Fall 2022

DESIGN AND SYNTHESIS OF PURINE BASED NEUROPROTECTORS AND NOVEL SYNTHETIC METHODS FOR THE TRIFLUOROMETHYLATION OF ALDEHYDE HYDRAZONES

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by

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A DISSERTATION

Presented to the Graduate Faculty of the

MISSOURI UNIVERSITY OF SCIENCE AND TECHNOLOGY

In Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

in

Chemistry

2022

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ABSTRACT

Purine-derived compounds are widely investigated as cyclin-dependent kinase inhibitors that have broad applications in the design of pharmaceuticals for treating diseases, such as diabetes, atherosclerosis, and cancers. Towards the goal of effective AGE-inhibitors, and neuroprotector compounds we have synthesized a series of novel purine-based triazoles and investigated their neuroprotective effects, using SHSY-3Y human neuroblastoma cell line. Through these studies, we have identified purine-based neuroprotector compounds that favorably modulate oxidative stress induced by the Fenton reaction-generated reactive oxygen species (ROS).

The C(sp^2−H)-trifluoromethylation of hydrazones would give access to the α-trifluoromethylated hydrazones that can serve as intermediates in the synthesis of pharmaceutically interesting, fluorinated compounds. Herein, we demonstrate two different synthetic routes for the C(sp^2−H)-trifluoromethylation of the aldehyde hydrazones using the readily available and cost-effective Langlois reagent (sodium trifluoromethanesulfinate). This reaction scheme is broadly applicable to a series of aromatic aldehyde *N*-amino morpholine hydrazones to give the corresponding C(sp^2)-trifluoromethyl hydrazones in moderate to high yields. Cu (II)-catalysis provides a cost-effective synthetic approach while Rose Bengal mediated photo redox catalyzed method provides environmentally benign synthetic method for the trifluoromethylation of aldehyde hydrazones.

ACKNOWLEDGMENTS

I express my deep gratitude and appreciation to my advisor Dr. V. Prakash Reddy for his endless supervision and support during my graduate program at Missouri University of Science and Technology. It was a great learning experience not only in terms developing technical knowledge but also in terms of learning work ethics, and discipline. He has been a wonderful supervisor and I would always be grateful to him. I would like to extend my acknowledgement to the dissertation evaluation committee members Dr. Jeffrey Winiarz, Dr. Paul Nam, Dr. Amitava Choudhury, and Dr. K Chandrashekhara for being in my advisory committee. I would like to thank my current and former lab members Dr. Jatin Mehta and Raheemat Rafiu, and all the undergraduate student researchers for their helpful discussions and assistance to complete my research work.

I thank the Department of chemistry for providing the teaching assistantship position during my graduate program. Finally, my family and friends have been a source of encouragement without whom I would not have made it this far.

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1. INTRODUCTION

Oxidative stress plays an important role in the development and manifestation of chronic diseases such as cardiovascular, diabetes, cancer, and neurodegenerative diseases. Oxidative stress is the status of imbalance between antioxidants and free radicals resulting to the interruption of redox signals[5,6]. The formation of free radicals is an inevitable byproduct of normal metabolic function of the body and can be aggravated by the unhealthy dietary intake and lifestyle. One of the metabolic functions resulting in oxidative stress is Maillard reaction or glycation. The protein glycation and modification of plasma in the body also results in the oxidative stress.

Louis Camilie Maillard in 1912 described the non-enzymatic browning reaction observed when reducing sugar and amino acids were heated. The reaction was named Maillard reaction after his name. The browning products that are formed during the Maillard reaction advanced glycation end products (AGEs) and the reaction is sometimes referred as glycation. Advanced glycation end products (AGEs) are a large group of protein-crosslink derived compounds, generated both exogenously (*in vitro*) and endogenously (*in vivo)* by a series of very slow complex non-enzymatic reactions between reducing sugars and amino groups in proteins, lipids, and nucleic acids. The glycation is initiated through a non-enzymatic reaction of amino groups of proteins, lipids, or nucleic acids with the carbonyl groups of reducing sugars resulting in the formation of an unstable Schiff base intermediate. Schiff base undergoes very slow chemical transformations over a period of weeks to form a highly reversible and stable

ketoamine intermediate (also known as Amadori product). Amadori products undergo dehydration and rearrangements to form AGE precursors (reactive dicarbonyls) which cause protein aggregation by developing a crosslink between adjacent proteins and lead to the formation of advanced glycation end products (AGEs). Oxidation of sugars (auto-oxidative glycation), ketoamines-Amadori product (glycol-oxidation), lipids, and amino acids in the presence of transition metals and oxygen can also generate very reactive dicarbonyls as AGE precursors which can covalently bind to proteins and lead to the formation of AGEs. These AGEs are commonly known as reactive oxygen species, reactive nitrogen species or in a layman term free radical. There are around 40 different kinds of AGEs that have been isolated and characterize so far[10-11].

Yoshimura, Iijima, Watanabe and Nakazawa (1997) investigated the AGEs formed by the reaction of glucose as reducing sugar and glycine as amino acid and studied their metal chelating and reducing effects using electron spin resonance (ESR)[12-13].AGEs can be characterized by their cell surface receptors that contribute to mediating the activation of different signaling pathways. One of the best characterized pathways is the receptor for advanced glycation end products (RAGE). Besides RAGE, there are several other receptors known, for example the AGE-receptor complex (AGE-R). AGER consists of three components, namely AGE-R1 (OST-48), AGE-R2 (80K-H) and AGE-R3 (galectin-3)[15-17]. RAGE was first reported in 1992 as signal transduction receptor of immunoglobulin family that helped in characterization of AGE structures. RAGE is found in an oligomeric or preassembled state within the plasma membrane. The level of RAGE is relatively low in a healthy adult tissues but escalates under the pathological conditions such as cancer, cardiovascular disease and diabetes[16]. RAGE also undergoes

rearrangement to form free radicals commonly known as reactive oxygen species (ROS). The activation of RAGE by various ligands is known to be responsible for oxidative stress and eventually results in inflammation, proliferation, and cell apoptosis[18] in cells and tissues through the diverse activation of intracellular signaling pathway such as mitogen-activated protein kinase (MAPK)[19] which is responsible for transmission of mitogens. The MAPK pathway is known to be responsible for increased mitochondrial fragmentation promoting tumor growth and chemoresistance through the phosphorylation of the mitochondrial protein resulting in different kinds of cancers[20-22]. RAGE is also responsible for the cell migration through the transforming growth factor beta (TGF-β) signal cascade leading to multiple cellular signaling pathway. This pathway is involved in the cause of oxidative stress resulting in the development of diabetes, inflammatory disease cardiovascular diseases[23]. The activation of RAGE signaling pathway in the liver contribute to the various hepatic disorders such as non-alcoholic steatohepatitis, liver cirrhosis, and cancers[24]. RAGE has also been studied to mediate the transportation of the pathophysiologically relevant concentration of amyloid-β-peptide into the central nervous system (CNS)[25] resulting in nuclear Factor Kappa B (NF- KB) activation[26]. NF-KB is involved in the regulation of the important cellular behaviors such as inflammatory and immune response, cellular growth and apoptosis[26]. The activation of NF-KB leads to the release to the pro-inflammatory cytokines[27], induction of cytokines, and chemokines[28].

AGE breakers show inhibitory effect either by breaking the protein cross link or by chelation of free radicals [29]. There are numbers of compound with nucleophilic functional groups and dicarbonyl-trapping activity. Alagebrium (3-phenacyl-4,5-dimethylthiazolium chloride, ALT-711) is a new class of thiazolium therapeutic agents

that break established protein-glucose cross-links[30]. ALT-711 has an enzymatic characteristic which breaks the covalent bond formed between protein and glucose restoring the normal function of the protein[31]. Alagebrium phase III clinical studies have been successfully conducted and this molecule has been proved to have positive effects on cardiovascular sclerotic hypertrophy, diabetes hypertension, and vascular sclerotic pathologies[31].

Fluorine containing compounds are widely used in the field of pharmaceuticals and agrochemicals. Fluorinated compounds are getting more attention mostly because of their high metabolic stability, enhanced lipophilicity, membrane permeability, and exhibit enhanced binding affinity as compared to the non-fluorinated compounds[11]. Thus, the organic molecules containing a trifluoromethyl group have been the most popular derivatives of fluorinated compounds and the research from both academia and industry has been focused on developing a feasible, efficient, and accessible method that will allow incorporation of CF_3 moiety to the position of interest. Recently, several methods have been reported for the electrophilic, nucleophilic, and free- radical trifluoromethylation. The commonly reported methods have used expensive trifluoro methylating reagents such as Togni's and Umemoto's reagents. Another commercially available trifluoromethylation reagent is Langlois reagent (CF_3SO_2Na, sodium trifluoromethanesulfinate). Langlois's reagent is stable, readily available, and easy to handle[12]. It was first reported in 1980 as an electrophilic trifluoromethyl radical in the addition to electron-rich double bonds and arenes. Nevertheless, the application of Langlois's reagent as a trifluoromethylation reagent is still needed to be explored. In this dissertation, we have developed the trifluoromethylation of the morpholine hydrazones of

aromatic aldehydes using Langlois's reagent as the trifluoromethylation reagent, potassium persulfate as an oxidizing agent and Copper (II) sulfate as a catalyst[13]. Feng and the co-workers, in 2017, reported the trifluoromethylation of aldehyde derivatives using Langlois's reagent and hypervalent iodine as an oxidizing agent[13]. Inspired by their work, and as an attempt to improve the method we developed a trifluoromethylating method using potassium persulfate as oxidizing agent and sodium trifluoromethane sulfinate as CF_3 radical source. The major drawback of Feng and co-worker's method exist because of the use of (Diacetoxyiodo) benzene in stoichiometric amount, which is toxic and difficult to handle. Replacing the (Diacetooxyiodo) benzene with potassium persulfate makes this work cost effective and easy to handle. Copper as a catalyst is considered more cost effective, sustainable, and less toxic than any other transition metal catalysts. Trifluoromethyl hydrazone derivatives, because of being biologically active, have occupied an important space in the synthesis of fluorinated molecules. Alam and the co-workers have studied different biological activities such as antimicrobial, analgesic, and anti-inflammatory, anti-cancer, central nervous system, antiprotozoal and cardio protective activities of hydrazones. The specific roles of the trifluoromethyl group (CF_3) in biologically active molecules promote the development of novel methods to construct C–CF_3 bonds in the past few years. Among the many methods developed, copper-catalyzed trifluoromethylation has gained enormous interest due to its high efficiency and cost effectiveness[14-15].

2. DESIGN AND SYNTHESIS OF NOVEL PURINE BASED TRIAZOLES AS NEUROPROTECTORS

Purine is a heterocyclic moiety present in chemical structure of many bioactive molecules. Several purine analogs e.g., thiopurines, pentostatin, acyclovir, penciclovir, ganciclovir, aza-thiopurine, vidarabine and theophylline have been used in the treatment of several diseases including acute leukemias, immunological disorders, tumors, and asthma[1]. Purine moiety has been established as an important pharmacophore in the development of anti-cancer, anti-microbial, anti-convulsant, and anti-hypertensive[2]. Published research showed that the purine based triazoles also acts as antioxidants to neutralize the free radicals. The free radicals are generated because of the exposure to pollution, cigarette, smoke, drugs, illness, stress, and even excessive exercise. When the excess free radicals cannot be neutralized, their accumulation in the body generates a phenomenon called oxidative stress[3]. The free radicals are reactive oxygen species (ROS) with one or more unpaired electron. The most common free radicals produced in human body are superoxide, hydroxyl radical, and nitric oxide radical. During the normal metabolic process, free radicals are produced in the body which are then neutralized by the antioxidants produced by the cells to wipe the undesired free radicals. Apart from this, there are several external factors that contribute to the production of excess free radicals in the body. Factors like, diet, lifestyle, medical conditions, environmental factors such as pollution and radiation cause the excess production of free radicals in the body. The generation of free radicals play a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases[4,5]. The human body has several

mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Guttering and Halliwell classified antioxidants into three groups based on their mechanism of action; (1) primary antioxidant, which functions as a free radical terminator, (2) secondary antioxidants, which retard the chain reactions that's responsible for generating free radicals, (3) tertiary antioxidants which repair the damaged tissues and protein. Phenolic compounds such as Tannin, Rutin, with more than one hydroxy group are primary antioxidants as they are capable of donating proton to free radicals contributing to their stability[4].

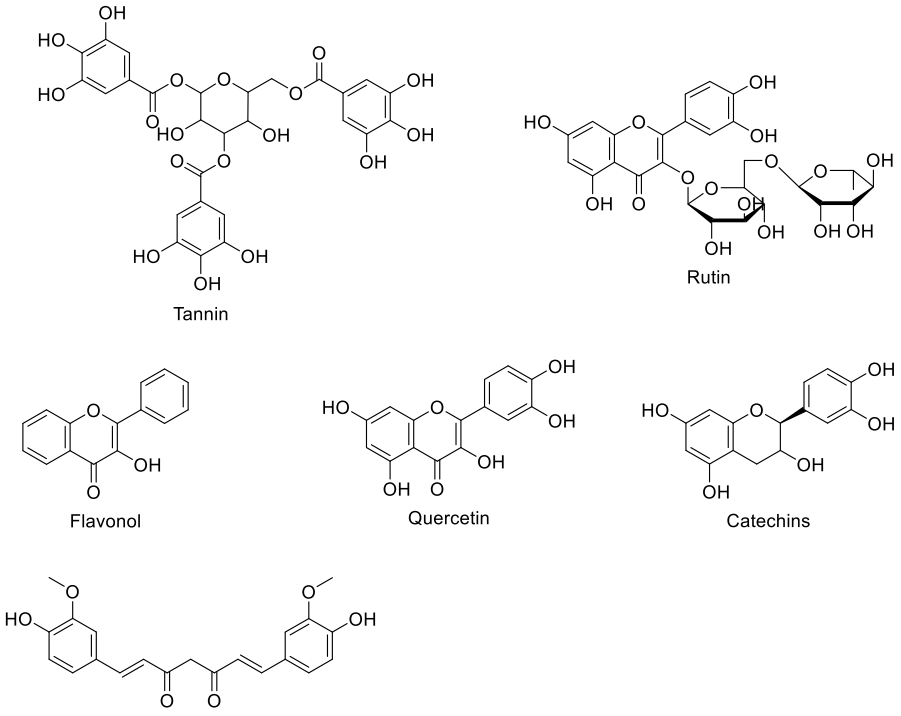


Figure 2.1. Primary Polyphenolic Antioxidants

Figure 2.1 shows the most common primary polyphenolic antioxidants. Primary polyphenols are classified under the class of flavonoids, which is further subdivided into

chalcones, flavones, flavanols and isoflavones[5-14]. Flavonoids, natural products with variable phenolic groups, are founds in plants mostly in fruits, vegetables, grains, flowers, and leaves.[11] The secondary antioxidants inhibit the oxidation of protein, lipids, and DNA by quenching the free radical formation. Ascorbic acid is an example of secondary antioxidant that is capable of regenerating primary antioxidant whereas Ethylenediamine- N', N-tetra acetic acid (EDTA) is a very common example of metal chelating antioxidant. Tertiary antioxidants act in repairing oxidized molecules in proteolytic enzymes or enzymes found in DNA through the sources like dietary or consecutive antioxidants[5]. For this project we are focusing on the tertiary antioxidants that would protect the damaged neuronal cells or antioxidants that act as neuroprotectors. The natural antioxidants are plant based secondary metabolites ranging from small molecules to highly polymerized molecules. The most common natural antioxidants are Flavonoids and phenolic acid which comprises of more than 60% of plant-based antioxidants.

Even though there has been significant attention on the antioxidant properties of polyphenolic compounds and their neuroprotective effectiveness in some cases, purine based compounds as antioxidants has received relatively less attention.[6] We have envisioned that purine-based triazoles can be tailored for neuroprotection, by incorporating polyphenolic and benzothiazole moieties onto the purine ring. Recently, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention because of their synthetic and effective biological importance. Many 1,2,4-triazole-containing ring system have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants

sedatives, antianxiety, antimicrobial agents, and antimycotic activity such as fluconazole, itraconazole, voriconazole. Also, there are known drugs containing the 1,2,4-triazole group e.g., Triazolam, Alprazolam, Etizolam, and Furacylin[3]. Hassan and Hammed synthesized and evaluated the antioxidant activities of triazole thiol derivative. They studied 1,2,4-triazole as a free radical scavenger with ascorbic acid as a standard compound and their results shows that the triazoles are effectives as an antioxidant compared to ascorbic acid. Sancak et al. reported on the antioxidant's activities of 1,2,3 Triazoles[7].

2.1. RESULTS AND DISCUSSION

We synthesized the purine derived triazoles starting from commercially available 2,6 dichloro purine. Medicinally active groups such as benzothiazole, benzylamine, and morpholine were attached in the purine ring (reaction scheme 1, 2, and 3) before the triazoles were formed. For compound 1, we replaced chloro group at 6^{th} position was replaced with amino- benzothiozole and the chloro-group at 2^{nd} position was left as it is. Benzothiozole is a very popular pharmaceutical compound that has been proven to have antimicrobial[67], anticonvulsive[68]properties. For compound 2, the chloro group at 2^{nd} position is replaced with morpholine group. Morpholine is another important pharmaceutical molecule that exhibits physiochemical, biological, and metabolic properties[70-71]. The completion of the reaction for each step was identified by TLC using dichloromethane and methanol (1:1 v/v) as solvent followed by proton NMR. The work up techniques and final product details are under experimental section. The ^{1}H, ^{13}C, and ^{19}F NMR of the final pure products are attached in the end of the section.

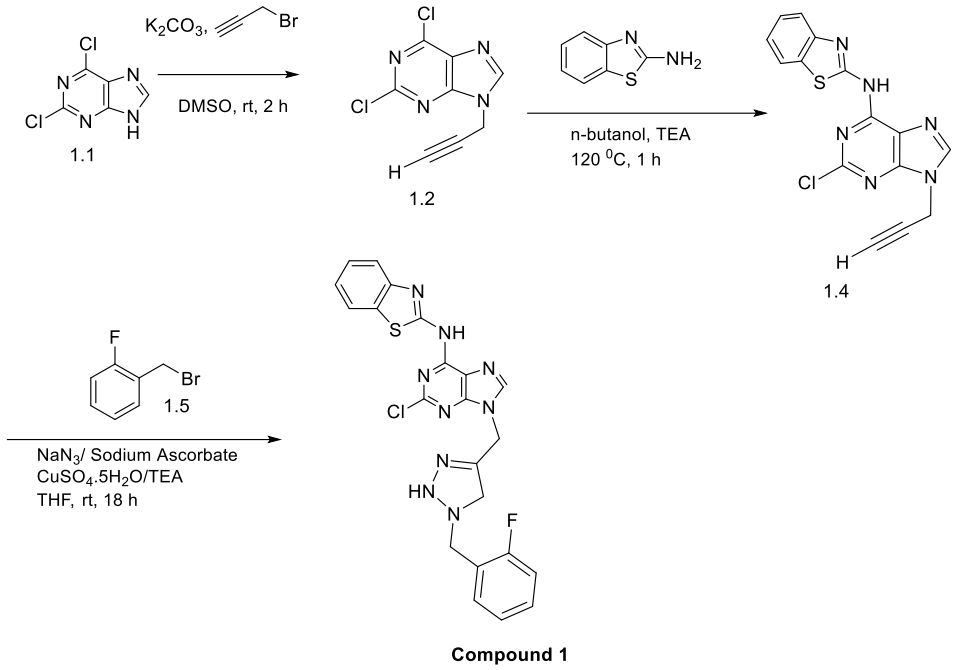
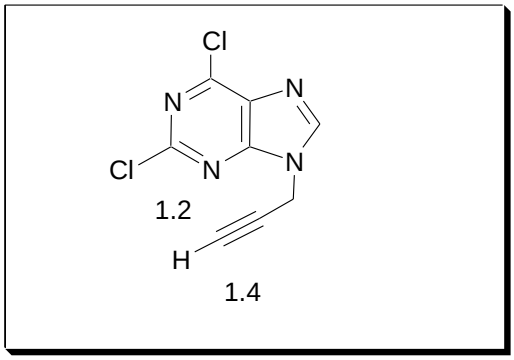
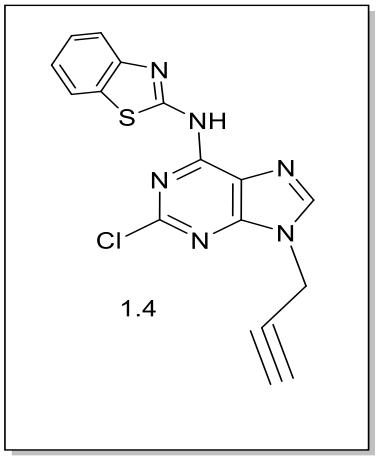


Figure 2.2. Reaction Scheme for the Synthesis of Compound 1

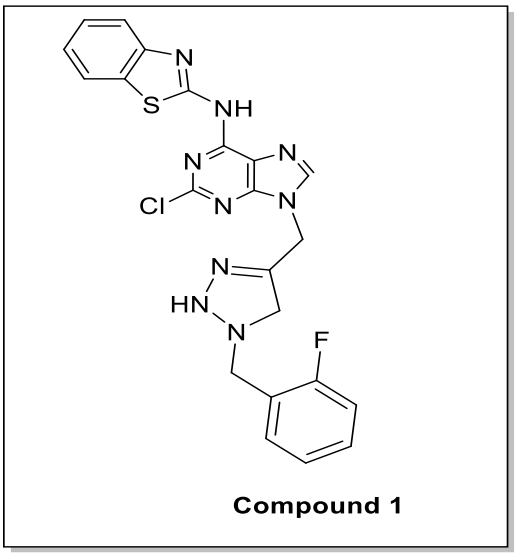
2.1.1. Experimental. To a solution of 2, 6 dichloro purine (500 mg, 2.64 mmol) in THF (5 mL), propargyl bromide (312 mg, 2.64 mmol) and potassium carbonate (3.96 mmol, 546.5 mg) was also added, and the resulting mixture was allowed to stir at room temperature for 3 to 4 hours. Once the reaction was completed by NMR, water was added to the mixture and precipitate was filtered and washed with water 2 times. Light pink colored product was obtained (476 mg). 1H NMR (400 MHz, CDCl3) δ 8.78 (s, 1H), δ 5.18 (s, 2H, CH2), δ 3.60 (1H, CH). 13C NMR (100 MHz, CDCl3) δ 152.96 (s), δ152.27 (s), δ 149.95 (s), δ 147.77 (s), δ 130.49 (s), δ 77.14 (d, J C-H= 15 Hz), δ 33.58 (s). Copy of NMR spectra is attached in the end of the section. The reaction scheme for the synthesis is outlined in the Figure 2.2.



1.4: To a solution (450 mg, 1.32 mmol) of 1.2 in THF (5 mL) and Triethylamine (132.5 mg, 1.32 mmol) was also added, and the reaction mixture allow to heat to 50 °C. Once the mixture reaches 50 °C, 4-aminobenzothiophene (198 mg, 1.32 mmol) and the reaction mixture allow to reflux for 4 hours or until the reaction was completed by NMR. Upon completion of the reaction solvent was evaporated and triturated with ether and washed with water. A light, yellow-colored products were obtained (402 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, CH), δ 7.71- 7.69 (m, 2H, ArH), δ 7.65- 7. 7.63 (dd, 1H, ArH), δ 7.42- 7.38 (dd, 1H, ArH), δ 5.63 (broad, NH, 1H), δ 5.14 (s, CH2, 2H), δ 2.72 (s, CH, 1H). ^{13}C NMR (100 MHz, CDCl3) δ 166.11 (s), ^{13}C NMR (100 MHz, DMSO) δ153. 48 (s), 152.71(s), 152.24 (d, J_{C-H}= 4Hz), 145.09 (s), 132.77 (d, J_{C-H}= 83 Hz) 126.17 (s), 122.49 (d, J_{C-H}= 139 Hz) 119.39 (s), 74.73 (s), 34.09 (s).



Compound 1: To a solution of sodium azide (42 mg, 0.52 mmol) in DMSO (3 mL), benzyl bromide (110 mg, 0.44 mmol mmol) was added dropwise and stirred at room temperature for 30 mins. To that mixture sample 2 (0.44 mmol, 150 mg), triethyl amine (4.4 mg, 0.04 mmol) and $CuSO_4$. $5H_2O$ (9.96 mg, 0.04 mmol) were added to the reaction mixture and was allowed to stir at room temperature for 18 h. Once the reaction was completed by NMR, the mixture was poured into ice cold water (15 mL) and the resulting pale white precipitate was filtered and washed with dilute NH4OH (20 mL) and water (50 mL) and recrystallized using ethanol to give the final product 1.4 (172 mg, 77%). 1H NMR (400 MHz, DMSO) δ 8.79 (s, CH, 1H), δ 8.22 (s, CH, 1H), δ 7.45 (broad, NH, s, 1H), δ 7.44-7.42 (m, ArH, 2H), δ 7. 40- 7.38 (m, ArH, 1H), δ 7. 30- 7.28 (m, ArH, 2H), δ 7. 26- 7.24 (m, ArH, 1H), δ 7.20- 7.16 (m, ArH, 2H), δ 6.99 (s, CH, 1H), δ 5.63 (s, CH, 1H) δ 5.57 (s, CH, 1H) δ 4.49 (s, CH2, 2H) (Figure 2.6). ^{13}C NMR (100 MHz, DMSO) δ 153.17 (s), 152.06 (s), 146.08 (s), 131.58 (d, J_{C-H}= 33.24), δ 130.95 (s), δ126.36 (s), δ 125.18 (s), δ 123.41 (d, J_{C-H}= 154 Hz), δ 121.24 (s), δ 116.31 (d, J_{C-H} = 21 Hz), δ 48.29 (s), δ 46.17 (s), δ 39.21 (s) (Figure 2.7). ^{19}F NMR (376 MHz, DMSO) δ 117.78 (d, J_{C-F}= 7.52 Hz) (Figure 2.8).



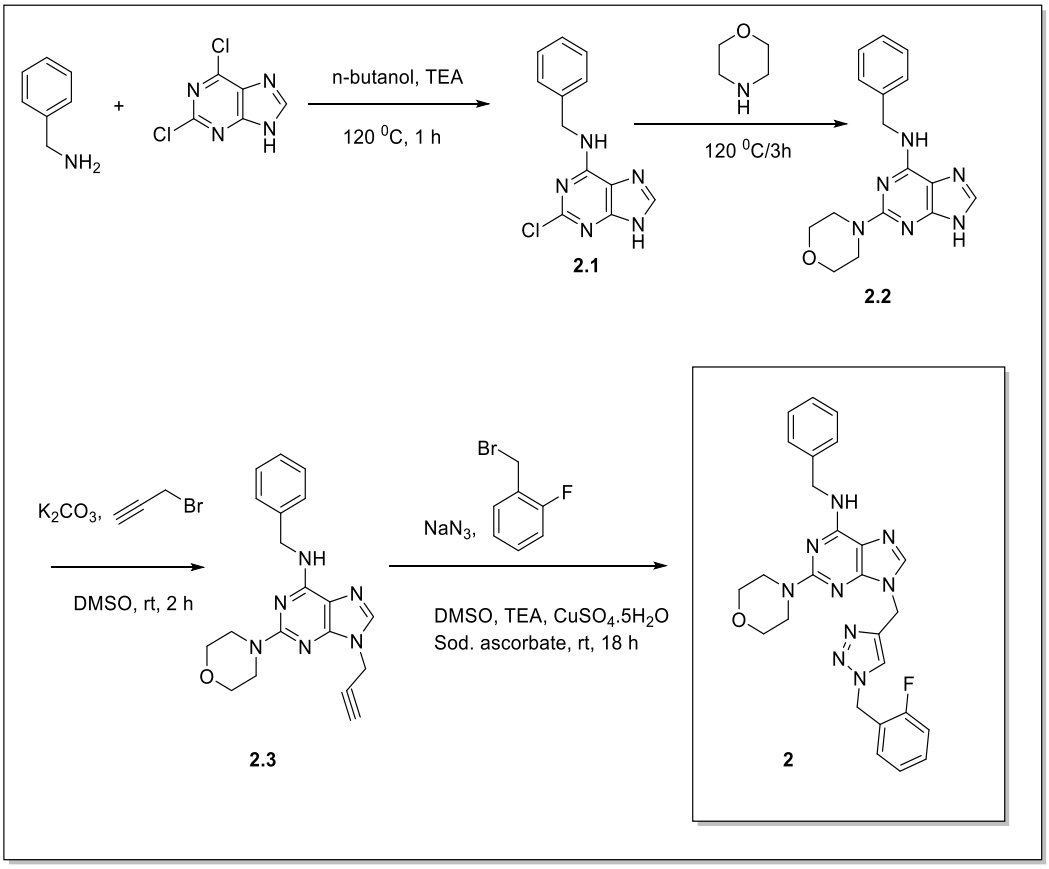
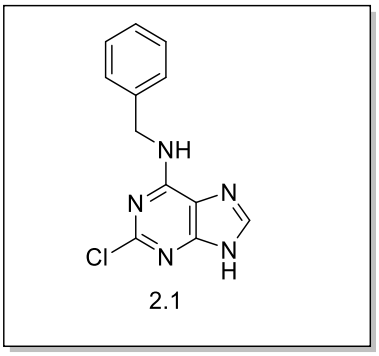


Figure 2.3. Reaction Scheme for the Synthesis of Compound 2

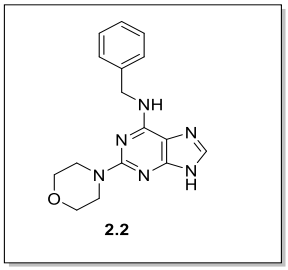
2.1**:** To a solution of 2, 6 dichloropurine (500 mg, 2.64 mmol) in n-butanol (5 mL) trimethylamine (399 mg, 3.96 mmol) was added. The mixture was stirred at 60°C for 15 minutes and benzylamine (282 mg, 2.64 mmol) was added to the mixture was reflux at 120°C for 2h. The resulting precipitate was filtered, washed with water (20 mL) and methanol (20 mL), and dried overnight. Peach colored product was obtained (596 mg, 87%). ^{1}H NMR (400 MHz, DMSO) δ 13.09 (broad, NH), δ 8.70 (s, 1H) δ 7.36-7.28 (m, 5H), δ 4.62 (d, 2H). ^{13}C NMR (100 MHz, DMSO) δ 155.12 (s), δ 153.70 (s), δ 150.72 (s), δ 140.2 (s), δ 139.38 (s), 136. 05 (s), δ 128.32 (d, J_{C-H} = 21 Hz), δ 127.45 (s), δ 126.87 (d, J_{C-H} = 36 Hz).



2.1

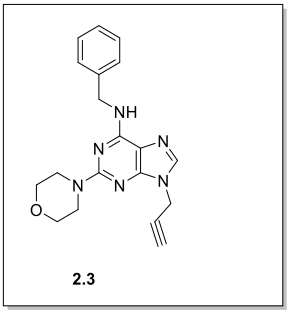
2.2: 2- Chloro-6-benzylaminopurine (500 mg, 1.93 mmol) was dissolved in excess morpholine (3 mL) and the mixture was refluxed at 120 C for 2 hours. Completion of the reaction was determined by proton NMR. Once the reaction was completed the mixture was cooled to room temperature and water was added. The resulting precipitates was filtered and washed with water to get light pink colored 2 Morpholino-6-benzylamino purine product (489 mg). The reaction scheme is outlined in the Figure 2.3. ^{1}H NMR (400 MHz, DMSO) δ 12.27 (s, NH), δ8.12 (s), δ 7.36- 7.34 (m, 2H, ArH), 7.29-7.26 (m, 2H, ArH), δ 7. 17- 7.17 (M, 1H, ArH) δ 4.56 (s, 2H, CH_2), δ 3.58 (m, 8H). ^{13}C

NMR (100 MHz, DMSO) δ 158.86 (s), δ 153.93 (s), δ 149.08 (s), δ 147.98 (s), δ 136.42 (d, J_{C-H} = 16 Hz), δ (135.43 (s), δ 123.60 (s), 113.29 (s), 66.22 (s), 44.98 (s), 41.06 (s).

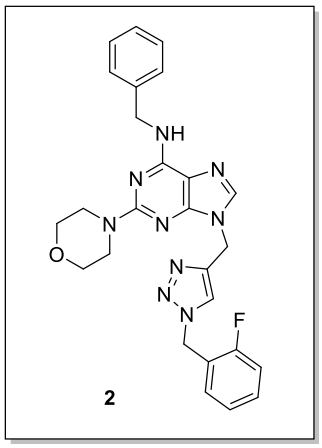


2.2

2.3: To a solution of benzyl amine morpholine (450 mg, 1.45mmol) in DMSO, propargyl bromide (171 mg, 1.45 mmol) was added and potassium carbonate (300 mg, 2.18 mmol) was also added. The mixture was allowed to stir for 3 hours at room temperature after the reaction was completed by NMR, water was added to the mixture. The resulting precipitate was filtered, washed with water, and triturated with ether. ^{1}H NMR (400 MHz, DMSO) δ 8.05 (s, 1H), δ 7.83 (s, 1H), δ 7.33-7.29 (m, 2H, ArH), δ 7.25(m, 1H ArH,), δ 7.20-7.18 (m, 2H, ArH), δ 4.85 (s, 2H), δ 4. 60 (s, 2H), δ 3.60 (m, 8H), δ 3.49(s, 1H). ^{13}C NMR (100 MHz, DMSO) 158.86 (S), 153.93 (s), 149. 08 (s), 147.98 (s), 136.26(s), 135.43 (s), 123.60 (s), 113. 29 (s), 66.22 (s), 44.98 (s), 41. 06 (s).



2.3



2

2: To a solution of sodium azide (80 mg, 1 mmol) in DMSO (5mL), benzyl bromide (125mg, 1 mmol) was added dropwise and stirred at room temperature for 30 minutes. To that mixture 2.3 (1 mmol, 348 mg), triethyl amine (11mg, 0.1 mmol) and $CuSO_4$. $5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (198 mg, 1 mmol) were added to the reaction mixture and allowed to stir at room temperature for 18 h. Once the reaction was complete, as shown by TLC or by ^{1}H NMR spectra, the mixture was poured into ice cold water (15 mL) and the resulting pale white precipitate was filtered and washed with dilute NH_4OH (20 mL) and water (50 mL) and recrystallized using ethanol to give the final product 2 (off white crystal, yield: 69%; 398 mg). ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), δ 7.36 (s, 1H), δ 7.30- 7.28 (m, 1H), δ 7.26- 7.21 (m, 5H), δ 7.19- 7.16 (1H, m), δ 7.14- 7.13 (m, 2H), δ 5.57 (s, 2H, δ 5.23 (s, 2H), δ 4.55 (s, 2H), 3.54 (m, 8H) (Figure 2.9). ^{13}C NMR (100 MHz, DMSO) δ 161.32(s), 158.88 (d, J_{C-H} = 24 Hz), δ 143.00 (s), δ 140.63 (s), δ 130.77 (s), δ 128.12 (s), δ 127.42 (d, J_{C-H} = 10 Hz), δ 126.53 (s), δ 124.86 (d, J_{C-H} = 3 Hz), δ 122.83 (s), δ 115.75 (d, J_{C-H} = 21 Hz) δ 66.07, δ 44.94, δ 43.16, δ 37.74 (Figure 2.10). ^{19}F NMR (376 MHz, DMSO) δ -117.85 (Figure 2.11).

3.2: To a solution of (3.1) 2,6-dichloropurine (1 g, 5.25 mmol) in n-butanol (10 mL), triethylamine (1.34 g, 13.22 mmol) was added, and the mixture was heated to 50 ^{0}C. Then 3-aminomethylpyridine (5.03 g, 9.52 mmol) was added at 50 ^{0}C and finally the reaction was heated and stirred at 120 ^{0}C for 1 h. After completion of reaction confirmed by ^{1}H NMR, the reaction mixture was cooled to rt and then to 0 ^{0}C using an ice-water bath. The peach-colored precipitate was filtered and washed with water (20 mL) and dried under air overnight to obtain pure compound 3.2 (796 mg, 52%). ^{1}H NMR (400 MHz, DMSO-

d6) δ 13.09 (br s, 1H), 8.76 (br s, 1H), 8.58 (s, 1H), 8.44-8.45 (d, 1H), 8.14 (s, 1H), 7.74-7.76 (d, *J*= 8 Hz, 1H), 7.32-7.35 (t, *J*= 4 Hz, 1H), 4.65 (d, 2H).

