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4-Acyl-1,2,3-Triazoles: synthesis and use as key intermediates for new hydroxy-1,2,3-triazoles and quinolone-based molecular hybrids

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Abstract

Azevedo, Marcelo Folhadella Martins Faria; Müller, Camilla Djenne Buarque (Advisor). 4-Acyl-1,2,3-Triazoles: synthesis and use as key intermediates for new aryl-triazoyl-methanols and quinolone-based molecular hybrids**.** Rio de Janeiro, 2025. 261p. Tese de Doutorado - Departamento de Química, Pontifícia Universidade Católica do Rio de Janeiro.

Nitrogen-based heterocycles are of broad interest in medicinal chemistry. Among these, triazoles stand out, mainly due to their physicochemical properties and the bioisosteric nature of *trans*-amides. The 1,3-dipolar cycloaddition between enaminones and azides has proven to be a more direct and efficient approach for the synthesis of derivatives of these compounds. However, direct methodologies that allow the obtention of 4-acyl-1,2,3-triazoles without the need for purification by column chromatography or the use of catalysts nor solvents have not yet been described in the literature. In this way, a methodology of enaminone-azide cycloaddition between acetophenones and aryl-azides in the presence of DMF-DMA, under metal-free and solvent-free conditions, were developed. The products were obtained in pure form using ethanol, without the need for additional column chromatographic purification steps. The reaction proved to be highly regioselective, providing exclusively the 1,4-disubstituted isomers, with yields ranging from 40 to 88%. The simplicity of this approach paves the way for the use of 4-acyl-1,2,3-triazoles as key intermediates in the synthesis of new bioactive compounds, a field still little explored in the literature but with great potential. In this regard, novel aryl-triazolyl-methanols were obtained by reduction of the acyl moiety with $NaBH_4$ in methanol, at 50 ºC, for 2 hours. All synthesized compounds were submitted for biological evaluation, showing relevant activity against different targets, including arboviruses, *Leishmania amazonensis*, and mutations associated with cystic fibrosis. Aiming to consolidate 4-acyl-1,2,3-triazoles as versatile synthetic platforms, the concept of molecular hybridization was explored as a strategy for their combination with other bioactive scaffolds. In this context, quinolones emerge as privileged structures, widely present in commercial drugs and natural products. Thus, *N*-(2-(1-aryl-1*H*-1,2,3-triazole-4-

carbonyl)phenyl)acetamide, obtained by the methodologies previously described, were used as precursors for the synthesis of new quinolone-based compounds. The formation of 2-(phenylamino)quinolin-4(1*H*)-one required the formation of an intramolecular C–N bond, followed by a ring-opening isomerization. For this, the triazoles were treated with KOH in DMF under white light irradiation, resulting in the formation of 22 new compounds with yields from 34% to 91%, isolated as pure precipitates. Seeking selective cyclization of the triazoles, deprotection, which occurs *in situ*, was performed first and submitted under the same conditions, which made it possible to obtain 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-one. However, due to the almost instantaneous release of nitrogen after the isomerization, only two examples were possible to be isolated, with yields between 45% and 59%. When heating was employed as the activation source instead of light, 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one hybrids were obtained together with (arylamino)quinolin-4(1*H*)-ones, through a mechanism involving aldol condensation. The use of methanol as a solvent allowed the selective obtention of the former. In total, 14 new compounds were synthesized with yields from 10% to 65%, all isolated by direct precipitation. Thus, not only the simplicity and versatility of 4-acyl-1,2,3-triazoles were demonstrated, but also their applicability as synthetic platforms for the generation of bioactive compounds and molecular hybrids with pharmacological potential.

Keywords

4-acyl-1,2,3-triazoles, quinolin-4(1H)-one, quinolin-2(1H)-one, molecular hybrids

Resumo

Azevedo, Marcelo Folhadella Martins Faria; Müller, Camilla Djenne Buarque (Orientadora). 4-Acil-1,2,3-Triazóis: síntese e aplicação como intermediários chave para novos hidroxi-1,2,3-triazois e híbridos moleculares baseados em quinolonas. Rio de Janeiro, 2025. 261p. Tese de Doutorado - Departamento de Química, Pontifícia Universidade Católica do Rio de Janeiro.

Compostos baseados em heterociclos nitrogenados despertam amplo interesse na química medicinal. Dentre eles, os triazóis se destacam, principalmente por suas propriedades físico-químicas e pelo caráter bioisostérico das trans-amidas. A cicloadição 1,3-dipolar entre enaminonas e azidas tem se mostrado uma abordagem mais direta e eficiente para a síntese de derivados desses compostos. No entanto, até o momento, não foram descritas na literatura metodologias diretas que permitam a obtenção de 4-acil-1,2,3-triazóis sem a necessidade de purificação por cromatografia em coluna ou uso de catalisadores. Com base nisso, foram desenvolvidas metodologias baseadas na cicloadição entre acetofenonas e aril-azidas na presença de DMF-DMA, em condições livres de metais e solvente. Os produtos foram obtidos como precipitados puros em etanol, sem necessidade de etapas adicionais de purificação por coluna cromatográfica. A reação revelou-se altamente regiosseletiva, fornecendo exclusivamente os isômeros 1,4-dissubstituídos, com rendimentos de 40 a 88%. A simplicidade desta abordagem abre caminho para o uso dos aciltriazóis como intermediários-chave na síntese de novos compostos bioativos, um campo ainda pouco explorado na literatura, mas com amplo potencial. Nesse sentido, aril-triazoyl-metanois inéditos foram obtidos por redução da porção acil com $NaBH_4$ em metanol, a 50 °C, por 2 horas. Todos os compostos sintetizados foram submetidos à avaliação biológica, apresentando atividade relevante frente a diferentes alvos, incluindo arboviroses, *Leishmania amazonensis* e mutações associadas à fibrose cística. Visando consolidar os 4-acil-1,2,3-triazóis como plataformas sintéticas versáteis, explorou-se o conceito de hibridização molecular como estratégia para sua combinação com outros núcleos bioativos. Nesse contexto, as quinolonas surgem como estruturas privilegiadas, amplamente

presentes em fármacos comerciais e produtos naturais. Assim, os *N*-(2-(1-aril-1*H*-1,2,3-triazol-4-carbonil)fenil)acetamida, obtidos pelas metodologias anteriormente descritas, foram utilizados como precursores para a síntese de novos compostos a base de quinolonas. A formação de 2-(arilamino)quinolin-4(1*H*)-ona exigiu a formação de uma ligação C–N intramolecular, seguida por uma isomerização de abertura de anel. Para isso, os triazóis foram tratados com KOH em DMF sob irradiação de luz branca, resultando na formação de 22 novos compostos com rendimentos de 34% a 91%, isolados como precipitados puros. Buscando uma ciclização seletiva dos triazóis, realizou-se a desproteção, que ocorre in situ, e submetido nas mesmas condições, o que possibilitou a obtenção de 3-aril-3,4-dihidro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ona. No entanto, devido à liberação quase instantânea de nitrogênio durante a reação, apenas dois exemplos foram isolados, com rendimentos entre 45% e 59%. Quando o aquecimento foi empregado como fonte de ativação no lugar da luz, híbridos 4-(1-aril-1H-1,2,3-triazol-4-il)quinolin-2(1*H*)-ona foram obtidos juntamente com (arilamino)quinolin-4(1*H*)-onas, por meio de um mecanismo envolvendo condensação aldólica. O uso de metanol como solvente permitiu a obtenção seletiva dos primeiros. No total, 14 novos compostos foram sintetizados com rendimentos de 10% a 65%, todos isolados por precipitação direta. Dessa forma, demonstrou-se não apenas a simplicidade e a versatilidade dos 4-acil-1,2,3-triazóis, mas também sua aplicabilidade como plataformas sintéticas para a geração de compostos bioativos e híbridos moleculares com potencial farmacológico.

Palavras-chave

4-acil-1,2,3-triazoles, quinolin-4(1H)-ona, quinolin-2(1H)-ona, híbridos moleculares

Sumário

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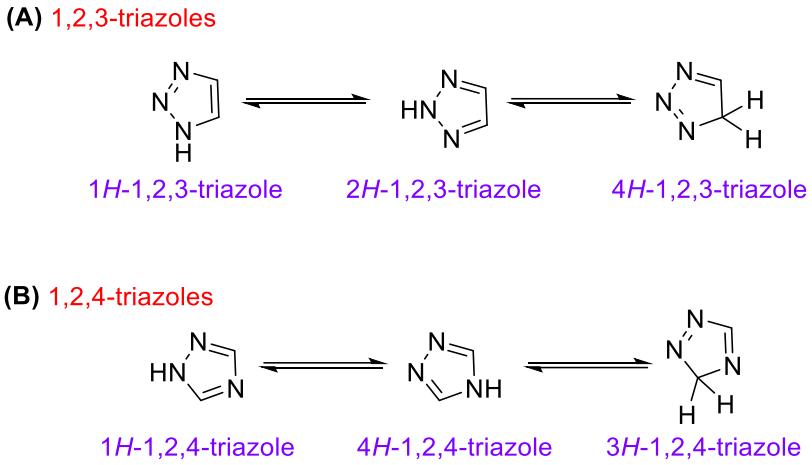
Mischief Managed

J.K. Rowling

1. Introduction

Triazoles are the perfect example of versatile nitrogen-based heterocycles with applications in different areas. These molecules have a 5-membered ring containing 3 nitrogen atoms in their structure. Therefore, 2 constitutional isomers can be found, the vicinal triazole (1,2,3-triazole) and the symmetrical triazole (1,2,4-triazole). Both of them have a tautomeric equilibrium, with the 1*H* specie the most stable, due its aromatic nature (**Scheme 1.1**).[1]



Scheme 1.1: 1,2,3 and 1,2,4-triazole equilibrium

The versatility of this nucleus lies in its range of applications in the most diverse areas of knowledge.[2,3] In medicinal chemistry triazoles stands out among the majority, not only because of the number of publications in recent decades on the subject which triazole-based compounds are present, but also thanks to the specific characteristics and properties of this nuclear unit.[1] The most import one is the bioisosteric proprieties of *trans*-amides that 1,4-dissubistituted 1,2,3-triazoles have. Several structural features corroborate to that (**Figure 1.1**): (i) C(4) can has electrophilic proprieties and the C-H bond act as a hydrogen bond donor (HBD; pink); (ii) lone pair in N(2) and N(3) can accept hydrogen bonds (HBA; green); (iii) when overlapped, the substituents have similar distances (3,1 A in trans-amides and 5 A in triazole) and orientation angle (142° in *trans*-amides and 162° in triazole).[4]

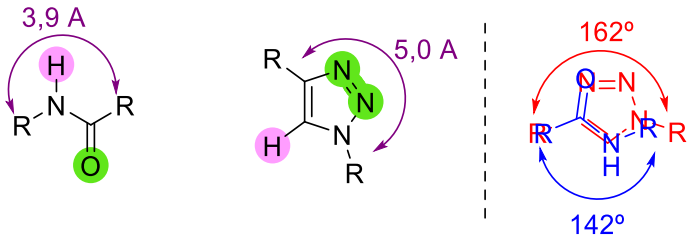
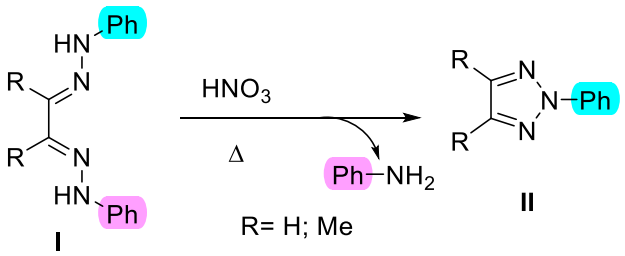


Figure 1.1: triazole's trans-amide bioisosterism

Another important intrinsic characteristic is their stability. Due to its aromatic nature, the compound resists metabolic degradation in the body, leading to better efficiency and easier formulations in drug development. Triazoles can also modulate the physicochemical properties of the molecule leading to a better ratio of lipophilicity and water solubility, important characteristic to a good drug. The possibility of interacting directly with biological targets through intermolecular interactions such as hydrogen bond (HB), dipole-dipole and π-π Stacking ensures the triazole's pharmacophoric character.[5]

1.1. Synthesis of 1,2,3-triazoles

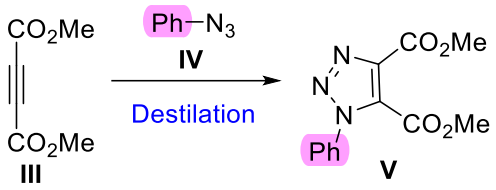
Triazoles were first synthesized by Pechmann in 1888. In this work, 2-aryl-1,2,3-*2H*-triazoles (**II**) was obtained by the thermal treatment of 1,2-dicarbonilic *bis*-phenyl-hydrazones derivative (**I**) with nitric acid (HNO_3) (**Scheme 1.2**).[6] After that, numerous synthetic methodologies have been developed to obtain these heterocycles.



Scheme 1.2: Pechmann synthetic approach to obtain triazoles

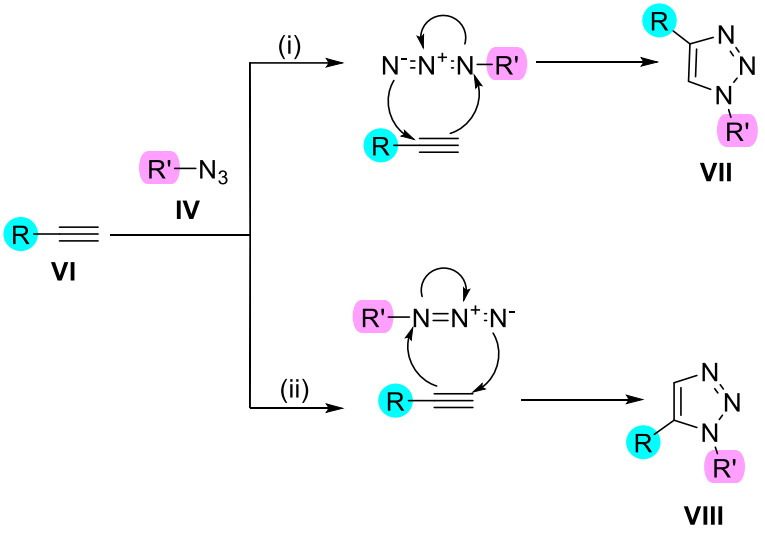
In 1893 Arthur Michael could isolate the triazole product of 1,3-dipoplar cycloaddition between Dimethyl acetylenedicarboxylate (**III**) and

azidobenzenes (**IV**) (**Scheme1.3**).[7]



Scheme 1.3: Michael's ynthetic approach to obtain triazoles

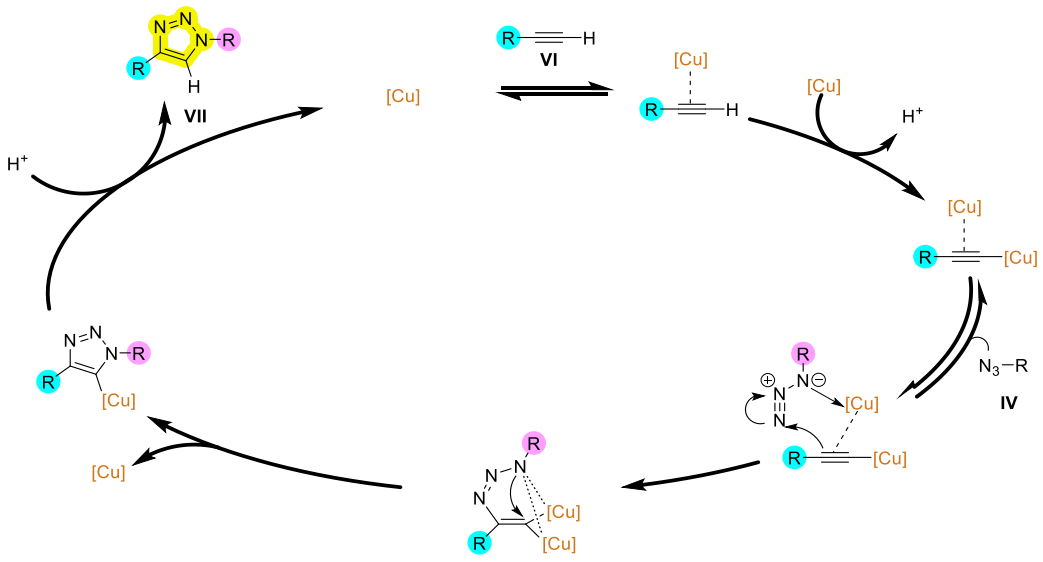
This seminal work inspired Huisgen's approach years later, in 1967. By heating phenyl acetylene (**VI**) and **IV**, Huisgen obtained triazole 1,4 (**VII**) and 1,5-dissubstituted (**VIII**) (**Scheme 1.4**).[8] The high temperature required, the nature of the reagents and the low selective, are drawbacks that make their widespread use unfeasible. In a mechanistic point of view, there is a HOMO-LUMO interaction between the azide (dipole) and alkyne (dipolarophile). Since there is a little difference in energy level between the species, the low selectivity is explained by the similar probability of $HOMO_{(dipole)}$-$LUMO_{(dipolarophile)}$ or $HOMO_{(dipolarophile)}$-$LUMO_{(dipole)}$ occur.



Scheme 1.4: Huisgen's synthetic approach to obtain triazoles

It was only in 2001 that Sharpless and co-workers solved this problem. By introduction a copper catalyst, it was possible to obtain the same triazoles in mild conditions and with controlled regioselectivity. This reaction was then known as Copper Catalyzed Akyne-Azide Cycloaddition

(CuAAC) and became the spokesperson for the so-called “click chemistry” concept created by the same author. Although CuAAC is commonly mistreated as a synonym of it, “click chemistry” is a more comprehensive concept of any reaction that uses readily available reagents, with good yields, simple purification and other parameters related to the aqueous solvents use and obtaining by-products that are harmless to the environment. Mechanistically, the coordination of the alkyne in the copper ion determinate the regioselectivity in a way that only the 1,4 isomer is formed. Although not completely elucidated, the reaction mechanism is presented in **Scheme 1.5**. This reaction was a real breakthrough, which made possible the development of other reactions to obtain triazole-based compounds such as organocatalyzed cycloadditions,[9] Strain-promoted Azide-Alkyne Cycloaddition (SPAAC),[10] in addition to various other metal-free methodologies with different scaffolds.[1]

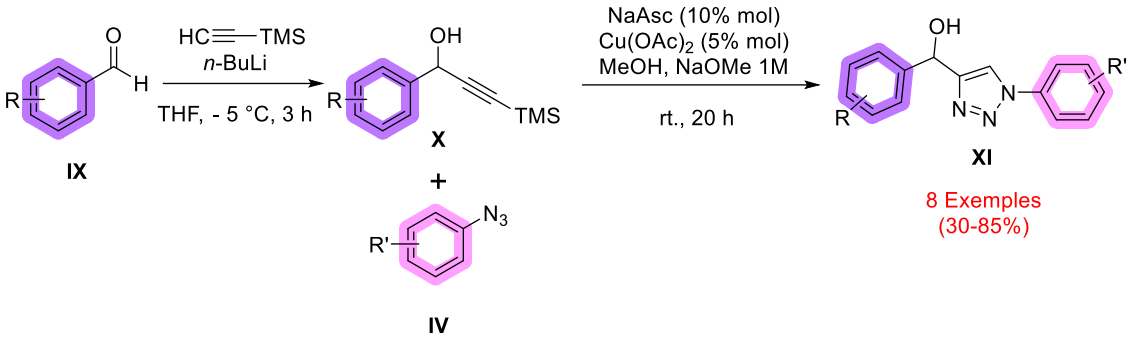


Scheme 1.5: Copper Catalyzed Akyne-Azide Cycloaddition approach to obtain triazoles.

Although extremely versatile, especially for simpler molecules, when it comes to biological activity, more refined compounds are desired. And in these cases, the use of CuAAC could become more laborious, especially when it comes to obtaining the necessary reagents to achieve the cyclization.

Aryl-triazoyl-methanols, also known as hydroxy-1,2,3-triazoles (**XI**)

are the best example, with biological activities against several targets such as glycine transporter inhibitors,[11] *Leishmania amazonensis*[12] and cystic fibrosis.[13,14] Our research group has expertise in obtain these compounds. As already been reported, these compounds can be easily obtained by CuAAC between propargyl alcohols (**X**) and aryl-azides (**IV**) (**Scheme 1.6**). Beside its simplicity, several problems such the necessity of dry reaction conditions and use of unstable reagents to obtain the **X** from benzaldehydes (**IX**) are extremely negative points that prevent the reaction from being fully accessible.



Scheme 1.6: LabSint's synthesis of aryl-triazoyl-methanols

1.2. 4-acyl-1,2,3-triazoles

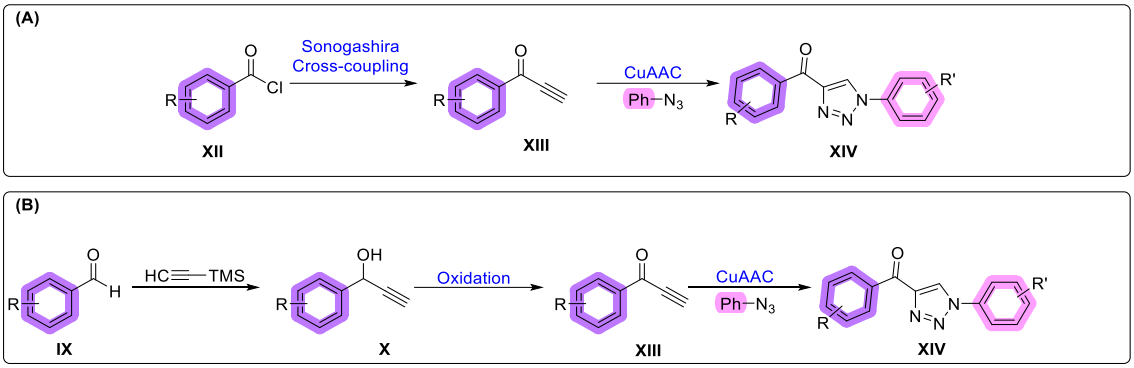
The possibility to use another triazole class as precursor is a viable alternative to simplify the process, making it greener and even more accessible. 4-acyl-1,2,3-triazole gained strength in recent years with several applications in different areas.[15]

1.3. Synthesis of 4-acyl-1,2,3-triazoeles

1.3.1. Classical approaches

These scaffolds can be synthesized using various methods that employ different starting reagents, with the CuAAC being the more conventional approach in the key step between intermediate **XIII** and aryl azide (**Scheme 1.7**). Intermediate **XIII** can be obtained even by Sonogashira's cross-coupling with benzoyl chlorides (**XII**) [16–18] or by the addition of the anion of alquinil-silil to aldehydes (**IX**), followed by oxidation

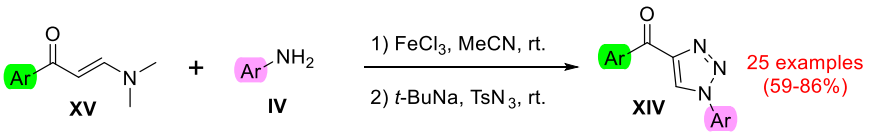
of the propargyl alcohols (**X**). [19–21]



Scheme 1.7: CuAAC strategies to achieve 4-acyl-1,2,3-triazoles

Different approaches have been gaining prominence with the increase in discussions about green chemistry and click chemistry, which are always seeking cleaner processes and milder conditions. The use of non-classical reagents such as ketones,[22–25] alkenes,[23,26,27] cyclopropanes[28] and others, not only make the hole synthesis processes more accessible, but also denote new molecular skeleton possibilities.

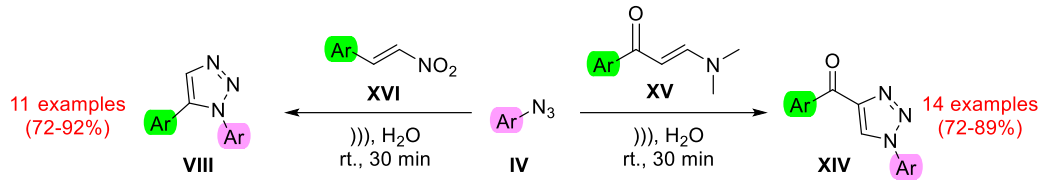
The enaminone-azide cycloadditions (EACA) stand out and gained strength, given several plus points, such as commercial availability of building blocks, mild conditions, possibility to obtain 4-acyl-1,2,3-triazoles straightforwardly. Different approaches were found in literature to achieve this skeleton. Wan and co-workers reported the synthesis of *N*-Substituted 1,2,3-Triazoles via Enaminone–Azide Cycloaddition Involving Regitz Diazo Transfer starting with enaminone **XV** and anilines **IV** in presence of $FeCl_3$, *t*-BuONa and TsN_3. Twenty-five examples of 4-acyl-1,2,3-triazoles **XIV** were obtained in up to 86% yield (**Scheme 1.8**).[29]



Scheme 1.8: Wan and co-workers enaminone-azide cycloaddition aproach to obtain 4-acyl-1,2,3-triazole

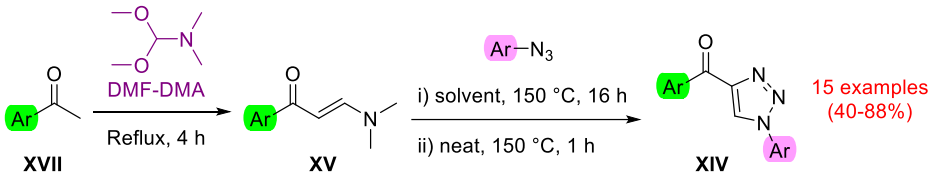
In 2021 Kiranmye and co-workers demonstrated the use of ultrasound irradiation to obtain 1,4 and 1,5 disubstituted 4-acyl-1,2,3-triazoles (**XIV**). With 14 and 11 examples, respectively, and yields up to

92%, the authors demonstrated the possibility of easily obtaining triazoles in metal free conditions, although the use of more expensive technology can be a downgrade in its processes (**Scheme 1.9**).[30]



Scheme 1.9: Karthikeyan and co-workers enaminone-azide cycloaddition aproach to obtain 4-acyl-1,2,3-triazole

In 2022, was demonstrated alternative ways to obtain **XIV**.[31] By using solvothermal and neat conditions or research group demonstrated the first report of metal and solvent-free EACA with 15 compounds reported and yields up to 88% (**Scheme 1.10**). Mechanistic insights were also proposed in this work in which the mechanism of this reaction, until such time unexplored, could be proven to have a concerted asynchronous reaction character, with the 1,4 disubstituted isomer being selective formed. Hammet correlations also demonstrated that aryl azides substituted with withdrawing groups accelerate the reaction.



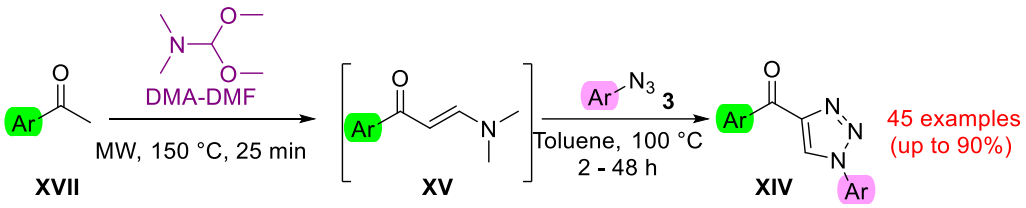
Scheme 1.10: Gaspar and co-workers enaminone-azide cycloaddition aproach to obtain 4-acyl-1,2,3-triazole

1.3.2. Telescopic approaches

Straightforward alternative methodologies have become more important in recent years, especially for industrial applications. This helps bridge the gap between academia and industry, enabling the development of large-scale reactions and the use of bench-scale technologies. Telescopic and tandem approaches provide an alternative to traditional

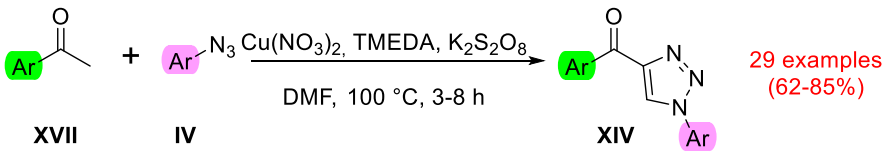
procedures that require multiple purification steps. This strategy involves performing sequential reactions without isolating any intermediates, which are used immediately to form more complex structures. Eliminating intermediate purifications not only cuts operational costs but can also simplify final product purification and allow the use of more accessible reagents to build more complex structures.[32]

Telescopic methodologies to obtain 4-acyl-1,2,3-triazoles are present as well in literature. Dehan and co-workers reported in 2016 the first metal-free telescopic approach to get type **XIV** triazoles. By reacting commercially available **XVII** in presence of DMF-DMA under microwave irradiation, followed by addition of **IV** and reflux in toluene for 12h, obtaining more than 40 examples of **XIV** in 43-90% yield (**Scheme 1.11**).[33]



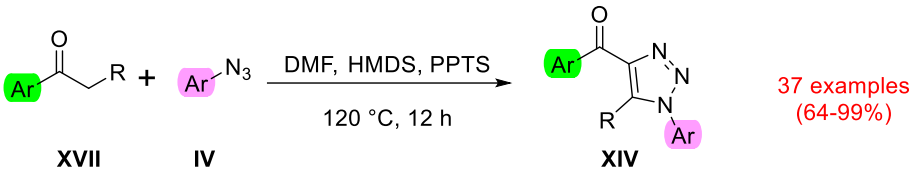
Scheme 1.11: Dehan and co-workers telescopic approach to synthesize 4-acyl-1,2,3-triazoles

Cheng and co-workers presented in 2017 a multicomponent synthesis of **XIV** from **XVII** and aril-azides in dimethylformamide (DMF) as the solvent. This reaction utilized $Cu(NO_3)_2$, $K_2S_2O_8$, and TMEDA at 100 °C for up to 8 h, to achieve 29 examples with yields up to 85 % (**Scheme 1.12**).[22] The same group also reported the use of $Cu(NO_3)_2$, dimethyl carbonate (DMC) as the solvent, triethylamine as the base, and ligands such as triphenylphosphine or 2,2′-bipyridine under an air atmosphere to achieve similar triazoles in comparable yields.[34]



Scheme 1.12: Cheng and co-workers telescopic approach to synthesize 4-acyl-1,2,3-triazoles

In 2024, Liang and co-workers recently demonstrated the use of in situ-generated formamidine as an important compound for synthesizing functionalized **XIV**. Using acetophenones and azides with DMF, Hexamethyldisilazane (HMDS), and pyridinium p-toluenesulfonate (PPTS) as a catalyst without solvent, they successfully produced thirty-seven examples with yields reaching up to 99% (**Scheme 1.13**).[35]



Scheme 1.13: Liang and co-workers telescopic approach to synthesize 4-acyl-1,2,3-triazoles

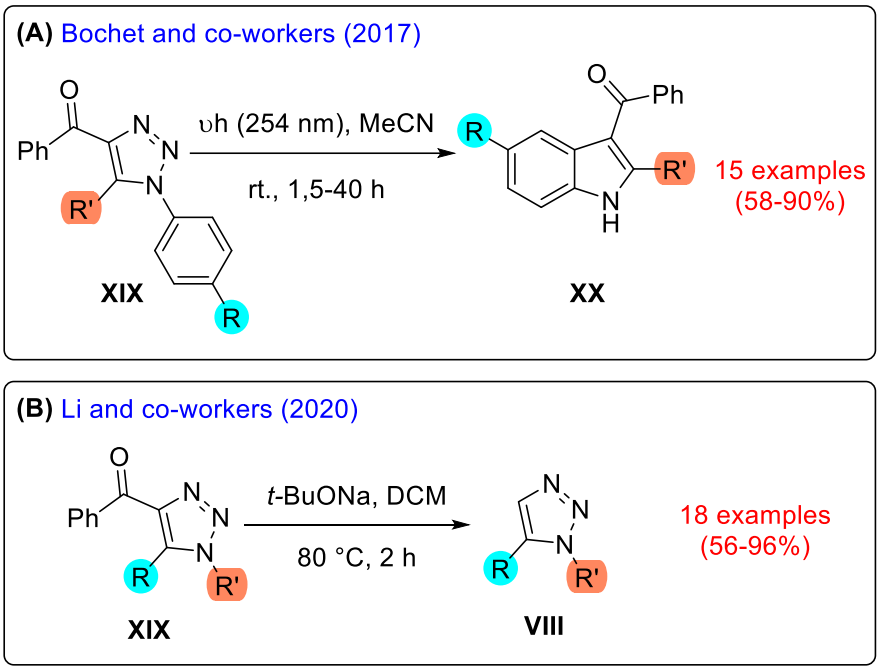
In the same year, Ramachary showed that 2,4-diketoesters, when combined with an organocatalyst 1,1,3,3-Tetramethylguanidine (TMG), can produce trissubistituted 4-acyl-1,2,3-triazoles (**XIX**) with yields up to 93% (**Scheme 1.14**).[36]

Scheme 1.14: Ramachary and co-workers telescopic approach to synthesize 4-acyl-1,2,3-triazoles.

After all reports, it's clear that there is still a journey ahead to find a straightforward method, to achieve triazoles like **XIV**. Our research group's 2022 paper shows it is possible to produce 4-acyl-1,2,3-triazoles in a metal- and solvent-free way with simple purification. This principle should guide us, as the main goal is to establish these triazoles as a platform for synthesizing more complex scaffolds, which is the core purpose of this thesis.

1.4. Use of 4-acyl-1,2,3-triazoles as intermediates

The literature includes a few examples employing 4-acyl-1,2,3-triazoles to generate new heterocycle species and, so far, only 1,4,5-trisubstituted ones have been used for this purpose. In 2017 Bochet and co-workers reported the use of trisubstituted triazoles to achieve the indole moiety under UV irradiation (**Scheme 1.8a**).[37] In 2020 Li and co-workers used the same framework to promote the synthesis of 1,5-dissubistituted triazoles. Using *t*-BuONa as base, the acetophenone component could be eliminated generating **VIII** in up to 95% yiled.[38]



Scheme 1.15: 4-acyl-1,2,3-triazoles used as synthetic precursors: (a) Bochet and co-workers (2017); (b) Li and co-workers (2020).

This gap in literature presents a significant research opportunity, particularly for the efficient synthesis of novel bioactive molecules. As our group has a specific interest in the hydroxy-1,2,3-triazole moiety, a straightforward reduction of the carbonyl group could yield promising drug candidates, especially for cystic fibrosis mutations, which constitute the primary biological focus of LabSint.

1.5. Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease, being caused by mutations in the gene that encodes the transmembrane conductance regulatory protein (CFTR), a chloride channel activated by protein kinase A (PKA) dependent phosphorylation and that is located in the apical plasma membrane (PM) of various epithelia.[39,40]

CFTR dysfunctions lead to abnormal ion transport and airway surface liquid dehydration, what leads to the impairment of mucociliary clearance. As consequence, individuals with CF face recurrent respiratory infections and chronic inflammation that ultimately cause severe lung damage.[41,42]

The nullification of a phenylalanine residue at position 508 (p.Phe508del) is the most common CF-causing mutation, occurring in 85% of CF cases. The p.Phe508del-CFTR protein, when misfolded, is unstable and is therefore retained by the endoplasmic reticulum quality control (ERQC), that quickly directs it to degradation.[43,44] However, p.Phe508del-CFTR traffic can be partially rescued by low temperature incubation of cells that express this mutant, as was demonstrated in several studies in past years.[45–47]

Due to experimental evidence demonstrating that the protein's function can be restored, the search for new molecules that act as modulators to restore traffic (correctors) and function (potentiators) of p.Phe508del-CFTR has gained importance.

Currently, the most effective treatment for this is Trikafta, a triple combination of two CFTR correctors (Elexacaftor and Tezacaftor) and a potentiator (Ivacaftor) (**Figure 2**).[48] These drugs have significantly improved the outlook for most people with CF, demonstrating impressive clinical efficacy and greatly enhancing their quality of life. However, despite their effectiveness, the CFTR protein is only partially restored, and the high cost of approximately 360 thousand dollars per patient per year (R$92.000,00) since its inclusion in SUS makes treatment less accessible. Additionally, Trikafta's inability to treat all CF mutations presents another major challenge. This highlights the need for future research to develop more

accessible and comprehensive therapies.

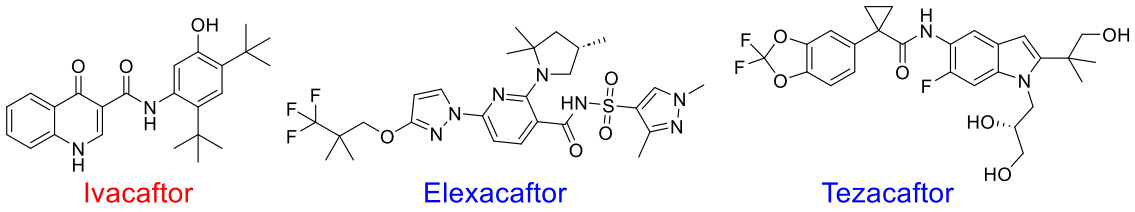


Figure 1.2: trikafta composition

1.5.1. LabSint's compounds against CF muatations and molecular hybridization

Targeting new therapeutic options, LabSint has shown the potential of aryl-triazoyl-methanols (**XI**) in rescuing CFTR trafficking across various CF mutations. As **Scheme 1.4** outlined, the compounds were synthesized and tested against p.Phe508del-CFTR and p. Arg334Trp-CFTR.[13,49] Compounds **XIa-d** demonstrate a promising ability to restore CFTR function, with compound **XIa** especially notable. It exhibits activity against both mutations with EC_{50} values of 2.70 and 1.24 µM, respectively (**Figure 1.3**). This highlights the therapeutic potential of triazoles as alternative treatments for CFTR mutations and emphasizes the need to develop new triazole-based structures targeting novel drug candidates for CF.

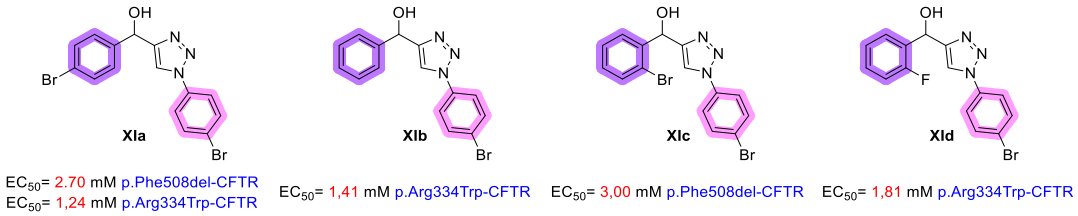


Figure 1.3: LabSint's aryl-triazoyl-methanols with biological activity against CFTR mutations

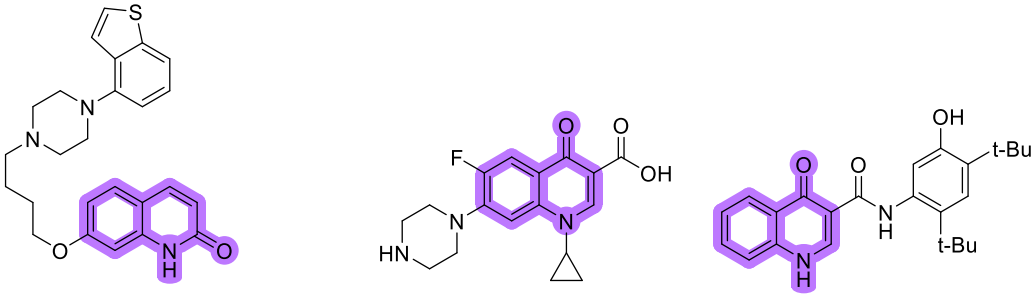
In the search for new bioactive compounds, the basics of molecular hybridization stand out as a key idea. This process involves merging two or more important pharmacophore unities responsible for a drug's activity, with the aim of designing new hybrid molecules that have better biological activity, target multiple sites, or even reduce side effects.[50,51] The most well-known example of this strategy is acetylsalicylic acid. By adding an acetyl

group, therapeutic properties are improved, mainly by increasing gastric tolerability and enabling more effective delivery of the active ingredient.[52]

1.6. Quinolin-4(1*H*)-one and Quinolin-2(1*H*)-one

In the eyes of the molecular hybridization and targeting new CF drug candidates, quinolones appear as perfect match to combine with triazoles. Derived from quinine, exists in two isomeric forms (Quinolin-4(1*H*)-one and Quinolin-2(1*H*)-one) maintains a dynamic tautomeric equilibrium with its respective hydroxyquinoline species.

These moieties are wide found in several commercial drugs with different applications (**Figure 1.4**).[53,54] Ciprofloxacin antibiotic series is undoubtedly the most representative example of the potential of Quinolin-4(1*H*)-one.[55] Brexpiprazole can exemplify the potential of Quinolin-2(1*H*)-one with antipsychotic effects in human body.[56] Since our research group has a particular interest in cystic fibrosis, ivacaftor is the best example of the versatility of quinolone scaffold being the first and more powerful tool targeting cystic fibrosis.[57]



9
Brexpiprazole
(antipsychotic)

10
Ciprofloxacin
(antibiotic)

11
Ivacaftor
(cystic fibrosis)

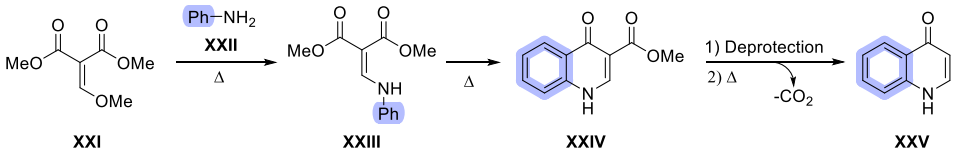
Figure 1.4: quinolone-based commercial drugs

1.6.1. Synthesis of Quinolones

The synthesis of these privilege structures is well documented in the literature. Preparing Quinolin-4(1*H*)-one has depended on several well-established multi-step procedures, mainly using aniline derivatives as core building blocks. Although reliable, these methods often pose challenges

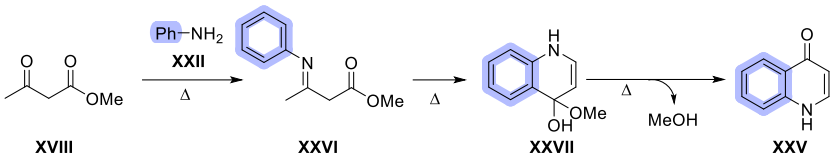
related to reaction conditions and overall process efficiency.[58]

The Gould-Jacobs reaction is the most traditional method to achieve quinolones with a thermal cyclization strategy (**Scheme 1.16**).[59] This method commences with the condensation of diethyl ethoxymethylidenedimalonate (**XXI**) and anilines (**XXII**). The resulting diester (**XXIII**) undergoes subsequent cyclization, typically under drastic thermal conditions exceeding 250 °C, often proceeding through a ketene intermediate, to afford 4-hydroxy-3-ethoxycarbonylquinoline (**XIV**). A two-step post-cyclization sequence involves hydrolysis of the ester functionality to a carboxylic acid, followed by decarboxylation, ultimately yielding the desired Quinolin-4(1*H*)-one (**XXV**). While instrumental in the commercial synthesis of bioactive compounds, this classical approach is characterized by generally low overall yields. Furthermore, the high temperatures required frequently induce product decomposition and undesirable side reactions.



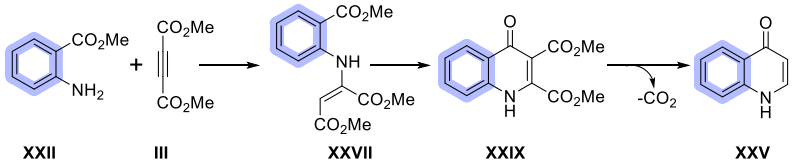
Scheme 1.16: Gould-Jacobs reaction to achieve Quinolin-4(1*H*)-one

Another well-known classical route is the Conrad-Limpach method (**Scheme 1.17**).[60] This reaction involves the condensation of aniline (**XXII**) with **XVIII**, forming an iminoester (**XXVI**) that exists in equilibrium with its iminoenol tautomer. The iminoenol then undergoes an intramolecular hetero-Diels-Alder reaction, yielding a hemiketal intermediate (**XXVII**). Subsequent elimination of alcohol and keto-enol tautomerization furnish the **XXV**. Although efficient, the Conrad-Limpach method necessitates harsh conditions, including high temperatures and strong acid catalysis, and the solvents employed can be costly and challenging to remove from the reaction mixture.



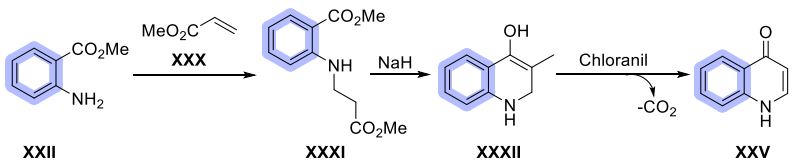
Scheme 1.17: Conrad-Limpach method to achieve Quinolin-4(1*H*)-one

The Biere-Seelen synthesis (**Scheme 1.18**) offers an alternative classical pathway.[61] This procedure initiates with a Michael addition of **III** to methyl anthranilate (**XXII**), forming an enaminoester (**XXVIII**). This compound undergoes though cyclization in the presence of a strong base to yield **XXIX**. Hydrolysis of the ester can be achieved using aqueous sodium hydroxide solution. The final **XXV** is obtained via thermal decarboxylation. This method demonstrates enhanced yields under specific conditions compared to earlier classical syntheses.



Scheme 1.18: Biere-Seelen synthesis to achieve Quinolin-4(1*H*)-one

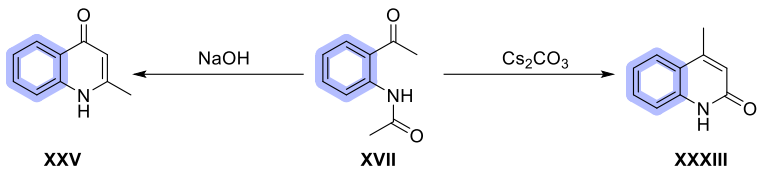
Dieckmann's condensation (**Scheme 1.19**) offers another method to achieve **XXV**. [62] Using an intramolecular cyclization, the reaction of **XXII** with methyl acrylate (**XXX**) yields a diester **XXXI**, which then undergoes intramolecular cyclization in the presence of sodium hydride to form a dihydroquinolinone (**XXXII**). Subsequent oxidation, typically with chloranil, completes the synthesis of the **XXV**.



Scheme 1.19: Dieckmann's condensation to achieve Quinolin-4(1*H*)-one

The Camps' method (**Scheme 1.20**) involves the base-catalyzed intramolecular cyclization of *N*-(2-acylaryl)amides (**XVII**), which can be

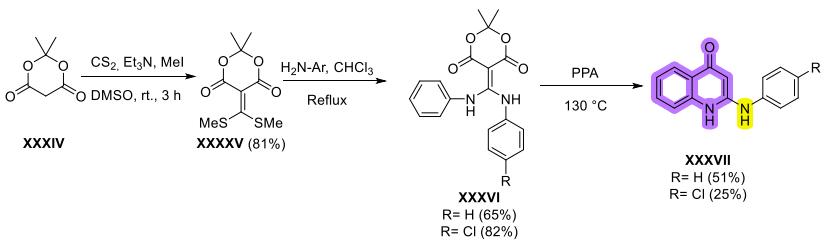
readily prepared from 2-aminoacetophenone.[63] The regioselectivity of this cyclization is reaction conditions dependent, in particular, for the base employed. A strong base, such as sodium hydroxide, promotes deprotonation at the α position of the ketone, leading to intramolecular aldol condensation and the formation of the **XXV**. Cs_2CO_3 leads to **XXXIII** in similar mechanism as a result of the deprotonation at the γ position of the amide portion.



Scheme 1.20: Camps' method to achieve Quinolin-4(1*H*)-one

Despite the widespread application of these classical methods for producing various quinolone derivatives, their use is complicated by the aim of obtaining more complex molecular skeletons. Molecular hybrids between quinolones and triazoles and *N*-aril substituted quinolones are examples of these exceptions that need other synthetic strategies.

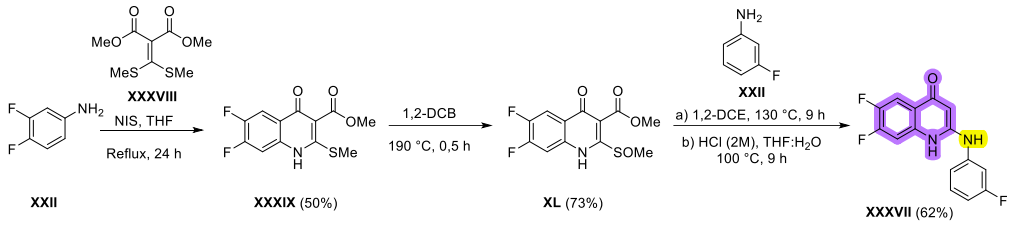
The 2-(arylamino)quinolin-4(1*H*)-one (**XXXVII**) is a notable example with a simple structure and significant potential. Despite extensive research, only three methods have been identified for their synthesis. Erb and co-workers reported in reported using Meldrum's acid to produce type **XXXVII,** involving just two examples via a three-step process with yields ranging from 25% to 51%. (**Scheme 1.21**).[64]



Scheme 1.21: Erb and co-workers methodology to achieve 2-(arylamino)quinolin-4(1*H*)-one

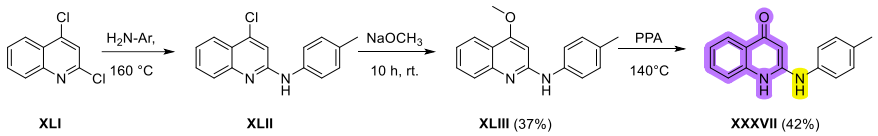
Similarly, Shin and co-workers reported only one example in 2023 the use of dithioacetals **XXXVIII** to achieve **XXXVII** skeleton targeting potent

inhibitors of SARS-CoV-2. In five steps with 22% combined yield, the authors reported the synthesis of compound **XXXVII** (**Scheme 1.22**).[65]



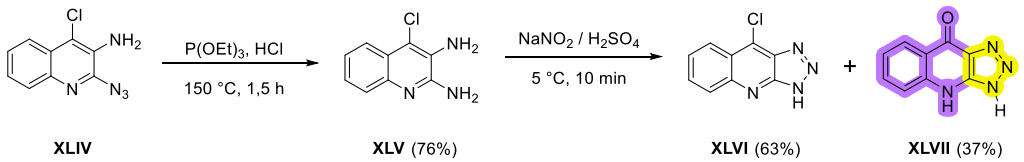
Scheme 1.22: Shin and co-workers methodology to achieve 2-(arylamino)quinolin-4(1*H*)-one

With a different approach, Manoj and co-workers proposed in 2021 the use of 2,4-dichloroquinolines (**XLI**) to achieve different compounds including **XXXVII** as the only example with poor yields and a 3-step route (**Scheme 1.23**).[66]



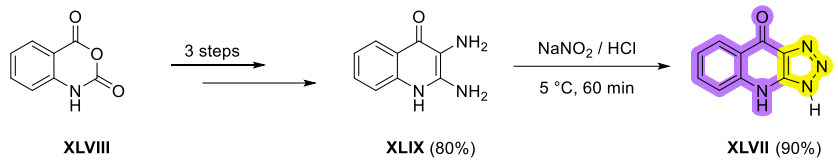
Scheme 1.23: Manoj and co-workers methodology to achieve 2-(arylamino)quinolin-4(1*H*)-one

Another important moiety is 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones (**XLVII**). These hybrid structures offer a synergistic combination of triazole and quinolone pharmacophore characteristics with conformational rigidity important for several applications.[67] in literature, only three examples have been found so far. In 2015, E.J. Mauriño-Reyes and co-workers reported a single example of a fused quinolone-triazole obtained by accident.[68] **XLV** was reacted in the presence of $NaNO_2/H_2SO_4$, obtaining **XLVII** with 37% (**Scheme 1.24**).



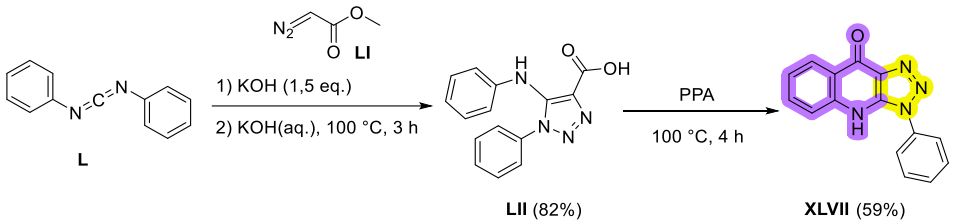
Scheme 1.24: E.J. Mauriño-Reyes and co-workers methodology to achieve 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones

In 2016, [69] ŠIMÁČEK and co-workers similarly reported the synthesis **XLVII** from **XLIXX** obtained in 90% yield as single example (**Scheme 1.25**).



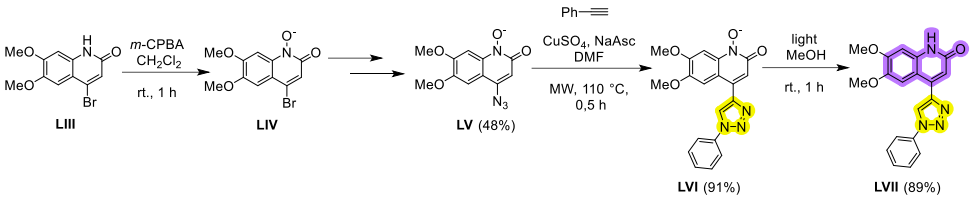
Scheme 1.25: ŠIMÁČEK and co-workers methodology to achieve 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones

Recently, Wang and co-workers described, in 2021, a single example of **XLVII**. As a way to demonstrate post-synthetic possibilities of the trisubstituted triazoles synthesized by the authors, after an ester hydrolysis and cyclization step of intermediate **LII** with phenylpropanolamine (ppa), the final product was obtained in 59% yield (**Scheme 1.26**).[70]



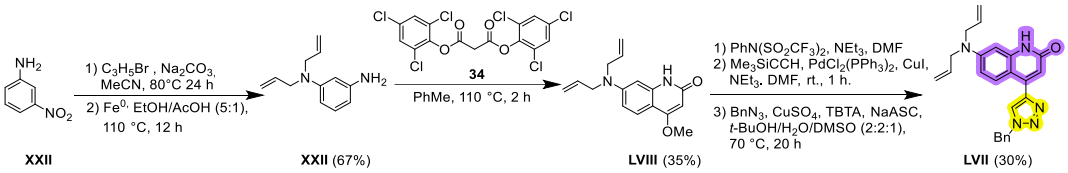
Scheme 1.26: Wang and co-workers methodology to achieve 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones

4-(1-aryll-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones (**LVII**) also possess highly promising applications, primarily due to their luminescent properties. Only two examples of similar structures were found so far. As reported by Glasnov and Kappe in 2007, through a three-step reaction followed by microwave-assisted CuAAC, starting from **LIII,** the authors obtained compound **LVII** in 89% (**Scheme 1.27**).[71]



Scheme 1.27: Glasnov and Kappe methodology to achieve of 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones

In the same year, Sames and co-workers also reported the obtention of **LVII** to use as chelators in rare earth complexes. In seven steps starting from 3-nitro aniline (**XXII**), **LVII** could be obtained in 30% final yield (**Scheme 1.28**).[72]



Scheme 1.28: Sames and co-workers methodology to achieve 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones

Although many synthetic methods are theoretically appealing, their practical use in creating compound libraries often faces key obstacles. One major issue is the dependency on highly toxic reagents and solvents, which raises environmental and safety concerns. Additionally, obtaining specialized or rare starting materials can be a significant hurdle. The process is further complicated by multistep purifications using chromatographic columns, which are time-consuming and resource heavy. These practical challenges often lead to low yields, hindering scaling up and wider application. Given this, developing simpler methods to construct complex structures should be a priority for creating new molecules with various potential applications. 4-Acyl-1,2,3-triazoles serve as a versatile key precursor, offering multiple reactive sites that can generally be used to generate diverse scaffolds.

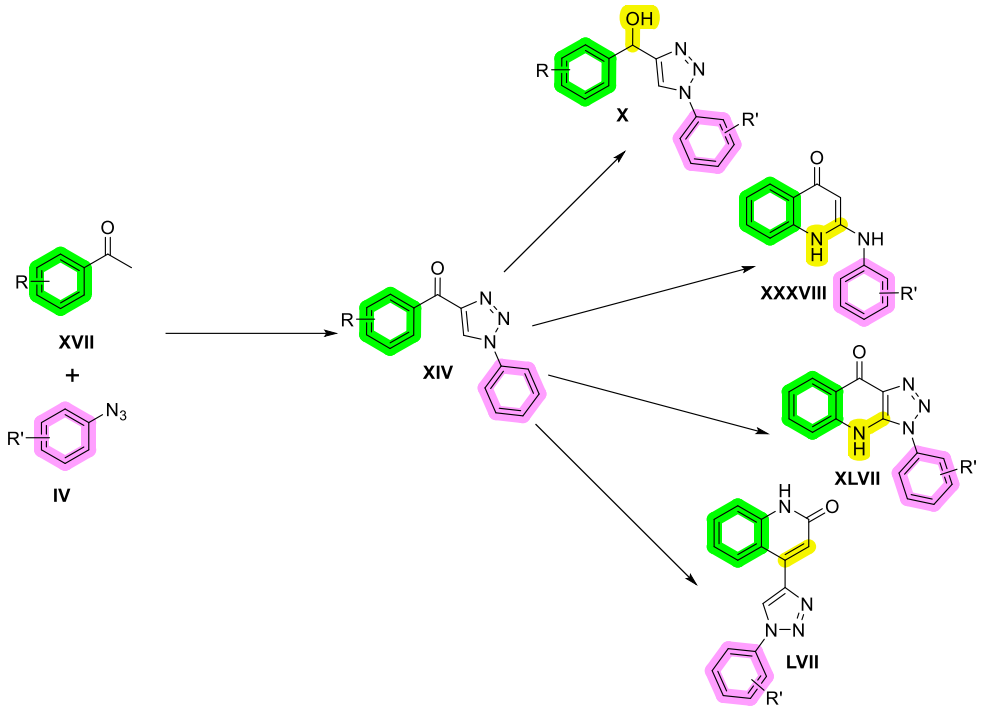
2. Objectives

2.1. General objectives

The primary goal of this thesis is to develop a simple, metal- and solvent-free telescopic reaction to produce 4-acyl-1,2,3-triazoles thay wil be used as key precursors for synthesizing new aryl-triazoyl-methanols with potential biological activity for different mutarions of cystic fibrosis. Additionally, the project aims to use 4-acyl-1,2,3-triazoles to create more complex molecular hybrids such as 2-(arylamino)quinolin-4(1*H*)-one, 3-arnyl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones, and 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones with potential biological activity for cystic fibrosis.

2.2. Specific objectives

- Develop a simple, metal- and solvent-free telescopic reaction to produce 4-acyl-1,2,3-triazoles from commercial reagents.
- Use 4-acyl-1,2,3-triazoles as a key intermediate to achieve compounds with potential biological activity, such as aryl-triazoyl-methanols, 2-(arylamino)quinolin-4(1*H*)-one, 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones, and 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones.
- Consolidate 4-acyl-1,2,3-triazoles as a versatile platform to achieve new heterocycles and more complex structures.

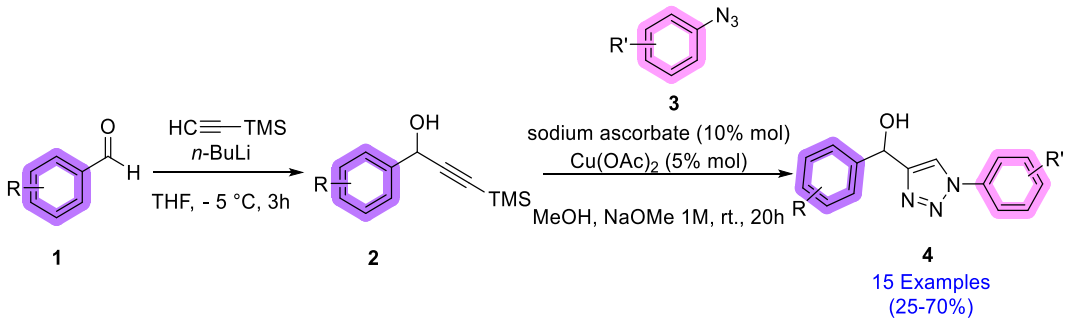


Scheme 2.1: 4-acyl-1,2,3-triazole: from synthesis to key precursor of new complex structures with potential applications.

3. Direct access of 4-acyl-1,2,3-triazoles from acetophenones: a synthetic shortcut for novel p.Phe508del-CFTR traffic correctors

3.1. Introduction

1,2,3-triazole derivatives have become an important in medicinal chemistry due to their broad range of applications. The well-established synthesis of 1,2,3-triazoles by copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been widely used,[73–75] including by our research group.[11,76] We utilized CuAAC between aryl-azide and propargyl alcohols **3**, first prepared from aldehydes **1**. The aryl-triazoyl-methanols **4** presented different biological activities, including Glycine Transporter 1 Inhibitors[11] *Leishmania amazonensis*,[12] and CFTR modulators[13,14] (Scheme 3.1).



Scheme 3.1: Hydroxy-1,2,3-triazoles synthesis by CuAAC reaction

Searching for a simpler methodology to obtain novel aryl-triazoyl-methanols potentially active for CFTR traffic correctors, 4-acyl-1,2,3-triazoles appear as a potential forerunner. Thereby we investigated herein the Enaminone-Azide Cycloadditions (EACA), a simpler and direct way to achive.

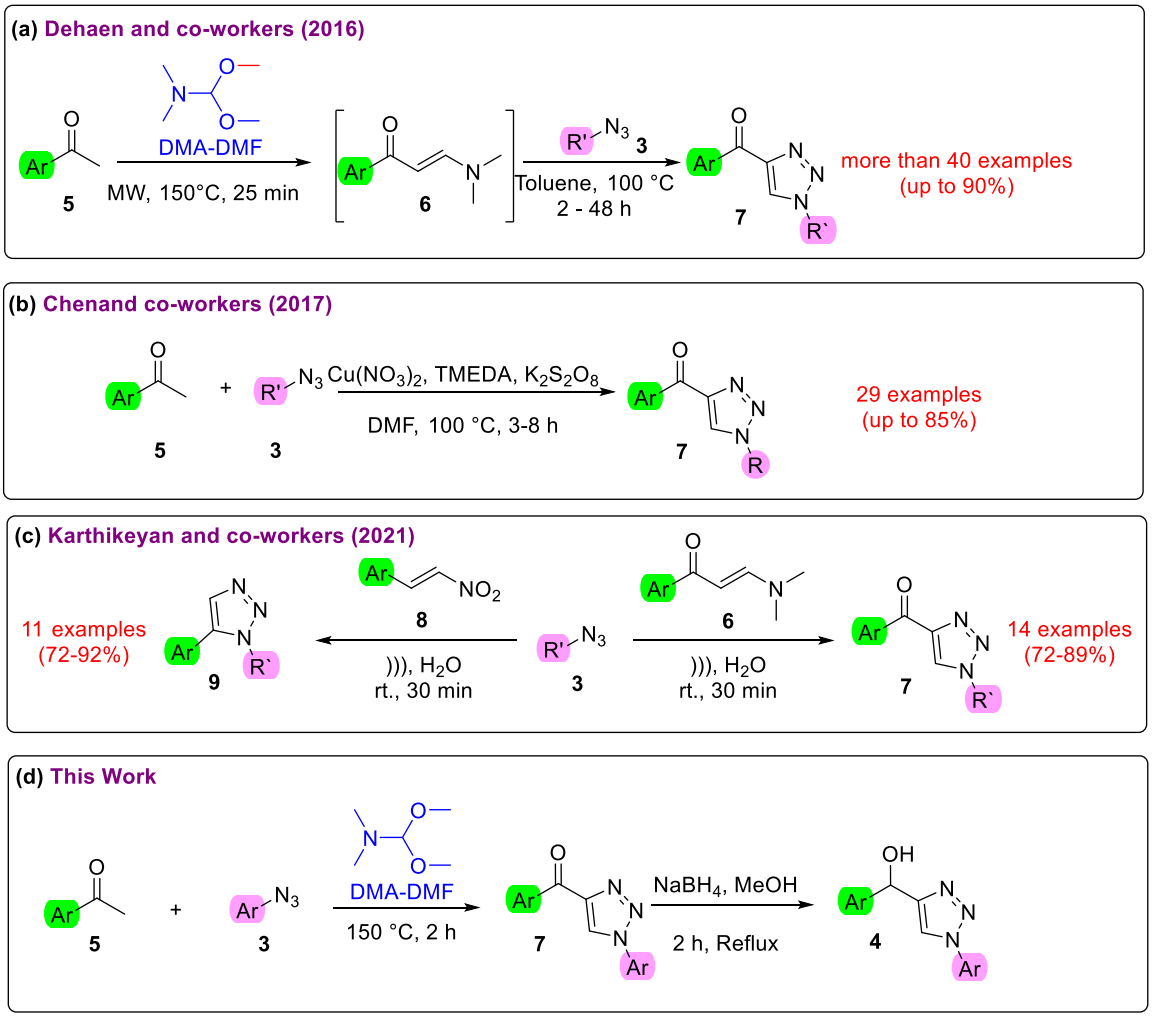
In 2016, Dehaen and co-workers reported a two-step metal-free methodology to achieve 4-acyl-1,2,3-triazoles.[33] In this method, enaminones **7** were first prepared from acetophenones **5** with DMF-DMA in toluene, 100 °C, 12 h. For the second stage, after reaching room temperature, **7** was allowed to react with **3** in using toluene as solvent in a 12-hour reaction to obtain **6** (**Scheme 3.2a**).

In 2017, Chen and co-workers reported a multicomponent synthesis of 4-acyl-1,2,3-triazoles between acetophenones **5**, azides **3** using DMF as a solvent.[22] The reaction was performed in the presence of $Cu(NO_3)_2$ as cathalyst, $K_2S_2O_8$ as oxidizer, TMEDA as base at 100 °C for up to 8 h. Using this methodology, twenty-nine examples with yields of up to 85% were synthesized (**Scheme 3.2b**). Another report by this same author in 2022 described obtaining 4-acyl-1,2,3-triazoles in similar conditions under air atmosphere.[34]

The ultrasound irradiation method, as described by Karthikeyana and co-workers to synthesize 4-acyl-1,2,3-triazole though EACA, has been acknowledged for its efficiency and environmental friendliness (**Scheme 3.2C**).[30] However, its industrial applications are limited due to scale constraints. The metal-free EACA was also applied by our research group for the synthesis of 4-acyl-1,2,3-triazoles.[31] In this case, a small scope of compounds was described, as we were interested in the mechanistic investigation through Hammet correlation and computational studies.

All methodologies described above are undoubtedly powerful synthetic tools for obtaining 4-acyl-1,2,3-triazoles. However, all these methodologies require the use of metals, long reaction times, bases, ligands and need chromatographic column purifitations. This practice is less environmentally friendly and complicates the scaling-up process and industrial applications, drawbacks with potential for improvement.

As part of our continuous effort to identify new drug candidates for treating cystic fibrosis (CF), we sought an improved synthetic route to key aryl-triazoyl-methanol intermediates. We successfully developed a more environmentally friendly process: a solvent- and metal-free, one-pot reaction that directly synthesizes 4-acyl-1,2,3-triazoles from readily available acetophenones and aryl-azides. This process is highly attractive for industrial application because the reaction completes in under two hours under thermal conditions and completely eliminates the need for chromatographic column purification (**scheme 3.2d**).



Scheme 3.2: Summary for the synthesis of 4-acyl-1,2,3-triazoles

The selected compounds were evaluated by their ability to rescue p.Phe508del-CFTR traffic, the most common CF-causing variant affecting.[41] CF is a genetic disorder caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, a cAMP-regulated Cl^-/HCO_3^- channel located at the apical plasma membrane (PM) of several epithelia.[41] It is a chronic disease that has a multiorgan involvement, but the high morbidity and mortality rates are primarily due to the progressive deterioration of lung function.

Over the last decade, modulator drugs rescuing p.Phe508del-CFTR traffic (corrector) and function (potentiator) have been developed, targeting the fundamental cause of CF. Recently, a triple combination composed of two CFTR correctors (VX-661 and VX-445) and a CFTR potentiator (VX-

770) was approved for clinical use after demonstrating safety and efficacy in phase III trials for people with CF carrying at least one copy of p.Phe508del-CFTR.[77–79] Despite this accomplishment, the combination only partially rescues p.Phe508del-CFTR traffic and function.[80] Moreover, many PwCF eligible for this therapy are not taking it due to its prohibitive costs, particularly in low- and middle-income countries (LMICs).[81] Therefore, novel CFTR modulators are still needed not only to provide more robust therapeutic benefits but also to reduce the financial burden with alternative options. By testing these compounds, we expect to identify new therapeutic options for PwCF and contribute to the development of more effective treatments for this devastating disease.

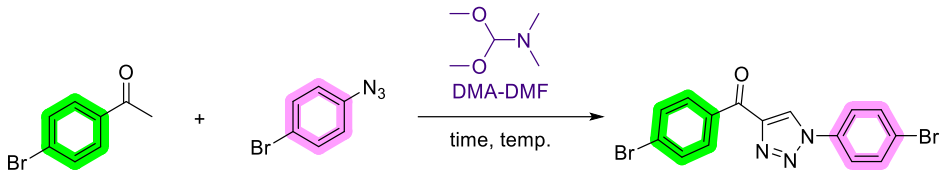
3.2. Results and Discussion

3.2.1. Chemistry

Triazole **6aa** was selected as the reaction model. For the optimization of the reaction, 4-bromo-acetophenone (**5a**) and 1-azido-4-bromobenzene (**3a**) at a 1.5 eq. ratio, employing 1 eq. of DMF-DMA and heating the mixture to 100 °C, **7aa** was obtained in 30% yield. The pure product was then isolated by precipitation in ethanol (**Table 3.1,** entry 1).

To optimize the conditions, we conducted a systematic study by varying the equivalents of DMF-DMA, reaction temperature, and reaction time, as detailed in **Table 3.1**. Our investigations indicated that the most effective conditions for synthesizing triazole **7aa** were achieved by using 2 equivalents of DMF-DMA, 1.5 equivalents of aryl azide **3a**, and heating the reaction mixture to 150 °C for 2 hours. Under these optimized conditions (entry 7), we obtained an average yield of 80%, which was significantly higher than the yields obtained under other reaction conditions. It is noteworthy that increasing the amount of DMF-DMA or reaction temperature beyond a certain point did not improve the yield of triazole **7aa** and led to no product formation. Therefore, our results suggest that the optimized conditions described in entry 7 are critical for the successful synthesis of triazole **7aa**.

Table 3.1: Optimization of the reaction

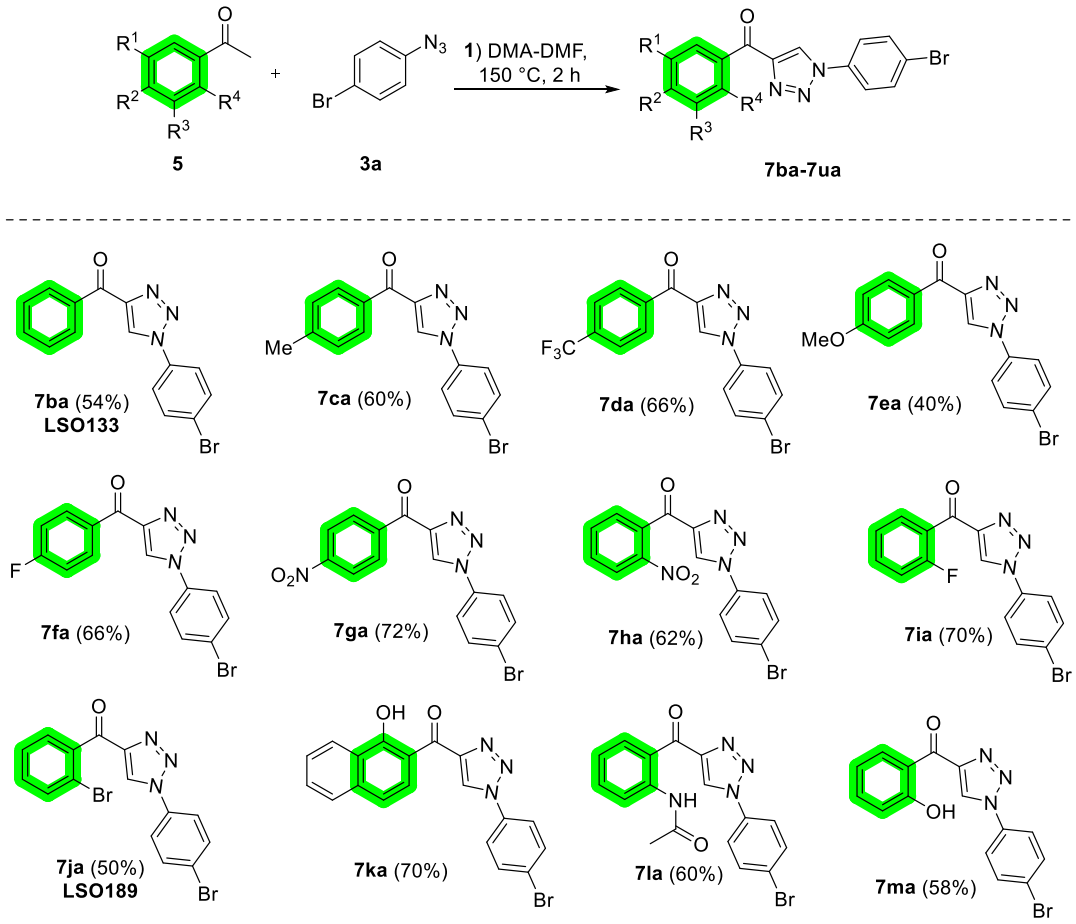


5a **3a** **7aa LSO147**

Entry	DMF-DMA	Temperature (°C)	Time (h)	Yield (%)
1	1 eq	100	1	30
2	1 eq	150	2	50
3	2 eq	150	1	55
4	2 eq	150	2	70
5	2 eq	200	2	No Product
6	3 eq	150	2	50
7*	2 eq	150	2	80

*Average yield using argon atmosphere.

We explored the scope of available acetophenones with different substituition patterns, reacted with aryl azide **3a,** due its well-known behavior in the imposed reaction conditions (**Scheme 3.3**).[12–14] **7ba-7ga** showed yields ranging from 40-66%, with *para*-substituted groups and the *ortho*-substituted acetophenones **7ha-7la**, were achive with 42-70% yields. It is noteworthy that the highest yields were related to compounds that contain groups capable of carbonyl-hydrogen bonding, such as compounds **7ia** and **7la**. This interaction increases the acidity of the alpha carbon thereby allowing for better performance of the reaction.

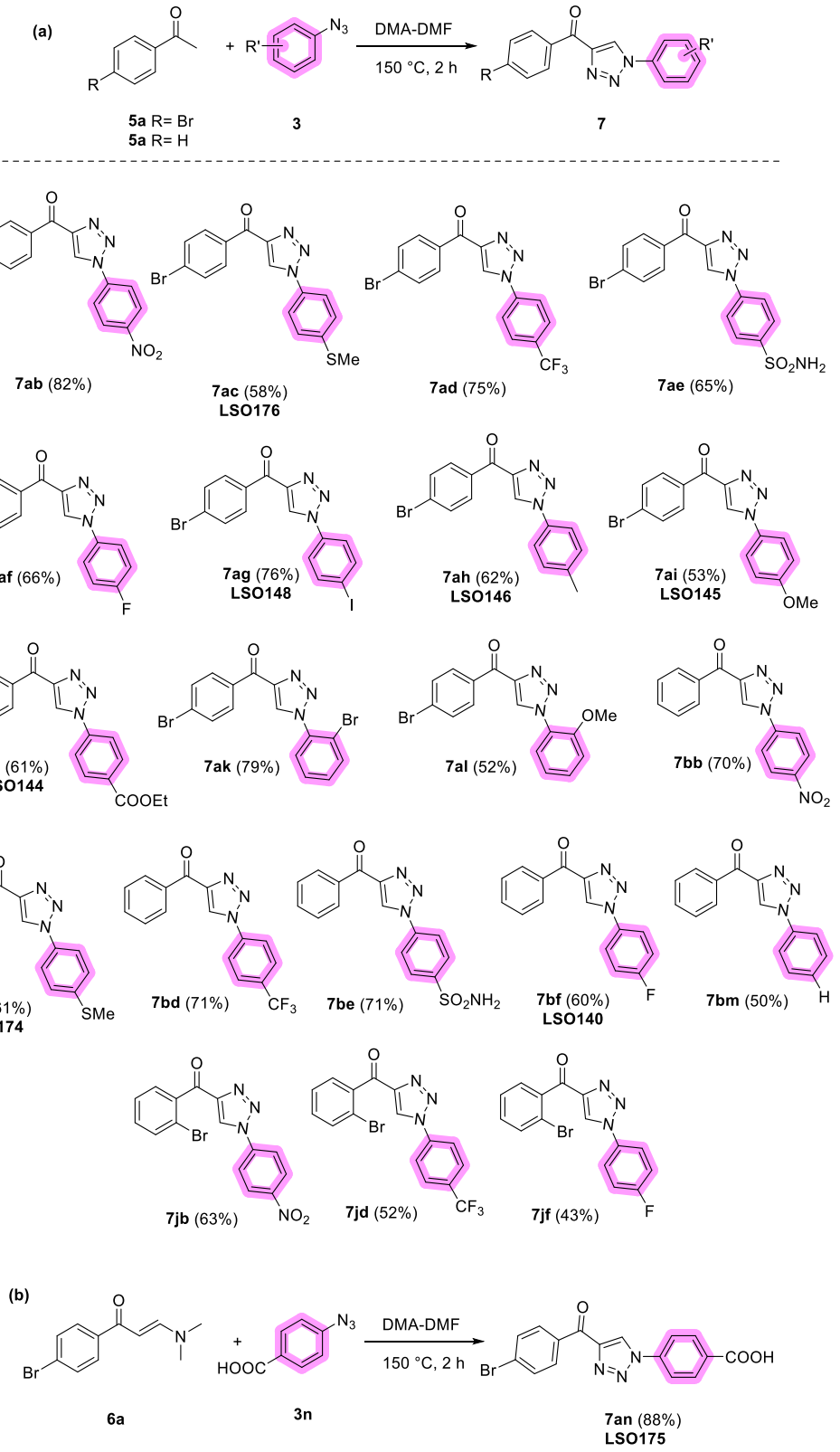


Scheme 3.3: Acetophenone scope reaction

We proceeded by exploring the reaction using various substituted compound **3** derivatives, specifically modifying the para position. We focused on this position because of its significant role in many bioactive compounds.[12–14] By reacting these aryl azides with key Acetophenone derivatives (**Scheme 3.4a**), we successfully synthesized new compounds, including some previously described by our group, more simply and efficiently.

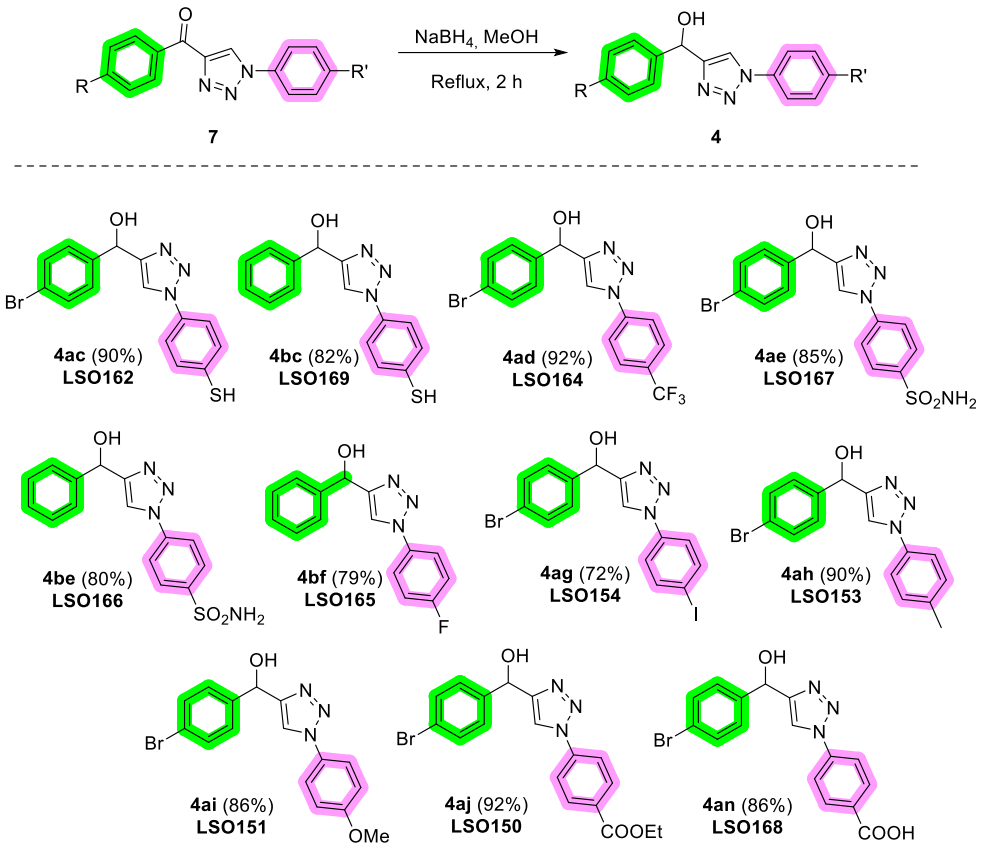
As expected, aryl azides **3** containing withdrawing substituents in the *para* position showed better results as they positively influenced the reaction[31] and led to yields ranging from 50 to 88%. *Ortho* position substitutions were also explored, leading to the synthesis of compounds **7ak-7al** in yields up to 79%. As an exaption of our methodology, compound **7an** had to be prepared using our previous methodology as the deprotonation of 4-azidobenzoic acid (**3n**) led to side reactions due to the *in-situ* formation of methoxide ions from DMF-DMA.[33] Nevertheless, the

compound was obtained in a pure precipitated form in ethanol with an 88% yield (**Scheme 3.4b**).



Scheme 3.4: (a) Azides scope reaction (b) Reaction between enaminones and 4-azidobenzoic acid.

To obtain aryl-triazoyl-methanols **4**, a simple acyl reduction is the most efficient method, allowing 4-acyl-1,2,3-triazoles **7** To be straightforward to obtain. These chass of compounds are promising small molecules that can rescue p.Phe508del-CFTR traffic and potentiate p.Arg334Trp-CFTR function, as demonstrated in recent publications.[13,14] For this purpose, 4-acyl-1,2,3-triazoles with different substitutions in the azide ring were selected based on preliminary results. These compounds were then reduced in the presence of $NaBH_4$, resulting in the formation of **4** with yields ranging from 72 to 92% (**Scheme 3.5**).



Scheme 3.5: Scope of aryl-triazoyl-methanols from acyl reduction

3.2.2. Cystic Fibrosis (CF)

We aimed to discover new p.Phe508del-CFTR correctors, i.e., compounds that rescue the defective folding and traffic. To this end, we evaluated aryl-triazoyl-methanols analogs of **LSO18** and **LSO24**, which were previously identified as potential correctors for CF.[82] Moreover, our goal was not only to identify new scaffolds but also to determine whether 4-acyl-1,2,3-triazoles compounds would have a similar role in rescuing p.Phe508del-CFTR trafficking and function.

Cells were incubated for 24 hours with test compounds, and then the HS-YFP microfluorimetric assay was carried out. Cells were also incubated with the correctors VX-445 and VX-661, and the vehicle DMSO as positive and negative controls, respectively. The rescue of p.Phe508del-CFTR in this assay is measured by the rate of cell fluorescence quenching, which is caused by iodide (I^-) influx through the functional CFTR channels. Following acute stimulation with forskolin plus genistein (as a potentiator), we found that 2 out of 23 compounds (**LSO162** and **LSO168**) significantly increased the cell fluorescence quenching rate, indicating rescue of p.Phe508del-CFTR traffic (**Figure 3.1a**). None of the 4-acyl-1,2,3-triazoles demonstrated the ability to rescue p.Phe508del-CFTR traffic and function, including **LSO147**, the precursor triazole of **LSO24**, which was previously described with an EC_{50} value of 2.7 µM. Similarly, the 4-acyl-1,2,3-triazoles precursors of LSO162 and LSO168 showed an identical profile.

To further evaluate the efficacy and potency of the active compounds, cells were treated for 24 hours at various concentrations in the range of 0.03 to 30 µM the HS-YFP microfluorimetric assay was repeated (**Figure 3.1b**). Both **LSO162** and **LSO168** were demonstrated to be active in the low micromolar range, with EC_{50} values of 2.41 µM and 1.91 µM (**Table 3.2**), suggesting a shared mechanism of action (MoA) with the clinically approved drug VX-445, a CFTR corrector with an EC_{50} of 0.245 µM that is present in the triple combinatorial therapy marketed as Trikafta® in the US and Kaftrio® in Europe.[82]

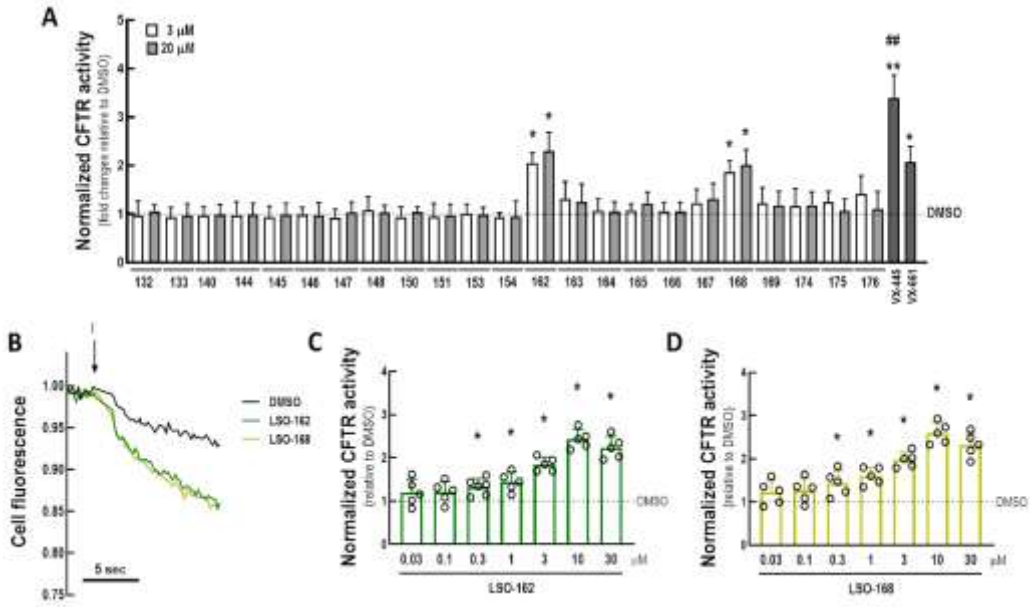


Figure 3.1: (a) CFBE cells co-expressing p.Phe508del-CFTR and the HS-YFP were treated with compounds for 24 h and then acutely stimulated (30 min) with forskolin (10 µM) and genistein (50 µM). CFTR activity was determined based on the HS-YFP quenching rate and normalized to the negative control, DMSO, dashed line); (b) Representative cell fluorescence recording on a plate reader of DMSO and the active compounds: **LSO162** and **LSO168**. Data are shown as means + SD of four independent experiments: vs. DMSO *P<0.05, **P<0.01; vs. VX-661 ##P<0.01. Dose-response relationship for the compounds **LSO162** and **LSO168** were also determined by the HS-YPF assay on a plate reader. Data are shown as means + SD of five independent experiments: vs. DMSO *P<0.05.

The theoretical ADME properties of **LSO162** and **LSO168** were determined based on Lipinski's rule of five,[83] which states that a small molecule should have MW ≤ 500 Da, nHBD ≤ 5, nHBA ≤ 5, nRB ≤ 10, and LogP ≤ 5 to be bioavailable orally (**Table 3.2**). TPSA should also be ≤ 140 Å^2 since it affects absorption and PM permeability. Both **LSO162** and **LSO168** followed Lipinski's rule of five and have a TPSA ≤ 140 Å^2, indicating they have good gastrointestinal absorption. Furthermore, they were not identified as PAINS,[84] i.e., molecules containing "promiscuous" structures that potentially respond in assays independently of the target.

Table 3.2: Dose-response relationship* and in silico determination of absorption, distribution, metabolism, and excretion (ADME)**

Comp	EC_{50} (μM)*	MW**	LogP**	nHBD**	nHBA**	nRD**	TPSA ($Å^2$)**	GI absorption**	PAINS alert**
8ac	2.41	362.24	3.03	1	3	3	89.74	High	0
8al	1.91	374.19	2.32	2	5	4	88.24	High	0

MW: molecular weight; LogP: values corresponding to Consensus $LogP_{w/o}$; nHBD: number of H-bond donors; nHBA: number of H-bond acceptors; nRB: number of rotatable bonds; TPSA: topological polar surface area; GI gastrointestinal; PAINS: pan-assay interference structures.
*Data obtained by the HS-YFP quenching experiments.
**Data obtained by using SwissADME software.

Given the demonstrated *in vitro* ability of compounds **LSO162**, **LSO168, LSO18,** and **LSO24** (previously reported) to act as correctors for p.Phe508del-CFTR trafficking, alongside the structural variations between type **7** precursors and their type **4** derivatives, we utilized a molecular docking protocol within the elexacaftor binding site (PDB ID: 8EIQ), as illustrated in **Figure 2**.

To validate our approach, we used the docking protocol with the ChemPLP score function. We confirmed its reliability by redocking a PM7-optimized elexacaftor structure into its known binding site, which yielded an excellent RMSD value of 0.6167 Å.

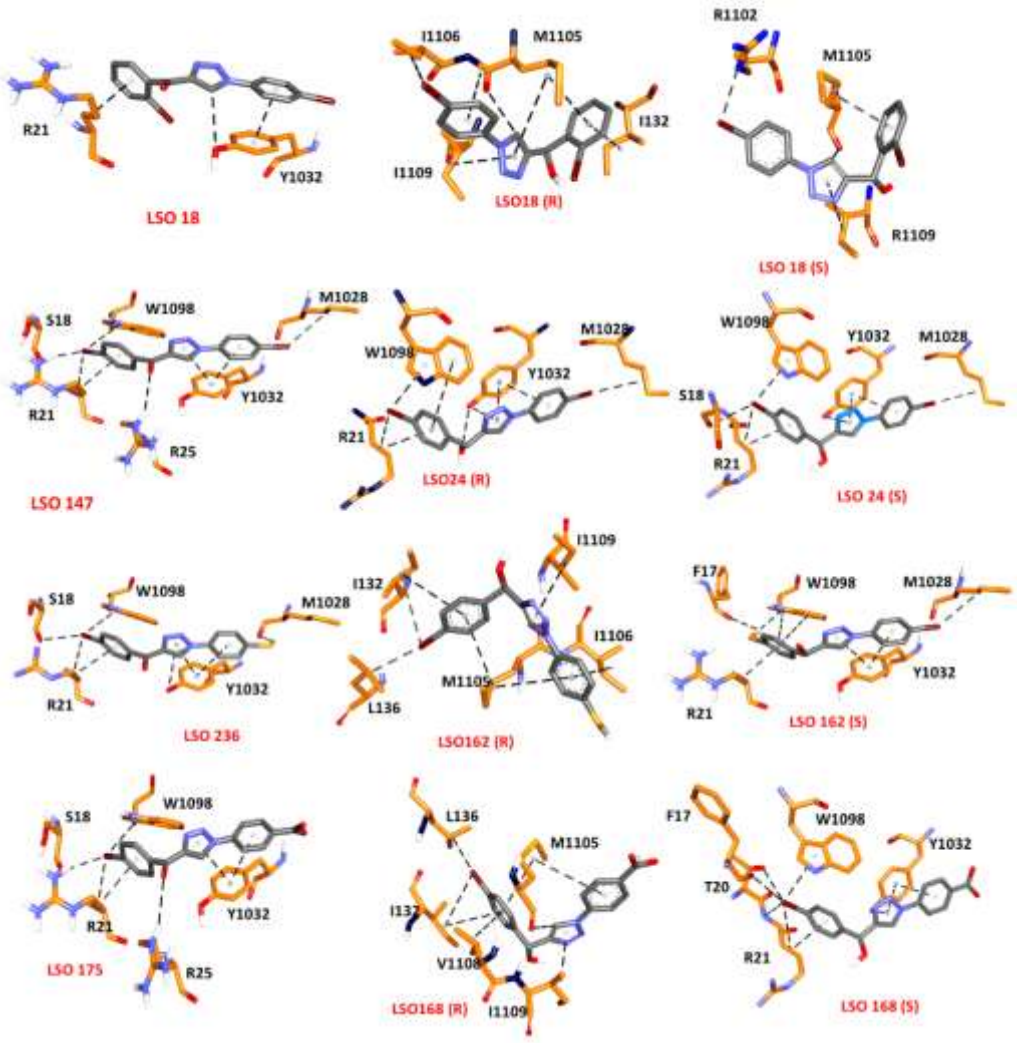


Figure 3.2: 4-acyl-1,2,3-triazoles and the hydroxy-1,2,3-triazole derivatives into a R/S configuration docked in the elexacaftor binding site.

Based on our simulation, we identified two key residues, R21 (in the Lasso motif) and Y1032 (in the TM10 subunit), important for the recognition of type **7** precursors. These results highlight the significance of these residues in mediating molecular interactions within the elexacaftor binding pocket. The aromatic ring of the acetophenone portion establishes a non-classical C–H•••π hydrogen bond with the side chain of R21, while the triazole ring predominantly forms π-π stacking interactions with the side chain of Y1032. The presence of the carbonyl group in type **7** precursors confers conformational rigidity due to sp^2 hybridization. Consequently, slight deviations in the dihedral angles between the aromatic rings of the acetophenone and 1,2,3-triazole subunits occur, ranging from 74.86° to 81.95°. These structural restrictions, as indicated by our computational

analysis, appear to prevent the optimal accommodation of these molecules within the elexacaftor binding pocket.

However, in hydroxylated derivatives following carbonyl reduction, the restrictions decrease as the sp^3-hybridized carbon allows for simple rotational bonds, leading to greater conformational adaptability within the protein pocket. As a result, all hydroxy-1,2,3-triazole derivatives exhibit an increase in docking scores compared to their corresponding carbonylated precursors, indicating a greater affinity for the elexacaftor binding site.

While hydroxy-1,2,3-triazole derivatives did not consistently act with the same intermolecular interactions, they exhibit a preference for molecular complementarity with the side chains composing the TM10 and TM11 subunits. For the potential p.Phe508del-CFTR traffic correctors, **LSO162** and **LSO168**, the R-isomers maintain consistent non-covalent contacts with the side chains of I132 (TM2) through non-classical C–H•••Br interactions. Additionally, the aryl moiety establishes C–H•••π interactions with the side chain of M1105 (TM11), and the centroid of the 1,2,3-triazole fragment exhibits a conserved C–H•••π interaction with the side chain of I1109 (TM11).

Interestingly, the *S*-derivatives display distinct interaction profiles within the cavity, suggesting that only one of the racemate structures should exert the observed *in vitro* p.Phe508del-CFTR traffic corrector activity. These compounds achieve stable conformations through dipole-dipole interactions with the residues R21 (Lasso motif), Y1032 (TM10), and W1098 (TM11).

Furthermore, the thiol and carboxyl substituents in both **LSO162** and **LSO168** do not participate in intermolecular contact with key residues essential for stabilizing the elexacaftor ligand in the binding site. Consequently, we infer that these regions of the compounds are non-auxophoric, contrasting with the acetophenone counterpart.

3.3. Conclusion

This strightfoward methodology proved to be a powerful synthetic strategy for obtaining 4-acyl-1,2,3-triazoles. A wide scope of substrates was studied, and the compounds were obtained in yields from 40% to 88% without the need of chromatographic column purification.

Moreover, 4-acyl-1,2,3-triazoles were used as a precursor to bioactive compounds obtained easily through acyl reduction. Aryl-triazoyl-methanols were obtained with yields from 72% to 92%. For the evaluated for their ability to rescue p.Phe508del-CFTR traffic the selected Twenty-three compounds were tested, and 2 aryl-triazoyl-methanols (**LSO162** and **LSO168**) were able to perform the desired function with EC_{50} 2.41 uM and 1.91 uM, respectively.

Docking Analysis reveals insight into the structure-activity relationship. Particularly, the presence of a halogen substituent in the para-position of the acetophenone ring entity enhances molecular recognition within the binding site, while the 1,2,3-triazole fragment serves as a pivotal pharmacophore group. Moreover, the reduction of the acyl group to a hydroxy-derivative mitigates conformational restrictions, which facilitates greater adaptability during induced docking. Although we found no direct interactions between the substituents in compounds **LSO162** and **LSO168**, the notable difference in their effectiveness strongly suggests that electronic interactions are the key explanatory factor. This conclusion identifies 4-aryl-triazoyl-methanols as excellent candidates for development as new p.Phe508del-CFTR traffic correctors.

3.4. Materials and methods

All reagents were bought from Sigma-Aldrich, Start BioScience, or Proquímios and used as received. Reactions were monitored by thin-layer chromatography using Merck TLC Silica gel 60 F254. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR (^{1}H-decoupled) using $CDCl_3$ or DMSO-d6 as solvents. The chemical shifts (d) were given in parts per million (ppm) and tetramethylsilane was used as an internal standard.

The multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets and td = triplet of doublets. All coupling constants (J values) were given in Hz. High-resolution mass spectra were obtained by a BrukerMicrOTOF II instrument. FTIR measurements were carried out on a Bruker ALPHA II FTIR, using the attenuated total reflection (ATR) technique with an Eco-ATR QuickSnap™ sampling accessory and a diamond/ZnSe crystal plate.

3.4.1. General Procedure for the reaction optimization

To a 4 mL vial wrapped in aluminum foil was added 0.5 mmol of **5a** and 0.75 mmol **3a** followed by *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) with quantities according to **Table 1**. The vial was sealed, and the reaction occurred under different conditions. After that, the reaction was poured into ice cold ethanol and allowed to precipitate for 30 minutes in the refrigerator. The product **7aa** was vacuum filtered and washed with ice-cold ethanol and dried under reduced pressure.

7aa (4-bromophenyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 80% ; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.41 (d, *J* = 8.7 Hz, 2H), 7.76 – 7.66 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 148.6, 135.2, 134.9, 133.2, 132.2, 131.8, 129.0, 126.3, 123.5, 122.2.

3.4.2. General procedure for the direct access of 4-acyl-1,2,3-triazoles

To a 4 mL vial equipped with a magnetic stirring bar and wrapped in aluminum foil was added 0,5 mmol of the appropriate acetophenone and 0.75 mmol of the appropriate azidobenzene followed by 1.0 mmol of DMF-DMA. The vial was sealed with an inert atmosphere using argon and heated at 150 °C in a graphite bath for 2 h. After that, the reaction was poured into ice-cold ethanol or hexane (depending on the solubility) and allowed to

precipitate in the refrigerator. The product was vacuum filtered and washed with ice-cold ethanol and dried under reduced pressure.

7ab (4-bromophenyl)(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 55%; dark Yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 9.81 (s, 1H), 8.50 (d, *J* = 9.1 Hz, 2H), 8.36 (d, *J* = 9.1 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.81, 149.08, 146.88, 140.42, 134.73, 132.22, 131.94, 129.30, 126.42, 125.76, 125.63, 121.07, 119.39. HRMS(ESI) m/z calculated for C15H9BrN4O3+Na [M+Na]+, 394,9756; found 394,9753.

7ac (4-bromophenyl)(1-(4-(methylthio)phenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 58%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 2H), 7.70 (t, *J* = 8.7 Hz, 4H), 7.40 (d, *J* = 8.7 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.22, 148.40, 141.34, 135.07, 133.23, 132.25, 131.80, 128.89, 127.15, 126.23, 121.13, 15.54. HRMS(ESI) m/z calculated for C16H12BrN3OS+Na [M+Na]+, 395,9777; found 395,9777.

7ad (4-bromophenyl)(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 75%; Pale yellow solid. 1H NMR (400 MHz, CDCl3) δ 8.78 (s, 1H), 8.45 – 8.39 (m, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.73 – 7.68 (m, 2H). 13C NMR (101 MHz, DMSO) δ 184.4, 147.4, 135.8, 132.4, 132.2, 131.3, 128.8, 128.1, 120.8.

7ae 4-(4-(4-bromobenzoyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide[86]

Yield 65%; White solid. ^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 8.24 (dd, *J* = 13.2, 8.7 Hz, 6H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 3H), 7.63 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 184.43, 147.55, 145.06, 138.52, 135.86, 132.42, 132.25, 129.04, 128.21, 127.93, 121.61, 120.63.

7af (4-bromophenyl)(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 66%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.46 – 8.39 (m, 2H), 7.83 – 7.76 (m, 2H), 7.73 – 7.68 (m, 2H), 7.32 – 7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.40, 164.21, 148.54, 134.98, 132.24, 131.84, 128.99, 126.61, 122.95, 122.86, 117.22, 116.99. HRMS(ESI) m/z calculated for C15H9BrFN3O+Na [M+Na]+, 367,9805; found 367,9803.

7ag (4-bromophenyl)(1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 76%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.41 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.17, 140.07, 140.00, 138.39, 138.32, 133.09, 133.02, 132.71, 131.45, 131.38, 131.04, 130.99, 127.26, 125.28, 123.13, 121.43. HRMS(ESI) m/z calculated for C15H9BrIN3O+Na [M+Na]+, 475,8866; found 475,8866.

7ah (4-bromophenyl)(1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 62%; Gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.42 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 3.9 Hz, 2H), 7.68 (d, *J* = 3.5 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.36, 148.30, 139.95, 135.12, 134.00, 132.26, 131.78, 130.52, 128.84, 126.44, 120.71, 29.71, 21.20, 21.17.

7ai (4-bromophenyl)(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 53%; Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.42 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 3.6 Hz, 1H), 7.69 (d, *J* = 3.2 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.36, 160.46, 148.25, 135.13, 132.25, 131.77, 129.62, 128.81, 126.49, 122.42, 115.03, 55.72, 55.68.

7aj ethyl 4-(4-(4-bromobenzoyl)-1*H*-1,2,3-triazol-1-yl)benzoate

Yield 61%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.44 – 8.39 (m, 1H), 8.29 – 8.25 (m, 1H), 7.96 – 7.86 (m, 1H), 7.75 – 7.66 (m, 1H), 4.44 (q, *J* = 7.1 Hz, 1H), 1.44 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.09, 165.19, 148.73, 148.64, 134.99, 134.92, 133.10, 133.03, 132.73, 132.68, 132.38, 132.32, 131.55, 131.46, 131.39, 131.06, 131.01, 130.73, 130.66, 129.08, 127.40, 125.42, 121.15, 121.10, 119.51, 119.46, 63.07, 61.64, 61.60, 60.17, 14.94, 13.68. HRMS(ESI) m/z calculated for C15H9BrIN3O+Na [M+Na]+, 422,0111; found 422,0110.

7ak (4-bromophenyl)(1-(2-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 79%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.43 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.50 – 7.42 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.21, 147.59, 135.82, 135.12, 134.15, 132.25, 131.82, 130.65, 128.80, 128.04, 118.60..

7al (4-bromophenyl)(1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 52%; Pale yellow solid. 1H NMR (400 MHz, CDCl3) δ 8.89 (s, 1H), 8.49 – 8.39 (m, 2H), 7.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.51 (td, *J* = 8.3, 1.6 Hz, 1H), 7.18 (ddd, *J* = 8.4, 6.8, 2.9 Hz, 2H), 3.97 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 184.64, 151.04, 147.42, 135.40, 132.25, 131.73, 130.81, 130.59, 128.62, 125.29, 121.35, 112.34, 56.08.

7bb (1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone[85]

Yield 70%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.49 (d, *J* = 7.7 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.26, 148.99, 138.81, 136.23, 133.65, 130.68, 128.54, 127.38, 126.27, 120.88.

7bc (1-(4-(methylthio)phenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone

Yield 61%; Gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.48 (dd, *J* = 5.2, 3.4 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.66 (t, *J* = 1.2 Hz, 1H), 7.65 (t, *J* = 2.0 Hz, 1H), 7.63 (t, *J* = 1.3 Hz, 1H), 7.55 (dd, *J* = 10.5, 4.7 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 2.55 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.53, 148.57, 141.16, 136.44, 133.46, 133.32, 130.67, 128.47, 127.12, 126.14, 121.14, 15.55. HRMS(ESI) m/z calculated for C16H13N3OS+Na [M+Na]+, 318,0672; found 318,0672.

7bd phenyl(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 71%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.49 (d, *J* = 7.4 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.28, 148.98, 138.80, 136.22, 133.67, 131.76, 131.43, 130.68, 128.55, 127.40, 126.30, 120.89.

7be 4-(4-benzoyl-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide[86]

Yield 71%; pale brown solid. ^{1}H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.43 (m, 4H), 7.36 (t, *J* = 7.4 Hz, 2H), 5.94 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 180.53, 153.56, 144.08, 139.16, 128.63, 127.92, 127.70, 126.99, 120.88, 120.62.

7bf (1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone[85]

Yield 60%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 3H), 8.52 – 8.46 (m, 6H), 7.84 – 7.77 (m, 6H), 7.66 (t, *J* = 7.4 Hz, 3H), 7.56 (t, *J* = 7.6 Hz, 6H), 7.30 (d, *J* = 8.4 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.45, 164.15, 161.66, 148.71, 136.38, 133.50, 130.66, 128.48, 126.50, 122.89, 117.15, 116.91.

7bm phenyl(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanone[85]

Yield 50%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.54 – 8.45 (m, 2H), 7.86 – 7.79 (m, 2H), 7.69 – 7.48 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.56 (s), 148.62, 136.4, 133.44, 130.68, 130.00, 129.55, 128.46, 126.35, 120.84.

7jb (2-bromophenyl)(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 63%; yellow solid. ^{1}H NMR (400 MHz, CDCl3) δ 8.79 (s, 1H), 8.54 – 8.36 (d, 2H), 8.12 – 7.99 (d, 2H), 7.68 (td, *J* = 26.6, 7.7, 1.4 Hz, 2H), 7.54 – 7.36 (td, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.30, 183.88, 148.23, 147.89, 140.39, 138.85, 136.51, 133.78, 132.39, 130.16, 127.30, 125.74, 125.59, 121.12, 120.10. HRMS(ESI) m/z calculated for C15H9BrN4O3+H [M+H]+, 372,9931; found 372,9930.

7jd (2-bromophenyl)(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 52%; pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.72 – 7.67 (m, 1H), 7.67 – 7.62 (m, 1H), 7.54 – 7.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.44, 147.98, 138.97, 138.68, 133.73, 132.27, 131.83, 130.18, 127.39, 127.36, 127.24, 125.66, 125.55, 124.73, 120.95, 120.08. HRMS(ESI) m/z calculated for C16H9BrF3N3O+H [M+H]+, 395,9954; found 395,9951.

7jf (2-bromophenyl)(1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 42%; pale yallow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.80 – 7.76 (m, 2H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.46 (td, *J* = 7.5, 1.1 Hz, 1H), 7.39 (td, *J* = 7.7, 1.8 Hz, 1H), 7.28 (d, 1H). 13C NMR (101 MHz, CDCl3) δ 187.57, 164.20, 161.70, 147.74, 139.11, 133.70, 132.54, 132.14, 130.16, 127.20, 125.84, 123.00, 122.91, 120.06, 117.19, 116.96. HRMS(ESI) m/z calculated for C15H9BrFN3O+H [M+H]+, 345,9986; found 345,9983.

7ba (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone[85]

Yield 69%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.59 – 8.43 (m, 2H), 7.72 (s, 4H), 7.64 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 133.5, 133.2, 130.6, 128.5, 126.1, 123.4, 122.2.

7ca (*p*-tolyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 60%; COLOR solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.41 (d, *J* = 8.2 Hz, 2H), 7.71 (s, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 184.93, 149.02, 144.57, 135.39, 133.78, 133.18, 130.83, 129.24, 126.09, 123.34, 122.18, 21.81. HRMS(ESI) m/z calculated for C16H12BrN3O+Na [M+Na]+, 364,0056; found 364,0055.

7da (4-(trifluoromethyl)phenyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 66%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.60 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.78 – 7.68 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 184.36, 148.36, 138.99, 135.18, 133.29, 131.00, 126.48, 125.51, 125.47, 123.68, 122.25, 60.43. HRMS(ESI) m/z calculated for C16H13N3OS+Na [M+Na]+, 417,9773; found 417,9772.

7ea (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanone

Yield 40%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.57 (d, *J* = 9.0 Hz, 2H), 7.71 (s, 4H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 212.61, 165.99, 133.31, 133.30, 133.11, 131.73, 131.73, 126.63, 123.56, 123.56, 122.25, 122.25, 117.53, 113.76, 112.06, 14.30.

7fa (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(4-fluorophenyl)methanone

Yield 66%; Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.90 (td, *J* = 7.6, 1.7 Hz, 1H), 7.71 (s, 4H), 7.58 (ddd, *J* = 15.2, 5.2, 1.7 Hz, 1H), 7.32 (dd, *J* = 11.0, 4.1 Hz, 1H), 7.25 – 7.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.59, 162.14, 159.60, 148.41, 135.28, 134.16, 133.20, 131.35, 126.07, 125.26, 124.21, 123.48, 122.25, 116.73, 116.51. HRMS(ESI) m/z calculated for C16H13N3OS+Na [M+Na]+, 417,9773; found 417,9772.

7ga (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(4-nitrophenyl)methanone

Yield 72%; Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.69 (d, *J* = 9.0 Hz, 2H), 8.39 (d, *J* = 9.0 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.65, 140.85, 139.28, 135.77, 131.75, 126.53, 123.57, 122.32. HRMS(ESI) m/z calculated for C15H9BrFN3O+Na [M+Na]+, 367,9805; found 367,9805.

7ha (2-nitrophenyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 62%; Dark Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.25 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.82 (td, *J* = 7.5, 1.2 Hz, 1H), 7.75 – 7.64 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 186.02, 147.69, 134.23, 133.23, 131.38, 129.29, 124.35, 124.16, 123.65, 122.28. HRMS(ESI) m/z calculated for C15H9BrN4O3+Na [M+Na]+, 394,9750; found 394,9750.

7ia (2-fluorophenyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 70%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.90 (td, *J* = 7.6, 1.7 Hz, 1H), 7.75 – 7.66 (m, 4H), 7.58 (ddd, *J* = 15.2, 5.2, 1.7 Hz, 1H), 7.31 (dd, *J* = 11.0, 4.1 Hz, 1H), 7.24 – 7.18 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.59, 162.14, 159.60, 148.41, 135.28, 134.20, 134.12, 133.20, 131.36, 131.34, 125.26, 124.23, 124.19, 123.48, 122.25, 116.73, 116.51. HRMS(ESI) m/z calculated for C15H9BrFN3O+Na [M+Na]+,

367,9805; found 367,9805.

7ja (2-bromophenyl)(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 50%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.73 – 7.66 (m, 5H), 7.64 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.46 (td, *J* = 7.5, 1.0 Hz, 1H), 7.40 (td, *J* = 7.7, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 187.49, 147.84, 139.07, 135.22, 133.71, 133.22, 132.17, 130.16, 127.20, 125.51, 123.56, 122.25, 120.07. HRMS(ESI) m/z calculated for C15H9Br2N3O+Na [M+Na]+, 427,9005; found 427,9004.

7ka (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(1-hydroxynaphthalen-2-yl)methanone

Yield 70%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.70 (s, 1H), 7.95 – 7.88 (m, 2H), 7.61 – 7.52 (m, 3H), 7.08 – 6.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.59, 164.01, 148.78, 139.19, 137.14, 135.86, 133.64, 126.61, 122.28, 119.39, 118.95, 118.21, 94.91. HRMS(ESI) m/z calculated for C19H12BrN3O2+Na [M+Na]+, 416,0011; found 416,0011.

7la *N*-(2-(1-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 60%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.72 (dd, *J* = 9.6, 5.0 Hz, 1H), 8.62 (s, 1H), 7.95 – 7.90 (m, 1H), 7.67 – 7.59 (m, 1H), 7.59 – 7.54 (m, 1H), 7.25 – 7.19 (m, 1H), 2.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.12, 169.20, 149.01, 141.32, 139.21, 135.88, 135.36, 134.00, 126.53, 122.61, 122.27, 121.91, 120.97, 94.89, 53.44, 25.50. HRMS(ESI) m/z calculated for C17H13BrN4O2+Na [M+Na]+, 407,0114; found 407,0114.

7ma (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(2-hydroxyphenyl)methanone

Yield 58%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.72 (s, 1H), 7.99 – 7.86 (m, 2H), 7.66 – 7.48 (m, 4H), 7.11 – 6.98 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.59, 164.01, 148.78, 139.19, 137.14, 135.86, 133.64, 126.61, 122.28, 119.39, 118.95, 118.21. HRMS(ESI) m/z calculated for C15H10BrN3O2+Na [M+Na]+, 365,9849; found 365,9849.

7pa (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(2-hydroxy-4-methoxyphenyl)methanone

Yield 95%; Brown solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 9.2 Hz, 1H), 8.66 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 4H), 7.26 (s, 1H), 6.74 – 6.24 (m, 2H), 3.89 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.46, 167.33, 166.89, 149.05, 135.34, 135.28, 133.21, 126.28, 123.45, 122.17, 113.07, 108.25, 100.83, 55.65. HRMS(ESI) m/z calculated for C15H10BrN3O2+Na [M+Na]+, 395,9954; found 395,5592.

7qa (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(2,4-dimethoxyphenyl)methanone

Yield 40%; Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.71 (s, 3H), 7.28 (s, 1H), 6.68 – 6.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.77, 164.34, 160.70, 149.58, 135.50, 133.41, 133.10, 124.86, 123.10, 122.10, 120.53, 104.75, 99.14, 55.88, 55.59. HRMS(ESI) m/z calculated for C17H14BrN3O3+Na [M+Na]+, 410,0111; found 410,0111.

7ra (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)methanone

Yield 52%; gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.96 (s, 2H), 7.74 (s, 4H), 4.00 (d, *J* = 1.6 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.56 (s), 152.99, 149.19, 135.33, 133.22, 131.13, 126.36, 123.43, 122.12,

108.38, 61.01, 56.33. HRMS(ESI) m/z calculated for C18H16BrN3O4+Na [M+Na]+, 440,0216; found 440,0216.

