Synthesis and functionalization of spirohydantoins with C(sp^2)-N cross-coupling reactions

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Acknowledgment

Here it is. Believe it or not. I did it, I wrote it, I completed it, but not without a little help from my friends.

With this thesis, I am completing my Master's degree in organic chemistry at the University of Oslo. The work was carried out under associated professor Alexander H. Sandtorv under the Organic chemistry section at the Department of Chemistry.

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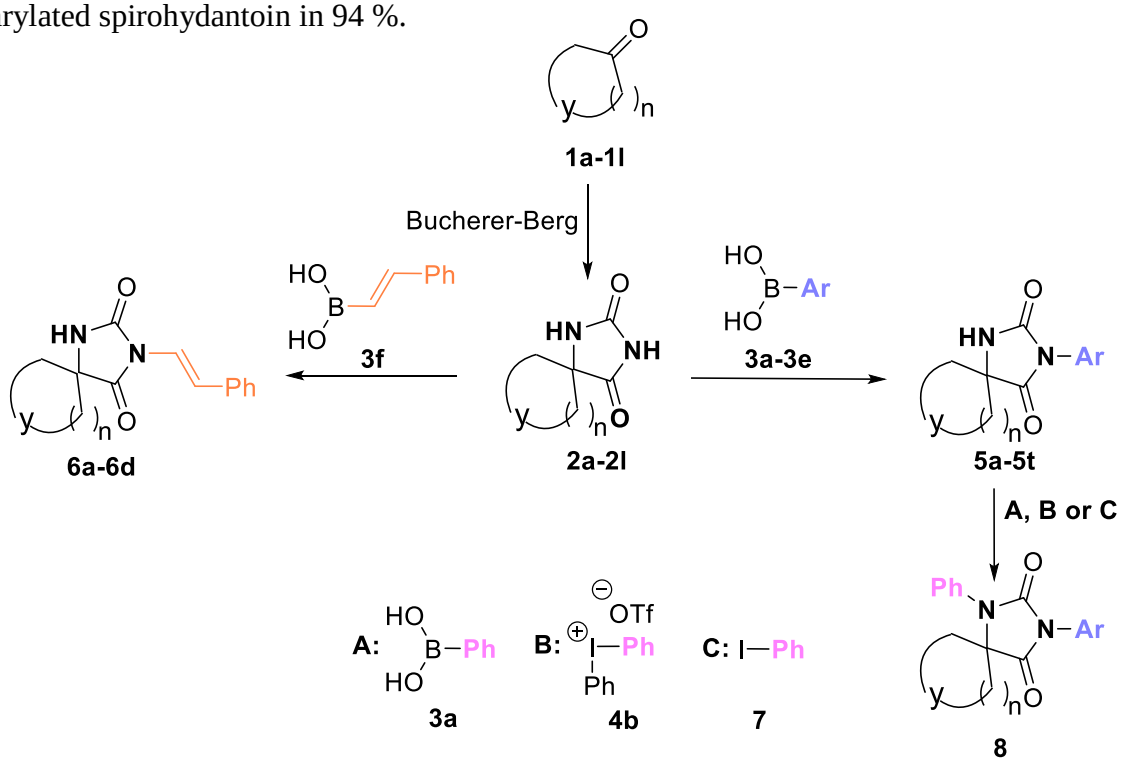
Abstract

Spirohydantoins are bicyclic compounds encountered in biologically active structures such as anticonvulsants and antibiotics. However, the synthesis of spirohydantoins is an underdeveloped field and is thus interesting to investigate. This study investigates the synthesis and functionalization of spirohydantoins, and is divided into three parts:

The first part describes a microwave-assisted synthesis of spirohydantoins. The investigation showed compatibility with cyclic ketones of varying ring sizes and ketones with substituents on the β-carbon. With the right stoichiometry, a dispirohydantoin was formed using the same method.

The second part describes a new, simple and efficient method for C(sp^2)-N-bond formation on spirohydantoins using a Cu-catalyzed cross-coupling reaction with boronic acid as coupling partner. The method showed excellent regioselectivity and allowed for the synthesis of a diverse scope of products with good to excellent yields. The synthesis operated well with neutral, electron-rich and electron-poor aryl boronic acids, as well as with thiophenyl- and styrylboronic acid. Overall, the investigation produced 13 new *N*-3-substituted spirohydantoin structures.

The third part describes an investigation into the underdeveloped synthesis of diarylated spirohydantoins. This investigation showed excellent results with a Cu-catalyzed cross-coupling using an aryl halide as coupling partner and resulted in the formation of a new diarylated spirohydantoin in 94 %.



Abbreviations

b	Broad (NMR)	**MS**	Mass spectrometry
COSY	Correlation spectroscopy	**nd**	Not detected
d	Doublet (NMR)	**NMR**	Nuclear magnetic resonance spectroscopy
DCM	Dichloromethane	**NOESY**	Nuclear Overhauser effect spectroscopy
DEPT	Distortions Enhancement by Polarization Transfer	**ppm**	Parts per million
		q	Quartet (NMR)
DMF	*N*,*N*-Dimethylformamide	**qn**	Quintet
DMSO	Dimethyl sulfoxide	$\boldsymbol{R_f}$	Retardation factor
EI	Electron ionization	**RT**	Room temperature
ESI	Electrospray ionization	**s**	Singlet (NMR)
FID	Free induction decay	**t**	Triplet (NMR)
HMBC	Heteronuclear multiple–bond correlation spectroscopy	**TOCSY**	Total correlation spectroscopy
HRMS	High–resolution mass spectrometry	**TEA**	Triethylamine
HSQC	Heteronuclear single–quantum correlation spectroscopy	**THF**	Tetrahydrofuran
IR	Infrared spectroscopy	**TLC**	Thin–layer chromatography
J	Coupling constant	**TMP**	Trimethoxyphenyl
m	Multiplet (NMR)		
m/z	Mass–to–charge ratio	**µW**	Microwave
Me_2CyDA	*trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine	***δ***	Chemical shift

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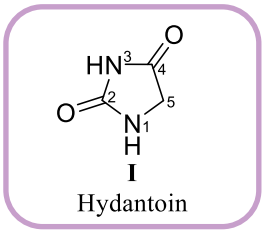
1 Introduction

1.1 Hydantoin

Hydantoin (**I**) is a five-membered heterocyclic structure with two nitrogen atoms in the 1 and 3 positions and carbonyl groups in the 2 and 4 positions of the ring (Figure 1). [1] The compound were first isolated in 1861 by Adolf von Bayer.[1, 2] The structure has both hydrogen-donating and -accepting properties, two α-protons available for substitution, in addition to two acidic protons. These properties implements much functionality to the structure and makes a interesting scaffold for multiple reactions. The C-5 carbon can for instance react in an aldol condensation or a halogenation reaction.[3, 4] The carbonyl oxygen's can be silylated under acidic conditions, while the nitrogen atoms can undergo cross-coupling reactions.[5,6]



I

Hydantoin

Figure 1: The structure of hydantoin with numbering of the atoms.

In coupling reactions, the two nitrogen protons have competitive acidic properties. From the literature, it is known that the *N*-3 proton with a pK_a of 15.0 is a more acidic proton than the *N*-1 proton.[8] The *N*-1 nitrogen is a part of a cyclic amide and has an estimated pK_a of 23.[9] The *N*-3 proton is more acidic due to the inductive and resonance effects from the two carbonyl groups nearby compared to the equivalent effects from only the one carbonyl near to the *N*-1 proton. The carbonyl groups pull the electron density further away from the N-H bond making it weaker.

Hydantoins are also applicable in biological systems. In microorganisms, hydantoins can undergo a microbial transformation and react to form quaternary amino acids. There is an enzyme, called hydantoinase, present in some plants and animals that catalyzes the hydrolysis of hydantoin to hydantoic acid.[10] The products of this reaction can lead to both natural and analogues of natural amino acids. Microorganisms relay heavily on amino acids as building blocks and thus their synthesis is important. The amino acids can also be used further to form bioactive peptide analogues.[11] The hydantoinase enzyme has been extracted from nature so that the hydrolysis can be done in the laboratory.[10]

Hydantoins are well known as fragments in multiple compounds with biological activity including pharmaceuticals (Figure 2).[12] The hydantoin nilutamide (**II**) is an antiandrogen used against prostate cancer, and the hydantoin mephenytoin (**III**) is an anticonvulsant compound used against epilepsy.[13] In the clinical candidate field one can also find hydantoins such as BMS-587101 (**IV**), an LFA-1 antagonist used in treatment of psoriasis, and GLGP-0492 (**V**), a selective androgen receptor modulator, used against cachexia.[11] The society today is facing multiple threats when it comes to illness and health. Especially in the view of antibacterial resistance and finding cures to lethal diseases like cancer.[14] Fittingly, there is still a big part of the hydantoin field that is underdeveloped and thus can be interesting to investigate further, given by its previous application in pharmaceuticals.

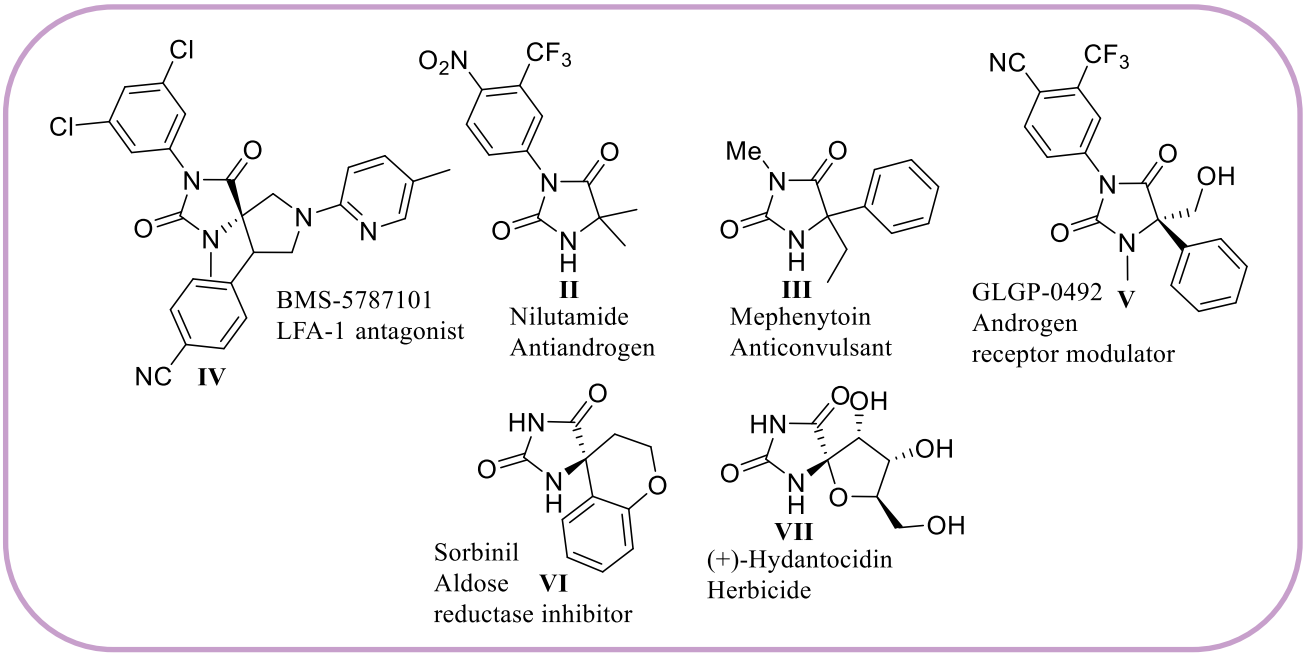


Figure 2: Biologically active structures and clinical candidates containing a 5,5-disubstituted hydantoin scaffold.

1.2 Spirohydantoins

One substitution pattern that can be found in several biologically active hydantoins is that of substituents on the C-5 carbon, as we can observe with previously mentioned nilutamide and mephenytoin. Other similar 5,5-disubstituted biologically active structures are sorbinil (**VI**), which can prevent diabetic neuropathies, and (+)-hydantocidin (**VII**), which regulates plant and herbicidal growth.[13] Both of these compounds are more accurately described as spirohydantoins. Spirohydantoins are a subclass of hydantoins, which are bicyclic, where the

two rings share one carbon, the C-5 (Figure 3).[13] In view of the structural similarity to normal hydantoin, they have much of the same functionality thus much of the same reaction capabilities, except the C-5 substitution sites which are blocked. There is endless room for variations in the spiro ring which can affect the hydantoin in its entirety, but all of them have in common an increased degree of sterically hindrance compared to unsubstituted hydantoin.

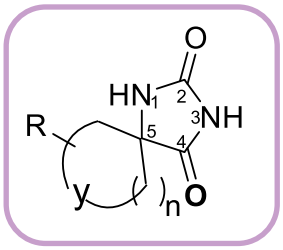
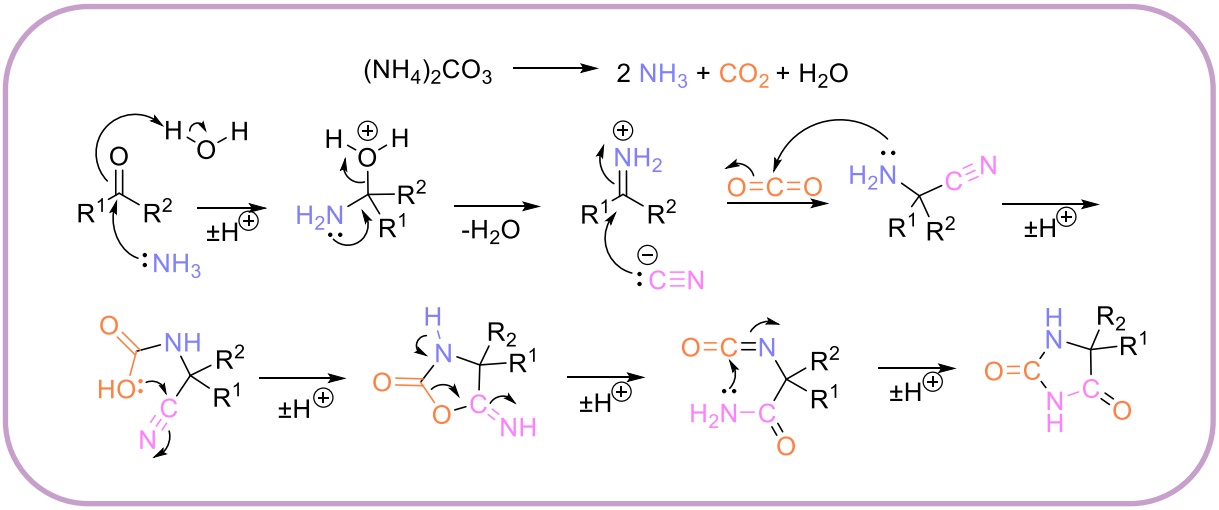


Figure 3: A general structure of spirohydantoin, where n is all integers > 1 and y is various functional groups

1.2.1 Synthesis of spirohydantoins

Hydantoin that are 5-substituted are most known to be synthesized by three methods: the Bucherer-Berg reaction, the Read reaction and the Biltz reaction.[11, 13] The Bucherer-Berg reaction is the principal reaction when it comes to the synthesis of spirohydantoins. The method allows for the formation of hydantoins with various substituents on the C-5 carbon. The reaction is known to yield the widest diversity of hydantoins from mono- and disubstituted, to symmetric and asymmetric. The method also handles electron-poor and rich aryl groups, alkyl chains, alkenes and spiro rings of different sizes, with or without substituents.[11, 15, 16]

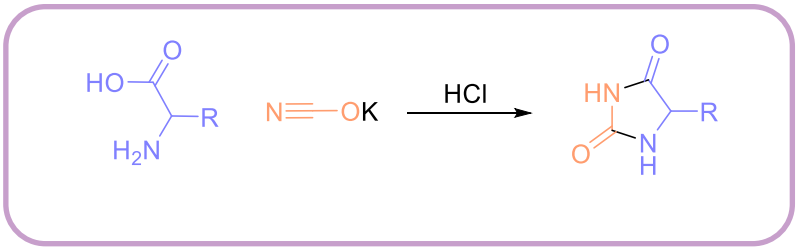
The Bucherer-Berg reaction is a multicomponent synthesis, starting with a substituted ketone or aldehyde, which ends with a cyclization of the hydantoin ring.[16] The reaction is usually carried out in thermal conditions. A ketone in combination with cyanide and ammonium carbonate in a 1:1 mixture of EtOH and water refluxes for several hours.[17] The reaction can also be carried out in minutes with microwave irradiation.[16, 17, 18] The mechanism for the reaction is presented in Scheme 1.



Scheme 1: The mechanism for the formation of hydantoin by the Bucherer-Berg reaction.[19]

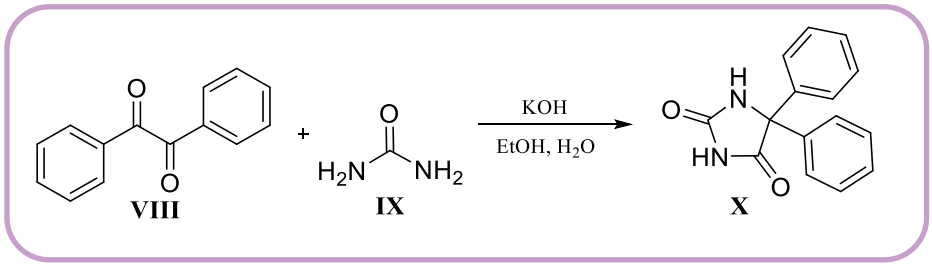
The mechanism starts with a nucleophilic attack, from the formed ammonia from ammonium carbonate, on the carbonyl carbon and a subsequent loss of water. Then cyanide reacts with the imine by another nucleophilic attack, leading to a tetrahedral intermediate. The amine nitrogen then attacks the carbon dioxide, also formed from ammonium carbonate, which leads to the cyclization of a five-membered ring. At this point a type of ring-opening and ring-closing mechanism happens, also known as an N→O migration.[20] The bond between the oxygen and the carbonyl group splits and the nitrogen from the amide attacks the isocyanate carbon, forming the hydantoin ring.

Another way to synthesize 5,5-disubtituted hydantoins are, as mentioned, with the Read conditions also known as the Urech reaction (Scheme 2). This synthesis forms urea derivatives from amino acids and inorganic cyanates. Then the urea derivative cyclizes under acidic conditions to form the hydantoin ring.[11] Since 2004, there have been only a few papers reporting syntheses of 5,5-disubstituted hydantoins with this method. Seeing as this method is a two-step procedure with harsh conditions, it was not further considered in this study.[2]



Scheme 2: A general Urech reaction under acidic conditions.[11]

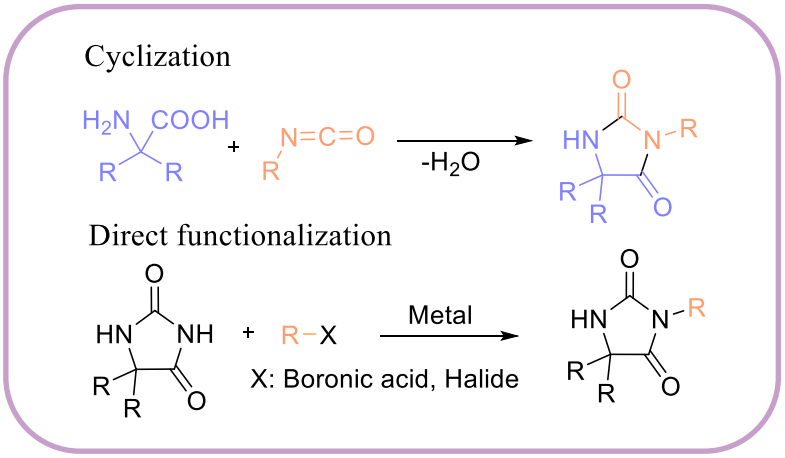
The last reaction, named the Biltz, is known for the synthesis of the biological active hydantoin, phenytoin (**X**) (Scheme 3).[11] The synthesis is a double condensation of urea (**IX**) with glyoxal derivatives (**VIII**), either in strong acidic or basic media to form 5- and 5,5-sisubstituted hydantoins.[21, 22, 23] Alternative procedures with microwave irradiation or ultrasonication have been discovered and developed which are greener and faster than the original conditions.[11] Even with greener and more efficient conditions, this method was not further considered for this thesis.



Scheme 3: The Biltz method for the synthesis of phenytoin.[11]

1.3 *N*-3 Functionalization of spirohydantoins

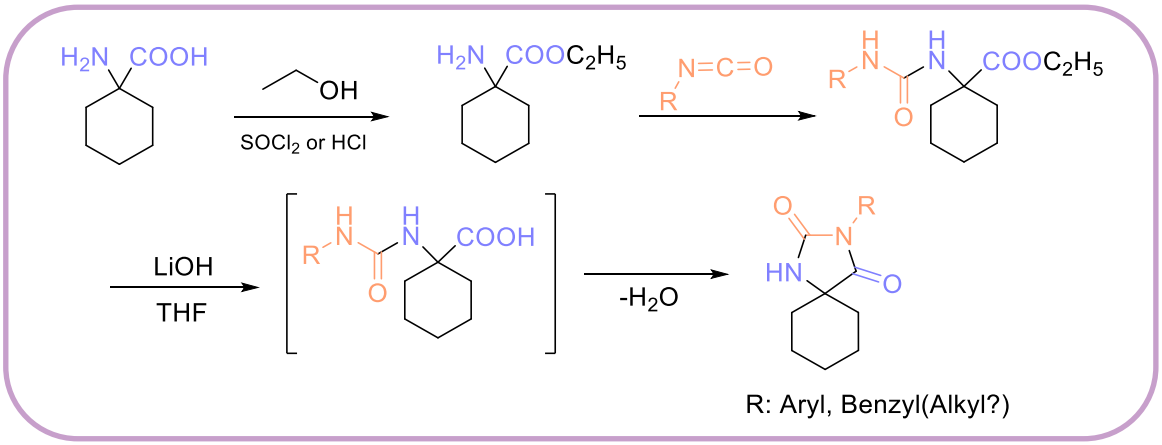
We have so far been focusing on the C-5 substitution of the previously mentioned biologically active hydantoins. Another repeating substitution pattern in such structures, like nilutamide, BMS-587101 and GLGP-0492, is that of substituents on the *N*-3 position. There are two principal methods for forming *N*-3-substituted hydantoins, either by a cyclization reaction or by direct functionalization (Scheme 4).[11] The hydantoin ring is formed by the cyclization method, while with direct functionalization, the hydantoin ring is present from the start.



Scheme 4: Two principal methods for formation of *N*-3-substituted hydantoins: cyclization and direct functionalization.[11]

1.3.1 Cyclization

The most reported method of these two are the cyclization reaction. Aboul-Enein *et al.* describes a multistep procedure that starts with a primary amino acid and an isocyanate that together form a urea derivative that under basic condition can undergo a cyclization to afford the *N*-3-substituted hydantoin (Scheme 5).[11, 24]



Scheme 5: The synthesis route for a cyclization of *N*-3-substituted spirohydantoin.[24]

The 1-amino-1-cyclohexane carboxylic acid is reacted with ethanol and thionyl chloride, or dry HCl gas, to form the corresponding ethyl ester. The ethyl ester is then reacted with the appropriate isocyanate in chloroform at 0 ºC, to form a urea through the amine. In the last step, when the urea is treated with lithium hydroxide in tetrahydrofuran (THF), the corresponding carboxylic acid is formed as an intermediate which then cyclizes to the *N*-3-substituted spirohydantoin.

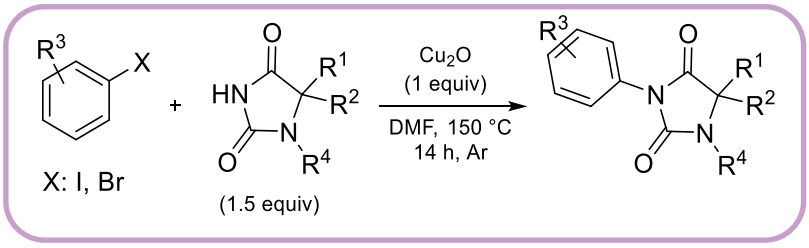
The paper presents a small scope of *N*-3-arylated spirohydantoins, with neutral, electron rich and electron poor aryl groups and some benzylic substituents. Although the method produces good yields (79-83 %).[24] The amino acids are not commercially available and the reaction requires three synthesis steps to isolate the desired compound, making it inefficient. In addition, the reaction demands highly toxic and harmful reagents like thionyl chloride, lithium hydroxide and isocyanates.[25-28] This altogether makes the reaction undesirable.

There exist also a reported multi-step procedure for the synthesis of *N*-3-arylated 5-substituted hydantoins with a four-component synthesis, called the Ugi reaction, combined with a cyclization under basic conditions.[29] The reaction is also undesirable with a multi-step procedure.

1.3.2 Direct functionalization

Direct functionalization is an approach where an N-H bond can be directly activated by a metal catalyst to form a C-N bond. Direct functionalization's of hydantoins are done with cross-coupling reactions.[30] A cross-coupling reaction uses a coupling partner with a metal catalyst and often a base.[31] Although this approach applied on hydantoins seems to be underdeveloped and unexplored with only a few reported procedures in the literature, there have recently been reported a few breakthroughs.[31-33]

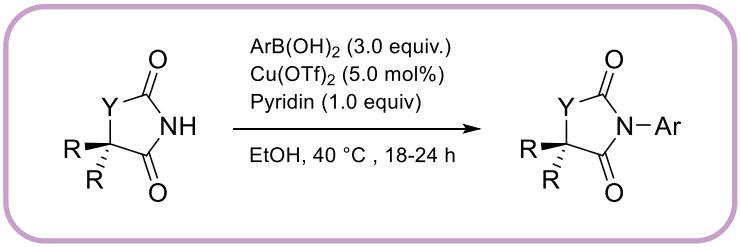
Thilmany and coworkers report a selective Cu-mediated *N*-3-arylation of hydantoins with good to excellent yields (69-98 %) (Scheme 6). The reaction is performed at 150 ºC for 14 hours and utilizes an aryl halide as the coupling partner and Cu(I) in excess.[33]



Scheme 6: The Cu-mediated reaction for *N*-3-arylation of hydantoins with aryl halide as the coupling agent.[33]

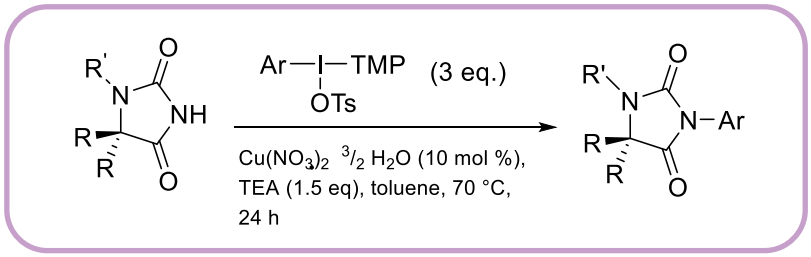
The paper presents a scope of arylated products of unsubstituted hydantoins, 5-monosubstituted hydantoins and 5,5-disubstituted hydantoins, where the structures with disubstitution on the C-5 carbon gives the highest yields. The scope includes neutral, electron-poor and electron-rich aryl groups. Nevertheless, the reaction requires harsh conditions. The reaction is carried out in a pressure tube at 150 ºC and demands an inert atmosphere, requiring specialized glassware and lab techniques. The method also utilizes *N*,*N*-dimethylformamide (DMF) as solvent making the reaction more hazardous.[33, 34]

A few years later, Berntsen and coworkers publish a Cu-catalyzed method for coupling cyclic imides with boronic acids to form C(sp^2)-N-bonds.[32] In this paper they report a simple procedure for *N*-3-arylation of hydantoin-like structures with good yields (75-100 %) (Scheme 7).[32] The reaction is based on the Chan-Lam reaction, with boronic acid as the coupling partner, pyridine as a base and Cu(II) salt as the catalyst in catalytic amount.[35, 36] Bentsen *et al*. reports a scope of arylated products with natural, electron-rich and electron-poor aryl groups, and heteroaryl groups, most of them with either mono- or disubstitution on the C-5 carbon.[32]



Scheme 7: A Cu-catalyzed *N*-arylation of cyclic imdes with boronic acid as the coupling agent.[32]

In the literature, we can also find a method for *N*-3-arylation with diaryliodonium as the arylation agent (Scheme 8). This method also uses Cu(II) as the catalyst but the amine is switched to triethylamine and the reaction is run in toluene, 70 ^{0}C for 24 h.[31]



Scheme 8: *N*-3-arylation of hydantoins with diaryliodonium salts as the coupling agent.[31]

Compared to the cyclization reaction and the Cu(I)-mediated coupling, is the method of Berntsen *et al*. with boronic acid an upgrade. The reaction is a one-step procedure with heating at 40 ºC for 18-24 h, unlike the multi-step cyclization method and Thilmany *et al*.'s method with 150 ºC, pressure tube and inert atmosphere.[32, 33] The reaction of Berntsen *et al*. utilizes a base but the reaction is optimized to catalytic amounts of catalyst compared to stoichiometric amounts with the method of Thilmany *et al*.[32,33] The three methods present a similar variety in scope and yield, but the simplicity in the experimental set-up, the catalytically amount of copper and the mild conditions makes the method of Berntsen *et al*. more desirable.[24, 32, 33]

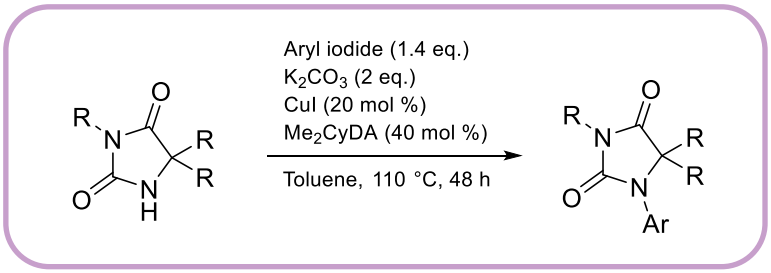
Thilmany *et al*.[33] and Berntsen *et al*.[32] reports arylation of 5,5-disubstituted hydantoins but neither present any work on spirohydantoins. Their work give a good prerequisite for the development for the unexplored field of *N*-3 coupled spirohydantoin, and thus can be interesting to further investigate.

1.4 *N*-1-Arylation of hydantoins

Another substitution pattern that is observed in some biologically active structures like in the clinical candidates in Figure 2, is the combined substitution on both *N*-3 and *N*-1 forming

diarylated hydantoins. Theoretically, there are two options for pursuing this with direct functionalization. One can either attempt to arylate both positions at the same time with a one-pot synthesis, or one can pursue doing it in a two-step procedure by first arylate the *N*-3 position and then the *N*-1 position. The literature reports only a few procedure for the formation of diarylated-hydantoins and even fewer for diarylated spirohydantoins, making this another undeveloped field interesting to investigate. The few reported diarylated spirohydantoin products were synthesized with a multistep cyclization method with isocyanate.[37] We will in this thesis focus on a two-step direct functionalization approach.

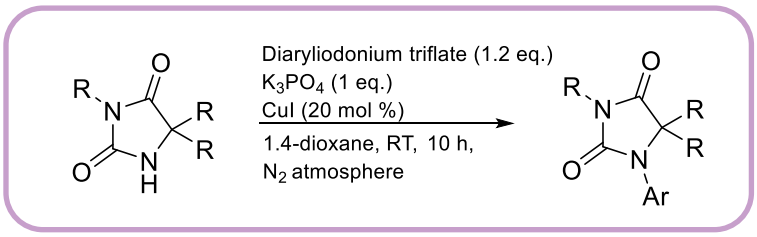
Thilmany *et al*.[33] report, in the same paper as for the *N*-3-coupling, a Cu-catalyzed method for coupling the *N*-1 position of *N*-3-arylated 5,5-substituted hydantoins (Scheme 9). The synthesis is dependent on both a ligand and a base and can utilize both aryl iodides and bromides as the arylation agent. The experimental procedure is run with harsh conditions (110 ^{0}C for 48 h) and is similar to the *N*-3-coupling, using a pressure tube and inert atmosphere. The paper presents good to excellent yields (65 – 96 %) and a wide scope with neutral, electron-poor and electron-rich aryl groups as well as heteroaryl groups. They only report one limitation with *ortho*-substituted arylating agents, yielding no product.[33]



Scheme 9: The reaction of Thilmany *et al*. for *N*-1-arylation of hydantoins.[33]

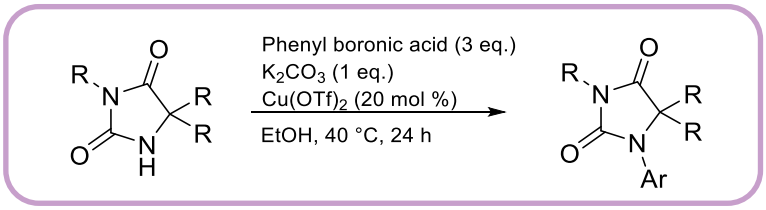
Two years later Saikia and coworkers present a Cu-catalyzed diaryliodonium salt *N*-1-coupling of *N*-3-arylated 5,5-disubstituted hydantoins (Scheme 10).[38] This method utilizes K_3PO_4 as base, 1,4-dioxane as solvent and is not dependent on a ligand. Compared to the method of Thilmany and coworkers, this method has milder conditions with the synthesis run at room temperature, for 10-22 h.[33] This method is also dependent on an inert atmosphere, but they do not report any evacuation and backfilling with inert gas. The scope presented has good to excellent yields (54 – 90 %) but a smaller scope than the method of Thilmany *et al*.[33, 38] They

nevertheless arylate the *N*-1 position with electron-poor, -rich and neutral aryl groups and have completed the coupling with both symmetrical and asymmetrical salts.[38]



Scheme 10: Saikia *et al*.'s reaction for *N*-1-arylation of hydantoins.[38]

Inspired by Thilmany *et al*.[33] and the Sandtorv group's earlier work, the research group is developing a new Cu(II)-catalyzed method for *N*-1-coupling of *N*-3-arylated hydantoins, which has yet to be published (Scheme 11).[39] This method utilizes boronic acids as the coupling agent and potassium carbonate as the base. The reaction has mild conditions with ethanol as the solvent and the reactions is run for 24 hours at 40 ºC, in open air.[39]



Scheme 11: the *N*-1-arylation reaction of hydantoins under development in the Sandtorv group.[39]

1.5 Description and aim of the study

The main goal of this thesis is to investigate the following: Is it possible to perform C(sp^2)-N cross-couplings on spirohydantoins. The project is divided into three parts in order to answer this (Scheme 12).

Part 1: Spirohydantoin synthesis.

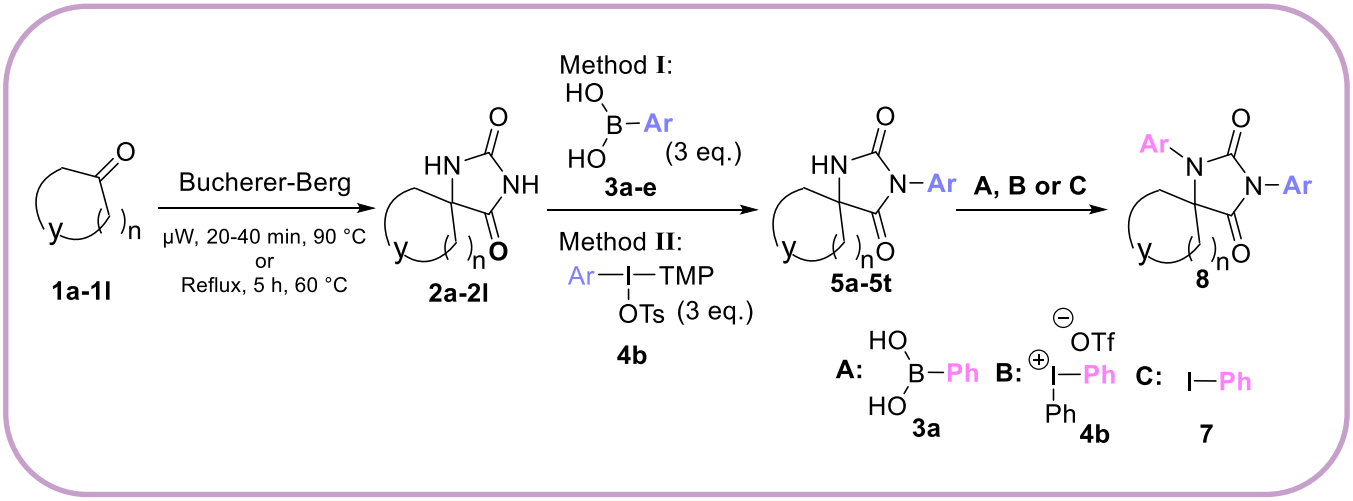
Spirohydantoins are not commercially available and hence have to be synthesized. In this thesis, we will investigate a microwave-assisted Bucherer-Berg reaction to synthesize spirohydantoins.[16] The research questions we want to investigate are: Is it possible to reproduce the reported results from the literature for this procedure? Does the method have limitation on substrate? How does an α-substituted substrate affect the reaction, given its steric hindrance? Is the reaction chemoselective when multiple ketones or other electronpositive carbons are present? Is it possible to form a hydantoin with a ketone in the spiro ring? Further, we know that two hydantoins with a shared spiro ring (dispirohydantoin) have been synthesized with thermal conditions, but can it be done with microwave irradiation? Lastly, we wanted to investigate which conditions are the most efficient for spirohydantoin synthesis in general, microwave-assisted or thermal.

Part 2*: N*-3-arylation of spirohydantoins

For this part, we have chosen two methods for *N*-3-arylation of hydantoin that has not been tested on spirohydantoins before, namely a diaryliodonium salt coupling and a boronic acid coupling. [31, 32] To start we wanted to investigate which of these methods are more suitable and efficient for this kind of substrate, and then investigate the scope and limitations of the most efficient method. What kind of aryl groups are allowed: neutral, electron-deficient, electron-rich, heteroaryl? How is the reaction affected by the variations in spiro ring size, are different degrees of steric effects induced? Is four-membered spiro rings stable enough to be coupled? Is the reaction regioselective to the *N*-3 position? Can the method synthesize new *N*-3-arylated spirohydantoin structures? Lastly, is it possible to *N*-3-alkenylate spirohydantoins with this method?

Part 3: *N*-1-Arylation of *N*-3-arylated spirohydantoins

We also want to investigate the underdeveloped field of *N*-1-arylation of *N*-3-substituted spirohydantoins to form diarylated spirohydantoins. For this part, we have chosen three methods, which have not been tested with spirohydantoin before: all methods are Cu-catalyzed but utilizes different coupling partners: boronic acid, diaryliodonium salt and arylhalide.[33, 38, 39] We want to investigate if it is possible to synthesize diarylated hydantoins with these methods and if so, with good yields.



Scheme 12: The study divided in three reactions steps.

2 Results and discussion

In this chapter, results and data from the three parts are presented and discussed in order.

2.1 Formation of spirohydantoins

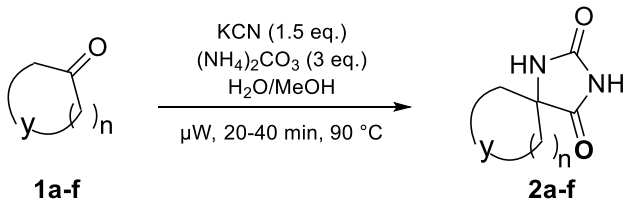
The formation of spirohydantoins has been preformed using the known Bucherer-Berg reaction. The specific method used in this work was a multicomponent, microwave assisted reaction starting from cyclic ketones.[16] The results from the reactions are presented in Table 1 and 2.

The first structure isolated was 1,3-diazaspiro[4.5]decane-2,4-dione **(2a).** The reaction resulted in a reaction of 67 % for the six-membered spiro structure, using mostly the same condition as reported, except the reaction time was extended to 20 minutes.[16] The synthesis was attempted tracked with thin layer chromatography (TLC), but due to low solubility of the product, its spot was hard to visualize. The starting material was however visible and seemed to be present after 15 minutes and gone after 20 minutes. The literature reports a reaction time of only 10 minutes with almost total conversion.[16] The reason for the difference in reaction time has not yet been discovered.

The yield from the synthesis is somewhat lower than expected since the literature reports a yield of 98 %.[16] In this reaction the product precipitates from the reaction mixture. The crude is first cooled to room temperature then further cooled in an ice bath, but the precipitation time was not specified.[16] The crude products were left to precipitate over a longer periods ranging from 2 hours to 4 days in a refrigerator, but such high yields as 98 % were never isolated. It is conceivable that Prevet *et al*.[16] may have let the crude product precipitate for an even longer time than attempted under this work. This may partly be the reason for the difference in yield.

A deviation from the literature in yield and reaction time was also observed for product **2b** and **2d,** probably due to the same reasons as discussed for **2a**. The literature reports yields of 91 % for **2b** and 95 % for **2d,** while the obtained yields were 65 % and 47 % respectively.[16] The four membered structure **2c** had on the other hand a more comparable result, with 60 % being reported and 61 % being obtained.[16] The reason for this may be from a difference in the work-up. The literature reports purification by flash chromatography but due to observation of precipitate, the structure was isolated with vacuum filtration, after cooling, like with **2a.**[16]

Table 1: The Reaction conditions and the results for the synthesis of hydantoin **2a-2f**. The yield presented are isolated yields. *not detected as pure compound.



1a-f **2a-f**

Entry	Substrate	Scale (mmol)	Reaction time	Product	Yield
1	**1a**	1.8	20 min	**2a**	67 %
2	**1b**	2.0	20 min	**2b**	65 %
3	**1c**	2.0	20 min	**2c**	61 %
4	**1d**	2.5	20 min	**2d**	47 %
5	**1e**	1.0	20 min	**2e**	nd
6	**1f**	2.0	40 min	**2f**	39 %*

Product **2d,** with a heteroatom in the spiro ring, obtained a lower yield then **2a-2c** with hydrocarbon spiro rings. This deviation in yield is probably because of the precipitation time. There were only completed one repetition with this substrate under these conditions, and the product was only let to precipitate for 1.5 hours. It is conceivable that with longer precipitation

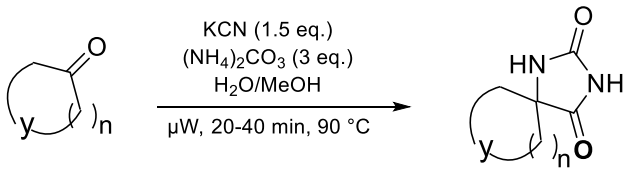
time, more product could have been isolated. Prevet *et al.* reports close related yields for **2d** as for **2a-2c**.[16]

A reaction was also preformed with cyclododecanone (**1e**) as the substrate to expand the ring size scope of the method (entry 5). The reaction was irradiated for 20 min, cooled to room temperature and further cooled in an refrigerator. A white precipitate was isolated after vacuum filtration and washing with water. The ^{1}H NMR spectrum did reveal a small signal typical for the *N*-1 proton of spirohydantoin but signals from unreacted substrate were dominating in the spectrum. Under the experiment it was observed that **1e** did not dissolve in the solvent mixture, as previous substrates had done. In view of that, the low conversion of ketone may be due to poor solubility. Other literature does report synthesis of **2e**, but at a 600 mmol scale.[40] There were no further efforts for synthesizing of **2e** after this.

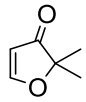
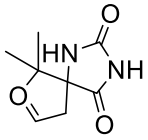
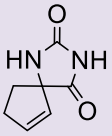
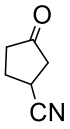
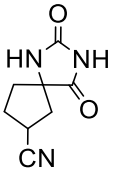
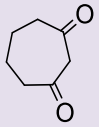
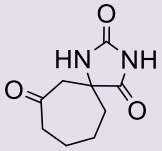
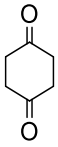
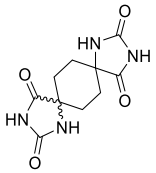
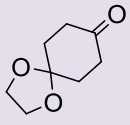
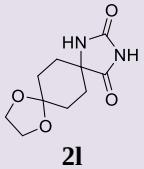
A substrate with a nitrogen in the spiro ring, was also tested. Piperidinone (**1f**) was reacted to make 1,3,8-triazaspiro[4.5]decane-2.4-dione (**2f**) with a yield of 39 %, however there is some uncertainty in this yield due to impure starting material. Piperidinone, **1f,** was bought as a hydrochloride monohydrate salt. Because of the danger of forming HCN when combining acid and cyanide, the hydrochloride salt was neutralized under basic conditions in an attempt to isolate the free piperidinone **1f**.[41] The Bucherer-Berg reaction with **1f,** led to some unknown impurities in the spiro ring area of the ^{1}H NMR spectrum, but the wanted structure was mainly detected. It is possible that the piperidinone makes the reaction more complex with its extra nitrogen leading to the formations of small amounts of byproducts.

As a part of the investigation, we also wanted to look into an α-substituted ketone to test the reaction's capability when it came to sterically hindered substrates. 2,2-Dimethylfura-3(2*H*)-one (**1g**) was chosen as a substrate. The reaction was run for a total of 40 min (20 + 10 + 10), but there was only little change observed by TLC, after 30 minutes. The products did neither precipitate at room temperature nor in an ice bath, thus the mixture was extracted and concentrated under vacuum. A brown oil was isolated and was analyzed with ^{1}H NMR. Signals for ethyl acetate, ethanol and acetone were detected but no signals from desired product. In addition to the solvent peaks, was the spectrum evenly loaded with random peaks from 9 to 1 ppm. The water phase was also analyzed with ^{1}H NMR, but no characteristic peaks for the wanted product were detected.

Table 2: The conditions and the results for the spirohydantoin synthesis of hydantoin **2g-2l**. The presented yields are isolated. **product 2h was not detected, but **1h** was converted to **1i** at 59 % yield. *not detected as pure compound.



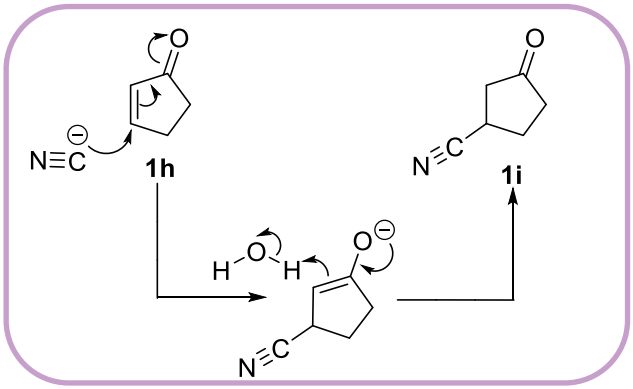
1g-l **2g-l**

Entry	Substrate	mmol	Reaction time	Product	Yield
7	 **1g**	1.9	40	 **2g**	nd
8	 **1h**	2.0	20	 **2h**	nd**
9	 **1i**	1.1	20	 **2i**	53 % 44/56
10	 **1j**	2.0 (MeOH) 1.0 (MeOH) 1.0 (EtOH)	30 30 40	 **2j**	< 5 %
11	 **1k**	1.0	20	 **2k**	86 %* 58/47 isomer ratio
12	 **1l**	2.0	20	 **2l**	59 %

The substrate **1g** has much functionality with an α,β-unsaturated ketone, an ether and α-substituents. It is conceivable that the α,β-unsaturated ketone in combination with the ether makes the reactivity at the β-carbon higher creating a second, different reaction site. Moreover,

that this sets in motion a cascade reaction that may lead to decomposition of the ring structure, since neither the starting material nor the desired product were detected.

On that note, a simpler substrate with some of the same functionality was tested, namely cylcopent-2-en-1-one (**1h**). The desired hydantoin was not synthesized with this substrate either. Instead 3-oxocyclopentane-1-carbonitrile (**1i)** was isolated at a yield of 59 %. This is because of the α,β-unsaturated carbonyl in the structure. This functional group is prone to 1,4-addition of nucleophiles, such as the cyanide ion.[42] A double bond in conjugation with a carbonyl will, because of resonance effects, give the β-carbon an electrophilic character and thus make that carbon preferred attack by certain nucleophiles, for nucleophilic attack. [43] The cyanide group as a good nucleophile will then attack the β-carbon, instead of the imine intermediate, and form **1i (**Scheme 13**)**. In view of this, it can be concluded that the reaction is not selective towards the carbonyl carbon when an α,β-unsaturated ketone is present.



Scheme 13: The mechanism for 1,4-addition of **1h** with cyanide.[43]

The β-substituted product, **1i,** was then successfully used as a substrate to form 2,4-dioxo-1,3-diazaspiro[4.4]nonane-7-carbonitile (**2i**) with the same reaction, since the ketone was still in place. The synthesis resulted in a yield of 53 % of a stereoisomer mixture. The structure contains two chiral carbon atoms leading to the possibility of four diastereomers; *R/R*, *S/S*, *R/S* and *S/R* (Figure 4).[44] The ^{1}H NMR analysis detected on the other hand only two stereoisomers, based on the observations of only two *N*-1 proton peaks (Figure 5). The reaction has formed all four stereoisomers but because two and two of the isomers are enantiomers, will those be detected as one. As showed in Figure 4 are the (*R/R*) and (*S/S*) structure, and the (*R/S*) and (*S/R*) structure enantiomers. This insinuates that one structure is a mirror image of the other and thus will have exactly the same through bond and through space NMR correlations and be detected as the

same.[44] The ^{1}H NMR analysis showed a 45/55 ratio between the (*R/R, S/S)* and the (*S/R, R/S).* The ^{1}H NMR assignment of the structures are described in the NMR section (2.4.1) below.

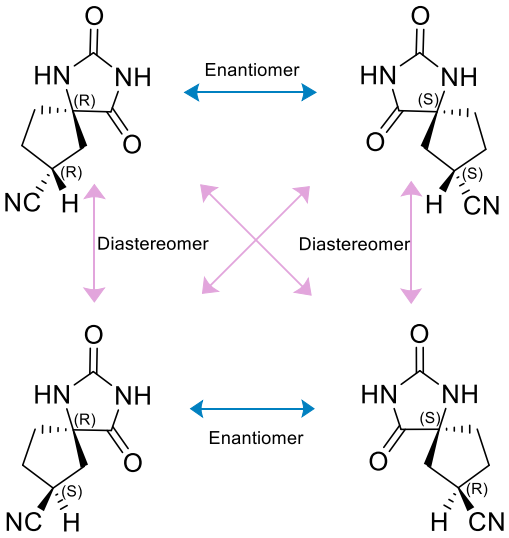


Figure 4: The four stereoisomer structures of **2i.**

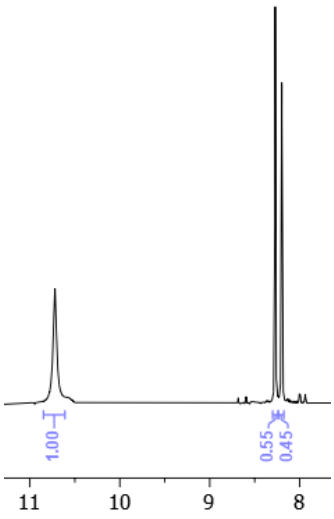


Figure 5: A section of the ^{1}H NMR (600 MHz, DMSO-d_6) spectra of **2i** from 11-8 ppm.

In figure 5 we also observe the *N*-3 protons but they are only detected as one signal. It is known from literature that the *N*-3 proton is the most acidic proton in the structure, and that acidic protons have a characteristic broad signal in ^{1}H NMR.[45] We would expect that the difference in chemical shift for the *N*-3 protons in the two enantimeric pairs is smaller than the change in chemical shift for the *N*-1 protons, since the change in the structure is closer to *N*-1 than *N*-3. Because the difference is small and the signals are broad, the peaks overlap and will be detected as one. With a stronger magnet the peaks could possibly be detected as individual signals.[45]

In the next entry (10) we wanted to test how the method is affected when reacted with a dione, with 1,3-cycloheptanedione (**1j**) as an example. Three repetitions with variations were carried out, with no isolation of desired product. The first repetition was run as usual at a 2 mmol scale, for 30 minutes in total, and was tracked with TLC. No precipitation was observed, either at room temperature or in the ice bath, therefore the reaction mixture was extracted with ethyl acetate (EtOAc). A brown oil was isolated in a small amount, equaling < 3 % yield. The ^{1}H NMR analysis showed characteristic signals for the nitrogen protons around 10 ppm and 8 ppm and spiro protons signals around 3-1 ppm, but in combination with numerous impurities (Figure 6). The spectrum showed two signals characteristic for the *N*-1

protons, which may indicate the formation of stereoisomers like in compound **2i**. It is conceivable that the reaction has reacted at both ketones.

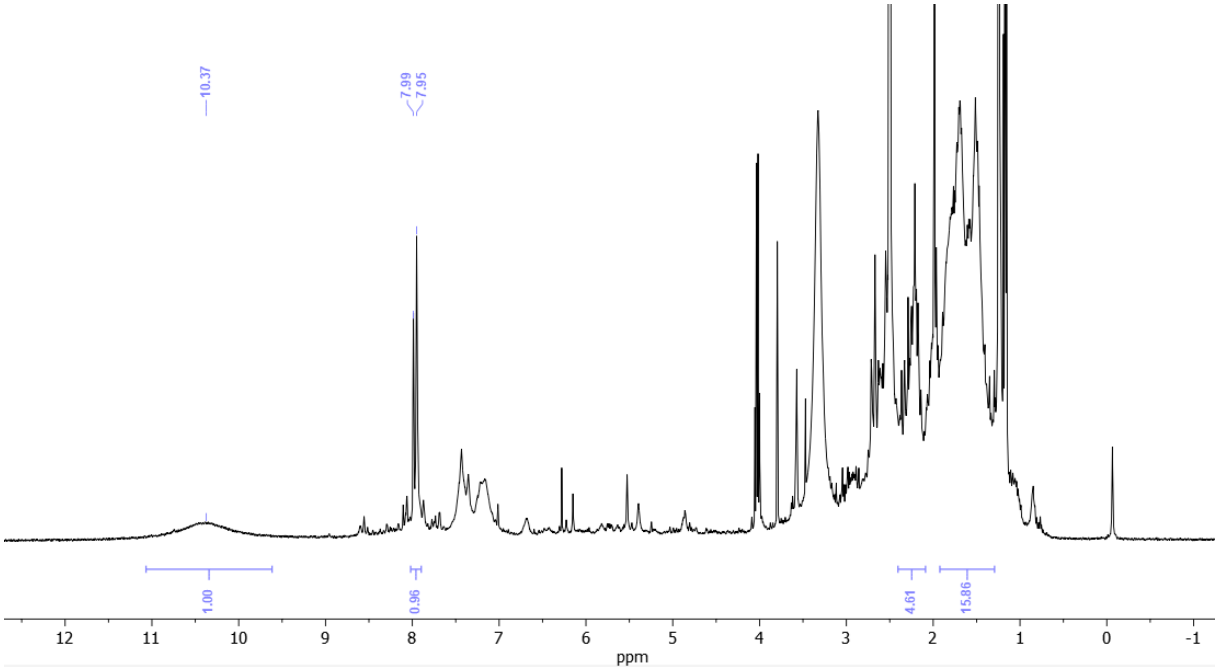


Figure 6: The ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of repetition one of entry 10.

The reason for the very low yield could be for stoichiometric reasons. Repetition 2 was hence run at a 1 mmol scale and double quantity of reagents, to favor a reaction on both carbonyls to possibly form a dispirohydantoin. As with the first repetition, no precipitate was observed, and the same preparation was preformed. An orange oil was isolated equaling < 5 % yield and the spectroscopic analysis showed the same appearance of characteristic signals and impurities.

A third repetition was run with a 1 : 8.25 : 4.13 ratio of substrate : carbonate : cyanide, based on a literature procedure for the synthesis of dispirohydantoins.[46] The repetition showed similar results as for the previous repetitions: < 4 % yield and similar signals in the NMR spectrum. In contrast to the other substrates tested, there was a gas formation observed during the preparation of the reaction of all repetitions for this substrate. The gas appeared after the addition of the ammonium carbonate and was probably carbon dioxide gas. The substrate 1,3-cycloheptanedione is different from the other substrates because of the highly acidic α-protons, between the carbonyl groups. It is conceivable that ammonia (or cyanide) have deprotonated the α-position and stopped the hydantoin synthesis. Carbon dioxide forms independently in the reaction, and will then not react further because the synthesis have stopped. Carbon dioxide as a gas could hence escape the reaction, as the observed gas. This could be an explanation for the very low isolated yields.

Another experiment was performed to form a dispirohydantoin, this time with 1,4-cylcohexandione (**1k,** entry 11), which was more successful. The conditions were the same as for the last repetition with substrate **1h,** 1 : 8.25 : 4.13 ratio, 1 mmol scale but with 20 minutes of reaction time. The synthesis formed 86 % of desired compound, but the ^{1}H NMR spectrum showed signs of impurities. Multiple efforts were made to purify the structure, both recrystallization and washing with various solvents (ethanol, hexane, dichloromethane (DCM), ethyl acetate, water) but with no success. (Figure 7). The product turned out to have a very low solubility and small particles remained suspended in all the tested solvents even when boiling. It was also made and effort to purify the product with flash chromatography but no suitable eluent system was found.

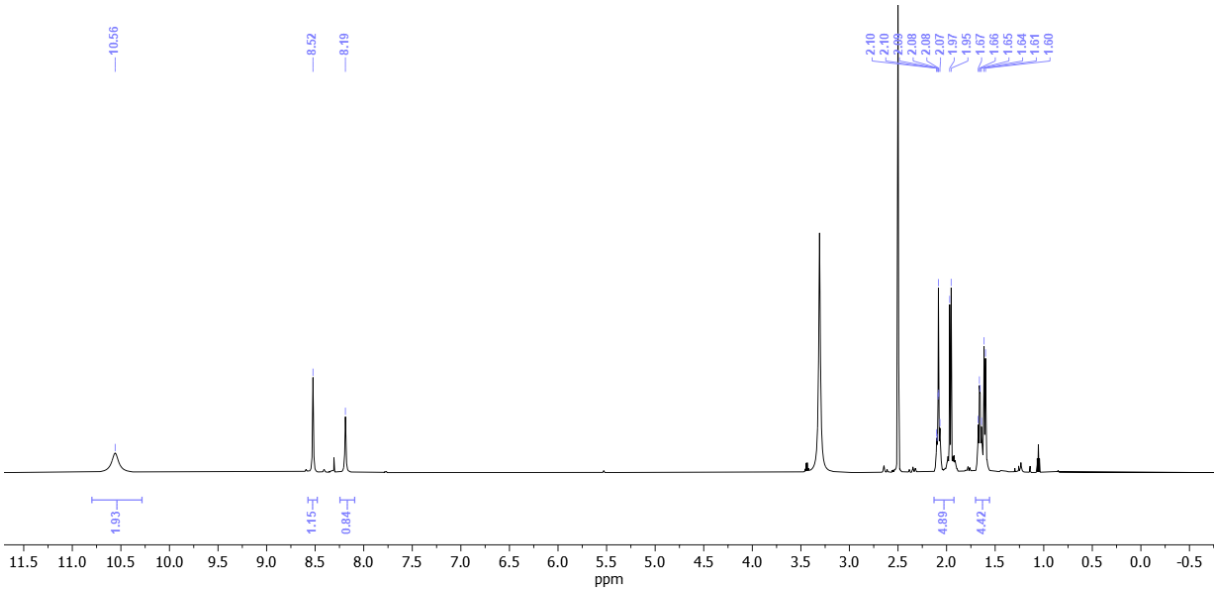


Figure 7: The ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **2k.**

At last we wanted to investigate the possibility forming a spirohydantoin with a ketone group in the spiro ring (entry 12). Ketone groups are often observed in biologic active structures, and furthermore does the group add more functionality to the structure making it an even better scaffold for further reactions. From the experiments with **1j** we have experienced that the reaction does not selectively react only once with plural ketones. For that reason was 1,4-dioxaspiro[4.5]decan-8-one (**1l**) chosen. One of the ketones is then protected as an acetal and can optimistically be deprotected to form the ketone after the hydantoin synthesis. A white compound 59 % was isolated with the general procedure after 20 min irradiation and 2 hours cooling in an ice bath for precipitation. The ^{1}H NMR analysis showed a clean spectrum of desired compound (**2l**).

To deprotect the ketone group, (0.1 mmol) of acetal hydantoin was refluxed at 60 ºC overnight (16 h) in a 0.1 M solution of *p*-toluenesulfonic acid in water.[47] The crude material was concentrated under vacuum and after a check by TLC the mixture was attempted purified with flash chromatography. The deprotection did not appear totally successful and a mixture of ketone and acetal was observed in the ^{1}H NMR spectrum (Figure 8). The acetal and ketone derivates had almost the same R_f value and eluated at the same time. There were made no further effort to separate the derivatives or to convert the rest of the acetalhydantoin.

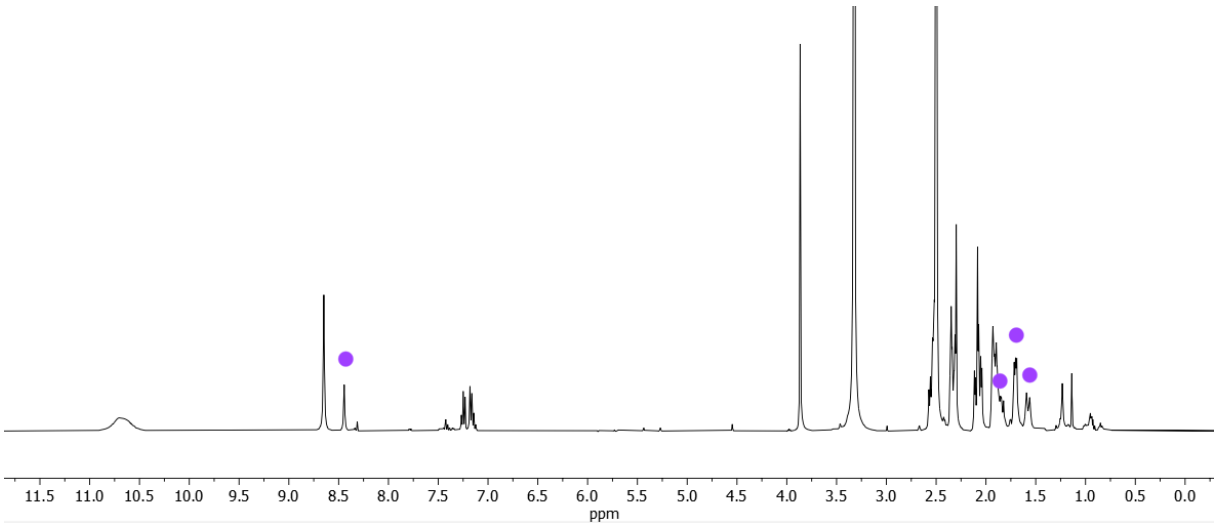


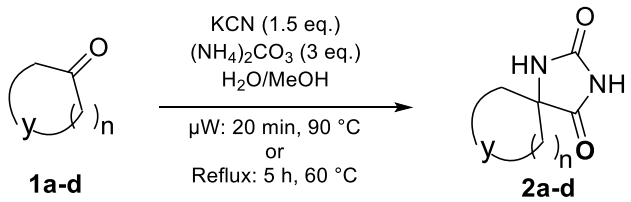
Figure 8: The ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of a mixture of protected and deprotected ketone derivate. The marked peaks belong to the protected ketone derivate.

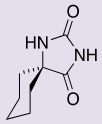
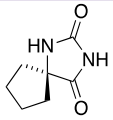
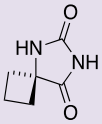
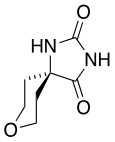
2.1.1 Microwave vs thermal conditions

Both thermal and microwave assisted conditions are known to form spirohydantoins.[13] Thus a small study on how the microwave versus thermal conditions does affect the reaction was conducted. The results from the study are presented in Table 3. The study was done with a selection of ketones, the three structures from the ring size study **1a-1c** and one structure with a heteroatom, **1d**. The difference in the reaction conditions were the reaction time and the energy source. The work-up for both methods involved precipitation, isolation by vacuum filtration and washing with water.

The microwave irradiated mixtures were reacted for 20 minutes at 90 ºC, while the reactions with thermal conditions were run for 5 hours at 60 ºC. The thermal conditions gave slightly higher yields of 54 -78 % compared to 47-67 % with the microwave.

Table 3: The result from the study of microwave versus thermal conditions. The presented yields are isolated.



	Microwave			Thermal		
	Reaction Time	**Precipitation time**	**Yield**	**Reaction Time**	**Precipitation time**	**Yield**
 **2a**	20 min	1 h	67 %	5 h	6 d	67 %
 **2b**	20 min	20 h	65 %	5 h	3 d	78 %
 **2c**	20 min	5 d	49 %	5 h	6 d	66 %
 **2d**	20 min	1.5 h	47 %	5 h	3 d	54 %

The precipitation time was varied based on observations. The study shows that the reactions with the longest precipitation time for product **2b-2d** gave the highest yields. The only product that resulted in the same yield with both methods were **2a**. Compound **2a** was precipitated for one hour after the microwave method and for six days after the thermal method. This may imply that the precipitation time alone is not the decisive factor and that the energy source may have a bigger impact.

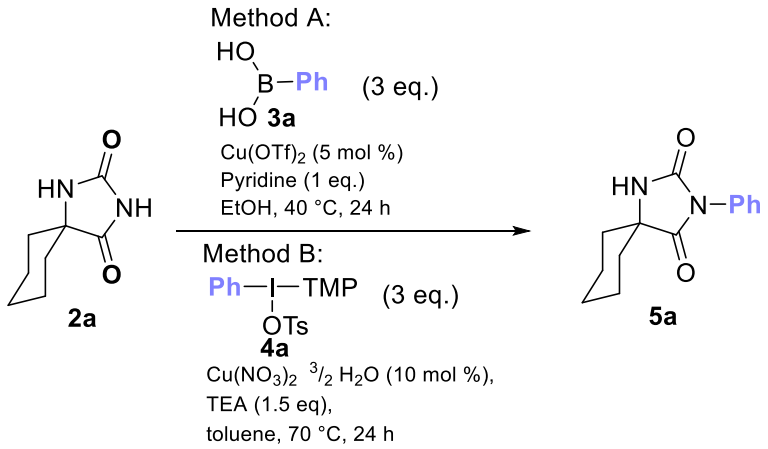
The microwave method does appear to produce slightly lower yields, but more efficient when considering the reaction time. One advantage with the thermal method is that the exposure of cyanide is minimized, making it more HSE friendly. Under the irradiation part of the study, the vial with the reaction mixture had to be transferred from the preparation laboratory to another room with the microwave apparatus and back to the laboratory for precipitation and work up. This increased the exposure risk to more people in case of an accident. With the thermal conditions, everything could be done safer in the same laboratory.

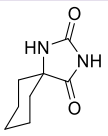
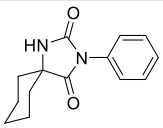
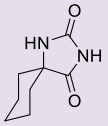
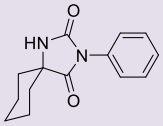
2.2 *N*-3-Arylation of spirohydantoins.

2.2.1 Selecting the method

Two methods were considered for the *N*-3-arylation of spirohydantoins. The first reaction, method I, is the Cu-catalyzed diaryliodonium coupling published by Berntsen *et al.*[31] The second, method II, is the Cu-catalyzed boronic acid coupling published in 2021.[32] Both methods were tested with 1,3-diazaspiro[4.5]decane-2,4-dione (**2a**) as the substrate and were reacted for 24 hours. The experimental conditions and resulting yields are presented in Table 4.

Table 4: The reaction conditions and resulting yields from the two *N*-3-arylation methods tested on spirohydantoin **2a**. The presented yields are isolated. *Not detected as pure compound.



Method	Substrate	Scale (mmol)	Time	Product	yield
I		0.40	24		87 %
II		0.18	24		46 %*

Both methods utilizes Cu(II) in catalytically amounts, however method II is optimized to 10 mol% while method **I** just require 5 mol% and is thus a little more desirable. Moreover, is method I dependent on commercially available boronic acids as the coupling agent while method **II** utilizes diaryliodonium salts that have to be synthesized, since they are either

expensive or not commercially available. Although the diaryliodonium salt synthesis is simple, it is time-consuming and atom-economically a disadvantage, given the multistep procedure.[48]

The desired compound was synthesized by both methods but the work-up in method II turned out to be somewhat more difficult. There was made an effort to purify the crude material with flash chromatography, with a slow eluent gradient (9:1 → 8:2→ 7:3, hexane/acetone), with no luck. The ^{1}H NMR analysis (Figure 9) showed that the method yielded the product in combination with impurities, both solvent peaks (hexane 0.88 ppm and ethanol at 1.26 ppm) and byproducts. Signals from trimethoxyphenyl (TMP) fragments can for example be observed at 3.87 and 3.83 ppm. The picked peaks mark the impurities in the spectrum. The impurities tailed on the column, and had an R_f value close to the product making it very complicated to do a successful separation. By contrast the work-up was not an issue for method I.

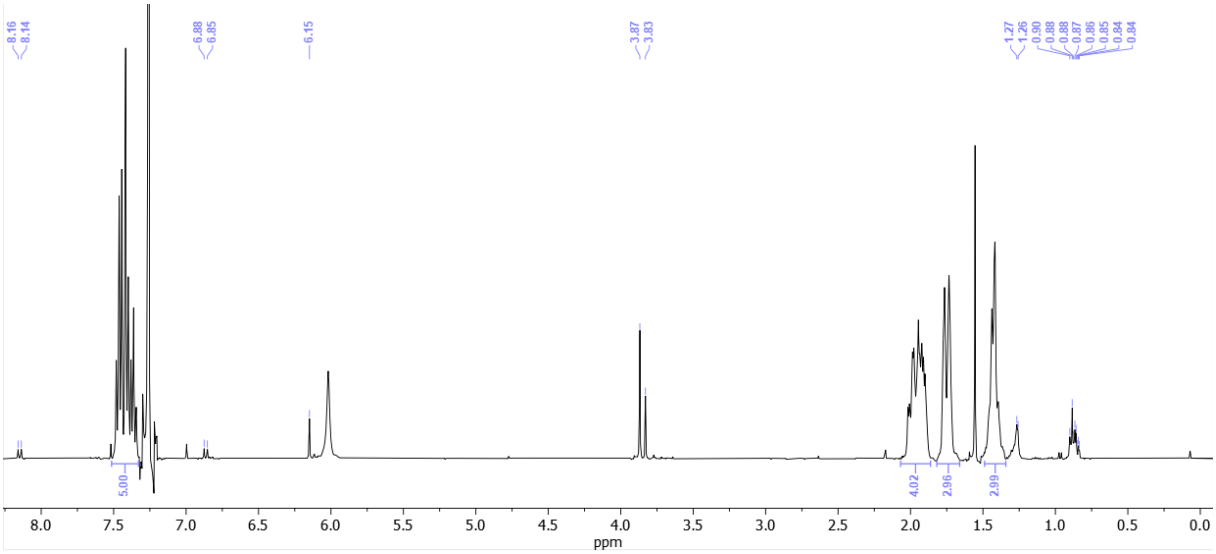


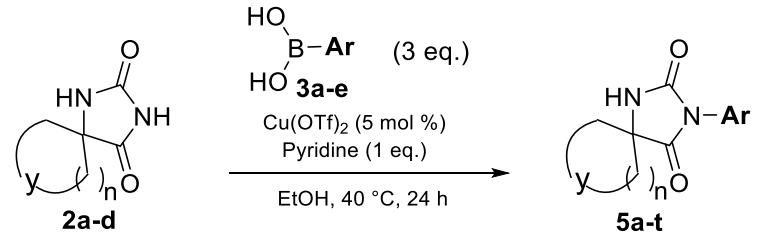
Figure 9: The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **5a,** synthesized using method II. The picked peaks mark the impurities in the spectrum.

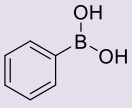
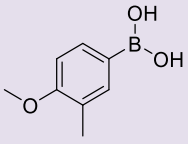
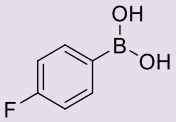
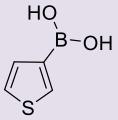
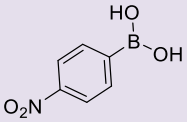
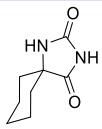
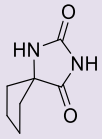
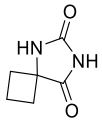
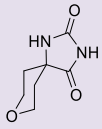
Considering the hazard risks, both methods employ acute toxic bases, but method I is in addition dependent on toluene as the solvent, which may be fatal if swallowed or inhaled.[49] In view of the complicated work-up, commercially unavailable diaryliodonium salts and hazardous chemicals, method II was rejected and method I was used as the primary method going forward in the study.

2.2.2 Scoping and method investigation

After selecting the Cu-catalyzed coupling using boronic acid, the reaction was further investigated by forming a scope to uncover the reactions capabilities and limitations. The results from the reactions are presented in Table 5. Four spirohydantoins were selected to be cross-coupled with five different boronic acids. The substrates were selected to test how the coupling reaction would perform on spirohydantoins with different ring sizes (4-6 membered) **2a**-**2c** and a spirohydantoin with a heteroatom **2d**.

Table 5: The *N*-3-arylation reactions and results of the study with 5 different boronic acids and four different spirohydantoins. The yields presented are isolated. Structures not reported before are marked with **New.**



	 **3a**	 **3b**	 **3c**	 **3d**	 **3e**
 **2a**	**5a** 87 %	**5e** 76 % **New**	**5i** 77 %	**5m** 79 % **New**	**5q** 87 %
 **2b**	**5b** 80 %	**5f** 92 % **New**	**5j** 75 % **New**	**5n** 84 % **New**	**5r** 85 %
 **2c**	**5c** 91 %	**5g** 81 % **New**	**5k** 81 %	**5o** 78 % **New**	**5s** 72 %
 **2d**	**5d** 87 %	**5h** 73 % **New**	**5l** 86 %	**5p** 81 % **New**	**5t** 97 %

When choosing the boronic acids, the electronic properties were in focus. Thus a neutral (phenylboronic acid **3a**), an electron-rich (4-methoxy-3-methylphenylboronic acid **3b**) and an electron-poor (4-nitrophenylboronic acid **3e**) boronic acid were chosen. Moreover, we also wanted to test how a boronic acid with a weakly electron deficient group, like a halogen (4-fluorophenylboronic acid **3c**), and a heteroaryl group (3-thienylboronic acid **3d**), would affect the reaction. These structures will in combination present a good overview of the methods capability for handling various electronic properties and substrates.

The reaction was first tested with phenylboronic acid (**3a**). All substrates gave good yields (80-91 %) of compound **5a-5d**. The small variation in yield may be due to small losses during work-up. All the products were isolated with flash chromatography. Compound **5a** had minor amounts of impurities that eluated together with the product, observed on TLC, but the impurities could not be detected by ^{1}H NMR. The spiro ring size variations and the heteroatom seemed to only have minor impact on the methods producebility.

The coupling reaction was also tested with the piperidine-based 1,3,8-triazaspiro[4.5]decane-2,4-dione (**2f)** as a substrate, and phenylboronic acid as the coupling agent (**3a**). The synthesis was run with the same conditions and work-up as the rest of the coupling reactions, but no desired compound was isolated. The flash chromatography fractions were analyzed with ^{1}H NMR, but only signals for phenyl-like structures were detected from the gathered fractions. In one set of fractions (Figure 10), were signals that could be in accordance with a phenyl group detected or it corresponding boroxine. In another set of fractions (Figure 11), a mixture of two different phenyl structures seemed to be detected. In view of that, it can be concluded that the boronic acid has reacted with something but not the hydantoin structure and the desired compound was not synthesized. This substrate, compared to the others, has an extra coupling position with the nitrogen in the spiro ring (*N*-8) creating another competitive position for the *N*-3 coupling in addition to the *N*-1 position. The *N*-8 nitrogen could probably also coordinate to the metal and act as a ligand.[50] Compound **2f** was removed from the scope of the method due to the time-consuming work required to reproduce pure spiro substrate (see discussion on spirohydantoin).

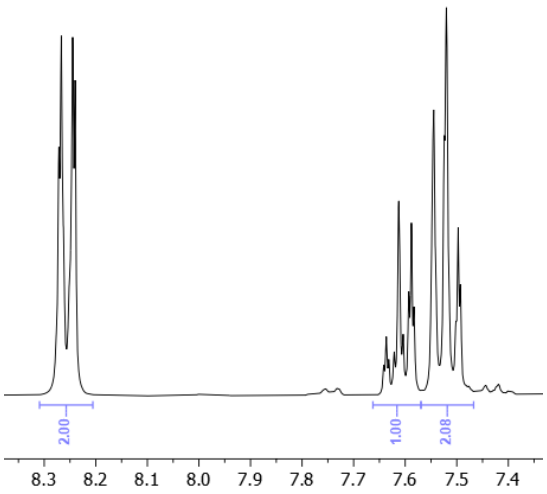


Figure 10: A section of the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of a side product from the failed reaction between **2f** and **3a** from 8.3-7.4 ppm.

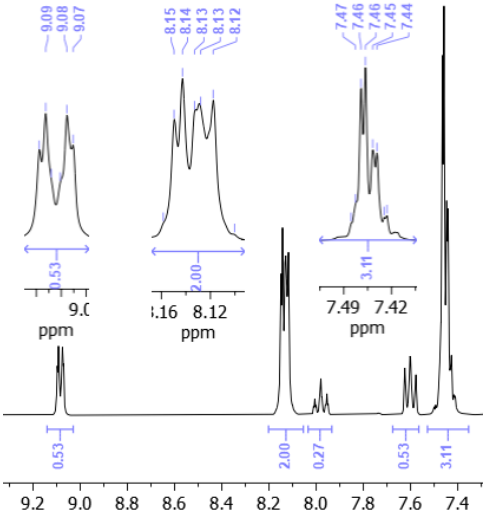


Figure 11: A section of the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of a byproduct from the failed reaction between **2f** and **3a** from 9.2-7.4 ppm.

The method was further run with the electron-rich boronic acid and showed good performance. The spirohydantoins (**2a-2d**) were coupled with 4-methoxy-3-methylphenylboronic acid (**3b),** which led to the formation of four new structures **5e-5h,** with good to excellent yields (73-92 %). This was also the case when the substrates were coupled with 3-thienylboronic acid (**3d**), as a heteroaryl. These couplings yielded another four new structures, **5m-5p,** in good yields (79-84 %), concluding that the method operates well with thiophene as an heteroaryl in addition to electron rich aryl groups.

Before the isolated products were characterized with 600 MHz NMR analysis, the products were checked with a 400 MHz ^{1}H NMR analysis for desired compounds. The 600 MHz analysis of **5n** detect some unexpected signals which seemed to be in accordance with an earlier isolated product **5g** (Figure 12). However, these signals had not been detected in the 400 MHz analysis of **5n**. Compound **5n** was analyzed again with a new NMR tube, in case the first NMR tube was the source of the error, but the signals from **5g** were still detected. In the time between the 400 MHz analysis and the 600 MHz, **5n** was somehow contaminated with **5g**, but we are confident that the desired product **5n** was isolated after column chromatography given the pure 400 MHz analysis.

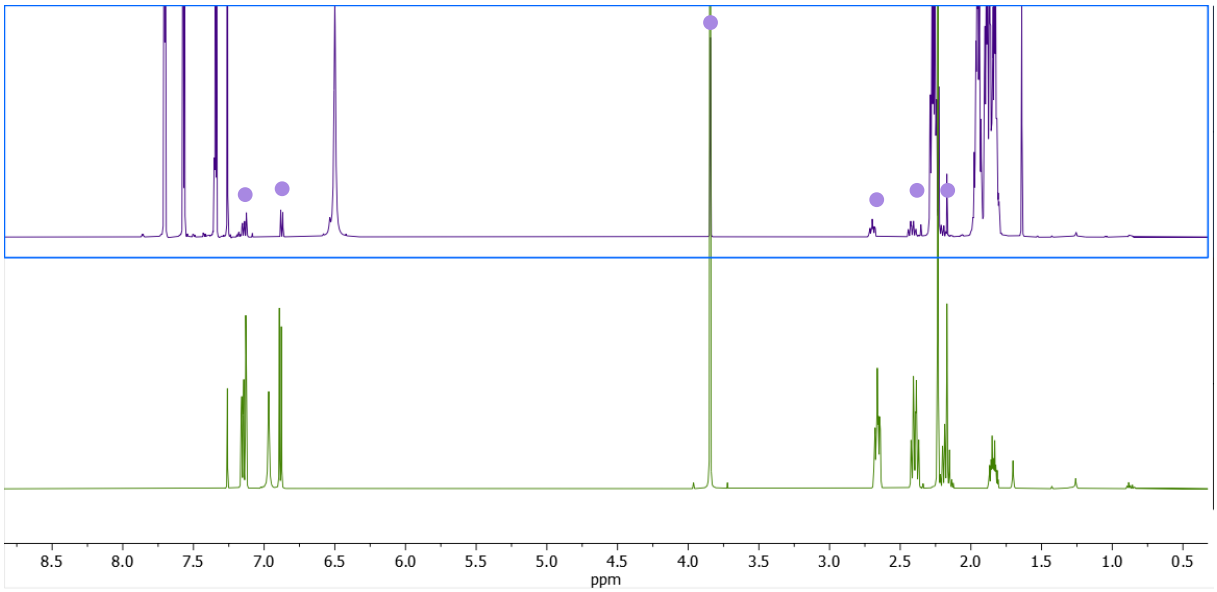


Figure 12: Two ^{1}H NMR (600 MHz, $CDCl_3$) spectra of *N*-3 arylated spirohydantoins. The purple spectrum presents the analysis of **5n** and the green spectrum presents the analysis of **5g.** The marked peaks are the detected peaks from **5g** in **5n**.

After the investigation of the electron-rich aryl groups, a weakly electron poor boronic acid was tested, 4-fluorophenylboronic acid (**3c).** The reaction allowed synthesis of product **5i-5l** in great yields 75-86 %. One of these couplings, 4-fluorophenyl coupled with cyclopentyl hydantoin yielded as well a new structure, **5j** in 75 %. At last was the method tested with 4-nitrophenylboronic acid (**3e).** Even with a strongly electron-withdrawing group, the method had no significant complications with the reaction and desired compound **5q**-**5t** (72-97 %) were isolated.

Most of the isolated compounds had remains of solvents, especially ethanol and hexane, detected in the ^{1}H NMR analysis. All the products were triturated and dried for at least 4 days under high vacuum, but the solvent signals were still detected. It is possible that the compounds have co-crystalized with the solvent, meaning that some solvent is stuck in the compound's crystal lattice.[51] Most of the compounds are for that reason characterized with spectra containing small amounts of solvent.

The combination of the pyran spirohydantoin (**2d**) and the electron-deficient boronic acid **3e**, produced the highest yield of 97 % (**5t**). The next best yield, 92 % (**5f)**, was formed with cyclopentyl hydantoin **2b** and the electron-rich boronic acid **3b**. However the electron-deficient, boronic acid **3e**, also produced the structure with the lowest yield of the scope (72%, **5s**) and the electron-rich boronic acid **3b** produced the next lowest yield (73 %, **5h**). This inconsistency may indicate that the variation in yield for the different structures is coincidental and that the

investigation showed no trends for how the reaction preformed when the substrate or the arylation agent were varied.

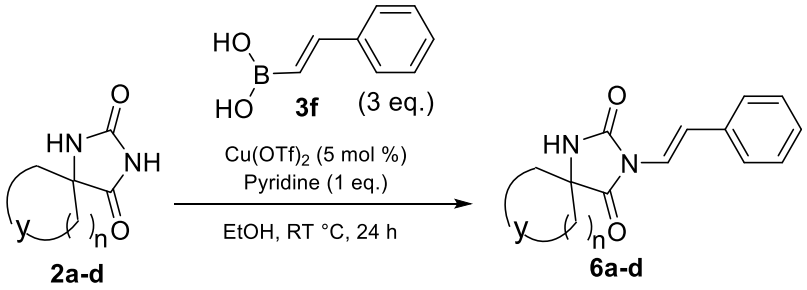
As mentioned in the introduction part, we know that the *N*-3 proton is more acidic than the *N*-1 proton.[8, 9] This makes the reactivity at the *N*-3 position higher and thus more preferred in a coupling reaction.[6] From a theoretical point of view, we would then expect the reaction to first couple at the *N*-3 position, as observed in the study, but we would anticipate some reaction on the *N*-1 position as well based on observations from earlier work in the group.[52] When the *N*-3 position is occupied, some of the excess boronic acid could be coupled onto the also reactive *N*-1 position, forming some amount of diarylated hydantoins. That has not been observed in our study, which gave high yields of only *N*-3-substituted products. This is likely because of the steric hindrance from the spiro ring next to the *N*-1 position.

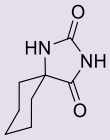
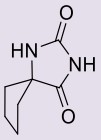
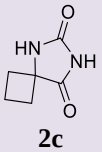
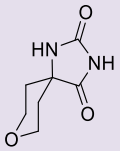
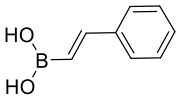
In the literature, it has been discovered that C-5 substituents on hydantoins have an impact on the regioselectivity in coupling reactions.[33] Thilmany *et al*. reports that *N*-3-substitution on 5,5-disubstituted hydantoins offer higher yields than C-5-monosubstituted and unsubstituted hydantoins.[33] The cause for this observation is probably the difference in steric effect in the substrates. The *N*-1 nitrogen on 5,5-disubstituted hydantoins is more sterically hindered than mono- and unsubstituted, thus making it harder and unfavored to react at that position, causing the reaction to be more regioselective at the *N*-3 position. This seems to be in accordance with our work. The spiro ring at C-5 will cause the same effect as observed in the literature and make a less competitive situation, leading to the possibility to isolate such high yields.

2.2.3 *N*-3-Alkenylation of spirohydantoins with styrylboronic acid

The investigation of *N*-3-arylation of spirohydantoins showed good to excellent results and therefore, we wanted to test some other *N*-3-couplings. Berntesen *et al*.[32] presented in the same article as the *N*-3-arylation method, a method for *N*-3-alkenylation of hydantoins. The methods are identical, except the temperature which is reduced to room temperature.[32] The four spirohydantoins from the arylation study were coupled with (*E*)-styrylboronic acid (**3f)**. The method and the results are presented in Table 6.

Table 6: The method, the coupling agents and the results used for *N*-3-alkenylation of spirohydantoins. The presented yields are isolated.



	 **2a**	 **2b**	 **2c**	 **2d**
 **3f**	**6a** 93 % **New**	**6b** 97 % **New**	**6c** 91 % **New**	**6d** 83 % **New**

The method allowed for the formation of products **6a-6d** in excellent yields (83-97%) and the structures synthesized are new structures not reported before. The yields are in accordance with the literature which reports the synthesis of *N*-3-alkenylated spirohydantoin-like structures (96-100 %) with this method.[32] Compounds **6a-6d** were also detected with small amount of solvent peaks in the ^{1}H NMR spectrum, assumed to be for the same reason as for the *N*-3-arylated compounds.

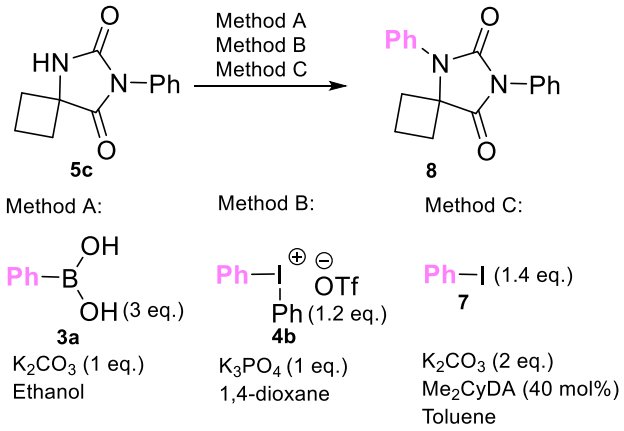
In both of the *N*-3-coupling methods is pyridine present. Previous work in the group has shown that the *N*-3-alkenylation of hydantoins is dependent on the presence of pyridine, but it is unclear what its function is in the reaction.[39] Pyridine, with its basic properties, is used to deprotonate the reaction site in such Chan-Lam-type reactions, and could probably also act as a Cu-ligand.[35, 53] Moreover, the reaction uses boronic acids as coupling partners, and boronic acids can be dehydrated to their corresponding boroxine form though an equilibrium.[54, 55] It is possible that the boroxine is the coupling partner in the reaction and not the boronic acid itself. We believe that the equilibrium of the styrylboronic acid is shifted to the boronic acid side, but since boroxine is known to be stabilized by nitrogen bases, another role of pyridine may be to stabilize the boroxine and make the coupling possible.[56, 57]

2.3 *N*-1-Arylation of *N*-3-arylated spirohydantoins

After finishing the *N*-3 investigation, we wanted to expand our study on spirohydantoins and moved the focus to the more complicated *N*-1 coupling and how to arylate that position when the *N*-3 position is preoccupied, forming diarylated spirohydantoins. It is suspected that the spiro ring, on the neighboring carbon to the reaction site, may affect the coupling possibility at the *N*-1 position because of its steric properties.[33] For that reason, the *N*-3 product with the least sterically spiro ring was chosen for this study, namely *N*-3-(phenyl)-spirobutylhydantoin (**5c**). The phenyl derivative was selected because of its neutral electron properties.

Three methods were tested to synthesize the desired compound and the reaction conditions and results are presented in Table 7. Method A is a simple method developed in the group. This method is a Cu(II)-catalyzed boronic acid coupling, with K_2CO_3.[39] Method B is a Cu(I)-catalyzed diaryliodonium salt coupling with K_3PO_4 under inert atmosphere.[38] And method C is a Cu(I)-catalyzed coupling under inert atmosphere with an aryl halide as the arylation agent, with K_2CO_3 and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (Me_2CyDA) as a ligand.[33]

Table 7: The three methods A, B and C for *N*-1-arylation of *N*-3-substituted spirohydantoins. The product yields and recovered starting material yields (SM) are isolated.



Method	Atmosphere	Time	Temp.	Catalyst (mol%)	Yield	SM
A	Air	24 h	40 ºC	$Cu(OTf)_2$ (20)	21 %	68 %
A	Air	96 h	40 ºC	$Cu(OTf)_2$ (20)	11 %	72 %
B	Ar	14 h	RT	CuI (20)	5 %	92 %
C	Ar	48 h	110 ºC	CuI (20)	94 %	nd

In method A, the reaction was heated at 40 ºC for 24 hours with access to air. After work-up, 21 % desired compound was isolated, in addition to 68 % of unreacted *N*-3-phenyl spirobutylhydantoin (**5c**). The reaction did form the desired compound but in a low yield. Earlier work in the group has shown similar low yields with this method, when C-5 is blocked. Coupling with 5-substituted *N*-3-phenyl-hydantoins gave 6 % yield, while coupling with 5-unsubstituted *N*-3-phenyl-hydantoins gave an 86 % yield.[52] This data confirms our initial suspicion about the impact of the C-5 substituent, having a big impact on the reaction.

Since a big share of the starting material did not react, we wanted to investigate if the conversion would increase with longer reaction time. Method A was run for 96 hours with the same conditions, but only 11 % of desired compound was isolated together with 72 % of starting material. This may indicate that the product has reacted further since almost the same amount of substrate has reacted, but isolated desired compound is reduced. The product could be targeted in a nucleophilic attack when both the acidic protons are substituted. K_2CO_3 as a good base could maybe form small amounts of EtO- in the solution, which could ring-open the hydantoin. The reduction in yield may also be a coincidence but that is impossible to discuss further without more investigation and data.

Method B was then tested: the reaction was run in a closed Schlenk tube with an argon atmosphere for 14 hours at room temperature. Only 5 % of desired compound was isolated after the reaction, with 92 % recovered starting material. The literature reports an isolated yield of 82 % for a similar structure, *N*-3-phenyl-5,5-dimethylhydantoin an isolated yield of 82 %, but does not specify why the reaction requires inert conditions and how the atmosphere is changed.[38] However, it is suspected that oxygen can oxidize Cu(I) to Cu(III) which might stop the catalytic cycle.[58] In this work, the atmosphere was changed by argon flow through the Schlenk flask, then the catalyst and base were added under that flow. The flask was closed and sealed before the reaction was run without any argon supply. A deviation between this exchange and the procedure may be the reason for the low isolated yield. It is possible that the flask was not fully sealed, or that some of the air did not exchange with argon in the first place and that some oxygen may have interfered with the reaction. In addition, there was a source of error under the addition of catalyst, and some amount of solid was blown away from the flask because of the flow, leading to the addition of a smaller amount of catalyst than reportedly needed. Both of these deviations may have had an impact on the reaction.

The third procedure, method C had on the other hand a more precise procedure. The literature report changing the atmosphere by evacuation and backfilling with argon three times, followed by addition of the catalyst under argon flow.[33] Using this method, the desired compound was synthesized in 94 % isolated yield after 48 hours of reaction at 110 ºC. No starting material was isolated. The reaction was run in a Schlenk flask to recreate the effect of a pressure tube. This method uses much harsher conditions compared to the other methods, with the combination of high temperature and high pressure, given it occurs in a closed system.

A considerable factor could be the reaction time, when comparing methods B and C. Both methods utilize Cu(I) and inert conditions, but method B has a much shorter reaction time (14 h) than method C (48 h). It is possible that with longer reaction time, and with a more controlled atmosphere, more product could have been formed with method B, but that cannot be concluded, without further investigation.

The reaction temperature seem to have a big impact on the reaction and is the biggest difference between method C (110 ºC) and the other two (40 ºC and RT). It is conceivable that the *N*-1 coupling of spirohydantoin has a higher transition state than typical couplings of 5-unsubstituted, 5-substituted and 5,5-disubstituted hydantoins, and therefore needs harsher conditions to overcome the activation energy. Method A and B use relatively mild conditions, enough to couple with 5-unsubstituted *N*-3-phenyl-hydantoin (method A) and *N*-3-phenyl-5,5-dimethylhydantoin (method B) but maybe not sufficient enough to couple with spirohydantoins. The reason for these mild conditions is first and foremost to minimize potential side reactions, so harsher conditions are avoided if they are not necessary. The boronic acids and iodonium salts are less stable than aryl halides and can with harsh conditions decompose and stop the reaction.[54, 59, 60]

2.4 NMR structure assignment

In this section, spiro-cyclobutylhydantoin **2c** (Figure 13) will be assigned as an example of how the structures were assigned with NMR spectroscopy. Spectroscopic data used were from ^{1}H NMR, ^{13}C NMR, HSQC, HMBC, NOESY and DEPT135 spectra.

The first step to solving the structure is to extract relevant data from the ^{1}H NMR and ^{13}C NMR spectra, the data are presented in Table 8 and 9. From the data we know that there are eight protons in total where two pair of protons are spectroscopically alike. Six of the protons are detected in a typical area for sp^3-hybridized carbon protons, which is in agreement with the number of spiro ring protons.[45, 61] Downfield in the spectrum are two signals observed in a typical area for amide protons and acidic protons, which can be in agreement with the two protons on the nitrogens.[45, 61]

Table 8: The spectroscopic data from ^{1}H NMR (600 MHz, DMSO-d_6) analysis.

Shift	Integral	Multiplicity
10.48	1	bs
8.27	1	s
2.42-2.29	2	m
2.26-2.20	2	m
1.91-1.83	1	m
1.74-1.68	1	m

Table 9: The spectroscopic data from ^{13}C NMR (151 MHz, DMSO-d_6) analysis.

Shift	Integral	Multiplicity
178.7	1	s
156.1	1	s
60.9	1	s
32.1	2	s
13.2	1	s

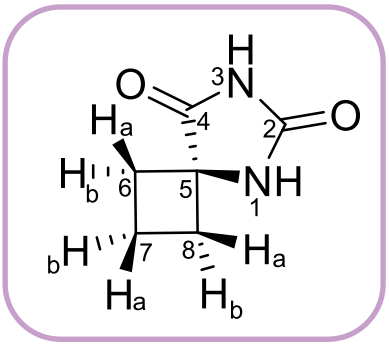


Figure 13: The structure of **2c** with specified room orientation and numbering of the atoms.

The ^{13}C NMR analysis detected five spectroscopically different carbons witch also are in agreement with the structure, since C-6 and C-8 are chemically and magnetically alike. Below 100 ppm, where sp and sp^3 carbons are detected, there are three signals fitting with the spiro carbons.[45, 62] Meanwhile there are detected two signals above 150 ppm, in the area for carbonyls, agreeing with the C-2 and C-4 carbons.[45, 62]

The next step to solve the structure is to assign the signals. First were the nitrogen protons assigned. As mentioned in the introduction do we know that the *N*-3 proton is more acidic then the *N*-1 proton. Highly acidic protons is usually detected as broad singlets, which could be in accordance with the 10.48 ppm signal. Acidic protons are also characteristically detected at around 10-12 ppm and amide protons at around 5-9 ppm.[45, 61] Based on that, were the signal at 10.48 ppm assigned the *N*-3 proton, and 8.27 ppm assigned *N*-1 proton.

The HSQC analysis showed no proton correlation from the signal at 60.9 ppm (Figure 14), therefore it can be assumed that this is the C-5 carbon, being the only sp^3-hybridized quaternary carbon. This is also in accordance with the DEPT analysis. Elsewhere in the HSQC analysis, there is a correlation between the multiplets at 2.23 and 2.35 ppm and the carbon signal at 32.1 ppm. The two multiplets integrate to four protons in total. This leads to the carbon signal at 32.1 ppm being assigned to the two chemically alike carbons C-6 and C-8, since this is the only way one carbon signal can correlate directly to four protons in this structure. The multiplets 2.23 and 2.35 ppm are then assigned to a combination of H-6 and H-8 protons.

In the same analysis, there is a correlation between the carbon signal 13.2 ppm and the two multiplets at 1.71 and 1.87 ppm (in total two protons). These multiplets correlate in HMBC to the C-6 and C-8 signal (32.1 ppm) (Figure 15), making the 13.2 ppm signal the neighboring carbon to C-6 and C-8. The signals, 13.2 are therefore assigned the C-7 and 1.71 and 1.87 ppm assigned the H-7, this being the only neighboring carbon with protons. The H-7 protons are detected as individual signals, even though they are on the same carbon. This means that the protons have different spatial environments.

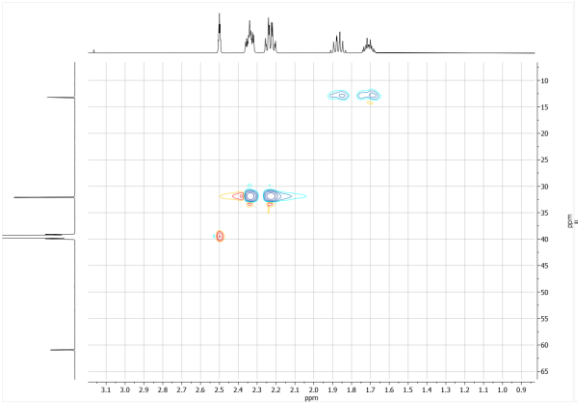


Figure 14: A section of the HSQC (600 MHz, DMSO-d_6) spectrum of **2c,** ^{13}C NMR: 8-44 ppm, ^{1}H NMR: 2.7-1.5 ppm.

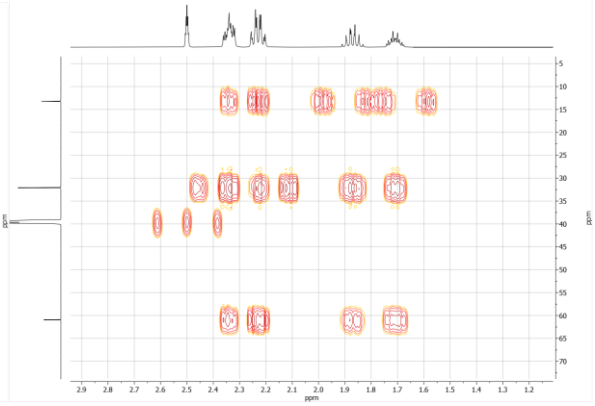


Figure 15: A section of the HMBC (600 MHz, DMSO-d_6) spectrum of **2c**, ^{13}C NMR: 5-70 ppm, ^{1}H NMR: 2.9-1.2 ppm.

Since the H-7 protons are detected as individual signals, is that probably the case for the H-6 and H-8 protons as well. If we look closer on the H-8 protons (Figure 16), we can observe that the H-8a will spatially be closer to the *N*-1 nitrogen while the H-8b will be closer to the C-4 carbonyl. Both of the groups will have a deshielding effect that shifts the signal downfield but not equally, making the signal appear individually. However there are only two signals detected for the 4 protons (H-6 and H-8). The reason for this is as mentioned earlier, that two of the protons are alike, but they are coupled on each its own carbon. The protons on C-6 and C-8 pointing to the same side of the spiro ring will then be chemically and spatially alike and therefore be detected as the same chemical shift and appear as one signal. This can be observed in the NOESY spectrum (Figure 17). The *N*-1 proton only correlates to one of the multiplets (2.23 ppm). In the view of this we can assume that the multiplet at 2.23 ppm belongs to H-8a and H-6a and that the multiplet at 2.35 ppm belongs to H-8b and H-6b.

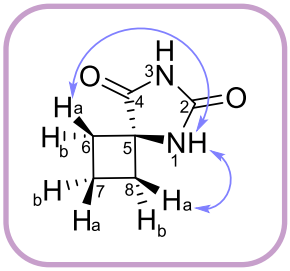


Figure 16: The structure of **2c** with the NOESY correlations from *N*-1.

In the HMBC spectrum there was a correlation between the H-6 and H-8 multiplets (2.23 and 2.35 ppm) and one of the carbonyl signals (178.7 ppm) (Figure 18). This carbonyl carbon has to be closer than the other, as the other carbonyl carbon did not correlate. The 178.7 ppm carbon signal is therefore assigned to the C-4 carbon. The C-2 carbon must then be assigned to the 156.1 ppm signal, being the last carbon signal.

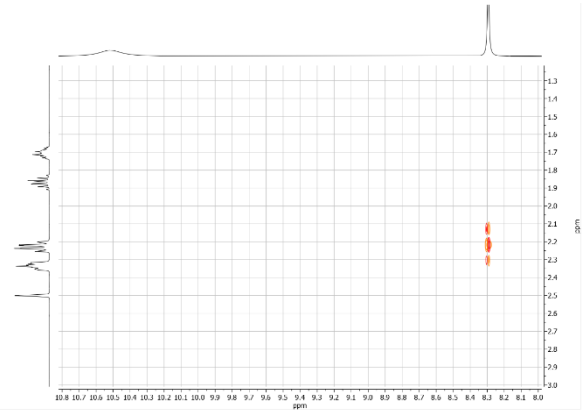


Figure 17: A section of the NOESY (600 MHz, DMSO-d_6) spectrum of **2c,** ^{1}H NMR: 1.3-3.0 ppm, ^{1}H NMR: 10.8-8.0 ppm.

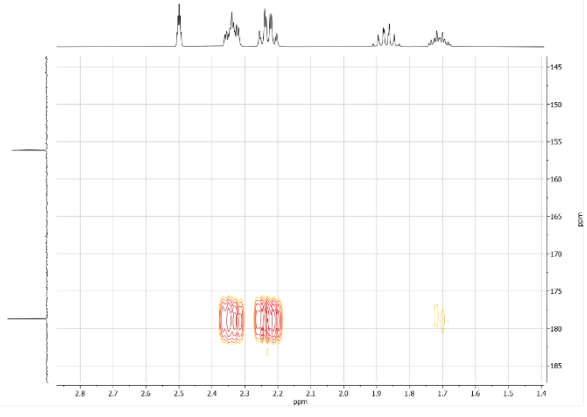


Figure 18: A section of the HMBC (600 MHz, DMSO-d_6) spectrum of **2c,** ^{13}C NMR: 145-185 ppm, ^{1}H NMR: 2.8-1.4 ppm.

2.4.1 Structure assigning, 2,4-dioxo-1,3-diazaspiro[4.4]nonane-7-carbonitrile

One of the spirostructures synthesized in this study was made as a mixture of stereoisomers, 2,4-dioxo-1,3-diazaspiro[4.4]nonane-7-carbonitrile (**2i**) (Figure 19). This section describes how the signals were assigned to their stereoisomer pairs. A ^{1}H NMR spectrum and a selective 1D TOCSY spectrum in combination with DEPT135, COSY, HSQC, HMBC and NOESY spectra were utilized. Regretfully, not all signals were possible to assign to their respective structure and position. The data and the assigning for the protons are presented in Table 10 and 11.

Table 10: The ^{1}H NMR (600 MHz, DMSO-d_6) peaks, integral, multiplicity and assigning for Structure 1.

Shift	Integral	Multiplicity	Assignmet
10.72	1	bs	H-3
8.20	1	s	H-1
3.22	1	qn	H-7
2.24-2.18	2	m	H-6a, H-8
2.16-2.09	2	m	H-9b, H-6b
2.0-1.96	1	m	H-8
1.80-1.75	1	m	H-9a

Table 11: The ^{1}H NMR (600 MHz, DMSO-d_6) peaks, integral, multiplicity and assignment for Structure 2.

Shift	Integral	Multiplicity	Assignment
10.72	1	bs	H-3
8.27	1	s	H-1
3.17	1	qn	H-7
2.48-2.46	1	m	H-6b
2.25-2.19	1	m	H-8
2.04-1.99	1	m	H-8
1.97-1.91	2	m	H-9b, H-6a
1.88-1.84	1	m	H-9a

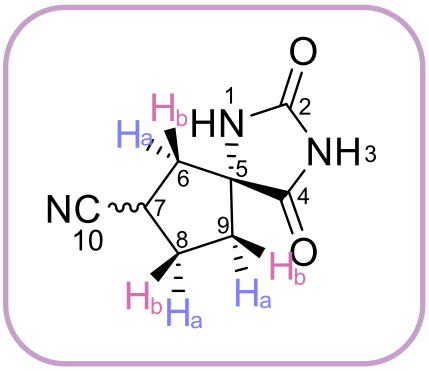


Figure 19: The structure and specified room orientation and numbering of **2i.**

First we wanted to assign which signals belong to which structure. It was assumed that the two signals at 3.22 and 3.17 ppm belonged to different structures and were hence used for differentiating in the selective TOCSY analysis (Figure 20). The analysis showed that the multiplets between 1.7 and 2.3 ppm are overlapping signals from the different stereoisomers. From the analysis, it was possible to divide the signals into two groups called structure 1 and structure 2. The signals that correlate to the 3.22 peak, the green spectrum in Figure 20, belong to structure 1 and the signals correlating to the 3.17 peak, the blue spectrum, belongs to structure 2.

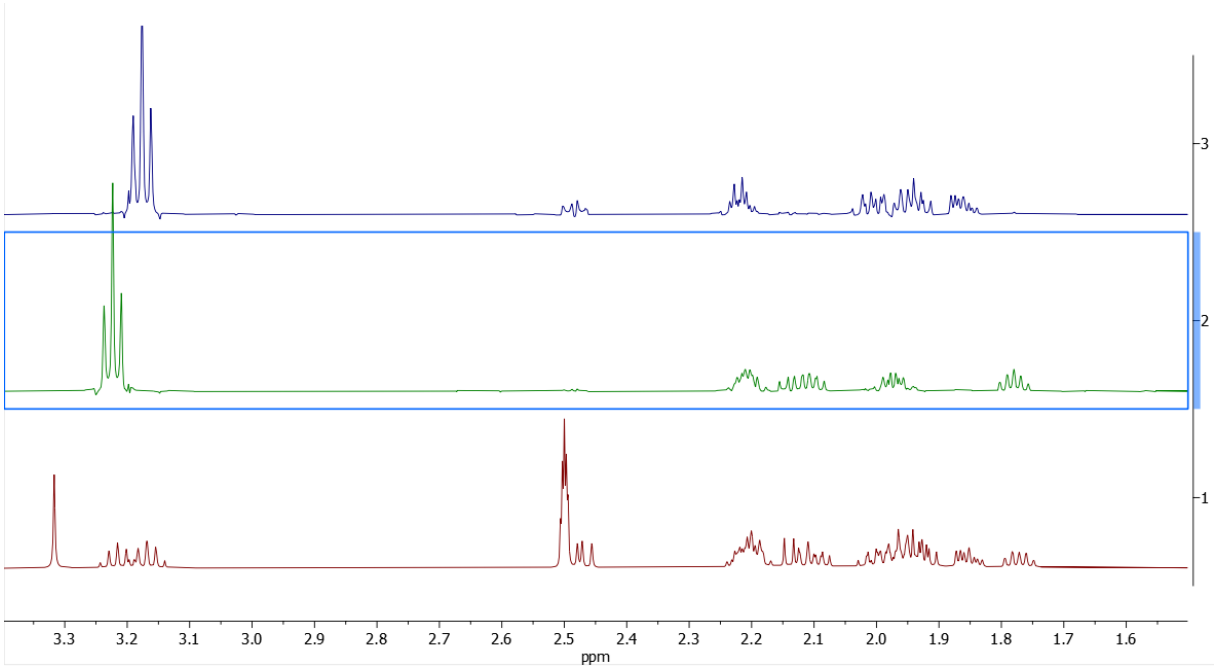


Figure 20: Three ^{1}H NMR (600 MHz, DMSO-d_6) spectra, 3.3 -1.6 ppm. The blue spectrum illustrates the selective TOCSY analysis where the signal at 3.17 ppm is selectively irradiated, the green illustrates the selective TOCSY where the signal at 3.22 is selectively irradiated and the red illustrates the normal ^{1}H NMR analysis.

Further was most of the ^{1}H NMR and ^{13}C NMR signals assigned to their structure and their position. The DEPT135, COSY, HSQC, HMBC and NOESY spectra, was used as shown in the example above, in combination with the selective TOKSY analysis.

The NMR analysis did not reveal any clear correlation leading to deciding which stereoisomer is which. However, in the NOESY spectrum there was detected a weak correlation between the H-7 proton from structure 2, and the multiplet at 2.48-2.46 ppm, assigned to H-6b (Figure 21). This seems to be in accordance with the *R/S*, *S/R* stereoisomer pair (Figure 22). In addition is there detected a weak correlation between the overlapping multiplet at 2.18-2.25 and the H-7 protons in structure 1. From the TOCSY analysis we know that the multiplet are a combination of signals from both structure 1 (2.24-2.18 ppm, H-6a, H-8) and structure 2 (2.25-2.19 ppm, H-8). It is conceivable that the H-7 from structure 1 correlates to the H-6a in the multiplet, which also has a NOESY correlation to H-1 (Figure 22). If this is true, structure 1 could be assigned the *R/R* and *S/S* stereoisomer pair, but that is not possible to confirm because of the overlapping multiplets.

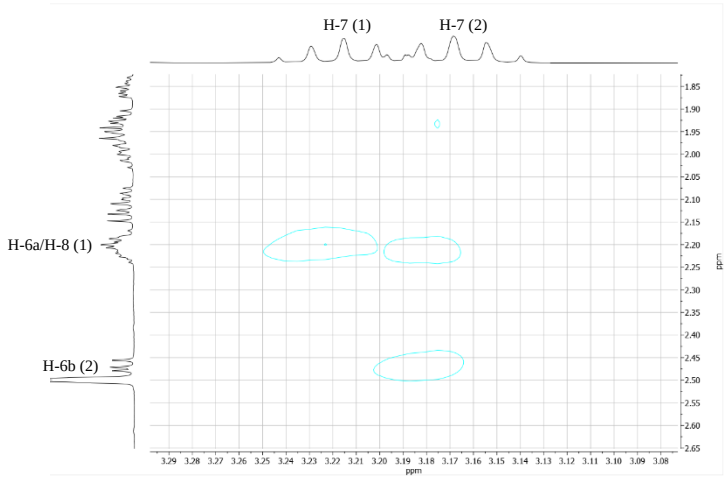


Figure 21: A section of the NOESY (600 MHz, DMSO-d_6) spectra of **2i,** ^{1}H NMR: 3.29-3.08 ppm, ^{1}H NMR: 1.85-2.65 ppm. The relevant peaks are marked with assigned proton number (structure number).

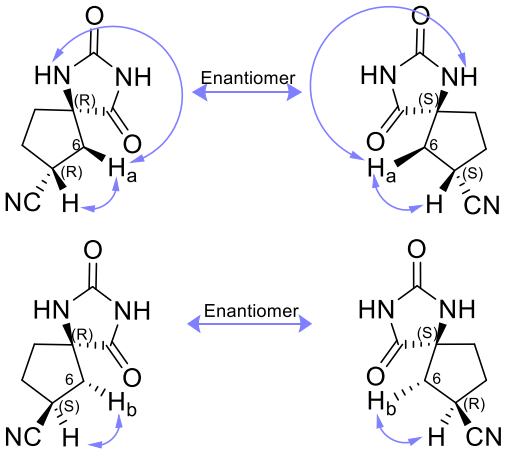


Figure 22: The detected NOESY correlations from H-7 and H-6 in the stereoisomer structures of structure **2i.**

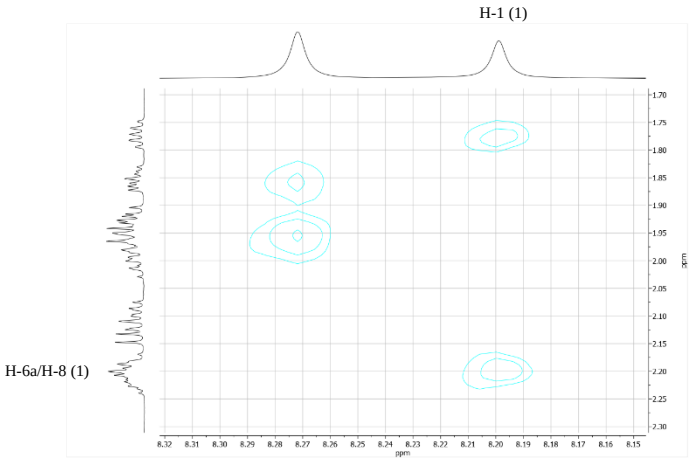


Figure 23: A section of the NOESY (600 MHz, DMSO-d_6) spectra of **2i,** ^{1}H NMR: 1.70-2.30 ppm, ^{1}H NMR: 8.12-8.15 ppm. The relevant peaks are marked with: assigned proton number (structure number).

3 Conclusion

The investigation of the microwave-assisted Bucherer-Berg synthesis showed good ability to produce a medium range of products, but the method did in general produce lower yields than expected from the literature. The method operated well with substrates of varying ring size (4-6) and was compatible with oxygen as a heteroatom in the ring. However, the method seemed to have some incompatibilities with a 12-membered cyclic ketone, presumably because of solubility. The reaction showed not to be chemoselective and did not allow α-substituted and α,β-unsaturated ketones, but did work with β-substituted substrates forming a stereoisomer mixture. The method allowed formation of a desired dispirohydantoin, with suitable amounts of the reactant present. Lastly, the method did allowed for the synthesis of a hydantoin with an acetal-protected ketone in the spiro ring.

The study of the energy source showed that the reaction with thermal conditions produced higher yields (67-78 %) than the microwave irradiation (47-67 %). The thermal reaction is dependent on a prolonged reaction time compared to the microwave-assisted, but is however a safer procedure with minimal exposure risk to cyanide.

A simple *N*-3-arylation of spirohydantoins with boronic acids showed excellent results. The spiro ring seemed to be an advantage for the regioselectivity of the reaction, hindering the competitive *N*-1 position. The boronic acid method was used to couple four different spirohydantoins and showed excellent capabilities with an array of aryl groups: neutral, electron-poor, electron-rich as well as a heteroaryl group. Only one desired structure did not couple, the piperidine based spirohydantoin, because of the conceivably multifunctional amine group in the spiro ring. The method also produced great to excellent yields of 72-97 %. Even though the isolated yields had some variation, the results seemed arbitrary and no trends were found. The diaryliodonium method were rejected because of complicated work-up, commercially unavailable diaryliodonium salts and hazardous chemicals. The boronic acid method showed similarly excellent results with styrylboronic acid as a coupling agent (83-97 % yields). Overall, this *N*-3-arylation using boronic acids produced 13 new spirohydantoins. No other arylation methods were investigated.

The *N*-1-arylation of *N*-3-substituted spirohydantoin showed varied results with the three chosen methods, but the desired compound was isolated with all methods. Another boronic acid

method and the diaryliodonium salt method of Saikia *et al*. showed low conversion to the desired product and most of the starting material was recovered after the reactions. However the aryl halide method of Thilmany *et al*. did show excellent conversion. The product seemed to be dependent on relatively harsh conditions and an inert atmosphere, which resulted in 94 % of isolated diarylated spirohydantoin.

Further Work

It would be interesting to do a further investigation into the *N*-1-coupling reaction of spirohydantoins with the method of Thilmany *et al*. to see how the spiro ring would affect the reaction. It could also be interesting to *N*-1-alkenylate the *N*-3-alkenylated spirohydantoins. It is known from literature that hydantoins can undergo a ring-opening reaction and end up as quaternary amino acids. This could be interesting to perform on the synthesized spirohydantoins to form complicated and new amino acids. Lastly it would also be interesting to analyze the products for biological activity and use the results from the analyses on a more targeted investigation.

4 Experimental section

4.1 General

All chemicals and solvents were used as received from Sigma-Aldrich, VWR, Tokyo Chemical Industry and Kebo AB Stockholm, unless stated otherwise. Deuterated solvents were delivered from Cambridge Isotope Laboratories, stored in an desiccator with molecular sieves, and used as received. Hexane was distilled before use. All reactions were performed in air unless stated otherwise.

Thin-Layer chromatography (TLC) was performed with 60 F254 silica coated aluminium plates from merck. The chemicals were detected using UV light and/or $KMnO_4$-stain (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL 10% NaOH in 200 mL water). Flash chromatography was executed with silica gel from merck (silicagel 60, 0.040-0.063 mm).
The nuclear magnetic resonance (NMR) spectrum for ^{1}H and ^{13}C were recorded on Bruker AVI600 and AVII600 (600 MHz (^{1}H), 151 MHz (^{13}C)). The spectrum for ^{19}F was recorded on AVNEO400 or AVIII400 (377 MHz) and are reported uncorrected. Chemical shifts (δ) were reported in parts per million (ppm) and the samples were solved in and calibrated after following solvents reference peaks: $CDCl_3$ (^{1}H: 7.26 ppm; ^{13}C: 77.2 ppm), DMSO-d_6 (^{1}H: 2.50 ppm; 13C: 39.5 ppm), CD_3CN (1H: 1.94 ppm; 13C: 1.3 ppm). All spectrum were recorded at 298 K. ^{1}H NMR multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), pentet (p), sextet (sext), heptet (h), doublet of doublets (dd) and multiplets (m). Coupling constants (*J*) are reported in hertz. ^{13}C NMR analysis were ^{1}H decoupled unless stated otherwise.

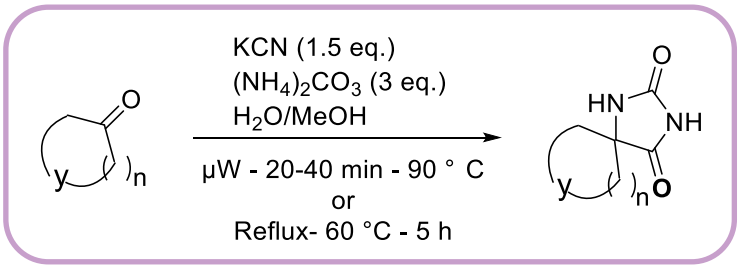
The mass spectrometry (MS) analysis were obtained by electron spray ionization (ESI) and electron ionization (EI) on Bruker Daltonik GmbH MAXIS II ETD spectrometer, by Osamu Sekiguci, Lina Aarsborg or Sverre Løyland. The signals are measured with mas-to-range ratio (m/z).

The FTIR spectrum were obtained by ATR (Bruker ATR A225/Q) on a Vertex 80 Bruker infrared spectrophotometer and DTGS detector (recorded at 4 cm^{-1} resolution). Characteristic peaks were assigned using standard IR spectrum tables.

