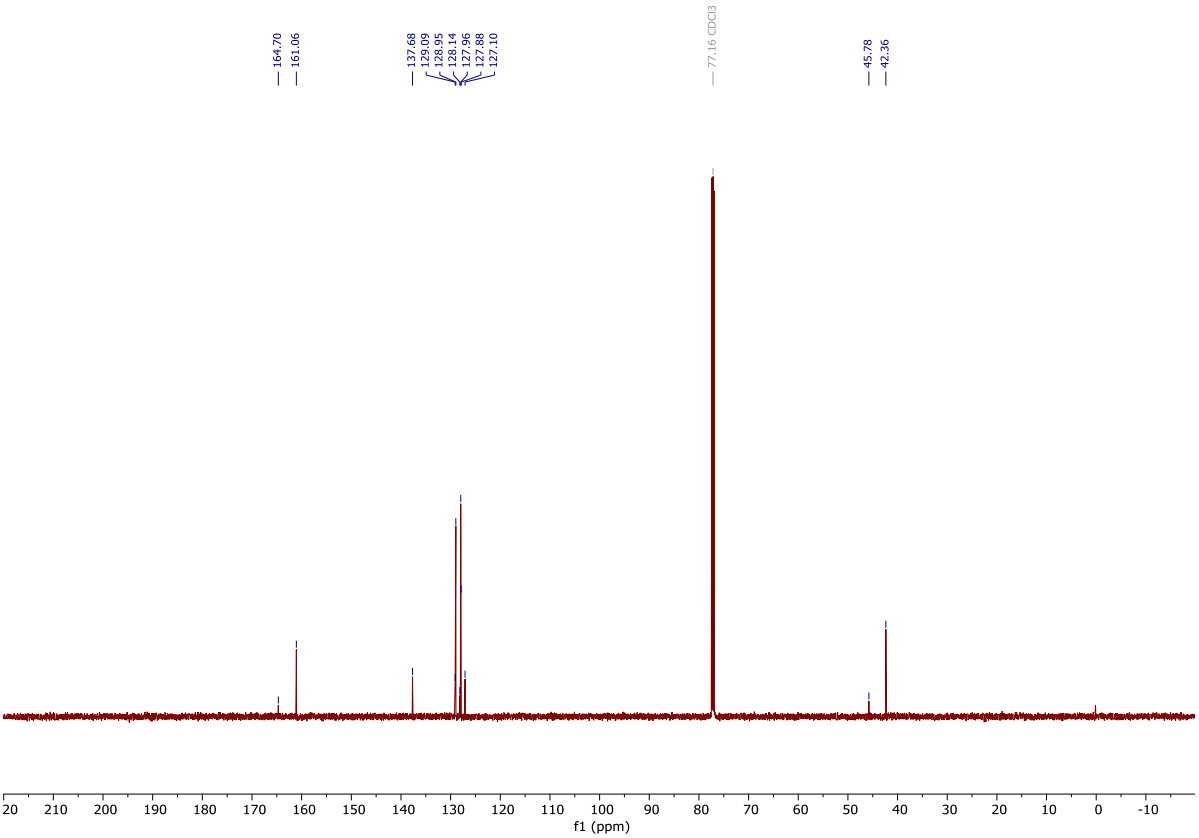
4.50
4.44
4.43
0.77
0.23
5.15
1.19
2.00
f1 (ppm)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161.06
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129.09
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128.14
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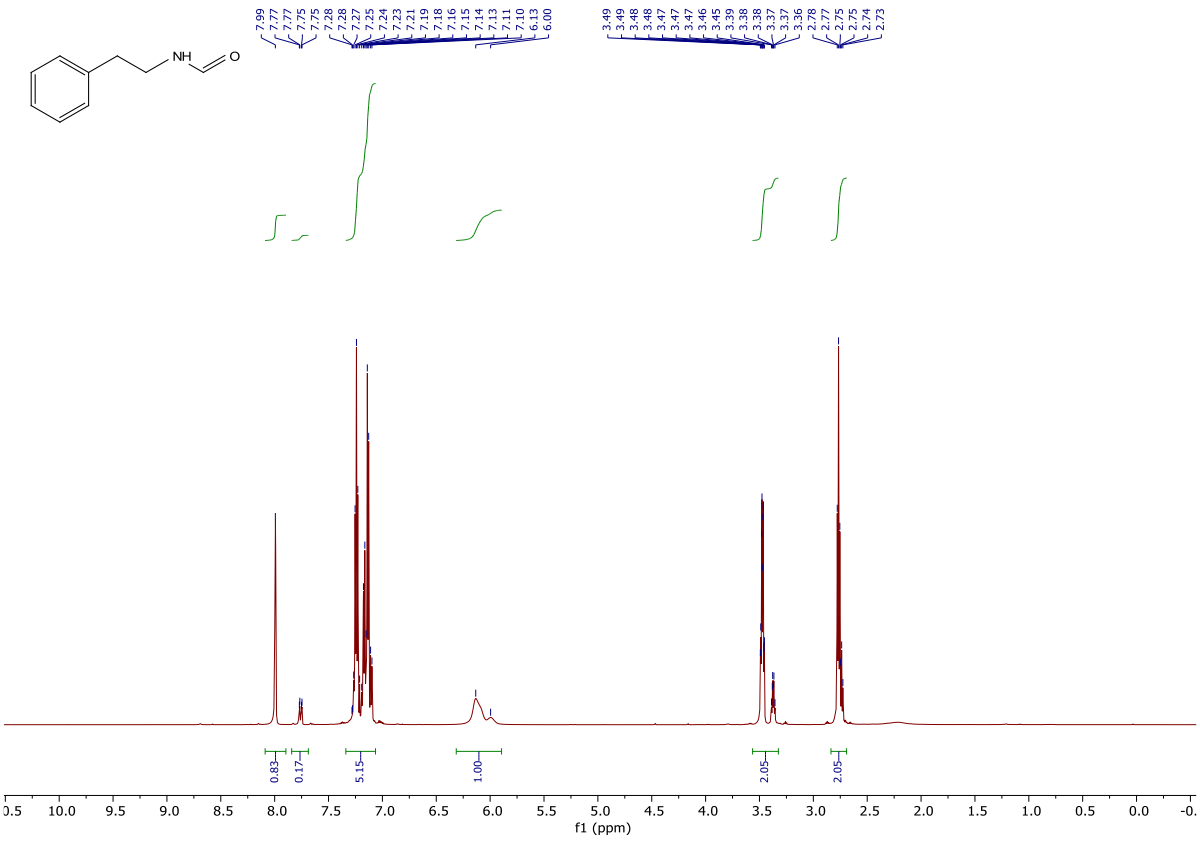
127.88
127.10
77.16 CDCl3
45.78
42.36
f1 (ppm)


NH
O
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7.77
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7.75
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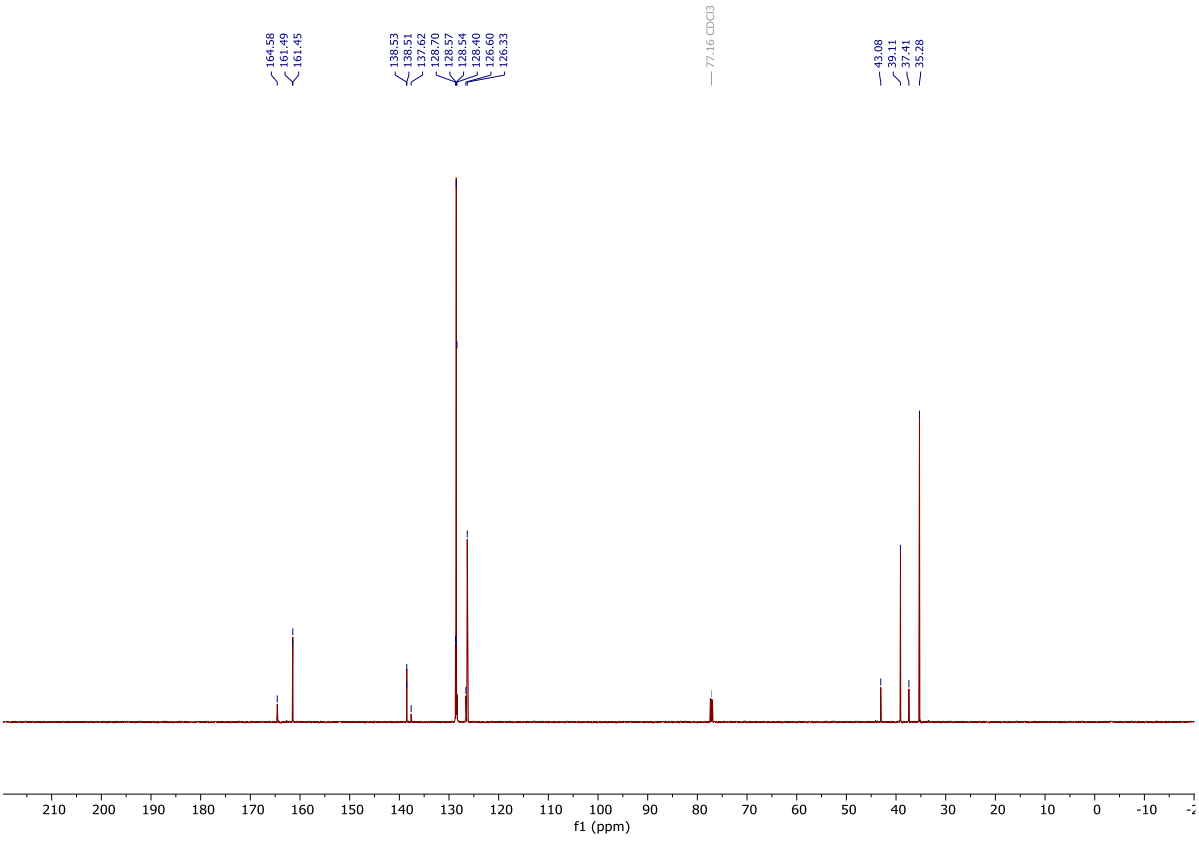
7.28
7.27
7.25
7.24
7.23
7.21
7.19
7.18
7.16
7.15
7.14
7.13
7.11
7.10
6.13
6.00
3.49
3.49
3.48
3.48
3.47
3.47
3.47
3.46
3.45
3.39
3.38
3.38
3.37
3.37
3.36
2.78
2.77
2.75
2.75
2.74
2.73
0.83
0.17
5.15
1.00
2.05
2.05
f1 (ppm)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161.45
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137.62
128.70
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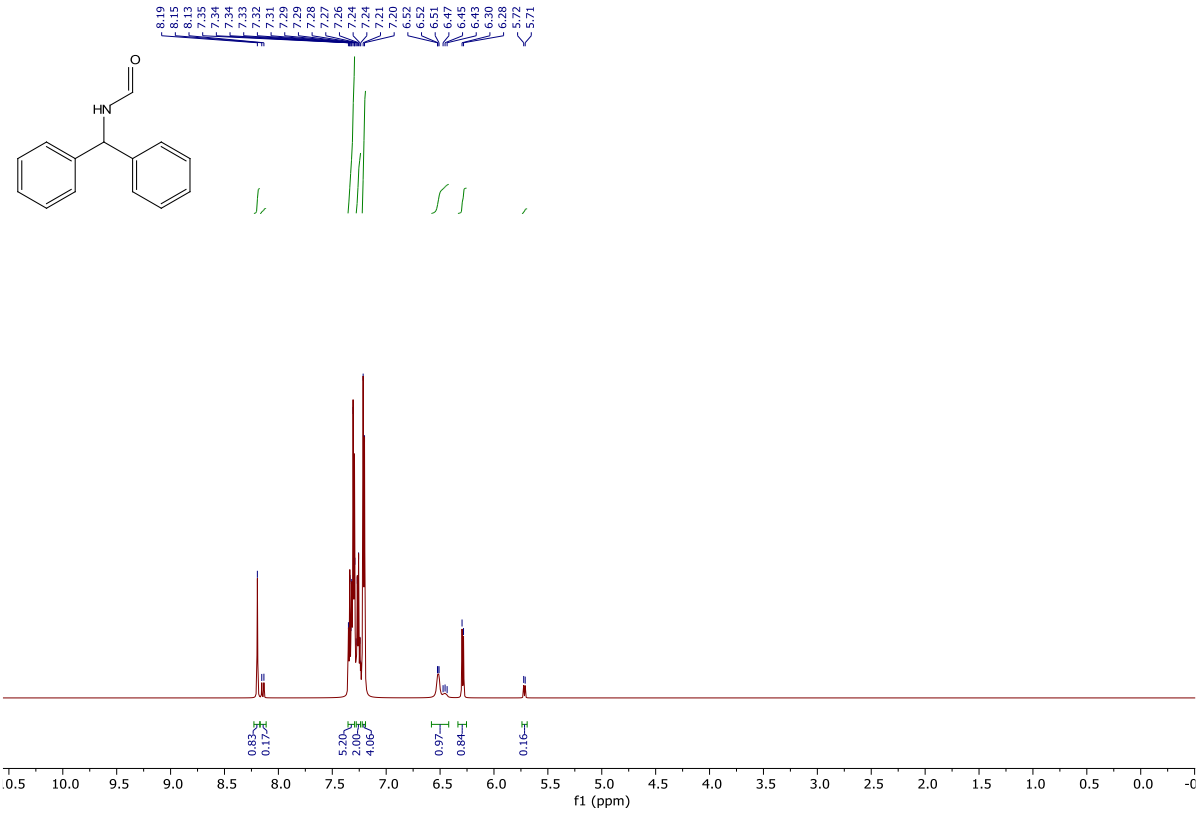
126.60
126.33
77.16 CDCl3
43.08
39.11
37.41
35.28
f1 (ppm)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8.15
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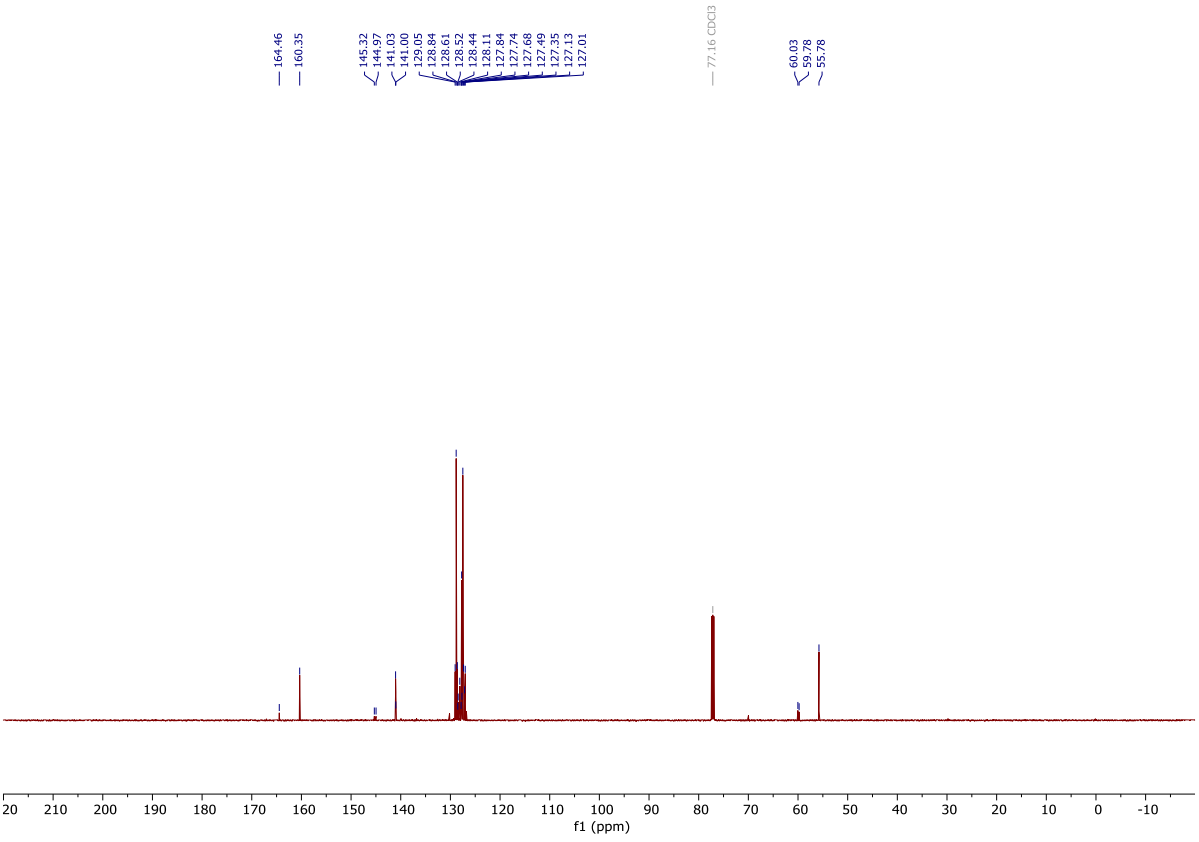
7.34
7.33
7.32
7.31
7.29
7.29
7.28
7.27
7.26
7.24
7.24
7.21
7.20
6.52
6.52
6.51
6.47
6.45
6.43
6.30
6.28
5.72
5.71
O
HN
0.83
0.17
5.20
2.00
4.06
0.97
0.84
0.16
f1 (ppm)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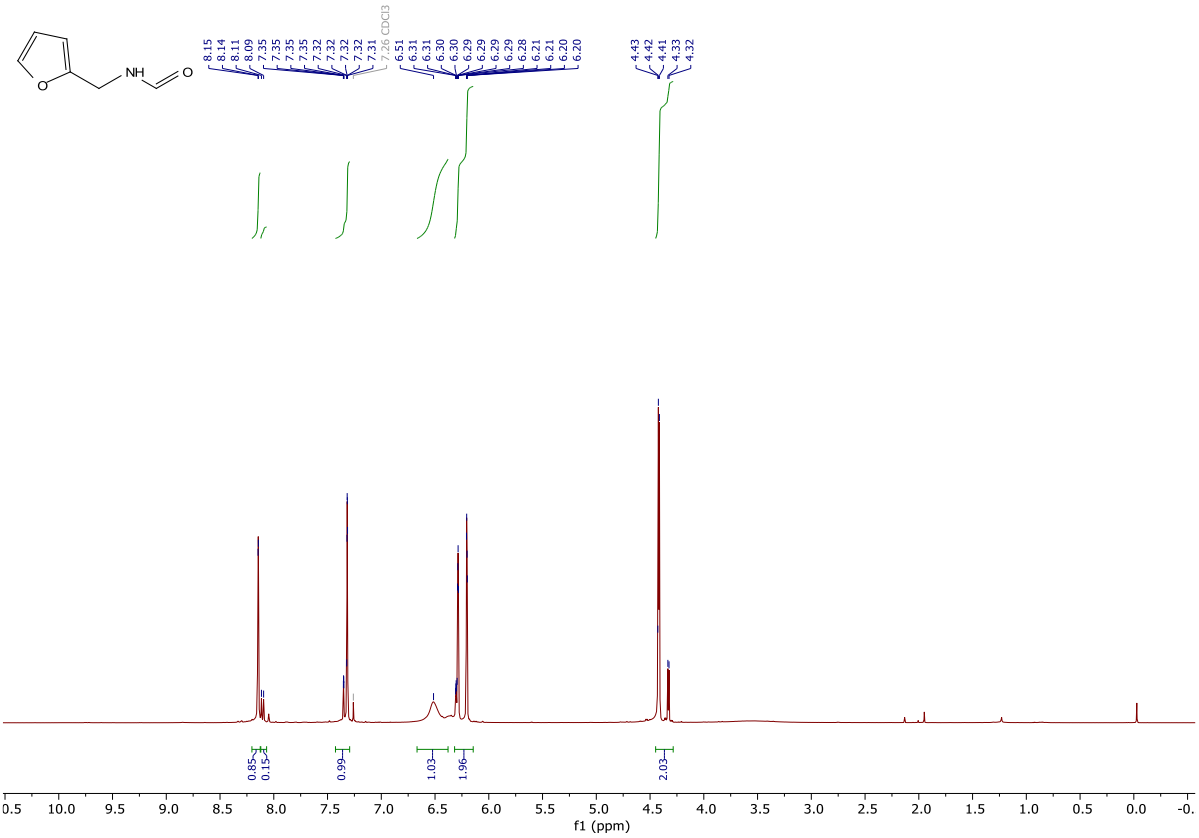
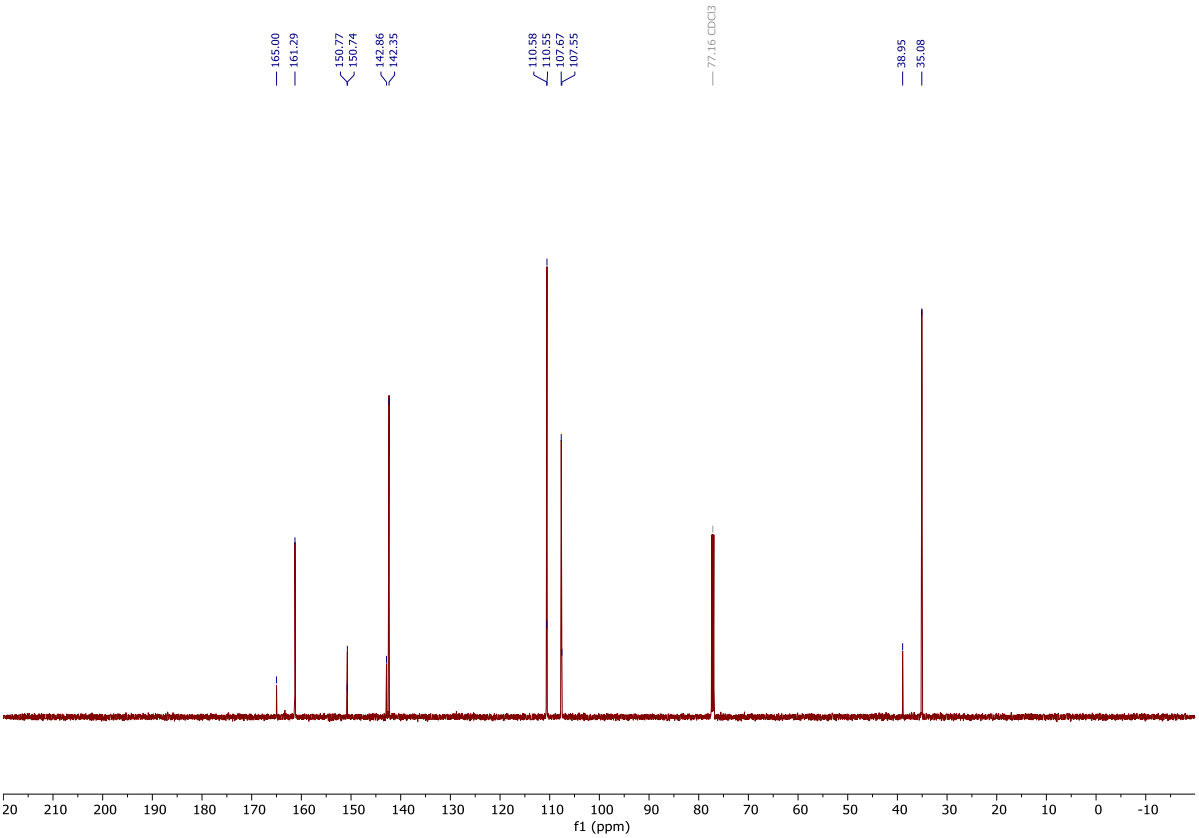
141.00
129.05
128.84
128.61
128.52
128.44
128.11
127.84
127.74
127.68
127.49
127.35
127.13
127.01
77.16 CDCl3
60.03
59.78
55.78
f1 (ppm)


NH
O
O
8.15
8.14
8.11
8.09
7.35
7.35
7.35
7.32
7.32
7.32
7.32
7.31
7.26 CDCl3
6.51
6.31
6.31
6.30
6.30
6.29
6.29
6.29
6.29
6.28
6.21
6.21
6.20
6.20
4.43
4.42
4.41
4.33
4.32
0.85
0.15
0.99
1.03
1.96
2.03
f1 (ppm)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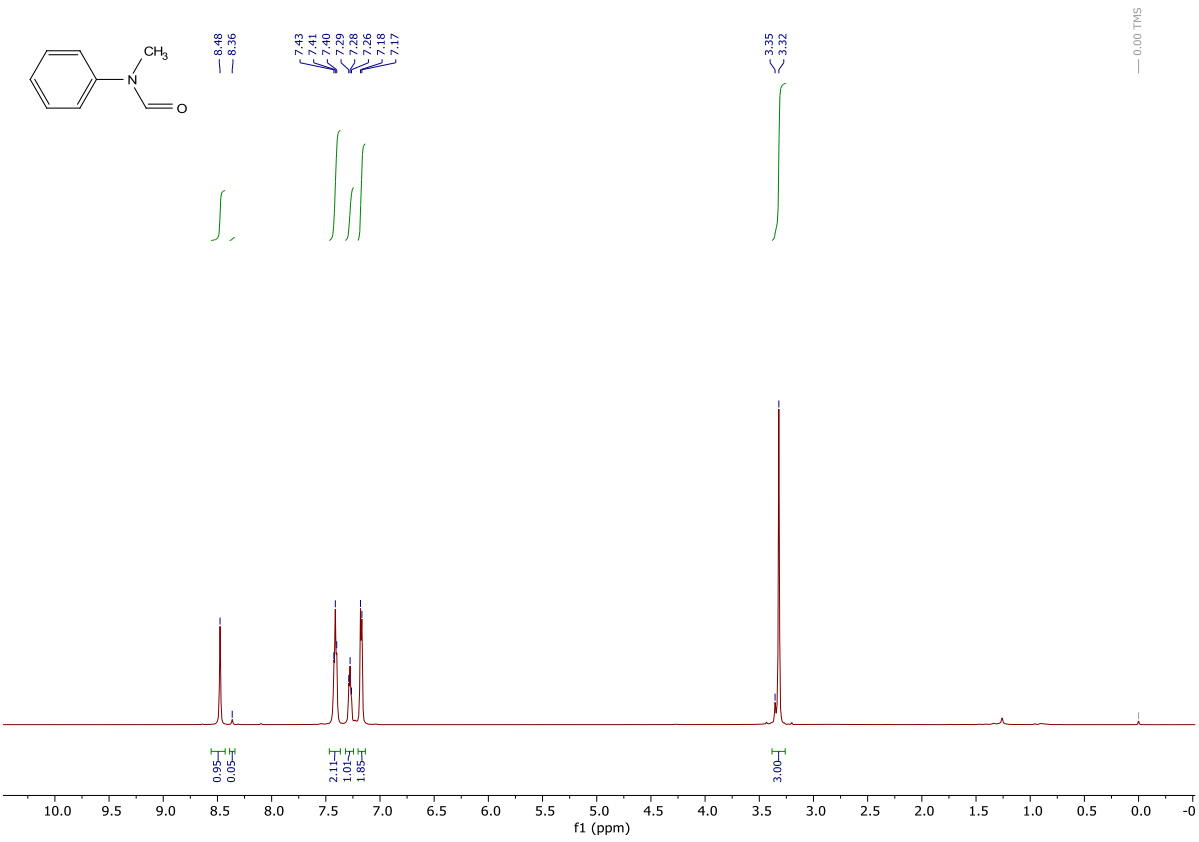
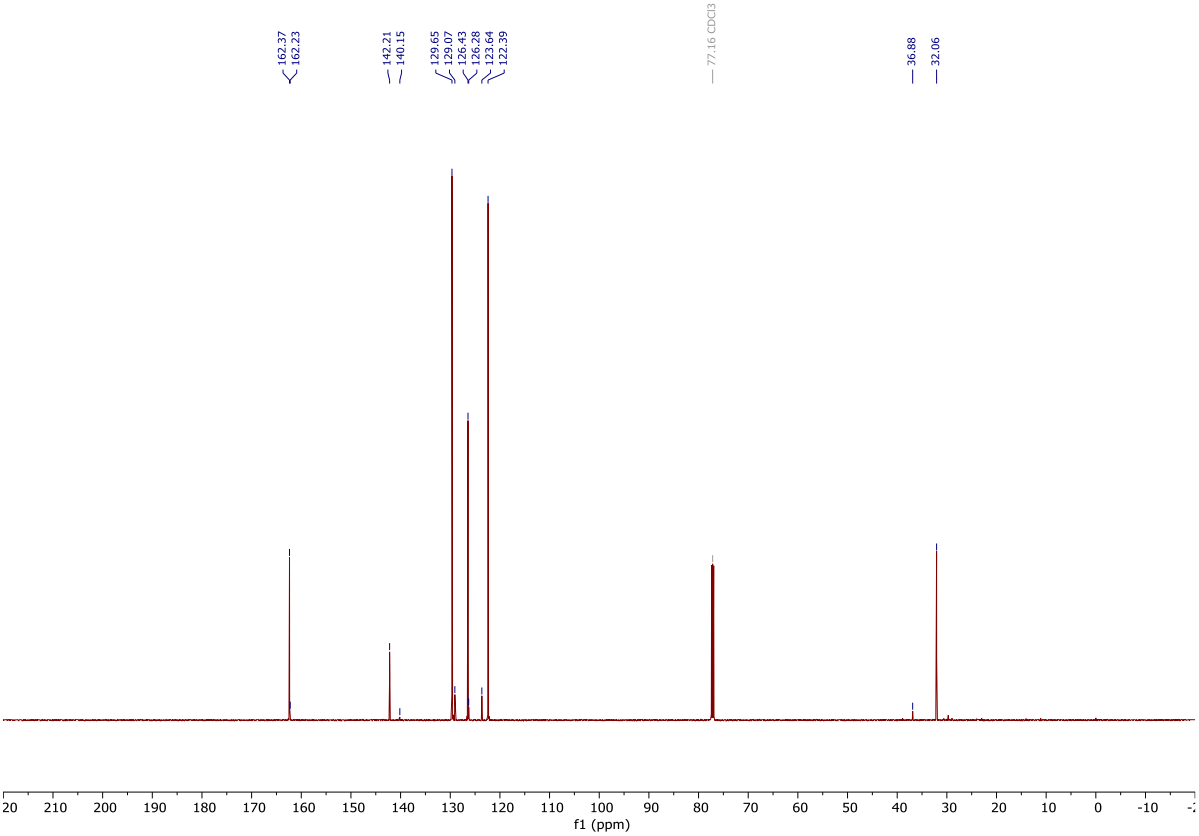
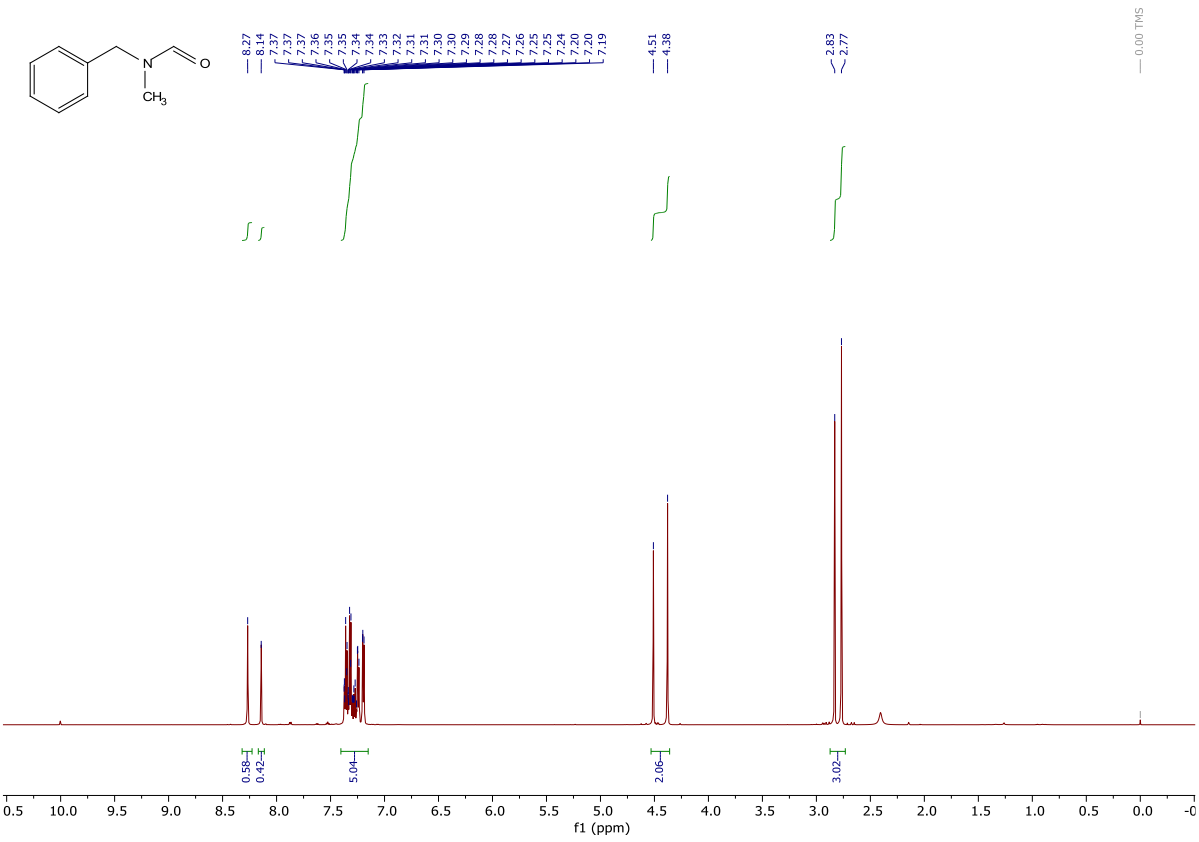
161.29
150.77
150.74
142.86
142.35
110.58
110.55
107.67
107.55
77.16 CDCl3
38.95
35.08
f1 (ppm)


CH3
N
O
8.48
8.36
7.43
7.41
7.40
7.29
7.28
7.26
7.18
7.17
3.35
3.32
0.00 TMS
0.95
0.05
2.11
1.01
1.85
3.00
f1 (ppm)


162.37
162.23
142.21
140.15
129.65
129.07
126.43
126.28
123.64
122.39
77.16 CDCl3
36.88
32.06
f1 (ppm)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7.37
7.37
7.37
7.36
7.35
7.35
7.34
7.34
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7.32
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7.31
7.30
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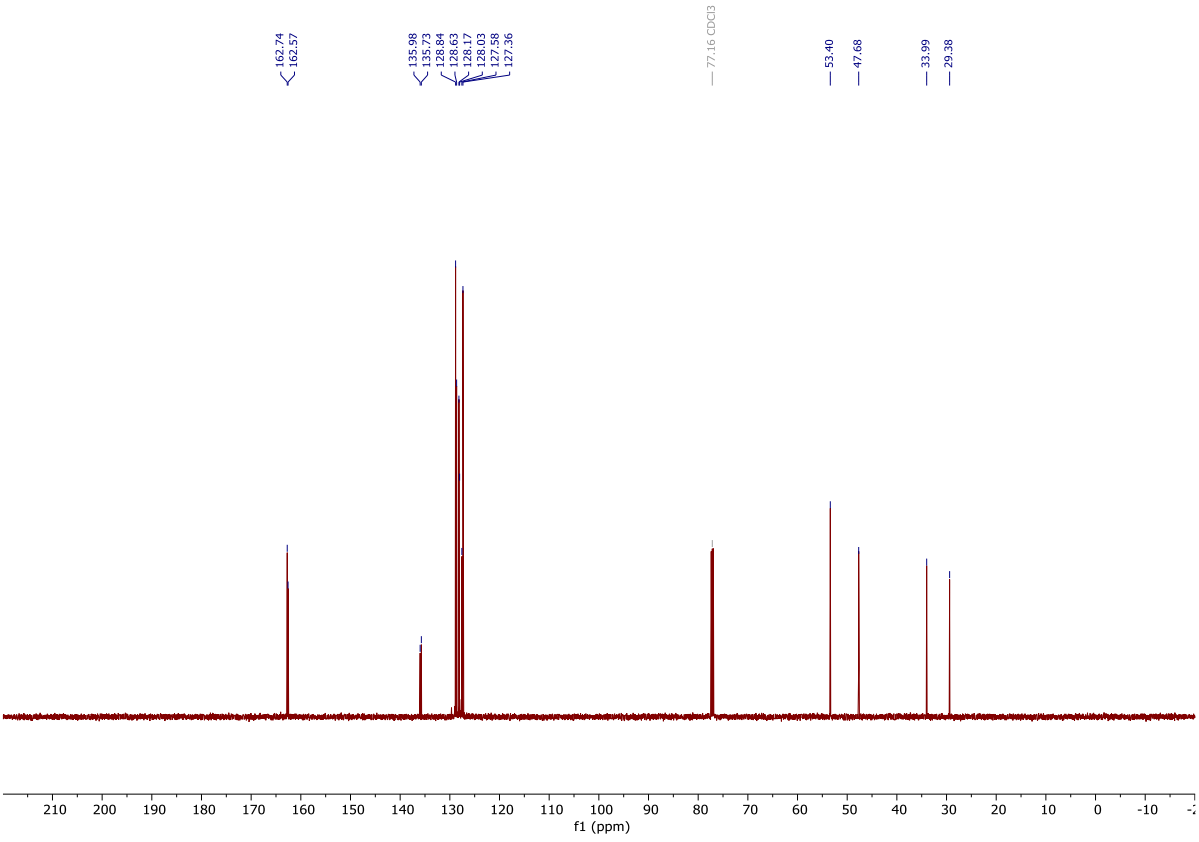
7.28
7.28
7.27
7.26
7.25
7.25
7.24
7.20
7.20
7.19
4.51
4.38
2.83
2.77
0.00 TMS
0.58
0.42
5.04
2.06
3.02
f1 (ppm)


162.74
162.57
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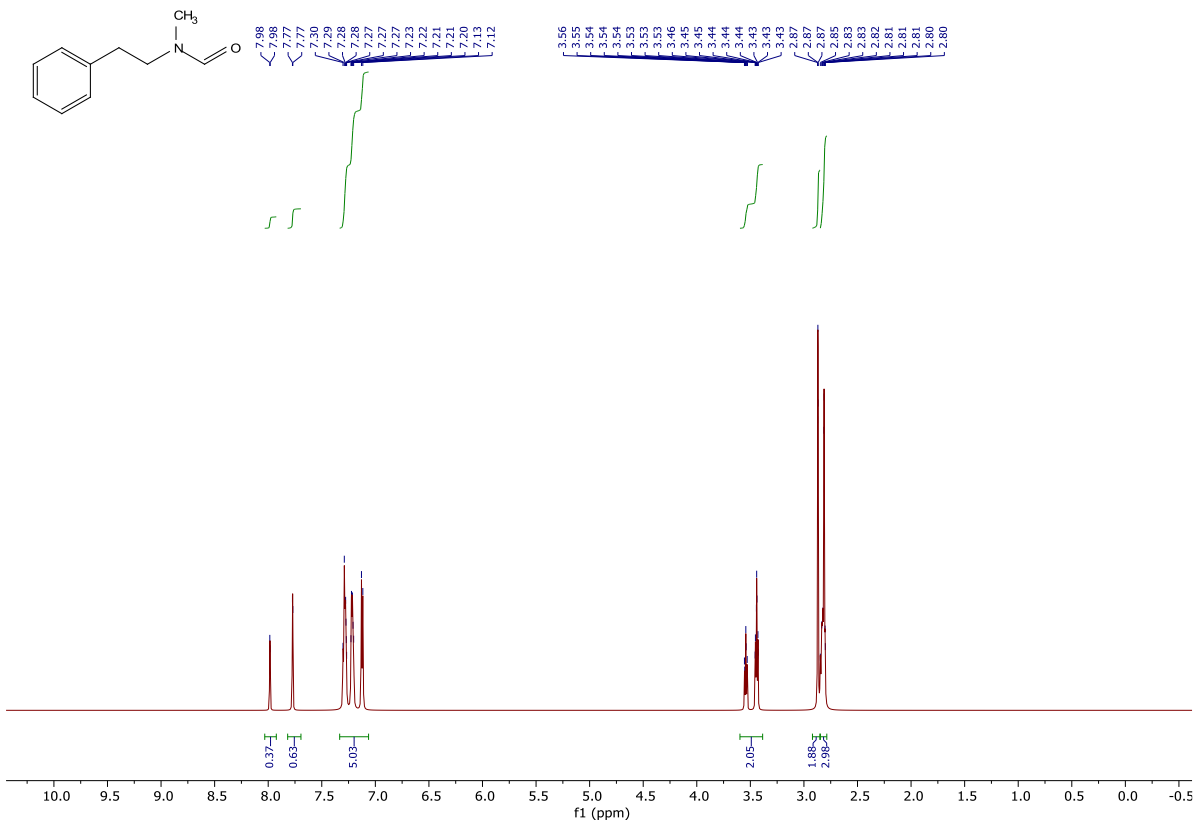
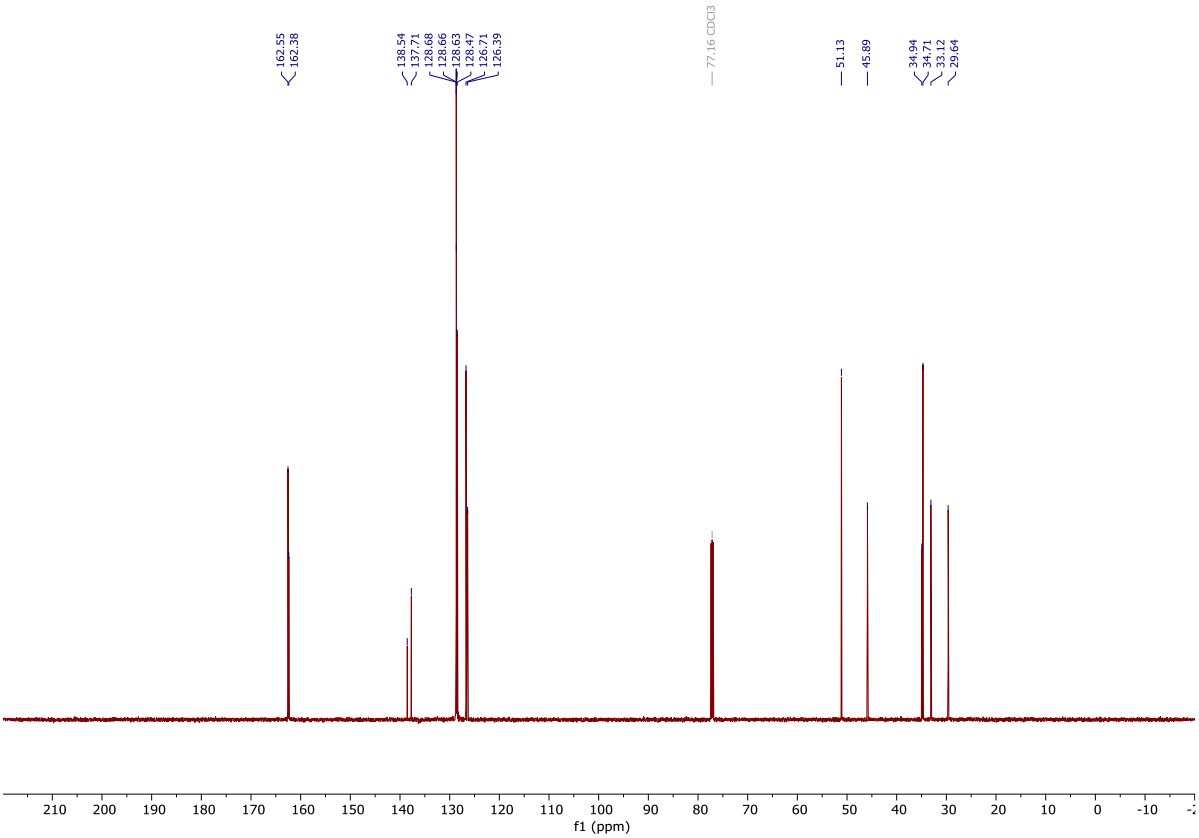
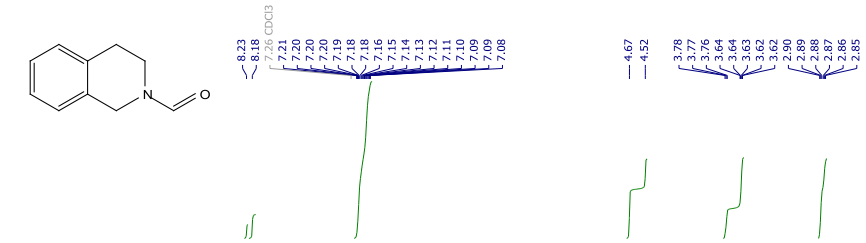
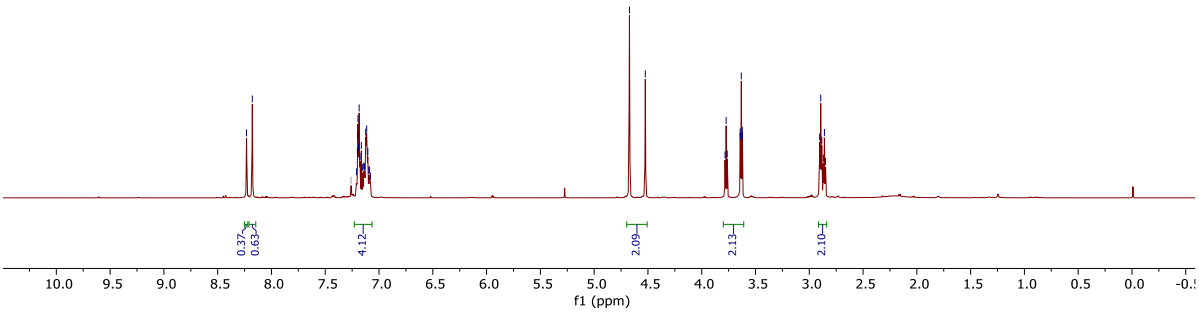
135.73
128.84
128.63
128.17
128.03
127.58
127.36
77.16 CDCl3
53.40
47.68
33.99
29.38
f1 (ppm)

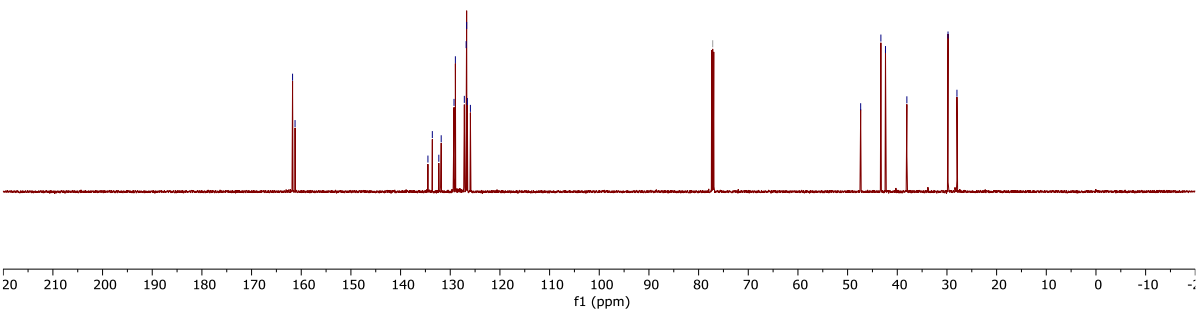

CH3
N
O
7.98
7.98
7.77
7.77
7.30
7.29
7.28
7.28
7.27
7.27
7.27
7.23
7.22
7.21
7.21
7.20
7.13
7.12
3.56
3.55
3.54
3.54
3.54
3.54
3.53
3.53
3.46
3.45
3.45
3.44
3.44
3.44
3.43
3.43
3.43
2.87
2.87
2.87
2.85
2.83
2.83
2.82
2.81
2.81
2.81
2.80
2.80
0.37
0.63
5.03
2.05
1.88
2.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

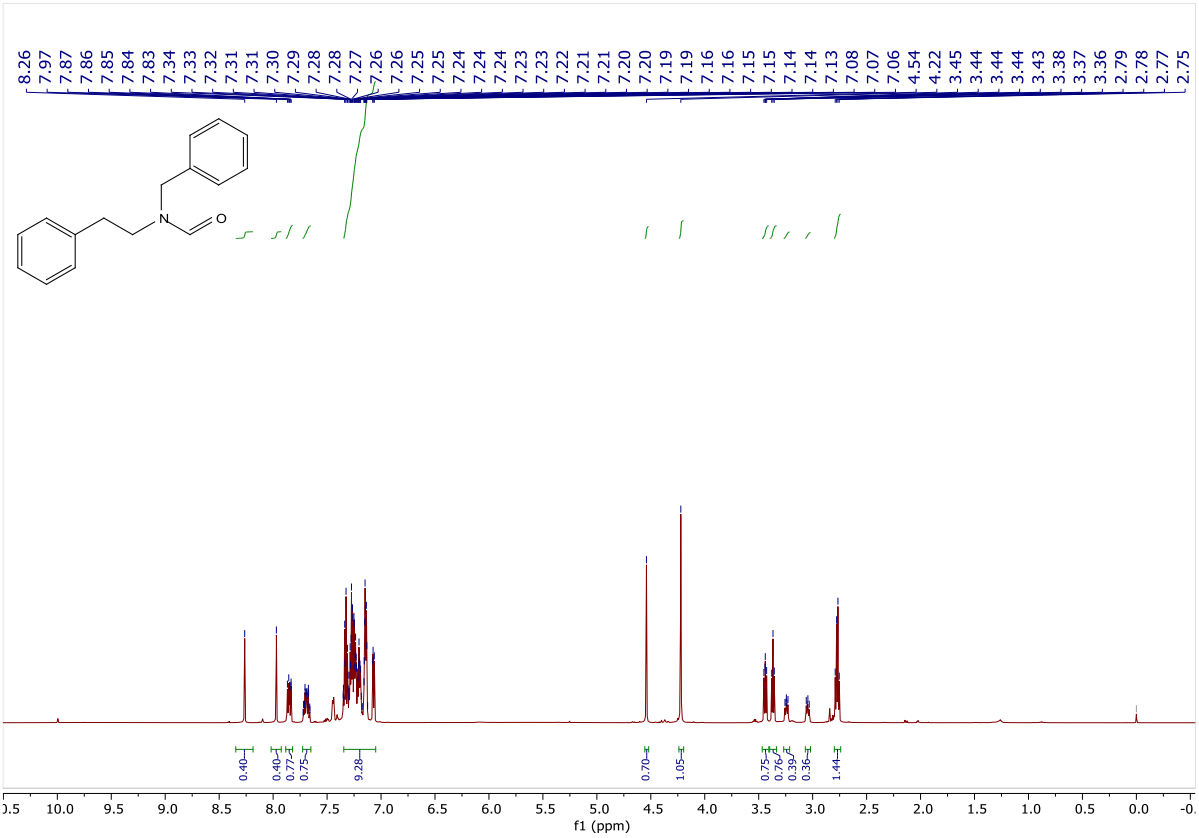

162.55
162.38
138.54
137.71
128.68
128.66
128.63
128.47
126.71
126.39
77.16 CDCl3
51.13
45.89
34.94
34.71
33.12
29.64
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

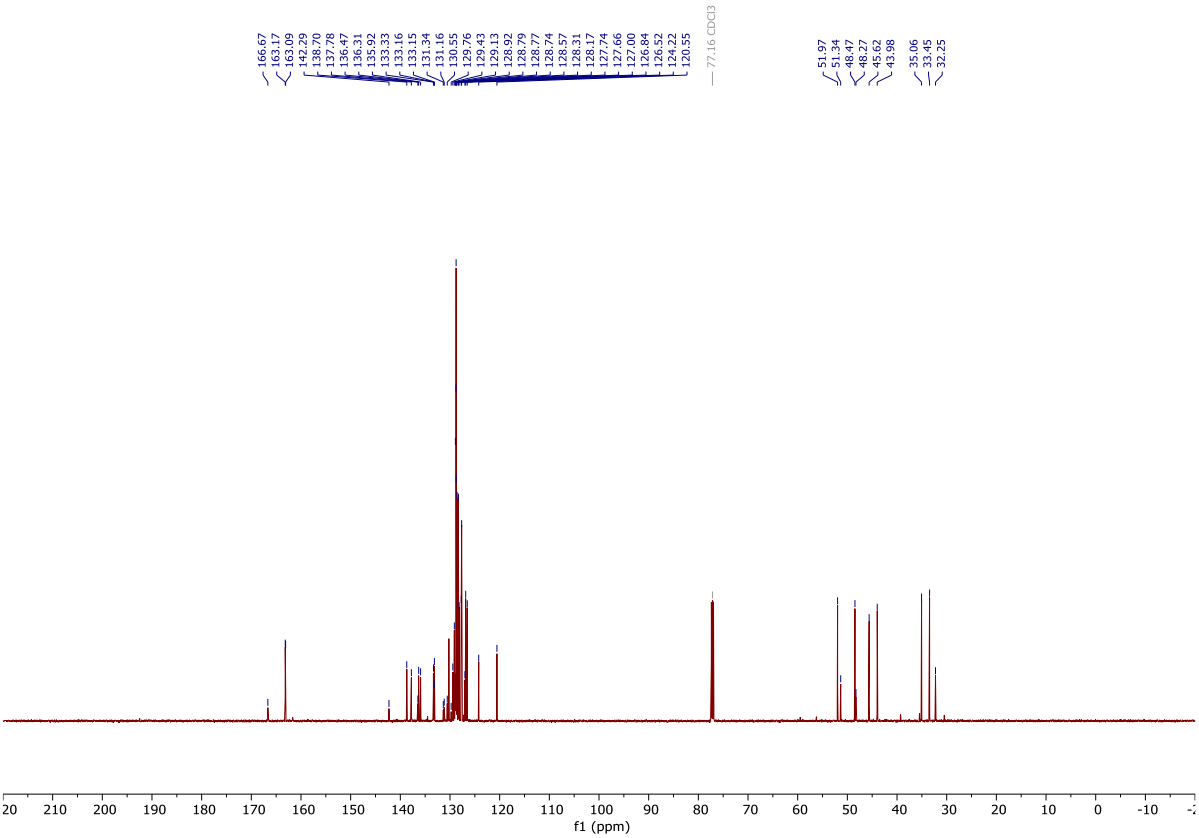

8.23
8.18
7.26 CDCl3
7.21
7.20
7.20
7.20
7.19
7.18
7.18
7.16
7.15
7.14
7.13
7.12
7.11
7.10
7.09
7.09
7.08
4.67
4.52
3.78
3.77
3.76
3.64
3.64
3.63
3.62
3.62
2.90
2.89
2.88
2.87
2.86
2.85

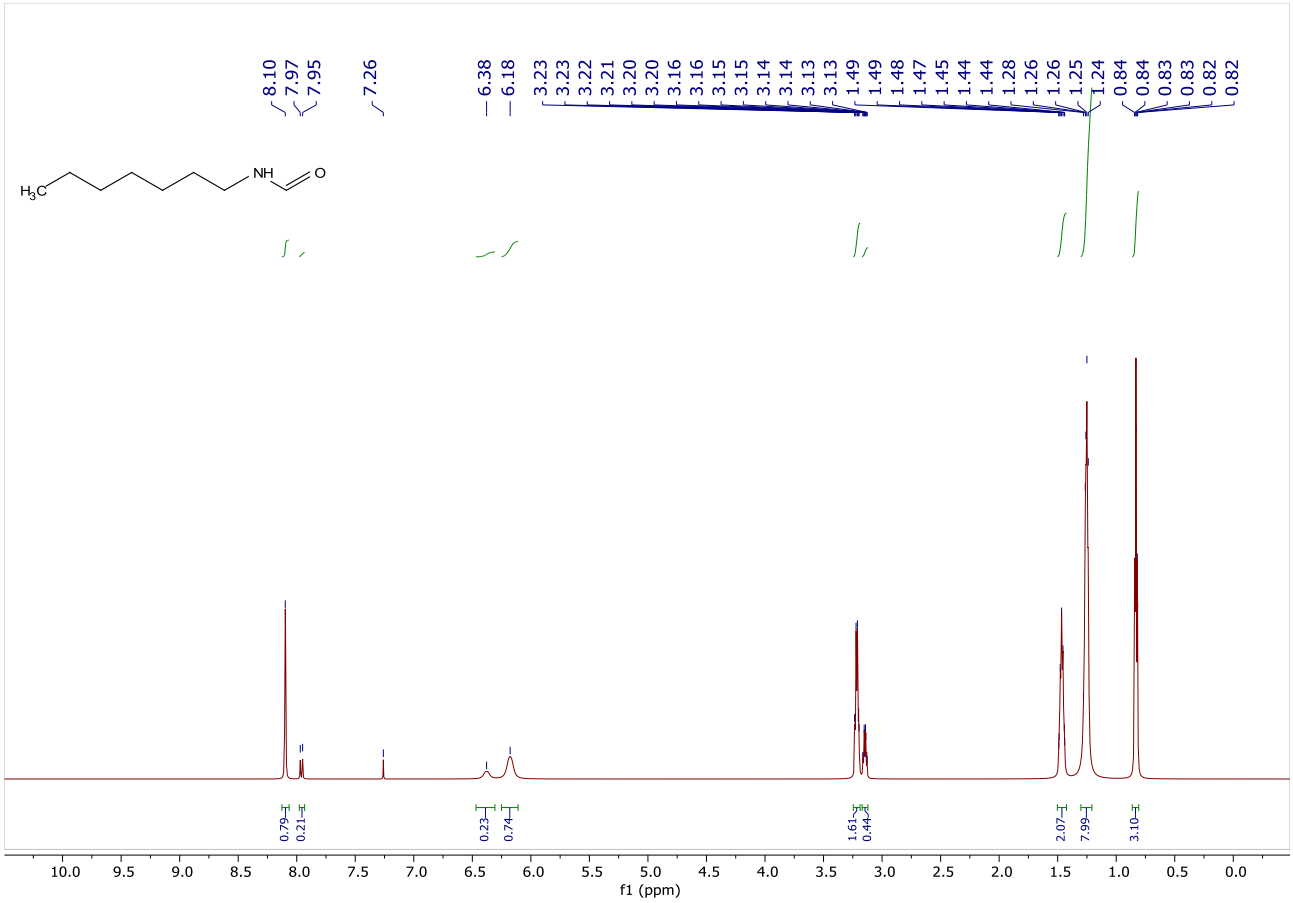

0.37
0.63
4.12
2.09
2.13
2.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

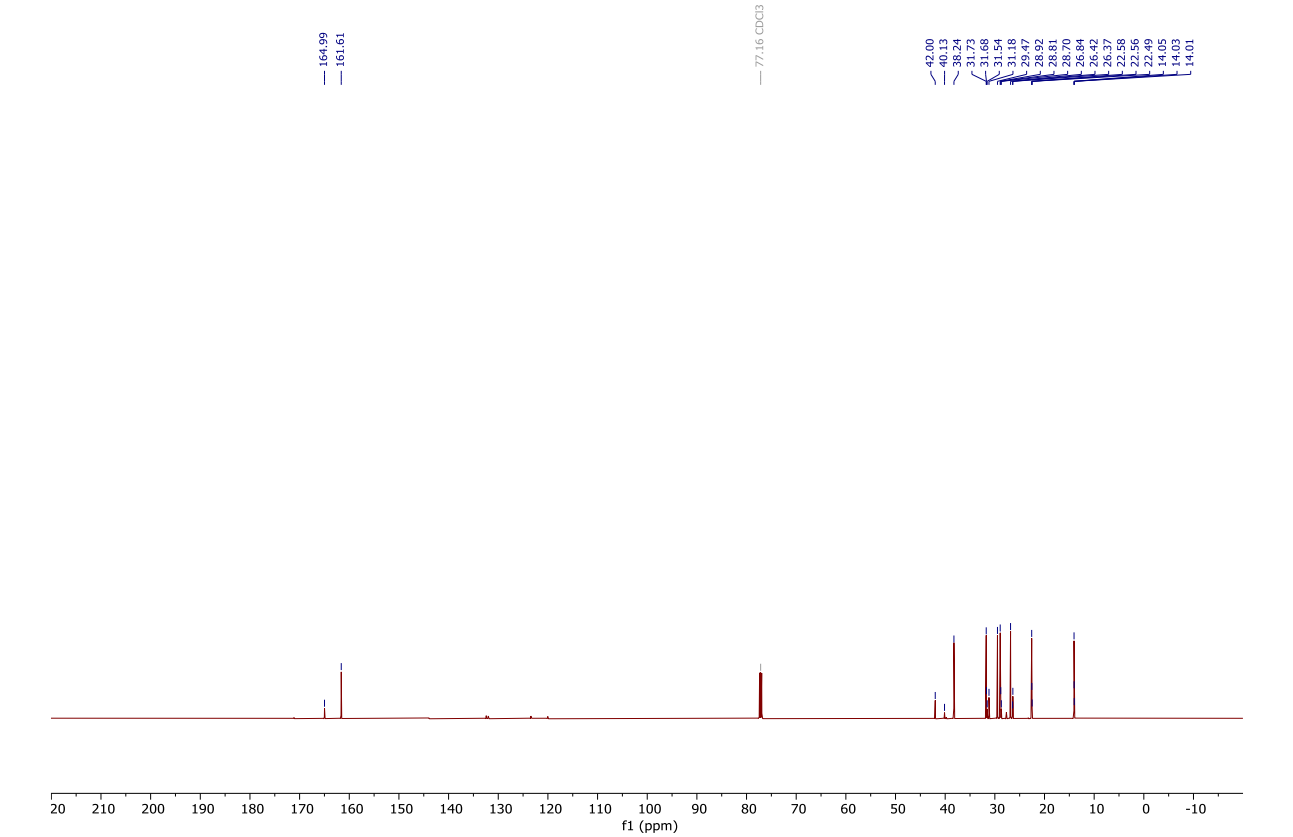

161.75
161.24
134.50
133.61
132.30
131.82
129.24
128.97
127.17
126.80
126.70
126.55
125.94
77.16 CDCl3
47.37
43.30
42.37
38.07
29.78
27.99

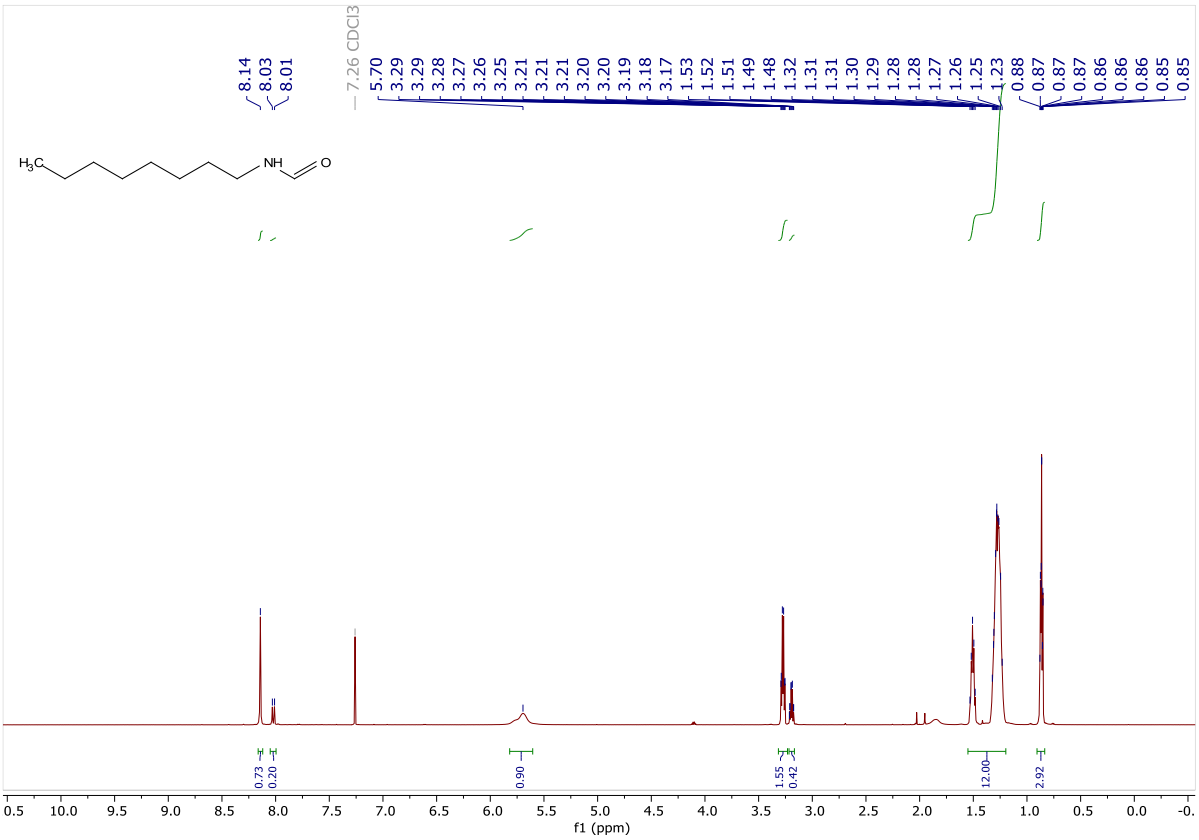

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

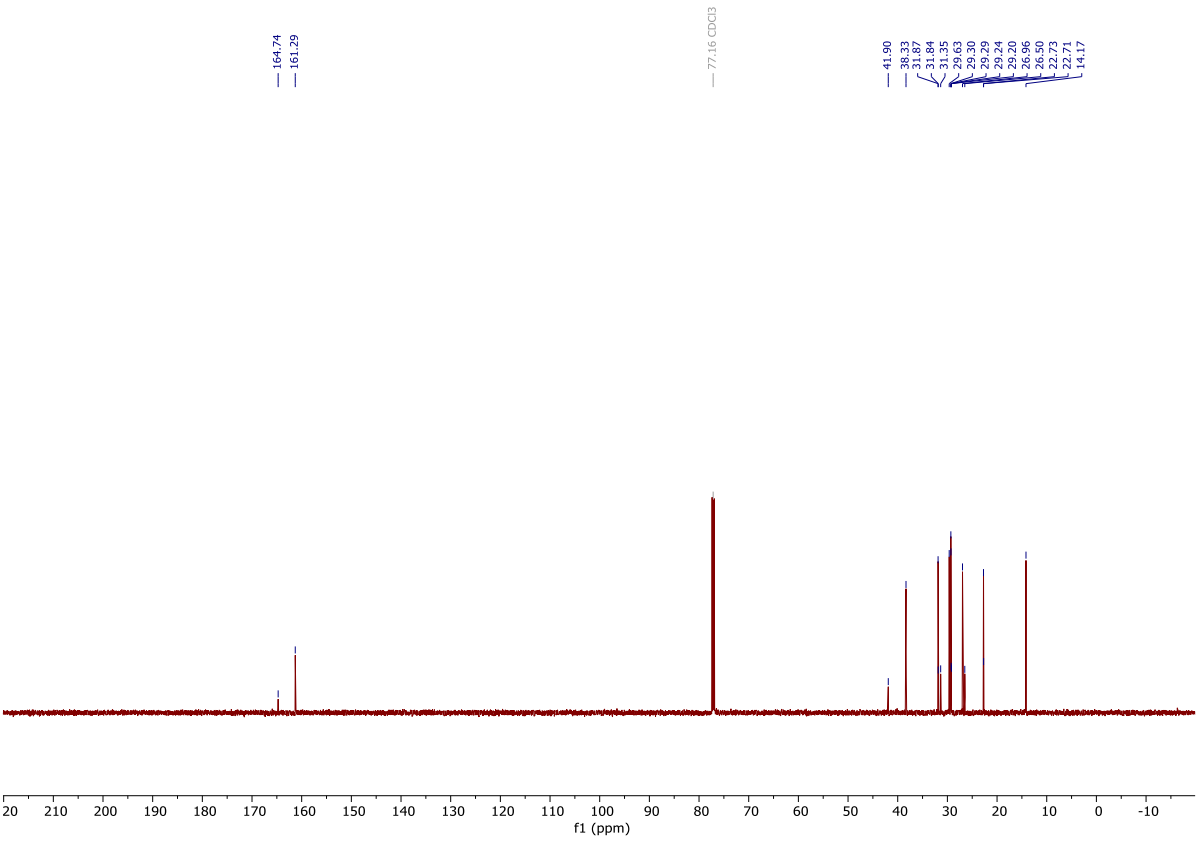

8.26 7.97 7.87 7.86 7.85 7.84 7.83 7.34 7.33 7.32 7.31 7.31 7.30 7.29 7.28 7.28 7.27 7.26 7.26 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.22 7.21 7.21 7.20 7.20 7.19 7.19 7.16 7.16 7.15 7.15 7.14 7.14 7.13 7.08 7.07 7.06 4.54 4.22 3.45 3.44 3.44 3.44 3.43 3.38 3.37 3.36 2.79 2.78 2.77 2.75
N
O
0.40 0.40 0.77 0.75 9.28 0.70 1.05 0.75 0.76 0.39 0.36 1.44
f1 (ppm)

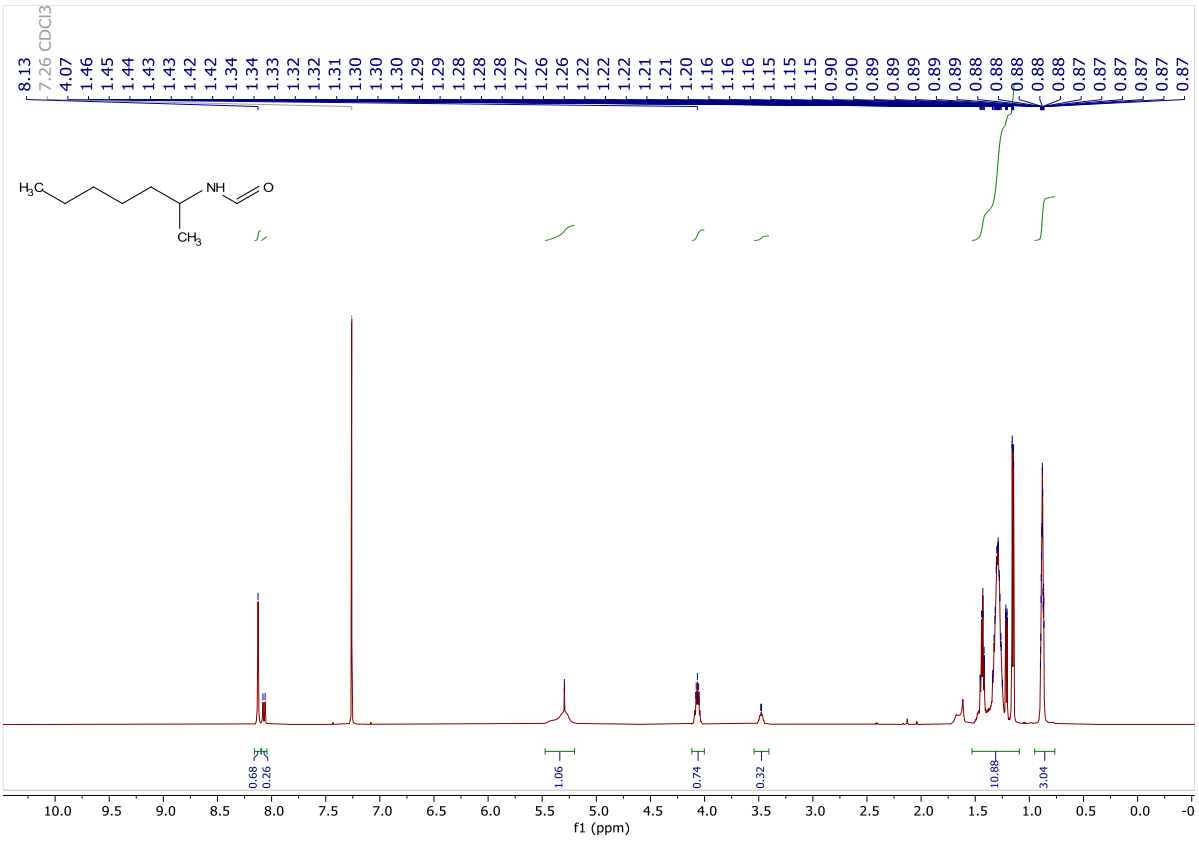

166.67 163.17 163.09 142.29 138.70 137.78 136.47 136.31 135.92 133.33 133.16 133.15 131.34 131.16 130.55 129.76 129.43 129.13 128.92 128.79 128.77 128.74 128.57 128.31 128.17 127.74 127.66 127.00 126.84 126.52 124.22 120.55
77.16 CDCl3
51.97 51.34 48.47 48.27 45.62 43.98 35.06 33.45 32.25
f1 (ppm)

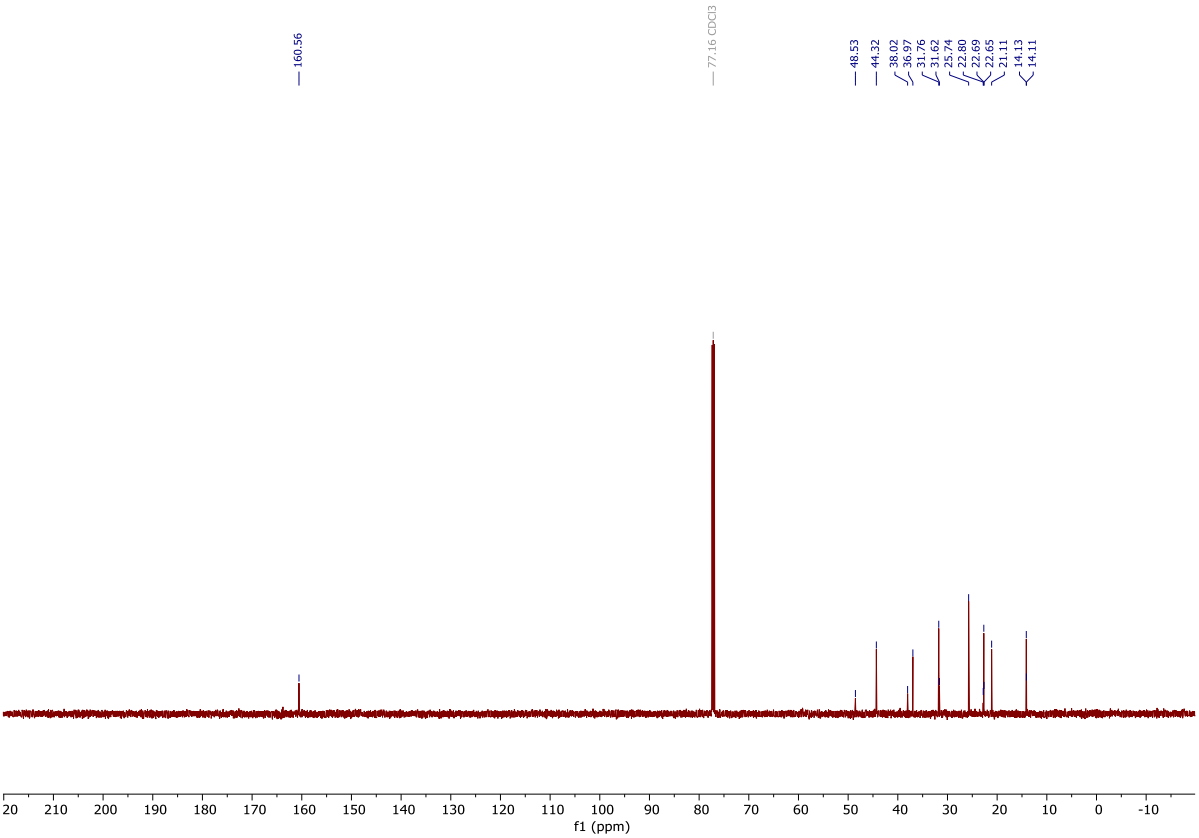

8.10
7.97
7.95
7.26
6.38
6.18
3.23
3.23
3.22
3.21
3.20
3.20
3.16
3.16
3.15
3.15
3.14
3.14
3.13
3.13
1.49
1.49
1.48
1.47
1.45
1.44
1.44
1.28
1.26
1.26
1.25
1.24
0.84
0.84
0.83
0.83
0.82
0.82
NH
O
H3C
0.79
0.21
0.23
0.74
1.61
0.44
2.07
7.99
3.10
f1 (ppm)

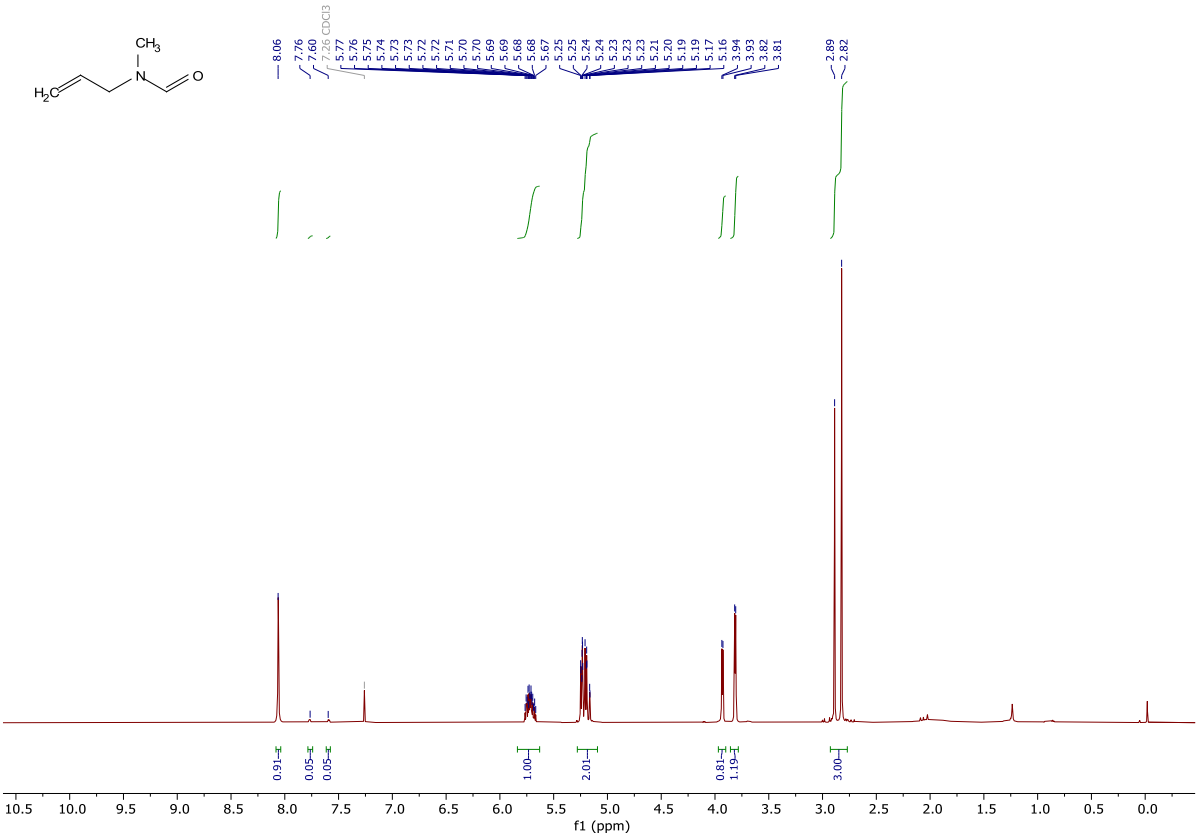

164.99
161.61
77.16 CDCl3
42.00
40.13
38.24
31.73
31.68
31.54
31.18
29.47
28.92
28.81
28.70
26.84
26.42
26.37
22.58
22.56
22.49
14.05
14.03
14.01
f1 (ppm)

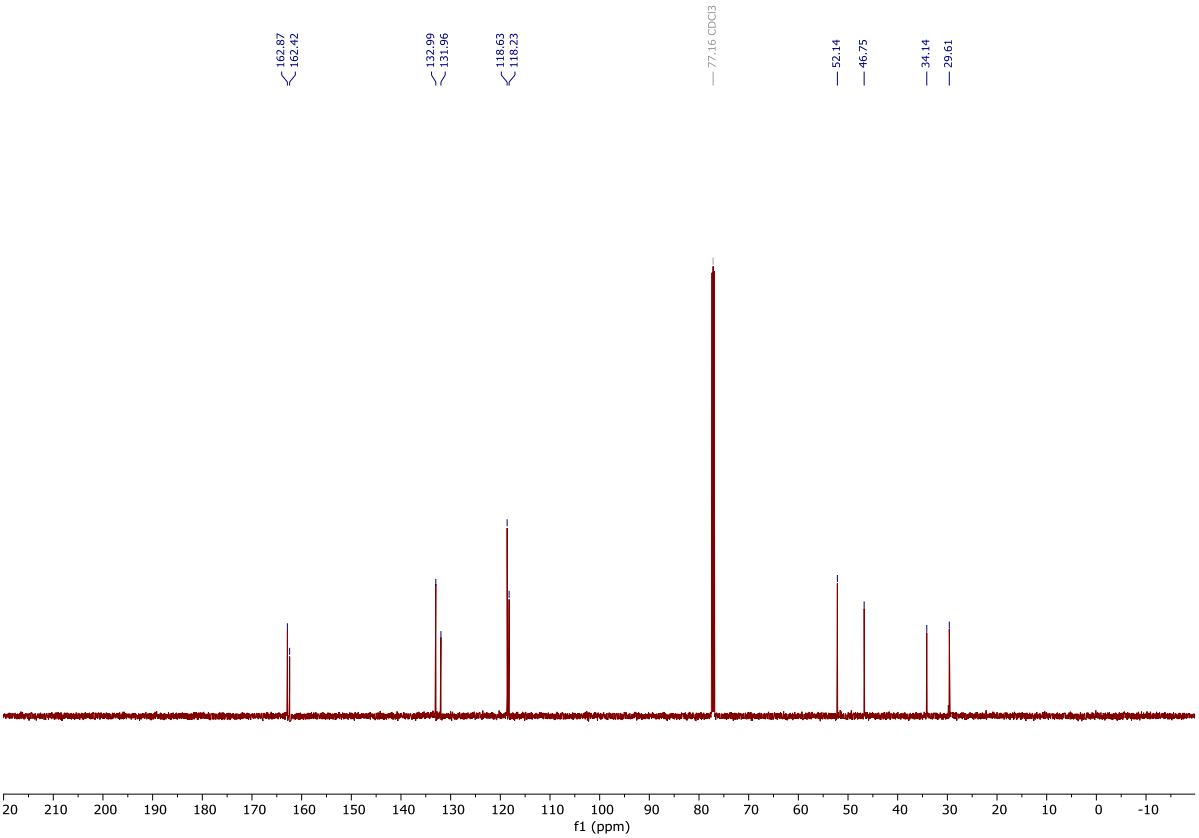

8.14
8.03
8.01
7.26 CDCl3
5.70
3.29
3.29
3.28
3.27
3.26
3.25
3.21
3.21
3.21
3.20
3.20
3.19
3.18
3.17
1.53
1.52
1.51
1.49
1.48
1.32
1.31
1.31
1.30
1.29
1.28
1.28
1.27
1.26
1.25
1.23
0.88
0.87
0.87
0.87
0.86
0.86
0.86
0.85
0.85
H3C
NH
O
0.73
0.20
0.90
1.55
0.42
12.00
2.92
f1 (ppm)

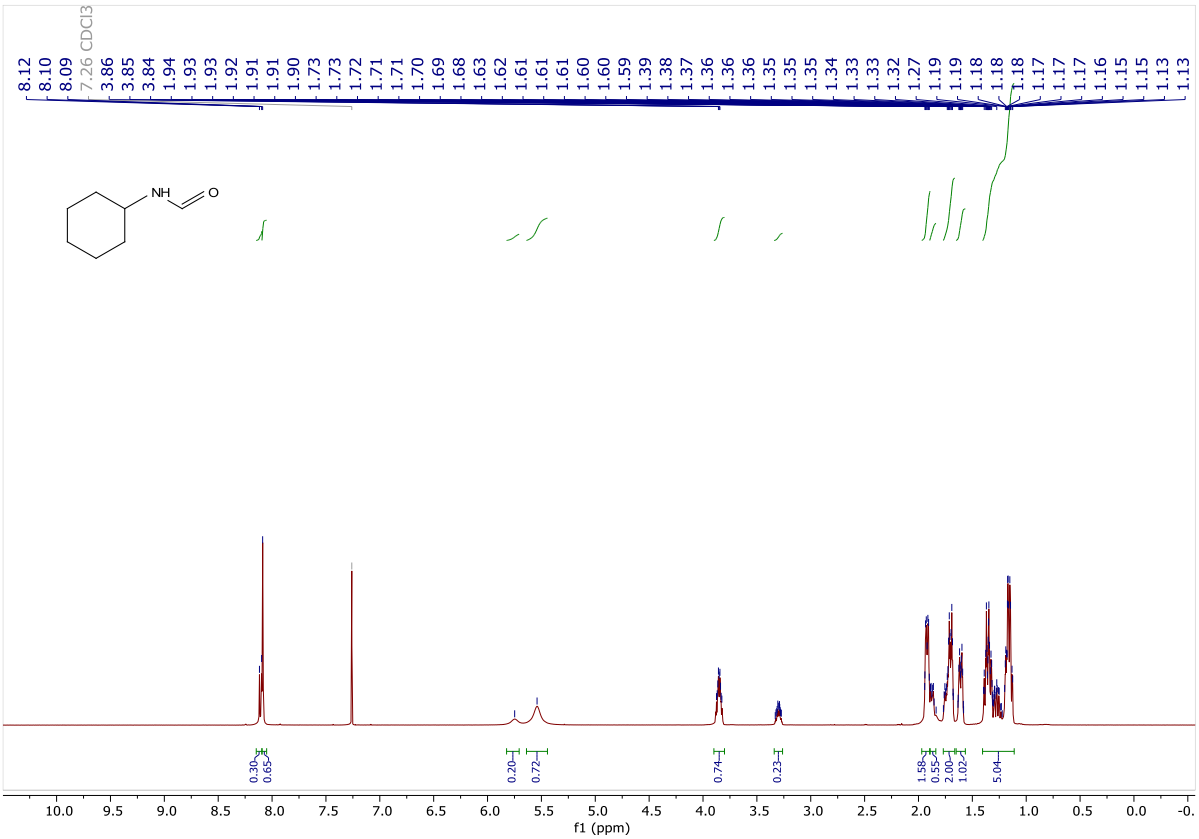

164.74
161.29
77.16 CDCl3
41.90
38.33
31.87
31.84
31.35
29.63
29.30
29.29
29.24
29.20
26.96
26.50
22.73
22.71
14.17
f1 (ppm)

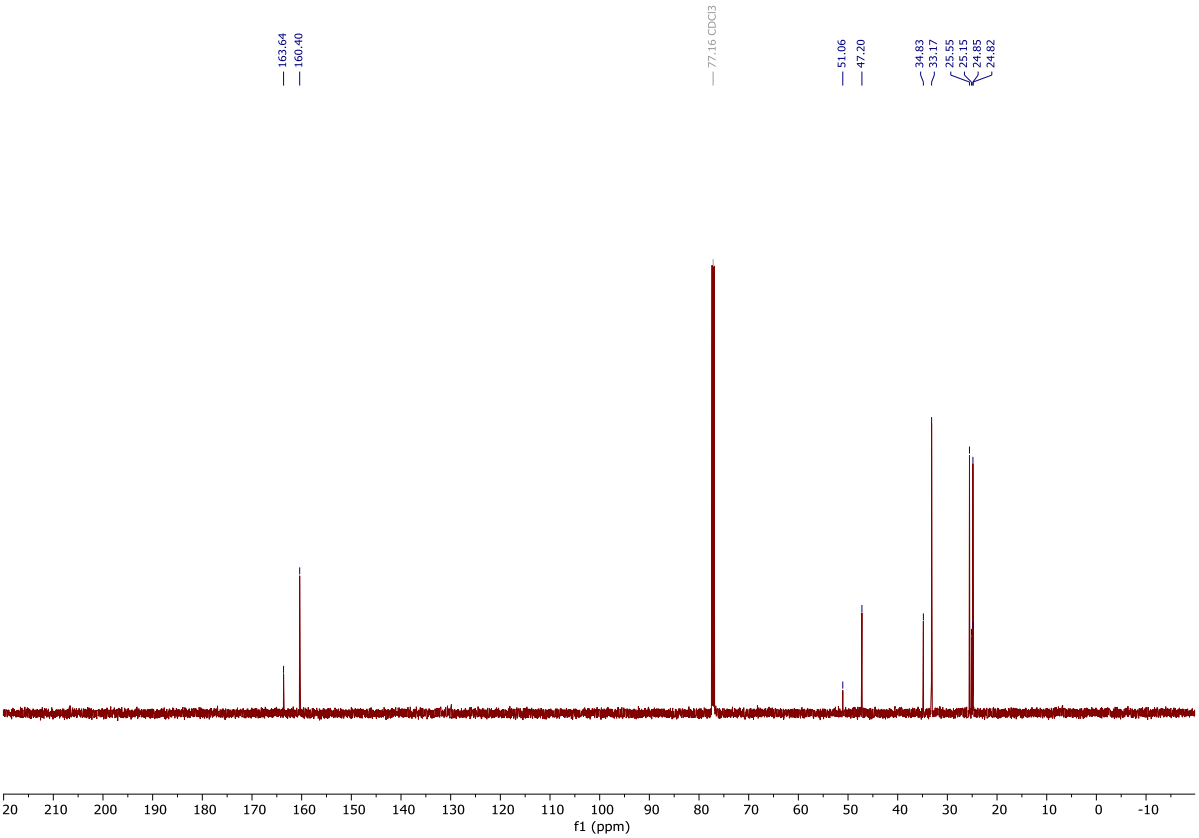

8.13
7.26 CDCl3
4.07
1.46
1.45
1.44
1.43
1.43
1.42
1.42
1.34
1.34
1.33
1.32
1.32
1.31
1.30
1.30
1.30
1.29
1.29
1.28
1.28
1.28
1.27
1.26
1.26
1.22
1.22
1.22
1.21
1.21
1.20
1.16
1.16
1.16
1.15
1.15
1.15
0.90
0.90
0.89
0.89
0.89
0.89
0.89
0.89
0.88
0.88
0.88
0.88
0.88
0.87
0.87
0.87
0.87
0.87
0.87
H3C
NH
O
CH3
0.68
0.26
1.06
0.74
0.32
10.88
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

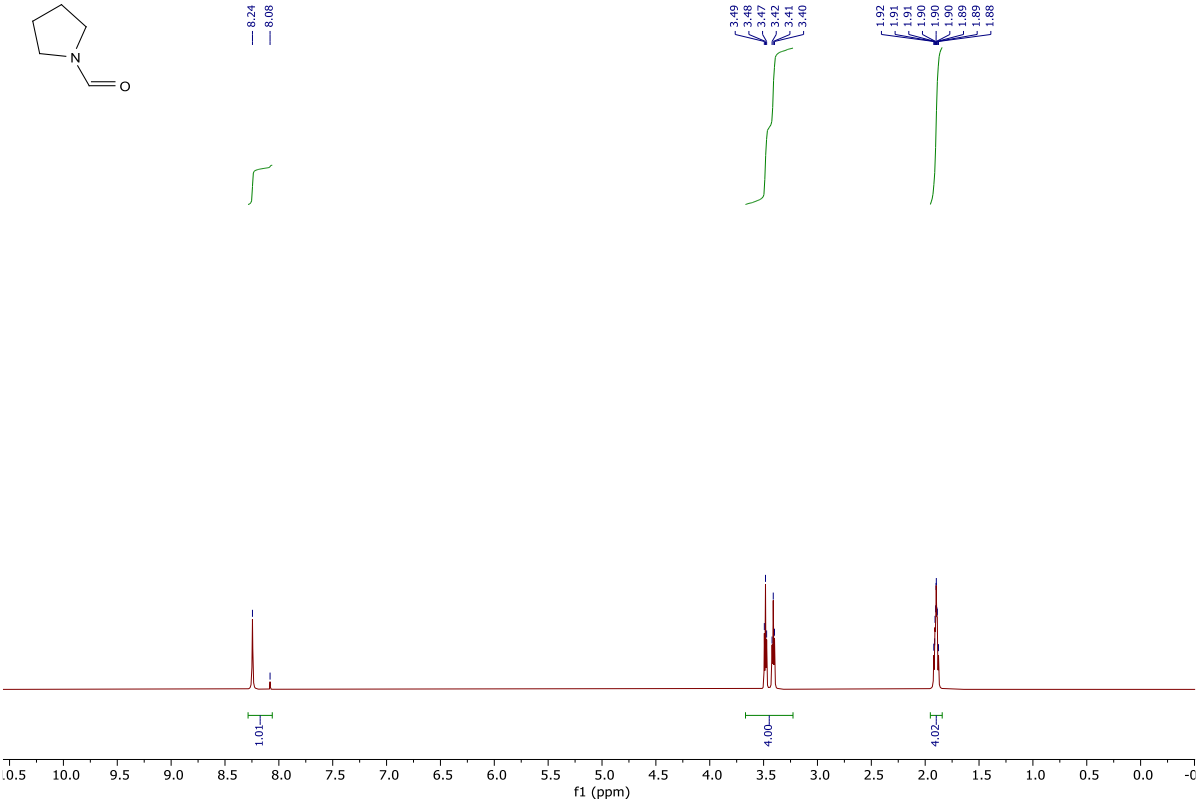

160.56
77.16 CDCl3
48.53
44.32
38.02
36.97
31.76
31.62
25.74
22.80
22.69
22.65
21.11
14.13
14.11
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CH3
N
O
H2C
8.06
7.76
7.60
7.26 CDCl3
5.77
5.76
5.75
5.74
5.73
5.73
5.72
5.72
5.71
5.70
5.70
5.69
5.69
5.68
5.68
5.67
5.25
5.25
5.24
5.24
5.23
5.23
5.23
5.21
5.20
5.19
5.19
5.17
5.16
3.94
3.93
3.82
3.81
2.89
2.82
0.91
0.05
0.05
1.00
2.01
0.81
1.19
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


162.87
162.42
132.99
131.96
118.63
118.23
77.16 CDCl3
52.14
46.75
34.14
29.61
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.12
8.10
8.09
7.26 CDCl3
3.86
3.85
3.84
1.94
1.93
1.93
1.92
1.91
1.91
1.90
1.73
1.73
1.72
1.71
1.71
1.70
1.69
1.68
1.63
1.62
1.61
1.61
1.61
1.60
1.60
1.59
1.39
1.38
1.37
1.36
1.36
1.36
1.35
1.35
1.35
1.34
1.33
1.33
1.32
1.27
1.19
1.19
1.18
1.18
1.18
1.17
1.17
1.17
1.16
1.15
1.15
1.13
1.13
NH
O
0.30
0.65
0.20
0.72
0.74
0.23
1.58
0.55
2.00
1.02
5.04
f1 (ppm)


163.64
160.40
77.16 CDCl3
51.06
47.20
34.83
33.17
25.55
25.15
24.85
24.82
f1 (ppm)


8.24
8.08
3.49
3.48
3.47
3.42
3.41
3.40
1.92
1.91
1.91
1.90
1.90
1.90
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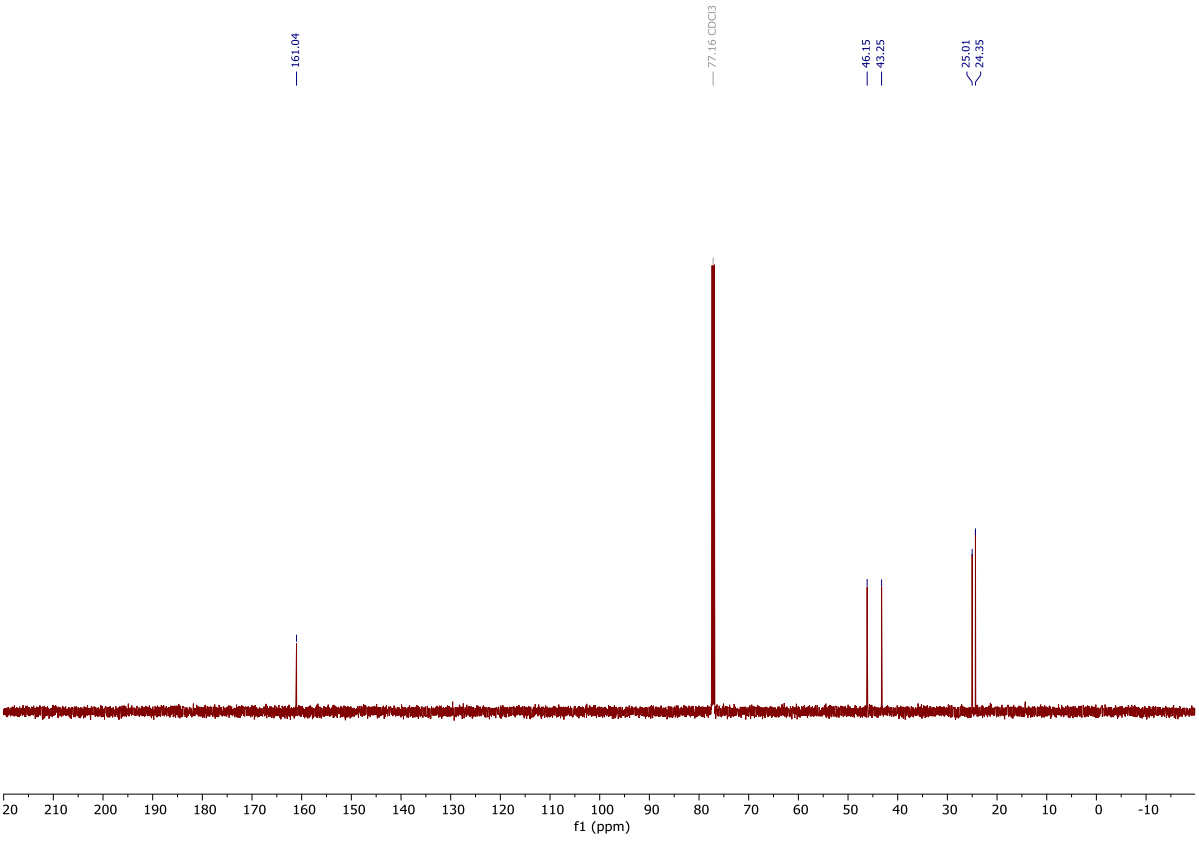
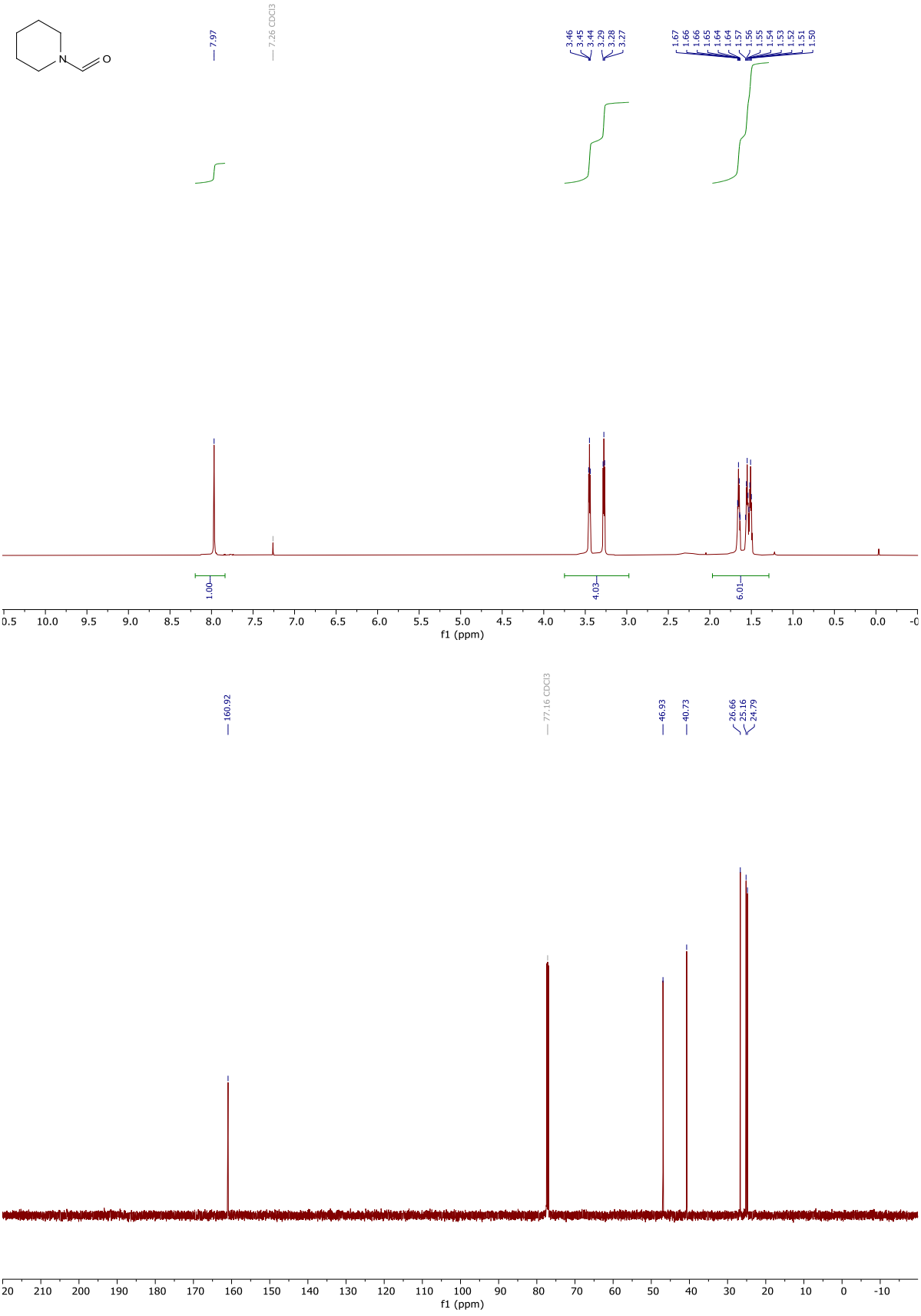
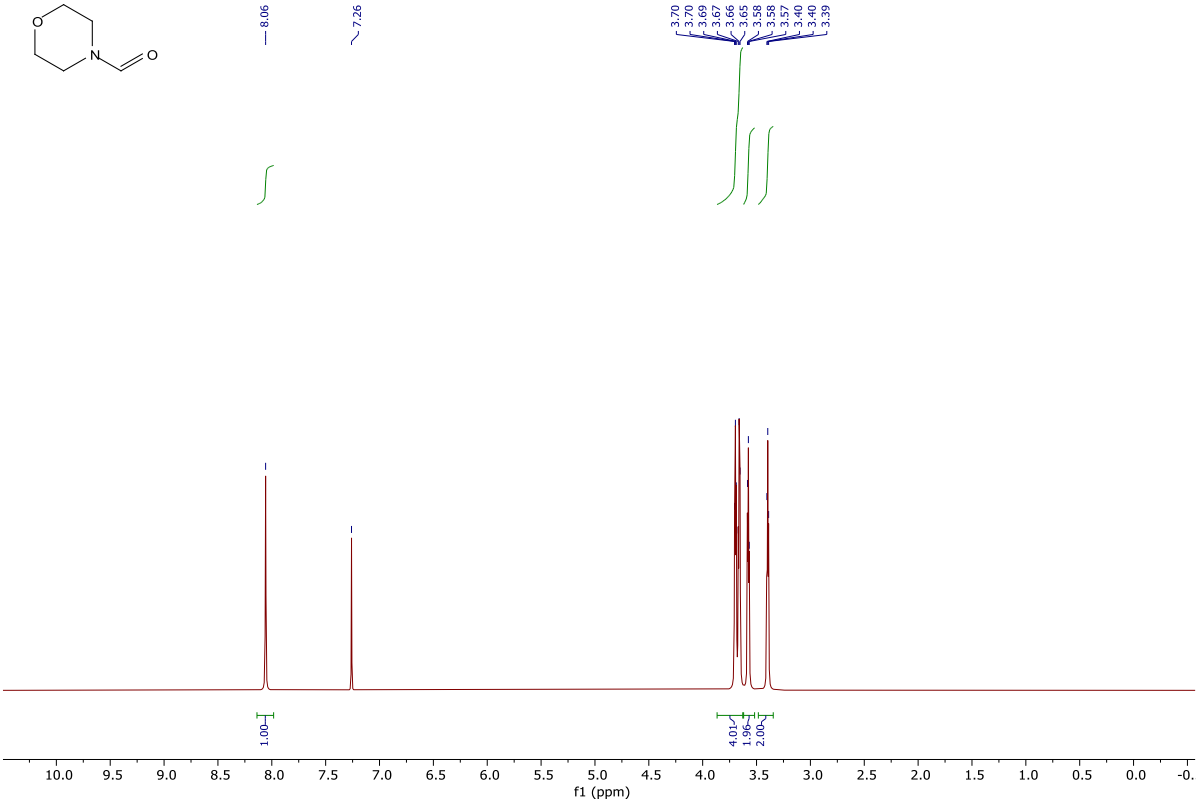
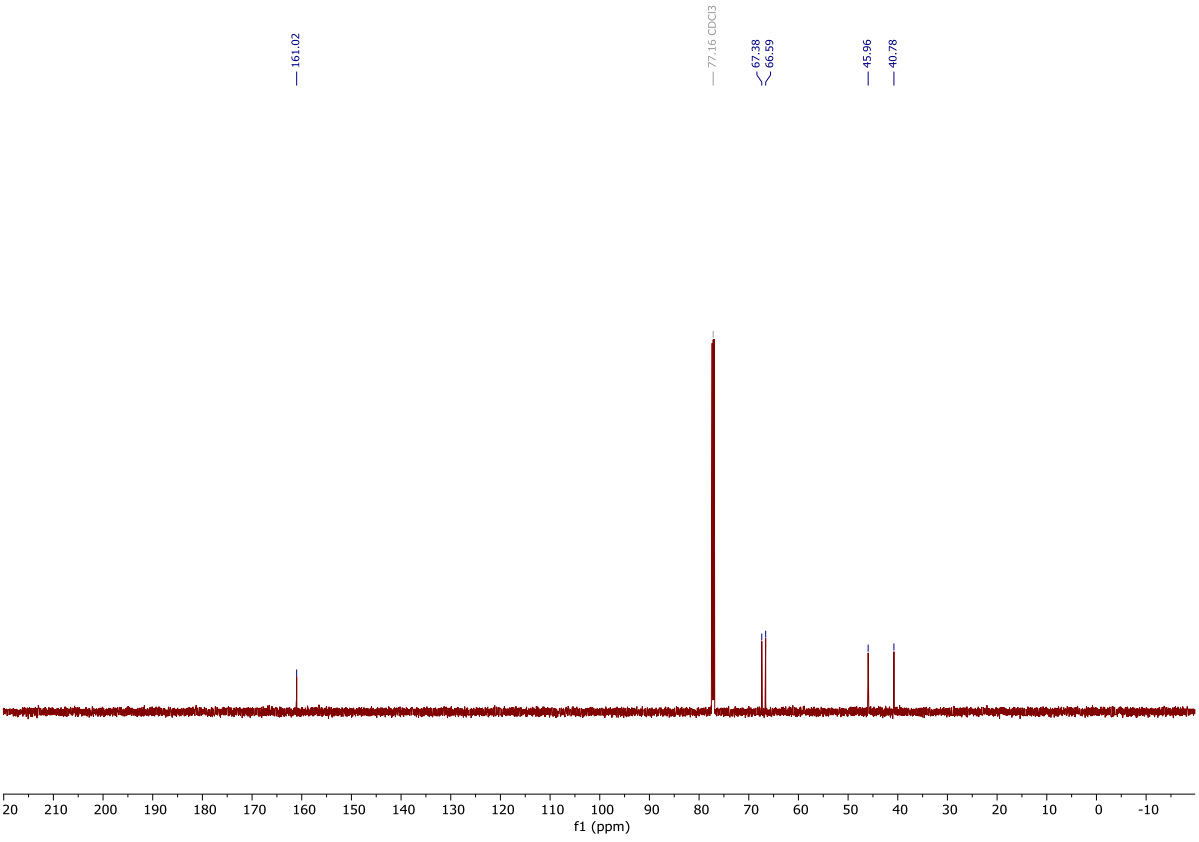
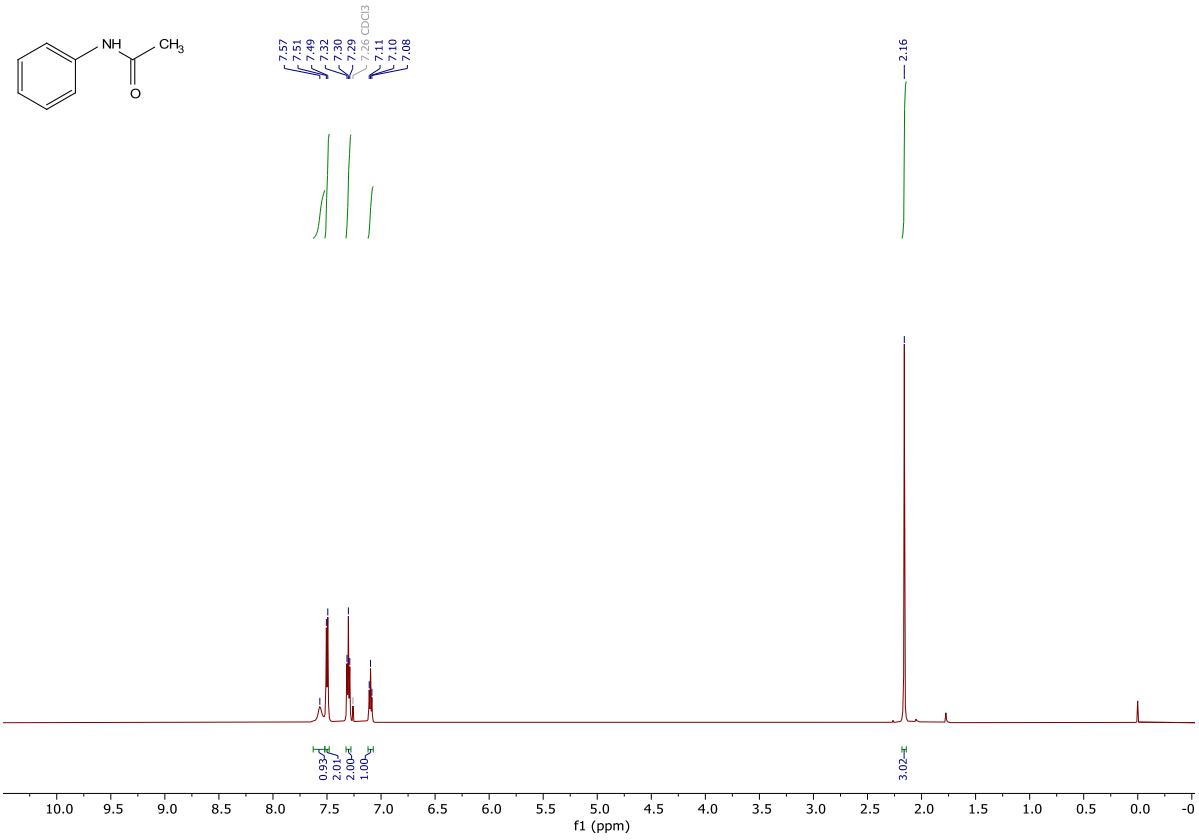
1.89
1.88
1.01
4.00
4.02
f1 (ppm)

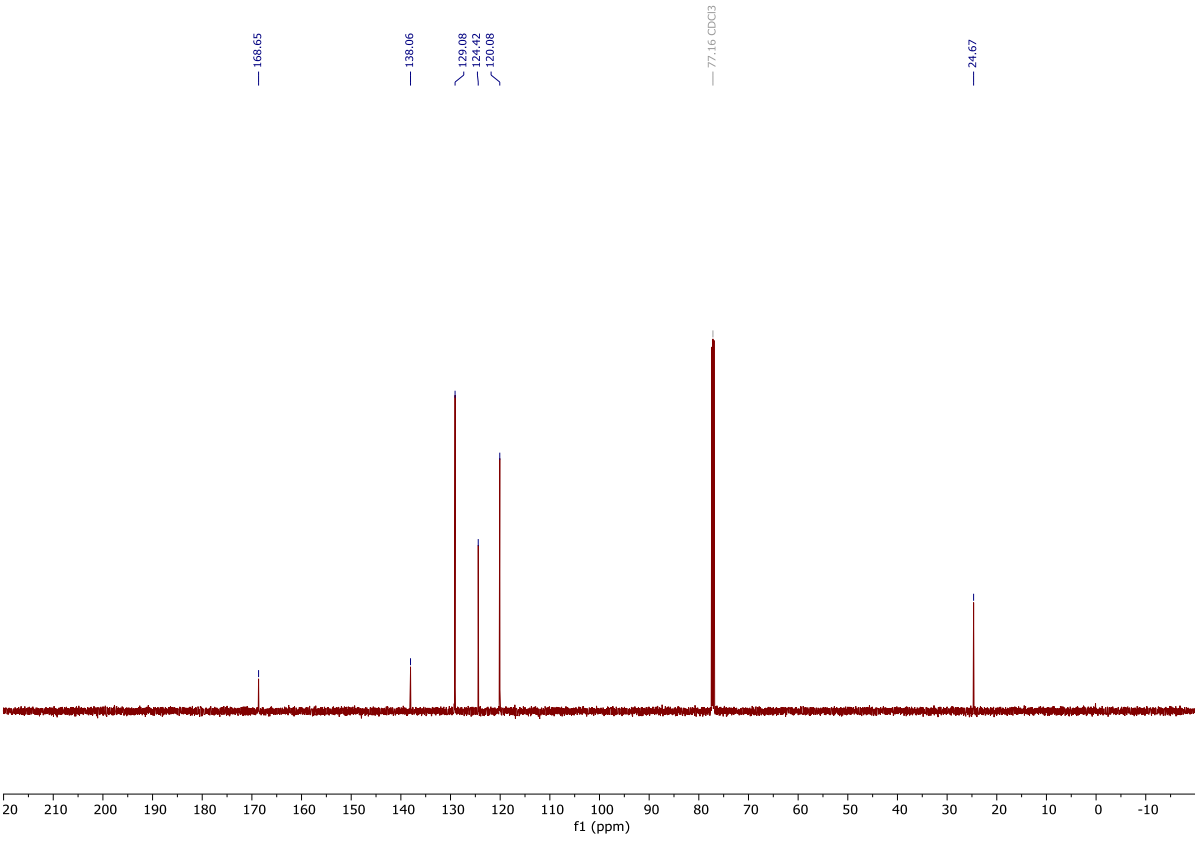

161.04
77.16 CDCl3
46.15
43.25
25.01
24.35
f1 (ppm)

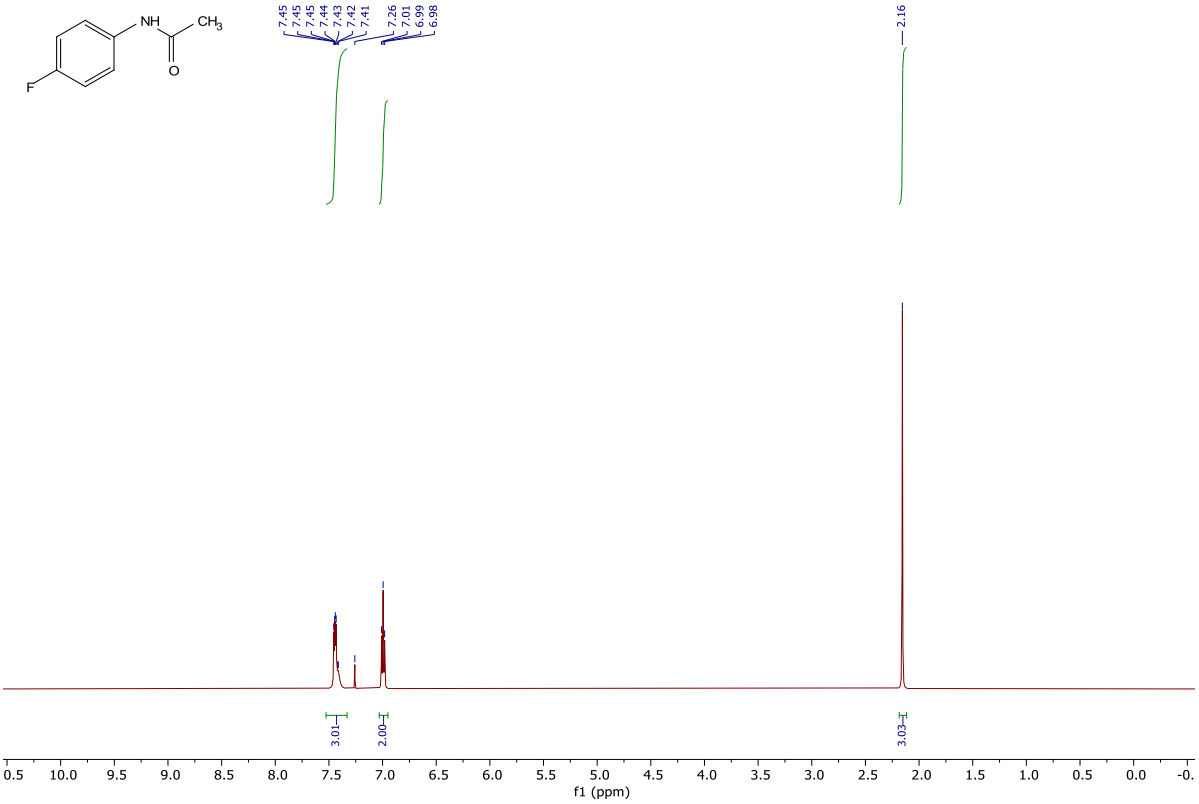

7.97
7.26 CDCl3
3.46
3.45
3.44
3.29
3.28
3.27
1.67
1.66
1.66
1.65
1.64
1.64
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.00
4.03
6.01
f1 (ppm)
160.92
77.16 CDCl3
46.93
40.73
26.66
25.16
24.79
f1 (ppm)

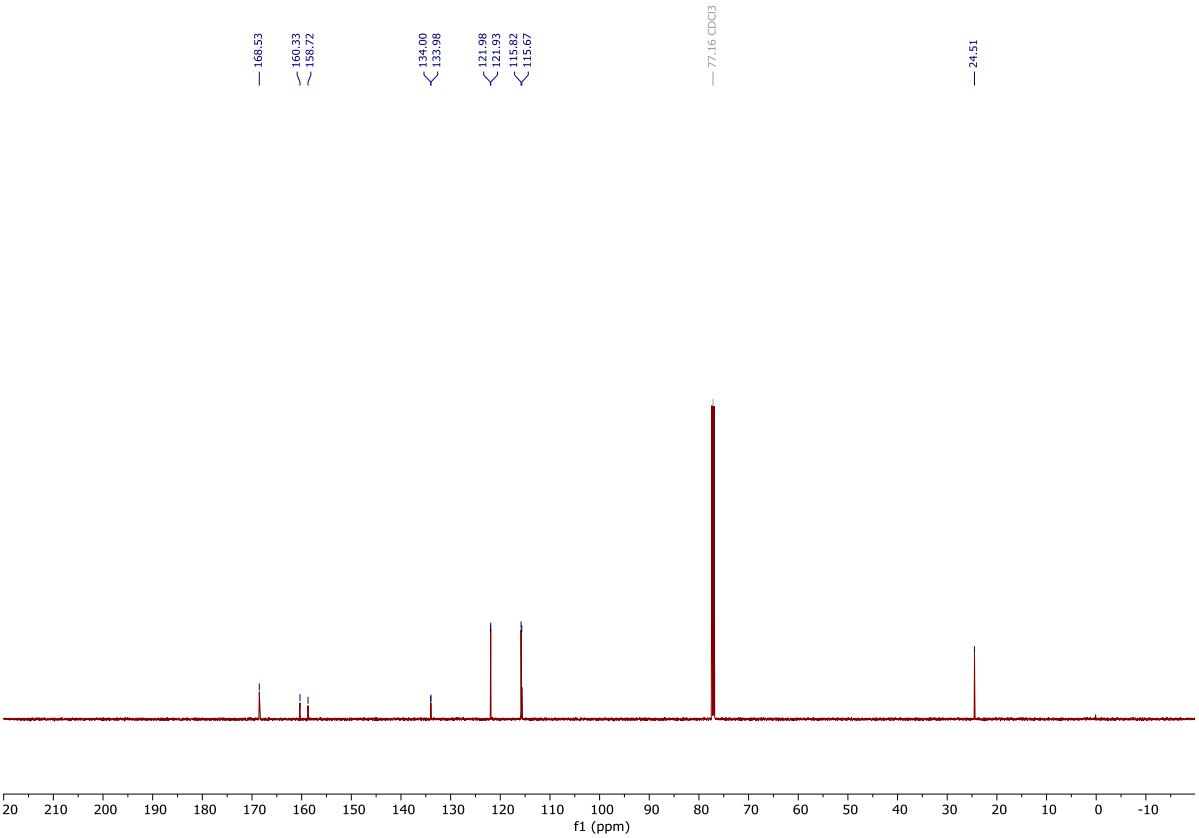

8.06
7.26
3.70
3.70
3.69
3.67
3.66
3.65
3.58
3.58
3.57
3.40
3.40
3.39
1.00
4.01
1.96
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

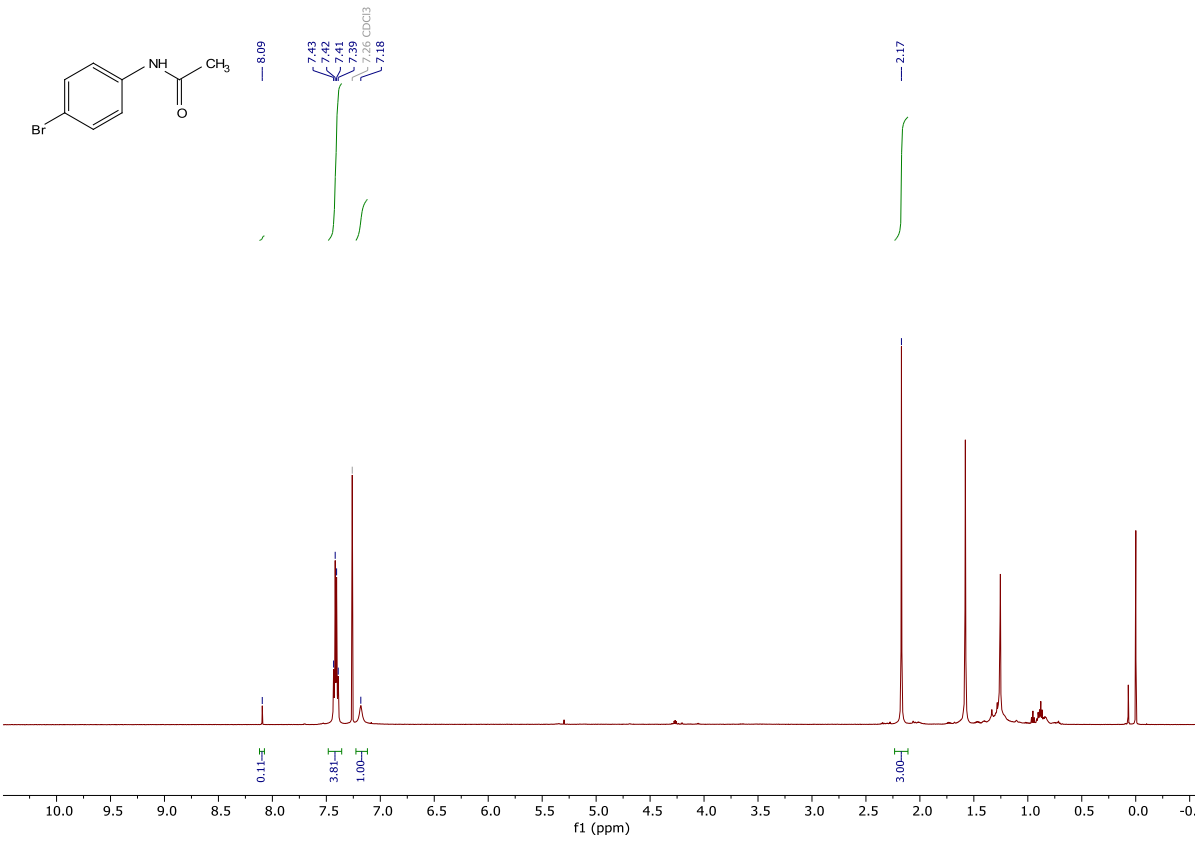

161.02
77.16 CDCl3
67.38
66.59
45.96
40.78
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

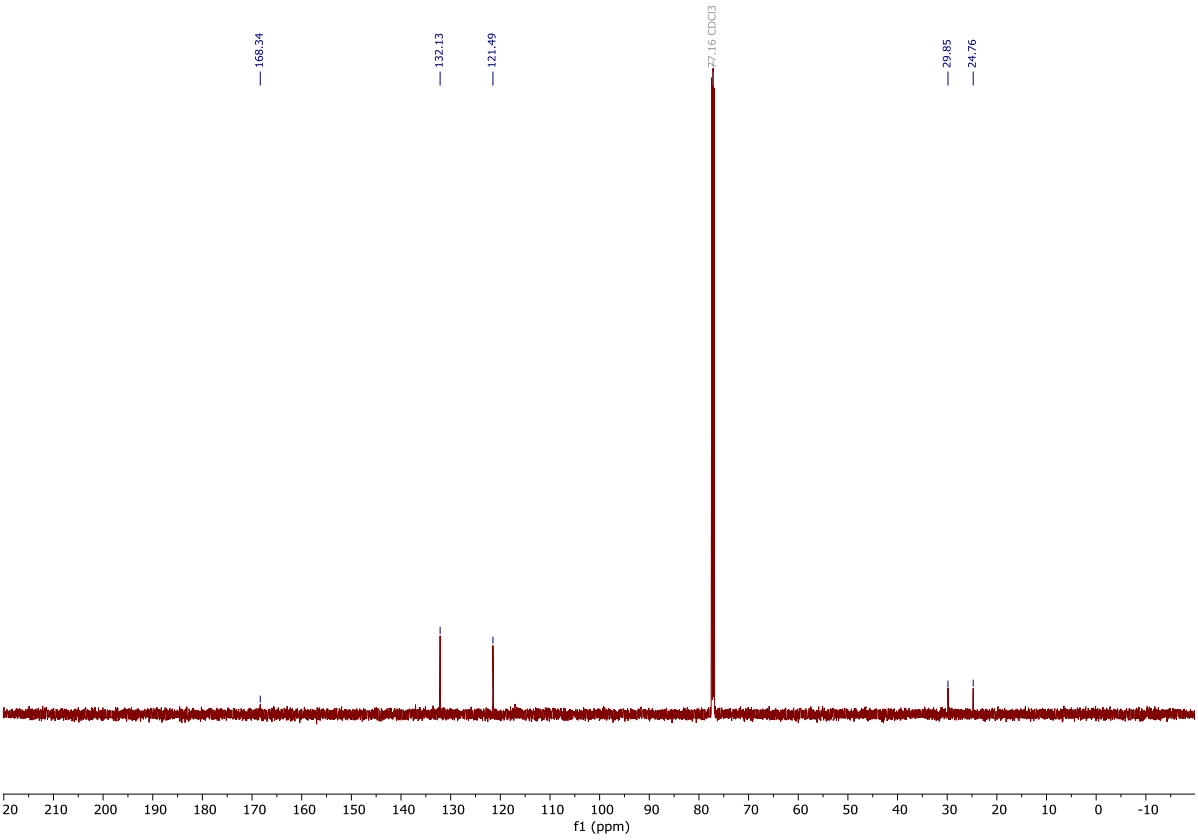

NH
CH3
O
7.57
7.51
7.49
7.32
7.30
7.29
7.26 CDCl3
7.11
7.10
7.08
2.16
0.93
2.01
2.00
1.00
3.02
f1 (ppm)

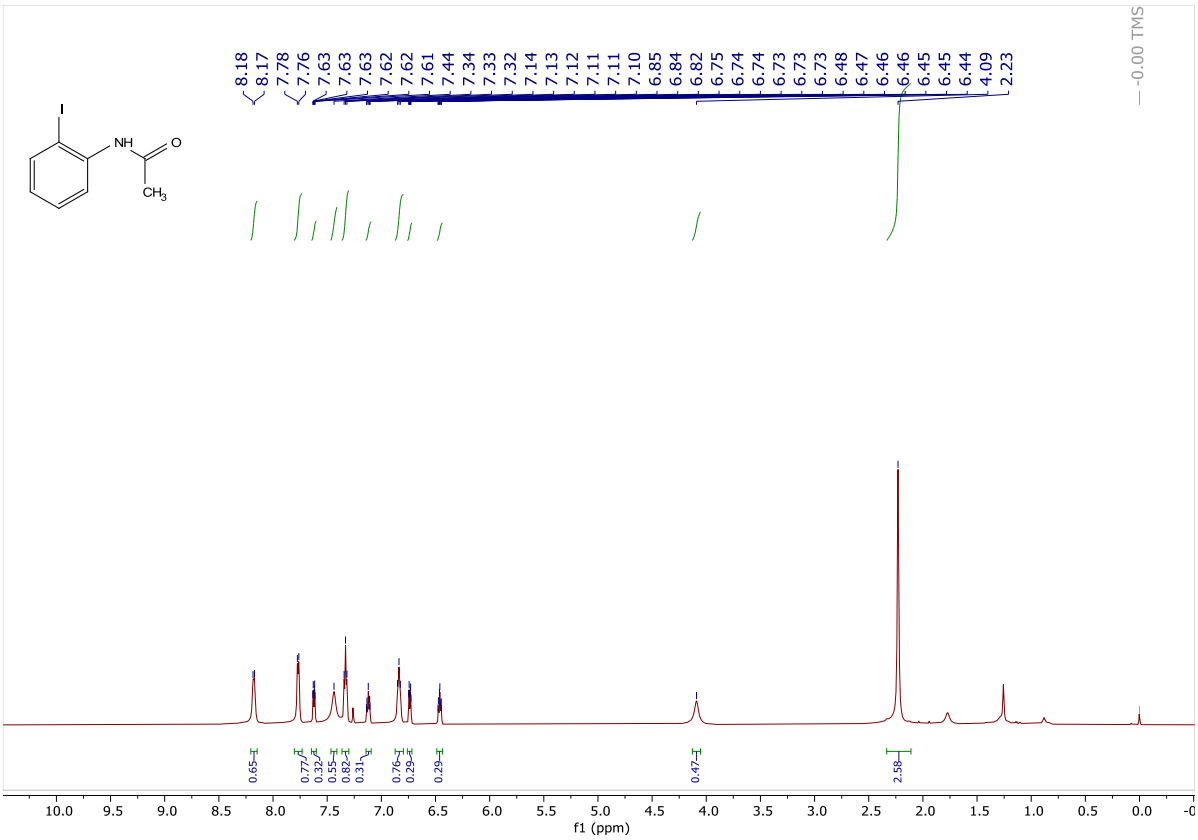

168.65
138.06
129.08
124.42
120.08
77.16 CDCl3
24.67
f1 (ppm)

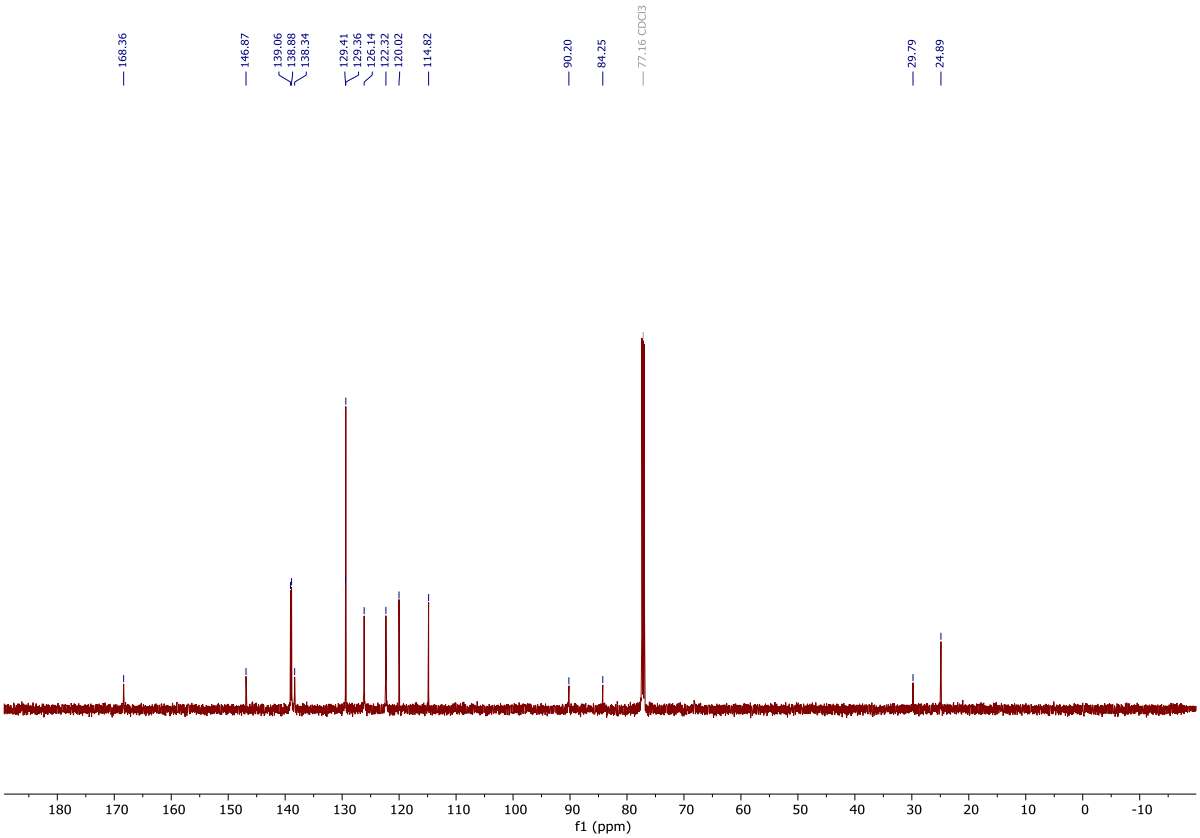

NH
CH3
O
F
7.45
7.45
7.45
7.44
7.43
7.42
7.41
7.26
7.01
6.99
6.98
2.16
3.01
2.00
3.03
f1 (ppm)

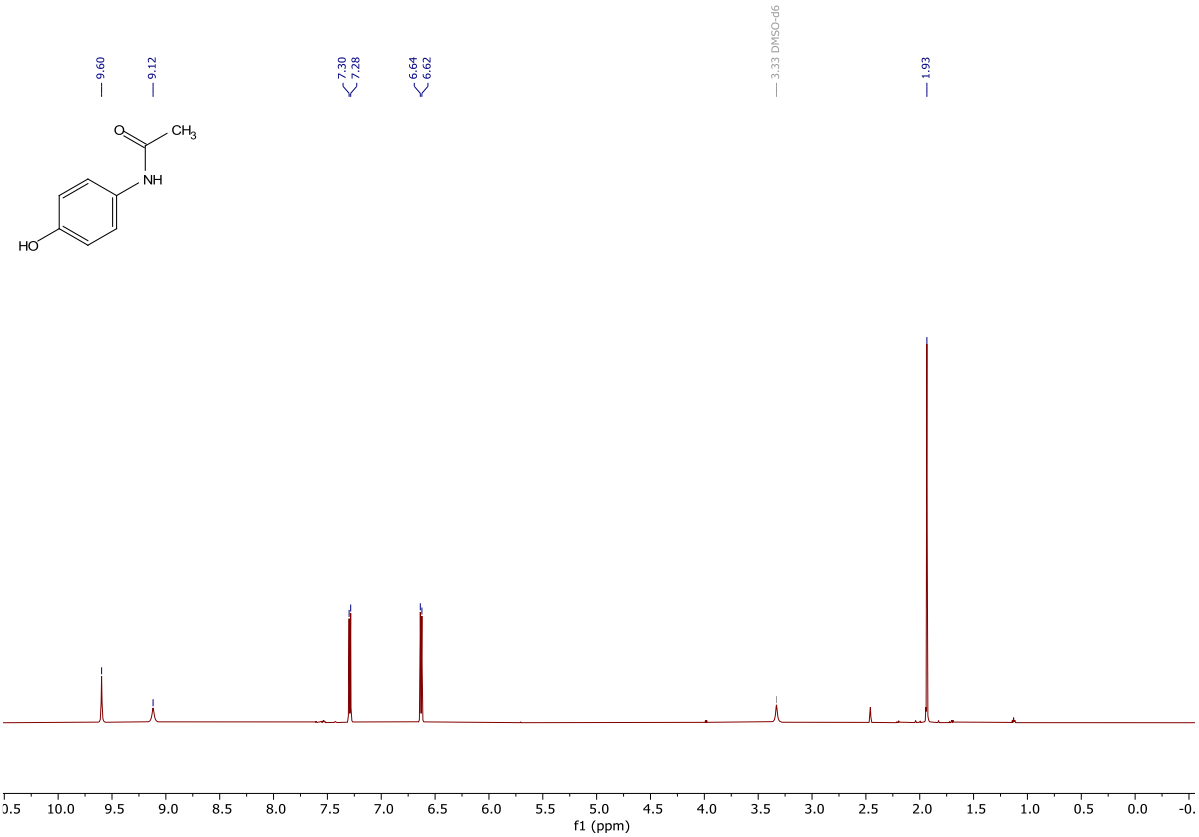

168.53
160.33
158.72
134.00
133.98
121.98
121.93
115.82
115.67
77.16 CDCl3
24.51
f1 (ppm)

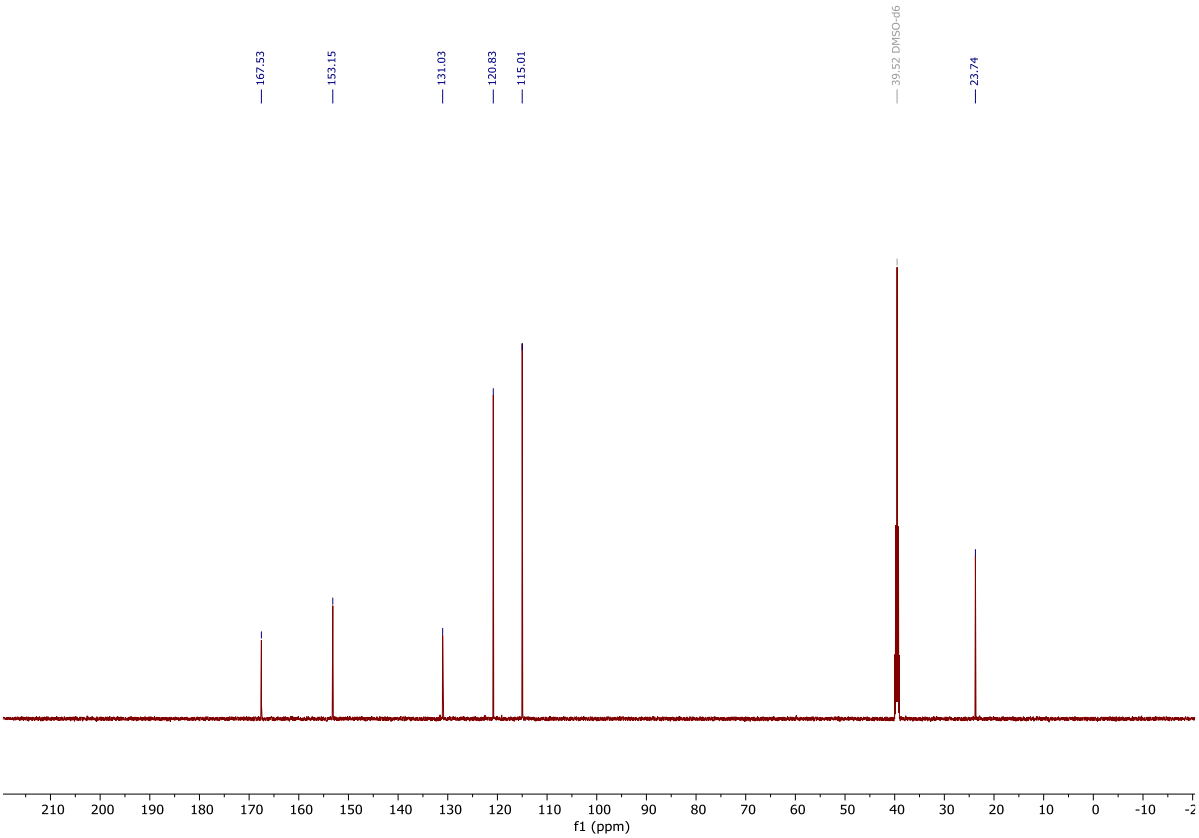

NH
CH3
O
Br
8.09
7.43
7.42
7.41
7.39
7.26 CDCl3
7.18
2.17
0.11
3.81
1.00
3.00
f1 (ppm)

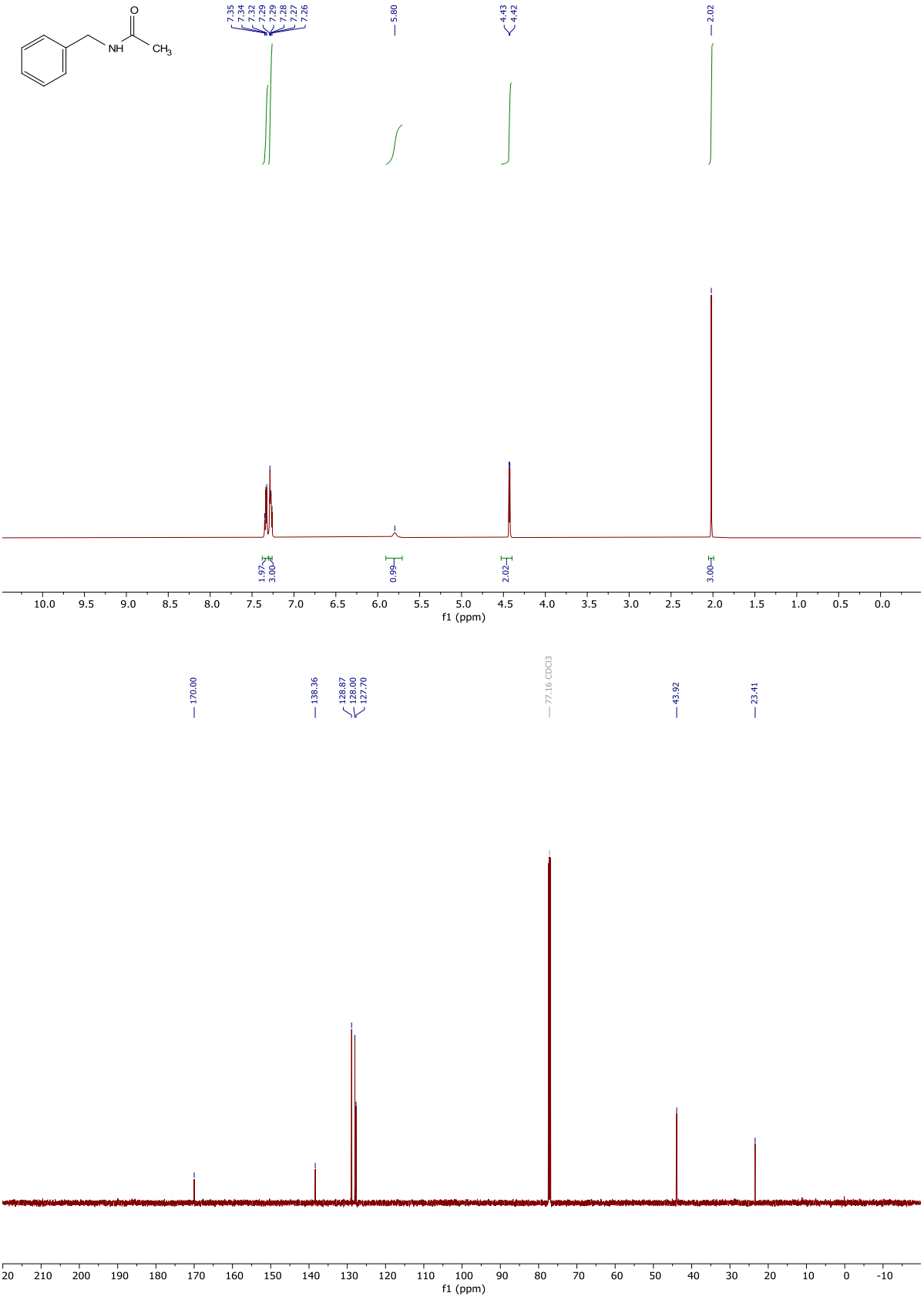

168.34
132.13
121.49
77.16 CDCl3
29.85
24.76
f1 (ppm)

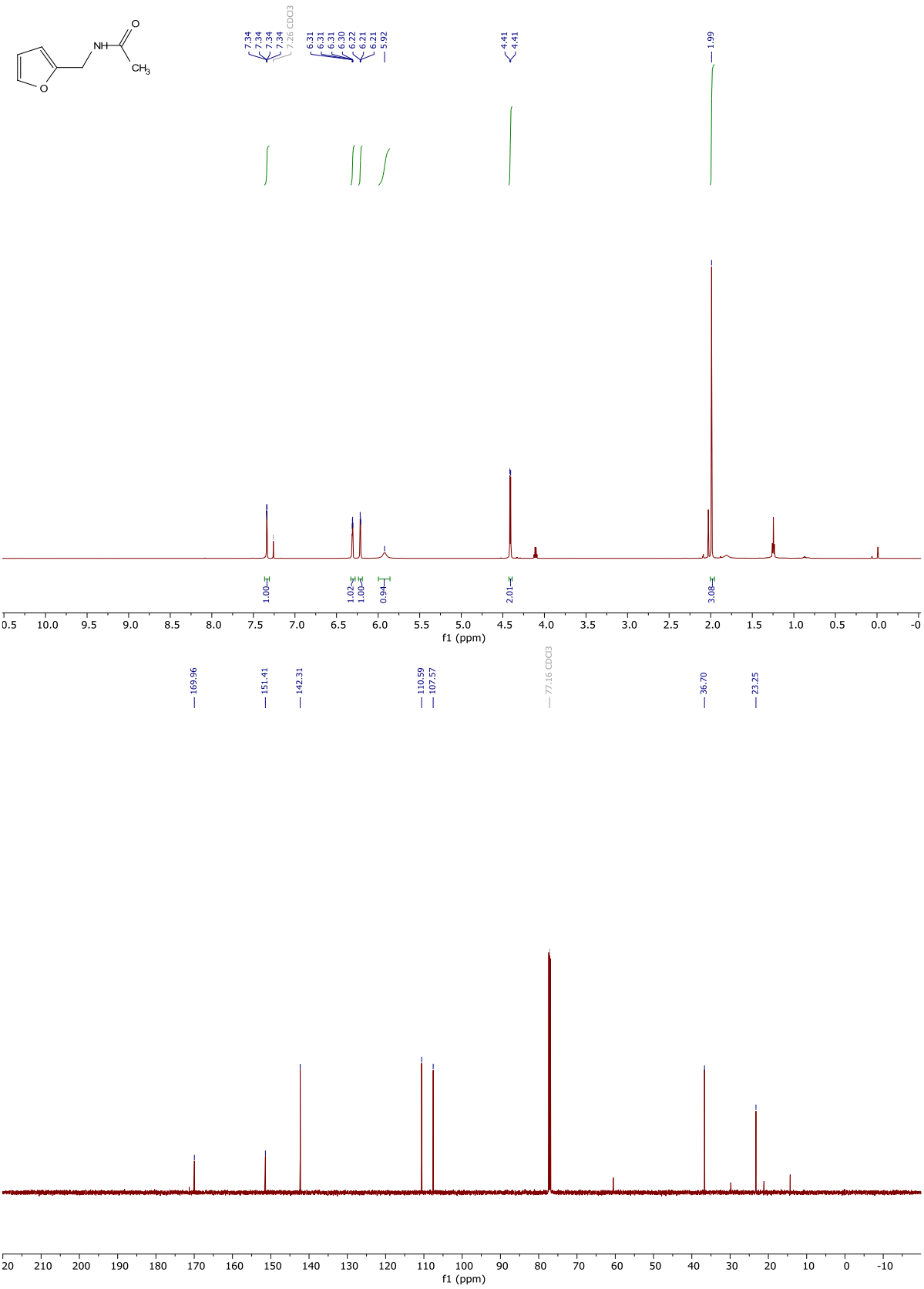

8.18
8.17
7.78
7.76
7.63
7.63
7.63
7.62
7.62
7.61
7.44
7.34
7.33
7.32
7.14
7.13
7.12
7.11
7.11
7.10
6.85
6.84
6.82
6.75
6.74
6.74
6.73
6.73
6.73
6.48
6.47
6.46
6.45
6.45
6.44
4.09
2.23
-0.00 TMS
I
NH
O
CH3
0.65
0.77
0.32
0.55
0.82
0.31
0.76
0.29
0.29
0.47
2.58
f1 (ppm)