7ta benzo[*d*][1,3]dioxol-5-yl(1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methanone

Yield 94%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.34 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.96 (d, *J* = 1.7 Hz, 1H), 7.77 – 7.68 (m, 4H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.09 (s, 2H). 13C NMR (101 MHz, CDCl3) δ 183.09, 152.40, 149.07, 148.07, 135.37, 133.19, 130.81, 127.99, 126.16, 123.36, 122.18, 110.16, 108.08, 101.91. HRMS(ESI) m/z calculated for C16H10BrN3O3+Na [M+Na]+, 393,9798; found 393,9798.

3.4.3. General procedure for 7an synthesis

Both compounds were synthesized by the methodology published in 2022.[85] The appropriated enaminone **6** (0,5 mmol) and **3n** (0,75 mmol) were mixed and heated in a 4 mL vial equipped with a magnetic stirring bar and wrapped in aluminum foil. After 1 hour heating at 150 °C, the reaction was poured into ice-cold ethanol and allowed to precipitate in the refrigerator. The product was vacuum filtered and washed with ice-cold ethanol and dried under reduced pressure.

7an 4-(4-(4-bromobenzoyl)-1*H*-1,2,3-triazol-1-yl)benzoic acid[85]

Yield 88%; Yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 9.74 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 184.44, 147.57, 135.81, 132.43, 132.15, 128.25, 121.82.

3.4.4. General procedure for 4-hydroxy-1,2,3-triazole synthesis

To a round round bottom flask was added 100 mg of the appropriated 4-acyl-1,2,3-triazole **7** and 5 mL of methanol and allowed to stir for a couple minutes. After that 40 mg of $NaBH_4$ was added carefully and the reaction was refluxed for 2 hours. After that, the reaction was poured in ice cold

water, and the pH was dropped using 6 M sulfuric acid. The product was vacuum filtered and washed with ice-cold water and dried under reduced pressure.

4ac (4-bromophenyl)(1-(4-mercaptophenyl)-1*H*-1,2,3-triazol-4-yl)methanol

Yield 90%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.10 (s, 1H), 3.47 (s, 1H). 13C NMR (101 MHz, CDCl3) δ 152.13, 140.50, 131.87, 128.15, 127.11, 122.23, 120.46, 119.31, 68.51. FTIR-ATR (CM^{-1}): 3283; 3130; 1588; 1499; 1424; 1404; 1260; 1220; 1191; 1095; 1047; 1008; 989; 966; 819; 788; 743; 720; 679; 554; 543; 521; 455 HRMS(ESI) m/z calculated for C15H12BrN3OS+Na [M+Na]+, 383,9777; found 383,9777.

4bc (1-(4-mercaptophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol

Yield 82%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.07 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.61, 140.78, 140.19, 133.95, 131.76, 128.17, 127.15, 122.02, 120.90, 119.31, 68.49. FTIR-ATR (CM^{-1}): 3216; 2917; 1639; 1590; 1501; 1404; 1320; 1219; 1191; 1097; 1052; 1009; 989; 815; 773; 743; 549; 514; 469; 417. HRMS(ESI) m/z calculated for C16H15N3OS+Na [M+Na]+, 320,0826; found 320,0826.

4ad (4-bromophenyl)(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanol

Yield 92%; pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 – 7.53 (m, 2H), 7.52 – 7.46 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.28 (m, 2H), 6.07 (s, 1H), 3.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.63 (s), 140.79 (s), 140.18 (s), 133.93 (s), 131.75 (s), 128.17 (s), 127.11 (s), 122.01 (s), 120.90 (s), 119.33 (s), 68.46 (s). FTIR-ATR (cm^{-1}): 3237; 3136; 1591; 1575; 1518; 1481; 1400; 1381; 1319; 1273; 1226; 1192; 1175; 1053; 1033; 1006; 992; 947; 859; 843; 820; 787; 703; 665; 627; 548; 519; 484; 451; 420.

HRMS(ESI) m/z calculated for C16H15N3OS+Na [M+Na]+, 419,9930; found 419,9930.

4ae 4-(4-((4-bromophenyl)(hydroxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide

Yield 85%; Gray solid. ^{1}H NMR (400 MHz, DMSO) δ 8.89 – 8.57 (m, 1H), 8.25 – 7.89 (m, 6H), 7.73 – 7.28 (m, 8H), 6.06 – 5.60 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.02, 144.16, 143.44, 139.11, 131.52, 129.21, 127.91, 121.06, 120.77, 120.64, 67.65. FTIR-ATR (CM^{-1}): 3342; 1626; 1592; 1494; 1326; 1153; 1089; 911; 834; 763; 695; 589; 545. HRMS(ESI) m/z calculated for C16H15N3OS+Na [M+Na]+, 430,9784; found 430,9784.

4be 4-(4-(hydroxy(phenyl)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide

Yield 80%; Gray solid. ^{1}H NMR (400 MHz, DMSO) δ 84H), 7.36.78 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.44 (m, (t, *J* = 7.4 Hz, 2H), 5.94 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.56, 144.08, 139.16, 128.63, 127.92, 127.70, 126.99, 120.88, 120.62, 68.44. FTIR-ATR (CM^{-1}): 3244; 2924; 2409; 2259; 2090; 1715; 1629; 1588; 1489; 1428; 1414; 1327; 1278; 1191; 1152; 1127; 1085; 1012; 970; 908; 838; 820; 715; 630; 587; 540; 511; 450. HRMS(ESI) m/z calculated for C15H14N4O3S+Na [M+Na]+, 353,0684; found 353,0684.

4bf (1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol

Yield 79%; Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 – 7.57 (m, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.34 – 7.28 (m, 1H), 7.16 (t, *J* = 8.5 Hz, 2H), 6.11 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.67, 161.19, 152.30, 141.81, 128.66, 128.10, 126.42, 126.21, 122.54, 119.73, 116.76, 116.53, 69.06. FTIR-ATR (CM^{-1}): 3219; 3159; 1601; 1568; 1510; 1454; 1342; 1294; 1267; 1227; 1190; 1154; 1099; 1077; 1048; 990; 915; 833; 814; 805; 787; 757; 695; 643; 621; 607; 545; 518; 479; 451. HRMS(ESI) m/z calculated for C15H12FN3O+Na [M+Na]+, 292,0857; found 292,0857.

4ag (4-bromophenyl)(1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl)methanol

Yield 72%; Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.82 (s, 3H), 7.54 (s, 3H), 7.52 (s, 5H), 7.45 (d, *J* = 8.9 Hz, 6H), 7.42 – 7.39 (m, 5H), 7.38 (s, 2H), 6.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.89, 131.84, 128.14, 125.53, 122.02, 119.11, 68.63. FTIR-ATR (cm^{-1}): 3194; 2260; 1584; 1488; 1397; 1227; 1189; 1059; 1041; 1022; 1010; 986; 883; 838; 806; 777; 722; 690; 630; 536; 512; 489; 461; 424; 405. HRMS(ESI) m/z calculated for C15H11BrIN3O+Na [M+Na]+, 477,9022; found 477,9022.

4ah (4-bromophenyl)(1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methanol

Yield 90%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.56 (s, 1H), 7.53 (d, *J* = 1.5 Hz, 2H), 7.51 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.08 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.39, 140.75, 139.09, 135.78, 134.60, 131.78, 130.25, 128.18, 125.53, 122.05, 120.48, 119.42, 68.59, 21.10. FTIR-ATR (cm^{-1}): 3237; 3136; 1591; 1575; 1518; 1481; 1400; 1381; 1319; 1273; 1226; 1192; 1175; 1053; 1033; 1006; 992; 947; 859; 843; 820; 787; 703; 665; 627; 548; 519; 484; 451; 420. HRMS(ESI) m/z calculated for C16H14BrN3O+Na [M+Na]+, 366,0218; found 366,0218.

4ai (4-bromophenyl)(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanol

Yield 86%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.61 – 7.58 (m, 1H), 7.58 – 7.56 (m, 1H), 7.56 – 7.50 (m, 2H), 7.41 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.04 – 6.98 (m, 2H), 6.09 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.93, 151.38, 140.81, 131.76, 130.32, 128.18, 122.23, 122.01, 119.62, 114.76, 68.54, 55.64. FTIR-ATR (cm^{-1}): 3281; 3128; 1608; 1591; 1516; 1482; 1455; 1440; 1408; 1303; 1252; 1220; 1181; 1107; 1065; 1048; 1030; 1009; 989; 832; 800; 784; 655; 628; 614; 554; 534; 473; 424. HRMS(ESI) m/z calculated for C16H14BrN3O2+Na [M+Na]+, 382,0162; found 382,0162.

4aj ethyl 4-(4-((4-bromophenyl)(hydroxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzoate

Yield 92%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.12 (m, 1H), 7.83 – 7.75 (m, 1H), 7.55 – 7.51 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 6.09 (s, 1H), 1.62 (s, 1H), 1.31 – 1.10 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 165.69, 152.77, 152.32, 143.28, 143.26, 143.10, 140.03, 135.50, 131.33, 131.30, 131.24, 129.52, 129.00, 127.90, 120.75, 120.60, 120.52, 120.08, 120.01, 67.49, 67.43, 62.46. FTIR-ATR (cm^{-1}): 3557; 3130; 2949; 1717; 1606; 1517; 1484; 1442; 1401; 1348; 1311; 1284; 1226; 1196; 1176; 1111; 1064; 1039; 1009; 989; 960; 901; 859; 814; 781; 766; 690; 628; 546; 513; 463. HRMS(ESI) m/z calculated for C18H16BrN3O3+Na [M+Na]+, 424,0267; found 424,0267.

4an 4-(4-((4-bromophenyl)(hydroxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzoic acid

Yield 86%; brown solid. ^{1}H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 6.4 Hz, 1H), 8.13 – 8.08 (m, 2H), 8.07 – 8.02 (m, 2H), 7.61 – 7.51 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.91 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.89, 152.95, 143.40, 140.01, 131.52, 130.91, 129.22, 121.09, 120.98, 120.77, 120.16, 67.63. FTIR-ATR (cm^{-1}): 2921; 2851; 2554; 1678; 1606; 1519; 1483; 1408; 1321; 1290; 1235; 1210; 1176; 1132; 1117; 1068; 1044; 1007; 990; 935; 862; 835; 811; 768; 723; 706; 687; 628; 542; 511; 451; 416. HRMS(ESI) m/z calculated C16H12BrN3O3+Na [M+Na]+, 395,9954; found 395,9954.

3.4.5. Cell culture

Cystic Fibrosis Bronchial Epithelial (CFBE) cells co-expressing F508del-CFTR and the halide sensitive yellow fluorescence protein (HS-YFP H148Q/I152L) were cultured in Eagle's minimum essential medium (#BE12-611F, Lonza, Basel, Switzerland) complemented with 10% fetal bovine serum (#LTI 10270-106, Gibco, Carlsbad, CA, USA), 2 $\mu g.mL^{-1}$ puromycin (#P8833, Sigma-Aldrich, St. Louis, MO, USA) and 0.6 $mg.mL^{-1}$ G418 (#A1720, Sigma-Aldrich, St. Louis, MO, USA). Cells were maintained at 37ºC and 5% CO_2 in a humidified incubator.

3.4.6. Assessment of CFTR rescue by the HS-YFP assay on a plate reader

Cells were seeded at a density of 50,000 cells/well onto clear-bottom 96-well black plates (#655090, Greiner Bio-One, Kremsmünster, Austria).[87] After incubation with test compounds for 24 h, cells were washed twice with phosphate-buffered saline (PBS) and then incubated for 30 min with 60 µL of PBS containing 20 µM forskolin (Fsk, #F6886, Sigma-Aldrich, St. Louis, MO, USA) plus 50 µM genistein (#G6649, Sigma-Aldrich, St. Louis, MO, USA) for stimulation of CFTR channels. Thereafter, cells were transferred to a plate reader (Tecan Infinite 200 Pro) to determine CFTR activity. The plate reader was equipped with high-quality excitation (485 ± 20 nm) and emission (535 ± 25 nm) filters for YFP. The fluorescence was recorded for 2s before and 12 s after injection of 165 µL of an I^--containing solution (PBS with NaI instead of NaCl, final I^- concentration = 100 mM). Data were normalized to the initial background-subtracted fluorescence. In order to determine I^- influx rate, the final 11s of the data for each well were fitted with an exponential function to extrapolate the initial slope. All conditions were carried out in triplicated on each plate.

3.4.7. Assessment of in silico absorption, distribution, metabolism, and excretion (ADME)

ADME analysis was performed with the free online software SwissADME (http://www.swissadme.ch) as described.[88] The following physicochemical parameters were evaluated based on Lipinski's rule of five[89]: molecular weight (MW); number of H-bond donors (nHBD); number of H-bond acceptors (nHBA); number of rotatable bonds (nRB); the calculated logarithm of the octanol-water partition coefficient (LogP); in addition to the topological polar surface area (TPSA). Active compounds were also subjected to filters for the identification of pan-assay interference compounds (PAINS).

3.4.8. Molecular docking protocol

Before docking, all structures were designed using Discovery Studio visualizer software following the structural elucidation information developed in this study. Subsequently, molecules were geometrically optimized using the semi-empirical PM7 method in MOPAC. For docking, the crystalline protein structure of ΔF508 CFTR, complexed with TRIKAFTA IFA (elexacaftor, tezacaftor, ivanacaftor), was downloaded from the Protein Data Bank with the PDB ID 8EIQ. The protein was inspected in Biovia DS, and non-important co-crystals were removed for the calculation. Finally, 50 runs were applied for each ligand in the semiflexible model at the elexacaftor binding site using CSD GOLD software. This binding site was used as a model, considering the previous results reported by our group.[7] The ChemPLP scoring function was selected, and the docking pose with the best score was chosen for visual inspection. The computational routine validation was verified using the redocking technique.

4. Amide-derived 4-acyl-1,2,3-triazoles: a versatile platform for the synthesis of novel quinolone-based scaffolds

4.1. Introduction

Triazole-based compounds, especially those containing a carbonyl moiety, have been extensively investigated as drug candidates due to their inherent versatility and ability to act as *trans*-amide bioisosteres. The literature demonstrates numerous such candidates with diverse applications, including anticancer (**1**), antiviral (**2**), and neurotrophic effects (**3**) (**Figure 4.1a**).[90]

Quinolones, which are structurally derived from quinoline (a scaffold originally obtained from quinine), exist in tautomeric equilibrium with hydroxyquinolines, predominantly as quinolin-4(1*H*)-one and quinolin-2(1*H*)-one isomers. These compounds are frequently found in natural products and widely used in commercial drugs. Their well-established antibacterial activity is exemplified by ciprofloxacin (**4**). Additionally, they exhibit regulatory effects in the human body (e.g., ivacaftor, **5**), antipsychotic effects (e.g., brexpriprazole **6**), and various other applications (**Figure 4.1b**).[54,55,91]

While transformations of functionalized triazoles are well-documented, the direct conversion of 4-acyl-1,2,3-triazoles into diverse heterocyclic systems remains relatively unexplored. Recent reviews highlight the utility of triazoles as versatile building blocks for nitrogen-containing heterocycles.[92] Our research group has previously demonstrated the straightforward reduction of the carbonyl group in these compounds using $NaBH_4$, yielding hydroxy-1,2,3-triazole derivatives with broad biological activity.[12,93–95] Conversely, quinolones are also emerging as promising candidates for molecular hybridization. An illustrative example is the work by Doiron and co-workers, who examined the effectiveness of 1,2,3-triazoles as *trans*-amide bioisosteres in cystic fibrosis modulators, specifically analogues of VX-770 (**7**) (**Scheme 4.1c**).[96]

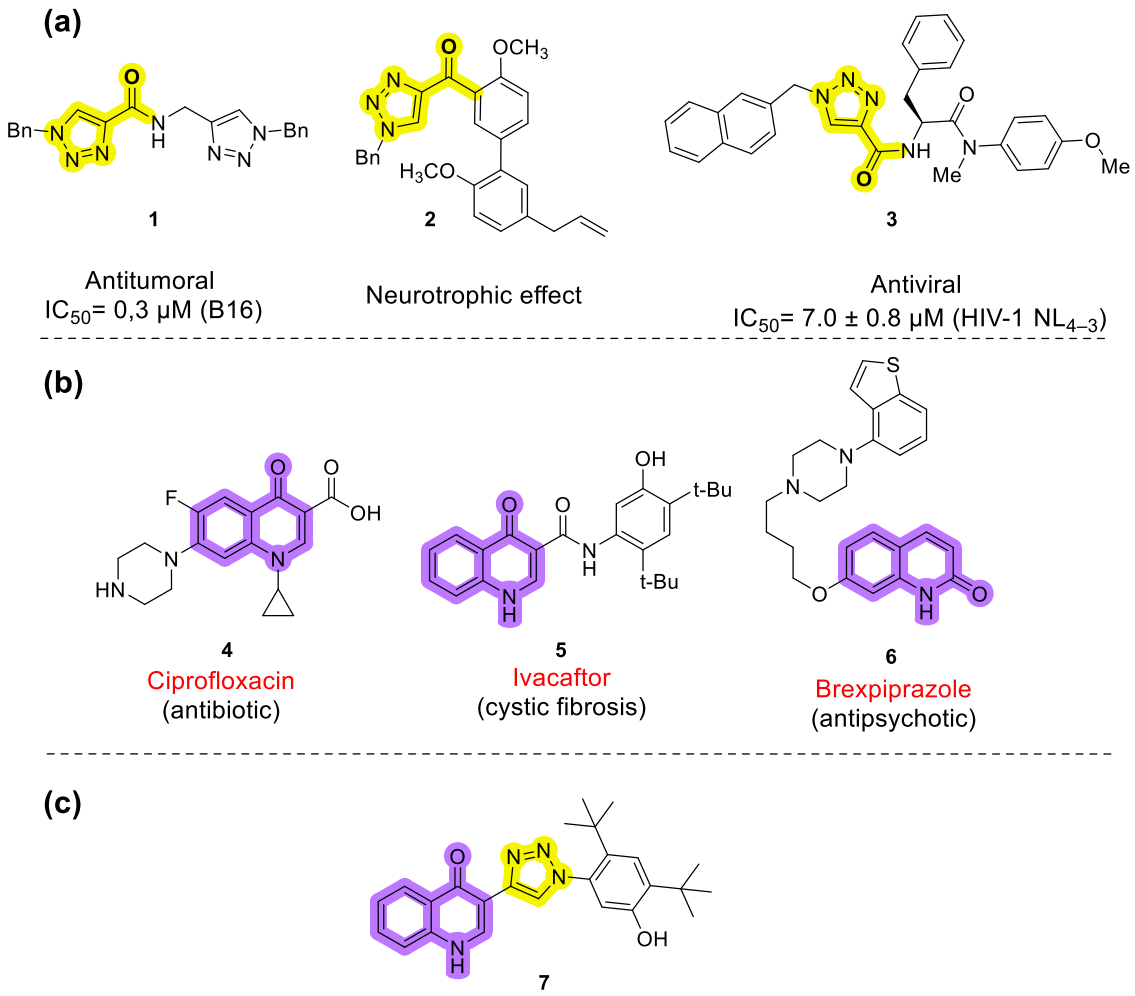
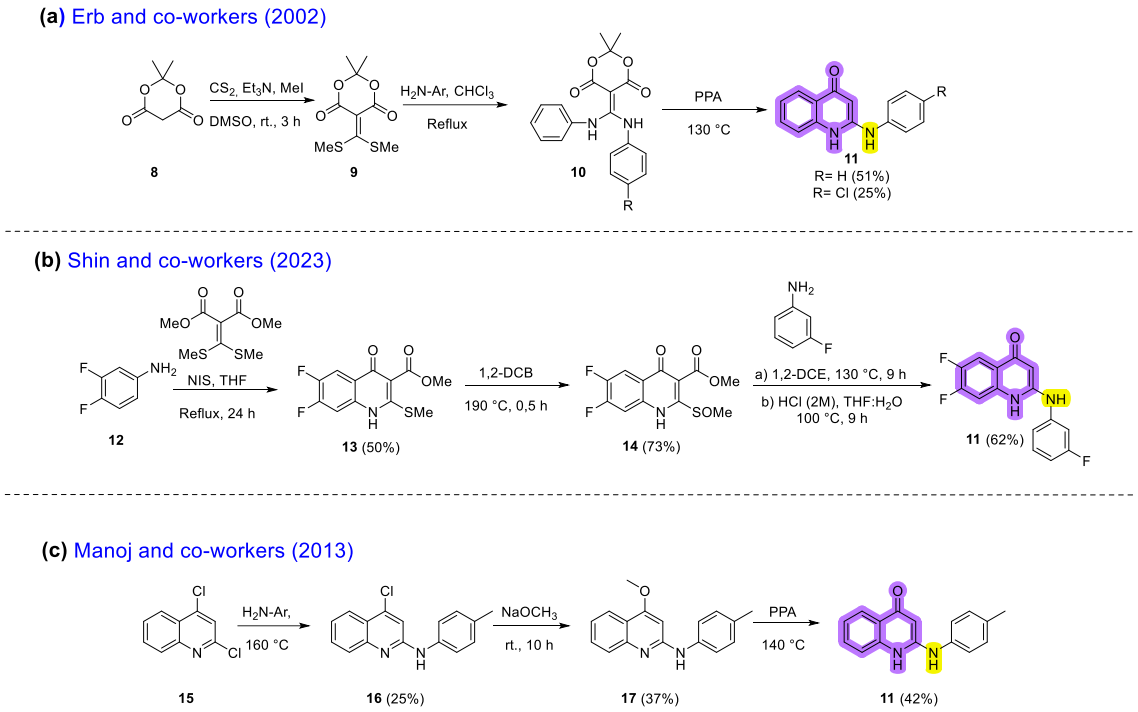


Figure 4.1: (a) Biologically active 4-acyl-1,2,3-triazoles; (b) Commercial quinolone drugs; (c) Ivacaftor-triazole hybrid.

Nevertheless, specific examples originating from 4-acyl-1,2,3-triazoles remain notably scarce. Consequently, pioneering novel synthetic routes from these intermediates constitutes a highly relevant and innovative contribution to contemporary heterocyclic chemistry, particularly for accessing quinolone scaffolds.

The 2-(arylamino)quinolin-4(1*H*)-one (**11**) stands out as a notable example with a simple structure and significant potential. Despite extensive research, only three synthetic methods for these compounds have been reported. Erb and co-workers described a technique using Meldrum's acid to produce type **11**, involving a three-step process with two examples and

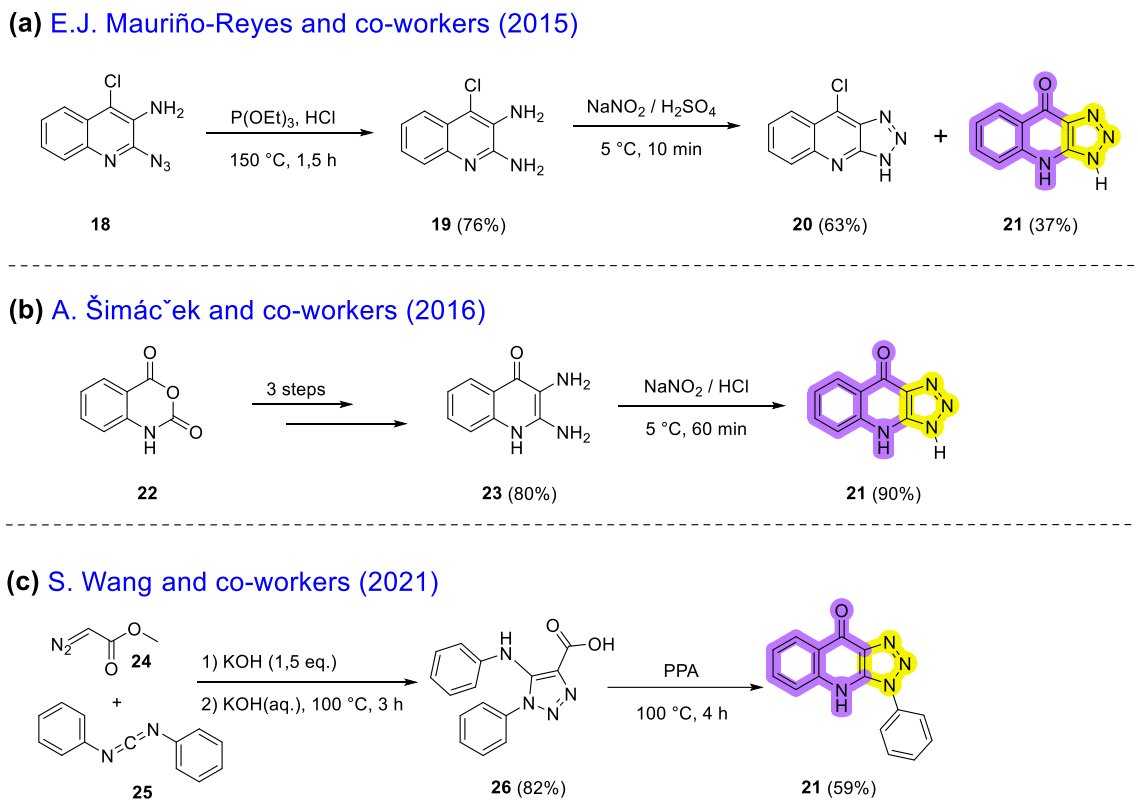
yields ranging from 25% to 51% (**Scheme 4.1a**). Similarly, in 2023, Shin and co-workers reported a single example using dithioacetals to construct compounds like **11**, targeting potent inhibitors of SARS-CoV-2, obtained after a five-step synthesis with a total yield of 22% (**Scheme 4.1b**). Taking a different approach, Manoj and co-workers proposed in 2021 using 2,4-dichloroquinolines (**15**) to synthesize various compounds, including **11** as a sole example. However, only one example of a similar structure was reported with poor yields via a three-step route (**Scheme 4.1c**).[66]



Scheme 4.1: Reported Syntheses of 2-(arylamino)quinolin-4(1*H*)-ones synthesis in the Literature.

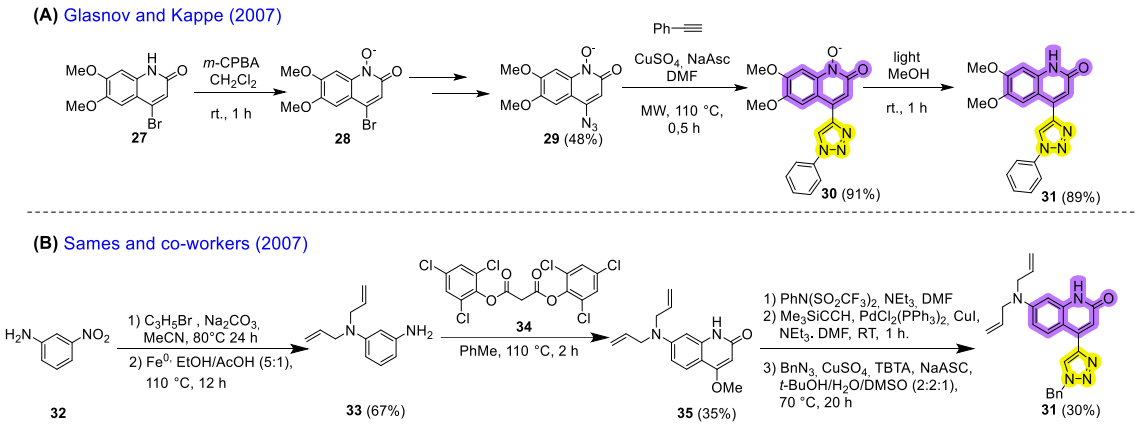
Another important moiety is 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones (**21**). These hybrid structures offer a synergistic combination of triazole and quinolone pharmacophore characteristics with conformational rigidity important for several applications.[67] in literature, only three examples have been found so far. In 2015, E.J. Mauriño-Reyes and co-workers reported a single example of a fused quinolone-triazole obtained by accident.[68] **18** was reacted in the presence of $NaNO_2/H_2SO_4$, obtaining **21** with 37% by accident (**Scheme 1.24**). In 2016,[69] ŠIMÁČEK and co-workers similarly reported the synthesis **21** from **22** obtained in 90% yield as single

example (**Scheme 1.25**). Recently, Wang and co-workers described, in 2021, a single example of **21**. As a way to demonstrate post-synthetic possibilities of the trisubstituted triazoles synthesized by the authors, after an ester hydrolysis and cyclization step of intermediate **26** with phenylpropanolamine (ppa), the final product was obtained in 59% yield (**Scheme 1.26**).[70]



Scheme 4.2: Reported Syntheses of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones in the Literature

4-(1-aryll-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones (**31**) also possess up-and-coming applications, primarily due to their luminescent properties. Only two examples of similar structures were found so far. As reported by Glasnov and Kappe in 2007, through a three-step reaction followed by microwave-assisted CuAAC, starting from **27,** the authors obtained compound **31** in good yields (**Scheme 4.3a**).[71] In the same year, Sames and co-workers also reported the obtention of **31** to use as chelators in rare earth complexes. In seven steps starting from 3-nitro aniline (**32**), **31** could be obtained in 30% final yield (**Scheme 4.3b**).[72]



Scheme 4.3: Reported Syntheses of 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones in the Literature.

Despite the theoretical appeal of many synthetic methodologies, their practical implementation for creating compound libraries often encounters significant hurdles. A frequent concern is the reliance on highly toxic reagents and solvents, posing considerable environmental and safety challenges. Furthermore, access to specialized or uncommon starting materials can be a major impediment, a flaw often compounded by multistep purifications using chromatographic columns that are both time-consuming and resource intensive. Ultimately, these practical limitations frequently culminate in undesirable low yields, hindering scalability and broader applicability.

Therefore, developing simpler and more efficient methods is crucial for constructing complex heterocyclic scaffolds. In this context, 4-acyl-1,2,3-triazoles emerge as versatile key precursors, providing multiple reactive sites suitable for producing a variety of molecular architectures.

Building upon our group's expertise in the synthesis and application of 4-acyl-1,2,3-triazoles, and motivated by the therapeutic importance of the quinolin-4(1*H*)-one core in drugs such as those used to treat cystic fibrosis, we aimed to address these challenges.

Building upon our group's expertise in the synthesis and application of 4-acyl-1,2,3-triazoles, and motivated by the therapeutic importance of the quinolin-4(1*H*)-one core in drugs such as those used to treat cystic fibrosis, we aimed to address these challenges. Our goal is to develop

straightforward methodologies for the synthesis of quinolone-triazole hybrids starting from acetamide-based 4-acyl-1,2,3-triazoles. This work explores novel C-N and C-C bond-forming cyclization reactions to not only generate new heterocyclic systems but also to establish 4-acyl-1,2,3-triazoles as a powerful and multifunctional synthetic platform.

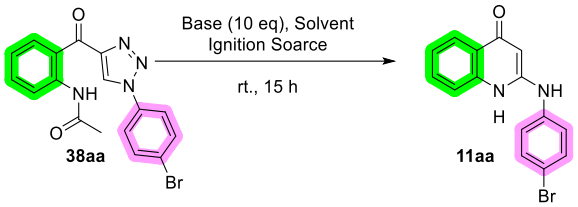
4.2. Results and Discussion

We synthesized the target acetamide-based 4-acyl-1,2,3-triazoles by reacting N-(2-acetylphenyl)acetamides (**36a**) with various aryl azides (**37**) in the presence of DMF-DMA, following our group's established methodology.[97] The acetyl protecting group was crucial to preventing the formation of quinolin-4(1*H*)-one, an undesired byproduct formed when the unprotected amine reacts with DMF-DMA.[98] New *N*-(2-(1-aryl-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamides (**38**) were obtained in up to 86% yields. To explore the impact of different substitutions on the acetophenone ring, we investigated a bromo-substituted precursor, reflecting our group's ongoing interest in halogenated compounds. Accordingly, reacting N-(2-acetyl-4-bromophenyl)acetamide (**36b**) afforded the desired triazoles in yields of up to 52%. We also explored hydroxylated analogues for their potential applications, successfully using N-(2-acetyl-4,5-dimethoxyphenyl)acetamide (**36c**) to synthesize a corresponding triazole in 41% yield.

These triazoles served as key intermediates for the synthesis of quinolone-based compounds. The crucial intramolecular C-N bond formation was accomplished using DMF and KOH under white light, conditions previously reported for the synthesis of similar heterocyclic systems. This method successfully triggered the cyclization, immediately followed by a ring-opening isomerization. This cascade reaction, which proceeded with an observable release of nitrogen gas, afforded the desired 2-(arylamino)quinolin-4(1*H*)-one (**11aa**) in 79% yield without requiring purification by column chromatography.

To better understand the reaction and optimize the methodology a serie of control experiments were caried out. First, we determined the role of light: the reaction occurred even without light, though with a lower yield (39%), and using a 440 nm Kessel lamp produced a yield similar to the original conditions, indicating that light mainly affects the reaction but is not determinant to occur (**entries 2-4**). Next, we identified several critical factors for success. The reaction failed when DMF was replaced with DMSO, MeCN, or MeOH (**entries 5-7**), or when weaker bases like K_2CO_3 or $NaHCO_3$ replaced KOH (**entries 8-9**). These results suggest a strong base is necessary, likely to initiate the reaction through deprotection before the cyclization step. Interestingly, the reaction was surprisingly tolerant of water, giving comparable yields in undried DMF or a DMF:H_2O (4:1) mixture (**entries 10-11**). Finally, using an alternative method reported by Zou and co-workers (*t*-butoxide, DMSO) also produced **11aa** in a similar yield (**entry 12**).

Table 4.1: Investigating the Synthesis of 2-(arylamino)quinolin-4(1*H*)-ones through Control Reactions

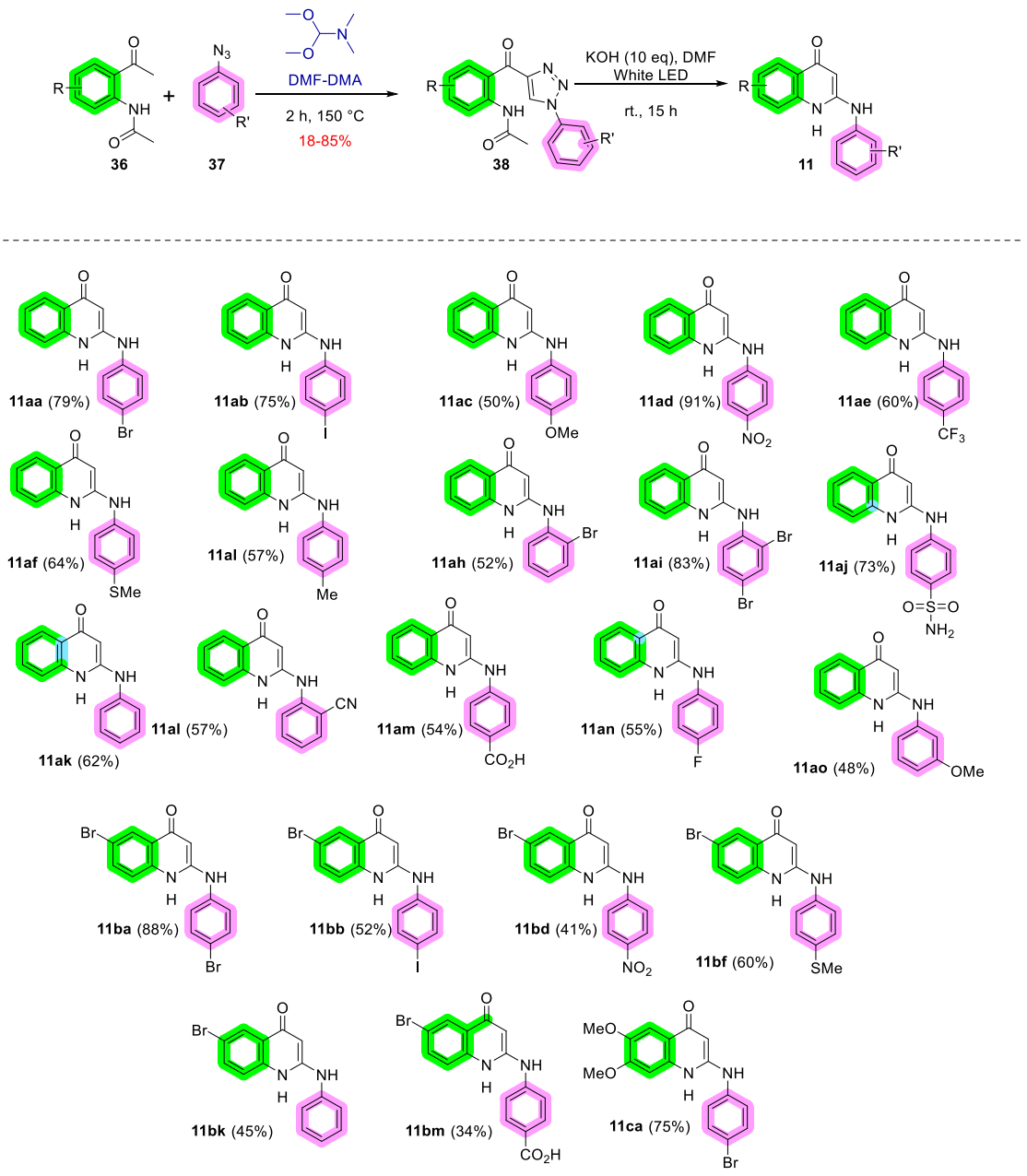


Entry	Ignition source	Solvent	Base	Yield (%)
1	White LED	DMF	KOH	79
2	No Light	DMF	KOH	39
3	Dark	DMF	KOH	35
4	Kessil Lamp 440nm	DMF	KOH	68
5	White LED	DMSO	KOH	No reaction
6	White LED	MeCN	KOH	No reaction
7	White LED	MeOH	KOH	No reaction
8	White LED	DMF	$NaHCO_3$	No reaction
9*	White LED	DMF	K_2CO_3	No reaction
10	White LED	DMF (dry)	KOH	65
11	White LED	DMF:H_2O 4:1	KOH	62
12	No Light	DMSO	t-BuOK	66

*With argon atmosphere

With all the information and to support this straightfoward approach, different **38** were reacted with KOH in DMF under white light overnight. As a result, 22 new compounds with diverse substitutions were synthesized, achieving yields ranging from 41% to 91% (**Scheme 4.4**). The positive influence of electron-withdrawing groups on the triazole ring was evident, as higher yields were associated with more electron-deficient systems. Additionally, electron-donating groups on the acetophenone-derived ring

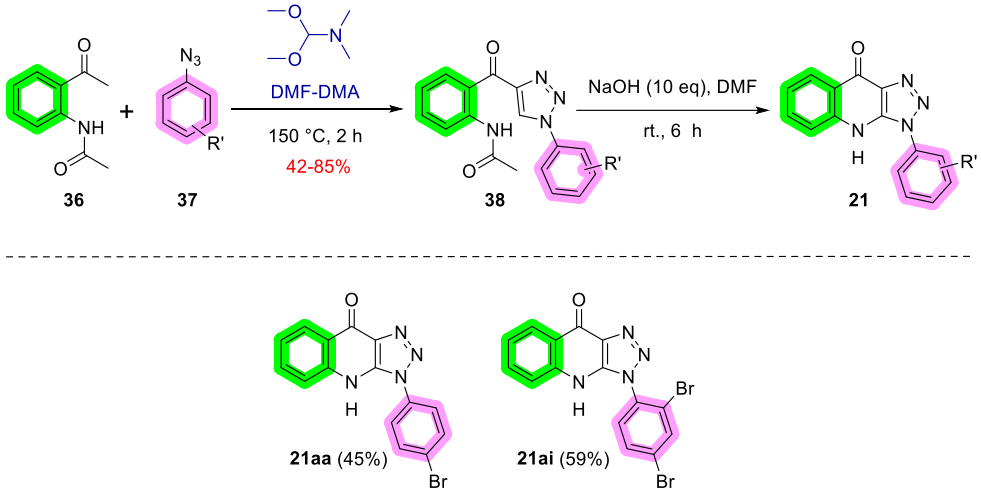
also enhanced reaction efficiency, further increasing yields.



Scheme 4.4: Synthesis of 2-(arylamino)quinolin-4(1*H*)-ones **11aa**-**11-ca**

As previously demonstrated, the literature highlights the significance of these rarely explored **11**-type molecules. Existing synthetic methodologies are often lengthy, involve toxic reagents, and result in low yields. These challenges further underscore the versatility of 4-acyl-1,2,3-triazoles as intermediates for synthesizing quinolone-based structures, particularly given that the desired products can be obtained in a single step with straightforward purification.

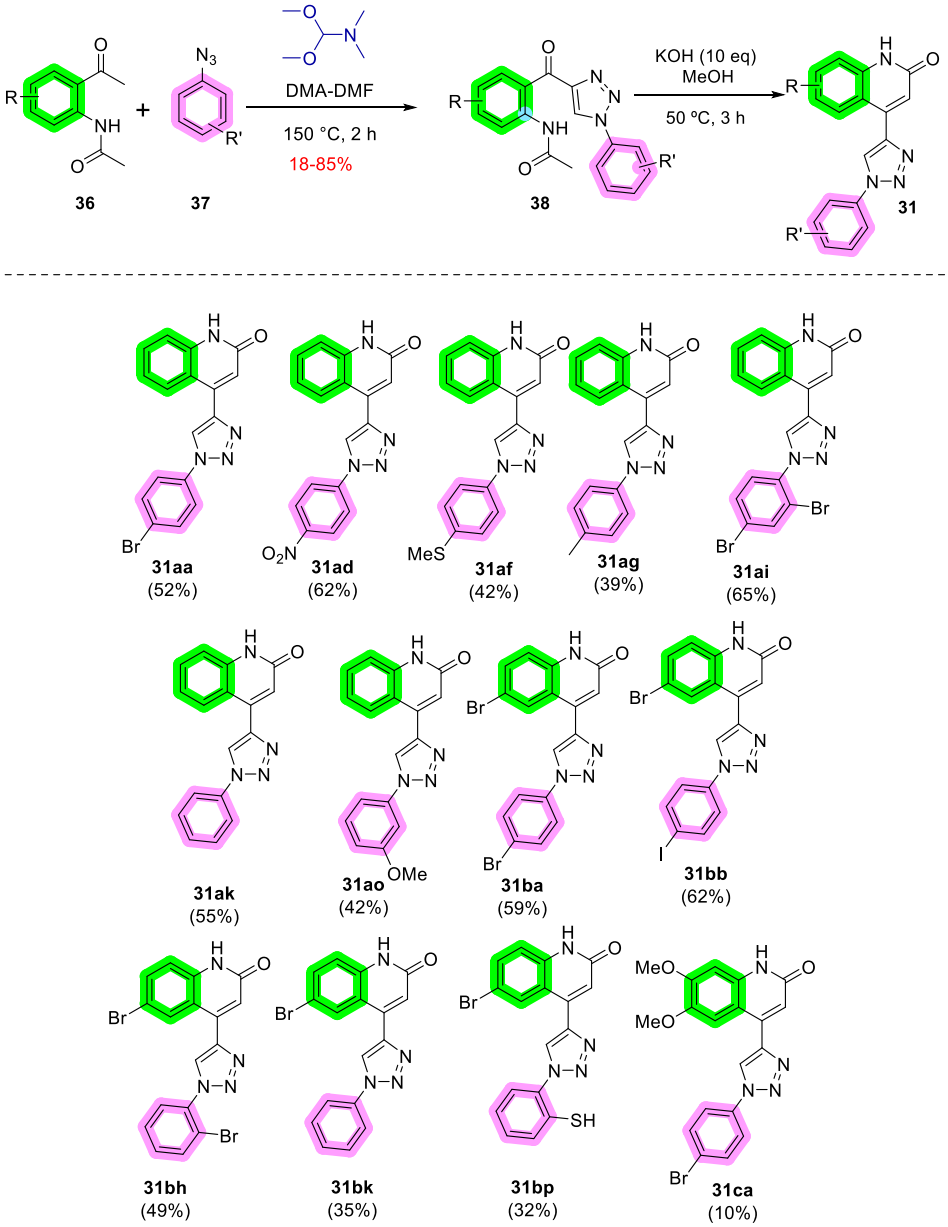
Focusing on the exclusive formation of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones (**21**) through C-N bond cyclization a more precise reaction control is needed to suppress the rapid extrusion of dinitrogen (N_2).[99] Although other methods exist for synthesizing these compounds, such as the one reported by Wang and co-workers, we found that our target molecules could only be isolated in significant yields by treating compound **11** with NaOH in the absence of light for 6 hours.[70] While this approach is novel and straightforward, its scope was unfortunately limited by the facile extrusion of N_2 from the triazole intermediate. Consequently, only two examples were successfully isolated, with yields reaching 59% (**Scheme 4.6**). This success might be attributed to the pronounced stabilizing effect of the bromine substituent on the azide-derived ring. By increasing electron density at the *ortho* and *para* positions, the bromine atom stabilizes the triazole, thereby retarding the competing ring-chain isomerization.



Scheme 4.5: Synthesis of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones **21aa** and **21ab**

Switching from photochemical to thermal conditions produced the expected thermodynamic product **11** along with a new, insoluble byproduct, which we identified as 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one (**31**). The formation of this quinolin-2-one resembles the aldol condensation reported by Zou and co-workers for a similar system. Guided by this precedent, we sought to optimize the synthesis of **31** from precursor **38**.

After testing various solvents, we found that heating **38** with KOH in refluxing MeOH yielded the desired product (**31**) in 53% yield without the need for purification by column chromatography. Compound **31** was reacted with triazoles possessing a range of substitution patterns to explore the reaction's breadth. This procedure afforded 13 new compounds with yields ranging from 32 to 65% (**Scheme 4.7**). As expected, electron-withdrawing groups had a greater influence on the reaction kinetics, leading to increased yields.



Scheme 4.6: Synthesis of 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones **31aa**-**31ca**

Comparing all the reactions presented here the imposed conditions involve a crucial change in energy input, which has significant implications. The photochemical approach to achive compound 11, While not critical, this result indicates a favoring of the reaction. This could point to kinetically favored product due to the kinectic control which guides the reaction through the lowest energy of activation. In contrast, compound 31 was obtained via thermal conditions. This approach, often leads to thermodynamic control, yielding the product that is structurally the most stable.

4.3. Conclusion

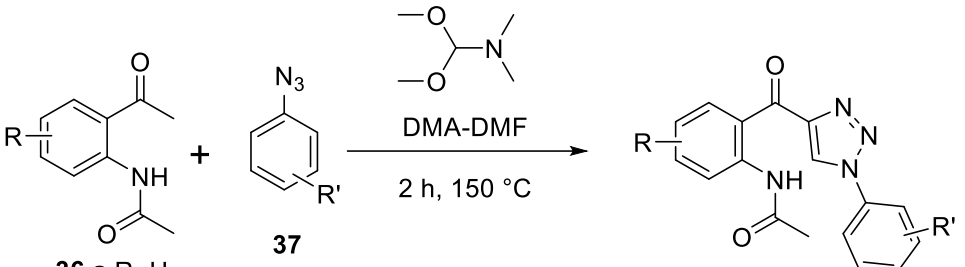
With all that, 4-acyl-1,2,3-triazoles proved to be a powerful synthetic platform enabling a single molecule to generate three distinct classes of potentially applicable molecules, achieved via simple procedures and easy purification without the use of chromatographic techniques. 22 new 2-(arylamino)quinolin-4(1*H*)-ones were obtained with yields from 41 to 91%. Only two examples of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones with 45 and 59% yield, due to mechanistic implications. Using a solvothermal approach, 14 novel 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones type compounds were obtained in yields of 10 to 65%.

4.4. Material and Methods

All reagents were bought from Sigma-Aldrich, Start BioScience, or isofar and used as received. Reactions were monitored by thin-layer chromatography using Merck TLC Silica gel 60 F254. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR (^{1}H-decoupled) using $CDCl_3$ or DMSO-d6 as solvents. The chemical shifts (d) were given in parts per million (ppm) and tetramethylsilane was used as an internal standard. The multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets and td = triplet of doublets. All coupling constants (J values) were given in Hz. High-resolution mass spectra were obtained by a

BrukerMicrOTOF II instrument. FTIR measurements were carried out on a Bruker ALPHA II FTIR, using the attenuated total reflection (ATR) technique with an Eco-ATR QuickSnap™ sampling accessory and a diamond/ZnSe crystal plate.

Synthesis of *N*-(2-(1-aryl-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamides



36 a R=H
36 b R= 3-Br
36 c R= 4,5- OMe

37

38

Acetamide-based triazoles were obtained as already been reported by our research group in 2025.[1] To sealed cap vial equipped with a magnetic stirring bar and wrapped in aluminum foil was added 2 mmol of the appropriate acetophenone and 3 mmol of the appropriate aryl-azide followed by 4 mmol of DMA-DMF. The vial was sealed with an inert atmosphere using argon and heated at 150°C in a graphite bath for 2 h. After that, the reaction was poured into ice-cold ethanol or hexane (depending on the solubility) and allowed to precipitate in the refrigerator. The product was vacuum filtered and washed with ice-cold ethanol and dried under reduced pressure.

***N*-(2-(1-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**[1]

Yield 60%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.72 (dd, J = 9.6, 5.0 Hz, 1H), 8.62 (s, 1H), 7.95 – 7.90 (m, 1H), 7.67 – 7.59 (m, 1H), 7.59 – 7.54 (m, 1H), 7.25 – 7.19 (m, 1H), 2.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.12, 169.20, 149.01, 141.32, 139.21, 135.88, 135.36, 134.00, 126.53, 122.61, 122.27, 121.91, 120.97, 94.89, 53.44, 25.50.

***N*-(2-(1-(4-iodophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 63%; White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 0H), 8.72 (ddd, *J* = 13.6, 8.3, 1.4 Hz, 1H), 8.62 (s, 0H), 8.00 – 7.87 (m, 1H), 7.63 (t, 0H), 7.57 (d, *J* = 8.8 Hz, 0H), 7.25 – 7.19 (m, 0H), 2.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.12, 169.20, 149.01, 141.32, 139.21, 135.88, 135.36, 134.00, 126.53, 122.61, 122.27, 121.91, 120.97, 53.44, 25.50. HRMS(ESI) m/z calculated for C17H13IN4O2+H [M+H], 433,0161; found 433,0161.

***N*-(2-(1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 41%; bronw solid; ^{1}H NMR (400 MHz, DMSO) δ 10.87 (s, 0H), 9.91 (s, 0H), 8.55 – 8.43 (m, 2H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.70 (t, 1H), 4.39 (s, 1H), 2.50 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 187.01, 168.63, 160.17, 147.77, 137.54, 132.94, 131.25, 129.89, 129.46, 127.69, 124.07, 123.19, 122.64, 115.38, 56.07, 24.12.

***N*-(2-(1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 71%; yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.72 (s, 1H), 8.53 – 8.44 (m, 2H), 8.39 – 8.31 (m, 2H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 1.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 184.82, 168.60, 150.93, 147.84, 147.68, 140.83, 136.05, 135.27, 132.74, 128.53, 126.03, 125.53, 121.77, 116.14, 23.84.

***N*-(2-(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole-4 carbonyl)phenyl)acetamide**

Yield 56%; pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 0H), 8.74 (dd, *J* = 8.1, 1.6 Hz, 0H), 8.73 – 8.69 (m, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.64 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 0H), 7.23 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 0H), 2.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.01, 169.21, 149.20, 141.38, 138.67, 135.48, 134.00, 131.59, 127.49, 127.45, 127.41, 127.38, 126.69, 122.63, 121.83, 121.01, 120.91, 25.50. HRMS(ESI)

m/z calculated for C18H13F3N4O2+H [M+H], 375,1069; found 375,1069.

_N_-(2-(1-(4-(methylthio)phenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 32%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.78 – 8.66 (m, 2H), 8.59 (s, 1H), 7.75 – 7.67 (m, 2H), 7.62 (dddd, *J* = 8.7, 7.3, 5.8, 1.7 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.22 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 2.55 (s, 2H), 2.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.27, 169.20, 148.75, 141.41, 141.35, 141.25, 135.44, 135.24, 134.02, 133.97, 133.14, 127.10, 126.73, 126.56, 125.53, 122.62, 122.59, 122.03, 121.55, 121.13, 121.01, 120.94, 25.49, 15.51. HRMS(ESI) m/z calculated for C18H16N4O2S+H [M+H], 353,1072; found 353,1072.

_N_-(2-(1-(p-tolyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 33%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 0H), 8.75 (dd, *J* = 8.1, 1.6 Hz, 0H), 8.73 – 8.66 (m, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.64 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 0H), 7.25 – 7.21 (m, 0H), 2.26 (s, 1H), 1.63 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.02, 169.22, 149.21, 141.38, 135.49, 134.00, 127.46, 127.42, 126.68, 122.64, 121.02, 120.91, 25.50, 23.24. HRMS(ESI) m/z calculated for C18H16N4O2+H [M+H], 321,1352; found 321,1351.

_N_-(2-(1-(2-bromophenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 46%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 2H), 8.79 – 8.67 (m, 3H), 8.61 (d, *J* = 1.0 Hz, 1H), 7.81 (ddd, *J* = 8.1, 3.8, 1.7 Hz, 2H), 7.67 – 7.60 (m, 3H), 7.55 (tt, *J* = 7.4, 2.2 Hz, 2H), 7.50 – 7.40 (m, 2H), 7.25 – 7.18 (m, 1H), 2.28 – 2.21 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.24, 169.23, 147.88, 141.28, 135.74, 135.29, 134.15, 133.95, 131.89, 130.94, 128.78, 128.07, 122.62, 122.05, 120.98, 118.54, 25.53. HRMS(ESI) m/z calculated for C17H13BrN4O2+H [M+H], 385,0300; found 385,0300.

_N_-(2-(1-(2,4-dibromophenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 69%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.70 (ddd, *J* = 11.5, 8.3, 1.4 Hz, 1H), 8.59 (s, 0H), 7.96 (d, *J* = 2.1 Hz, 0H), 7.67 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.61 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 0H), 7.21 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 0H), 2.24 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.01, 169.20, 148.01, 141.27, 136.55, 135.32, 134.79, 133.89, 132.04, 130.80, 128.92, 125.22, 122.60, 121.94, 120.97, 119.24, 25.48. HRMS(ESI) m/z calculated for C17H12Br2N4O2+H [M+H], 462,9405; found 462,9405.

_N_-(2-(1-(4-sulfamoylphenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 33%; white solid. ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, 0H), 9.55 (s, 0H), 8.30 – 8.21 (m, 1H), 8.09 – 8.01 (m, 1H), 7.83 (dd, *J* = 7.8, 1.6 Hz, 0H), 7.66 (dd, *J* = 8.2, 1.3 Hz, 0H), 7.61 (td, *J* = 7.7, 1.6 Hz, 0H), 7.30 (ddd, *J* = 8.9, 6.6, 1.5 Hz, 0H), 1.91 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 186.64, 168.61, 148.01, 144.86, 138.59, 137.14, 132.90, 130.87, 129.95, 128.14, 128.09, 127.96, 124.26, 123.35, 121.41, 119.96, 23.97.

_N_-(2-(1-phenyl-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 18%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.68 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.64 (s, 1H), 7.84 – 7.74 (m, 2H), 7.66 – 7.54 (m, 3H), 7.54 – 7.48 (m, 1H), 7.21 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.30, 169.22, 148.76, 141.23, 136.25, 135.22, 134.02, 130.05, 129.71, 126.83, 122.60, 122.05, 120.94, 120.83, 25.49.

_N_-(2-(1-(2-cyanophenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 22%; pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 0H), 8.73 (ddd, *J* = 13.8, 8.3, 1.4 Hz, 1H), 8.61 (s, 0H), 7.81 (dd, *J* = 8.0, 1.4 Hz, 0H), 7.68 – 7.59 (m, 1H), 7.55 (td, *J* = 7.7, 1.4 Hz, 0H), 7.47 (td, *J* = 7.7, 1.8

Hz, 0H), 7.25 – 7.20 (m, 0H), 2.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.24, 169.25, 147.87, 141.27, 135.73, 135.30, 134.15, 133.95, 131.90, 130.95, 128.79, 128.07, 122.63, 122.05, 120.98, 118.54, 25.55.

ethyl 4-(4-(2-acetamidobenzoyl)-1*H*-1,2,3-triazol-1-yl)benzoate

Yield 46%; pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.91 – 8.59 (m, 3H), 8.31 – 8.23 (m, 2H), 7.96 – 7.88 (m, 2H), 7.63 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.23 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.26 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.09, 169.21, 165.18, 149.07, 141.35, 139.18, 135.41, 134.01, 131.58, 131.53, 126.69, 122.62, 121.89, 120.99, 120.30, 61.64, 25.50, 14.31.

***N*-(2-(1-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 36%; pale brown solid. ^{1}H NMR (400 MHz, DMSO) δ 10.27 (s, 0H), 9.44 (s, 0H), 8.10 – 8.02 (m, 1H), 7.86 (dd, *J* = 7.8, 1.5 Hz, 0H), 7.73 – 7.67 (m, 0H), 7.60 (td, *J* = 7.7, 1.6 Hz, 0H), 7.49 (t, *J* = 8.8 Hz, 1H), 7.29 (td, *J* = 7.6, 1.2 Hz, 0H), 1.92 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 186.84, 168.60, 147.86, 137.34, 132.91, 131.05, 128.10, 124.16, 123.53, 123.45, 123.29, 117.42, 117.19, 24.05.

***N*-(4-bromo-2-(1-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 52%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.95 (d, *J* = 2.4 Hz, 1H), 8.69 – 8.60 (m, 2H), 7.78 – 7.67 (m, 5H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.94, 169.14, 148.62, 140.34, 137.99, 136.31, 135.10, 133.32, 126.80, 123.76, 123.18, 122.63, 122.23, 115.08, 25.50. HRMS(ESI) m/z calculated for C17H12Br2N4O2+H [M+H], 462,9405; found 462,9405.

***N*-(4-bromo-2-(1-(4-iodophenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 53%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 0H), 8.93 (d,

J = 2.4 Hz, 0H), 8.63 (s, 1H), 7.97 – 7.88 (m, 1H), 7.70 (dd, *J* = 9.0, 2.4 Hz, 0H), 7.58 – 7.53 (m, 1H), 2.24 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.89, 169.14, 148.59, 140.32, 139.25, 138.71, 137.95, 136.29, 135.76, 126.73, 123.17, 122.62, 122.27, 121.05, 115.07, 95.07, 25.50.

_N_-(4-bromo-2-(1-(4-(trifluoromethyl)phenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 29%; yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.95 (t, *J* = 2.6 Hz, 1H), 8.73 (s, 1H), 8.65 (ddd, *J* = 12.0, 9.0, 2.1 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.71 (dt, *J* = 9.1, 2.8 Hz, 1H), 2.25 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.14, 148.78, 140.39, 138.06, 137.75, 136.28, 134.03, 127.53, 127.49, 127.45, 127.42, 126.91, 123.09, 122.65, 122.50, 120.93, 115.07, 25.50.

_N_-(4-bromo-2-(1-(4-(methylthio)phenyl)-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 26%; brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.94 (d, *J* = 2.4 Hz, 1H), 8.67 – 8.57 (m, 2H), 7.75 – 7.65 (m, 3H), 7.44 – 7.36 (m, 2H), 2.55 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 185.16, 168.60, 147.52, 140.61, 136.27, 135.22, 133.43, 133.00, 131.91, 131.30, 127.72, 127.12, 125.94, 125.48, 121.71, 121.45, 116.02, 23.92, 15.00. HRMS(ESI) m/z calculated for C18H15BrN4O2S+H [M+H], 431,0177; found 431,0175.

_N_-(4-bromo-2-(1-phenyl-1_H_-1,2,3-triazole-4-carbonyl)phenyl)acetamide

Yield 24%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.97 (d, *J* = 2.4 Hz, 1H), 8.69 – 8.60 (m, 2H), 7.84 – 7.77 (m, 2H), 7.71 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.60 (t, 2H), 7.54 (t, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.10, 169.14, 148.41, 140.29, 137.86, 136.34, 136.17, 130.11, 129.84, 126.99, 123.30, 122.60, 120.85, 115.07, 25.50.

methyl 4-(4-(2-acetamido-5-bromobenzoyl)-1*H*-1,2,3-triazol-1-yl)benzoate

Yield 36%; pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 0H), 8.95 (d, *J* = 2.4 Hz, 0H), 8.73 (s, 0H), 8.64 (d, *J* = 9.0 Hz, 0H), 8.31 – 8.23 (m, 1H), 7.97 – 7.89 (m, 1H), 7.71 (dd, *J* = 9.0, 2.4 Hz, 0H), 3.98 (s, 1H), 2.25 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.87, 169.14, 165.62, 148.69, 140.37, 139.15, 138.02, 136.30, 131.61, 131.34, 126.88, 123.14, 122.63, 120.37, 115.07, 52.63, 25.50.

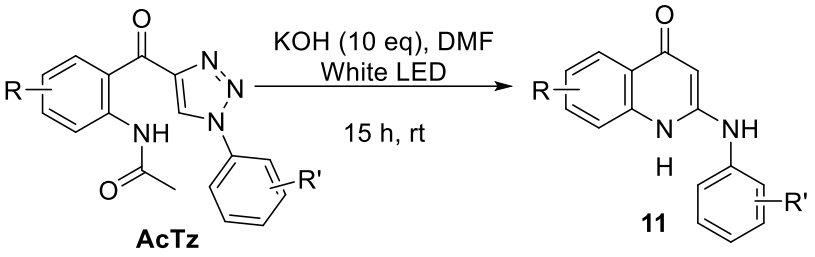
***N*-(4-bromo-2-(1-(2-(methylthio)phenyl)-1*H*-1,2,3-triazole-4-carbonyl)phenyl)acetamide**

Yield 33%; brown solid. ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.16 (s, 1H), 7.94 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.68 – 7.51 (m, 5H), 7.41 (t, *J* = 7.5 Hz, 1H), 2.50 (s, 0H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 185.15, 168.68, 146.62, 136.49, 136.23, 135.34, 134.46, 133.03, 131.86, 131.68, 131.56, 127.57, 127.38, 126.18, 125.56, 116.06, 23.95, 15.49.

***N*-(2-(1-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carbonyl)-4,5-dimethoxyphenyl)acetamide**

Yield 53%; yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.51 (s, 1H), 8.05 – 7.95 (m, 2H), 7.89 (s, 1H), 7.85 (dt, *J* = 9.8, 2.9 Hz, 3H), 3.86 (s, 2H), 3.79 (s, 2H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 185.85, 168.90, 153.55, 148.50, 144.43, 135.80, 135.31, 133.33, 128.29, 122.99, 122.57, 115.11, 105.62, 56.24, 56.20, 31.16, 24.78.

Synthesis of 2-(arylamino)quinolin-4(1*H*)-one from 4-acyl-1,2,3-triazoles



In a 4 mL screw cap vial, 0,25 mmol of the appropriated triazole was added alongside with 2,5 mmol of KOH (10 eq.). After addition of 0,5 mL of DMF, the vial was put under white led irradiation for 15 h. Ice cold water was added than to precipitate the product, which was filtered under vacuum and washed with ice cold ethyl acetate to achieve 2-(phenylamino)quinolin-4(1*H*)-one in pure form.

11aa 2-((4-bromophenyl)amino)quinolin-4(1*H*)-one

White solid; 79% yield; ^{1}H NMR (400 MHz, DMSO) δ 8.09 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.49 (m, 4H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 1H), 7.23 – 7.16 (m, 1H), 6.29 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.81, 153.40, 138.49, 136.27, 133.50, 133.18, 126.60, 125.25, 123.51, 119.31, 118.78, 117.44, 92.51. FTIR-ATR (cm^{-1}): 3386; 1651; 1608; 1488; 1400; 1309; 1251; 1215; 1179; 1137; 1107; 1073; 1037; 1007; 914; 875; 814; 754; 730; 651; 598; 559; 498; 472. HRMS(ESI) m/z calculated for C15H11BrN2O+H [M+H], 315,0133; found 315,0163.

11ab 2-((4-iodophenyl)amino)quinolin-4(1*H*)-one

White solid; 75% yield; ^{1}H NMR (400 MHz, DMSO) δ 8.02 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.73 (qd, *J* = 8.5, 1.6 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.42 (ddd, *J* = 8.2, 6.3, 1.8 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.68, 153.66, 140.53, 137.57, 132.84, 132.68, 125.23, 124.44, 123.39, 120.20, 118.29, 118.25, 117.60, 92.98, 92.92. FTIR-ATR (cm^{-1}): 3749; 3287; 3081; 2746; 2549; 2358; 2102; 2047; 1920; 1757; 1651; 1502; 1468; 1372; 1312; 1212; 1160; 1074; 1008; 954; 878; 775; 704; 613; 556; 497; 438; 423. HRMS(ESI) m/z calculated for C15H11IN2O+H [M+H], 362,9994; found 362,9982.

11ac 2-((4-methoxyphenyl)amino)quinolin-4(1*H*)-one

Brown solid; 50% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.55 (s, 1H), 8.06 – 7.99 (d, 1H), 7.78 (dd, *J* = 8.9, 1.7 Hz, 2H), 7.52 – 7.41 (td, 1H), 7.41 – 7.32 (d, 2H), 7.14 – 7.05 (d, 2H), 6.55 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.21, 158.85, 154.25, 138.13, 133.49, 128.70, 127.41, 125.10, 123.51, 118.37, 117.09, 115.67, 91.94, 55.95. FTIR-ATR (cm^{-1}): 3125; 2844; 2356; 2033; 1661; 1619; 1590; 1518; 1452; 1371; 1315; 1254; 1213; 1157; 1108; 1065; 1018; 983; 937; 875; 823; 785; 752; 720; 675; 653; 600; 556; 513; 460; 432. HRMS(ESI) m/z calculated for C16H14N2O2+H [M+H], 267,1134; found 267,1157.

11ad 2-((4-nitrophenyl)amino)quinolin-4(1*H*)-one

yellish solid; 91% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.37 – 8.28 (m, 2H), 8.10 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.93 – 7.80 (m, 2H), 7.76 (dd, *J* = 9.2, 2.3 Hz, 2H), 7.54 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 6.94 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.18, 152.56, 144.68, 143.79, 139.56, 133.51, 125.93, 125.60, 123.43, 122.00, 120.04, 118.01, 94.27. FTIR-ATR (cm^{-1}): 3568; 2752; 2359; 1654; 1612; 1583; 1496; 1441; 1341; 1252; 1185; 1109; 845; 757; 726; 676; 651; 595; 479; 447. HRMS(ESI) m/z calculated for C15H11N3O3+H [M+H], 282,0879; found 282,0906.

11ae 2-((4-(trifluoromethyl)phenyl)amino)quinolin-4(1*H*)-one

yellish solid; 60% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.05 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.85 – 7.70 (m, 6H), 7.45 (td, *J* = 7.4, 1.4 Hz, 1H), 6.76 – 6.71 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.16, 153.49, 142.49, 132.67, 127.10, 126.16, 124.64, 123.47, 123.24, 122.20, 120.92, 118.21, 93.79, 79.79, 79.46, 79.13. FTIR-ATR (cm^{-1}): 2946; 2361; 1652; 1612; 1501; 1464; 1442; 1162; 1108; 1081; 1015; 831; 778; 757; 650; 599; 559; 497; 429; 423. HRMS(ESI) m/z calculated for C16H11F3N2O+H [M+H], 305,0902; found 305,0929.

11af 2-((4-(methylthio)phenyl)amino)quinolin-4(1H)-one

Brown solid; 64% yield^{1}H NMR (400 MHz, DMSO) δ 10.12 (s, 0H), 8.00 (d, 0H), 7.75 – 7.61 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.27 (m, 1H), 6.45 (s, 0H), 2.50 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 153.94, 132.39, 127.92, 125.33, 124.06, 123.88, 123.36, 118.47, 92.86, 15.77. FTIR-ATR (cm^{-1}): 3855; 3733; 3676; 3648; 3587; 3253; 2917; 2360; 2340; 2098; 1956; 1917;

1870; 1796; 1740; 1680; 1620; 1582; 1526; 1492; 1453; 1412; 1368; 1320; 1289; 1248; 1208; 1163; 1101; 1068; 1028; 987; 951; 918; 875; 830; 797; 759; 734; 698; 654; 618; 586; 552; 522; 488; 452. HRMS(ESI) m/z calculated for C16H14N2OS+H [M+H], 283,0905; found 283,0931.

11ag 2-(p-tolylamino)quinolin-4(1*H*)-one

Pale brown solid; 38% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.74 (s, 0H), 8.03 (d, *J* = 8.1 Hz, 0H), 7.78 (d, *J* = 6.7 Hz, 1H), 7.48 (t, 0H), 7.37 – 7.27 (m, 2H), 6.68 (s, 0H), 2.36 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ ^{13}C NMR (101 MHz, DMSO) δ 166.51, 153.81, 138.10, 136.94, 133.74, 133.55, 130.88, 125.16, 125.02, 123.53, 118.38, 117.14, 92.00, 21.11. FTIR-ATR (cm^{-1}): 2747; 2360; 1738; 1651; 1616; 1513; 1505; 1490; 1468; 1448; 1406; 1362; 1342; 1325; 1241; 1211; 1169; 1121; 1073; 1024; 978; 869; 803; 760; 711; 660; 601; 561; 512; 457; 427. HRMS(ESI) m/z calculated for C15H13N3O3S+H [M+H], 250,3010; found 250,3026.

11ah 2-((2-bromophenyl)amino)quinolin-4(1*H*)-one

White solid; 52% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 8.07 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.81 (d, 2H), 7.64 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.51 (ddd, *J* = 8.2, 4.8, 3.4 Hz, 1H), 7.43 (td, *J* = 7.7, 1.7 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.92, 154.01, 138.07, 134.93, 134.30, 133.70, 130.51, 129.95, 129.76, 125.39, 123.63, 121.96, 118.41, 117.21, 91.93. HRMS(ESI) m/z calculated for C15H11BrN2O+H [M+H], 315,0133; found 315,0161.

11ai 2-((2,4-dibromophenyl)amino)quinolin-4(1*H*)-one

White solid; 83% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.40 (s, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.81 – 7.70 (m, 3H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.46 (ddd, *J* = 8.2, 5.5, 2.7 Hz, 1H), 6.50 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.60, 153.71, 136.03, 135.32, 133.13, 132.69, 130.57, 124.87, 123.67, 122.52, 121.05, 119.05, 118.23, 92.47. FTIR-ATR (cm^{-1}): 3307; 3082; 2724; 2552; 2360; 2340; 2106; 2087; 2021; 1985; 1926; 1871; 1823; 1756; 1702; 1653; 1605; 1542; 1472; 1420; 1376; 1328; 1284; 1235; 1181; 1136; 1100; 1063; 1014; 983; 931; 896; 870; 838; 803; 772; 730; 702; 670; 650; 617; 586; 557; 526; 488; 458; 428 HRMS(ESI) m/z calculated for

C15H10Br2N2O+H [M+H], 392,9238; found 392,9252.

11aj 4-((4-oxo-1,4-dihydroquinolin-2-yl)amino)benzenesulfonamide

White solid; 73% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 8.07 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.89 – 7.77 (m, 2H), 7.68 – 7.57 (m, 2H), 7.56 – 7.42 (m, 3H), 6.87 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.15, 152.94, 141.47, 140.30, 133.62, 127.88, 125.47, 123.51, 123.32, 119.06, 117.59, 93.11. FTIR-ATR (cm^{-1}): 3735; 3285; 3087; 2359; 2340; 2090; 2040; 1980; 1920; 1870; 1820; 1750; 1700; 1650; 1605; 1548; 1498; 1452; 1420; 1377; 1326; 1274; 1213; 1167; 1103; 1063; 1015; 980; 931; 898; 871; 838; 810; 777; 750; 717; 680; 654; 613; 570; 531; 500; 470; 446; 422. HRMS(ESI) m/z calculated for C15H13N3O3S+H [M+H], 316,0756; found 316,0736.

11ak 2-(phenylamino)quinolin-4(1*H*)-one

Pale brown solid; 62% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.52 (q, *J* = 7.7 Hz, 3H), 7.48 – 7.42 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.81, 153.59, 138.18, 136.62, 133.56, 130.43, 130.39, 127.19, 125.18, 124.61, 123.54, 118.47, 117.26, 92.09. FTIR-ATR (cm^{-1}): 2747; 2360; 1738; 1651; 1616; 1513; 1505; 1490; 1468; 1448; 1406; 1362; 1342; 1325; 1241; 1211; 1169; 1121; 1073; 1024; 978; 869; 803; 760; 711; 660; 601; 561; 512; 457; 427. HRMS(ESI) m/z calculated for C15H13N3O3S+H [M+H], 237,1028; found 237,1037.

11al 2-((4-oxo-1,4-dihydroquinolin-2-yl)amino)benzonitrile

White solid; 57% yield; ^{1}H NMR (400 MHz, DMSO) δ 7.70 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.31 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.19 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 6.40 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 162.10, 148.38, 139.10, 130.73, 125.17, 122.11, 121.30, 120.05, 115.87, 18.91.

11am 4-((4-oxo-1,4-dihydroquinolin-2-yl)amino)benzoic acid

Pale yellow solid; 54% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.19 (s, 1H), 8.01 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.36 (s, 1H), 6.60 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.47, 153.83, 144.37, 131.69, 131.59,

131.18, 124.92, 123.71, 123.04, 120.62, 119.84, 118.97, 94.37. FTIR-ATR (cm^{-1}): 3379; 2839; 2360; 2076; 2021; 1982; 1935; 1865; 1826; 1755; 1689; 1653; 1606; 1543; 1472; 1427; 1372; 1317; 1260; 1207; 1157; 1103; 1063; 1011; 963; 912; 867; 831; 792; 761; 730; 702; 661; 617; 586; 554; 522; 494; 472; 421. HRMS(ESI) m/z calculated for C16H12N2O3+H [M+H], 281,0926; found 281,0952.

11an 2-((4-fluorophenyl)amino)quinolin-4(1*H*)-one

Pale brown solid; 55% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.04 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.80 (d, 2H), 7.56 – 7.44 (m, 3H), 7.37 (t, *J* = 8.8 Hz, 2H), 6.69 (s, 1H). ^{13}C NMR (101 MHz,) δ 162.38, 153.97, 138.10, 133.57, 132.73, 132.70, 127.73, 127.64, 125.23, 123.53, 118.41, 117.34, 117.18, 117.12, 92.05. HRMS(ESI) m/z calculated for C15H11FN2O+H [M+H], 255,0934; found 255,0956.

11ap 2-((3-methoxyphenyl)amino)quinolin-4(1*H*)-one

Brown solid; 48% yield; ^{1}H NMR (400 MHz, DMSO) δ 13.40 (s, 0H), 10.94 (s, 0H), 8.07 – 8.00 (m, 0H), 7.80 (dd, *J* = 5.8, 1.5 Hz, 1H), 7.49 (s, 0H), 7.40 (s, 0H), 7.03 (t, *J* = 2.2 Hz, 0H), 7.00 – 6.87 (m, 1H), 3.81 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.96, 160.74, 153.45, 138.04, 137.71, 133.63, 131.15, 125.20, 123.55, 118.34, 117.20, 116.31, 113.02, 109.70, 92.03, 55.86. FTIR-ATR (cm^{-1}): 3344; 2809; 2538; 2361; 1733; 1651; 1601; 1505; 1503; 1494; 1449; 1440; 1397; 1364; 1344; 1314; 1283; 1253; 1230; 1205; 1163; 1106; 1088; 1063; 1036; 1000; 888; 877; 841; 771; 717; 682; 659; 625; 579; 526; 457; 426.

11ba 6-bromo-2-((4-bromophenyl)amino)quinolin-4(1*H*)-one

White solid; 88% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 9.40 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 8.00 – 7.85 (m, 2H), 7.65 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.60 – 7.36 (m, 4H), 6.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 160.08, 156.16, 147.50, 141.43, 132.93, 131.69, 128.94, 124.23, 120.81, 120.04, 114.35, 112.38, 95.60. FTIR-ATR (cm^{-1}): 3057; 2359; 1733; 1657; 1617; 1572; 1504; 1484; 1433; 1367; 1340; 1267; 1241; 1222; 1211; 1178; 1150; 1125; 1107; 1083; 1035; 1008; 935; 875; 825; 760; 691; 673; 659; 613; 574; 524; 424. HRMS(ESI) m/z calculated for C15H10Br2N2O+H [M+H], 394,0660; found 394,0655.

11bb 6-bromo-2-((4-iodophenyl)amino)quinolin-4(1*H*)-one

White solid; 52% yield; ^{1}H NMR (400 MHz, DMSO) δ 8.03 (d, *J* = 2.3 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 6.47 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 160.07, 141.89, 137.52, 132.92, 128.96, 124.22, 121.27, 114.37, 95.63. FTIR-ATR (cm^{-1}): 3017; 2359; 1740; 1608; 1585; 1508; 1493; 1450; 1367; 1238; 1177; 1107; 1069; 1030; 949; 910; 841; 800; 748; 698; 617; 559; 536. HRMS(ESI) m/z calculated for C15H10Br2N2O+H [M+H], 440,9099; found 440,9087.

11bd 6-bromo-2-((4-nitrophenyl)amino)quinolin-4(1*H*)-one

Green solid; 41% yield. ^{1}H NMR (400 MHz, DMSO) δ 10.37 (s, 1H), 8.20 (q, *J* = 9.5 Hz, 4H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.69 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 6.72 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 155.40, 148.81, 140.05, 133.05, 128.97, 125.53, 124.64, 121.24, 117.81, 115.13, 96.37. FTIR-ATR (cm^{-1}): 2970; 2360; 1739; 1605; 1541; 1457; 1420; 1369; 1238; 1177; 1107; 918; 879; 829; 787; 762; 698; 602; 534. HRMS(ESI) m/z calculated for C15H10BrN3O3+H [M+H], 359,9984; found 359,9969.

11be 6-bromo-2-((4-(trifluoromethyl)phenyl)amino)quinolin-4(1*H*)-one

Pale yellow solid; 50% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.18 (s, 1H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.78 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 1H), 6.58 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 163.11, 143.82, 134.18, 126.74, 124.86, 123.68, 120.21, 118.83, 95.28, 95.27, 68.43.

11bf 6-bromo-2-((4-(methylthio)phenyl)amino)quinolin-4(1*H*)-one

Brown solid; 60% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 8.07 (s, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.44 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.38, 134.97, 127.90, 127.75, 125.30, 123.94, 121.36, 119.90, 116.24, 93.83, 15.75. FTIR-ATR (cm^{-1}): 2917; 2360; 1608; 1585; 1493; 1450; 1439; 1342; 1242; 1177; 1157; 1119; 1069; 1013; 912; 805; 760; 729; 617; 546; 505. HRMS(ESI) m/z calculated for C16H13BrN2OS+H [M+H], 361,0010; found 361,0021.

11bk 6-bromo-2-(phenylamino)quinolin-4(1*H*)-one

White solid; 45% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.10 (s, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.58

(d, *J* = 7.9 Hz, 2H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.48 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 154.40, 134.77, 129.92, 125.31, 122.67, 120.18, 93.80. FTIR-ATR (cm^{-1}): 2929; 2350; 1595; 1576; 1505; 1465; 1446; 1419; 1377; 1245; 1189; 878; 811; 768; 750; 722; 699. HRMS(ESI) m/z calculated for C15H11BrN2O+H [M+H], 315,0133; found 315,0153.

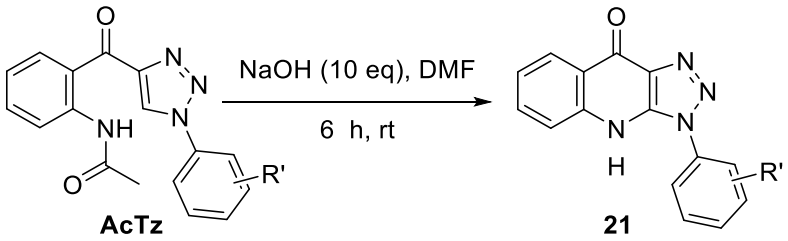
11bm 4-((6-bromo-4-oxo-1,4-dihydroquinolin-2-yl)amino)benzoic acid

Yellow solid; 34% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.16 (s, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.96 – 7.89 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 6.90 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.19, 165.43, 153.35, 141.66, 135.82, 131.43, 127.65, 125.42, 122.50, 119.43, 117.36, 94.22. FTIR-ATR (cm^{-1}): 3419; 2361; 1654; 1437; 1314; 1141; 1016; 952; 702. HRMS(ESI) m/z calculated for C16H11BrN2O3+H [M+H], 359,0031; found 359,0026.

11ca 2-((4-bromophenyl)amino)-6,7-dimethoxyquinolin-4(1H)-one

Dark yellow solid; 75% yield; ^{1}H NMR (400 MHz, DMSO) δ 12.90 (s, 0H), 10.72 (s, 0H), 8.79 (s, 0H), 7.69 (d, *J* = 7.9 Hz, 0H), 7.37 (t, *J* = 7.1 Hz, 1H), 6.67 (s, 0H), 3.91 – 3.85 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 166.15, 163.49, 154.50, 151.98, 147.80, 136.51, 134.50, 133.20, 126.44, 118.99, 110.70, 102.69, 100.12, 91.13, 56.50, 56.27. FTIR-ATR (cm^{-1}): 3326; 2731; 2361; 1737; 1662; 1646; 1541; 1456; 1420; 1369; 1304; 1238; 1207; 1177; 1107; 1069; 1009; 955; 878; 827; 760; 698; 615; 546; 445.

Synthesis of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones



In a 4 mL screw cap vial, 0,25 mmol of the appropriated triazole was added alongside with 2,5 mmol of NaOH (10 eq.). After addition of 1,0 mL of DMF, it was reacted for 6 h. Ice cold water was added than to precipitate the product, which was filtered under vacuum and washed with ice cold acetone to achieve 3-phenyl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones in pure form.

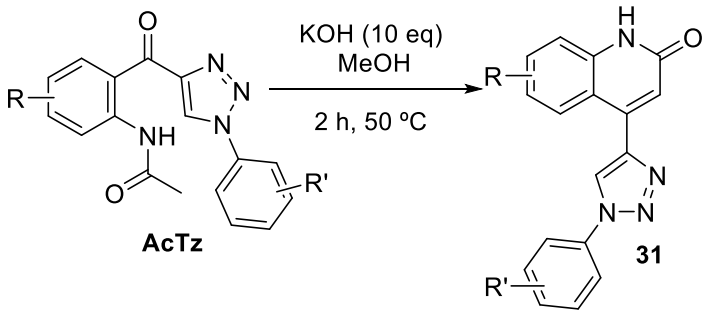
21aa 3-(4-bromophenyl)-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-one

Pale yellow solid; 45% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.27 (s, 1H), 7.95 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.12 (m, 1H), 6.29 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 161.68, 143.61, 140.05, 139.60, 136.19, 135.81, 132.53, 131.31, 130.64, 128.05, 126.86, 124.87, 122.56, 121.46, 120.86, 117.33, 116.37. FTIR-ATR (cm^{-1}): 2965; 1659; 1591; 1506; 1456; 1420; 1366; 1234; 1146; 1071; 1030; 876; 829; 779; 750; 698; 667; 602; 546; 482; 443.

21ai 3-(2,4-dibromophenyl)-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-one

Pale Brown solid; 59% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.23 (s, 1H), 8.39 – 8.31 (m, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.16 (m, 1H), 6.88 (s, 1H), 5.75 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.68, 143.61, 140.05, 139.60, 136.19, 135.81, 132.53, 131.31, 130.64, 128.05, 126.86, 124.87, 122.56, 121.46, 120.86, 117.33, 116.37. FTIR-ATR (cm^{-1}): 3083; 1662; 1608; 1496; 1450; 1373; 1331; 1242; 1223; 1180; 1111; 1069; 968; 914; 845; 748; 698; 621; 552; 496; 440.

Synthesis of 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones



In a 4 mL screw cap vial, 0,25 mmol of the appropriated triazole was added alongside with 2,5 mmol of KOH (10 eq.). After addition of 1,0 mL of MeOH, the vial was heated at 50°C for 2 h. Ice cold water was added than to precipitate the product, which was filtered under vacuum and washed with ice cold acetone to achieve 4-(1-phenyl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones in pure form.

31aa 4-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 52% yield; ^{1}H NMR (400 MHz, DMSO) δ 8.56 (s, 1H), 7.50 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.14 – 7.05 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.68 (ddd, *J* = 8.5, 7.1, 1.4 Hz, 1H), 6.52 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.47 – 6.41 (m, 1H), 6.36 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 6.02 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.91, 144.56, 139.94, 139.80, 136.03, 133.34, 131.37, 126.99, 124.22, 122.85, 122.66, 122.28, 121.28, 117.37, 116.39. FTIR-ATR (cm^{-1}): 2845; 1693; 1647; 1591; 1541; 1456; 1367; 1310; 1206; 1177; 1095; 1022; 887; 852; 781; 752; 696; 650; 619; 575; 513; 478; 442. HRMS(ESI) m/z calculated for C17H11BrN4O+H [M+H], 367,0194; found 367,0172.

31ad 4-(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

Pale yellow solid; 62% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 9.39 (s, 1H), 8.39 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.65 (dd, *J* = 8.6, 7.1 Hz, 2H), 7.62 – 7.51 (m, 1H), 7.43 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 6.92 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.93, 144.45, 139.98, 139.85, 136.80, 131.37, 130.46, 129.61, 127.06, 124.14, 122.70, 121.19, 120.90, 117.42, 116.33. FTIR-ATR (cm^{-1}): 3132; 2840; 1605; 1508; 1450; 1424; 1364; 1268; 1169; 1084; 1032; 995; 926; 872; 824; 752; 687; 640; 596; 525; 457; 430; 412. HRMS(ESI) m/z

calculated for C17H11N5O3+H [M+H], 334,0940; found 334,0941.

31ag 4-(1-(p-tolyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 39% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.94 (s, 1H), 9.39 (s, 1H), 8.45 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.58 (s, 0H), 7.49 – 7.39 (m, 3H), 7.26 (s, 0H), 6.93 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.78, 144.48, 140.03, 139.84, 139.19, 134.62, 131.22, 130.75, 127.15, 124.02, 122.47, 121.26, 120.71, 117.39, 116.26, 21.09. FTIR-ATR (cm^{-1}): 2837; 1652; 1581; 1502; 1452; 1373; 1298; 1238; 1026; 966; 862; 823; 760; 712; 648; 573; 513; 478; 442. HRMS(ESI) m/z calculated for C18H14N4O+H [M+H], 303,1246; found 303,1223.

31af 4-(1-(4-(methylthio)phenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

Brown solid; 42% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.95 (s, 0H), 9.42 (s, 0H), 8.44 (dd, *J* = 8.2, 1.4 Hz, 0H), 8.01 – 7.92 (m, 1H), 7.59 (s, 0H), 7.55 – 7.46 (m, 1H), 7.46 – 7.22 (m, 0H), 6.93 (s, 0H), 2.57 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.76, 144.50, 140.17, 140.01, 139.80, 133.82, 131.26, 127.21, 127.13, 124.02, 122.51, 121.54, 121.33, 121.28, 117.37, 116.27, 15.06. FTIR-ATR (cm^{-1}): 3131; 1660; 1508; 1449; 1362; 1267; 1169; 1100; 1030; 995; 926; 882; 820; 748; 687; 619; 557; 496; 430; 412. HRMS(ESI) m/z calculated for C18H14N4OS+H [M+H], 335,0967; found 335,0967.

31ai 4-(1-(2,4-dibromophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 65% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 9.24 (s, 1H), 8.28 (s, 1H), 8.05 – 7.74 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 6.89 (s, 1H), 5.76 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.67, 143.62, 140.04, 139.61, 136.20, 135.82, 132.53, 131.33, 130.64, 128.05, 126.88, 124.88, 122.57, 121.45, 120.86, 117.33, 116.34. FTIR-ATR (cm^{-1}): 2840; 1680; 1608; 1512; 1454; 1362; 1259; 1178; 1039; 999; 932; 889; 825; 748; 698; 619; 557; 496; 430. HRMS(ESI) m/z calculated for C17H10Br2N4O+H [M+H], 444,9300; found 444,9300.

31ak 4-(1-phenyl-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 55% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.44 (s, 1H), 8.44 (d, *J* = 8.2 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 2H), 7.62 – 7.53 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 6.94 (s, 1H). ^{13}C NMR (101 MHz,

DMSO) δ 161.78, 144.55, 140.00, 139.83, 136.87, 131.27, 130.44, 129.56, 127.12, 124.20, 122.53, 121.32, 120.89, 117.39, 116.28. FTIR-ATR (cm^{-1}): 2840; 1652; 1496; 1414; 1374; 1236; 1051; 982; 931; 870; 825; 764; 648; 575; 513; 478; 431. HRMS(ESI) m/z calculated for C15H9BrN4O3+H [M+H], 289,1089; found 289,1089.

31ap 4-(1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

Brown solid; 42% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.47 (s, 0H), 8.44 (d, *J* = 8.2 Hz, 0H), 7.60 – 7.52 (m, 1H), 7.43 (d, *J* = 8.2 Hz, 0H), 7.15 – 7.08 (m, 0H), 6.94 (s, 0H), 3.89 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.81, 148.70, 148.20, 144.26, 139.99, 139.84, 131.25, 127.09, 124.29, 122.52, 121.17, 117.36, 116.29, 114.74, 109.17, 102.73, 31.15. FTIR-ATR (cm^{-1}): 2839; 1681; 1584; 1504; 1452; 1420; 1362; 1238; 1215; 1169; 1084; 932; 851; 764; 648; 575; 513; 478; 440.

31ba 6-bromo-4-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 59% yield; ^{1}H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 8.06 (t, 0H), 7.84 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.21 (m, 2H), 6.43 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.84, 147.60, 138.21, 133.34, 127.46, 122.38, 121.85, 118.01, 114.02, 40.41, 40.20, 39.99, 39.78, 39.57. HRMS(ESI) m/z calculated for C17H10Br2N4O+H [M+H], 444,9300; found 444,9388.

31bh 6-bromo-4-(1-(2-bromophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 58% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 7.98 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.83 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.66 – 7.55 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.71, 143.56, 140.05, 139.71, 136.39, 134.18, 132.77, 131.30, 129.52, 129.28, 128.03, 126.93, 122.55, 121.38, 119.53, 117.37, 116.34, 79.64.

31bq 6-bromo-4-(1-(2-mercaptophenyl)-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

Pale yellow solid; 52% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.22 (s, 1H), 8.75 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.68 – 7.58 (m, 4H), 7.49 – 7.35 (m, 2H), 6.95 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.57, 143.53, 139.28, 138.42,

136.21, 134.68, 133.87, 131.45, 129.21, 128.01, 127.49, 127.31, 126.15, 122.23, 118.97, 118.55, 114.34, 15.44. HRMS(ESI) m/z calculated for C18H10BrF3N4O+H [M+H], 435,0068; found 435,0068.

31bk 6-bromo-4-(1-phenyl-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 35% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.52 (s, 1H), 8.76 (d, *J* = 2.2 Hz, 1H), 8.02 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 2H), 7.57 (s, 0H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.01 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 162.83, 145.59, 141.05, 140.88, 137.92, 132.32, 131.49, 130.61, 128.17, 125.25, 123.58, 122.37, 121.94, 118.44, 117.32.

31bb 6-bromo-4-(1-(4-iodophenyl)-1H-1,2,3-triazol-4-yl)quinolin-2(1*H*)-one

White solid; 62% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.52 (s, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.08 – 7.97 (m, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (101 MHz, DMSO) δ 161.51, 144.59, 139.17, 138.37, 136.47, 133.89, 129.25, 124.44, 122.72, 122.32, 118.90, 118.45, 114.38, 95.46. HRMS(ESI) m/z calculated for C17H10BrIN4O+H [M+H], 492,9161; found 492,9162.

31ca 4-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)-6,7-dimethoxyquinolin-2(1*H*)-one

White solid; 62% yield; ^{1}H NMR (400 MHz, DMSO) δ 9.52 (s, 1H), 8.72 (d, *J* = 2.2 Hz, 1H), 8.08 – 7.97 (m, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.44, 156.08, 150.96, 149.90, 140.59, 135.52, 133.13, 125.75, 123.09, 122.

5. General conclusions

This work successfully establishes 4-acyl-1,2,3-triazoles as a powerful and versatile synthetic platform for generating novel complex structures with potential applications in varius fields.

The thesis addresses a significant gap in the literature by presenting a simple, metal- and solvent-free methodology for the synthesis of 4-acyl-1,2,3-triazoles from readily available acetophenones and azidobenzenes. This approach yielded products that can be isolated as pure precipitates in ethanol, thereby eliminating the need for costly and time-consuming chromatographic purification. More than 80 examples were presented with different substitiution patterns with 18-95% yield, which denotes the synthetic power of this approach for generating 4-acyl-1,2,3-triazoles lies in its simplicity, efficiency, and accessibility.

These obtained 4-acyl-1,2,3-triazoles acted as key intermediate to bioactive compounds aryl-triazoyl-methanols. With a simple acyl reduction with $NaBH_4$ new derivatives with yields up to 92% were obtained with pure precipitation in water. Two of these compounds, with acid and tiol portions were identified as potential correctors for the p.Phe508del-CFTR trafficking defect with EC_{50} of 2.41 and 1.91 μM.

Acetamide-based 4-acyl-1,2,3-triazoles also act as key precursors of different quinolone-based molecules. Twenty-four new 2-(arylamino)quinolin-4(1*H*)-ones were obtained in good yields 34-91% via a base-catalyzed intramolecular C–N bond formation followed by a Dimroth rearrangement without the need of chromatographic purification. Due to the near-instantaneous release of nitrogen gas after the Dimroth rearrangement, only two examples of 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones could be isolated in pure form, with yields ranging from 45% to 59%. 4-(1-aryl-1*H*-1,2,3-triazol-4-yl)quinolin-2(1*H*)-ones also could be isolated without the need of purification through a solvothermal aldol condensation using methanol as a solvent enabled the selective synthesis of seventeen new compounds, with yields from 10% to 65%.

This research not only provides a powerful, simple, and versatile synthetic strategy to achieve 4-acyl-1,2,3-triazoles derivatives, but also demonstrates the broad applicability as precursors for novel bioactive compounds and complex molecular hybrids with pharmacological potential without any chromatographic colum purification needed.

6. Perspectives

Due to the potential biological activity of these structures, our future work involves expanding the biological evaluation of the synthesized compounds especially against our research group's key targets: Leishmania amazonensis, arboviruses, cystic fibrosis, and cancer.

The one-pot telescopic methodology principle can also be expanded to achieve different triazole moieties such as 1,5-disubstituted or even 1,4,5-trisubstittuted triazoles.

Another important future goal is to explore the potential of 4-acyl-1,2,3-triazoles and the described metodologies to generate different heterocycle-based scaffolds and complex structures with also biological potential such as chromenones, tiochromenones, cumarins, fluorenones and many others.

Finally, the work opens a path for seeking new synthetic alternatives for fused-quinolone triazoles. As demonstrated by the mechanistic challenges in isolating the desired 3-aryl-3,4-dihydro-9*H*-[1,2,3]triazolo[4,5-*b*]quinolin-9-ones. This indicates the need to develop alternative synthetic routes to achieve straightforwardly these valuable structures.

7. **References**

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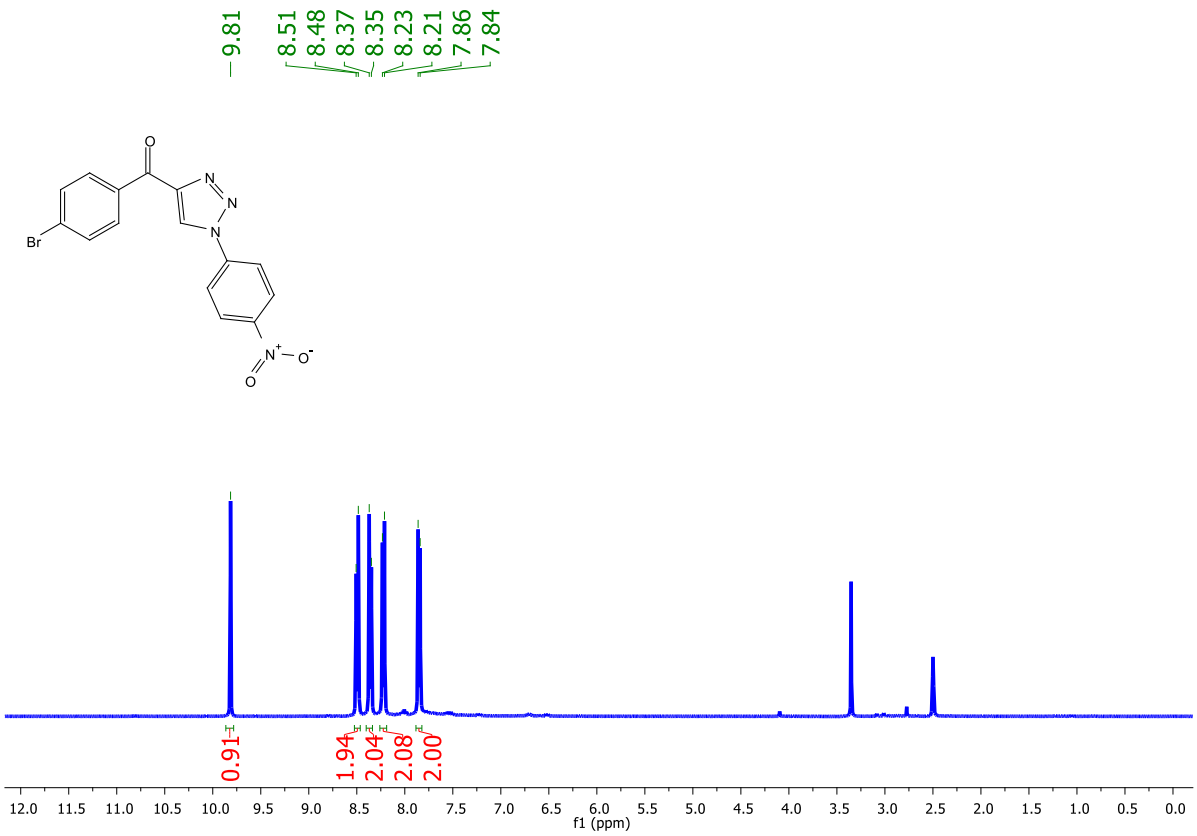
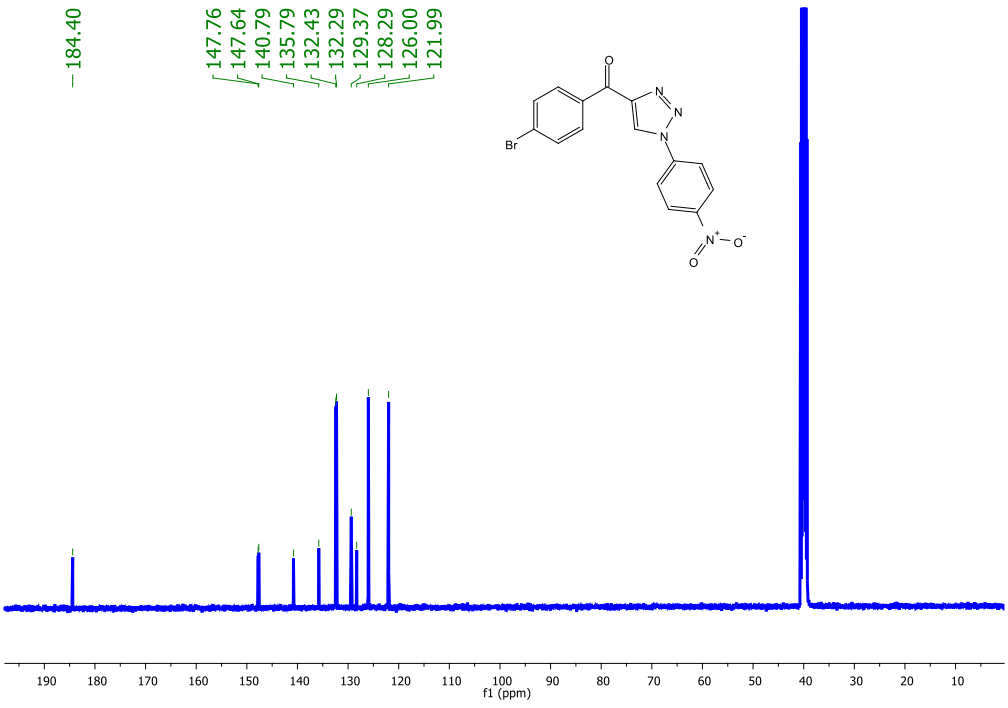
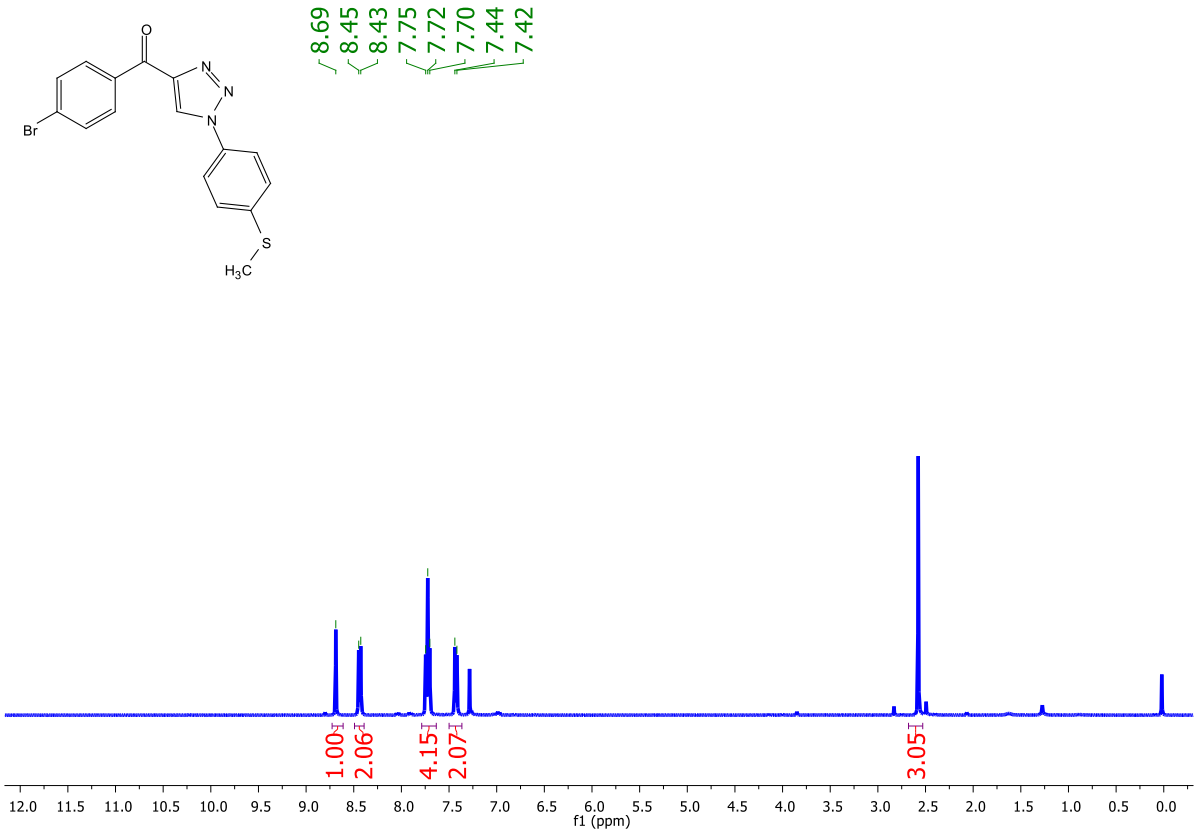
8. Appendix A: chapter 3 characterizations



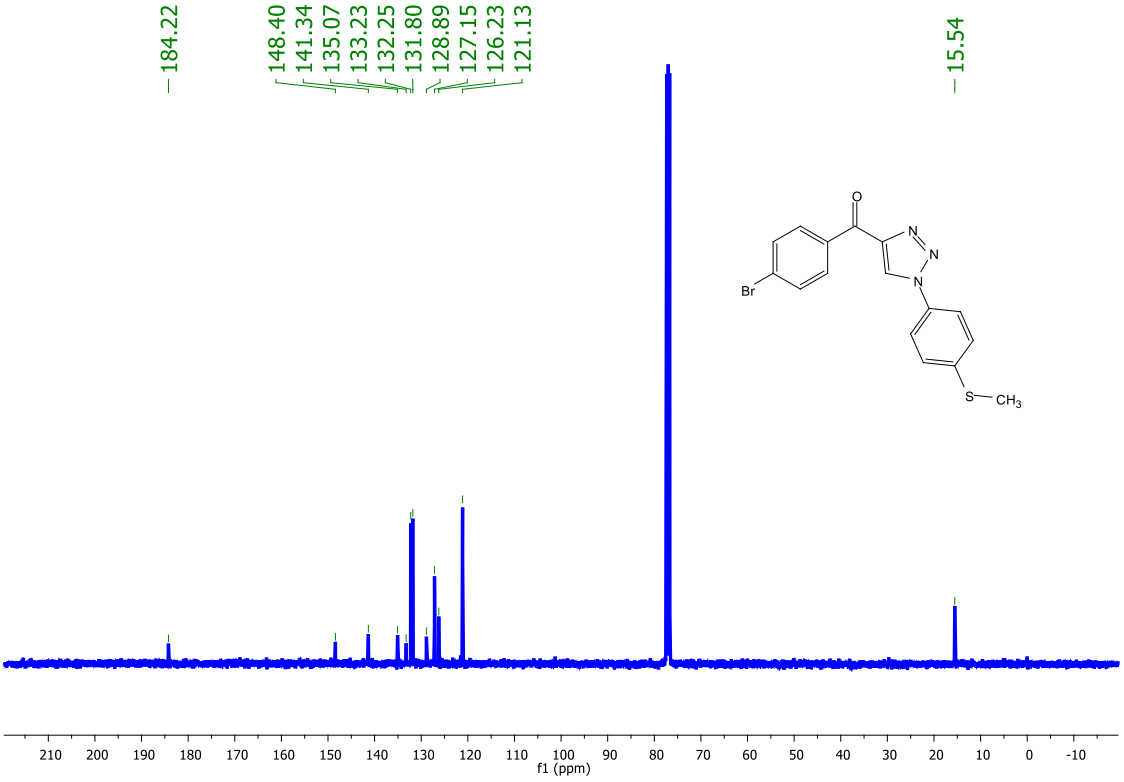
Spectrum 1: ^{1}H NMR (400 MHz; DMSO-d6) 7ab



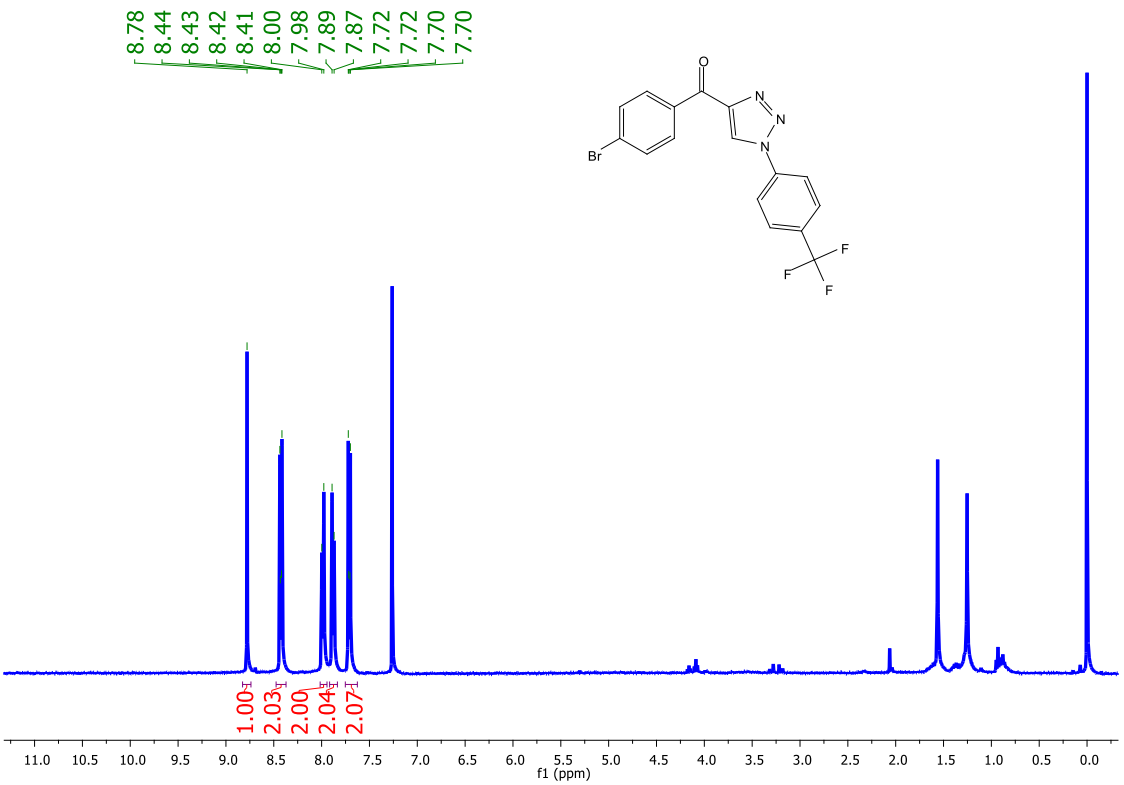
Spectrum 2: ^{13}C NMR (100 MHz; DMSO-d6) 7ab



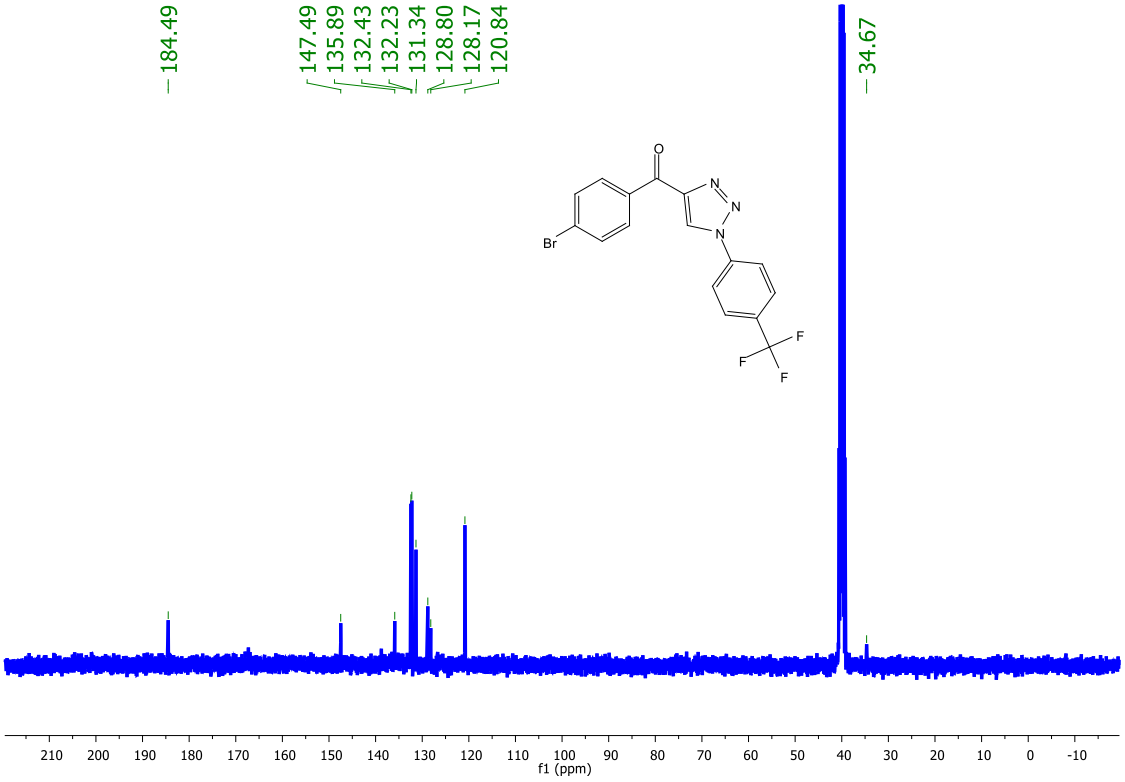
Spectrum 3: ^{1}H NMR (400 MHz; $CDCl_3$) 7ac



Spectrum 4: ^{13}C NMR (100 MHz; $CDCl_3$) 7ac



Spectrum 5: ^{1}H NMR (400 MHz; DMSO-d6) 7ad



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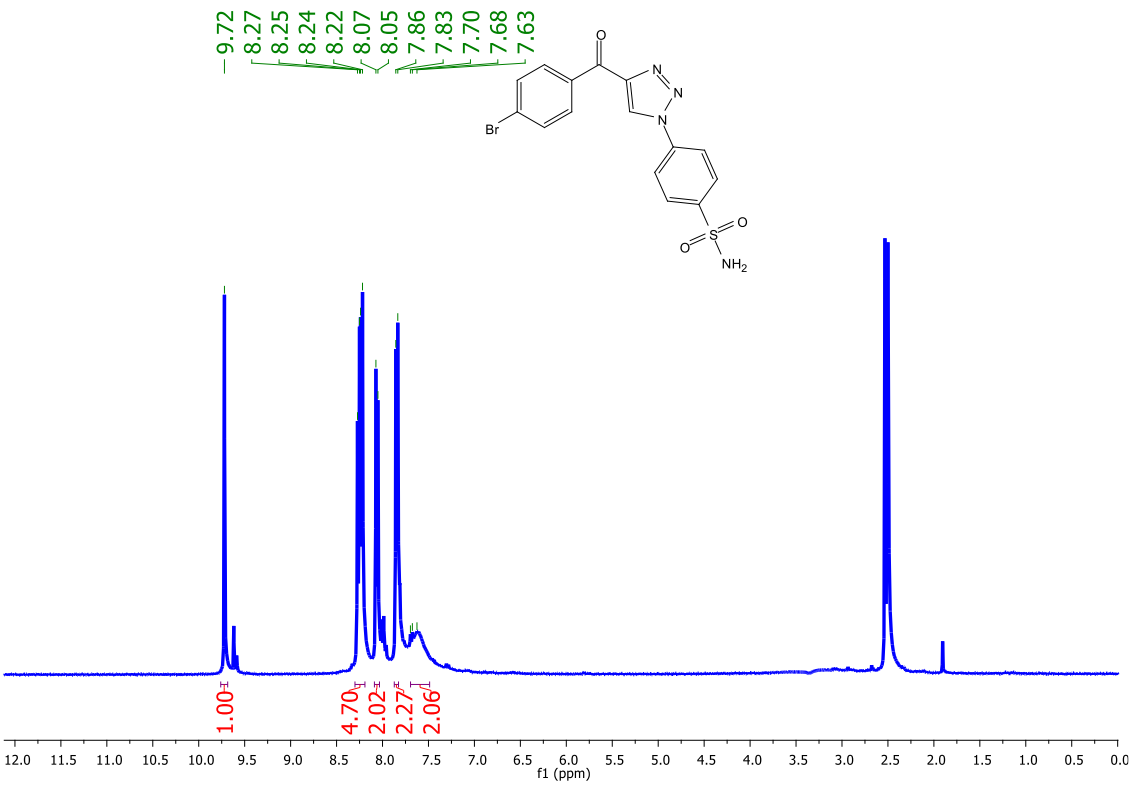