All melting points were measured with Stuart SMP10 melting point apparatus and are reported uncorrected

4.2 Spirohydantoins

General procedures for preparation of spirohydantoins



Method 1: Microwave-assisted synthesis of spirohydantoins. The method is based on a procedure from the literature.[16]

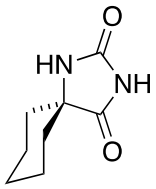
In a microwave vial with a cap: the desired cyclic ketone (1.8 mmol, 1 eq.) was stirred in a solution of MeOH/H_2O (1:1, 3 mL) with a stirring bar. Then ammonium carbonate (3 eq.) were added in one portion, followed by potassium cyanide (1.5 eq.) in one portion. The mixture was then heated under microwave irradiation for 20 minutes at 90 °C. Afterwards the mixture was cooled to RT. The desired spiro structures were purified and isolated with a suitable method as specified. The product was dried under high vacuum.

Method 2: Thermal synthesis of spirohydantoins.

In a 25 mL round bottom flask: the desired cyclic ketone (2 mmol) was mixed with a solution of methanol and water (1:1, 3 mL total) with a stirring bar. To the same flask, ammonium carbonate (6 mmol, 3 eq.) and potassium cyanide (3 mmol 1.5 eq.) were sequentially added. The mixture was then refluxed at 65 °C for 5 hours. The reaction was monitored by TLC to check conversion. When the reaction was completed, the mixture was then cooled to room temperature over night in open air. And then further cooled in a refridgerater for several days 5-7 to promote precipitation. The precipitate was isolated by suction filtration, and then washed with water (3 x 2 mL). The product was dried under high vacuume.

In those cases where no precipitate was observed the product was isolated by extraction with ethyl acetate (3 x 3 mL) and dried with magnesium sulfate, before it was concentrated with evaporation and vacuume.

1,3-diazaspiro[4.5]decane-2,4-dione (2a) [CAS: 702-62-5**]**



The product was isolated with the general procedures for the synthesis of spirohydantoins, both method 1 and 2, with some adjustment.

Method 1: The reaction was run with 1.8 mmol of cyclohexanone (**1a**), irradiated for 20 min, when the reaction was finished, the mixture was cooled in room temperature for 20 min before further cooled in an ice bath for an hour. The desired product was isolated as white crystals, 202 mg, 1.2 mmol, 67 %.

Method 2: The reaction was run with 2 mmol of cyclohexanone. The mixture was cooled in a refrigerator for 6 days before isolation of the precipitant as white crystals, 229 mg, 1.36 mmol, 67 %.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.52 (s, 1H), 8.37 (s, 1 H), 1.67-1.40 (m, 9H), 1.51-1.17 (m, 1H)

^{13}C NMR (151 MHz, DMSO-d6): δ 178.5, 156.3, 62.0, 33.2, 24.5, 20.8.

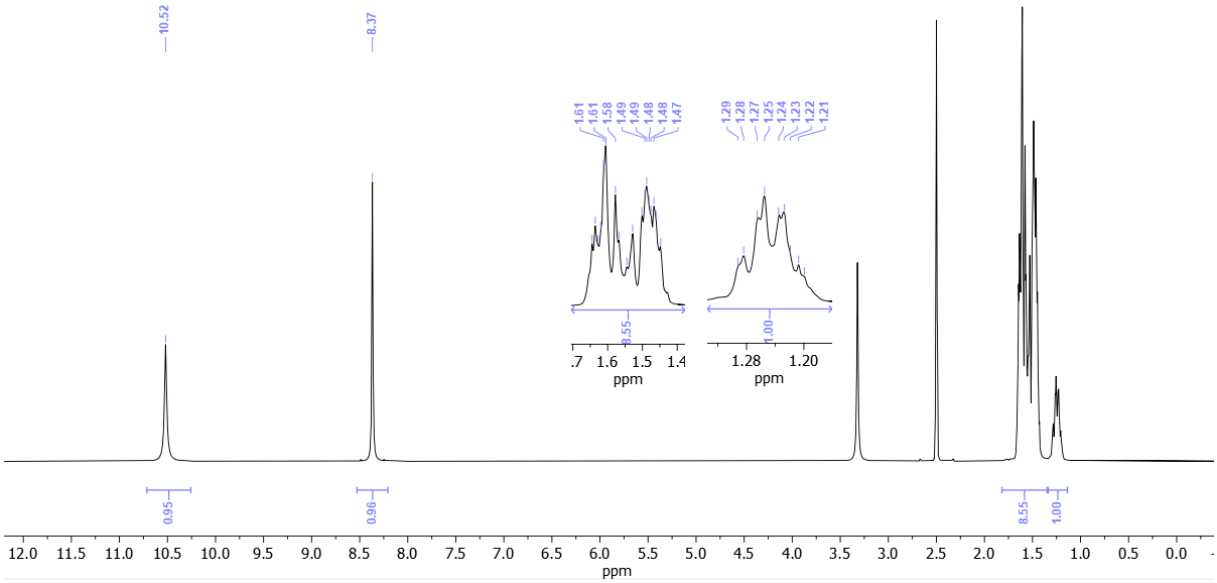
MS (EI): m/z (relative intensity (%)): 168.2 (10), 113.1 (26), 54.2 (60), 41.2 (100), 39.2 (49).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_8H_{12}N_2NaO_2^{+}$: 191.0791, found: 191.0791

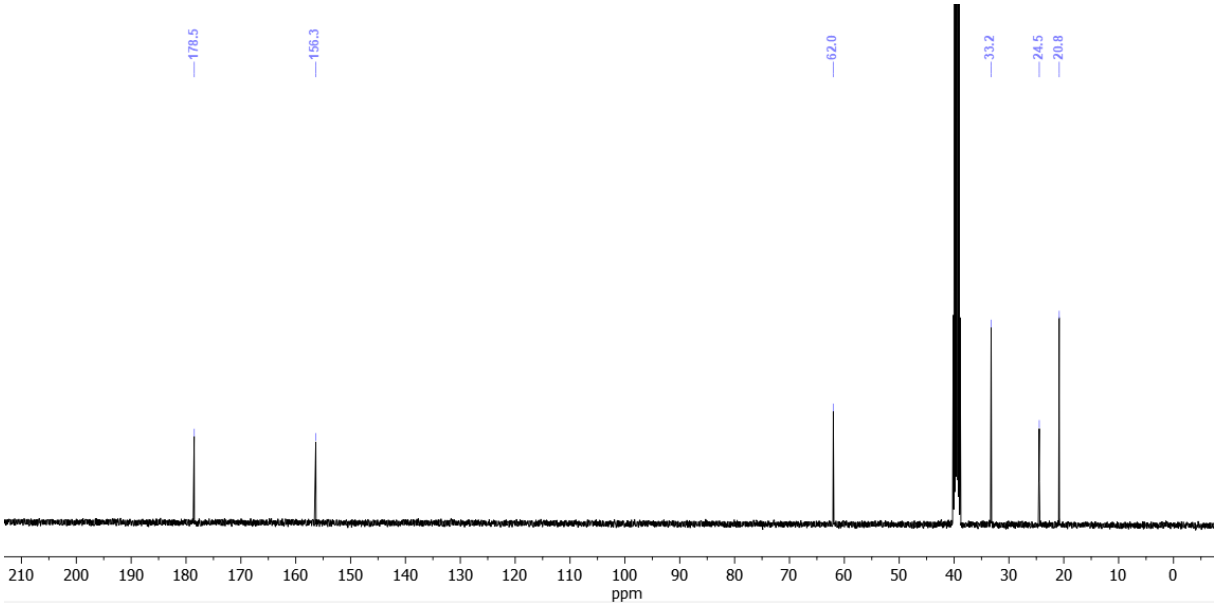
FT-IR (neat, V_{max} 1/cm): 3184.31, 3068,59, 2927.79, 1743.56, 1733.92, 1407.96

Melting point: 215-217 °C

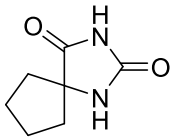
^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2a.



^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2a.



1,3-diazaspiro[4.4]nonane-2,4-dione (2b) [699-51-4]



The product was isolated with the general procedures for the synthesis of spirohydantoins, method 1 and 2, with some adjustments.

Method 1: 2 mmol cyclopentanone (**1b**) were irradiated for 20 min, cooled down in room temperature for 20 min and overnight in refrigerator. Precipitate was observed in room temperature. 201 mg, 1.3 mmol (65 %), white crystals were isolated after suction filtration and washing with water.

Method 2: 2 mmol cyclopentanone were refluxed for 5 h. Cooled overnight in room temperature and in refrigerator for several days. 241.5 mg, 1.57 mmol (79 %) white crystals were isolated after suction filtration and washing with water.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.54 (s, 1H), 8.13 (s, 1H), 1.93-1.89 (m, 2H), 1.77 – 1.63 (m, 6H).

^{13}C NMR (151 MHz, DMSO-d6): δ 179.5, 156.5, 68.3, 37.1, 24.7.

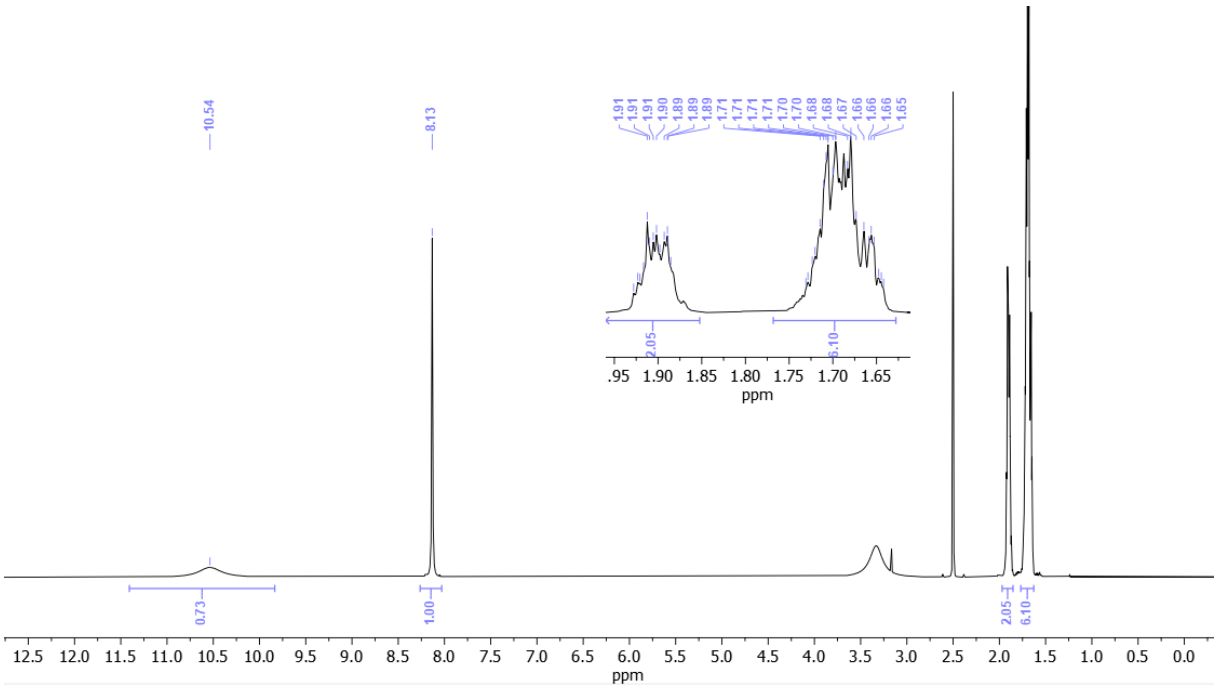
MS (ESI): m/z (%): 154.1/155.2 (17.1/1.5), 112.1 (24), 83.2 (38), 55.2 (38), 54.2 (100), 41.2 (86), 39.2 (48).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_7H_{10}N_2NaO_2$: 177.0634, Found: 177.0634

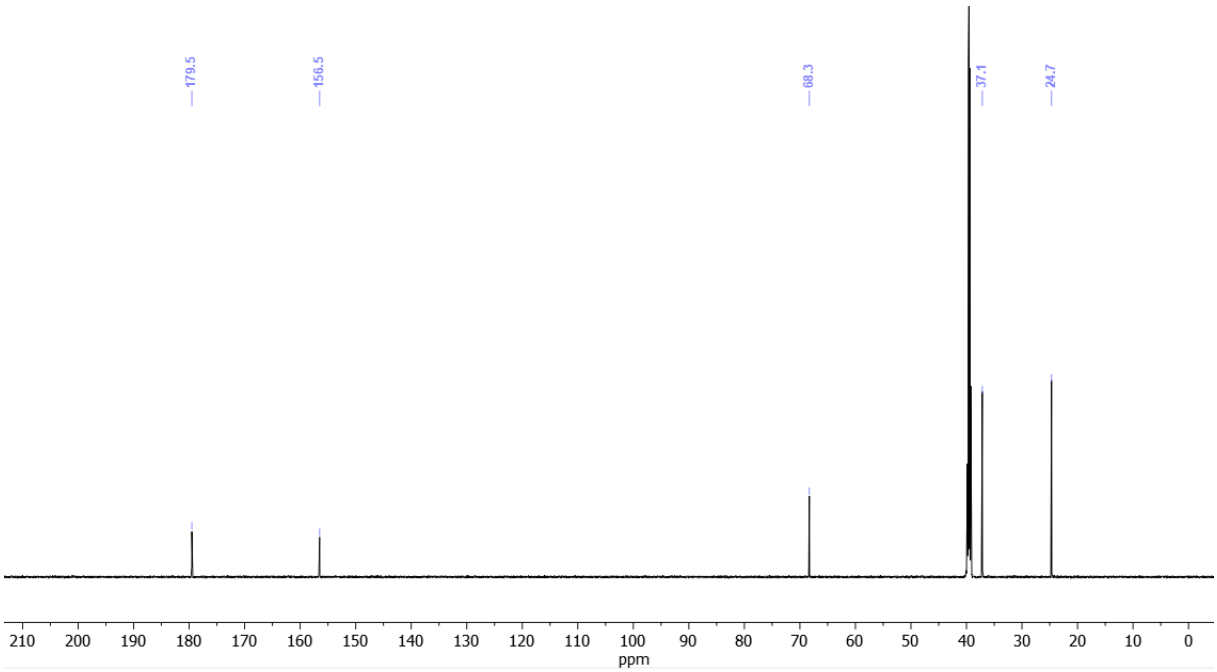
FT-IR (neat, V_{max} 1/cm): 3157.31, 3147.66, 2958.65, 2875.72, 1730.06, 1411.82

Melting point: 202-206 ºC

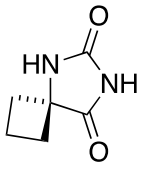
^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2b.



^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2b.



5,7-Diazaspiro[3.4]octane-6,8-dione(2c) [CAS: 89691-88-3**]**



The product was isolated with the general procedures for the synthesis of spirohydantoins, method one and two, with some adjustments.

Method 1: 2 mmol of cyclobutanone (**1c**), the reaction mixture was irradiated for 20 min, cooled down in room temperature for half an hour, precipitate was observed. The reaction was then further cooled in an refrigerator for five days. The precipitate was isolated with suction filtration and washed with water. 154 mg, 1.1 mmol, 61 %, white crystals were isolated.

Method 1: 2 mmol cyclobutanone (**1c**), with the rest of the reactions, was refluxed for 5 h. The reaction was cooled down to room temperature overnight, no precipitate was observed the next morning. A little shake with the flask promoted precipitation. The mixture was further cooled in an refrigerator for 6 days before 180 mg, 1.3 mmol, 65 % white crystals were isolated, after suction filtration and washing with water.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.48 (bs, 1H), 8.27 (s, 1H), 2.36-2.32 (m, 2H), 2.26-2.20 (m, 2H), 1.91-1.83 (m, 1H), 1.74-1.68 (m, 1H)

^{13}C NMR (151 MHz, DMSO-d6): δ 178.7, 156.1, 60.9, 32.1, 13.2.

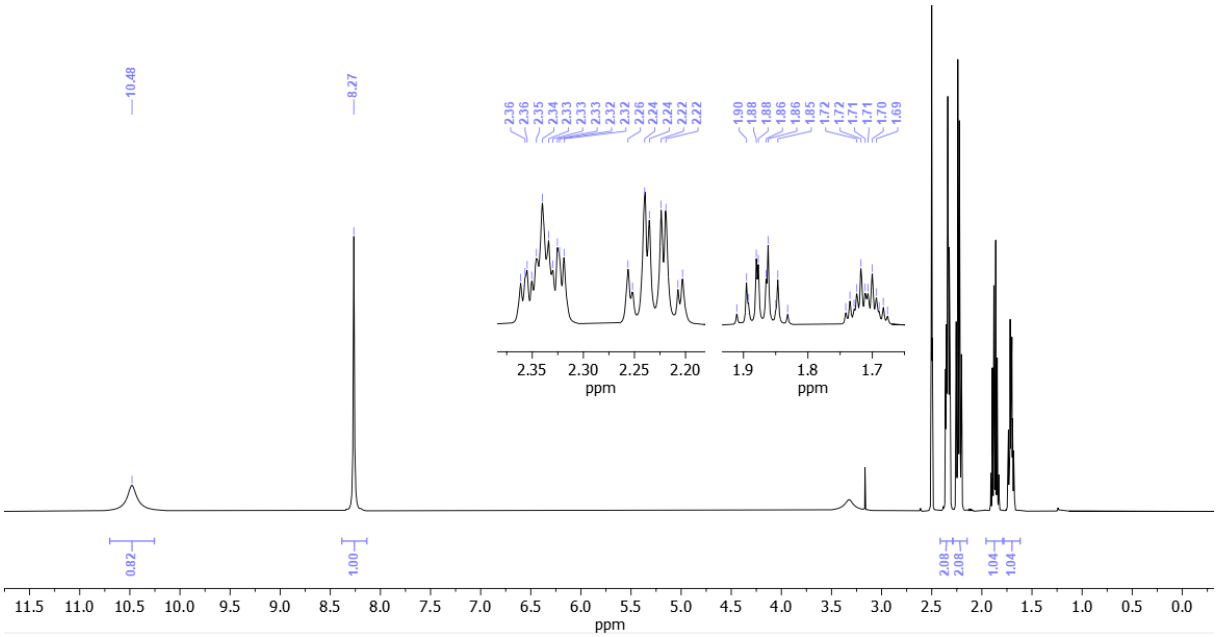
MS (EI): m/z (%): 140.1 (1), 112.1 (25), 41.2 (100).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_6H_8N_2NaO_2^+$: 163.0478, Found: 163.0478

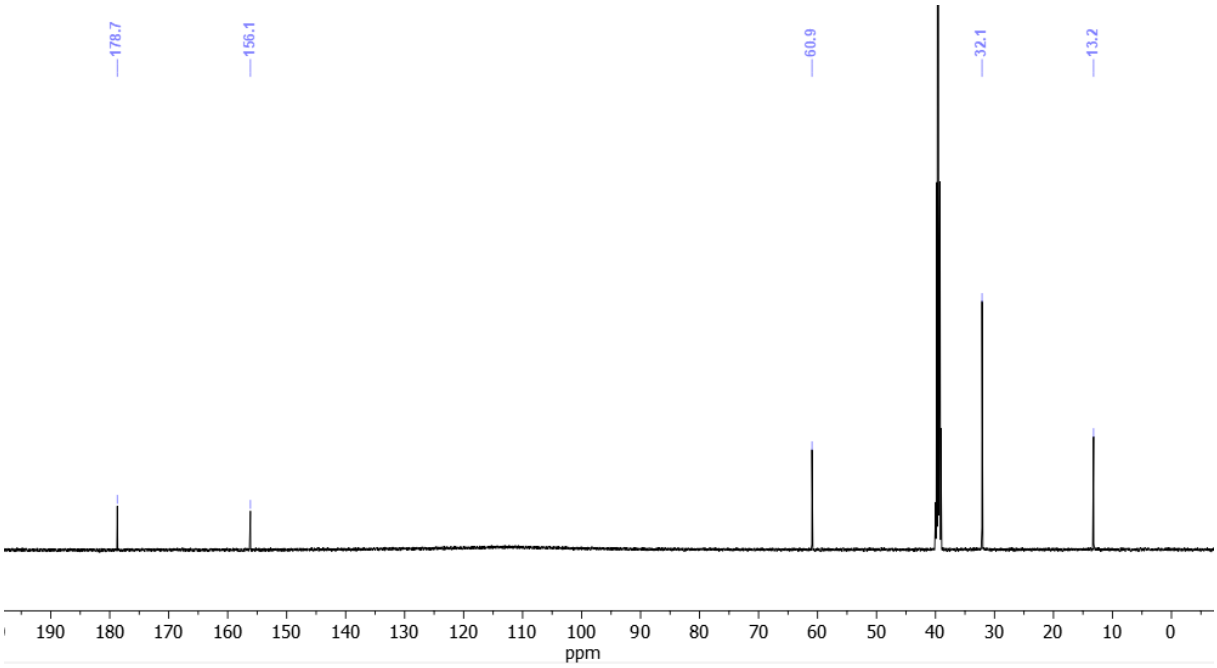
FT-IR (neat, V_{max} 1/cm): 3118.74, 2952.87, 1716.55, 1390.03, 1298.026, 1120.58, 640.33.

Melting point: 220-222 °C

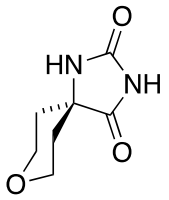
^{1}H NMR (600 MHz, DMSO-d_6) of compound 2c.



^{13}C NMR (151 MHz, DMSO-d_6) of compound 2c.



8-Oxa-1,3-diazaspiro[4.5]decane-2,4-dione (2d) [CAS: 39124-19-1**]**



The product was isolated with the general procedures for the synthesis of spirohydantoins, method 1 and 2, with some adjustments.

Method 1: 2.5 mmol of tetrahydro-4H-pyran-4-one (**1d**), with the rest of the reactions, were irradiated (**1d**) for 20 min (15 min + 5 min), cooled down in room temperature for 20 min and then in an ice bath for 1.5 h. Precipitate was observed in room temperature. 200.8 mg, 1.18 mmol (47 %), white crystals were isolated after suction filtration and washing with water.

Method 2: 2 mmol of tetrahydro-4H-pyran-4-one (**1d**), with the rest of the reactions, were refluxed for 5 h, cooled in room temperature for three days and 3 days in refrigerator. 184 mg, 1.08 mmol (54 %), white crystals were isolated with suction filtration after washed with water.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.69 (bs, 1H), 8.60 (s, 1H), 3.82-3.79 (m, 2H), 3.61-3.57 (m, 2H), 1.85-1.81 (m, 2H), 1.48 (d, 2H, *J* = 13.18 Hz).

^{13}C NMR (151 MHz, DMSO-d6): δ 171.6, 156.4, 62.5, 59.4, 33.3.

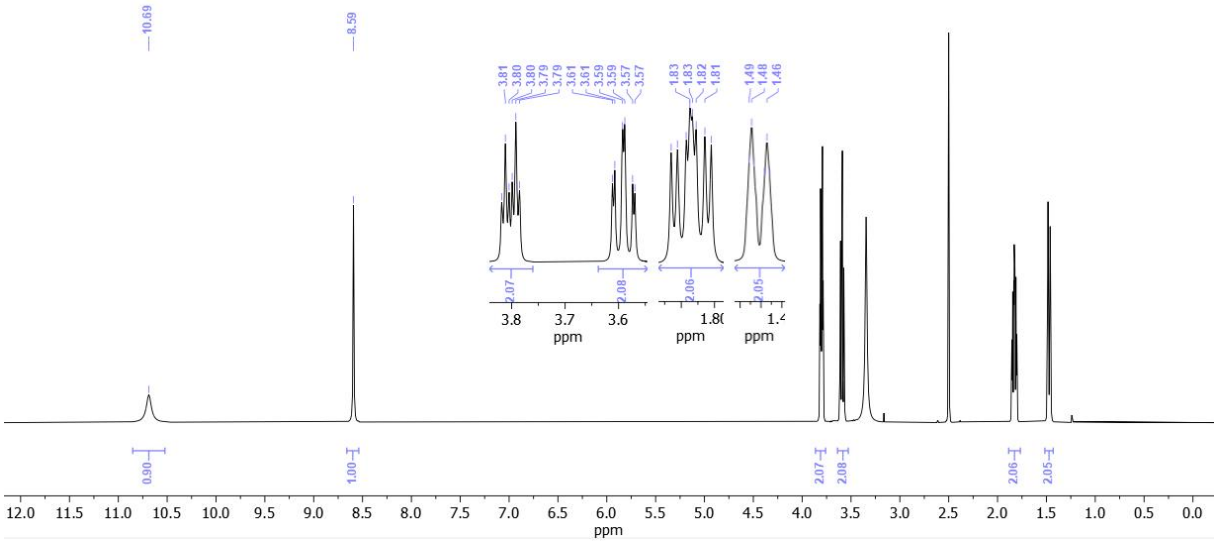
MS (ESI): m/z (%): 126.1/127.2 (96/6), 55.2 (71), 54.1 (40), 42.2 (39), 41.2 (100), 39.2 (19).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_7H_{10}N_2NaO_3$: 193.0584, found 193.0584

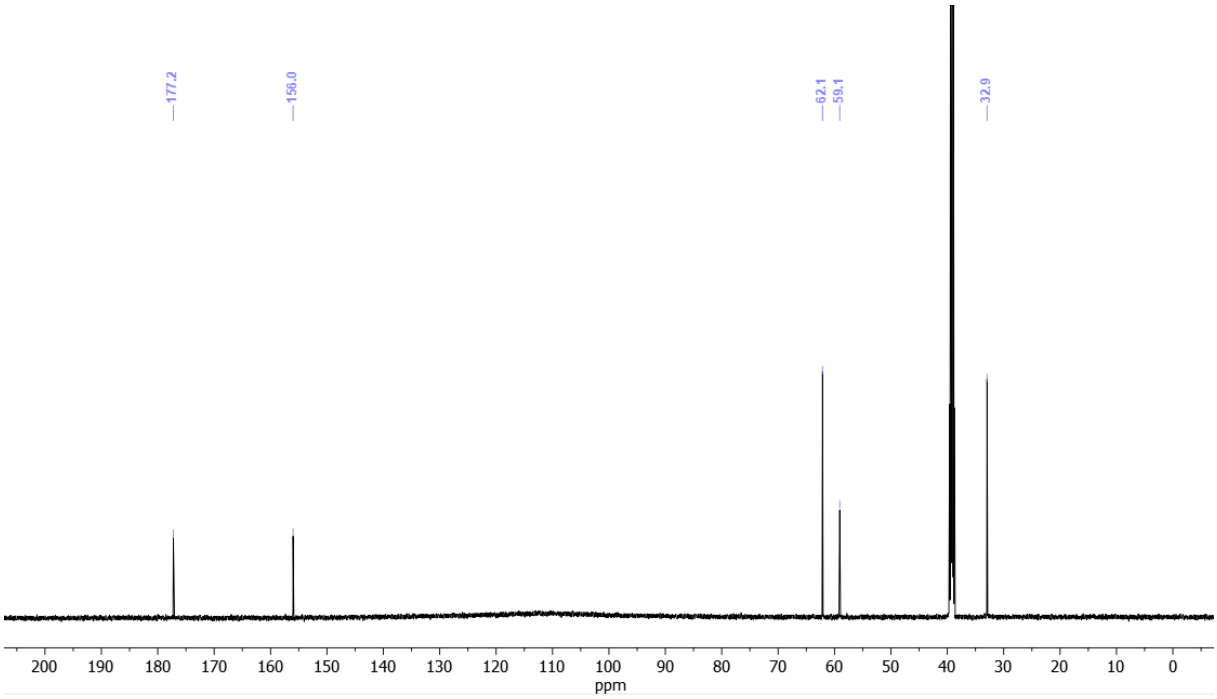
FT-IR (neat, V_{max} 1/cm): 3151.52, 3068.58, 2868.00, 1726.20, 1406.03, 1234.38.

Melting point: 255-256 **°C**

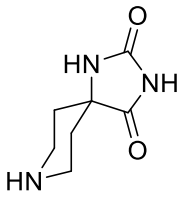
^{1}H NMR (600 MHz, DMSO-d_6) of compound 2d.



^{13}C NMR (151 MHz, DMSO-d_6) of compound 2d.



1,3,8-triazaspiro[4.5]decane-2,4-dione (2f) [13624-39-3]



The product was isolated with the general procedure for the synthesis of spirohydantoins, method 1. 4-piperidone was prepeared from 4-piperidone monohydate hydrochloride. The 4-piperidone in a solution of 2 N NaOH was extracted with EtOAc three times, dried with magnesium sulfate and concentrated. Some impurities were observed on ^{1}H NMR analysis.

2 mmol 4-piperidone (**1f**), with the rest of the reactions, was irradiated for 20 min + 20 min. Some startmaterial was observed on the TLC analysis (9:2 EtOAc/MeOH). Cooled down 20 min in room temperature and 2 hours in ice bath. The precipitate was filtered of with suction filtration and triturated with water. 131.2 mg, 0.78 mmol (39 %) solid was isolated with some impurities.

^{1}H NMR (600 MHz, DMSO-d6): δ 8.45 (s, 1H), 2.83 (d, 2H, *J* = 12.8 Hz), 2.96 (t, 2H, J = 11.5 Hz), 1.70-1.65 (m, 2H), 1.37 (d, 2H).

^{13}C NMR (151 MHz, DMSO-d6): δ 178.0, 156.3, 61.1, 41.2, 33.8.

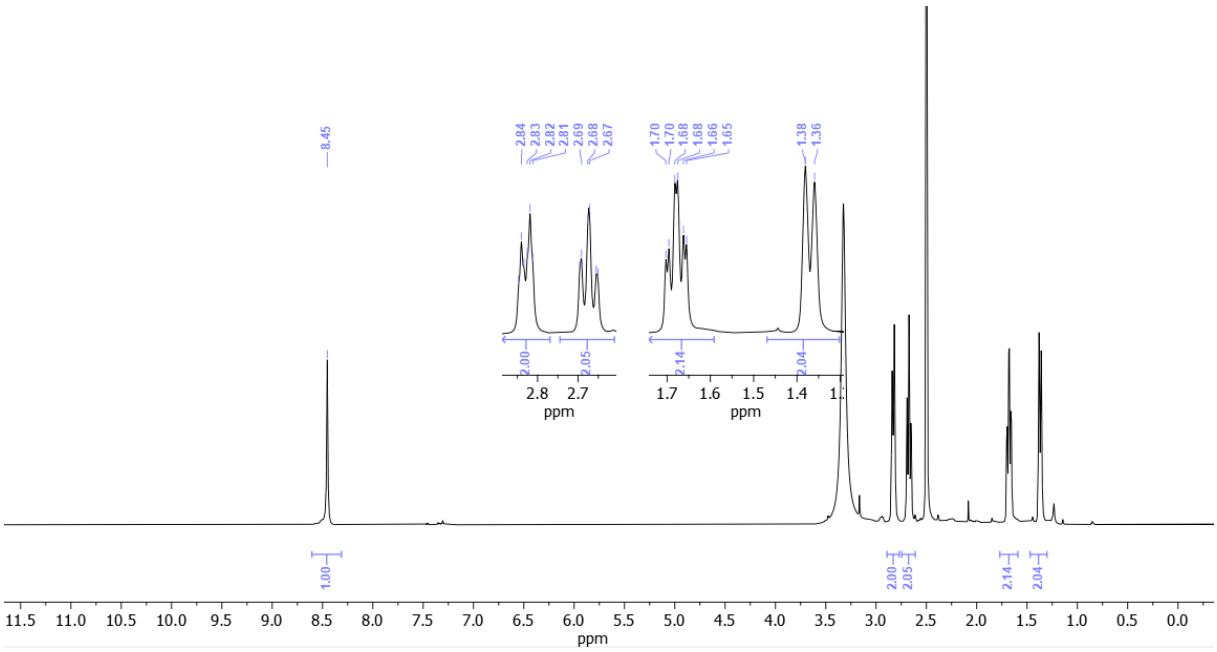
MS (ESI): m/z (%): 169.0 (3), 57.1 (100), 56.1 (45).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_7H_{12}N_3NaO_2$: 170.0924, Found: 170.0924

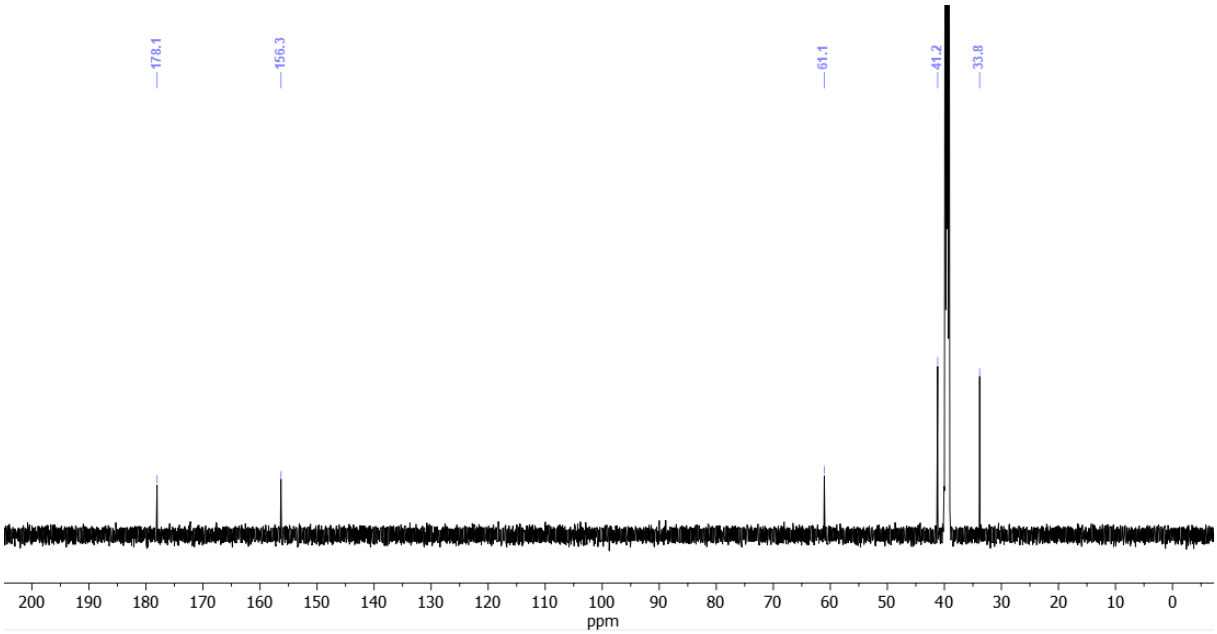
FT-IR (neat, V_{max} 1/cm): 3168.88, 2825.57, 2358.82, 1726.20, 1606.62, 1375.18, 1307.67

Melting point: decomposed at 294 ºC

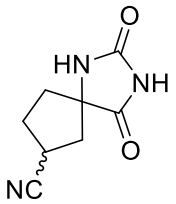
^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2f.



^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2f.



2,4-dioxo-1,3-diazaspiro[4.4]nonane-7-carbonitrile (2i) [811438-49-0]



0.77 mmol 3-oxocyclopentane-1-carbonitrile (**2h**) were reacted with ammonium carbonate (3.42 mmol, 4.4 eq.) and potassium cyanide (1.71 mmol, 2.2 eq.) with the general procedure for the synthesis of spirohydantoins. No precipitation was observed after cooling, thus was the crude extracted with ethyl acetate (3 x 3 mL), dried over magnesium sulfate and concentrated under vacuum. The synthesis resulted in a yield of 73.1 mg, 0.41 mmol, 53 % of desired product as a white solid.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.72 (s, 1H), 8.27 (s, 1H), 3.28 – 3.10 (m, 1H), 2.25 – 2.16 (m, 2H), 2.16 – 2.06 (m, 1H), 2.04 – 1.89 (m, 3H), 1.85 (m, *J* = 12.7, 7.6, 4.3 Hz, 1H), 1.77 (dtd, *J* = 13.2, 7.2, 1.2 Hz, 1H).

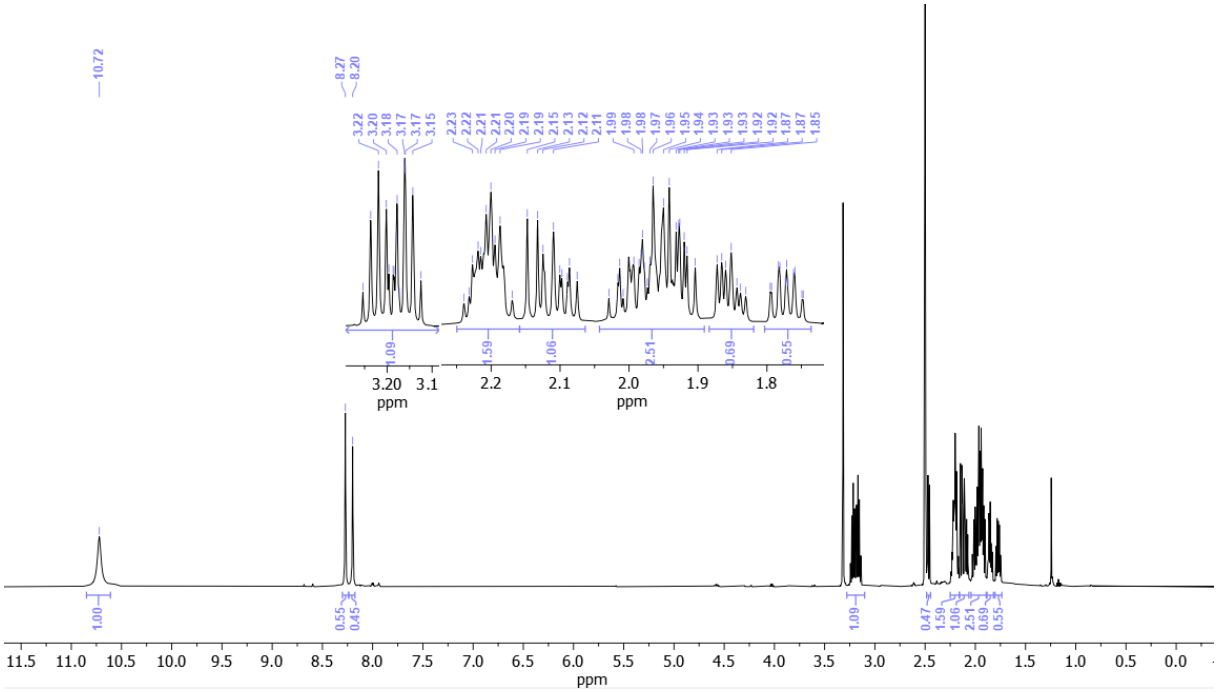
^{13}C NMR (151 MHz, DMSO-d6): δ 178.22, 177.66, 156.07, 156.04, 122.27, 122.25, 67.56, 67.21, 40.62, 39.87, 36.33, 36.30, 29.58, 29.48, 26.40, 26.22.

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_8H_9N_3NaO_2$: 202.0587, Found: 202.0585.

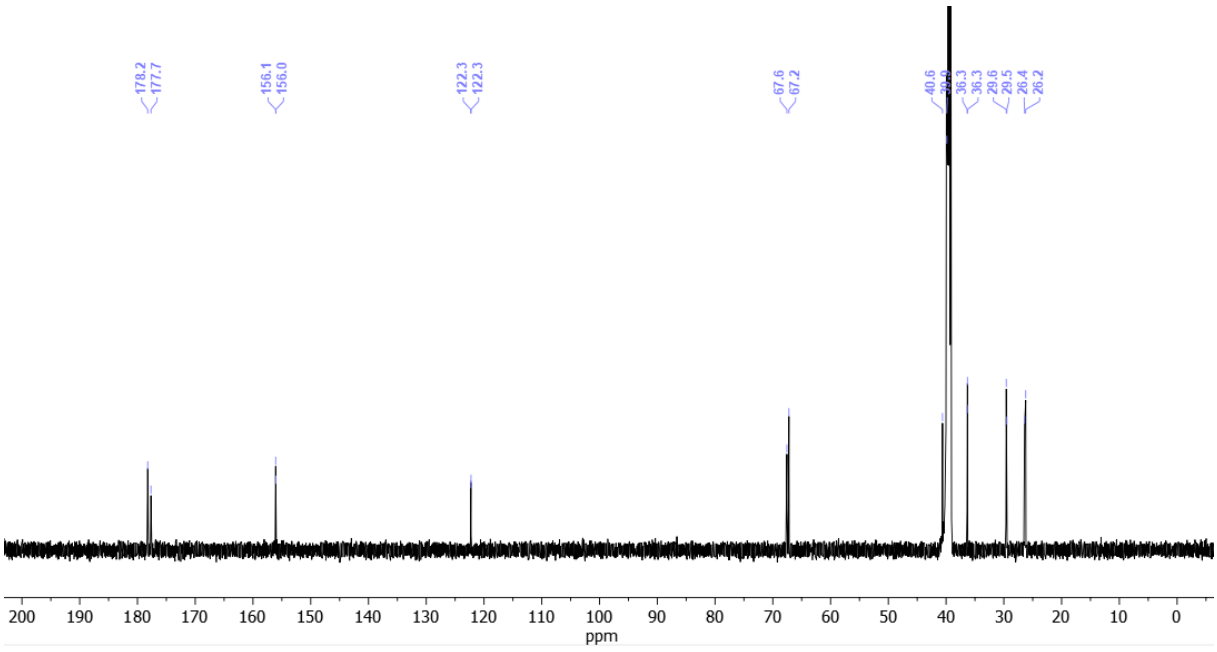
FT-IR (neat, V_{max} 1/cm): 3199.74, 2358.82, 1774.42, 1731.99, 1409.98.

Melting point: 194-196 ºC

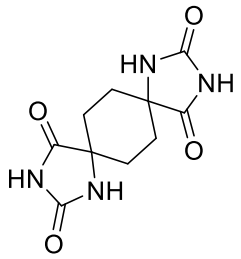
^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2i.



^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2i.



1,3,9,11-Tetraazadispiro[4.2.4.2]tetradecane-2,4,10,12-tetrone (2k) [1469462-75-6]



1 mmol of 1,4-cyclohexanedione (**1k**) were reacted with ammonium carbonate (8.25 mmol) and potassium cyanide (4.13 mmol) with the general procedure for the synthesis of spirohydantoins. The mixture was irradiated for 20 minutes and desired compound 217.9 mg, 0.86 mmol, 86 % were isolated as a white solid. The ^{1}H NMR showed some impurities integrating for around 5 %. Multiple solvents (EtOH, hexane, DCM, ethyl acetate, water) were tested for purifying the product with both washing an rekrystallization with no luck.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.56 (s, 2H), 8.52 (s, 1H), 8.19 (s, 1H), 2.13 – 1.92 (m, 5H), 1.70 – 1.56 (m, 4H).

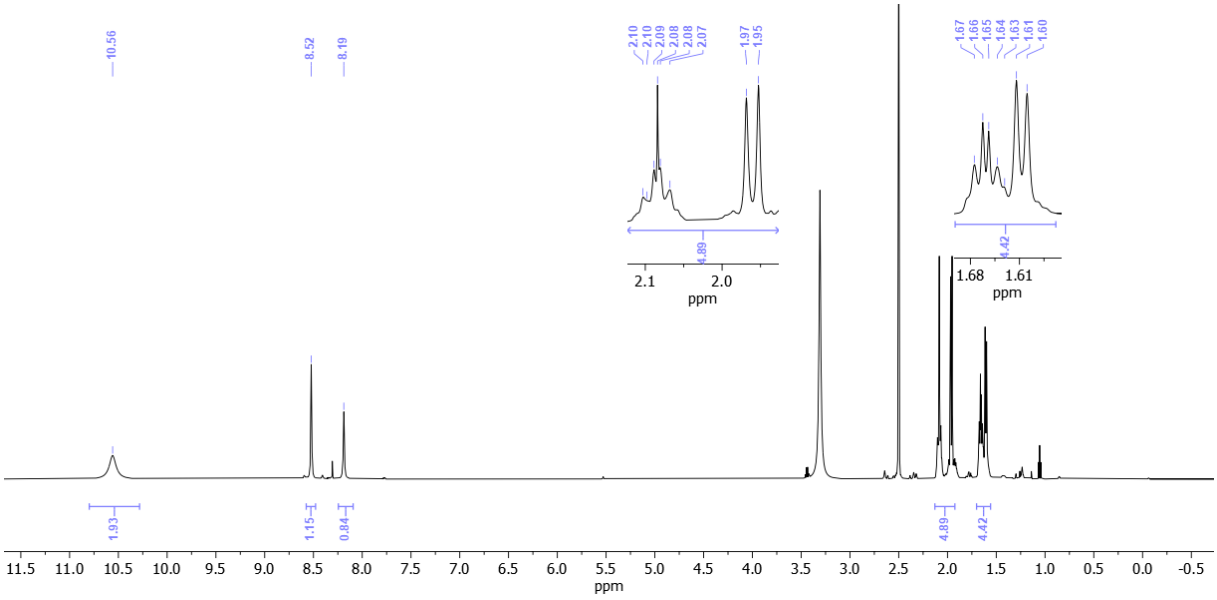
^{13}C NMR (151 MHz, DMSO-d6): δ 188.17, 187.96, 166.50, 70.87, 69.72, 50.06, 39.14, 38.60.

HRMS (ESI) m/z [M + Na - H]$^{+}$: Calculated for $C_{10}H_{11}N_4NaO_4$: 251.0786, Found: 251.0785

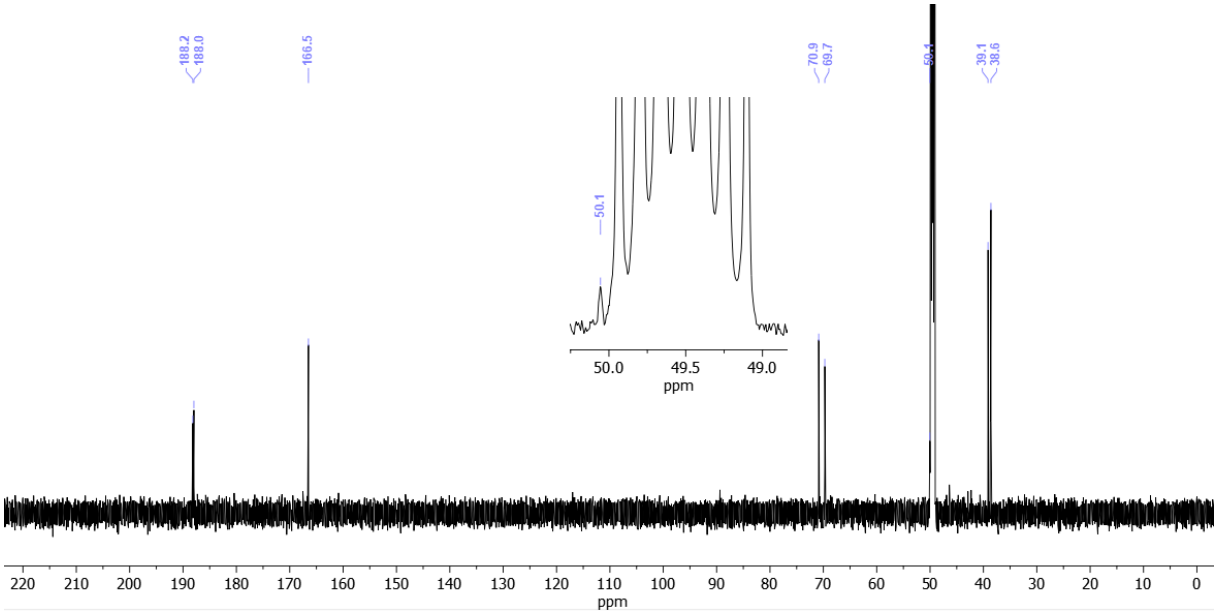
FT-IR (neat, V_{max} 1/cm): 3155.38, 3064.73, 1722.32, 1409.89, 1301.88.

Melting point: decomposed at 343 ºC

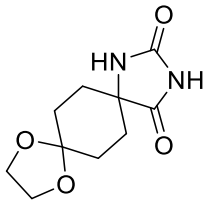
^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2k.



^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2k.



9,12-Dioxa-1,3-diazadispiro[4.2.4.2]tetradecane-2,4-dione (2l) [54621-17-9]



2 mmol of 1,4-cyclohexanedione ethylene monoketal (**1l**), with the rest of the reaction, was irradiated for 20 min with the general procedure for the synthesis of spirohydantoins. 268.6 mg, 1.19 mmol, 59 % of desired product as a white solid were isolated after vacuum filtration and washing with water.

^{1}H NMR (600 MHz, DMSO-d6): δ 10.57 (s, 1H), 8.42 (s, 1H), 3.86 (s, 4H), 1.91 – 1.81 (m, 2H), 1.76 – 1.66 (m, 4H), 1.61 – 1.54 (m, 2H).

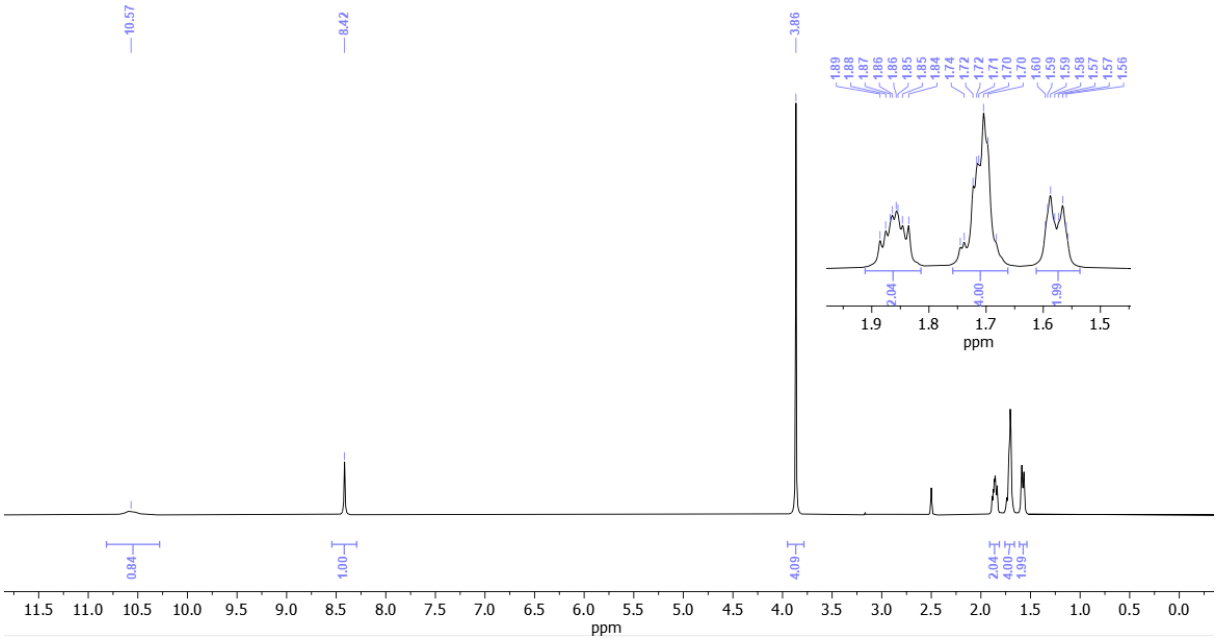
^{13}C NMR (151 MHz, DMSO-d6): δ 178.75, 156.84, 107.29, 64.20, 64.14, 61.48, 31.82, 30.32.

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_{10}H_{14}N_2NaO_4$: 249.0846, Found: 249.0847

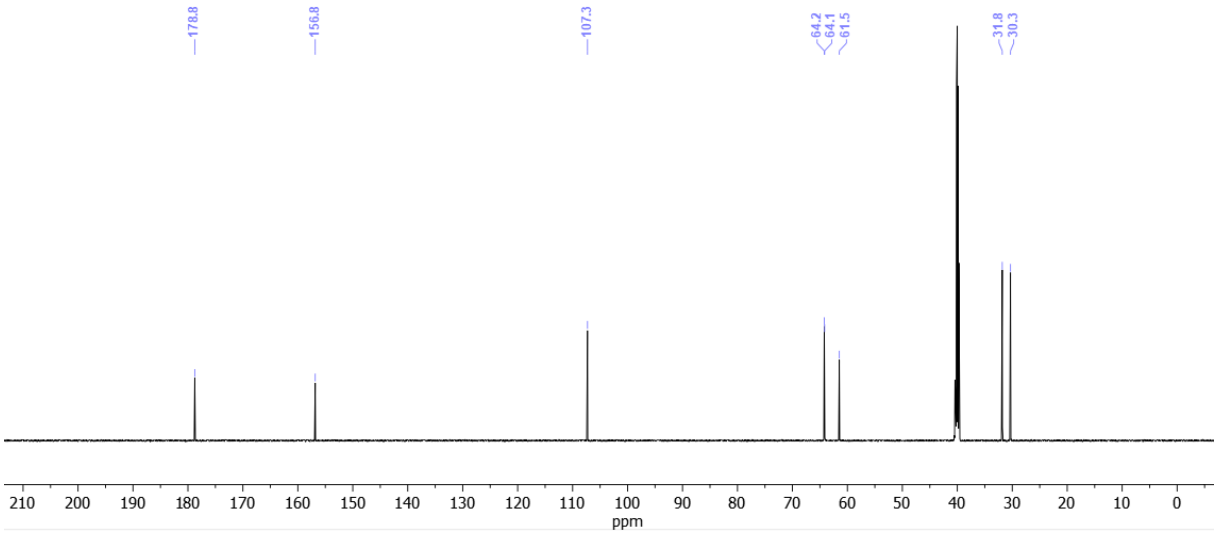
FT-IR (neat, V_{max} 1/cm): 3155.38, 3057.02, 2362.68, 1726.20, 1413.75.

Melting point: 243-245 ºC

^{1}H NMR (600 MHz, DMSO-d$_6$) of compound 2l.

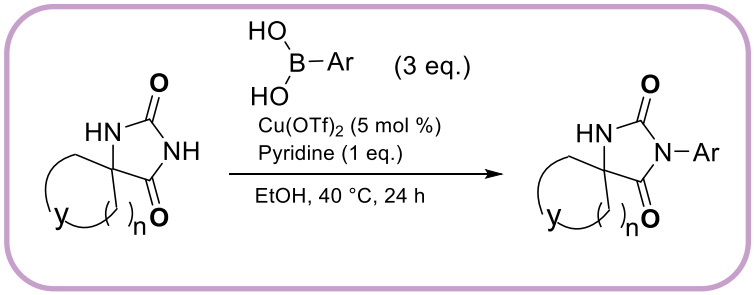


^{13}C NMR (151 MHz, DMSO-d$_6$) of compound 2l.



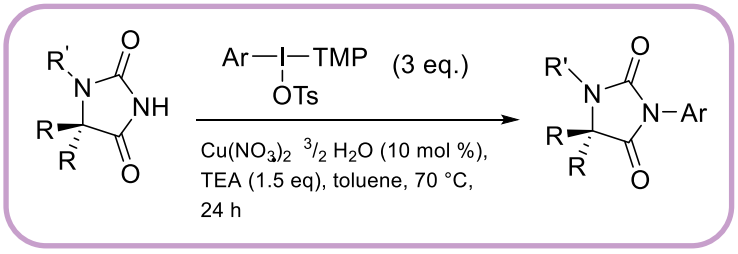
4.3 *N*-3-Arylated spirohydantoins

General procedures for the synthesis for *N*-3-arylation of spirohydantoins



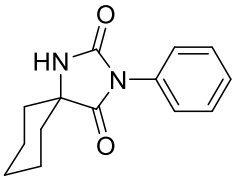
The method is based on a procedure from the literature. [32] Desired spirohydantoin (0.4 mmol, 1 eq.) was measured in a 5 mL round bottom flask. Then desired boronic acid (1.2 mmol, 3 eq.), $Cu(OTf)_2$ (0.02 mmol, 5 mol%) and pyridine (0.4 mmol, 1 eq.), were measured out and transferred to the same flask with a stirring bar. 2 mL ethanol were added afterwards before the flask was placed on a preheated heating block with a condenser, the mixture was then refluxed at 40 ºC, for 24 hours. After the reaction, the mixture was concentrated under vacuum and purified with an appropriate method, to isolate the desired compounds. All compounds were dried under high vacuum.

Procedure for the synthesis of *N*-3-arylation of spirohydantoins with diaryliodonium salts.



The method is based on a procedure from the literature.[31] Desired spirohydantoin (0.2 mmol, 1 eq.) together with phenylI(TMP)OTs (0.6 mmol, 3 eq.), $Cu(NO_3)_2 \cdot 5/2H_2O$ and a stirring bar were measured and added to a 7 mL vial with a septum screw cap. 2 mL toluene were added before the vial was closed and placed on a preheated heating block at 70 ºC. Triethylamine (0.3 mmol, 1.5 eq.) was then added with a syringe through the septum and the reaction was stirred for 24 h. After reaction stop, the mixture was cooled to room temperature and concentrated under vacuum overnight. The crude was purified with appropriate method to isolate desired compounds.

3-phenyl-1,3-diazaspiro[4.5]decane-2,4-dione (5a) [726-97-6]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2a** and boronic acid **3a.** The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (8:2→7:3). R_f: 0.47 with hex/acetone 7:3. The crude was dry loaded. A white colorless solid , 85.1 mg, 0.35 mmol (87 %) of desired compound, were isolated.

The desired product was as well synthesized with the procedure for *N*-3-arylation of spirohydantoins with diaryliodonium salts. 0.18 mmol of 1,3-diazaspiro[4.5]decane-2,4-dione (**2a**) were reacted with the rest of the reagents and stirred for 24 h. The crude was purified by flash chromatography with eluent gradient 9:1 → 8:2 → 7:3 hex /acetone. 20.1 mg, 0.08 mmol, 46 % slightly yellow product were isolated. Desired compound was detected on the ^{1}H NMR analysis but with impurities.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 4.42-7.40 (m, 2H), 7.38-7.35 (m, 1H), 6.69 (s, 1H), 1.98-1.94 (m, 2H), 1.90-1.87 (m, 2H), 1.76-1.71 (m, 3H), 1.46-1.41 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.9, 155.9, 131.7, 129.1, 128.1, 126.3, 61.7, 33.8, 24.6, 21.8.

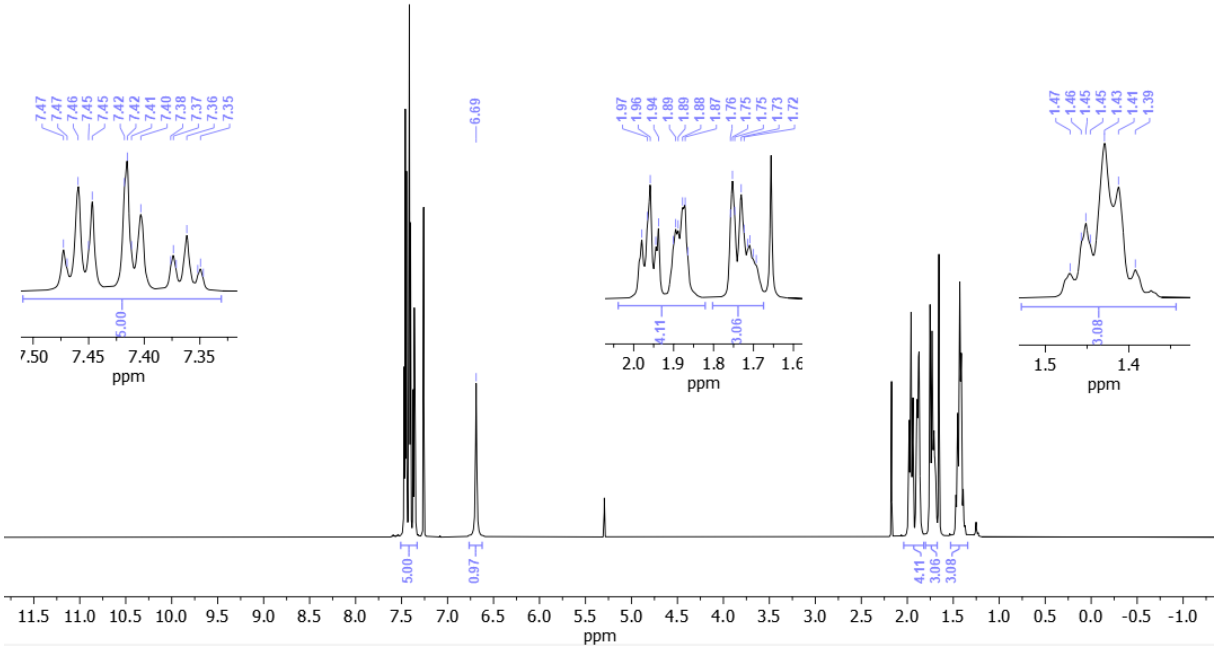
MS (ESI): m/z (%): 244.1/245.2 (28/5), 189.0 (42), 119.0 (91), 91 (55), 54.1 (100)

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{14}H_{16}N_2NaO_2$: 267.1104, Found: 267.1104

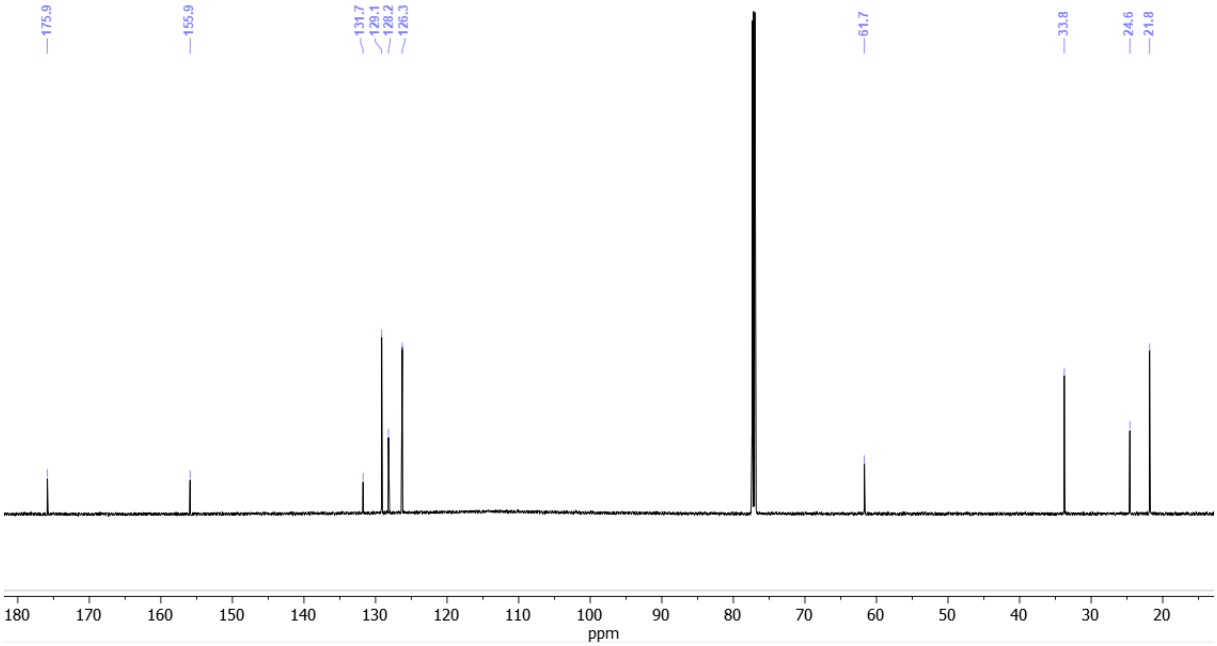
FT-IR (neat, V_{max} 1/cm): 3234.46, 2935.51, 2864.14, 2333.75, 1766.70, 1708.84, 1407.96.

Melting point: 224-225 °C

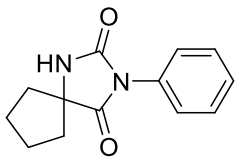
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5a.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5a.



3-Phenyl-1,3-diazaspiro[4.4]nonane-2,4-dione (5b) [1292805-97-0]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2b** and boronic acid **3a**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (8:2→7:3). R_f: 0.29 with 7:3 hexane/acetone. The crude was dry loaded. A white colorless solid, 74 mg, 0.32 mmol, (80 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48-7.35 (m, 5H), 6.48 (bs, 1H), 2.30-22.5 (m, 2H), 1.96-1.80 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.7, 155.9, 131.8, 129.2, 128.2, 126.3, 68.0, 38.3, 25.3

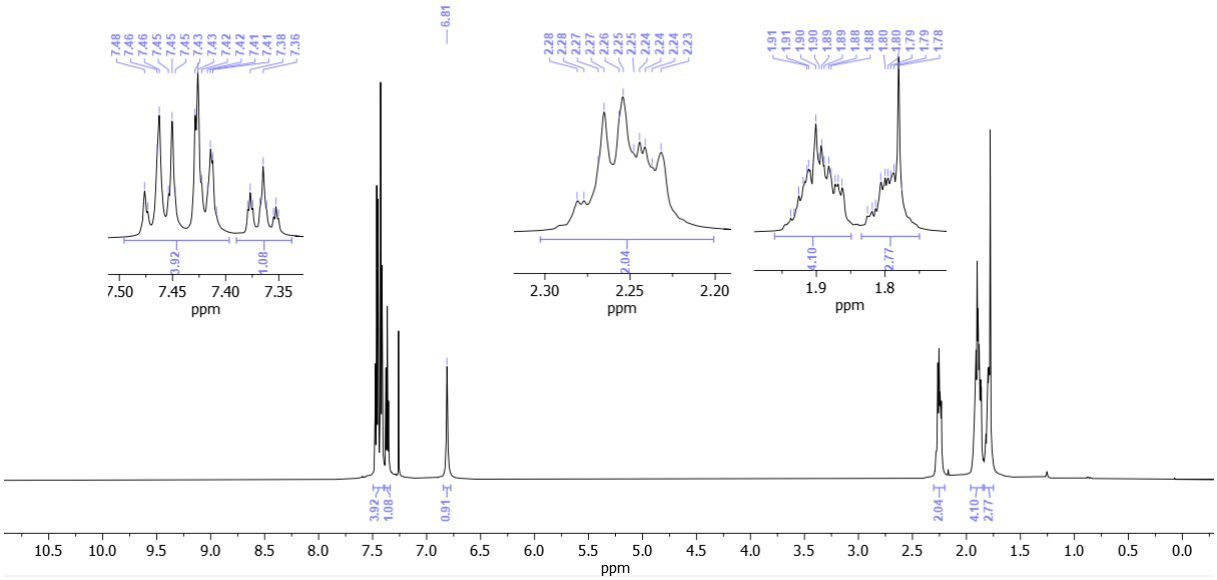
MS (EI): m/z (%): 230.1/231.1 (19/3), 189.0 (27), 119.0 (90), 83.0 (54), 54.1 (100)

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{13}H_{14}N_2NaO_2$: 253.0947, Found: 253.0947

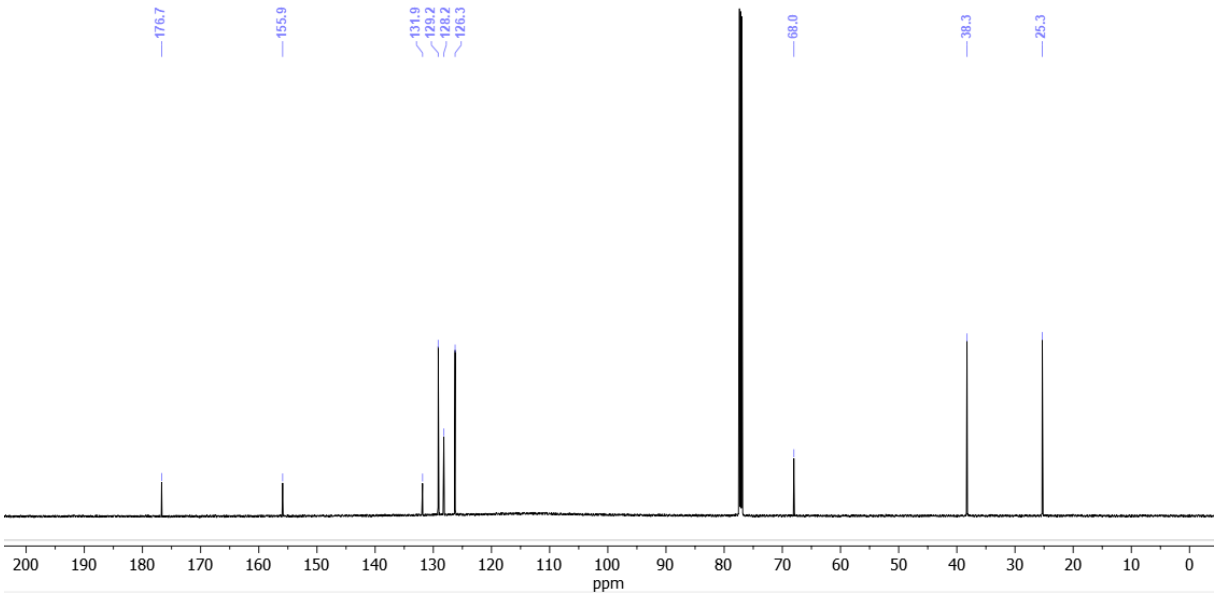
FT-IR (neat, V_{max} 1/cm): 3234.46, 2956.721735.85, 1712.07, 1417.61, 711.69.

Melting point: 178-179 °C

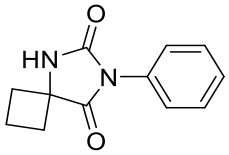
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5b.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5b.



7-Phenyl-5,7-diazaspiro[3.4]octane-6,8-dione (5c) [935429-52-0]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with 0.37 mmol of desired spirohydantoin **2c** and boronic acid **3a**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (8:2→7:3). *R_f*: 0.28 with 7:3 hexane/acetone. The crude was dry loaded. A white colorless solid, 74 mg, 0.34 mmol (92 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.43 – 7.35 (m, 3H), 6.82 (s, 1H), 2.71-2.66 (m, 2H), 2.46 – 2.37 (m, 2H), 2.23-2.15 (m, 1H), 1.89-1.84 (m, 1H)

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.8, 155.7, 131.7, 129.2, 128.3, 126.3, 60.6, 33.4, 13.9.

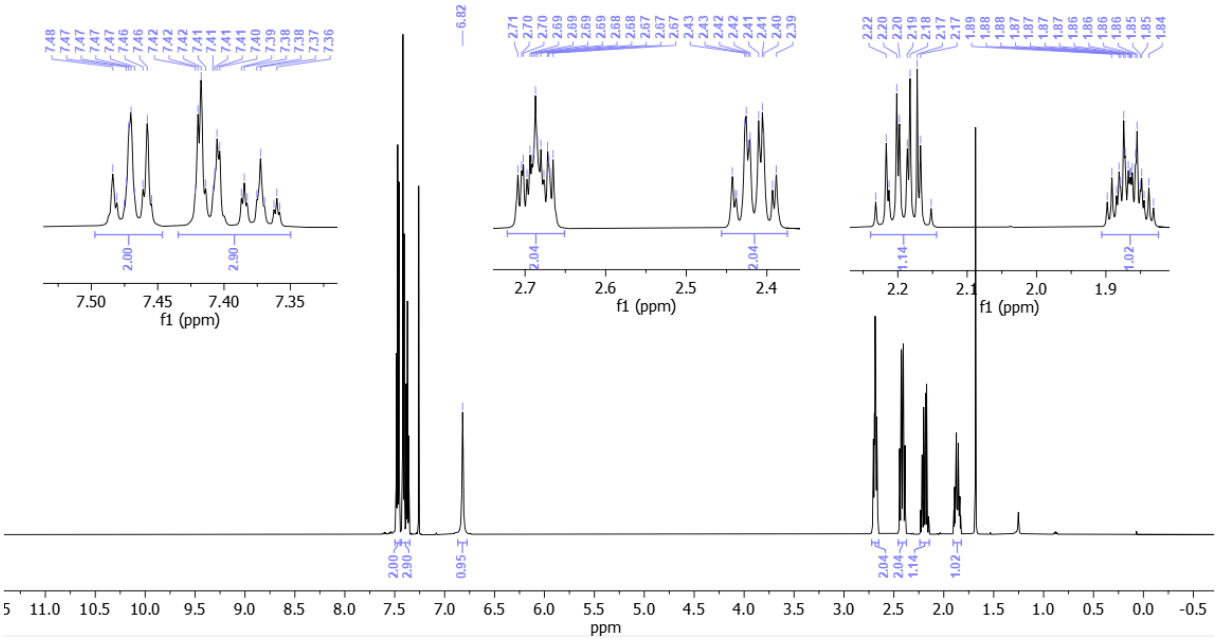
MS (EI): m/z (%): 216.0/217.1 (31/4), 188.0 (100), 146.0 (57), 119.0 (77), 91 (87).

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{12}H_{12}N_2NaO_2$: 239.0791, Found: 239.0790

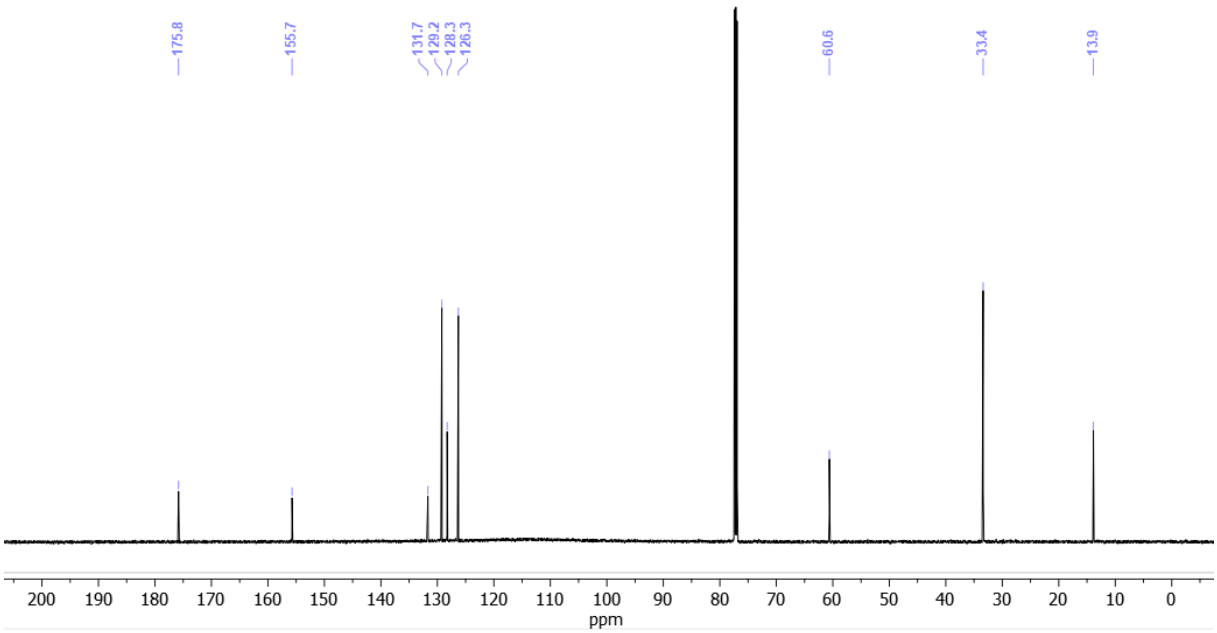
FT-IR (neat, V_{max} 1/cm): 3300.03, 2937.44, 1776.35, 1704.99, 1400.25, 1126.37.

Melting point: 161-162 °C

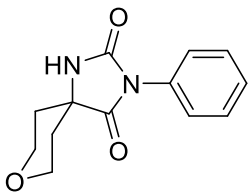
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5c



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5c.



8-Oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 3-phenyl- (5d) [1552075-00-9]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2d** and boronic acid **3a**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (8:2→8:8). R_f: 0.25 with 7:3 hexane/acetone. The crude was dry loaded. A white colorless solid, 86 mg, 0.35 mmol (88 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.43 – 7.36 (m, 3H), 7.10 (s, 1H), 4.09 (dt, *J* = 12.2, 4.5 Hz, 2H), 3.70-3-66 (m, 2H), 2.26-2.22 (m, 2H), 1.75-1.72 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.6, 156.0, 131.4, 129.3, 128.5, 126.2, 63.6, 58.9, 334.0

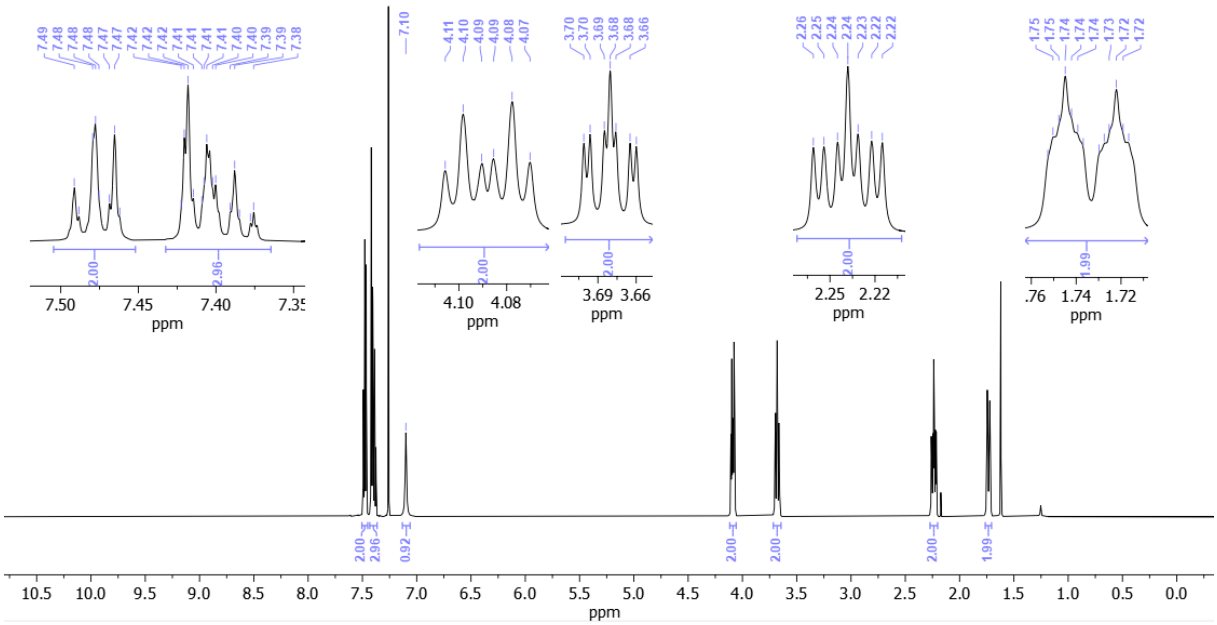
MS (EI): m/z (%): 246.1/247.1 (13/2), 202.0 (100), 119.0 (100), 91.0 (75), 55.1 (73).

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{13}H_{14}N_2NaO_3$: 269.0897, Found: 269.0896

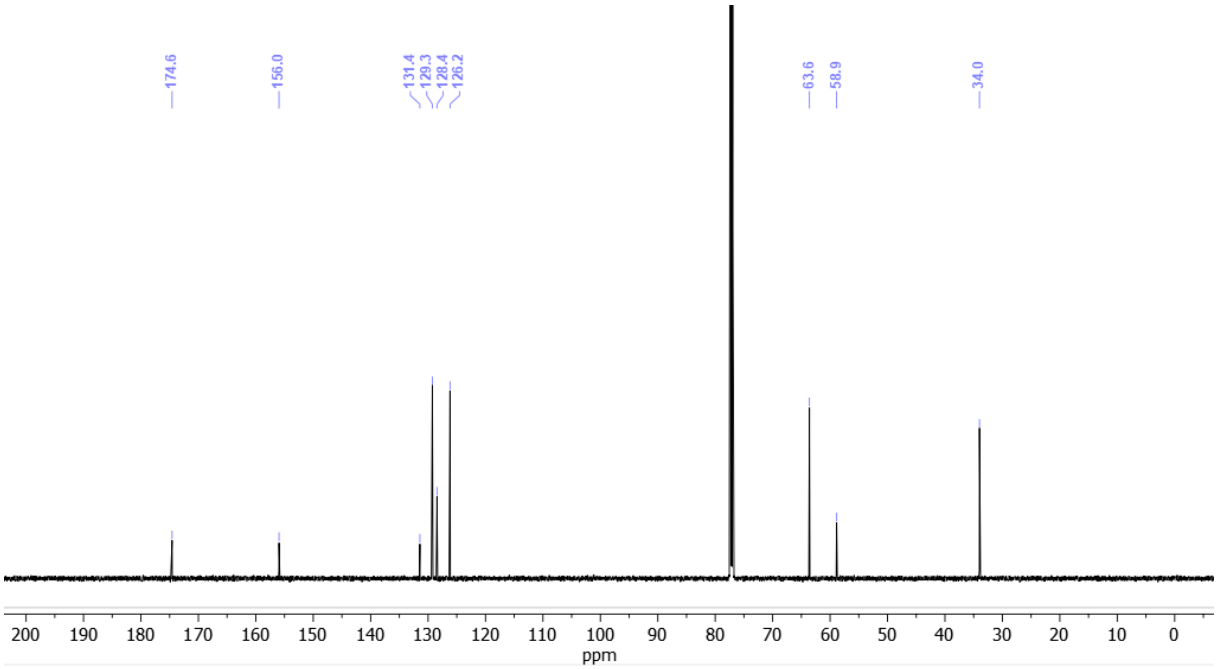
FT-IR (neat, V_{max} 1/cm): 3188.17, 2964.44, 2362.68, 1722.34, 1407.96, 1203.52.

Melting point: 231-232 °C

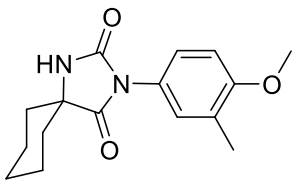
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5d



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5d.



3-(4methoxy-3-methylphenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (5e) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2a** and boronic acid **3b**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2→7:3). R_f: 0.21 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 88 mg, 0.31 mmol (76 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 – 7.09 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.35 (s, 1H), 2.01 – 1.84 (m, 4H), 1.76 – 1.67 (m, 3H), 1.49 – 1.36 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.2, 157.7, 156.3, 128.8, 127.8, 125.2, 123.7, 110.3, 61.6, 55.7, 33.7, 24.6, 21.9, 16.4.

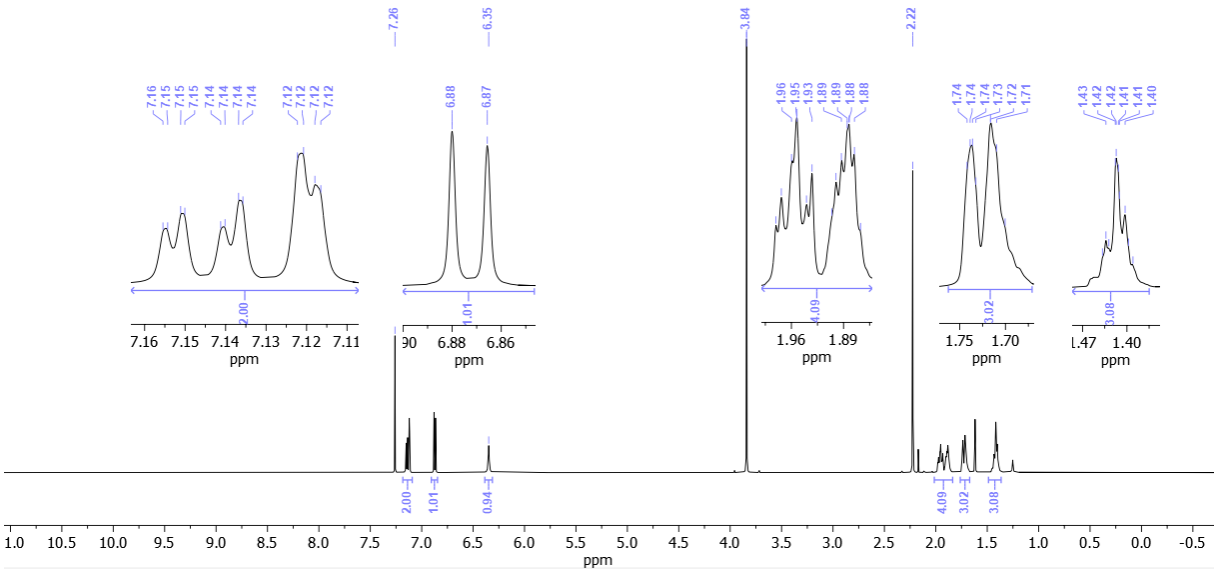
MS (EI): m/z: 288.1, 163.0, 147.9,122.0, 77.0.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{16}H_{20}N_2NaO_3$: 311.1366, Found: 311.1365.

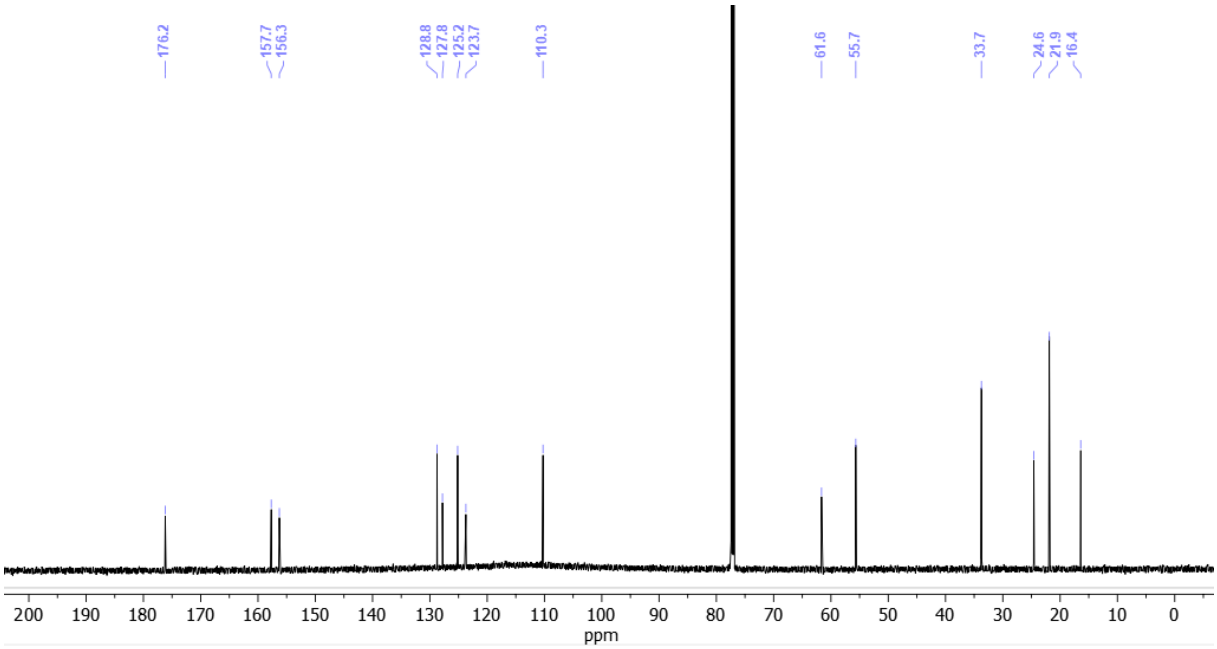
FT-IR (neat, V_{max} 1/cm): 3197.81, 2939.36, 1703.06, 1500.54, 1259.45, 1209.31.

Melting point: 168-176 °C.

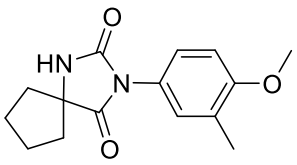
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5e



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5e.



3-(4methoxy-3-methylphenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (5f) [NEW]



The desired product was isolated with the general procedure for *N-3-aryl*ation of spirohydantoins with desired spirohydantoin **2b** and boronic acid **3b**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2→7:3). R_f: 0.2 with 9:2 hexane/acetone. The crude was dry loaded. A white crystalline solid, 102 mg, 0.37 mmol (93 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 – 7.08 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.38 (s, 1H), 3.84 (s, 3H), 2.33 – 2.20 (m, 5H), 1.97 – 1.74 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 177.1, 157.7, 156.4, 128.8, 127.8, 125.2, 123.9, 110.3, 68.0, 55.7, 38.2, 25.3, 16.4.

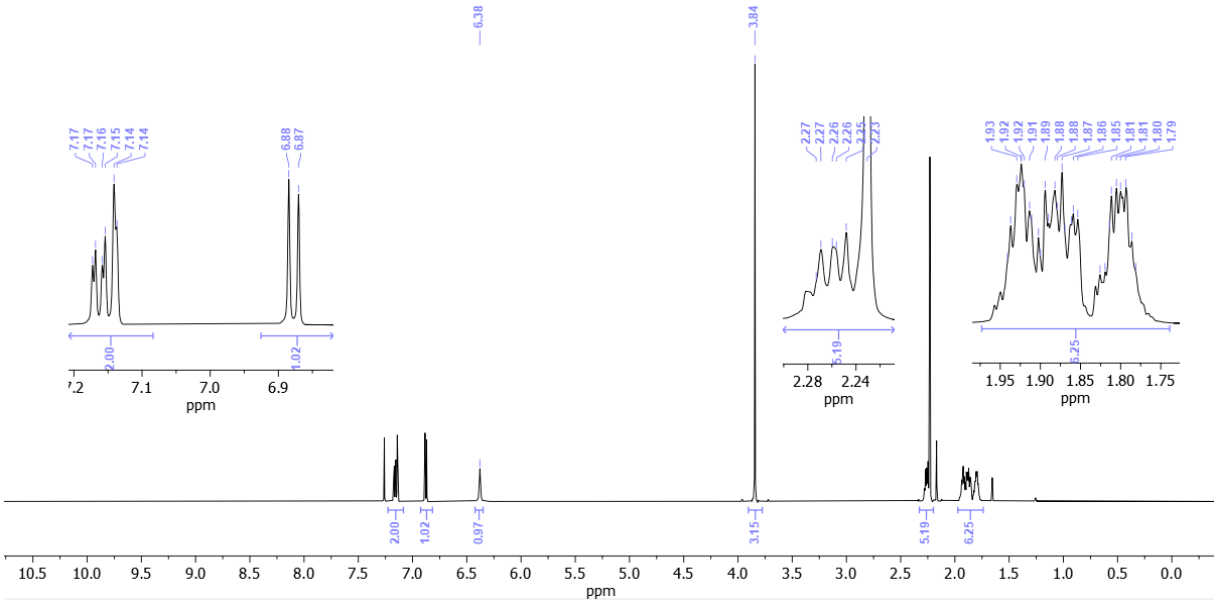
MS (EI): M/z: 274.1, 163.0, 148.0, 77.0

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{15}H_{18}N_2NaO_3$: 297.1210, Found: 297.1209

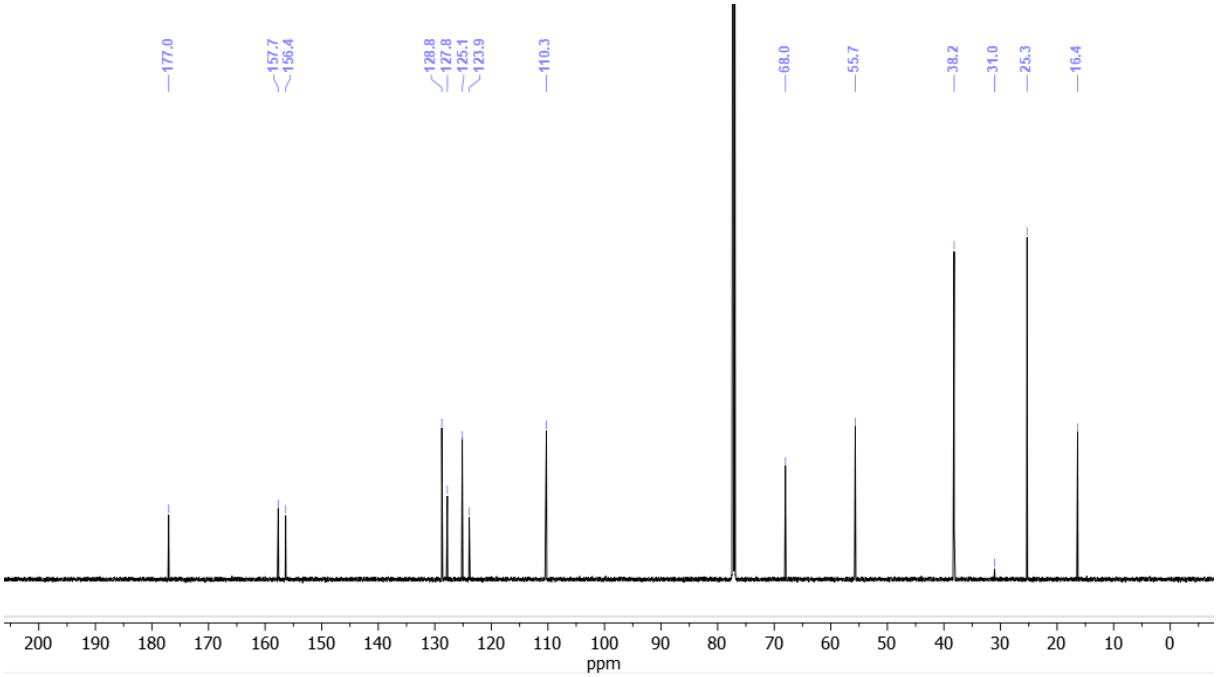
FT-IR (neat, V_{max} 1/cm): 3163.10, 2970.22, 1704.99, 1502.47, 1427.25, 1226.66.

Melting point: 163-165 °C

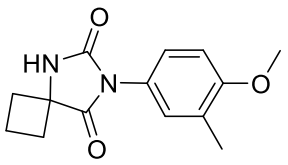
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5f



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5f.



7-(4methoxy-3-methylphenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5g) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with a 0.41 scale of desired spirohydantoin **2c** coupled with boronic acid **3b**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2→7:3). R_f: 0.13 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 86 mg, 0.33 mmol (81 %) were isolated.

^{1}H NMR (600 MHz,$CDCl_3$): δ 7.18 – 7.10 (m, 2H), 6.97 (s, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 2.70 – 2.62 (m, 2H), 2.40 (qd, *J* = 10.0, 2.8 Hz, 2H), 2.27 – 2.11 (m, 5H), 1.87-1.81 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.2, 157.7, 156.3, 128.8, 127.9, 125.2, 123.7, 110.3, 60.6, 55.7, 33.3, 16.4, 13.8.

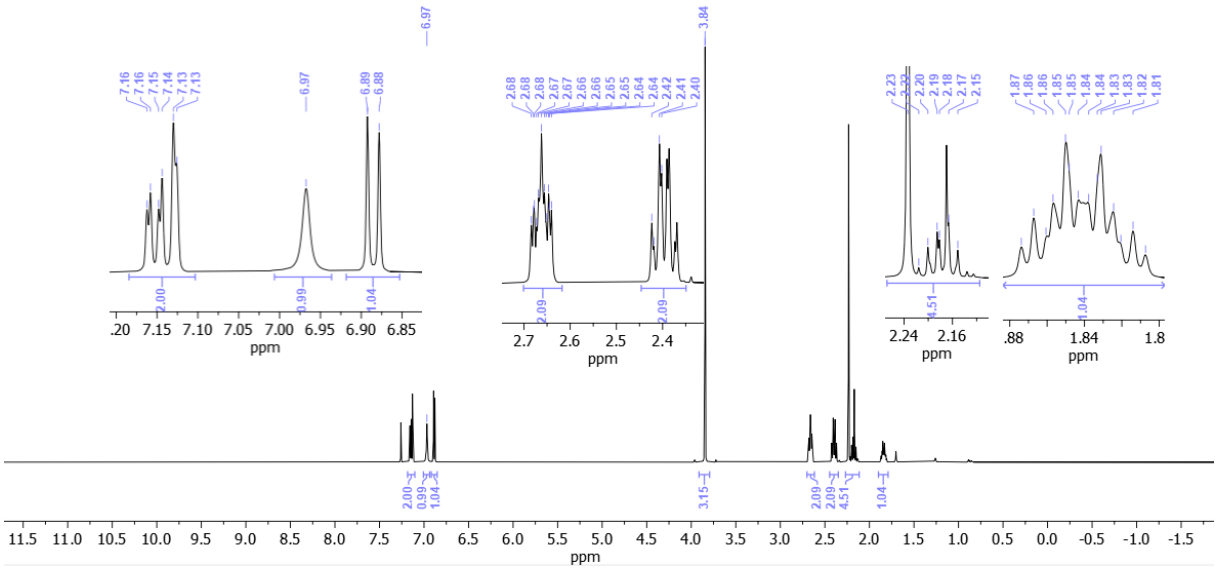
MS (ESI): m/z: 260.1, 232.1, 217.0, 163.0, 148.0, 77.0

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{14}H_{16}N_2NaO_3$: 283.1953, Found: 283.1052

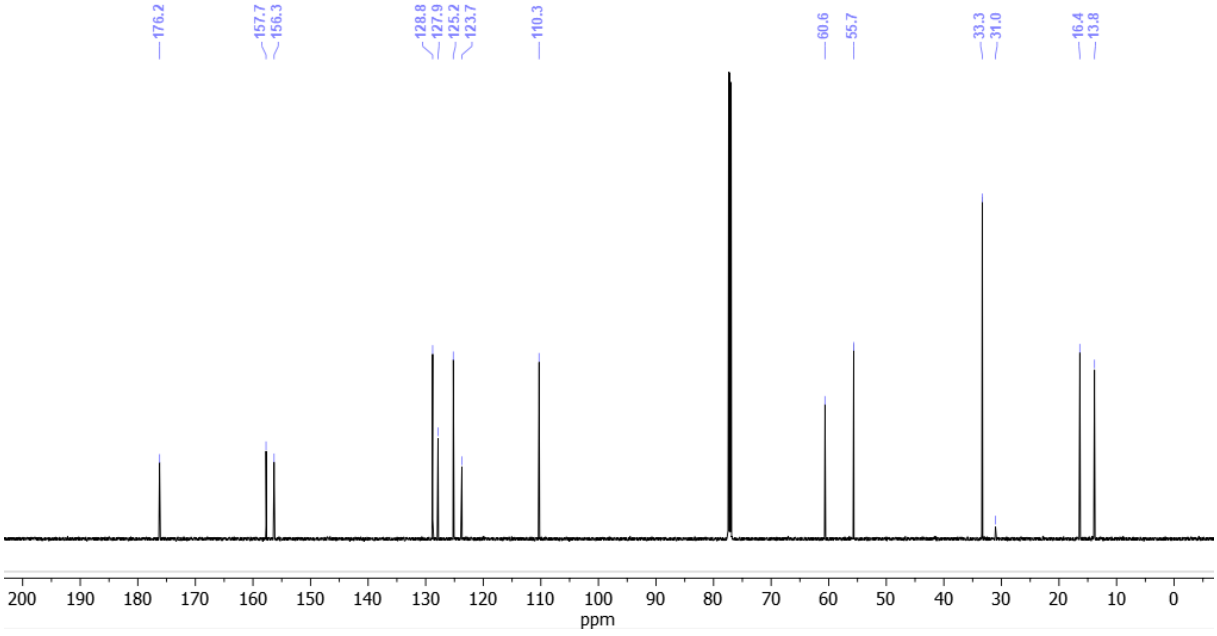
FT-IR (neat, V_{max} 1/cm): 3247.96, 2947.08, 1708.84, 1502.47, 1425.32, 1234.38.

Melting point: 139-145 °C

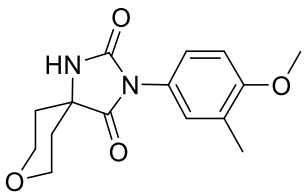
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5g.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5g.



3-(4methoxy-3-methylphenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5h) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with desired spirohydantoin **2d** and boronic acid **3b**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:2→9:4). R_f: 0.2 with 9:4 hexane/acetone. The crude was dry loaded. A white colorless solid, 85 mg, 0.29 mmol (73 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 – 7.07 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 1H), 4.07 (dt, *J* = 12.1, 4.5 Hz, 2H), 3.85 (s, 3H), 3.69-3.65 (m, 2H), 2.26 – 2.18 (m, 5H), 1.73-1.70 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.0, 157.8, 156.5, 128.6, 127.9, 125.1, 123.4, 110.3, 63.6, 58.8, 55.7, 34.0, 16.4.

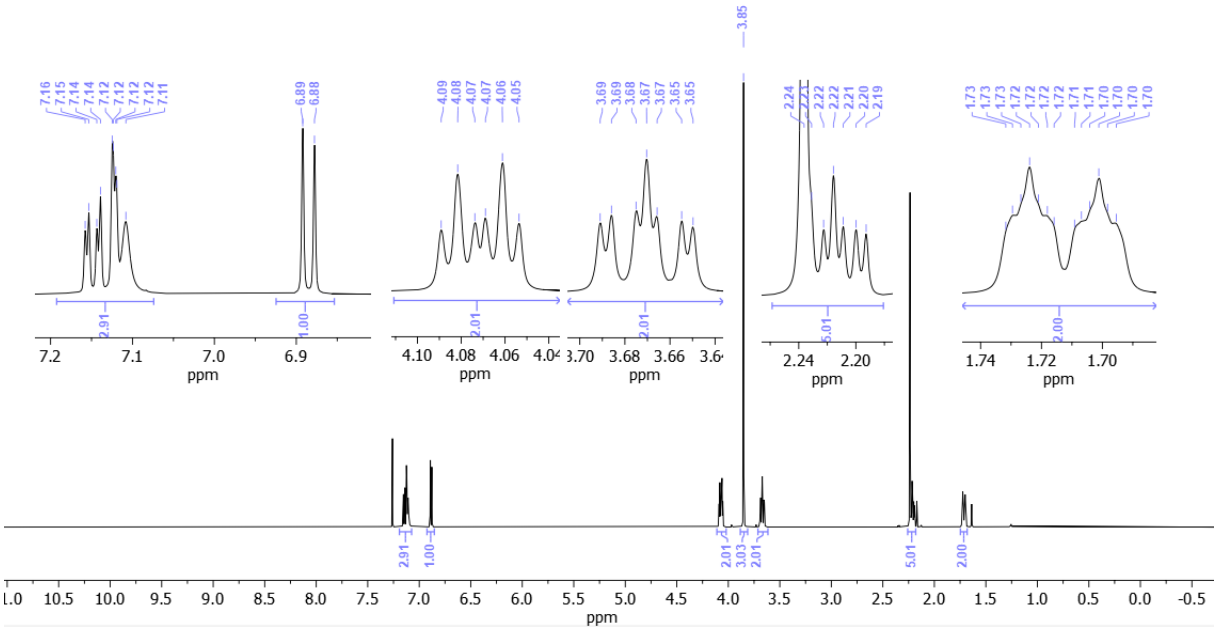
MS (ESI): m/z: 290.1, 246.1, 163.0, 148.0, 77.0.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{15}H_{18}N_2NaO_4$: 313.1159, Found: 313.1158

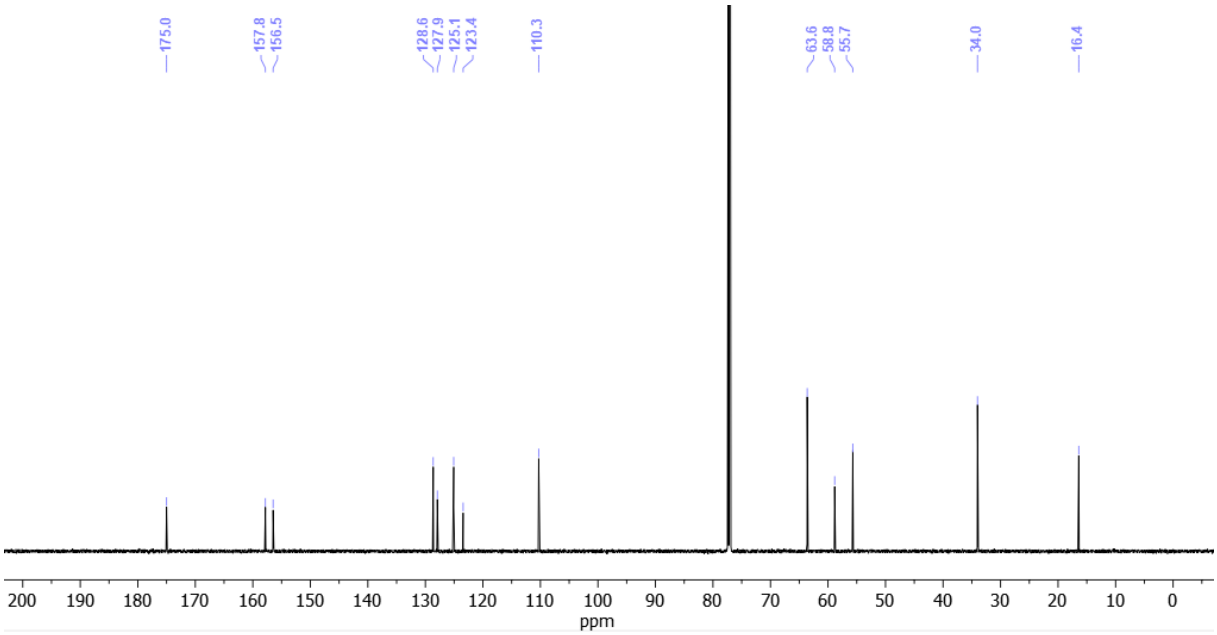
FT-IR (neat, V_{max} 1/cm): 3213.24, 3105.23, 1704.99, 1502.47, 1249.81.

Melting point: 178-180 °C

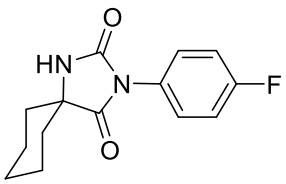
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5h



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5h.



3-(4-fluorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (5i) [133466-16-7]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2a** and boronic acid **3c**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:0.5→9:1→9:2→7:3). R_f: 0.35 with 9:2 hexane/acetone. The crude was dry loaded. A white crystalline solid, 81 mg, 0.31 mmol (78 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.36 (m, 2H), 7.16-7.13 (m, 2H), 6.54 (s, 1H), 1.99-1-88 (m, 4H), 1.75-1.72 (m, 3H), 1.50 – 1.35 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.7, 162.8, 161.2, 155.7, 128.1, 128.0, 127.7, 127.7, 116.2, 116.1, 61.7, 33.8, 24.6, 21.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ -113.05.

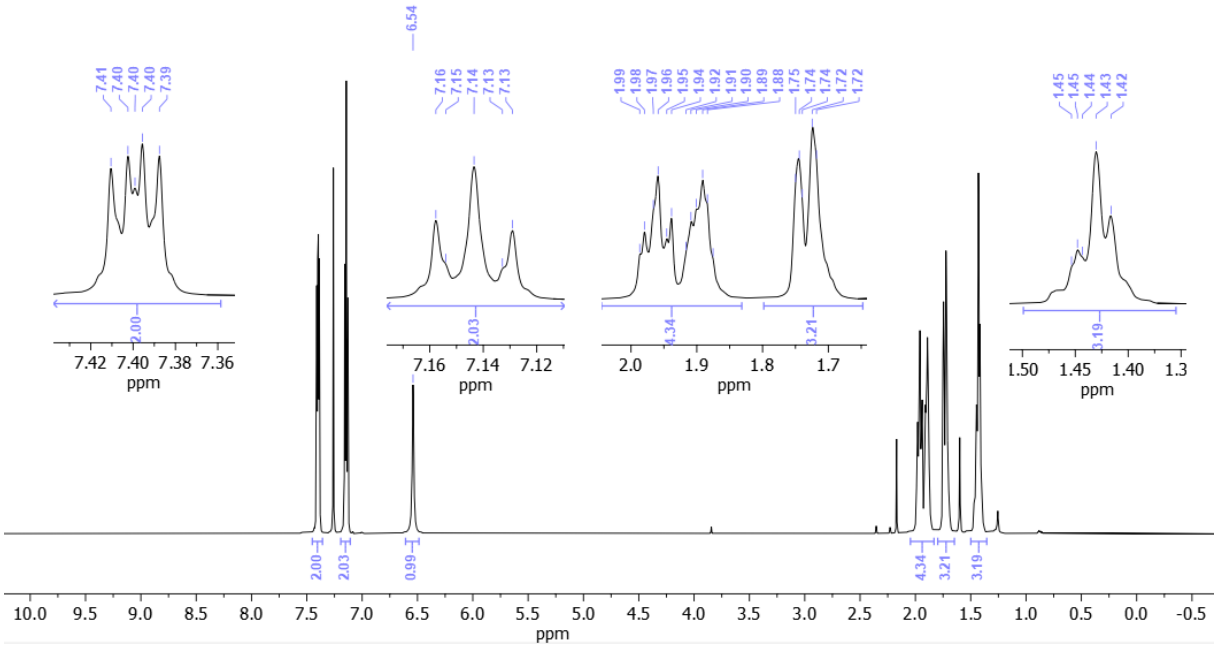
MS (ESI): m/z: 262.1, 207.0, 136.9, 108.9.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{14}H_{15}N_2FNaO_2$: 285.101, Found: 285.101

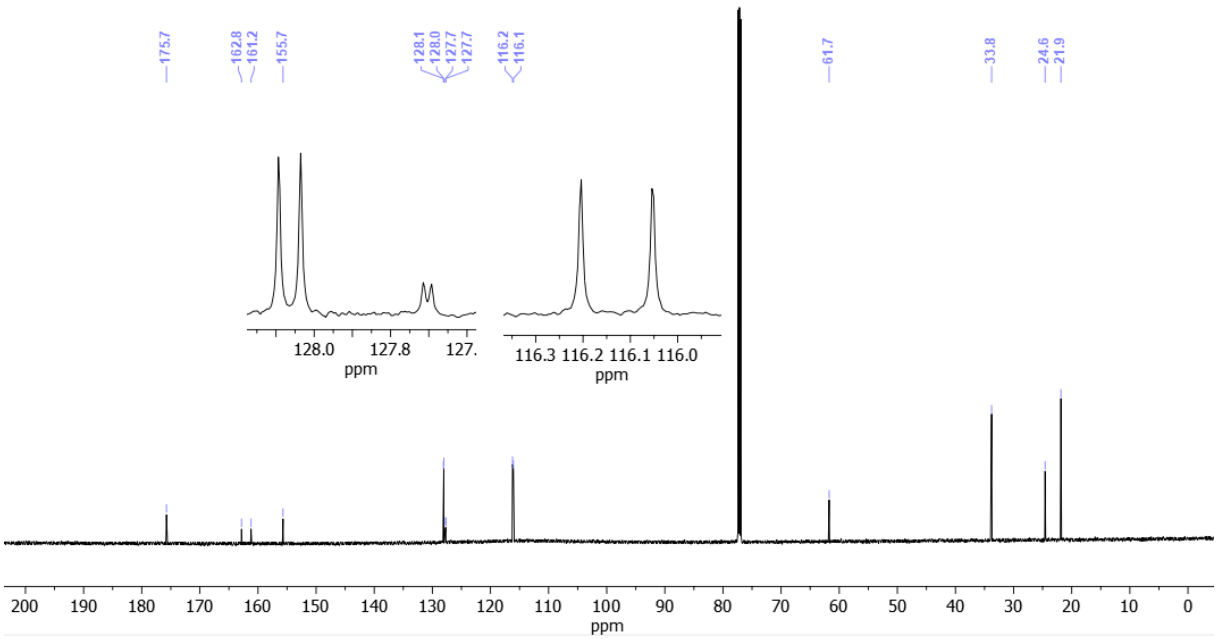
FT-IR (neat, V_{max} 1/cm): 13301.96, 2929.72, 1758.99, 1703.06, 1510.18, 1407.96.

Melting point: 238-241 °C

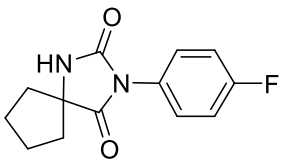
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5i



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5i.



3-(4-fluorophenyl)-1,3-diazaspiro[4.5]nonane-2,4-dione (5j) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with 0.41 mmol spirohydantoin **2b** and boronic acid **3c**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:0.5→9:1→9:2→9:4). R_f: 0.12 with 9:1 hexane/acetone. The crude was dry loaded. A white colorless solid, 76 mg, 0.31 mmol (76 %) were isolated after washing with hexane (1 mL x 3).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.37 (m, 2H), 7.20 – 7.11 (m, 2H), 6.41 (s, 1H), 2.31 – 2.23 (m, 2H), 1.98 – 1.78 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.6, 162.8, 161.2, 155.7, 128.1, 128.0, 116.2, 116.0, 68.1, 38.3, 25.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ -113.08.

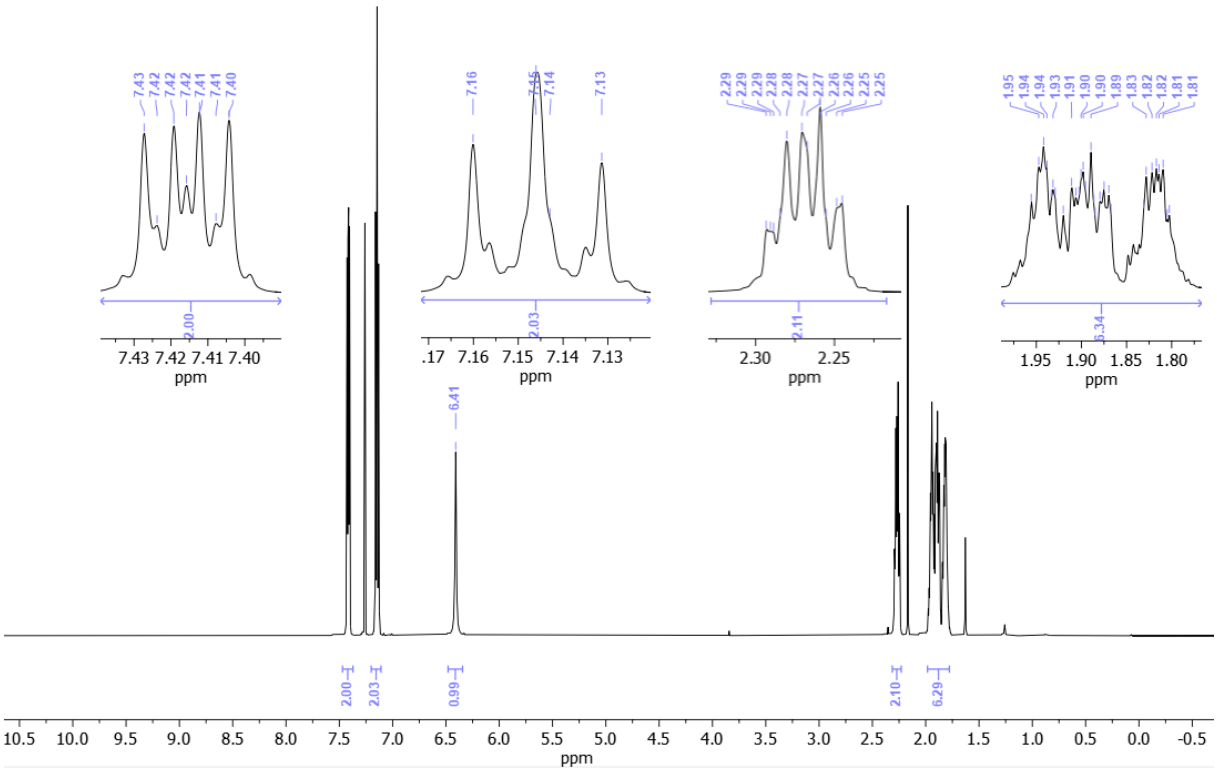
MS (ESI): m/z: 248.1, 207.0, 137.0, 108.9, 83.0

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{13}H_{13}N_2FNaO_2$: 271.0853, Found: 271.0853.

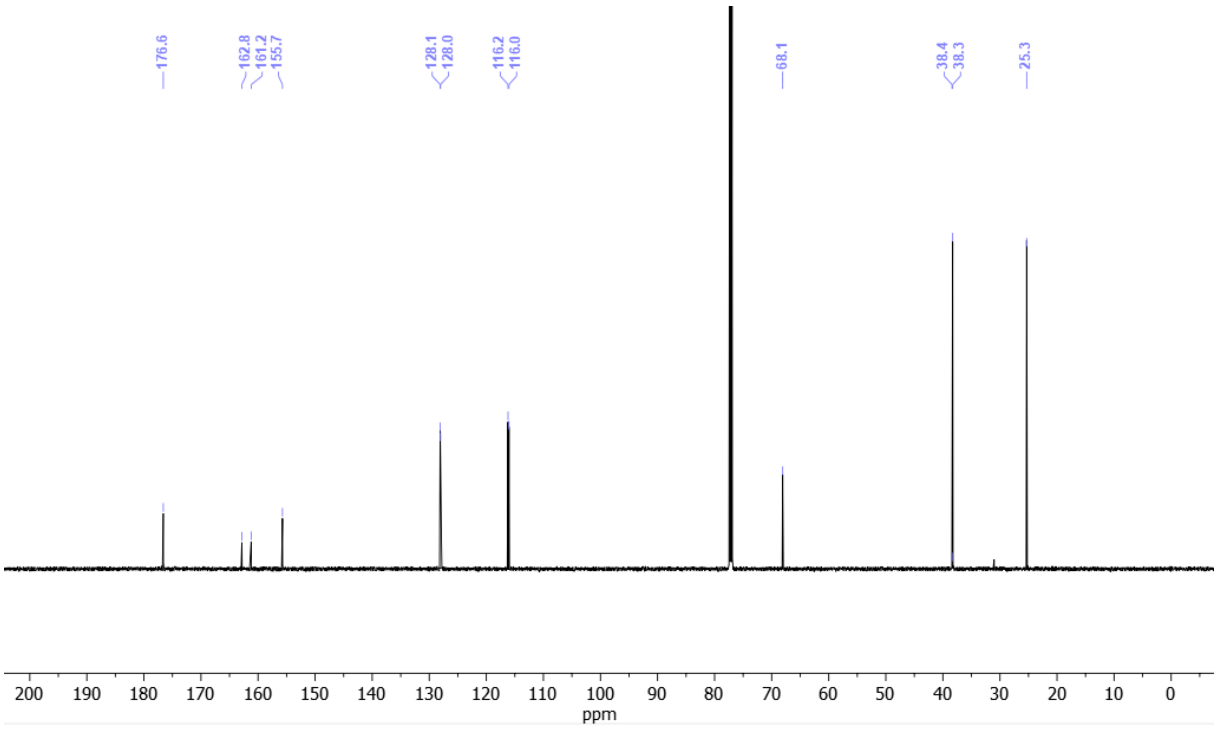
FT-IR (neat, V_{max} 1/cm): 3273.03, 2970.22, 1701.13, 1512.11, 1415.68, 1211.23.

Melting point: 205-206 °C

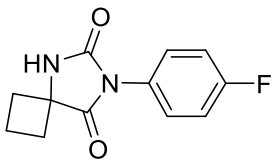
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5j.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5j.



7-(4-fluorophenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5k) [1505761-74-9]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2c** and boronic acid **3c**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:0.5→9:1→9:2→9:3). R_f: 0.26 with 9:2 hexane/acetone. The crude was dry loaded. A slightly yellow solid, 77 mg, 0.33 mmol (82 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.36 (m, 2H), 7.21 – 7.12 (m, 2H), 6.41 (s, 1H), 2.75 – 2.66 (m, 2H), 2.48 – 2.37 (m, 2H), 2.26 – 2.15 (m, 1H), 1.91-1.88 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5, 162.7, 161.1, 155.2, 128.0, 127.9, 116.1, 116.0, 60.5, 33.4, 13.7.

^{19}F NMR (377 MHz, $CDCl_3$): δ **–** 112.97.

