Investigations into Cu-catalyzed methods for C(sp^2)-N-couplings of hydantoins at both nitrogen atoms

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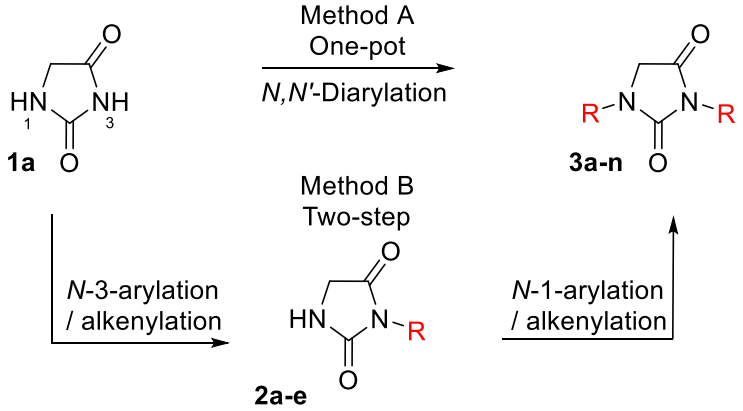
Magnhild Sandsbråten Solum

Abstract

N,N'-Diarylated hydantoins have previously been difficult to synthesize and a method for a direct *N,N'*-diarylation does not exist. This thesis describes a carefully investigated one-pot *N,N'*-diarylation reaction of hydantoin, using diaryliodonium salts. In addition, have the arylation of the nitrogen atoms been explored in two separate steps.

In this study we found a direct method for *N,N'*-diarylating hydantoin. It has been used it to synthesize three molecules, although the outcome of the reaction relies heavily on the aryl group being coupled and the yield varies significantly. The method is time-efficient and mild, but is limited to arylation of hydantoin without substituents at C-5.



The Sandtorv group has also found a new method for *N*-1-arylation of *N*-3-functionalised hydantoin and the limitations have been investigated in this thesis. Nine molecules have been synthesized with this method and it is vulnerable, in regards to both the coupling partner and the starting material. The method is mild, but therefore also limited to C-5-unsubstituted hydantoins. We acknowledge that the methods have a narrow area of application, but these molecules cannot be synthesized from hydantoins with other methods.

Abbreviations

ATR - Attenuated total reflectance

BARF - Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

Calcd. - Calculated

COSY - Correlation spectroscopy

DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene

DEPT - Distortionless Enhancement by Polarization Transfer

DMEDA - *N,N*'-Dimethylethane-1,2-diamine

DMF - *N,N*-Dimethylformamide

DMSO - Dimethyl sulfoxide

Eq. - Equivalent

ESI - Electrospray ionization

HMBC - Heteronuclear multiple-bond correlation spectroscopy

HRMS - High-resolution mass spectrometry

HSQC - Heteronuclear single-quantum correlation spectroscopy

IR - Infrared spectroscopy

m/z - Mass-to-charge ratio

***m*-CPBA** - 3-Chloroperbenzoic acid

MCR - Multicomponent reaction

Me_2CyDA - *trans-N,N'*-dimethylcyclohexane-1,2-diamine

nd - None detected

NM - Not measurable

NMR - Nuclear magnetic resonance spectroscopy

NOESY - Nuclear Overhauser effect spectroscopy

ppm - Parts per million

R_f - Retardation factor

SHMBC - Selective heteronuclear multiple-bond correlation spectroscopy

SHSQC - Selective heteronuclear single-quantum correlation spectroscopy

TEA - Trimethylamine

TFA - Trifluoroacetate

TMA - Trimethylamine

TMP - 2,4,6-Trimetoxyphenyl

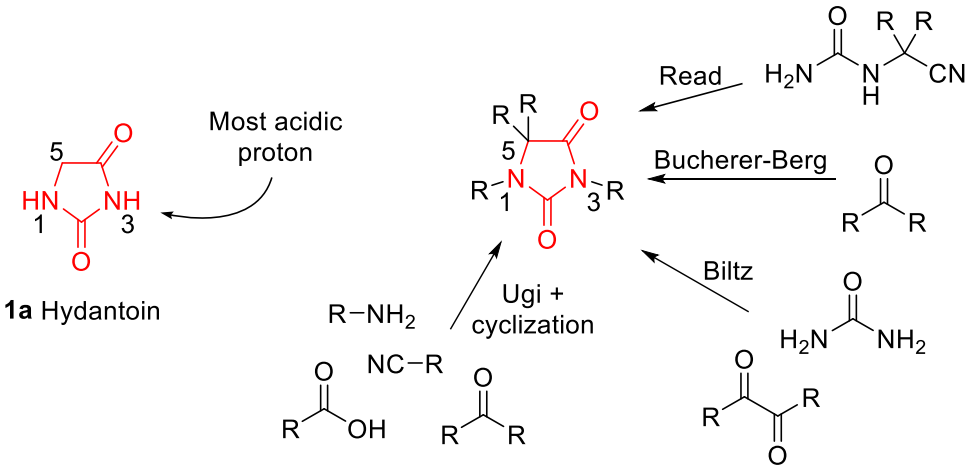
$\tilde{\nu}$ - Wavenumber

1 Table of Contents

2 Introduction

1.1 Hydantoin

Hydantoin is a five-membered heterocycle, first synthesized by Adolf Baeyer in 1861 (Scheme 1.1).[1] It has been isolated from a number of natural sources, for example *Platanus orientalis*, a broad-leaf tree.[2] Hydantoin is both a hydrogen-donating and -accepting molecule, and it has both amide and imide functionality, which results in multiple acidic areas. The *N*-3 proton is the most acidic (numeration in Scheme 1.1) because of the two electron-withdrawing carbonyl groups nearby. The measured pK_a value of the *N*-3 proton, is 15.0 in DMSO (dimethyl sulfoxide).[3] The acidity of the *N*-1 proton is only directly affected by one carbonyl group since the *N*-1 is part of an amide. The pK_a is most likely as other amides, around 20 in DMSO.[4] The C-5 proton is also weakly acidic.[5]



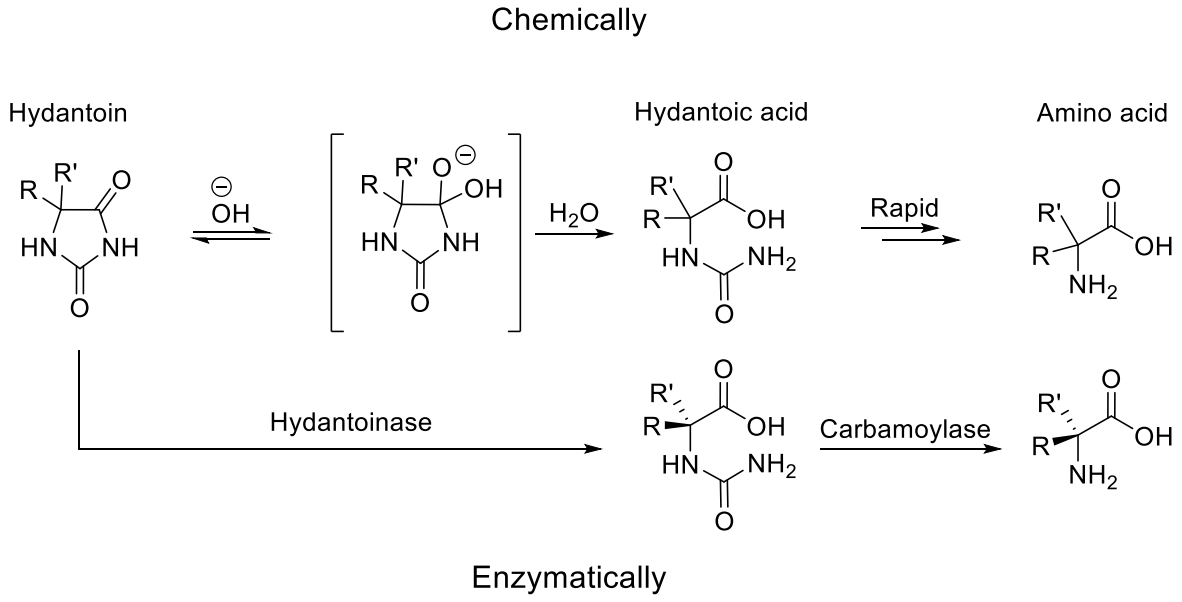
Scheme 1.1: Structure, numbering and methods to syntehesize hydanoins.[6-10]

A range of different types of hydantoins exists. What and where the substituents are, decides the class of hydantoin. They can have substituents in the *N*-1, *N*-3 and C-5 positions, but can also be polycyclic, spiro-, alkylidene- or aminohydantoins. The many possible variations of hydantoins combined with the many uses, makes it a compound worth studying.[6]

The most important synthetic methods for making hydantoins are the Read[7], Bucherer-Berg[8], and Biltz[9] reactions, as well as more recent, multicomponent reactions (MCRs)[10,11] (Scheme 1.1).[6] The Read, Bucherer-Berg and Biltz reactions are all

cyclization reactions, originally limited to the synthesis of C-5-substituted hydantoins. MCRs are easy, one-step reactions and have good yields.[10] Different combinations of reactants results in different substituted hydantoins. One example is the utilization of an Ugi reaction to link the reactants and then a base catalyzed cyclization to form the hydantoin.[10]

Hydantoins have many areas of use, including as reagents in the synthesis of amino acids. This is relatively easy and has been important because of the lack of alternative reactions to make amino acids. In the original procedure, the hydantoin is heated with a large excess of barium hydroxide in water, causing the ring to hydrolyze and form hydantoic acid (Scheme 1.2). The hydantoic acid will, in this environment, hydrolyze further to an amino acid.[12] Other chemical reactions works as well, most of them being harsh with strongly basic environments and high temperatures.[6] The major drawback with these methods is the separation of the enantiomers, which is a time-consuming process. Alternatively, one can synthesize amino acids enantioselectively from hydantoins with enzymatic reactions. Two enzymes, D-hydantoinase and D-*N*-carbamoylase, are used to synthesize the D-amino acid enantioselectively. Some enzymes can also synthesize L-amino acids, but through more complex reactions.[6,13]



Scheme 1.2: Chemical hydrolysis of hydantoin to an amino acid and enzymatic reaction of hydantoin to an enantiomerically pure amino acid.[6,12]