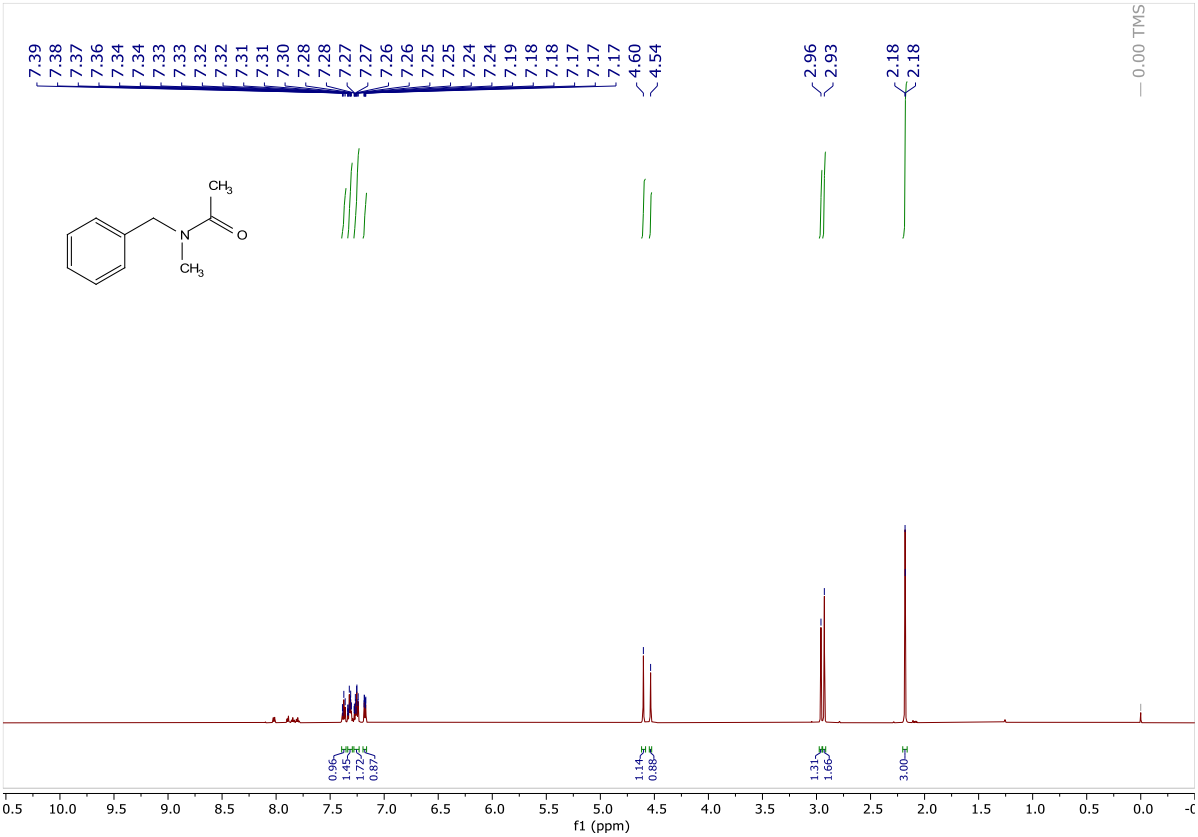

168.36
146.87
139.06
138.88
138.34
129.41
129.36
126.14
122.32
120.02
114.82
90.20
84.25
77.16 CDCl3
29.79
24.89
f1 (ppm)

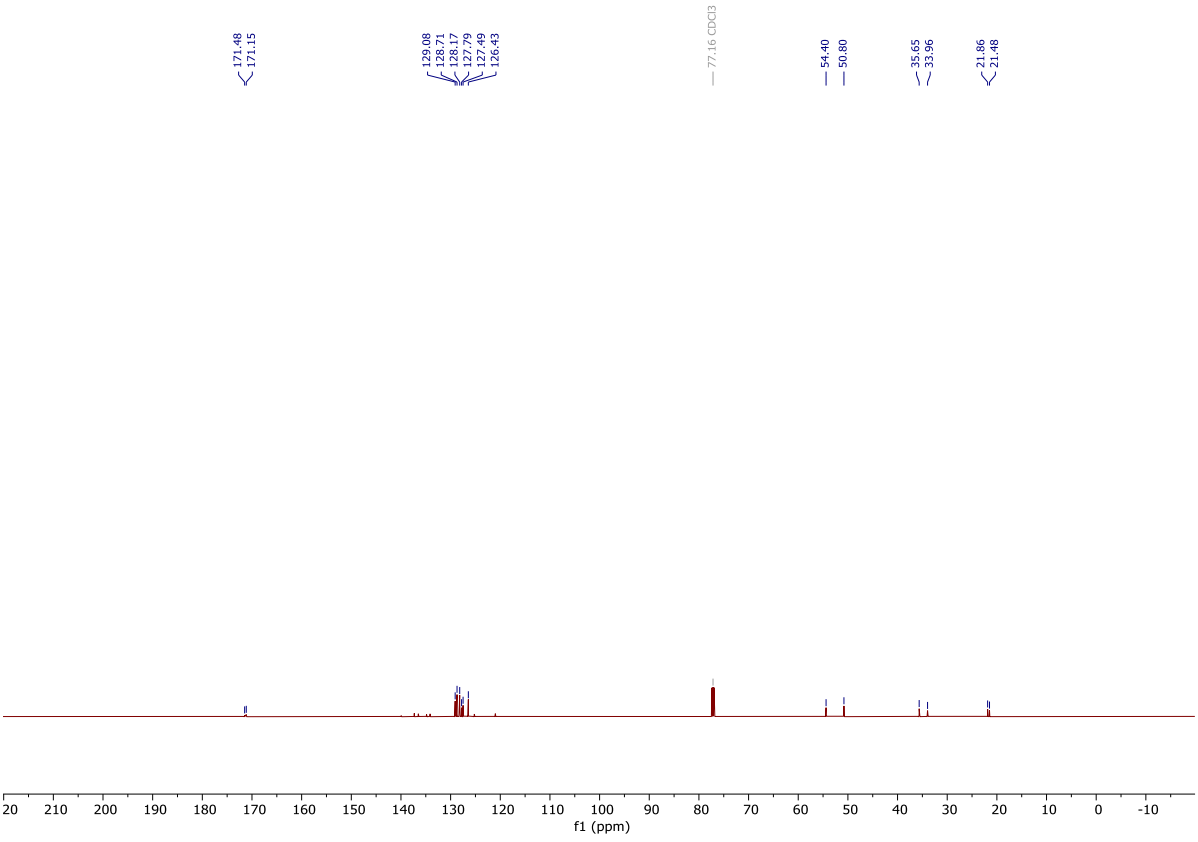

9.60
9.12
7.30
7.28
6.64
6.62
3.33 DMSO-d6
1.93
O
CH3
NH
HO
f1 (ppm)

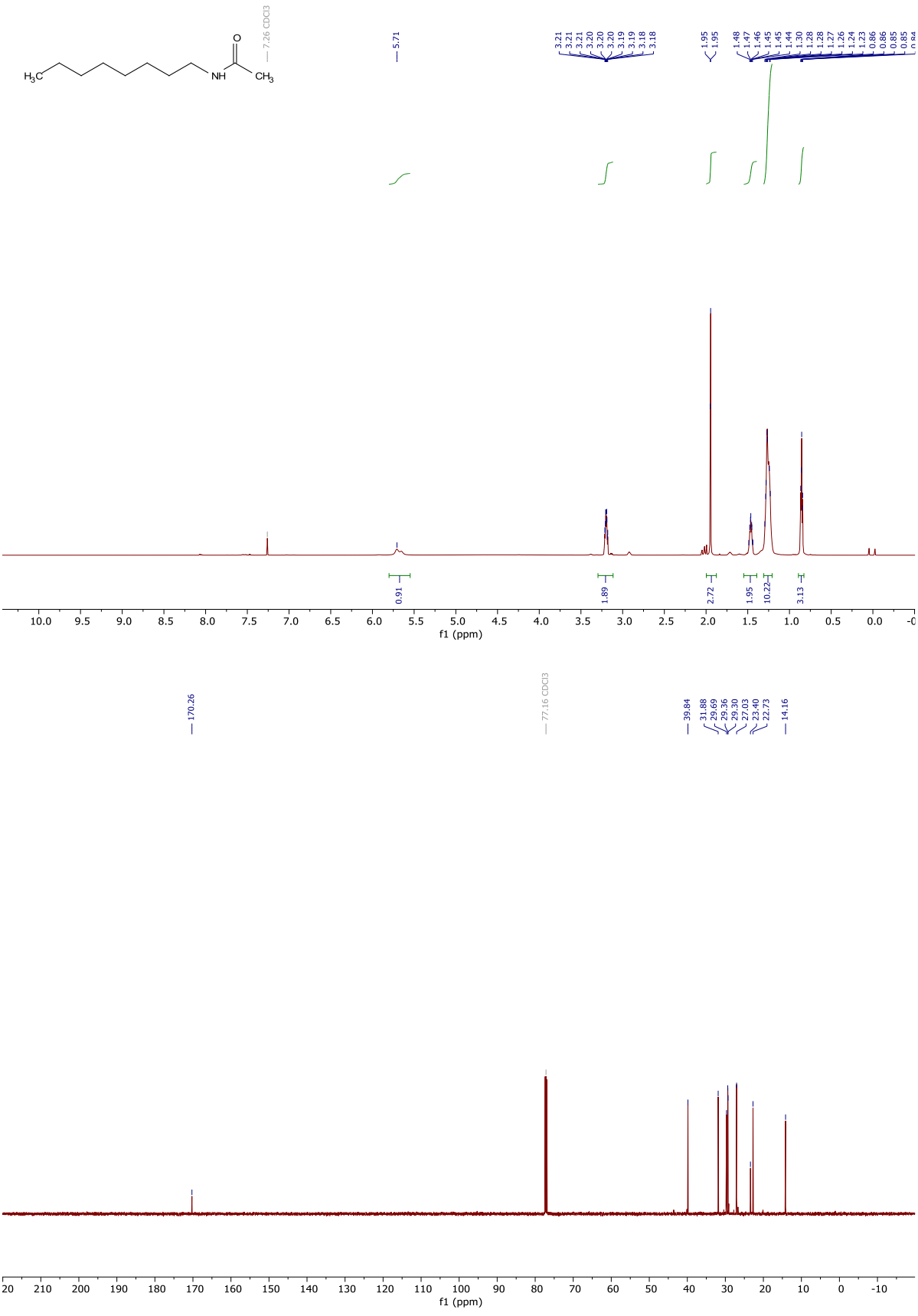

167.53
153.15
131.03
120.83
115.01
39.52 DMSO-d6
23.74
f1 (ppm)

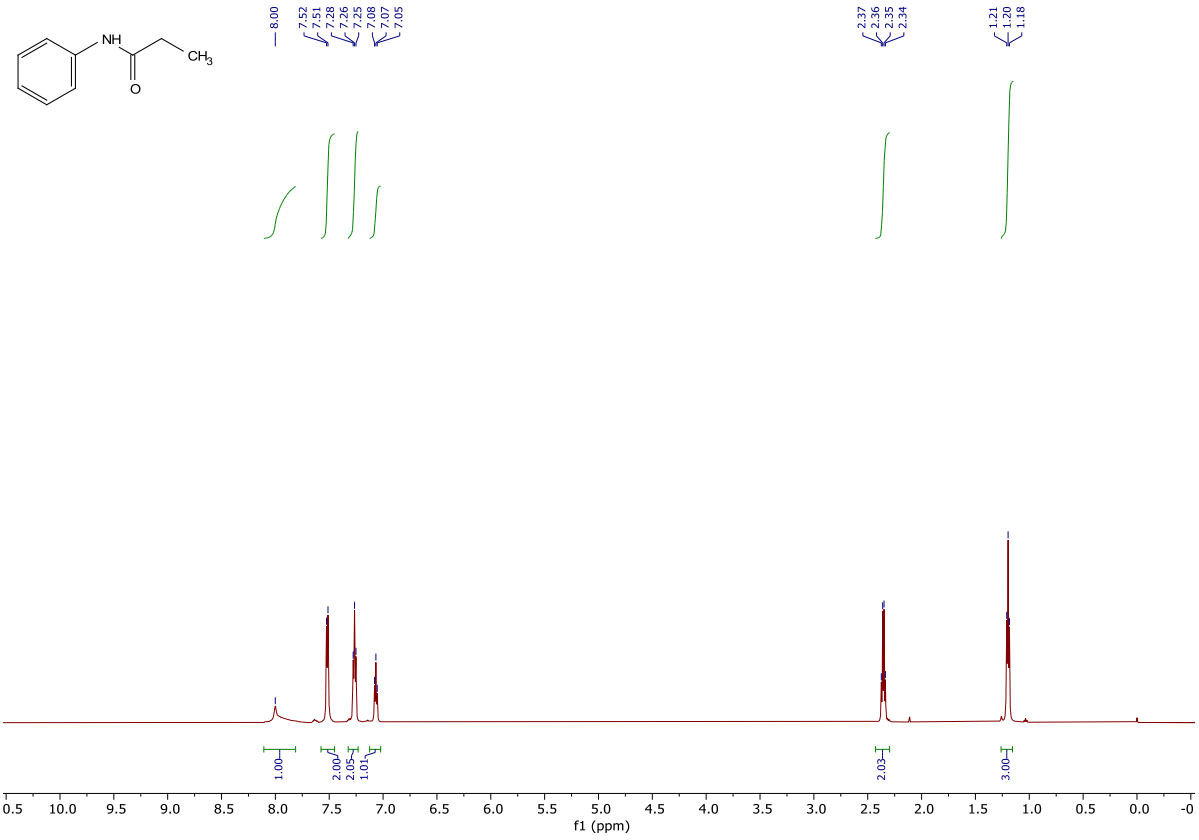

O
NH
CH3
7.35
7.34
7.32
7.29
7.29
7.28
7.27
7.26
5.80
4.43
4.42
2.02
1.97
3.00
0.99
2.02
3.00
f1 (ppm)
170.00
138.36
128.87
128.00
127.70
77.16 CDCl3
43.92
23.41
f1 (ppm)

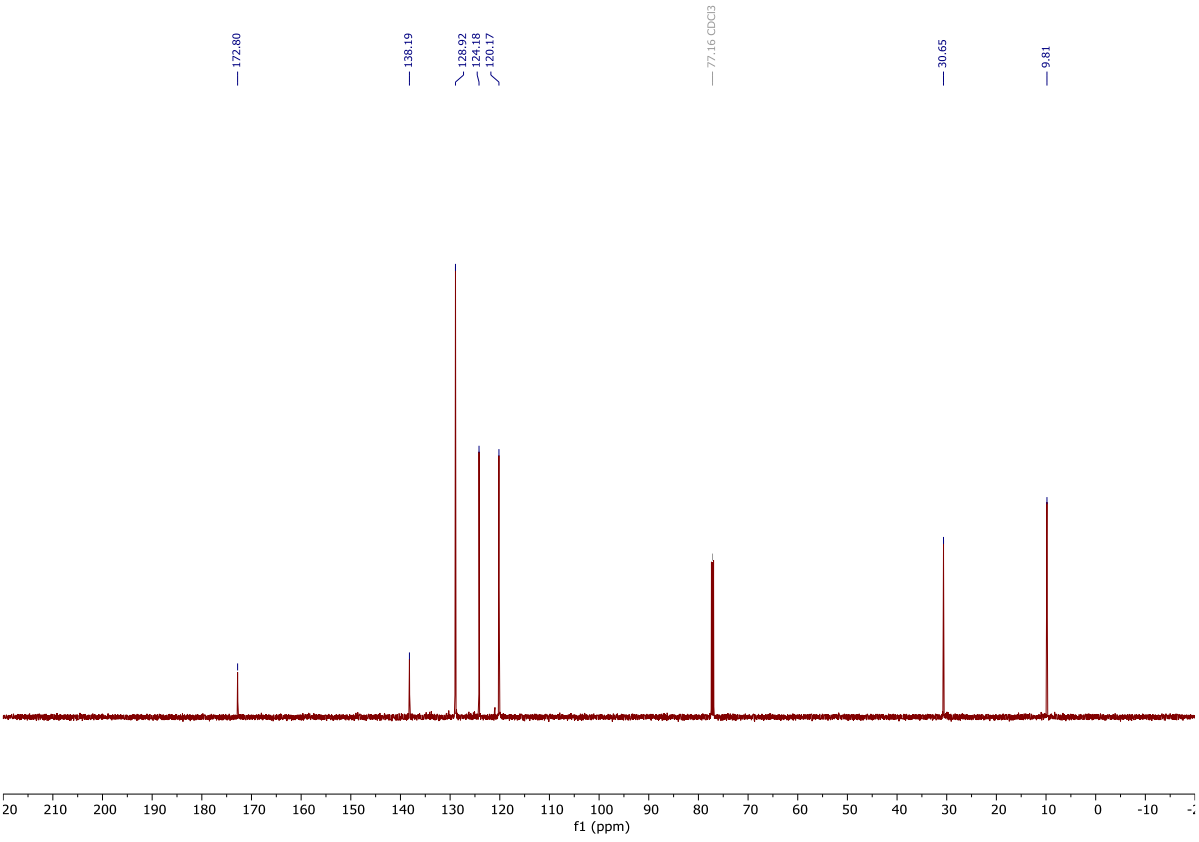

NH
O
CH3
O
7.34
7.34
7.34
7.34
7.26 CDCl3
6.31
6.31
6.31
6.30
6.22
6.21
6.21
5.92
4.41
4.41
1.99
1.00
1.02
1.00
0.94
2.01
3.08
f1 (ppm)
169.96
151.41
142.31
110.59
107.57
77.16 CDCl3
36.70
23.25
f1 (ppm)

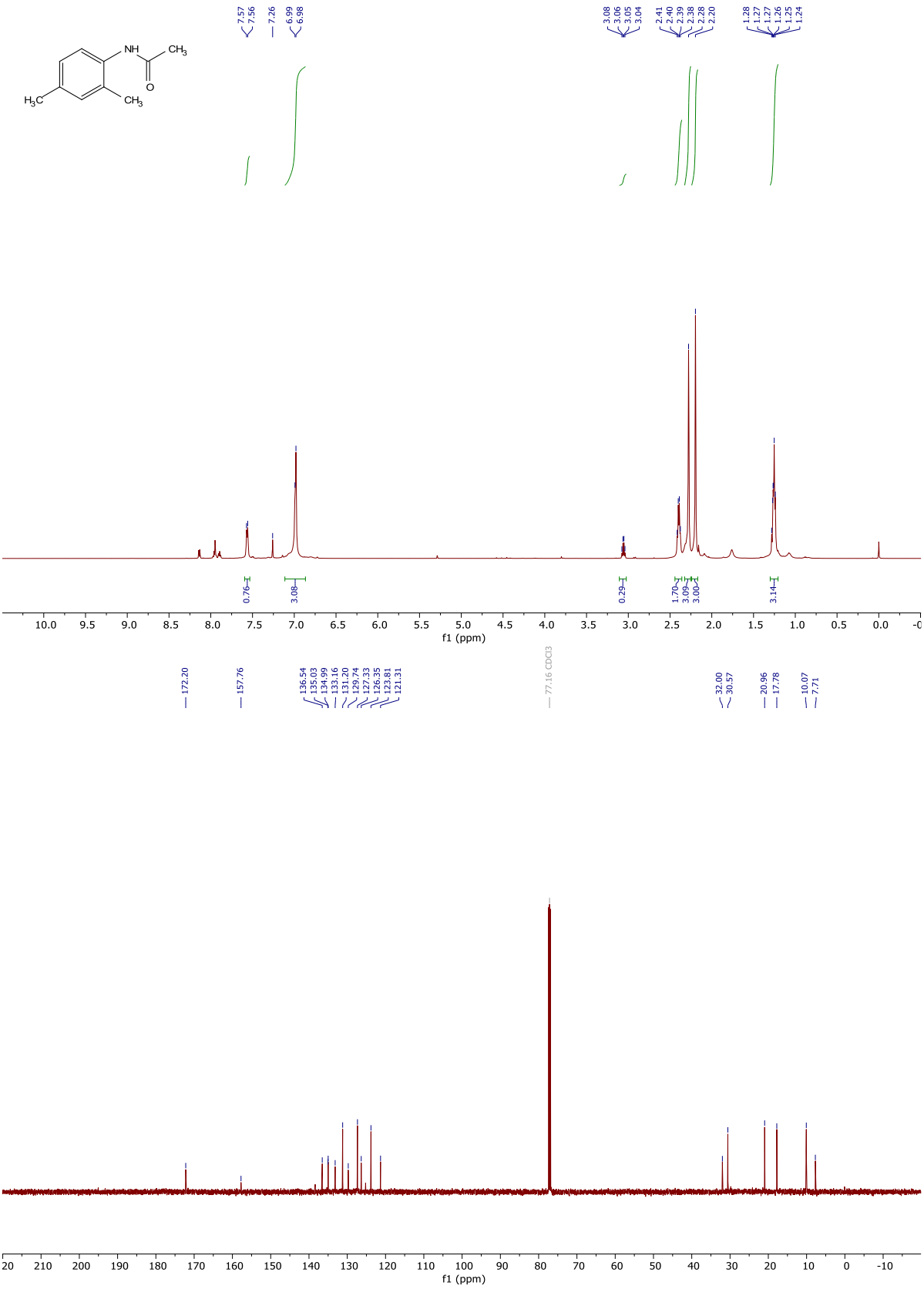

7.39
7.38
7.37
7.36
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
7.19
7.18
7.18
7.17
7.17
7.17
4.60
4.54
2.96
2.93
2.18
2.18
0.00 TMS
CH3
N
O
CH3
0.96
1.45
1.72
0.87
1.14
0.88
1.31
1.66
3.00
f1 (ppm)

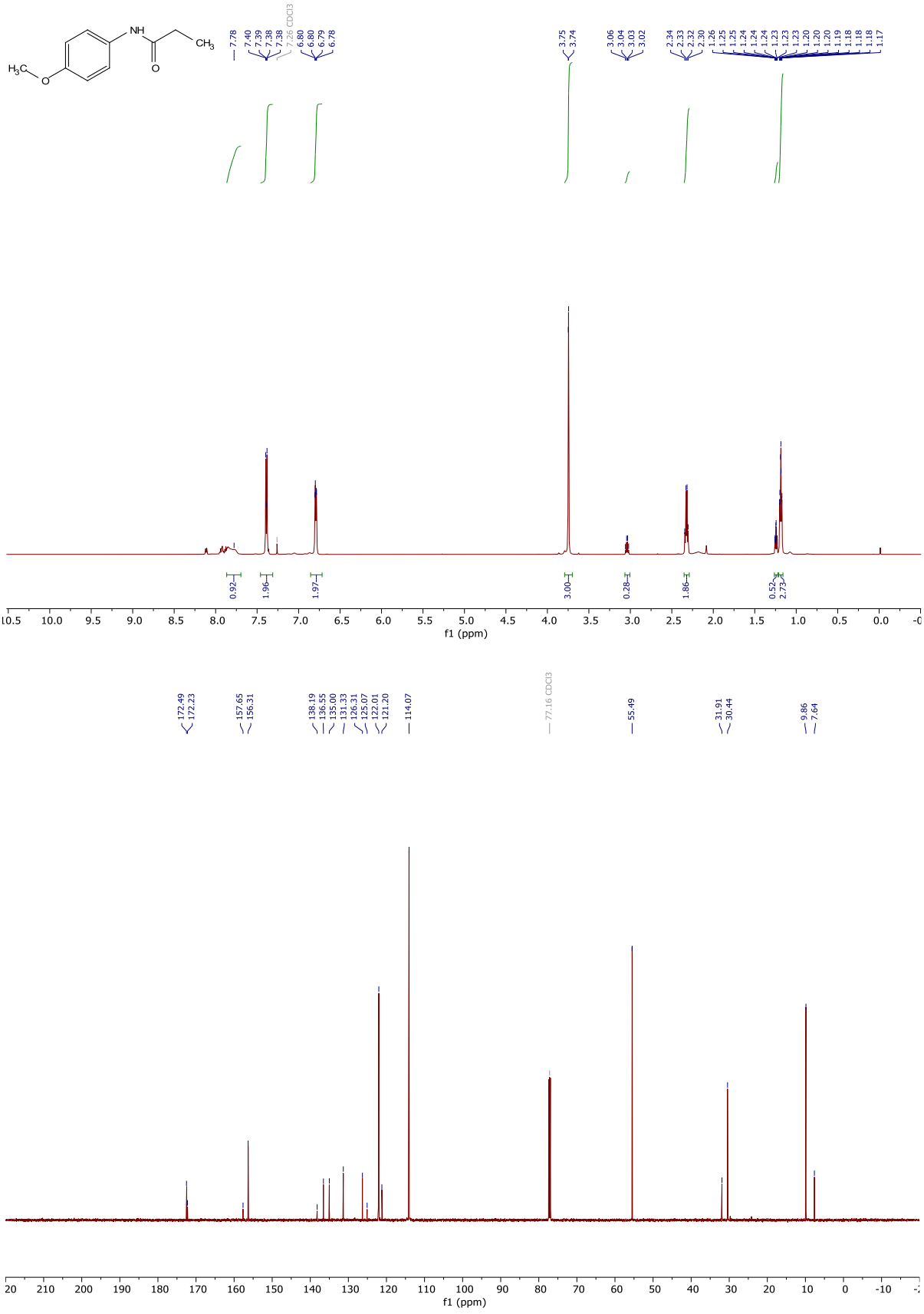

171.48
171.15
129.08
128.71
128.17
127.79
127.49
126.43
77.16 CDCl3
54.40
50.80
35.65
33.96
21.86
21.48
f1 (ppm)

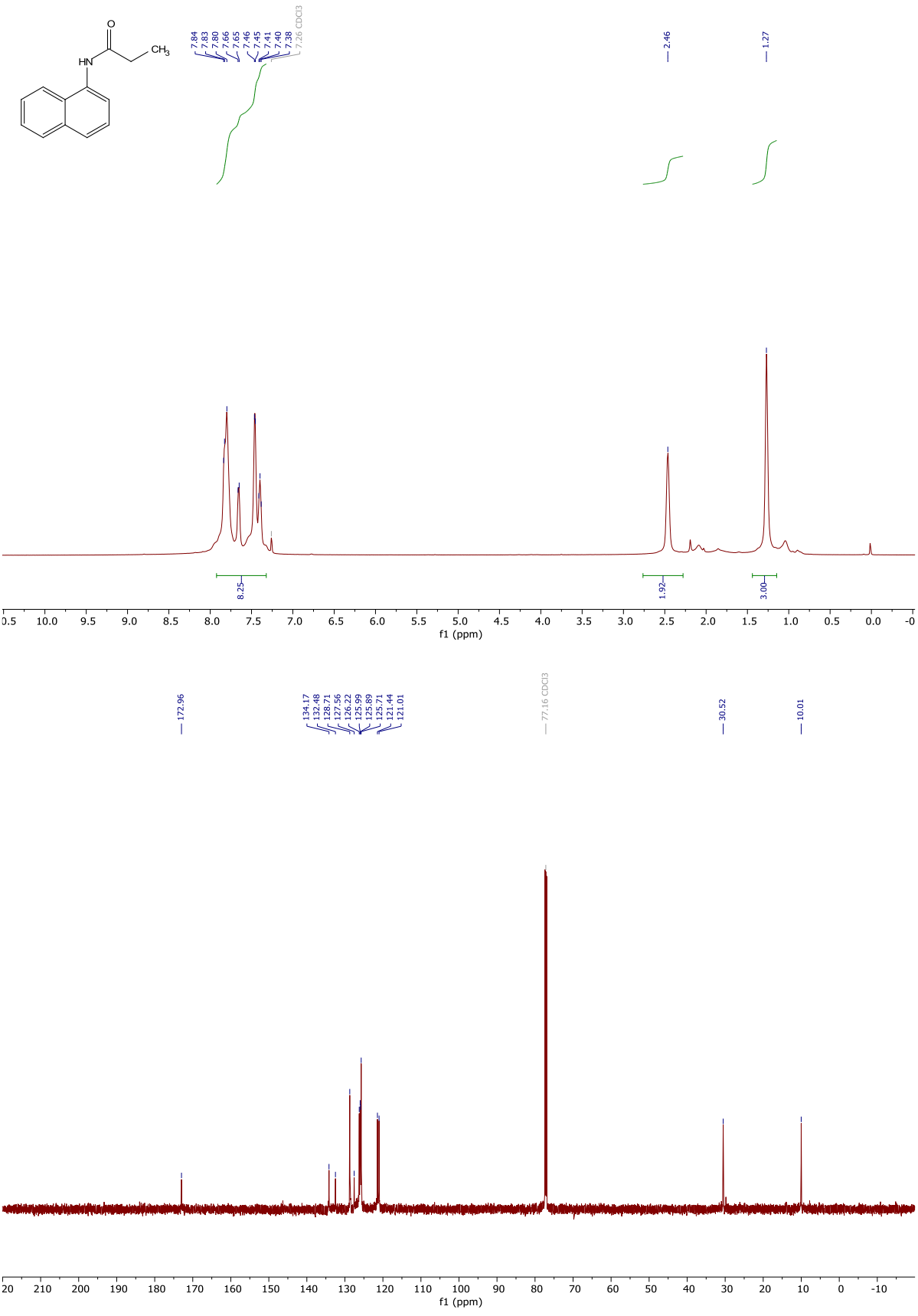

O
NH
H_3C
CH_3
7.26 CDCl3
5.71
3.21
3.21
3.21
3.20
3.20
3.20
3.19
3.19
3.18
3.18
1.95
1.95
1.48
1.47
1.46
1.45
1.45
1.44
1.30
1.28
1.28
1.27
1.26
1.24
1.23
0.86
0.86
0.85
0.85
0.91
1.89
2.72
1.95
10.22
3.13
f1 (ppm)
170.26
77.16 CDCl3
39.84
31.88
29.69
29.36
29.30
27.03
23.40
22.73
14.16
f1 (ppm)

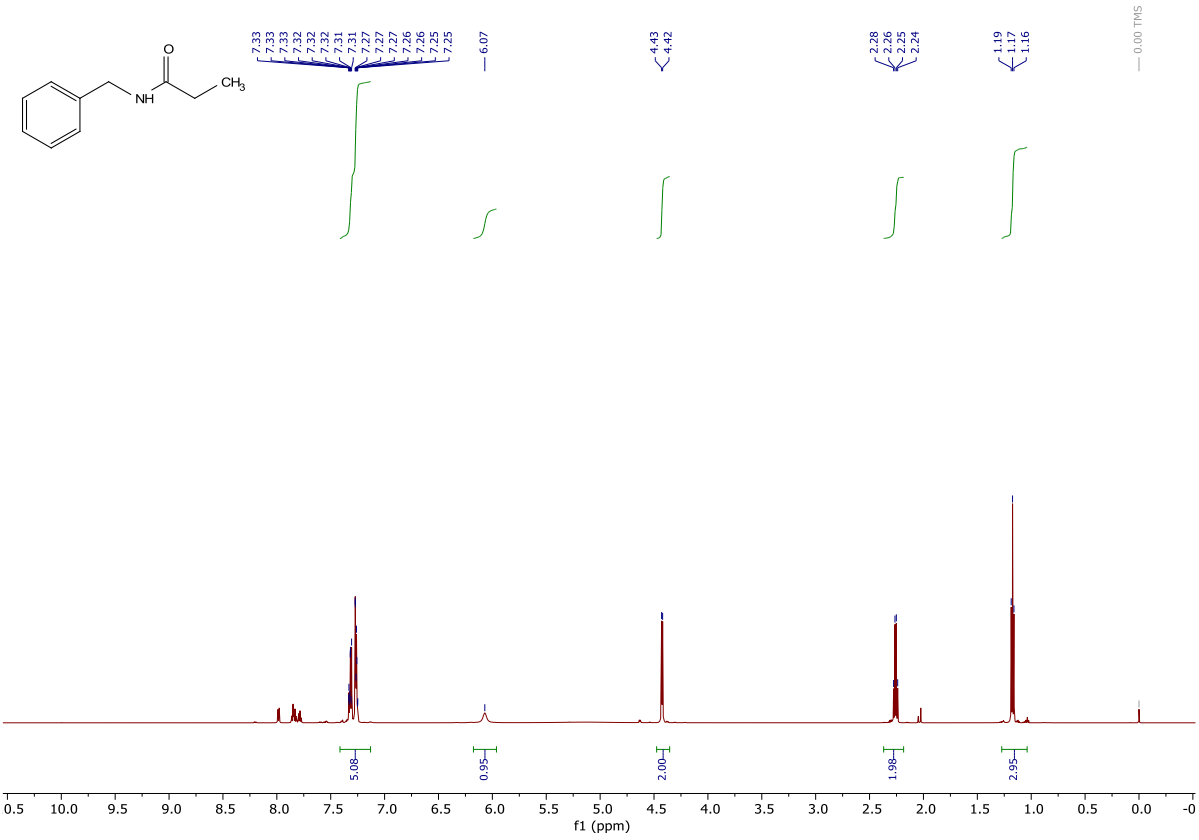

NH
CH3
O
8.00
7.52
7.51
7.28
7.26
7.25
7.08
7.07
7.05
2.37
2.36
2.35
2.34
1.21
1.20
1.18
1.00
2.00
2.05
1.01
2.03
3.00
f1 (ppm)

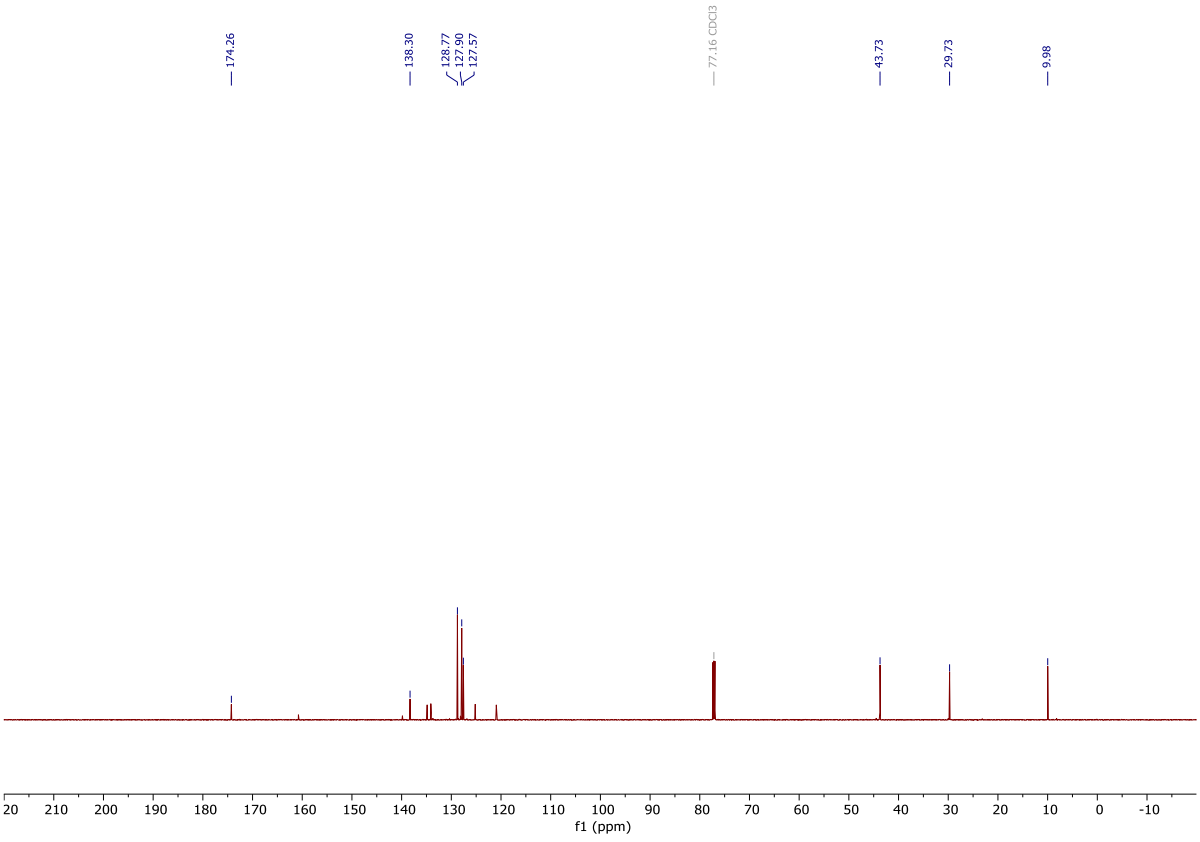

172.80
138.19
128.92
124.18
120.17
77.16 CDCl3
30.65
9.81
f1 (ppm)

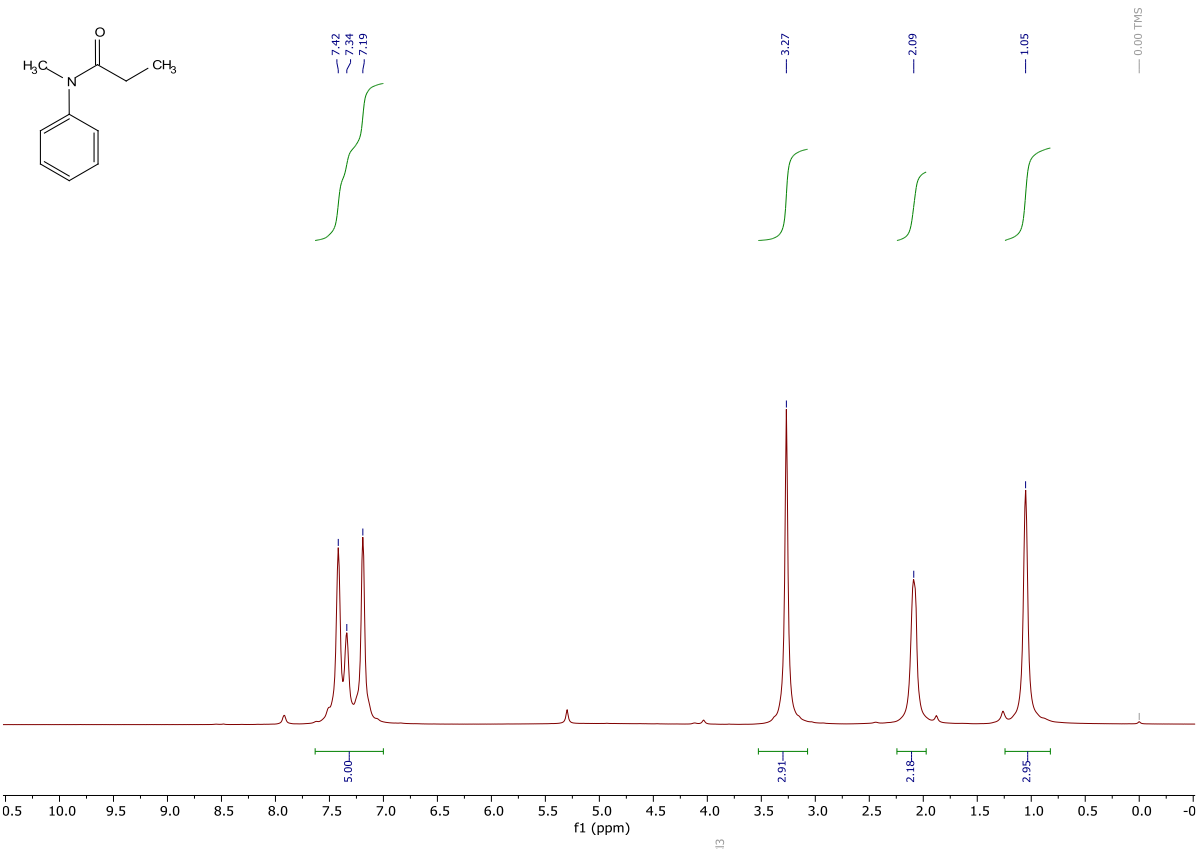

NH
CH3
O
H3C
CH3
7.57
7.56
7.26
6.99
6.98
3.08
3.06
3.05
3.04
2.41
2.40
2.39
2.38
2.28
2.20
1.28
1.27
1.27
1.26
1.25
1.24
0.76
3.08
0.29
1.70
3.09
3.00
3.14
f1 (ppm)
172.20
157.76
136.54
135.03
134.99
133.16
131.20
129.74
127.33
126.35
123.81
121.31
77.16 CDCl3
32.00
30.57
20.96
17.78
10.07
7.71
f1 (ppm)

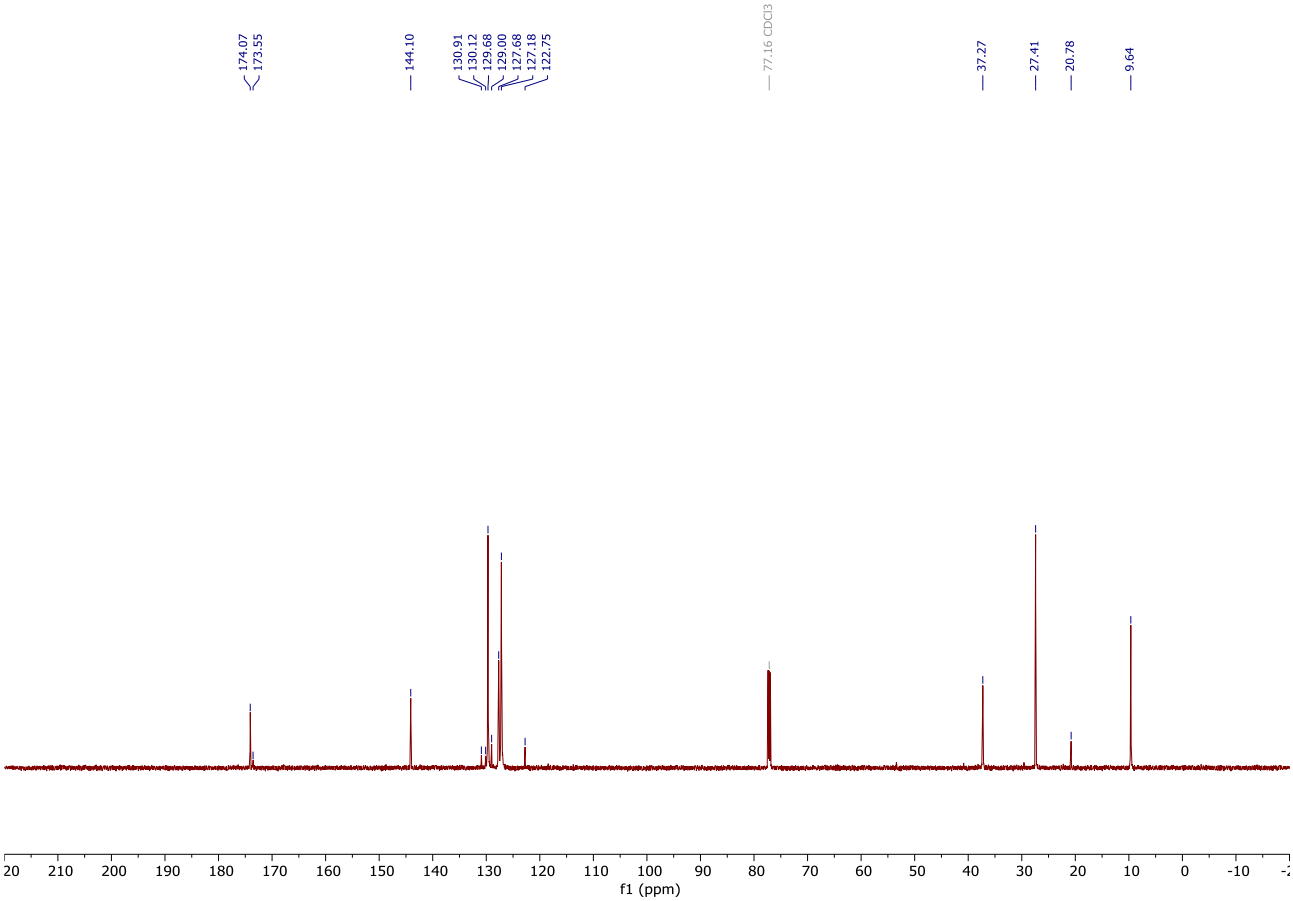

NH
CH3
H3C
O
O
7.78
7.40
7.39
7.38
7.38
7.26 CDCl3
6.80
6.80
6.79
6.78
3.75
3.74
3.06
3.04
3.03
3.02
2.34
2.33
2.32
2.30
1.26
1.25
1.25
1.24
1.24
1.24
1.23
1.23
1.23
1.20
1.20
1.20
1.19
1.18
1.18
1.18
1.17
0.92
1.96
1.97
3.00
0.28
1.86
0.52
2.73
f1 (ppm)
172.49
172.23
157.65
156.31
138.19
136.55
135.00
131.33
126.31
125.07
122.01
121.20
114.07
77.16 CDCl3
55.49
31.91
30.44
9.86
7.64
f1 (ppm)

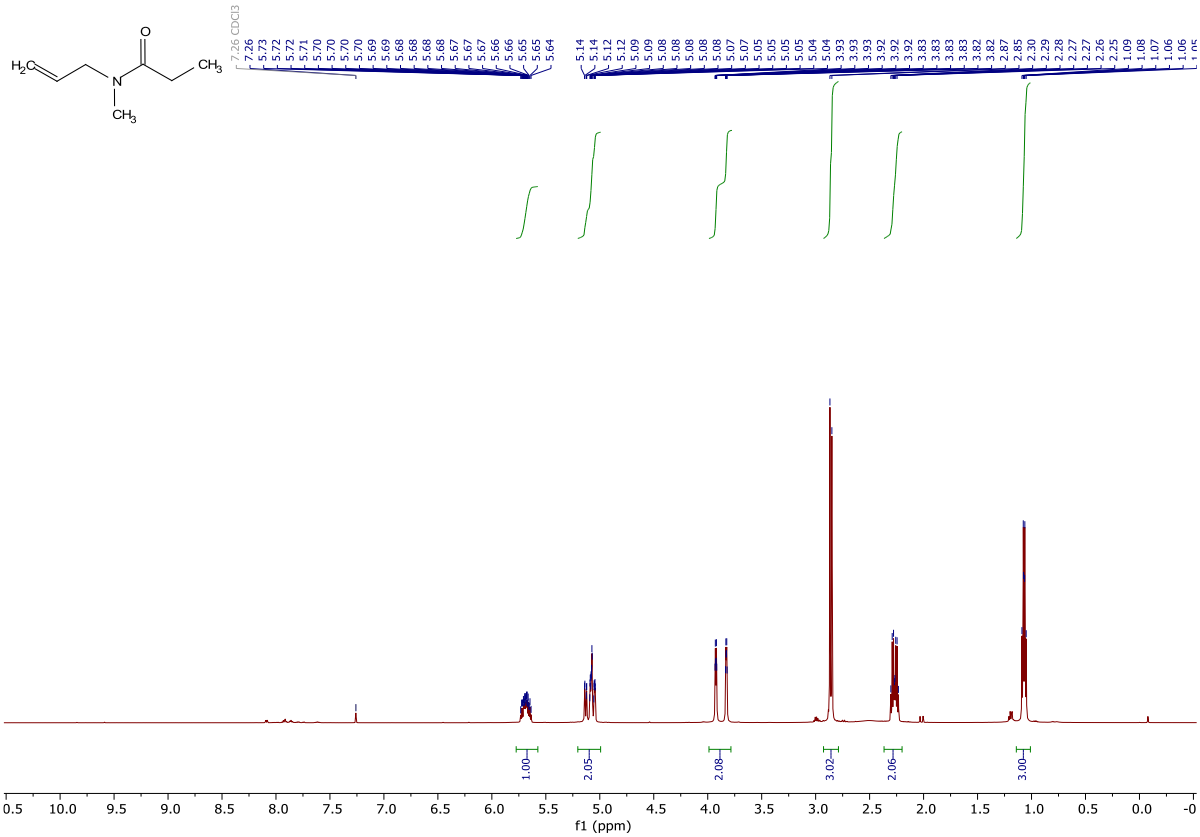

O
HN
CH3
7.84
7.83
7.80
7.66
7.65
7.46
7.45
7.41
7.40
7.38
7.26 CDCl3
2.46
1.27
8.25
1.92
3.00
f1 (ppm)
172.96
134.17
132.48
128.71
127.56
126.22
125.99
125.89
125.71
121.44
121.01
77.16 CDCl3
30.52
10.01
f1 (ppm)

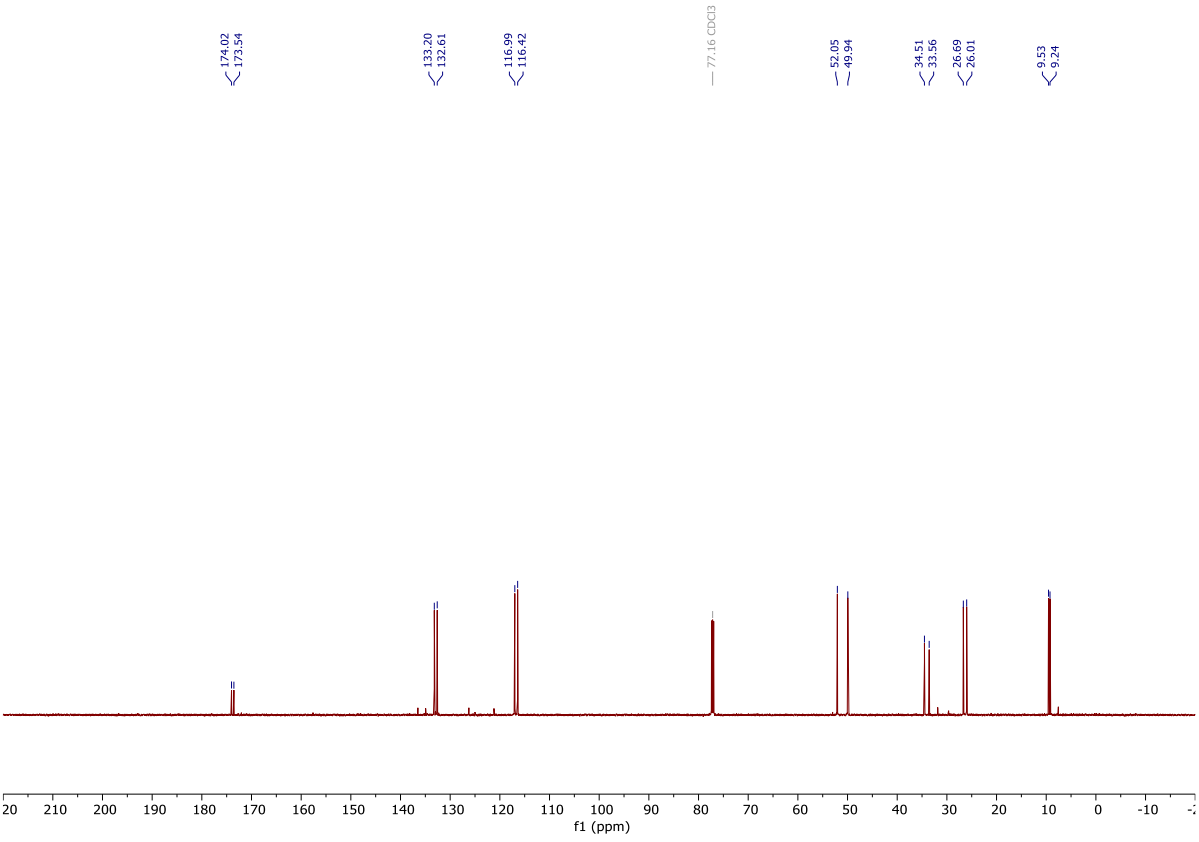

O
NH
CH3
7.33
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.27
7.27
7.27
7.26
7.26
7.25
7.25
6.07
4.43
4.42
2.28
2.26
2.25
2.24
1.19
1.17
1.16
0.00 TMS
5.08
0.95
2.00
1.98
2.95
f1 (ppm)

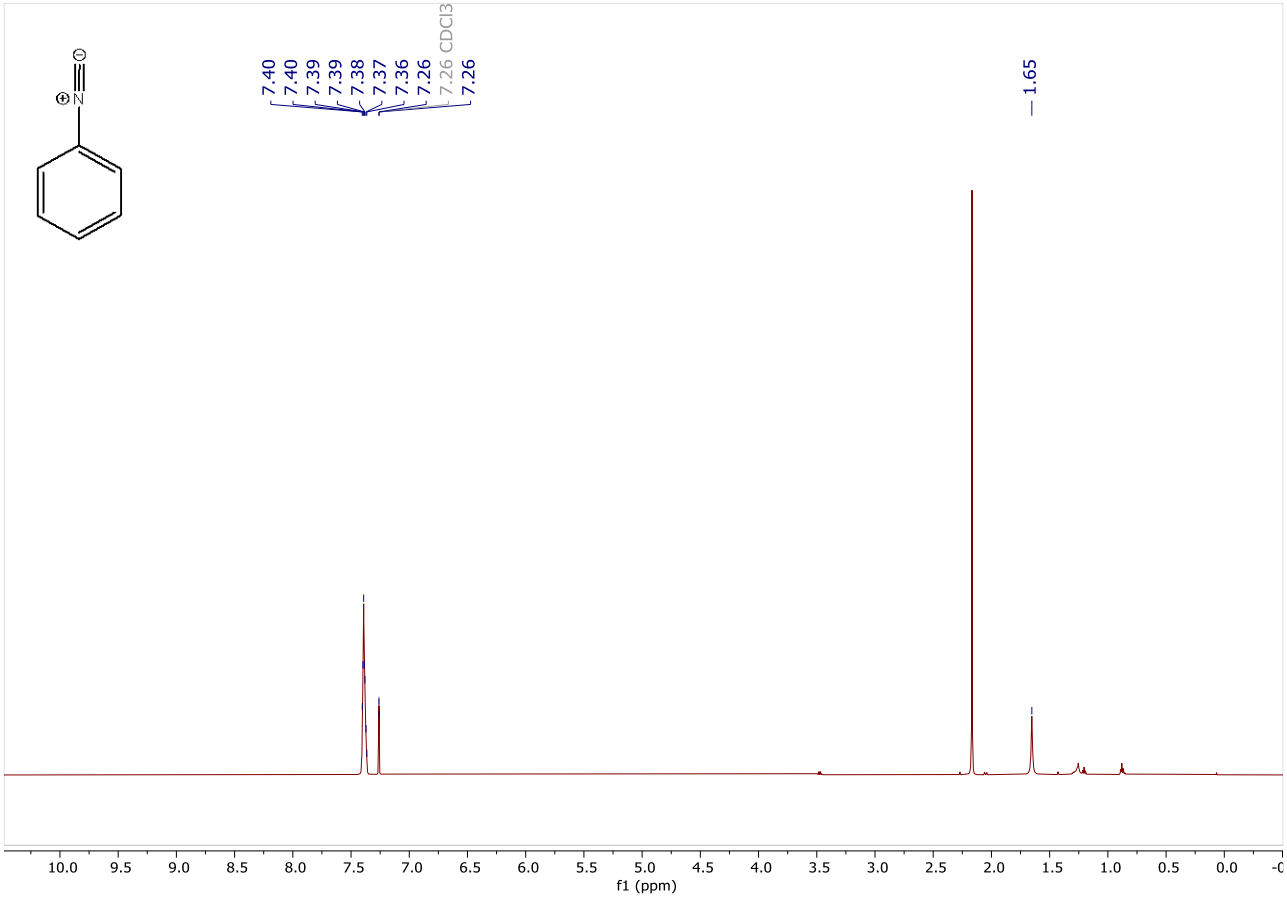

174.26
138.30
128.77
127.90
127.57
77.16 CDCl3
43.73
29.73
9.98
f1 (ppm)

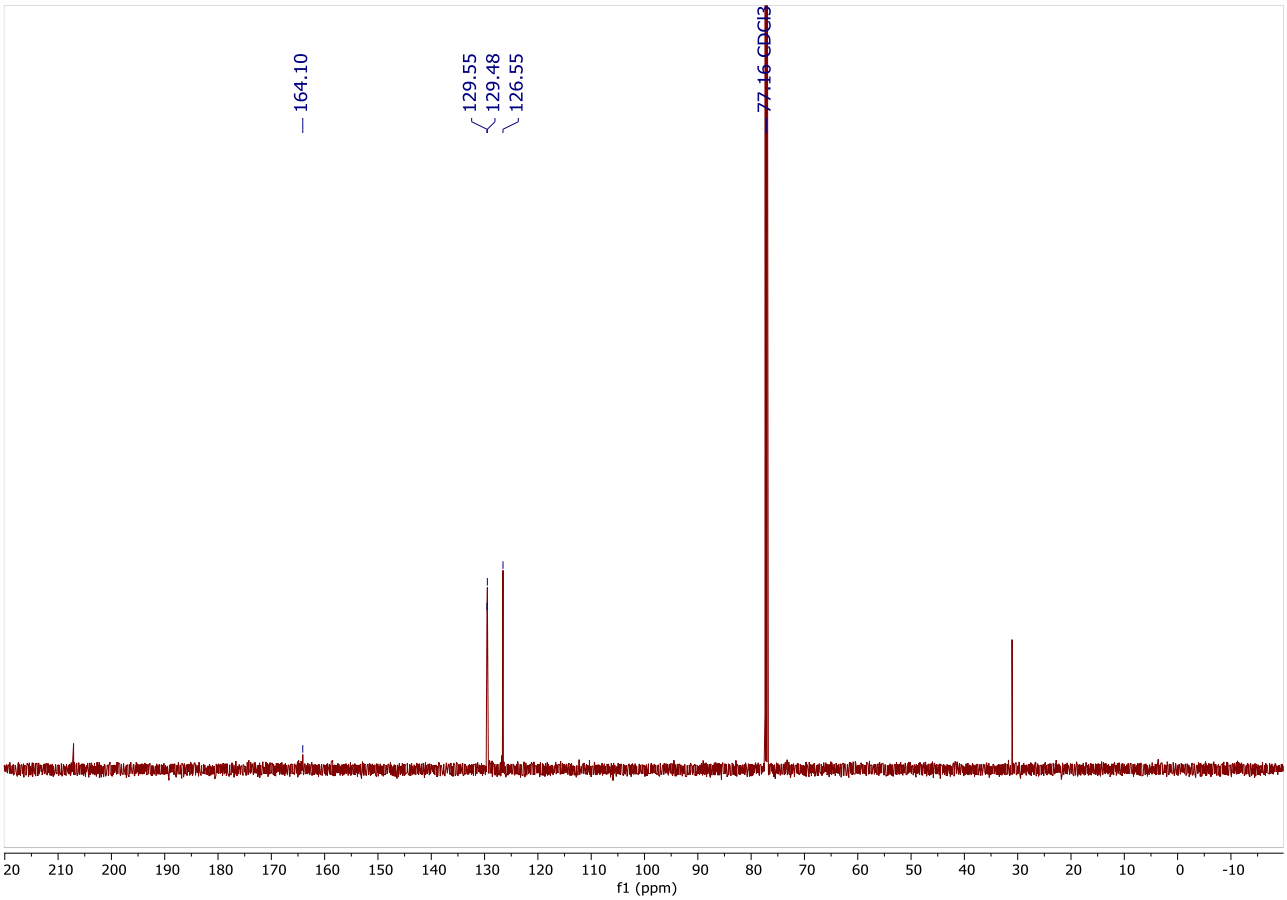

O
H3C
N
CH3
7.42
7.34
7.19
3.27
2.09
1.05
0.00 TMS
5.00
2.91
2.18
2.95
f1 (ppm)

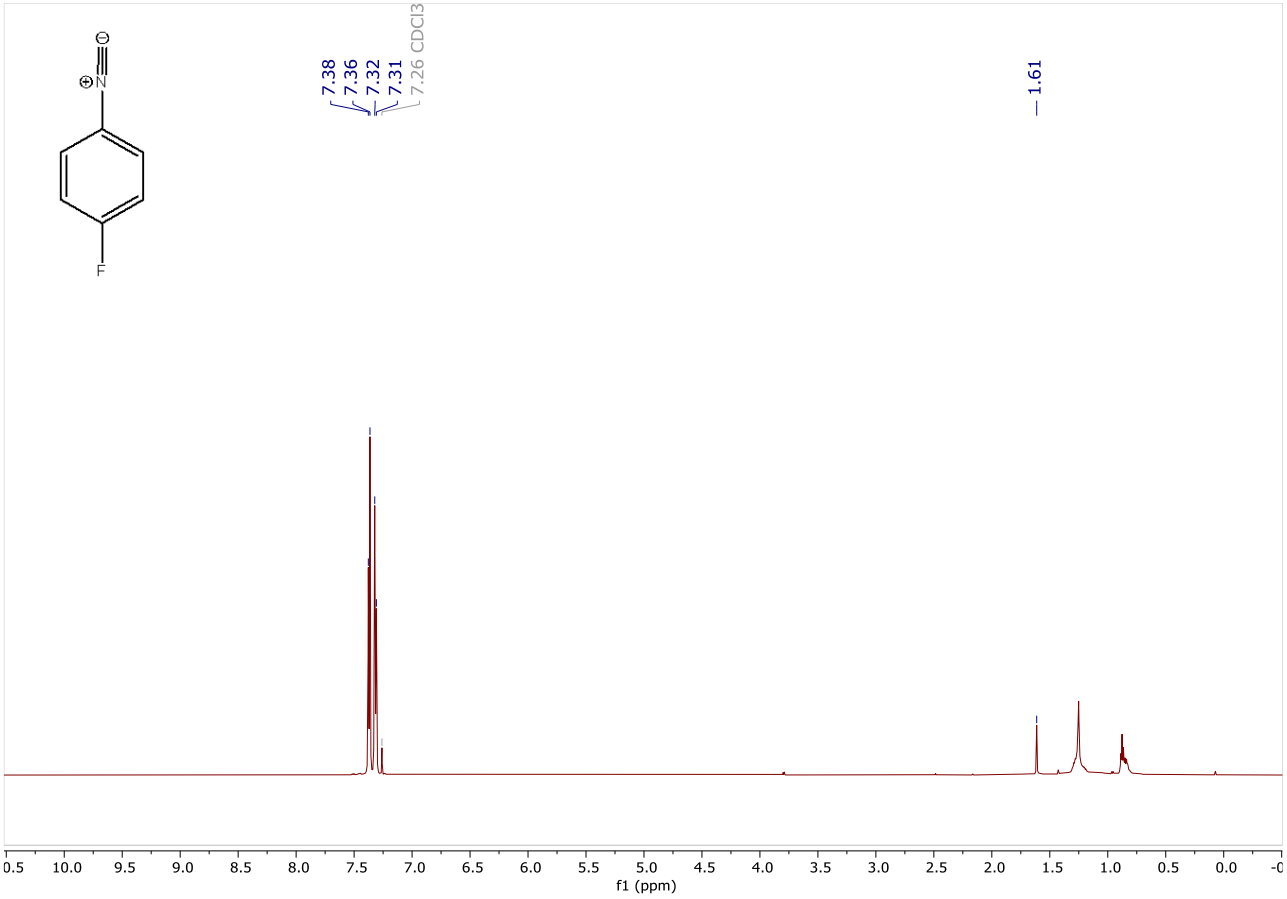

174.07
173.55
144.10
130.91
130.12
129.68
129.00
127.68
127.18
122.75
77.16 CDCl3
37.27
27.41
20.78
9.64
f1 (ppm)

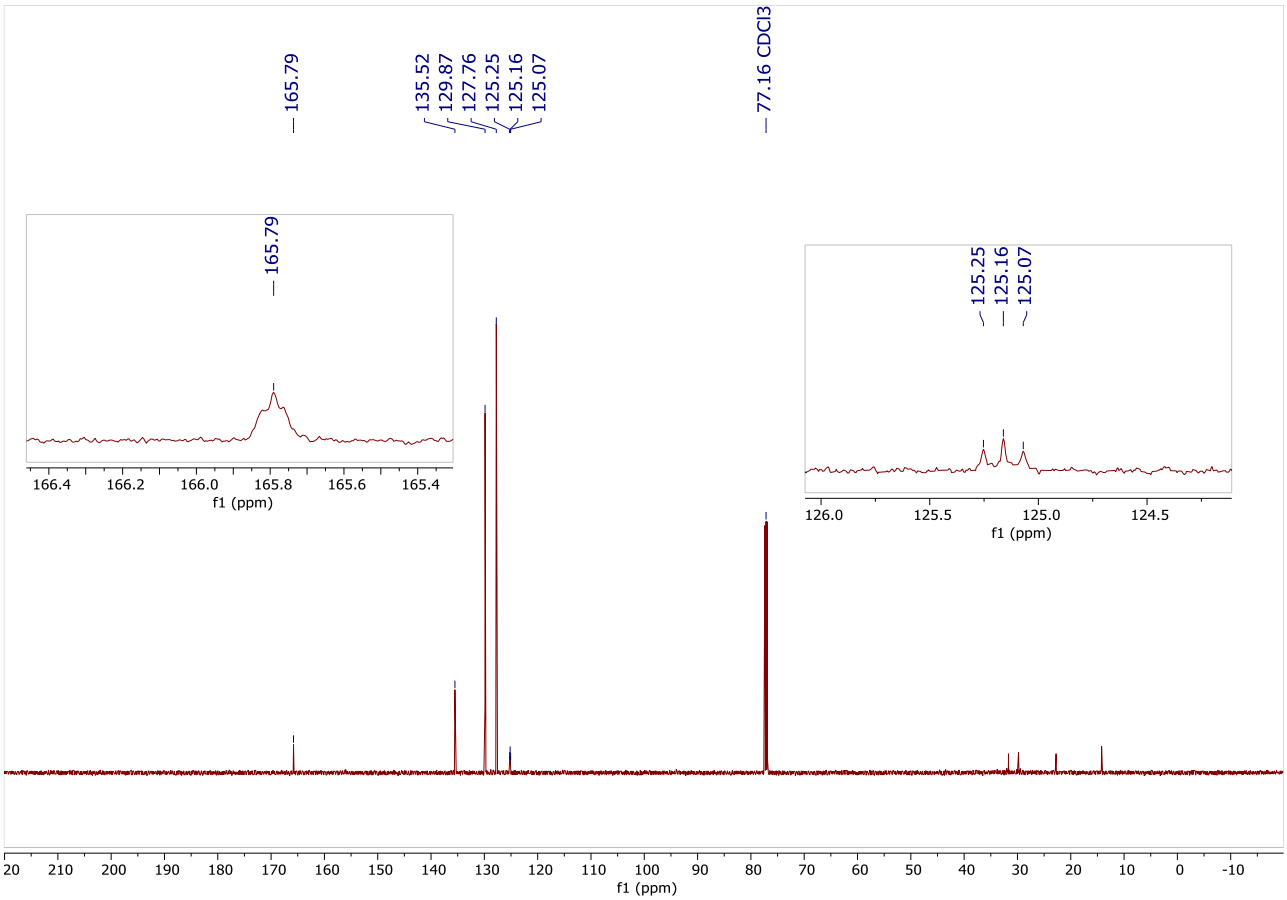

7.26 CDCl3
1.00
2.05
2.08
3.02
2.06
3.00
f1 (ppm)

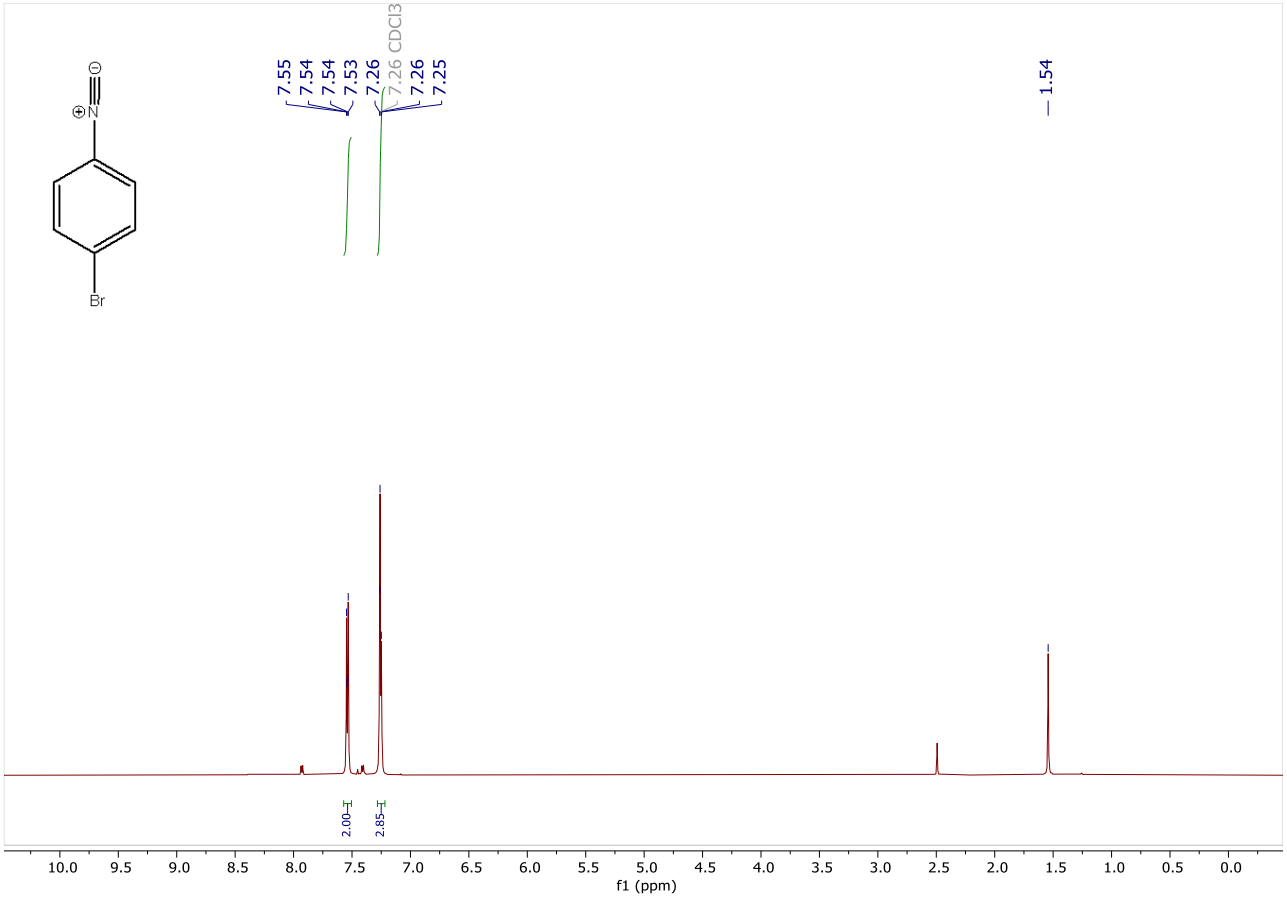

174.02
173.54
133.20
132.61
116.99
116.42
77.16 CDCl3
52.05
49.94
34.51
33.56
26.69
26.01
9.53
9.24
f1 (ppm)

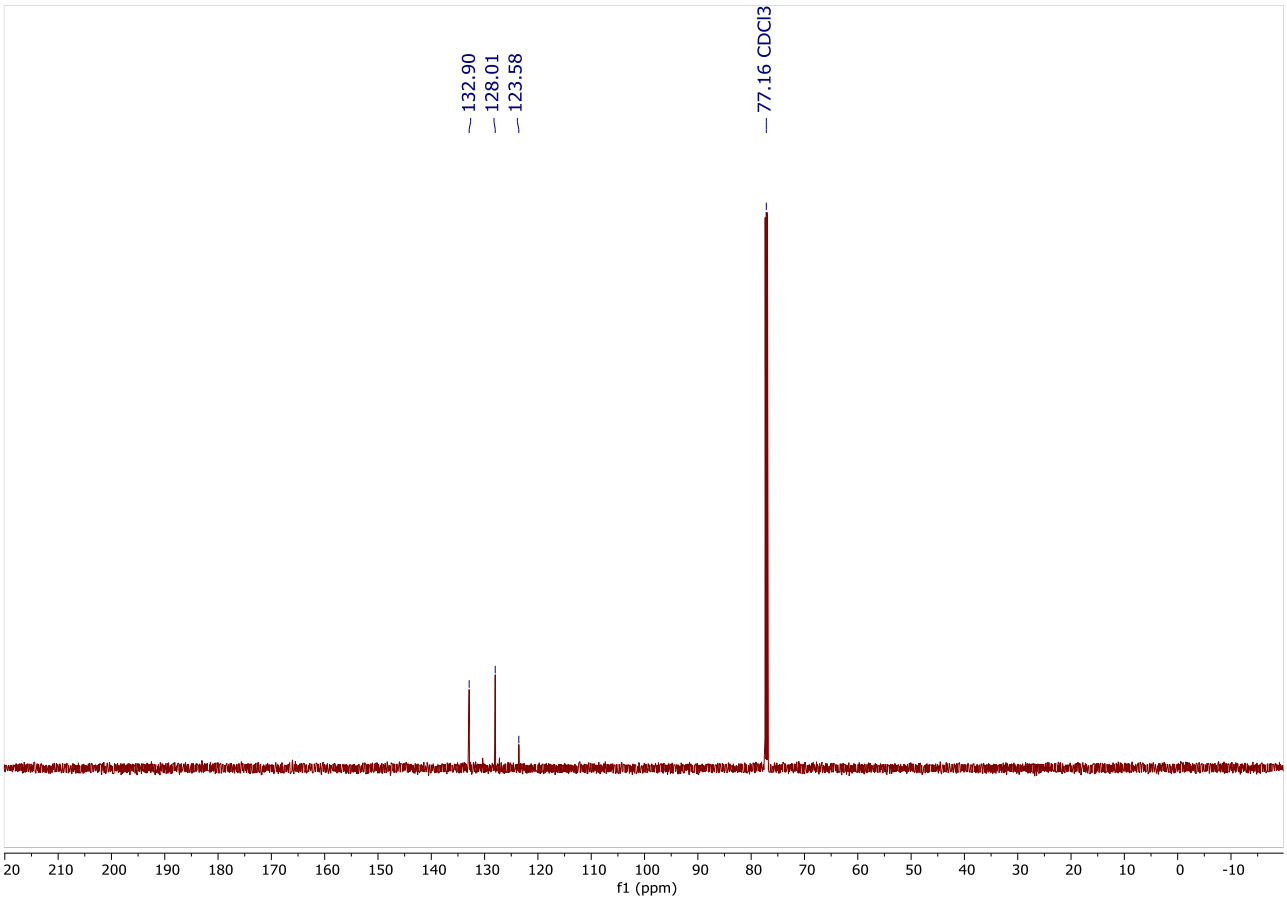

7.40
7.40
7.39
7.39
7.38
7.37
7.36
7.26
7.26 CDCl3
7.26
1.65
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

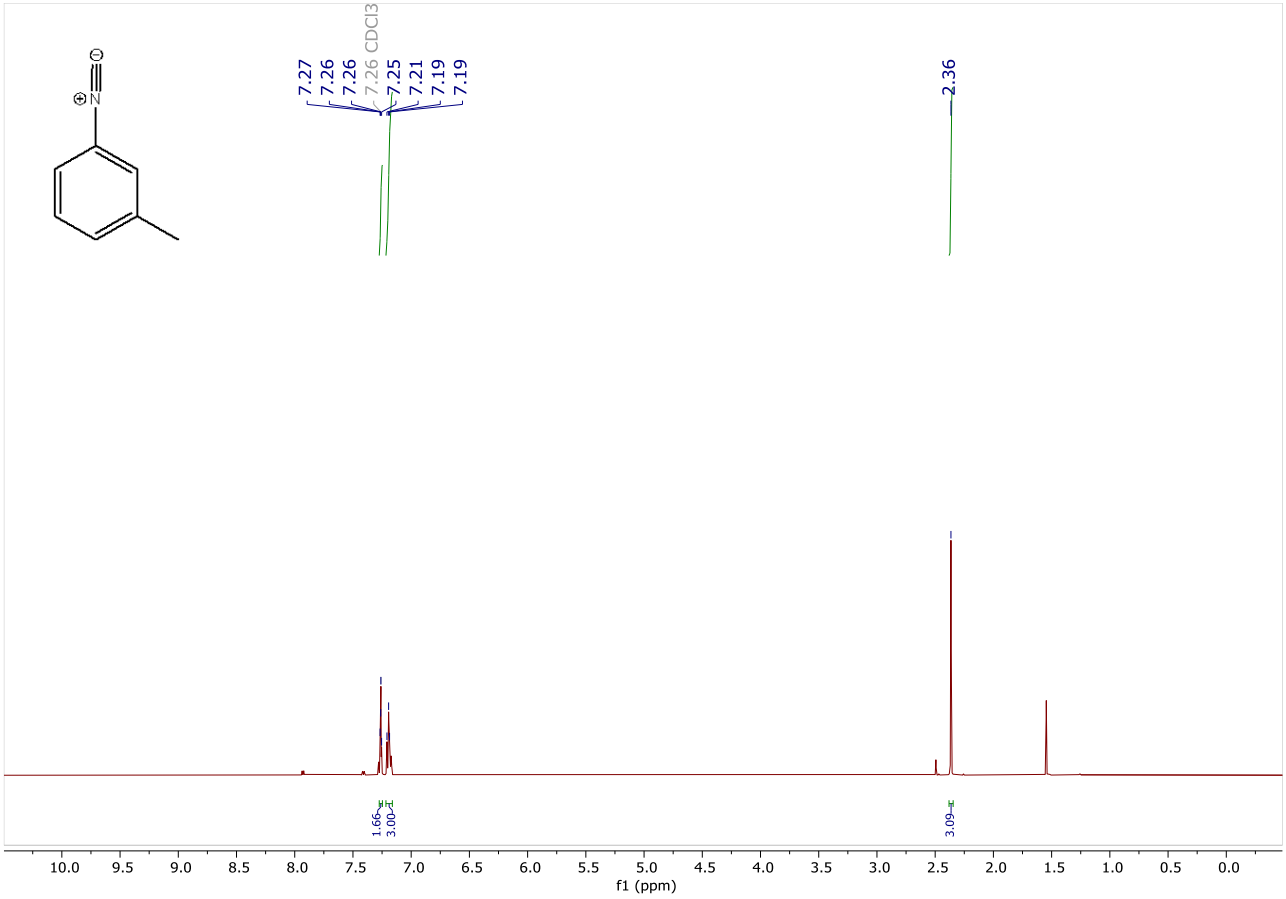

164.10
129.55
129.48
126.55
77.16 CDCl3
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

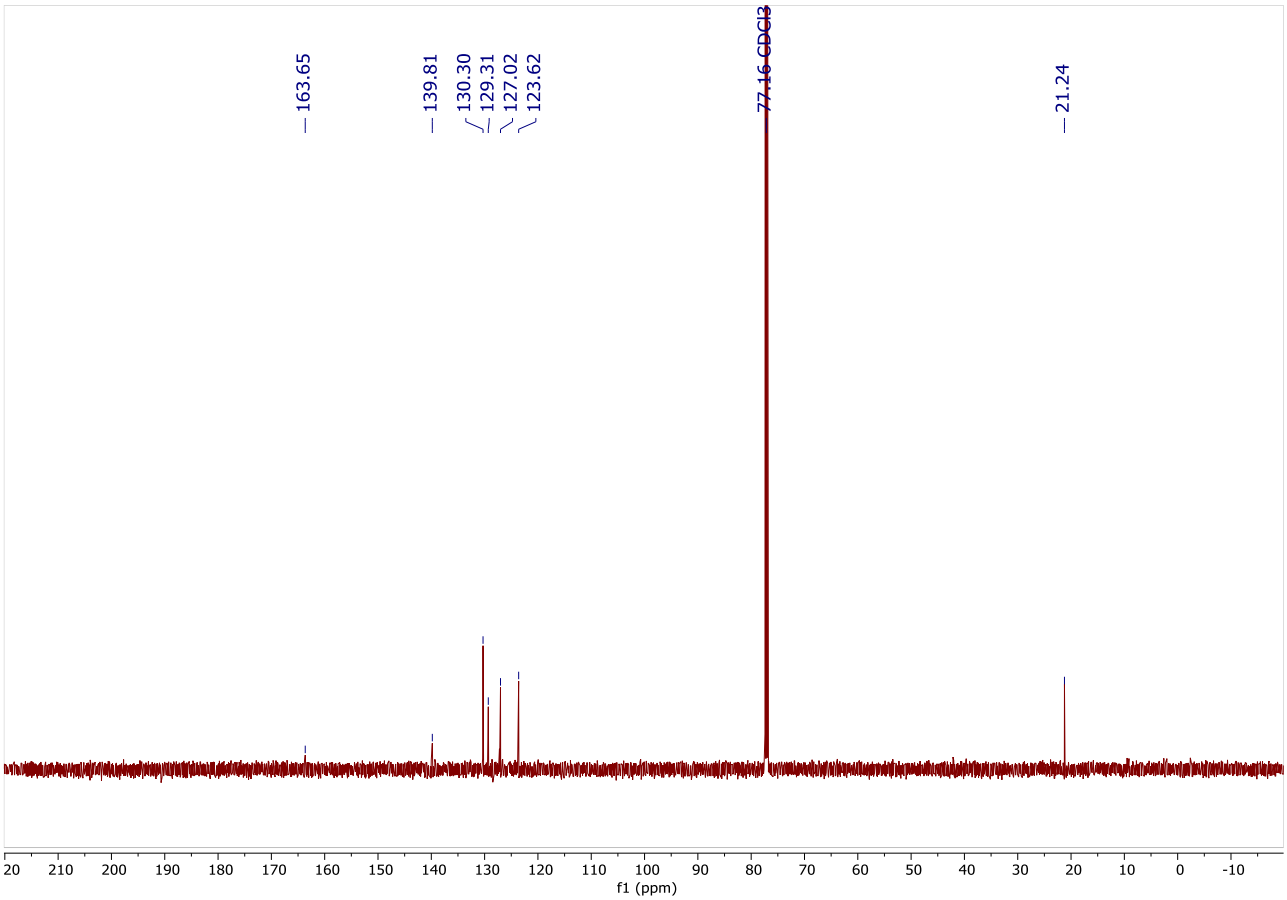

7.38
7.36
7.32
7.31
7.26 CDCl3
1.61
f1 (ppm)

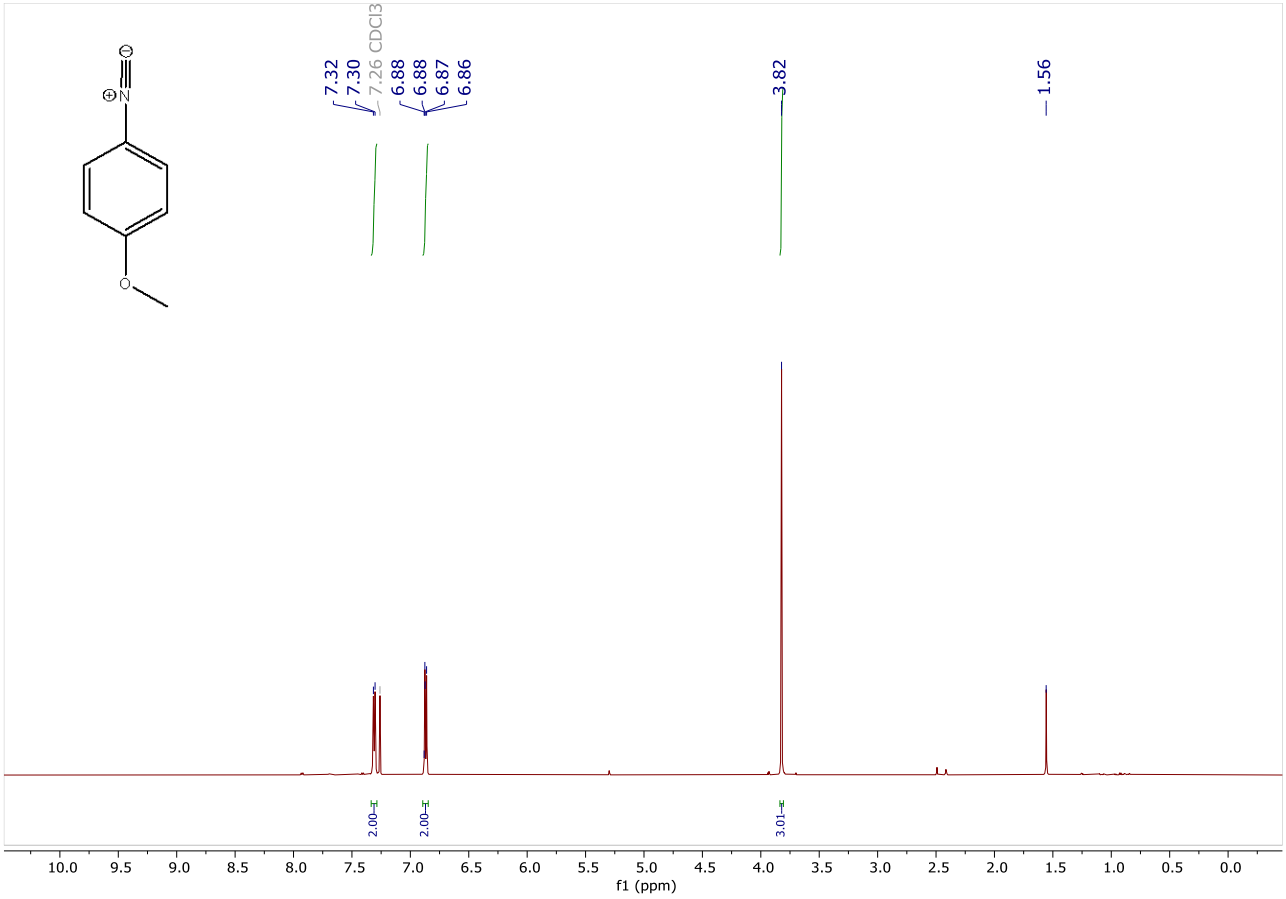

165.79
135.52
129.87
127.76
125.25
125.16
125.07
77.16 CDCl3
165.79
f1 (ppm)
125.25
125.16
125.07
f1 (ppm)
f1 (ppm)

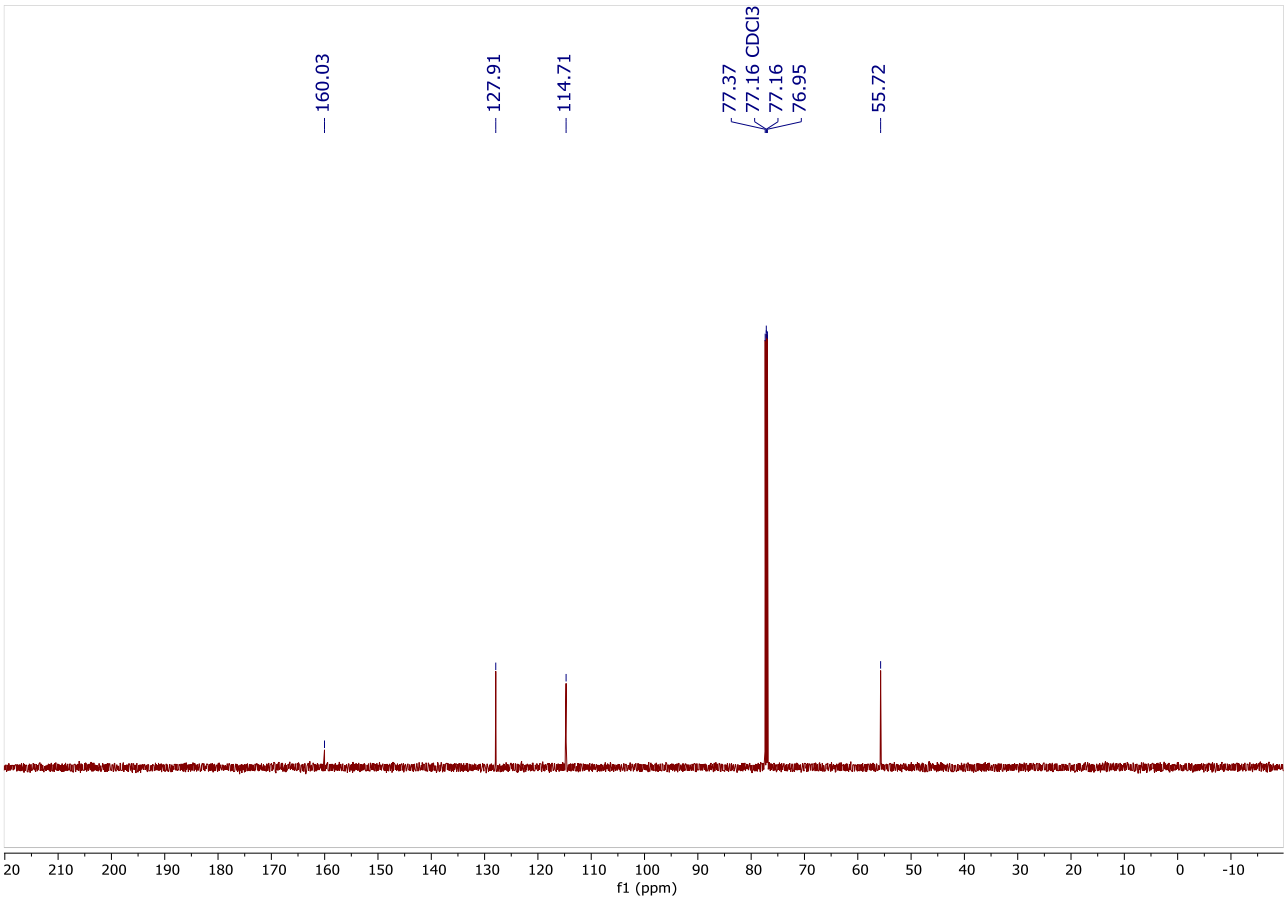

7.55
7.54
7.54
7.53
7.26
7.26 CDCl3
7.26
7.25
1.54
Br
2.00
2.85
f1 (ppm)

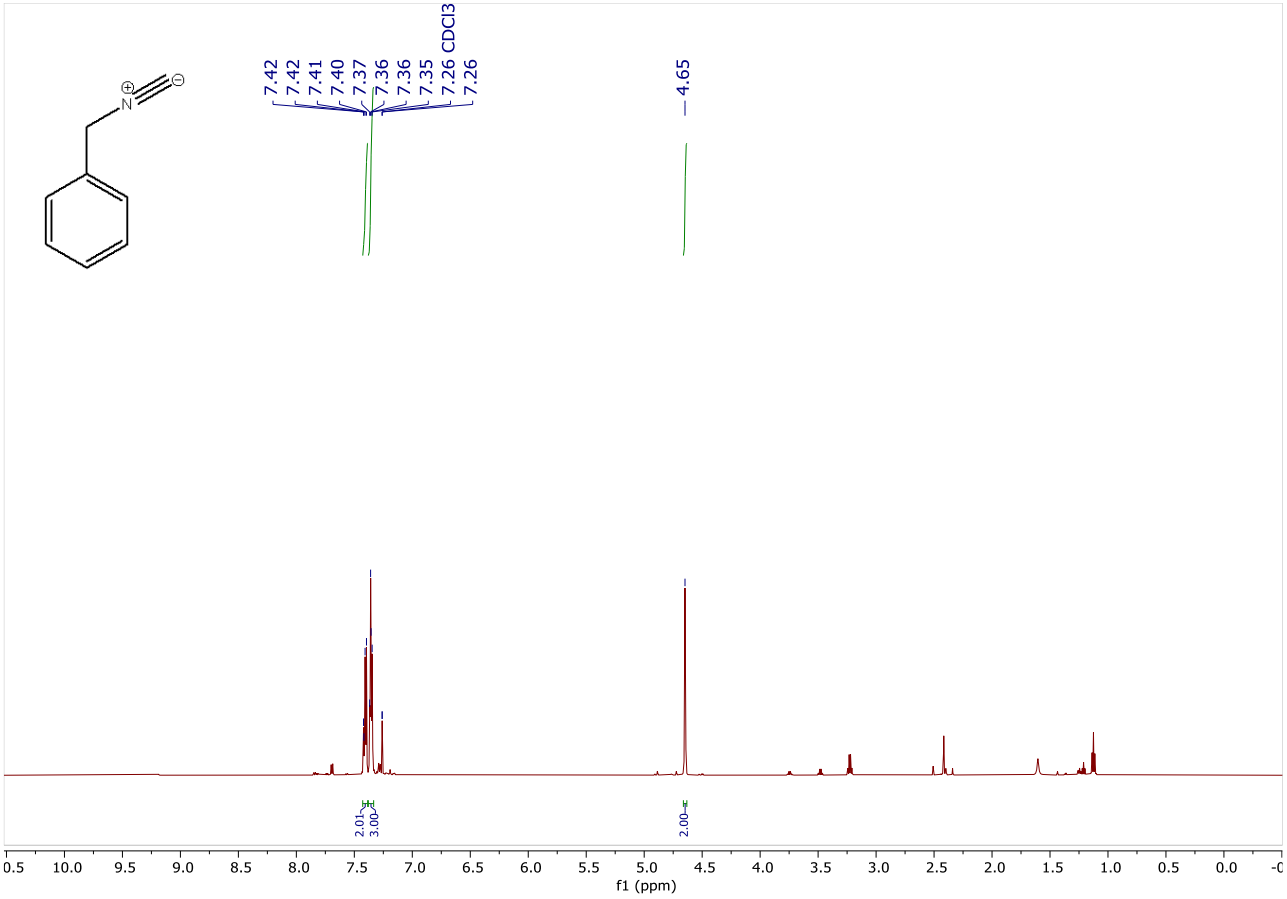

132.90
128.01
123.58
77.16 CDCl3
f1 (ppm)

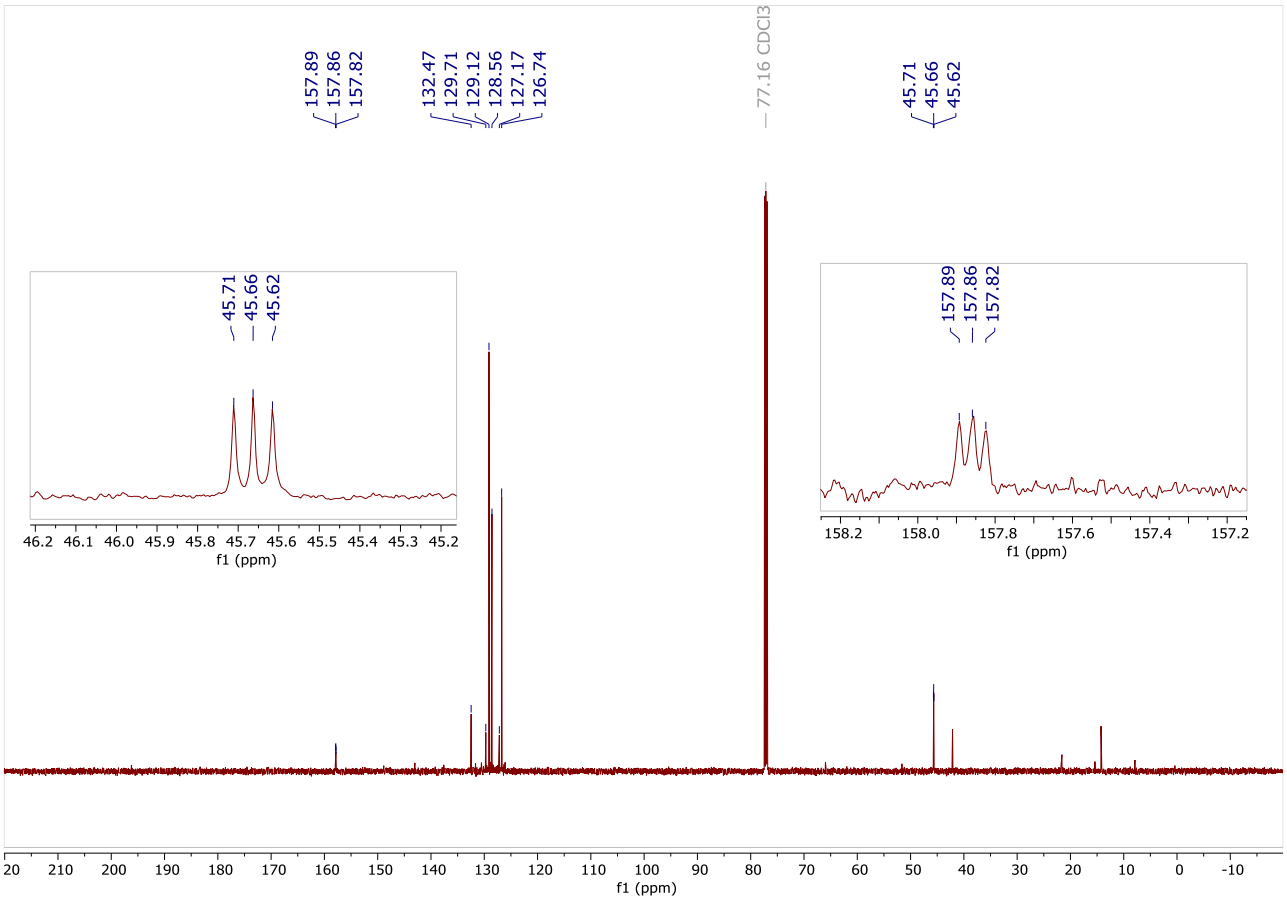

7.27
7.26
7.26
7.26 CDCl3
7.25
7.21
7.19
7.19
2.36
1.66
3.00
3.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

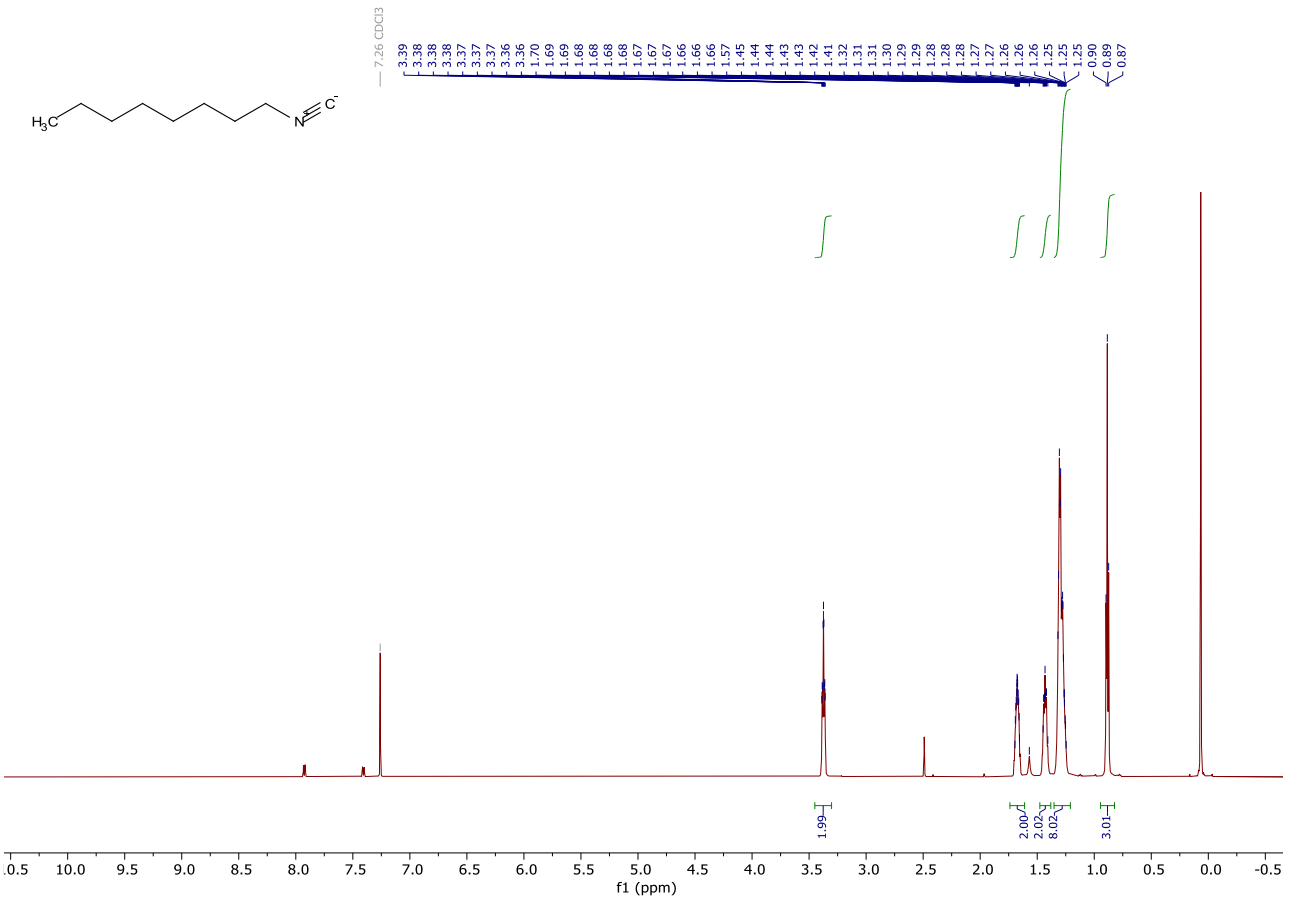

163.65
139.81
130.30
129.31
127.02
123.62
77.16 CDCl3
21.24
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

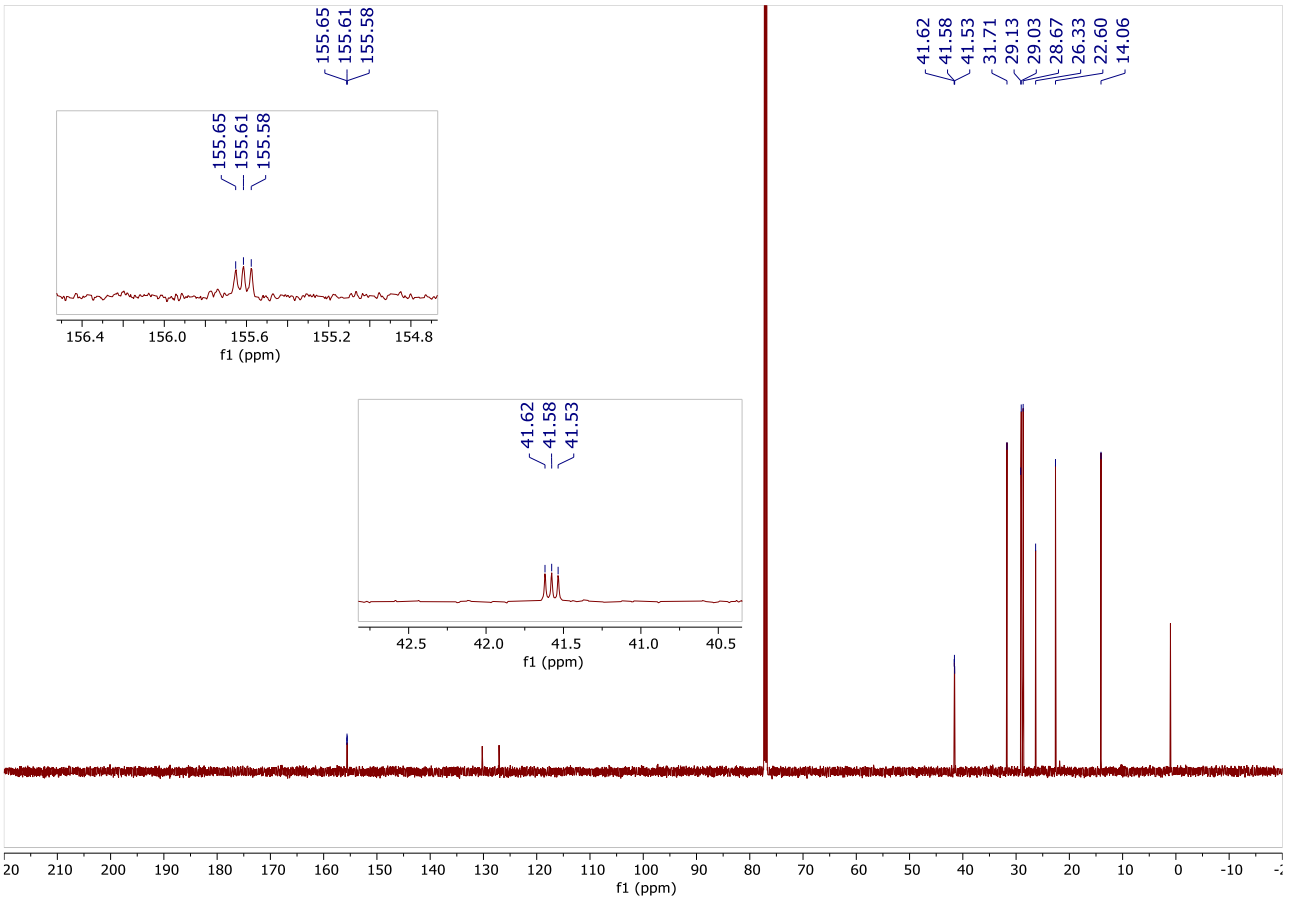

7.32
7.30
7.26 CDCl3
6.88
6.88
6.87
6.86
3.82
1.56
2.00
2.00
3.01
f1 (ppm)

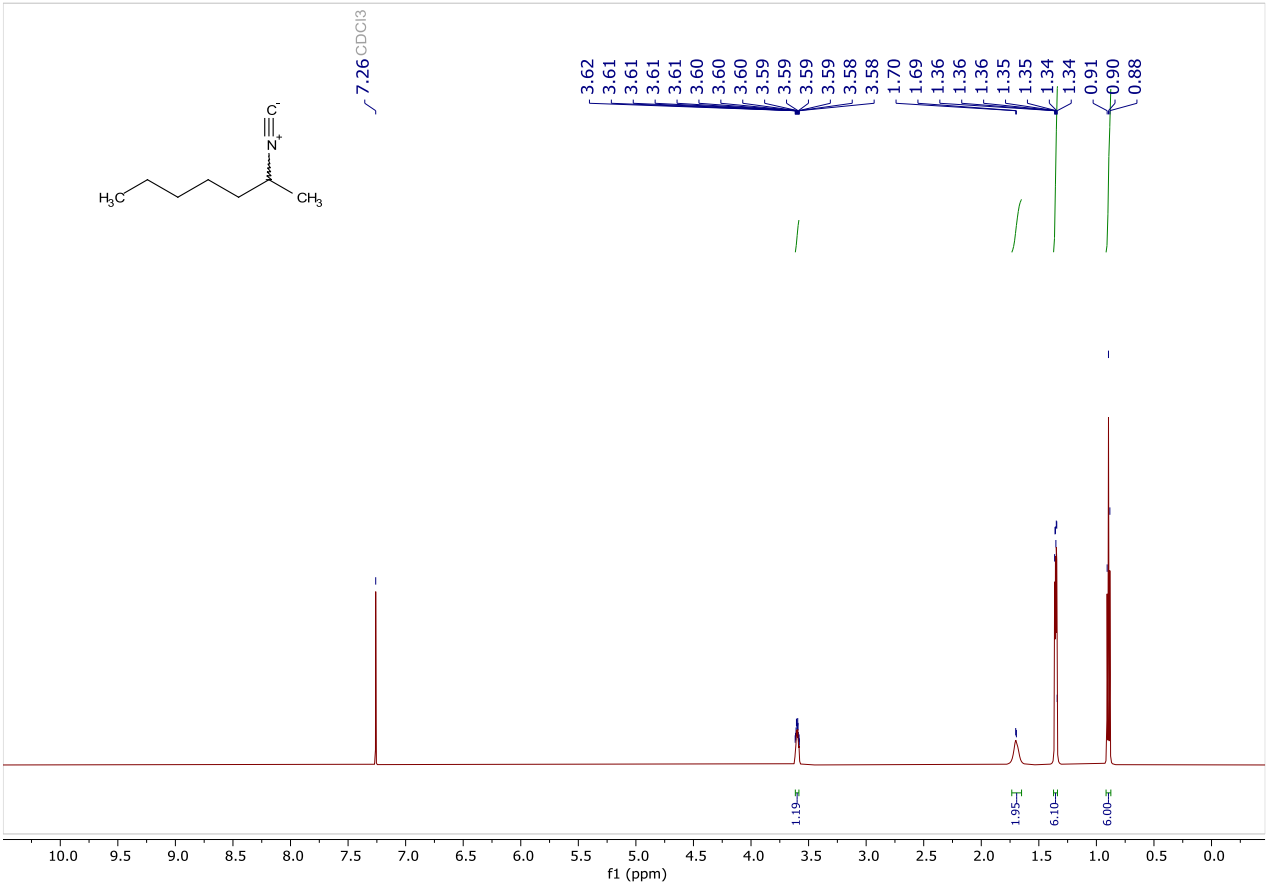

160.03
127.91
114.71
77.37
77.16 CDCl3
77.16
76.95
55.72
f1 (ppm)

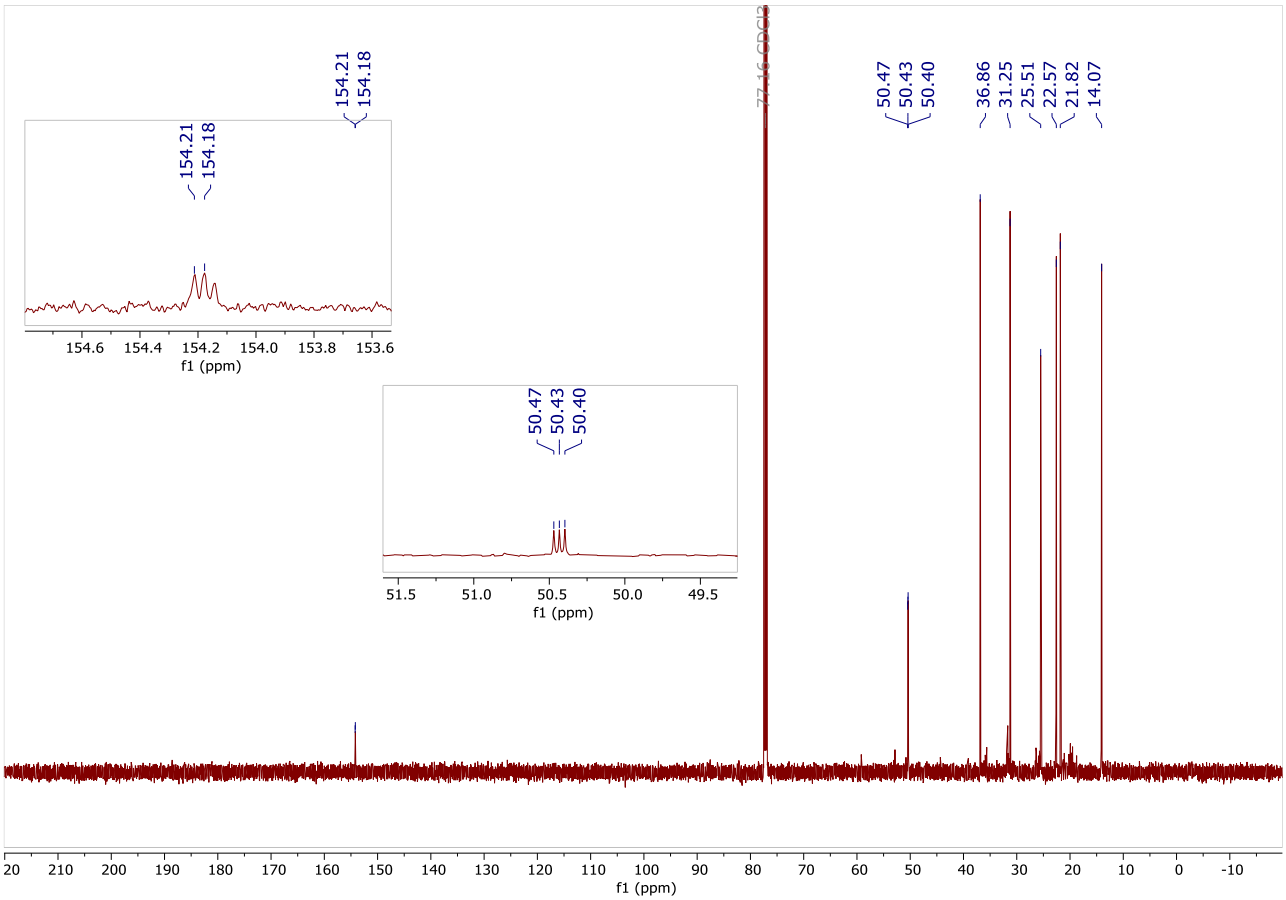

7.42
7.42
7.41
7.40
7.37
7.36
7.36
7.35
7.26 CDCl3
7.26
4.65
2.01
3.00
2.00
f1 (ppm)

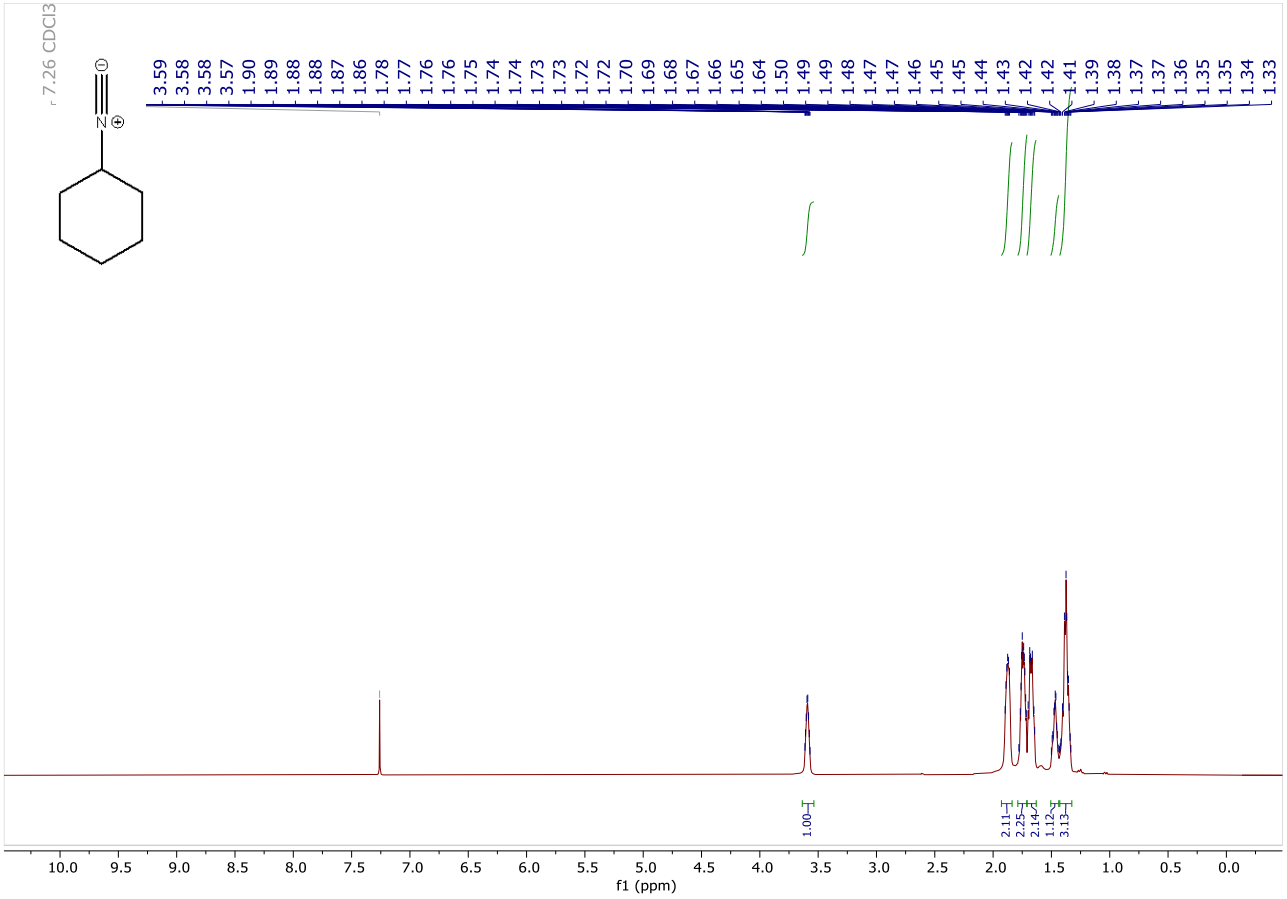

157.89
157.86
157.82
132.47
129.71
129.12
128.56
127.17
126.74
77.16 CDCl3
45.71
45.66
45.62
f1 (ppm)

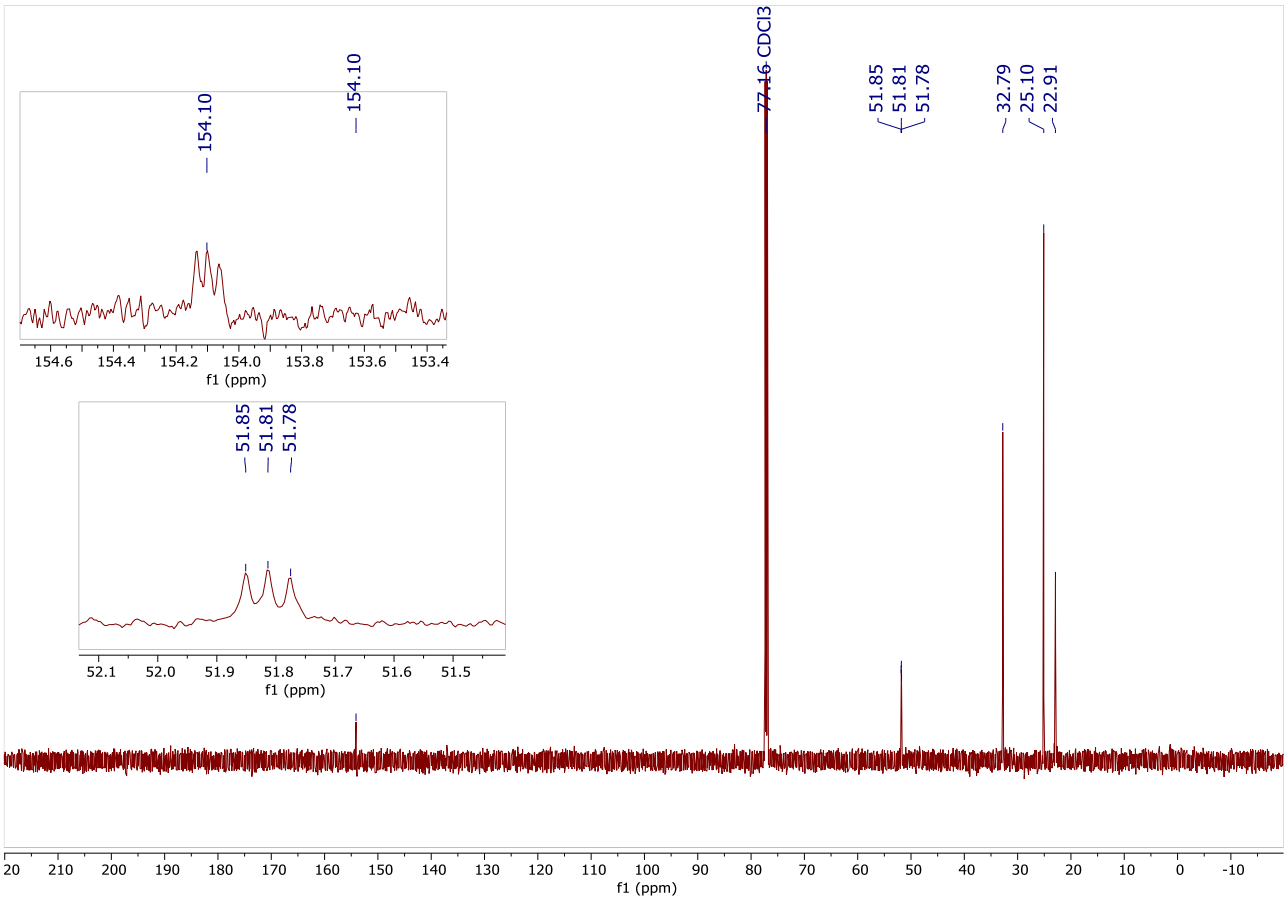

7.26 CDCl3
3.39 3.38 3.38 3.38 3.37 3.37 3.37 3.36 3.36 1.70 1.69 1.69 1.68 1.68 1.68 1.68 1.67 1.67 1.67 1.66 1.66 1.66 1.57 1.45 1.44 1.44 1.43 1.43 1.42 1.41 1.32 1.31 1.31 1.30 1.29 1.29 1.28 1.28 1.28 1.27 1.27 1.26 1.26 1.26 1.25 1.25 1.25 0.90 0.89 0.87
1.99
2.00
2.02
8.02
3.01
f1 (ppm)

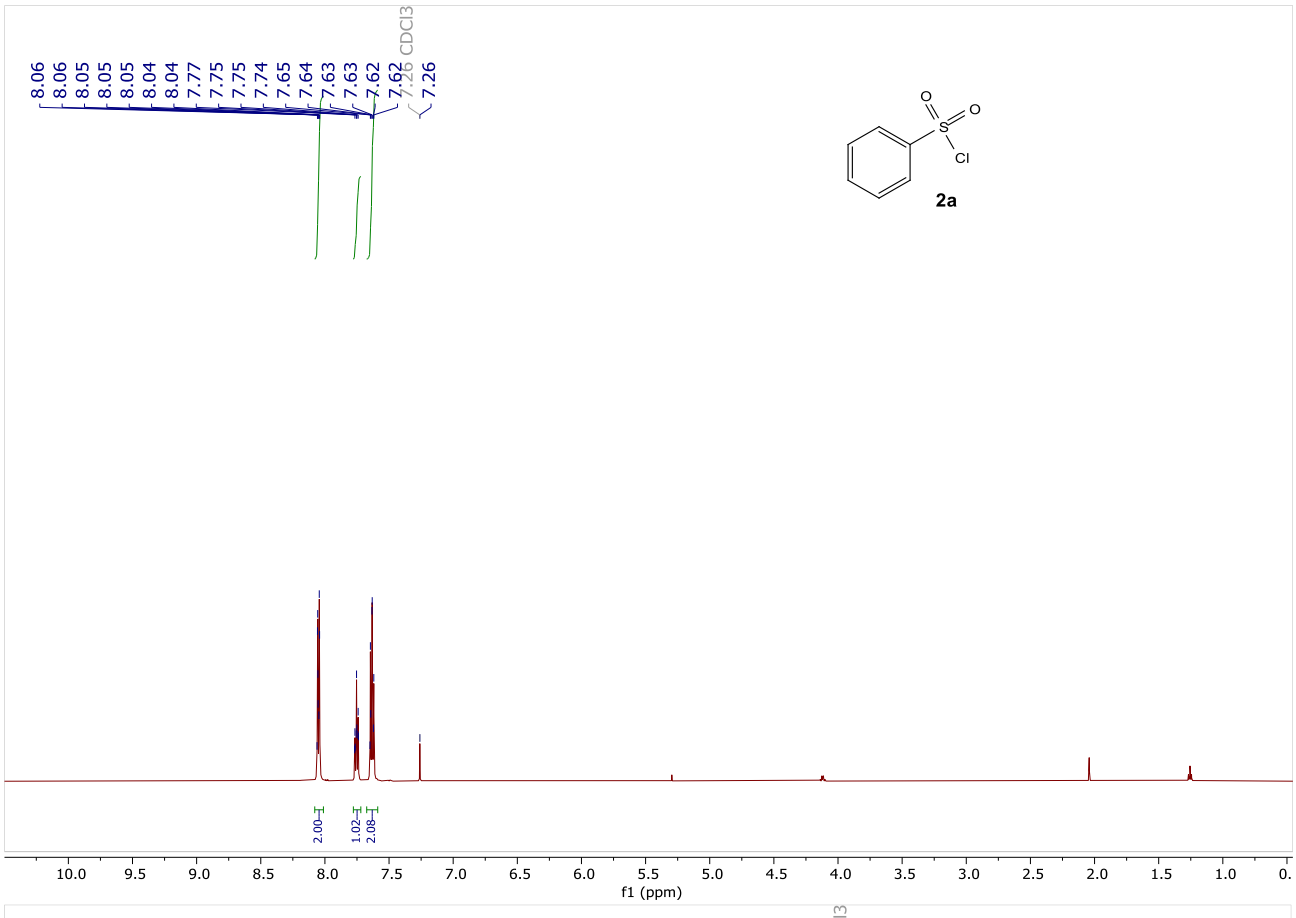

155.65 155.61 155.58
41.62 41.58 41.53 31.71 29.13 29.03 28.67 26.33 22.60 14.06
f1 (ppm)

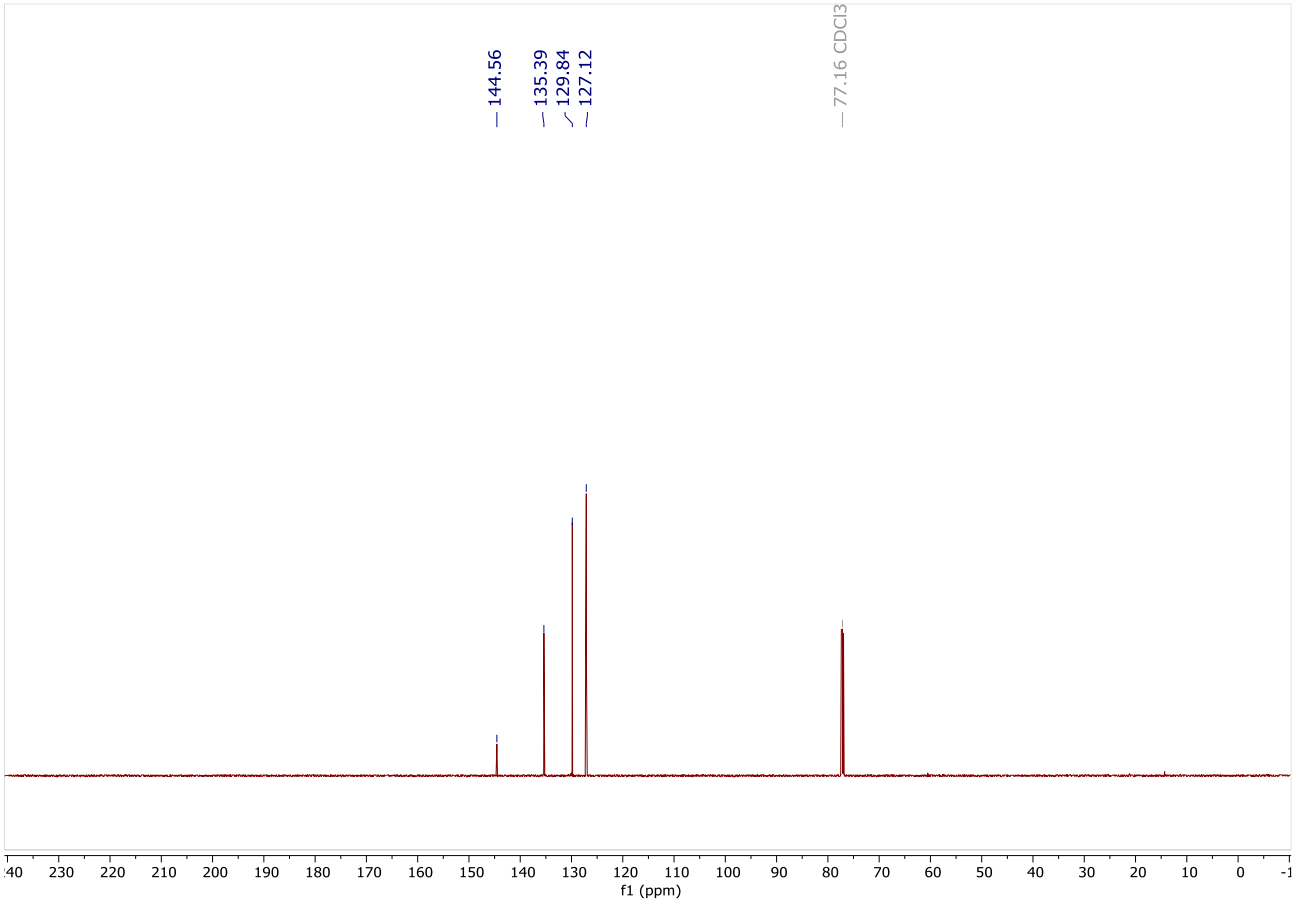

7.26 CDCl3
3.62
3.61
3.61
3.61
3.60
3.60
3.60
3.59
3.59
3.59
3.59
3.58
3.58
1.70
1.69
1.36
1.36
1.36
1.35
1.35
1.34
1.34
0.91
0.90
0.88
1.19
1.95
6.10
6.00
f1 (ppm)

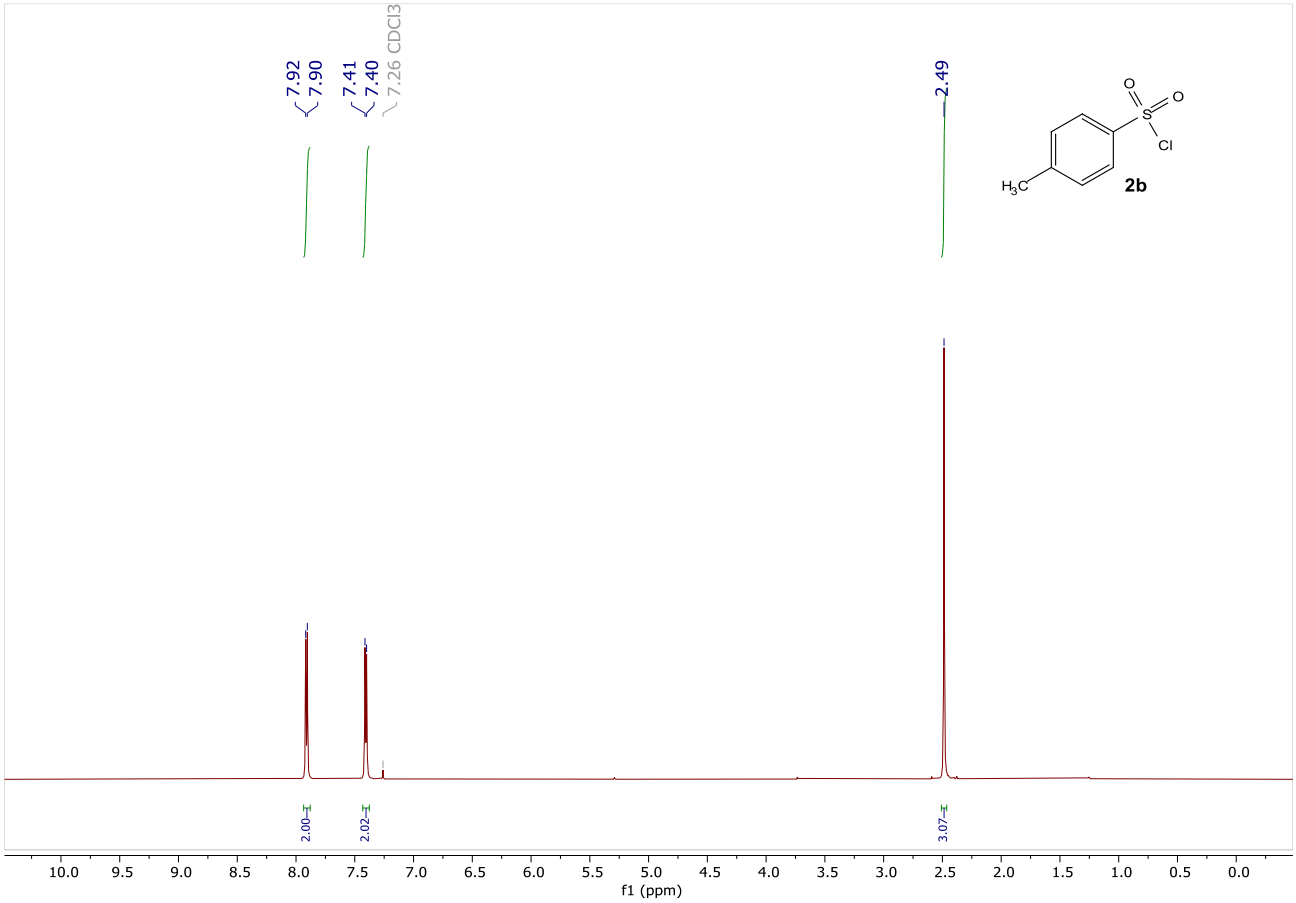

154.21
154.18
77.16 CDCl3
50.47
50.43
50.40
36.86
31.25
25.51
22.57
21.82
14.07
f1 (ppm)


7.26 CDCl3
3.59 3.58 3.58 3.57 1.90 1.89 1.88 1.88 1.87 1.86 1.78 1.77 1.76 1.76 1.75 1.74 1.74 1.73 1.73 1.72 1.72 1.70 1.69 1.68 1.67 1.66 1.65 1.64 1.50 1.49 1.49 1.48 1.47 1.47 1.46 1.45 1.45 1.44 1.43 1.42 1.42 1.41 1.39 1.38 1.37 1.37 1.36 1.35 1.35 1.34 1.33
1.00
2.11
2.25
2.14
1.12
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


154.10
154.10
154.6 154.4 154.2 154.0 153.8 153.6 153.4
f1 (ppm)
51.85
51.81
51.78
52.1 52.0 51.9 51.8 51.7 51.6 51.5
f1 (ppm)
77.16 CDCl3
51.85
51.81
51.78
32.79
25.10
22.91
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

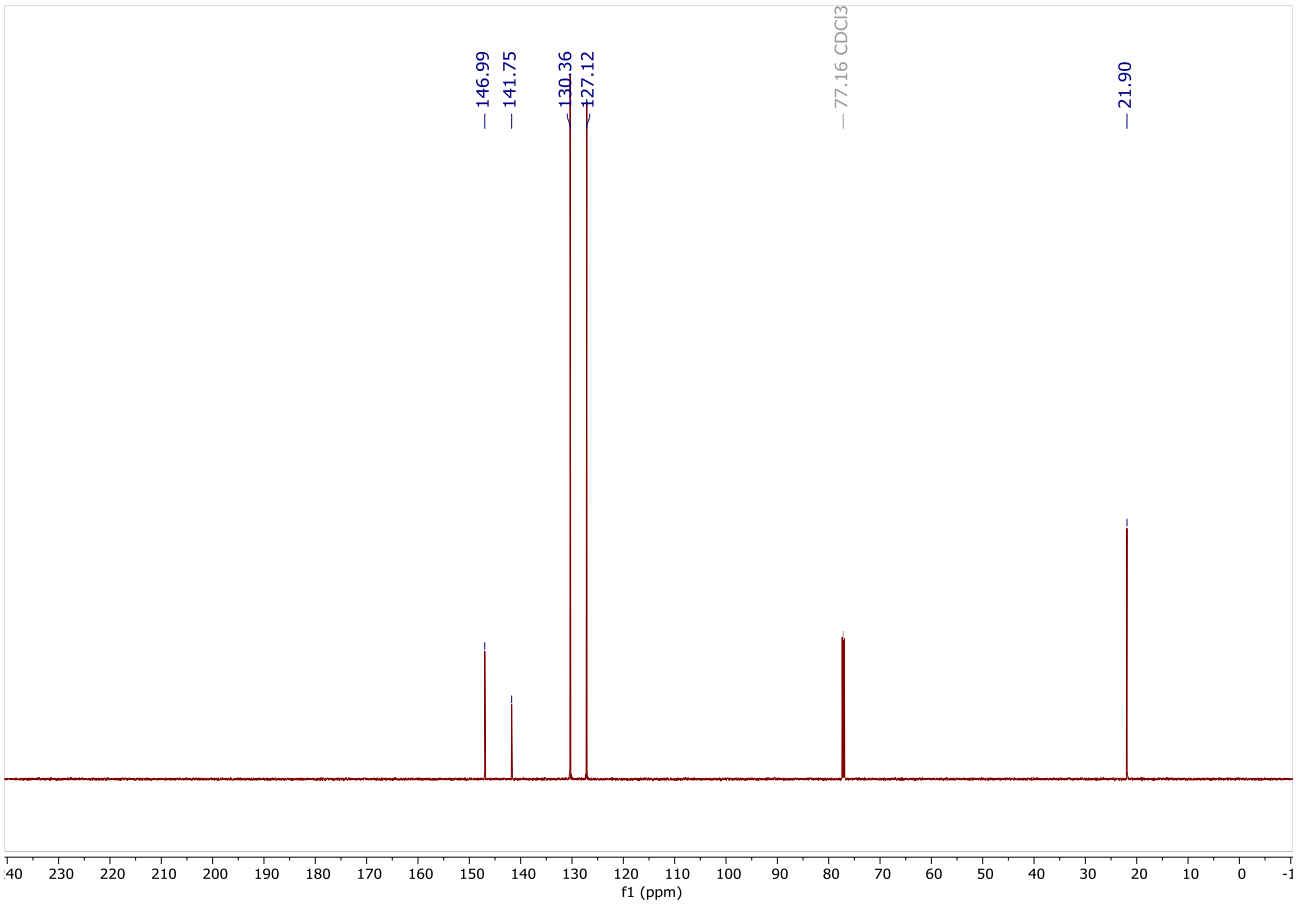

8.06
8.06
8.05
8.05
8.05
8.04
8.04
7.77
7.75
7.75
7.74
7.65
7.64
7.63
7.63
7.62
7.62
7.26 CDCl3
7.26
O
O
S
Cl
2a
2.00
1.02
2.08
f1 (ppm)

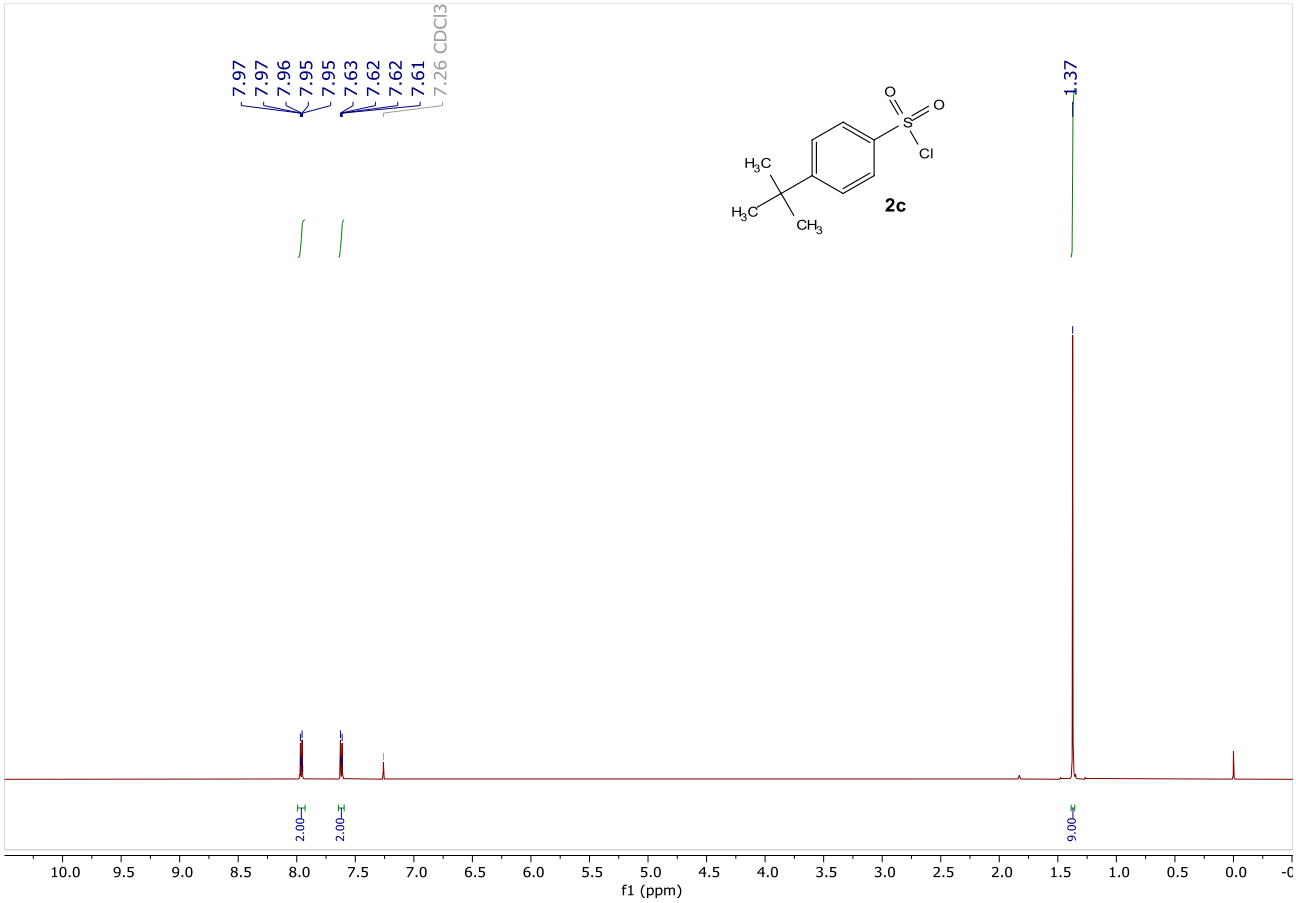

144.56
135.39
129.84
127.12
77.16 CDCl3
f1 (ppm)

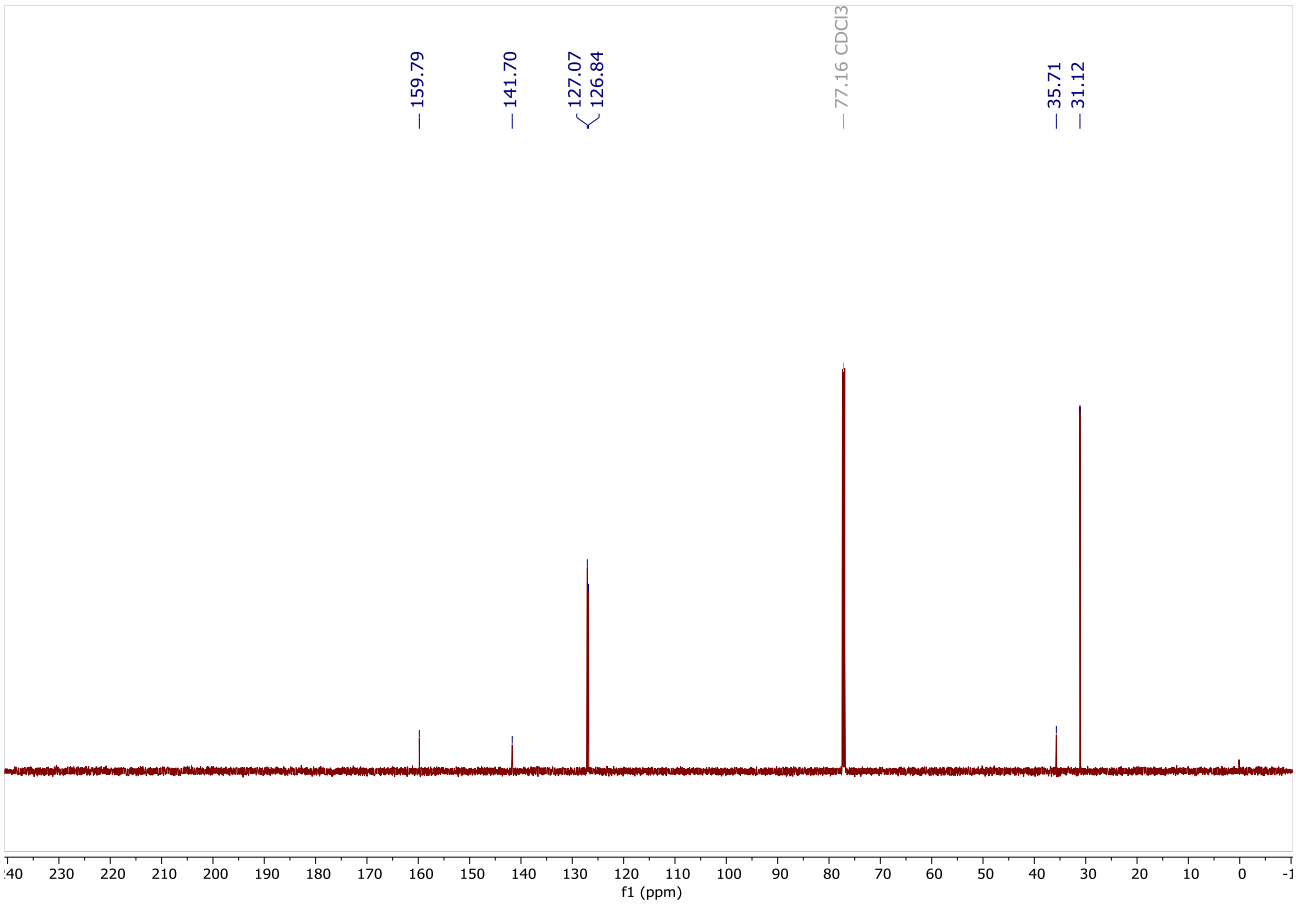

7.92
7.90
7.41
7.40
7.26 CDCl3
2.49
2.00
2.02
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

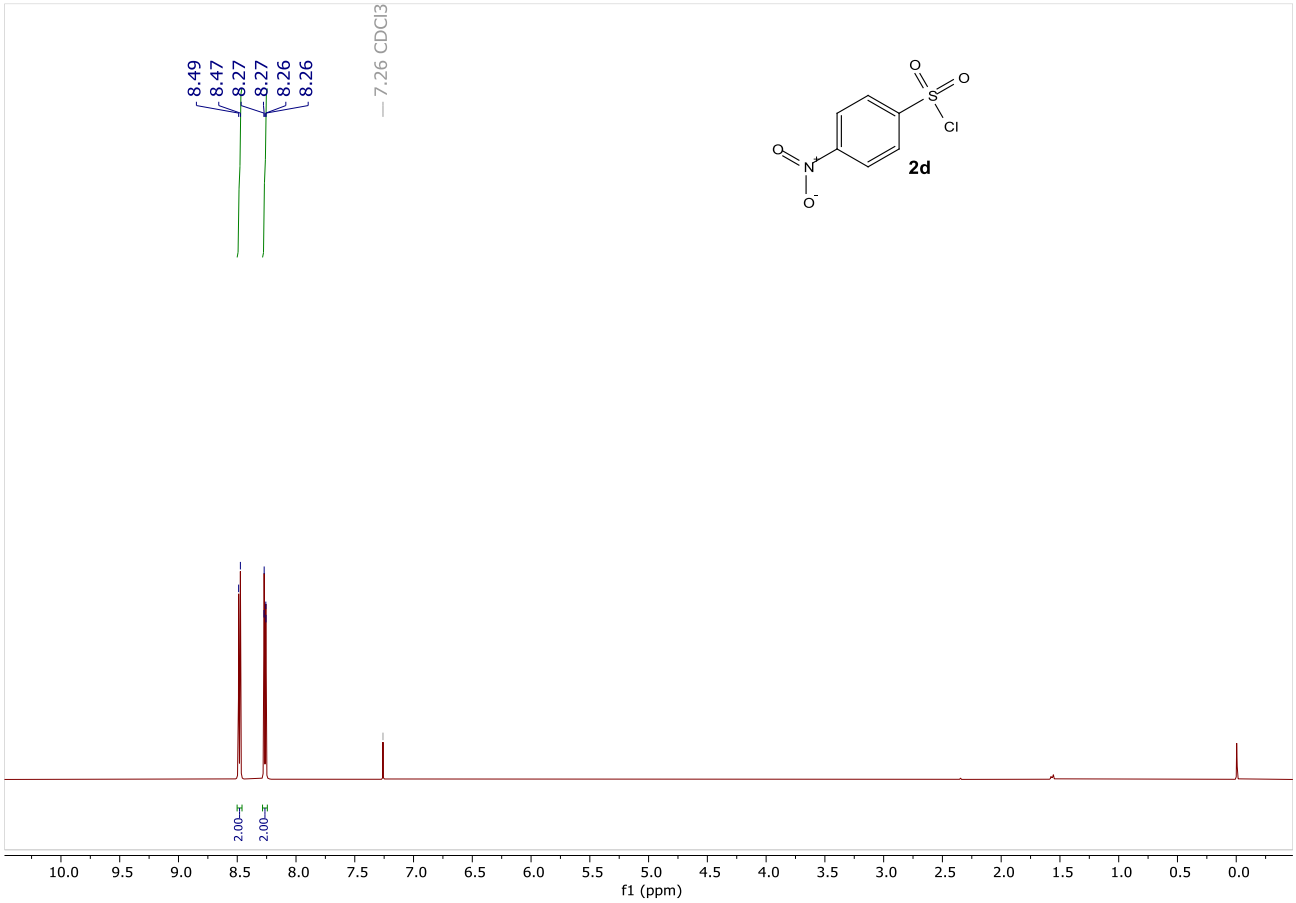
O
O
S
Cl
H3C

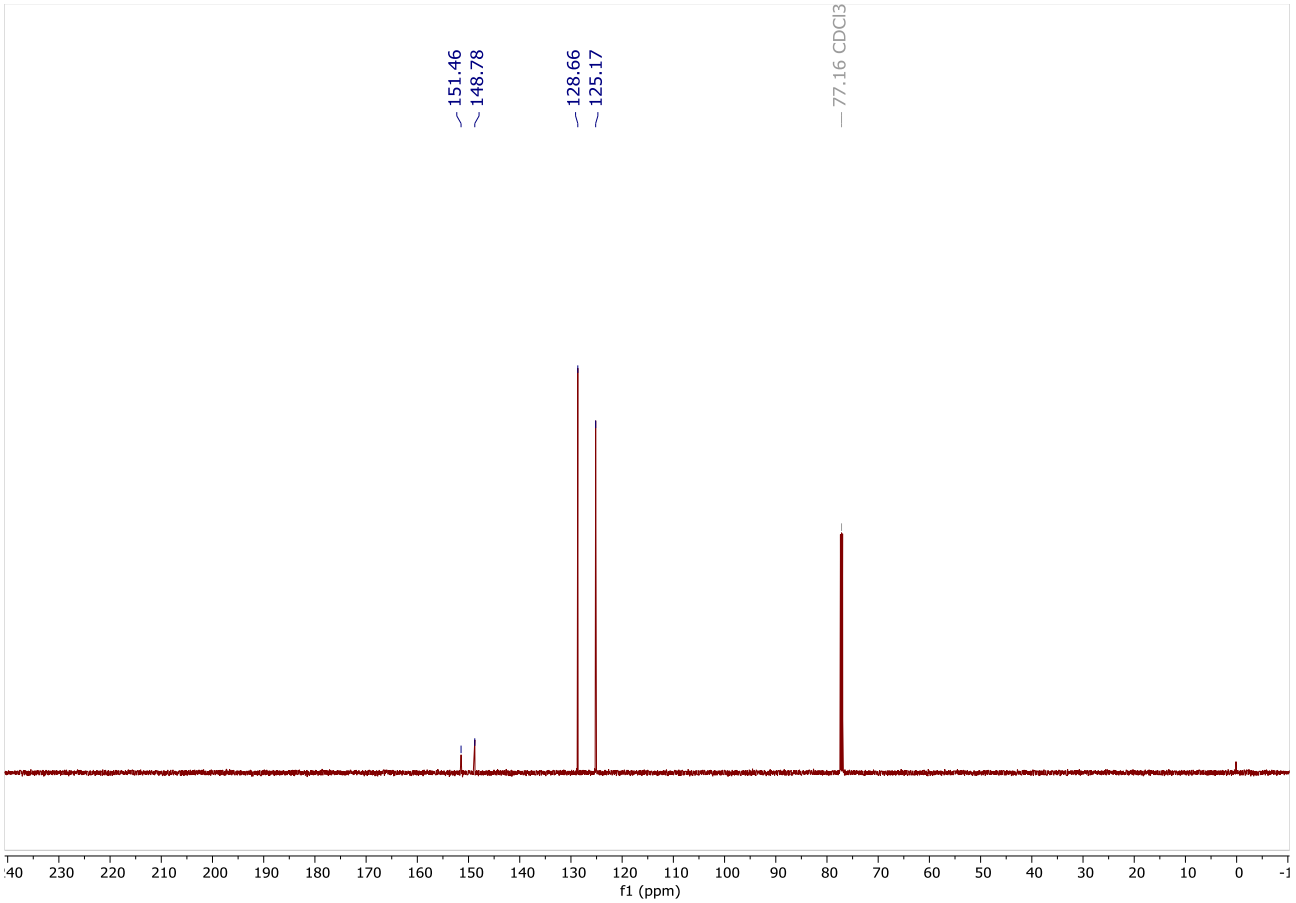
2b

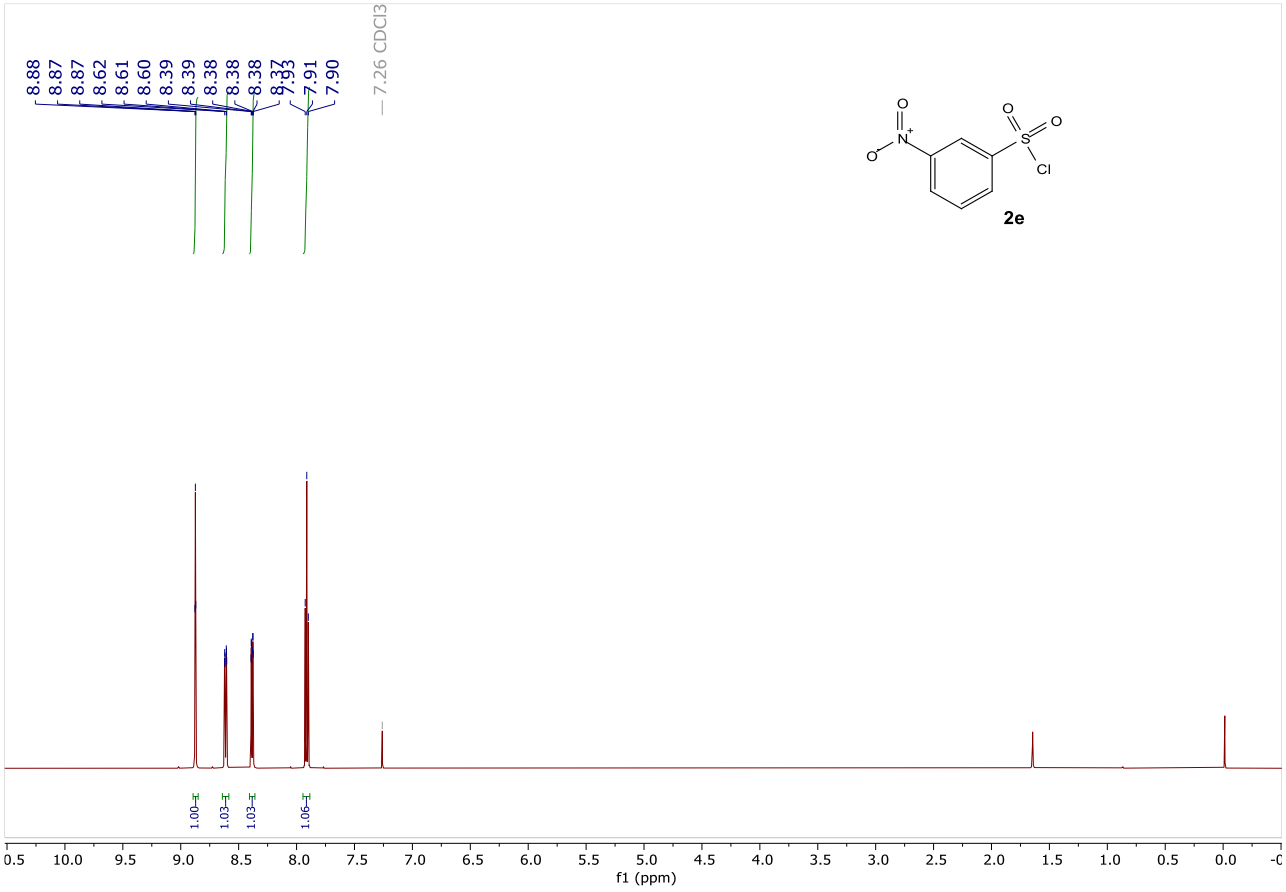

146.99
141.75
130.36
127.12
77.16 CDCl3
21.90
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