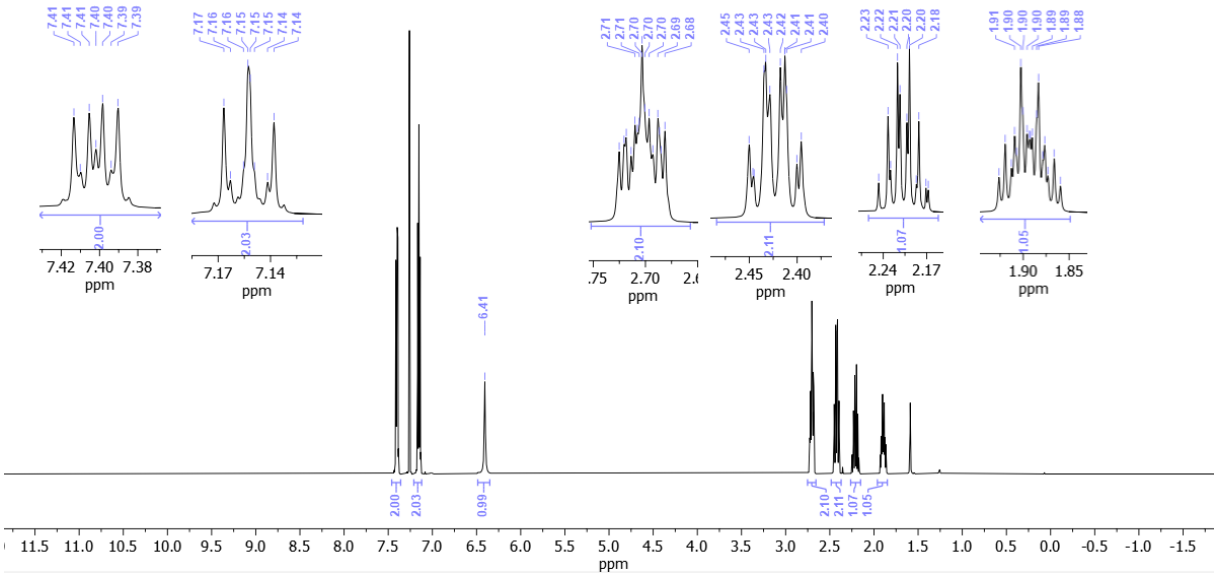
MS (ESI): m/z: 234.1, 206.0, 164.0, 135.9, 108.9.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{12}H_{11}N_2FNaO_2$: 257.0697, Found: 257.0696

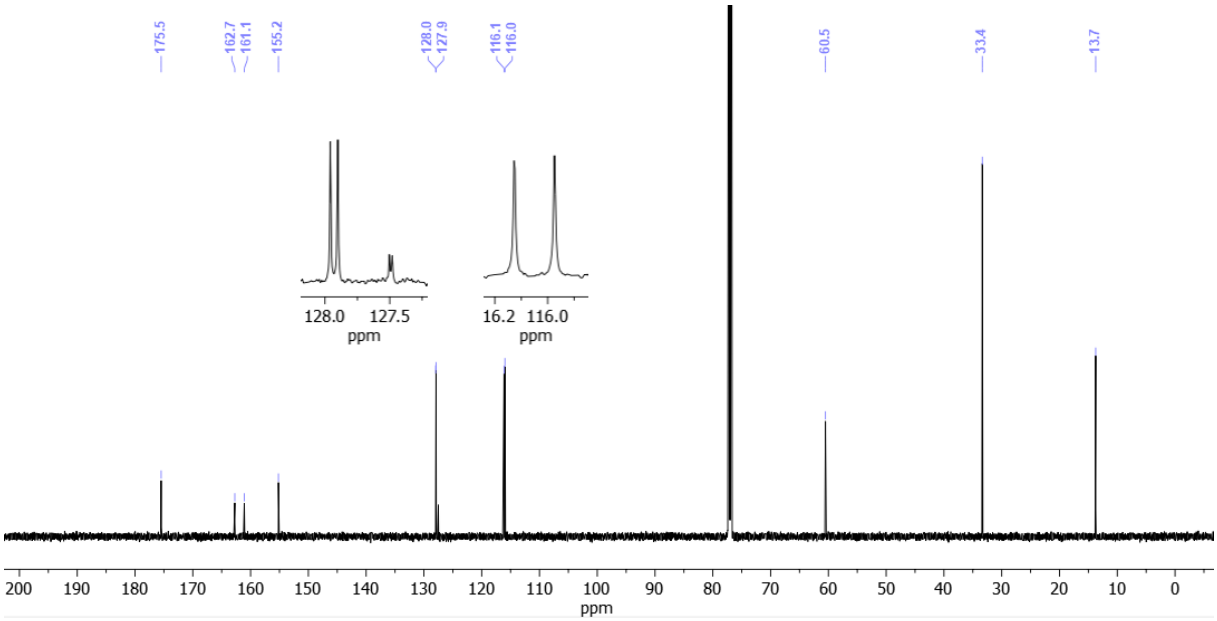
FT-IR (neat, V_{max} 1/cm): 3309.68, 2935.51, 1778.28, 1704.99, 1512.11, 1404.11, 1218.95.

Melting point: 140-141 °C

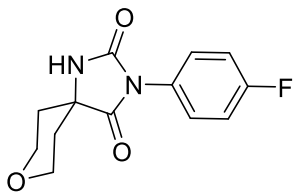
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5k.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5k.



3-(4-fluorophenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5l) [1547679-96-8]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2d** and boronic acid **3c**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:0.5→9:1→9:2→9:3). R_f: 0.04 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 91.3 mg, 0.35 mmol (87 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.34 (m, 2H), 7.20 – 7.12 (m, 2H), 6.96 (s, 1H), 4.09 (dt, *J* = 12.1, 4.6 Hz, 2H), 3.70-3.65 (m, 2H), 2.25-2.21 (m, 2H), 1.78 – 1.67 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3, 162.8, 161.2, 155.6, 63.4, 58.8, 33.9, 30.9.

^{19}F NMR (377 MHz, $CDCl_3$): δ -112.57.

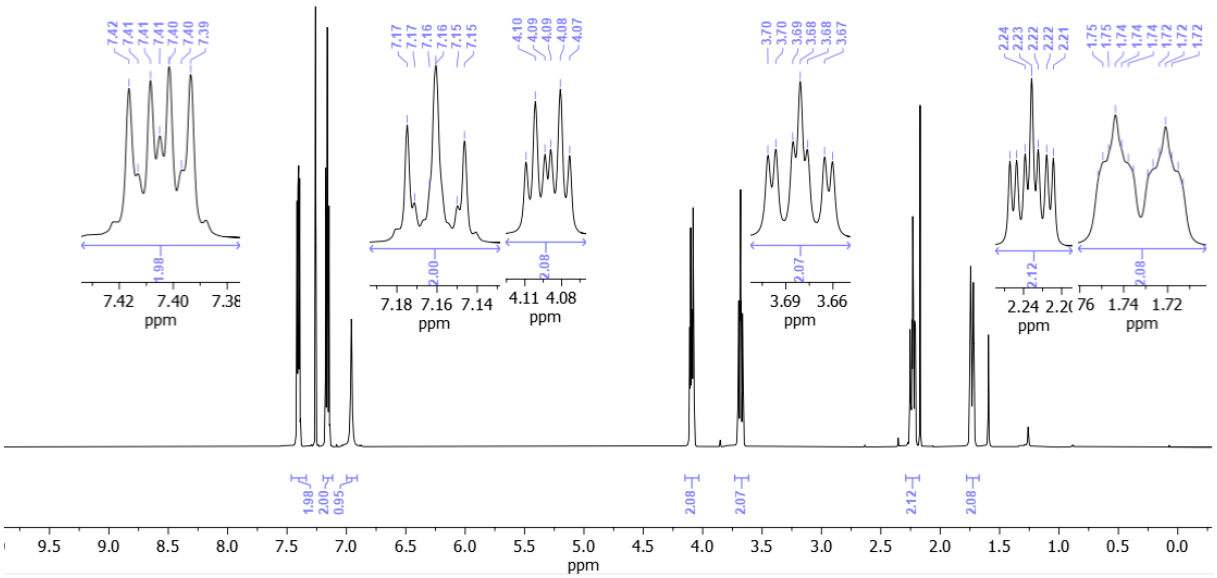
MS (ESI): m/z: 234.1, 206.0, 164.0, 135.9, 108.9.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{13}H_{13}N_2FNaO_3$: 287.0802 , Found: 287.0802

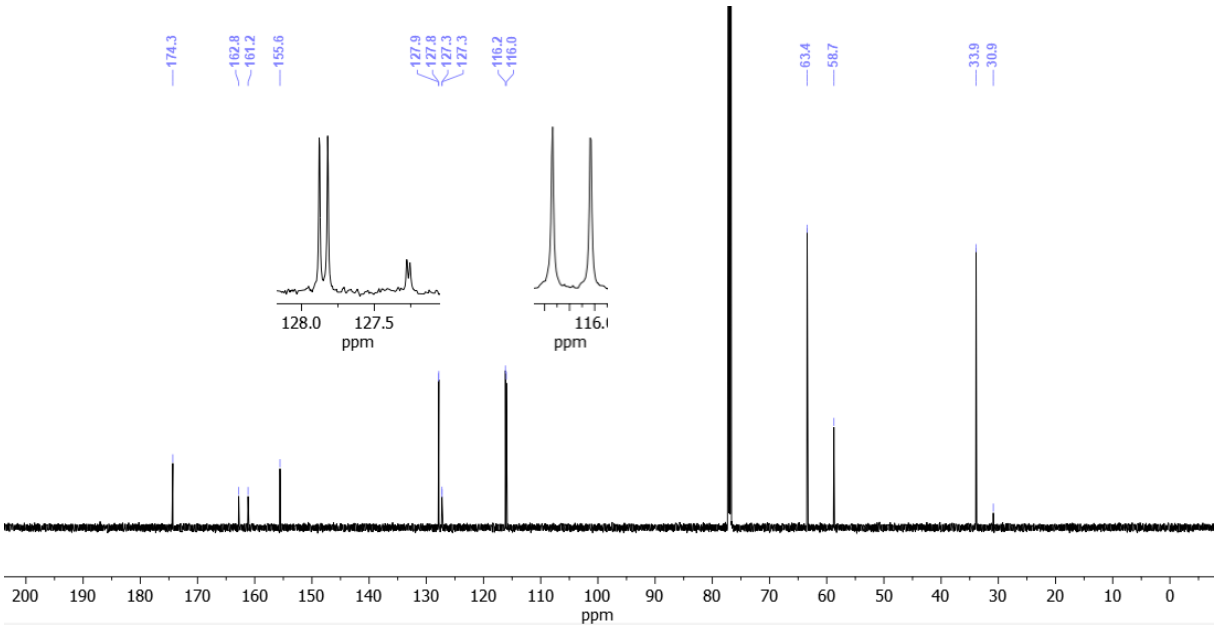
FT-IR (neat, V_{max} 1/cm): 3180.45, 2858.36, 1712.70, 1510.19, 1407.96, 1205.45.

Melting point: 230-232 °C

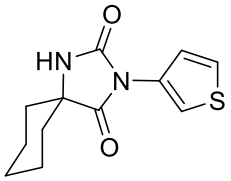
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5l.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5l.



3(thiophen-3-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (5m) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2a** and boronic acid **3d**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2). R_f: 0.33 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 79 mg, 0.32 mmol (80 %) were isolated after a washing with pentane (2 mL x 3).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 3.3, 1.4 Hz, 1H), 7.57 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.34 (dd, *J* = 5.3, 3.2 Hz, 1H), 6.80 (s, 1H), 2.00-1.87 (m, 4H), 1.79 – 1.66 (m, 3H), 1.53 – 1.35 (m, 3H).

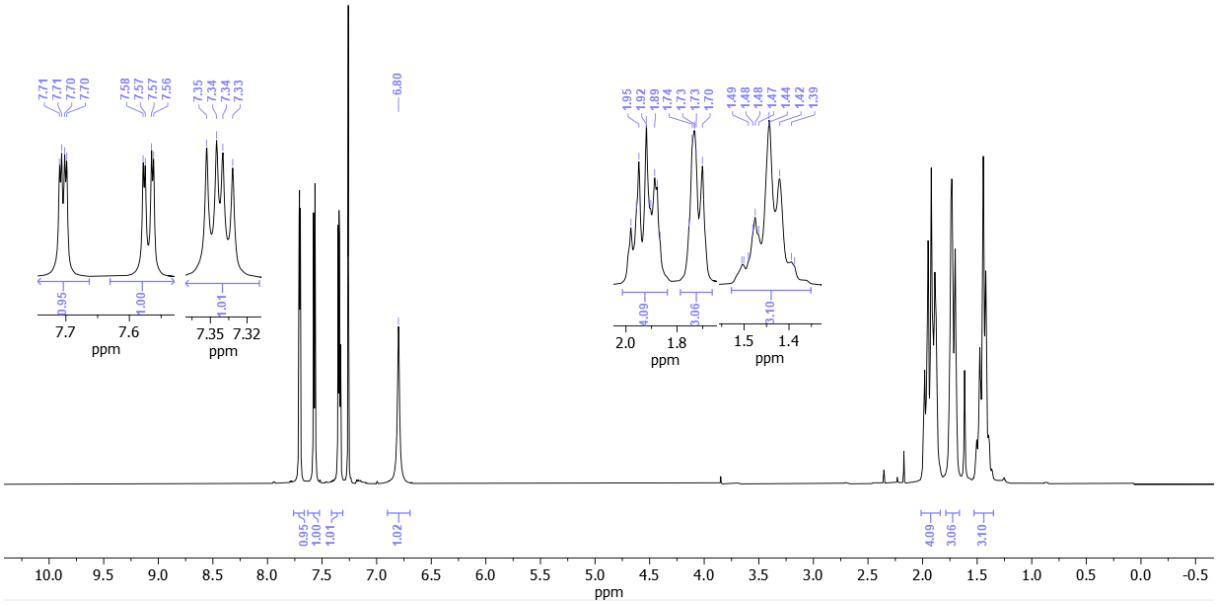
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.06, 155.40, 130.10, 124.68, 122.97, 117.12, 61.38, 33.84, 24.63, 21.87.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{12}H_{14}N_2NaO_2S$ 273.0668, Found: 273.0667.

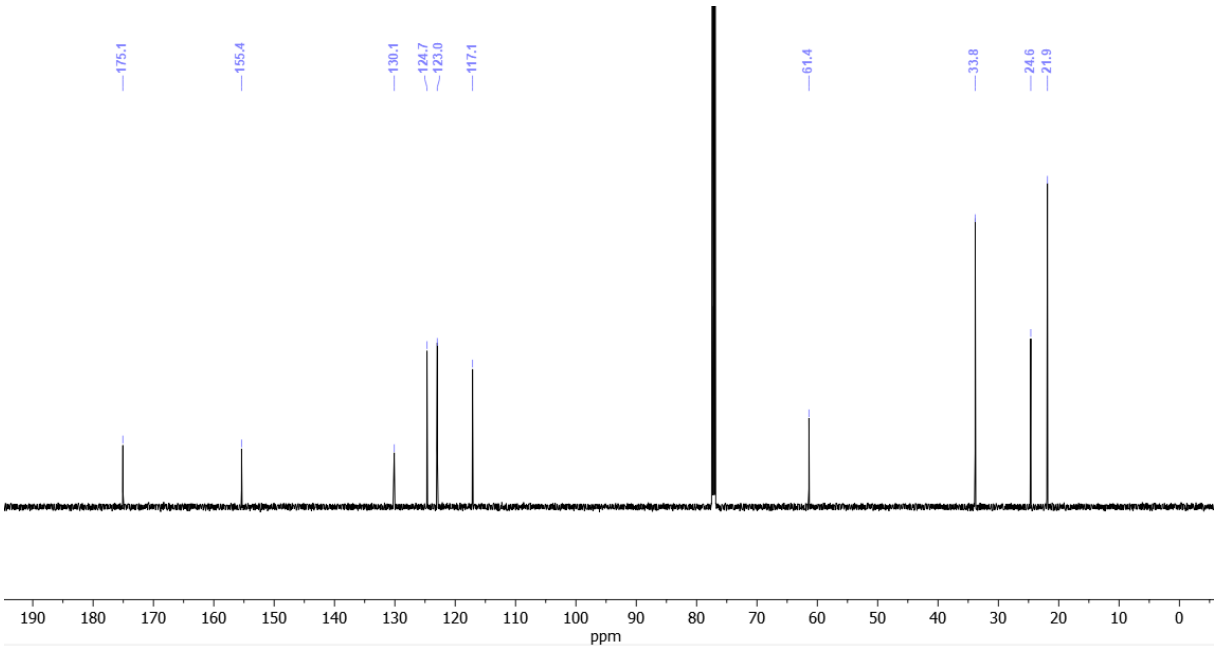
FT-IR (neat, V_{max} 1/cm): 3219.03, 2929.72, 1720.42, 1434.97, 1215.09.

Melting point: 231-233 °C

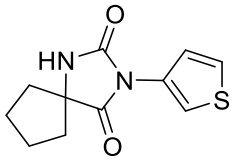
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5m.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5m.



3(thiophen-3-yl)-1,3-diazaspiro[4.5]decane-2,4-nonane (5n) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2b** and boronic acid **3d**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2). R_f: 0.28 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 80 mg, 0.34 mmol (84 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 3.3, 1.3 Hz, 1H), 7.57 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.34 (dd, *J* = 5.2, 3.3 Hz, 1H), 2.31 – 2.24 (m, 2H), 1.98 – 1.92 (m, 2H), 1.91 – 1.81 (m, 4H).

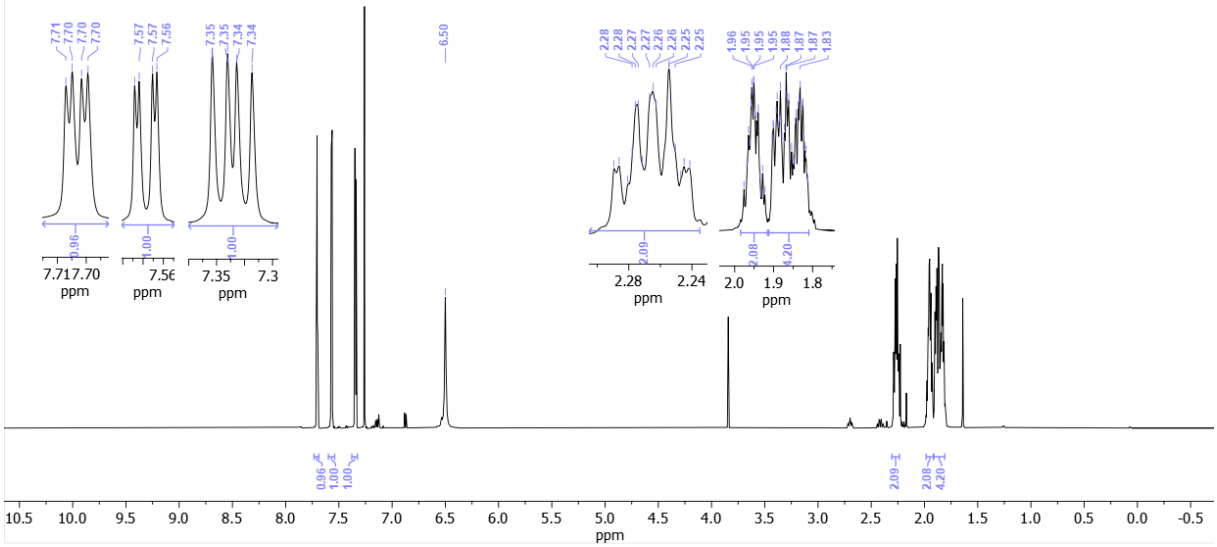
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.76, 155.23, 130.00, 124.58, 122.84, 117.02, 67.59, 38.20, 25.17.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{11}H_{12}N_2NaO_2S$: 259.0512 , Found: 259.0511 .

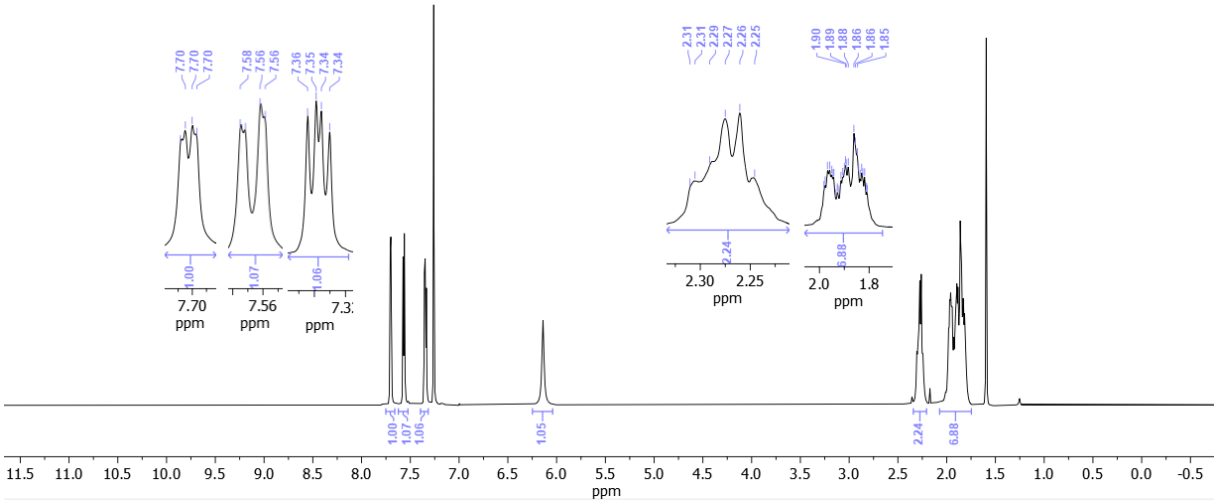
FT-IR (neat, V_{max} 1/cm): 3220.96, 2970.22, 1722.34, 1373.25.

Melting point: 188-190 °C.

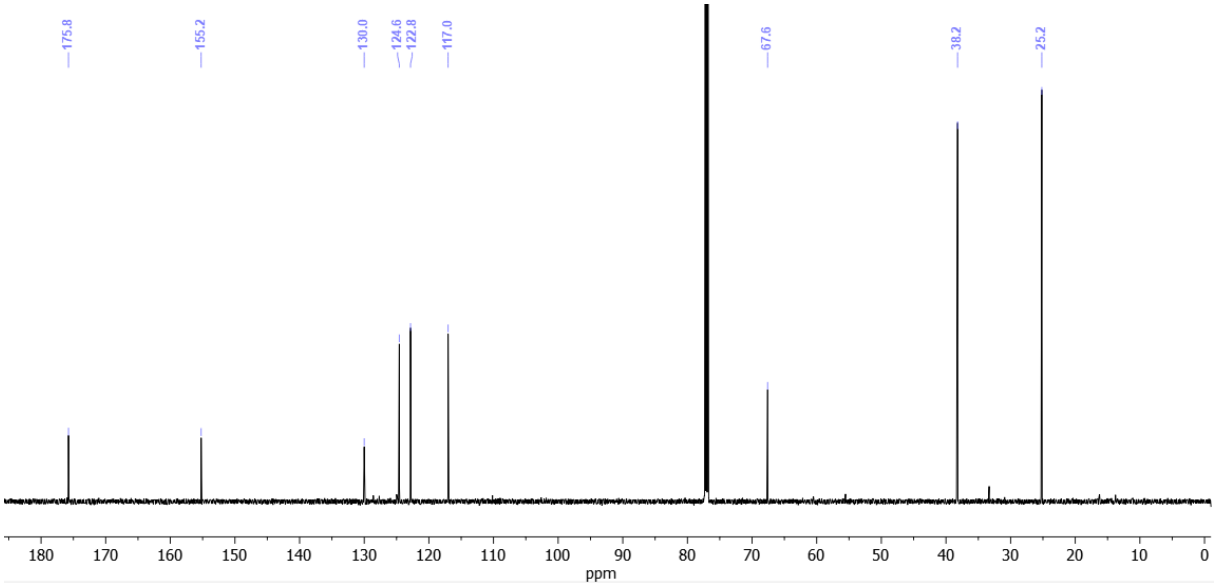
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5n.



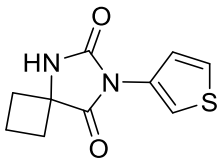
^{1}H NMR (400 MHz, $CDCl_3$-d_6) of compound 5n.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5n



7-(thiophen-3-yl)-5,7-diazaspiro[3.4]octane-6,8-dione (5o) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins 0.41 mmol of desired spirohydantoin **2c** coupled with boronic acid **3d**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2). R_f: 0.24 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 71 mg, 0.32 mmol (78 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 3.2, 1.3 Hz, 1H), 7.55 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.35 (dd, *J* = 5.3, 3.3 Hz, 1H), 6.61 (s, 1H), 2.74 – 2.65 (m, 2H), 2.46 – 2.36 (m, 2H), 2.26-2.17 (m, 1H), 1.93-1.86 (m,1H).

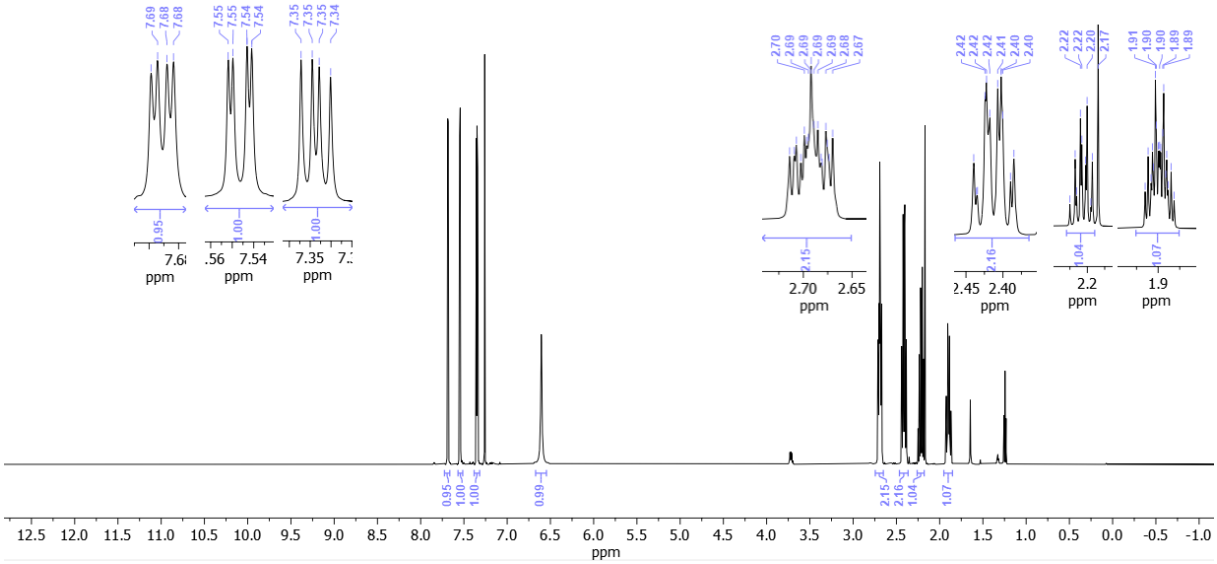
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.0, 155.0, 130.0, 124.8, 123.0, 117.4, 60.4, 33.5, 13.9.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{10}H_{10}N_2NaO_2S$: 245.0355, Found: 245.0355.

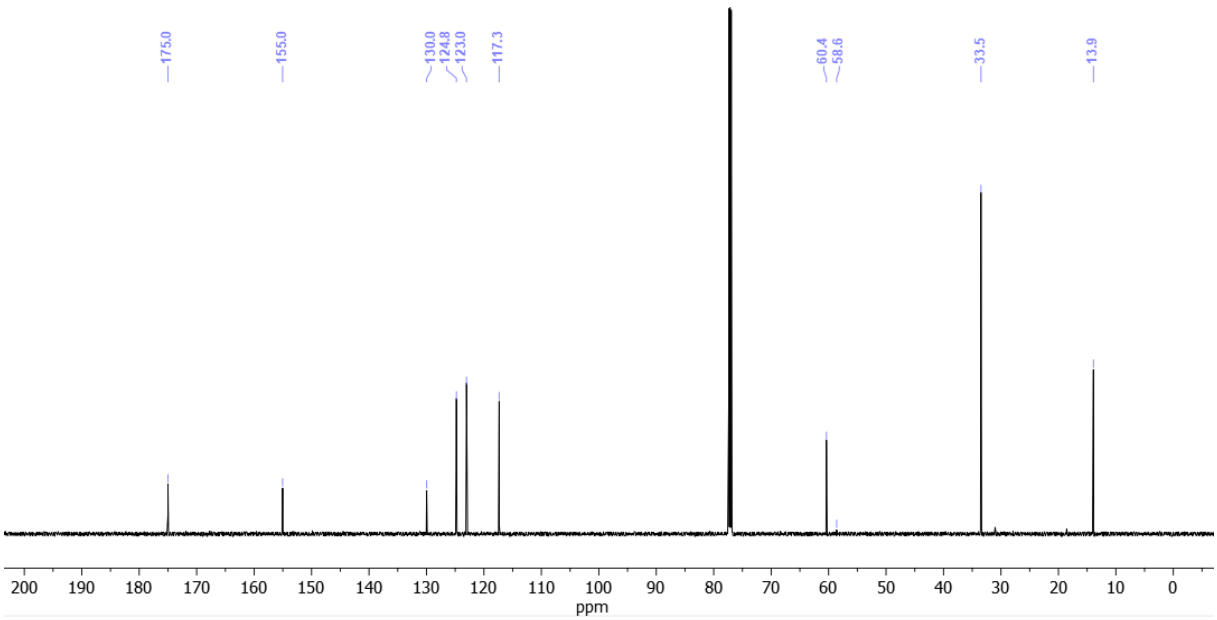
FT-IR (neat, V_{max} 1/cm): 3315.54, 2939.37, 1776.35, 1701.13, 1369.39, 1311.53.

Melting point: 152-154 °C.

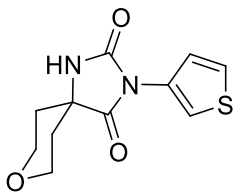
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5o.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5o.



3-(thiophen-3-yl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5p) [NEW]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2d** and boronic acid **3d**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:2→9:3→9:4). R_f: 0.15 with 9:2 hexane/acetone. The crude was dry loaded. A white colorless solid, 82.1 mg, 0.33 mmol (81 %) were isolated.

^{1}H NMR (600 MHz, DMSO-d6): δ 9.16 (s, 1H), 7.70 (dd, *J* = 3.2, 1.3 Hz, 1H), 7.59 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.42 (dd, *J* = 5.2, 1.3 Hz, 1H), 3.87 (dt, *J* = 11.9, 4.3 Hz, 2H), 3.70-3.65 (m, 2H), 1.99-1.93 (m, 2H), 1.71 – 1.57 (m, 2H).

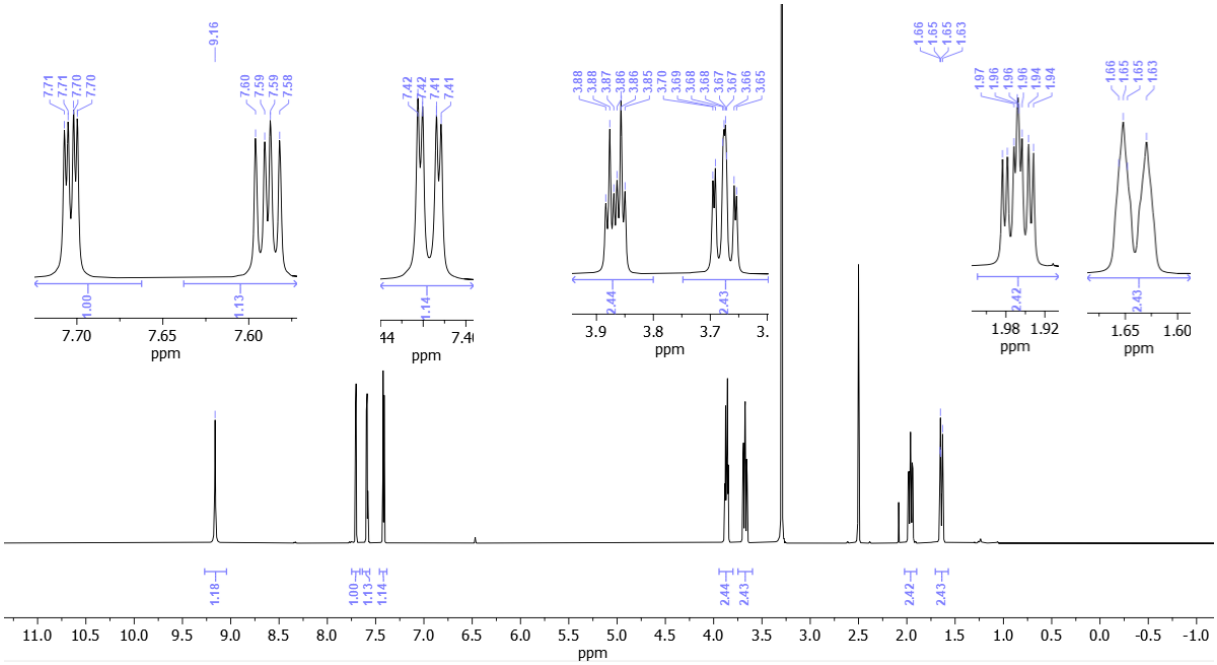
^{13}C NMR (151 MHz, DMSO-d6): δ 174.1, 154.0, 130.0, 125.0, 123.6, 117.9, 62.4, 58.0, 33.4.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{11}H_{12}N_2NaO_3S$: 275.0461, Found: 275.0460

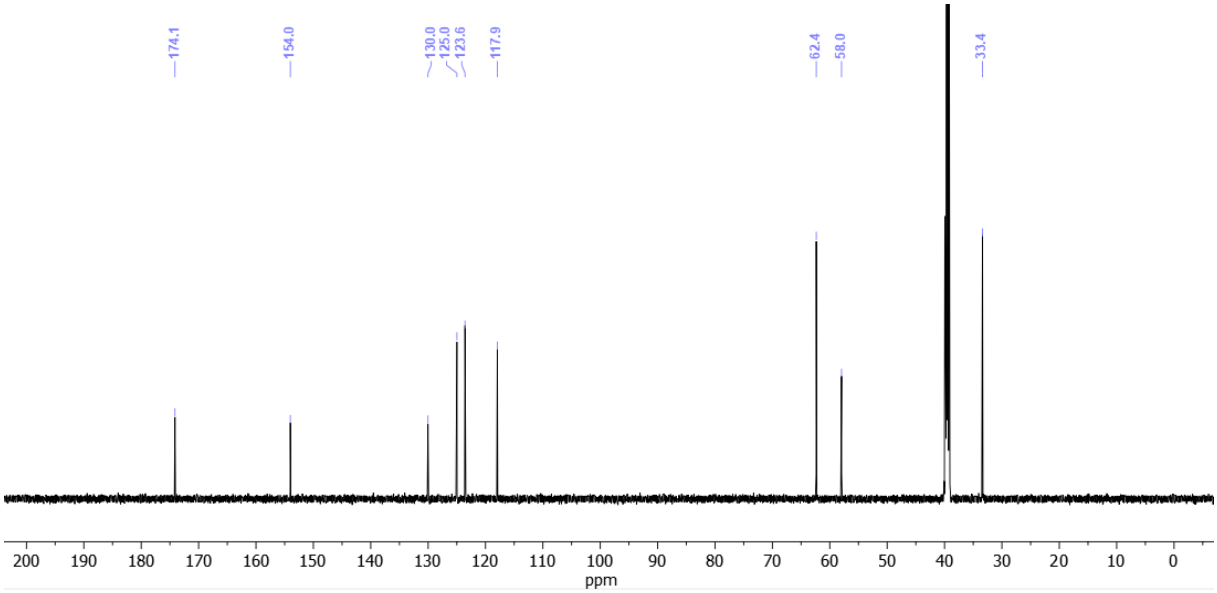
FT-IR (neat, V_{max} 1/cm): 3205.53, 2964.43, 1712.70, 1436.89, 1379.03, 1099.37.

Melting point: 262-264 °C

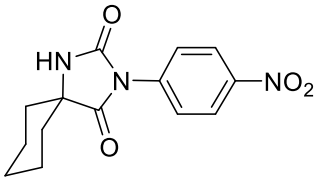
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5p.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5p.



3-(4-nitrophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione(q) [1308139-00-5]



The desired product was isolated with the general procedure for *N-3-aryl*ation of spirohydantoins with desired spirohydantoin **2a** and boronic acid **3e**. The product was purified with column chromatography with SiO_2 and a hexane/EtOAc gradient (3:1→2:1). R_f: 0.31 with 3:1 hexane/EtOAc. The crude was dry loaded. A yellow solid, 100 mg, 0.35 mmol (87 %) were isolated.

^{1}H NMR (600 MHz, DMSO-d$_6$): δ 9.15 (s, 1H), 8.39 – 8.29 (m, 2H), 7.81 – 7.71 (m, 2H), 1.78-1.65 (m, 6H), 1.63 – 1.53 (m, 3H), 1.37-130 (m, 1H).

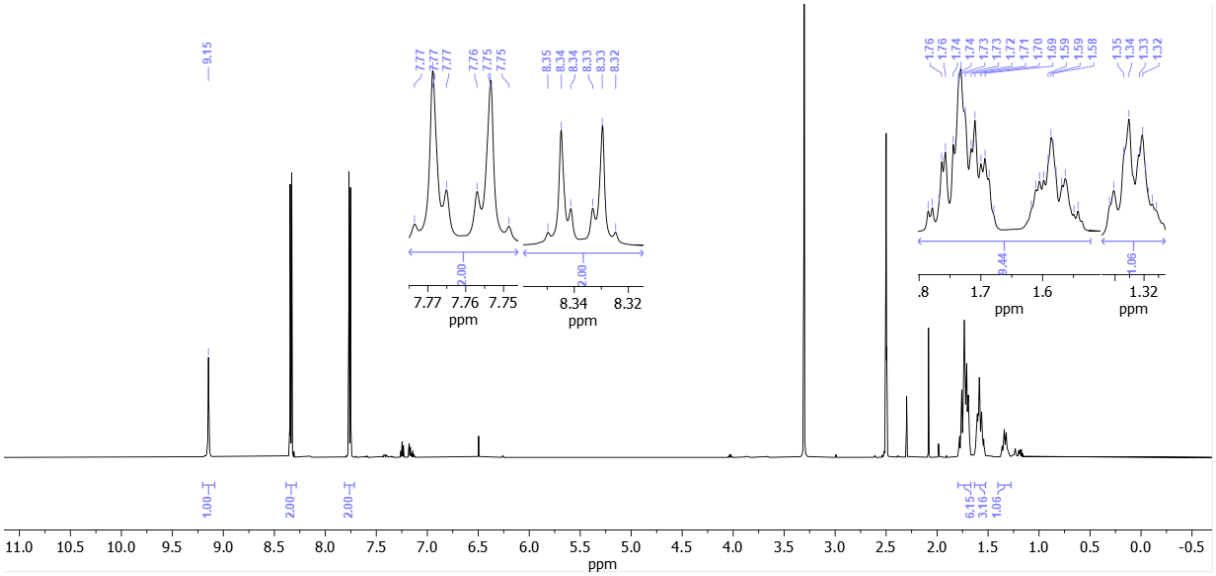
^{13}C NMR (151 MHz, DMSO-d$_6$): δ 175.26, 153.63, 145.75, 138.05, 126.80, 123.92, 60.98, 33.22, 24.33, 20.72.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{14}H_{15}N_3NaO_4$: 312.0955, Found: 312.0954

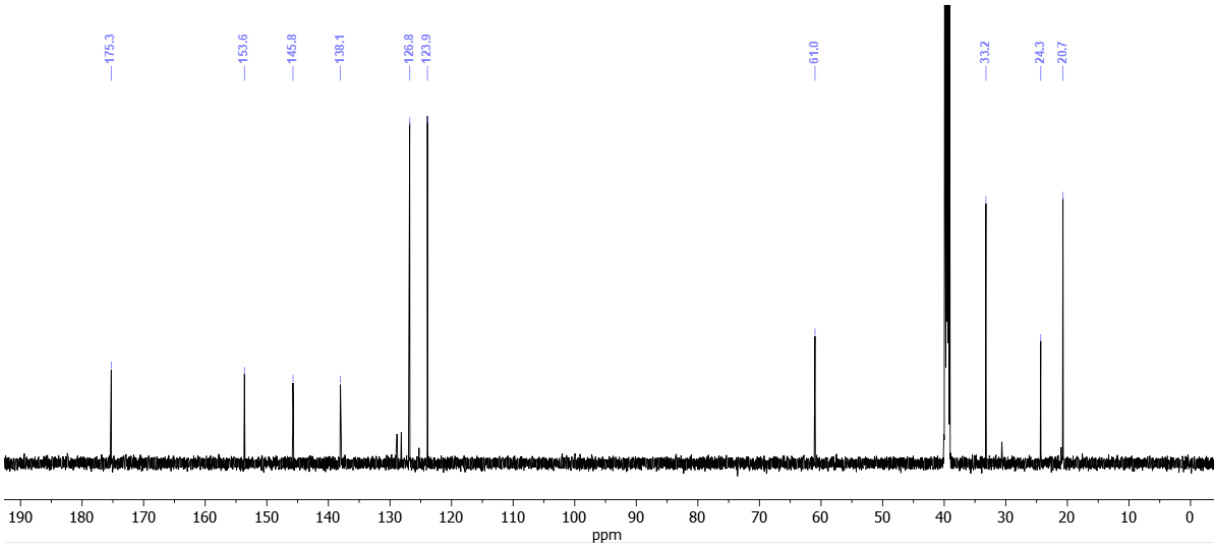
FT-IR (neat, V_{max} 1/cm): 3236.39, 2945.15, 1718.49, 1525.62, 1406.03, 1334.67.

Melting point: 269-271 °C

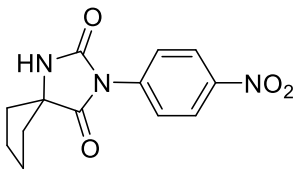
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5q.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5q.



3-(4-nitrophenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (5r) [1304895-82-6]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2b** and boronic acid **3e**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:1→9:2→9:4). $_{Rf}$: 0.26 with 9:2 hexane/acetone. The crude was dry loaded. A yellow solid, 94 mg, 0.34 mmol (85 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 – 8.29 (m, 2H), 7.86 – 7.74 (m, 2H), 6.31 (s, 1H), 2.41 – 2.26 (m, 2H), 2.09 – 1.78 (m, 6H).

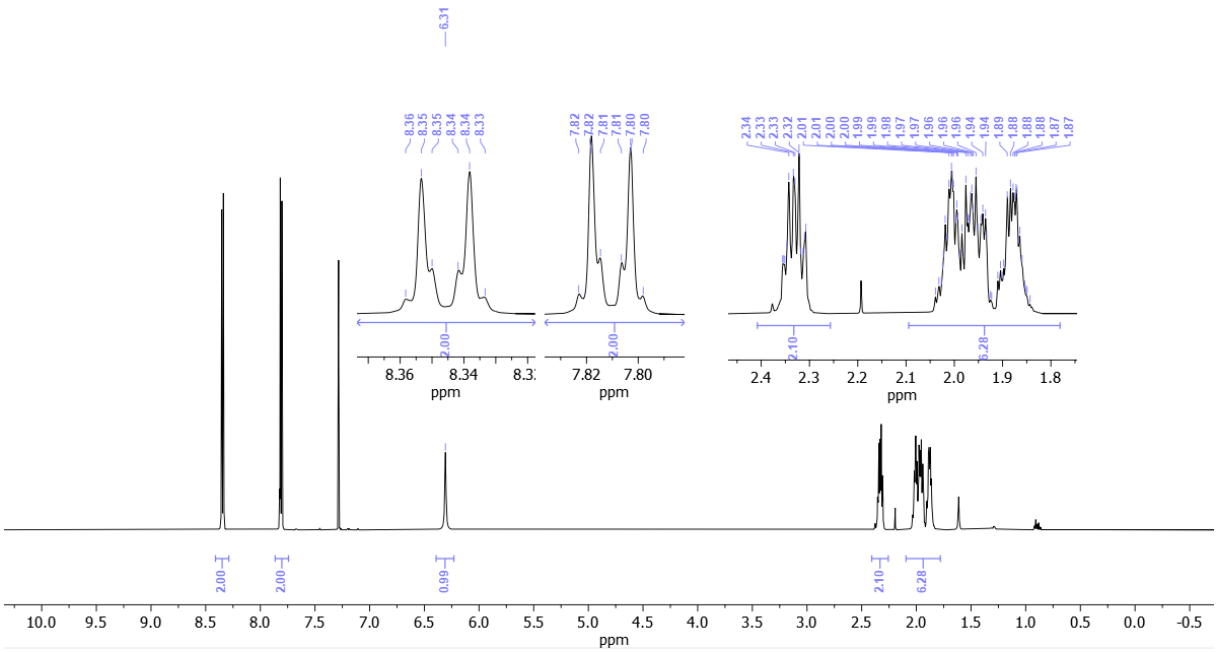
^{13}C NMR (151 MHz, $CDCl_3$): δ 176.0, 154.5, 146.5, 137.8, 125.9, 124.4, 68.1, 38.5, 25.4.

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_{13}H_{13}N_3NaO_4$: 298.0798, Found: 298.0798

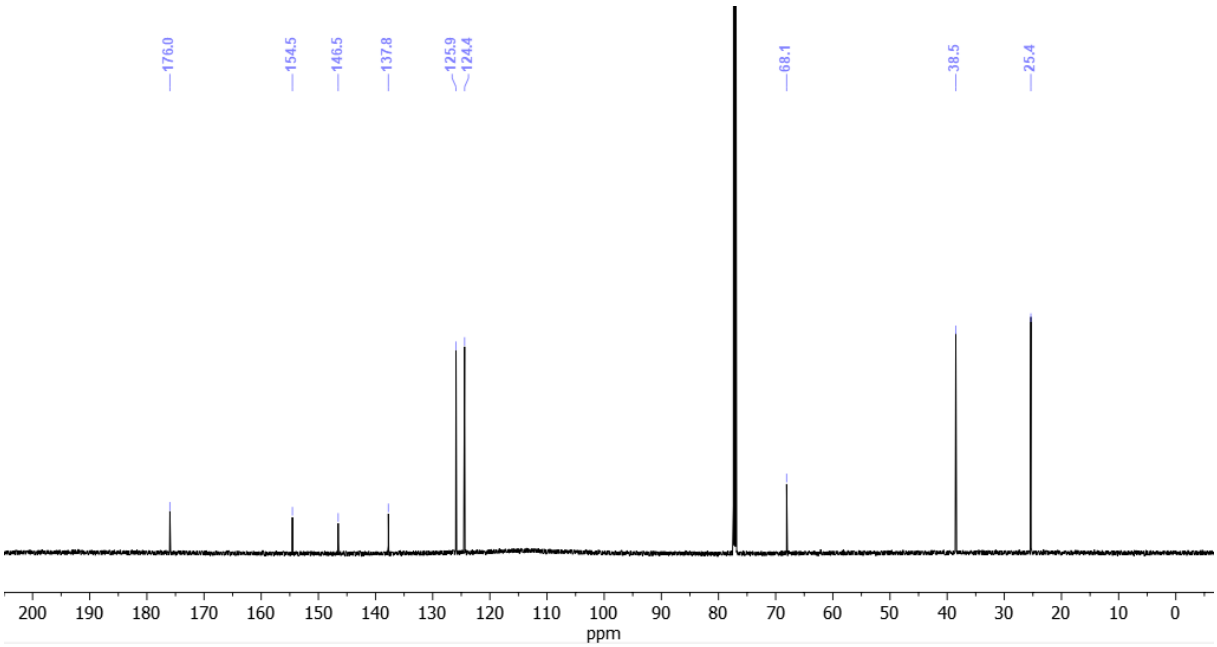
FT-IR (neat, V_{max} 1/cm): 3240.24, 2972.15, 1720.42, 1496.68, 1340.46.

Melting point: 232-234 °C

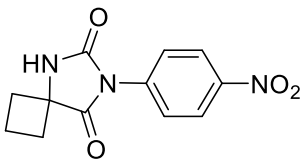
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5r.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5r.



7-(4-nitrophenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5s) [1501415-34-4]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2c** and boronic acid **3e**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:2→9:4). R_f: 0.24 with 9:2 hexane/acetone. The crude was dry loaded. A yellow solid, 75 mg, 0.29 mmol (72 %) were isolated.

Note: Under the preparation for the dryloading of the crude, some of the silca with product was lost under concentration with vacuum.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 – 8.29 (m, 2H), 7.83 – 7.74 (m, 2H), 6.52 (s, 1H), 2.78 – 2.69 (m, 2H), 2.51 – 2.42 (m, 2H), 2.29-2.18 (m, 1H), 1.98-1.89 (m, 1H).

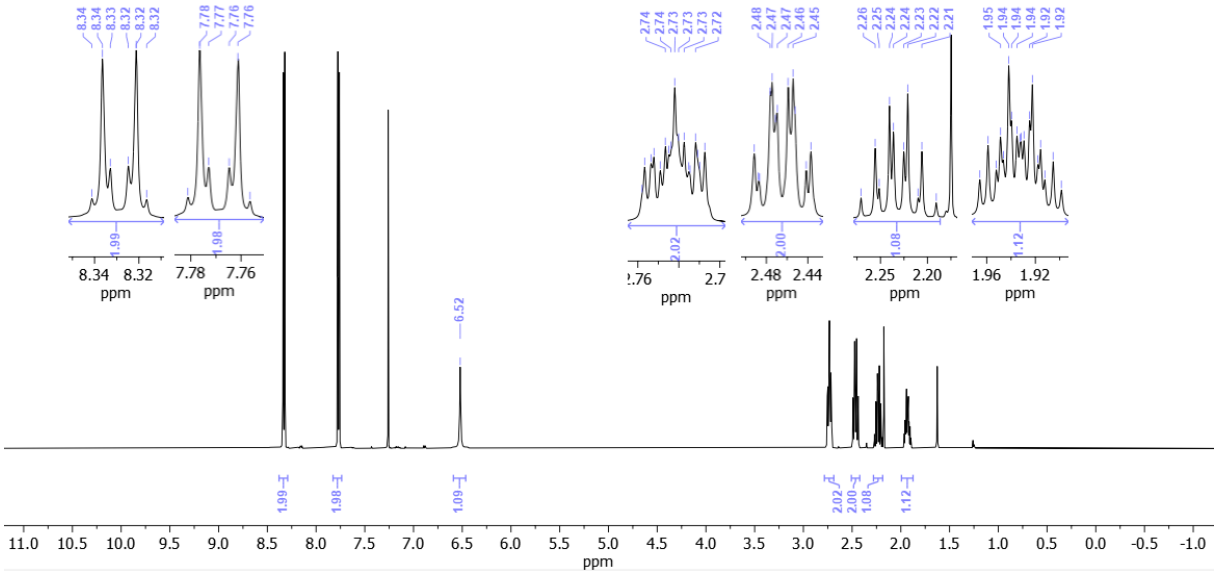
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.00, 154.24, 146.49, 137.54, 125.95, 124.46, 100.13, 100.10, 60.63, 33.56, 13.88.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{12}H_{11}N_3NaO_4$: 284.0642, Found: 284.0641

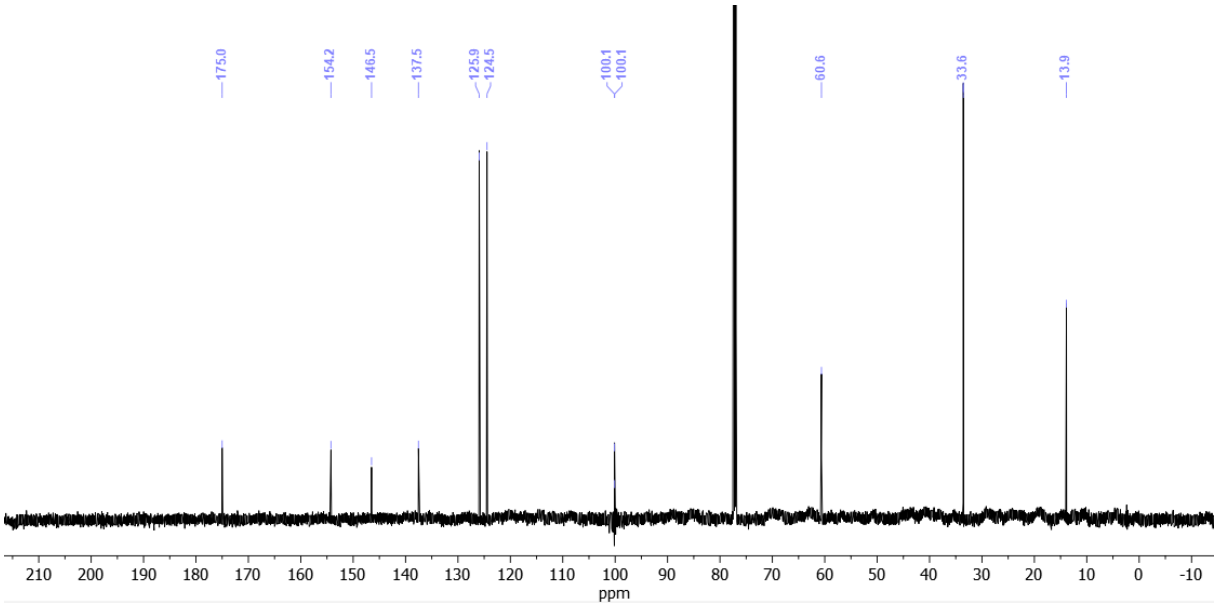
FT-IR (neat, V_{max} 1/cm): 3230.60, 2970.22, 1722.344, 1498.61, 1338.53.

Melting point: 194-196 °C

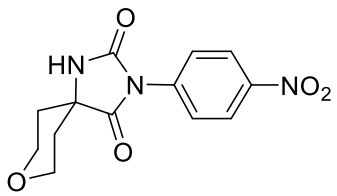
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5s.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5s.



3-(4-nitrophenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5t)[1553596-59-0]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins with desired spirohydantoin **2d** and boronic acid **3e**. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient (9:2→9:4). R_f: 0.13 with 9:2 hexane/acetone. The crude was dry loaded. A yellow solid, 102 mg, 0.39 mmol (97 %) were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 – 8.31 (m, 2H), 7.80 – 7.74 (m, 2H), 6.89 (s, 1H), 4.12 (dt, *J* = 12.2, 4.6 Hz, 2H), 3.72-3.68 (m, 2H), 2.29-2.24 (m, 2H), 1.79-1.74 (m, 2H).

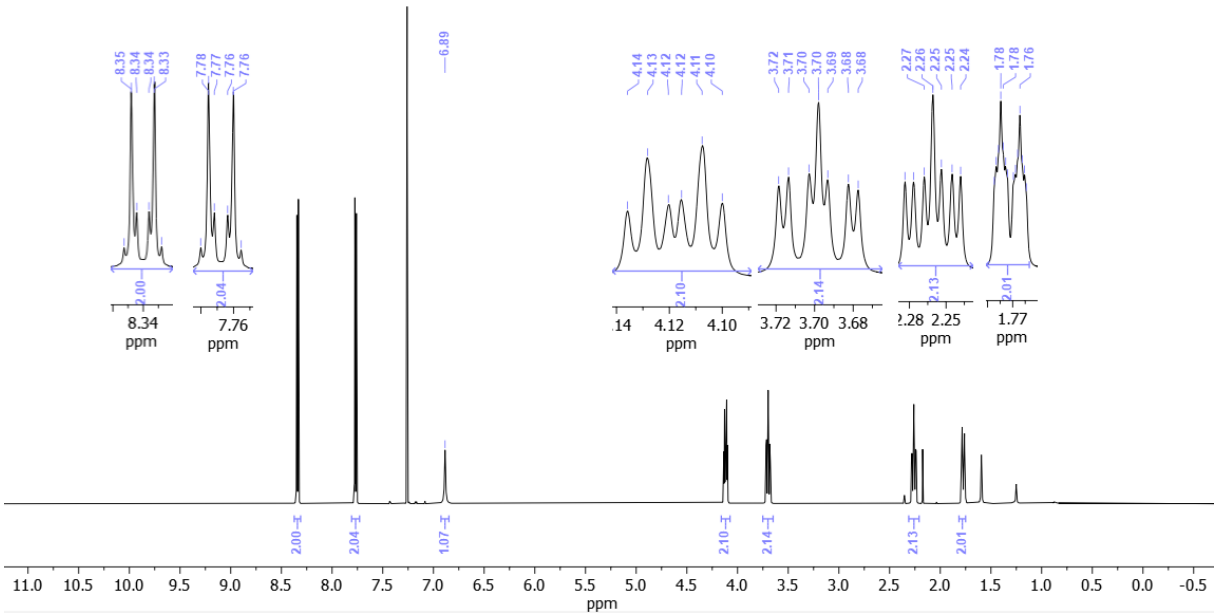
^{13}C NMR (151 MHz, $CDCl_3$): δ 154.5, 146.5, 137.1, 125.8, 124.4, 100.00, 63.4, 58.8, 33.9.

HRMS (ESI) m/z $[M + Na]^+$: Calculated for $C_{13}H_{13}N_3NaO_5$ 314.0747, Found: 314.0747

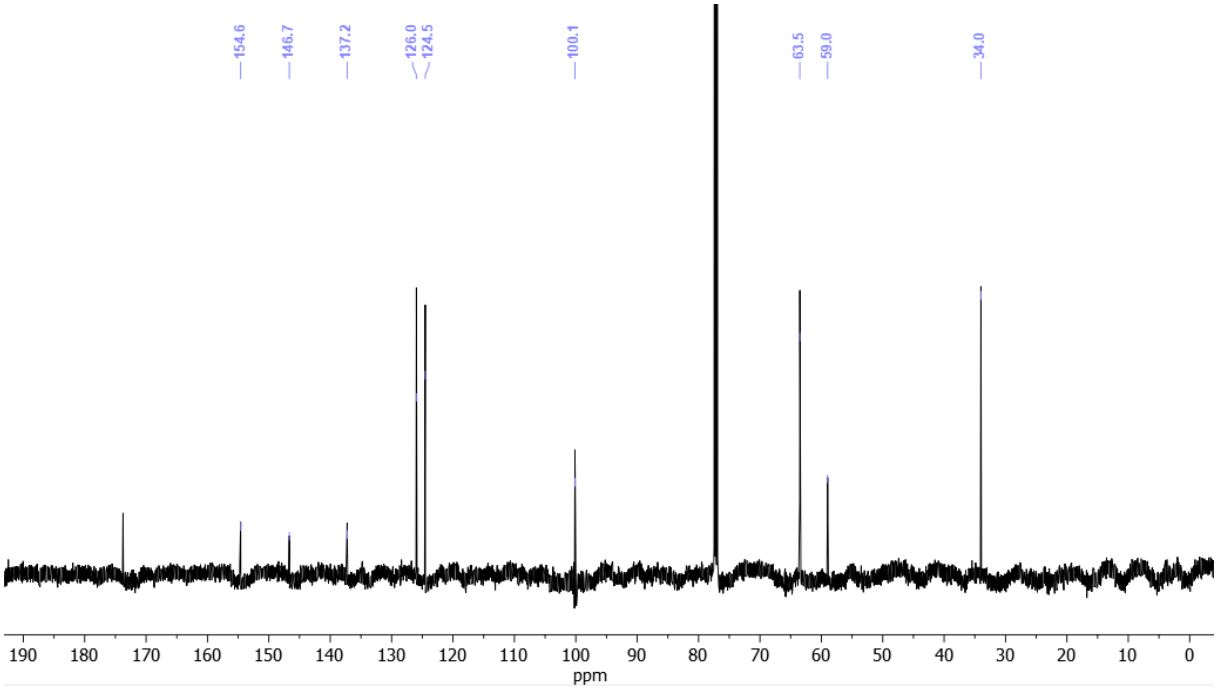
FT-IR (neat, V_{max} 1/cm): 3193.96, 3103.31, 1718.49, 1517.90, 1342.39.

Melting point: 231-233 °C

^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 5t.

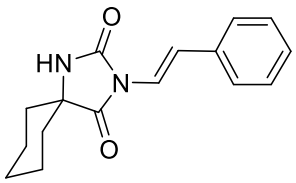


^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 5t.



4.4 *N*-3-Alkenylated spirohydantoins

(E)-3-styryl-1,3-diazaspiro[4.5]decane-2,4-dione (6a) [New]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with desired spirohydantoin **2a** and boronic acid **3f**, with a reflux at 25 ºC for 24 h. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 9:1→9:2. R_f: 0.29 with hex/acetone 9:2. The crude was dry loaded. A white colorless solid, 101 mg, 0.37 mmol (93 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 15.0 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 15.2 Hz, 1H), 7.10 (s, 1H), 1.98 – 1.84 (m, 4H), 1.78-1.72 (m, 1H), 1.72 – 1.66 (m, 2H), 1.54 – 1.38 (m, 3H).

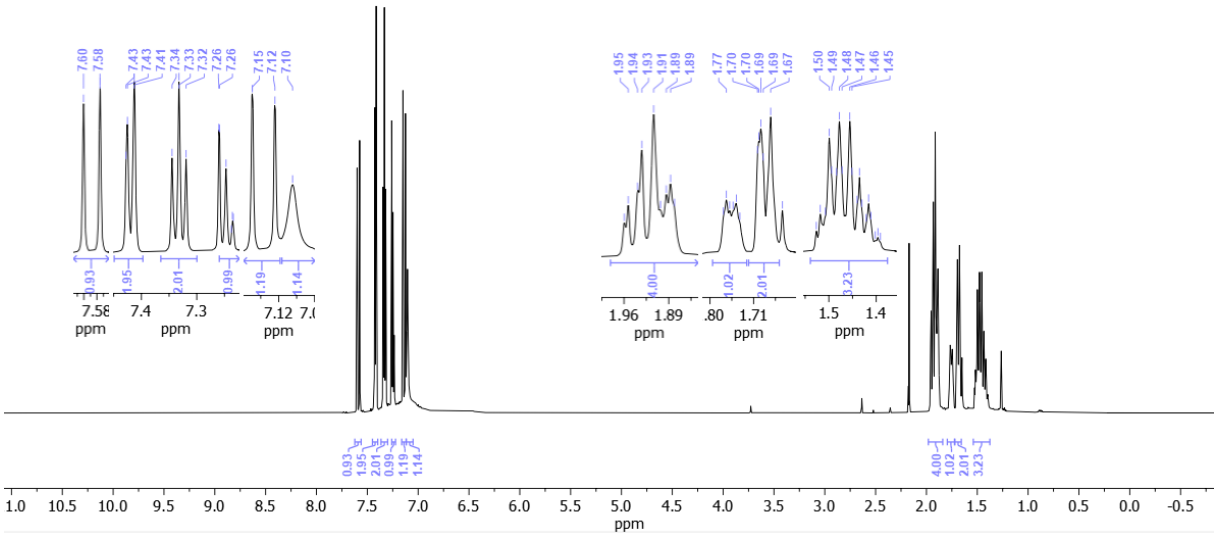
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.1, 155.3, 136.0, 128.8, 127.7, 126.3, 120.4, 118.1, 61.1, 33.8, 24.7, 21.8.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{16}H_{18}N_2NaO_2$: 293.1260, Found: 293.1260

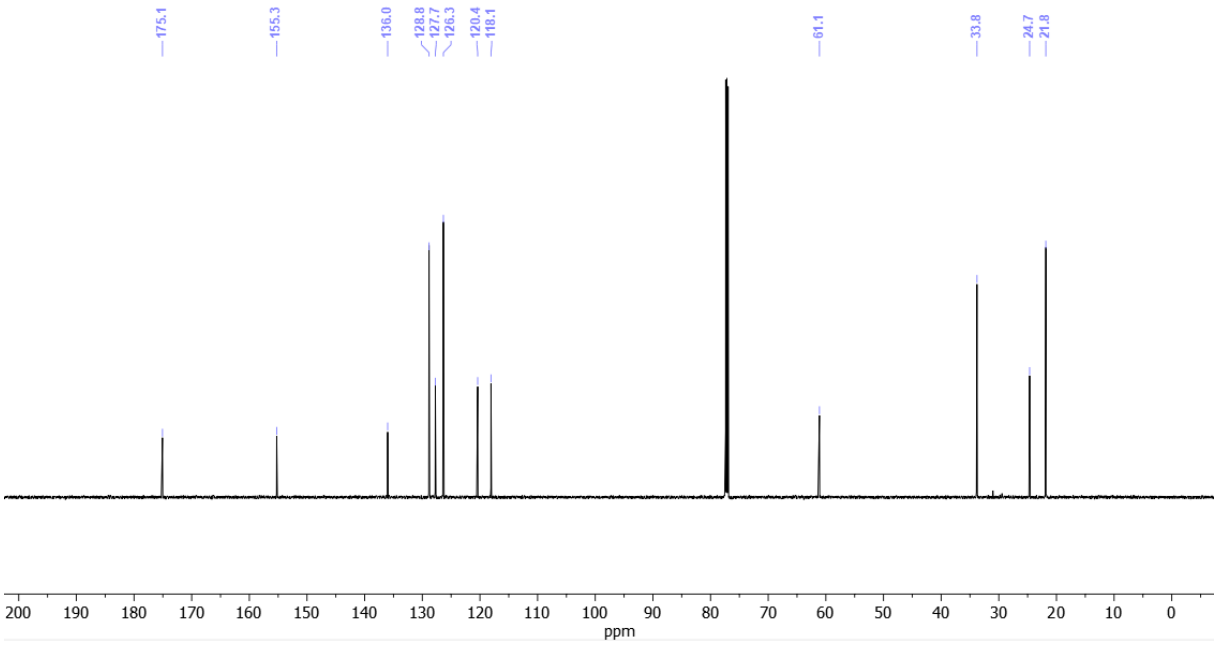
FT-IR (neat, V_{max} 1/cm): 3290.39, 2931.65, 1760.92, 1703.06, 1411.82, 1093.58.

Melting point: 206-209 °C

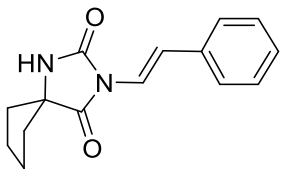
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 6a.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 6a.



(E)-3-styryl-1,3-diazaspiro[4.4]nonane-2,4-dione (6b) [New]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with desired spirohydantoin **2b** and boronic acid **3f**, with a reflux at 25 ºC for 24 h. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 9:1→9:2. R_f: 0.25 with hex/acetone 9:2. The crude was dry loaded. A white colorless solid, 99 mg, 0.39 mmol (97 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 15.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.33 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.14 (d, *J* = 15.2 Hz, 1H), 6.37 (s, 1H), 2.31 – 2.20 (m, 2H), 2.03 – 1.91 (m, 2H), 1.91 – 1.78 (m, 4H).

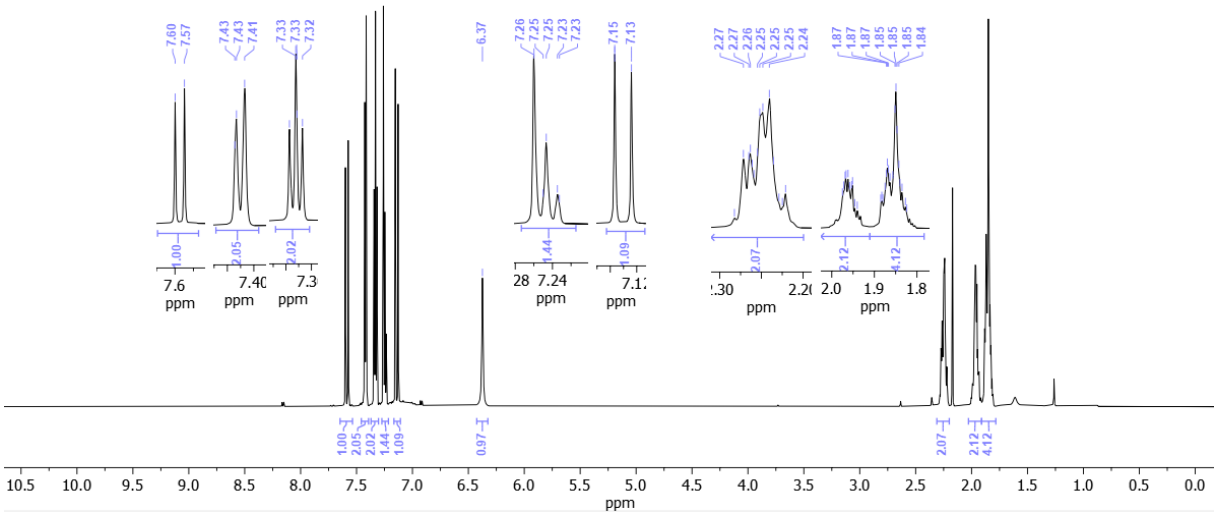
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.75, 154.94, 135.99, 128.84, 127.75, 126.36, 120.33, 118.07, 67.40, 38.27, 25.31.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{15}H_{16}N_2NaO_2$: 279.1104, Found: 279.1103

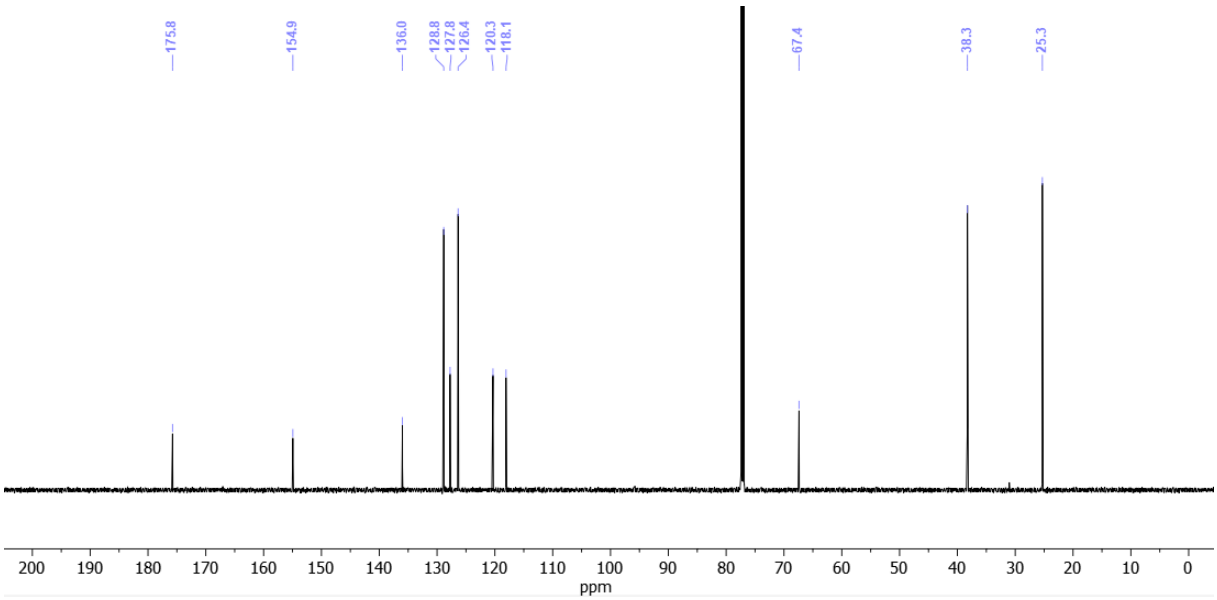
FT-IR (neat, V_{max} 1/cm): 2970.22, 1714.63, 1411.82, 1218.95, 1095.51, 947.00.

Melting point: 171-174 °C

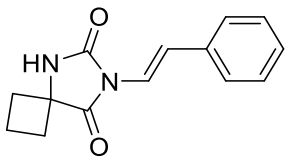
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 6b.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 6b.



(E)-7-styryl-5,7-diazaspiro[3.4]octane-6,8-dione (6c) [New]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with desired spirohydantoin **2c** and boronic acid **3f**, with a reflux at 25 ºC for 24 h. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 9:1→9:2. R_f: 0.29 with hex/acetone 9:2. The crude was dry loaded. A white colorless solid, 88 mg, 0.36 mmol (91 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 15.1 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 15.1 Hz, 1H), 6.42 (s, 1H), 2.73-2.62 (m, 2H), 2.45 – 2.37 (m, 2H), 2.25-2.17 (m, 1H), 1.95-1.85 (m, 1H).

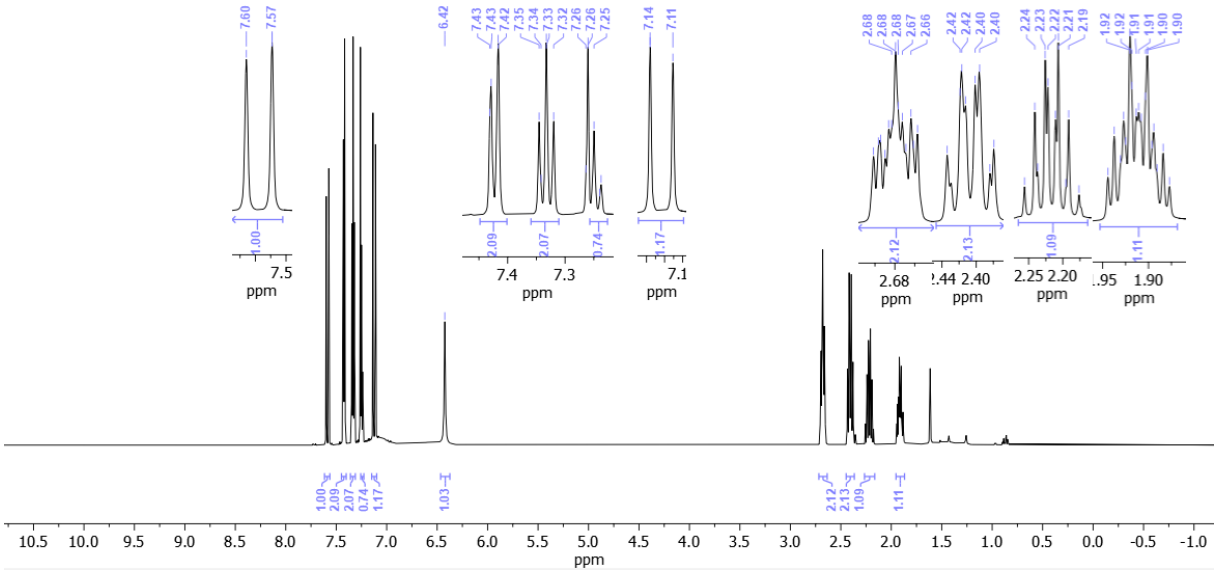
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.9, 154.5, 135.9, 128.9, 127.8, 126.4, 120.4, 117.9, 60.0, 33.4, 13.9.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{14}H_{14}N_2NaO_2$: 265.0947, Found: 265.0947

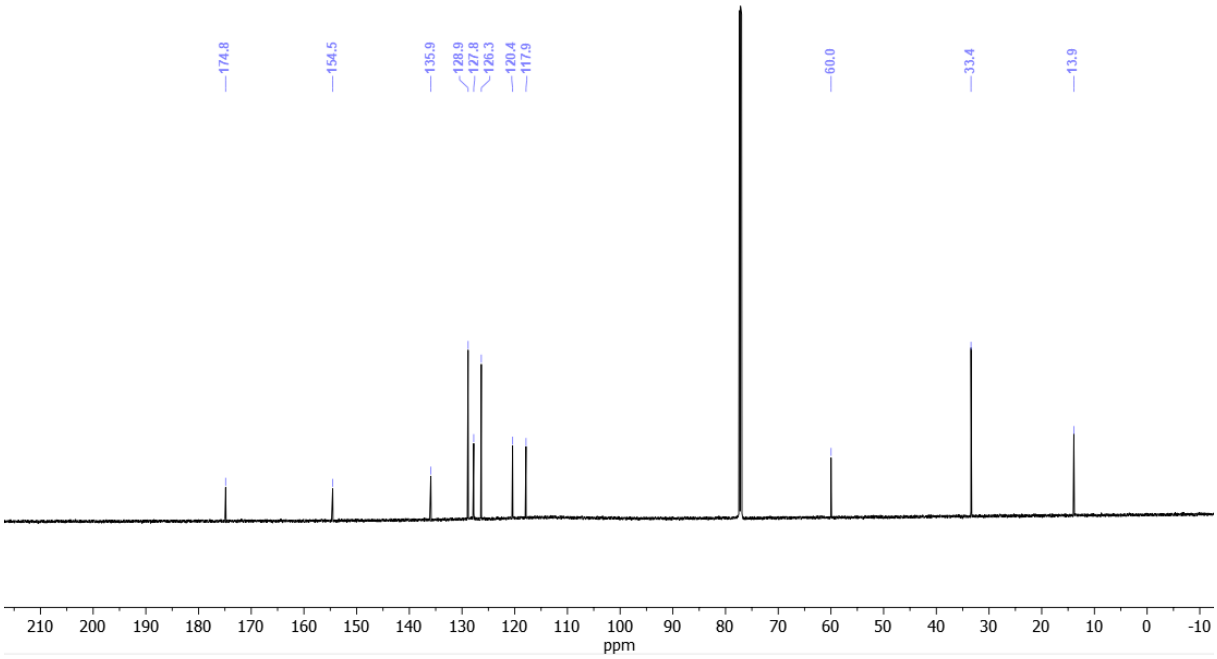
FT-IR (neat, V_{max} 1/cm): 3112.95, 1722.34, 1411.82, 1218.95, 1097.44.

Melting point: 158-161 °C

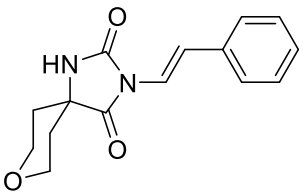
^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 6c.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 6c.



(E)-3-styryl-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (6d) [New]



The desired product was isolated with the general procedure for *N*-3-arylation of spirohydantoins, with desired spirohydantoin **2d** and boronic acid **3f**, with a reflux at 25 ºC for 24 h. The product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 9:2→9:3. R_f: 0.26 with hex/acetone 9:3. The crude was dry loaded. A white colorless solid, 90 mg, 0.33 mmol (83 %), were isolated.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 15.1 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.34 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.30 (s, 1H), 7.28 – 7.24 (m, 2H), 7.13 (d, *J* = 15.1 Hz, 1H), 4.12 (dt, *J* = 12.2, 4.4 Hz, 2H), 3.71 (m, 2H), 2.25-2.20 (m, 2H), 1.72 – 1.65 (m, 2H).

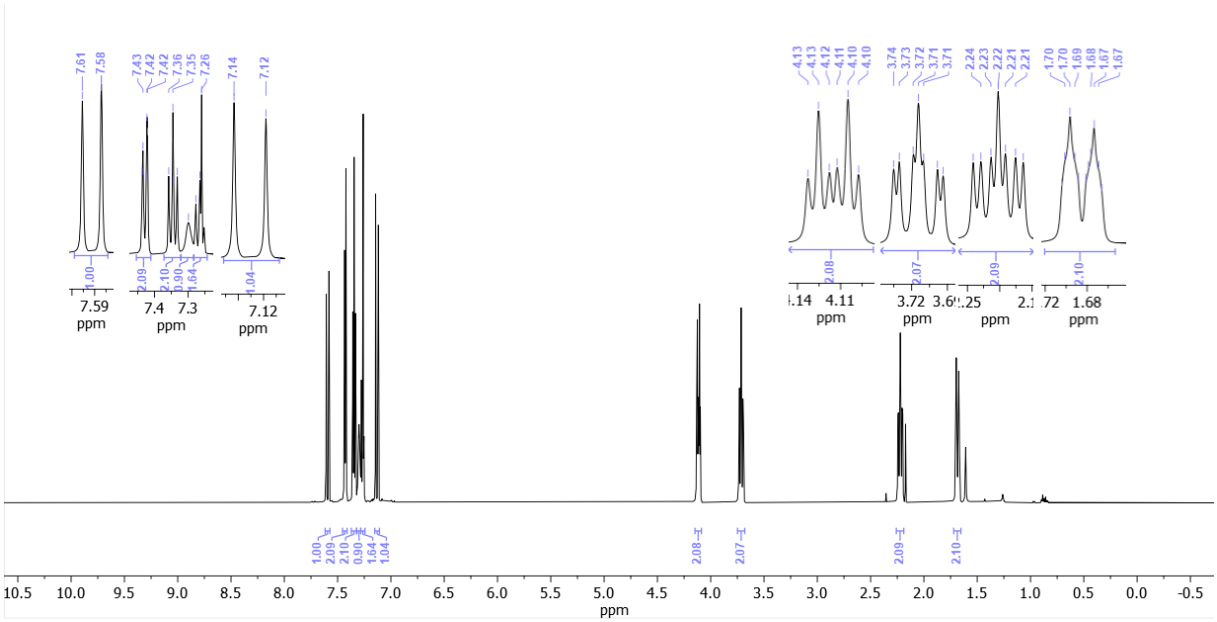
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.61, 135.69, 128.91, 127.96, 126.40, 120.91, 117.71, 63.63, 58.18, 33.99.

HRMS (ESI) m/z $[M + Na]^+$: Calculated for $C_{15}H_{16}N_2NaO_3$: 295.1053, Found: 295.1052

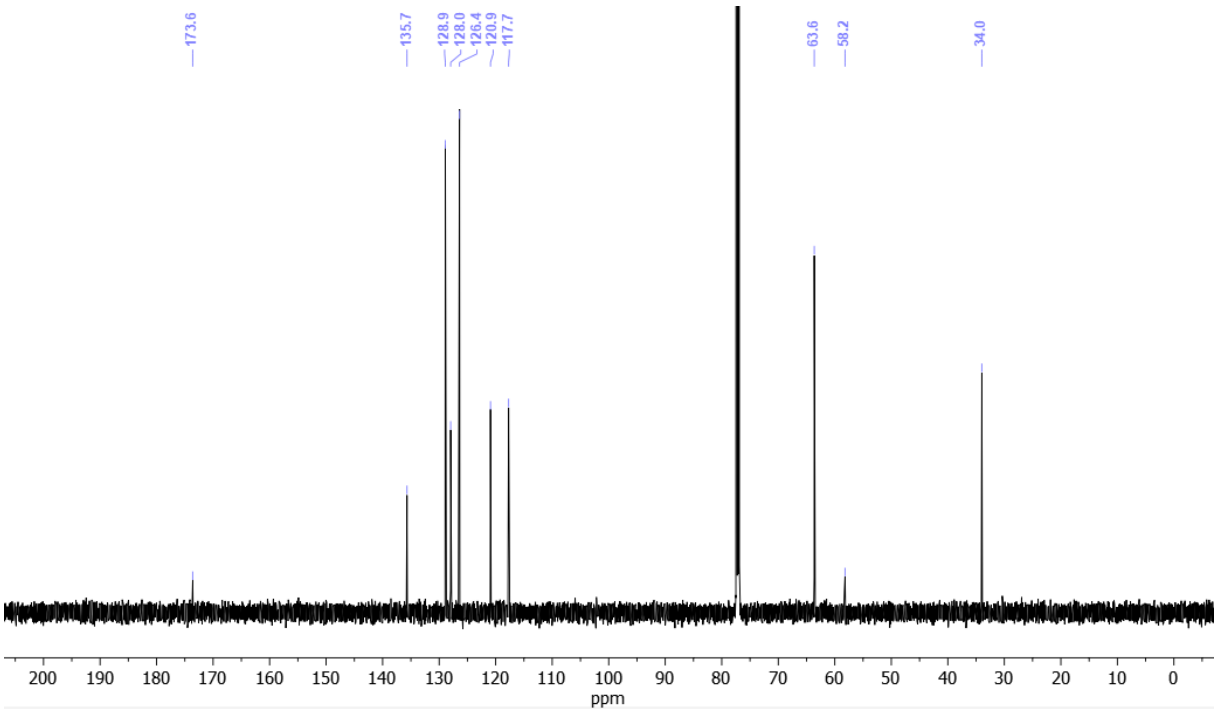
FT-IR (neat, V_{max} 1/cm): 3163.09, 2968.29, 1720.42, 1409.89, 1103.23.

Melting point: 210-211 °C

^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 6e.



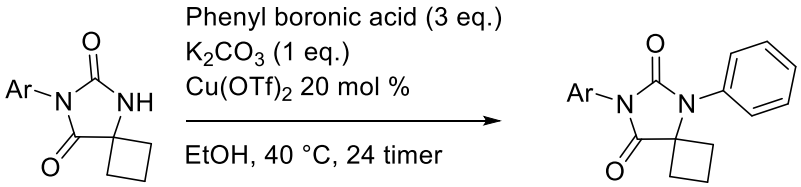
^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 6e.



4.5 *N*-1-Arylated spirohydantoins

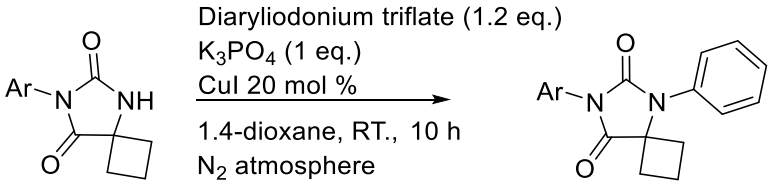
General methods used for *N*-1-arylation of *N*-3 substituted spirohydantoins

Method A:



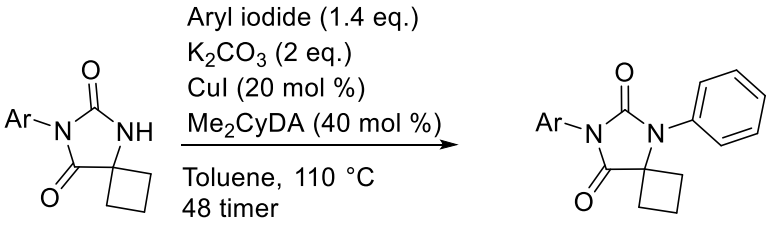
The procedure is based on a method developed in the group.[39] Desired *N*-3 substituted spirohydantoin (0.2 mmol, 1 eq.) was measured in a 5 mL round bottom flask. Then desired boronic acid (0.6 mmol, 3 eq.), $Cu(OTf)_2$ (0.04 mmol, 20 mol%) and potassium carbonate (0.2 mmol, 1 eq.) were measured out and transferred to the same flask with a stirring bar. 1 mL ethanol was added afterwards, before the flask was placed on a preheated heating block with a condenser, the mixture was then refluxed at 40 ºC, for 24 hours. After the reaction, the mixture was concentrated under vacuum and purified with an appropriate method, to isolate the desired compounds.

Method B:



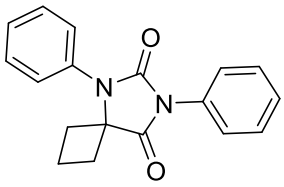
The procedure is based on method from the literature.[38] Desired *N*-3 substituted spirohydantoin (0.2 mmol, 1 eq.) and diphenyliodonium triflate (0.24, 1.2 eq.) were measured and added to a oven dried 25 mL schlenk flask with a stirring bar. Afterwards were CuI (0.04 mmol, 20 mol%) and potassium phosphate tribasic (0.2 mmol, 1 eq.) added under argon atmosphere. A septum was placed on the flask and anhydrous 1,4-dioxane (2 mL) was added with a syringe under argon atmosphere. The mixture was stirred in room temperature for 14 h. After reaction end was the crude product filtered through a layer of celite and washed with ethyl acetate and acetone. The crude was then concentrated under vacuum and purified with appropriate method, to isolate the desired compounds.

Method C:



The procedure is based on a method from the literature.[33] Desired *N*-3 substituted spirohydantoin (0.2 mmol, 1 eq.), CuI (0.04 mmol, 20 mol%) and potassium carbonate (0.4 mmol, 2 eq.) were added to 15 mL pressure tube. A septum was placed on the tube and the mixture was evacuated and filled with argon three times. Iodobenzene (0.28 mmol, 1.4 eq.), Me_2CyDA (0.08 mmol, 40 mol%) and anhydrous toluene (1 mL) were then added with a syringe under argon flow. The septum was then exchanged with a teflon screw cap and the reaction as stirred at 110 ºC, with an oil bath, for 48 h. Afterwards was the reaction cooled to room temperature and filtered over a layer of celite and washed with ethyl acetate and acetone. The filtrate was then concentrated under vacuum and purified with appropriate method, to isolate the desired compounds.

5,7-diphenyl-5,7-diazaspiro[3.4]octane-6,8-dione (8) [New]



The desired product was synthesized with the three methods for *N*-1-arylation of *N*-3 substituted spirohydantoins.

Method A: Repetition 1: the desired product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 95:5→90:10. R_f: 0.23 with 9:1 hexane/acetone. 11.9 mg, 0.045 mmol, 21 % of desired product were isolated as a white solid.

Repetition 2: 0.15 mmol of desired *N*-3 substituted spirohydantoins were refluxed for 96 hours at 40 ºC. The desired product was purified with column chromatography with SiO_2 and a hexane/acetone gradient 95:5→90:10. 5.5 mg, R_f: 0.22 with 9:1, hexane/acetone. 0.018 mmol, 11 % of desired product were isolated as a white solid.

Method B: the desired product was purified with column chromatography with SiO_2 and a 8:2 hexane/acetone eluent. R_f: 0.36 with 8:2 hexane/acetone. 2.8 mg, 0.01 mmol, 5 % of desired product were isolated as a white solid.

Method C: the desired product was purified with column chromatography with SiO_2 and a 85:15 hexane/acetone eluent. R_f: 0.38 with 8:2 hexane/acetone. 56.9 mg, 0.19 mmol, 94 % of desired product were isolated as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 – 7.44 (m, 7H), 7.40 – 7.33 (m, 3H), 2.67 – 2.58 (m, 2H), 2.53 – 2.44 (m, 2H), 2.26-2.17 (m, 1H), 1.68-1.59 (m, 1H).

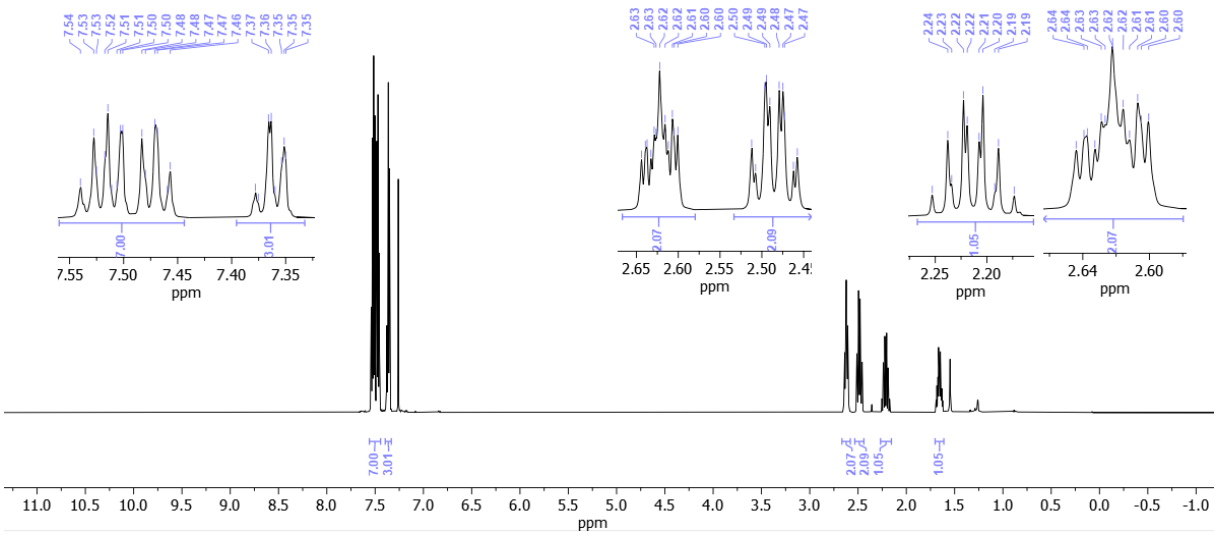
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.07, 154.08, 134.11, 131.94, 129.87, 129.79, 129.10, 128.98, 128.09, 126.19, 65.21, 31.04, 14.03.

HRMS (ESI) m/z [M + Na]$^+$: Calculated for $C_{18}H_{16}N_2NaO_2$: 315.1104, Found: 315.1103

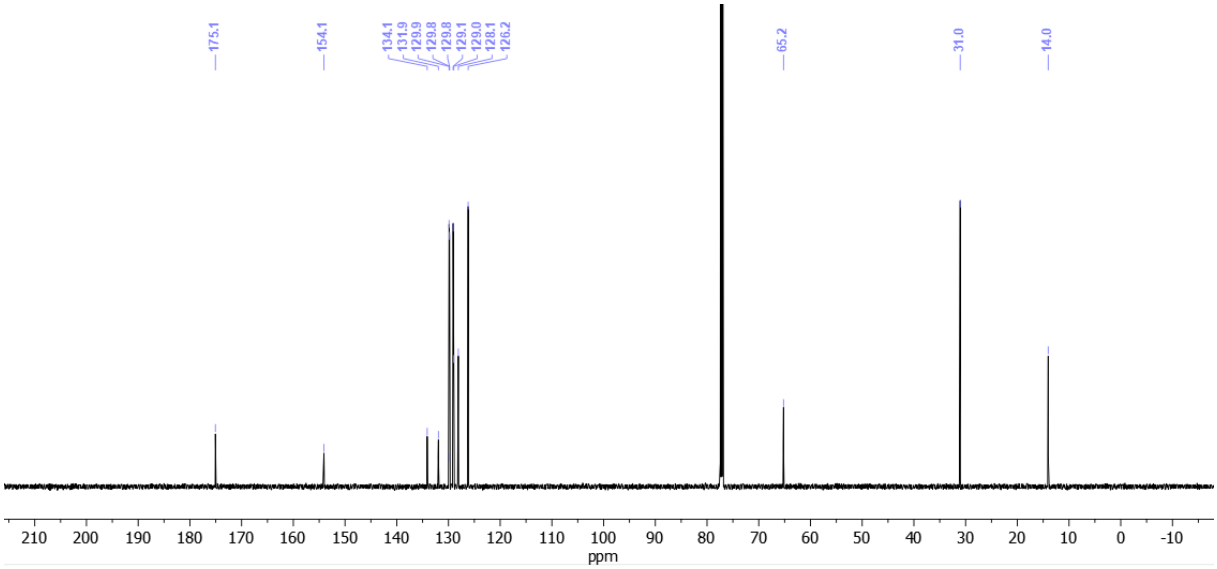
FT-IR (neat, V_{max} 1/cm): 1761.85, 1710.77, 1492.83, 1396.39.1137.94.

Melting point: 119-122 ºC

^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 8.

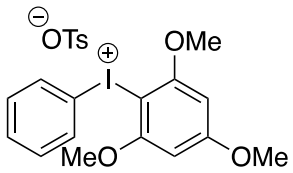


^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 8.



4.6 Diaryliodonium salt

Iodonium, phenyl(2,4,6-trimethoxyphenyl)-, 4-methylbenzenesulfonate (4a) [936326-60-2**]**



The procedure is based on a method from the literature.[63] To a 50 mL round bottom flask: were aryl iodide (5 mmol, 1 eq.), acetonitrile (5 mL) and a magnetic stirring bar added. Then were toluensulfonic acid (5.05 mmol, 1.01 eq.) and m-CPBA (5.05, 1.01 eq.) added sequentially. The mixture was then refluxed for 30 min at 77 ºC. The mixture changed color to a yellow solution with a white sediment. 1,3,5-Trimethoxybenzene (5.05 mmol, 1.01 eq.) was then added and the reaction was refluxed for 5 more minutes. This induced a strong pink color. After the reaction ended was the mixture concentrated under vacuum and triturated with ethyl acetate. At last was the product vacuum filtrated and washed with ethyl acetate and dried further under high vacuum. 1.8185 g (3.35 mmol, 67 %) of desired product were isolated.

^{1}H NMR (600 MHz, DMSO-d6): δ 7.91 (dd, 2H, *J* = 1.12, 8.05 Hz), 7.60 (t, 1H, *J* = 7.43 Hz), 7.49-7.45 (m, 4H), 7.10 (d, 2H, *J* = 7.79 Hz), 6.47 (s, 2H), 3.94 (s, 6H), 3.87 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d6): δ 166.2 (s, 1C), 159.4 (s, 1C), 145.8 (s, 1C), 137.5 (s, 1C), 134.3 (s, 1C), 131.6 (s, 1C), 131.5 (s, 1C), 128.0 (s, 1C), 125.5 (s, 1C), 116.1 (s, 1C), 92.1 (s, 1C), 87.0 (s, 1C), 57.3 (s, 1C), 56.2 (s, 1C), 20.8 (s, 1C).

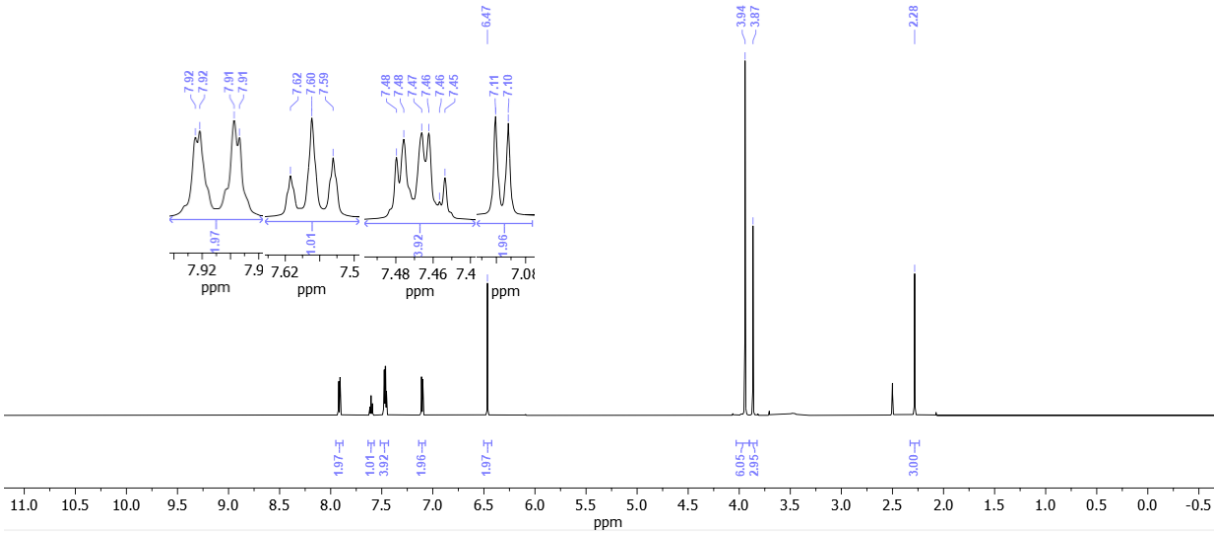
MS (EI), m/z (%): 294.0/295.1 (72/8), 137.1 (100), 122.1 (64), 79.1 (50), 69.1 (70), 50.2 (70).

HRMS (ESI) m/z [M + Na]$^{+}$: Calculated for $C_{15}H_{16}IO_3$: 371.0139, Found: 371.0138

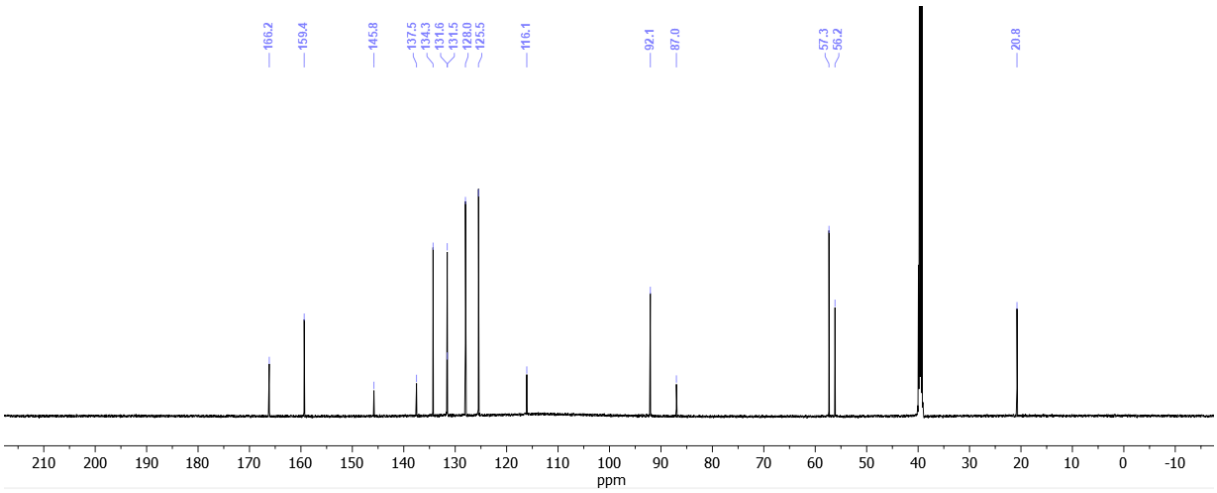
FT-IR (neat, V_{max} 1/cm): 158.55, 1413.75, 1411.82, 1344.32, 1174.59, 1116.73

Melting point: 176-179 °C

^{1}H NMR (600 MHz, $CDCl_3$-d_6) of compound 4a.



^{13}C NMR (151 MHz, $CDCl_3$-d_6) of compound 4a.



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6 HSE

INTRODUCTION/PURPOSE

The purpose of this SOP is to describe in detail the handling of potassium cyanide for use in small scale organic synthesis experiments.

responsibilities and SAFETY

The general responsibility for HSE at the Department of Chemistry lies with the Head of the Department. However, the room responsible person must have control and knowledge of all ongoing activities that take place in space, ensure that activities follow established procedures, and provide adequate labelling of laboratory chemicals. For more details on responsibility, see KI's HSE manual.

See the general UiO procedure Risk management policy in laboratories for an overview of responsibilities at UiO.

General laboratory safety applies. For more information, see KI's HSE manual.

NECESSARY SAFETY EQUIPMENT




Fume

Chemical and Biological Hazard

4.1 Chemicals

Potassium cyanide (KCN)

M3148 from Sigma Aldrich (MSDS)

CAS no: 151-50-8

H290: May be corrosive to metals

H300 + H310 + H330: Fatal if swallowed, in contact with skin or if inhaled.

H372: Causes damage to organs (thyroid) through prolonged or repeated exposure.

H410 Very toxic to aquatic life with long lasting effects.

P262: Do not get in eyes, on skin, or on clothing.

P273: Avoid release to the environment.

P280: Wear protective gloves/ eye protection.

P30 1+ P310 + P330: IF SWALLOWED: Immediately call a POISON CENTER or doctor/ physician. Rinse mouth.

P302 + P352 + P310: IF ON SKIN: Wash with plenty of water. Immediately call a POISON CENTER/doctor.

P304 + P340 + P310: IF INHALED: remove person to fresh air keep comfortable for breathing. Immediately call a POISON CENTER/doctor.

EUH032: Contact with acids liberates very toxic gas.

Special cautions necessary due to reproductive toxicity

Generally, because of cyanides toxicity, it is not recommended to work with it if you are pregnant.

PROCEDURES: Description of procedure

Necessary equipment:

Pipettes

Spatulas

Syringe

Weight

25 mL Round-bottom flask

Stirring bar

Heating block

Thermometer

Condenser

Buchner funnel

Erlenmeyer flask

filterpaper

Separatory funnel

funnel

Cyanide waste bin

Cyanide destruction bath

pH-paper

Destructed cyanide liquid waste container

General Procedure:

This procedure is based on the procedure from a microwave assisted synthesis,[1] although it is performed with thermic heating.

1. In a 25 mL round bottom flask, a cyclic ketone (2 mmol) is mixed with a solution of methanol and water (1:1, 3 mL total) with a stirring bar.
2. To the same flask, ammonium carbonate (6 mmol, 3 eq.) and potassium cyanide (3 mmol 1.5 eq.) is sequentially added.
3. The mixture is then refluxed at 50-70 °C.
4. The reaction is monitored by TLC to check conversion. The mixture is then cooled to room temperature when reaction is complete.
5. The precipitate is isolated by suction filtration, and then washed with water (3 x 2 mL).
6. In those cases where no precipitate is observed the product is isolated by extraction with ethyl acetate (3 x 3 mL) and dried with magnesium sulfate, before it is concentrated with evaporation and vacuum.

RISK ASSESSMENT

The likelihood is assessed by assuming the user following the precautions stated in the step-by-step risk assessment (SJA) below.

Risk assessment; step by step

Part of procedure		**Unwanted scenarios**	**Precautions**	**Emergency planning**	**S*K**
Step	Same points as in the procedure	What can go wrong?	What can be done to prevent.	What precautions are in place to minimize the consequences in the event of an incident	
1	Mixing cyclic ketone with MeOH/water (1:1)	Chemical and solution can be spilled. Chemical can be inhaled Skin can be contaminated Chemical can be ingested. Chemical can get on fire. Glass equipment can break.	Read the safety data sheets for the chemicals before use. Be careful while adding solution and chemicals Work in a fume hood. Use protective gloves, glasses and lab coat. Never eat or drink in the lab. Keep away from heat, hot surfaces, sparks, open flames etc. Check the equipment for damage before use.	Cyclic ketone: Be aware of the chemicals hazards before the experiment, know how to safely tidy up the chemical. Various cyclic ketones are employed, so the SDS-information for each ketone must be assessed. Methanol: If inhaled: remove person to fresh air and keep comfortable for breathing. Call a poison center/doctor. If swallowed: immediately call a poison center/doctor	2*1
2	Adding ammonium carbonate	Chemical can be inhaled Skin can be contaminated Chemical can get in the eye. Chemical can be ingested: harmful if swallowed Chemical can be spilled	Read the safety data sheet before use. Work in a fume hood. Use protective gloves, glasses and lab coat. Never eat or drink in the lab Be careful while adding solution and chemicals	After inhalation: move exposed to fresh air. Give artificial respiration if necessary. If breathing is difficult give oxygen. Get medical assistance. After skin contact: rinse/flush exposed skin gently using soap and water for 15-20 min. søk medisinsk hjelp if discomfort or irritation persists. After eye contact: protect unexposed eye. Rinse/flush exposed eye gently using water for 15-20 min. remove contact lenses if able to do so during rinsing. Seek medical attention if irritation persists or of concerned. After swallowing: rinse mouth thoroughly. Do not induce vomiting. Have exposed individual drink sips of water. Seek medical attention iff	2*1

				irritation, discomfort or vomiting persists. Never give anything by mouth to an unconscious person.	
2	Weighing and adding potassium cyanide	Chemical can be spilled. In the fume hood. Skin can be contaminated Chemical can be inhaled Chemical can be exposed to the environment.	See precautions: cyanide, below the table.	See Emergency planning: cyanide, below at p. 6	2*3
3	Reflux	Glass equipment can break. Mixture can get spilled	Check the equipment for damage before use.	Follow the same emergency planning as for the previous steps. For spills of reaction mixture, follow spill response as outlined below.	2*3
5	Suction filtration	The mixture can be, inhaled, be ingested, get in skin contact or get in the eye.	Check the equipment for damage before use.	Follow the same emergency planning as for the previous steps. For spills of reaction mixture, follow spill response as outlined below.	2*3
6	Extraction (if necessary)	Glass equipment can break. Mixture can get spilled	Check the equipment for damage before use.	Follow the same emergency planning as for the previous steps. For spills of reaction mixture, follow spill response as outlined below.	2*3

Precautions: Cyanide

The precautions are based on the precautions from Harvard´s laboratory safety guideline for cyanide.[2]

Cyanide may generate HCN with acids or water – ensure that acids and/or non-alkaline water is never in contact with cyanide or cyanide containing solutions.

Never work alone when using cyanide. Always use the buddy system. Another lab member, a so-called "buddy" should always be present and available to assist in the event of a cyanide emergency. Both the user and "buddy" should have a thorough understanding of these guidelines, cyanide hazards, and their protocols prior to beginning work. The user notifies this buddy, and also notifies the supervisor/room responsible prior to the experiment, and after the experiment is conducted.

Before starting work:

- Review the manufacturer's Safety Data Sheet for the specific cyanide compound and additional chemical information
- Ensure that a written experimental protocol including safety information is available
- Be familiar with general University emergency procedures
- Identify the location of the nearest eyewash and shower and verify that they are accessible
- Always remove cyanide from its secondary container in a chemical fume hood to safely vent any accumulated vapor.
- Always weigh cyanide in a fume hood
- Ensure that the cyanide is handled exclusively in the fume hood – it should not be removed or transferred between rooms.
- Locate and verify that appropriate cyanide spill cleanup materials are available, including the following: 5-10 % bleach solution for destruction. A bath of bleach solution should always be available in the fume hood.
    - For liquids: polypropylene absorbent pads or equivalent
    - For solids: disposable dust pan and brush
- Post a sign in the work area (fume hood): "Danger: KCN used in this area"
- Do not work alone! Use the buddy system as described above.

Training:

- Each employee working in a lab that handles cyanide (or procedures that generate cyanide) must receive lab- specific instruction on the dangers of cyanides and be trained on:
    - Exposure routes (e.g., ingestion, inhalation, and skin absorption) and the associated short- and long-term adverse health effects;
    - Prevention of exposure (e.g., proper lab protocol, use of laboratory apparatus and chemical fume hoods, personal protective equipment);
    - Emergency evacuation procedures;
    - Recognizing cyanide exposure and poisoning;
    - Medical response procedures for a suspected cyanide exposure;
    - Buddy System requirements for work with cyanide.

During work

- AVOID INHALATION! Perform all operations in a certified chemical fume hood. Sash lowered as much as possible. Always work at least 6 inches into the fume hood;
- AVOID CONTACT! Use appropriate personal protective equipment (PPE):
    - o Wear a lab coat, long pants, shirt and closed-toed shoes.
    - o Wear double-gloved nitrile gloves.
    - o Gloves must be thoroughly inspected prior to each use. Do not use damaged gloves
    - o Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with cyanide
    - o Change gloves (outer and inner) at least once an hour and immediately whenever you suspect cyanide has contacted your gloves

- Wash hands and forearms thoroughly with soap and water each time gloves are removed.

- Always work behind fume hood sash
- Wear chemically protective goggles or safety glasses.

- Use materials and containers appropriate for cyanide use and remain aware of potential incompatibilities. Polypropylene works well.
- Keep all containers tightly closed when not in use and during transport.
- Any equipment that is in contact with KCN (such as spatulas, beakers etc) are immediately submerged in the bleach bath for destruction after use.

After completing the work:

- The equipment that has been in contact with cyanide is submerged in the destruction bath with bleach overnight. Thereafter all the equipment shall be washed with water, then acetone.
    - Always check the pH-value of the destruction bath before and after destruction. The pH must be over 10.
- Store all equipment that usually is in contact with cyanide in an appropriate container, well-marked "Cyanide equipment"
- Solid cyanide waste is disposed in a separate waste bin well marked "Cyanide waste"
- Destruction bath and other liquid cyanide waste is to be disposed in a separate waste container well marked "Destructed cyanide solution"

Emergency planning

The emergency planning is based on the emergency planning from Harvard's laboratory safety guideline for cyanide.[2]

Contact cyanide "buddy", supervisor and HSE administrator for the institute of chemistry and explain the situation. Leave the room where the cyanide spill has happened. Await instructions on how to proceed.

If anyone suspects cyanide or HCN exposure, or shows signs of cyanide poisoning, immediately call 113: specify that there has been an incident of cyanide exposure.

- Seek immediate medical attention in the event of a cyanide exposure.
- When EMS arrives, notify them what actions have been taken so they can continue with proper first aid administration.

Early or Mild Cyanide Poisoning may be indicated by general weakness, heaviness of the arms and legs, difficulty breathing, headache, giddiness, nausea, vomiting, irritation of the nose, mouth, and throat.

Severe Cyanide Poisoning may be indicated by nausea, cyanosis, gasping for breath, unconsciousness or convulsions.

First Aid

SKIN CONTACT: Wash with plenty of soap and water for at least 15 minutes. Will pass through unbroken skin. Exposures can be fatal. Remove any exposed clothing as well as any jewelry that may be trapping cyanide.

EYE CONTACT: Using eyewash, flush eyes while holding eyelids open. Continue flushing eyes with water until emergency medical personnel arrive.

INHALATION: If cyanide is inhaled, immediately move to get fresh air

INGESTION: Do not induce vomiting. Never give anything by mouth to an unconscious person

Spill response

IMPORTANT! DO NOT USE PLAIN WATER TO CLEAN UP A CYANIDE SPILL. WATER REACTS WITH CYANIDE COMPOUNDS TO FORM HIGHLY TOXIC HYDROGEN CYANIDE GAS.

OUTSIDE FUME HOOD OR VENTILATED ENCLOSURE

- Alert others and evacuate to a safe distance and prevent entry.
- Contact cyanide "buddy", supervisor and EHS administrator
- Remain in a safe location until EHS or other response personnel arrive.

INSIDE FUME HOOD OR VENTILATED ENCLOSURE (< 500 ml)

- Contact cyanide "buddy", supervisor and EHS administrator
- If trained and confident, you may assist in the clean-up effort of small amounts, wearing PPE described above and using appropriate spill supplies.
    - If solid, use dustpan and brush to collect materials. If solution, apply polypropylene absorbent pads as described above.
    - Dispose all material that is contaminated with cyanide in the cyanide waste bin.
    - Wipe area with dilute bleach or hydroxide solution and place this cleanup material in the cyanide waste bin.
- Otherwise close the fume hood sash and await support.

Overall risk assessment for this SOP

Risk categories

- Red: S*K=10-25 the overall risk is an unacceptable risk. New precautions to reduce the risk should be established.
- Yellow: S*K=4-9 the overall risk is medium. New precautions to reduce the risk should be considered.
- Green: S*K=1-4 the overall risk is fully acceptable - minimal risk.

If S*K of the step-by-step risk assessment falls into different categories (as listed above), the overall risk is set to the highest S*K value.

When following this SOP, there is MEDIUM risk associated with this procedure, as the highest S*K values equal to 6.

WASTE DISPOSAL

Waste type	Approx volume	Disposal method	Environmental risk
Contaminated gloves and used disposable equipment	-	Dispose in hazardous waste box.	None, since this is according to procedure and handled by trained staff and collected by professionals.
Quenched solution / waste	50mL	Pour into 50mL falcon or other appropriate container,labelled “Alkaline waste – quenched cyanide” Leave in fume hood to evaporate.	None, since this is according to procedure and handled by trained staff and collected by professionals.
Non-hazardous chemical leftovers	50mL	Pour into 50mL falcon or other appropriate container and dispose in hazardous waste box.	None, since this is according to procedure and handled by trained staff and collected by professionals

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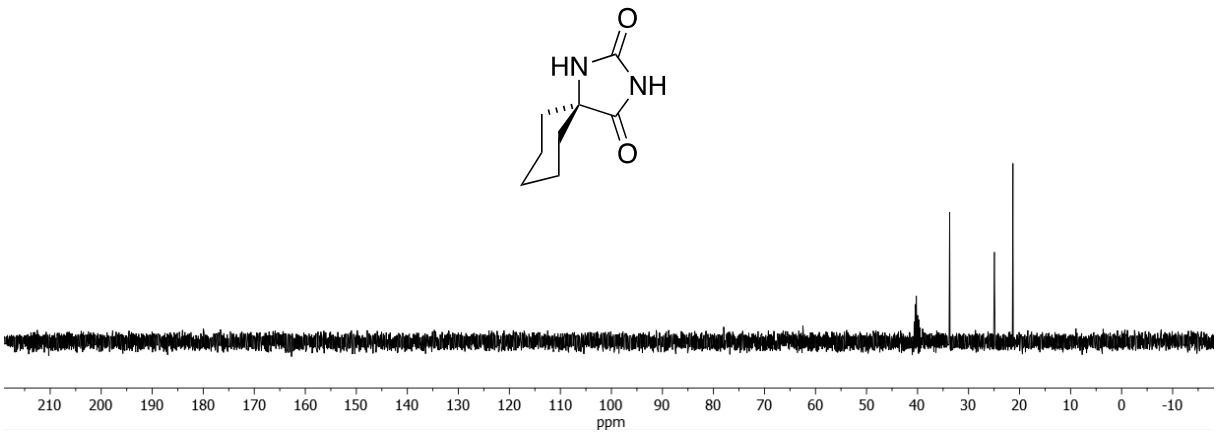
7 Appendix

This section will contain supplementary spectrum for documentation of isolated structures and spectrum used in the discussion.

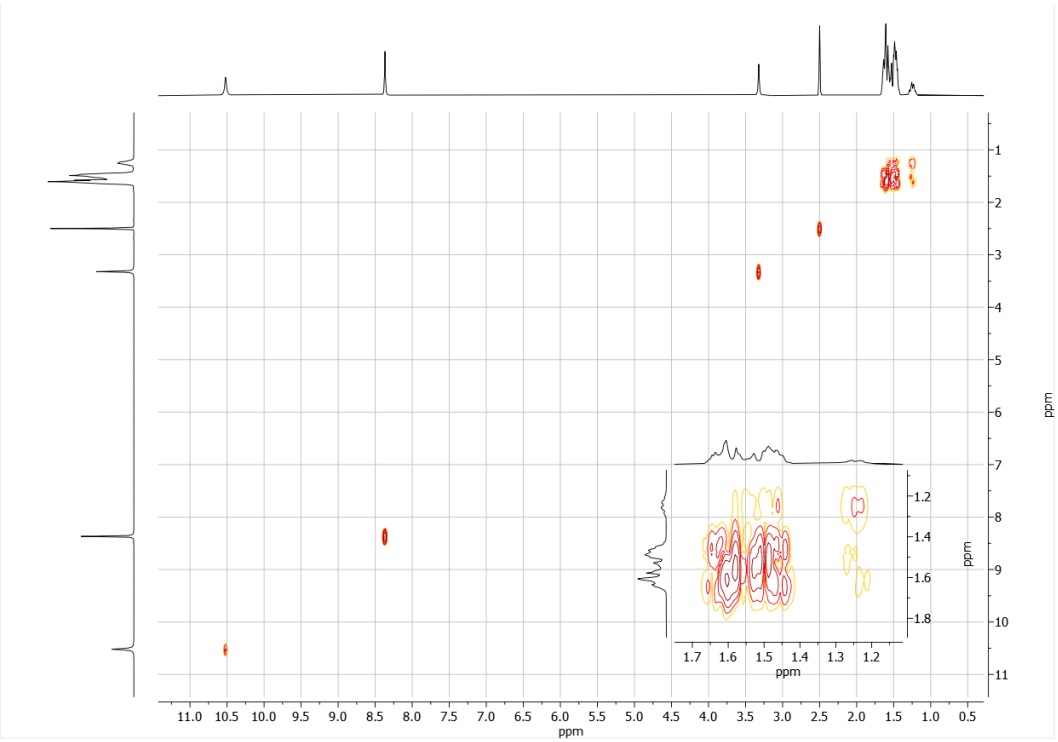
7.1 Spirohydantoins

1,3-diazaspiro[4.5]decane-2,4-dione (2a) [CAS: 702-62-5**]**

DEPT45 (151 MHz, DMSO-d_6) spectrum of 2a.



COSY (600 MHz, DMSO-d_6) spectrum of 2a.