Hydantoins have many biological properties and an important role of hydantoins is therefore in medicinal chemistry.[6] Marketed drugs that are hydantoin derivatives

include anticonvulsants, antiandrogens, antibacterials and muscle relaxants. (Figure 1.1). It is believed that Phenytoin (**A**), a drug with anticonvulsant and antiarrhythmic properties, inhibit seizure activity by acting on the voltage-dependent sodium channels of neurons and their calcium efflux.[6] Nilutamide (**B**) is used to treat prostate cancer and inhibits cellular growth of the prostatic tissue. Nitrofurantoin (**C**) is an antibiotic, used to treat urinary tract infections. Enzymes reduce **C** and the products damage the DNA of the bacteria. Other uses of hydantoins include as insecticides[14], as catalysts for hydrocarbon polymerizations[15], as ligands in metal catalysts[16] and as a component in textile printing and production of resins and plastic.[6,12]

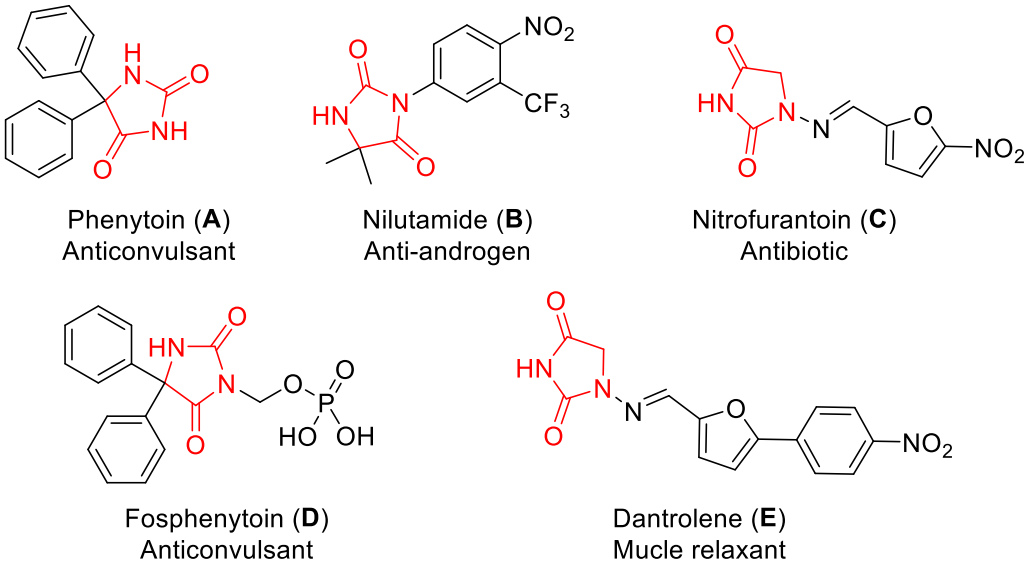


Figure 1.1: Some marceted drugs contining hydantoin rings.[6]

In this project the focus will be on *N,N'*-diarylated hydantoins (Figure 1.2). Enzalutamide (**F**), an *N,N'*-diarylated hydantoin derivate, is used as an anticancer drug to treat prostate cancer.[17] Unfortunately, resistance against **F** has been developed, making it even more important to investigate these type of molecules.[18]

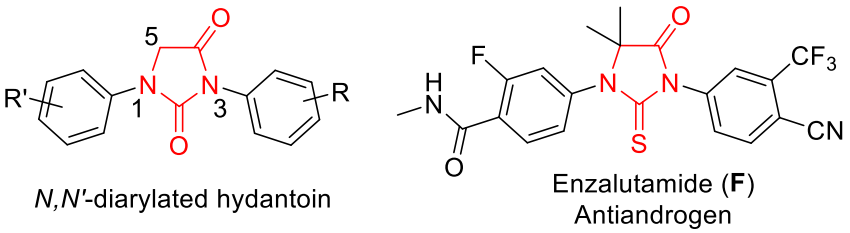


Figure 1.2: Generalized *N,N'*-diarylated hydantoin and Enzalutamide.[6,17]

1.2 Synthesis of *N*-arylated hydantoins

N-arylated hydantoins are synthesized either by cyclization or direct arylation.[6] Cyclization of the hydantoin is done with the aryl groups already attached to the nitrogen atoms. The bonds made in the reaction are those within the hydantoin ring. Direct arylations, on the other hand, use hydantoin as the staring material. They often involve coupling reactions between an arylating agent and the nitrogen atoms in hydantoin. Activation of the reaction site (often halogenation) is skipped in these direct reactions. Figure 1.3 illustrates the bonds formed in the two reaction types.

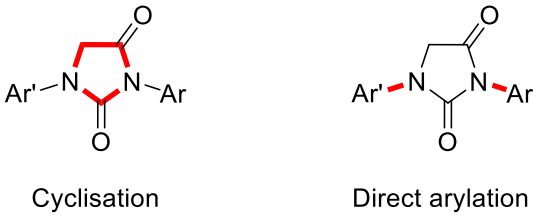
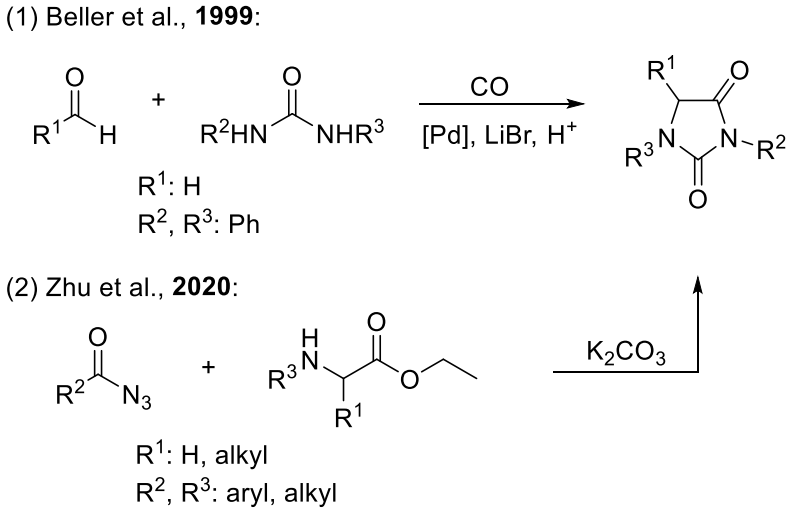


Figure 1.3: illustration of bonds formed (in red) in the cyclization reaction and the direct arylation of hydantoin.[6]

Numerous reactions can be categorized as cyclization reactions, among these are the Read, Bucherer-Berg and Biltz reactions.[6] With cyclization reactions, many different classes of hydantoins can be made, but very few have *N,N'*-diarylated hydantoins as products. There are many different *N*-1-substituted hydantoins synthesized with cyclization reactions. The same applies for *N*-3-substituted hydantoins, but this is not the case for *N,N'*-diarylated hydantoins. The first was the reaction Beller *et al.* developed in 1999, which was a palladium-catalyzed coupling reaction between an aldehyde and a urea.[19] The method allowed for different substituents in the *N*-1, *N*-3 and C-5 positions. Beller *et al*. only reported one *N,N'*-diarylated hydantoin product. (Scheme 1.3 (1)).[19] A more interesting development is the reaction by Zhu *et al*. in 2020. (Scheme 1.3 (2)).[20] In this reaction, an acyl azide cyclizes with an amino acid ethyl ester. They report a few examples of *N,N'*-diarylhydantoins, both C-5-substituted and -unsubstituted. In addition to aryl groups, hydantoins with alkyl groups on the nitrogen atoms were also synthesized. No C-5-disubstituted hydantoins are reported. Acyl azides start to decompose at temperatures over 0 ºC, and there are safety concerns when working with them.[21-23]



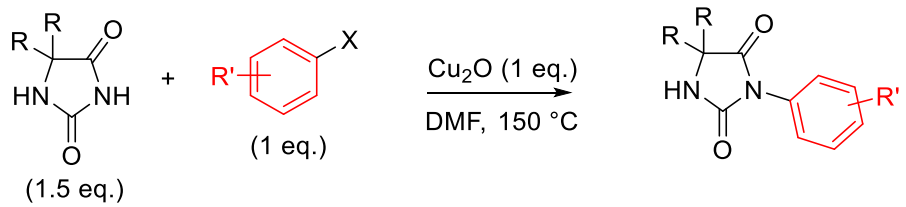
Scheme 1.3: (1): Palladium-catalyzed carbonylation with urea derivative, giving an *N,N'*-diarylated hydantoin.[19] (2): Acyl azide reacts with an amino acid ethyl ester, giving an *N,N'*-diarylated hydantoin.[20]

The method of Zhu *et al.* has advantages; high yields, good atom economy, and it works well with different substituents.[20] The safety precautions are a drawback and an alternative method is therefore desirable.

A direct arylation of hydantoin, formally a C(sp^2)-N-coupling, offers a complimentary approach. This is an underdeveloped area. Because the *N*-3 position is more acidic than the *N*-1 position, it is the easiest to functionalize.[6,24] This has been taken advantage of in *N*-3-arylations of hydantoins.[25-27] In these reactions, there can be some diarylated hydantoin as a side product, but the selectivity is relatively good. Steric hindrance will also affect the selectivity of a coupling reaction like this. Meaning, the bulkiness of the substituent on C-5 in hydantoin is important for the ratio of *N*-3- to *N,N'*-difunctionalization.[28]

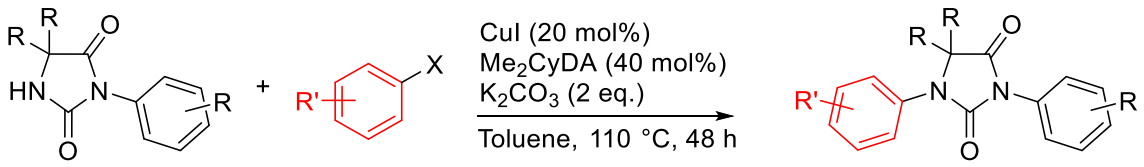
Direct arylations of the *N*-3 position in hydantoin was first done in 1992, but with only one example.[29] This is a copper-catalyzed coupling reaction based on the Goldberg reaction, in which a bond is formed between an amine and an sp^2 carbon. A key difference between the 1992 method by Lopez-Alvarado *et al*. and the original Goldberg reaction is the arylating agent, which uses aryllead acetates instead of aryl iodides.[30] Using an aryllead acetate makes it possible to reduce the temperature, although the high toxicity of lead makes the method less attractive overall.[29] In 2019, Petit, Evano and co-workers published a method for *N*-3-arylation of C-5-blocked hydantoins (Scheme 1.4). The reaction is copper-mediated, uses aryl iodides or bromides as coupling partners and is ligand and base free.[27] This method has a broad

scope and high yields, but the method does not work well with C-5 unsubstituted hydantoins. Petit, Evano and co-workers tried the copper-mediated method on bare hydantoin, and reported getting a mixture of *N*-1-arylated and *N,N'*-diarylated hydantoin as products.[27] This is surprising, when theoretically the *N*-3 position is the first and easiest to functionalize.