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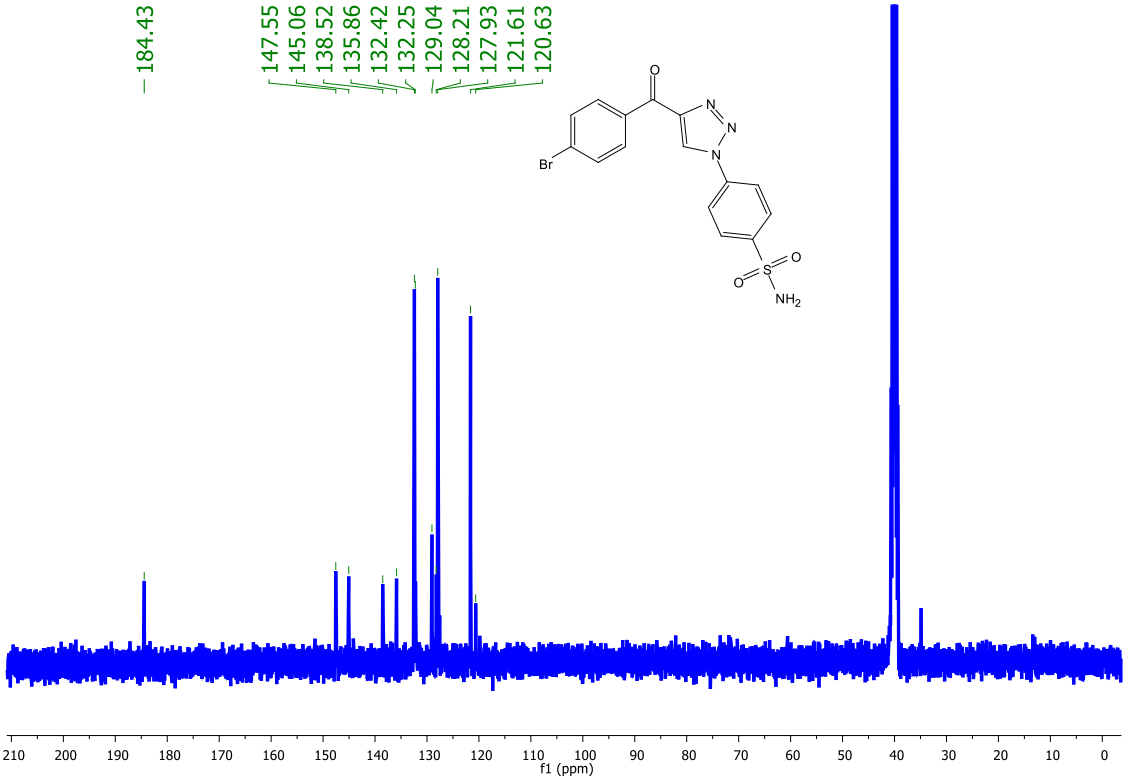
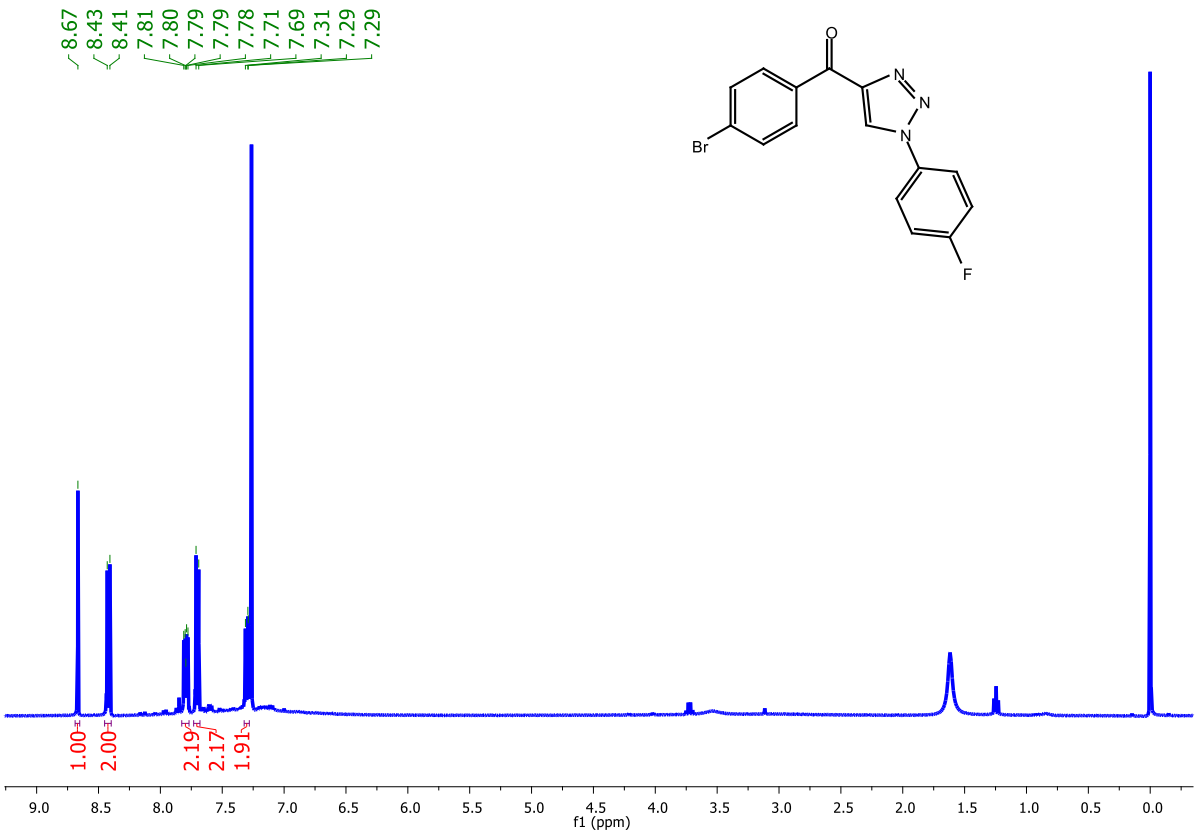
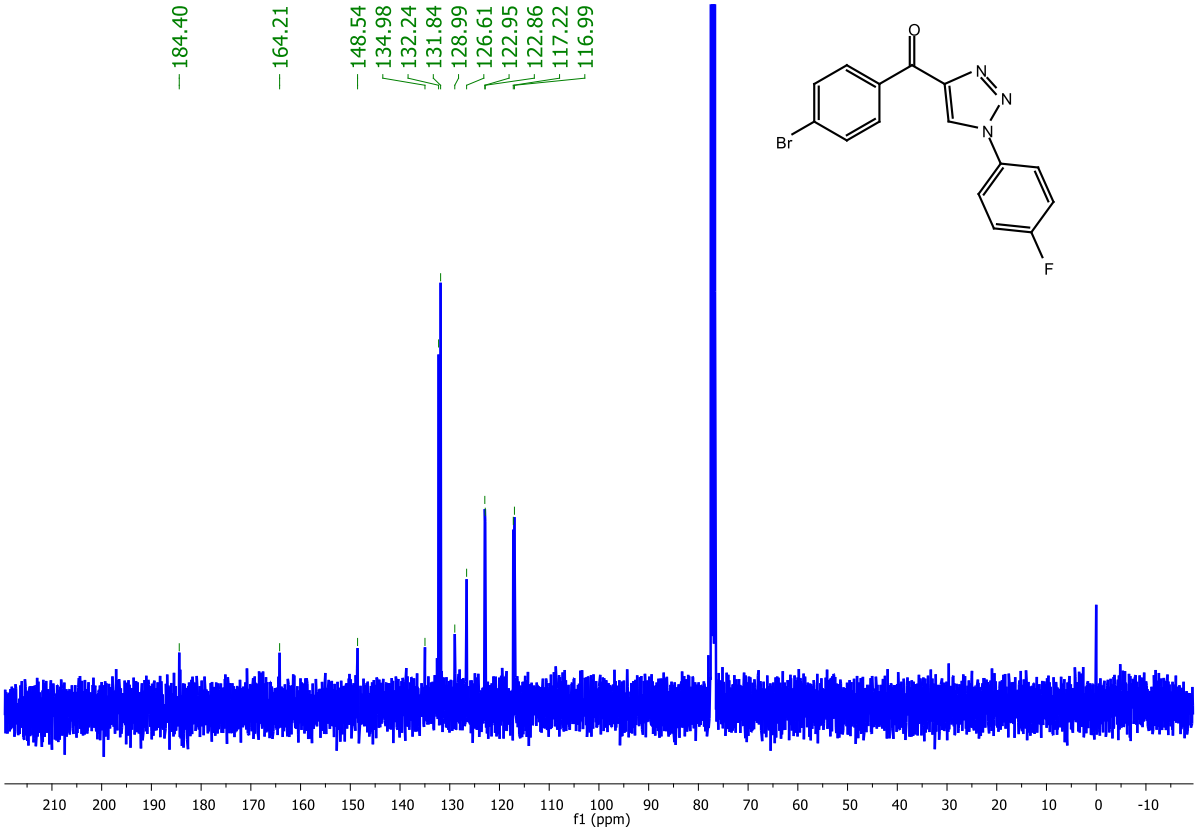


Spectrum 8: ^{13}C NMR (100 MHz; DMSO-d6) 7ae



Spectrum 9: ^{1}H NMR (400 MHz; $CDCl_3$) 7af



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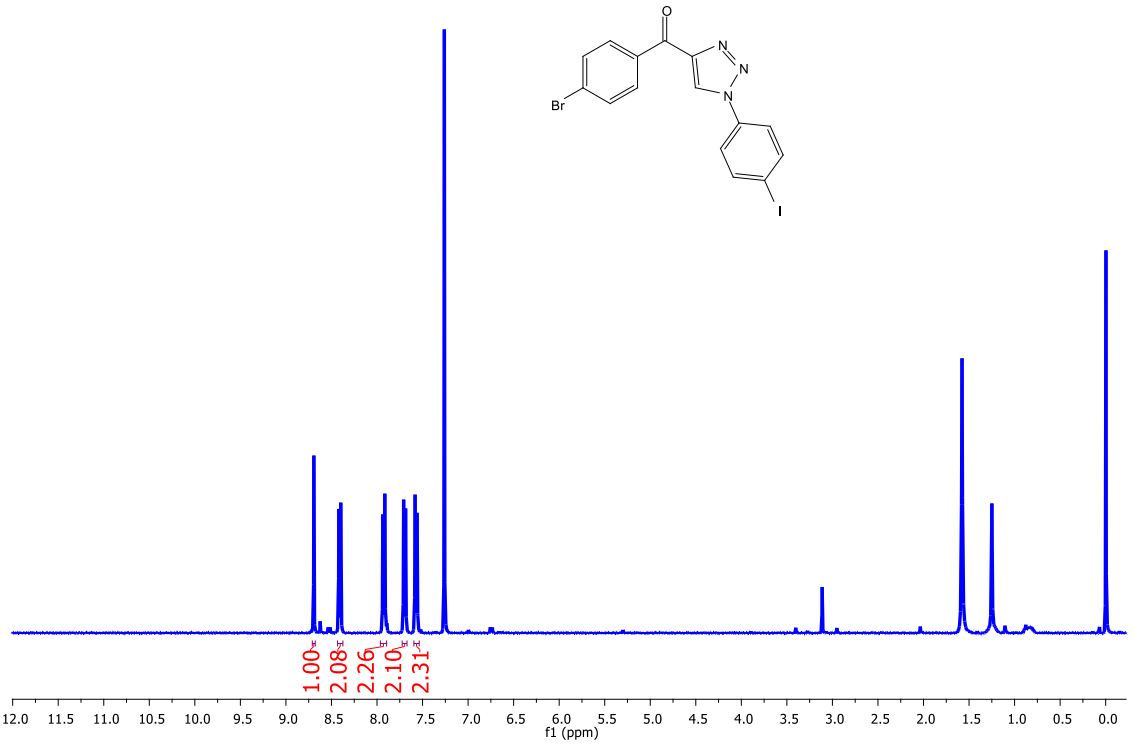
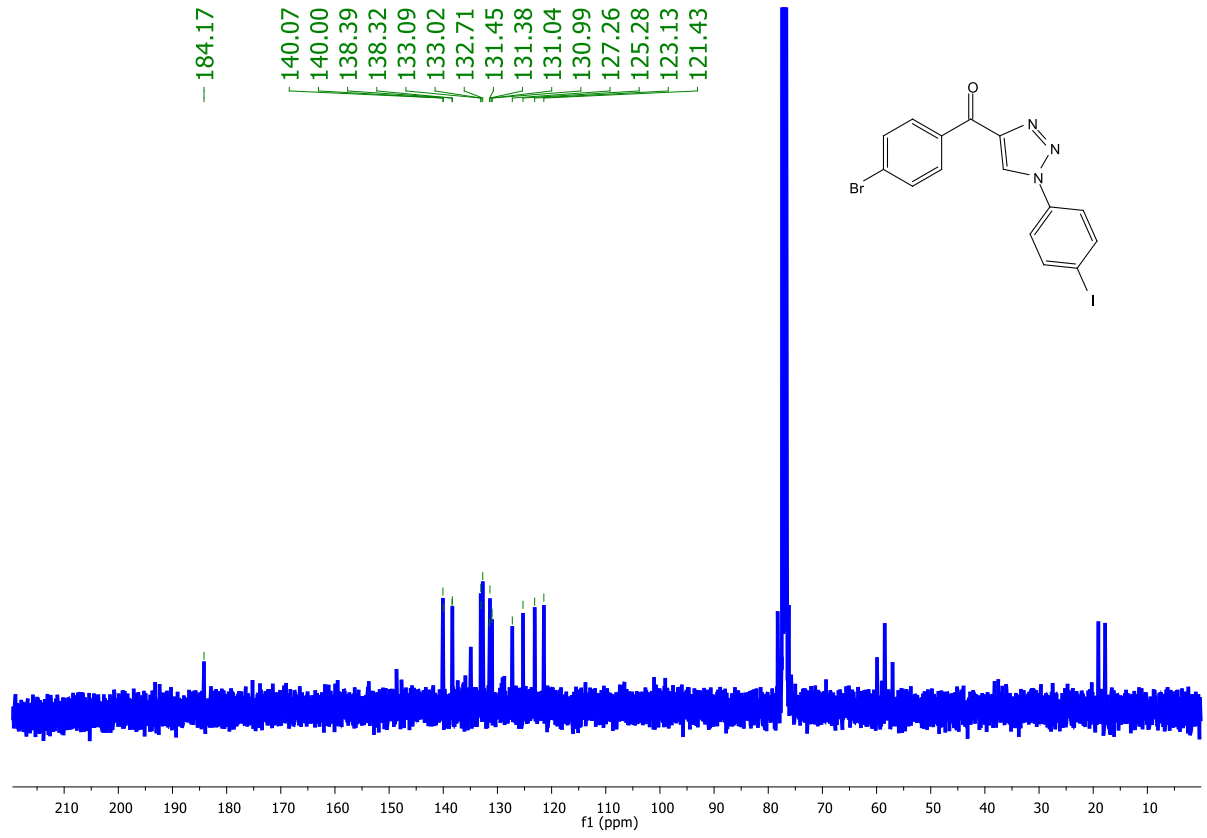


Spectrum 11: ^{1}H NMR (400 MHz; $CDCl_3$) 7ag



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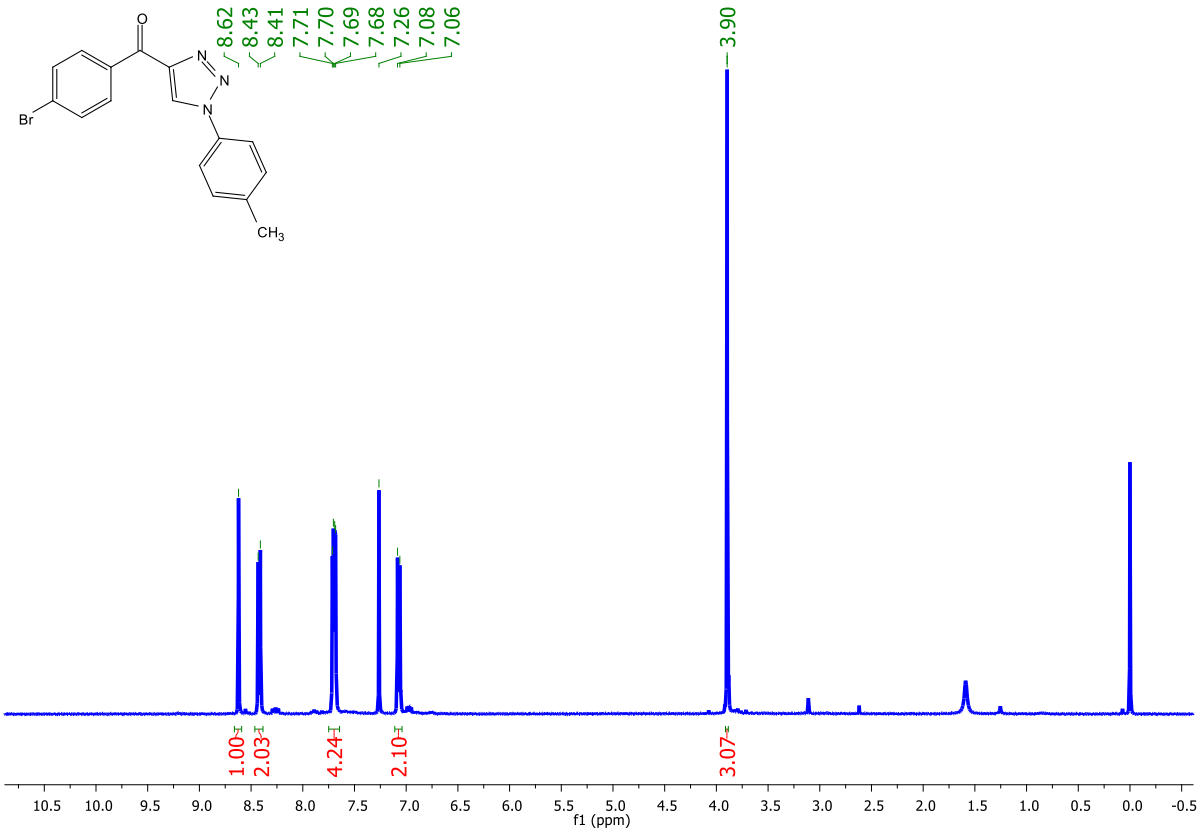

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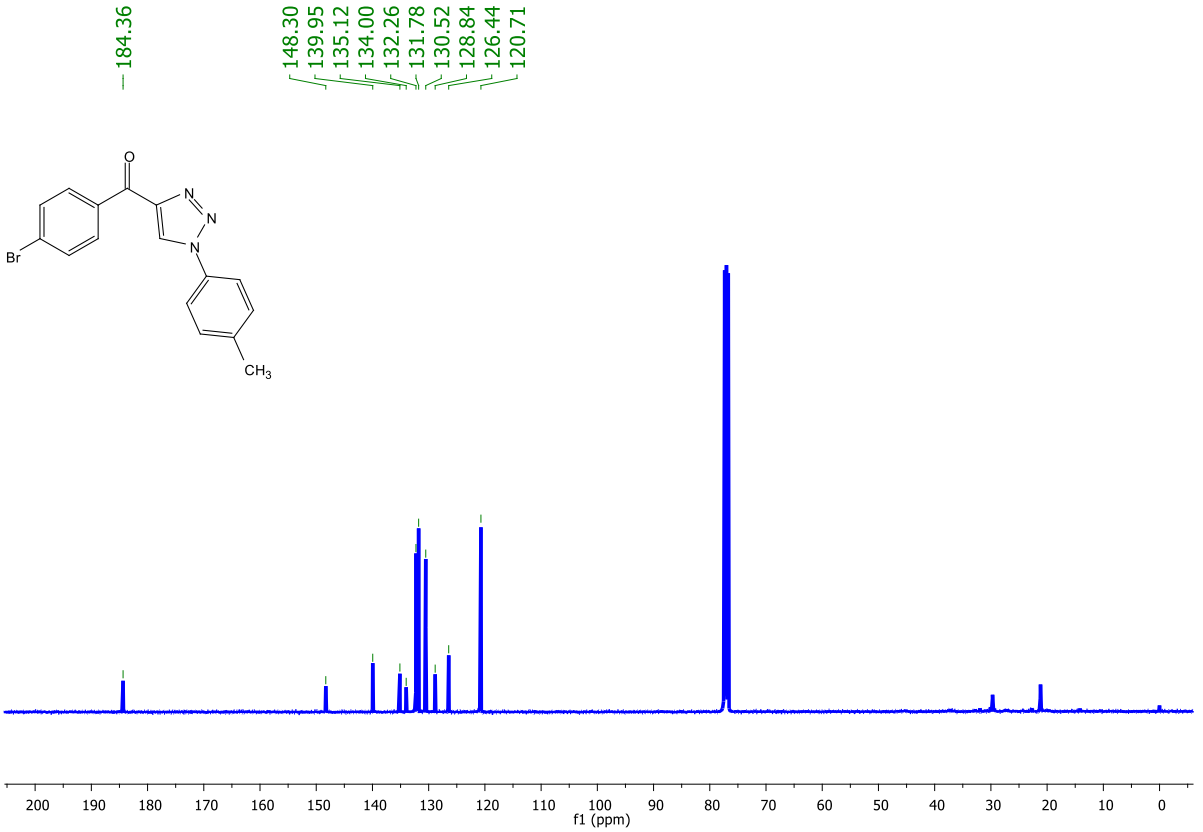

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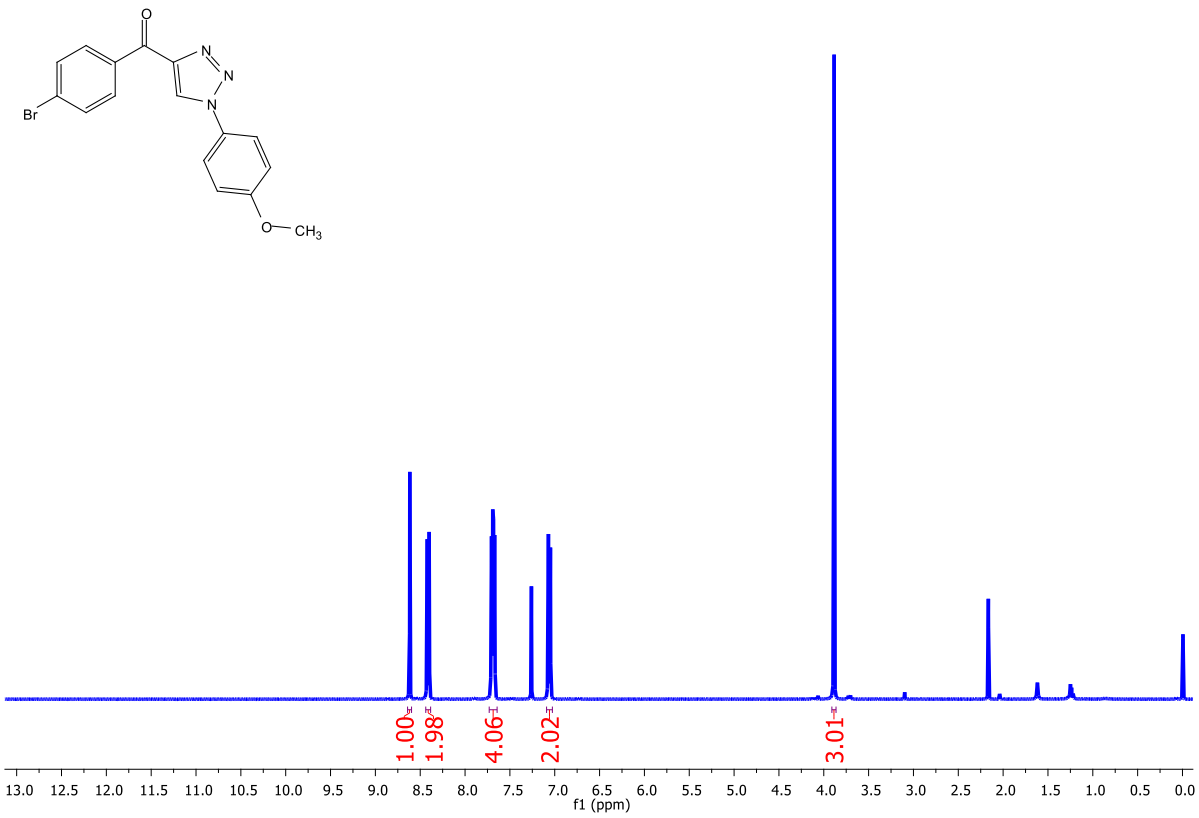
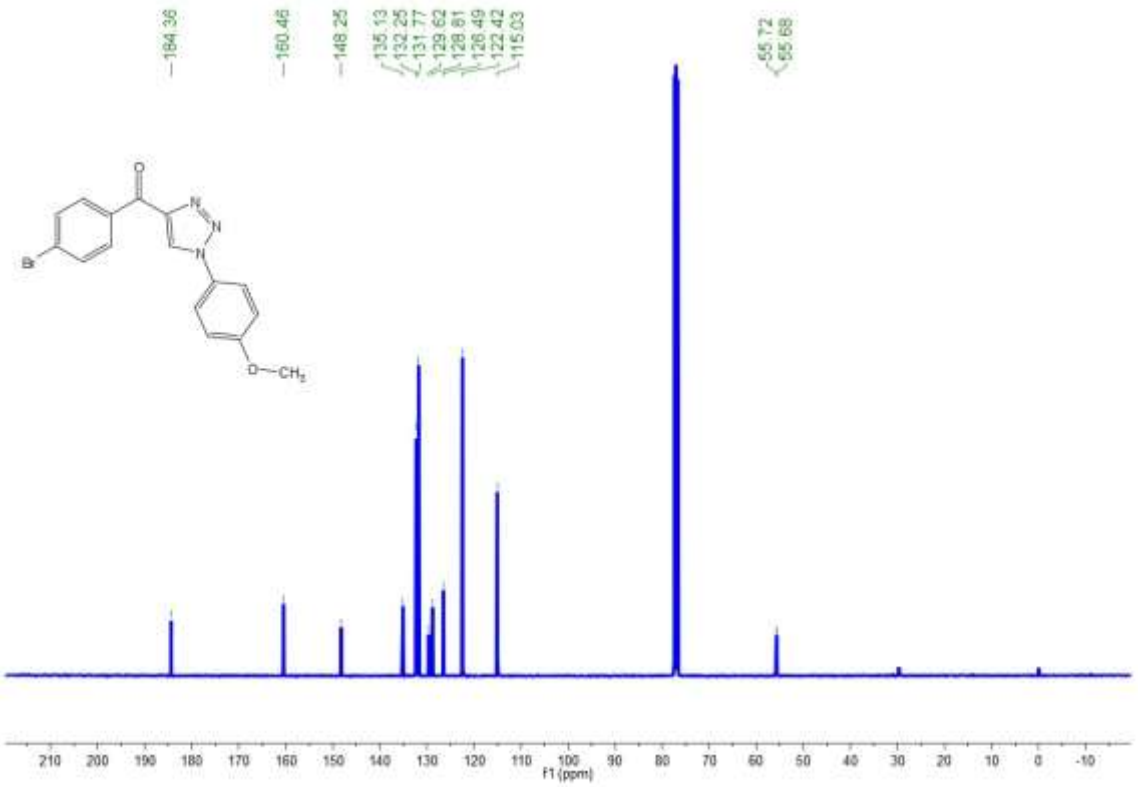


Spectrum 15: ^{1}H NMR (400 MHz; $CDCl_3$) 7ai



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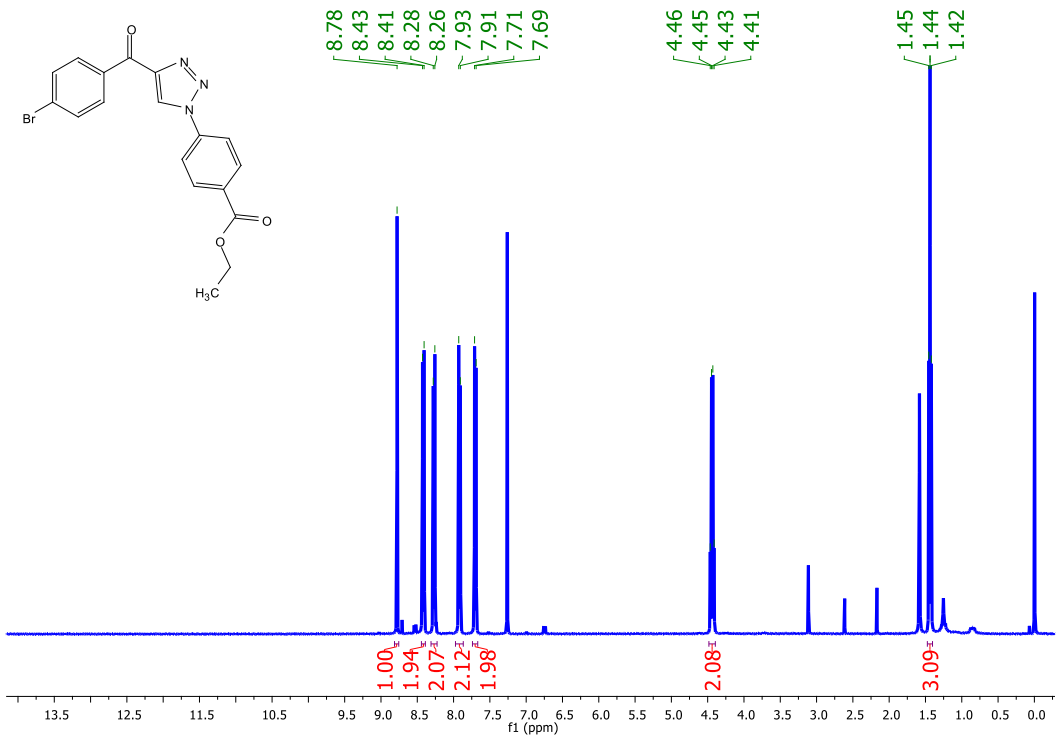
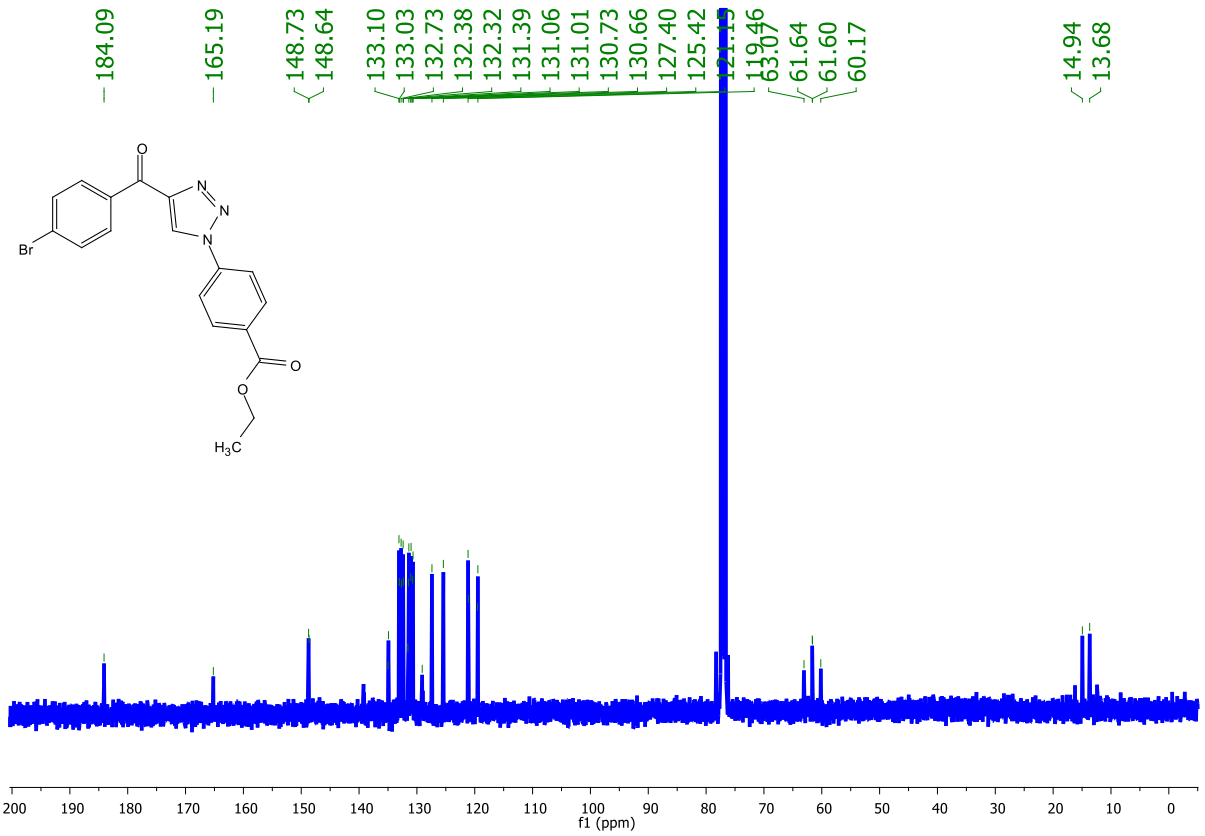
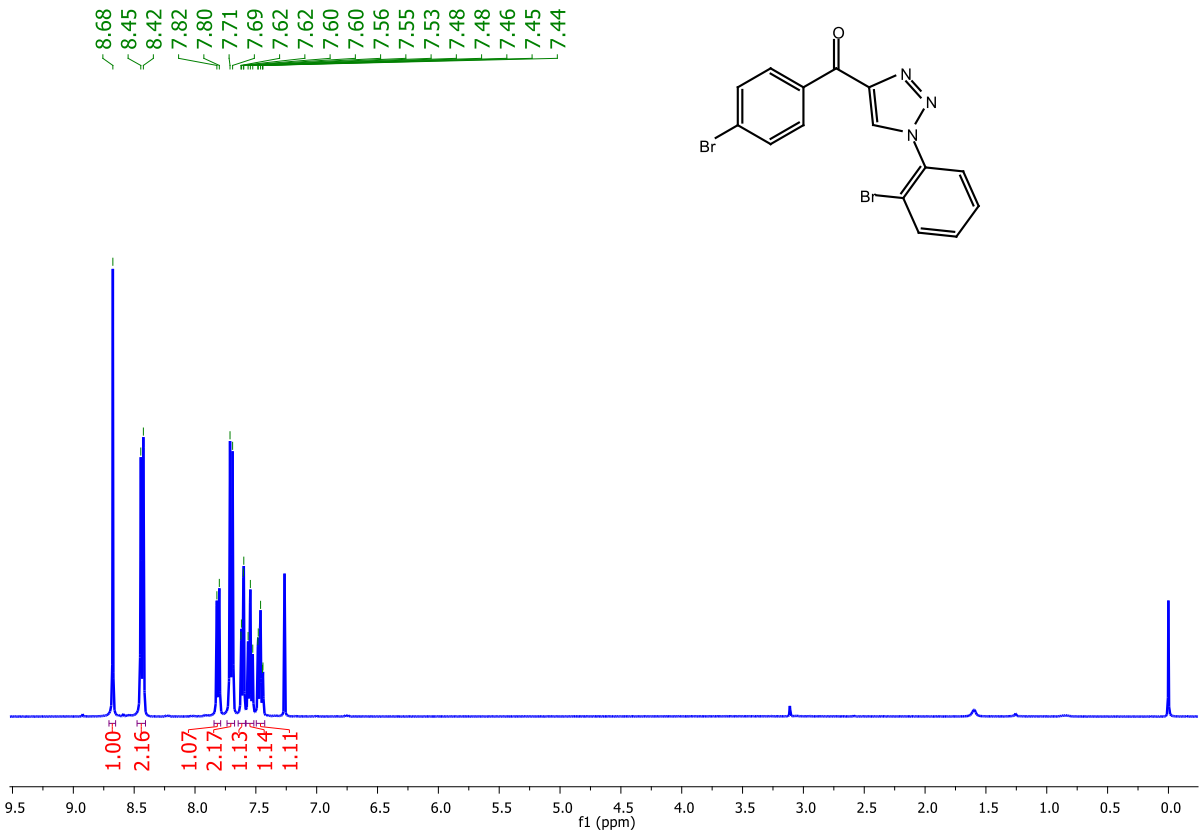


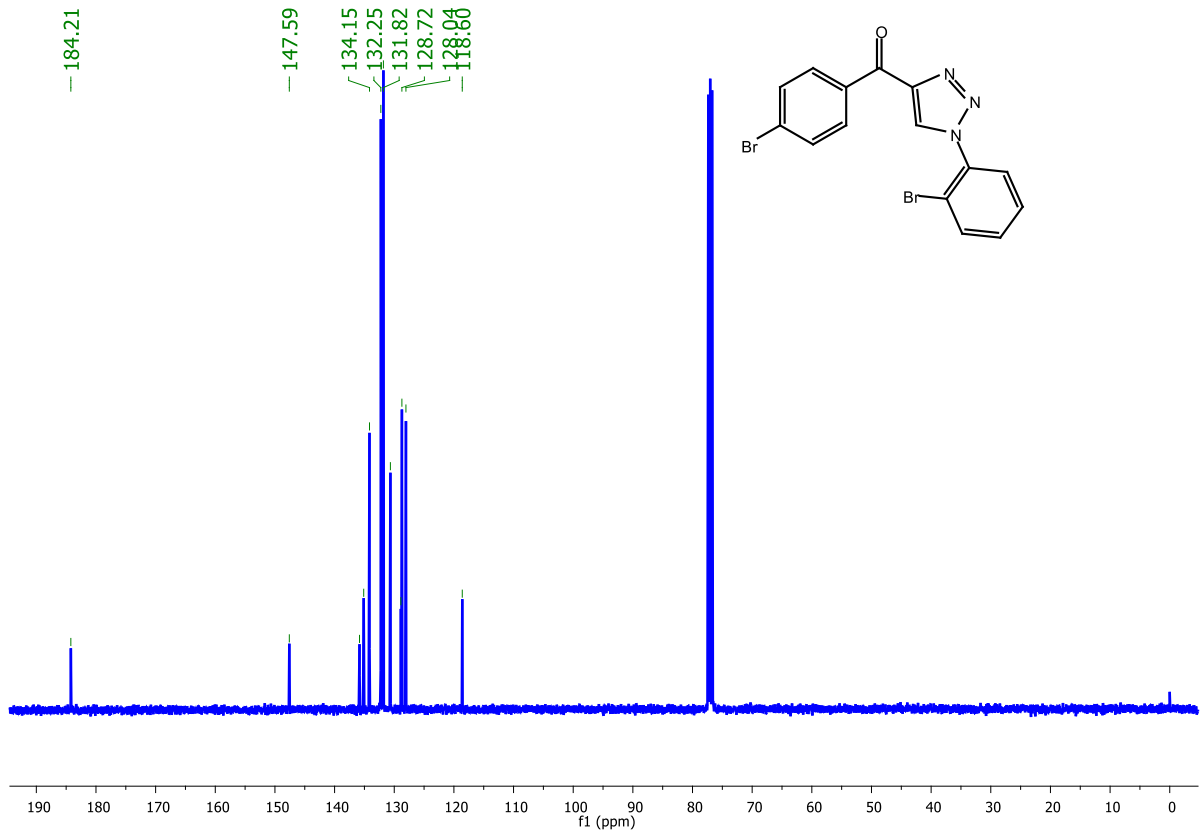
Spectrum 17: ^{1}H NMR (400 MHz; $CDCl_3$) 7aj



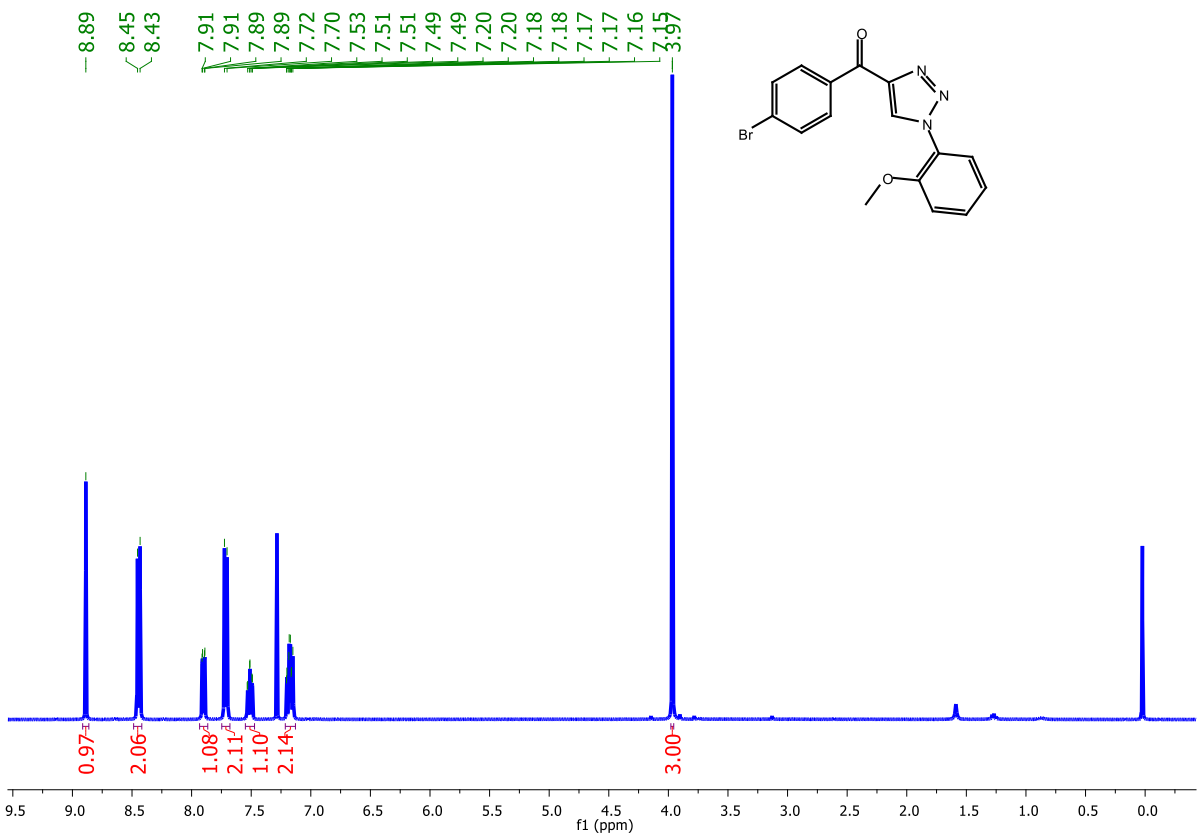
Spectrum 18: ^{13}C NMR (100 MHz; $CDCl_3$) 7aj



Spectrum 19: ^{1}H NMR (400 MHz; $CDCl_3$) 7ak



Spectrum 20: ^{13}C NMR (100 MHz; $CDCl_3$) 7ak



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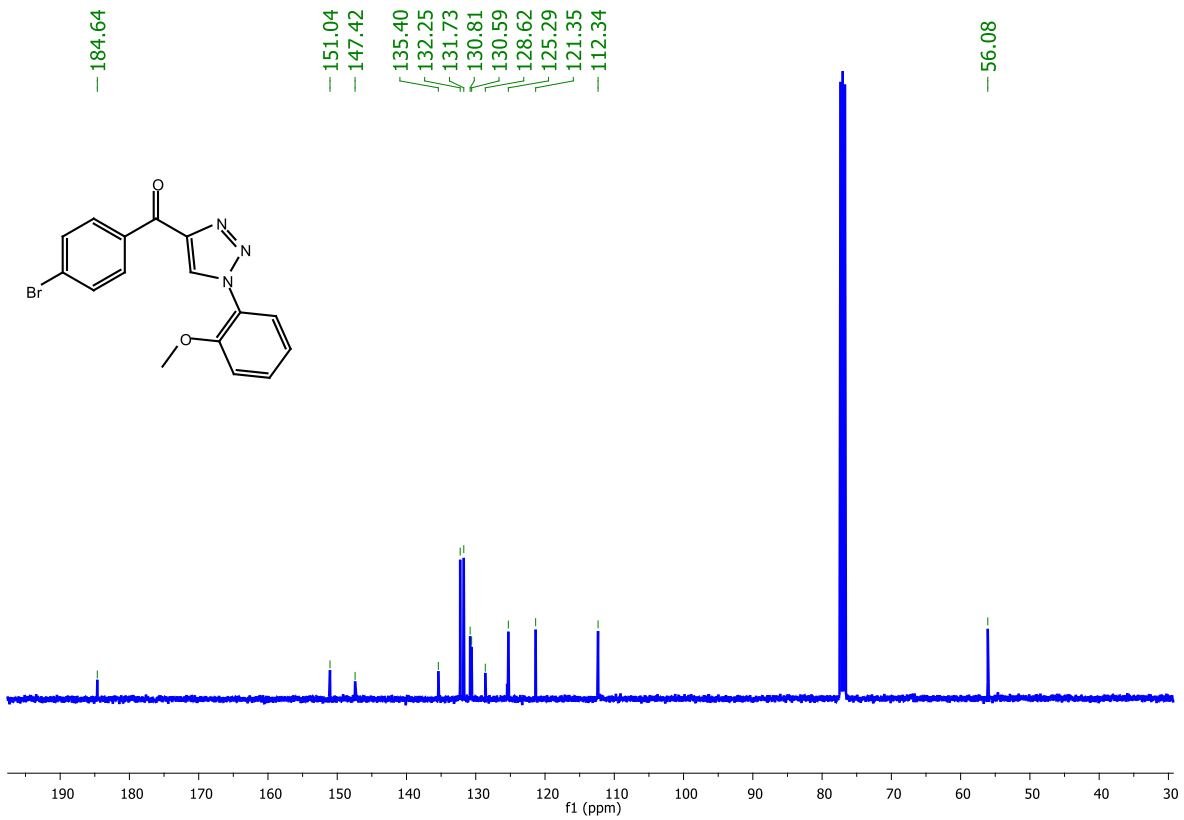

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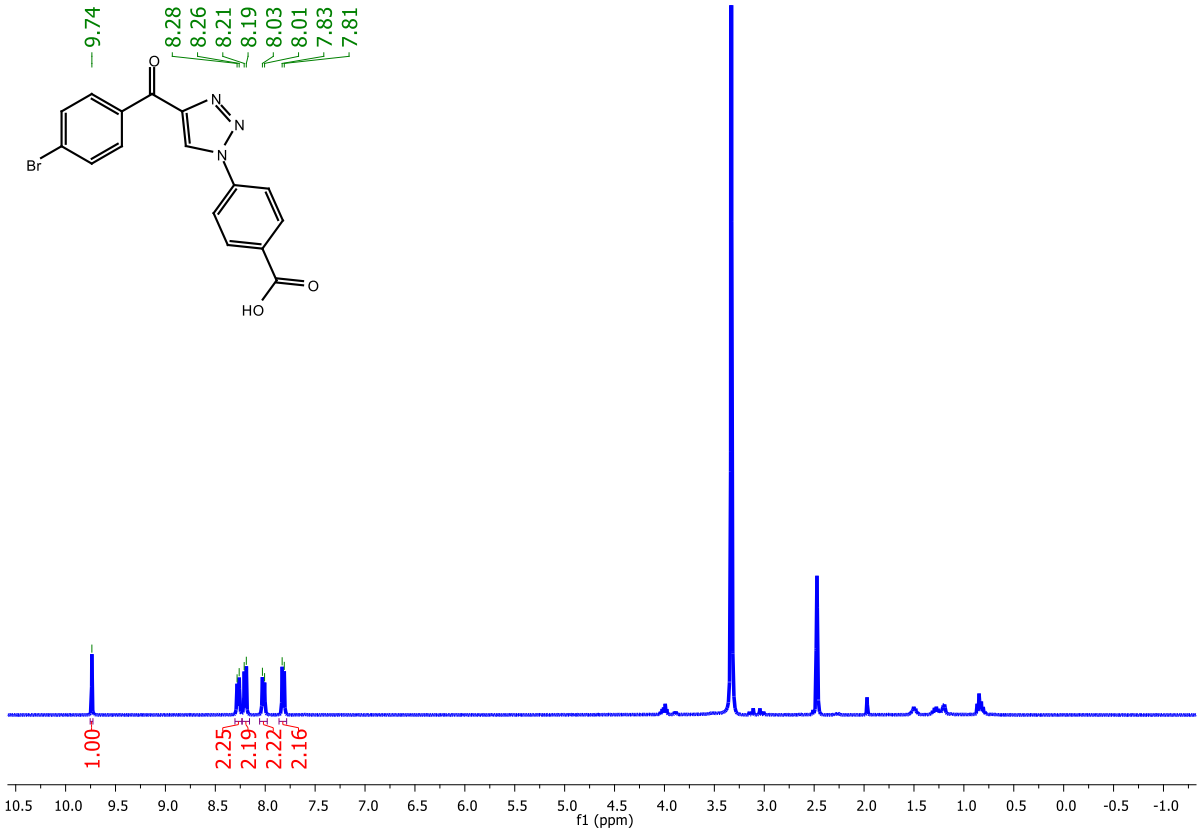

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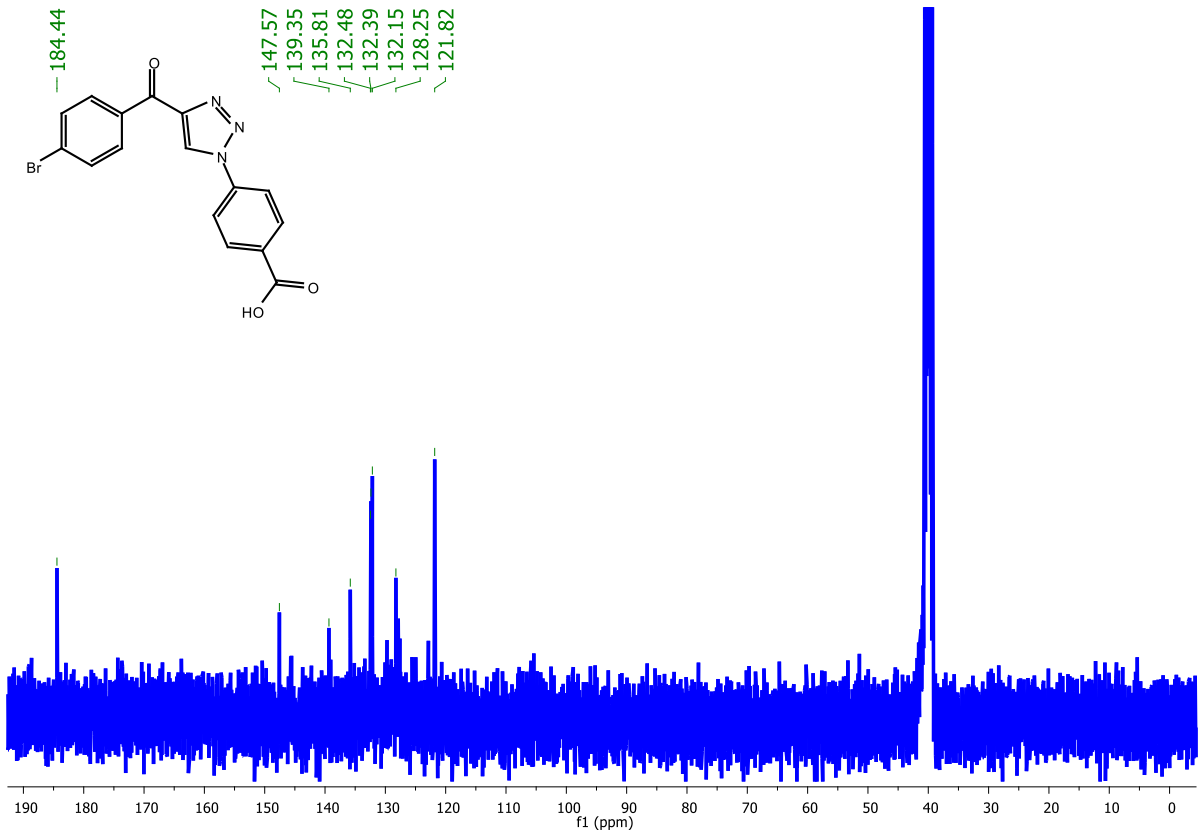

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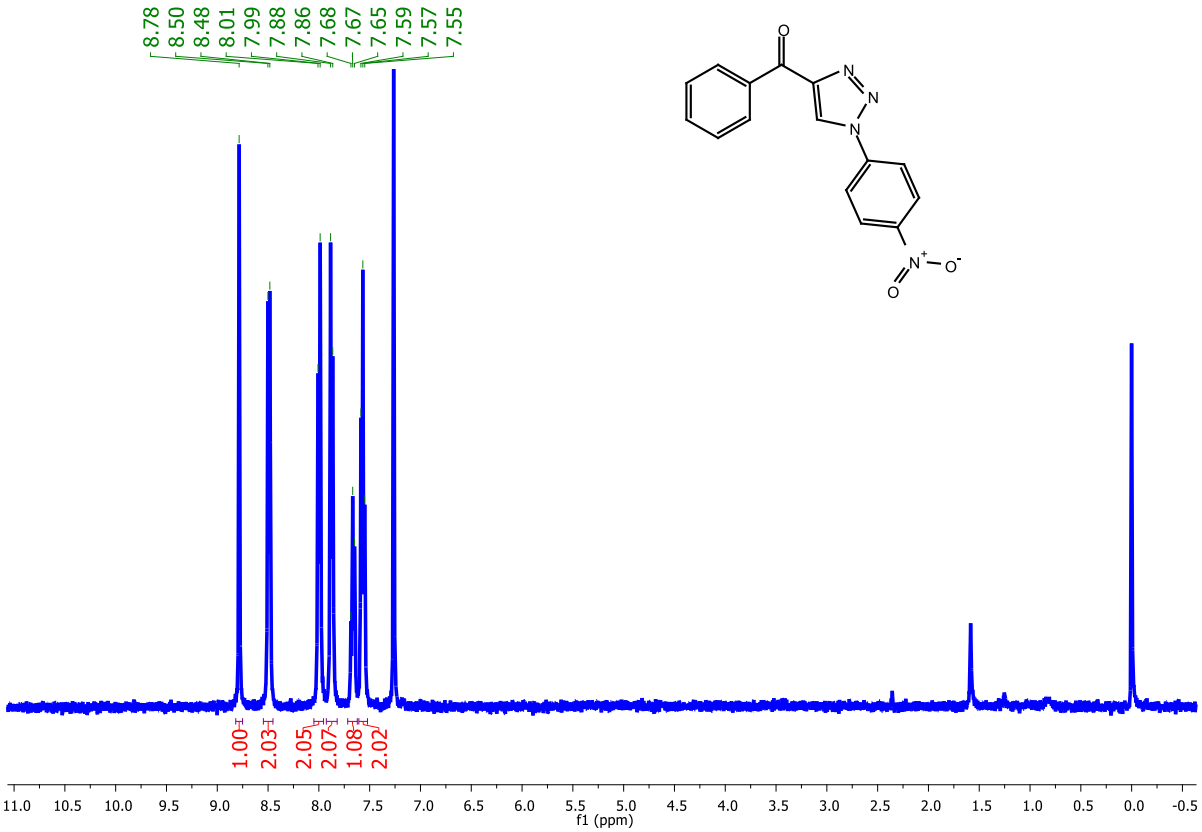

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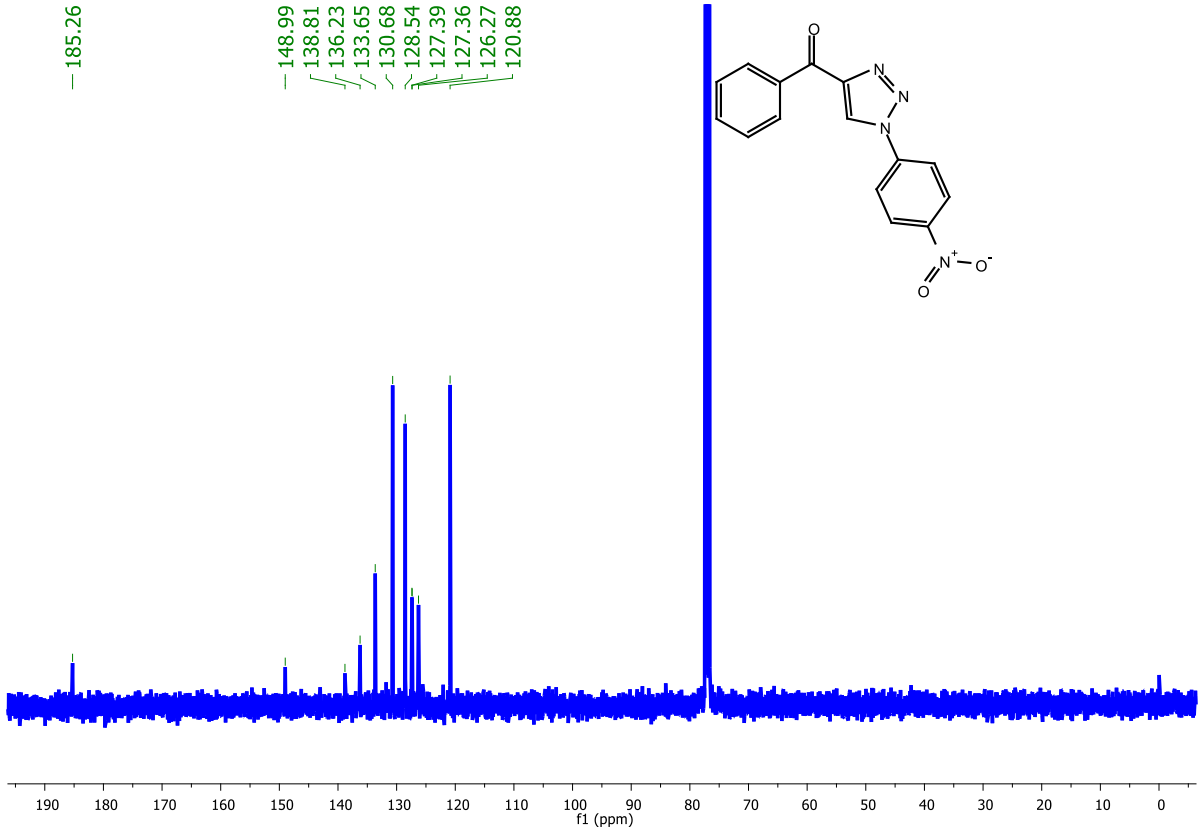

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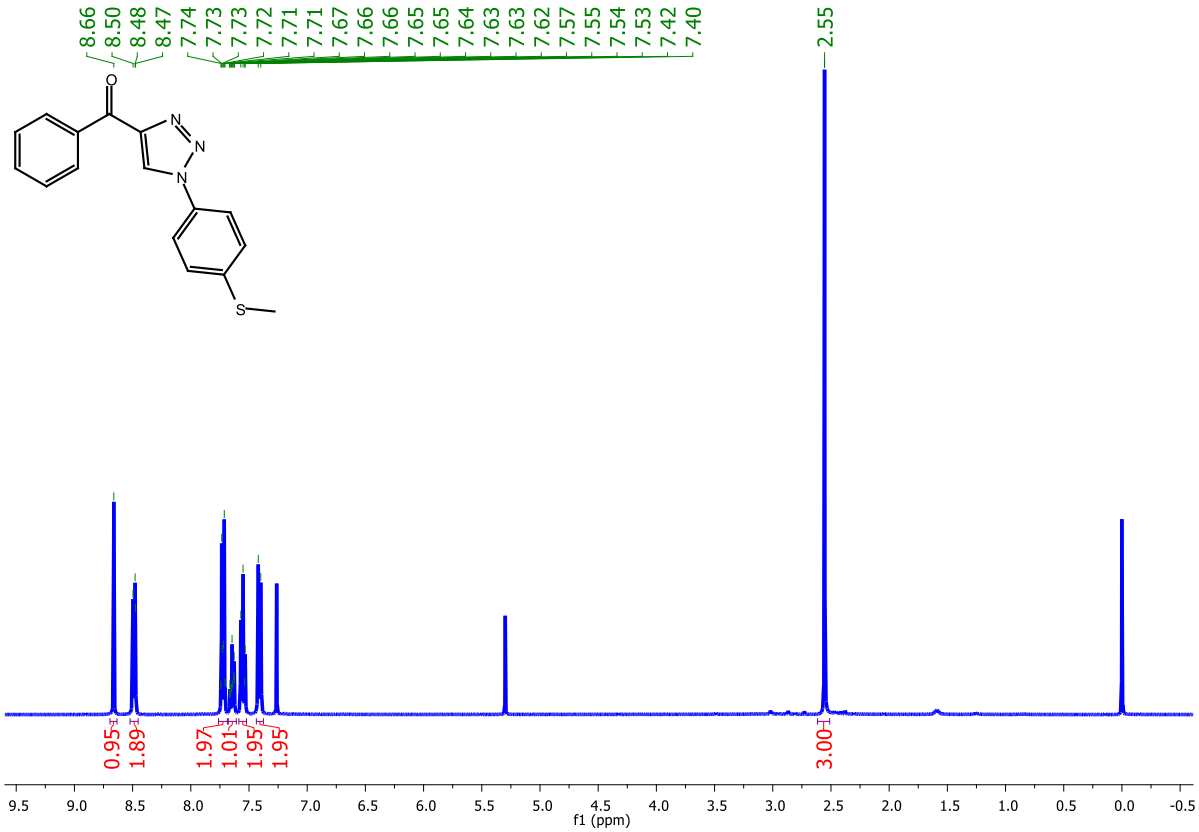

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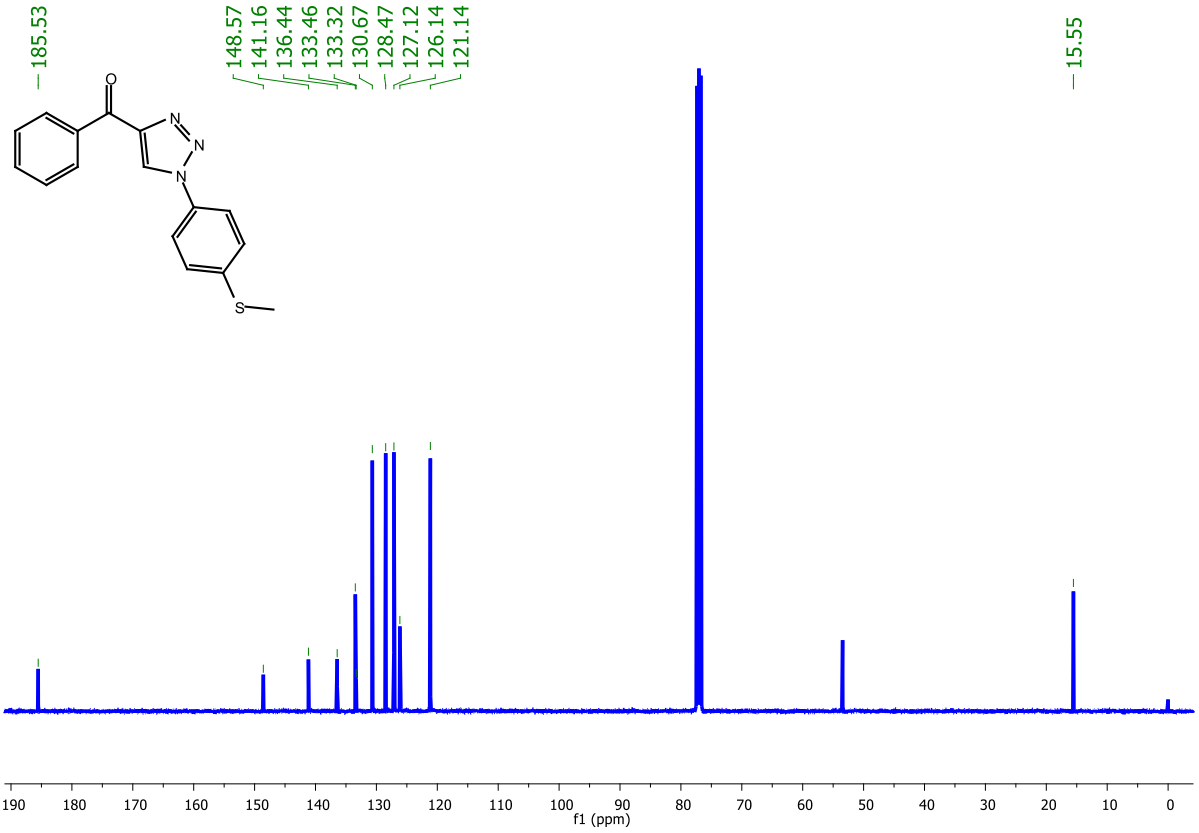

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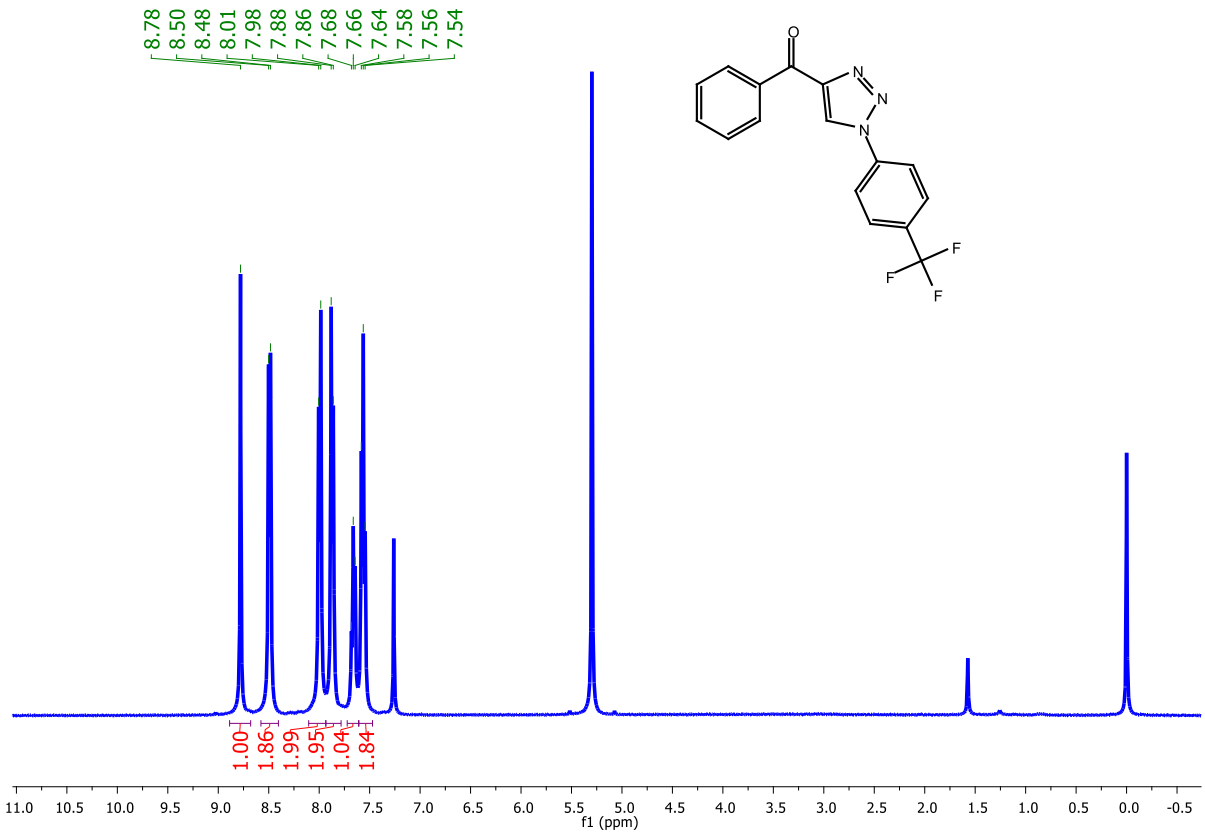
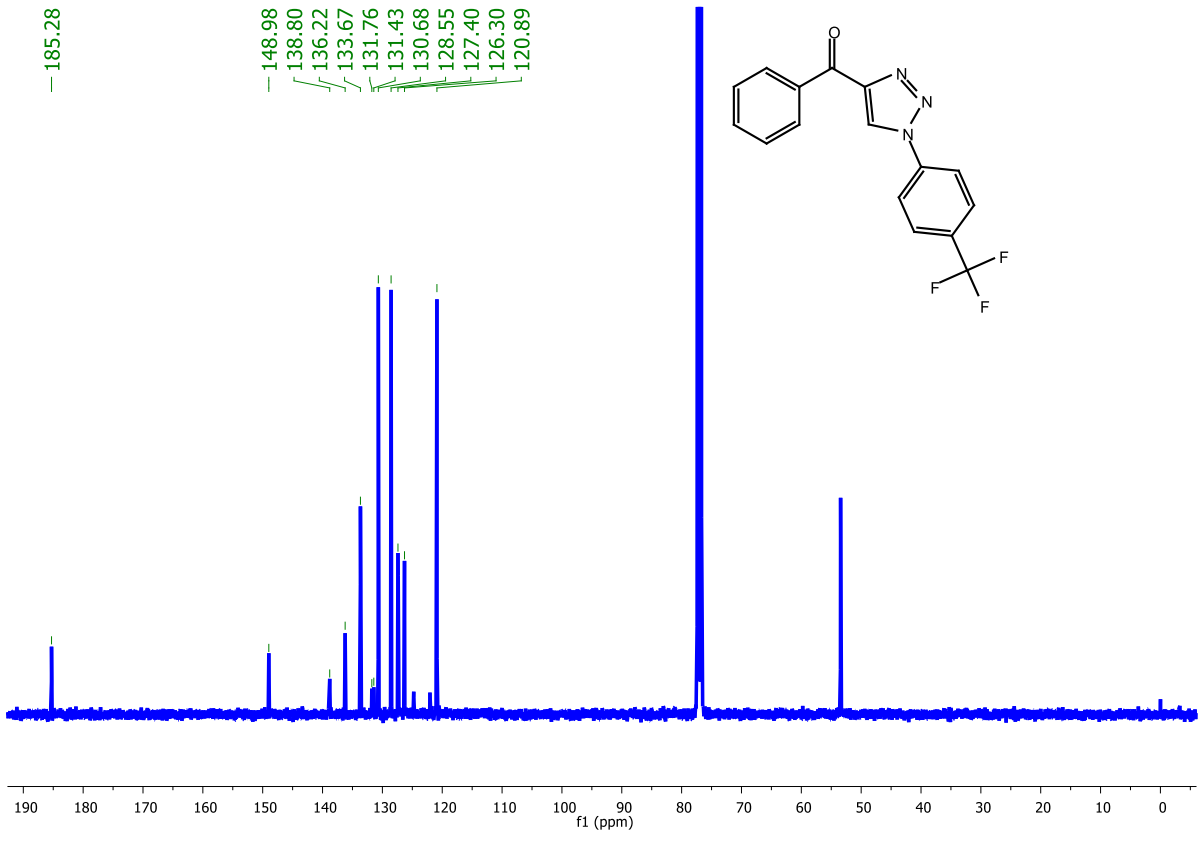
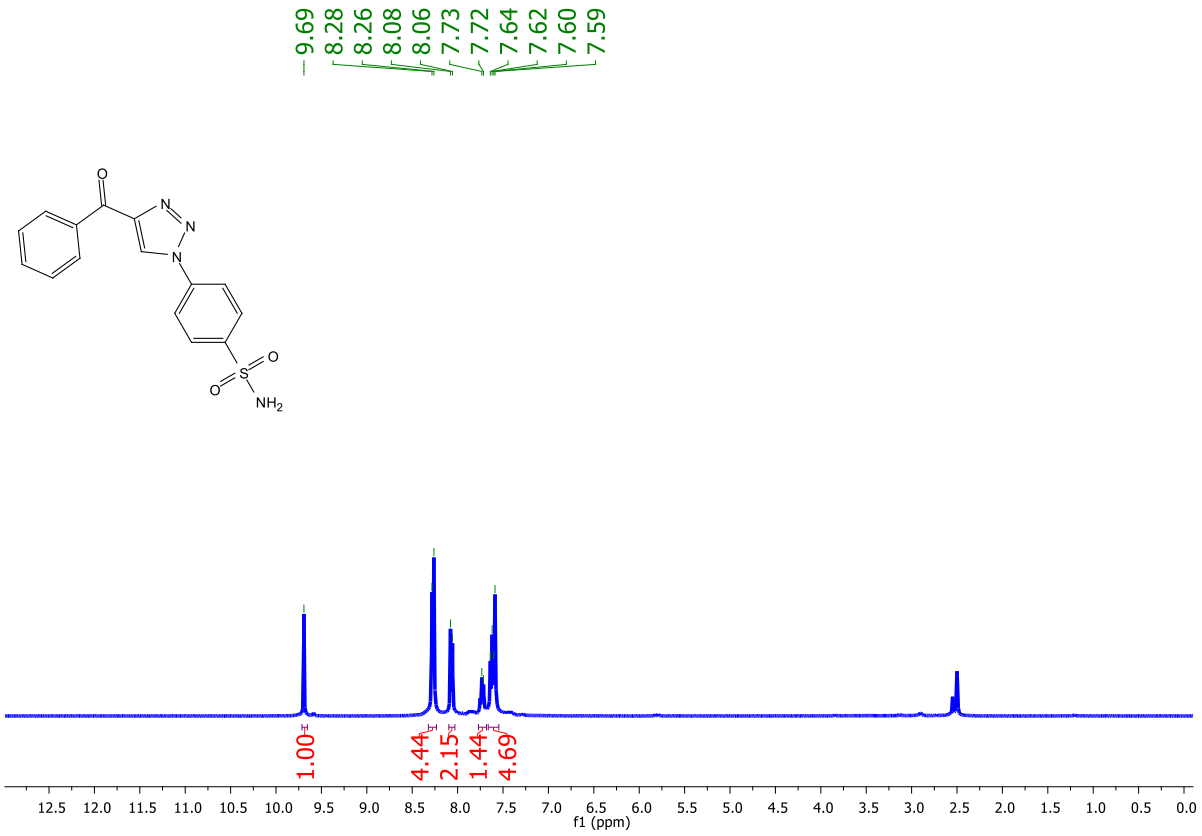


Spectrum 29: ^{1}H NMR (400 MHz; $CDCl_3$) 7bd



Spectrum 30: ^{13}C NMR (100 MHz; $CDCl_3$) 7bd



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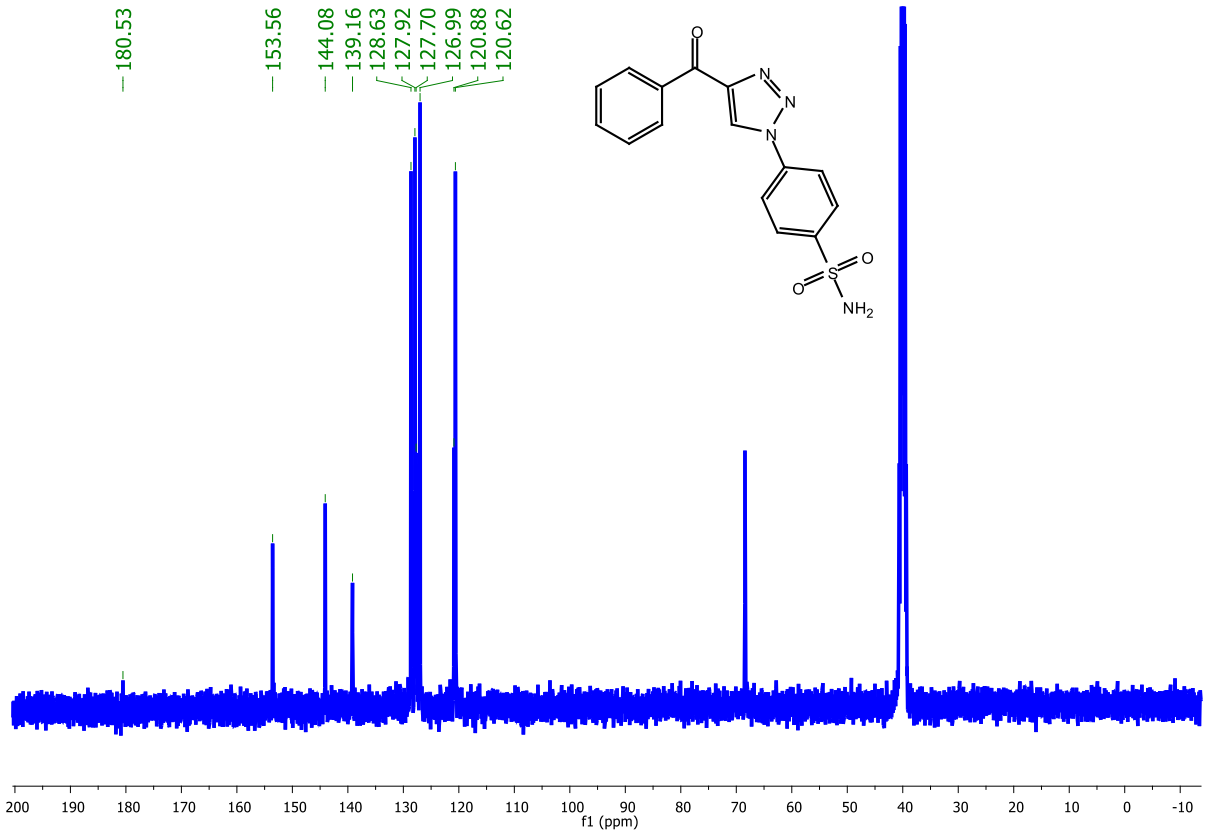

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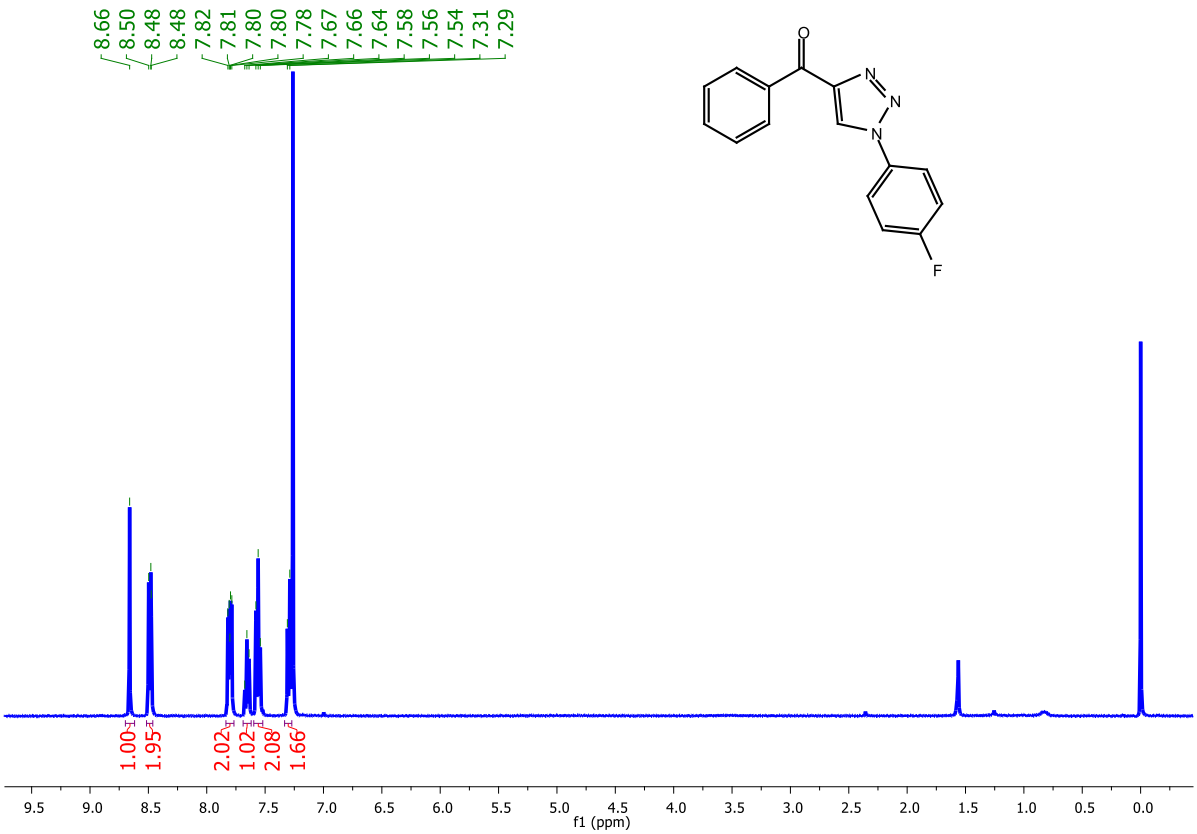

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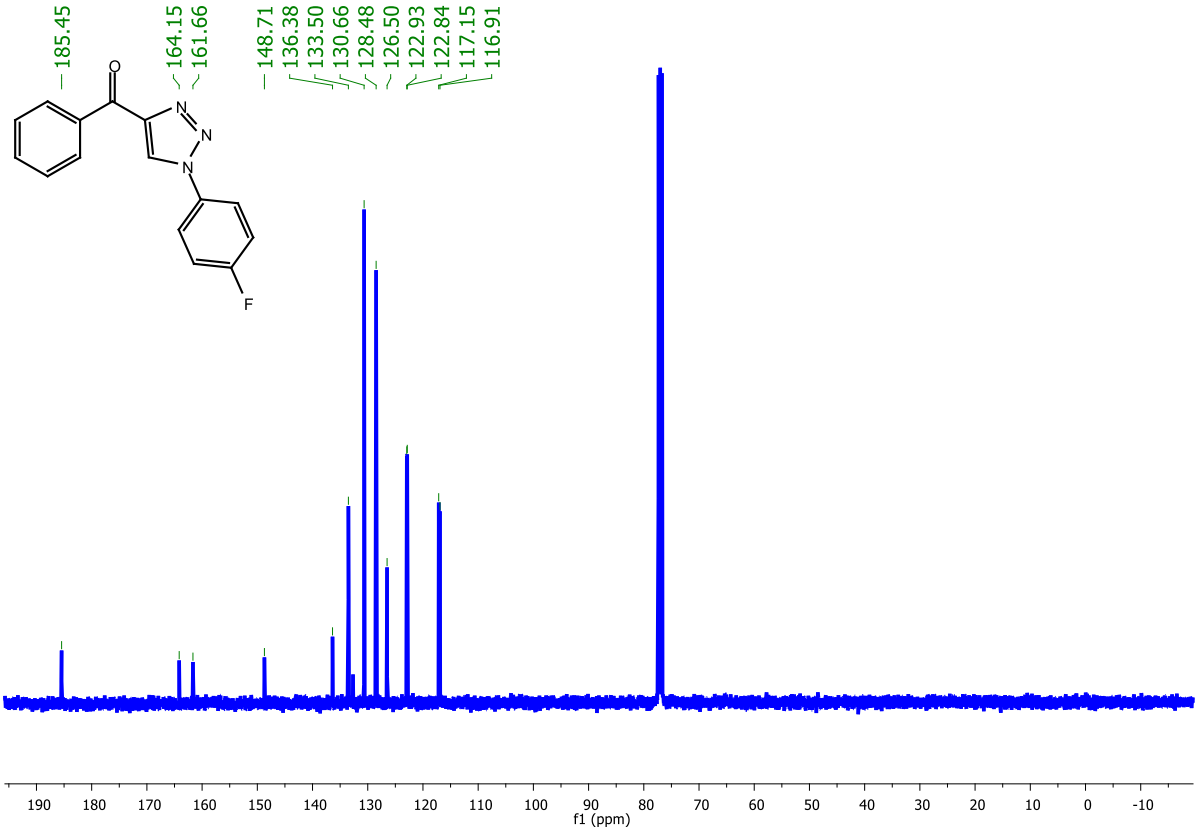

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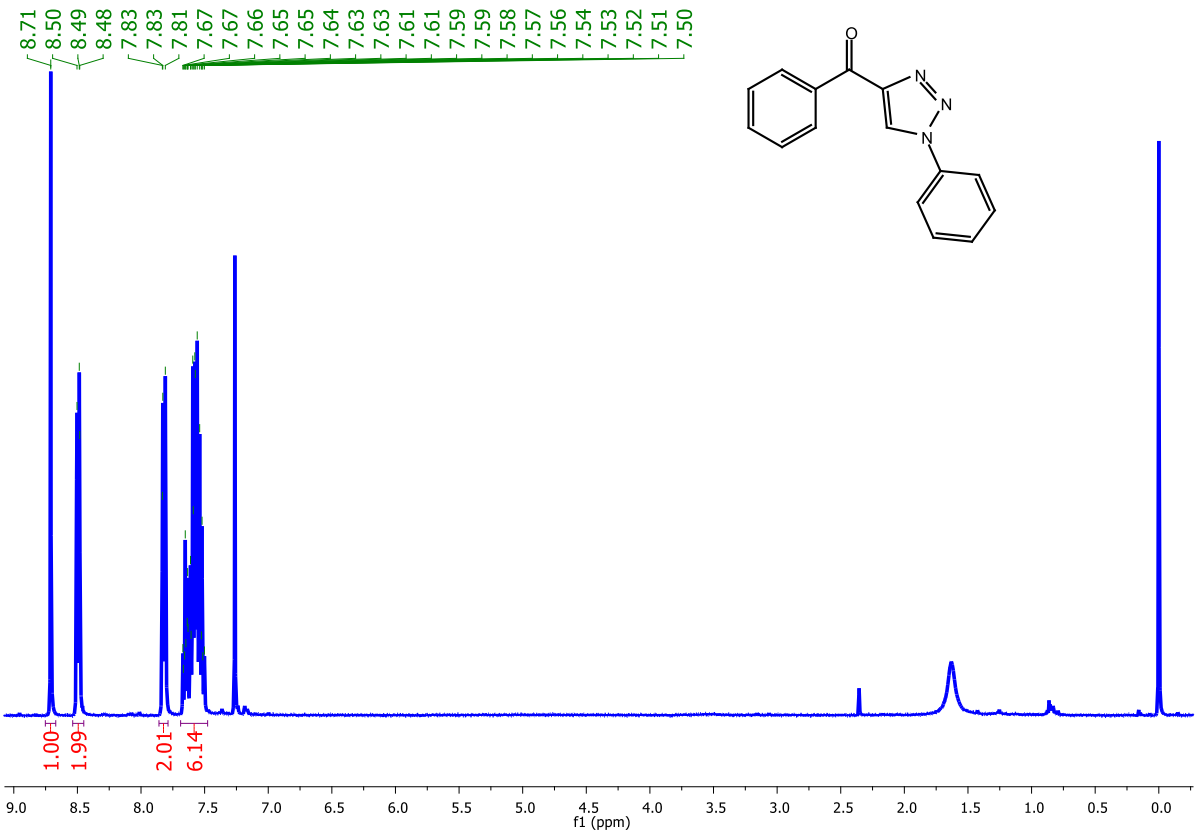

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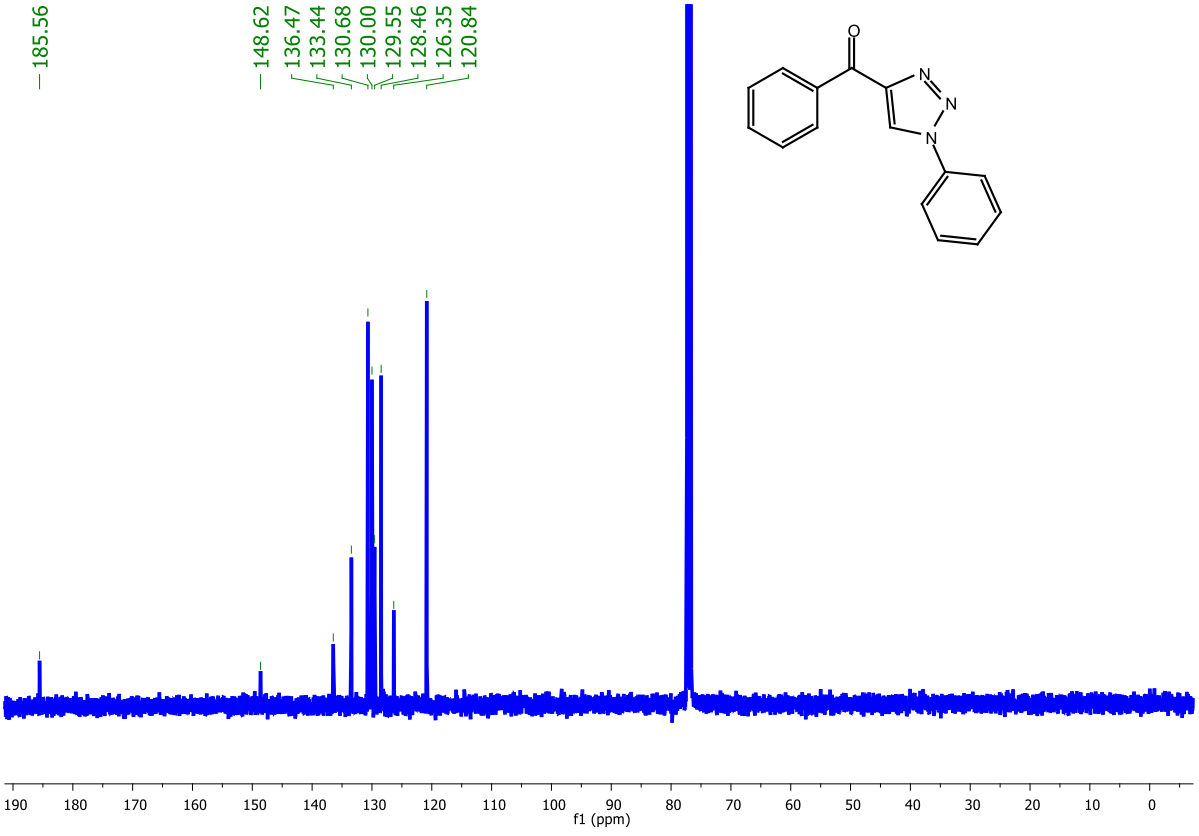

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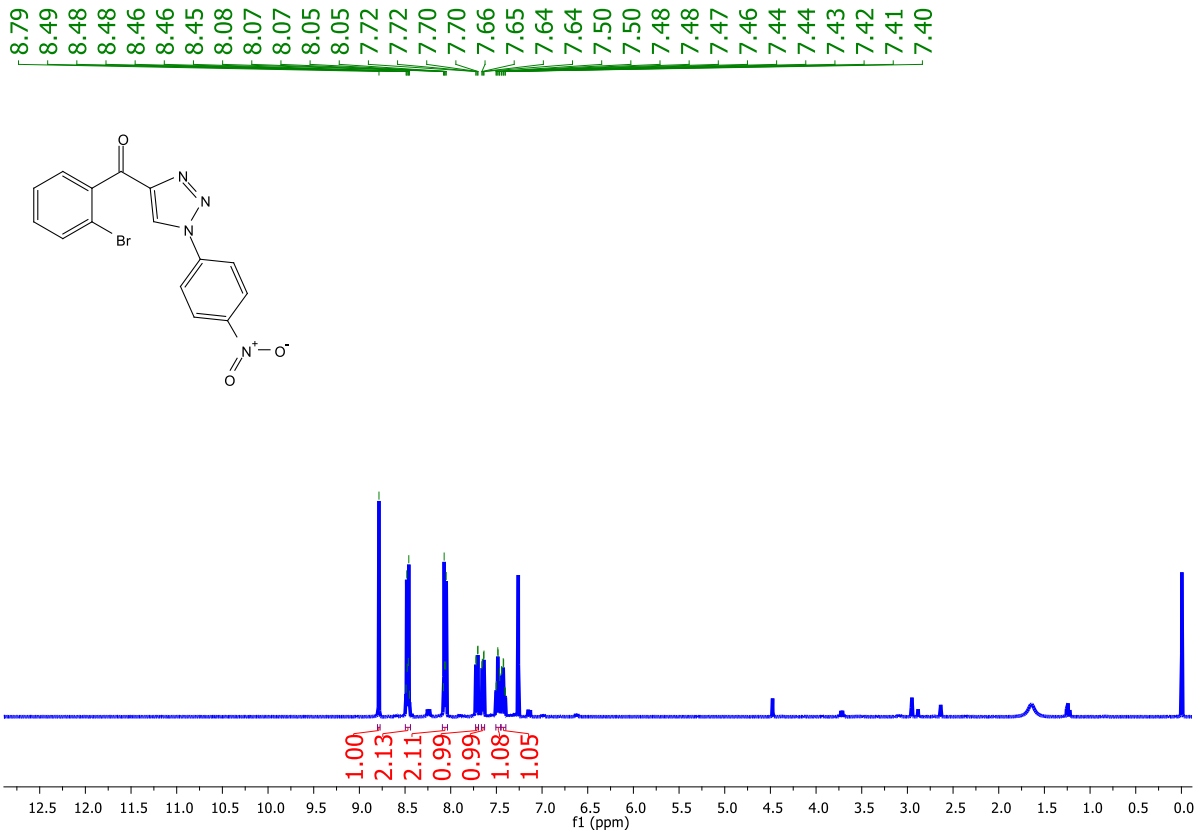
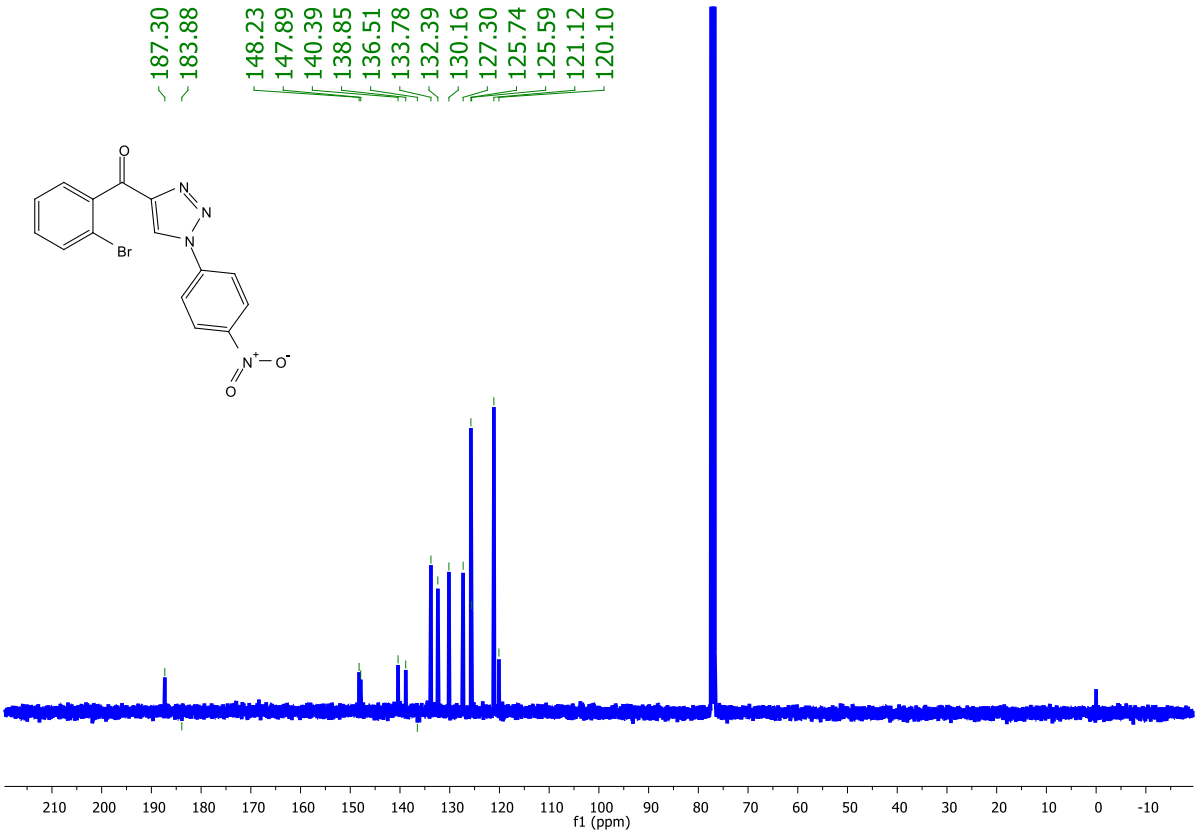
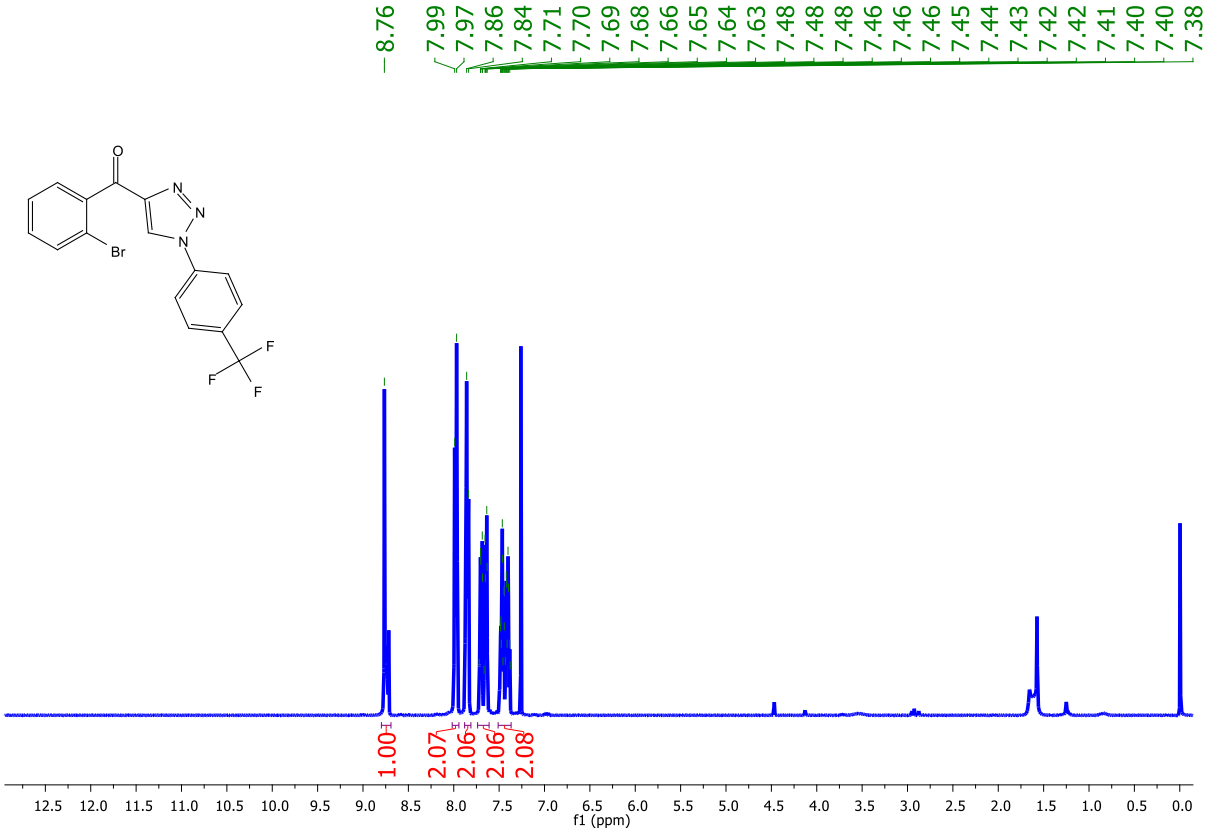


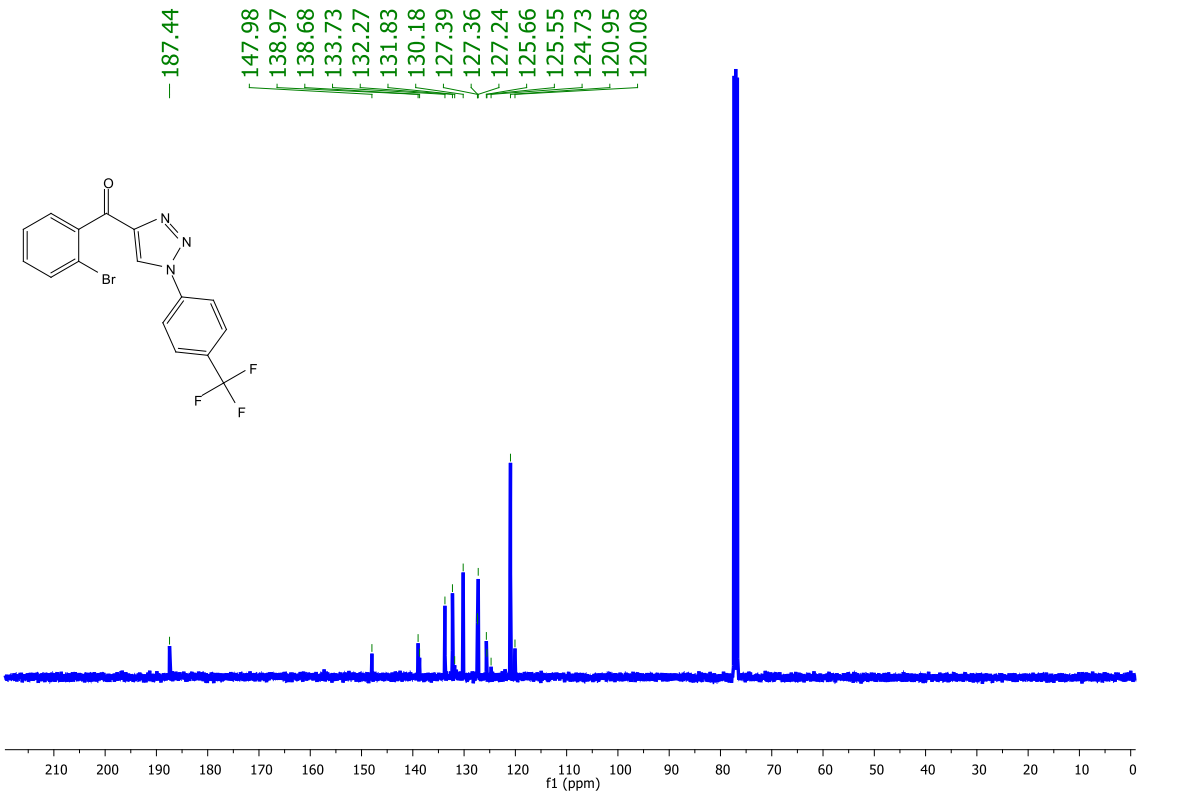
Spectrum 37: ^{1}H NMR (400 MHz; $CDCl_3$) 7jb



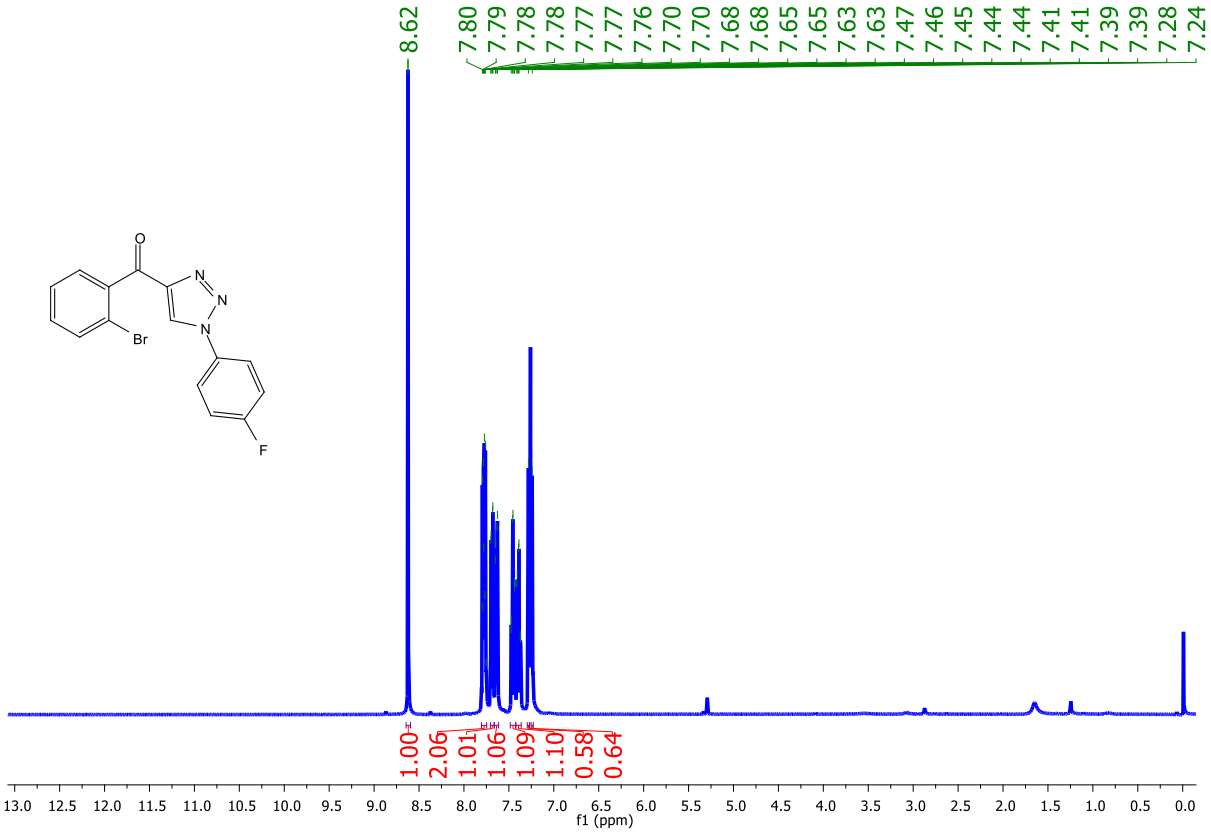
Spectrum 38: ^{13}C NMR (100 MHz; $CDCl_3$) 7jb



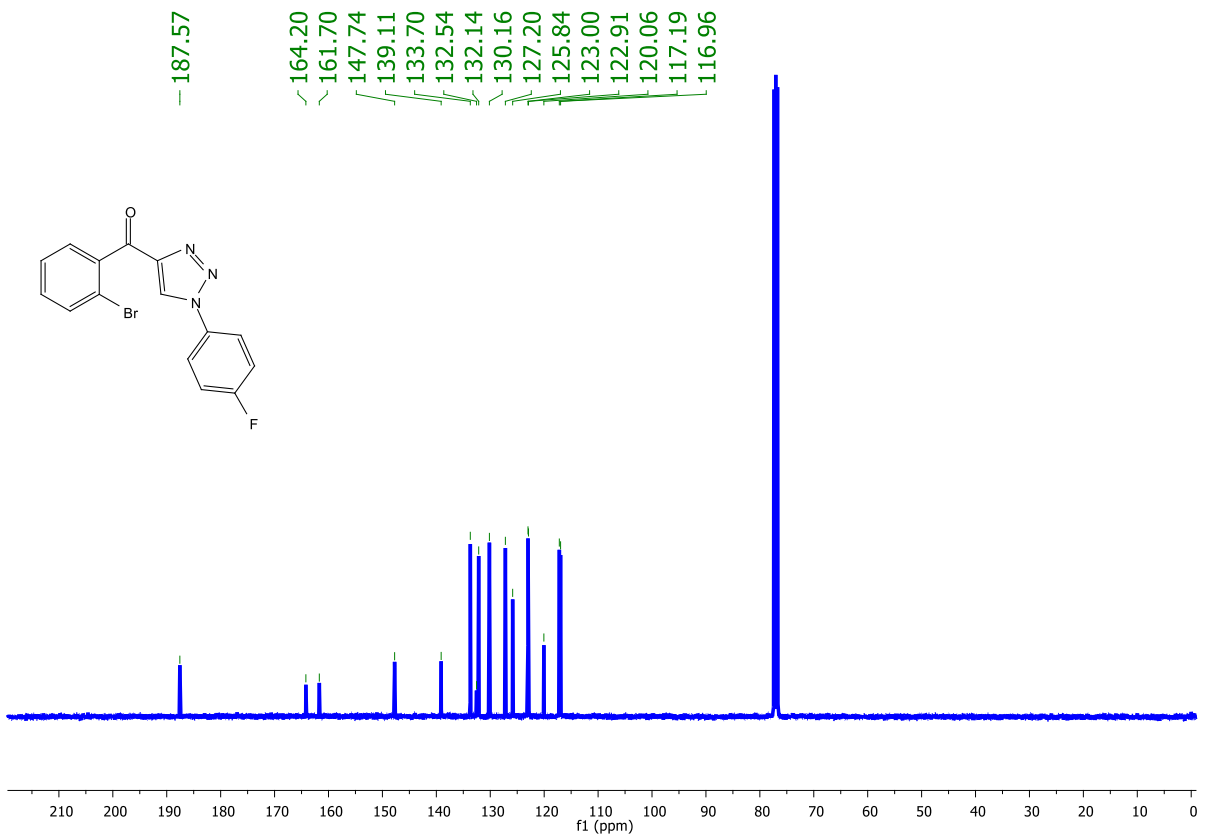
Spectrum 39: ^{1}H NMR (400 MHz; $CDCl_3$) 7jd



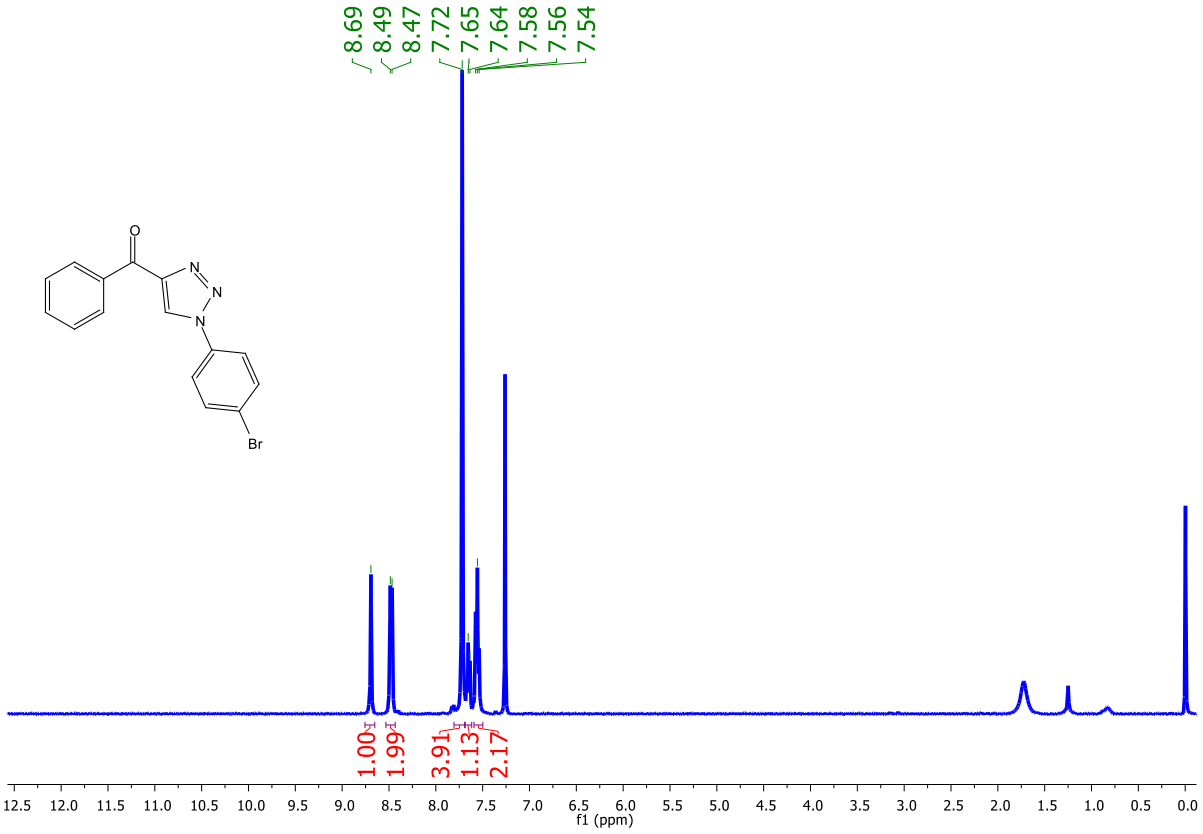
Spectrum 40: ^{13}C NMR (100 MHz; $CDCl_3$)7jd



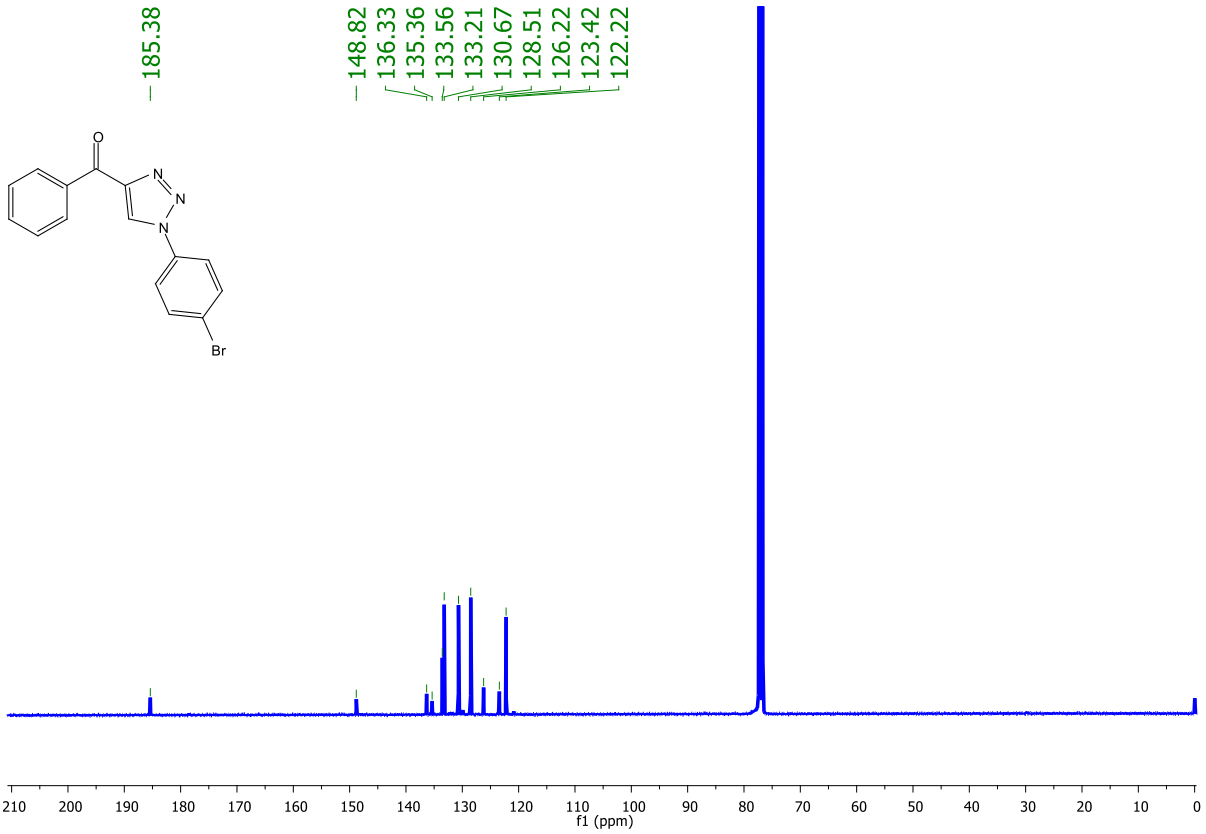
Spectrum 41: ^{1}H NMR (400 MHz; $CDCl_3$) 7jf