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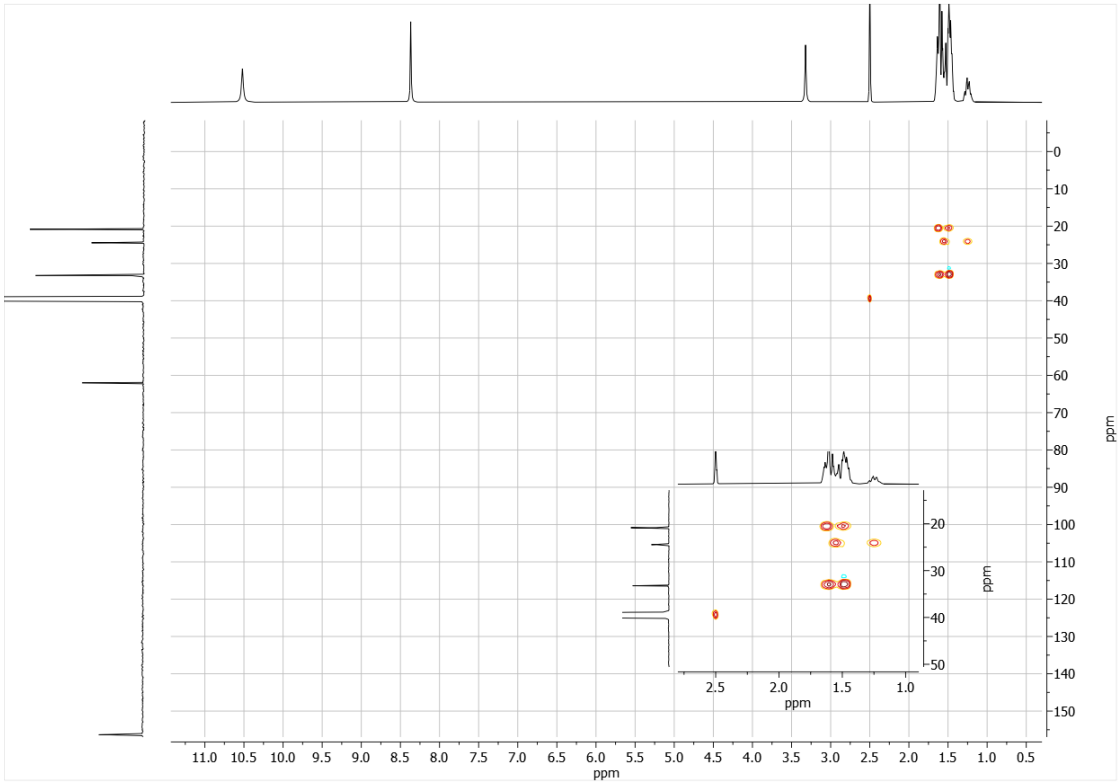
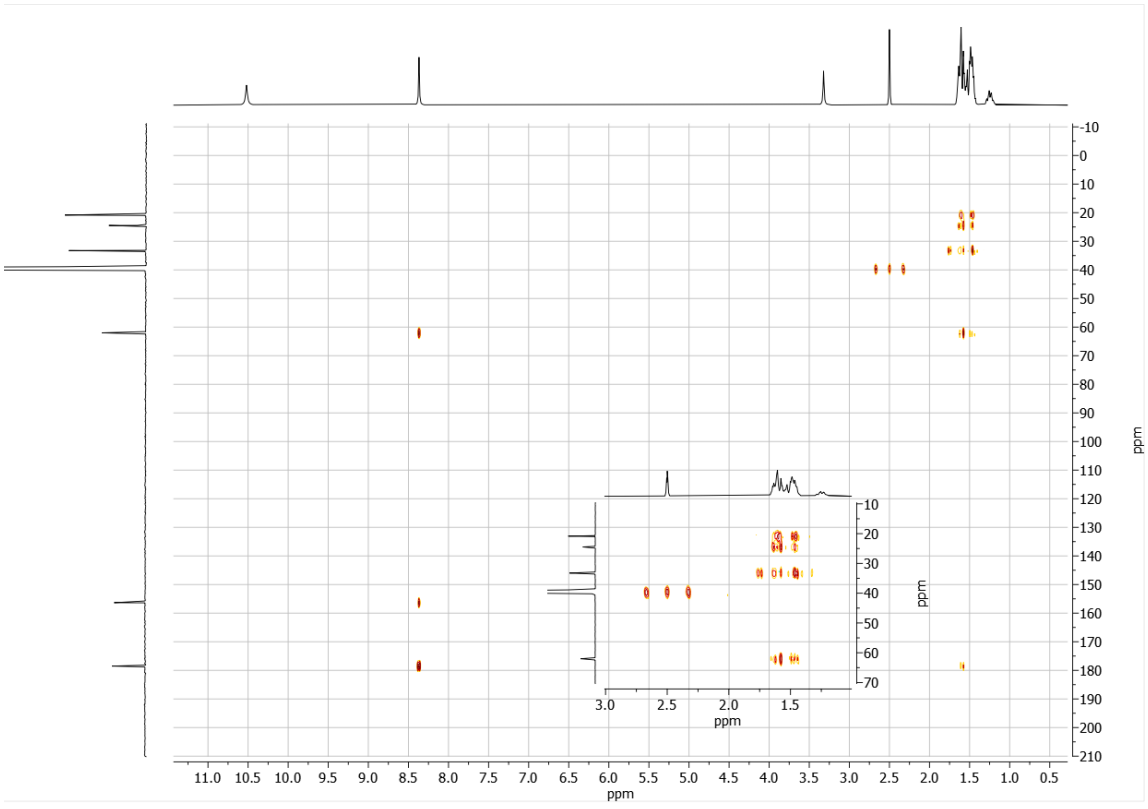
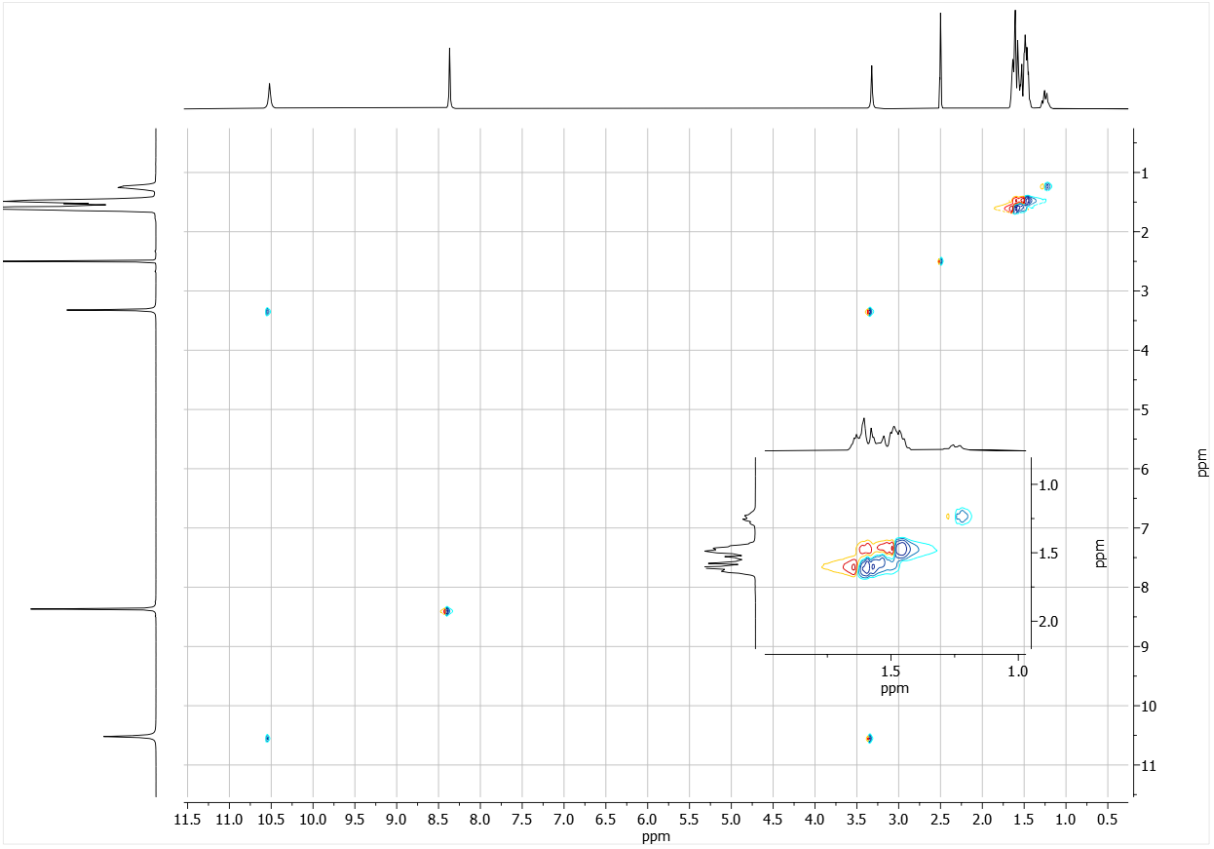


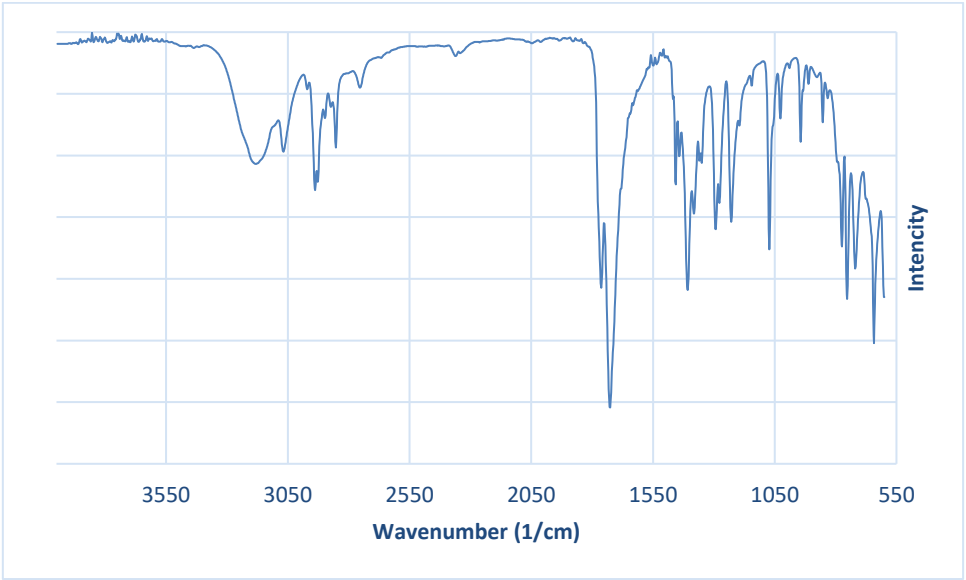
HMBC (600 MHz, DMSO-d_6) spectrum of 2a



NOESY (600 MHz, DMSO-d_6) spectrum of 2a

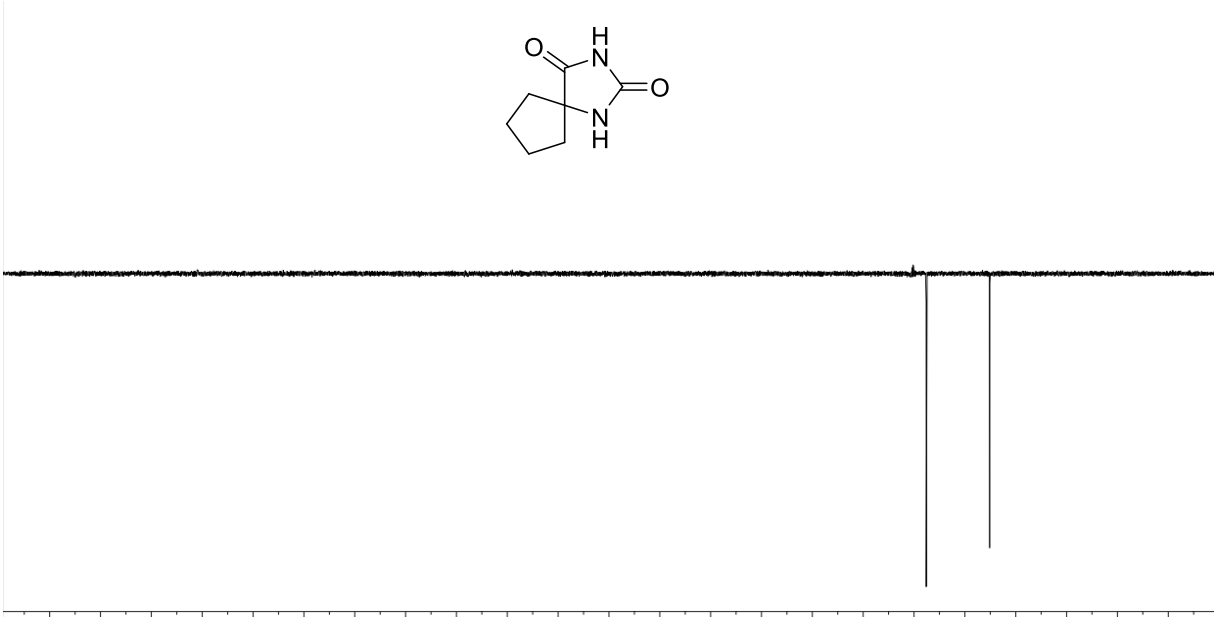


IR spectrum of 2a

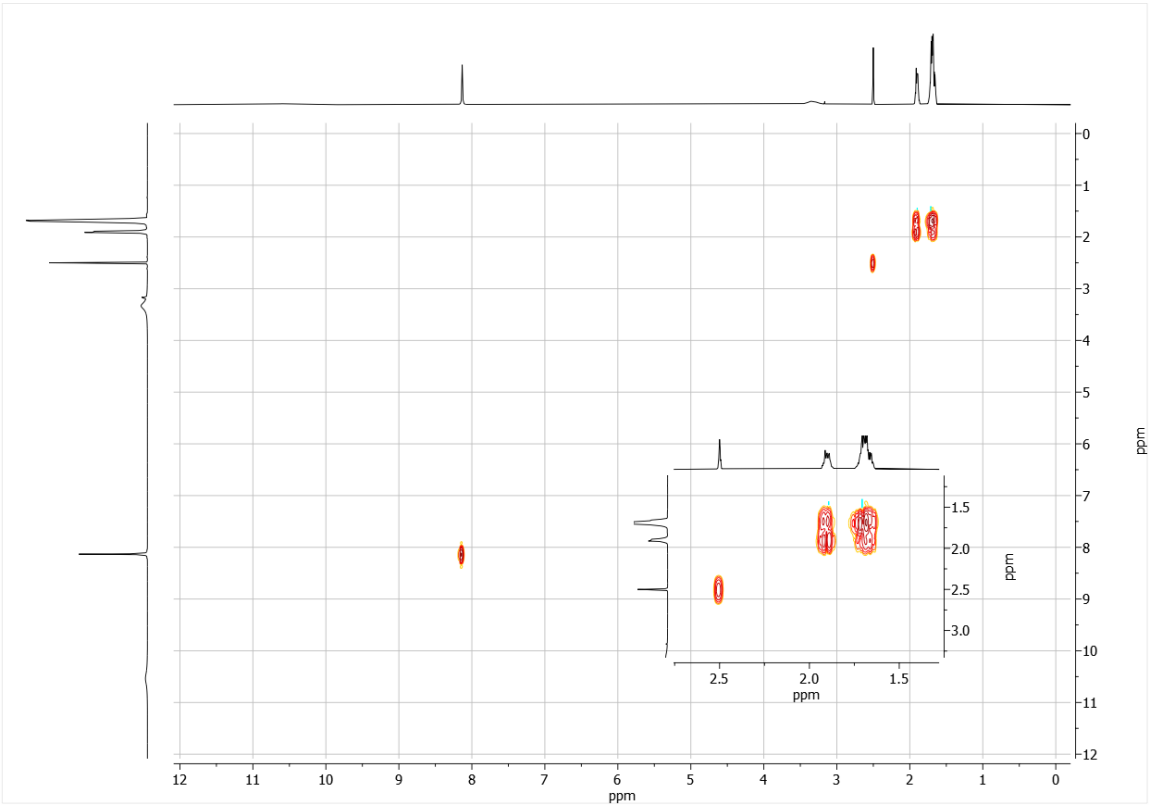


1,3-diazaspiro[4.4]nonane-2,4-dione (2b) [699-51-4]

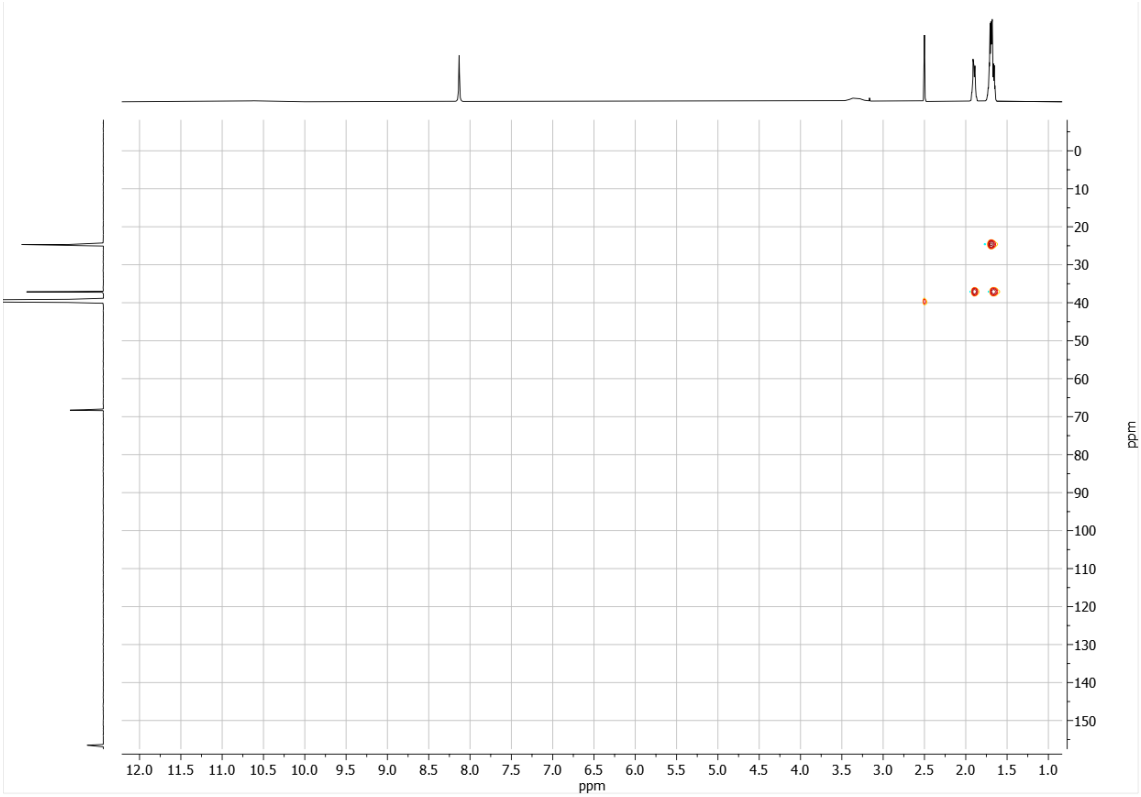
DEPT135 (151 Mhz, DMSO-d_6) spectrum of 2b.



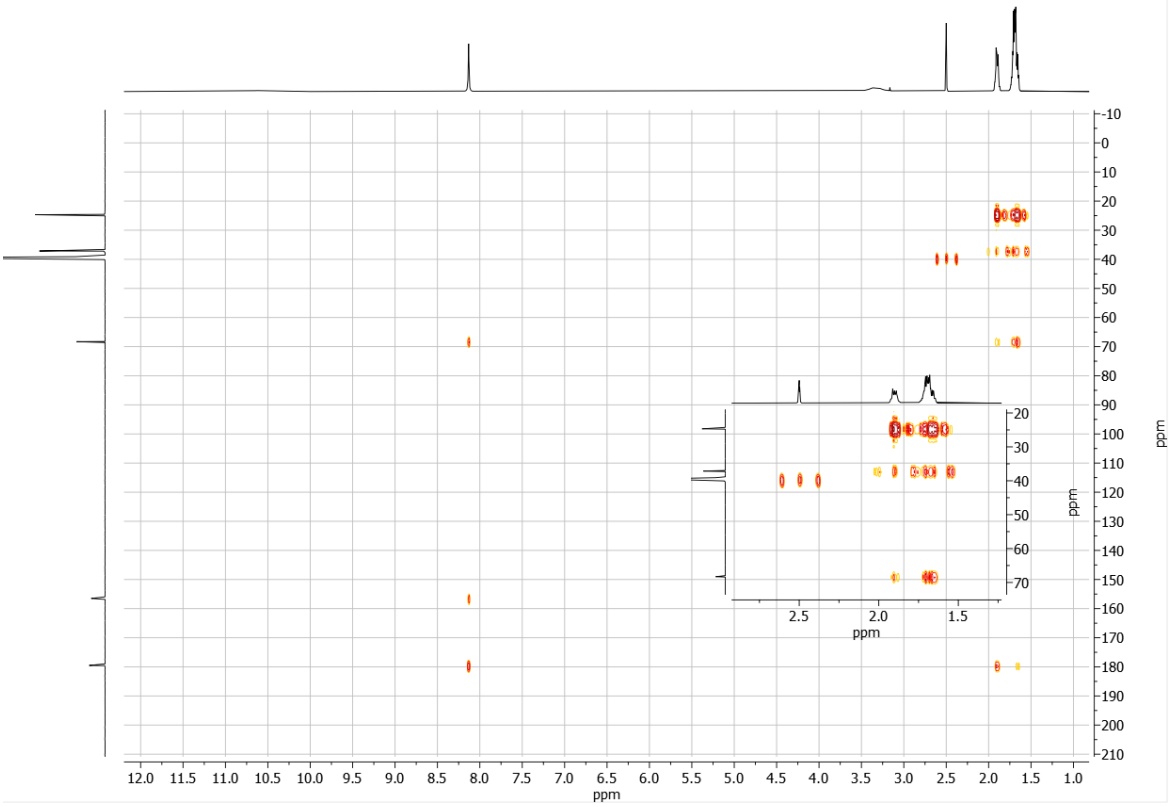
COSY (600 MHz, DMSO-d_6) spectrum of 2b



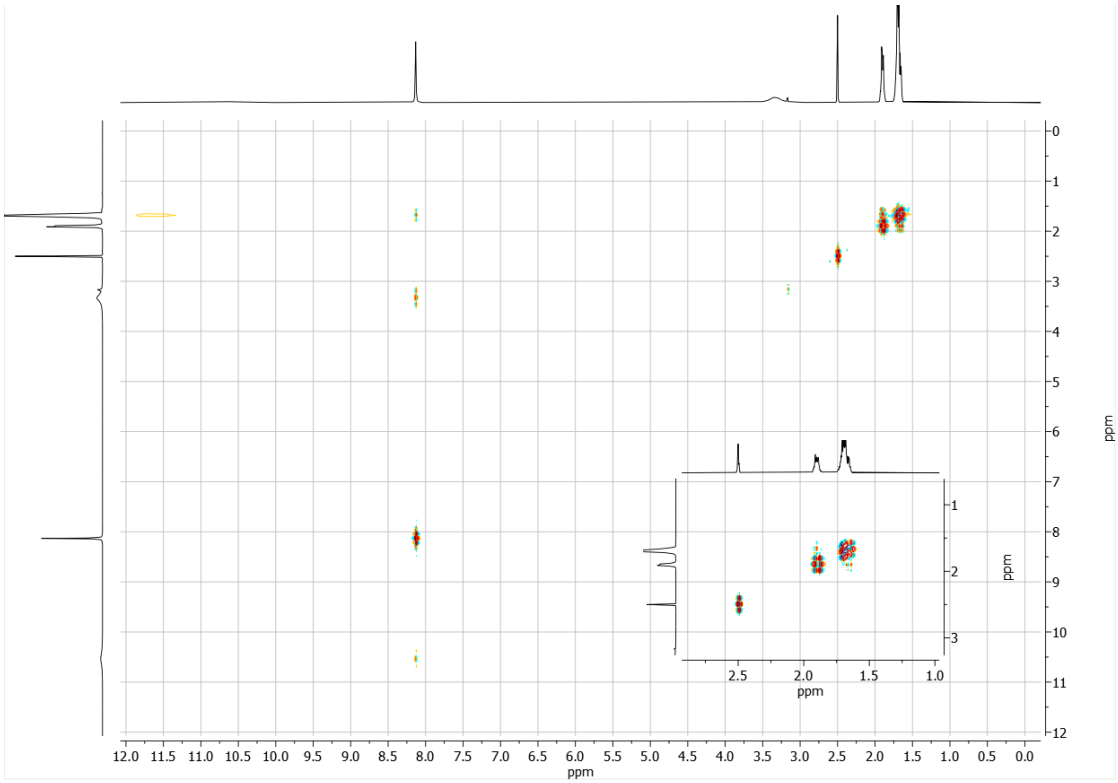
HSQC (600 MHz, DMSO-d_6) spectrum of 2b



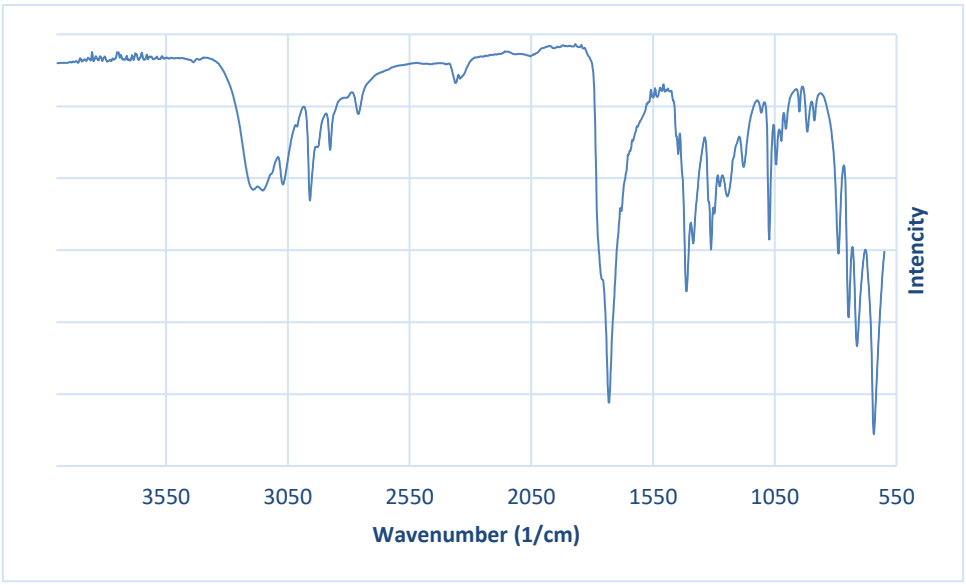
HMBC (600 MHz, DMSO-d_6) spectrum of 2b



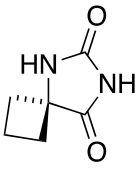
NOESY (600 MHz, DMSO-d_6) spectrum of 2b.



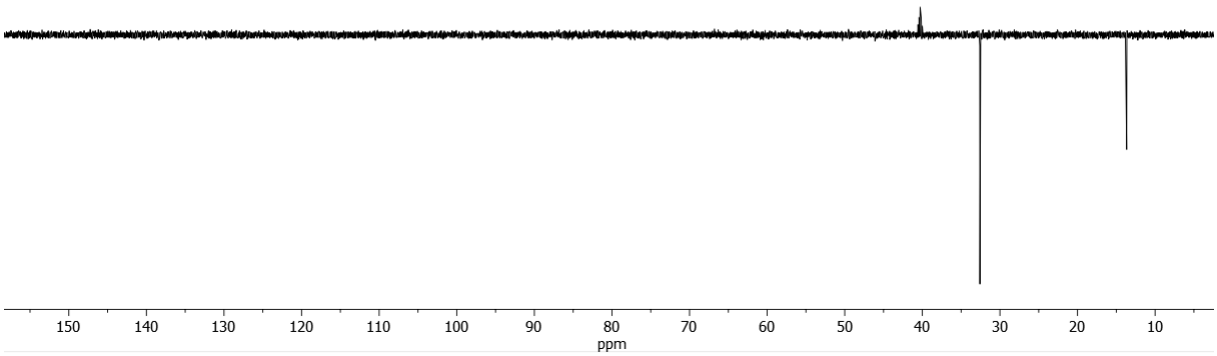
IR spectrum of 2b.



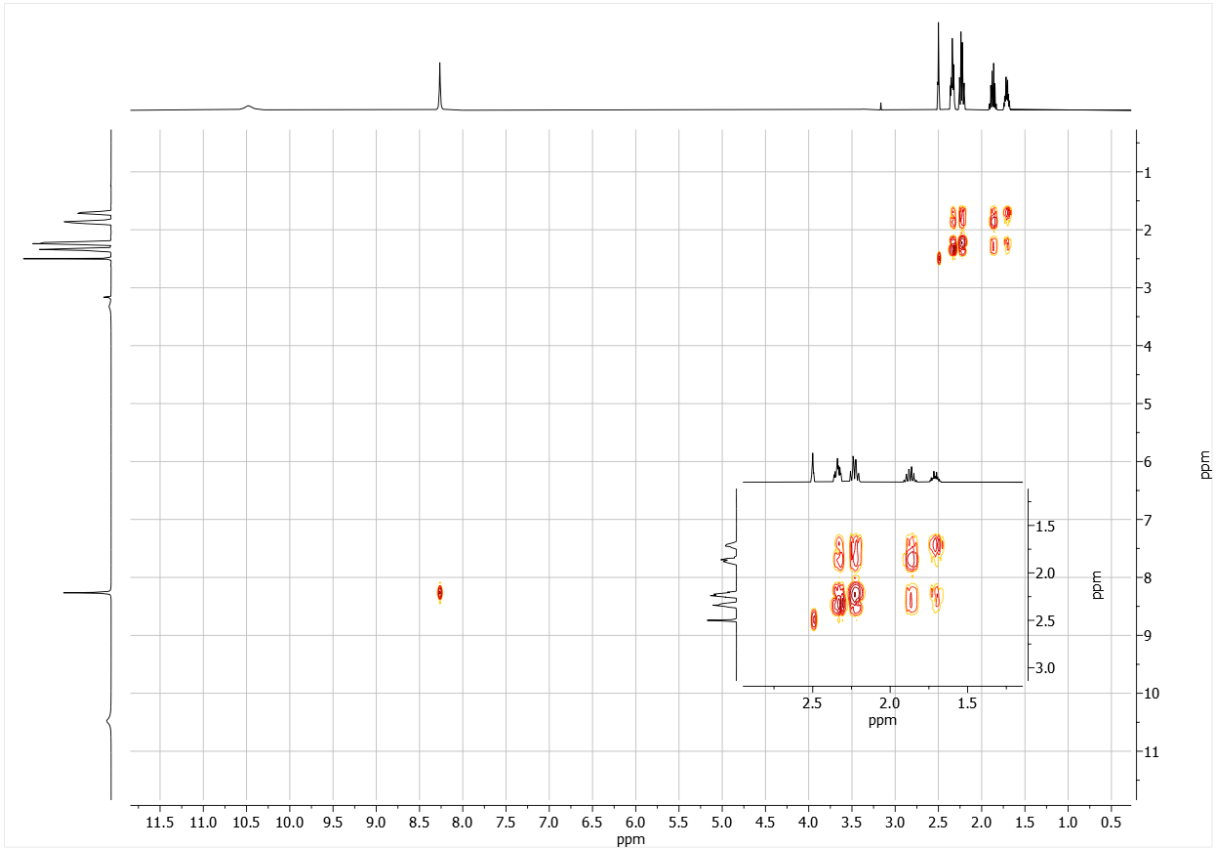
5,7-Diazaspiro[3.4]octane-6,8-dione(2c) [CAS: 89691-88-3]



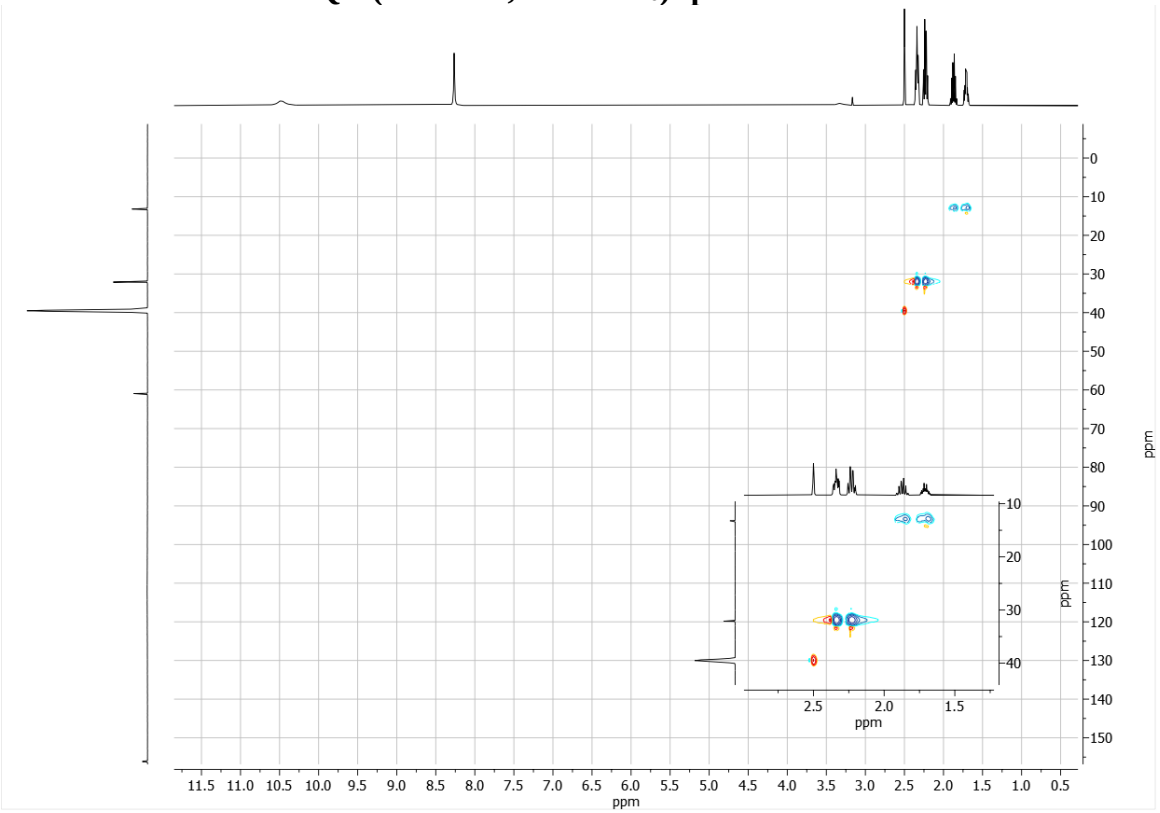
DEPT135 (151 Mhz, DMSO-d$_6$) spectrum of 2c.



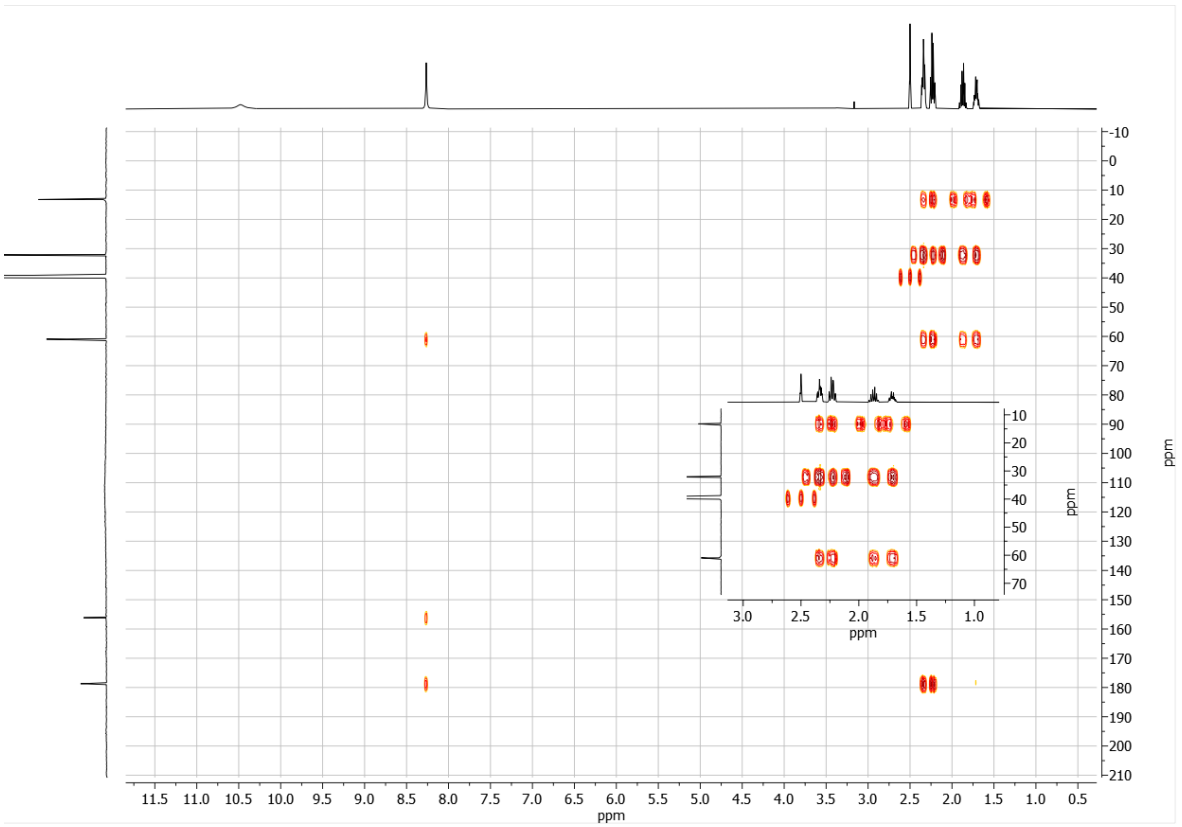
COSY (600 MHz, DMSO-d$_6$) spectrum of 2c.



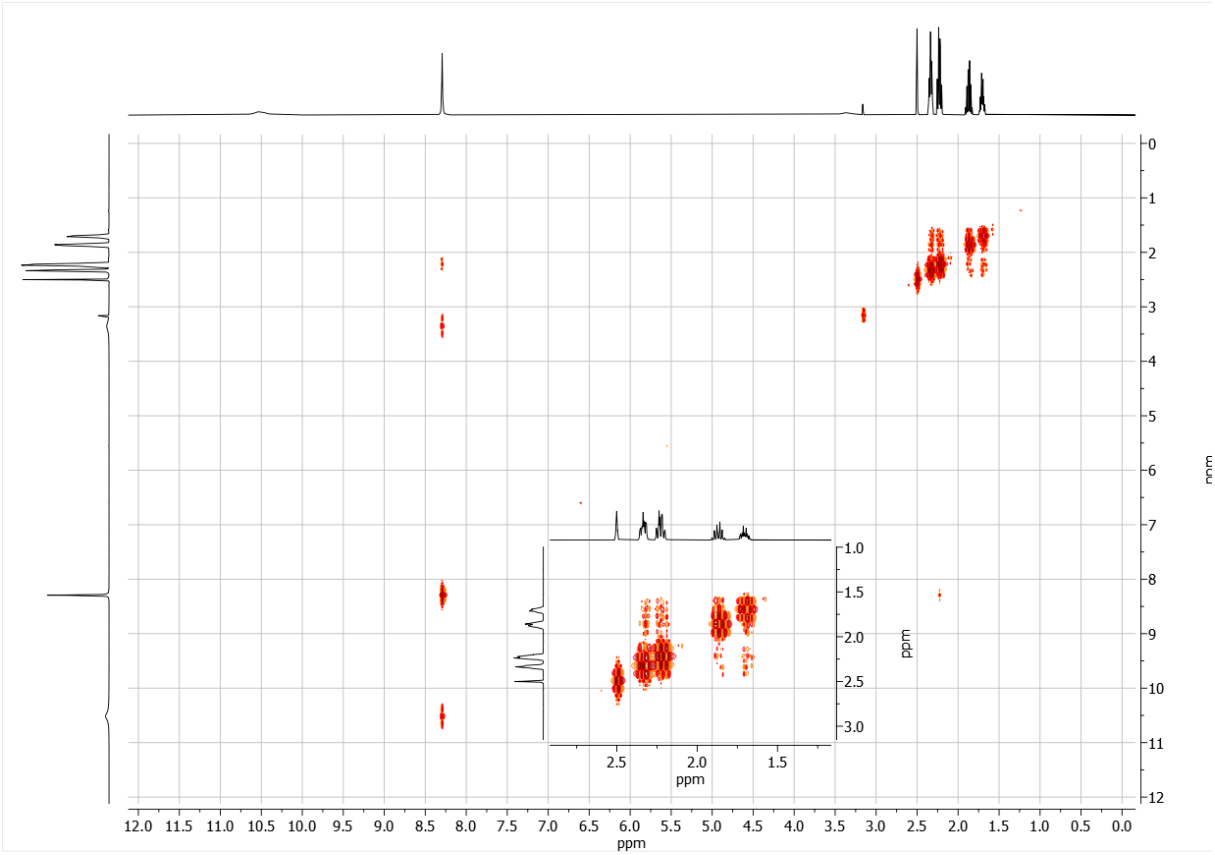
HSQC (600 MHz, DMSO-d_6) spectrum of 2c.



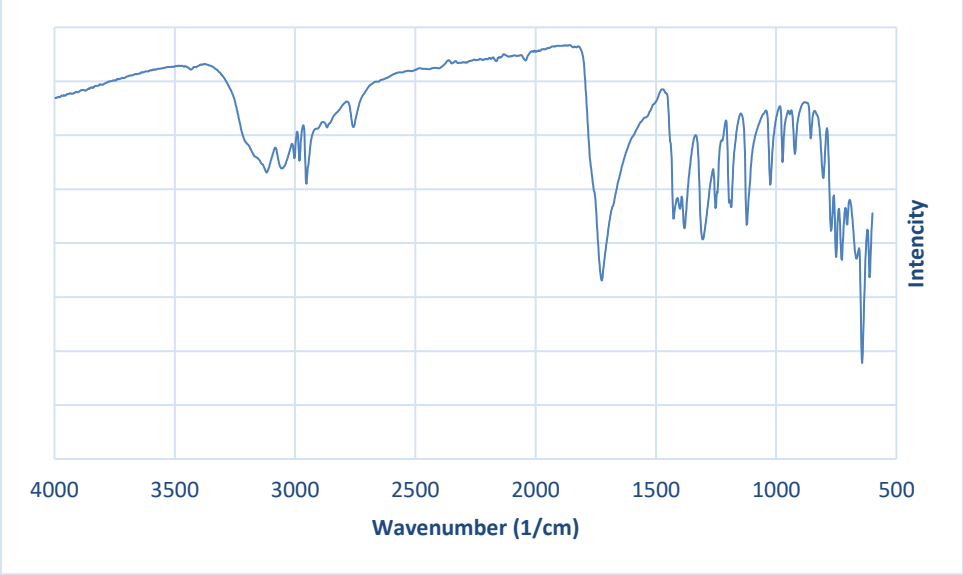
HMBC (600 MHz, DMSO-d_6) spectrum of 2c.



NOESY (600 MHz, DMSO-d_6) spectrum of 2c.

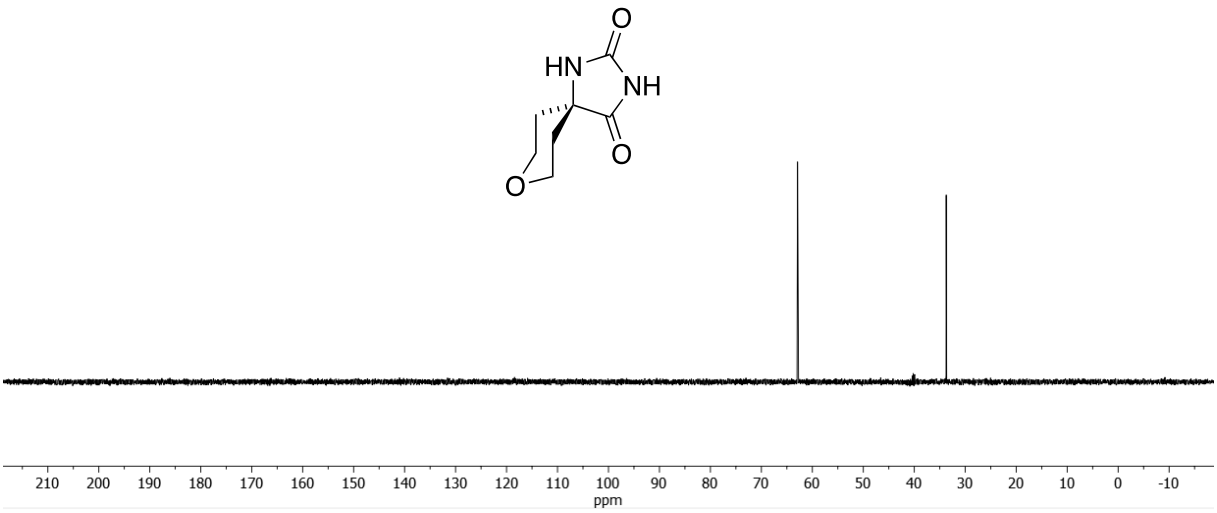


IR spectrum of 2c.

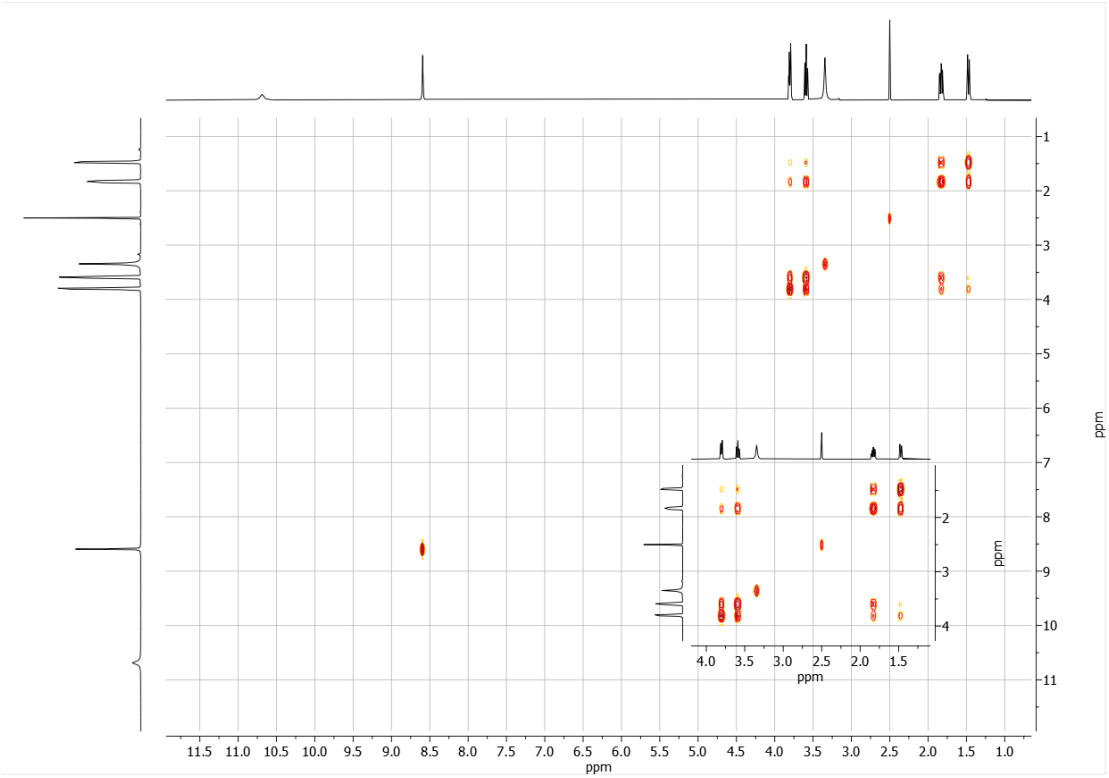


8-Oxa-1,3-diazaspiro[4.5]decane-2,4-dione(2d) [CAS: 39124-19-1**]**

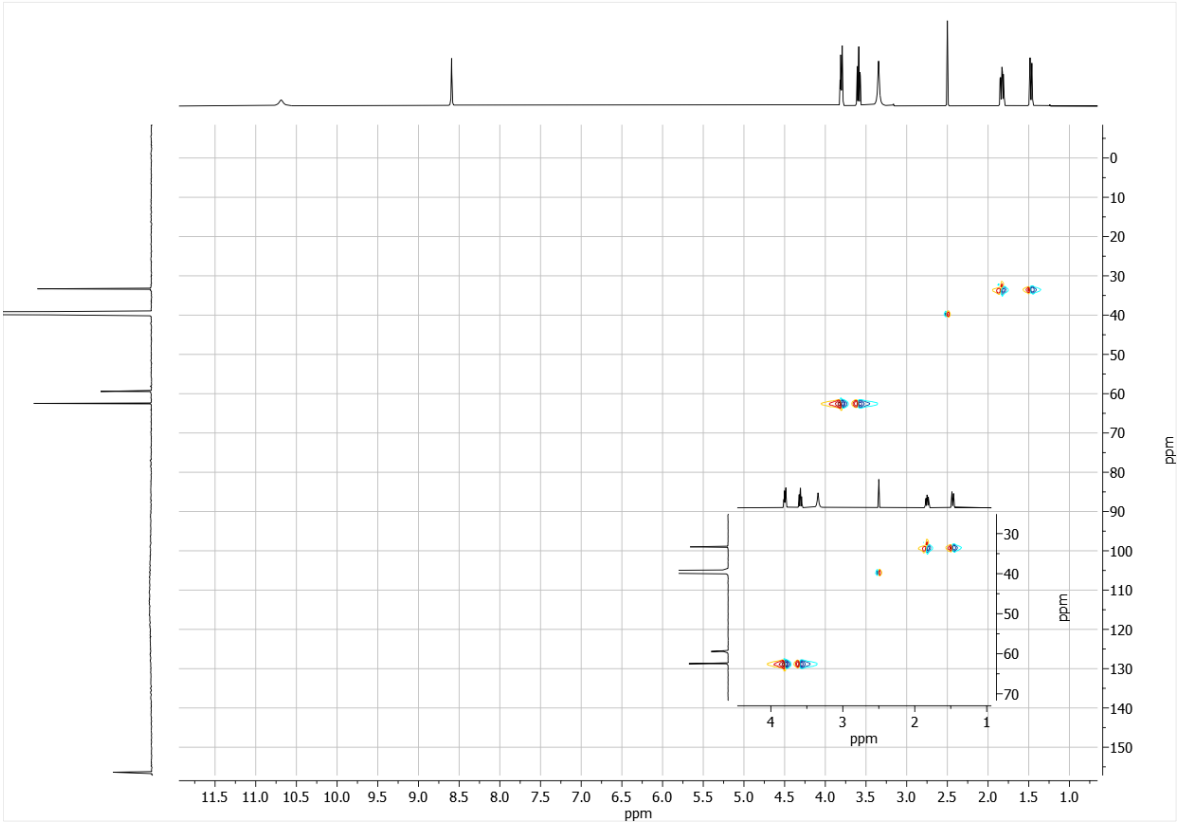
DEPT45 (151 Mhz, DMSO-d_6) spectrum of 2d.



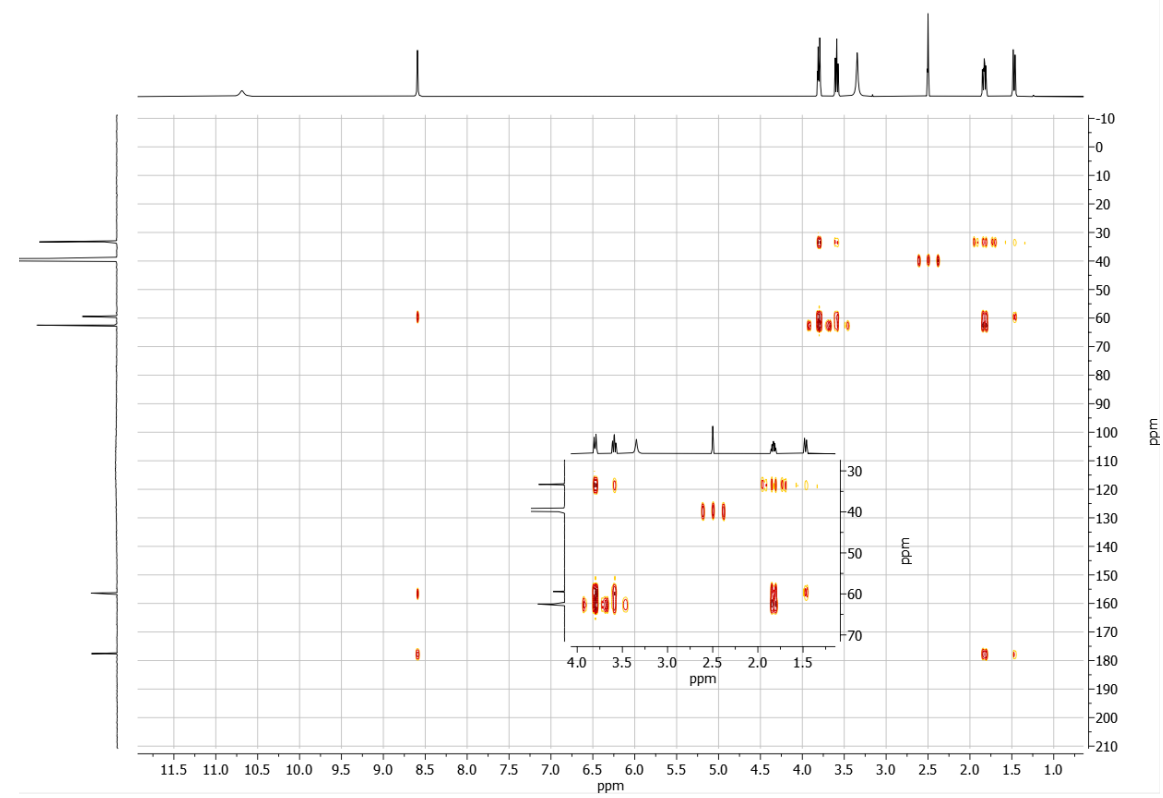
COSY (600 MHz, DMSO-d_6) spectrum of 2d.



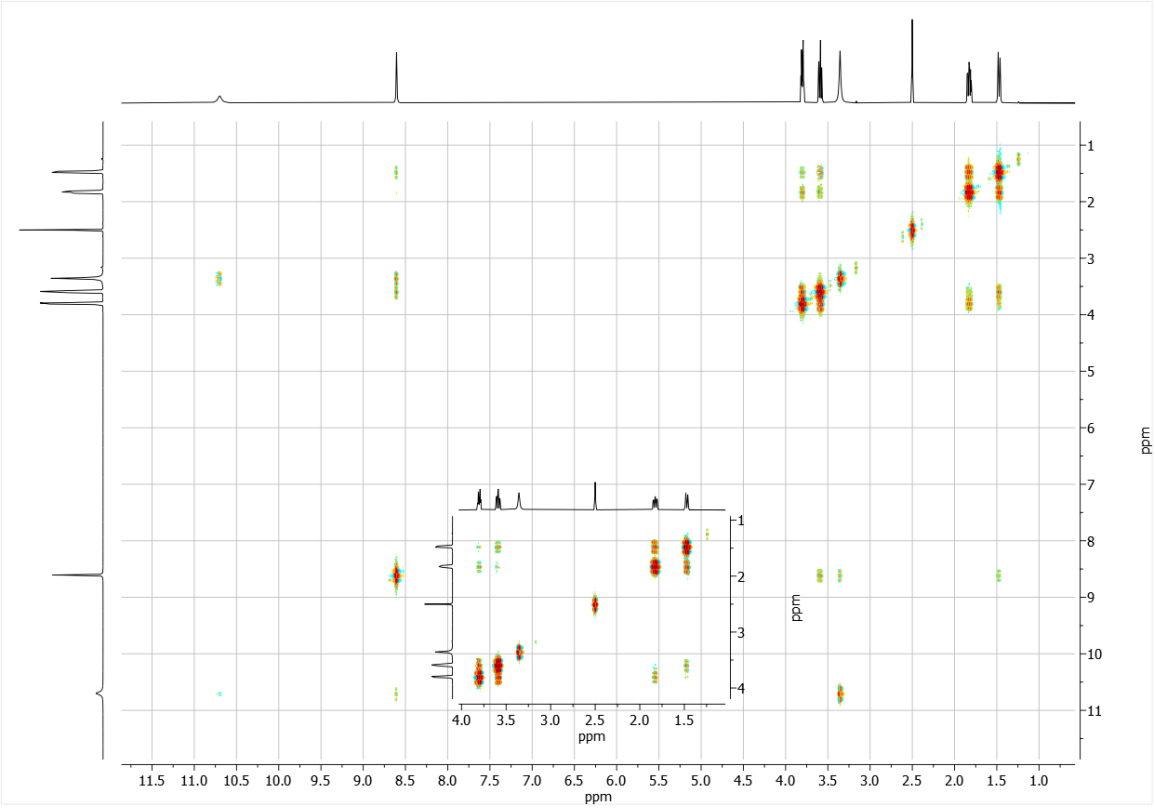
HSQC (600 MHz, DMSO-d_6) spectrum of 2d.



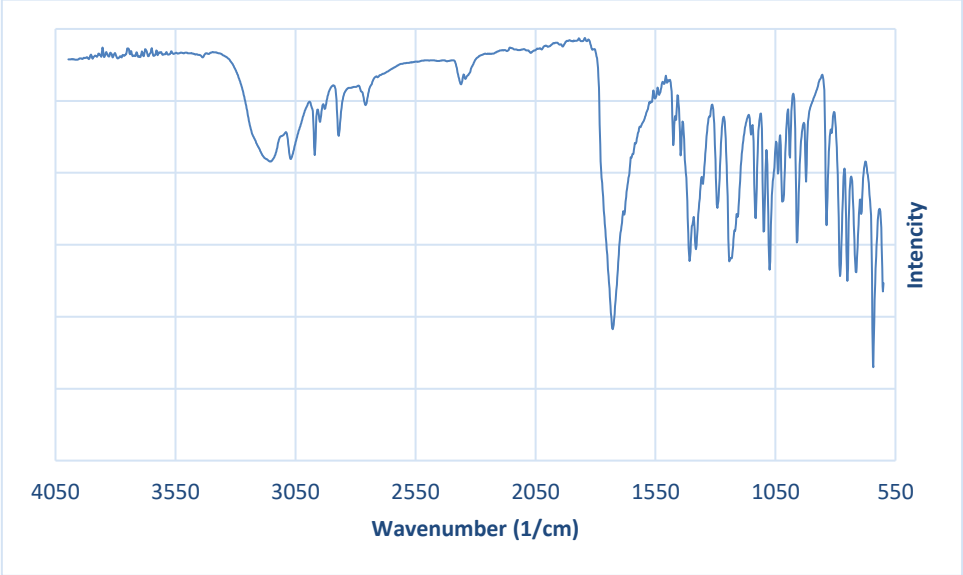
HMBC (600 MHz, DMSO-d_6) spectrum of 2d.



NOESY (600 MHz, DMSO-d_6) spectrum of 2d.

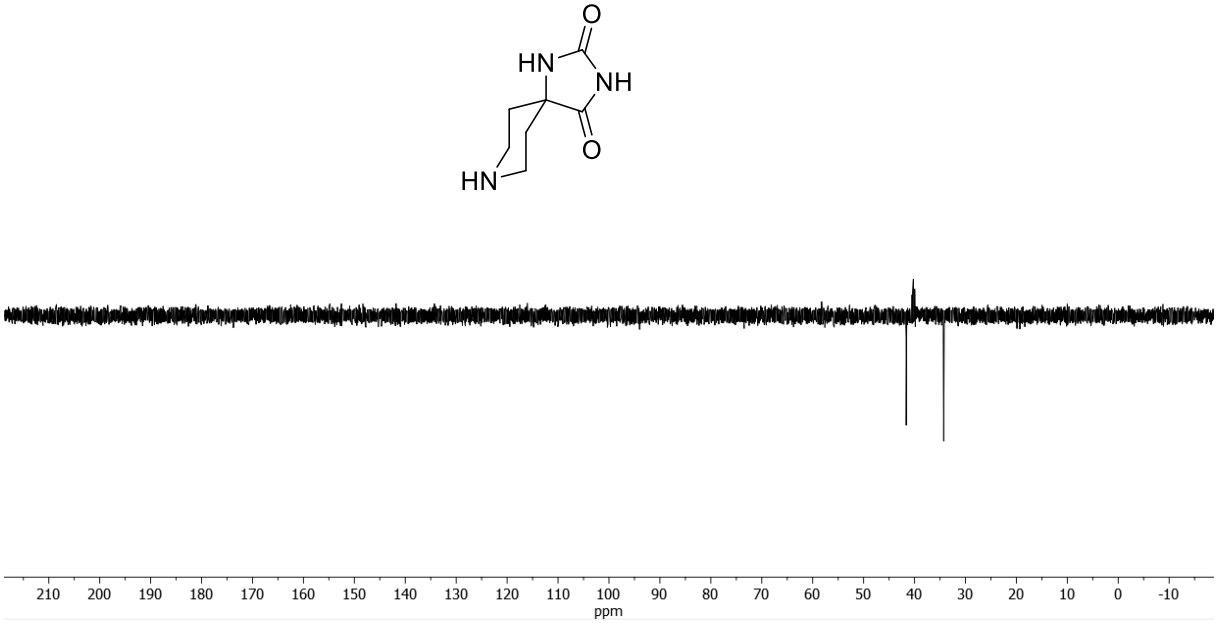


IR spectrum of 2d.

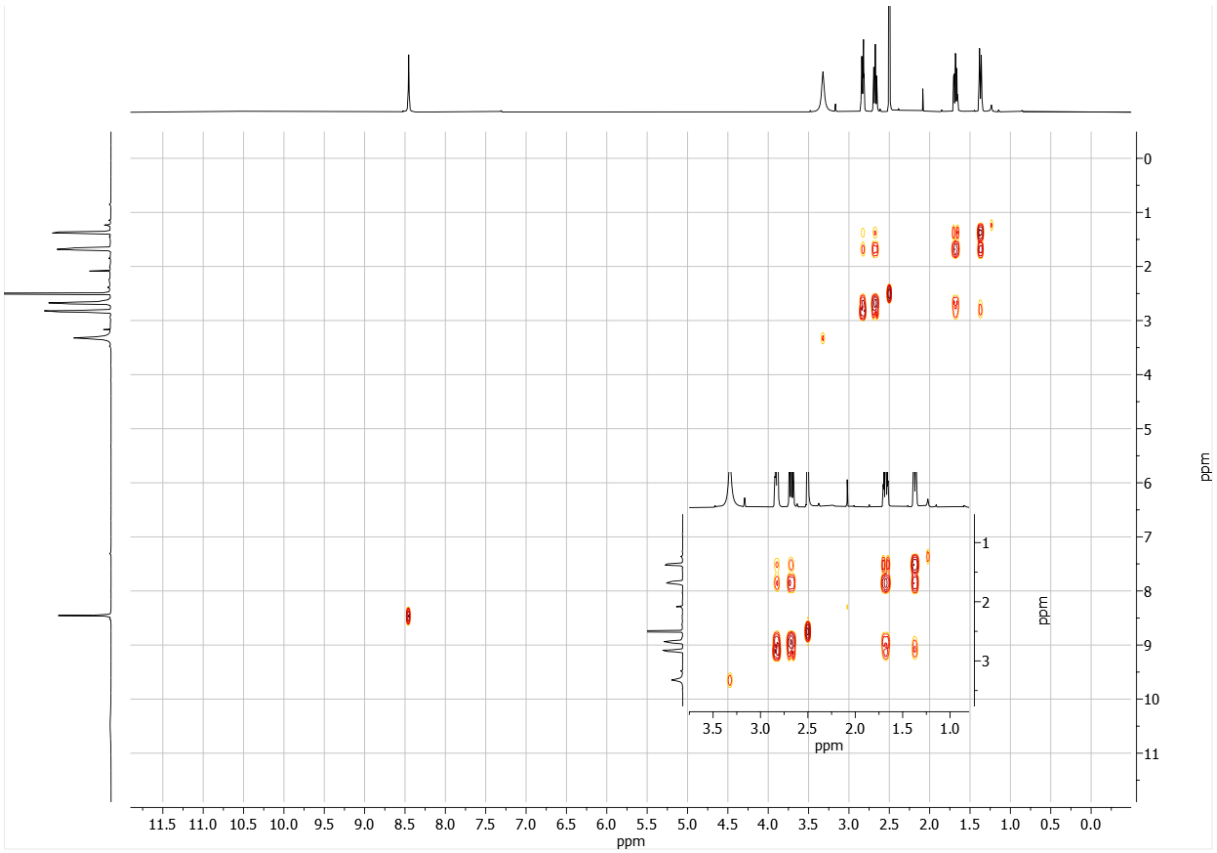


1,3,8-triazaspiro[4.5]decane-2,4-dione (2f) [13624-39-3]

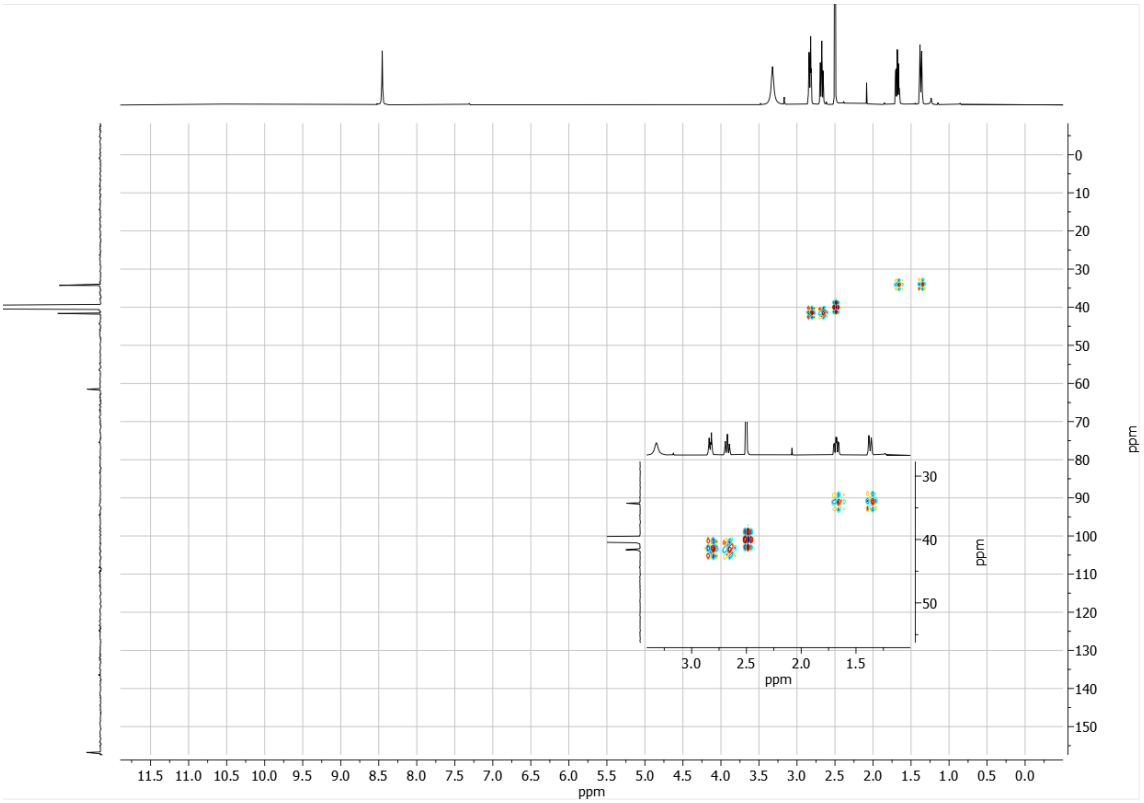
DEPT135 (151 Mhz, DMSO-d_6) spectrum of 2f.



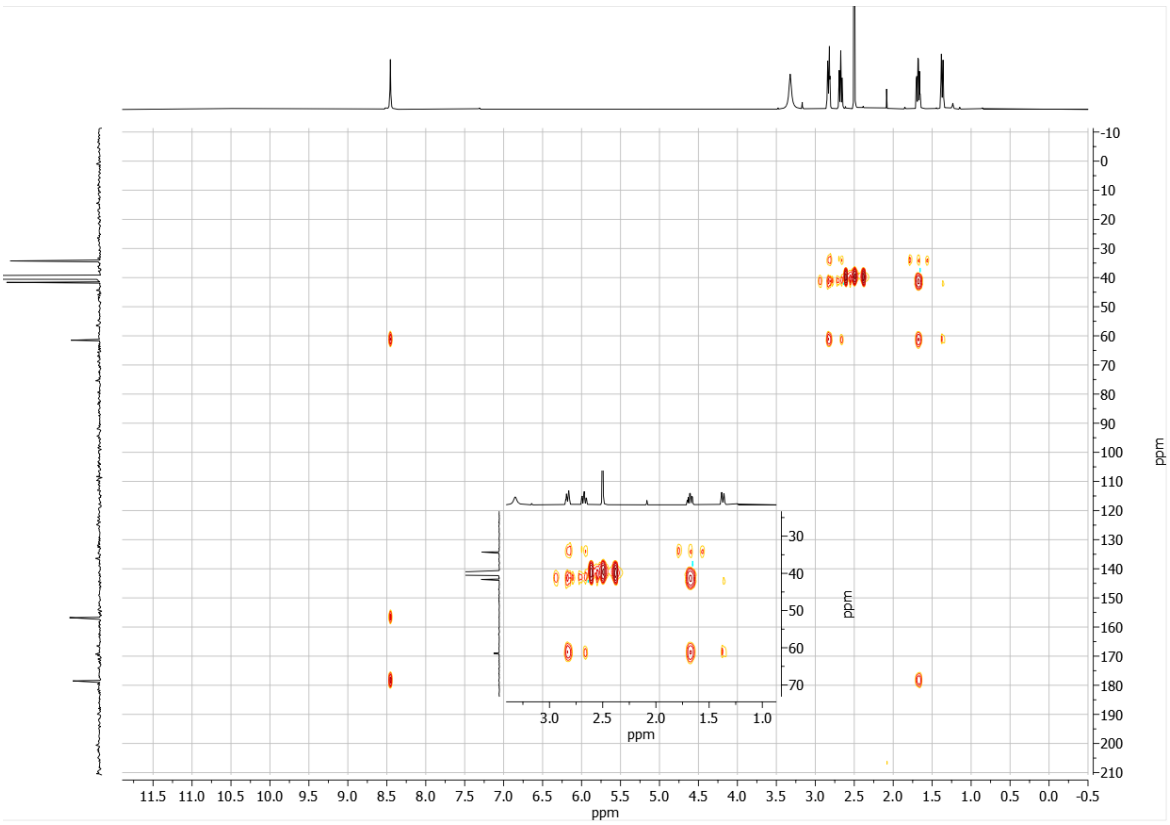
COSY (600 MHz, DMSO-d_6) spectrum of 2f.



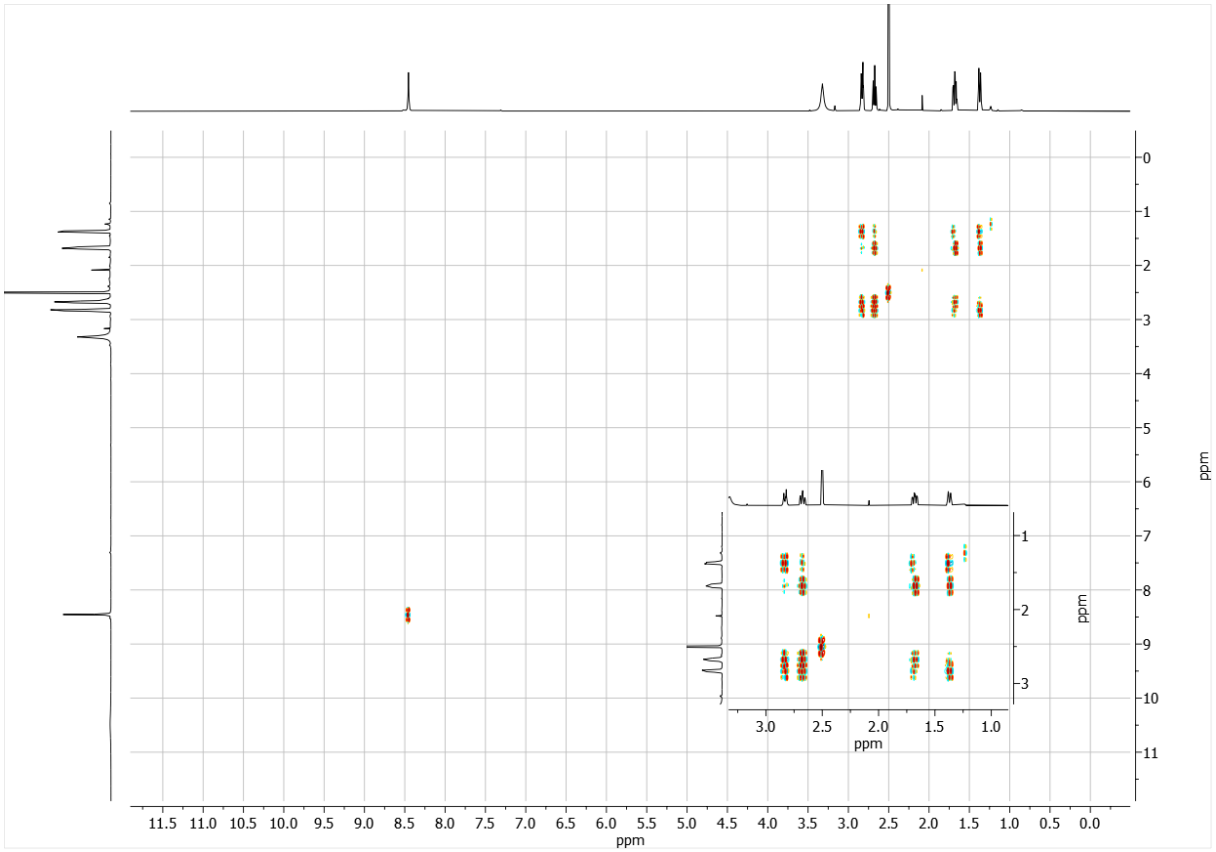
HSQC (600 MHz, DMSO-d_6) spectrum of 2f.



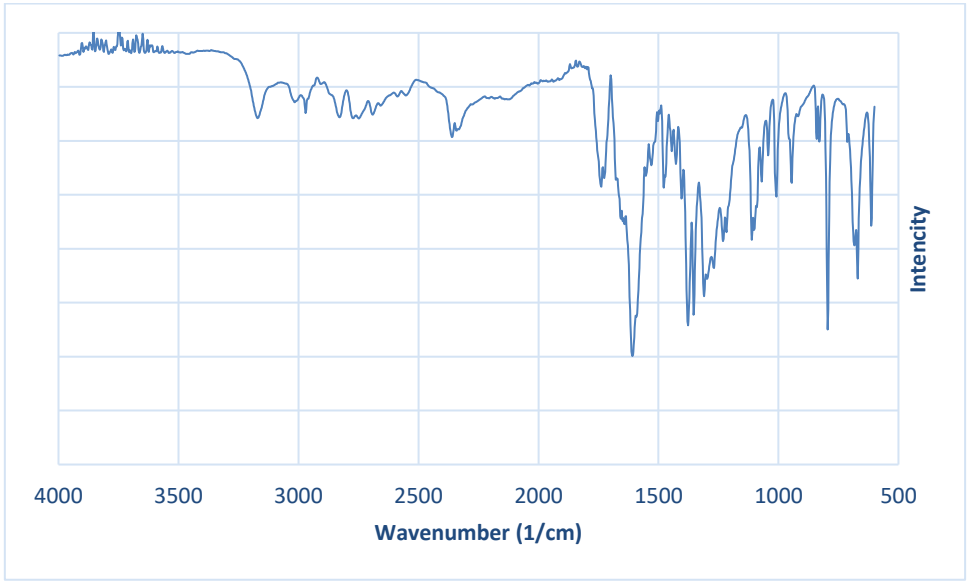
HMBC (600 MHz, DMSO-d_6) spectrum of 2f.



NOESY (600 MHz, DMSO-d_6) spectrum of 2f.

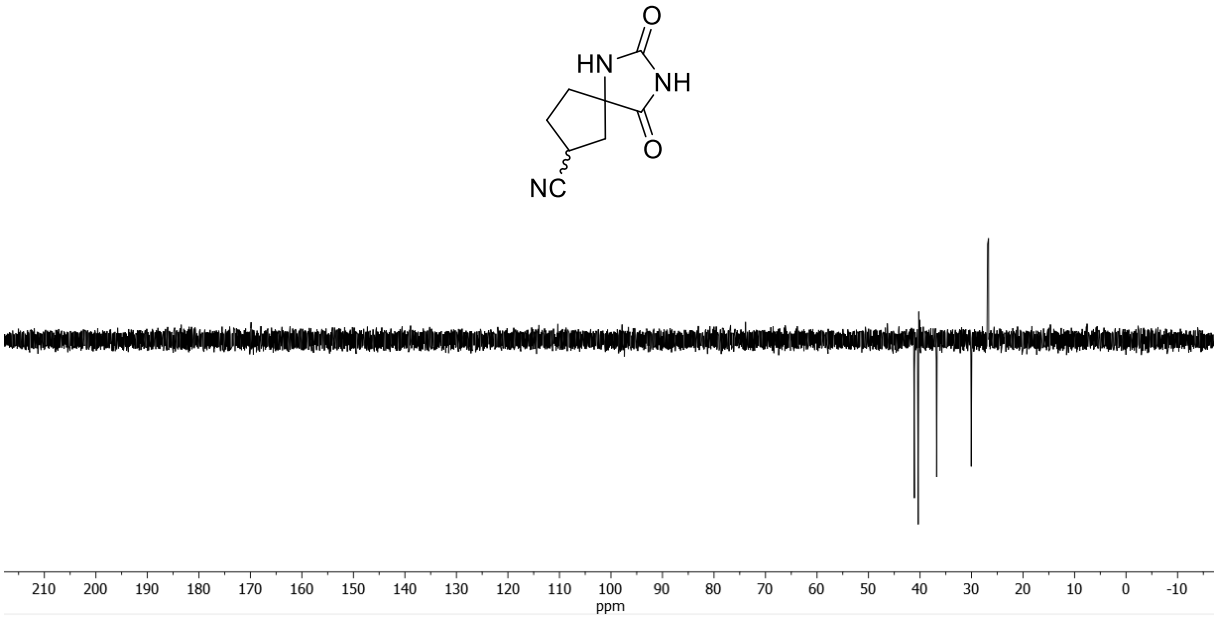


IR spectrum of 2f.

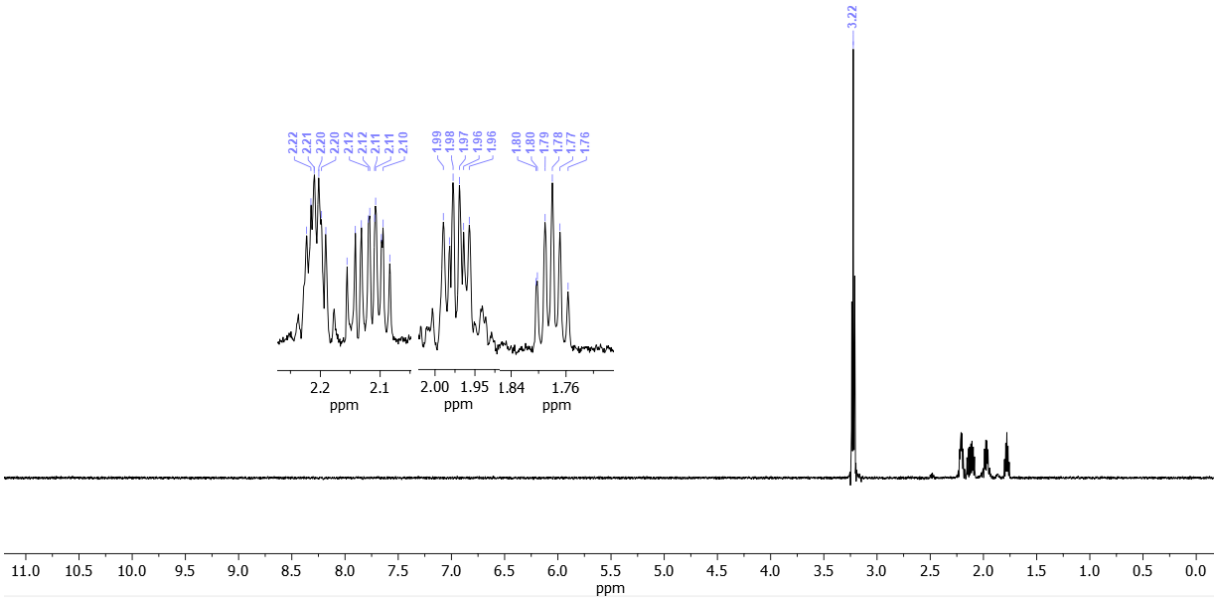


2,4-dioxo-1,3-diazaspiro[4.4]nonane-7-carbonitrile (2i) [811438-49-0]

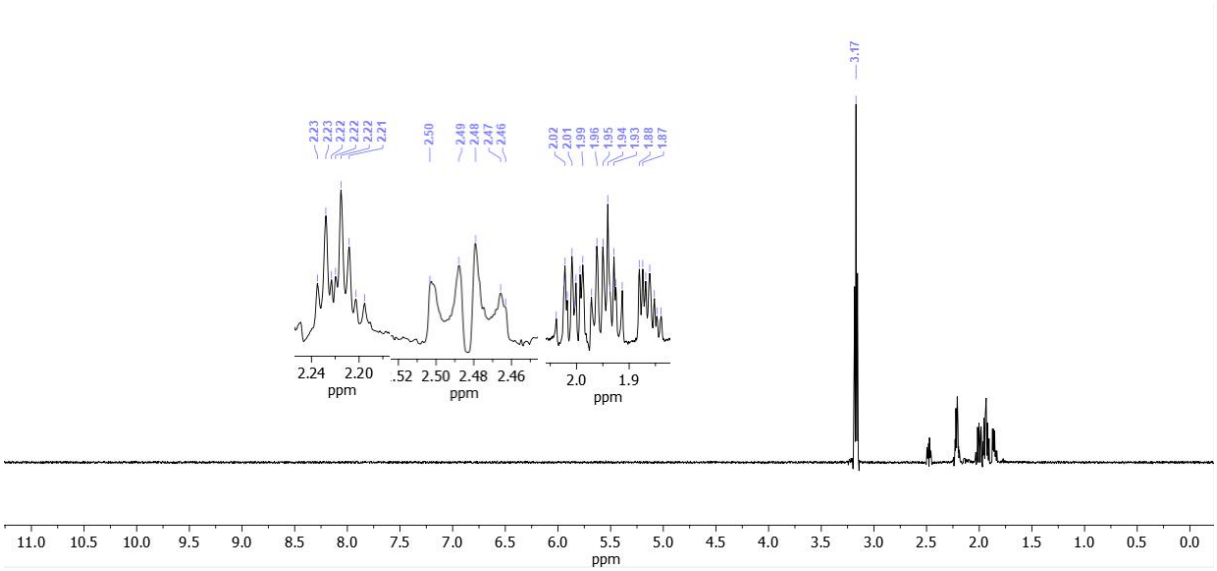
DEPT135 (151 MHz, DMSO-d_6) spectrum of 2i.



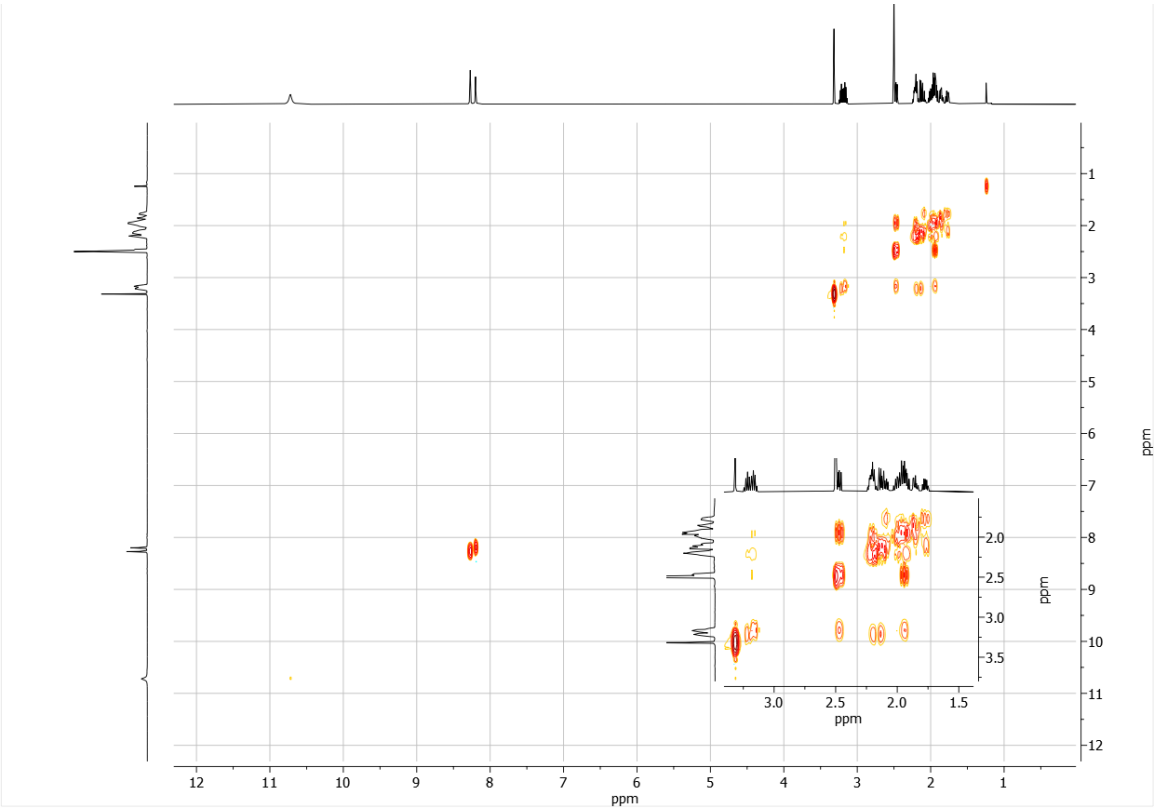
Selective TOKSY (600 MHz, DMSO-d_6) of 2i.



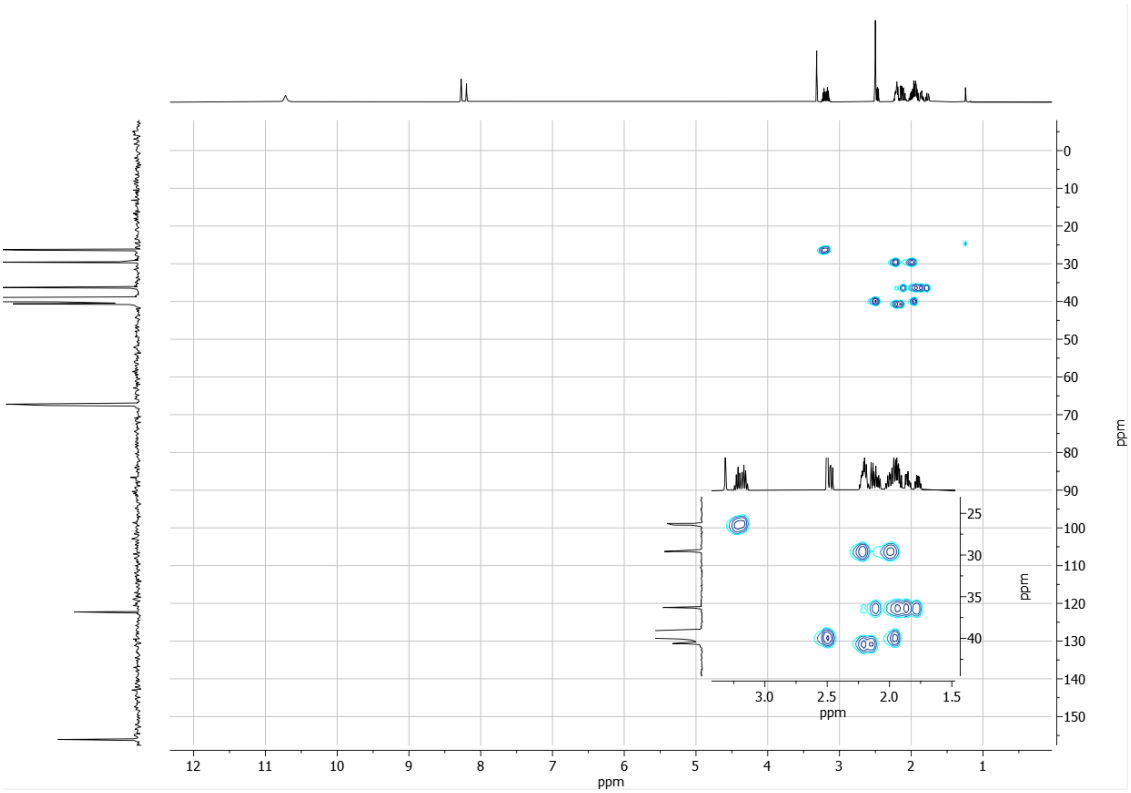
Selective TOKSY (600 MHz, DMSO-d_6) of 2i.



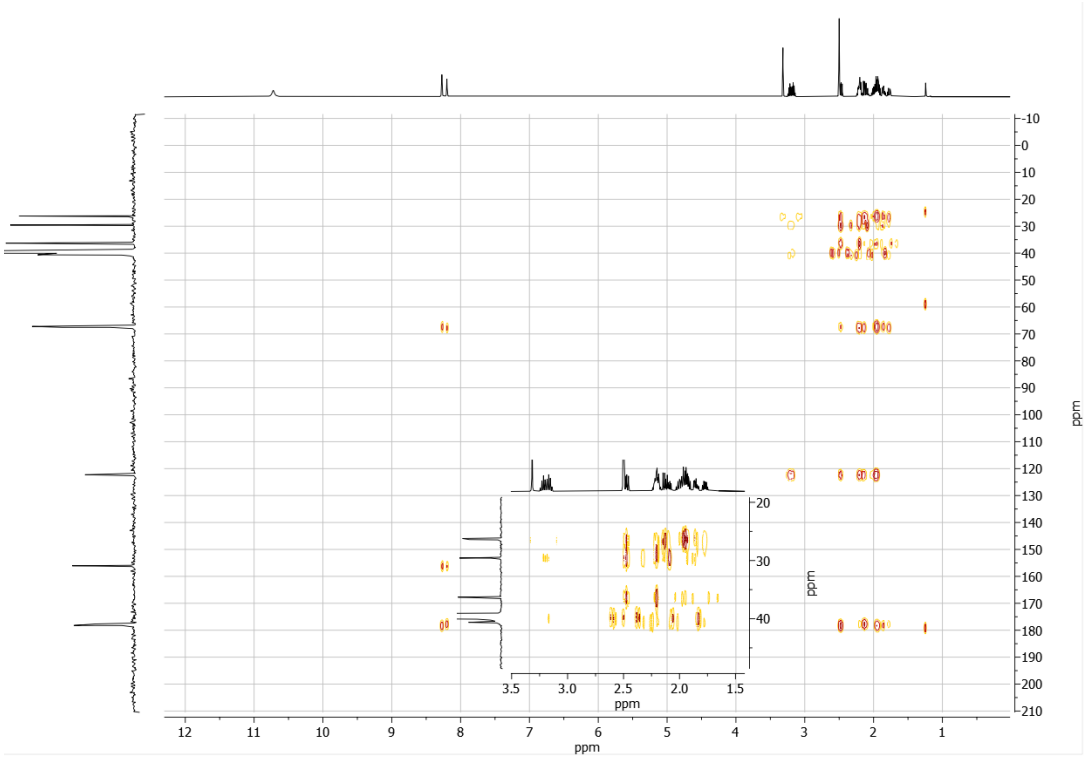
COSY (600 MHz, DMSO-d_6) spectrum of 2i.



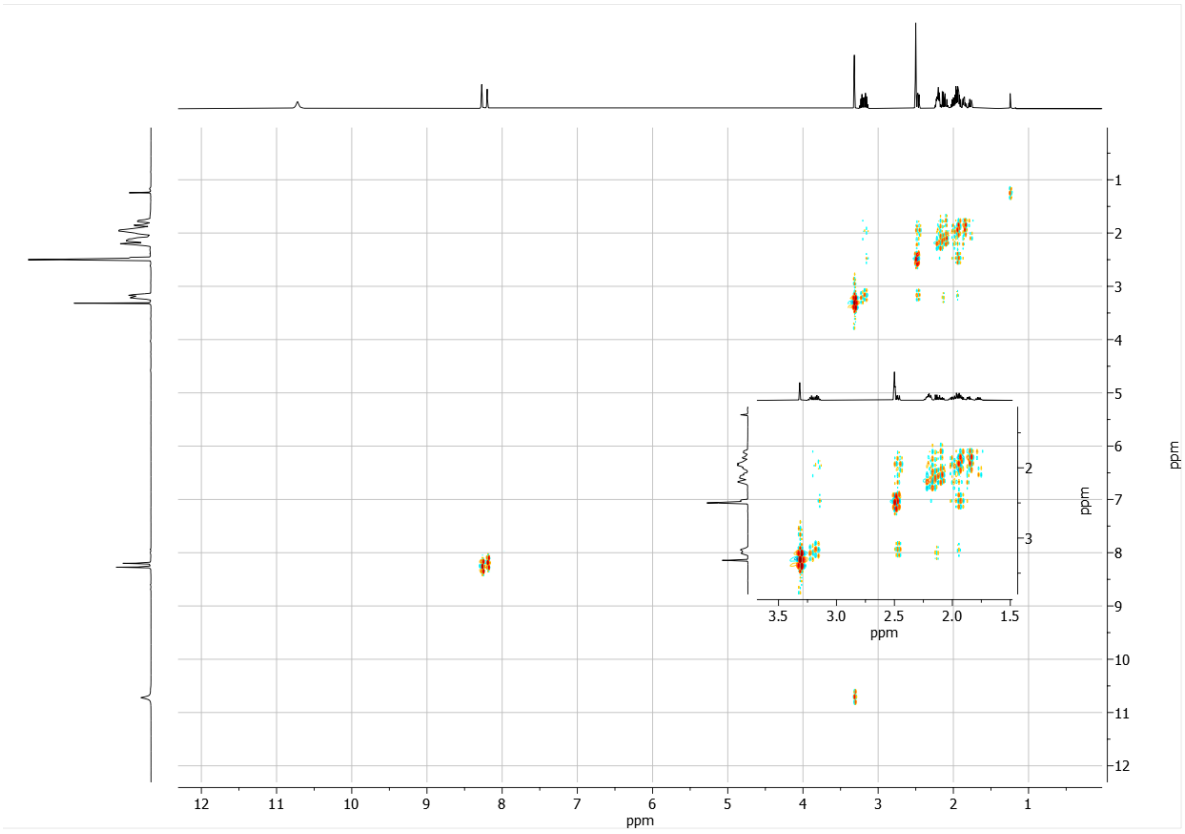
HSQC (600 MHz, DMSO-d_6) spectrum of 2i.



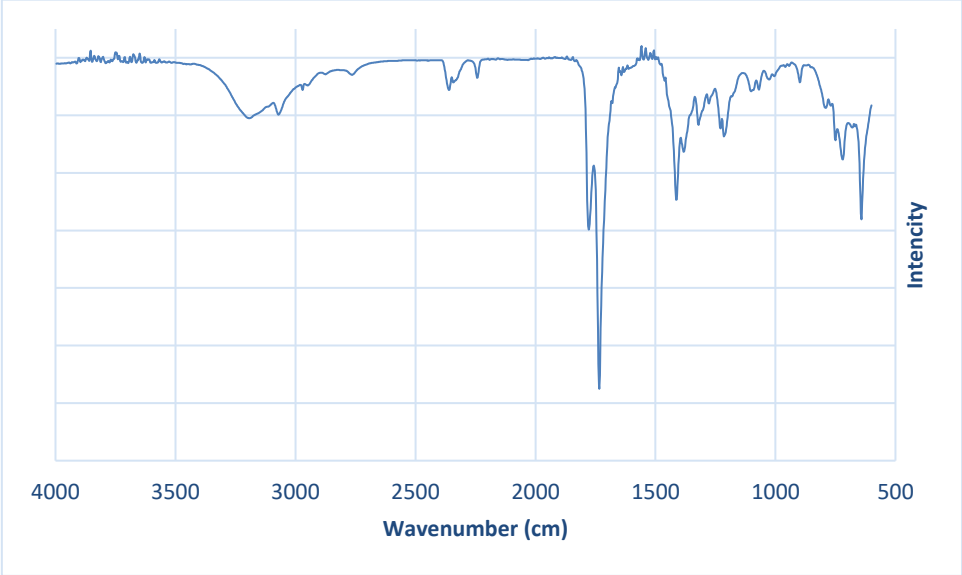
HMBC (600 MHz, DMSO-d_6) spectrum of 2i.



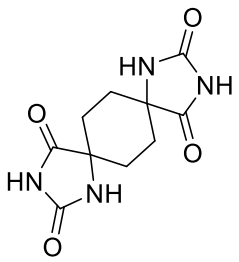
NOESY (600 MHz, DMSO-d_6) spectrum of 2i.



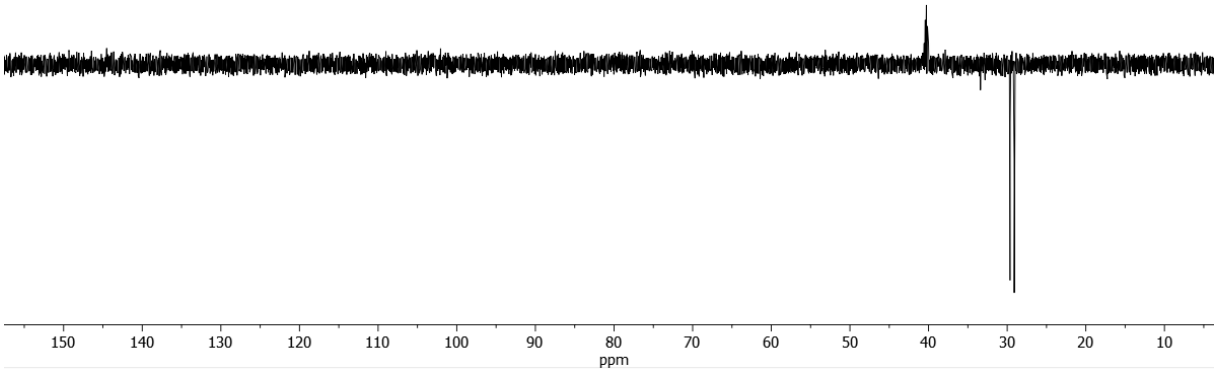
IR spectrum of 2i.



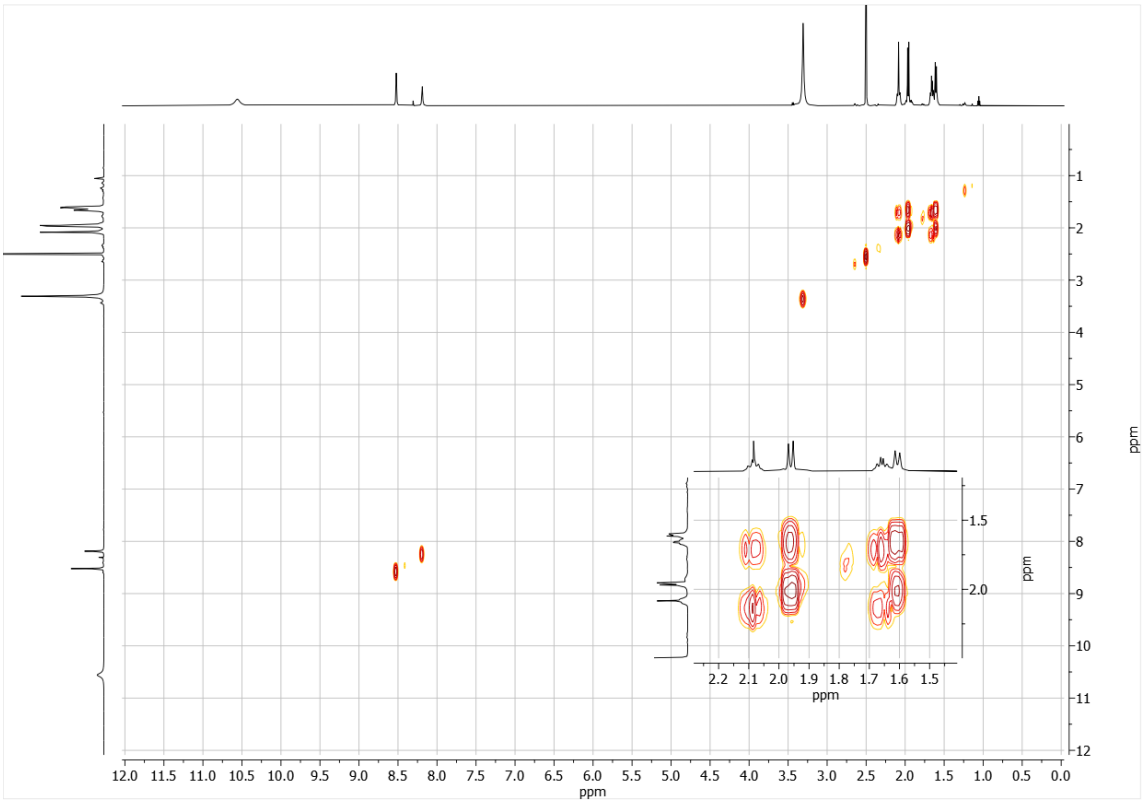
1,3,9,11-Tetraazadispiro[4.2.4.2]tetradecane-2,4,10,12-tetrone (2k) [1469462-75-6]



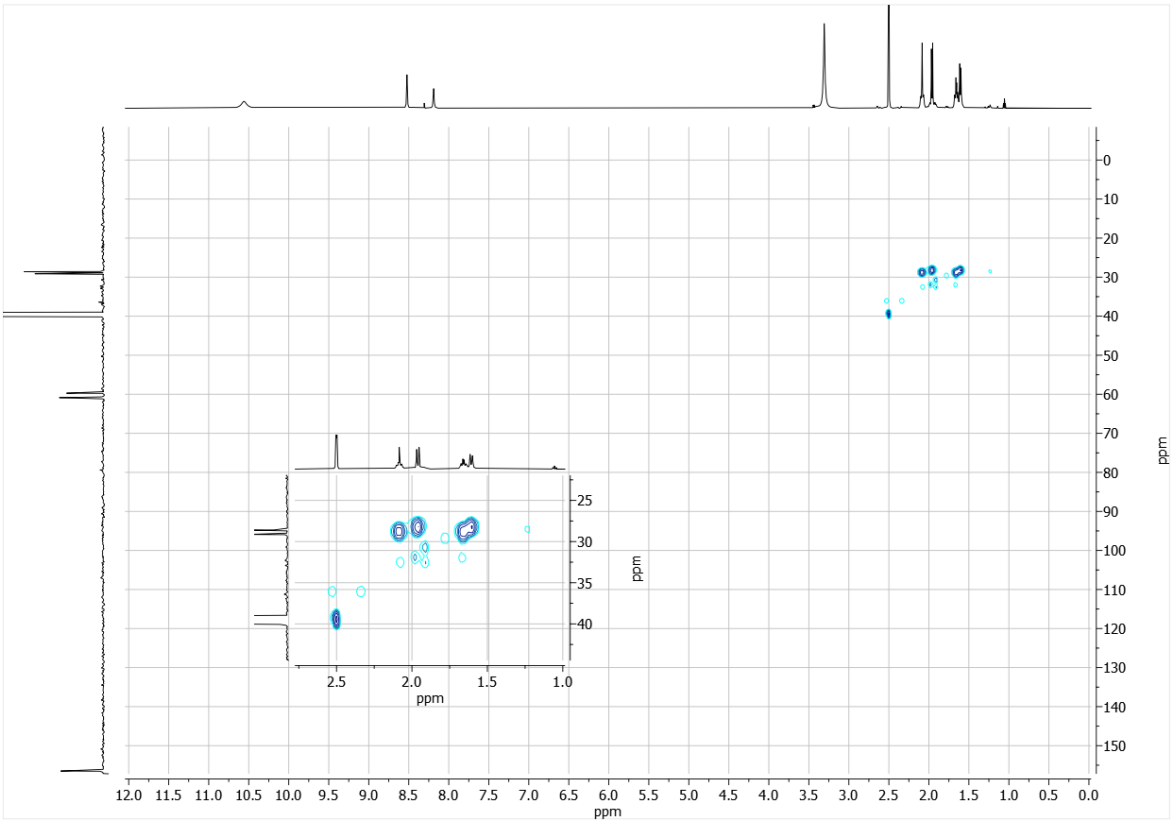
DEPT135 (151 MHz, DMSO-d_6) spectrum of 2k.



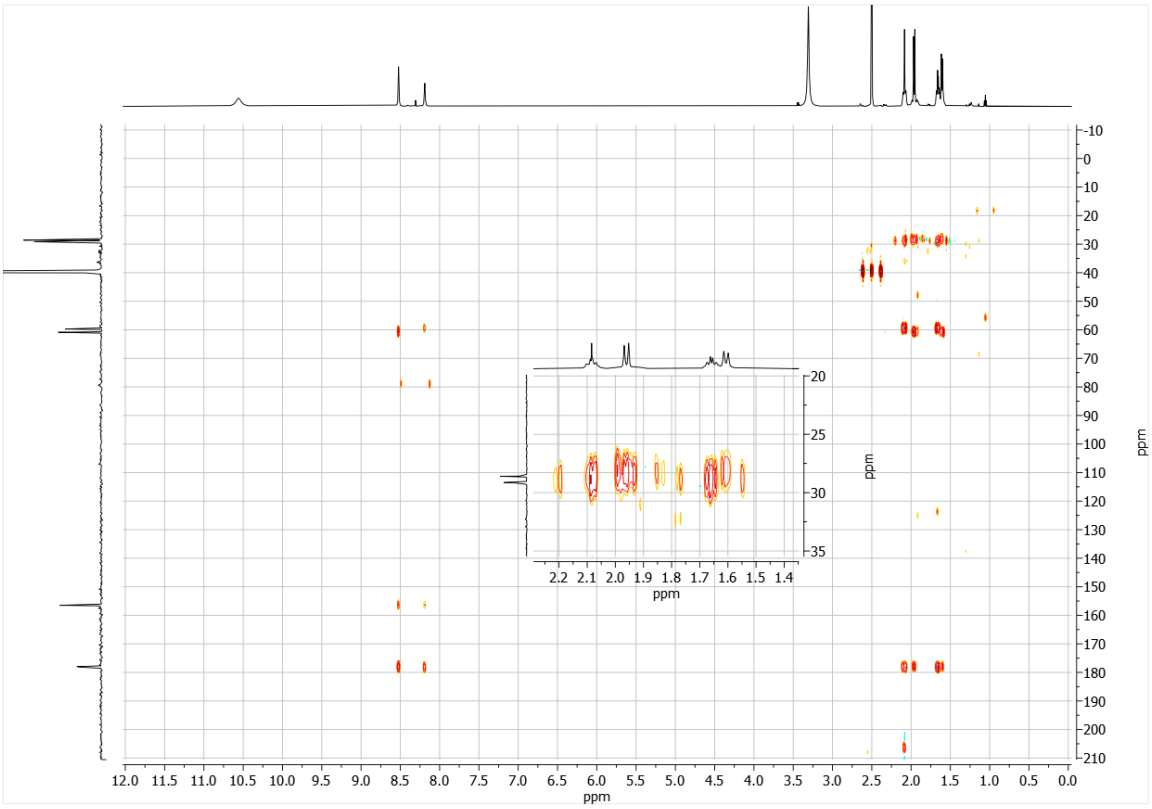
COSY (600 MHz, DMSO-d_6) spectrum of 2k.



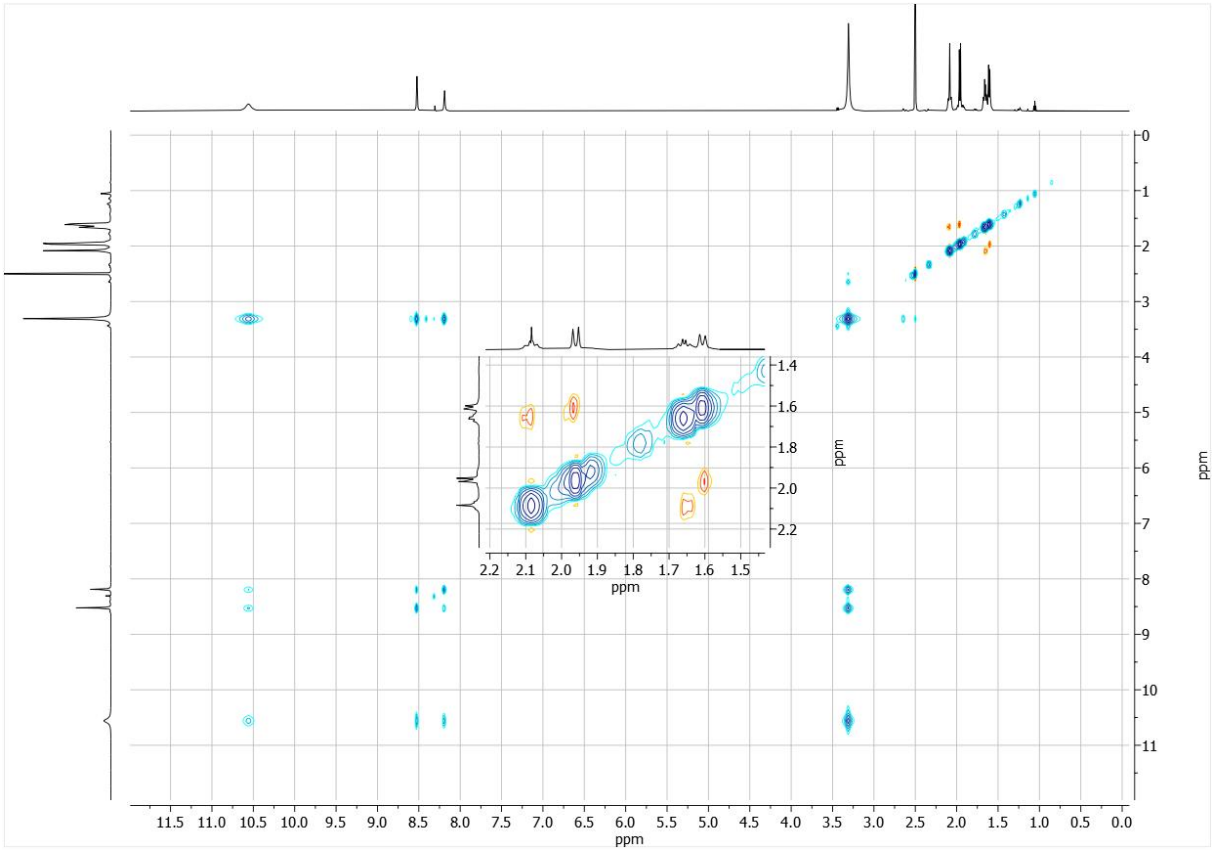
HSQC (600 MHz, DMSO-d_6) spectrum of 2k.



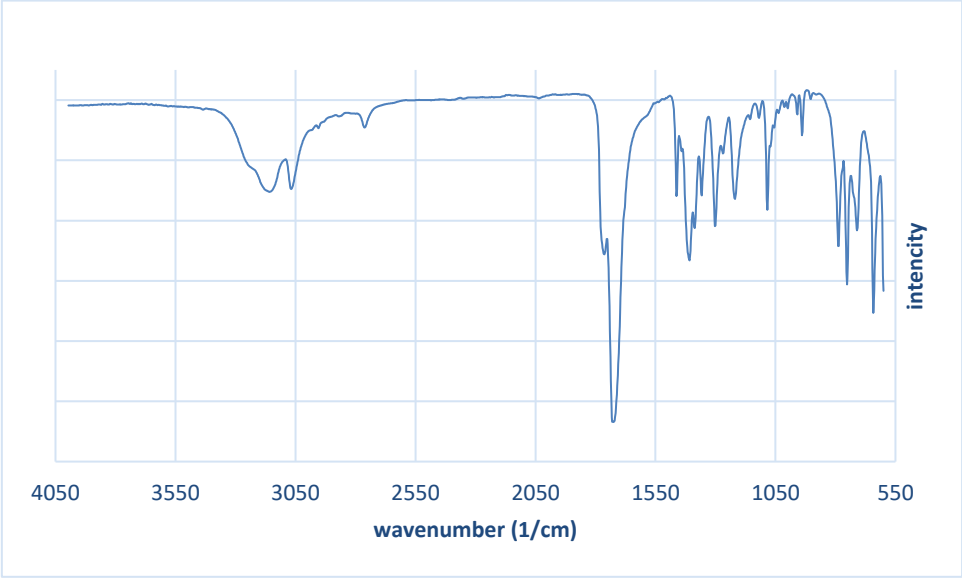
HMBC (600 MHz, DMSO-d_6) spectrum of 2k.



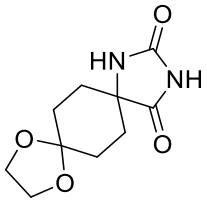
NOESY (600 MHz, DMSO-d_6) spectrum of 2k.



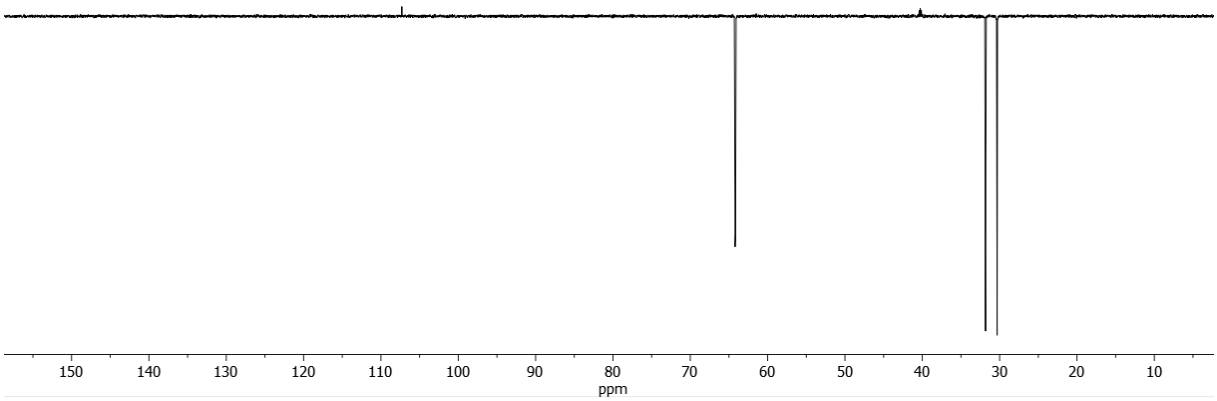
IR spectrum of 2k.



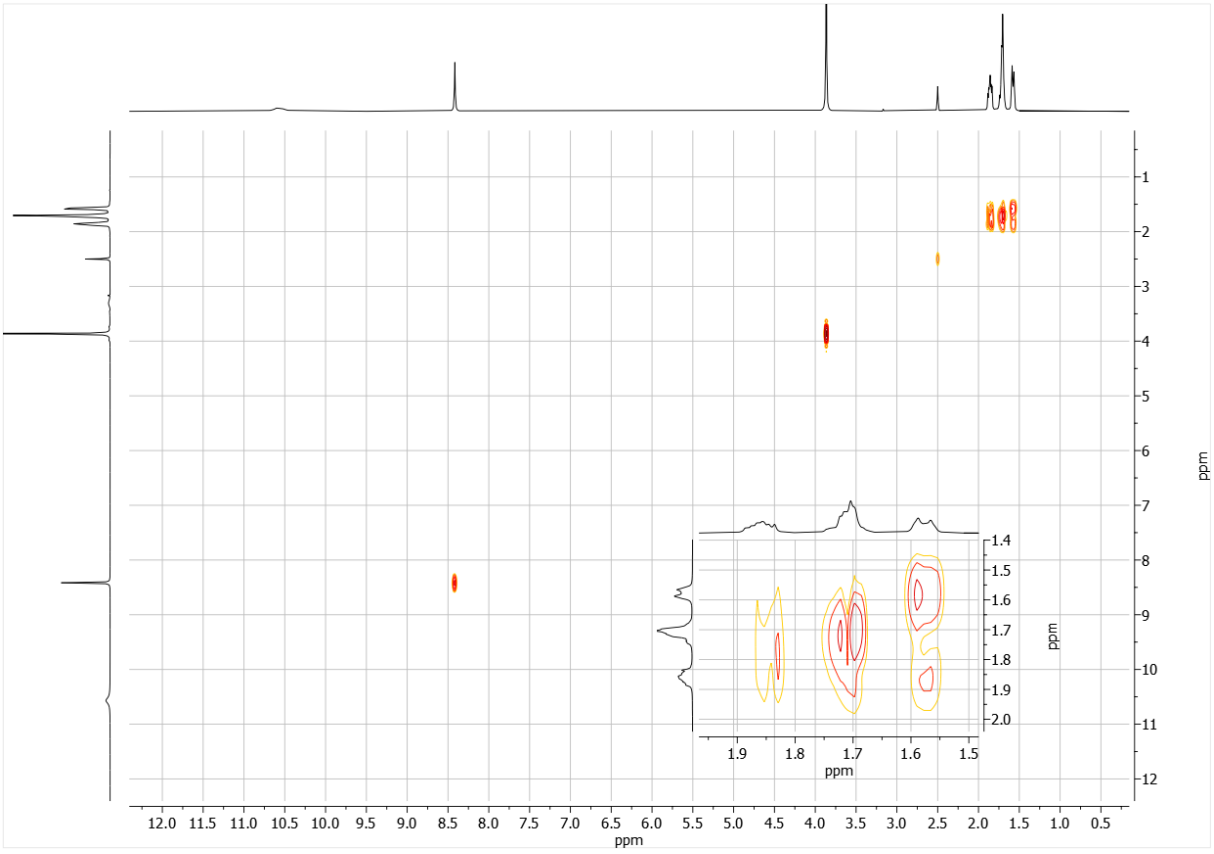
9,12-Dioxa-1,3-diazadispiro[4.2.4.2]tetradecane-2,4-dione (2l) [54621-17-9]



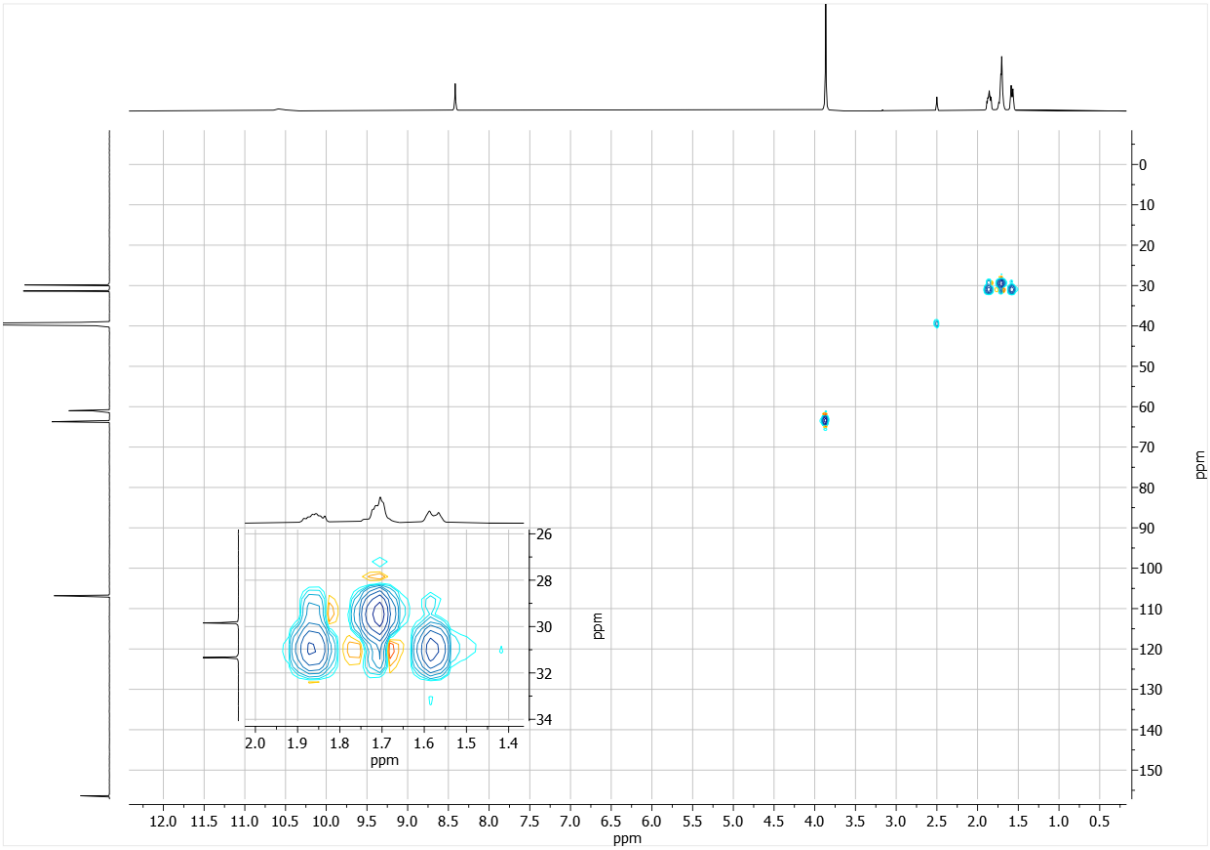
DEPT135 (151 MHz, DMSO-d$_6$) spectrum of 2l.