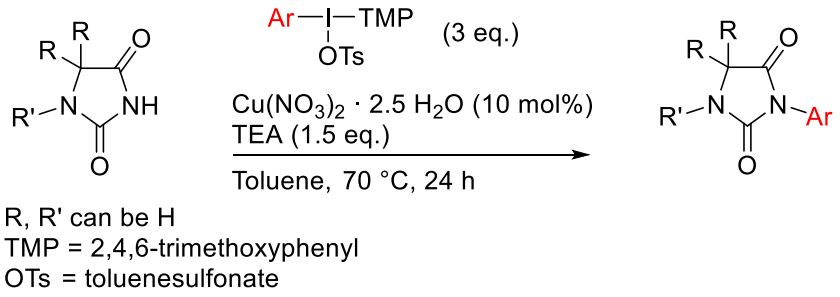
Scheme 1.4: *N*-3 arylation of C-5 blocked hydantoins as reported by Petit, Evano and co-workers.[27]

Petit, Evano and co-workers also developed a copper-catalyzed method for *N*-1-arylhydantoins (Scheme 1.5). The reaction uses aryl iodides as coupling partner, 20 mol% copper iodide and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (Me_2CyDA) as a ligand. A base, K_2CO_3, is also needed. The *N*-1-arylation works on different *N*-3-arylated hydantoins, but the *N*-1-arylation of a C-5-unsubstituted *N*-3-arylated hydantoin was not attempted. The method has a relatively long reaction time of 48 hours.[27]



Scheme 1.5: *N*-1-arylaton of *N*-3-arylated C-5 substituted hydantoin.[27]

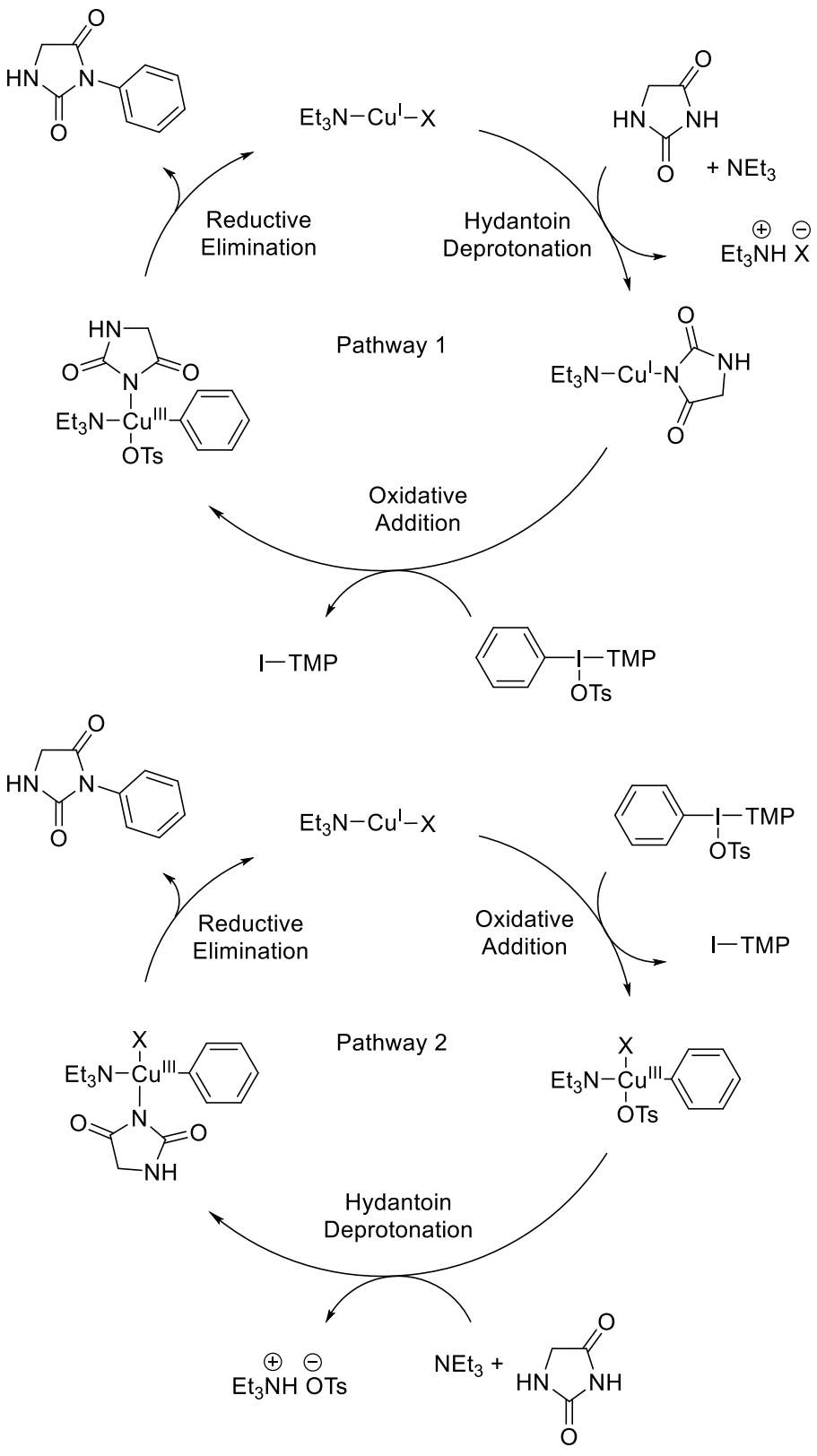
The first regioselective *N*-3-arylation of C-5-unsubstituted hydantoins was reported by the Sandtorv group in 2020 (Scheme 1.6).[25] This work is based on the reaction of Petit, Evano and co-workers, but uses diaryliodonium salts as the arylating agent. Diaryliodonium salts are more reactive than aryl iodides and the temperature is therefore lowered. The reaction is copper-catalyzed, using 10 mol% copper(II)nitrate hemipentahydrate, making it greener than the copper-mediated method of Petit, Evano and co-workers.[27]



R, R' can be H
TMP = 2,4,6-trimethoxyphenyl
OTs = toluenesulfonate

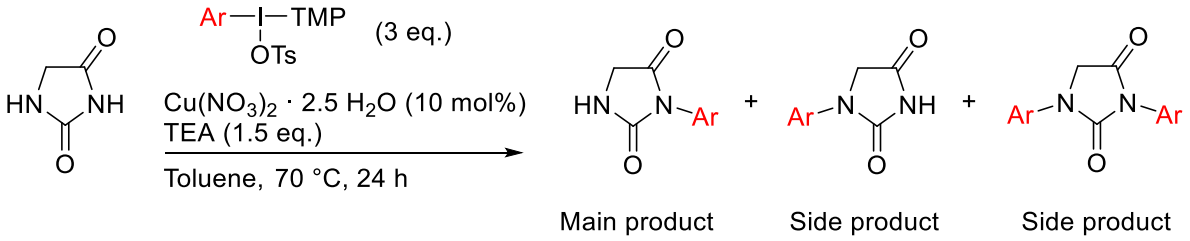
Scheme 1.6: Copper-catalyzed *N*-3-arylation of hydantoin using diaryliodonium salts as reported by the Sandtorv group.[25]

Two different mechanisms were proposed for this copper-catalyzed reaction (Scheme 1.7). Both pathways include a Cu(I)/Cu(III) cycle. Cu(II) is believed to be reduced to Cu(I) before the catalytic cycle begins. Pathway 1 is based on an Ullman-type C-N-coupling reaction with aryl iodide. In this proposed mechanism, the deprotonation of the hydantoin occurs before the oxidative addition, and the reductive elimination to the product is the last step. Pathway 2 is based on a proposed mechanism for the copper-catalyzed reactions using diaryliodonium salts as arylating agent. In this mechanism, the oxidative addition is the first step, followed by the deprotonation of hydantoin and then the reductive elimination to the product. Triethylamine (TEA) is in both cases present as a ligand and a base.[25]



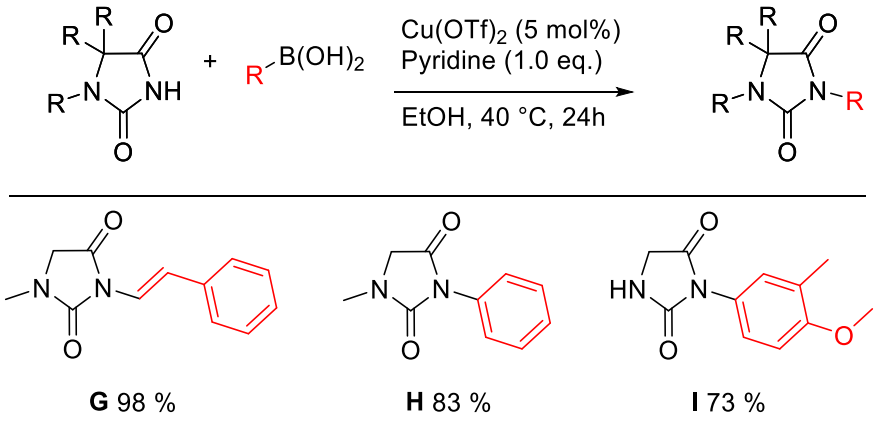
Scheme 1.7: Proposed mechanisms for the copper-catalyzed *N*-3-arylation of hydantoin as reported by the Sandtorv group.[25]

Working with the *N*-3-arylations, the Sandtorv group observed interesting side products in some of the reactions. The *N*-3-arylated hydantoin was the main product, but the *N*-1-arylated and the *N,N'*-diarylated hydantoin were produced in small amounts (<10%) (Scheme 1.8).[25] Inspired by this, Neerbye Berntsen did a few experiments to promote the diarylation. No reaction with high and reproducible yields were found.[31]



Scheme 1.8: Main product and side products of the method for *N*-3-arylation of hydantoin with diaryliodonium salts as reported by the Sandtrorv group.[25]

Another *N*-3-arylation reaction developed in the Sandtorv group is a copper-catalyzed C(sp^2)-N coupling with boronic acids (Scheme 1.9).[32] Hydantoin is the model substrate, but the reaction works with other cyclic imides. The reported method focuses on *N*-3-alkenylation, but also has examples of *N*-3-arylation. The method is inspired by the Chan-Lam reaction, which is a copper-catalyzed C(sp^2)-heteroatom coupling reaction with boronic acids as coupling partners.[33] It is believed that pyridine has a role as both base and ligand, as well as to stabilize boroxine *in situ*, the anhydride trimer of boronic acids. *N*-1- and *N,N'*-diarylated products were not observed in any particular degree.[32]



Scheme 1.9: *N*-3 Functionalization of hydantoin with boronic acid with examples of products as reported by the Sandtorv group.[32]