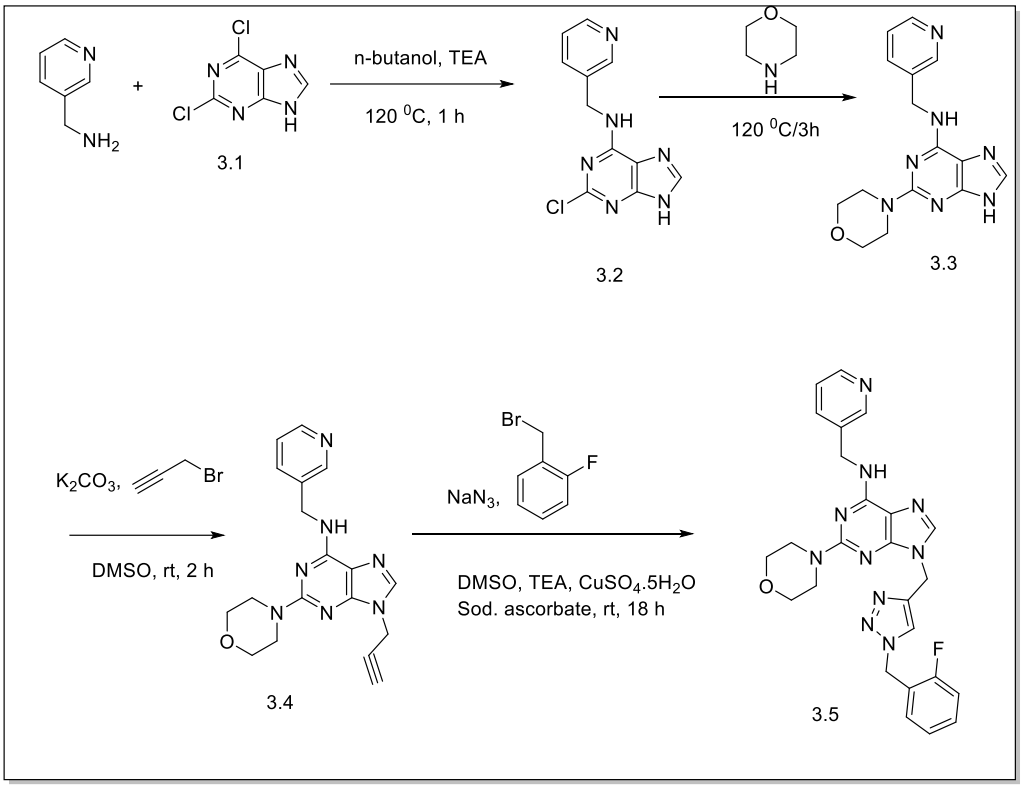
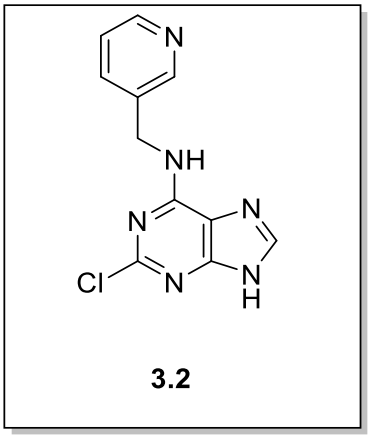
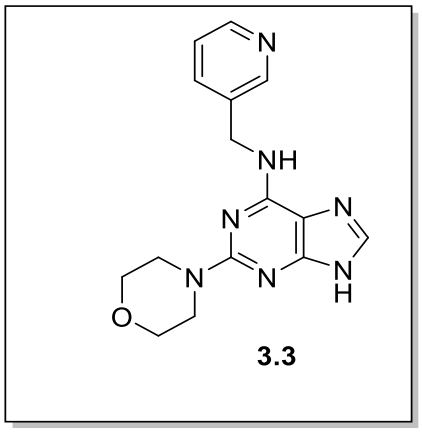


Figure 2.4. Reaction Scheme for the Synthesis of Compound 3



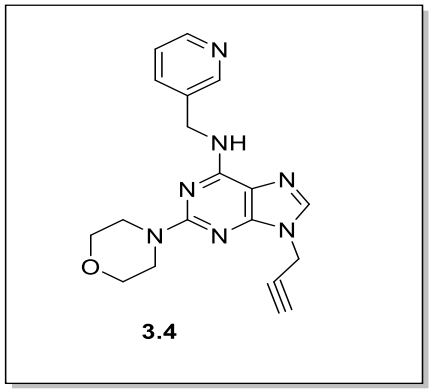
2- Chloro-6-benzylaminopurine (500 mg, 1.93 mmol) was dissolved in excess morpholine (3 mL) and the mixture was refluxed at 120 ^{0}C for 2 hours. Completion of the reaction was determined by proton NMR. Once the reaction was completed the mixture was cooled to room temperature and water was added. The resulting precipitates was filtered and washed with water to get light pink colored 2 Morpholino-6-benzylamino purine product (63%, 489 mg). The reaction scheme is outlined in the Figure 2.4. ^{1}H NMR (400 MHz, DMSO) δ 12.27 (s, NH), δ8.12 (s), δ 7.36- 7.34 (m, 2H, ArH), 7.29- 7.26 (m, 2H, ArH), δ 7. 17- 7.17 (M, 1H, ArH) δ 4.56 (s, 2H, CH2), δ 3.58 (m, 8H). ^{13}C NMR (100 MHz, DMSO) δ 158.86 (s), δ 153.93 (s), δ 149.08 (s), δ 147.98 (s), δ 136.42 (d, J_{C-H} = 16 Hz), δ (135.43 (s), δ 123.60 (s), 113.29 (s), 66.22 (s), 44.98 (s), 41.06 (s).



3.3

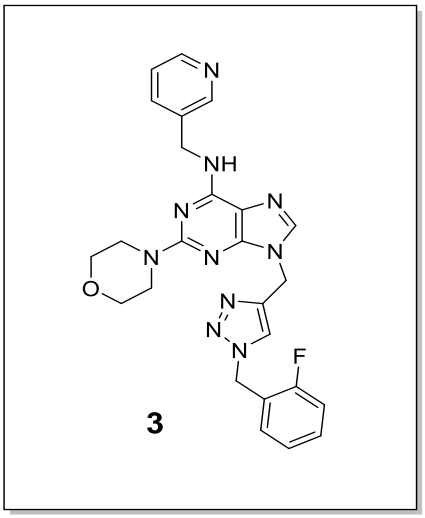
3.4: To a solution of 3.3 (450 mg, 1.45mmol) in DMSO, propargyl bromide (171 mg, 1.45 mmol) was added and potassium carbonate (300 mg, 2.18 mmol) was also added. The mixture was allowed to stir for 3 hours at room temperature after the reaction was completed by NMR, water was added to the mixture. The resulting precipitate was filtered, washed with water, and triturated with ether (gray solid; yield 69%, 516mg). ^{1}H NMR (400 MHz, DMSO) δ 8.33 (b, 1H), δ 7.41-7.39 (m, 1H), δ 7.38 (s, 1H, ArH), δ 7.25(m, 1H ArH,), δ 7.20-7.18 (m, 2H, ArH), δ 4.62 (s, 2H), δ 4. 48 (s, 2H), δ 3.42-3.40

(m, 4H), δ 3.64-3.62 (m, 4H), δ 3.44(s, 1H). ^{13}C NMR (100 MHz, DMSO) 158.86 (S), 153.93 (s), 149. 08 (s), 147.98 (s), 136.26(s), 135.43 (s), 123.60 (s), 113. 29 (s), 66.22 (s), 44.98 (s), 41. 06 (s).



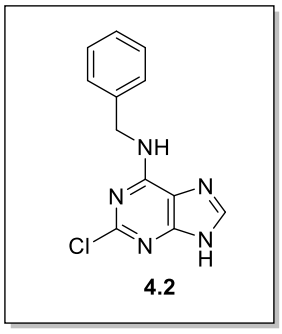
3.4

3.4: To a solution of sodium azide (80 mg, 1 mmol) in DMSO (5mL), benzyl bromide (125mg, 1 mmol) was added dropwise and stirred at room temperature for 30 minutes. To that mixture 3.4 (1 mmol, 349 mg), triethyl amine (11mg, 0.1 mmol) and $CuSO_4$. $5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (198 mg, 1 mmol) were added to the reaction mixture and allowed to stir at room temperature for 18 h. Once the reaction was completed by NMR, the mixture was poured into ice cold water (15 mL) and the resulting brown precipitate was filtered and washed with dilute NH_4OH (20 mL) and water (50 mL) and recrystallized using ethanol to give the final product 3. (Brown, 416 mg, 83%). ^{1}H NMR (400 MHz, DMSO) δ 8.31 (b, 1H), δ 7.45-7.43 (m, 3H), δ 7.38- 7.34 (m, 4H), δ 5.82 (b, 1H), δ 4.43 (b, 3H), δ 3.74(b, 8H), δ 2.72 (s, 1H) (Figure 2.12). ^{13}C NMR (100 MHz, DMSO) δ 161.55, 159.08, δ 143.16, δ 137.55, δ 130.95, δ 128.38, δ 125.49 (d, J_{C-H} = 8.9 Hz), δ 124.98, δ 124.16, δ 122.83, δ 115.75, δ 66.07, δ 44.94, δ 43.16, δ 37.74(Figure 2.13) (^{19}F NMR (376 MHz, DMSO) δ -117.83 (Figure 2.14).



3

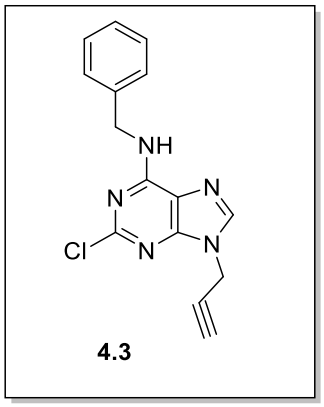
4.2: To a solution of 2, 6 dichloropurine (500 mg, 2.64 mmol) in n-butanol (5 mL) trimethylamine (399 mg, 3.96 mmol) was added. The mixture was stirred at 60 °C for 15 minutes and benzylamine (282 mg, 2.64 mmol) was added to the mixture was reflux at 120 for 2h. The resulting precipitate was filtered, washed with water (20 mL) and methanol (20 mL), and dried overnight. Peach colored product was obtained (596 mg, 87%). ^{1}H NMR (400 MHz, DMSO) δ 13.09 (broad, NH), δ 8.70 (s, 1H) δ 7.36-7.28 (m, 5H), δ 4.62 (d, 2H). ^{13}C NMR (100 MHz, DMSO) δ 155.12, δ 153.70, δ 150.72, δ 140.2, δ 139.38, 136. 05, δ 128.32 (d, J_{C-H} = 21 Hz), δ 127.45, δ 126.87.



4.2

4.3: To a solution of 4.2 (450 mg, 1.45mmol) in DMSO, propargyl bromide (171 mg, 1.45 mmol) was added and potassium carbonate (300 mg, 2.18 mmol) was also

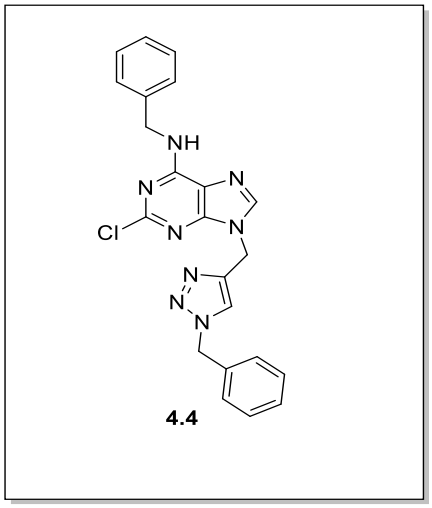
added. The mixture was allowed to stir for 3 hours at room temperature after the reaction was completed by NMR, water was added to the mixture. The resulting precipitate was filtered, washed with water, and triturated with ether. ^{1}H NMR (400 MHz, DMSO) δ 8.05 (s, 1H), δ 7.83 (s, 1H), δ 7.33-7.29 (m, 2H, ArH), δ 7.25(m, 1H ArH,), δ 7.20-7.18 (m, 2H, ArH), δ 4.85 (s, 2H), δ 4. 60 (s, 2H), δ 3.49(s, 1H). ^{13}C NMR (100 MHz, DMSO) 158.86, 153.93, 149. 08, 147.98, 136.26, 135.43, 123.60, 113. 29, 41.06.



4.3

4.4: To a solution of sodium azide (80 mg, 1 mmol) in DMSO (5mL), benzyl bromide (125mg, 1 mmol) was added dropwise and stirred at room temperature for 30 minutes. To that mixture 4.3 (1 mmol, 348 mg), triethyl amine (11mg, 0.1 mmol) and CuSo4. $5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (198 mg, 1 mmol) were added to the reaction mixture and allowed to stir at room temperature for 18 h. Once the reaction was completed by NMR, the mixture was poured into ice cold water (15 mL) and the resulting pale white precipitate was filtered and washed with dilute NH4OH (20 mL) and water (50 mL) and recrystallized using ethanol to give the final product sample 4. ^{1}H NMR (400 MHz, DMSO) δ 8.04 (s, 1H), δ 7.36 (s, 1H), δ 7.30- 7.28 (m, 1H), δ 7.26-7.21 (m, 5H), δ 7.19- 7.16 (1H, m), δ 7.14- 7.13 (m, 2H), δ 5.57 (s, 2H, δ 5.23 (s, 2H), δ 4.55 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 161.32(s), 158.88 (d, J_{C-H} = 24 Hz), δ

143.00 (s), δ 140.63 (s), δ 130.77 (s), δ 128.12 (s), δ 127.42 (d, J_{C-H} = 10 Hz), δ 126.53, δ 124.86 (d, J_{C-H} = 3 Hz), δ 122.83, δ 115.75 (d, J_{C-H} = 21 Hz), δ 43.16, δ 37.74. ^{19}F NMR (376 MHz, DMSO) δ -117.84.

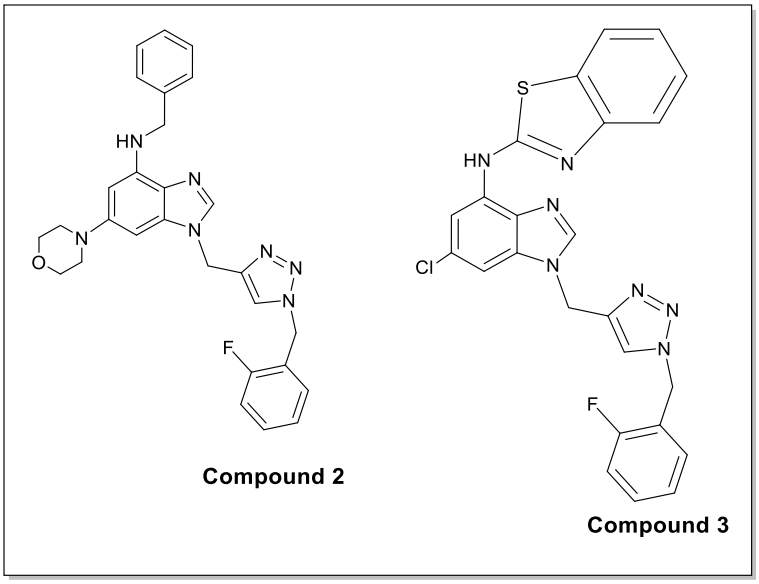


4.4

2.1.2. Oxidative Stress Attenuation by Purine-based Triazoles. The SH-SY5Y human neuroblastoma cell line was obtained from the commercial sources and cell were expanded in the growth culture medium for 7-8 days and differentiation followed by 24 h incubation. Using the ideal values, the cells were treated with the concentration of the respective compound and then again treated with 700 μM H_2O_2 solution. The concentrations were chosen according to the previous study done[8].

Hydrogen peroxide (H_2O_2) is naturally present in the living cells and is produced through different cellular activities. The H_2O_2 present in the cells is controlled by various antioxidants and the concentration is between 1 nm to 700 nm and does no harm to cells but rather acts as an intracellular signaling molecule for cell survival by activating or inactivating proteins related to cell survival[9]. The concentration of H_2O_2 above 1 micromolar is considered fatal for the cells. Hydrogen peroxide (H_2O_2) belongs to the

non-radical form of ROS and is easily converted to hydroxyl radical which cause damage to many cellular components or even cell death of neuronal and glial cells[10].



Several studies have indicated that H_2O_2 activates a condition in the cell cultural medium. Immortalized and proliferative cell line SH-SY5Y derived from neuroblastoma cells were used for the experiment. activates numbers of signaling cascade including extracellular signal regulated kinase (ERK)11. In our study, extra cellular H_2O_2 is used to create an experimental cytotoxicity.

We used 10 μM concentration of compound 3, and 10 nM of compound 2 for the oxidative stress studies. 700 μM of H_2O_2 was used to create the oxidative stress in the cell cultural medium. We then investigated the potential protective effect of the single treatment or a combined treatment with H_2O_2-induced oxidative stress.

Oxidative Stress Attenuation Study Compounds **2** and **3** on SHSY-5Y Neuroblastoma Cells

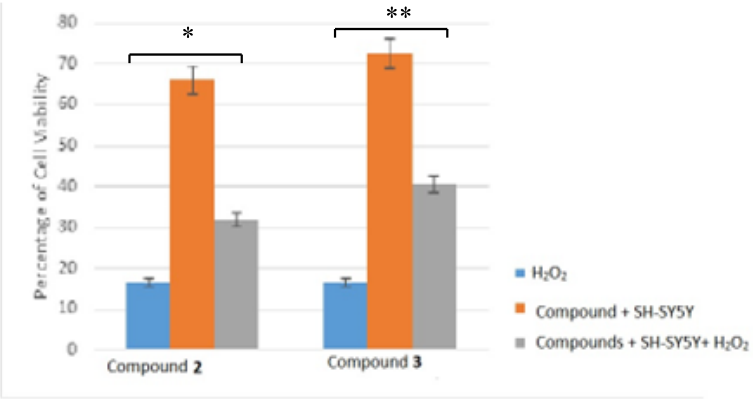


Figure 2.5. Effect of H_2O_2-induced oxidative stress on the cell viability of human neuroblastoma SH-SY5Y cells.
[(in the presence and absence of compounds 2 and 3; error bars represent the standard deviation of three independent measurements (n = 3; *p = 0.0036; **p = 0.0037)].

The incubation with 700 µM of H_2O_2 for 90 min induced the slight reduction of the cell viability. The exposure on hydrogen peroxide decreased the cell population. The incubation of the cells with 700 µm of H_2O_2 treated with compounds showed some protective effects against oxidative stress. Figure 2.5 shows the protective effect of compound **2** and **3** respective against oxidative stress caused by hydrogen peroxide. Each column represents the mean of three separate experiments (n=3).

2.1.3: ^{1}H, ^{13}C, and ^{19}F NMR Spectra of Triazoles. All chemicals were obtained from the commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR, and ^{19}F NMR were recorded on a Bruker Avance–400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and ^{19}F NMR) in DMSO-d_6. NMR, and ^{19}F NMR were recorded on

a Bruker Avance–400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and ^{19}F NMR) in DMSO-d_6.

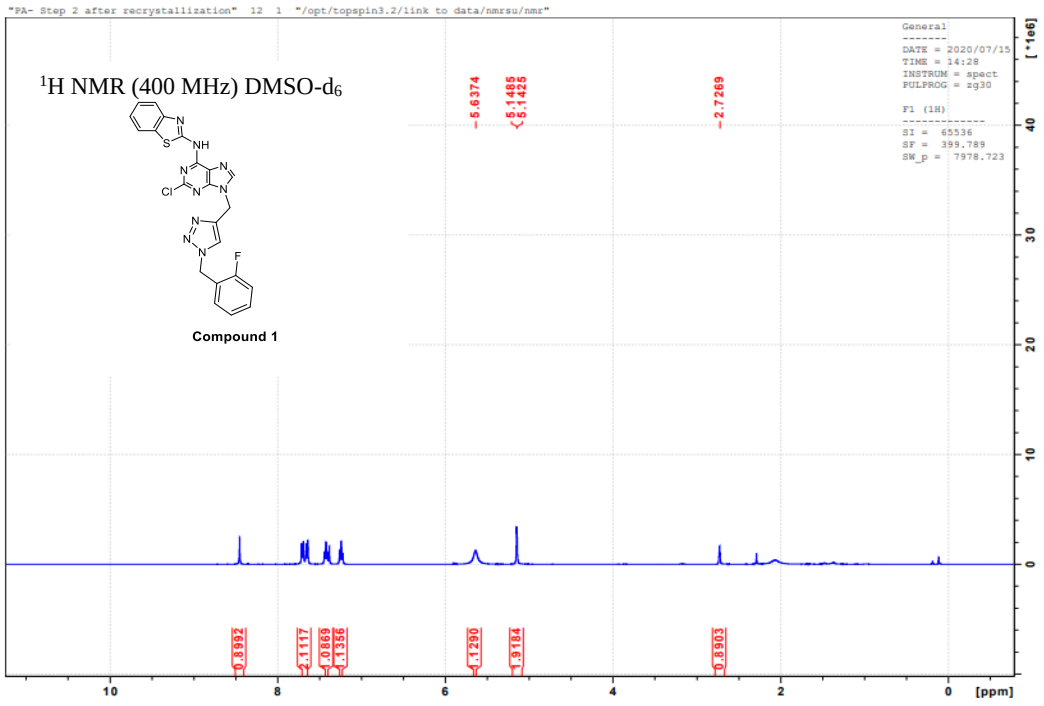


Figure 2.6. Proton NMR of the Compound 1

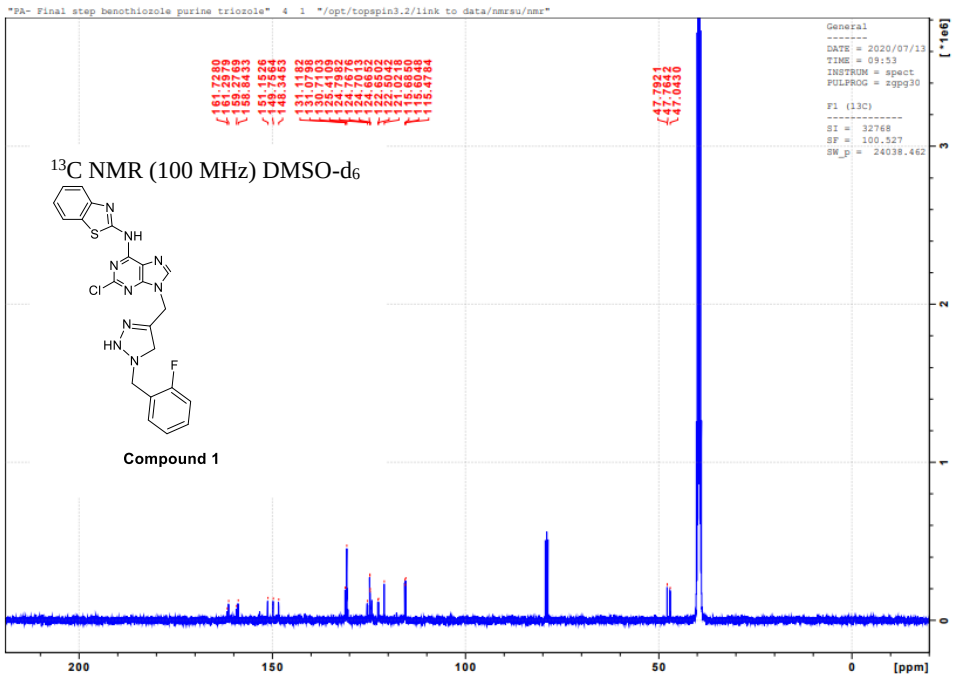


Figure 2.7. ^{13}C NMR of Compound 1

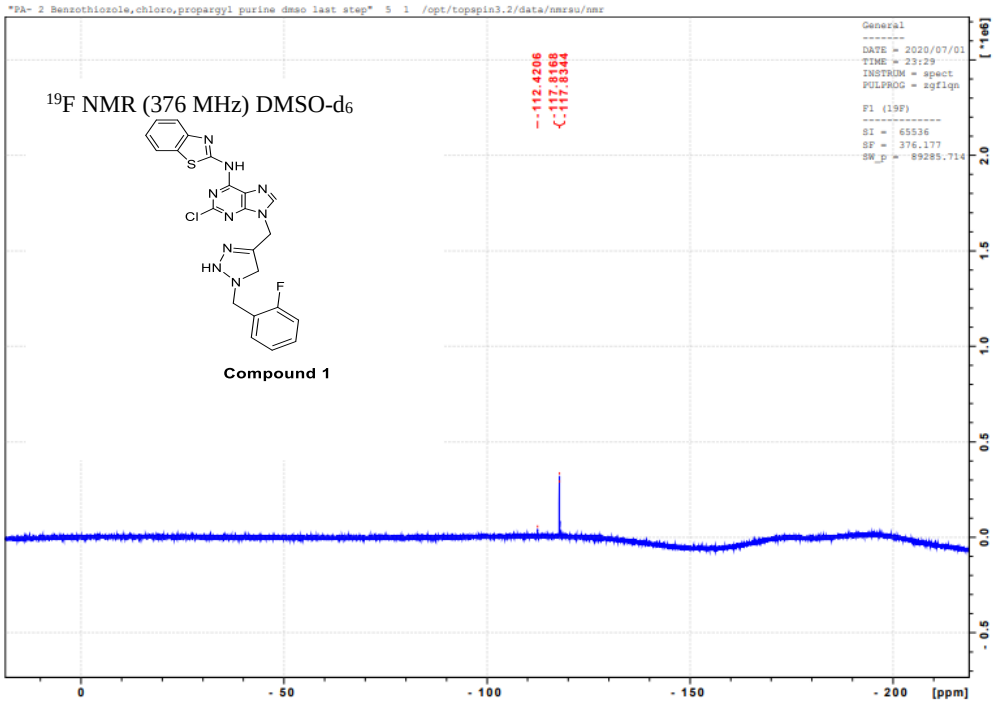


Figure 2.8. ^{19}F NMR of Compound 1

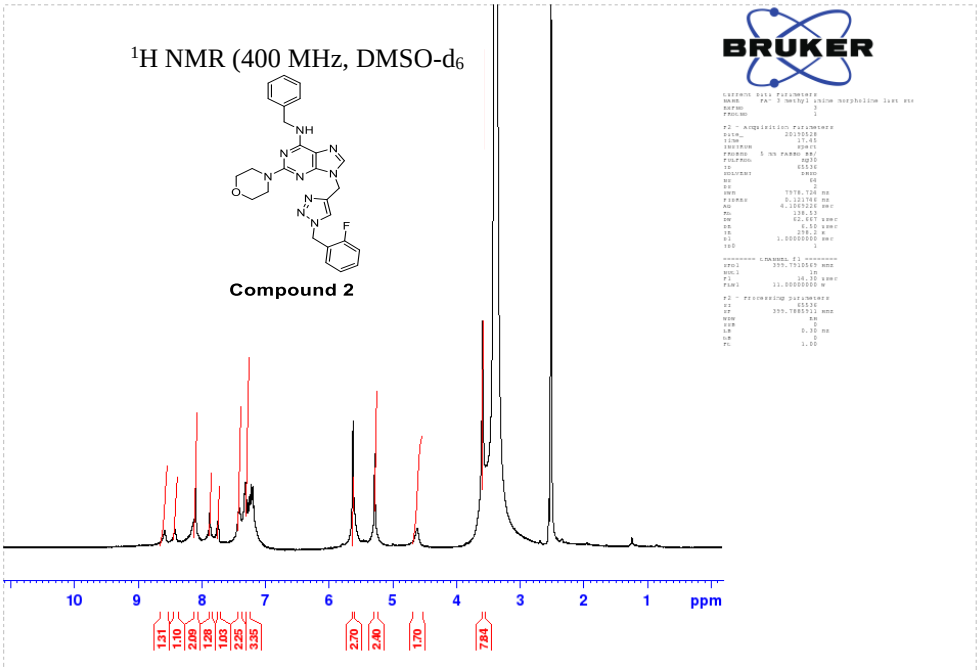


Figure 2.9. Proton NMR of Compound 2

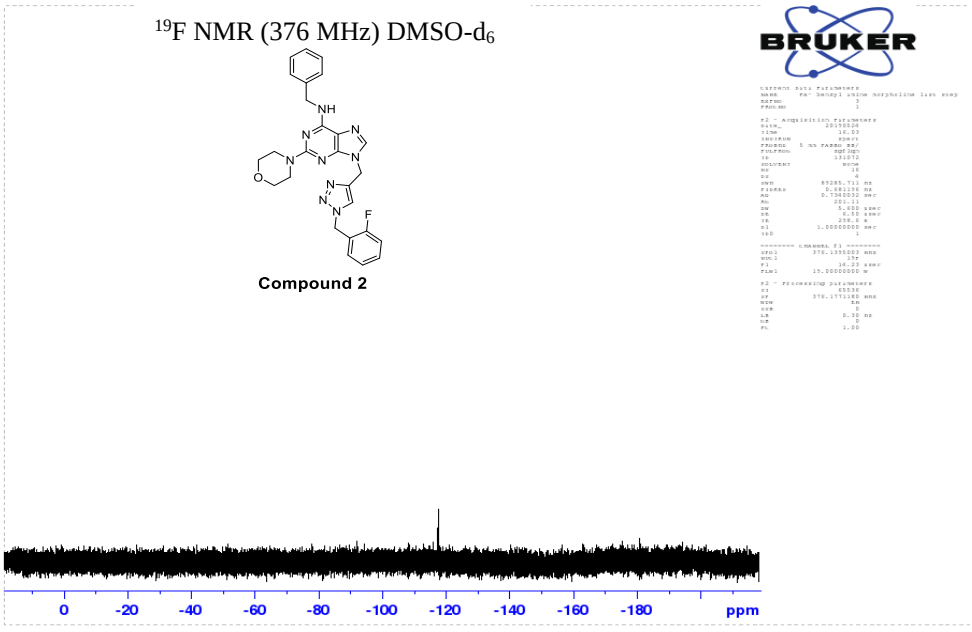


Figure 2.10. ^{19}F NMR of Compound 2

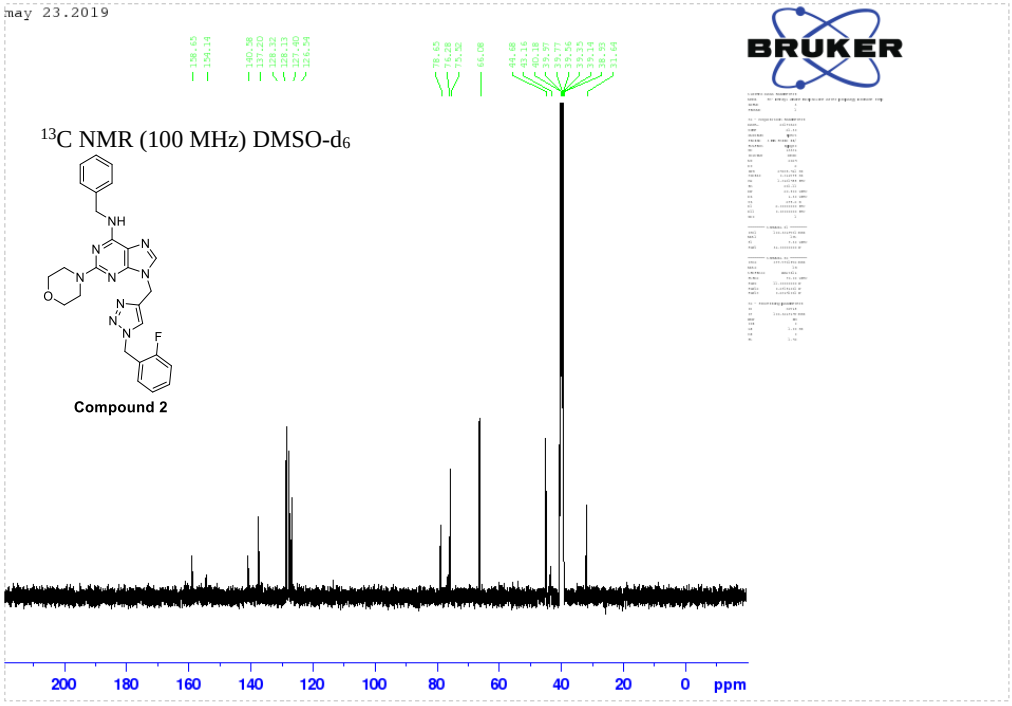


Figure 2.11. ^{13}C NMR of Compound 2

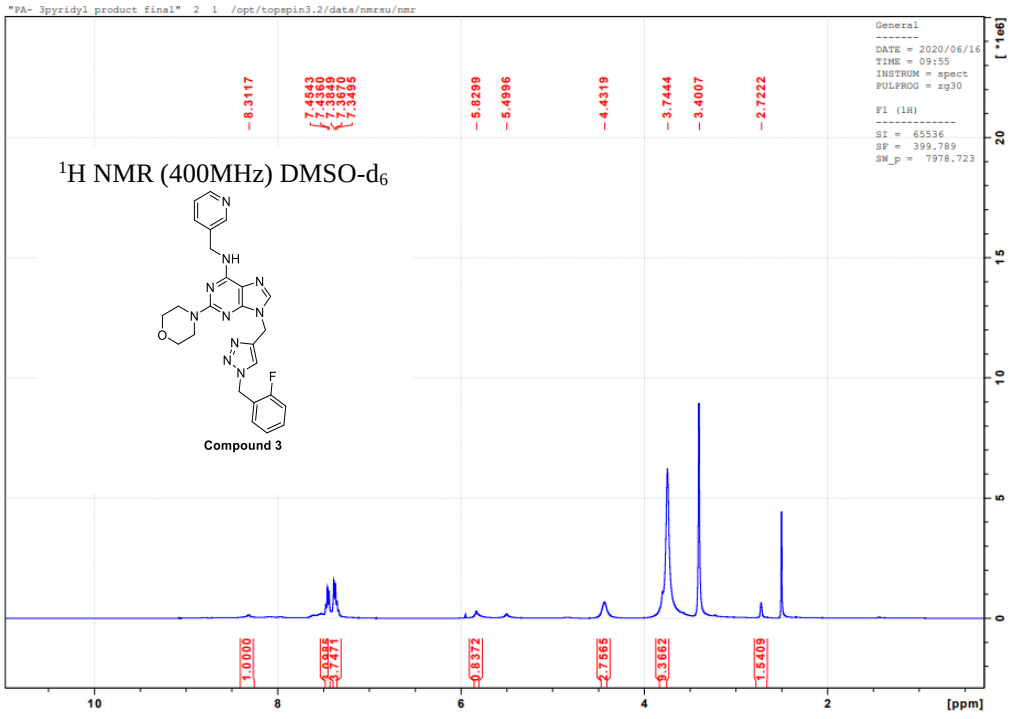


Figure 2.12. Proton NMR of Compound 3

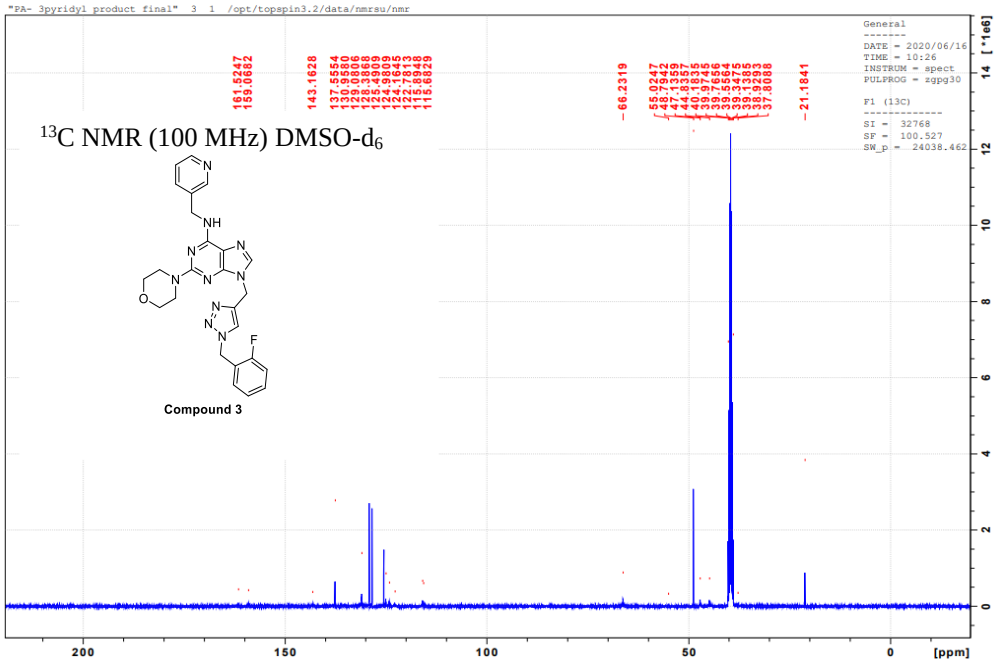


Figure 2.13. ^{13}C NMR of Compound 3

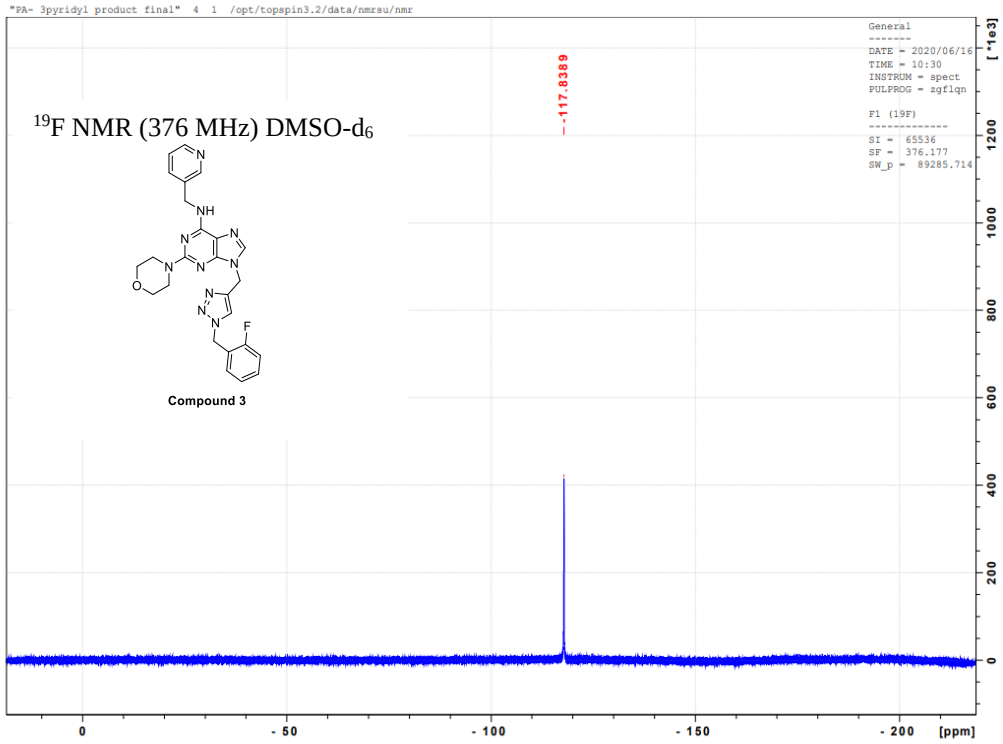


Figure 2.14. ^{19}F NMR of Compound 3

3. NOVEL SYNTHETIC METHODS FOR THE TRIFLUOROMETHYLATION OF ALDEHYDE HYDRAZONES

3.1. CU(II) CATALYZED TRIFLUOROMETHYLATION OF ALDEHYDE HYDRAZONES

α-Trifluoromethylated amines and imines have important applications in the drug design and medicinal chemistry as isosteric and isopolar bioisosteres of the amide or peptide moieties[34-37]. Furthermore, the relatively higher electronegativity of the trifluoromethyl group diminishes the basicity of the adjacent amino moiety, thereby modulating the pharmacokinetics of the drug candidates. Nucleophilic trifluoromethylation of N-alkylimines using Ruppert–Prakash reagent (CF_3SiMe_3) under relatively strong acidic conditions gives the corresponding α-trifluoromethylamines[64]. Nucleophilic trifluoromethylation of chiral N-tert-butanesulfinylimines, which are activated to the nucleophilic additions by the adjacent sulfinyl moiety, using Ruppert-Prakash reagent gives the corresponding trifluoromethylated products with high diastereoselectivities and yields under mild conditions.[38] Catalytic enantioselective trifluoromethylation of the azomethine imines gave high yields of the corresponding □-trifluoromethylated amines. We have recently developed the nucleophilic trifluoromethylation of N-(p-toluenesulfonyl)aldimines under nonacidic conditions, using N-heterocyclic carbene (NHC) catalysts.[39] The commonly reported methods have used expensive trifluoro methylating reagents such as Togni's and Umemoto's reagents (Figure 3.1).