7.97
7.97
7.96
7.95
7.95
7.63
7.62
7.62
7.61
7.26 CDCl3
1.37
2c
2.00
2.00
9.00
f1 (ppm)


159.79
141.70
127.07
126.84
77.16 CDCl3
35.71
31.12
f1 (ppm)

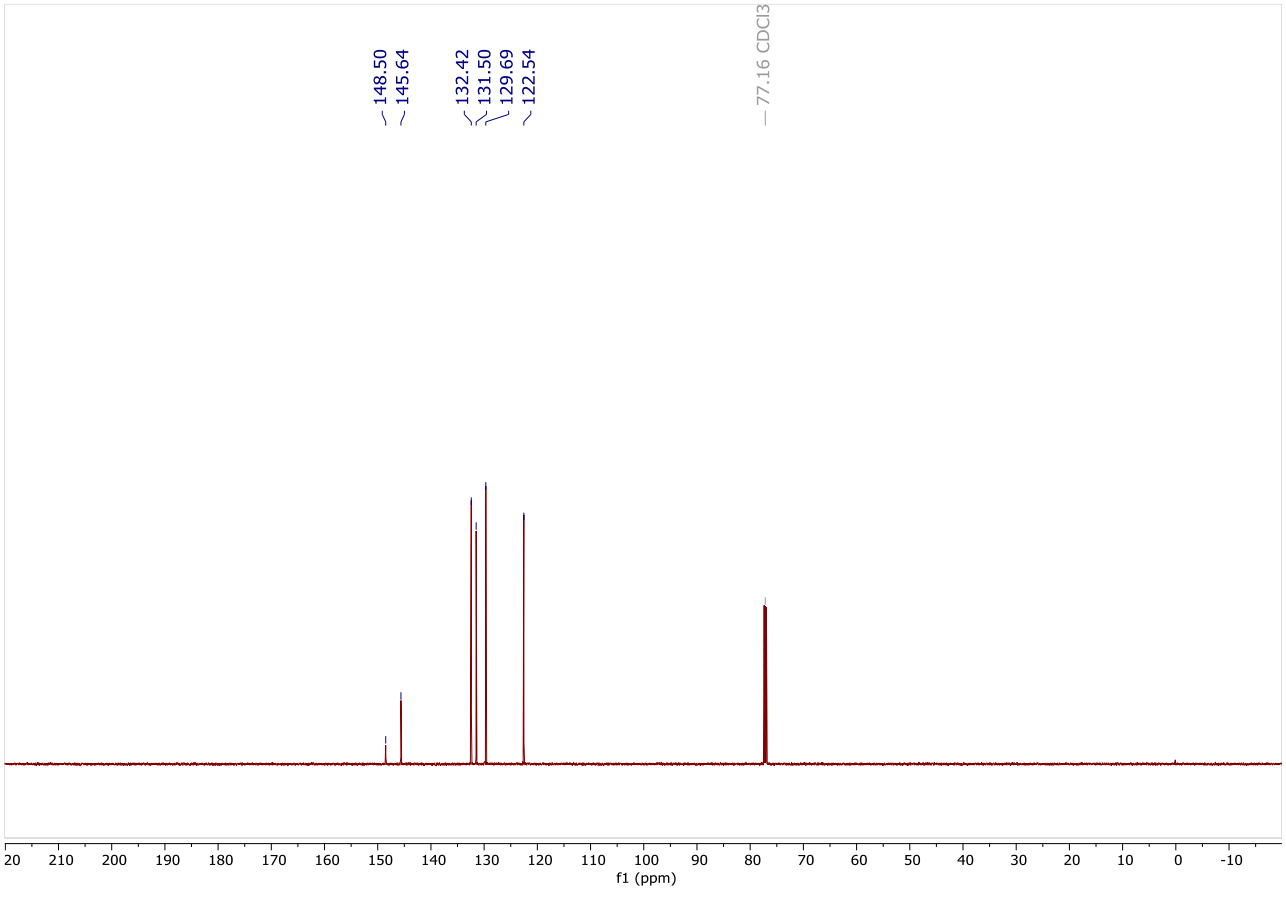

8.49
8.47
8.27
8.27
8.26
8.26
7.26 CDCl3
2d
2.00
2.00
f1 (ppm)

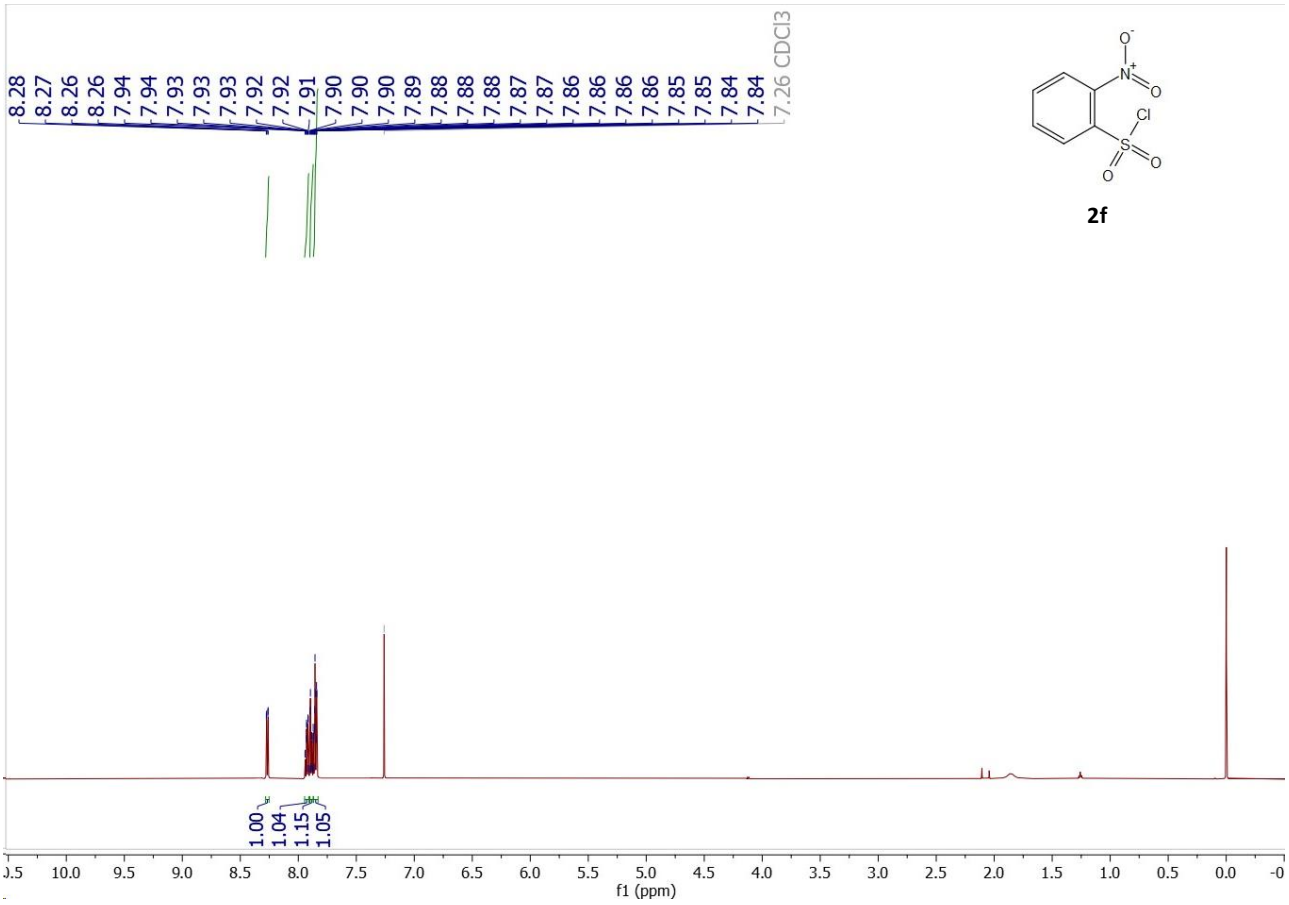

151.46
148.78
128.66
125.17
77.16 CDCl3
f1 (ppm)


8.88
8.87
8.87
8.62
8.61
8.60
8.39
8.39
8.38
8.38
8.38
7.93
7.91
7.90
7.26 CDCl3
1.00
1.03
1.03
1.06
f1 (ppm)

O
N+
O
O
S
O
Cl

2e


148.50
145.64
132.42
131.50
129.69
122.54
77.16 CDCl3
f1 (ppm)


8.28
8.27
8.26
8.26
7.94
7.94
7.93
7.93
7.93
7.92
7.92
7.91
7.90
7.90
7.90
7.89
7.88
7.88
7.88
7.87
7.87
7.86
7.86
7.86
7.86
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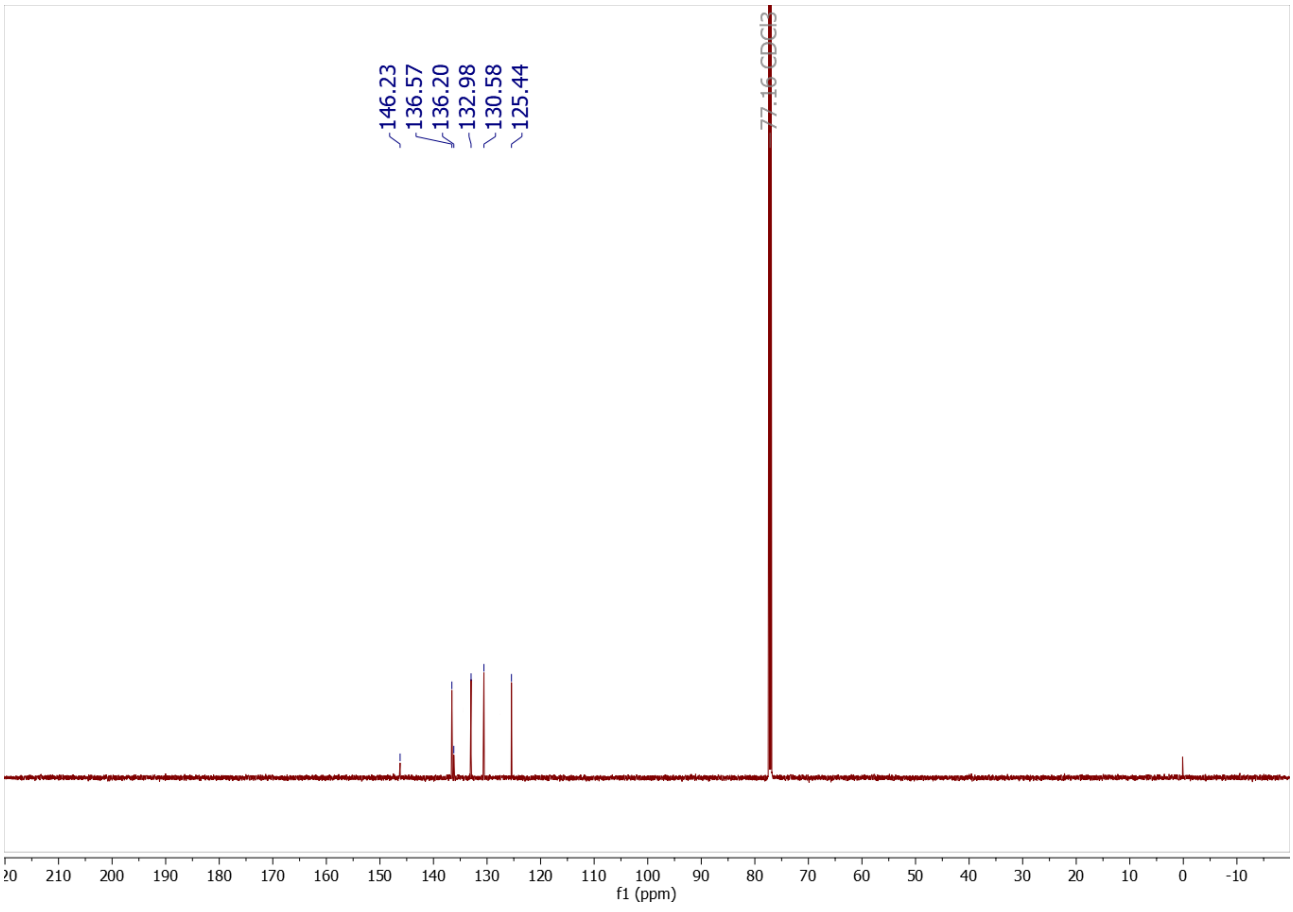
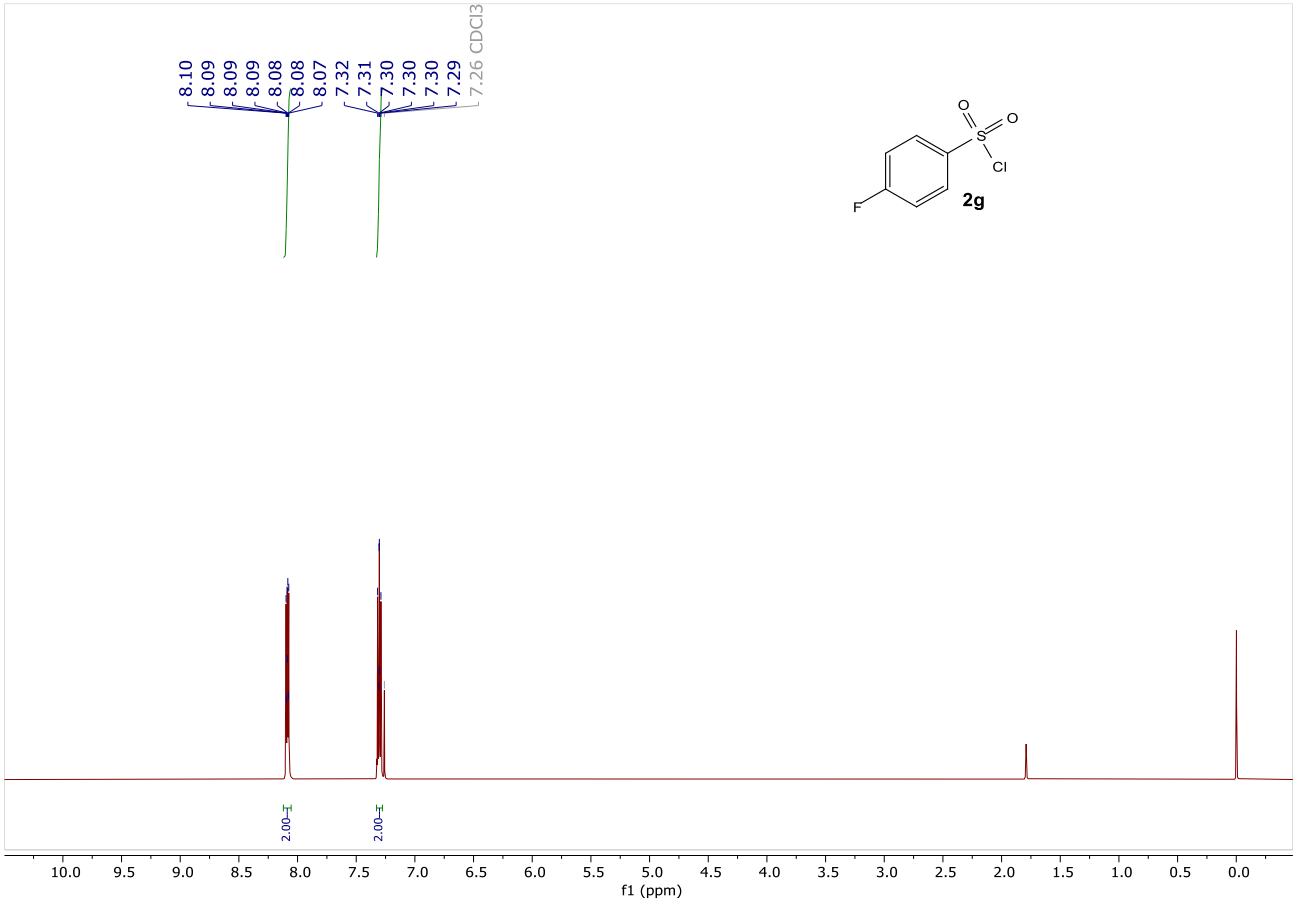
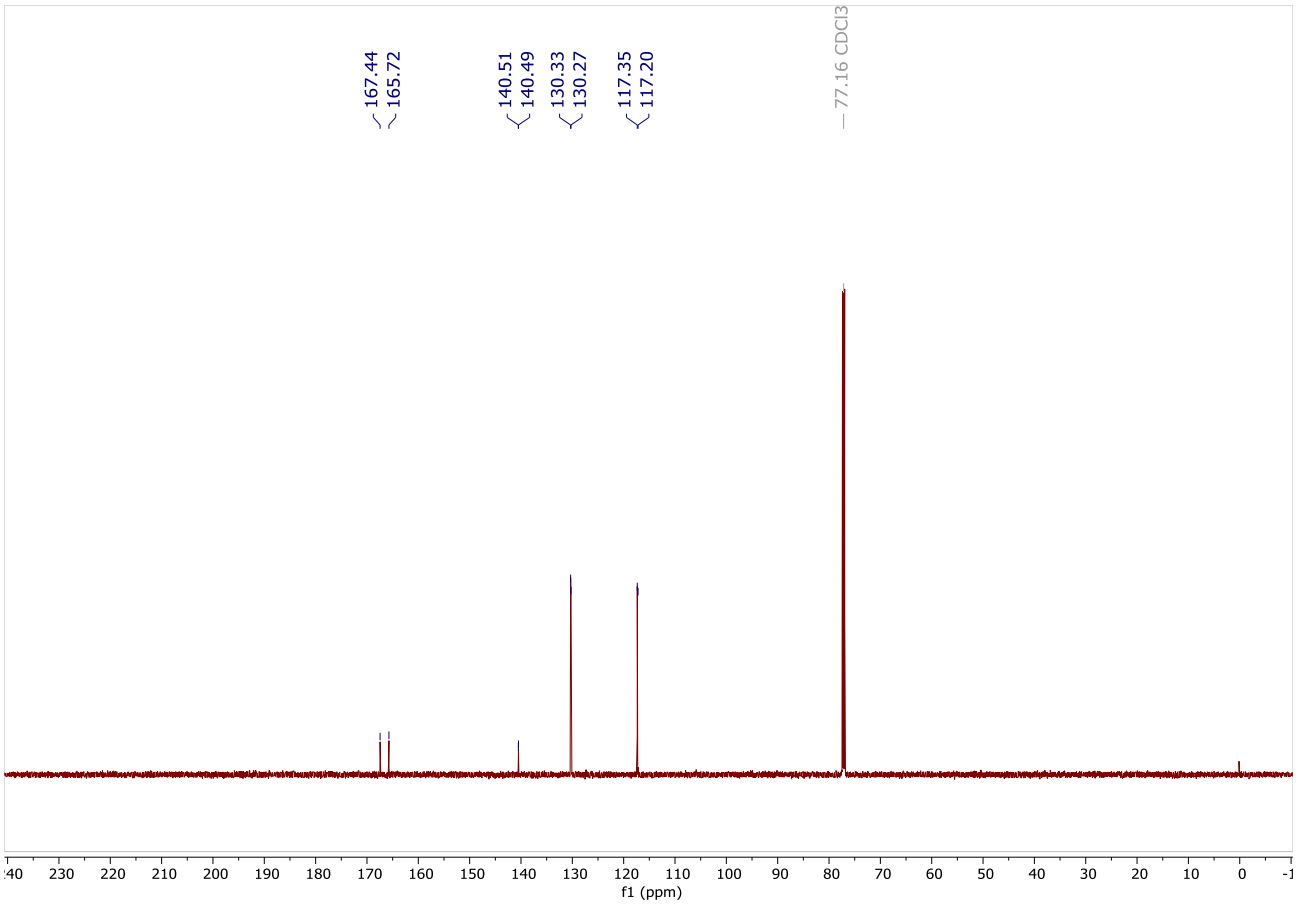
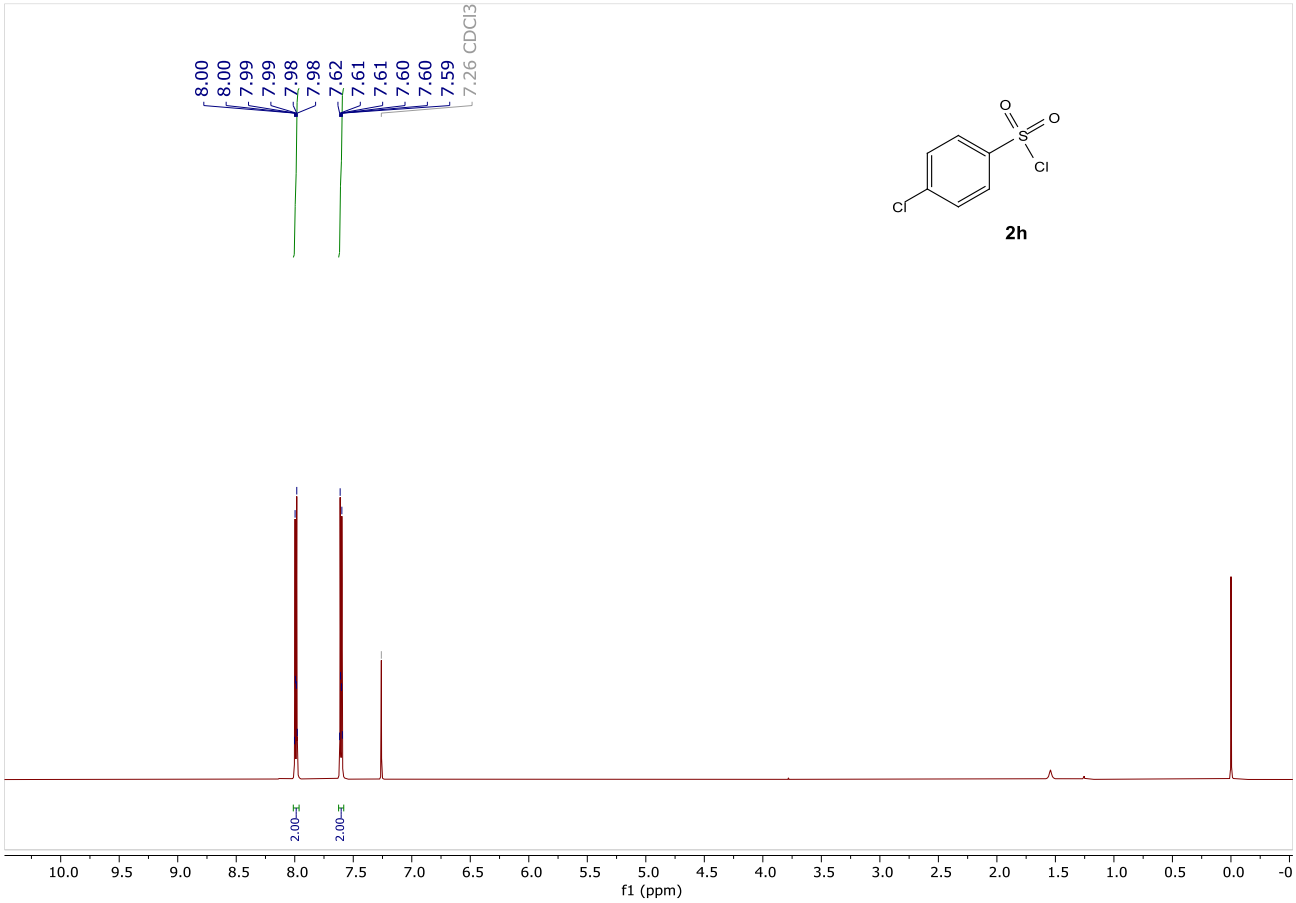
7.84
7.84
7.26 CDCl3
1.00
1.04
1.15
1.05
f1 (ppm)

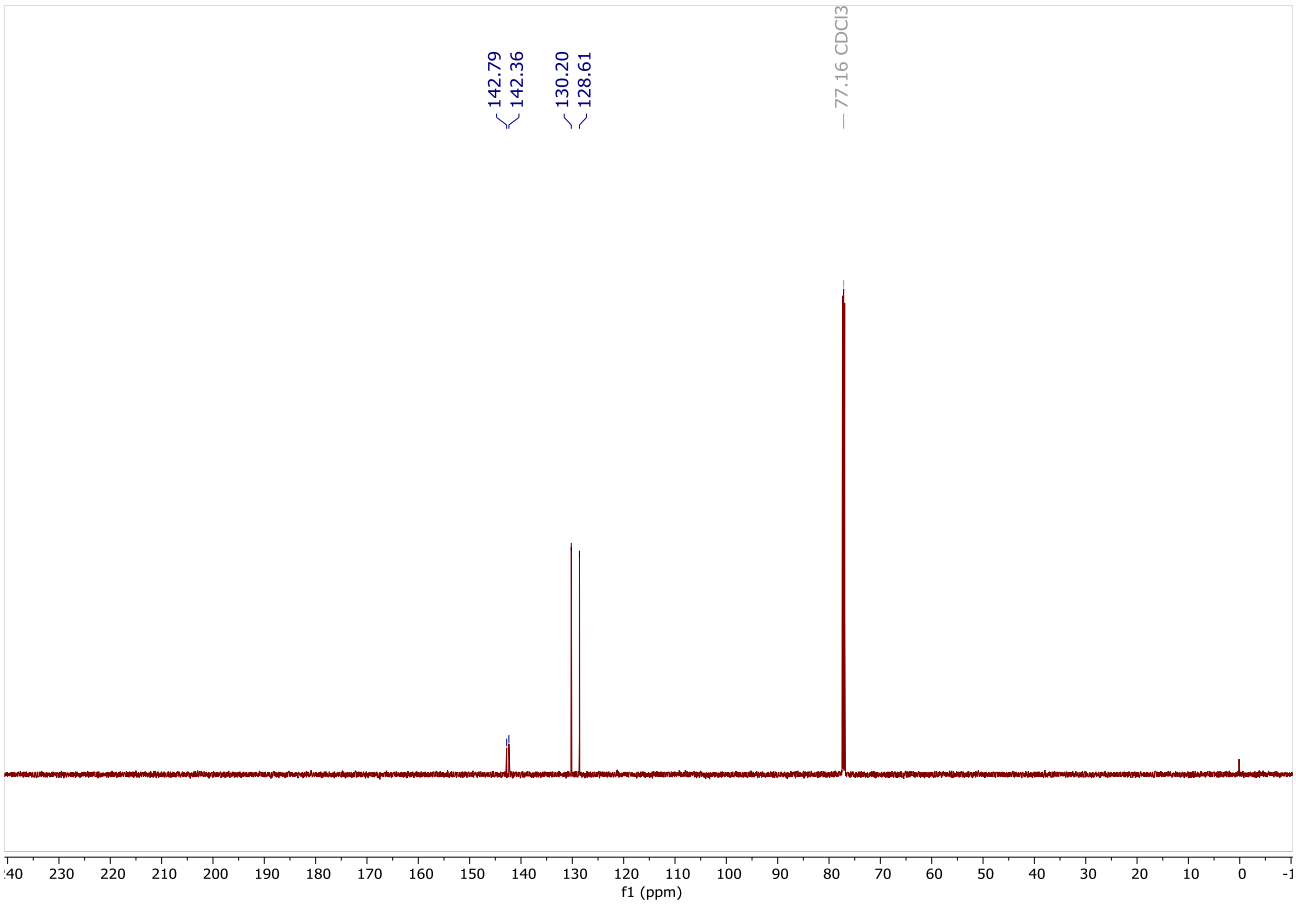
2f

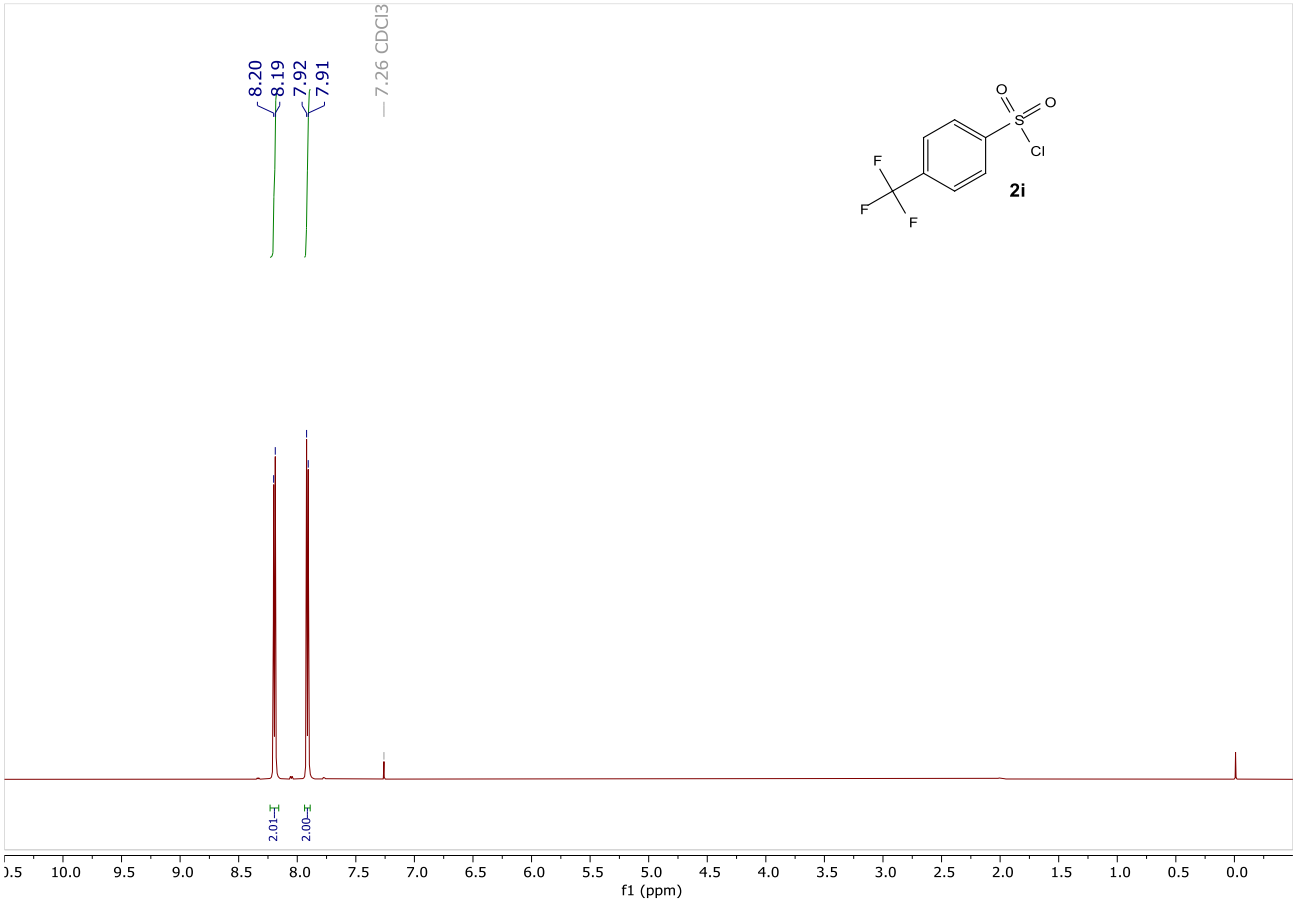

146.23
136.57
136.20
132.98
130.58
125.44
77.16 CDCl3
f1 (ppm)


8.10
8.09
8.09
8.09
8.08
8.08
8.07
7.32
7.31
7.30
7.30
7.30
7.29
7.26 CDCl3
O
O
S
Cl
F
2g
2.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


167.44
165.72
140.51
140.49
130.33
130.27
117.35
117.20
77.16 CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

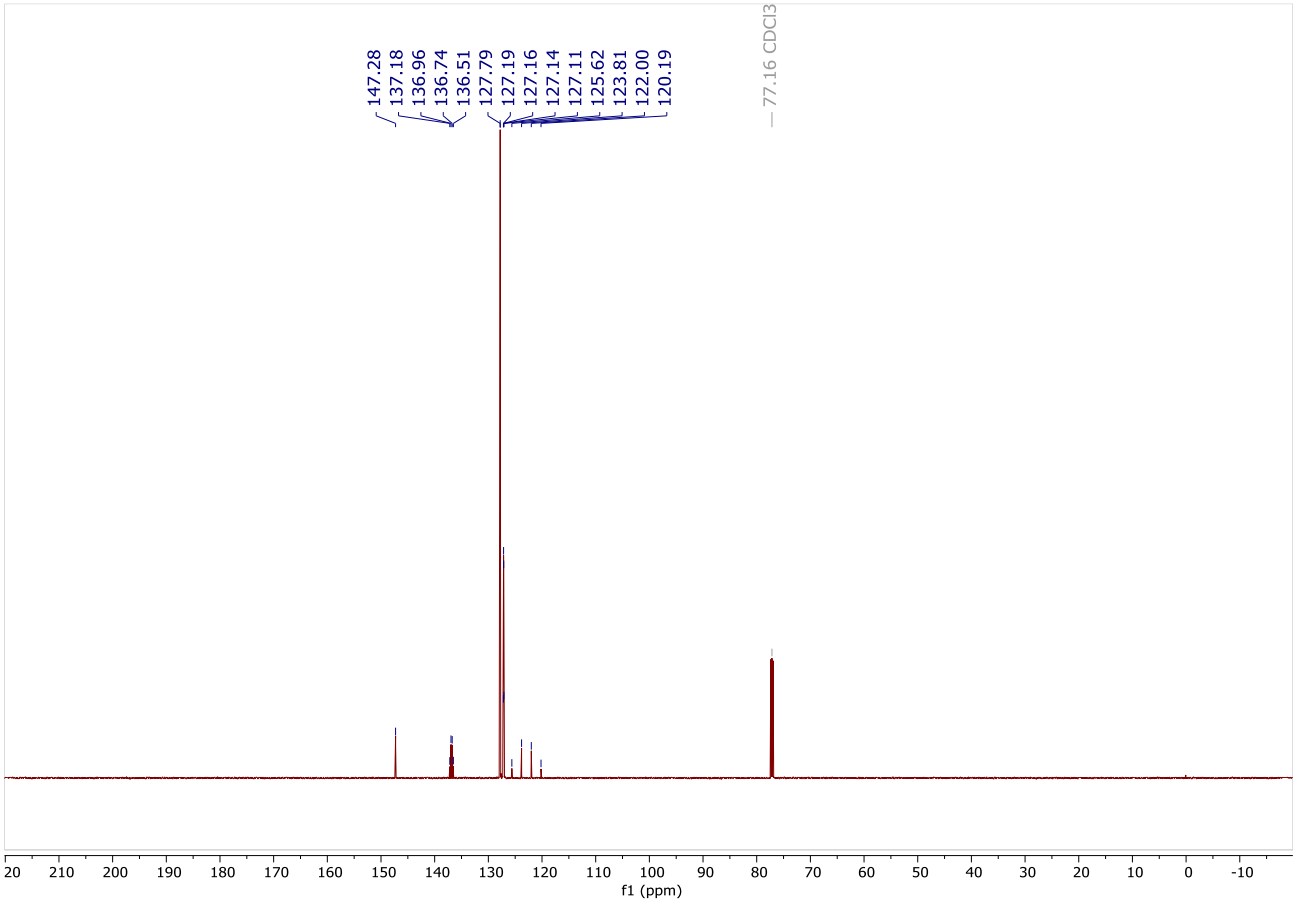

8.00
8.00
7.99
7.99
7.98
7.98
7.62
7.61
7.61
7.60
7.60
7.59
7.26 CDCl3
O
S
O
Cl
Cl
2h
2.00
2.00
f1 (ppm)

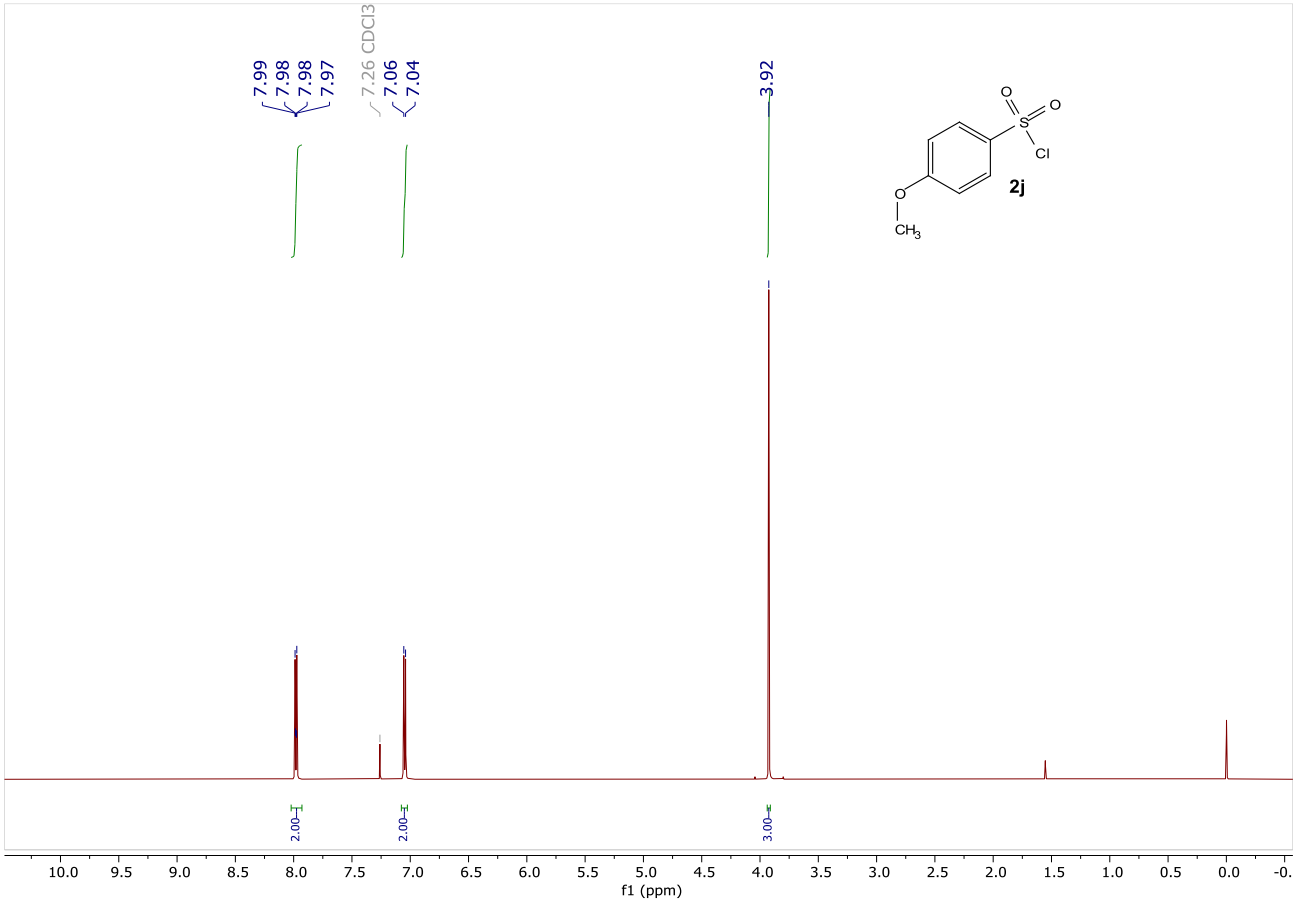

142.79
142.36
130.20
128.61
77.16 CDCl3
f1 (ppm)

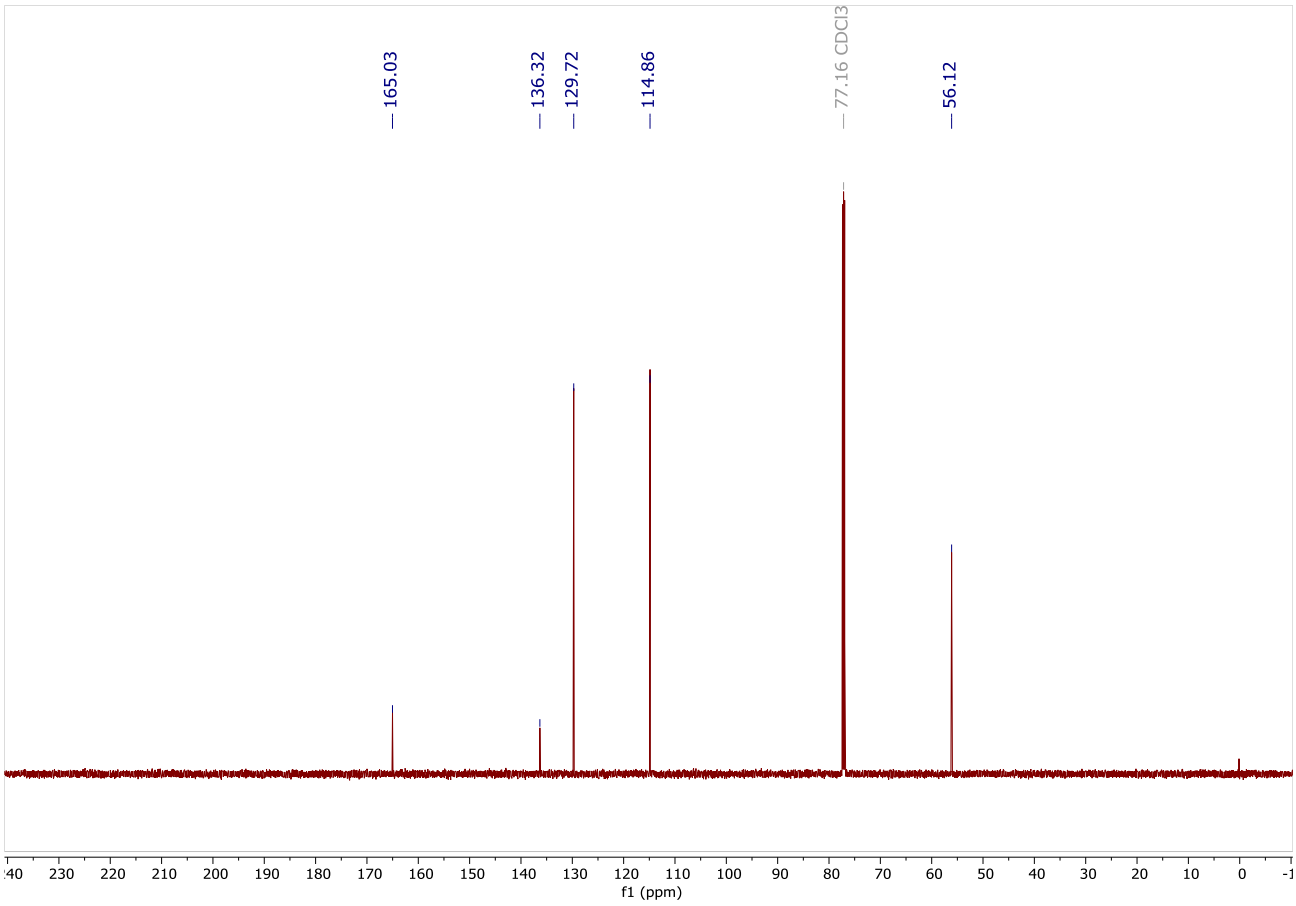

8.20
8.19
7.92
7.91
7.26 CDCl3
2.01
2.00
f1 (ppm)

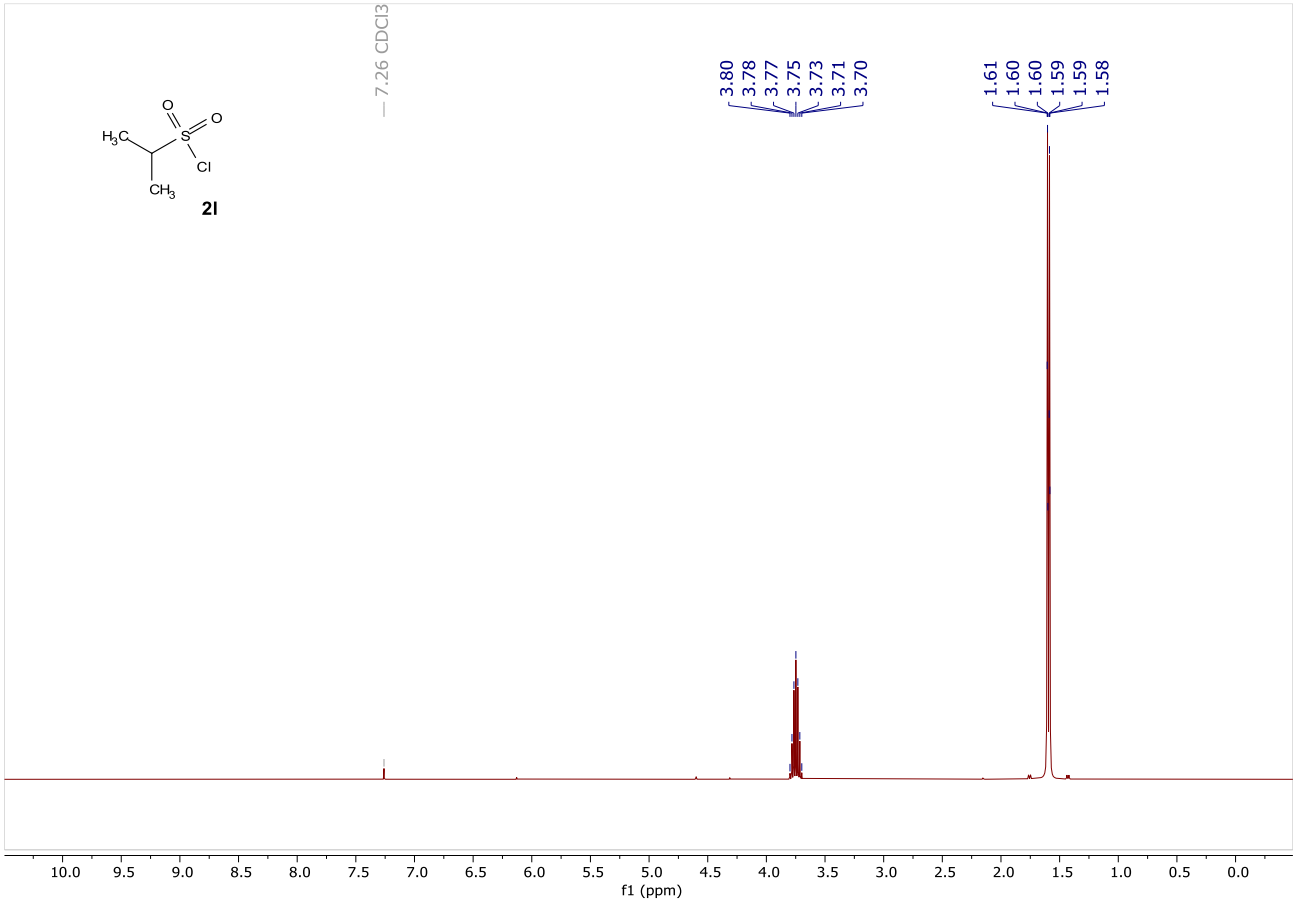
O
O
S
Cl
F
F
F

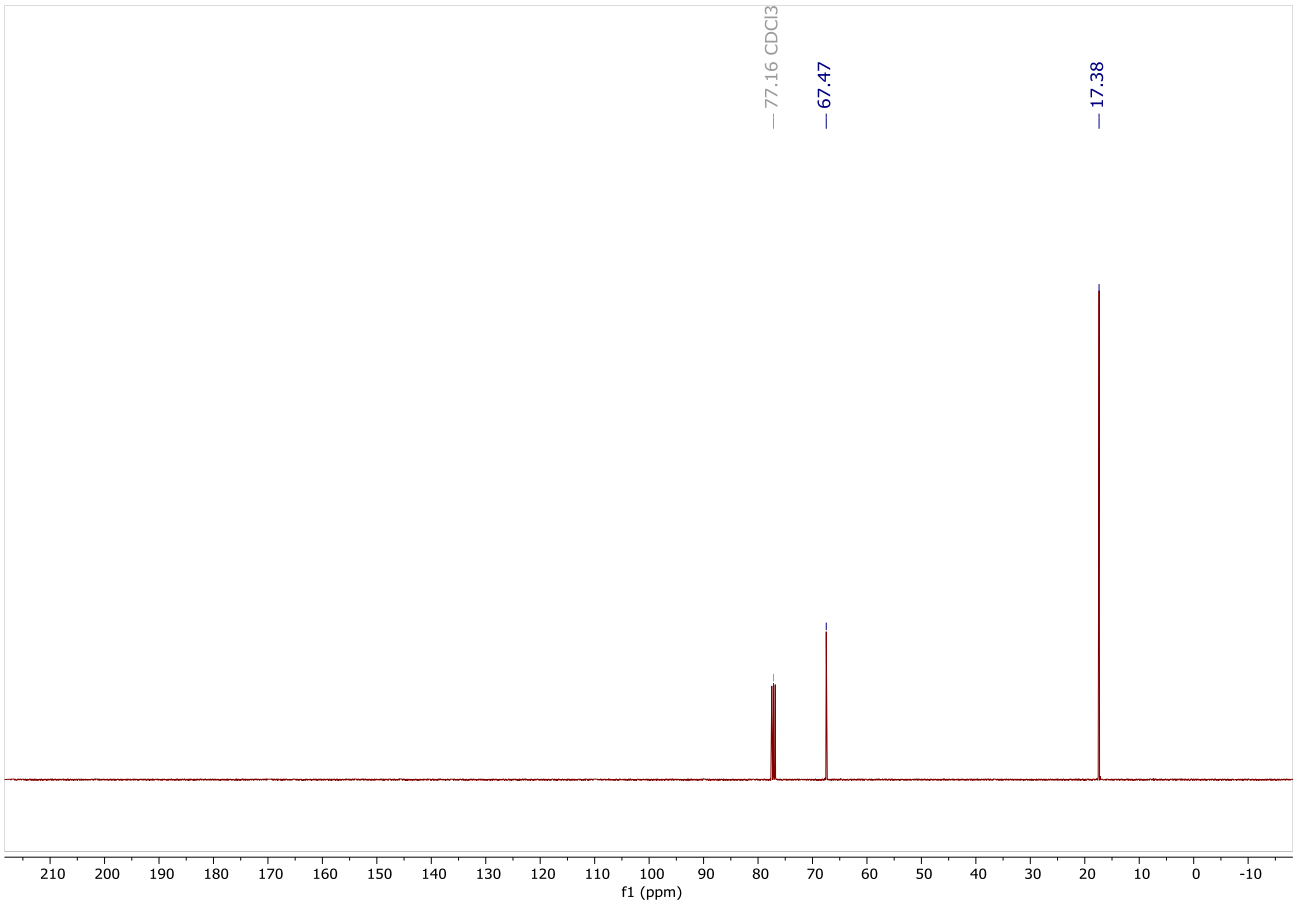
2i

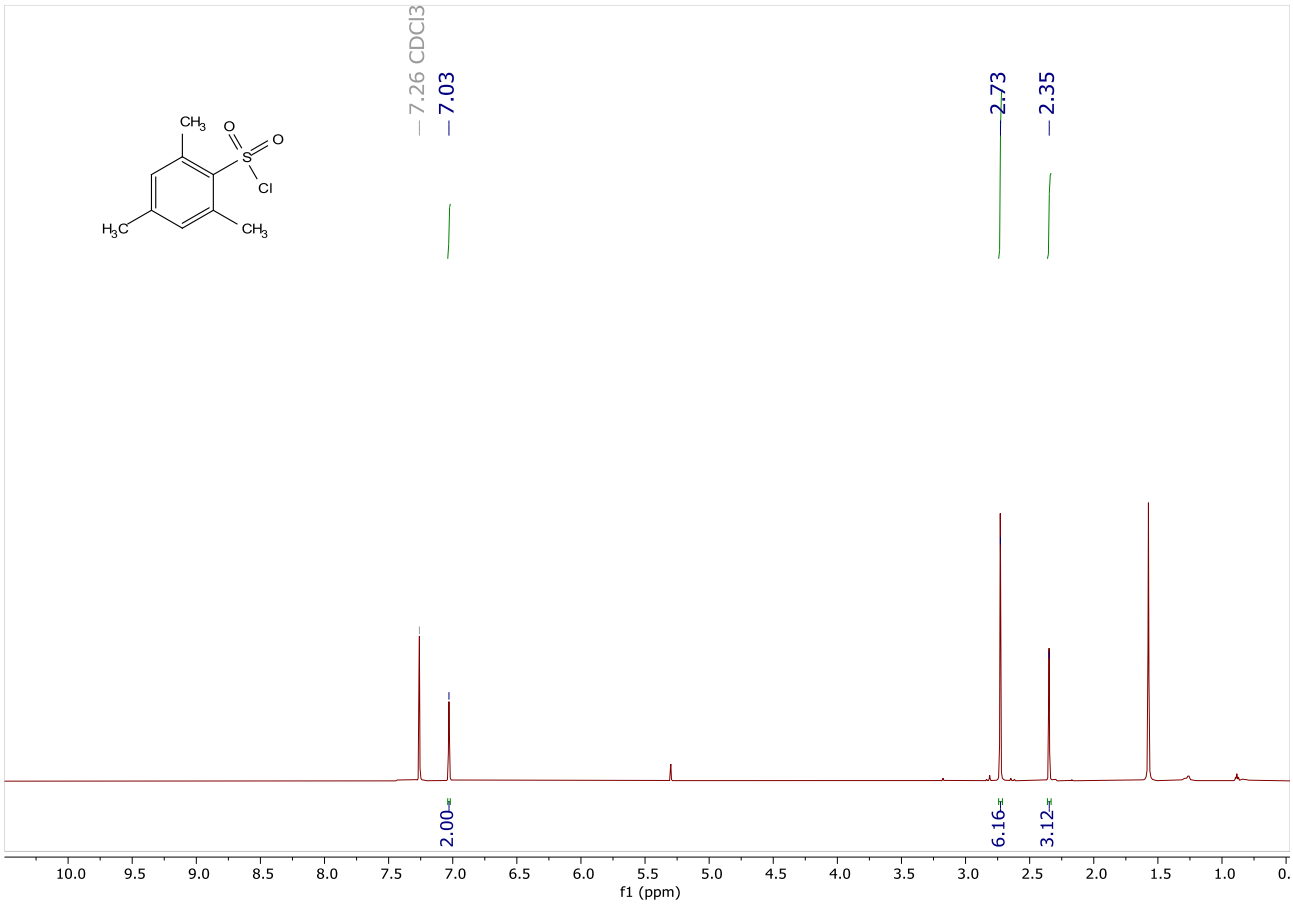

147.28
137.18
136.96
136.74
136.51
127.79
127.19
127.16
127.14
127.11
125.62
123.81
122.00
120.19
77.16 CDCl3
f1 (ppm)

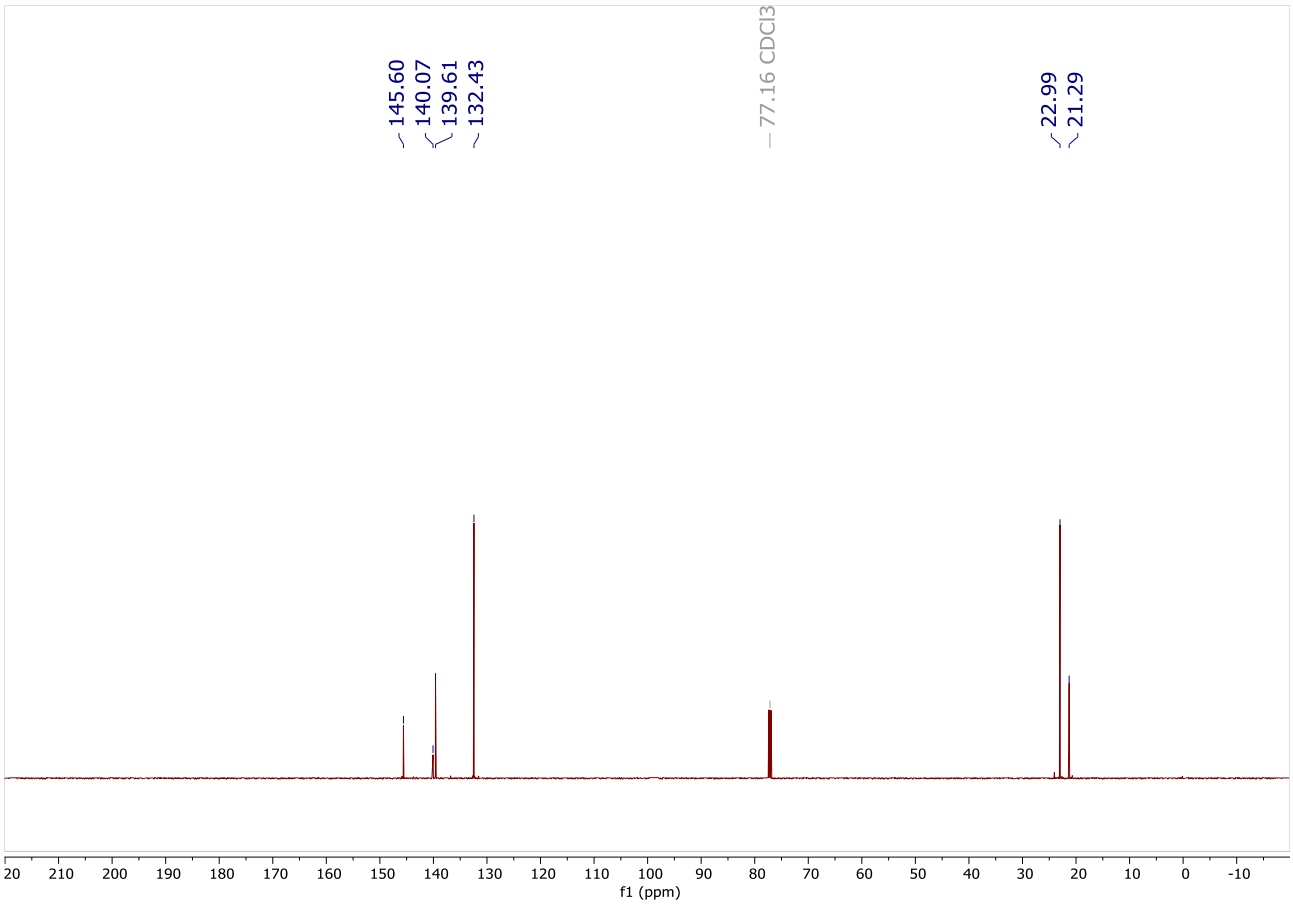

7.99
7.98
7.98
7.97
7.26 CDCl3
7.06
7.04
3.92
O
O
S
Cl
O
CH3
2j
2.00
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

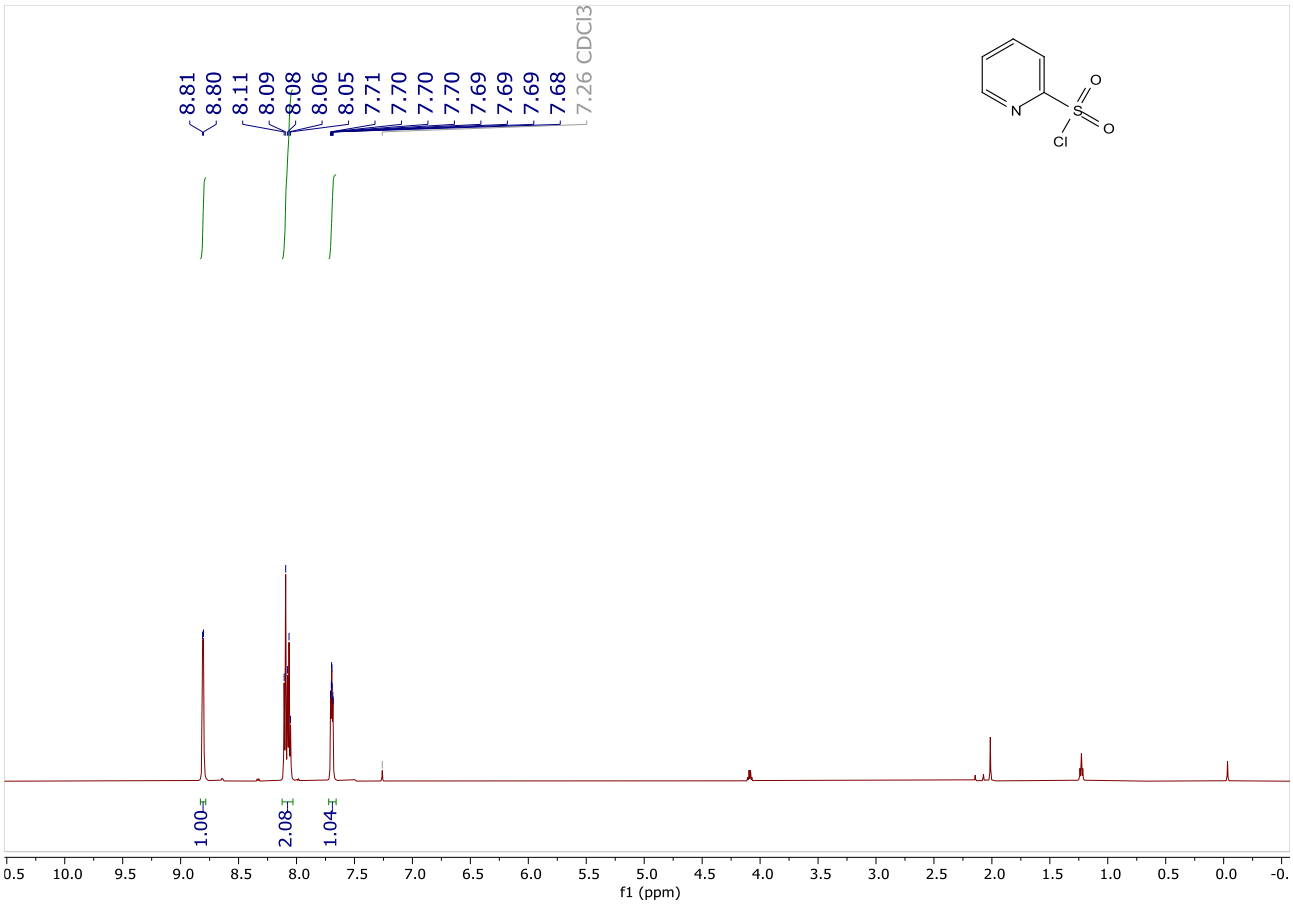

165.03
136.32
129.72
114.86
77.16 CDCl3
56.12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

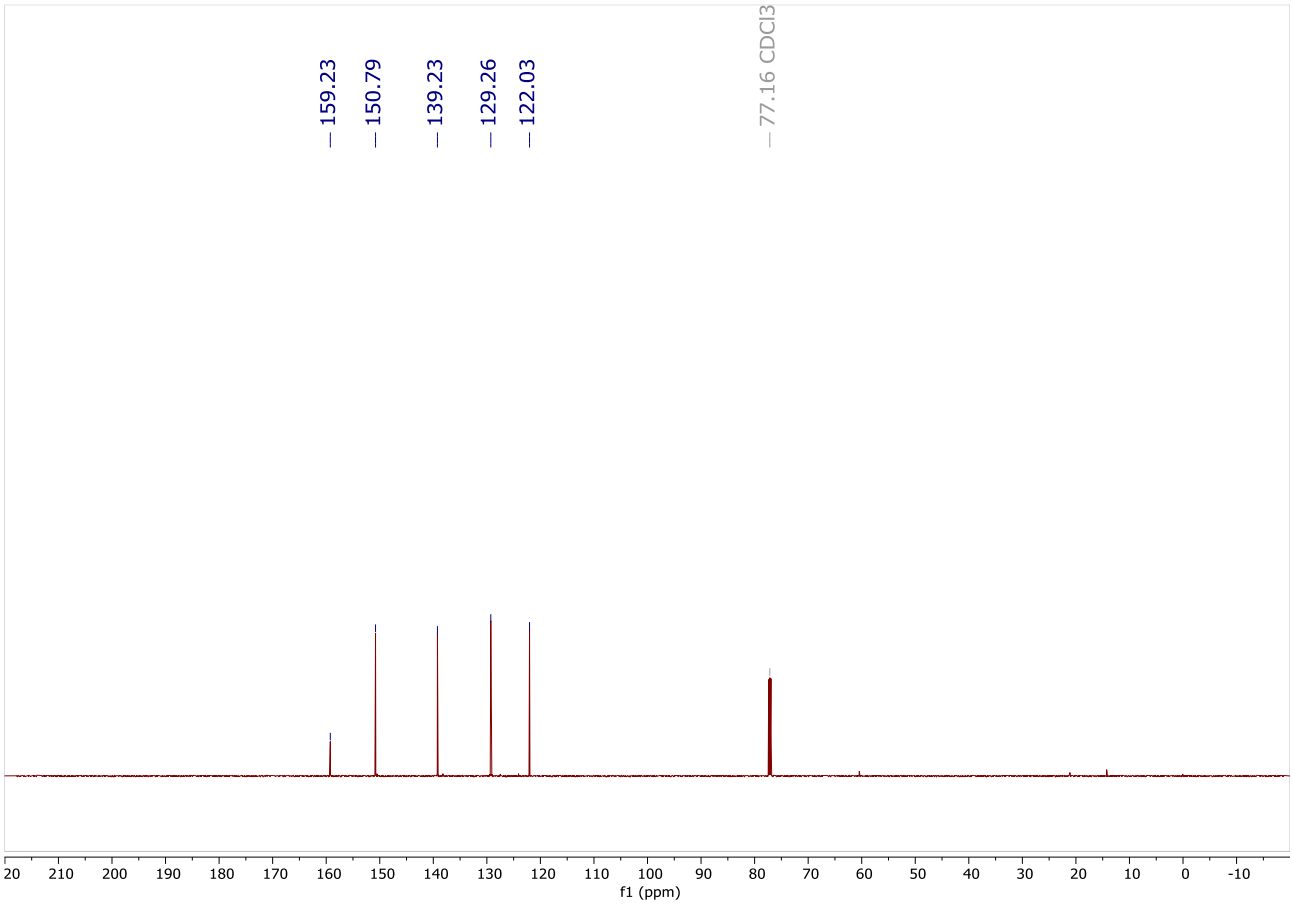

7.26 CDCl3
3.80
3.78
3.77
3.75
3.73
3.71
3.70
1.61
1.60
1.60
1.59
1.59
1.58
O
O
H3C
S
Cl
CH3
2l
f1 (ppm)

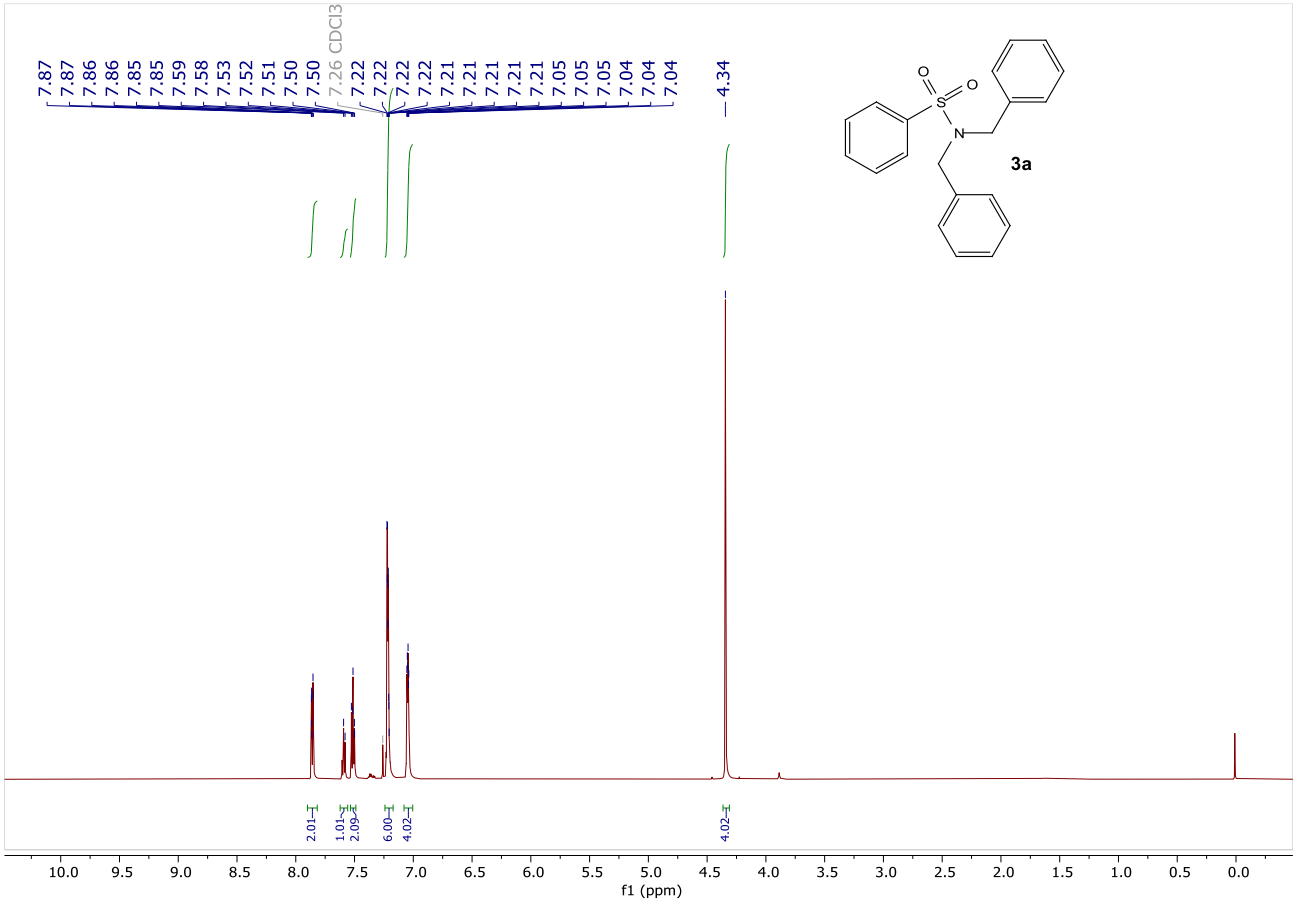

77.16 CDCl3
67.47
17.38
f1 (ppm)

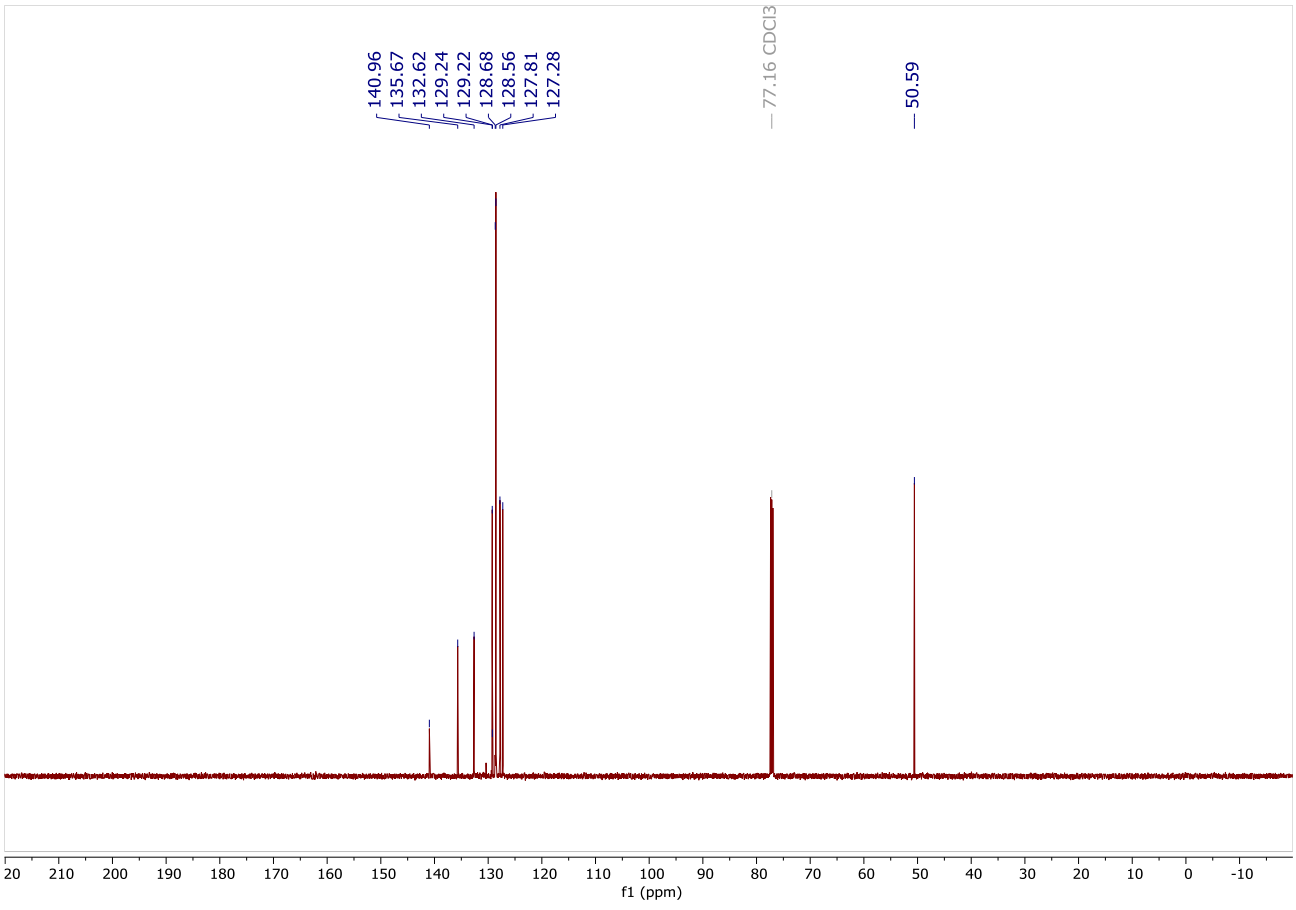

7.26 CDCl3
7.03
2.73
2.35
2.00
6.16
3.12
f1 (ppm)

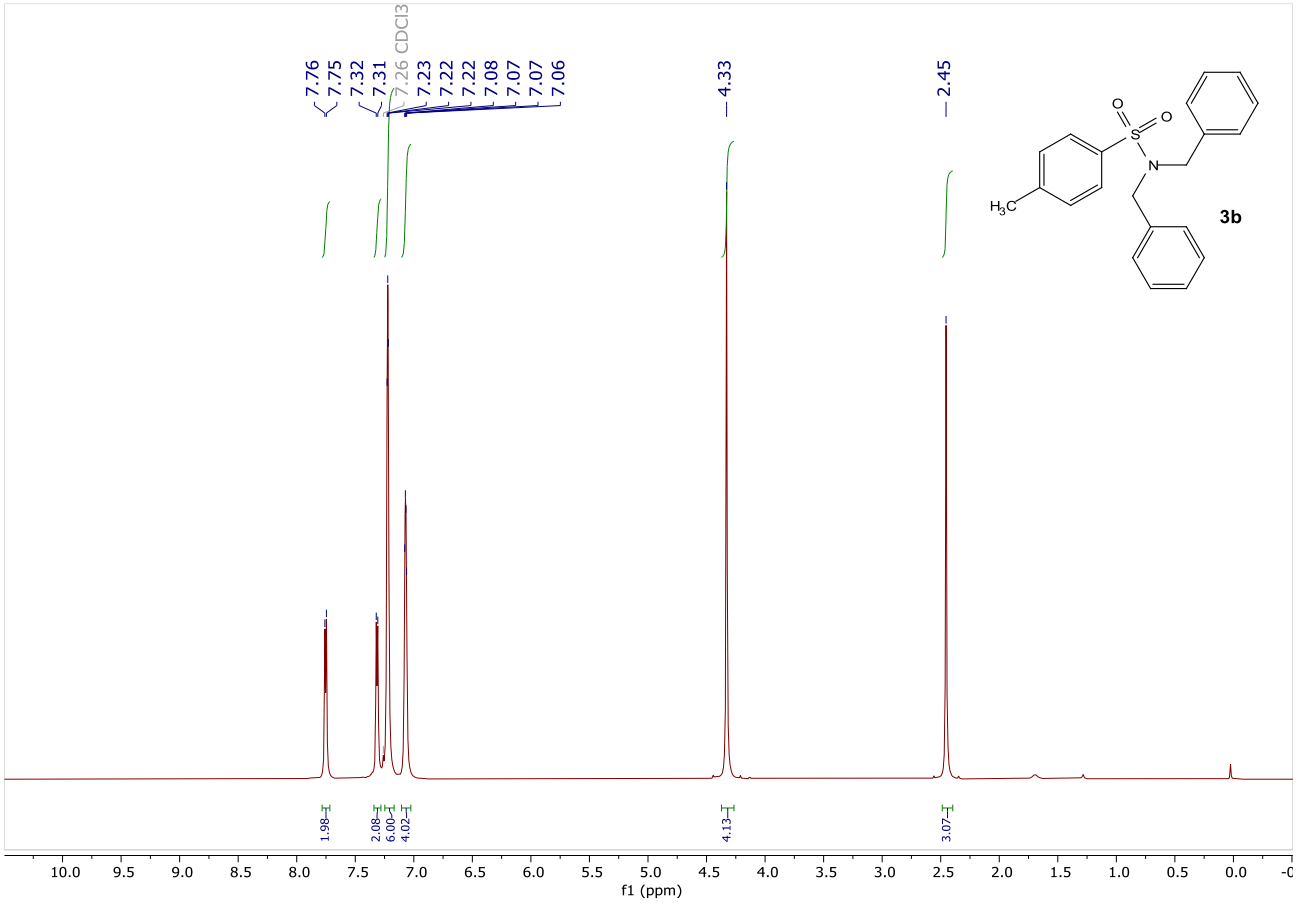

145.60
140.07
139.61
132.43
77.16 CDCl3
22.99
21.29
f1 (ppm)

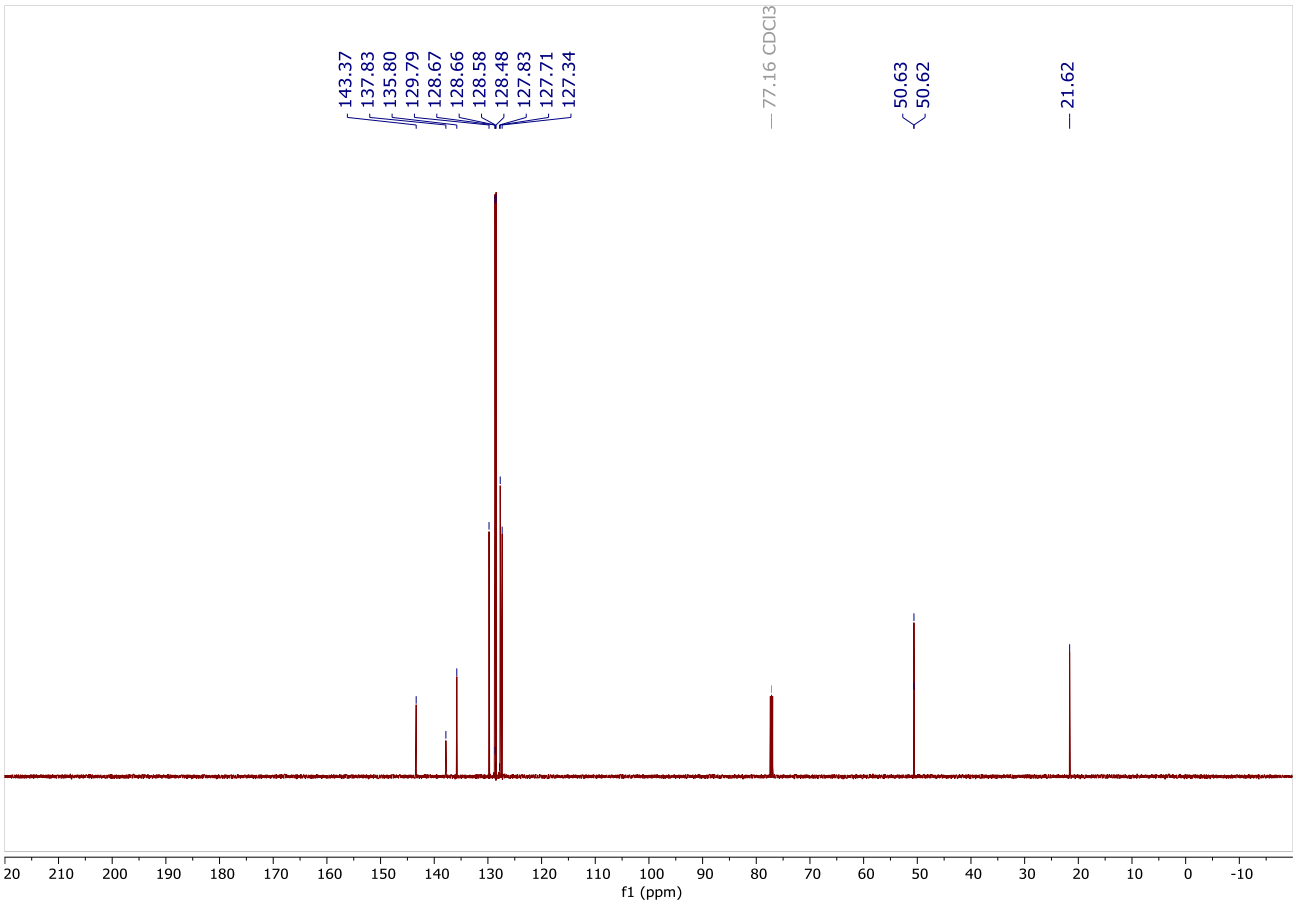

8.81
8.80
8.11
8.09
8.08
8.06
8.05
7.71
7.70
7.70
7.70
7.69
7.69
7.69
7.68
7.26 CDCl3
O
S
O
N
Cl
1.00
2.08
1.04
f1 (ppm)

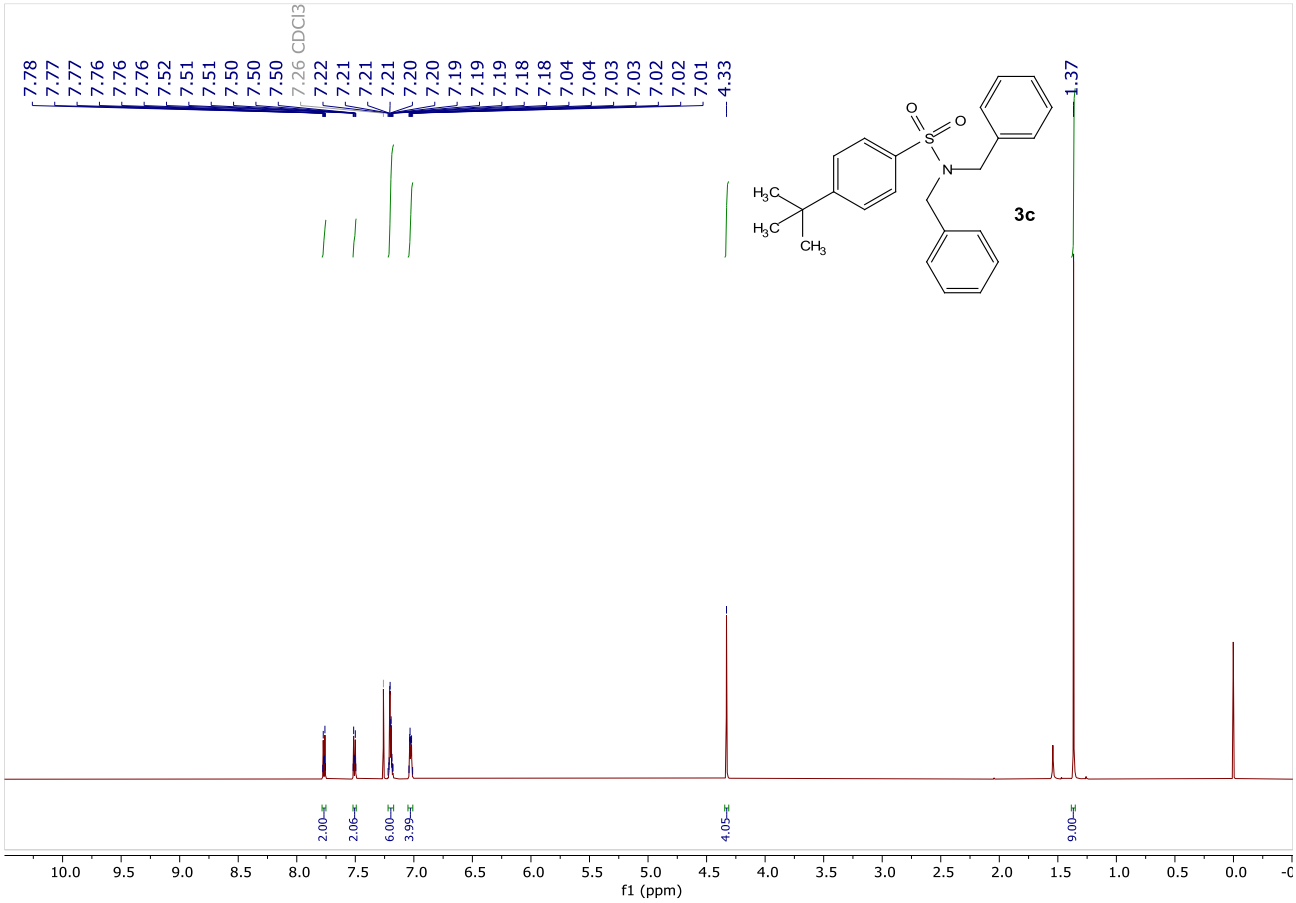

159.23
150.79
139.23
129.26
122.03
77.16 CDCl3
f1 (ppm)


7.87
7.87
7.86
7.86
7.85
7.85
7.59
7.58
7.53
7.52
7.51
7.50
7.50
7.26 CDCl3
7.22
7.22
7.22
7.21
7.21
7.21
7.21
7.05
7.05
7.04
7.04
7.04
4.34
3a
2.01
1.01
2.09
6.00
4.02
4.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


140.96
135.67
132.62
129.24
129.22
128.68
128.56
127.81
127.28
77.16 CDCl3
50.59
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.76
7.75
7.32
7.31
7.26 CDCl3
7.23
7.22
7.22
7.08
7.07
7.07
7.06
4.33
2.45
1.98
2.08
6.00
4.02
4.13
3.07
f1 (ppm)


143.37
137.83
135.80
129.79
128.67
128.66
128.58
128.48
127.83
127.71
127.34
77.16 CDCl3
50.63
50.62
21.62
f1 (ppm)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7.77
7.77
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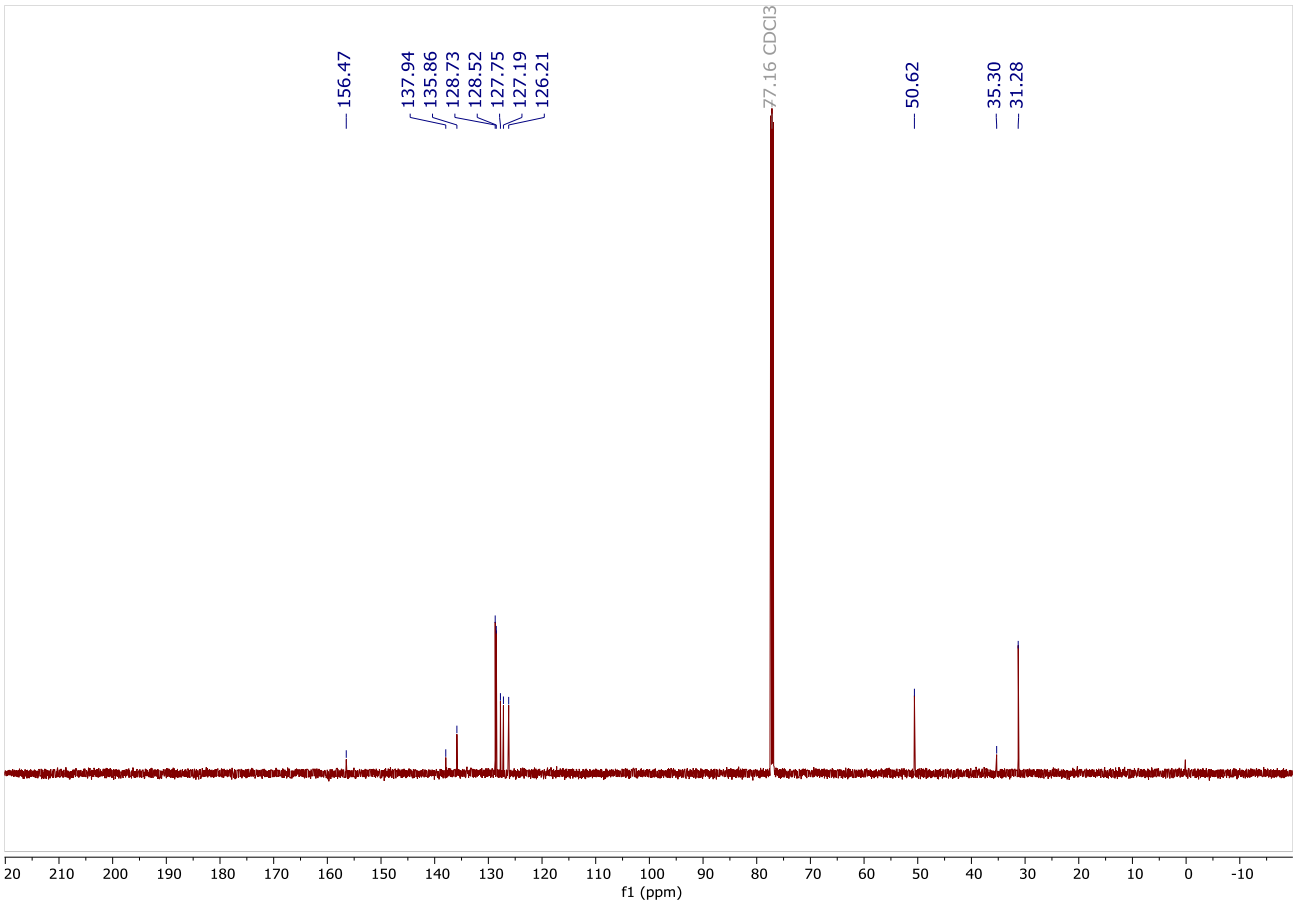
7.76
7.76
7.52
7.51
7.51
7.50
7.50
7.50
7.26 CDCl3
7.22
7.21
7.21
7.21
7.20
7.20
7.19
7.19
7.19
7.18
7.18
7.04
7.04
7.03
7.03
7.02
7.02
7.01
4.33
1.37
3c
2.00
2.06
6.00
3.99
4.05
9.00
f1 (ppm)


156.47
137.94
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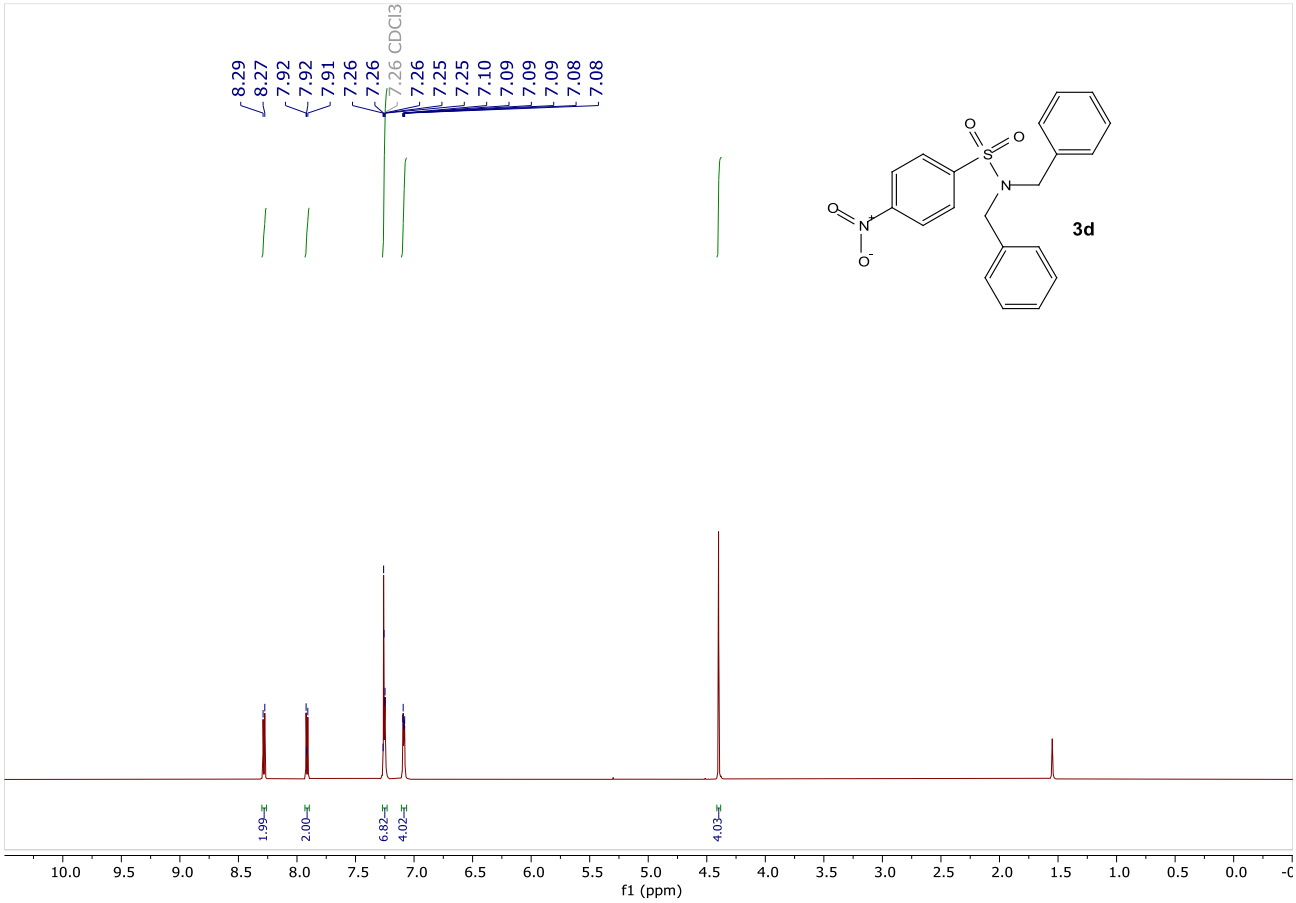
128.52
127.75
127.19
126.21
77.16 CDCl3
50.62
35.30
31.28
f1 (ppm)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8.27
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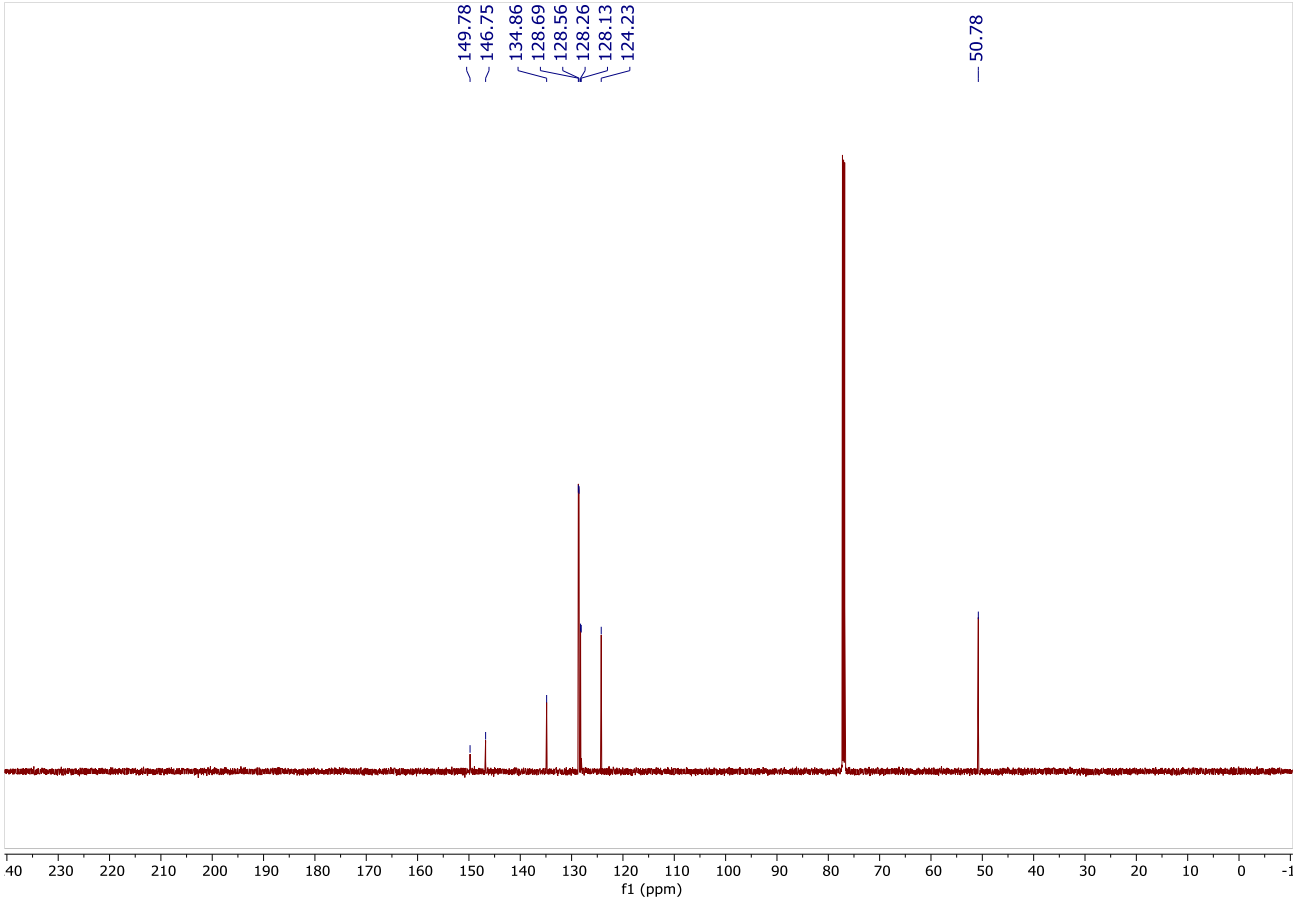
7.92
7.91
7.26
7.26
7.26 CDCl3
7.26
7.25
7.25
7.10
7.09
7.09
7.09
7.08
7.08
3d
1.99
2.00
6.82
4.02
4.03
f1 (ppm)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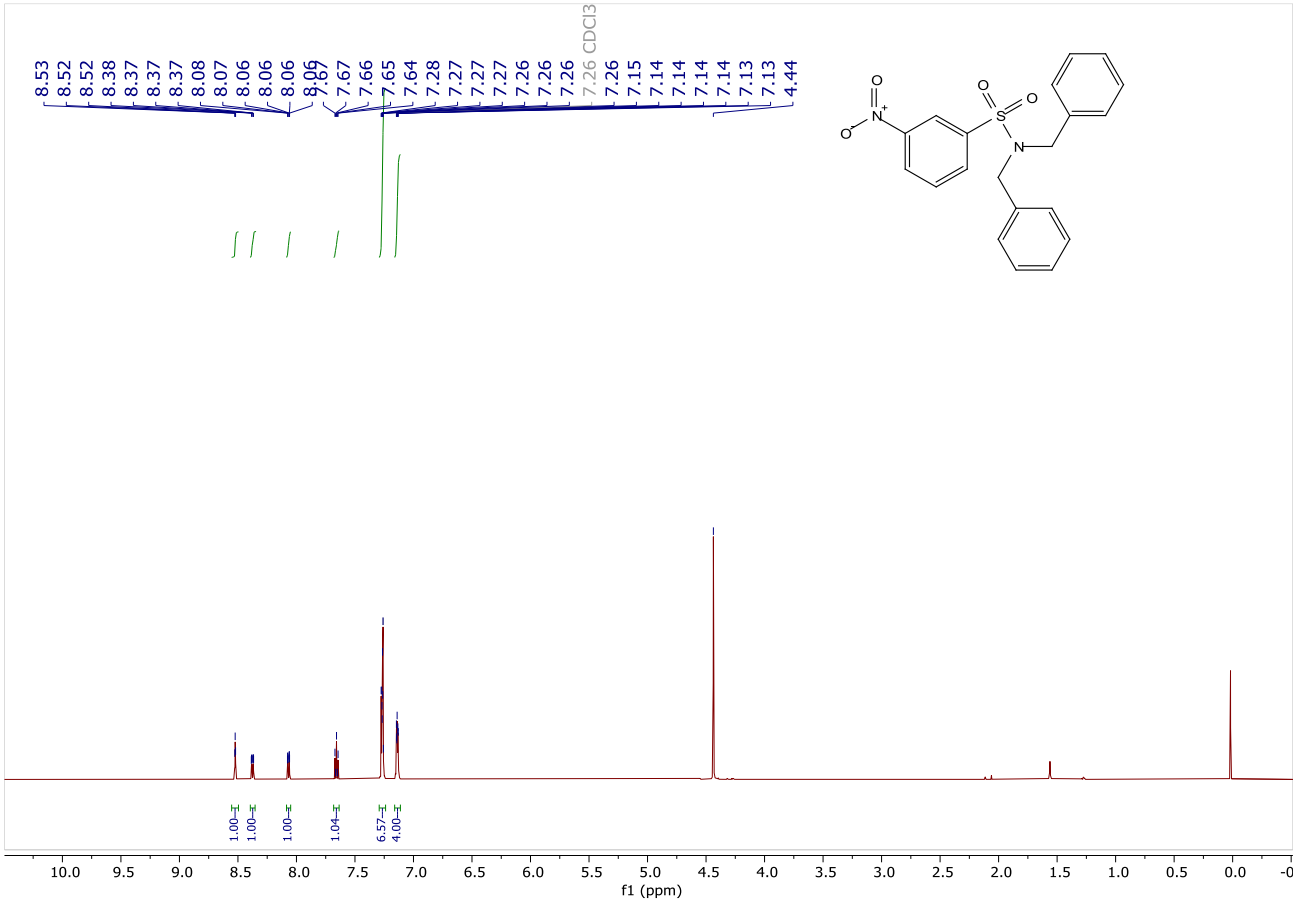
128.26
128.13
124.23
50.78
f1 (ppm)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8.37
8.37
8.08
8.07
8.06
8.06
8.06
8.06
8.06
7.67
7.66
7.65
7.64
7.28
7.27
7.27
7.27
7.26
7.26
7.26
7.26 CDCl3
7.26
7.15
7.14
7.14
7.14
7.14
7.13
7.13
4.44
O
N+
O-
O
S
O
N
1.00
1.00
1.00
1.04
6.57
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
1.5
1.0
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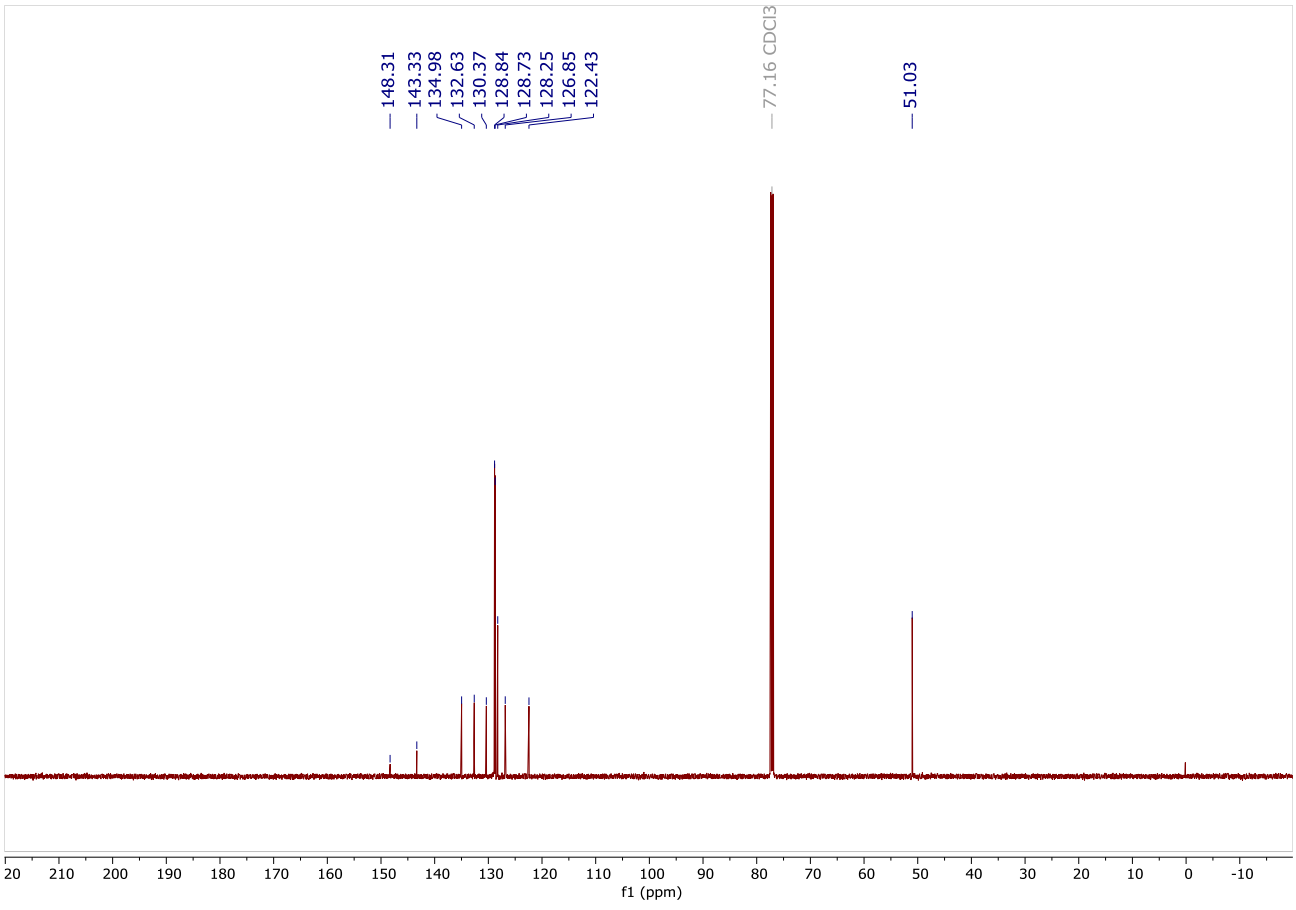
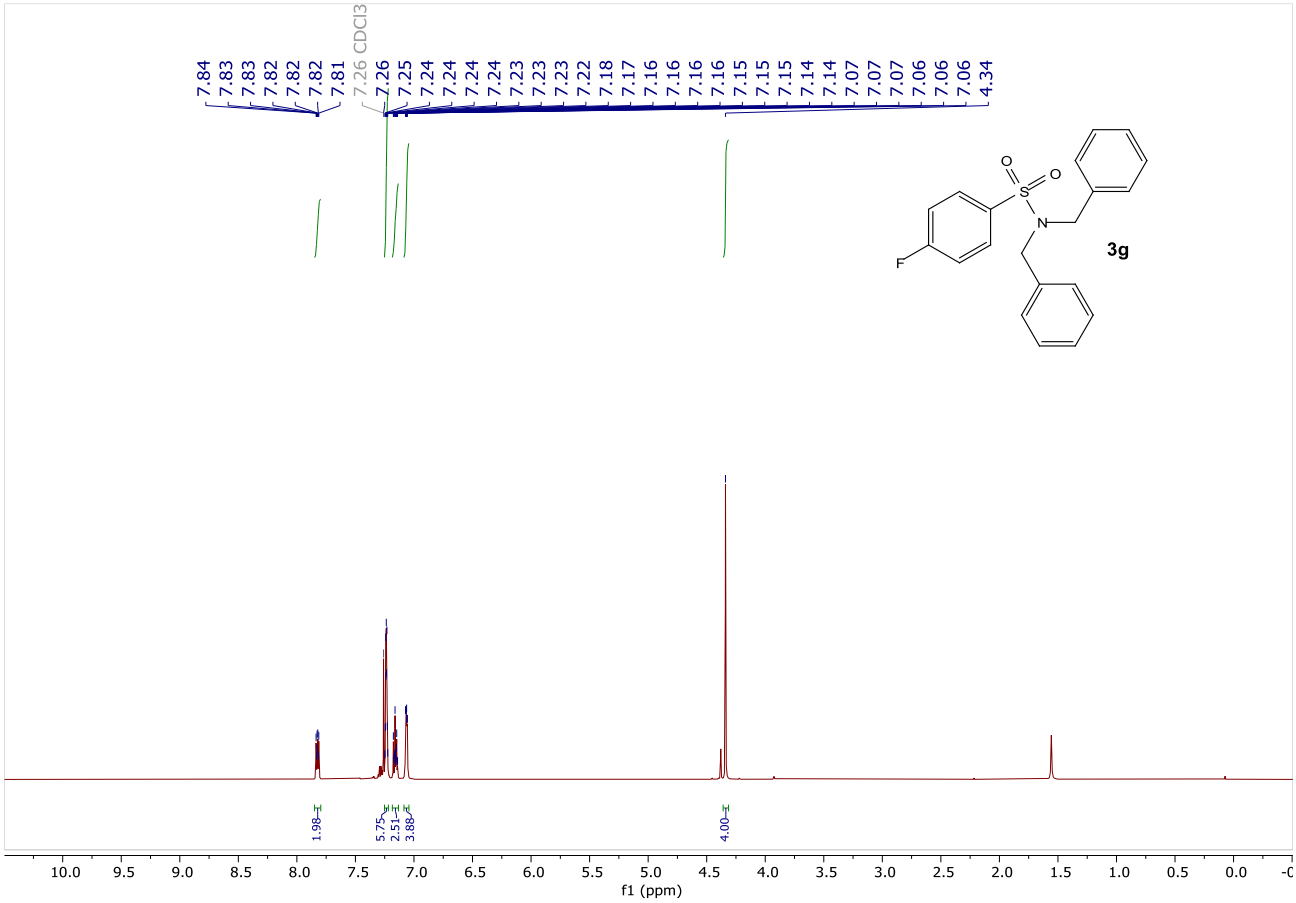
0.0
f1 (ppm)


148.31
143.33
134.98
132.63
130.37
128.84
128.73
128.25
126.85
122.43
77.16 CDCl3
51.03
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.84
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7.83
7.82
7.82
7.82
7.81
7.26 CDCl3
7.26
7.25
7.24
7.24
7.24
7.24
7.23
7.23
7.23
7.22
7.18
7.17
7.16
7.16
7.16
7.16
7.15
7.15
7.15
7.14
7.14
7.07
7.07
7.06
7.06
7.06
4.34
O
O
S
N
F
3g
1.98
5.75
2.51
3.88
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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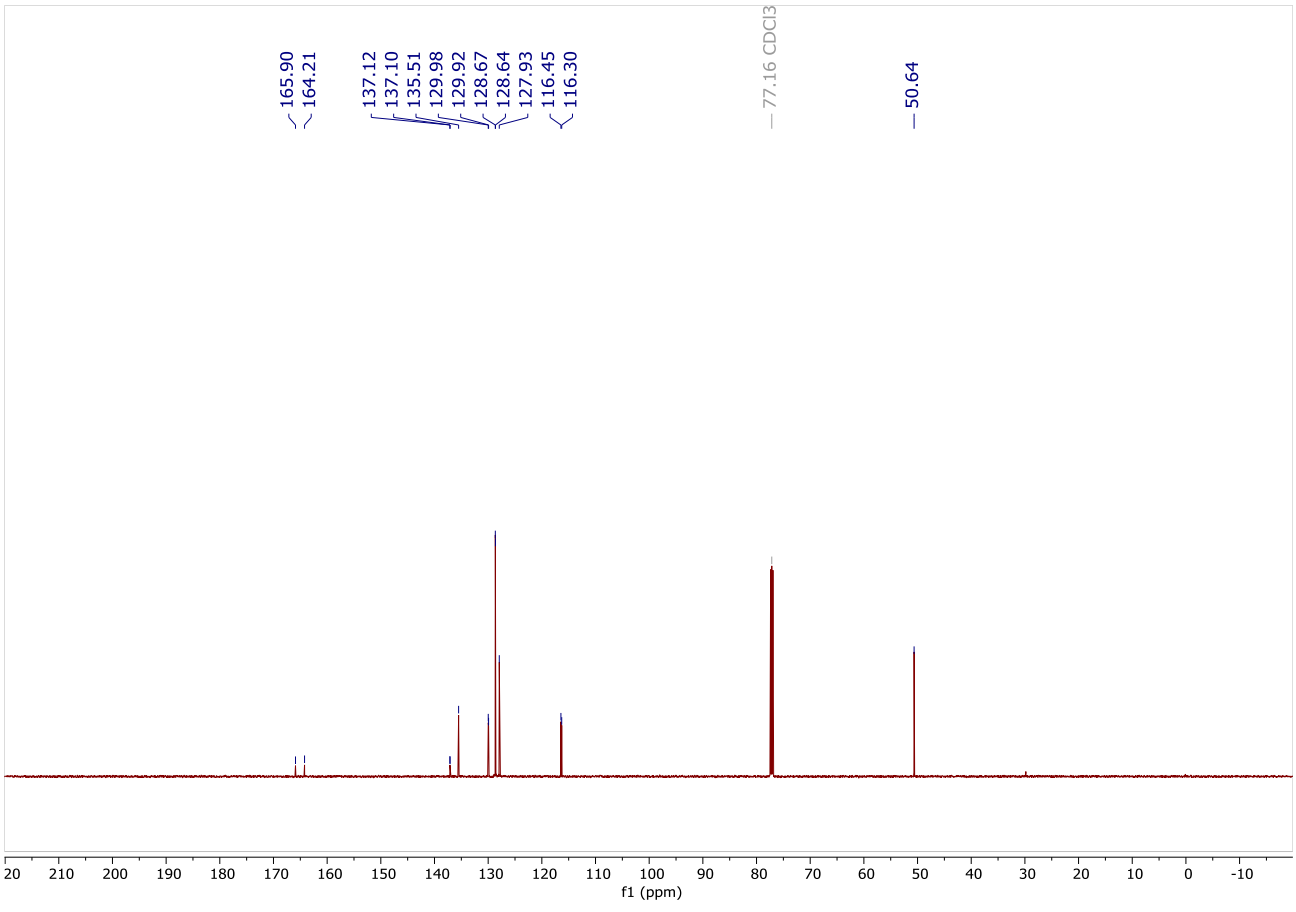
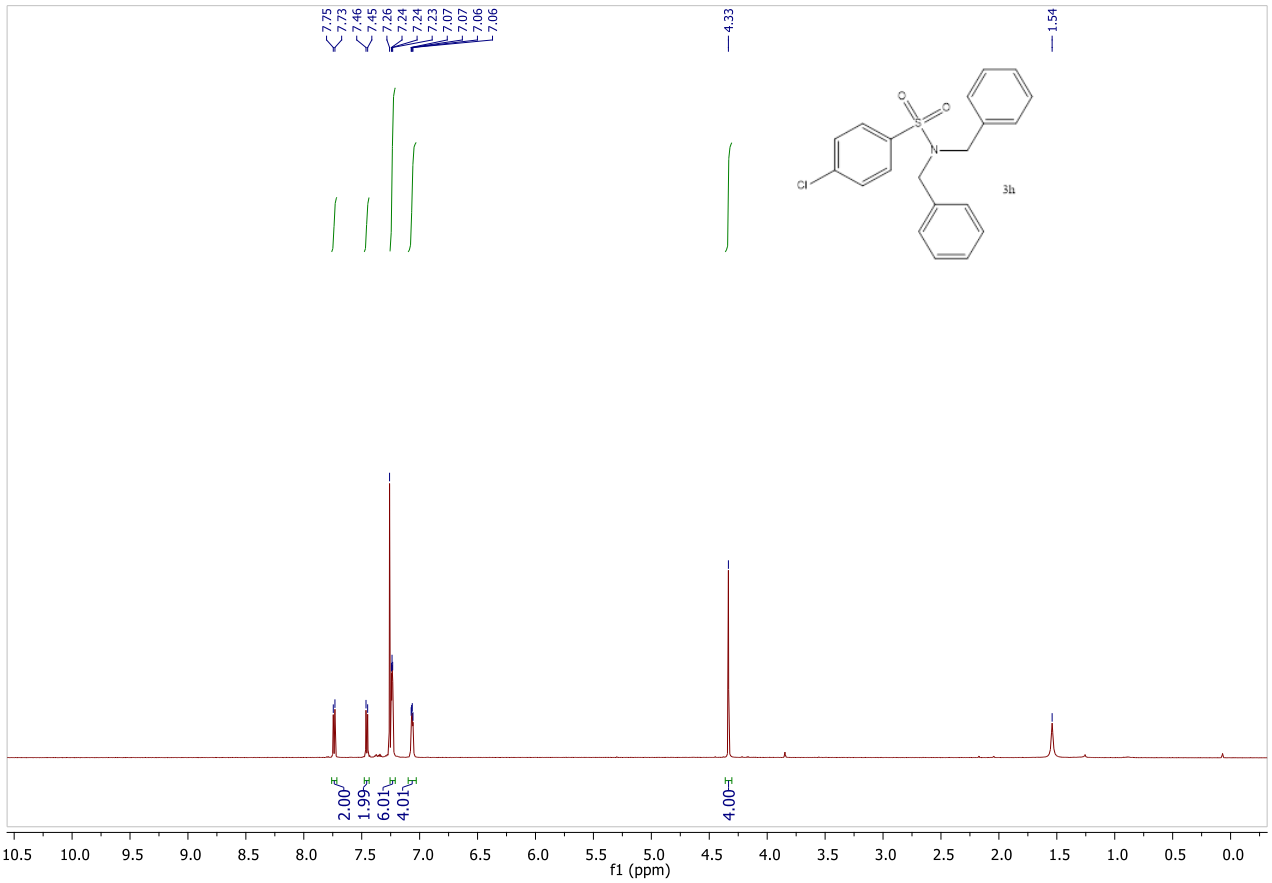
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


165.90
164.21
137.12
137.10
135.51
129.98
129.92
128.67
128.64
127.93
116.45
116.30
77.16 CDCl3
50.64
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.73
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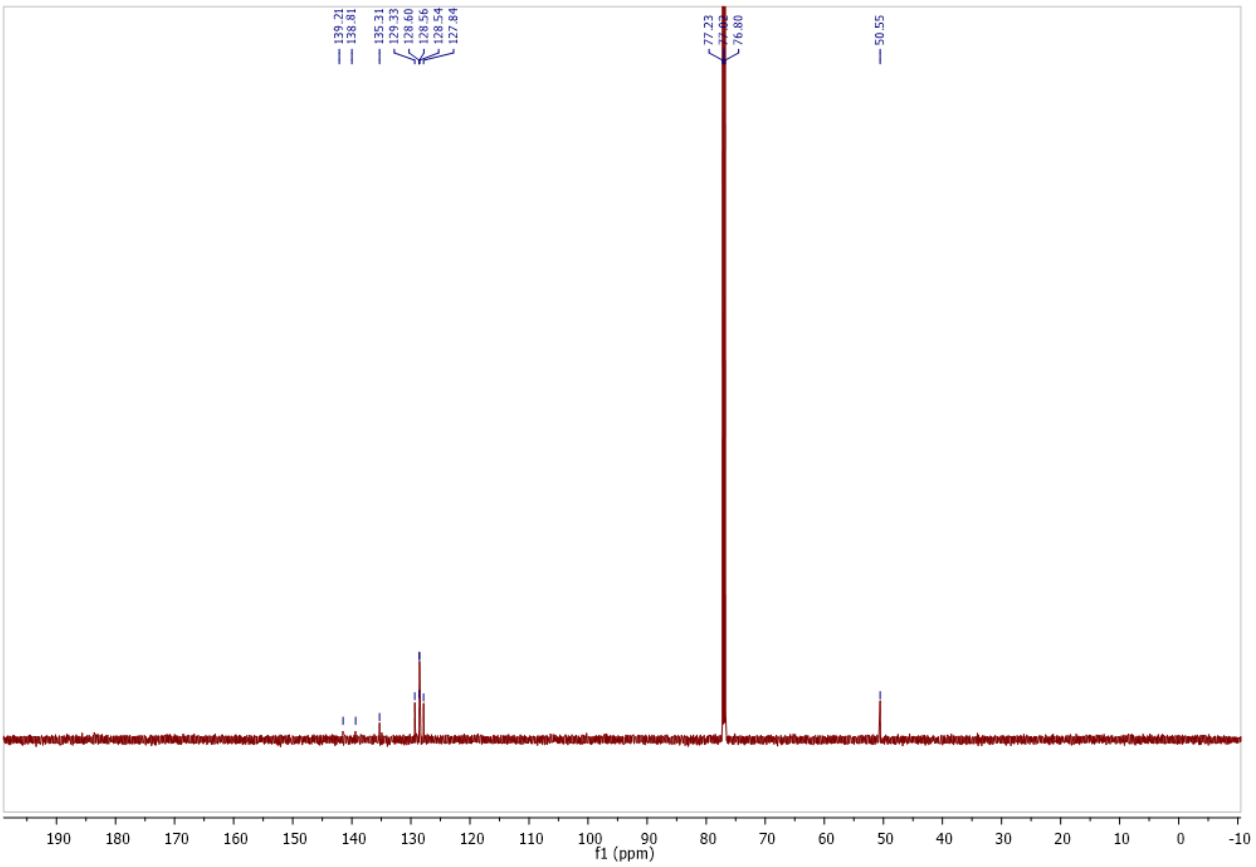
7.45
7.26
7.24
7.24
7.23
7.07
7.07
7.06
7.06
4.33
1.54
Cl
3h
2.00
1.99
6.01
4.01
4.00
f1 (ppm)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138.81
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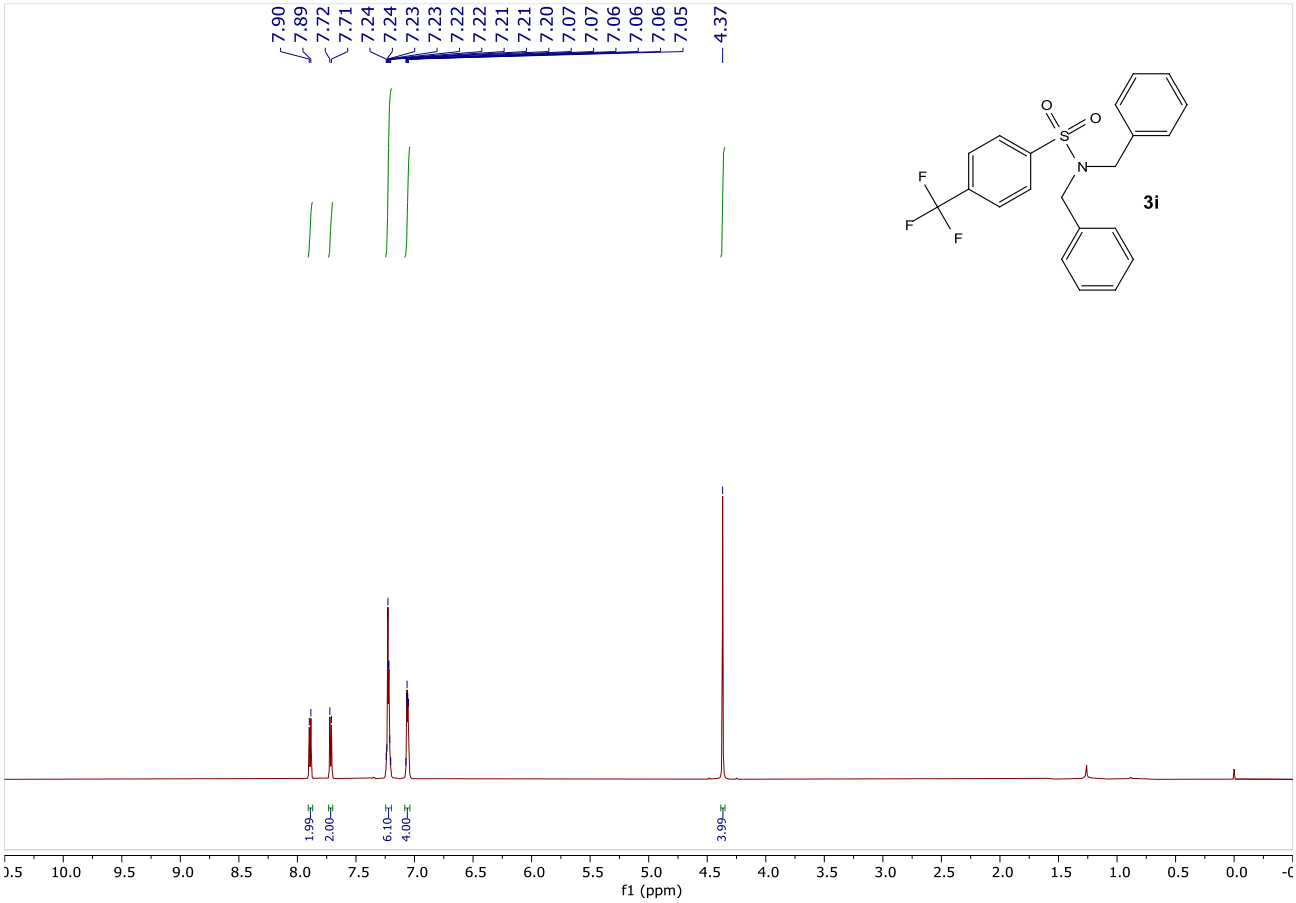
129.33
128.60
128.56
128.54
127.84
77.23
76.80
50.55
f1 (ppm)


7.90
7.89
7.72
7.71
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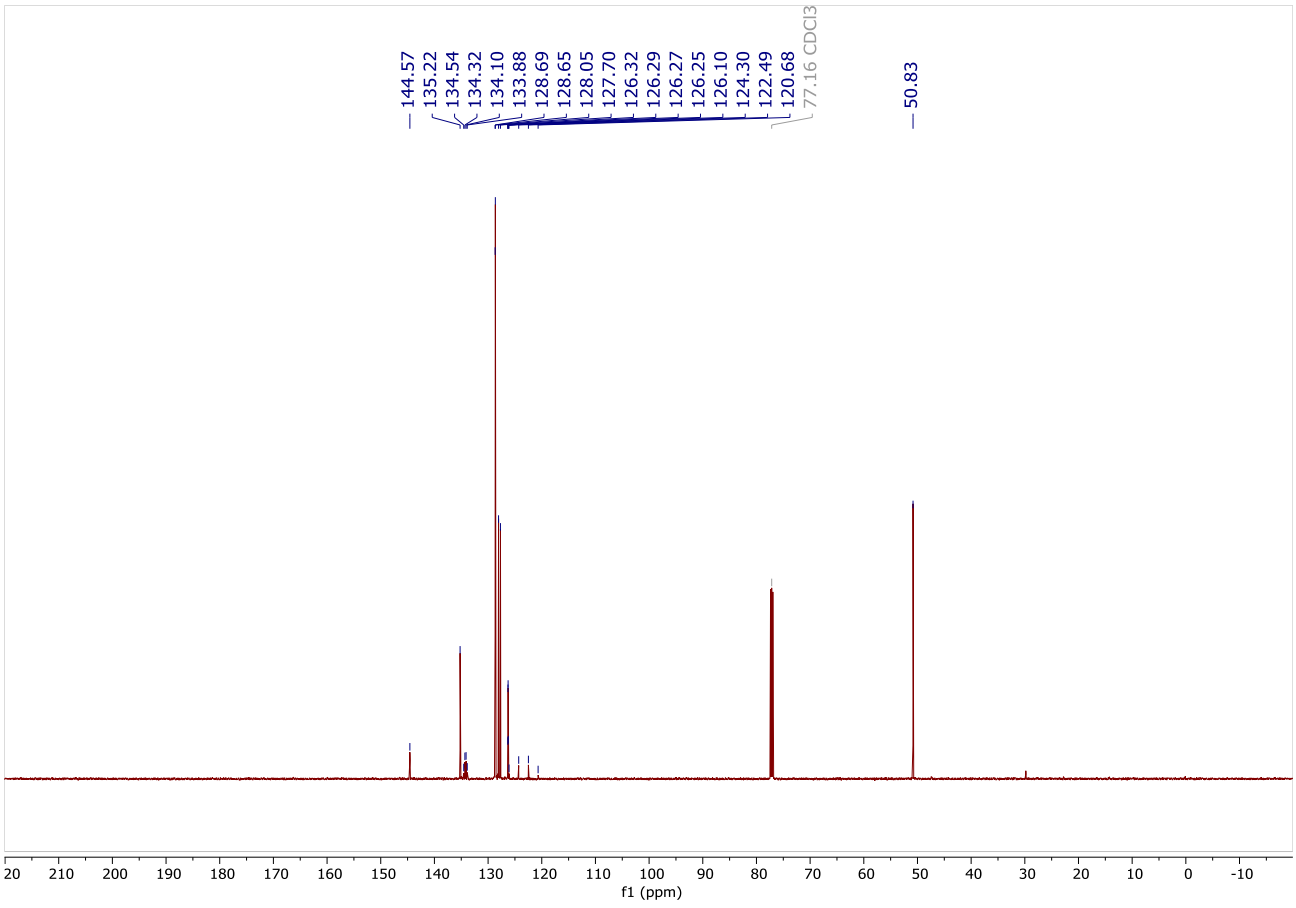
7.24
7.23
7.23
7.22
7.22
7.21
7.21
7.20
7.07
7.07
7.06
7.06
7.06
7.05
4.37
O
O
S
N
F
F
F
3i
1.99
2.00
6.10
4.00
3.99
f1 (ppm)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128.65
128.05
127.70
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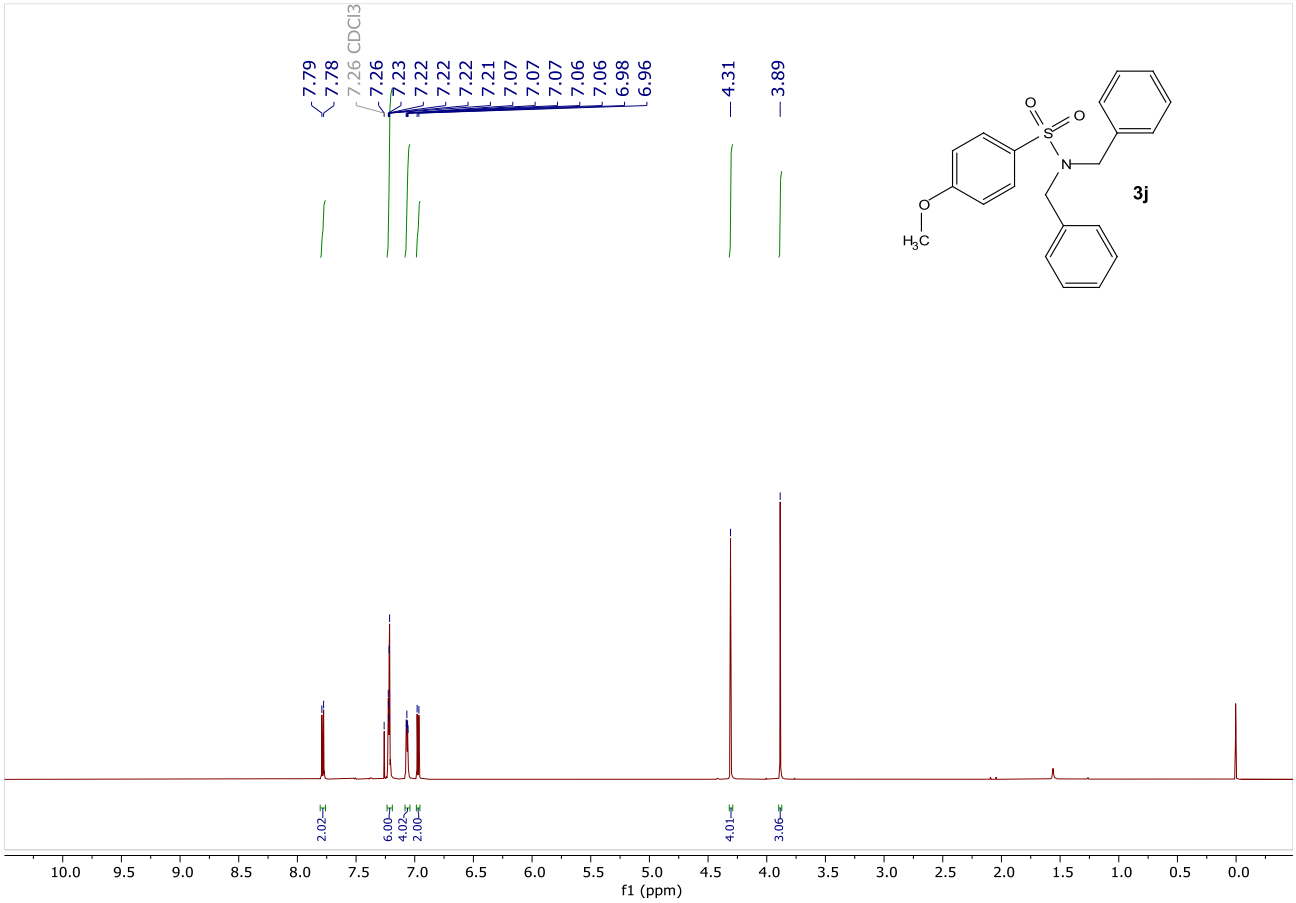
126.27
126.25
126.10
124.30
122.49
120.68
77.16 CDCl3
50.83
f1 (ppm)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7.78
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7.22
7.21
7.07
7.07
7.07
7.06
7.06
6.98
6.96
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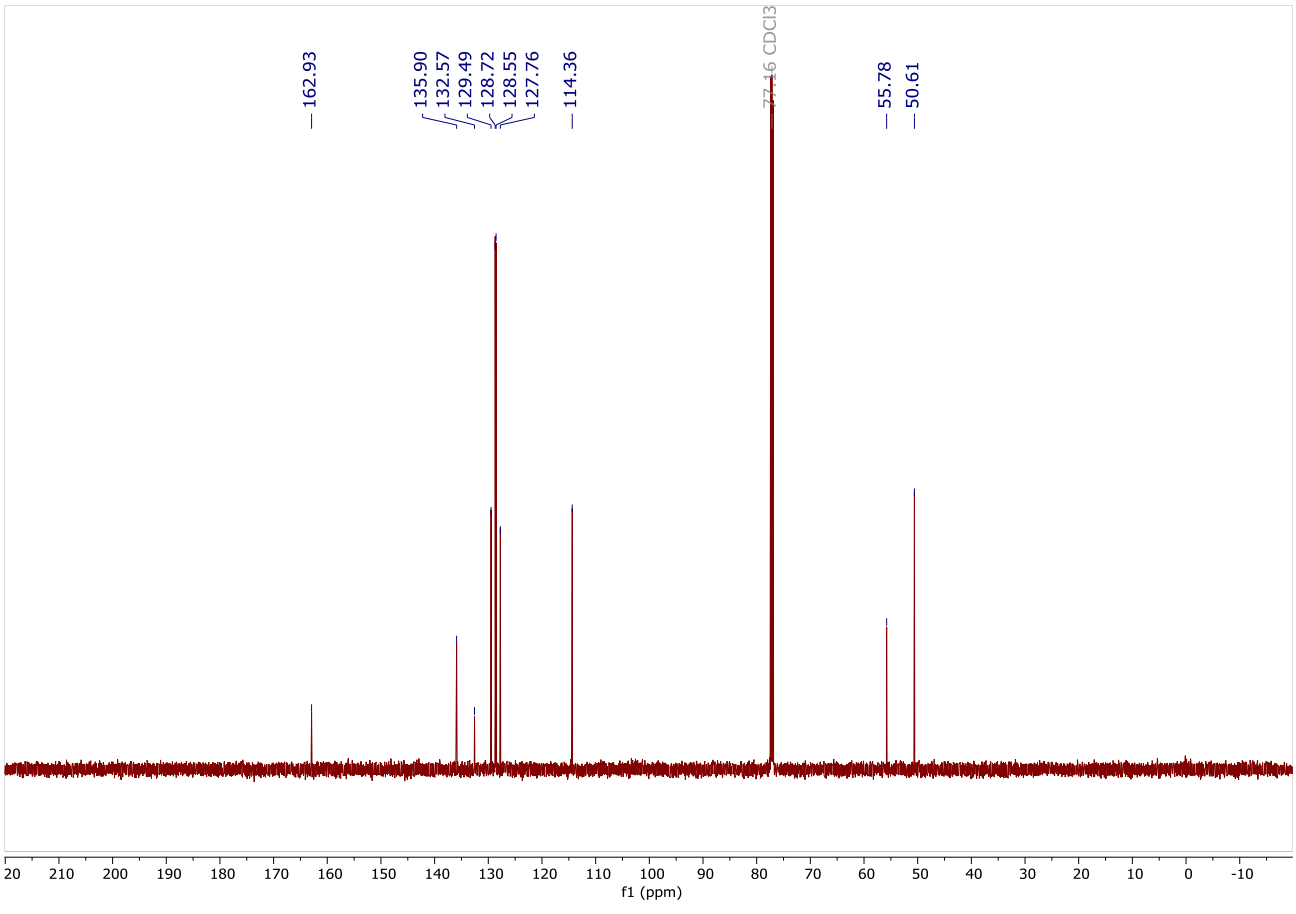
6.00
4.02
2.00
4.01
3.06
f1 (ppm)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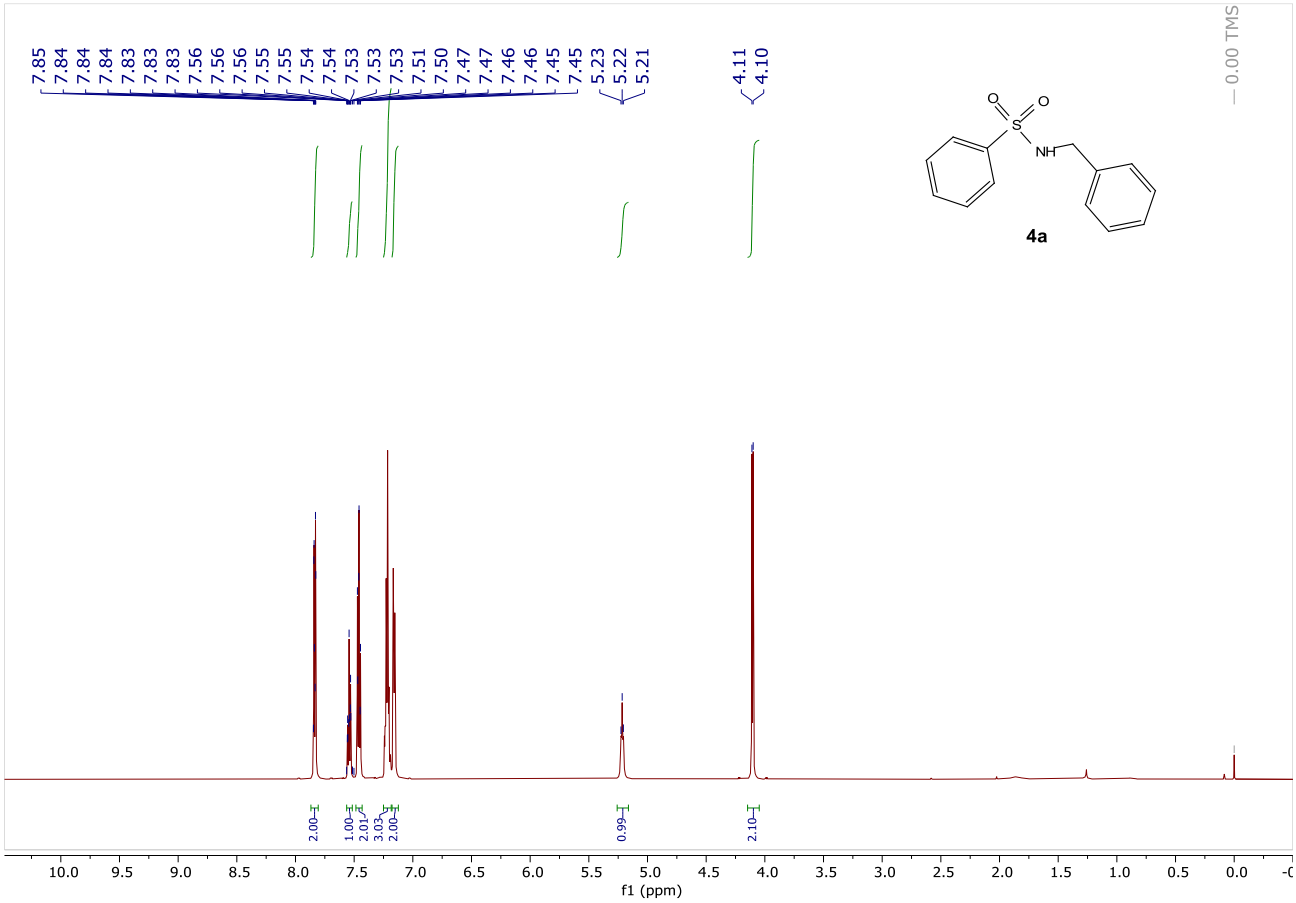
127.76
114.36
77.16 CDCl3
55.78
50.61
f1 (ppm)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7.83
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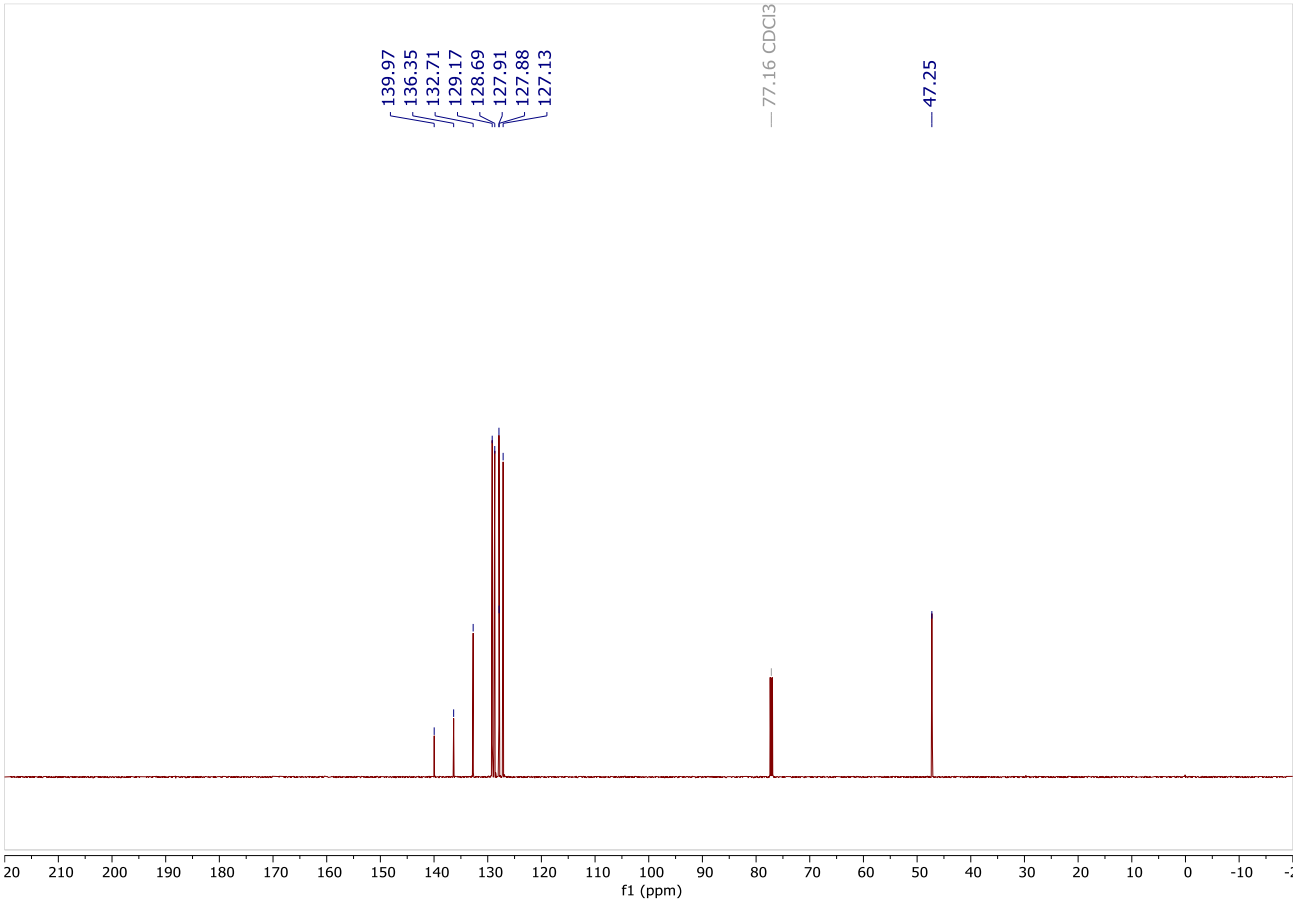
7.54
7.53
7.53
7.53
7.51
7.50
7.47
7.47
7.46
7.46
7.45
7.45
5.23
5.22
5.21
4.11
4.10
0.00 TMS
O
S
O
NH
4a
2.00
1.00
2.01
3.03
2.00
0.99
2.10
f1 (ppm)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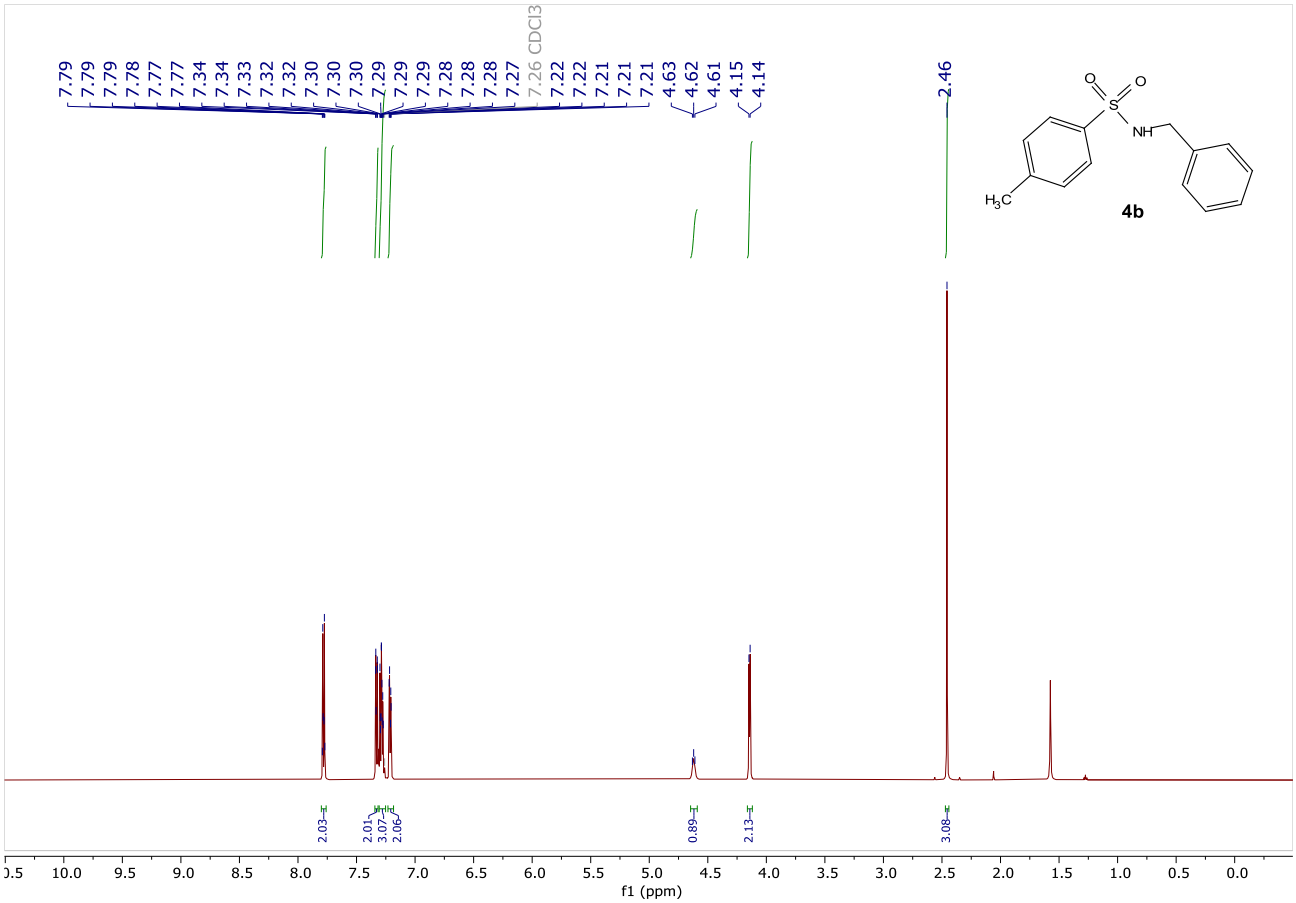
127.88
127.13
77.16 CDCl3
47.25
f1 (ppm)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7.32
7.32
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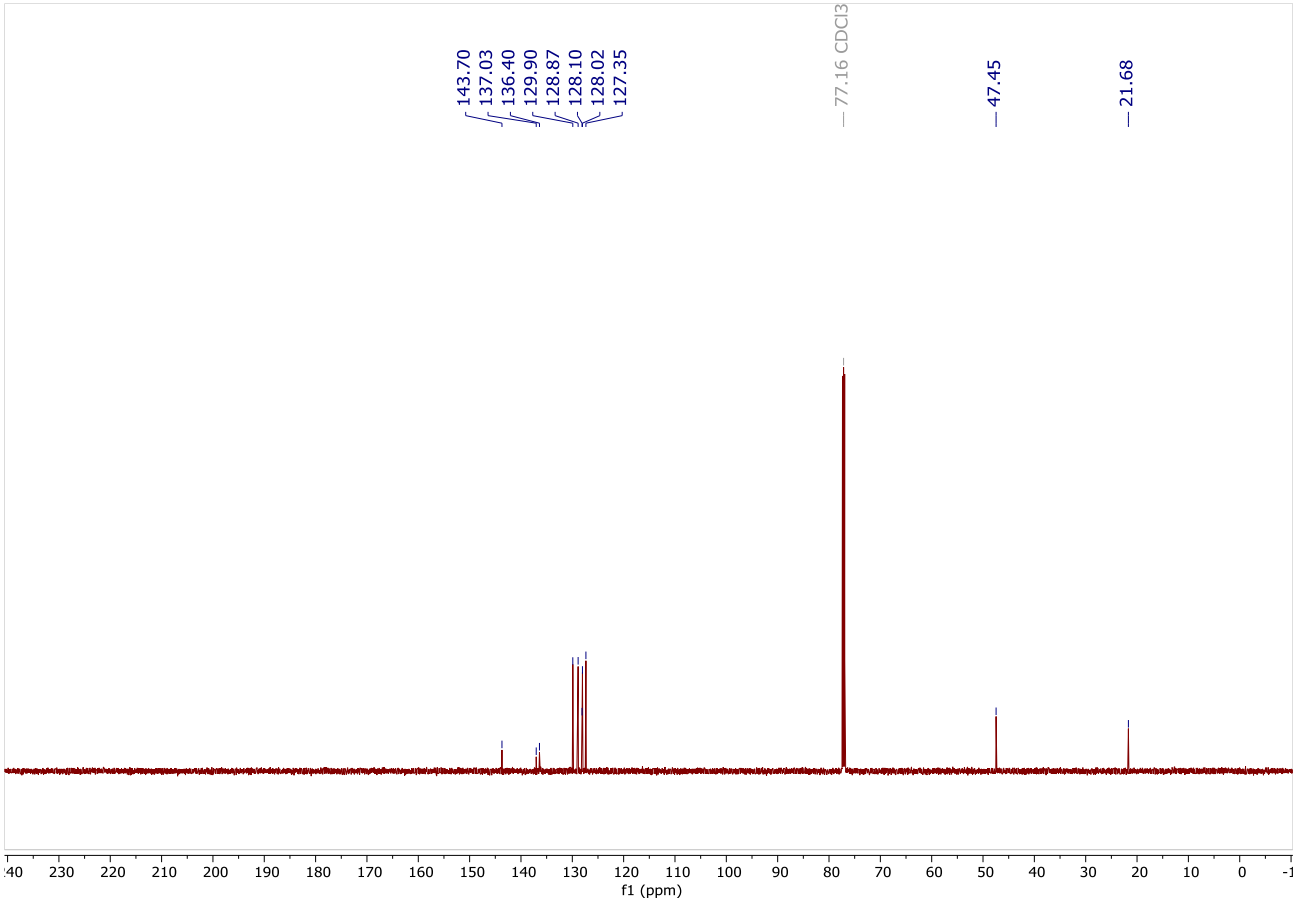
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.28
7.27
7.26 CDCl3
7.22
7.22
7.21
7.21
7.21
4.63
4.62
4.61
4.15
4.14
2.46
O
O
S
NH
H3C
4b
2.03
2.01
3.07
2.06
0.89
2.13
3.08
f1 (ppm)