Coupling partners

Diaryliodonium salt

Diaryliodonium salts are used as an arylating agent in the *N*-3-arylation of hydantoin, developed in the Sandtorv group. Diaryliodonium salts are non-toxic and relatively easy to synthesize. They are often used instead of heavy metal-based oxidants and expensive organometallic catalysts.[34] An important quality of diaryliodonium salts utilized here is the fact that they can transfer an aryl group to a nucleophile.[25,35-37] Diaryliodonium salts consists of two aryl groups bound to a positive iodine as well as a counterion (Figure 1.4). They can be symmetric and asymmetric in terms of the aryl groups. They are often chemoselective, meaning there is a control over which aryl is transferred. The iodine in diaryliodonium salts are hypervalent and is therefore more reactive than aryl iodides.[38]

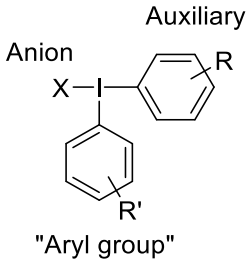
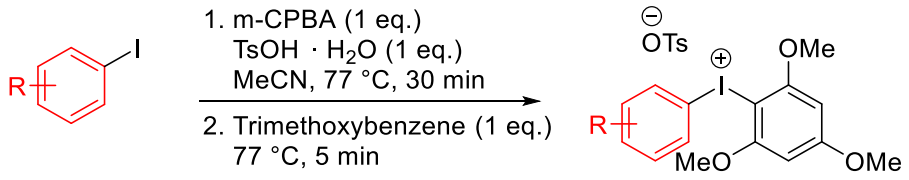


Figure 1.4: Generalized diaryliodnium salt.[38]

One example of diaryliodonium salts synthesis is the method developed by Seidl *et al*. in 2016. The method is designed for aryl(2,4,6-trimethoxyphenyl)iodonium tosylates (ArI(TMP)OTs) and is a two-step, one-pot reaction (Scheme 1.10).[39] It is an easy and fast reaction with high yields and the scale size can be increased with the yields intact. The first step is an oxidation of an aryl iodide from oxidation state +1 to +3, done with *m*-CPBA. An electrophilic aromatic substitution occurs between 1,3,5-trimethoxybenzene and the iodonium cation. The method works with different aryl groups and similar reactions can make diaryliodonium salts with other auxiliaries.

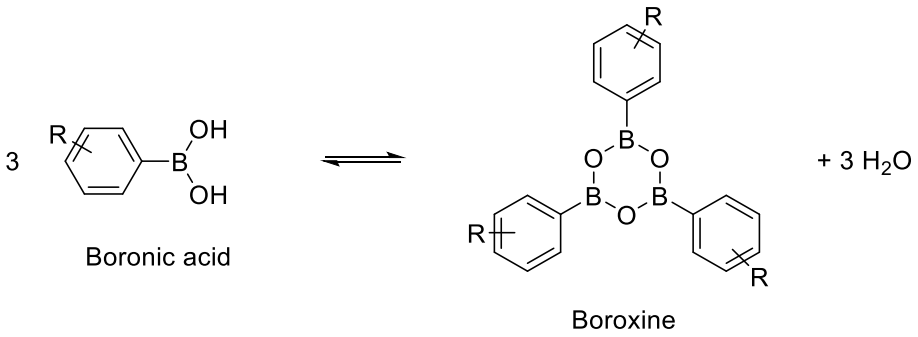


Scheme 1.10: The two-step, one-pot reaction to synthesize ArI(TMP)OTs as reported by Seidl *et al*.[39]

Methods similar to that of Siedl *et al*. can also synthesize diaryliodonium salts with different anions, but there are many limitations.[40,41] Hence, an anion exchange reaction is also useful.[39] A diaryliodonium tosylate is dissolved in water and a sodium salt with the desired anion is added. When the mixture is cooled, the diaryliodonium salt will precipitate with the anion replaced. To have a high probability that the desired anion coordinates to the iodonium cation, an extreme excess of the sodium salt is needed. The amount used varies, but can be up to 100 equivalents. This is an easy reaction, but the atom economy is unusually poor, and it adds an additional step.

Boronic acids

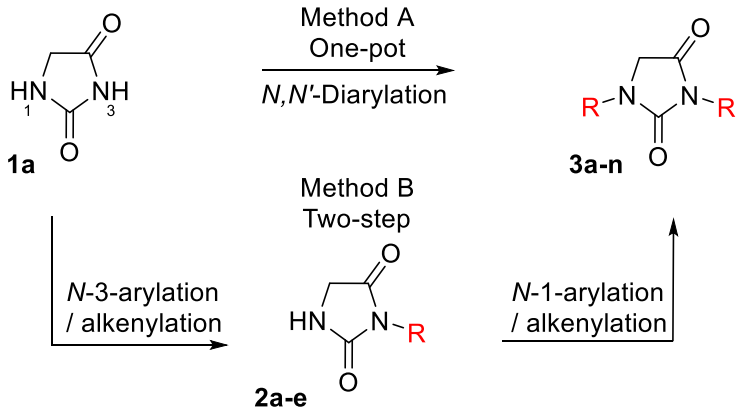
Boronic acids are green, non-toxic and stable coupling partners. Boroxine is the dehydrated trimer of boronic acid (Scheme 1.11). In solution, boronic acids are in equilibrium with their boroxine form. The reaction is a dehydration where three boronic acids cyclize to form the boroxine. Pyridine, or amines, can stabilize the boroxine and have an impact on the equilibrium constant. The equilibrium constant is dependent on the substituents, both electronically and sterically.[42,43] The Sandtorv group has done some experiments to try to understand if boronic acid or boroxine is the active coupling partner in the C-N-coupling reaction. However, no conclusion on the relation between boronic acid, boroxine and substrate was made.[32]



Scheme 1.11: The equilibrium between boronic acid and boroxine.[42]

3 Aim of the study

The aim of the study was to explore different methods to arylate the nitrogen atoms of hydantoin. The project was separated into two parts; a one-pot diarylation reaction (method A) and a two-step reaction (method B) (Scheme 2.1). The main goal was to optimize the one-pot reaction.



Scheme 2.1: Functionalization of hydantoin with methods A and B.

Questions that were to be answered in this thesis:

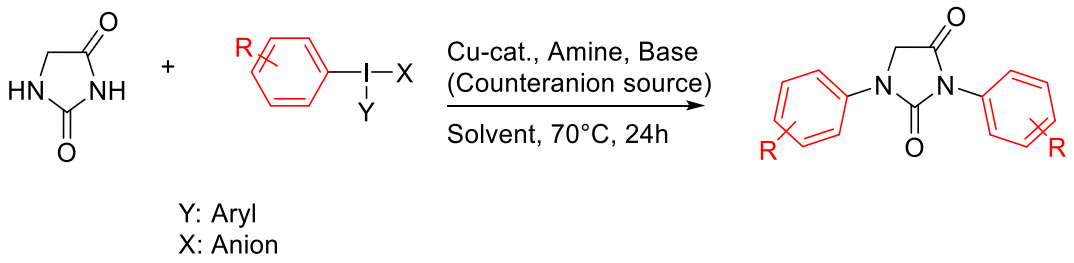
- Can the yields of the one-pot *N,N'*-diarylation of hydantoin using diaryliodonium salts be improved?
- Are we able to reproduce the synthetization of *N*-3-functionalized hydantoins?
- Can copper-catalyzed coupling reactions occur at *N*-1 in C-5-unsubstituted hydantoins?
- What are the limitations of the methods?
- How do method A and B compare to the *N*-3- and *N*-1-arylation methods by Petit, Evano and co-workers?

4 Results and discussion

In this chapter, the reactions of both the one-pot and two-step diarylations will be presented and discussed. A large optimization study of the one-pot reaction was performed. Our thoughts and predictions about the methods will be presented. Lastly a comparison of the methods will be done, with focus on areas of use.

3.1 One-pot diarylation reaction – Method A

Method A is the one-pot *N,N'*-diarylation reaction (Scheme 3.1). It is carefully investigated and the most studied reaction in this project. The study has been developed after a few initial reactions by fellow group member L. Neerbye Berntsen. Neerbye Berntsen managed to improve the yield of diarylated product from under 10 % to a maximum isolated yield of 65 %. This result was not reproducible and higher yields were desired.



Scheme 3.1: The *N,N'*-diarylation of hydantoin with the different components of the reaction.

Yields of the reactions were calculated using an internal standard in the crude mixture and recorded a ^{1}H NMR spectrum. Doing this allowed for investigation into a great number of conditions. The alternative was to isolate the products, but in these reactions, a complicated separation by column chromatography is necessary. Even though much time was saved using an internal standard to calculate the yields, these measurements have a higher uncertainty. This means that the measurements can only be interpreted as trends, such that before concluding, we have purified the product of some of the reactions and calculated the isolated yields.

Variables of the reactions

The arylation reaction of hydantoin has different components, and all of them can have an impact on the reaction. The reaction studied here is a C(sp^2)-N-coupling reaction. Other C(sp^2)-N-coupling reactions have been thoroughly investigated previously, and observations from these have been taken into account when planning this study. The coupling reaction consist of an arylating agent, a copper-catalyst, a ligand, a base, solvent and in some cases, an additional counteranion source.

Arylating agent

In the one-pot arylation reaction, a diaryliodonium salt is used as an arylating agent. These are, as mentioned, more reactive than aryl iodides, which is the arylating agent in older coupling reactions.[34] This means that the reaction can be performed at lower temperatures and in other solvents. The Sandtorv group has seen that arylation with diaryliodonium salts can proceed at 70 ºC and that decomposition occurs quickly at temperatures higher than this. All the reactions in method A is therefore performed at 70 ºC. It has been shown that which type of diaryliodonium salt used has an impact on the yield.[25] It is proposed that the anion of the diaryliodonium salt is a ligand in the copper-complex. Different counteranions sources have therefore been tested.

An overview of the synthesis of the diaryliodonium salts used in the optimization studies is presented in Table 3.1. All the diaryliodonium salts were prepared according to literature procedures.[39-41] The yields of the salts **4a**, **4d** and **4f** are good (entry 1-3). However, the yield of **4e** is low, even though excellent yields have been reported.[41] An explanation could be that the reaction was not attempted at the same scale as reported by Olofsson. It was a big advantage that the synthesis of **4a** was scalable, because of the high consumption of diaryliodonium salts in the optimization studies. The method still gave high yields on 10 mmol scale. All of these reactions are relatively fast, but **4d** needs two steps; first the formation of the diaryliodonium salt and then an anion exchange. The atom economy of the anion exchange is very poor and an *in situ* exchange in the coupling reaction is therefore desirable. Exchange of the anions have been attempted both before the reaction and in the reaction mixture.