Unlike α-trifluoromethylated amines, α -trifluoromethylated hydrazones are relatively less explored as substrates in the drug design, presumably owing to the synthetic challenges involved in the preparation of these compounds. The □-

trifluoromethyl hydrazones can be hydrogenated to give the corresponding hydrazines, which are useful substrates in the preparation of the pharmaceutically interesting compounds, or hydrolyzed to give the trifluoromethyl ketones, which are used as serine protease inhibitors in the drug design.[40] Aldehyde or ketone hydrazones, in contrast to the related imines, do not undergo nucleophilic trifluoromethylations because the electrophilicity of the imino carbon is attenuated due to the resonance interaction of the adjacent amino group. Therefore, free-radical trifluoromethylation of hydrazones has received renewed attention as an alternative for the synthesis of the corresponding C-(sp^2–H)-trifluoromethylated products.[21-26] Baudoin, Bouyssi, Monteiro, and coworkers reported C-(sp2–H)-trifluoromethylation of the aldehyde-hydrazones (1) using the Togni's reagent (1-trifluoromethyl-1,2-benziodoxol-3(1H)-one) as the electrophilic trifluoromethylating reagent, which in the presence of the Cu(I) catalyst, generates the trifluoromethyl free radical as the reaction intermediate.[22, 23] Moderate to high yields of the trifluoromethylated hydrazones 2 were obtained in this reaction. Studer and coworkers have achieved similar C-(sp^2–H)-trifluoromethylation of aromatic aldehyde N,N-dimethylhydrazones using the Togni's reagent and tetrabutylammonium iodide (TBAI) as the radical initiator.[42-43] Feng and coworkers have developed the free-radical trifluoromethylation of the aldehyde hydrazones using the Langlois reagent (CF3SO2Na) and $PhI(OAc)_2$ as the radical initiator. Xu and coworkers have used photoredox catalysis for the trifluoromethylation of hydrazones in the presence of trifluoromethanesulfonyl chloride (CF_3SO_2Cl) (Scheme 1).[31] However, these synthetic methods, although elegant, require the use of the potentially explosive hypervalent iodine(III) reagents (as in the

case of the Togni's reagent, Figure 3.1), especially when used in large scale synthesis, or expensive reagents (Togni's reagent, $99.90/g; CF3SO2Cl, $65.60/5 g) .[27-29]

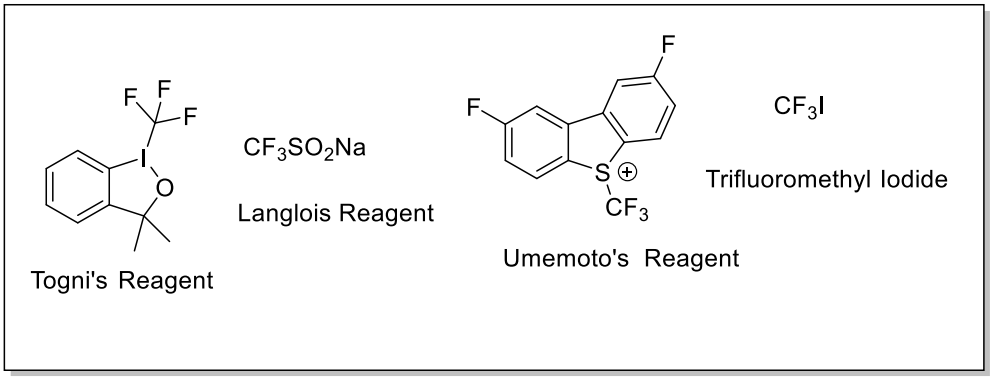


Figure 3.1. Common Reagents for Trifluoromethylation

Toward the goal of developing cost-effective and efficient approaches for the synthesis of the trifluoromethylated hydrazones, we now report the trifluoromethylation of the aldehyde hydrazones under mild reaction conditions, using the inexpensive and nontoxic, bench stable Langlois reagent in the presence of Cu(II) salts as the free-radical initiators.

3.1.1. Results and Discussion. We have explored Langlois reagent as the trifluoromethyl radical (CF_3·) and Cu(II) salts as the initiators for the C-(sp^2–H)-trifluoromethylation of aldehyde hydrazones toward the development of the environmentally benign and cost-effective synthetic methods. We have initially investigated the radical trifluoromethylation of aldehyde N-aminomorpholine hydrazones, using the benzaldehyde hydrazone 1 as a model substrate. Use of various other hydrazones, such as N,N-dimethylhydrazones, gave lower yields of the trifluoromethylated products.

However, further optimizing the reaction of compound 1 with the Langlois reagent (sodium trifluoromethanesulfinate), under various conditions, gave the C(sp^2)-trifluoromethyl hydrazone **2**, in high yields of up to 94% (Table 3.1). Typically, the trifluoromethylation reactions of the hydrazones were performed using Langlois reagent in the presence of potassium persulfate, as a stoichiometric oxidant, a Cu(II) salt, as a catalyst, and 4 Å molecular sieves, under N_2 atmosphere in acetonitrile solvent, at 80 ^oC for 24 h during the optimization of the reaction conditions, with few exceptions as noted in Table 3.1. Use of the catalytic amounts of MnO_2 and $K_2S_2O_8$ in DMF solvent (Table 3.1; entry 18) and di-*tert*-butyl peroxide (DTBP), in the absence of any catalyst, in DMSO solvent (Table 3.1; entry 17) gave only trace amounts of the trifluoromethylated product (by ^{19}F NMR). No reaction was observed when $Mn(OAc)_2.5H_2O$ was used as an oxidant, in the absence of the Cu(II) catalyst, in acetone as a solvent (Table ; entry 16). When ethyl acetate was used as a solvent instead of acetonitrile, the yields were drastically reduced to 7–12% (Table 3.1; entries 9 and 10). Similarly, poor yields (12%) were obtained when the reaction was carried out in dichloromethane as a solvent (Table 3.1; entry 6) and the reaction did not proceed in the DMPU solvent (entry 11). When the reaction was performed using Cu $(OAc)_2$ (0.25 mol equiv) and $K_2S_2O_8$ (2 mol equiv), the C(sp^2)-trifluoromethyl hydrazone 2a was obtained in 48 % yield (Table 3.1; entry 1). Further increase in the amount of $K_2S_2O_8$ (3 mol equiv) dramatically improved the product yield by up to 91% (Table 3.1; entry 2) and increasing the amount of Langlois reagent (3 mol equiv) resulted in the lowering of the product yield to 71% (Table 3.1; entry 3). We also investigated the effect of various other Cu(II) salts as catalysts in this reaction. When Cu(II) triflate ($Cu(OTf)_2$; $Cu(OSO_2CF_3)_2$) was used as a catalyst, the

$C(sp^2)$-trifluoromethyl hydrazone 2a was obtained in 83% yield (Table 3.1; entry 7) and there was no reaction when Cu(II)Cl_2 was used as the catalyst (Table 3.1; entry 8). Although $Cu(OAc)_2$ and $Cu(OTf)_2$ gave satisfactory yields, we have investigated $CuSO_4.5H_2O$ as a catalyst because $Cu(OAc)_2$ and $Cu(OTf)_2$ are relatively expensive reagents ($Cu(OAc)_2$: \$160 per 100 g; $Cu(OTf)_2$: \$96 per 25 g). On the other hand, $CuSO_4.5H_2O$ is a cost-effective reagent (\$36 per 100 g), and gratifyingly, the trifluoromethylated product 2 was formed in high yield (94 %) using $CuSO_4.5H_2O$ (Table 3.1; entry 5) as the catalyst. We have also investigated various other reaction conditions, using $CuSO_4$ as the catalyst, to fine tune the reaction conditions; for example, at room temperature (Table 3.1; entry 14), in the absence of the molecular sieves (Table 3.1; entry 13), and in the absence of the nitrogen atmosphere (Table 3.1; entry 12). In all these cases, low yields of the $C(sp^2)$-trifluoromethyl hydrazone 2a were observed. Although use of 0.5 equiv of $CuSO_4$ is optimal for high yields of the trifluoromethylated product, use of 0.25 equiv of $Cu(OAc)_2$ or $Cu(OTf)_2$ also gives similarly high yields (Table 3.1, entries 2 and 7). We have not further optimized to lower the concentration of the Cu(II) catalysts, and used the $CuSO_4.5H_2O$, as a cost-effective catalyst, for the trifluoromethylation reactions. With the optimized reaction conditions in hand, we then explored the scope of reaction for aromatic substrates with electron-withdrawing as well as electron-releasing substituents and aliphatic aldehyde hydrazones, and the results are summarized in Figure 3.2.

As shown in Figure 3.2, N-aminomorpholine hydrazones derived from their corresponding aromatic aldehydes with electron-withdrawing groups, irrespective of the position of the group on aromatic ring, gave the $C(sp^2)$-trifluoromethyl hydrazones (2b, 2c,

2d, 2f, 2g) in high yields (87%–96%) in 24 h. However, in case of the N-aminomorpholine hydrazones derived from the aromatic aldehydes bearing electron-releasing substituents, longer reaction times of 30–46 h were required to afford the corresponding C(sp^2)-trifluoromethyl hydrazones (2e, 2h, and 2n) in good yields (55%–77%). The trifluoromethylation reaction of heteroaromatic aldehyde hydrazones also proceeds readily under these conditions, although relatively longer reaction times were required for optimal yields; thus, the radical trifluoromethylation of 2-furfural N-aminomorpholinehydrazone after a reaction time of 30 h gave the corresponding C(sp^2)-trifluoromethyl hydrazone 2k in 80% yield. The trifluoromethylation of 1-naphthaldehde N-aminomorpholinehydrazone 1j, under the optimized reaction conditions, gave the corresponding (C-sp^2)-trifluoromethyl hydrazone 2j in 46% yield after 6 h of reaction time. In the latter case, extending the reaction time to more than 6 h resulted in the formation of the undesirable byproducts. Trifluoromethylation of the aliphatic aldehyde hydrazones, however, were not successful in these trifluoromethylation reactions. The initially formed trifluoromethyl hydrazone 2m apparently degraded under these conditions. The trifluoromethylation N-aminomorpholine hydrazones derived from the aromatic aldehydes bearing hydroxy substituents, such as 1i, similarly, was not successful and resulted in the formation of the undesirable products, and the expected product 2i was not observed.

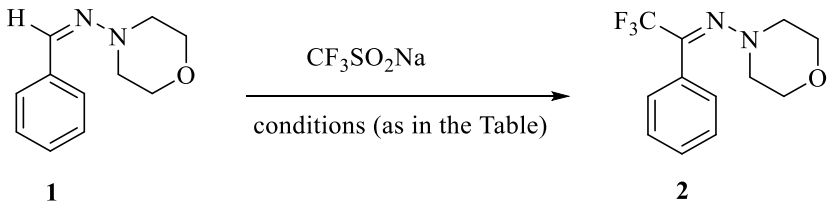


Figure 3.2. Reaction method for the Trifluoromethylation of Aldehyde Hydrazones

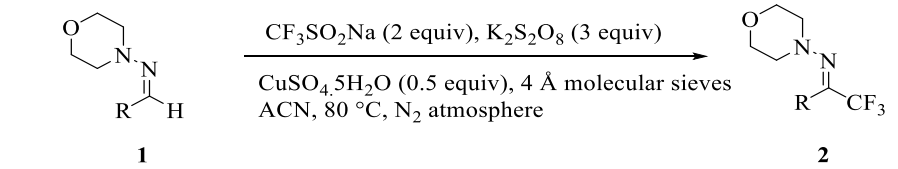
[a] Unless otherwise specified, all reactions were carried out using the hydrazone **1** (0.1 mmol) and CF_3SO_2Na (2 mol equiv) in 2 mL of solvent, under N_2 atmosphere, at 80 ^oC for 21–24 h. [b] Yields estimated by GC-MS. [c] 3 mol equiv of CF_3SO_2Na was used. [d] Reaction was carried out in the absence of the N_2 atmosphere. [e] Reaction was carried out in the absence of the molecular sieves. [f]Reactions were carried out at room temperature. [g]Reactions were performed at 60 ^oC; NR = no reaction.

Based on the mechanisms suggested earlier for the related Cu-catalyzed free-radical trifluoromethylation of hydrazones using the Togni's reagent,[16] we propose the following mechanism for the Cu-catalyzed trifluoromethylation reactions (Figure 3.3). The Langlois reagent is initially oxidized by the Cu(II) to give the $CF_3\cdot$ radical and the stoichiometric oxidant $K_2S_2O_8$ regenerates the Cu(II) from the Cu(I) formed in the latter step. The latter trifluoromethyl radical may also be generated by the direct oxidation of the Langlois reagent by $K_2S_2O_8$,[17-18] although relatively poor yields of the trifluoromethylated products were obtained in the absence of the Cu(II) catalysis (Table 3.1, entry 15). The $CF_3\cdot$ radical addition to the hydrazone **1** then gives the aminyl radical (**1**-$CF_3\cdot$), which is further oxidized by the Cu(II) to give the nitrenium cation **1**-CF_3^+, stabilized by resonance from the morpholine moiety. Deprotonation of the latter nitrenium cation by a mild base, such as $KHSO_4$ would then give the trifluoromethylated hydrazone **2**. The involvement of aminyl radicals and nitrenium cations in the free-radical additions to hydrazones is well documented in the literature.[19-21]

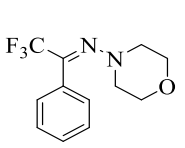
Table 3.1. Optimization of Reaction Conditions (Method 1)

Entry	Catalyst (equiv)	Oxidant (equiv)	Solvent	Yield %[b]
1.	$Cu(OAc)_2$ (0.25)	$K_2S_2O_8$ (2)	ACN	65
2.	$Cu(OAc)_2$ (0.25)	$K_2S_2O_8$ (3)	ACN	91
3[c].	$Cu(OAc)_2$ (0.25)	$K_2S_2O_8$ (2)	ACN	71
4.	$CuSO_4.5H_2O$ (0.25)	$K_2S_2O_8$ (3)	ACN	48
5.	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	ACN	94
6.	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	DCE	12
7.	$Cu(OTf)_2$ (0.25)	$K_2S_2O_8$ (3)	ACN	83
8.	$CuCl_2$ (0.25)	$K_2S_2O_8$ (3)	ACN	NR
9.	$Cu(OAc)_2$ (0.25)	$K_2S_2O_8$ (3)	EtOAc	12
10.	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	EtOAc	7
11.	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	DMPU	NR
12[d].	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	ACN	55
13[e].	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	ACN	81
14[f].	$CuSO_4.5H_2O$ (0.5)	$K_2S_2O_8$ (3)	ACN	9
15.	None	$K_2S_2O_8$ (3)	ACN	58
16[f].	None	$Mn(OAc)_2.4H_2O$ (0.2)	Acetone	NR
17[g]	None	DTBP (0.2)	DMSO	trace
18[g]	MnO_2 (0.12)	$K_2S_2O_8$ (0.12)	DMF	trace

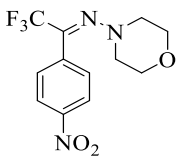
[a] Unless otherwise specified, all reactions were carried out using the hydrazone **1** (0.1 mmol) and CF_3SO_2Na (2 mol equiv) in 2 mL of solvent, under N_2 atmosphere, at 80 °C for 21–24 h. [b] Yields estimated by GC-MS. [c] 3 mol equiv of CF_3SO_2Na was used. [d] Reaction was carried out in the absence of the N_2 atmosphere. [e] Reaction was carried out in the absence of the molecular sieves. [f]Reactions were carried out at room temperature. [g]Reactions were performed at 60 °C; NR = no reaction.



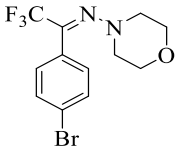
1 **2**



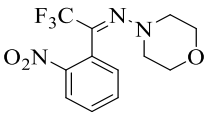
2a, 91% (75%)
1 mmol scale



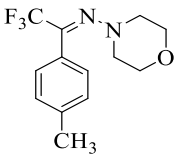
2b, 87% (70%)



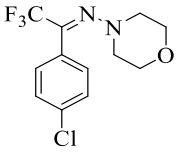
2c, 89% (72%)



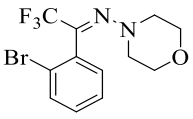
2d, 93% (72%)



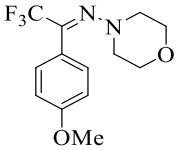
2e, 87% (68%), 38 h



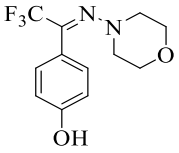
2f, 96% (70%)
0.1 mmol scale



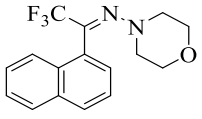
2g, 86% (72%)



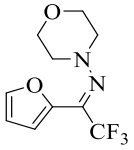
2h, 77%, 38 h



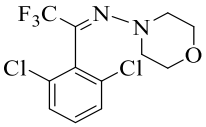
2i, N.D (degraded)



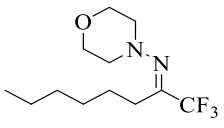
2j[c], 46%, 6 h



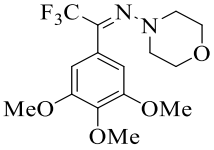
2k, 87%, 30 h



2l, 80%, 38 h



2m, N.D (degraded)



2n, 55%, 46 h
0.3 mmol scale

[a]Unless otherwise specified, all reactions were carried out using 1 (0.5 mmol), CF_3SO_2Na (2 mol equiv), $K_2S_2O_8$ (3 mol equiv), and ACN (10 mL) at 80 ^oC for 24 h under N_2 (balloon) atmosphere. [b]Yields were estimated by GC-MS (values reported in parenthesis are for the isolated yields). [c]Reaction was terminated after 6 h because of the formation of the undesired products after longer reaction times.

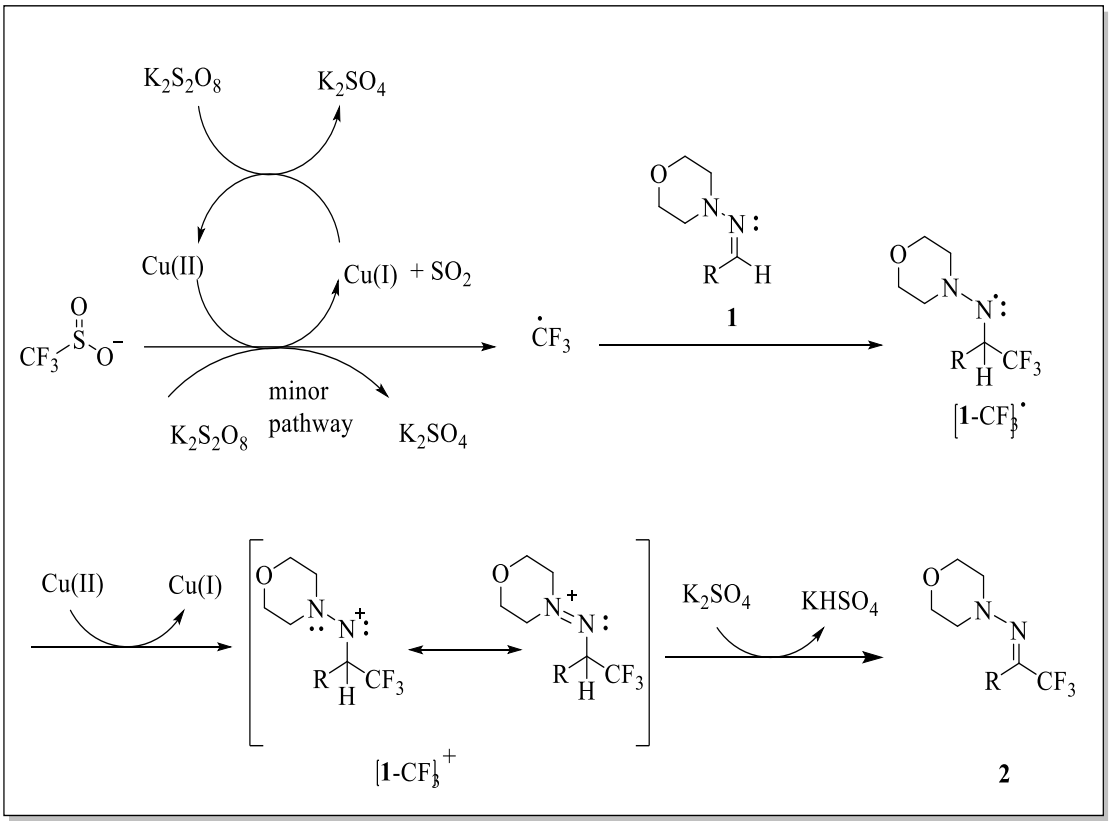


Figure 3.3. Proposed Mechanism for the Cu-Catalyzed Method

3.1.2. Conclusion. In summary, the Cu-catalyzed trifluoromethylation of aromatic aldehyde N-aminomorpholine hydrazones in the presence of the Langlois reagent, and $K_2S_2O_8$ as a stoichiometric oxidant, gave the corresponding C(sp^2)-trifluoromethyl hydrazones in moderate to high yields. The reaction tolerates a wide variety of electron-withdrawing and electron-donating substituents, such as Cl, Br, OMe,

NO_2, on the aromatic ring and heterocyclic aromatic rings such as furan. The reaction also obviates the use of expensive and relatively toxic or potentially hazardous hypervalent iodine reagents, such as the widely used Togni's reagent[22-25] and thus affords an efficient and cost-effective synthetic method for the synthesis of the (C-sp^2)-trifluoromethyl hydrazones.

3.1.3. Experimental Section. The aldehyde hydrazones (1a–n) were synthesized according to literature procedures with minor modifications, as follows.[21, 26-28]

3.1.4. General Procedure for the Synthesis of Hydrazones. To a solution of aldehyde (10 mmol) in 10 mL of dichloromethane, was added 4-aminomorpholine (20 mmol; 1.2 mol equiv) and anhydrous $MgSO_4$ (240 mg; 20 mmol; 2 mol equiv). The resulting solution was stirred at room temperature for 12 h. After completion of the reaction as monitored by ^{1}H NMR. $MgSO_4$ was filtered off, and the solvent was evaporated under reduced pressure. The hydrazones were purified either by recrystallization from absolute ethanol (in case of solid products) or by flash chromatography using dichloromethane as an eluent (in case of liquid products). The ^{1}H and ^{13}C NMR spectra of the compounds are in agreement with the literature data.[21, 26-28]

(E)-N-morpholino-1-phenylmethanimine ***(1a).*** 54 % yield; ^{1}H NMR (400 MHz, DMSO- d_6) δ^1H 7.68 (s, 1H, C**H**=N), 7.62- 7.58 (m, 2H, *m*-ArH), 7.34- 7.31 (m, 2H, C_2-ArH), 7.27- 7. 23 (m, 1H, C_4-ArH), 3.87- 3.85 (apparent t, 4H, C**H**$_2$O), 3.16-3.14 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 136.8, 136.4, 129, 128.8, 126.7, 67.0, 52.4.

(E)-N-morpholino-1-(4-nitrophenyl)methanimine ***(1b).*** 76 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 8.18-8.16 (m, 2H, C_3-ArH), 7.69-7.67 (m, 2H, C_2-ArH), 7.51 (s, 1H,

C**H**=N), 3.89- 3.86 (apparent t, 4H, C**H**$_2$O), 3.26-3.23, (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 147.1, 142.6, 131.8, 126.4, 124.2, 66.4, 51.4.

(E)-1-(4-bromophenyl)-N-morpholinomethanimine ***(1c).*** 65 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.48 (s, 1H, C**H**=N), 7.44 (apparent s, 4H, ArH), 3.87-3.85, (apparent t, 4H, C**H**$_2$O) 3.16-3.14 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 135.2, 134.7, 131.8, 127.8, 122.3, 66.6, 51.9.

(E)-N-morpholino-1-(2-nitrophenyl)methanimine ***(1d).*** 86 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 8.05-8.09 (m, 2H, ArH), 7.92-7.94 (m, 1H, ArH), 7.56 (s, 1H, C**H**=N), 7.52-7.54 (m, 1H, ArH), 3.86- 3.88 (apparent t, 4H, C**H**$_2$O), 3.23-3.25, (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C (ppm) 147.6, 133.2, 131.2, 130.2, 128.3, 127.7, 124.8, 66.5, 51.6.

(E)-N-morpholino-1-(p-tolyl)methanimine ***(1e).*** 50 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.66 (s, 1H, C**H**=N), 7.58-7.56 (m, 2H, ArH), 7.33- 7.23 (m, 2H, ArH), 3.95 - 3.94 (apparent t, 4H, C**H**$_2$O), 3.24-3.22, (apparent t, 4H, C**H**$_2$O), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 138.5, 136.9, 133.4, 129.4, 126.4, 66.7, 52.2, 21.5.

(E)-1-(4-chlorophenyl)-N-morpholinomethanimine ***(1f).*** The title compound was prepared according to the general procedure **1** using 4-chlorobenzaldehyde and 4-aminomorpholine (82 mg, 66 % yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.52 (s, 1H, C**H**=N), 7.50-7.49 (m, 2H, ArH), 7.30-7.27 (m, 2H, ArH), 3.87- 3.85 (apparent t, 4H, C**H**$_2$O), 3.13-3.11, (apparent t, 4H, C**H**$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 134.7, 134.1, 128.9, 127.5, 66.6, 51.9.

(E)-1-(3-bromophenyl)-N-morpholinomethanimine ***(1g).*** The title compound was prepared according to the general procedure **1** using 3-bromobenzaldehyde and 4-

aminomorpholine (370 mg, 51% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.76- 7.75 (m, 1H, ArH), 7.45 (s, 1H, C**H**=N), 7.38- 7.36 (m, 2H, ArH), 7.20-7.16 (m, 1H, ArH), 3.87-3.85 (apparent t, 4H, C**H**$_2$O), 3.17-3.15 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (400 MHz, $CDCl_3$) δ^{13}C 138.3, 134, 131.2, 130.2, 128.9, 125, 123, 66.6, 51.8.

(E)-1-(4-methoxyphenyl)-N-morpholinomethanimine ***(1h).*** The title compound was prepared according to the general procedure **1** using *p*-anisaldehyde and 4-aminomorpholine (94 mg, 53% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.57 (s, 1H, C**H**=N), 7.50- 7.47 (m, 2H, ArH), 7.30- 7.27 (m, 2H, ArH), 3.87 (s, 3H, OCH_3), 3.86 - 3.80 (apparent t, 4H, C**H**$_2$O), 3.13-3.11, (apparent t, 4H, C**H**$_2$N) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 160.1, 136.9, 127.7, 114.2, 66.7, 55.5, 52.3.

(E)-4-((morpholinoimino)methyl)phenol ***(1i).*** The title compound was prepared according to the general procedure **1** using 4-hydroxybenzaldehyde and 4-aminomorpholine (109 mg, 36% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.56 (s, 1H, C**H**=N), 7.48- 7.46 (m, 2H, ArH), 6.79-6.77 (apparent t, 2H, ArH), 3.87-3.85 (apparent t, 4H, C**H**$_2$O), 3.13-3.10, (m, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 156.4, 137.3, 128.8, 128.0, 115.7, 66.7, 52.3.

(E)-N-morpholino-1-(naphthalen-2-yl)methanimine ***(1j).*** The title compound was prepared according to the general procedure **1** using 1-naphthaldehyde and 4-aminomorpholine (380 mg, 58% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 8.51-8.54 (m, 1H, ArH), 8.27 (s, 1H, C**H**=N), 7.50-7.86 (m, 3H, ArH), 7.44-7.49 (m, 3H, ArH), 3.91 - 3.94 (apparent t, 4H, C**H**$_2$O), 3.27-3.29, (apparent t, 4H, C**H**$_2$O); ^{13}C NMR (400 MHz, $CDCl_3$) δ^{13}C 135.5, 134.1, 131.6, 130.9, 129, 128.9, 126.6, 125.9, 125.7, 125.5, 124, 66.7, 52.2.

(E)-1-(furan-2-yl)-N-morpholinomethanimine ***(1k).*** The title compound was prepared according to the general procedure **1** using 2-furfural and 4-aminomorpholine (230 mg, 65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.44 (s, 1H, C**H**=N), 7.40 (s, 1H, ArH), 6.39-6.45 (apparent t, 2H, ArH), 3.84 - 3.86 (apparent t, 4H, C**H**$_2$O), 3.12-3.14, (apparent t, 4H, C**H**$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 151.4, 143, 126.9, 111.6, 109.4, 66.5, 51.9.

(E)-1-(2,6-dichlorophenyl)-N-morpholinomethanimine ***(1l).*** The title compound was prepared according to the general procedure **1** using 2,6-dichlorobenzaldehyde and 4-aminomorpholine (351 mg, 84% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.61 (s, 1H, C**H**=N), 7.31-7.29 (m, 2H, ArH), 7.11 (m, 1H, ArH), 3.90 - 3.88 (apparent t, 4H, C**H**$_2$O), 3.23-3.21, (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 134.7, 132.4, 131.3, 129, 128.9, 128, 66.4, 54.4, 51.6.

(E)-N-morpholinoheptan-1-imine ***(1m).*** The title compound was prepared according to the general procedure **1** using heptanal and 4-aminomorpholine (450 mg, 52% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 6.93 (s, 1H, C**H**=N), 3.78-3.77 (apparent t, 4H, C**H**$_2$O) 2.90-2.92, (apparent t, 4H, C**H**$_2$N), 2.20-2.19 (m, 2H, CH_2) 1.43-1.25 (m, 8H, 4CH_2) 0.84-0.83 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 142.6, 66.5, 52.6, 33.1, 31.7, 28.9, 27.4, 22.6, 14.1.

(E)-N-morpholino-1-(3,4,5-trimethoxyphenyl)methanimine ***(1n).*** The title compound was prepared according to the general procedure **1** using 3,4,5-trimethoxybenzaldehyde and 4-aminomorpholine (560 mg, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^{1}H 7.49 (s, 1H, C**H**=N), 6.83 (s, 2H, ArH), 3.88 (s, 9H, 3CH_3), 3.88- 3.83

(apparent t, 4H, C**H**$_2$O), 3.16 - 3.13 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 153.6, 138.7, 136.3, 131.8, 103.4, 66.6, 61.1, 56.3, 52.1.

3.1.5. General Procedure for Trifluoromethylation of Aldehyde Hydrazones. An oven-dried round-bottom flask (25 mL), equipped with a magnetic stir bar, powdered 4 Å mol. sieves, and a N_2 balloon, was added Compound 1 (1 mmol), CF_3SO_2Na (2 mol equiv; 2 mmol), $K_2S_2O_8$ (3 mol equiv, 3 mmol), $CuSO_4.5H_2O$ (50 mol%, 0.5 mmol) at room temperature. A 10 mL portion of acetonitrile was added to the contents with a syringe under N_2. The resulting solution was stirred at 80 ^{o}C, and the progress of the reaction was monitored by GC-MS. After the reaction was complete, the reaction mixture was filtered to remove the molecular sieves, the solvent was removed by rotary evaporation, and the resulting product was subjected to column chromatography on silica gel (eluent: 10% ethyl acetate in hexane) to afford products 2. The products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and GC-MS, and are in accordance with literature data.[21, 29-31]

*(E)-2,2,2-trifluoro-N-morpholino-1-phenylethan-1-imine (***2a***)*. The compound **2a** was obtained as a yellow colored oil (75% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.4 (m, 5H, ArH), 3.58-3.61 (apparent t, 4H, C**H**$_2$O), 2.95-2.97 (apparent t, 4H, C**H**$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 136.6 (q, $^2J_{C\text{-}F}$ = 33 Hz), 131.8, 130, 129, 128.6, 122.7 (q, $^1J_{C\text{-}F}$ = 280 Hz), 66.5, 54.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F -66.7 (s, 3F); GC-MS (m/z (relative %)): t_R = 2.3 min; m/z 258 (100, $M^{\cdot+}$), 199 (36), 131 (50), 104 (49), 86 (38), 77 (51) [21,18,26].

*(E)-2,2,2-trifluoro-N-morpholino-1-(4-nitrophenyl)ethan-1-imine (***2b***)*. The compound **2b** was obtained as a yellow colored solid (70% yield): ^{1}H NMR (400 MHz,

$CDCl_3$) δ^1H 8.25 (d, 2H, *J*= 8 Hz), 7.6 (d, 2H, *J*= 8 Hz), 3.6-3.63 (apparent t, 4H, C**H**$_2$O), 2.98-3.01 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 148.6, 138.3, 132.6 (q, $^2J_{C\text{-}F}$ = 34 Hz), 130, 124.2, 122.5 (q, $^1J_{C\text{-}F}$ = 271 Hz), 66.1, 54.6 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F -66.1(s, 3F); GC-MS (m/z (relative %)): t_R = 4.2 min; m/z 303 ($M^{\cdot+}$), 288 (13), 244 (21), 198 (35), 176 (31), 103 (38), 85 (36), 56 (100)[21,25].

*(E)-1-(4-bromophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (***2c***)*. The compound **2c** was obtained as a yellow oil (72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.47 (d, 2H, *J*= 8 Hz), 7.21 (d, 2H, *J*= 8 Hz), 3.53-3.55 (apparent t, 4H, C**H**$_2$O), 2.9-2.92 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 135.4 (q, $^2J_{C\text{-}F}$ = 34 Hz), 132.3, 130.5, 130.2, 124.4, 122.5 (q, $^1J_{C\text{-}F}$ = 270 Hz), 66.2, 54.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F-66.6 (s, 3F); GC-MS (m/z (relative %)): t_R = 3.5 min; m/z 338 ($M^{\cdot+}$+1), 279 (23), 199 (29), 157 (23), 102 (22), 86 (57), 56 (100)[32,21].

*(E)-2,2,2-trifluoro-N-morpholino-1-(2-nitrophenyl)ethan-1-imine (***2d***)*. The compound **2d** was obtained as a yellow oil (72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 8.14 (d, 1H, *J* = 8Hz), 7.68 (d, 1H, *J* = 8Hz), 7.65- 7.7 (m, 1H), 7.62-7.65 (M, 1H), 3.57-3.59 (apparent t, 4H, C**H**$_2$O), 2.97-2.99 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 148.2, 134.1, 132.1(q, $^2J_{C\text{-}F}$ = 33 Hz), 131.7, 127.6, 125.5, 122.6 (q, $^1J_{C\text{-}F}$ = 280 Hz), 66.6, 54.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F -66.5 (s, 3F); GC-MS (m/z (relative %)): t_R = 3.9 min; 303 (4, M.+), 203 (6), 123 (38), 43 (100)[21,26].

(E)-2,2,2-trifluoro-N-morpholino-1-(p-tolyl)ethan-1-imine (**2e**). The compound **2e** was obtained as a yellow oil as a yellow oil (68% yield): ^{1}H NMR (400 MHz, $CDCl_3$); δ^1H 7.29 (d, 2H, *J*= 8 Hz), 7.2 (d, 2H, *J*= 8 Hz), 3.59-3.61 (apparent t, 4H, C**H**$_2$O), 2.95-2.97 (apparent t, 4H, C**H**$_2$N), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 130.4, 128.8, 66.6,

54.7 21.9; ^{19}F NMR (376 MHz, $CDCl_3$); δ^{19}F -66.8 (s, 3F); GC-MS (m/z (relative %)): t_R = 2.7 min; 272 (100, $M^{\cdot+}$), 215 (35), 145(40), 118 (42), 86 (47), 56 (71)[26,21].

(E)-1-(4-chlorophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine ***(2f)***. The compound **2f** was obtained as a yellow oil (70% yield): ^{1}H NMR (400 MHz, $CDCl_3$); δ^1H 7.38 (m, 4H,ArH), 3.6-3.62 (apparent t, 4H, $2CH_2$), 2.96-2.99 (apparent t, 4H, $2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 136.7 (q, $^2J_{C\text{-}F}$ = 36 Hz), 130.4, 129.7, 122.9 (q, $^1J_{C\text{-}F}$ = 272 Hz), 66.5, 54.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F -66.8 (s, 3F); GC-MS (m/z (relative %)): t_R = 3.0 min; 292 (86, $M^{+\cdot}$), 235 (32), 165 (37), 138 (44), 86 (55), 56 (100)[21,26],.

(E)-1-(3-bromophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine ***(2g*** The compound **2g** was obtained as a yellow oil as a yellow oil (72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.53-7.57 (m, 2H, ArH), 7.28-7.33 (m, 2H, ArH), 3.61-3.63 (apparent t, 4H, C**H**$_2$O), 2.98-3.0 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 134.4 (q, $^2J_{C\text{-}F}$ = 33 Hz), 133.7, 133.2, 131.6, 130.5, 127.4, 123.1, 122.6 (q, $^1J_{C\text{-}F}$ = 275 Hz), 66.2, 54.5; ^{19}F NMR (376 MHz) δ^{19}F -66.5 (s, 3F); GC-MS (m/z (relative %)): t_R = 3.3 min; 338 (47, $M^{\cdot+}$+1), 279 (18), 199 (47), 184 (9), 102 (23), 56 (100)[21,25,,32].

(E)-1-(4-hydroxyphenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine ***(2h)***. The compound **2c** was obtained as a yellow oil (72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ^1H 7.47 (d, 2H, *J*= 8 Hz), 7.21 (d, 2H, *J*= 8 Hz), 3.53-3.55 (apparent t, 4H, C**H**$_2$O), 2.9-2.92 (apparent t, 4H, C**H**$_2$N); ^{13}C NMR (100 MHz, $CDCl_3$) δ^{13}C 135.4 (q, $^2J_{C\text{-}F}$ = 34 Hz), 132.3, 130.5, 130.2, 124.4, 122.5 (q, $^1J_{C\text{-}F}$ = 270 Hz), 66.2, 54.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ^{19}F-66.6 (s, 3F); GC-MS (m/z (relative %)): t_R = 3.5 min; m/z 338 ($M^{\cdot+}$+1), 279 (23), 199 (29), 157 (23), 102 (22), 86 (57), 56 (100)[32,21].