143.70
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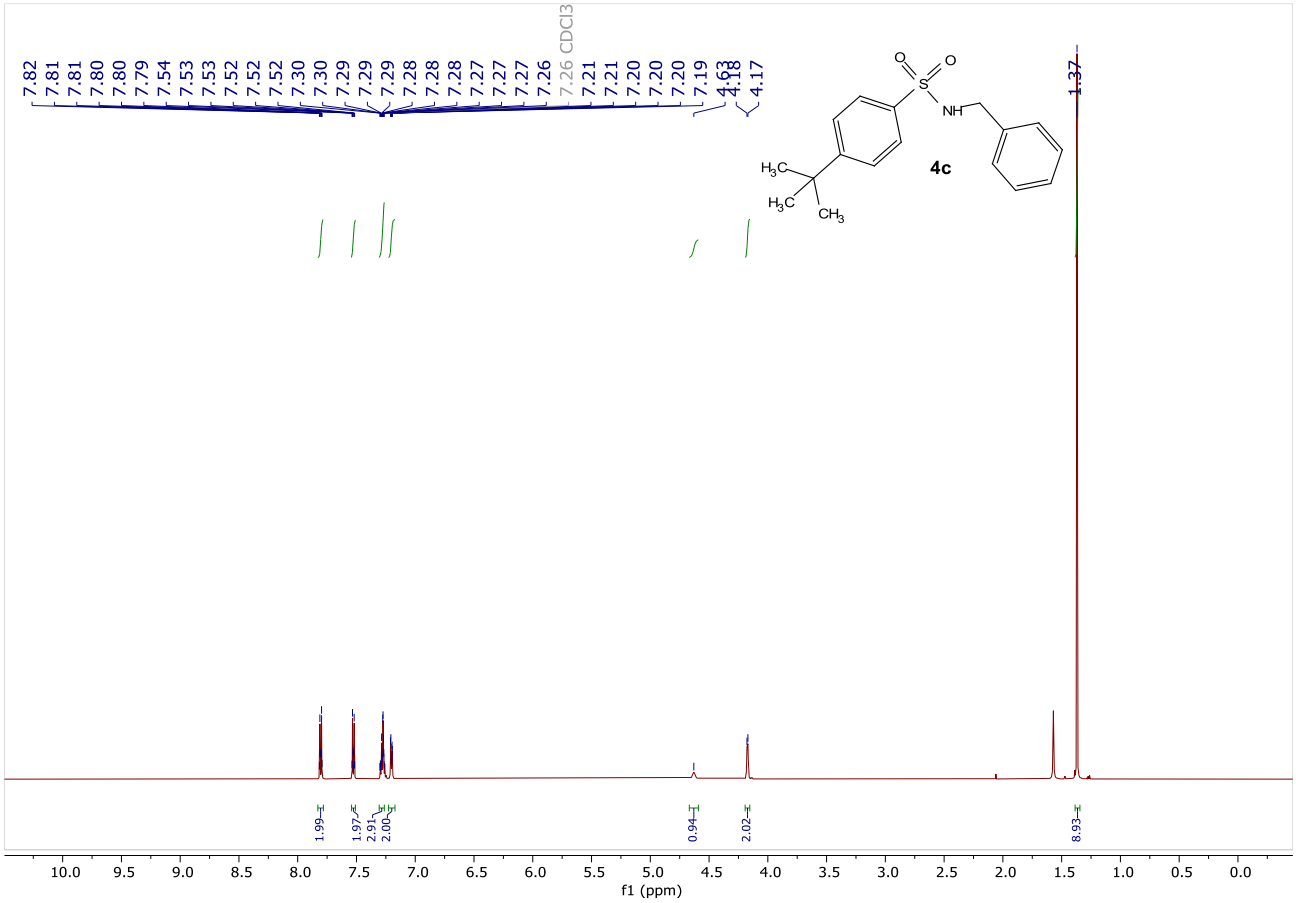
128.87
128.10
128.02
127.35
77.16 CDCl3
47.45
21.68
f1 (ppm)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7.30
7.30
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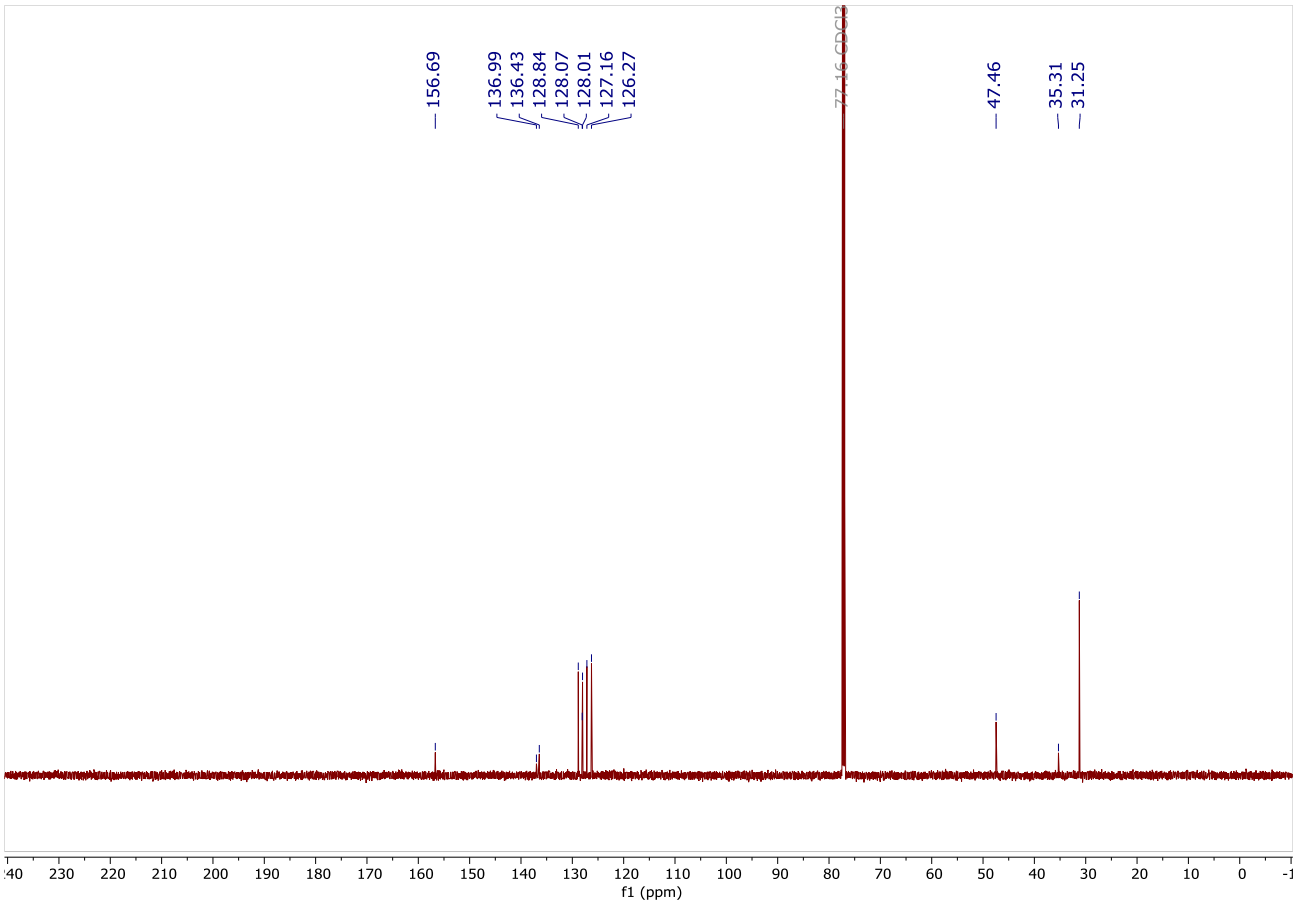
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.27
7.26
7.26 CDCl3
7.21
7.20
7.20
7.20
7.19
4.63
4.18
4.17
1.37
4c
1.99
1.97
2.91
2.00
0.94
2.02
8.93
f1 (ppm)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136.99
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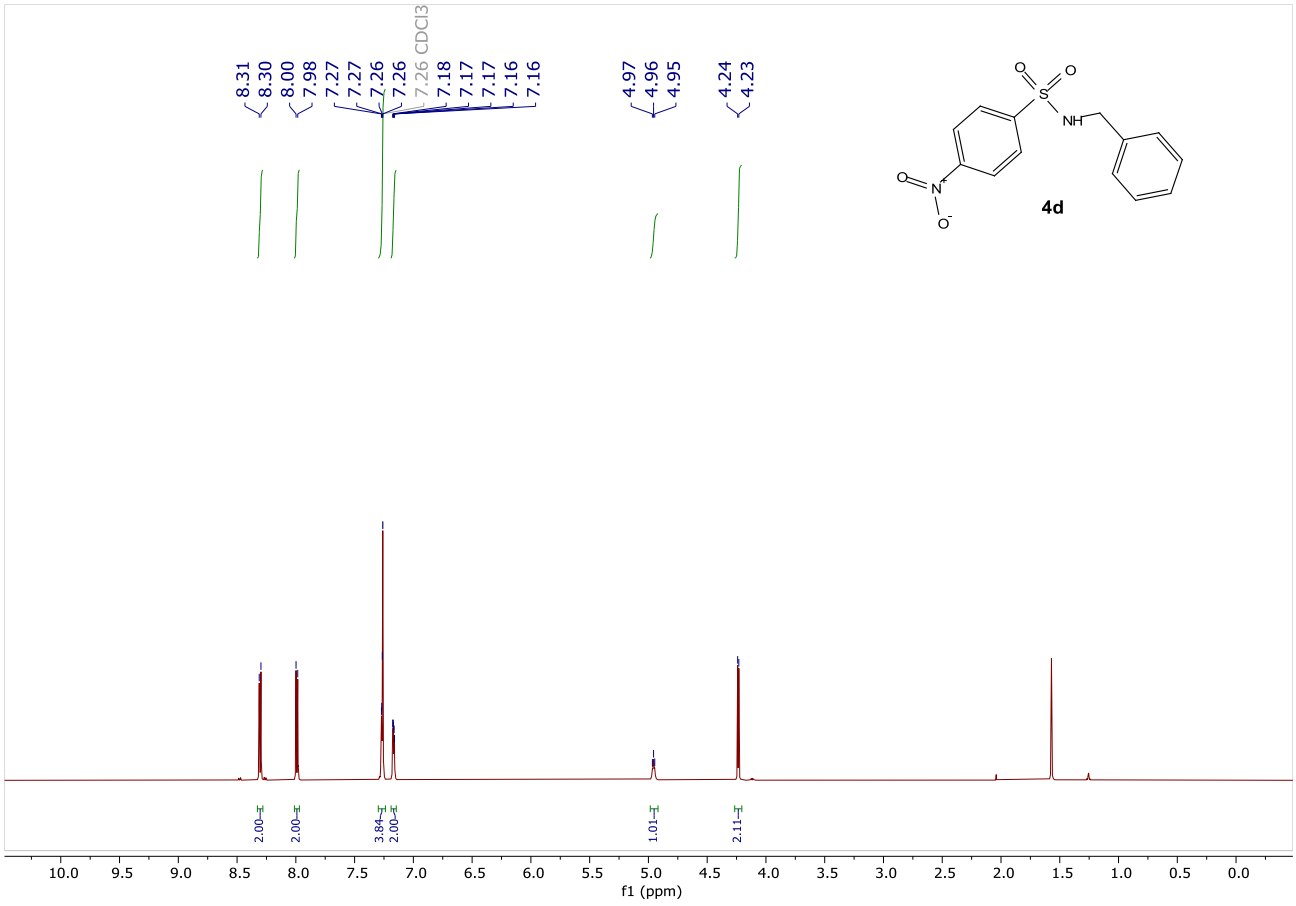
128.07
128.01
127.16
126.27
77.16 CDCl3
47.46
35.31
31.25
f1 (ppm)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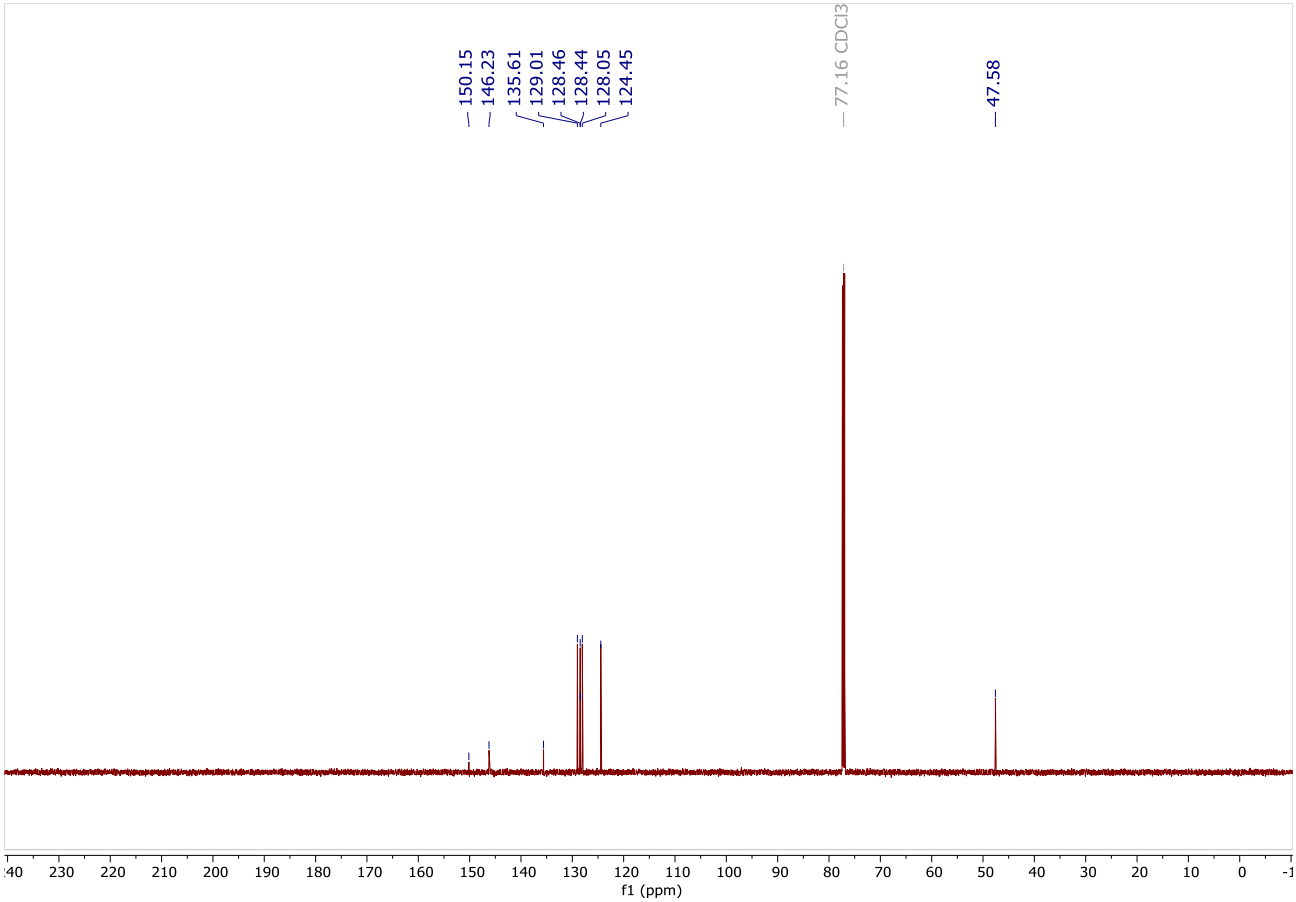
7.26
7.26
7.26 CDCl3
7.18
7.17
7.17
7.16
7.16
4.97
4.96
4.95
4.24
4.23
NH
4d
2.00
2.00
3.84
2.00
1.01
2.11
f1 (ppm)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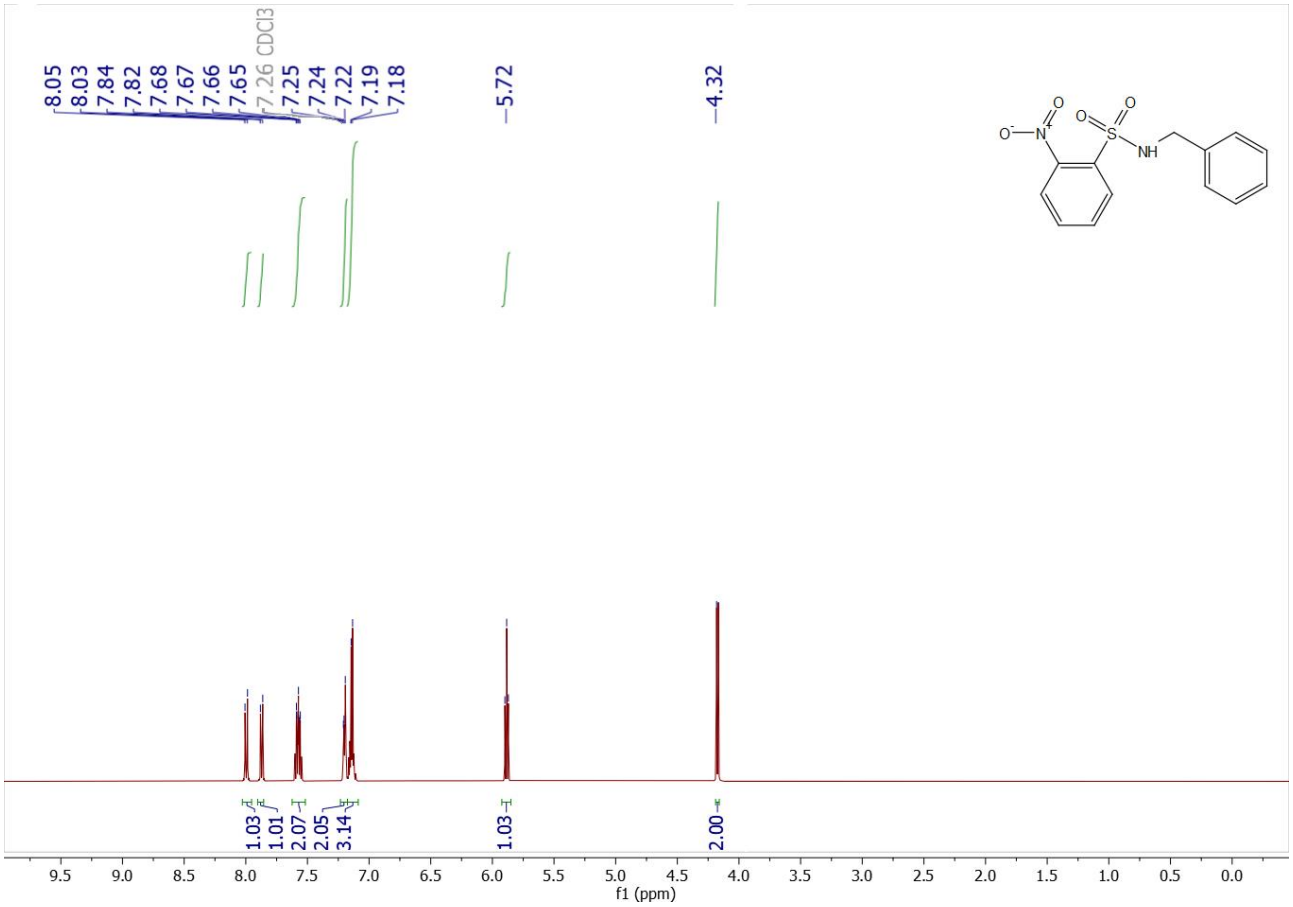
128.44
128.05
124.45
77.16 CDCl3
47.58
f1 (ppm)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7.68
7.67
7.66
7.65
7.26 CDCl3
7.25
7.24
7.22
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7.18
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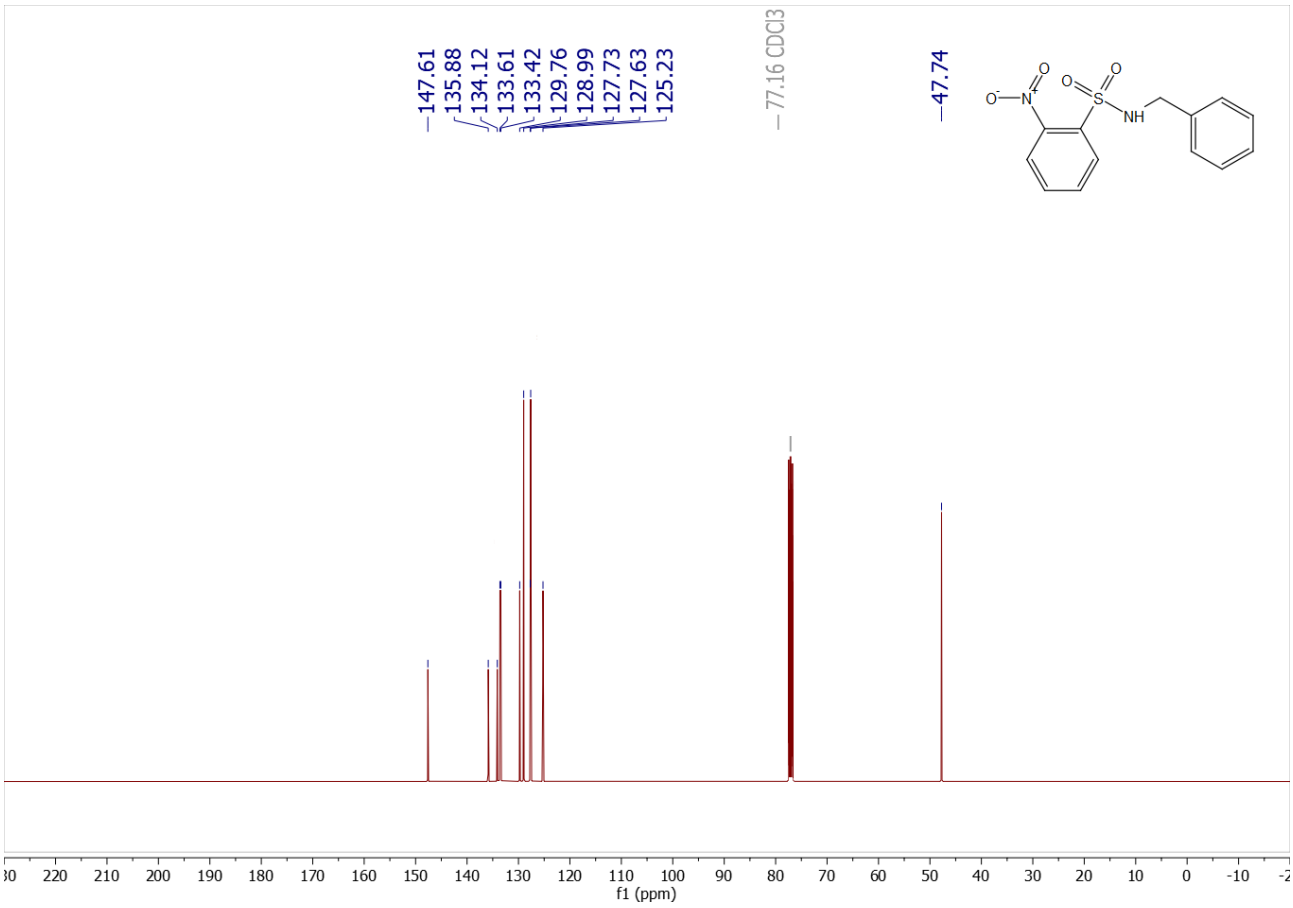
4.32
1.03
1.01
2.07
2.05
3.14
1.03
2.00
f1 (ppm)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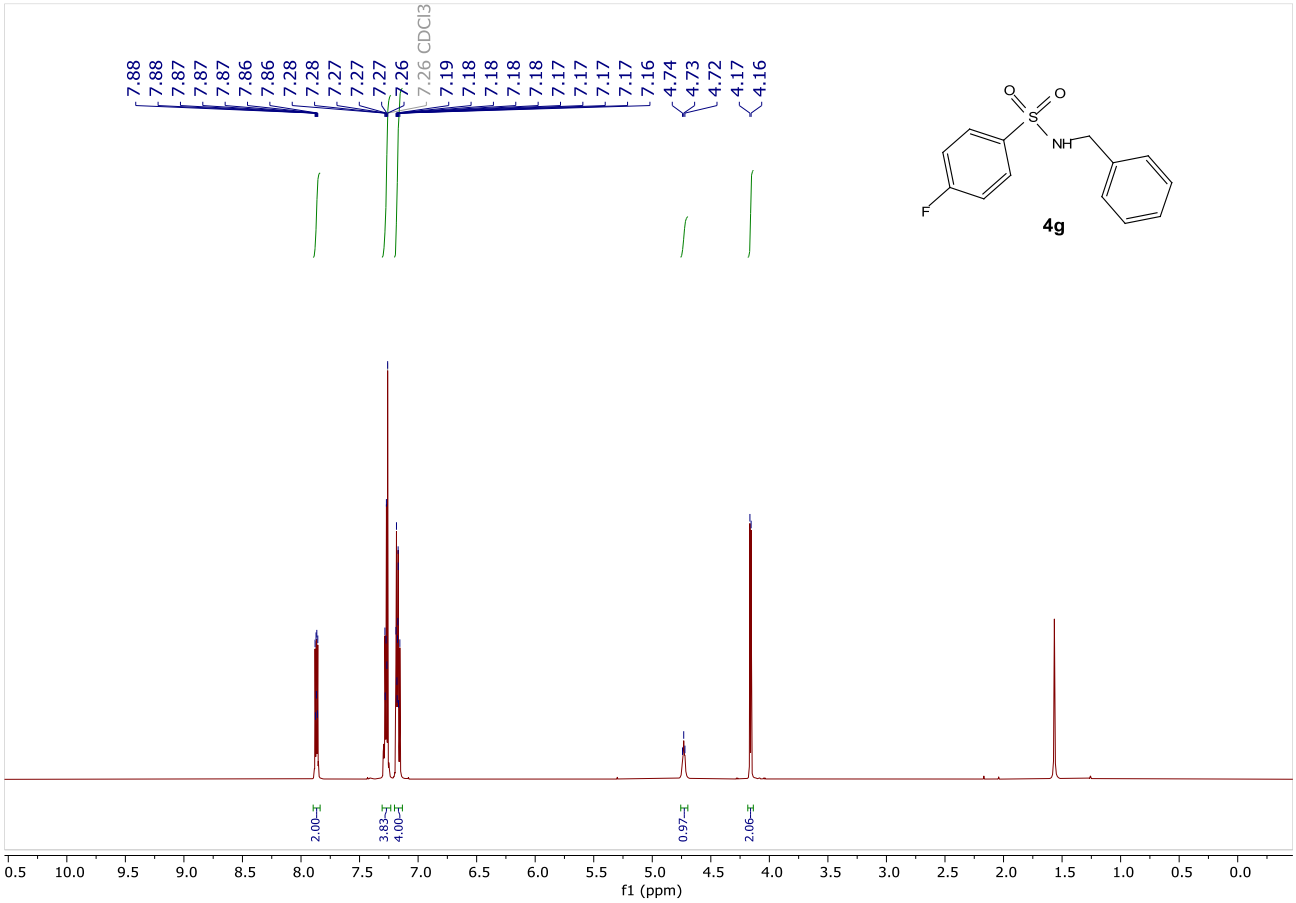
127.63
125.23
77.16 CDCl3
47.74
f1 (ppm)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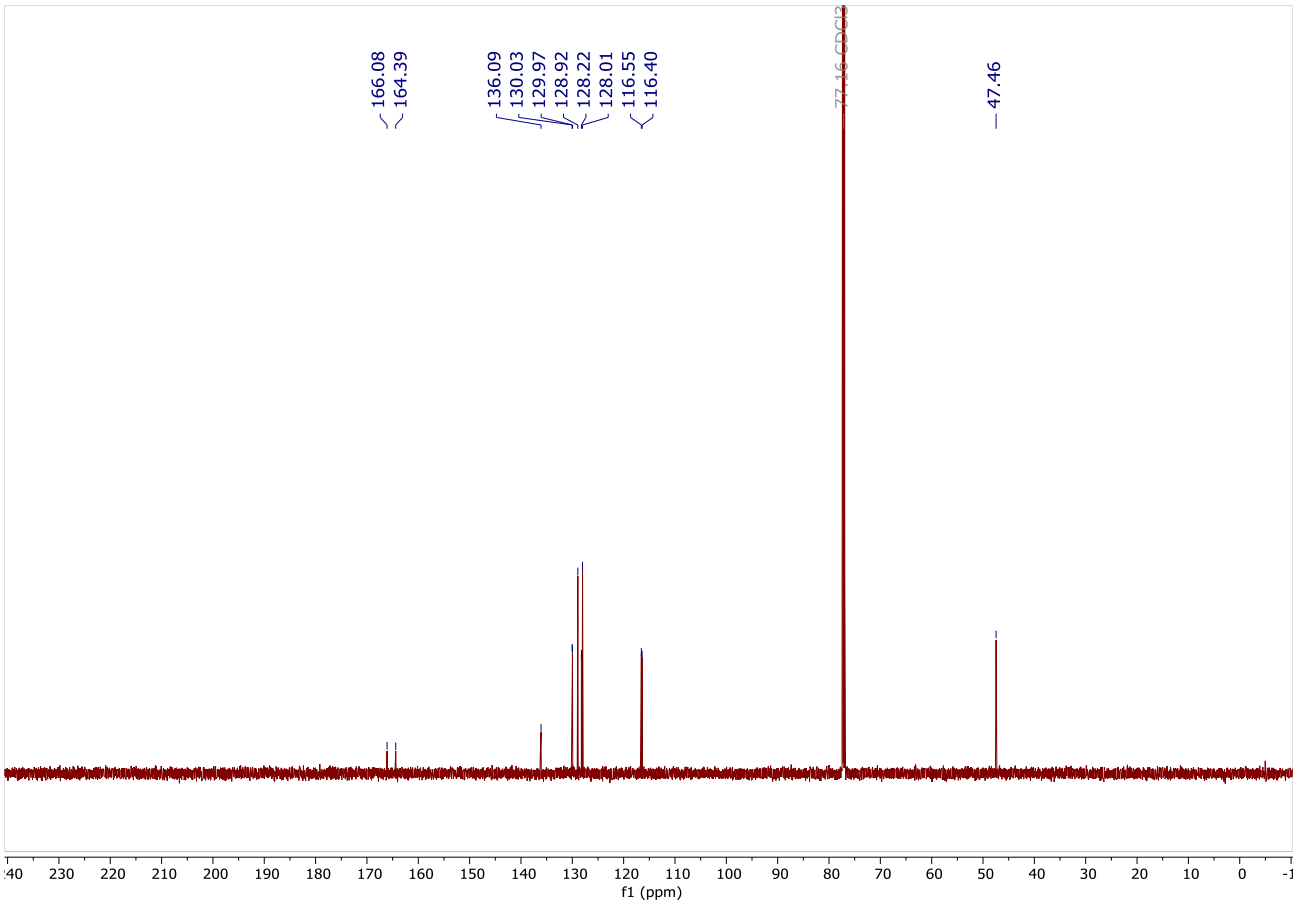
7.86
7.28
7.28
7.27
7.27
7.27
7.26
7.26 CDCl3
7.19
7.18
7.18
7.18
7.17
7.17
7.17
7.17
7.16
4.74
4.73
4.72
4.17
4.16
O
O
S
NH
F
4g
2.00
3.83
4.00
0.97
2.06
f1 (ppm)


166.08
164.39
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129.97
128.92
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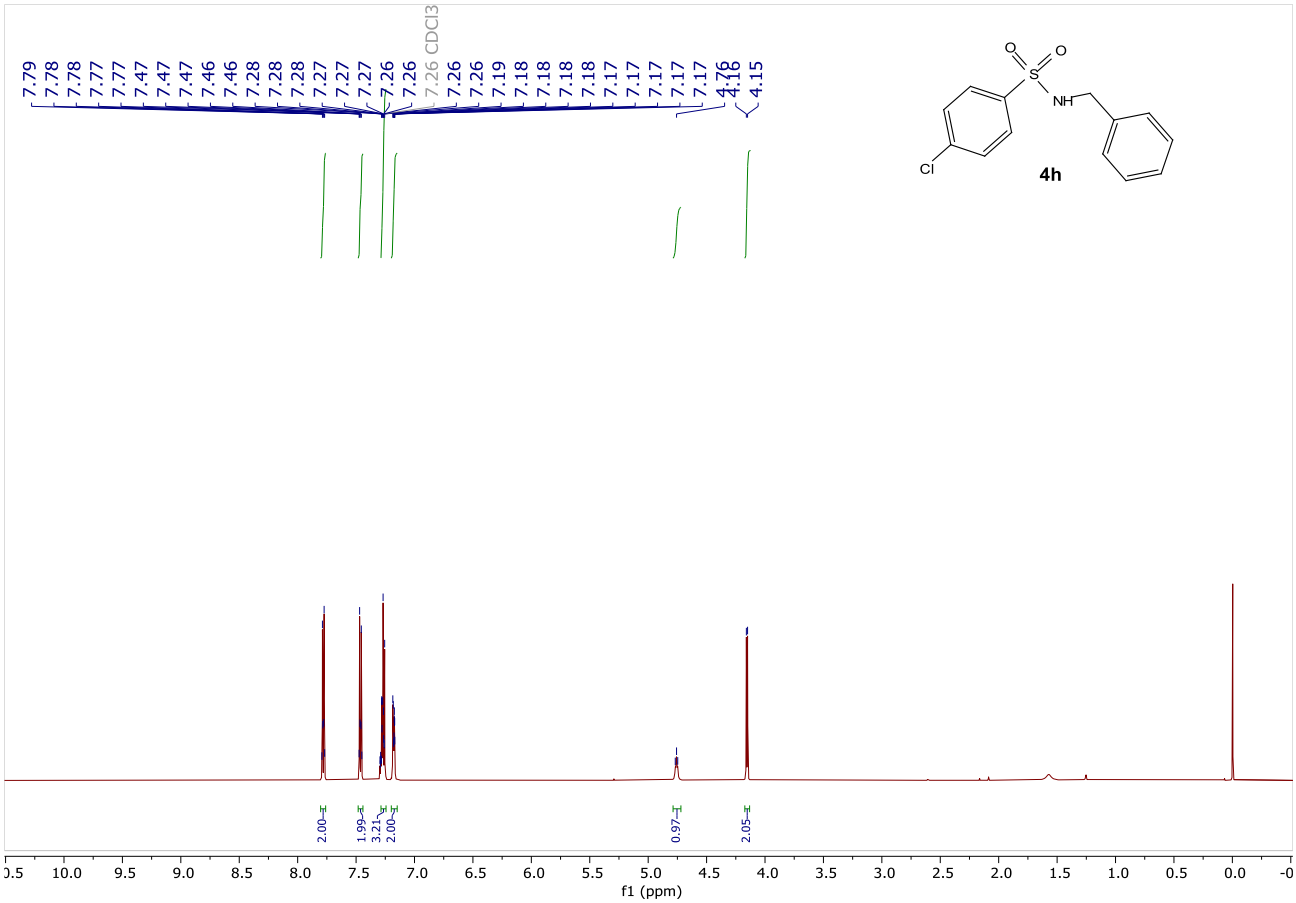
128.01
116.55
116.40
77.16 CDCl3
47.46
f1 (ppm)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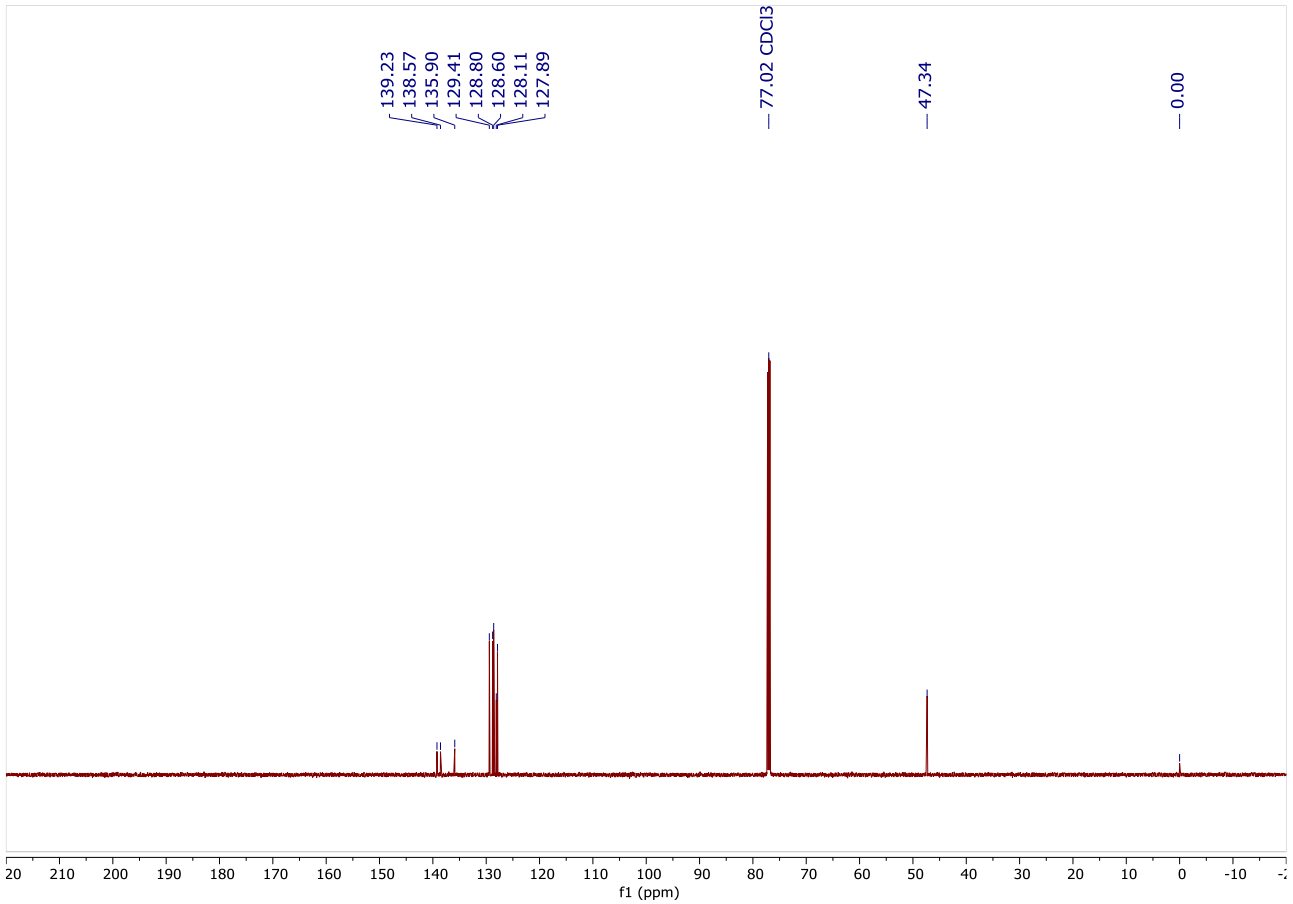
7.27
7.26
7.26
7.26 CDCl3
7.26
7.19
7.18
7.18
7.18
7.17
7.17
7.17
7.17
4.16
4.15
O
O
S
NH
Cl
4h
2.00
1.99
3.21
2.00
0.97
2.05
f1 (ppm)


139.23
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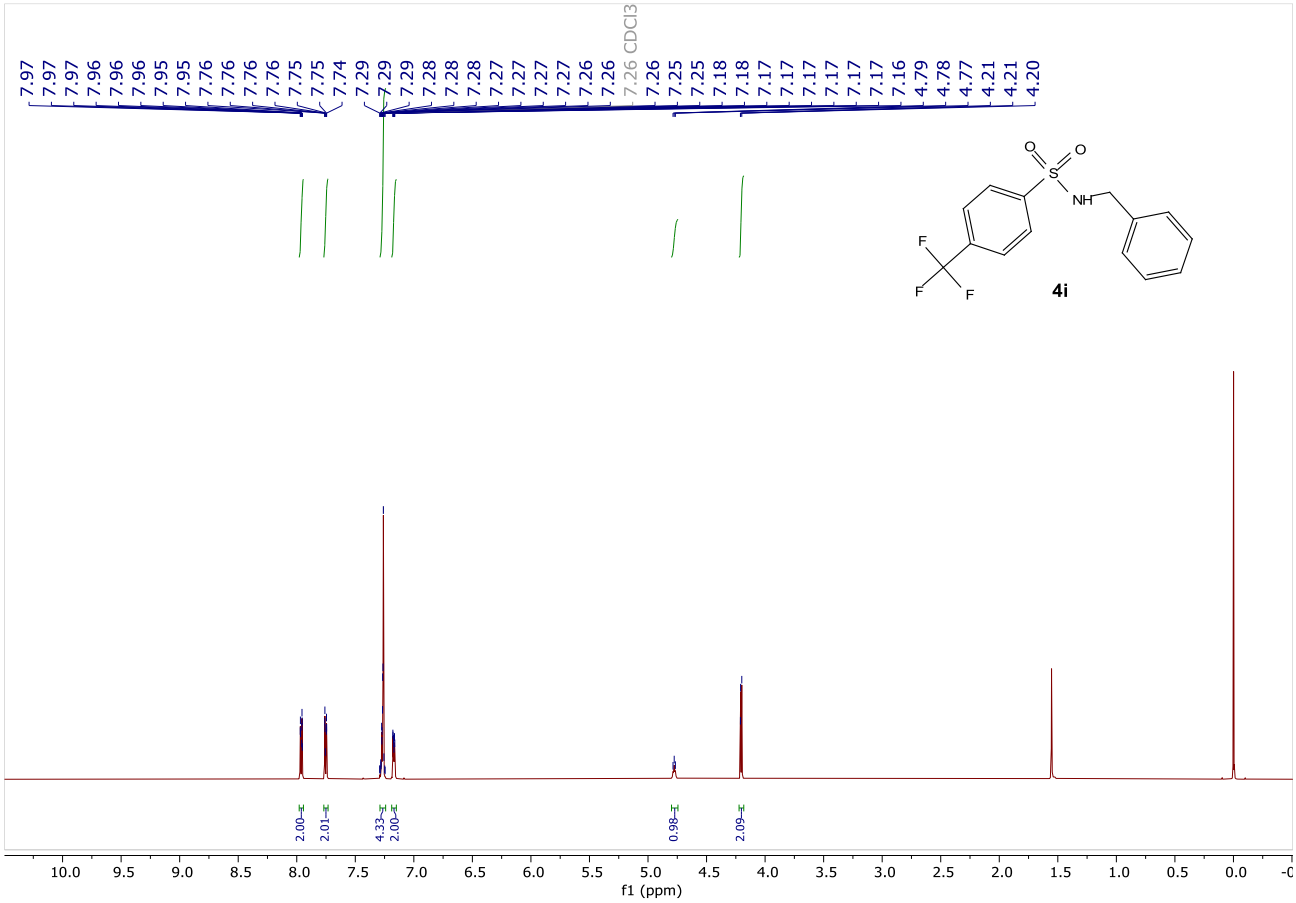
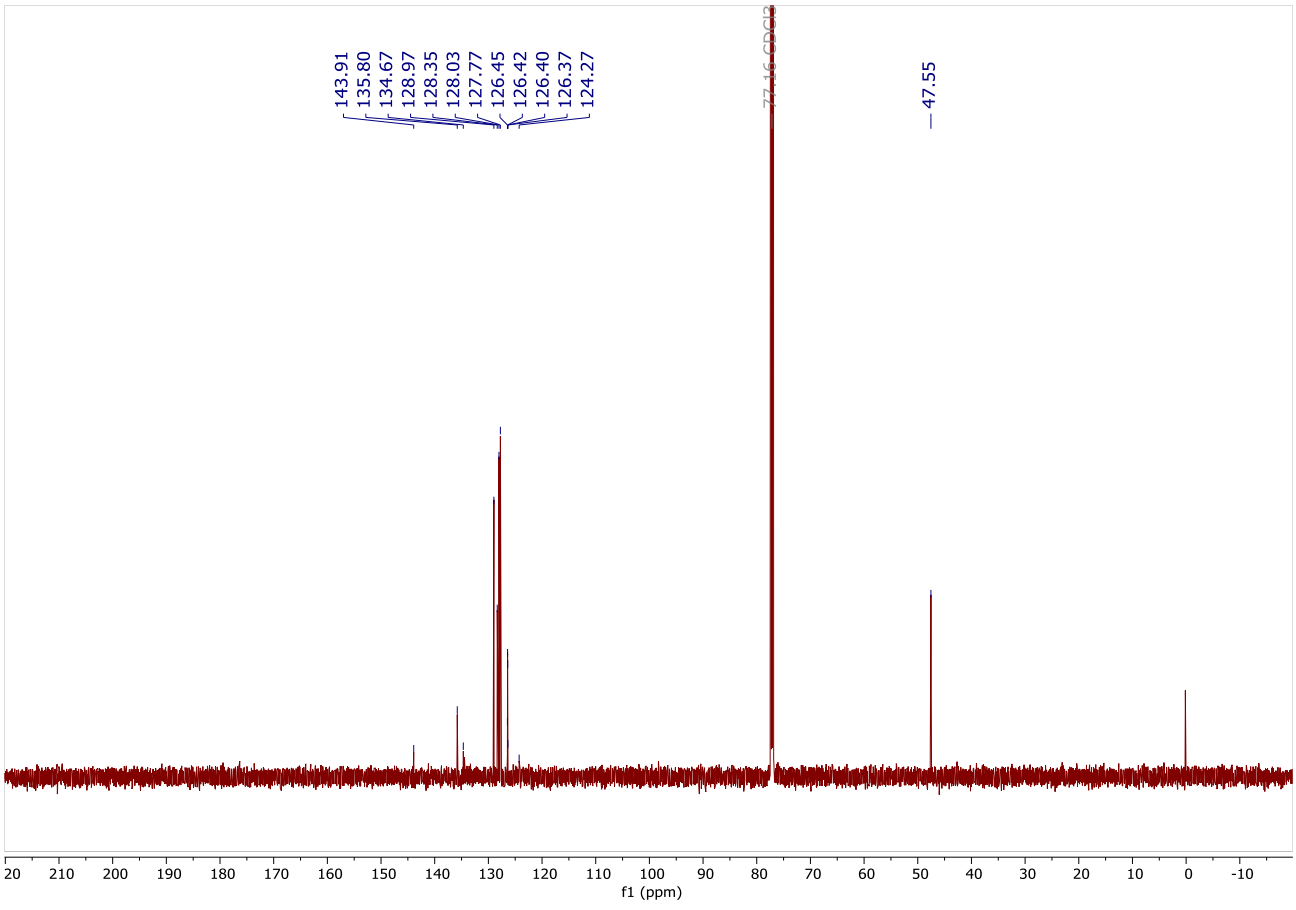
128.11
127.89
77.02 CDCl3
47.34
0.00
f1 (ppm)


7.97 7.97 7.97 7.96 7.96 7.96 7.95 7.95 7.76 7.76 7.76 7.76 7.75 7.75 7.74 7.29 7.29 7.29 7.28 7.28 7.28 7.27 7.27 7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.18 7.18 7.17 7.17 7.17 7.17 7.17 7.17 7.16 4.79 4.78 4.77 4.21 4.21 4.20
7.26 CDCl3
O
O
S
NH
F
F
F
4i
2.00
2.01
4.33
2.00
0.98
2.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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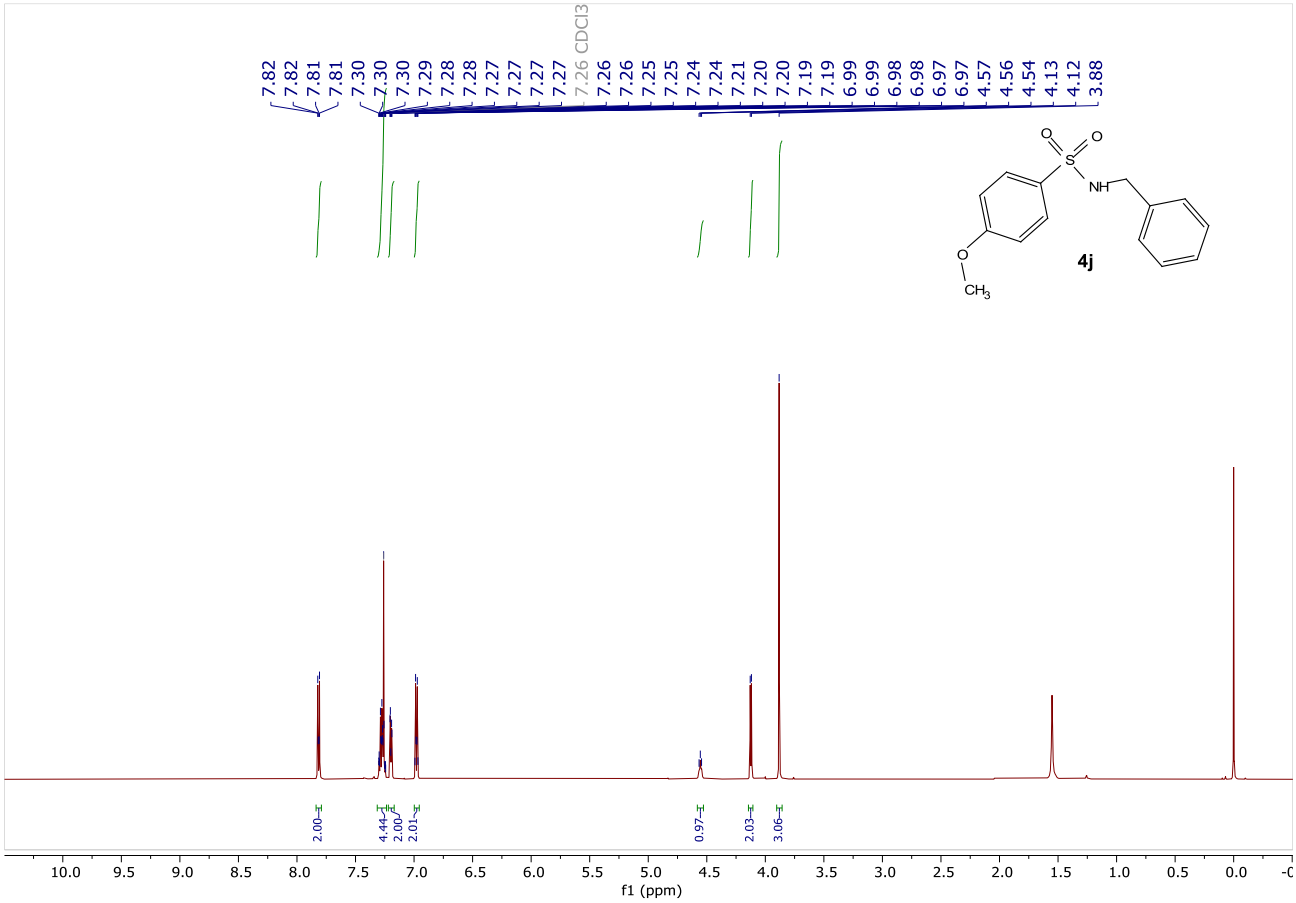
128.97
128.35
128.03
127.77
126.45
126.42
126.40
126.37
124.27
77.16 CDCl3
47.55
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.29
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7.28
7.27
7.27
7.27
7.27
7.26 CDCl3
7.26
7.26
7.25
7.25
7.24
7.24
7.21
7.20
7.20
7.19
7.19
6.99
6.99
6.98
6.98
6.97
6.97
4.57
4.56
4.54
4.13
4.12
3.88
O
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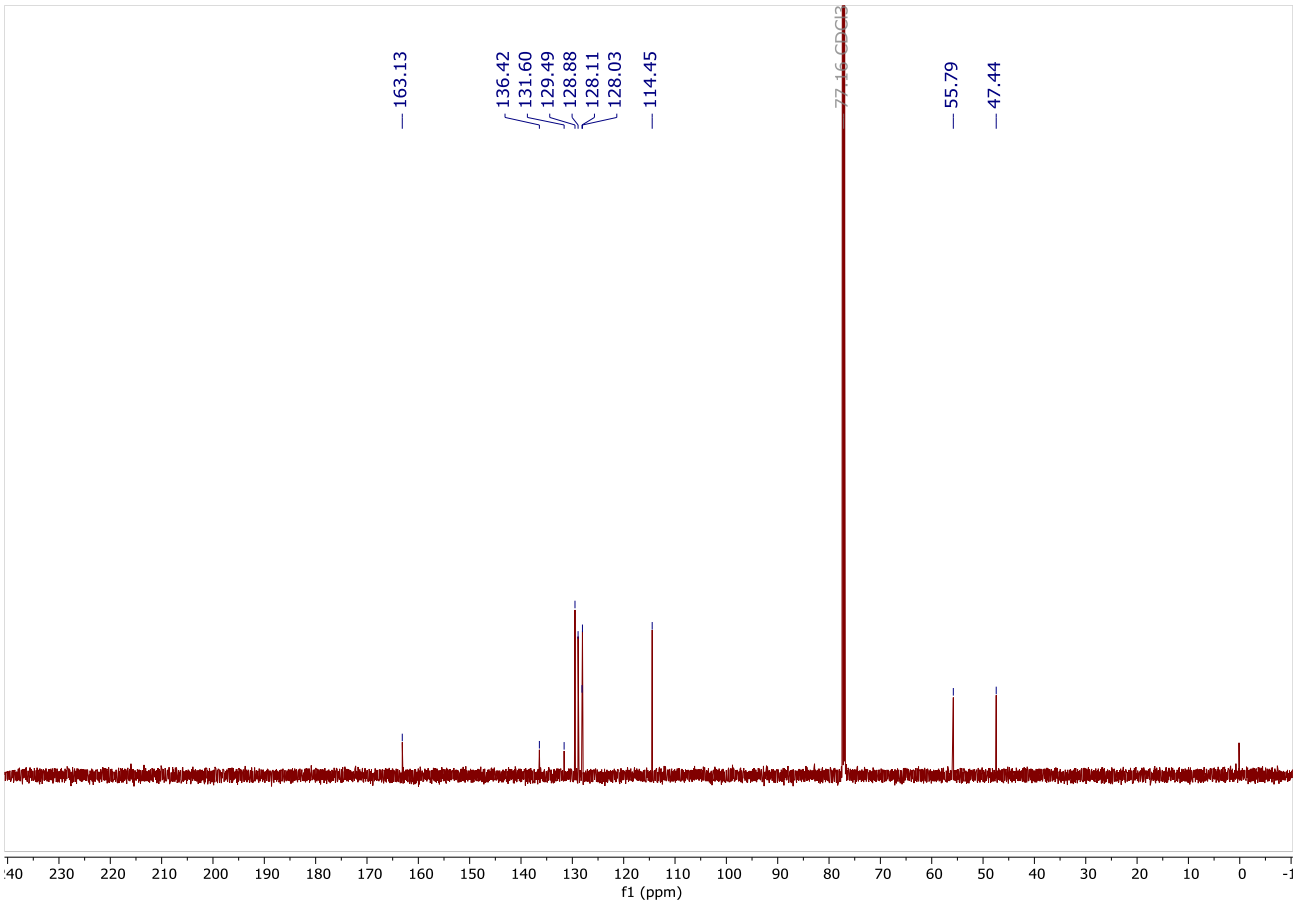
S
NH
O
CH3
4j
2.00
4.44
2.00
2.01
0.97
2.03
3.06
f1 (ppm)


163.13
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114.45
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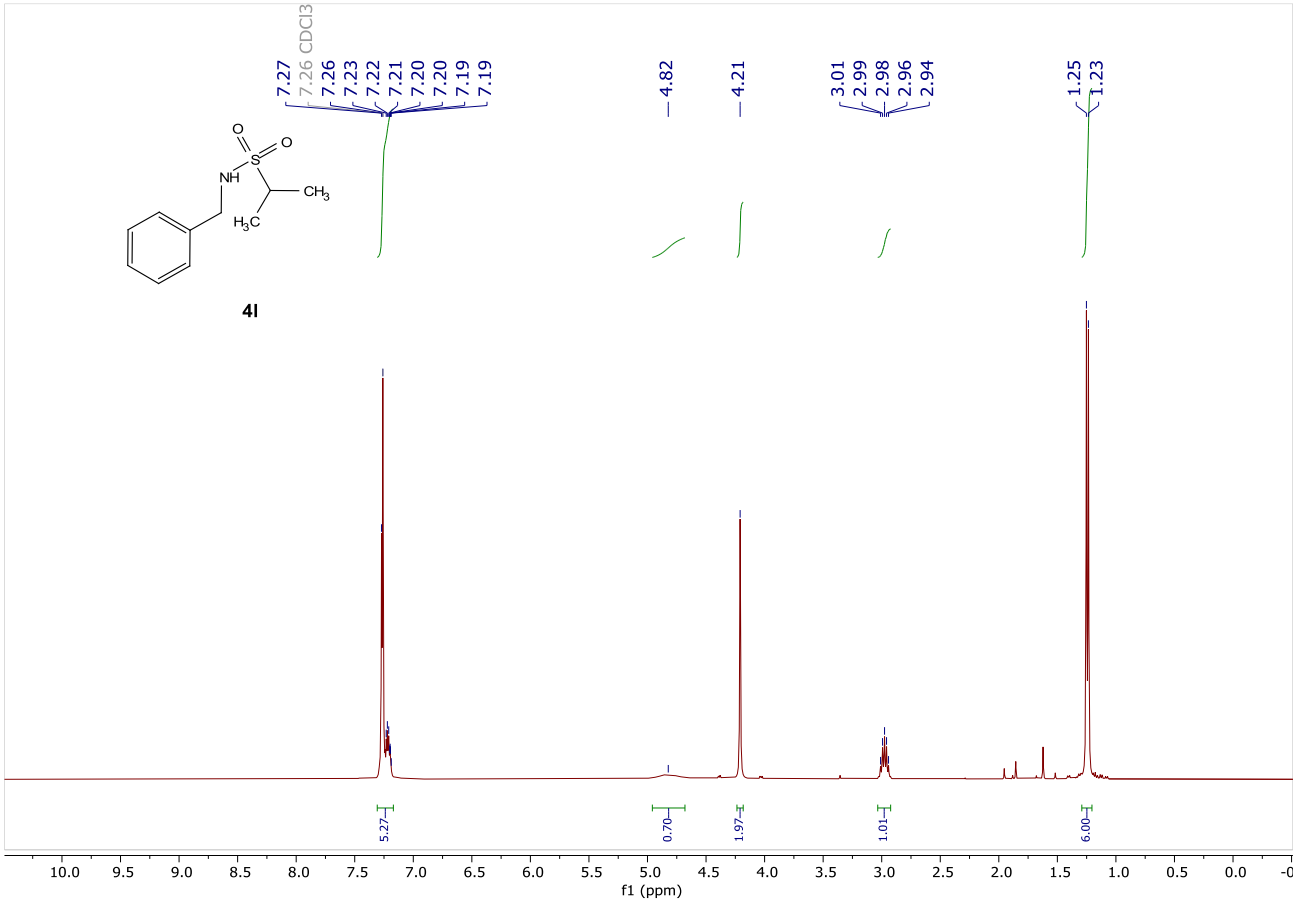
47.44
f1 (ppm)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7.20
7.20
7.19
7.19
4.82
4.21
3.01
2.99
2.98
2.96
2.94
1.25
1.23
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O
NH
CH3
H3C
4l
5.27
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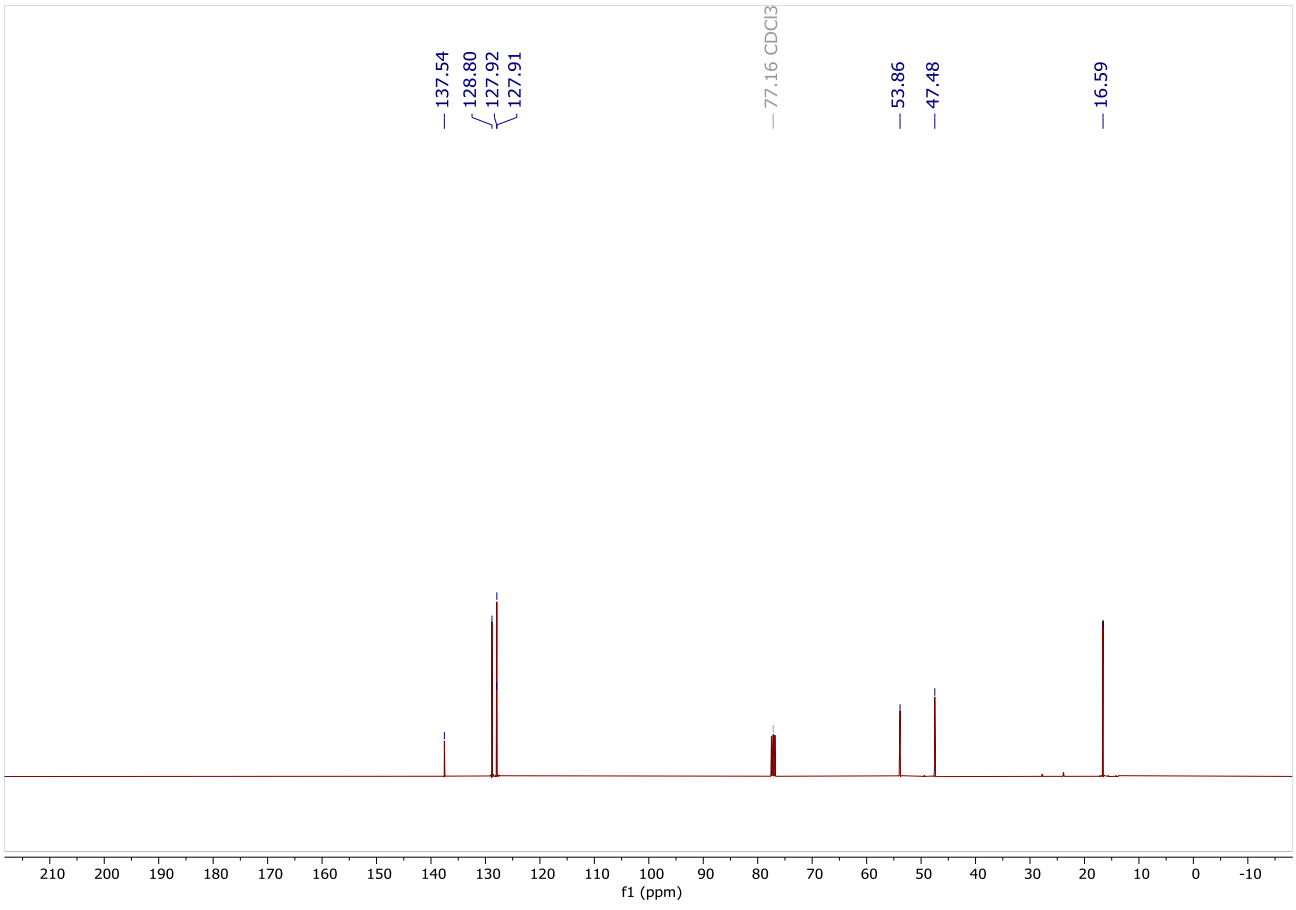
1.97
1.01
6.00
f1 (ppm)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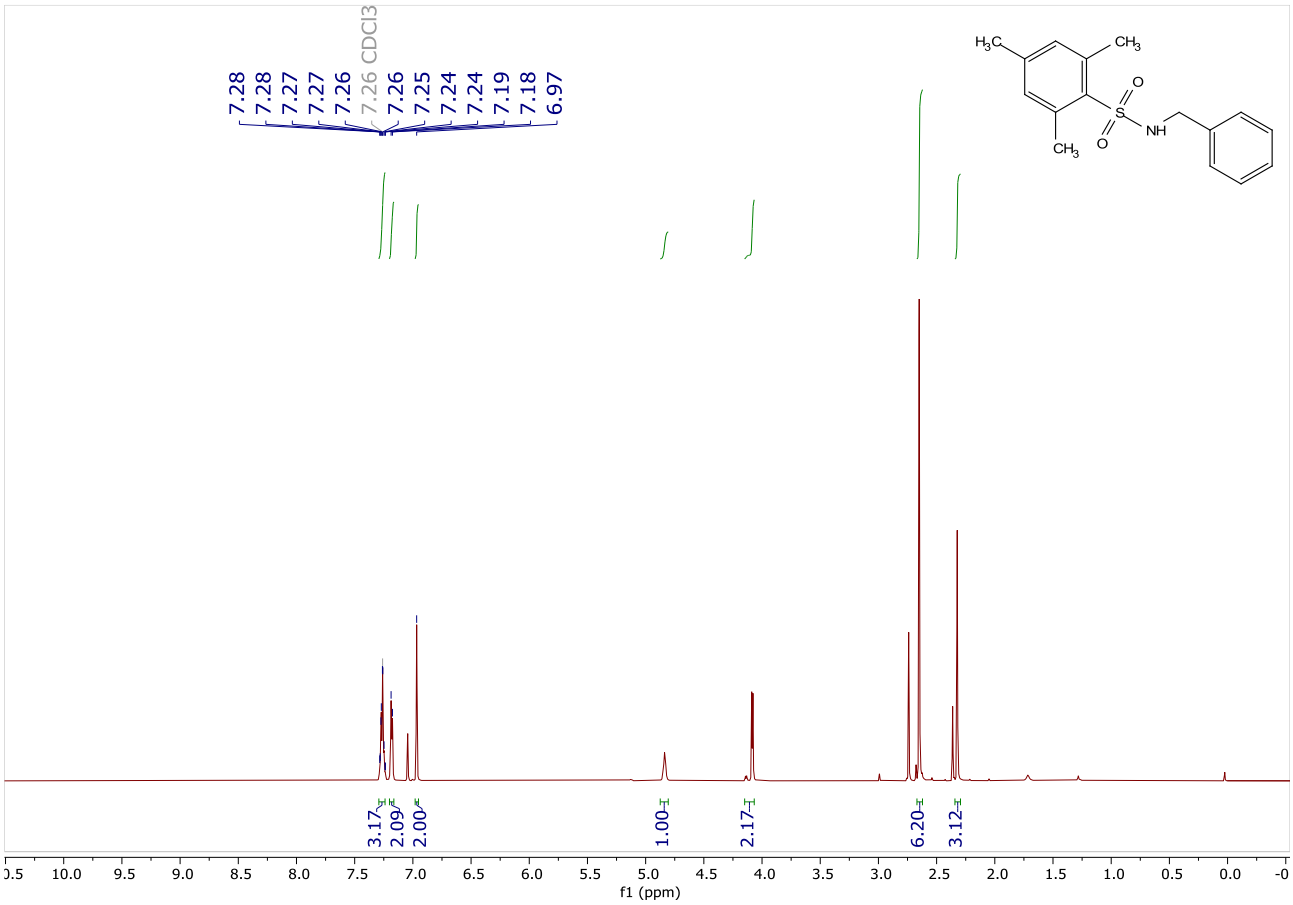
16.59
f1 (ppm)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7.26
7.25
7.24
7.24
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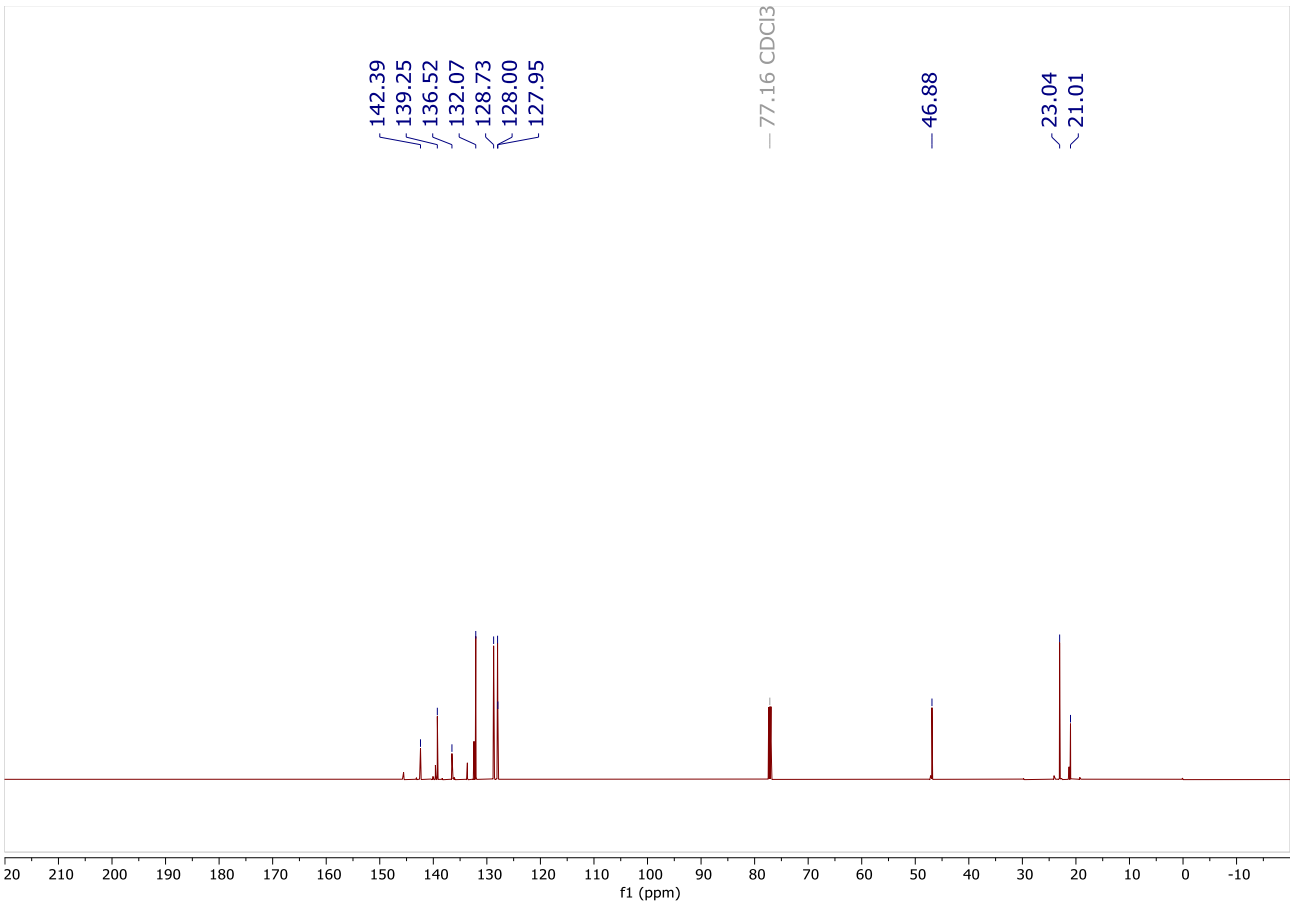
7.18
6.97
3.17
2.09
2.00
1.00
2.17
6.20
3.12
f1 (ppm)


142.39
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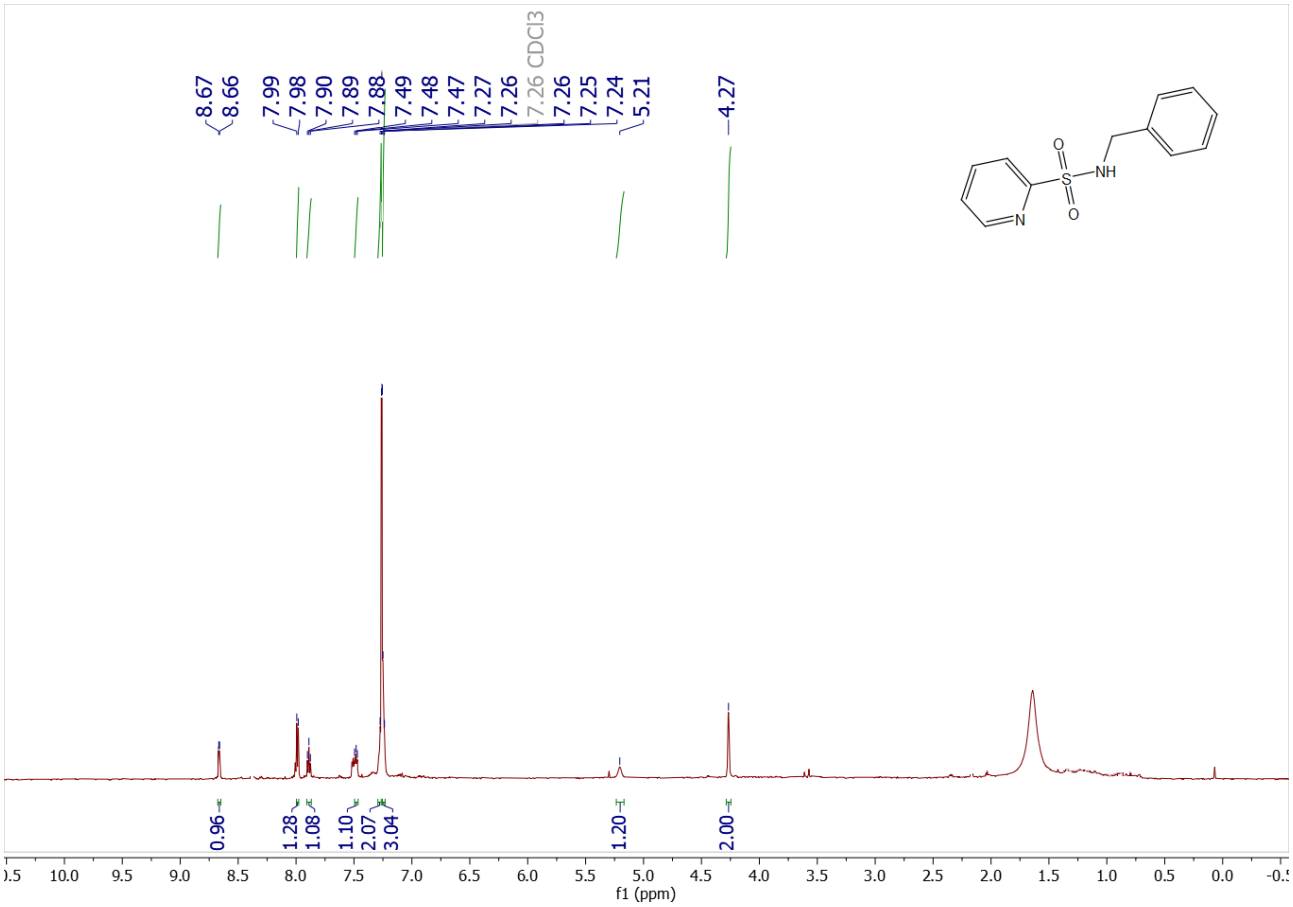
77.16 CDCl3
46.88
23.04
21.01
f1 (ppm)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7.27
7.26
7.26 CDCl3
7.26
7.25
7.24
5.21
4.27
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N
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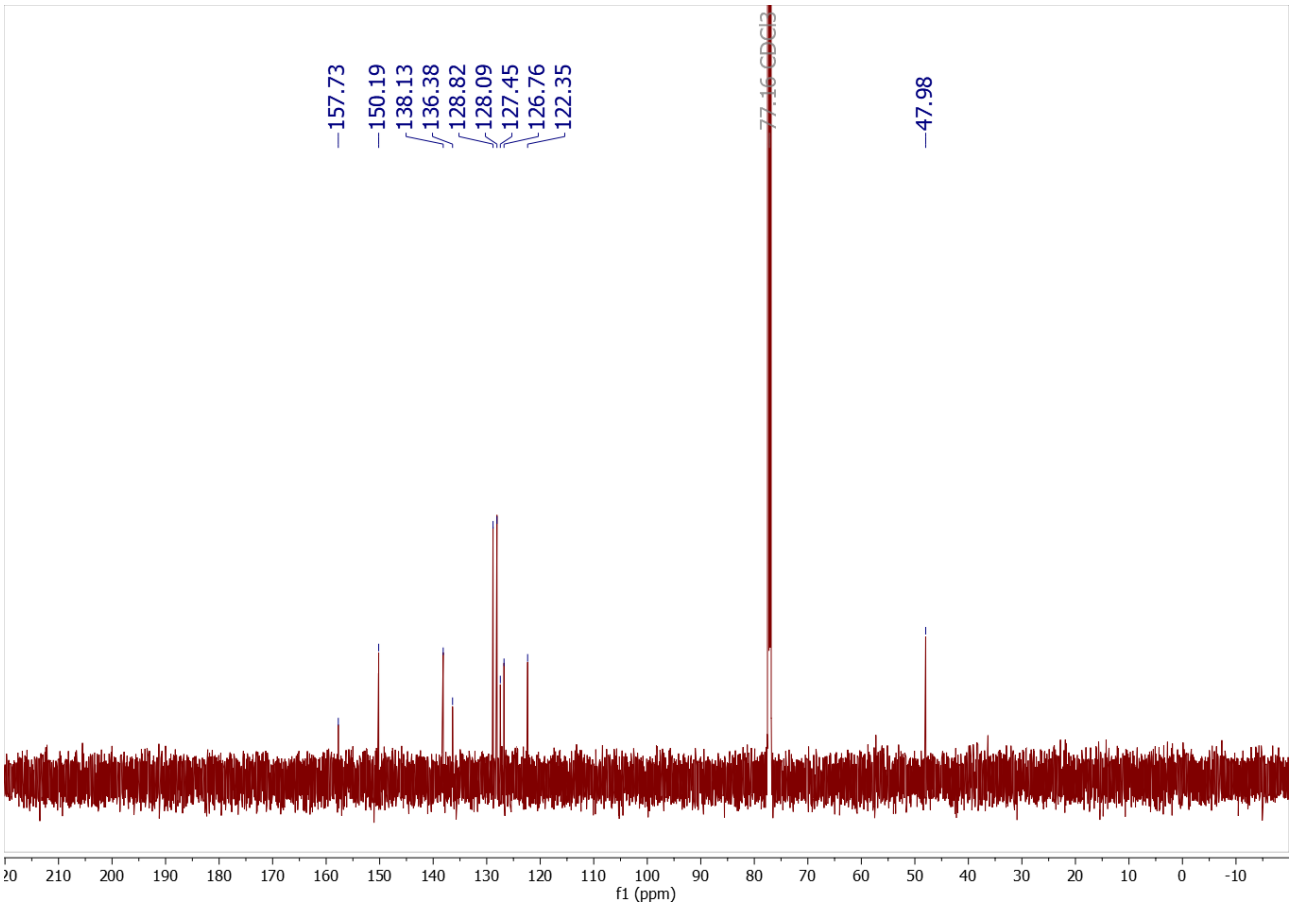
1.08
1.10
2.07
3.04
1.20
2.00
f1 (ppm)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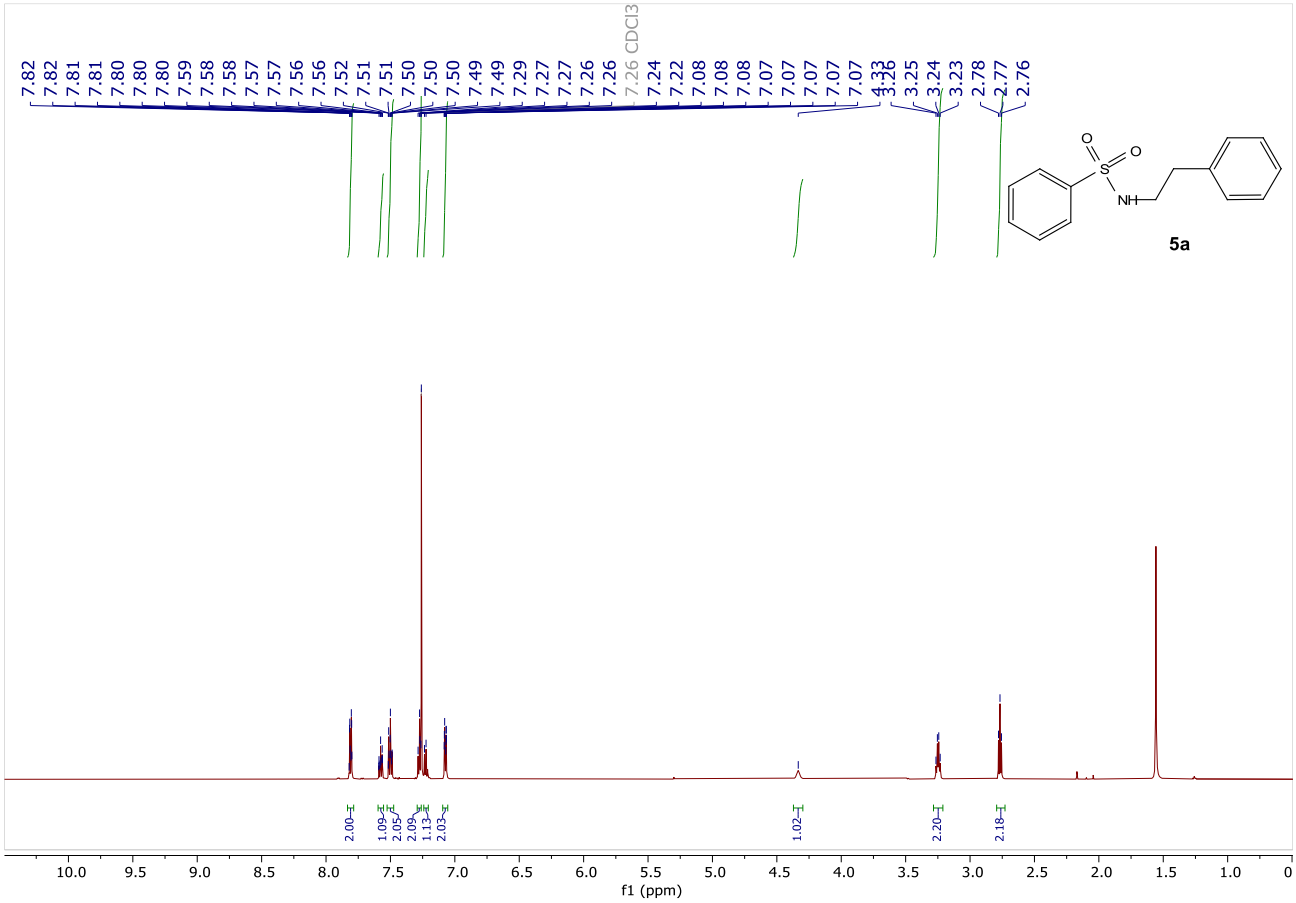
126.76
122.35
77.16 CDCl3
47.98
f1 (ppm)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7.59
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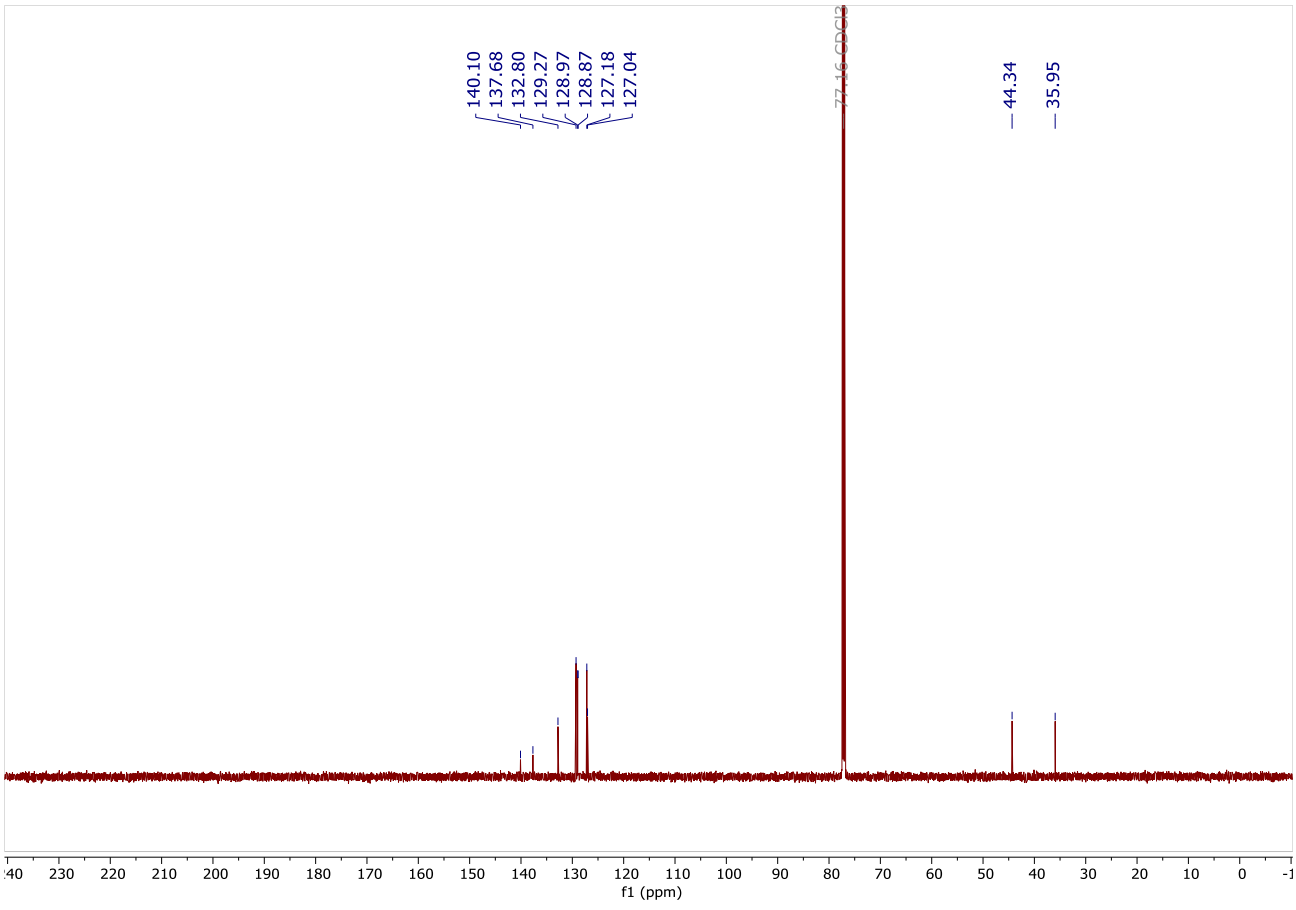
7.58
7.57
7.57
7.56
7.56
7.52
7.51
7.51
7.50
7.50
7.50
7.49
7.49
7.29
7.27
7.27
7.26
7.26
7.26 CDCl3
7.24
7.22
7.08
7.08
7.08
7.07
7.07
7.07
7.07
7.07
4.33
3.26
3.25
3.24
3.23
2.78
2.77
2.76
O
O
S
NH
5a
2.00
1.09
2.05
2.09
1.13
2.03
1.02
2.20
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
f1 (ppm)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128.87
127.18
127.04
77.16 CDCl3
44.34
35.95
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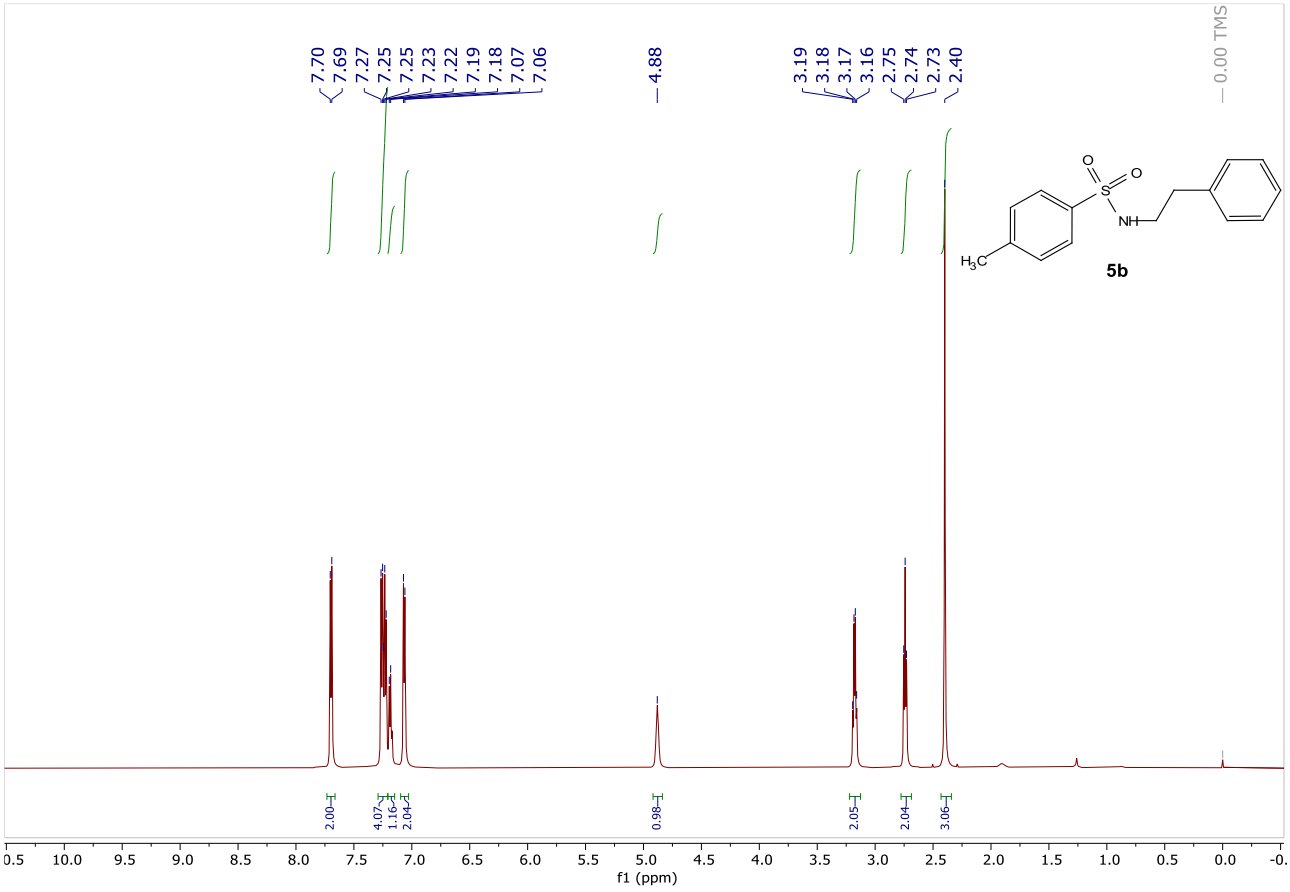
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)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7.69
7.27
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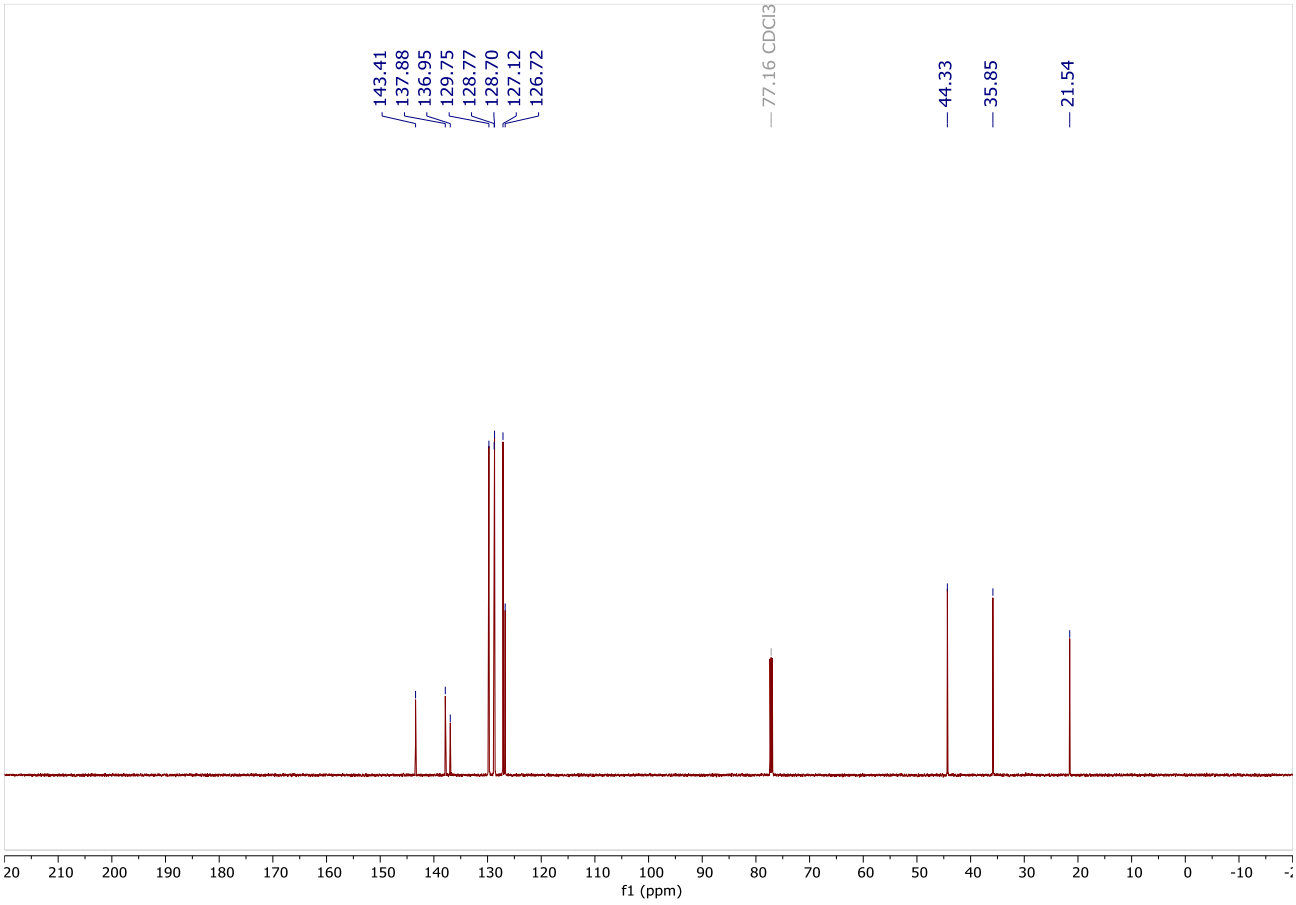
7.25
7.23
7.22
7.19
7.18
7.07
7.06
4.88
3.19
3.18
3.17
3.16
2.75
2.74
2.73
2.40
0.00 TMS
O
O
S
NH
H3C
5b
2.00
4.07
1.16
2.04
0.98
2.05
2.04
3.06
f1 (ppm)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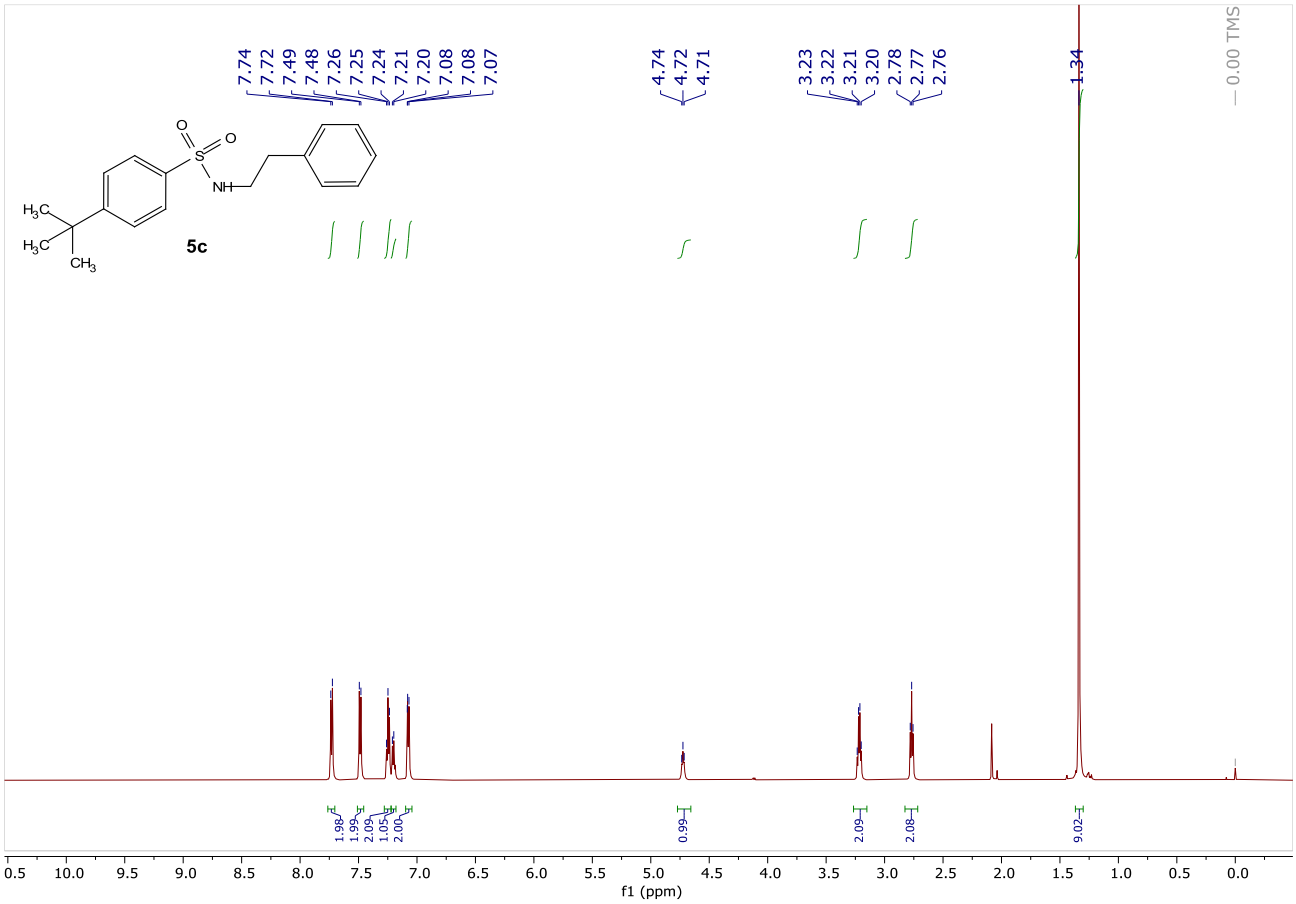
128.77
128.70
127.12
126.72
77.16 CDCl3
44.33
35.85
21.54
f1 (ppm)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7.48
7.26
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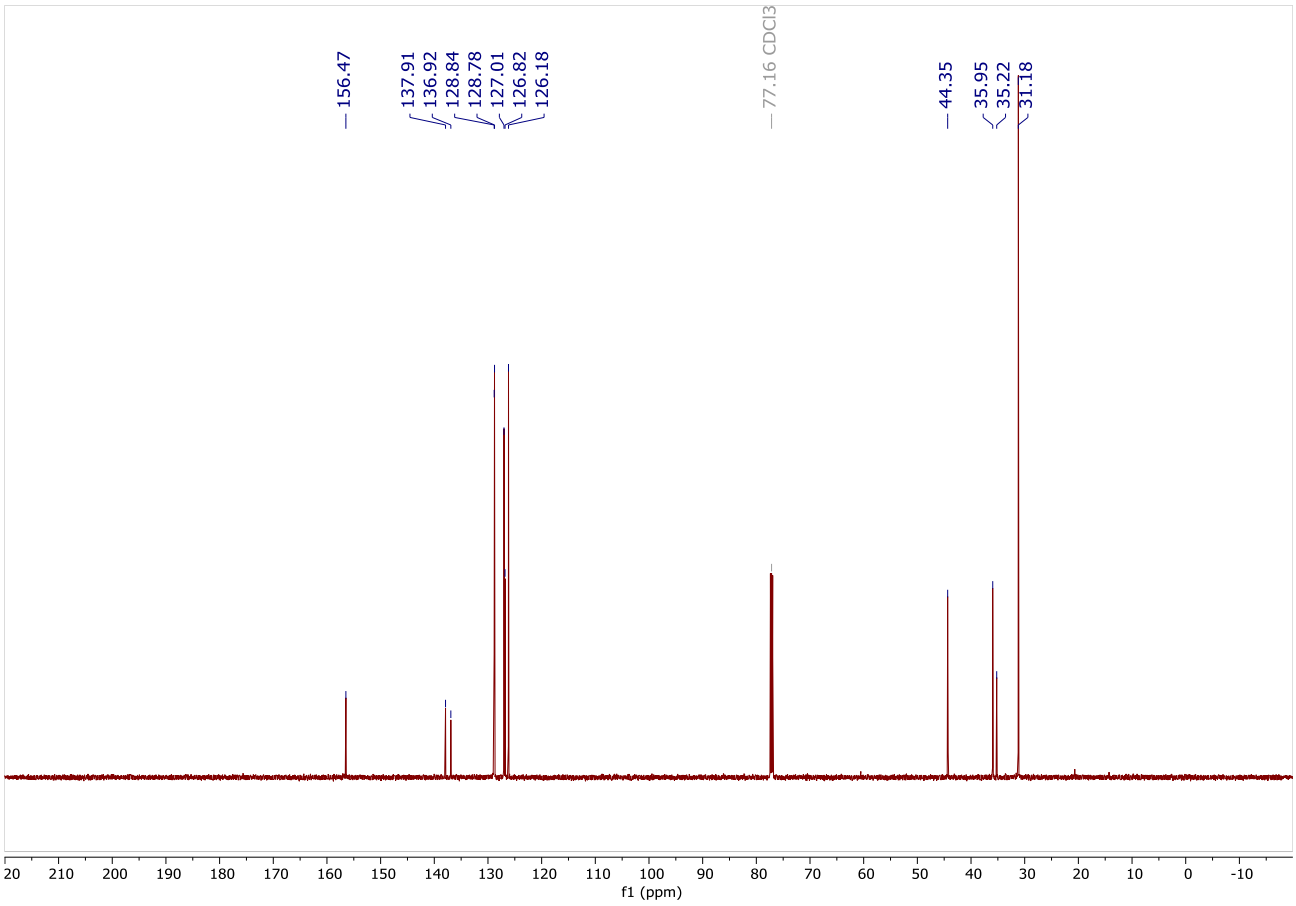
7.24
7.21
7.20
7.08
7.08
7.07
4.74
4.72
4.71
3.23
3.22
3.21
3.20
2.78
2.77
2.76
1.34
0.00 TMS
5c
1.98
1.99
2.09
1.05
2.06
0.99
2.09
2.08
9.02
f1 (ppm)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136.92
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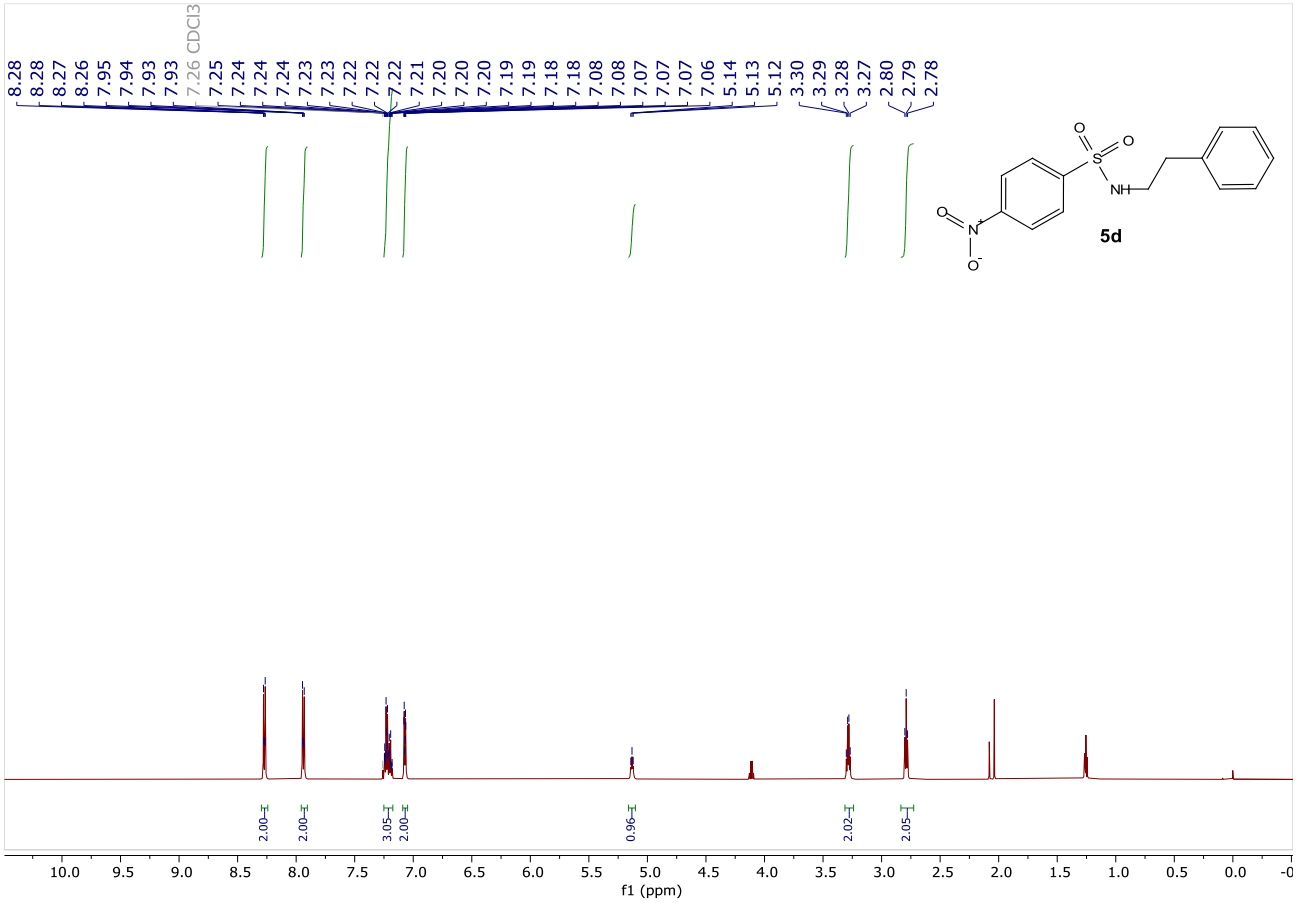
128.78
127.01
126.82
126.18
77.16 CDCl3
44.35
35.95
35.22
31.18
f1 (ppm)


8.28
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7.94
7.93
7.93
7.26 CDCl3
7.25
7.24
7.24
7.24
7.23
7.23
7.22
7.22
7.22
7.21
7.20
7.20
7.20
7.19
7.19
7.18
7.18
7.08
7.08
7.07
7.07
7.07
7.06
5.14
5.13
5.12
3.30
3.29
3.28
3.27
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2.79
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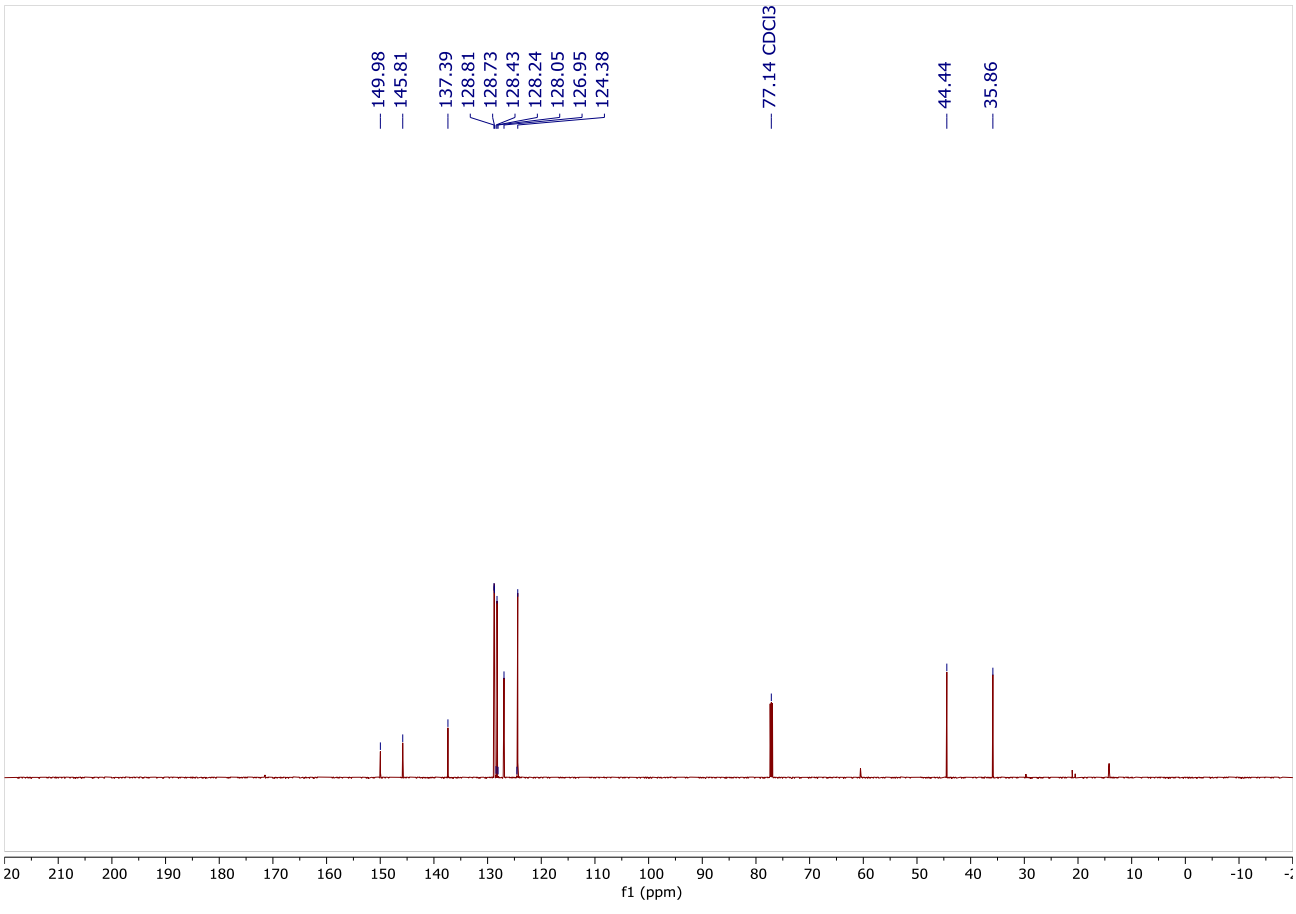
5d
2.00
2.00
3.05
2.00
0.96
2.02
2.05
f1 (ppm)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128.43
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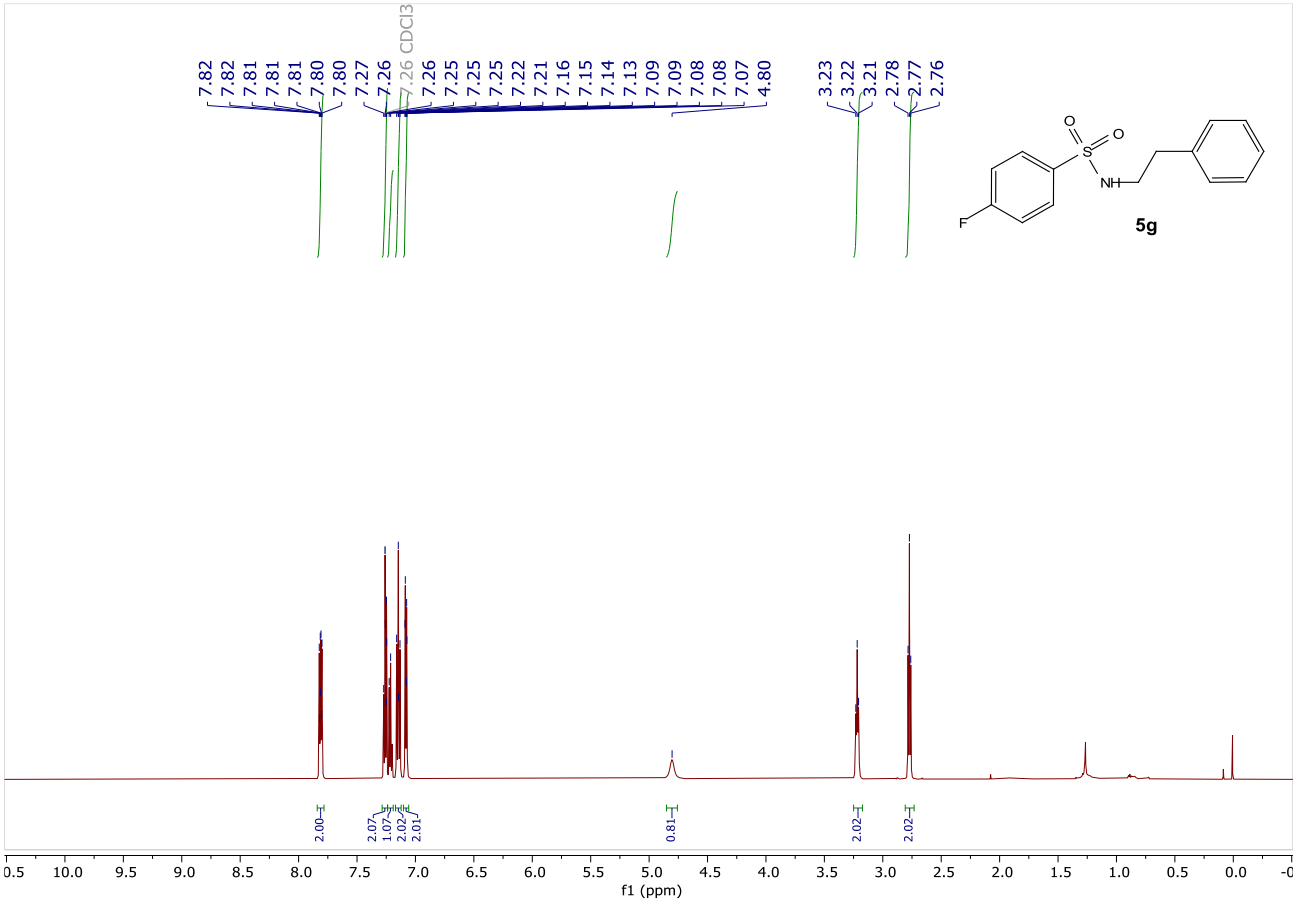
128.05
126.95
124.38
77.14 CDCl3
44.44
35.86
f1 (ppm)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7.82
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7.81
7.81
7.80
7.80
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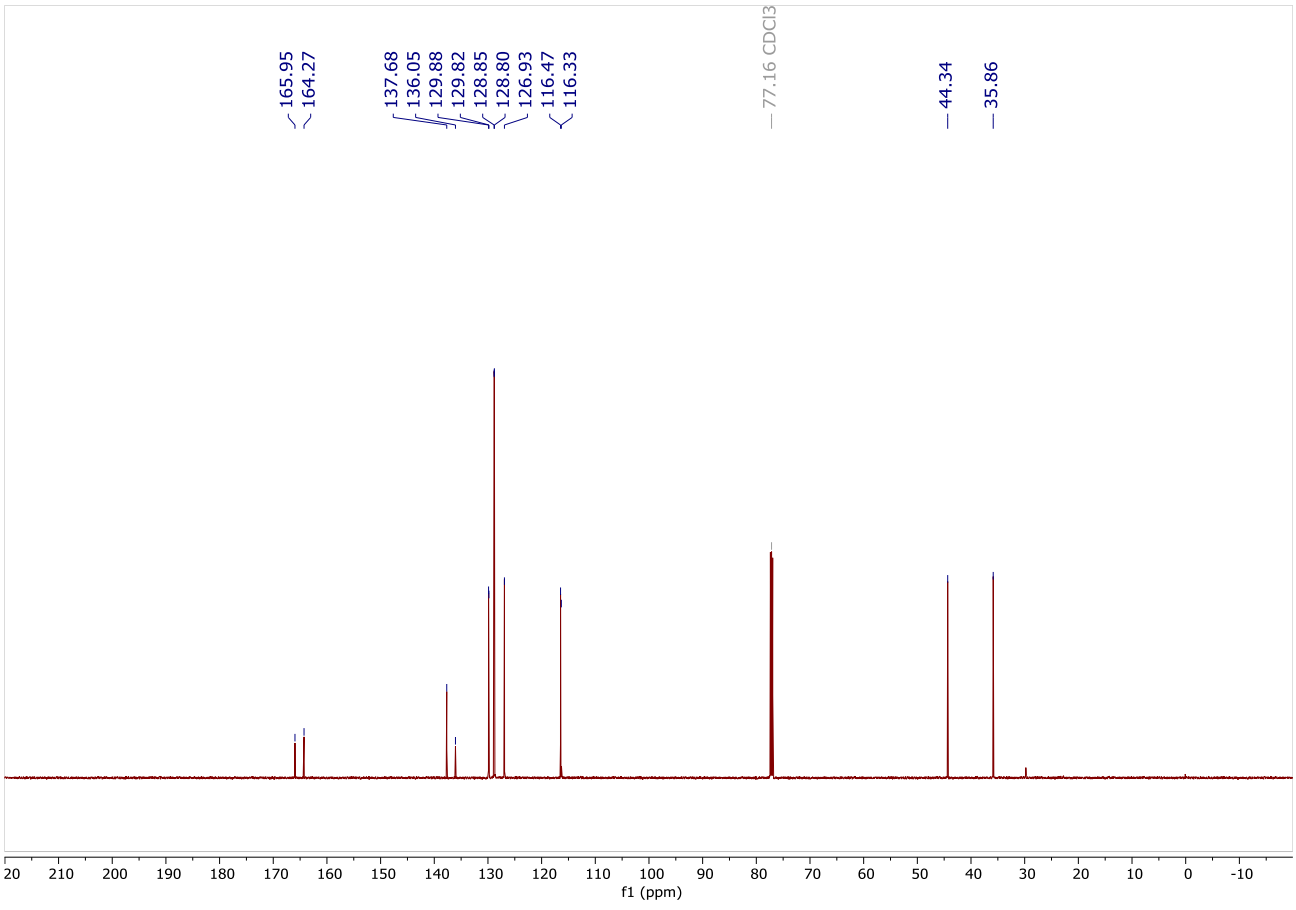
7.26
7.26 CDCl3
7.26
7.25
7.25
7.25
7.22
7.21
7.16
7.15
7.14
7.13
7.09
7.09
7.08
7.08
7.07
4.80
3.23
3.22
3.21
2.78
2.77
2.76
O
O
S
NH
F
5g
2.00
2.07
1.07
2.02
2.01
0.81
2.02
2.02
f1 (ppm)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128.80
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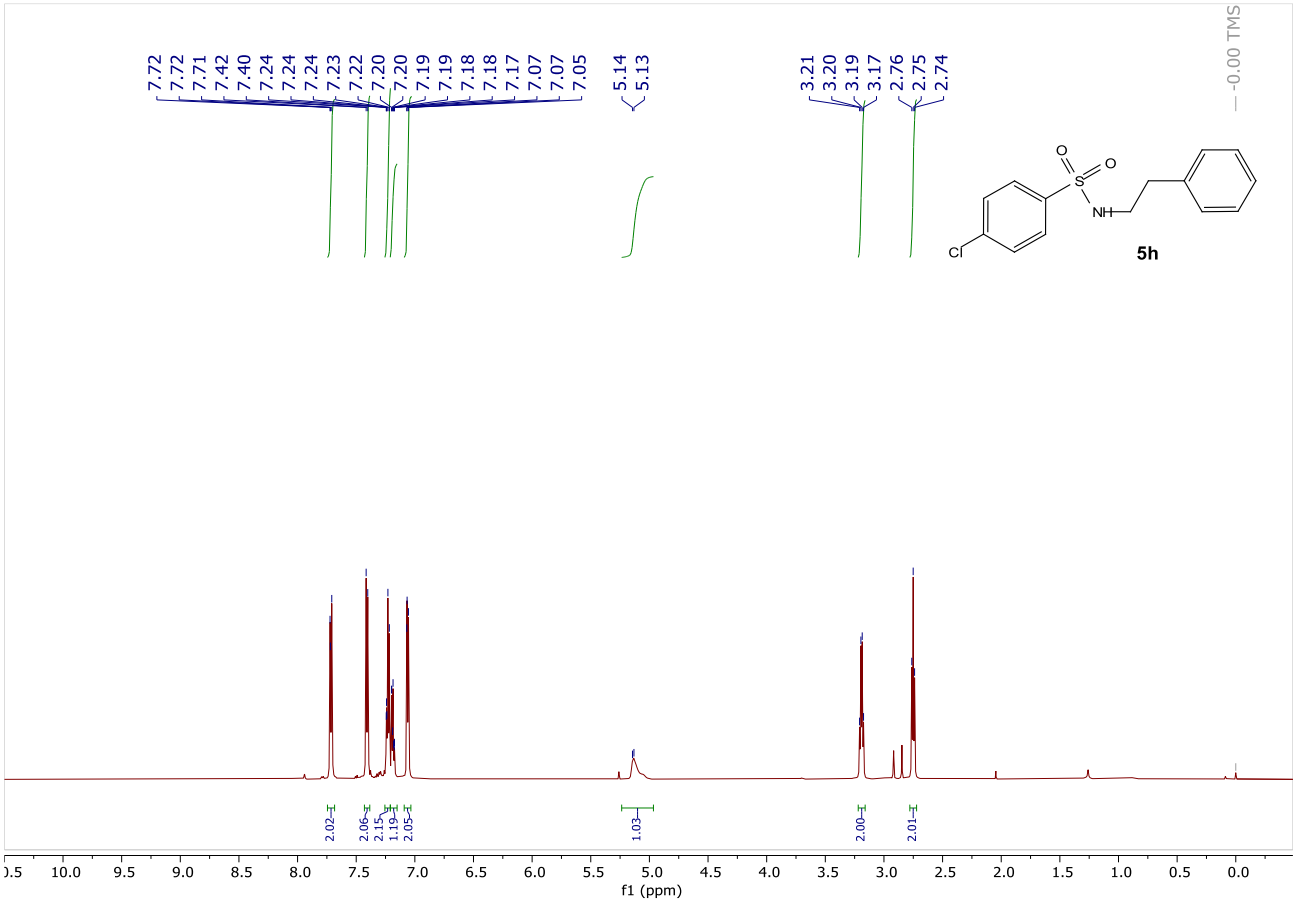
116.47
116.33
77.16 CDCl3
44.34
35.86
f1 (ppm)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7.19
7.19
7.18
7.18
7.17
7.07
7.07
7.05
5.14
5.13
3.21
3.20
3.19
3.17
2.76
2.75
2.74
-0.00 TMS
O
S
O
NH
Cl
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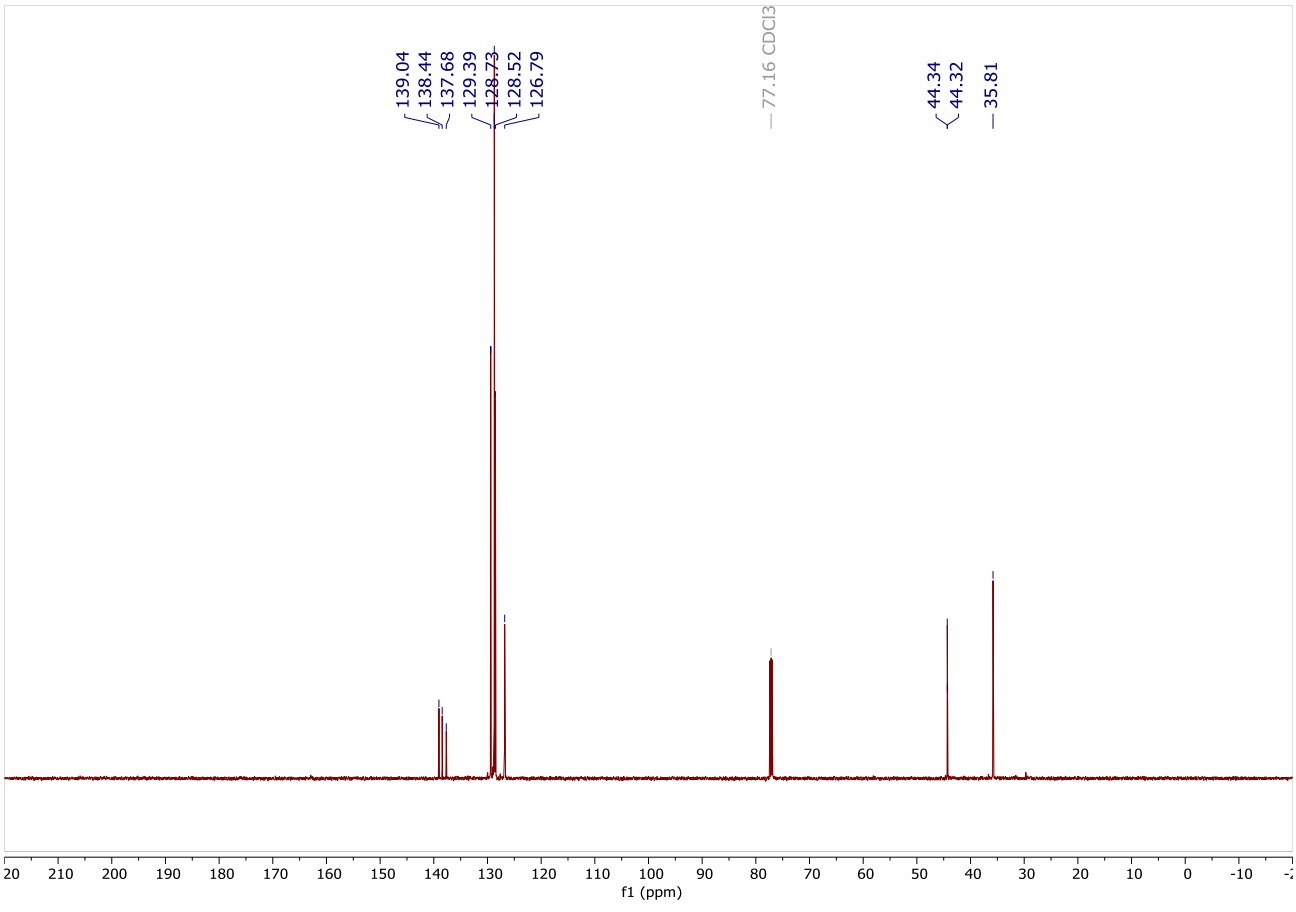
2.02
2.06
2.15
1.19
2.05
1.03
2.00
2.01
f1 (ppm)


139.04
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129.39
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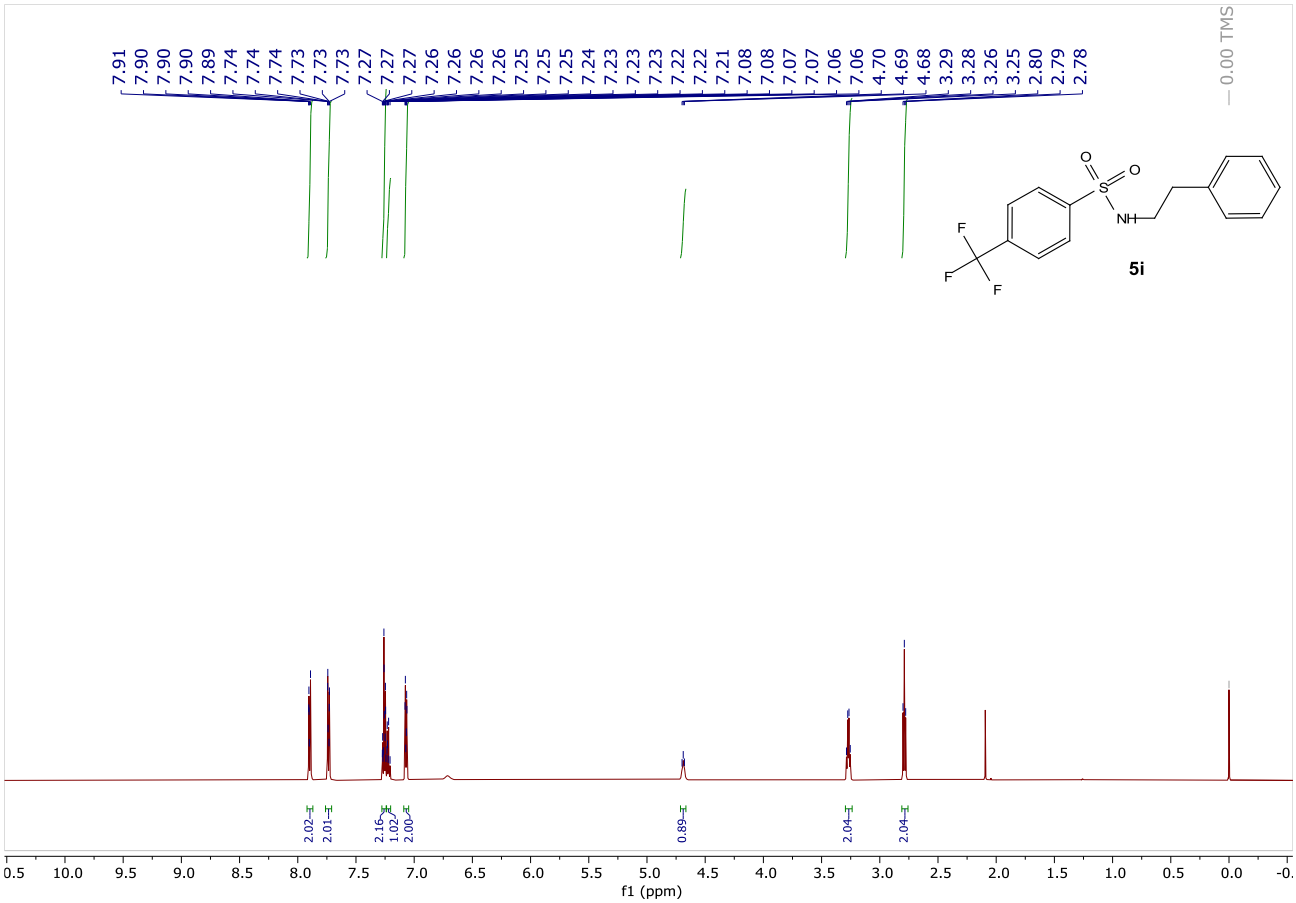
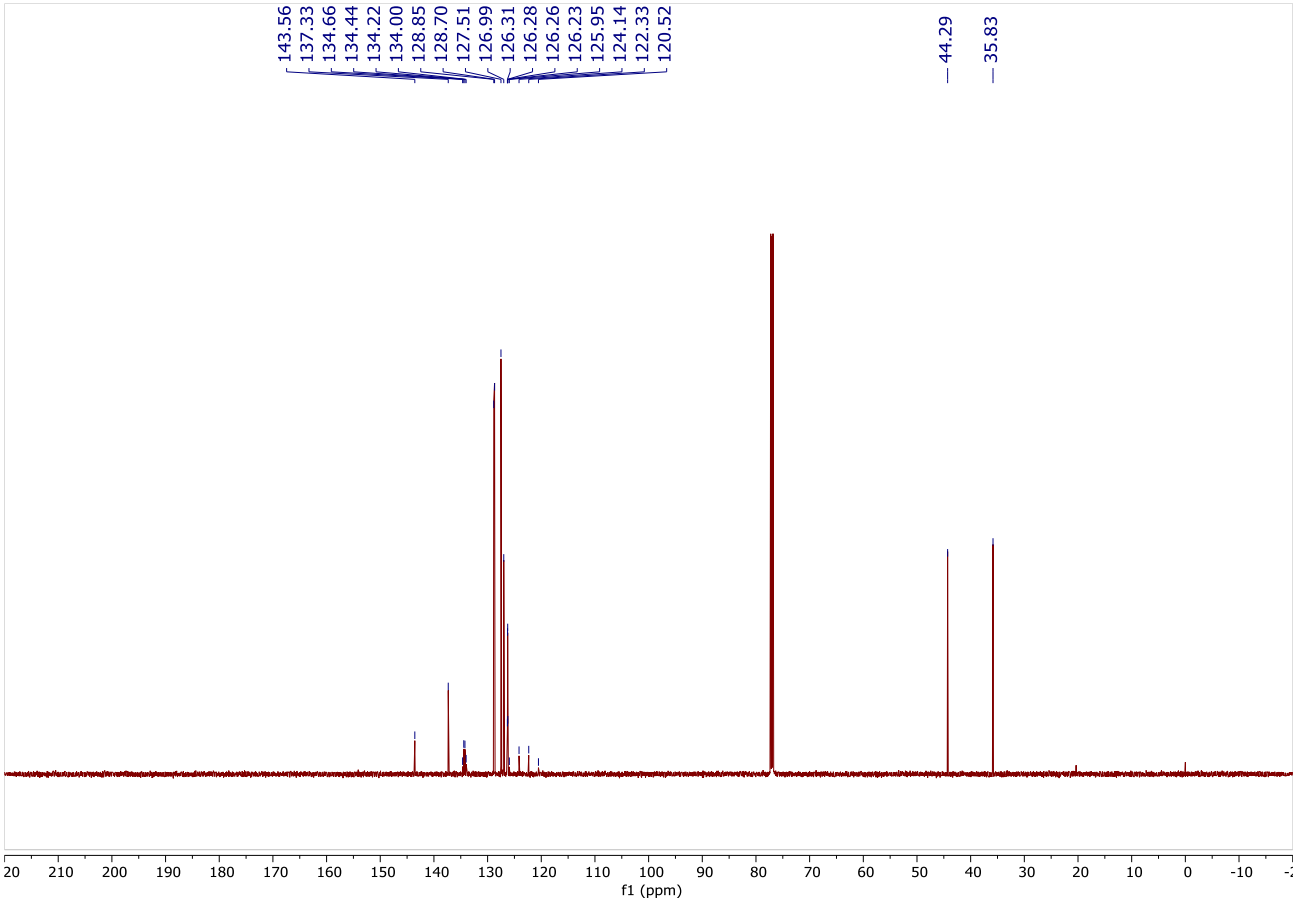
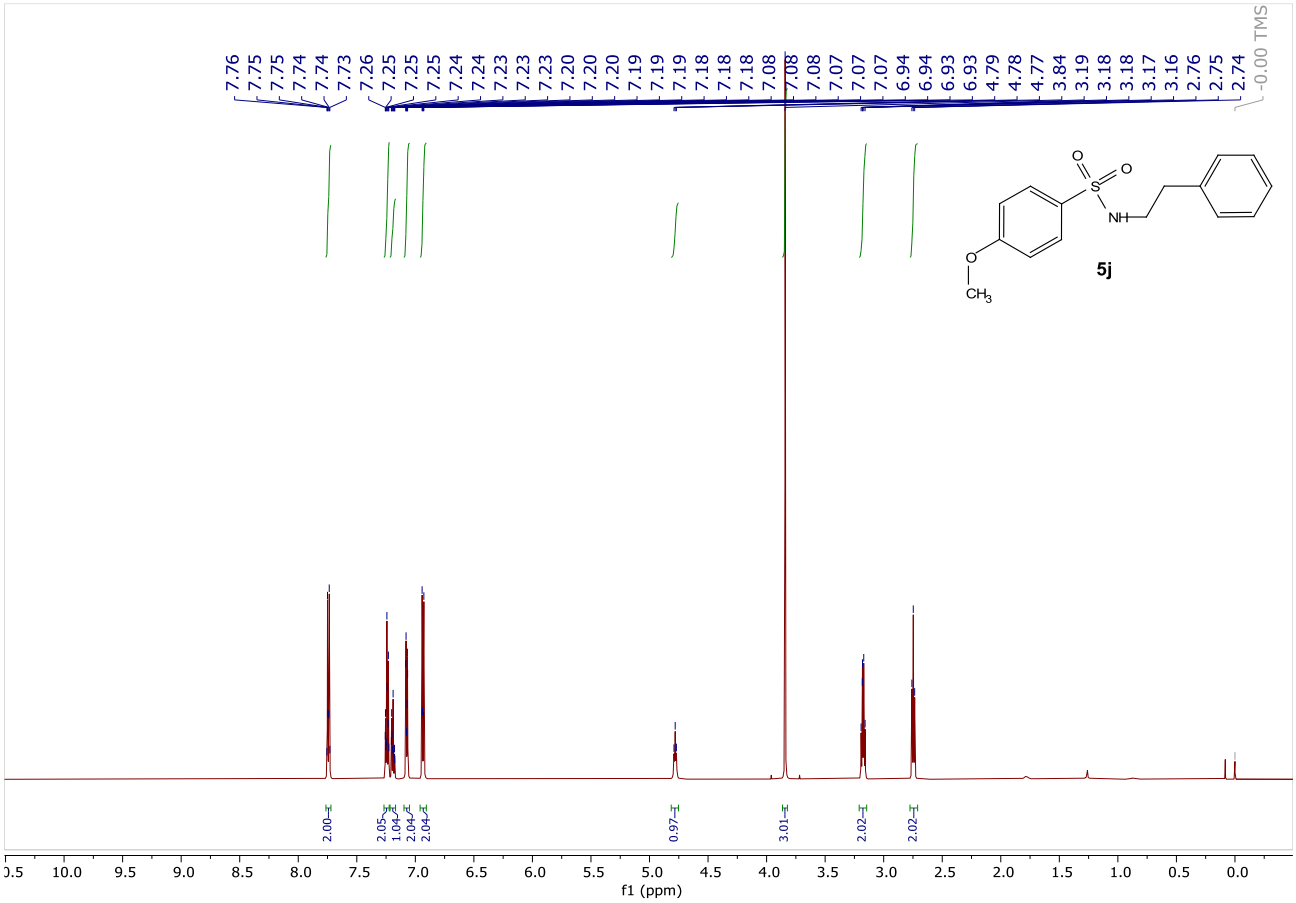
128.52
126.79
77.16 CDCl3
44.34
44.32
35.81
f1 (ppm)


7.91 7.90 7.90 7.90 7.89 7.74 7.74 7.73 7.73 7.73 7.27 7.27 7.27 7.26 7.26 7.26 7.26 7.25 7.25 7.25 7.24 7.23 7.23 7.23 7.22 7.22 7.21 7.08 7.08 7.07 7.07 7.06 7.06 4.70 4.69 4.68 3.29 3.28 3.26 3.25 2.80 2.79 2.78
0.00 TMS
O
O
S
NH
F
F
F
5i
2.02
2.01
2.16
1.02
2.00
0.89
2.04
2.04
f1 (ppm)


143.56 137.33 134.66 134.44 134.22 134.00 128.85 128.70 127.51 126.99 126.31 126.28 126.26 126.23 125.95 124.14 122.33 120.52
44.29
35.83
f1 (ppm)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7.23
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7.20
7.20
7.19
7.19
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7.18
7.18
7.18
7.08
7.08
7.08
7.07
7.07
7.07
6.94
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6.93
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4.78
4.77
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3.18
3.18
3.17
3.16
2.76
2.75
2.74
-0.00 TMS
O
O
S
NH
O
CH3
5j
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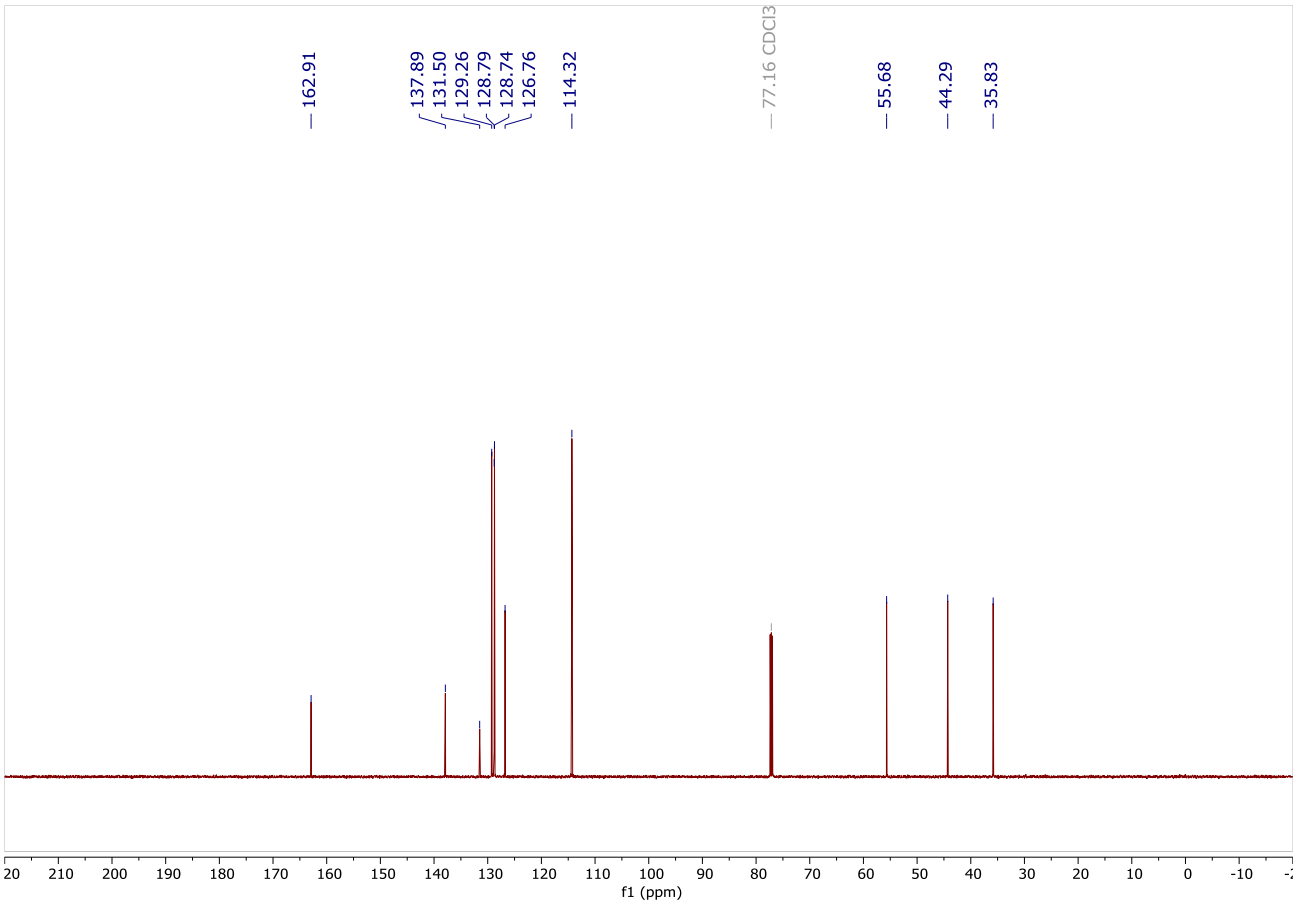
2.05
1.04
2.04
2.04
0.97
3.01
2.02
2.02
f1 (ppm)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137.89
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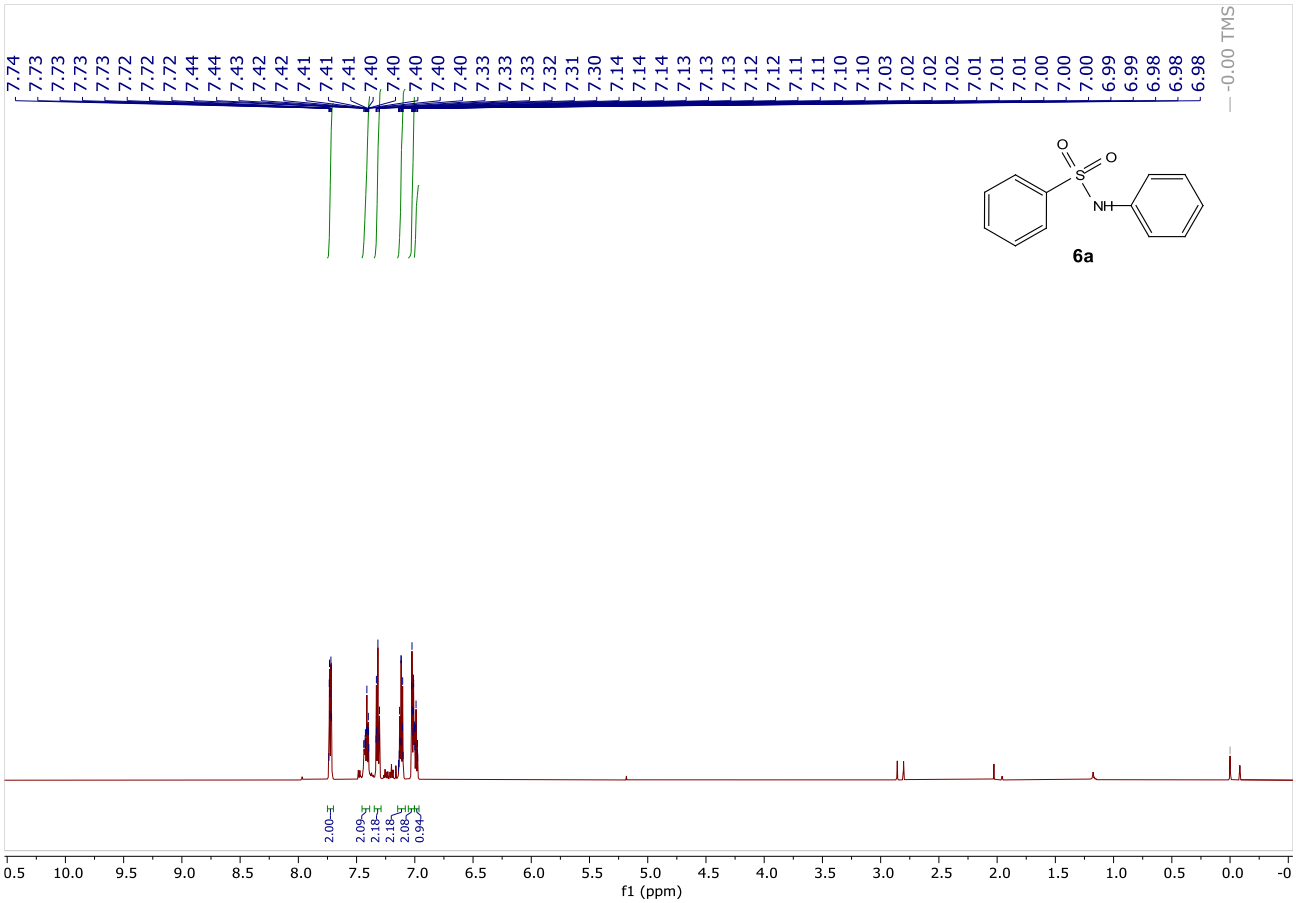
128.79
128.74
126.76
114.32
77.16 CDCl3
55.68
44.29
35.83
f1 (ppm)