Table 3.1: Yields of the synthetization of diaryliodonium salts.

#	Diaryliodonium salt	Comment	Yield (%)[a]
1	PhI(TMP)OTs (**4a**)	Scalable	94[b]
2	PhI(TMP)BF_4 (**4d**)	Two steps. Bad atom economy in step 2	80
3	PhI(TMP)TFA (**4f**)		85
4	Ph_2IOTf (**4e**)	Excellent yields have been reported[41]	24

[a] Yield of total reaction.
[b] 10 mmol scale.

The term salt is not entirely correct, since it is believed that the anion and cation in the diaryliodonium salts still have a bond in solution. This will then result in different solubilities, with triflates and tetrafluoroborates having a higher solubility than halides.[38] Because of the bond between the anion and cation, the identity if the anion can also affect the rate of the oxidative addition. This will again affect the rate of the reaction. Optimization of the anion can therefore have a positive effect.

Catalyst

Copper-catalysts have been shown to work with C(sp^2)-N bond formation similar to the reaction investigated in this thesis.[25-27] Copper is therefore an obvious choice for metal catalyst over the commonly used palladium. The effect of different Cu-catalysts with oxidation state 1 and 2, has been investigated. Both of these could theoretically work with the proposed mechanism for the *N*-3-arylation of C-5-unsubstituted hydantoin previously developed in the Sandtorv group. Cu(II) is believed to be a precatalyst for Cu(I).[25] Copper was used in stoichiometric amounts in older C(sp^2)-N coupling reactions. With more reactive arylating agents, the oxidative addition is easier and catalytic amounts of copper is therefore sufficient. Because of the big advantage of using less catalyst, we wanted to start with 10 mol% copper.

Ligand

Both C(sp^2)-N-coupling reactions with and without ligands are possible.[25,27] Amines have been used as ligands in Cu-catalyzed *N*-arylation of hydantoins before, and have shown to be important in these types of reactions. Petit, Evano and co-workers have in their optimization of the *N*-1-arylation of hydantoins, studied the effect different

amines as ligands in the presumed created Cu-complex.[27] A similar investigation was done in this thesis. The starting point was TEA as used in the *N*-3-arylation developed in the Sandtorv group. Amines with different bulkiness, rigidity and basicity were explored.

Base

Some kind of base is needed to deprotonate the hydantoin in the reaction. In many of the reactions tried in this project, the amine is used as a base as well as a ligand. Amines with p*Ka* values between 5 and 13 were tested.[44,45] However, we wanted to understand if an additional base was necessary, and did therefore try basic salts in combination with the amines. Both basic organic and inorganic salts were used.

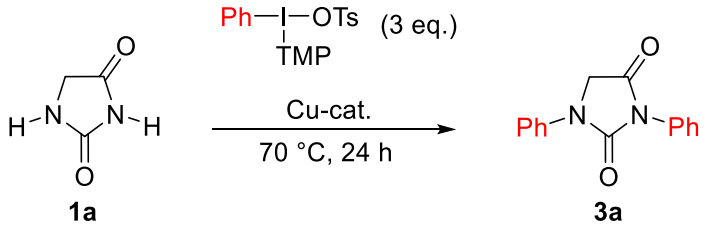
Solvent

The last component of the reaction is the solvent. The first reported C-(sp^2)-N reactions were done with polar solvents with high boiling points.[46] However, toluene was working well for the *N*-3-arylation reaction developed in the group. Toluene was therefore the starting point.[25] 1,4-Dioxane has been used in *N*-1-arylation reactions and was an obvious solvent to investigate as well.[27] A couple of other solvents have also been tested.

Study 1: Reactions with PhI(TMP)OTs

In the first couple of experiments in the project, the focus was on the catalyst, the base/ligand and to find out more about their impact on the reaction. (Table 3.2). All of the reactions in Table 3.2 were done with phenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (**4a**) as the arylating agent. It was not possible to recreate the yield of Neerbye Berntsen's best experiment (entry 1). Neerbye Berntsen got a yield of 72 %, but in this project, only 40 % was measured (entry 1-2).[31] It is unknown why, but a hypothesis is that the catalyst was not as good as it was when it was freshly opened.

Table 3.2: Initial one-pot reactions with hydantoin and PhI(TMP)OTs.



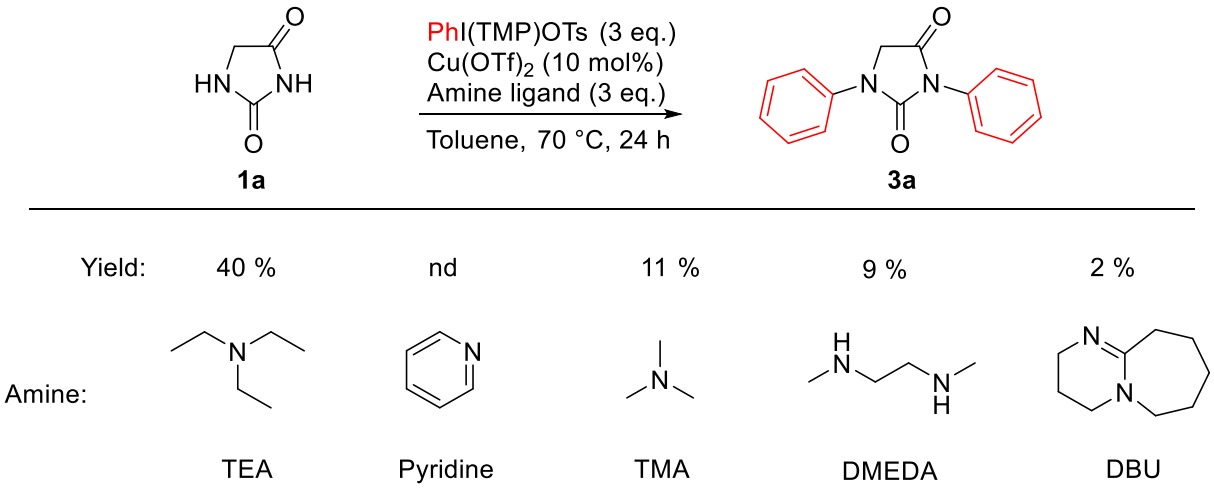
#	Catalyst (10 mol%)	Base / Ligand (3 eq.)	Solvent	Yield (%)[a]
1	$Cu(OTf)_2$	TEA	Toluene	72[b]
2	$Cu(OTf)_2$	TEA	Toluene	40
3	$Cu(NO_3)_2 \cdot 2.5\ H_2O$	TEA	Toluene	29
4	CuI	TEA	Toluene	44
5	$Cu(OTs)_2$	TEA	Toluene	6
6	$Cu(OTf)_2$	TEA	1,4-dioxane	51
7	$Cu(OTf)_2$	K_3PO_4	Toluene	nd
8	$Cu(OTf)_2$	Pyridine	Toluene	nd
9	$Cu(OTf)_2$	TMA	Toluene	11
10	$Cu(OTf)_2$	DMEDA	Toluene	2
11	$Cu(OTf)_2$	DBU	Toluene	9

[a] Yield measured with mesitylene as internal standard in ^{1}H NMR analysis of crude.
[b] Result by Neerbye Berntsen.[31]

The catalysts copper(II)nitrate hemipentahydrate, copper(I)iodide and copper(II) tosylate were tried in addition to copper(II)triflate (entry 2-5). $Cu(OTf)_2$ and CuI gave almost the same result, $Cu(NO_3)_2 \cdot 2.5\ H_2O$ was not as good, and reaction using $Cu(OTs)_2$ gave only 6 % measured yield. This supports the assumption that the reaction can proceed regardless of the oxidation state of the catalyst. As mentioned, toluene and 1,4-dioxane have previously been used in *N*-3- and *N*-1-arylation reactions of hydantoins and the use of 1,4-dioxane resulted in a small increase of the yield (entry 6) compared to toluene (entry 2).

It can be interpreted from Table 3.2 that the reaction needs an amine. This is consistent with the mechanism proposed for the *N*-3-arylation of hydantoin developed in the Sandtorv group. The amine is expected to act as a ligand. The experiment without amine, but with potassium phosphate instead (entry 7) did not give the product. We cannot say that the reaction would not proceed with other inorganic bases. However, it is an advantage that amines can be used as both base to deprotonate the hydantoin and as a coordinating ligand in the complex. The structures of the organic nitrogen bases tested and the yields they gave in the reactions can be seen in Scheme 3.2.

None of the organic bases improved the yield, compared to TEA (entry 7-10). Trimethylamine (TMA) and *N,N'*-dimethylethylenediamine (DMEDA) gave low yields and pyridine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not give or gave only trace amounts of the product.



Scheme 3.2: The different amines tried in study 1 (Table 2), with corresponding yields of the reaction.

Ligands may not directly effecting coupling reactions, but they can be utilized to limit the production of byproducts.[47] Finding the fitting ligand for the desired reaction is therefore important. The catalyst is affected mostly by the electron-donating abilities of the ligand. Both the oxidative addition and the reductive elimination can be more or less favorable when changing the ligand.[46] The presence of π-electrons in pyridine and DBU seems to be an unfavorable effect on how they donate electrons to the copper atom. In addition, the steric properties are varied, and these are also affecting the catalyst. Pyridine and DBU are maybe too rigid and bulky to work as ligands in the catalytic cycle, and therefore affects and destroys the reaction. In addition, the basicity can also affect the deprotonation of the hydantoin, making this too complex to understand fully from these experiments.

All of the yields in Table 3.2 were calculated with mesitylene as internal standard in ^{1}H NMR sample. None of the products of the reactions were isolated. Because of this, the results can only be interpreted as trends. With that said, study 1 did not give any satisfactory results, but an amine will hereafter always be included in the *N,N'*-diarylation reaction. To summarize, we have shown that the catalyst has a great impact on the reaction, $Cu(OTf)_2$ and CuI were the best ones tested, the two solvents gave

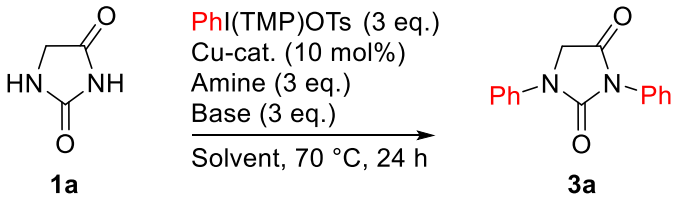
approximately the same yields, and an amine in needed with TEA being the best one tested.