3.2. ACETIC ACID-PROMOTED TRANSITION METAL-FREE, PHOTOREDOX CATALYZED TRIFLUOROMETHYLATION OF ALDEHYDE HYDRAZONES

Organofluorine compounds, including the trifluoromethyl- and other fluoroalkyl-substituted compounds, are widely used in pharmaceutical, agrochemical, and materials applications, owing to their unique properties, such as relatively high C-F bond strength, enhanced lipophilicity, metabolic stability, and due to their optimal pharmacokinetic properties.[32-36] The C-CF_3 bond is isopolar with the carbonyl group, and due to its basicity-lowering effect on the adjacent amino moiety, the a-trifluoromethylamine moiety is emerging as a peptide bioisostere in peptidomimetic compounds.[37-40]

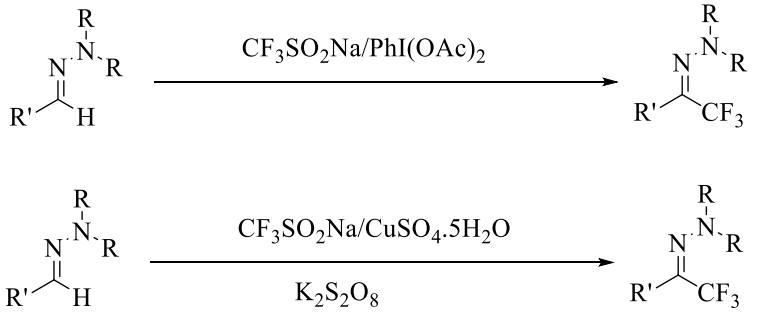
Although many efficient synthetic methods have been developed for the preparation of the a-trifluoromethylamines, through the nucleophilic trifluoromethylation of the corresponding aldimine derivatives,[41-54] the synthesis of the related C(sp^2)-H trifluoromethylated hydrazones, and their pharmaceutical or materials application, is relatively less well developed. The aldehyde hydrazones, in contrast to the aldimines, do not undergo nucleophilic trifluoromethylations due to the decreased electrophilicity of the imino carbon in these compounds. On the other hand, these compounds undergo free-radical additions with fluoroalkyl radicals, and thus recent interest in the synthesis of the trifluoromethyl and other fluoroalkyl derivatives of aldehyde hydrazones is focused on the free-radical mediated reactions.[16, 21, 30, 55-57]

The state-of-the-art synthetic methods for the free-radical trifluoromethylation of hydrazones involve the use of the Togni's reagent[16, 55] or sodium trifluoromethanesulfinate (Langlois reagent) in the presence of the (diacetoxyiodo)benzene as the oxidant (Figure

3.4).[21] Photoredox catalysis using trifluoromethanesulfonyl chloride (CF3SO2Cl), under reductive conditions gave the a-trifluoromethyl hydrazones (Scheme 1a).[30] The fluoroalkylation of the hydrazones was also effected using Ir(III)-photoredox-catalyzed reactions.[56] These synthetic methods require either the use of hydrolytically unstable and expensive reagents (CF_3SO_2Cl; 5g/$67.50) or the use of the transition-metal catalysts, which often requires removal of the toxic transition metal ions in the drug discovery.

We have earlier achieved C(sp^2)-H trifluoromethylation of aryl aldehyde hydrazones under oxidative conditions using the bench sable and cost-effective Langlois reagent and Cu(II) catalysis (Figure 3.4).[57]

(a) Previous work on the trifluoromethylation of hydrazones:



(b) This work: Oxidative trifluoromethylation under metal-free photoredox conditions

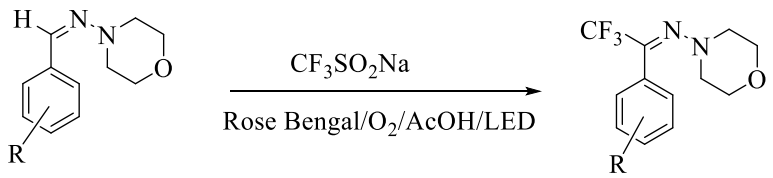


Figure 3.4. Reported Methods for Trifluoromethylation of Aldehyde Hydrazones

3.2.1. Results and Discussion. The photoredox-catalyzed trifluoromethylation of hydrazones using the bench-stable and non-toxic Langlois reagent would provide a cost-effective and environmentally benign alternative to the state-of-the-art synthetic methods. However, these trifluoromethylation reactions have not been reported to date. In this manuscript, toward the goal of developing environmentally benign and cost-effective trifluoromethylation of hydrazones, we have explored photoredox catalysis and the in situ generated singlet oxygen as the oxidant, thus obviating the use of the somewhat toxic Cu(II) and other transition metal ions.

Photoredox-catalysis often serves as an environmentally benign synthetic method and there is emerging interest in the photoredox-catalyzed reactions using transition metal catalysts as well as using visible-light absorbing organic compounds as photocatalysts.[58-63] The use of organic photocatalysts obviates the expensive removal of the metal ions at the end of the synthesis in the drug discovery areas. We have now developed a convenient, transition-metal-free photoredox catalyzed reaction for the C(sp^2-H) trifluoromethylation of aldehyde hydrazones.

Using the cost-effective Langlois reagent as the source of the trifluoromethyl radical, we have investigated the use of various organic photocatalysts for the photoredox catalysis in the trifluoromethylation of the aldehyde N-morpholinohydrazones. We have found that the conventionally used organic photocatalysts, such as 2,3-butanedione (diacetyl) and 9-fluorenone were ineffective in the trifluoromethylation of hydrazones. We have identified Rose Bengal (RB), in the presence of air, as an optimal photoredox catalyst for the trifluoromethylation of hydrazones. The latter reactions presumably involve the in-situ generation of the singlet oxygen as a strong oxidant, the formation of

which is mediated by the photoexcited Rose Bengal, RB* (*vide infra*, Figure 3.7). During the optimization of the reaction conditions, we have observed that acetic acid substantially accelerated these photoredox reactions and suppressed the adventitious byproducts. This photoredox-catalyzed trifluoromethylation of hydrazones, in the presence of acetic acid as the promoter, thus provides convenient access to the $C(sp^2)$-H trifluoromethylated hydrazones under mild reaction conditions.

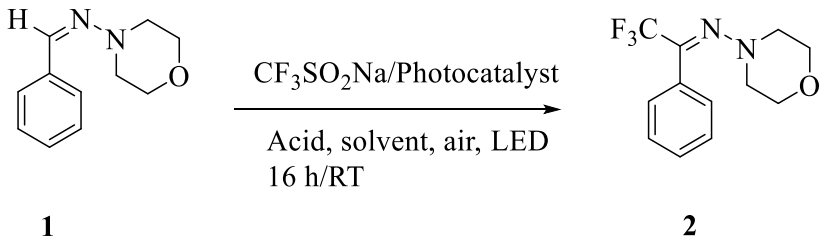
After initial optimization studies for the RB-catalyzed trifluoromethylation reactions, we have determined the optimal condition as follows: 7 mol% RB, 0.26 mmol of the hydrazone **1**, 0.52 mmol of the Langlois reagent, 1.82 mmol of acetic acid, pre-air-bubbled solvent; two 2-Watts LED light sources, DMSO solvent, 16 h/RT (Table 3.1). Under these conditions, at a reaction time of 4 h, 11 h, and 16 h, compound **1** gave the corresonding trifuoromethylated product **2** in yields of 24%, 72%, and 86%, respectively (yields are averages of three separate experiments). Further increase of reaction time resulted in the formation of adventitious byproducts. Thus, we have used a reaction time of 16 h for each of the experiments in Table 3.2.

Relatively high yield of upto 86% (estimated by ^{19}F NMR) was obtained when pre-air-bubbled DMSO was used as the solvent in the presence of acetic acid and the when the reactions were carried out under an air-balloon (entry 8, Table 3.1). Using these standard conditions, we have systematically screened various solvents, light sources, photocatalysts, acids, and various oxidizing agents, as follows. Use of THF, CH_3CN, acetone, and THF as solvents gave consistently low yields of 16% to 34% (Table 3.1, entries 1–3 and 6). Only trace amounts of product **2** was obtained when 1,2-

dichloroethane (DCE), and N,N-dimethylformamide (DMF) were used as solvents (Table 3.1, entries 4 and 5).

In the absence of acetic acid as promoter, the reaction was relatively slow and after 24 h of reaction time, the product **2** was obtained in 80% yield (Table 3.1, entry 7). Use of the acids stronger than acetic acid, such as methanesulfonic acid (MSA) and trifluoroacetic acid (TFA) resulted in trace yields of the product **2** (Table 3.1, entries 9 and 10). Lowering the concentration of MSA to 0.5 equiv, however, afforded 37% yield of the product **2**. The relatively stronger acids MSA and TFA may protonate the iminyl nitrogen, thereby disfavoring the electrophilic trifluoromethyl radical addition to the hydrazones. Use of 7 equiv of acetic acid additive, on the other hand, gave relatively the highest yield of the product **2** (Table 3.1, entry 8). Acetic acid not only accelerated the rate of trifluoromethylation, but also suppressed the formation of the adventitious byproducts, as shown by the ^{19}F NMR of the reaction mixture (Figure. 3.5). These observations are also consistent with the rate-accelerating effect of acetic acid in the visible-light photoredox-catalyzed N-demethylation reactions.[64] Further research to delineate the role and scope of acetic acid-promoted photoredox reactions is in progress in our laboratory

Scheme 2**.** Optimization of the reaction conditions[a]



1 **2**

Table 3.2. Optimization of Reaction Conditions (Method 2)

Entry	**Catalyst**	**Solvent**	**LED Light**	**Acid**	**Oxidizing Agent**	**Yield**
1	Rose Bengal (7 mol%)	THF	2*2W Green	Acetic acid	Air	16%
2	Rose Bengal (7 mol%)	ACN	2*2W Green	Acetic acid	Air	21%
3	Rose Bengal (7 mol%)	Acetone	2*2W Green	Acetic acid	Air	34%
4	Rose Bengal (7 mol%)	DCE	2*2W Green	Acetic acid	Air	Trace
5	Rose Bengal (7 mol%)	DMF	2*2W Green	Acetic acid	Air	Trace
6	Rose Bengal (7 mol%)	THF	2*2W Green	Acetic acid	Air	16%
7	Rose Bengal (7 mol%)	DMSO	2*2W Green	No acid	Air	80%[b]
8	Rose Bengal (7 mol%)	DMSO	2*2W Green	Acetic acid	Air	86%
9	Rose Bengal (7 mol%)	DMSO	2*2W Green	MethaneSulfonic acid	Air	Trace (37%)[c]
10	Rose Bengal (7 mol%)	DMSO	2*2W Green	Trifluoracetic acid	Air	Trace
11	Rose Bengal (5 mol%)	DMSO	2*2W Green	Acetic acid	Air	69%
12	Biacetyl (7 mol%)	DMSO	2*2W Green	Acetic acid	Air	21%[b]
13	Biacetyl (1 equiv) + Rose Bengal (7 mol%)	DMSO	2*2W Green	Acetic acid	Air	58%[b]
14	Fluorenone (7 mol%)	DMSO	2*2W Green	Acetic acid	Air	Trace
16	Xanthone (7 mol%)	DMSO	2*2W Green	Acetic acid	Air	Trace

Table 3.2. Optimization of Reaction Conditions (Method 2) (cont…)

17	**No Catalyst**	**DMSO**	**2*2W Green**	**Acetic acid**	**Air**	**Trace**
18	Rose Bengal (7 mol%)	DMSO	2*2W Green	Acetic acid	DTBP	13%
19	Rose Bengal (7 mol%)	DMSO	2*2W Green	Acetic acid	$K_2S_2O_8$	Trace
20	Rose Bengal (7 mol%)	DMSO	2*2W Green	Acetic acid	Under N_2	87%
21	Rose Bengal (7 mol%)	DMSO	2*2 W Blue	Acetic acid	Air	44%
22	Rose Bengal (7 mol%)	DMSO	2*2 W White	Acetic acid	Air	Trace
23	Rose Bengal (7 mol%)	DMSO	No LED	Acetic acid	Air	NR

[a]Reaction conditions: **1** (0.26 mmol), (RB) Photocatalyst (7 mol%), Langlois reagent (0.52 mmol; 2 equiv), pre-air-bubbled solvent (4 mL; air bubbling time: 15 min, and an air balloon was used throughout the reaction), two 2 watts Green LEDs, 16 h/RT: Acid (1.82 mmol; 7 equiv); [b]reaction time 24h; [c]37% yield using 0.13 mmol (0.5 equiv) of MSA; [d]DTBP instead of air; [e]$K_2S_2O_8$ instead of air; yields estimated by ^{19}F NMR.

We have also evaluated other organophotocatalysts, such as diacetyl, 9-fluoreneone, and xanthone. Whereas the use of diacetyl gave compound **2** in 21% yield, only trace amounts of the product **2** were obtained when 9-fluorenone and xanthone were used as the photocatalyst (Table 3.2, entries 11–13). When the reaction was carried out in the absence of a photocatalyst, only trace amount of the product **2** was obtained (Table 3.2, entry 14). We also screened various other widely used oxidizing agents, including di-*tert*-butyl peroxide (DTBP), and $K_2S_2O_8$, as alternatives to the use of air and found that air is a superior oxidizing agent as compared to the latter oxidizing agents. Thus, use of DTBP gave the product **2** in 13% yield, whereas the use of potassium persulfate ($K_2S_2O_8$) as the oxidizer gave the product in only trace amounts (Table 3.2, entries 15 and 16). Use of the Blue LEDs gave 44% of the product (Table 3.2, entry 17) whereas the use of White

LEDs gave only a trace amount of the product (Table 3.2, entry 18). In the absence of LED light sources, there was no reaction (Table 3.2, entry 19). There was also no reaction when the reaction was carried out under nitrogen atmosphere, in the absence of any oxidizing agent.

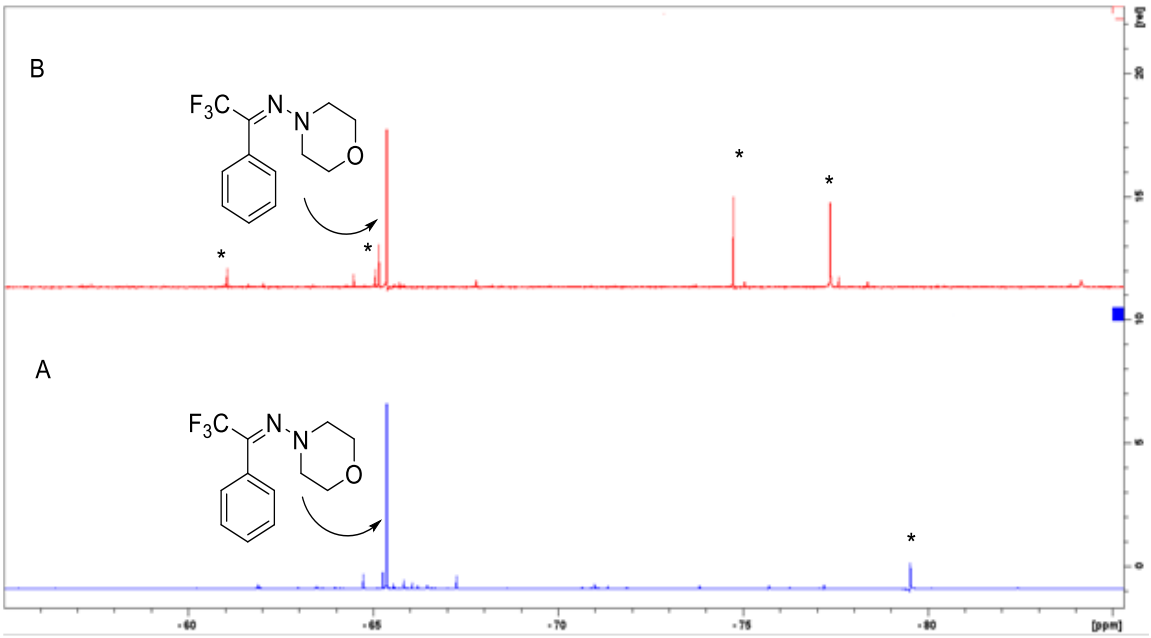


Figure 3.5.^{19}F NMR of the reaction mixture in Acetic Acid
[(presence of acetic acid (A) and absence (B) of acetic acid (7 equiv), under the standard conditions of Scheme 2, after 16 h; asterisks indicate the adventitious byproducts.]

We evaluated the substrate scope as outlined in scheme **2** using the optimal reaction conditions: 7 mol% of RB, two 2W green LEDs, pre-air-bubbled DMSO, 7 equivalents of acetic acid; and the reaction was carried out under an air-balloon. The progress of the reaction was monitored by TLC and the reaction was complete in about 16 h. As shown in the reaction Scheme, the hydrazones derived from the corresponding aromatic aldehydes with electron-donating and electron-withdrawing groups gave the corresponding C(sp^2)-H trifluoromethylated products (**2**) in moderate to high yields (60%

to 83% isolated yields; 62% to 90%, as estimated by ^{19}F NMR). The reaction could also be extended to heterocyclic arenes to give the corresponding trifluoromethylated products (**13** and **14**) in good yields. However, the trifluoromethylation reaction was not successful for the aliphatic aldehyde hydrazones (e.g., **18**) and for the corresponding N,N-dimethylhydrazones (e.g. 19). We have not further optimized the reaction conditions for the latter reactions. The progress of the reaction was monitored by TLC and the reaction was complete in about 16 h.

Based on our observation that these photoredox trifluoromethylation reactions proceed in good yields in the presence of the dioxygen (air), whereas substantially diminished yields were observed in the absence of the dioxygen, we propose a mechanism as outlined in Figure 3.7. The photoexcited singlet RB transforms the triplet dioxygen to the singlet dioxygen, which is involved in the regeneration of the RB from its radical anion. Intersystem crossing of the singlet RB to the photoexcited triplet RB, followed by the single-electron transfer oxidation of the trifluoromethanesulfinate anion forms the trifluoromethanesulfinyl radical, which spontaneously loses SO_2 to give the trifluoromethyl radical. The hydrazinyl radical (1-$CF_3^{\cdot -}$) formed through addition of the $CF_3^{\cdot}$ to the hydrazone 1 may be oxidized either by the radical anion $O_2^{\cdot -}$ or by the photoexcited RB (RB*) to give the aminyl cation (1-CF_3^{+}). A subsequent deprotonation of the aminyl cation by the mild bases generated during the reaction, such as oxygen dianion (O_2^{2-}) would give the C(sp^2)-H trifluoromethyl hydrazones 2.

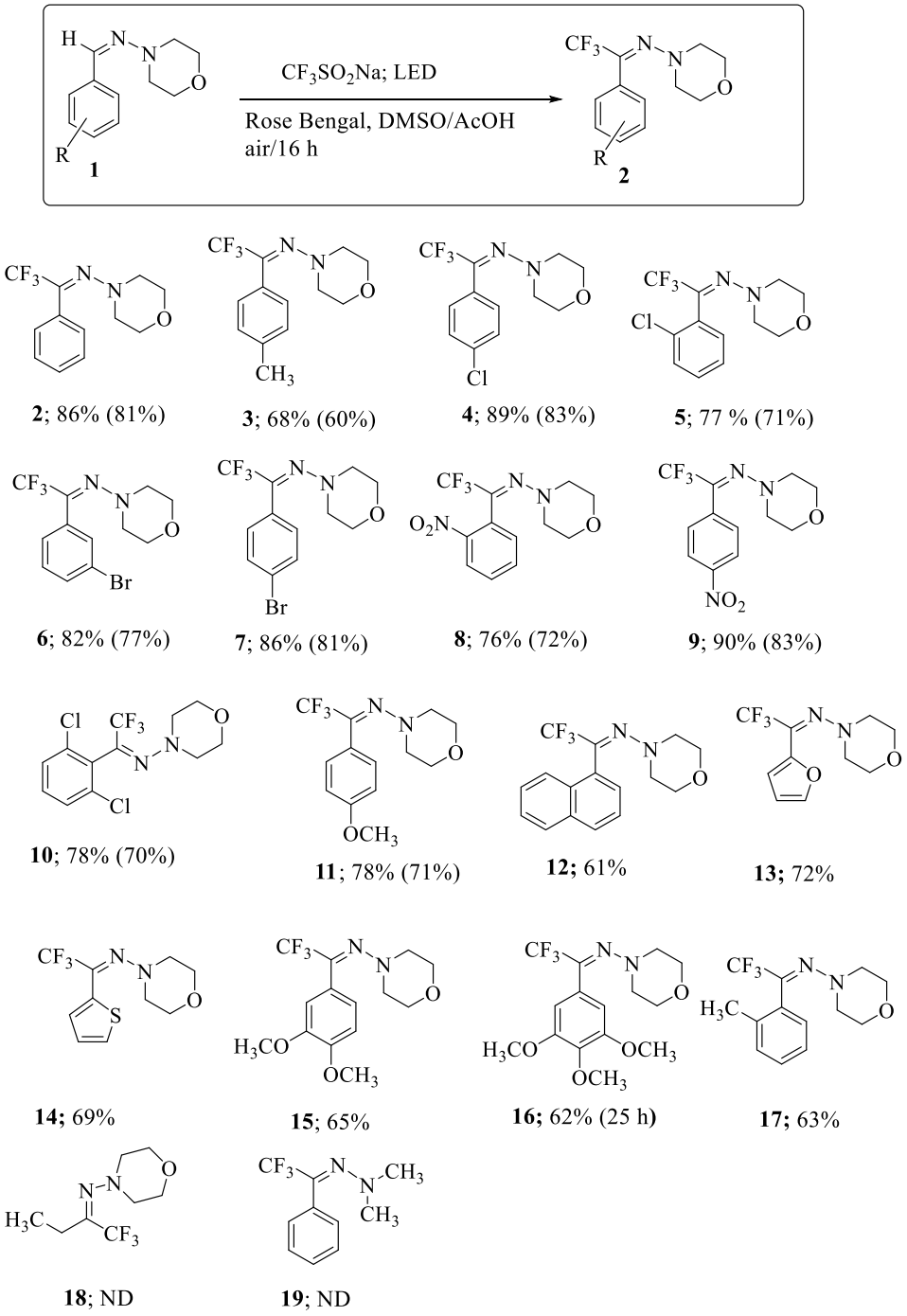


Figure 3.6. Substrate scope for the C(sp^2)-H trifluoromethylation of the Hydrazone 1

Reaction conditions: Hydrazone **1** (1 equiv), CF_3SO_2Na (2 equiv), acetic acid (7 equiv) Rose Bengal (RB) (7 mol%)/DMSO (pre-air-bubbled and reaction carried out under an air-balloon); two 2W green LEDs; 16 h); yields determined by ^{19}F NMR (isolated yields in parenthesis) (ND = not detected).

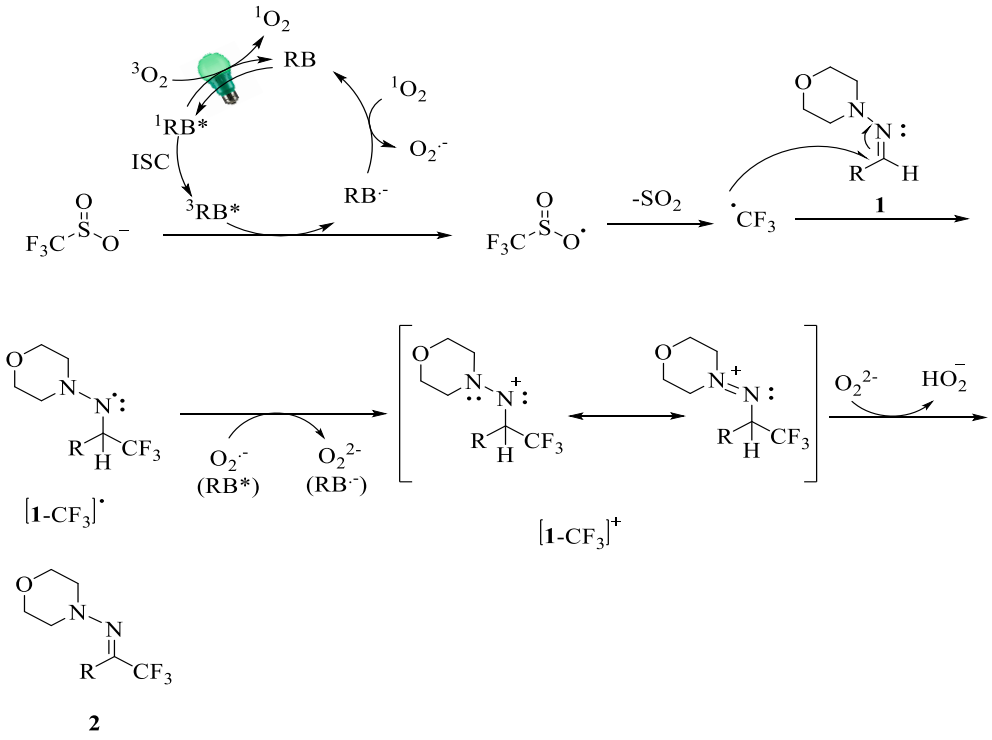


Figure 3.7. Proposed mechanism for the Photo-catalyzed Method
(RB = Rose Bengal, ISC = intersystem crossing)

Based on our observation that these photoredox trifluoromethylation reactions proceed in good yields in the presence of the dioxygen (air), whereas substantially diminished yields were observed in the absence of the dioxygen, we propose a mechanism as outlined in Figure 3.7. The photoexcited singlet RB transforms the triplet dioxygen to the singlet dioxygen, which is involved in the regeneration of the RB from its radical anion. Intersystem crossing of the singlet RB to the photoexcited triplet RB,

followed by the single-electron transfer oxidation of the trifluoromethanesulfinate anion forms the trifluoromethanesulfinyl radical, which spontaneously loses SO_2 to give the trifluoromethyl radical. The hydrazinyl radical (**1**-$CF_3^{\cdot -}$) formed through addition of the $CF_3^{\cdot}$ to the hydrazone **1** may be oxidized either by the radical anion $O_2^{\cdot -}$ or by the photoexcited RB (RB*) to give the aminyl cation (**1**-CF_3^{+}). A subsequent deprotonation of the aminyl cation by the mild bases generated during the reaction, such as oxygen dianion (O_2^{2-}) would give the C(sp^2)-H trifluoromethyl hydrazones **2**. The substrate scope of the reaction method is outlined in the Figure 3.6.

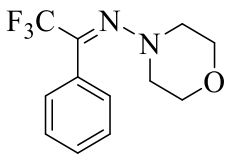
3.2.2. Experimental. All chemicals were obtained from the commercial suppliers and used without further purification. 1H NMR and 13C NMR were recorded on a Bruker Avance–400 spectrometer (400 MHz for 1H, 100 MHz for 13C, and 376 MHz for 19F) in CDCl3. For estimation of the yields by 19F NMR trifluorotoluene was used as an internal standard. The 1H and 13C NMR spectra of the compounds are in agreement with the literature data.

After initial optimization studies for the Rose Bengal-catalyzed trifluoromethylation reactions, we have determined the optimal condition as follows: 7 mol% Rose Bengal, 0.26 mmol of the hydrazone 1, 0.52 mmol of the Langlois reagent, 1.82 mmol of acetic acid, pre-air-bubbled solvent; two 2-Watts LED light sources, DMSO solvent, 16 h/RT (Table 3.2). Relatively high yield upto 90% (estimated by ^{19}F NMR) was obtained when pre-air-bubbled DMSO was used as the solvent along with the acetic acid and carrying the reaction under an air-balloon (entry 3, Table 3.2). Using these standard conditions, we have systematically screened various solvents, reaction time, light sources, photocatalysts, acids, and various oxidizing agents, as follows. Use

of acetone and acetonitrile solvents under these standard conditions gave poor yields of the trifluoromethylated product 2 (entries 1 and 2, Table 3.2).

For the general procedure for the trifluoromethylation of aldehyde hydrazones. To a 10-mL quartzreaction vial, equipped with a magnetic stir bar, was added a mixture of the hydrazone **2** (0.26 mmol, 1 equiv), Langlois reagent (0.52 mmol, 2 equiv), acetic acid (1.82 mmol, 7 equiv), and Rose Bengal (0.024 mmol, 7 mol%) in DMSO (4 mL; pre-air-bubbled for 15 min). The resulting mixture was irradiated with two 2 Watts green LEDs and stirred at room temperature for 16 h under an air atmosphere (air balloon). Water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and purified by column chromatography (silica gel as the stationary phase) using ethyl acetate/hexane as an eluent to afford the desired products.

(E)-2,2,2-Trifluoro-N-morpholino-1-phenylethan-1-imine (**2**)[31, 57]

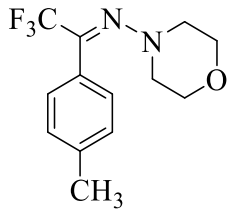


2

The compound **2** was preparedaccording to the general procedure using (*E*)-N-morpholino-1-phenylmethanimine (50 mg; 0.26 mmol), CF_3SO_2Na (84 mg; 0.52 mmol, 2 equiv), Rose Bengal (36.5 mg; 0.024 mmol) and acetic acid (110 mg; 1.82 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl)benzene (46.8 mg; 0.26 mmol) was added into the resulting mixture to estimate the crude yield by ^{19}F NMR. The crude product was purified through silica gel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a pale-yellow oil (54.3 mg,yield: 81%); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.39 (broad s, 5H), 3.60–3.58 (m, 4H), 2.97–2.95 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, (q, $^2J_{CF}$ = 32.6 Hz) 131.8, 130.0, 129.3, 126.5, 121.4. (q, $^1J_{CF}$ = 273 Hz), 66.3, 54.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.44 (s).

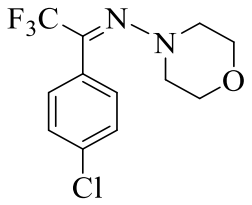
*(E)-2,2,2-trifluoro-N-morpholino-1-(4-methylphenyl) ethan-1-imine (**3**)*[21, 57]



3

The compound **3** was prepared according to the general procedure using (*E*)-N-morpholino-1-(4-methylphenyl)methanimine (50 mg, 0.246 mmol, 1 equiv), CF_3SO_2Na (80 mg, 0.5 mmol, 2 equiv), Rose Bengal (34 mg, 0.035 mmol) and acetic acid (103 mg; 1.722 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl)benzene (44.28 mg; 0.246 mmol) was added into the resulting mixture to estimate the yield by ^{19}F NMR. The crude product was purifiedthrough silica gel column chromatography, using EtOAc/Hexane (1:9 v/v) as an eluent, to afford a colorless oil (40.1 mg, yield: 60%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.26-7.21 (m, 2H) 3.87-3.85 (m, 4H), 3.16-3.13 (m, 4H), 2.41 (s, 3H). δ -66.81(s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.6 (q, $^2J_{C\text{-}F}$ = 33.2 Hz),130.1, 129.2, 127.0 121.2 (q, $^2J_{C\text{-}F}$ =271 Hz), 67.3, 52.8, 22.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.3 (s).

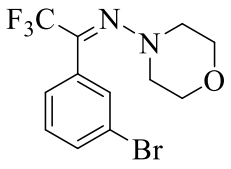
*(E)-1-(4chlorophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (**4**)*[21, 57]



4

The compound 4 was prepared according to the general procedure using (*E*)-N-morpholino-1-(4-chlorophenyl)methanimine (50 mg; 0.22 mmol), CF_3SO_2Na (70 mg; 0.44 mmol, 2 equiv), Rose Bengal (26 mg; 0.03mmol) and acetic acid (92 mg; 1.54 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl) benzene (39.6 mg; 0.22 mmol) was added into the resulting mixture to estimate the yield by ^{19}F NMR. The crude product was purified through silica gel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a brown oil (52 mg, yield: 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.49 (m, 2H), 7.30-7.27 (m, 2H) 3.87-3.85(m, 4H) 3.16-3.14 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.39 (s).

*(E)-1-(3-bromophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (**6**)* [21, 57]

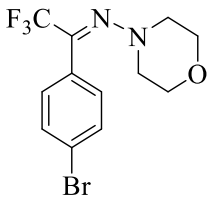


6

The compound **6** was prepared according to the general procedure using (*E*)-N-morpholino-1-(3-bromophenyl)methanimine (50 mg; 0.184 mmol), CF_3SO_2Na (60 mg; 0.37 mmol, 2 equiv), Rose Bengal (25 mg; 0.026 mmol), acetic acid (77 mg; 1.288 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl) benzene (33.12 mg;

0.184 mmol) was added into the resulting mixture to estimate the yield by ^{19}F NMR. The crude productwas purified through silica gel column chromatography, using EtOAc/Hexane (1:9 v/v) as an eluent, to afford a colorless oil (47.6 mg, yield: 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 1H),7.54-7.52 (m, 1H) 7. 35-7.33 (m, 1H) 7.29-7.26(m, 1H) 3.63-3.61 (m, 4H), 3.0-2.98 (m, 4H). ^{19}FNMR (376 MHz, $CDCl_3$) δ -66.54 (s).

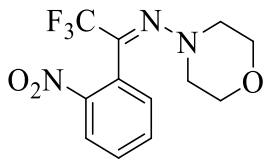
*(E)-1-(4-bromophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (**7**)*[21, 57]



7

The compound **7** was prepared according to the general procedure using (*E*)-N-morpholino-1-(4-bromophenyl)- methanimine (50 mg; 0.184 mmol, 1 equiv), CF_3SO_2Na (60 mg; 0.37 mmol, 2 equiv), Rose Bengal (25 mg; 0.026 mmol) and acetic acid (77 mg; 1.288 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl) benzene (0.0184 mmol, 33.12 mg) was added into the resulting mixture to estimate the yield by ^{19}F NMR. The crude product was purified through silica gel column chromatography, using EtOAc/Hexane (1:9 v/v) as an eluent, to afford a brown oil (50 mg, yield:81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.23-7.21 (m, 2H) 3.55-3.53 (m, 4H), 2.92-2.90 (m, 4H)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135. 4, (q, $^{2}J_{CF}$ = 34 Hz) 135.0, 132.6, 130.8, 130.6, 124.7(q, $^{1}J_{C\text{-}F}$ = 268 Hz), 66.5, 54.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.63 (s).

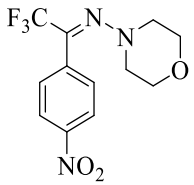
*(E)-2,2,2-trifluoro-N-morpholino-1-(2-nitrophenyl) ethan-1-imine (**8**)*[21, 57]



8

The compound **8** was prepared according to the general procedure using (*E*)-N-morpholino-1-(2-nitrophenyl) methaneamine (50 mg; 0.212 mmol), CF_3SO_2Na (68 mg; 0.42 mmol, 2 equiv), Rose Bengal(28 mg; 0.030 mmol) and acetic acid (89 mg; 1.484 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl) benzene (38.16 mg; 0.212 mmol) wasadded into the resulting mixture to estimate the yield by ^{19}F NMR. The crude product was purifiedthrough silica gel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a light-yellow solid (46.2 mg, yield: 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15-8.13 (m, 1H), 7.70-7.68 (m, 1H) 7.65-7.62(m, 1H), 7.47- 7.45 (m, 1H), 3.59-3.57 (m, 4H), 2.99-2.97 (m, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.49 (s).

*(E)-2,2,2-trifluoro-N-morpholino-1-(4-nitrophenyl) ethan-1-imine (**9**)*[21, 57]

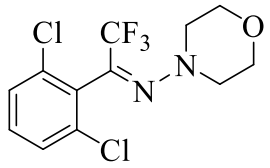


9

The compound **9** was prepared according to the general procedure using (*E*)-N-morpholino-1-(4 -nitrophenyl) methanimine (0.212 mmol; 50 mg), CF_3SO_2Na (68 mg;

0.42 mmol, 2 equiv) and Rose Bengal (28 mg; 0.03mmol), acetic acid (89 mg; 1.484 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl)benzene (38.16 mg; 0.212 mmol) was added into theresulting mixture to estimate the yield by ^{19}F NMR. The crude product was purified through silicagel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a light-yellow solid (53.29 mg, yield: 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 7.42-7.40 (d, $^{3}J_{HH}$ = 8.8 Hz, 2H) 3.62-3.59 (m, 4H), 2.99-2.96 (m, 4H)); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.11 (s).

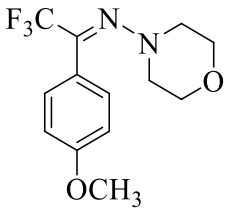
(*E*)-1-(2,6 dichlorophenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (**10**)[21]



10

The compound **10** was prepared according to the general procedure using (*E*)-N-morpholino-1-(2,6 dichlorophenyl)methanimine (50 mg; 0.192 mmol), CF_3SO_2Na (60 mg; 0.39 mmol, 2 equiv), Rose Bengal (26 mg; 0.026 mmol) and acetic acid (81 mg; 1.344 mmol, 7 equiv). An internal standard 4-chloro-1-(trifluoromethyl)benzene (33.12 mg; 0.192 mmol) was added into the resulting mixture to estimate the yield by ^{19}F NMR. The crude productwas purified through silica gel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a colorless oil (43.8 mg, yield:70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.365-7.360(m, 1H), 7.344-7.342 (m, 1H) 7. 31(s, 1H) 3.66-3.66 (m, 4H), 3.14-3.11 (m, 4H)); ^{19}F NMR (376 MHz) $CDCl_3$) δ -64.60 (s).

*(E)-1-(4methoxyphenyl)-2,2,2-trifluoro-N-morpholinoethan-1-imine (**11**)*[21]



11

The compound **11** was prepared according to the general procedure using (*E*)-N-morpholino-1-(4methoxyphenyl) methanimine (50 mg; 0.22 mmol), CF_3SO_2Na (70 mg; 0.44 mmol, 2 equiv), Rose Bengal (26 mg; 0.03mmol) and acetic acid (92 mg; 1.54 mmol, 7 equiv). An internal standard, 4-chloro-1-(trifluoromethyl) benzene (39.6 mg; 0.22 mmol), was added to the resulting mixture for estimating the yield by ^{19}F NMR. The crude product was purified through silica gel column chromatography, using EtOAc/Hexane (1.5:8.5 v/v) as an eluent, to afford a brown oil (44.5 mg, yield:71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (apparent d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 6.86-6.83 (apparent d, $^{3}J_{HH}$ = 8.8 Hz, 2H), 3.80-3.66 (s, 3H) 3.71-3.69 (m, 4H), 2.94-2.92 (m, 4H)). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.90 (s).

3.2.3. Conclusions. In conclusion, we have demonstrated oxidative C(sp^2)-H trifluoromethylation of aromatic and heterocyclic aromatic aldehyde morpholino-hydrazones under visible light photoredox catalysis, using relatively nontoxic, cost-effective, and bench-stable Langlois reagent and RB as the photocatalyst, in the presence of acetic acid as the promoter and air as the oxidant. Acetic acid substantially suppresses the formation of the adventitious byproducts and accelerates the rates of the trifluoromethylation reactions. A series of aromatic and heterocyclic aromatic compounds, with electron-releasing as well as electron-withdrawing groups, give moderate to high yields of the corresponding trifluoromethylated hydrazones.

3.2.4. Spectral Data of Morpholine Hydrazones. All chemicals were obtained from the commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance–400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 376 MHz for ^{19}F) in $CDCl_3$. For estimation of the yields by ^{19}F NMR trifluorotoluene was used as an internal standard. The ^{1}H and ^{13}C NMR spectra of the compounds are in agreement with the literature data. The spectra are attached in the appendix.

4. CONCLUSION

In the first part of the work, purine based triazoles were synthesized, characterized and studied for their ability to protect the neuronal cells against the oxidative damage caused by metabolic function of the body. Hydrogen peroxide was used to create the oxidative stress environment in SHSY-5Y cell cultural medium. The preliminary results show that triazoles have been effectively working as neuroprotectors. However, the further studied needs to be done to support the preliminary results.