7.74 7.73 7.73 7.73 7.72 7.72 7.72 7.44 7.44 7.43 7.42 7.42 7.41 7.41 7.41 7.40 7.40 7.40 7.40 7.40 7.33 7.33 7.32 7.31 7.30 7.14 7.14 7.14 7.13 7.13 7.13 7.12 7.12 7.11 7.11 7.10 7.10 7.03 7.02 7.02 7.02 7.01 7.01 7.01 7.00 7.00 7.00 6.99 6.99 6.98 6.98 6.98
-0.00 TMS
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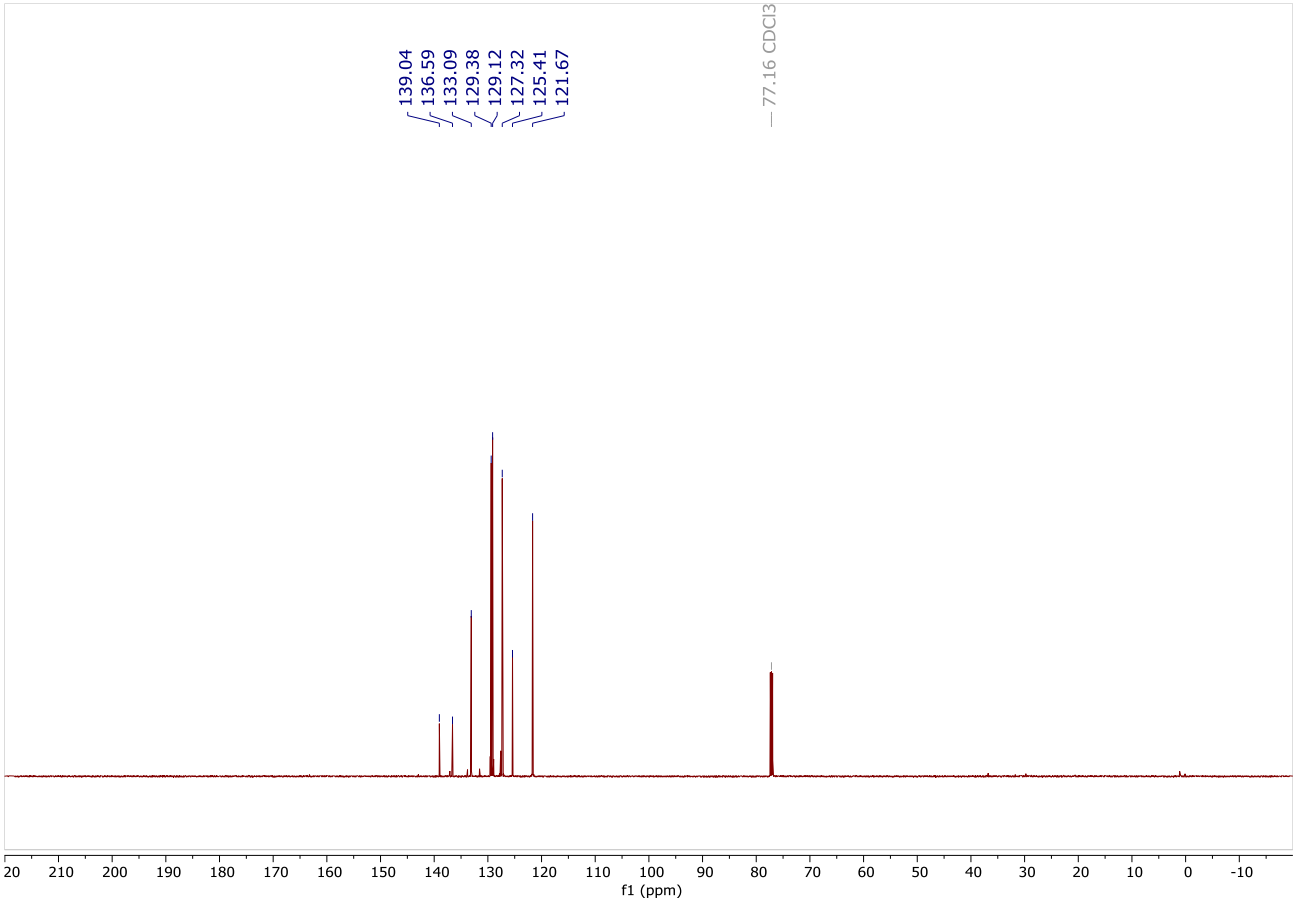
O
S
NH
6a
2.00
2.09
2.18
2.18
2.08
0.94
f1 (ppm)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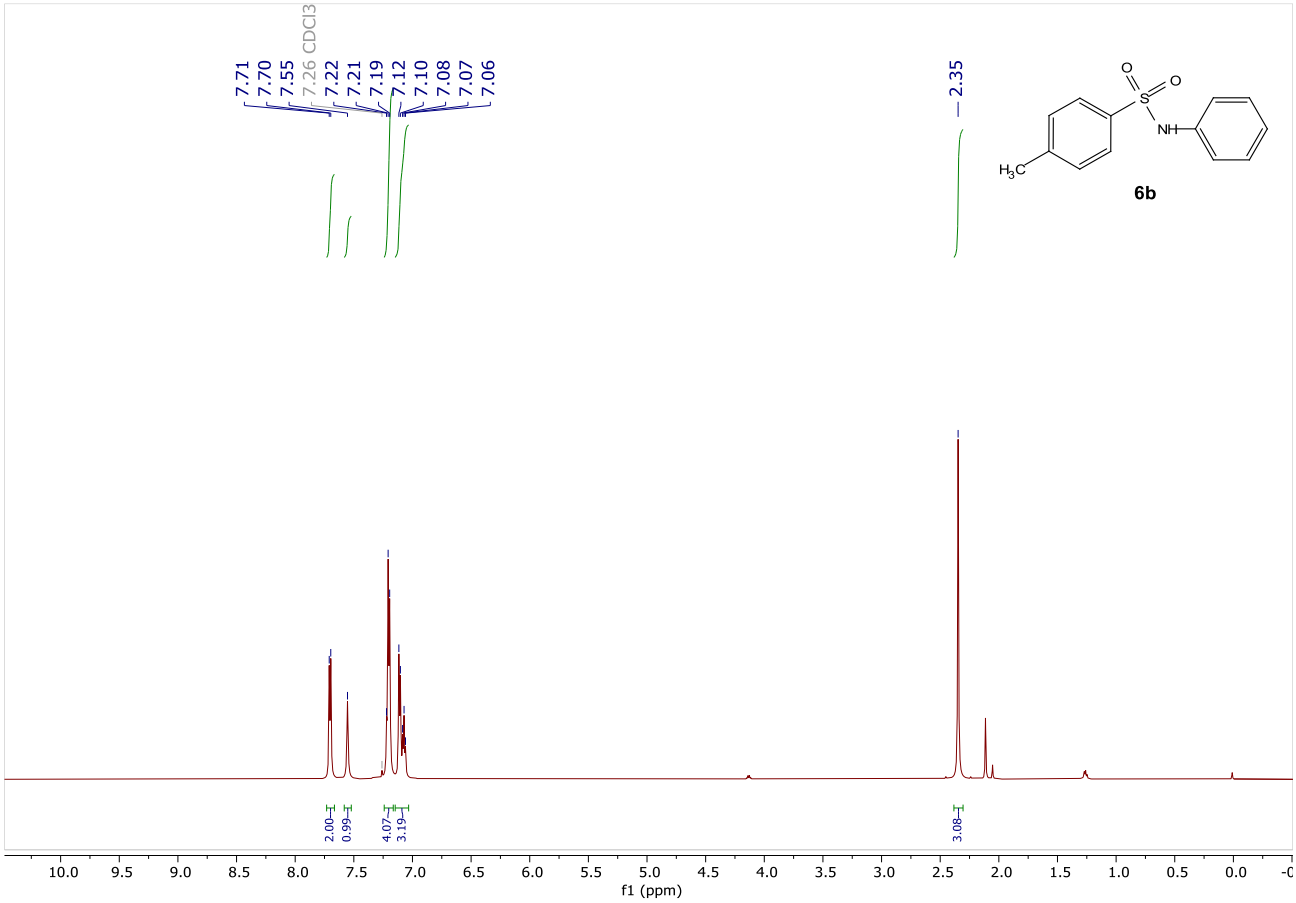
127.32
125.41
121.67
77.16 CDCl3
f1 (ppm)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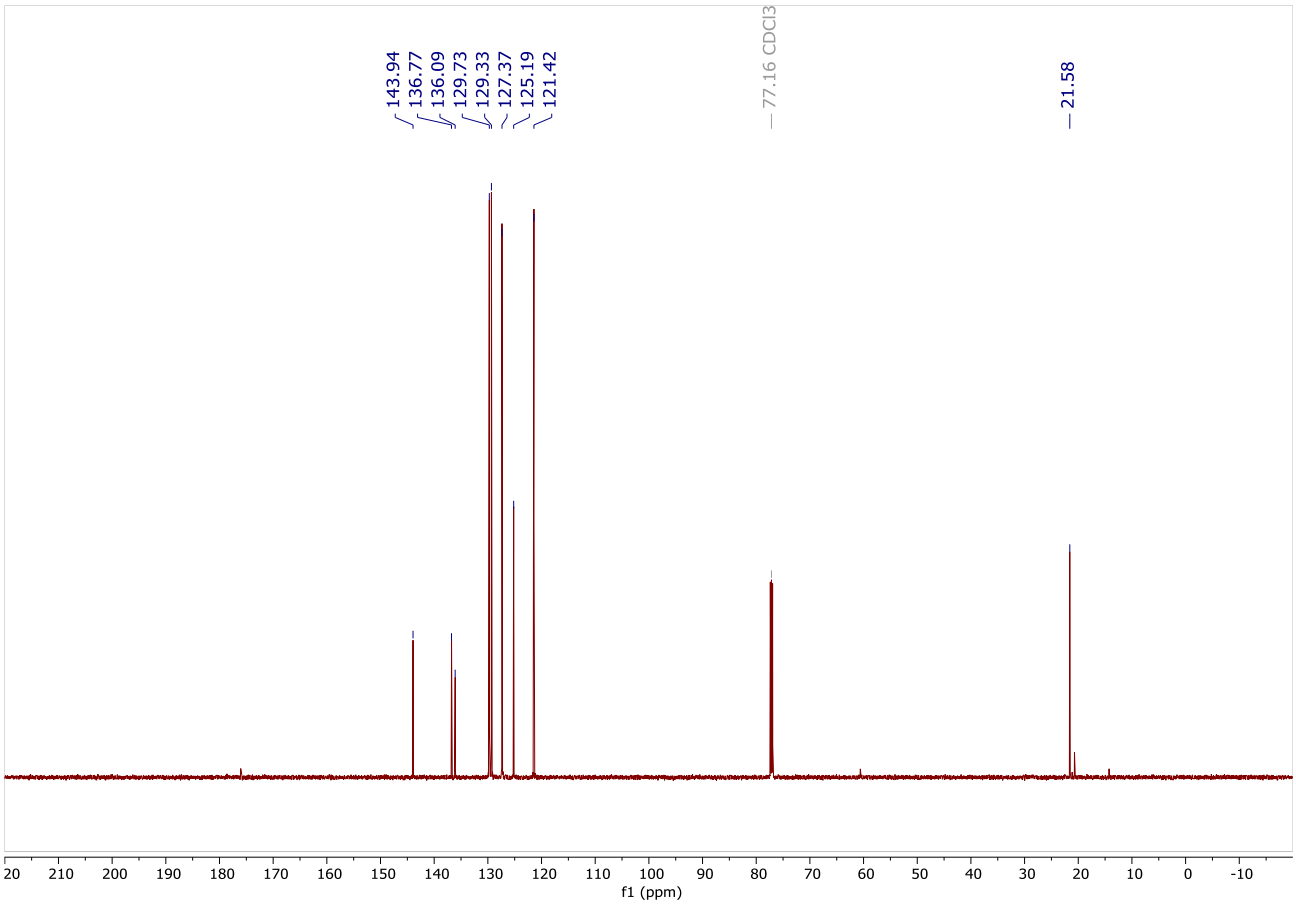
7.19
7.12
7.10
7.08
7.07
7.06
2.35
6b
2.00
0.99
4.07
3.19
3.08
f1 (ppm)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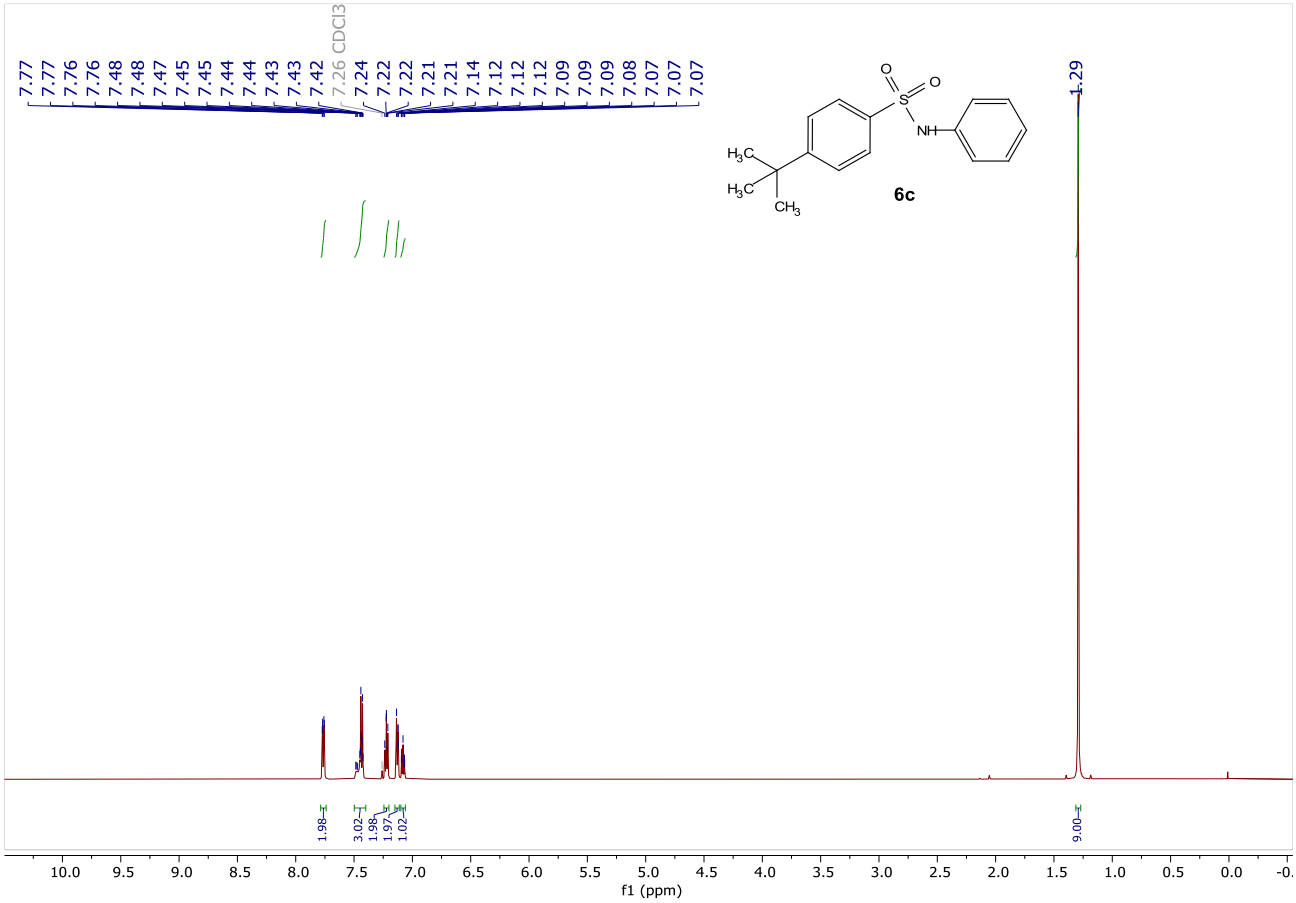
121.42
77.16 CDCl3
21.58
f1 (ppm)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7.44
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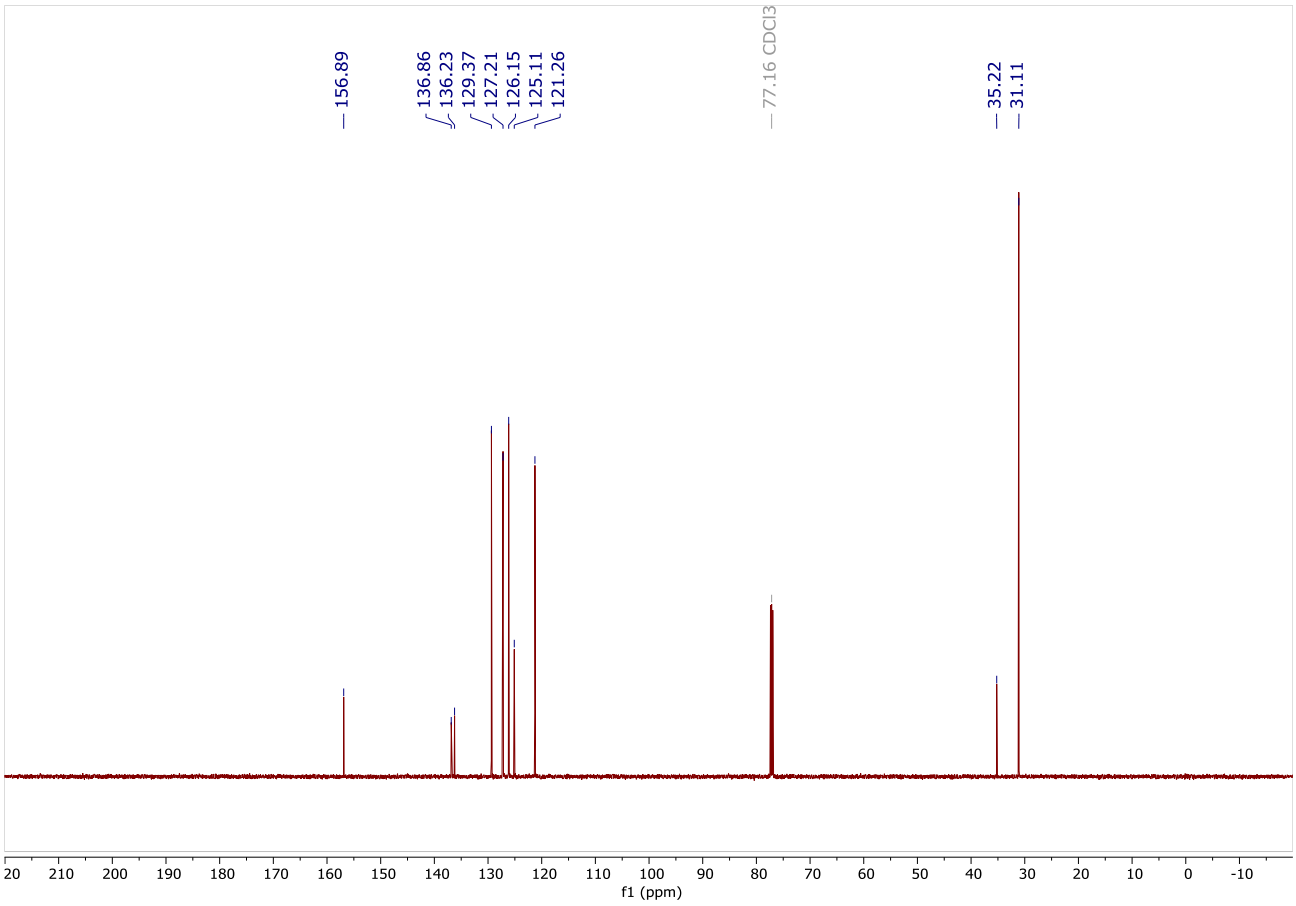
7.43
7.42
7.26 CDCl3
7.24
7.22
7.22
7.21
7.21
7.14
7.12
7.12
7.12
7.09
7.09
7.09
7.08
7.07
7.07
7.07
1.29
O
S
O
NH
H3C
H3C
CH3
6c
1.98
3.02
1.98
1.97
1.02
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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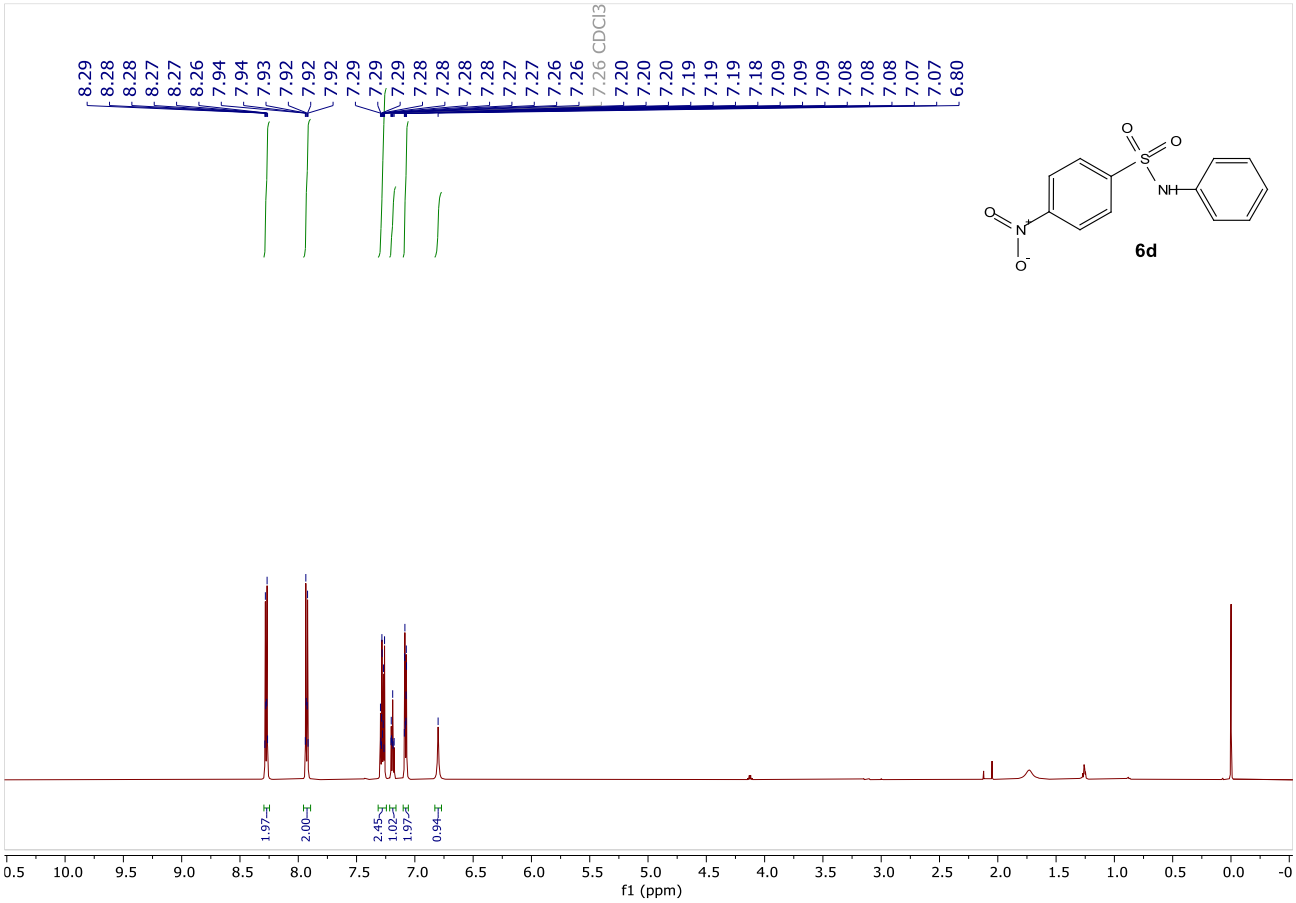
127.21
126.15
125.11
121.26
77.16 CDCl3
35.22
31.11
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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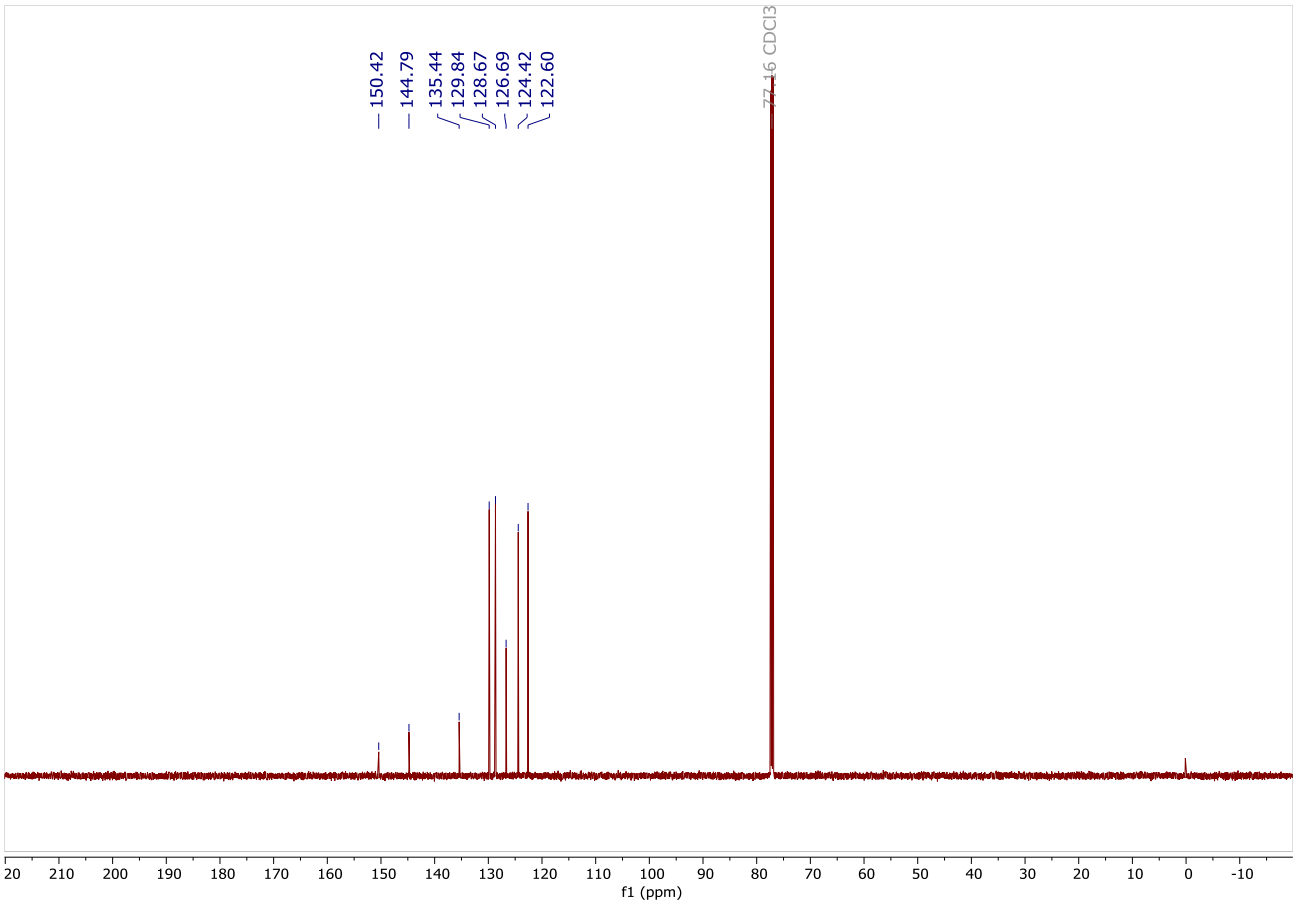
8.28
8.27
8.27
8.26
7.94
7.94
7.93
7.92
7.92
7.29
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.26
7.26
7.26 CDCl3
7.20
7.20
7.20
7.19
7.19
7.19
7.18
7.09
7.09
7.09
7.08
7.08
7.07
7.07
6.80
NH
6d
1.97
2.00
2.45
1.02
1.97
0.94
f1 (ppm)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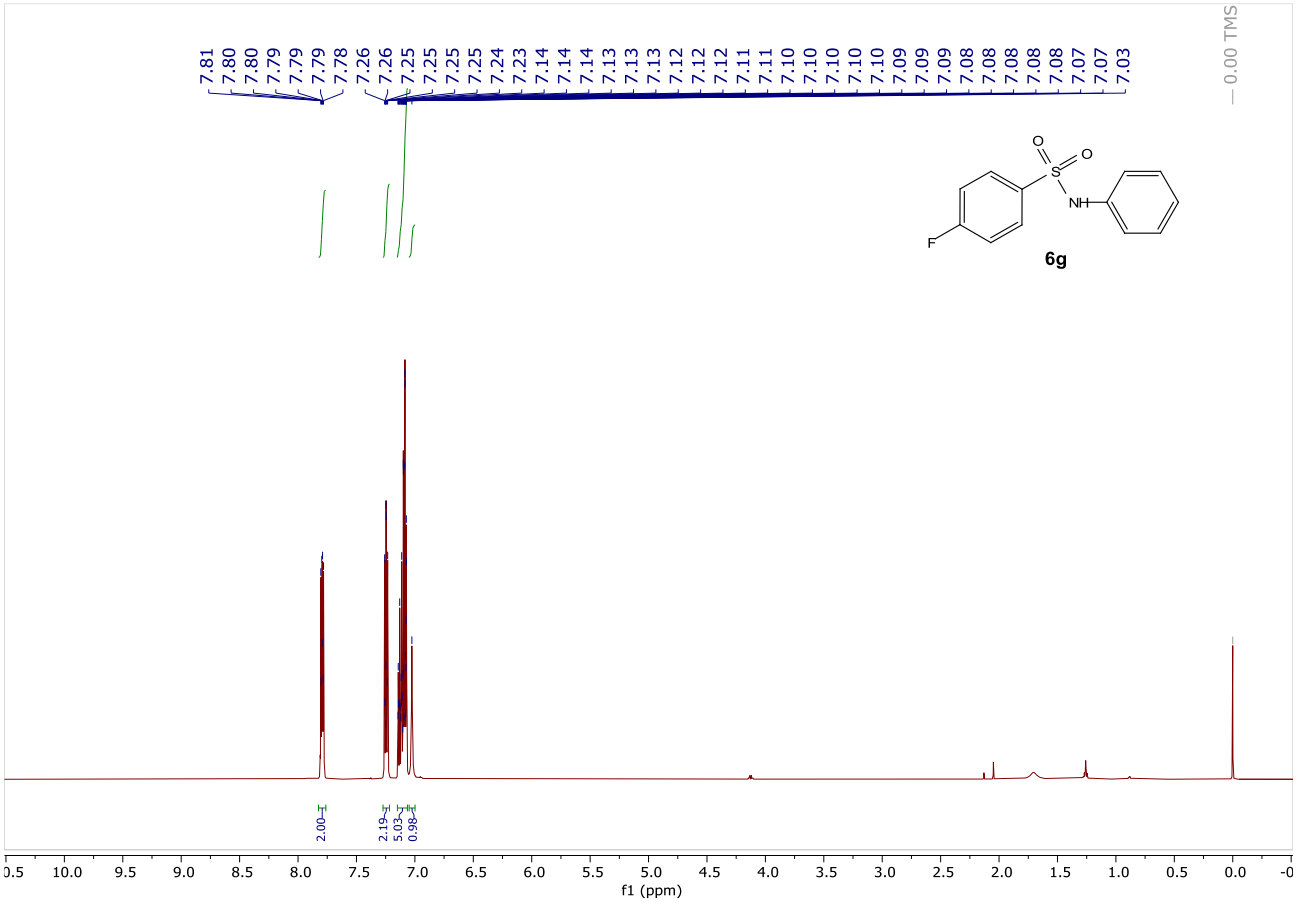
128.67
126.69
124.42
122.60
ZZ-16 CDCl3
f1 (ppm)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7.79
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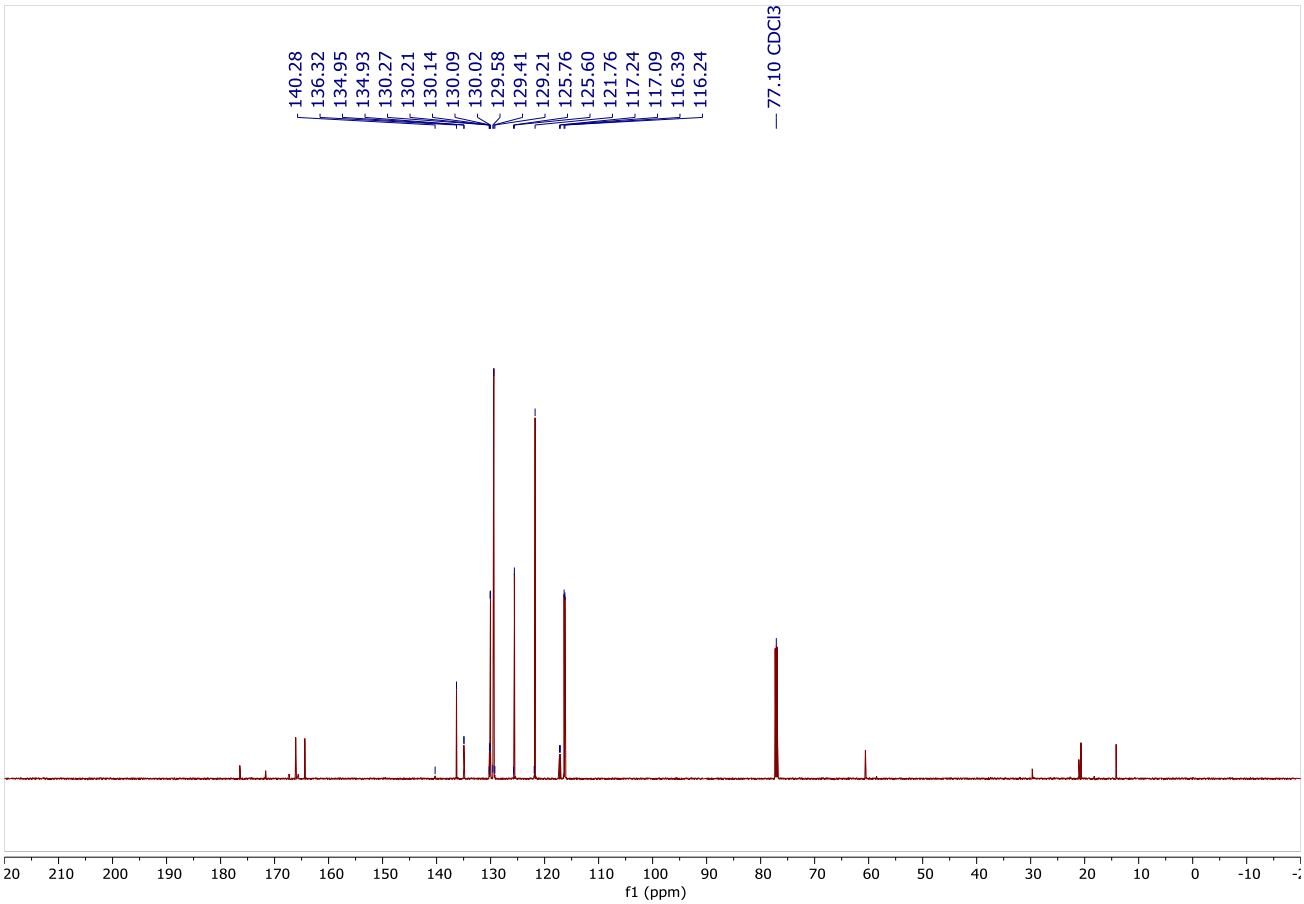
7.25
7.25
7.25
7.25
7.24
7.23
7.14
7.14
7.14
7.13
7.13
7.13
7.12
7.12
7.12
7.11
7.11
7.10
7.10
7.10
7.10
7.10
7.09
7.09
7.09
7.08
7.08
7.08
7.08
7.08
7.07
7.07
7.03
— 0.00 TMS
O
O
S
NH
F
6g
2.00
2.19
5.03
0.98
f1 (ppm)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130.21
130.14
130.09
130.02
129.58
129.41
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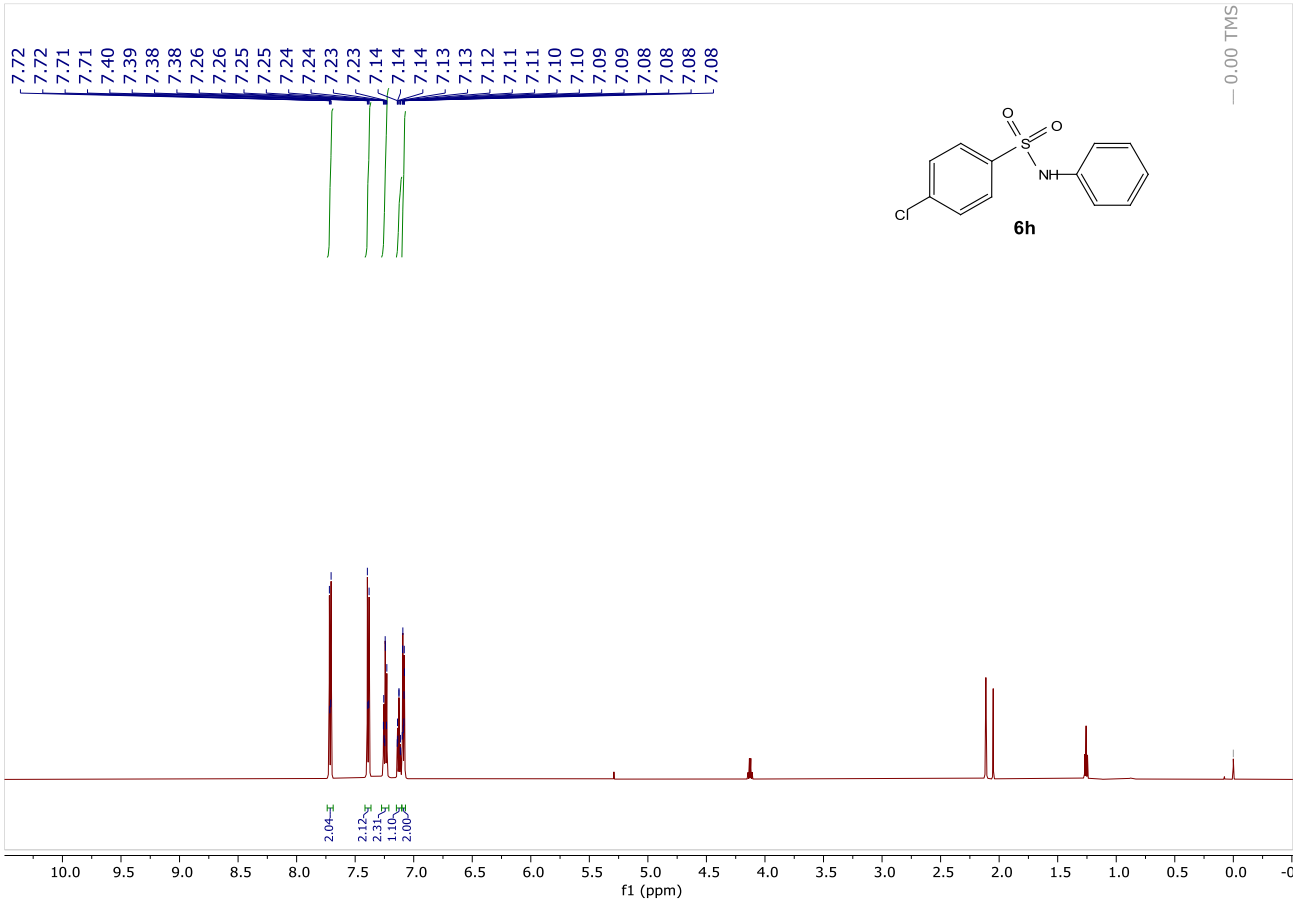
125.76
125.60
121.76
117.24
117.09
116.39
116.24
— 77.10 CDCl3
f1 (ppm)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7.39
7.38
7.38
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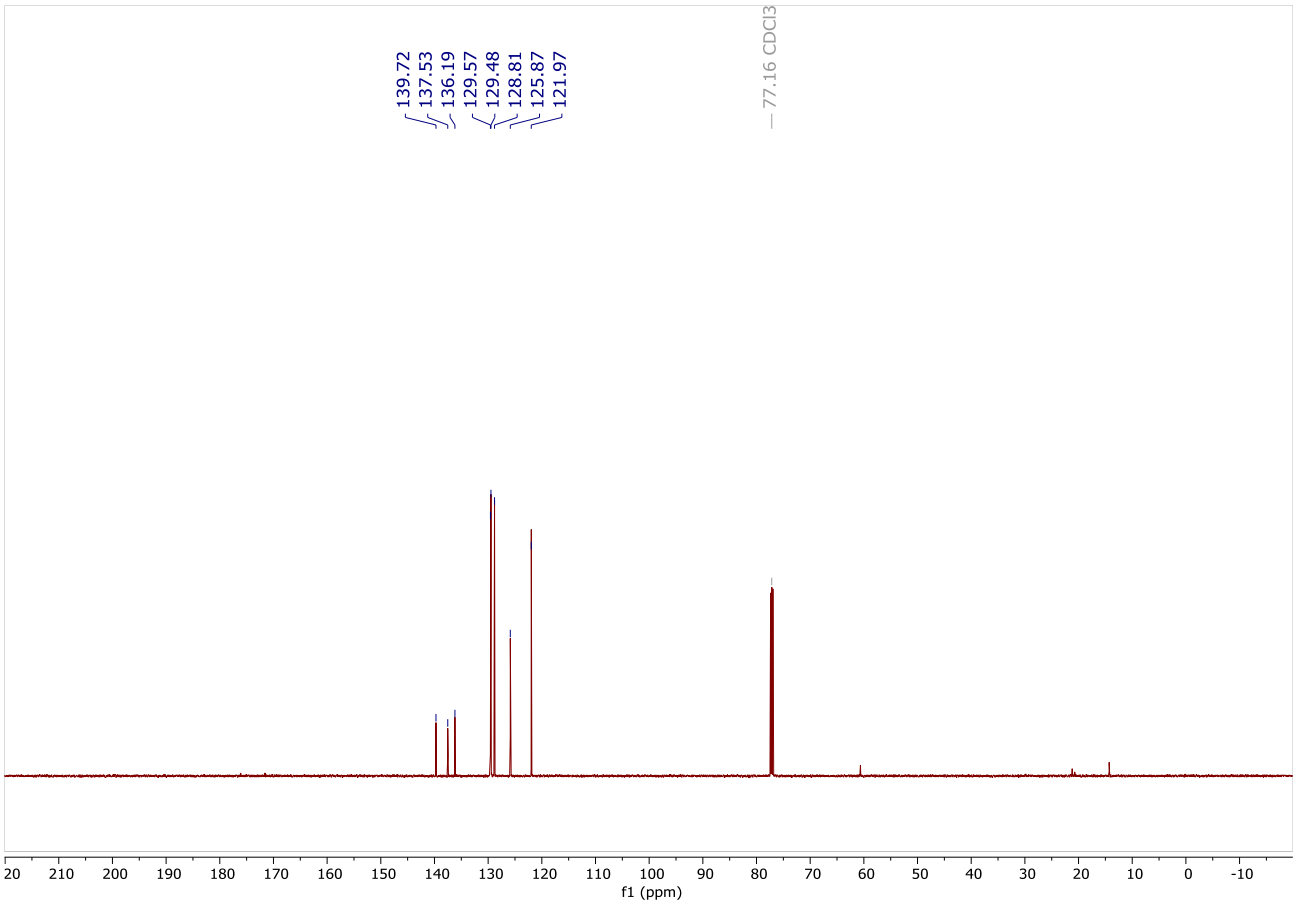
7.25
7.25
7.24
7.24
7.23
7.23
7.14
7.14
7.14
7.13
7.13
7.12
7.11
7.11
7.10
7.10
7.09
7.09
7.08
7.08
7.08
7.08
0.00 TMS
O
O
S
NH
Cl
6h
2.04
2.12
2.31
1.10
2.00
f1 (ppm)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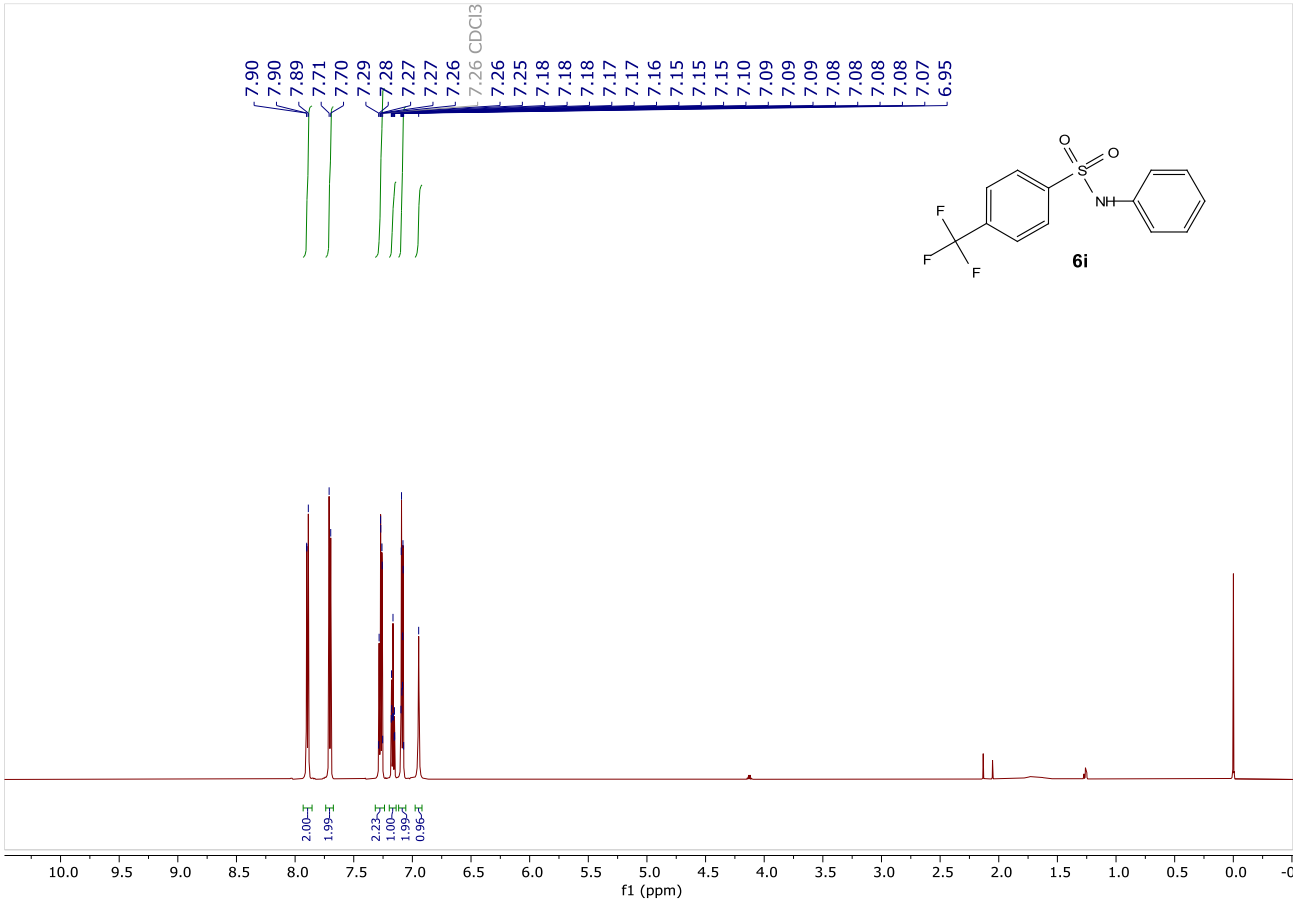
128.81
125.87
121.97
77.16 CDCl3
f1 (ppm)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7.90
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7.28
7.27
7.27
7.26
7.26 CDCl3
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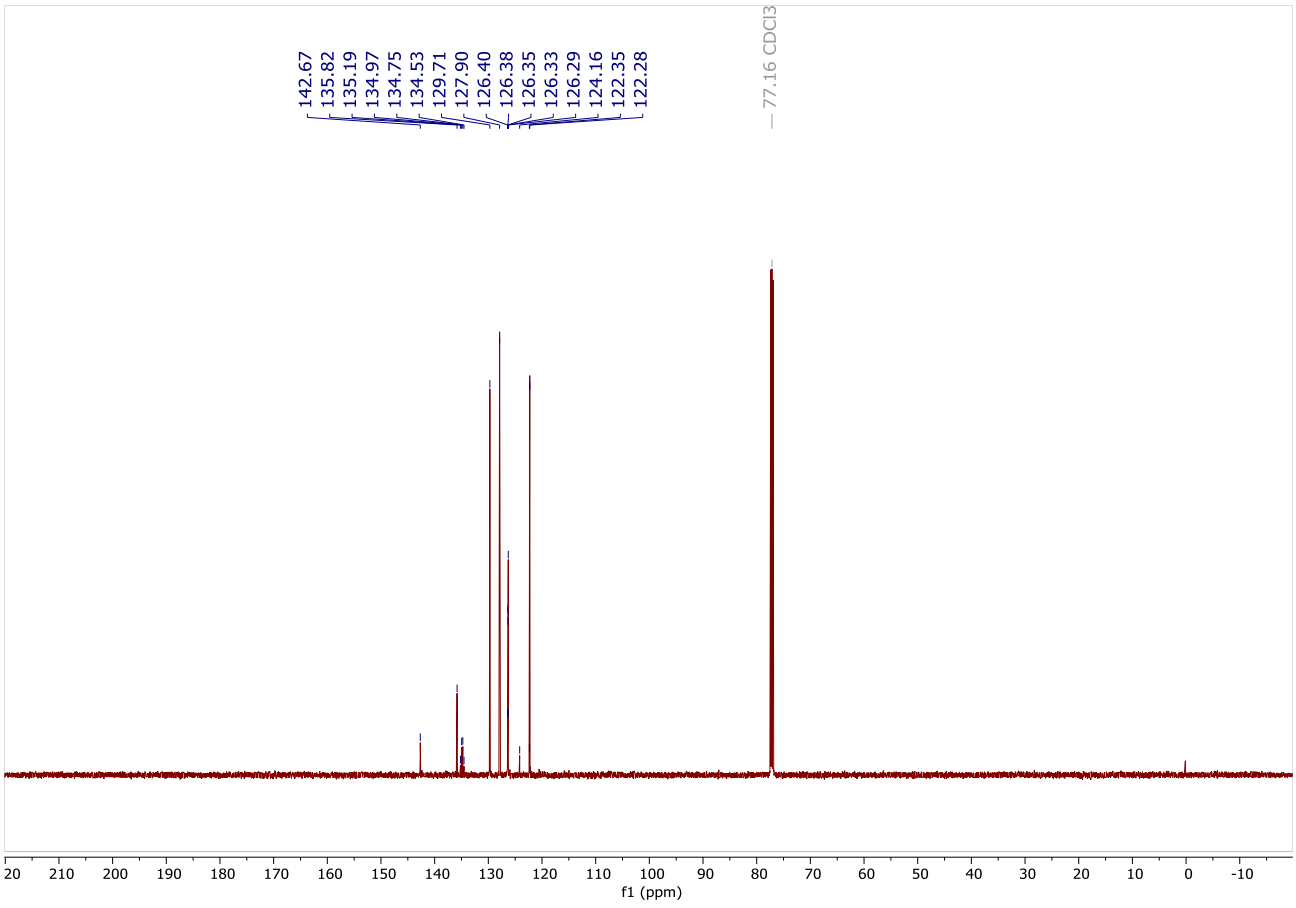
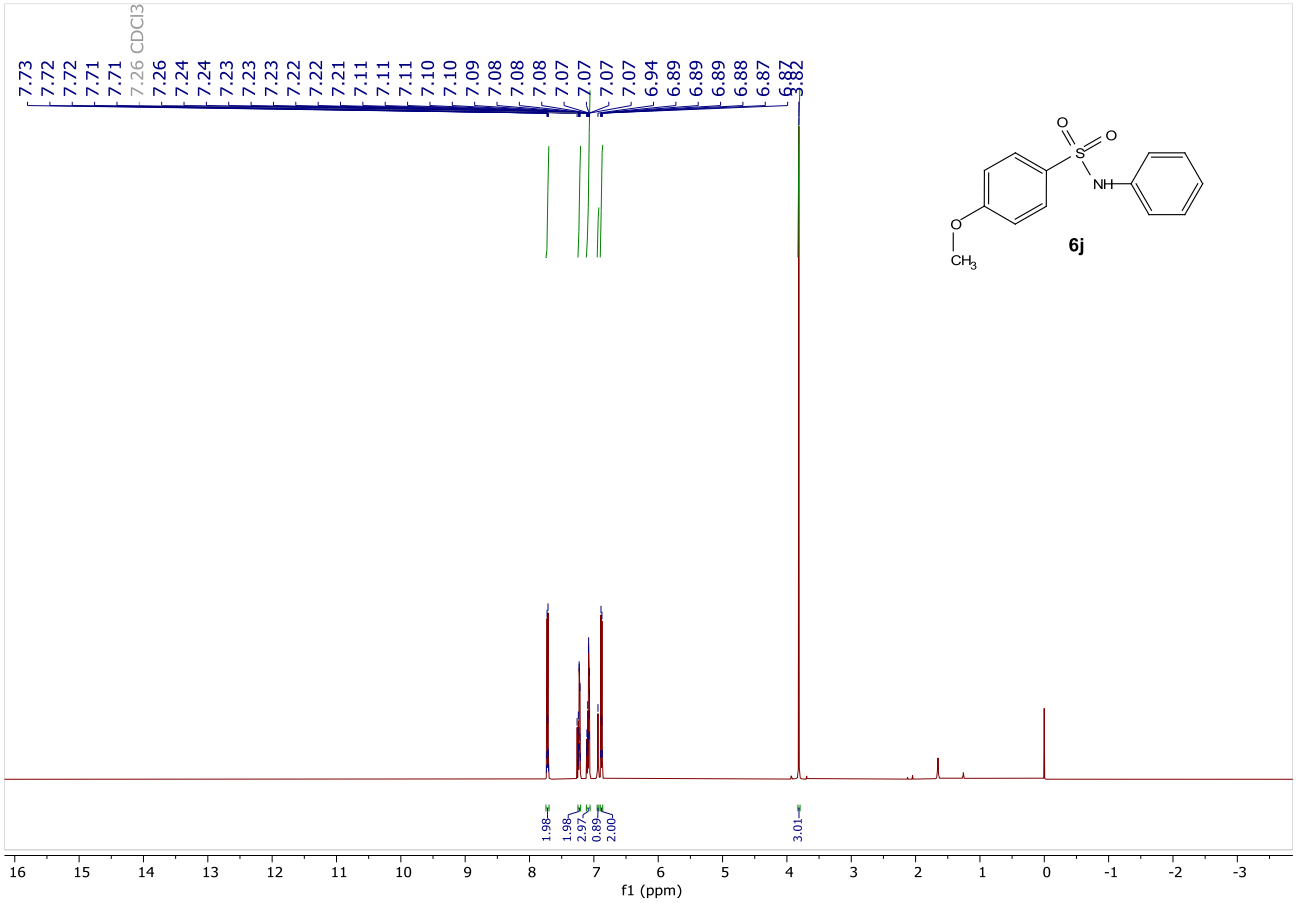
7.25
7.18
7.18
7.17
7.17
7.16
7.15
7.15
7.15
7.10
7.09
7.09
7.09
7.08
7.08
7.08
7.08
7.07
6.95
O
O
S
NH
F
F
F
6i
2.00
1.99
2.23
1.00
1.99
0.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


142.67
135.82
135.19
134.97
134.75
134.53
129.71
127.90
126.40
126.38
126.35
126.33
126.29
124.16
122.35
122.28
77.16 CDCl3
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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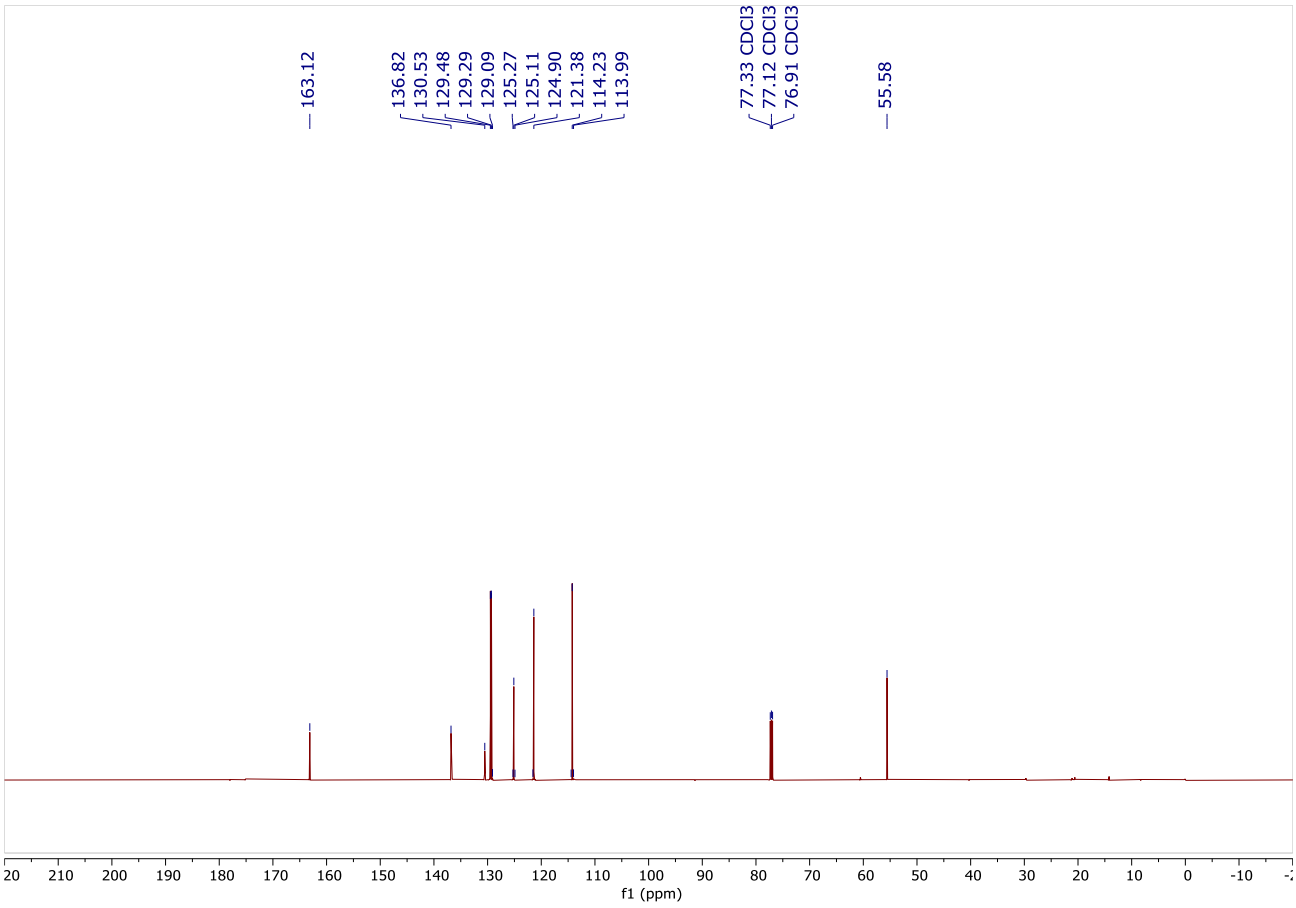
7.72
7.72
7.71
7.71
7.26 CDCl3
7.26
7.24
7.24
7.23
7.23
7.23
7.22
7.22
7.21
7.11
7.11
7.11
7.10
7.10
7.09
7.08
7.08
7.08
7.07
7.07
7.07
7.07
6.94
6.89
6.89
6.89
6.88
6.87
6.87
3.82
O
S
O
NH
O
CH3
6j
1.98
1.98
2.97
0.89
2.00
3.01
f1 (ppm)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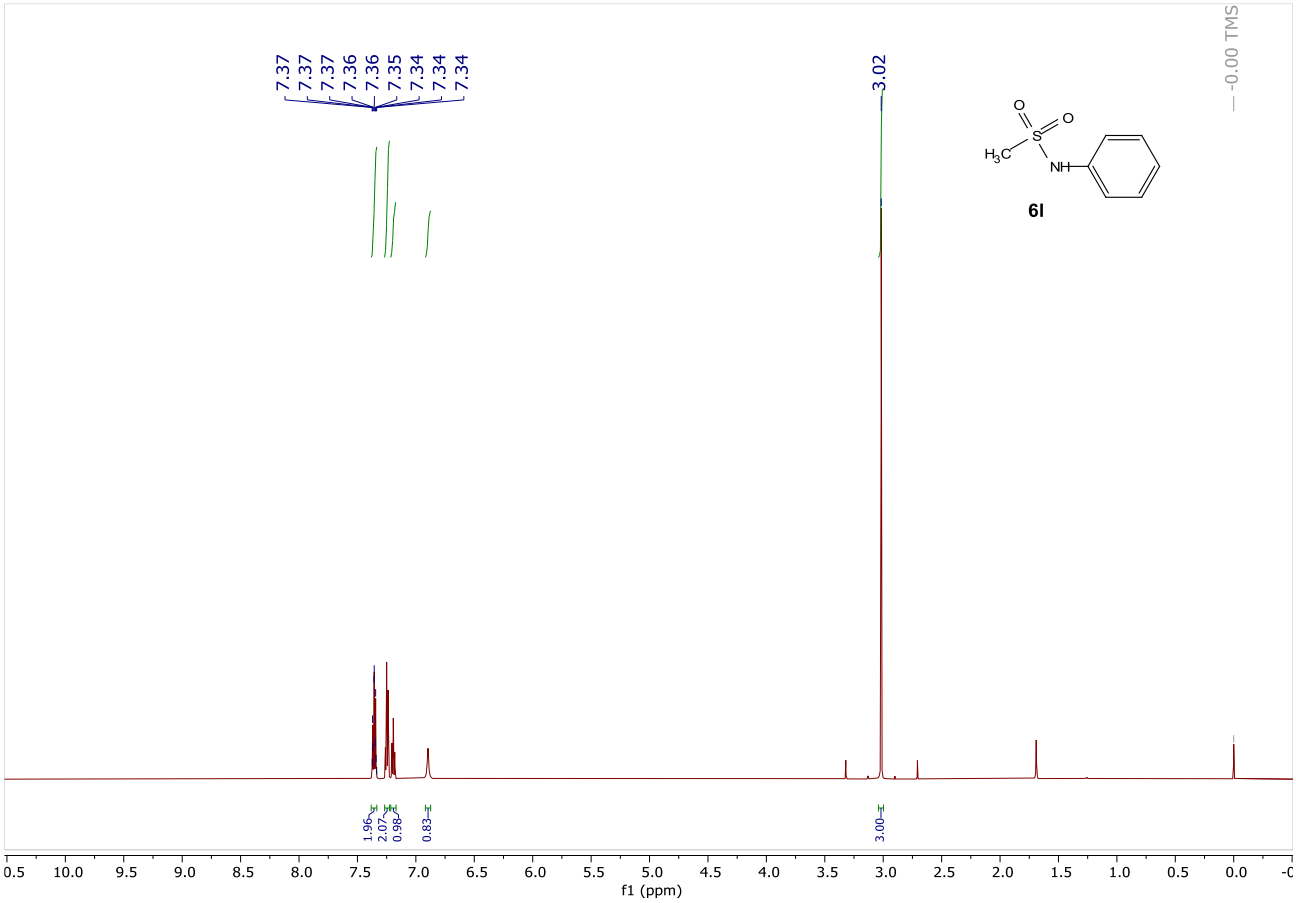
129.48
129.29
129.09
125.27
125.11
124.90
121.38
114.23
113.99
77.33 CDCl3
77.12 CDCl3
76.91 CDCl3
55.58
f1 (ppm)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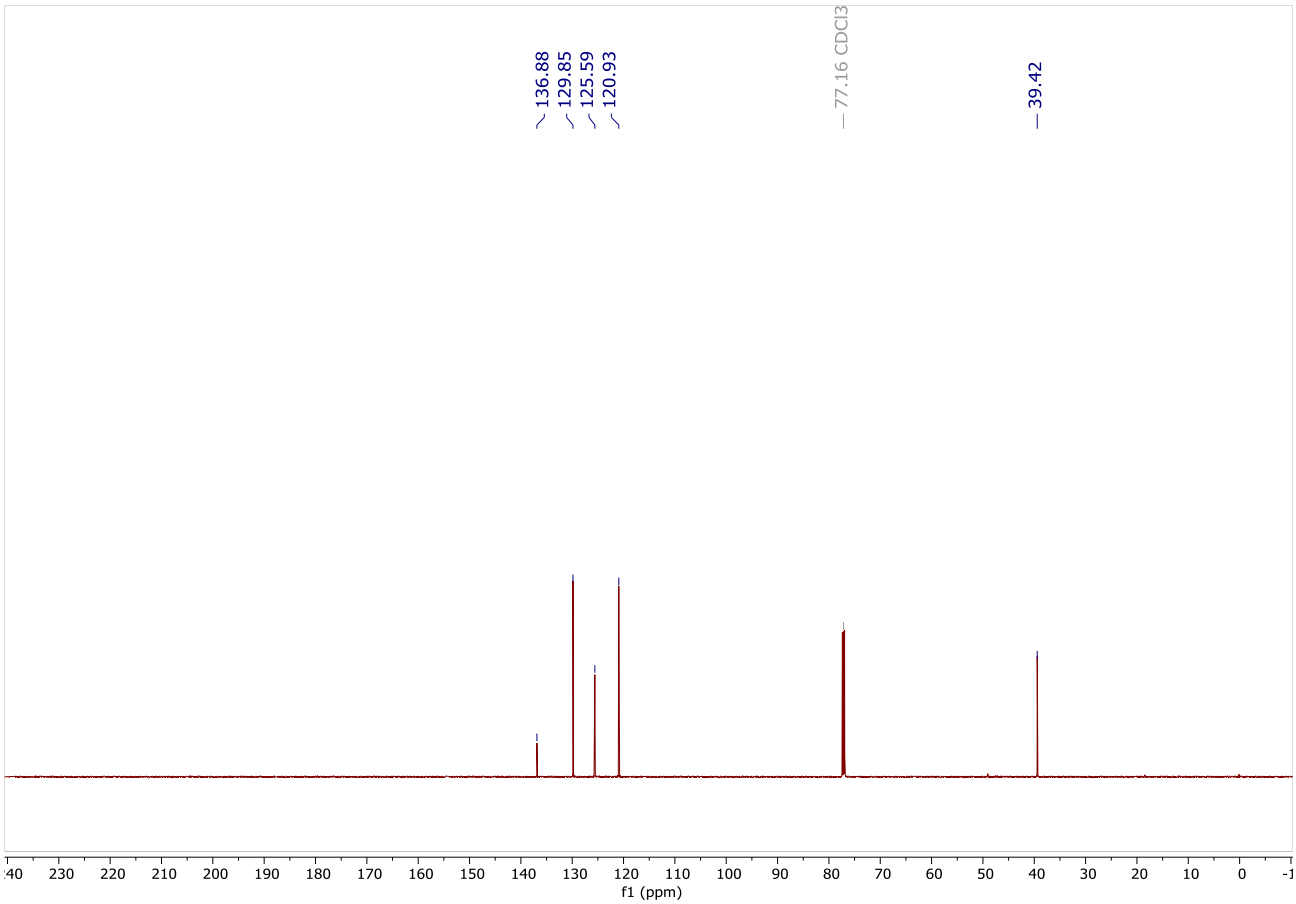
7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.34
3.02
-0.00 TMS
O
S
O
H3C
NH
6l
1.96
2.07
0.98
0.83
3.00
f1 (ppm)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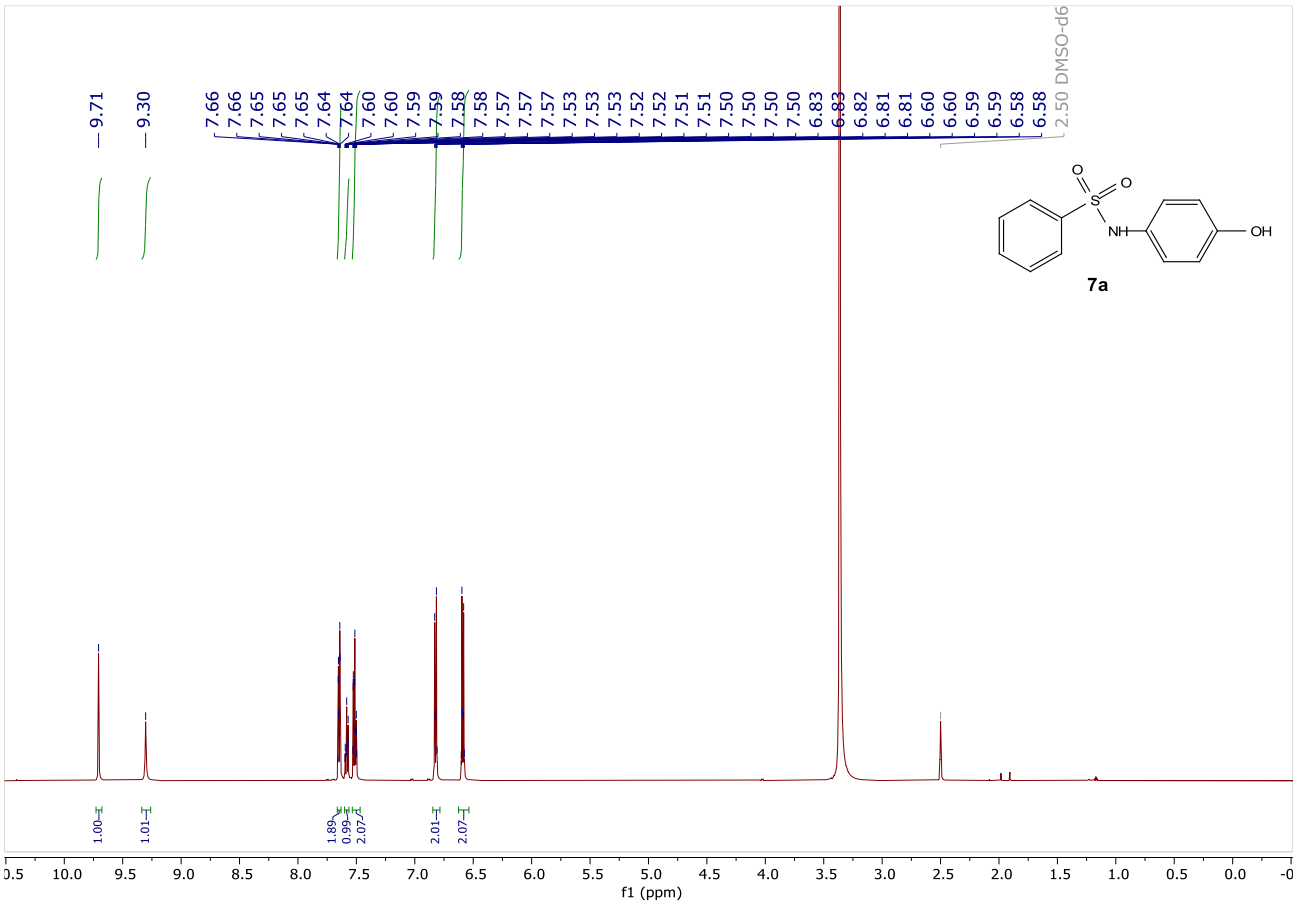
120.93
77.16 CDCl3
39.42
f1 (ppm)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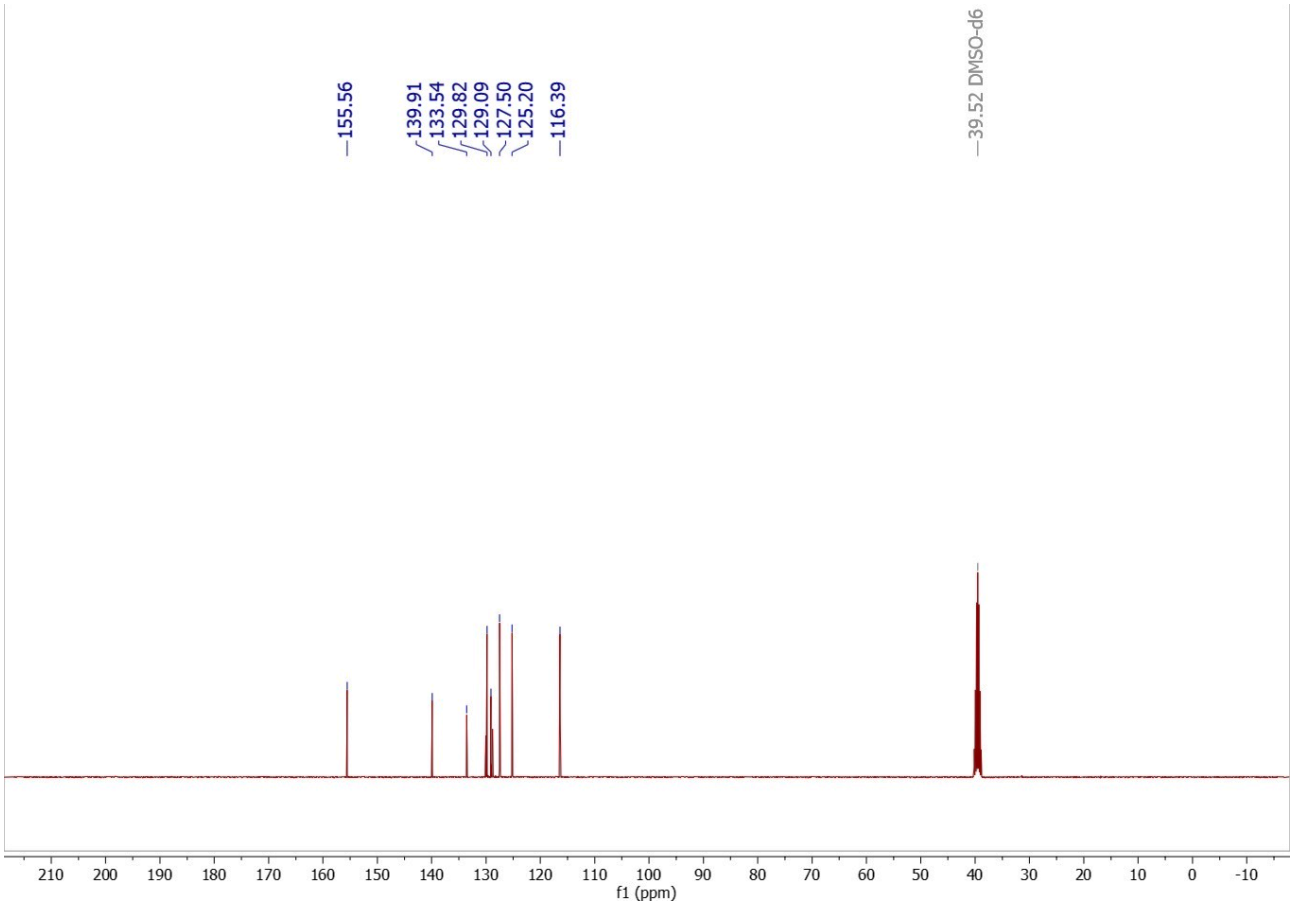
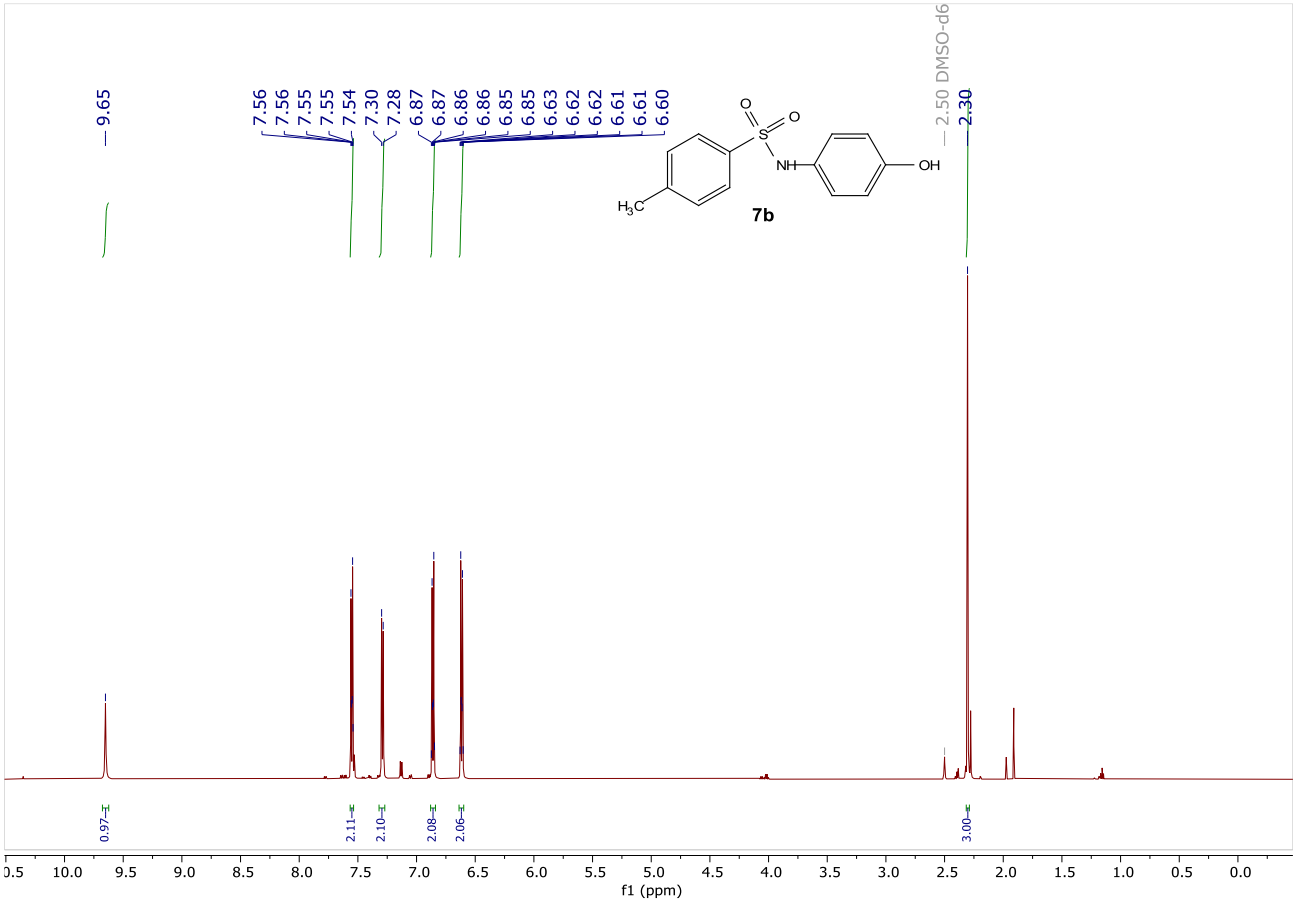
7.65
7.65
7.64
7.64
7.60
7.60
7.59
7.59
7.58
7.58
7.57
7.57
7.57
7.53
7.53
7.52
7.52
7.51
7.51
7.50
7.50
7.50
6.83
6.82
6.81
6.81
6.60
6.60
6.59
6.59
6.58
6.58
2.50 DMSO-d6
1.00
1.01
1.89
0.99
2.07
2.01
2.07
f1 (ppm)

7a


155.56
139.91
133.54
129.82
129.09
127.50
125.20
116.39
39.52 DMSO-d6
f1 (ppm)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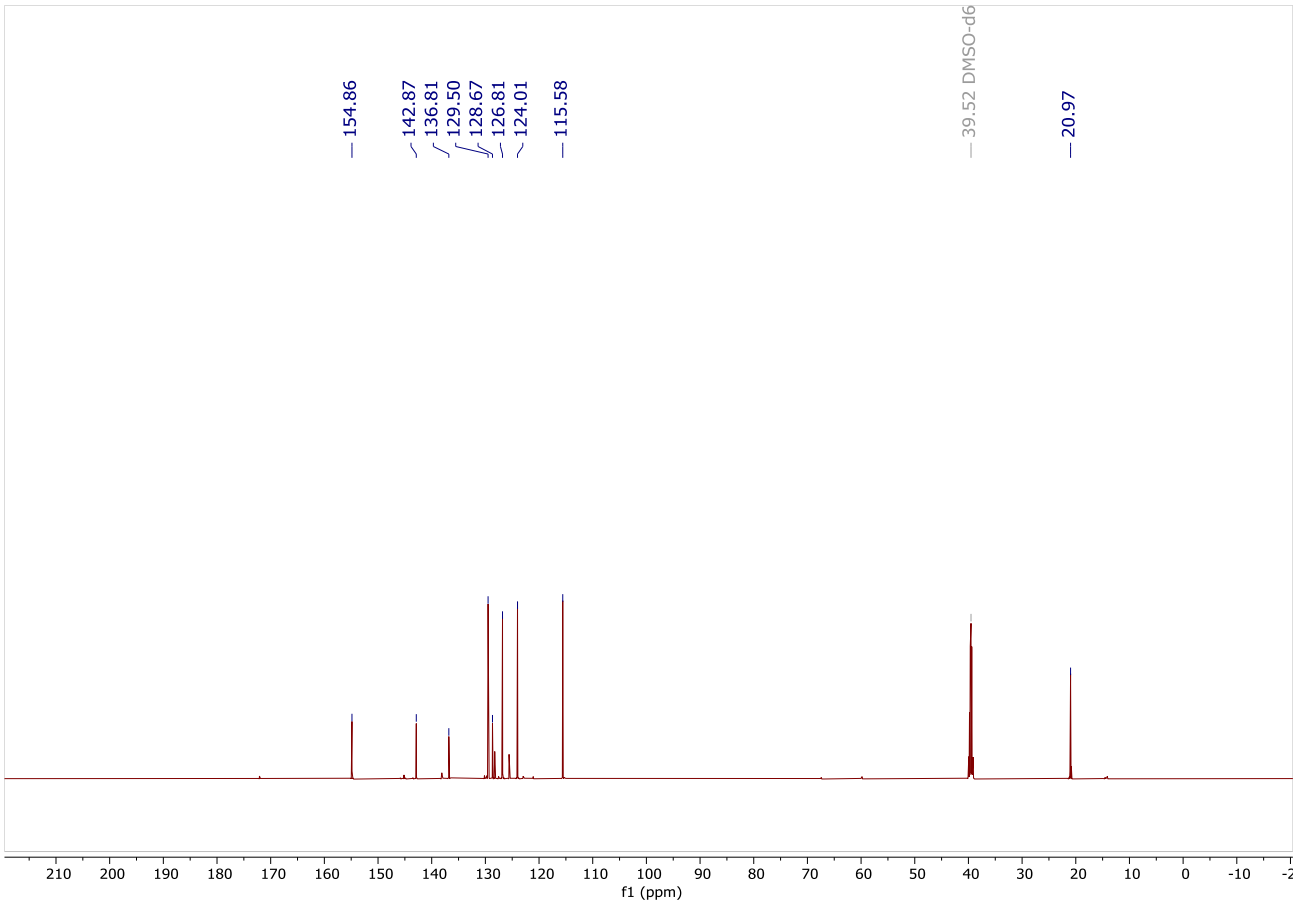
7.56
7.56
7.55
7.55
7.54
7.30
7.28
6.87
6.87
6.86
6.86
6.85
6.85
6.63
6.62
6.62
6.61
6.61
6.60
2.50 DMSO-d6
2.30
O
S
O
NH
OH
H3C
7b
0.97
2.11
2.10
2.08
2.06
3.00
f1 (ppm)


154.86
142.87
136.81
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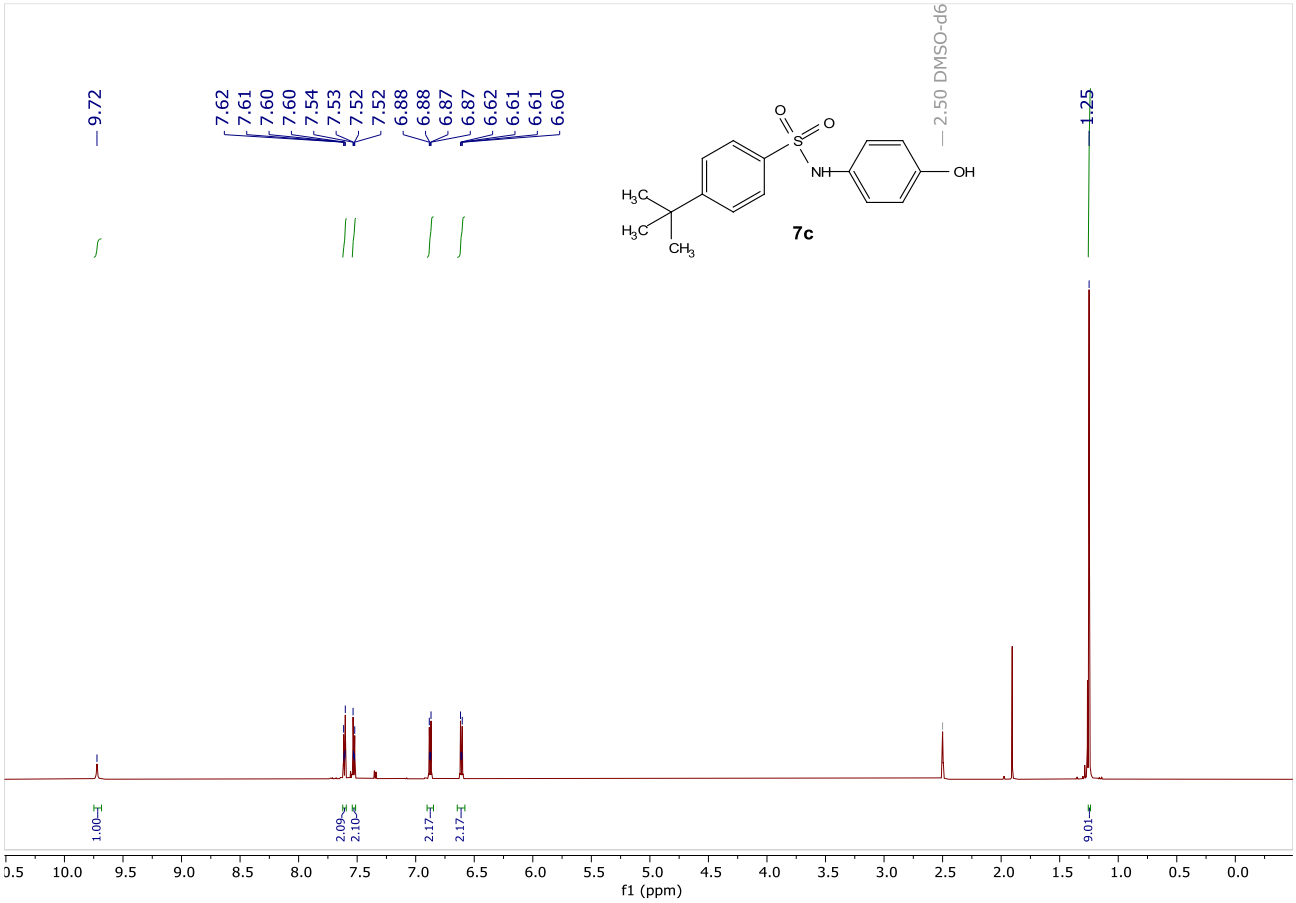
126.81
124.01
115.58
39.52 DMSO-d6
20.97
f1 (ppm)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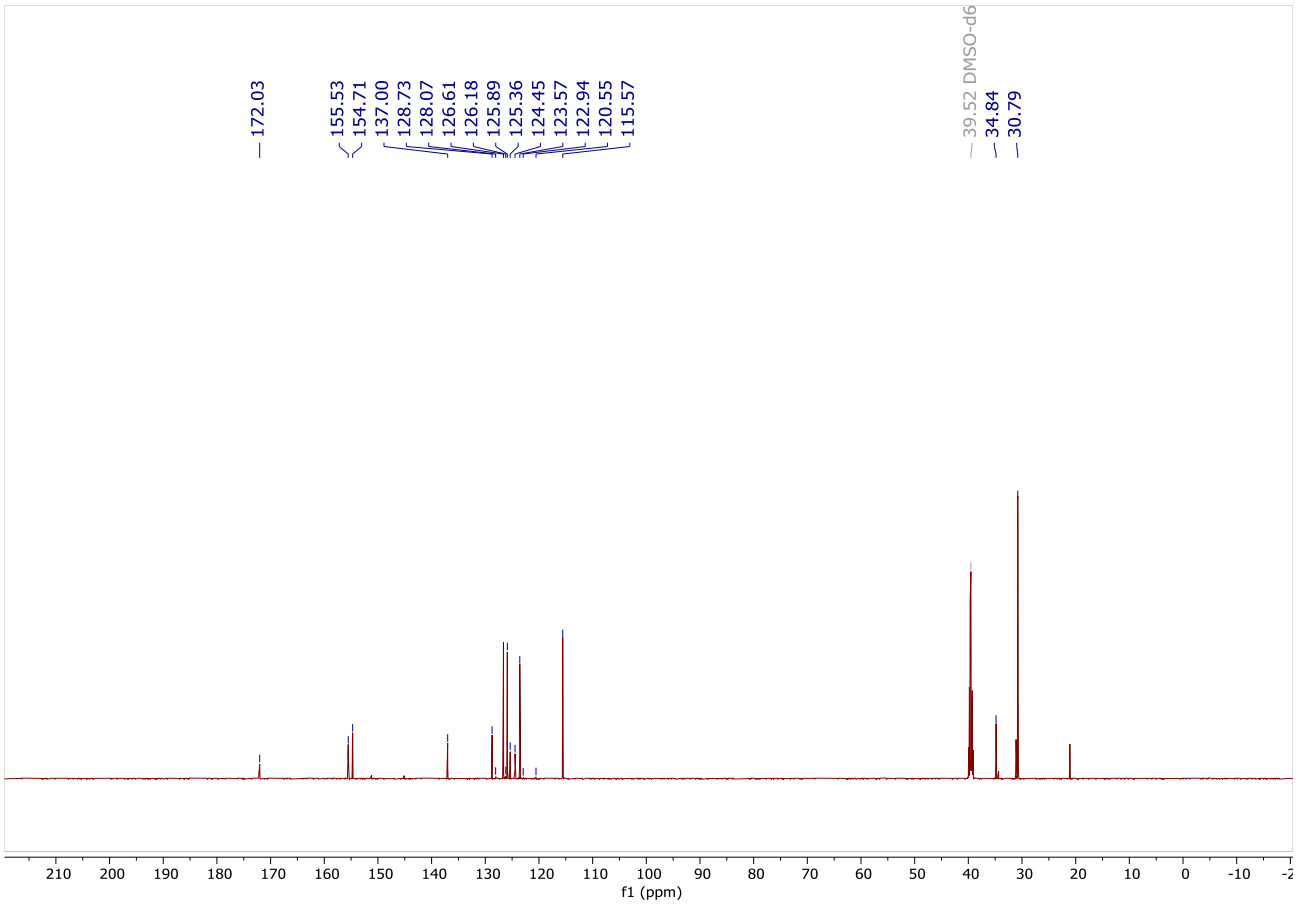
6.87
6.87
6.62
6.61
6.61
6.60
2.50 DMSO-d6
1.25
O
O
S
NH
OH
H3C
H3C
CH3
7c
1.00
2.09
2.10
2.17
2.17
9.01
f1 (ppm)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126.18
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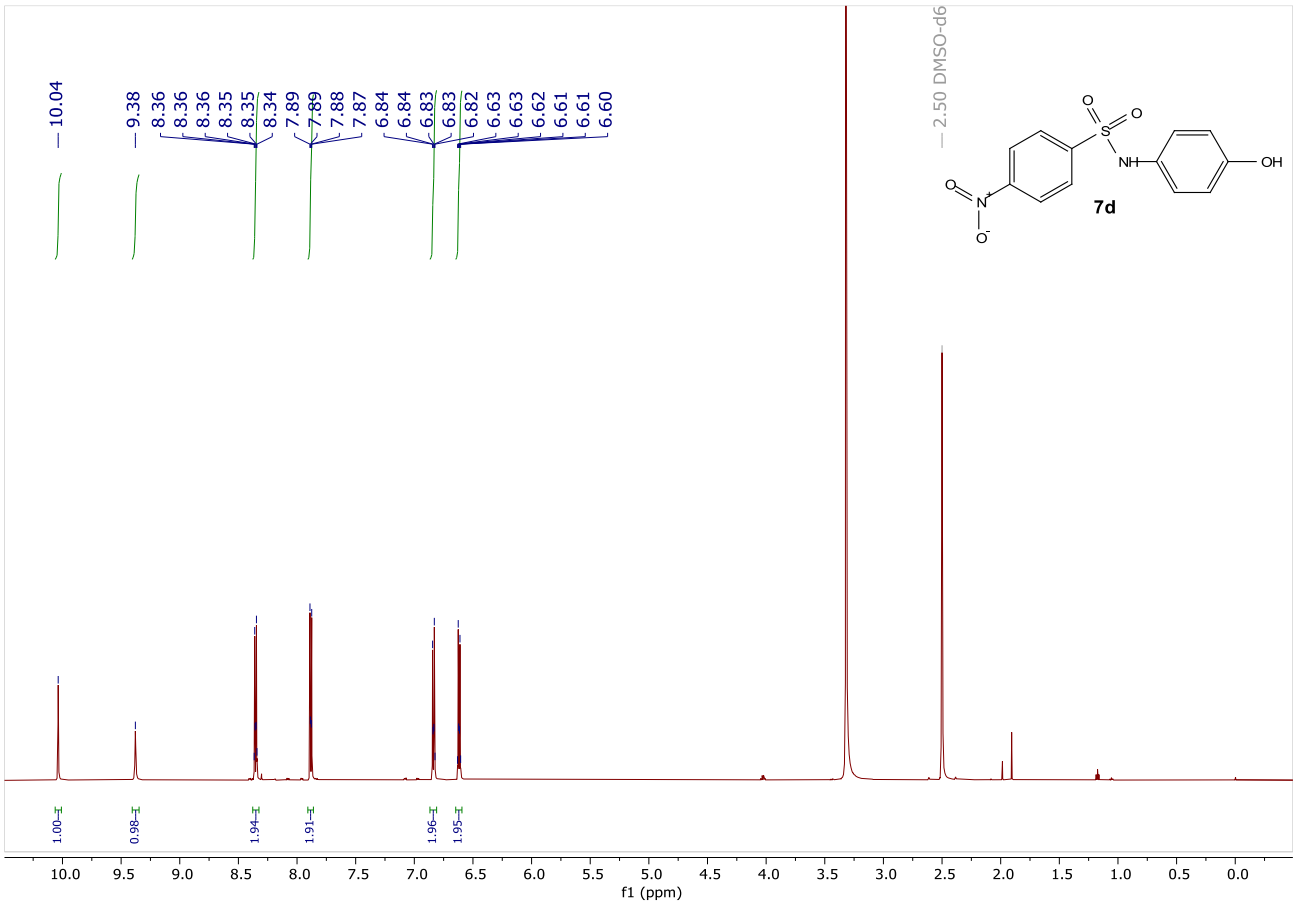
123.57
122.94
120.55
115.57
39.52 DMSO-d6
34.84
30.79
f1 (ppm)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8.34
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7.89
7.88
7.87
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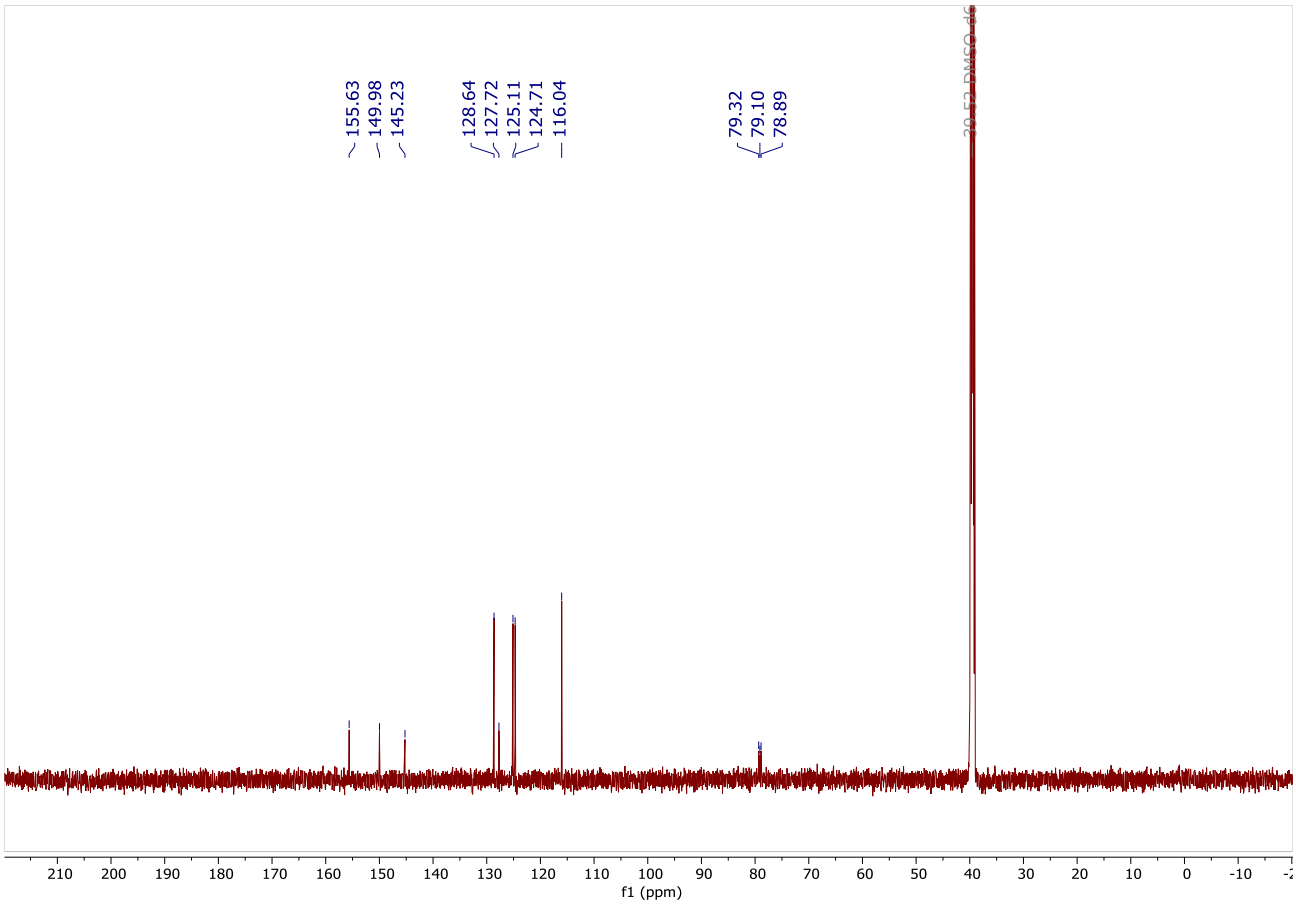
6.84
6.83
6.83
6.82
6.63
6.63
6.62
6.61
6.61
6.60
2.50 DMSO-d6
7d
1.00
0.98
1.94
1.91
1.96
1.95
f1 (ppm)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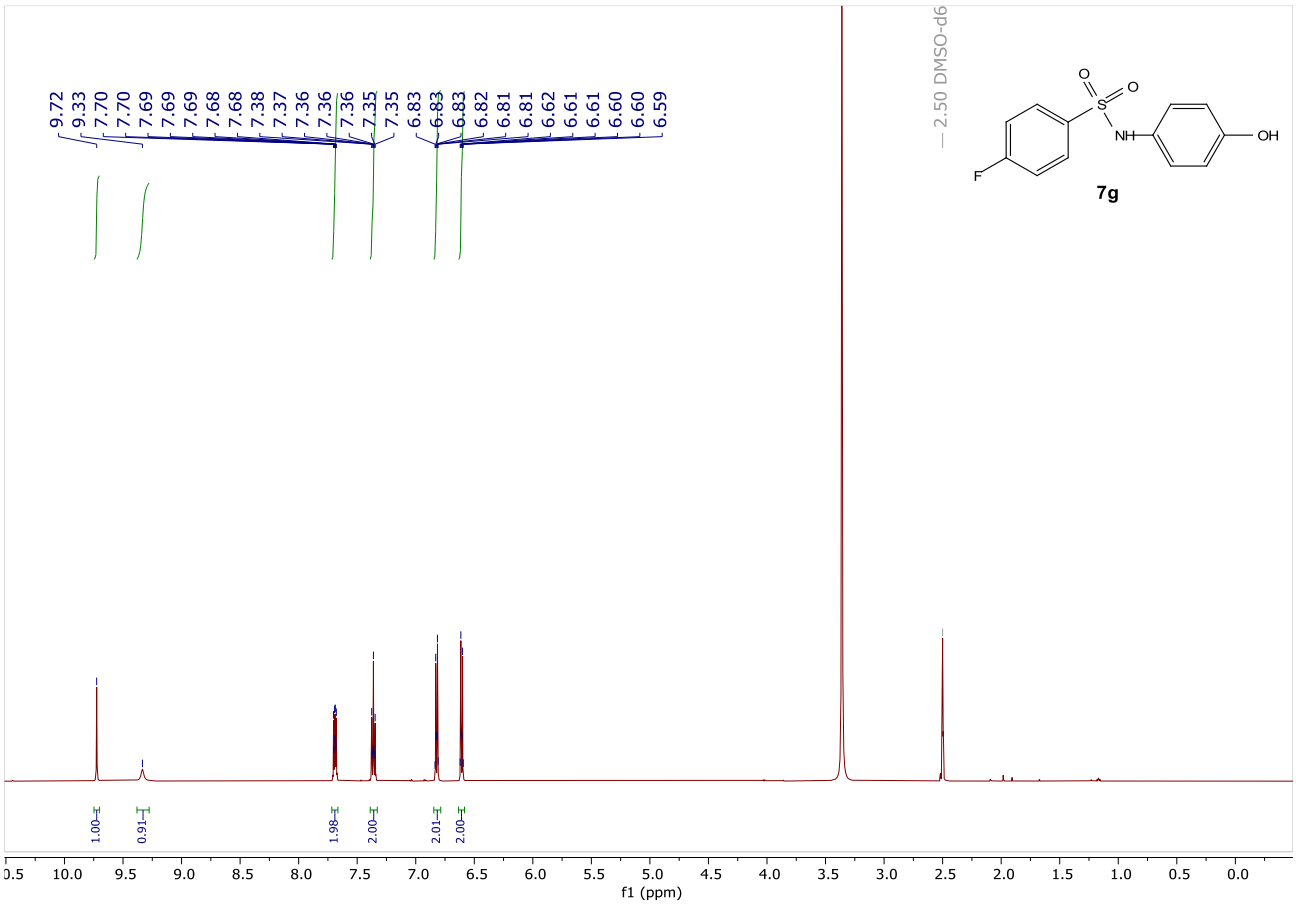
124.71
116.04
79.32
79.10
78.89
39.52 DMSO-d6
f1 (ppm)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7.68
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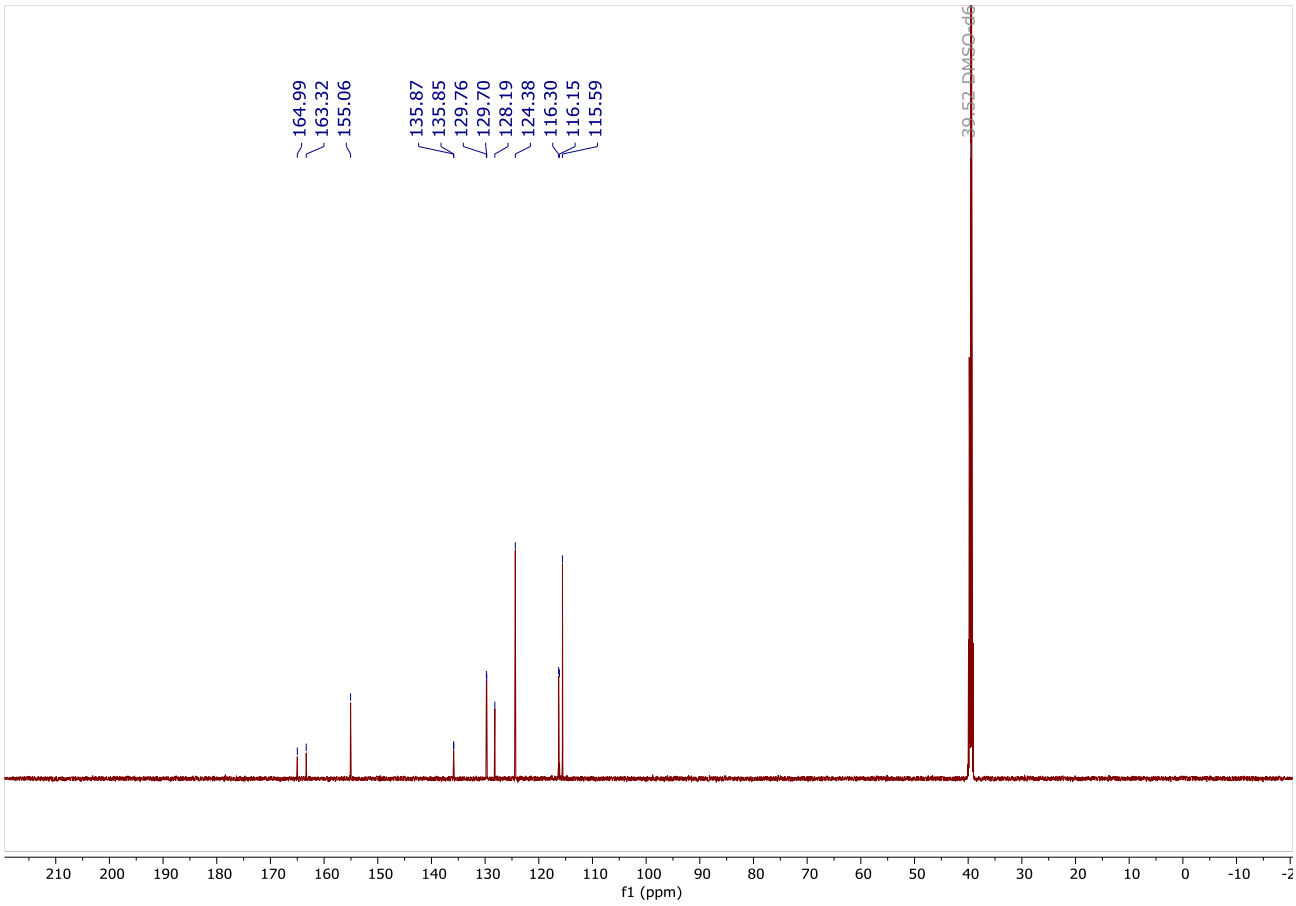
6.83
6.83
6.82
6.81
6.81
6.62
6.61
6.61
6.60
6.60
6.59
2.50 DMSO-d6
O
S
O
NH
OH
F
7g
1.00
0.91
1.98
2.00
2.01
2.00
f1 (ppm)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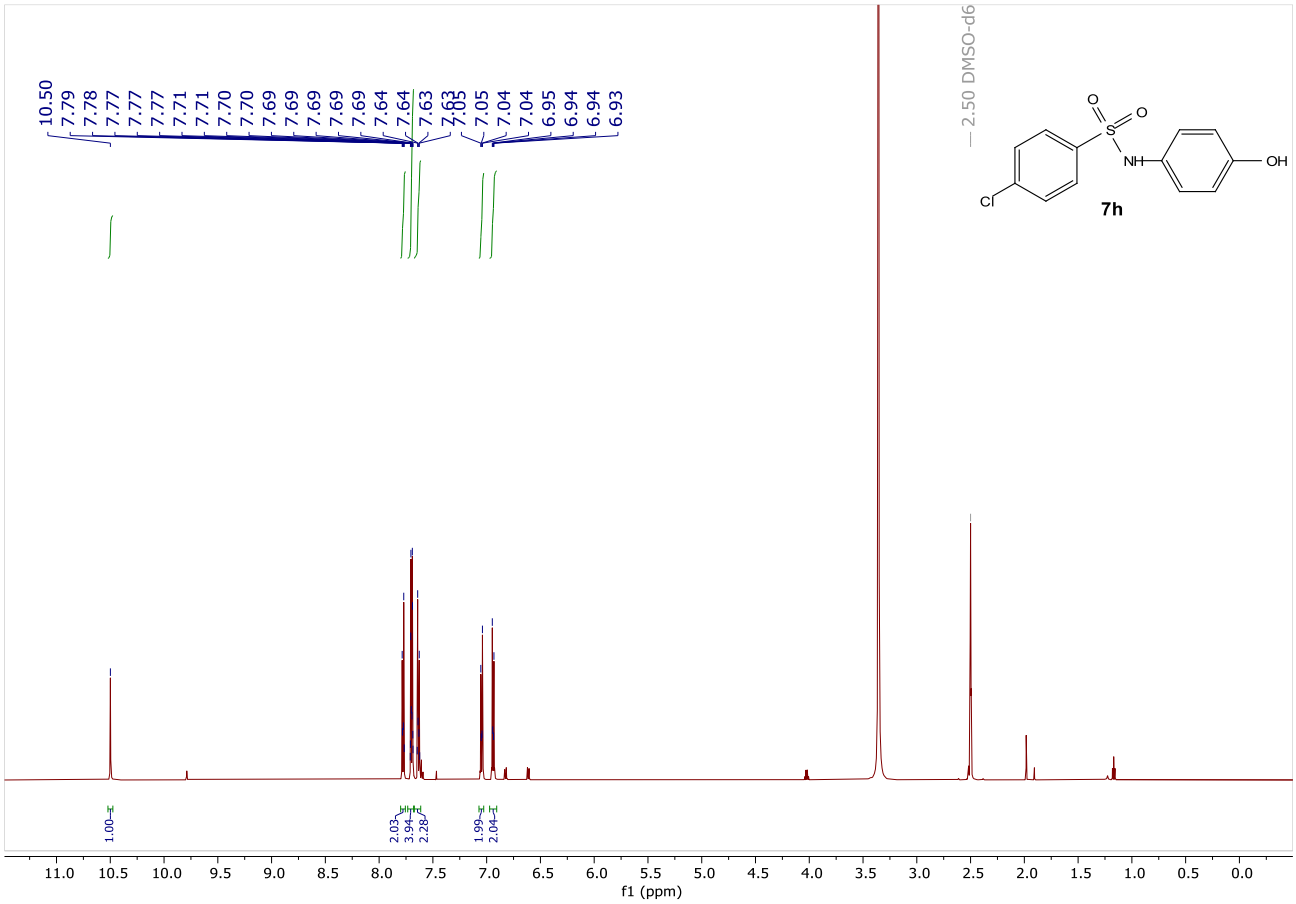
124.38
116.30
116.15
115.59
39.52 DMSO-d6
f1 (ppm)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7.77
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7.71
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7.70
7.69
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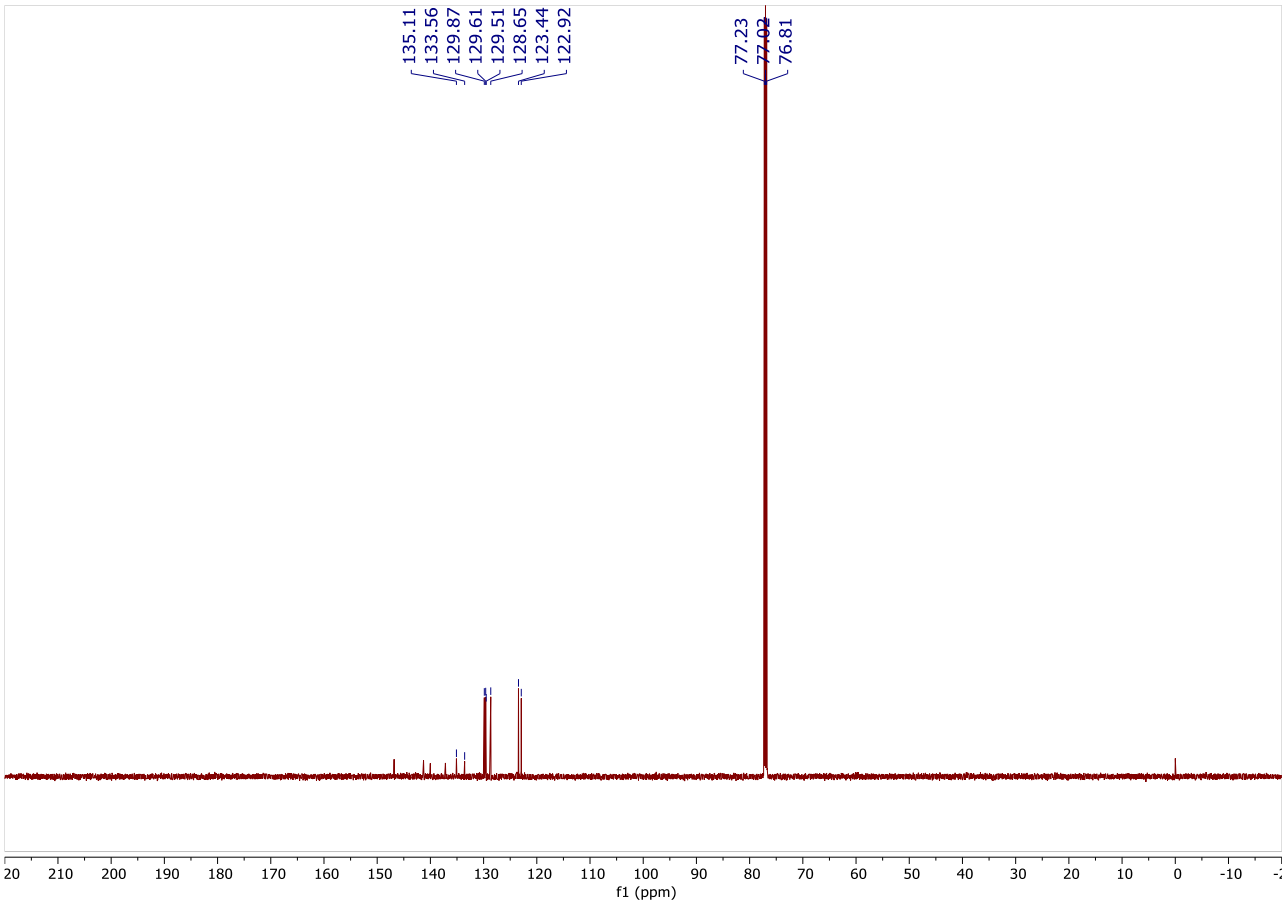
7.69
7.69
7.64
7.64
7.63
7.63
7.05
7.05
7.04
7.04
6.95
6.94
6.94
6.93
2.50 DMSO-d6
O
S
O
NH
OH
Cl
7h
1.00
2.03
3.94
2.28
1.99
2.04
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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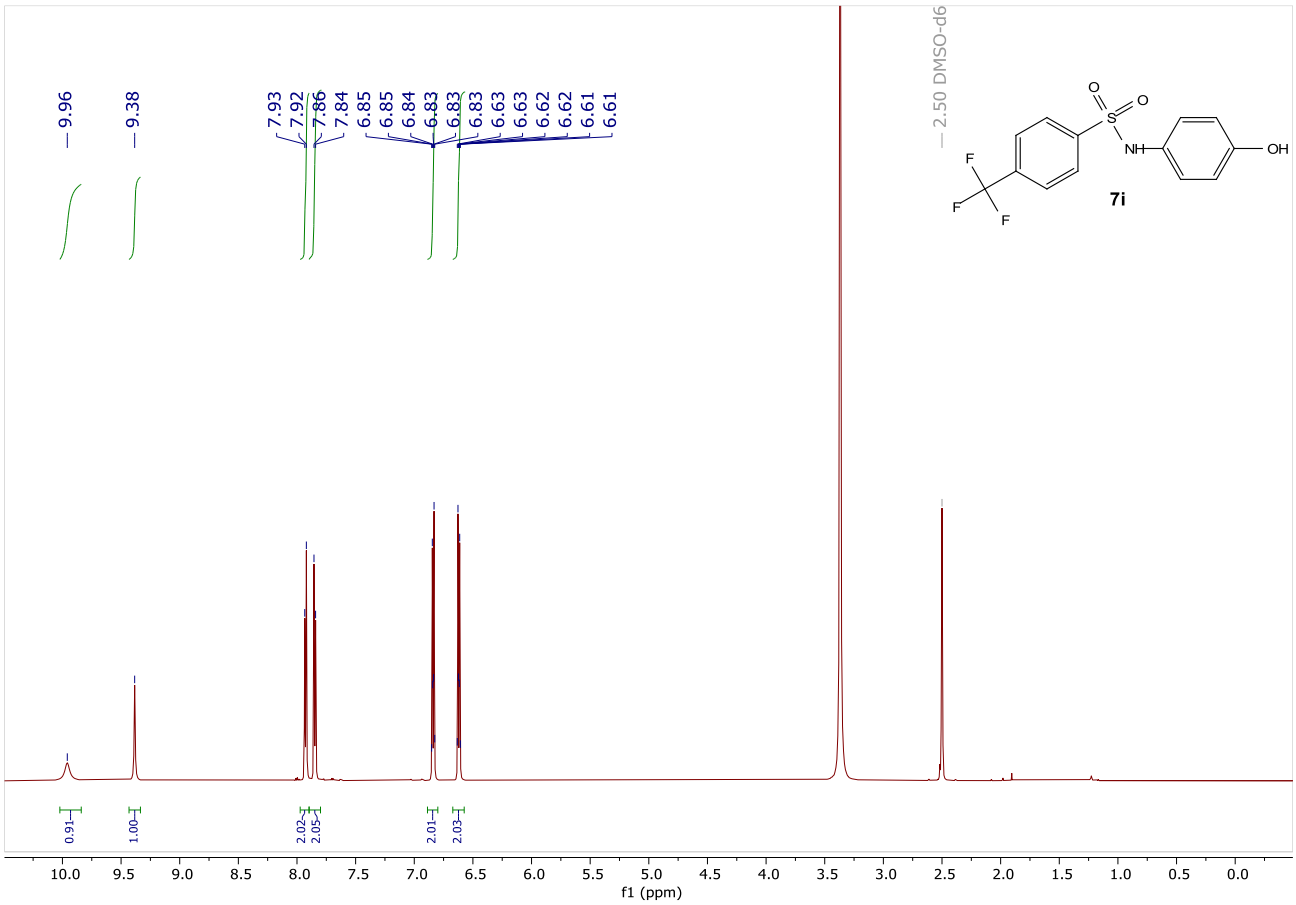
129.61
129.51
128.65
123.44
122.92
77.23
77.02
76.81
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.92
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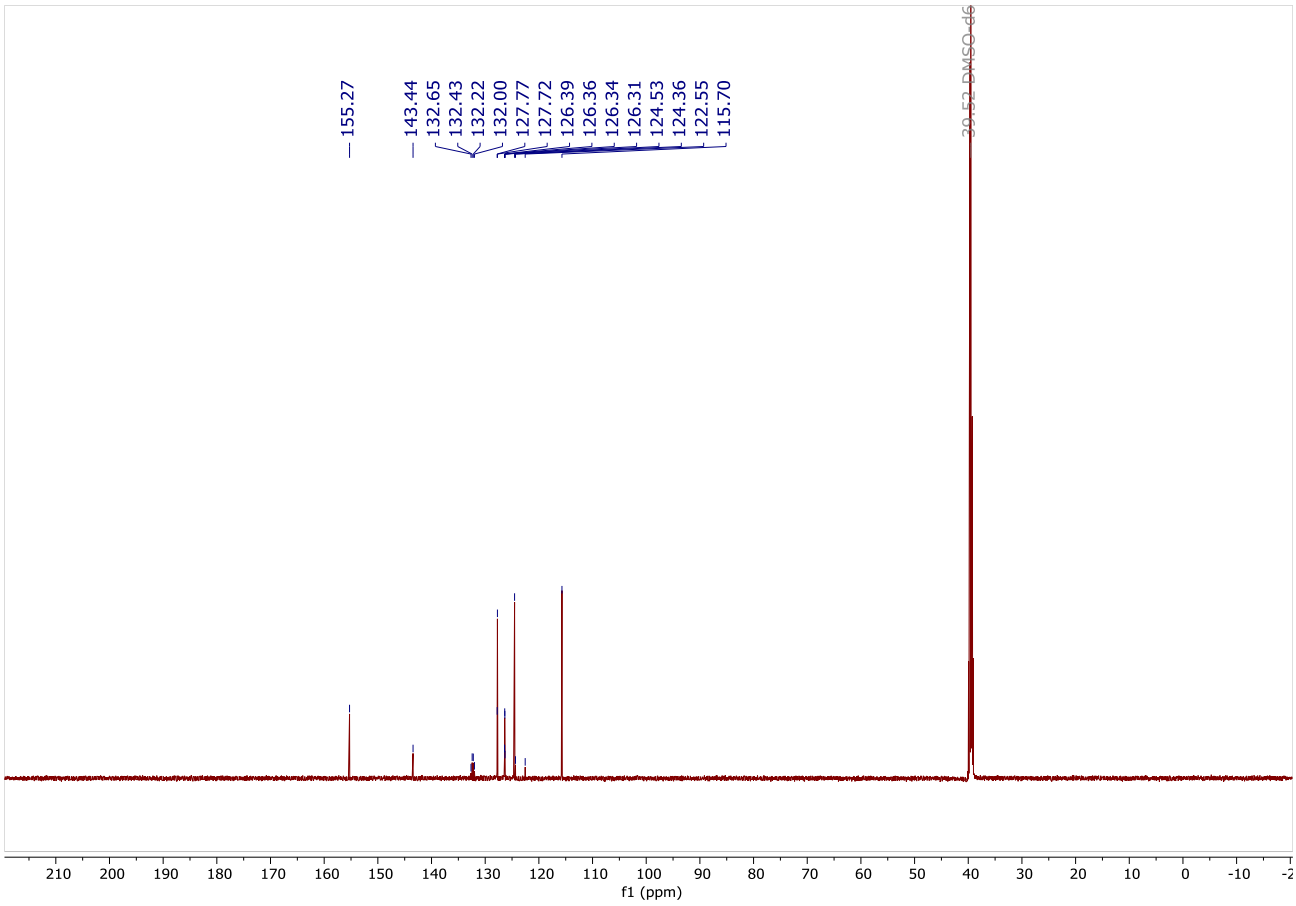
6.85
6.84
6.83
6.83
6.63
6.63
6.62
6.62
6.61
6.61
2.50 DMSO-d6
O
O
S
NH
OH
F
F
F
7i
0.91
1.00
2.02
2.05
2.01
2.03
f1 (ppm)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126.34
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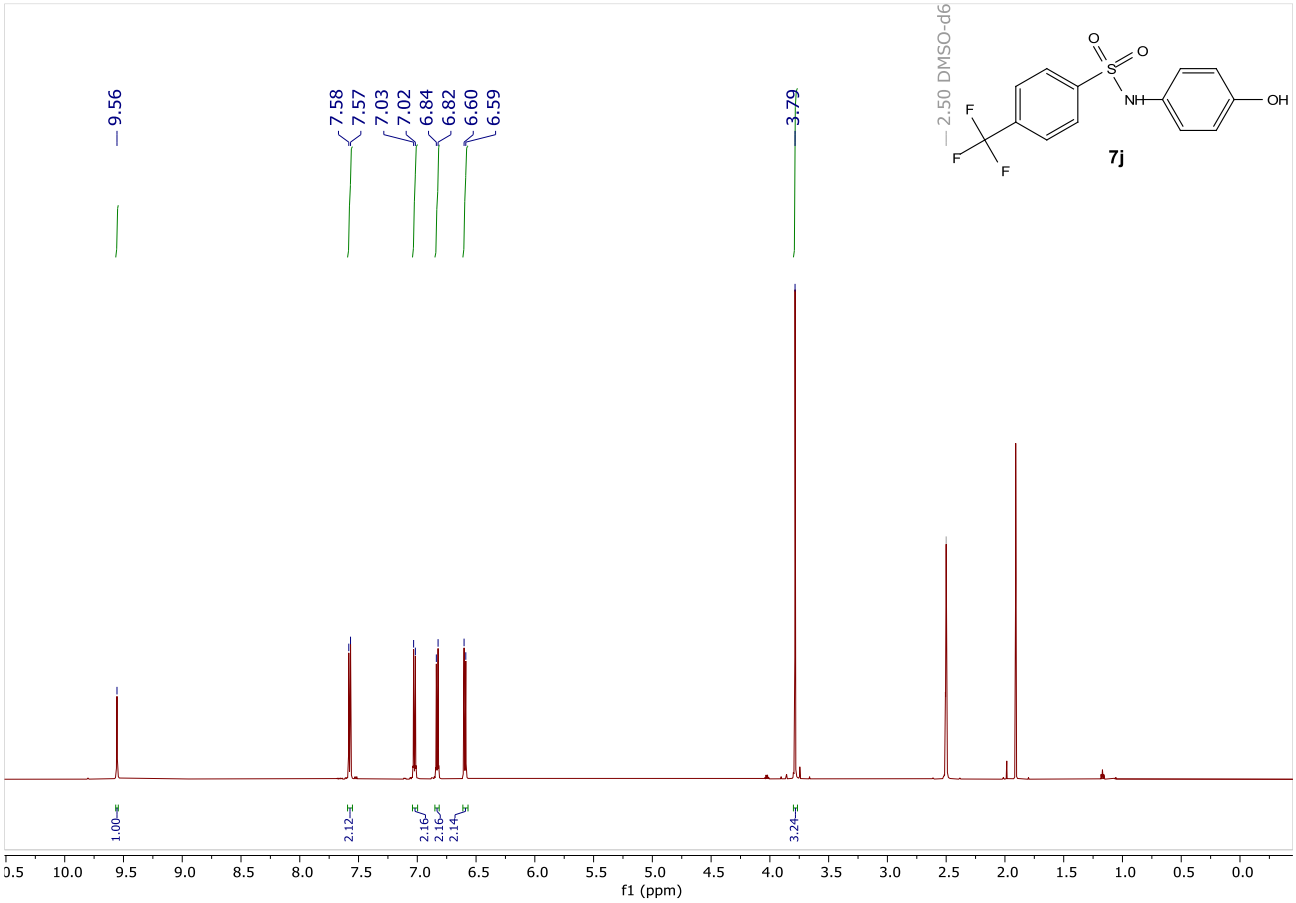
124.53
124.36
122.55
115.70
39.52 DMSO-d6
f1 (ppm)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7.57
7.03
7.02
6.84
6.82
6.60
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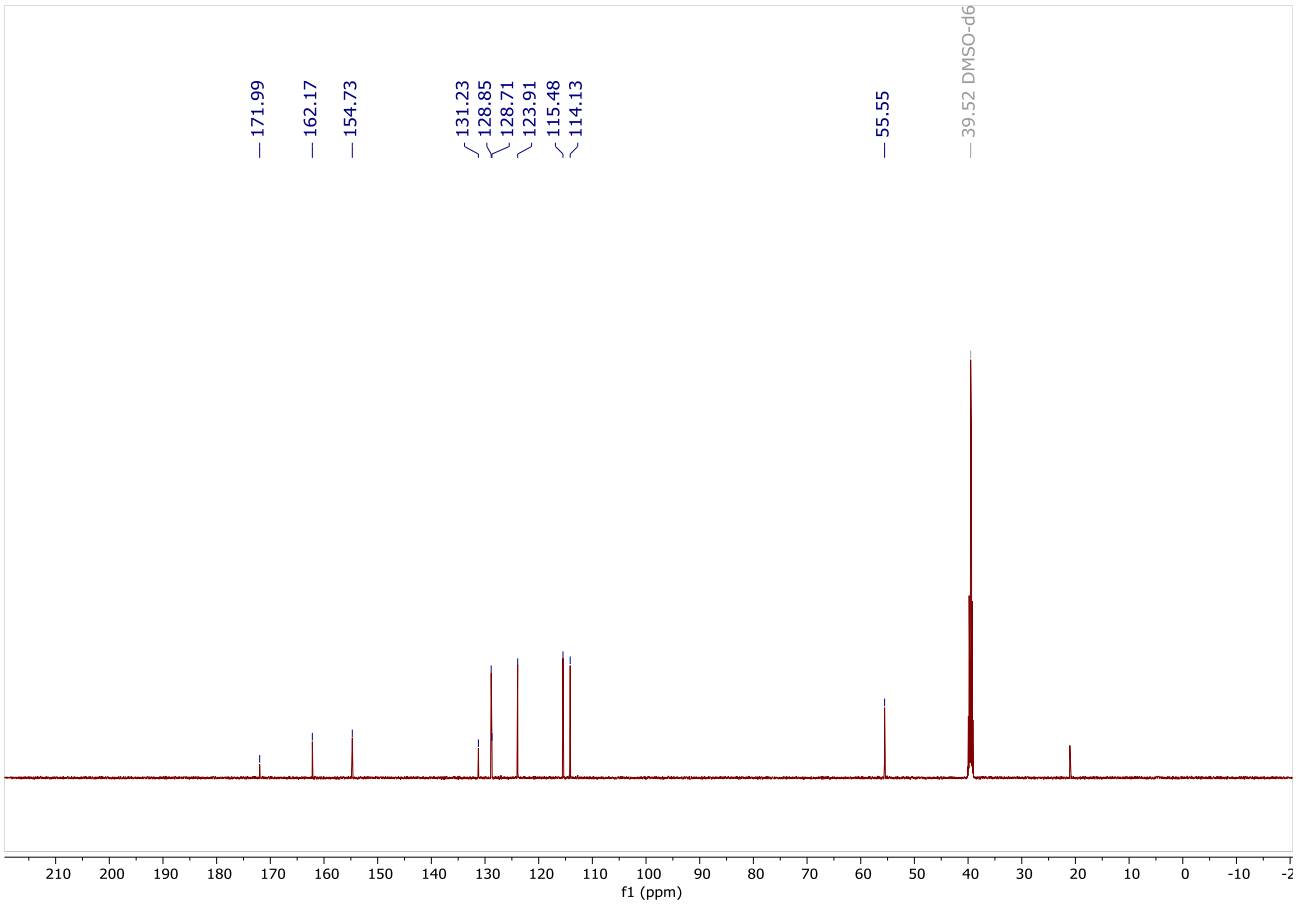
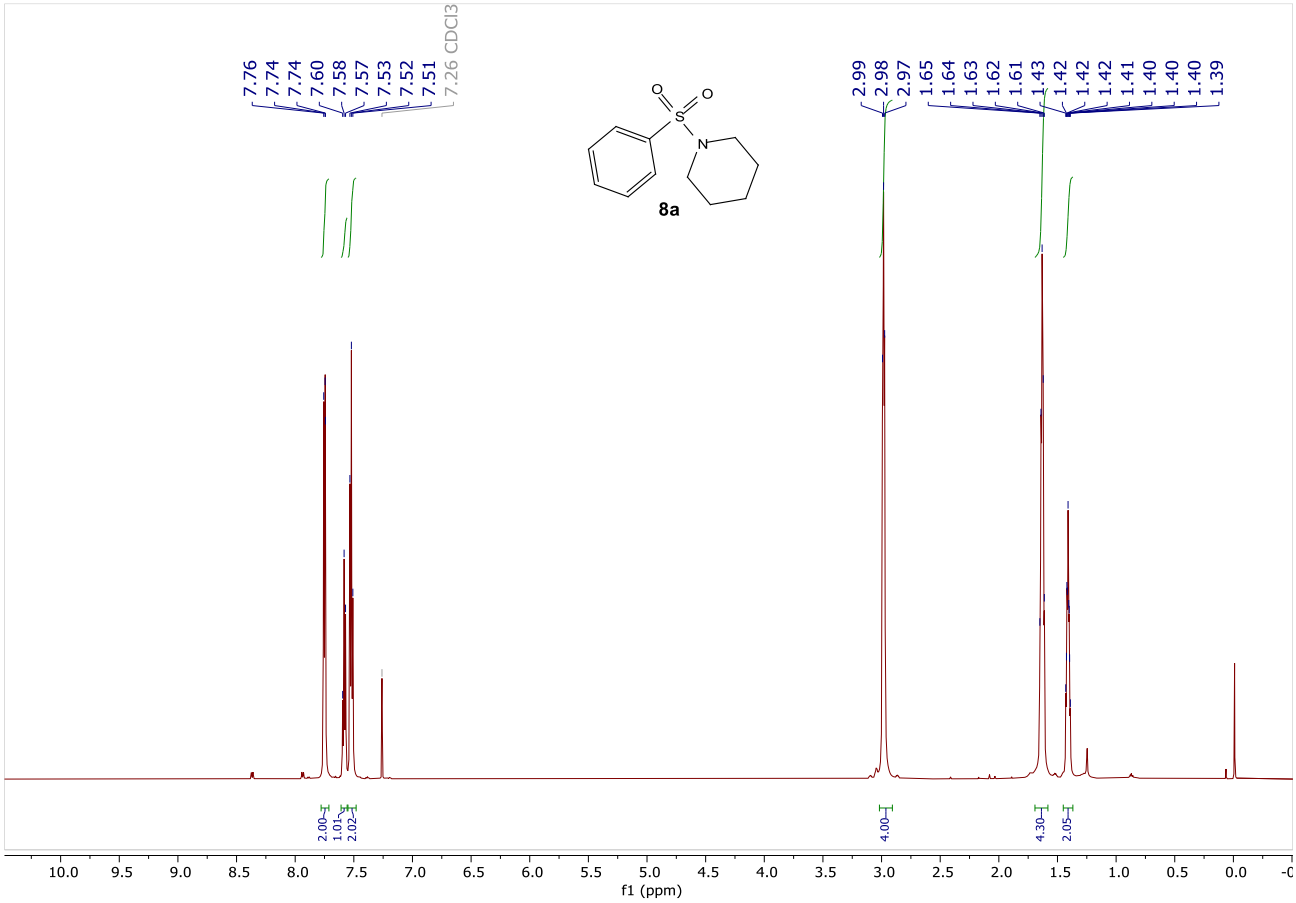
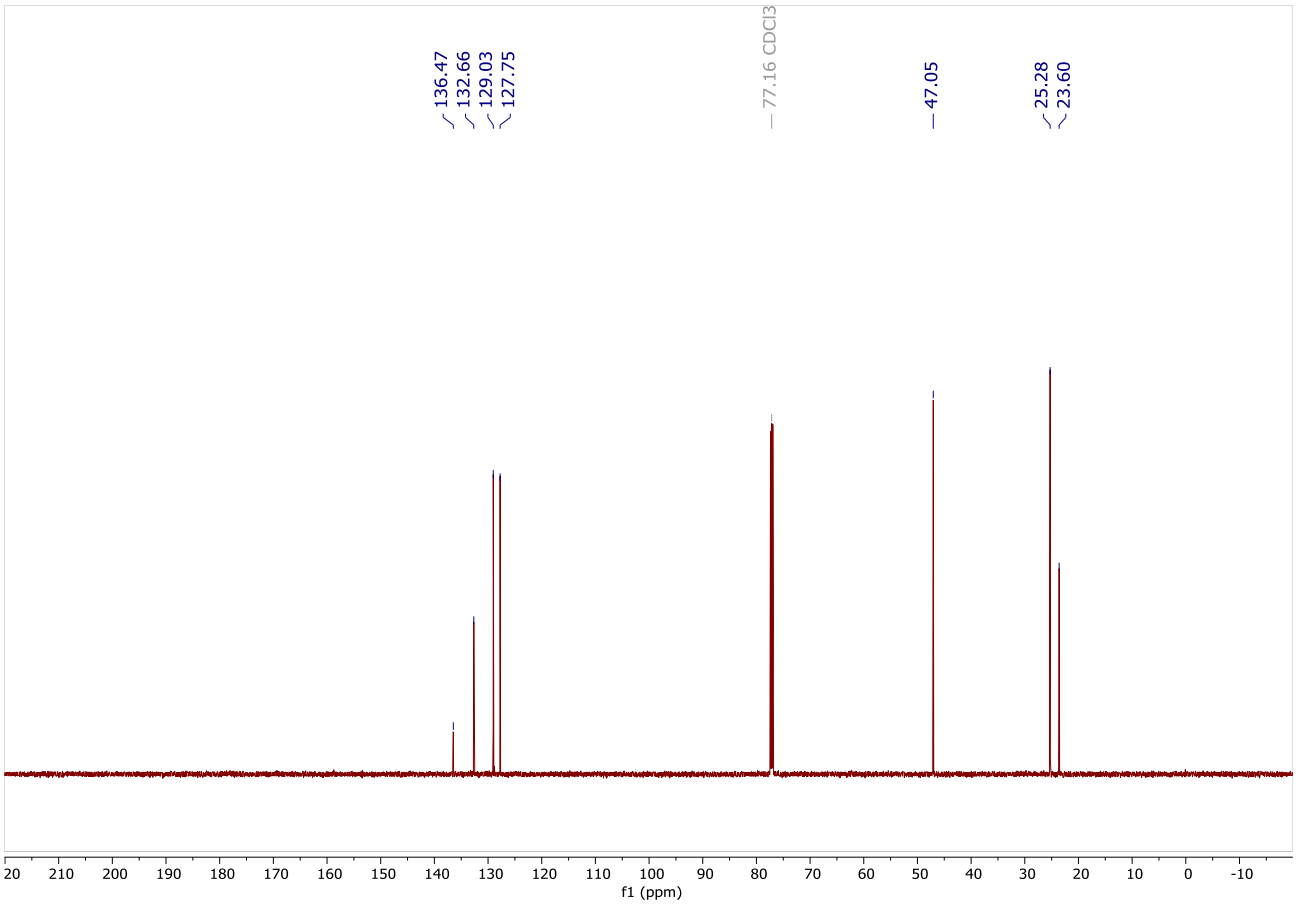
2.16
2.14
3.24
f1 (ppm)


171.99
162.17
154.73
131.23
128.85
128.71
123.91
115.48
114.13
55.55
39.52 DMSO-d6
f1 (ppm)