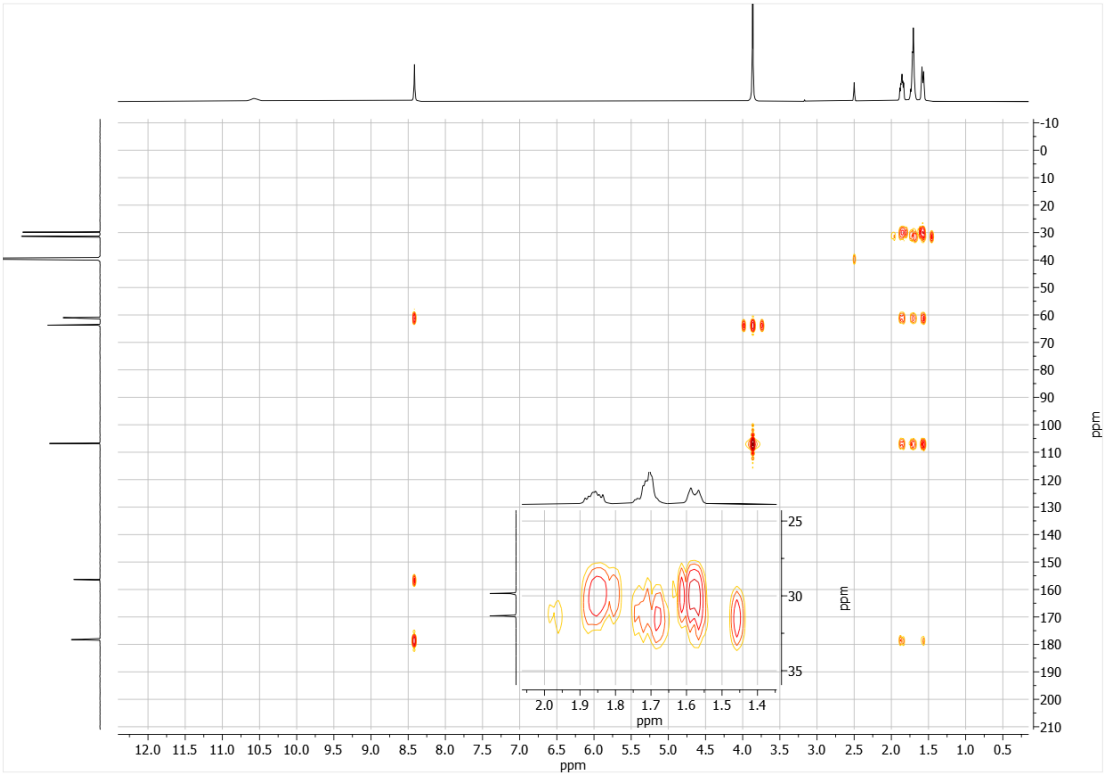
COSY (600 MHz, DMSO-d$_6$) spectrum of 2l.



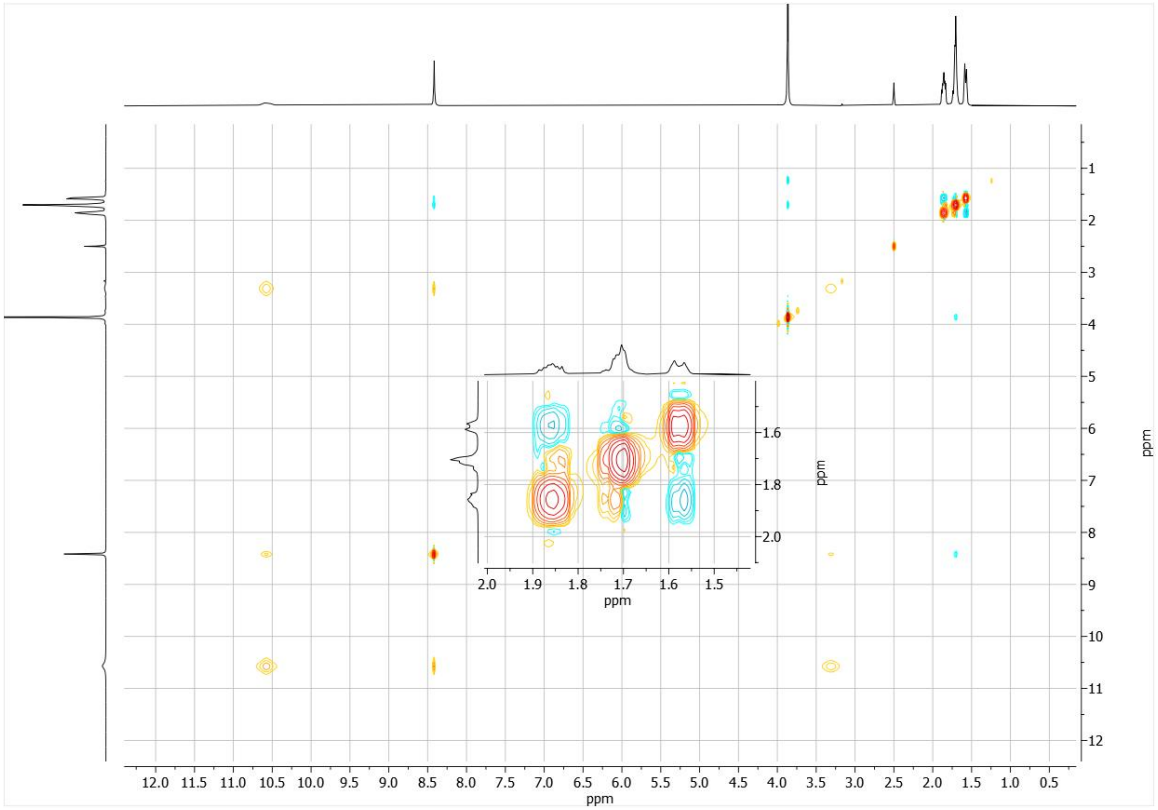
HSQC (600 MHz, DMSO-d_6) spectrum of 2l.



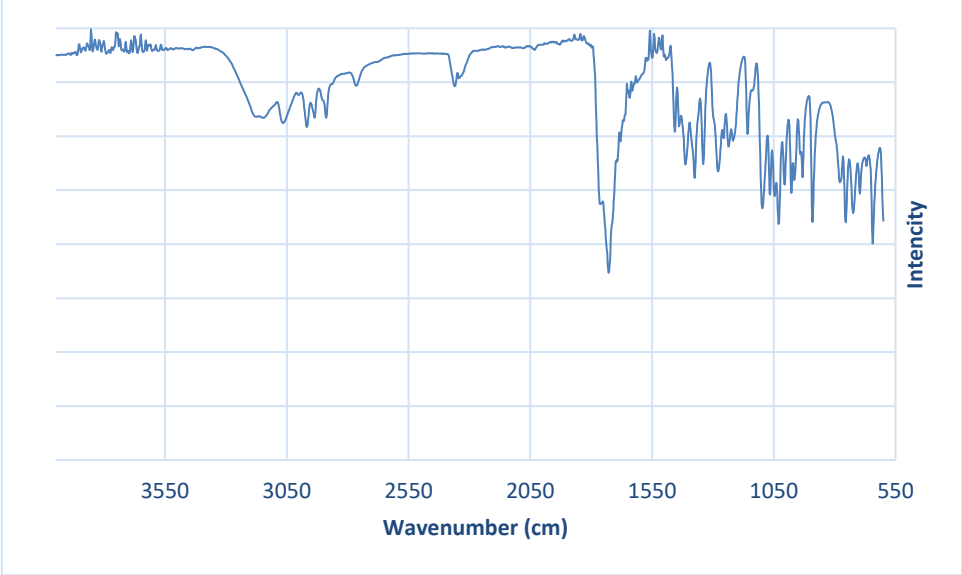
HMBC (600 MHz, DMSO-d_6) spectrum of 2l.



NOESY (600 MHz, DMSO-d_6) spectrum of 2l.



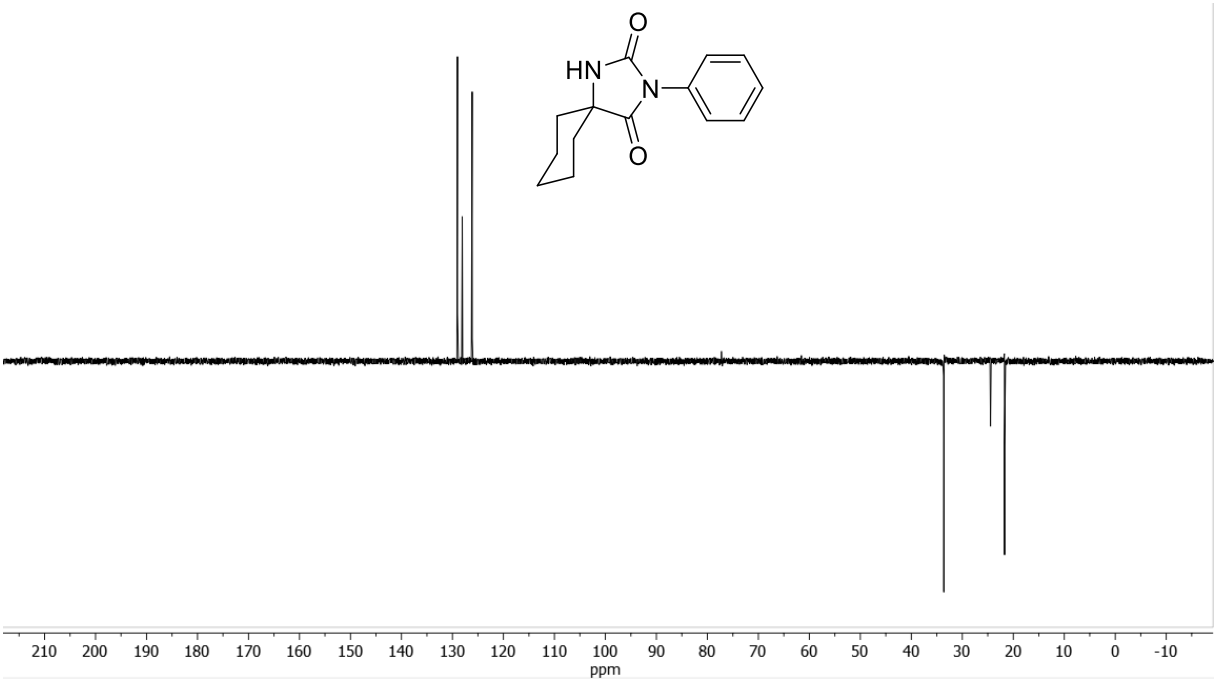
IR spectrum of 2l.



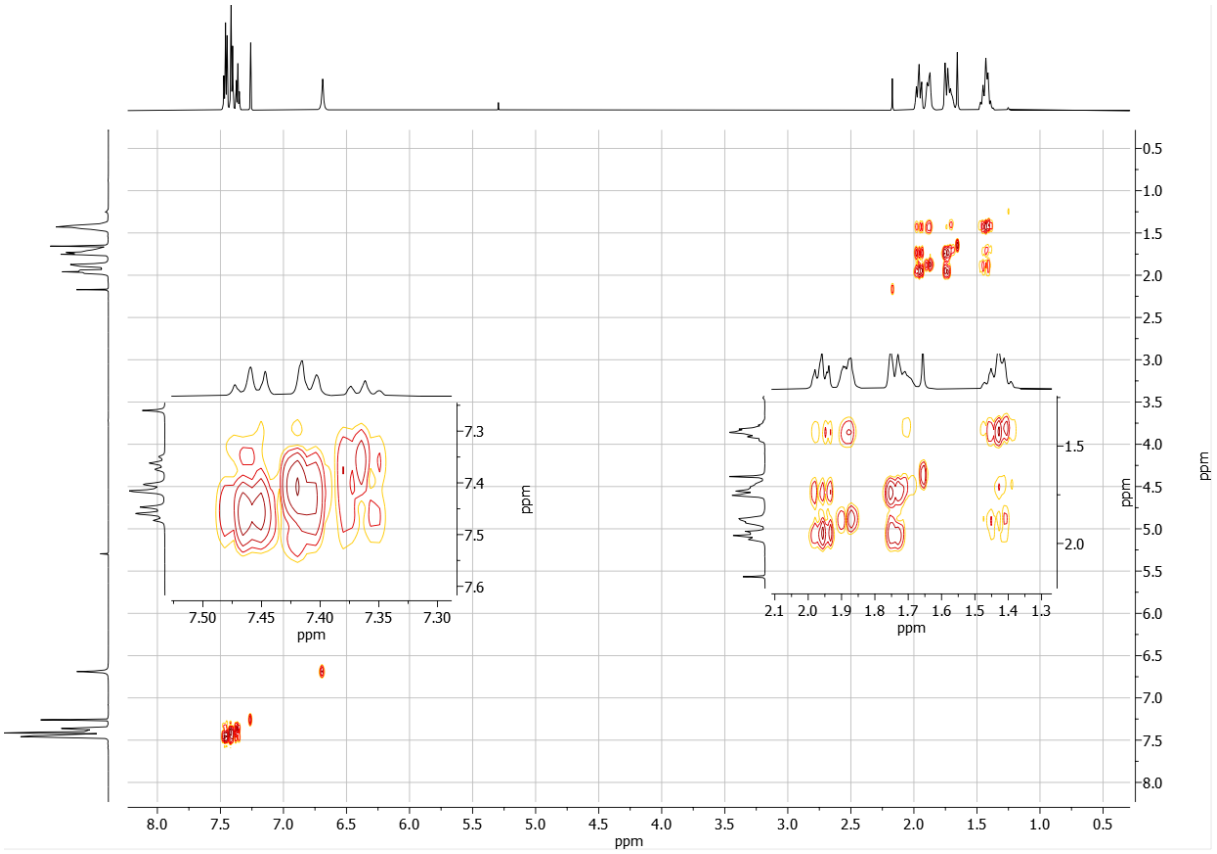
7.2 *N*-3-Arylated spirohydantoins

3-phenyl-1,3-diazaspiro[4.5]decane-2,4-dione (5a) [726-97-6]

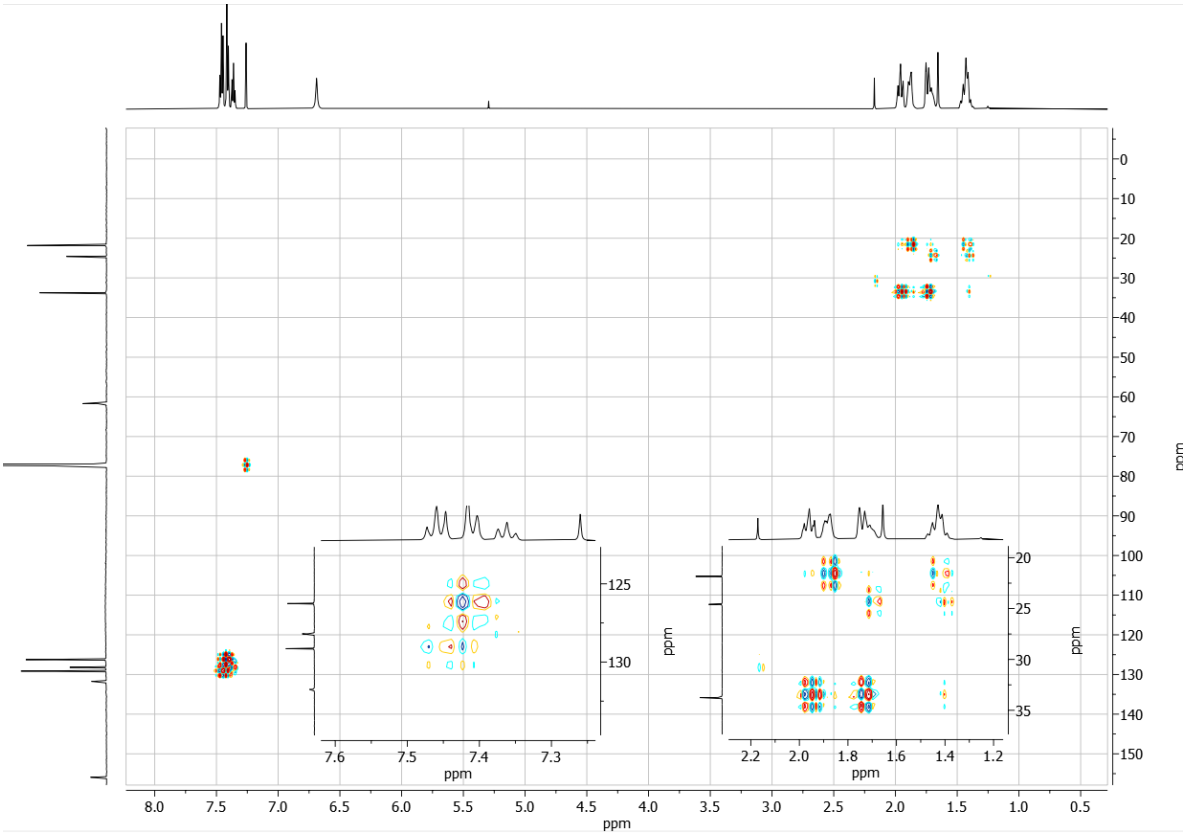
DEPT135 (151 MHz,$CDCl_3$) spectrum of 5a.



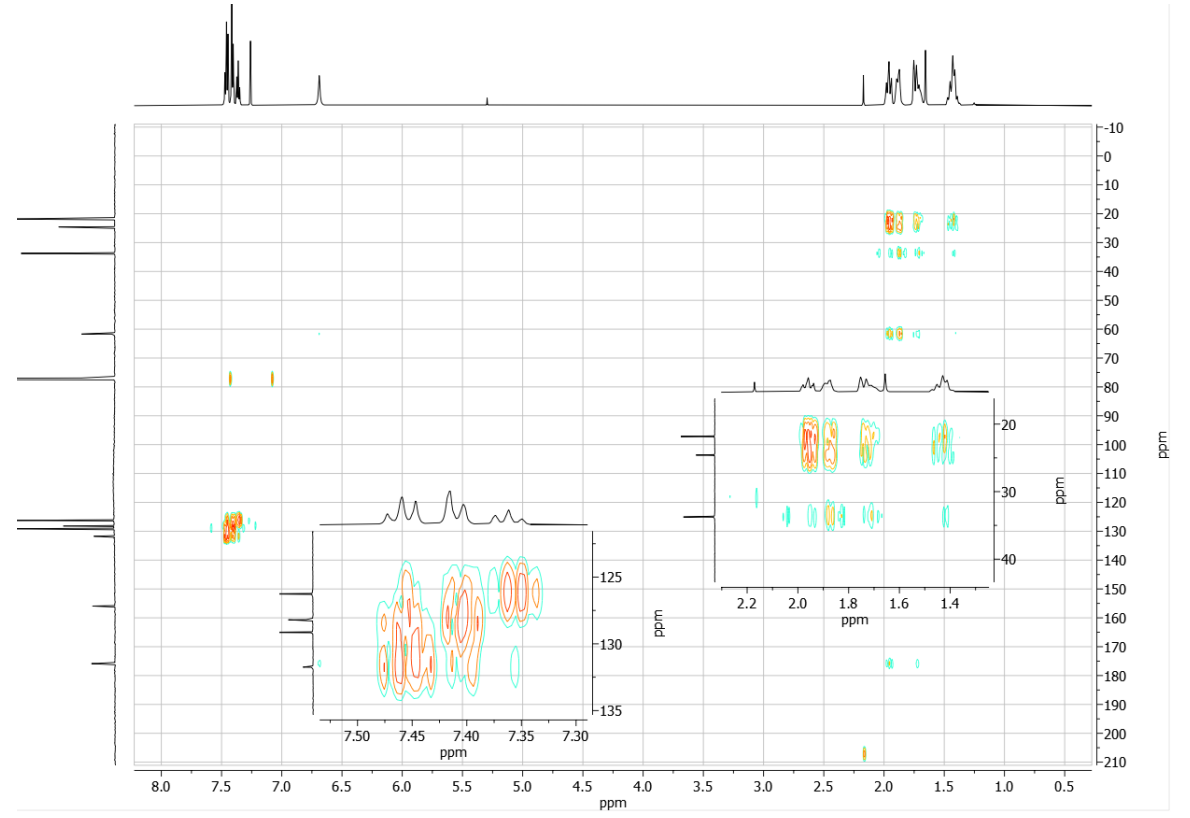
COSY (600 MHz, $CDCl_3$) spectrum of 5a.



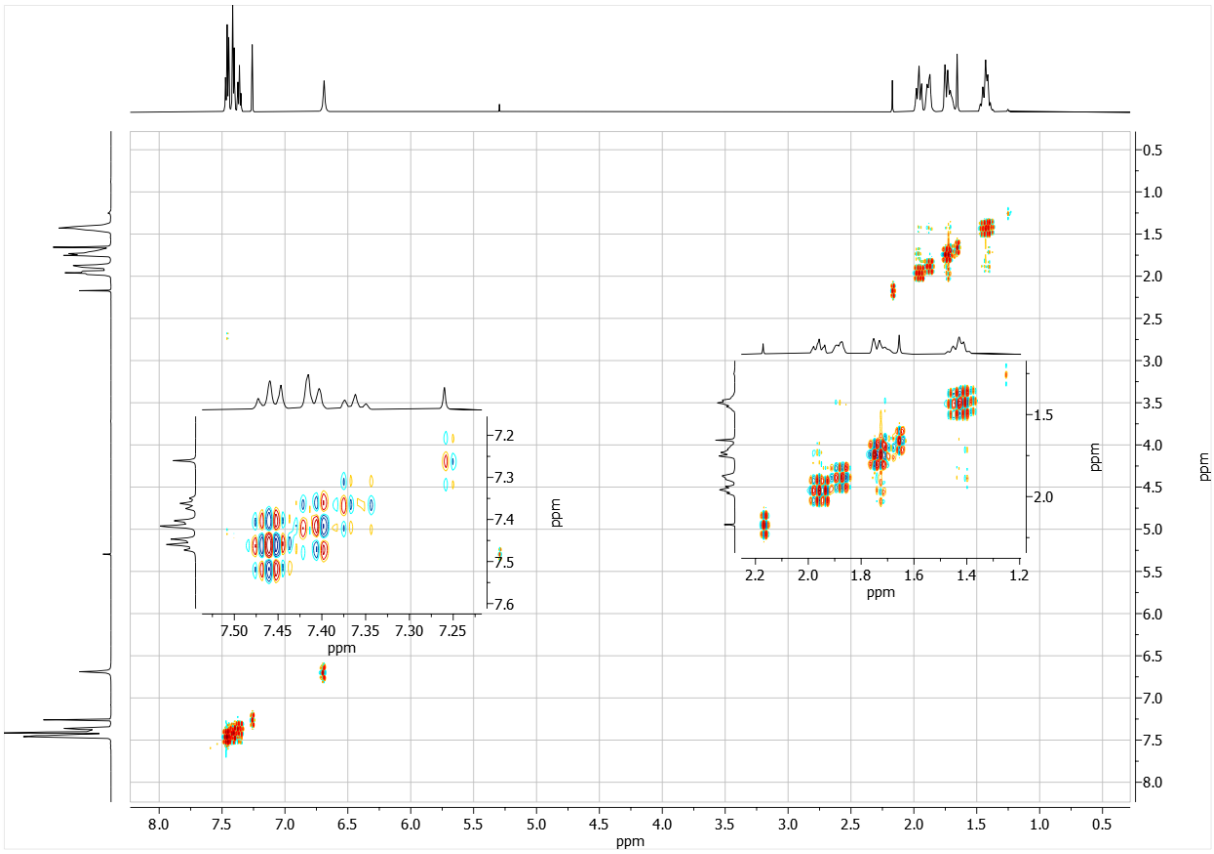
HSQC (600 MHz, $CDCl_3$) spectrum of 5a.



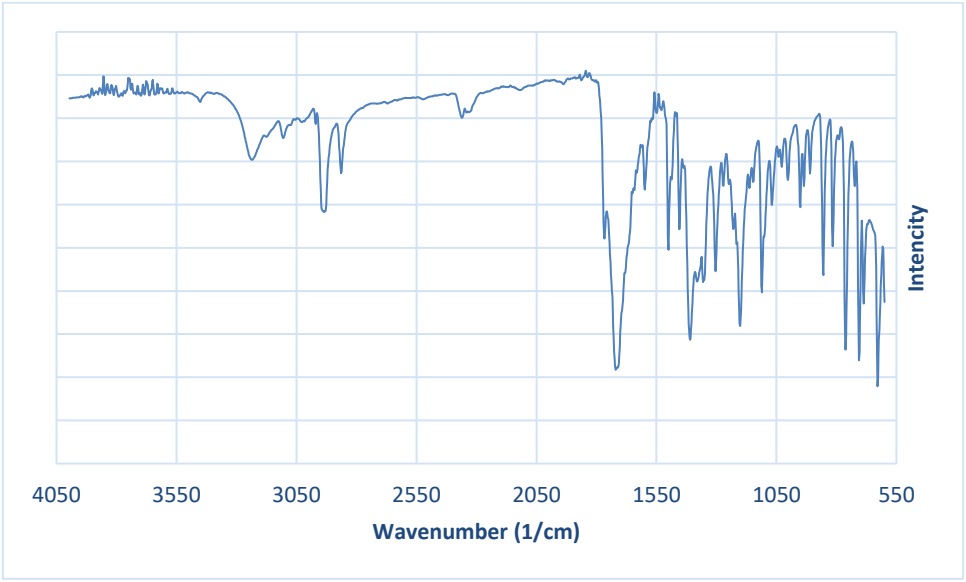
HMBC (600 MHz, $CDCl_3$) spectrum of 5a.



NOESY (600 MHz, $CDCl_3$) spectrum of 5a.

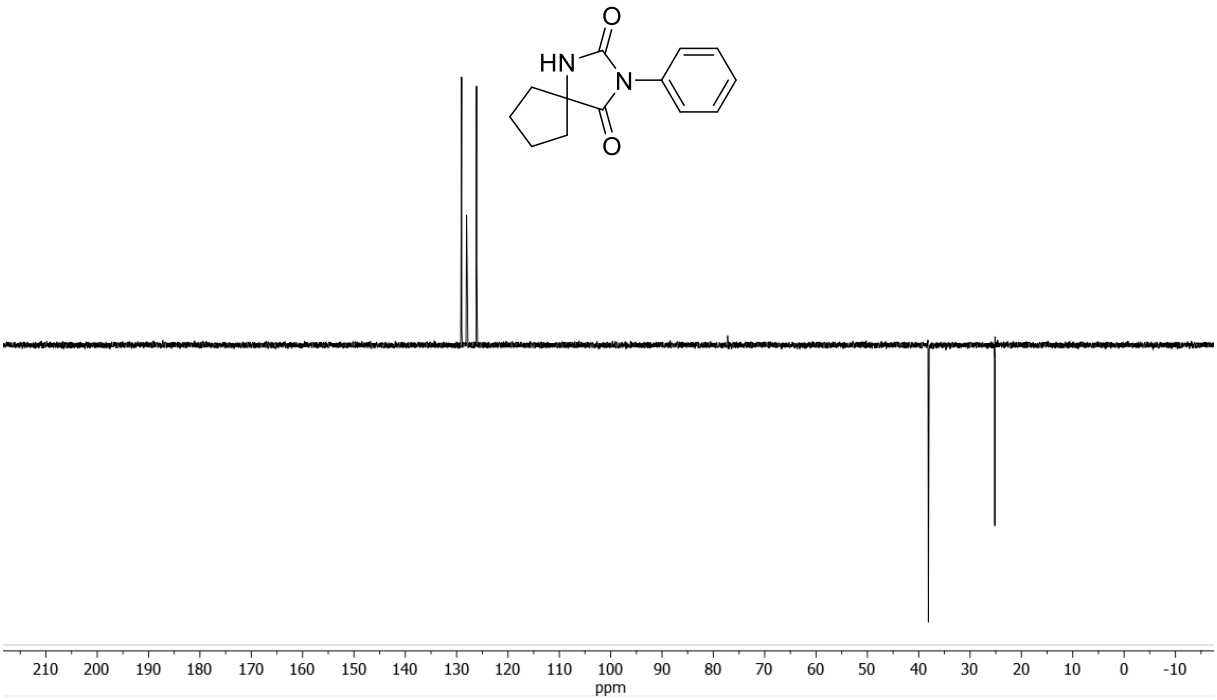


IR spectrum of 5a.

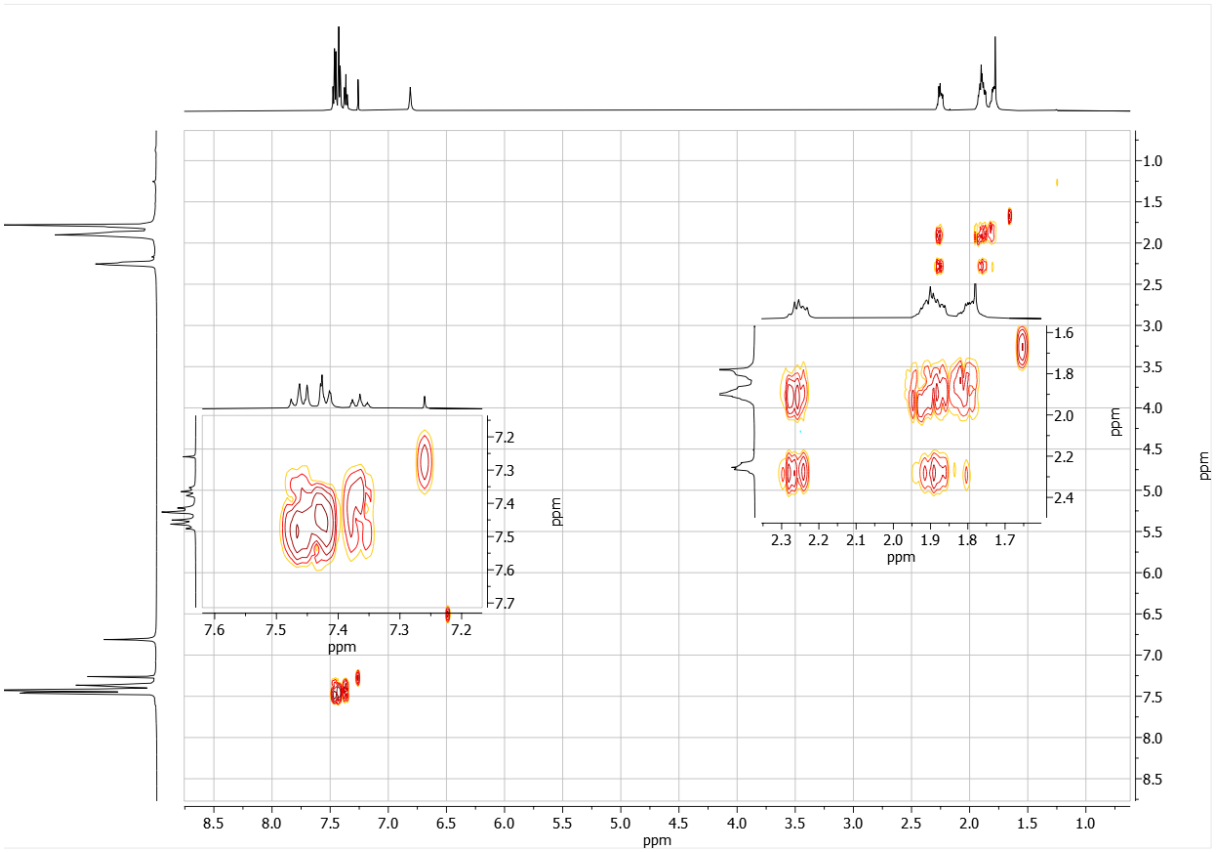


3-Phenyl-1,3-diazaspiro[4.4]nonane-2,4-dione (5b) [1292805-97-0]

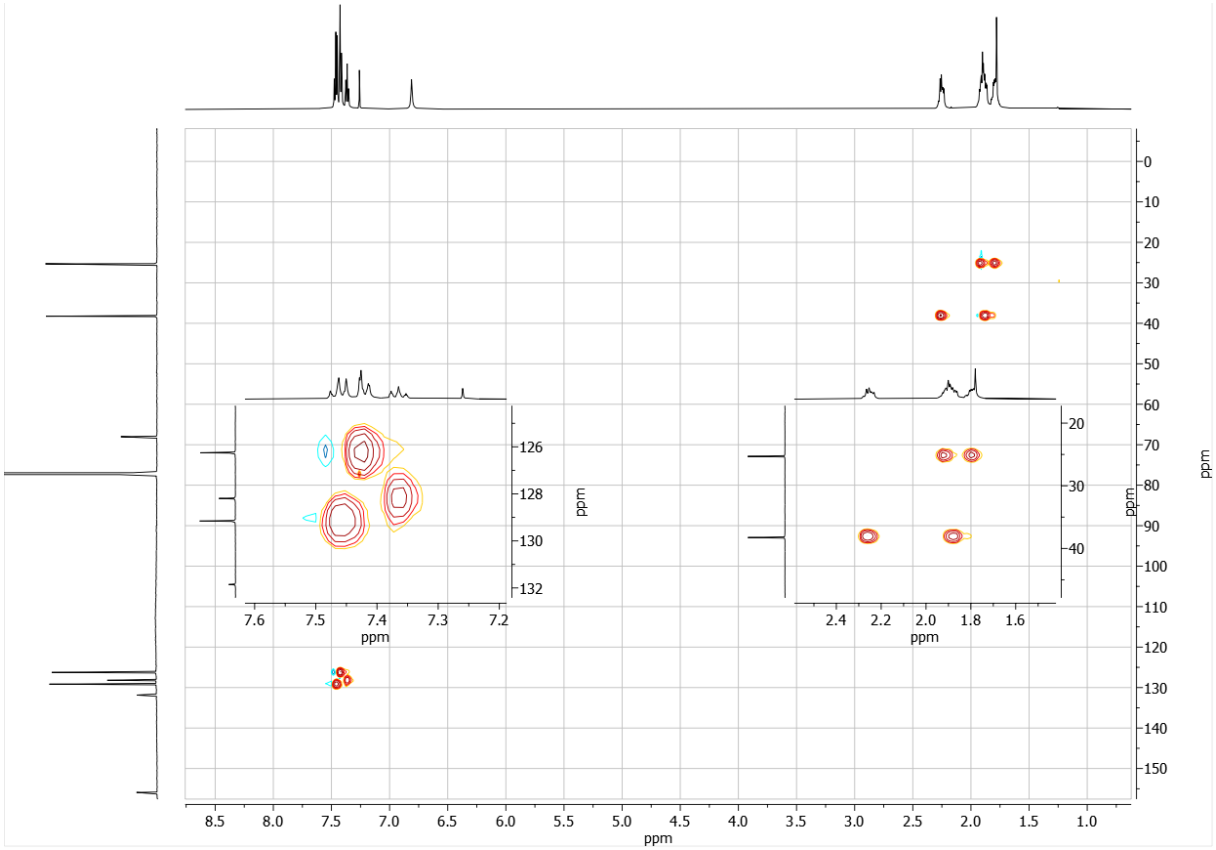
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5b.



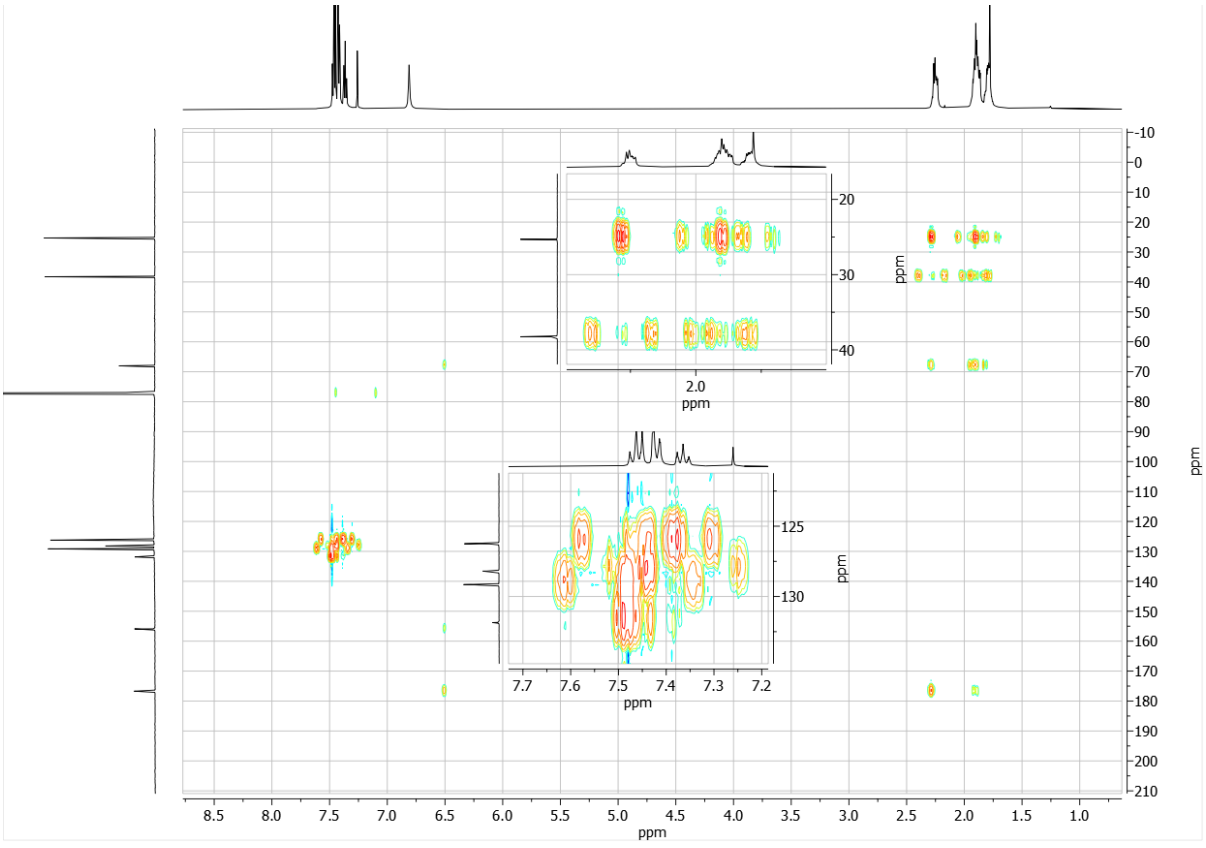
COSY (600 MHz, $CDCl_3$) spectrum of 5b.



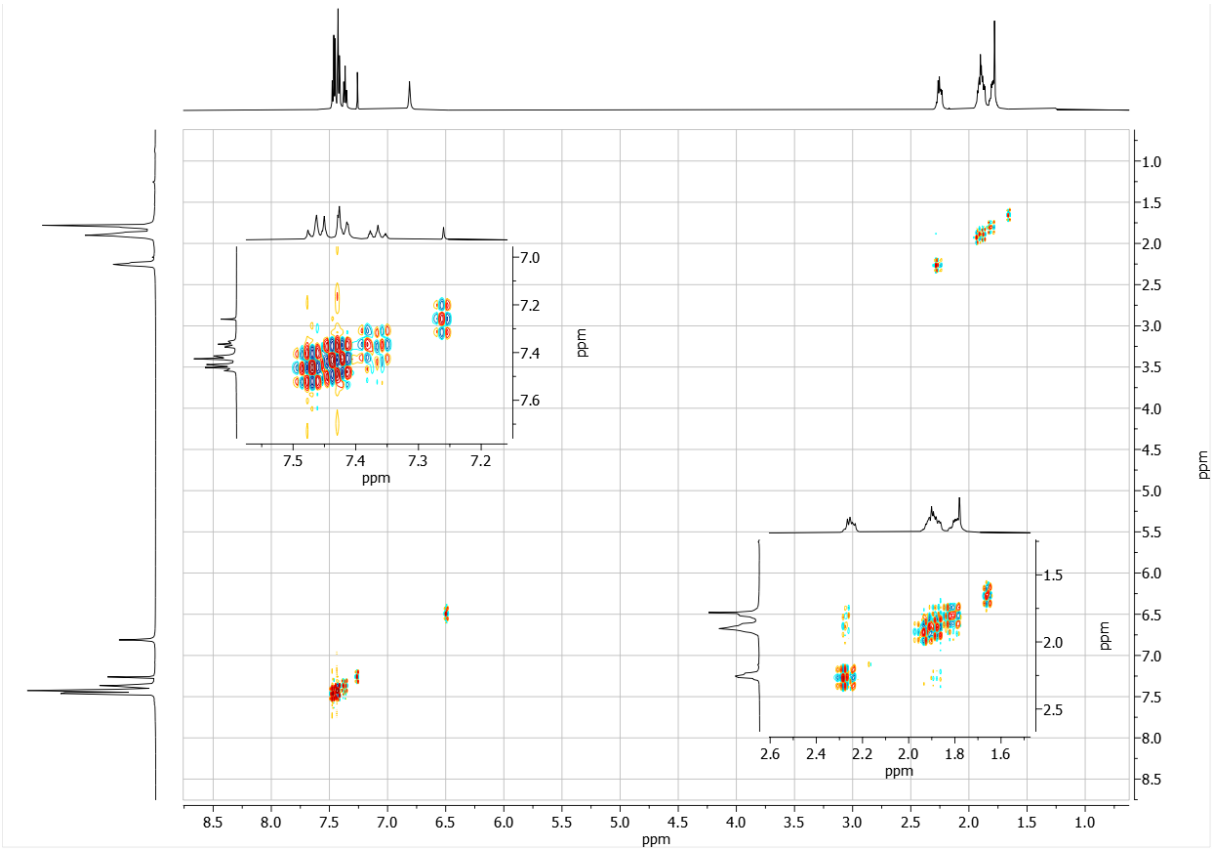
HSQC (600 MHz, $CDCl_3$) spectrum of 5b.



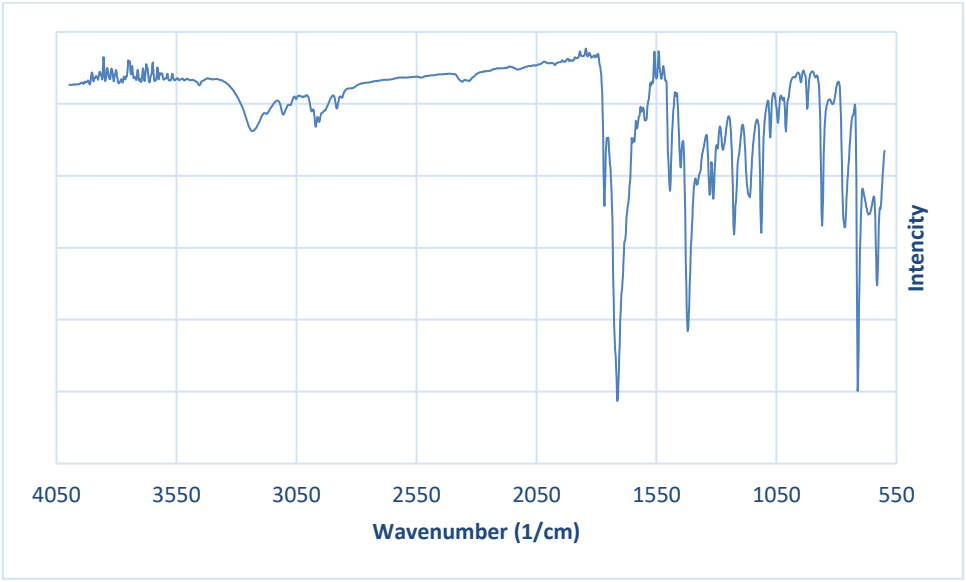
HMBC (600 MHz, $CDCl_3$) spectrum of 5b.



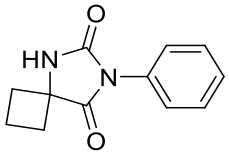
NOESY (600 MHz, $CDCl_3$) spectrum of 5b.



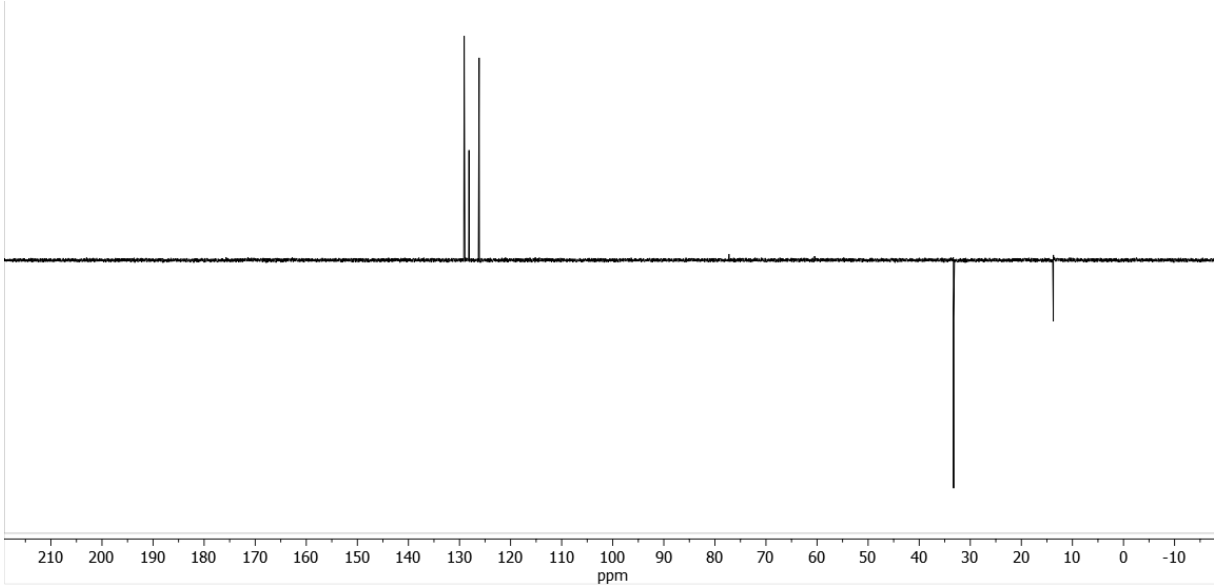
IR spectrum of 5b.



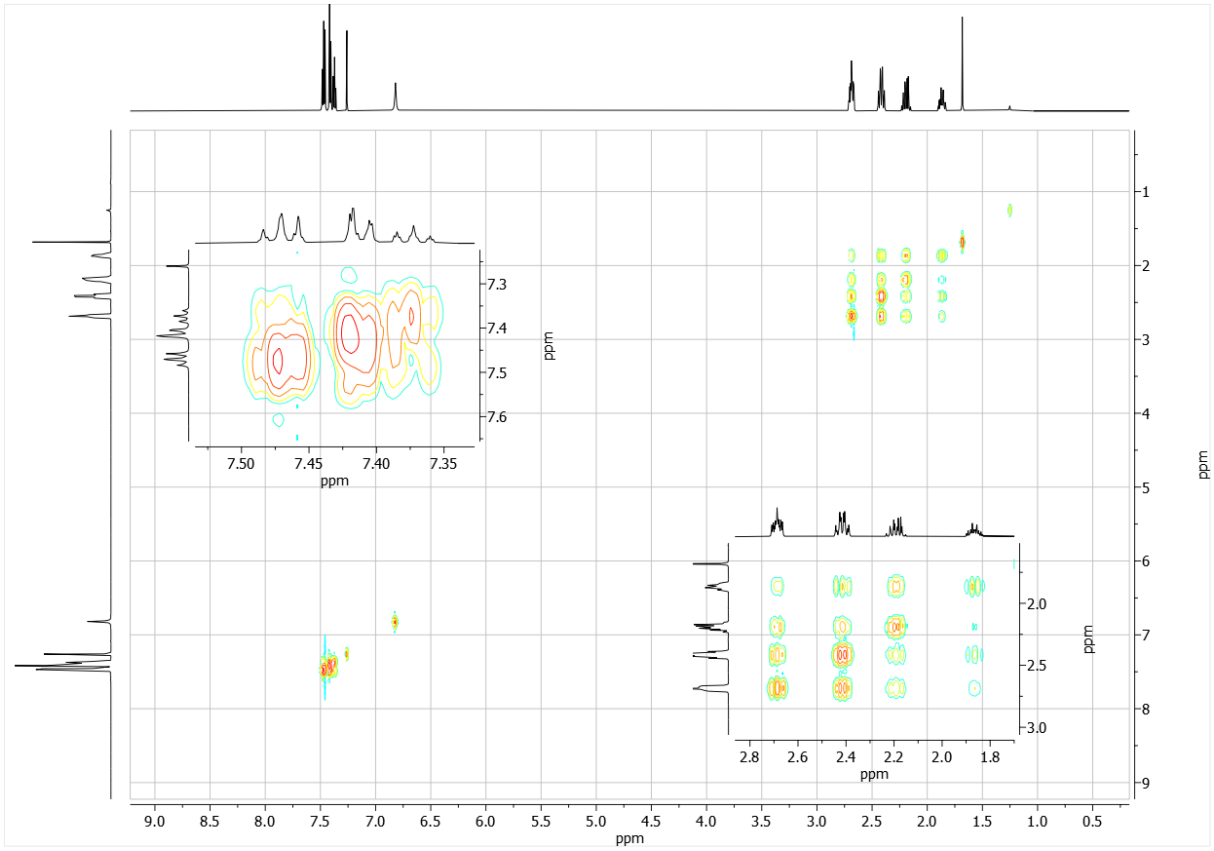
7-Phenyl-5,7-diazaspiro[3.4]octane-6,8-dione (5c) [935429-52-0]



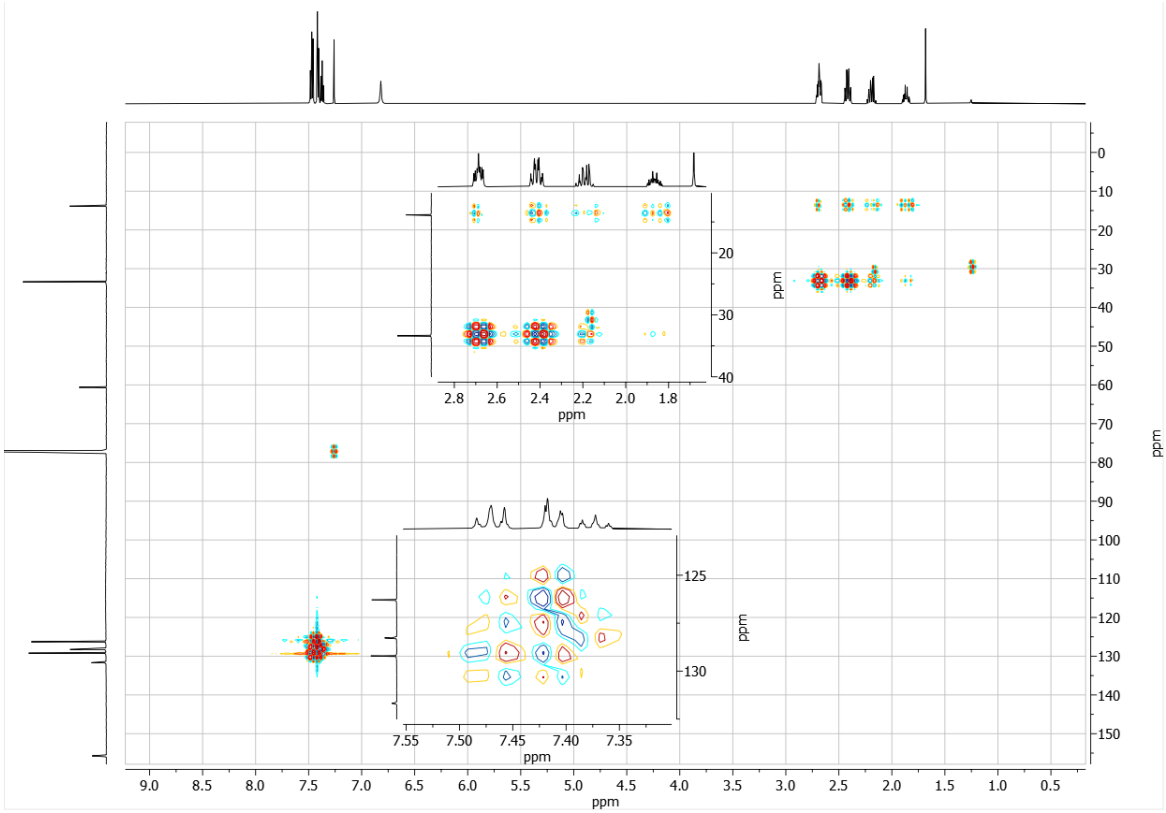
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5c.



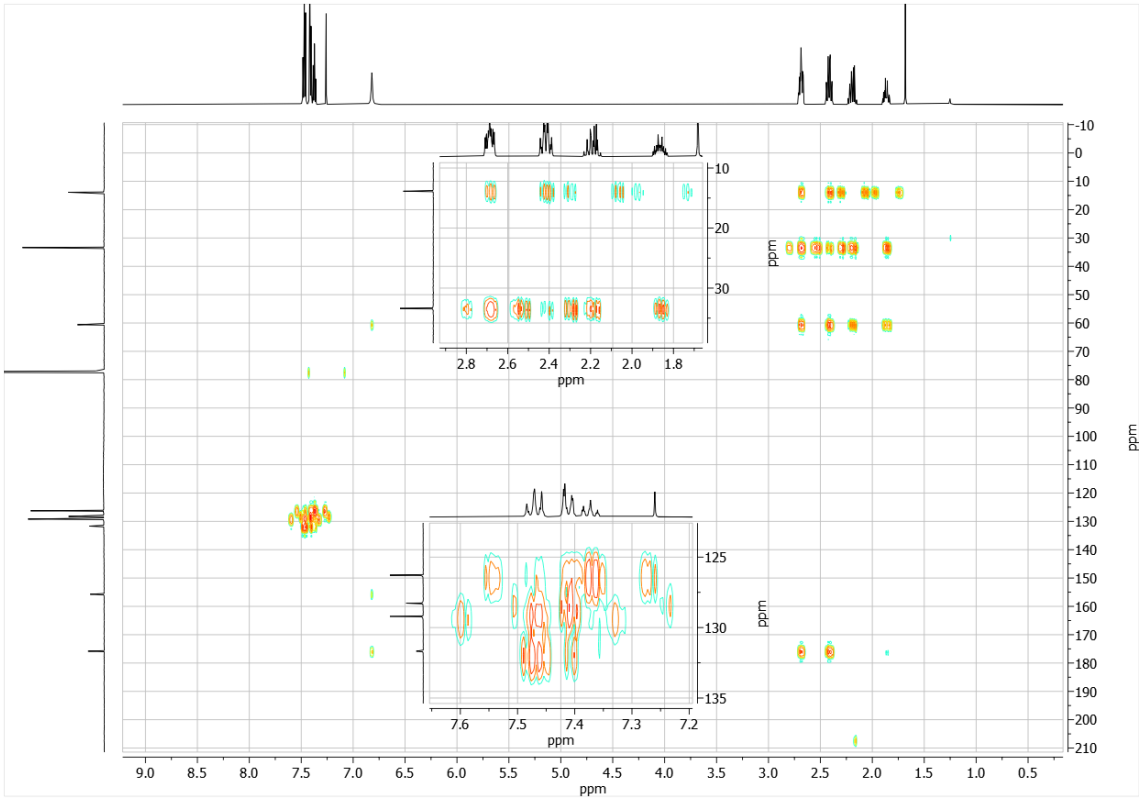
COSY (600 MHz, $CDCl_3$) spectrum of 5c.



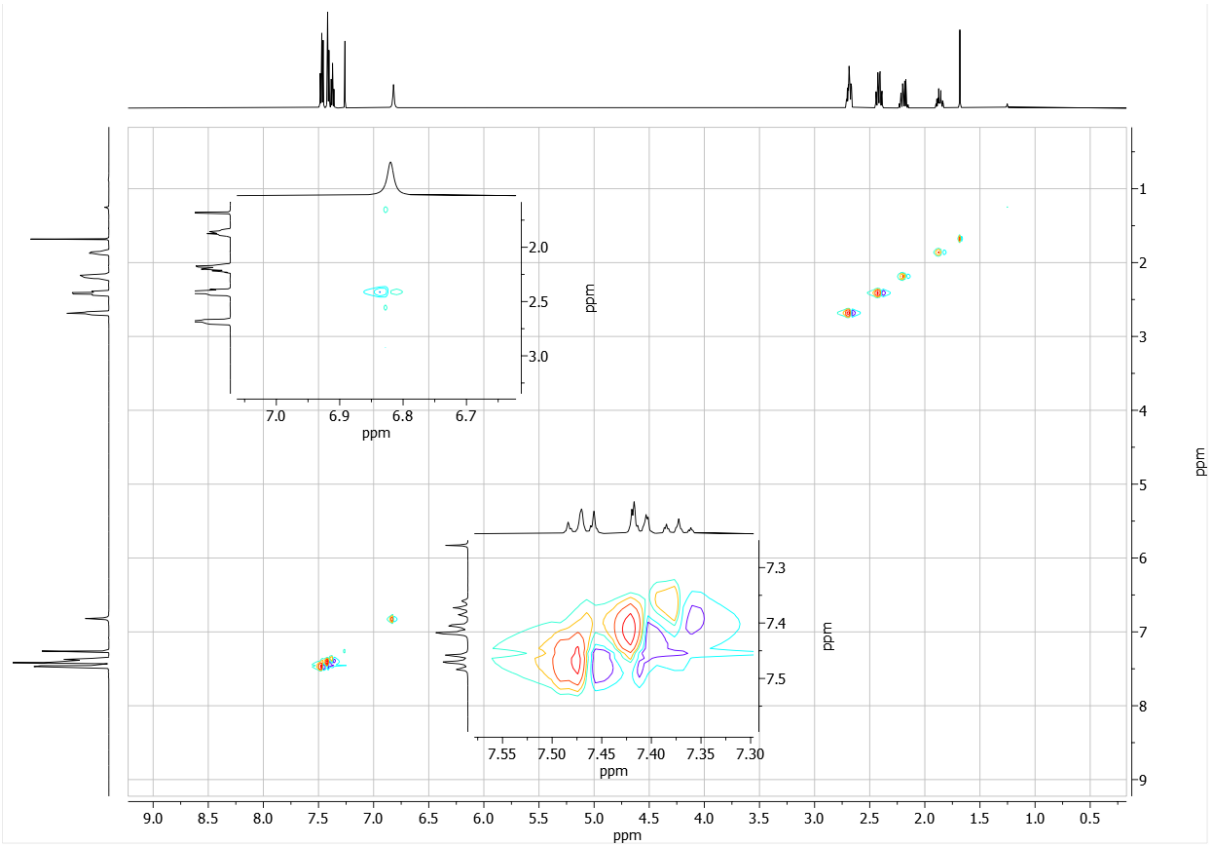
HSQC (600 MHz, $CDCl_3$) spectrum of 5c.



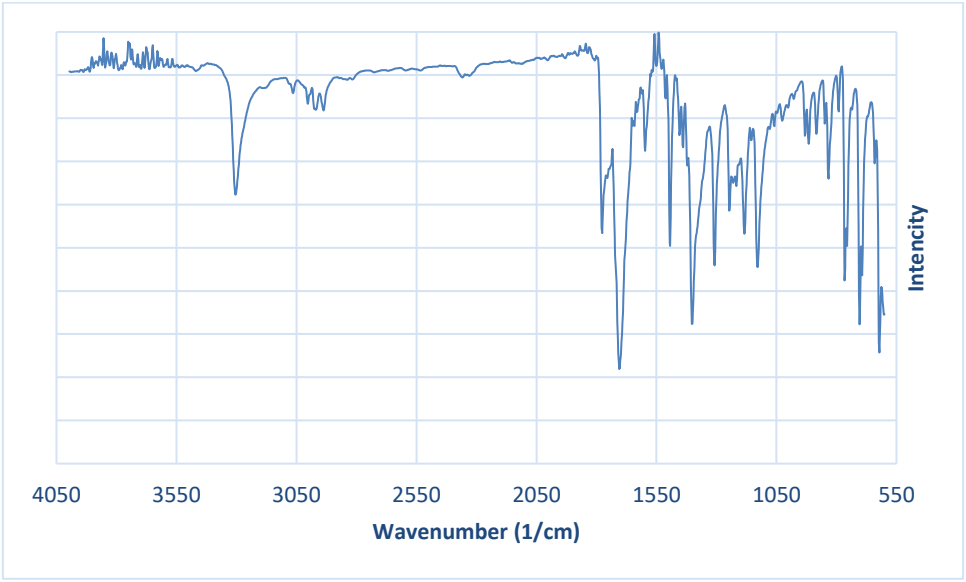
HMBC (600 MHz, $CDCl_3$) spectrum of 5c.



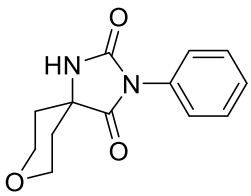
NOESY (600 MHz, $CDCl_3$) spectrum of 5c.



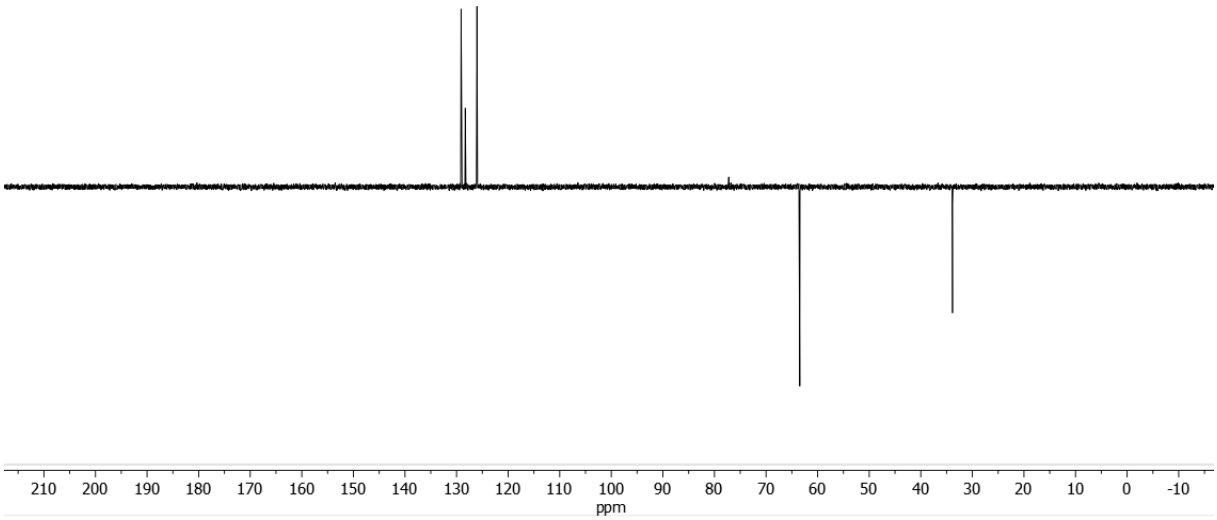
IR spectrum of 5c.



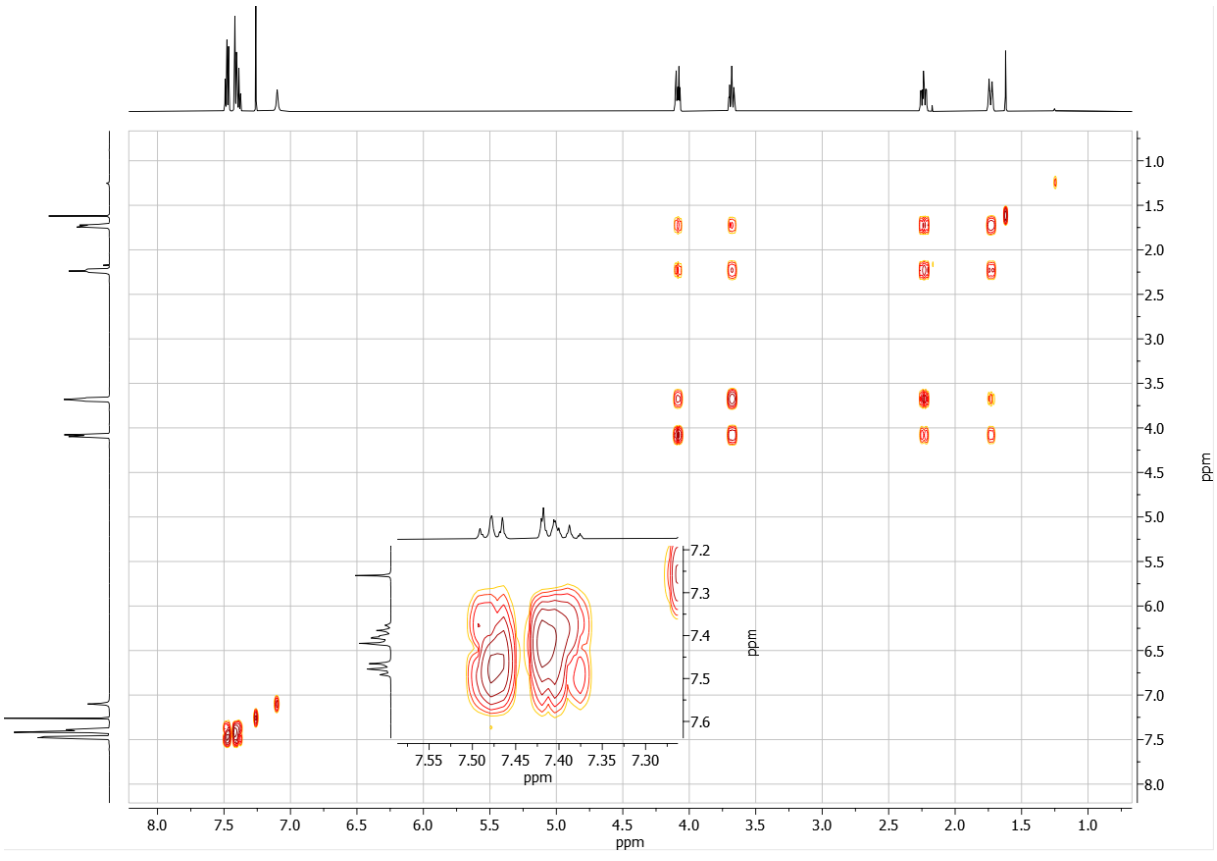
3-phenyl-8-Oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5d) [1552075-00-9]



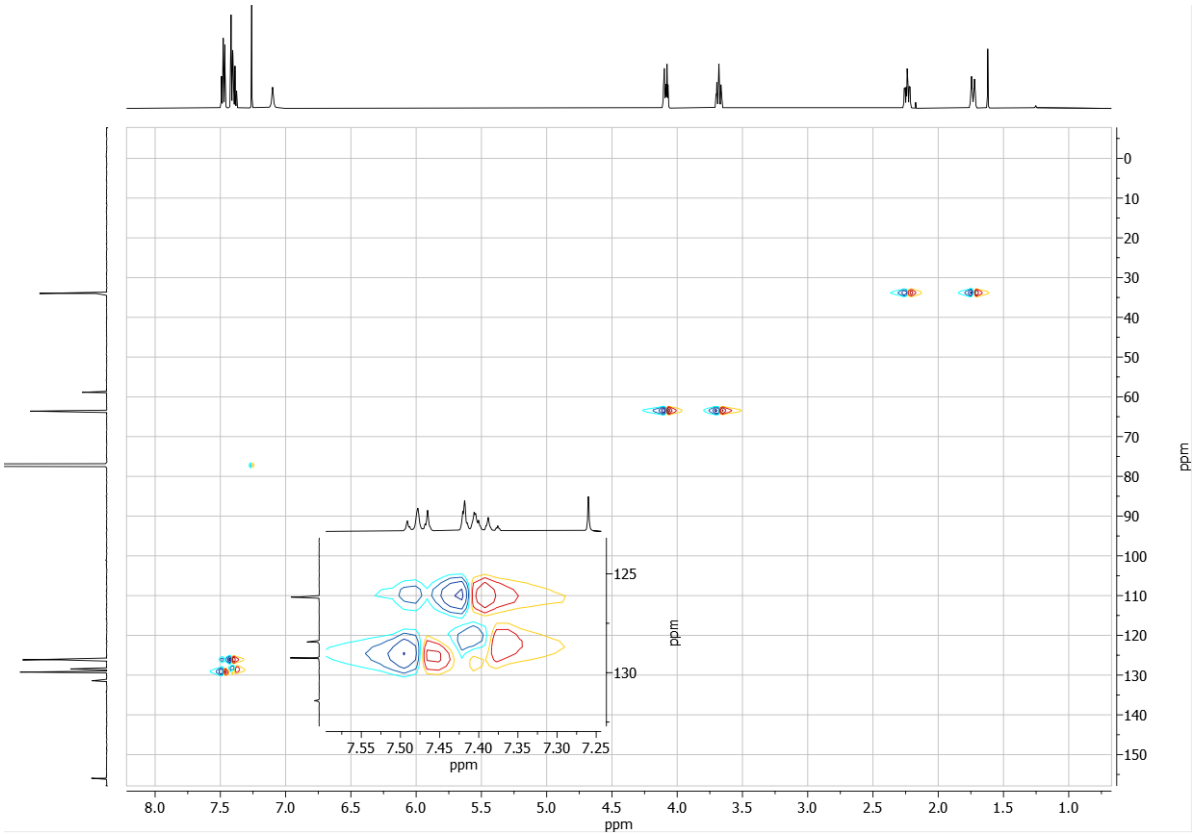
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5d.



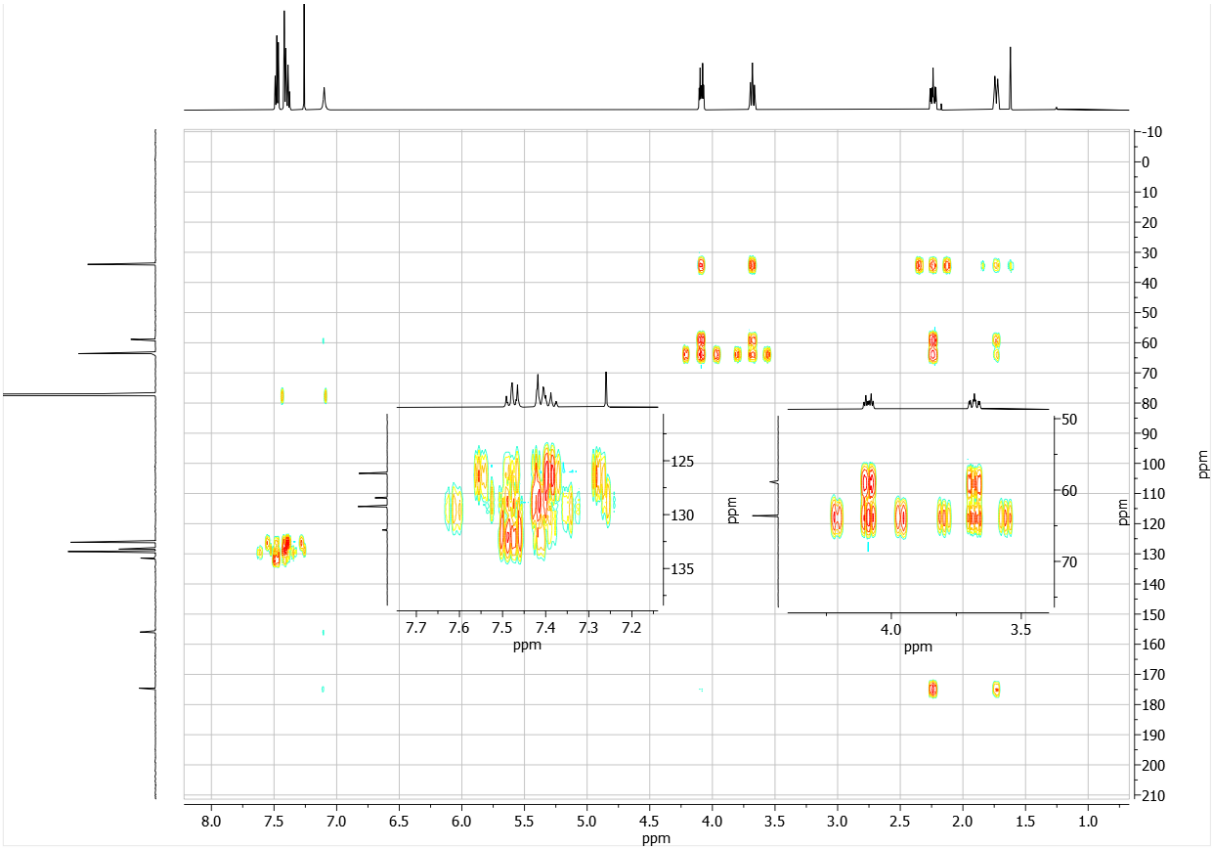
COSY (600 MHz, $CDCl_3$) spectrum of 5d.



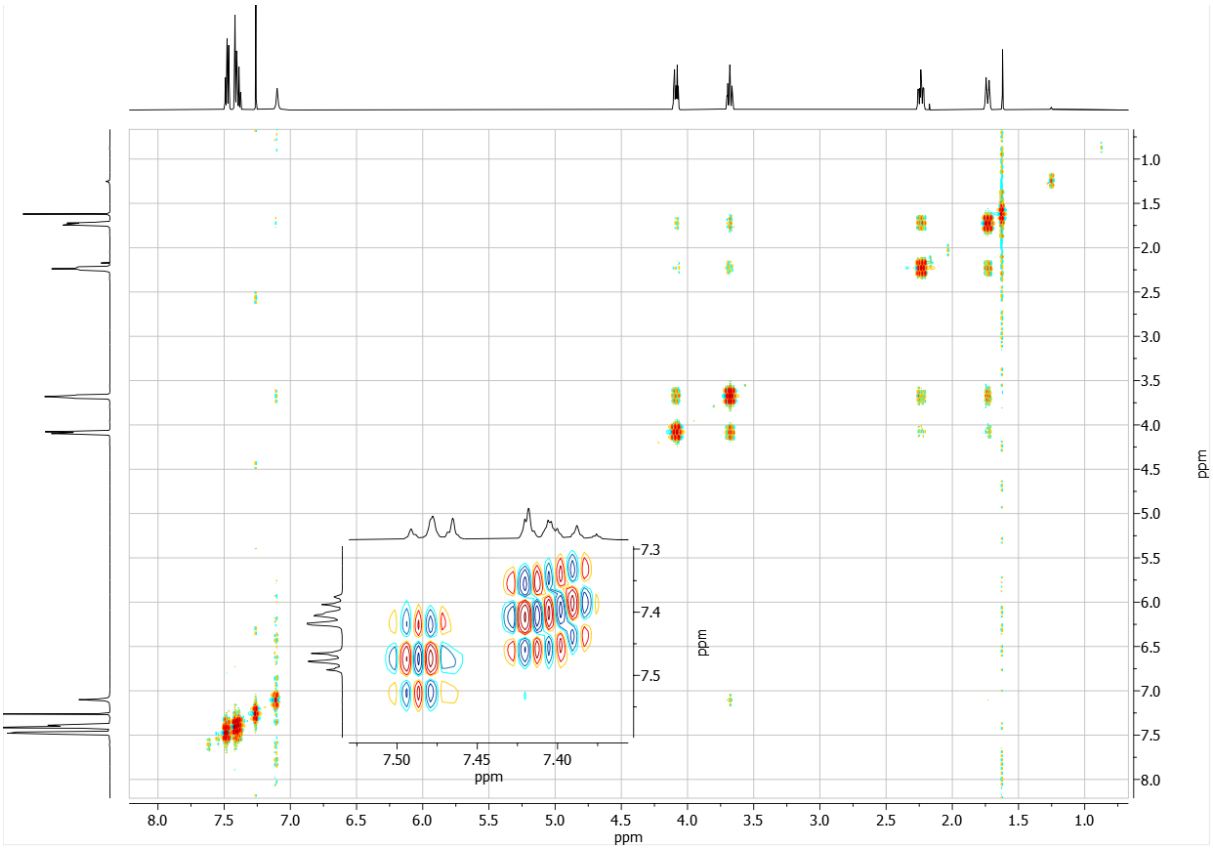
HSQC (600 MHz, $CDCl_3$) spectrum of 5d.



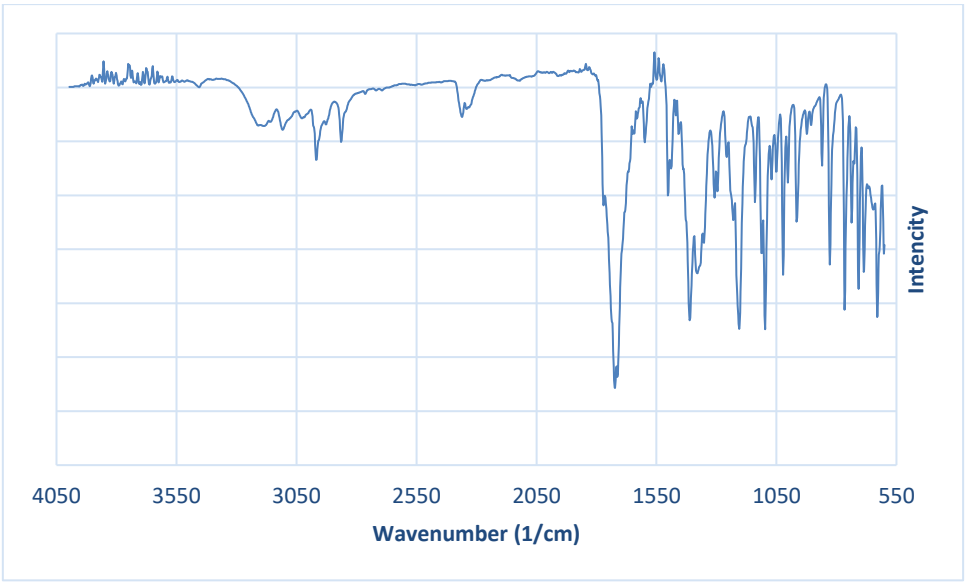
HMBC (600 MHz, $CDCl_3$) spectrum of 5d.



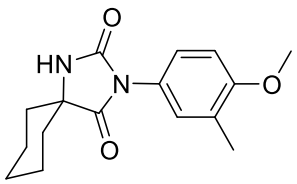
NOESY (600 MHz, $CDCl_3$) spectrum of 5d.



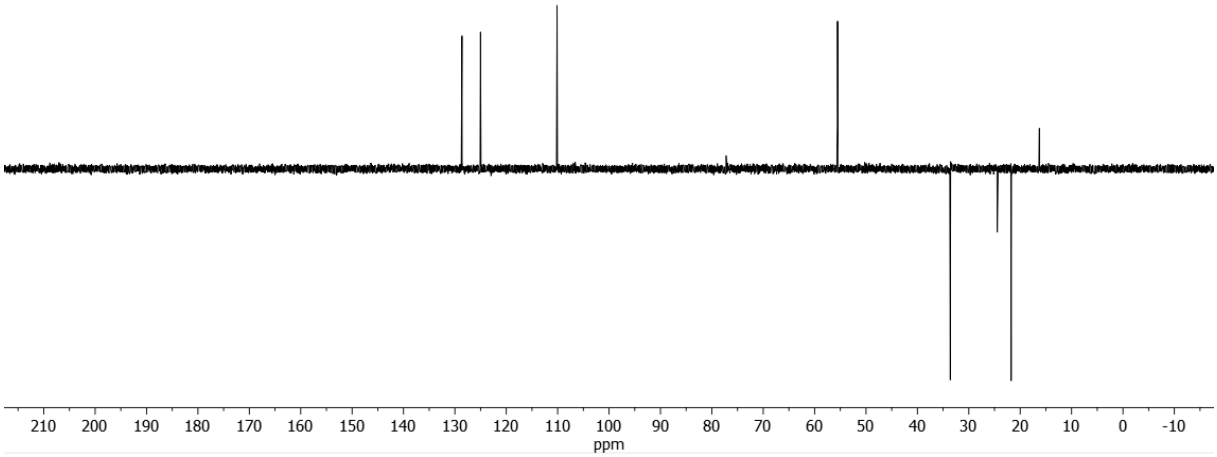
IR spectrum of 5d.



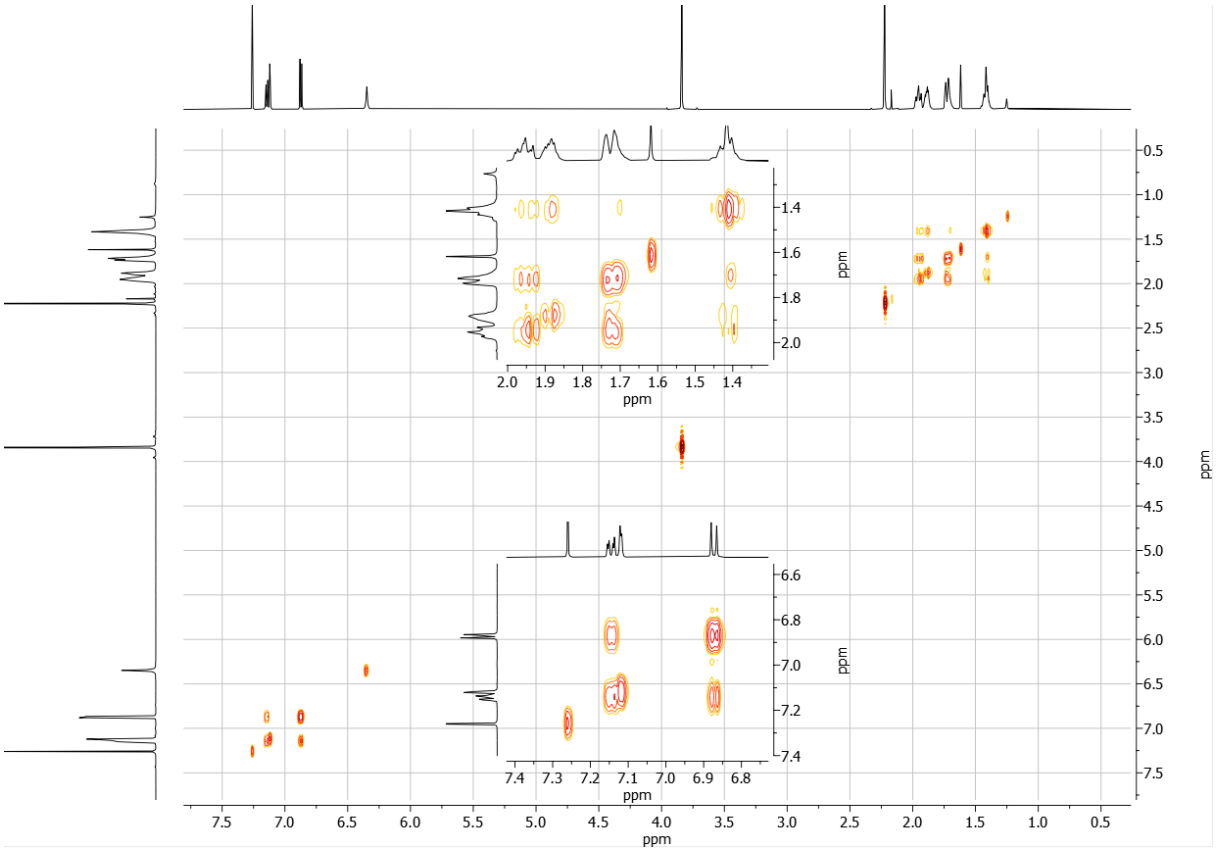
3-(4methoxy-3-methylphenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (5e) [NEW]



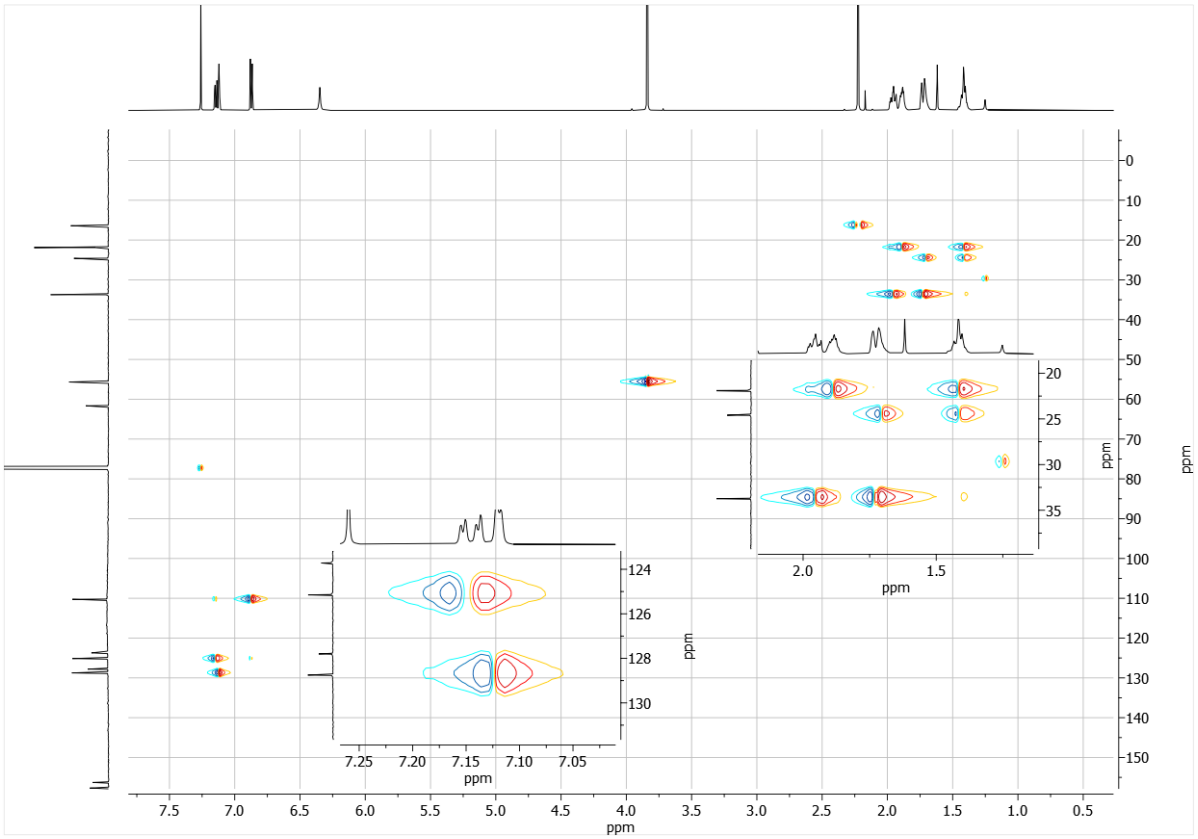
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5e.



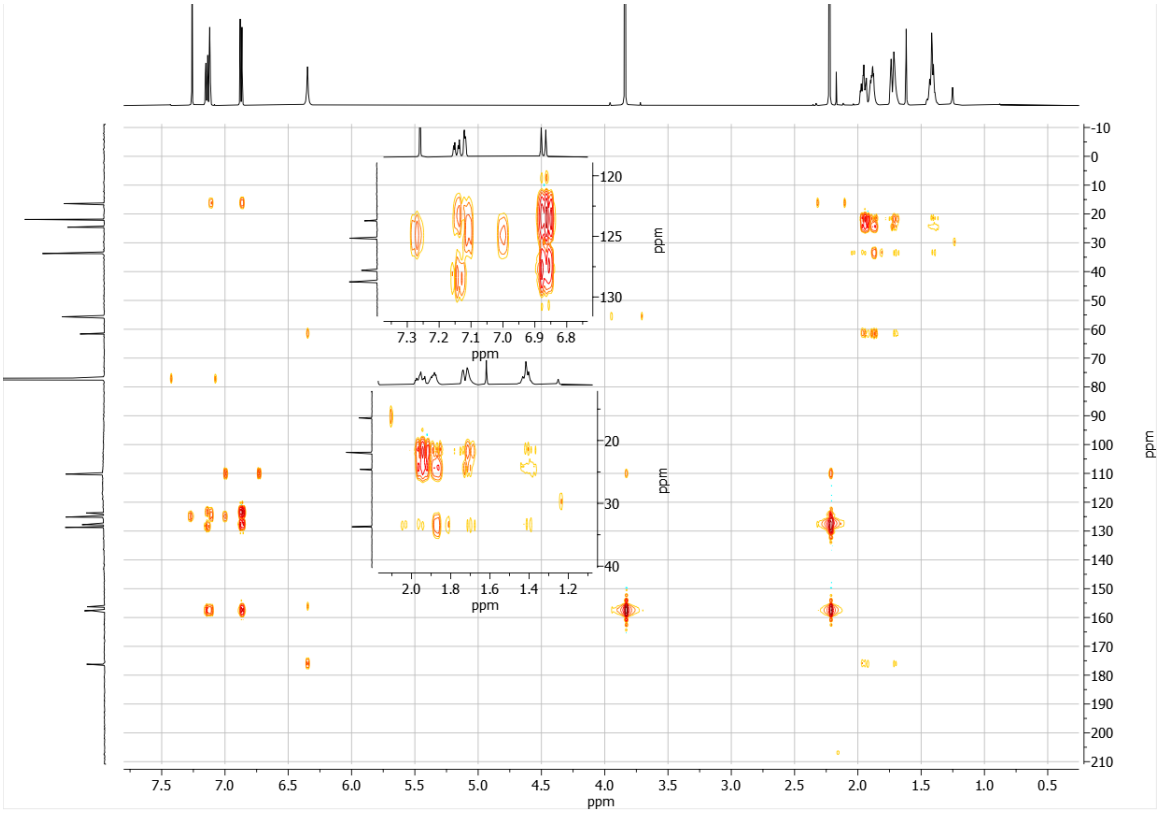
COSY (600 MHz, $CDCl_3$) spectrum of 5e.



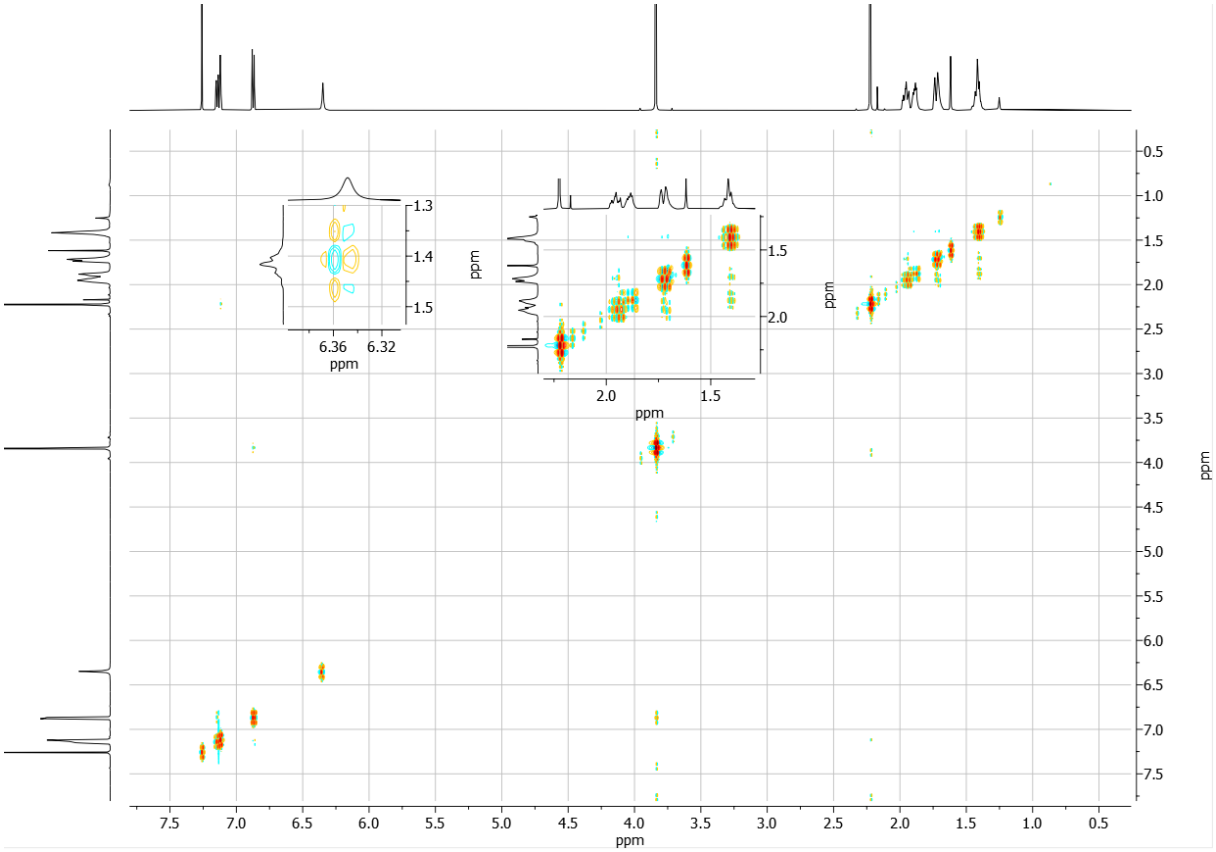
HSQC (600 MHz, $CDCl_3$) spectrum of 5e.



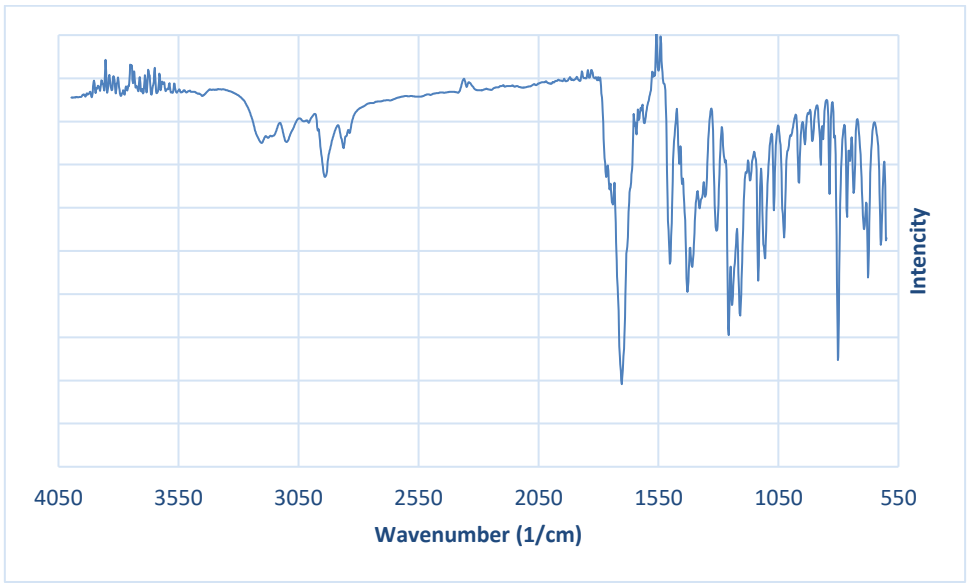
HMBC (600 MHz, $CDCl_3$) spectrum of 5e.



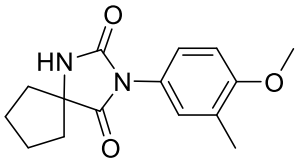
NOESY (600 MHz, $CDCl_3$) spectrum of 5e.



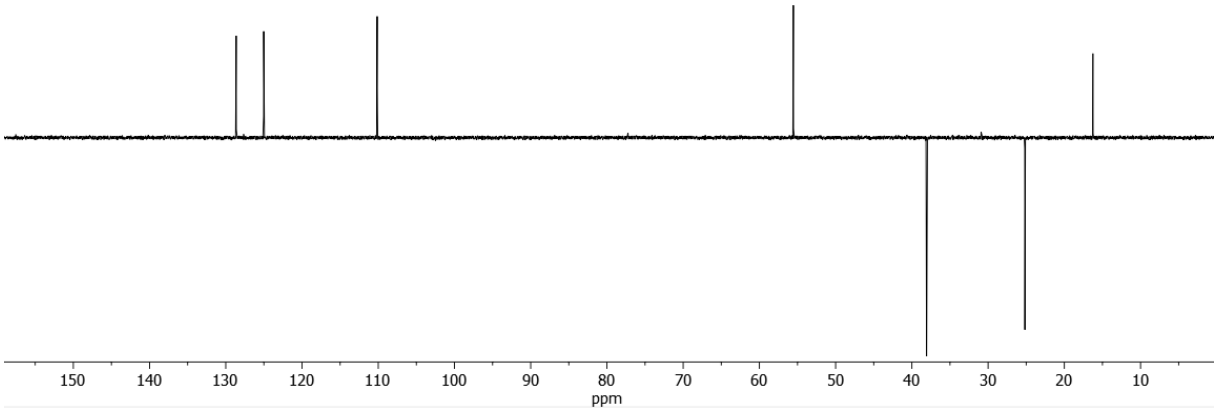
IR spectrum of 5e.



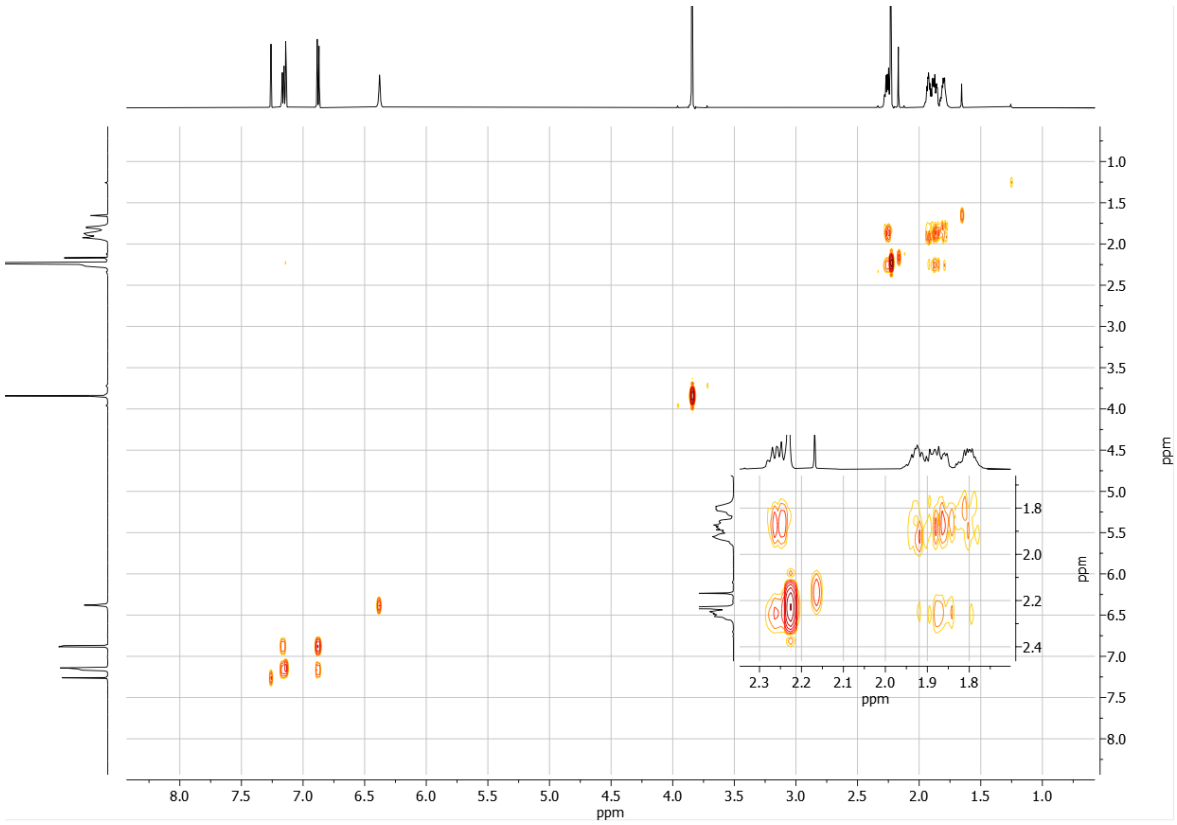
3-(4methoxy-3-methylphenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (5f) [NEW]



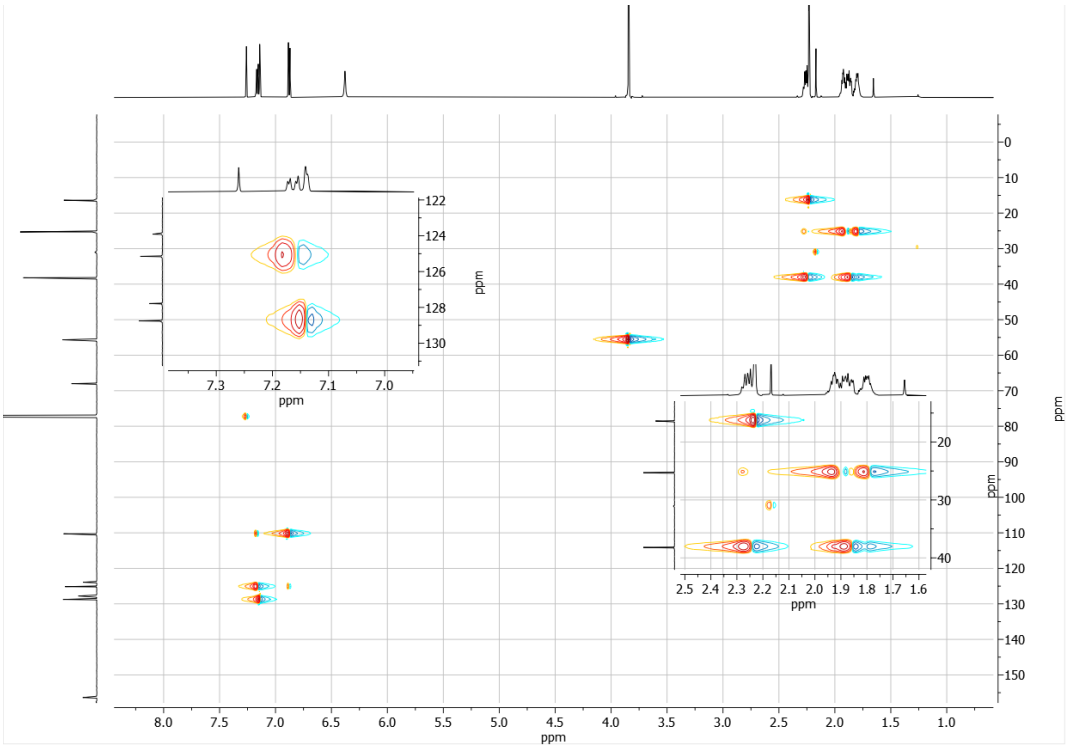
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5f.



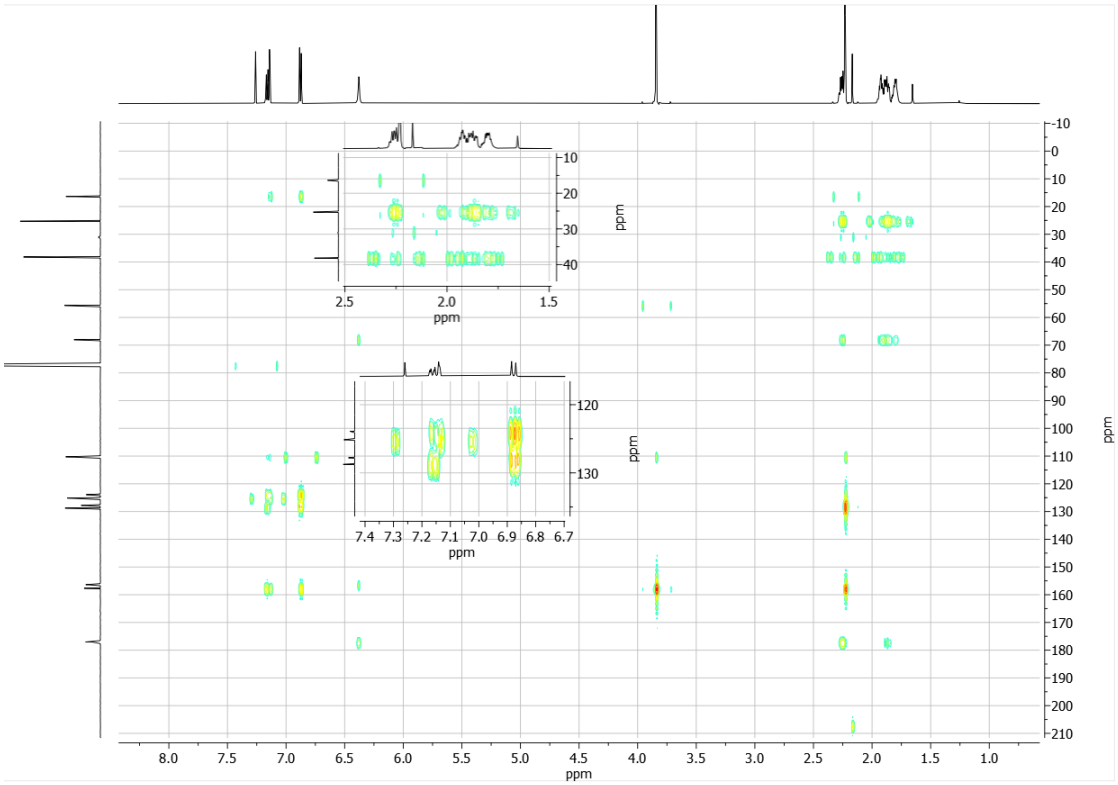
COSY (600 MHz, $CDCl_3$) spectrum of 5f.



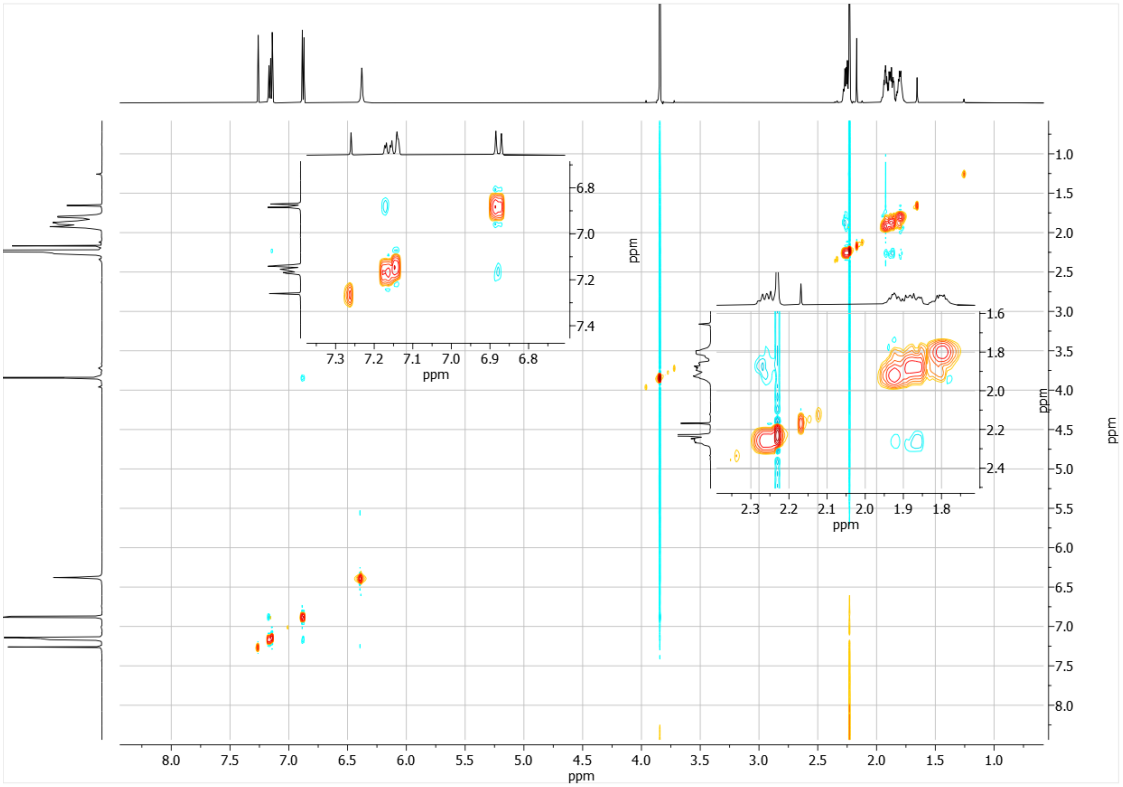
HSQC (600 MHz, $CDCl_3$) spectrum of 5f.



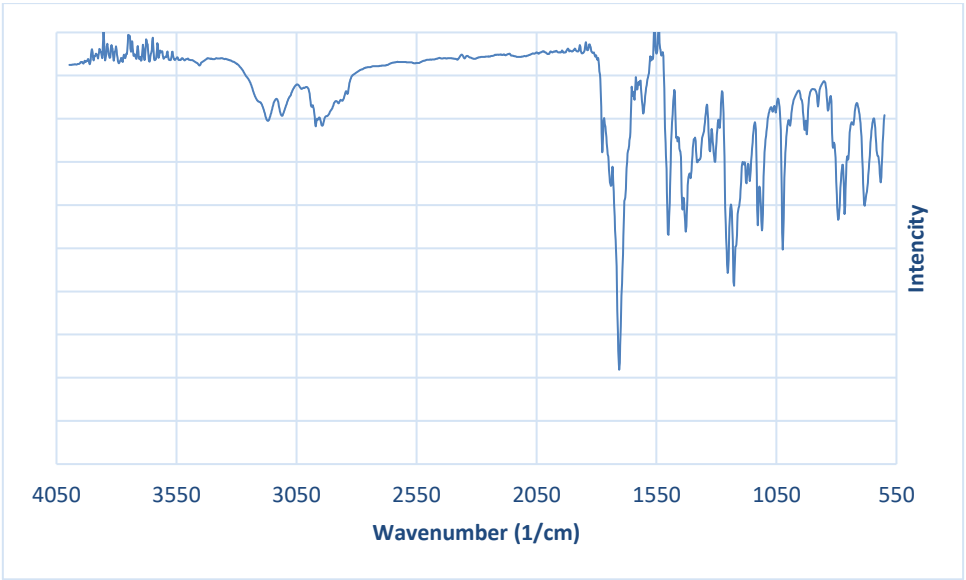
HMBC (600 MHz, $CDCl_3$) spectrum of 5f.



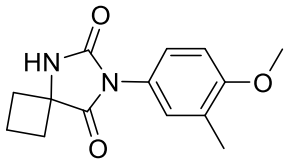
NOESY (600 MHz, $CDCl_3$) spectrum of 5f.



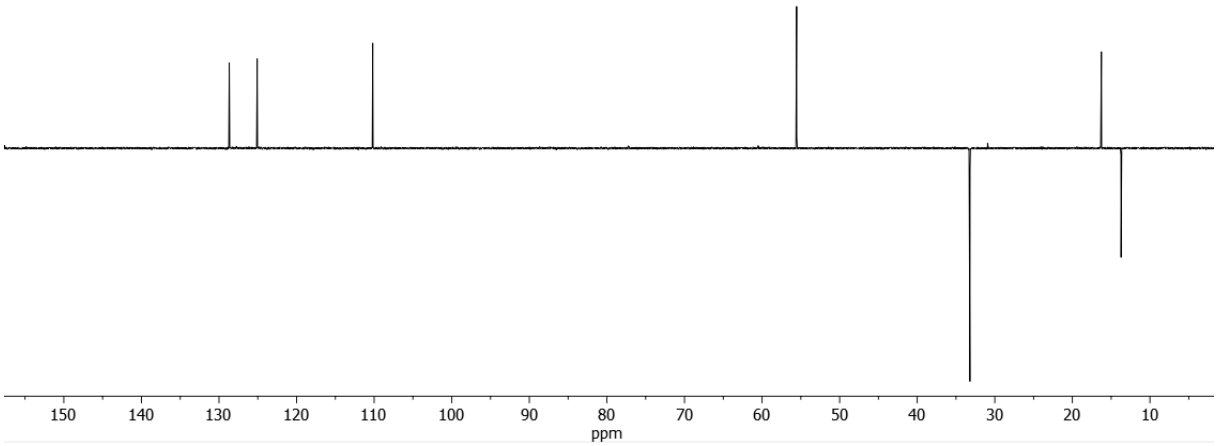
IR spectrum of 5f.



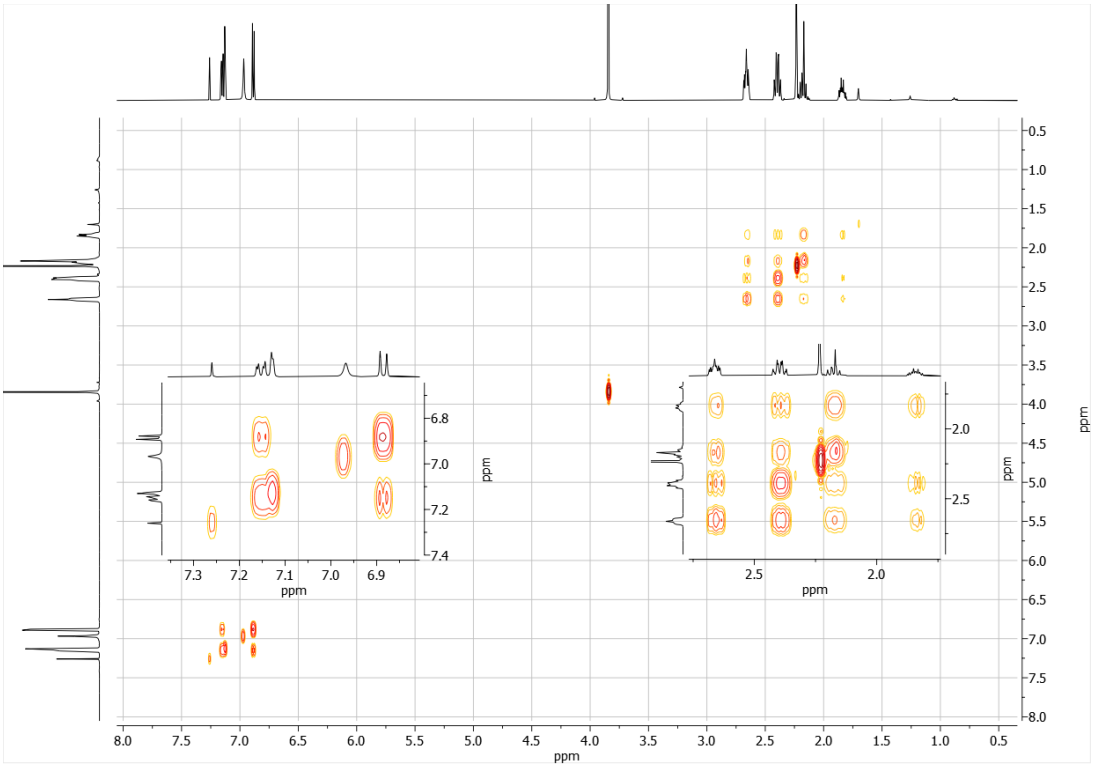
7-(4methoxy-3-methylphenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5g) [NEW]



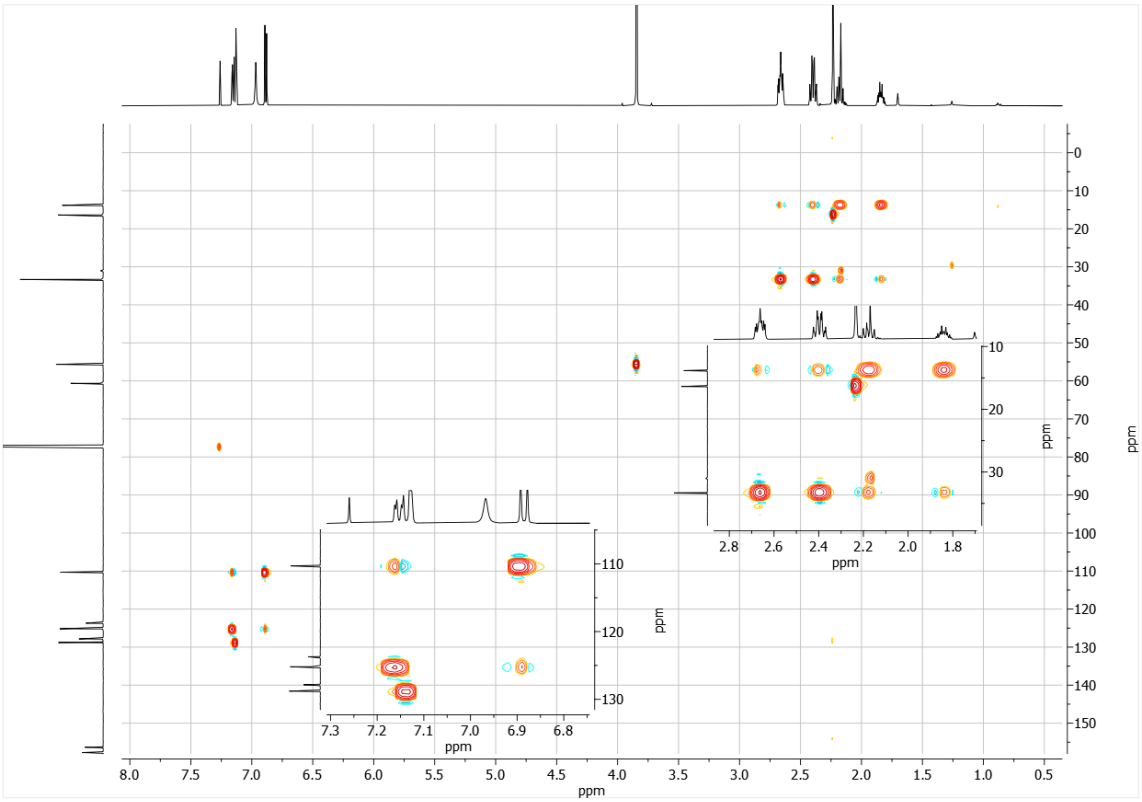
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5g.



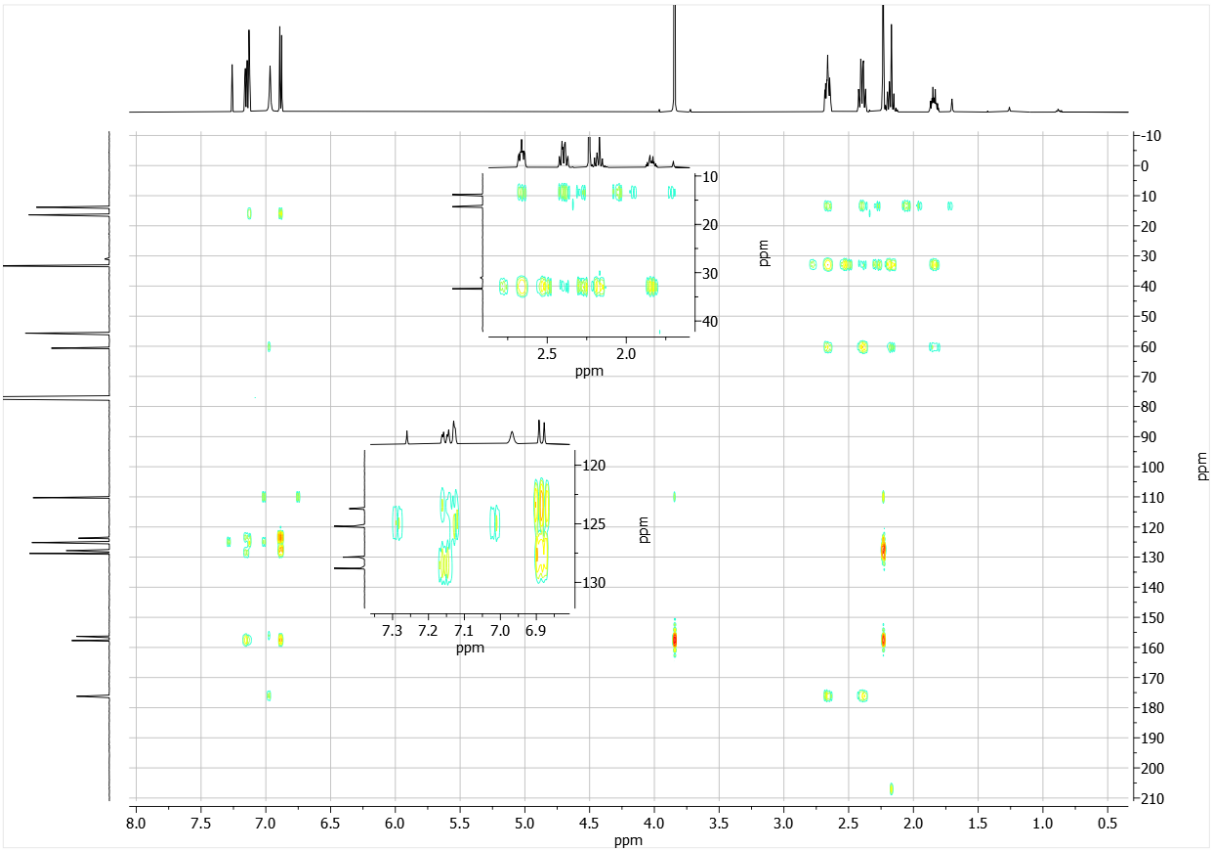
COSY (600 MHz, $CDCl_3$) spectrum of 5g.