Study 2: Detailed study of PhI(TMP)X

With the conclusions from study 1 in mind, a new study 2 was designed. Combinations of all the different chosen variables were tested to have a better chance of finding trends. From study 1, copper(I)iodide and copper(II)triflate remained as catalysts. Both solvents, 1,4-dioxane and toluene, were continued. In the *N*-1-arylation of hydantoins by Petit, Evano and co-workers, the best amine studied was *trans-N,N'*-dimethylcyclohexane-1,2-diamine (Me_2CyDA).[27] Me_2CyDA is expensive, but worth buying after no promising results in study 1. TEA, the best amine form study 1, and Me_2CyDA were therefore the amines tested in study 2. Since the *N*-1 proton is less acidic than the *N*-3 proton, it is possible that the *N*,*N'*-diarylation reaction needs stronger base to promote the coupling, compared to *N*-3-arylartion. Potassium carbonate was therefore used in combination with both TEA and Me_2CyDA. Potassium carbonate was chosen because Petit, Evano and co-workers used it in combination with Me_2CyDA. TEA was also tested without the base to try to understand more about the deprotonation step.

An overview of the experiments and their yields can be seen in Table 3.3. Both the yield of the *N,N'*-diarylated and *N*-3-arylated product were attempted calculated, but the *N*-3-arylated product could not always be measured (NM). The problem was because of overlap between ^{1}H NMR signals. We wanted to measure the *N*-3-arylated product because it could give more information on what happened in the reactions. The calculated *N*-3-arylated yields are not discussed here, but can be seen in the section “Controls and optimization data”.

Table 3.3: Reactions of *N,N'*-diarylation of hydantoin.



#	Solvent	Catalyst (10 mol%)	Ligand (3 eq.) / Base (3 eq.)	Yield (%)[a]
1	Toluene	CuI	TEA	44
2	Toluene	CuI	$Me_2CyDA + K_2CO_3$	51
3	Toluene	CuI	$TEA + K_2CO_3$	10
4	Toluene	$Cu(OTf)_2$	TEA	40
5	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	30
6	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	6
7	1,4-dioxane	CuI	TEA	13
8	1,4-dioxane	CuI	$Me2CyDA + K_2CO_3$	30
9	1,4-dioxane	CuI	$TEA + K_2CO_3$	a: 35 b: 60
10	1,4-dioxane	$Cu(OTf)_2$	TEA	51
11	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	45
12	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	42

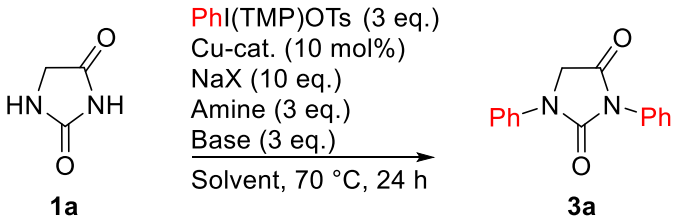
[a] Yield measured with mesitylene or 2,4,6-trimehoxybenzealdehyde as internal standard in ^{1}H NMR analysis of crude mixture.

Results of the reactions presented in Table 3.3 have a variating outcome, and no high yields were measured. We have not been able to find trends in regards to combinations of TEA, TEA + K_2CO_3 and $Me_2CyDA + K_2CO_3$. The same applies for use of solvent and catalyst. Which of these being beneficial seems to depend on all of the other parts of the reaction. None of the crude mixtures were calculated with high yields and purification was therefore not done.

The role of the anion of the diaryliodonium salt was one of the thing the group wanted to learn more about. When dissolved, it is believed that the anion can change in the mixture, similar to the anion exchange reaction of diaryliodonium salts. Because of the poor atom economy in the anion exchange reaction, an *in situ* exchange of the anion was first attempted. Two aspects were taken into consideration doing this. A high probability of coordination between the new anion and diaryliodonium salt was desirable, but with a too large excess of the added anion, a solvation problem could happen. An additional sodium salt with the desired anion was therefore added in 10 equivalents. This was seen as a compromise between the probability of coordination

and the limit of solvation. Experiments done with additional counteranion source can be seen in Table 3.4.

Table 3.4: Reactions of *N,N'*-diarylation of hydantoin with additional counteranion in study 2.



1a **3a**

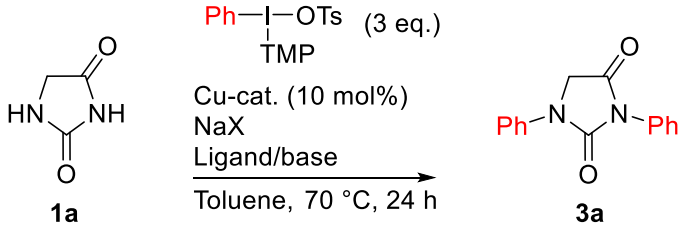
#	Solvent	Catalyst (10 mol%)	Ligand (3 eq.) / Base (3 eq.)	X	Yield (%)[a]
1	Toluene	CuI	TEA	BF_4	26
2	Toluene	CuI	$Me_2CyDA + K_2CO_3$	BF_4	nd
3	Toluene	CuI	$TEA + K_2CO_3$	BF_4	42
4	Toluene	$Cu(OTf)_2$	TEA	BF_4	18
5	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	BF_4	3
6	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	BF_4	32
7	Toluene	CuI	TEA	I	nd
8	Toluene	CuI	$Me_2CyDA + K_2CO_3$	I	nd
9	Toluene	CuI	$TEA + K_2CO_3$	I	nd
10	Toluene	$Cu(OTf)_2$	TEA	I	nd
11	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	I	nd
12	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	I	nd
13	1,4-dioxane	CuI	TEA	BF_4	40
14	1,4-dioxane	CuI	$Me_2CyDA + K_2CO_3$	BF_4	35
15	1,4-dioxane	CuI	$TEA + K_2CO_3$	BF_4	a: 52 b: 56, 35[b]
16	1,4-dioxane	$Cu(OTf)_2$	TEA	BF_4	16
17	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	BF_4	27
18	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	BF_4	47
19	1,4-dioxane	CuI	TEA	I	3
20	1,4-dioxane	CuI	$Me_2CyDA + K_2CO_3$	I	nd
21	1,4-dioxane	CuI	$TEA + K_2CO_3$	I	7
22	1,4-dioxane	$Cu(OTf)_2$	TEA	I	nd
23	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	I	nd
24	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	I	1

[a] Yield measured with mesitylene or 2,4,6-trimehoxybenzealdehyde as internal standard in ^1H NMR analysis of crude mixture.
[b] Isolated yield.

One very notable observation was that no reactions done with NaI as an additive (entry 7-12 and 19-24) gave any product, except in trace amounts. The mixtures were relatively thick, and it is therefore believed that with addition of NaI, a solvating problem

appeared. With thick mixtures, it is more difficult for the reactants to coordinate and this will therefore stop or slow down the reaction. This is observed with both toluene and 1,4-dioxane as the solvent. A short test reaction was performed, using fewer equivalents of the sodium salt (Table 3.5). For the reactions with NaI, a reduction of the amount did not help (entry 7/8 vs. 3/4). These mixtures were also very thick and the problem is most likely still the solvation. Addition of NaI was after this excluded from the study. We now know that NaI is destructive for the reaction, but it is unclear how iodine performs solely as a ligand.

Table 3.5: Yields of the reactions done with 4 equivalents of sodium salt compared to 10 equivalents.



#	Catalyst (10 mol%)	Ligand (3 eq.) / Base (3 eq.)	X	Eq. of NaX	Yield (%)[a]
1	CuI	TEA + K_2CO_3	BF_4	10	42
2	$Cu(OTf)_2$	TEA	BF_4	10	18
3	CuI	TEA + K_2CO_3	I	10	nd
4	$Cu(OTf)_2$	TEA	I	10	nd
5	CuI	TEA + K_2CO_3	BF_4	4	2
6	$Cu(OTf)_2$	TEA	BF_4	4	10
7	CuI	TEA + K_2CO_3	I	4	nd
8	$Cu(OTf)_2$	TEA	I	4	nd

[a] Yield measured with 2,4,6-trimehoxybenzealdehyde as internal standard in ^{1}H NMR analysis of crude.

It can be see from both Table 3.4 and 3.5 that the presence of $NaBF_4$ has an impact. The impact seems quite random, but many of the reactions gave a lower yield with $NaBF_4$. When comparing entry 3 in Table 3.3 and entry 3 in Table 3.4, it is a significant improvement of the yield adding $NaBF_4$, but when looking at entry 2, Table 3.3 and 2, Table 3.4, it is the total opposite. Not only is the addition of $NaBF_4$ important, but the amount of $NaBF_4$ is also important (entry 1/2 vs. 5/6 Table 3.5). It is obvious that $NaBF_4$ has an effect on the reaction, but how and on which level, is not clear. None of the new reactions resulted in significantly better yields than the starting point. Normally, an anion can be used as ligand to the copper atom and affect the oxidative addition.[25] The

reaction system is complex and it is therefore difficult to find the perfect combination of components. This also makes it difficult to understand the role of the anion.

It can be observed in Table 3.4, that all the reactions with $NaBF_4$ performs slightly better with both TEA and K_2CO_3 compared to only TEA. This can likely be a coincidence, but with thicker mixtures, it would be more difficult to deprotonate the hydantoin because of the base being less accessible. The addition of a secondary base can therefore be favorable.

From study 2, we have confirmed that this is a complex reaction because of the double coupling reaction per hydantoin and the many components. Study 2 did not result in desired yields. However, we found some information on combination of reactants not working and some components worth exploring further.

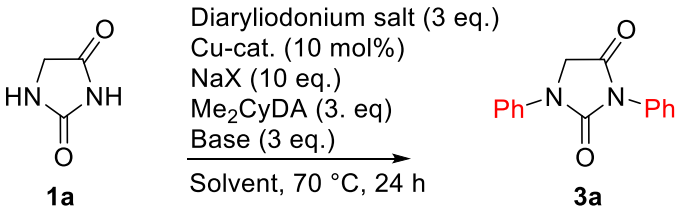
Study 3: In-depth study of results from study 2

After study 2, we knew that the reaction was complex, but we wanted to do a last attempt on finding a reaction with better yield. Our thought process was to start from the best result from study 2 and do one alteration at a time.

In study 1, the yields were measured by internal standard in ^{1}H NMR using acetonitrile as the solvent. Acetonitrile was substituted for chloroform, for economical reasons. When doing this, the internal standard needed to be changed from mesitylene to 2,4,6-trimethoxybenzealdehyde. Some time after this, problems with the integration appeared. Signals can change in NMR spectra, depending on the solvent. Overlapping of signals happened to a greater extend. Because of a miscommunication, a tool in the NMR processing was overused. This led to changing the integral of the signal measured, and resulted therefore in wrong measured yields. We discovered this after discussion of several measurements over 100 %. At this point, study 3 was already constructed and started. Study 3 was therefore based on an experiment believed to be better than it actually was.