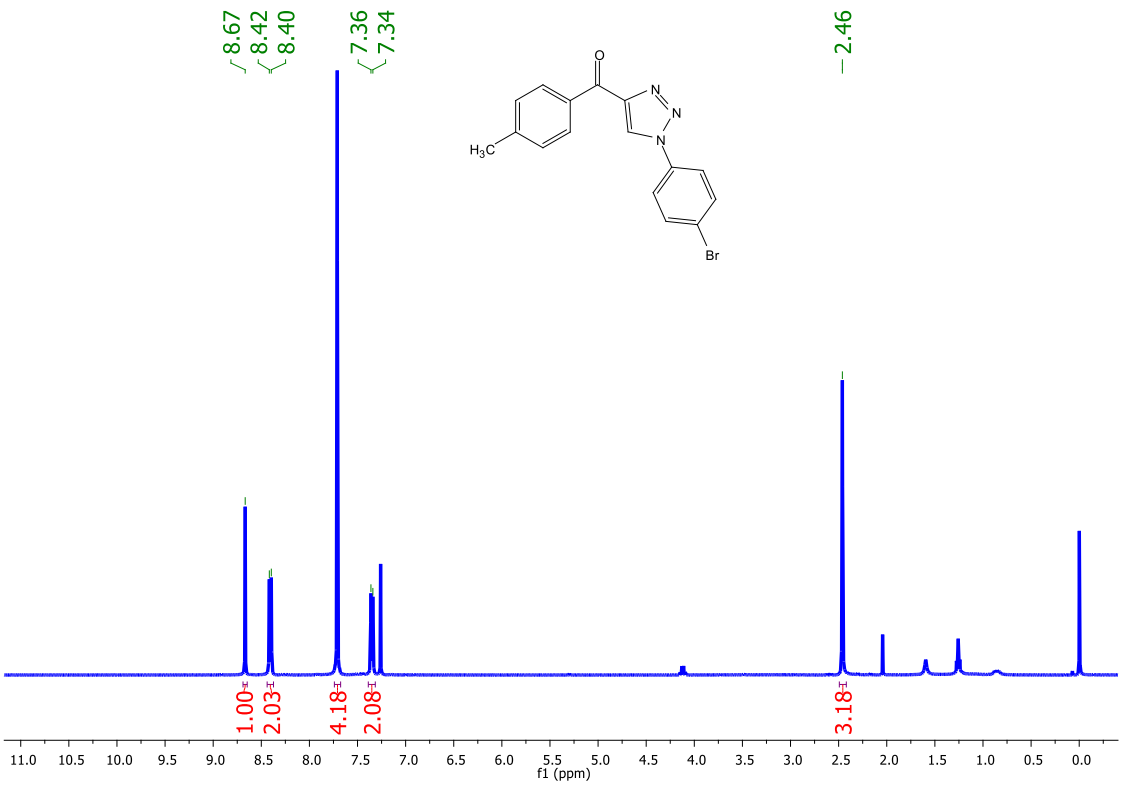
Spectrum 42: ^{13}C NMR (100 MHz; $CDCl_3$) 7jf



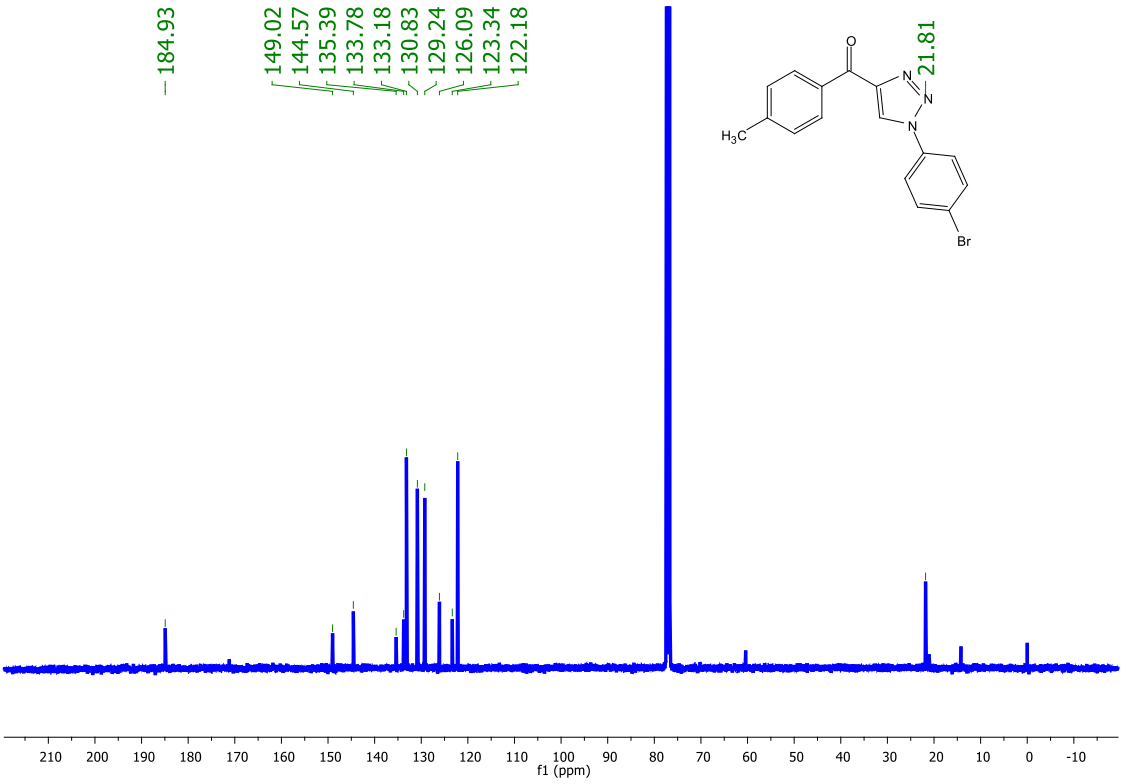
Spectrum 43: ^{1}H NMR (400 MHz; $CDCl_3$) 7ba



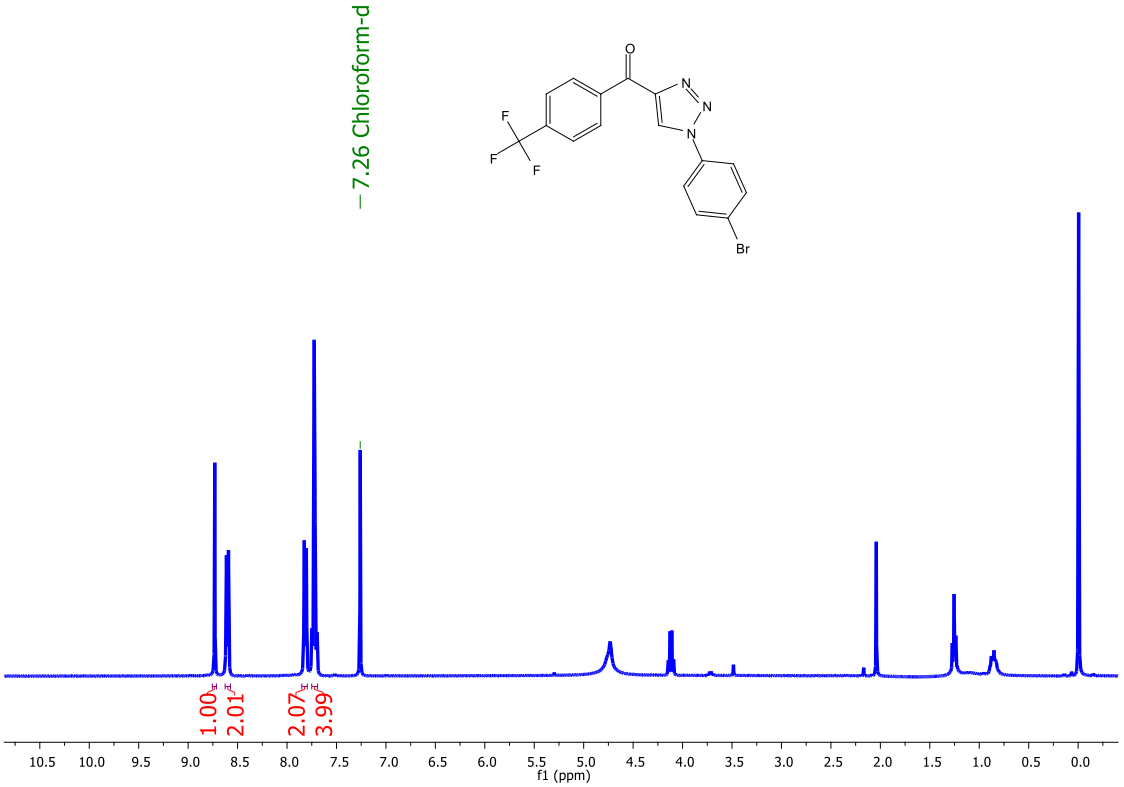
Spectrum 44: ^{13}C NMR (100 MHz; $CDCl_3$) 7ba



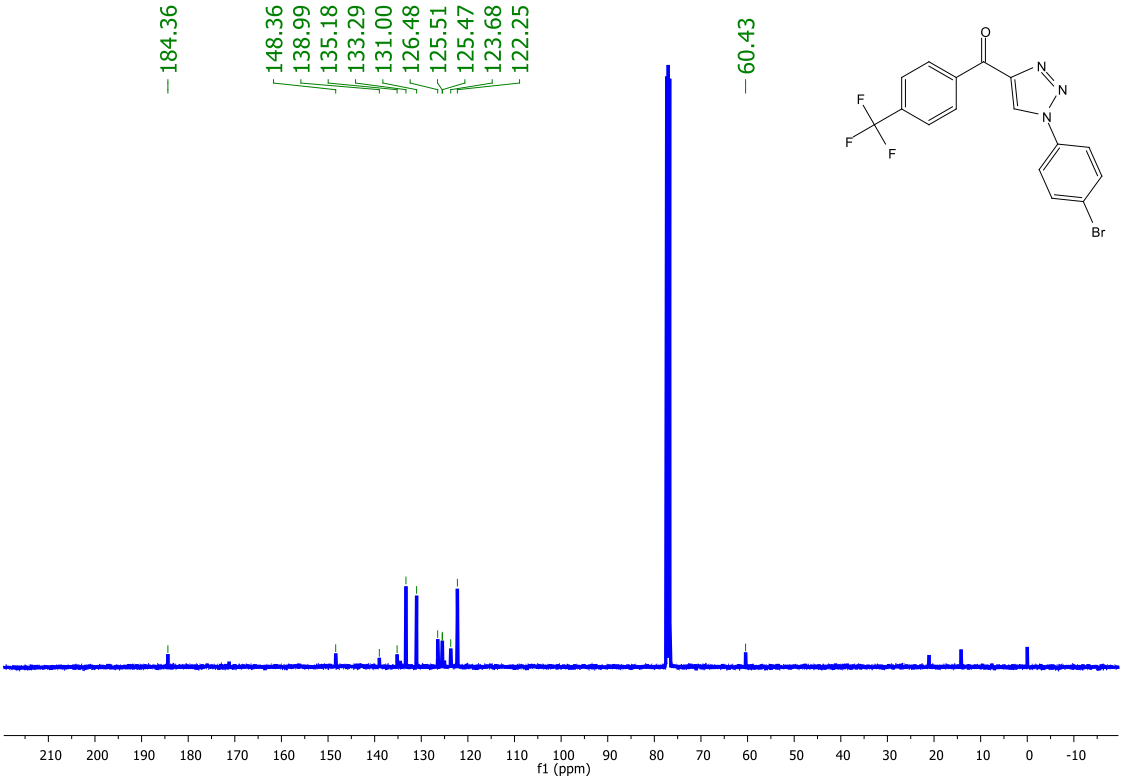
Spectrum 45: ^{1}H NMR (400 MHz; $CDCl_3$) 7ca



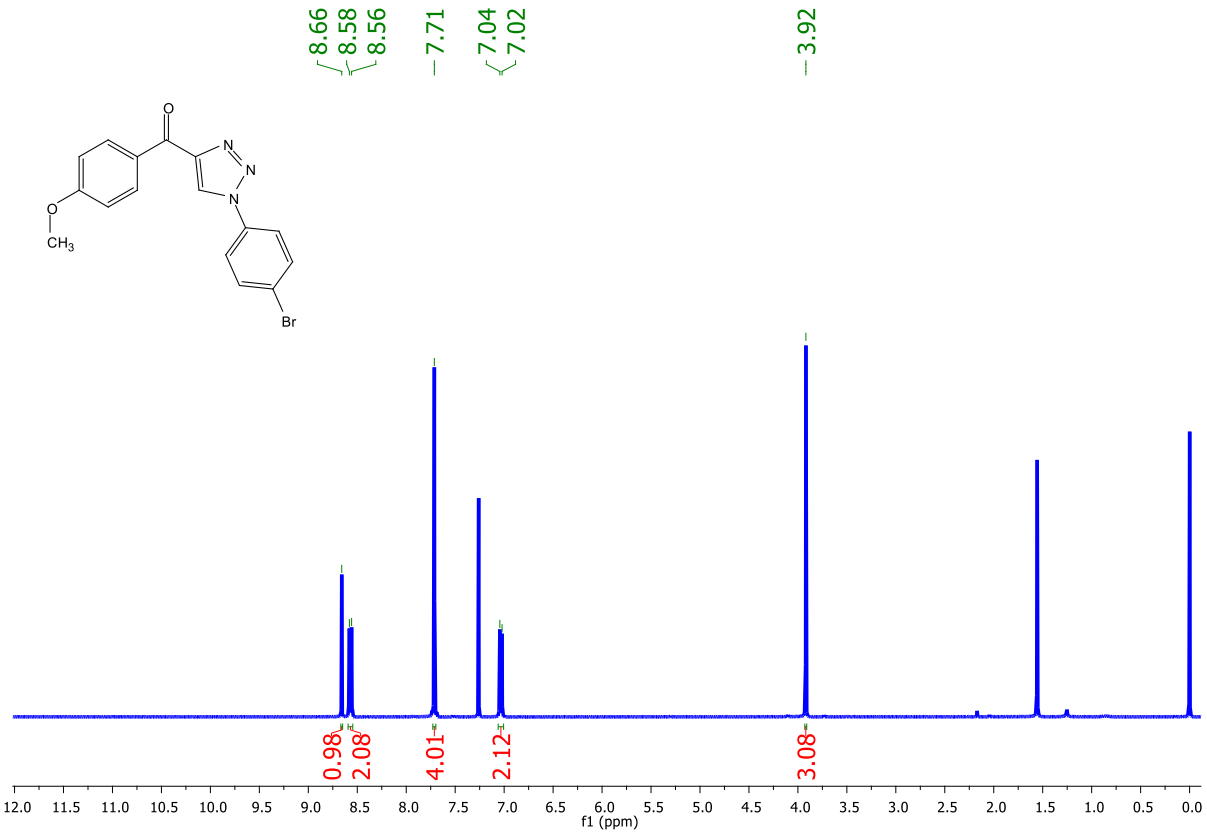
Spectrum 46: ^{13}C NMR (100 MHz; $CDCl_3$) 7ca



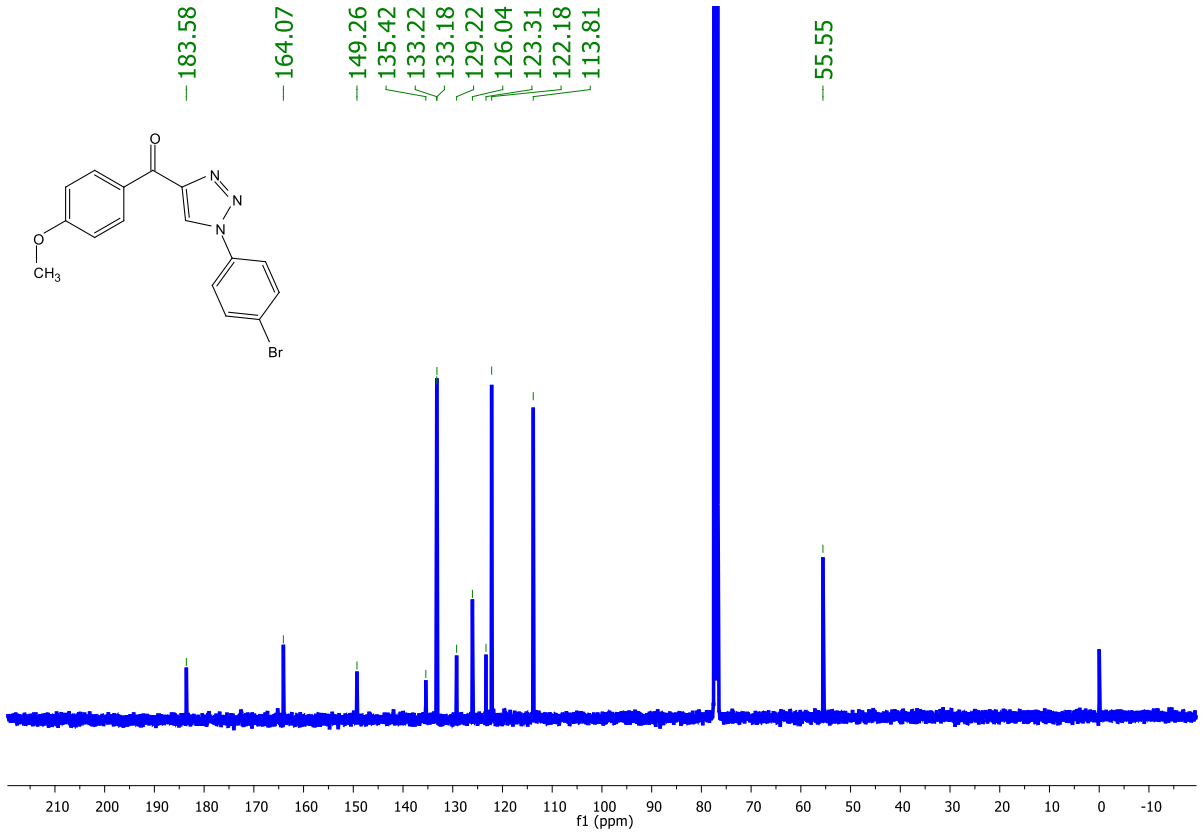
Spectrum 47: ^{1}H NMR (400 MHz; $CDCl_3$) 7da



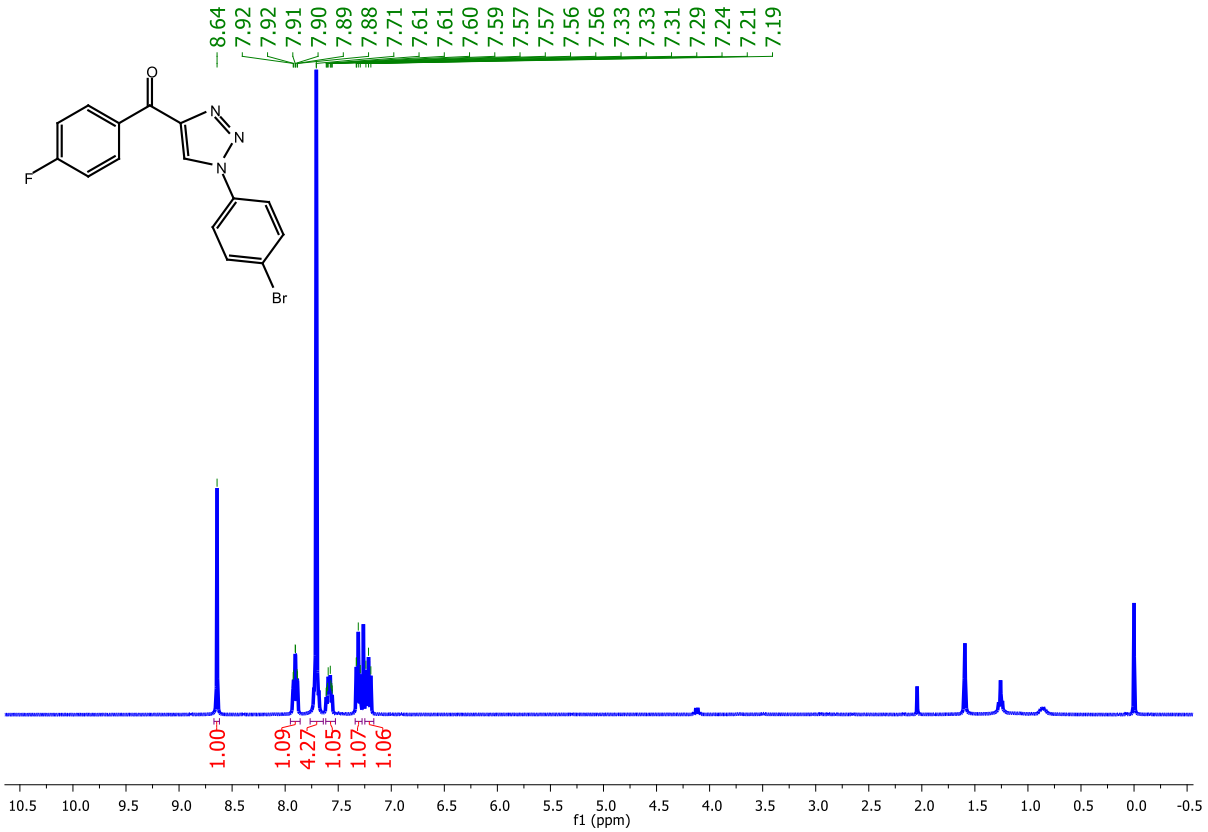
Spectrum 48: ^{13}C NMR (100 MHz; $CDCl_3$) 7da



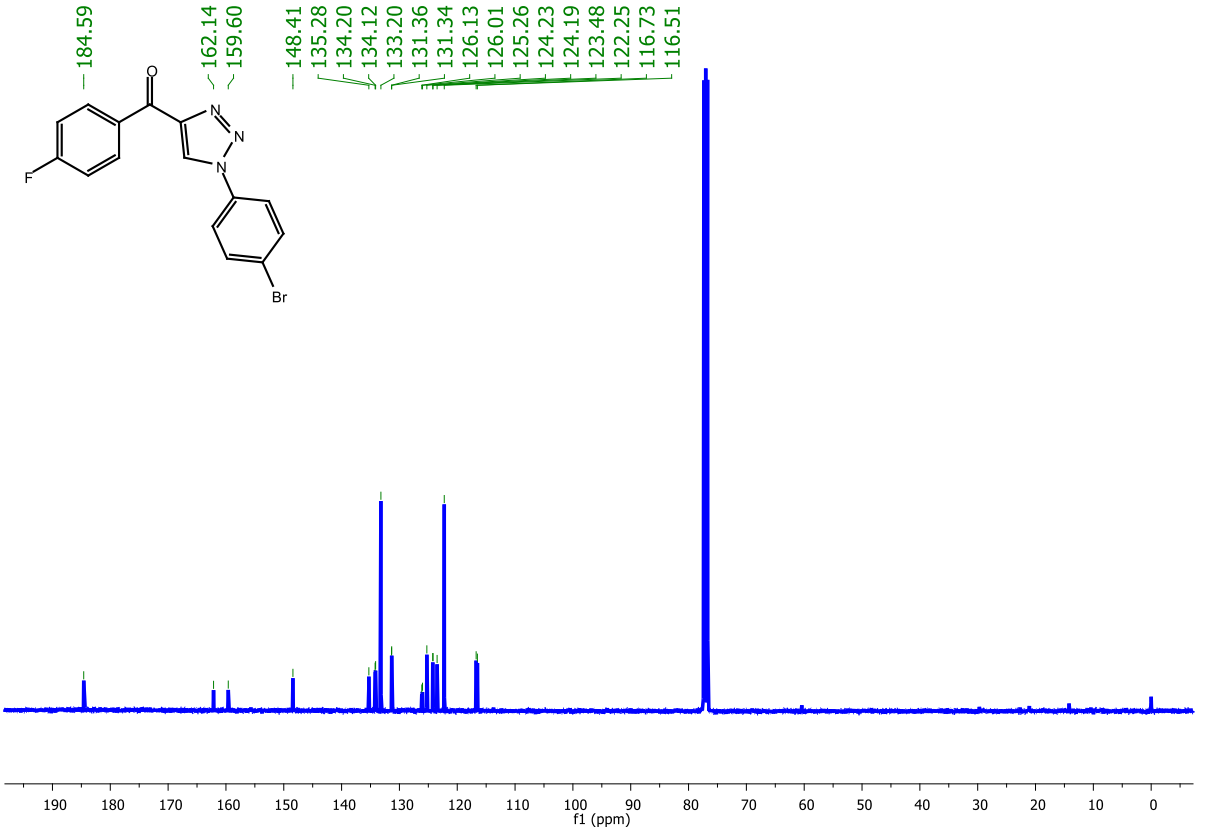
Spectrum 49: ^{1}H NMR (400 MHz; $CDCl_3$) 7ea



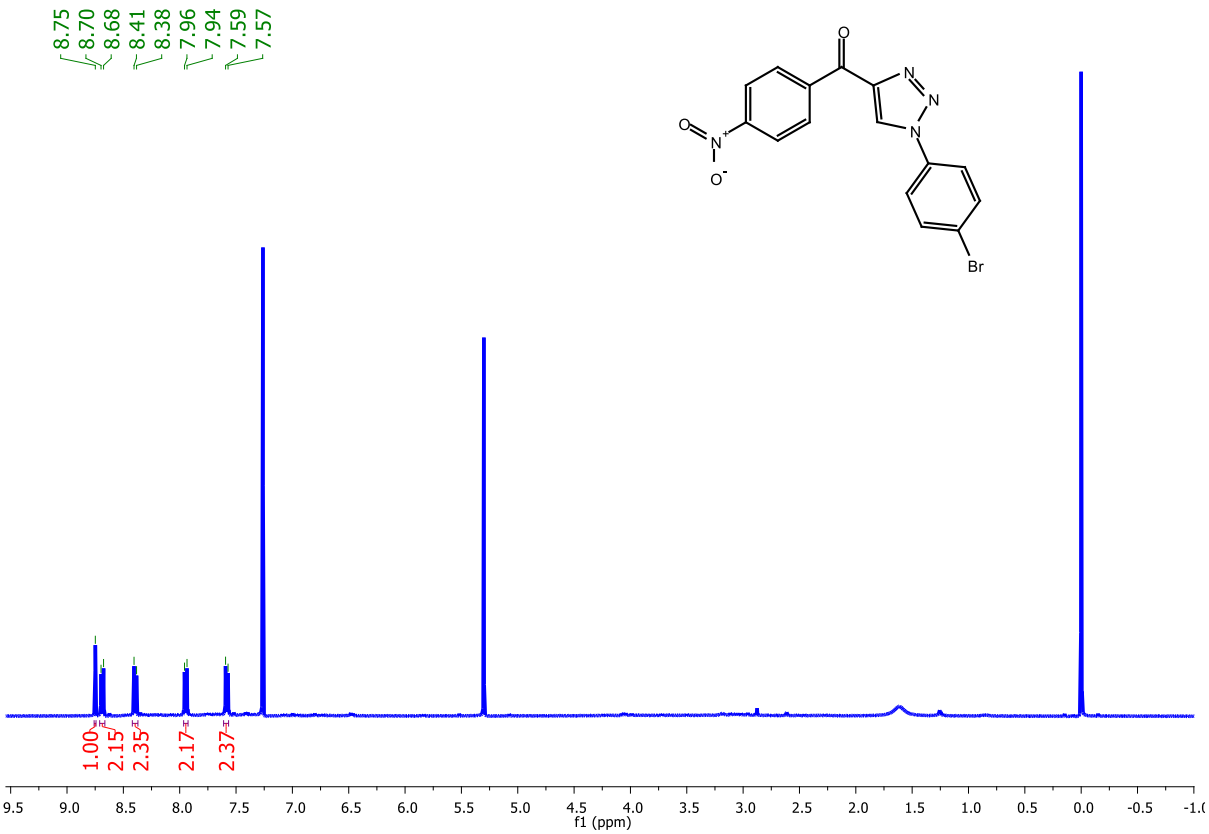
Spectrum 50: ^{13}C NMR (100 MHz; $CDCl_3$) 7ea



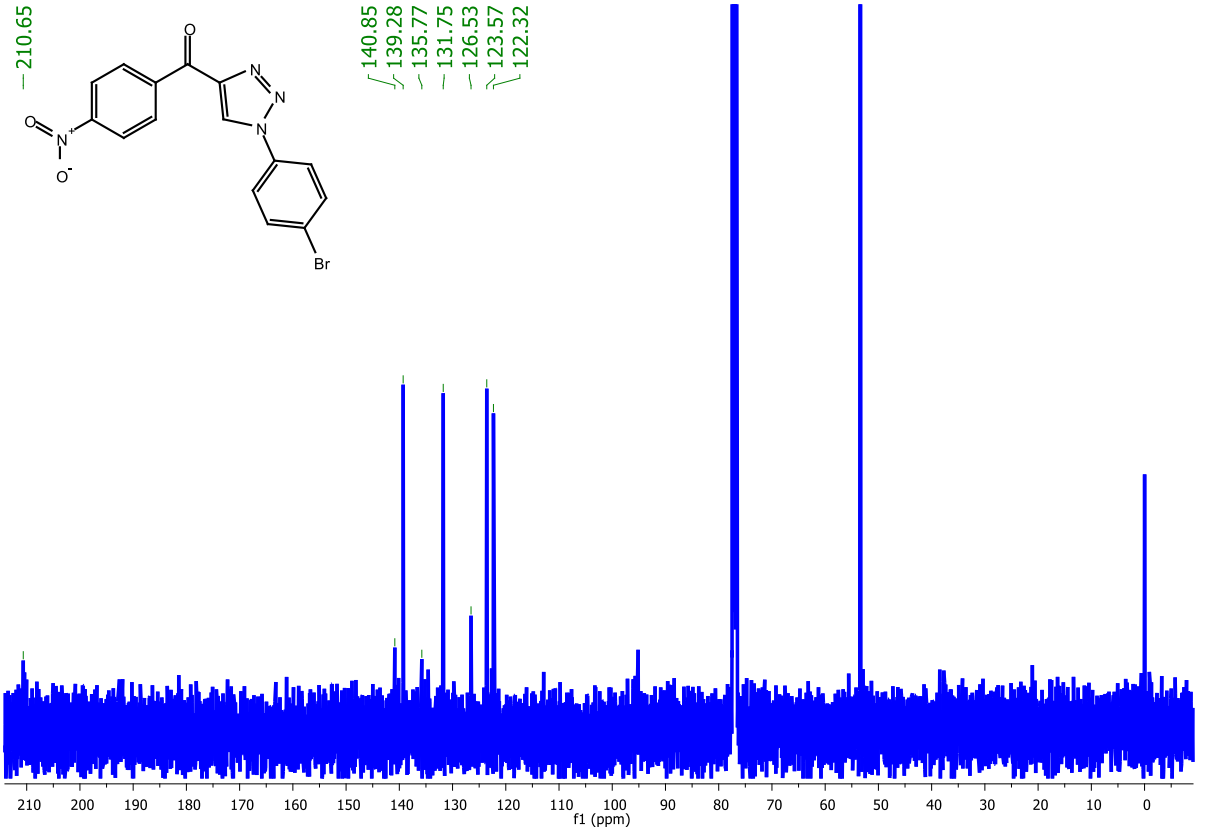
Spectrum 51: ^{1}H NMR (400 MHz; $CDCl_3$) 7fa



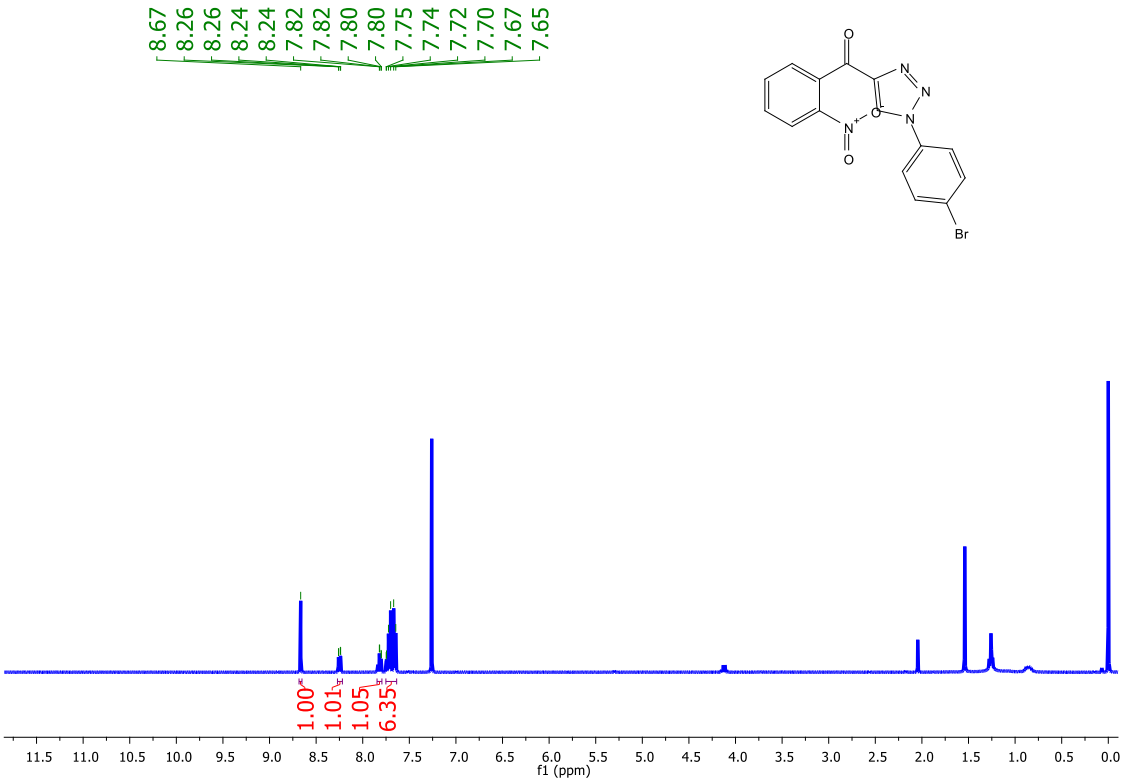
Spectrum 52: ^{13}C NMR (100 MHz; $CDCl_3$) 7fa



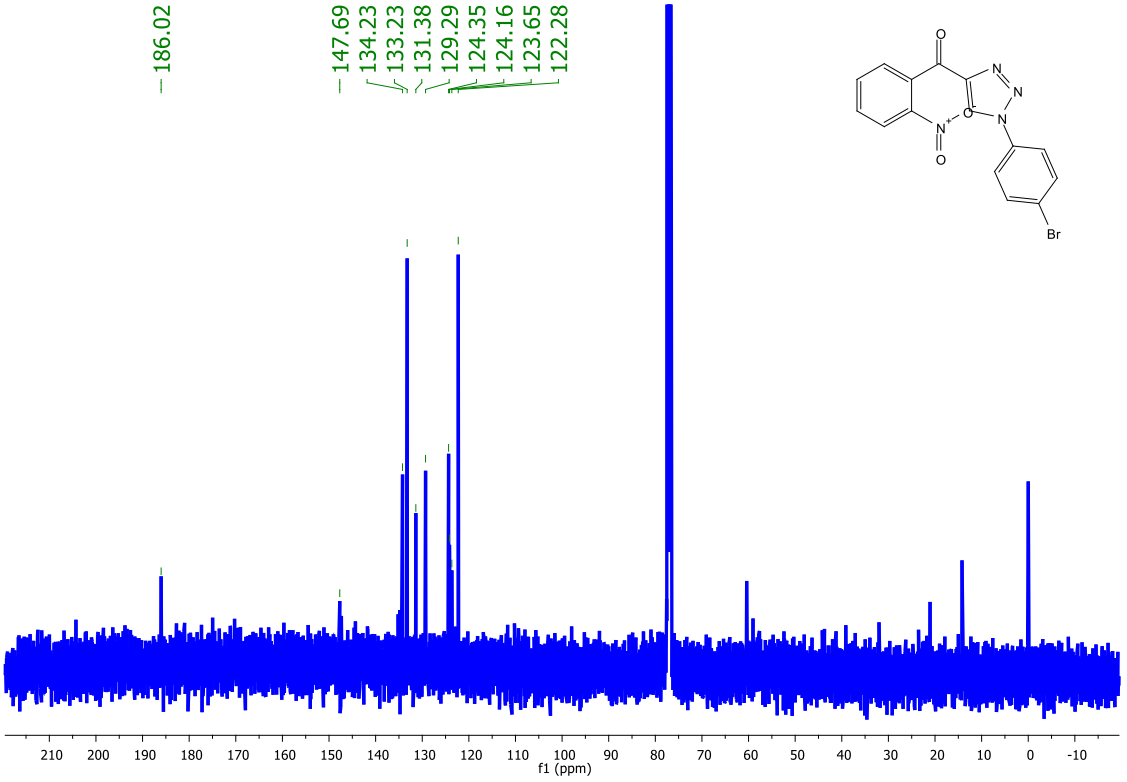
Spectrum 53: ^{1}H NMR (400 MHz; $CDCl_3$) 7ga



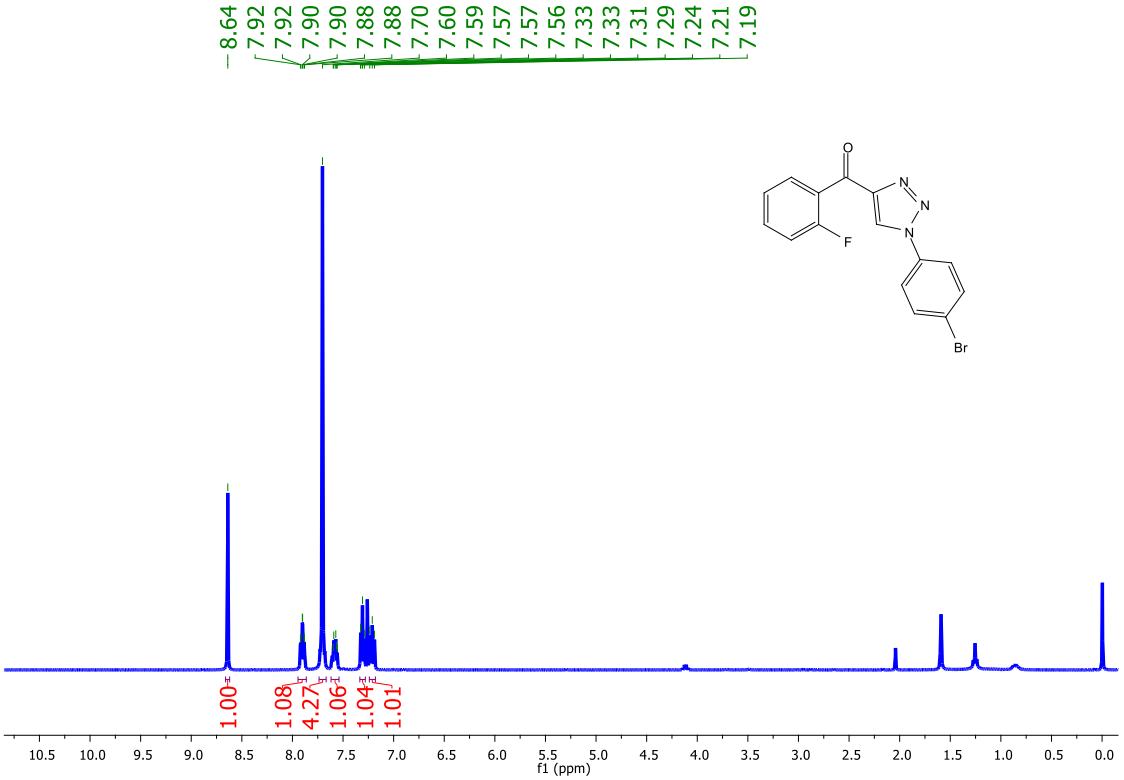
Spectrum 54: ^{13}C NMR (100 MHz; $CDCl_3$) 7ga



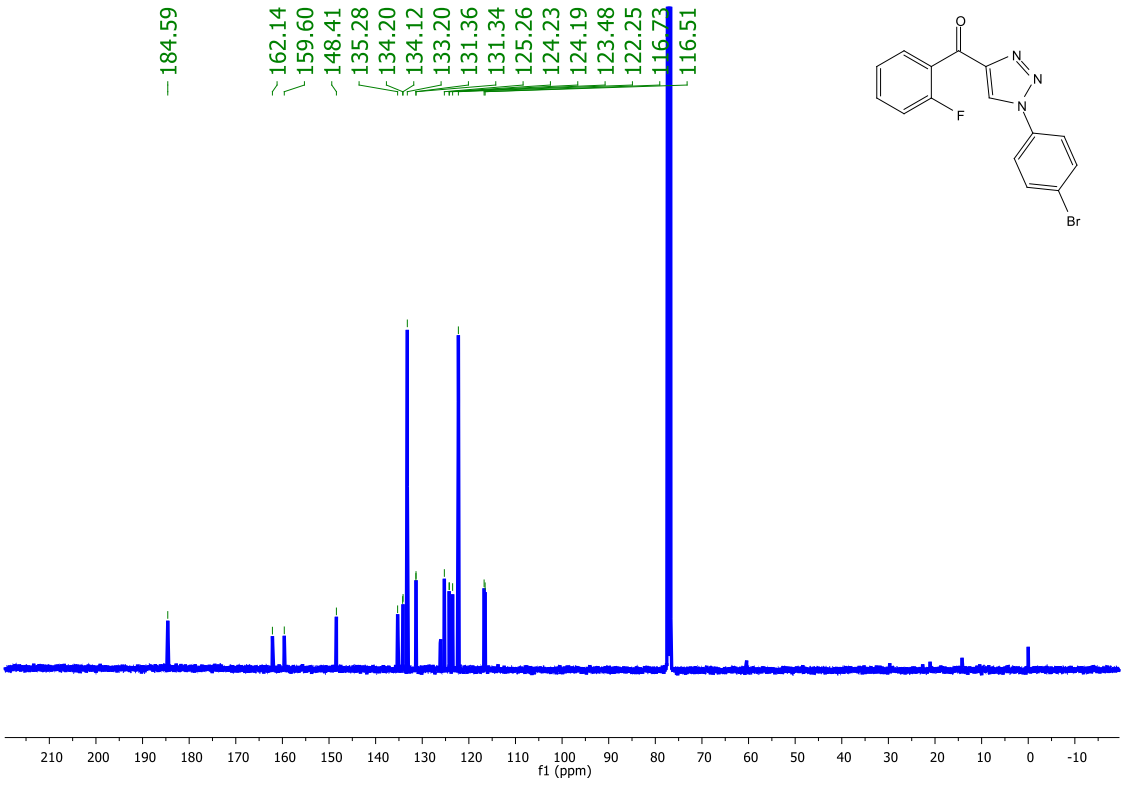
Spectrum 55: [1]H NMR (400 MHz; CDCl3) 7ha



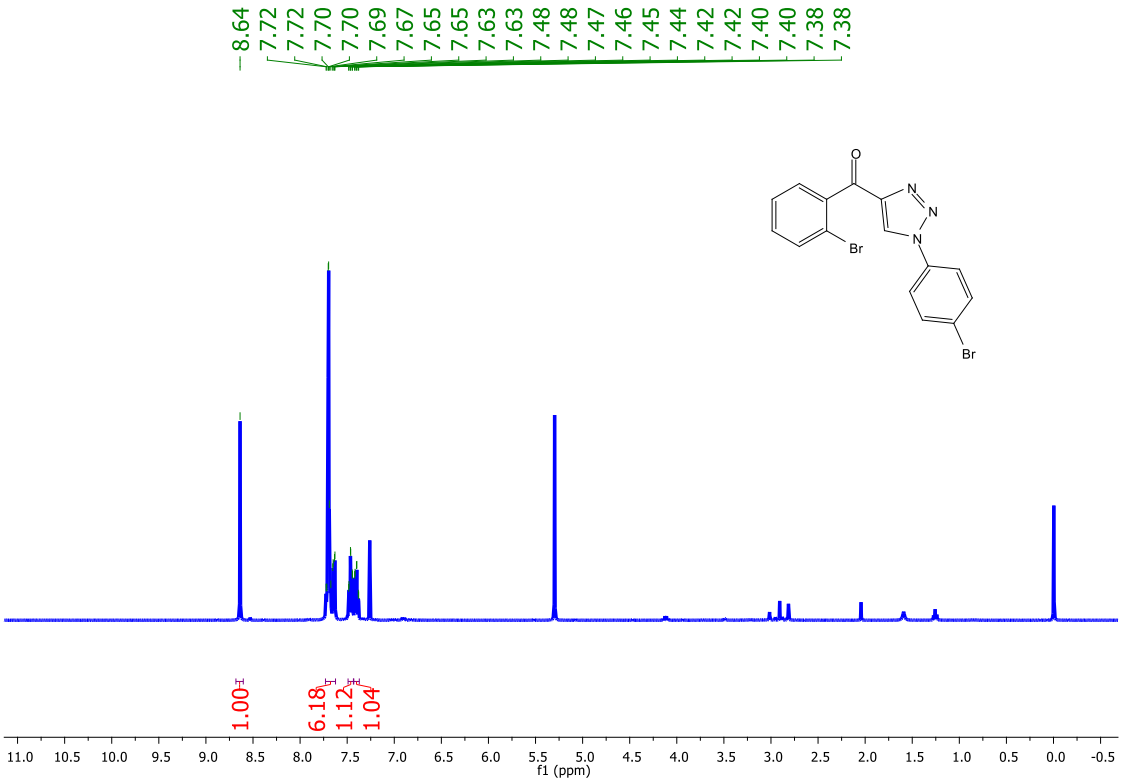
Spectrum 56: [13]C NMR (100 MHz; $CDCl_3$) 7ha



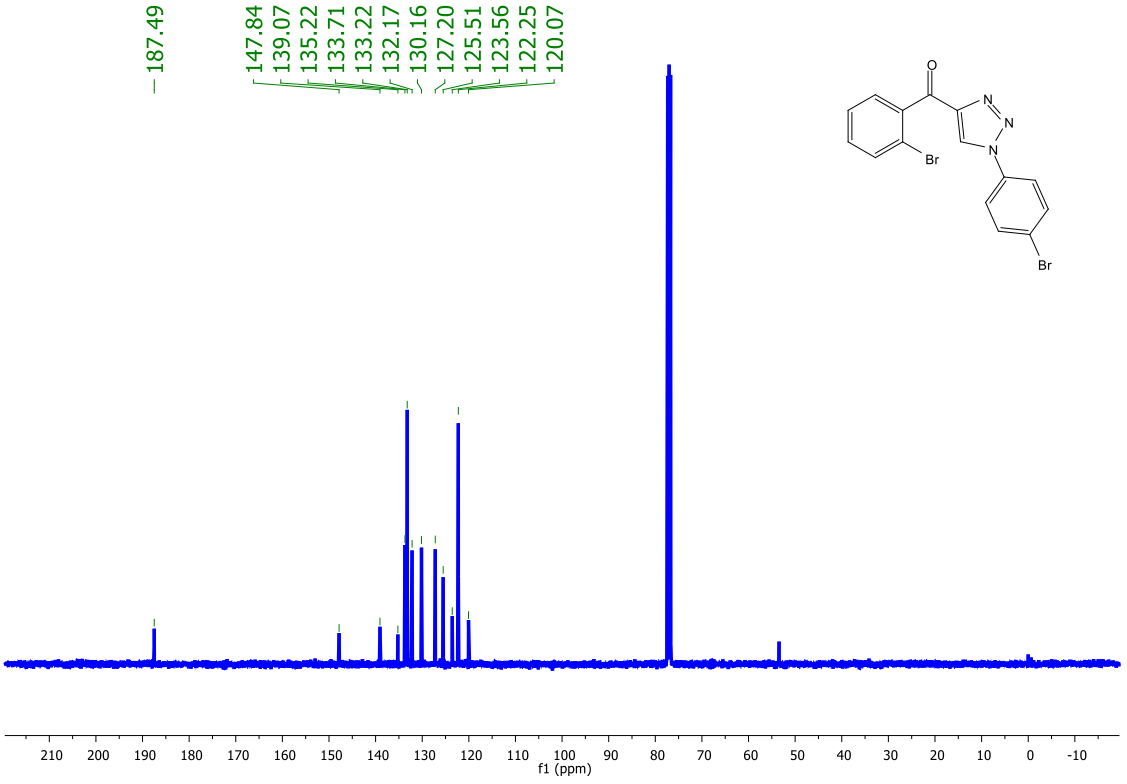
Spectrum 57: ^{1}H NMR (400 MHz; $CDCl_3$) 7ia



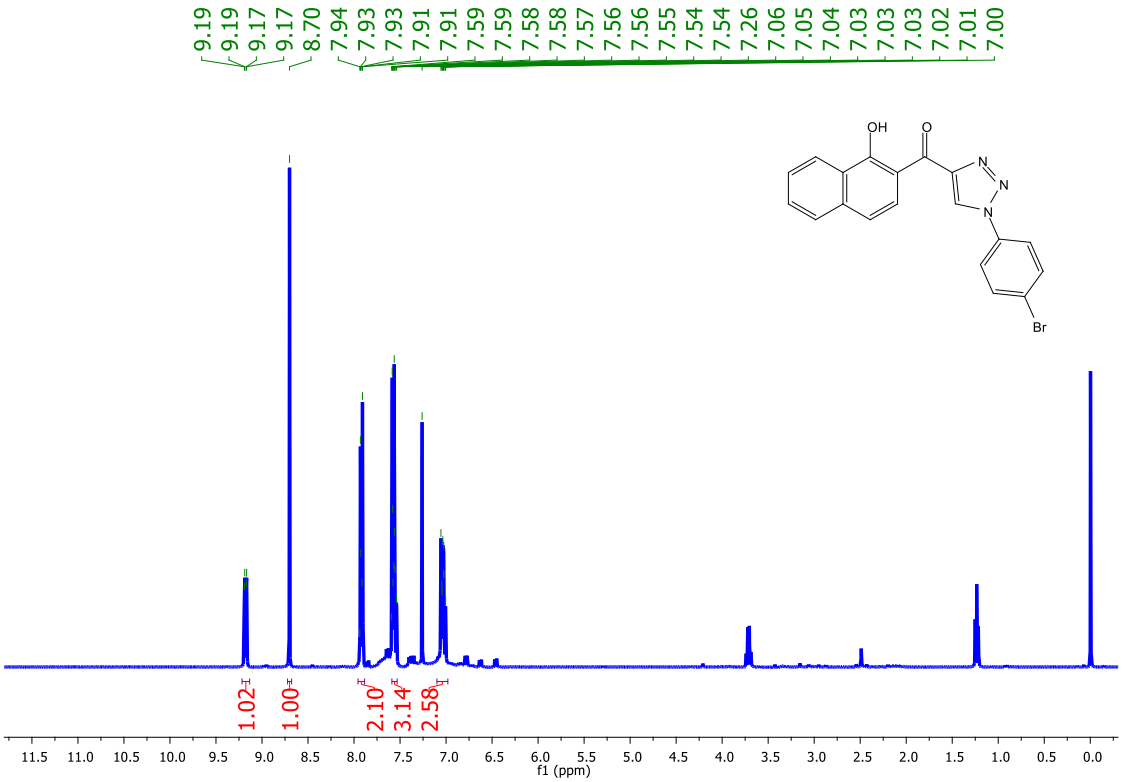
Spectrum 58: ^{13}C NMR (100 MHz; $CDCl_3$) 7ia



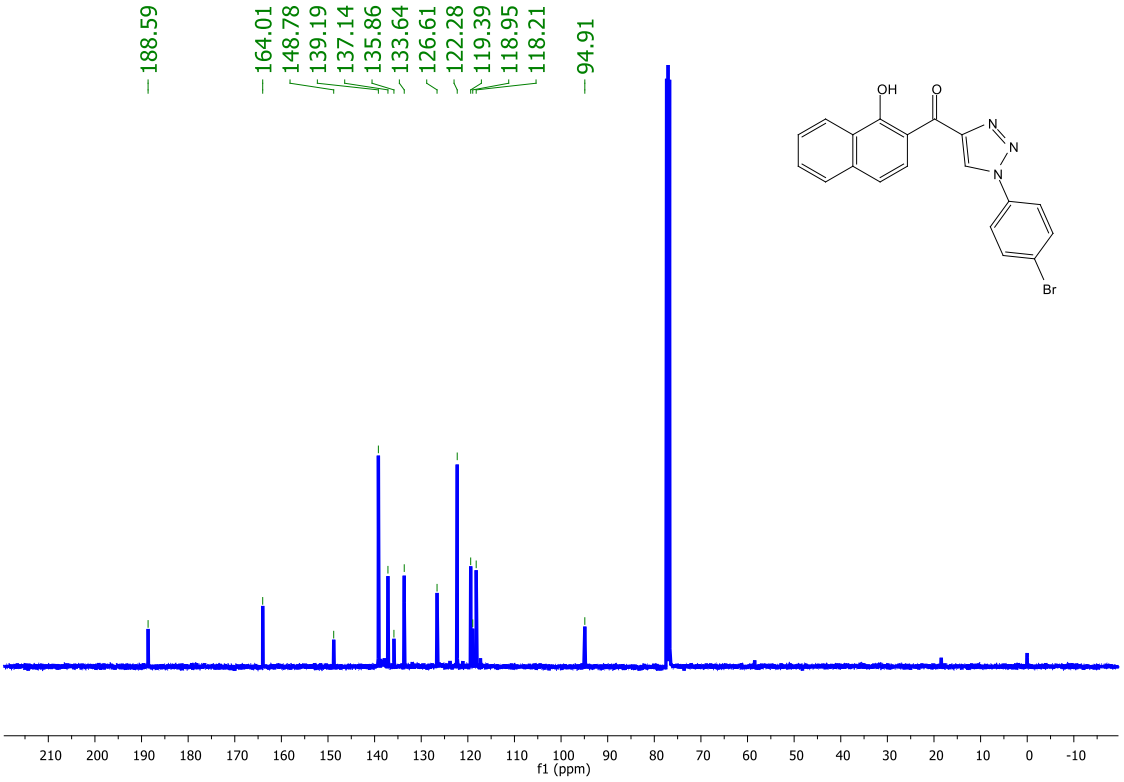
Spectrum 59: ^{1}H NMR (400 MHz; $CDCl_3$) 7ja



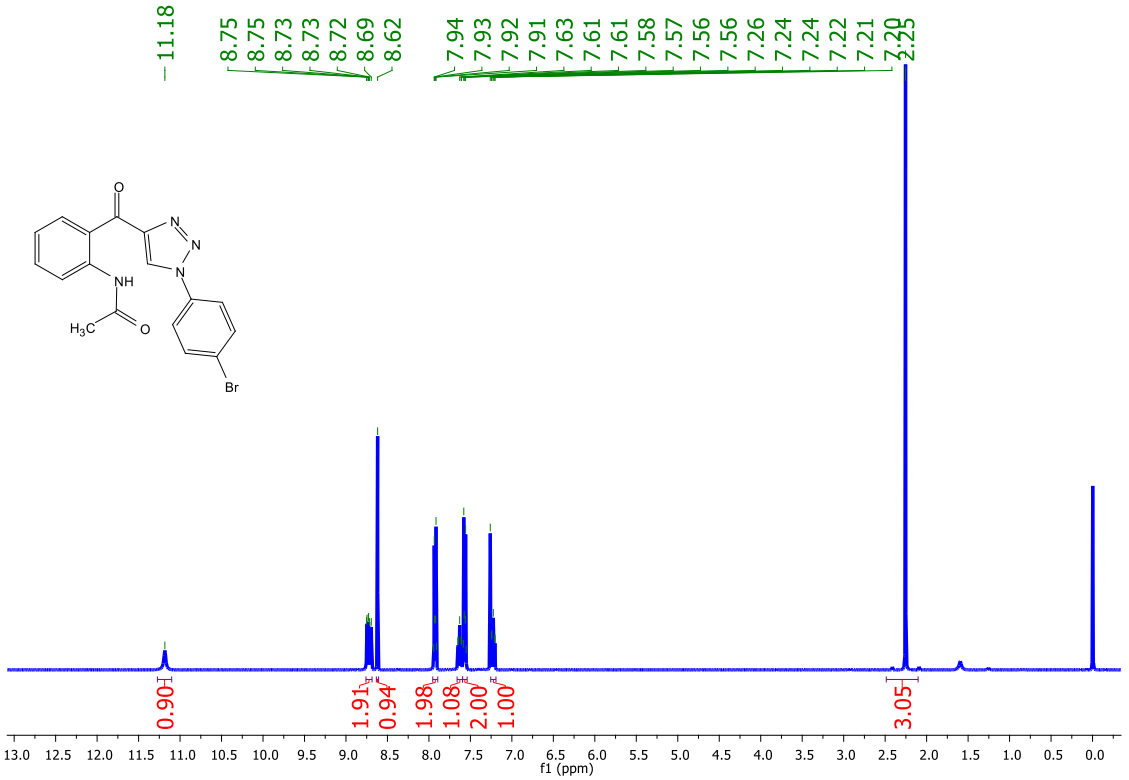
Spectrum 60: ^{13}C NMR (100 MHz; $CDCl_3$) 7ja



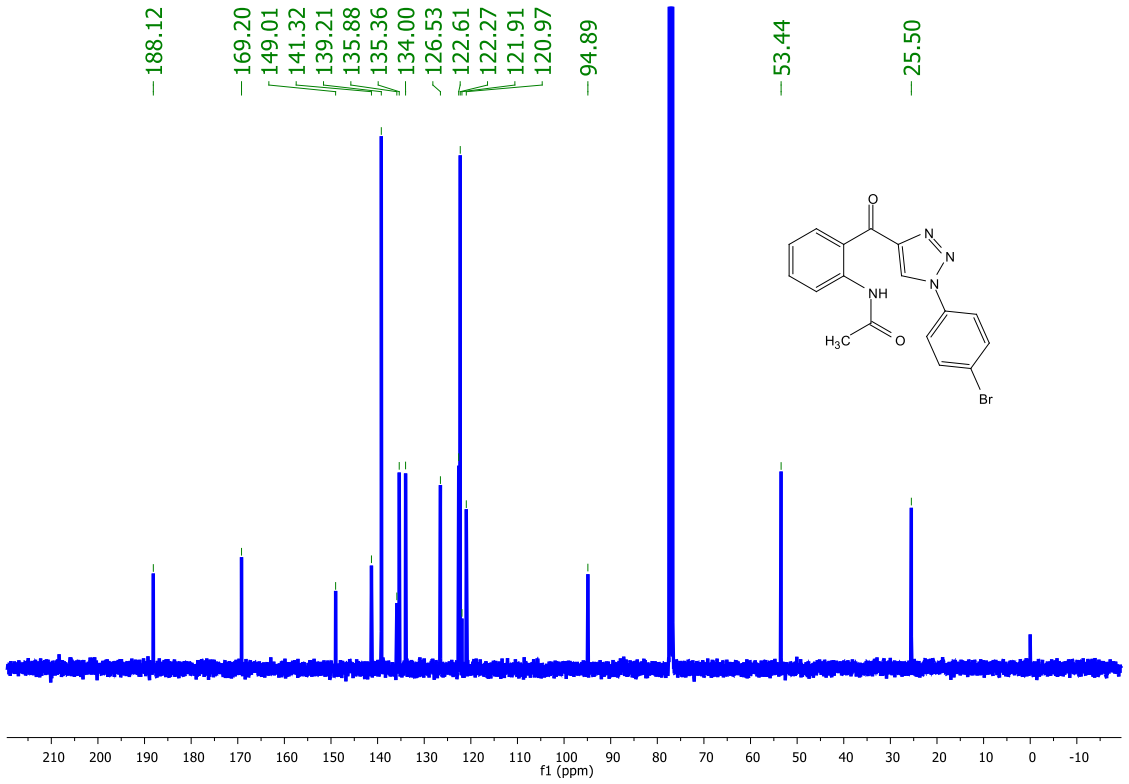
Spectrum 61: ^{1}H NMR (400 MHz; $CDCl_3$) 7ka



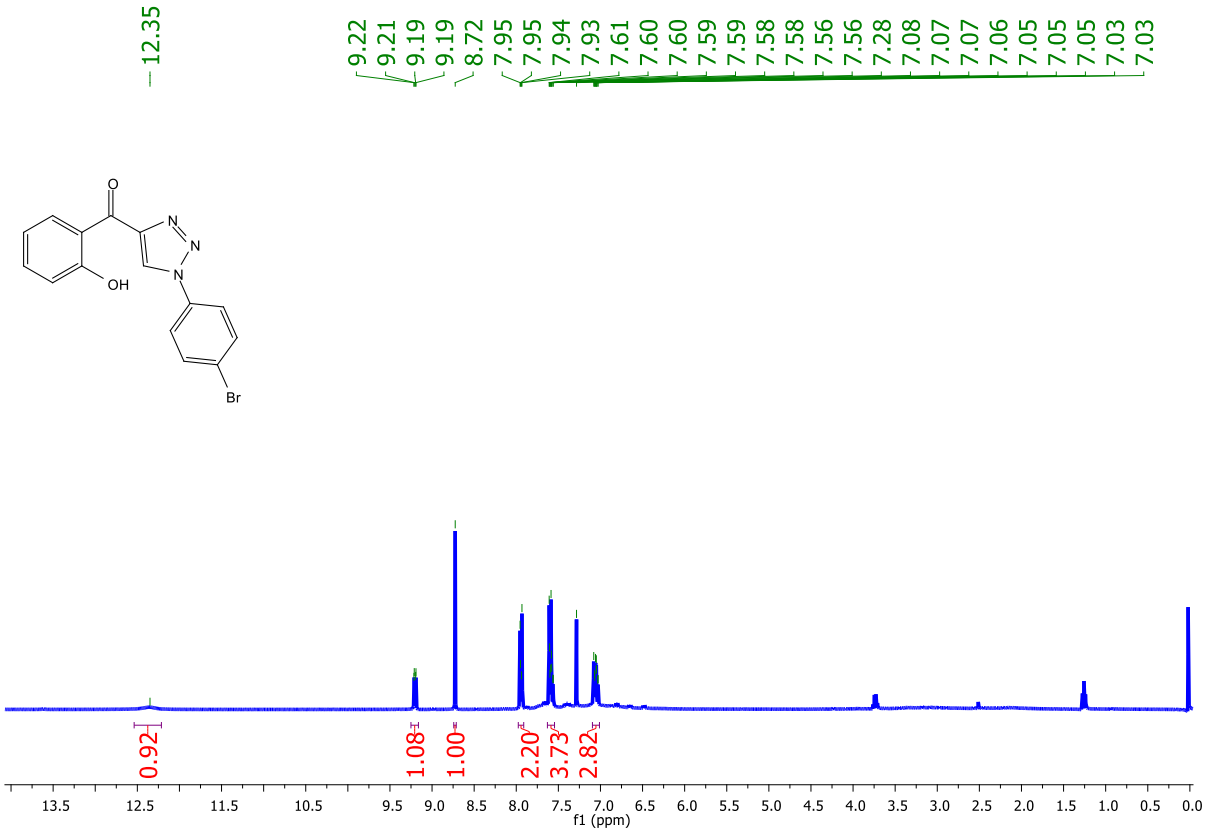
Spectrum 62: ^{13}C NMR (100 MHz; $CDCl_3$) 7ka



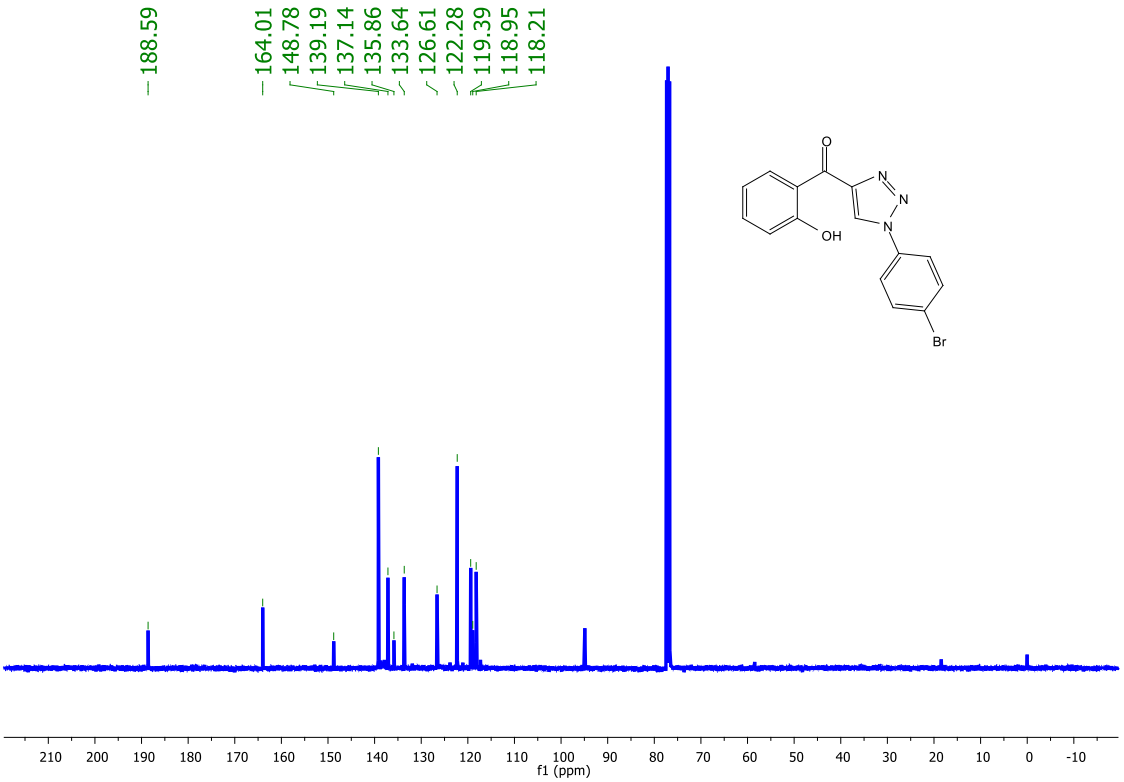
Spectrum 63: ^{1}H NMR (400 MHz; $CDCl_3$) 7la



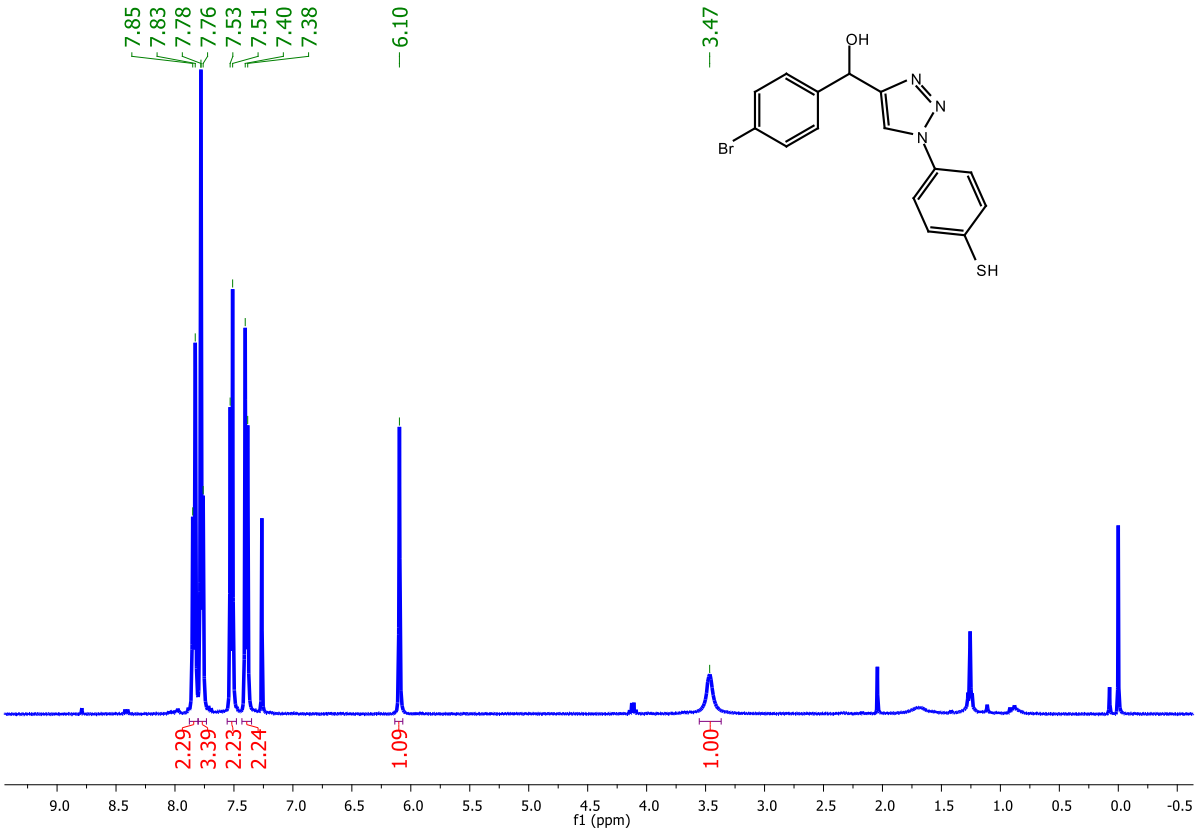
Spectrum 64: ^{13}C NMR (100 MHz; $CDCl_3$) 7la



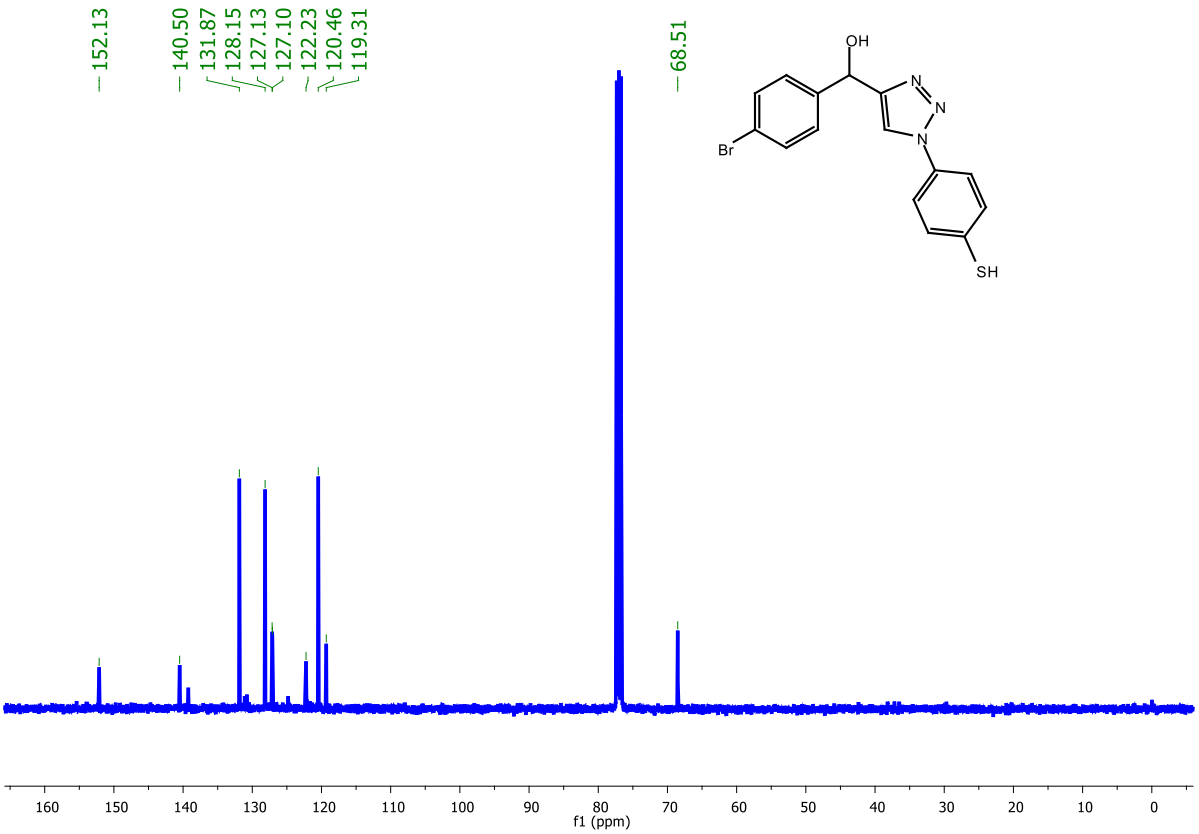
Spectrum 65: ^{1}H NMR (400 MHz; $CDCl_3$) 7ma



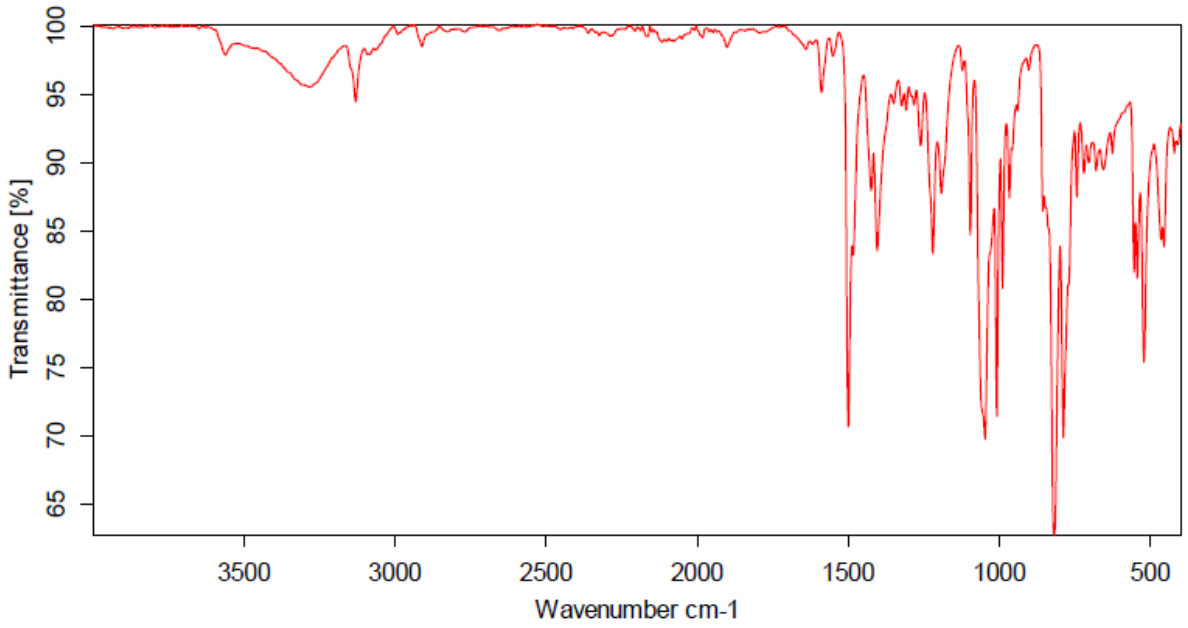
Spectrum 66: ^{13}C NMR (100 MHz; $CDCl_3$) 7ma



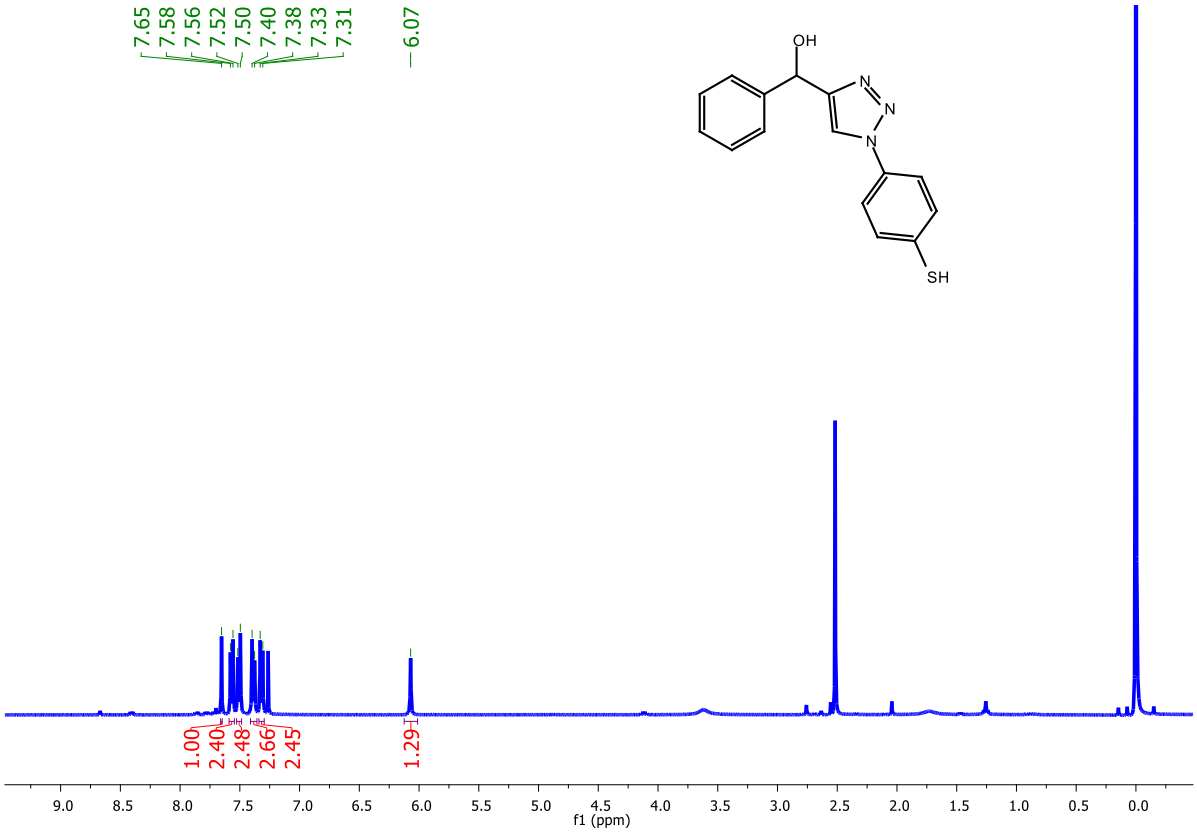
Spectrum 67: ^{1}H NMR (400 MHz; $CDCl_3$) 4ac



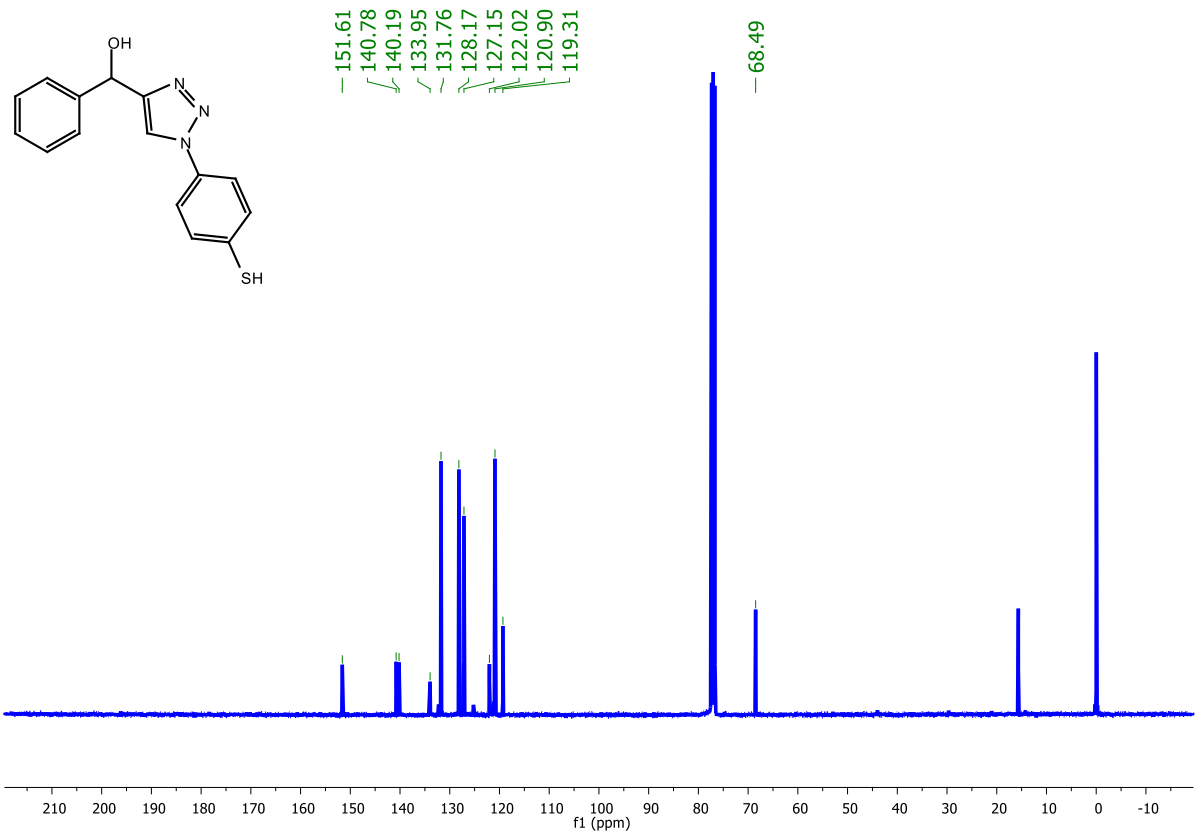
Spectrum 68: ^{13}C NMR (100 MHz; $CDCl_3$) 4ac



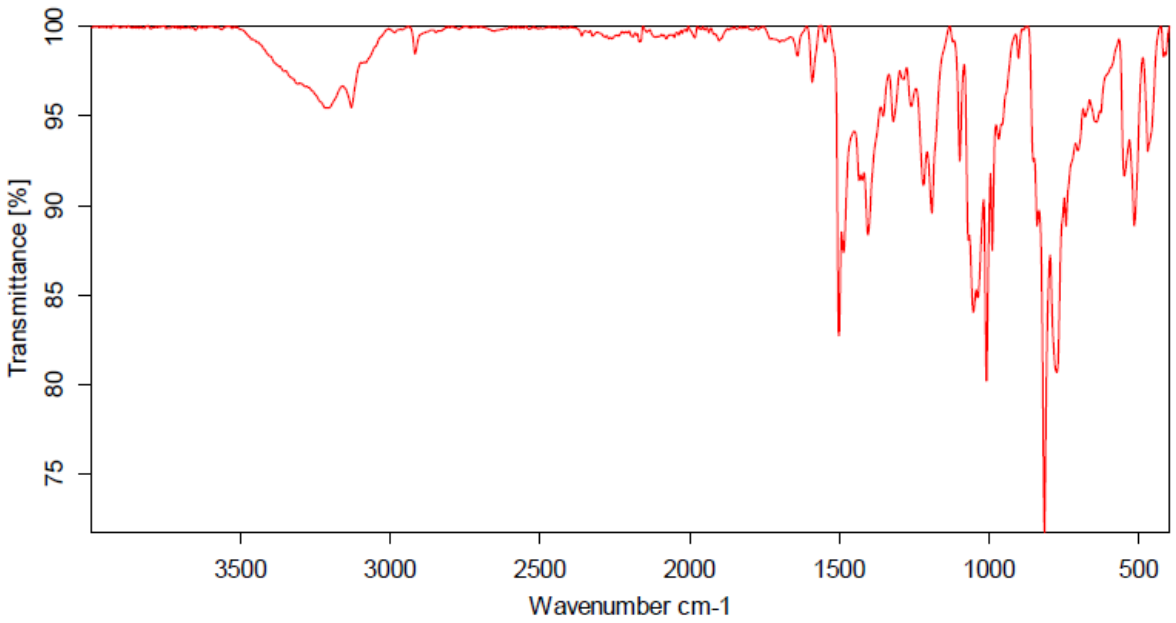
Spectrum 69: FTIR-ATR 4ac



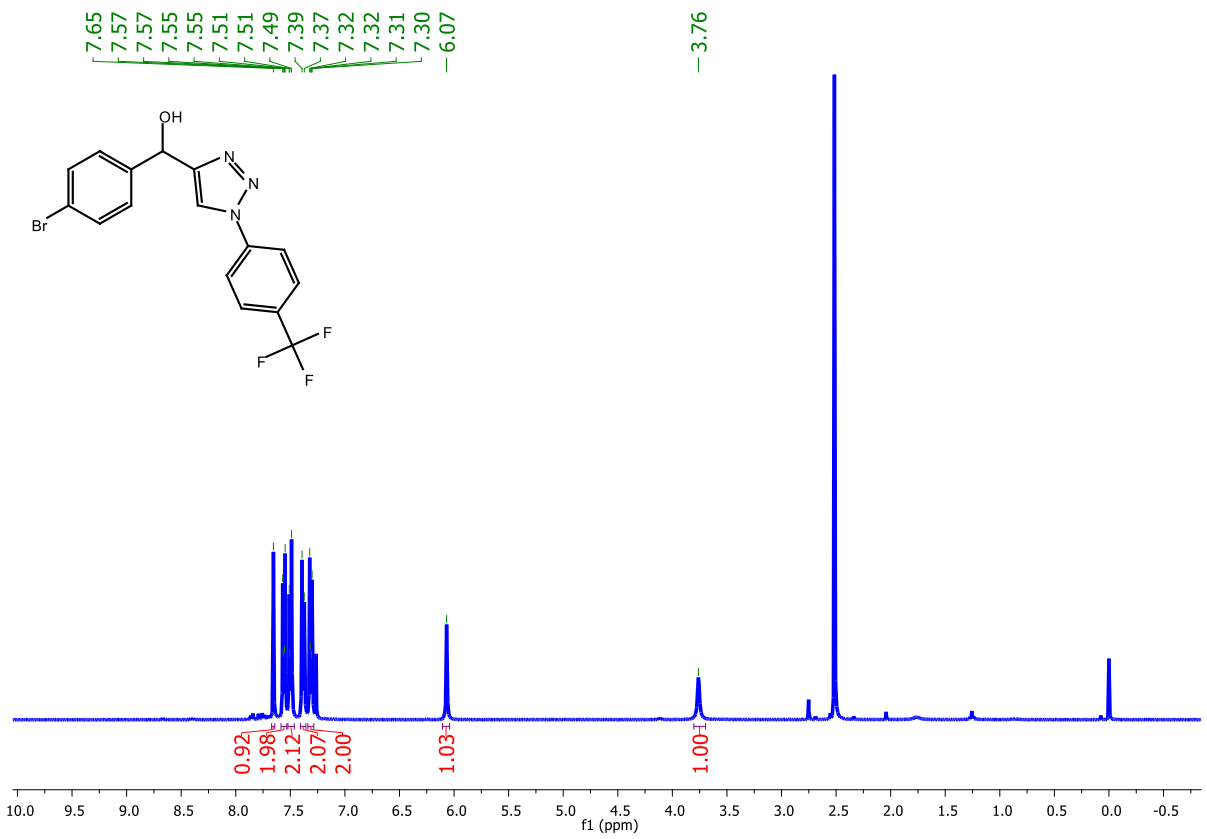
Spectrum 70:1H NMR (400 MHz; DMSO-d6) 4bc



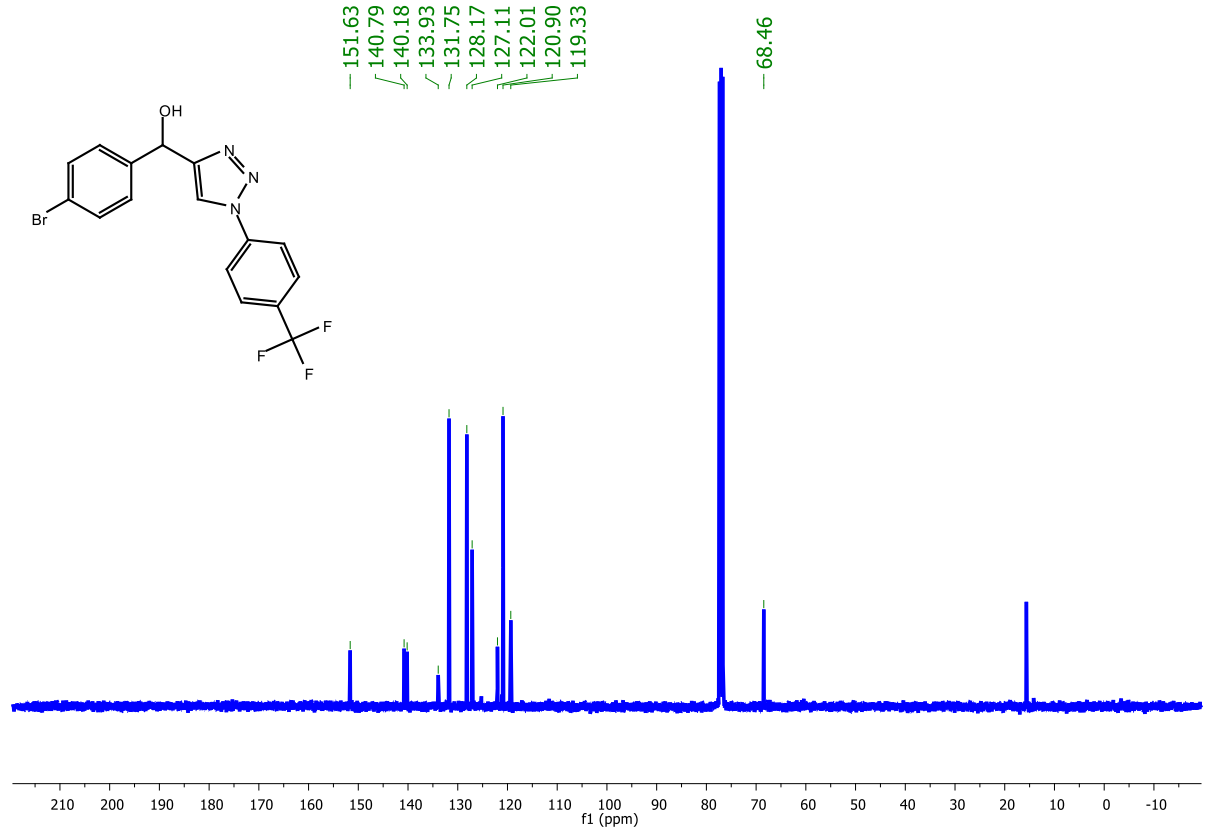
Spectrum 71: ^{13}C NMR (100 MHz; $CDCl_3$) 4bc



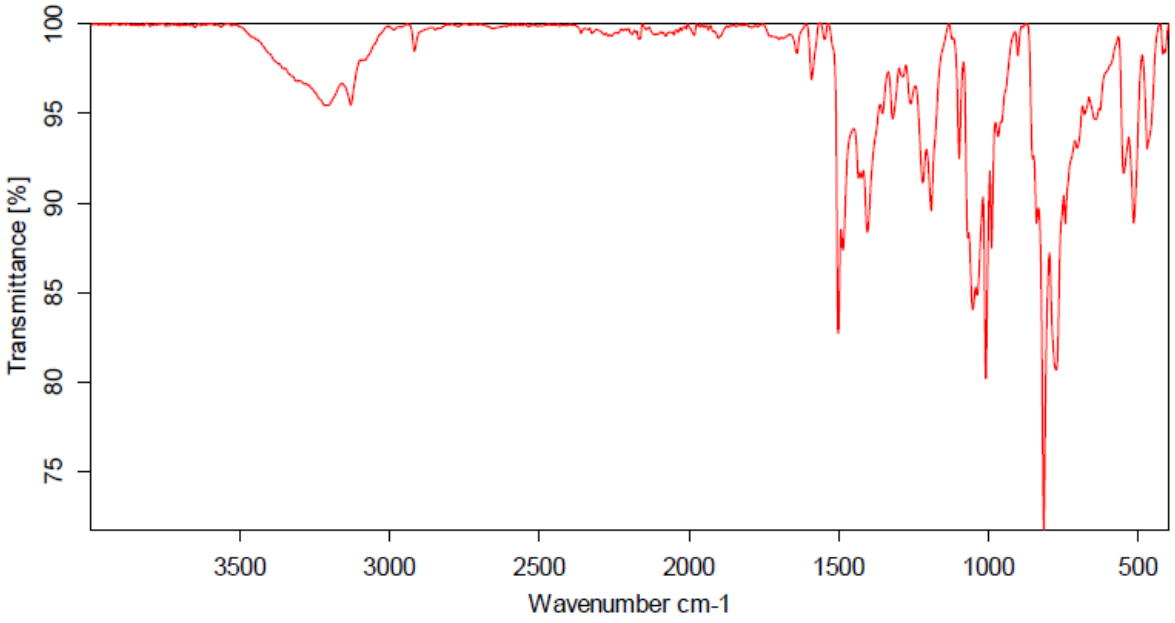
Spectrum 72: FTIR-ATR 4bc



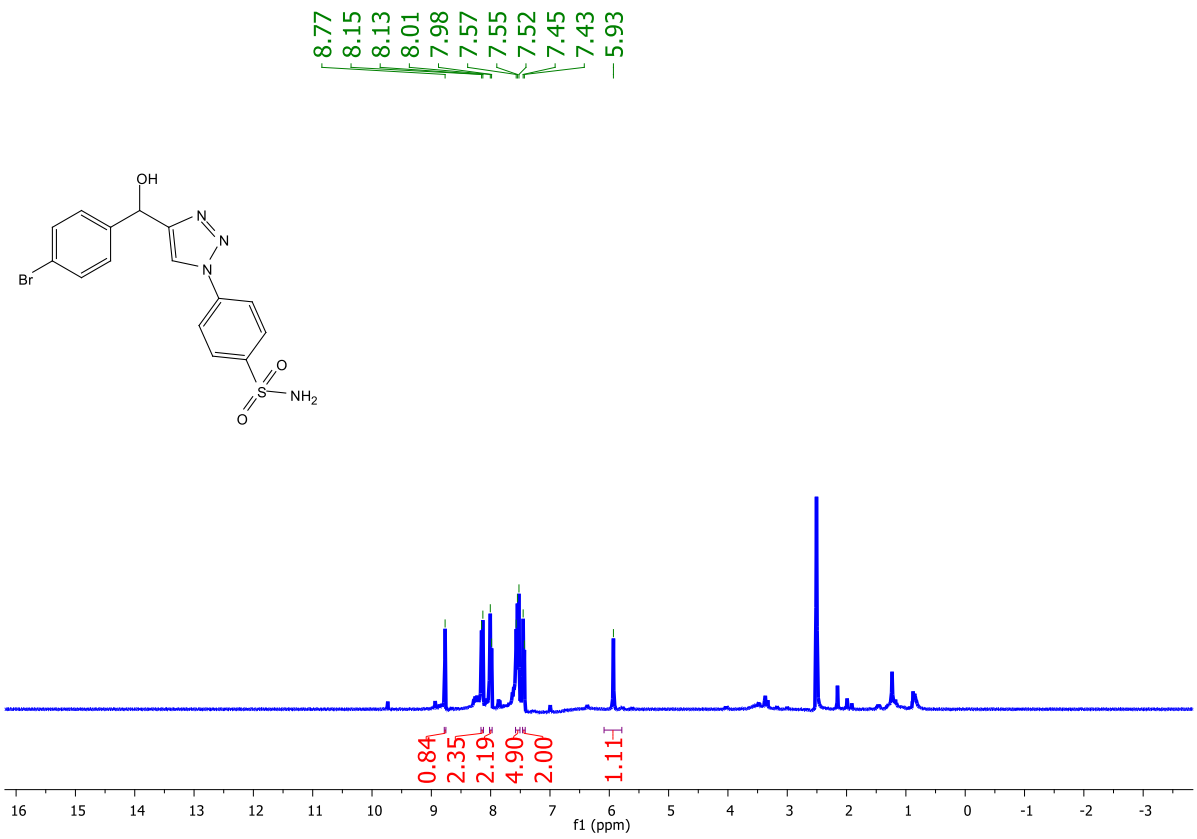
Spectrum 73: 1H NMR (400 MHz; DMSO-d6) 4ad



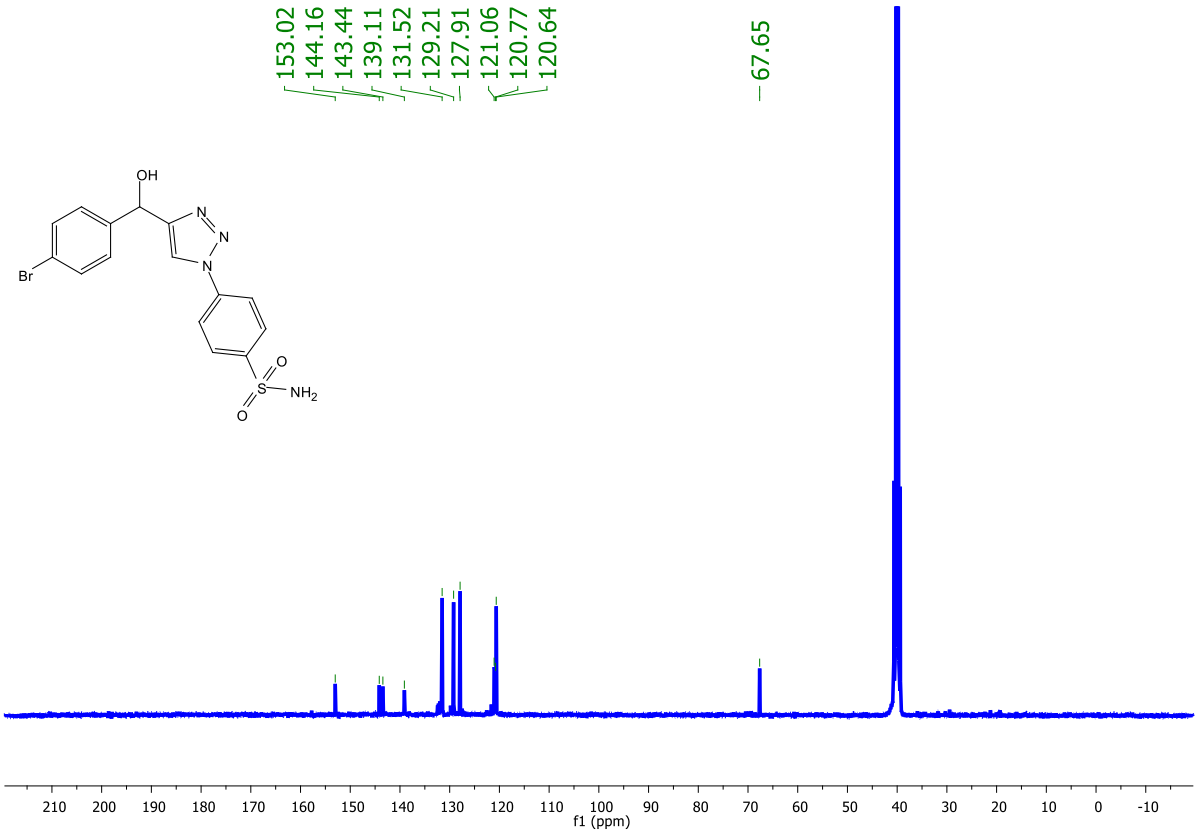
Spectrum 74: ^{13}C NMR (100 MHz; DMSO-d6) 4ad



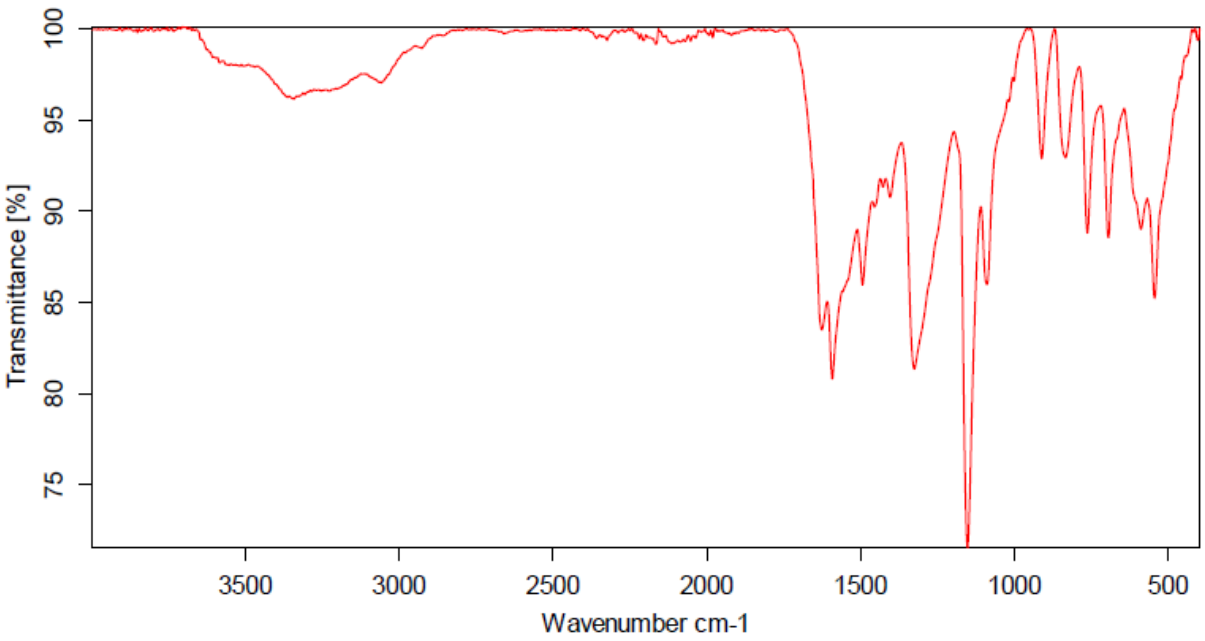
Spectrum 75: FTIR-ATR 4ad



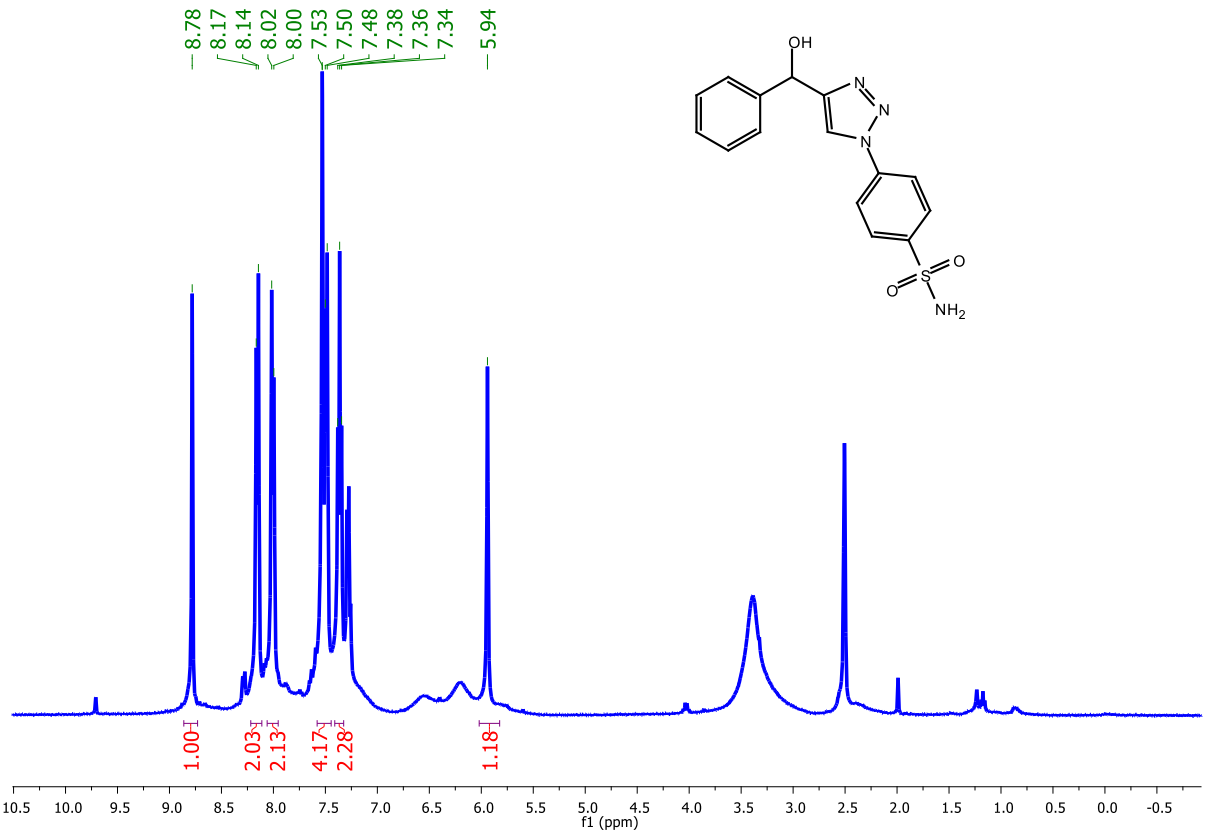
Spectrum 76: ^{1}H NMR (400 MHz; DMSO-d6) 4ae



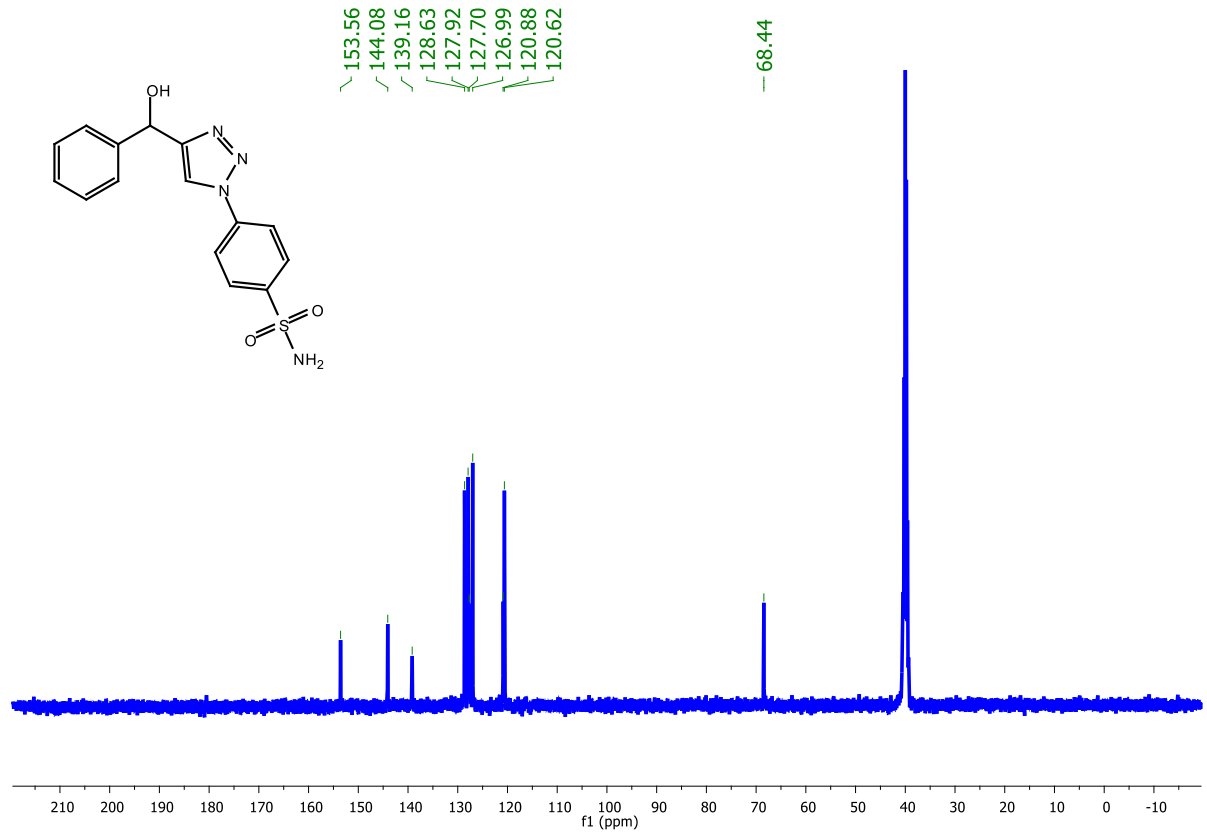
Spectrum 77: ^{13}C NMR (100 MHz; DMSO-d6) 4ae



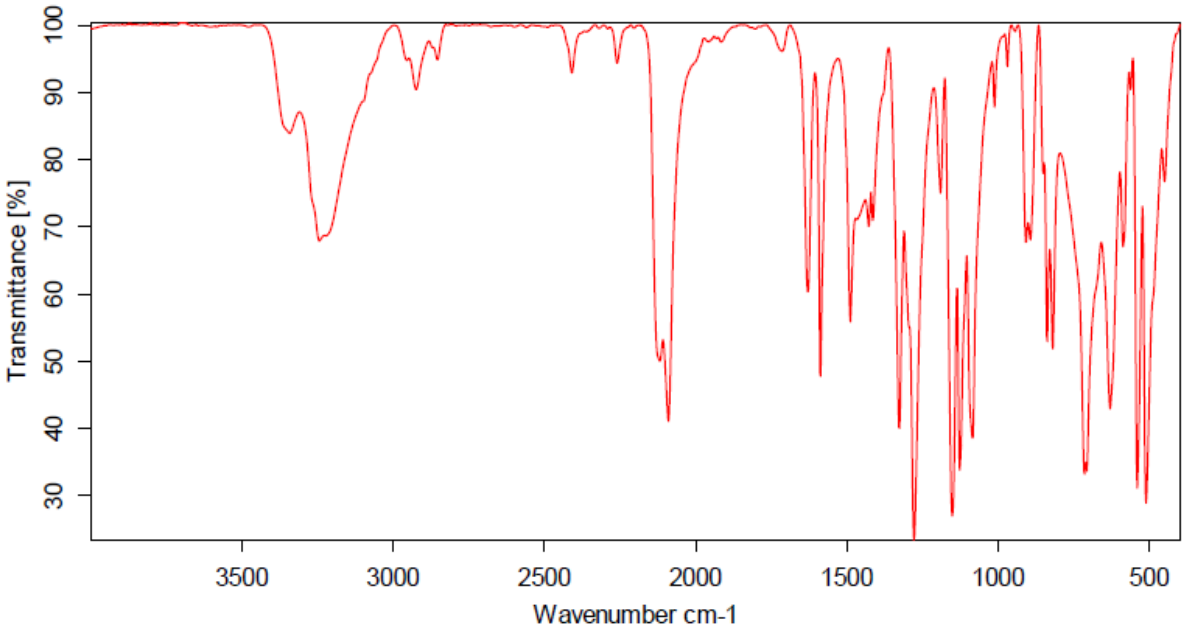
Spectrum 78: FTIR-ATR 4ae



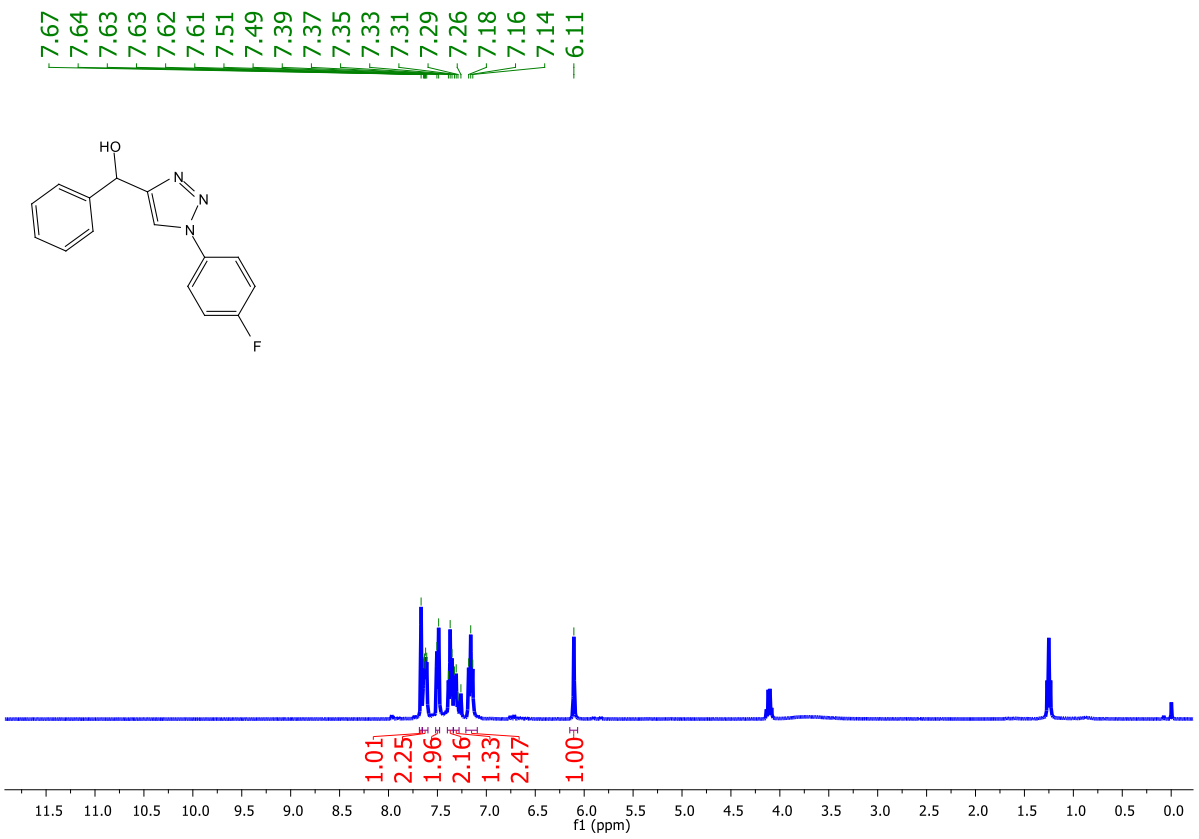
Spectrum 79: ^{1}H NMR (400 MHz; DMSO-d6) 4be