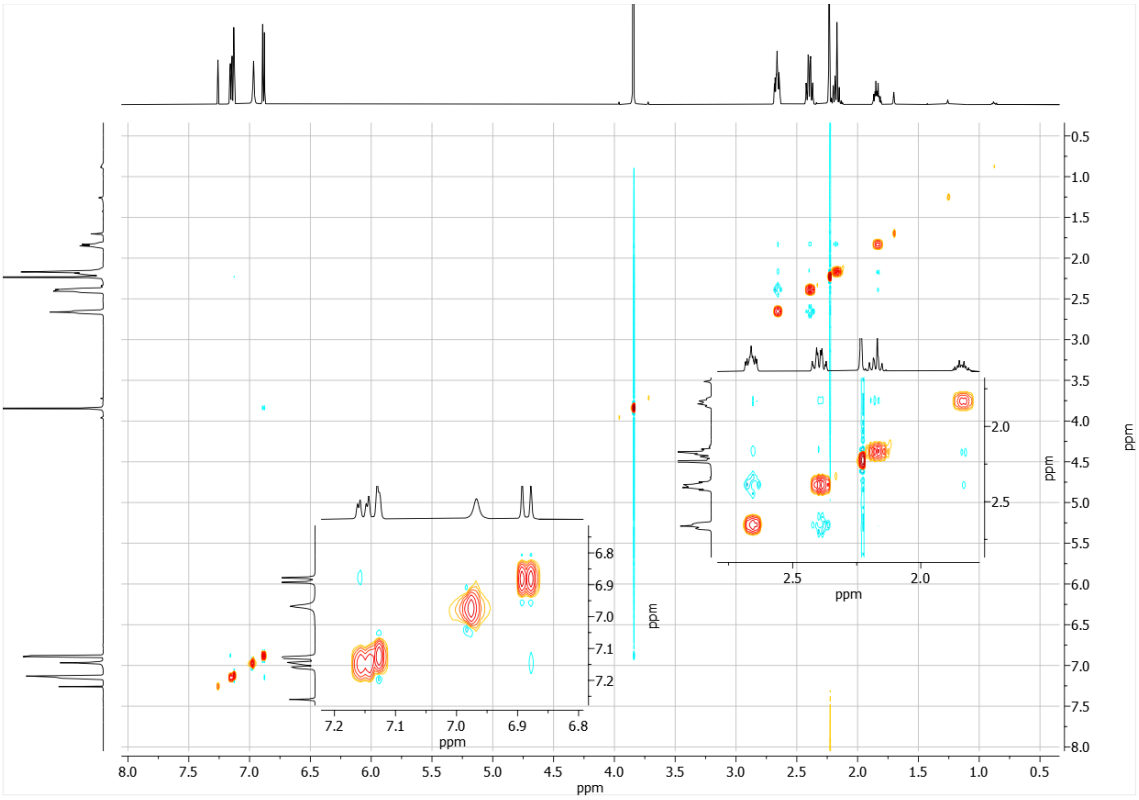
HSQC (600 MHz, $CDCl_3$) spectrum of 5g.



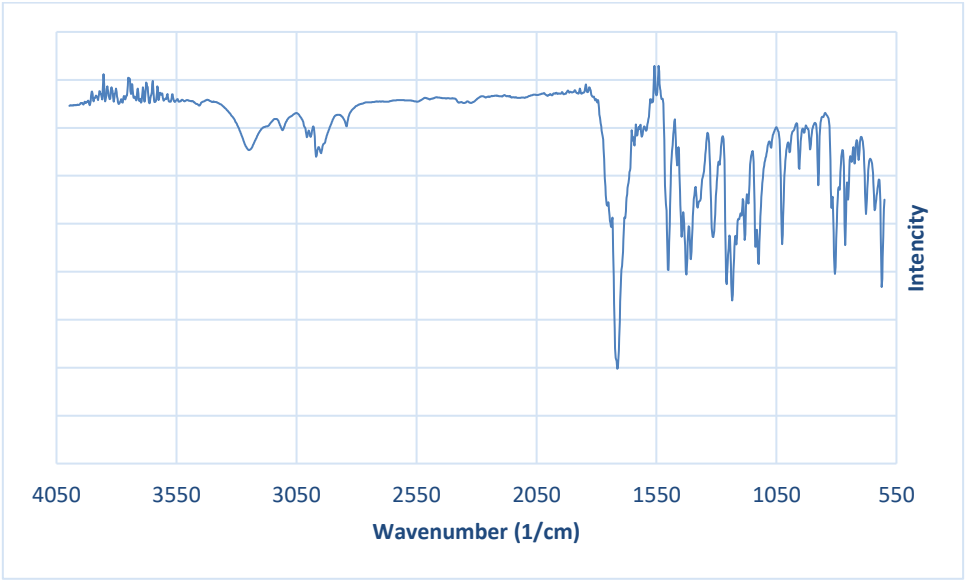
HMBC (600 MHz, $CDCl_3$) spectrum of 5g.



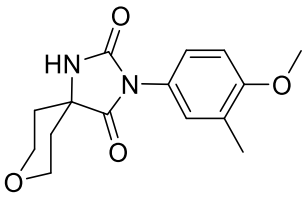
NOESY (600 MHz, $CDCl_3$) spectrum of 5g.



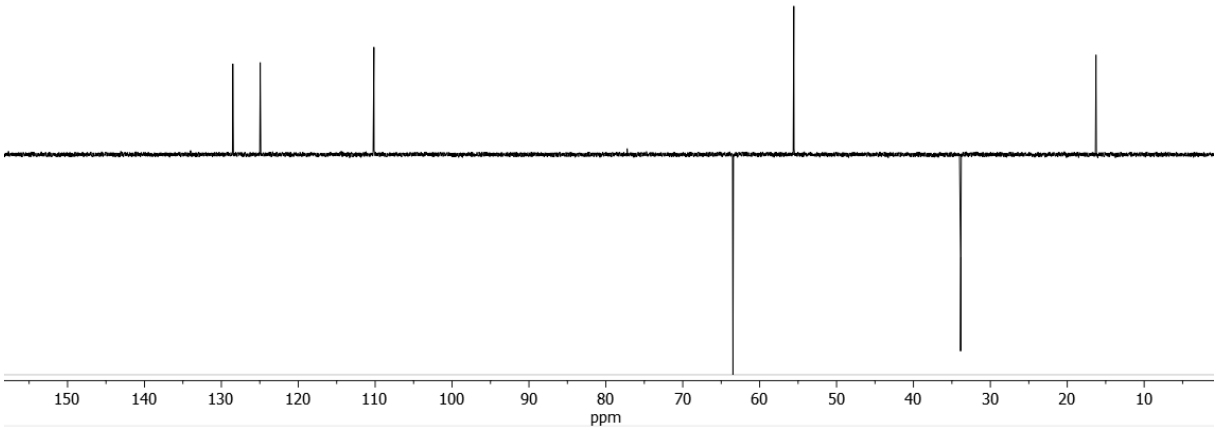
IR spectrum of 5g.



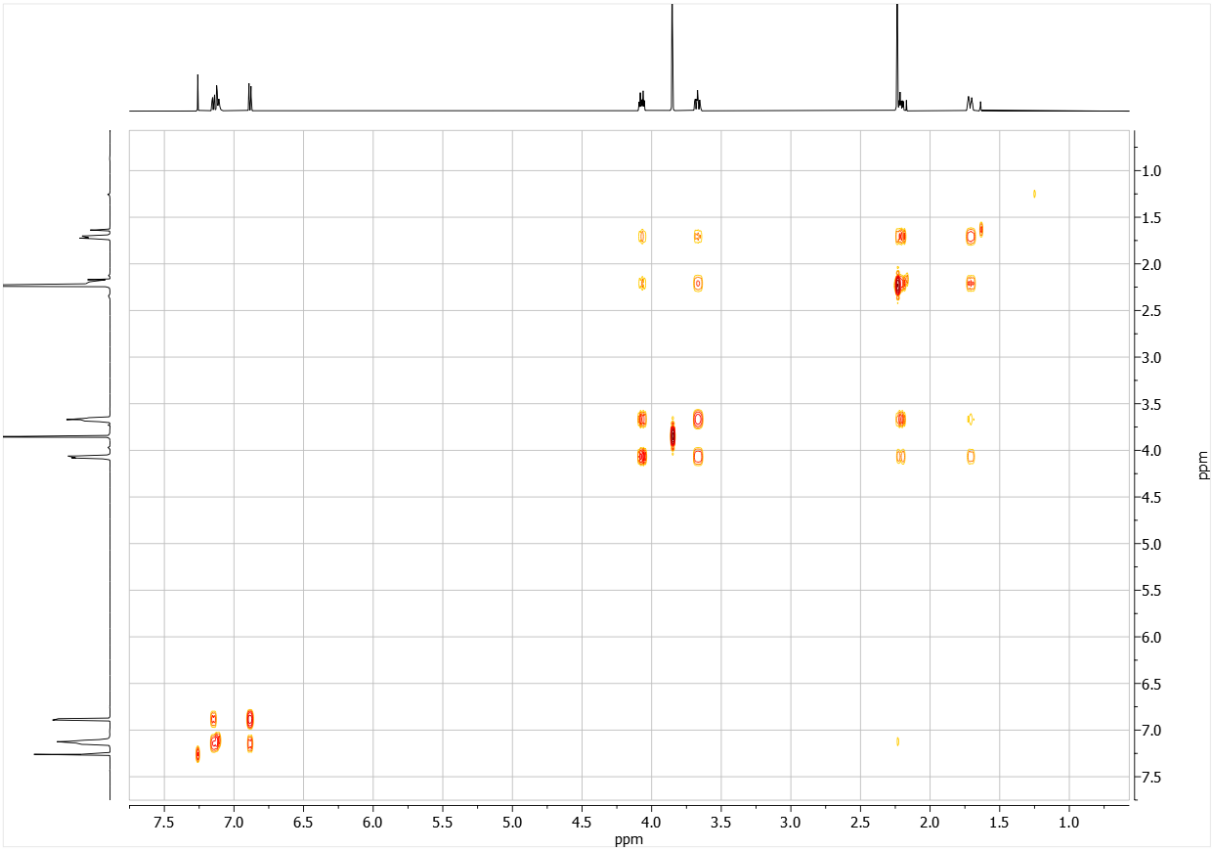
3-(4methoxy-3-methylphenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5h) [NEW]



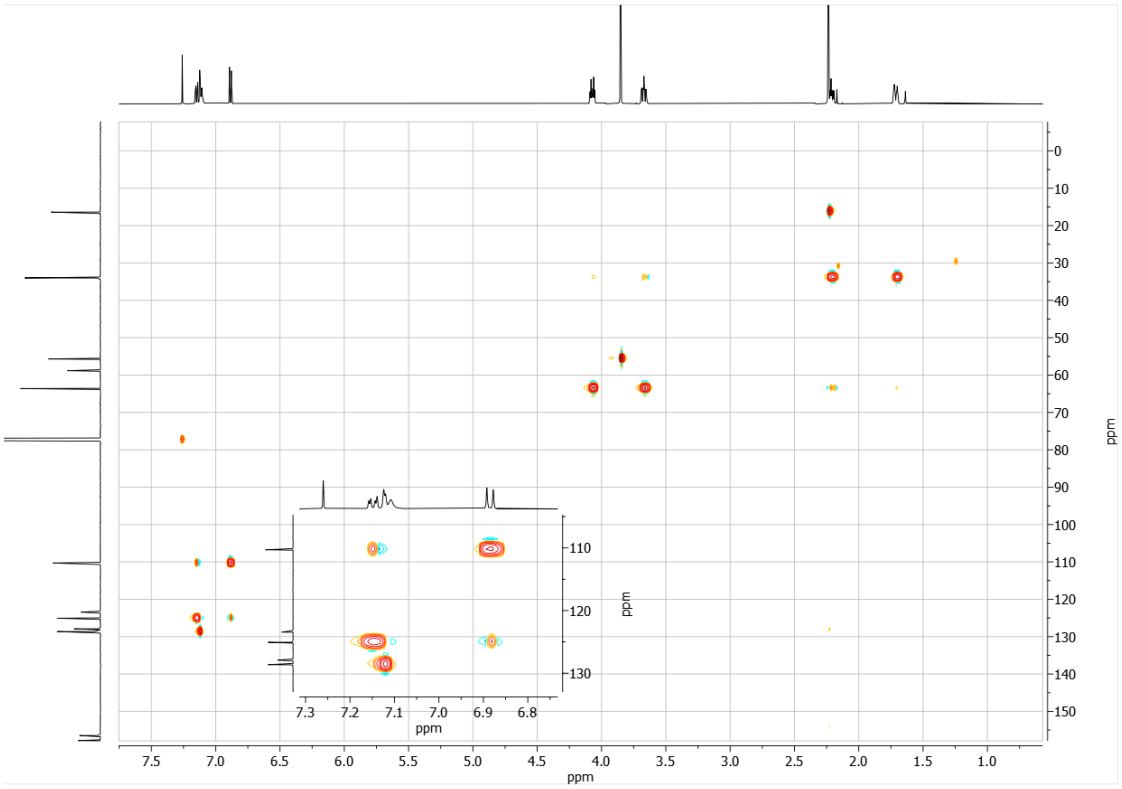
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5h.



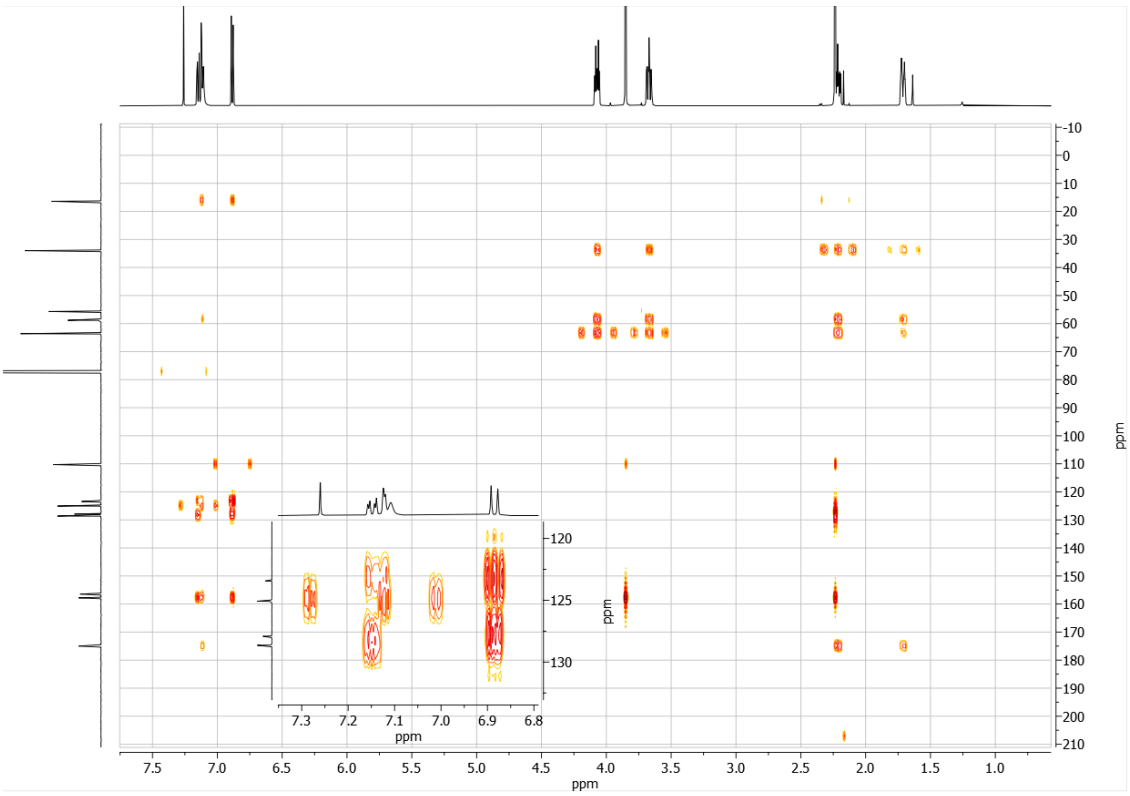
COSY (600 MHz, $CDCl_3$) spectrum of 5h.



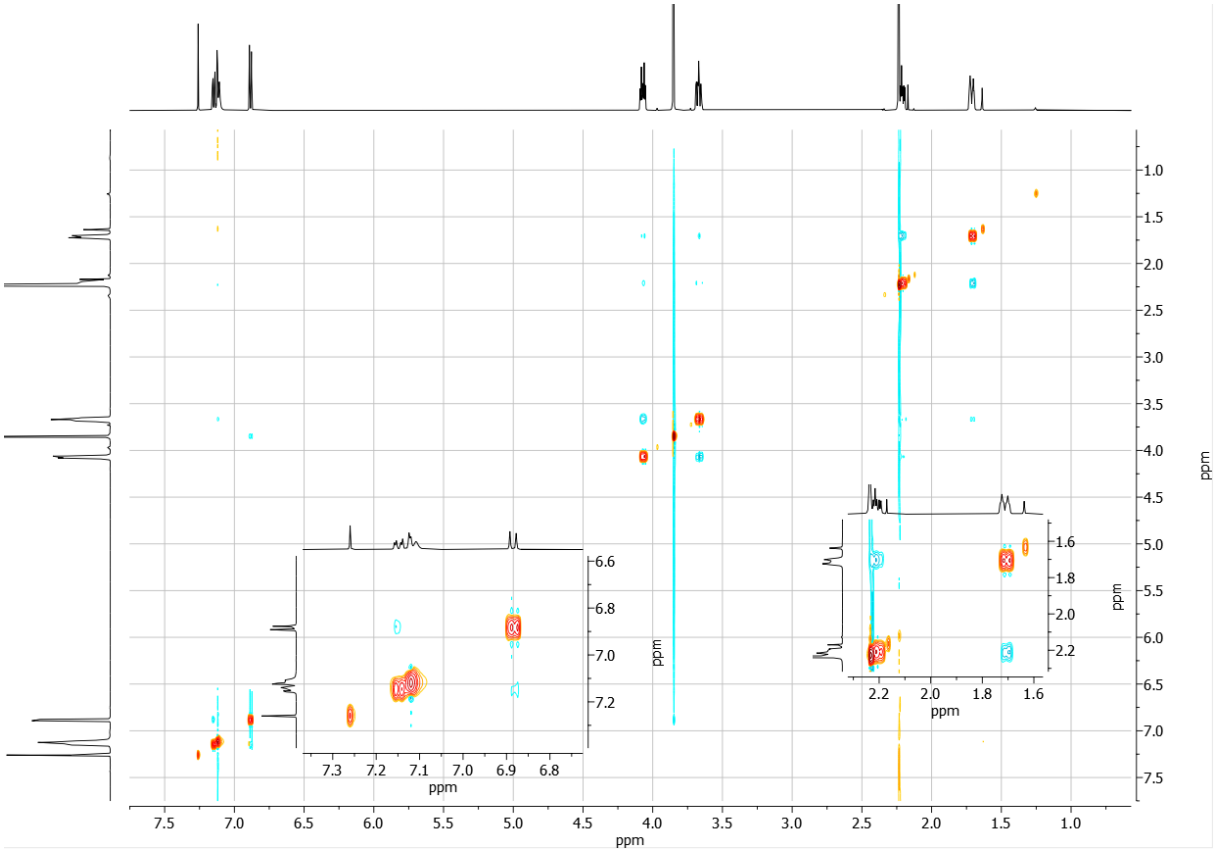
HSQC (600 MHz, $CDCl_3$) spectrum of 5h.



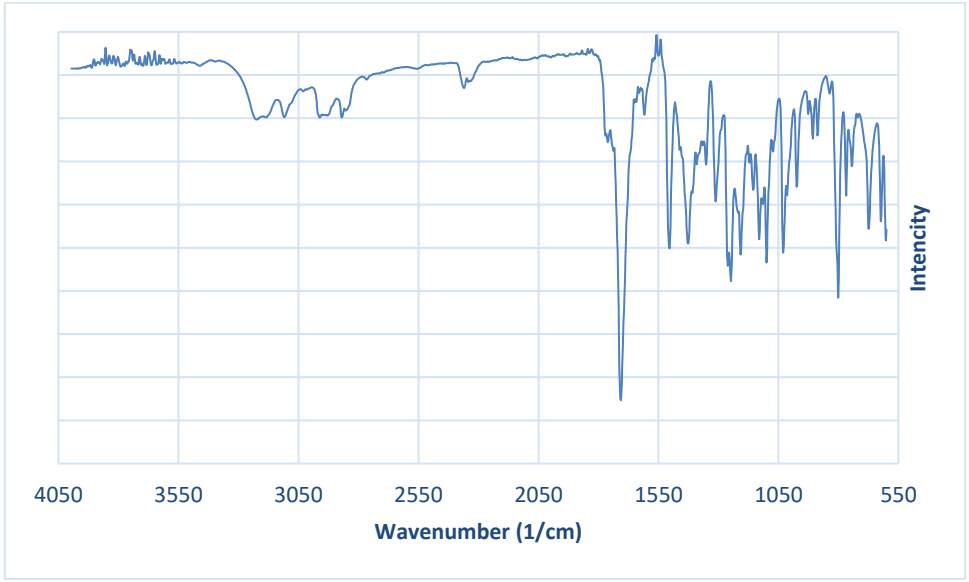
HMBC (600 MHz, $CDCl_3$) spectrum of 5h.



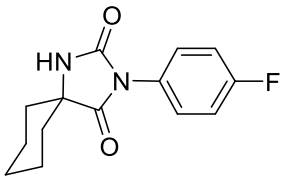
NOESY (600 MHz, $CDCl_3$) spectrum of 5h.



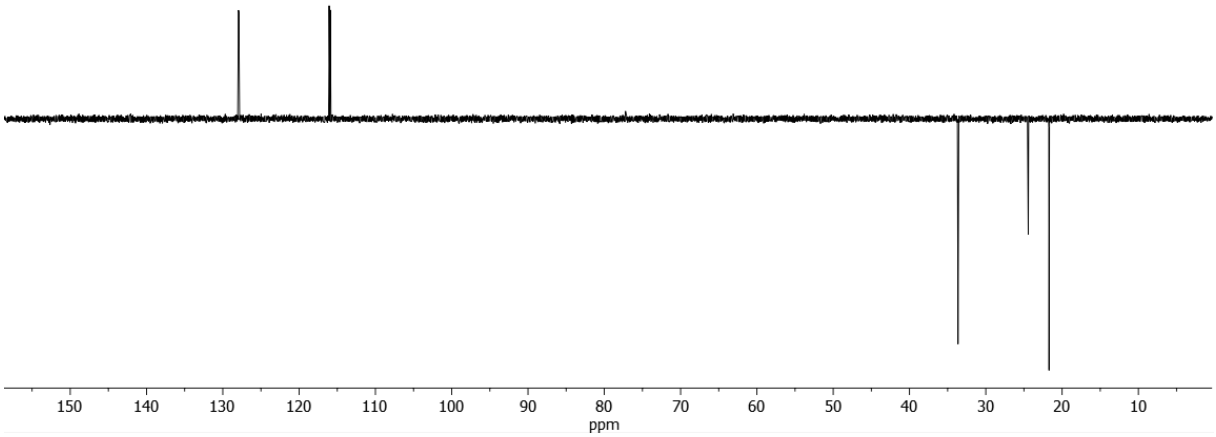
IR spectrum of 5h.



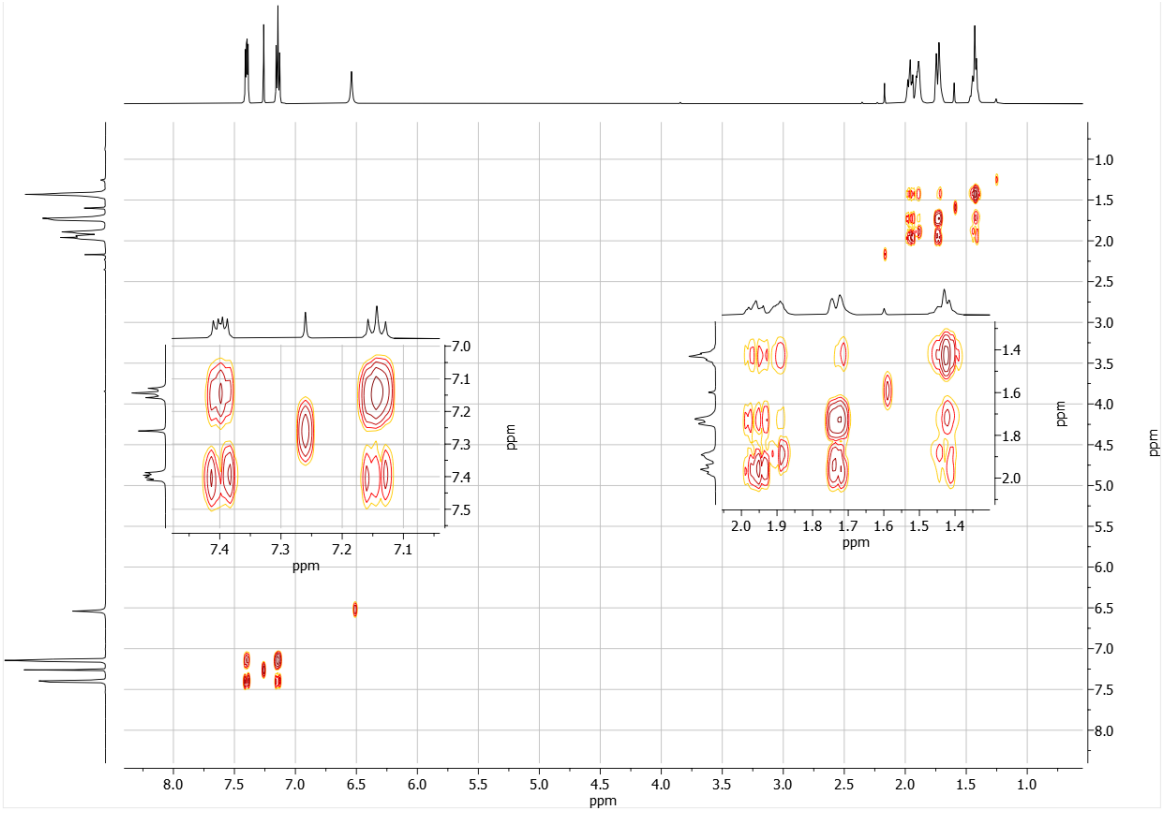
3-(4-fluorophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (5i) [133466-16-7]



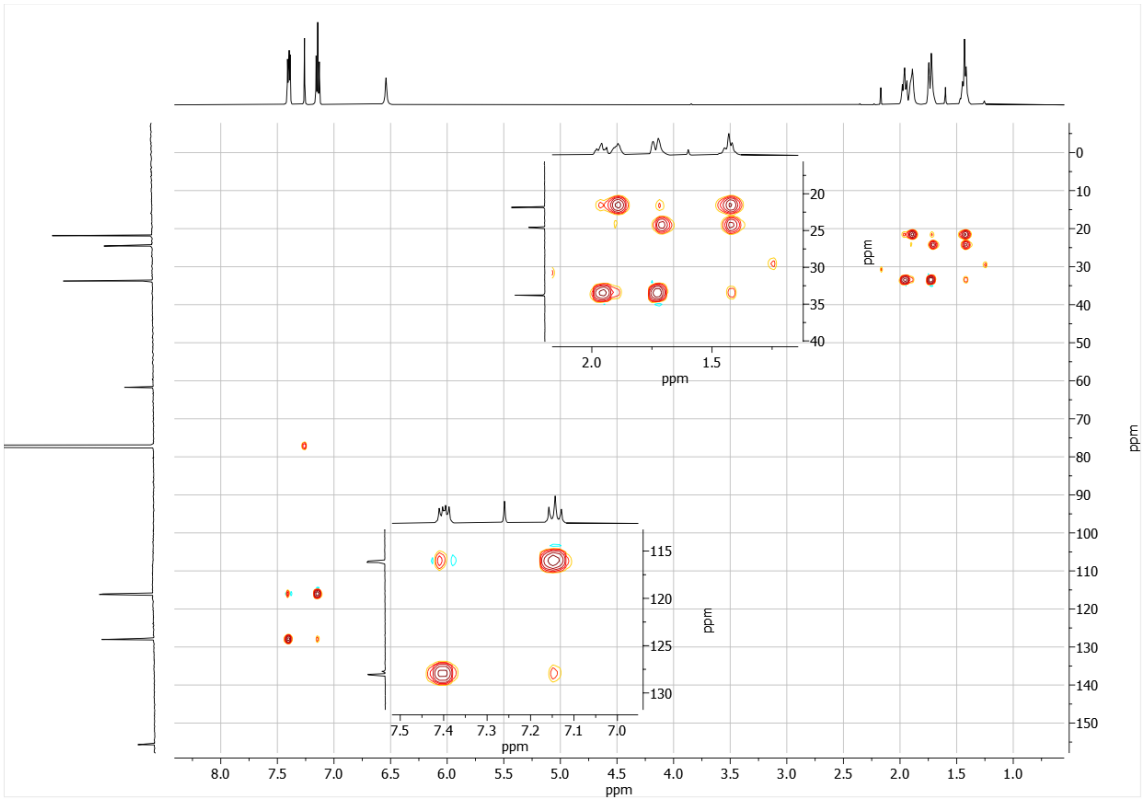
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5i.



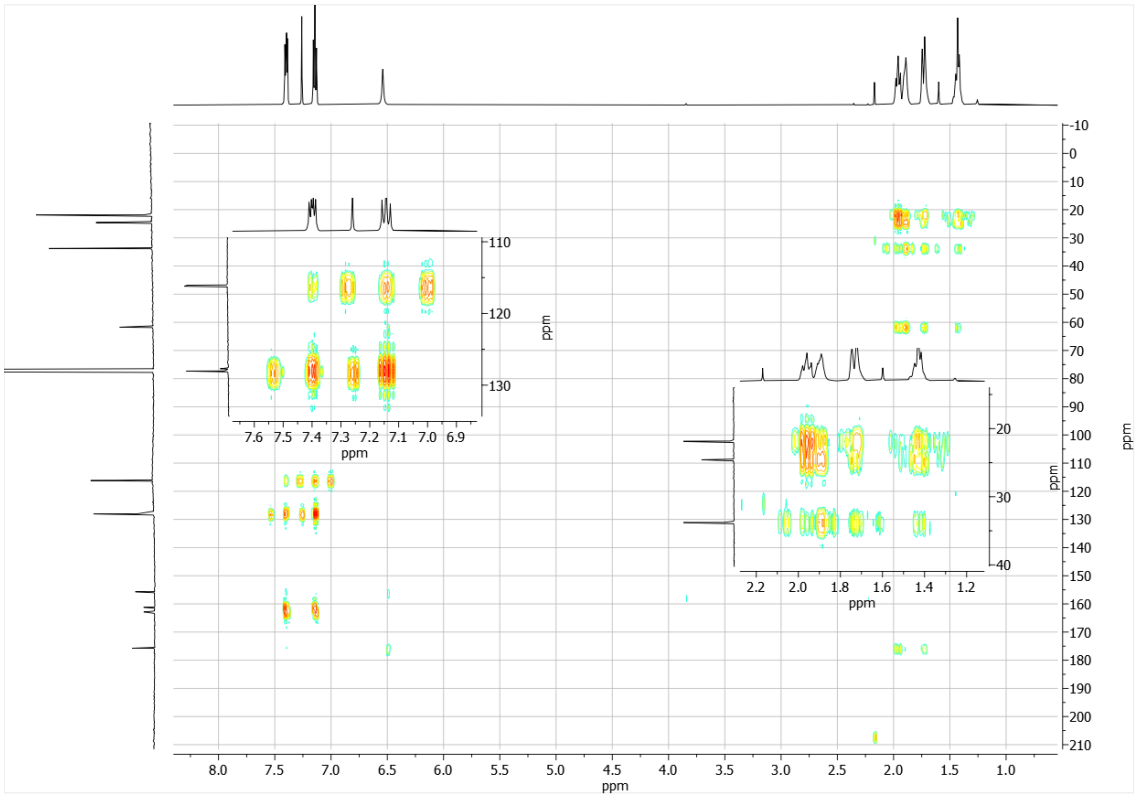
COSY (600 MHz, $CDCl_3$) spectrum of 5i.



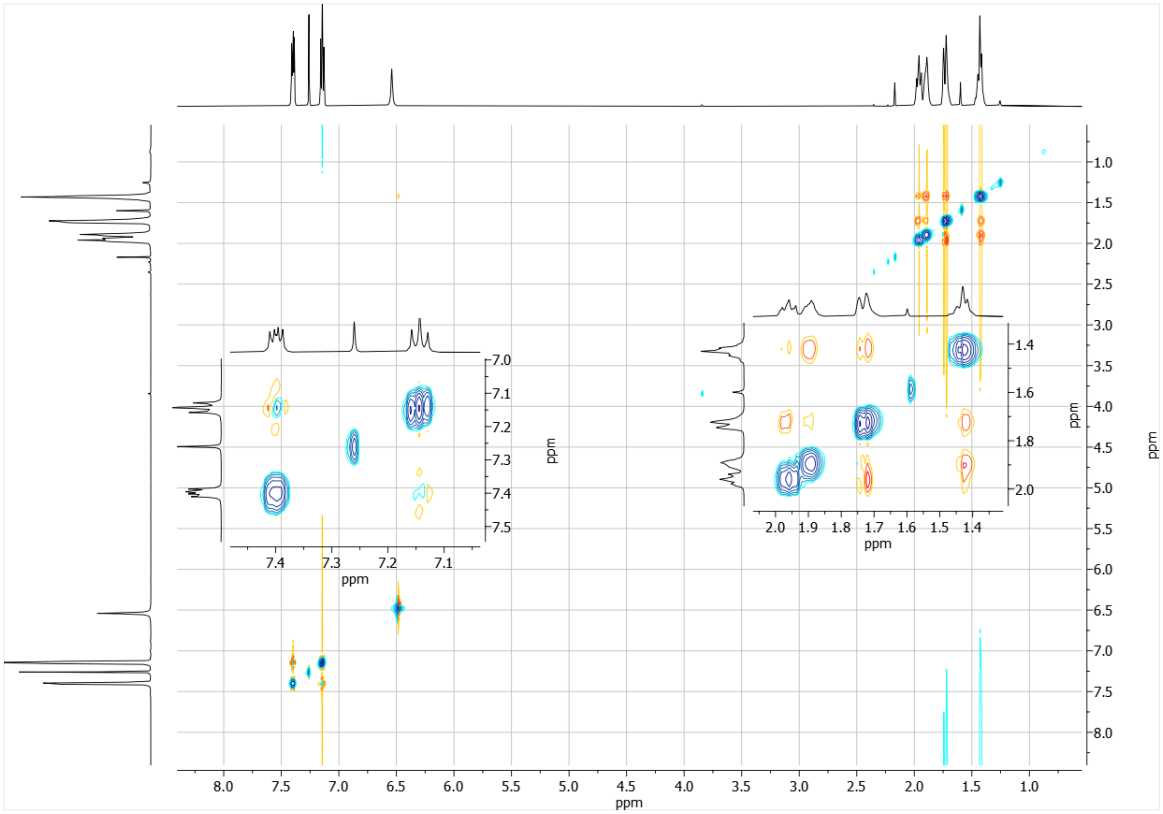
HSQC (600 MHz, $CDCl_3$) spectrum of 5i.



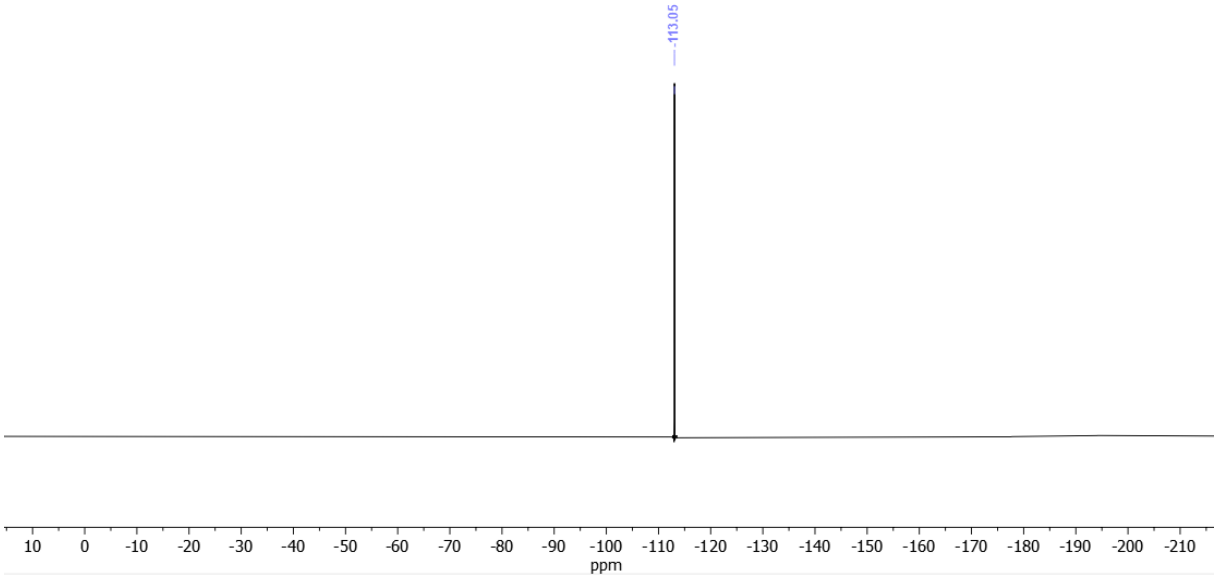
HMBC (600 MHz, $CDCl_3$) spectrum of 5i.



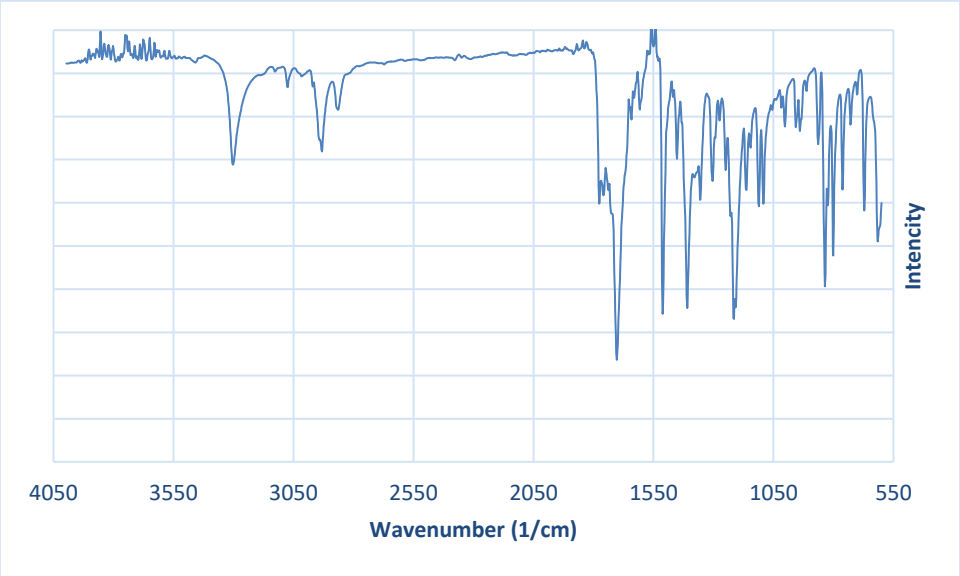
NOESY (600 MHz, $CDCl_3$) spectrum of 5i.



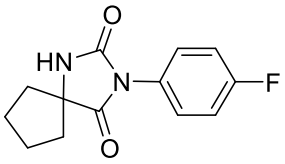
^{19}F NMR (377 MHz, $CDCl_3$) spectrum of 5i.



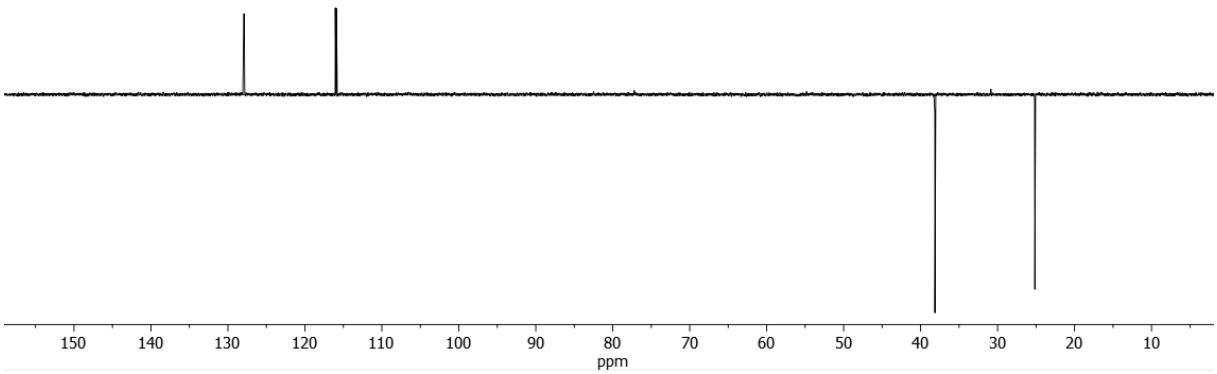
IR spectrum of 5i.



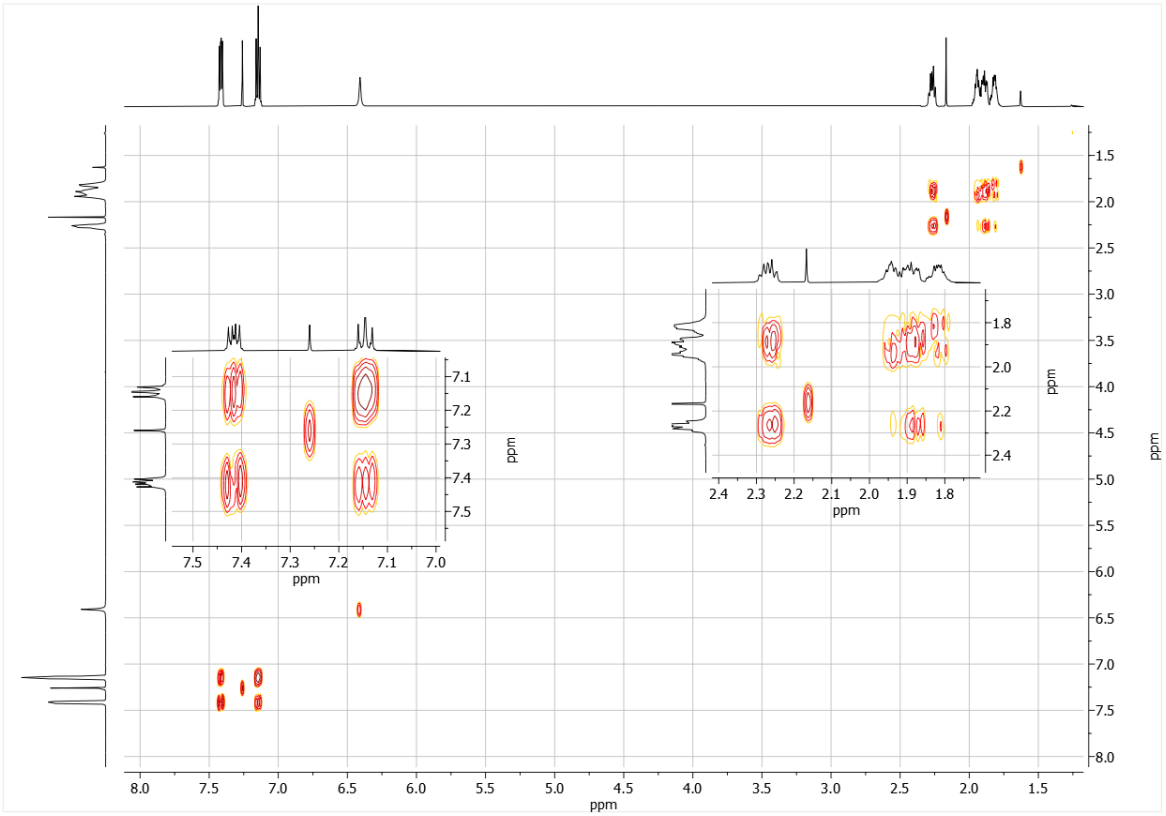
3-(4-fluorophenyl)-1,3-diazaspiro[4.5]nonane-2,4-dione (5j) [NEW]



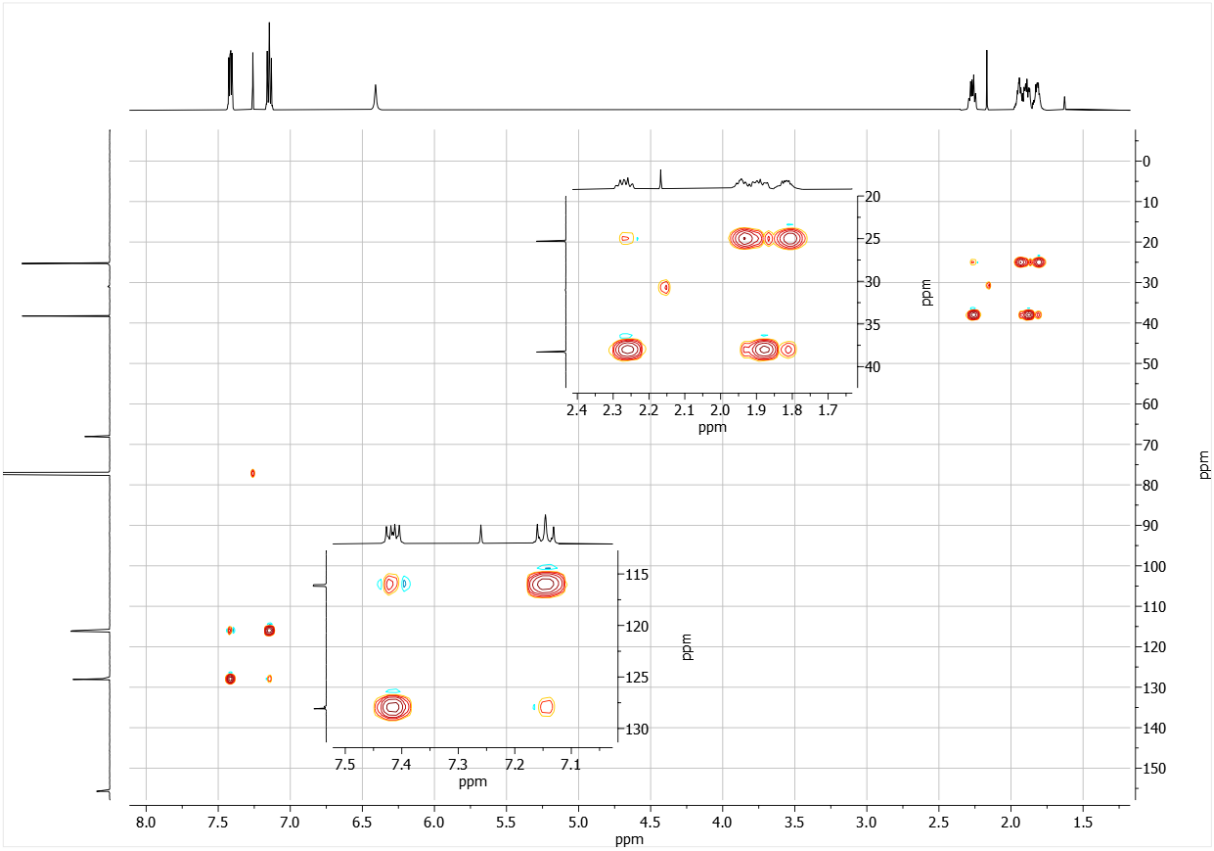
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5j.



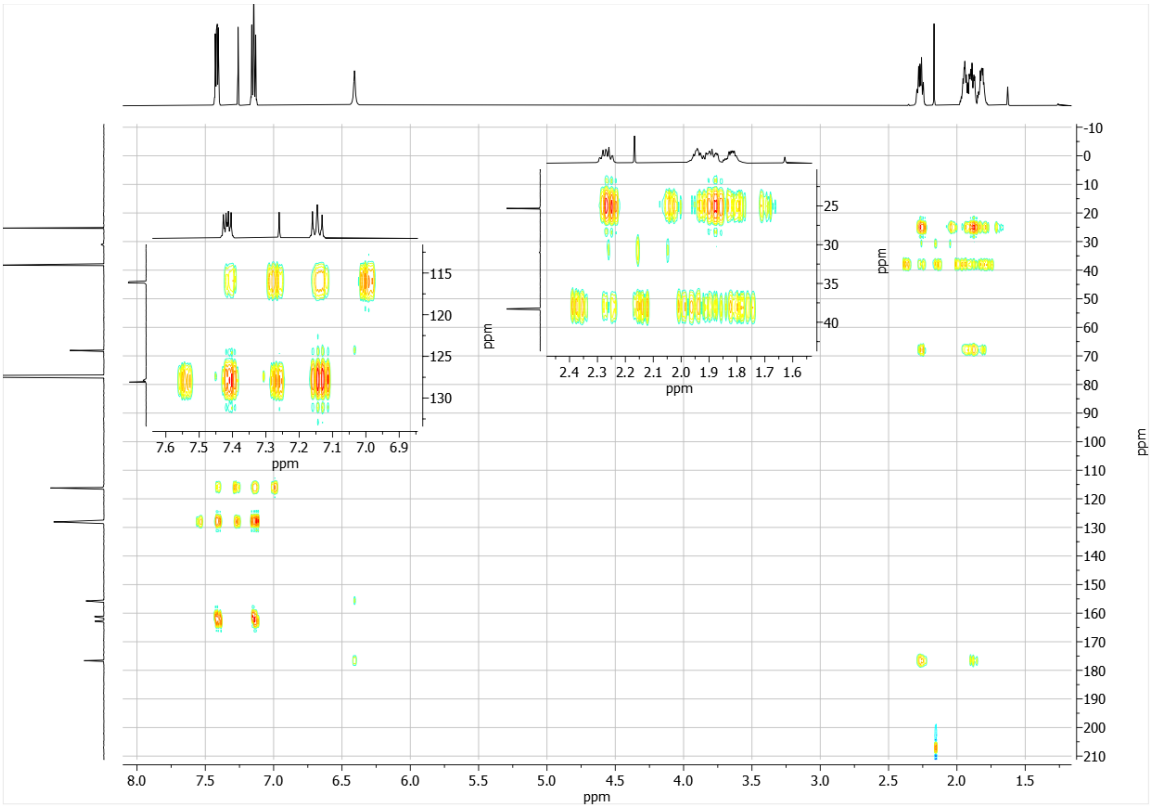
COSY (600 MHz, $CDCl_3$) spectrum of 5j.



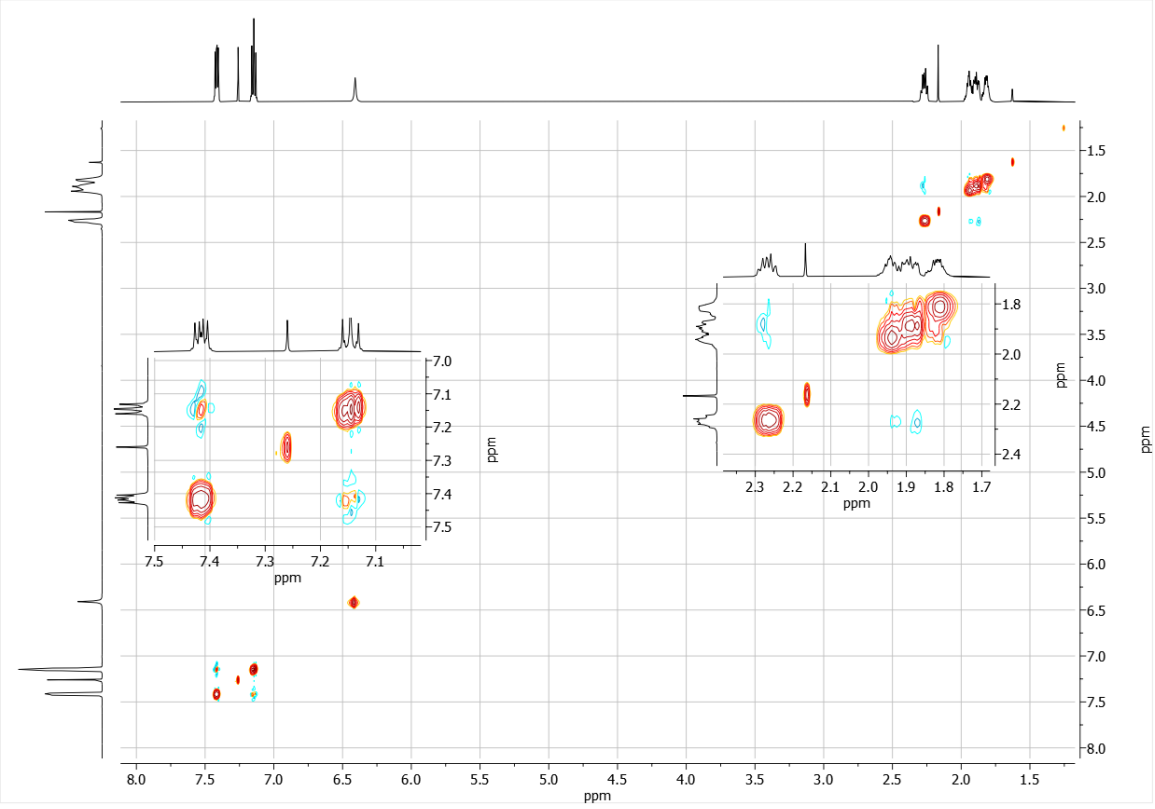
HSQC (600 MHz, $CDCl_3$) spectrum of 5j.



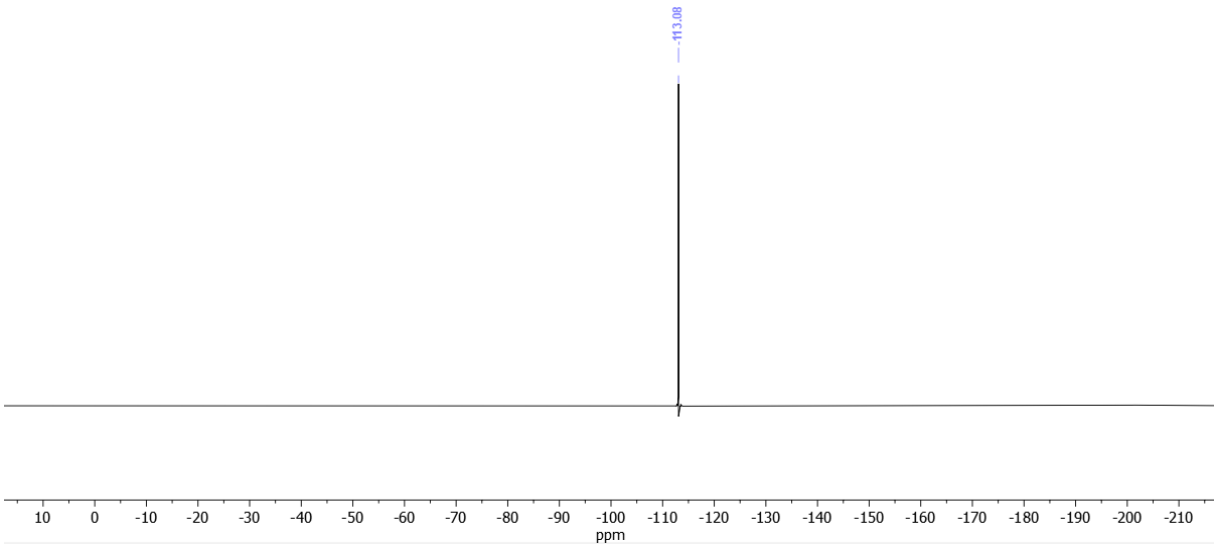
HMBC (600 MHz, $CDCl_3$) spectrum of 5j.



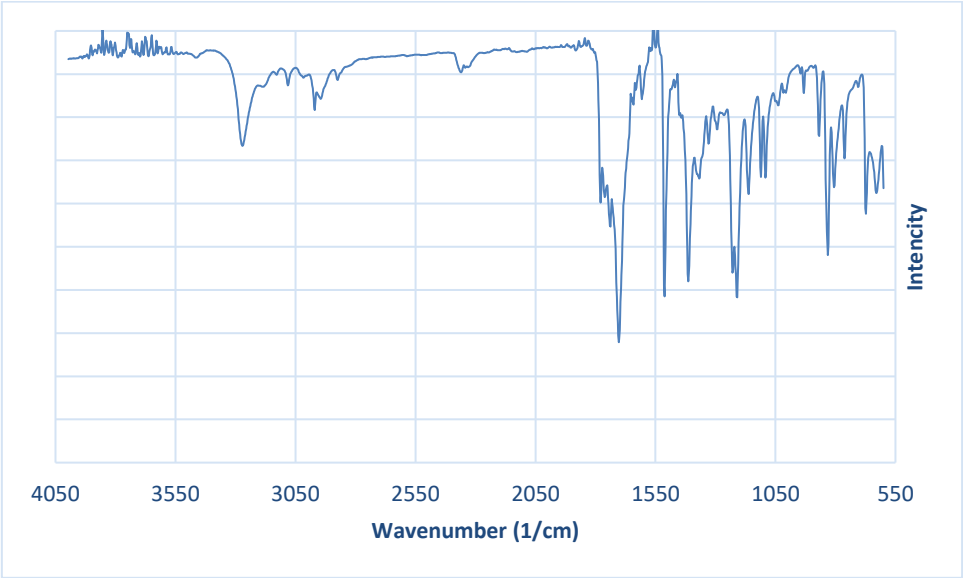
NOESY (600 MHz, $CDCl_3$) spectrum of 5j.



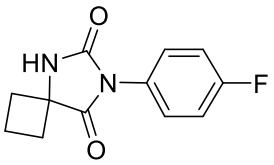
^{19}F NMR (377 MHz, $CDCl_3$) spectrum of 5j.



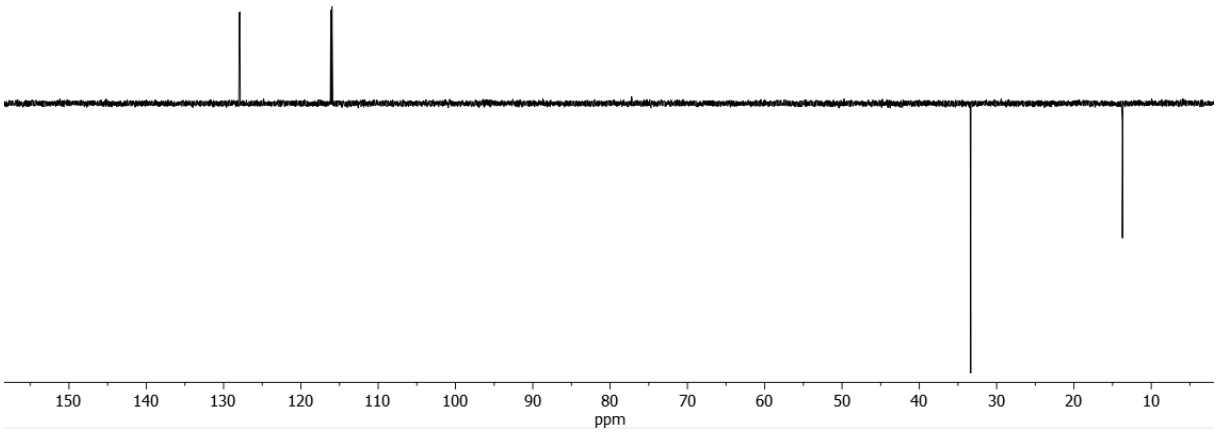
IR spectrum of 5j.



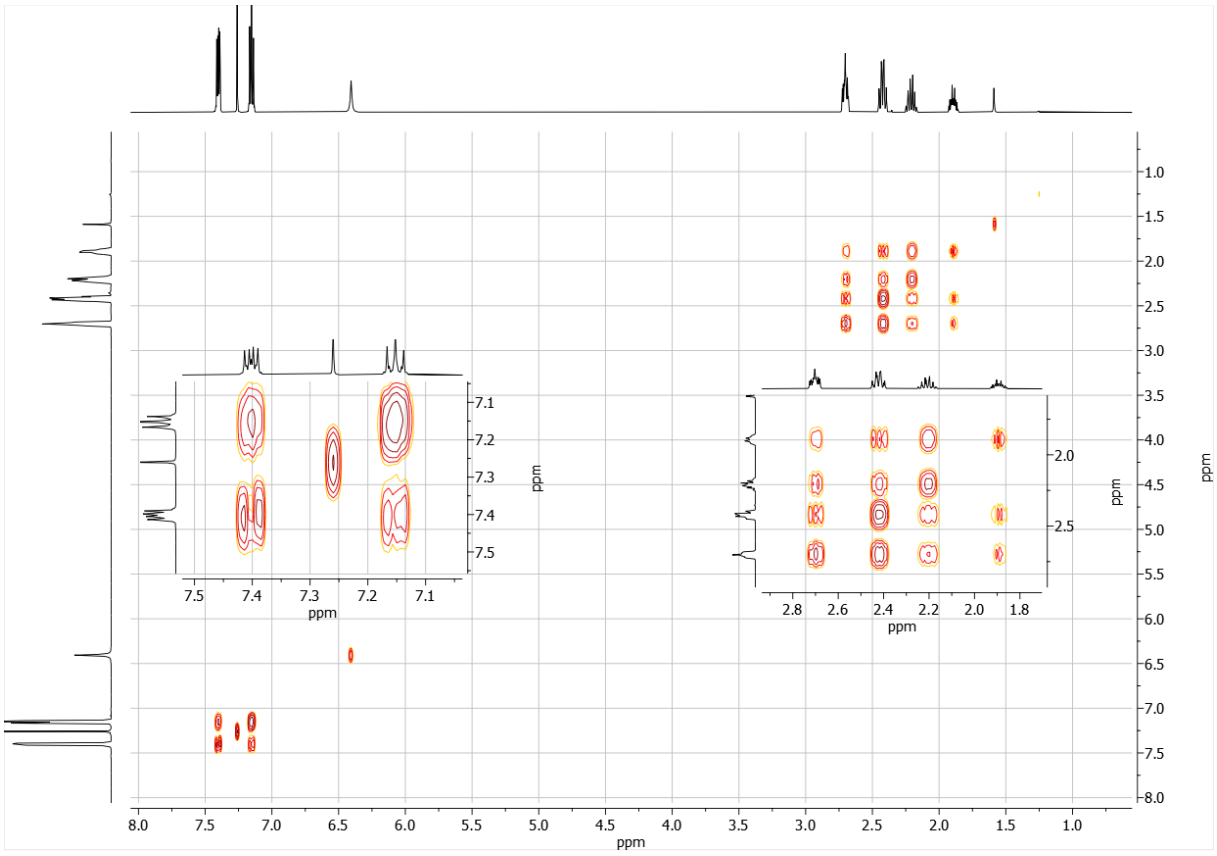
7-(4-fluorophenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5k) [1505761-74-9]



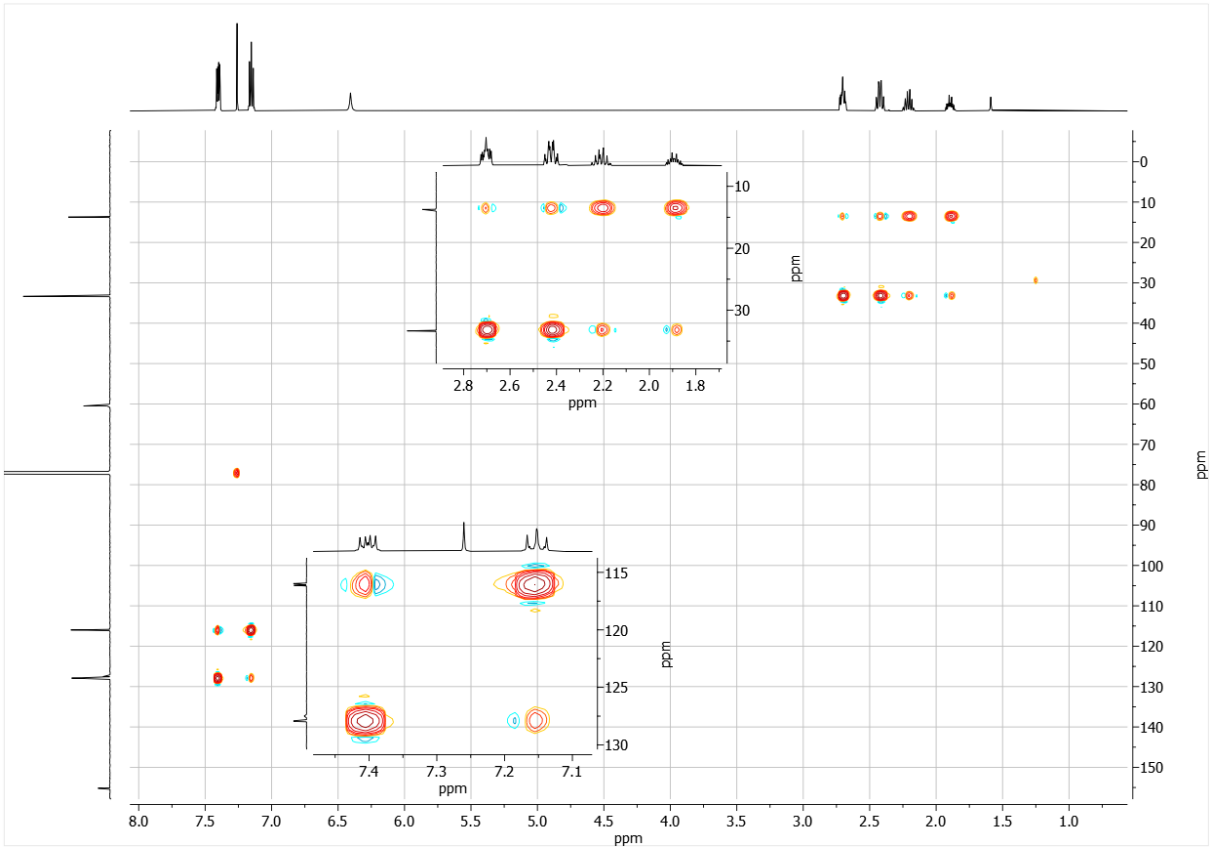
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5k.



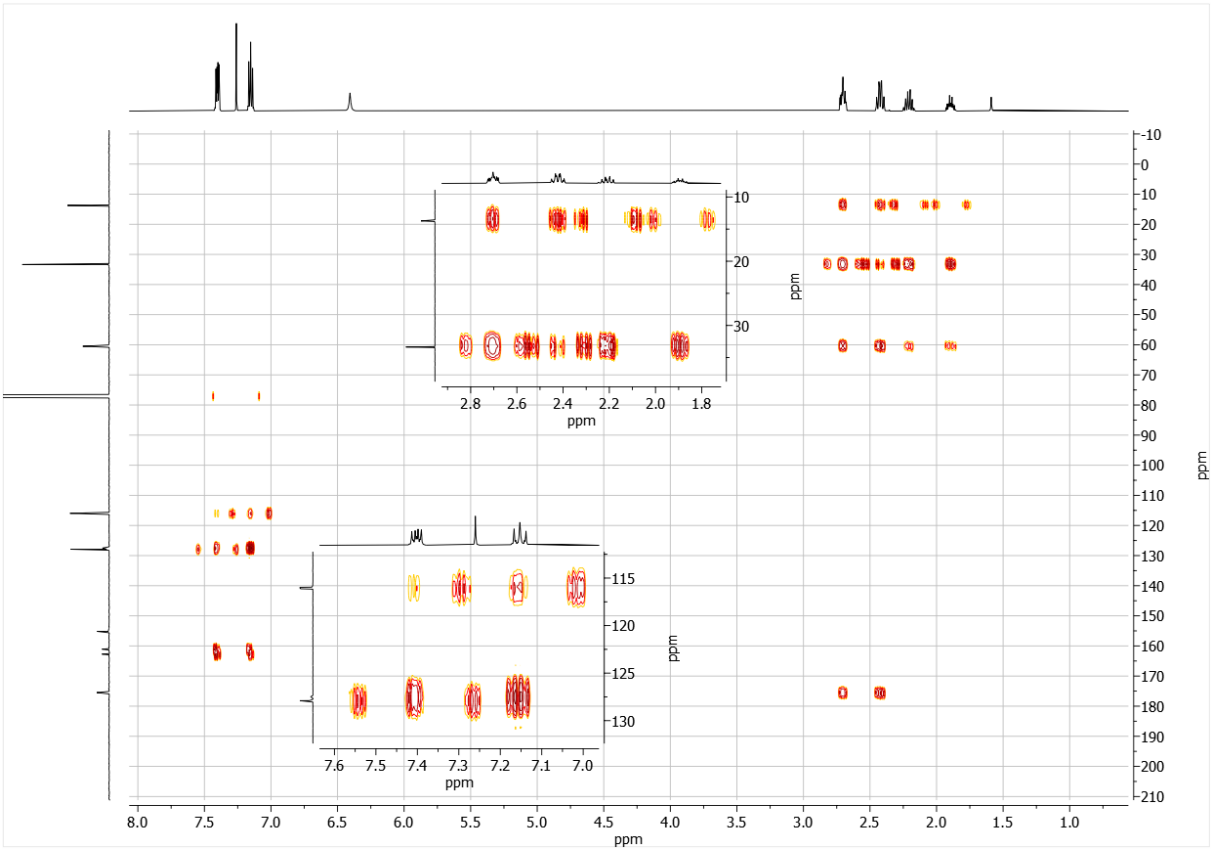
COSY (600 MHz, $CDCl_3$) spectrum of 5k.



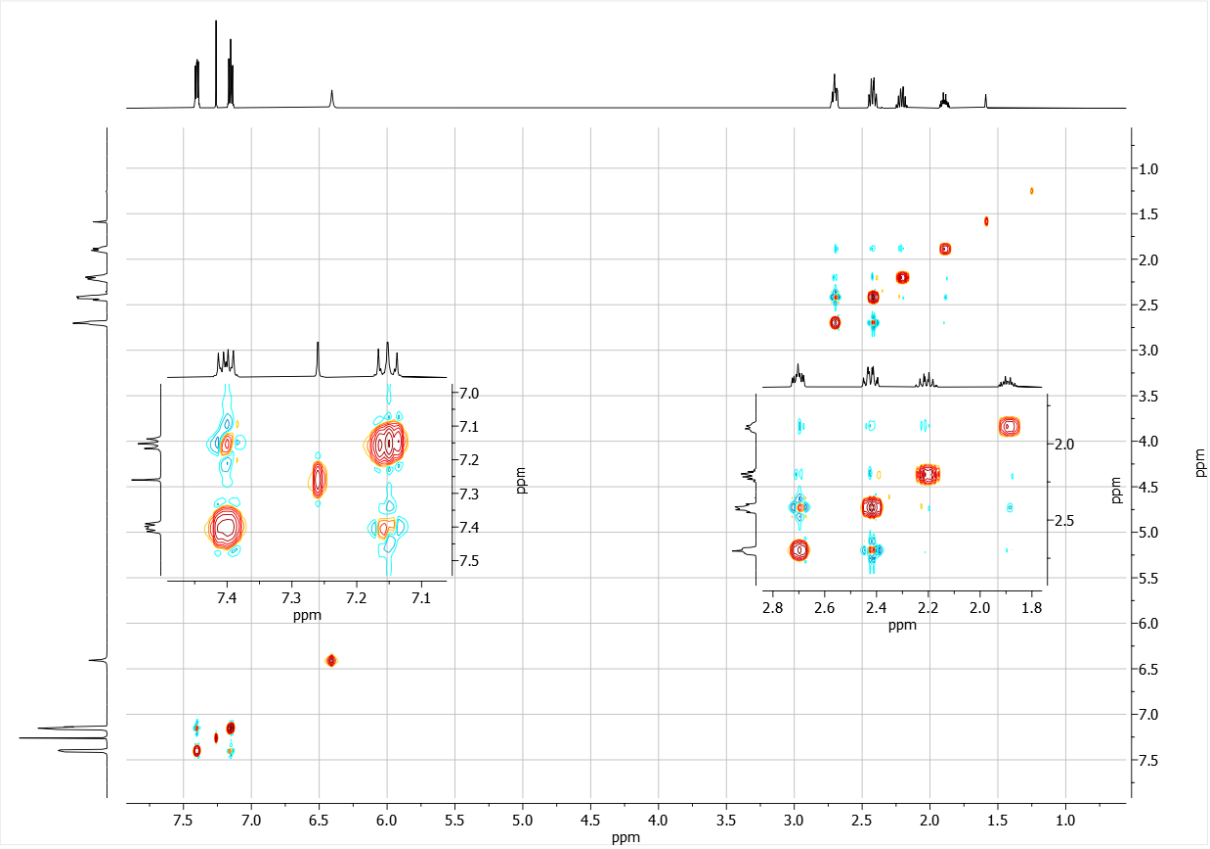
HSQC (600 MHz, $CDCl_3$) spectrum of 5k.



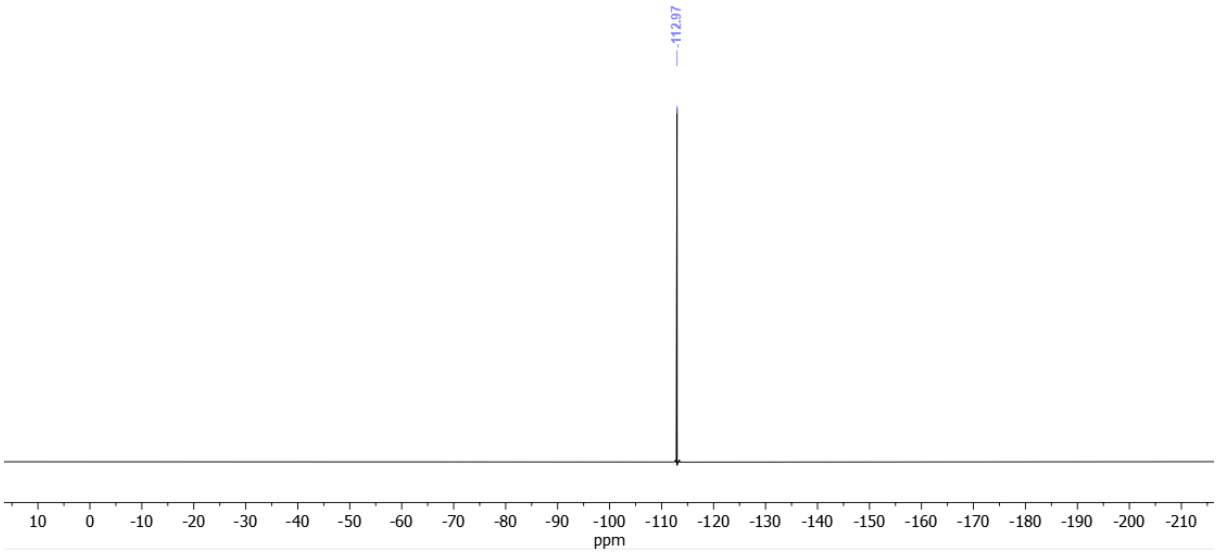
HMBC (600 MHz, $CDCl_3$) spectrum of 5k.



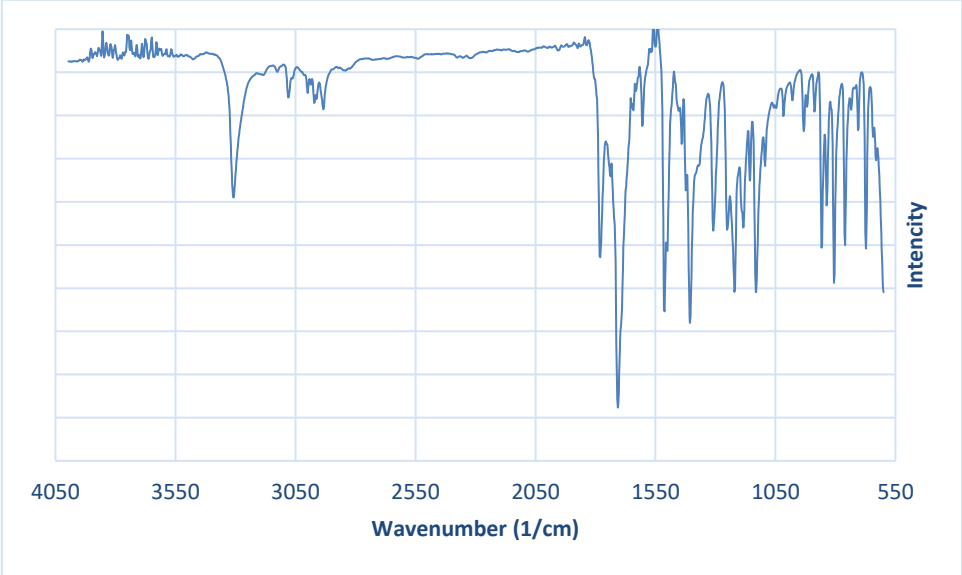
NOESY (600 MHz, $CDCl_3$) spectrum of 5k.



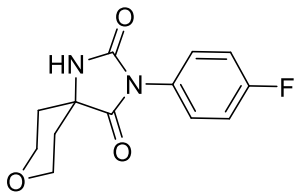
^{19}F NMR (377 MHz, $CDCl_3$) spectrum of 5k.



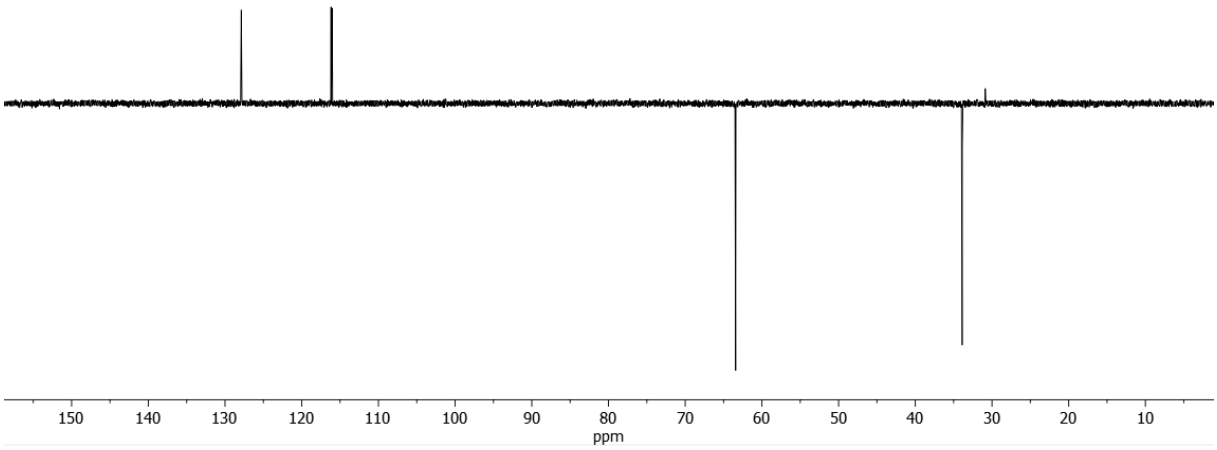
IR spectrum of 5k.



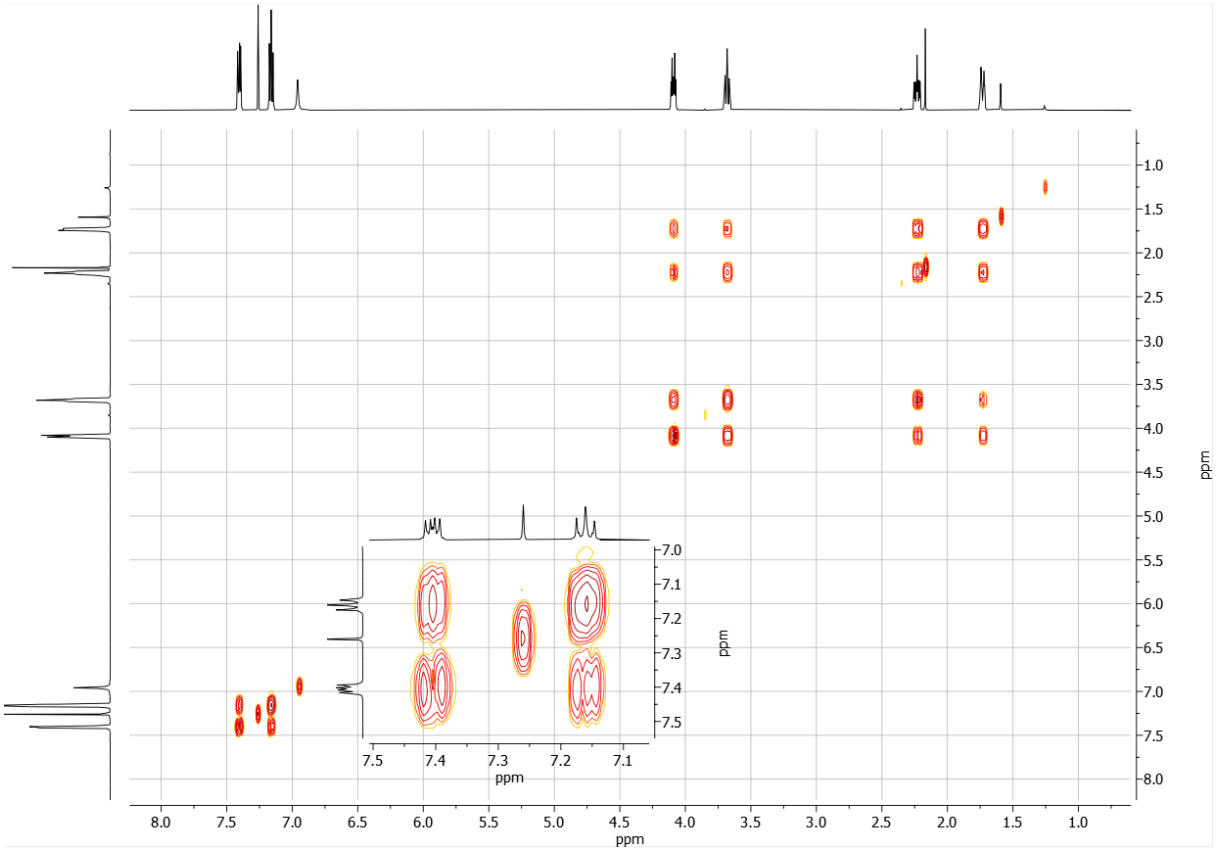
3-(4-fluorophenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5l) [1547679-96-8]



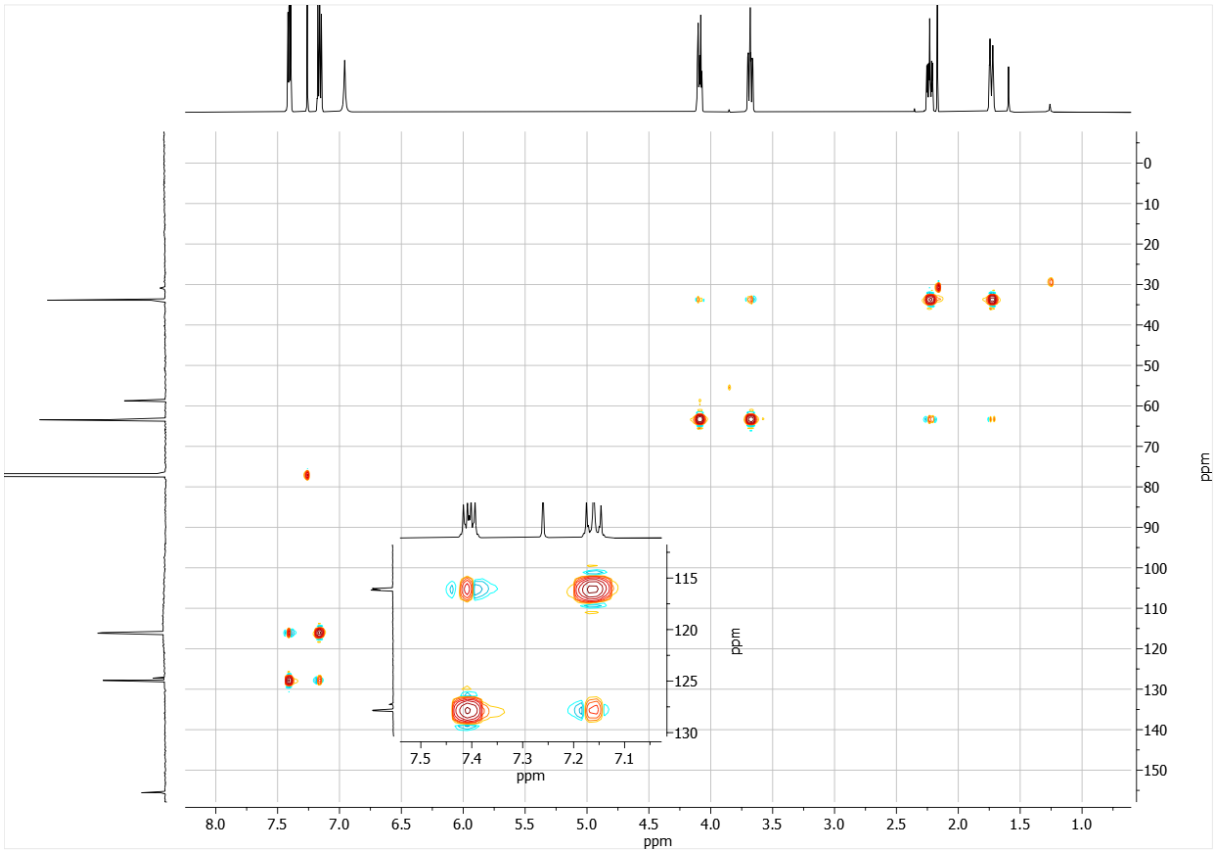
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5l.



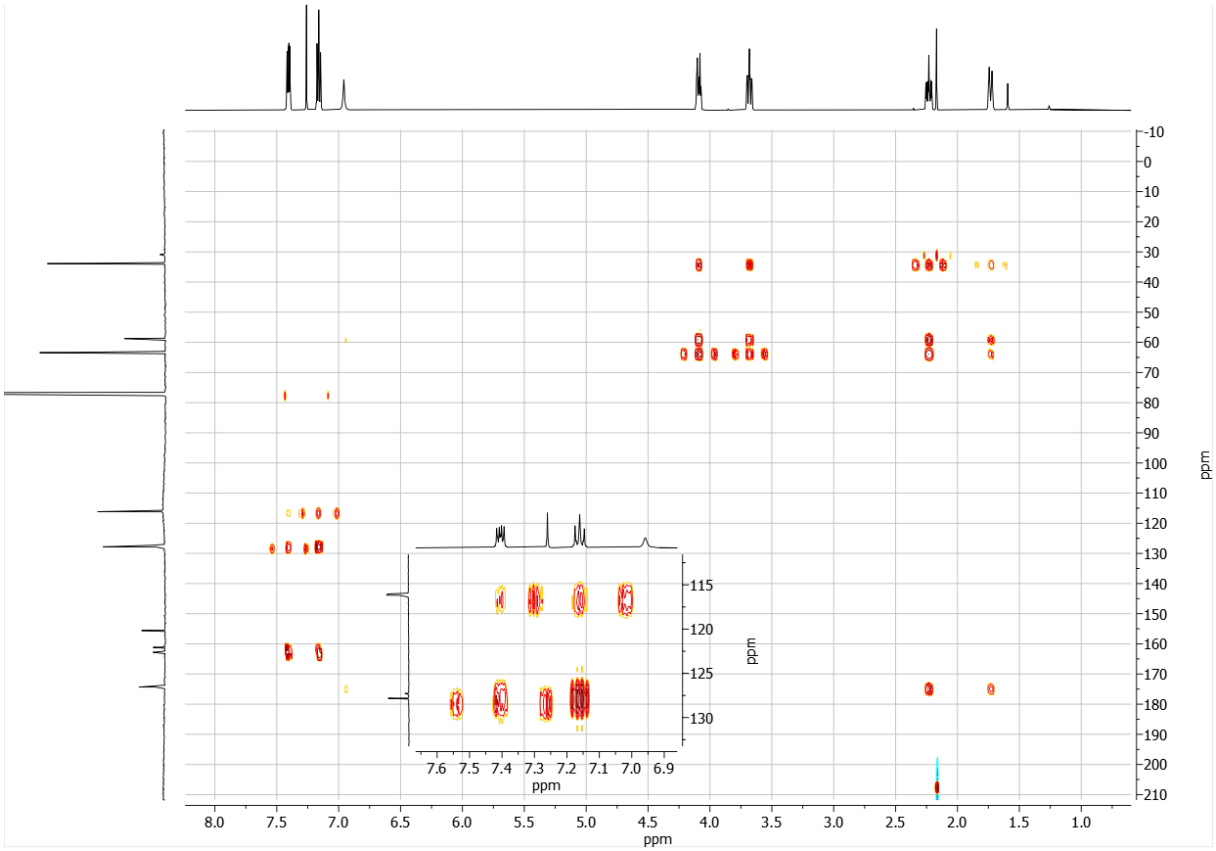
COSY (600 MHz, $CDCl_3$) spectrum of 5l.



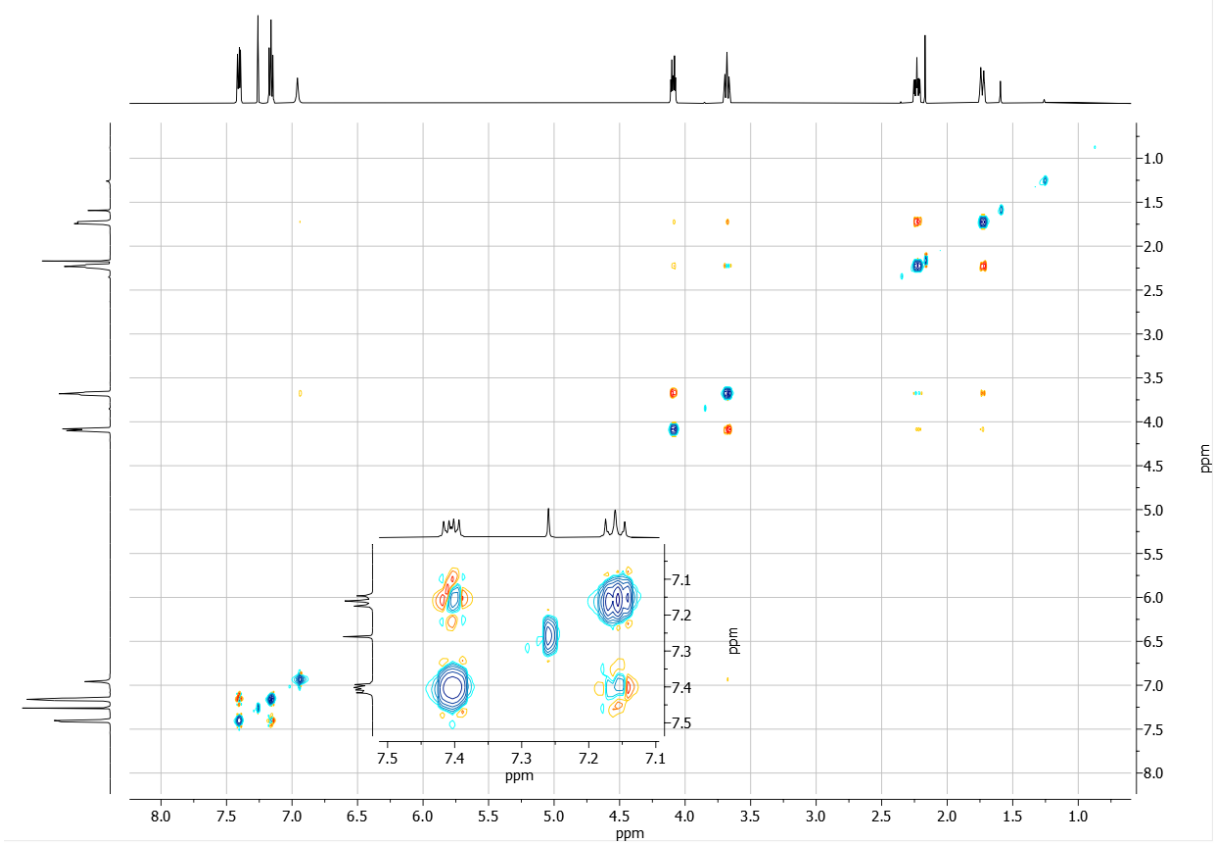
HSQC (600 MHz, $CDCl_3$) spectrum of 5l.



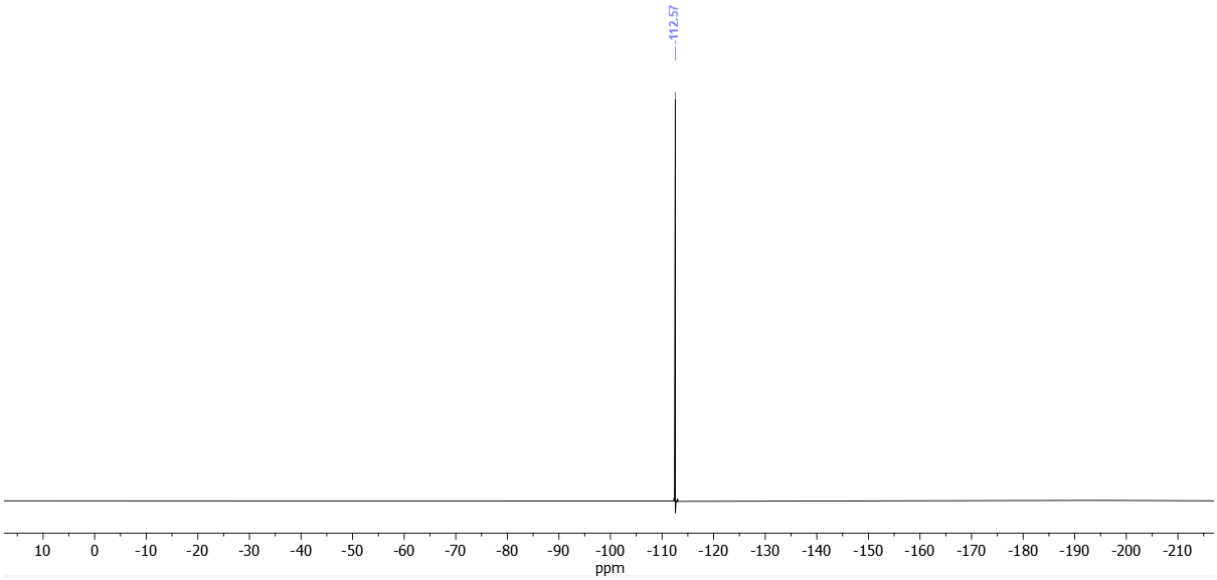
HMBC (600 MHz, $CDCl_3$) spectrum of 5l.



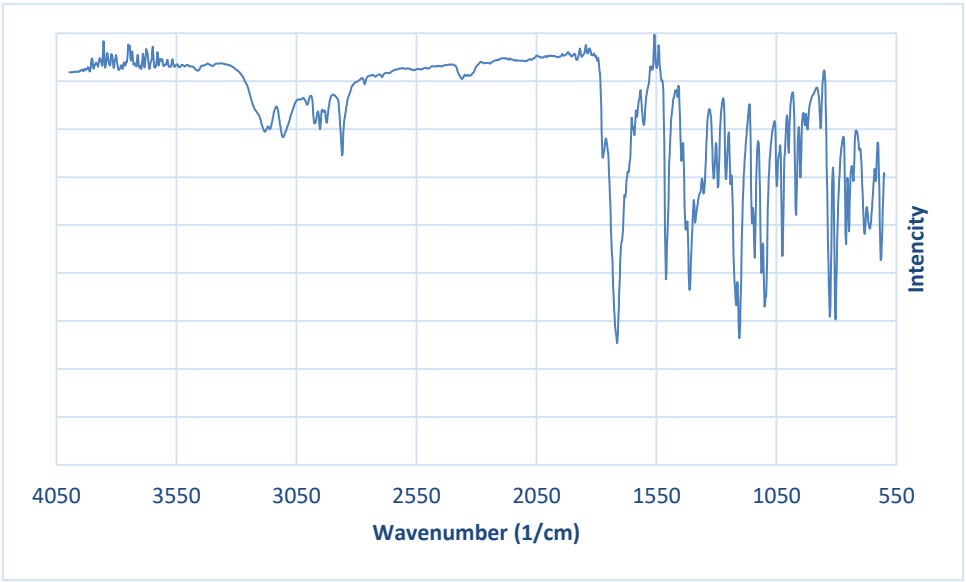
NOESY (600 MHz, $CDCl_3$) spectrum of 5l.



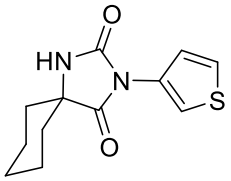
^{19}F NMR (377 MHz, $CDCl_3$) spectrum of 5l.



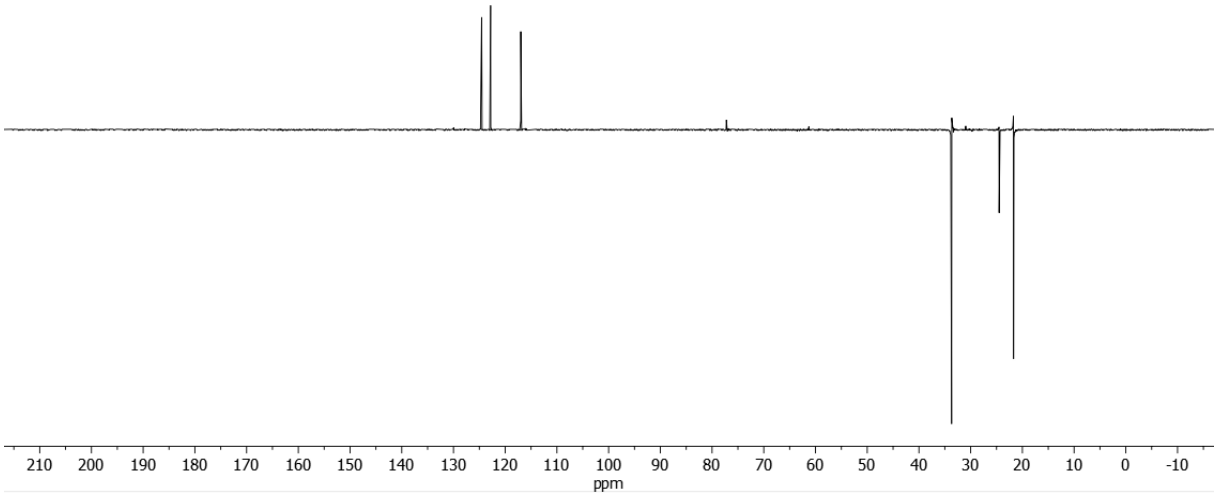
IR spectrum of 5l.



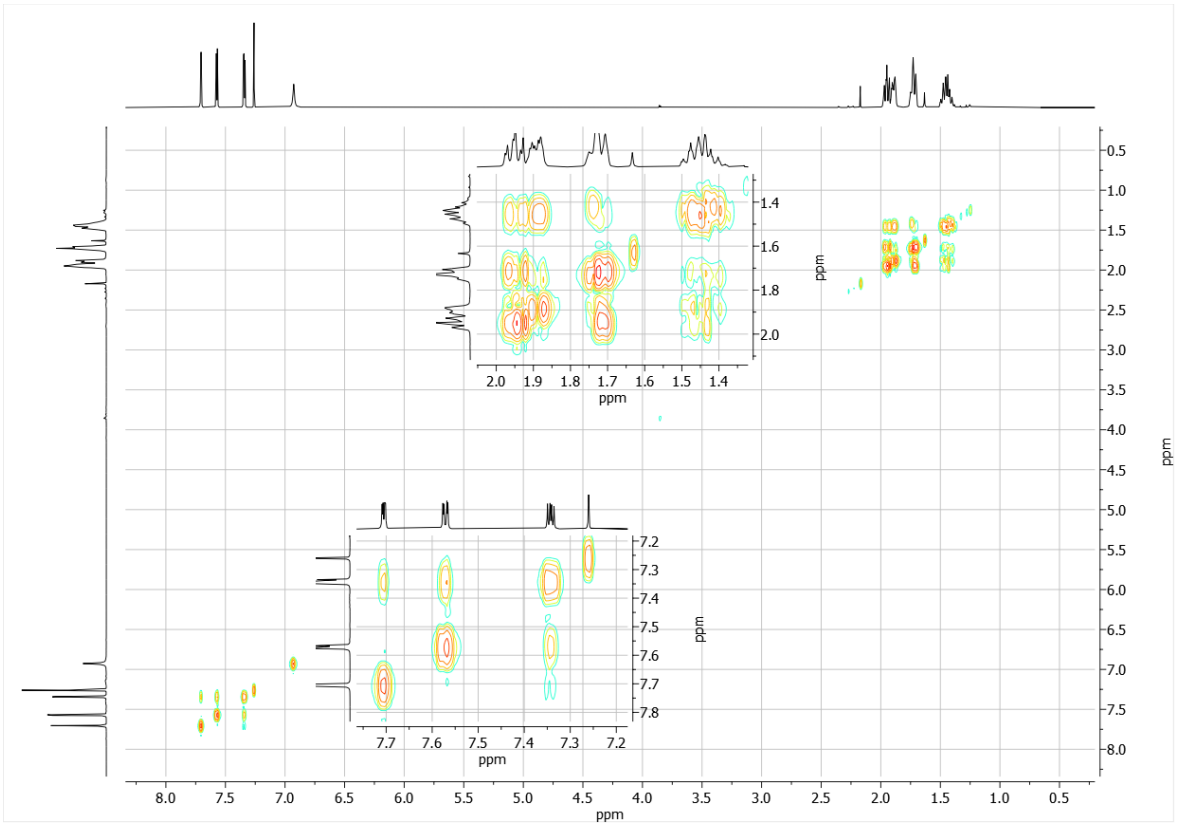
3(thiophen-3-yl)-1,3-diazaspiro[4.5]decane-2,4-dione (5m) [NEW]



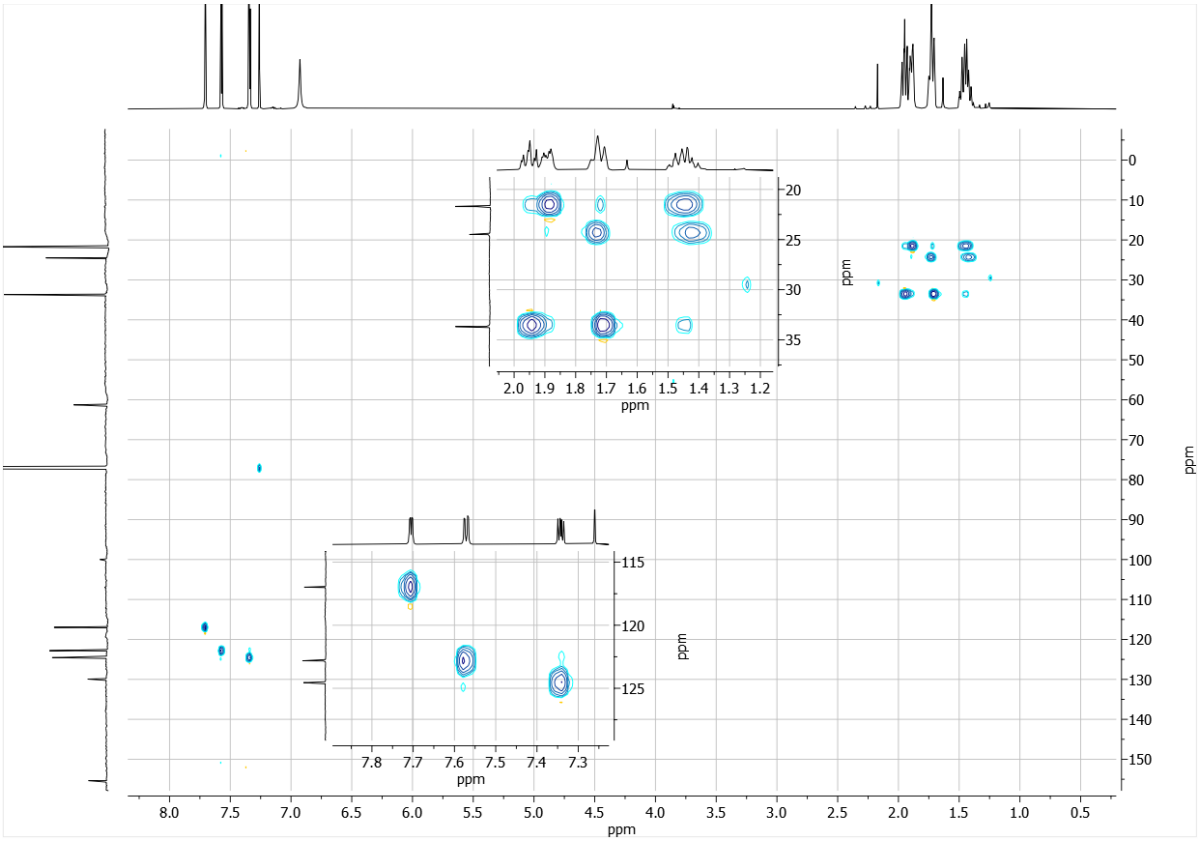
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5m.



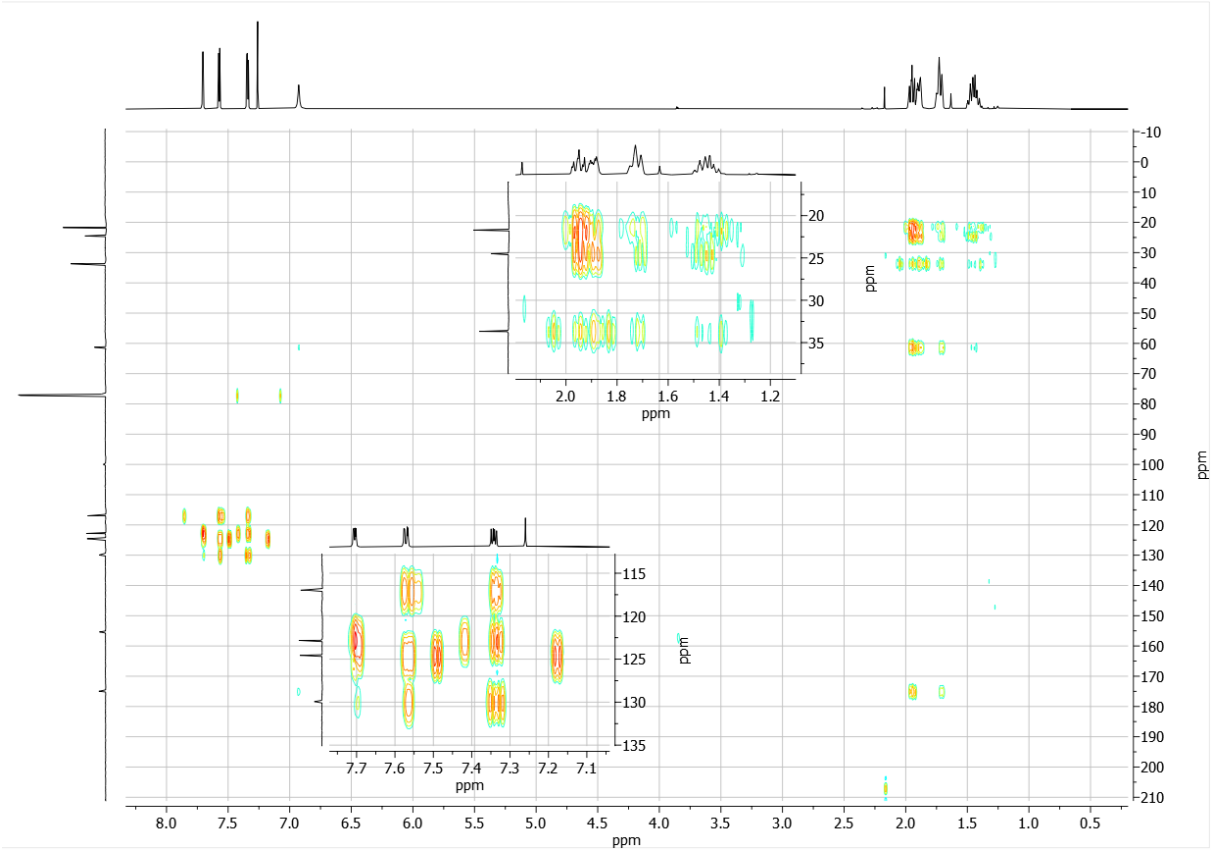
COSY (600 MHz, $CDCl_3$) spectrum of 5m.



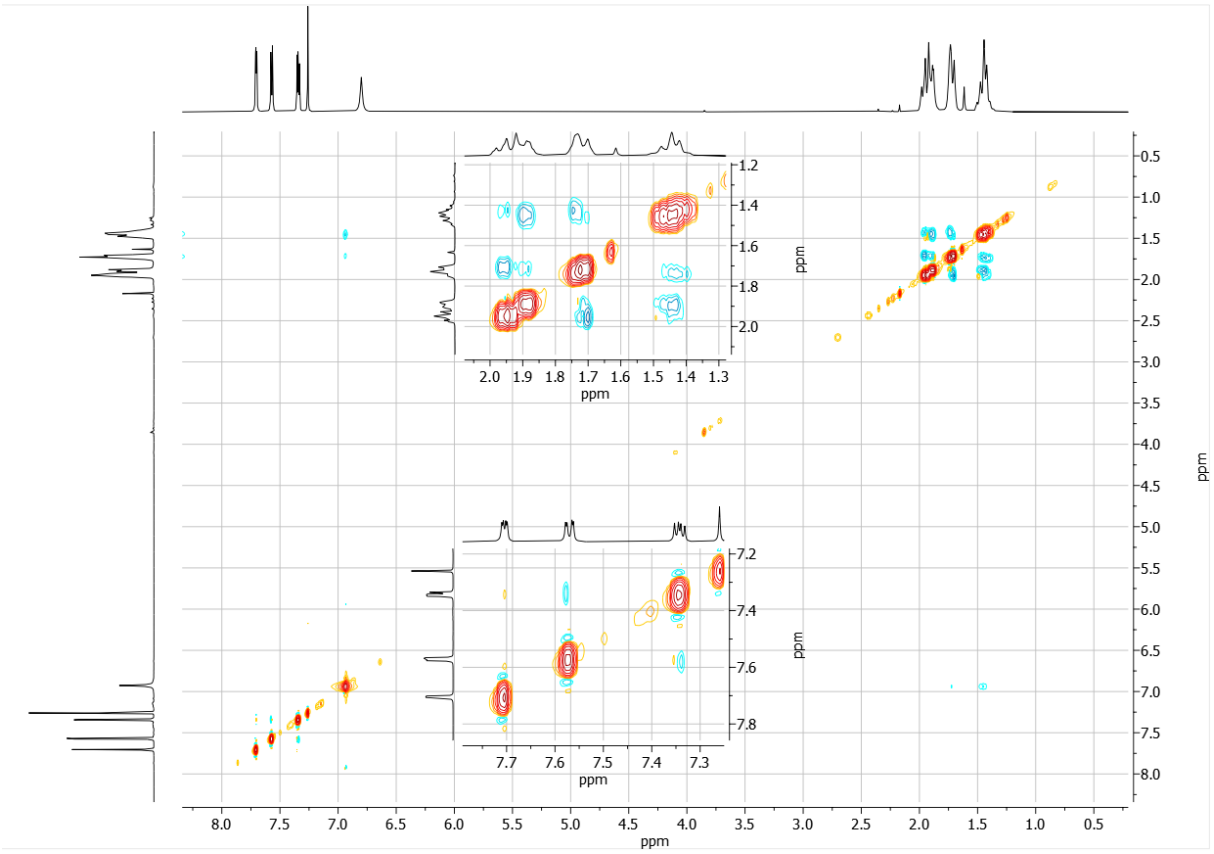
HSQC (600 MHz, $CDCl_3$) spectrum of 5m.



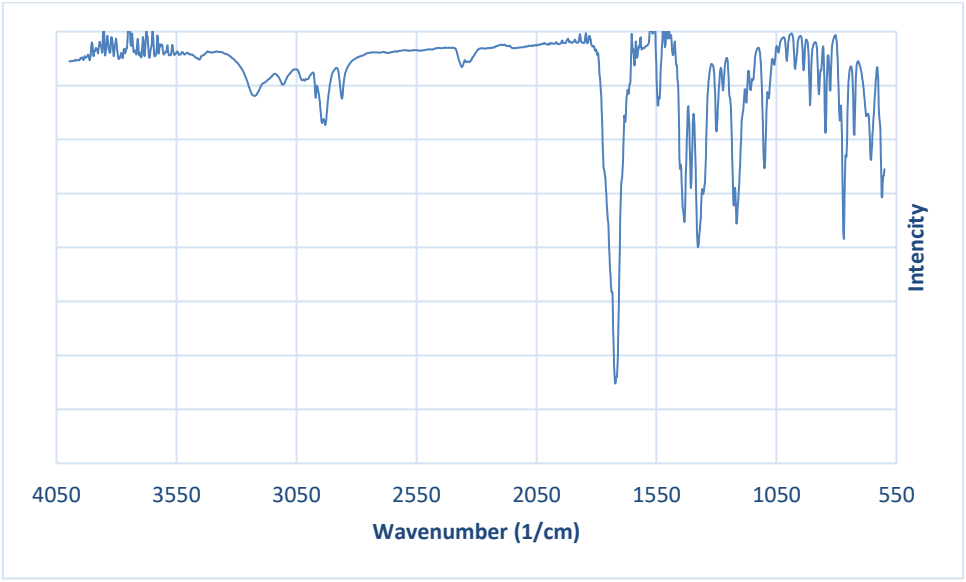
HMBC (600 MHz, $CDCl_3$) spectrum of 5m.



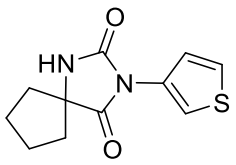
NOESY (600 MHz, $CDCl_3$) spectrum of 5m.



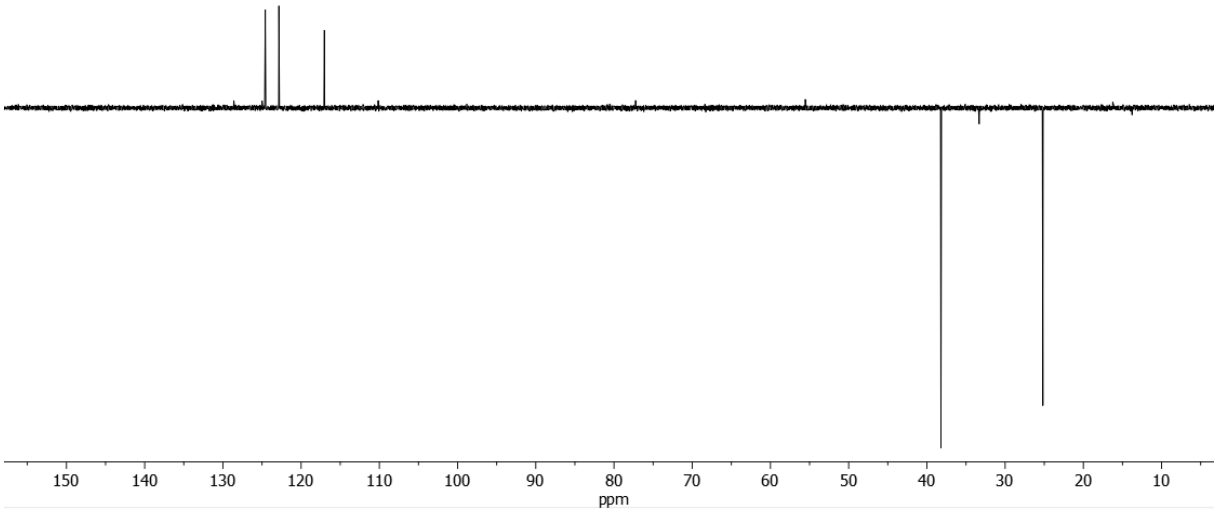
IR spectrum of 5m.