In study 3, we wanted to go in-depth on the reaction with the best yield from study 2 (Table 3.6). The base, diaryliodonium salt, additional counteranion and the solvent was changed to optimize the conditions for the reaction.

Table 3.6: Reactions of *N,N'*-diarylation of hydantoin in study 3.



1a **3a**

#	Catalyst (10 mol%)	Base (3 eq.)	Diaryliodonium salt (3 eq.)	X	Solvent	Yield (%)[a]
1	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	a: 35 b: 29
2	$Cu(OTf)_2$	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	27
3	CuI	-	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	6
4	CuI	*t*-BuOK	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	29
5	CuI	NaOH	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	65, 8[b]
6	CuI	*t*-BuOLi	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	8
7	CuI	$NaHCO_3$	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	19
8	CuI	K_3PO_4	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	a: 108 b: 106, 5[b] c: 53, 8[b]
9	CuI	K_3PO_4	PhI(TMP)OTs (**4a**)	-	1,4-dioxane	31
10	CuI	K_2CO_3	PhI(TMP)BF_4 (**4d**)	-	1,4-dioxane	32
11	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	-	1,4-dioxane	34
12	CuI	K_2CO_3	PhI(TMP)TFA (**4f**)	-	1,4-dioxane	43
13	CuI	K_2CO_3	Ph_2IOTf (**4e**)	-	1,4-dioxane	43
14	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	OTf	1,4-dioxane	a: 4 b: 36[c]
15	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	Toluene	nd
16	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	Acetonitril	10
17	CuI	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	Acetic acid	nd
18	CuI[d]	K_2CO_3	PhI(TMP)OTs (**4a**)	-	1,4-dioxane	53
19	CuI[d]	K_2CO_3	PhI(TMP)OTs (**4a**)	BF_4	1,4-dioxane	95, 63[b]

[a] Yield measured with 2,4,6-trimehoxybenzealdehyde as internal standard in ^{1}H NMR analysis of crude.
[b] Isolated yield.
[c] 3 eq. NaOTf instead of 10 eq.
[d] 1 eq. of catalyst.

The problems with the internal standard continued into study 3, but now a new problem. A reaction was repeated three times, with all the same conditions (entry 8). The internal standard gave the yields a: 108, b: 106 and c: 53 %. The yield is obviously not over 100 %, but we did not trust the 53 % yield either. It was necessary to isolate the yields, and these were only b: 5 and c: 8 %. In these reactions, it is an unusually high uncertainty in the measurements. It is important in an internal standard measurement, that the mixtures are homogeneous. For some reason, with this combination of reactants the solvation in deuterated chloroform was not as good as the other mixtures.

We do not believe there is uncertainty this big in all the other experiments, but we have more trust in the measurements in study 1 and 2, than study 3.

The other copper-catalyzed experiments in study 3 did not give as high calculated yields as the ones in entry 8, the next highest was the reaction reported in entry 5, which gave 65 %. The product in this reaction was also isolated, but gave no satisfactory result. We think, due to entry 3, that reactions with Me_2CyDA needs a base. With TEA as the amine, the reaction is not dependent on a base, but with Me_2CyDA, adding a base is more beneficial. None of the other bases tried, gave better yields than the starting point, potassium carbonate. Me_2CyDA is a secondary amine, TEA is a tertiary amine, and because of the electron density from the substituents, Me_2CyDA is presumed to be a weaker base. This is in accordance with Me_2CyDA needing an additional base and TEA not needing one.

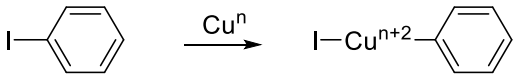
In this study, we wanted to understand more about the anion of the reaction. Since study 2 did not give us indisputable information, we decided to do more experiments investigating this. We did experiments with diaryliodonium salts with the desired anion already exchanged, instead of addition of the anion in a sodium salt. This results in less complex reactions, and we avoided a solvation problem with the measurement of the yields. It is also no longer an uncertainty regarding which anion is coupled to the iodonium cation form the start. There is still different anions in the mixtures, both from the diaryliodonium salt and the copper-catalyst. In the reactions of entry 10-12, only the anion of the diaryliodonium salt is varied and this does not seem to have much impact on the reaction. Using a symmetrical diaryliodonium salt, Ph_2IOTf (**4e**), resulted in yields in the same range, 31-43 % (entry 13). An experiment with NaOTf as an addition was also tried. (We did this because the PhI(TMP)OTf decomposed after a period stored at 0 ºC.) This only decreased the yield (entry 14). We believe this also has to do with the solvation. When we reduced the NaOTf to 3 equivalents instead of 10 we got the same yield-range as the reaction without NaOTf (entry 11), indicating that these anions are affecting the reaction the same way.

Some other solvents were tried. Toluene, which has been used in many of the reaction in the previous studies, did not promote product (entry 15). It seems, that the combination of toluene, Me_2CyDA and $NaBF_4$ is unfavorable. They can separately give

mediocre yields, but together only trace amounts of product. Neither acetonitrile nor acetic acid gave satisfactory results.

Finally, two experiments were done with 1 equivalent of the catalyst, instead of 10 mol% (entry 18-19). We had low hopes for these experiments. In the development of the copper-catalyzed *N*-3-arylation with diaryliodonium salt, Neerbye Berntsen did one experiment with one equivalent copper-catalyst. This resulted in a very low yield, under 10 %.[31] We were therefore surprised to see the good internal standard yield of the mediated *N,N'*-diarylation. We measured the internal standard yields to be 95 and 53 %, for the mediated reactions with and without addition of $NaBF_4$. The yield of the reaction with $NaBF_4$ was reduced from 95 to 63 % when isolating. This, once again shows the uncertainty in these measurements, but also that we can interpret them as trends. The 63 % isolated yield is the highest we found and is therefore the chosen method. This is not the yield we wanted for the reaction, but we have concluded this reaction is too complex to find good yields with this approach. Going forward, it would hopefully be more successful to do a multivariate regression analysis. This could be easier to find patterns and this could lead to better results.

To attempt to explain why the mediated reaction works better than the catalyzed, we need to return to the mechanism. We presume the mechanism of the *N,N'*-diarylation is the same as in the *N*-3-arylation reaction developed by the Sandtorv group. The proposed mechanism (presented in section 1.2) is a cycle with deprotonation of hydantoin, oxidative addition and reductive elimination. 2,4,6-Trimethoxyphenyl iodide is a byproduct of this cycle.[25] It is known that copper can react with phenyl iodide in an oxidative addition (Scheme 3.3). In these type of reactions, it is believed the oxidation numbers of copper are +1 and +3.[48]



Scheme 3.3: Reaction between phenyl iodide and copper catalyst.[48]

The question is; can copper react with TMPI in the same way as other aryl iodides in copper-catalyzed coupling reactions (Figure 3.1)? First of all, we have not seen the formation of the byproduct 3-(2,4,6-trimethoxyphenyl)hydantoin (Scheme 3.4).[31] As far as we know, no copper-catalyzed coupling reaction with TMPI has been reported.

However, this do not mean that copper and TMPI not interact. TMPI is both electronically and sterically different form phenyl iodide, but we do not see any reason why they cannot react.

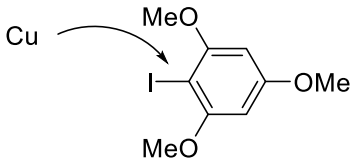
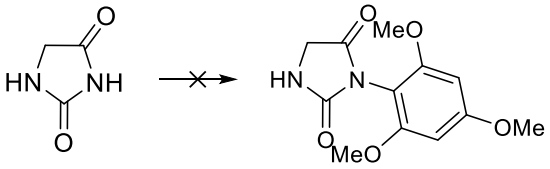
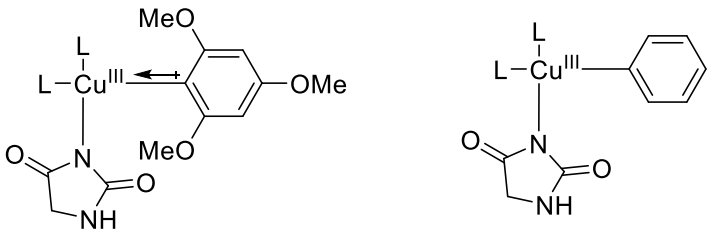


Figure 3.1: Reaction between copper and TMPI.



Scheme 3.4: 3-(2,4,6-Trimethoxyphenyl)hydantoin has not been observed as a product of the reactions.

If we assume copper reacts with TMPI, we do not know how this complex would be or if hydantoin can correlate as well (Figure 3.2). Using basic chemical principals, we can argue that the TMP group will donate electrons to the highly energetic copper +3, resulting in a more stable complex. If all these assumption are correct, the more stable complex is presumed to have a longer lifetime. This will result in the copper being occupied.



Pressumed more stable Pressumed less stable

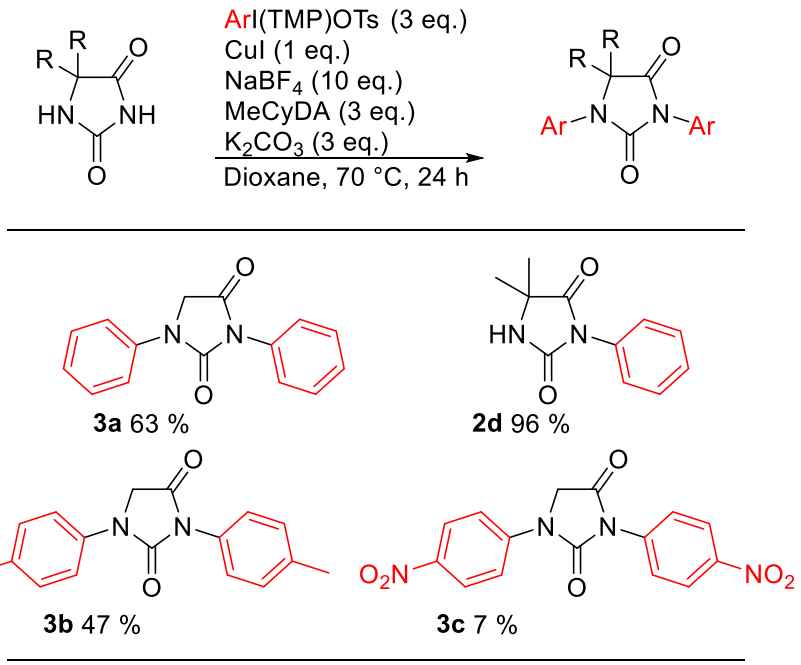
Figure 3.2: Complex of TMP and phenyl coupled to the copper atom.