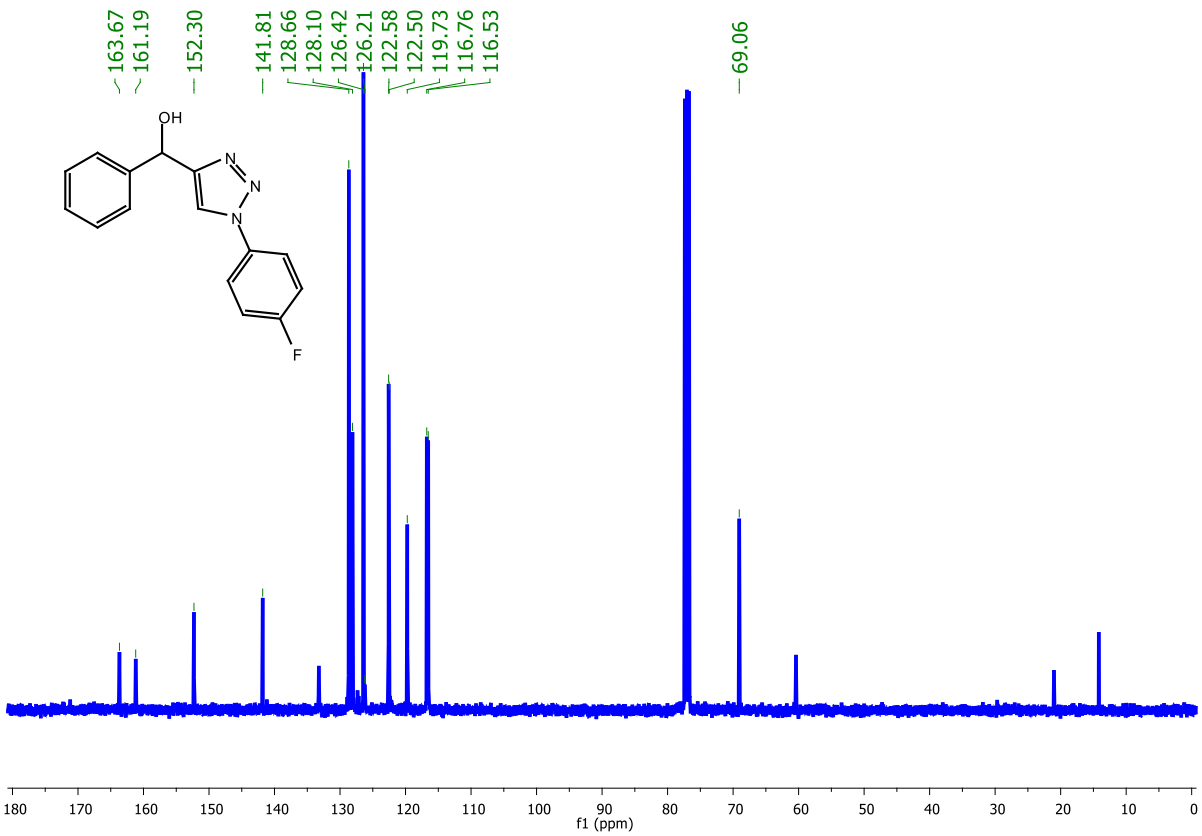
Spectrum 80: ^{13}C NMR (100 MHz; DMSO-d6) 4be



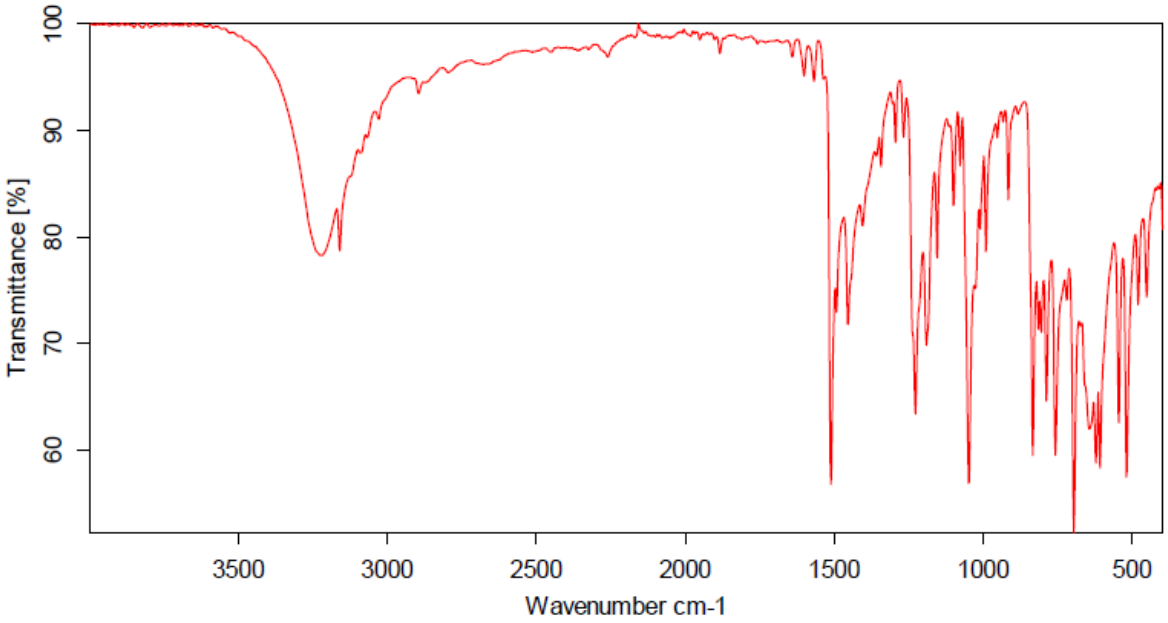
Spectrum 81: FTIR-ATR 4be



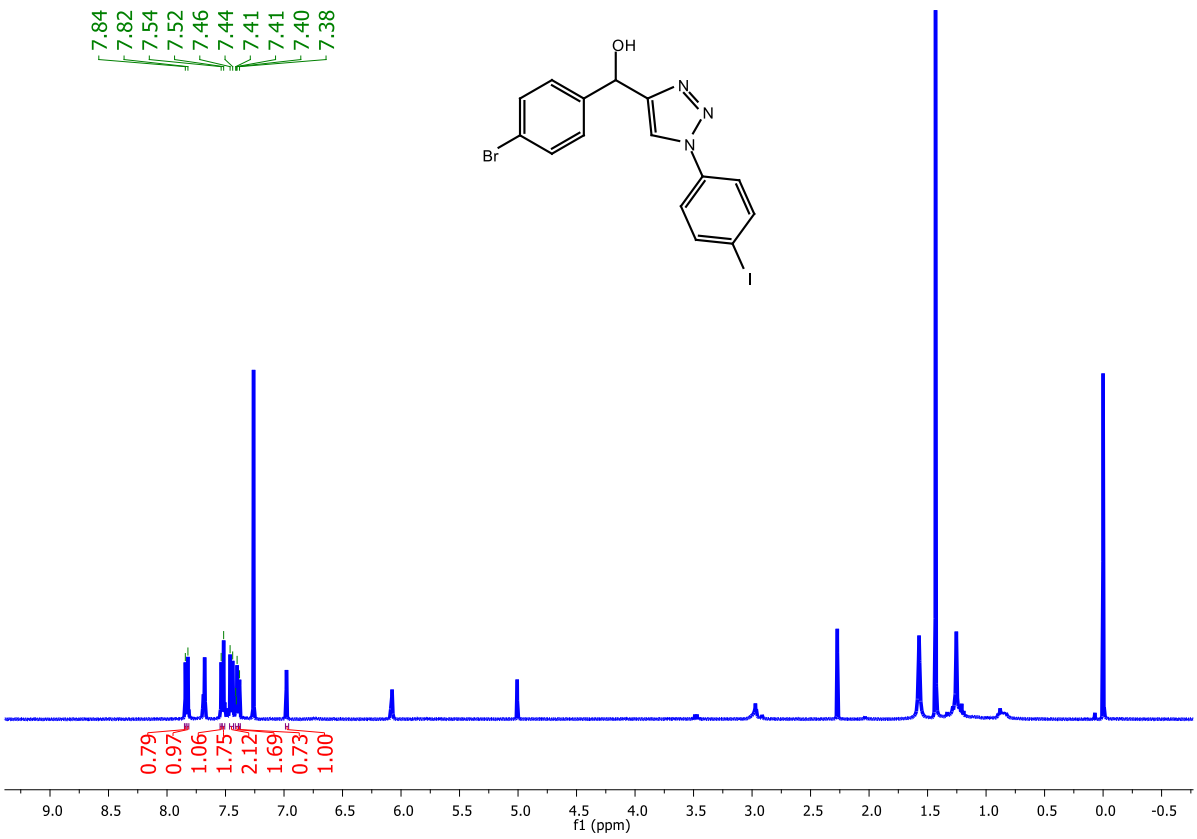
Spectrum 82: ^{1}H NMR (400 MHz; DMSO-d6) 4bf



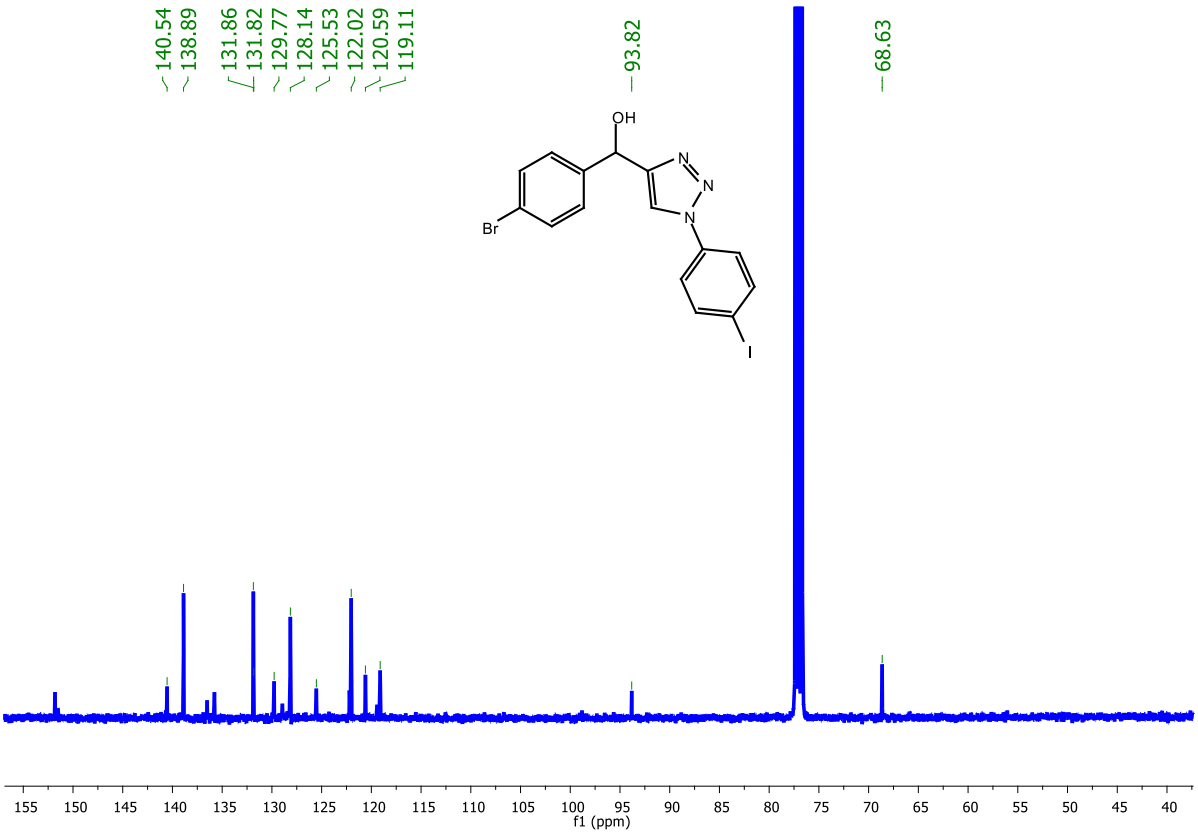
Spectrum 83: ^{13}C NMR (100 MHz; DMSO-d6) 4bf



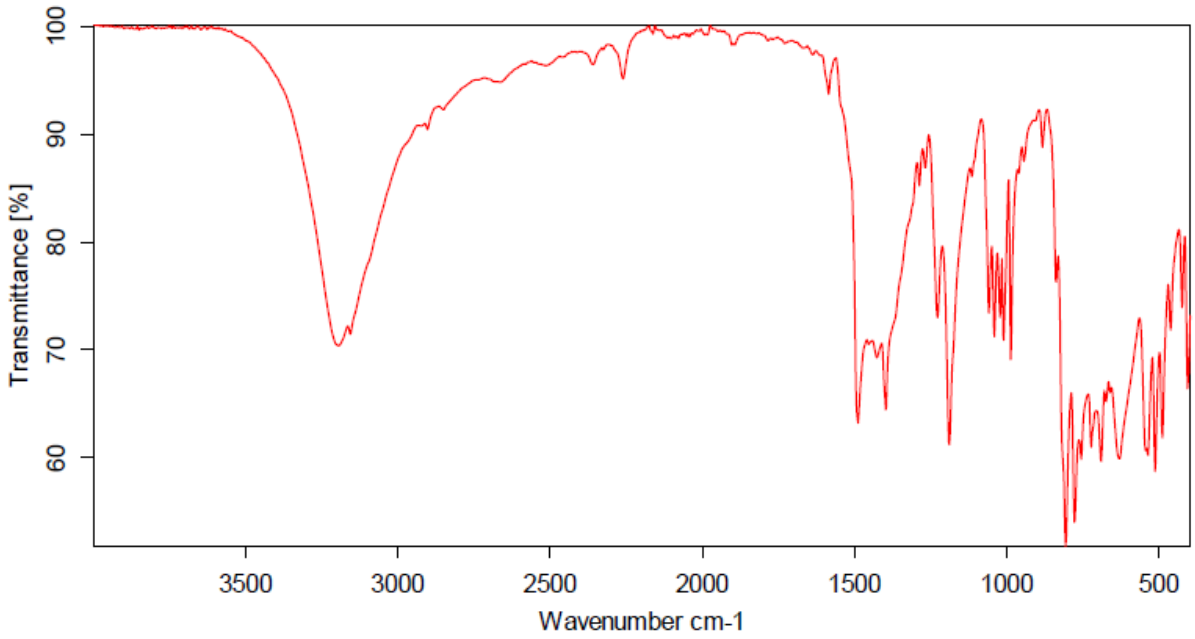
Spectrum 84: FTIR-ATR 4bf



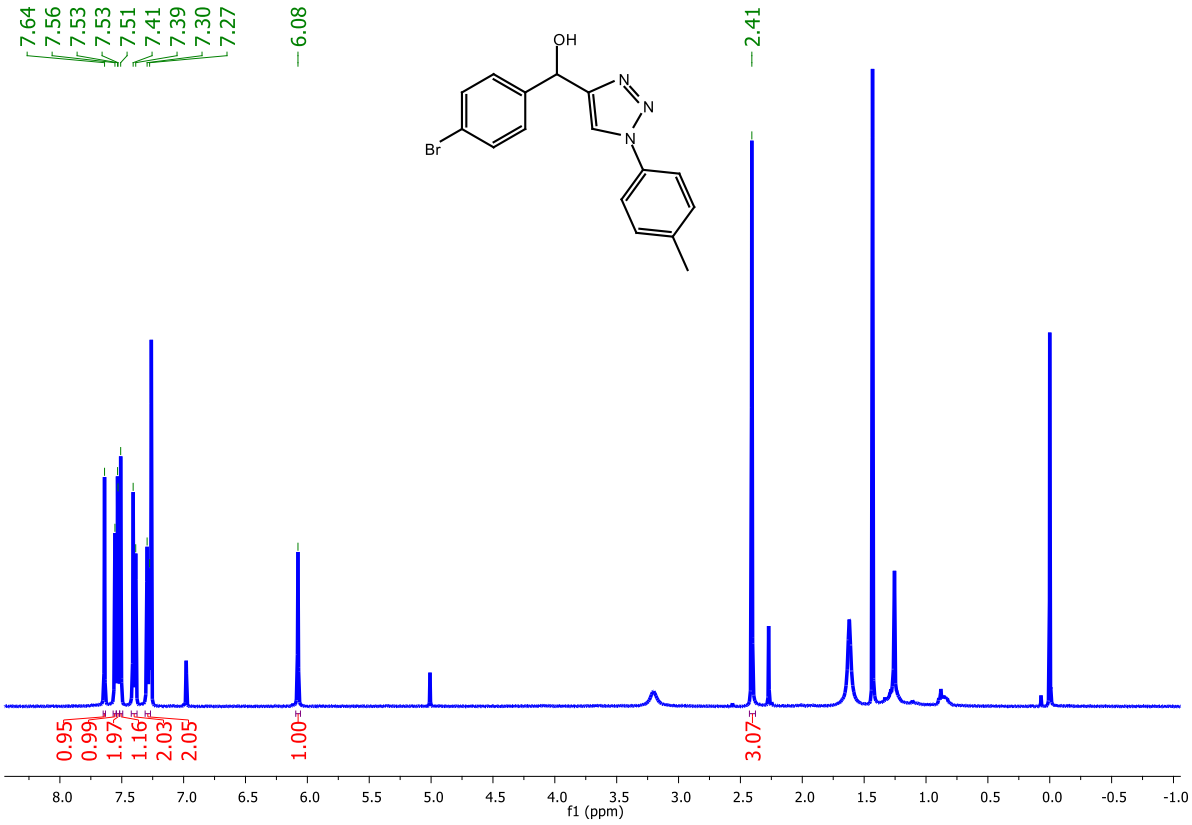
Spectrum 85: ^{1}H NMR (400 MHz; $CDCl_3$) 4ag



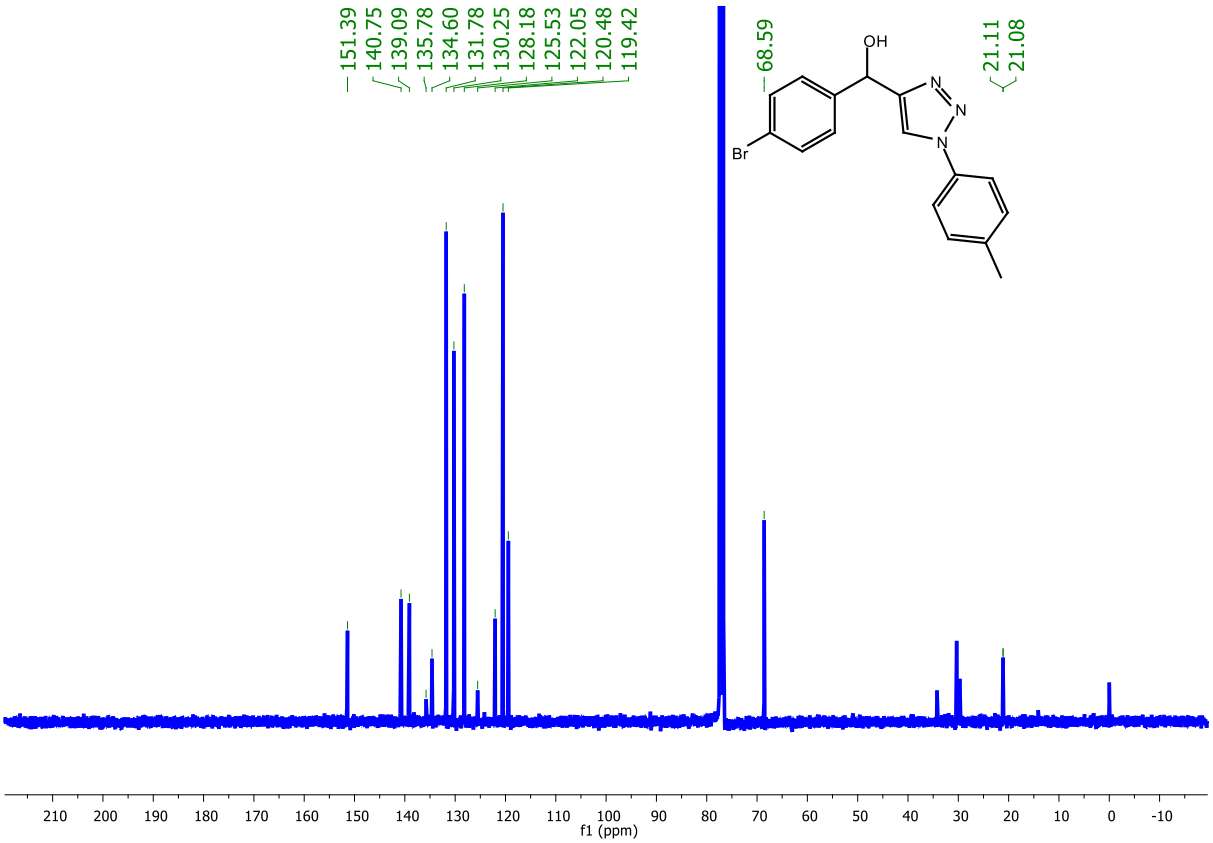
Spectrum 86: ^{13}C NMR (100 MHz; $CDCl_3$) 4ag



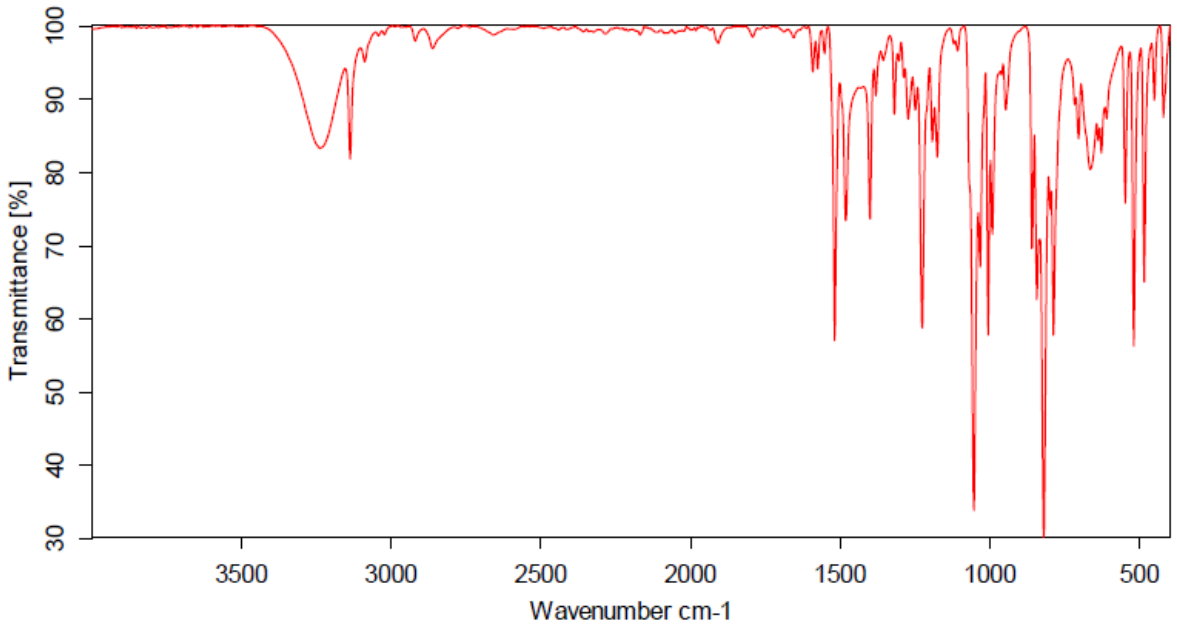
Spectrum 87: FTIR-ATR 4ag



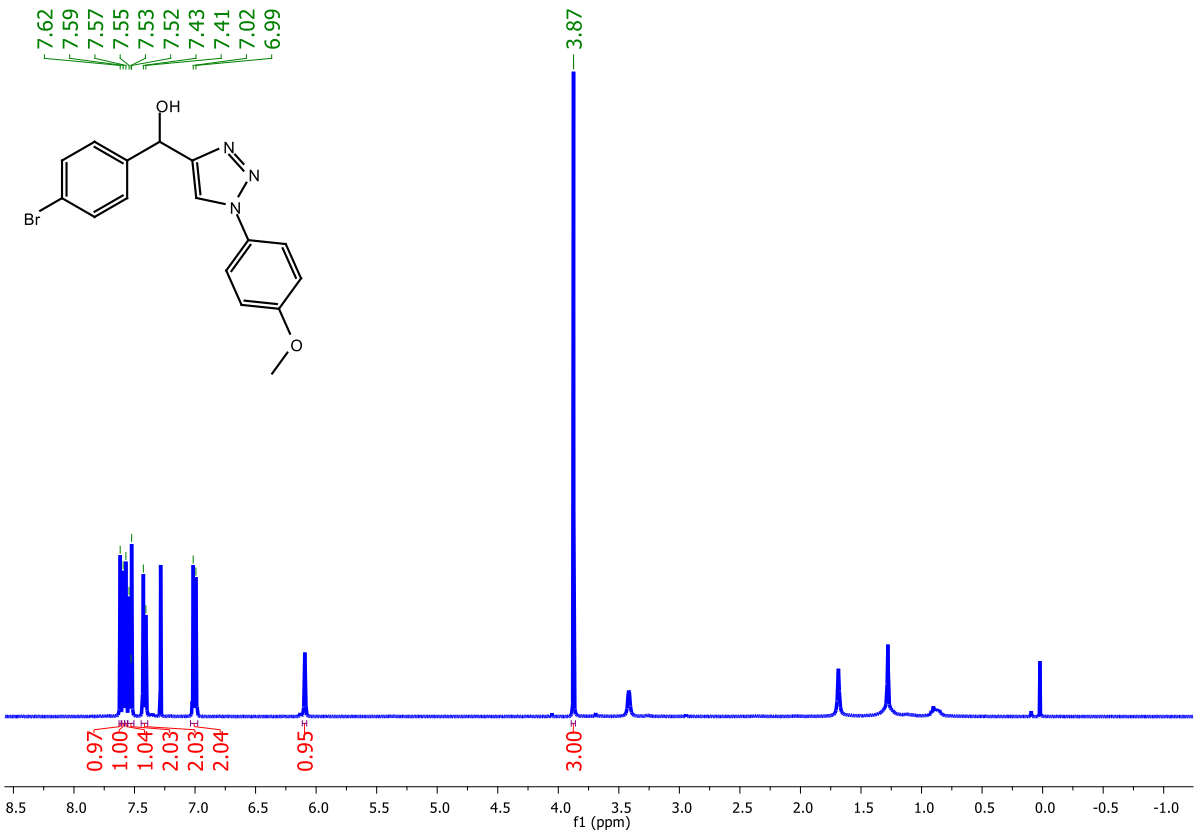
Spectrum 88: ^{1}H NMR (400 MHz; $CDCl_3$) 4ah



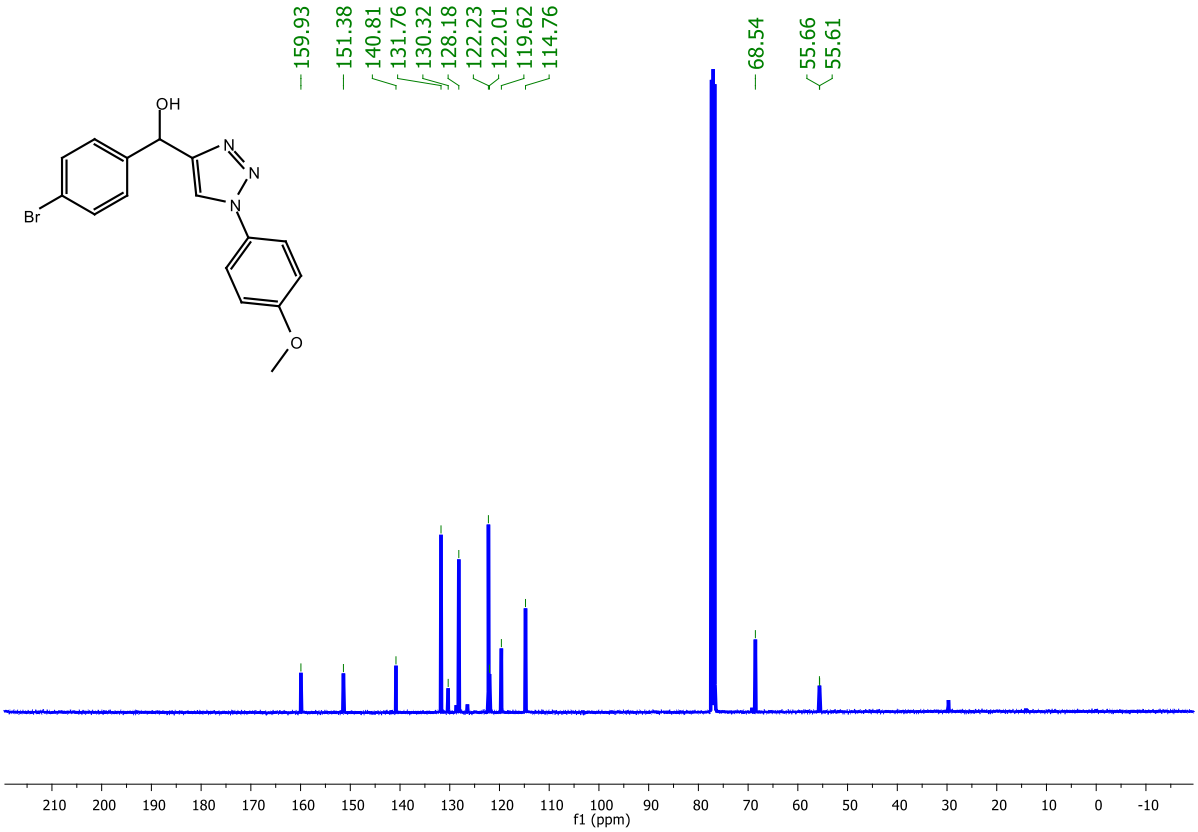
Spectrum 89: ^{13}C NMR (100 MHz; $CDCl_3$) 4ah



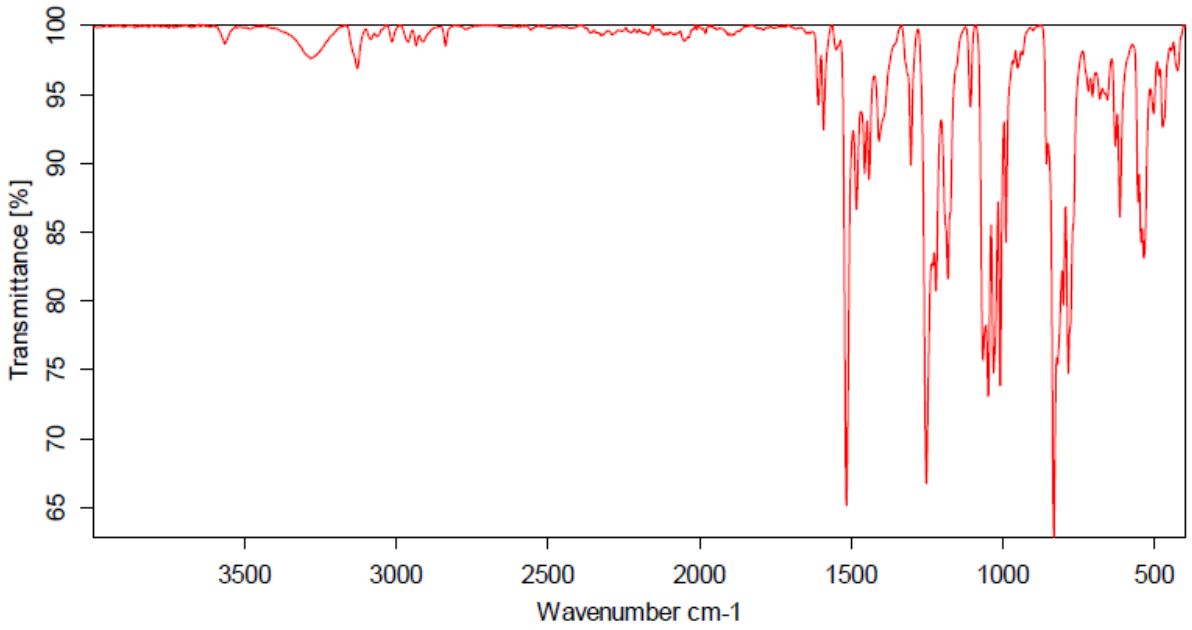
Spectrum 90: FTIR-ATR 4ah



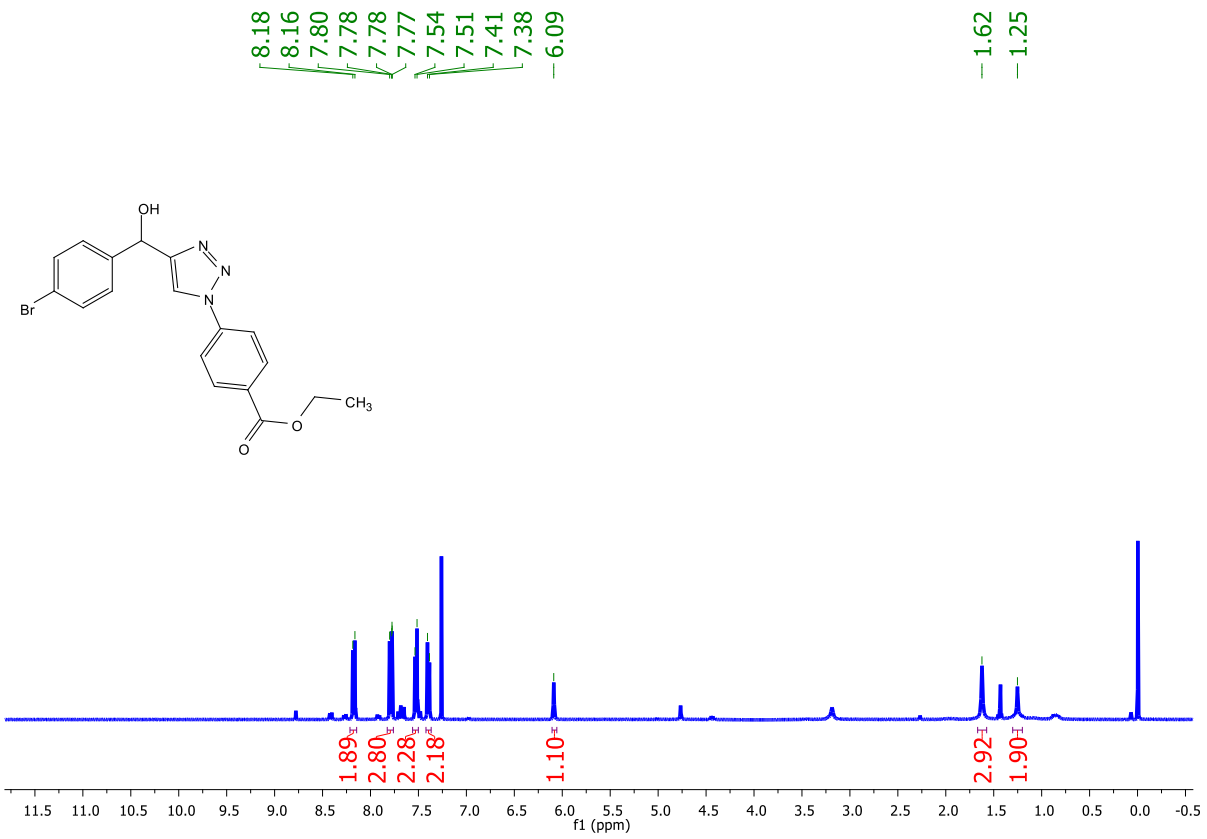
Spectrum 91: ^{1}H NMR (400 MHz; $CDCl_3$) 4ai



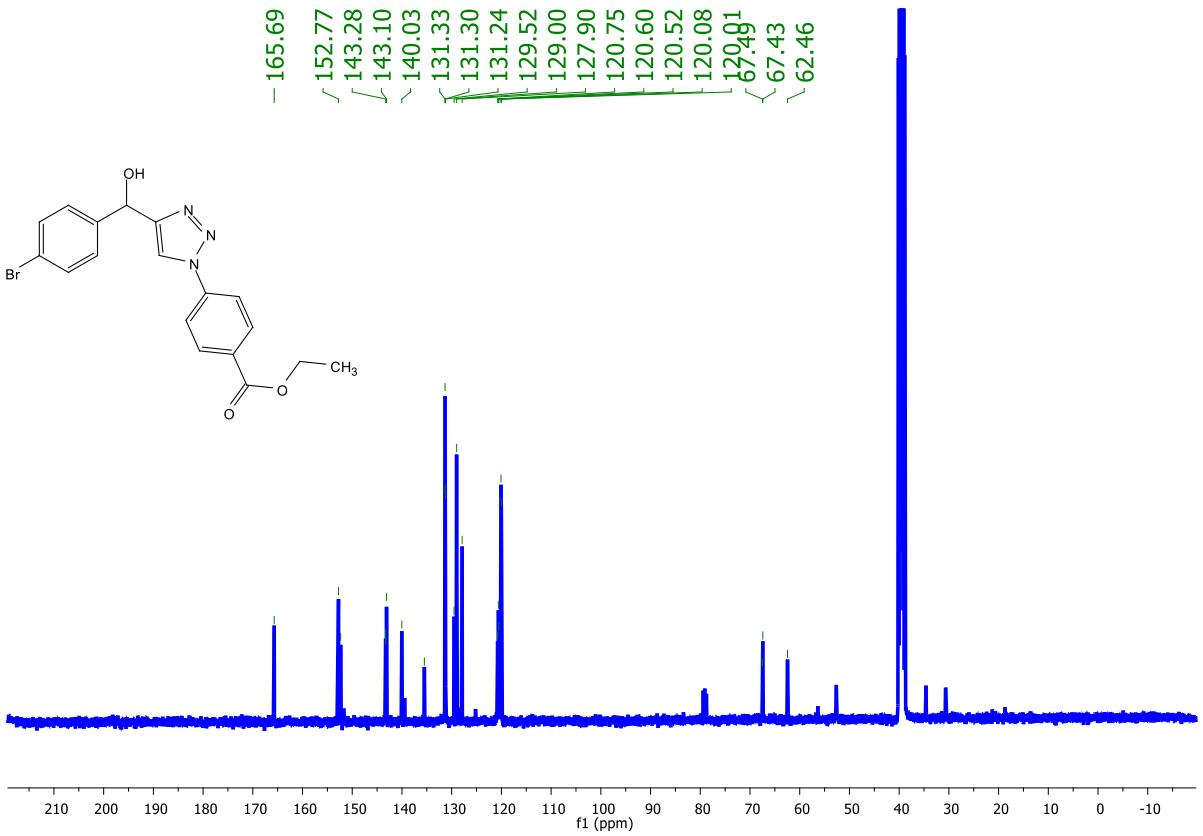
Spectrum 92: ^{13}C NMR (100 MHz; $CDCl_3$) 4ai



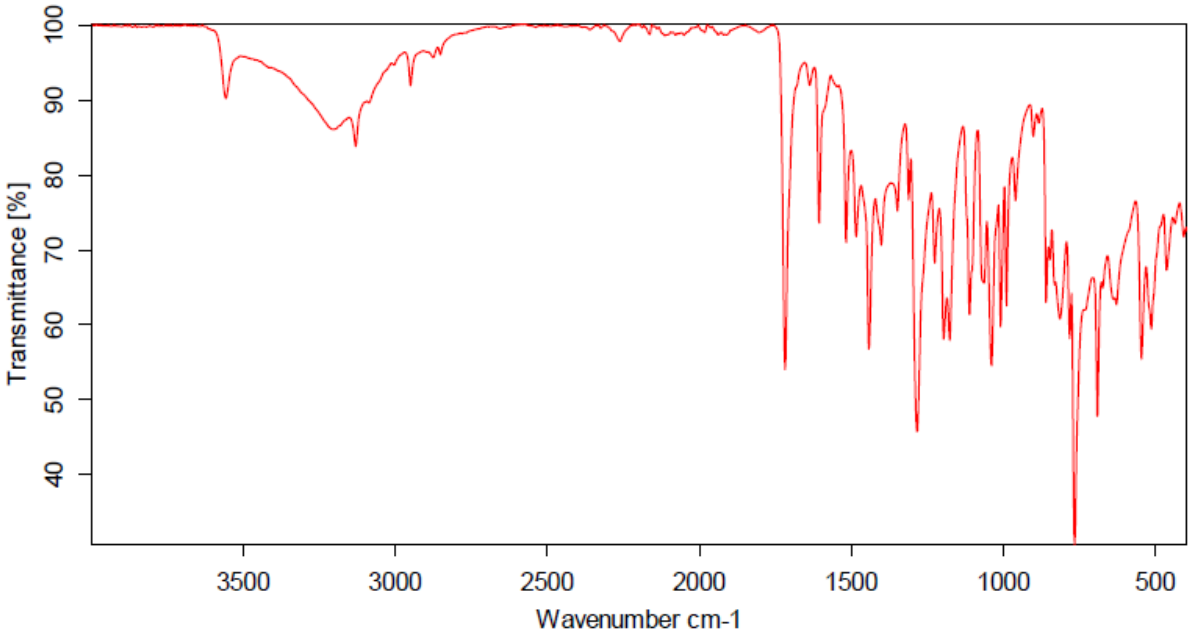
Spectrum 93: FTIR-ATR 4ai



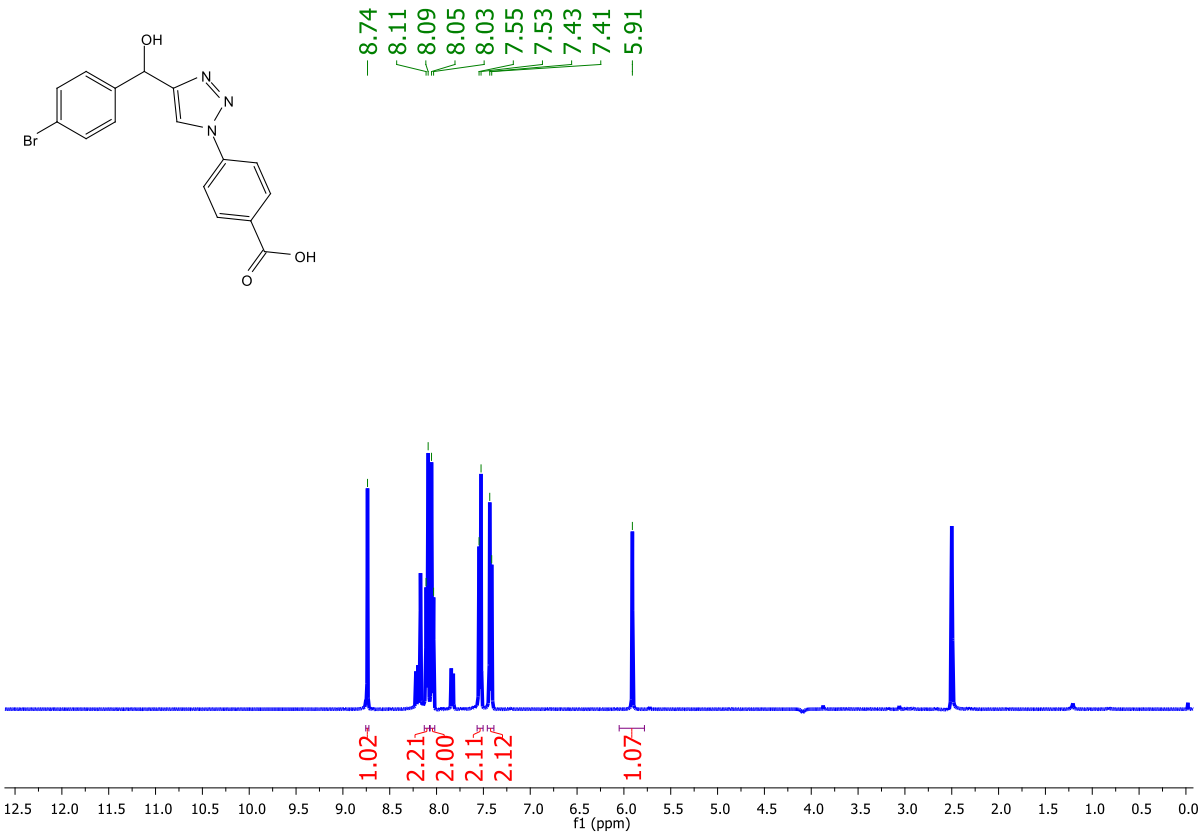
Spectrum 94: ^{1}H NMR (400 MHz; $CDCl_3$) 4aj



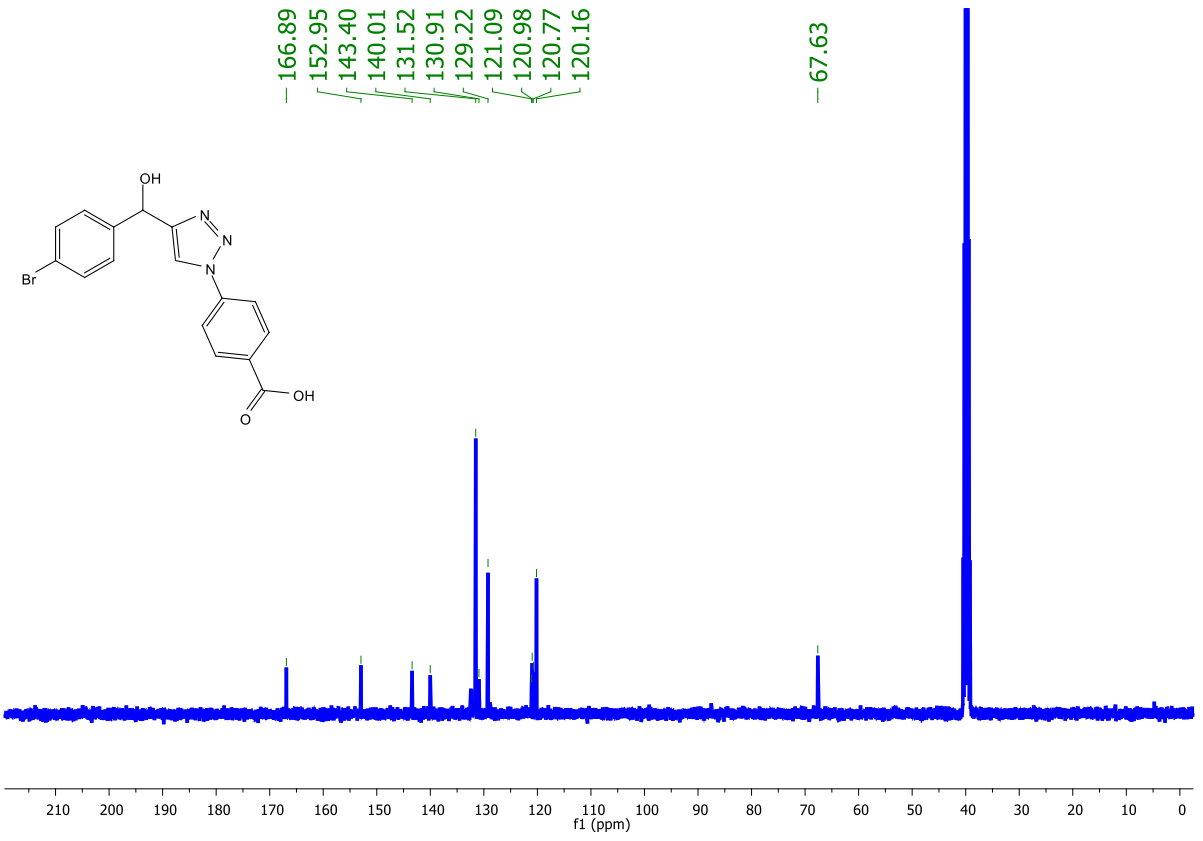
Spectrum 95: ^{13}C NMR (100 MHz; $CDCl_3$) 4aj



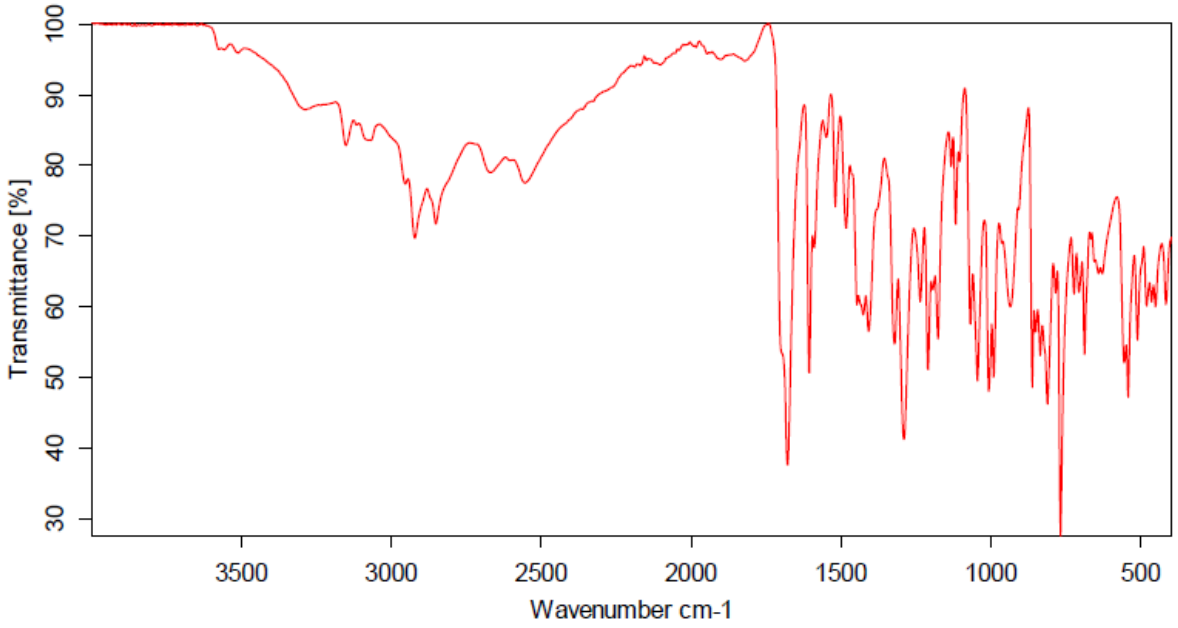
Spectrum 96: FTIR-ATR 4aj



Spectrum 97: ^{1}H NMR (400 MHz; $CDCl_3$) 4an

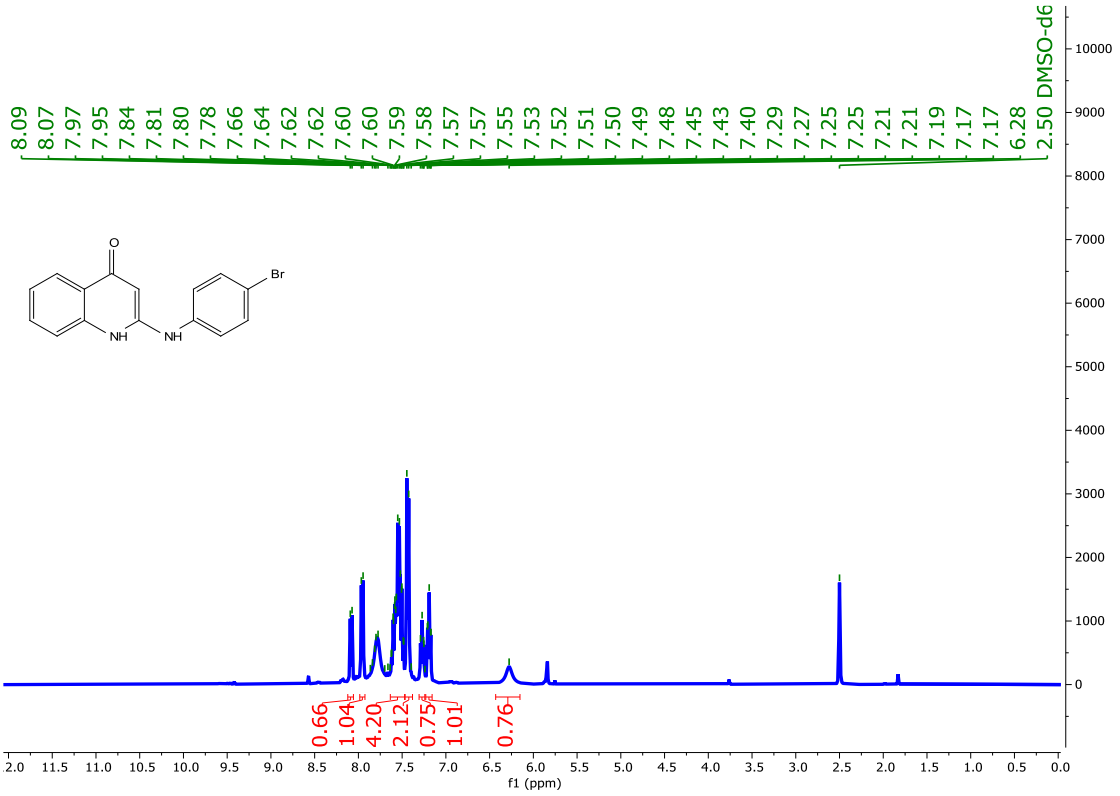


Spectrum 98: ^{13}C NMR (100 MHz; $CDCl_3$) 4an

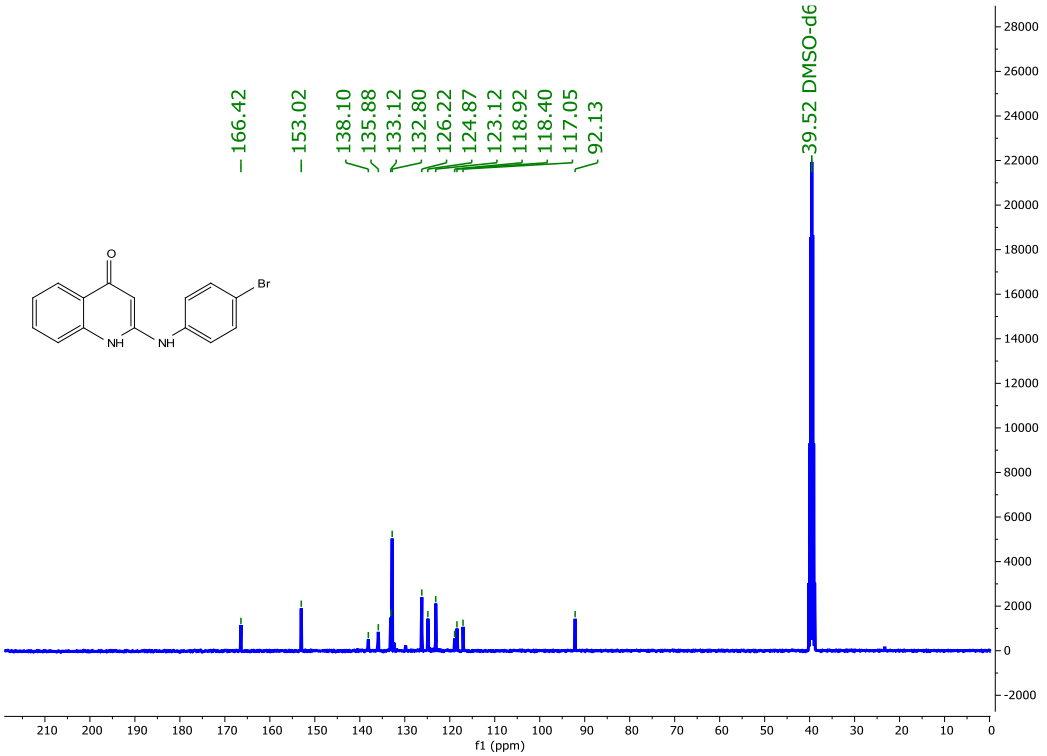


Spectrum 99: FTIR-ATR 4an

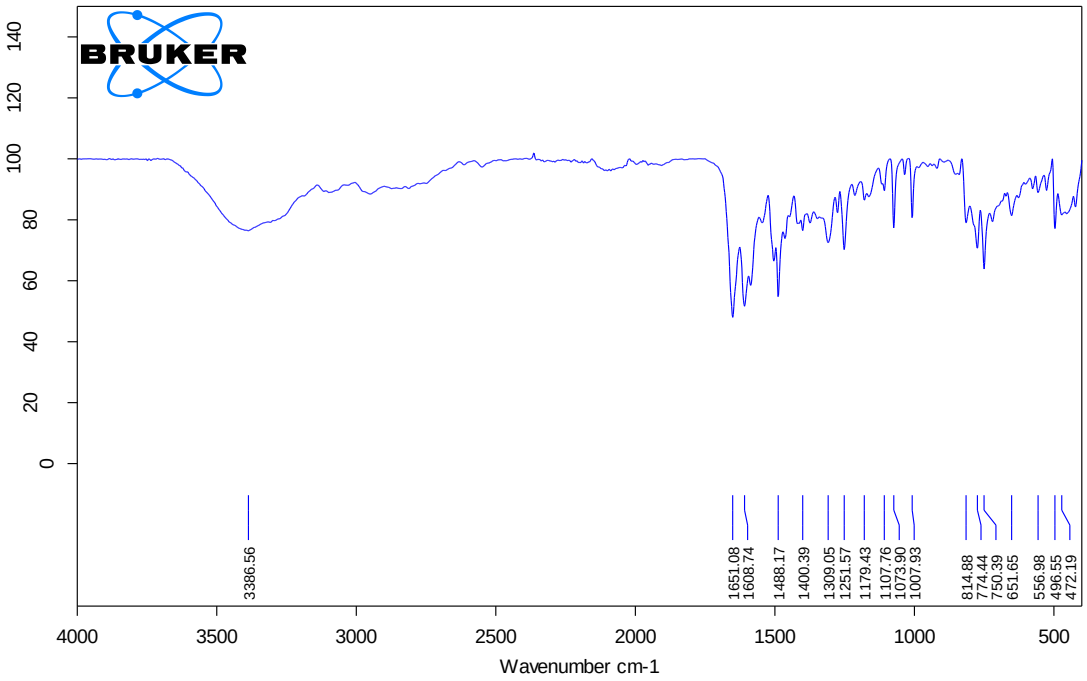
9. Appendix B: chapter 4 characterizations



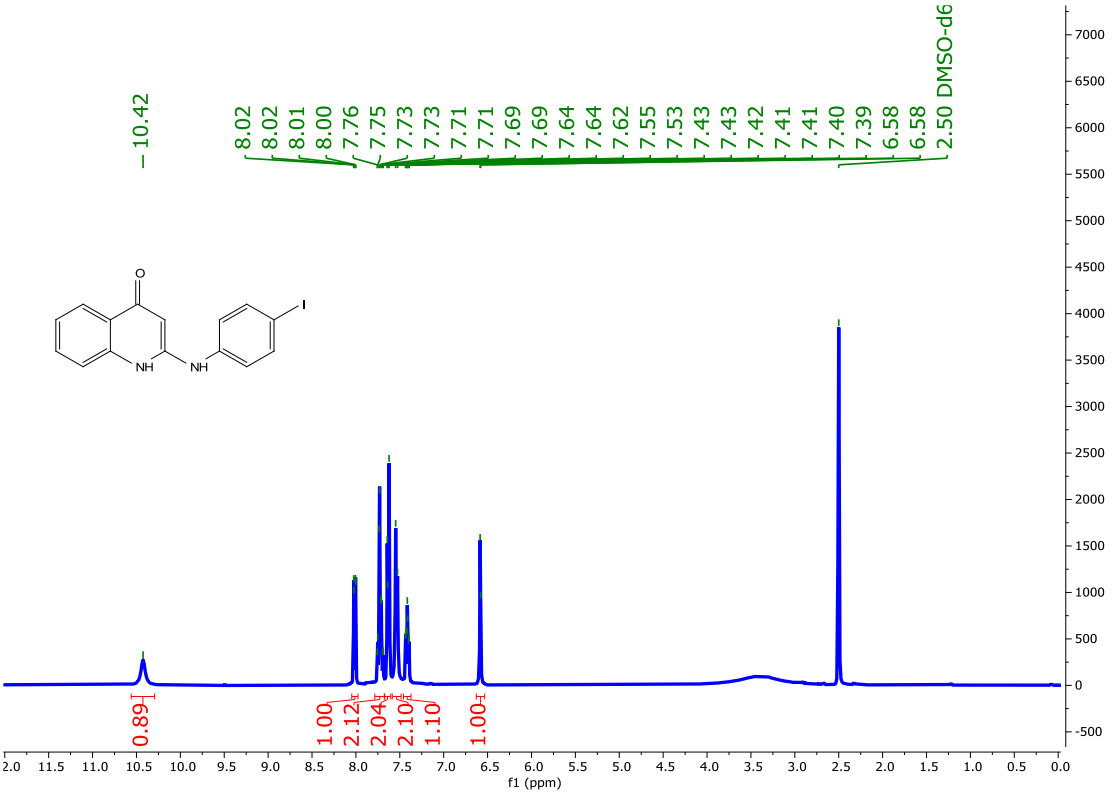
Spectrum 100: 11aa ^{1}H NMR (DMSO-d6, 400 MHz)



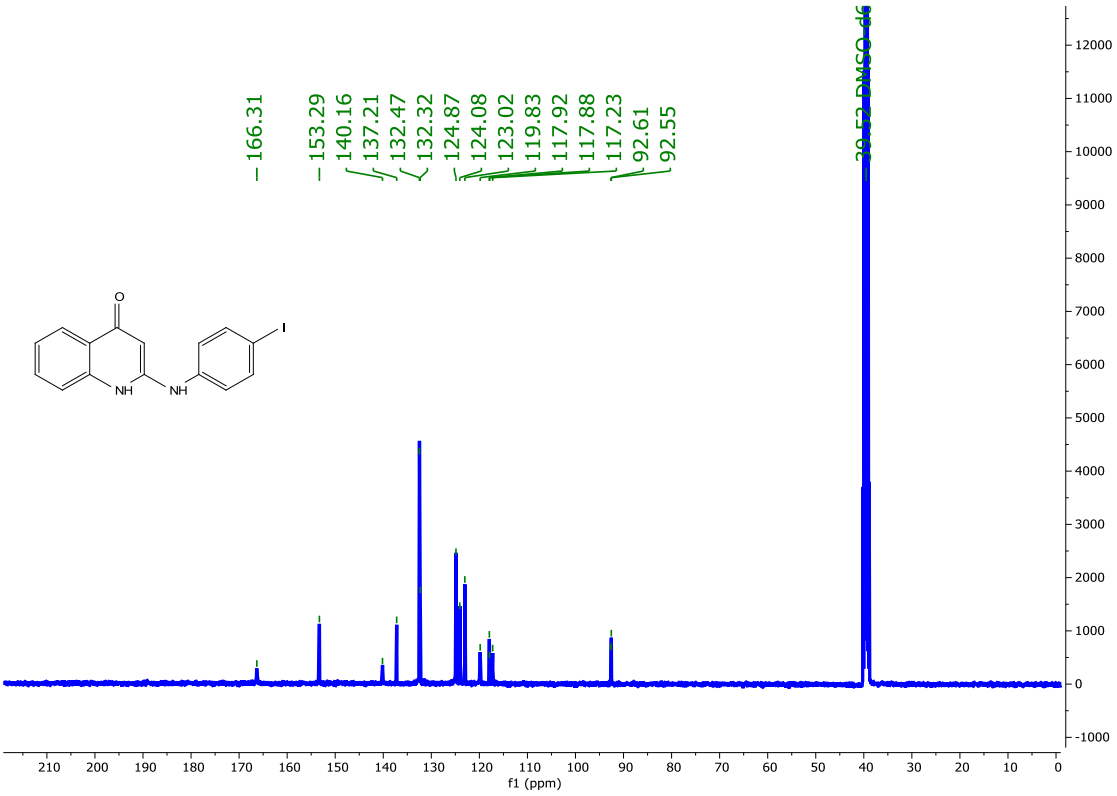
Spectrum 101: 11aa ^{13}C NMR (DMSO-d6, 101 MHz)



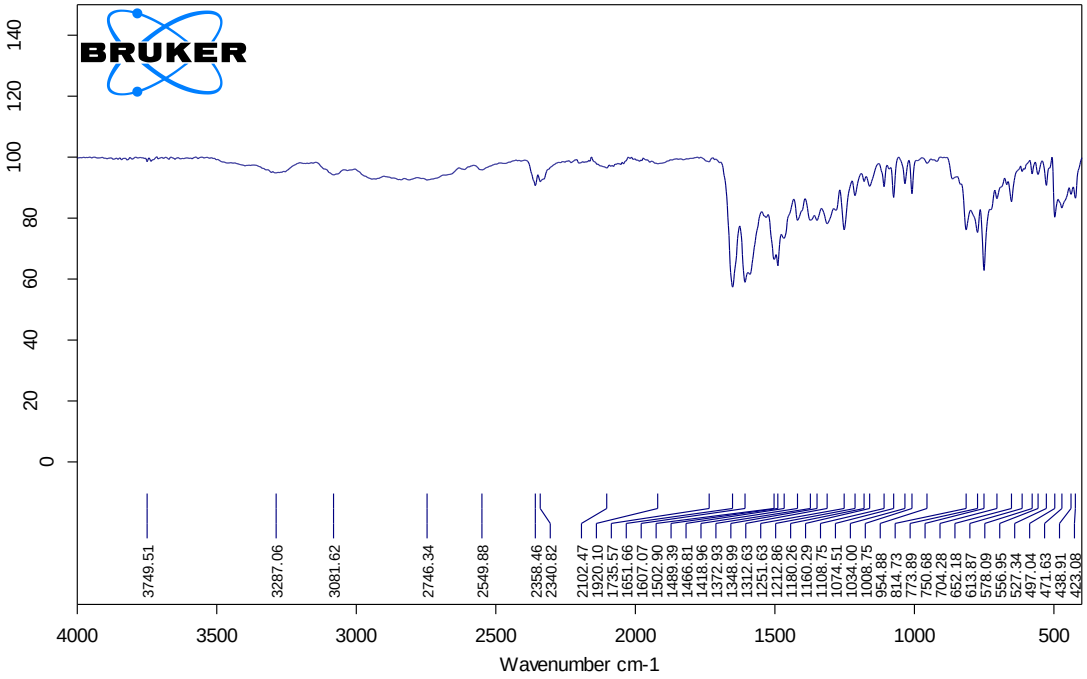
Spectrum 102: 11aa FTIR-ATR



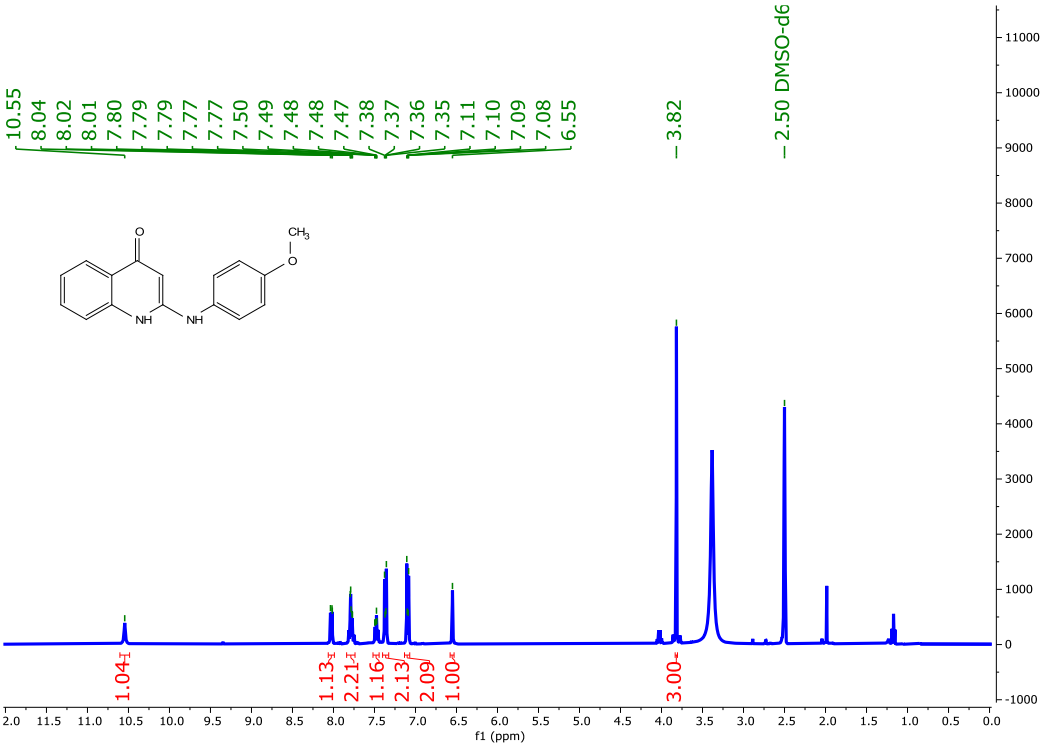
Spectrum 103: 11ab ^{1}H NMR (DMSO-d6, 400 MHz)



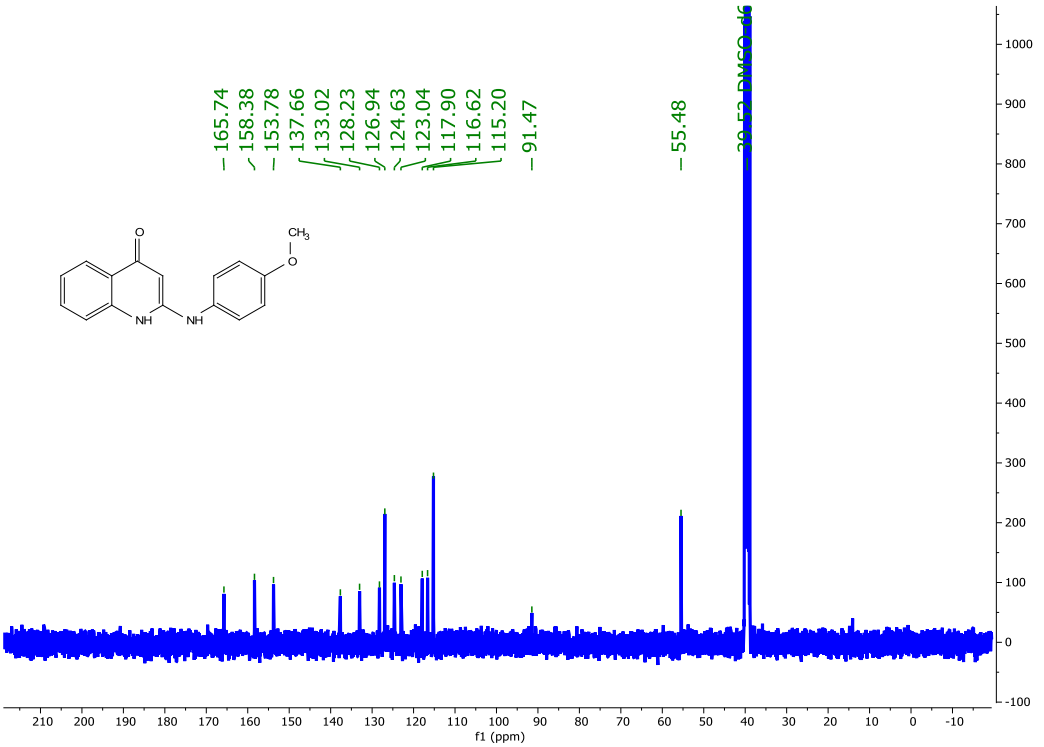
Spectrum 104: 11ab ^{13}C NMR (DMSO-d6, 101 MHz)



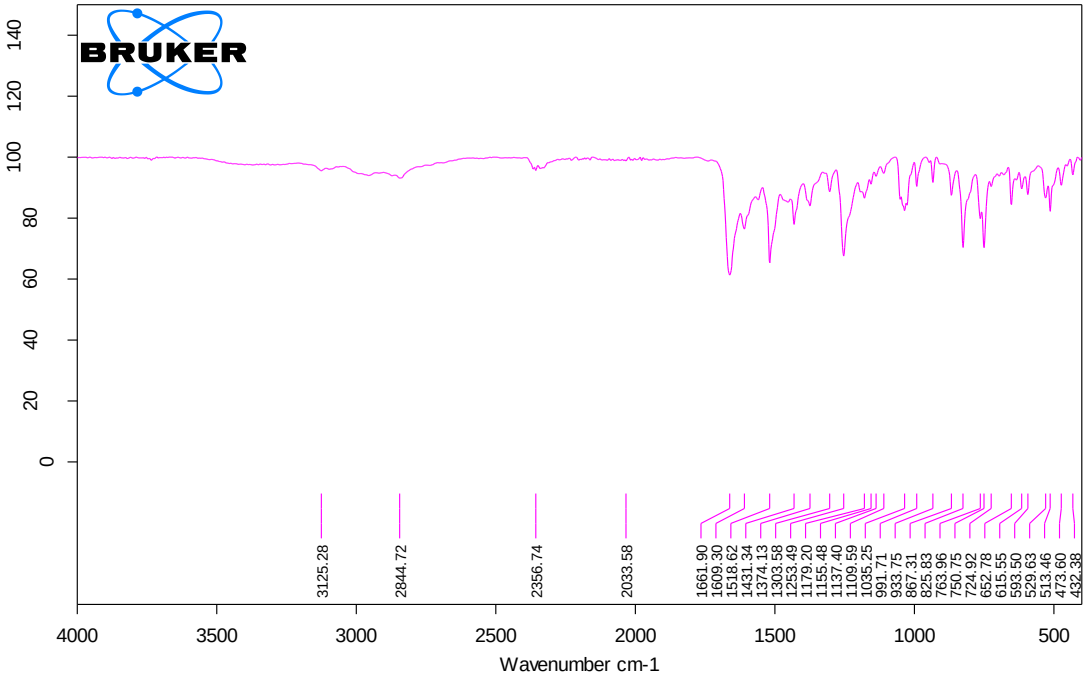
Spectrum 105: 11ab FTIR-ATR



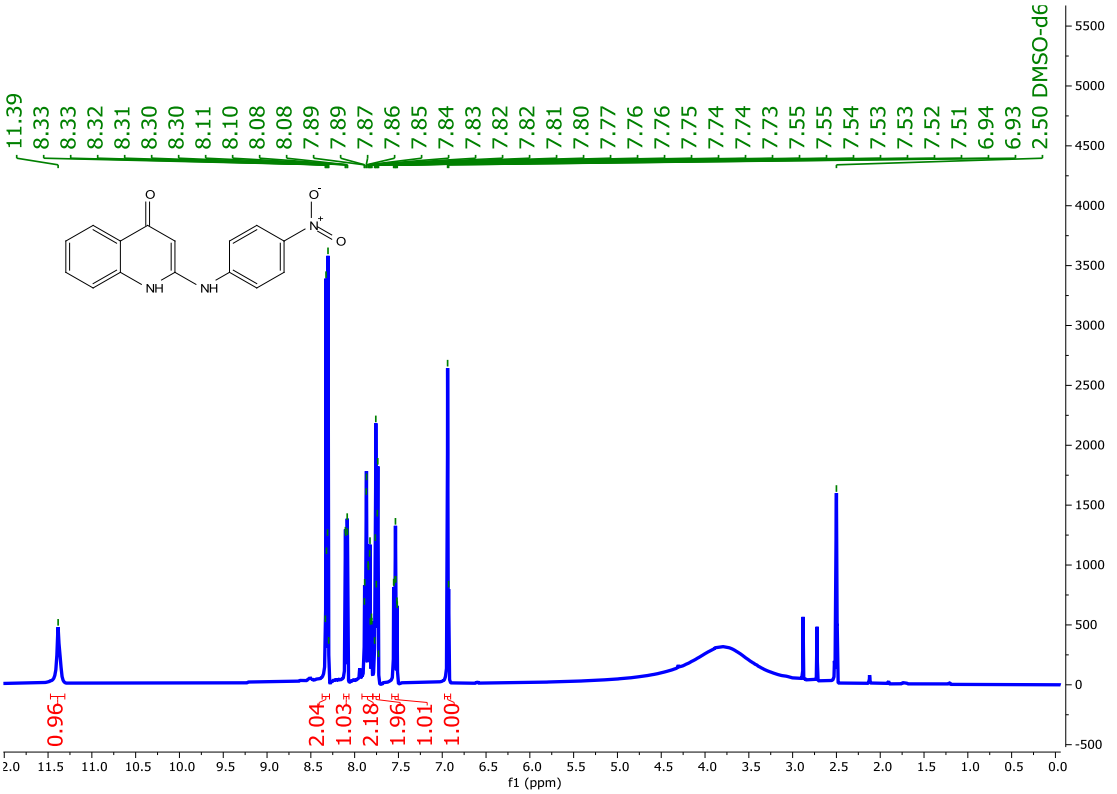
Spectrum 106: 11ac ^{1}H NMR (DMSO-d6, 400 MHz)



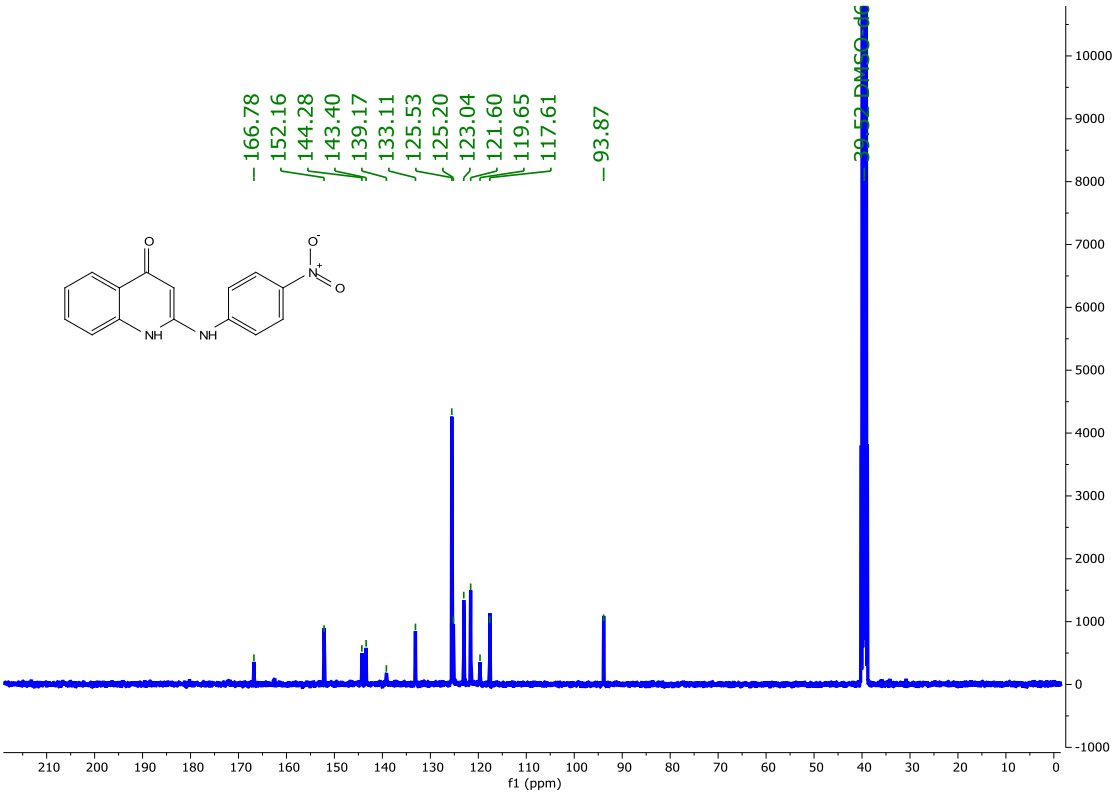
Spectrum 107: 11ac ^{13}C NMR (DMSO-d6, 101 MHz)



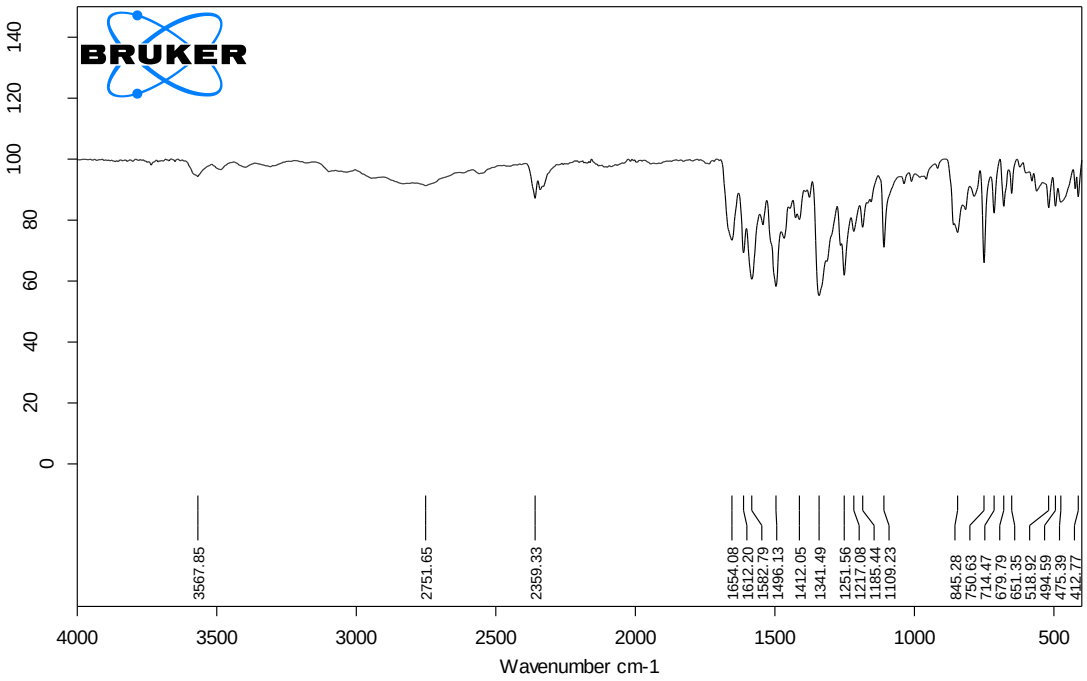
Spectrum 108: 11ac FTIR-ATR



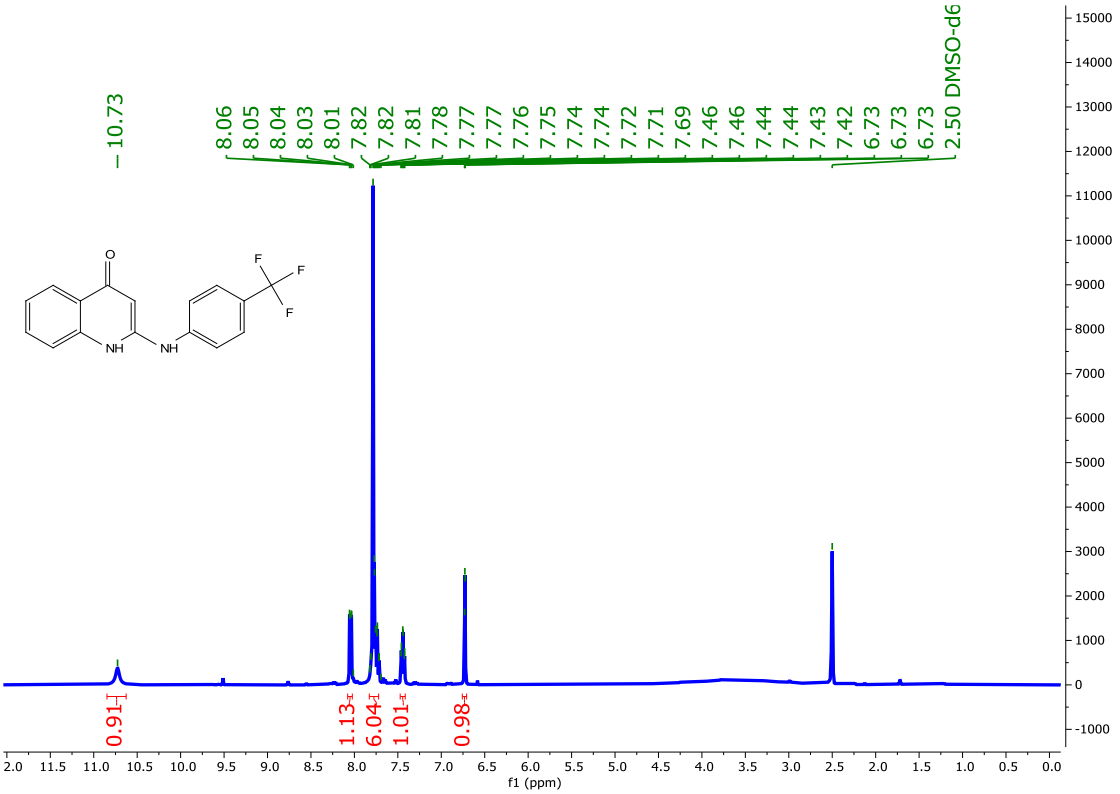
Spectrum 109: 11ad ^{1}H NMR (DMSO-d6, 400 MHz)



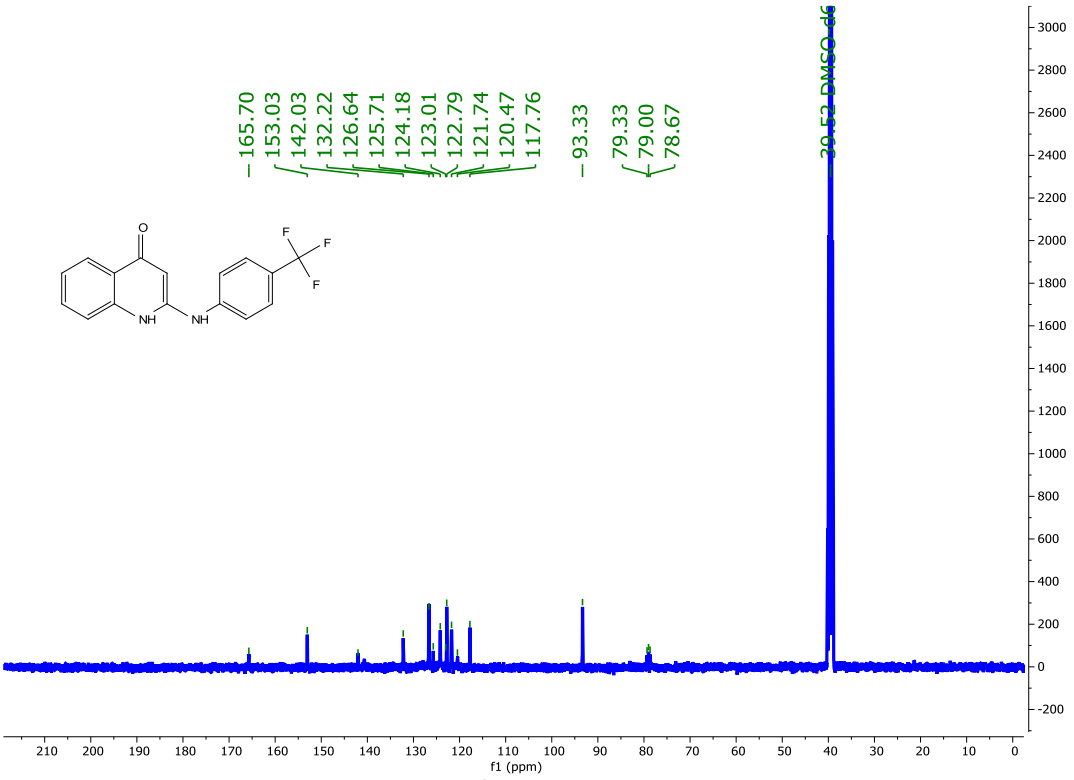
Spectrum 110: 11ad ^{13}C NMR (DMSO-d6, 101 MHz)



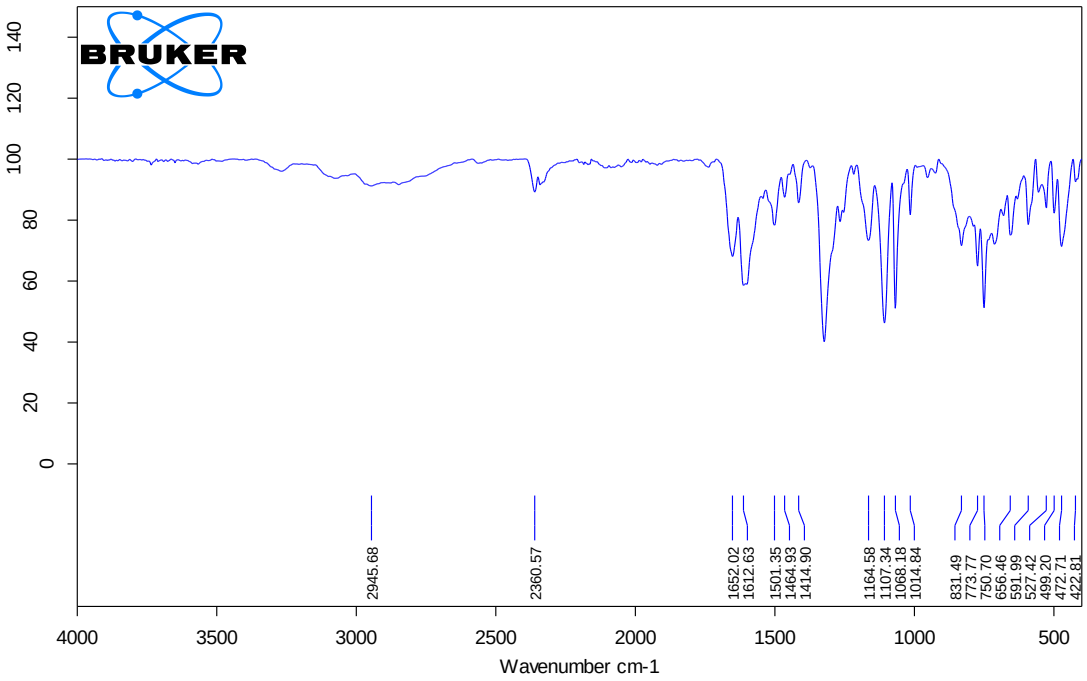
Spectrum 111: 11ad FTIR-ATR



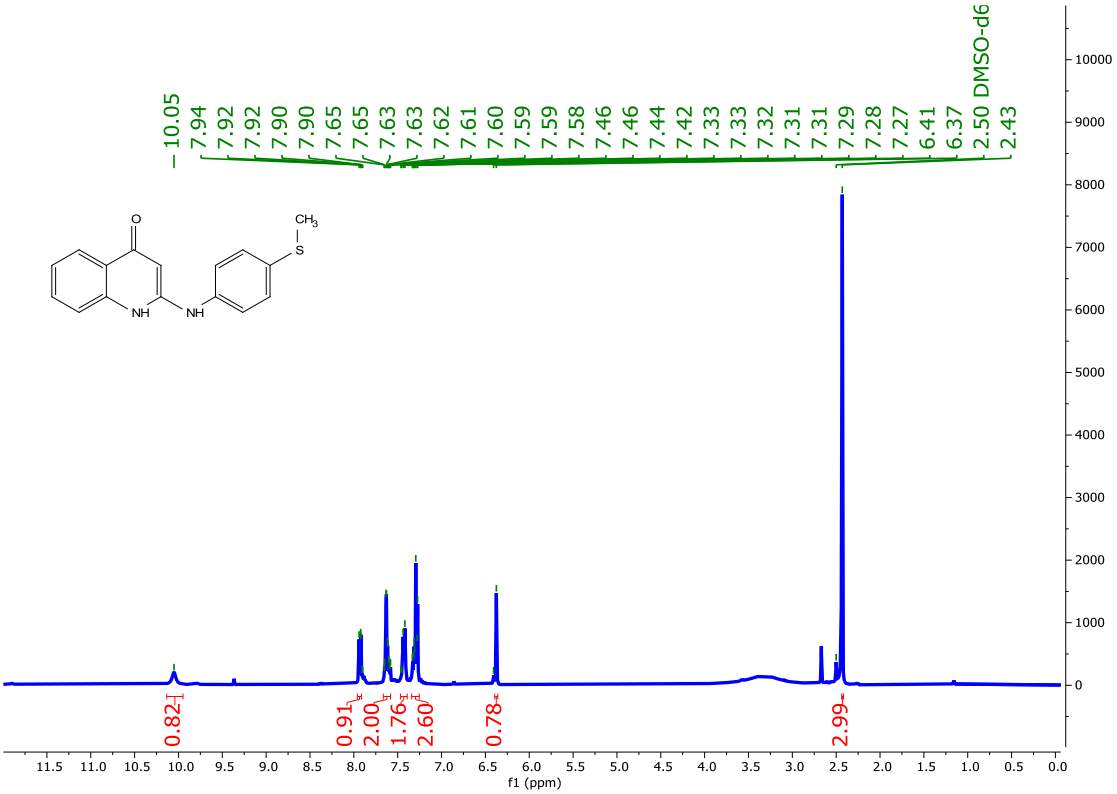
Spectrum 112: 11ae ^{1}H NMR (DMSO-d6, 400 MHz)



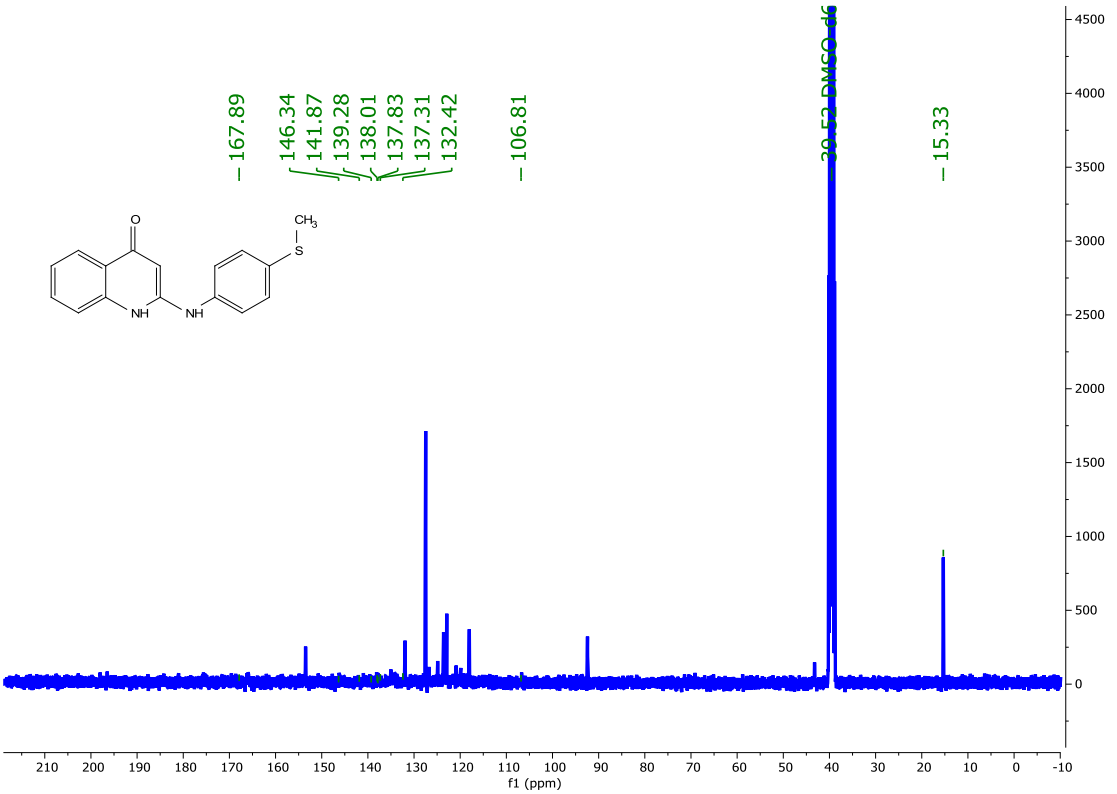
Spectrum 113: 11ae ^{13}C NMR (DMSO-d6, 101 MHz)



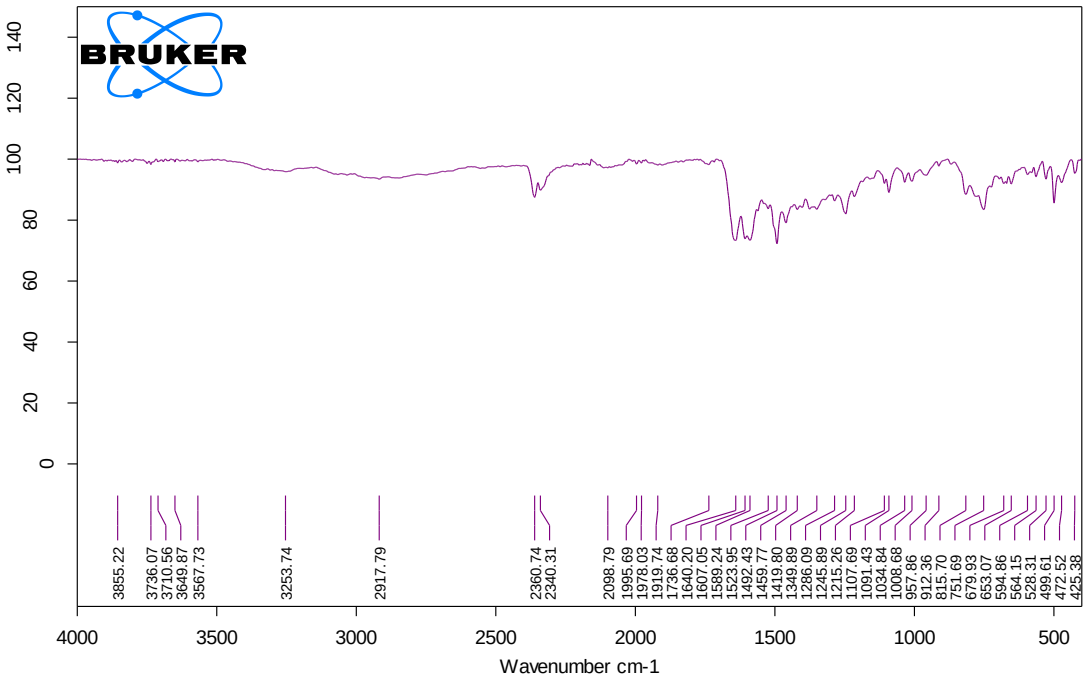
Spectrum 114: 11ae FTIR-ATR



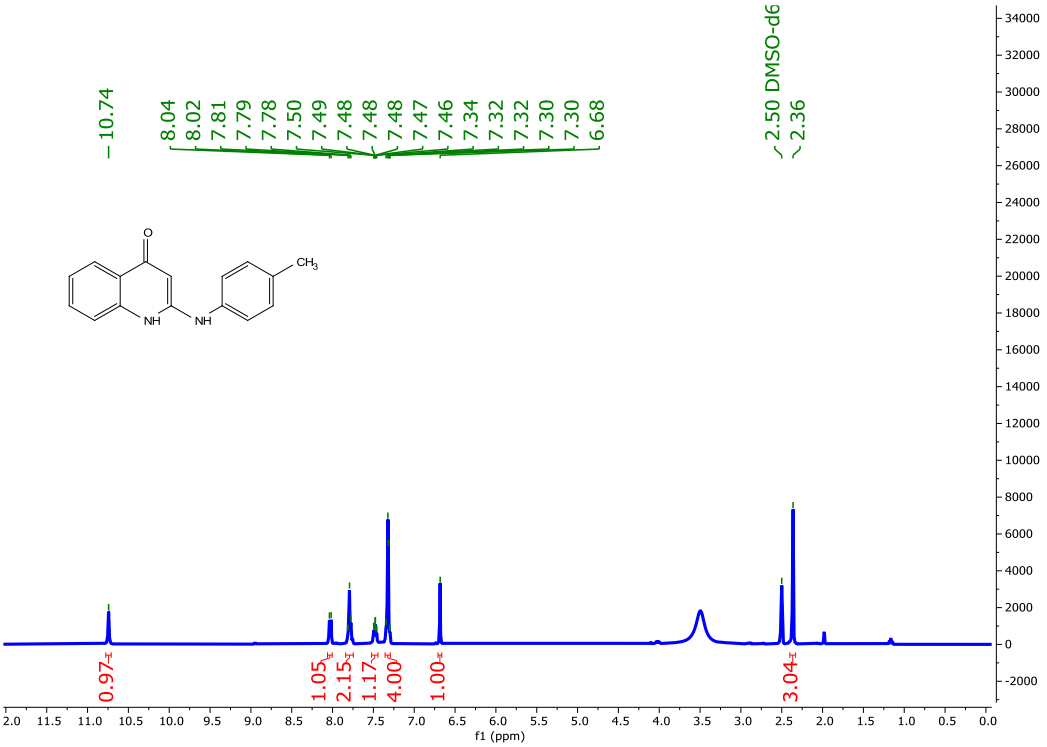
Spectrum 115: 11af ^{1}H NMR (DMSO-d6, 400 MHz)



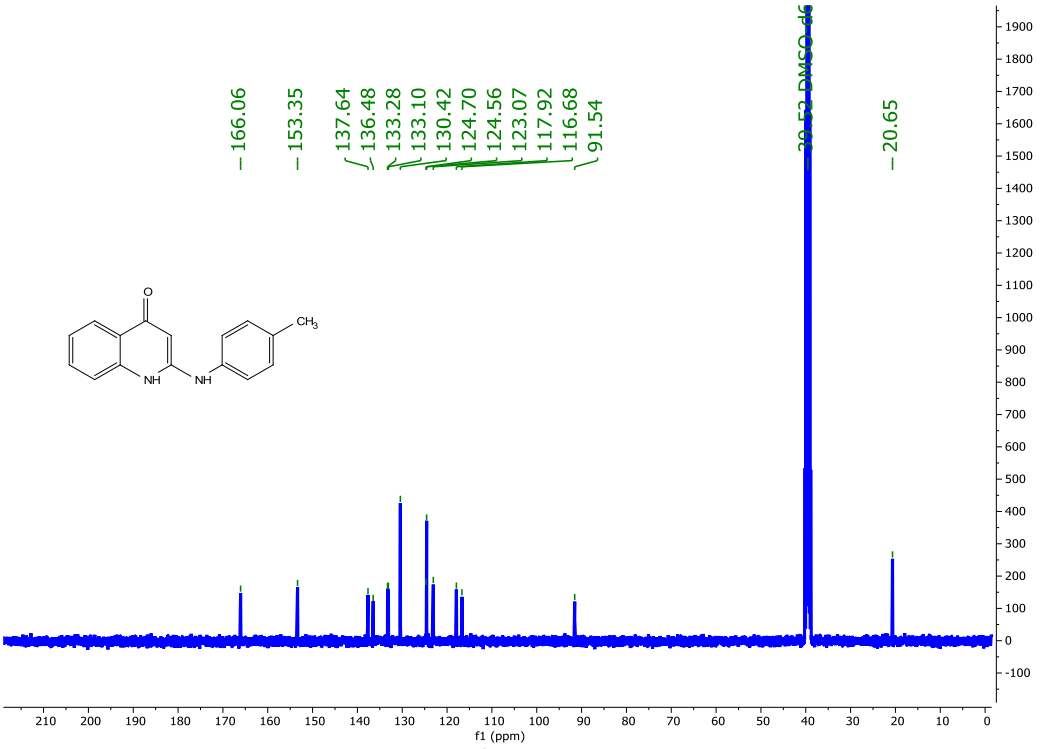
Spectrum 116: 11af ^{13}C NMR (DMSO-d6, 101 MHz)



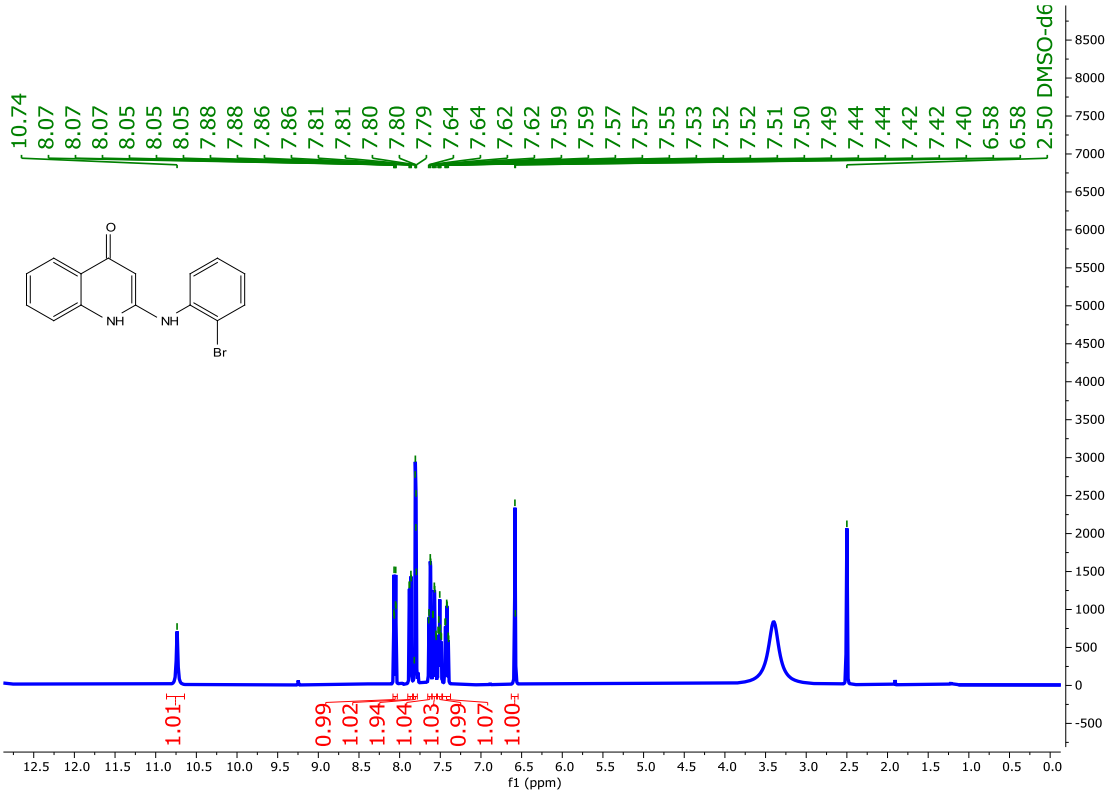
Spectrum 117: 11af FTIR-ATR



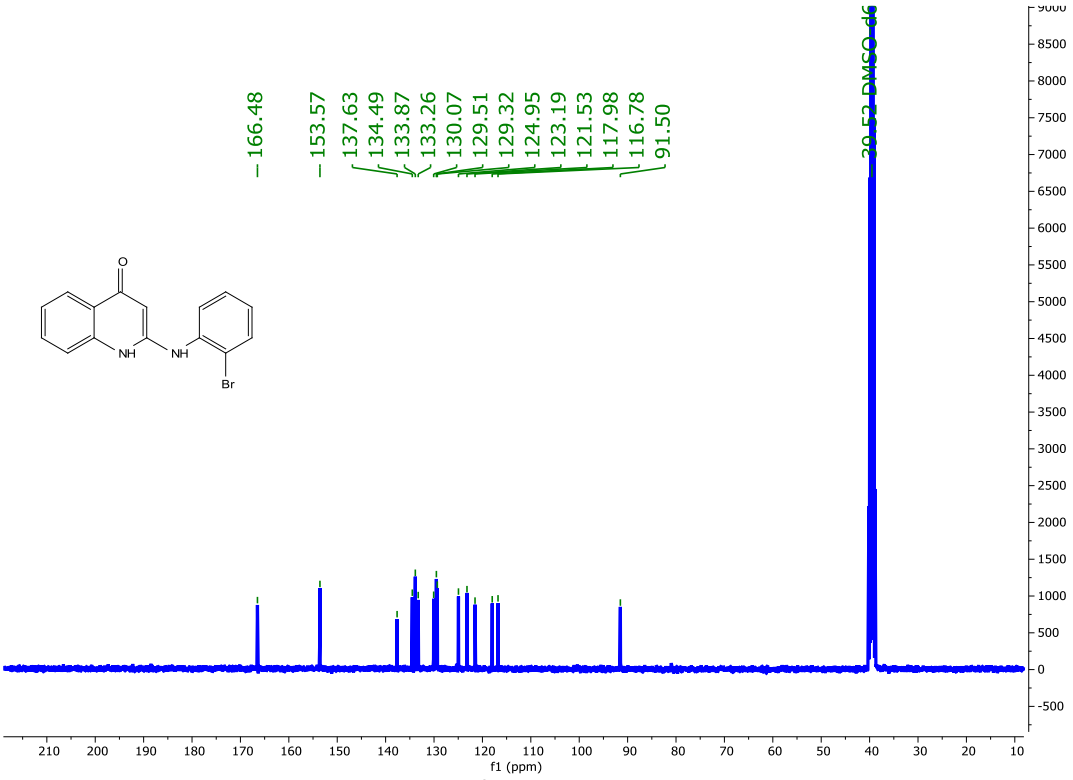
Spectrum 118: 11ag ^{1}H NMR (DMSO-d6, 400 MHz)



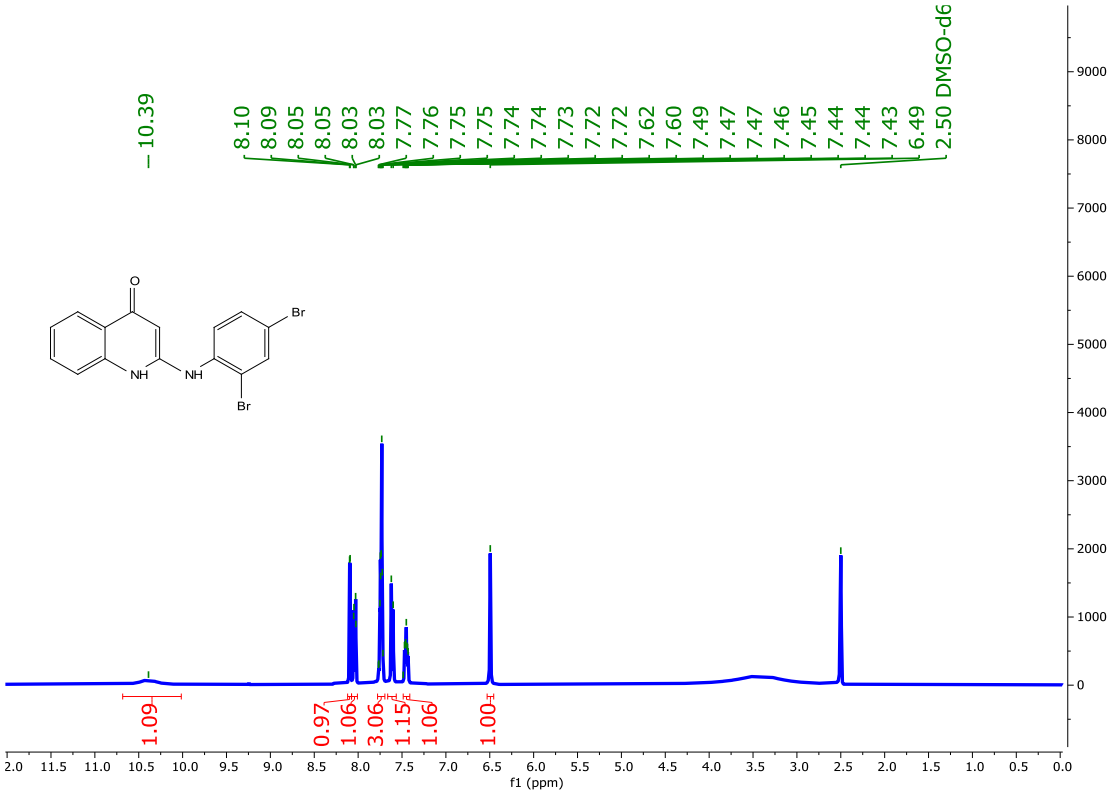
Spectrum 119: 11ag ^{13}C NMR (DMSO-d6, 101 MHz)



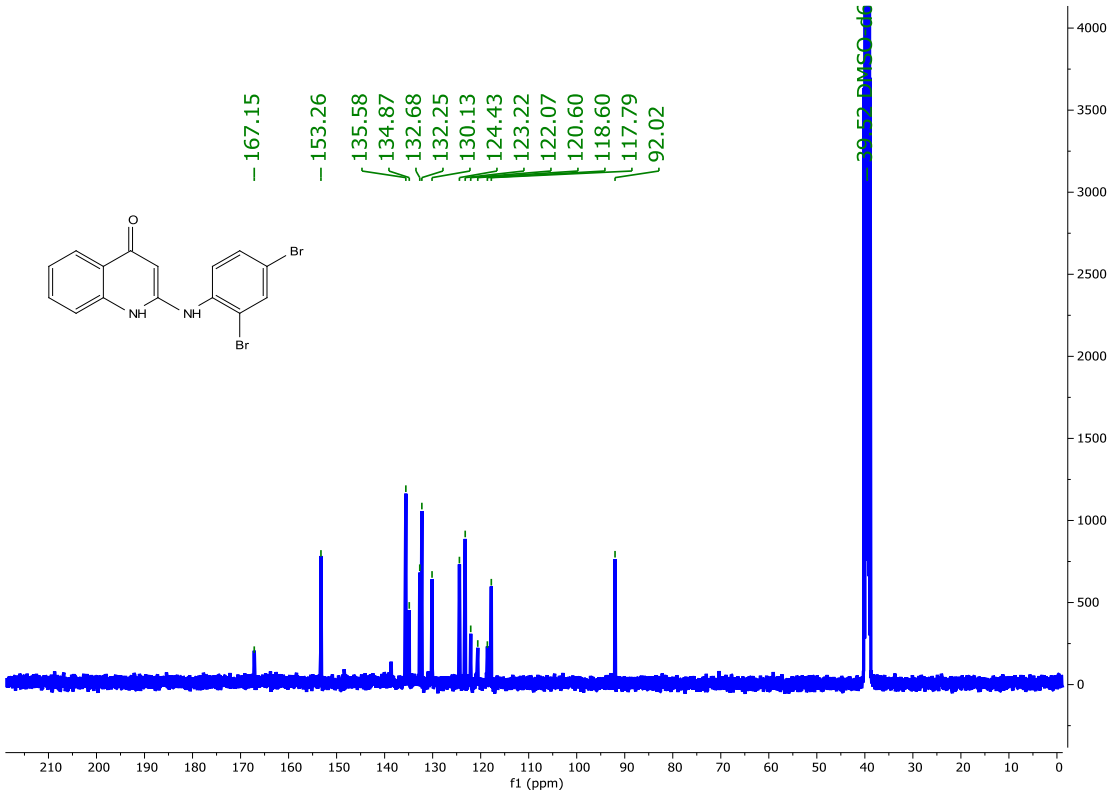
Spectrum 120: 11ah ^{1}H NMR (DMSO-d6, 400 MHz)