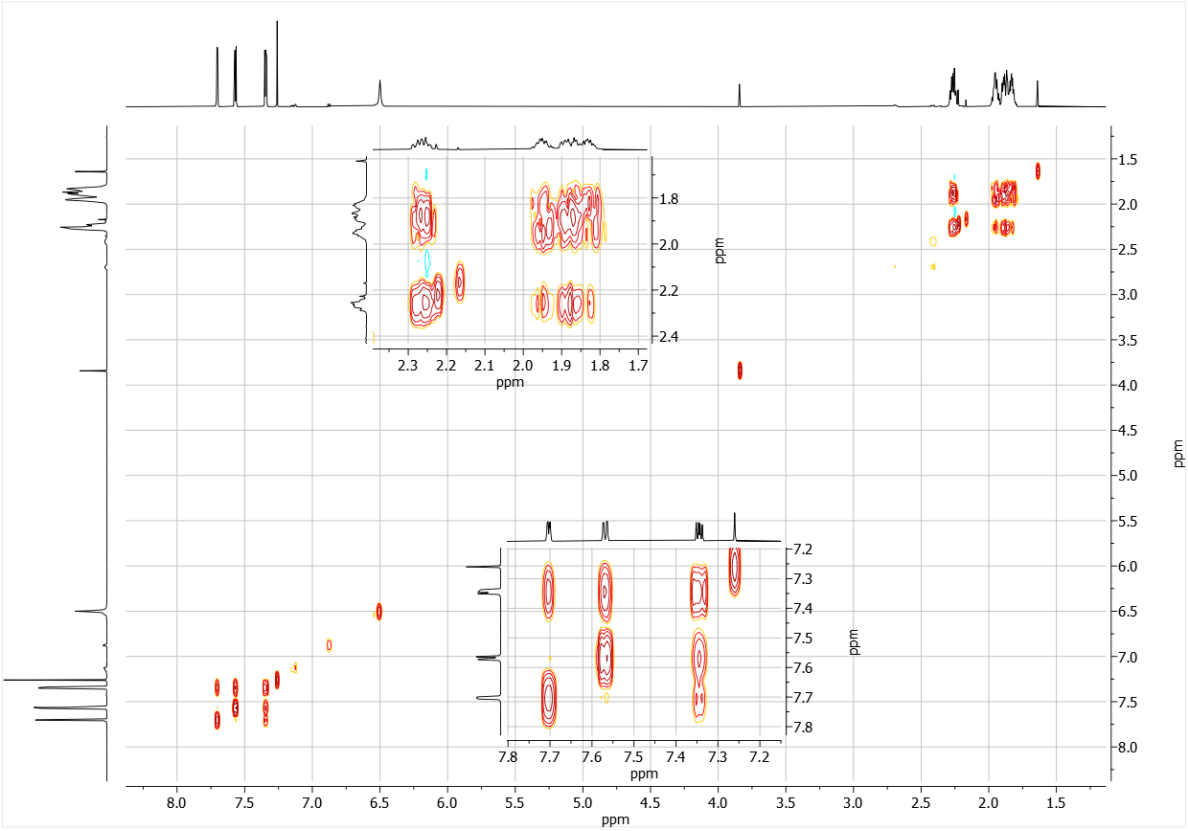
3(thiophen-3-yl)-1,3-diazaspiro[4.5]decane-2,4-nonane (5n) [NEW]



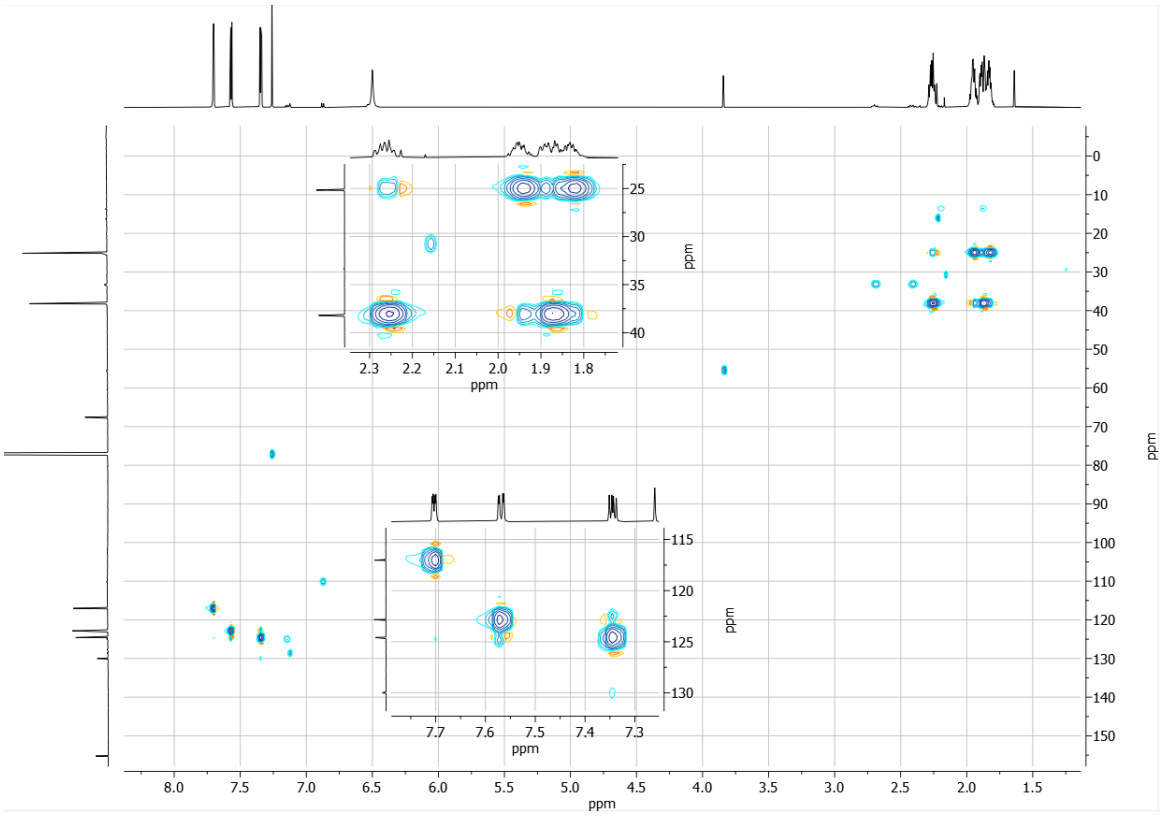
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5n.



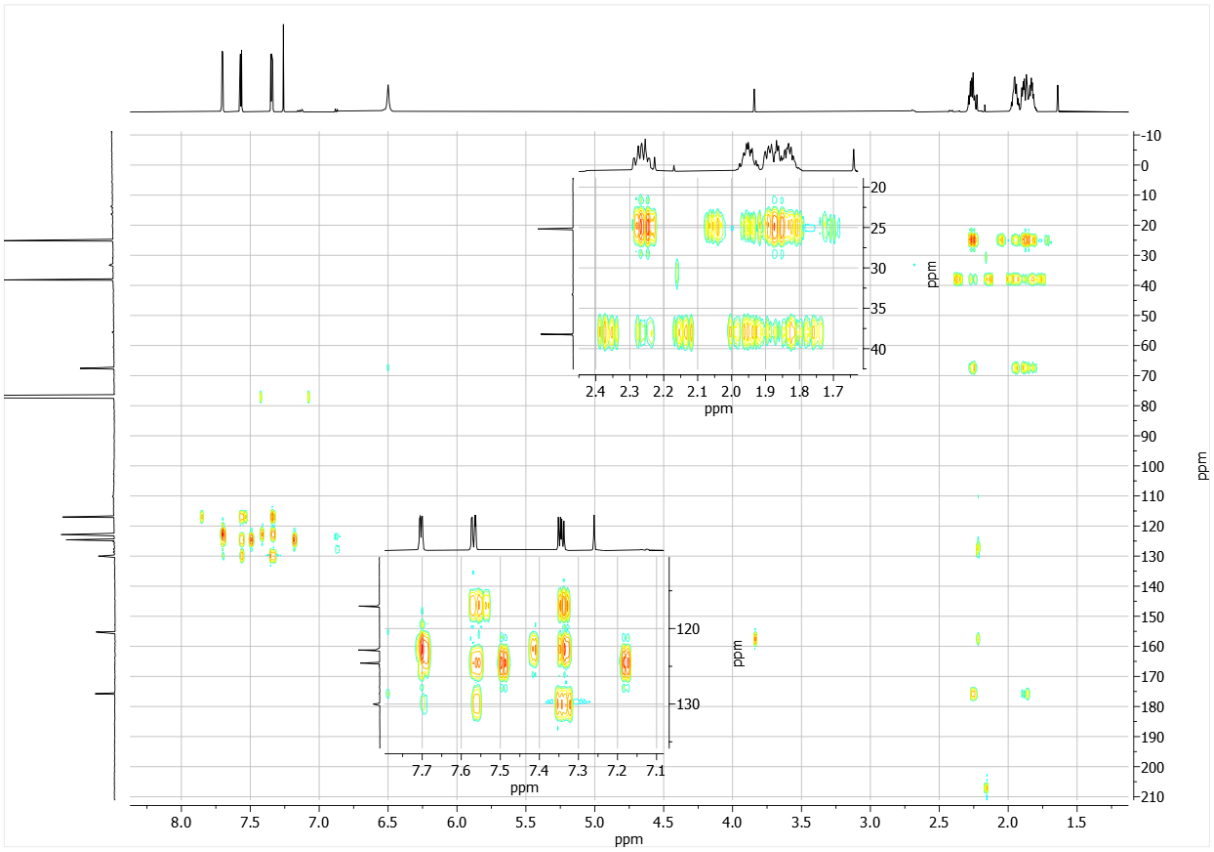
COSY (600 MHz, $CDCl_3$) spectrum of 5n.



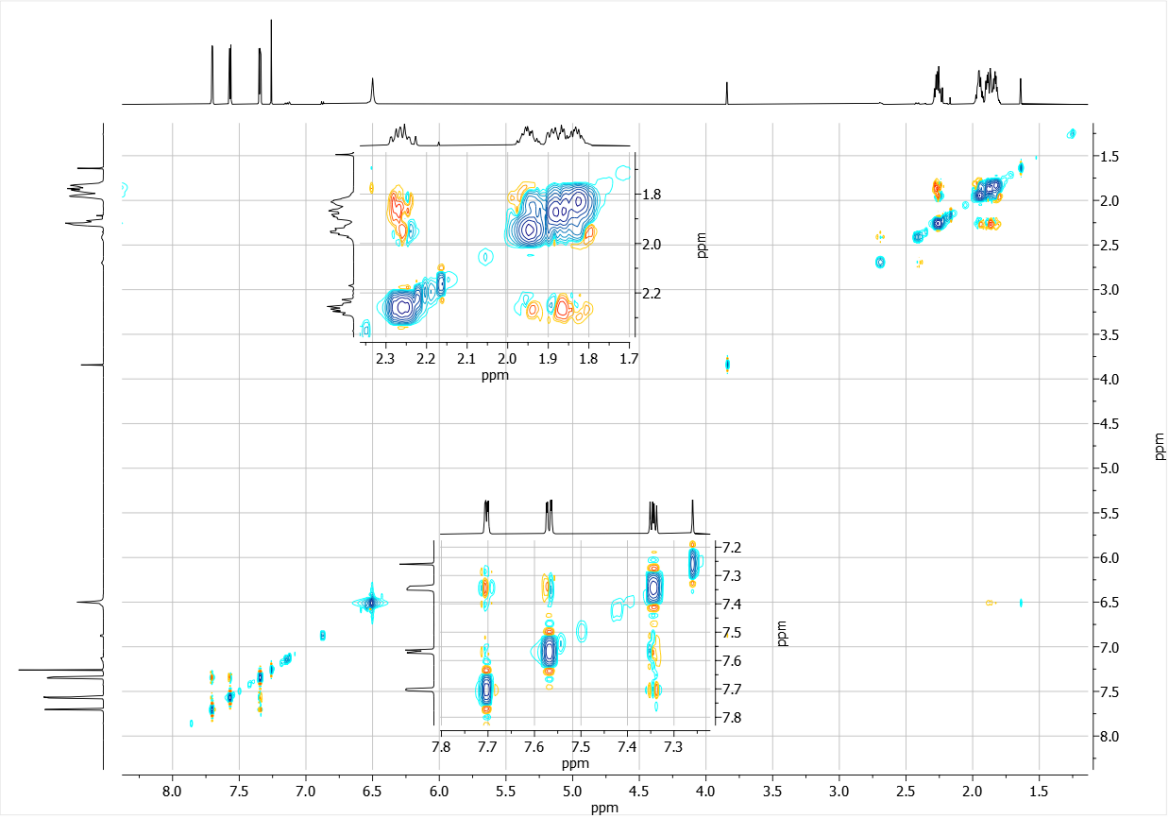
HSQC (600 MHz, $CDCl_3$) spectrum of 5n.



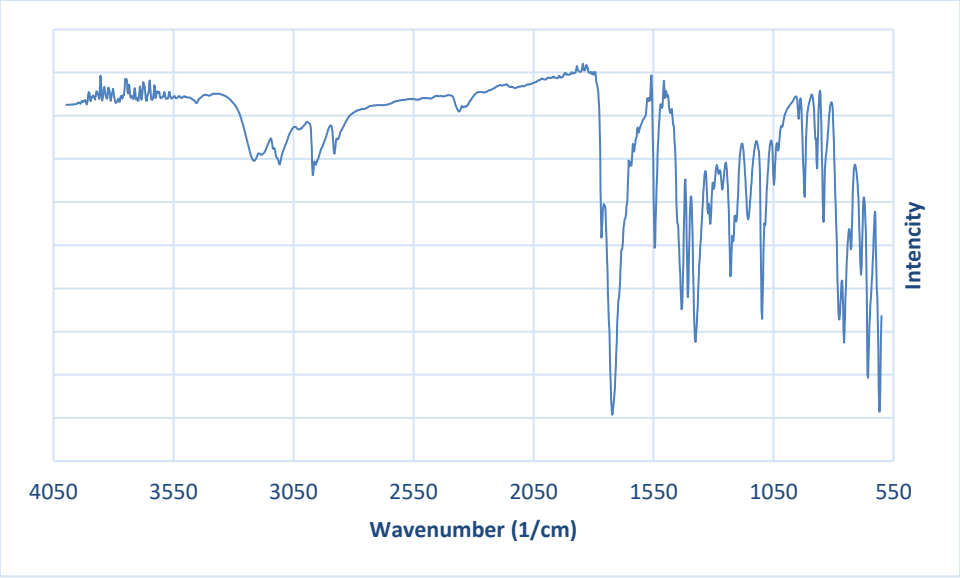
HMBC (600 MHz, $CDCl_3$) spectrum of 5n.



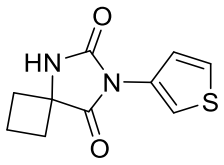
NOESY (600 MHz, $CDCl_3$) spectrum of 5n.



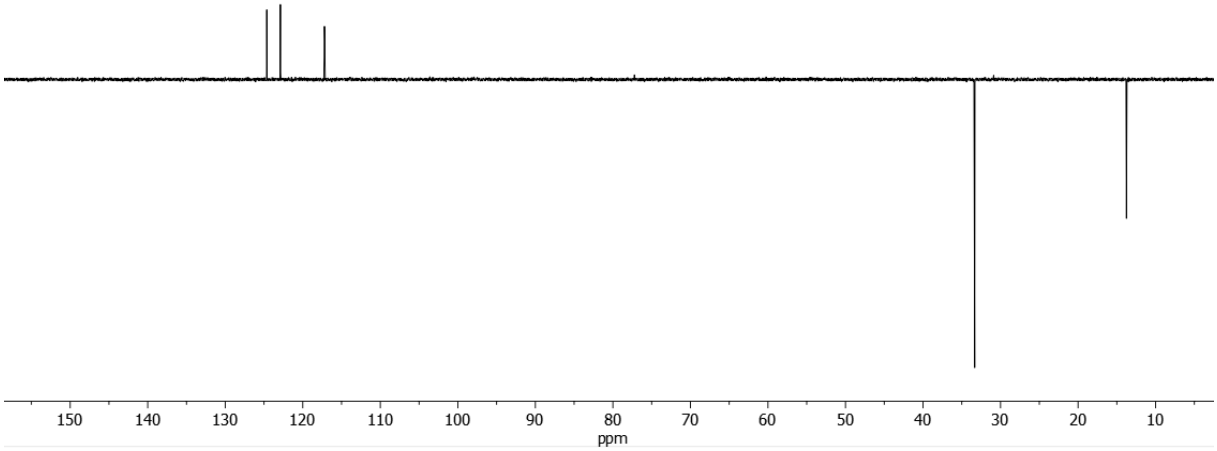
IR spectrum of 5n.



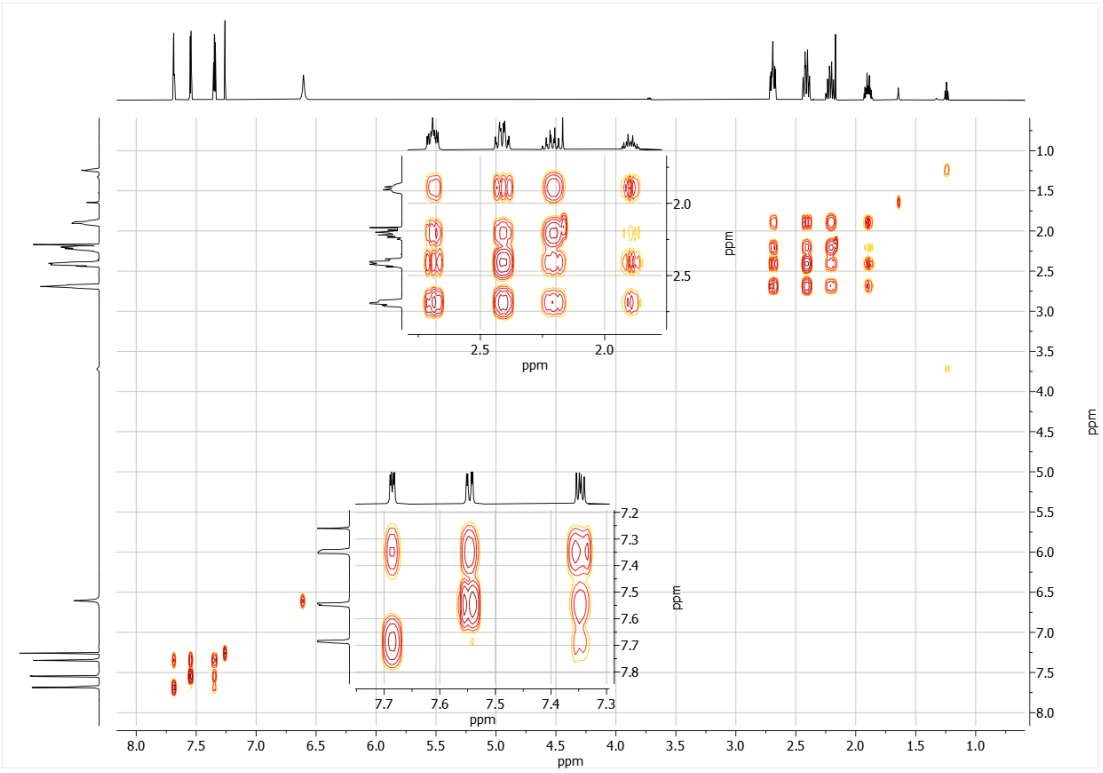
7-(thiophen-3-yl)-5,7-diazaspiro[3.4]octane-6,8-dione (5o) [NEW]



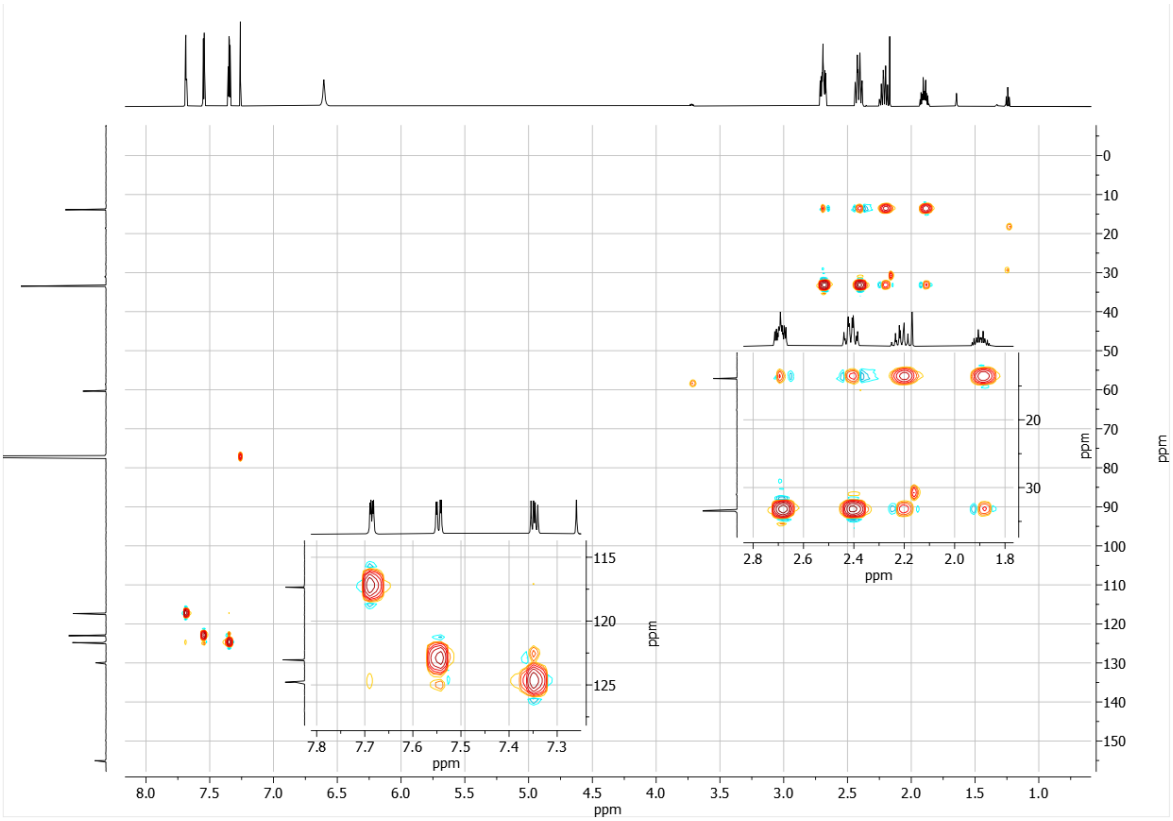
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5o.



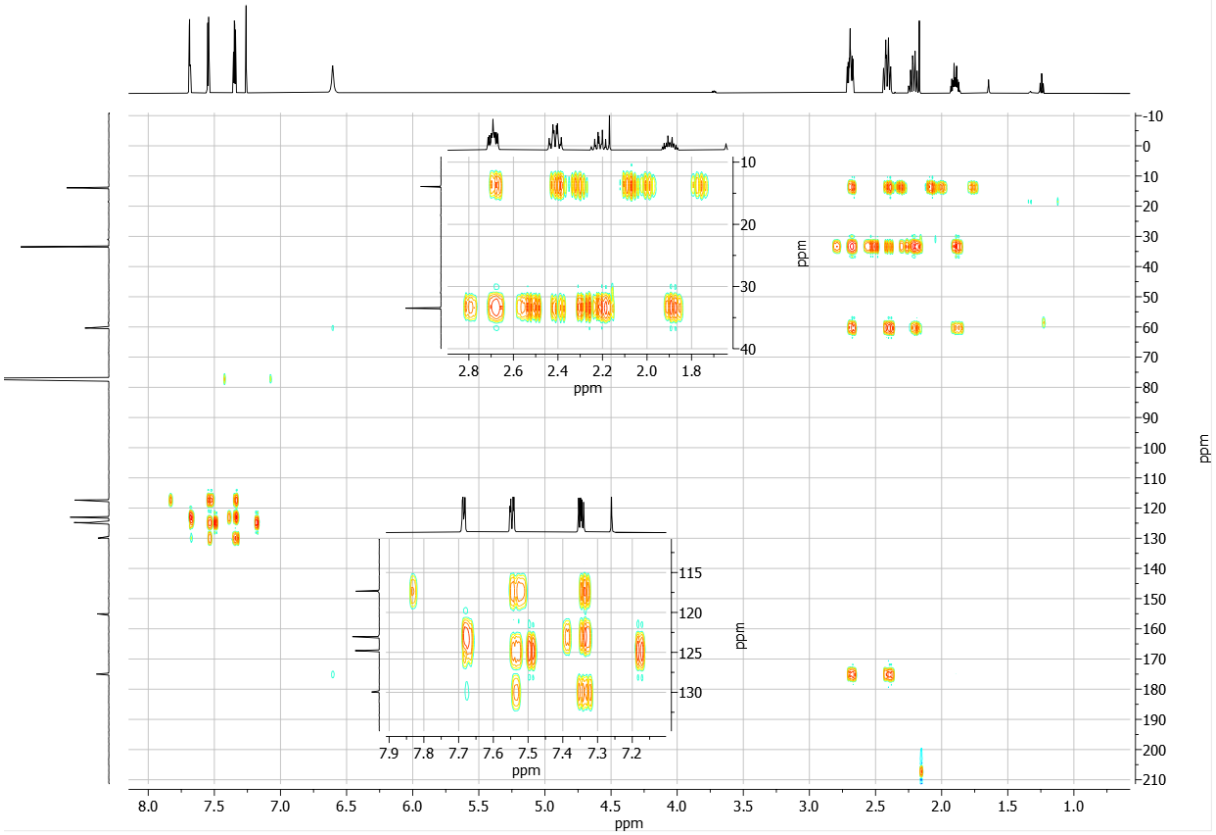
COSY (600 MHz, $CDCl_3$) spectrum of 5o.



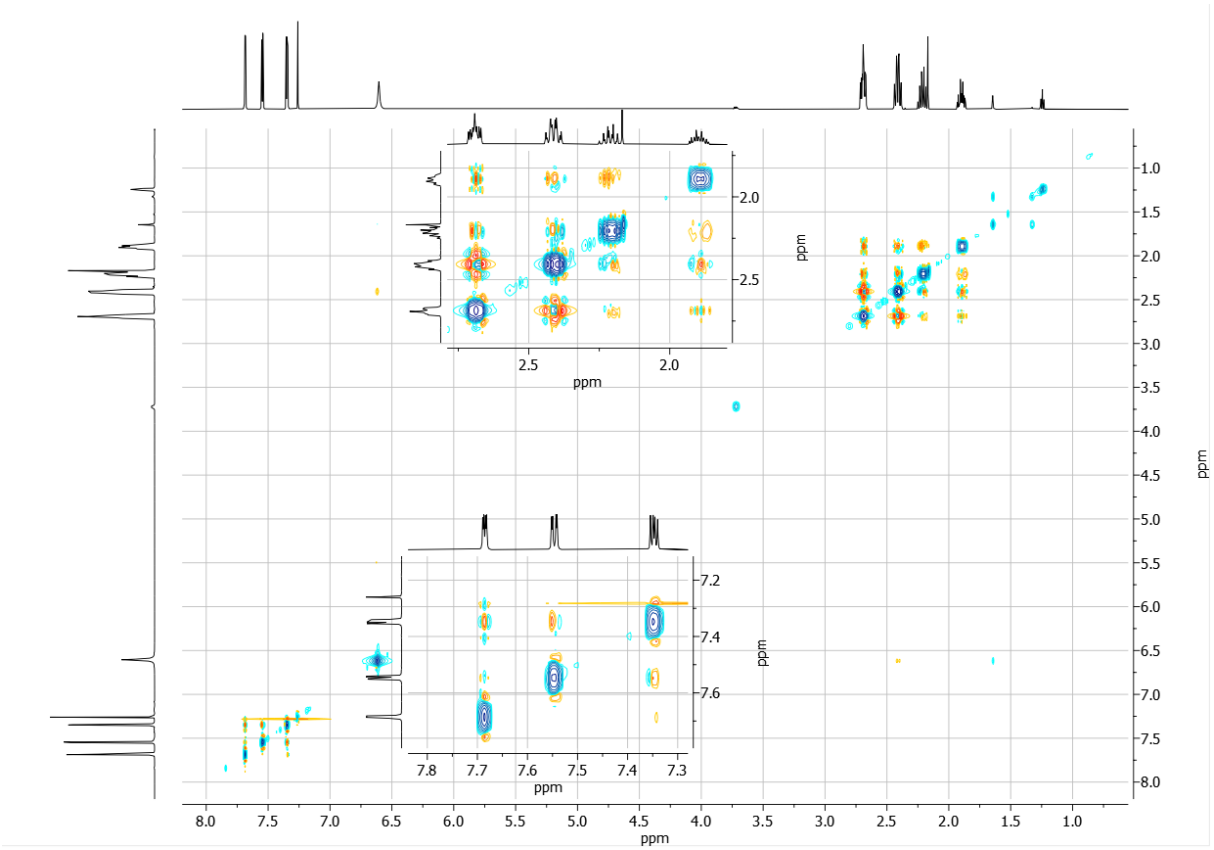
HSQC (600 MHz, $CDCl_3$) spectrum of 5o.



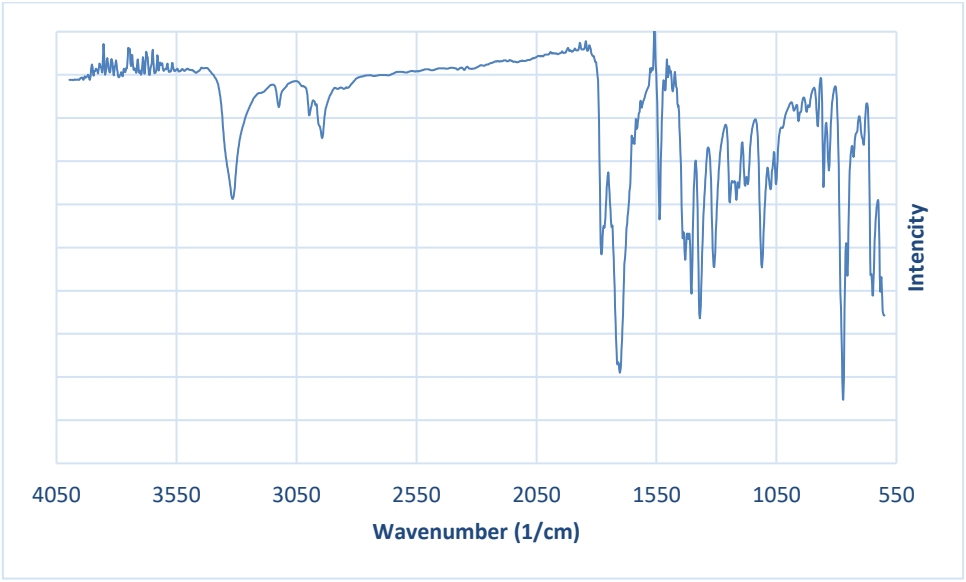
HMBC (600 MHz, $CDCl_3$) spectrum of 5o.



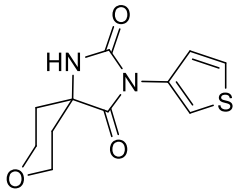
NOESY (600 MHz, $CDCl_3$) spectrum of 5o.



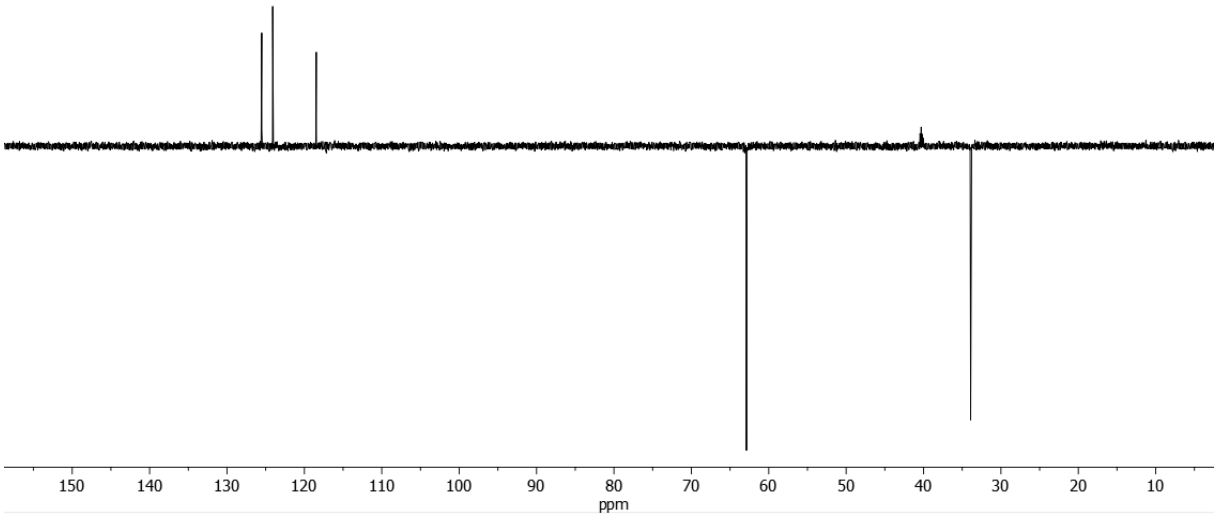
IR spectrum of 5o.



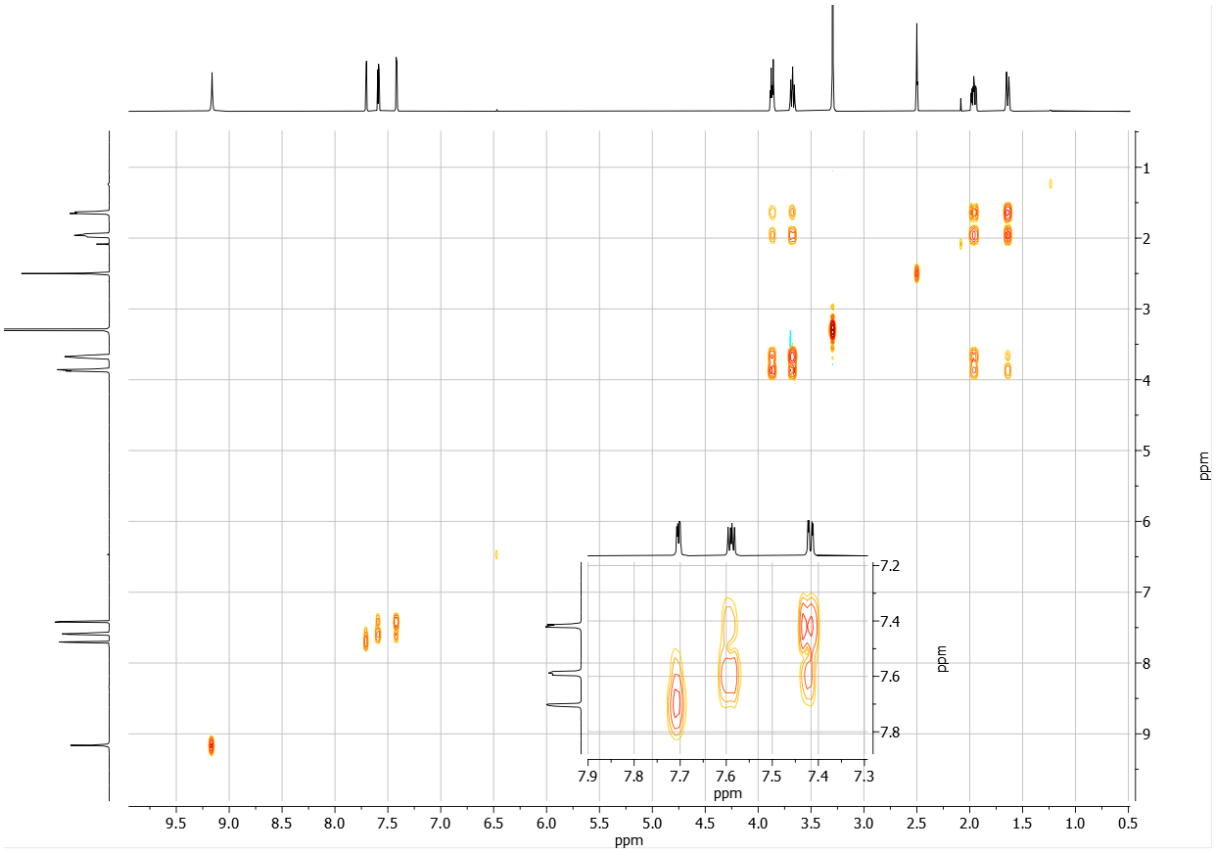
3-(thiophen-3-yl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5p) [NEW]



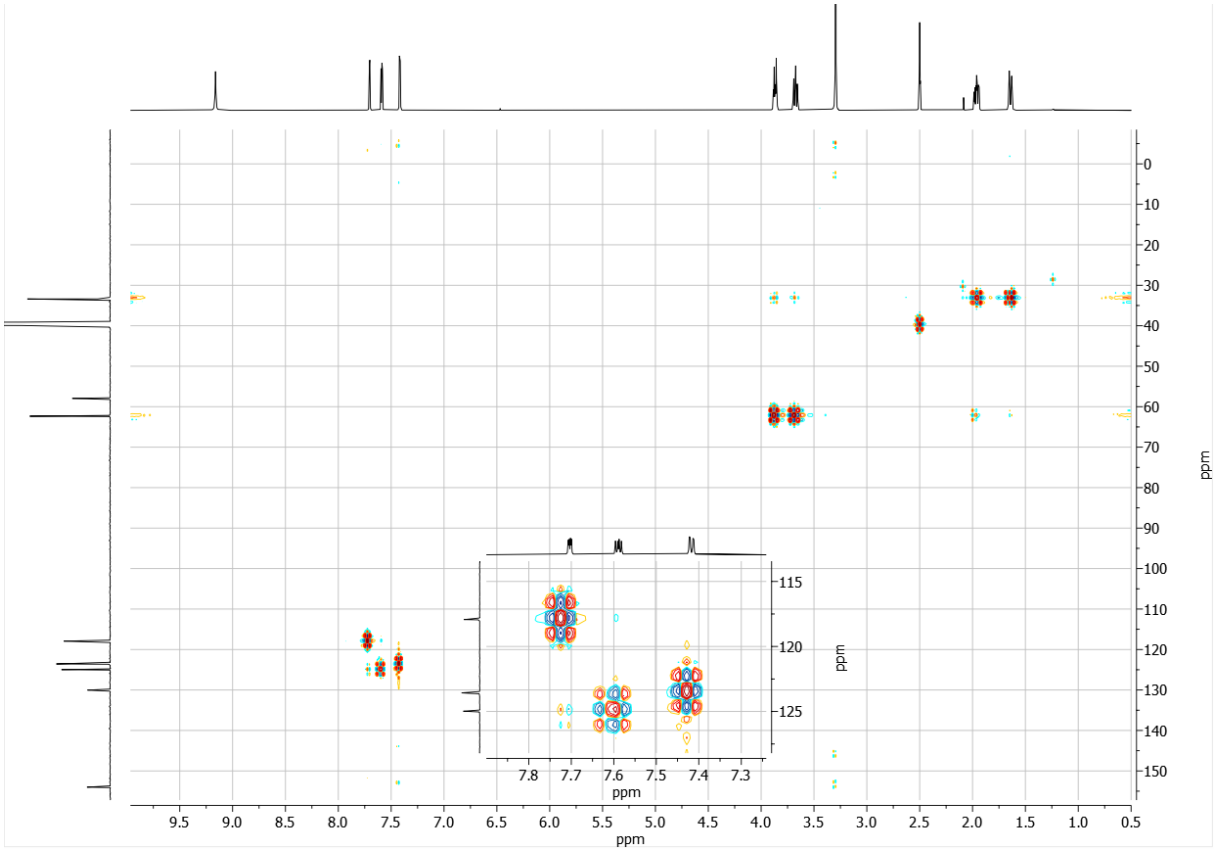
DEPT135 (151 MHz, DMSO-d6) spectrum of 5p.



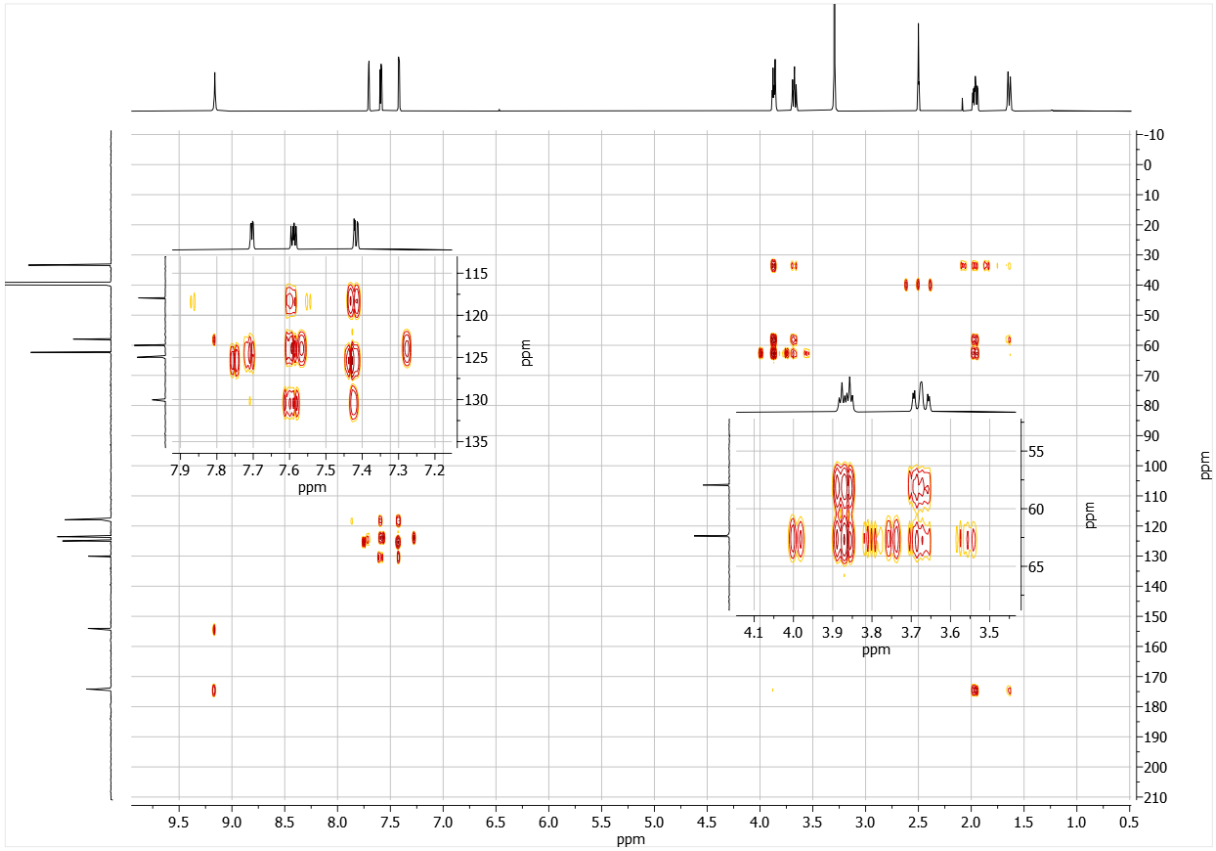
COSY (600 MHz, DMSO-d6) spectrum of 5p.



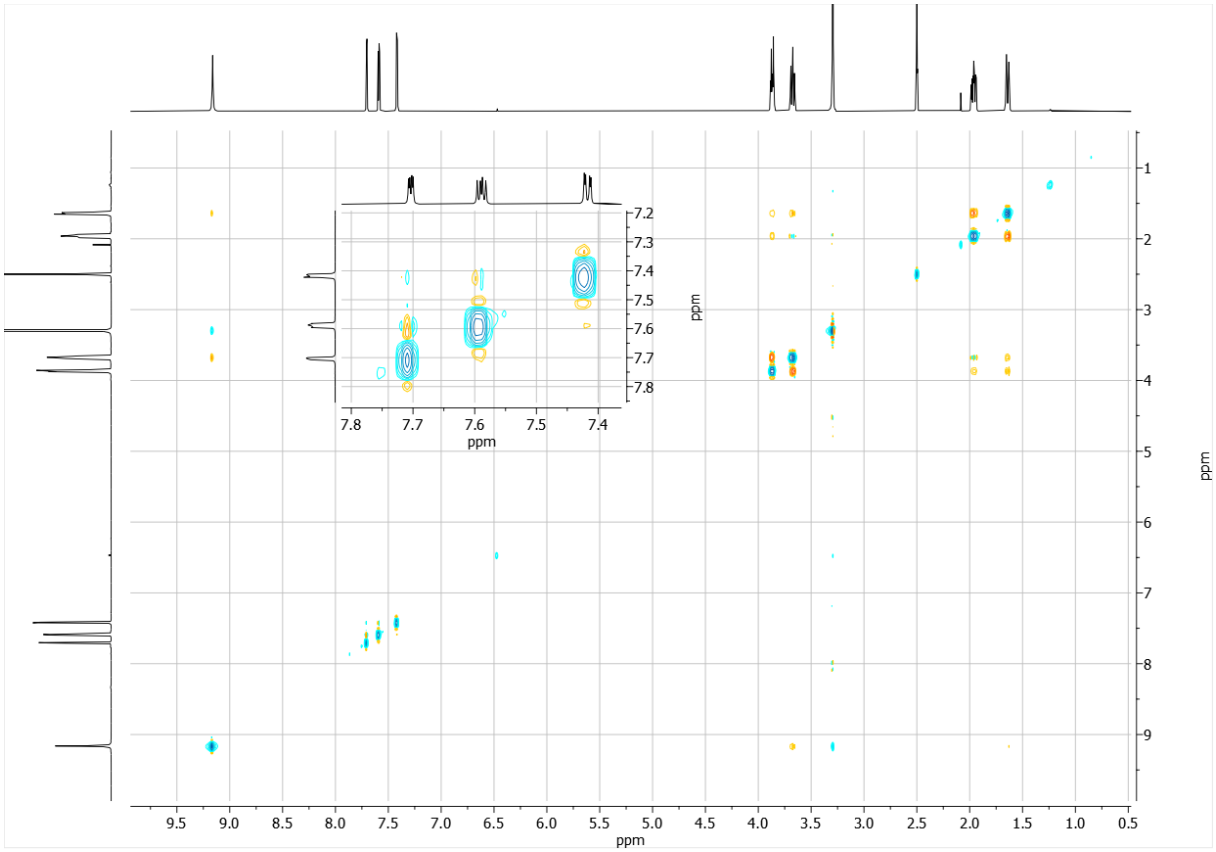
HSQC (600 MHz, DMSO-d_6) spectrum of 5p.



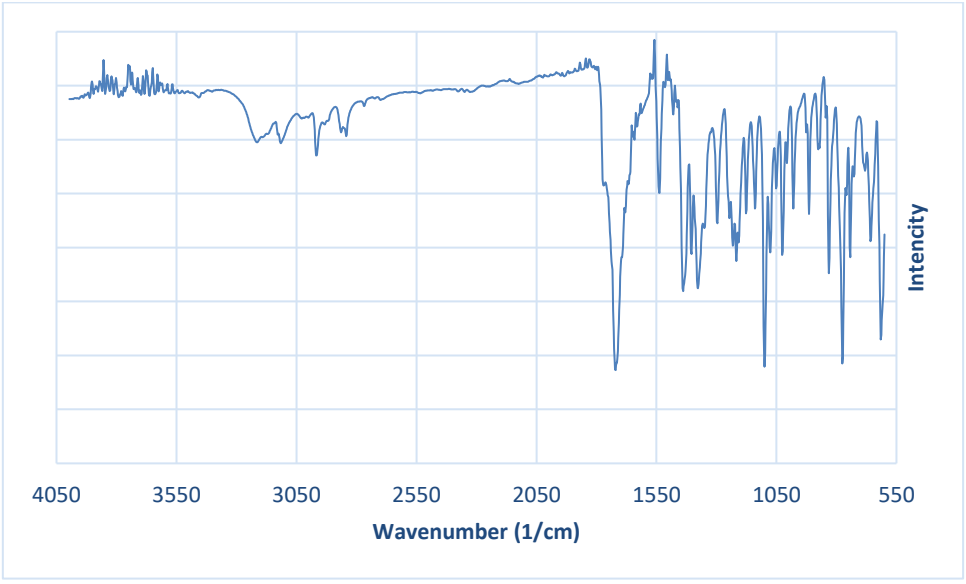
HMBC (600 MHz DMSO-d_6) spectrum of 5p.



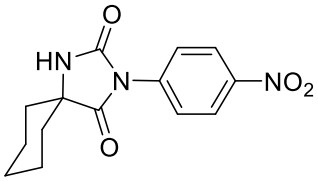
NOESY (600 MHz, DMSO-d_6) spectrum of 5p.



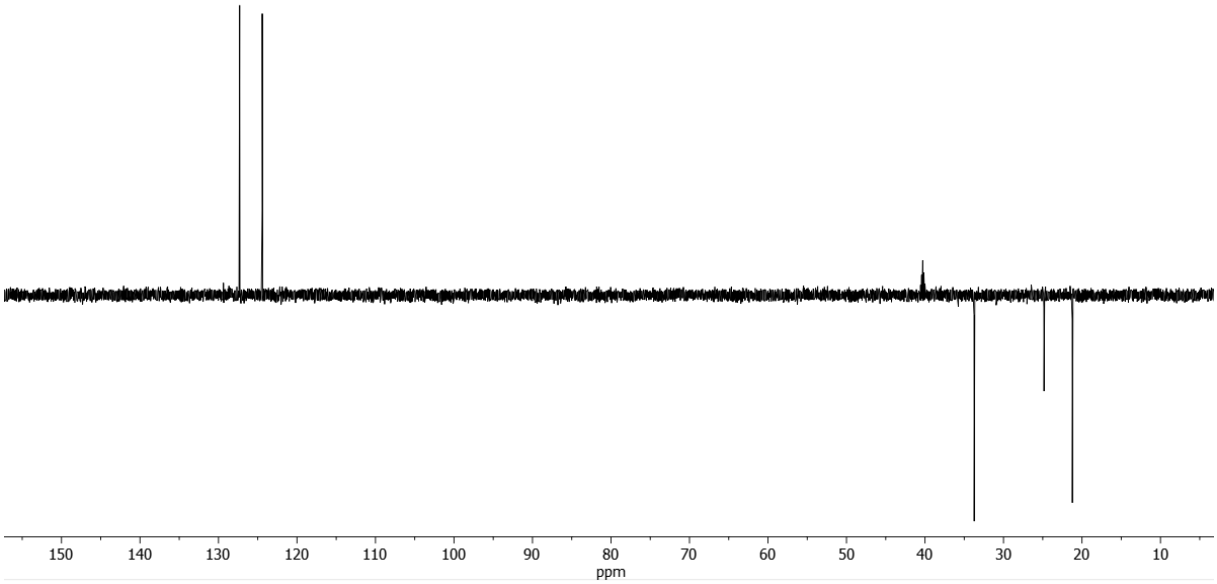
IR spectrum of 5p.



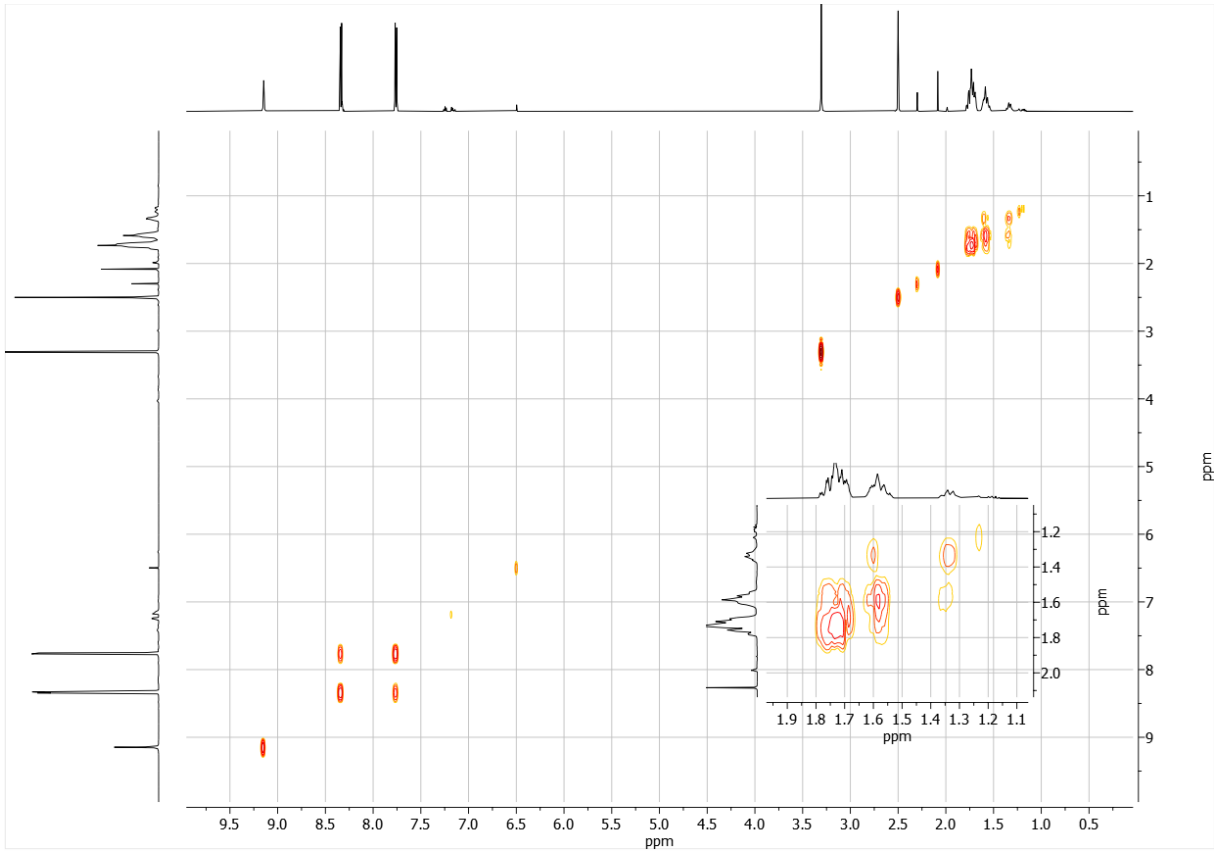
3-(4-nitrophenyl)-1,3-diazaspiro[4.5]decane-2,4-dione (5q) [1308139-00-5]



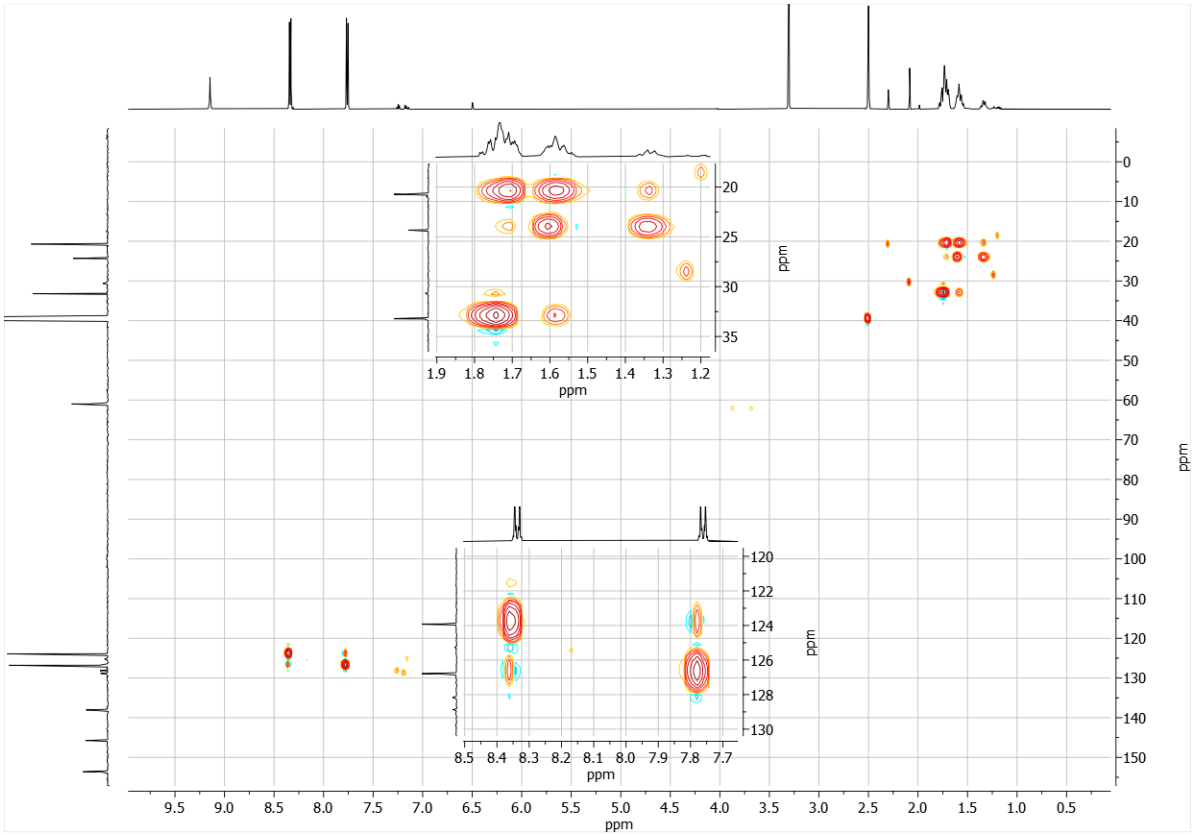
DEPT135 (151 MHz, DMSO-d$_6$) spectrum of 5q.



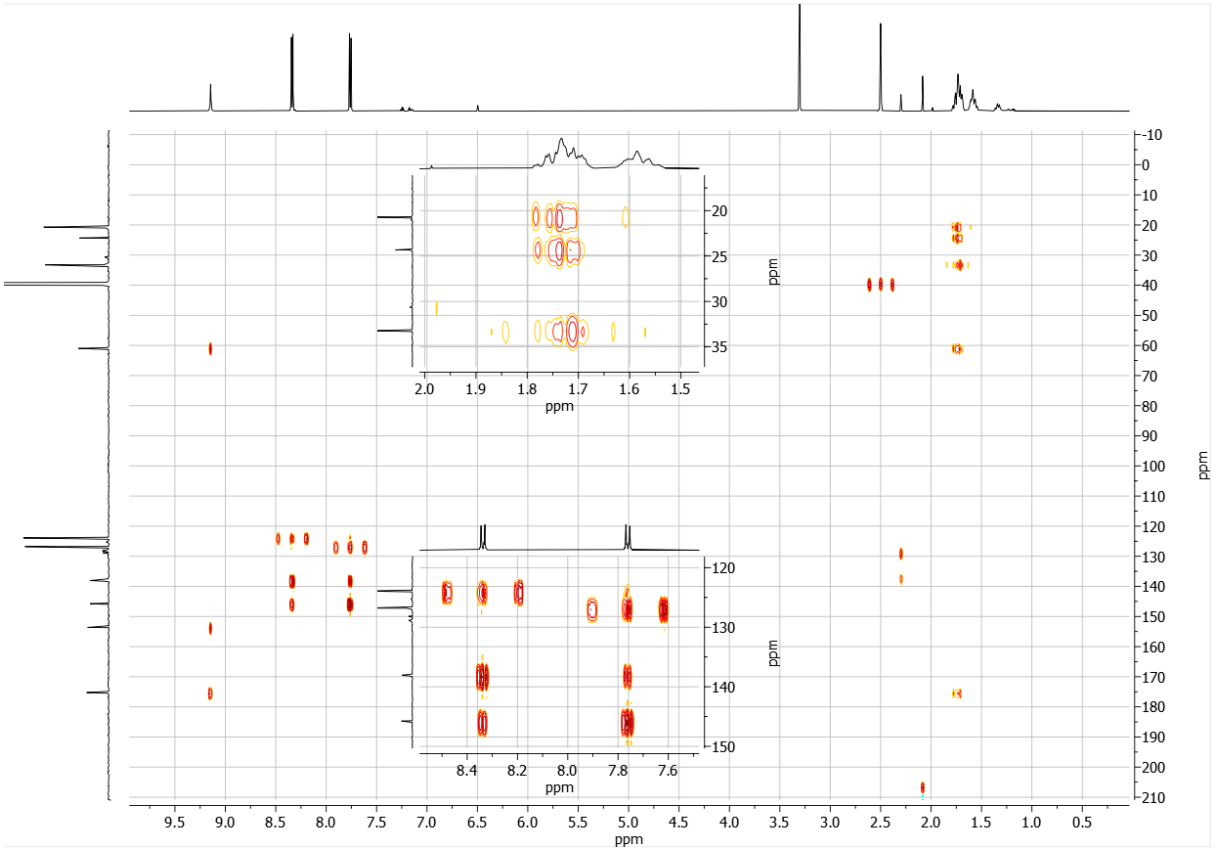
COSY (600 MHz, DMSO-d$_6$) spectrum of 5q.



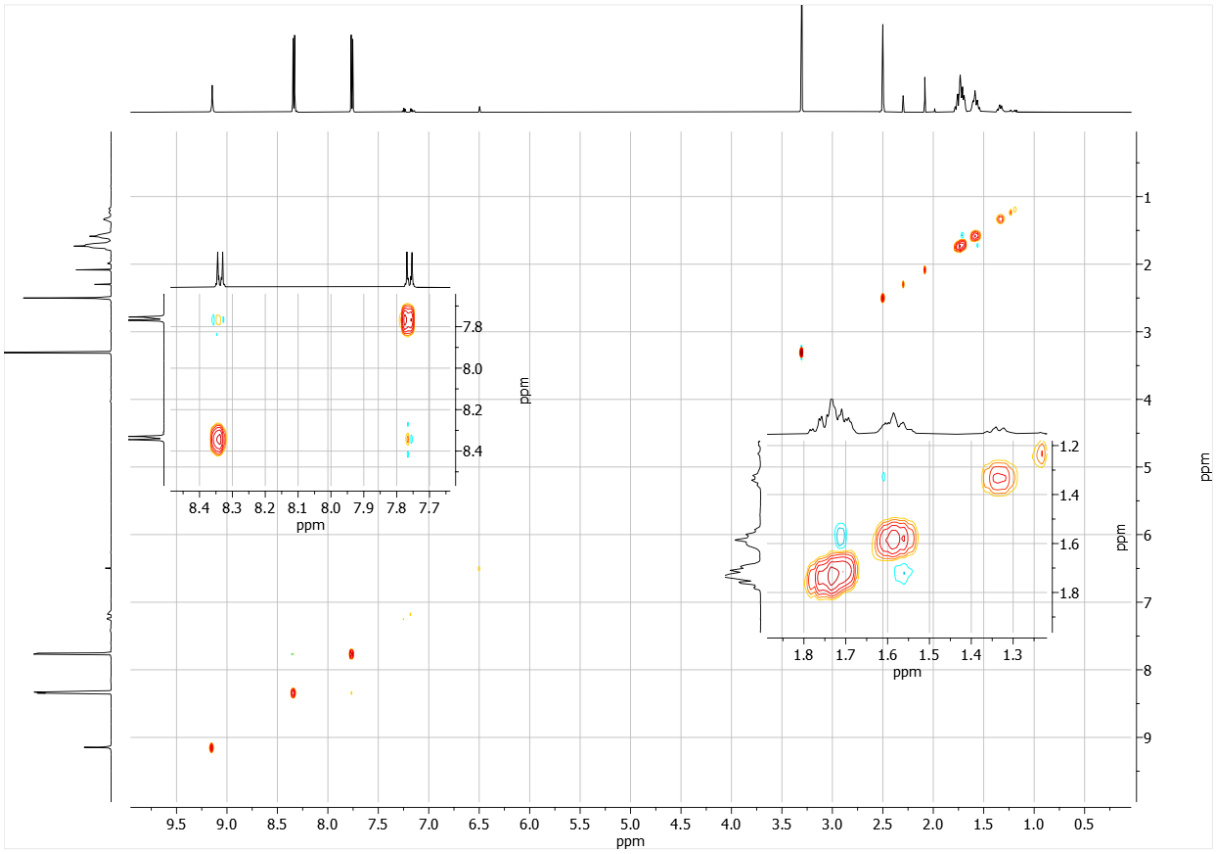
HSQC (600 MHz, DMSO-d_6) spectrum of 5q.



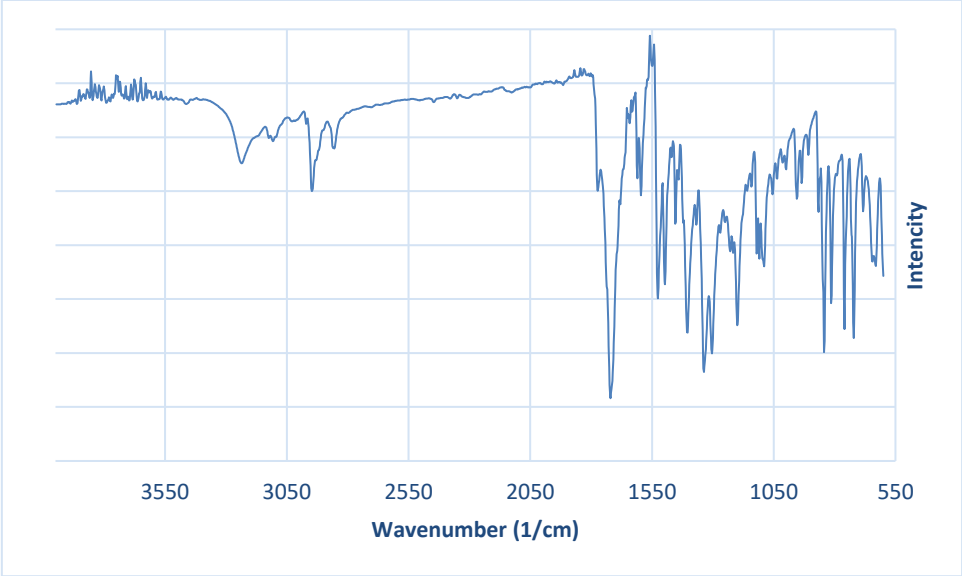
HMBC (600 MHz, DMSO-d_6) spectrum of 5q.



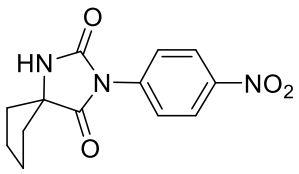
NOESY (600 MHz, DMSO-d_6) spectrum of 5q.



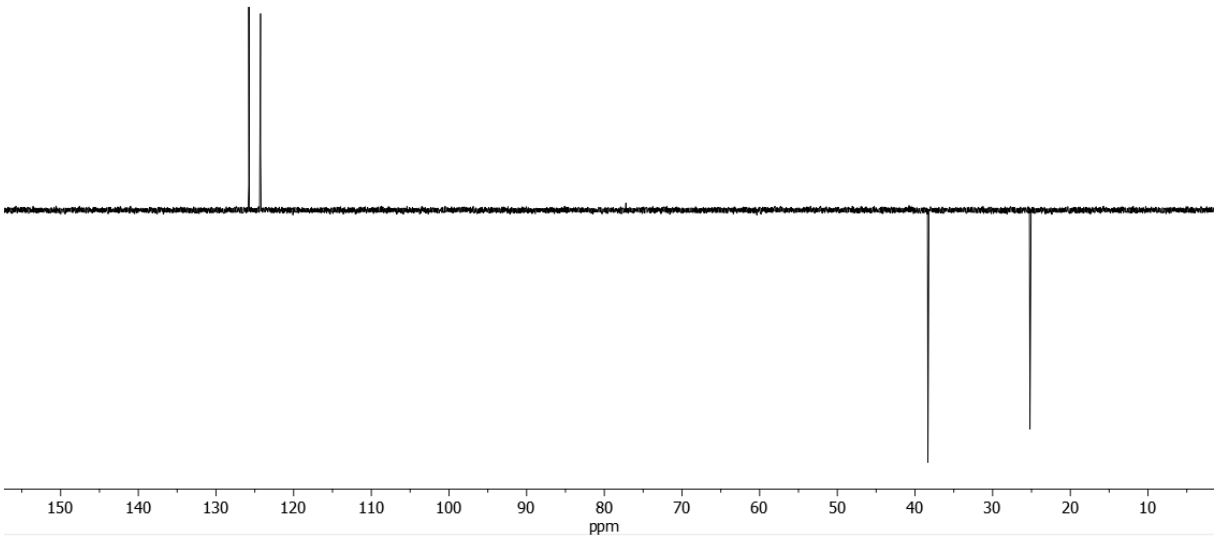
IR spectrum of 5q.



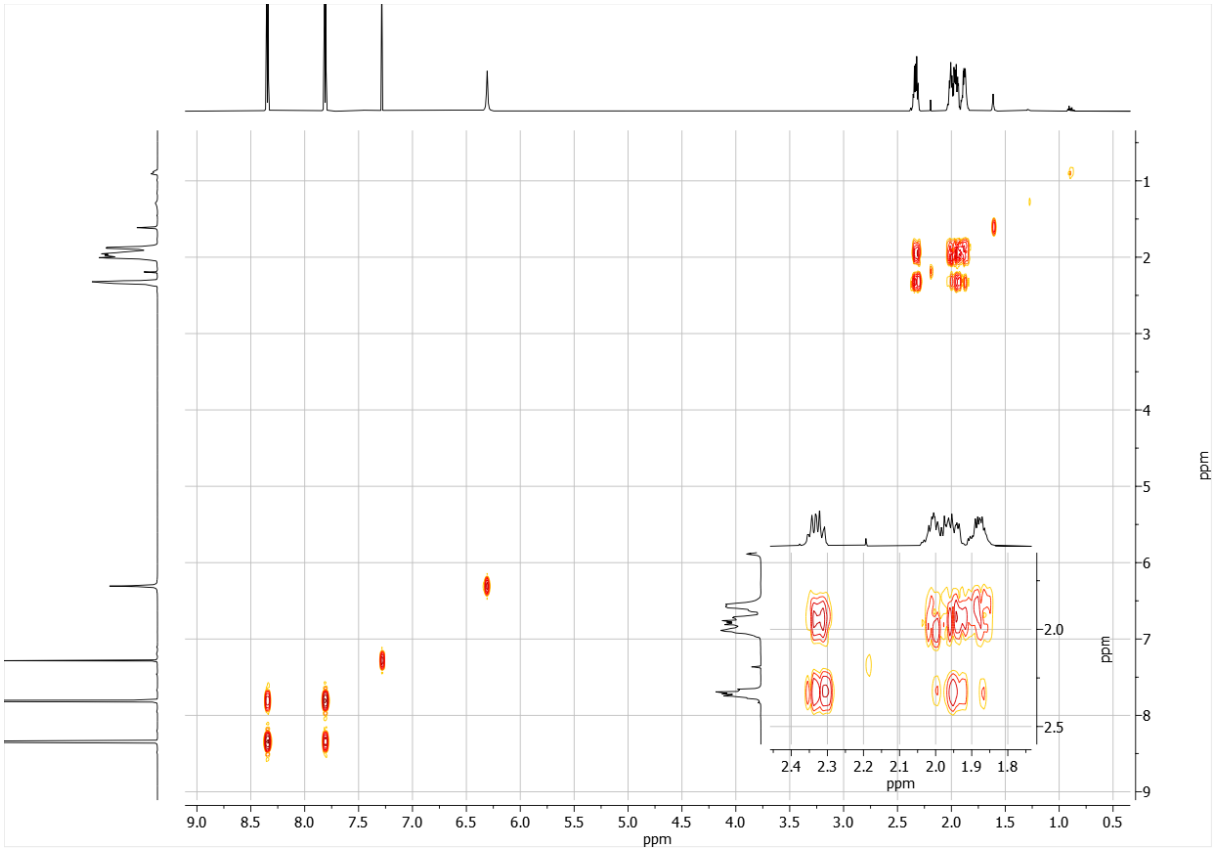
3-(4-nitrophenyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (5r) [1304895-82-6]



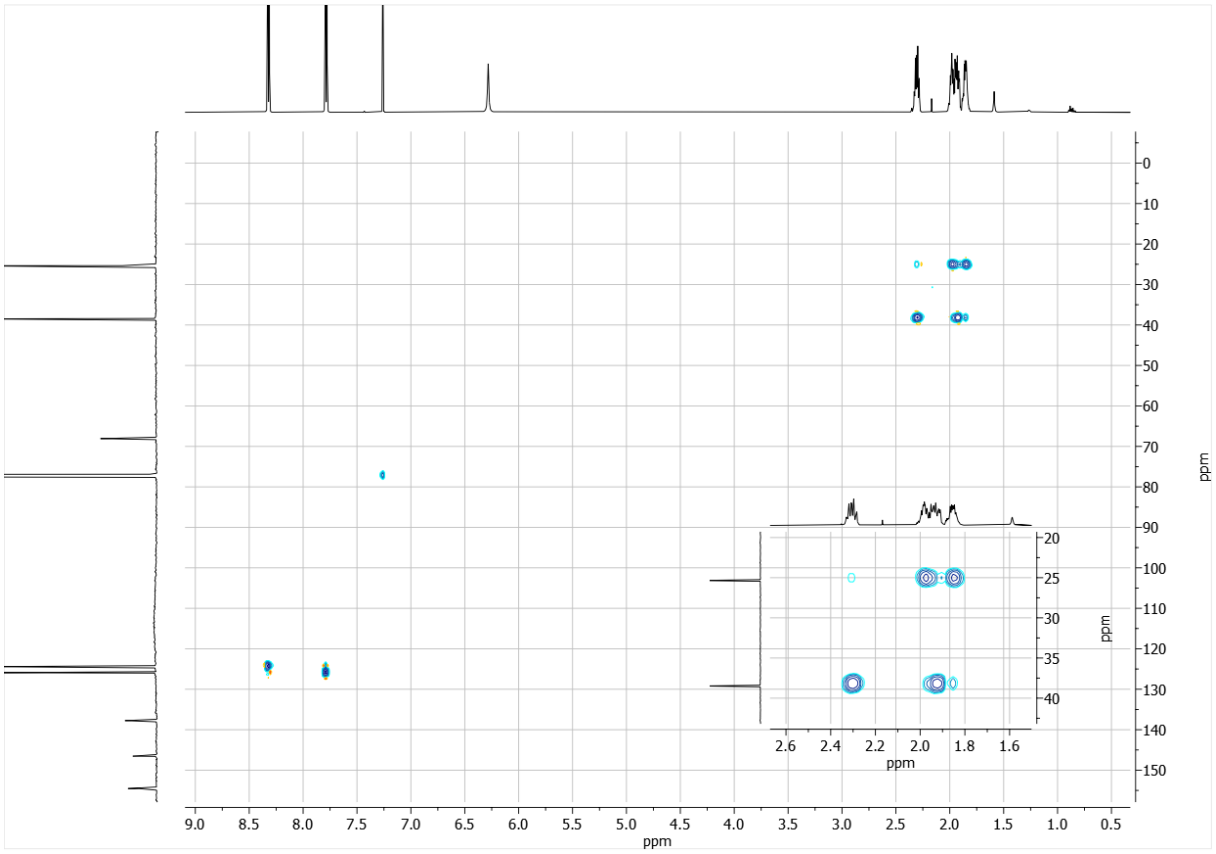
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5r.



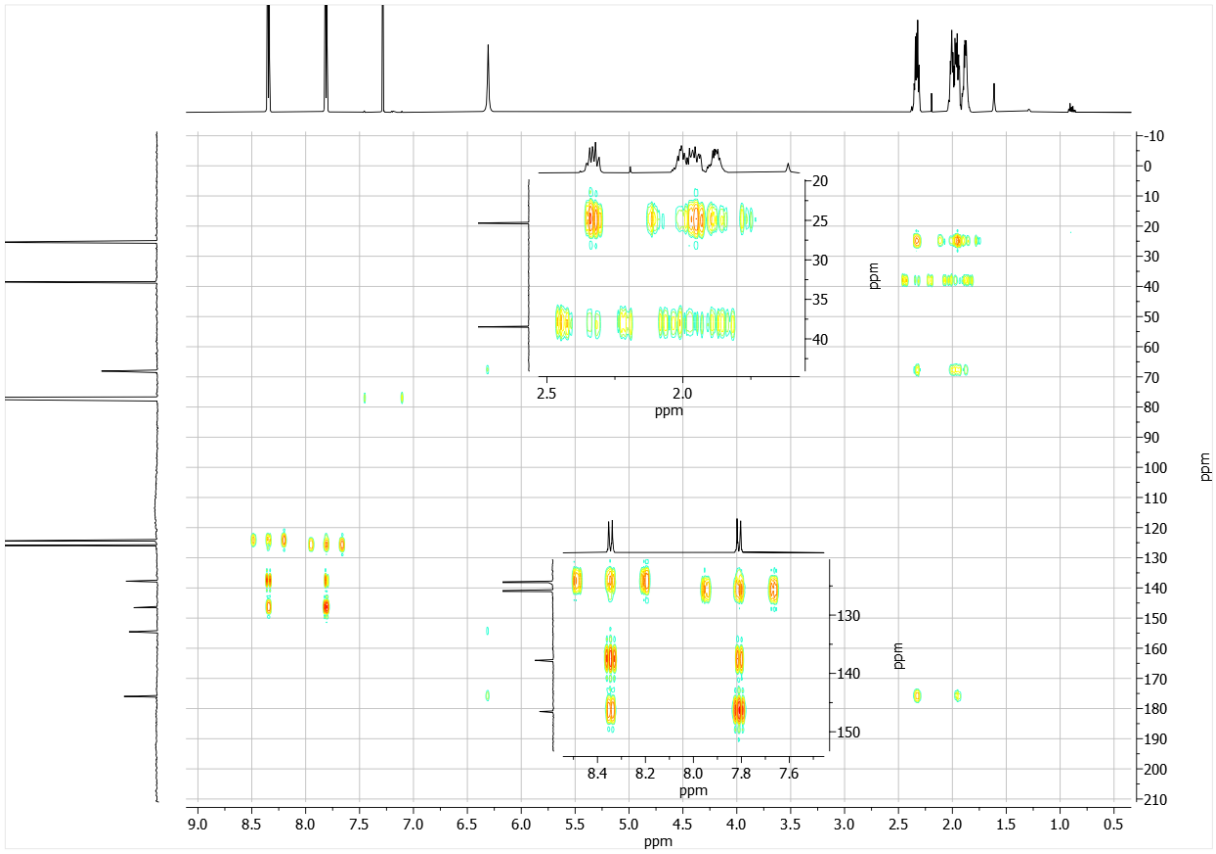
COSY (600 MHz, $CDCl_3$) spectrum of 5r.



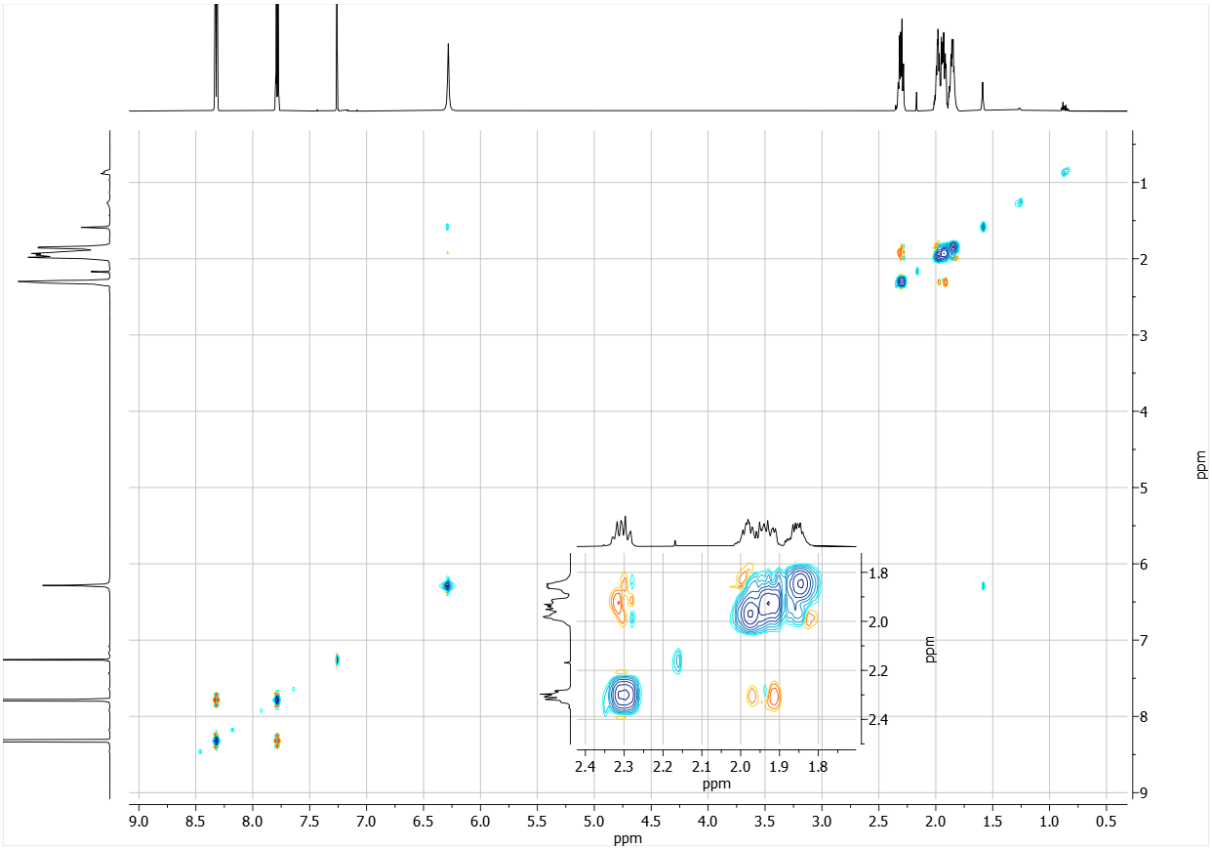
HSQC (600 MHz, $CDCl_3$) spectrum of 5r.



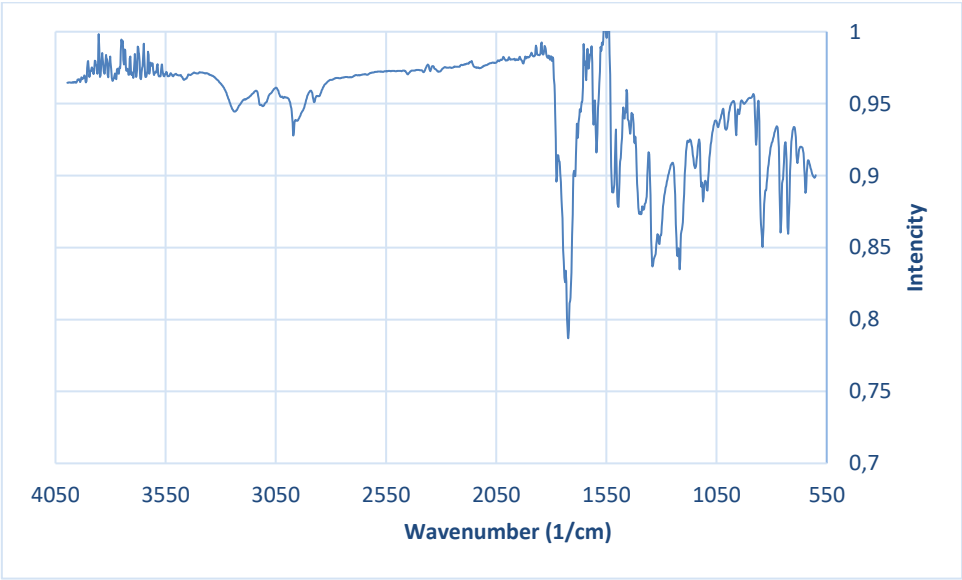
HMBC (600 MHz, $CDCl_3$) spectrum of 5r.



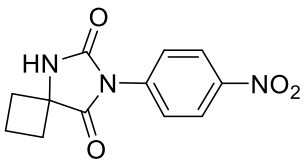
NOESY (600 MHz, $CDCl_3$) spectrum of 5r.



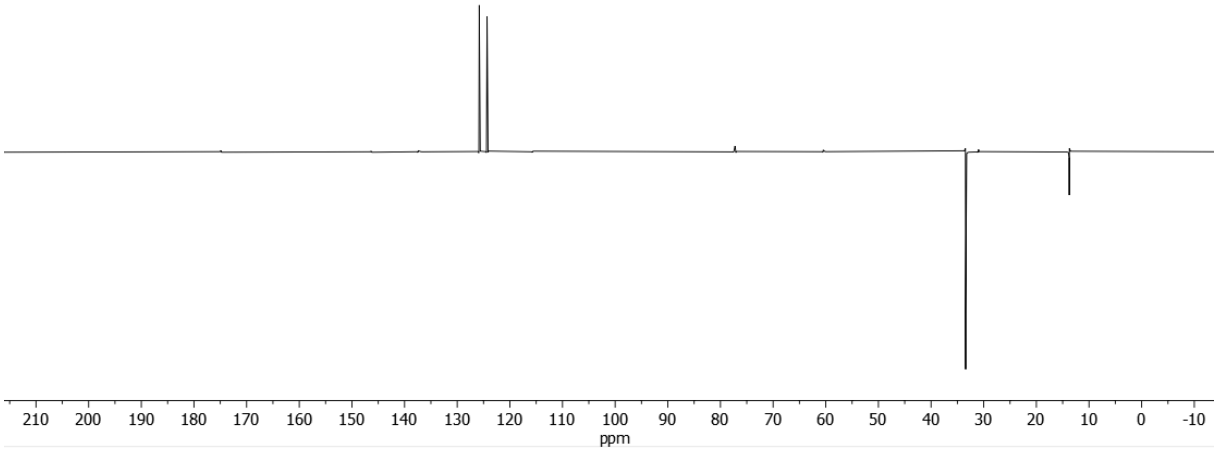
IR spectrum of 5r.



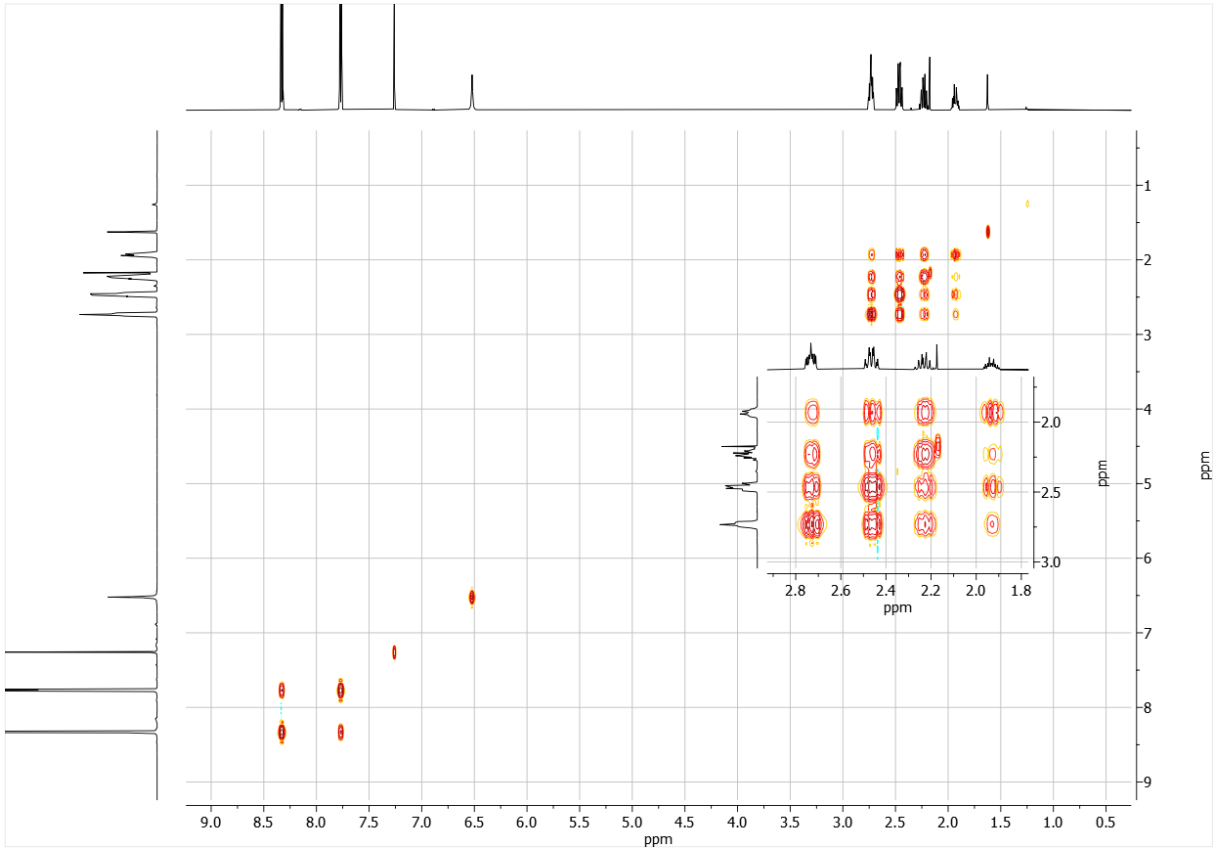
7-(4-nitrophenyl)-5,7-diazaspiro[3.4]octane-6,8-dione (5s) [1501415-34-4]



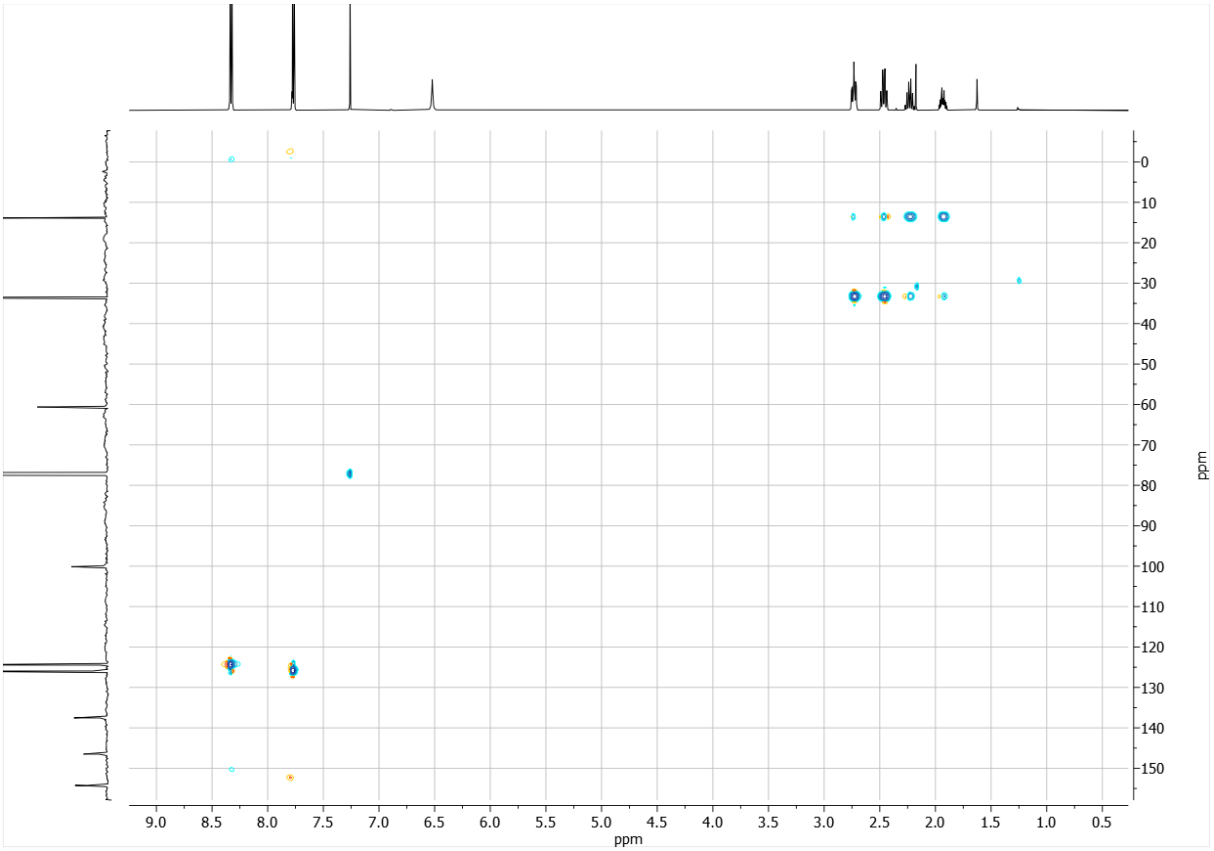
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5s.



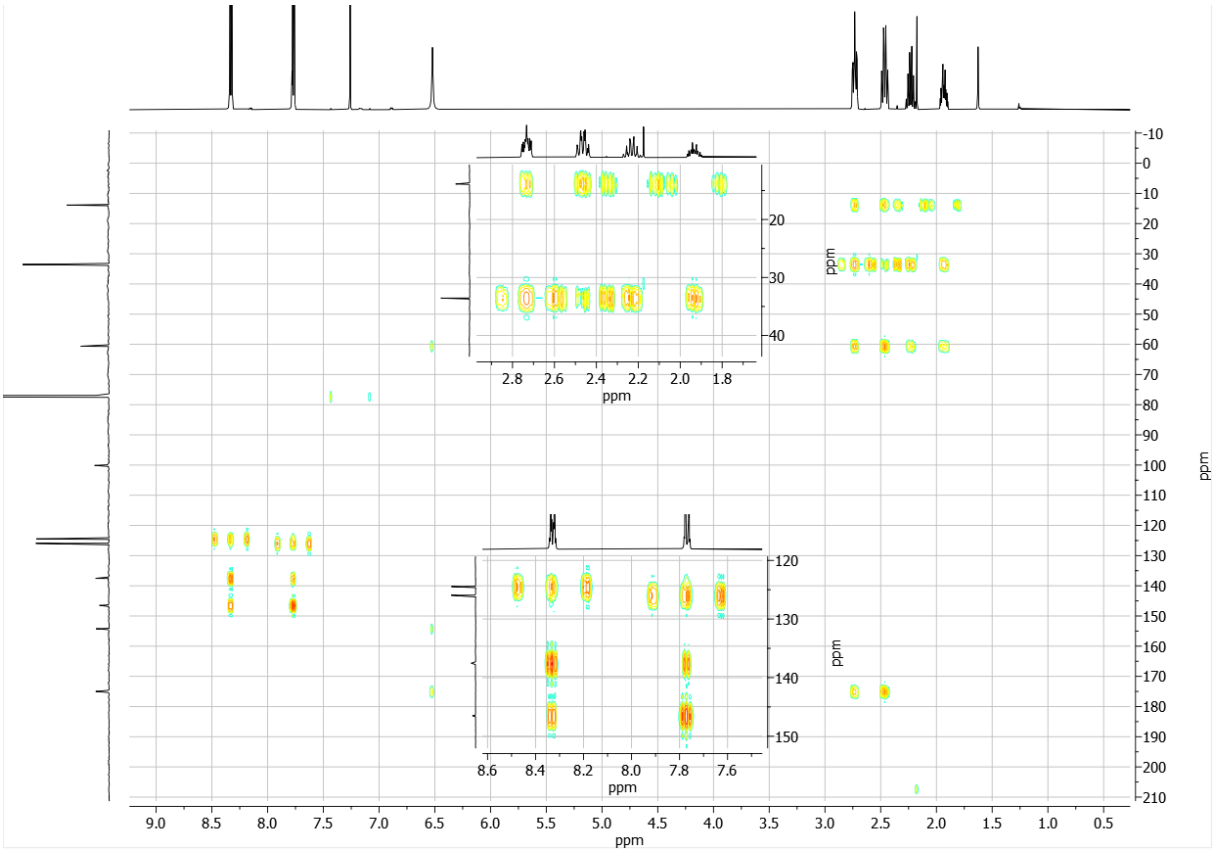
COSY (600 MHz, $CDCl_3$) spectrum of 5s.



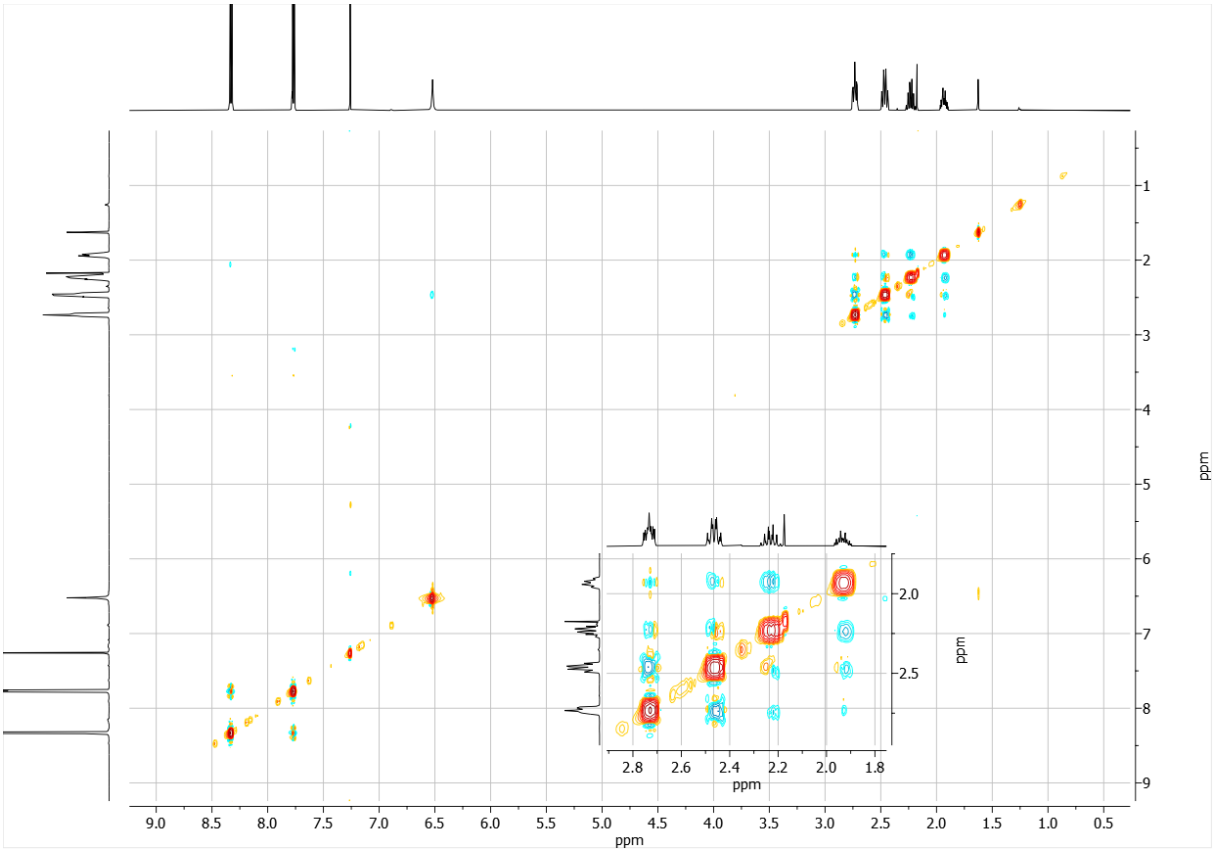
HSQC (600 MHz, $CDCl_3$) spectrum of 5s.



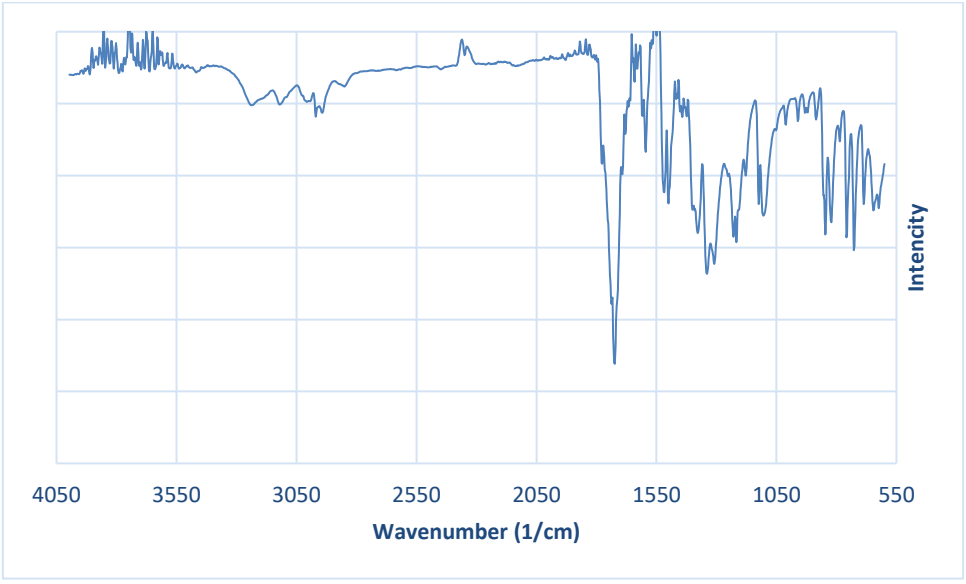
HMBC (600 MHz, $CDCl_3$) spectrum of 5s.



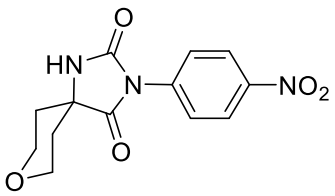
NOESY (600 MHz, $CDCl_3$) spectrum of 5s.



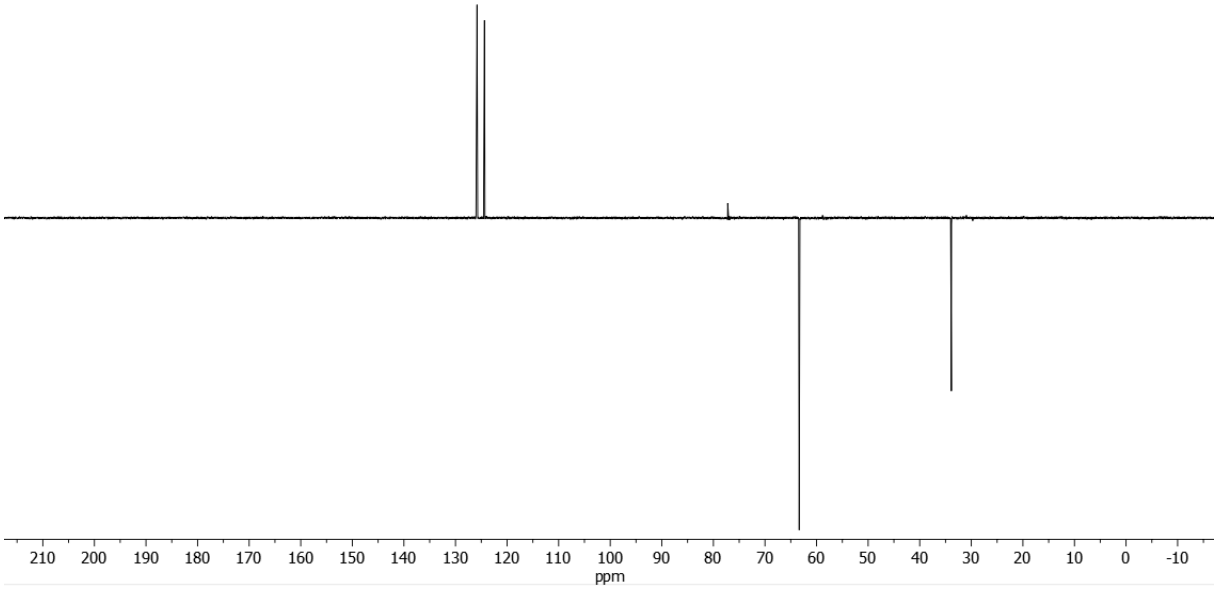
IR spectrum of 5s.



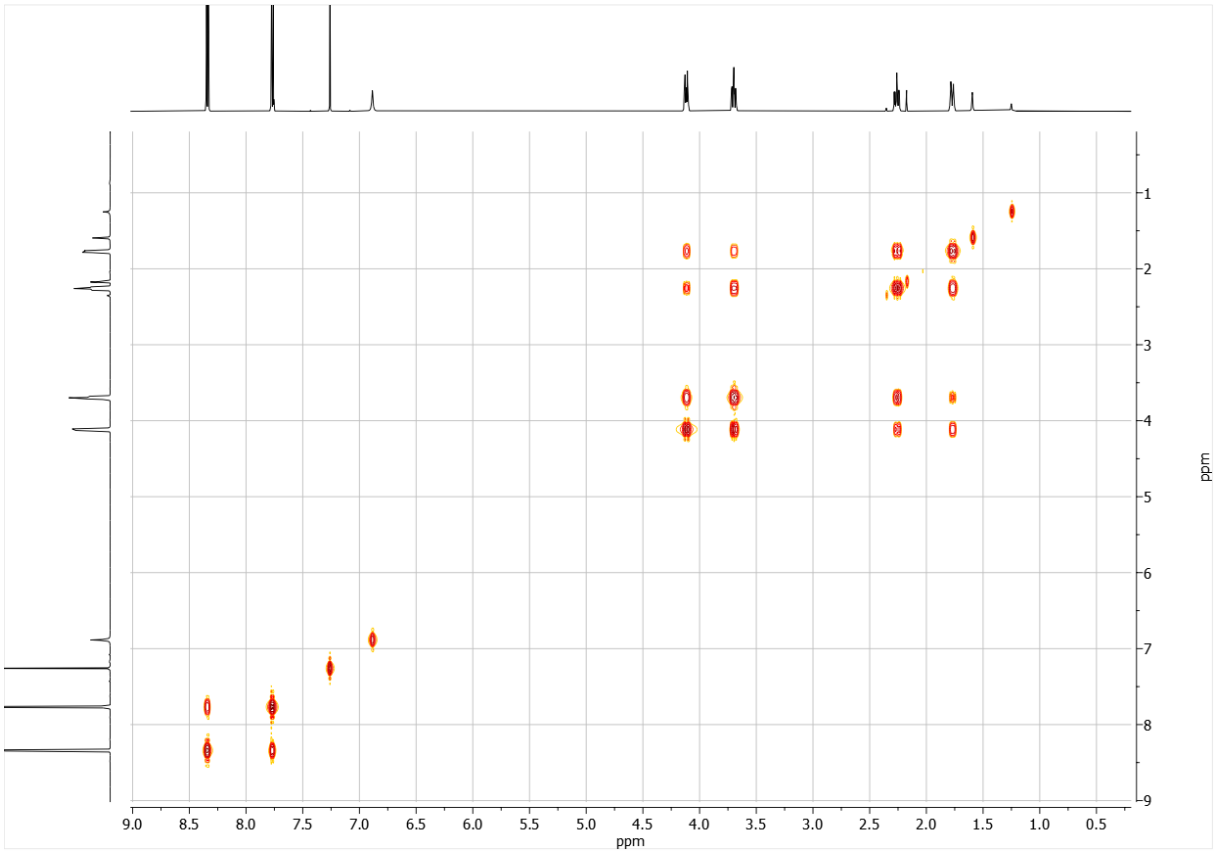
3-(4-nitrophenyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (5t) [1553596-59-0]



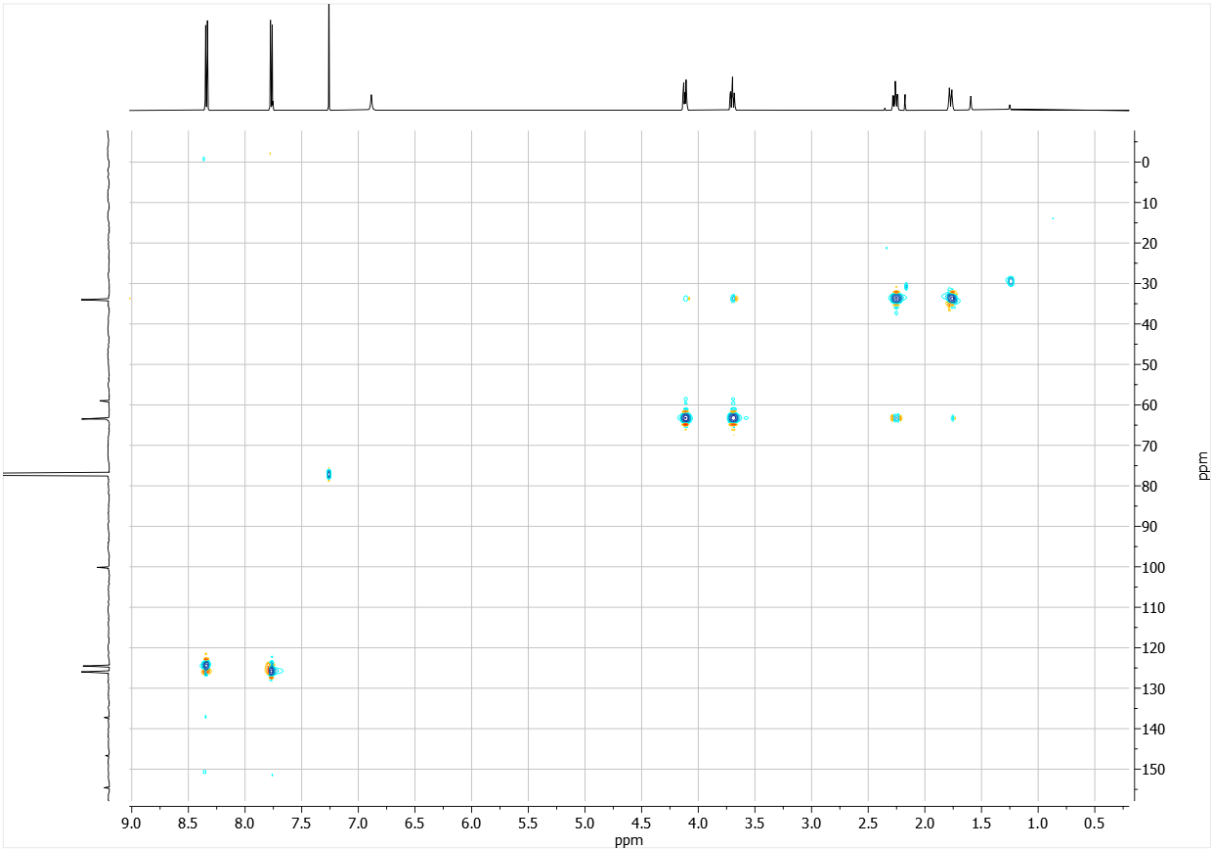
DEPT135 (151 MHz, $CDCl_3$) spectrum of 5t.



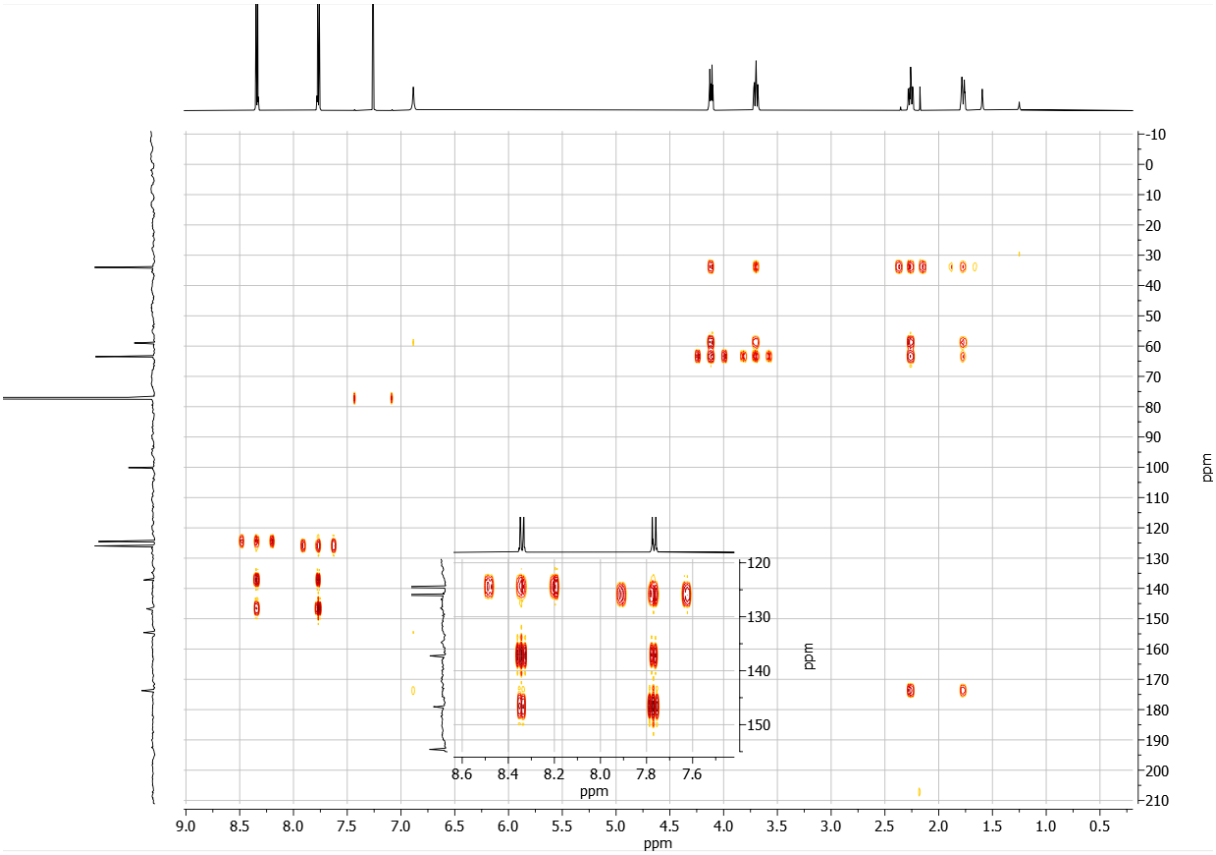
COSY (600 MHz, $CDCl_3$) spectrum of 5t.



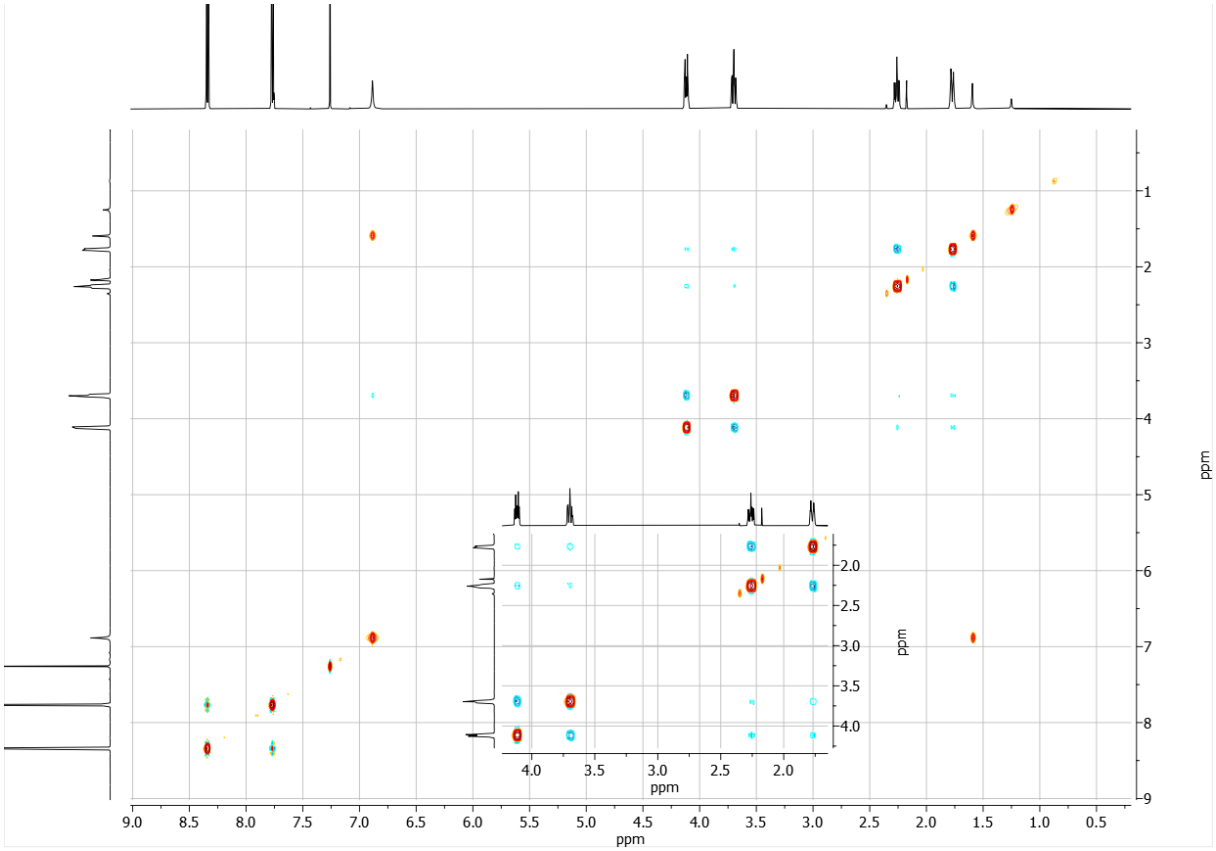
HSQC (600 MHz, $CDCl_3$) spectrum of 5t.



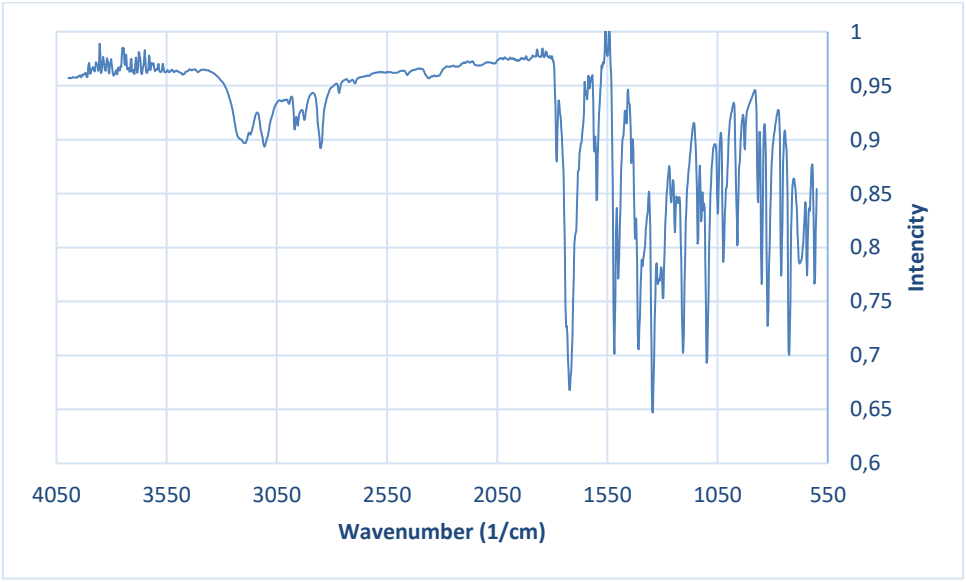
HMBC (600 MHz, $CDCl_3$) spectrum of 5t.



NOESY (600 MHz, $CDCl_3$) spectrum of 5t.

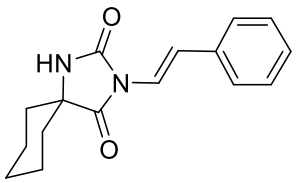


IR spectrum of 5t.