7.76
7.74
7.74
7.60
7.58
7.57
7.53
7.52
7.51
7.26 CDCl3
2.99
2.98
2.97
1.65
1.64
1.63
1.62
1.61
1.43
1.42
1.42
1.42
1.41
1.40
1.40
1.39
8a
2.00
1.01
2.02
4.00
4.30
2.05
f1 (ppm)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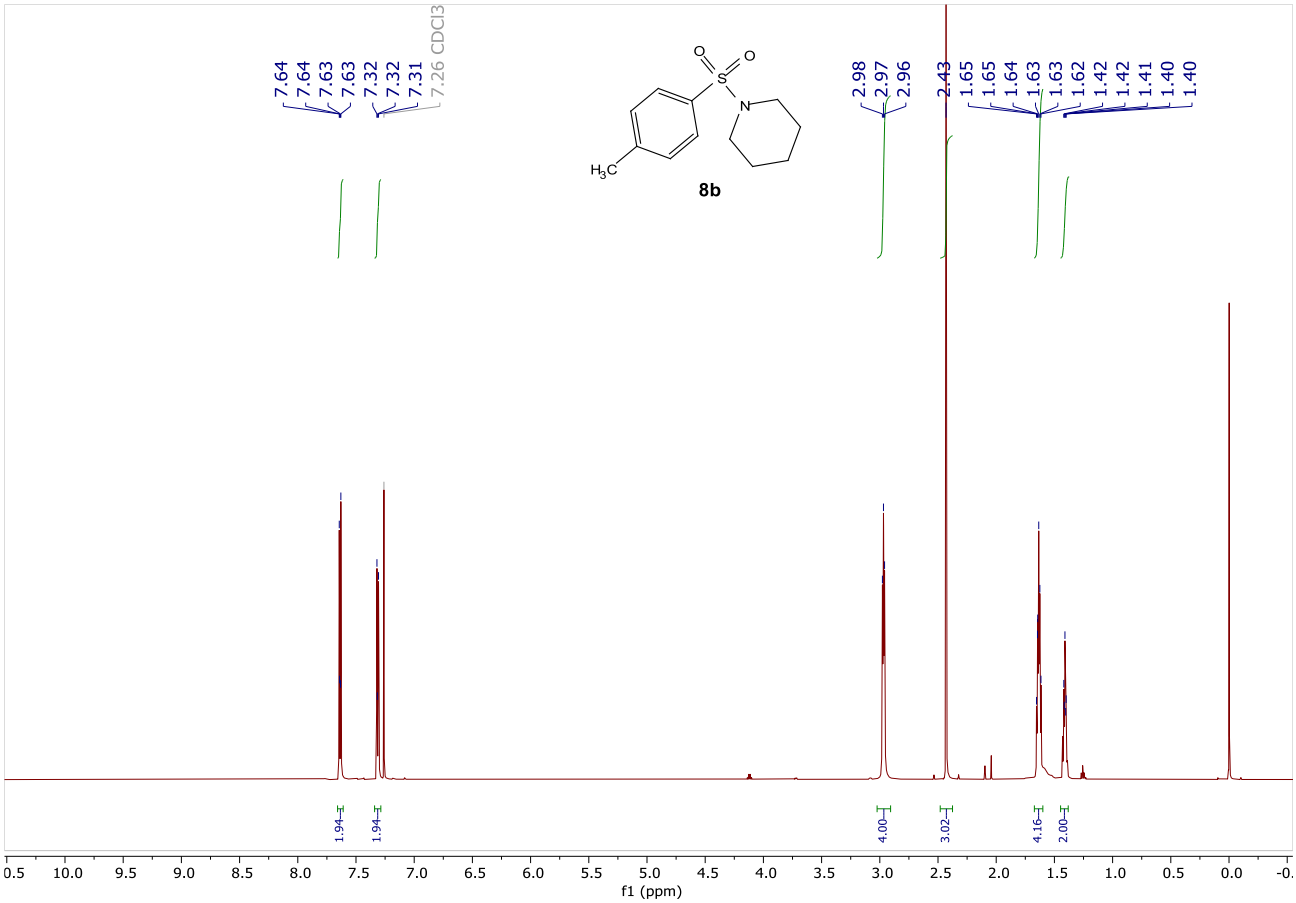
132.66
129.03
127.75
77.16 CDCl3
47.05
25.28
23.60
f1 (ppm)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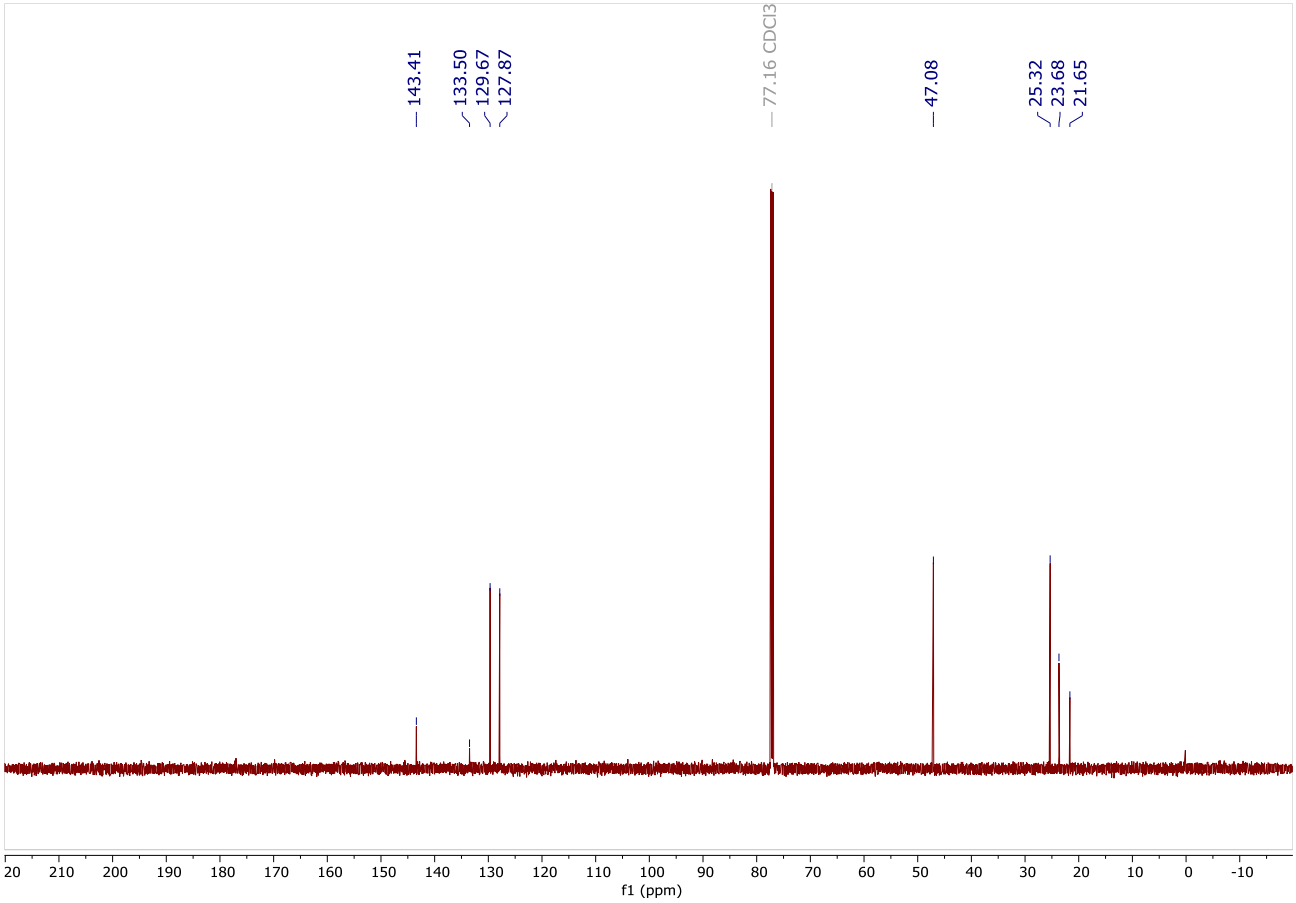
7.64
7.63
7.63
7.32
7.32
7.31
7.26 CDCl3
2.98
2.97
2.96
2.43
1.65
1.65
1.64
1.63
1.63
1.62
1.42
1.42
1.41
1.40
1.40
8b
1.94
1.94
4.00
3.02
4.16
2.00
f1 (ppm)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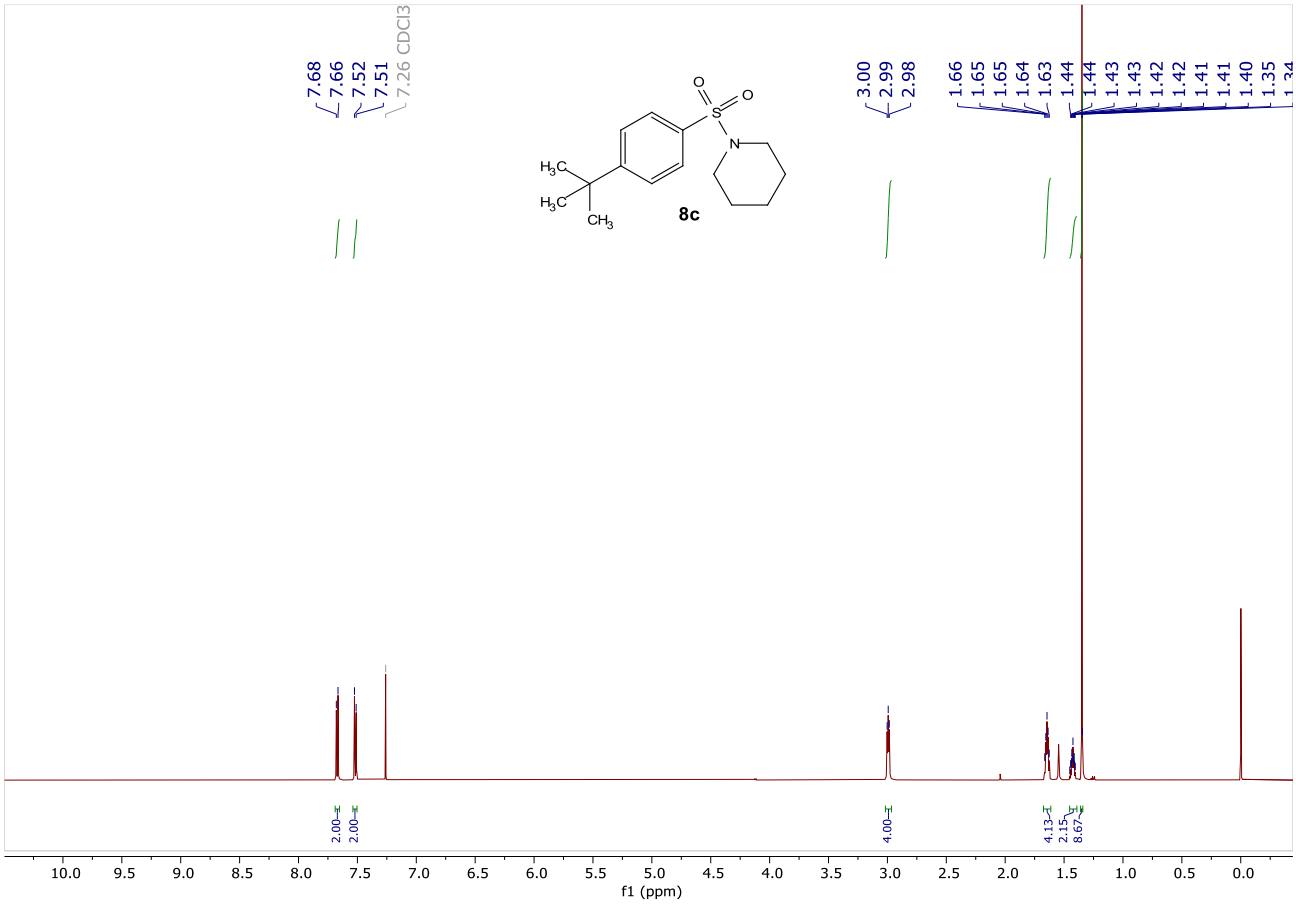
133.50
129.67
127.87
77.16 CDCl3
47.08
25.32
23.68
21.65
f1 (ppm)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7.66
7.52
7.51
7.26 CDCl3
3.00
2.99
2.98
1.66
1.65
1.65
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1.63
1.44
1.44
1.43
1.43
1.42
1.42
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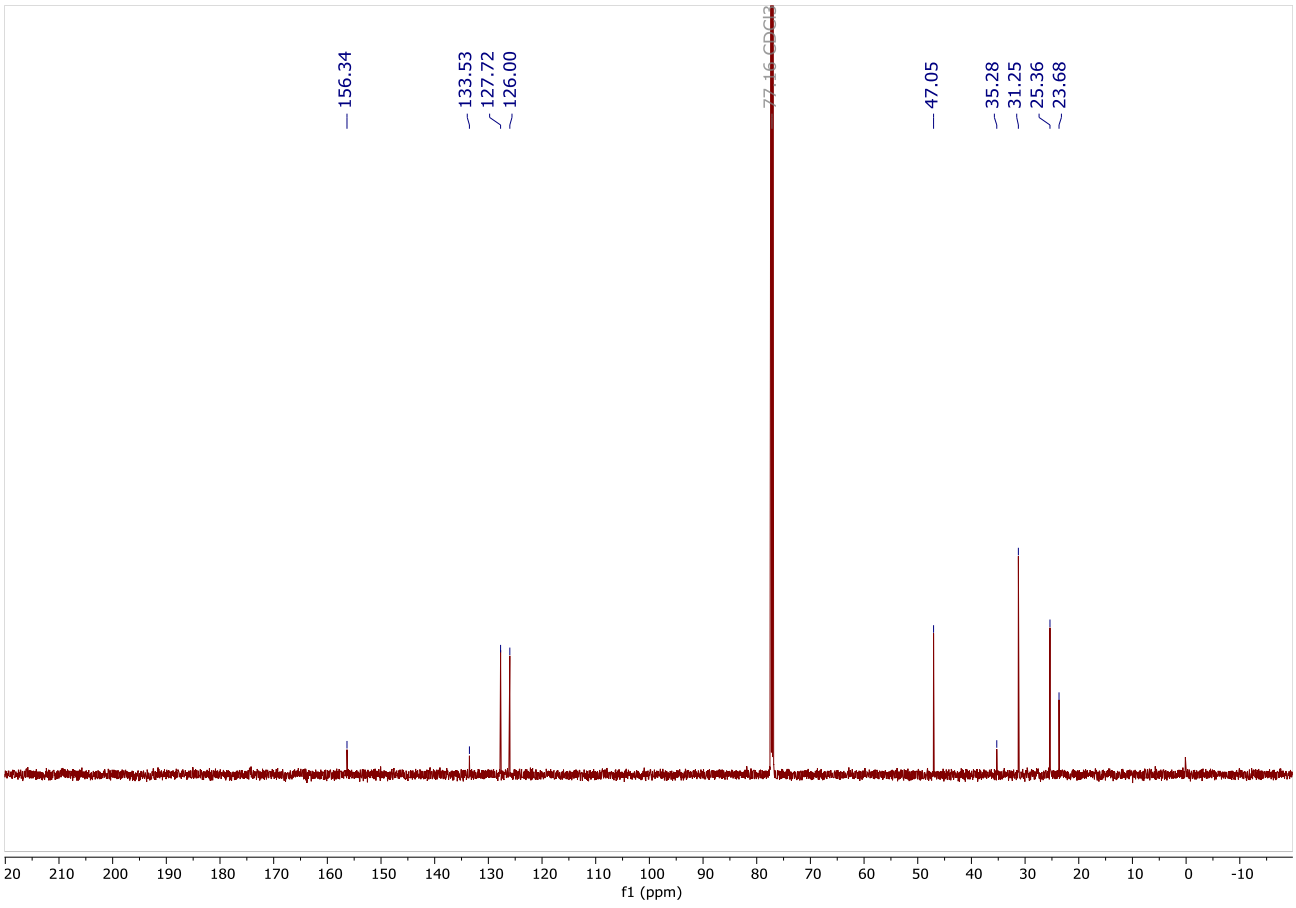
4.00
4.13
2.15
8.67
f1 (ppm)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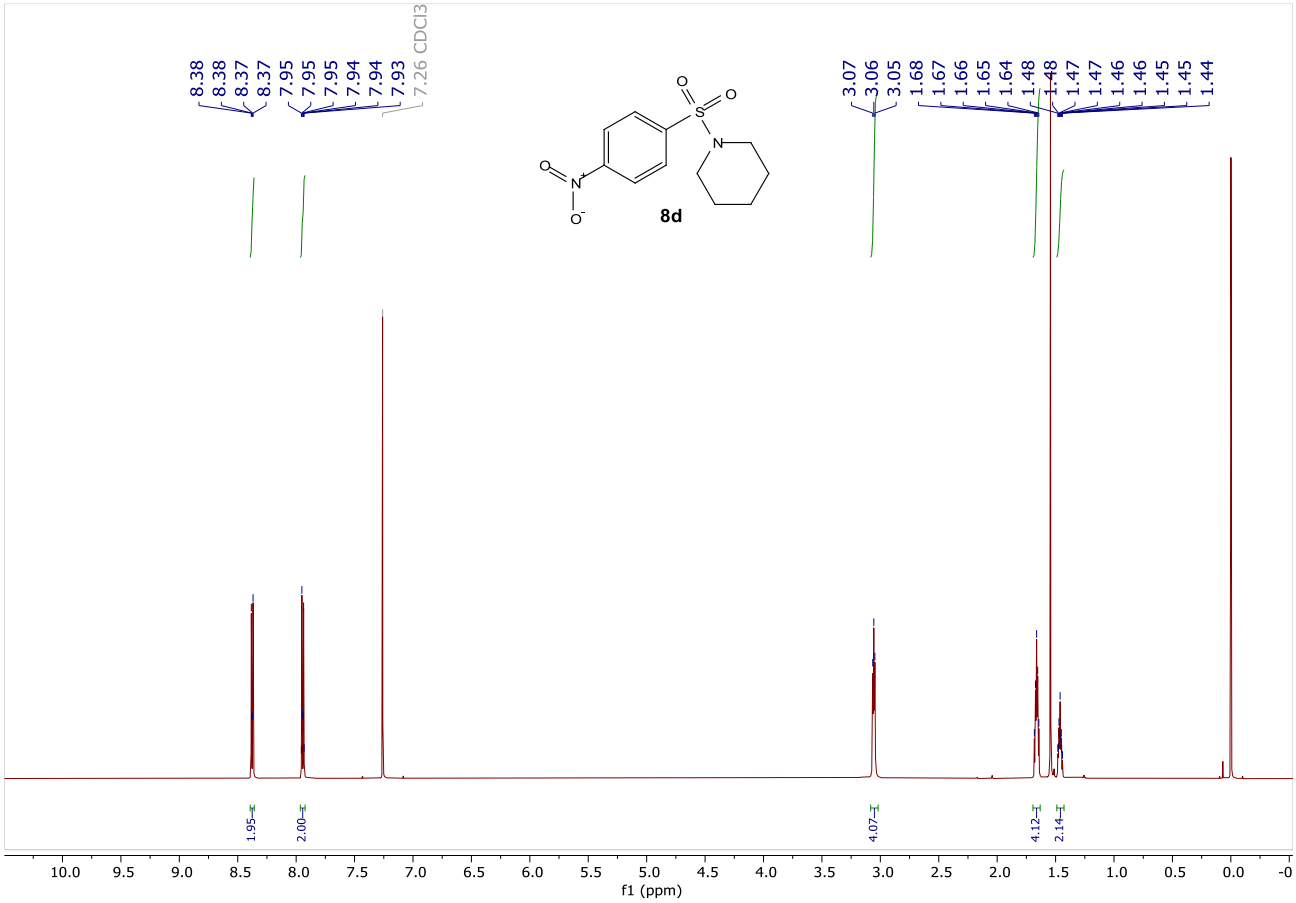
35.28
31.25
25.36
23.68
f1 (ppm)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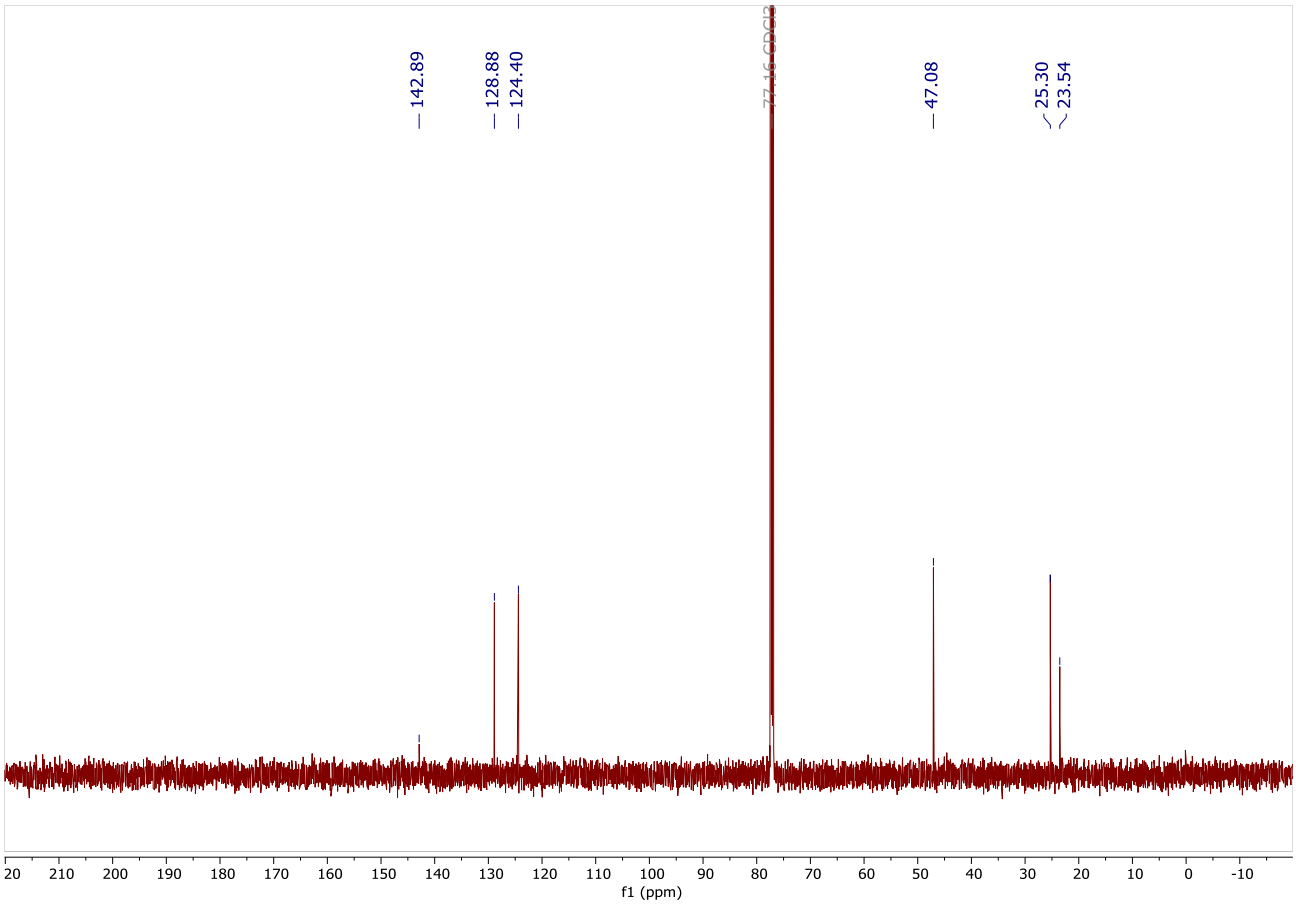
7.95
7.95
7.94
7.94
7.93
7.26 CDCl3
3.07
3.06
3.05
1.68
1.67
1.66
1.65
1.64
1.48
1.48
1.47
1.47
1.46
1.46
1.45
1.45
1.44
8d
1.95
2.00
4.07
4.12
2.14
f1 (ppm)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128.88
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47.08
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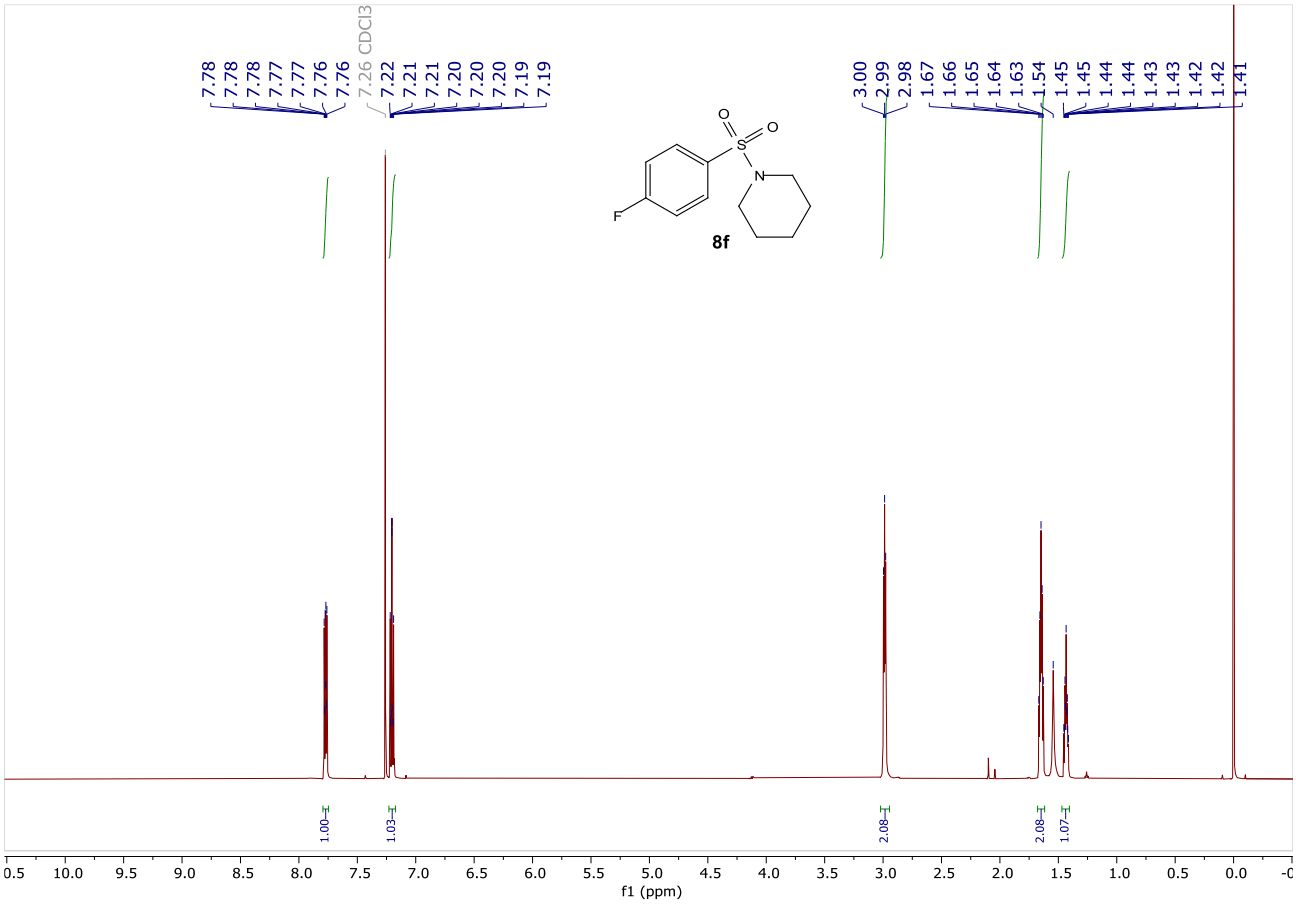
23.54
f1 (ppm)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7.78
7.78
7.77
7.77
7.76
7.76
7.26 CDCl3
7.22
7.21
7.21
7.20
7.20
7.20
7.19
7.19
3.00
2.99
2.98
1.67
1.66
1.65
1.64
1.63
1.54
1.45
1.45
1.44
1.44
1.43
1.43
1.42
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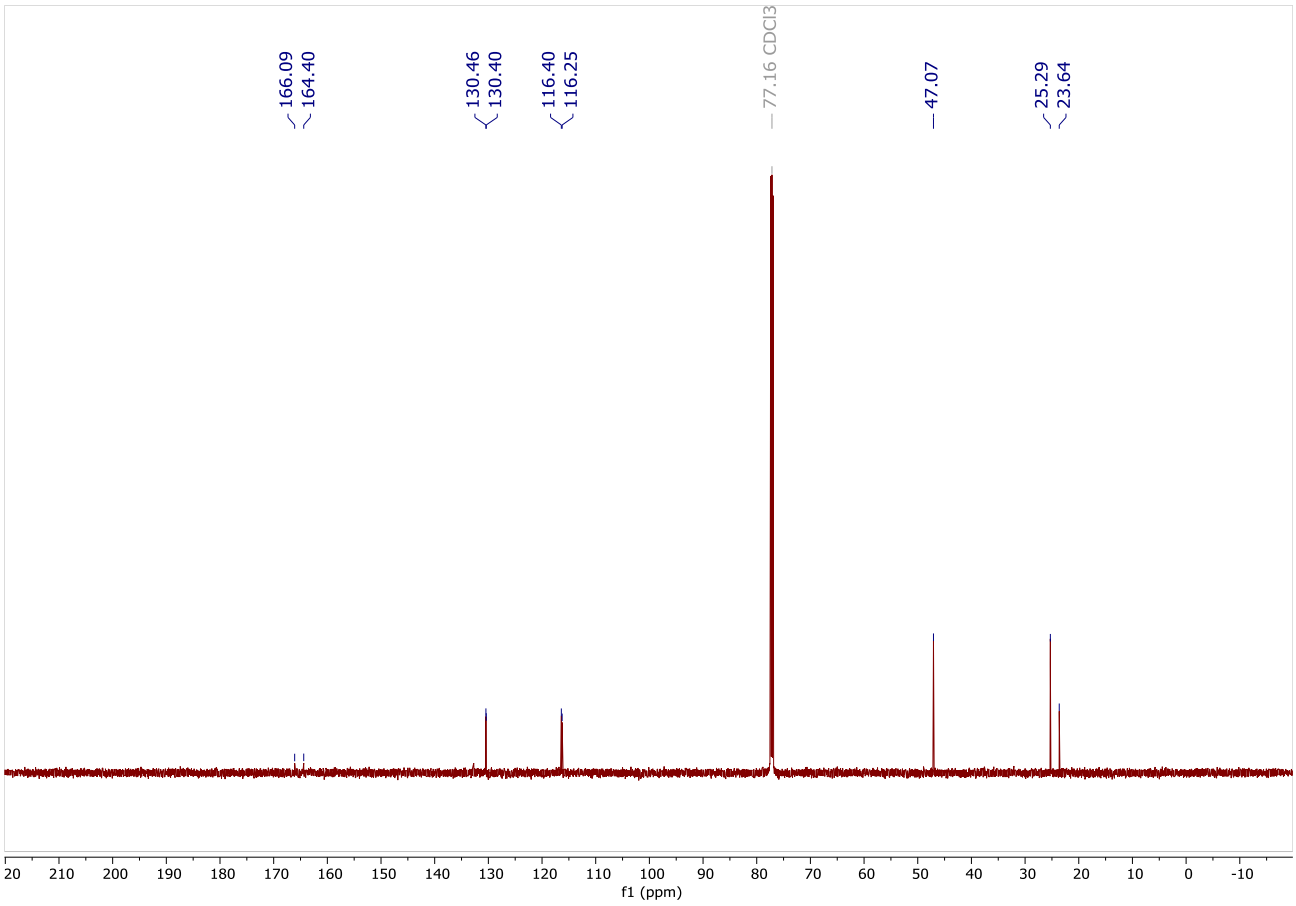
1.03
2.08
2.08
1.07
f1 (ppm)


166.09
164.40
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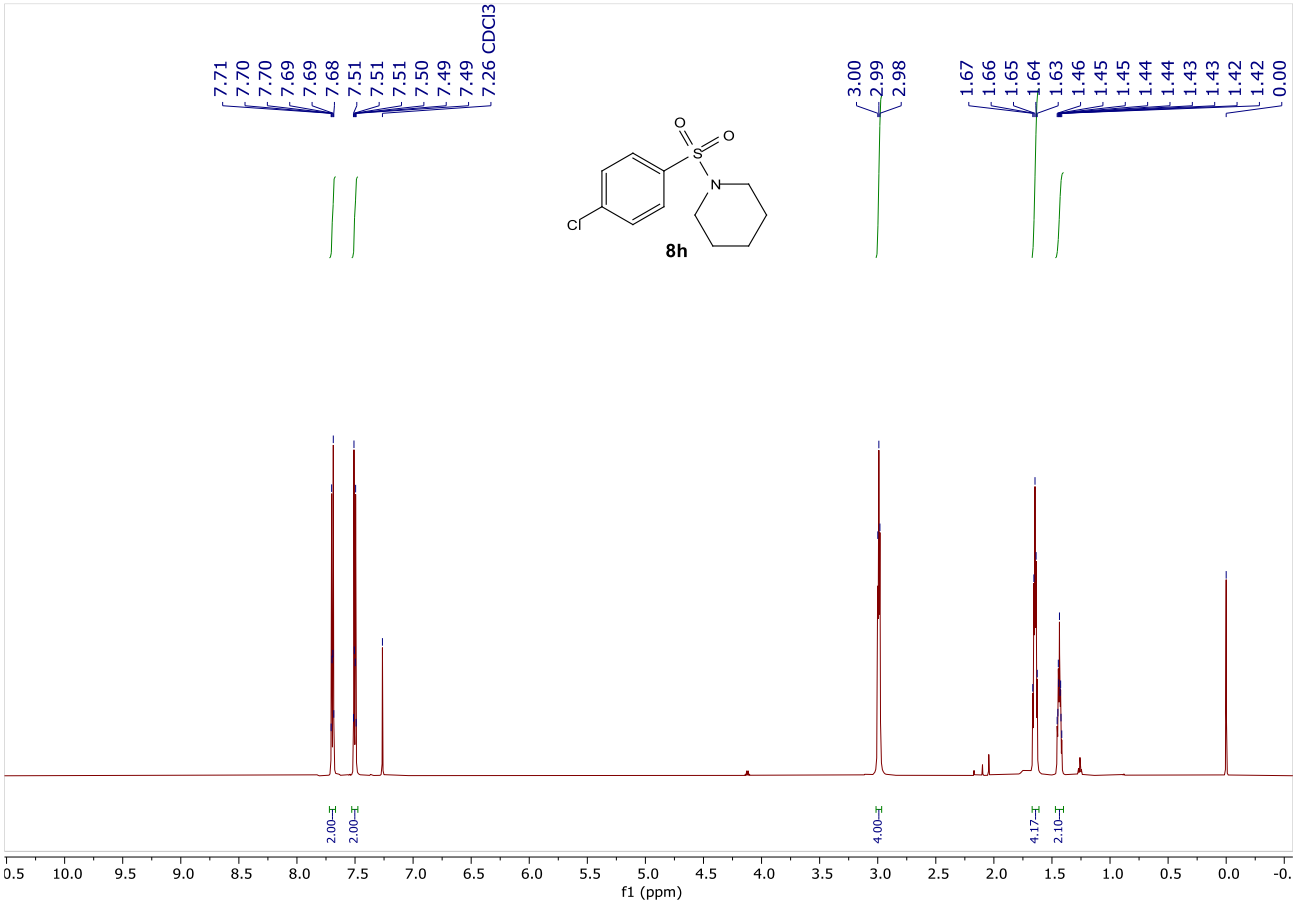
116.40
116.25
77.16 CDCl3
47.07
25.29
23.64
f1 (ppm)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7.70
7.70
7.69
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7.68
7.51
7.51
7.51
7.50
7.49
7.49
7.26 CDCl3
3.00
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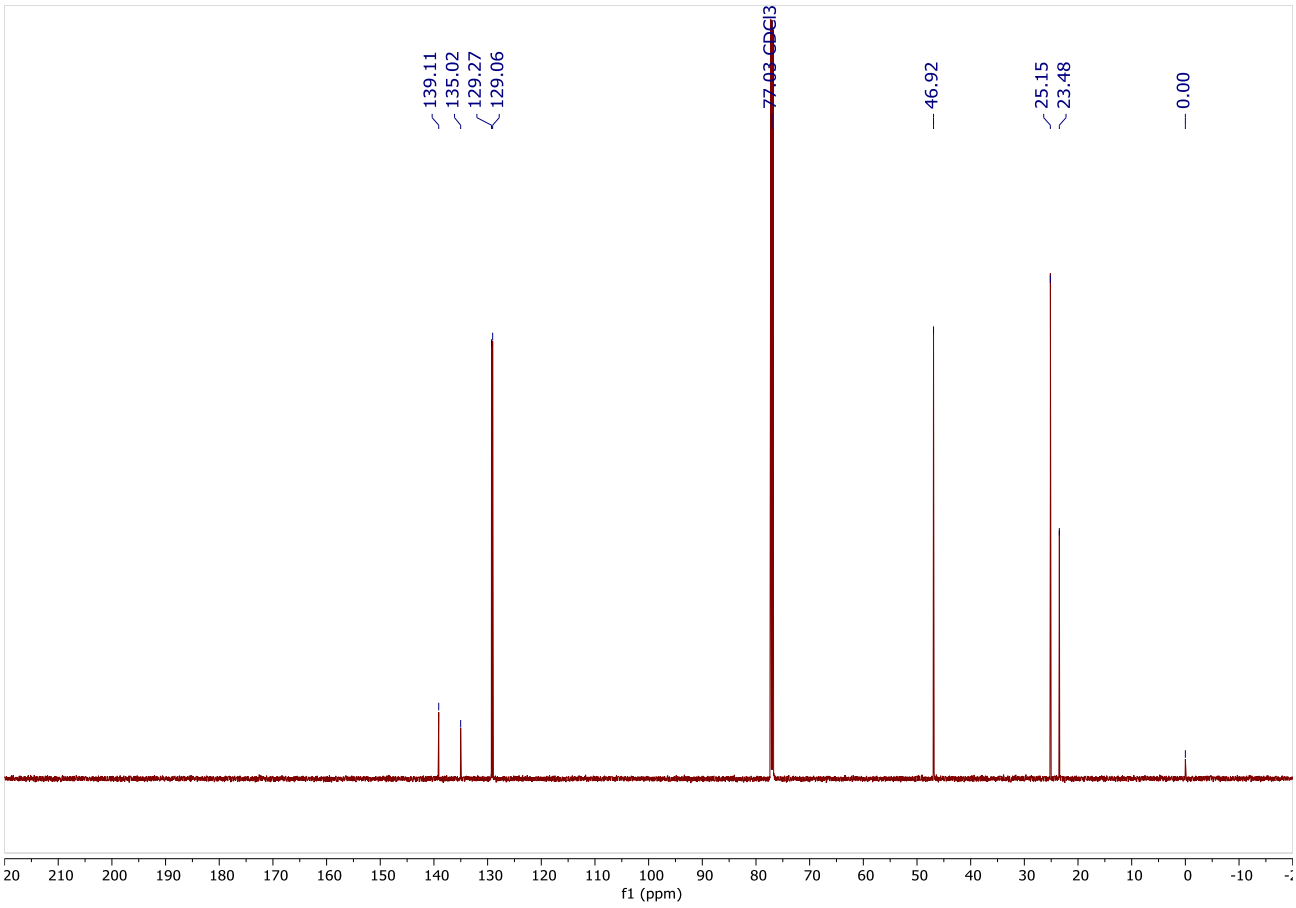
2.98
1.67
1.66
1.65
1.64
1.63
1.46
1.45
1.45
1.44
1.44
1.43
1.43
1.42
1.42
0.00
O
S
O
N
Cl
8h
2.00
2.00
4.00
4.17
2.10
f1 (ppm)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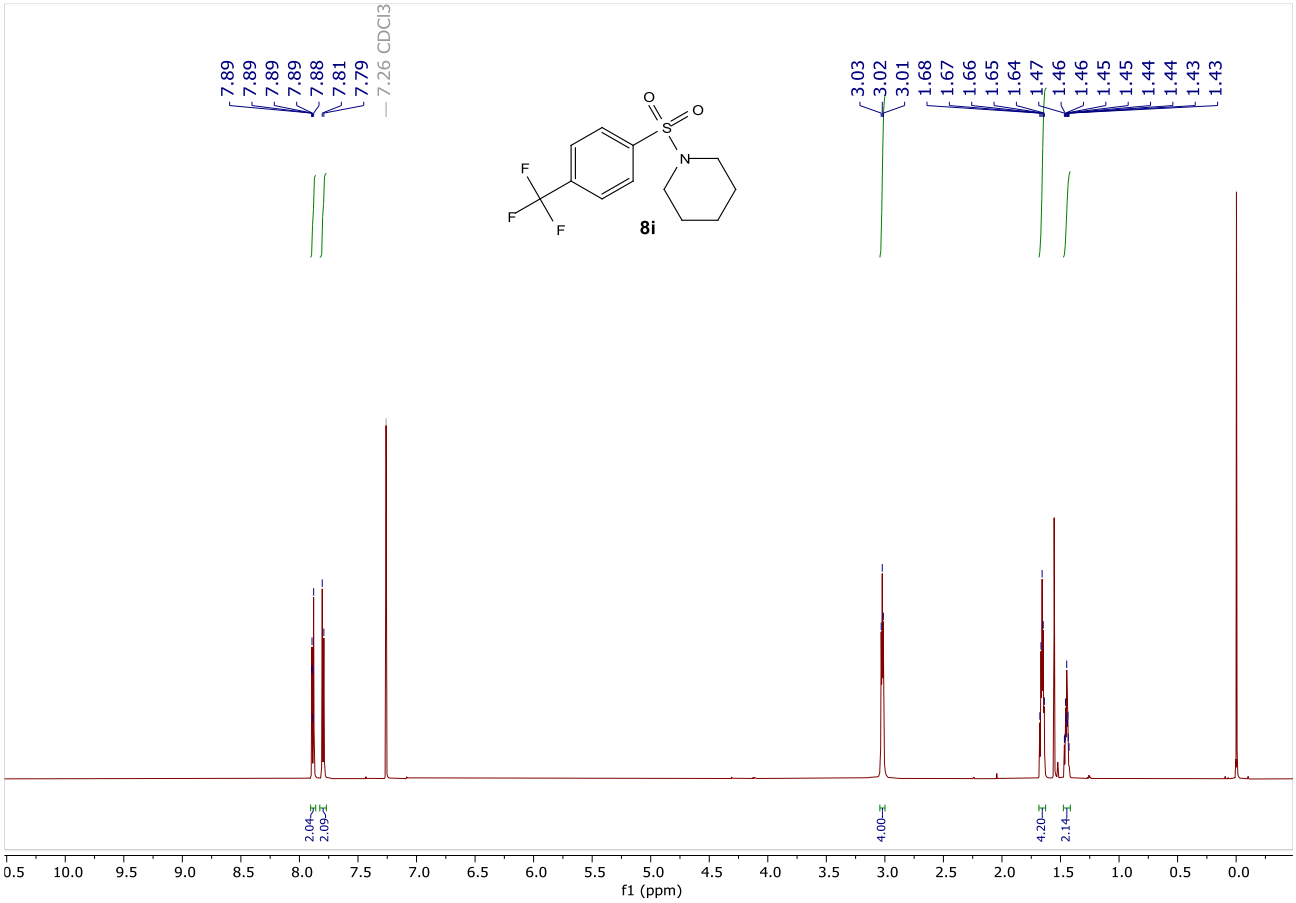
129.27
129.06
77.03 CDCl3
46.92
25.15
23.48
0.00
f1 (ppm)


7.89
7.89
7.89
7.89
7.88
7.81
7.79
7.26 CDCl3
3.03
3.02
3.01
1.68
1.67
1.66
1.65
1.64
1.47
1.46
1.46
1.45
1.45
1.44
1.44
1.43
1.43
O
O
S
N
F
F
F
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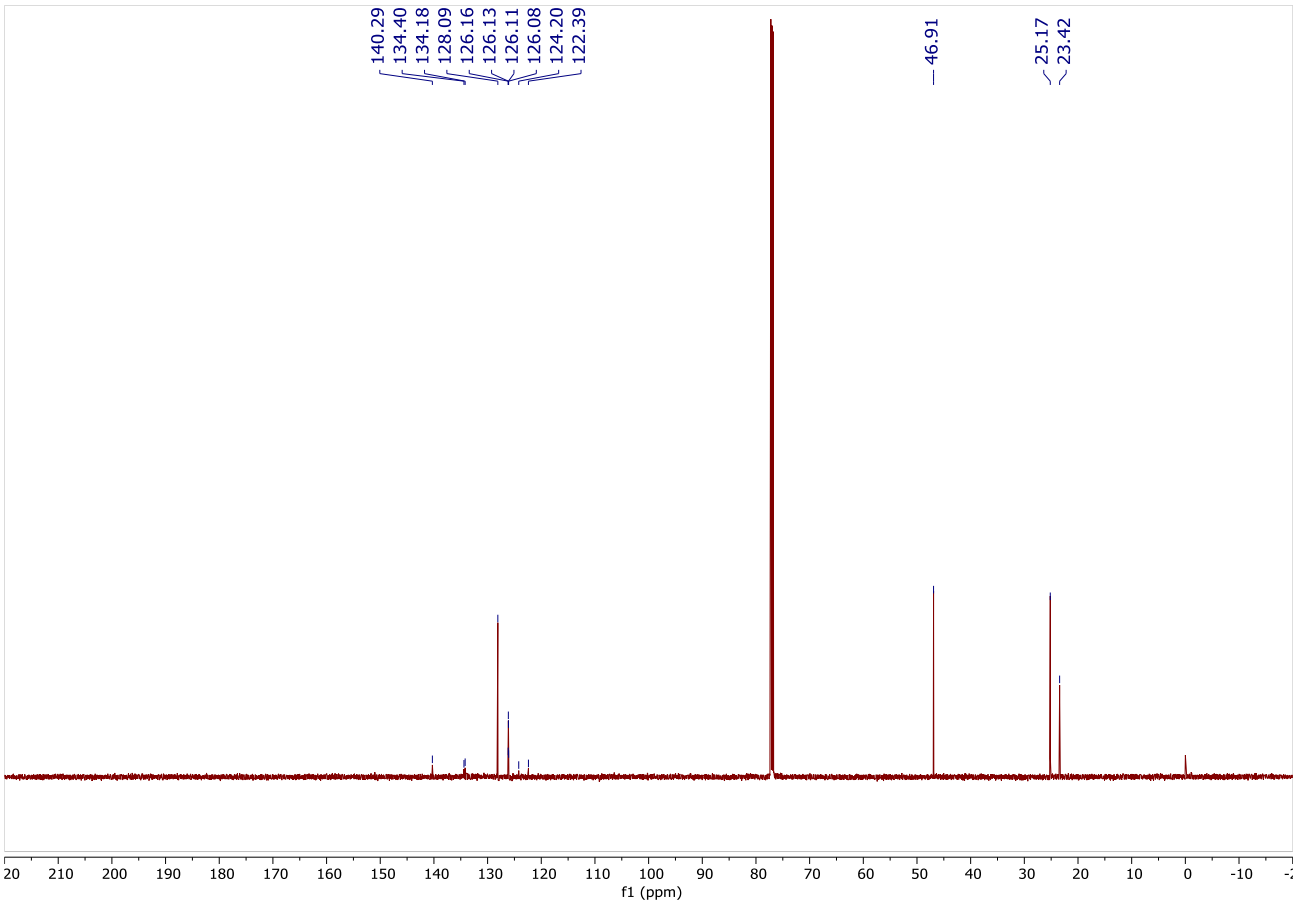
2.09
4.00
4.20
2.14
f1 (ppm)


140.29
134.40
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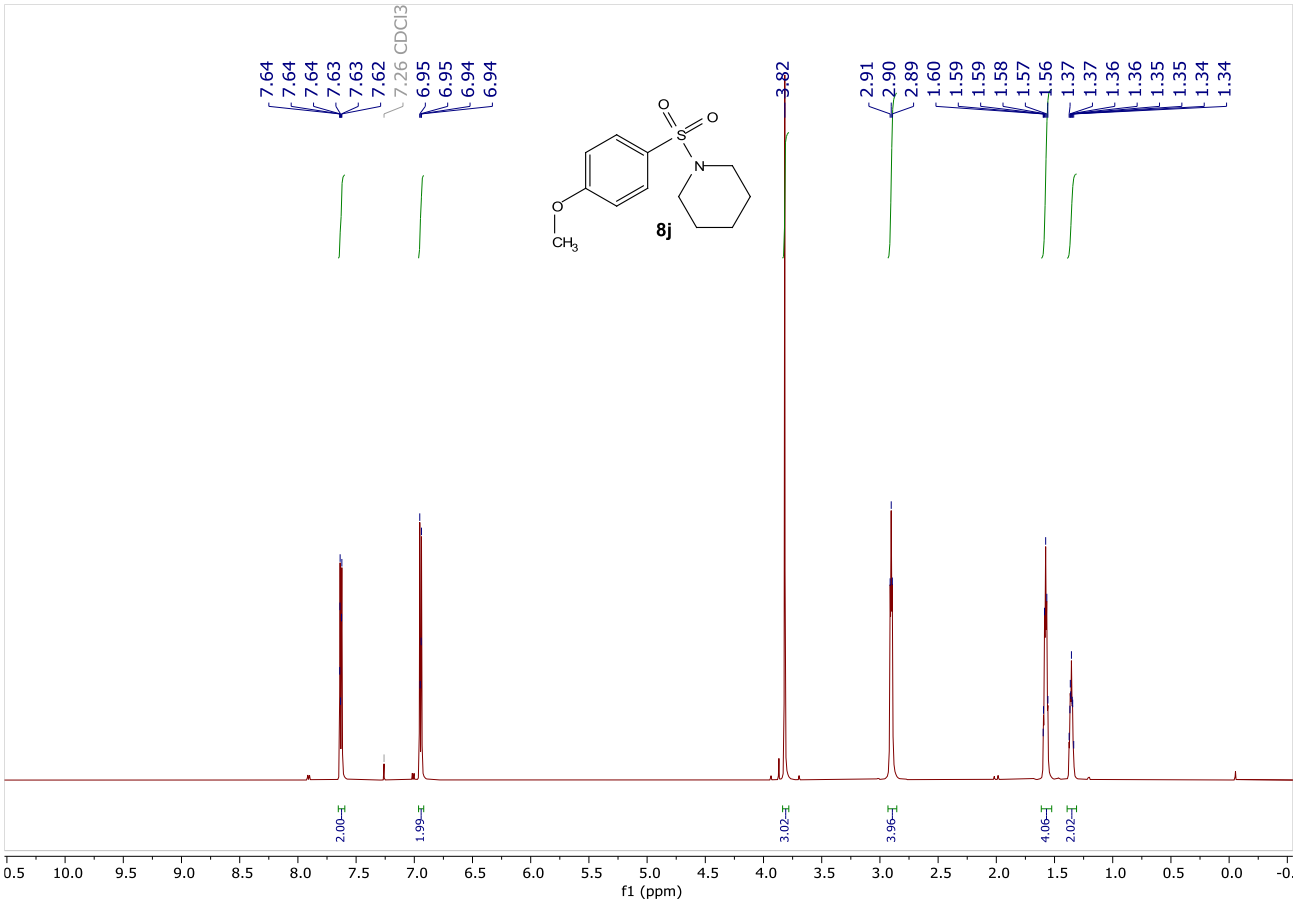
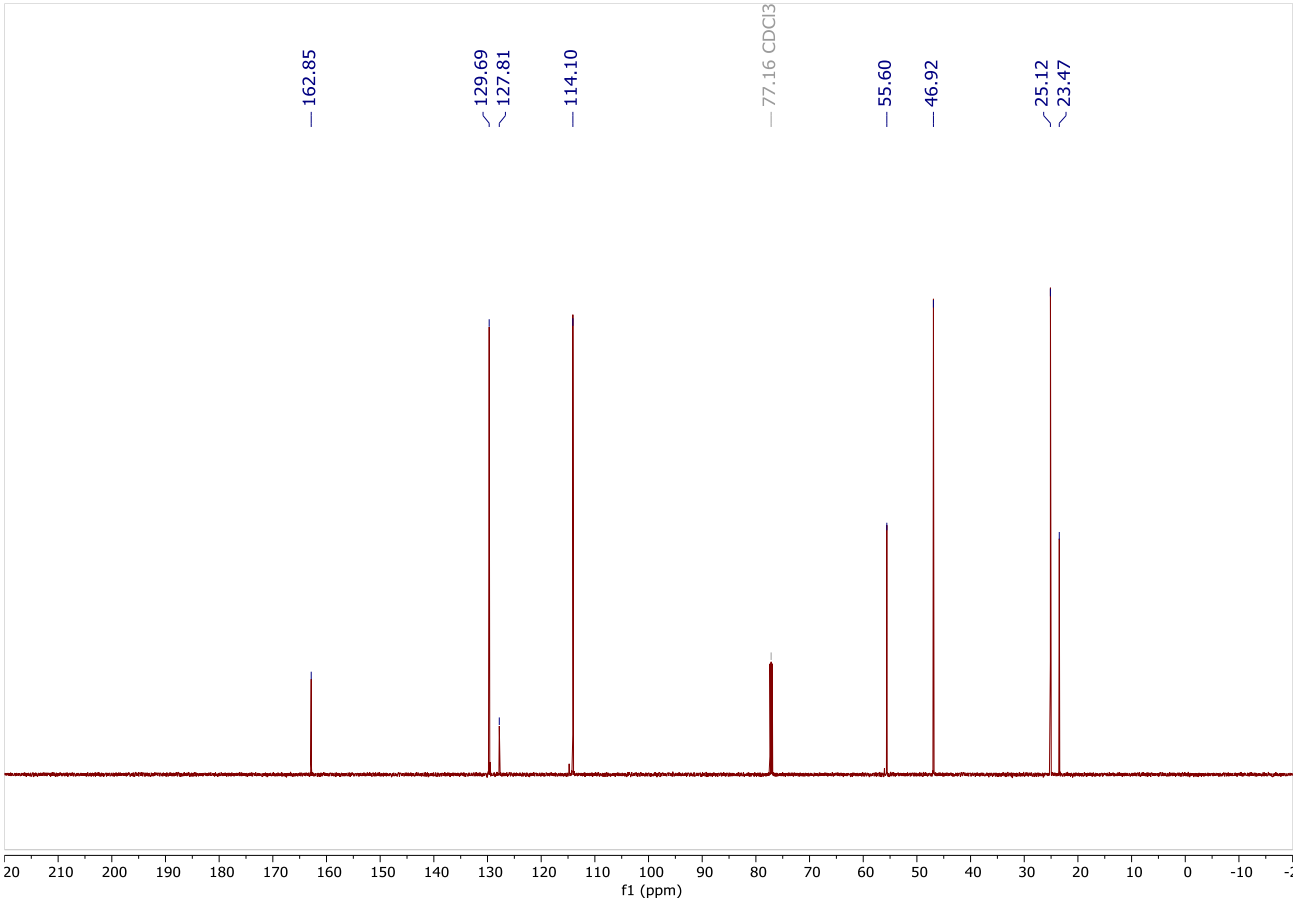
126.16
126.13
126.11
126.08
124.20
122.39
46.91
25.17
23.42
f1 (ppm)


7.64
7.64
7.64
7.63
7.63
7.62
7.26 CDCl3
6.95
6.95
6.94
6.94
3.82
2.91
2.90
2.89
1.60
1.59
1.59
1.58
1.57
1.56
1.37
1.37
1.36
1.36
1.35
1.35
1.34
1.34
O
S
O
N
O
CH3
8j
2.00
1.99
3.02
3.96
4.06
2.02
f1 (ppm)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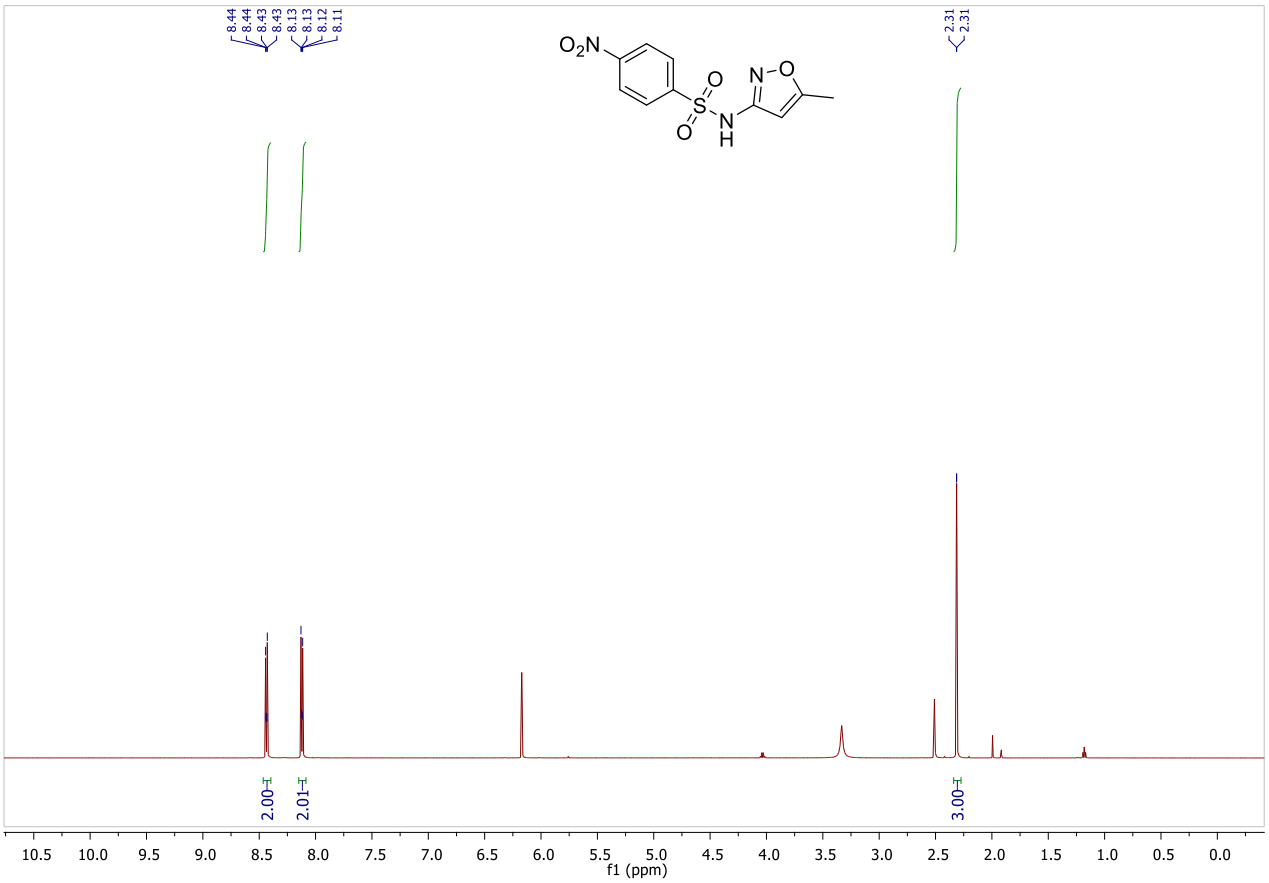
127.81
114.10
77.16 CDCl3
55.60
46.92
25.12
23.47
f1 (ppm)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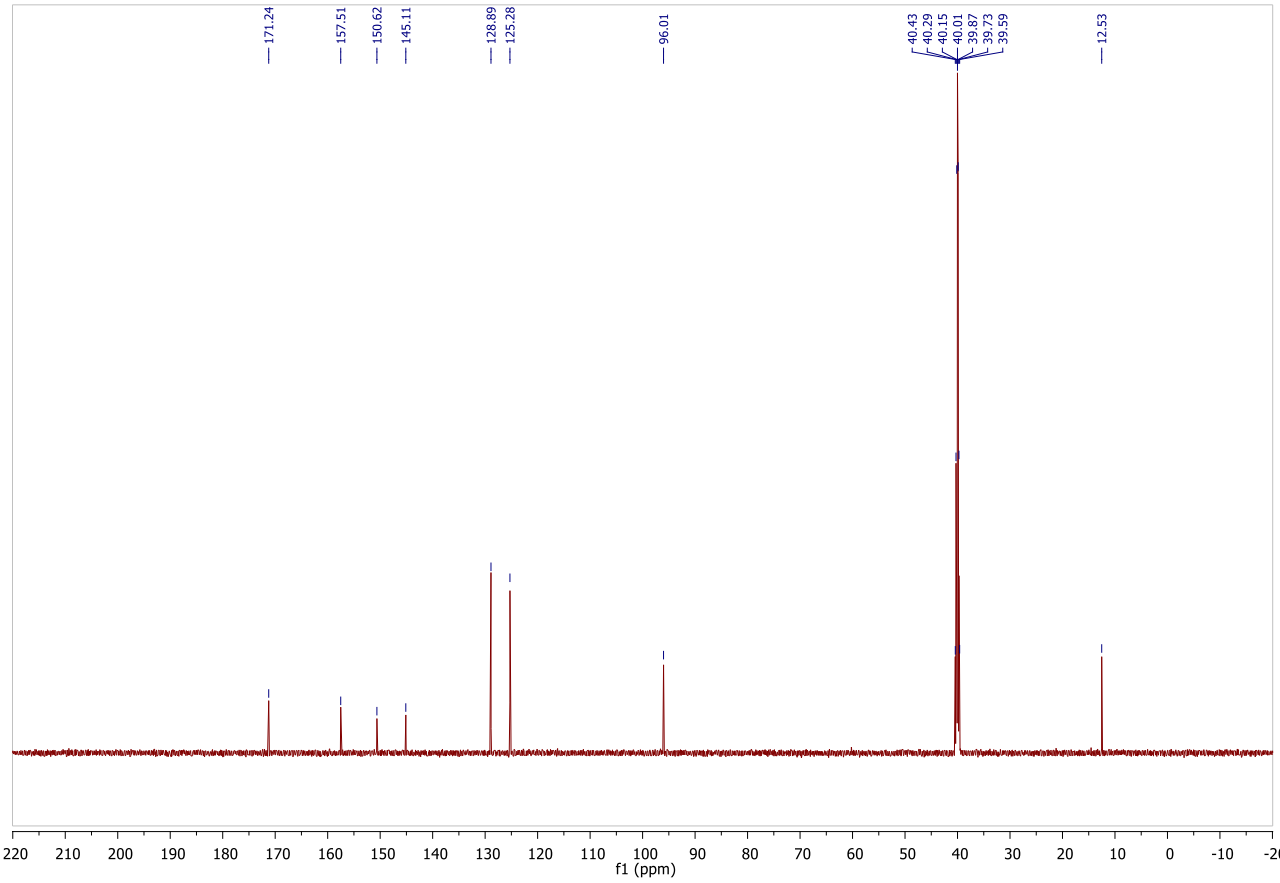
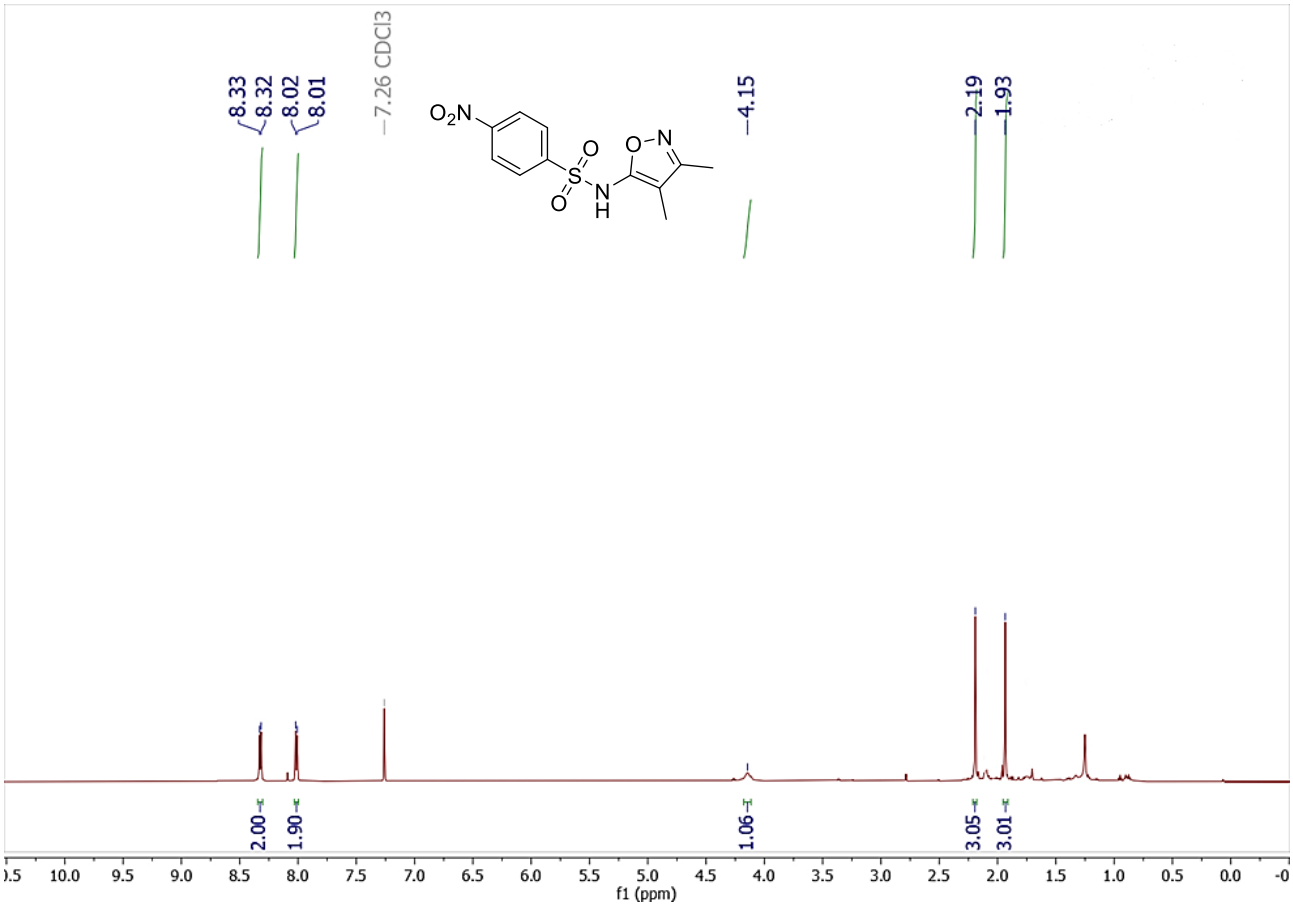
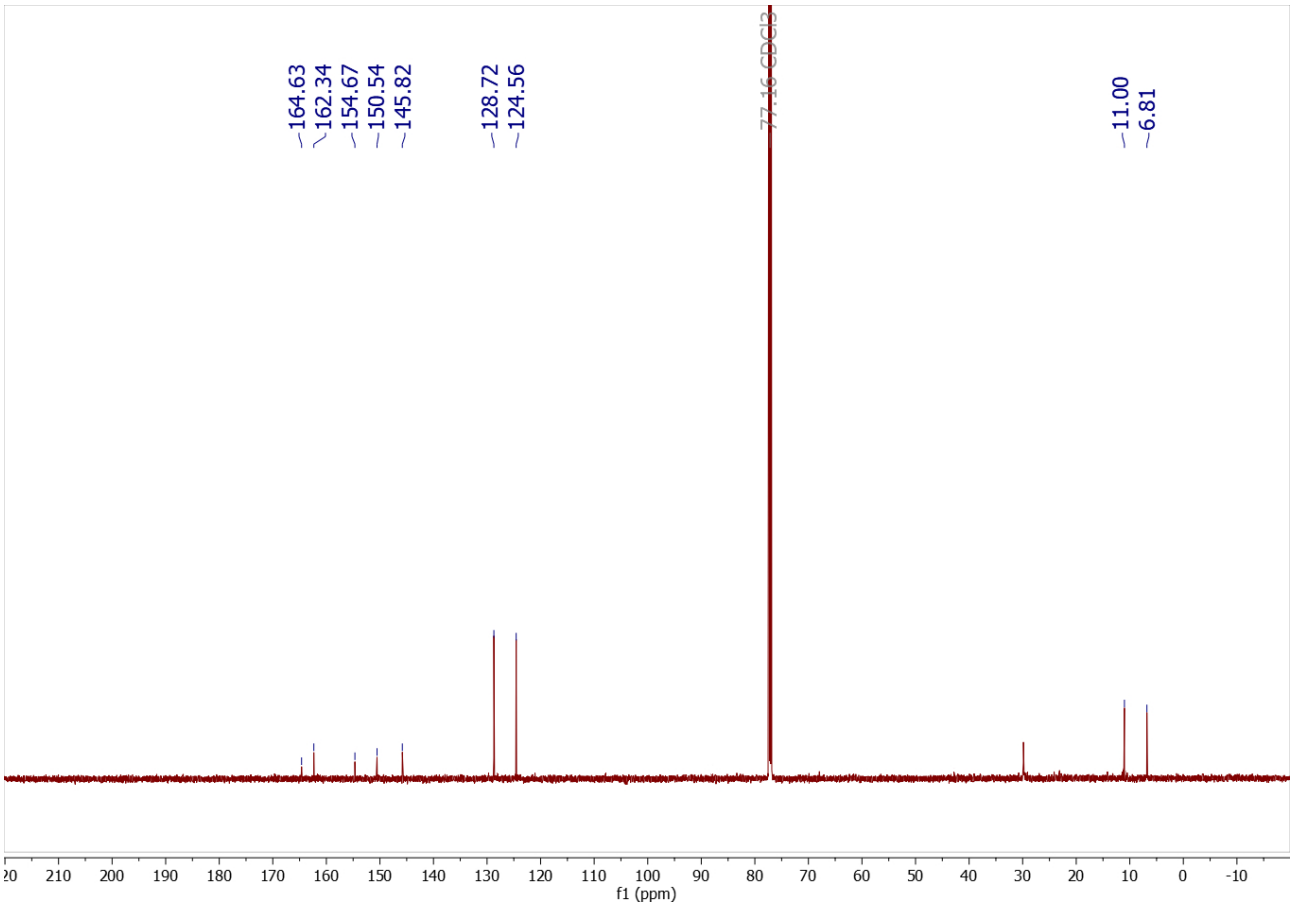
8.44
8.43
8.43
8.13
8.13
8.12
8.11
2.31
2.31
O2N
S
O
O
N
H
N
O
2.00
2.01
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


171.24
157.51
150.62
145.11
128.89
125.28
96.01
40.43
40.29
40.15
40.01
39.87
39.73
39.59
12.53
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


8.33
8.32
8.02
8.01
7.26 CDCl3
4.15
2.19
1.93
2.00
1.90
1.06
3.05
3.01
f1 (ppm)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154.67
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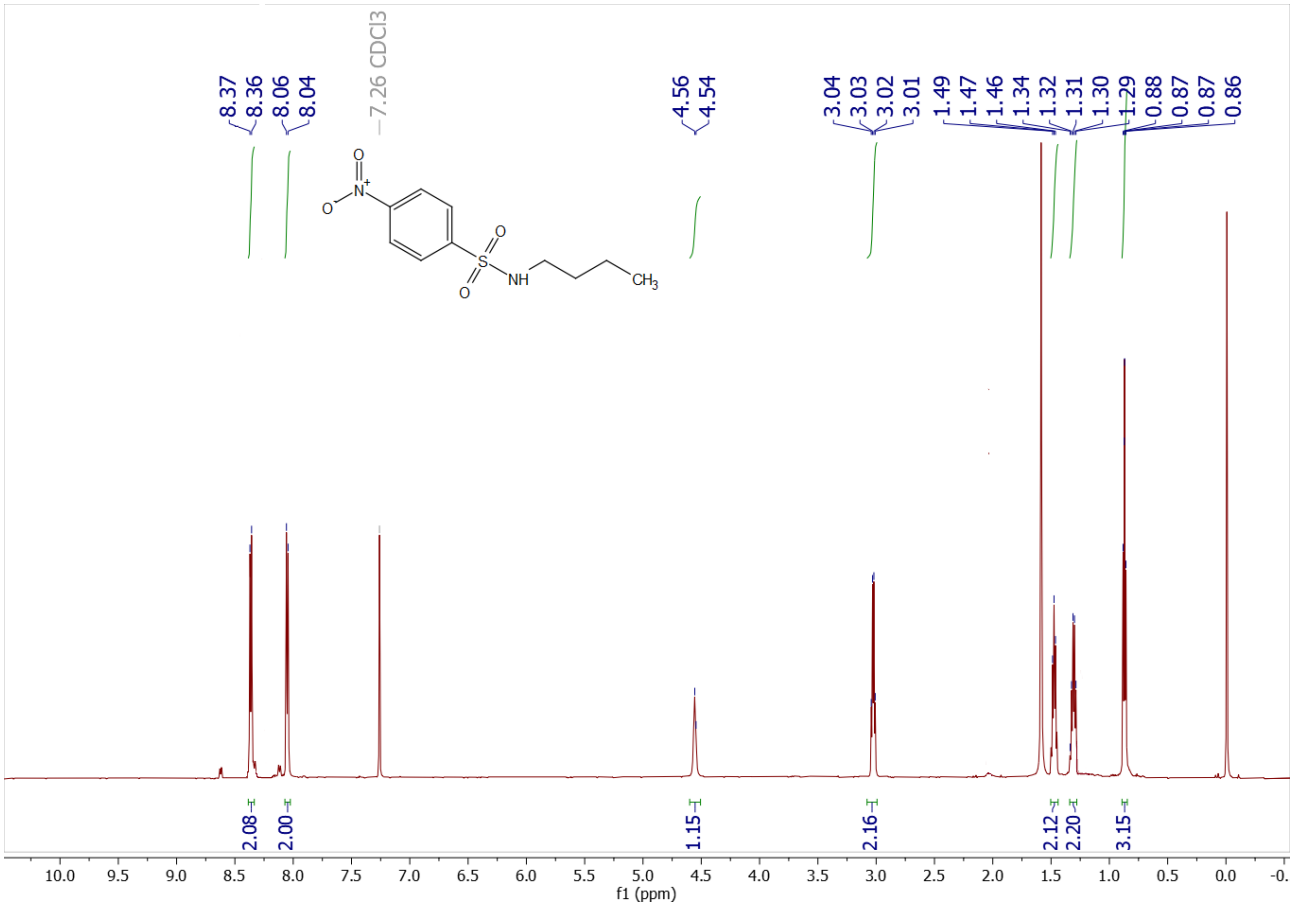
145.82
128.72
124.56
77.16 CDCl3
11.00
6.81
f1 (ppm)


8.37
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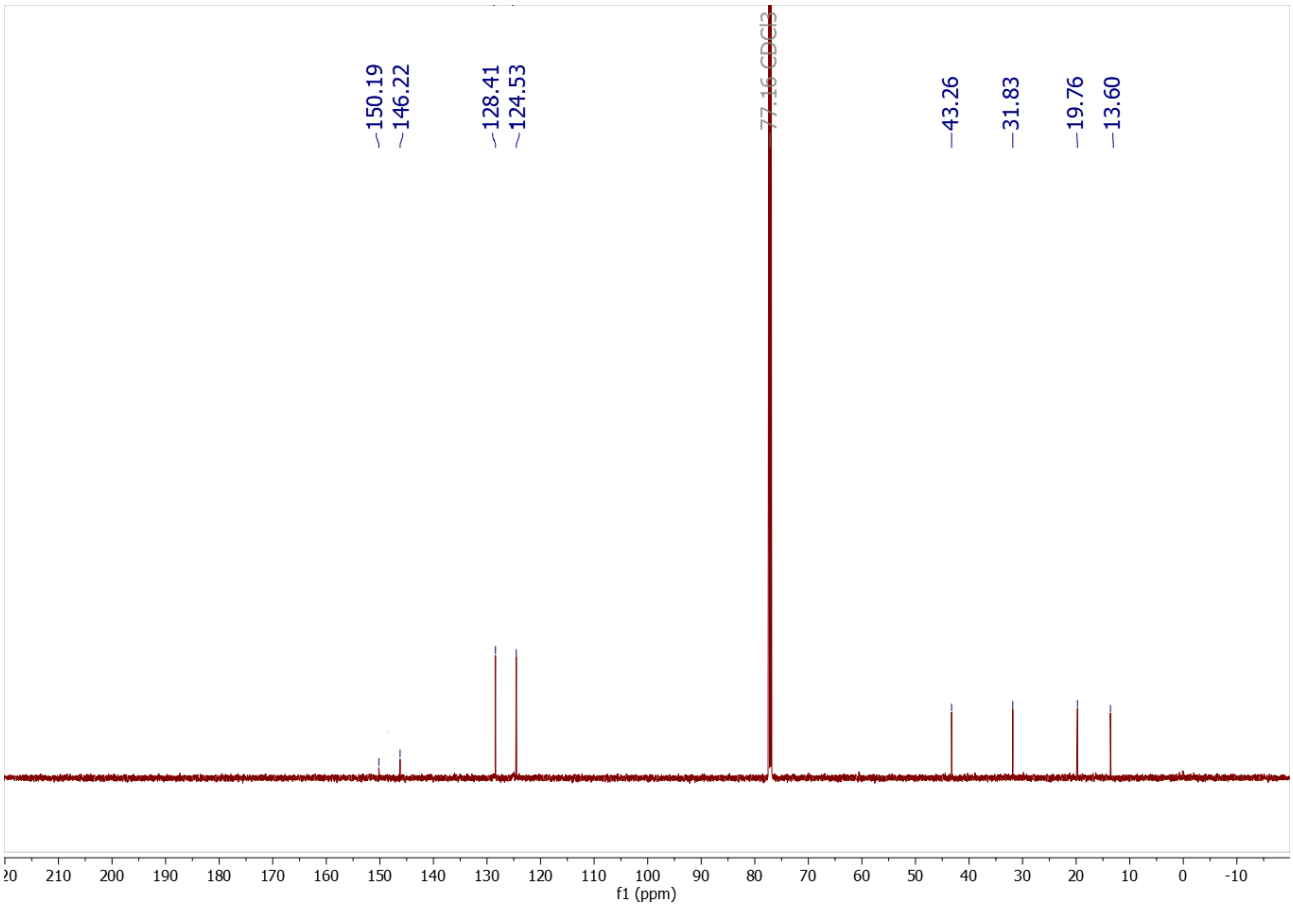
8.06
8.04
7.26 CDCl3
4.56
4.54
3.04
3.03
3.02
3.01
1.49
1.47
1.46
1.34
1.32
1.31
1.30
1.29
0.88
0.87
0.87
0.86
2.08
2.00
1.15
2.16
2.12
2.20
3.15
f1 (ppm)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128.41
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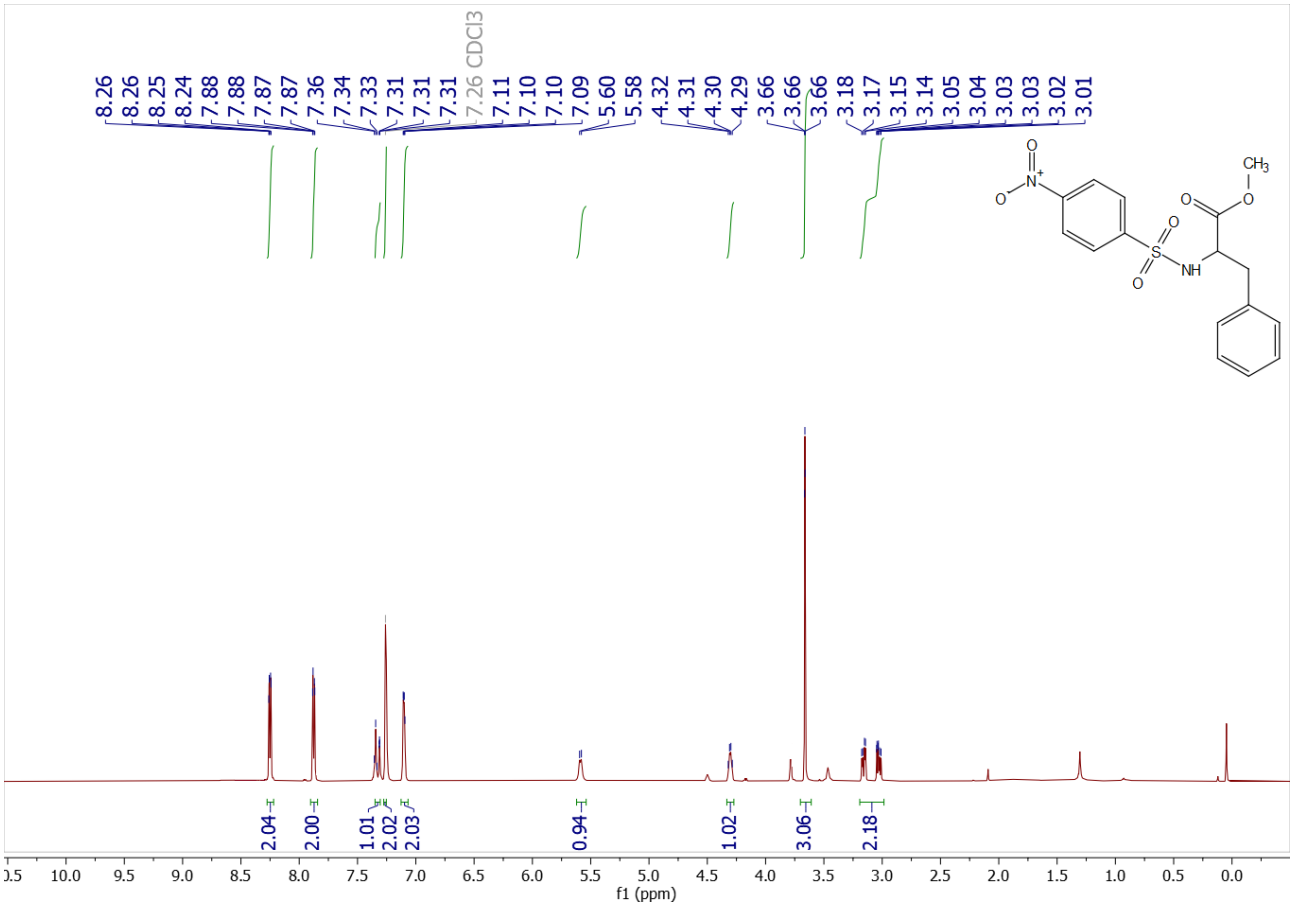
43.26
31.83
19.76
13.60
f1 (ppm)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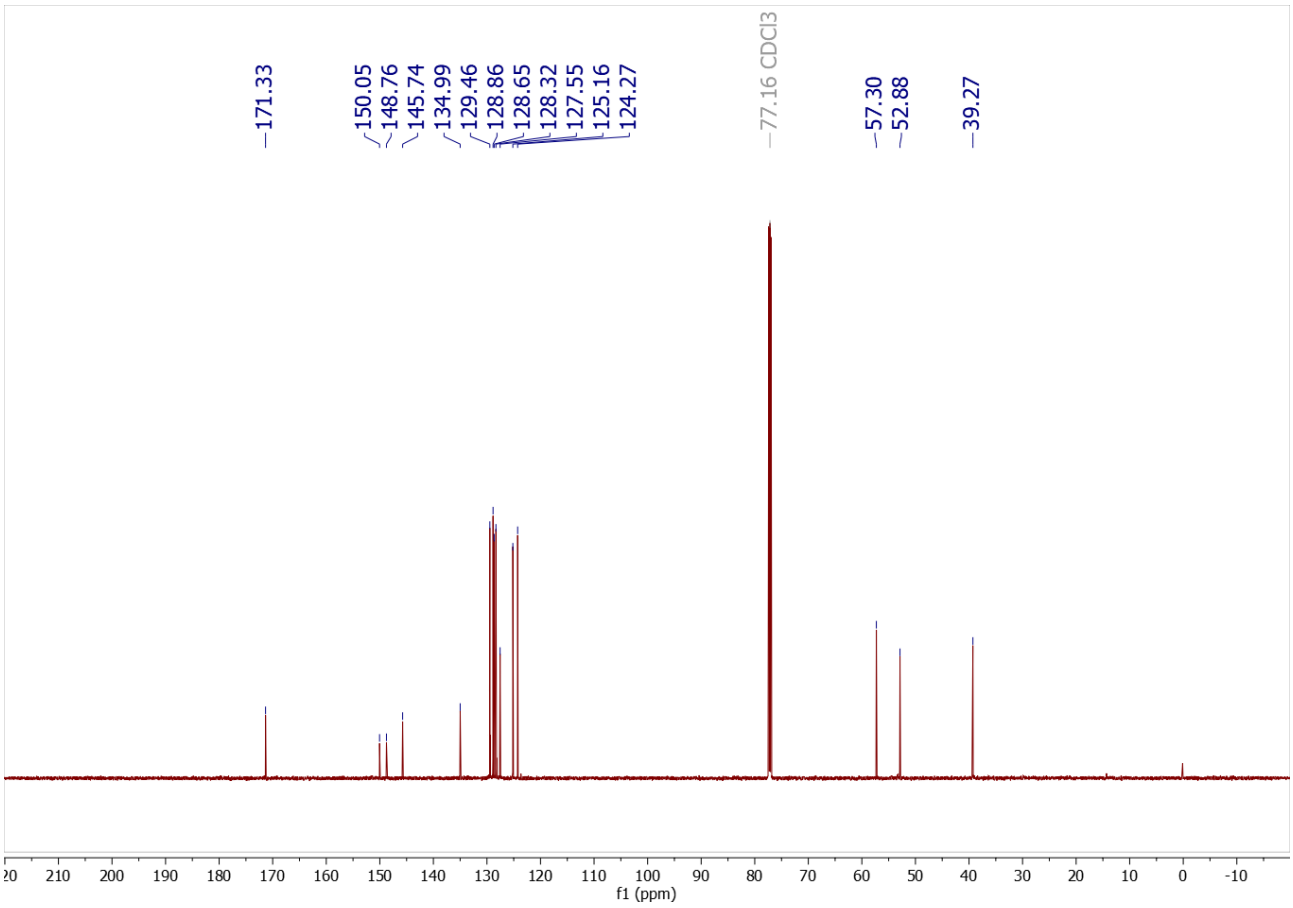
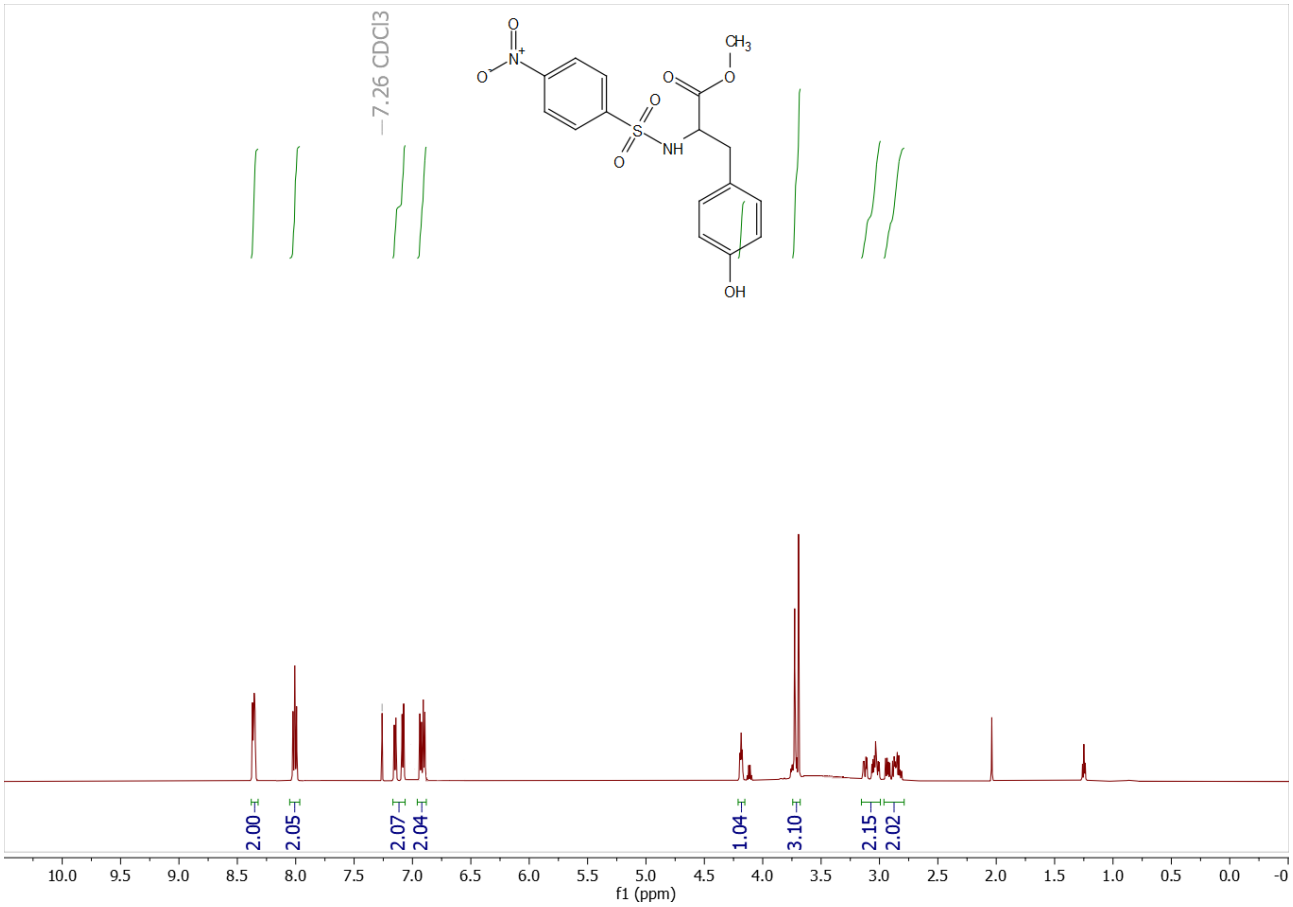
8.24
7.88
7.88
7.87
7.87
7.36
7.34
7.33
7.31
7.31
7.31
7.26 CDCl3
7.11
7.10
7.10
7.09
5.60
5.58
4.32
4.31
4.30
4.29
3.66
3.66
3.66
3.18
3.17
3.15
3.14
3.05
3.04
3.03
3.03
3.02
3.01
2.04
2.00
1.01
2.02
2.03
0.94
1.02
3.06
2.18
f1 (ppm)


171.33
150.05
148.76
145.74
134.99
129.46
128.86
128.65
128.32
127.55
125.16
124.27
77.16 CDCl3
57.30
52.88
39.27
f1 (ppm)


7.26 CDCl3
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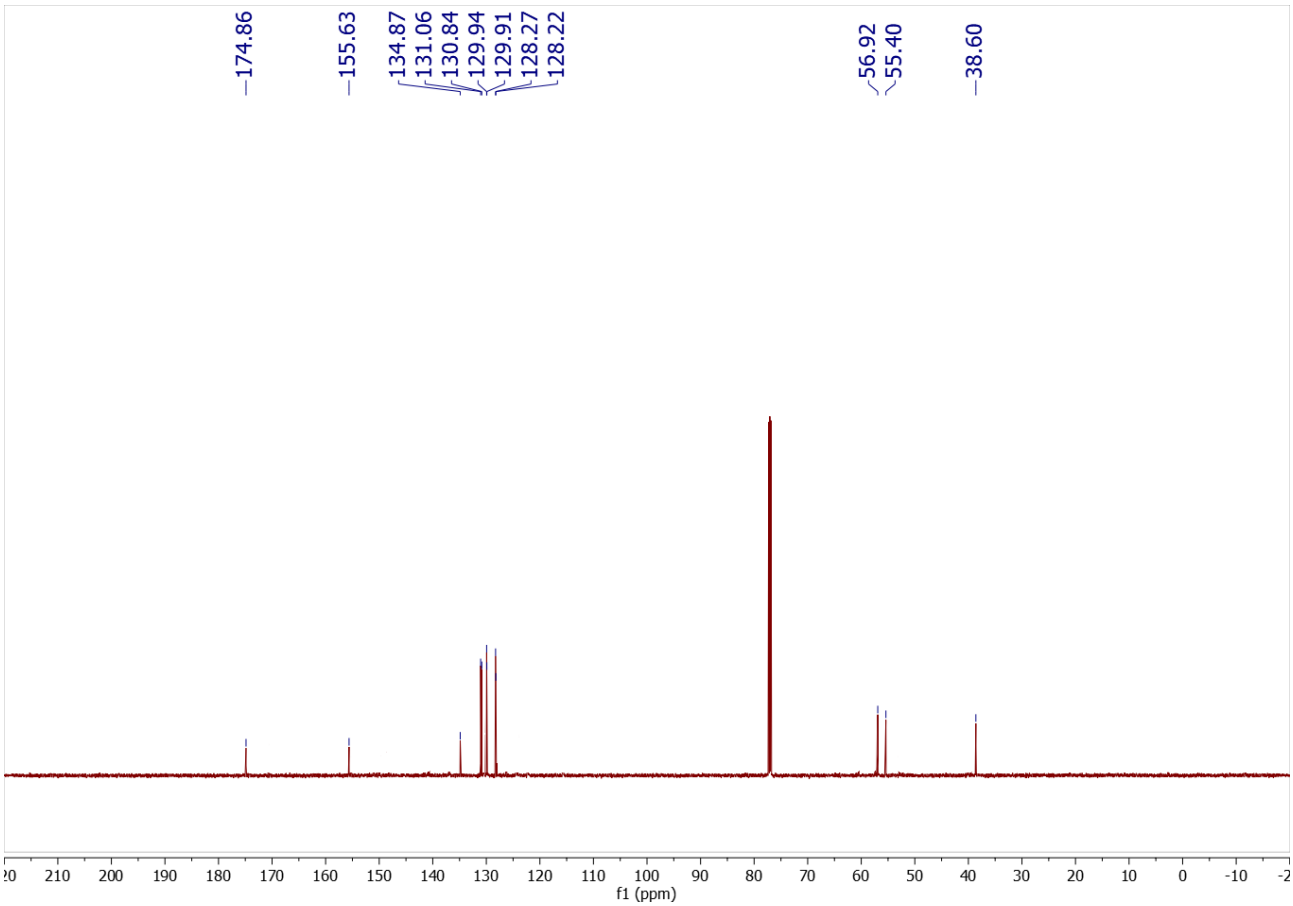
2.05
2.07
2.04
1.04
3.10
2.15
2.02
f1 (ppm)


174.86
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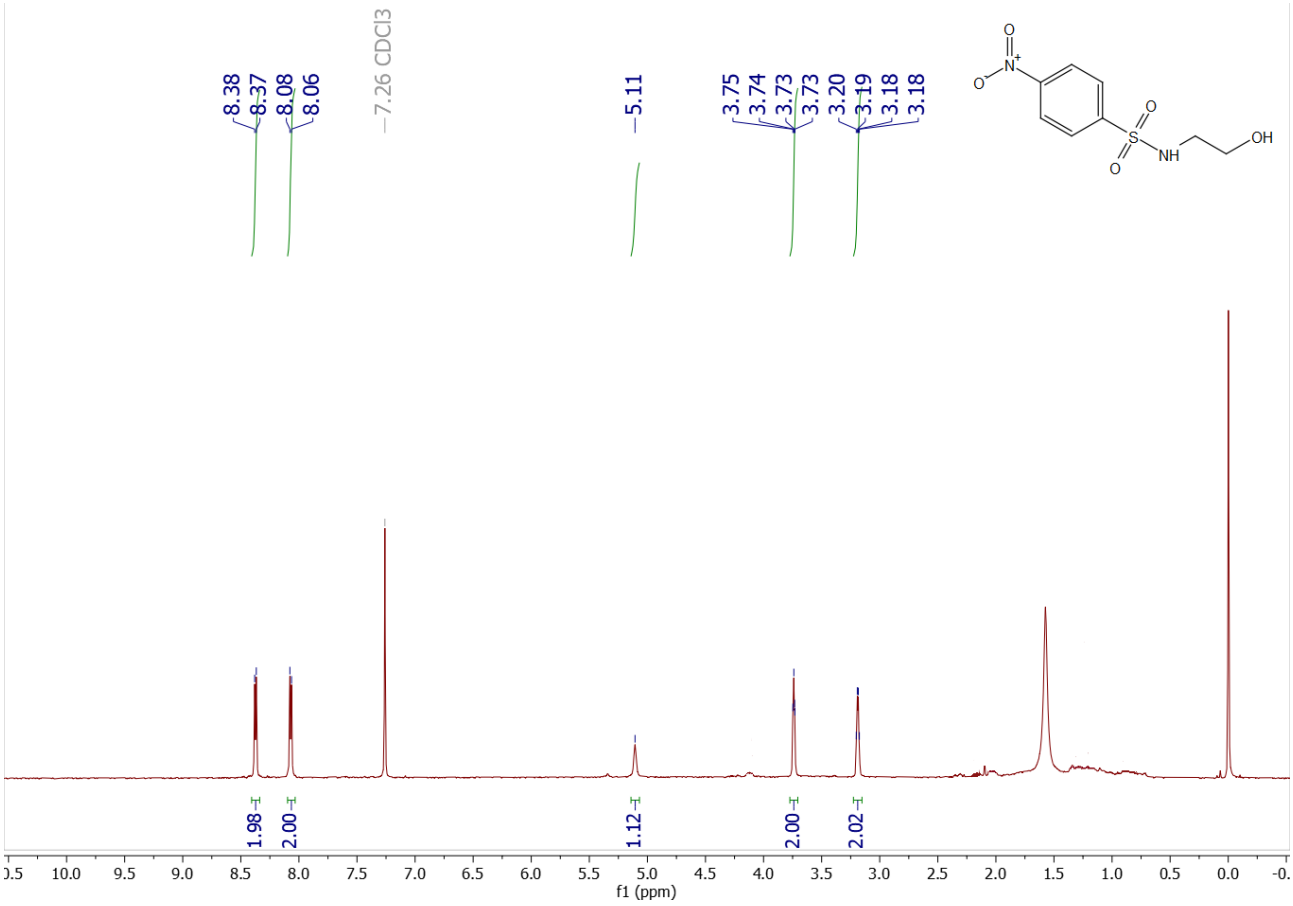
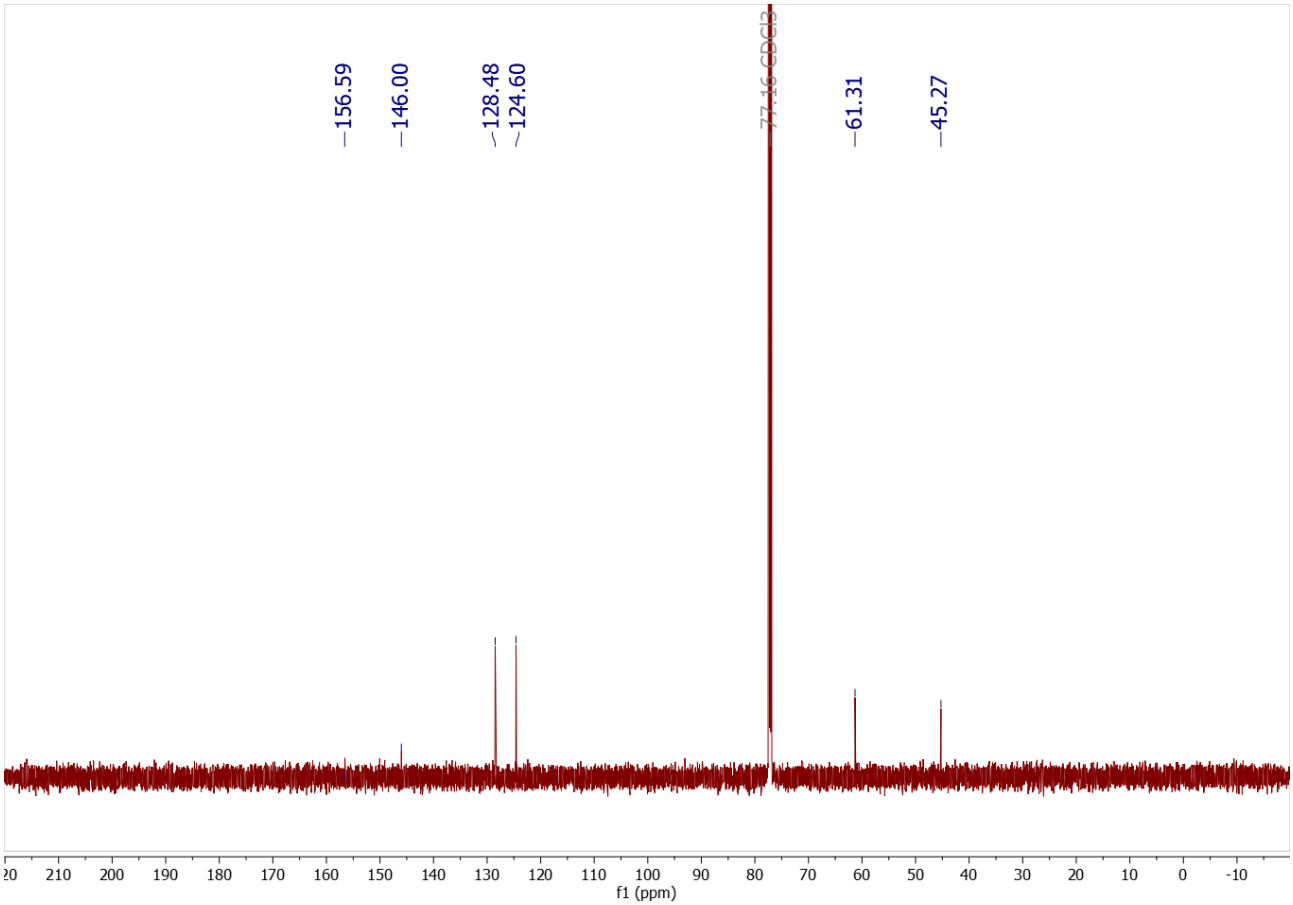
130.84
129.94
129.91
128.27
128.22
56.92
55.40
38.60
f1 (ppm)


8.38
8.37
8.08
8.06
7.26 CDCl3
5.11
3.75
3.74
3.73
3.73
3.20
3.19
3.18
3.18
O
N+
O-
O
S
O
NH
OH
1.98
2.00
1.12
2.00
2.02
f1 (ppm)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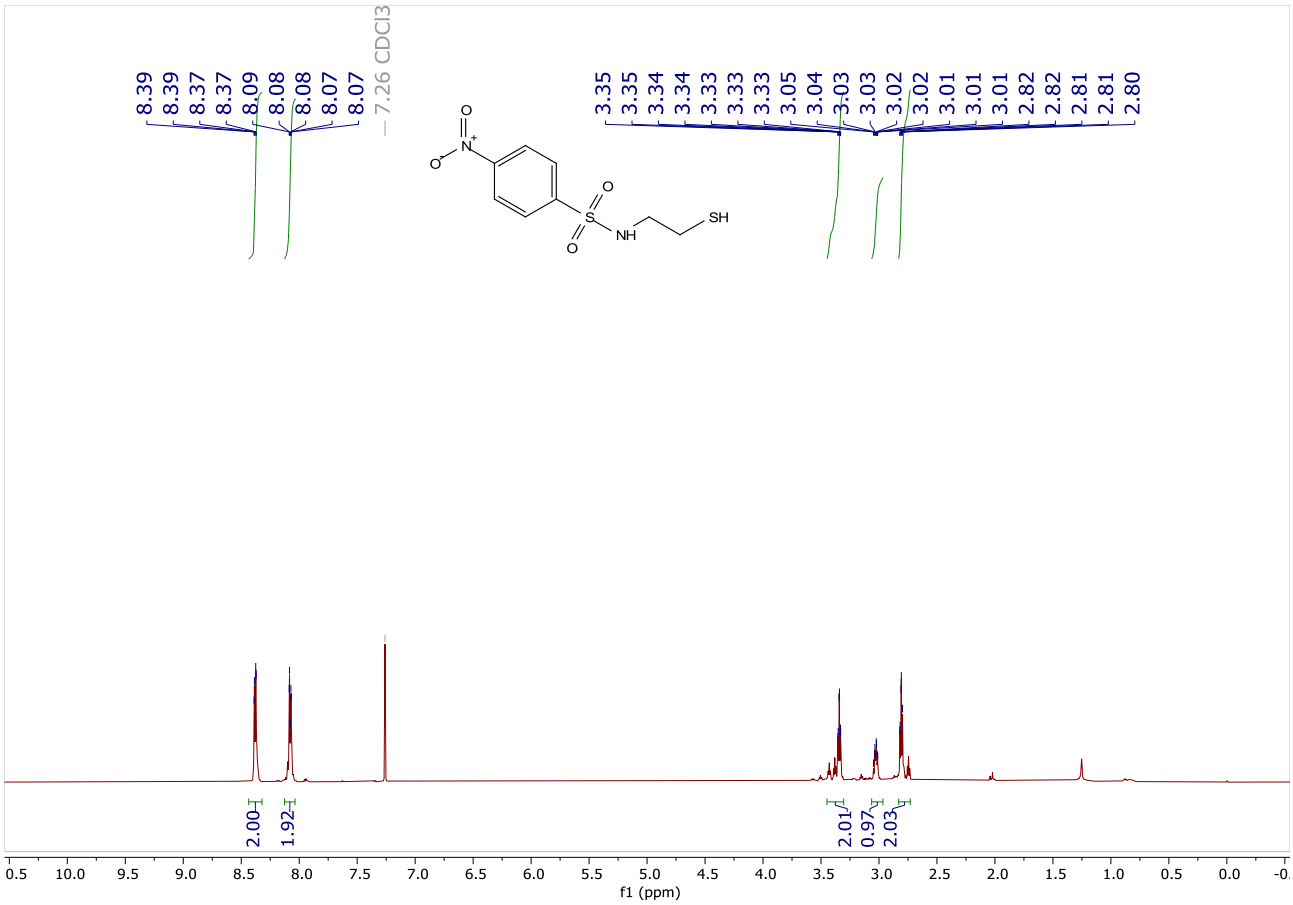
124.60
77.16 CDCl3
61.31
45.27
f1 (ppm)


8.39
8.39
8.37
8.37
8.09
8.08
8.08
8.07
8.07
7.26 CDCl3
3.35
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3.34
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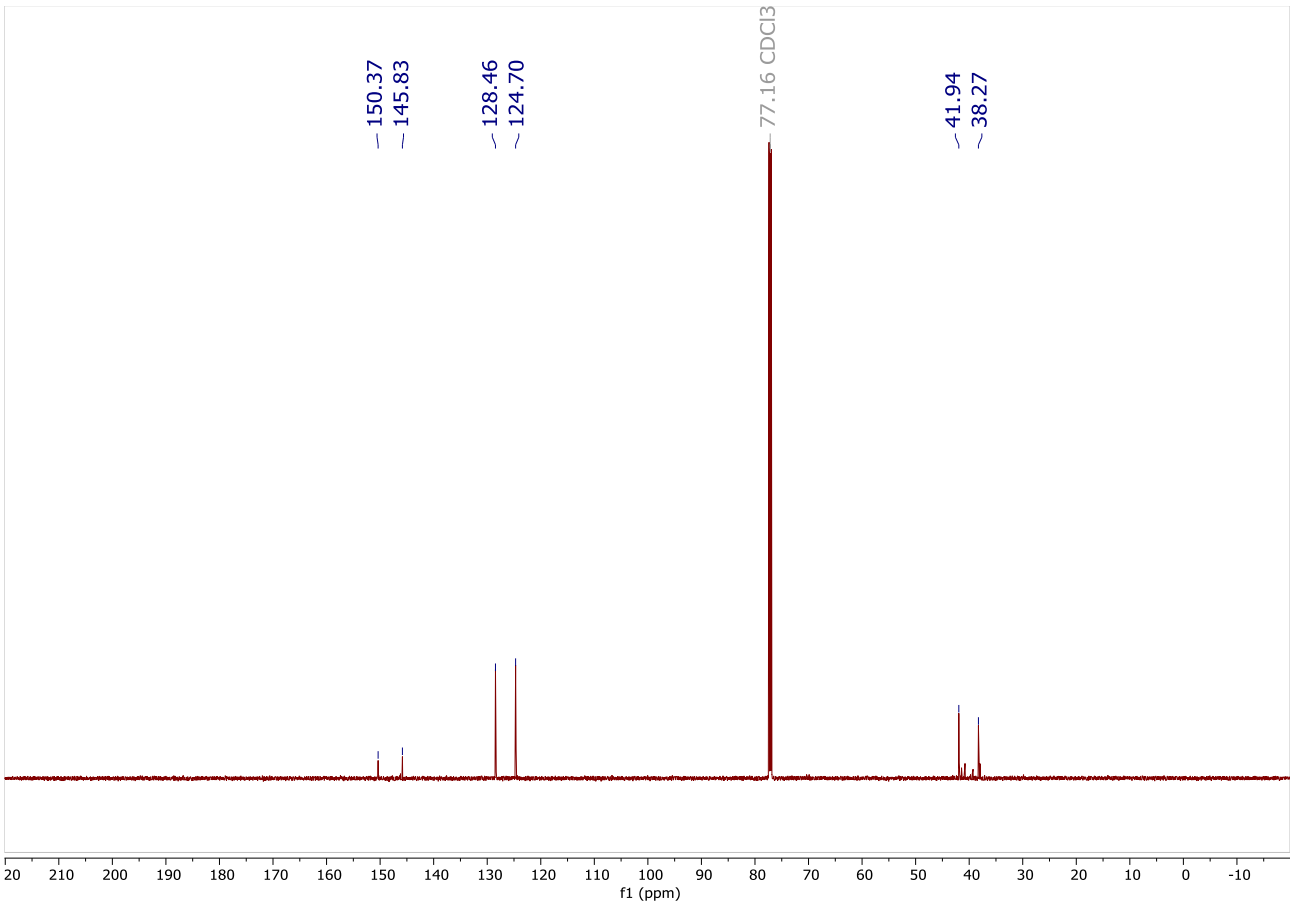
3.33
3.33
3.33
3.05
3.04
3.03
3.03
3.02
3.02
3.01
3.01
3.01
2.82
2.82
2.81
2.81
2.80
O
N+
O-
O
S
O
NH
SH
2.00
1.92
2.01
0.97
2.03
f1 (ppm)


150.37
145.83
128.46
124.70
77.16 CDCl3
41.94
38.27
f1 (ppm)

7.4 Syntheses and Characterizations of Compounds in Chapter IV

Synthesis of 2,2'-Bi(1,3,6,2-dioxazaborocane) compound **1**

A 10 mL stainless steel jar equipped with one milling ball of the same material (8 mm φ, $mass_{TOT}$ 2.09 g) was filled with tetrahydroxydiboron (1 mmol) and diethanolamine (2 mmol). The vessel was then closed, and the reaction was conducted for 20 minutes at 30 Hz. At the end of the reaction, the mixture was rinsed in EtOAc (10 mL), and the solvent was removed with a Pasteur pipette. Lastly, pure compound 1 evaporated under the fume hood for around 20 minutes.

General procedure for the synthesis of primary and secondary alcohols

A 10 mL stainless steel jar equipped with one milling ball of the same material (8 mm φ, masstot 2.09 g) was filled with aldehyde **IV-2a-IV-2u** (1 mmol) or ketone **IV-4a-IV-4f**, diboron compound **1** (2 mmol) and H_2O (2 mmol). Adding 1 mmol of LiCl was required for substrates **IV-2q-IV-2u** and ketones **IV-4a-IV-4f**. The vessel was then closed, and the reaction was conducted under ball milling conditions for 90 min at 30 Hz. At the end of the reaction, the crude was recovered with EtOAc (10 mL) and filtered on paper. A short silica pad (1 g) was required for further purification in a few cases for ketones and aliphatic aldehydes. Lastly, the solvent was removed under reduced pressure to afford the pure alcohols **IV-3a-IV-3u** and **IV-5a-IV-5f**.

Carbonyl competition experiments

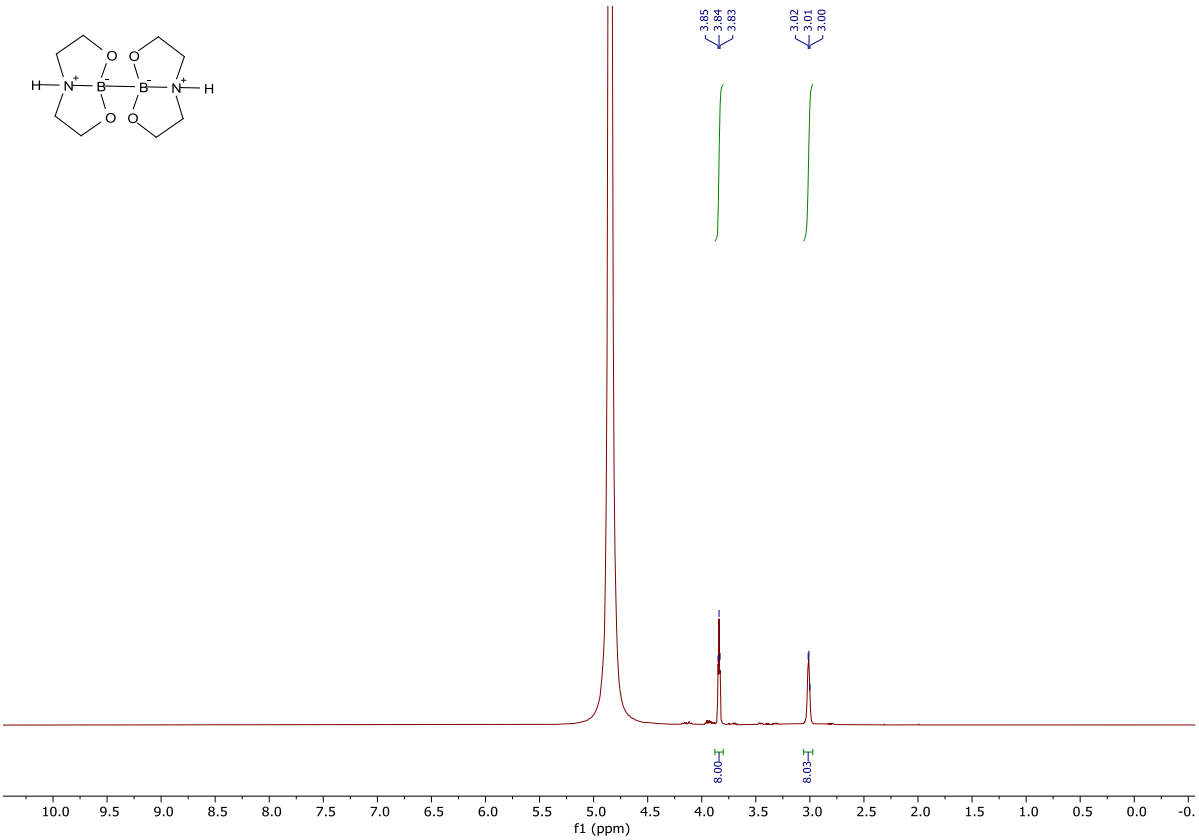
A 5 mL stainless steel jar equipped with one milling ball of the same material (8 mm φ, $mass_{tot}$ 2.09 g) was filled with aldehyde **IV-2a** (1 mmol) and ketone **IV-4a** (1 mmol), diboron compound **1** (1 mmol) and H_2O (1 mmol). The vessel was then closed, and the reaction was conducted under ball milling conditions for 90 min at 30 Hz. At the end of the reaction, the crude was recovered with EtOAc (10 mL) and filtered on paper. The crude was analyzed *via* GC-MS.

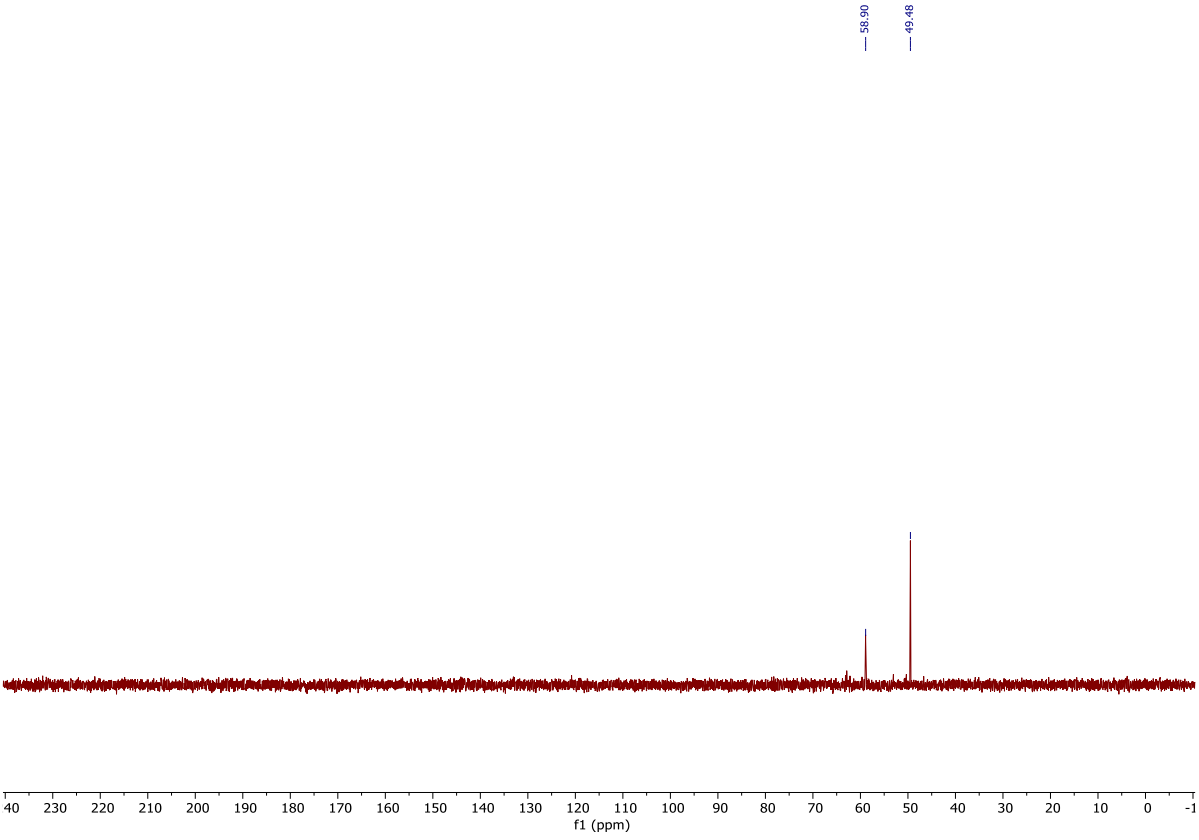
General procedure for the synthesis of alkenes, alkanes, and amines

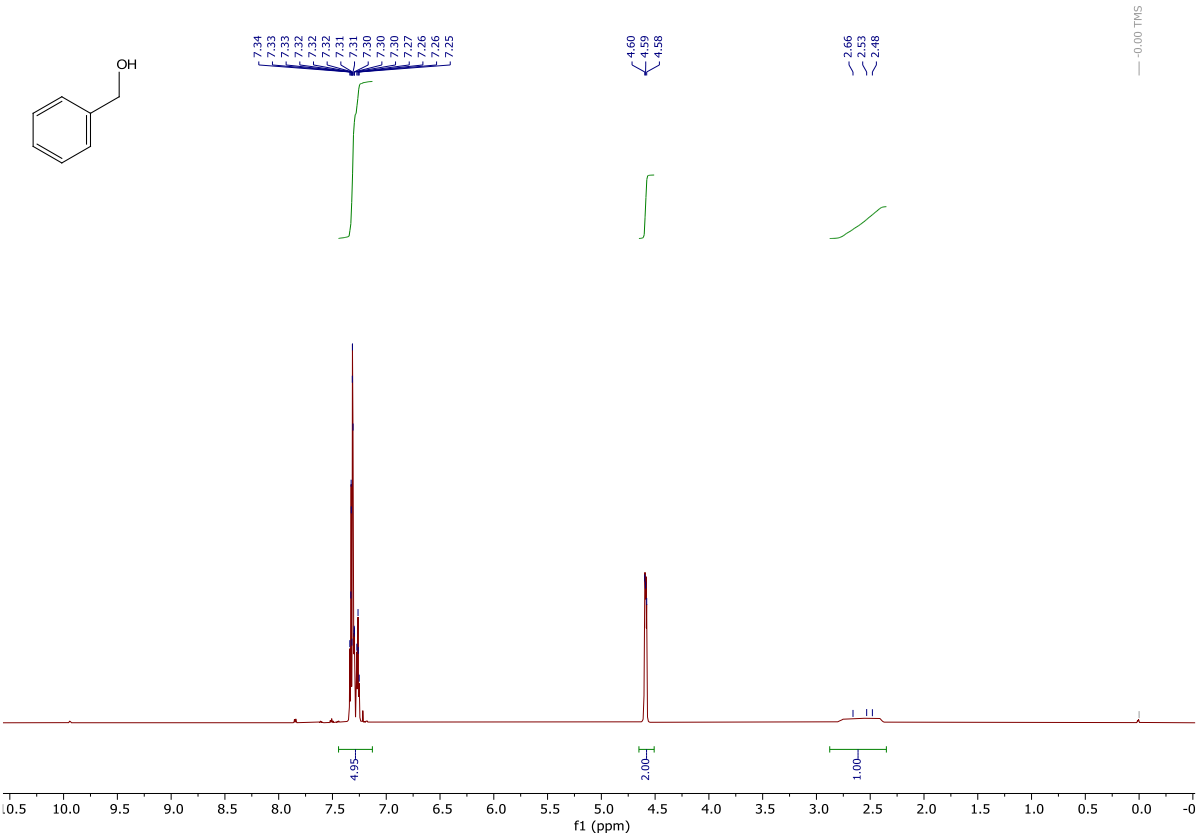
A 10 mL stainless steel jar equipped with one milling ball of the same material (8 mm φ, $mass_{tot}$ 2.09 g) was filled with alkyne **IV-6a-IV-6c** and **IV-6g** (1 mmol), **1** (2 mmol), Pd/C (3 mol %) and H_2O (2 mmol). The vessel was then closed, and the reaction was conducted for 90 min at 30 Hz. At the end of the reaction, the crude was recovered with EtOAc (10 mL). In some cases, a short silica pad (1 g) was required for further purification. Lastly, the solvent was removed under reduced pressure to afford the pure alkane **IV-8a-IV-8c** and **IV-8g**

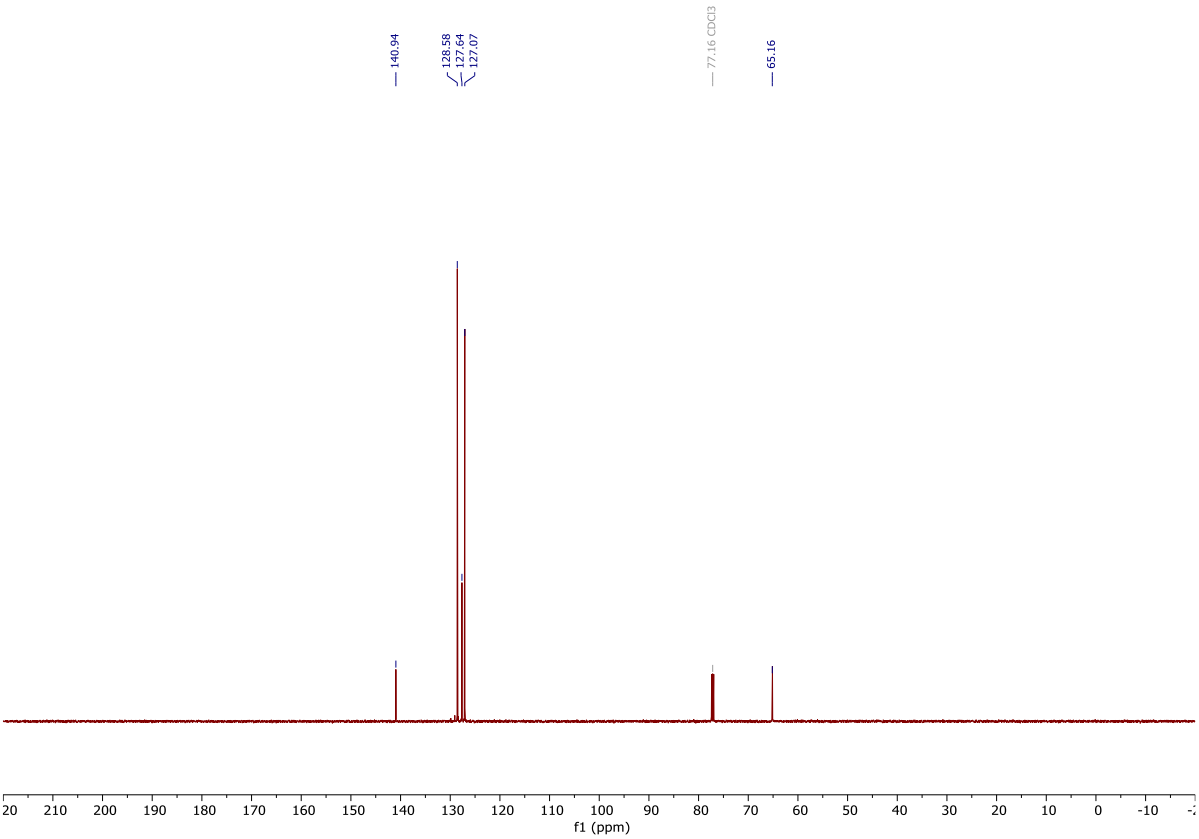
A 10 mL stainless steel jar was filled with alkene **IV-7a-IV-7b, IV-7d-IV-7f** and **IV-7g**, (1 mmol), 1 (2 mmol), Pd/C (3 mol %), and H_2O (2 mmol). The vessel was then closed, and the reaction was conducted for 90 min at 30 Hz *without grinding the ball*. At the end of the reaction, the crude was recovered with EtOAc (10 mL). Lastly, the solvent was removed under reduced pressure to afford the pure alkane **IV-8a-IV-8b, IV-8d-IV-8f** and **IV-8g**.

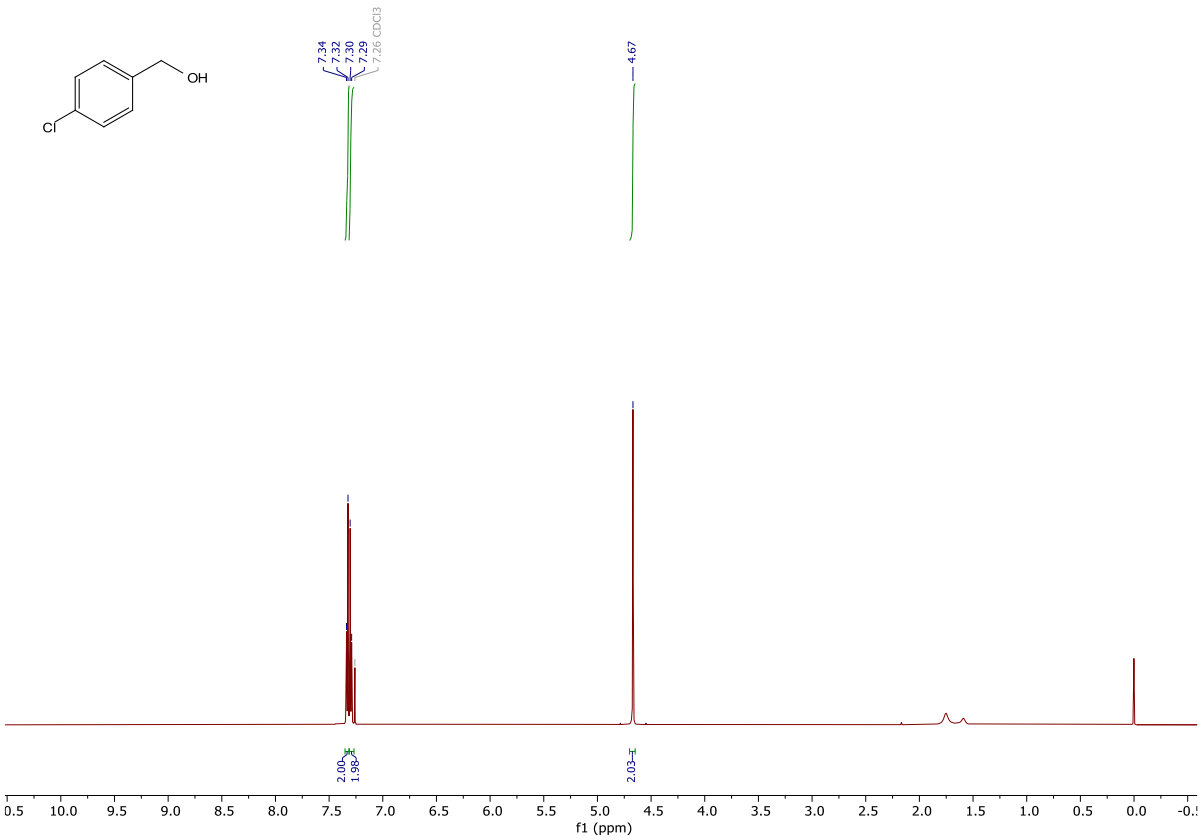
A 10 mL stainless steel jar equipped with one milling ball of the same material (8 mm φ, $mass_{tot}$ 2.09 g) was filled with nitro compounds **IV-9a-IV-9i** (1 mmol), **1** (3 mmol), Pd/C (3 mol %) and H_2O (3 mmol). The vessel was then closed, and the reaction was conducted for 90 min at 30 Hz. At the end of the reaction, the crude was recovered with EtOAc (10 mL). Lastly, the solvent was removed under reduced pressure to afford the pure amine **IV-10a-IV-10i**


3.85
3.84
3.83
3.02
3.01
3.00
8.00
8.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)


58.90
49.48
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


OH
7.34
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.27
7.26
7.26
7.25
4.60
4.59
4.58
2.66
2.53
2.48
0.00 TMS
4.95
2.00
1.00
f1 (ppm)


140.94
128.58
127.64
127.07
77.16 CDCl3
65.16
f1 (ppm)


OH
Cl
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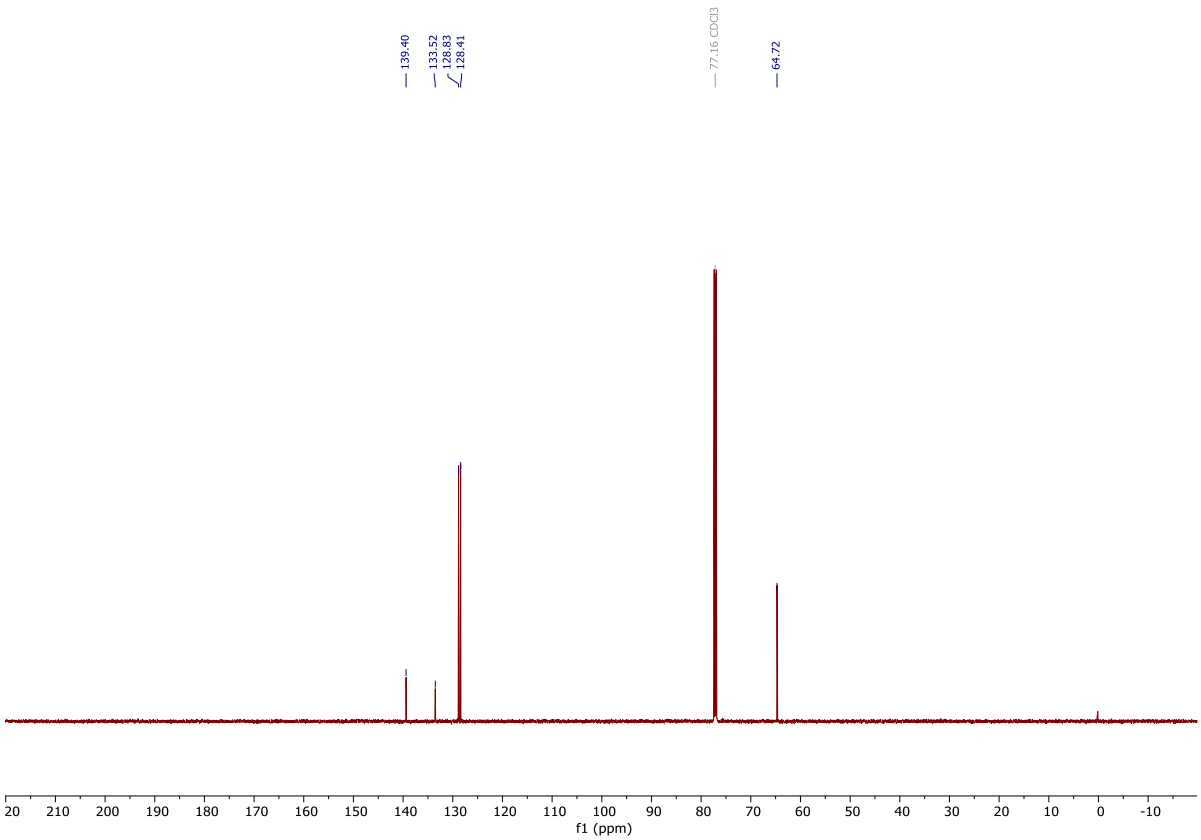
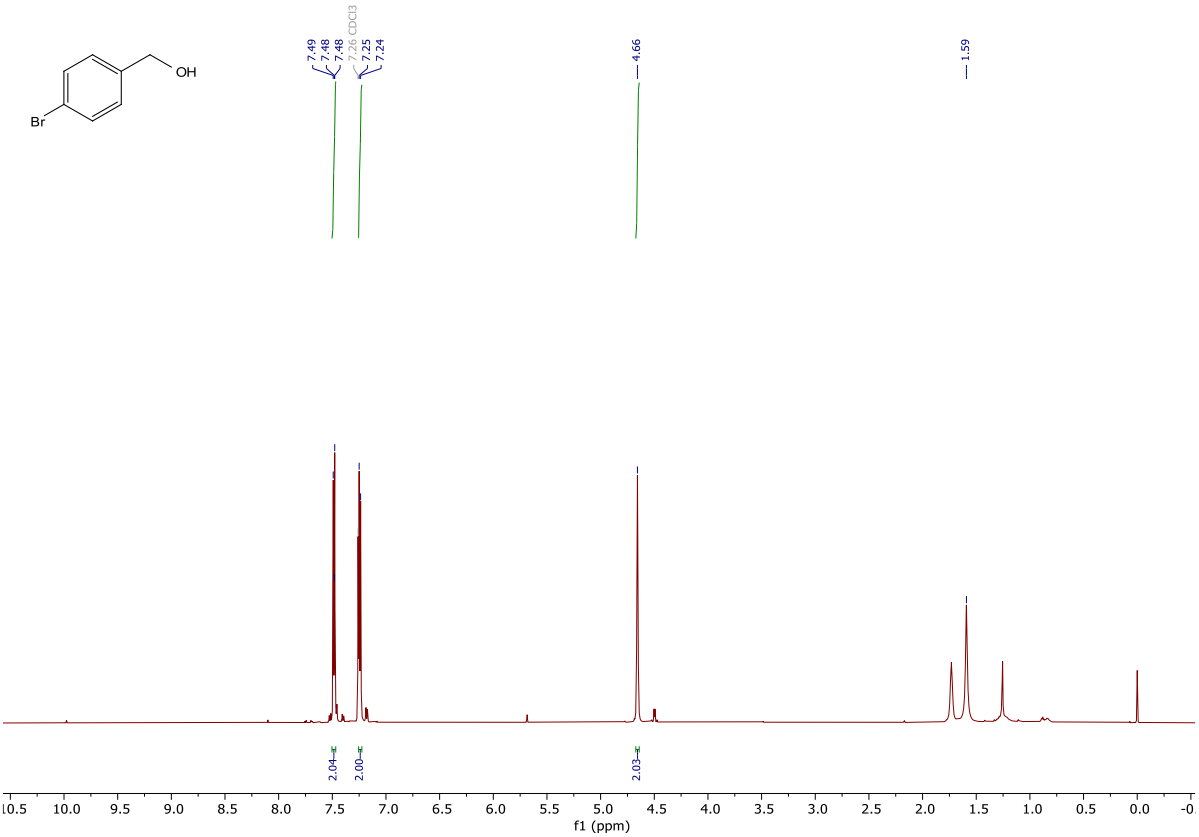
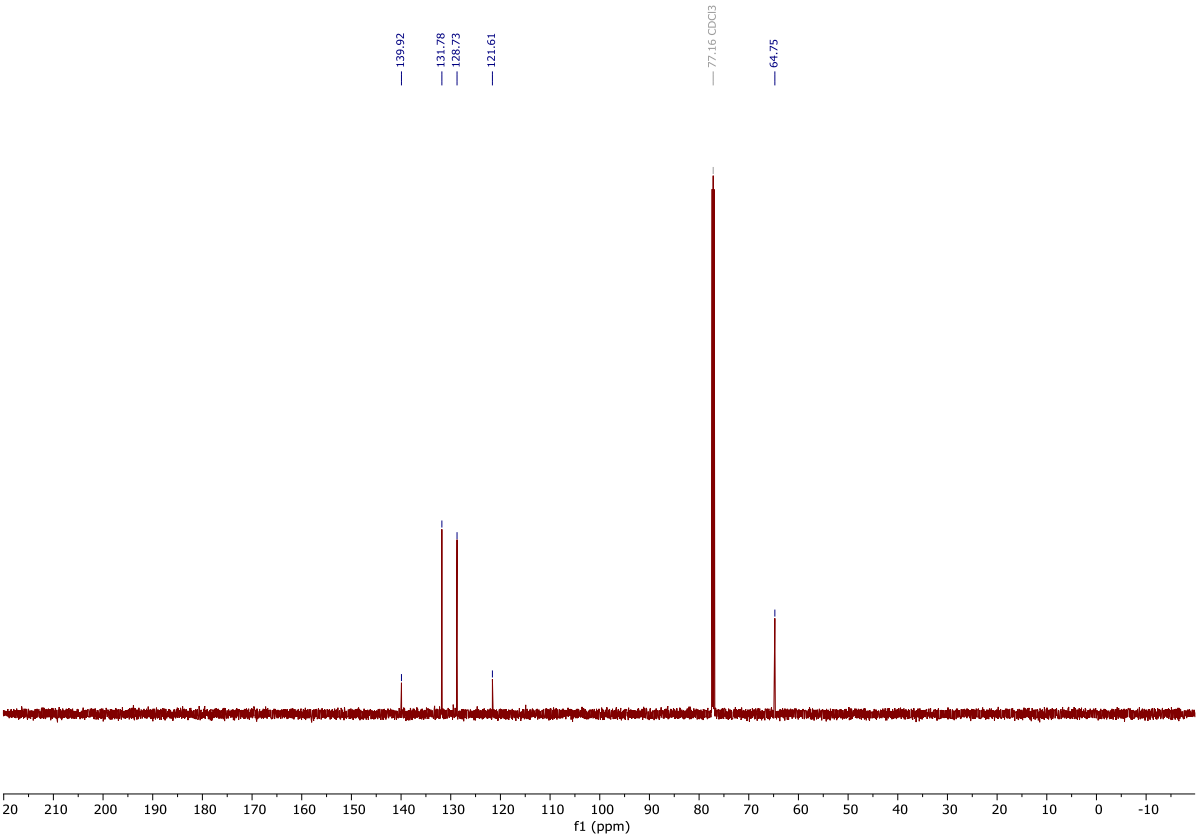
7.32
7.30
7.29
7.26 CDCl3
4.67
2.00
1.98
2.03
f1 (ppm)


139.40
133.52
128.83
128.41
77.16 CDCl3
64.72
f1 (ppm)


OH
Br
7.49
7.48
7.48
7.26 CDCl3
7.25
7.24
4.66
1.59
2.04
2.00
2.03
f1 (ppm)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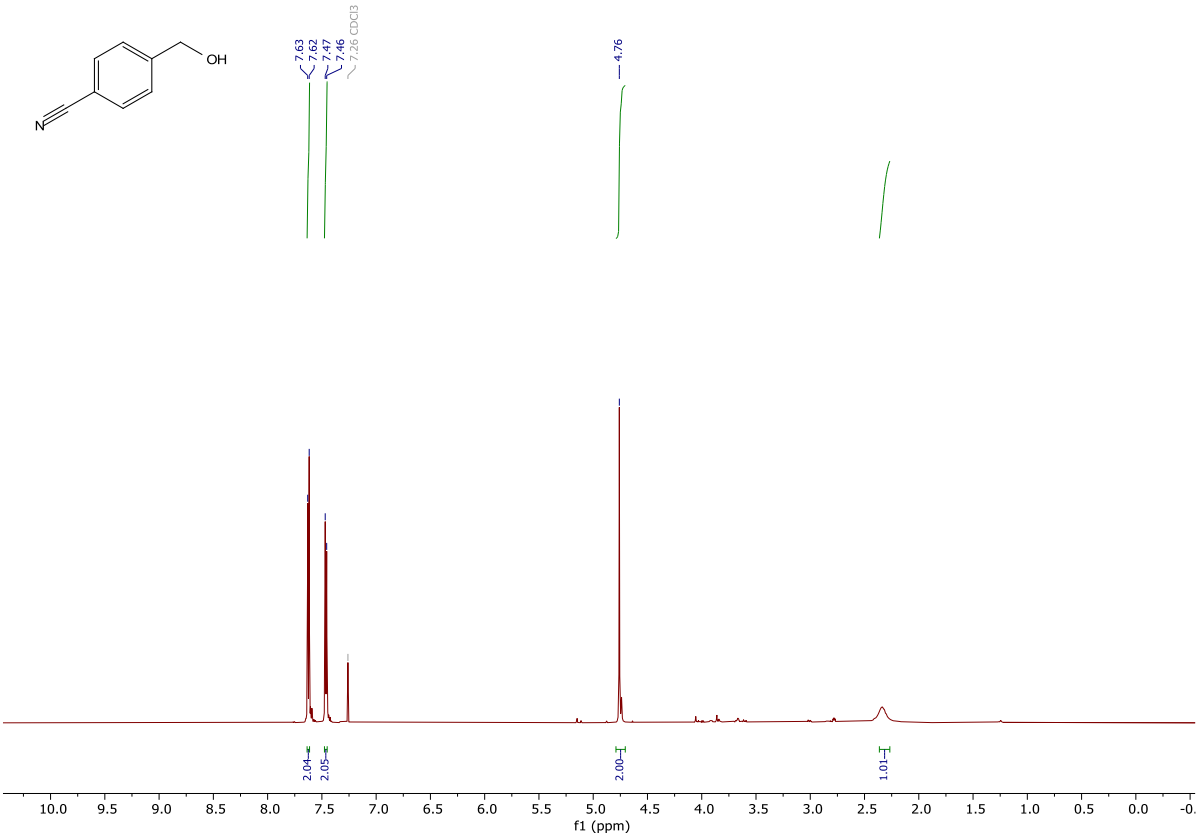
131.78
128.73
121.61
77.16 CDCl3
64.75
f1 (ppm)


OH
N
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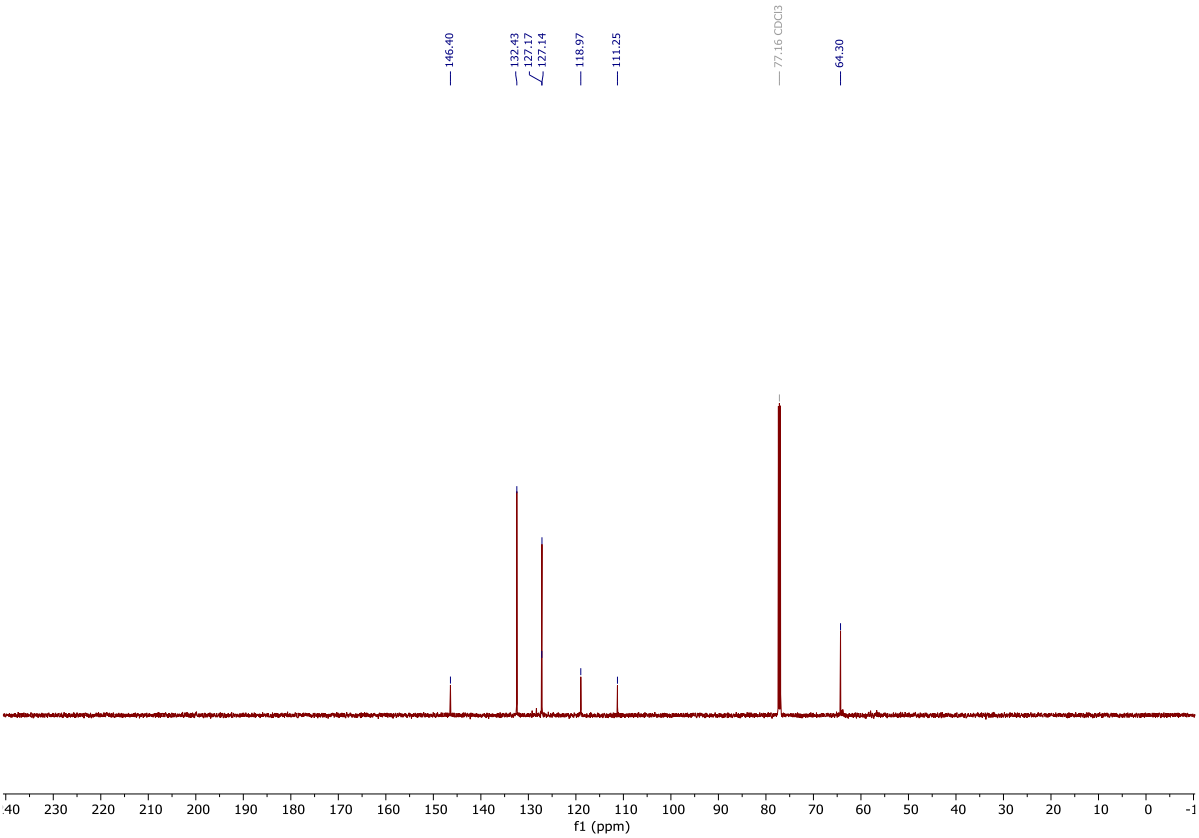
7.62
7.47
7.46
7.26 CDCl3
4.76
2.04
2.05
2.00
1.01
f1 (ppm)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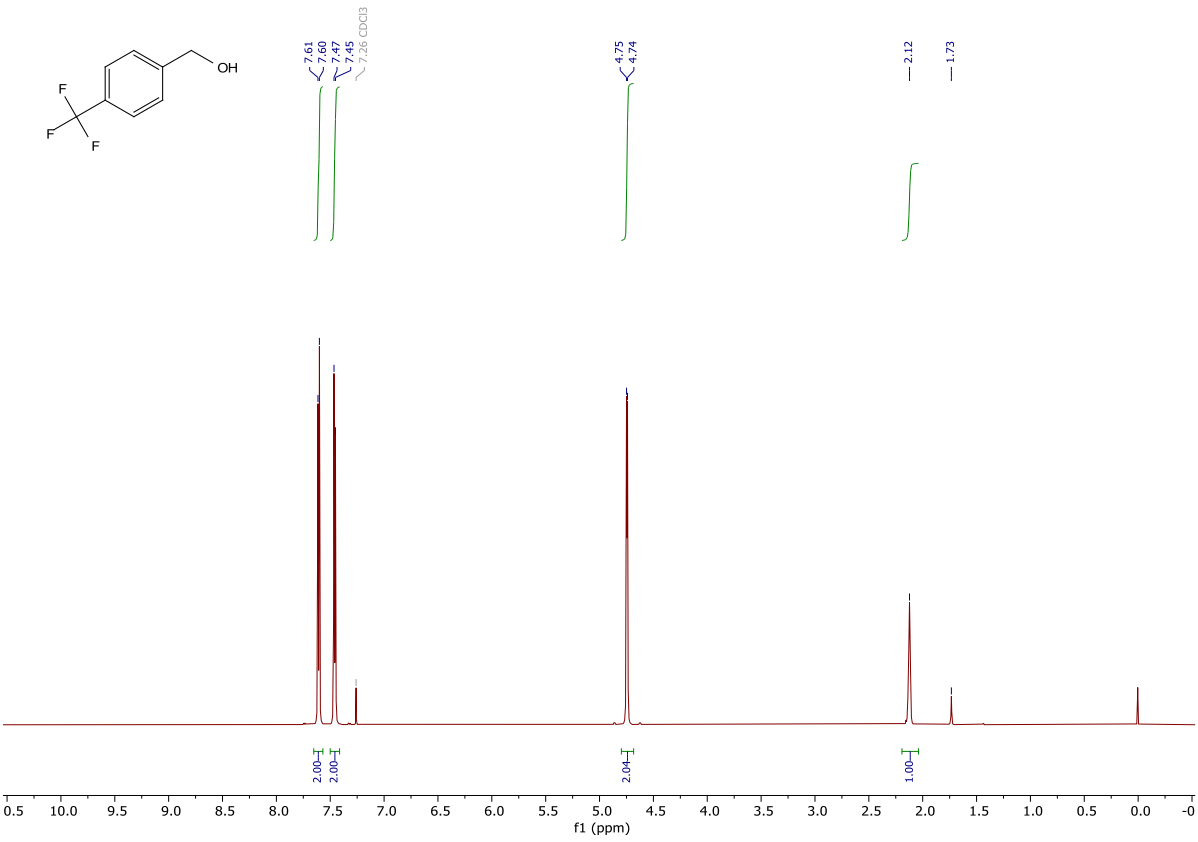
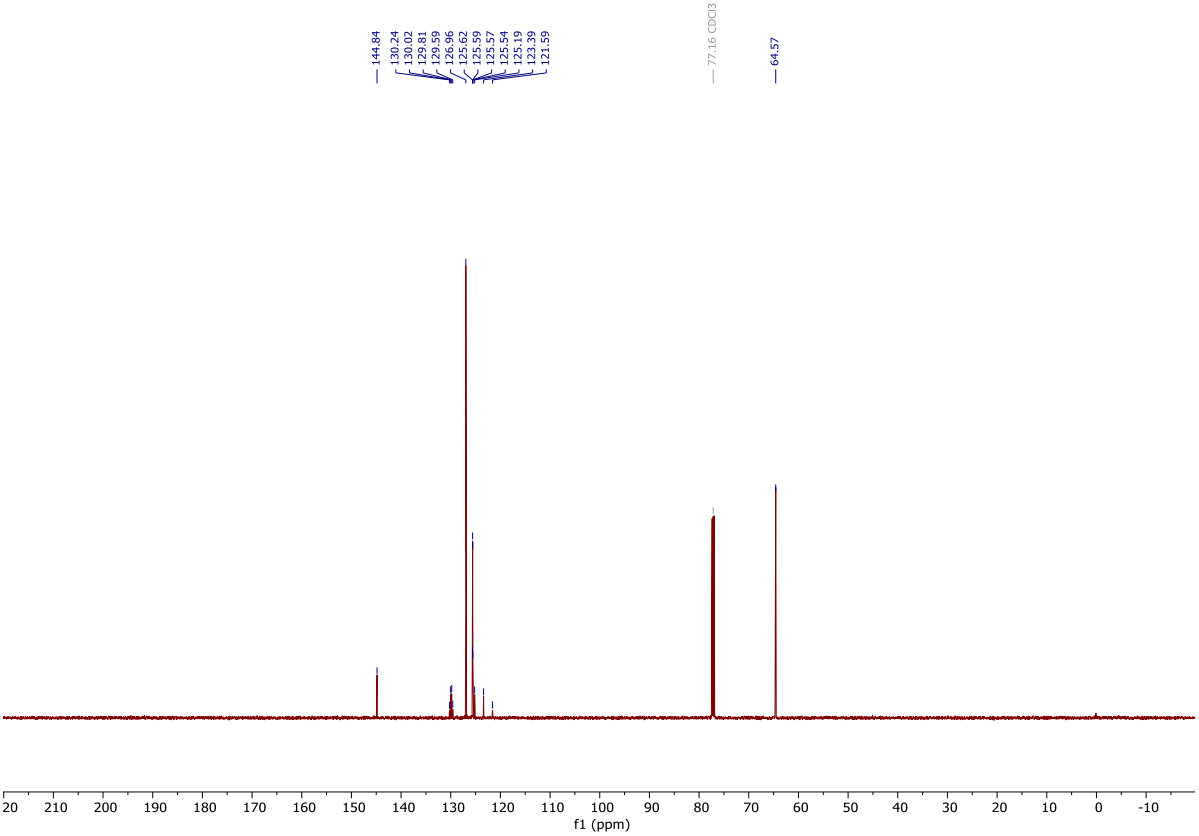
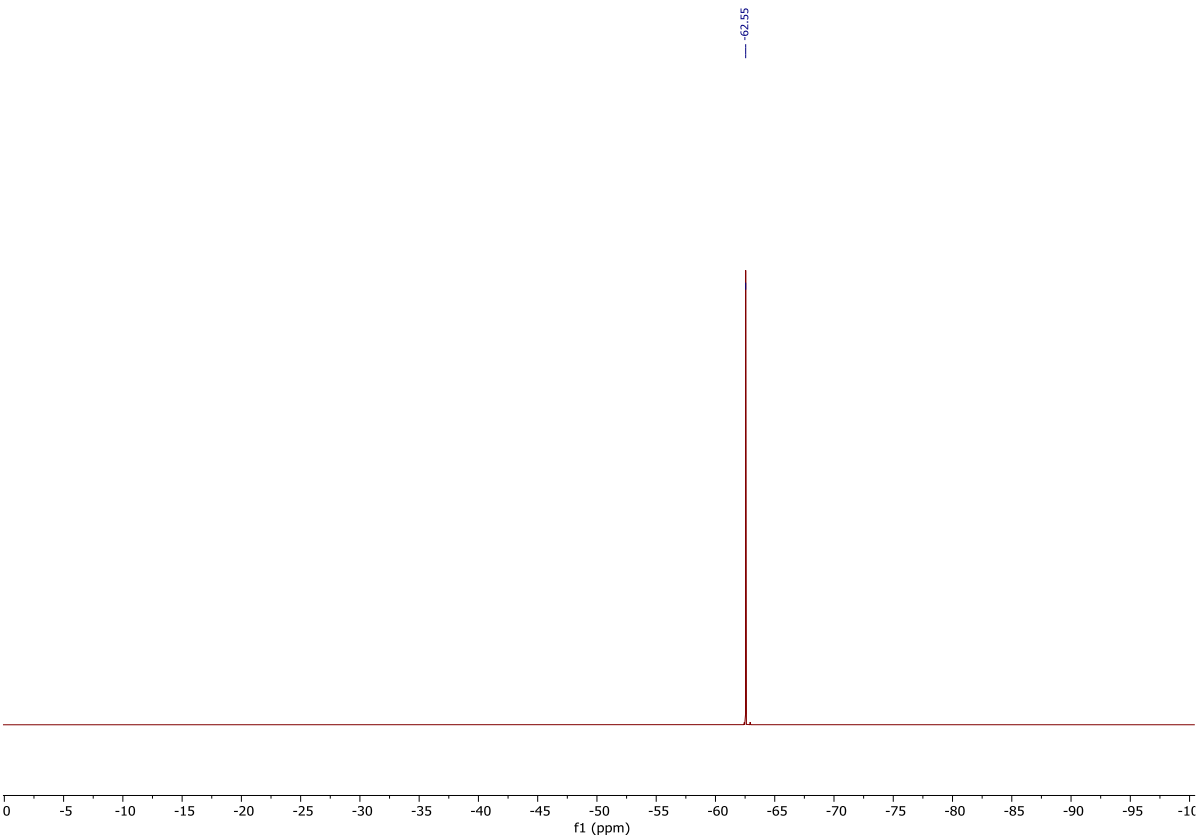
127.14
118.97
111.25
77.16 CDCl3
64.30
f1 (ppm)


F
F
F
OH
7.61
7.60
7.47
7.45
7.26 CDCl3
4.75
4.74
2.12
1.73
2.00
2.00
2.04
1.00
f1 (ppm)


144.84
130.24
130.02
129.81
129.59
126.96
125.62
125.59
125.57
125.54
125.19
123.39
121.59
77.16 CDCl3
64.57
f1 (ppm)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-5
-10
-15
-20
-25
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-40
-45
-50
-55
-60
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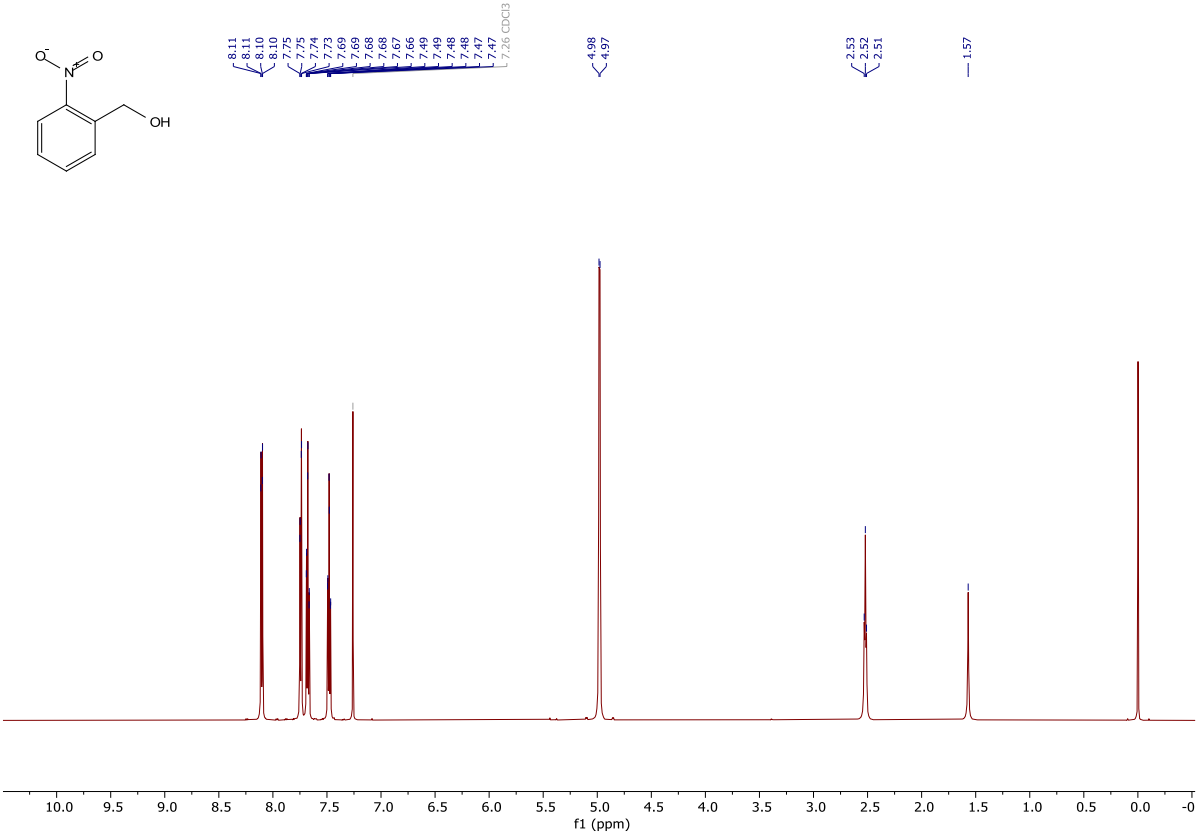
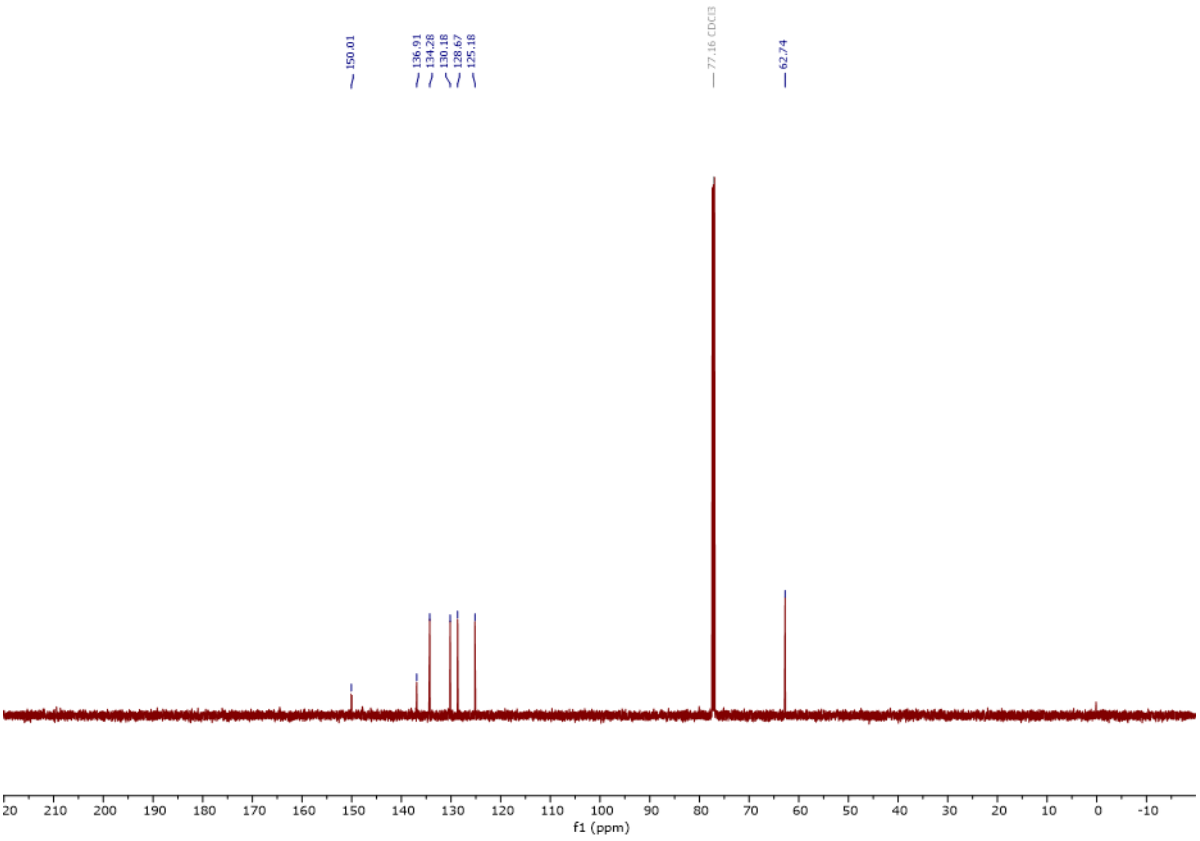
-75
-80
-85
-90
-95
f1 (ppm)