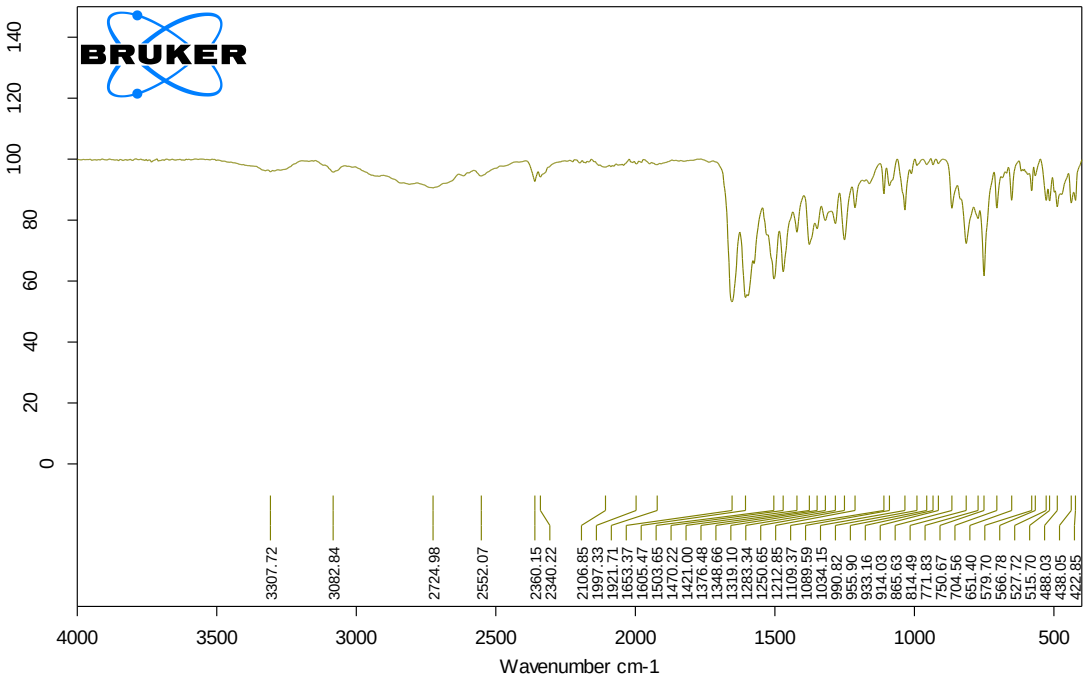
Spectrum 121: 11ah ^{13}C NMR (DMSO-d6, 101 MHz)



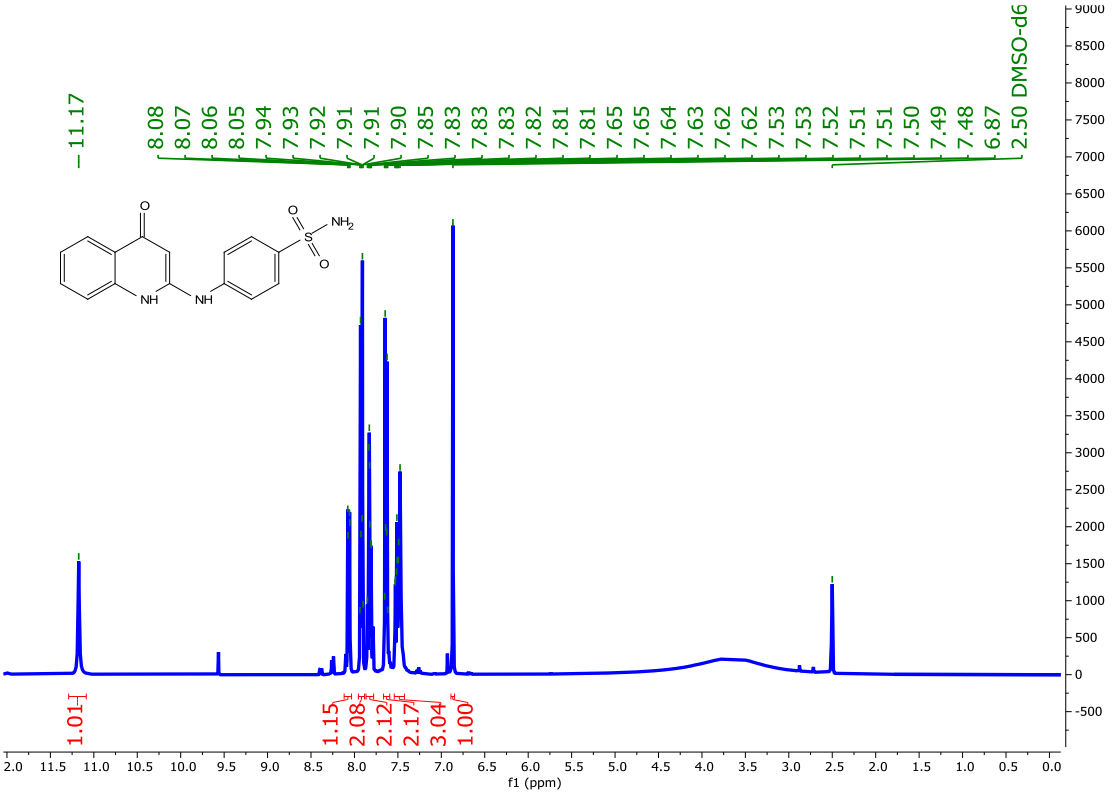
Spectrum 122: 11ai ^{1}H NMR (DMSO-d6, 400 MHz)



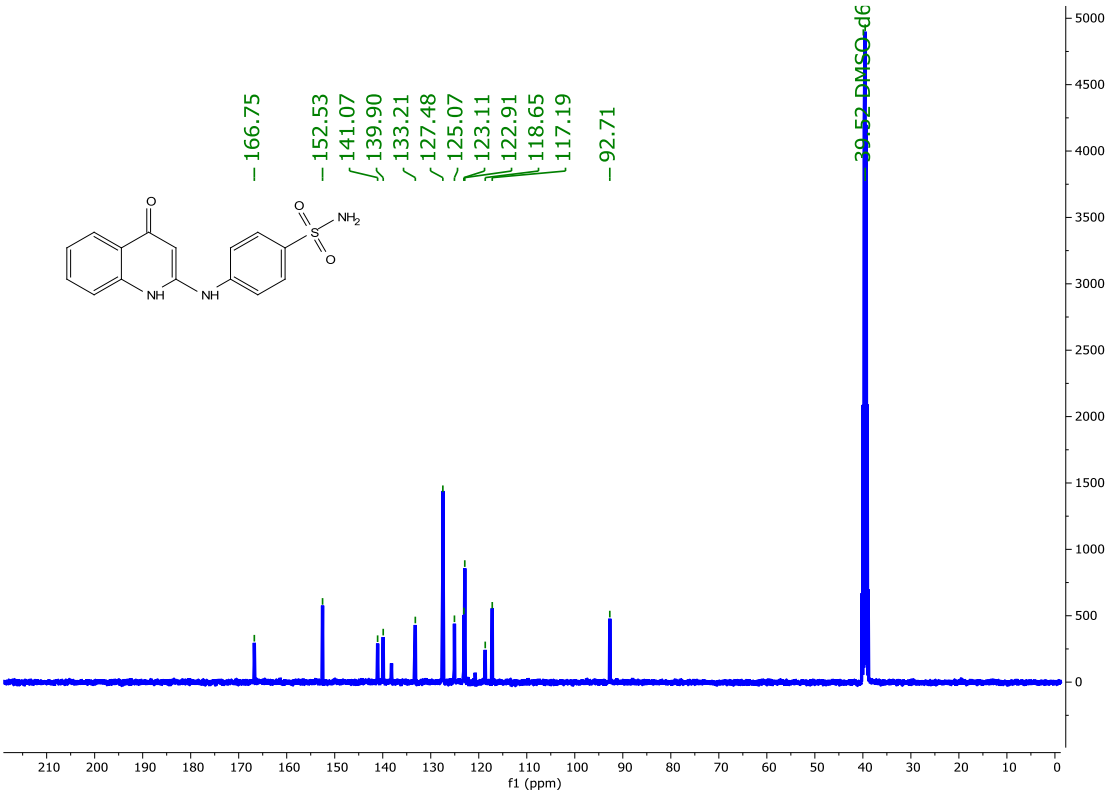
Spectrum 123: 11ai ^{13}C NMR (DMSO-d6, 101 MHz)



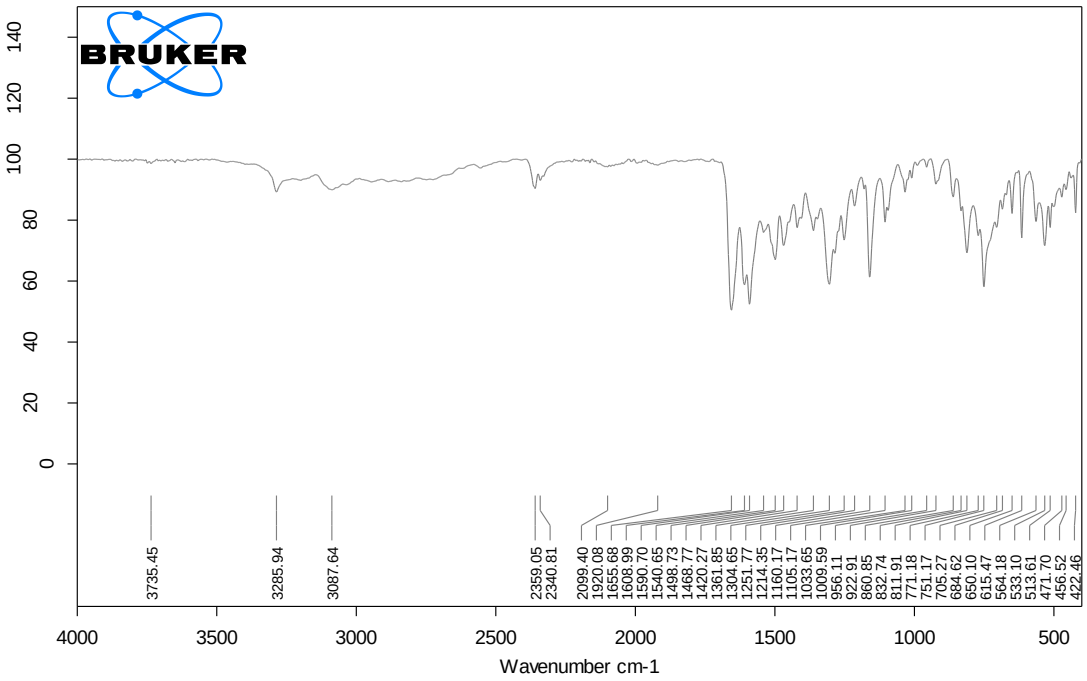
Spectrum 124: 11ai FTIR-ATR



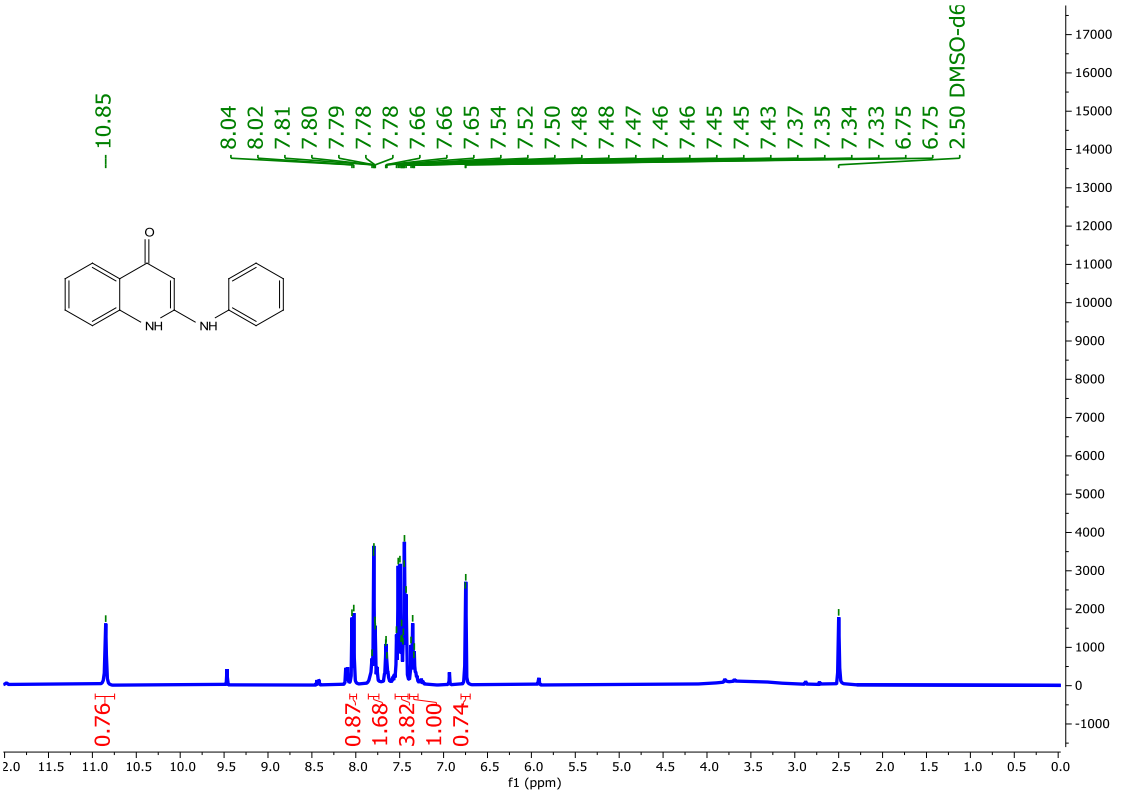
Spectrum 125: 11aj ^{1}H NMR (DMSO-d6, 400 MHz)



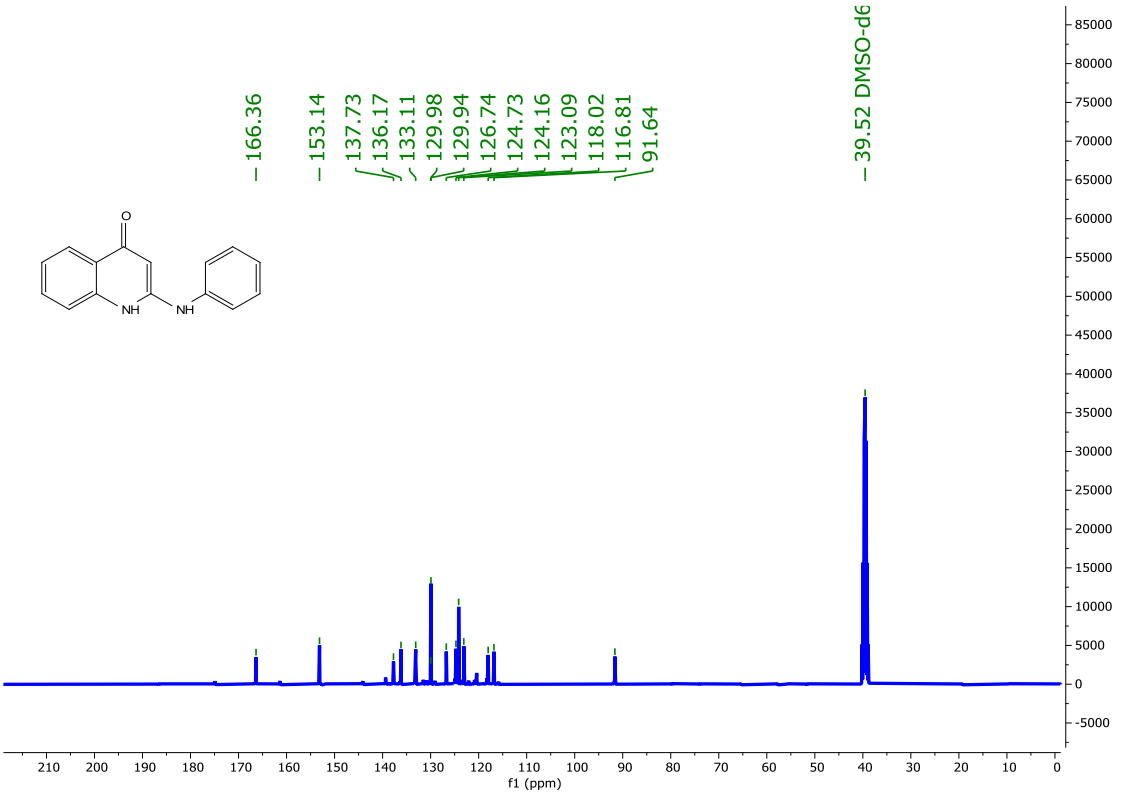
Spectrum 126: 11aj ^{13}C NMR (DMSO-d6, 101 MHz)



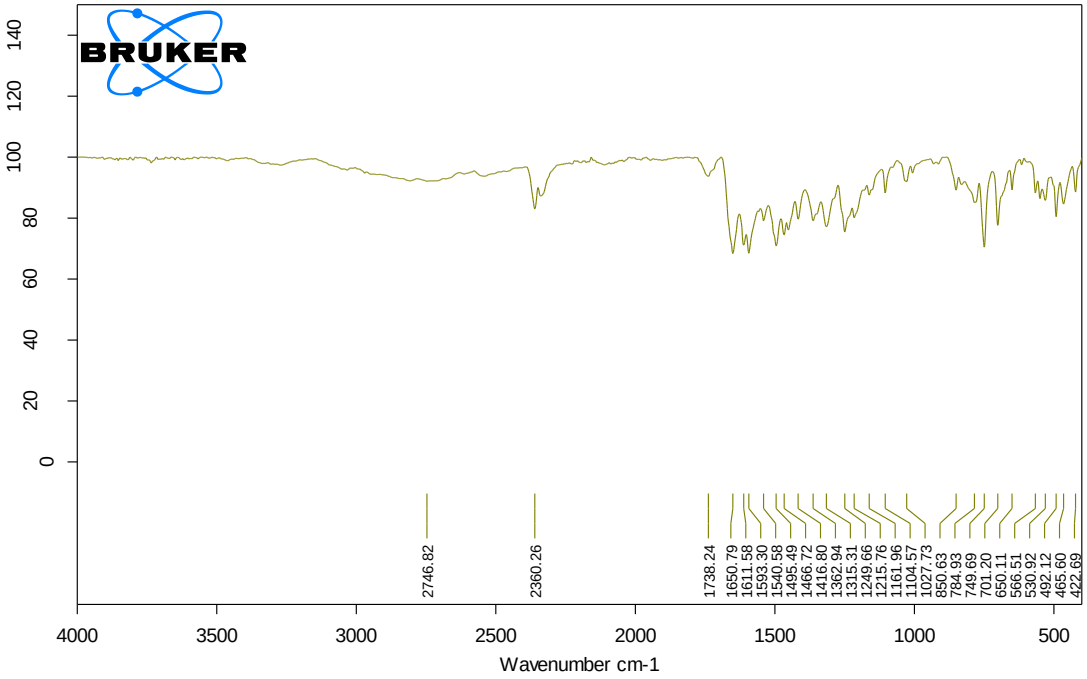
Spectrum 127: 11aj FTIR-ATR



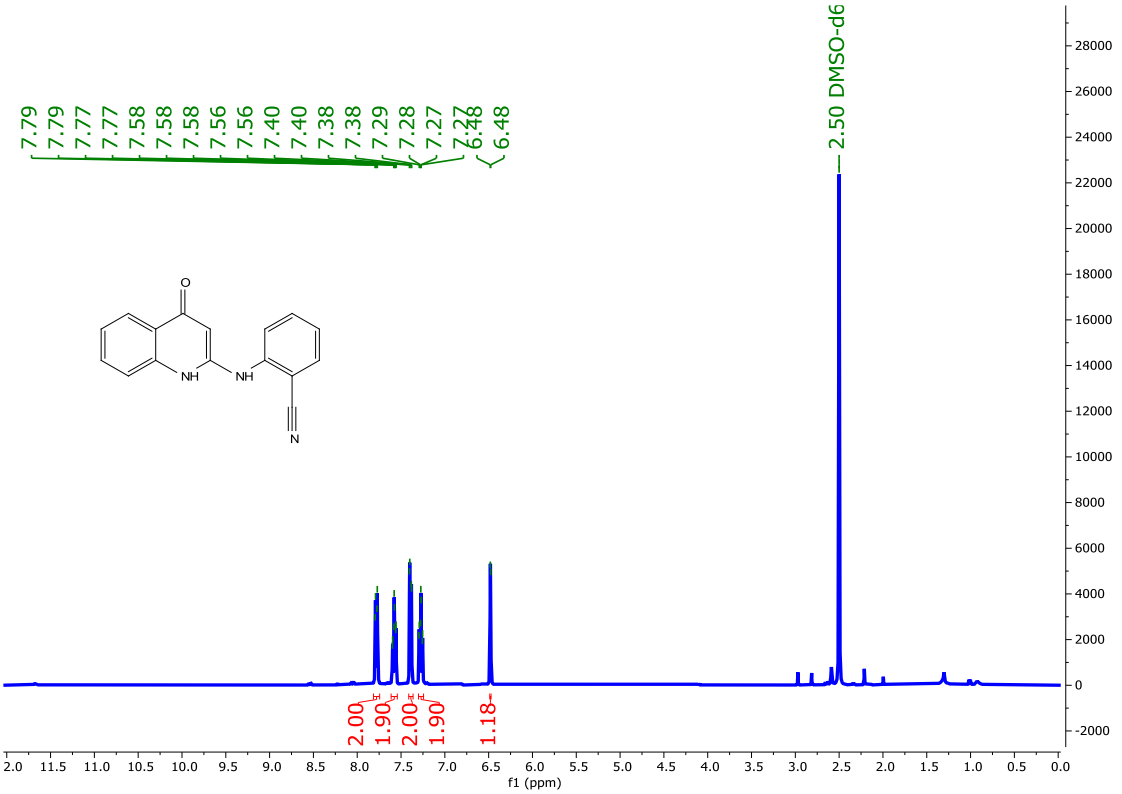
Spectrum 128: 11ak ^{1}H NMR (DMSO-d6, 400 MHz)



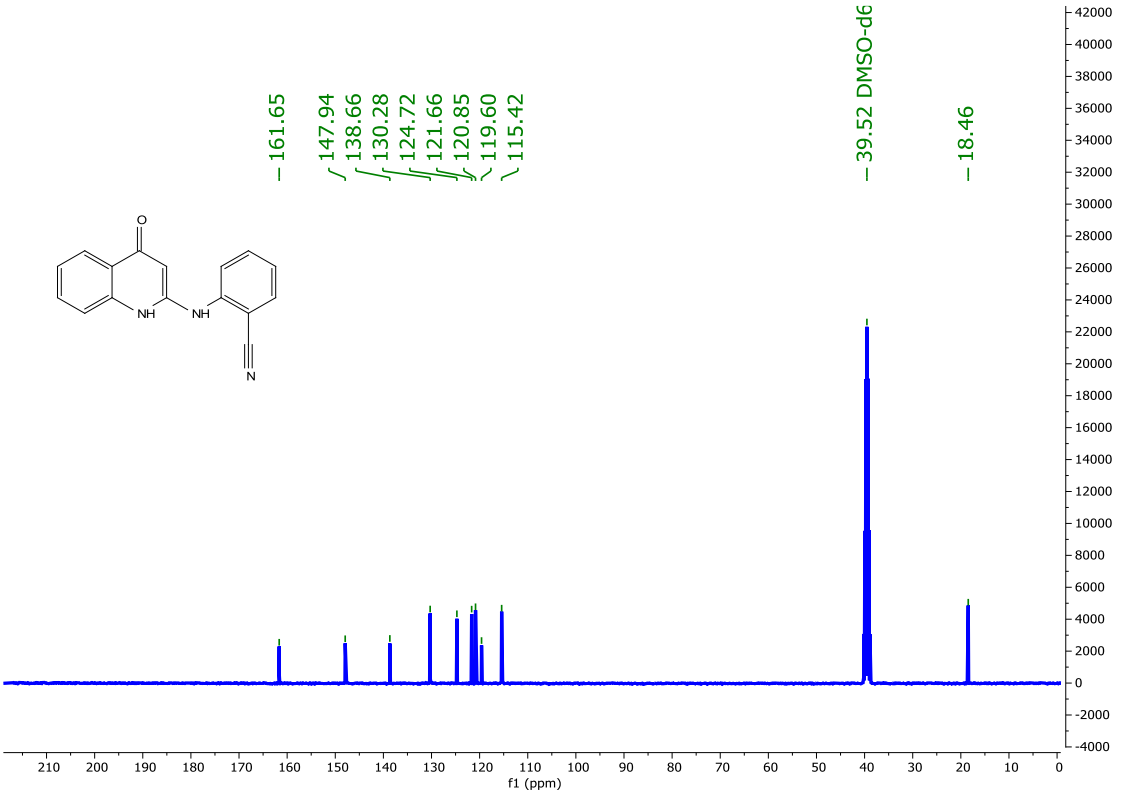
Spectrum 129: 11ak ^{13}C NMR (DMSO-d6, 101 MHz)



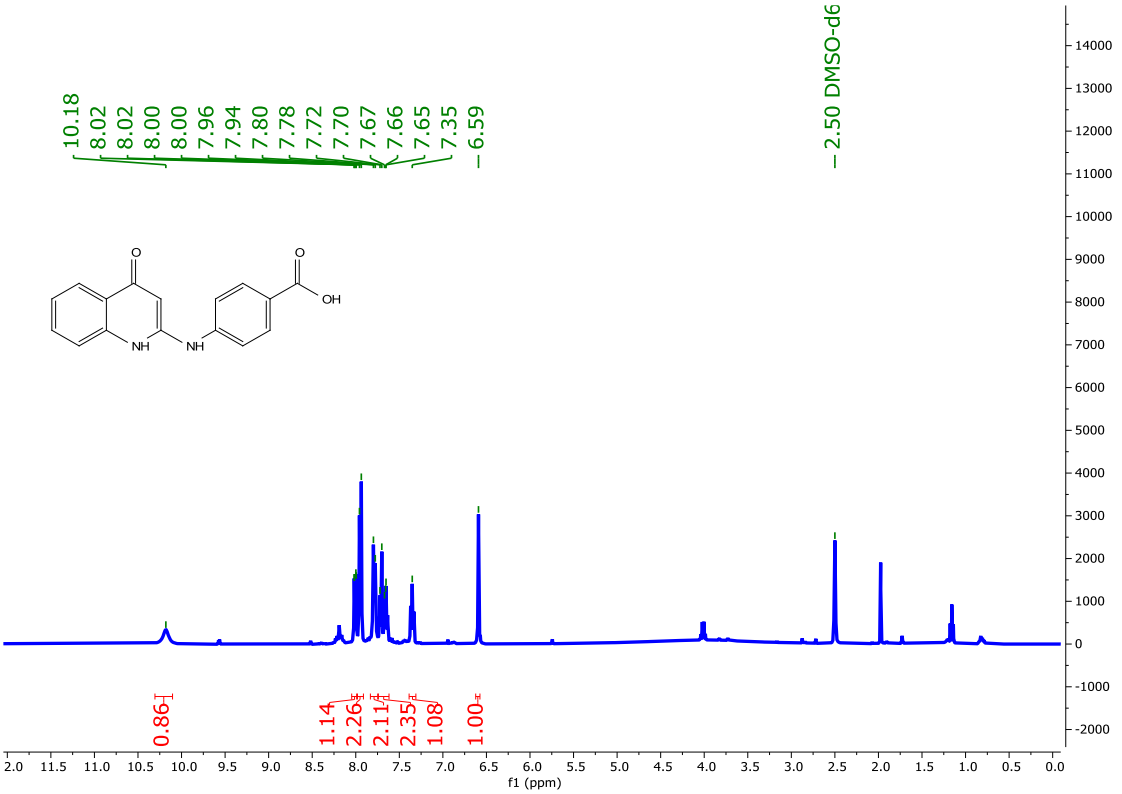
Spectrum 130: 11ak FTIR-ATR



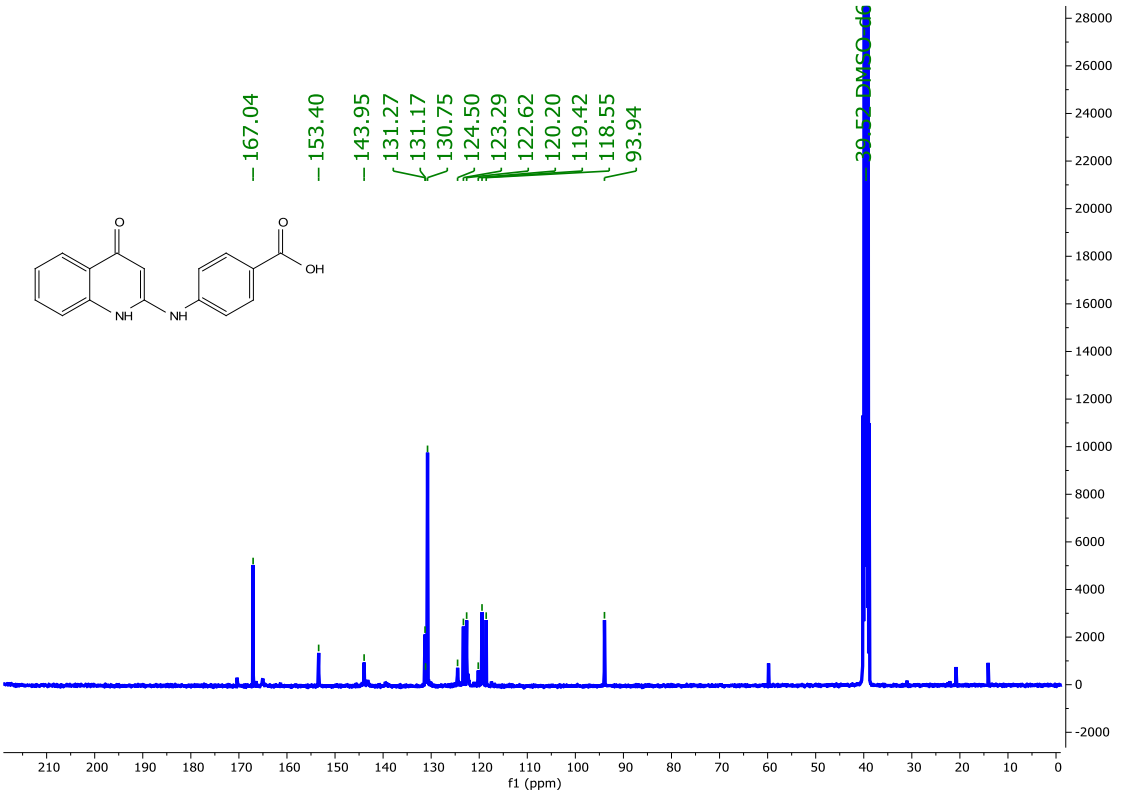
Spectrum 131: 11al ^{1}H NMR (DMSO-d6, 400 MHz)



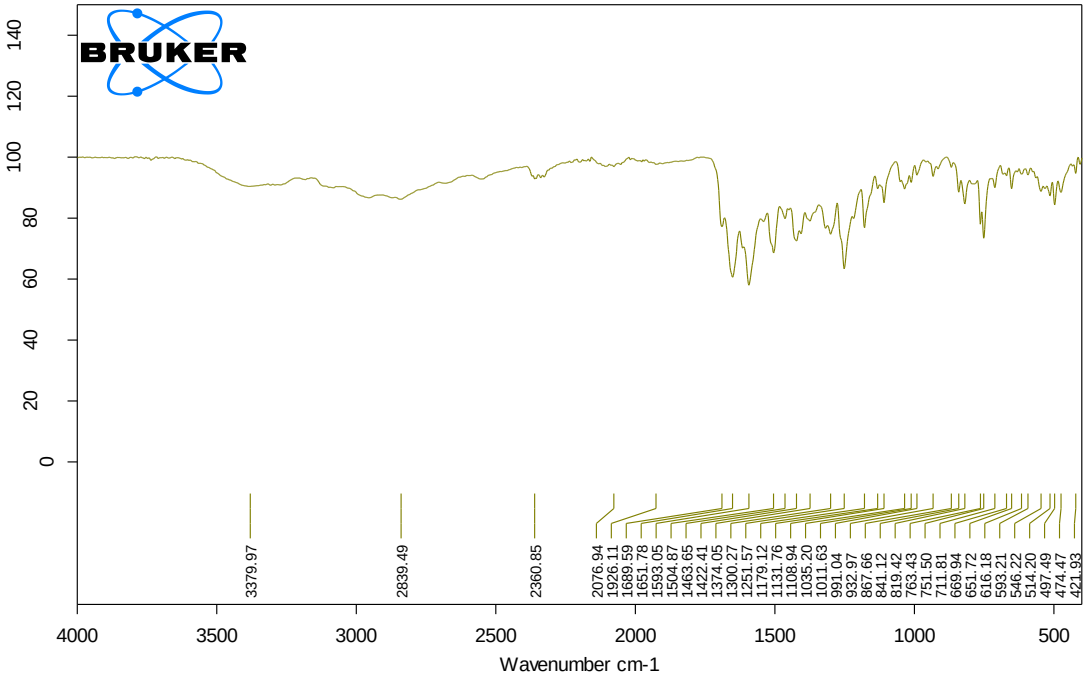
Spectrum 132: 11al ^{13}C NMR (DMSO-d6, 101 MHz)



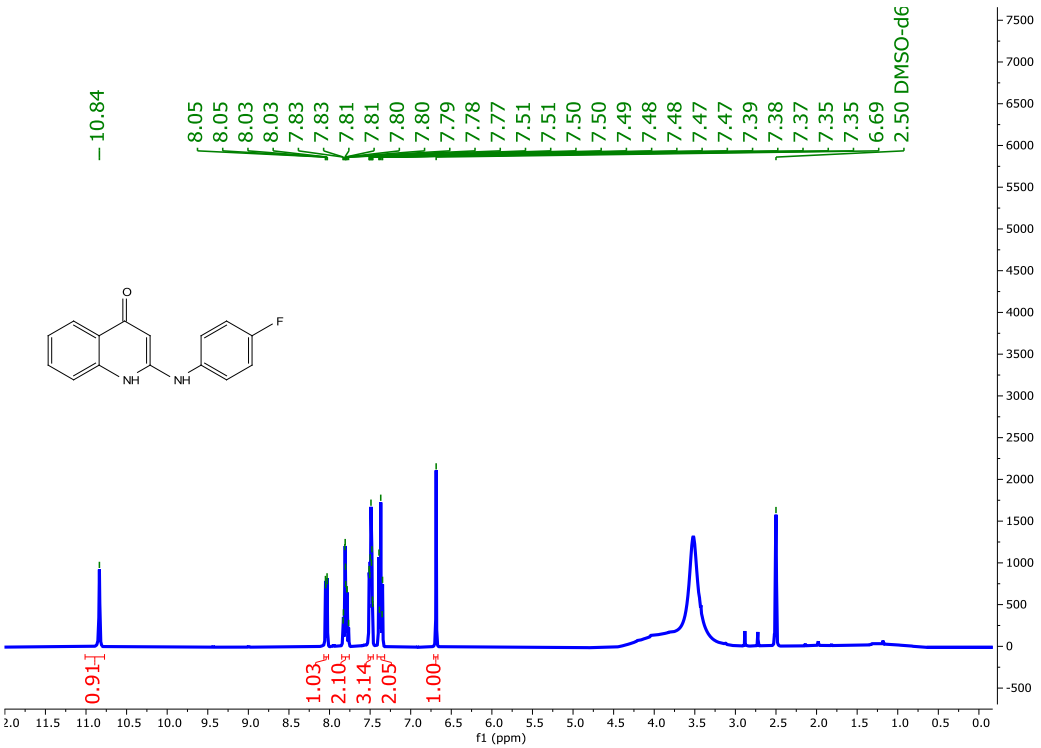
Spectrum 133: 11am ^{1}H NMR (DMSO-d6, 400 MHz)



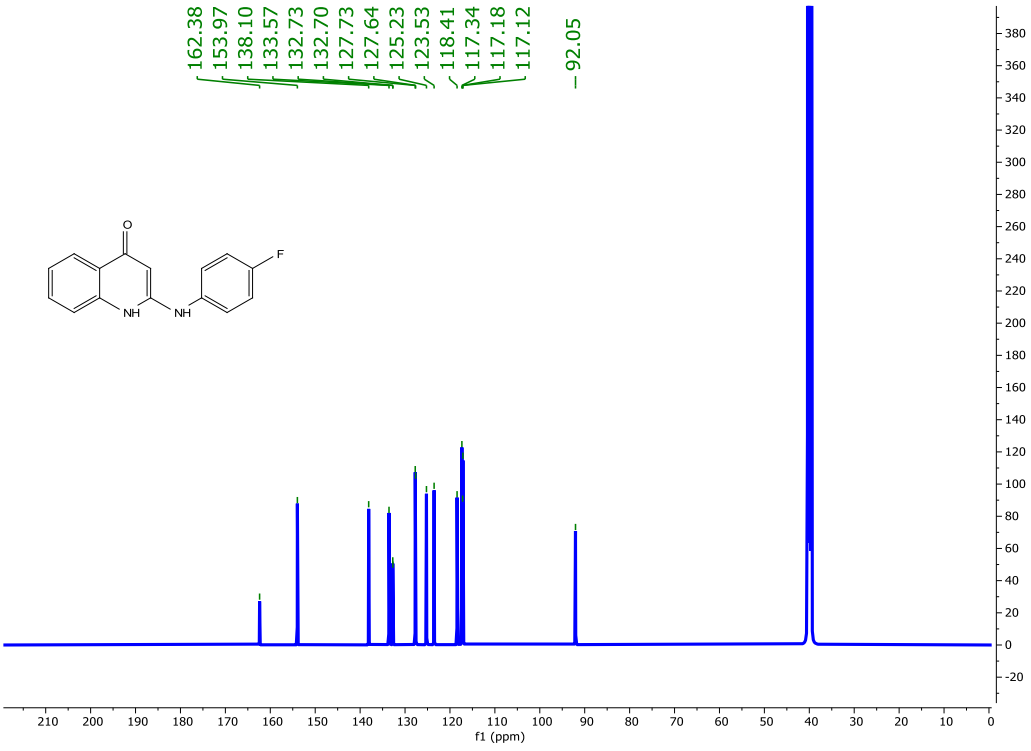
Spectrum 134: 11al ^{13}C NMR (DMSO-d6, 101 MHz)



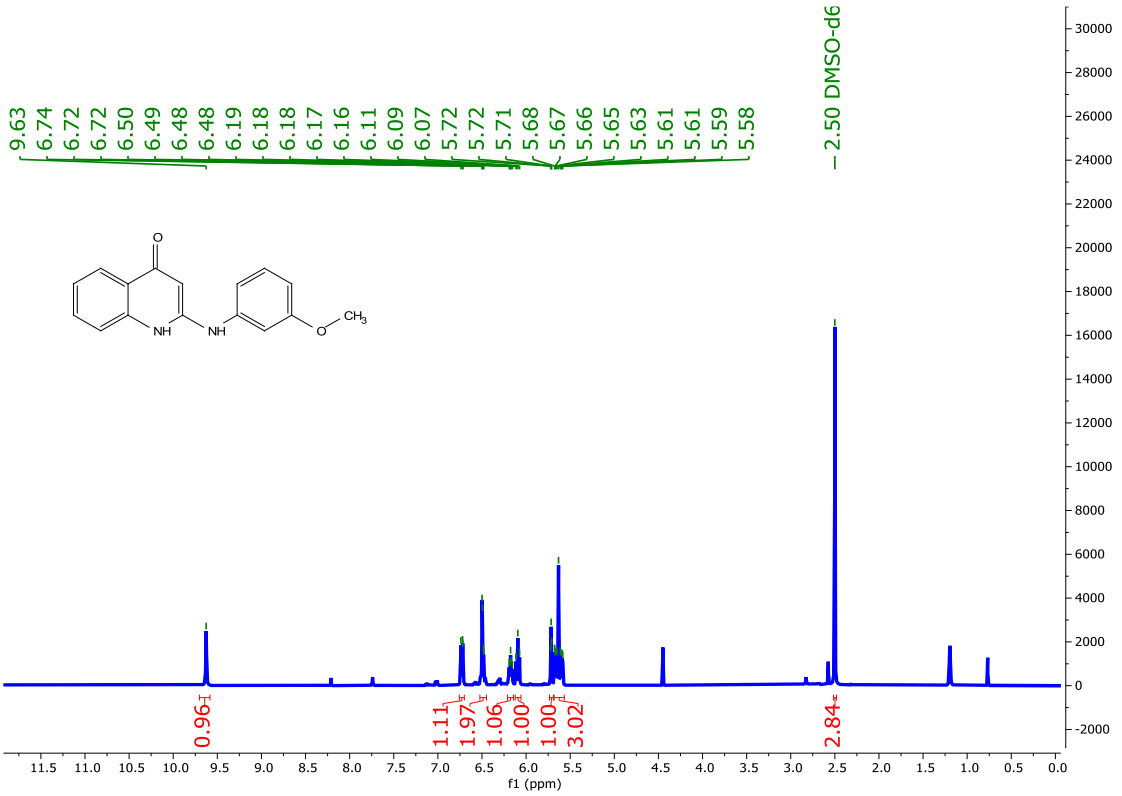
Spectrum 135: 11al FTIR-ATR



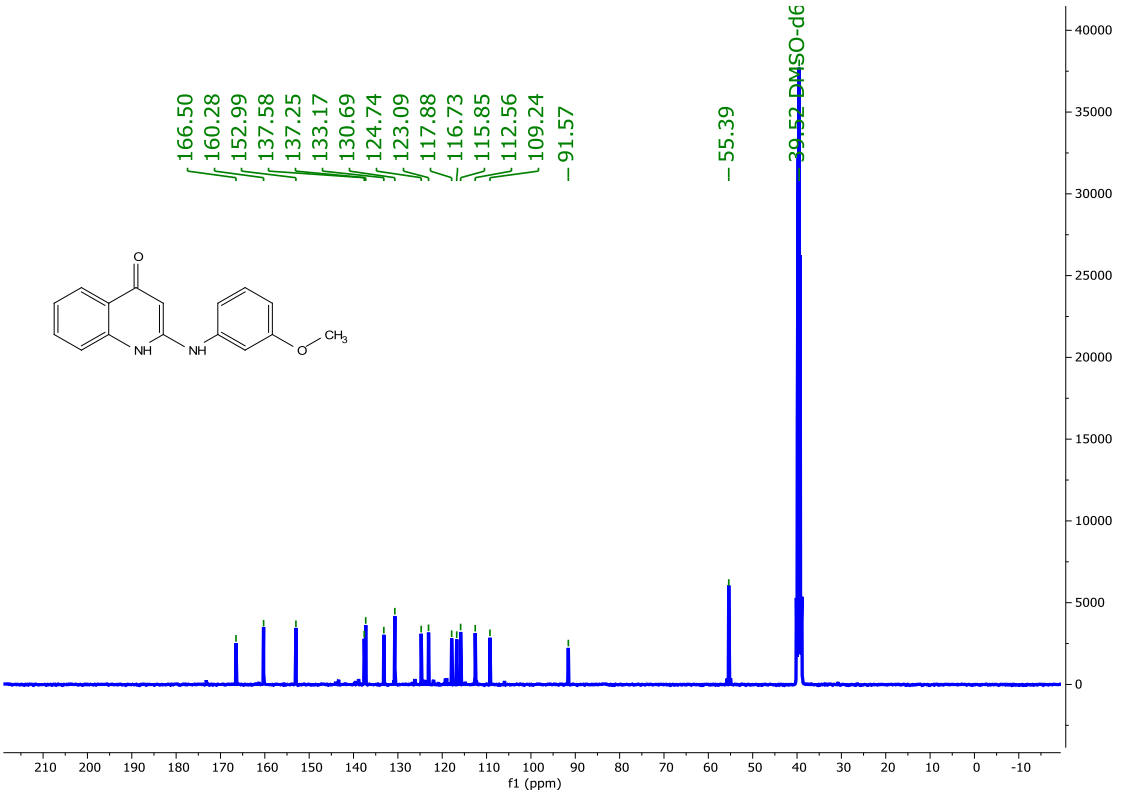
Spectrum 136: 11an ^{1}H NMR (DMSO-d6, 400 MHz)



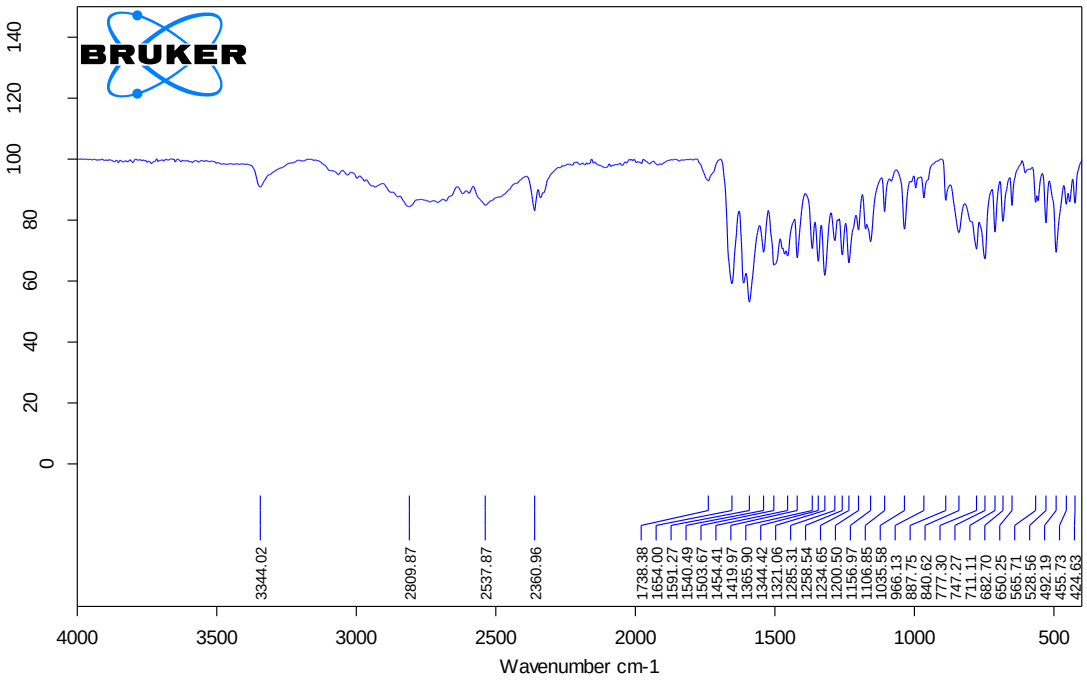
Spectrum 137: 11an ^{13}C NMR (DMSO-d6, 101 MHz)



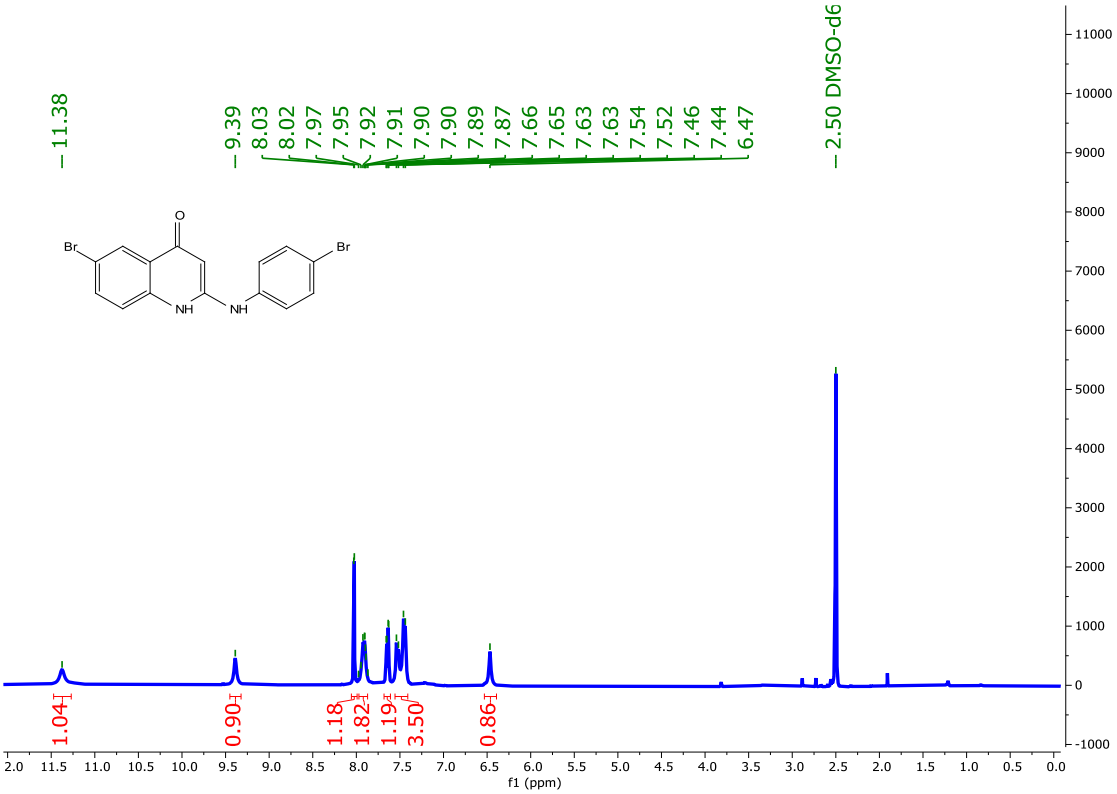
Spectrum 138: 11ap ^{1}H NMR (DMSO-d6, 400 MHz)



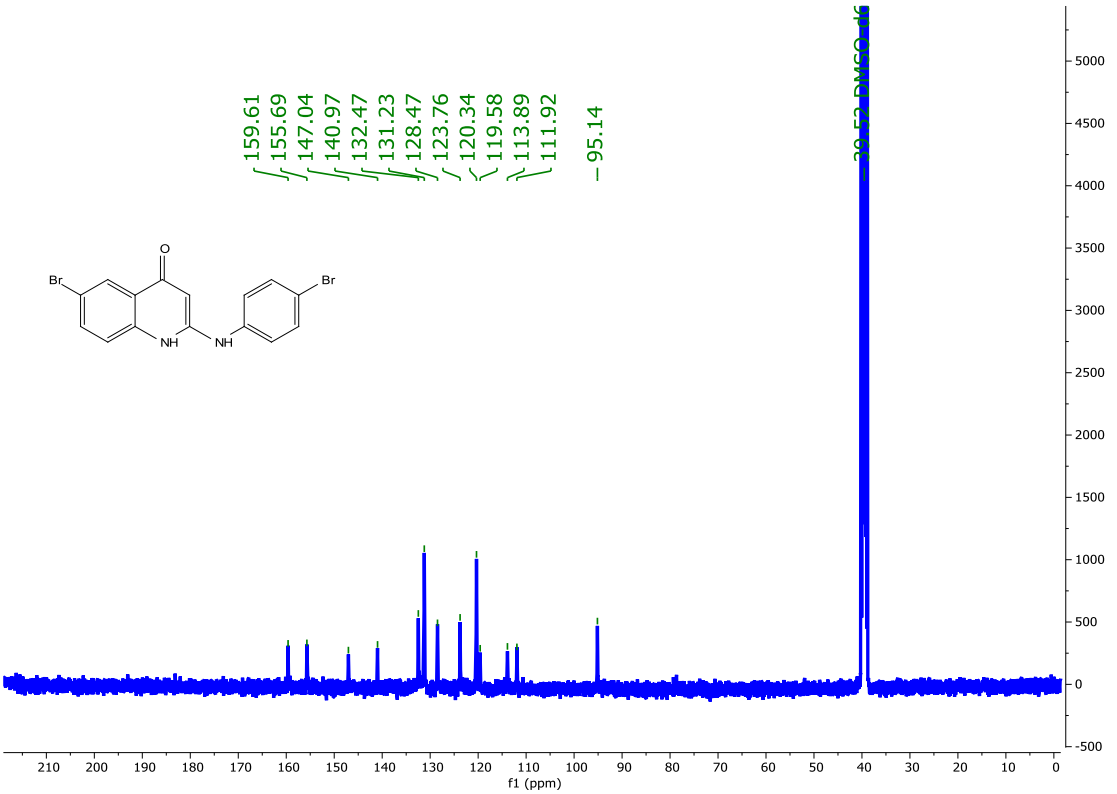
Spectrum 139: 11ap ^{13}C NMR (DMSO-d6, 101 MHz)



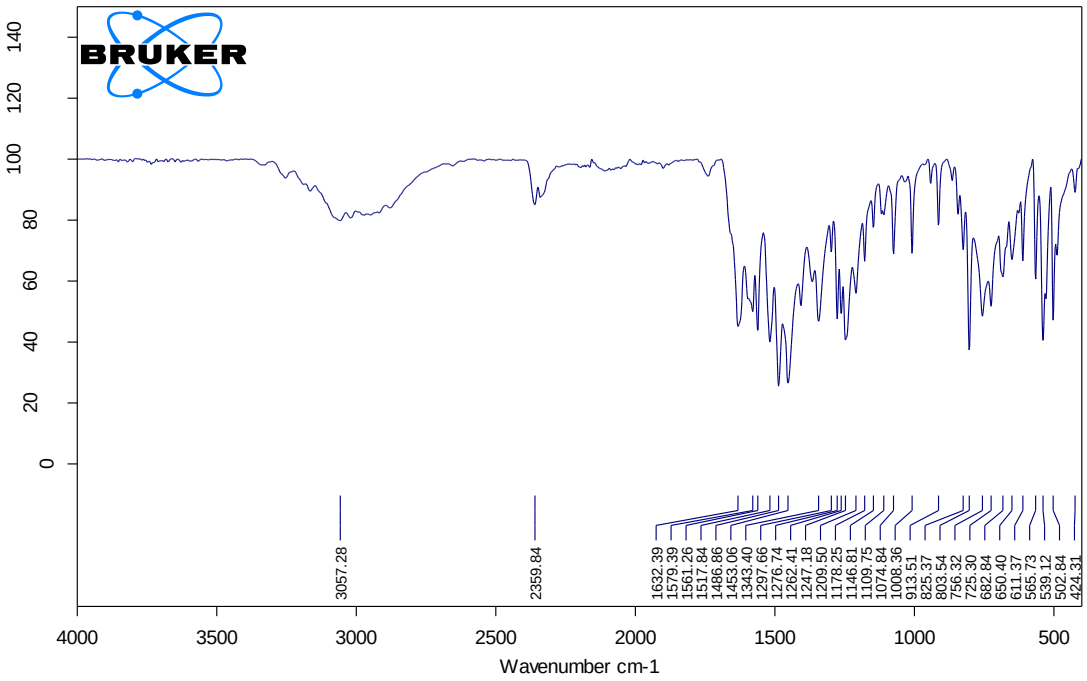
Spectrum 140: 11ap FTIR-ATR



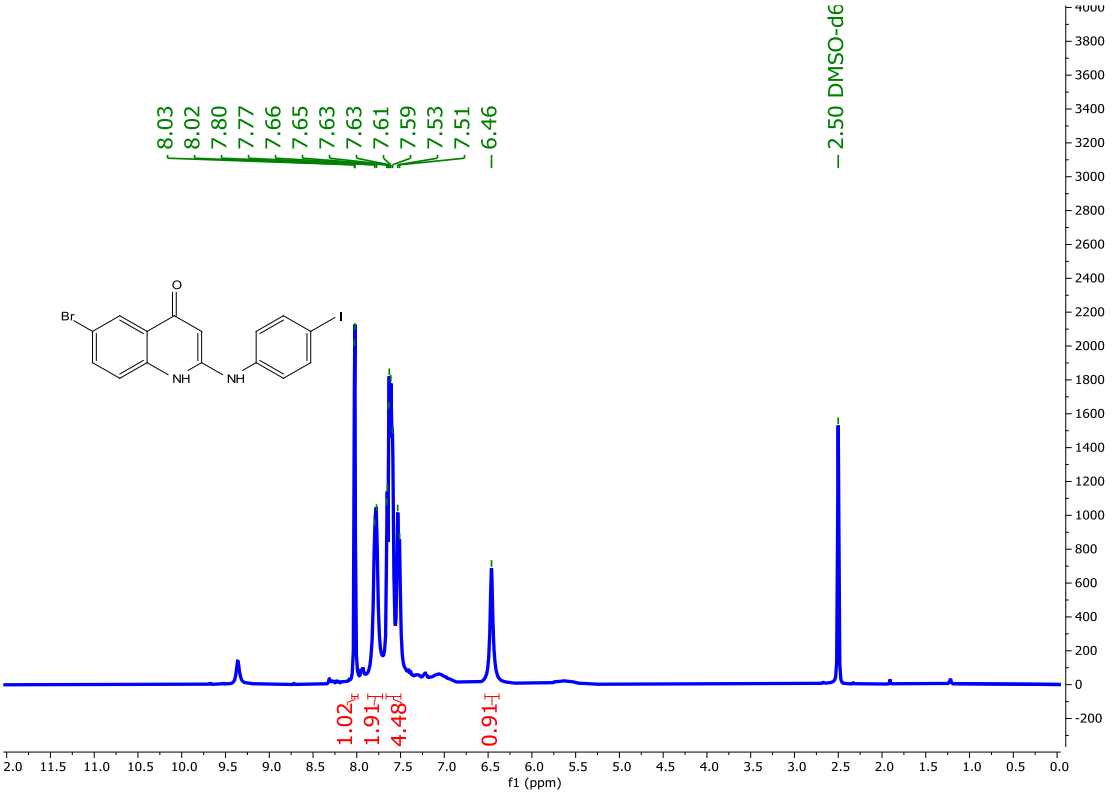
Spectrum 141: 11ba ^{1}H NMR (DMSO-d6, 400 MHz)



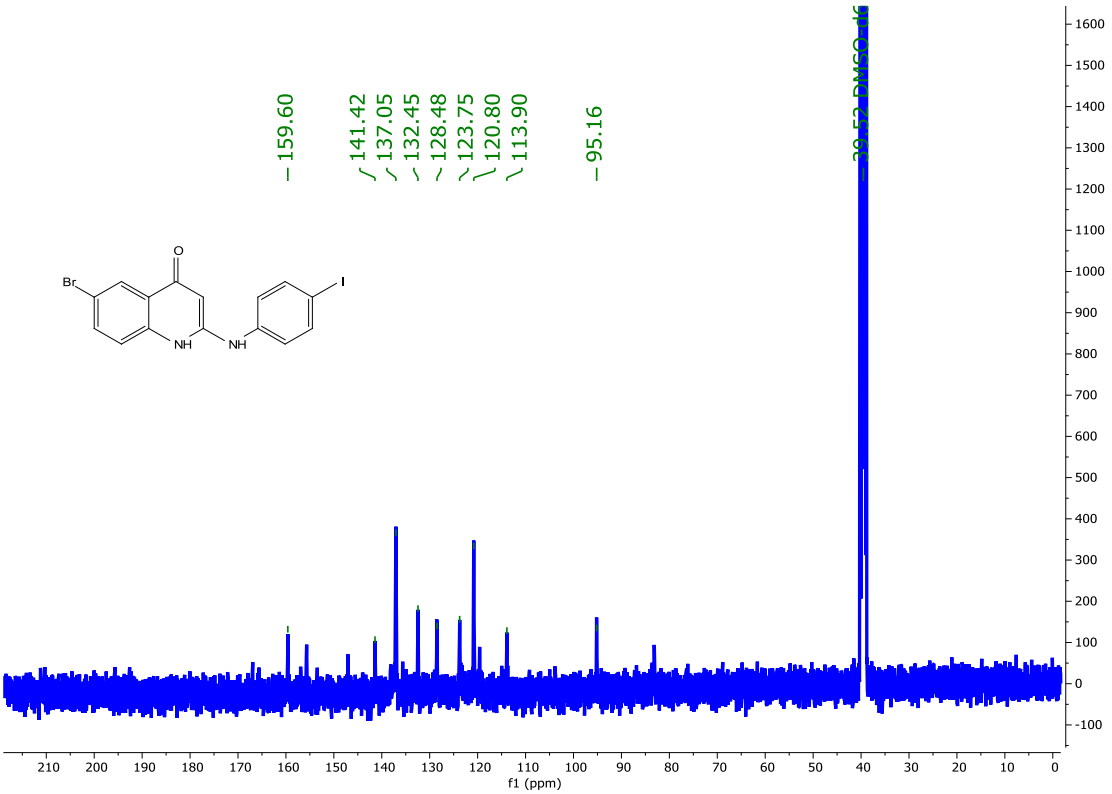
Spectrum 142: 11ba ^{13}C NMR (DMSO-d6, 101 MHz)



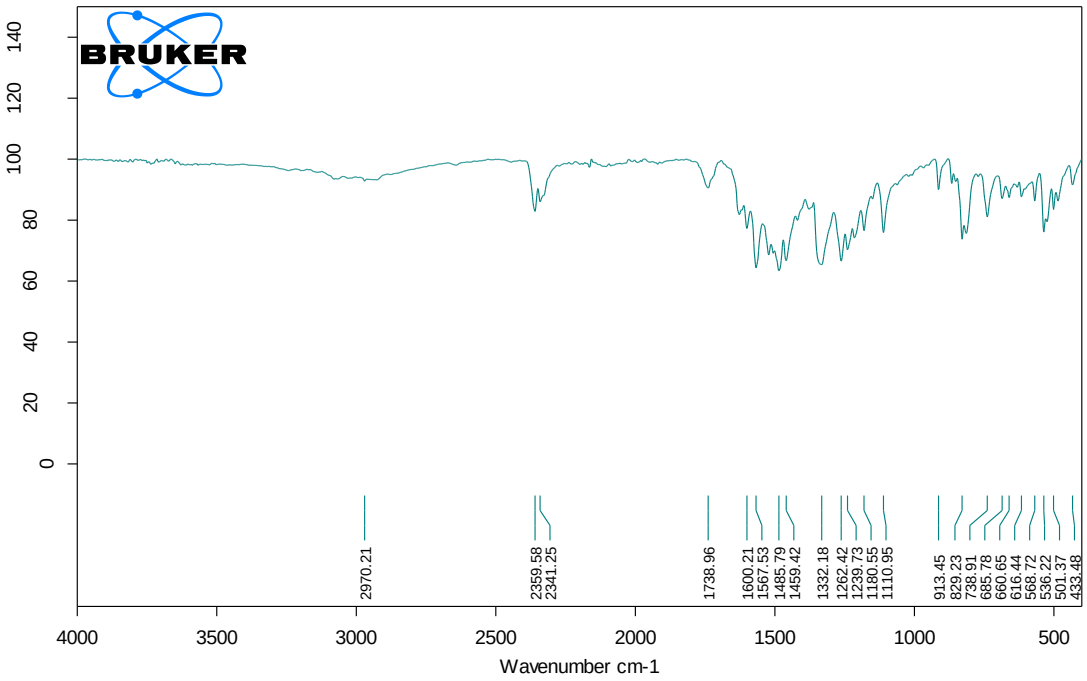
Spectrum 143: 11ba FTIR-ATR



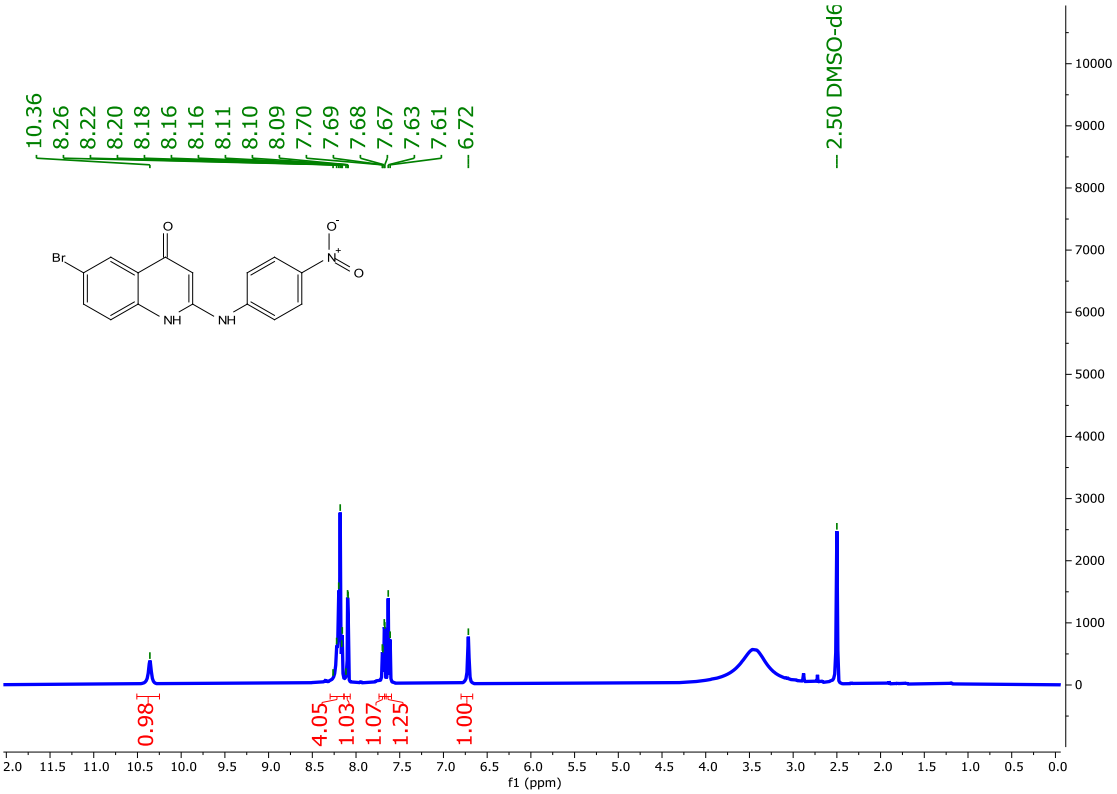
Spectrum 144: 11bb ^{1}H NMR (DMSO-d6, 400 MHz)



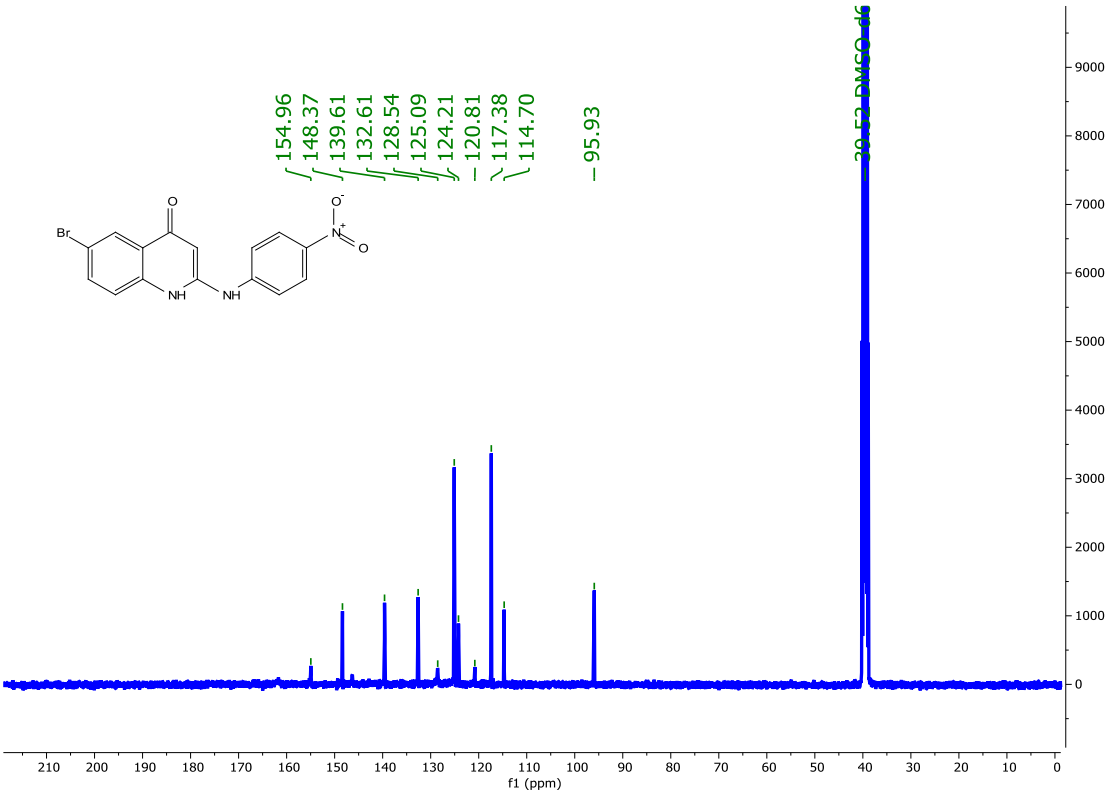
Spectrum 145: 11bb ^{13}C NMR (DMSO-d6, 101 MHz)



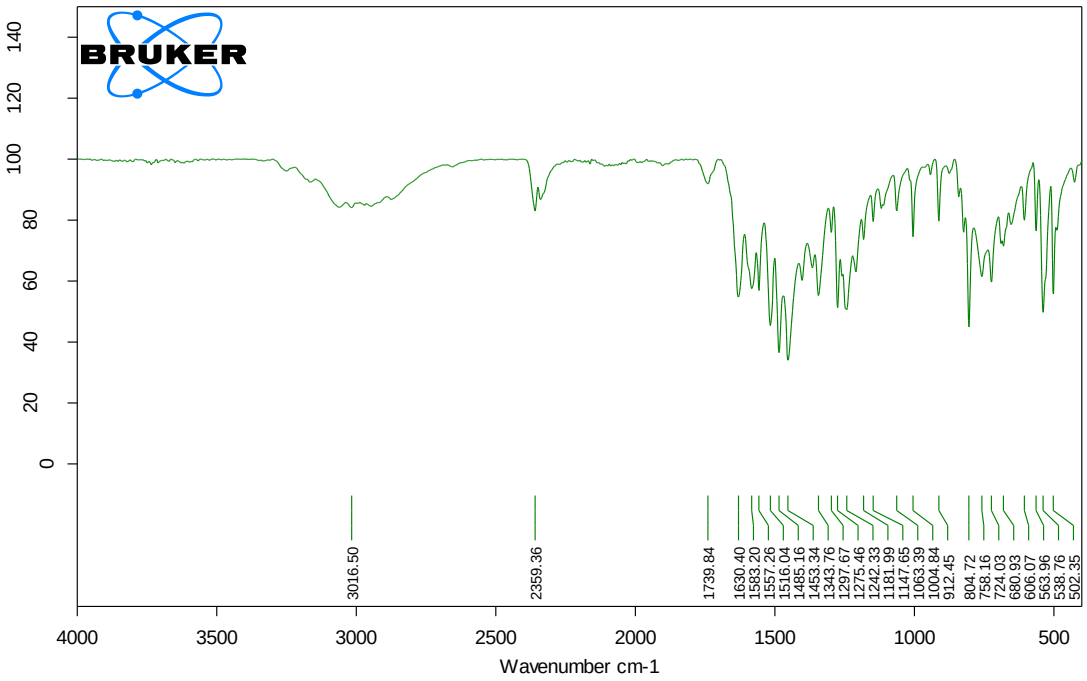
Spectrum 146: 11bb FTIR-ATR



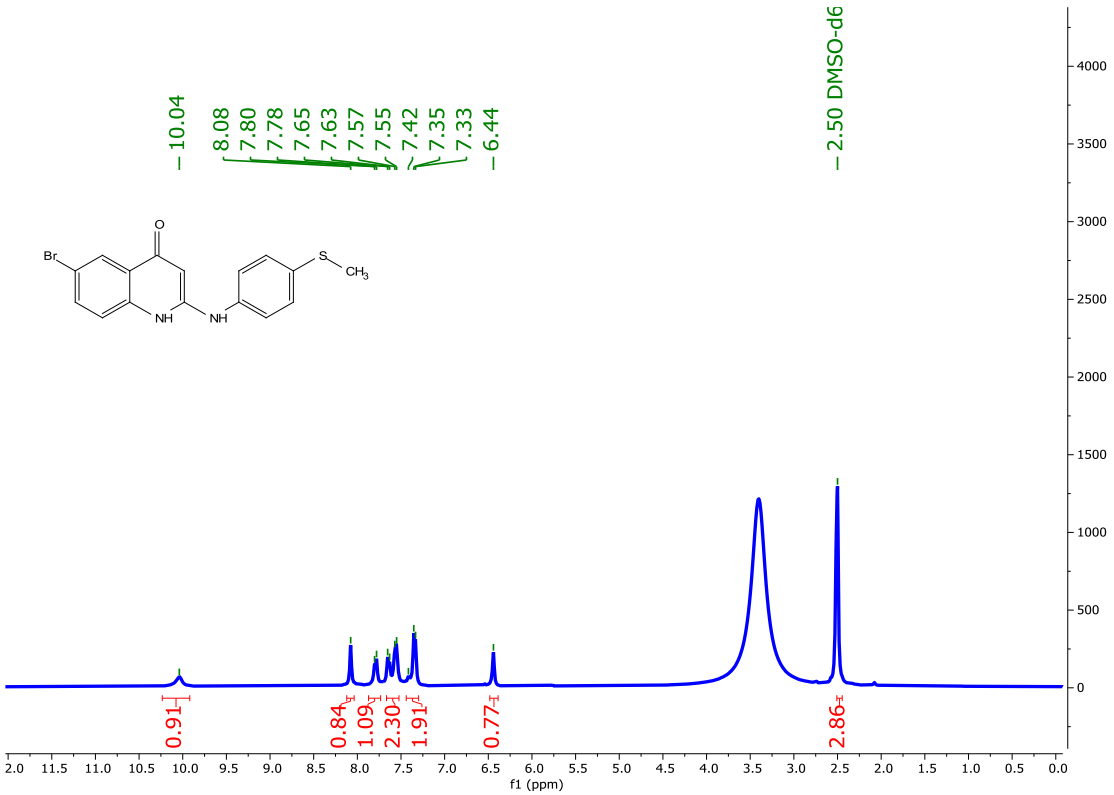
Spectrum 147: 11bd ^{1}H NMR (DMSO-d6, 400 MHz)



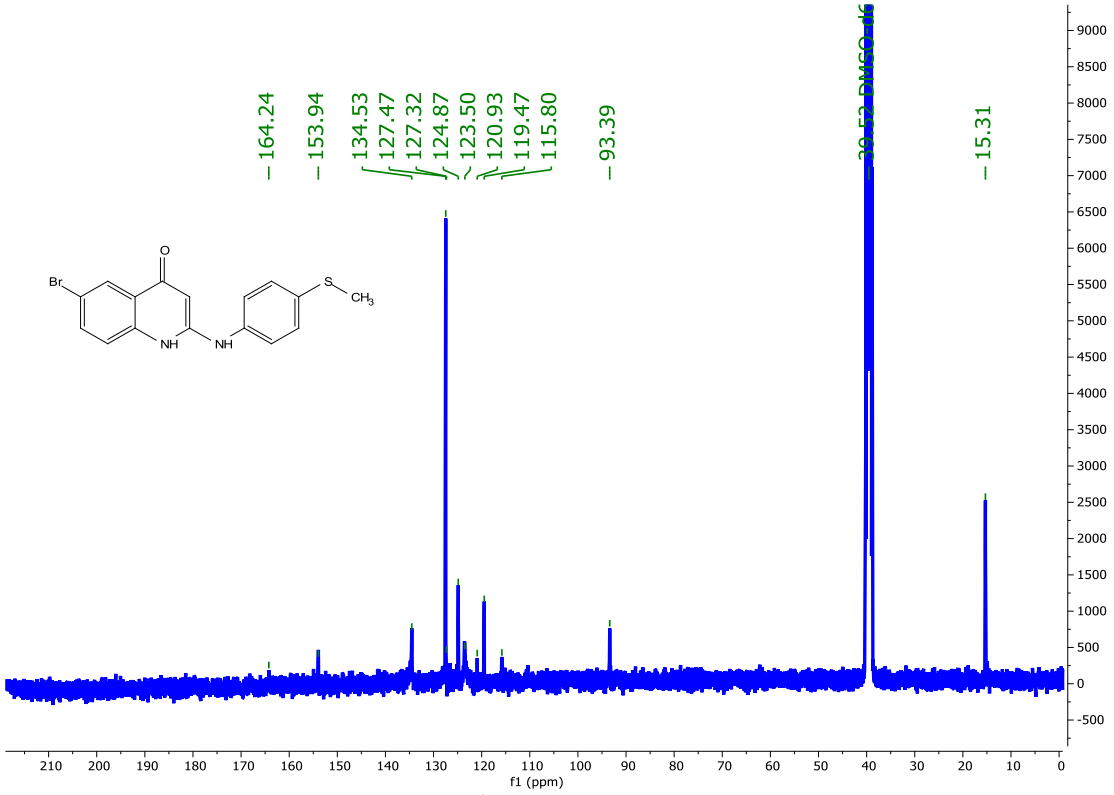
Spectrum 148: 11bd ^{13}C NMR (DMSO-d6, 101 MHz)



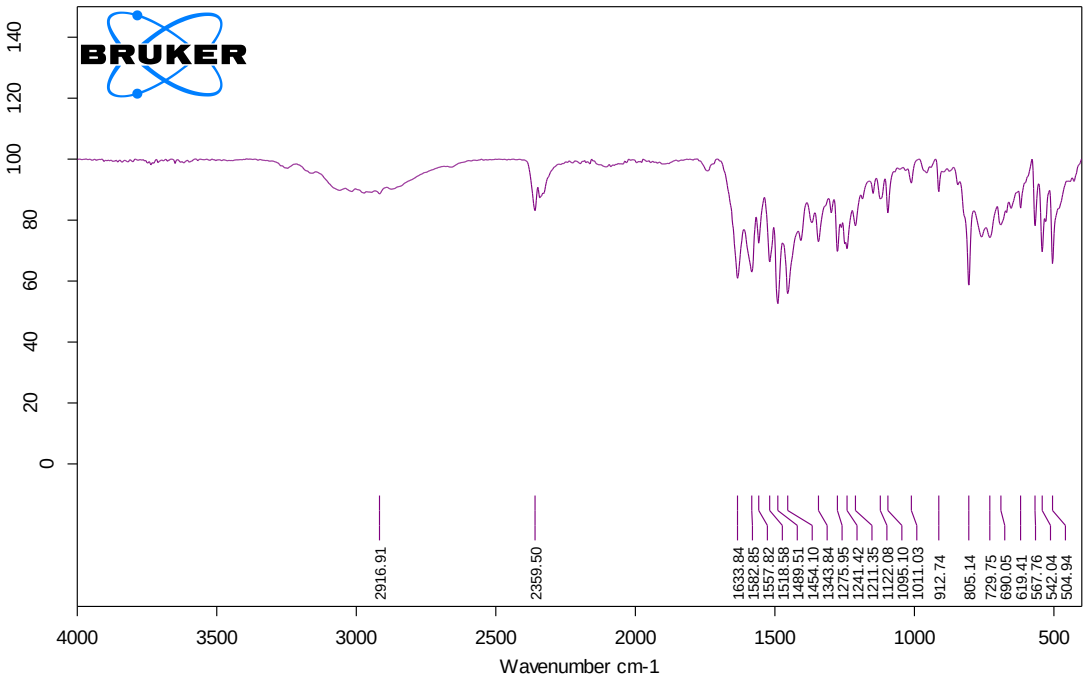
Spectrum 149: 11bd FTIR-ATR



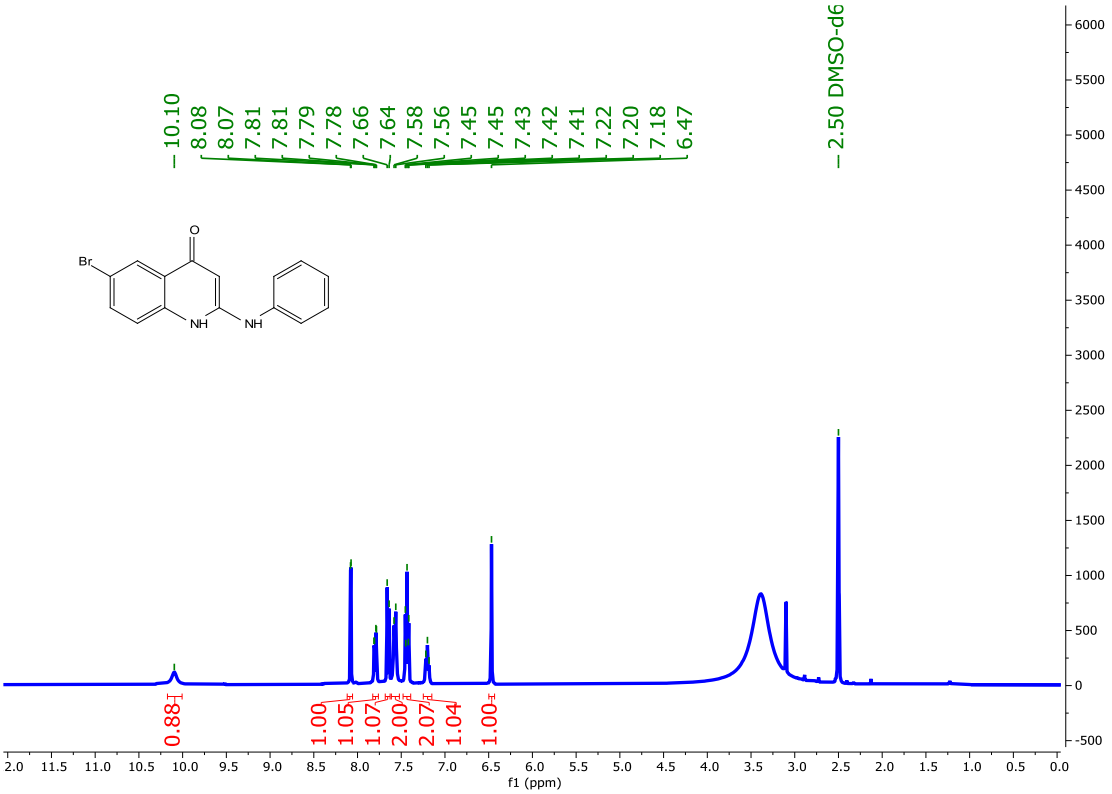
Spectrum 150: 11bf ^{1}H NMR (DMSO-d6, 400 MHz)



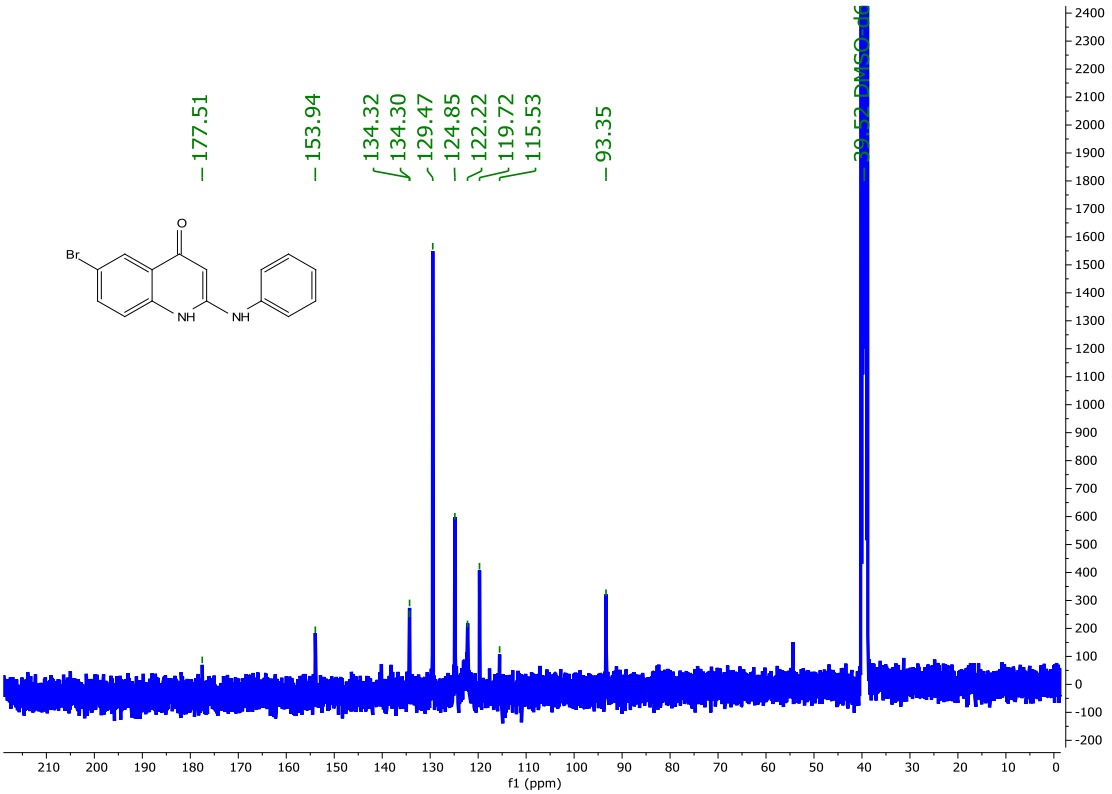
Spectrum 151: 11bf ^{13}C NMR (DMSO-d6, 101 MHz)



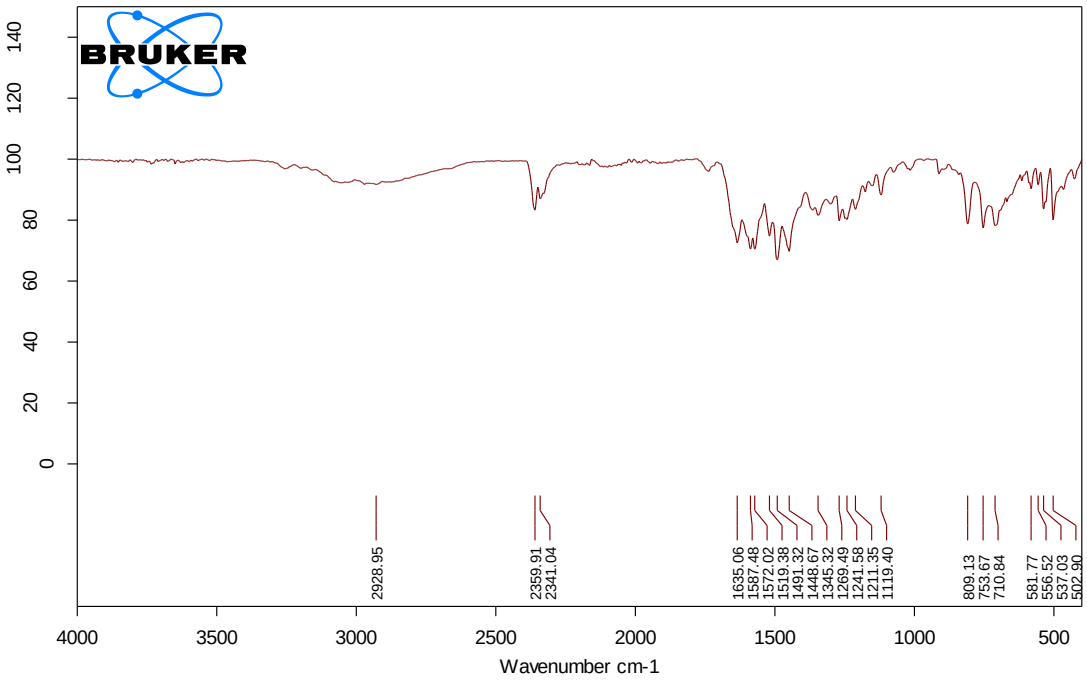
Spectrum 152: 11bf FTIR-ATR



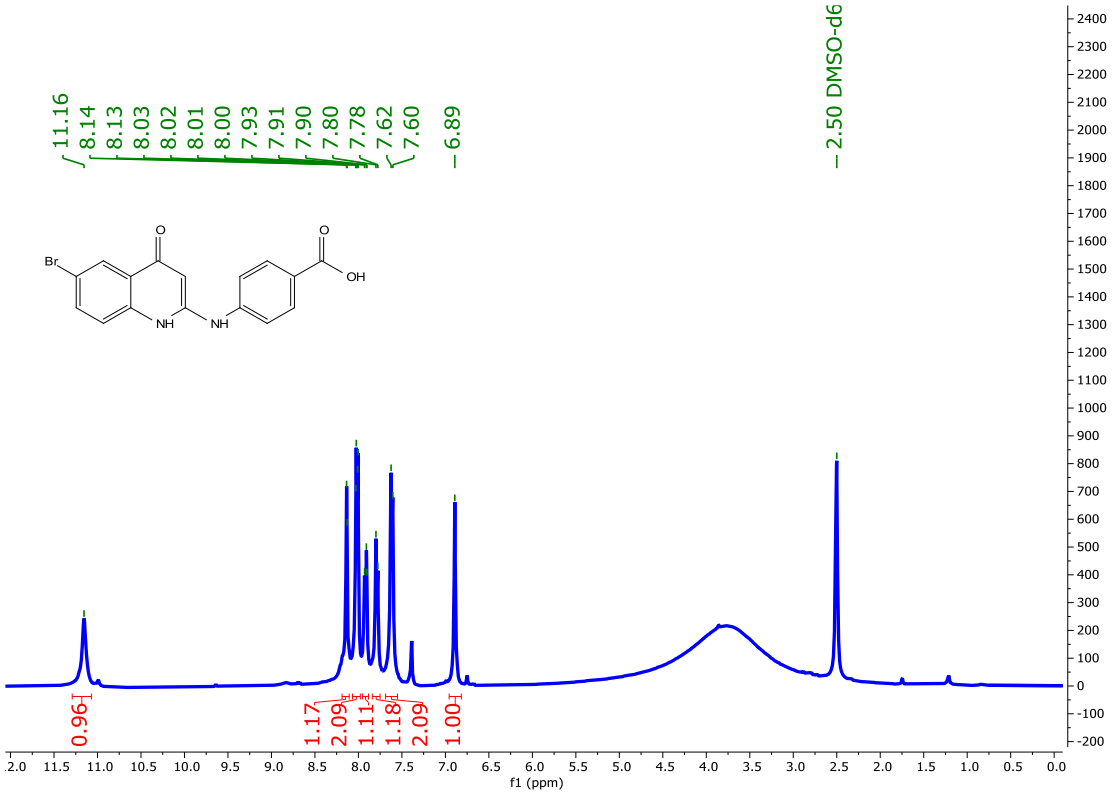
Spectrum 153: 11bk ^{1}H NMR (DMSO-d6, 400 MHz)



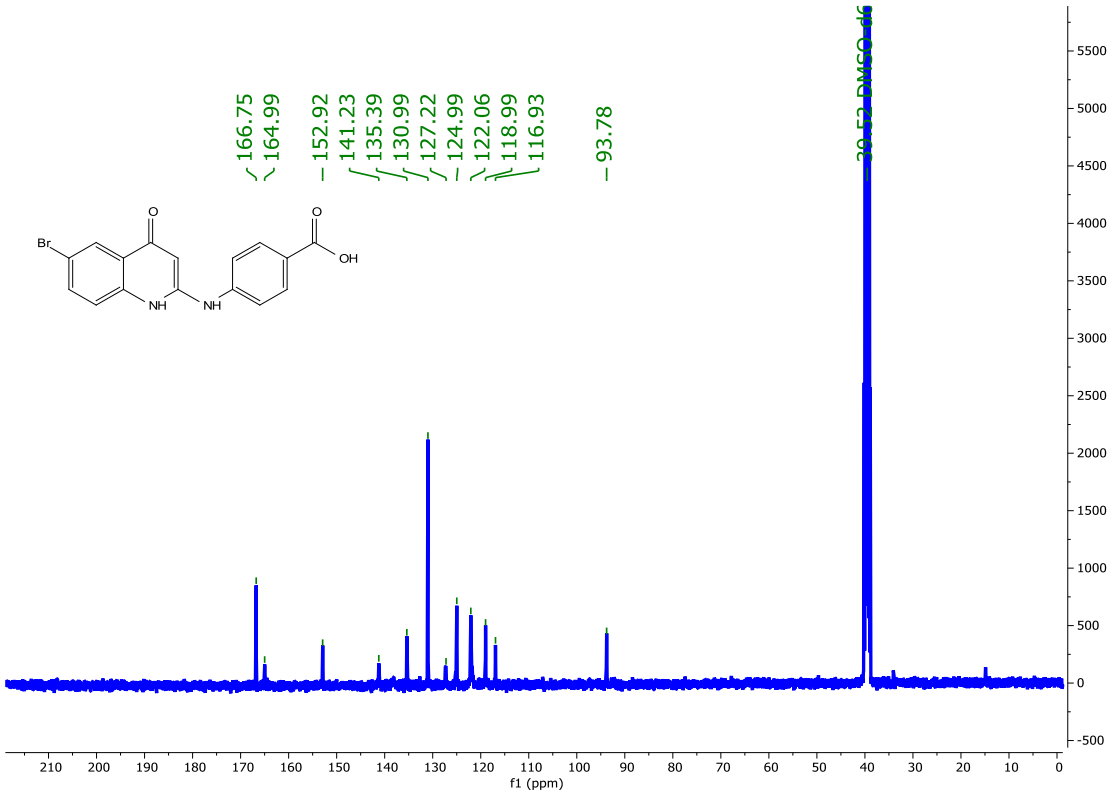
Spectrum 154: 11bk ^{13}C NMR (DMSO-d6, 101 MHz)



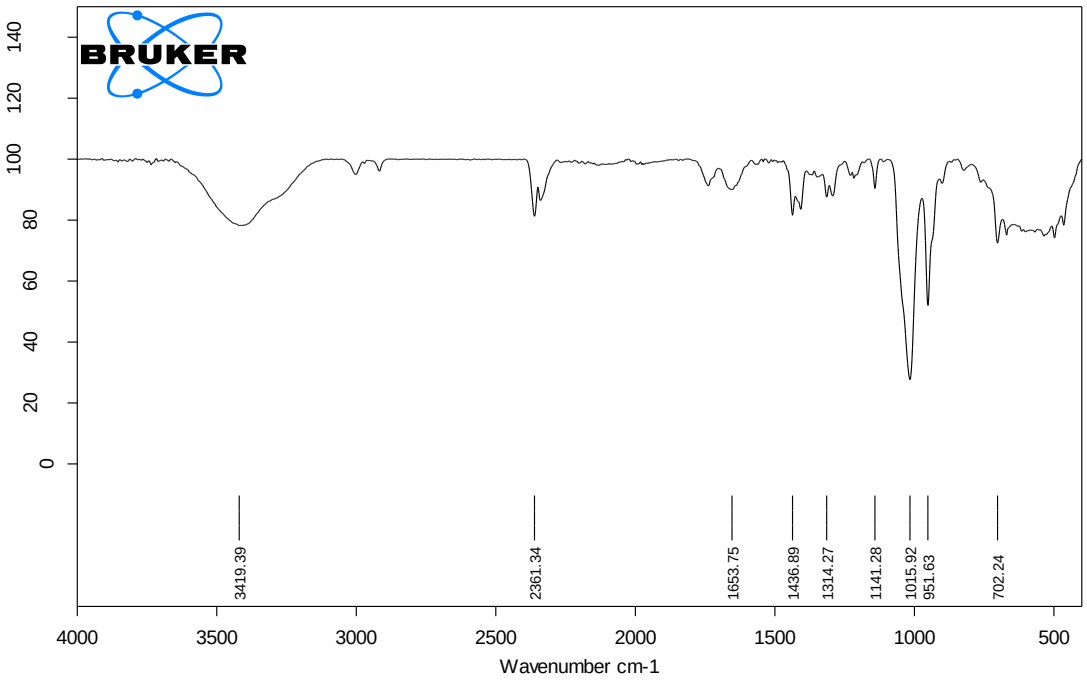
Spectrum 155: 11bk FTIR-ATR



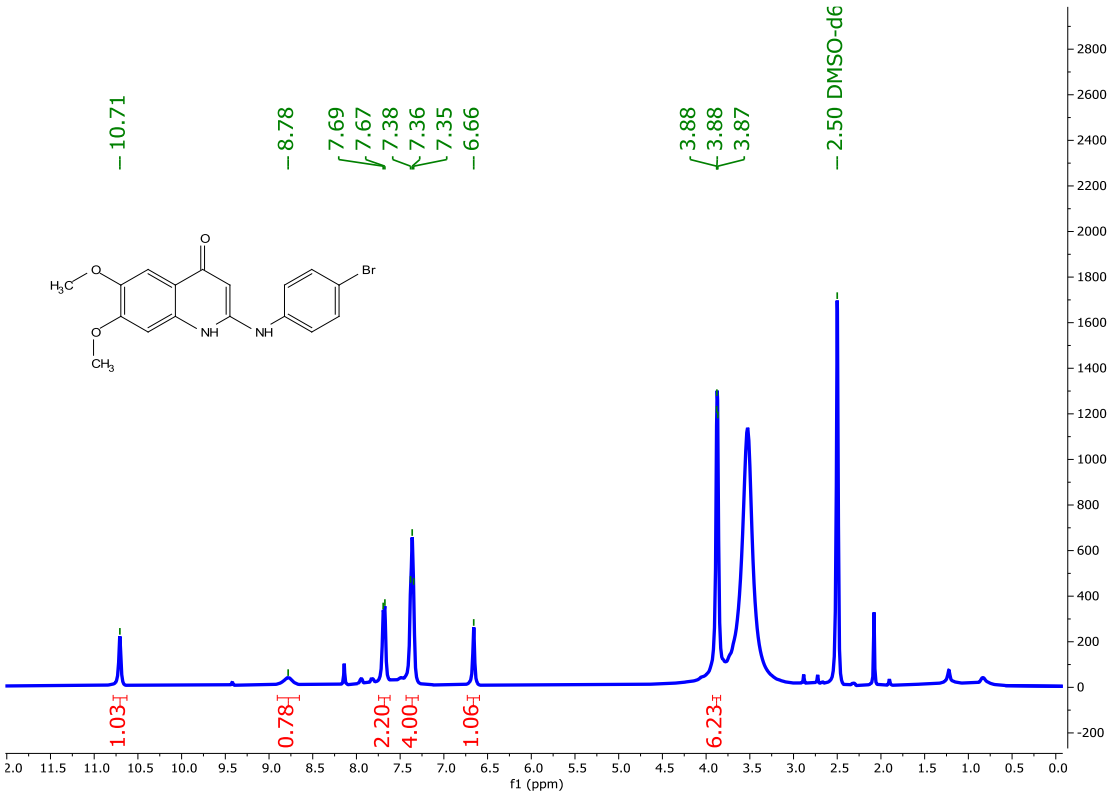
Spectrum 156: 11bm ^{1}H NMR (DMSO-d6, 400 MHz)



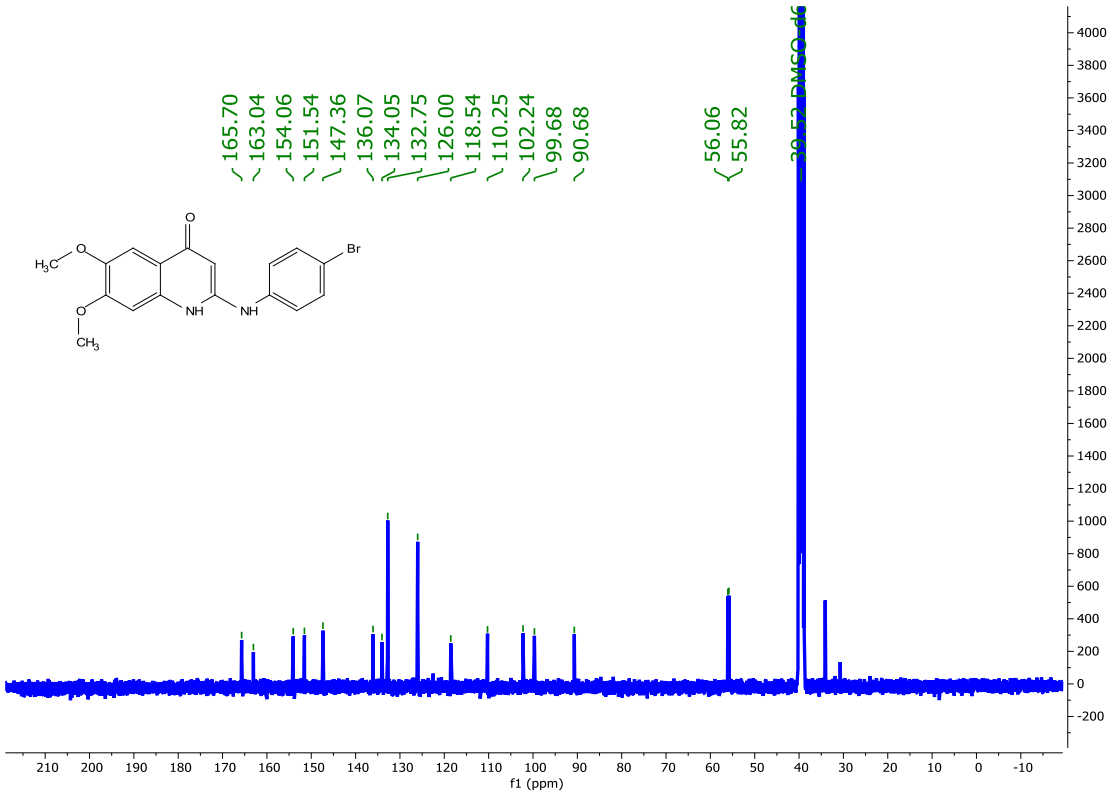
Spectrum 157: 11bm ^{13}C NMR (DMSO-d6, 101 MHz)



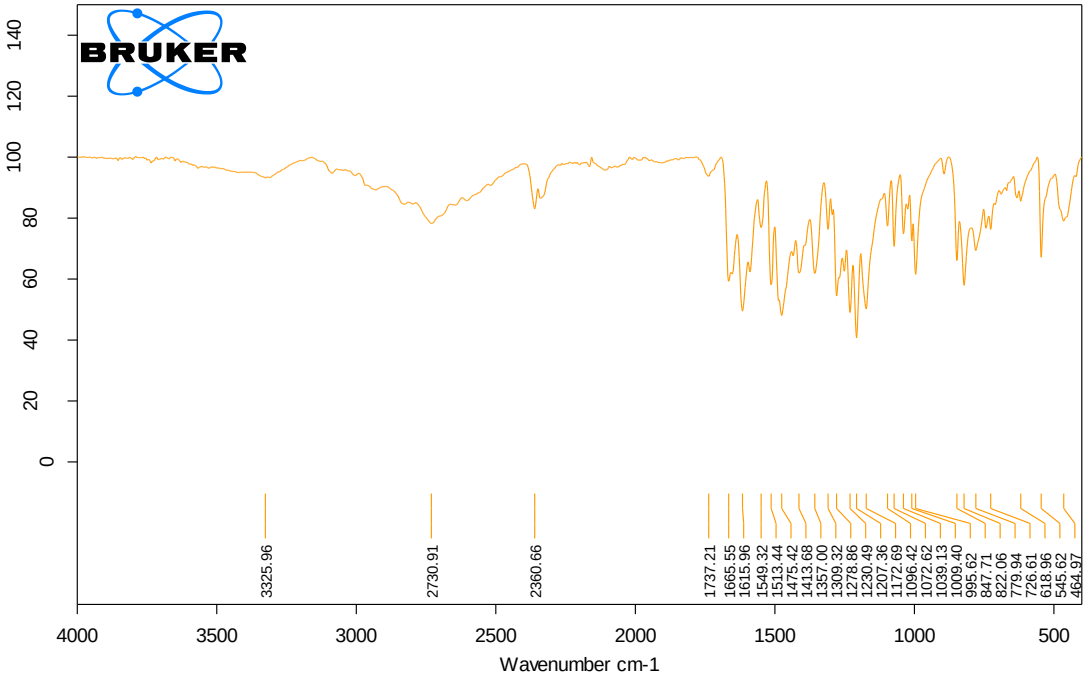
Spectrum 158: 11bm FTIR-ATR



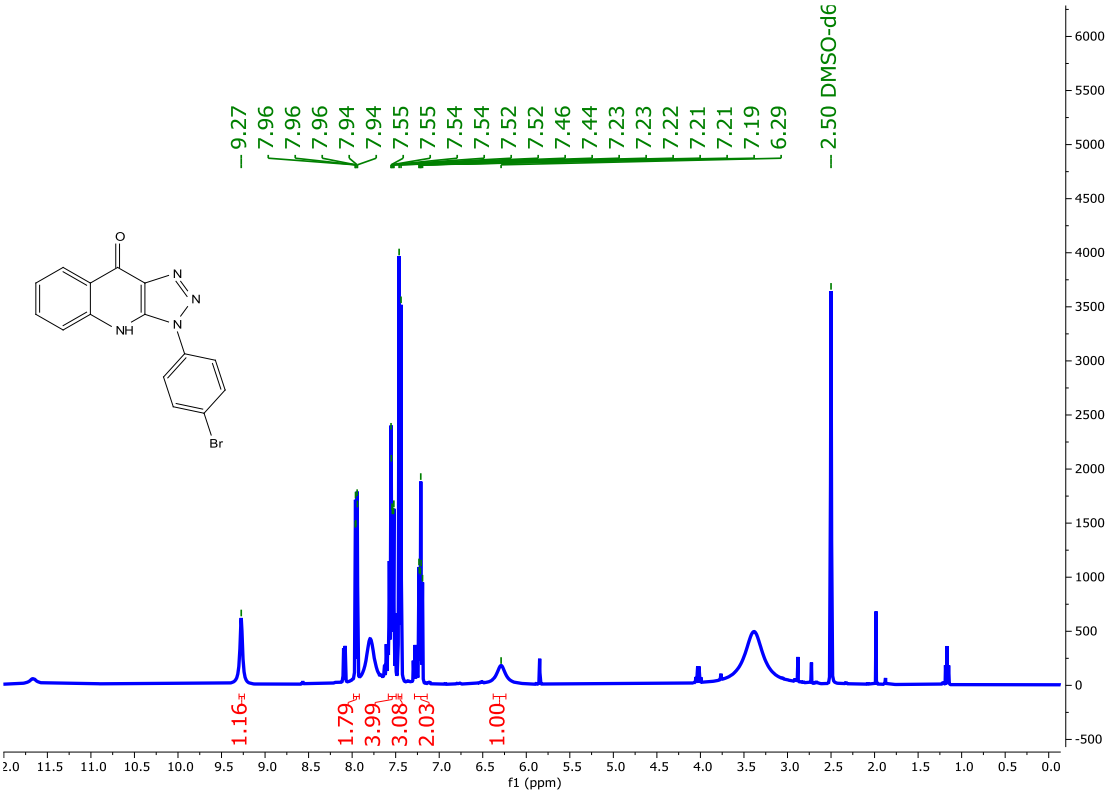
Spectrum 159: 11ca ^{1}H NMR (DMSO-d6, 400 MHz)



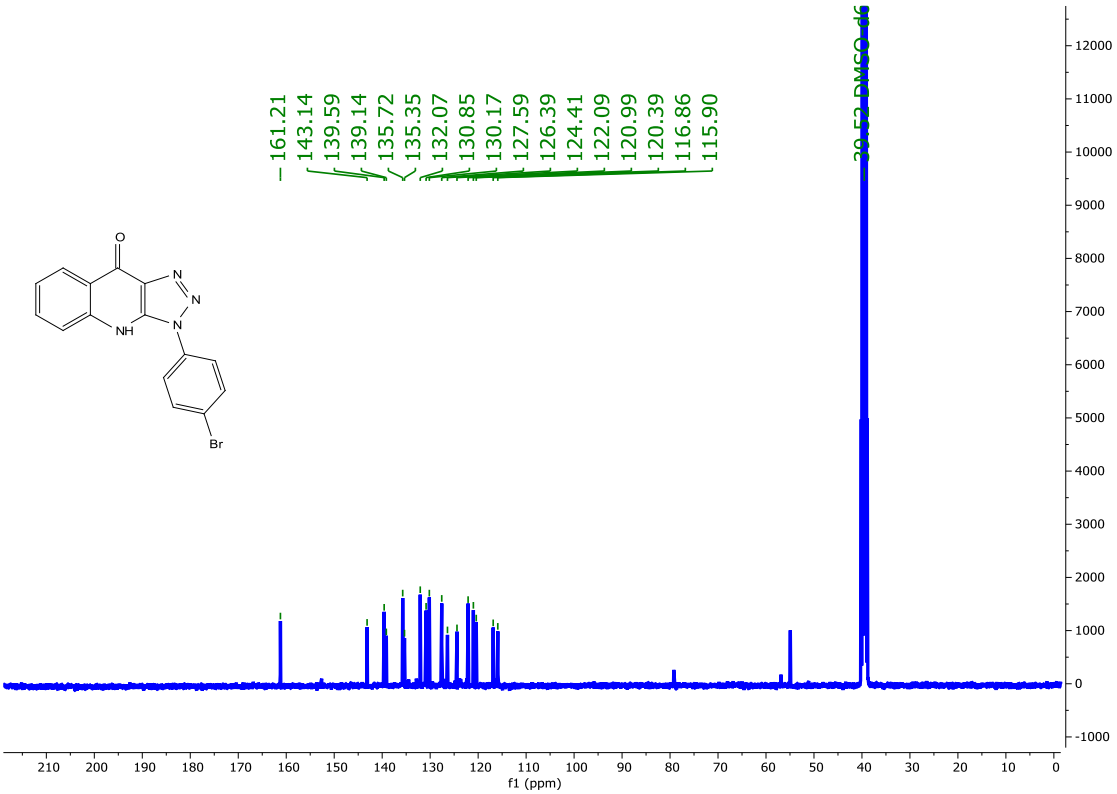
Spectrum 160: 11ca ^{13}C NMR (DMSO-d6, 101 MHz)



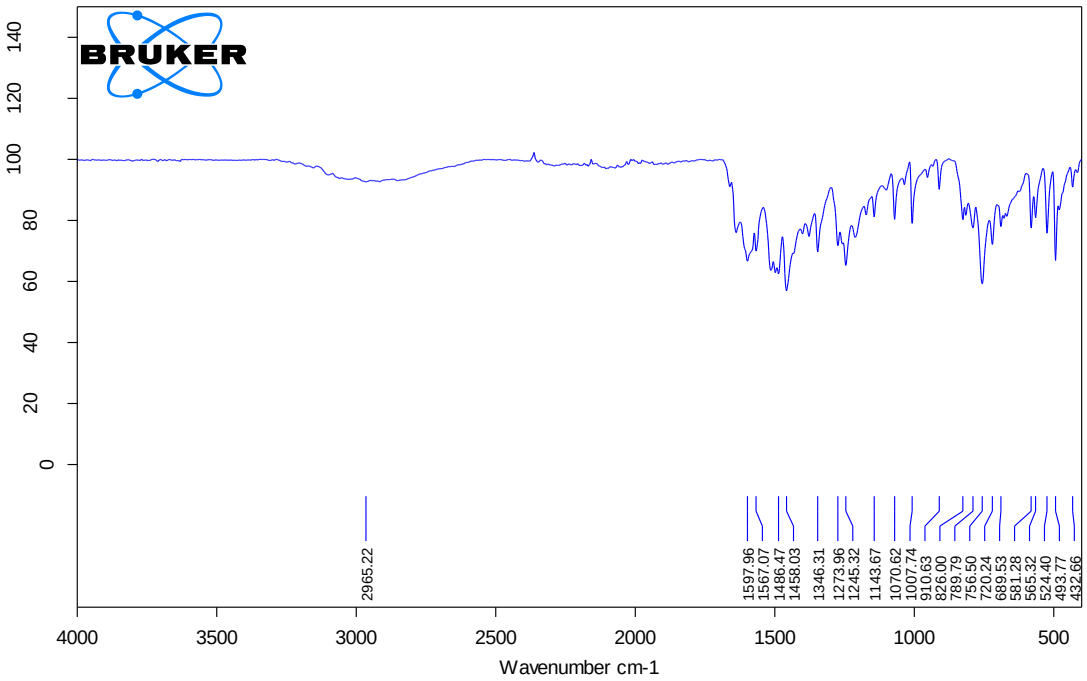
Spectrum 161: 11ca FTIR-ATR



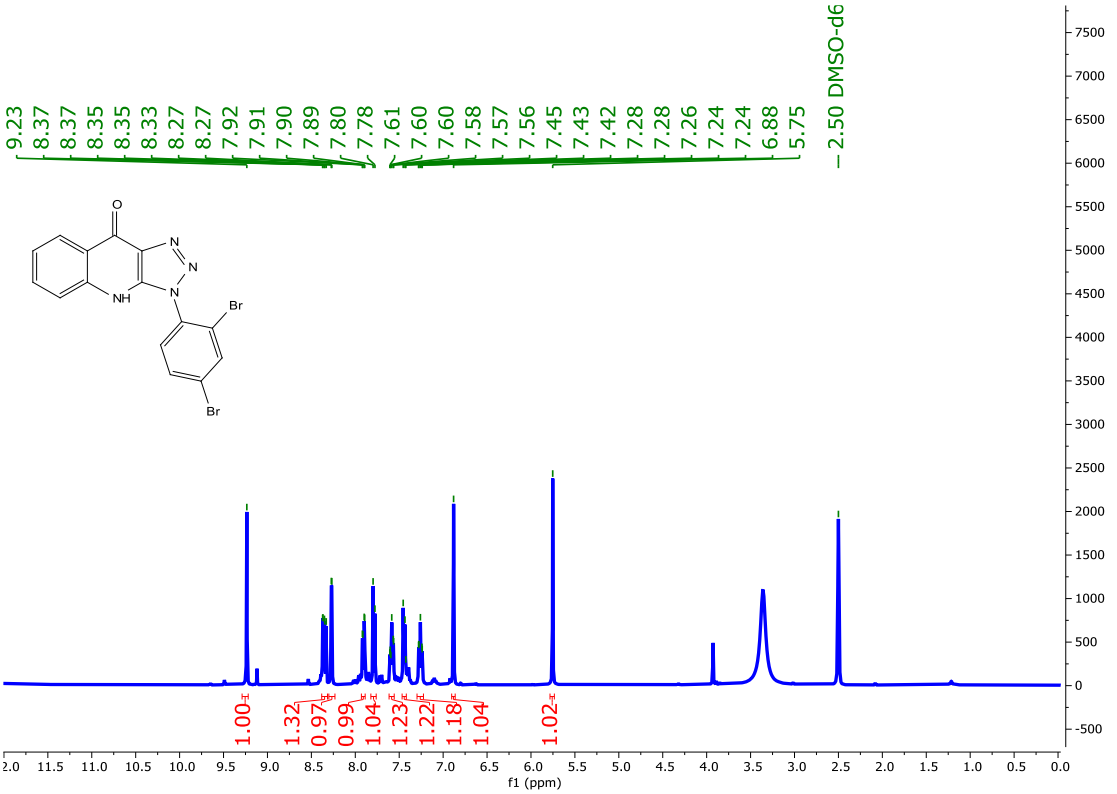
Spectrum 162: 21aa ^{1}H NMR (DMSO-d6, 400 MHz)