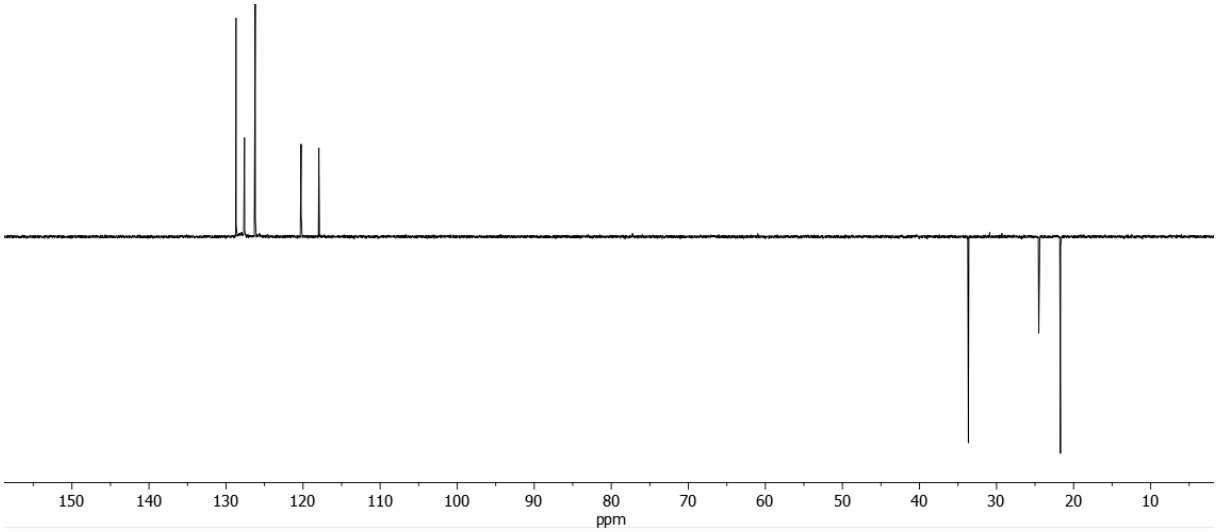


7.3 *N*-3-Alkenyl spirohydantoins

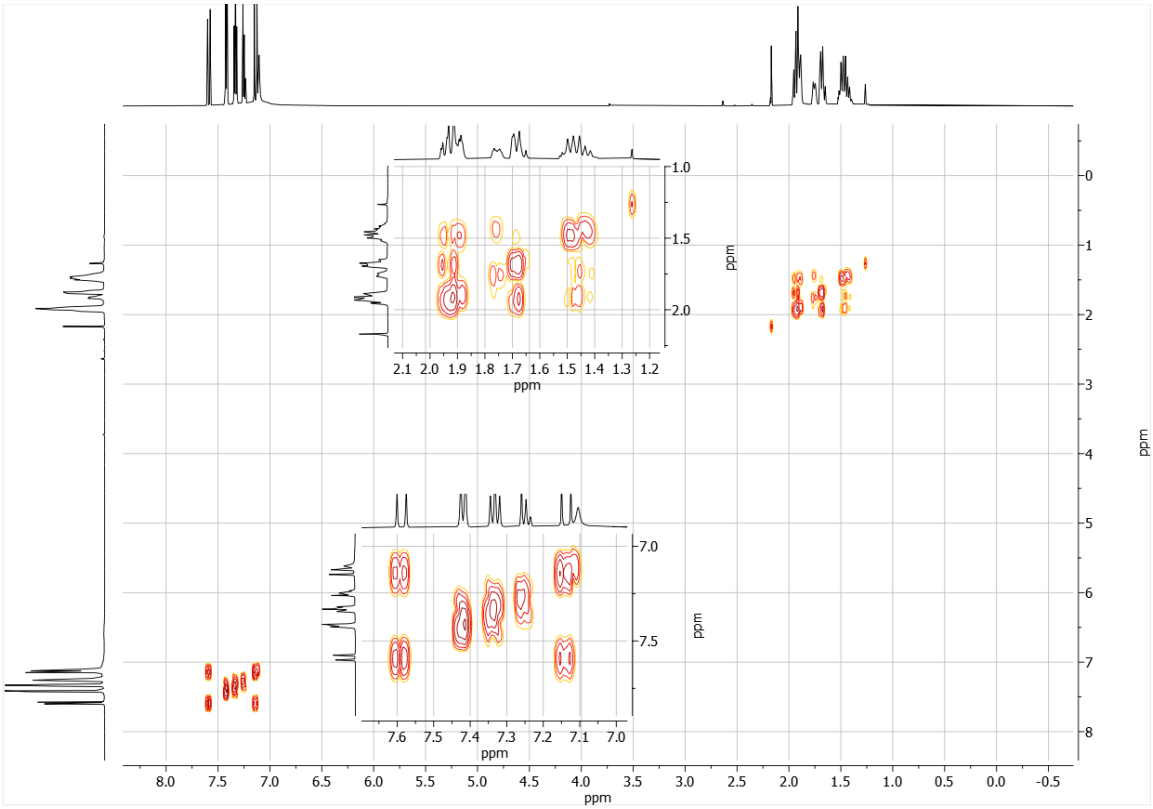
(E)-3-styryl-1,3-diazaspiro[4.5]decane-2,4-dione (6a) [new]



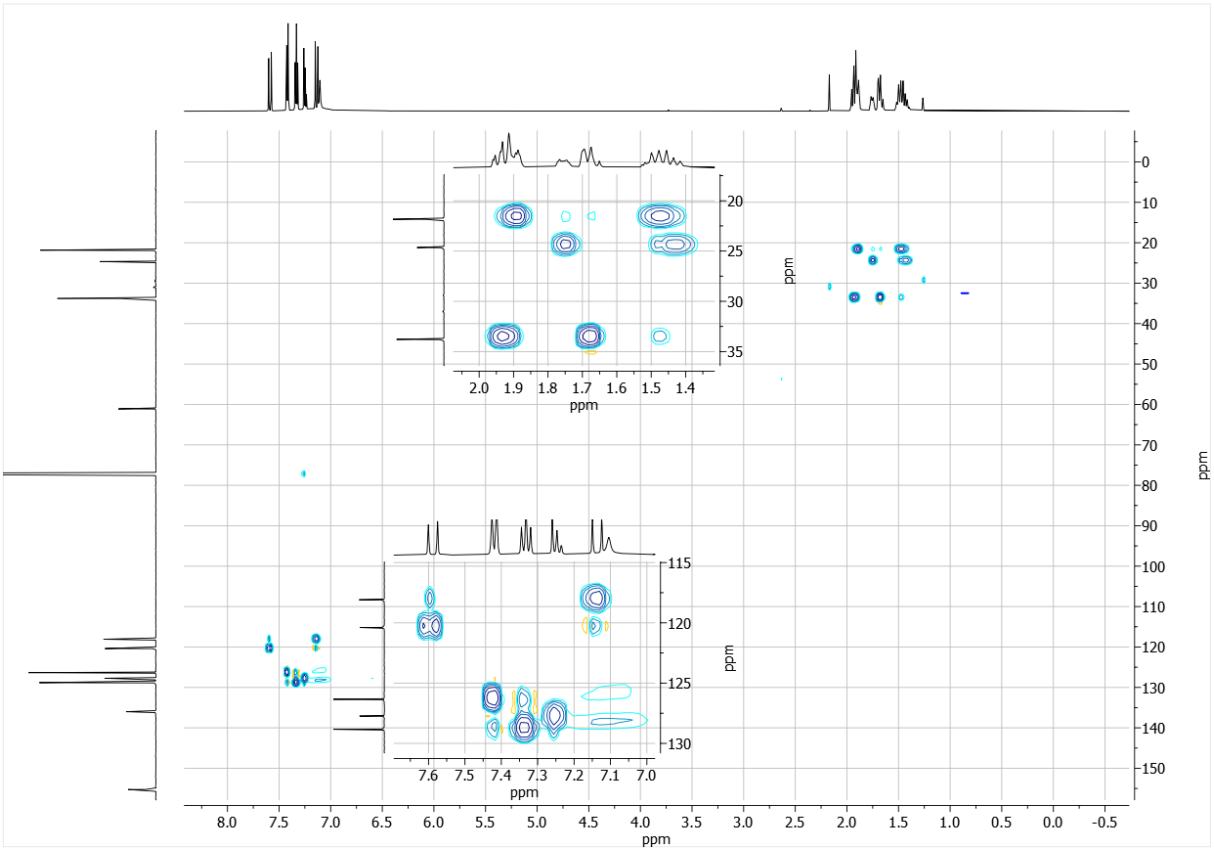
DEPT135 (151 MHz, $CDCl_3$) spectrum of 6a.



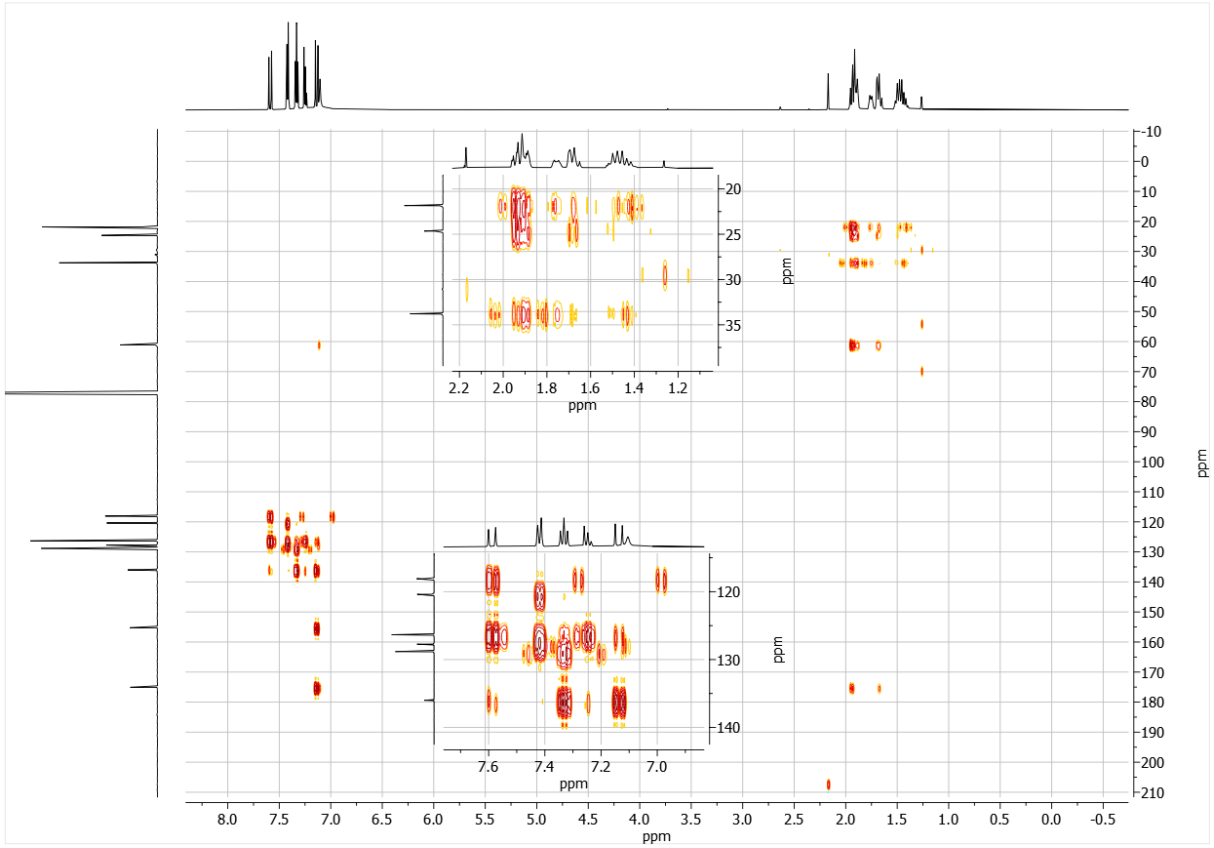
COSY (600 MHz, $CDCl_3$) spectrum of 6a.



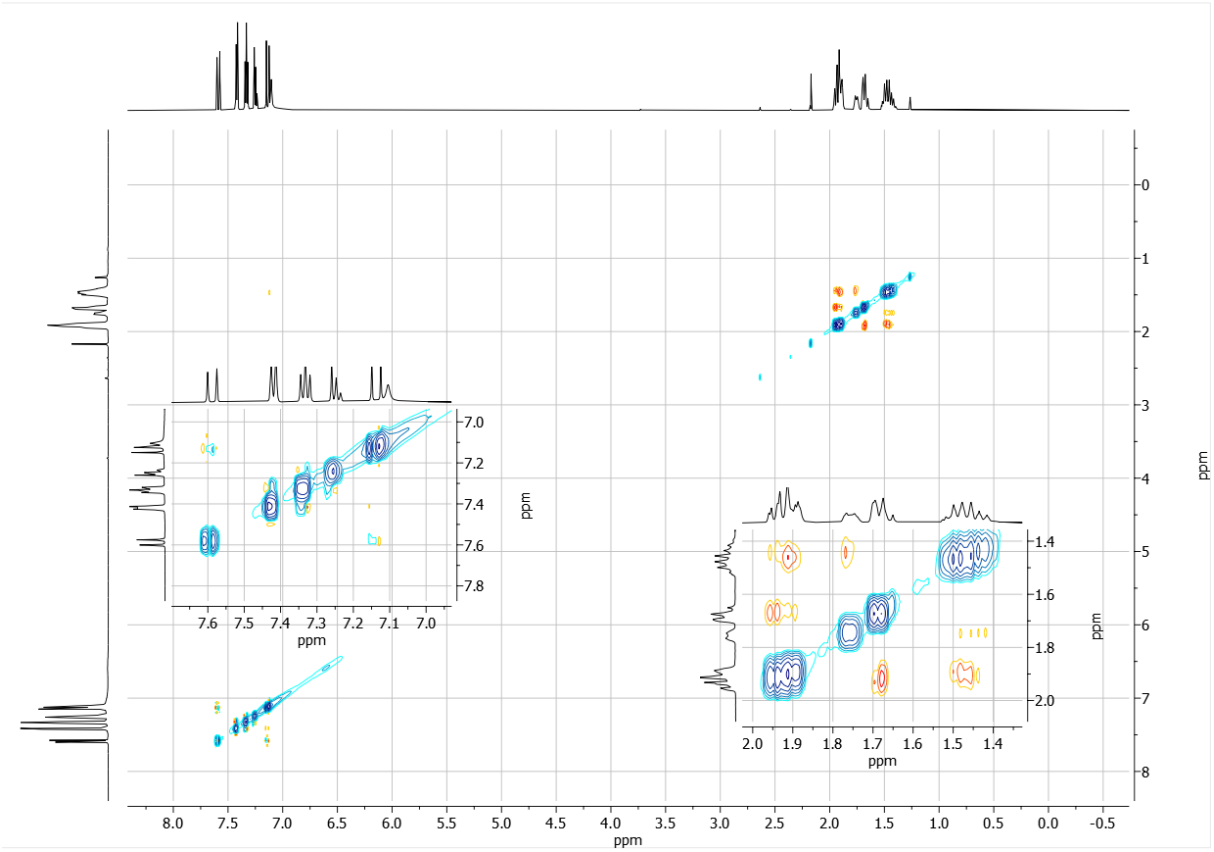
HSQC (600 MHz, $CDCl_3$) spectrum of 6a.



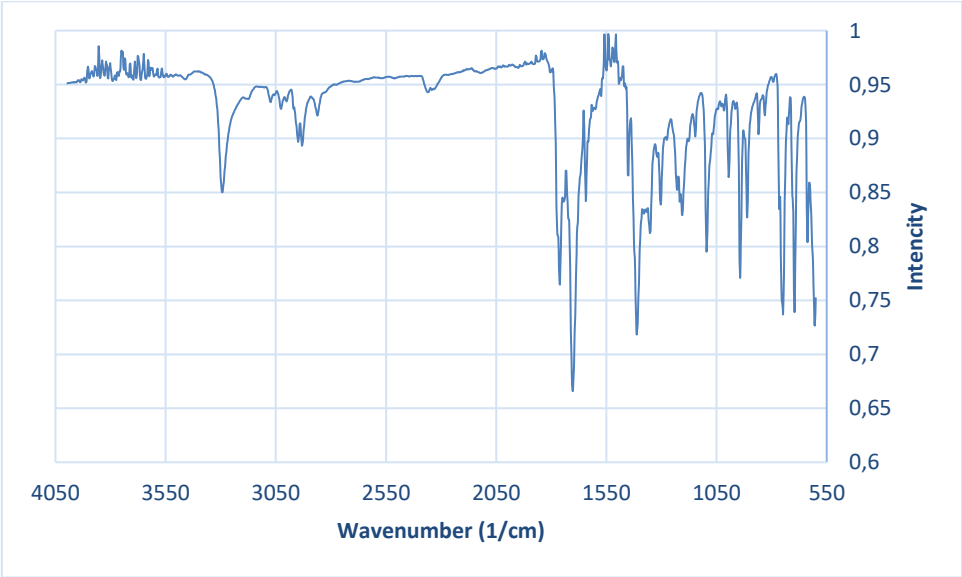
HMBC (600 MHz, $CDCl_3$) spectrum of 6a.



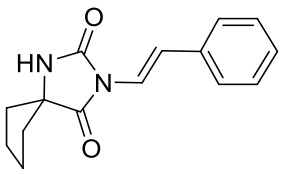
NOESY (600 MHz, $CDCl_3$) spectrum of 6a.



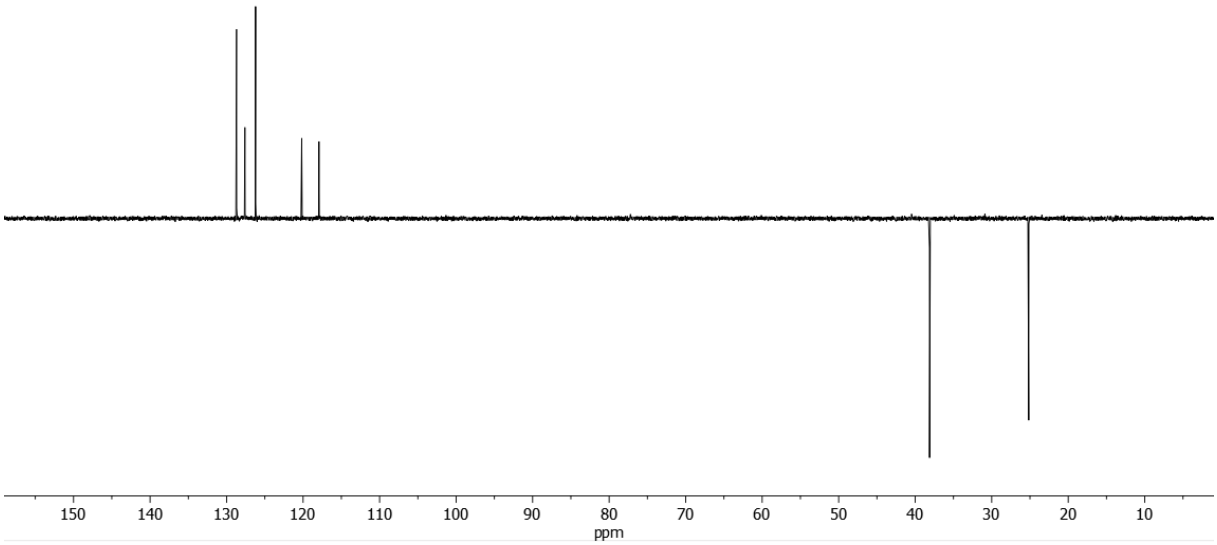
IR spectrum of 6a.



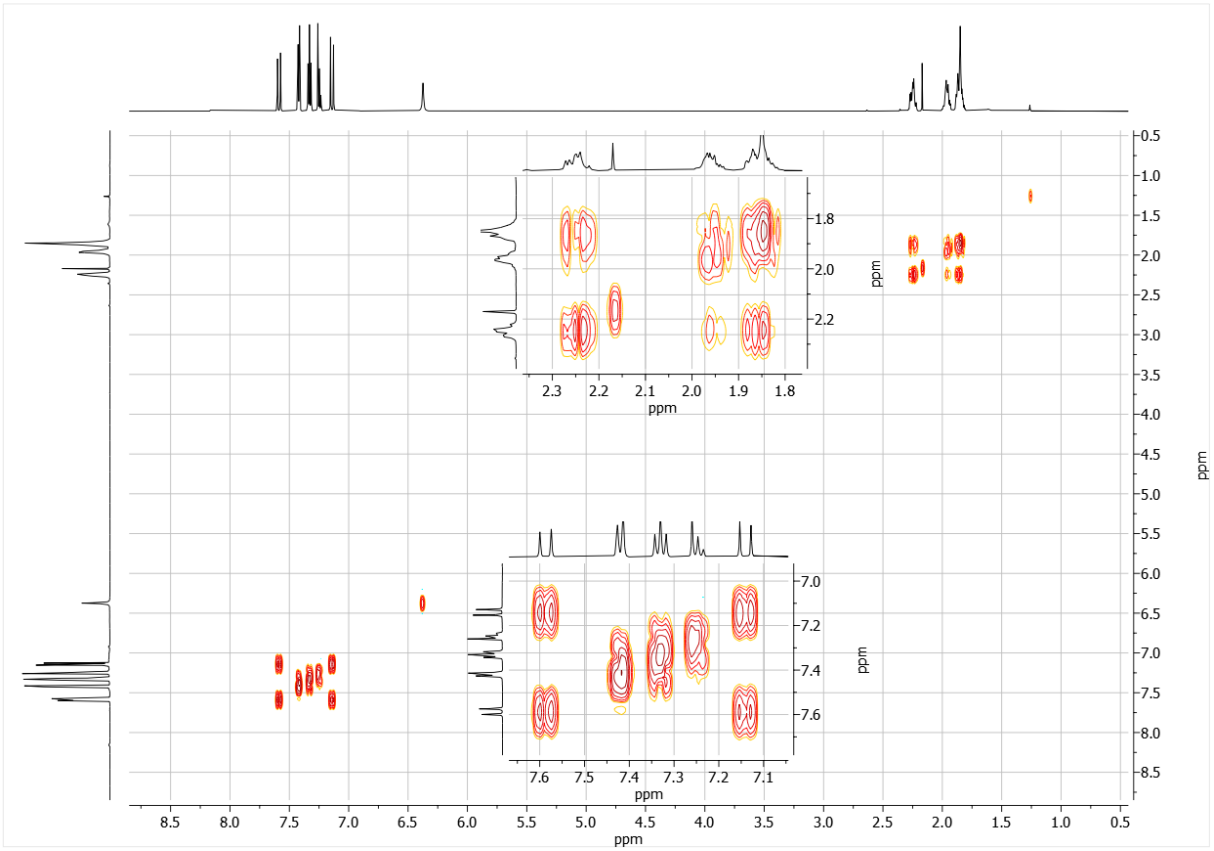
(E)-3-styryl-1,3-diazaspiro[4.4]nonane-2,4-dione (6b) [New]



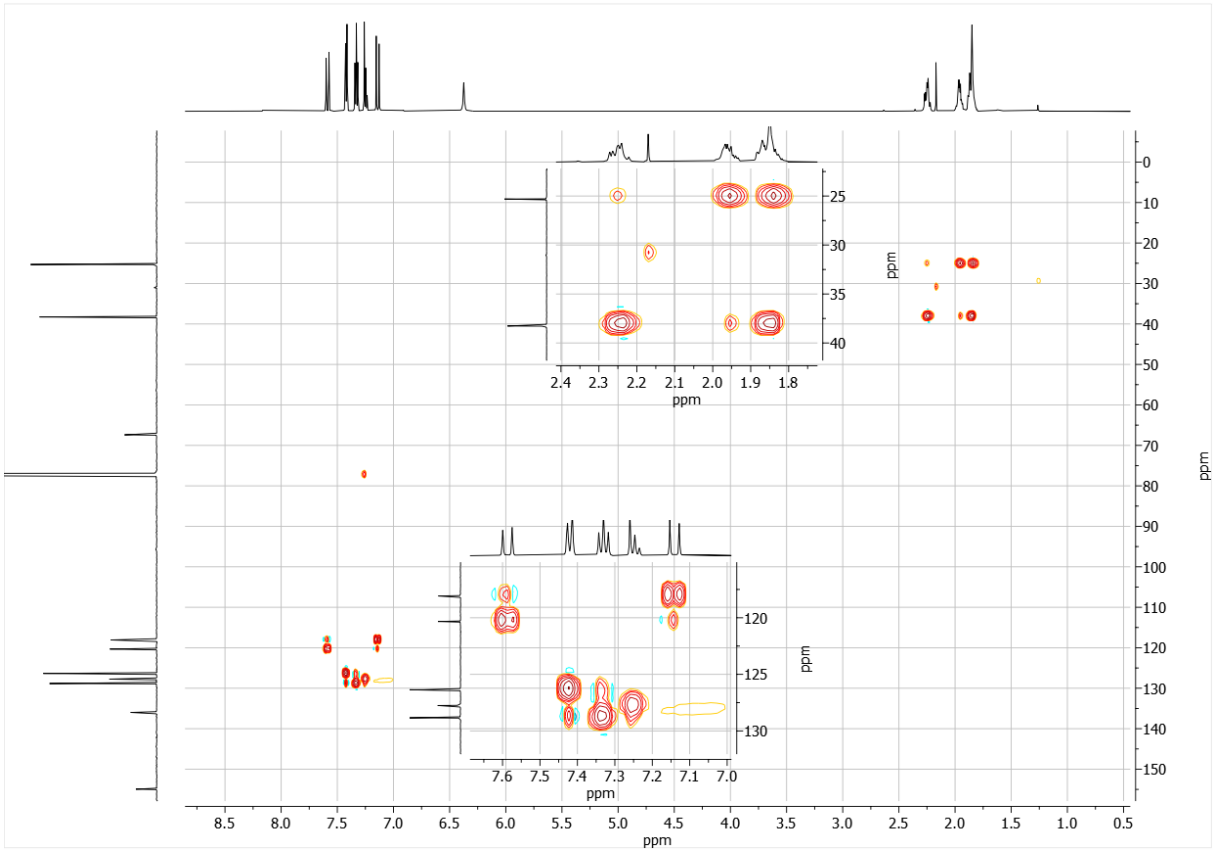
DEPT135 (151 MHz, $CDCl_3$) spectrum of 6b.



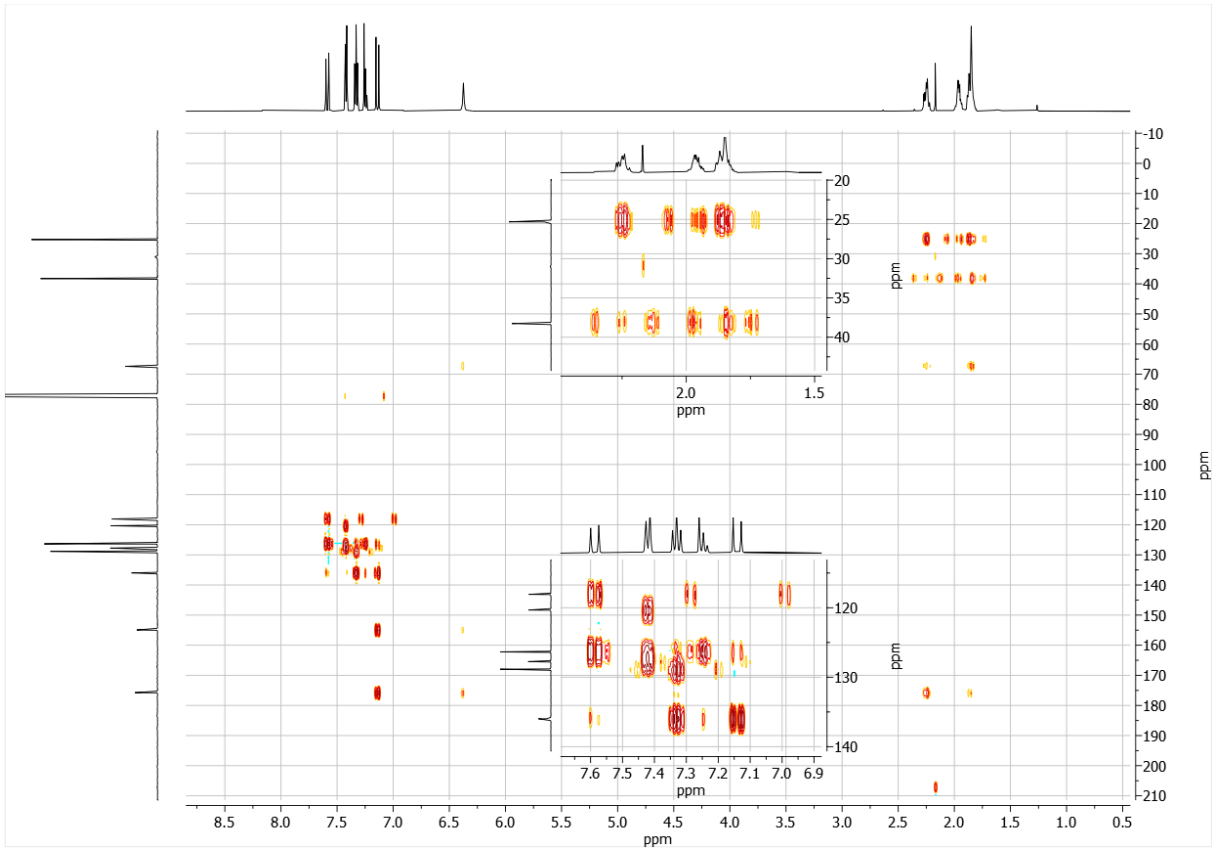
COSY (600 MHz, $CDCl_3$) spectrum of 6b.



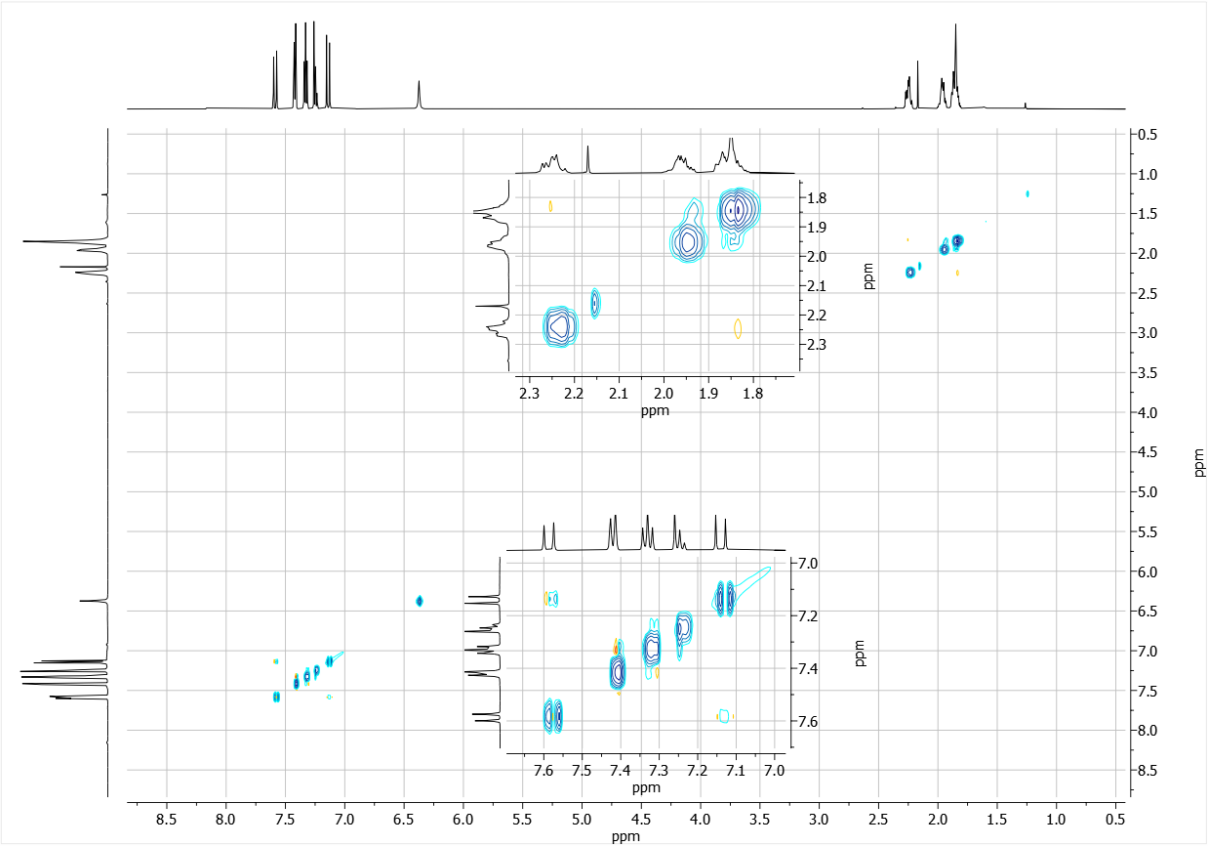
HSQC (600 MHz, $CDCl_3$) spectrum of 6b.



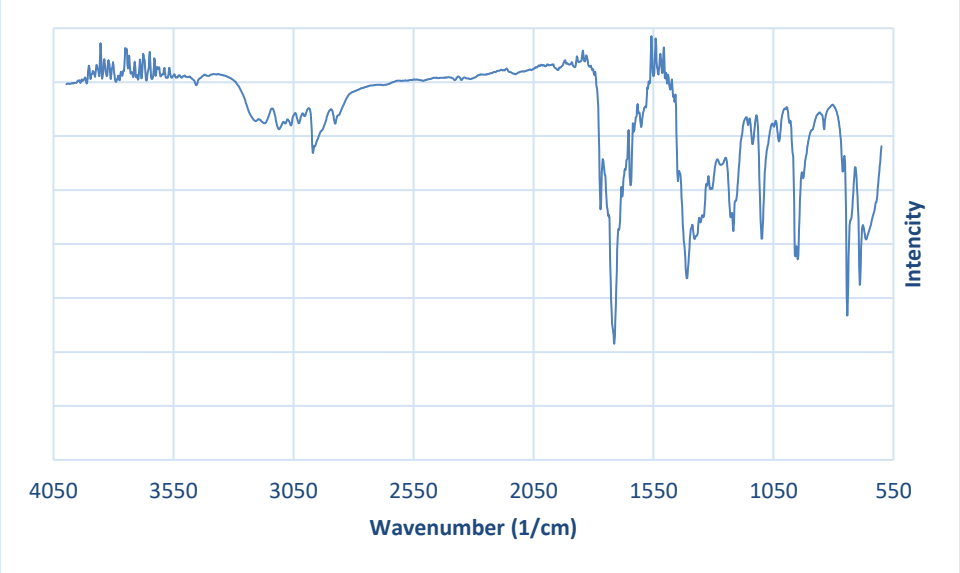
HMBC (600 MHz, $CDCl_3$) spectrum of 6b.



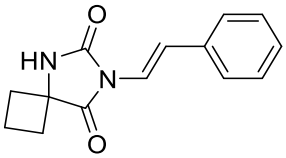
NOESY (600 MHz, $CDCl_3$) spectrum of 6b.



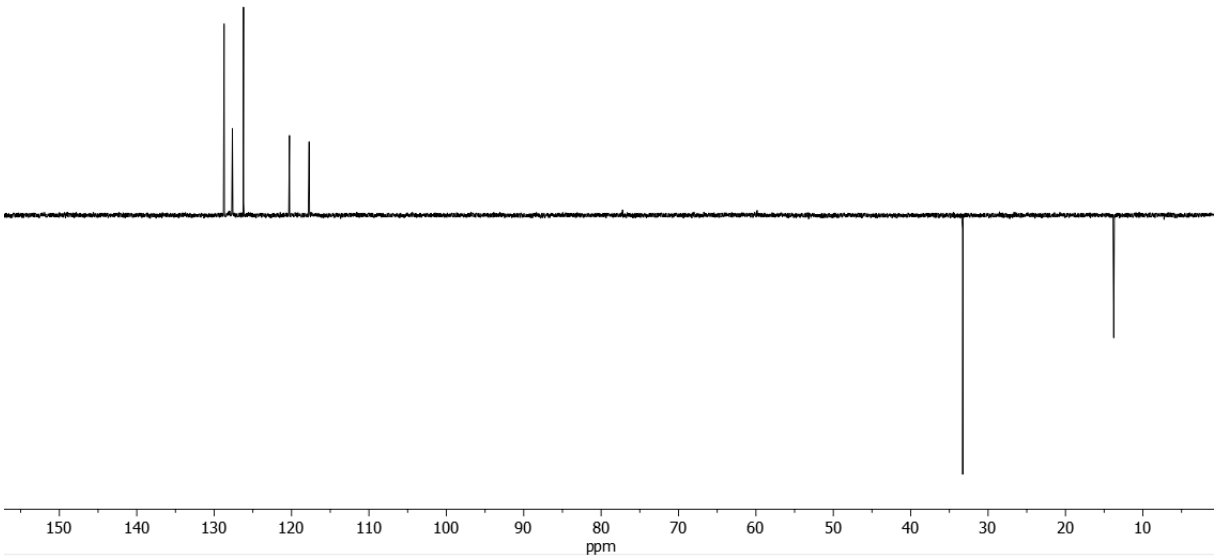
IR spectrum of 6b.



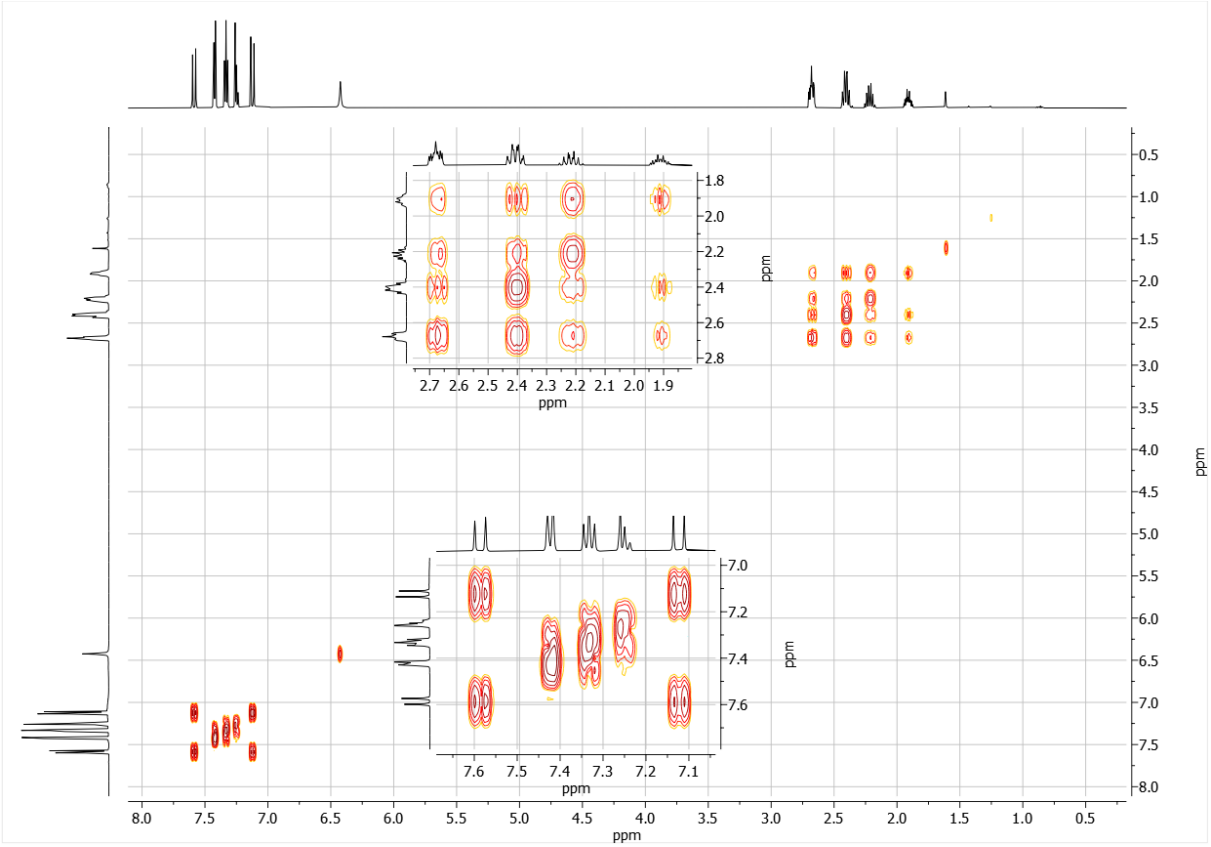
(E)-7-styryl-5,7-diazaspiro[3.4]octane-6,8-dione (6c)[New]



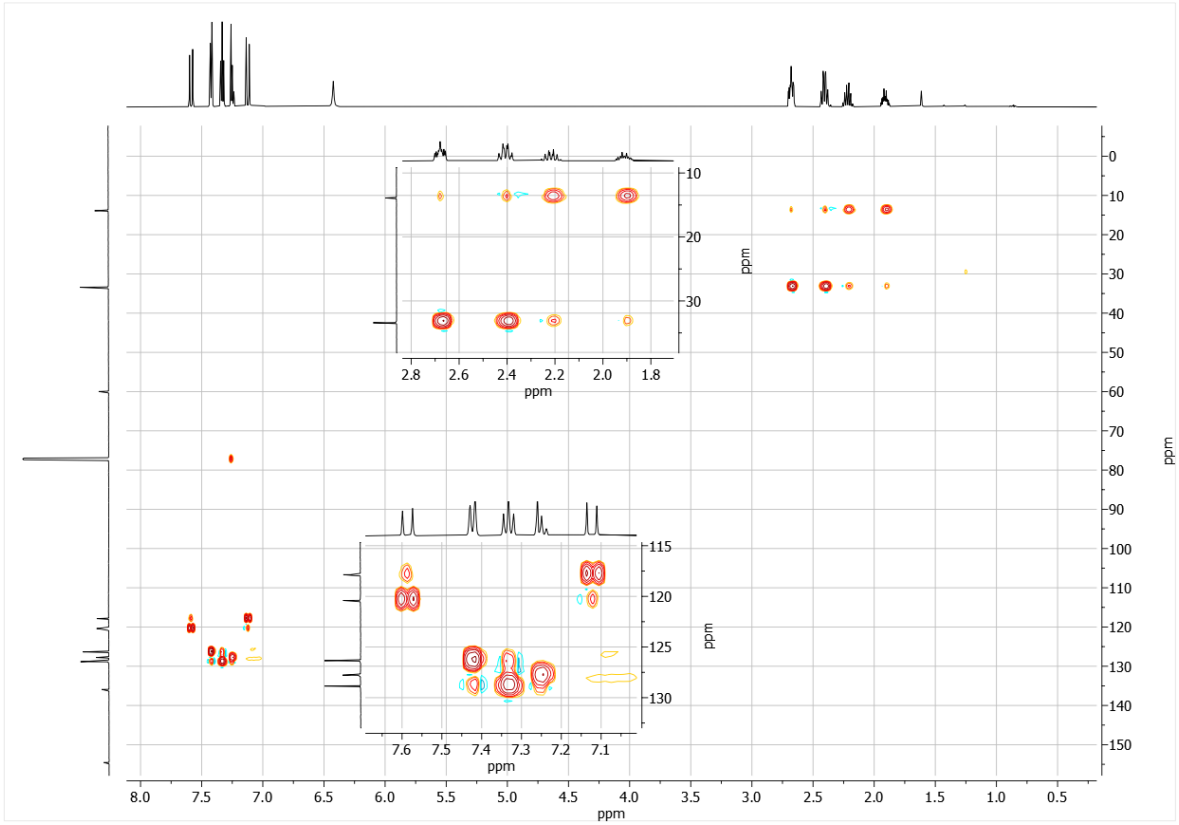
DEPT135 (151 MHz, $CDCl_3$) spectrum of 6c.



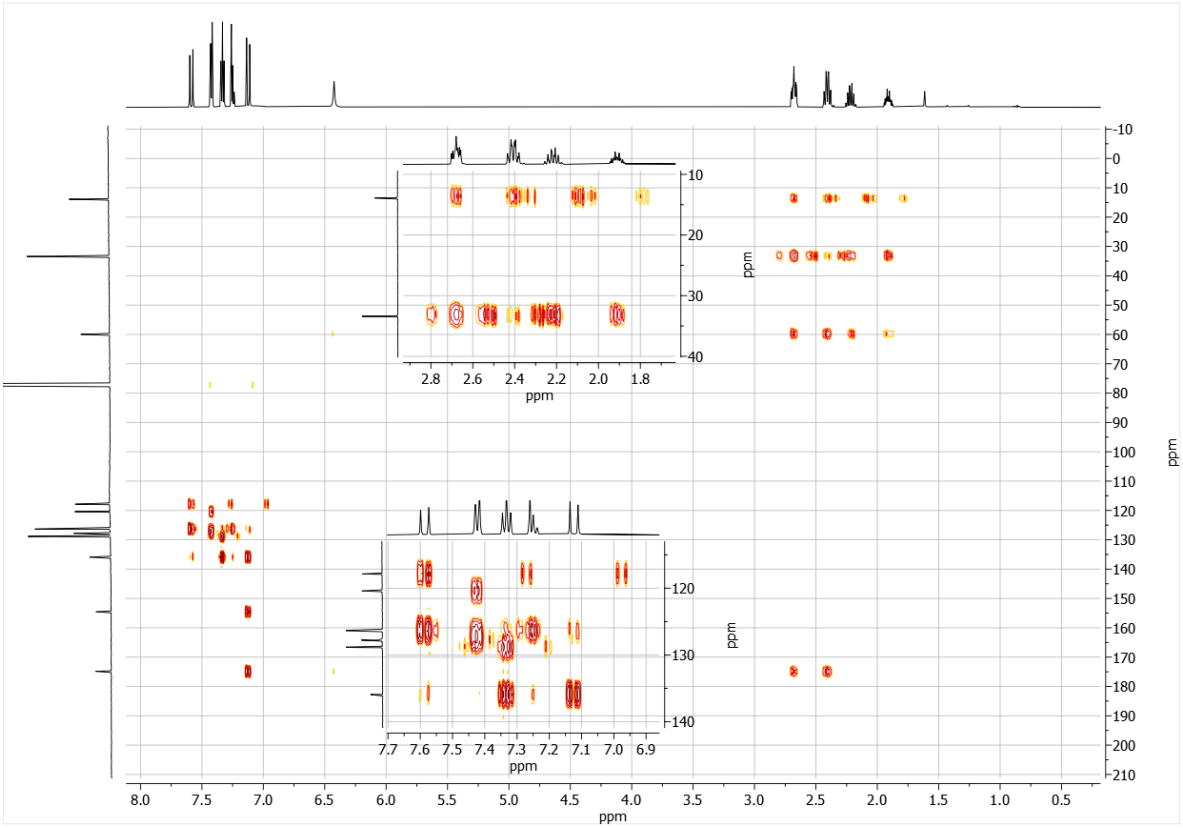
COSY (600 MHz, $CDCl_3$) spectrum of 6c.



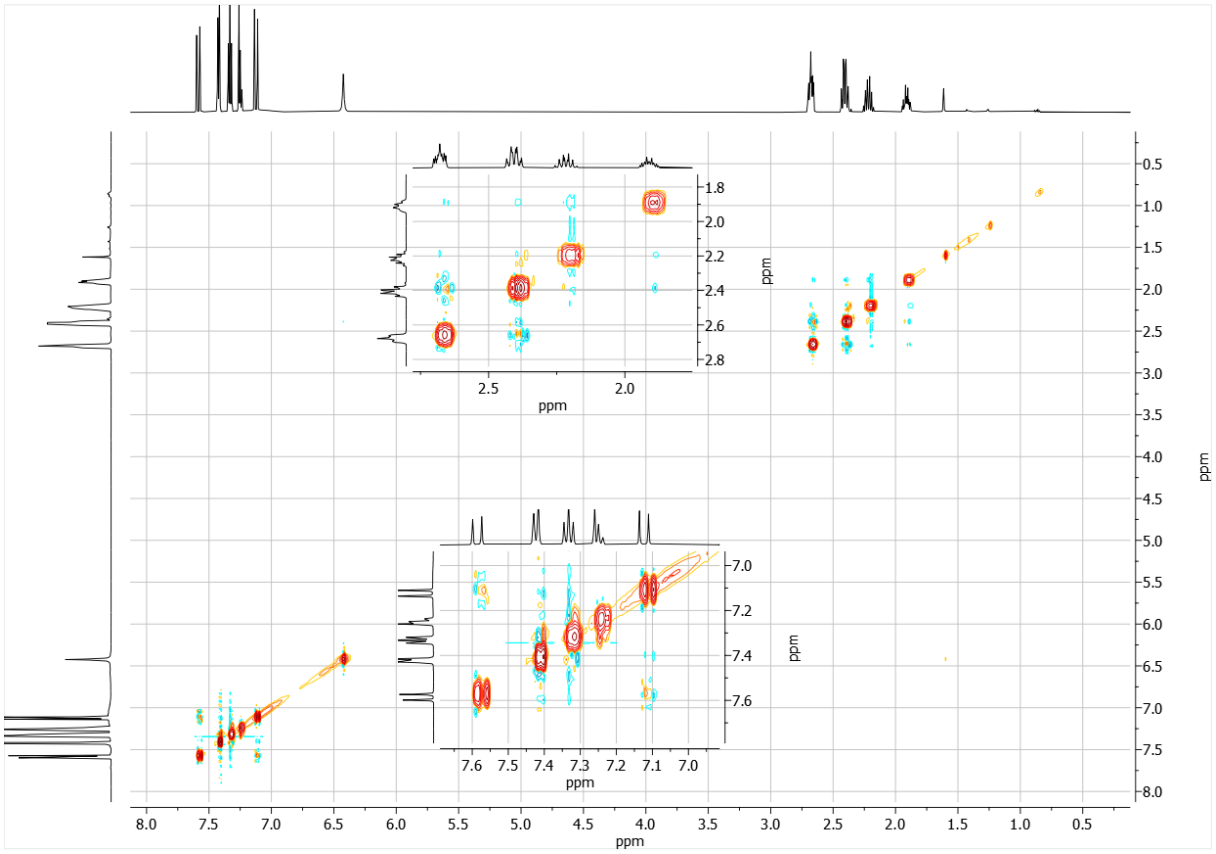
HSQC (600 MHz, $CDCl_3$) spectrum of 6c.



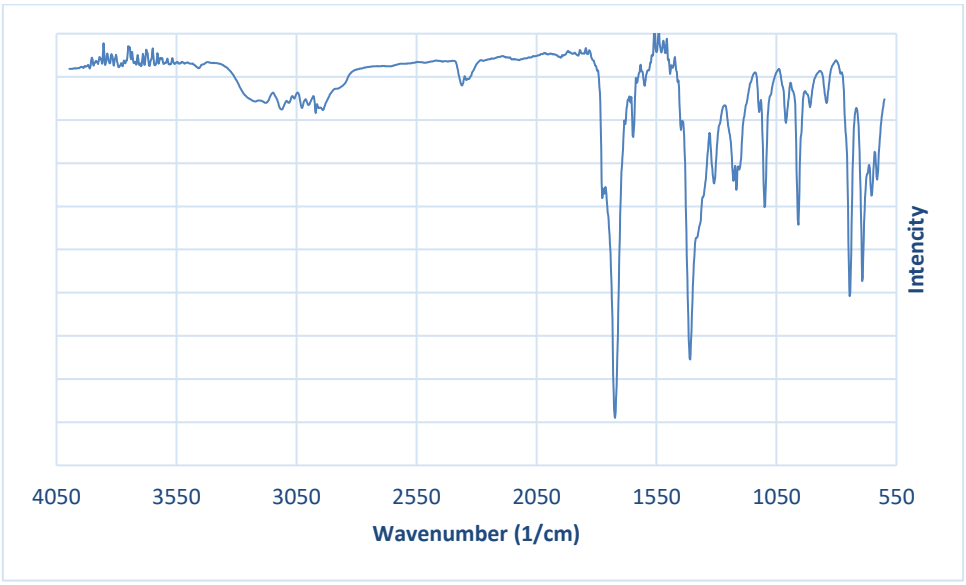
HMBC (600 MHz, $CDCl_3$) spectrum of 6c.



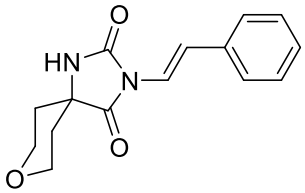
NOESY (600 MHz, $CDCl_3$) spectrum of 6c.



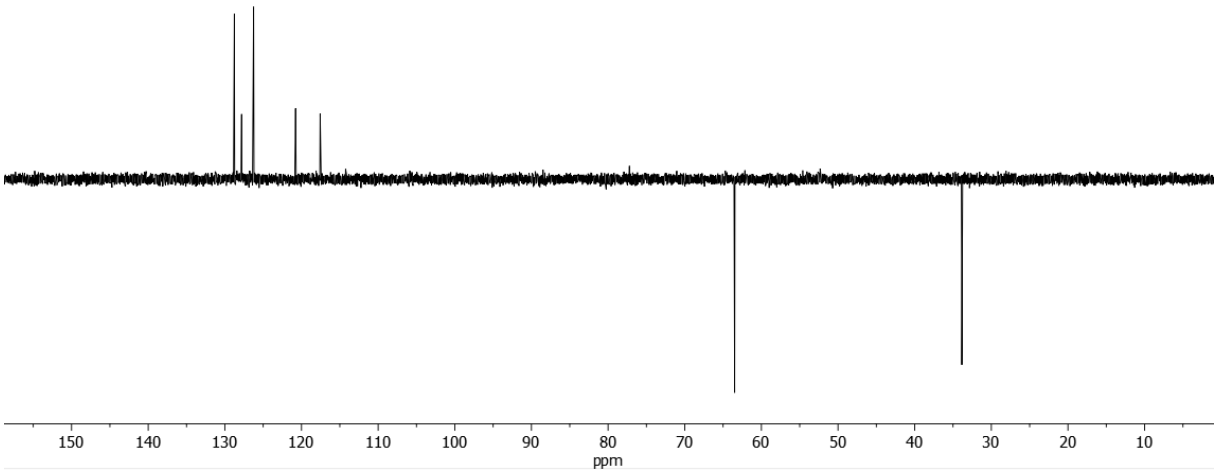
IR spectrum of 6c.



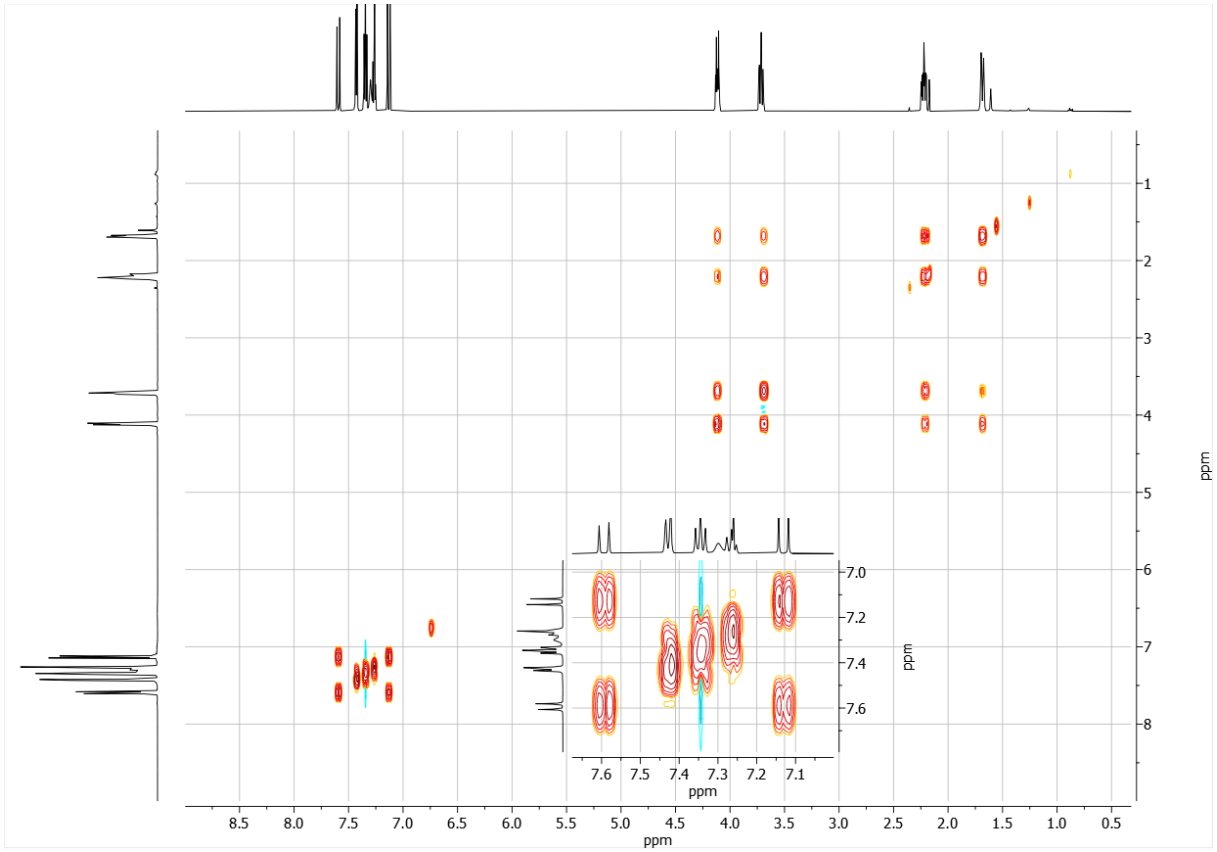
(E)-3-styryl-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione (6d) [New]



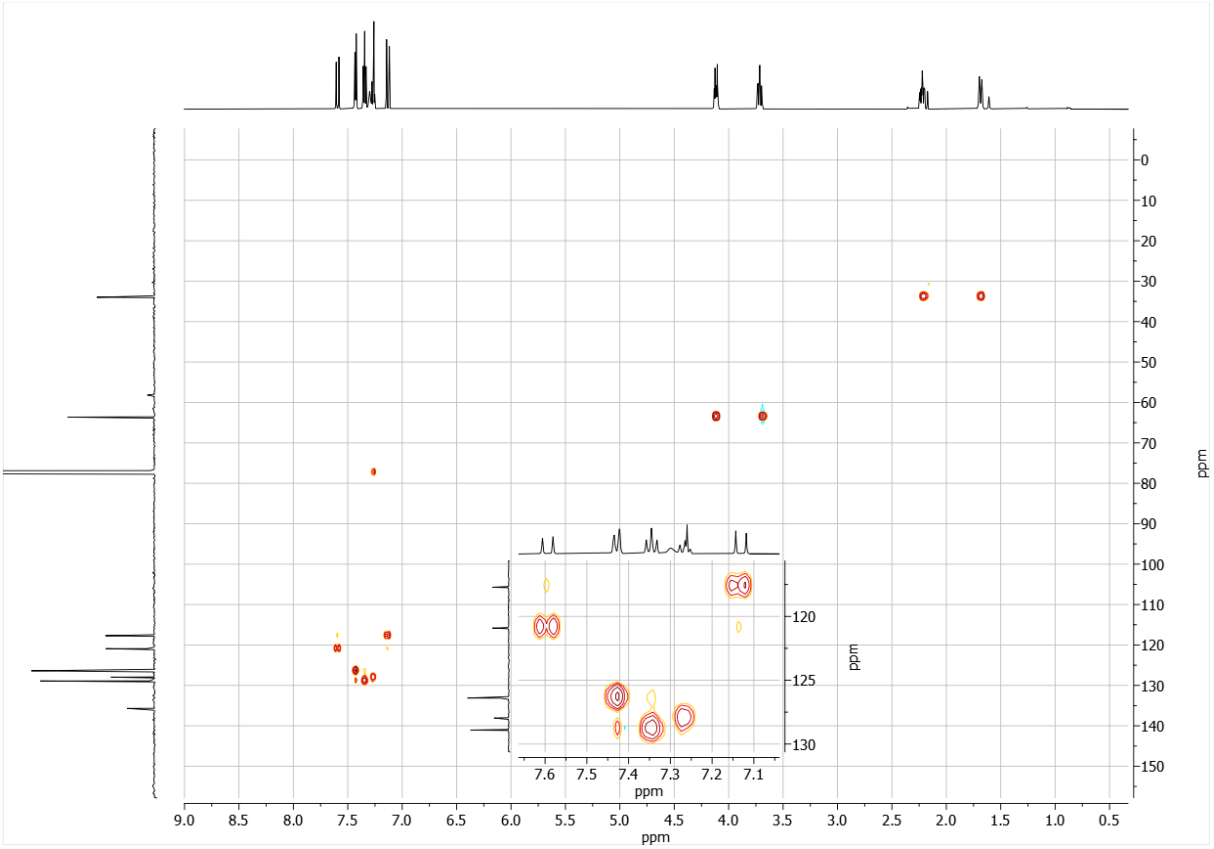
DEPT135 (151 MHz, $CDCl_3$) spectrum of 6d.



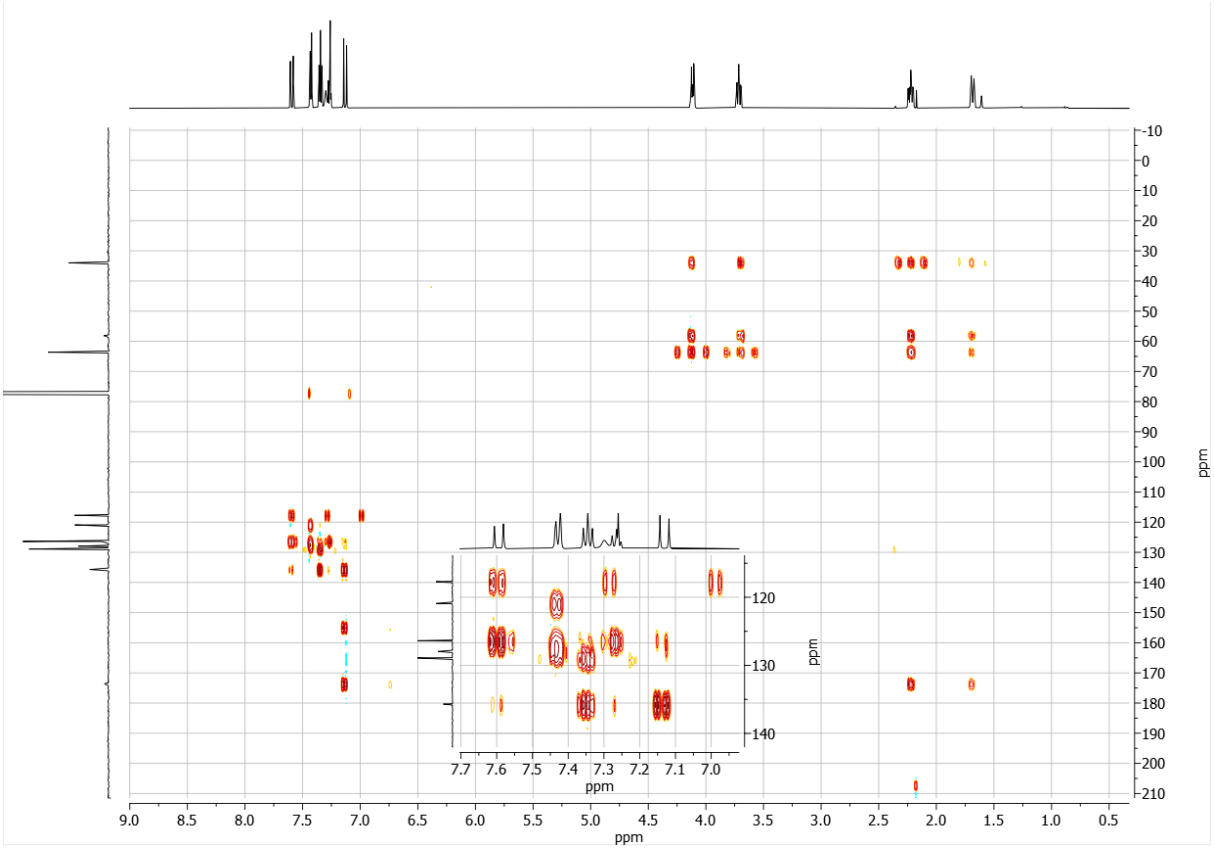
COSY (600 MHz, $CDCl_3$) spectrum of 6d.



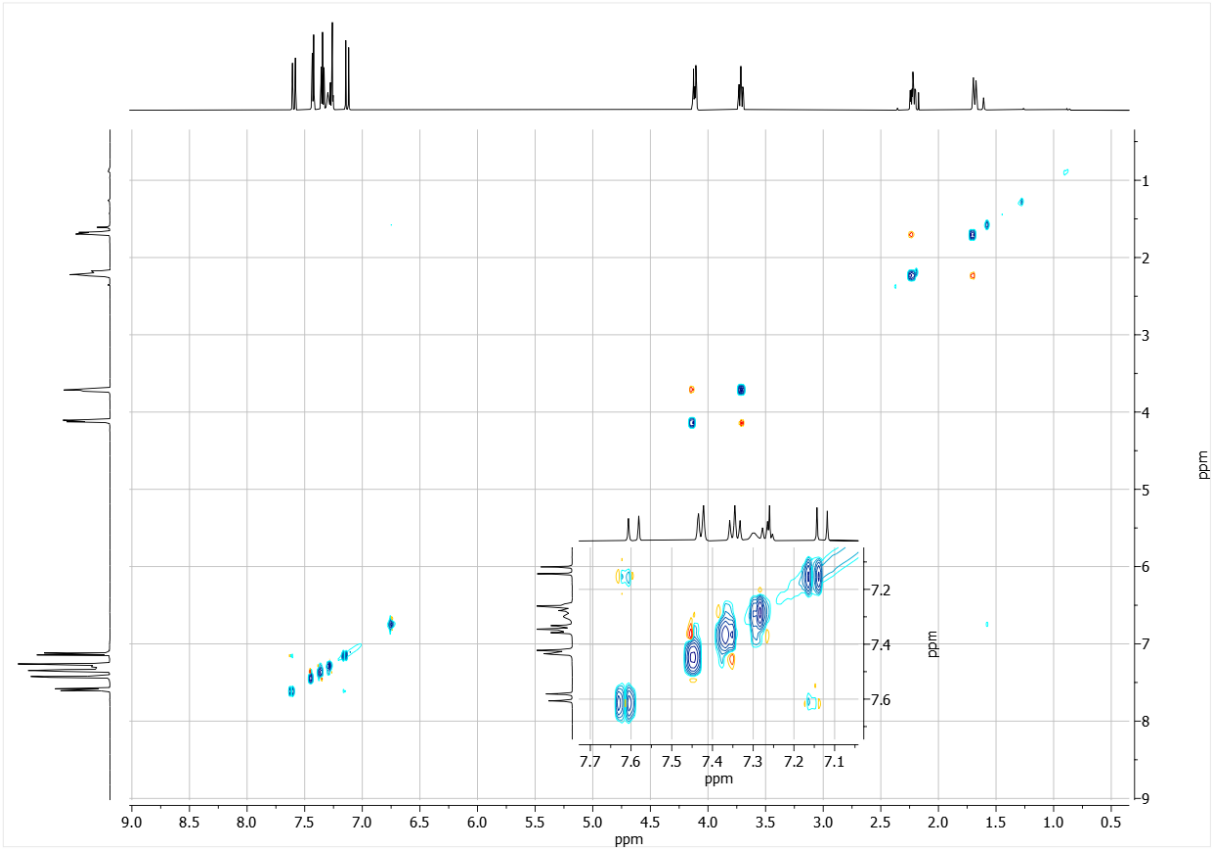
HSQC (600 MHz, $CDCl_3$) spectrum of 6d.



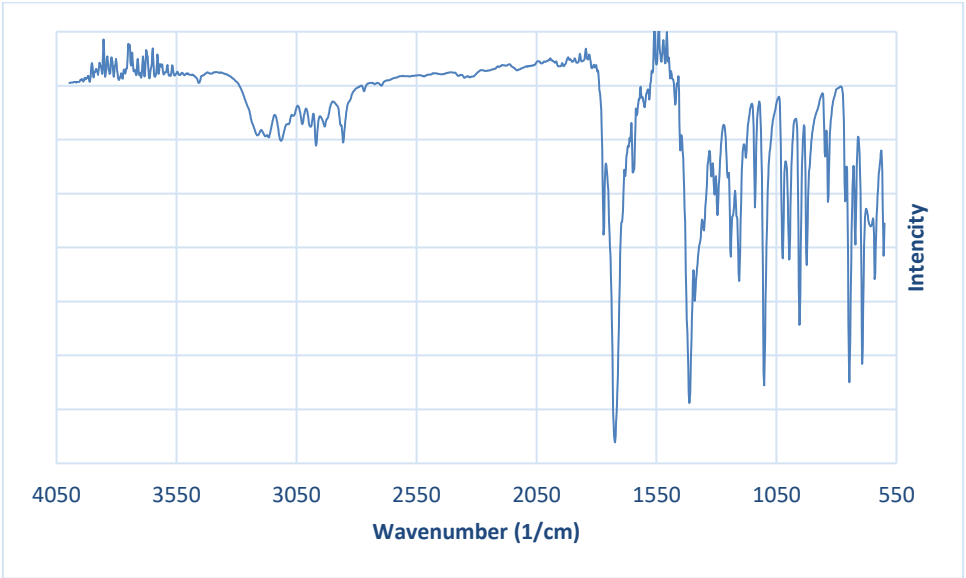
HMBC (600 MHz, $CDCl_3$) spectrum of 6d.



NOESY (600 MHz, $CDCl_3$) spectrum of 6d.

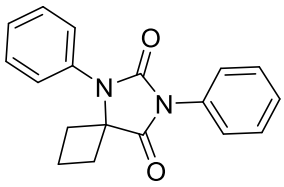


IR spectrum of 6d.

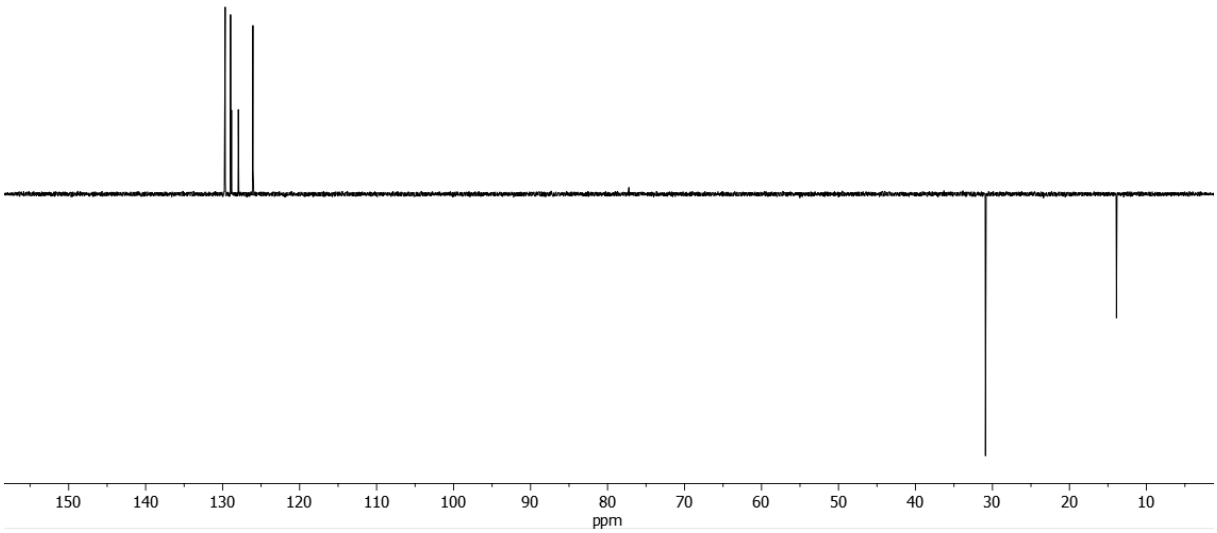


7.4 *N*-1-Arylated spirohydantoins

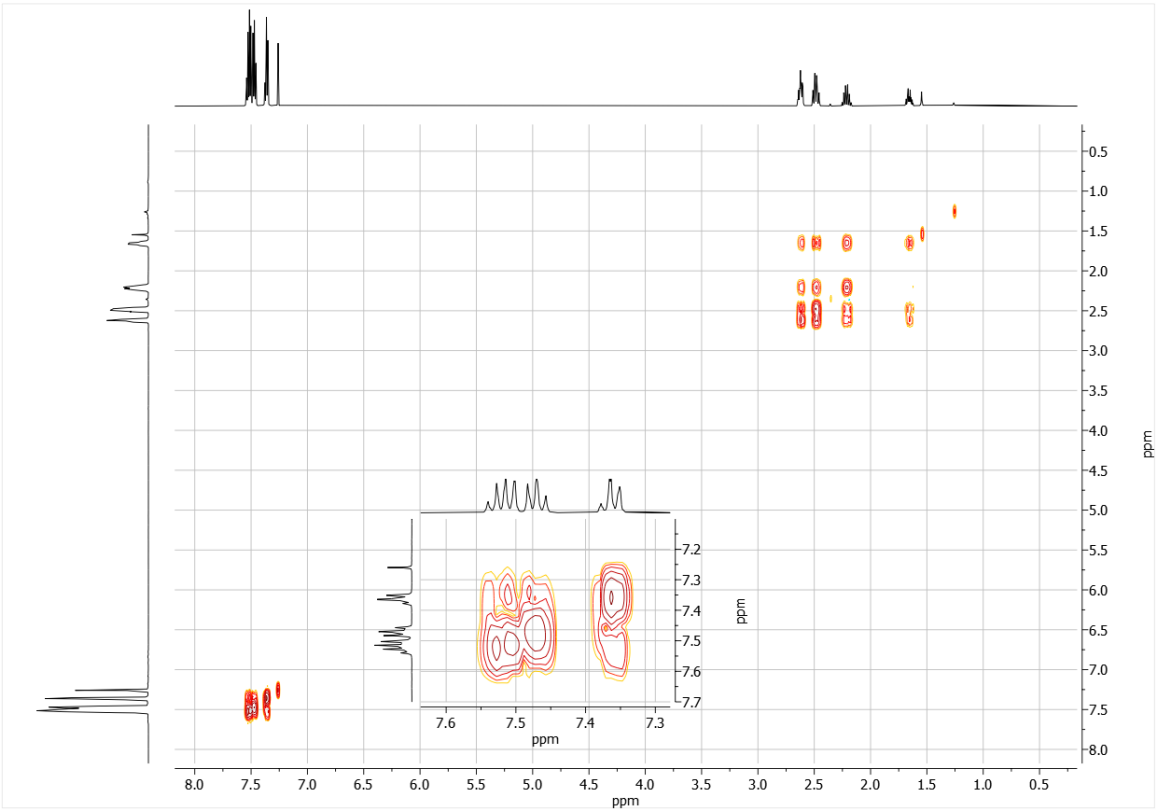
5,7-diphenyl-5,7-diazaspiro[3.4]octane-6,8-dione (8) [New]



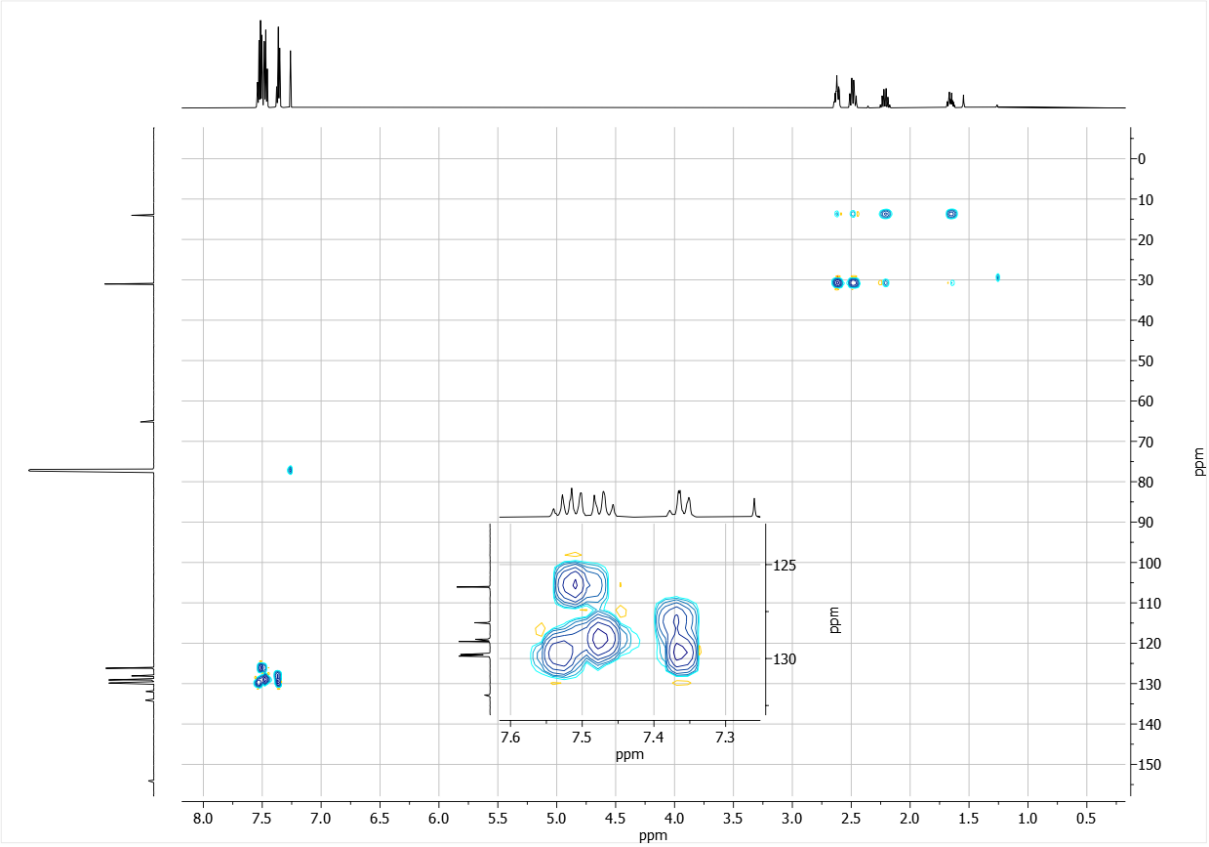
DEPT135 (151 MHz, $CDCl_3$) spectrum of 8.



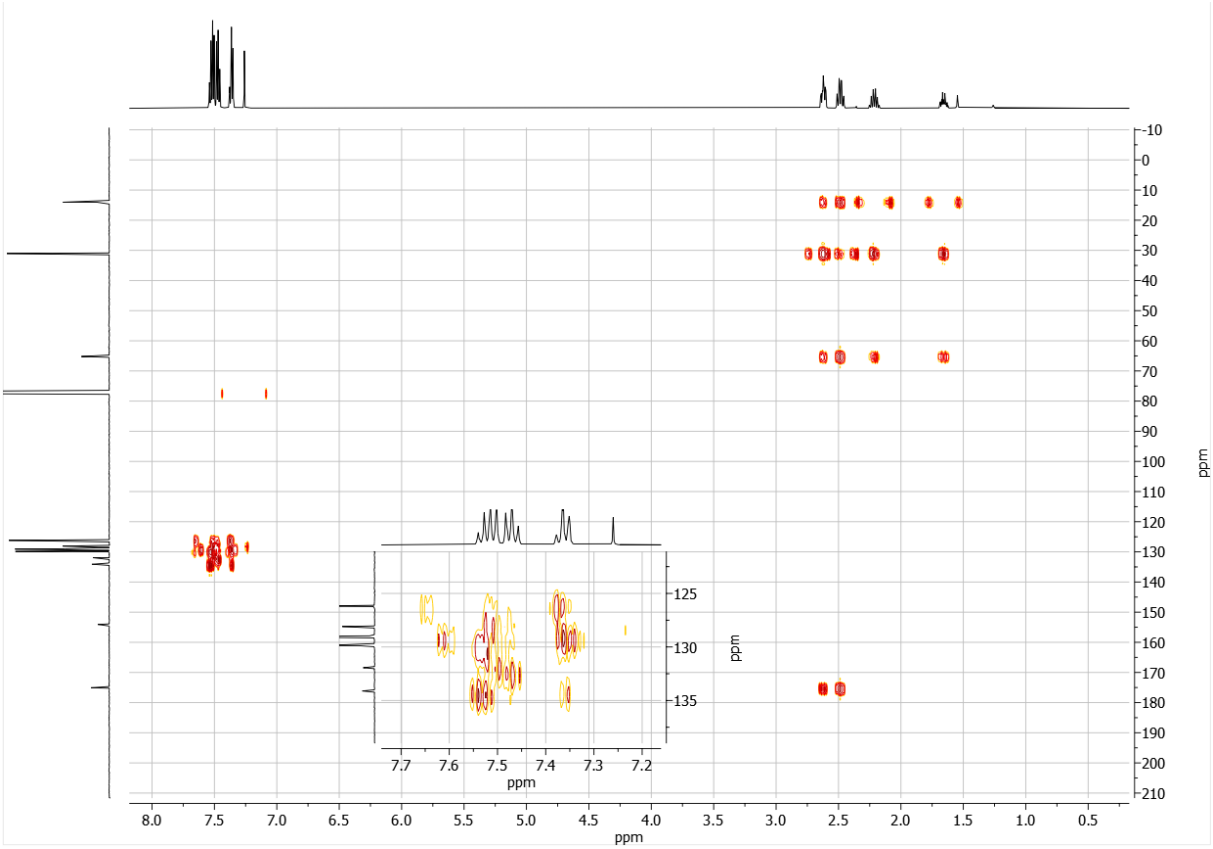
COSY (600 MHz, $CDCl_3$) spectrum of 8.



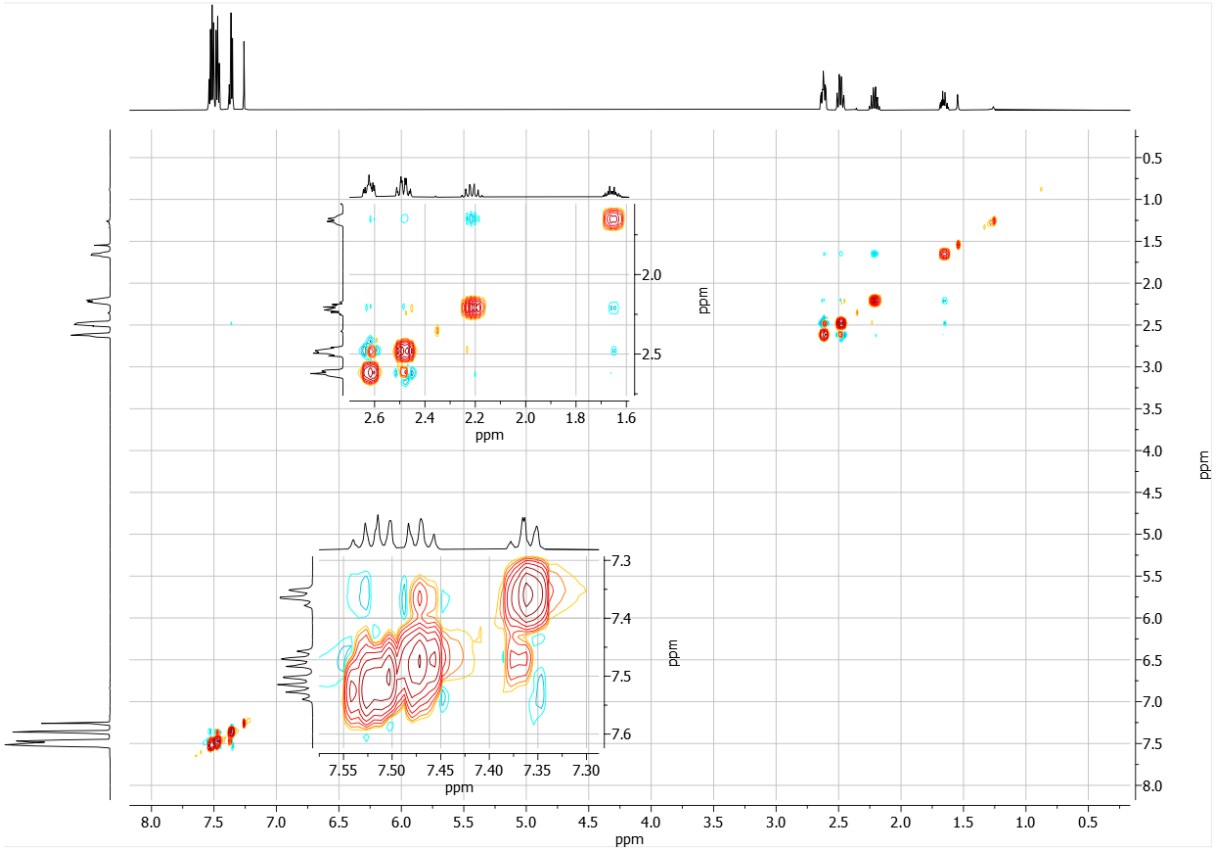
HSQC (600 MHz, $CDCl_3$) spectrum of 8.



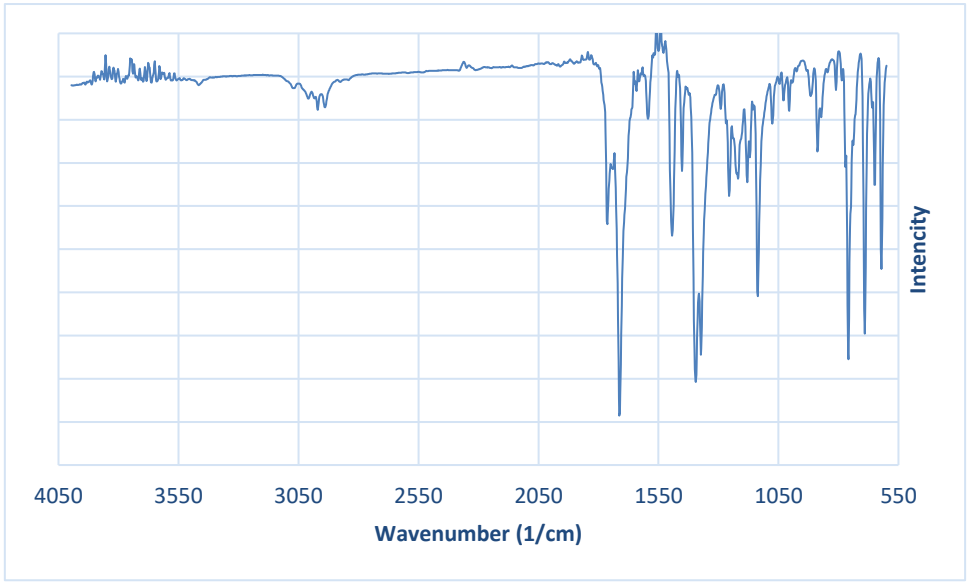
HMBC (600 MHz, $CDCl_3$) spectrum of 8.



NOESY (600 MHz, $CDCl_3$) spectrum of 8.

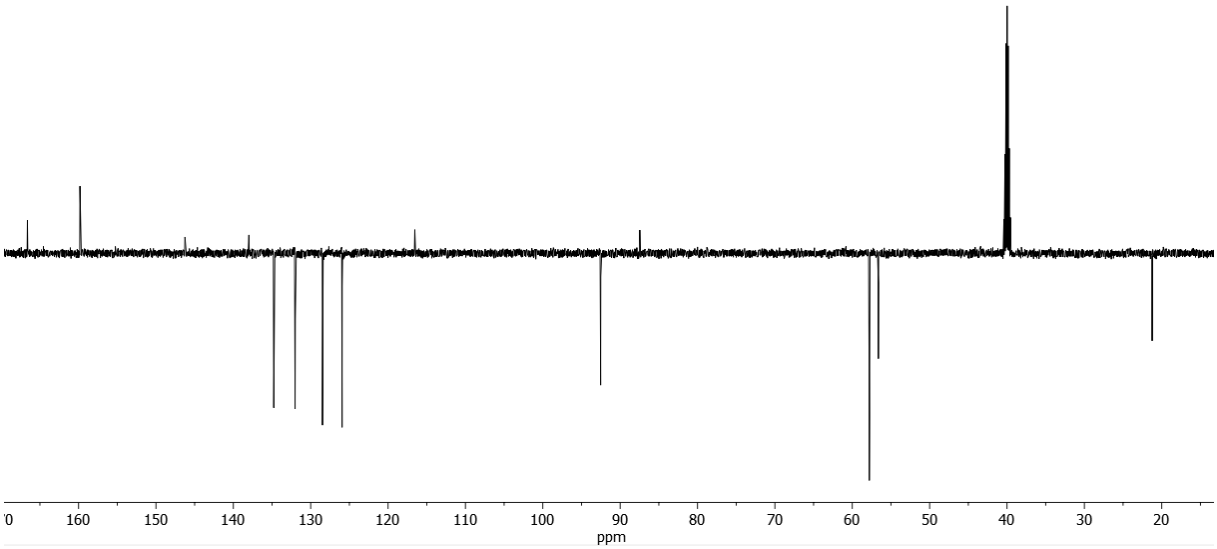


IR spectrum of 8.

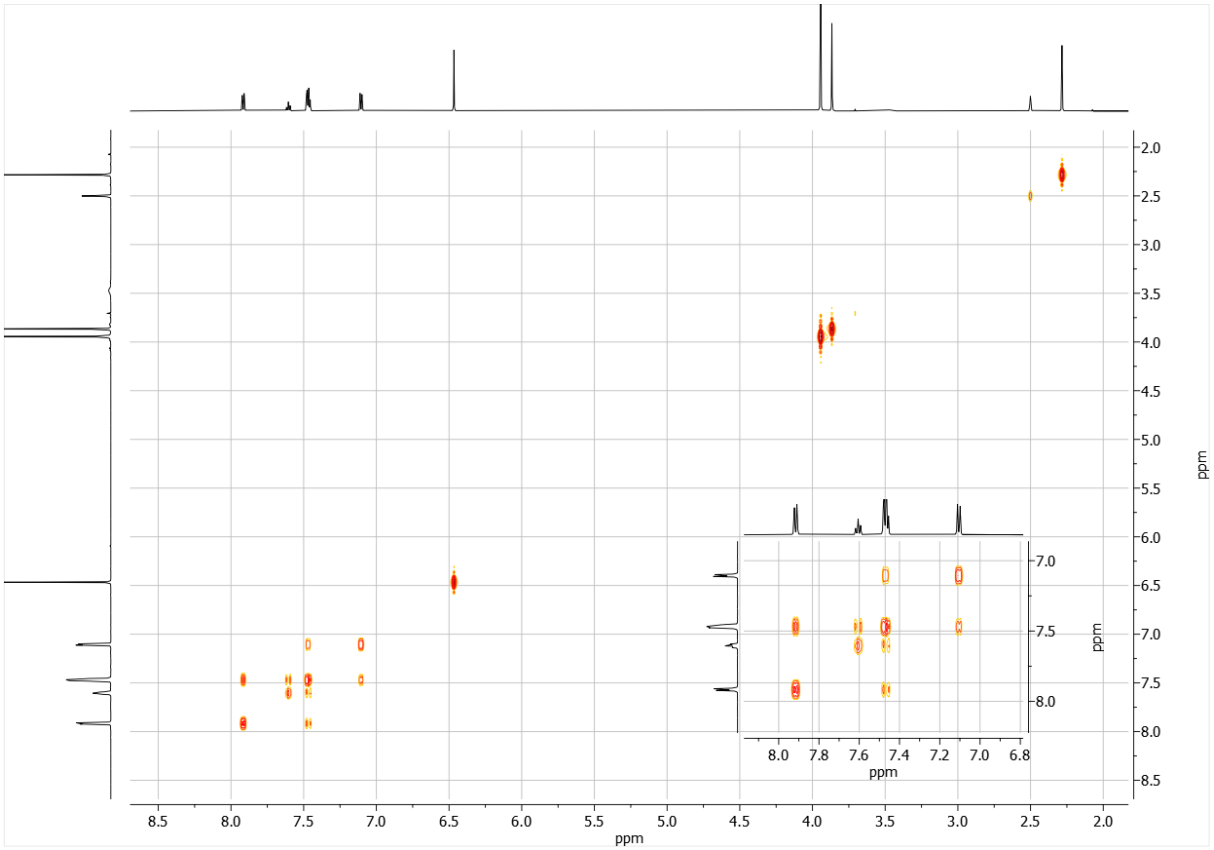


7.5 Diaryliodonium salt

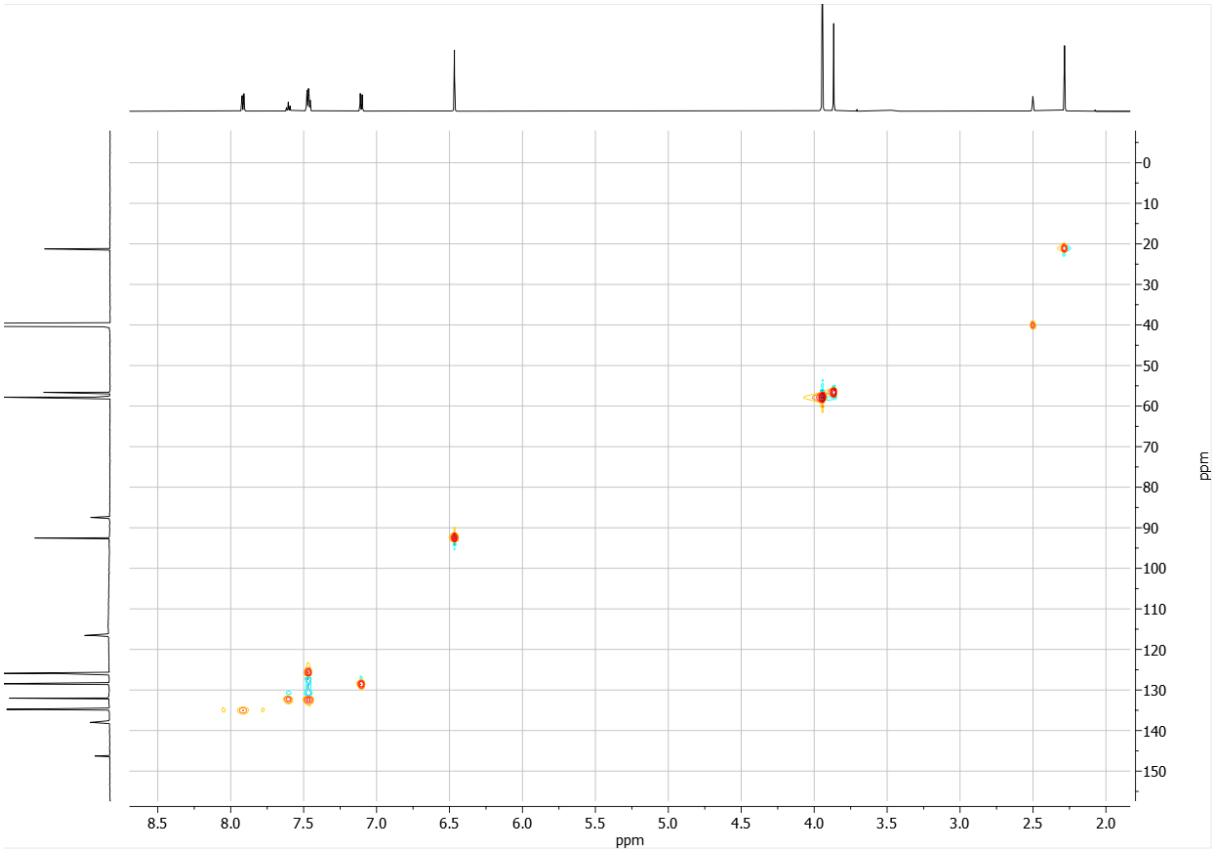
DEPT135 (151 MHz, DMSO-d_6) spectrum of 4a.



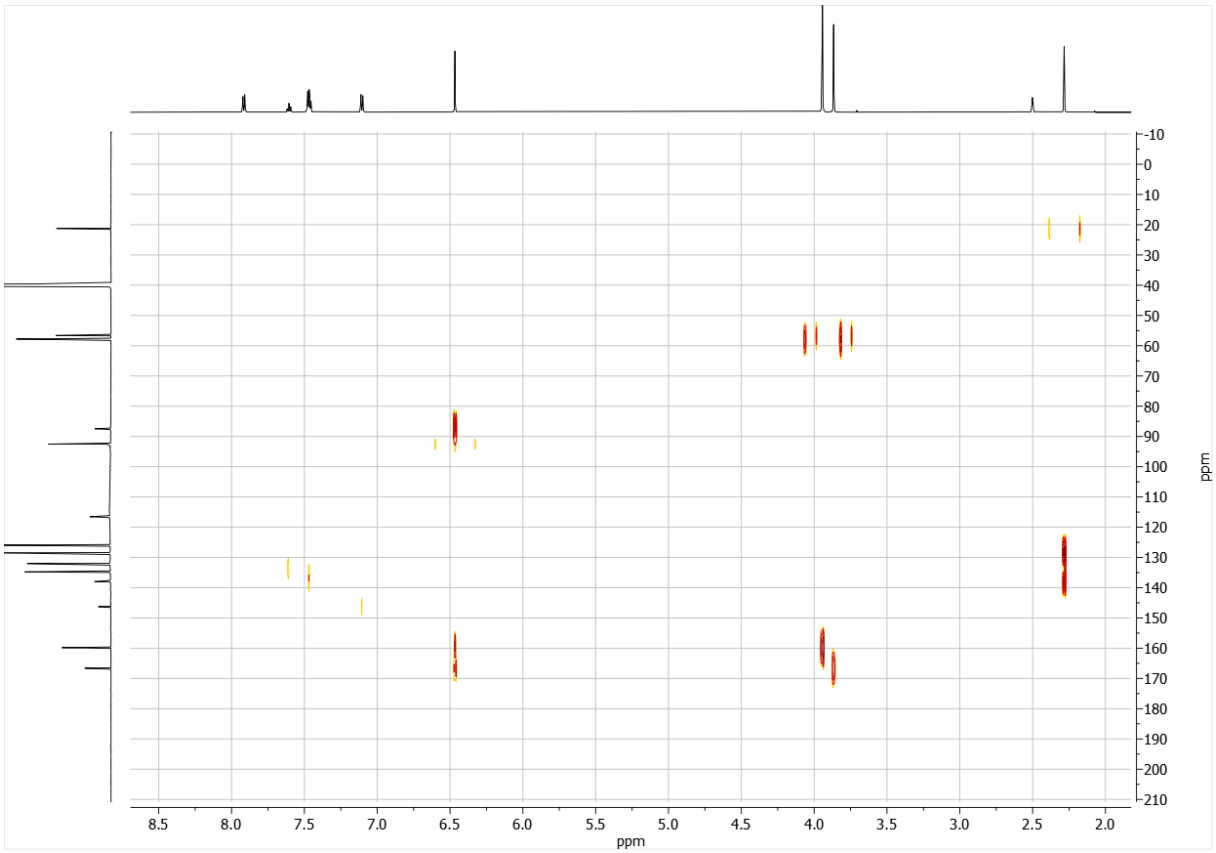
COSY (600 MHz, DMSO-d_6) spectrum of 4a.



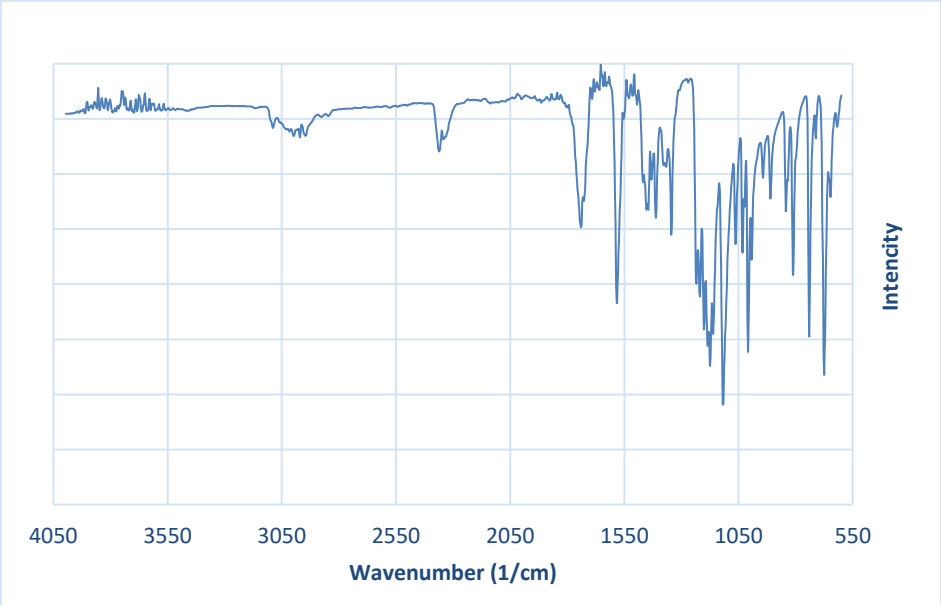
HSQC (600 MHz, DMSO-d_6) spectrum of 4a.



HMBC (600 MHz, DMSO-d_6) spectrum of 4a.



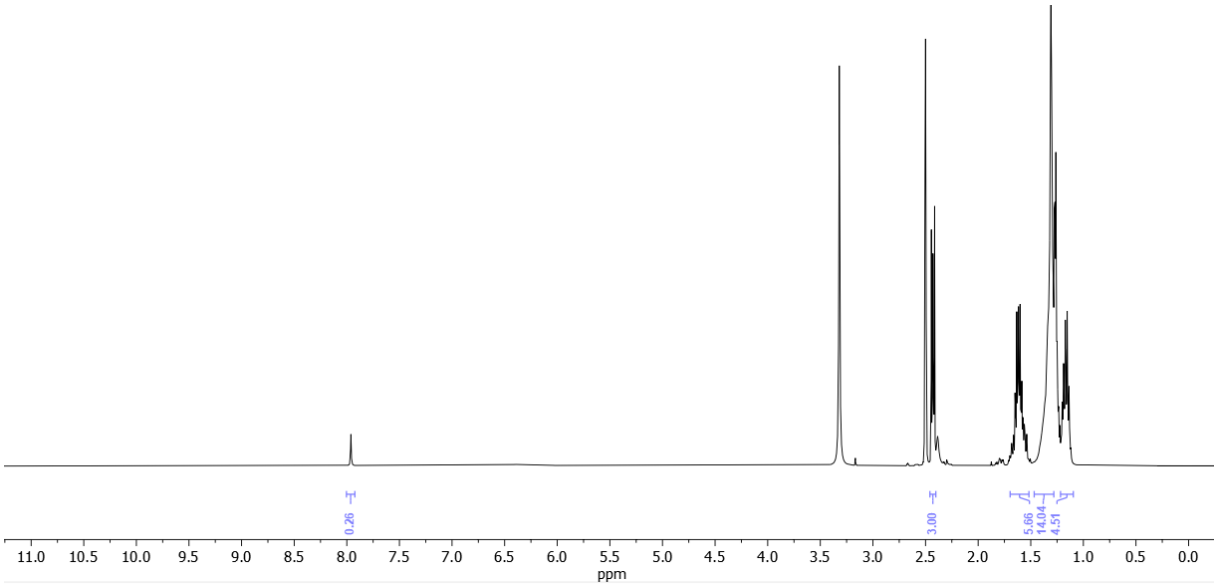
IR spectrum of 4a.



7.6 Attempted products

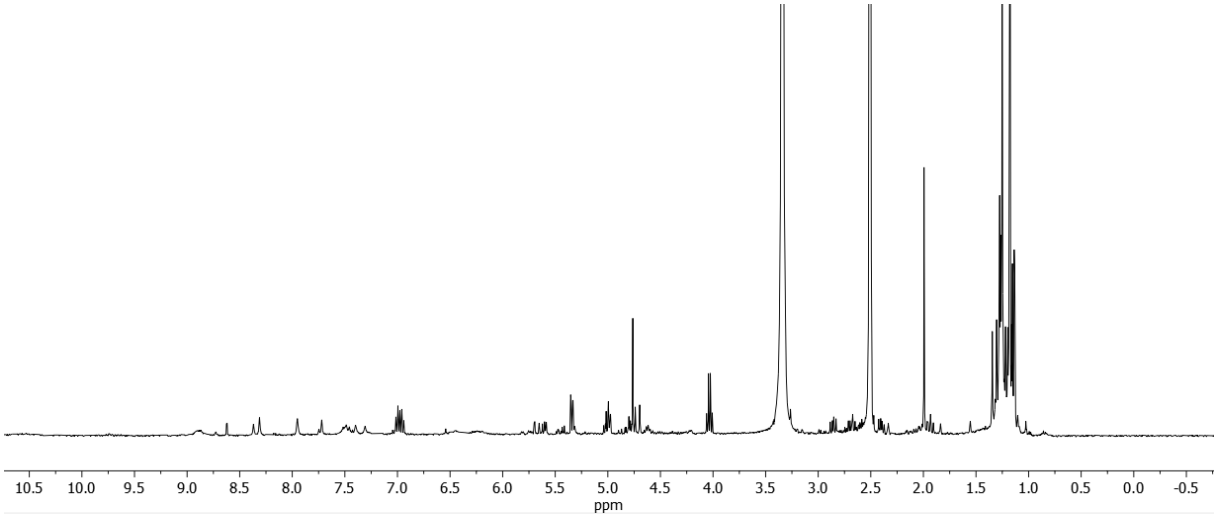
Attempted 2e.

^{1}H NMR (400 MHz, DMSO-d$_6$).

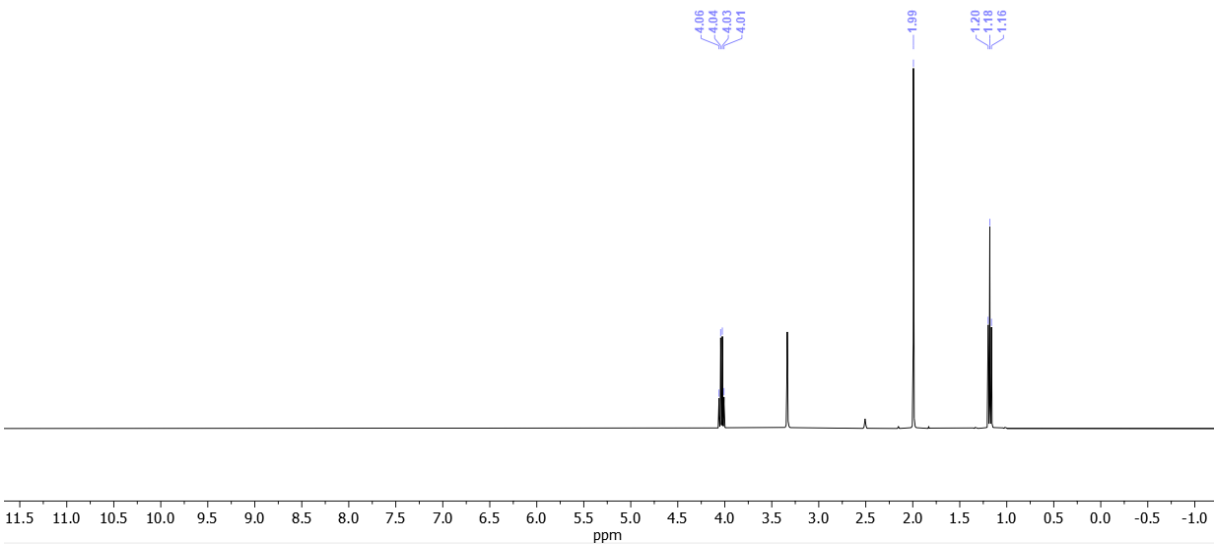


Attempted (2g)

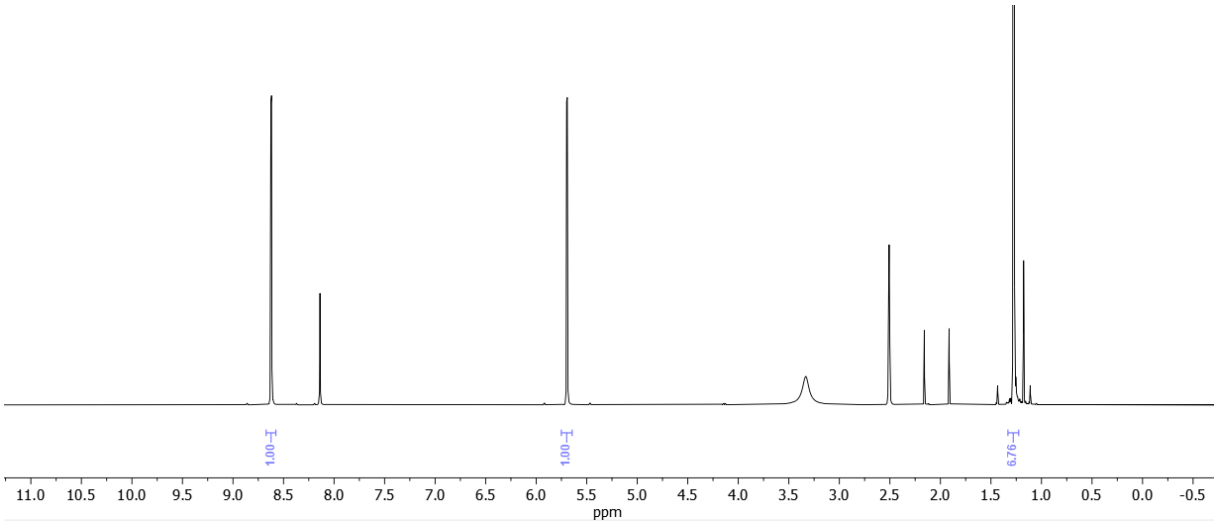
^{1}H NMR (400 MHz, DMSO-d_6) organic phase.



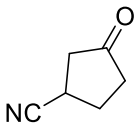
^{1}H NMR (400 MHz, DMSO-d_6) water phase.



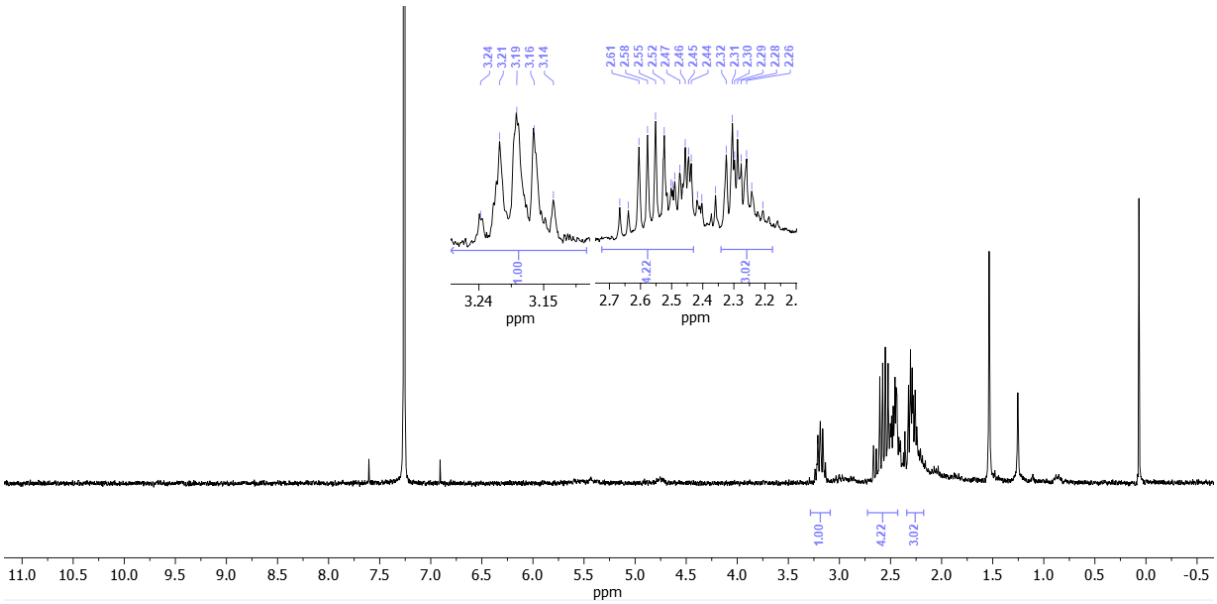
^{1}H NMR (400 MHz, DMSO-d_6) reagent 1g.



3-oxocyclopentane-1-carbonitrile (2h)

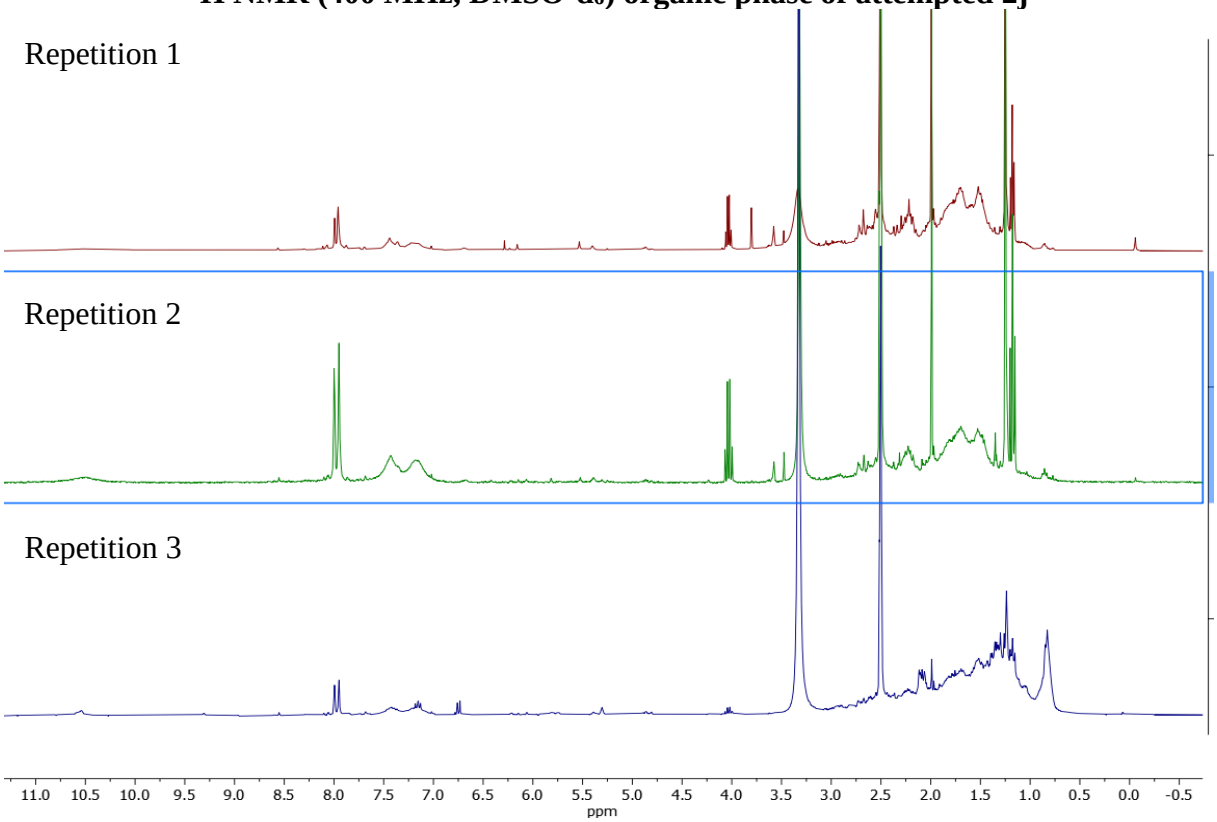


^{1}H NMR (400 MHz, $CDCl_3$) of compound 2h.

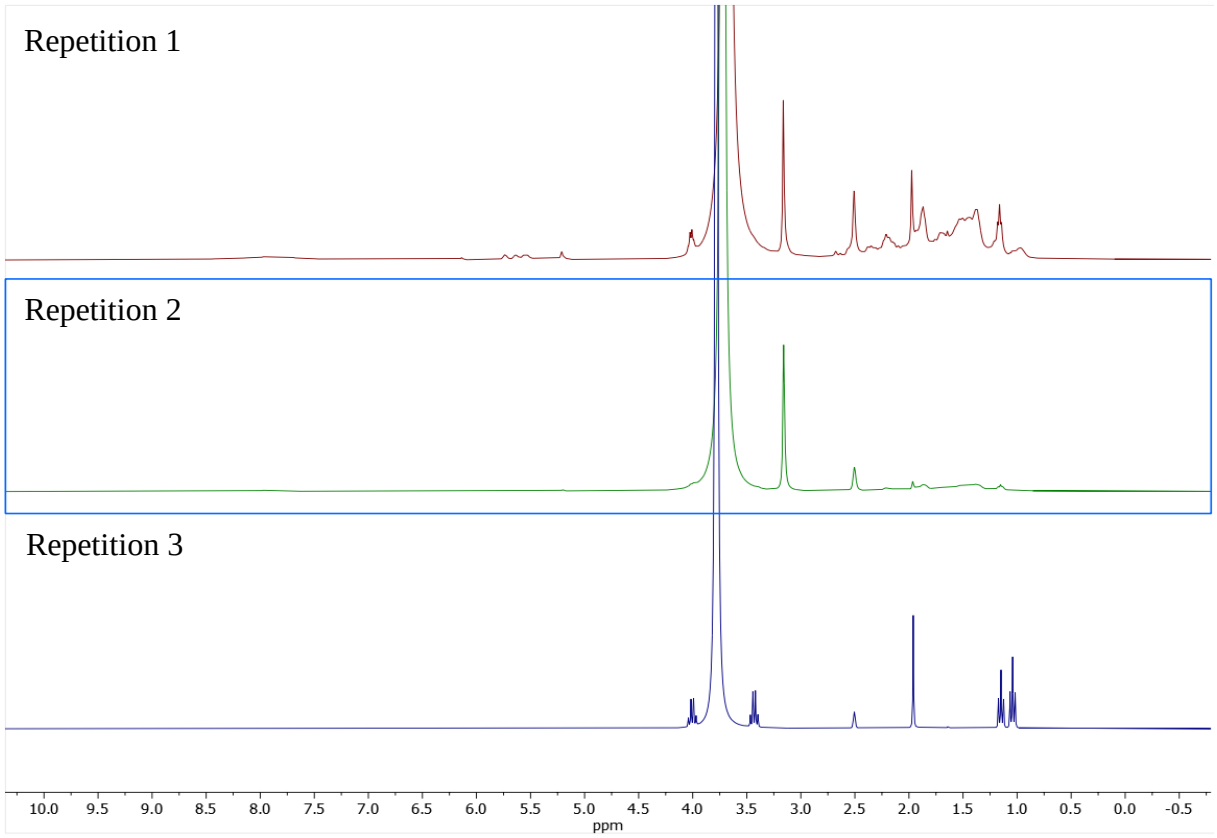


Attempted 2j

^{1}H NMR (400 MHz, DMSO-d_6) organic phase of attempted 2j

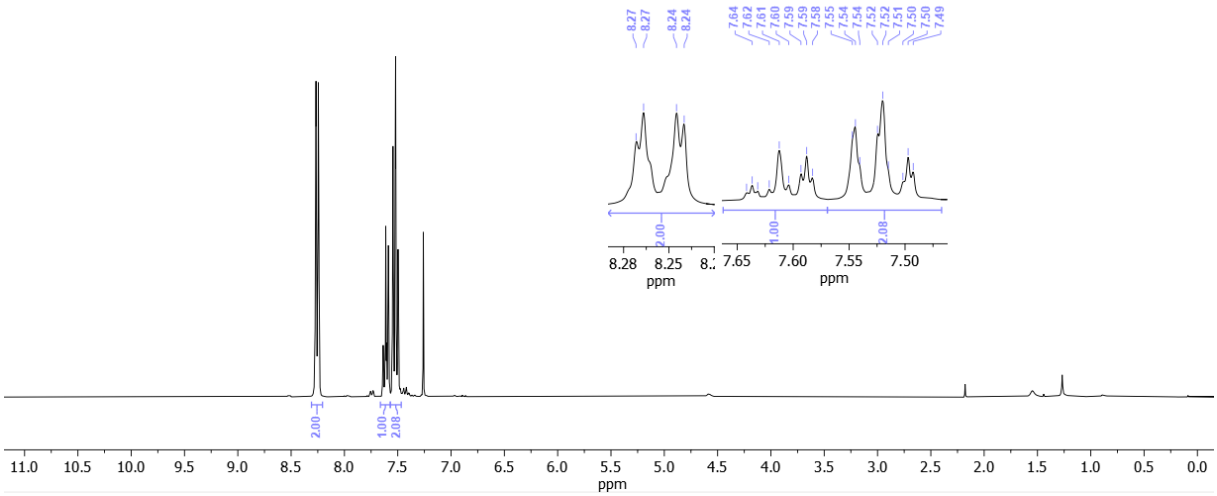


^{1}H NMR (400 MHz, DMSO-d_6) water phase of attempted 2j

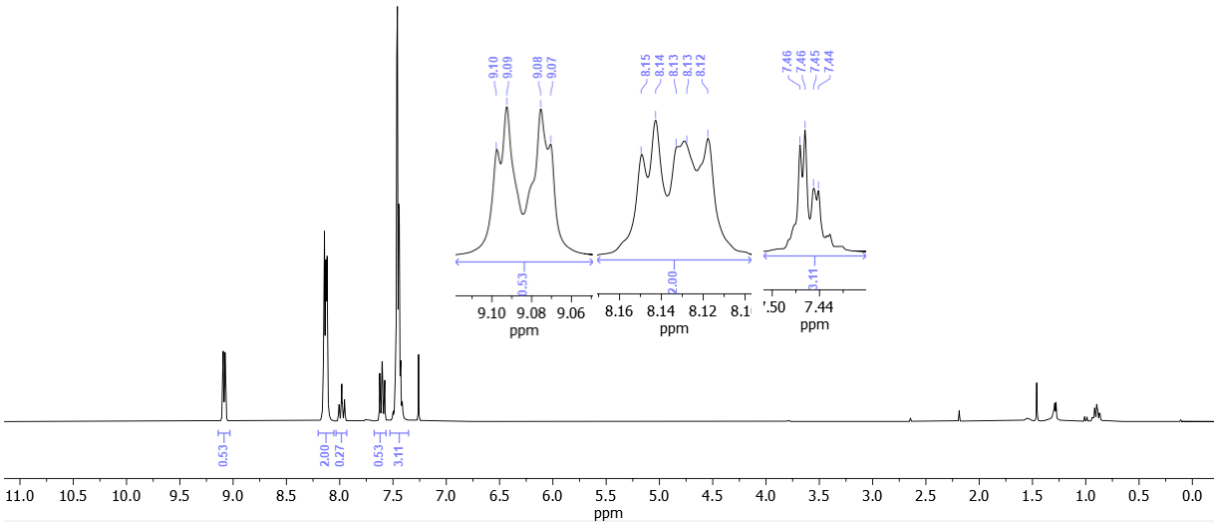


Attempted coupling reaction with 2e

^{1}H NMR (400 MHz, $CDCl_3$), of fraction 19-22.



^{1}H NMR (400 MHz, $CDCl_3$) of fraction 23-42.



^{1}H NMR (400 MHz, $CDCl_3$) of phenylboronic acid (3a)