8.11
8.11
8.10
8.10
7.75
7.75
7.74
7.73
7.69
7.69
7.68
7.68
7.67
7.66
7.49
7.49
7.48
7.48
7.47
7.47
7.26 CDCl3
4.98
4.97
2.53
2.52
2.51
1.57
OH
f1 (ppm)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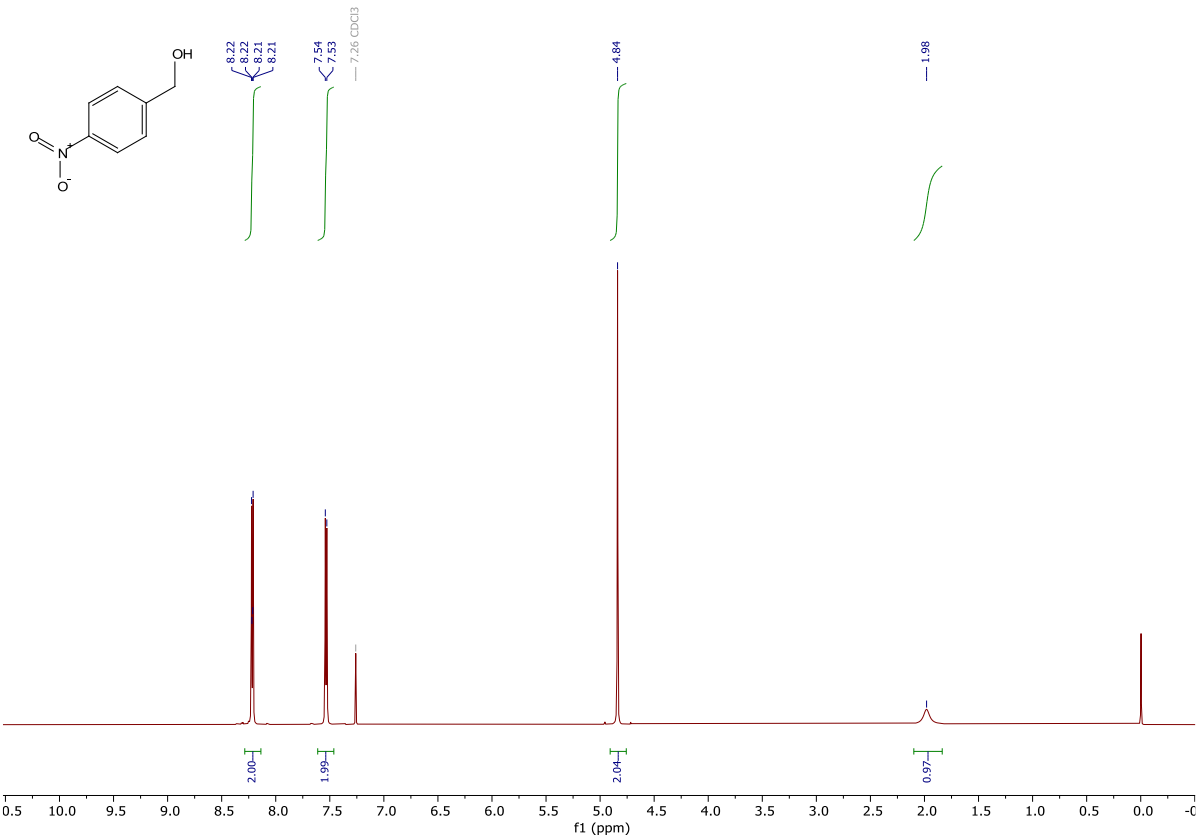
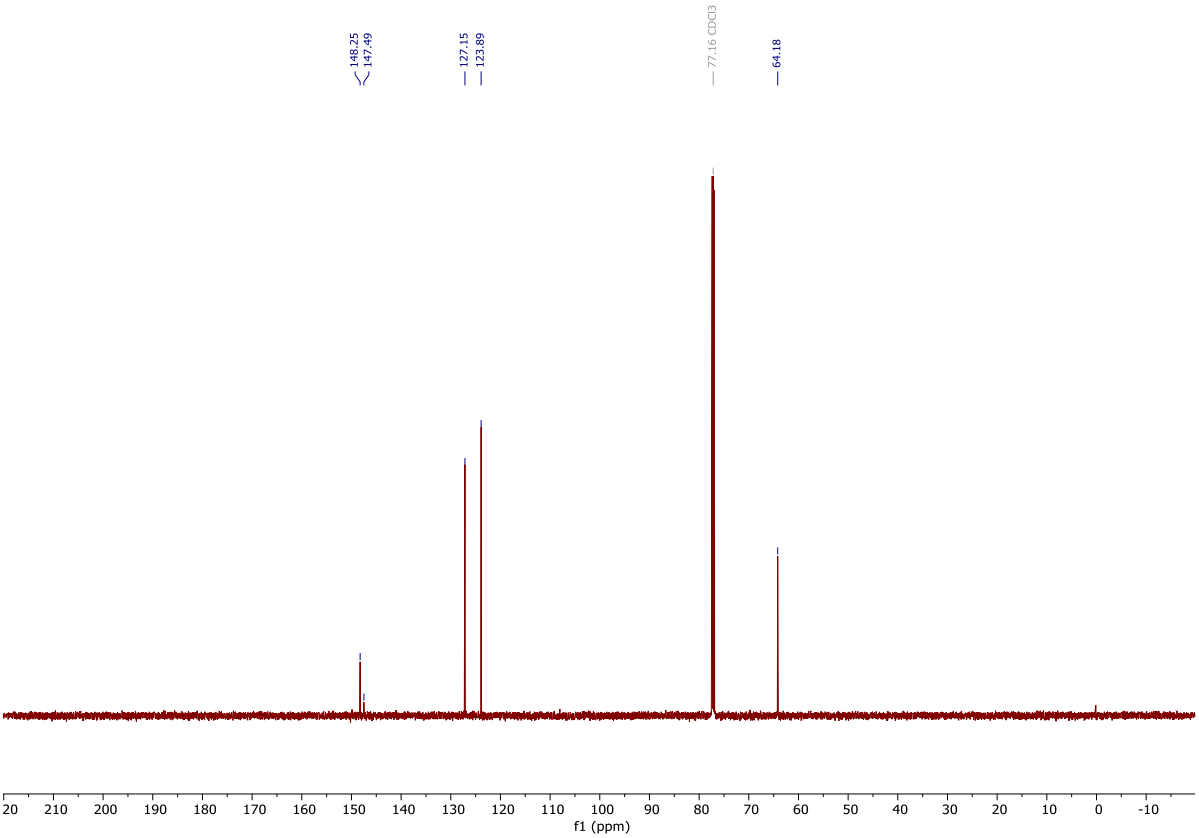
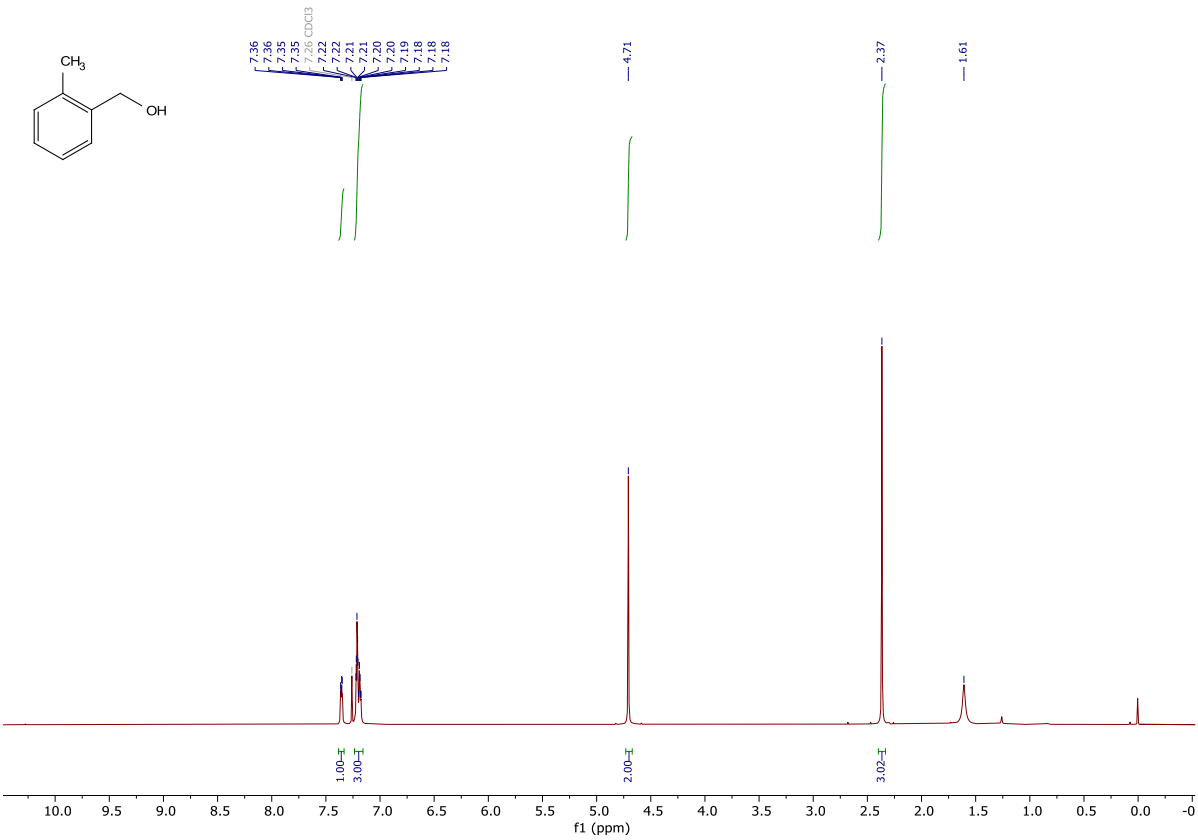
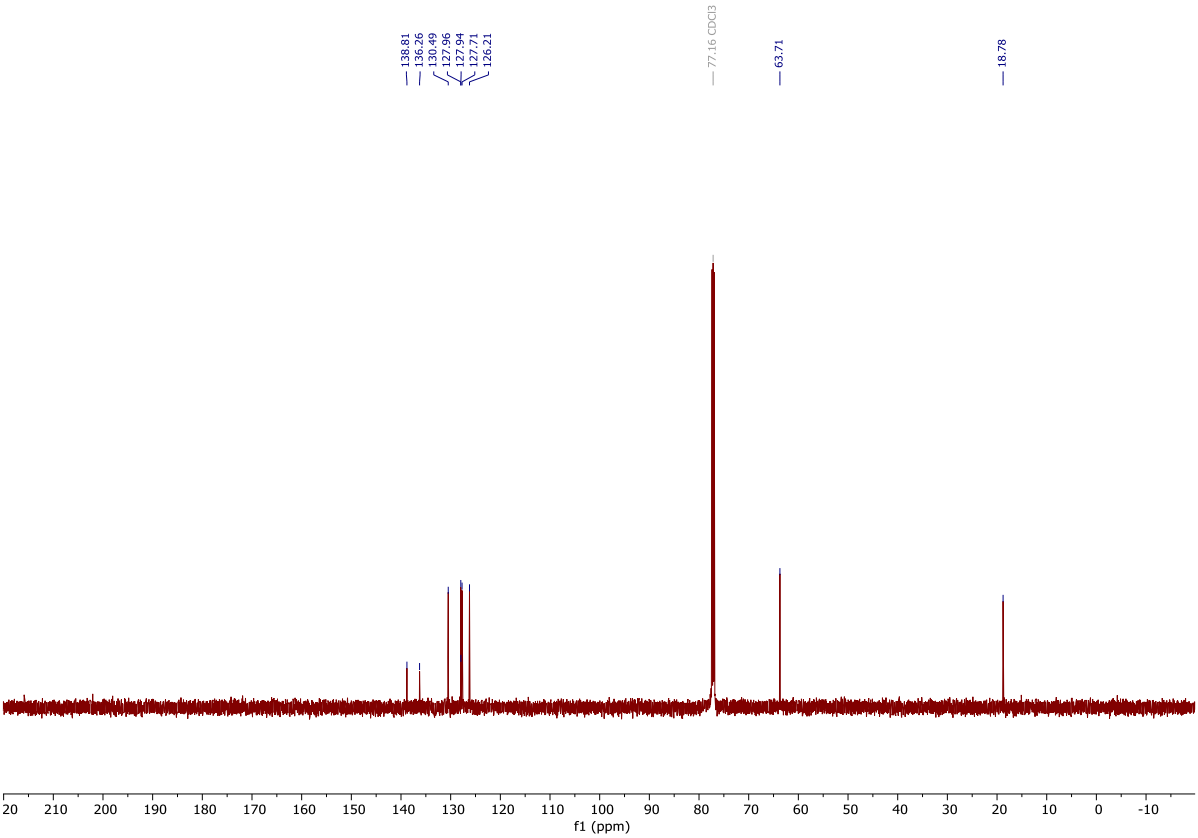
128.67
125.18
77.16 CDCl3
62.74
f1 (ppm)


OH
O
N+
O-
8.22
8.22
8.21
8.21
7.54
7.53
7.26 CDCl3
4.84
1.98
2.00
1.99
2.04
0.97
f1 (ppm)


148.25
147.49
127.15
123.89
77.16 CDCl3
64.18
f1 (ppm)


CH3
OH
7.36
7.36
7.35
7.35
7.26 CDCl3
7.22
7.21
7.21
7.20
7.20
7.19
7.18
7.18
7.18
4.71
2.37
1.61
1.00
3.00
2.00
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)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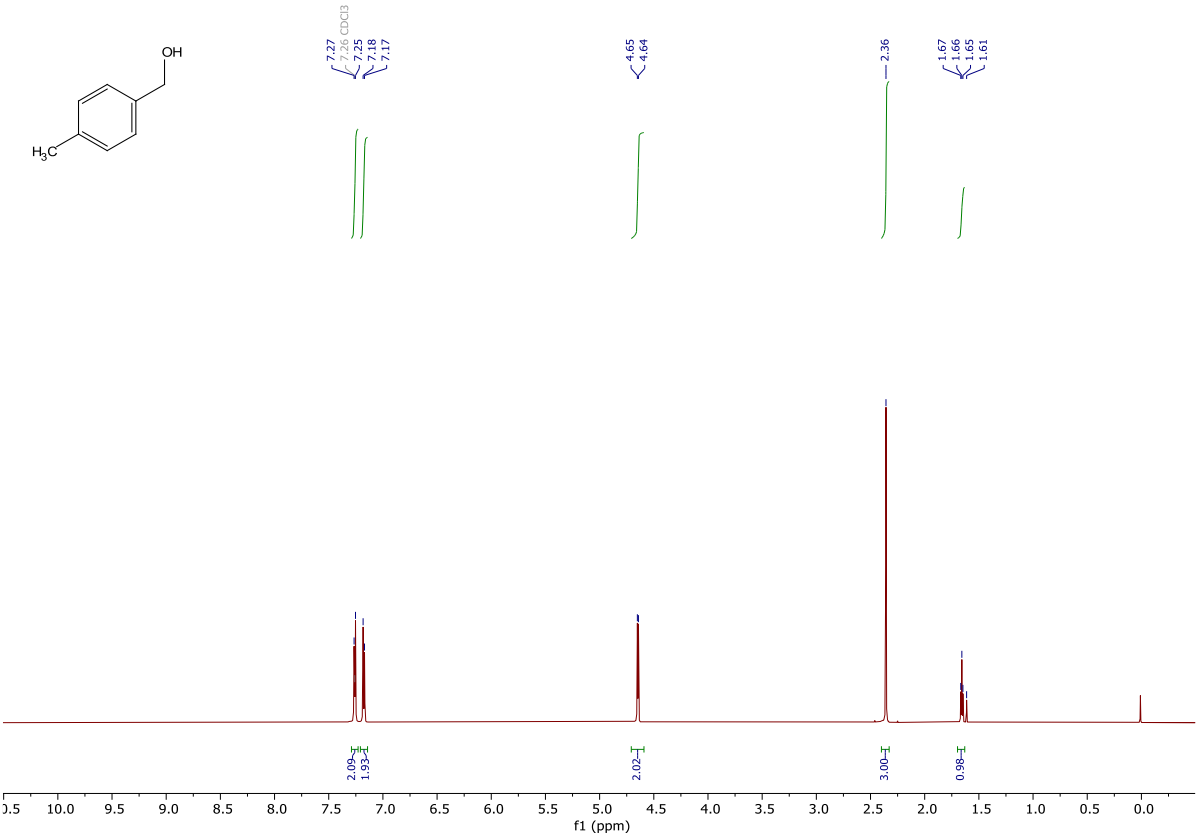
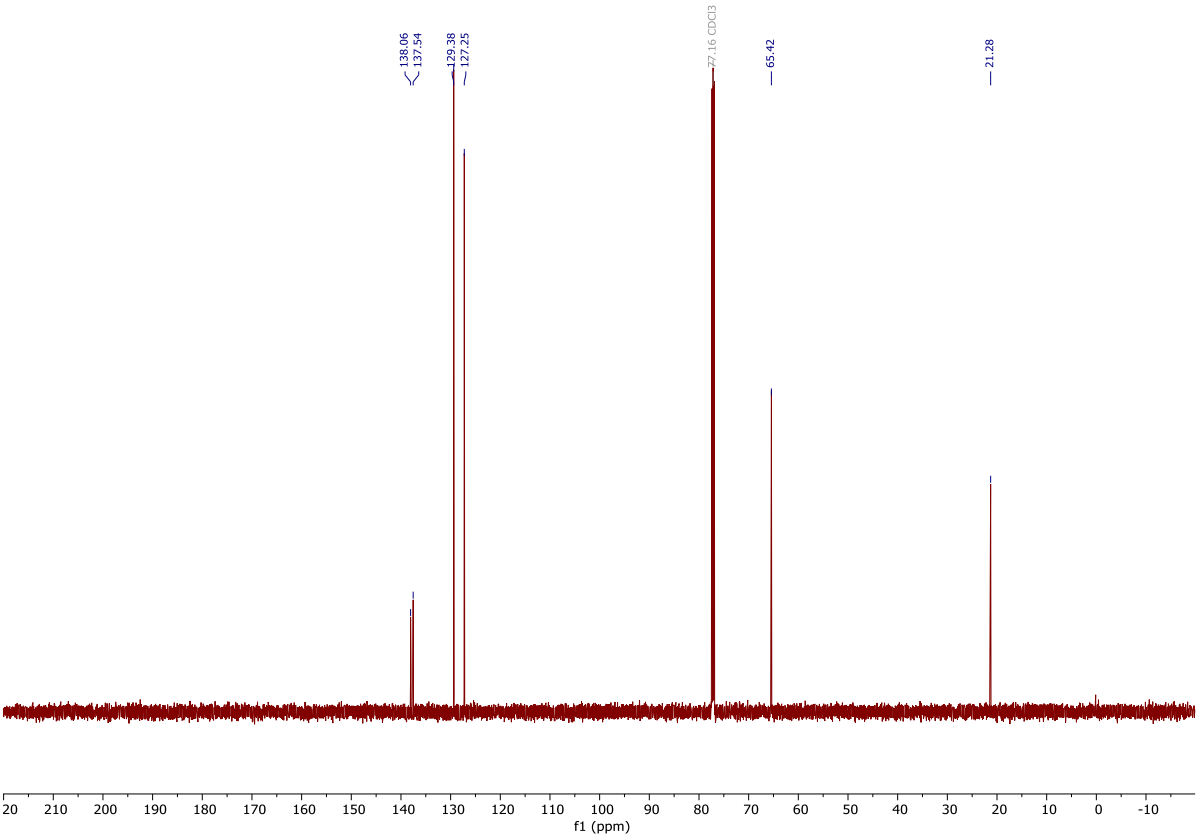
136.26
130.49
127.96
127.94
127.71
126.21
77.16 CDCl3
63.71
18.78
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
H3C
7.27
7.26 CDCl3
7.25
7.18
7.17
4.65
4.64
2.36
1.67
1.66
1.65
1.61
2.09
1.93
2.02
3.00
0.98
f1 (ppm)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127.25
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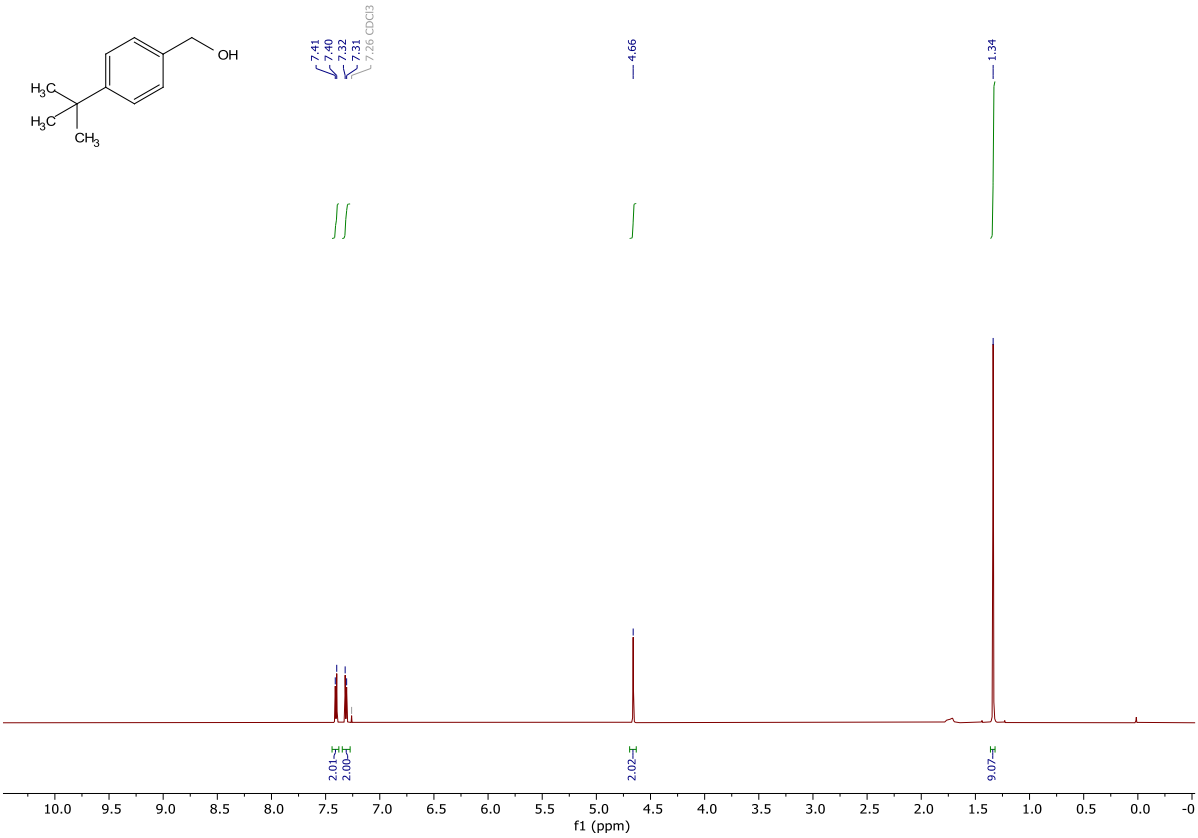
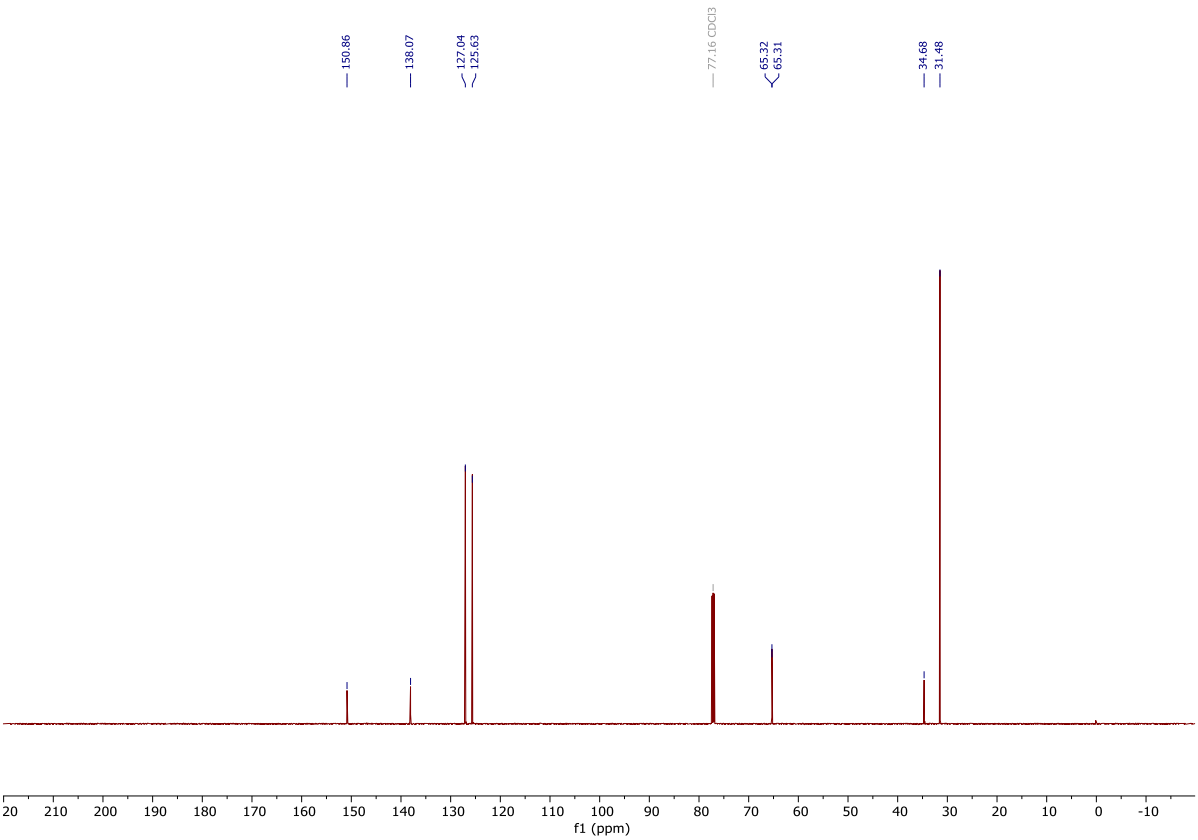
f1 (ppm)


OH
H3C
H3C
CH3
7.41
7.40
7.32
7.31
7.26 CDCl3
4.66
1.34
2.01
2.00
2.02
9.07
f1 (ppm)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65.31
34.68
31.48
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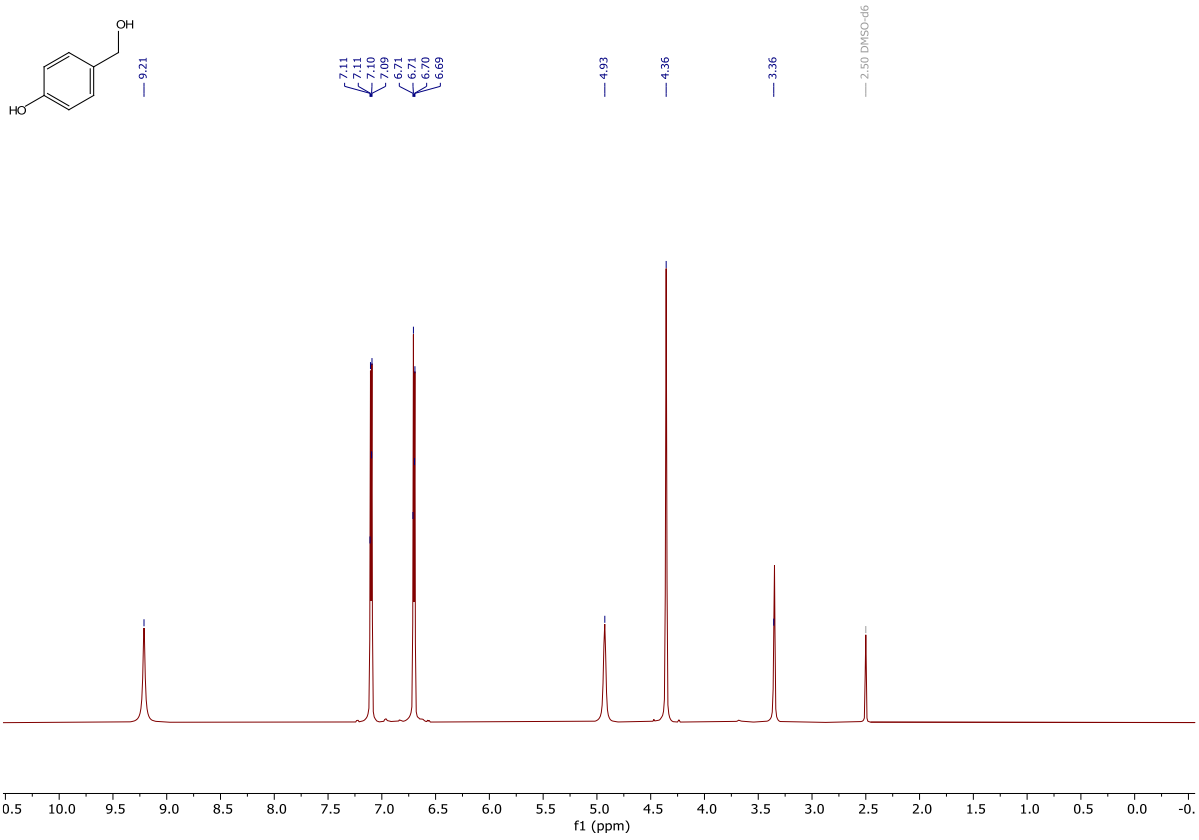
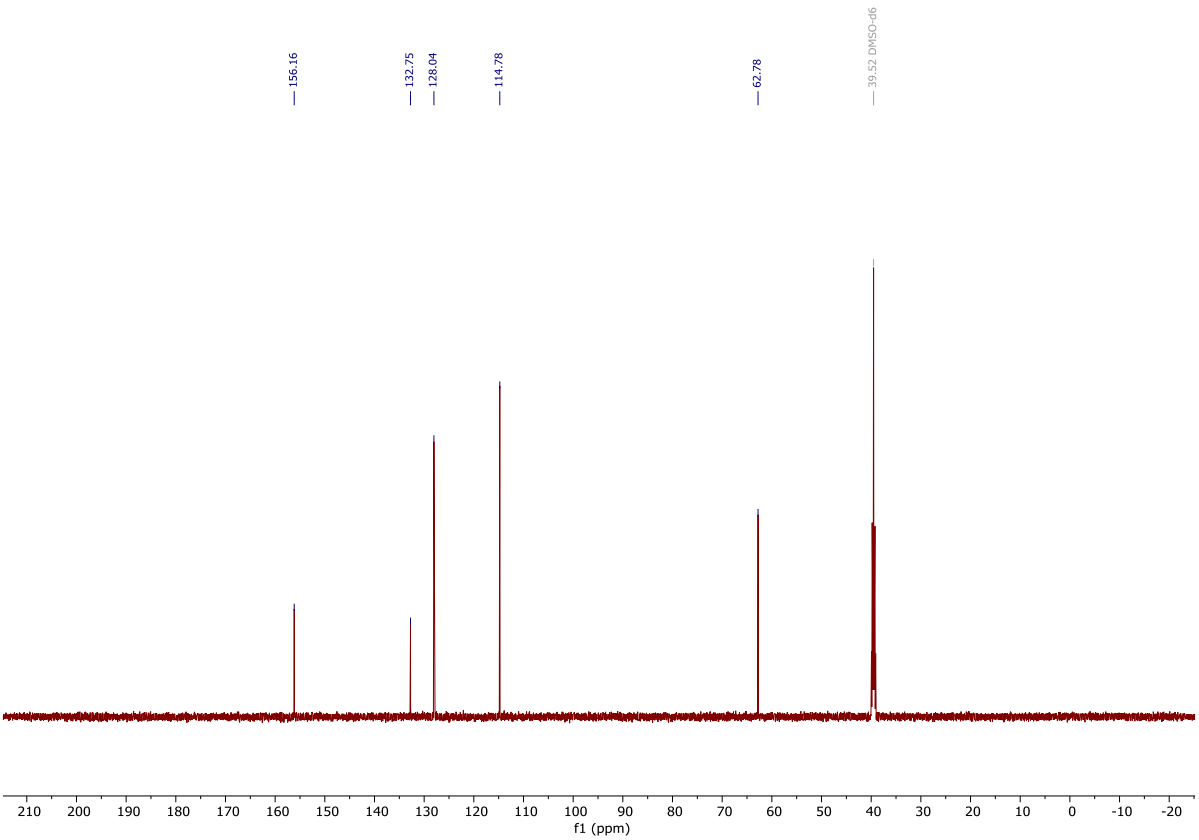

OH
HO
9.21
7.11
7.11
7.10
7.09
6.71
6.71
6.70
6.69
4.93
4.36
3.36
2.50 DMSO-d6
f1 (ppm)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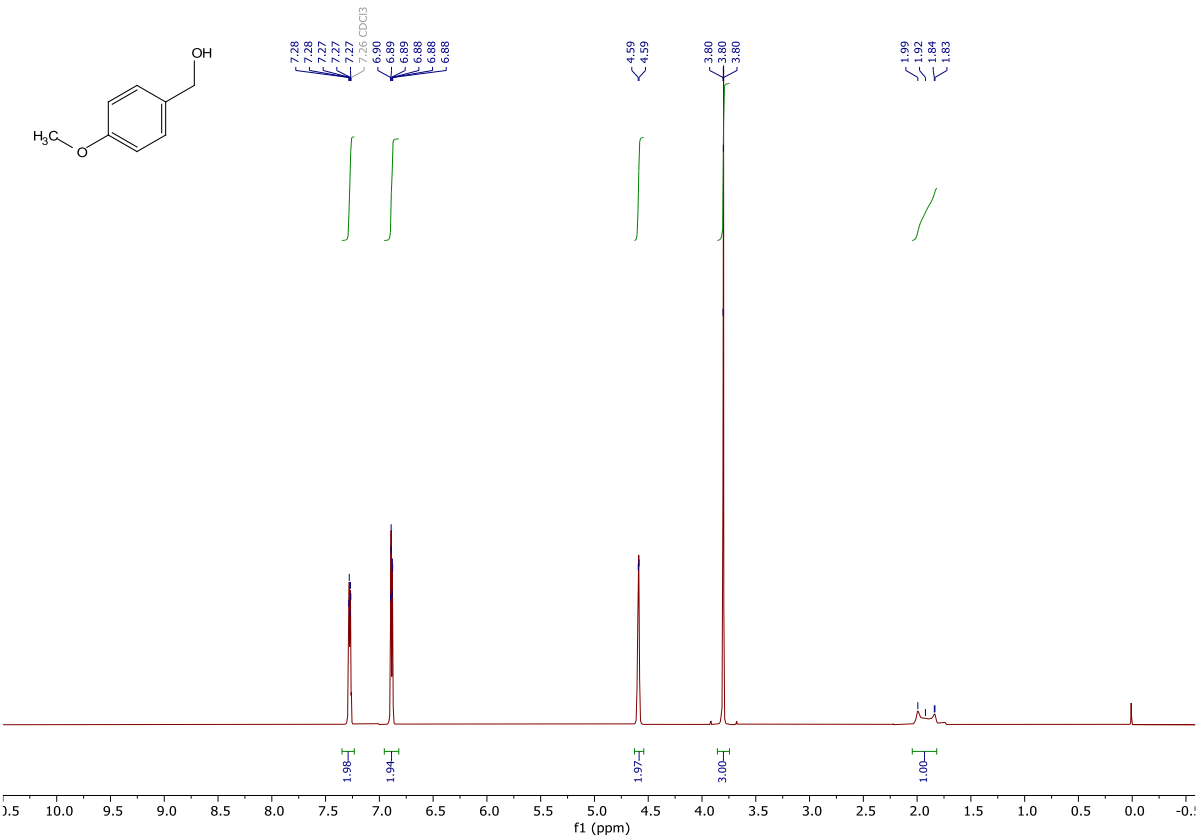
114.78
62.78
39.52 DMSO-d6
f1 (ppm)


OH
H3C
O
7.28
7.28
7.27
7.27
7.27
7.26 CDCl3
6.90
6.89
6.89
6.88
6.88
6.88
6.88
4.59
4.59
3.80
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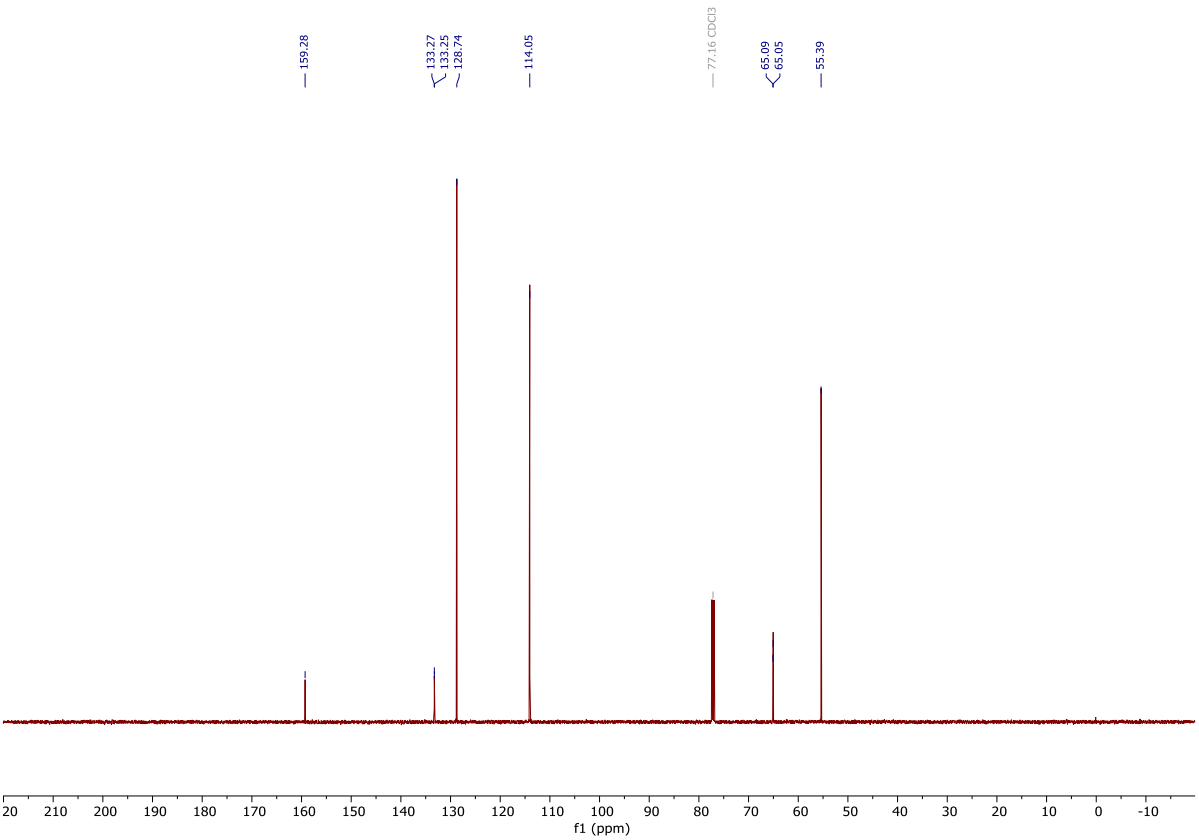
1.94
1.97
3.00
1.00
f1 (ppm)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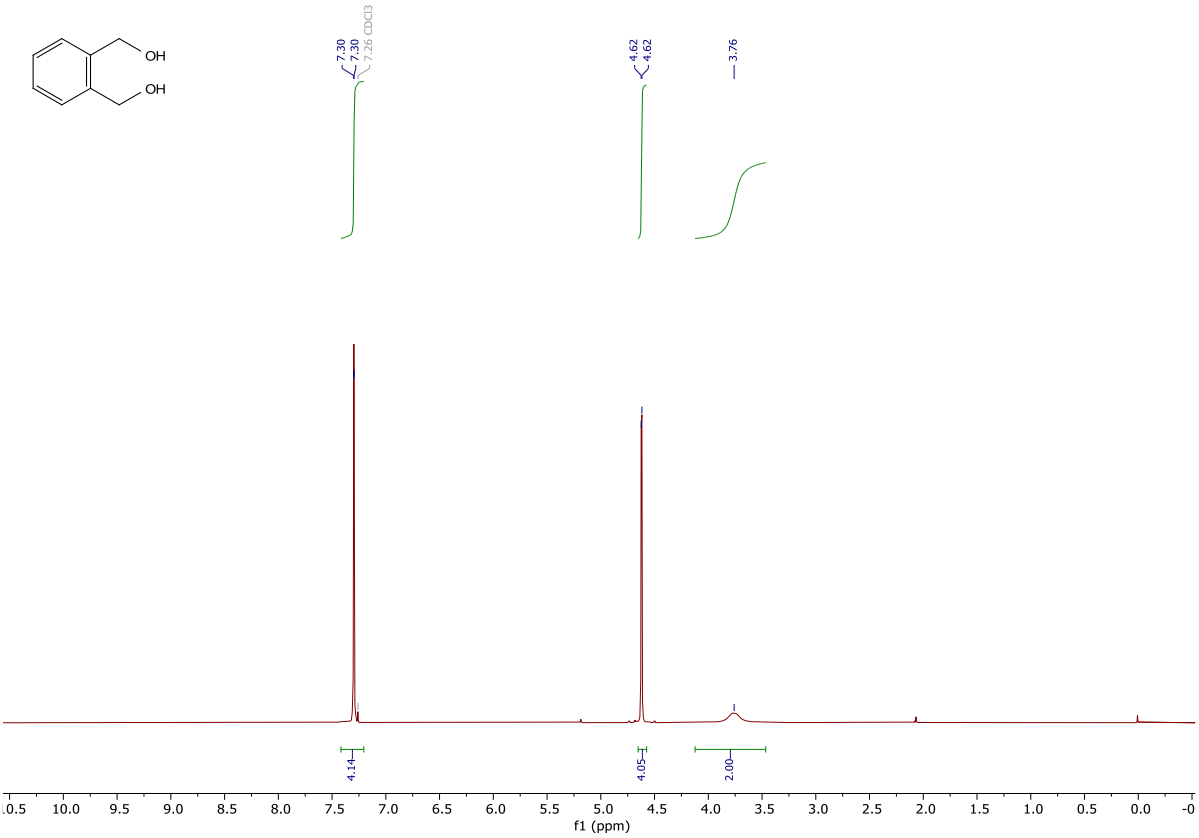
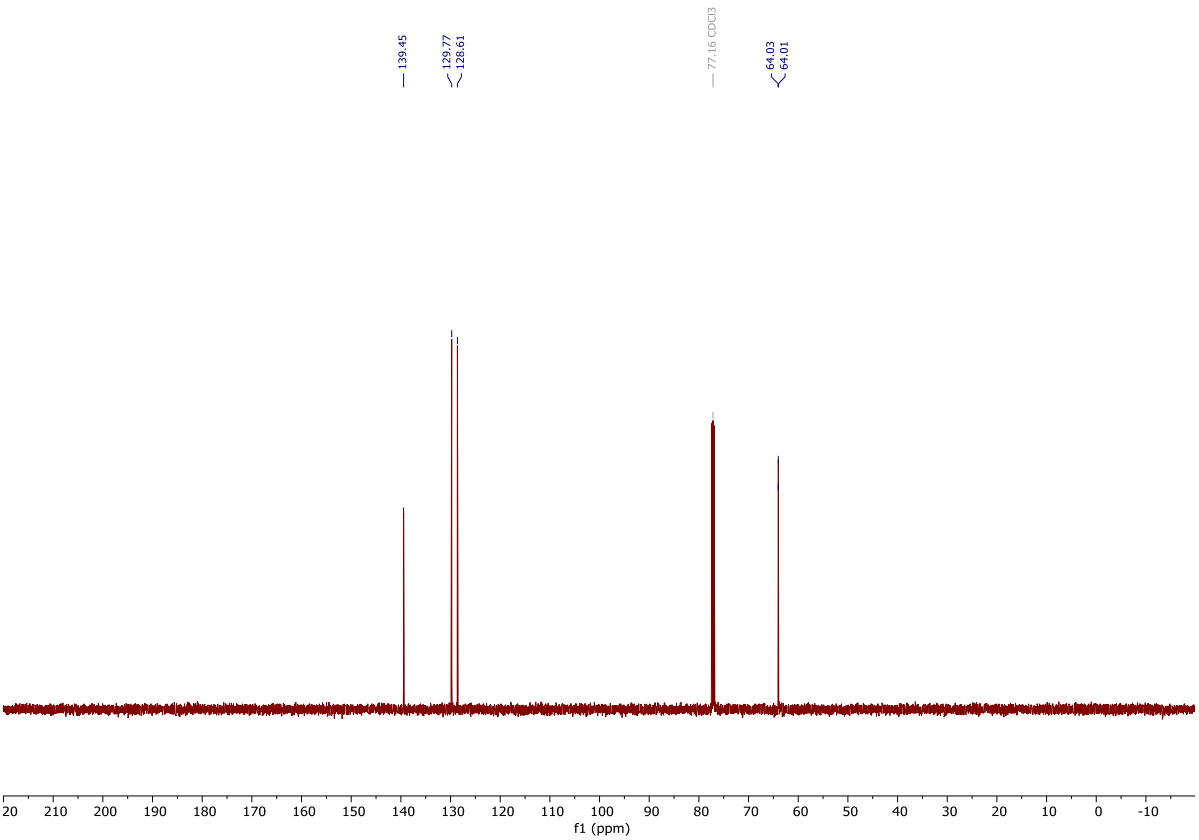
133.27
133.25
128.74
114.05
77.16 CDCl3
65.09
65.05
55.39
f1 (ppm)


OH
OH
7.30
7.30
7.26 CDCl3
4.62
4.62
3.76
4.14
4.05
2.00
f1 (ppm)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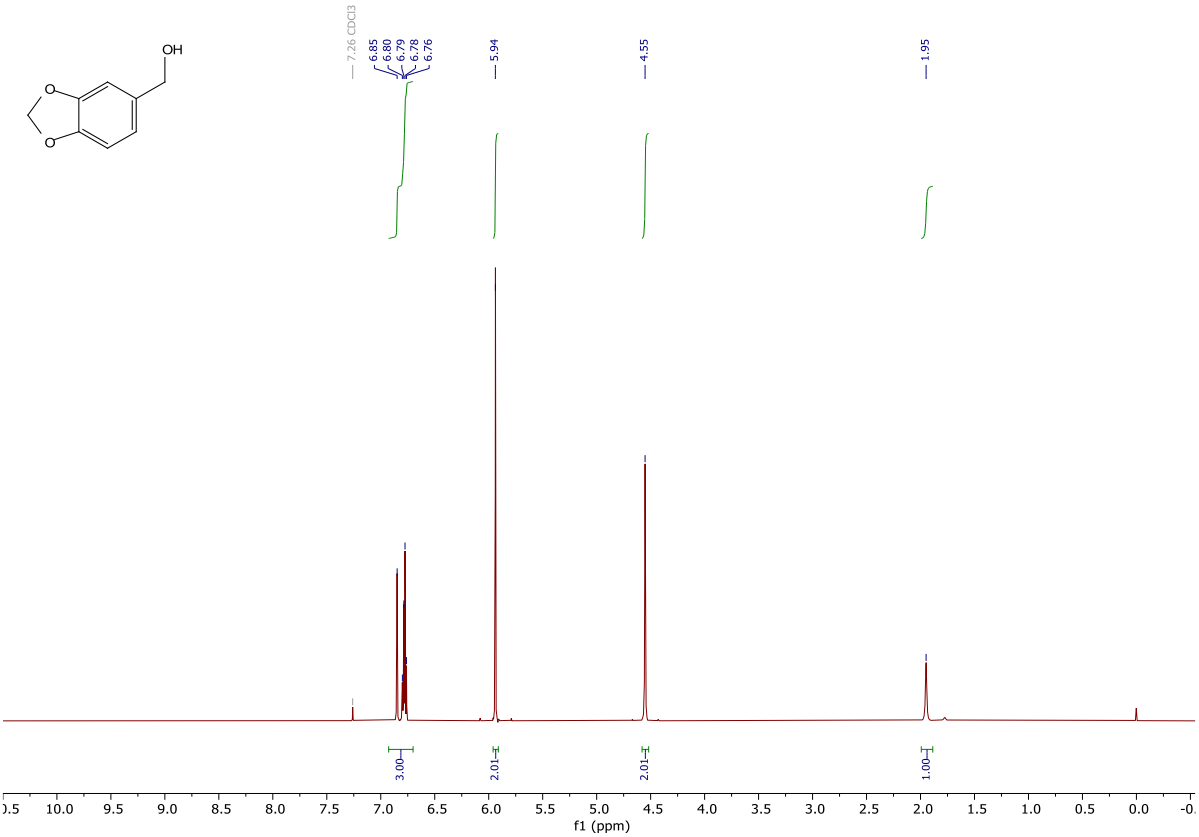
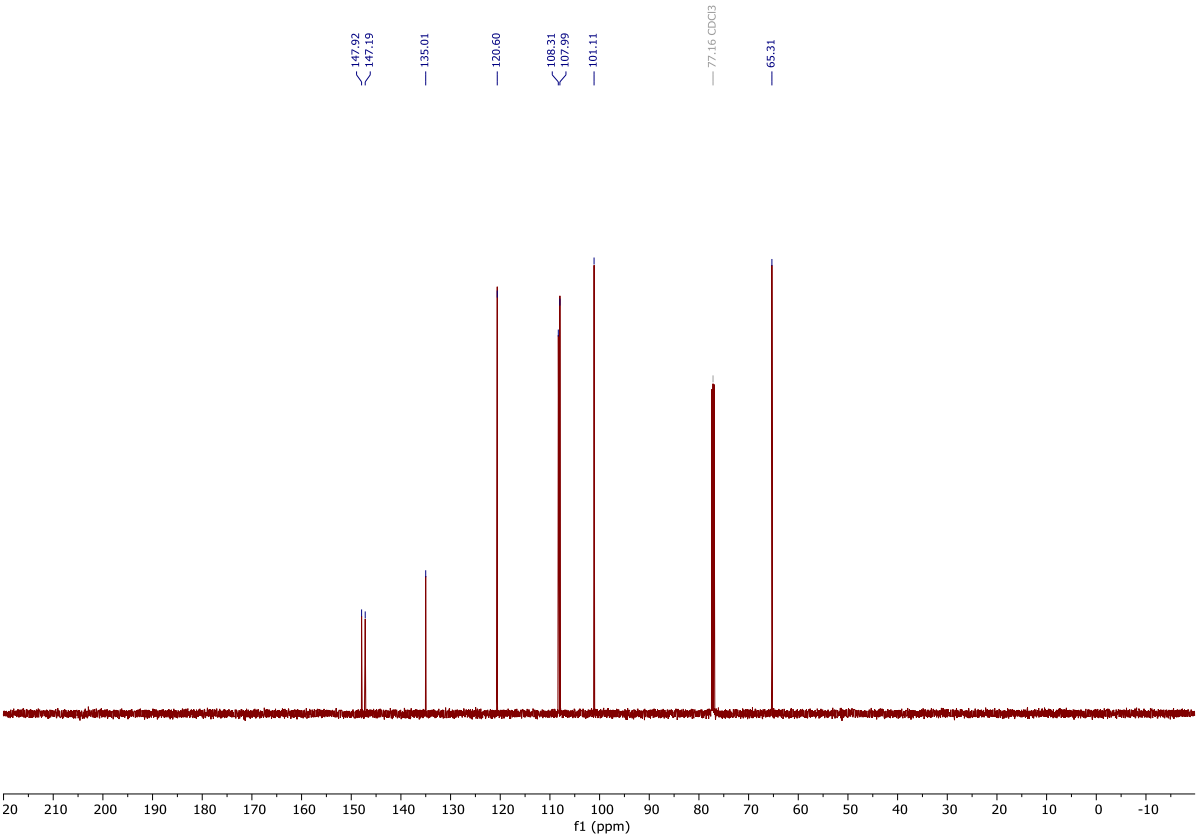
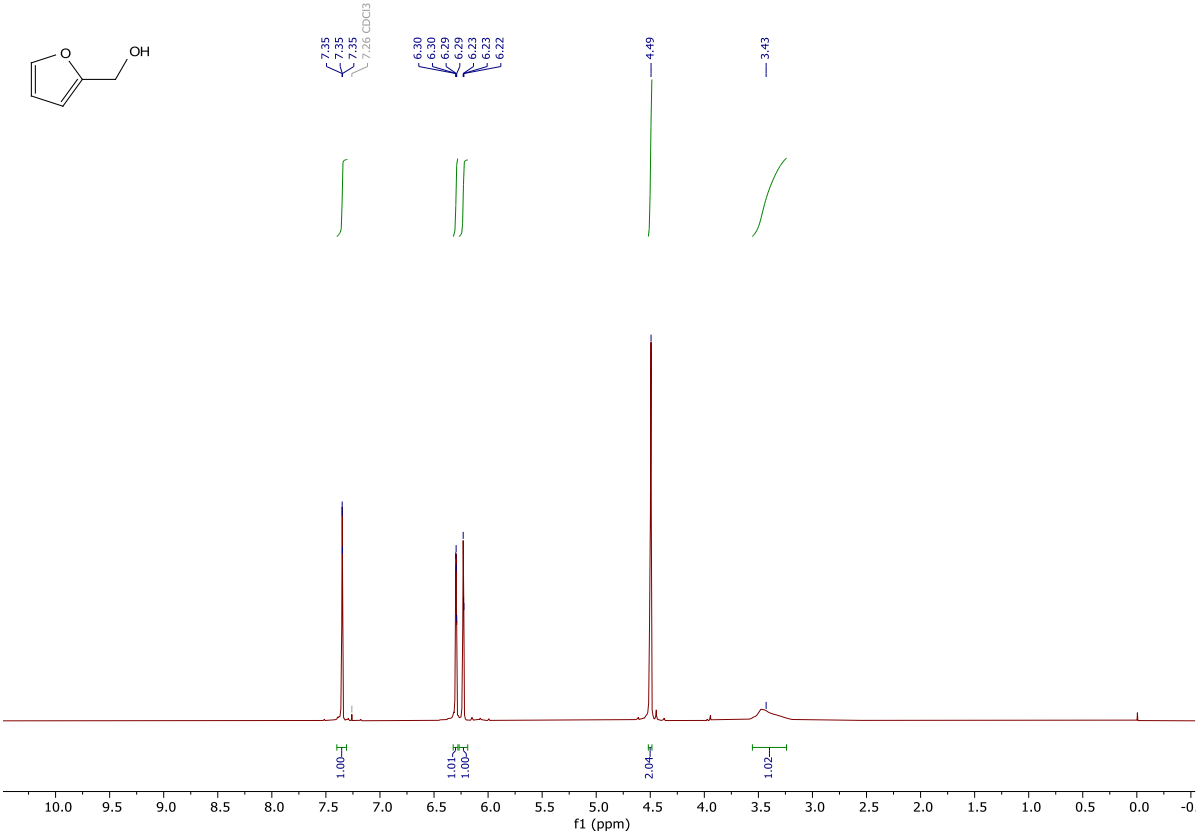
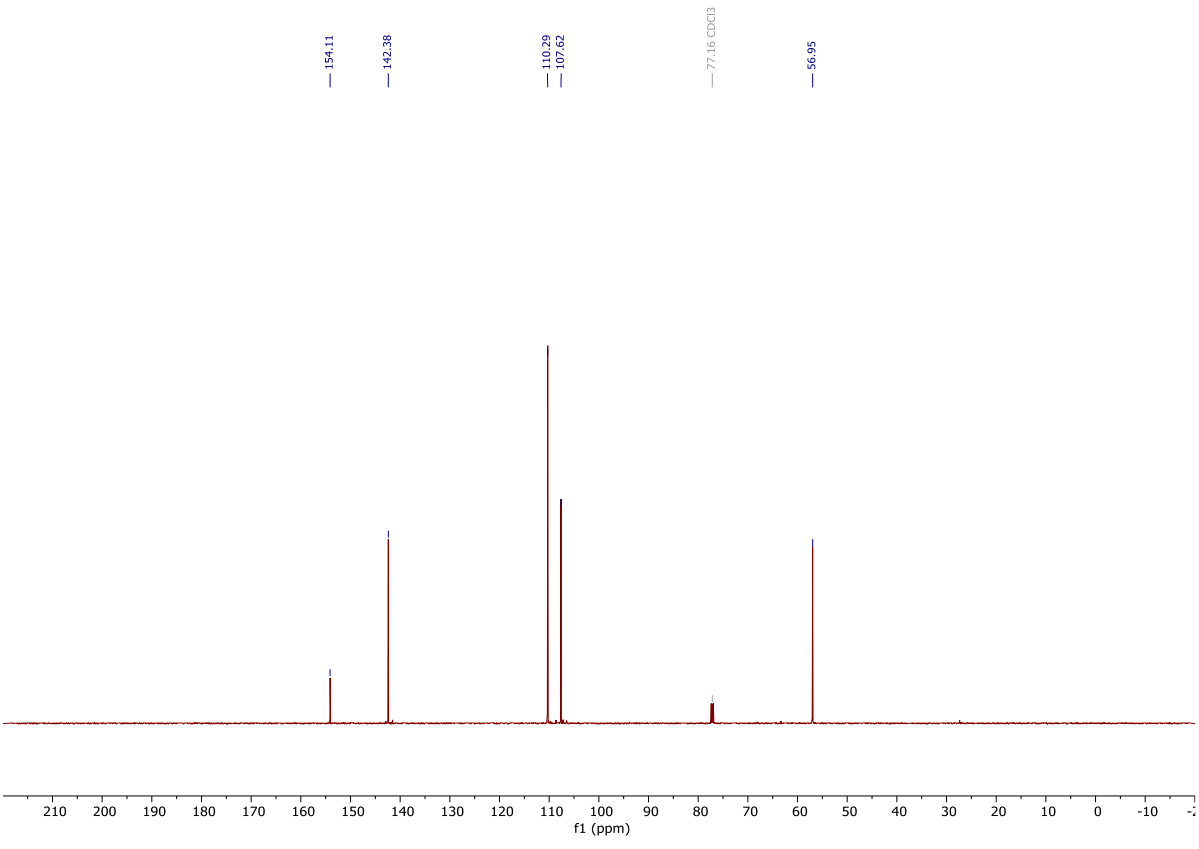
64.03
64.01
f1 (ppm)


OH
O
O
7.26 CDCl3
6.85
6.80
6.79
6.78
6.76
5.94
4.55
1.95
3.00
2.01
2.01
1.00
f1 (ppm)


147.92
147.19
135.01
120.60
108.31
107.99
101.11
77.16 CDCl3
65.31
f1 (ppm)


O
OH
7.35
7.35
7.35
7.26 CDCl3
6.30
6.30
6.29
6.29
6.23
6.23
6.22
4.49
3.43
1.00
1.01
1.00
2.04
1.02
f1 (ppm)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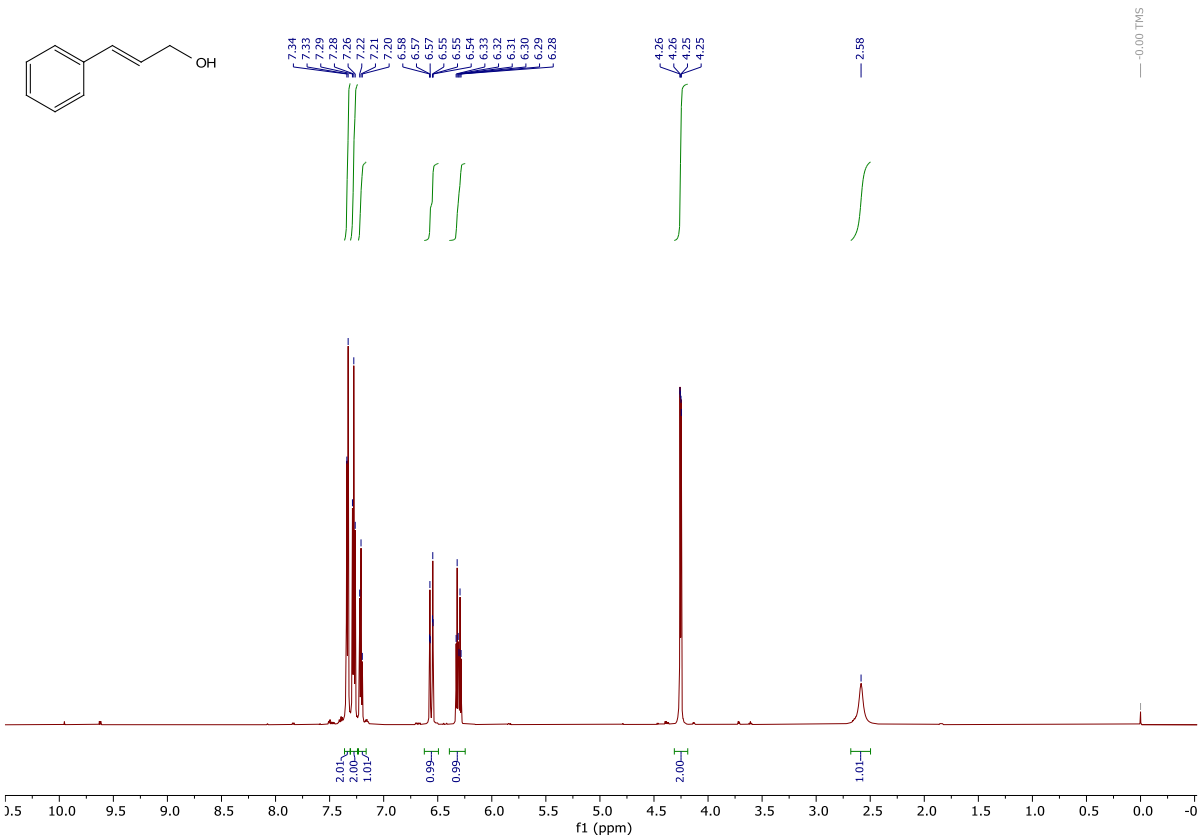
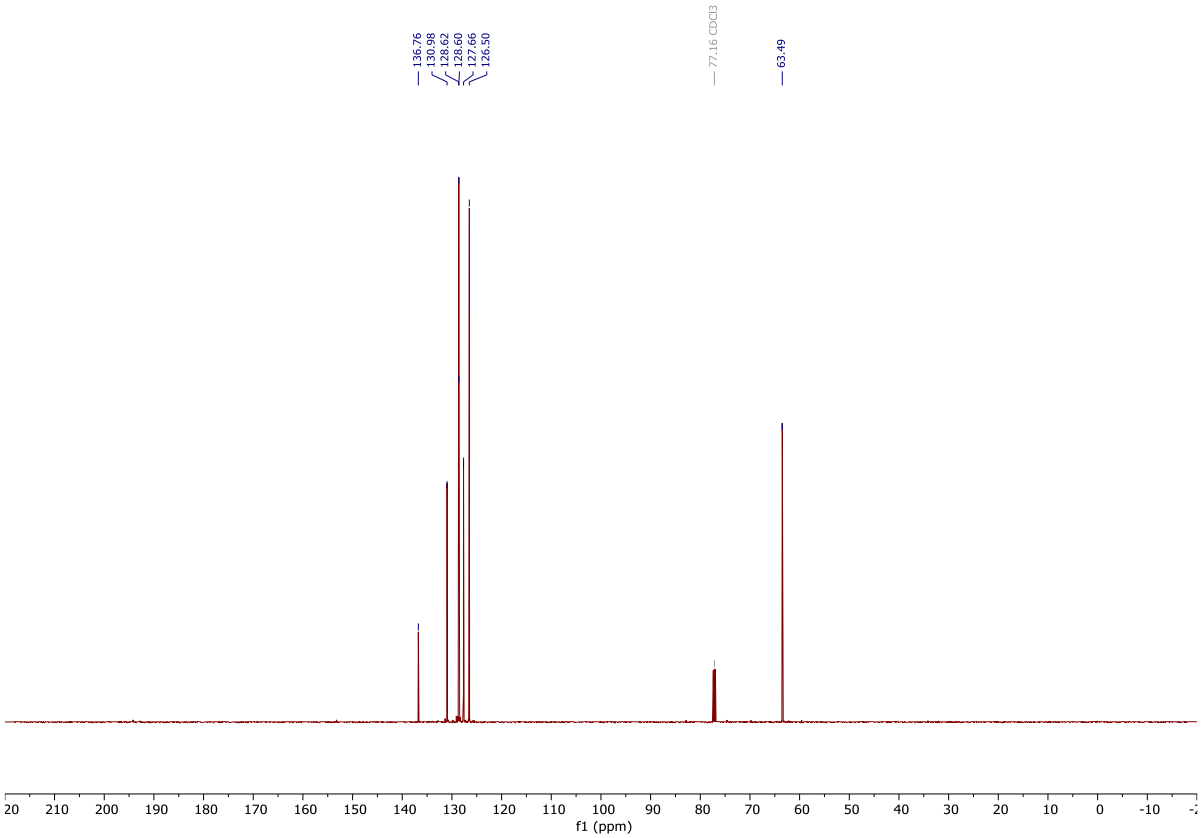
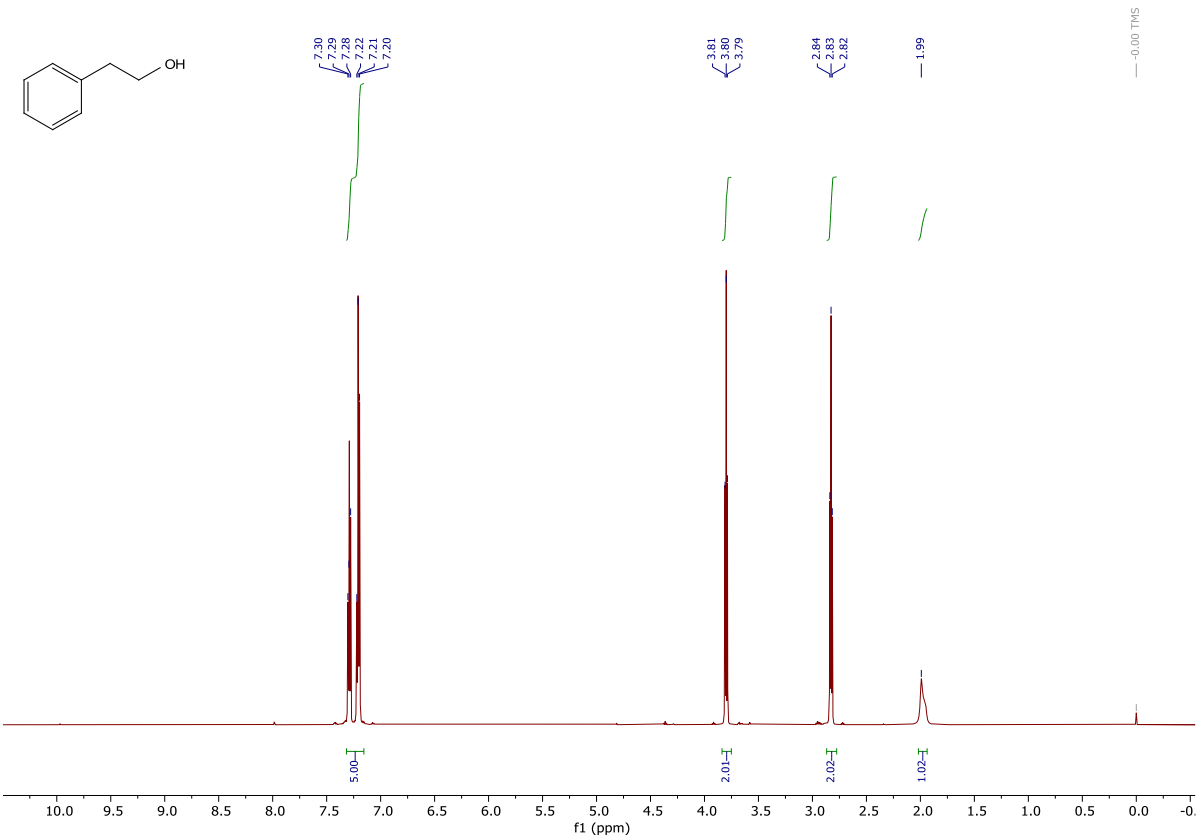
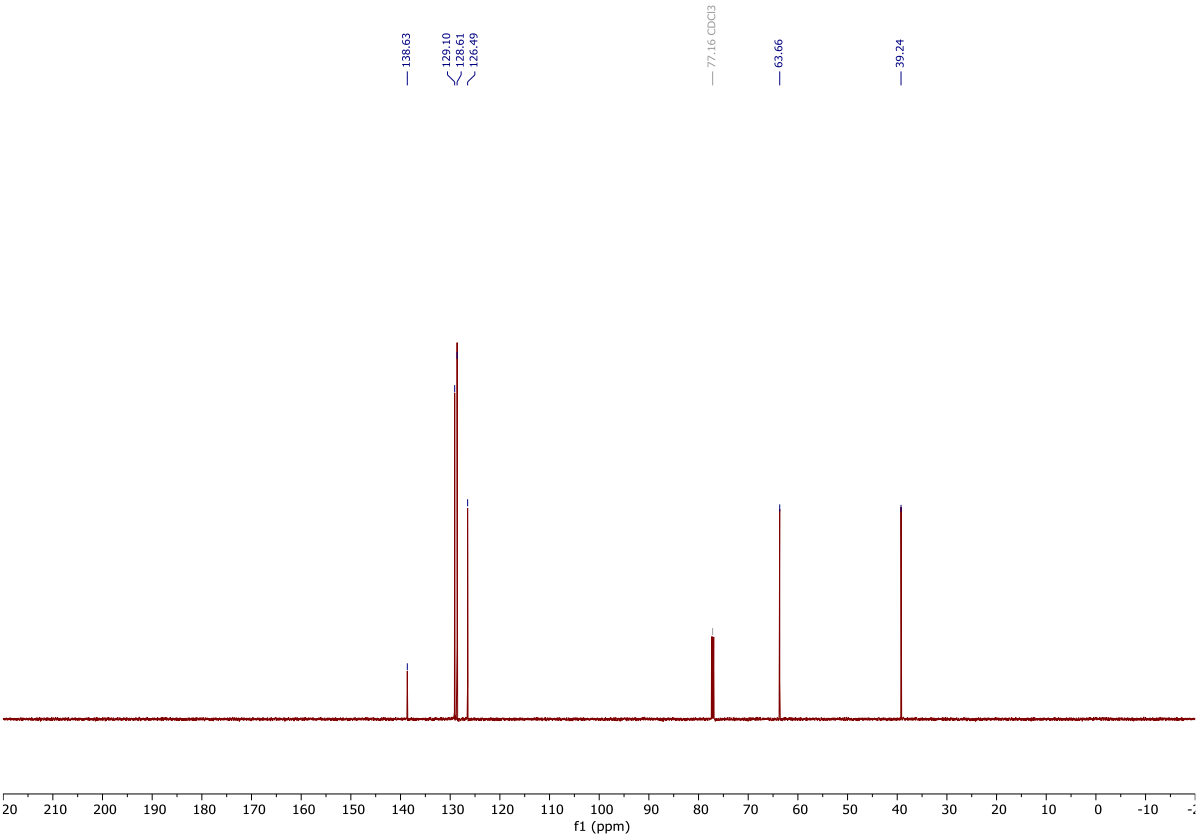
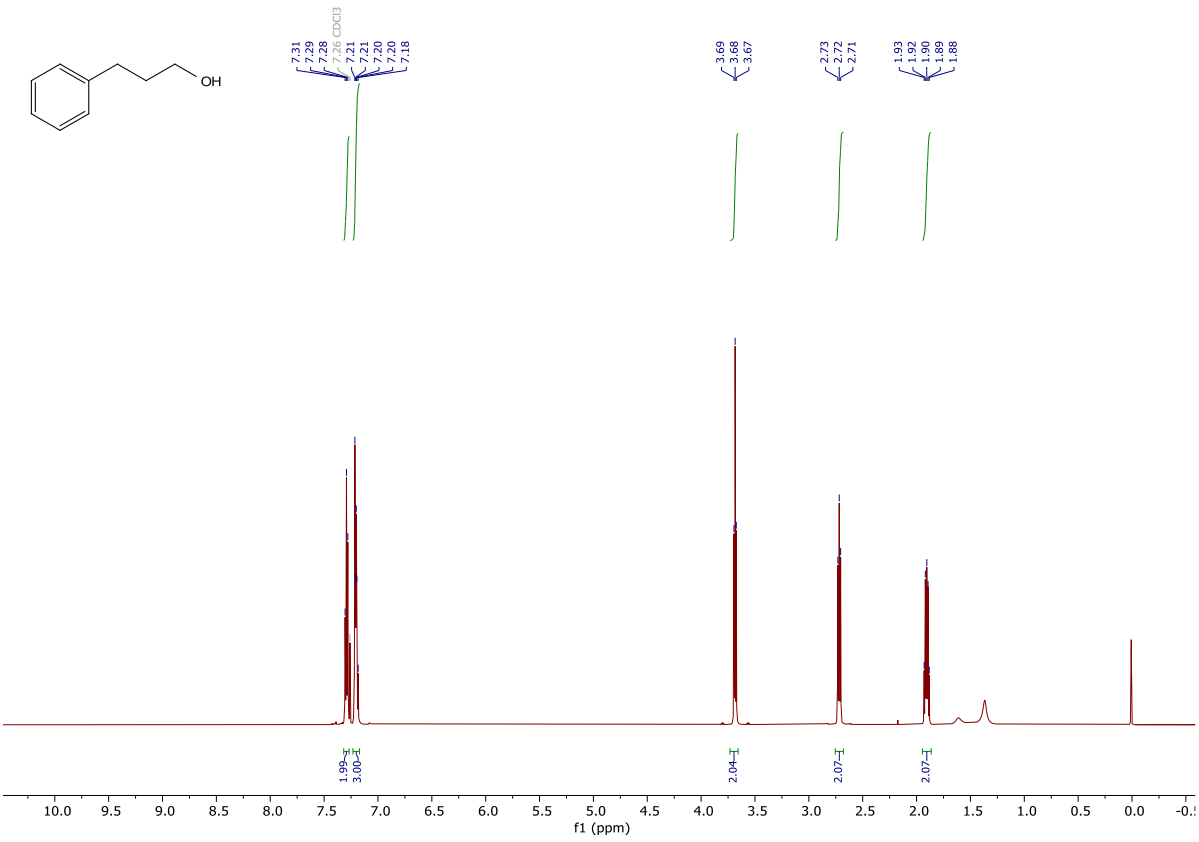
110.29
107.62
77.16 CDCl3
56.95
f1 (ppm)

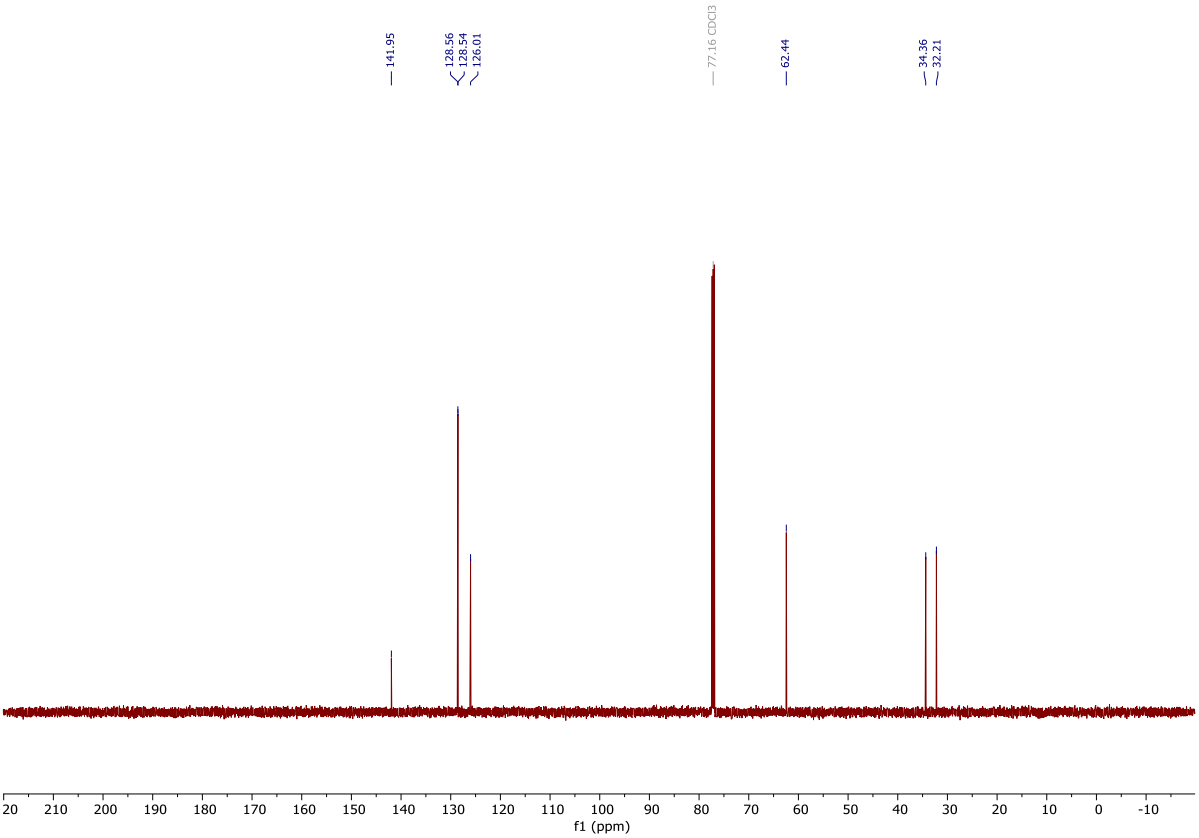

OH
7.34
7.33
7.29
7.28
7.26
7.22
7.21
7.20
6.58
6.57
6.57
6.55
6.55
6.54
6.33
6.32
6.31
6.30
6.29
6.28
4.26
4.26
4.25
4.25
2.58
0.00 TMS
2.01
2.00
1.01
0.99
0.99
2.00
1.01
f1 (ppm)

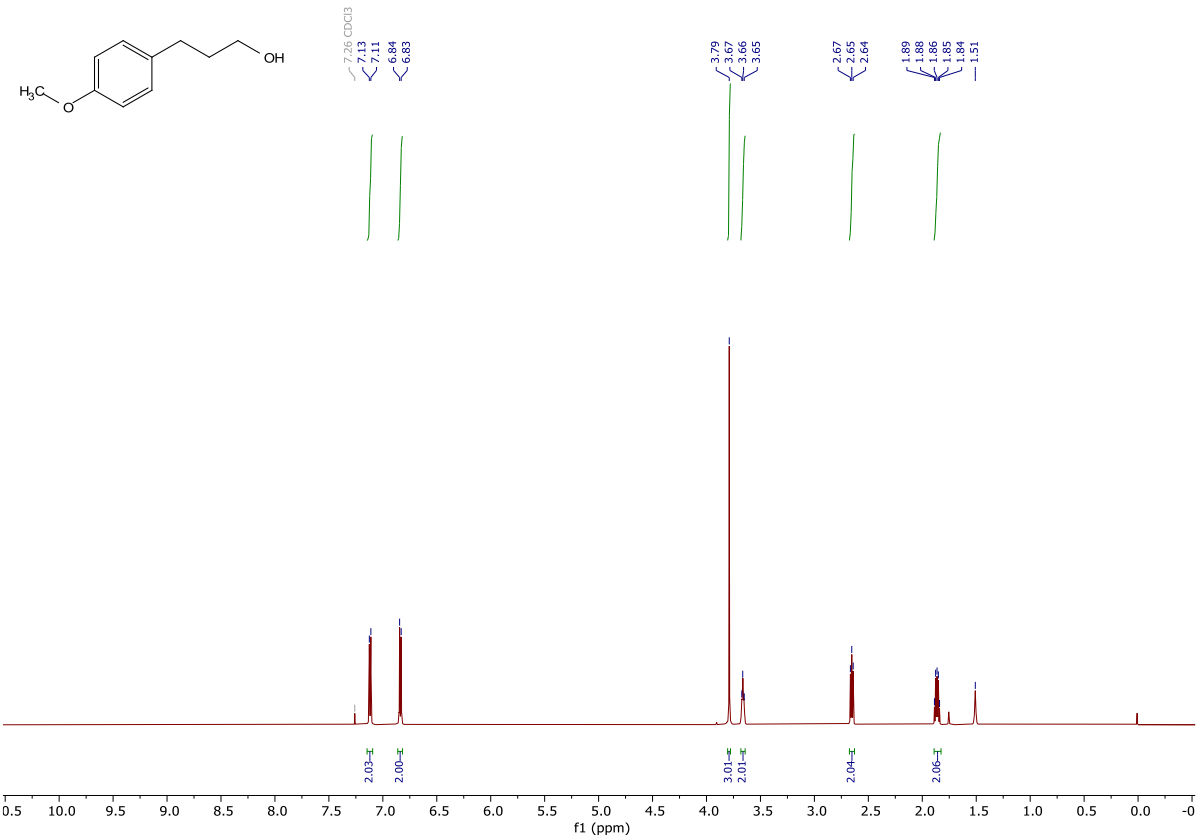

136.76
130.98
128.62
128.60
127.66
126.50
77.16 CDCl3
63.49
f1 (ppm)

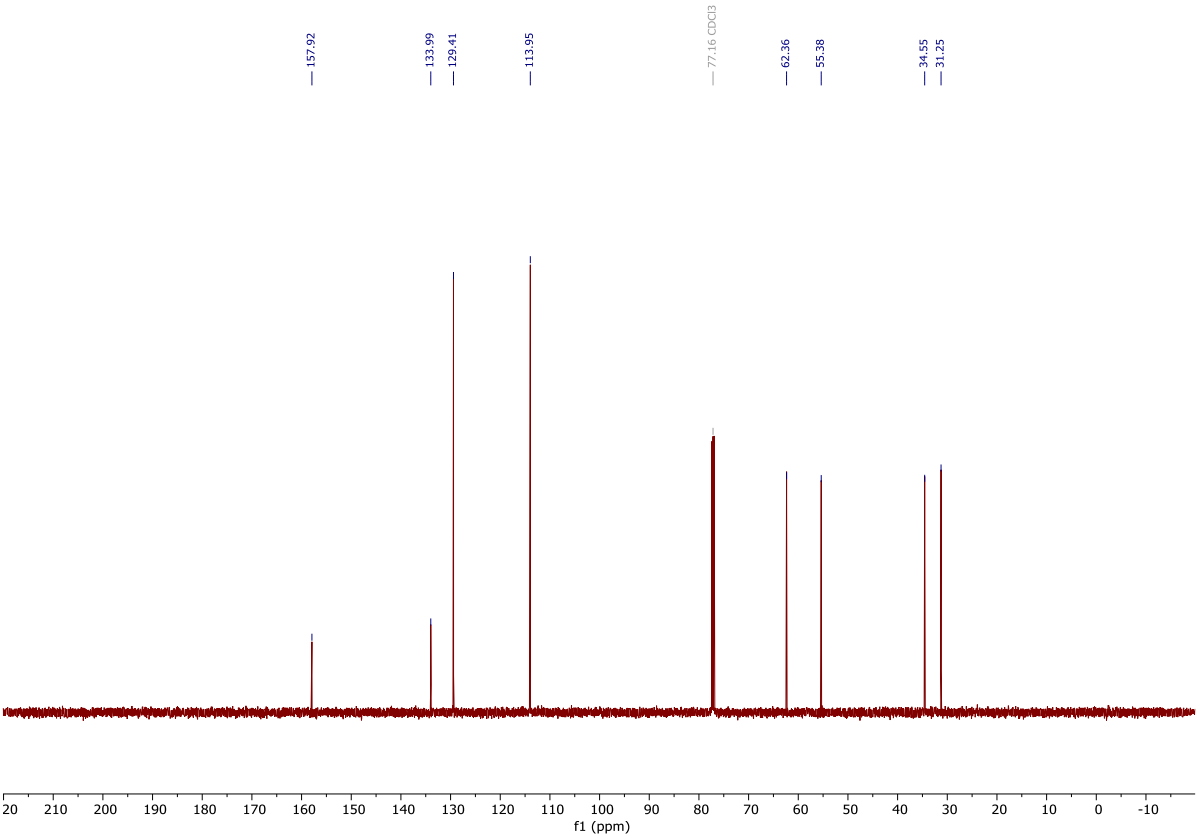

OH
7.30
7.29
7.28
7.22
7.21
7.20
3.81
3.80
3.79
2.84
2.83
2.82
1.99
0.00 TMS
5.00
2.01
2.02
1.02
f1 (ppm)

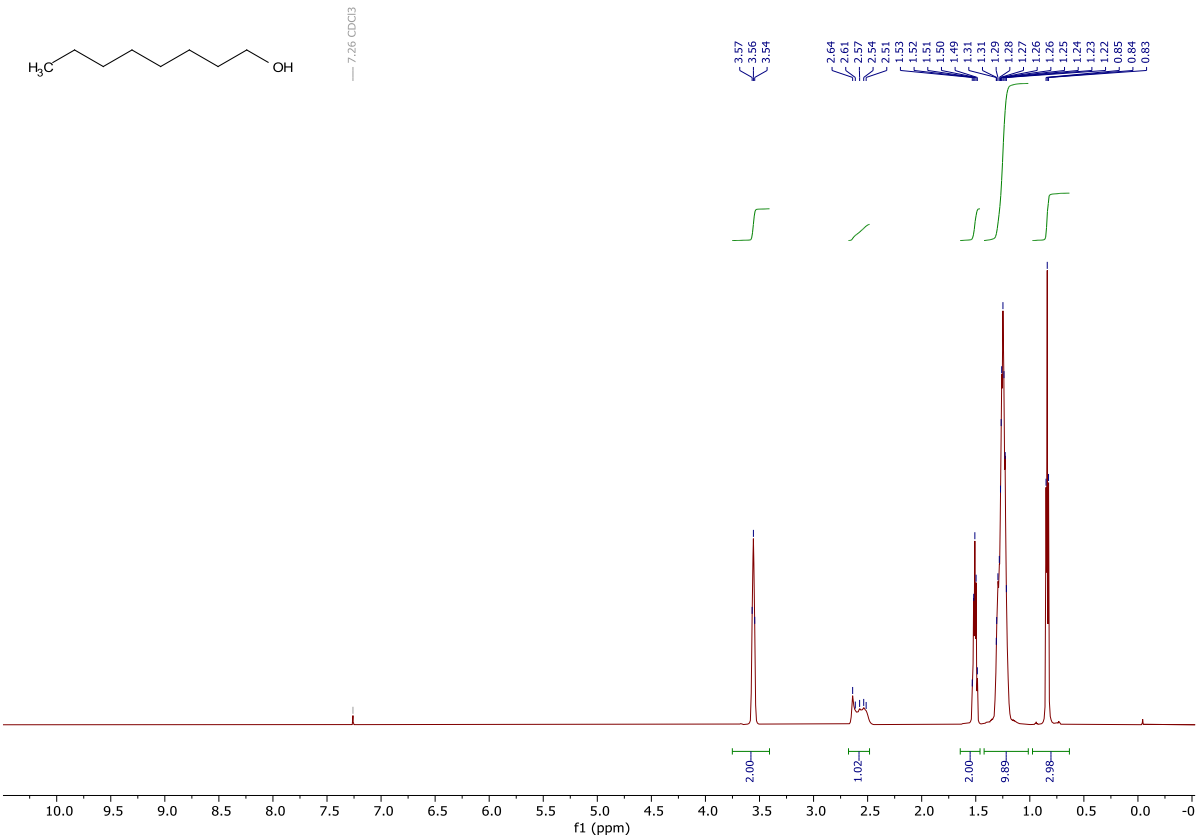

138.63
129.10
128.61
126.49
77.16 CDCl3
63.66
39.24
f1 (ppm)

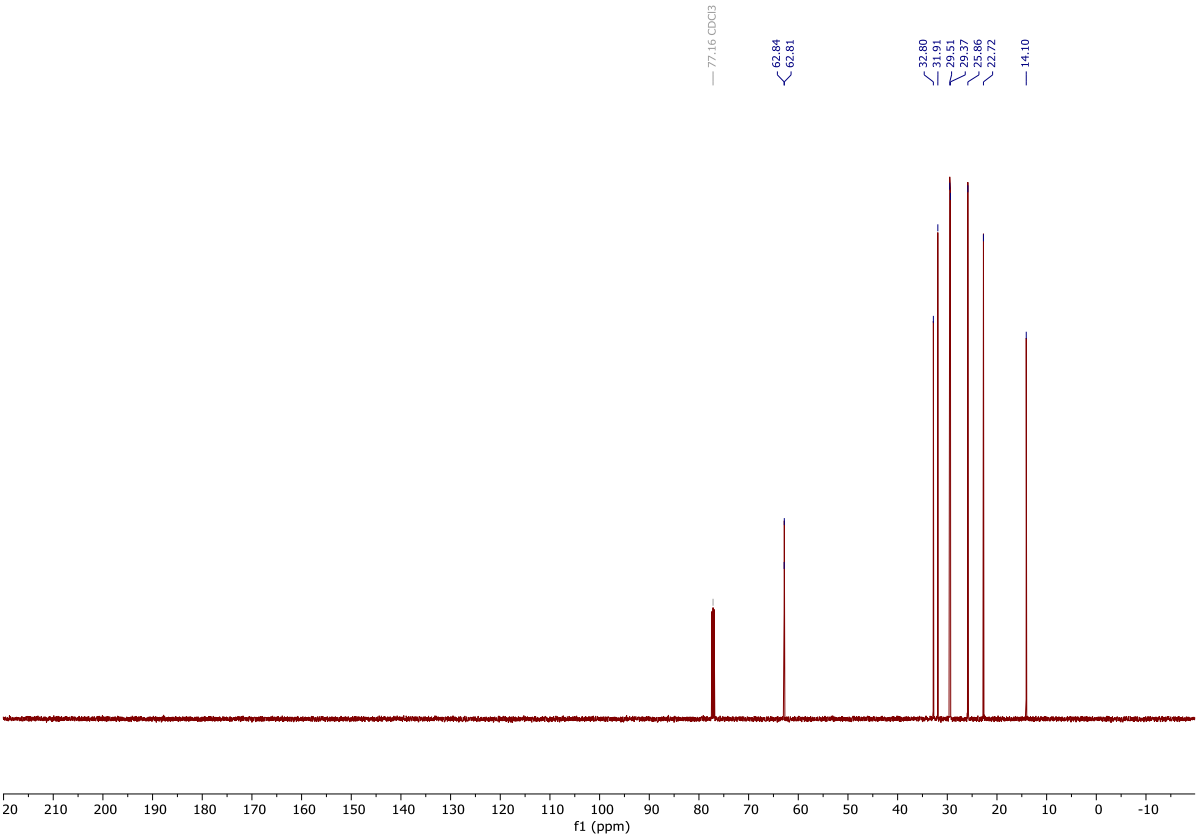

OH
7.31
7.29
7.28
7.26
CDCl3
7.21
7.20
7.20
7.18
3.69
3.68
3.67
2.73
2.72
2.71
1.93
1.92
1.90
1.89
1.88
1.99
3.00
2.04
2.07
2.07
f1 (ppm)

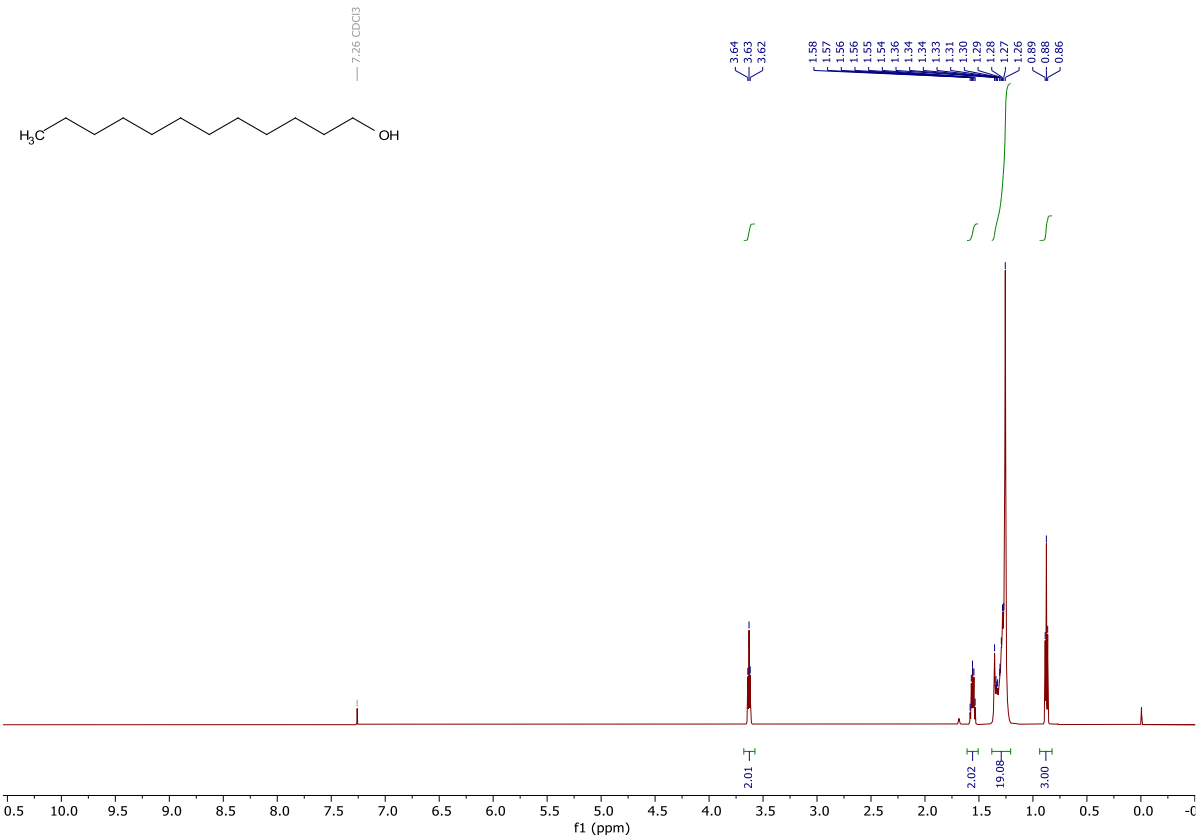

141.95
128.56
128.54
126.01
77.16 CDCl3
62.44
34.36
32.21
f1 (ppm)

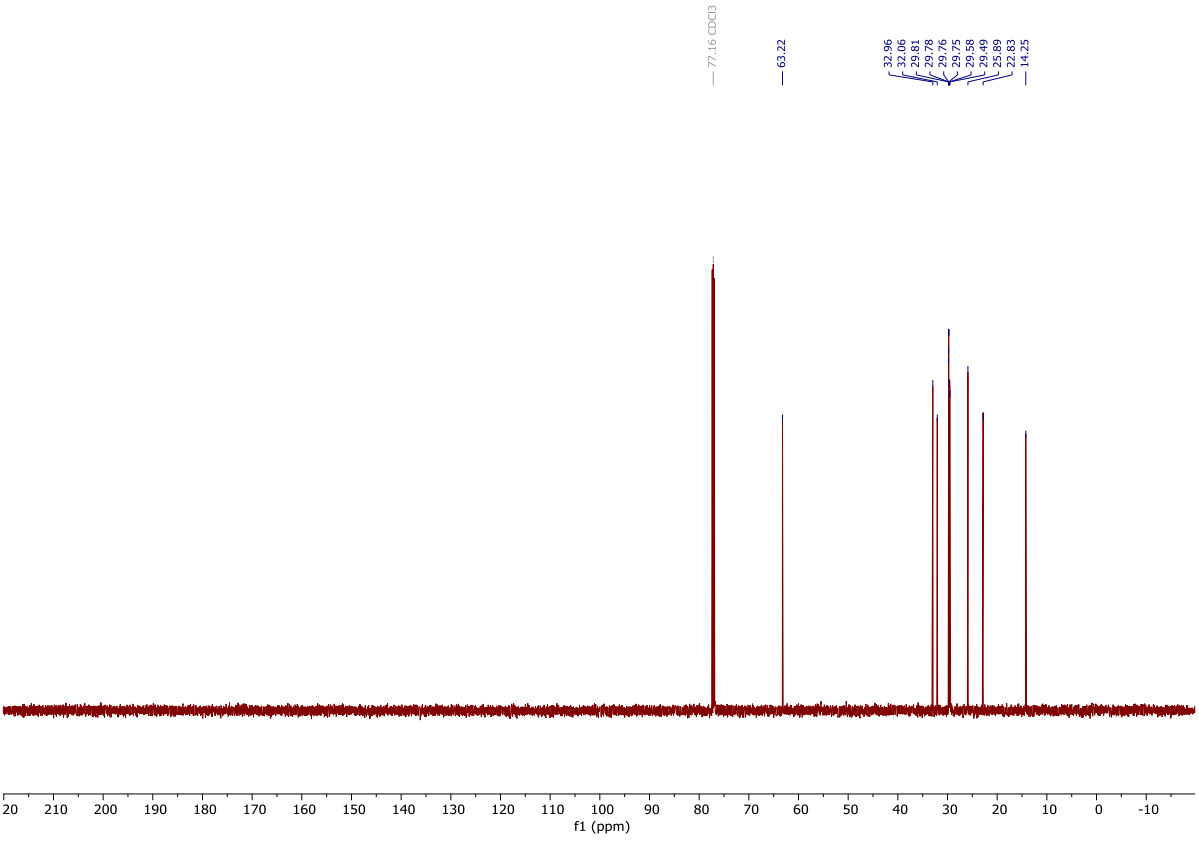

OH
H3C
O
7.26 CDCl3
7.13
7.11
6.84
6.83
3.79
3.67
3.66
3.65
2.67
2.65
2.64
1.89
1.88
1.86
1.85
1.84
1.51
2.03
2.00
3.01
2.01
2.04
2.06
f1 (ppm)

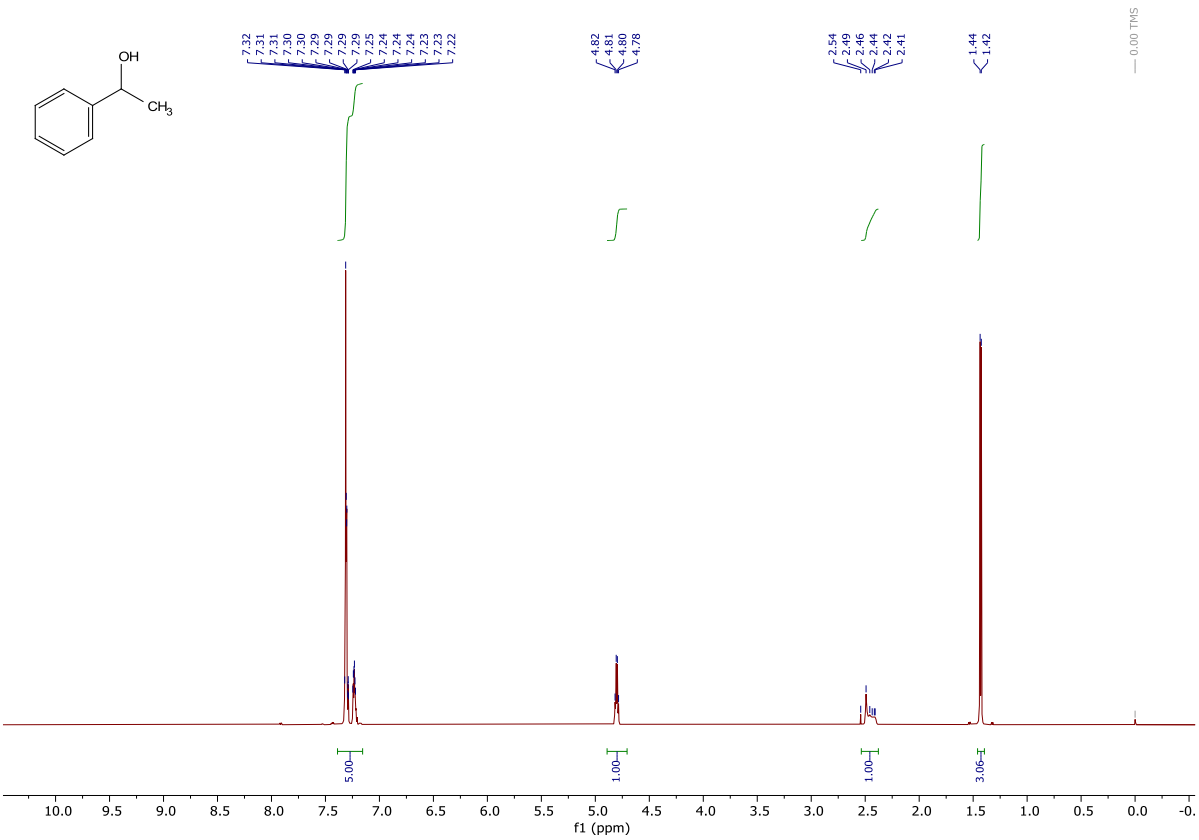

157.92
133.99
129.41
113.95
77.16 CDCl3
62.36
55.38
34.55
31.25
f1 (ppm)

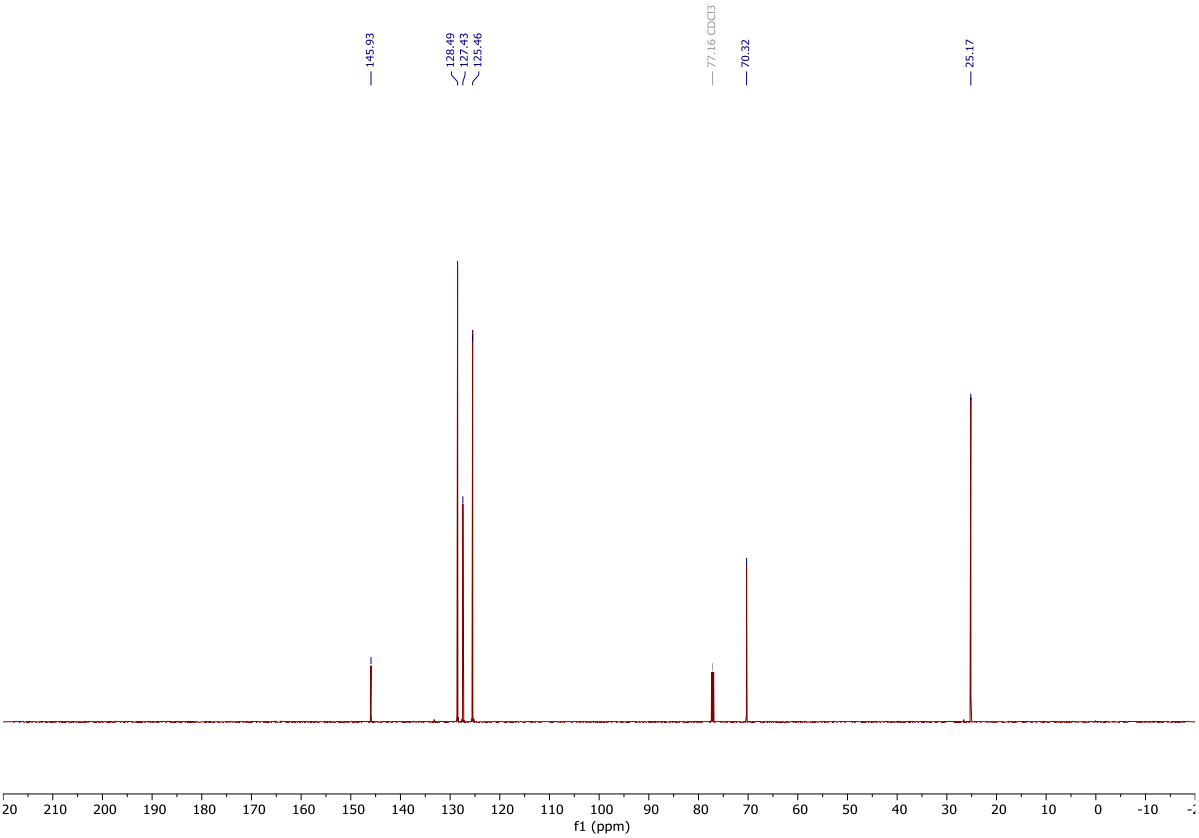

H3C
OH
7.26 CDCl3
3.57
3.56
3.54
2.64
2.61
2.57
2.54
2.51
1.53
1.52
1.51
1.50
1.49
1.31
1.31
1.29
1.28
1.27
1.26
1.26
1.25
1.24
1.23
1.22
0.85
0.84
0.83
2.00
1.02
2.00
9.89
2.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

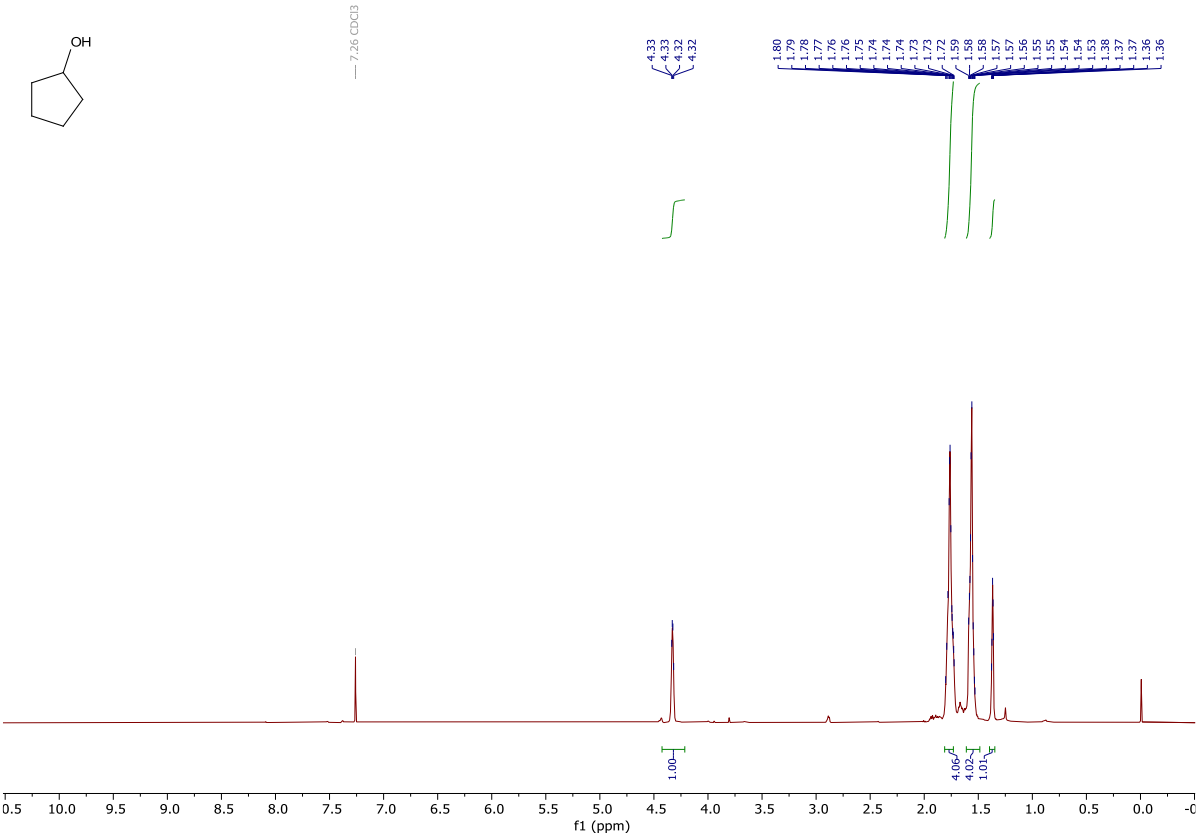

77.16 CDCl3
62.84
62.81
32.80
31.91
29.51
29.37
25.86
22.72
14.10
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
H3C
OH
3.64
3.63
3.62
1.58
1.57
1.56
1.55
1.54
1.36
1.34
1.34
1.33
1.31
1.30
1.29
1.28
1.27
1.26
0.89
0.88
0.86
2.01
2.02
19.08
3.00
f1 (ppm)


77.16 CDCl3
63.22
32.96
32.06
29.81
29.78
29.76
29.75
29.58
29.49
25.89
22.83
14.25
f1 (ppm)


OH
CH3
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.29
7.29
7.25
7.24
7.24
7.24
7.23
7.23
7.22
4.82
4.81
4.80
4.78
2.54
2.49
2.46
2.44
2.42
2.41
1.44
1.42
0.00 TMS
5.00
1.00
1.00
3.06
f1 (ppm)


145.93
128.49
127.43
125.46
77.16 CDCl3
70.32
25.17
f1 (ppm)


OH
7.26 CDCl3
4.33
4.33
4.32
4.32
1.80
1.79
1.78
1.77
1.76
1.76
1.75
1.74
1.74
1.74
1.73
1.73
1.72
1.59
1.58
1.58
1.57
1.57
1.56
1.55
1.55
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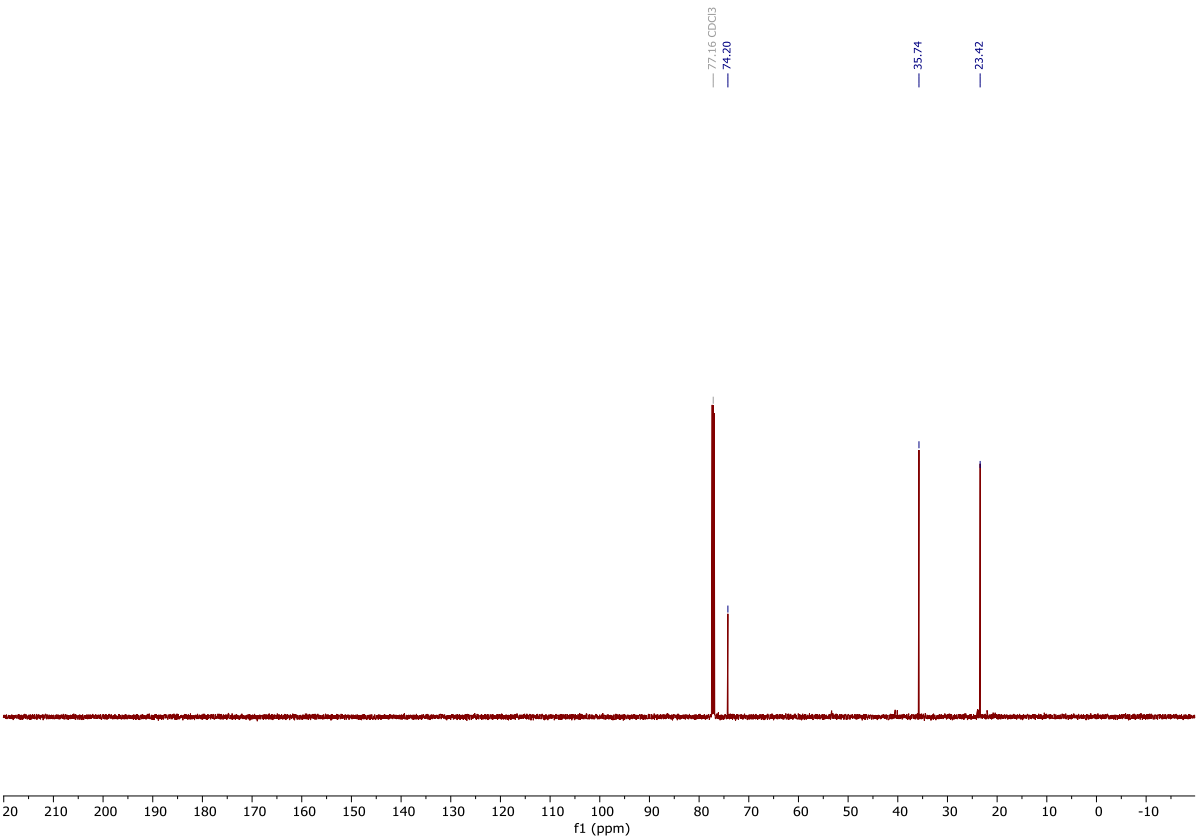
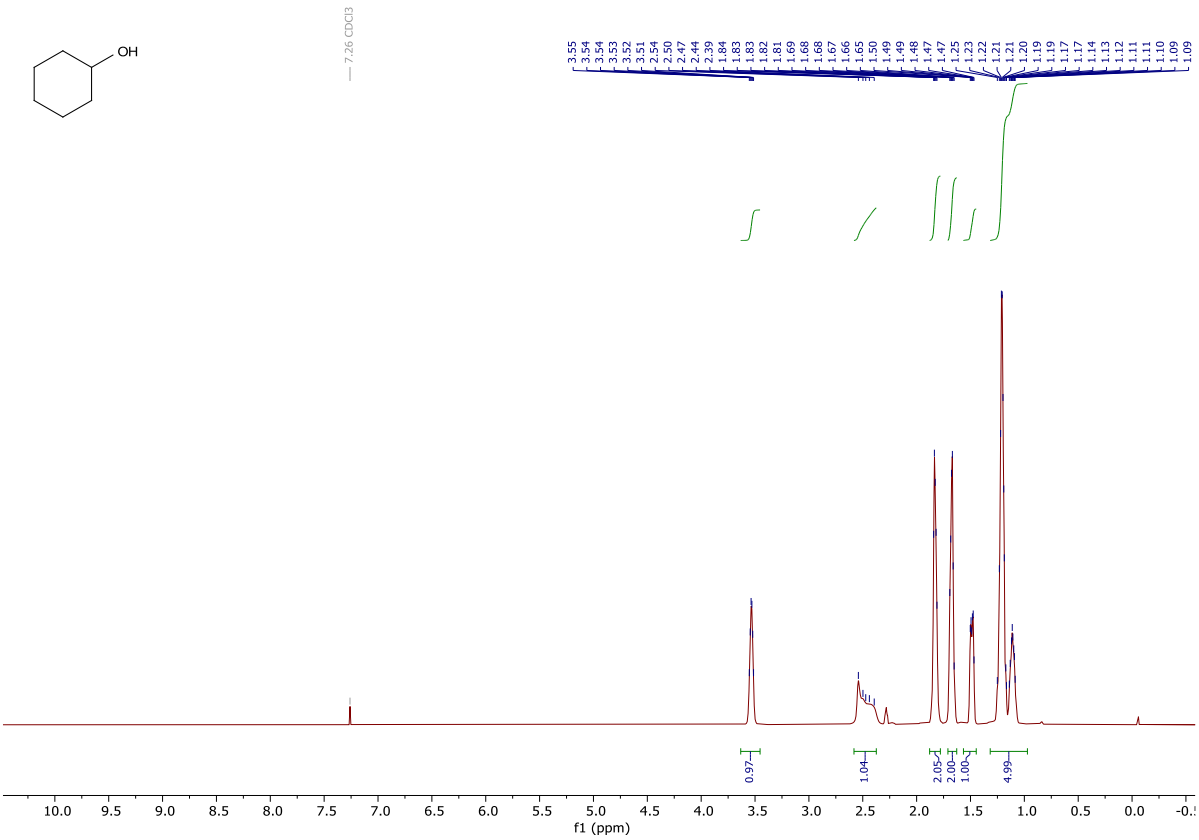
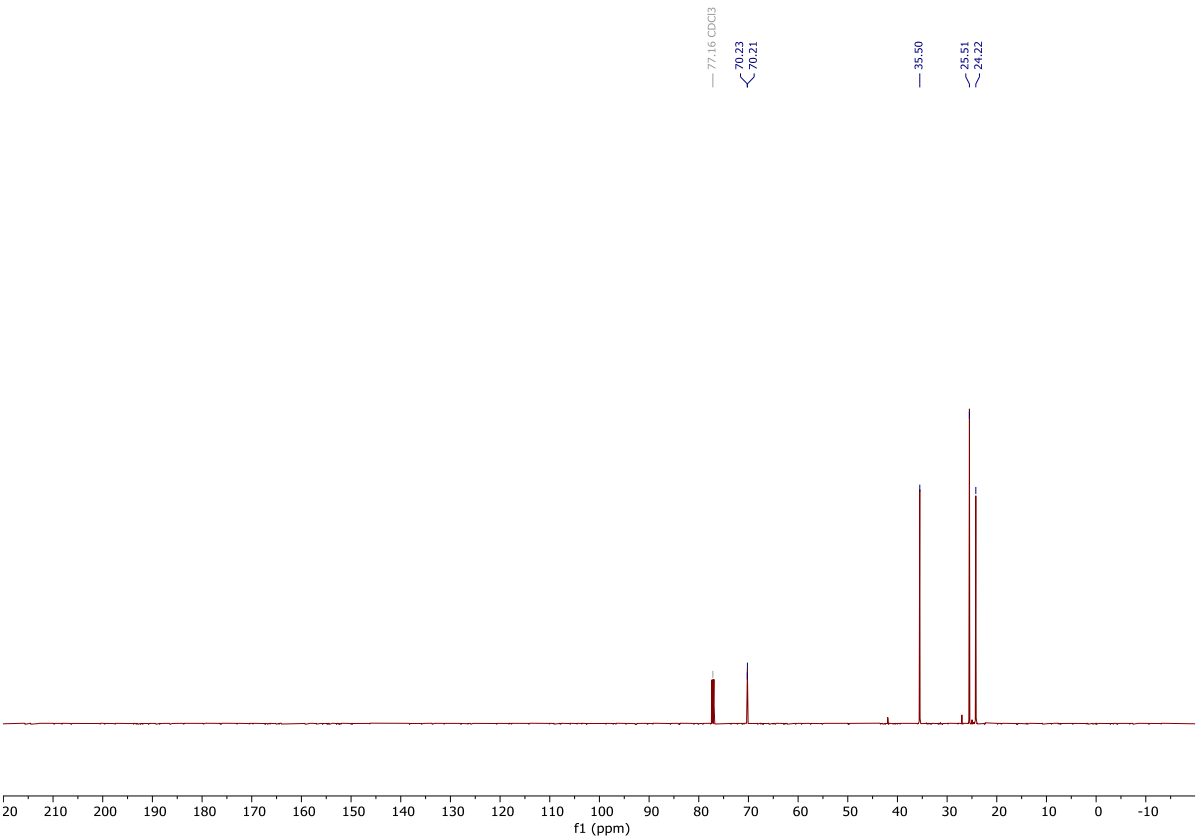
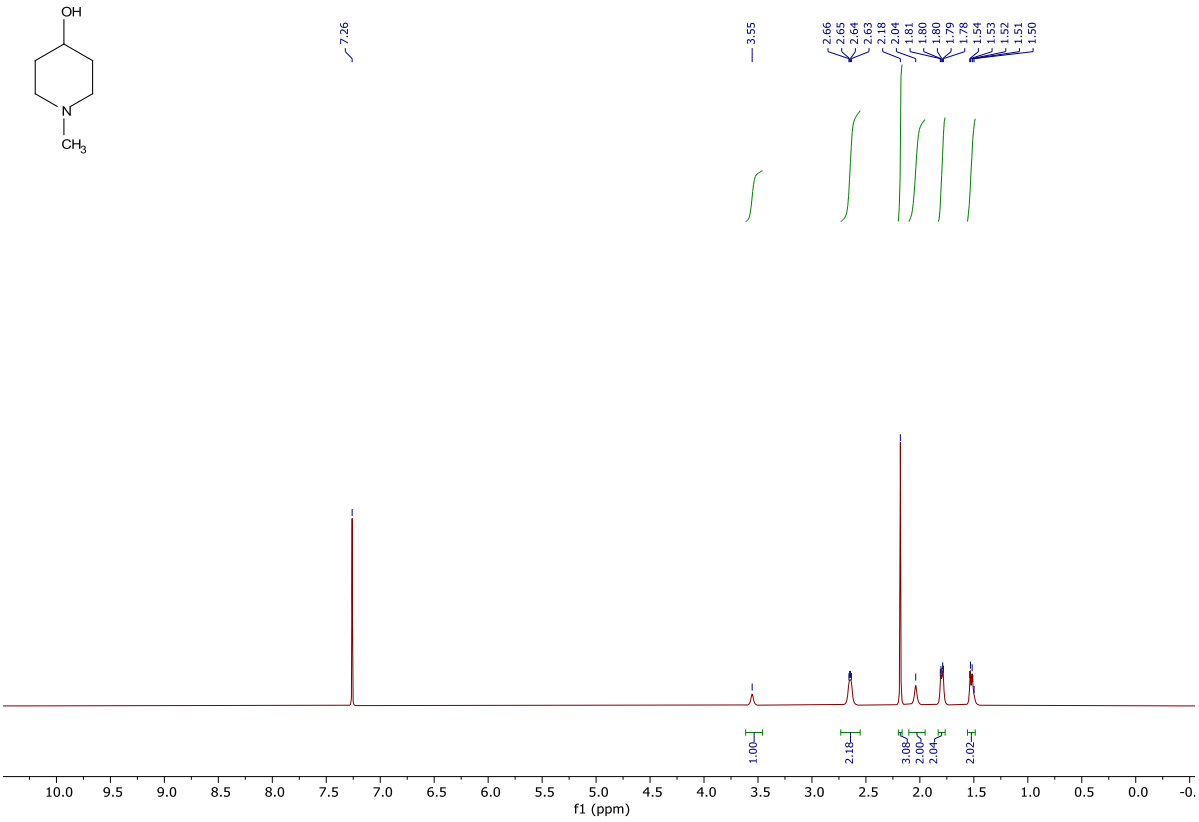
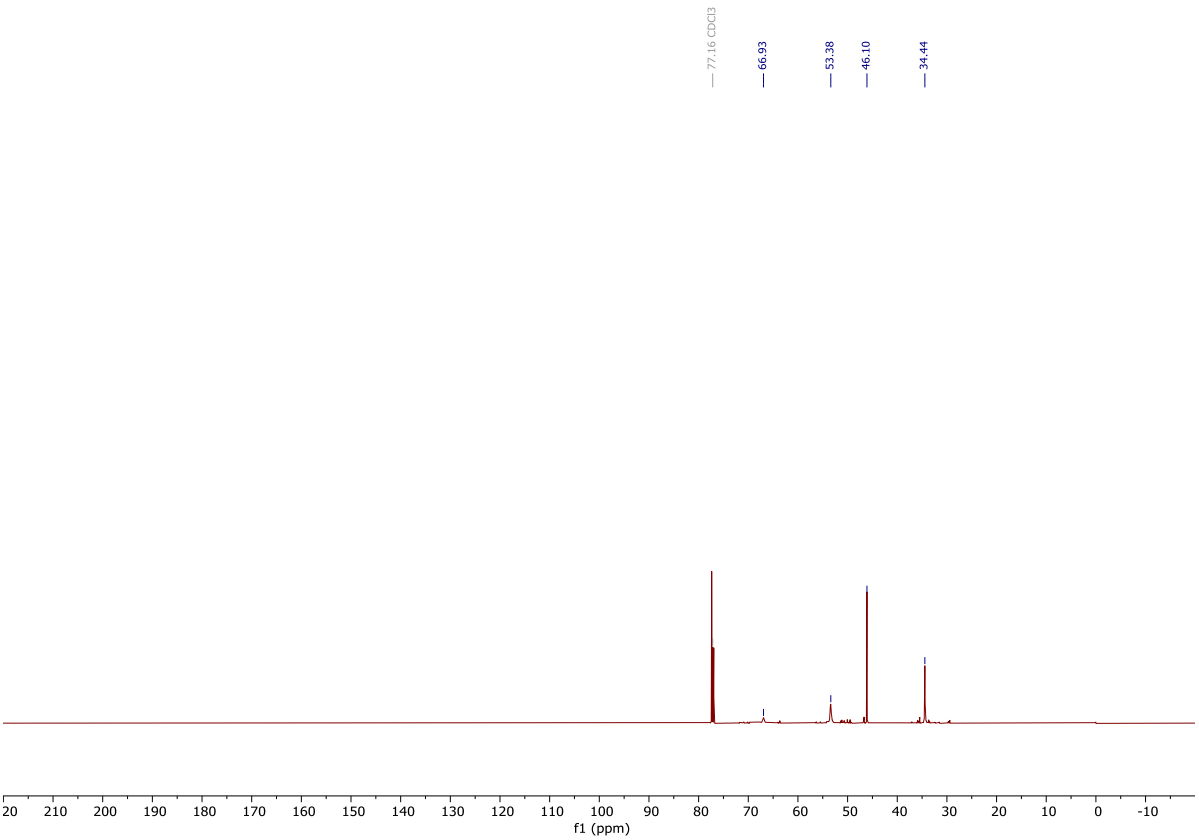
1.00
4.06
4.02
1.01
f1 (ppm)

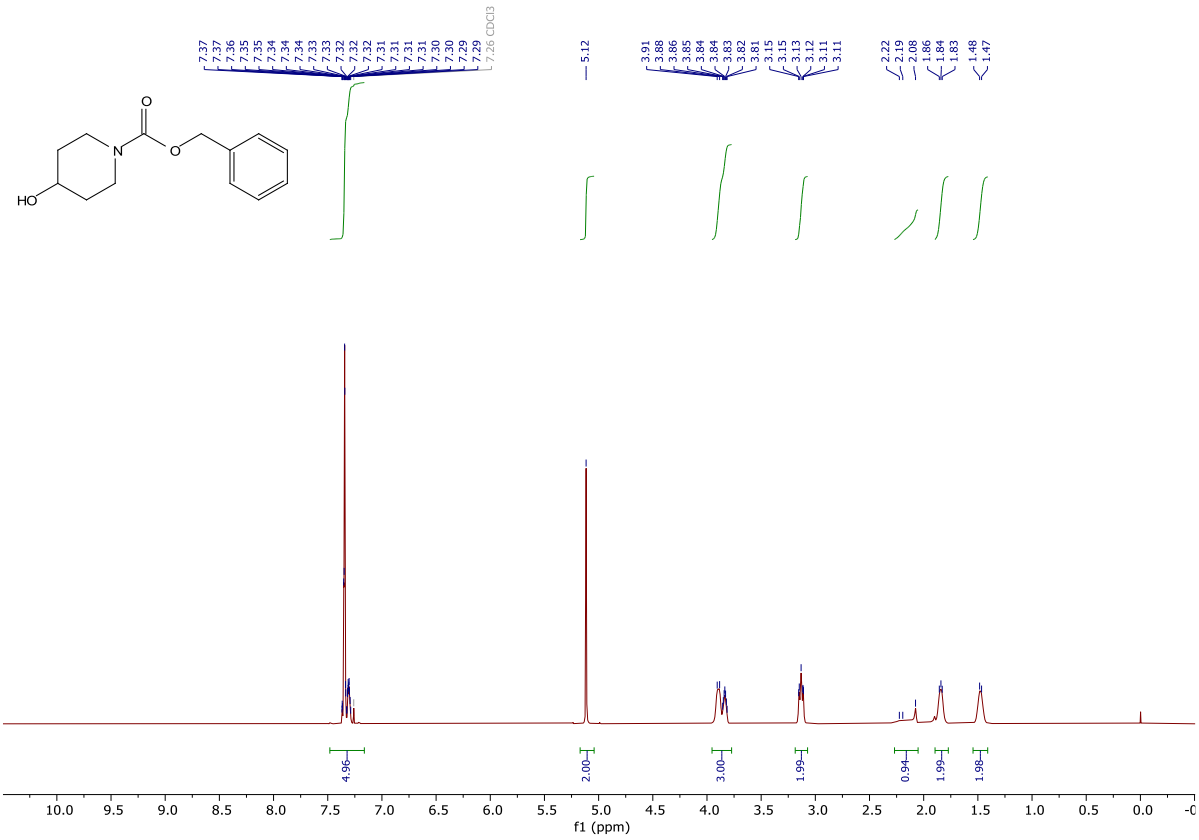

77.16 CDCl3
74.20
35.74
23.42
f1 (ppm)

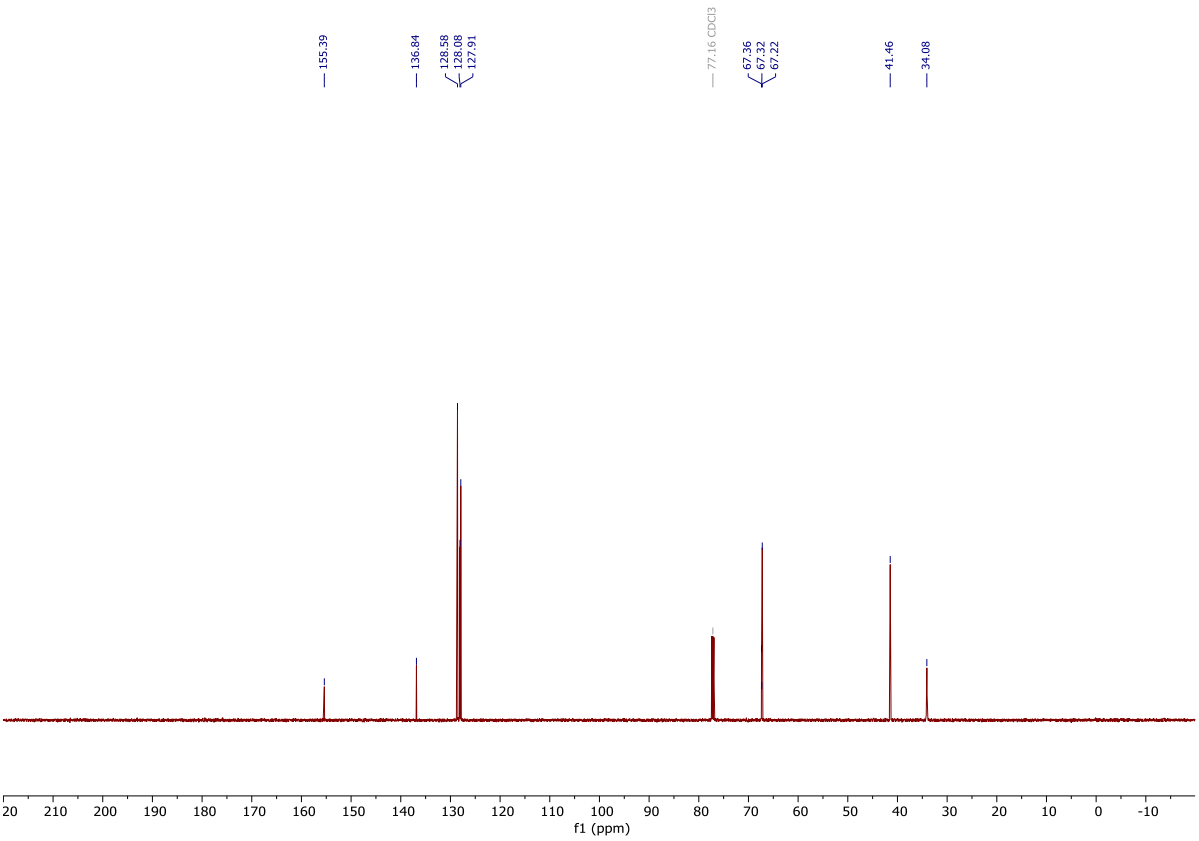

OH
7.26 CDCl3
3.55
3.54
3.54
3.53
3.52
3.51
2.54
2.50
2.47
2.44
2.39
1.84
1.83
1.83
1.82
1.81
1.69
1.68
1.68
1.67
1.66
1.65
1.50
1.49
1.49
1.48
1.47
1.47
1.25
1.23
1.22
1.21
1.21
1.20
1.19
1.19
1.17
1.17
1.14
1.13
1.12
1.11
1.11
1.10
1.09
1.09
0.97
1.04
2.05
2.00
1.00
4.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

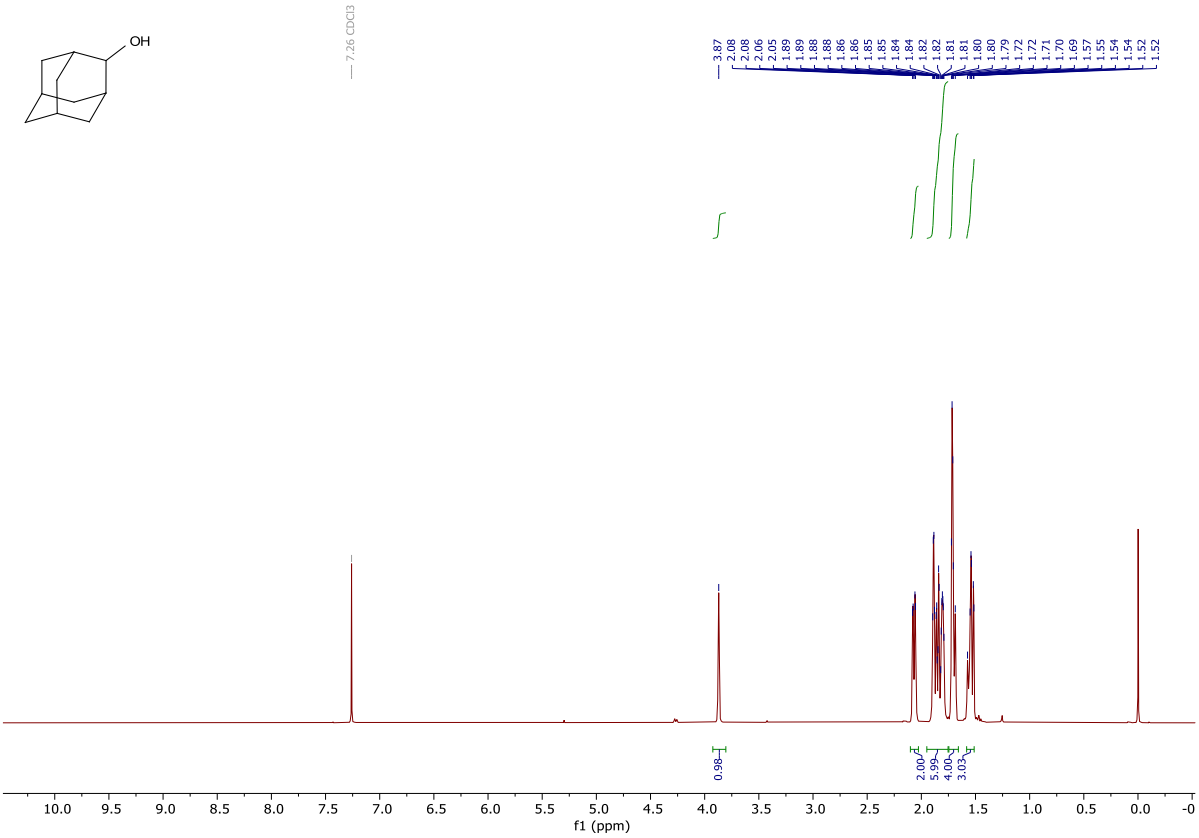

77.16 CDCl3
70.23
70.21
35.50
25.51
24.22
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

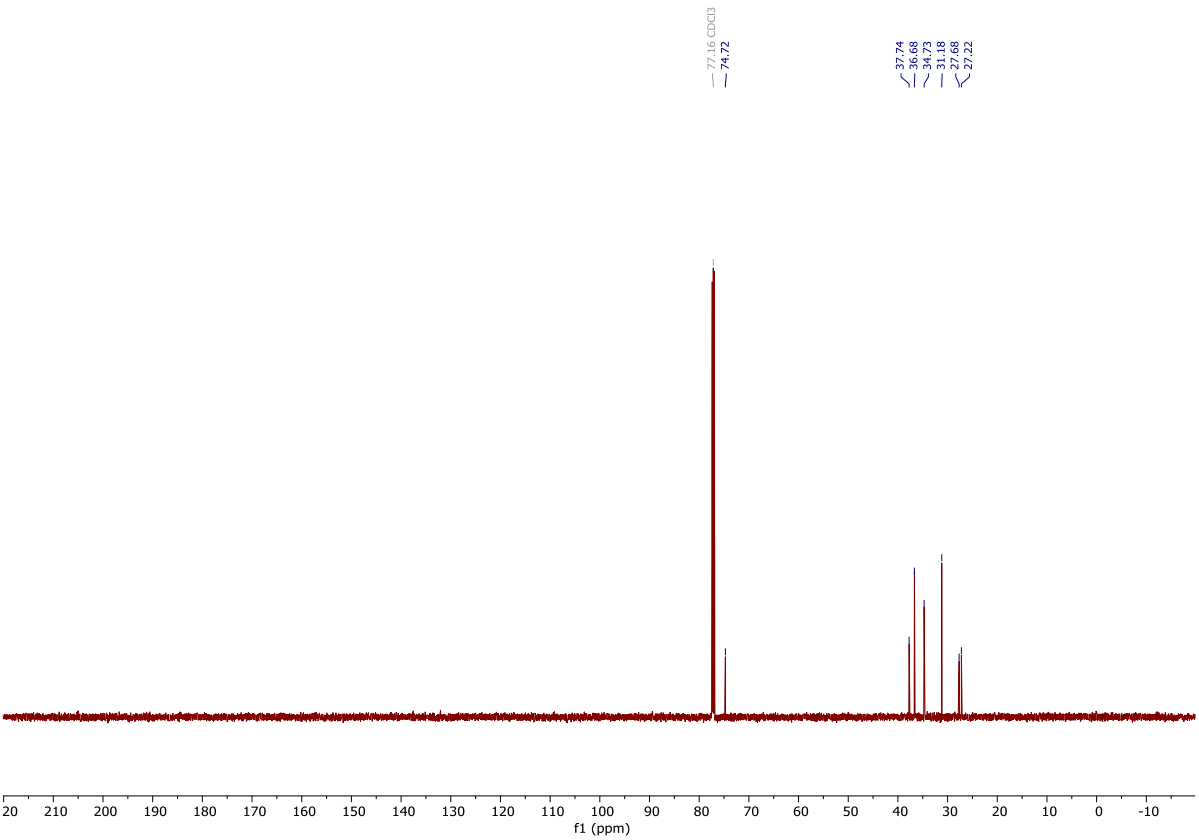

OH
N
CH3
7.26
3.55
2.66
2.65
2.64
2.63
2.18
2.04
1.81
1.80
1.80
1.79
1.78
1.54
1.53
1.52
1.51
1.50
1.00
2.18
3.08
2.00
2.04
2.02
f1 (ppm)

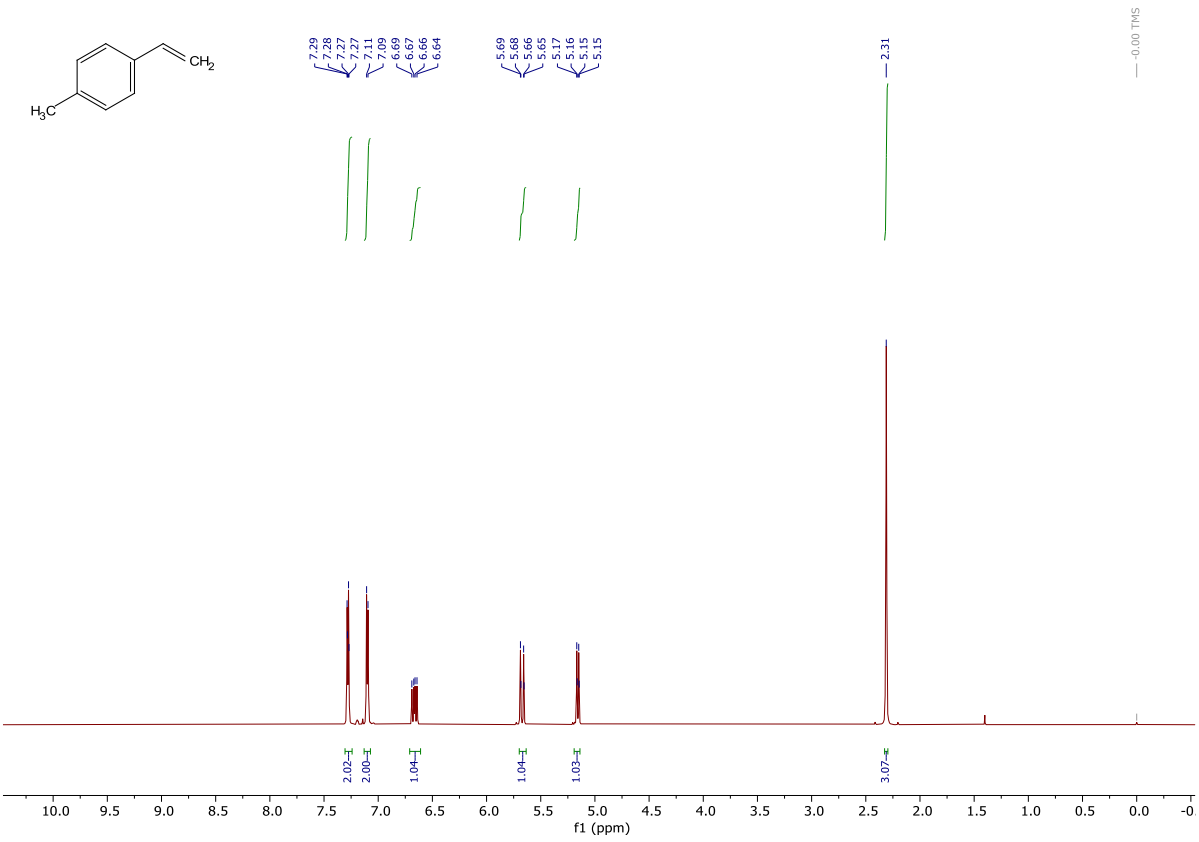

77.16 CDCl3
66.93
53.38
46.10
34.44
f1 (ppm)

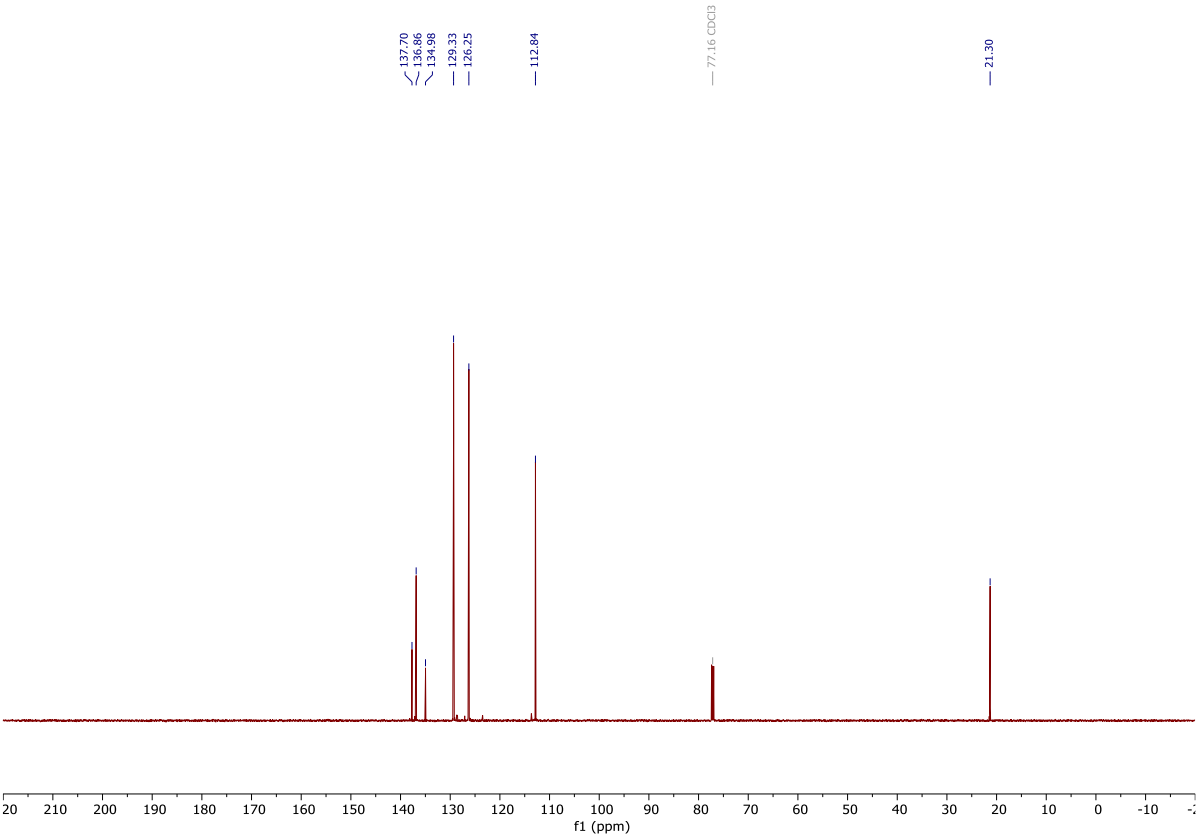

7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.26 CDCl3
5.12
3.91
3.88
3.86
3.85
3.84
3.84
3.83
3.82
3.81
3.15
3.15
3.13
3.12
3.11
3.11
2.22
2.19
2.08
1.86
1.84
1.83
1.48
1.47
O
N
O
HO
4.96
2.00
3.00
1.99
0.94
1.99
1.98
f1 (ppm)

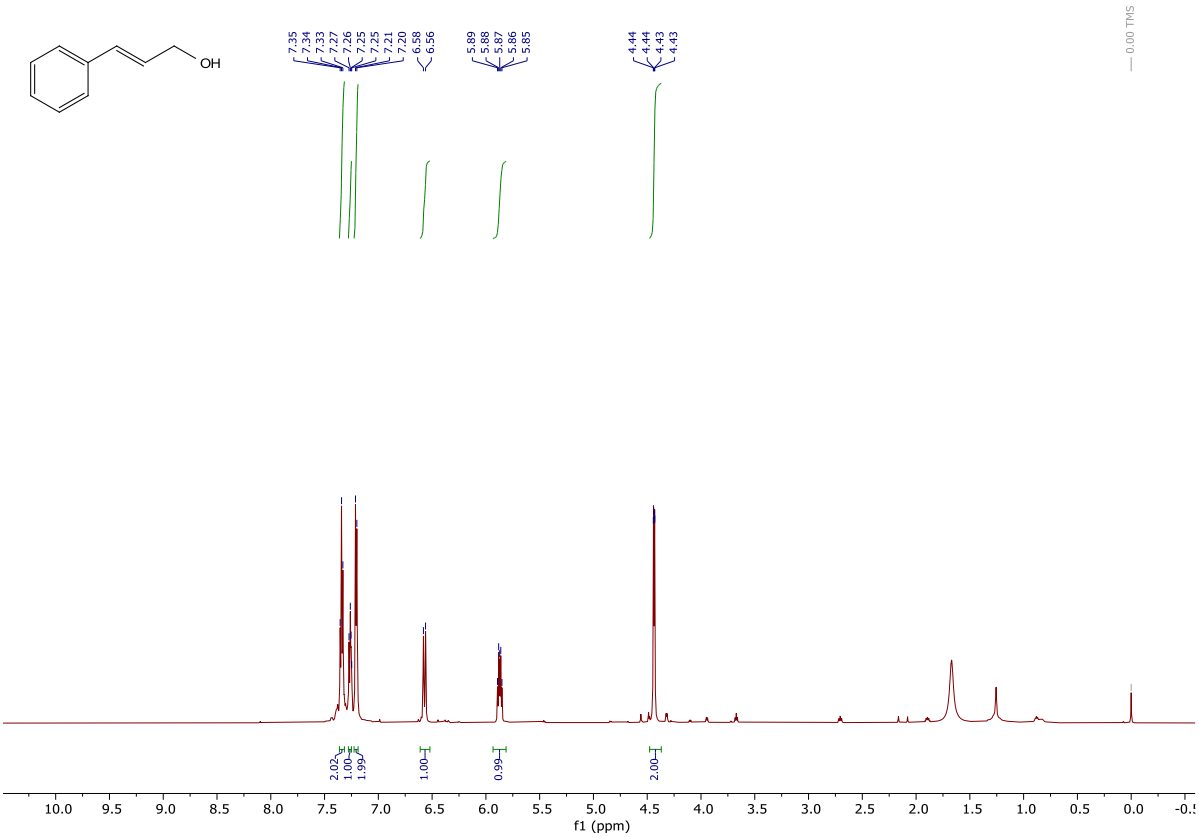

155.39
136.84
128.58
128.08
127.91
77.16 CDCl3
67.36
67.32
67.22
41.46
34.08
f1 (ppm)