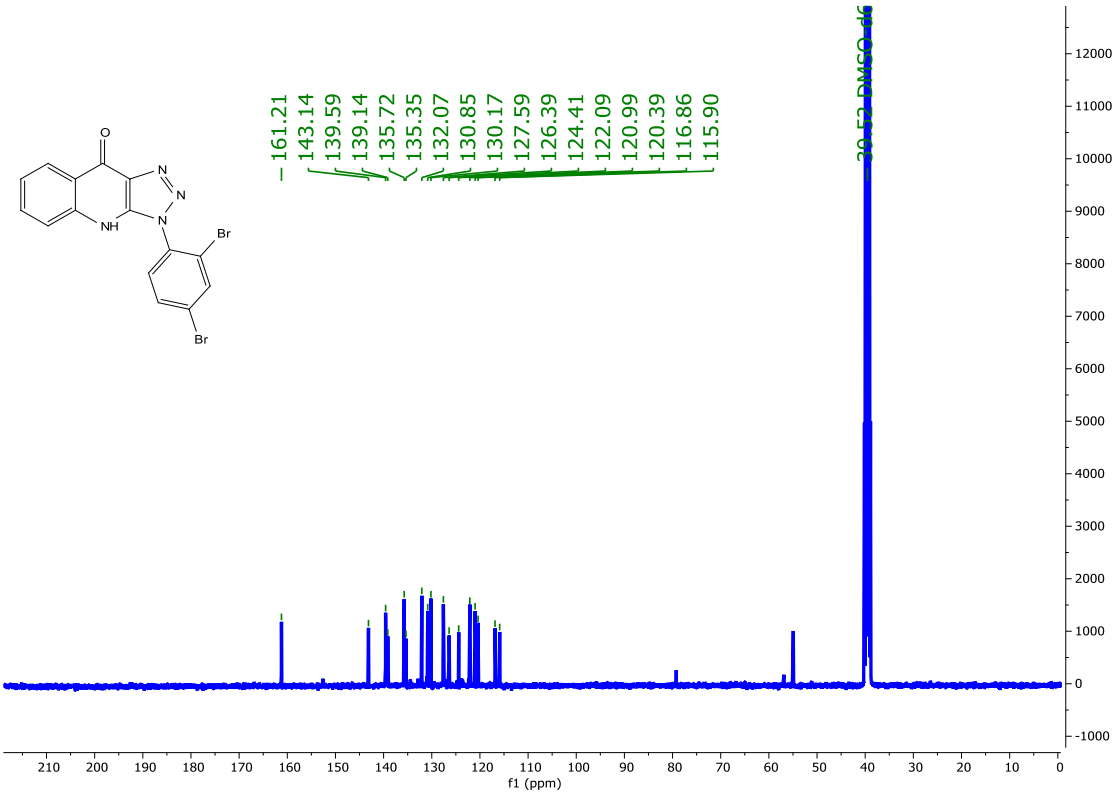
Spectrum 163: 21aa ^{13}C NMR (DMSO-d6, 101 MHz)



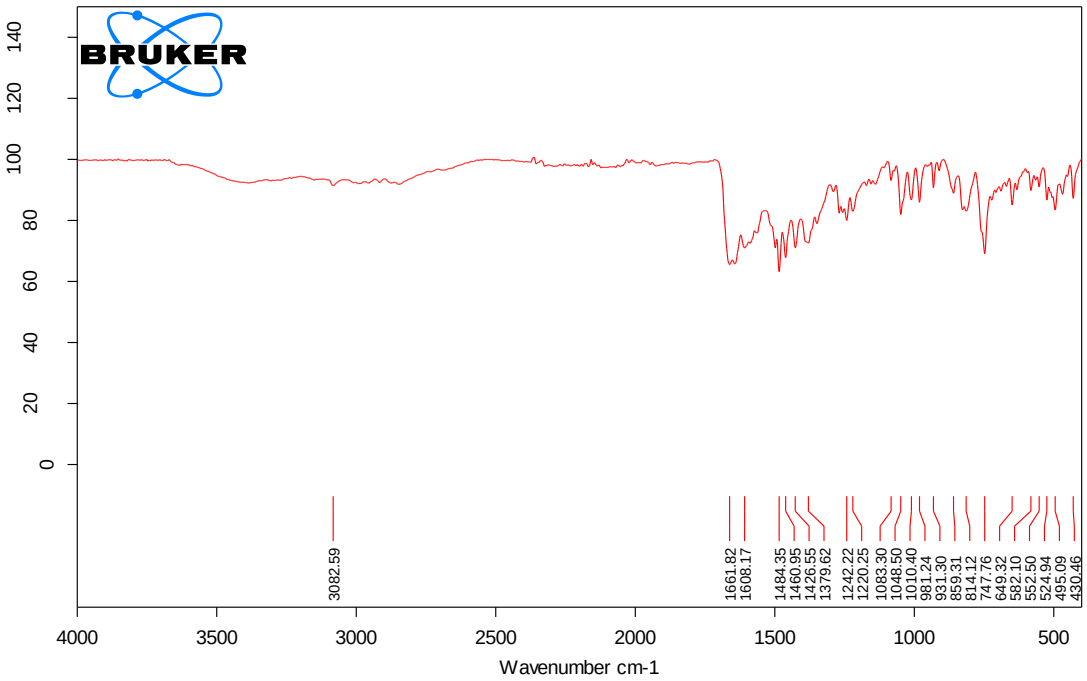
Spectrum 164: 21aa FTIR-ATR



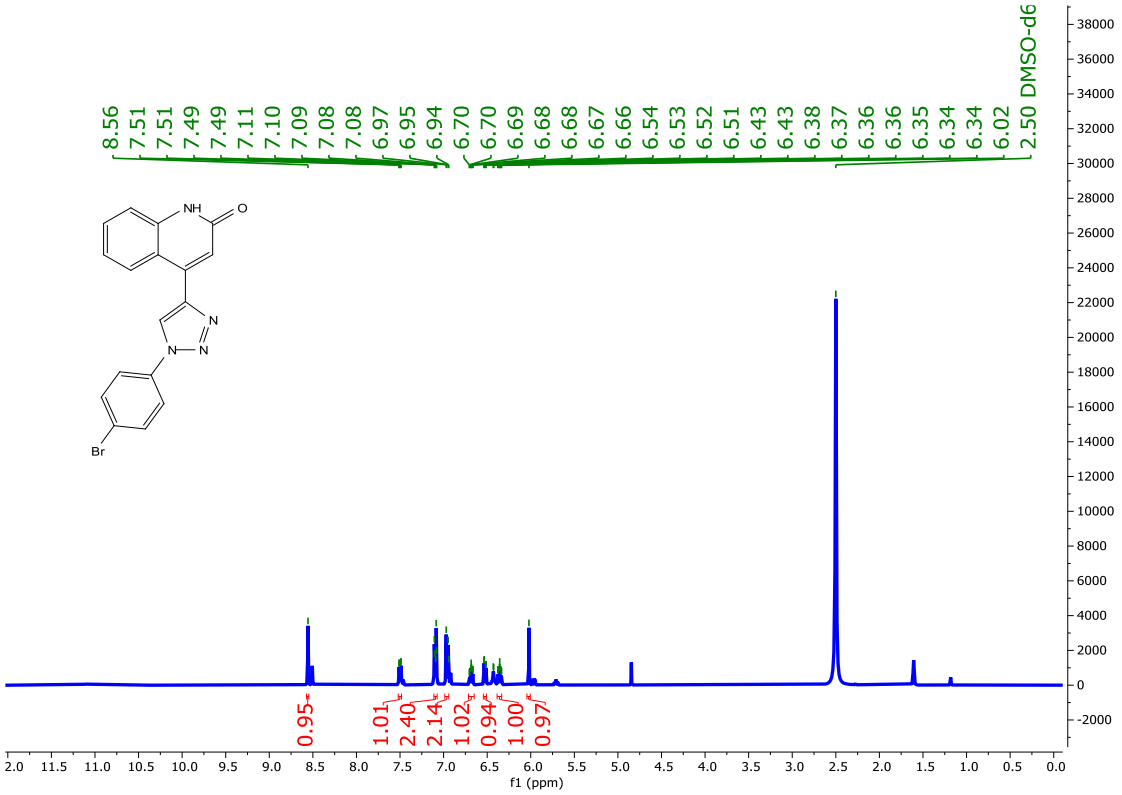
Spectrum 165: 21ai ^{1}H NMR (DMSO-d6, 400 MHz)



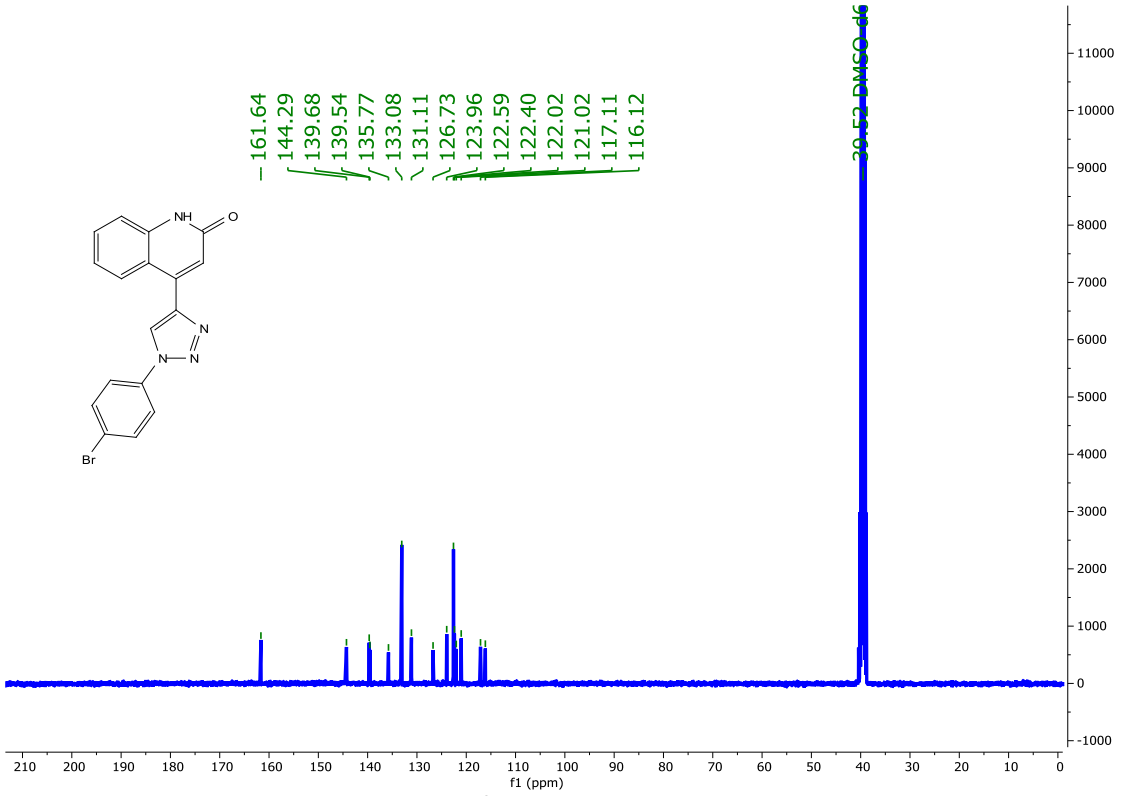
Spectrum 166: 21ai ^{13}C NMR (DMSO-d6, 101 MHz)



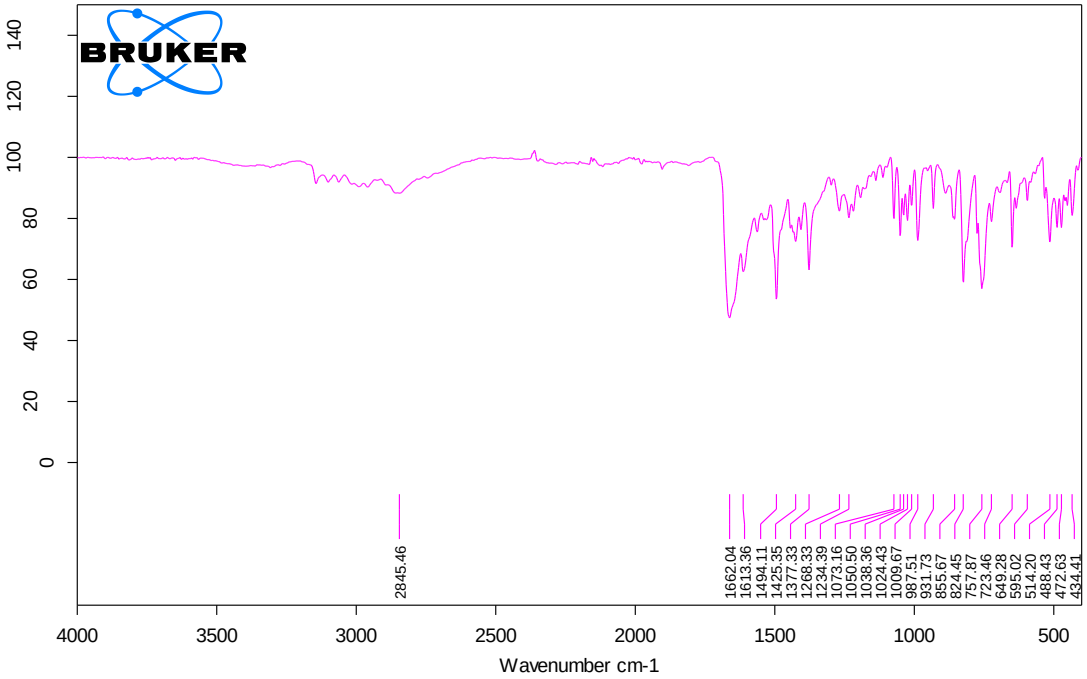
Spectrum 167: 21ai FTIR-ATR



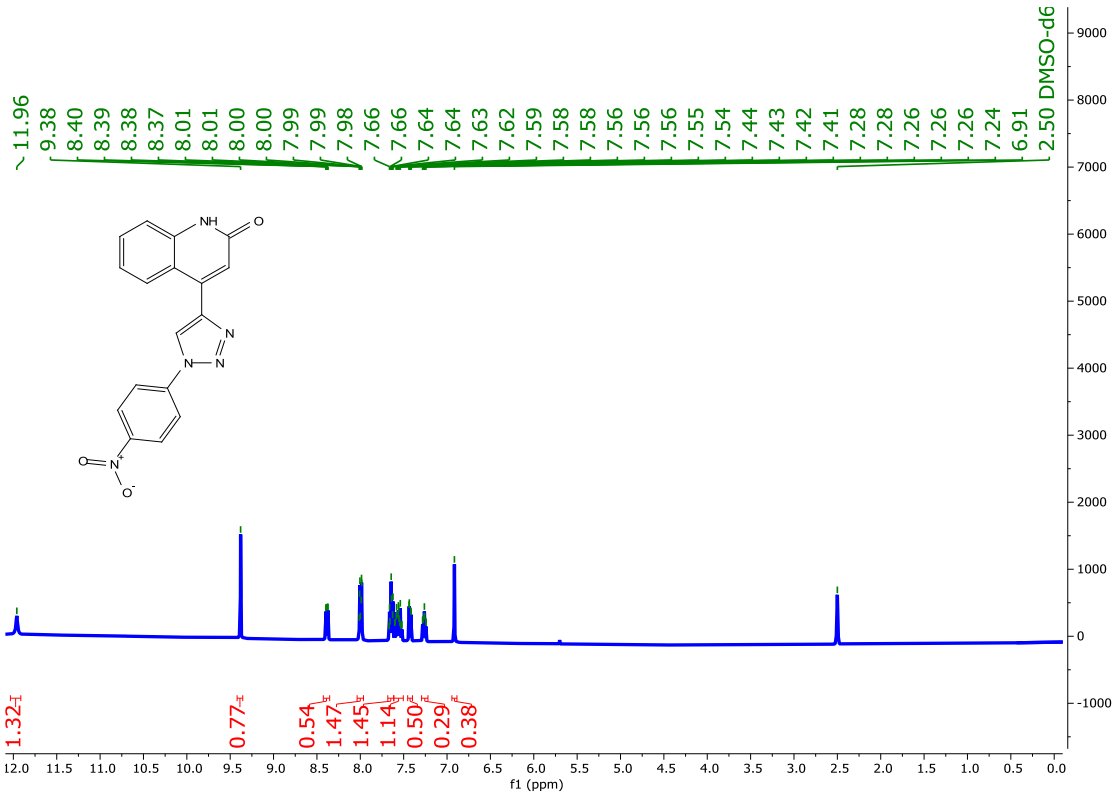
Spectrum 168: 31aa ^{1}H NMR (DMSO-d6, 400 MHz)



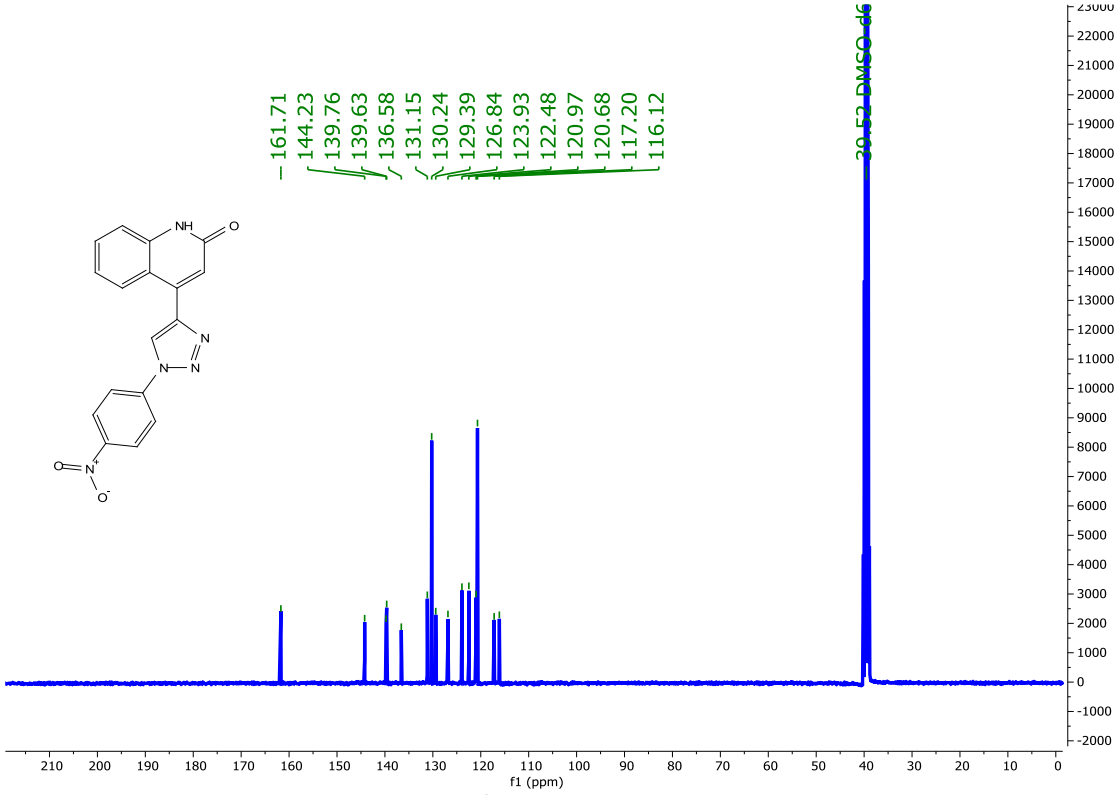
Spectrum 169: 31aa ^{13}C NMR (DMSO-d6, 101 MHz)



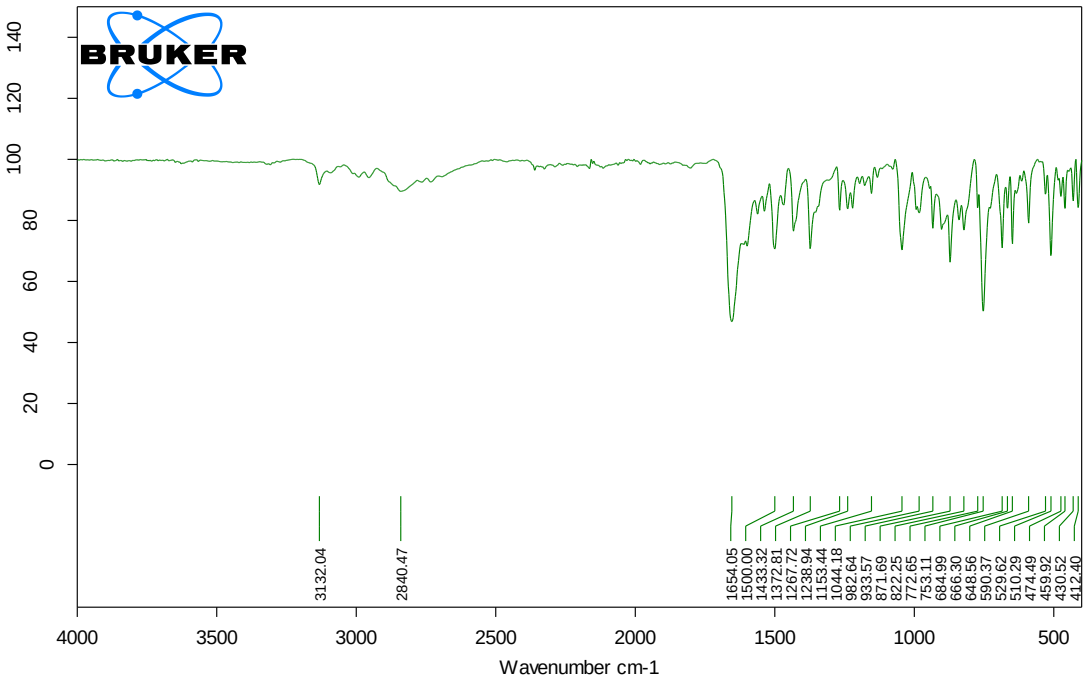
Spectrum 170: 31aa FTIR-ATR



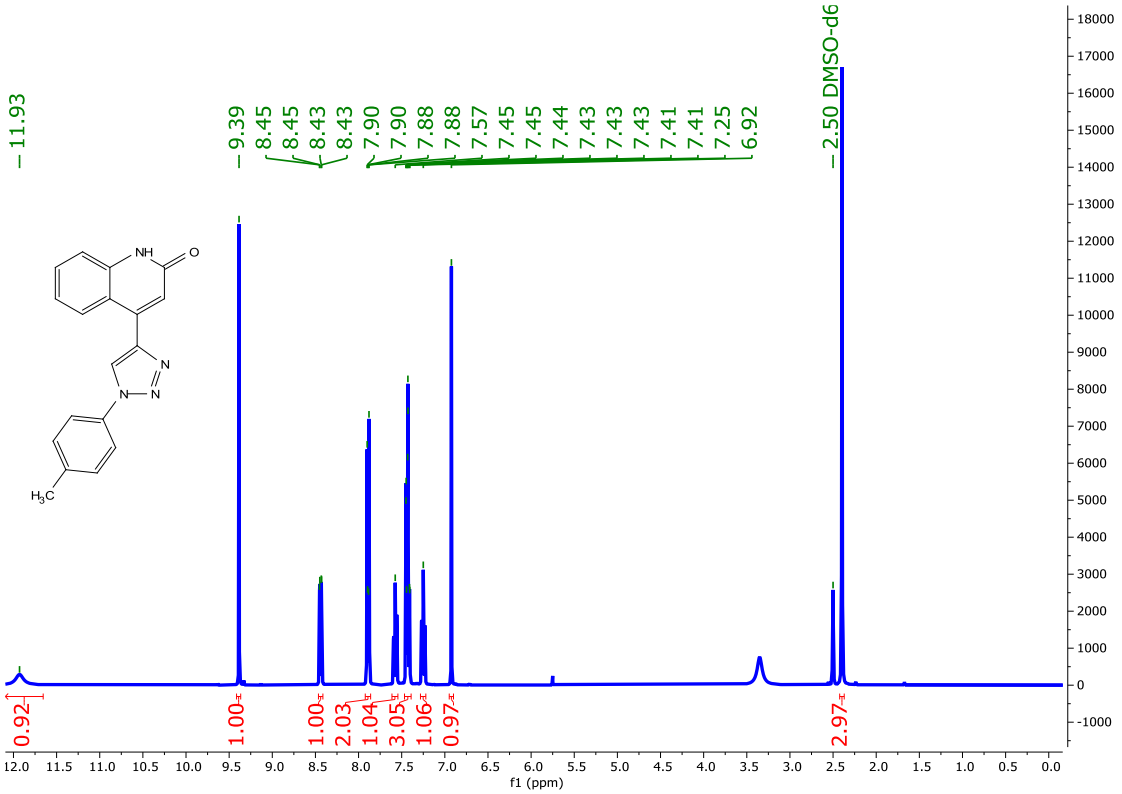
Spectrum 171: 31ad ^{1}H NMR (DMSO-d6, 400 MHz)



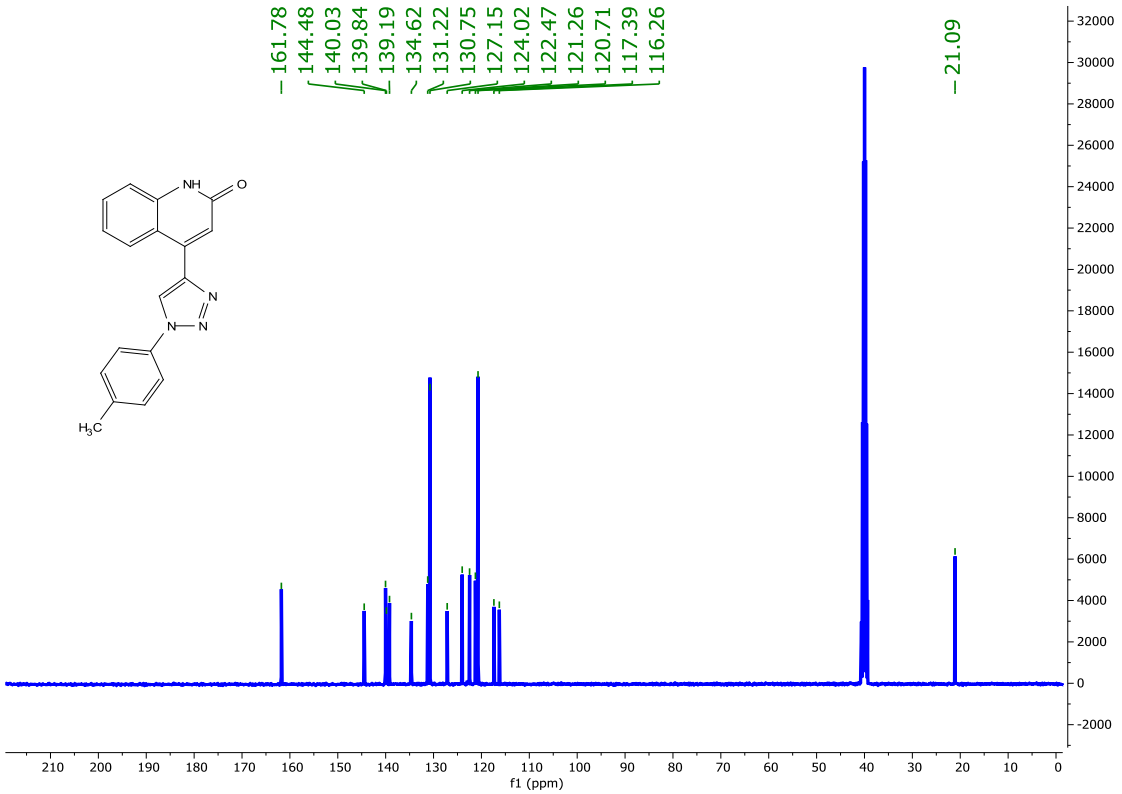
Spectrum 172: 31ad ^{13}C NMR (DMSO-d6, 101 MHz)



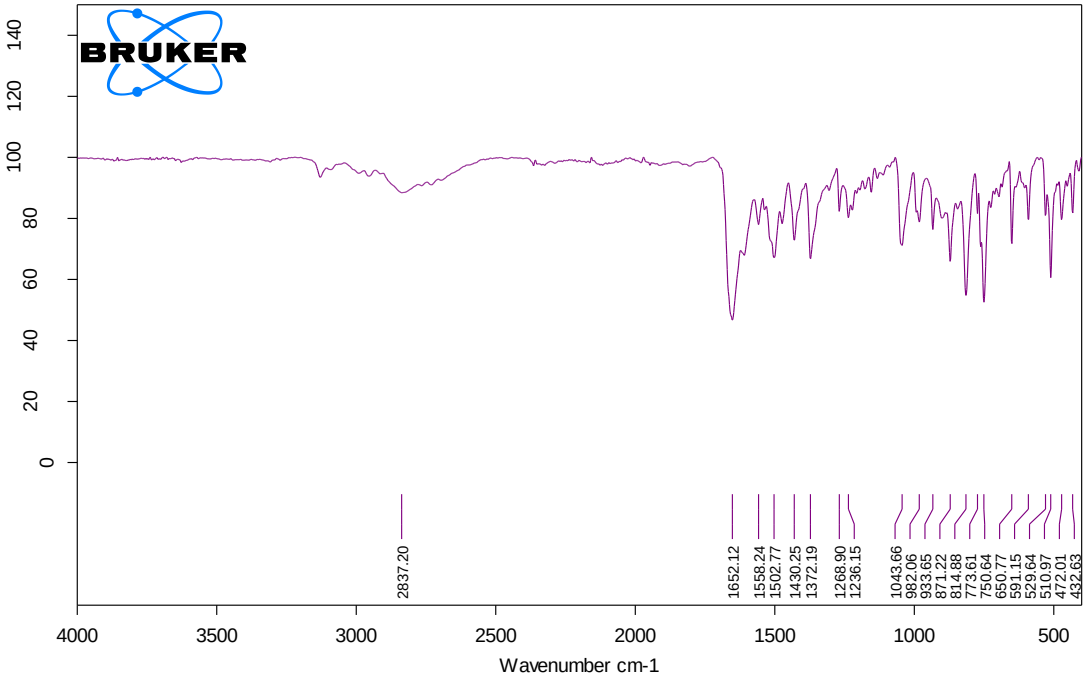
Spectrum 173: 31ad FTIR-ATR



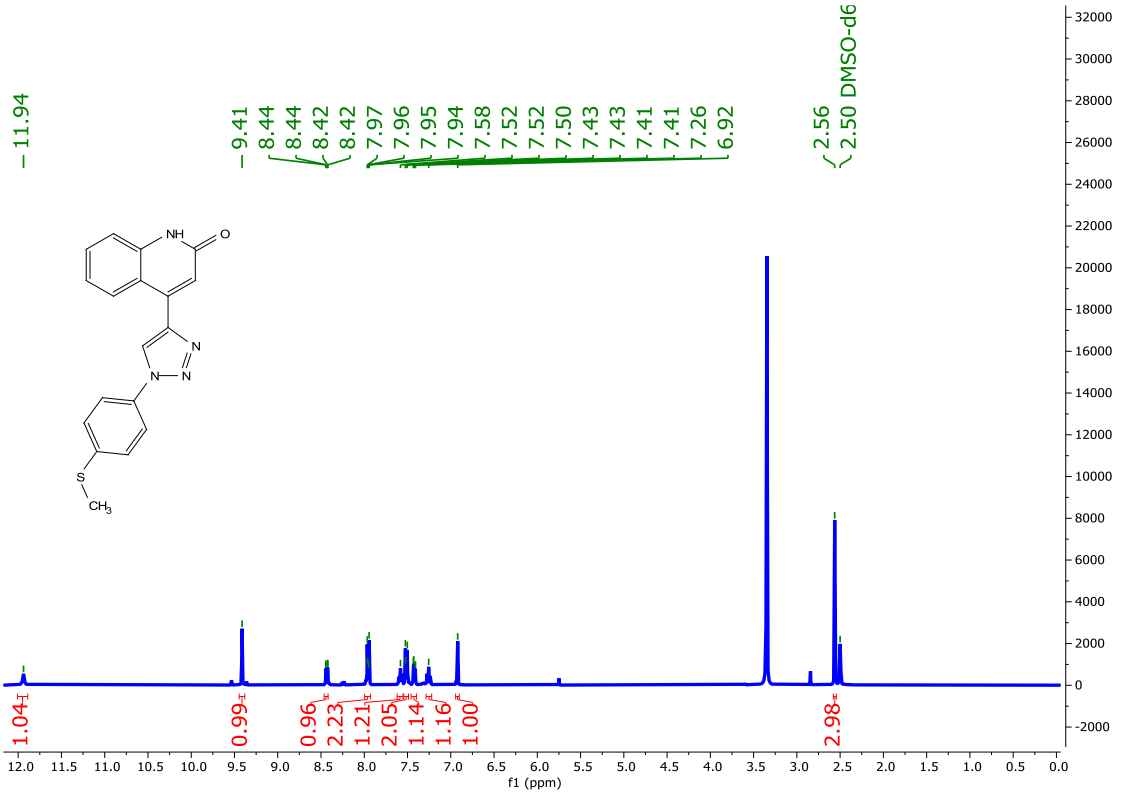
Spectrum 174: 31ag ^{1}H NMR (DMSO-d6, 400 MHz)



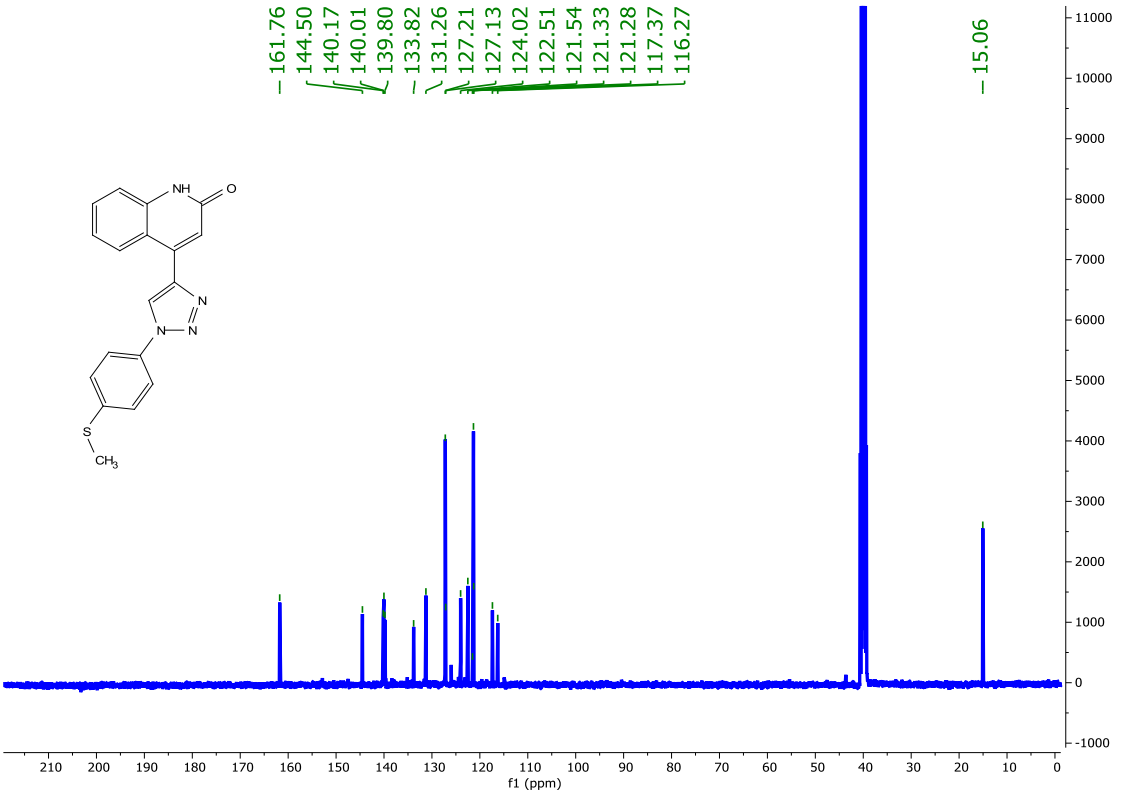
Spectrum 175: 31ag ^{13}C NMR (DMSO-d6, 101 MHz)



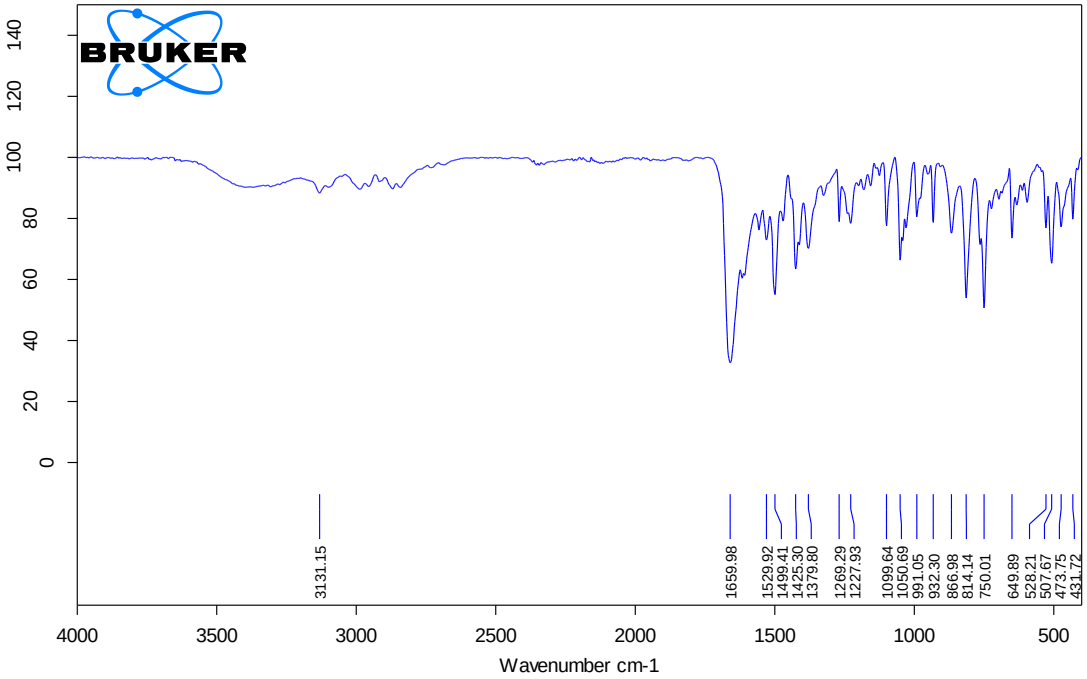
Spectrum 176: 31ag FTIR-ATR



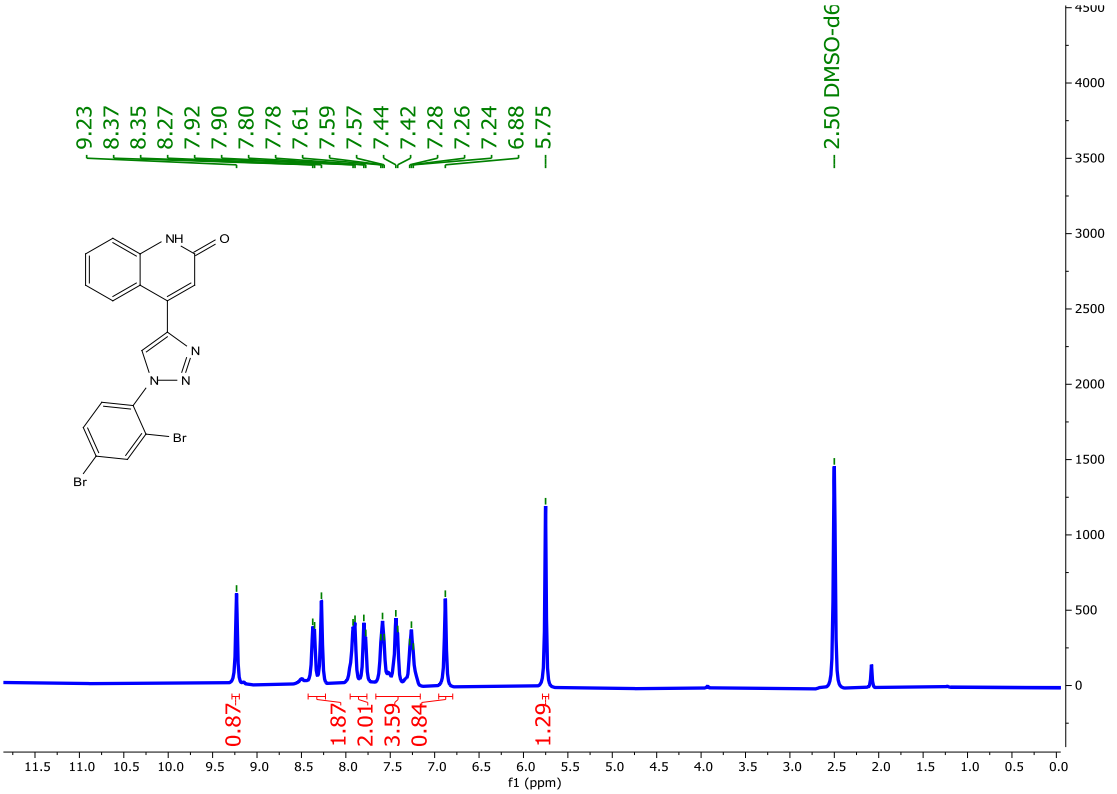
Spectrum 177: 31af ^{1}H NMR (DMSO-d6, 400 MHz)



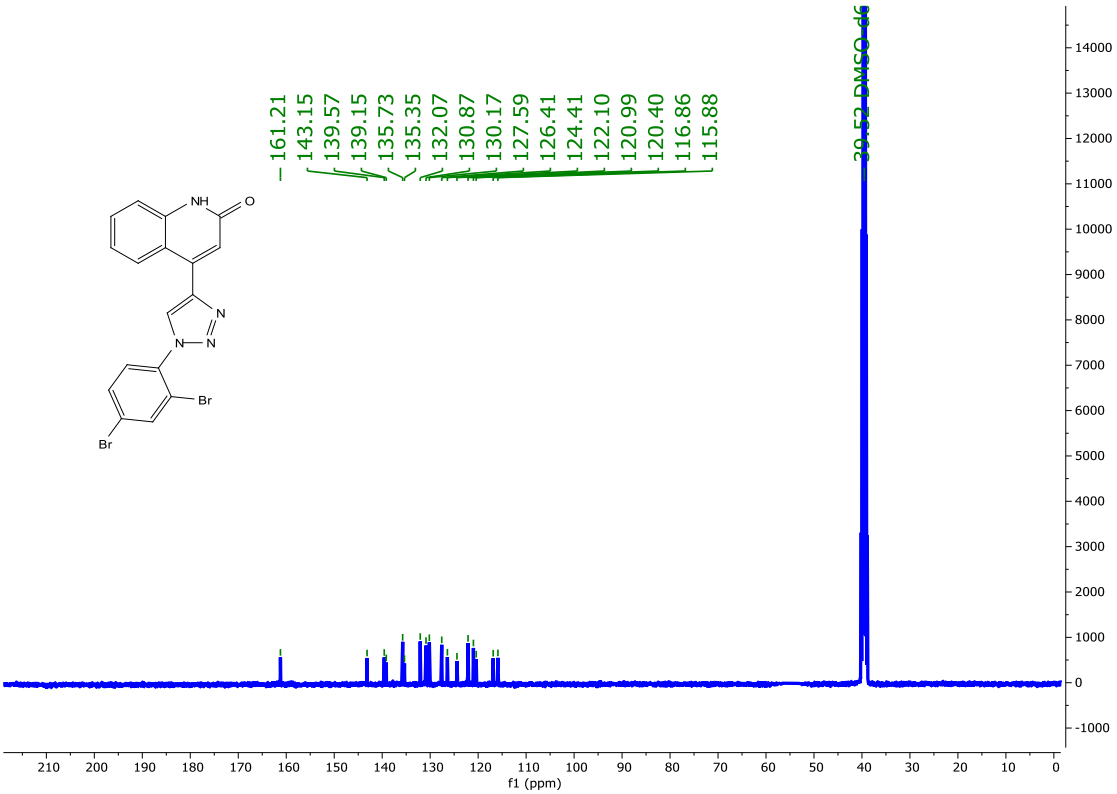
Spectrum 178: 31af ^{13}C NMR (DMSO-d6, 101 MHz)



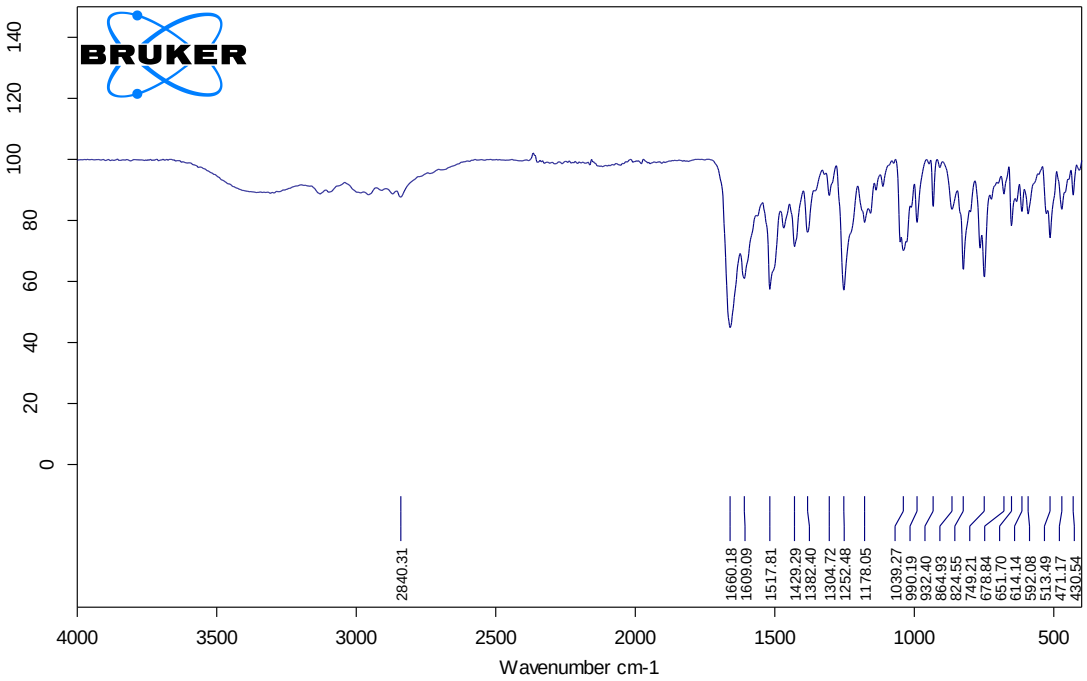
Spectrum 179: 31af FTIR-ATR



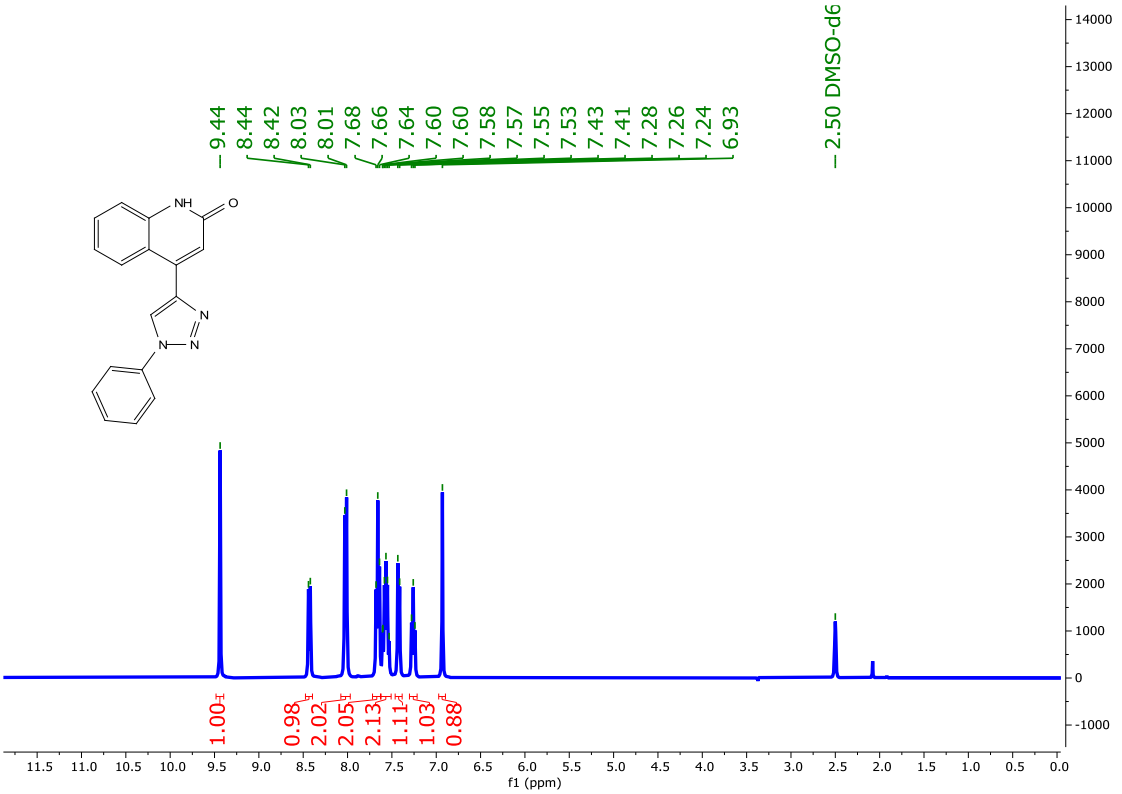
Spectrum 180: 31ai ^{1}H NMR (DMSO-d6, 400 MHz)



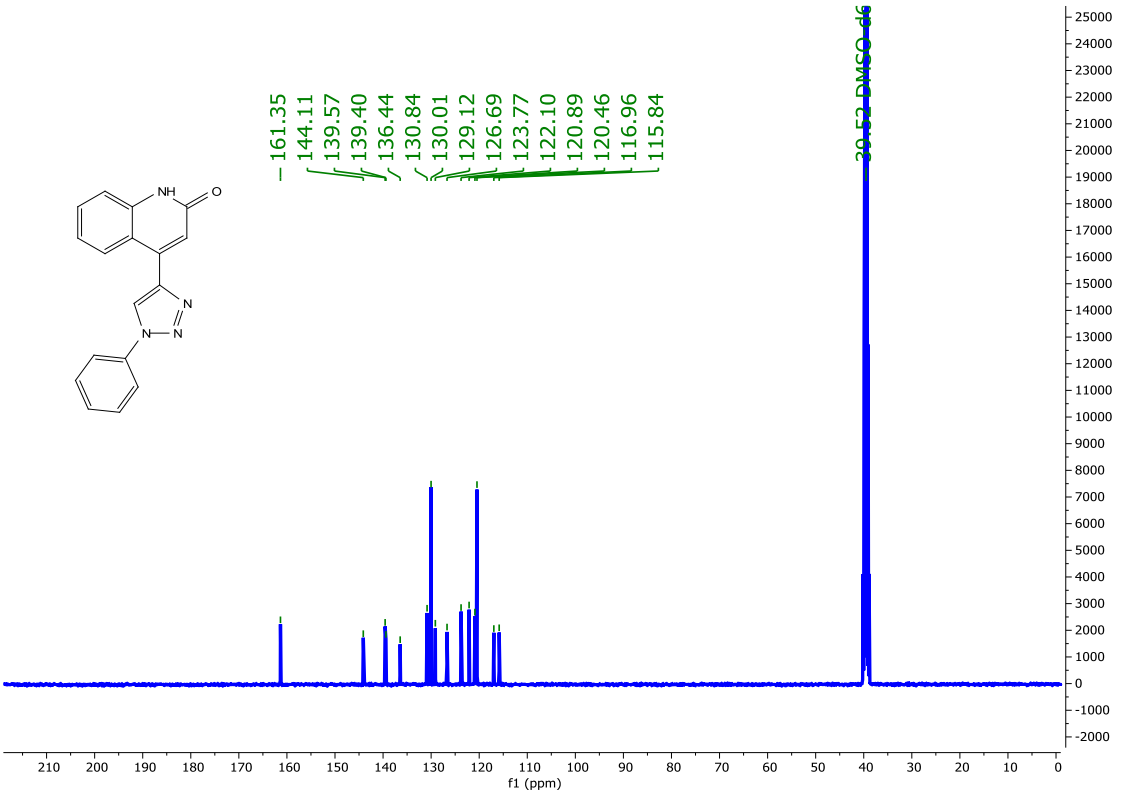
Spectrum 181: 31ai ^{13}C NMR (DMSO-d6, 101 MHz)



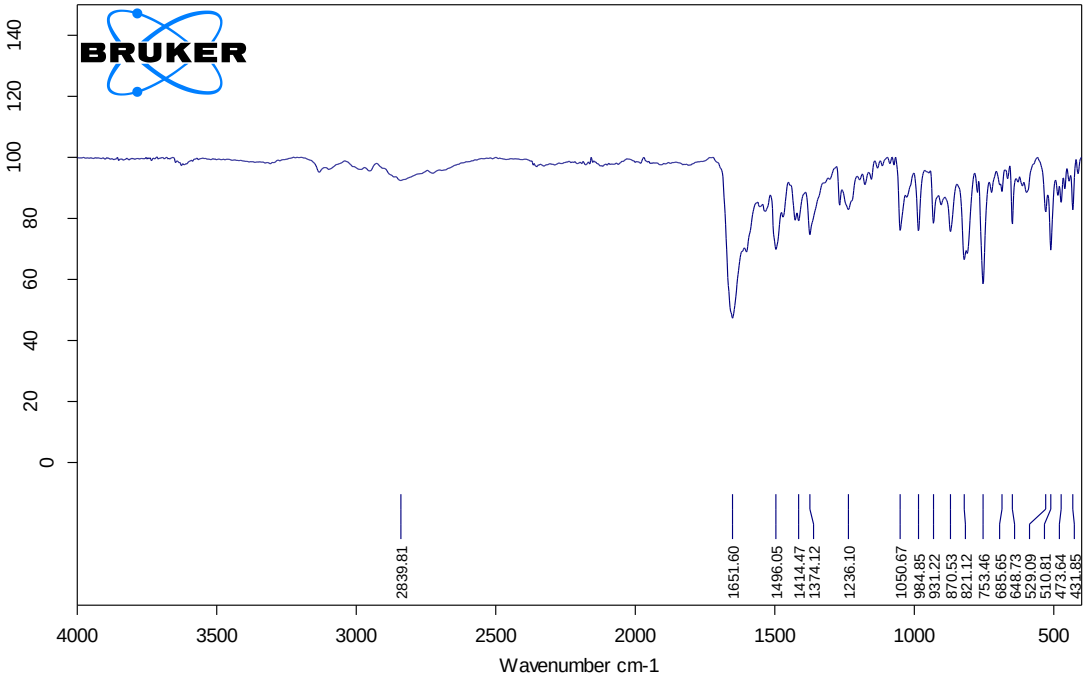
Spectrum 182: 31ai FTIR-ATR



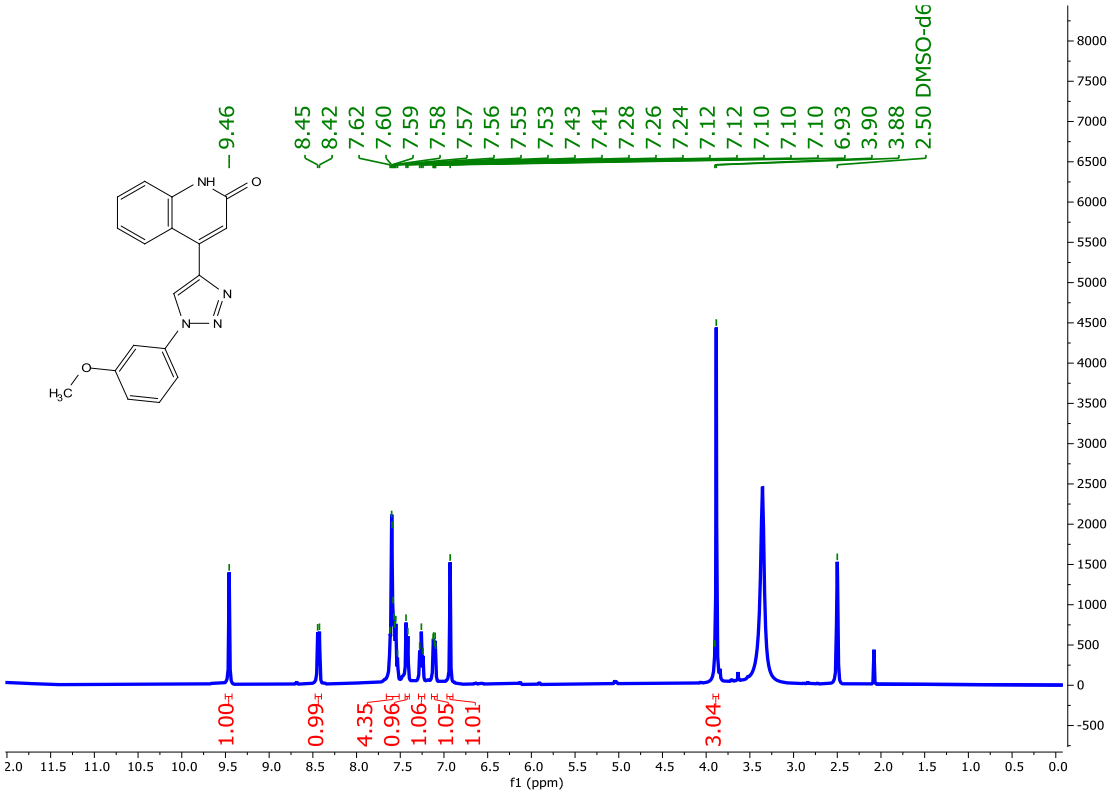
Spectrum 183: 31ak ^{1}H NMR (DMSO-d6, 400 MHz)



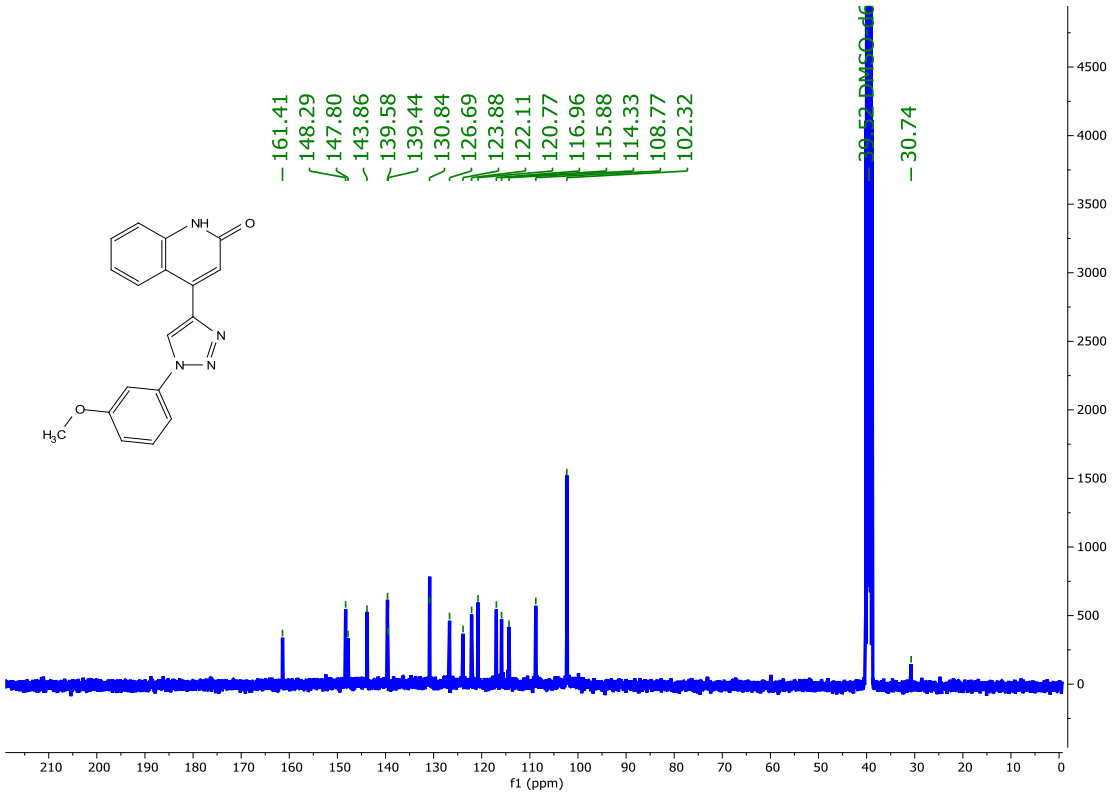
Spectrum 184: 31ak ^{13}C NMR (DMSO-d6, 101 MHz)



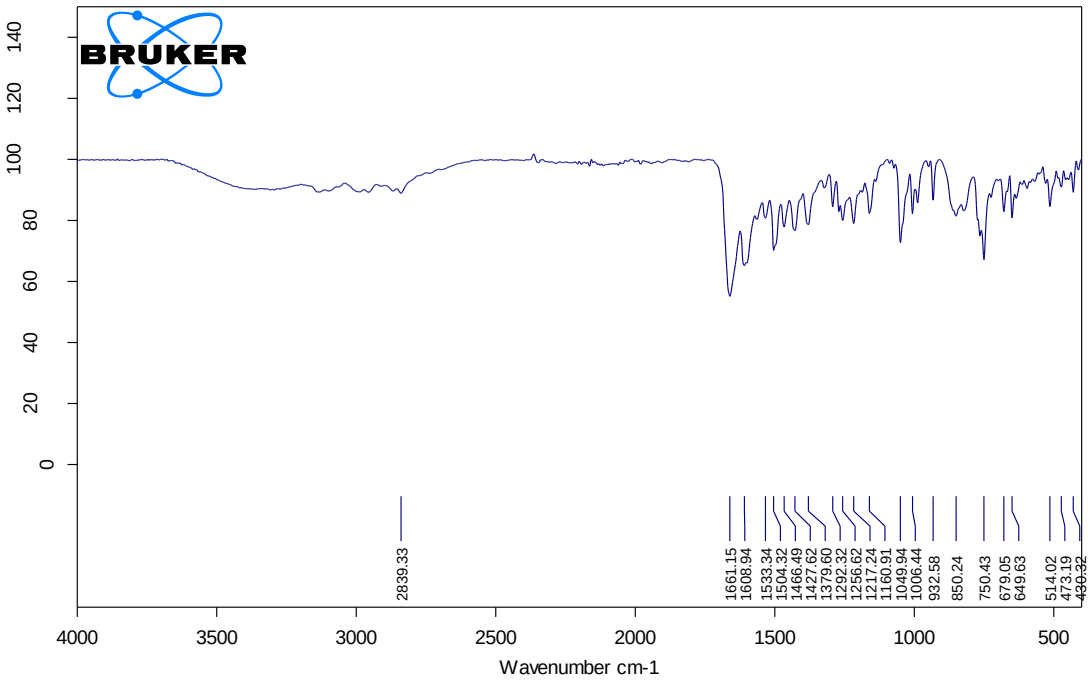
Spectrum 185: 31ak FTIR-ATR



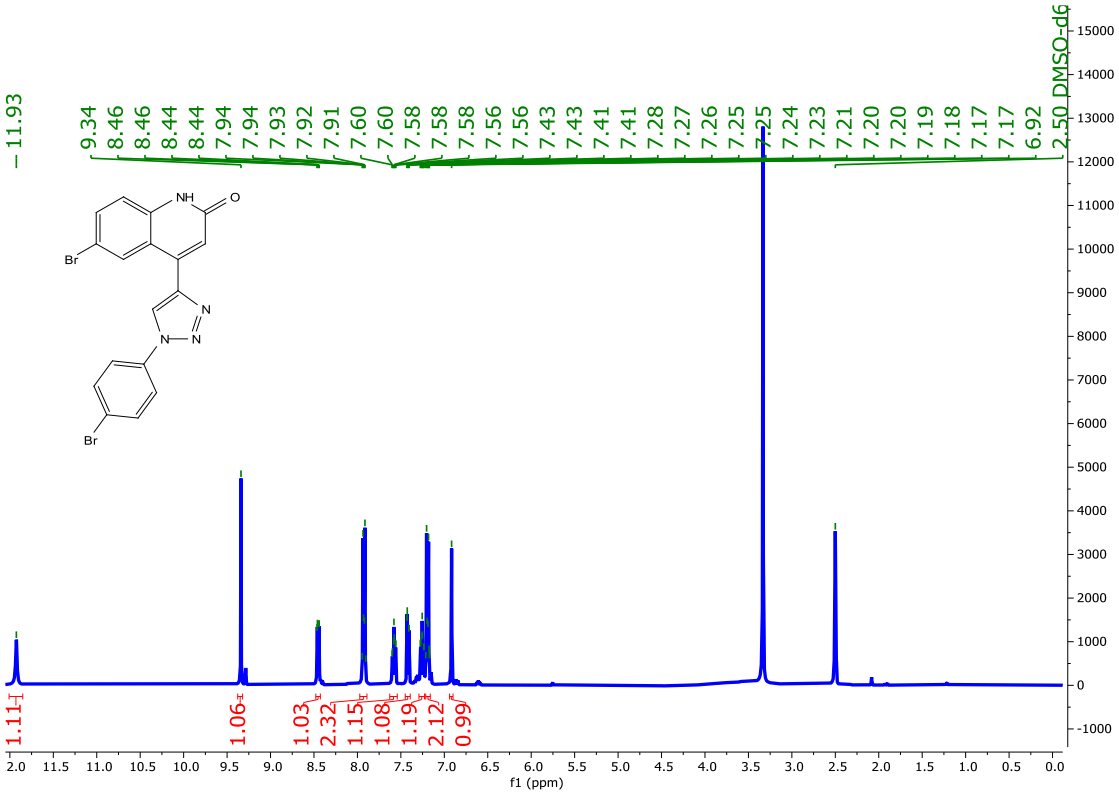
Spectrum 186: 31ap ^{1}H NMR (DMSO-d6, 400 MHz)



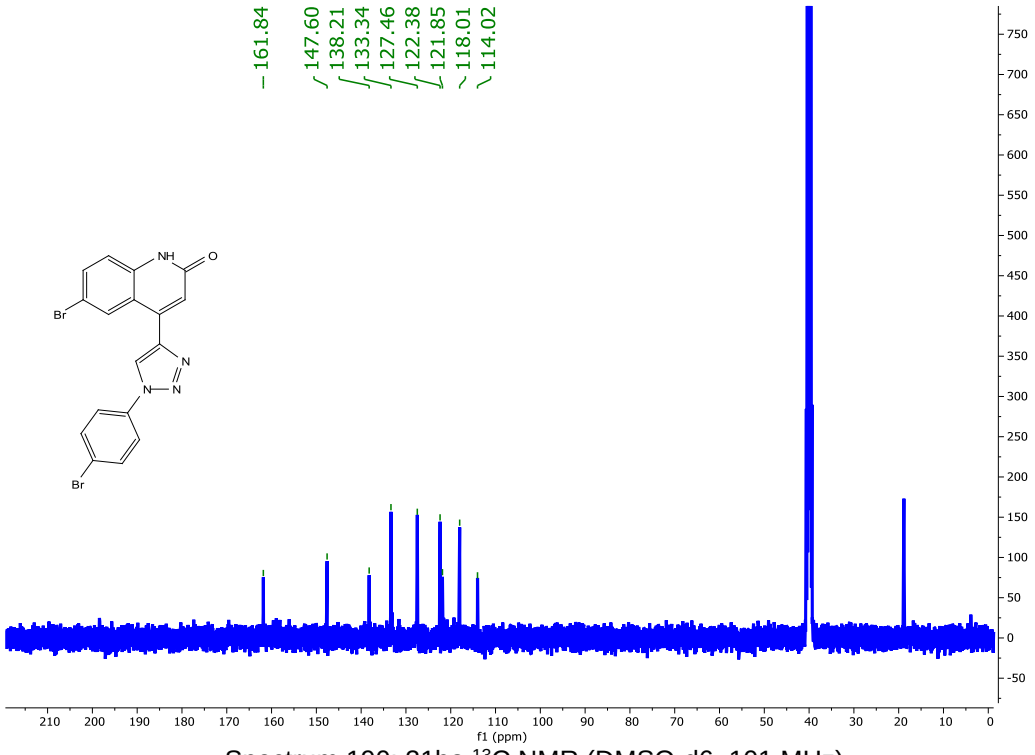
Spectrum 187: 31ap ^{13}C NMR (DMSO-d6, 101 MHz)



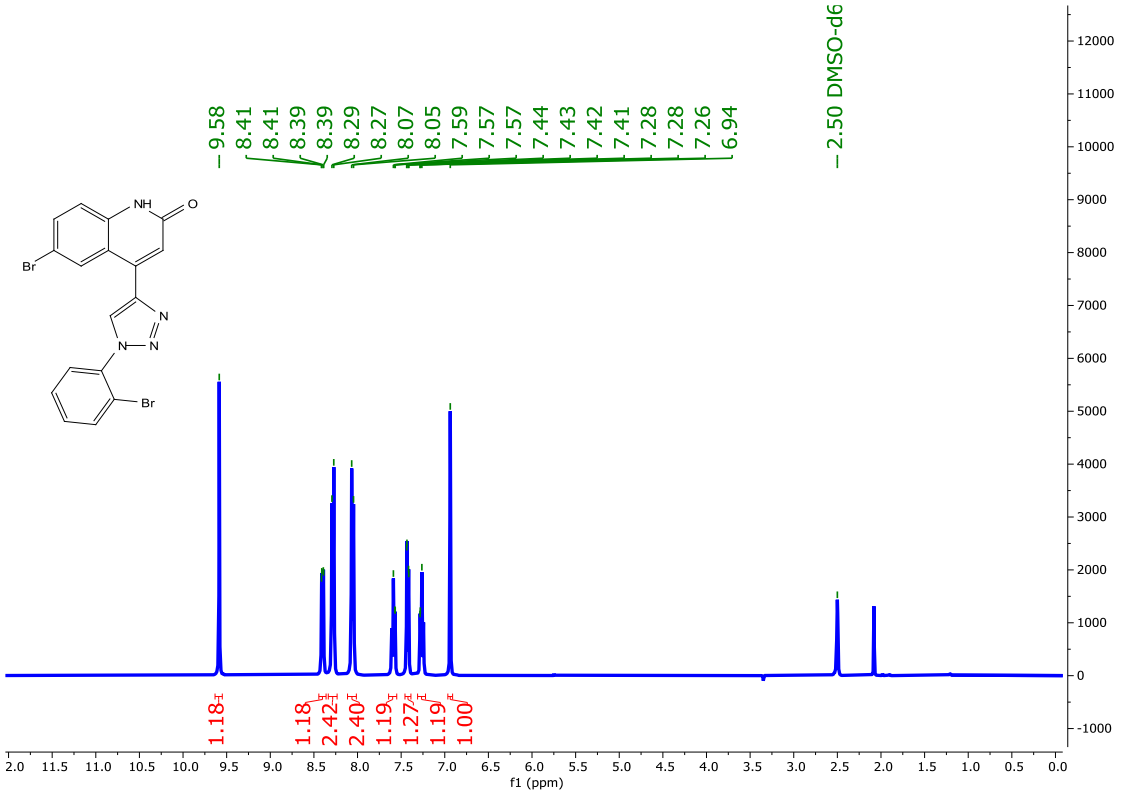
Spectrum 188: 31ap FTIR-ATR



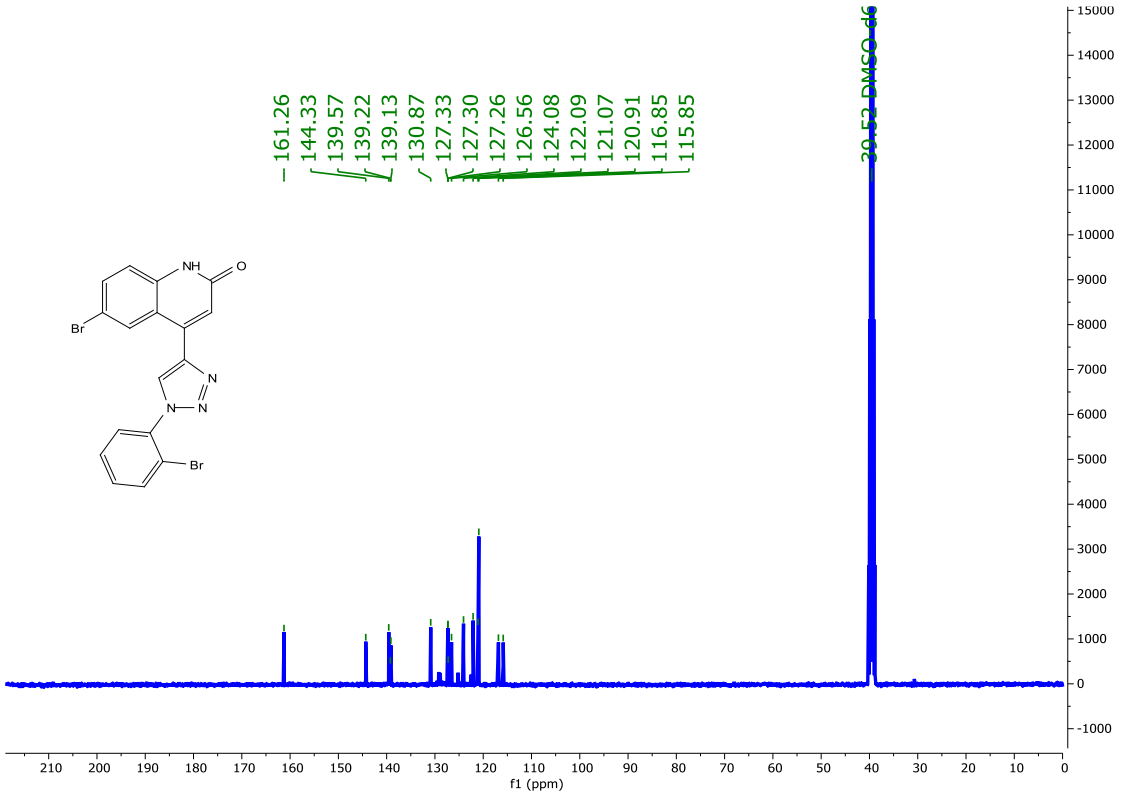
Spectrum 189: 31ba ^{1}H NMR (DMSO-d6, 400 MHz)



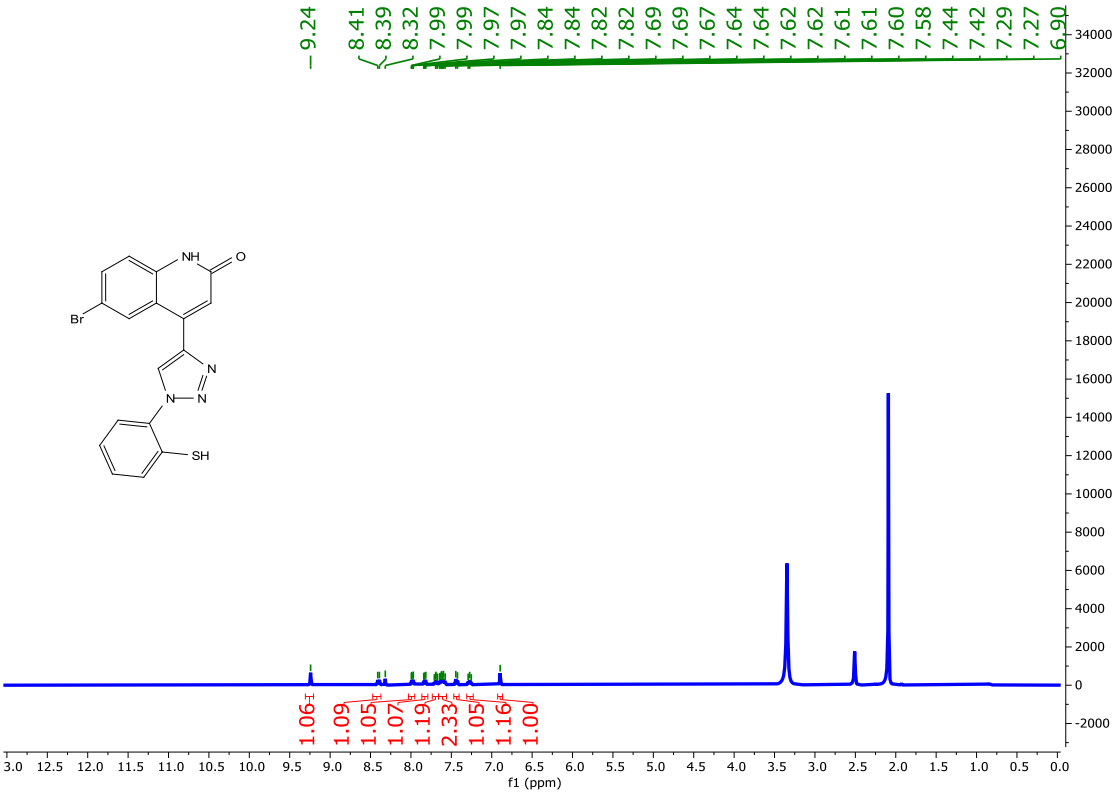
Spectrum 190: 31ba ^{13}C NMR (DMSO-d6, 101 MHz)



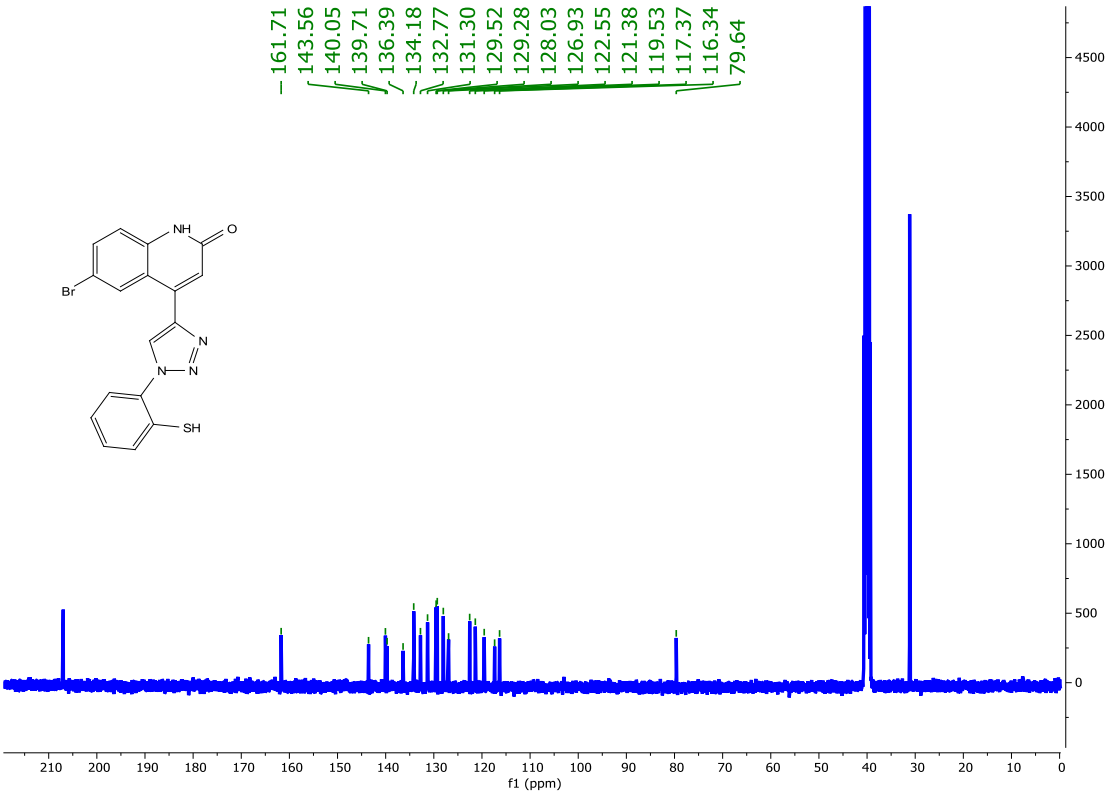
Spectrum 191: 31bh ^{1}H NMR (DMSO-d6, 400 MHz)



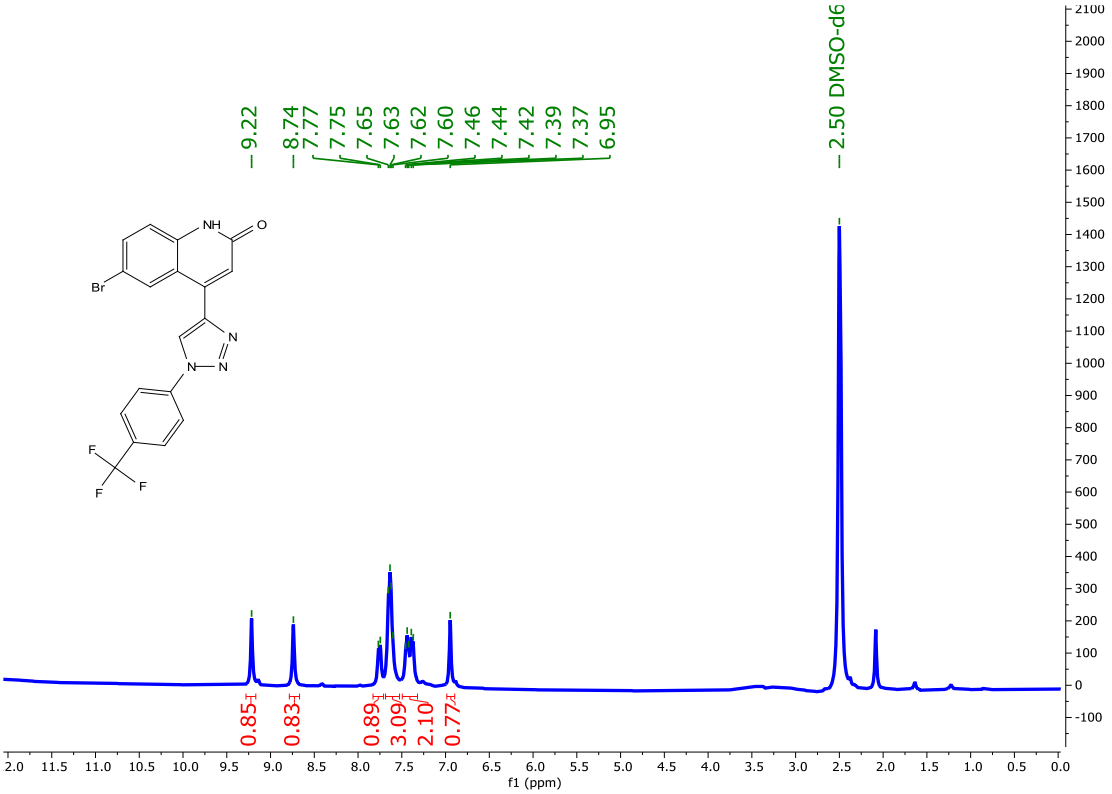
Spectrum 192: 31bh ^{13}C NMR (DMSO-d6, 101 MHz)



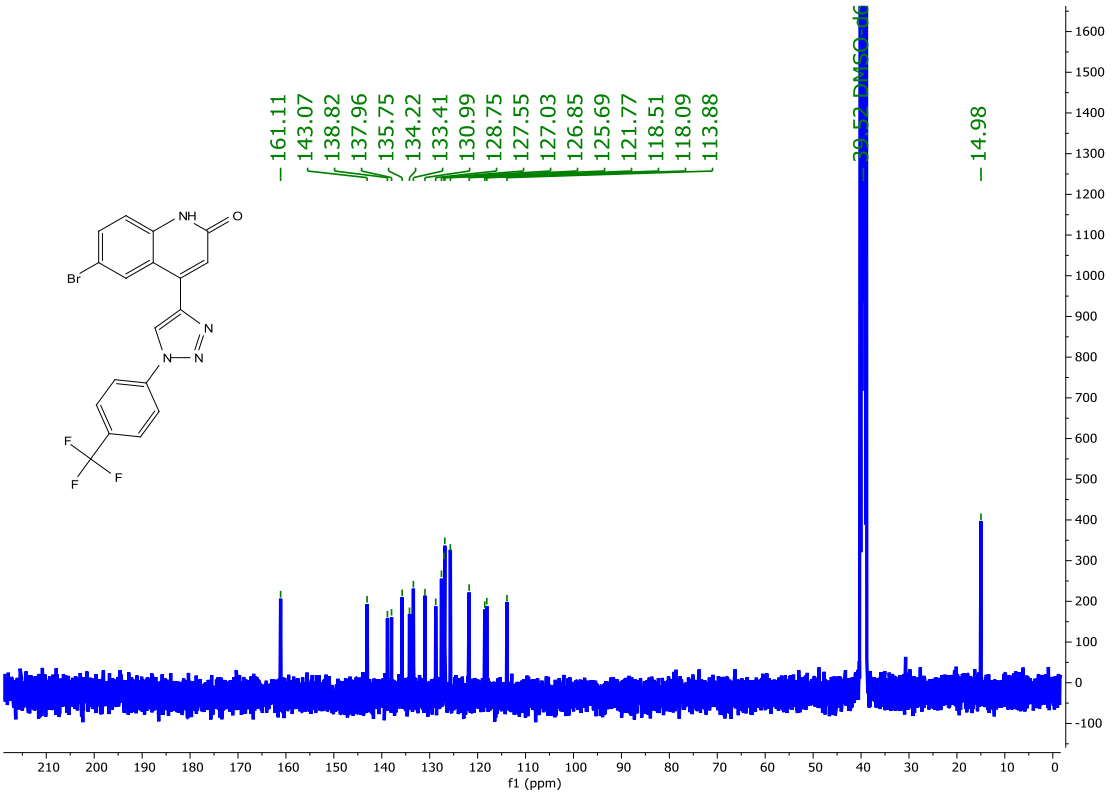
Spectrum 193: 31bq ^{1}H NMR (DMSO-d6, 400 MHz)



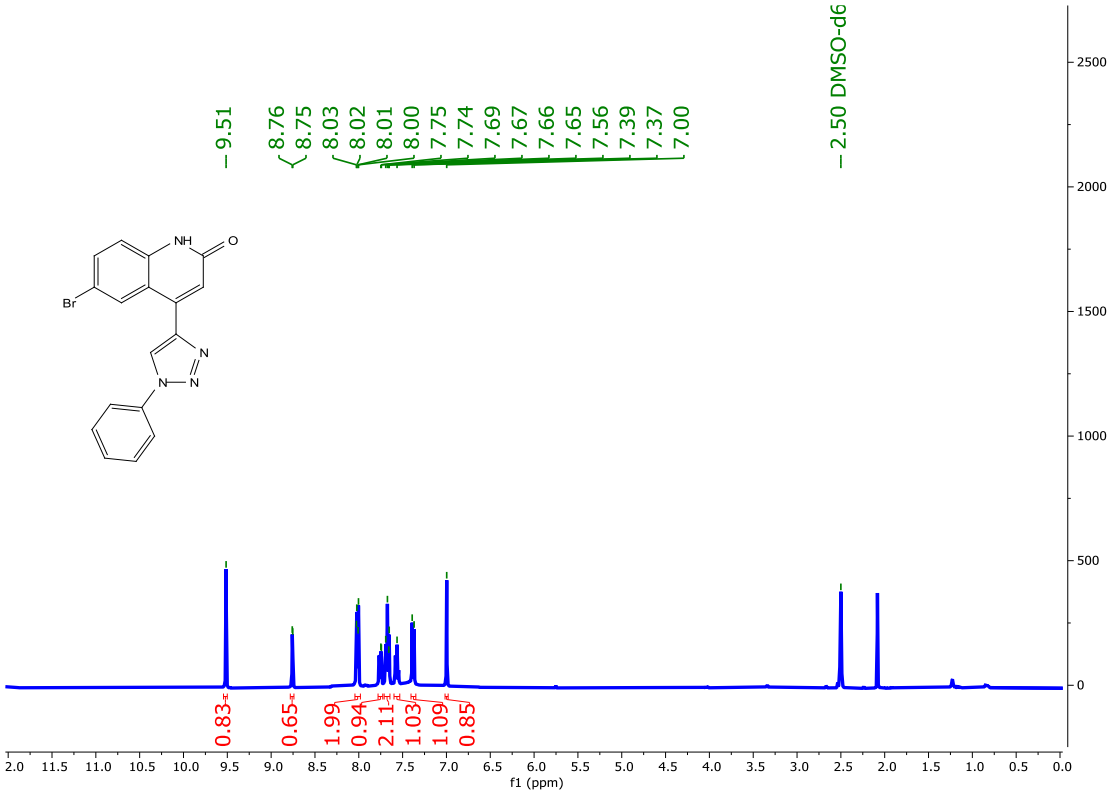
Spectrum 194: 31bq ^{13}C NMR (DMSO-d6, 101 MHz)



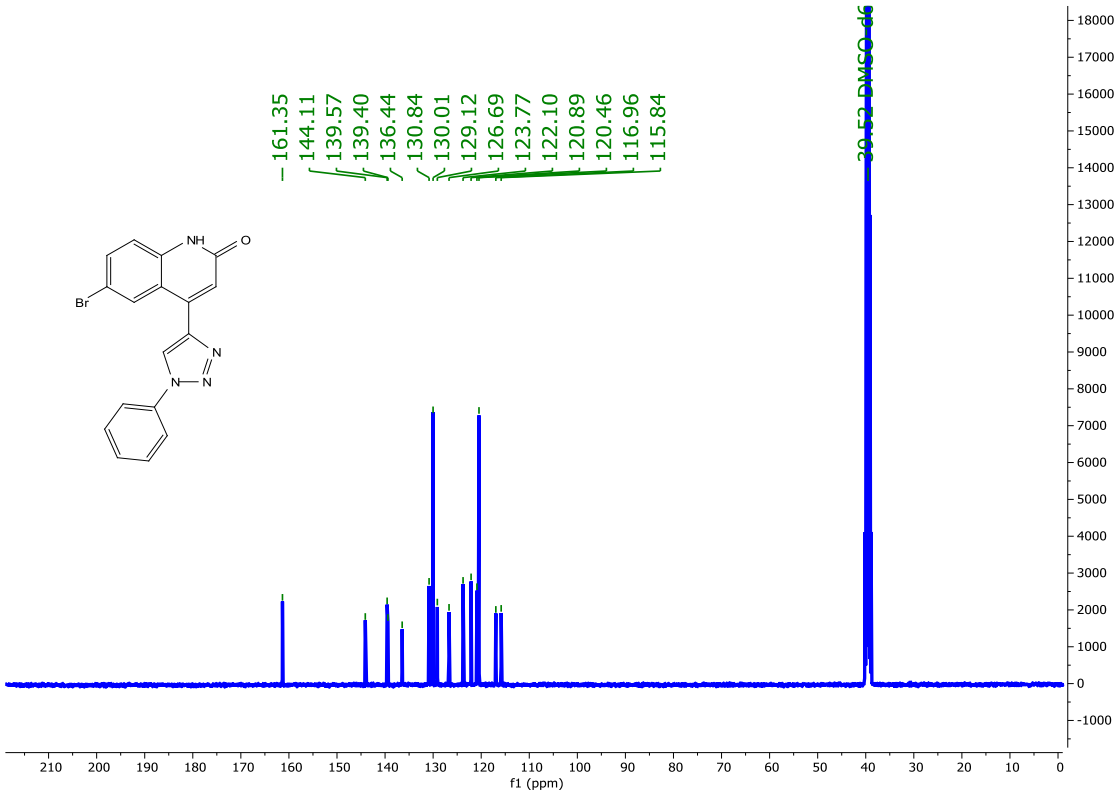
Spectrum 195: 31be ^{1}H NMR (DMSO-d6, 400 MHz)



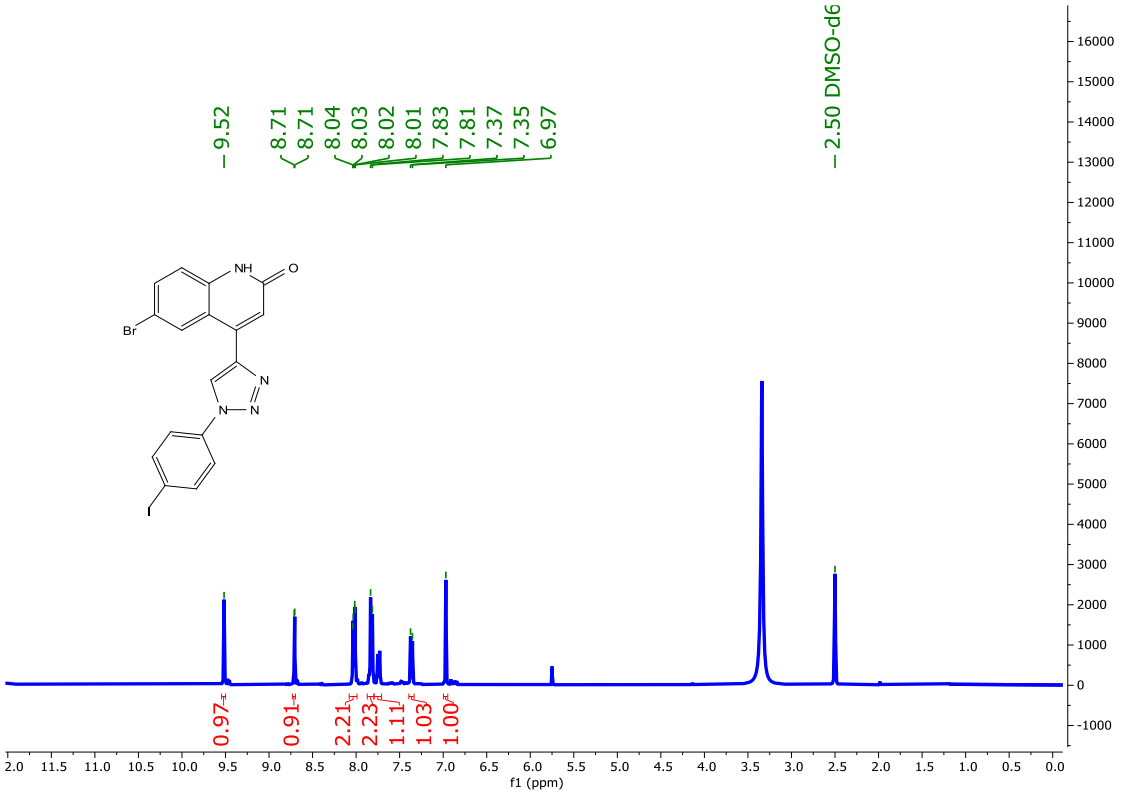
Spectrum 196: 31be ^{13}C NMR (DMSO-d6, 101 MHz)



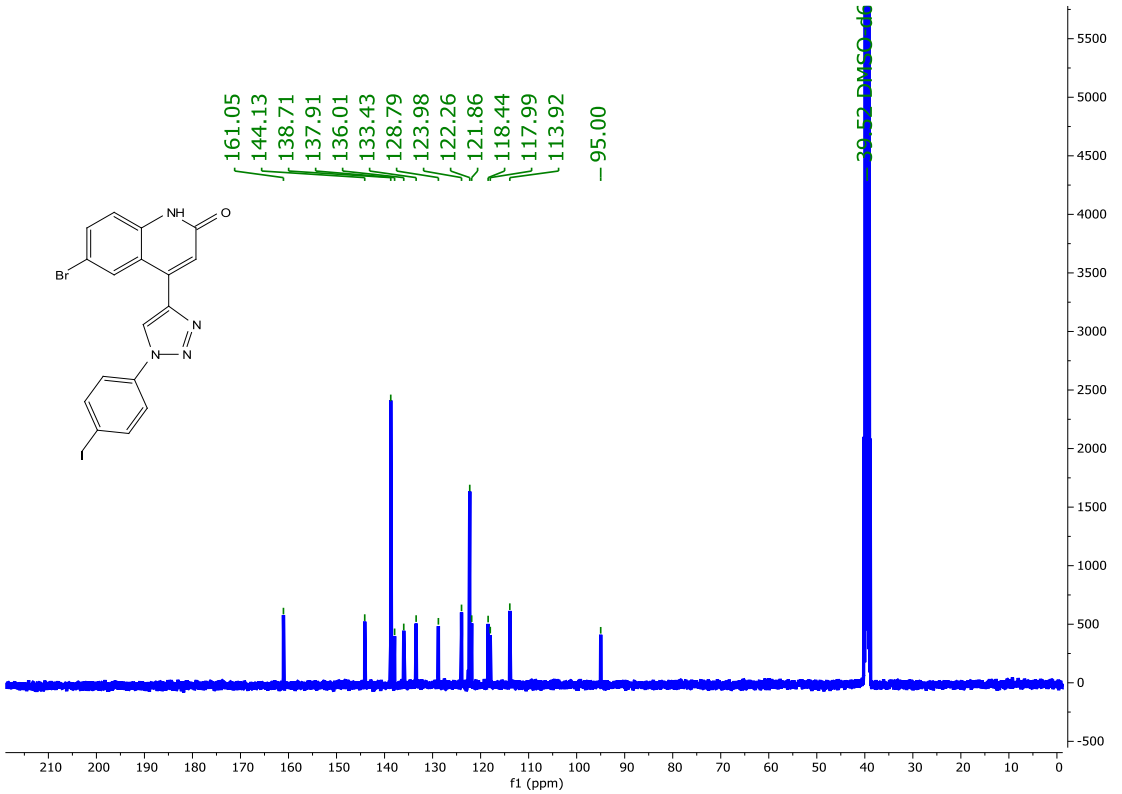
Spectrum 197: 31bk ^{1}H NMR (DMSO-d6, 400 MHz)



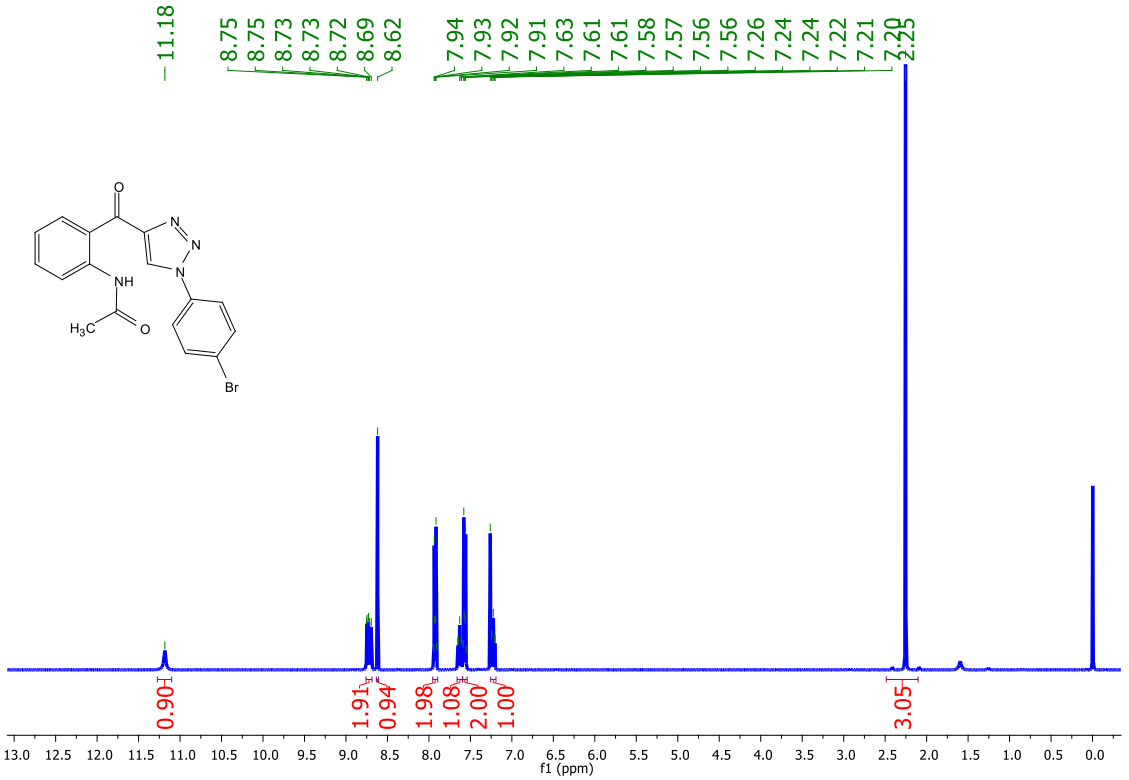
Spectrum 198: 31bk ^{13}C NMR (DMSO-d6, 101 MHz)



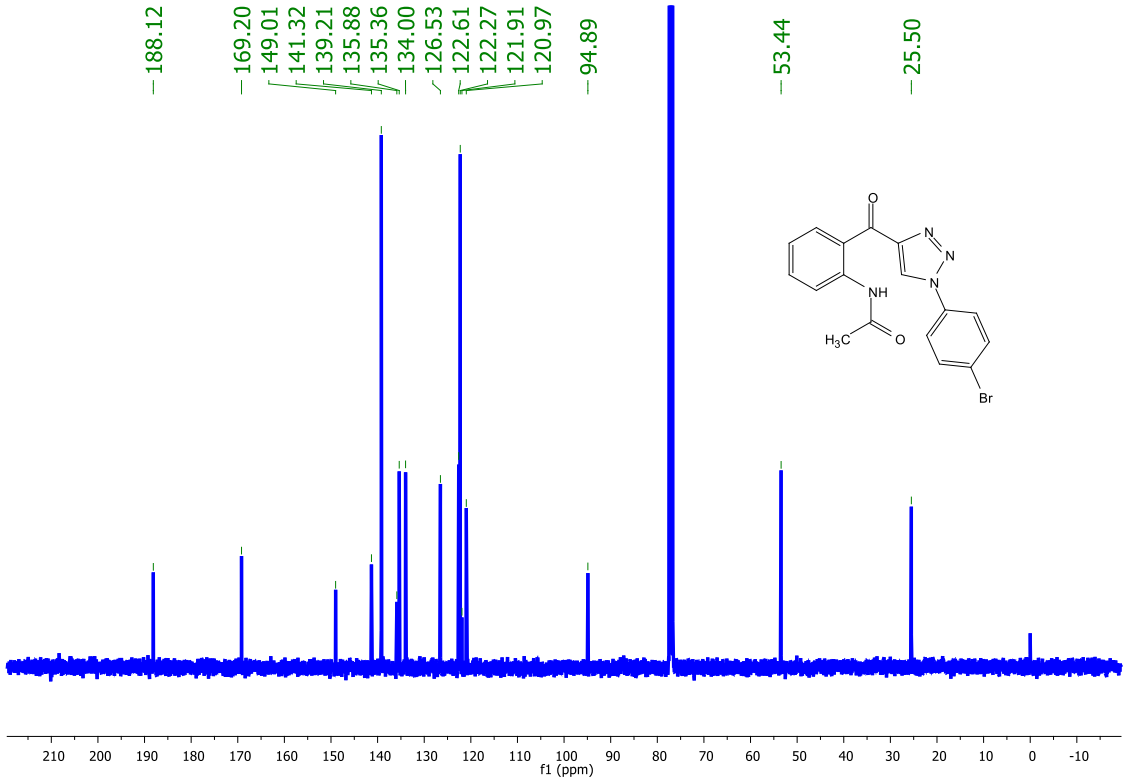
Spectrum 199: 31bb ^{1}H NMR (DMSO-d6, 400 MHz)



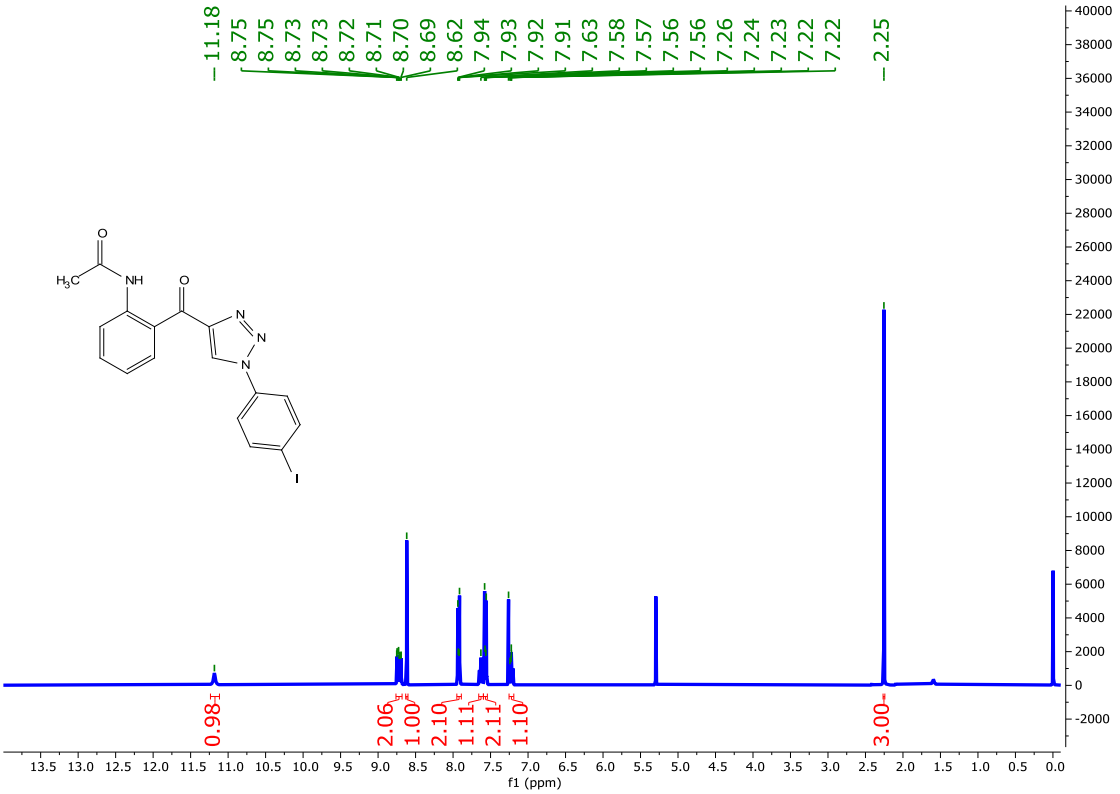
Spectrum 200: 31bb ^{13}C NMR (DMSO-d6, 101 MHz)



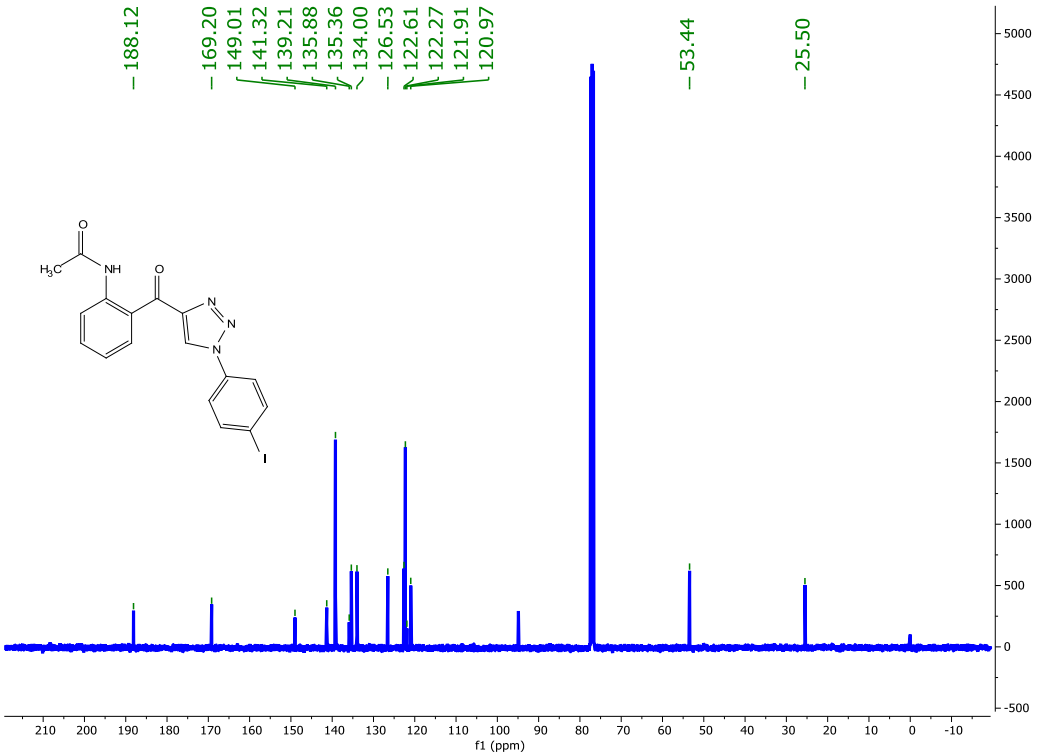
Spectrum 201: 38aa ^{1}H NMR ($CDCl_3$, 400 MHz)



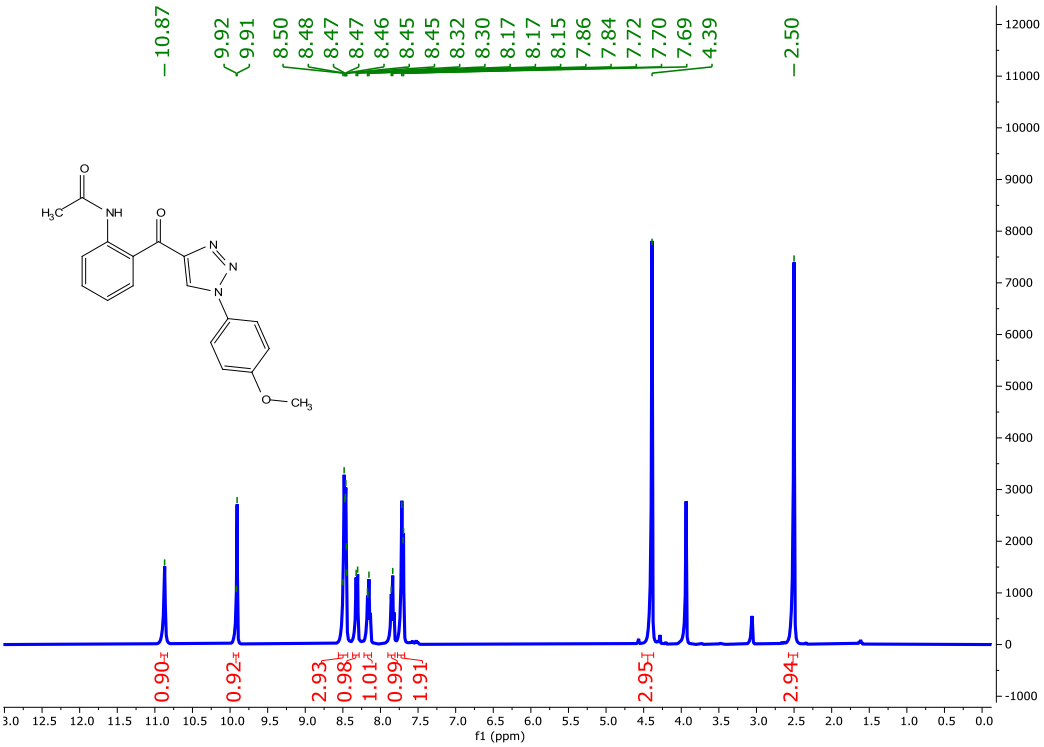
Spectrum 202: 38aa ^{13}C NMR ($CDCl_3$, 101 MHz)



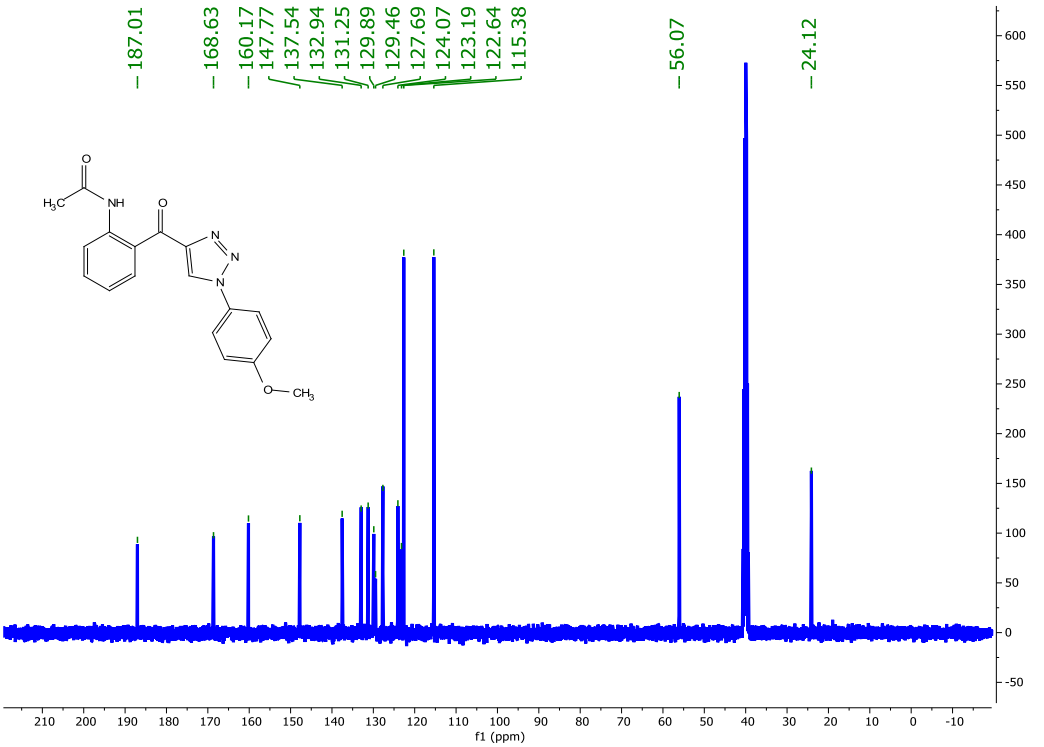
Spectrum 203: 38ab ^{1}H NMR ($CDCl_3$, 400 MHz)



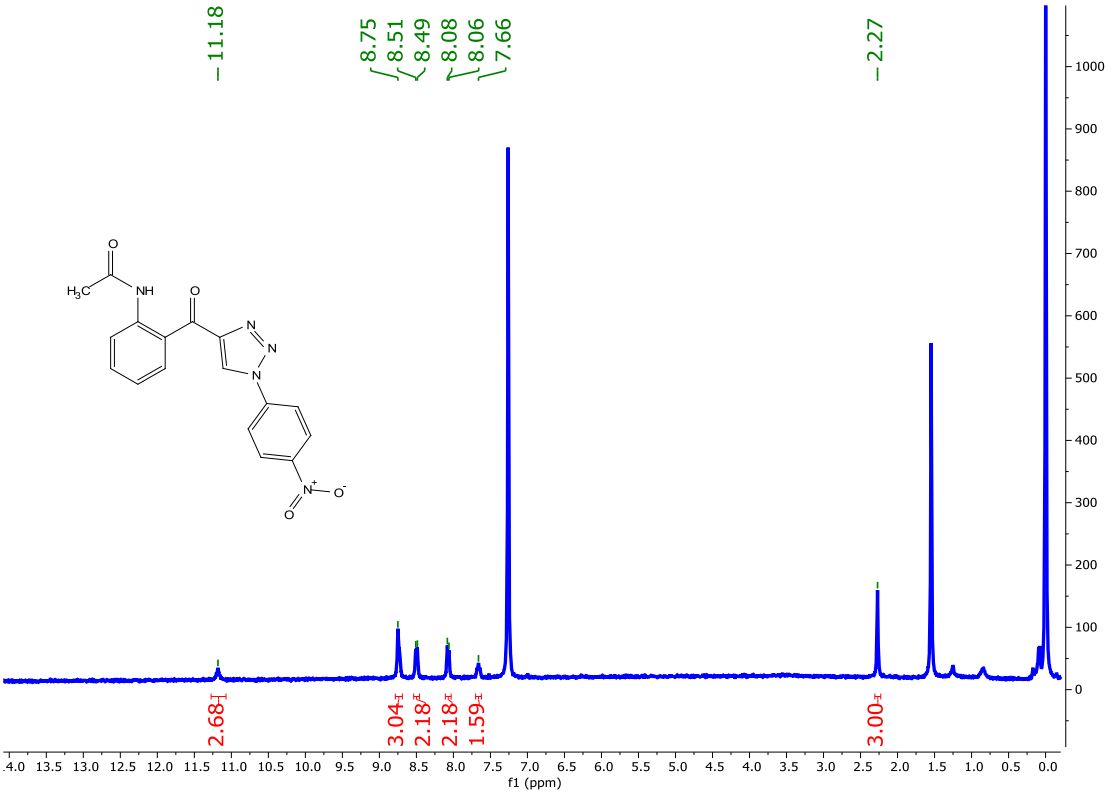
Spectrum 204: 38ab ^{13}C NMR ($CDCl_3$, 101 MHz)