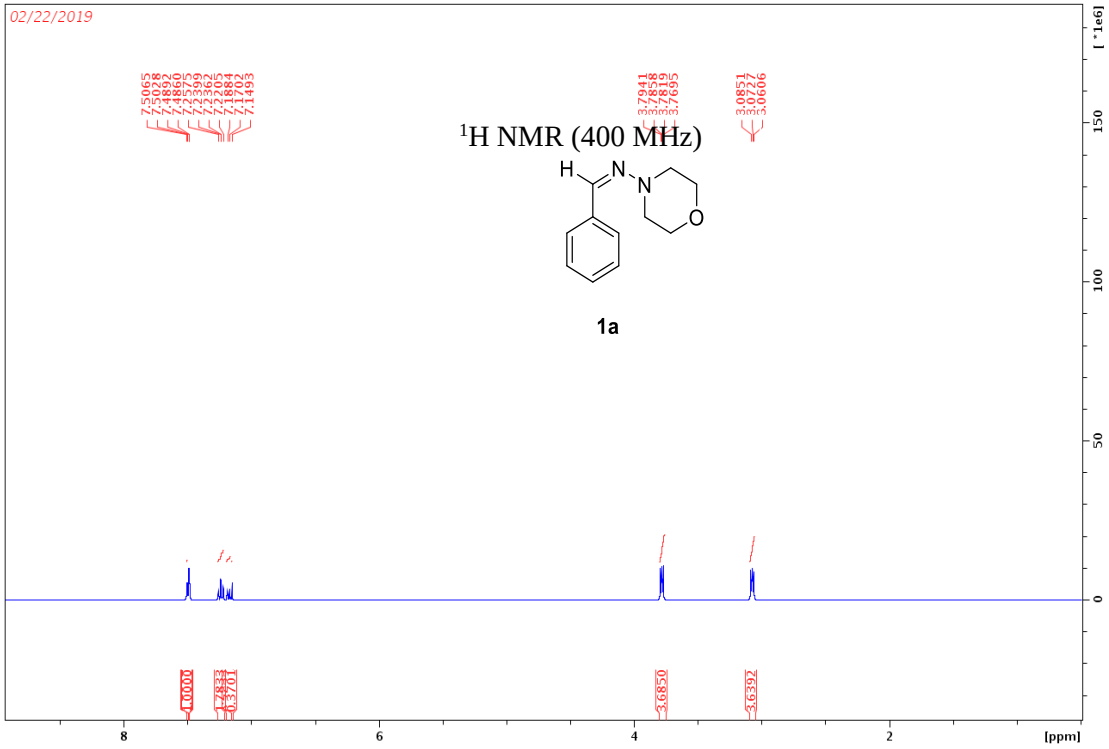
The second part of the work presents the two different synthetic routes for the trifluoromethylation of aldehyde hydrazones. The C(sp2−H)-trifluoromethylation of hydrazones would give access to the α-trifluoromethylated hydrazones that can serve as intermediates in the synthesis of pharmaceutically interesting, fluorinated compounds. Using the cost-effective Langlois reagent (sodium trifluoromethanesulfinate, CF3SO2Na) we have developed convenient synthetic methods for the a-trifluoromethylation of hydrazones, derived from aromatic aldehydes using Cu(II) catalysis and also under photoredox catalysis. The Cu(II)-catalyzed trifluoromethylation using Langlois reagent provides an alternative to the use of the relatively toxic and expensive reagents, such as Togni's reagent and hypervalent iodine compounds. A series of aromatic aldehyde morpholino hydrazones were trifluoromethylated under mild reaction conditions in moderate to high yields. The reaction generally tolerates electron-withdrawing and electron-releasing substituents on the aromatic ring.

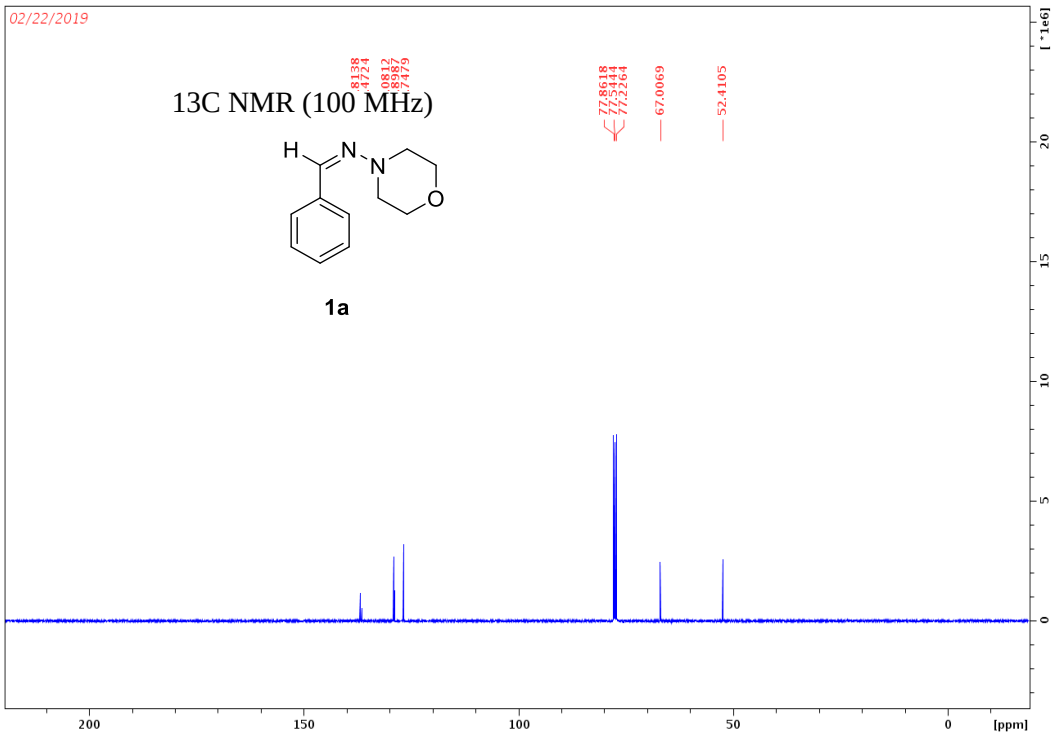
We have identified Rose Bengal as an efficient photoredox catalyst for the trifluoromethylation of aromatic aldehyde hydrazones using Langlois reagent as the source of the trifluoromethyl radical. Further optimization of reaction conditions led to

the observation of significantly improved yields for the trifluoromethylation in the presence of trace amounts of acetic acid as the co-catalyst. These convenient and cost-effective photoredox-catalyzed trifluoromethylations provide environmentally benign and cost-effective synthetic strategies for the synthesis of a-trifluoromethyl hydrazones. This a-trifluoromethylation reaction is broadly applicable for the aromatic aldehyde hydrazones with both electron-releasing and electron-withdrawing groups.

APPENDIX

1. NMR RESULTS OF MORPHOLINE HYDRAZONES




02/22/2019
13C NMR (100 MHz)
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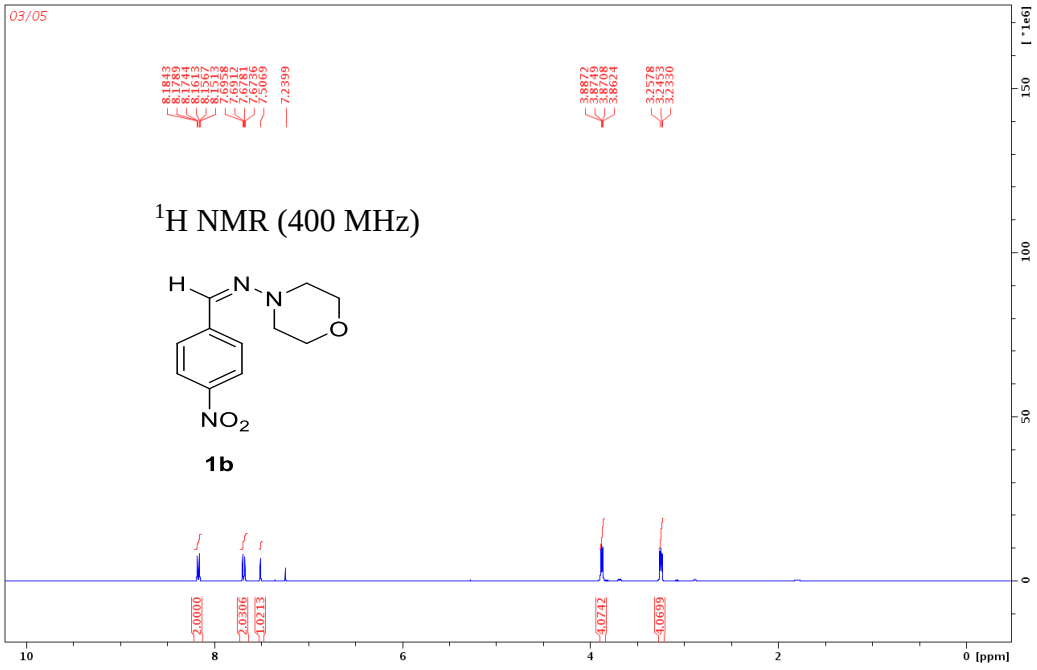
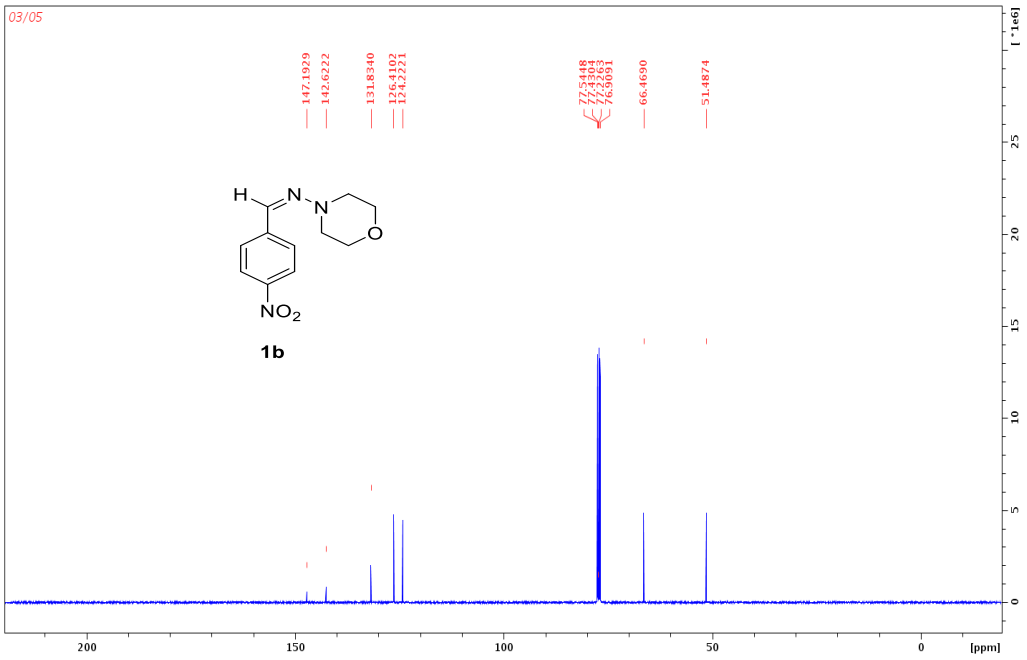
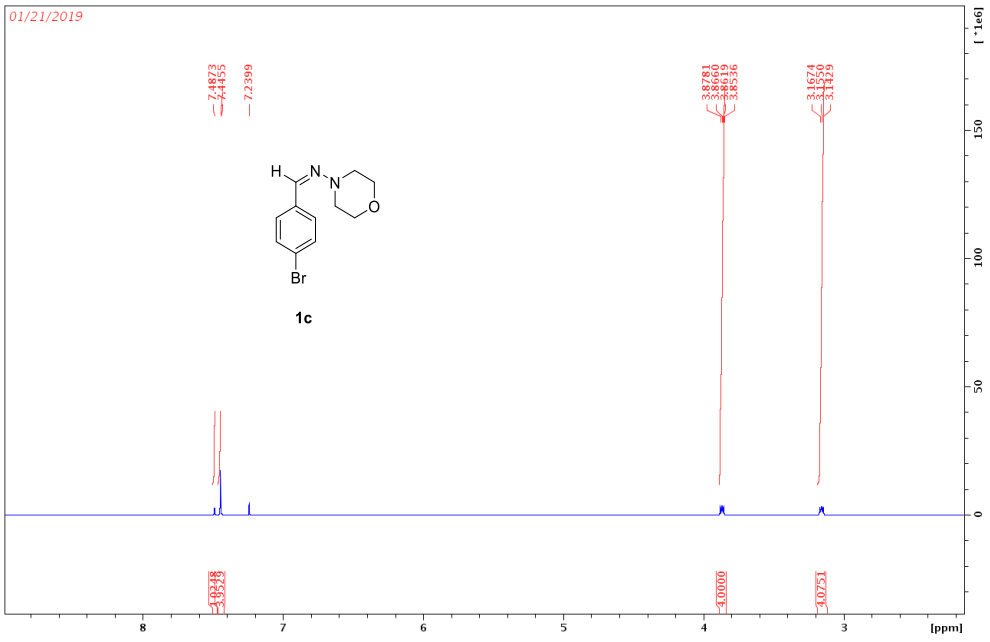
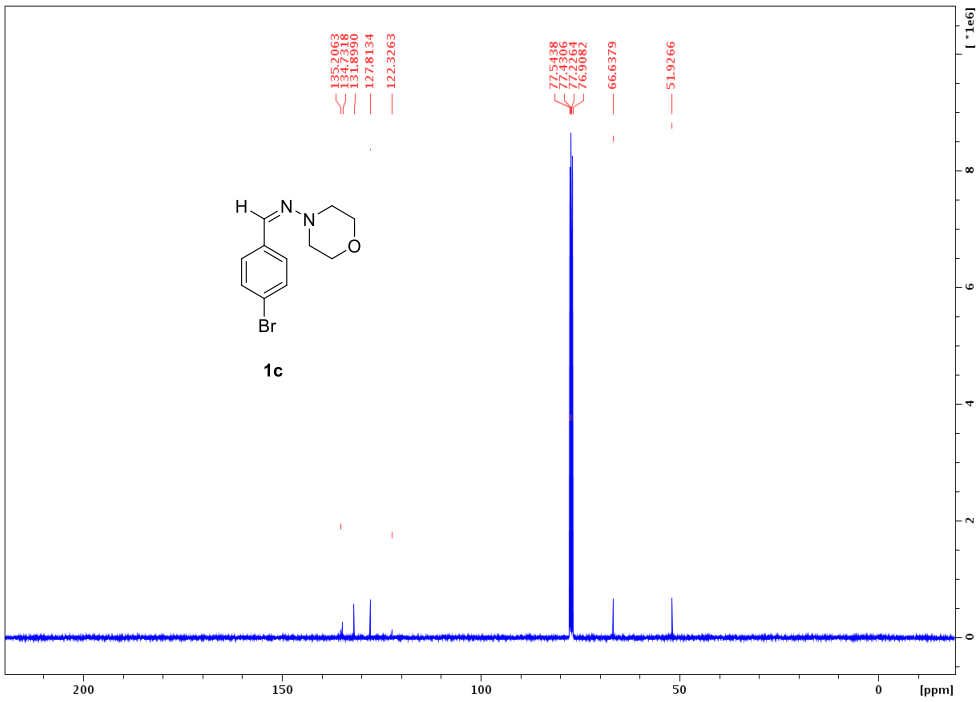
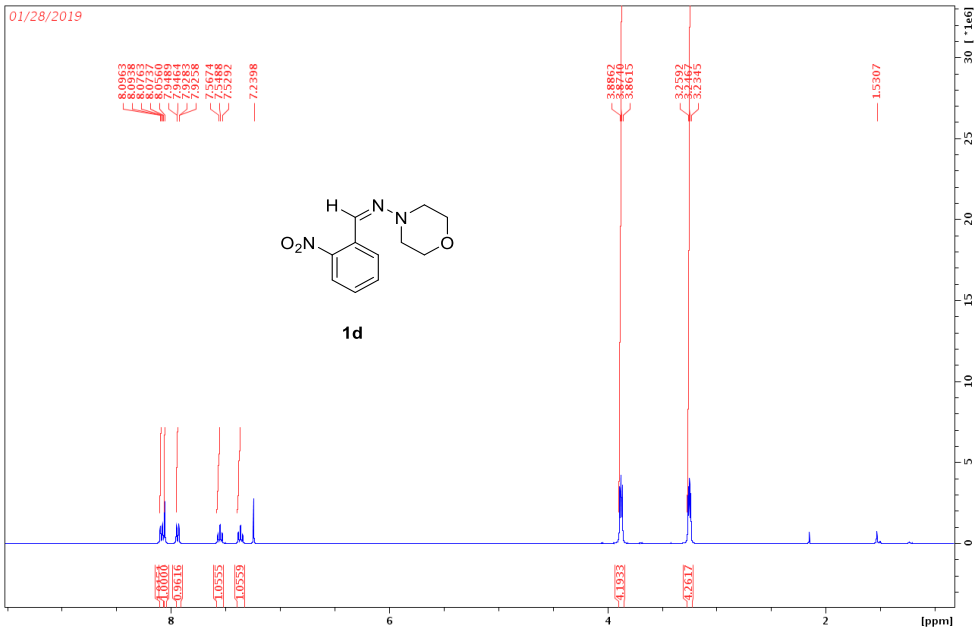
77.8618
77.3444
77.2264
67.0069
52.4105
[*1e6]
[ppm]


03/05
1H NMR (400 MHz)
1b
7.2399
3.8872
3.8749
3.8708
3.8624
3.2578
3.2453
3.2330
2.0000
2.0306
1.0213
4.0742
4.0699
[*1e6]
[ppm]


03/05
147.1929
142.6222
131.8340
126.4102
124.2221
77.5448
77.4304
77.2263
76.9981
66.4690
51.4874
1b
200
150
100
50
0
[ppm]
[1e6]


01/21/2019
7.4873
7.4455
7.2399
3.8781
3.8660
3.8539
3.8418
3.1674
3.1550
3.1429
1c
1.0348
3.9329
4.0000
4.0751
8
7
6
5
4
3
[ppm]
[1e6]


135.2063
134.2738
131.6990
127.8134
122.3263
77.5438
77.4306
77.2264
76.9082
66.6379
51.9266
H
N
N
O
Br
1c
200
150
100
50
0
[ppm]
[1e6]


01/28/2019
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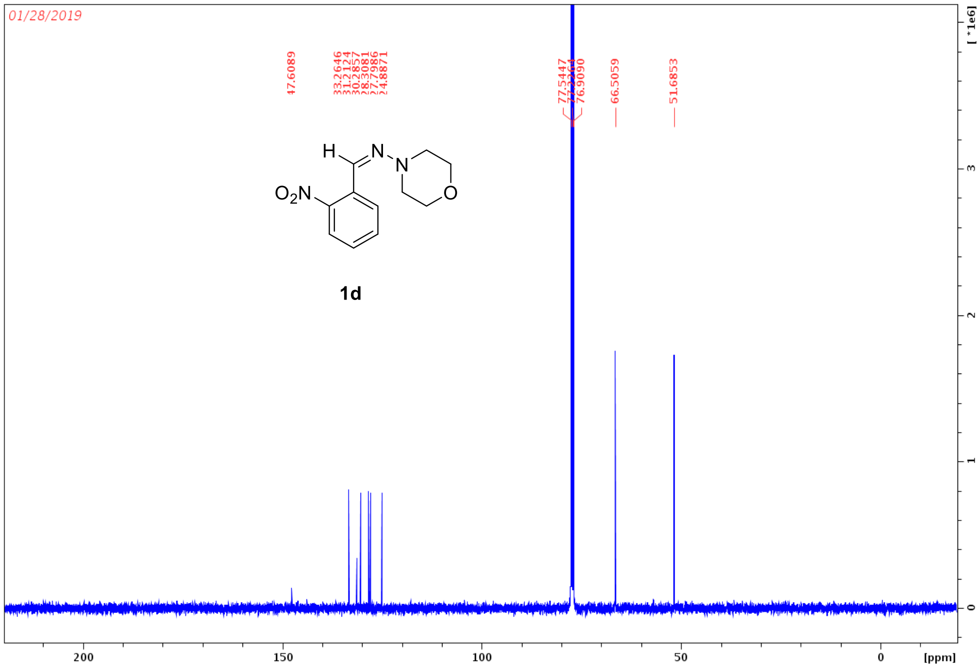
8.0938
8.0763
8.0737
8.0560
7.9489
7.9464
7.9283
7.9258
7.5674
7.5488
7.5297
7.2398
3.8862
3.8740
3.8615
3.2592
3.2467
3.2345
1.5307
1.0000
0.9616
1.0555
1.0559
4.1933
4.2617
H
N
N
O
O_2N
1d
8
6
4
2
[ppm]
[1e6]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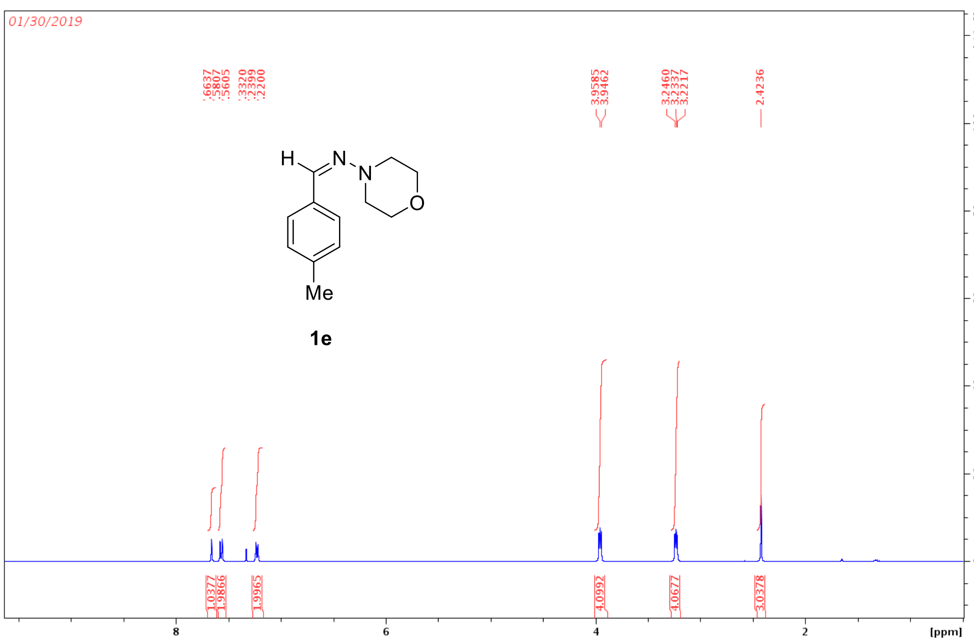
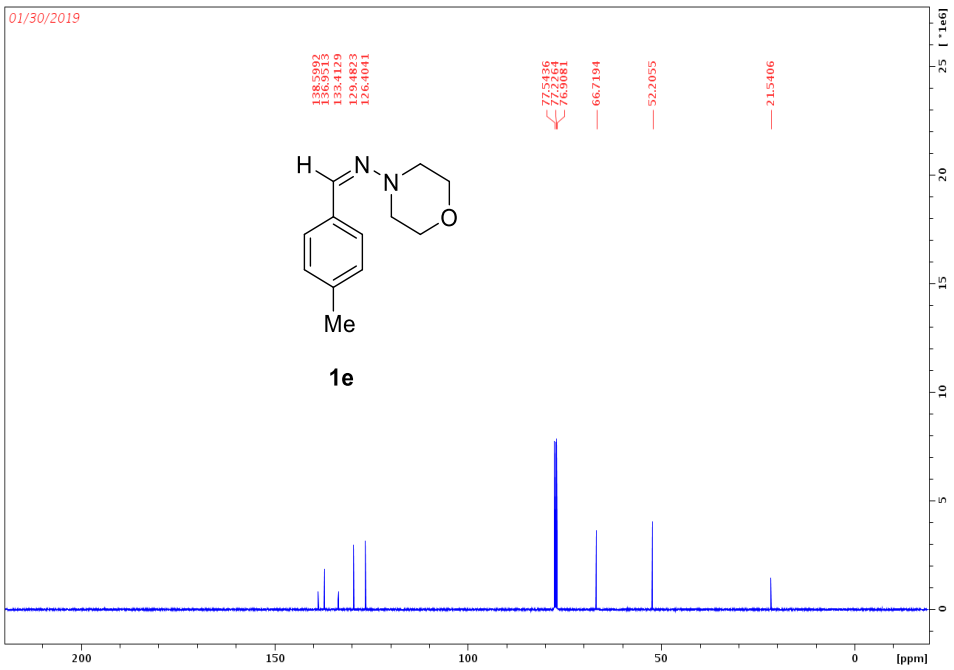
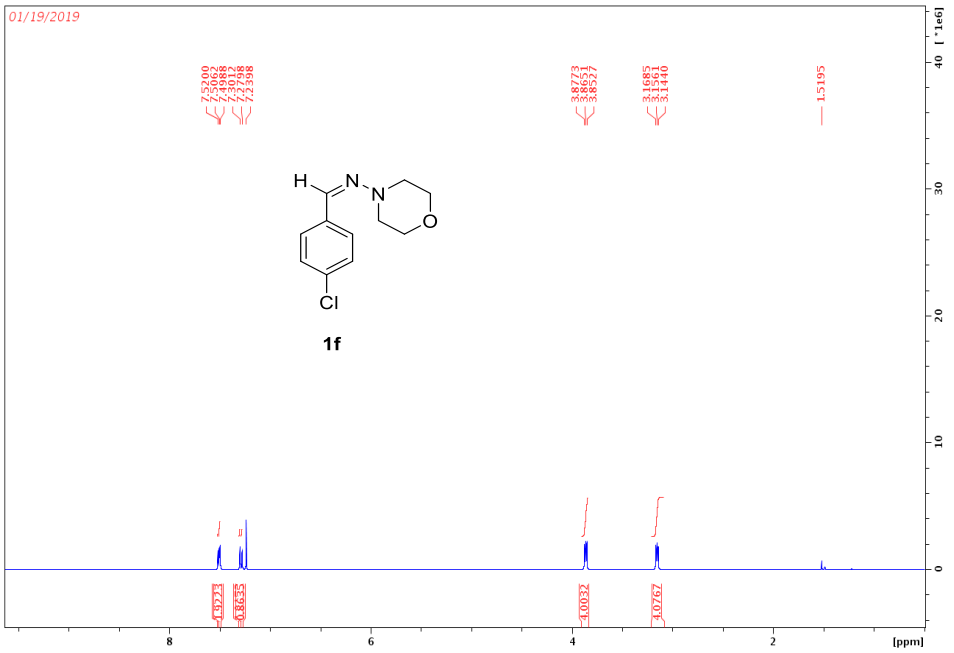
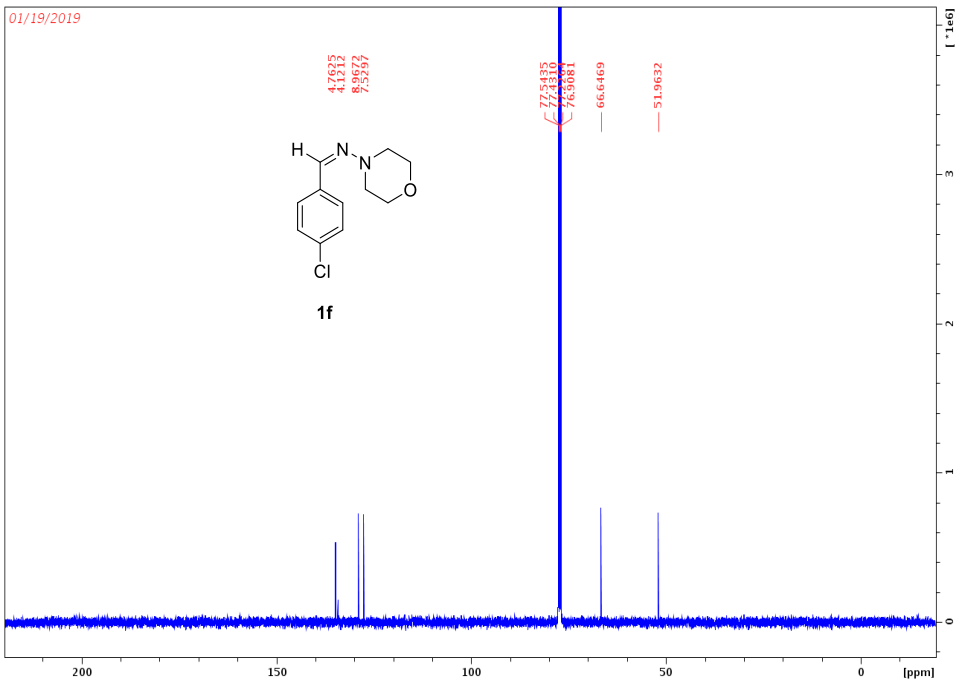
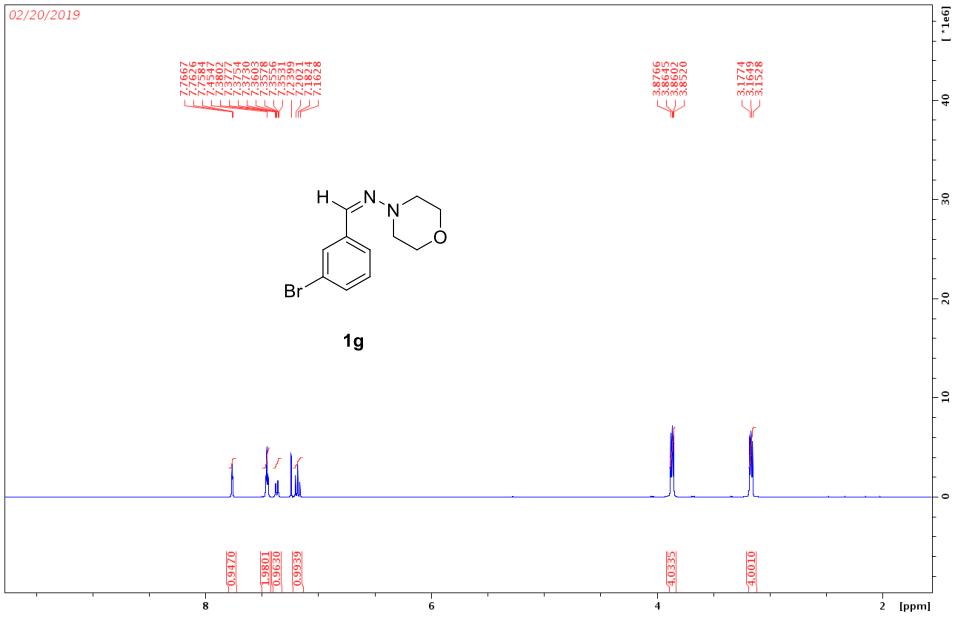
133.2646
131.2124
130.2857
128.3081
127.7986
124.8871
77.5447
76.9090
66.5059
51.6853
H
N
N
O
O2N
1d
200
150
100
50
0
[ppm]
[*1e6]


01/30/2019
3.9585
3.9462
3.2460
3.2217
2.4236
H
N
N
O
Me
1e
1.0377
1.9866
1.9965
4.0992
4.0677
3.0378
8
6
4
2
[ppm]
[*1e6]


01/30/2019
138.5992
136.9513
133.4129
129.4823
126.4041
77.5436
77.2264
76.9091
66.7194
52.2055
21.5406
H
N
N
O
Me
1e
200
150
100
50
0
[ppm]
[1e6]


01/19/2019
7.5200
7.5062
7.4968
7.4807
7.2708
7.2398
3.8773
3.8673
3.8527
3.1685
3.1541
3.1440
1.5195
H
N
N
O
Cl
1f
1.0223
0.8655
4.0032
3.0767
8
6
4
2
[ppm]
[1e6]


01/19/2019
47635
4.1712
8.9672
7.5297
77.5435
77.3310
77.1204
76.9081
66.6469
51.9632
H
N
N
O
Cl
1f
200
150
100
50
0
[ppm]
[*1e6]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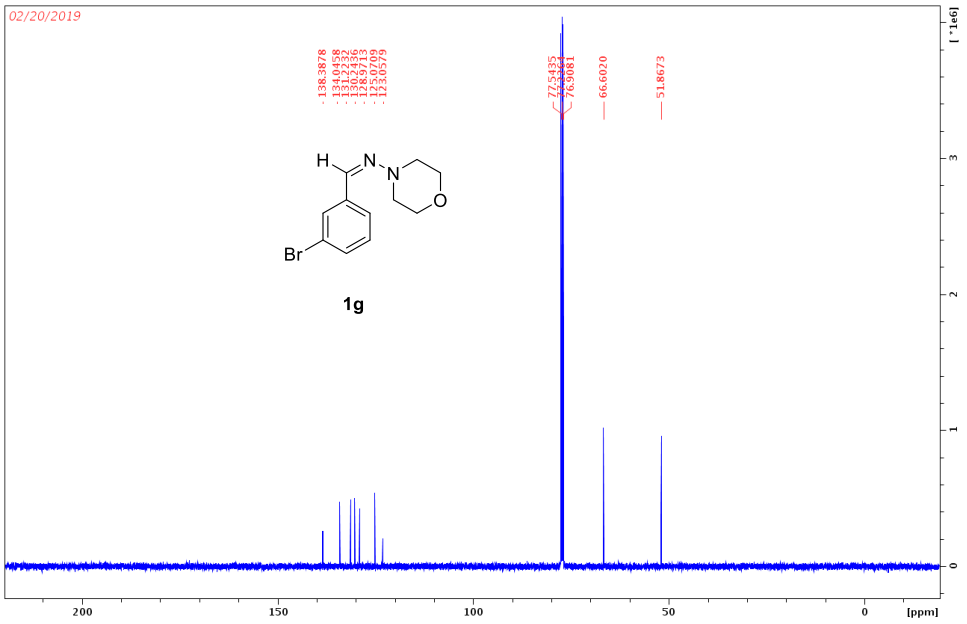
7.7616
7.7584
7.7547
7.4807
7.3977
7.3754
7.3720
7.3603
7.3576
7.3536
7.3531
7.2039
7.2021
7.1824
7.1628
3.8746
3.8675
3.8602
3.8520
3.1774
3.1649
3.1528
H
N
N
O
Br
1g
0.9470
1.9801
0.9630
0.9939
4.0335
4.0010
8
6
4
2
[ppm]
[*1e6]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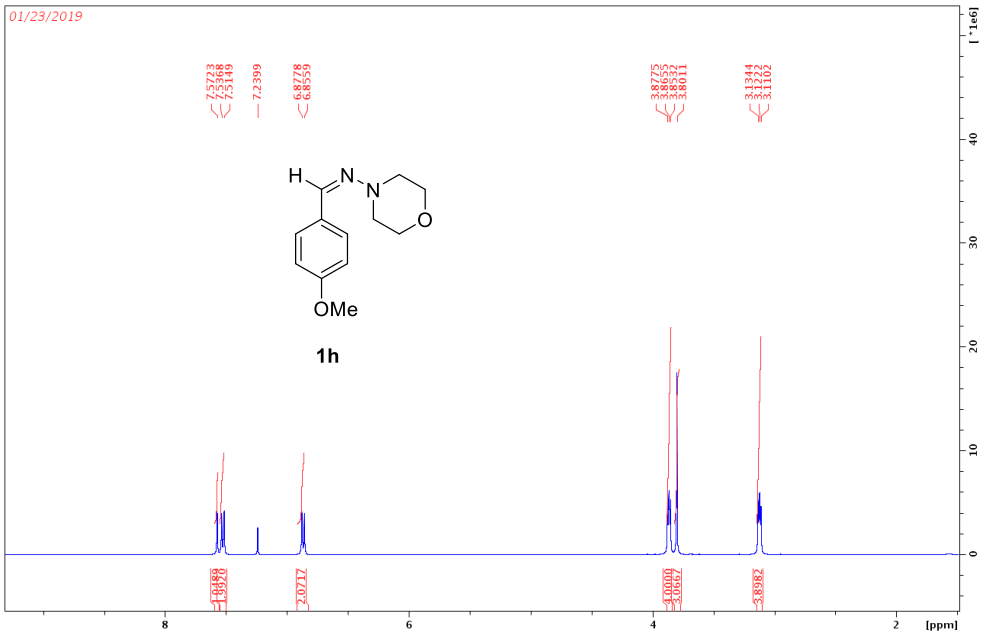
134.0458
131.7236
130.2436
128.9713
127.2709
123.0579
77.5435
77.2261
76.9081
66.6020
51.8673
H
N
N
O
Br
1g
200
150
100
50
0
[ppm]
[* 1e6]