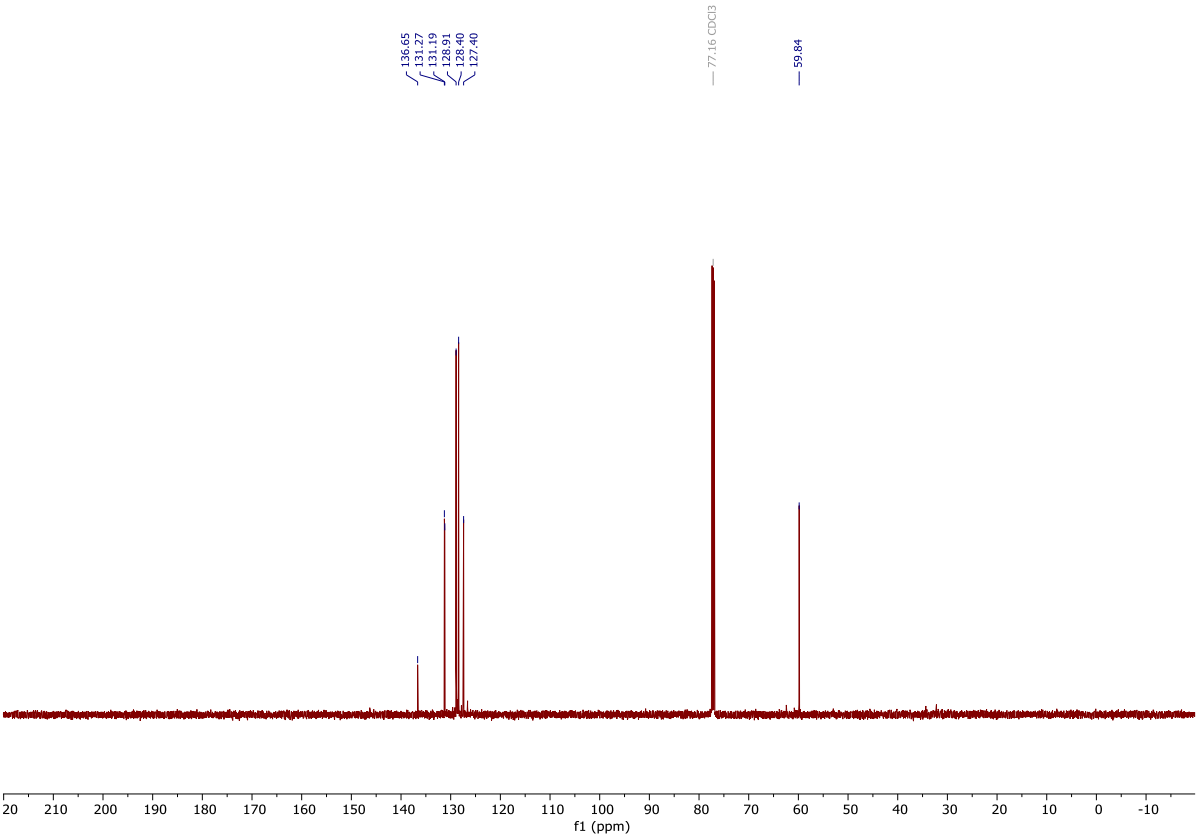

OH
7.26 CDCl3
3.87
2.08
2.08
2.06
2.05
1.89
1.89
1.88
1.88
1.86
1.86
1.85
1.85
1.84
1.84
1.82
1.82
1.81
1.81
1.80
1.80
1.79
1.72
1.72
1.71
1.70
1.69
1.57
1.55
1.54
1.54
1.52
1.52
0.98
2.00
5.99
4.00
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

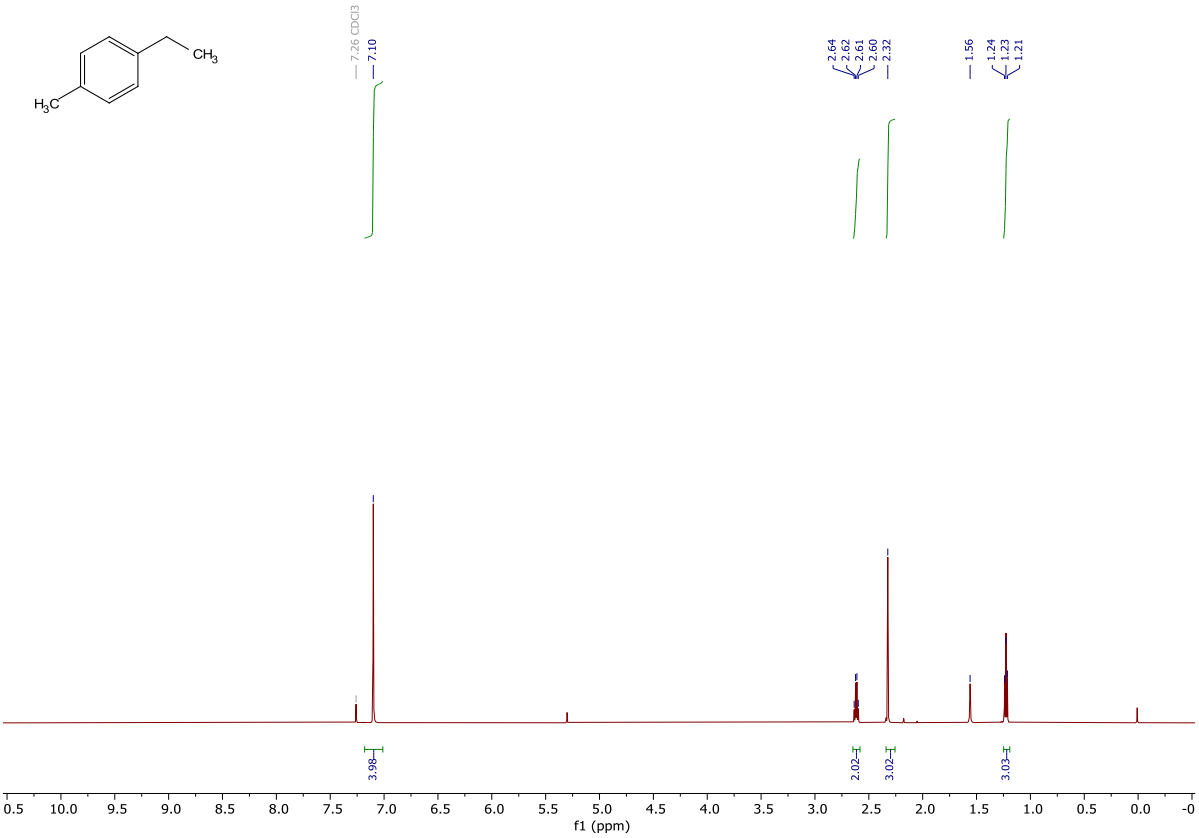

77.16 CDCl3
74.72
37.74
36.68
34.73
31.18
27.68
27.22
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

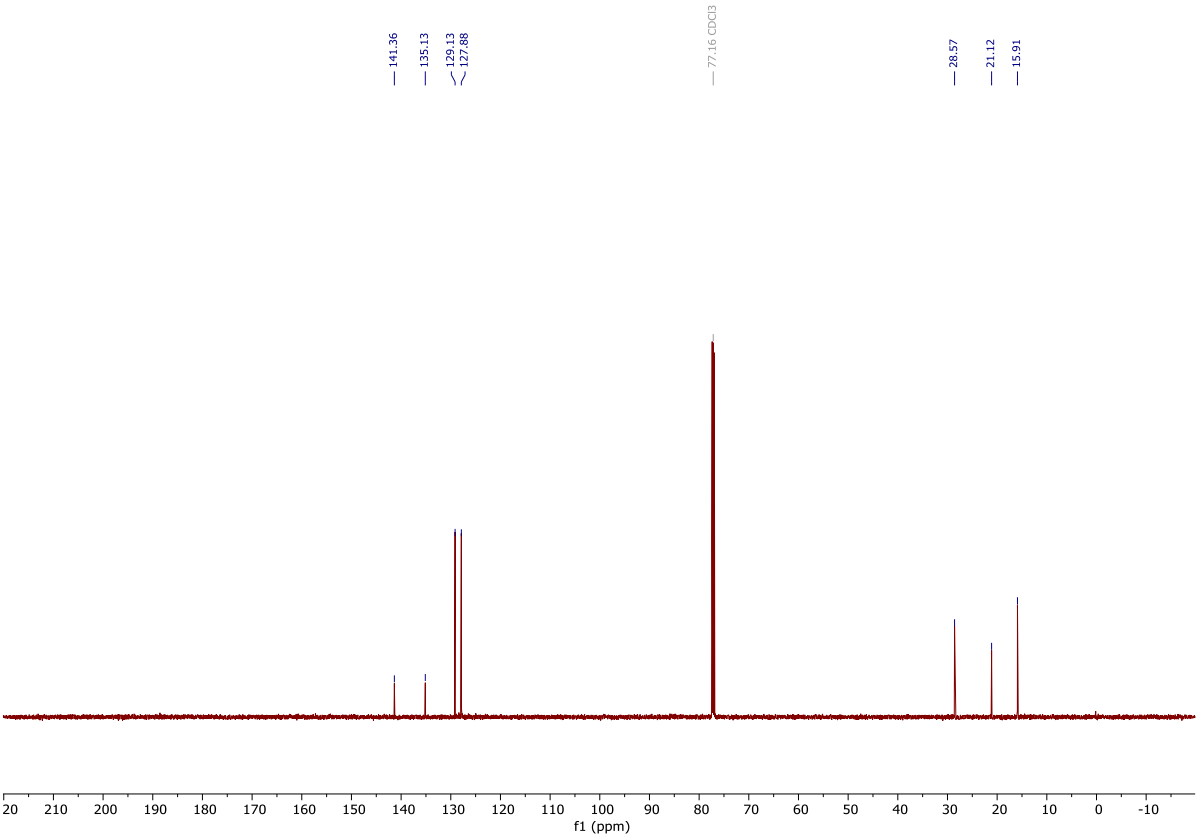

CH2
H3C
7.29
7.28
7.27
7.27
7.11
7.09
6.69
6.67
6.66
6.64
5.69
5.68
5.66
5.65
5.17
5.16
5.15
5.15
2.31
0.00 TMS
2.02
2.00
1.04
1.04
1.03
3.07
f1 (ppm)

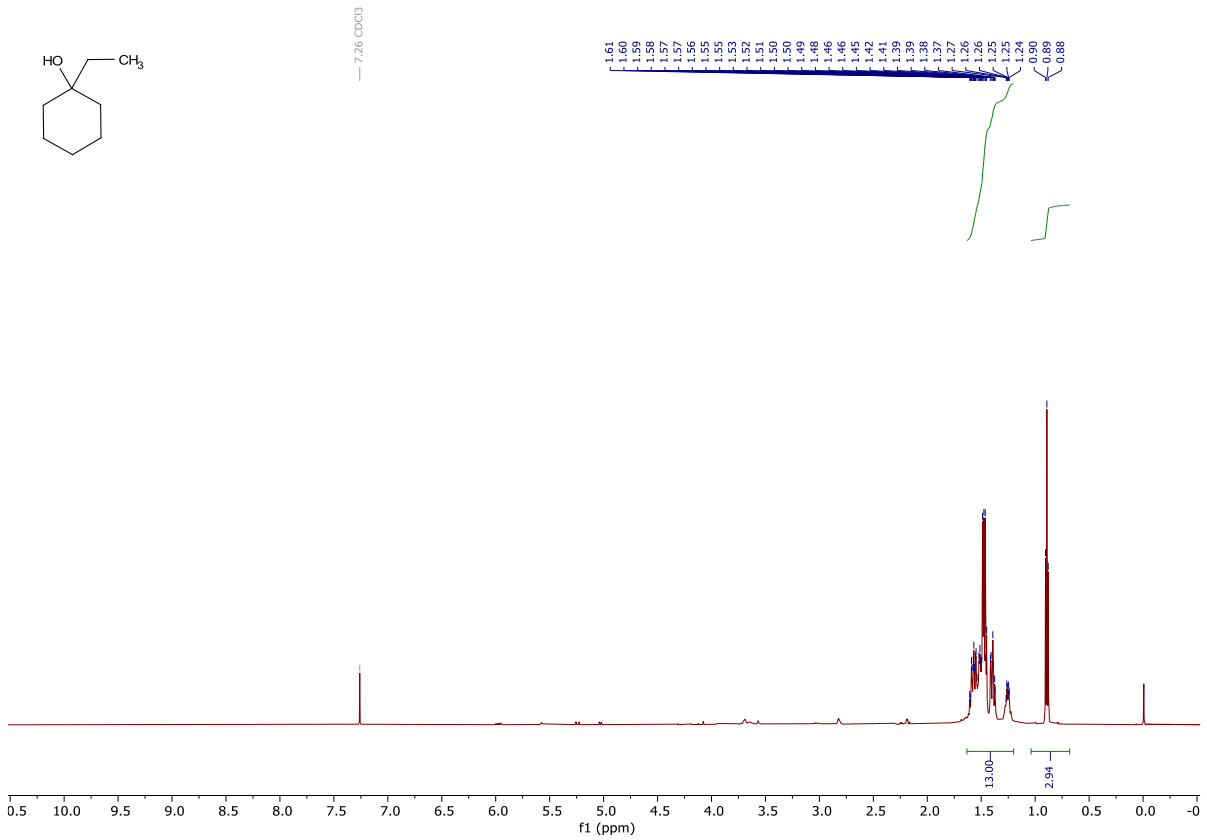

137.70
136.86
134.98
129.33
126.25
112.84
77.16 CDCl3
21.30
f1 (ppm)

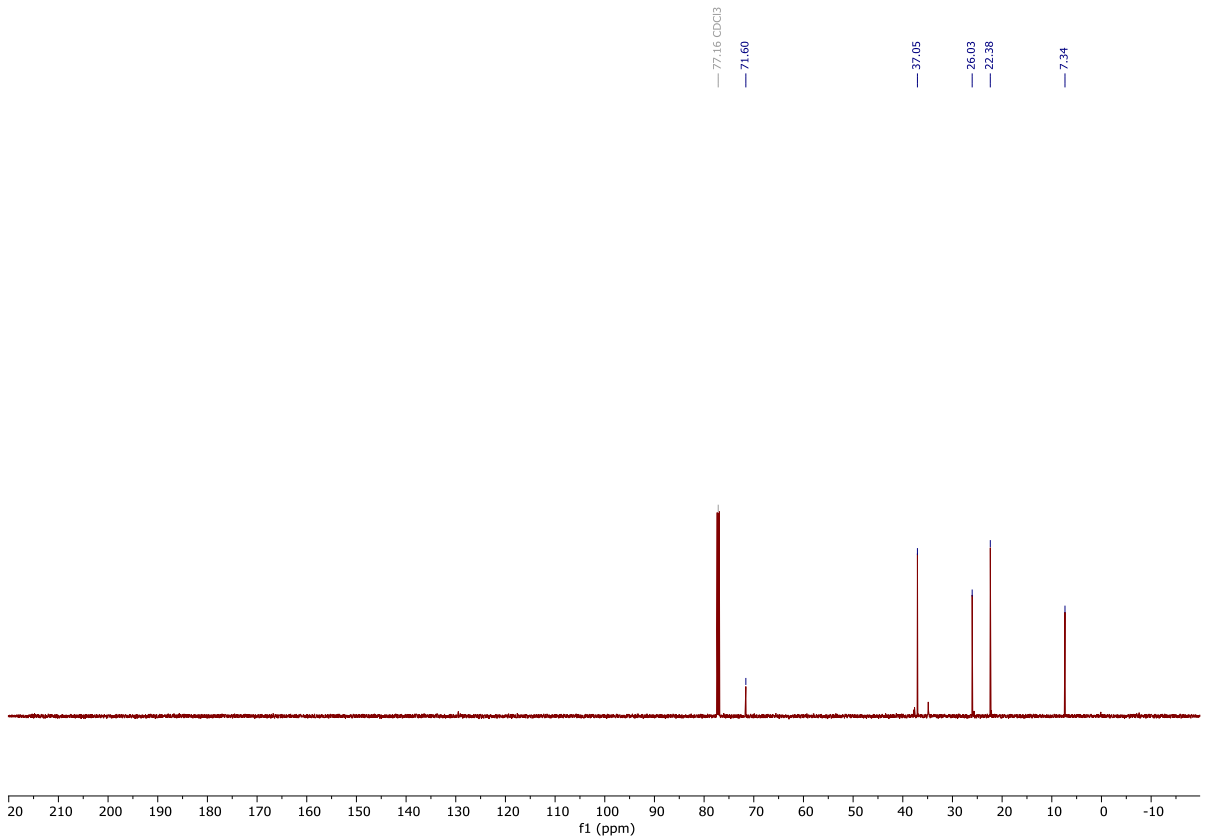

OH
7.35
7.34
7.33
7.27
7.26
7.25
7.25
7.21
7.20
6.58
6.56
5.89
5.88
5.87
5.86
5.85
4.44
4.44
4.43
4.43
0.00 TMS
2.02
1.00
1.99
1.00
0.99
2.00
f1 (ppm)

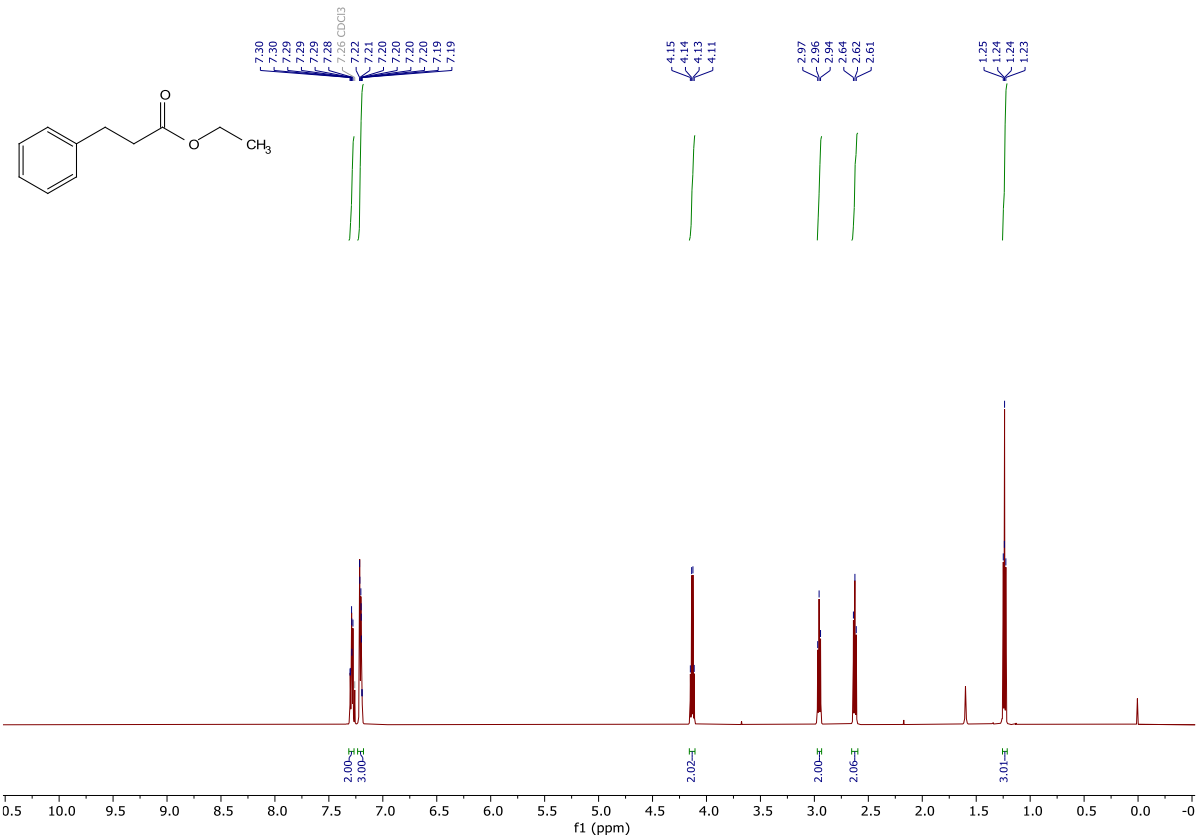

136.65
131.27
131.19
128.91
128.40
127.40
77.16 CDCl3
59.84
f1 (ppm)

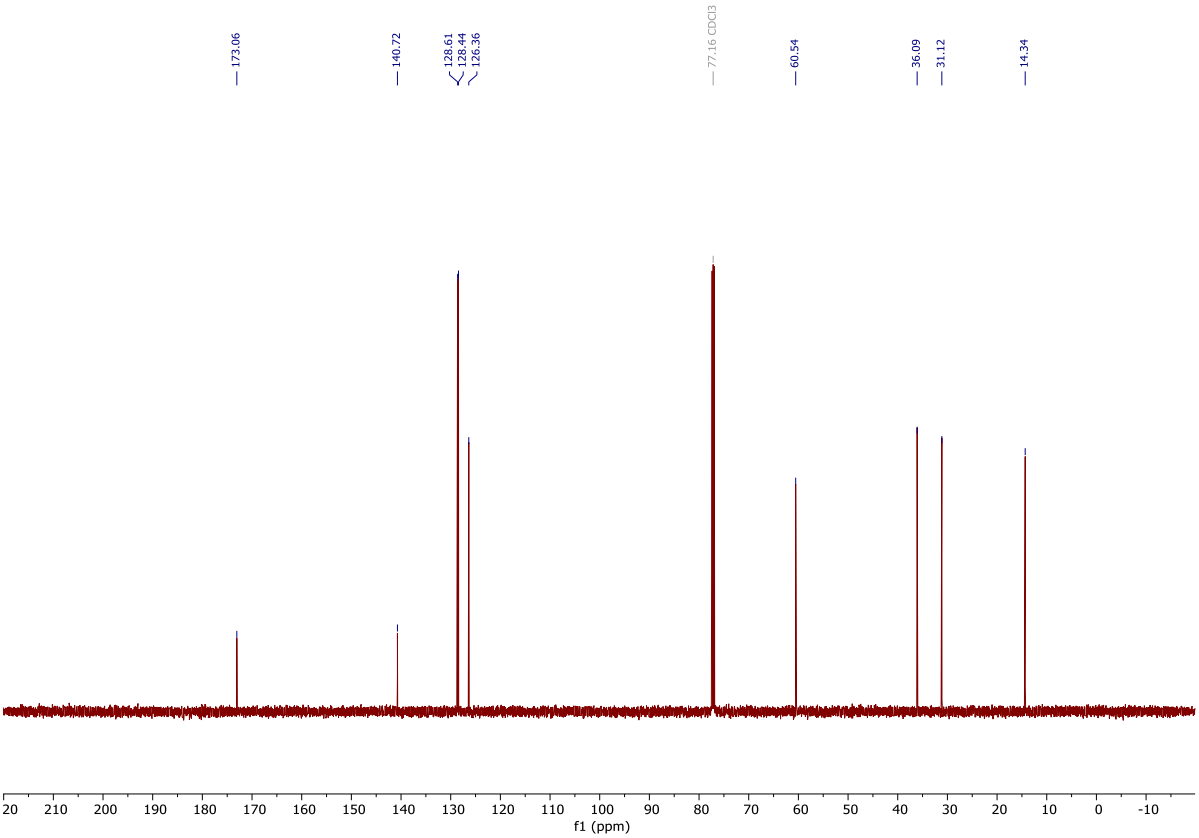

7.26 CDCl3
7.10
2.64
2.62
2.61
2.60
2.32
1.56
1.24
1.23
1.21
3.98
2.02
3.02
3.03
f1 (ppm)

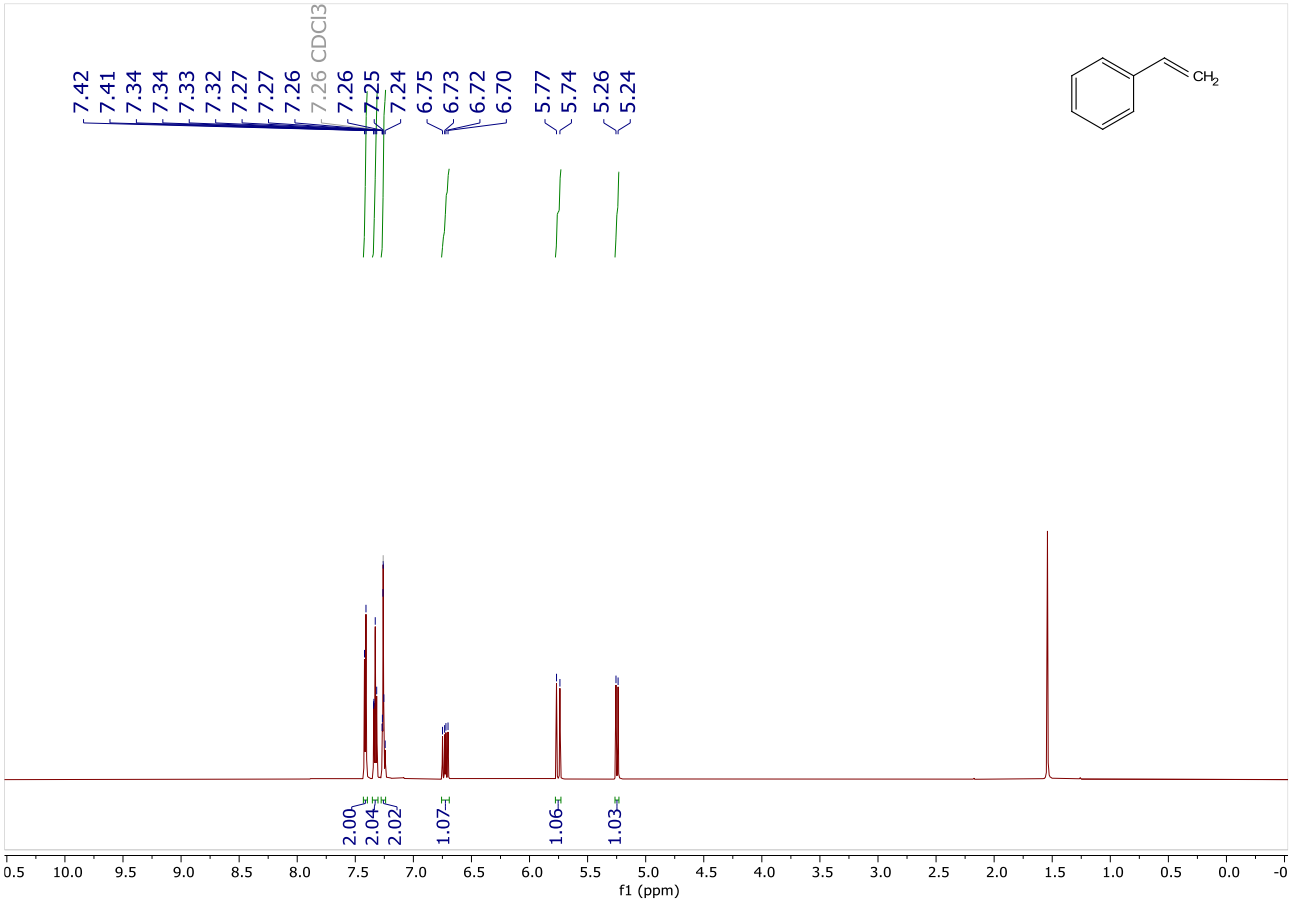

141.36
135.13
129.13
127.88
77.16 CDCl3
28.57
21.12
15.91
f1 (ppm)

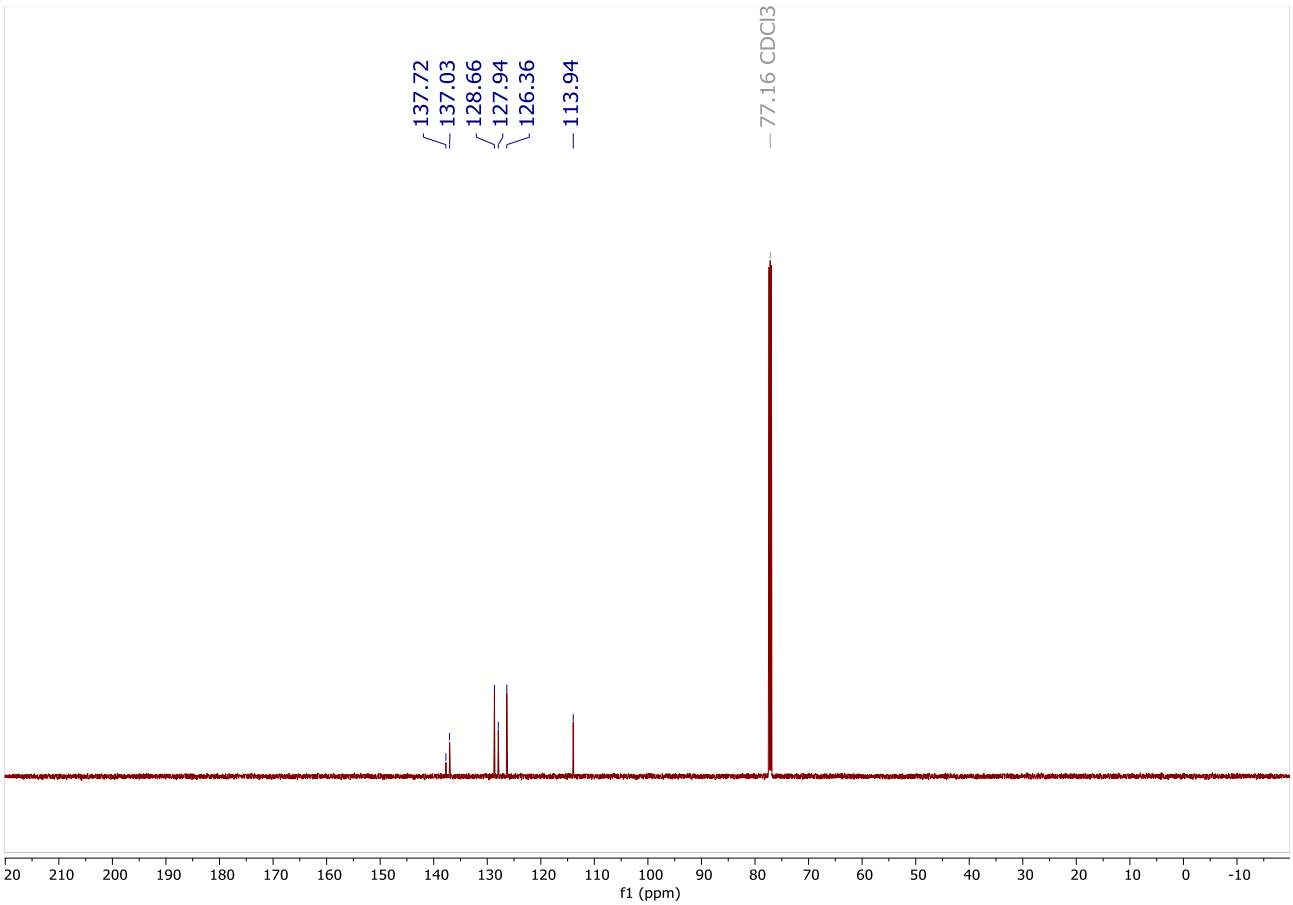

HO
CH3
7.26 CDCl3
1.61
1.60
1.59
1.58
1.57
1.57
1.56
1.55
1.55
1.53
1.52
1.51
1.50
1.50
1.49
1.48
1.46
1.46
1.45
1.42
1.41
1.39
1.39
1.38
1.37
1.27
1.26
1.26
1.25
1.25
1.24
0.90
0.89
0.88
13.00
2.94
f1 (ppm)

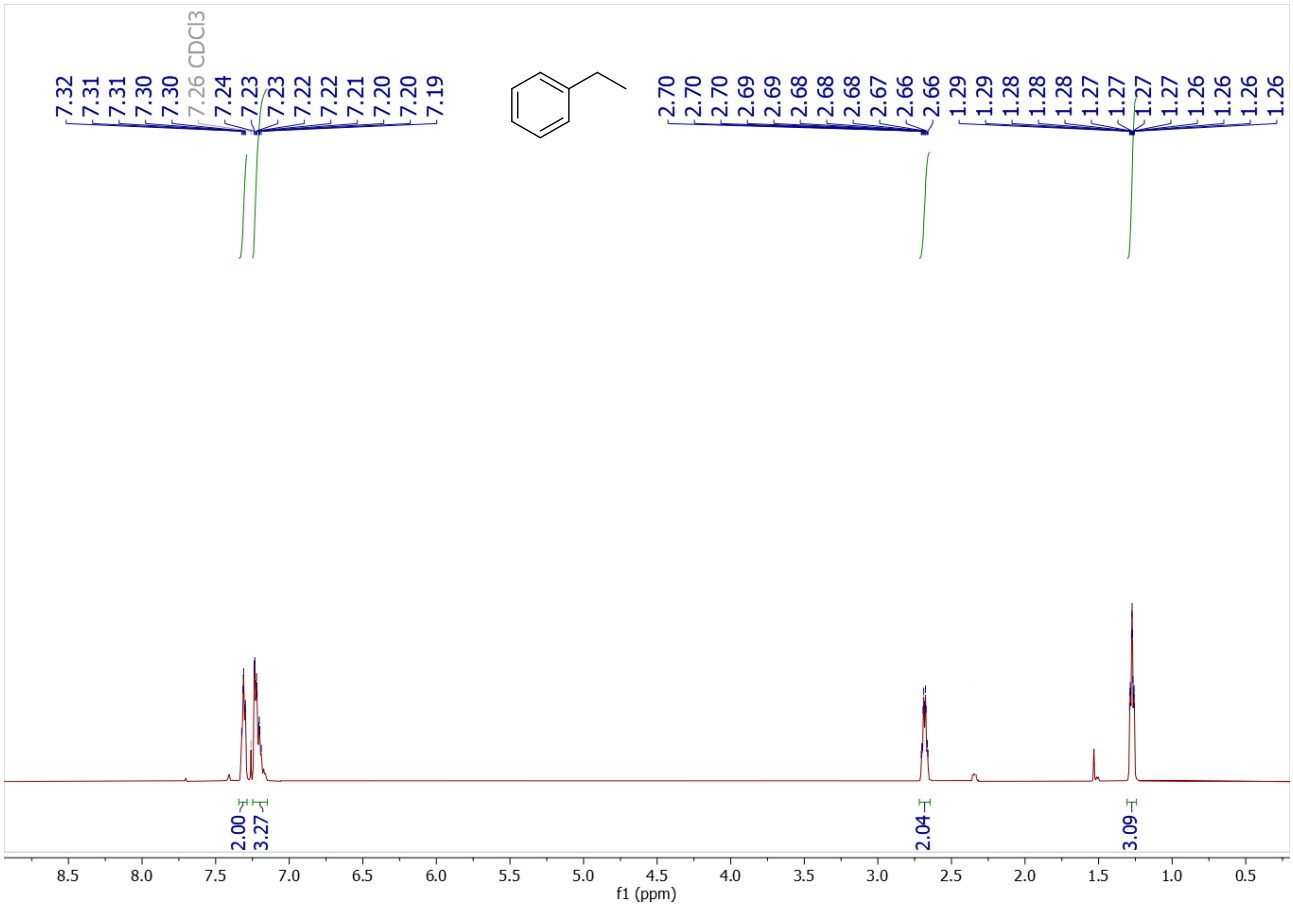

77.16 CDCl3
71.60
37.05
26.03
22.38
7.34
f1 (ppm)

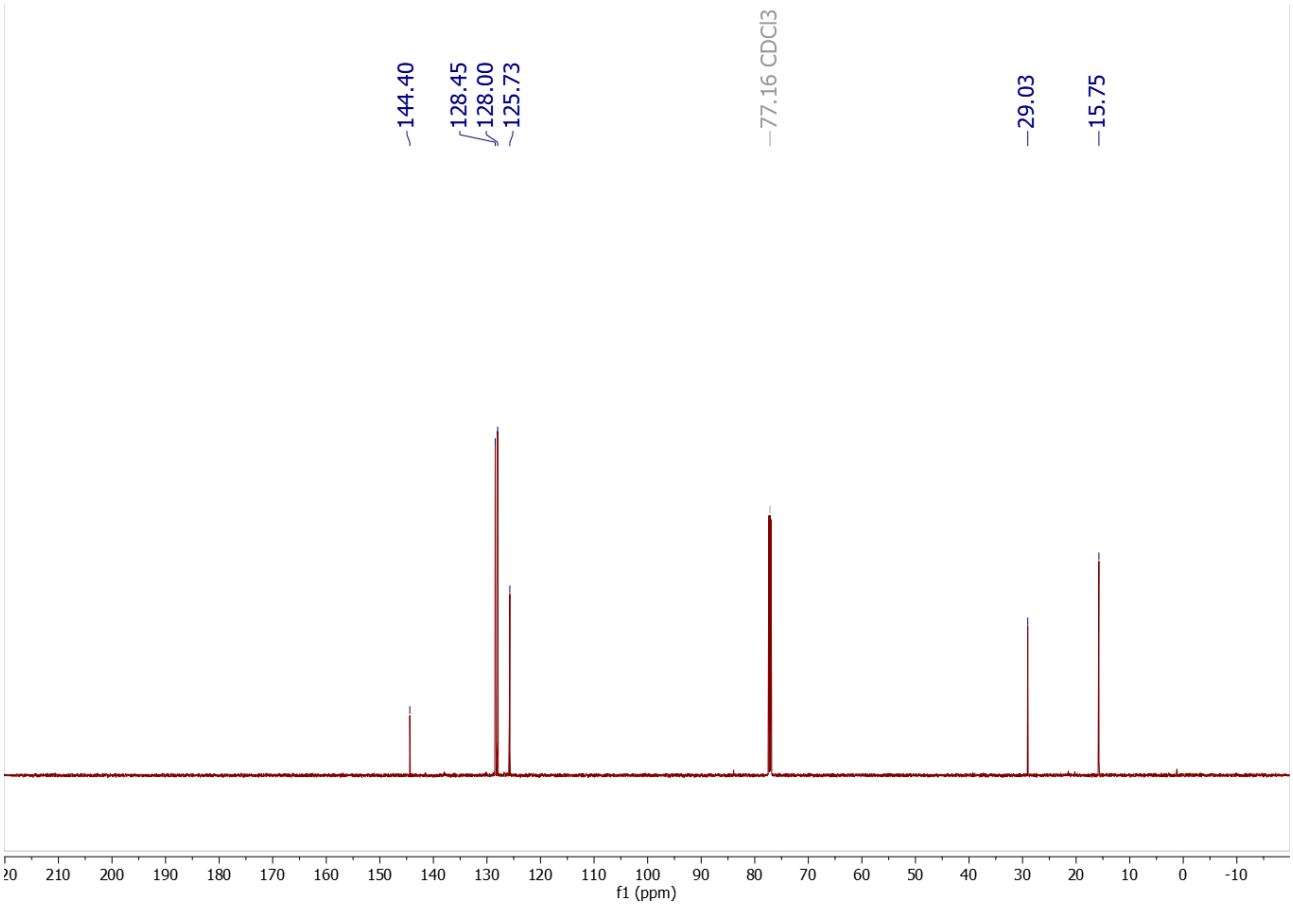

7.30
7.30
7.29
7.29
7.29
7.28
7.26 CDCl3
7.22
7.21
7.20
7.20
7.20
7.20
7.19
7.19
4.15
4.14
4.13
4.11
2.97
2.96
2.94
2.64
2.62
2.61
1.25
1.24
1.24
1.23
O
O
CH3
2.00
3.00
2.02
2.00
2.06
3.01
f1 (ppm)

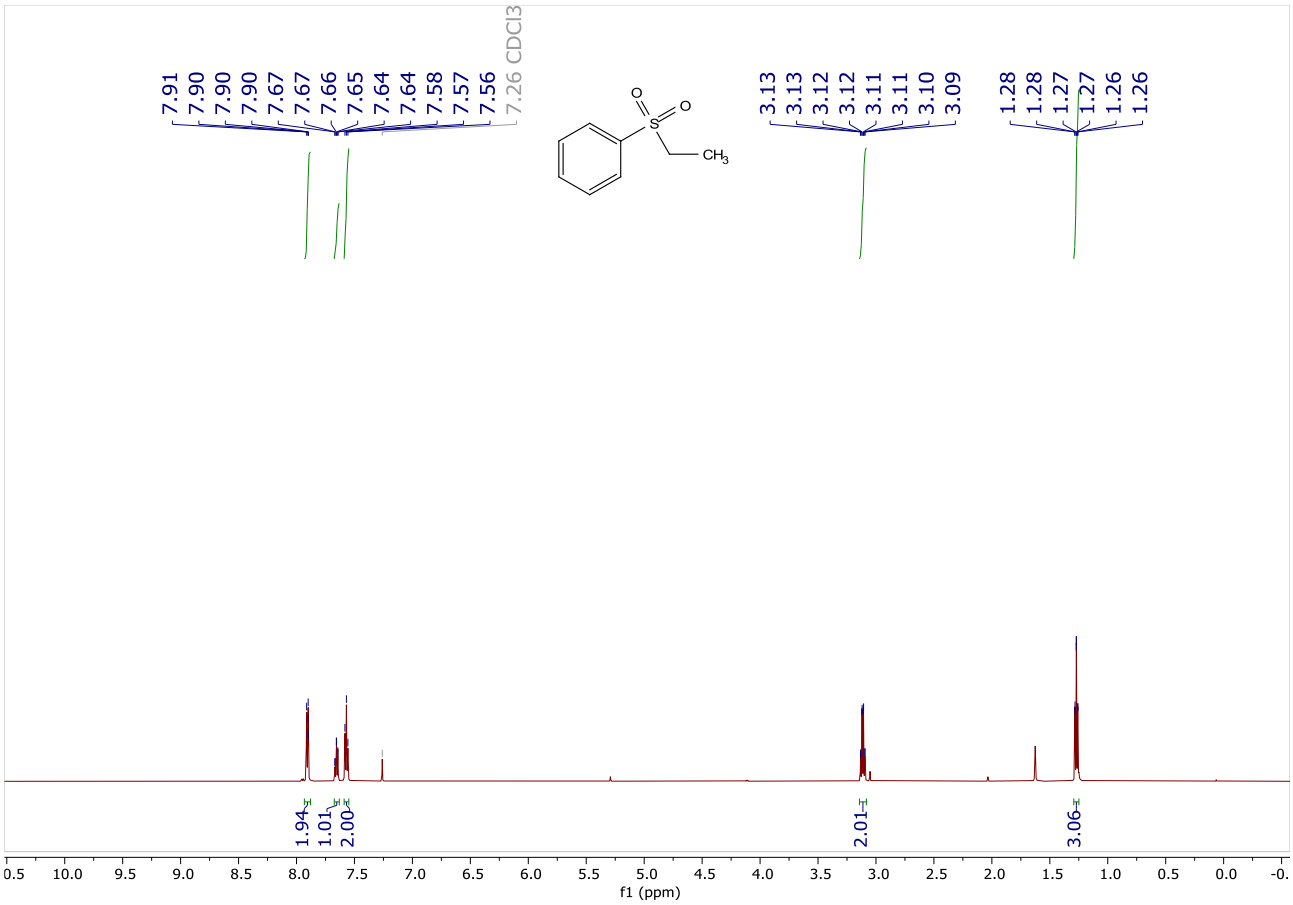

173.06
140.72
128.61
128.44
126.36
77.16 CDCl3
60.54
36.09
31.12
14.34
f1 (ppm)


7.42
7.41
7.34
7.34
7.33
7.32
7.27
7.27
7.26
7.26 CDCl3
7.26
7.25
7.24
6.75
6.73
6.72
6.70
5.77
5.74
5.26
5.24
CH2
2.00
2.04
2.02
1.07
1.06
1.03
f1 (ppm)


137.72
137.03
128.66
127.94
126.36
113.94
77.16 CDCl3
f1 (ppm)


7.32
7.31
7.31
7.30
7.30
7.26 CDCl3
7.24
7.23
7.23
7.22
7.22
7.21
7.20
7.20
7.19
2.70
2.70
2.70
2.69
2.69
2.68
2.68
2.68
2.67
2.66
2.66
1.29
1.29
1.28
1.28
1.28
1.27
1.27
1.27
1.27
1.26
1.26
1.26
1.26
2.00
3.27
2.04
3.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


144.40
128.45
128.00
125.73
77.16 CDCl3
29.03
15.75
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.91
7.90
7.90
7.90
7.67
7.67
7.66
7.65
7.64
7.64
7.58
7.57
7.56
7.26 CDCl3
3.13
3.13
3.12
3.12
3.11
3.11
3.10
3.09
1.28
1.28
1.27
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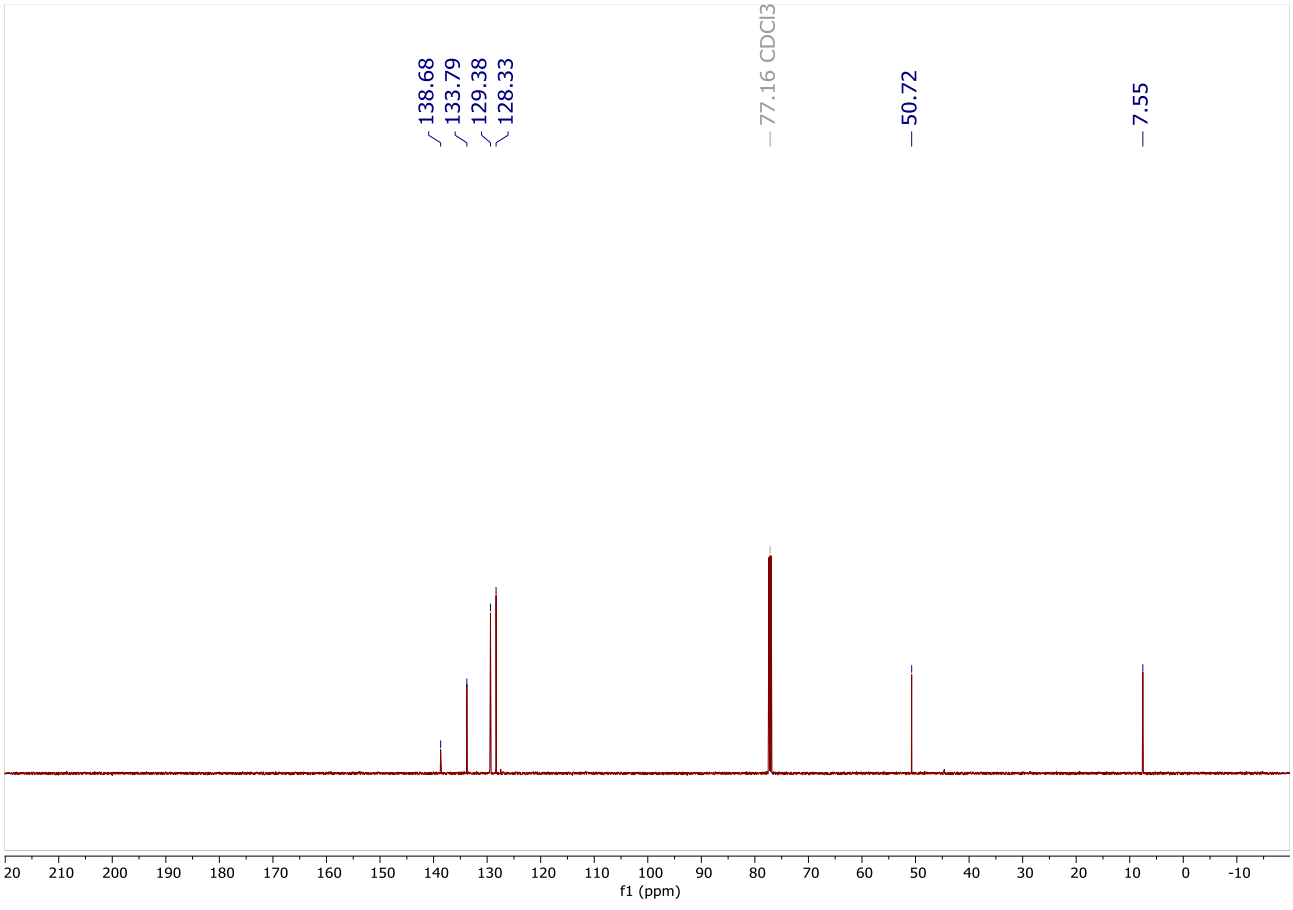
1.94
1.01
2.00
2.01
3.06
f1 (ppm)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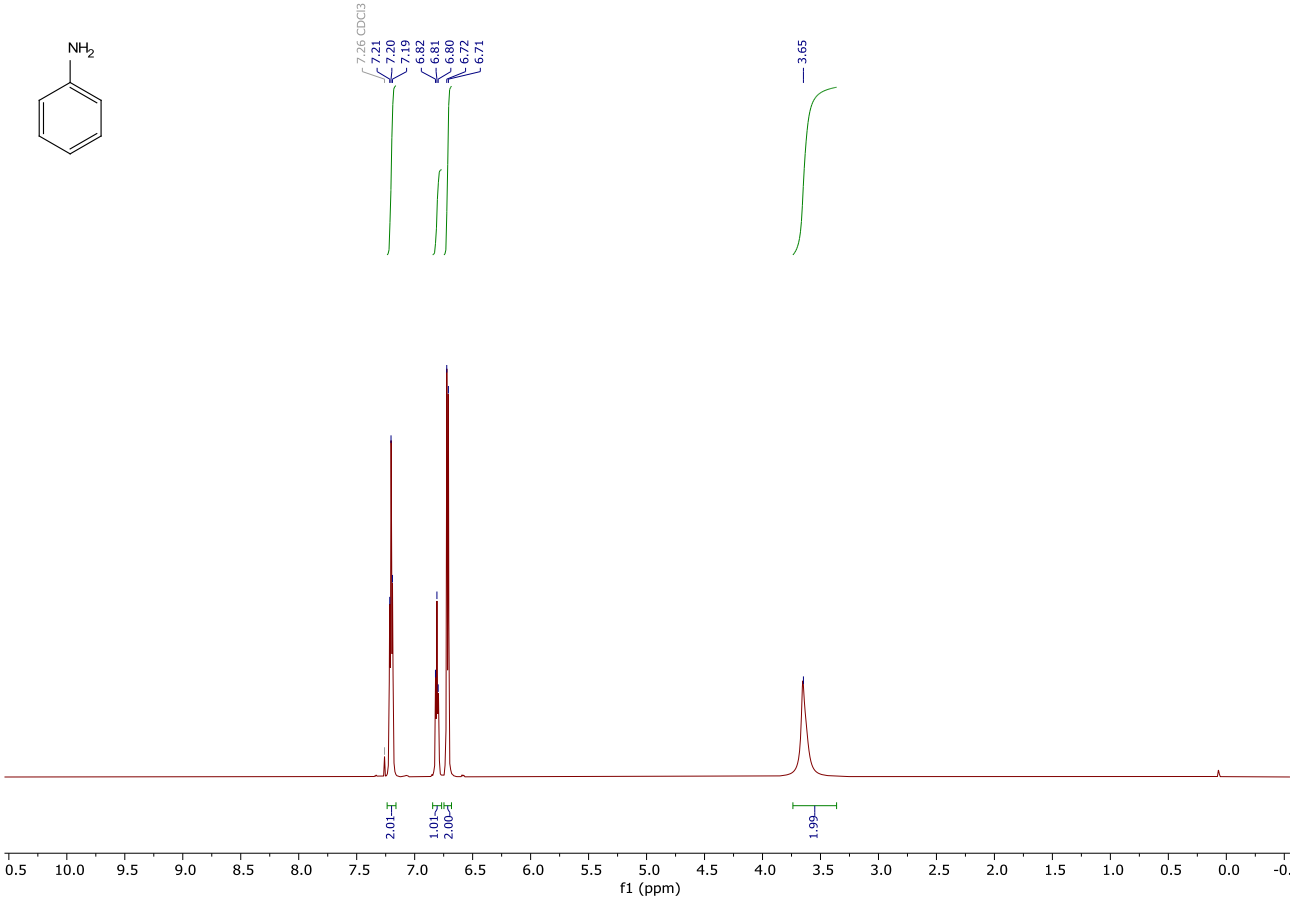
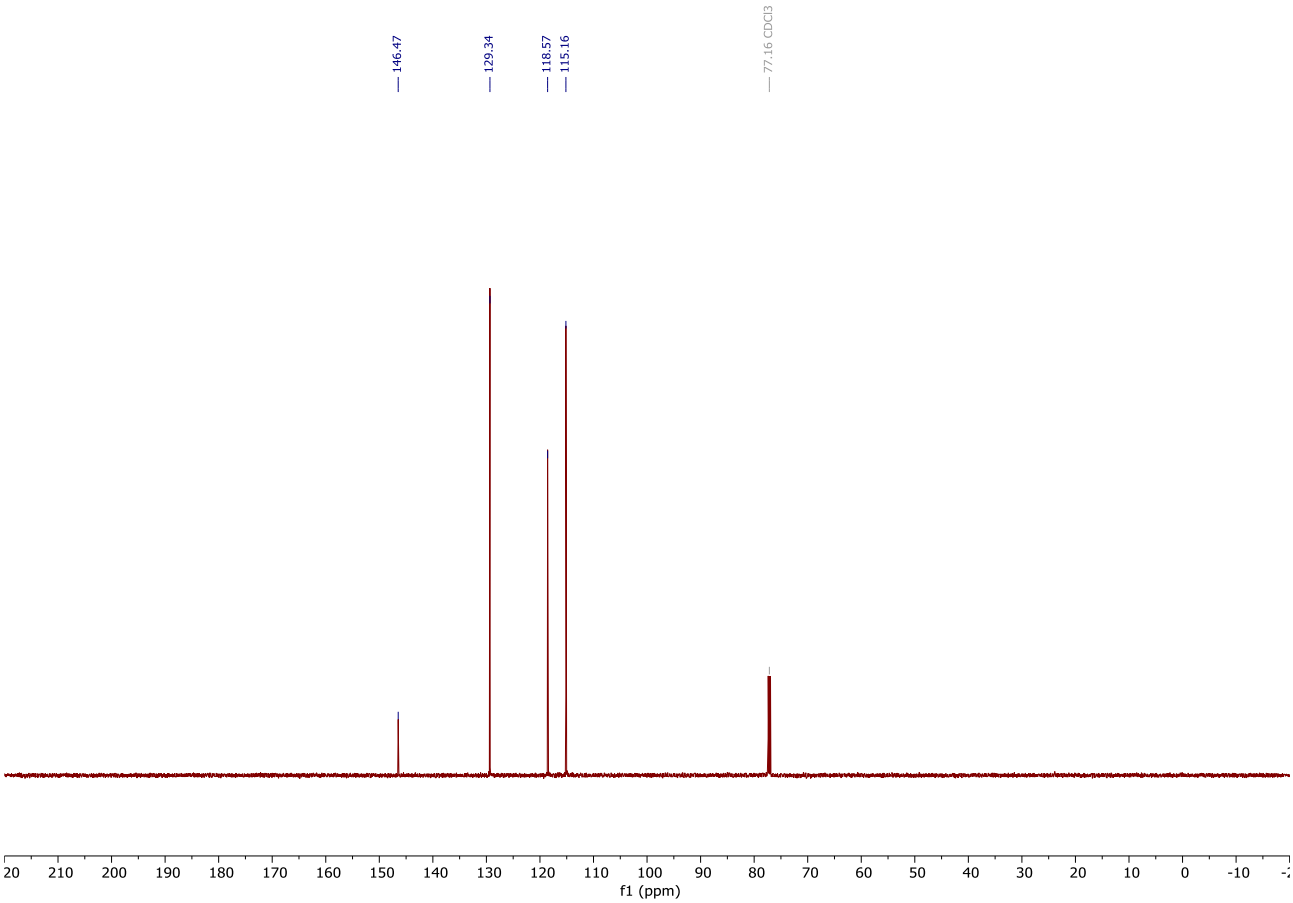
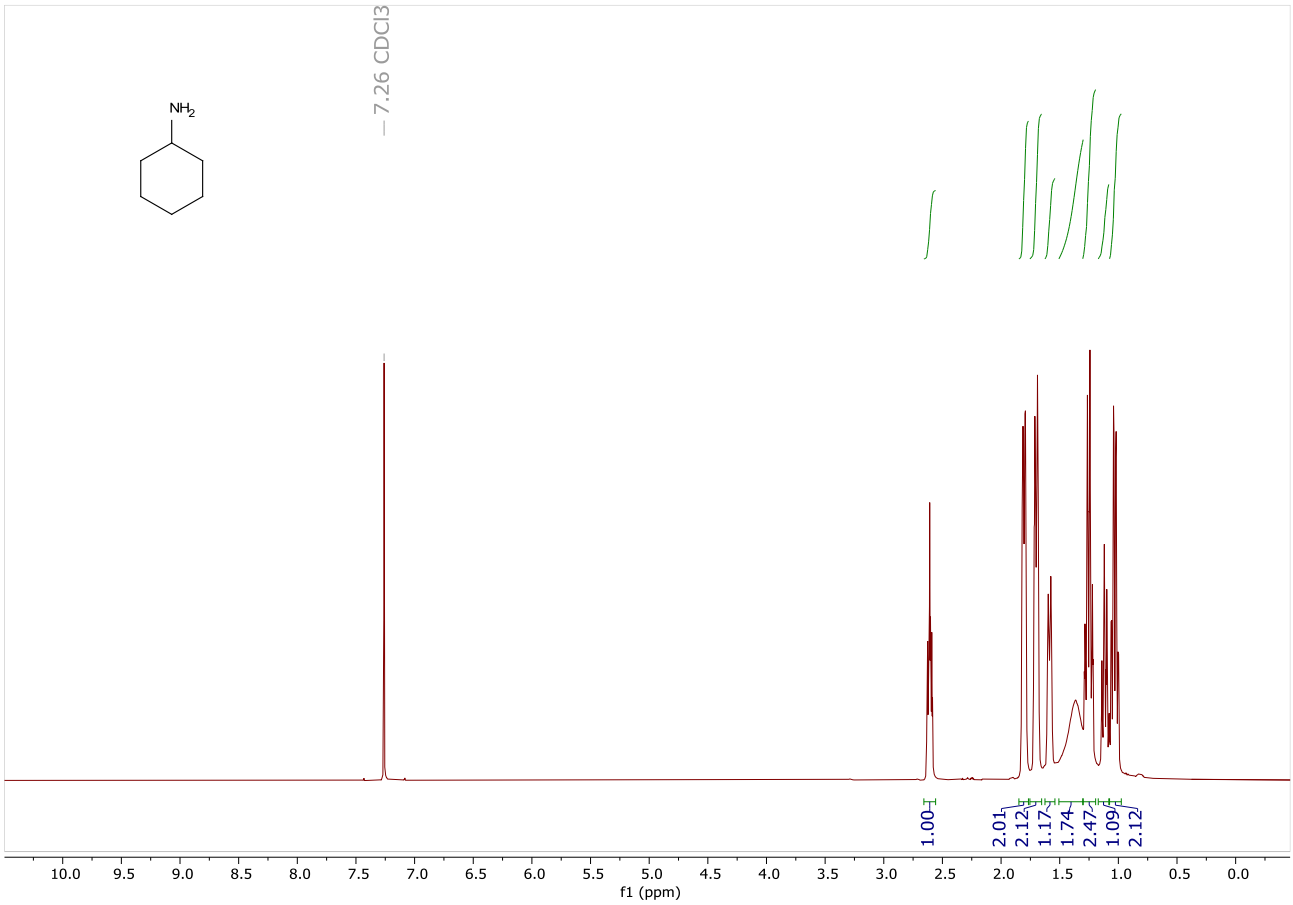
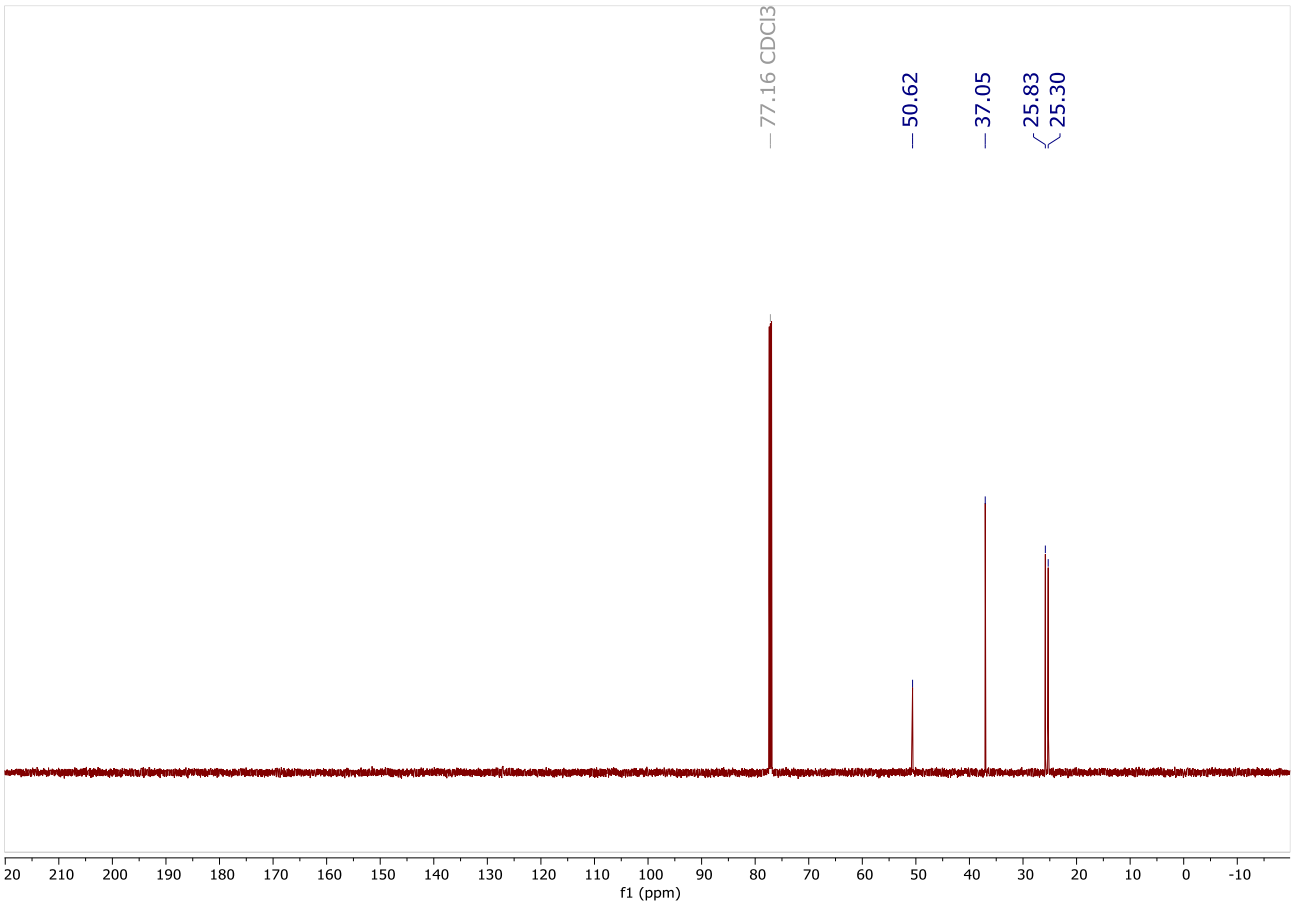
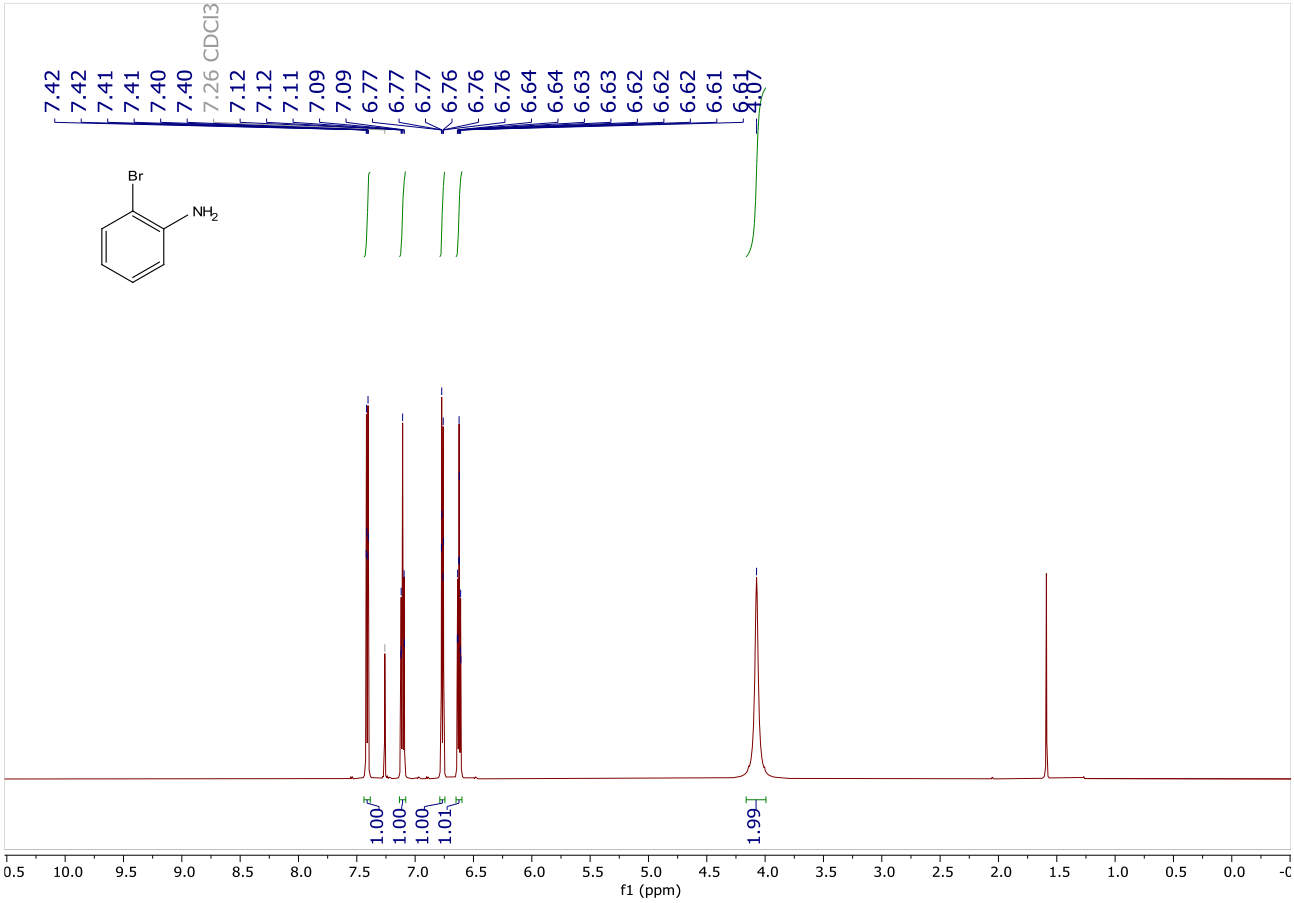
133.79
129.38
128.33
77.16 CDCl3
50.72
7.55
f1 (ppm)


NH2
7.26 CDCl3
7.21
7.20
7.19
6.82
6.81
6.80
6.72
6.71
3.65
2.01
1.01
2.00
1.99
f1 (ppm)


146.47
129.34
118.57
115.16
77.16 CDCl3
f1 (ppm)


NH2
7.26 CDCl3
1.00
2.01
2.12
1.17
1.74
2.47
1.09
2.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


77.16 CDCl3
50.62
37.05
25.83
25.30
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.42
7.42
7.41
7.41
7.40
7.40
7.26 CDCl3
7.12
7.12
7.11
7.09
7.09
6.77
6.77
6.77
6.76
6.76
6.76
6.64
6.64
6.63
6.63
6.62
6.62
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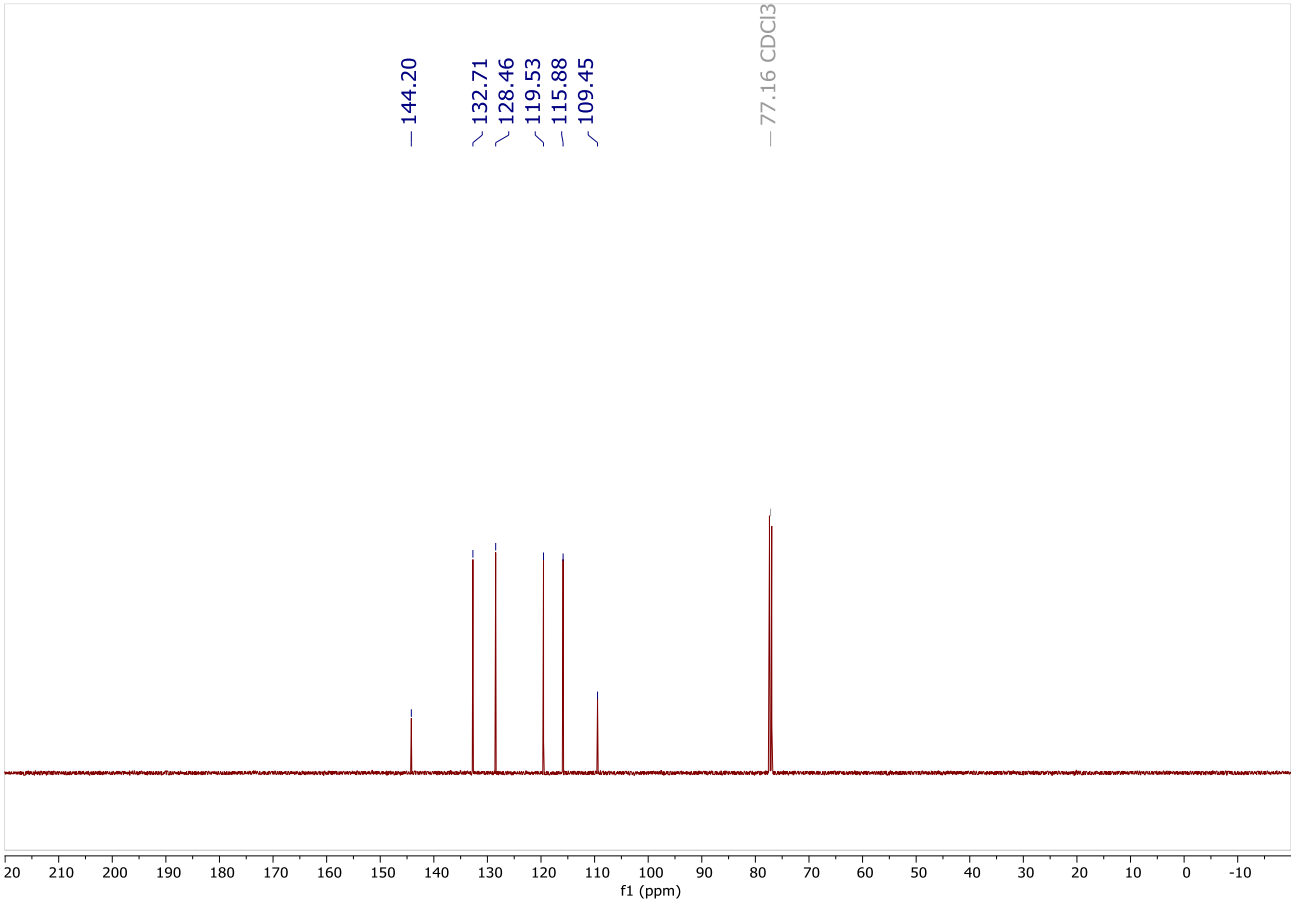
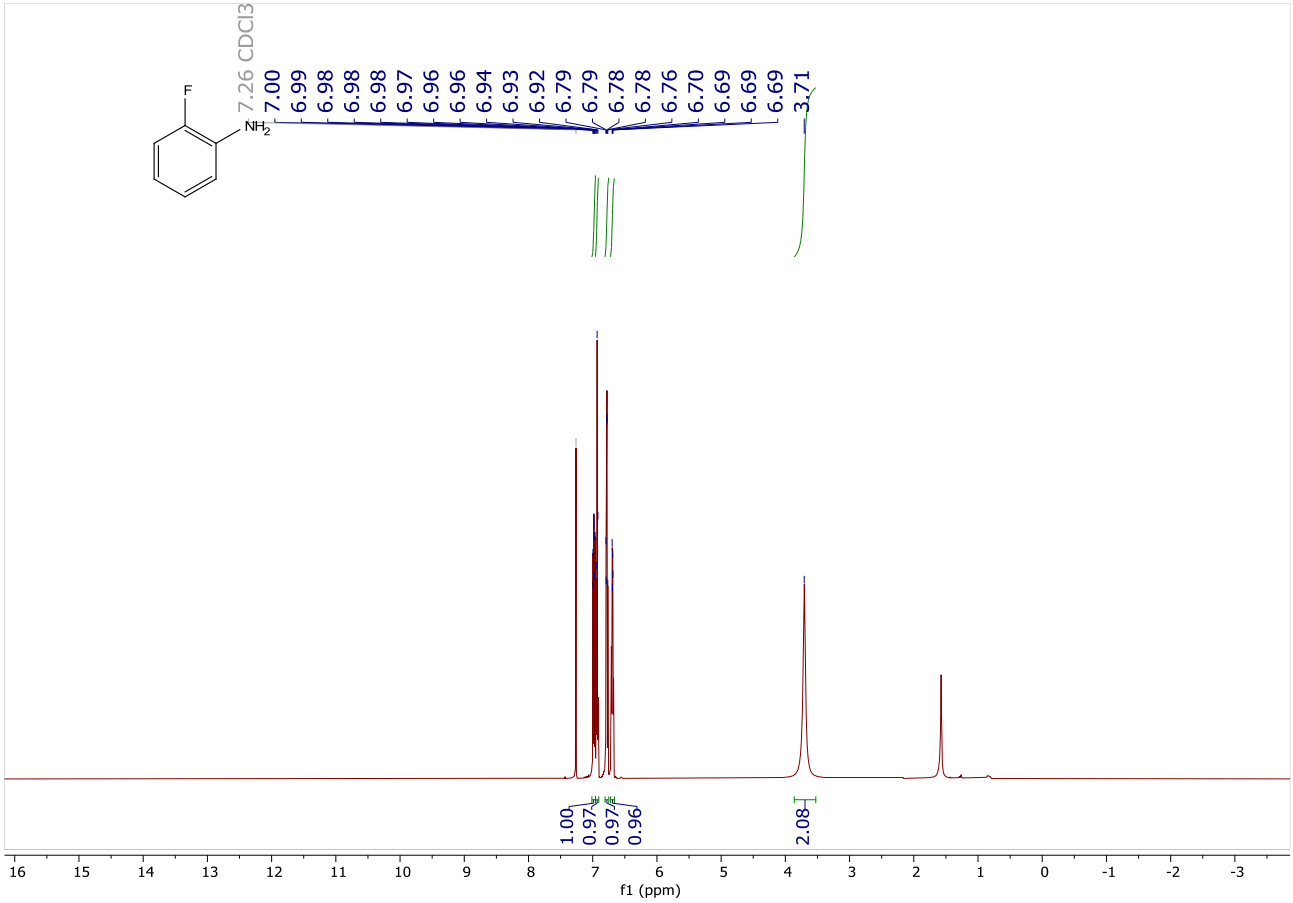
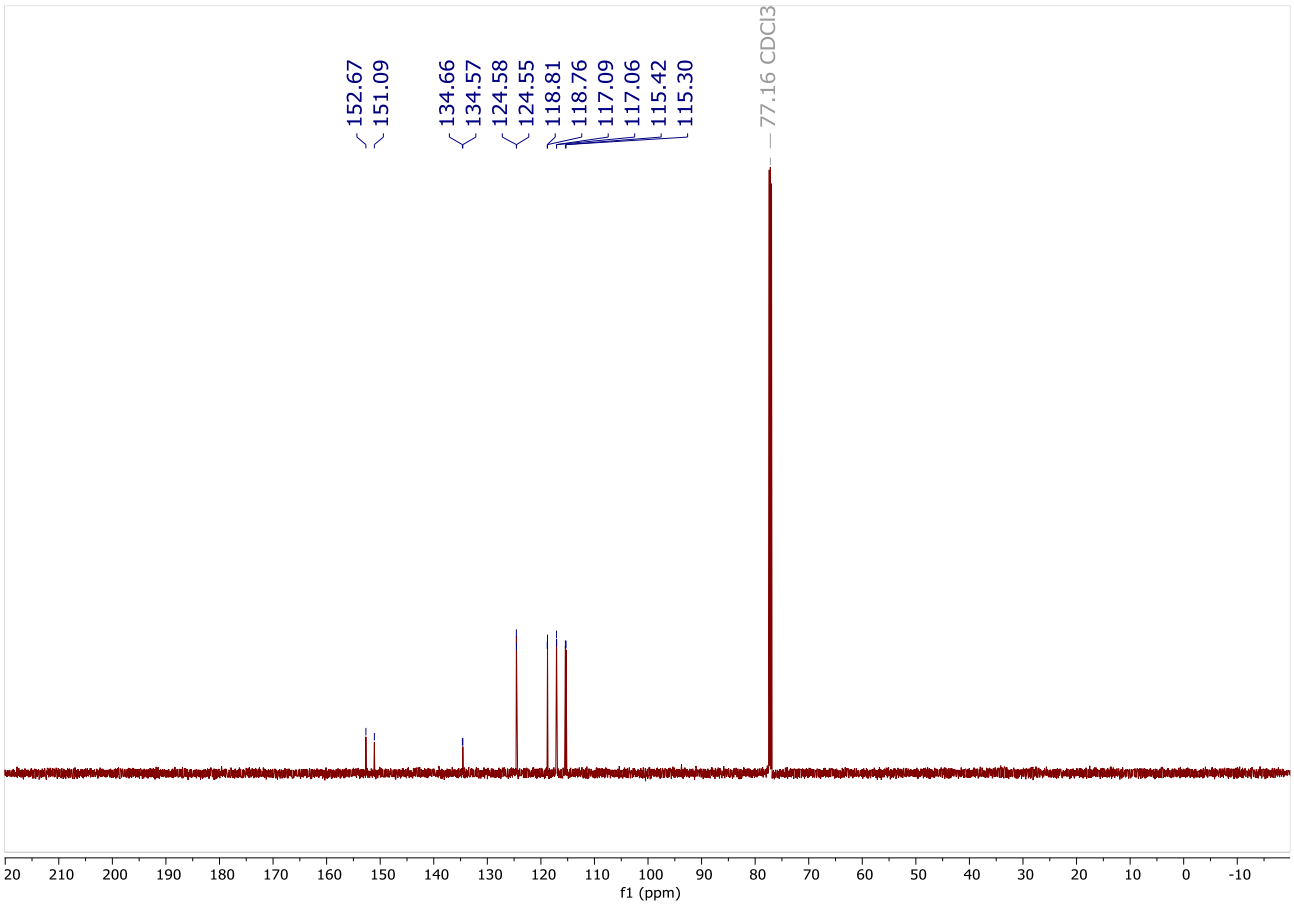
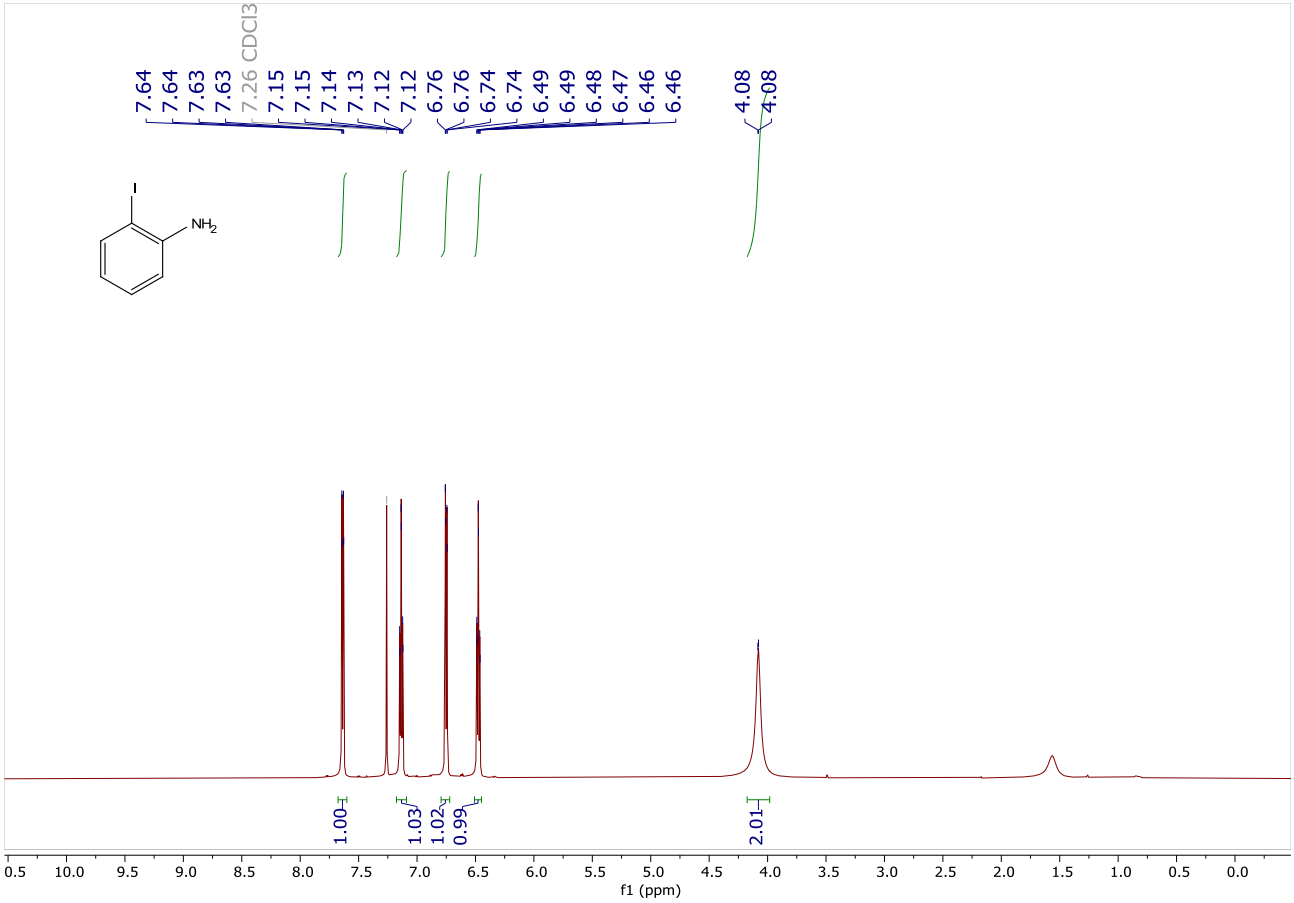
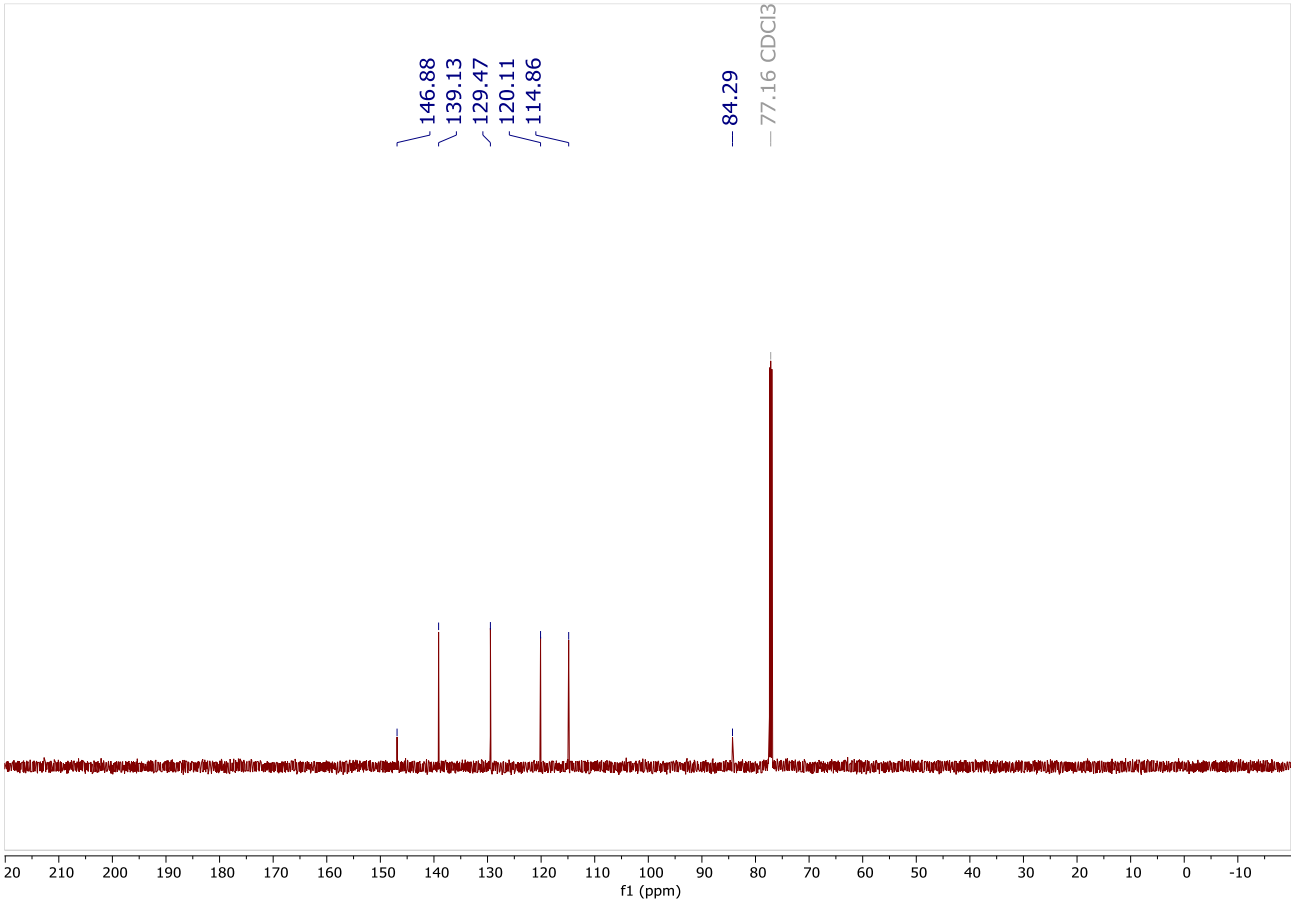
1.00
1.00
1.01
1.99
f1 (ppm)

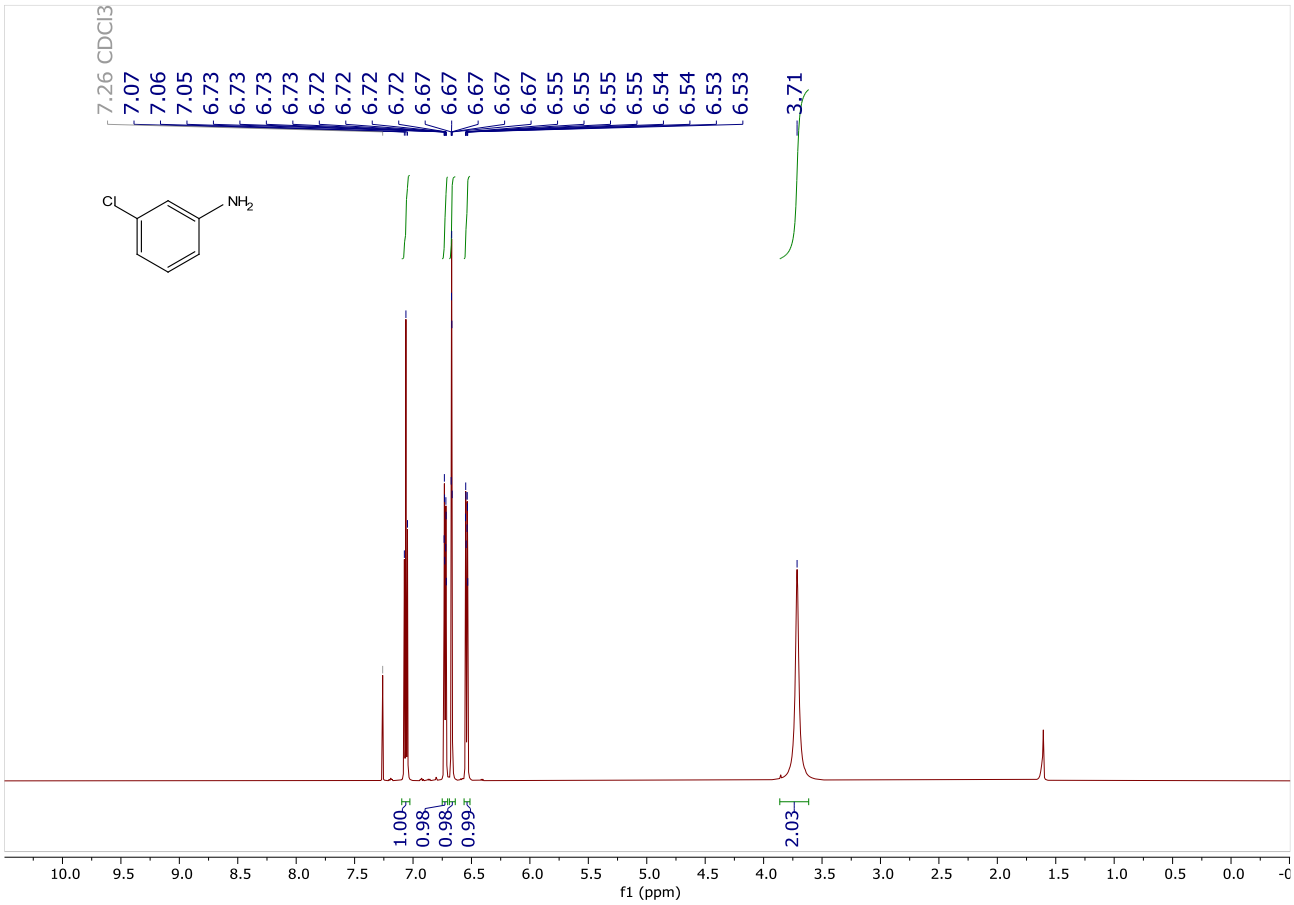

144.20
132.71
128.46
119.53
115.88
109.45
77.16 CDCl3
f1 (ppm)

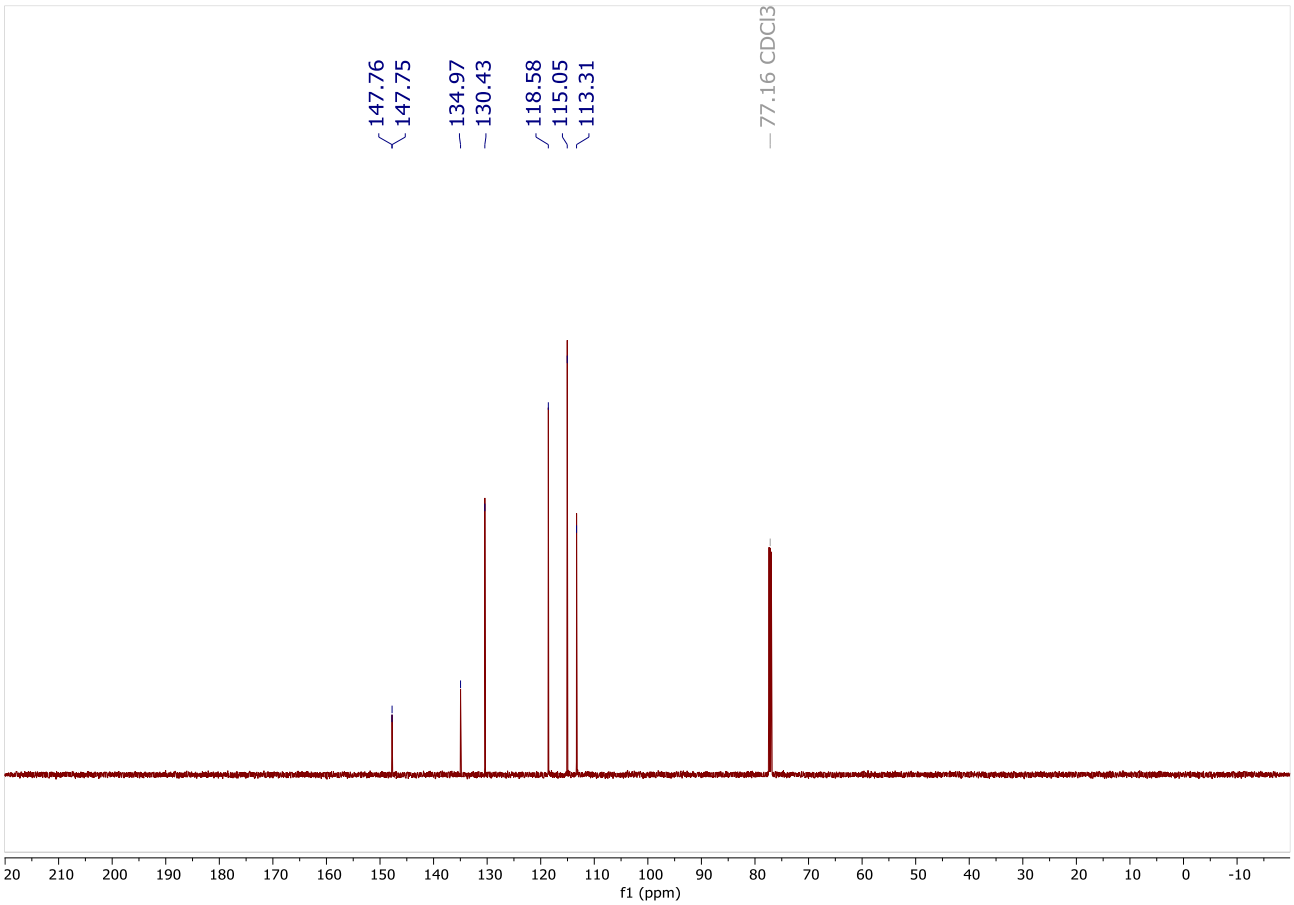

7.26 CDCl3
7.00
6.99
6.98
6.98
6.98
6.97
6.96
6.96
6.94
6.93
6.92
6.79
6.79
6.78
6.78
6.76
6.70
6.69
6.69
6.69
3.71
F
NH2
1.00
0.97
0.97
0.96
2.08
f1 (ppm)

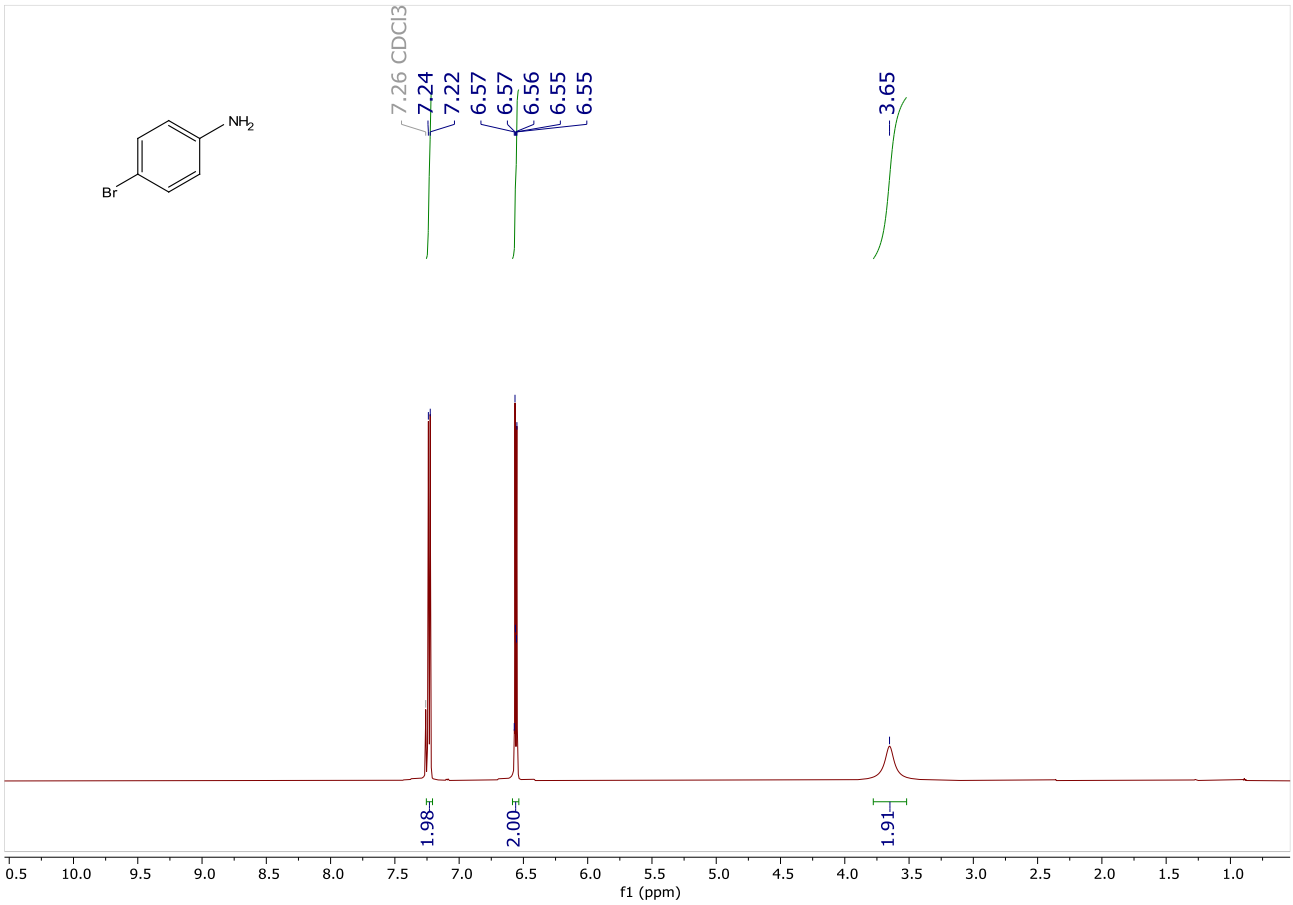

152.67
151.09
134.66
134.57
124.58
124.55
118.81
118.76
117.09
117.06
115.42
115.30
77.16 CDCl3
f1 (ppm)

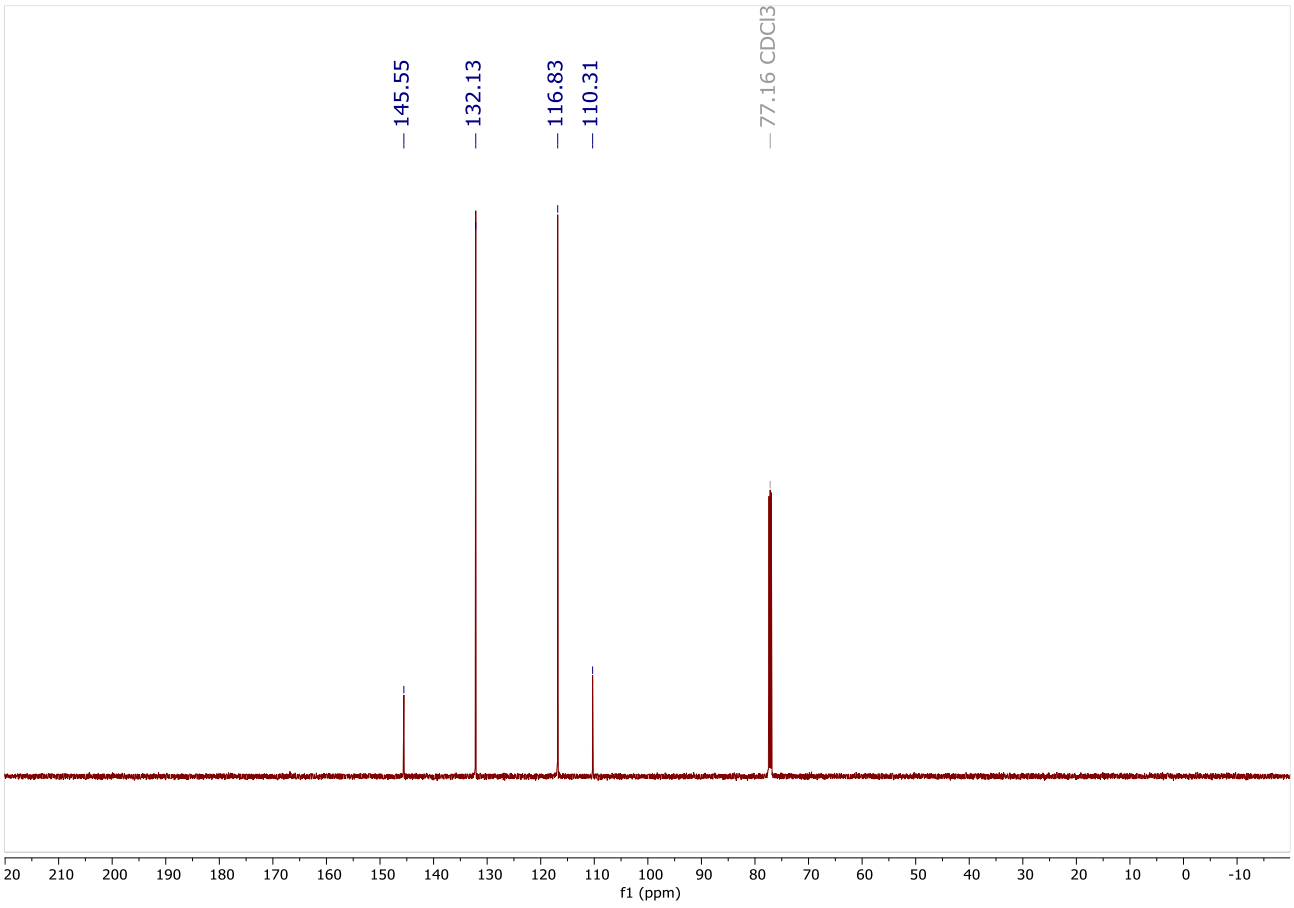

7.64
7.64
7.63
7.63
7.26 CDCl3
7.15
7.15
7.14
7.13
7.12
7.12
6.76
6.76
6.74
6.74
6.49
6.49
6.48
6.47
6.46
6.46
4.08
4.08
I
NH2
1.00
1.03
1.02
0.99
2.01
f1 (ppm)

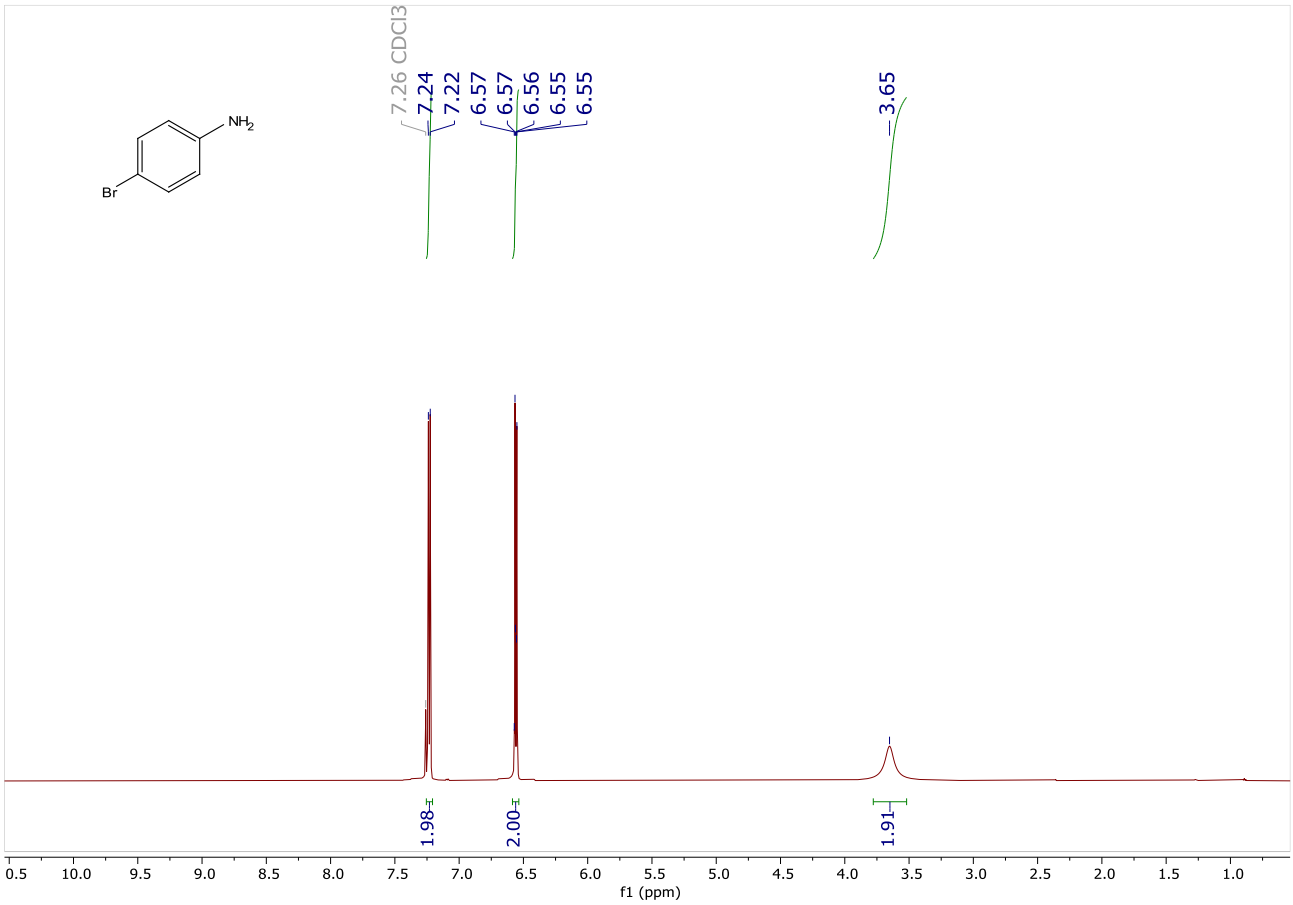

146.88
139.13
129.47
120.11
114.86
84.29
77.16 CDCl3
f1 (ppm)

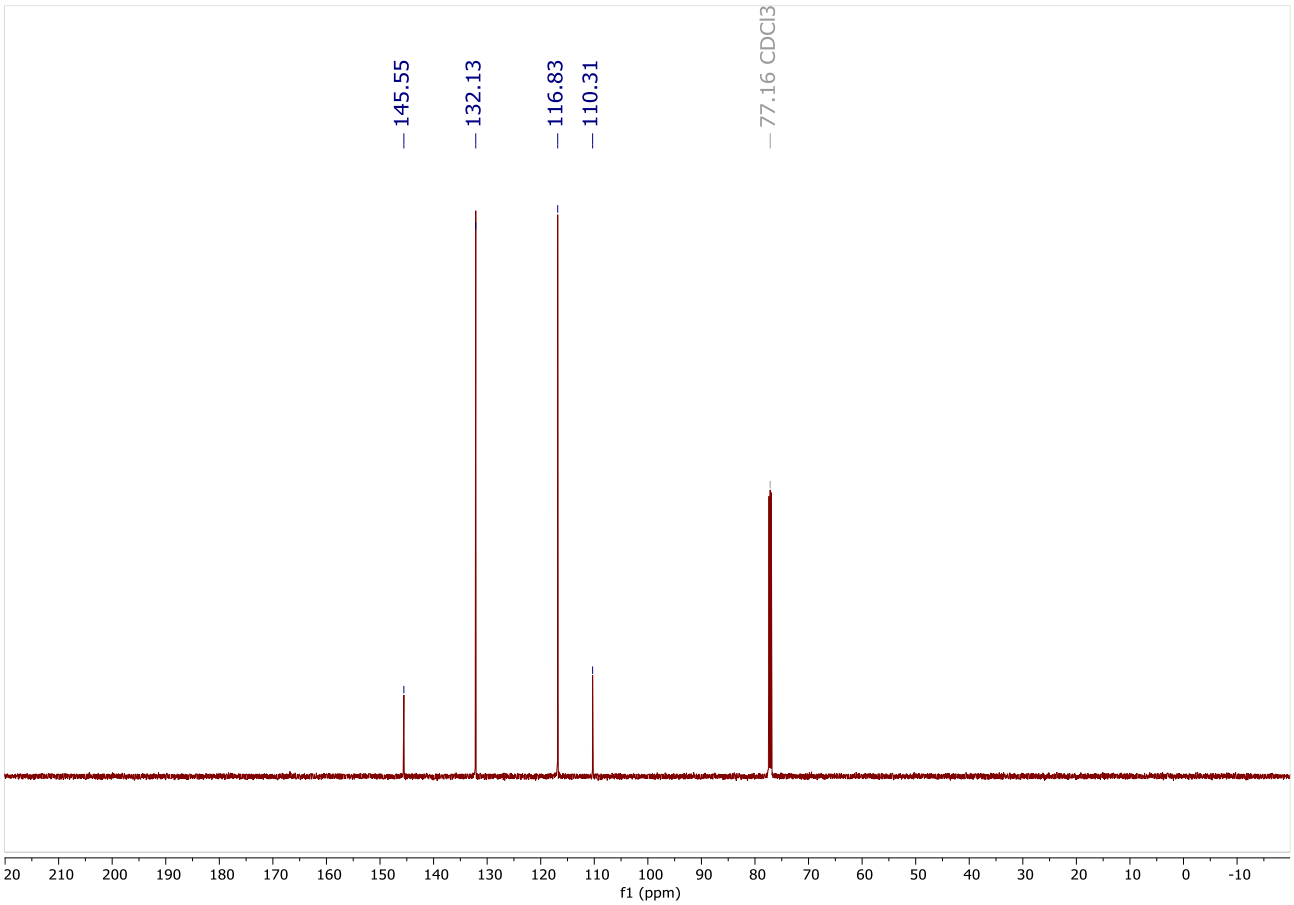

7.26 CDCl3
7.07
7.06
7.05
6.73
6.73
6.73
6.73
6.72
6.72
6.72
6.72
6.67
6.67
6.67
6.67
6.67
6.55
6.55
6.55
6.55
6.54
6.54
6.53
6.53
3.71
Cl
NH2
1.00
0.98
0.98
0.99
2.03
f1 (ppm)

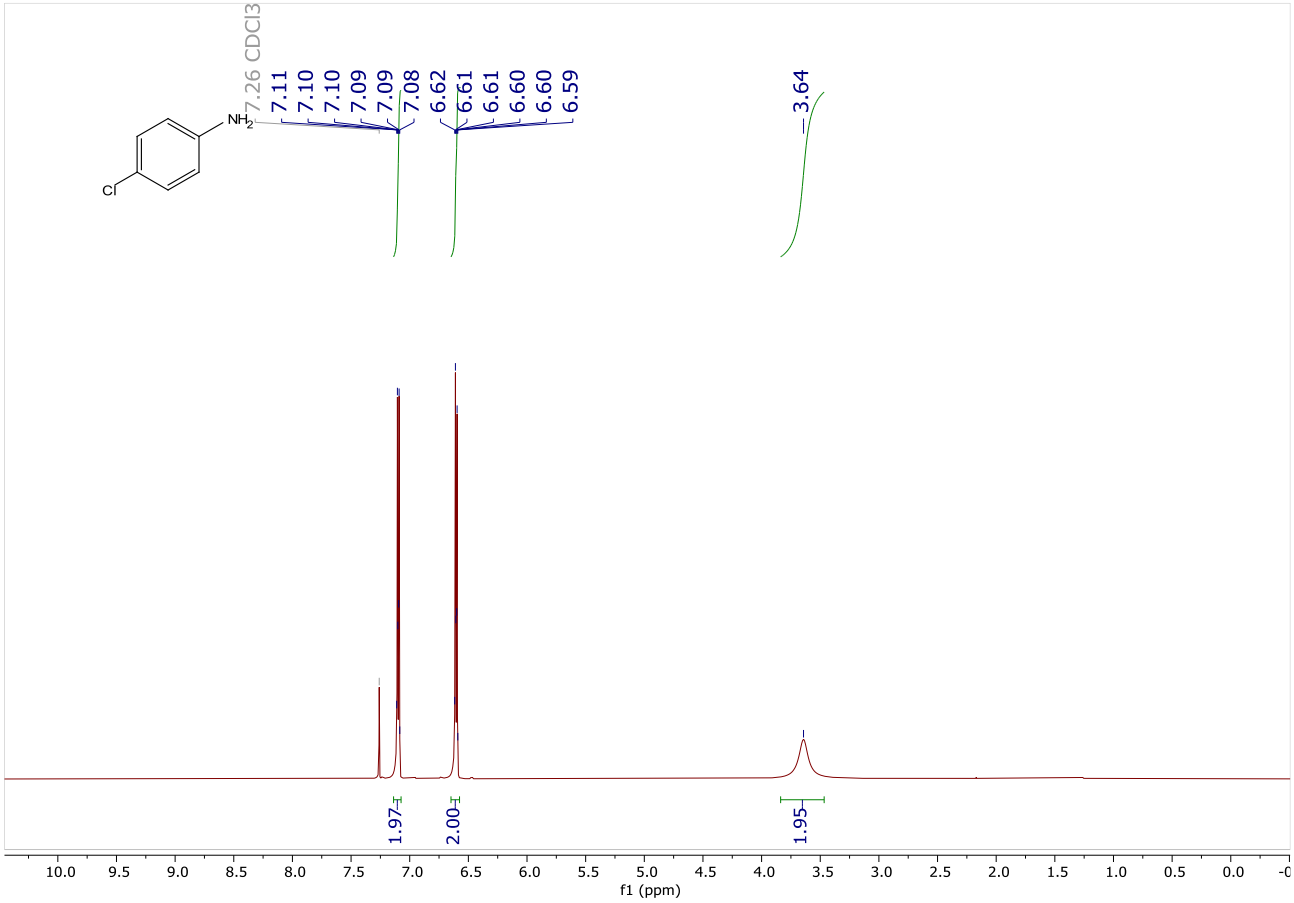

147.76
147.75
134.97
130.43
118.58
115.05
113.31
77.16 CDCl3
f1 (ppm)

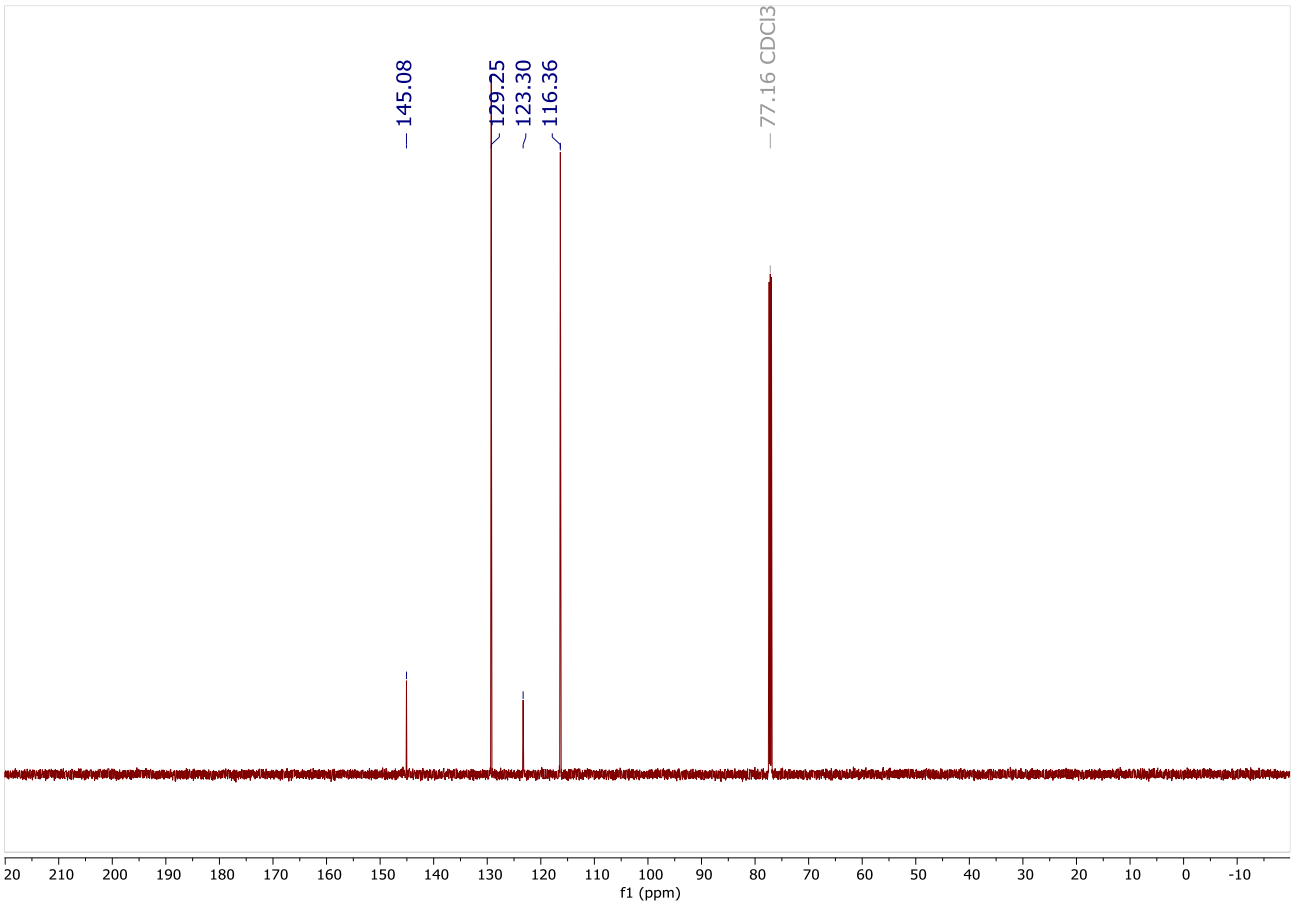

7.26 CDCl3
7.24
7.22
6.57
6.57
6.56
6.55
6.55
3.65
NH2
Br
1.98
2.00
1.91
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

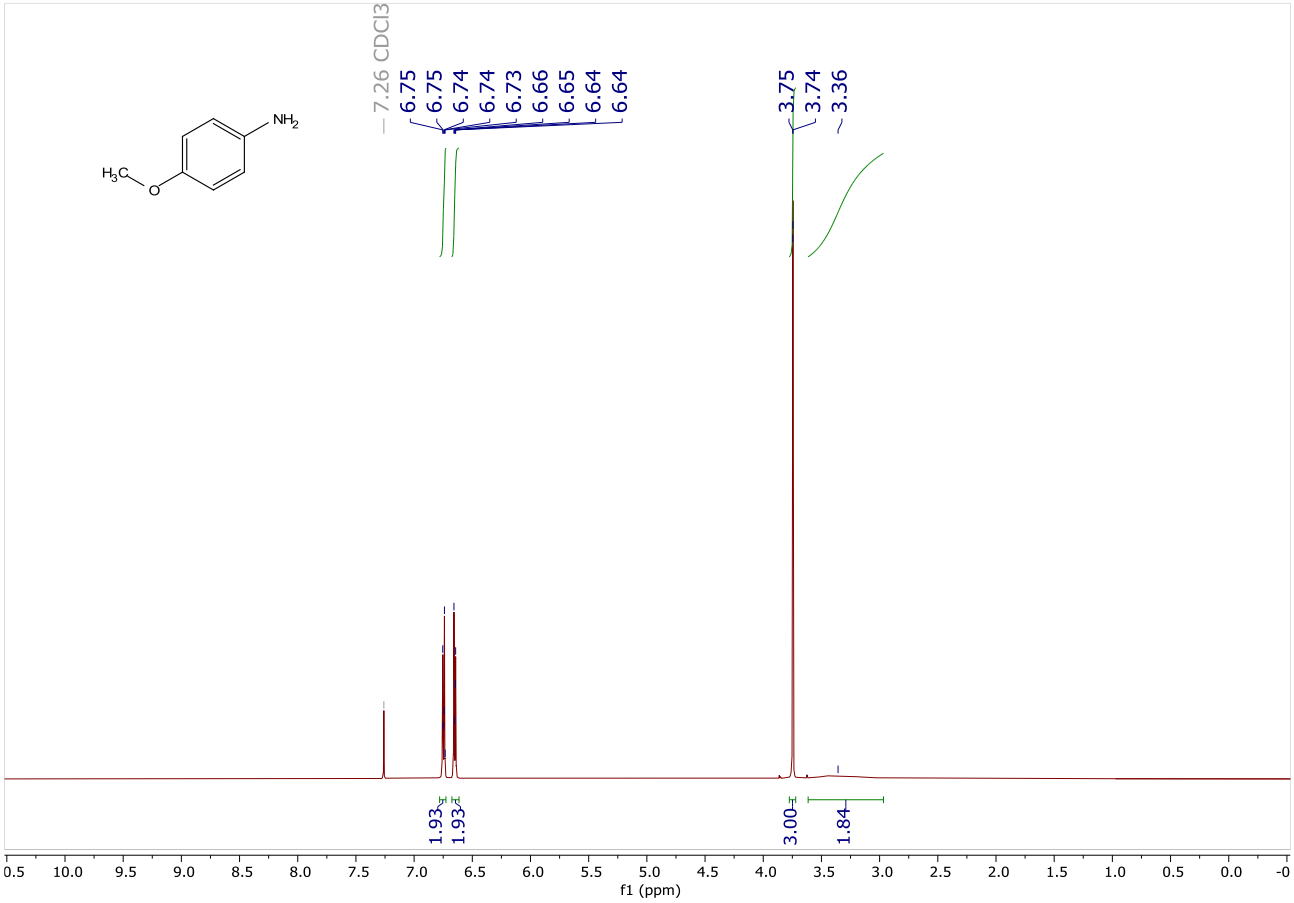

145.55
132.13
116.83
110.31
77.16 CDCl3
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26 CDCl3
7.24
7.22
6.57
6.57
6.56
6.55
6.55
3.65
NH2
Br
1.98
2.00
1.91
f1 (ppm)


145.55
132.13
116.83
110.31
77.16 CDCl3
f1 (ppm)


7.26 CDCl3
7.11
7.10
7.10
7.09
7.09
7.08
6.62
6.61
6.61
6.60
6.60
6.59
3.64
NH2
Cl
1.97
2.00
1.95
f1 (ppm)


145.08
129.25
123.30
116.36
77.16 CDCl3
f1 (ppm)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6.75
6.75
6.74
6.74
6.73
6.66
6.65
6.64
6.64
3.75
3.74
3.36
NH2
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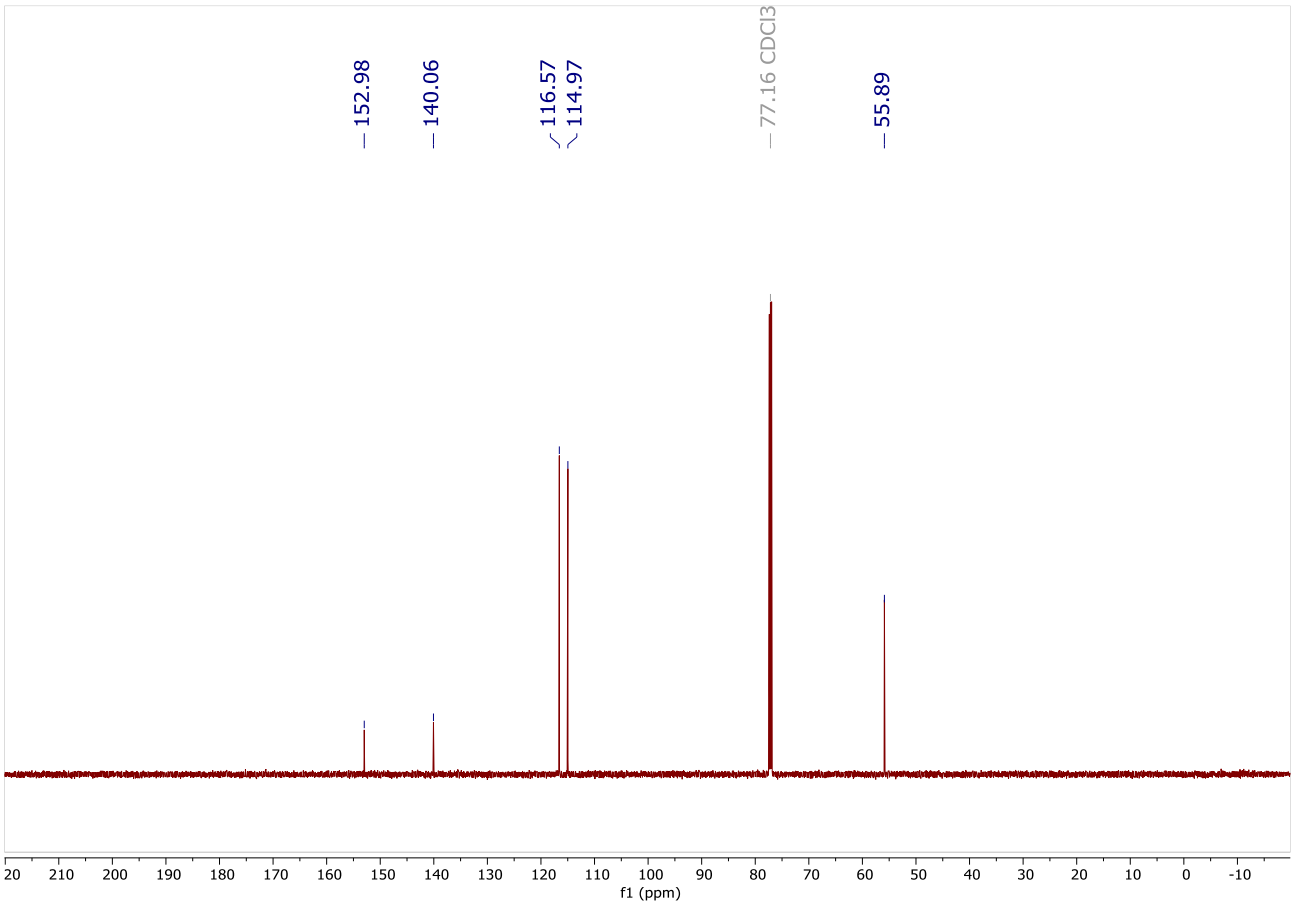
O
1.93
1.93
3.00
1.84
f1 (ppm)


152.98
140.06
116.57
114.97
77.16 CDCl3
55.89
f1 (ppm)

References

1 a) C. Webster, *Paracelsus: Medicine, Magic and Mission at the End of Time*, Yale University Press, New Haven, **2008**; b) J. F. Borzelleca, "Paracelsus: Herald of Modern Toxicology" *Toxicol. Sci.* 2000, **53**, 2–4.

2 O. Wallach, *Briefwechsel zwischen J. Berzelius und F. Wöhler (Correspondence between J. Berzelius und F. Wöhler)*, Vol. 1, W. Engelmann, Leipzig, **1901**, pp. 206–207.

3 J. J. Berzelius, *Lehrbuch der Chemie*, **1831**, IV (1), 356 (Wöhler's translation of *Lärbok i Kemien*, 1830).

4 Chisholm, Hugh, ed. (1911). "*Kekulé, Friedrich August*" . *Encyclopædia Britannica*. Vol. **15** (11th ed.). Cambridge University Press. pp. 717–718.

5 H. Kolbe, *Annalen der Chemie und Pharmacie* (in German), 1845, **54**, 145–188.

6 G. Vantomme, J. Crassous, *Chirality*.2021; **33**:597–601.

7 D. Yergin, *The Prize, The Epic Quest for Oil, Money & Power*. New York: Simon & Schuster, **1991** pp. 19–29. ISBN 9780671799328.

8 T. W. Graham Solomons, *Chimica organica*, 2ª ed., Bologna, Zanichelli, **2001**, ISBN 88-08-09414-6.

9 A. Baeyer, Viggo Drewsen, "Darstellung von Indigblau aus Orthonitrobenzaldehyd". *Berichte der deutschen chemischen Gesellschaft*, 1882, **15**, 2856–2864.

10 J.H. van 't Hoff," *Archives neerlandaises des sciences exactes et naturelles*, 1874, **9**, 445–454.

11 M. S. Tswett, Proceedings of the Warsaw Society of Naturalists [i.e., natural scientists], Biology Section)), , 1905, **14**, pp. 20–39.

12 J. J. Thomson, *Proceedings of the Royal Society* A, 1913 **89**, 1–20

13 P. Sabatier, *Ind. Eng. Chem.*, 1926, **18**, p. 1005

14 Fischer, E.; Jourdan, F., *Berichte der Deutschen Chemischen Gesellschaft*. 1883, **16**, 2241–2245.

15 H. Otten, *Journal of Antimicrobial Chemotherapy*, 1986, **17**, 689–696.

16 I. Ugi, , U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Int. Ed. Engl.*, **1965**, *4*: 472-484.

17 W. Ostwald, Handbuch der allgemeinen Chemie, Band I, *Academische Verlagsgesellschaft*, Leipzig **1919**.

18 N. E. S. Tay, D. Lehnherr, and T. Rovis, *Chem. Rev.* 2022, **122**, 2487–2649

19 L. Tackas, *Chem. Soc. Rev.*, 2013, **42**, 7649-7659

20 Selected books, reviews and articles discussing early mechanochemical studies: a) W. A. Yarbrough and R. Roy, *Nature*, 1986, **3**, 347–349; b) A. J. Lynch and C. A. Rowland, *The History of Grinding, Society of Mining, Metallurgy and Exploration*, Inc., Littleton, CO, 2005; c) P. A. Rehbinder, *Physico-Chemical Mechanics, A New Area of Science*, Izd. Znanije, Moscow, 1958; d) V. V Boldyrev, *Russ. Chem. Rev.*, 2006, **75**, 177–189; e) V. V. Boldyrev and E. G. Avvakumov, *Russ. Chem. Rev.* 1971, **40**, 847.

21 Selected reviews and articles discussing mechanical alloying: a) J. S. Benjamin, *Metall. Trans.*, 1970, **1**, 2943–2951; b) J. S. Benjamin and T. E. Volin, *Metall. Trans.*, 1974, **5**, 1929–1934; c) P. S. Gilman and J. S. Benjamin, *Ann. Rev. Mater. Sci.*, 1983, **13**, 279–300; d) M. Senna, Y. Kojima, T. Shinohara, S. Ono, K. Sumiyama and K. Suzuki, J. *Alloys Compd.*, 1995, **97**, 227.

22 Selected books, reviews, and articles discussing the mechanochemical treatment in material science: a) J. S. Benjamin, in *New Materials by Mechanical Alloying Techniques*, ed. E. Artz and L. Schultz, DGM Informationsgesellschaft, Oberursel, 1989, 3; b) P. Baláž, J. Briančin, Z. Bastl, L. Medvecký and V. Šepelák, *J. Mat. Sci.*, 1994, **29**, 4847–4851; c) A. L. Sanna, M. Carta, G. Pia, S. Garroni, A. Porcheddu and F. Delogu, *Sci. Rep.* 2022, **12**, 1–9; d) M. Carta, A. L. Sanna, A. Porcheddu, S. Garroni and F. Delogu, *Sci. Rep.* 2023, **13**, 2470; e) A. L. Sanna, G. Pia and F. Delogu, *Adv. Mater. Sci. Eng.* 2020, DOI 10.1155/2020/8844569.

23 V. André; M.T. Duarte; C.S.B. Gomes; M.C. Sarraguça, *Molecules* **2022**, *27*, 241

24 A.F. Silvaa, , J. Vercruyssec, C. Vervaetc, J.P. Remonc, J.A. Lopesd, T. De Beera, M.C. Sarraguça, *Eur. J. Pharm. Biopharm.* 128 (2018) 36–4

25 F. Gomollón-Bel, *Chem. Int.* 2019, **41**, 12-17

26 F. Cuccu, L. De Luca, F. Delogu, E. Colacino, N. Solin, R. Mocci and A. Porcheddu, *ChemSusChem*, 2022, **15**, e2022003

27 A. Stolle, T. Szuppa, Silke E. S. Leonhardta, and B. Ondruschkaa, *Chem. Soc. Rev.*, 2011, **40**, 2317-2329

28 For more information on COST Action CA18112 'Mechanochemistry for Sustainable Industry': http://www.mechsustind.eu (last accessed February 05, 2024).

29 W. R. Roy, R. A. Griffin, J. K. Mitchell and R. A. Mitchell, Environ. Geol. Water Sci., 1989, 13, 225–231; b) P. T. Anastas and J. B. Zimmerman, IEEE Eng. Manag. Rev., 2007, 35, 16; c) P. J. Dunn, A. S. Wells and M. T. Williams, Asymmetric Catalysis on Industrial Scale Green Chemistry and Catalysis Handbook of Green Chemistry – Green Catalysis Microwaves in Organic Synthesis Handbook of Green Chemistry – Green Solvents Supercritical Carbon Dioxide Solvent-free Organic Synthesis, **2010**.

30 N. D. Anastas, and J. C. Warner, *Chem. Health Saf.* 2005, **12**, 2, 9–13

31 P. T. Anastas, J. C. Warner Green Chemistry: Theory and Practice, Oxford University Press, Oxford, **1998**

32 F. Casti, F. Basoccu, R. Mocci, L. De Luca, A. Porcheddu, and F. Cuccu, *Molecules* 2022, **27**, 1988

33 For selected references concerning "One Health," please see a) F. Godlee and A. Waters, *BMJ*, 2018, **362**, 1–2; b) L. Kahn, *Nature,* 2017, **543**, S47; c) X. X. Shi, Z. Z. Wang, X. L. Sun, Y. L. Wang, H. X. Liu, F. Wang, G. F. Hao and G. F. Yang, *Green Chem.*, 2023, **25**, 2170–2219.

34 For an overview of APIs' regulation and sustainable production, please see a) https://www.europarl.europa.eu/RegData/etudes/STUD/2023/740070/IPOL_STU(2023)740070_EN.pdf (last accessed February 05, 2024); b) C. T. A. Moermond, N. Puhlmann, A. R. Brown, S. F. Owen, J. Ryan, J. Snape, B. J. Venhuis and K. Kümmerer, *Environ. Sci. Technol. Lett.*, 2022, **9**, 699–705; c) S. Kar, H. Sanderson, K. Roy, E. Benfenati and J. Leszczynski, *Chem. Rev.*, 2022, **122**, 3637–3710; d) H. B. Rose, B. Kosjek, B. M. Armstrong and S. A. Robaire, *Curr. Res. Green Sustain. Chem.*, 2022, **5**, 100324; e) S. G. Koenig, C. Bee, A. Borovika, C. Briddell, J. Colberg, G. R. Humphrey, M. E. Kopach, I. Martinez, S. Nambiar, S. V. Plummer, S. D. Ribe, F. Roschangar, J. P. Scott and H. F. Sneddon, *ACS Sustain. Chem. Eng.*, 2019, **7**, 16937–16951; f) P. D. García-Fernández, J. M. Coto-Cid and G. de Gonzalo, *Catalysts*, 2023, **13**, 368; g) R. A. Sheldon, *Green Chem.*, 2023, **25**, 1704; h) C. T. A. Moermond, N. Puhlmann, A. R. Brown, S. F. Owen, J. Ryan, J. Snape, B. J. Venhuis and K. Kümmerer, *Environ. Sci. Technol. Lett.*, 2022, **9**, 699–705.

35 Selected reviews and articles discussing the benefits of mechanochemistry for green academic and industrial applications: a) L. N. Ortiz-Trankina, J. Crain, C. Williams and J. Mack, *Green Chem.* 2020, **22**, 3638–3642; b) A. Porcheddu, F. Delogu, L. De Luca, C. Fattuoni and E. Colacino, Beilstein *J. Org. Chem.* 2019, **15**, 1786–1794; c) J. Mack, D. Fulmer, S. Stofel and N. Santos, *Green Chem.* 2007, **9**, 1041–1043; d) E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, R. Guerra, F. Delogu and J. Fullenwarth *Green Chem.* 2018, **20**, 2973–2977; e) D. E. Crawford, A. Porcheddu, A. S. McCalmont, F. Delogu, S. L. James and E. Colacino, *ACS Sustain. Chem. Eng.* 2020, **8**, 12230–12238; f) V. V. Boldyrev, *J. Mater. Sci.* 2004, **39**, 5117–5120; g) F. Basoccu, F. Cuccu and A. Porcheddu, ChemSusChem 2023, e202301034.

36 D. E. Fitzpatrick, C. Battilocchio, S. V. Ley, *ACS Cent. Sci.* 2016, **2**, 131–138

37 a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; b) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.

38 a) M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311; b) A. Mermer, T. Keles and Y. Sirin, *Bioorg. Chem.*, 2021, **114**, 105076.

39 For selected books, articles and reviews discussing the molecular and pharmaceutical relevance of indoles, please see: a) A. W. Schammel, G. Chiou and N. K. Garg, *Org. Lett.*, 2012, **14**, 4556–4559; b)L. Zu, B. W. Boal and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 8877–8879; c) A. Nishida, R. Tsuji and M. Nakagawa, *Heterocycles*, 2002, **58**, 587-593; d) J. H. Rigby and S. Sidique, *Org. Lett.* 2007, **9**, 1219–1221; e) S. Dadashpour and S. Emami, *Eur. J. Med. Chem.*, 2018, **150**, 9–29; f) A. Thakur, A. Singh, N. Kaur, R. Ojha and K. Nepali, *Bioorg. Chem.*, 2020, **94**, 103436; g) Y. Li, Y. Xiong, G. Zhang, L. Zhang, W. Yang, J. Yang, L. Huang, Z. Qiao, Z. Miao, G. Lin, Q. Sun, T. Niu, L. Chen, D. Niu, L. Li and S. Yang, *J. Med. Chem.*, 2018, **61**, 11398–11414; h) S. Oh, G. W. Go, E. Mylonakis and Y. Kim, *J. Appl. Microbiol.*, 2012, **113**, 622–628; i) S.-F. Fu, J.-Y. Wei, H.-W. Chen, Y.-Y. Liu, H.-Y. Lu and J.-Y. Chou, *Plant Signal. Behav.*, 2015, **10**, e1048052; j) A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021; k) T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10; l) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, 491-502; m) S. Lal and T. J. Snape, *Curr. Med. Chem.*, 2012, **19**, 4828–4837.

40 a) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184; b) M. Brindisi, J. Senger, C. Cavella, A. Grillo, G. Chemi, S. Gemma, D. M. Cucinella, S. Lamponi, F. Sarno, C. Iside, A. Nebbioso, E. Novellino, T. B. Shaik, C. Romier, D. Herp, M. Jung, S. Butini, G. Campiani, L. Altucci and S. Brogi, *Eur. J. Med. Chem.*, 2018, **157**, 127–138; c) D. Bates and A. Eastman, *Br. J. Clin. Pharmacol.*, 2017, **83**, 255–268; d) J. T. Ndongo, J. N. Mbing, M. F. Tala, A. Monteillier, D. E. Pegnyemb, M. Cuendet and H. Laatsch, *Phytochemistry*, 2017, **144**, 189–196; e) K.-H. Lim, O. Hiraku, K. Komiyama and T.-S. Kam, *J. Nat. Prod.*, 2008, **71**, 1591–1594; f) Y. Wang, F. Xie, B. Lin, M. Cheng and Y. Liu, *Chem. - A Eur. J.*, 2018, **24**, 14302–14315; g) S. Zeeli, T. Weill, E. Finkin-Groner, C. Bejar, M. Melamed, S. Furman, M. Zhenin, A. Nudelman and M. Weinstock, *J. Med. Chem.*, 2018, **61**, 4004–4019; h) J. E. Wilson, R. Kurukulasuriya, M. Reibarkh, M. Reiter, A. Zwicker, K. Zhao, F. Zhang, R. Anand, V. J. Colandrea, A.-M. Cumiskey, A. Crespo, R. A. Duffy, B. Ann Murphy, K. Mitra, D. G. Johns, J. L. Duffy and P. Vachal, *ACS Med. Chem. Lett.*, 2016, **7**, 261–265.

41 For selected articles and reviews discussing the synthesis of indoles, please refer to: a) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes and Y. Cai, *Org. Lett.*, 2006, **8**, 5769–5771; b) Y.-K. Lim and C.-G. Cho, *Tetrahedron Lett.*, 2004, **45**, 1857–1859; c) E. Yasui, M. Wada and N. Takamura, *Tetrahedron Lett.*, 2006, **47**, 743–746; d) A. Guy, J.-P. Guetté and G. Lang, *Synthesis,* **1980**, 222–223; e) Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa, Y. Kamimura and M. Izaki, *Heterocycles*, 1984, **22**, 1211–1216; f) S. Gore, S. Baskaran and B. König, *Org. Lett.*, 2012, **14**, 4568–4571; g) J. L. Rutherford, M. P. Rainka and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 15168–15169; h) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, 2002, **65**, 2452–2454; i) G. L. Rebeiro and B. M. Khadilkar, *Synthesis (Stuttg).*, 2001, **2001**, 370–372; j) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500–7501; k) B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 16625–16631; l) Y.-L. Li, J. Li, A.-L. Ma, Y.-N. Huang and J. Deng, *J. Org. Chem.*, 2015, **80**, 3841–3851; m) S.-L. Cui, J. Wang and Y.-G. Wang, *J. Am.*

Chem. Soc., 2008, **130**, 13526–13527; n) N. Zeidan, S. Bognar, S. Lee and M. Lautens, *Org. Lett.*, 2017, **19**, 5058–5061; o) M. Sayyad, Y. Nanaji and M. K. Ghorai, *J. Org. Chem.*, 2015, **80**, 12659–12667; p) D. Bhattacharya, D. W. Gammon and E. van Steen, *Catal. Letters*, 1999, **61**, 93–97; p) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2004, **60**, 3417–3420; q) A. Dhakshinamoorthy and K. Pitchumani, *Appl. Catal. A Gen.*, 2005, **292**, 305–311

42 Y. Qiu, K. Te Puni, C. C. Duplan, A. C. Lindsay and J. Sperry, *Tetrahedron Lett.*, 2021, **72**, 153068.

43 D. Margetić, *Pure and Applied Chemistry*, 2023, **95**, pp. 315–328

44 M. Rodrigues, , B. Baptista, , J.A. Lopes, M.C. Sarraguça, *Int. J. of Pharm.*, 2018, **547**, pp. 404–420

45 V. Canale, M. Kamiński, W. Trybała, M. Abram, K. Marciniec, X. Bantreil, F. Lamaty, J. R. Parkitna and P. Zajdel, *ACS Sustainable Chem. Eng.* 2023, 11, **45**, 16156–16164

46 T. I. Oprea, and C. Bologa, *J. Med. Chem.* 2023, **66**, 12710–12714

47 T. Böttcher, *J. of Mol. Evol.* 2018, **86**, 1–10

48 A. Porcheddu, R. Mocci, M. Brindisi, F. Cuccu, C. Fattuoni, F. Delogu, E. Colacino and M. V. D. Auria, *Green Chem.* 2022, **24**, 4859–4869

49 Fors selected articles and reviews discussing the relevance of isocyanides, please refer to: a) L. El Kaïm, L. Grimaud, *Eur. J. Org. Chem*., 2014, **35**, 7749-7762; b) L. El Kaïm, L. Grimaud, P. Patil, *Synlett* 2012; **23**, 1361-1363; c) M. Passerini, L. Simone, Gazz., *Chim. Ital.* 1921, **51**, 126–29; d) N. Liu, F. Chao, M. G. Liu, N. Y. Huang, K. Zou, L. Wang, *J. Org. Chem.* 2019, **84**, 2366–2371; e) H. Bienaymé, K. Bouzid, *Tetrahedron Lett.* 1998, **39**, 2735−2738; f) M. Leonardi, M. Villacampa, J. C. Menéndez, *Chem. Sci. 2018*, **9**, 2042–2064; g) J. G. Rudick, S. Shaabani, and A. Dömling, *Front. Chem.*, 2020, **7**, 918; h) R. Ramozzi, N. Chéron, B Braïda, P.C. Hiberty, P. Fleurat-Lessard, *New J. Chem.* 2012, **36**, 1137–1140; i) R. Arshady, M. Zecca, B. Corain, *React. Polym.*, 1993**,** **20**, 147-173; j) E. Singleton, H. E. Oosthuizen, *Adv. Organomet. Chem.* 1983, **22**, 209–310; k) Bassett, J.M., Farrugia, L. J., Gordon F., Stone F. G. A., *J. Chem. Soc.*, *Dalton Trans.,* 1980, **9**, 1789-1790

50 For a selected paper about the biological activity of sulfonamides, please see a) C. T. Supuran and A. Scozzafava, *J. Enzyme Inhib.*, 1997, **12**, 37–51; b) A. Scozzafava, L. Menabuoni, F. Mincione, F. Briganti, G. Mincione and C. T. Supuran, *J. Med. Chem.*, 1999, **42**, 2641–2650; c) L. E. Dorfman and J. P. Smith, *J. Urol.*, 1970, **104**, 482–483; d) G. L. Perlovich, V. P. Kazachenko, N. N. Strakhova and O. A. Raevsky, *J. Chem. Eng. Data*, 2014, **59**, 4217–4226; e) G. Culletta, M. Tutone, M. Zappalà and A. M. Almerico, *Curr. Med. Chem.*, 2022, **30**, 128–163.

51 I. Ugi, R. Meyr, *Chem. Ber.* 1960**,** **93***,* 239–248.

52 A. Massarotti, F. Brunelli, S. Aprile, M. Giustiniano and G. C. Tron, *Chem. Rev.* 2021, **17**, 10742–10788

53 a) W. P. Weber, G. W. Gokel, I. K. Ugi, *Angew. Chemie Int. Ed. English* 1972, **11**, 530–531; b) I. Okada, Y. Kitano, *Synth.* 2011, **24**, 3997-4002; c) Stephens, C. R., Bianco, E. J., Pilgrim, F. J., *J. Am. Chem. Soc.*, 1955, **77**, 1701-1702; d) A. Porcheddu, G. Giacomelli, D. Chimica, *J. Org. Chem.* 2005, **70**, 2361–2363; e) S. M. Creedon, H. K. Crowley, D. G. McCarthy, *J. Chem. Soc. - Perkin Trans. 1* 1998, **16**, 1015–1017.

54 a) A. Ovung, J. Bhattacharyya, *Biophys Rev.*, 2021, **13**, 259-272; b) T.J. Shah, M. Moshirfar, P.C. Hoopes, *Ophthalmol Ther*, 2018, **7**, 211–215; c) O. Sköld, *Drug Resist. Updat.*, 2000, **3**, 155–160.

55 For selected classical in-solution sulfonamide syntheses, please see a) S. W. Youn, T. Y. Ko, Y. H. Jang, *Angew. Chem. Int. Ed.*, 2017, **56**, 6636-6640; b) J. G. Kang, J. H. Hur, S. J. Choi, G. J. Choi, K. Y. Cho, L. N. Ten, K. H. Park and K. Y. Kang, *Biosci. Biotechnol. Biochem.*, 2002, **66**, 2677–2682; c) T. Kato, I. Okamoto, A. Tanatani, T. Hatano, M. Uchiyama, H. Kagechika, H. Masu, K. Katagiri, M. Tominaga, K. Yamaguchi and I. Azumaya, *Org. Lett.*, 2006, **8**, 5017–5020; d) H. Murase, K. Senda, M. Senoo, T. Hata and H. Urabe, *Chem. - A Eur. J.*, 2014, **20**, 317–322; e) X. Zheng, H. Oda, K. Takamatsu, Y. Sugimoto, A. Tai, E. Akaho, H. I. Ali, T. Oshiki, H. Kakuta and K. Sasaki, *Bioorganic Med. Chem.*, 2007, **15**, 1014–1021; f) M. E. Huber, L. Toy, M. F. Schmidt, H. Vogt, J. Budzinski, M. F. J. Wiefhoff, N. Merten, E. Kostenis, D. Weikert and M. Schiedel, *Angew. Chemie - Int. Ed.*, 2022, **61**, 1–5.

56 V. Štrukil, D. Margetić, *Heterocycles: Synth., Catal., Sus., and Charact.*, 2022, pp. 339–369

57 M. Tobiszewski, J. Namieśnik, and F. P. Pereira, *Green Chem.*, 2017, **19**, 1034-1042

58 M. T. Nazeri, A. B. Nowee, S. Javanbakht, H. Farhid, A. Shaabani, B. Notash, *Tetrahedron* 2021, **91**, 132243

59 F. Cuccu, F. Basoccu, C. Fattuoni, A. Porcheddu, *Molecules,* 2022, **27**, 5450

60 F. Basoccu, F. Cuccu, F. Casti, R. Mocci, C. Fattuoni, A. Porcheddu, *Beilstein J. Org. Chem.* 2022*,* **18**, 732–737

61 F. Cuccu, A. Porcheddu, *Green Chem.,* 2024, **26**, 2684-2691

62 Selected reviews and articles discussing the importance of the alcoholic moiety and catalytic hydrogenation in medicinal chemistry: a) O. Robles and D. Romo, *Nat. Prod. Rep.* 2014, **12**, 318–334; b) T. Henkel, R. M. Brunne, H. Müller and F. Reichel, *Angew. Chemie – Ed. Engl.* 1999, **38**, 643–647.; c) A. M. Smith and R. Whyman, *Chem. Rev.* 2014, **114**, 5477−5510; d) C. R. S. Maior, P. C. S. Costa, C. B. P. Ligiéro, L. S. De Moraes, G. R. S. Jr, S. G. Lima, P. M. Esteves and P. C. M. L. Miranda, *Chem. Eur. J.* 2023, **29**, e202203731

63 a) T. Portada, D. Margetić and V. Štrukil, *Molecules* 2018, **23**, 3163; b) Y. Sawama, M. Niikawa, H. Sajiki and Y. G. K. Kyokaishi, *Journal Synth. Org. Chem.* 2019, **77**, 1070–1077.

64 https://cen.acs.org/synthesis/Mechanochemists-want-shake-industrial-chemistry/100/i28 (Last accessed February 05, 2024)
65 P. Viereck, S. Krautwald, T. P. Pabst, and P. J. Chirik, *J. Am. Chem. Soc*. 2020, **142**, 3923–3930
66 C. Daia , Y. Zhoua, H. Penga, S. Huanga, P. Qina, J. Zhanga, Y. Yanga, L. Luoa, X. Zhangb, *J. of Ind. and Eng. Chem.* 2018, **62**, 106–119
67 M. Carta, F. Delogu and A. Porcheddu, *Phys. Chem. Chem. Phys*., 2021, **23**, 14178-14194, and references thereof; b) F. Cuccu, D. L. Browne and A. Porcheddu, *Chem. Cat. Chem.* 2023, 15, e202300762.
68 M. Flinker, H. Yin, R. W. Juhl, E. Z. Eikeland, J. Overgaard, D. U. Nielsen and T. Skrydstrup, Angew. Chemie - Int. Ed. 2017, 56, 15910–15915.
69 F. Cuccu, F. Basoccu, C. Fattuoni, A. Porcheddu, *Green Chem.,* 2024, **26**, 1927-1934