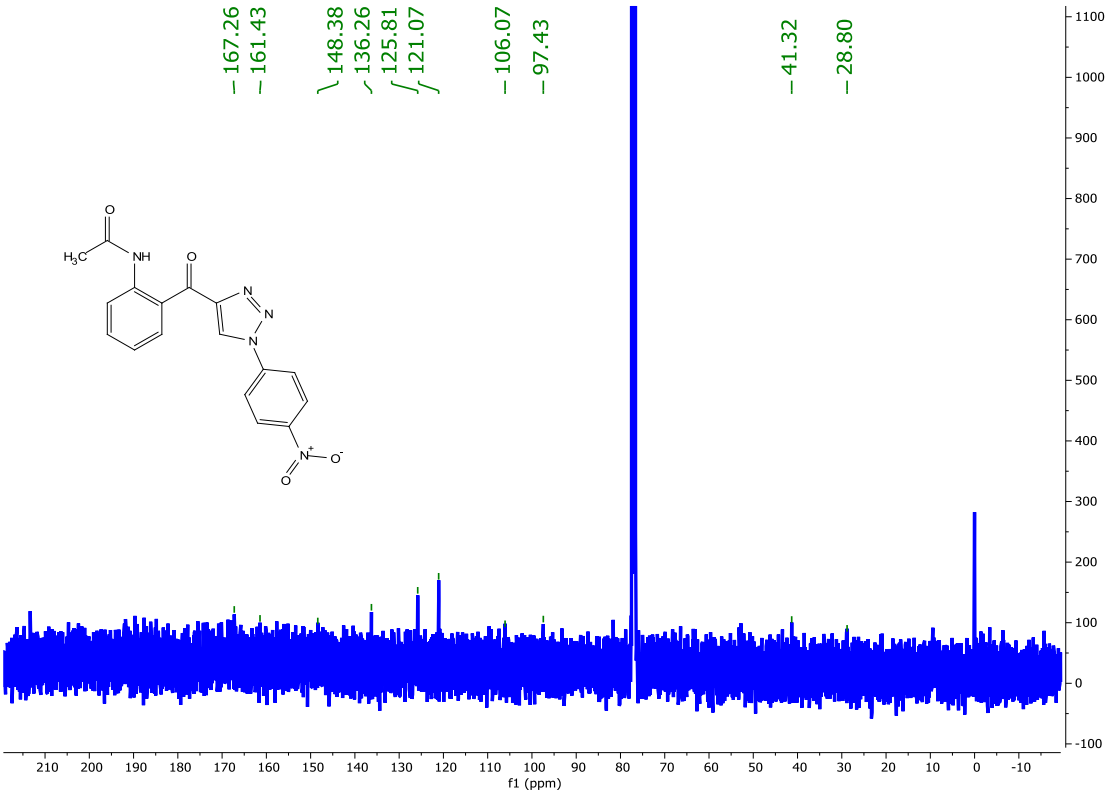
Spectrum 205: 38ac ^{1}H NMR ($CDCl_3$, 400 MHz)



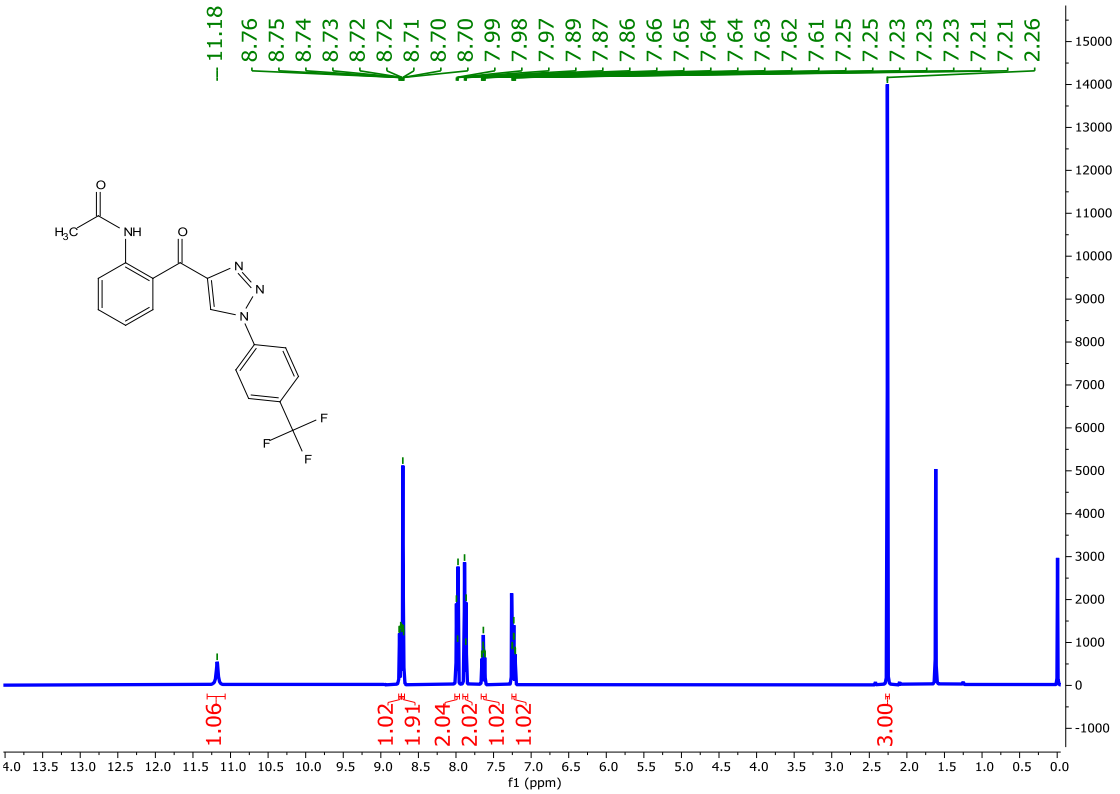
Spectrum 206: 38ac ^{13}C NMR ($CDCl_3$, 101 MHz)



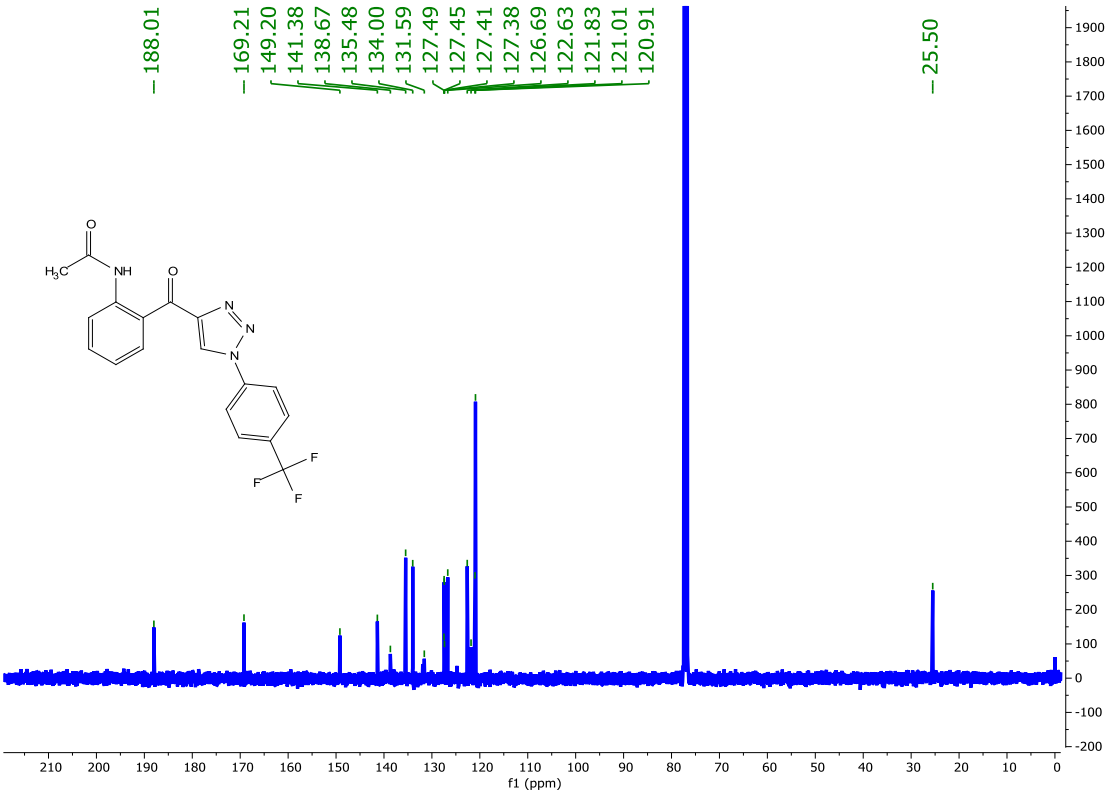
Spectrum 207: 38ad ^{1}H NMR ($CDCl_3$, 400 MHz)



Spectrum 208: 38ad ^{13}C NMR ($CDCl_3$, 101 MHz)

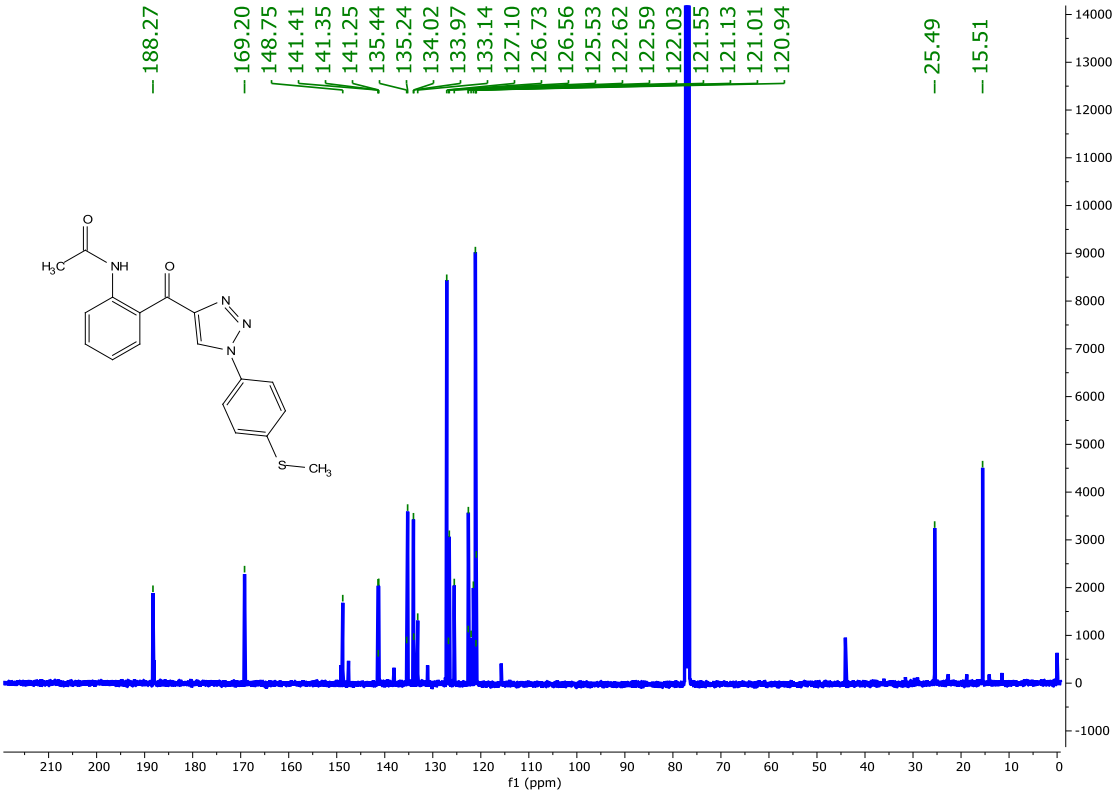


Spectrum 209: 38ae ^{1}H NMR ($CDCl_3$, 400 MHz)

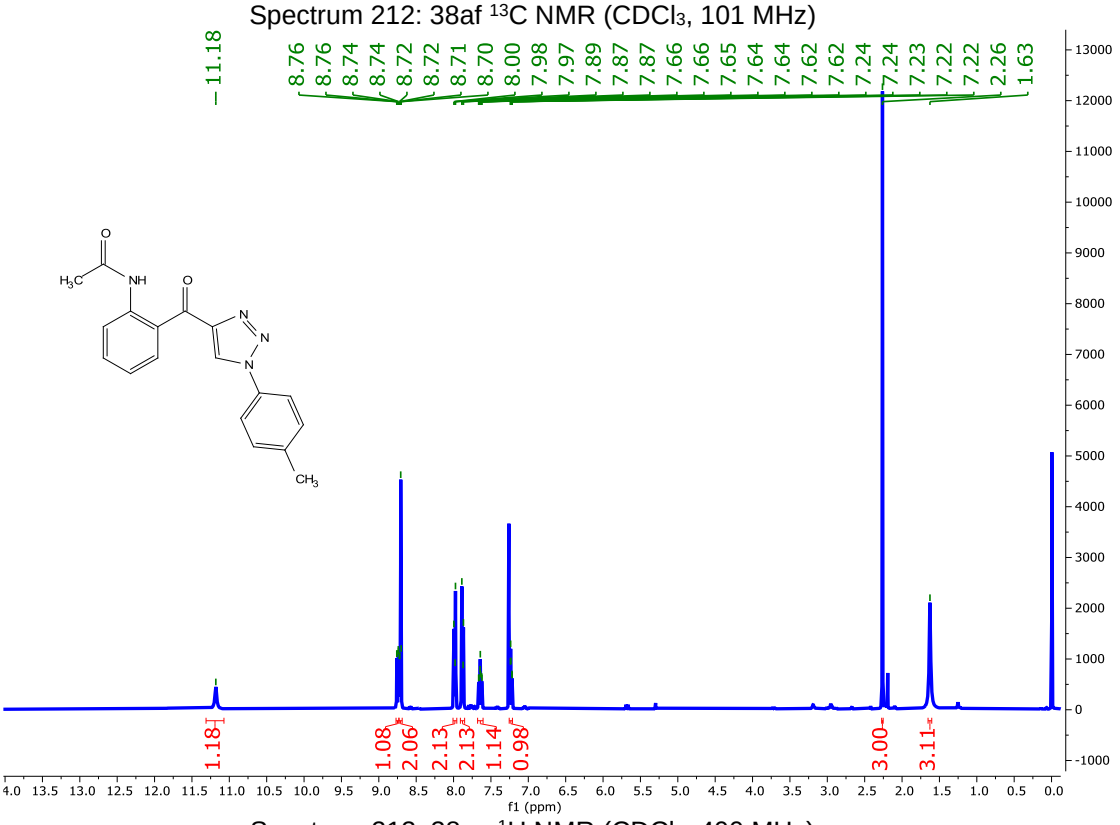


Spectrum 210: 38ae ^{13}C NMR ($CDCl_3$, 101 MHz)

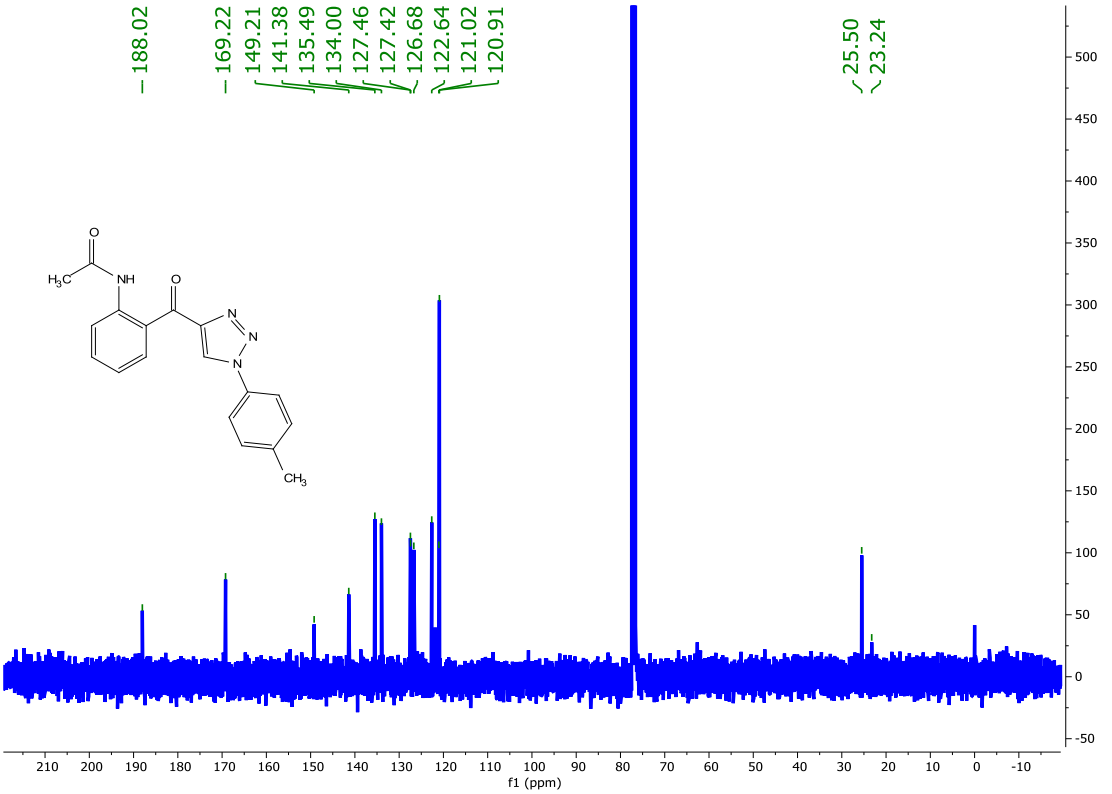
Spectrum 211: 38af ^{1}H NMR ($CDCl_3$, 400 MHz)



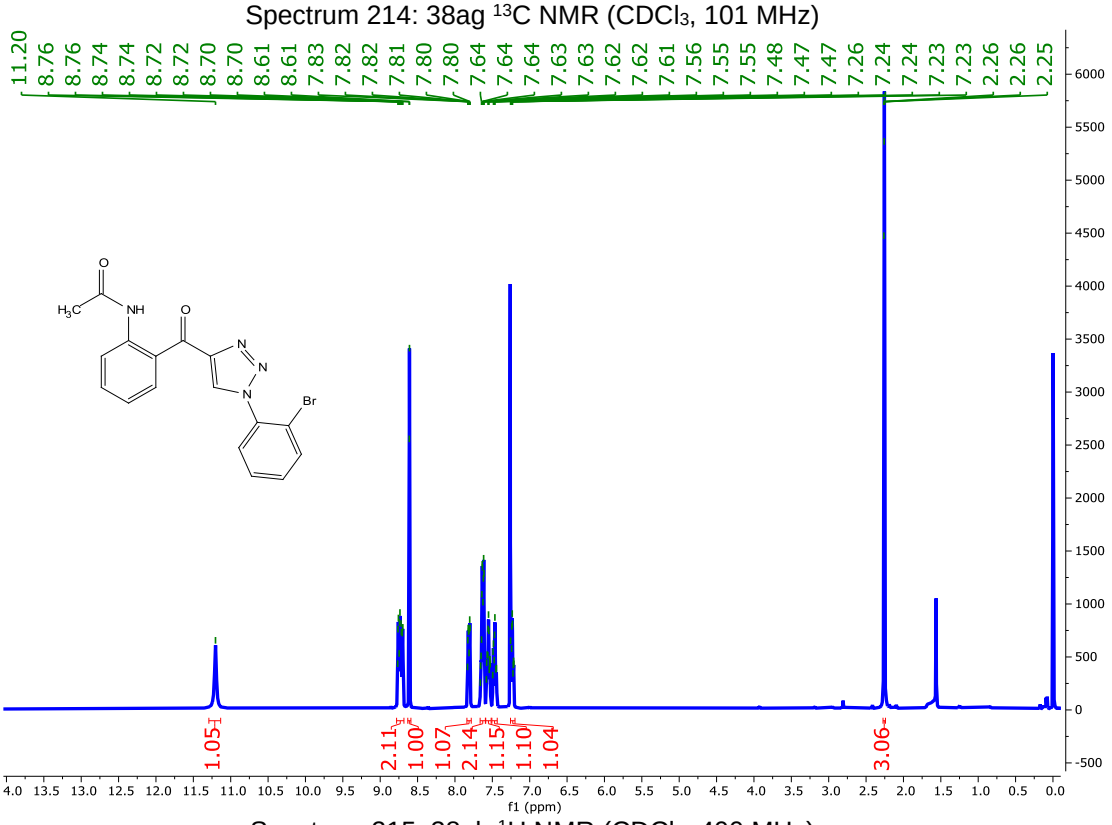
Spectrum 212: 38af ^{13}C NMR ($CDCl_3$, 101 MHz)



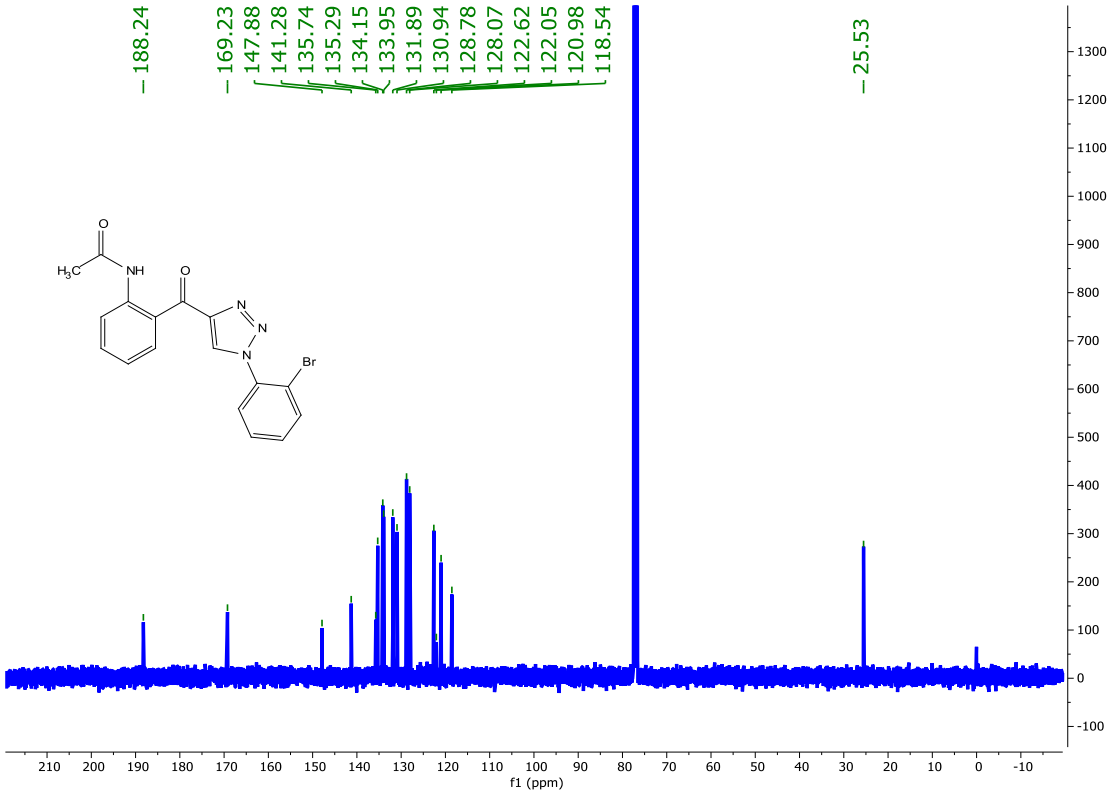
Spectrum 213: 38ag ^{1}H NMR ($CDCl_3$, 400 MHz)



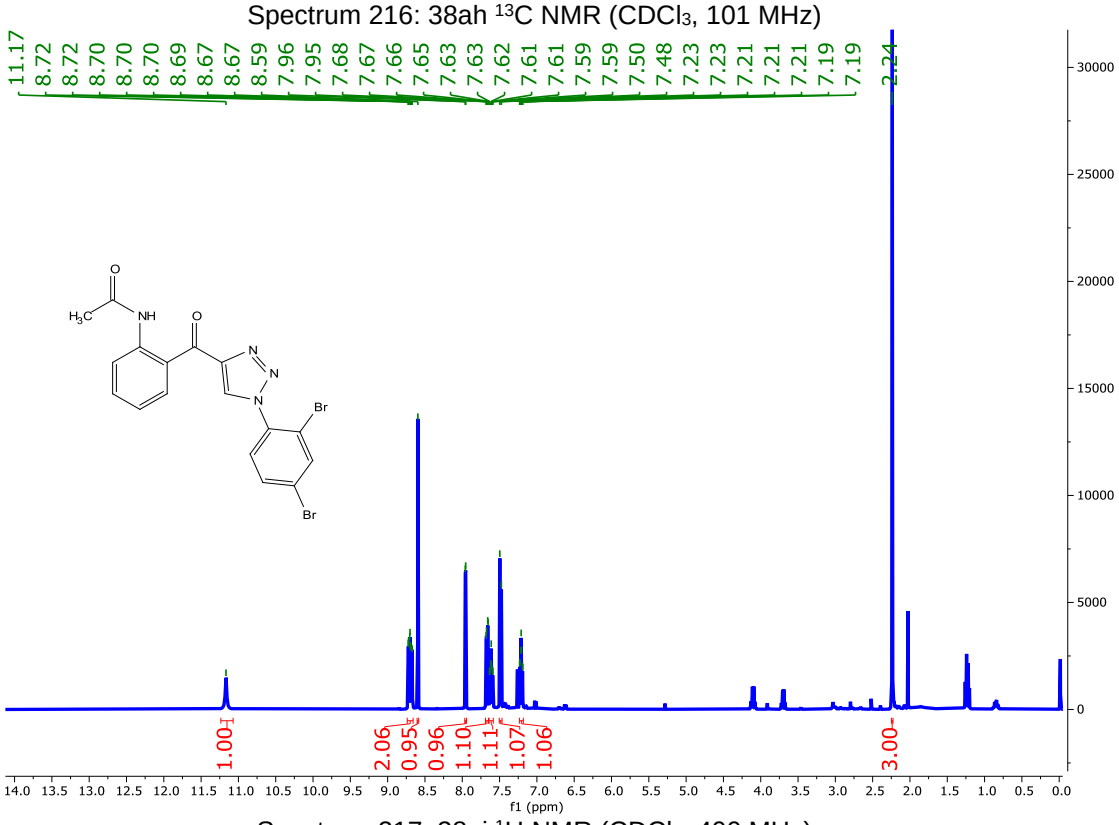
Spectrum 214: 38ag ^{13}C NMR ($CDCl_3$, 101 MHz)



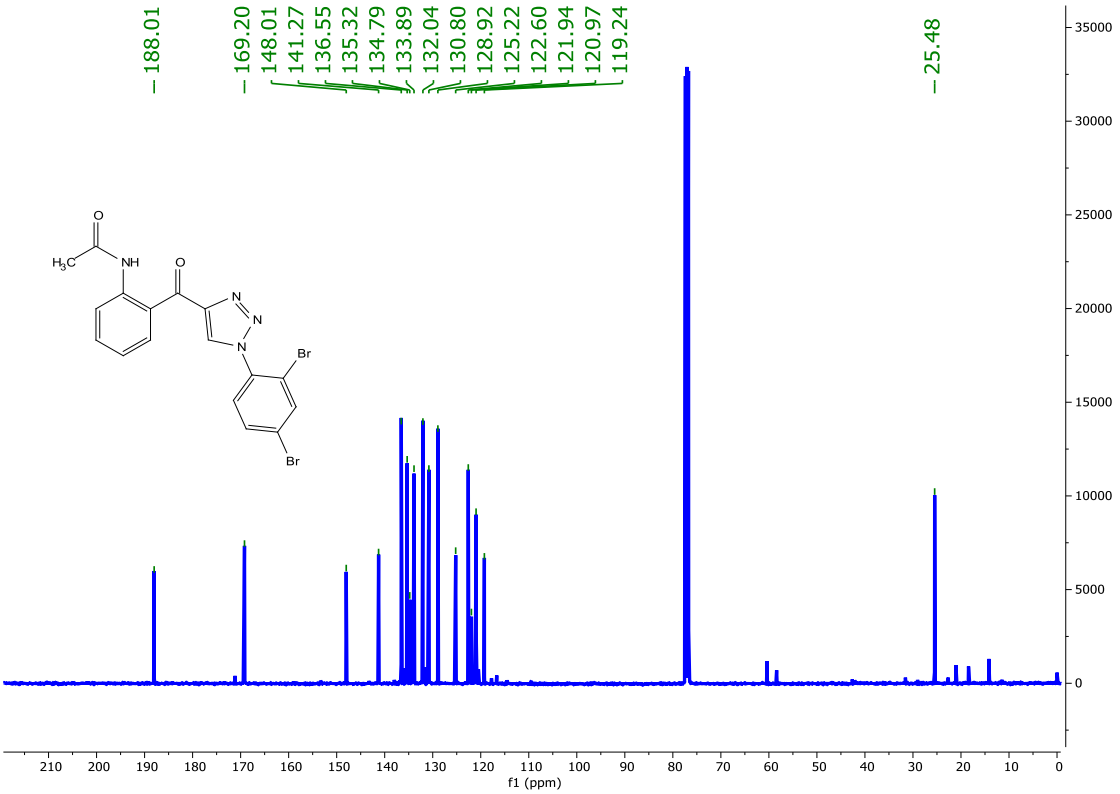
Spectrum 215: 38ah ^{1}H NMR ($CDCl_3$, 400 MHz)



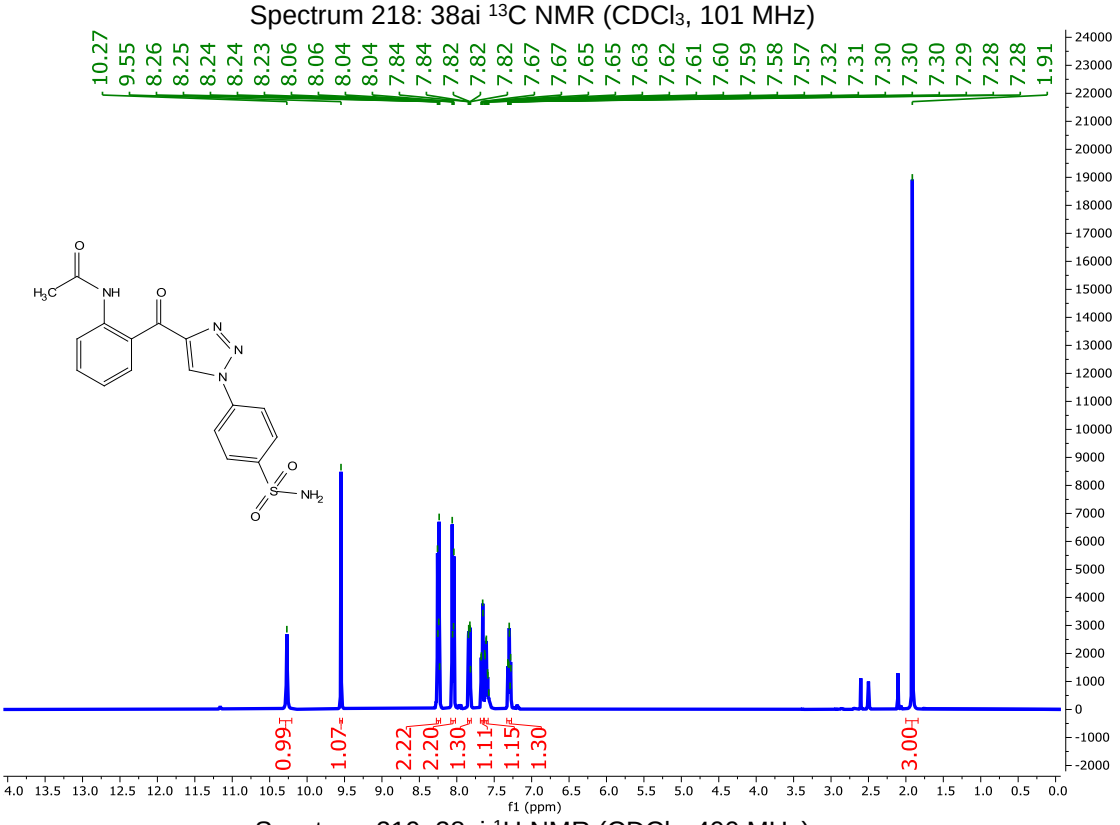
Spectrum 216: 38ah ^{13}C NMR ($CDCl_3$, 101 MHz)



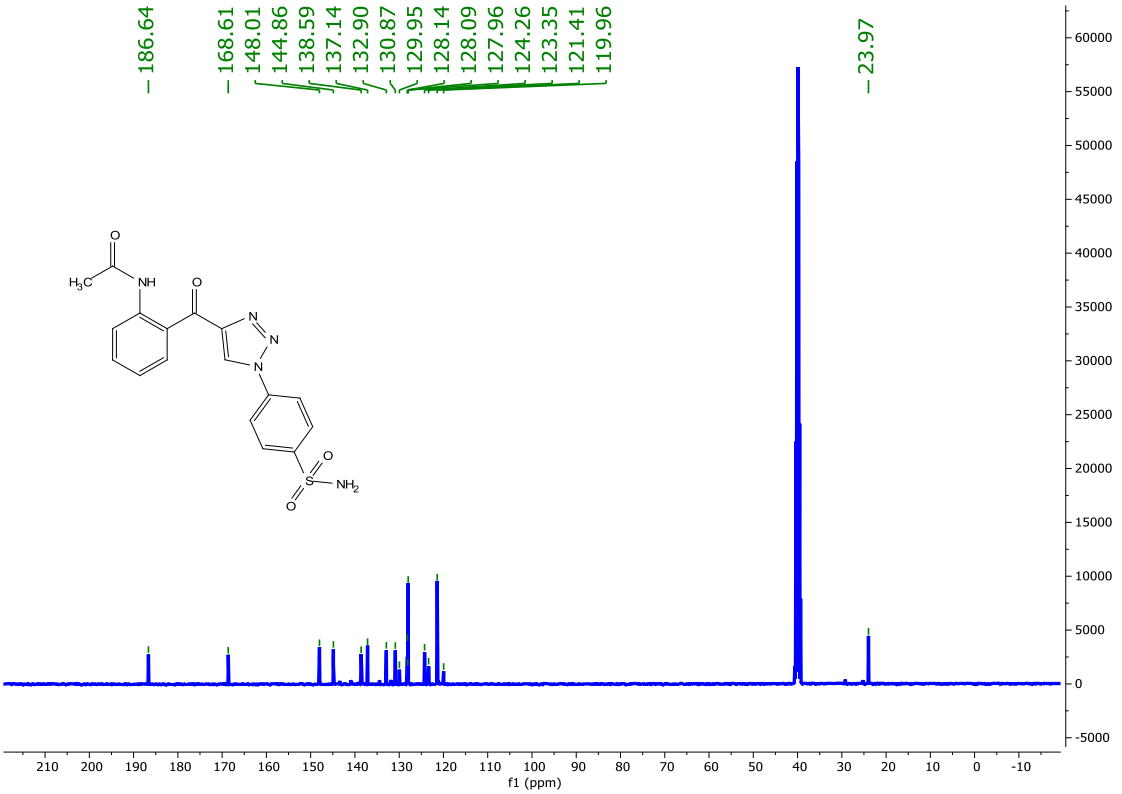
Spectrum 217: 38ai ^{1}H NMR ($CDCl_3$, 400 MHz)



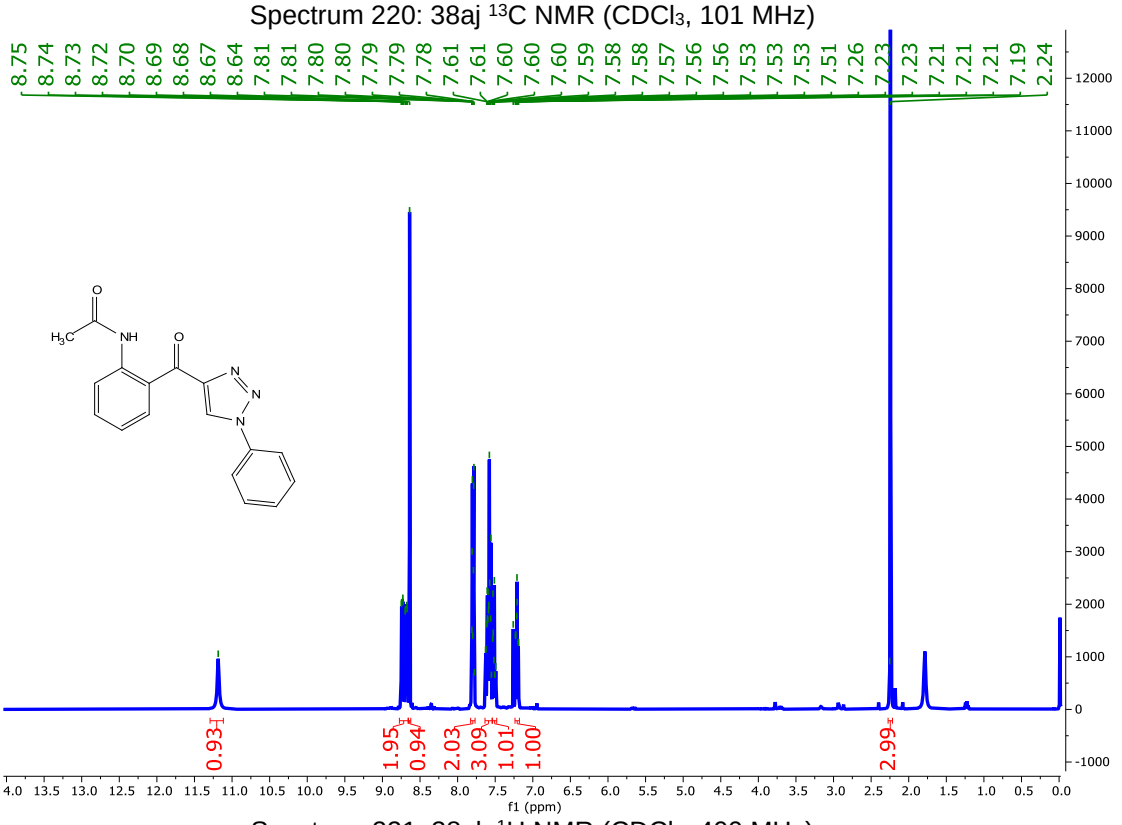
Spectrum 218: 38ai ^{13}C NMR ($CDCl_3$, 101 MHz)



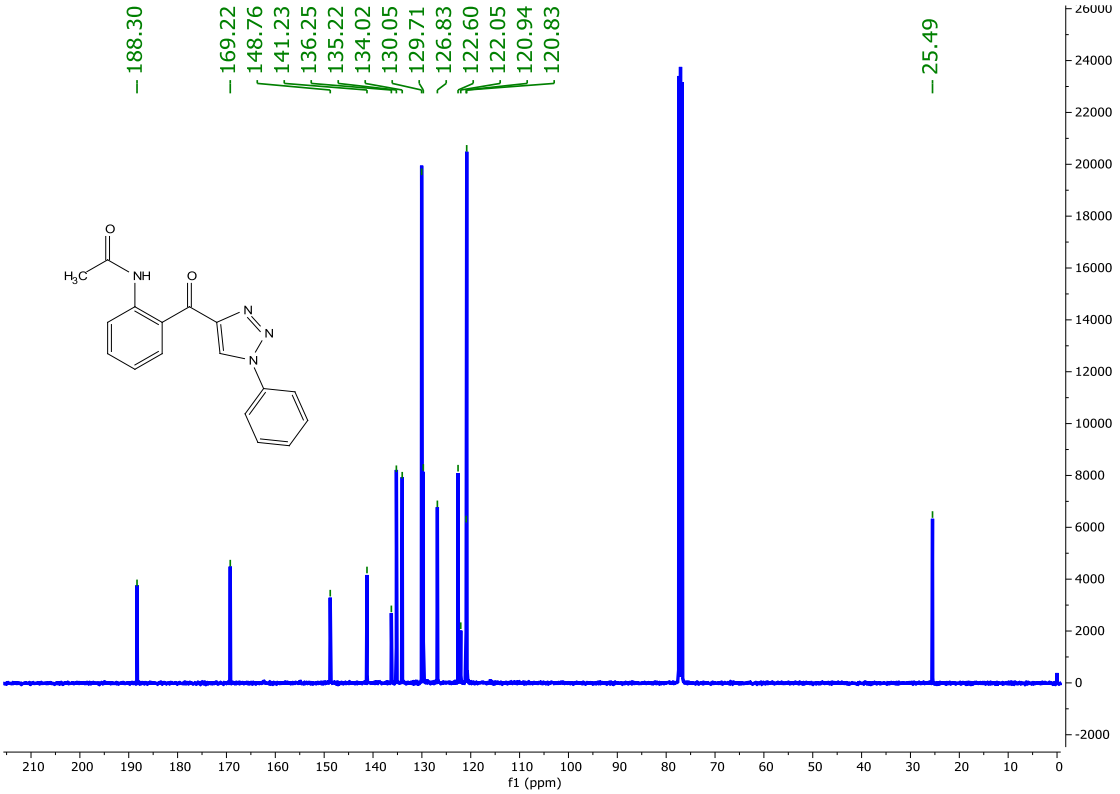
Spectrum 219: 38aj ^{1}H NMR ($CDCl_3$, 400 MHz)



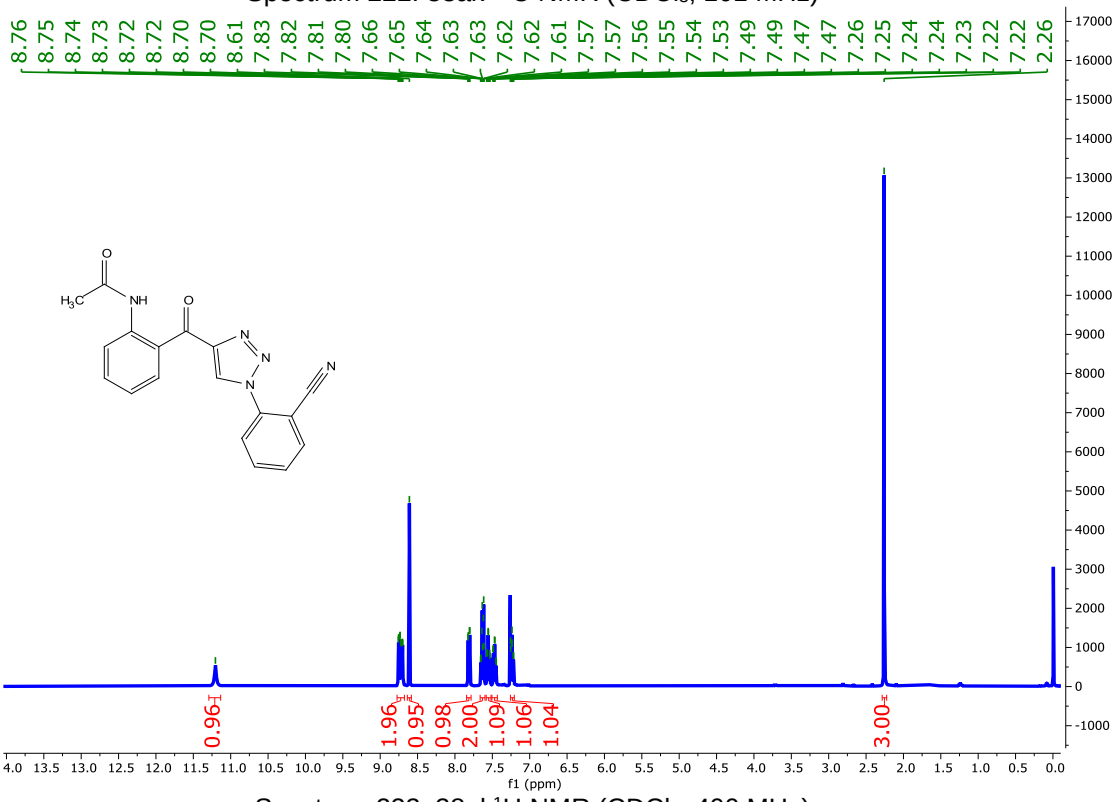
Spectrum 220: 38aj ^{13}C NMR ($CDCl_3$, 101 MHz)



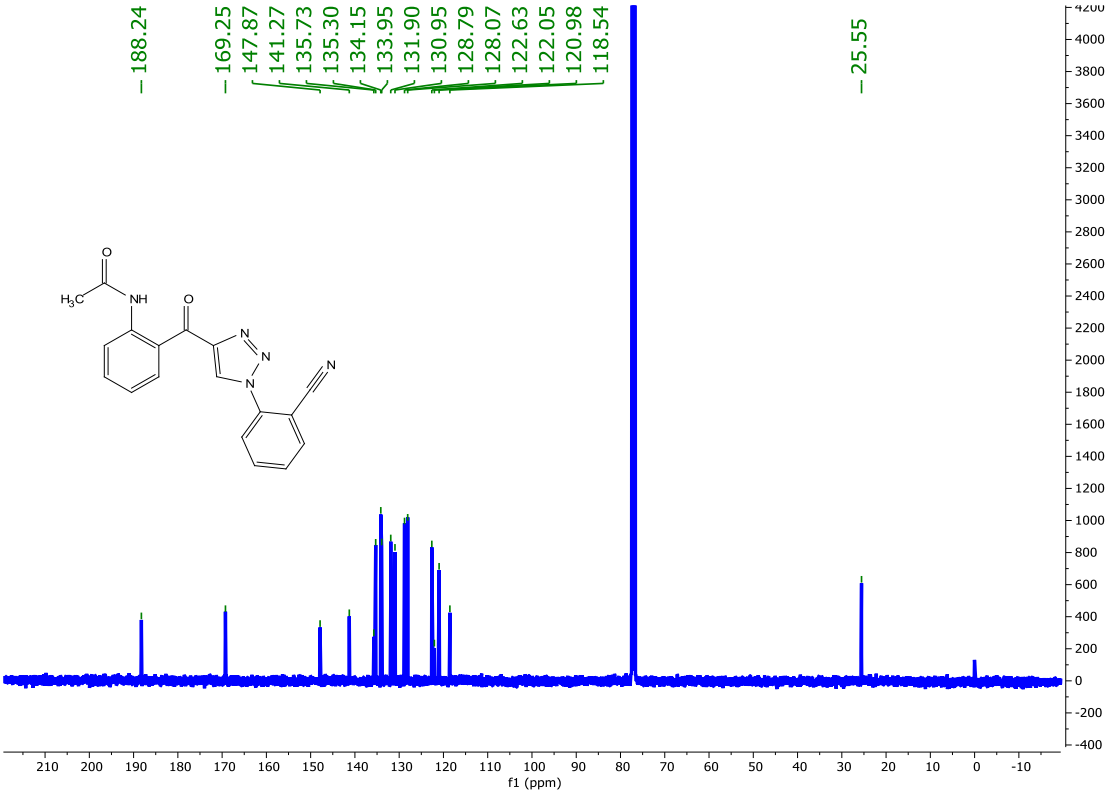
Spectrum 221: 38ak ^{1}H NMR ($CDCl_3$, 400 MHz)



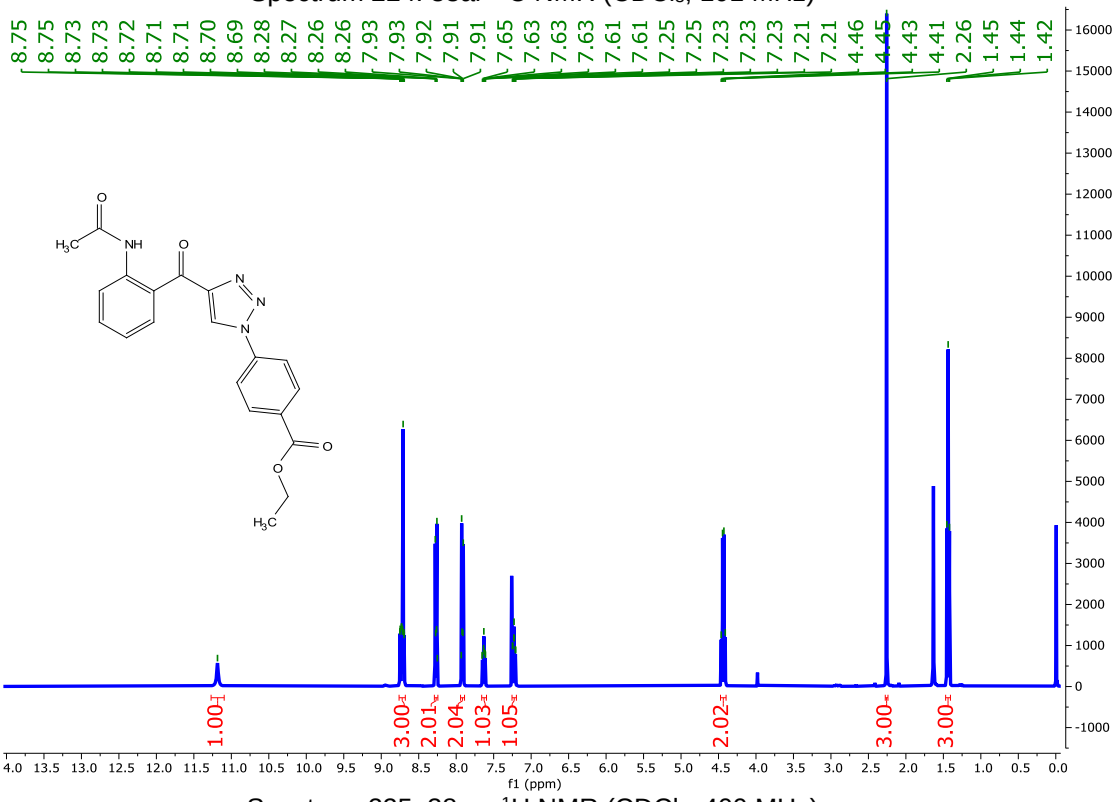
Spectrum 222: 38ak ^{13}C NMR ($CDCl_3$, 101 MHz)



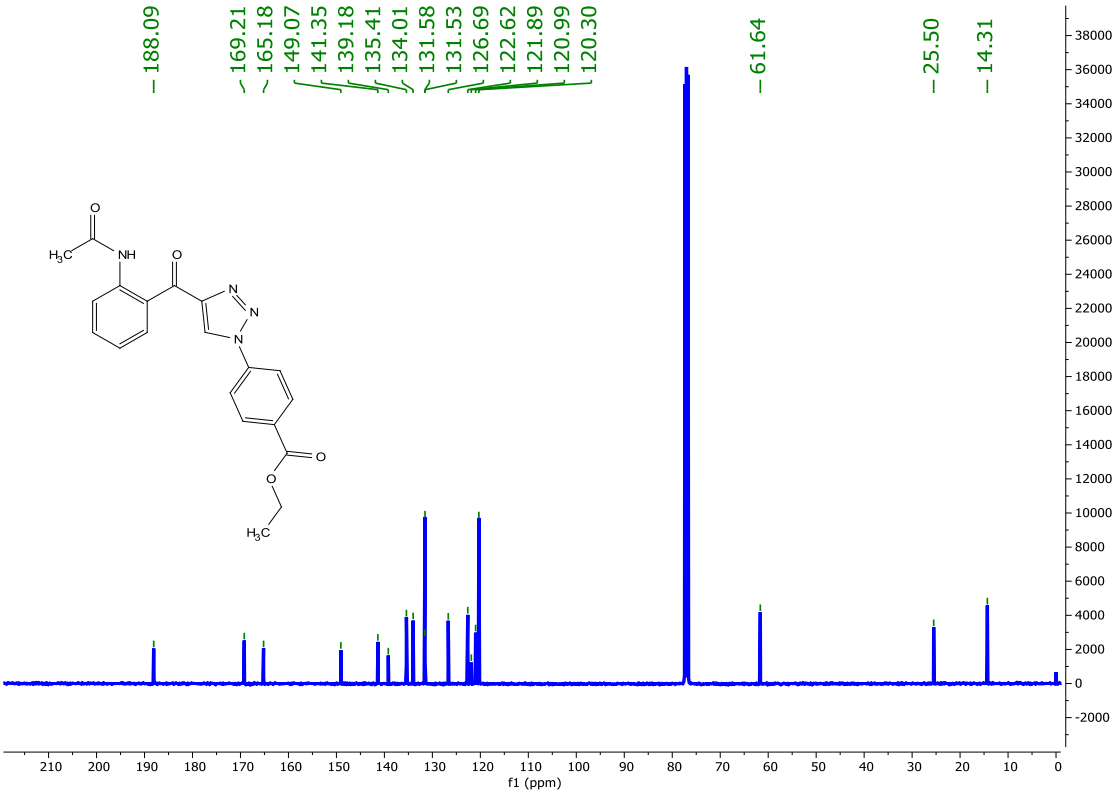
Spectrum 223: 38al ^{1}H NMR ($CDCl_3$, 400 MHz)



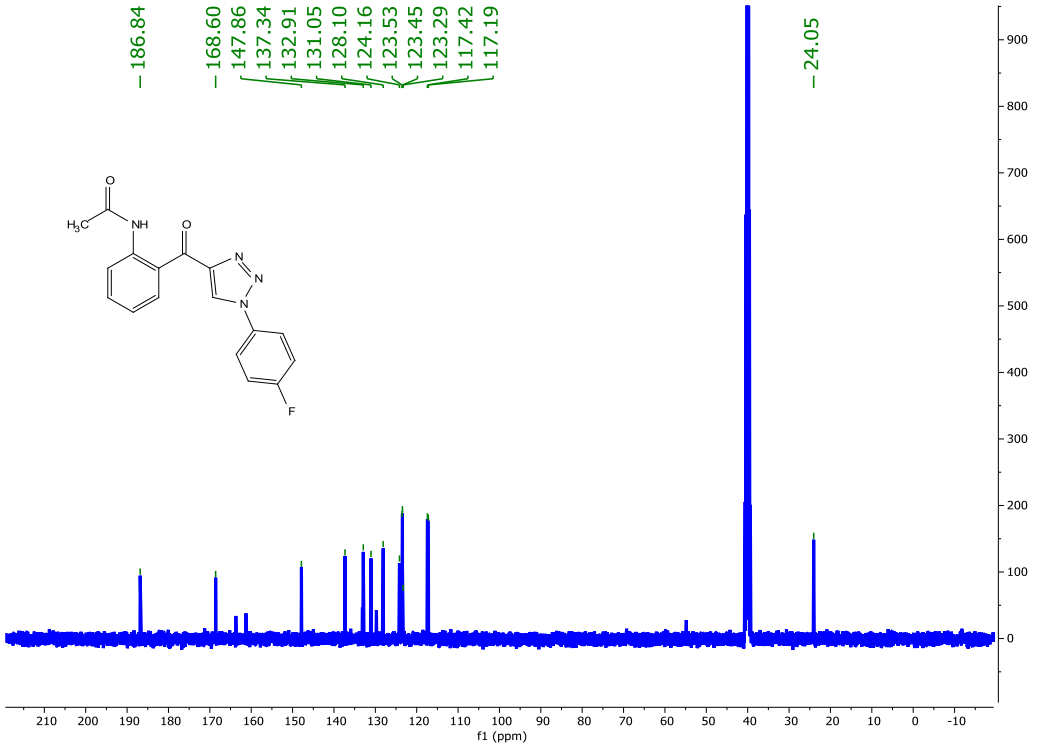
Spectrum 224: 38al ^{13}C NMR ($CDCl_3$, 101 MHz)



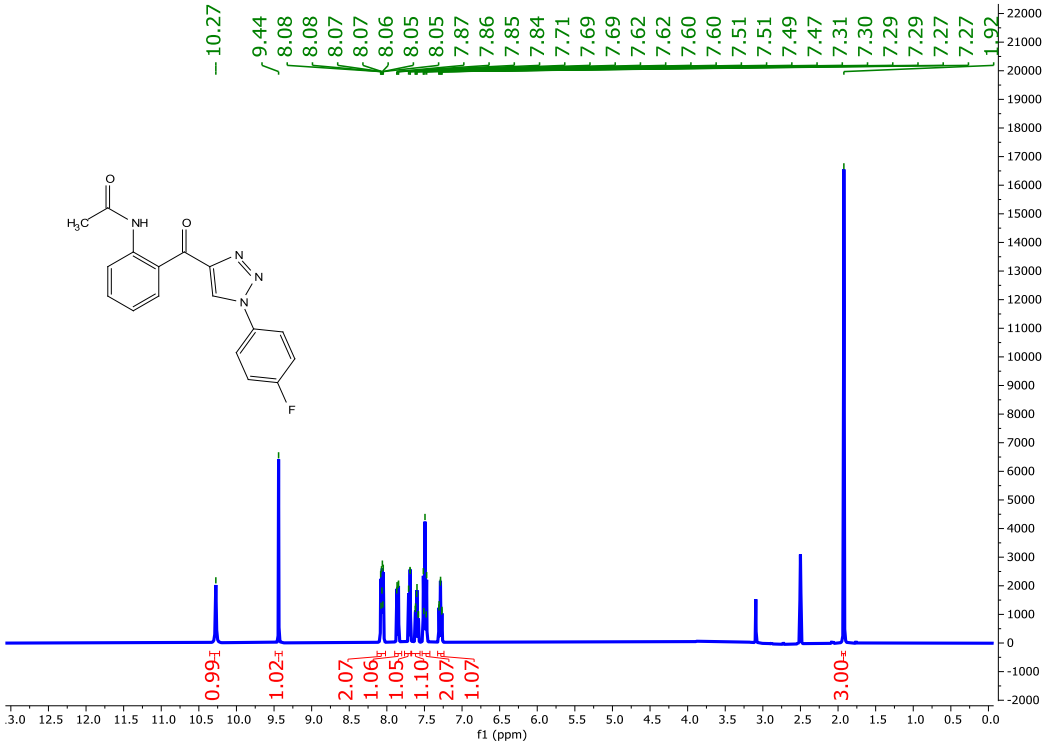
Spectrum 225: 38am ^{1}H NMR ($CDCl_3$, 400 MHz)



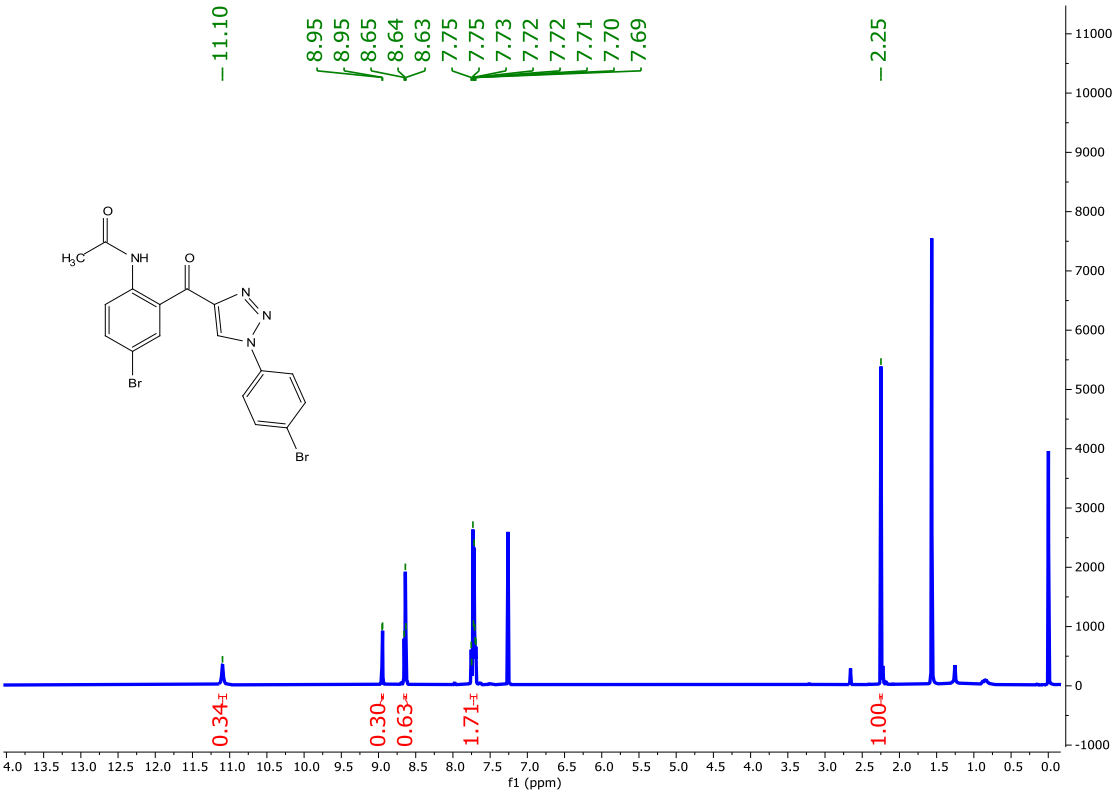
Spectrum 226: 38am ^{13}C NMR ($CDCl_3$, 101 MHz)



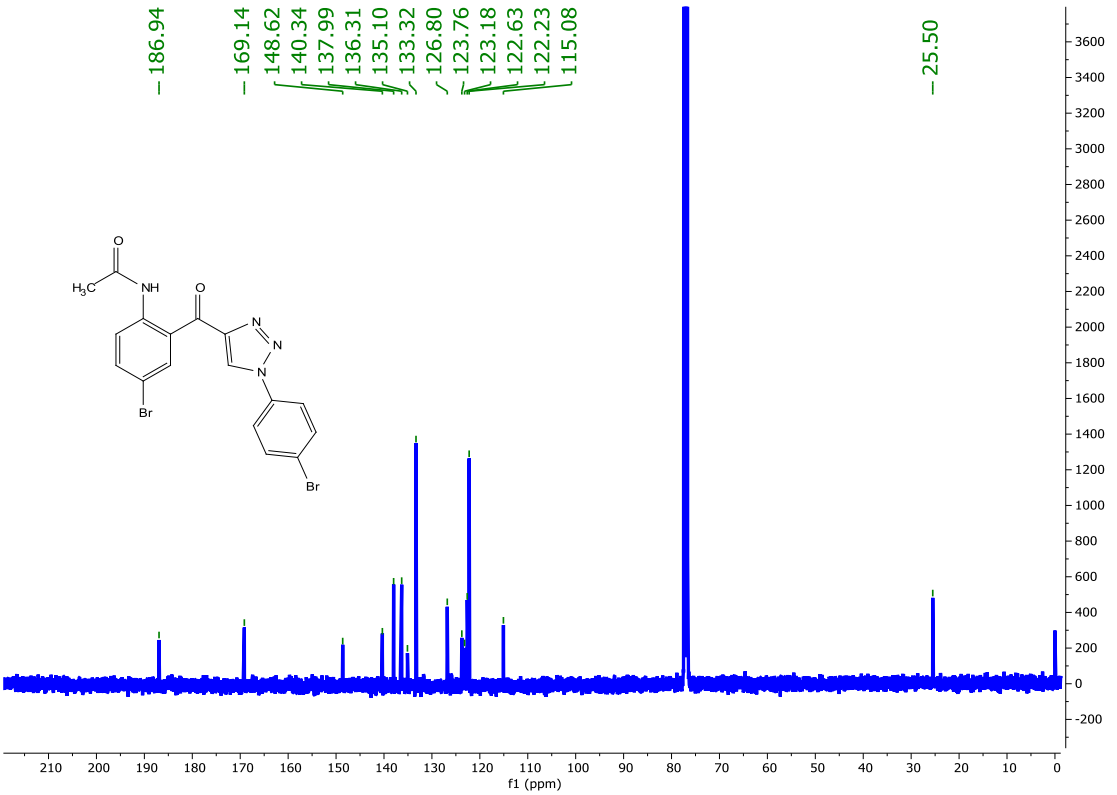
Spectrum 227: 38an ^{1}H NMR ($CDCl_3$, 400 MHz)



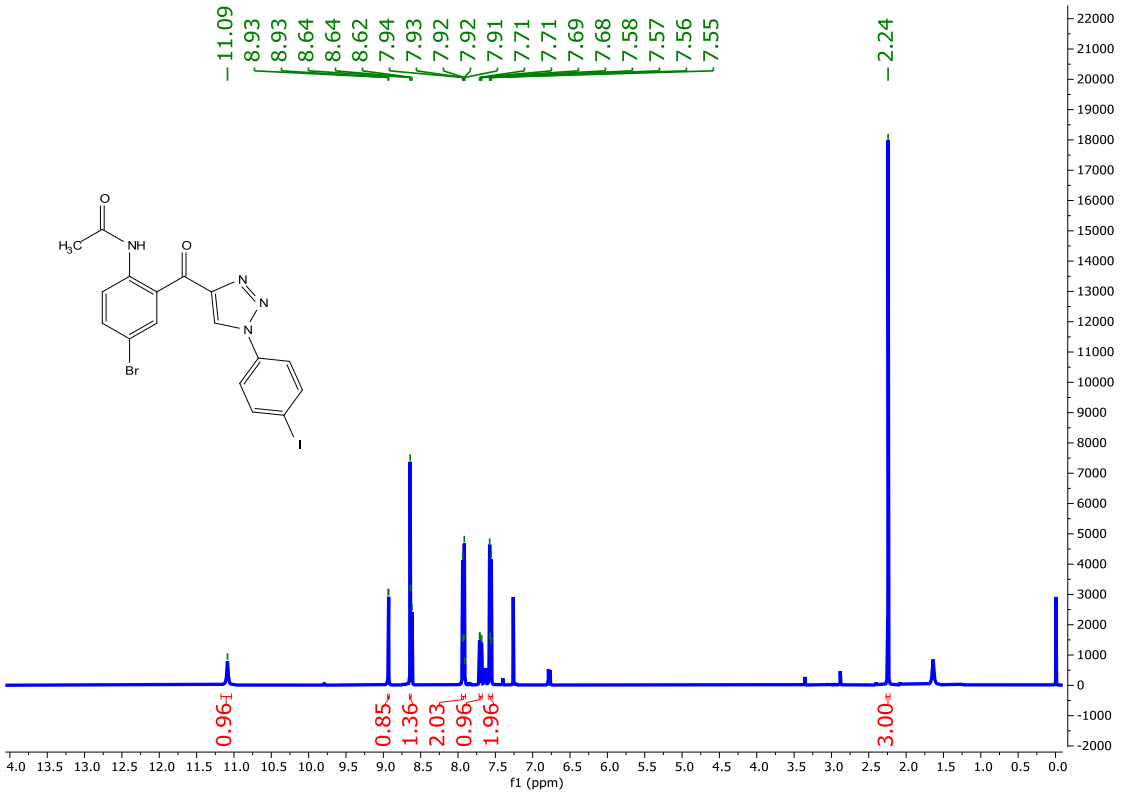
Spectrum 228: 38an ^{13}C NMR ($CDCl_3$, 101 MHz)



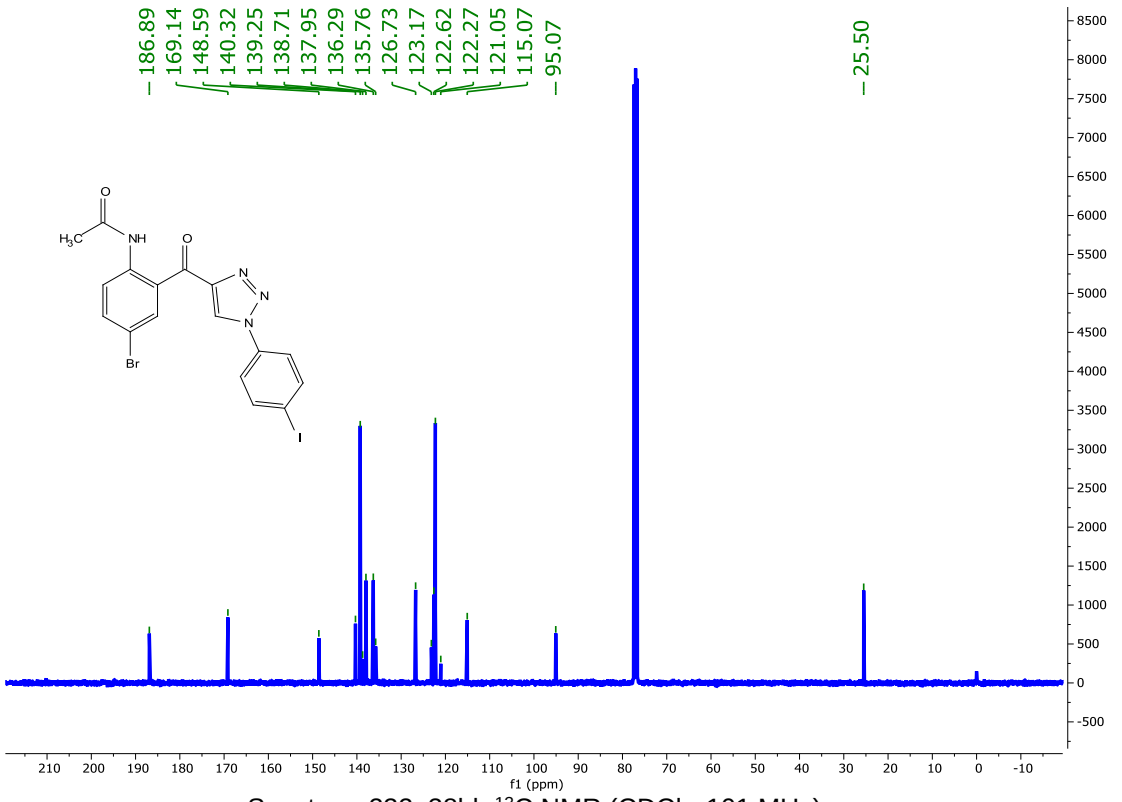
Spectrum 229: 38ba ^{1}H NMR ($CDCl_3$, 400 MHz)



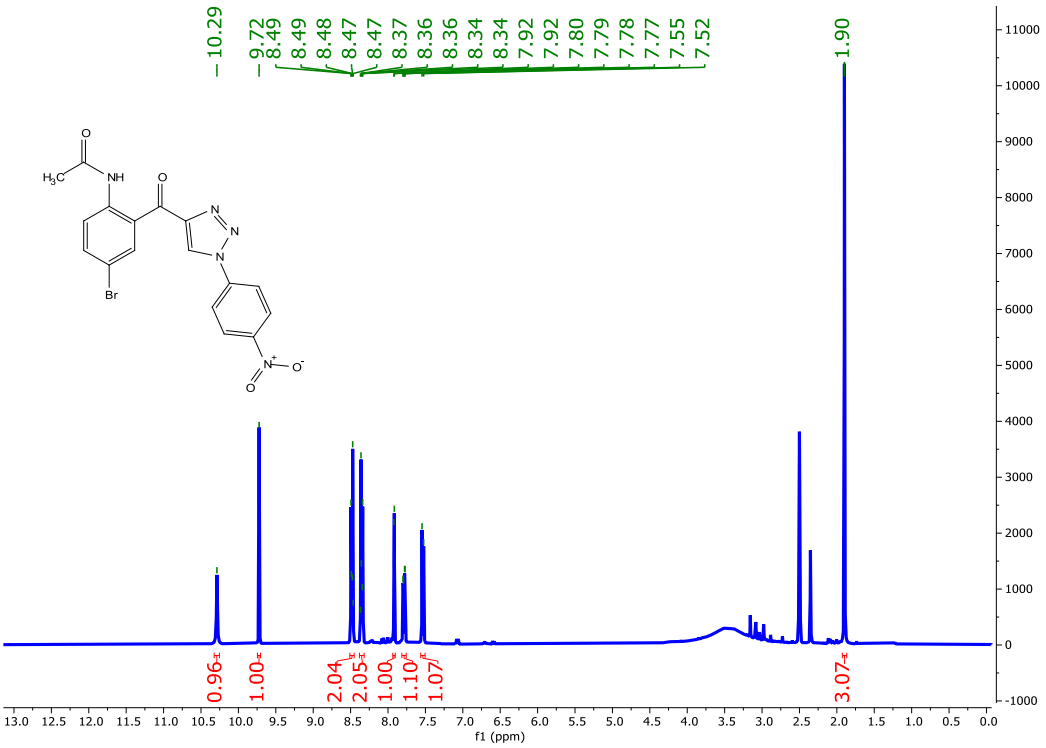
Spectrum 230: 38ba ^{13}C NMR ($CDCl_3$, 101 MHz)



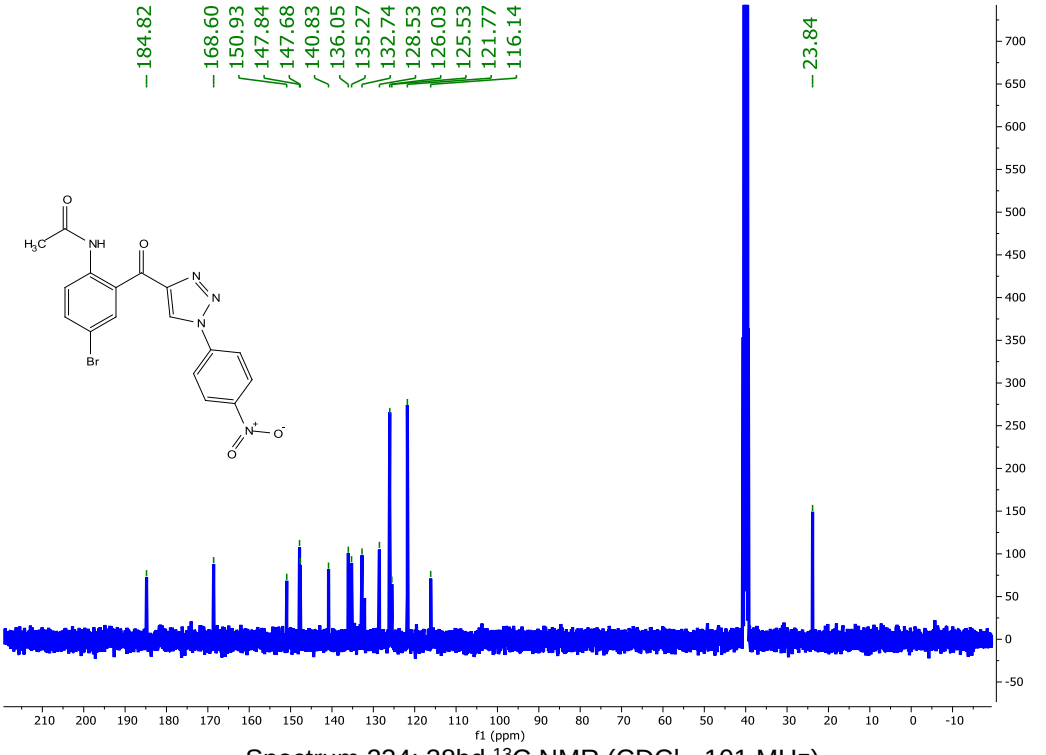
Spectrum 231: 38bb ^{1}H NMR ($CDCl_3$, 400 MHz)



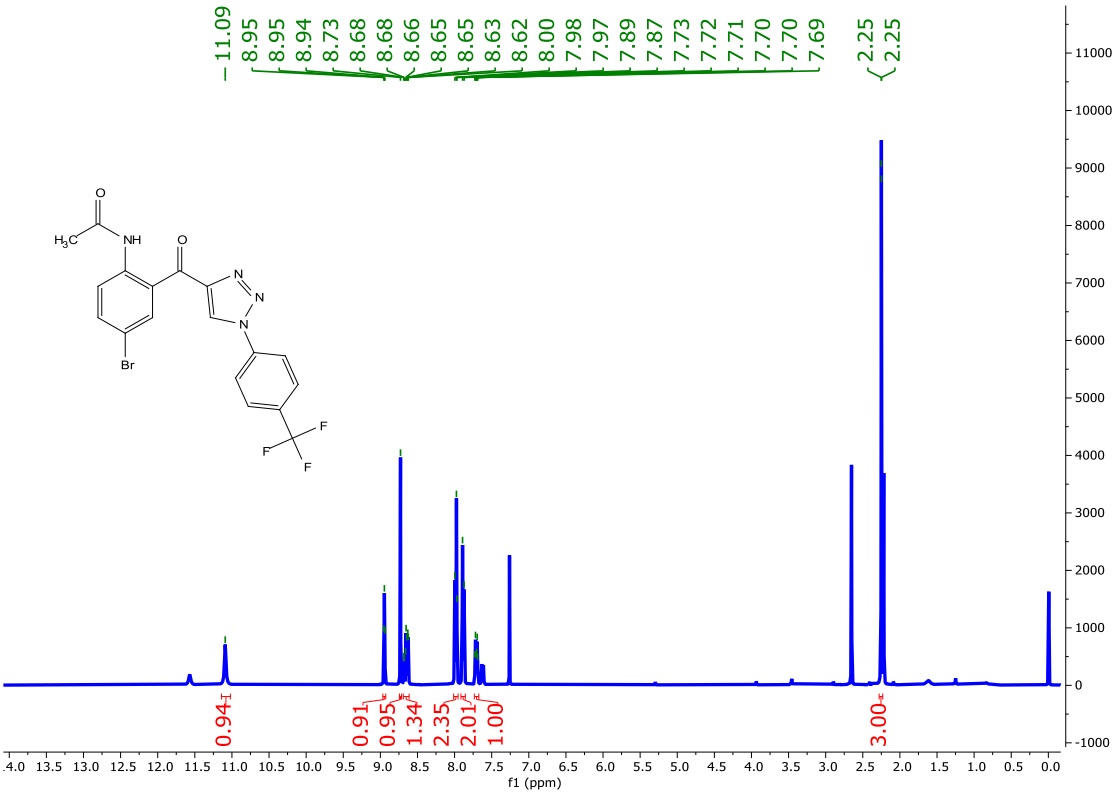
Spectrum 232: 38bb ^{13}C NMR ($CDCl_3$, 101 MHz)



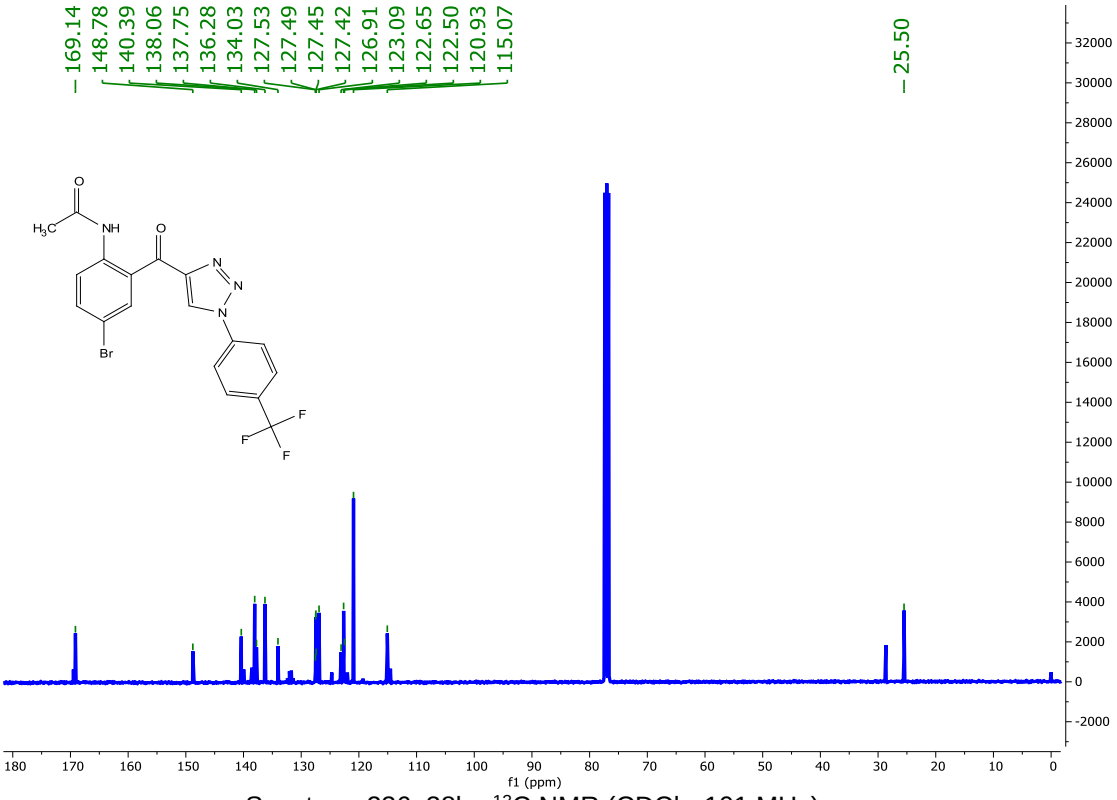
Spectrum 233: 38bd ^{1}H NMR ($CDCl_3$, 400 MHz)



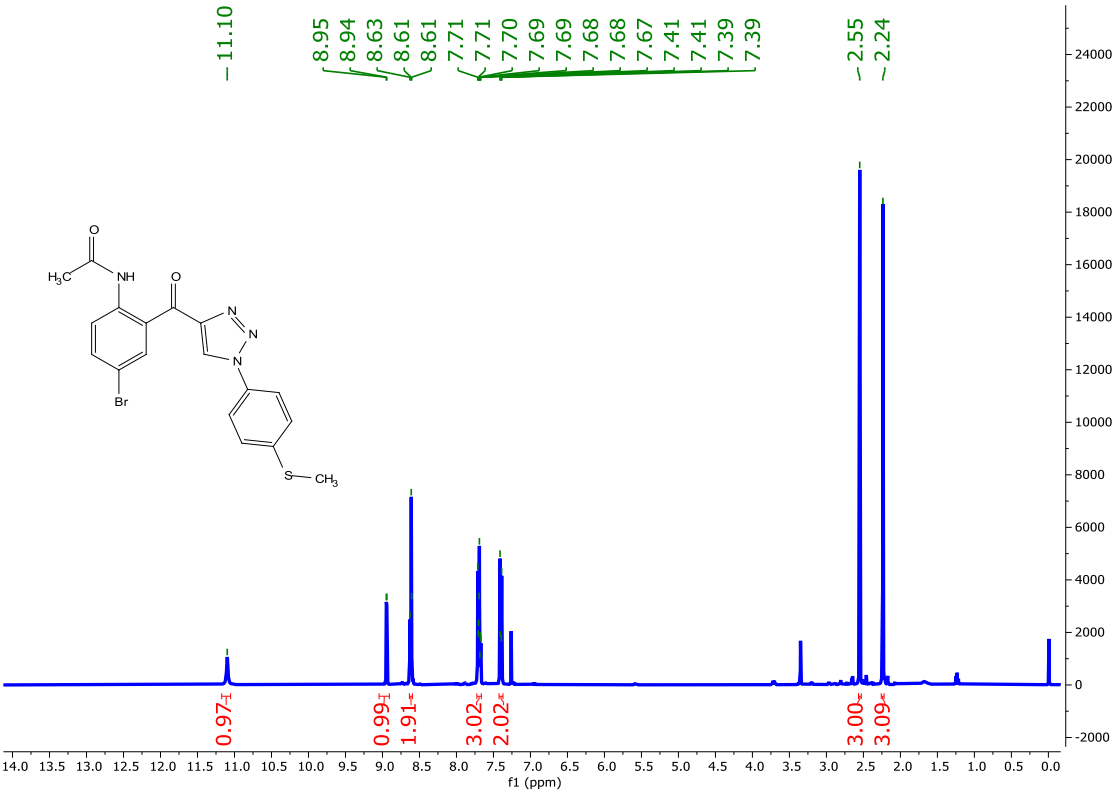
Spectrum 234: 38bd ^{13}C NMR ($CDCl_3$, 101 MHz)



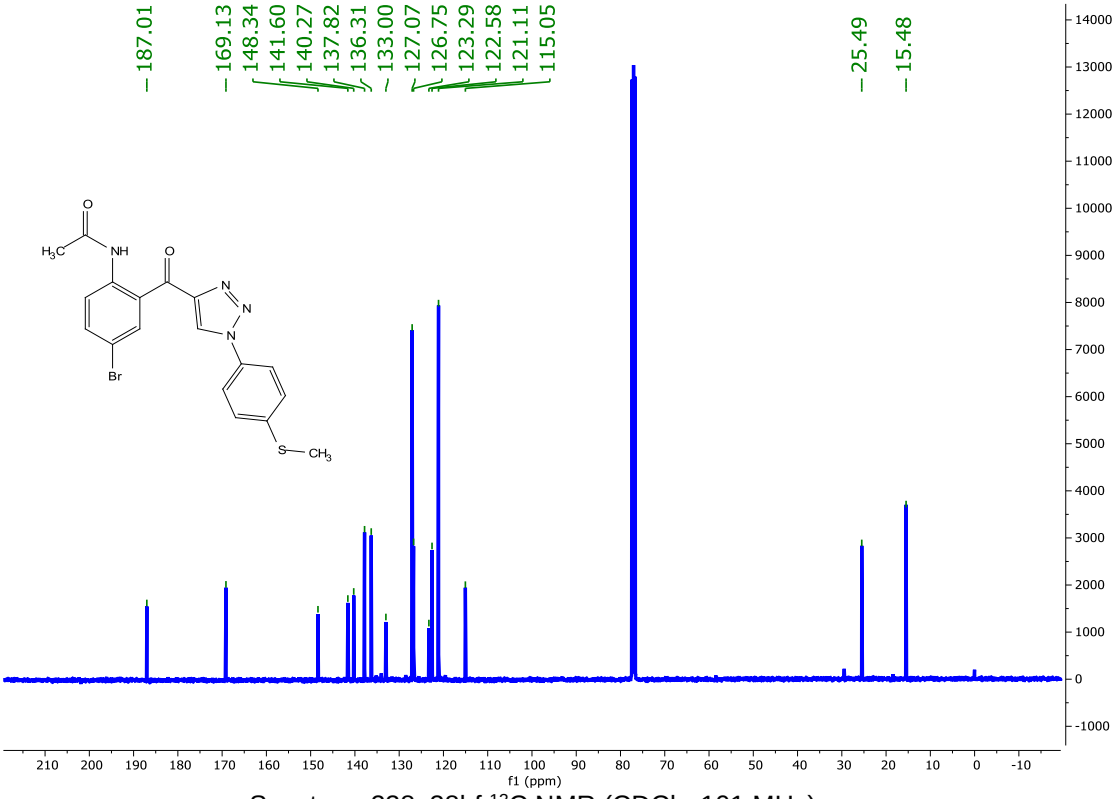
Spectrum 235: 38be ^{1}H NMR ($CDCl_3$, 400 MHz)



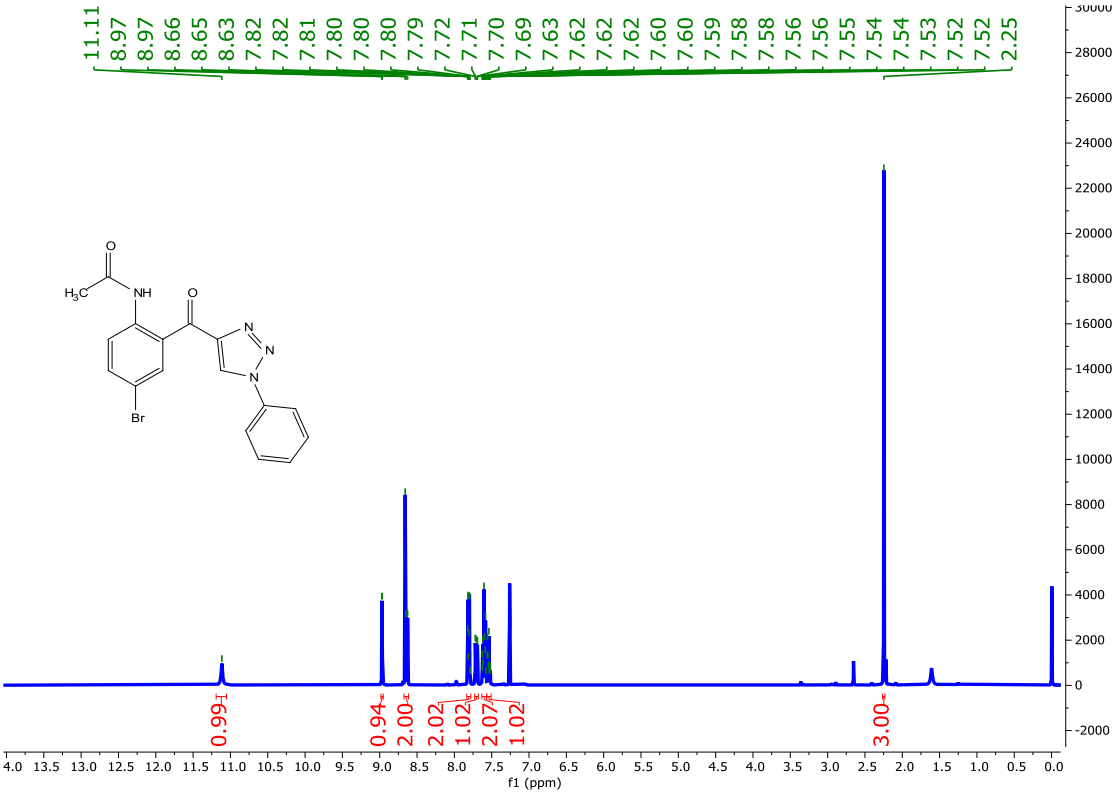
Spectrum 236: 38be ^{13}C NMR ($CDCl_3$, 101 MHz)



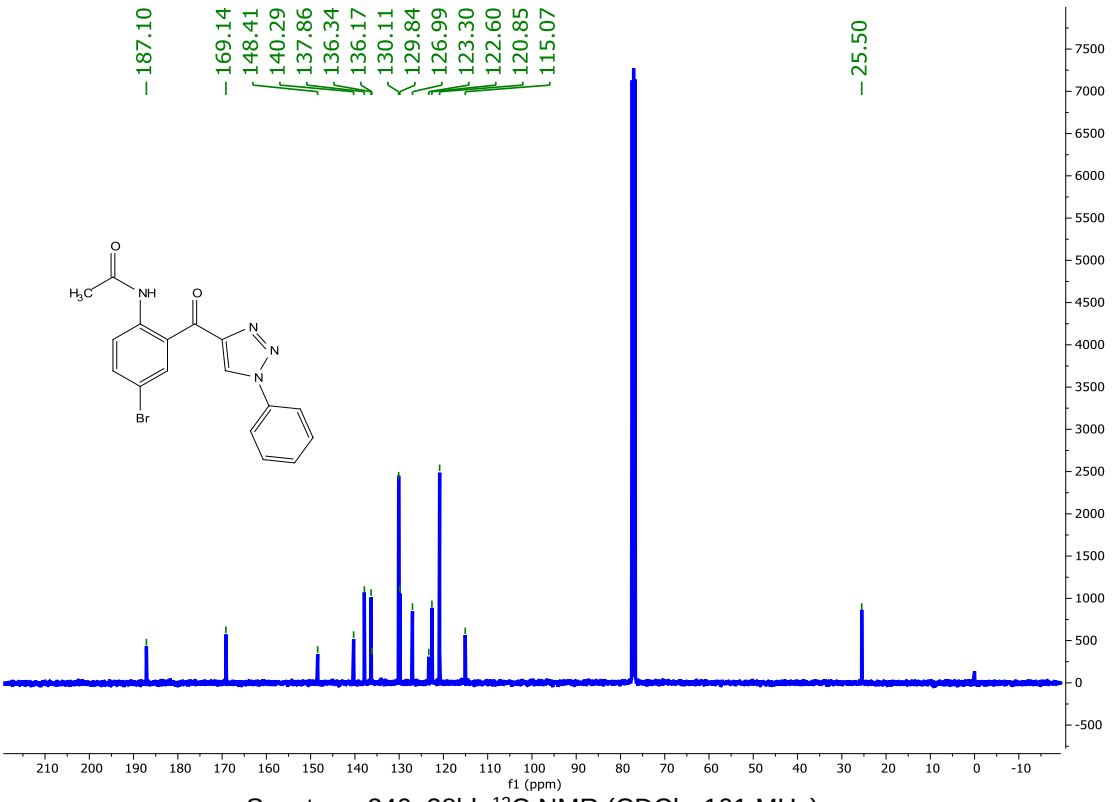
Spectrum 237: 38bf ^{1}H NMR ($CDCl_3$, 400 MHz)



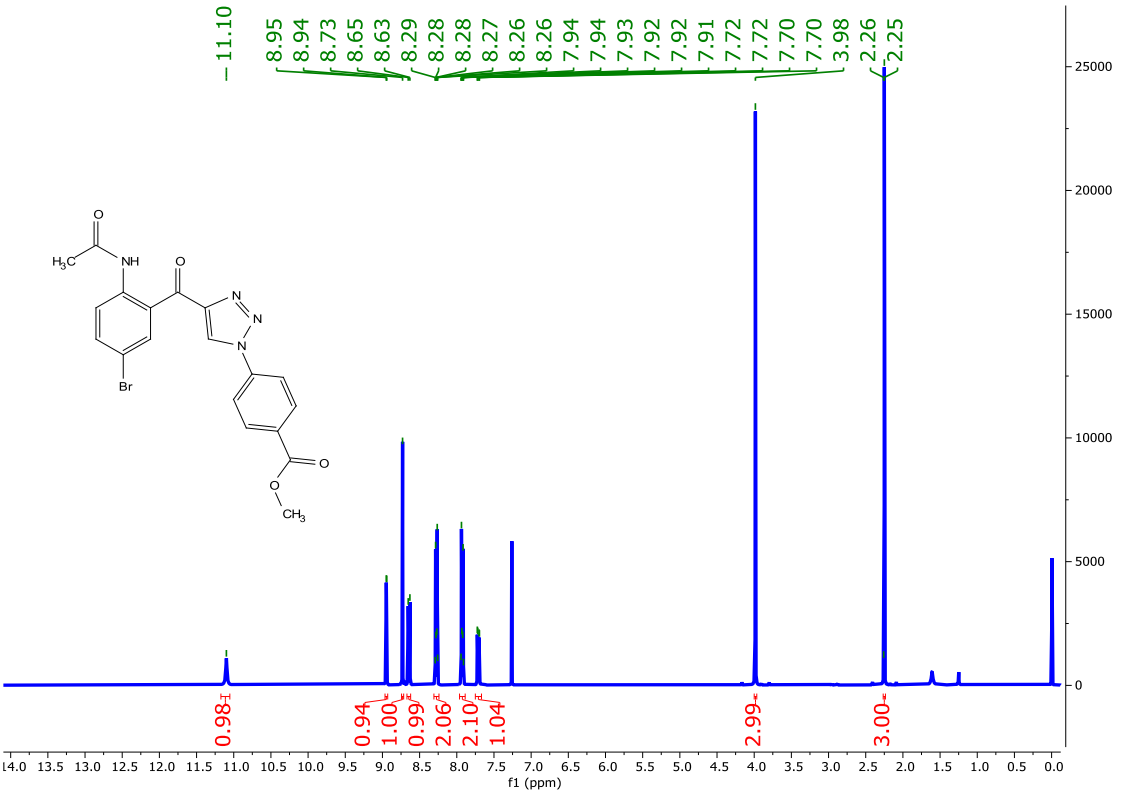
Spectrum 238: 38bf ^{13}C NMR ($CDCl_3$, 101 MHz)



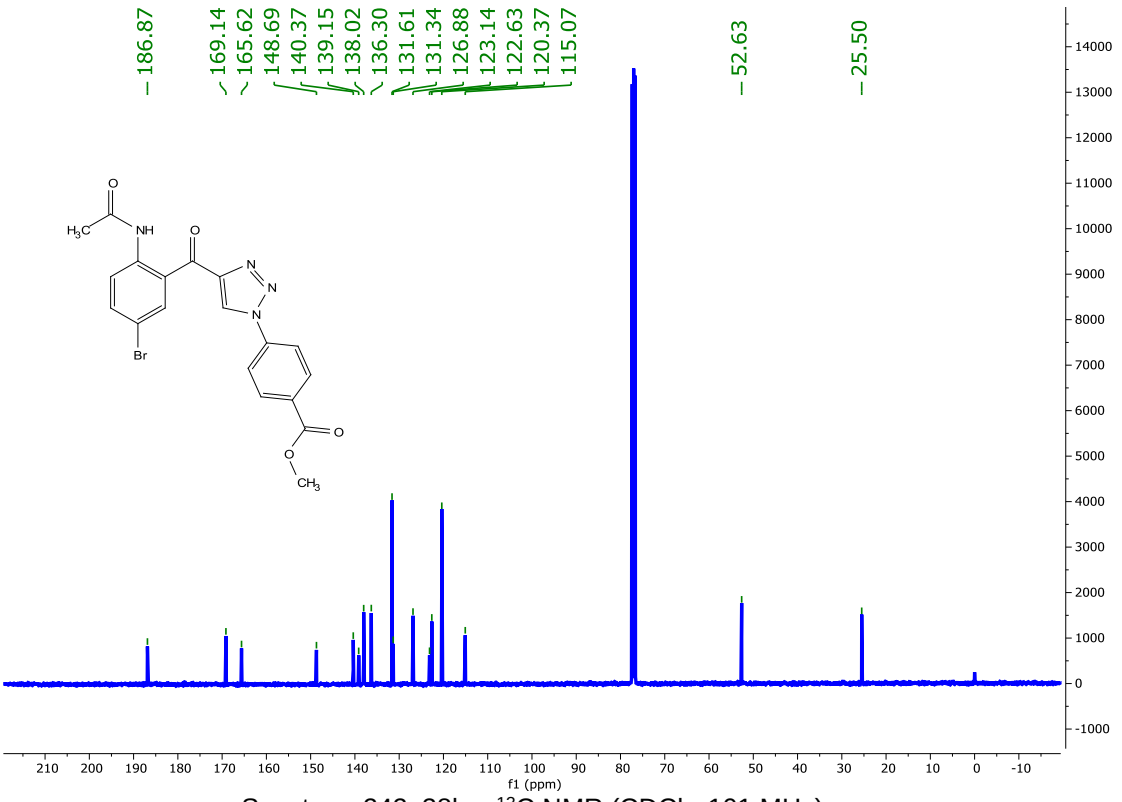
Spectrum 239: 38bk ^{1}H NMR ($CDCl_3$, 400 MHz)



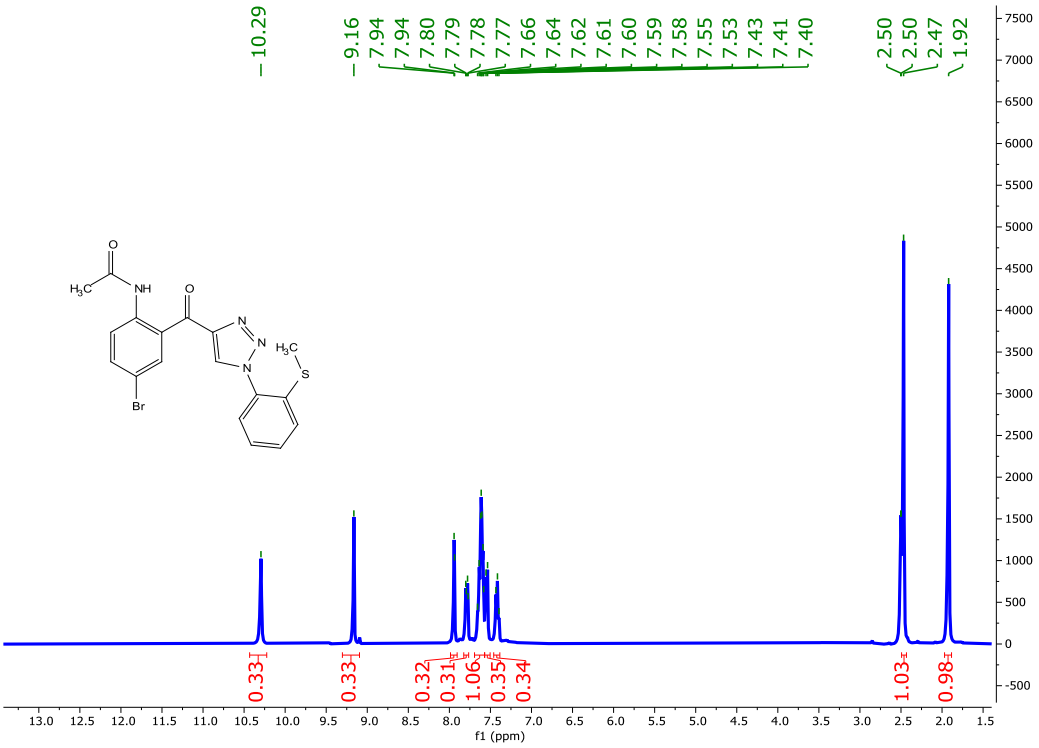
Spectrum 240: 38bk ^{13}C NMR ($CDCl_3$, 101 MHz)



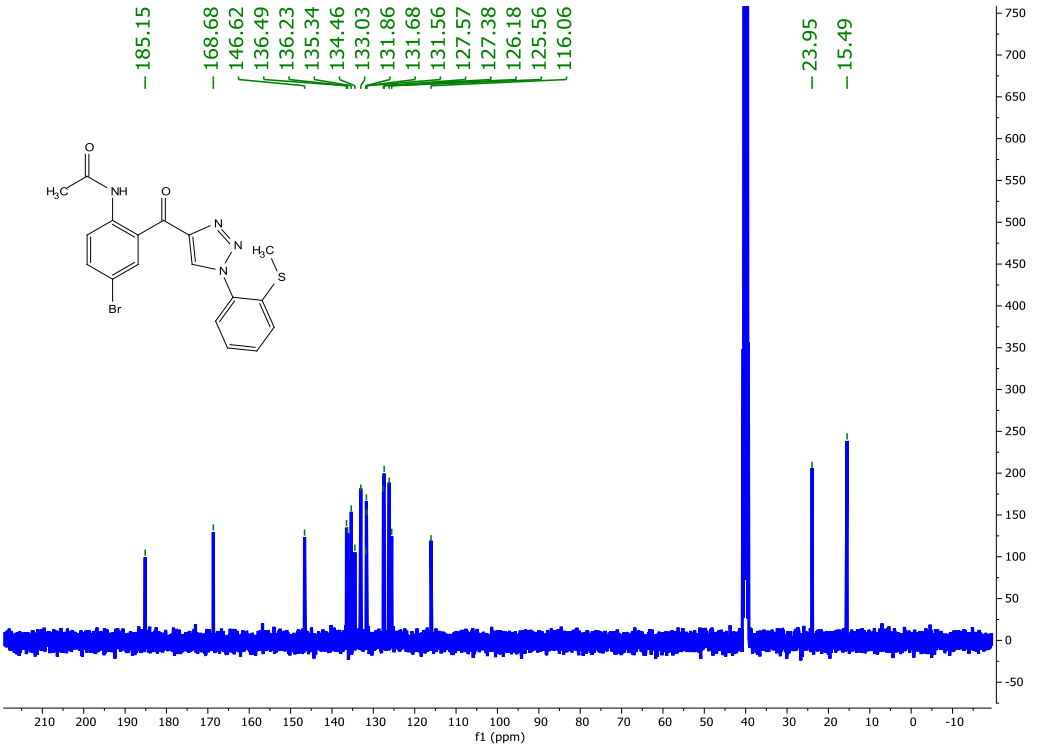
Spectrum 241: 38bm ^{1}H NMR ($CDCl_3$, 400 MHz)



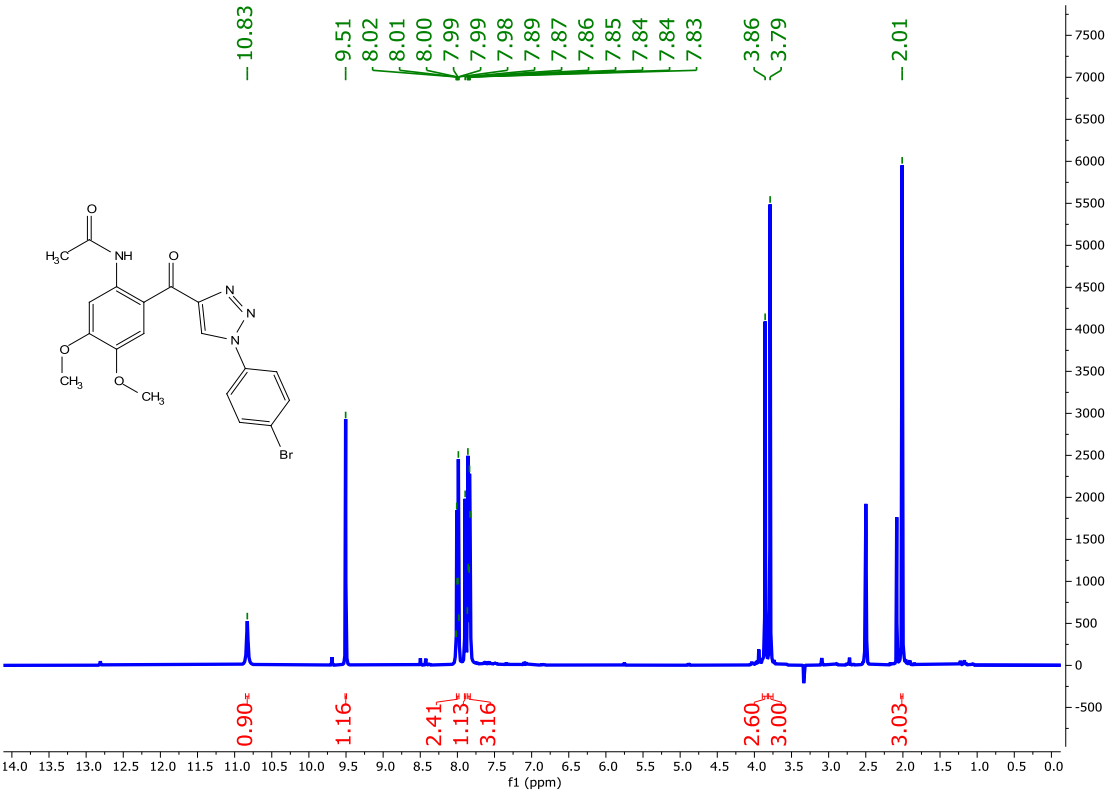
Spectrum 242: 38bm ^{13}C NMR ($CDCl_3$, 101 MHz)



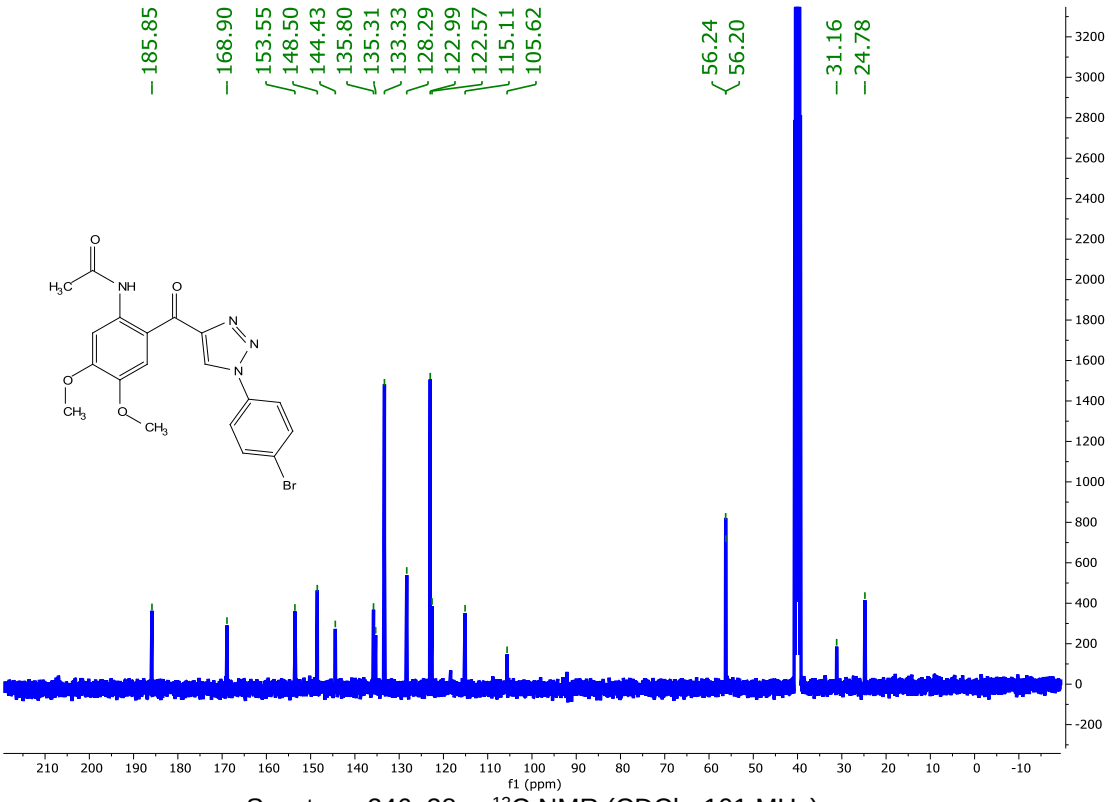
Spectrum 243: 38bp ^{1}H NMR ($CDCl_3$, 400 MHz)



Spectrum 244: 38bp ^{13}C NMR ($CDCl_3$, 101 MHz)



Spectrum 245: 38ca ^{1}H NMR ($CDCl_3$, 400 MHz)



Spectrum 246: 38ca ^{13}C NMR ($CDCl_3$, 101 MHz)

10. Appendix C: Published articles and patents

This work was developed during the 48 months of the Ph.D. Program at the Department of Chemistry of the Pontifical Catholic University of Rio de Janeiro (PUC-Rio). The lab work was performed at the LabSint in PUC-Rio under the supervision of Prof. Dr. Camilla Djenne Buarque. In addition to the two articles that comprise this written thesis, I collaborated on 4 more articles with co-workers from and colaborators from LabSint. Three additional articles, in collaboration with professors Ricardo Aucélio and Volodymyr Zaitsev, were also published during these four years. These collective works garnered numerous presentation awards at various conferences, most notably including: The Best Poster Award in 19th Brazilian Meeting on Organic Synthesis (2024); Oral presentation award in XVIII ENCONTRO REGIONAL DA SBQ-RIO (2022) and 1st place in the Best Oral Presentation category in VI Jornada de Pós-Graduação e Pesquisa em Química do Departamento de Química da PUC-Rio (2022). Furthermore, a book chapter titled " LABSINT: DOS HETEROCICLOS NITROGENADOS AOS MATERIAIS POROSOS NANOESTRUTURADOS" was published in the book *Química Orgânica Sintética: Brasil 2022*, in addition to a patent application (BR1020240127811) being filed. All these works are present below.

Journal of Molecular Structure
Volume 1321, Part 2, 5 February 2025, 139897

Direct access of 4-acyl-1,2,3-triazoles from acetophenones: A synthetic shortcut for novel p.Phe508del-CFTR traffic correctors

Marcelo Folhadella M.F. Azevedo [a], David C. Zeitune [a], Renan L. de Farias [a], Eduardo N.C. Junior [a], Mafalda Bacalhau [b], Margarida D. Amaral [b], Miquéias Lopes-Pacheco [b c], Camilla D. Buarque [a]

Tetrahedron
Volume 120, 13 August 2022, 132856

1,3-Dipolar cycloaddition reactions of enaminones and azides: Synthesis of 4-acyl-1,2,3-triazoles and mechanistic studies

Francisco V. Gaspar [a], Marcelo F.M.F. Azevedo [a], Leonardo S.A. Carneiro [a], Samuel B. Ribeiro [a], Pierre M. Esteves [b], Camilla D. Buarque [a]

Open Access Article

Rescue of Mutant CFTR Channel Activity by Investigational Co-Potentiator Therapy

by Mafalda Bacalhau [1], Filipa C. Ferreira [1], Marcelo Folhadella M. F. Azevedo [2], Talita P. Rosa [2], Camilla D. Buarque [2] and Miquéias Lopes-Pacheco [1,*,†]

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[2] Department of Chemistry, Pontifical Catholic University of Rio de Janeiro, Rio de Janeiro 22541-041, Brazil
* Author to whom correspondence should be addressed.
† Current address: Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, USA.

Open Access Original Article

Synthesis and antitumoral activity of novel biaryl hydroxy-triazole and fluorene-triazole hybrids

David Chafi Zeitune [†], Marcelo Folhadella Martins Faria Azevedo [†], Mariane Senna Rangel [†], Robert de Sousa Bastos [2], José de Brito Vieira Neto [2], Claudia do Ó Pessoa [2,3], Camilla Djenne Buarque [†]

Results in Chemistry
Volume 8, June 2024, 101589

In vitro study of the inhibitory potential of hydroxy-1,2,3-triazoles on the replication of ZIKA and chikungunya arboviruses

Claudio Cirne-Santos [a b], Rafael R.S. Batista [a], Caroline Souza Barros [b c], Marcelo F.M.F. Azevedo [d], Célia Machado Ronconi [e], Camilla Djenne Buarque [d], Izabel Christina Nunes de Palmer Paixão [a b]

Talanta
Volume 244, 1 July 2022, 123406

Use of selective quenching of a photoluminescent probe based on a Eu(III) β-diketonate complex for determination of methylmercury in produced water after liquid-liquid extraction

Juliana da S. Padilha, Marcelo F.M.F. Azevedo, Jarol R. Miranda-Andrades, Anna De Falco, Jiang Kai, Ricardo Q. Aucelio

Analytica Chimica Acta
Volume 1232, 1 November 2022, 340479

Silver-modified nitrogen-doped graphene quantum dots as a sensor for formaldehyde in milk using headspace micro-extraction o a single-drop of aqueous nanoparticles dispersion

Juliana da S. Padilha [a], Marlin J. Pedrozo-Peñafiel [a], Marcelo F.M.F. Azevedo [a], Anna De Falco [a], Dunieskys R.G. Larrudé [b], Marcelo E.H. Maia da Costa [c], Ricardo Queiroz Aucélio [a]

Separation and Purification Technology
Volume 330, Part C, 1 February 2024, 125525

Recovery of rare earth elements from waste phosphors using phosphonic acid-functionalized silica adsorbent

Olena Artiushenko [a], Wendy S. Rojano [a], Michael Nazarkovsky [a b], Marcelo Folhadella M.F. Azevedo [a], Tatiana D. Saint'Pierre [a], Jiang Kai [a], Volodymyr Zaitsev [a c]

LABSINT: DOS HETEROCICLOS NITROGENADOS AOS MATERIAIS POROSOS NANOESTRUTURADOS

Leonardo S. A. Carneiro[a], Verônica D. da Silva[a,b], Joseane A. Mendes[a], Marcelo F. M. F. Azevedo[a] e Camilla D. Buarque[a]