01/23/2019
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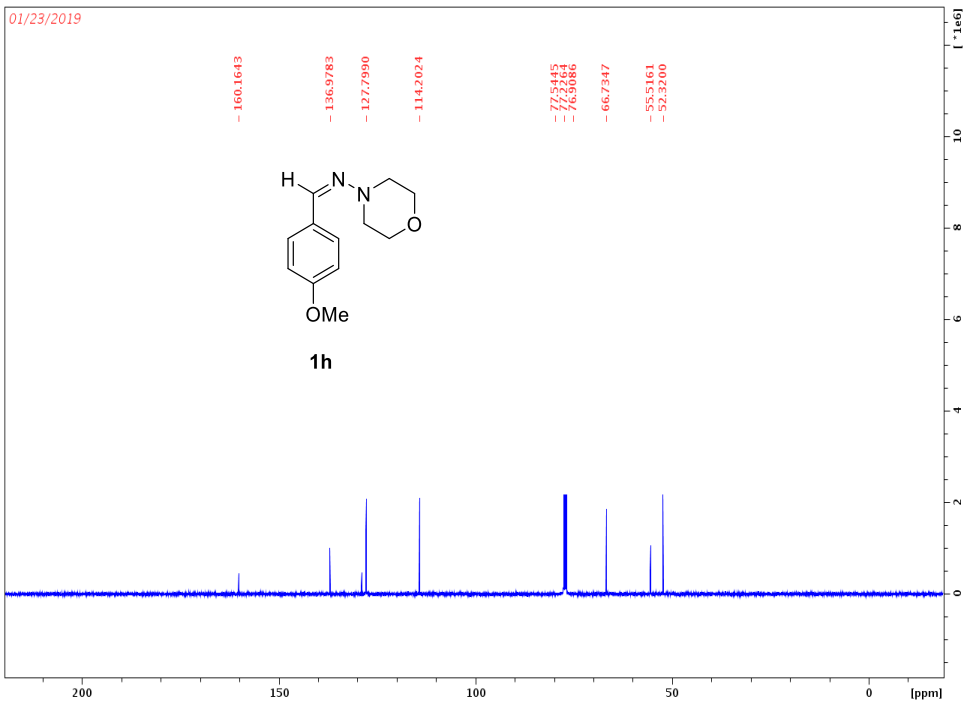
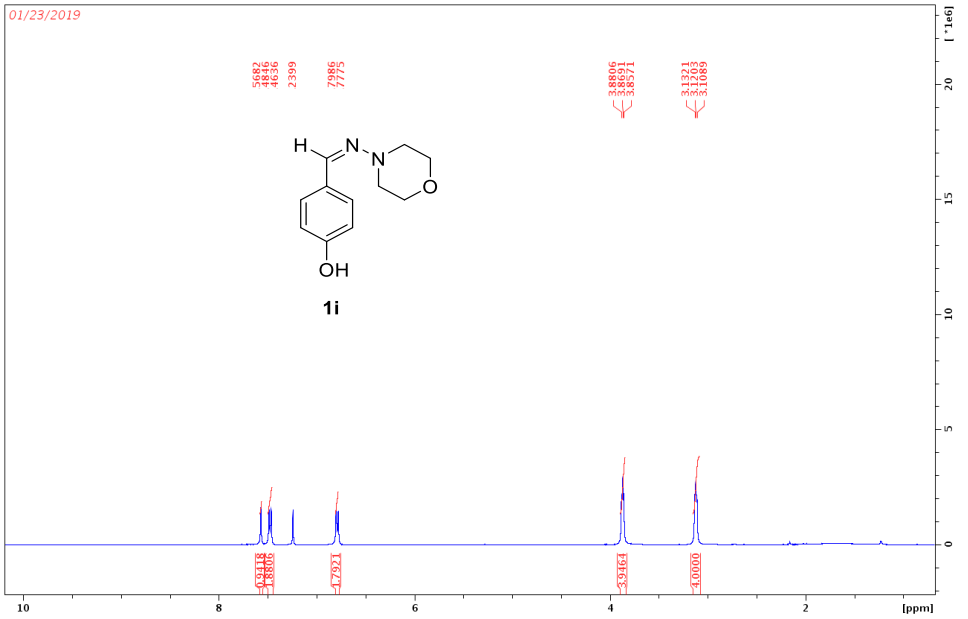
7.5488
7.5349
7.2399
6.8778
6.8559
3.8775
3.8675
3.8532
3.8011
3.1344
3.1222
3.1102
H
N
N
O
OMe
1h
1.0188
1.0000
1.9920
2.0717
4.0000
4.0067
3.8982
8
6
4
2
[ppm]
[* 1e6]


01/23/2019
160.1643
136.9783
127.7990
114.2024
77.5445
77.2264
76.9086
66.7347
55.5161
52.3200
H
N
N
O
OMe
1h
200
150
100
50
0
[ppm]
[*1e6]


01/23/2019
5682
4846
4636
2399
7986
7775
3.8806
3.8691
3.8571
3.1321
3.1203
3.1089
H
N
N
O
OH
1i
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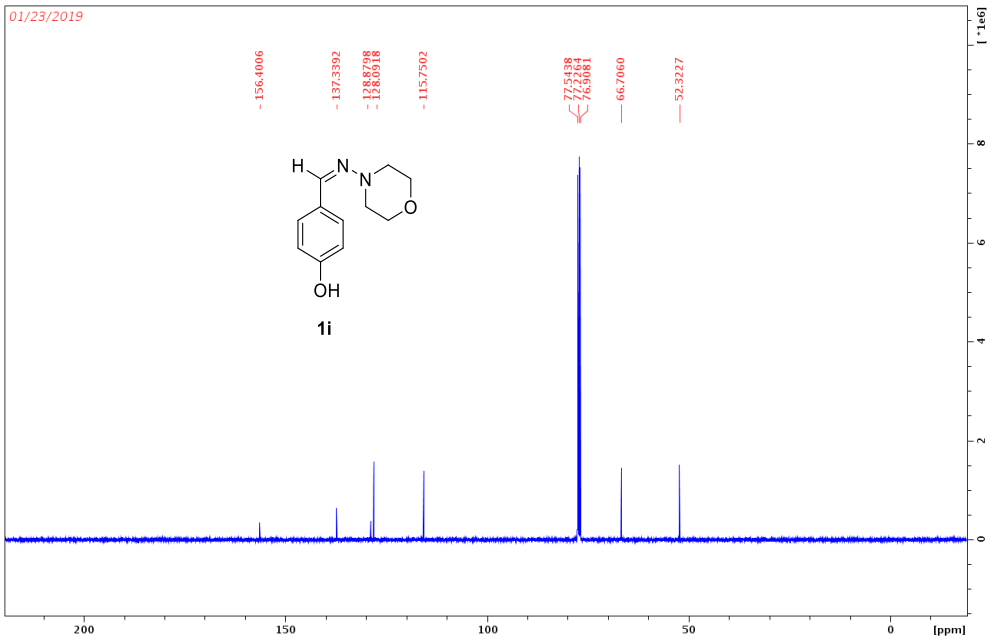
2.8806
1.7921
3.9464
4.0000
10
8
6
4
2
[ppm]
[*1e6]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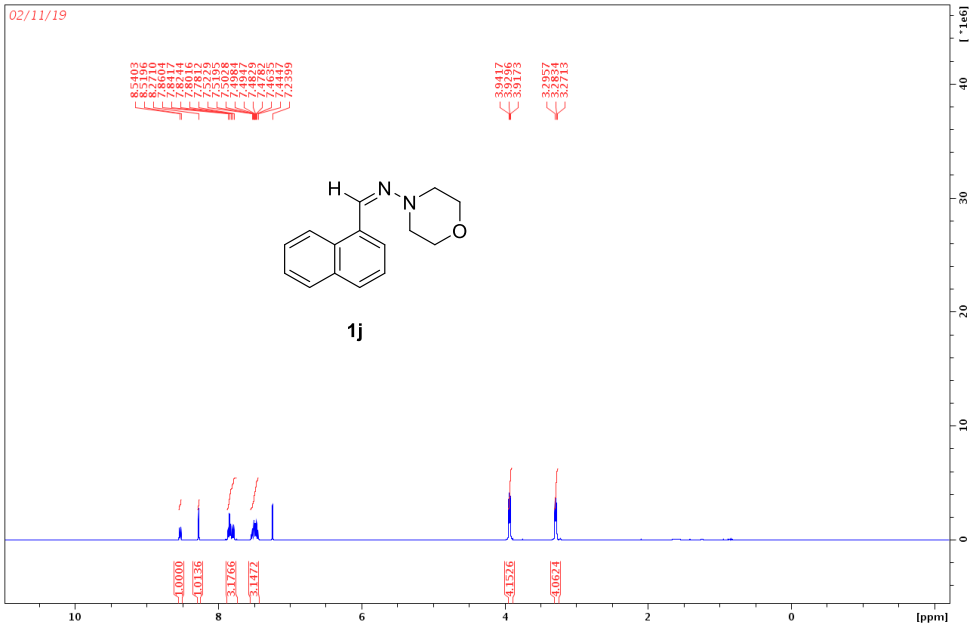
137.3392
128.8798
128.0918
115.7502
77.5438
77.2264
76.9081
66.7060
52.3227
H
N
N
O
OH
1i
[*1e6]
200
150
100
50
0
[ppm]


02/11/19
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8.5196
8.2710
8.2604
7.8417
7.8214
7.8016
7.7812
7.5319
7.5155
7.5058
7.4994
7.4829
7.4759
7.4655
7.4447
7.2399
3.9417
3.9266
3.9173
3.2957
3.2844
3.2713
H
N
N
O
1j
1.0000
1.0136
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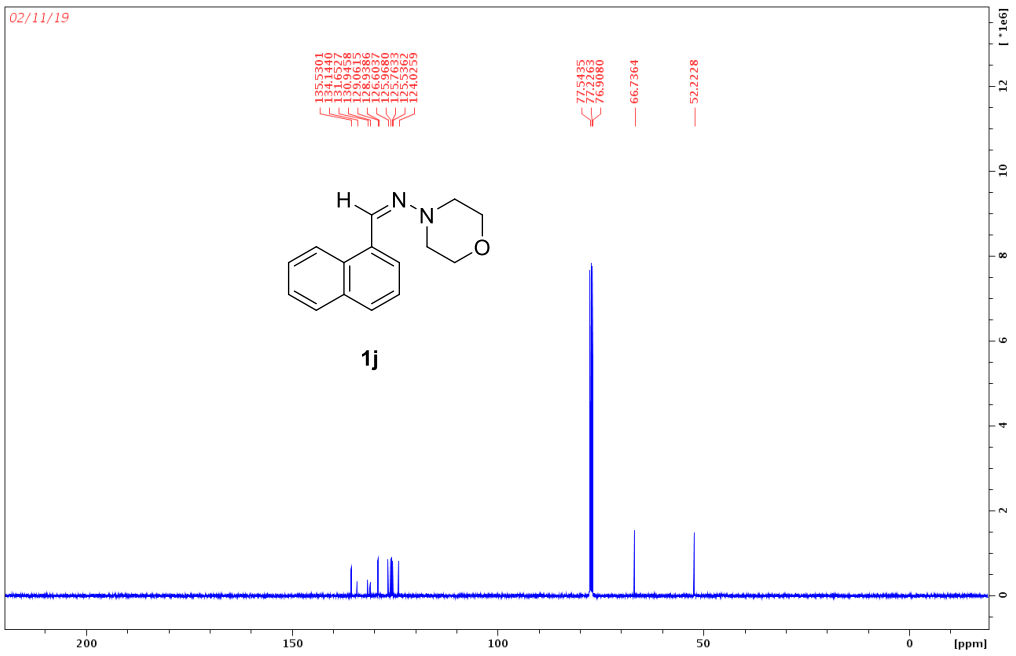
3.1472
4.1526
4.0624
[*1e6]
10
8
6
4
2
0
[ppm]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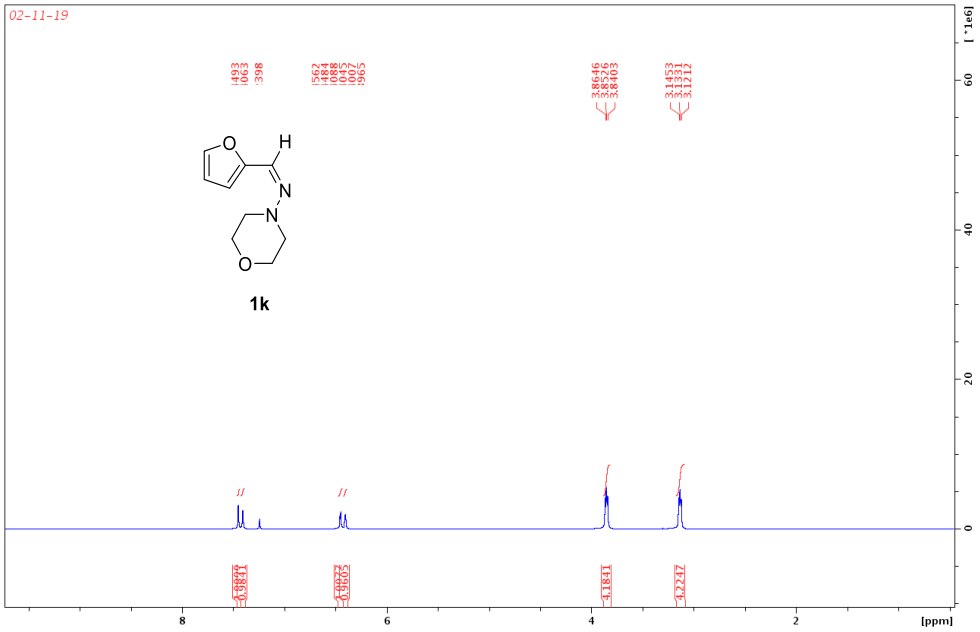
131.6527
130.0458
129.0115
128.9386
126.6037
125.7933
125.5362
124.0259
77.5435
77.2263
76.9080
66.7364
52.2228
H
N
N
O
1j
[*1e6]
200
150
100
50
0
[ppm]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7398
6562
6484
6088
6045
5007
4965
3.8646
3.8526
3.8403
3.1453
3.1331
3.1212
O
H
N
N
O
1k
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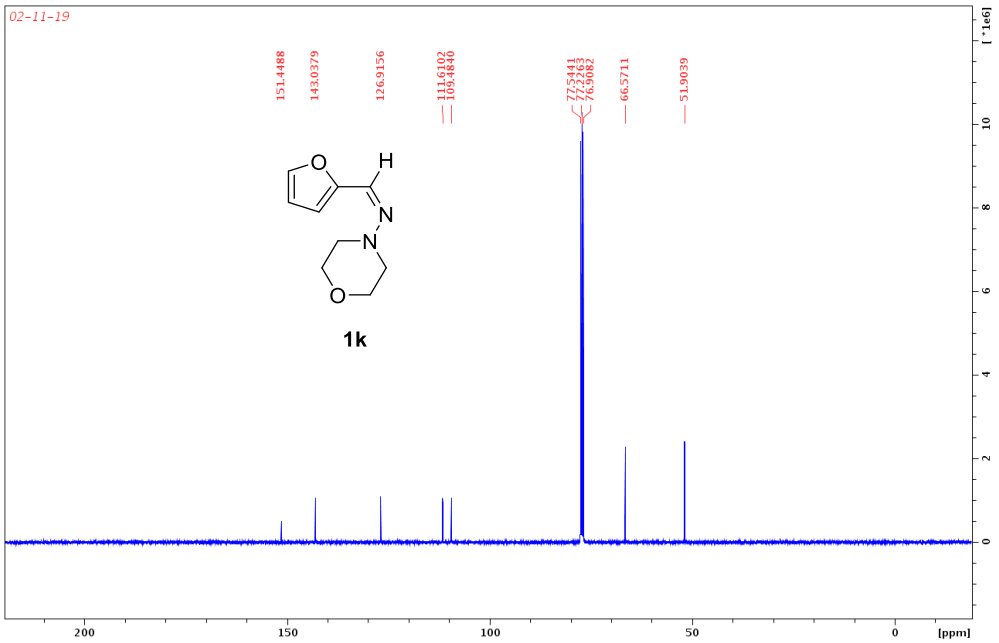
4.2247
8
6
4
2
[ppm]


02-11-19
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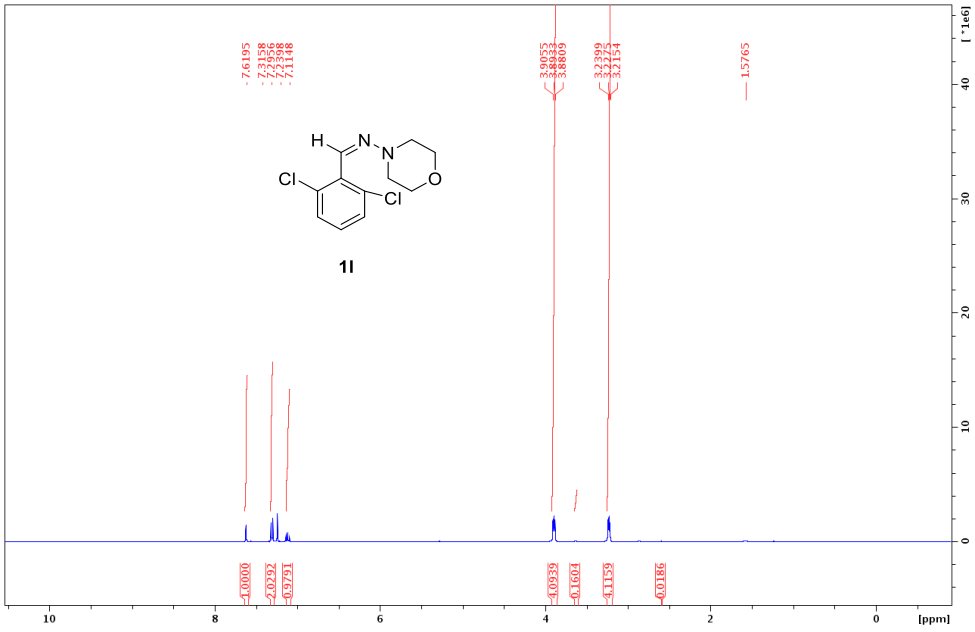
143.0379
126.9156
111.6102
109.4840
77.3441
77.2343
77.1245
76.9082
66.5711
51.9039
1k
[*1e6]
[ppm]


7.6195
7.3158
7.2956
7.2398
7.1148
3.9055
3.8883
3.8809
3.2289
3.2279
3.2154
1.5765
1l
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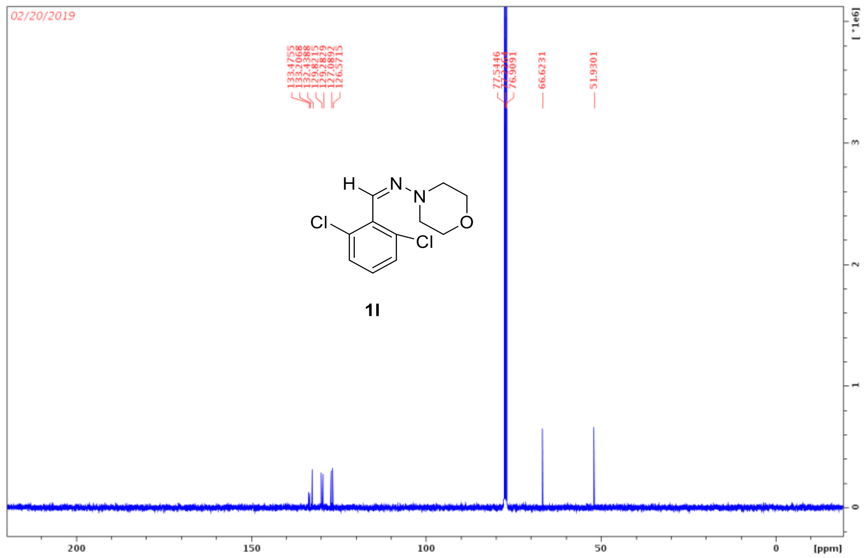
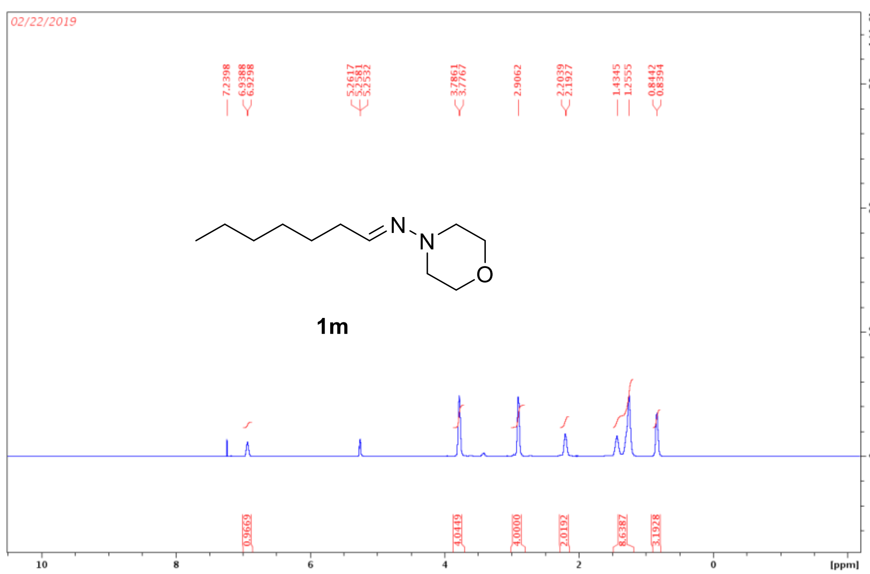
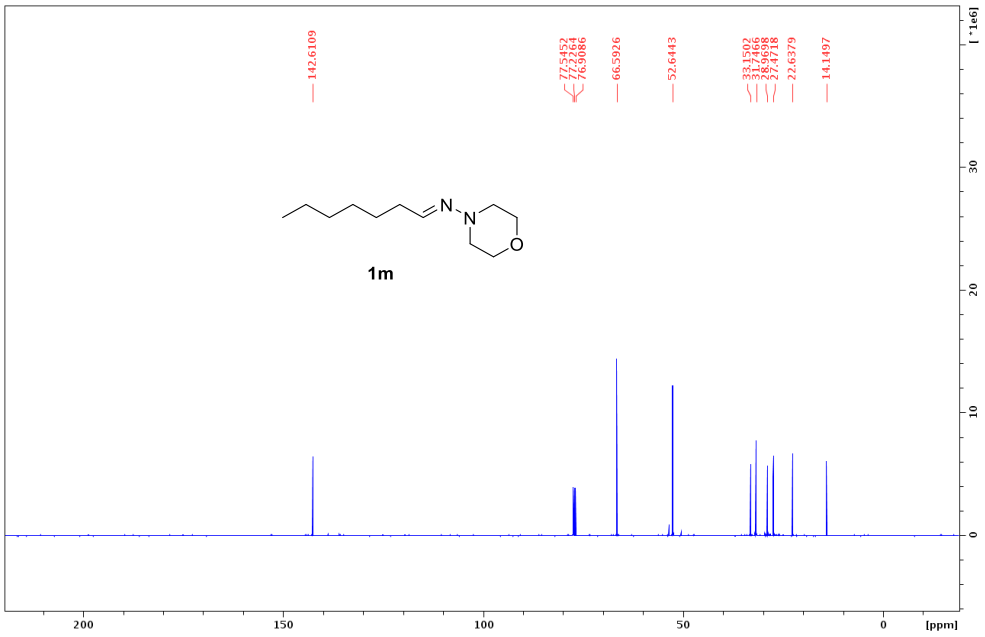
2.0292
0.3791
4.0939
0.1604
4.1159
0.0186
[*1e6]
[ppm]



1l



1m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77.5452
77.3264
76.9086
66.5926
52.6443
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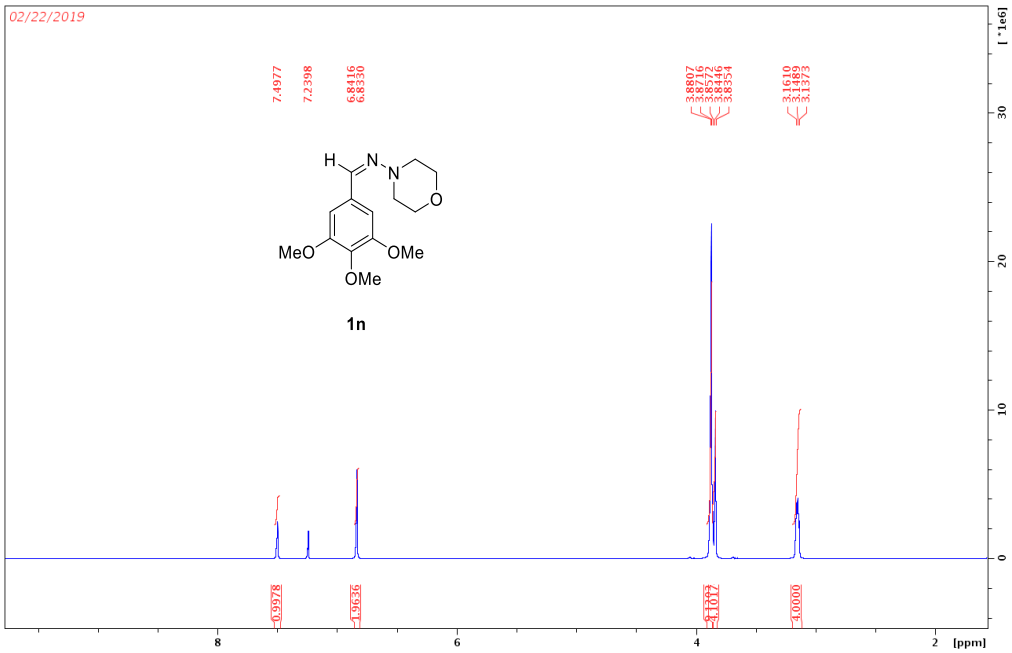
1m
200
150
100
50
0
[ppm]


02/22/2019
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6.8350
3.8807
3.8716
3.8577
3.8446
3.8354
3.1610
3.1489
3.1373
MeO
OMe
OMe
1n
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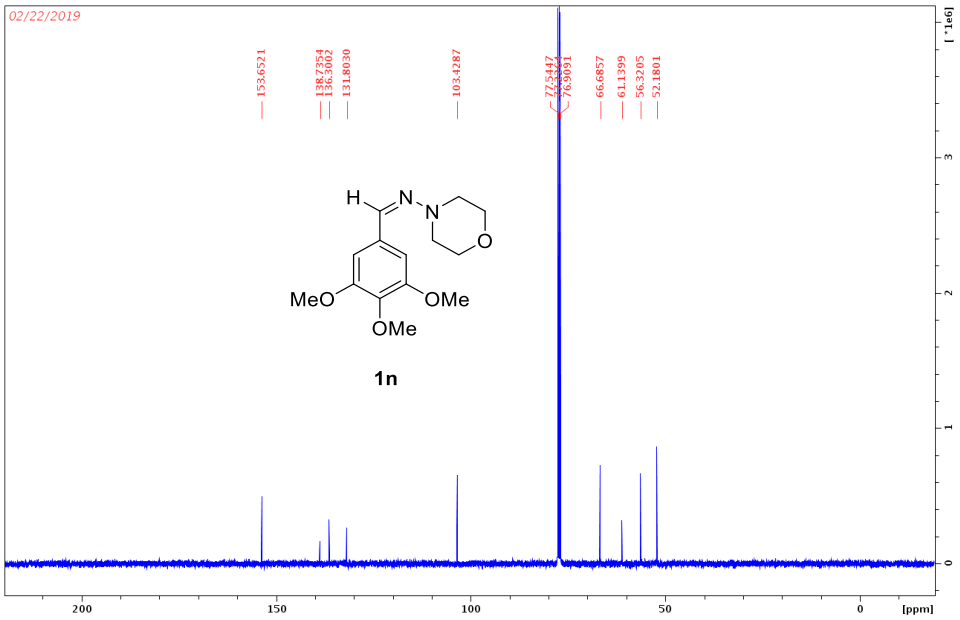
3.1017
4.0000
8
6
4
2
[ppm]


02/22/2019
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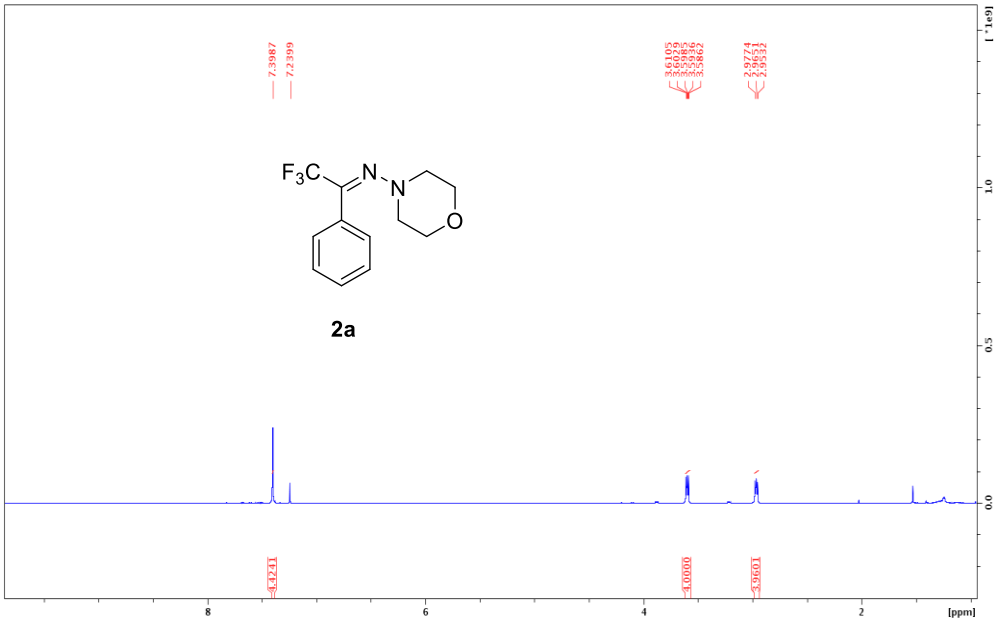
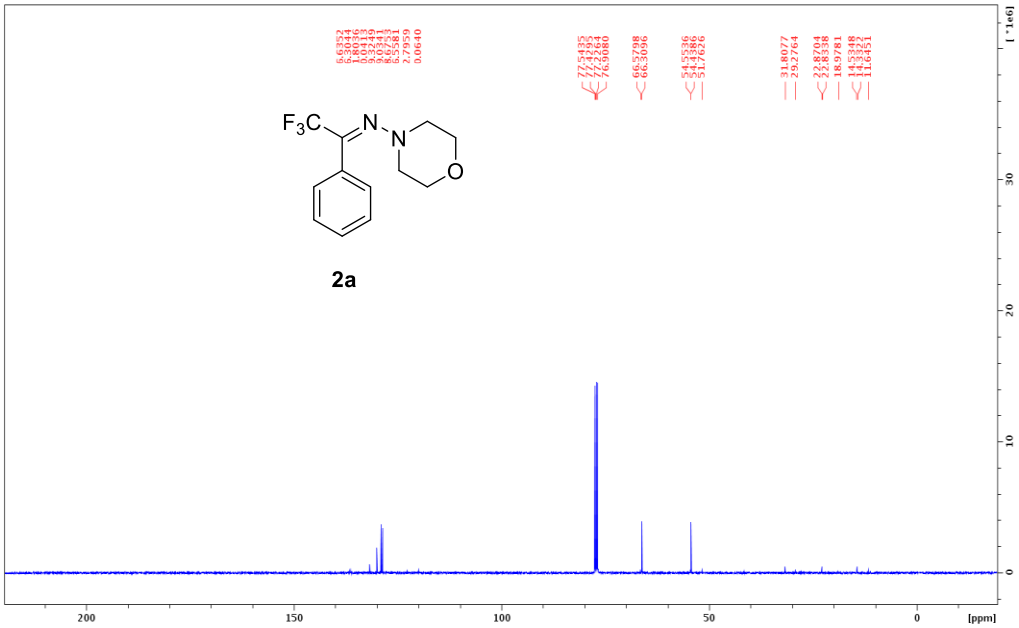
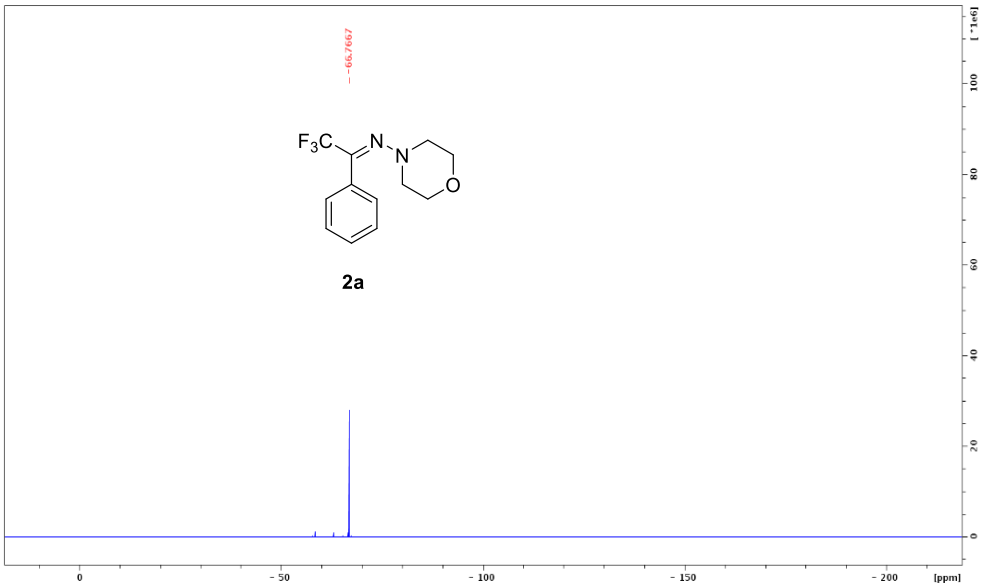
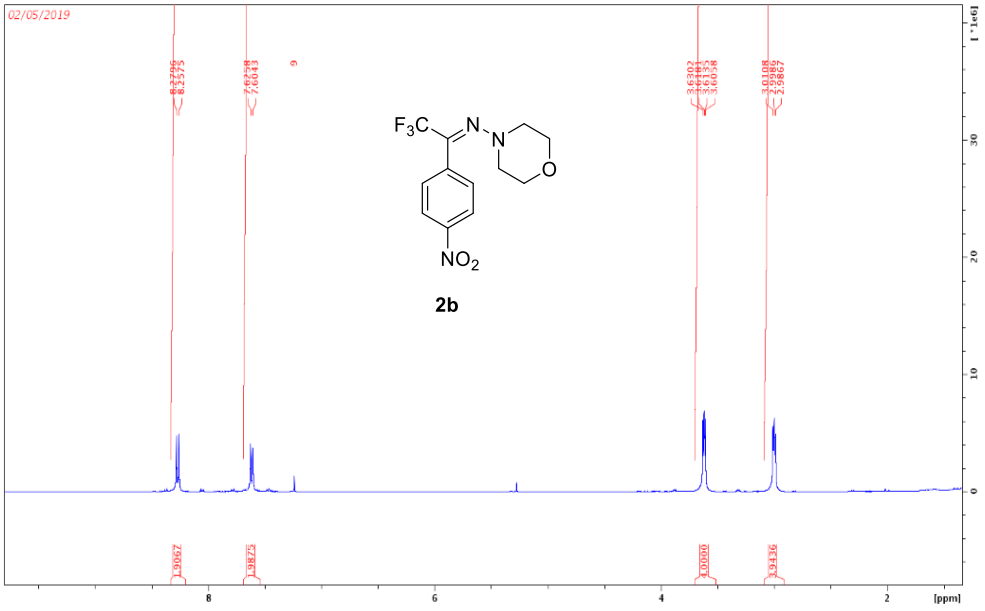
138.7554
136.3602
131.8030
103.4287
77.5447
77.2281
76.9051
66.6857
61.1399
56.3205
52.1801
H
N
N
O
MeO
OMe
OMe
1n
200
150
100
50
0
[ppm]
[e1]

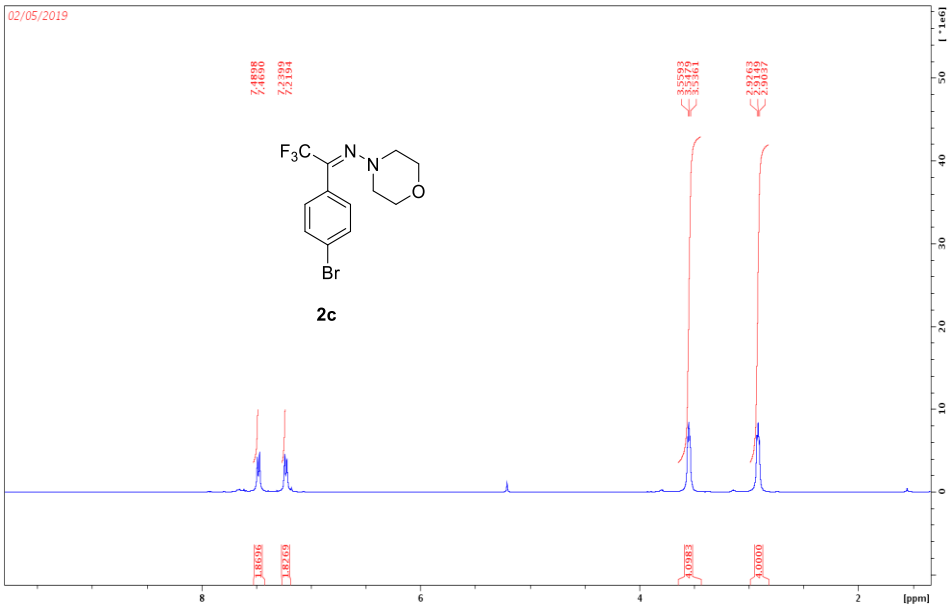
2. NMR DATA OF α- TRIFLUOROMETHYLATED IMINES

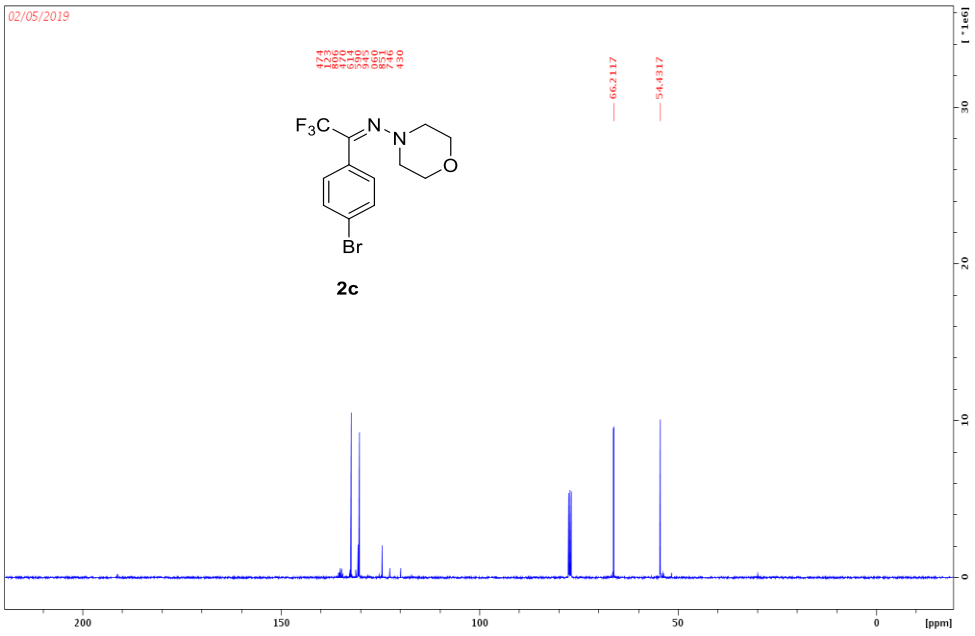


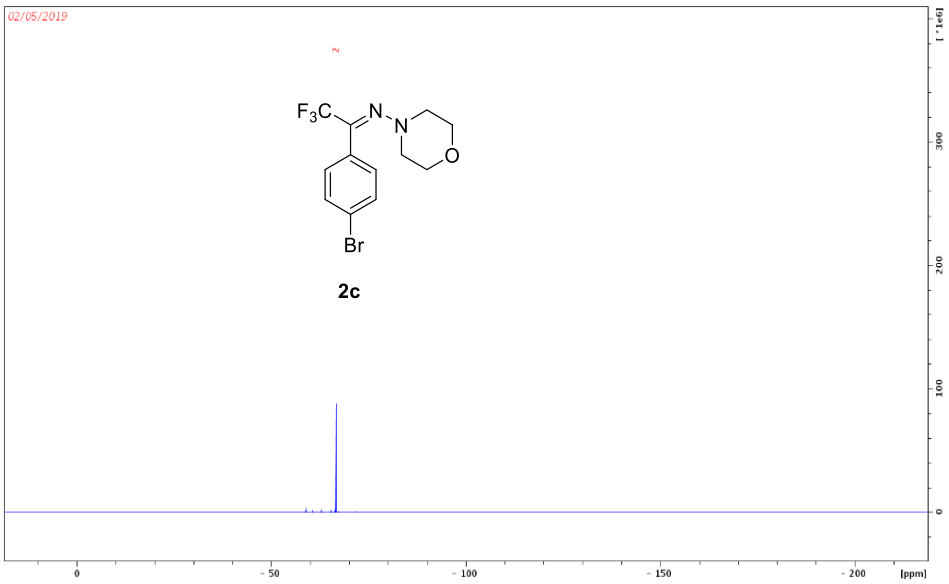



-66.7667
F3C
N
N
O
2a
[1e6]
100
80
60
40
20
0
0
-50
-100
-150
-200
[ppm]

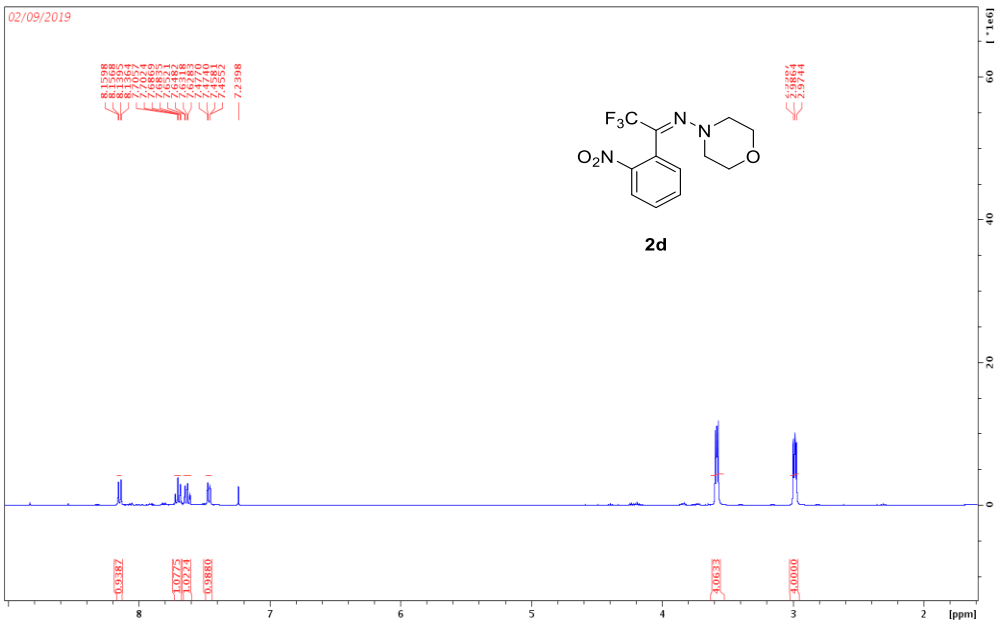

02/05/2019
8.2796
8.2575
7.6258
7.6043
3.6302
3.6181
3.6059
3.6038
3.0108
2.9986
2.9867
F3C
N
N
O
NO2
2b
1.0967
1.3875
3.0000
3.3436
[1e6]
30
20
10
0
8
6
4
2
[ppm]


02/05/2019
7.4898
7.4690
7.2399
7.2194
3.5593
3.5479
3.5361
2.9763
2.9449
2.9037
F3C
N
N
O
Br
2c
1.8696
1.8269
3.0983
3.0000
8
6
4
2
[ppm]
[*1e6]

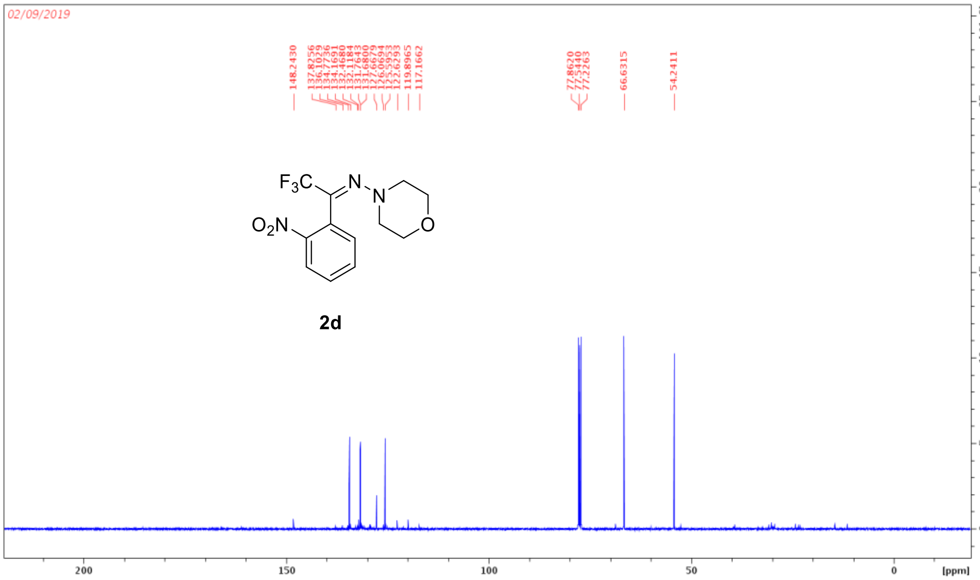

02/05/2019
66.2117
54.4317
F3C
N
N
O
Br
2c
200
150
100
50
0
[ppm]
[*1e6]

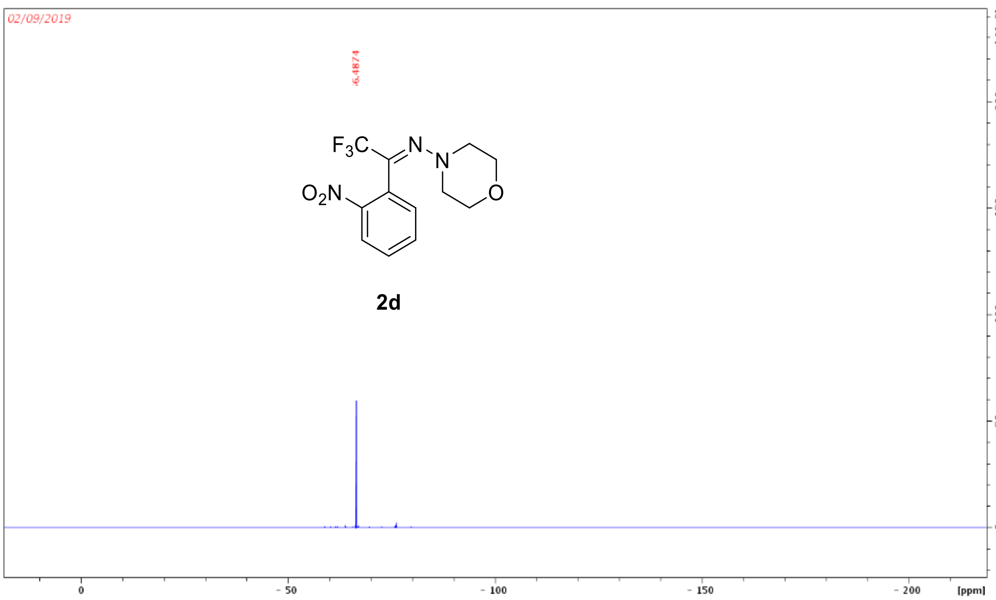

02/05/2019
F3C
N
N
O
Br
[1e6]
300
200
100
0
0
- 50
- 100
- 150
- 200
[ppm]

2c


02/09/2019
8.1598
8.1568
8.1395
8.1364
7.7074
7.7027
7.6889
7.6859
7.6521
7.6491
7.6318
7.6288
7.4770
7.4740
7.4581
7.4552
7.2398
5.4867
5.4814
5.3944
5.3914
F3C
N
N
O2N
O
[1e6]
60
40
20
0
0.9387
1.0775
1.0224
0.9880
3.0633
3.0000
8
7
6
5
4
3
2
[ppm]

2d


02/09/2019
148.2430
137.8256
136.1029
134.1736
134.1691
132.4680
132.1184
131.7643
131.6840
127.6679
126.0664
125.5953
122.6293
119.8965
117.1662
77.8620
77.5440
77.2263
66.6315
54.2411
F3C
N
N
O
O2N
2d
[ppm]
[*1e6]


02/09/2019
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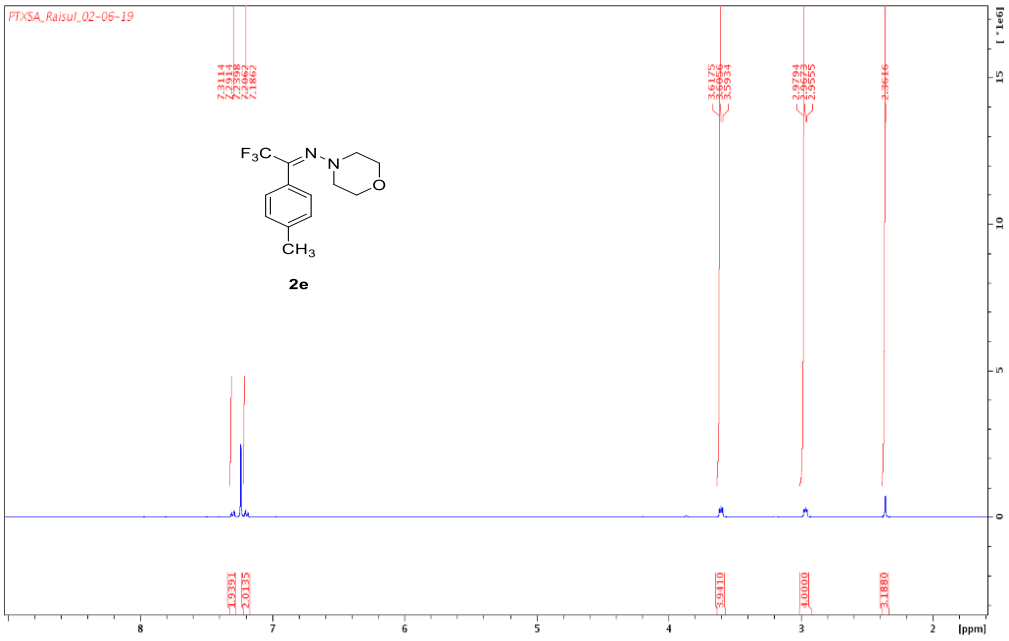
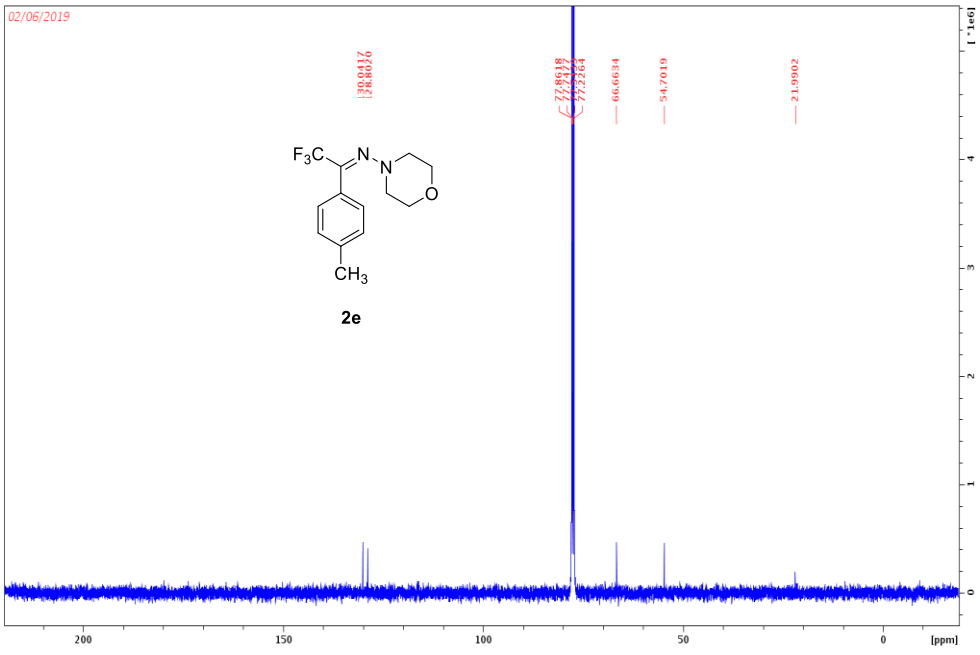
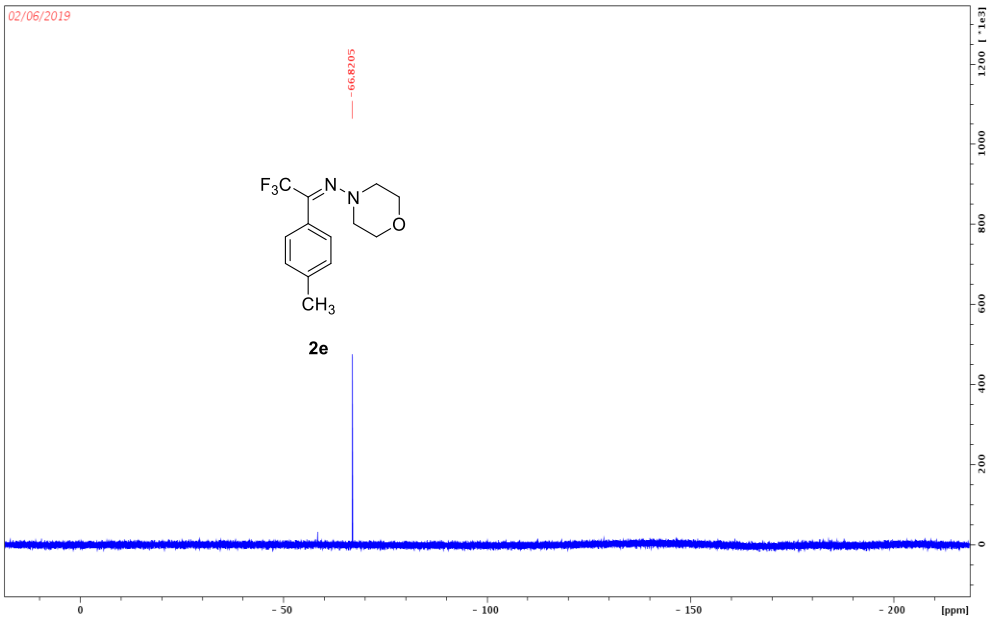
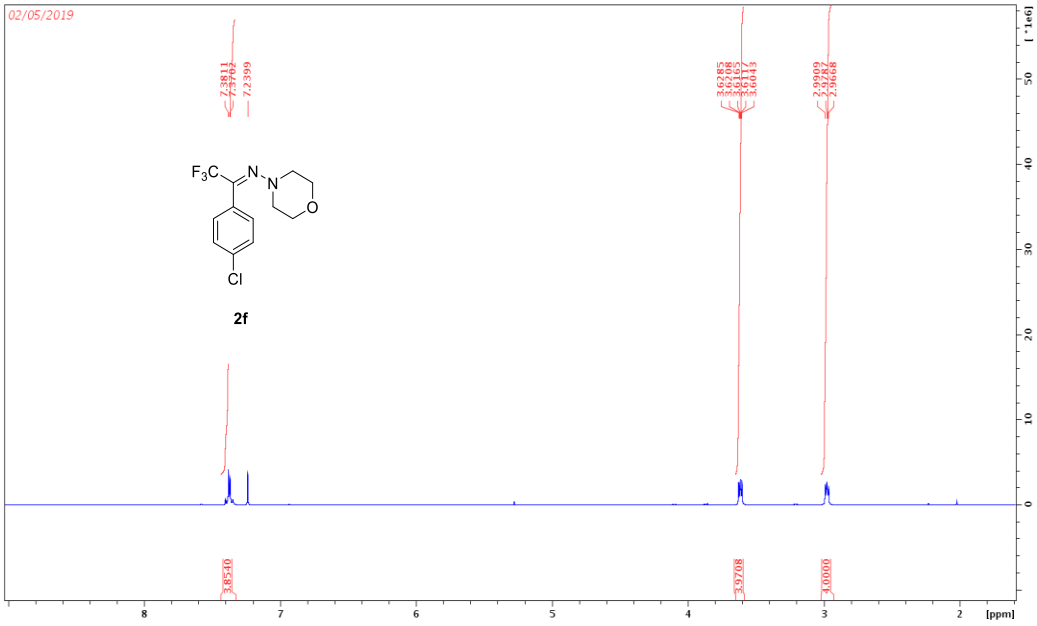
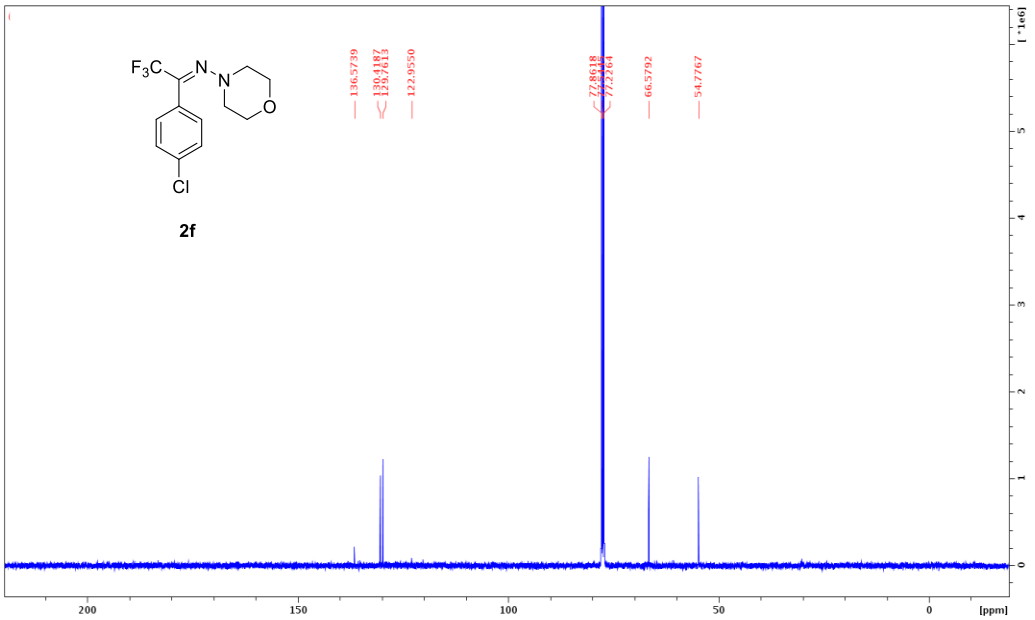
N
O
O2N
2d
[ppm]
[*1e6]

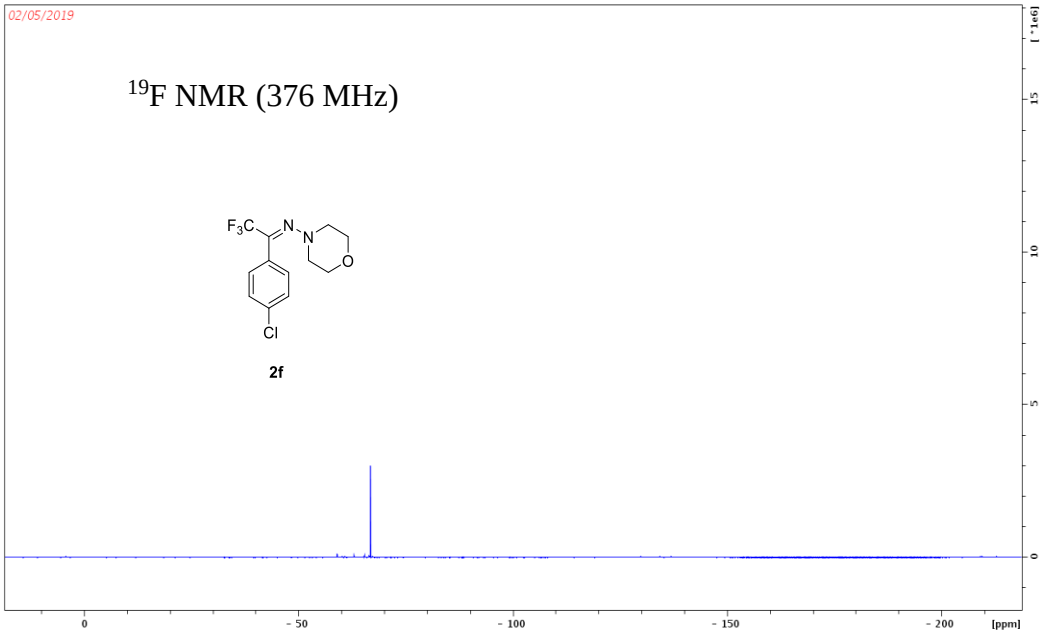

PTXSA_Raisul_02-06-19
F3C
N
N
O
CH3
2e
[*1e6]
[ppm]

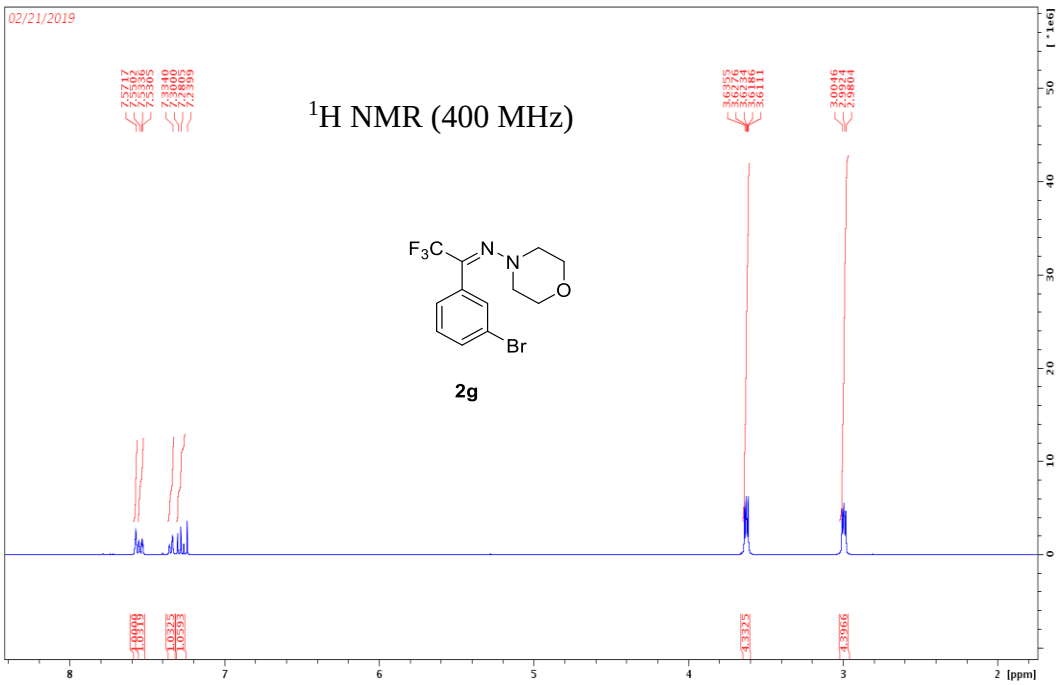

02/06/2019
F3C
N
N
O
CH3
2e
66.6634
54.7019
21.9902
[*1e6]
[ppm]

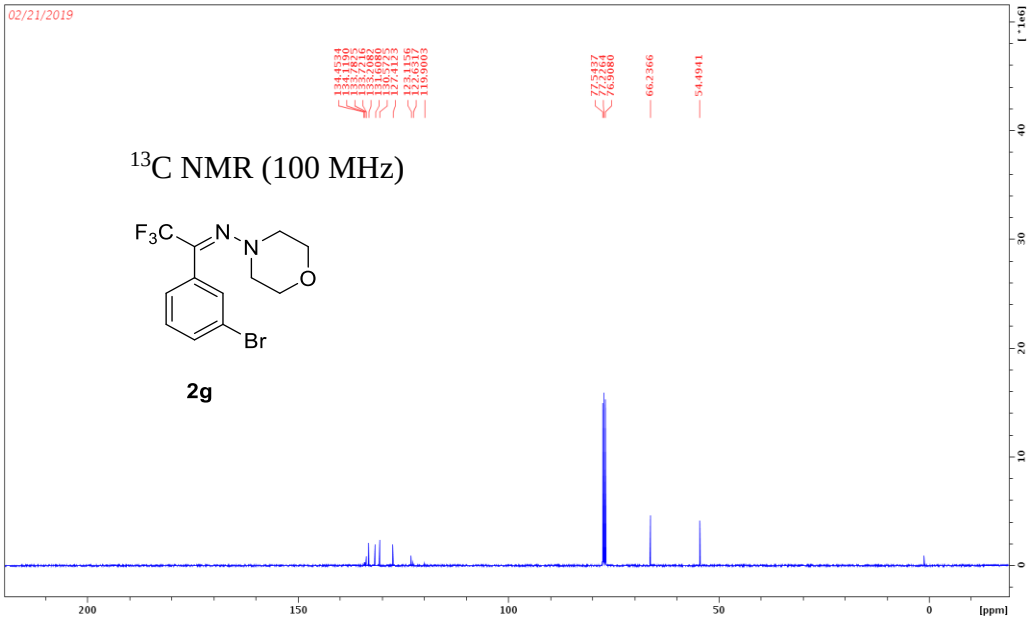

02/06/2019
-66.8205
F3C
N
N
O
CH3
2e
1200 [*1e3]
1000
800
600
400
200
0
0
-50
-100
-150
-200
[ppm]

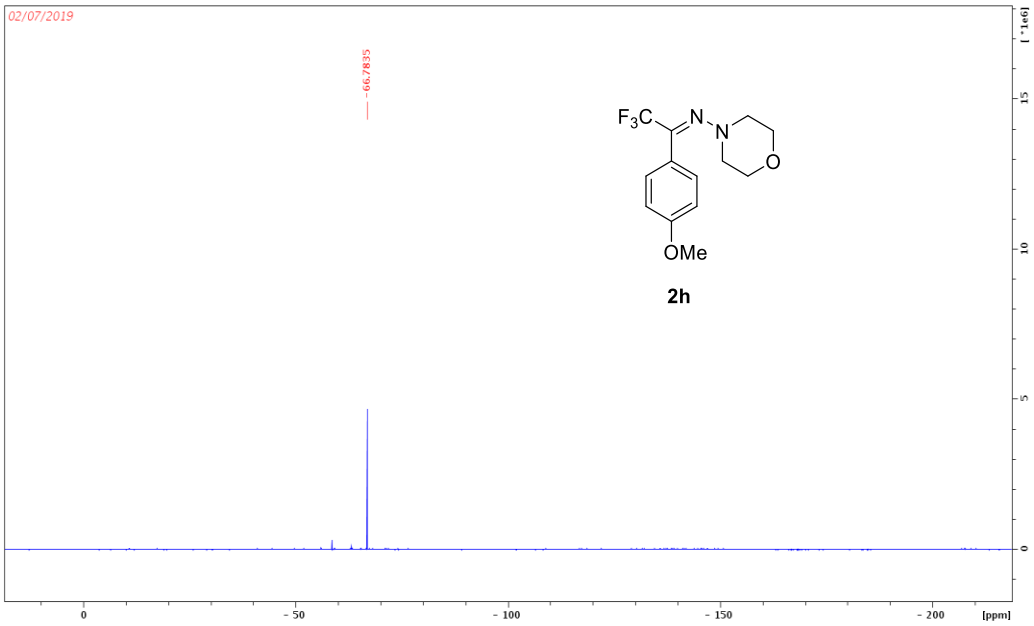

02/05/2019
7.3811
7.3908
7.3999
3.6285
3.6208
3.6115
3.6117
3.6043
2.9909
2.9787
2.9668
F3C
N
N
O
Cl
2f
3.8540
3.9708
4.0000
[*1e6]
50
40
30
20
10
0
8
7
6
5
4
3
2
[ppm]

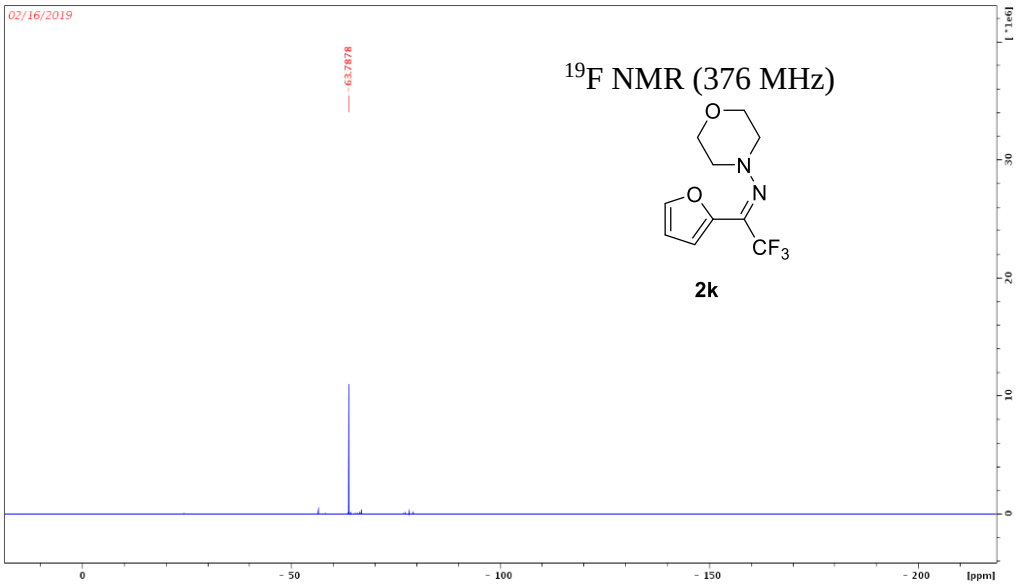

F3C
N
N
O
Cl
2f
136.5739
130.4187
129.0113
122.9550
77.8618
77.2264
66.5792
54.7767
[* 1e6]
200
150
100
50
0
[ppm]

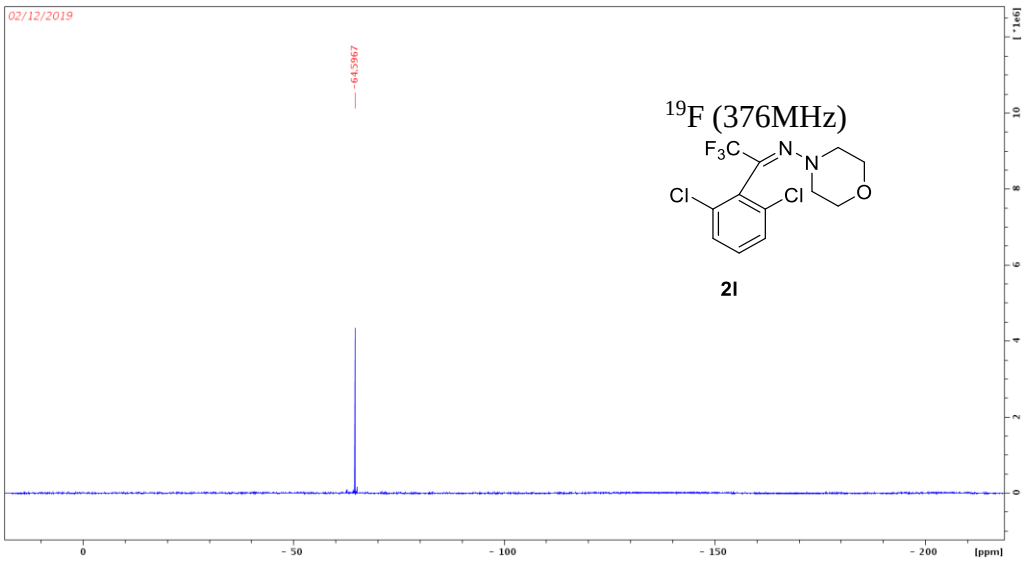

02/05/2019
19F NMR (376 MHz)
F3C
N
N
O
Cl
2f
[* 1e6]
0
- 50
- 100
- 150
- 200
[ppm]

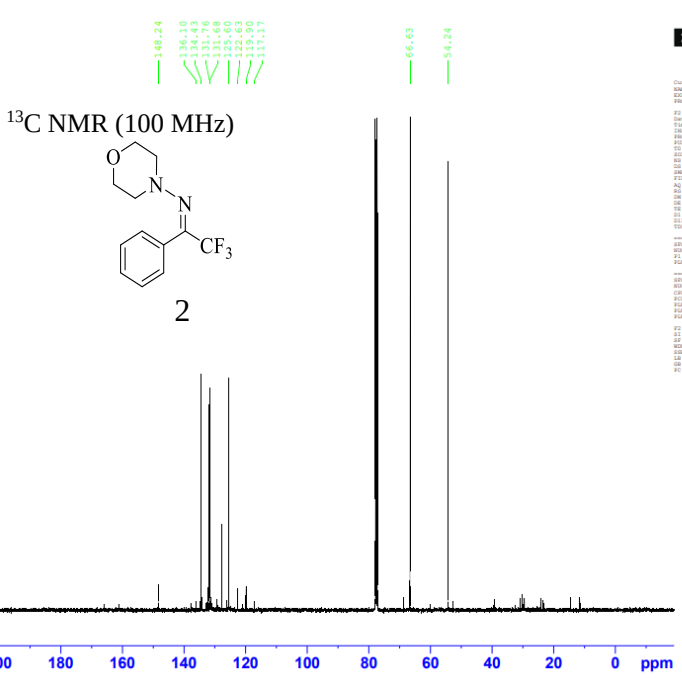

02/21/2019
^{1}H NMR (400 MHz)
F_3C
N
N
O
Br
2g
[* 1e6]
[ppm]

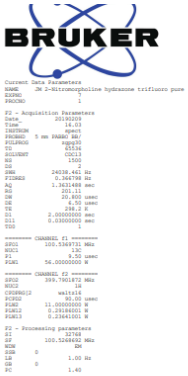

02/21/2019
^{13}C NMR (100 MHz)
F_3C
N
N
O
Br
2g
[* 1e6]
[ppm]


02/07/2019
-66.7835
F3C
N
N
O
OMe
2h
[1e6]
15
10
5
0
0
- 50
- 100
- 150
- 200
[ppm]

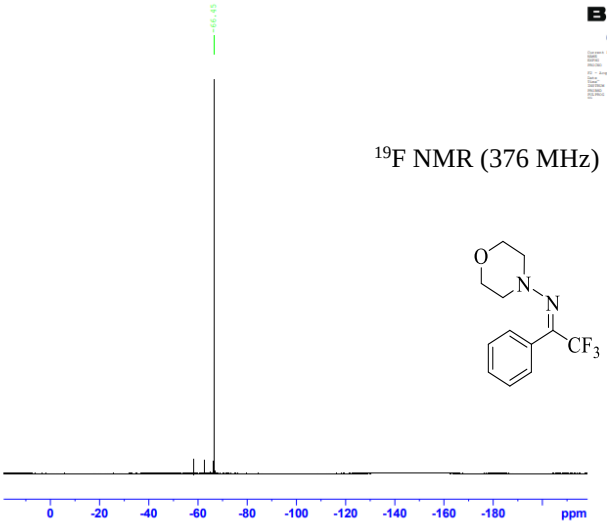

02/16/2019
-63.7878
19F NMR (376 MHz)
O
N
N
O
CF3
2k
[1e6]
30
20
10
0
0
- 50
- 100
- 150
- 200
[ppm]


02/12/2019
-64.5967
^{19}F (376MHz)
F_3C
N
N
Cl
Cl
O
2l
0
- 50
- 100
- 150
- 200
[ppm]

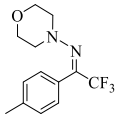

148.24
136.10
134.43
131.76
131.68
125.60
122.63
119.90
117.17
66.63
54.24
^{13}C NMR (100 MHz)
O
N
N
CF_3
2
200
180
160
140
120
100
80
60
40
20
0
ppm


BRUKER

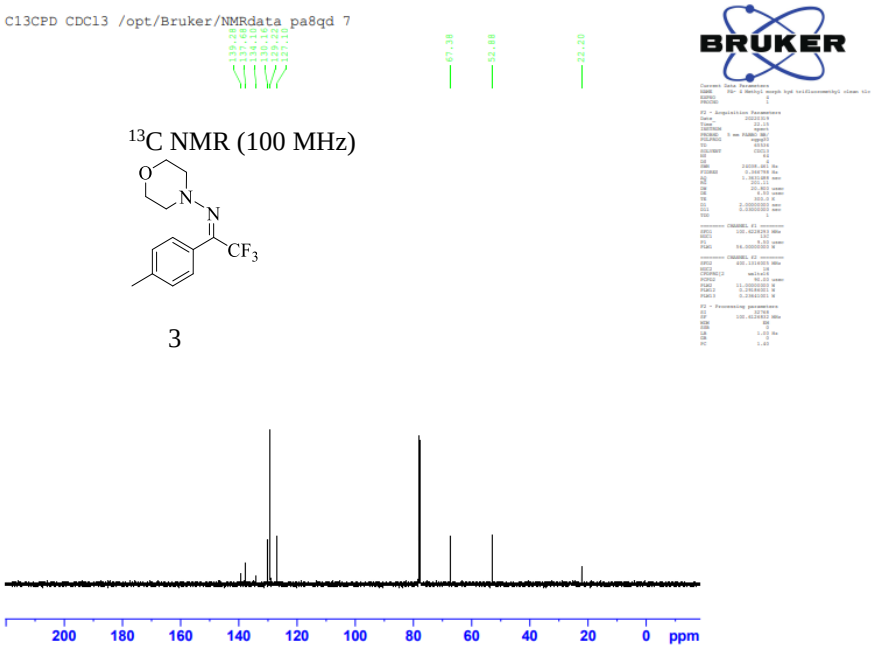
^{19}F NMR (376 MHz)

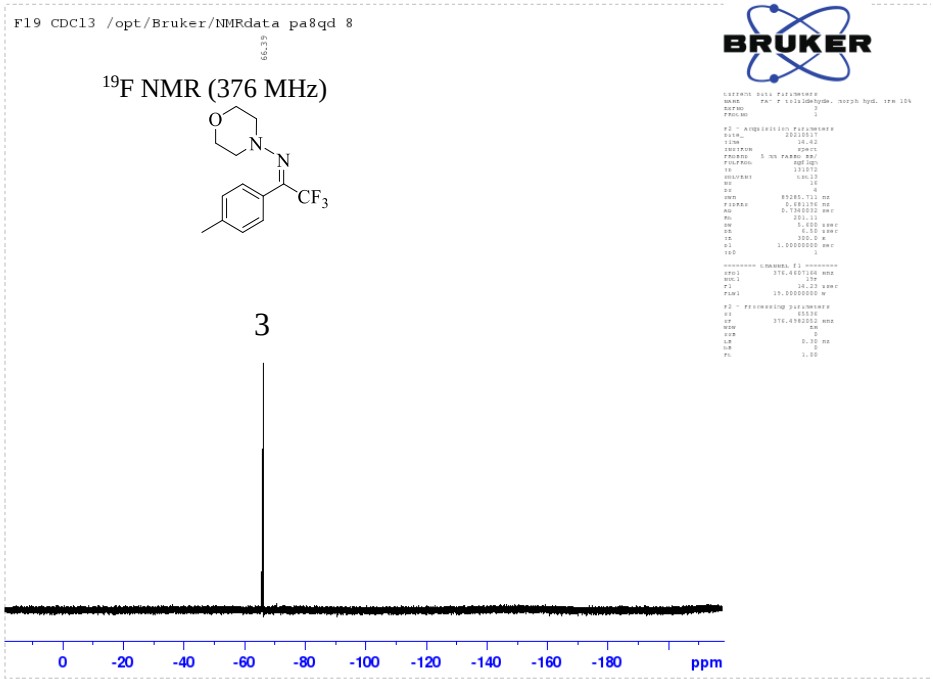


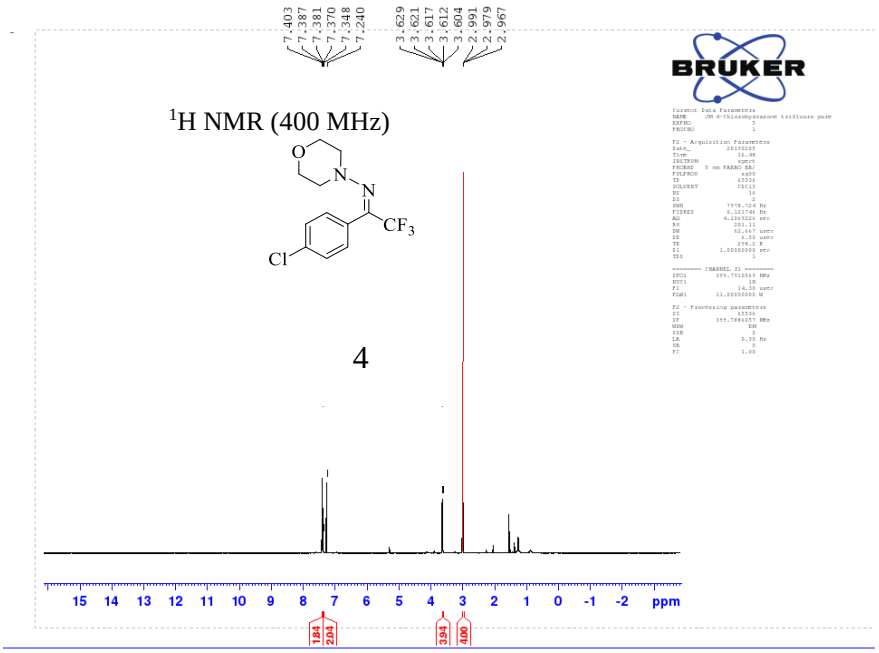
^{1}H NMR (400 MHz)

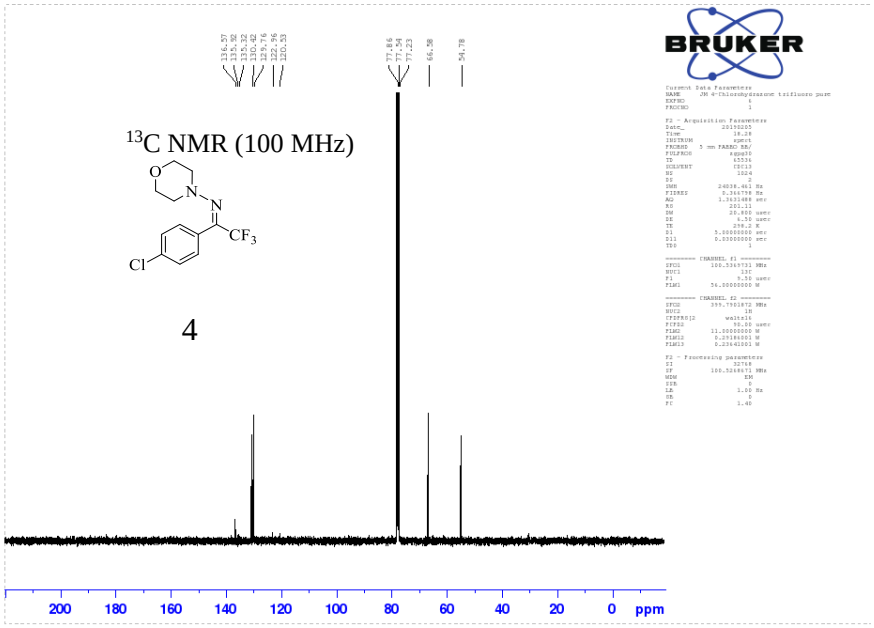


3

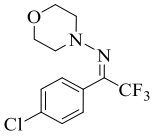

C13CPD CDCl3 /opt/Bruker/NMRdata pa8qd 7
BRUKER
^{13}C NMR (100 MHz)
3
200 180 160 140 120 100 80 60 40 20 0 ppm


F19 CDCl3 /opt/Bruker/NMRdata pa8qd 8
BRUKER
^{19}F NMR (376 MHz)
3
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm


7.403
7.387
7.381
7.370
7.348
7.240
3.629
3.621
3.617
3.612
3.604
2.991
2.979
2.967
BRUKER
^{1}H NMR (400 MHz)
4
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.83
2.04
3.94
4.00

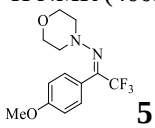

136.57
135.92
135.32
130.42
129.56
122.96
120.53
77.86
77.54
77.23
66.58
54.78
BRUKER
^{13}C NMR (100 MHz)
4
200 180 160 140 120 100 80 60 40 20 0 ppm

^{19}F NMR (376 MHz)

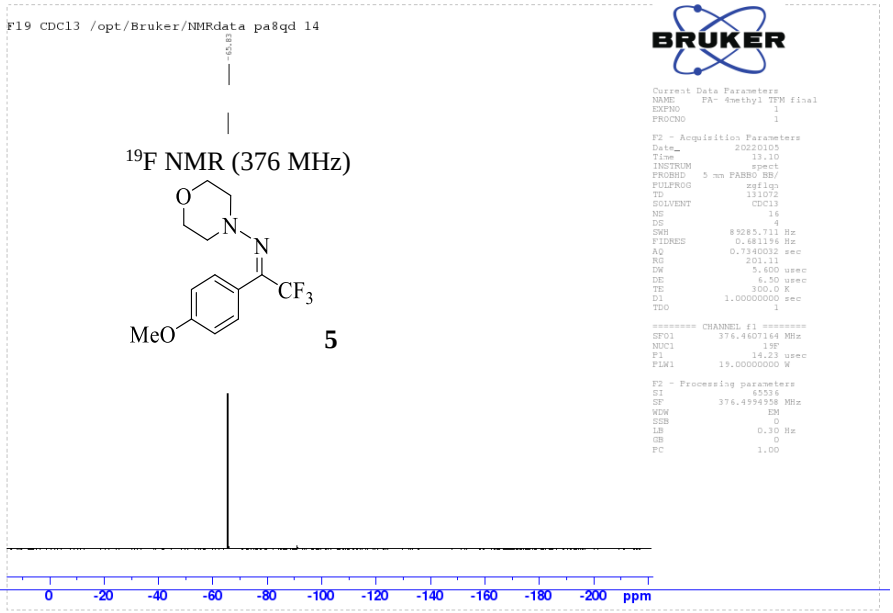


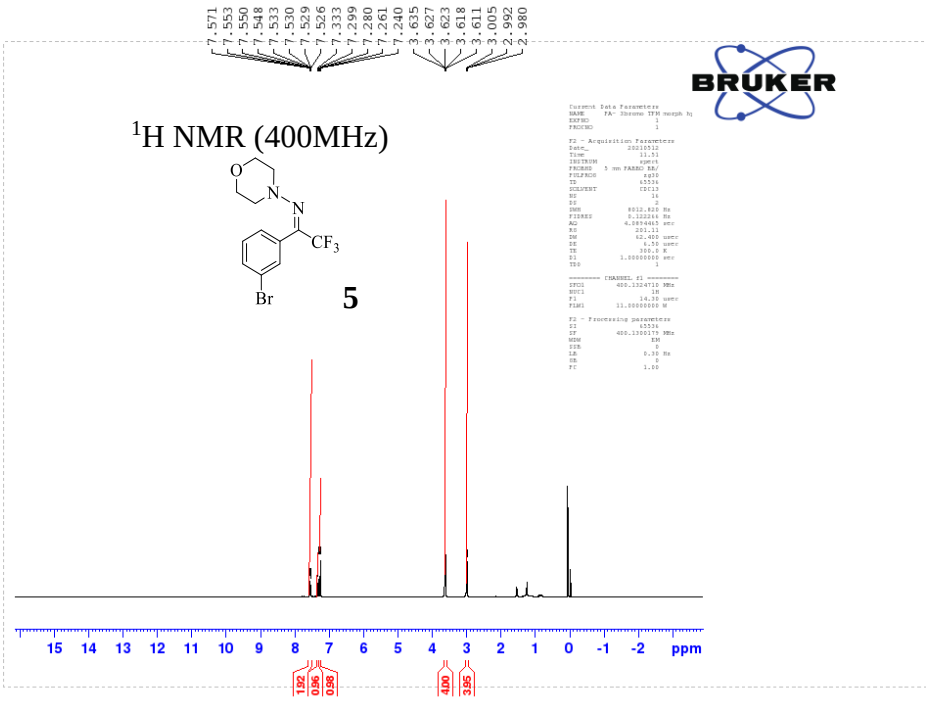
4

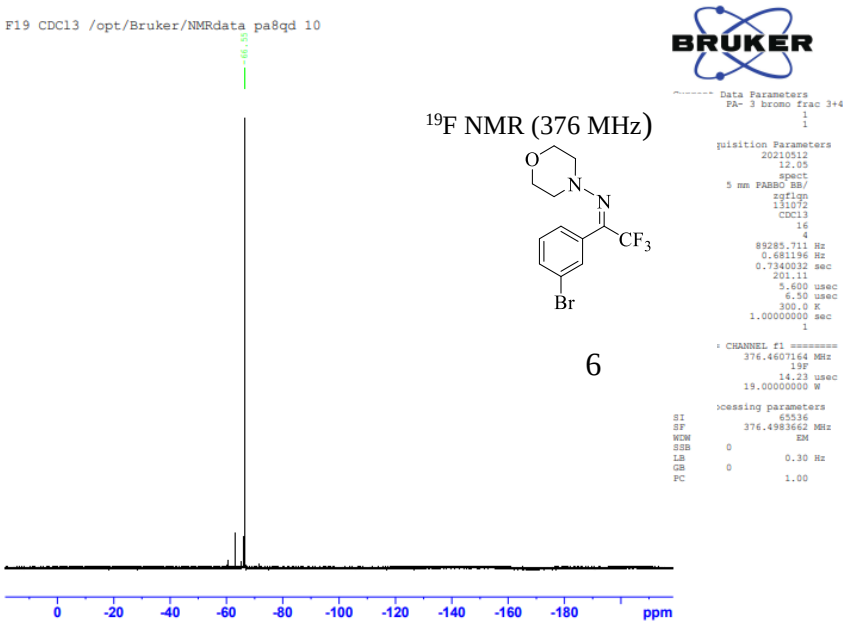
^{1}H NMR (400MHz)

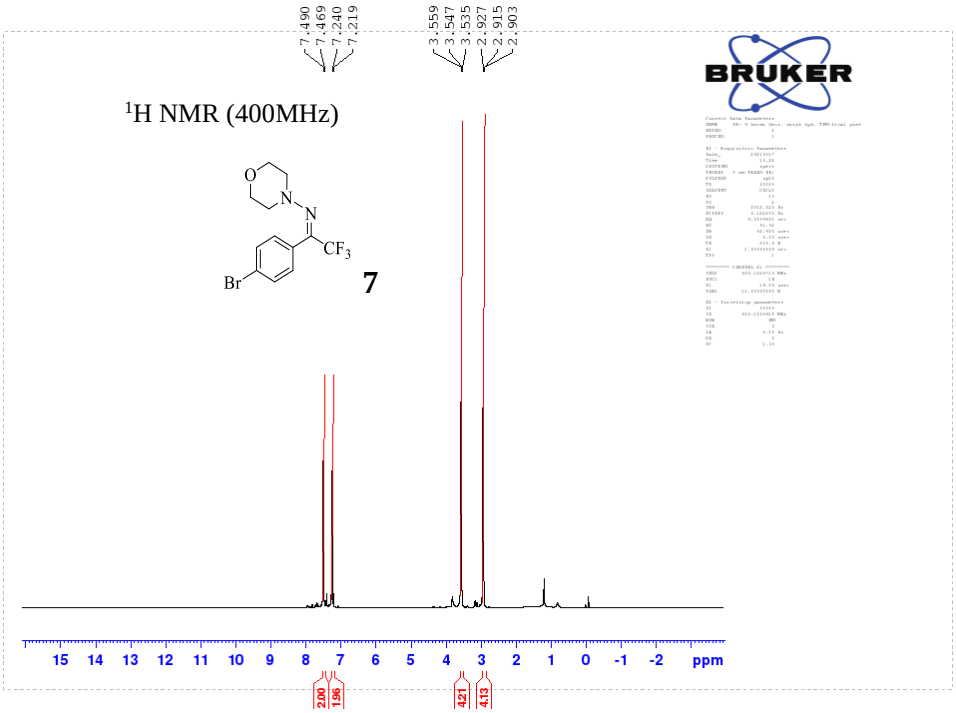


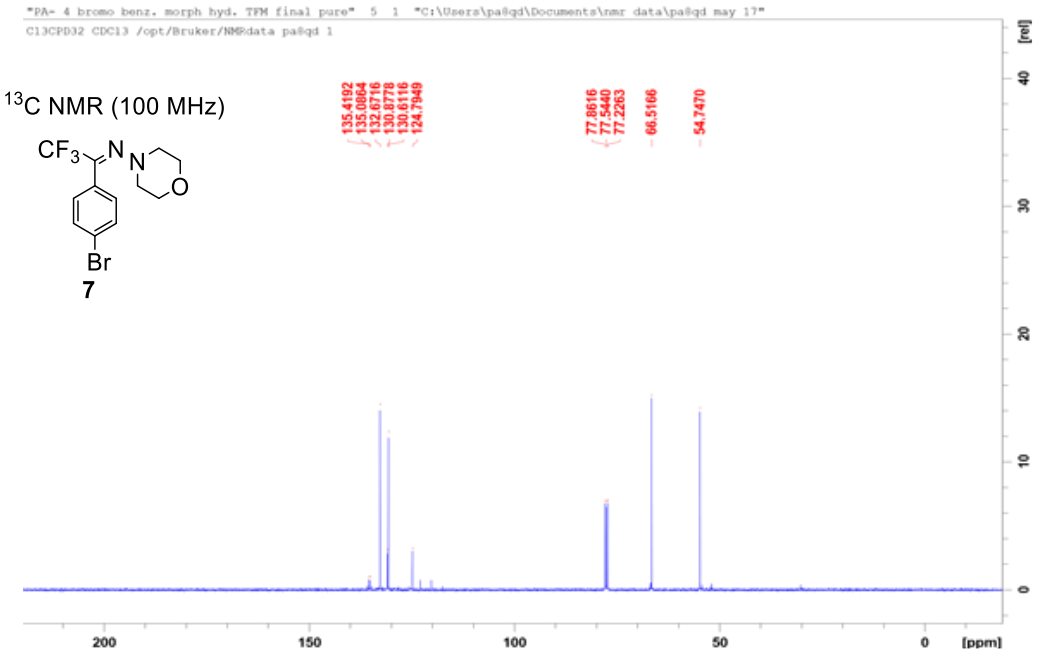
5

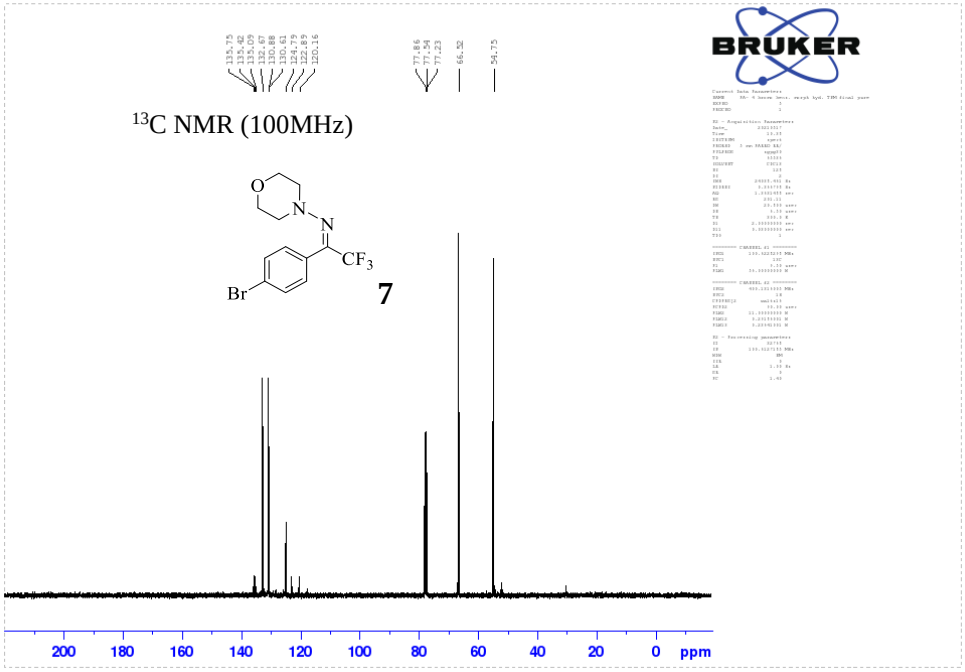

F19 CDCl3 /opt/Bruker/NMRdata pa8qd 14
BRUKER
^{19}F NMR (376 MHz)
MeO
CF$_3$
5
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

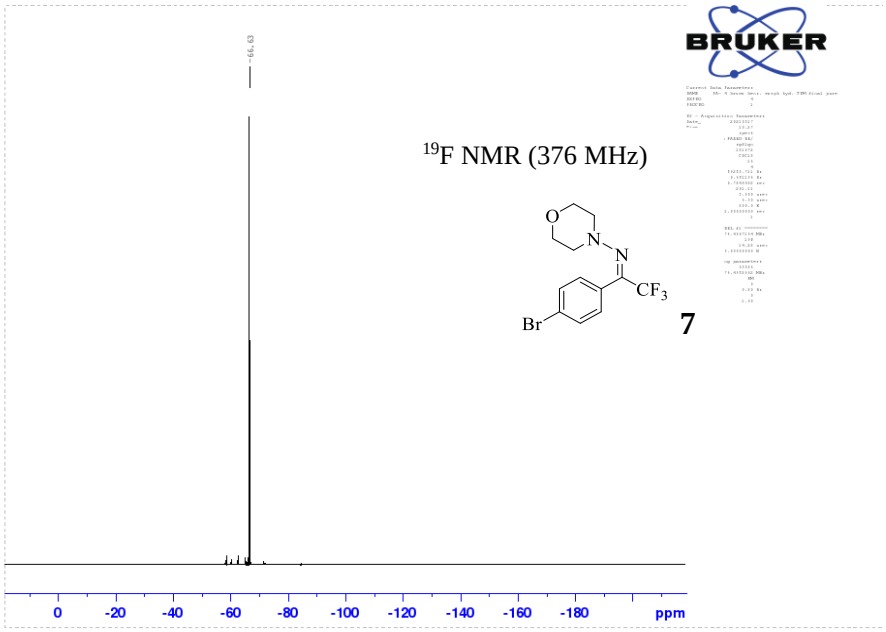

7.571 7.553 7.550 7.548 7.533 7.530 7.529 7.526 7.333 7.299 7.280 7.261 7.240 3.635 3.627 3.623 3.618 3.611 3.005 2.992 2.980
BRUKER
^{1}H NMR (400MHz)
Br
CF$_3$
5
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.92 0.96 0.88 4.00 3.95


F19 CDCl3 /opt/Bruker/NMRdata pa8qd 10
BRUKER
Data Parameters
PA- 3 bromo frac 3+4
19F NMR (376 MHz)
6
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm


7.490
7.469
7.240
7.219
3.559
3.547
3.535
2.927
2.915
2.903
BRUKER
1H NMR (400MHz)
7
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
2.00
1.96
4.21
4.13


"PA- 4 bromo benz. morph hyd. TFM final pure" 5 1 "C:\Users\pa@qd\Documents\nmr data\pa@qd may 17"
C13CPD32 CDCl3 /opt/Bruker/NMRdata pa@qd 1
13C NMR (100 MHz)
CF3
N
N
O
Br
7
135.4192
135.0864
132.6716
130.8778
130.6116
124.7949
77.8616
77.5440
77.2263
66.5166
54.7470
[rel]
40
30
20
10
0
200
150
100
50
0
[ppm]

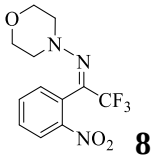

135.75
135.42
135.09
132.67
130.88
130.61
124.79
124.49
122.16
77.86
77.54
77.23
66.52
54.75
BRUKER
13C NMR (100MHz)
O
N
N
CF3
Br
7
200
180
160
140
120
100
80
60
40
20
0
ppm



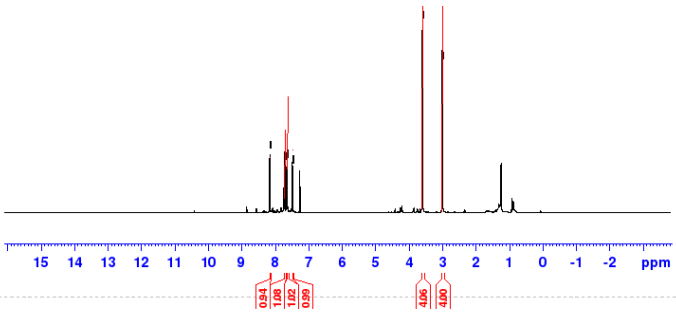
^{19}F NMR (376 MHz)

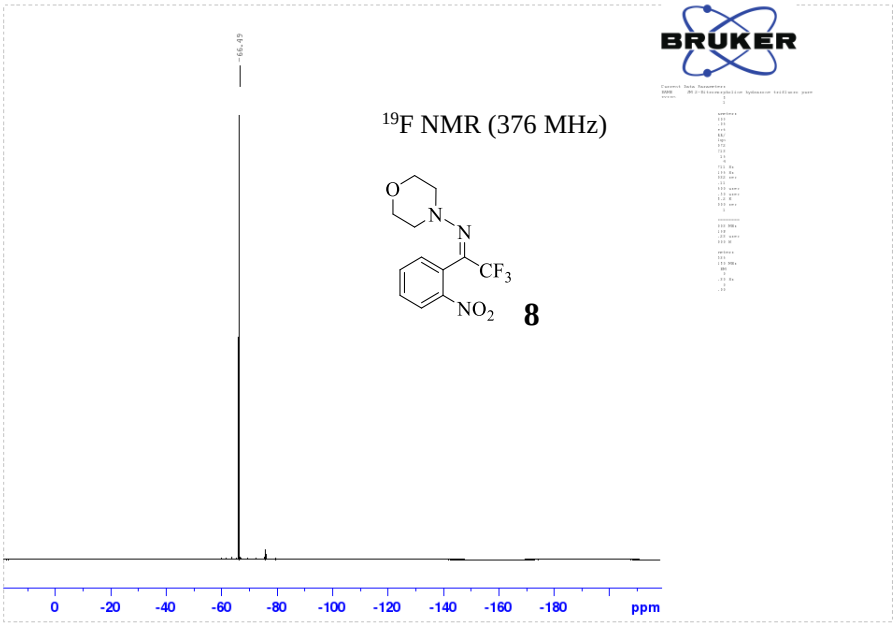
7

^{1}H NMR (400 MHz)



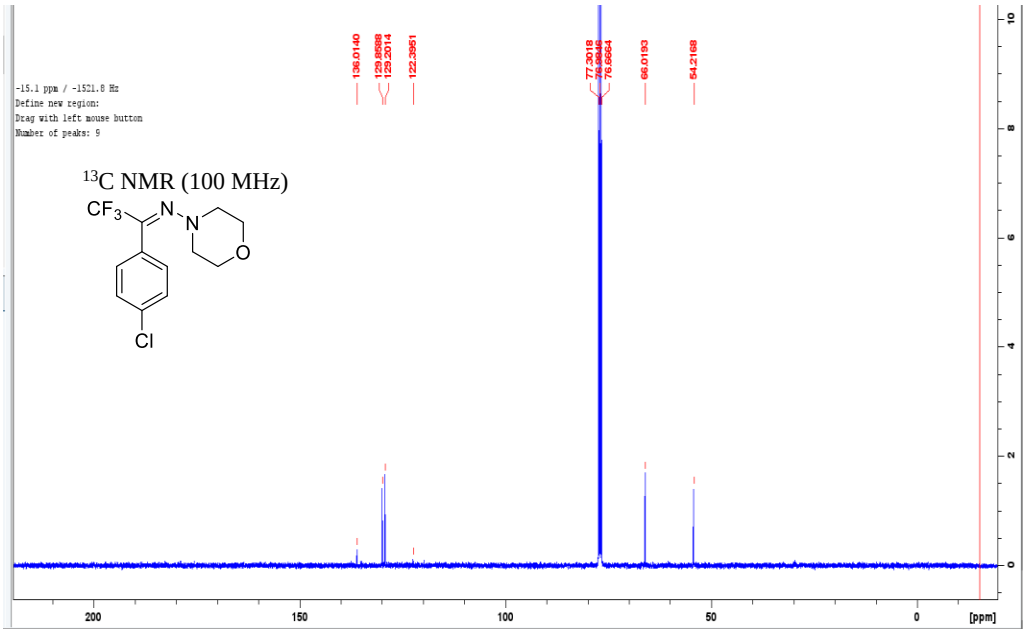
8



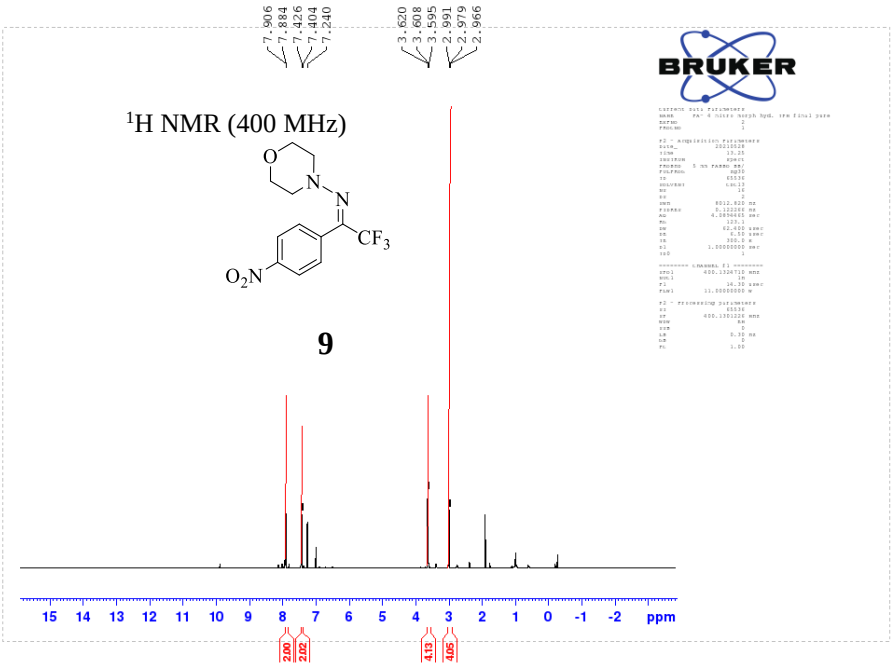


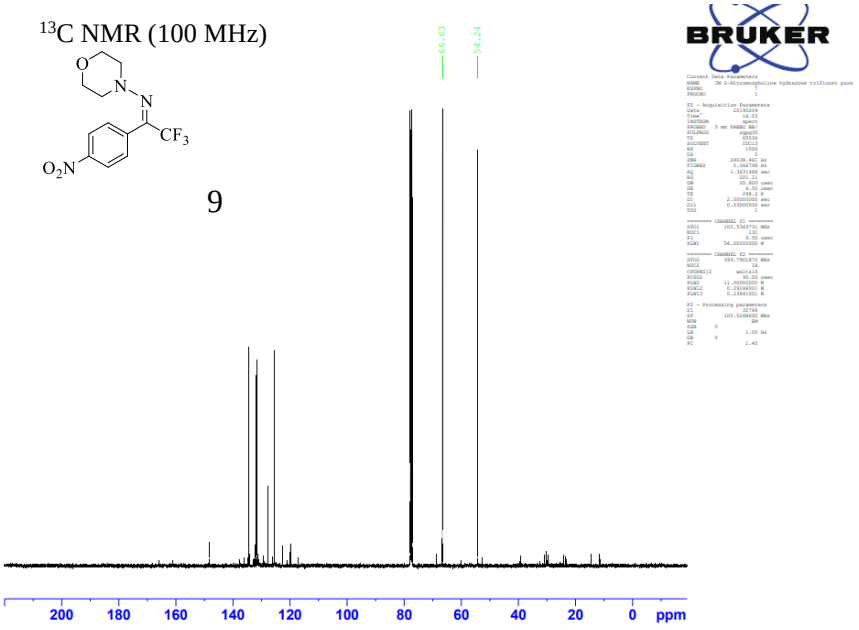
^{19}F NMR (376 MHz)

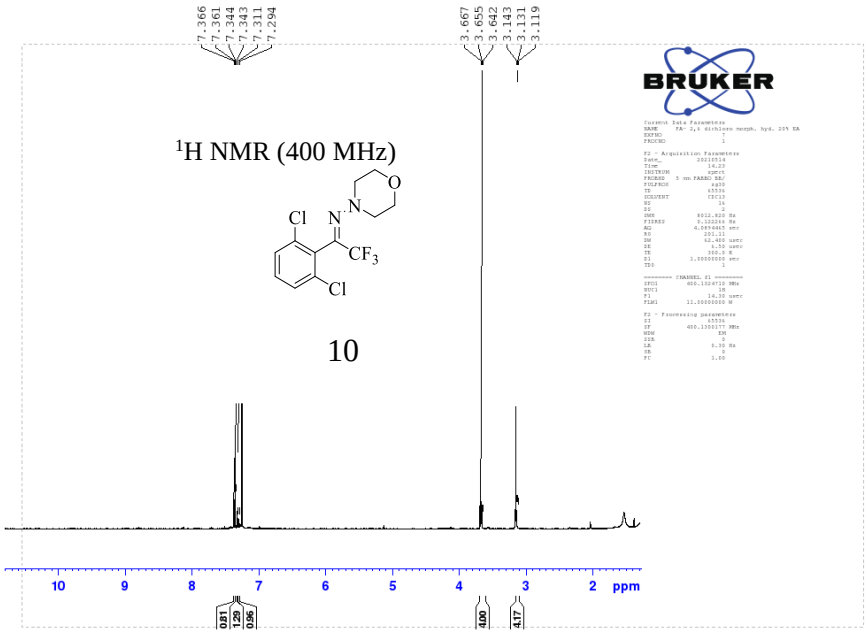
8

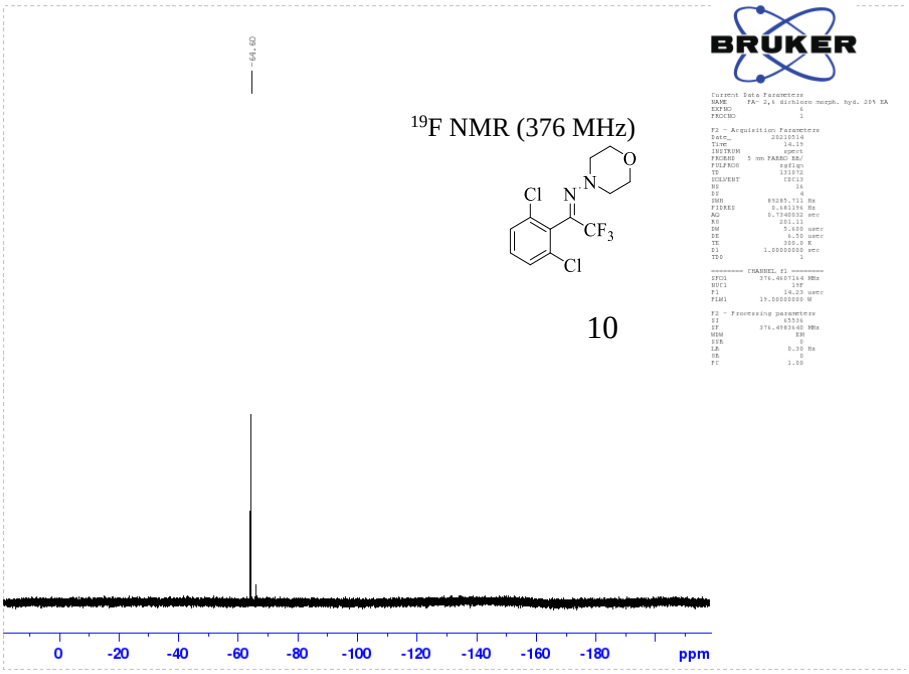


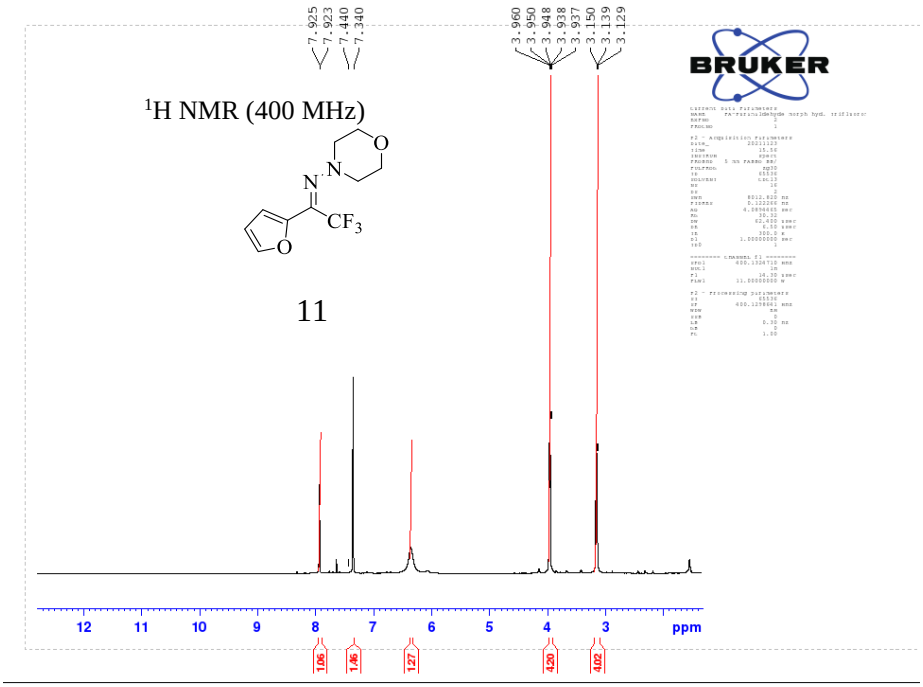
^{13}C NMR (100 MHz)


7.906
7.884
7.426
7.404
7.240
3.620
3.608
3.595
2.991
2.979
2.966
BRUKER
^{1}H NMR (400 MHz)
O_2N
CF_3
9
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
2.00
2.02
4.13
4.05


^{13}C NMR (100 MHz)
66.63
54.24
BRUKER
O_2N
CF_3
9
200 180 160 140 120 100 80 60 40 20 0 ppm

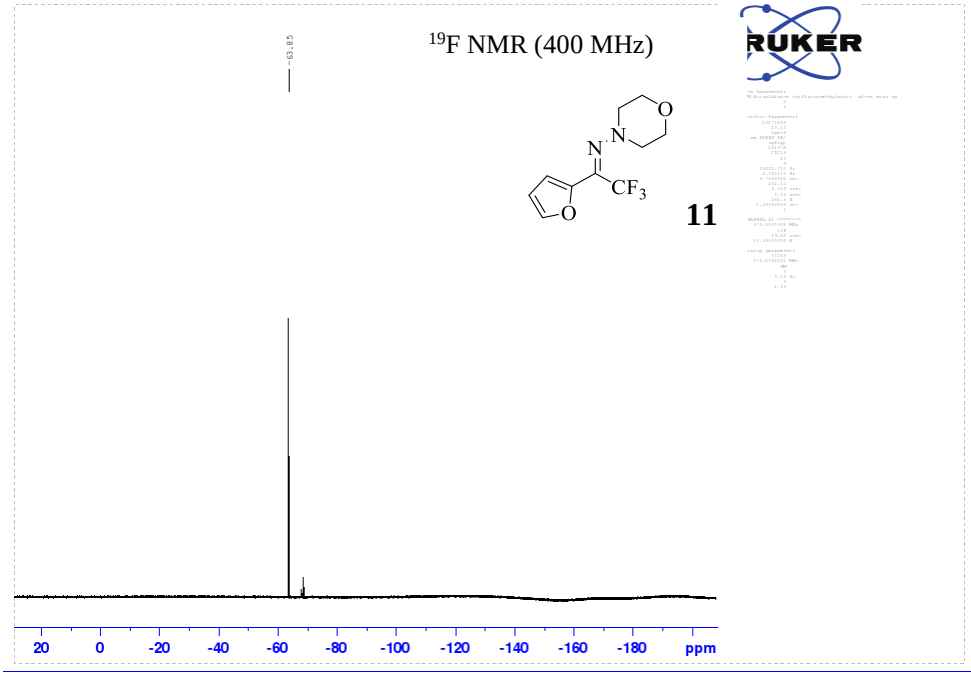

7.366
7.361
7.344
7.343
7.311
7.294
3.667
3.655
3.642
3.143
3.131
3.119
BRUKER
1H NMR (400 MHz)
Cl
N
O
CF3
Cl
10
10
9
8
7
6
5
4
3
2
ppm
0.81
1.29
0.96
4.00
4.17


-64.40
BRUKER
19F NMR (376 MHz)
Cl
N
O
CF3
Cl
10
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm



^{1}H NMR (400 MHz)

11



^{19}F NMR (400 MHz)

11

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VITA

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