Diaryliodonium salts can decompose over time in the reaction mixture.[31] Increasing the reaction time from 24 hours to seven days, gives the same results. Meaning no diaryliodonium salt is left and the decomposition is finished after 24 hours. This means if the coupling reaction takes too much time, the diaryliodoniumsalt will decompose before the coupling happens. In this project, hydantoin needs to perform the coupling two times. At the stage of the *N*-1-arylation, it could be a competition between the

desired reaction and formation of the complex with TMP. This can be an explanation of why the reaction works better with a bigger amount of copper. To clarify, we have used 1 equivalent of copper compared to hydantoin, and therefore 0.5 equivalent compared to *N*-H reaction sites. This means that the copper has been regenerated, since the yield is over 50 %.

Scoping of the one-pot method

After a conclusion of the conditions of the *N,N'*-diarylation reaction, a lite scope was done (Scheme 3.5). In addition to **3a**, three other reactions were attempted. We wanted to try the reaction on a C-5-substitited hydantoin and chose 5,5-dimethylhydantoin (**1b**). This reaction did not go as planned. It was anticipated that the *N*-1-arylation could be difficult because of more steric hindrance, and we could therefore end up with a mixture of *N*-3- and *N,N'*-diarylated product. However, the steric effect was significantly bigger than thought, and 96 % yield of the *N*-3-arylated product (**2d**) was therefore isolated. It is known that sterically groups on the C-5 atom will promote reaction on *N*-3 over *N*-1, so this is not shocking. It is worth noting that this is a significantly higher yield for synthetization of this molecule, compared to the copper-catalyzed *N*-3-arylation reaction with diaryliodonium salts developed by the Sandtorv group and the copper mediated *N*-3 arylation reaction by Petite, Evano and co-workers.[25,27]

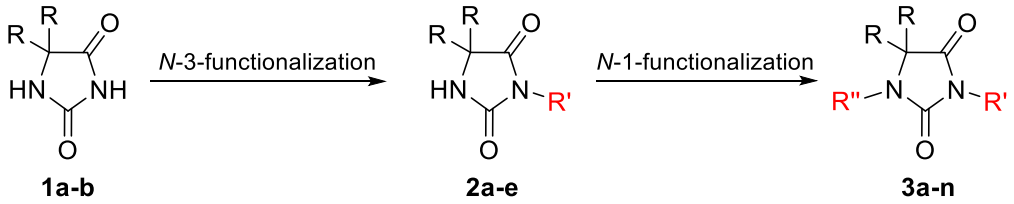


Scheme 3.5: Scope and limitations of the mediated *N,N'*-diarylation of hydantoins.

Reactions with other aryl groups were also tested; 4-tolyl and 4-nitrophenyl. In these reactions the *N,N'*-diarylated product was produced, but in significant lower yields than the reaction with phenyl groups (Scheme 3.5). Regarding the low yield of **3c**, it is not unusual that coupling reactions with as electron deficient groups as 4-nitrophenyl, give lower yields. The yield of the *N*-3-arylation reaction developed by the Sandtorv group reduces from 79 to 59 %, with 4-nitrophenyl instead of phenyl.[25] The reduction of the yield seen in the *N,N'*-diarylation is significantly bigger than in the *N*-3-arylation, but considered the coupling reaction of two electron deficient groups, it is not that surprising.

3.2 Two-step reaction – Method B

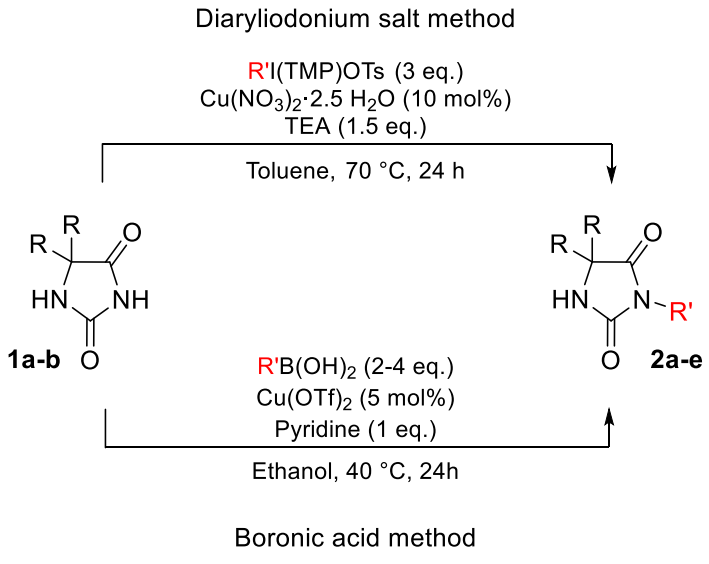
Method B consists of two steps, first the *N*-3-, then the *N*-1-functionalization (Scheme 3.6). In this chapter, different approaches will be discussed and compared. The base of this method is the two studies published by the Sandtorv group.[25,32]



Scheme 3.6: The general reaction of method B.

N-3-Functionalization

Both the diaryliodonium salt method[25] and the boronic acid method[32] have been used to functionalize *N*-3 in hydantoins (Scheme 3.7). Problems with the isolation have occurred with both methods. This resulted in different yields of some of the molecules than reported. Both methods can be used to arylate hydantoin, but the boronic acid method can alkenylate as well.

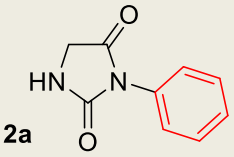
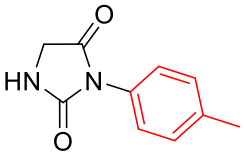
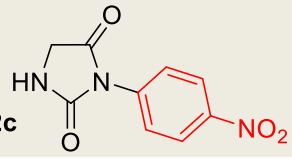
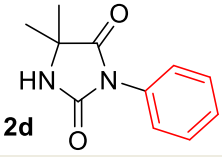
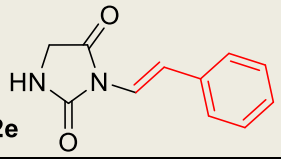


Scheme 3.7: Diaryliodonium salt method and the boronic acid method for *N*-3-functionalization of hydantoins.[25,32]

The result of the *N*-3-functionalization reactions can be seen in Table 3.7. Compound **2a** was first synthesized with both methods. The reported yield was not recreated in

the diaryliodonium salt method and was reduced from 79 to 39 %.[25] With these methods, there are many byproducts and they have R_f-values close to the products. This results in relatively long columns in the isolation, which again can lead to bigger loss of product, depending on personal laboratory techniques. This can explain a little decrease in the product yield, but we do not know why the yield was reduced to that degree.

Table 3.7: Yield of different *N*-3-fynctionalized hydantoins.

Molecule	Yield - diaryliodonium salt method[b]	Yield - boronic acid method[c]
 **2a**	39 %	15 %
 **2b**	63 %	
 **2c**	36 %	
 **2d**	71 % 96 %[a]	
 **2e**		76 %

[a] Mediated
[b] Conditions: Hydantoin **1a-b** (0.2 mmol, 1 eq.), ArI(TMP)OTs **4a-c** (0.6 mmol, 3 eq.), $Cu(NO_3)_2 \cdot 2.5\ H_2O$ (0.02 mmol, 10 mol%), TEA (0.3 mmol, 1.5 eq.) and toluene (2 mL).
[c] Conditions: Hydantoin **1a** (0.4 mmol, 1 eq.), boronic acid (1.6-1.2 mmol, 3-4 eq.), $Cu(OTf)_2$ (0.02 mmol, 5 mol%), pyridine (0.4 mmol, 1 eq.) and EtOH (2 mL).

In the synthesis of **2a** with the boronic acid method, both the *N*-3- (**2a**) and *N,N'*-diarylated (**3a**) products are present, with a distribution of 58 to 42 % relative to each other measured in crude mixture ^{1}H NMR (Figure 3.3). This is a larger amount of the diarylated product than reported by the Sandtorv group.[25] Worth noticing is the

absence of the reactant (hydantoin (**1a**) signal at 4.05 ppm in $CDCl_3$). Compound **1a** is poorly solved in chloroform and the amount of it can therefore be misleading. **2a** and **3a** have relatively different polarity and can be separated on a column, but boronic acid and byproducts from the arylating agent will interfere with **2a**. This is because the boronic acid decompose after interacting with the silica. This makes it more difficult to isolate the product and we therefore tried to decompose the boronic acid before we started the column. The quenching was done with hydrogen peroxide.[49] We ended up isolating 15 % of **2a**, but lost parts of the product in the isolation, on the column and maybe also in the quenching. We believe the yield of the product made in the reaction is bigger than the isolated yield.

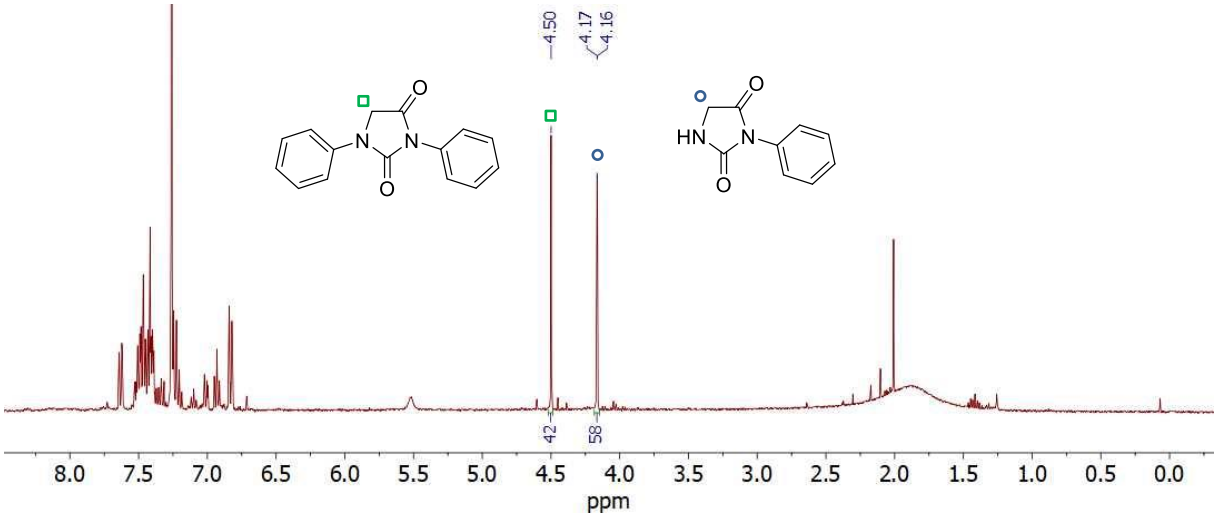


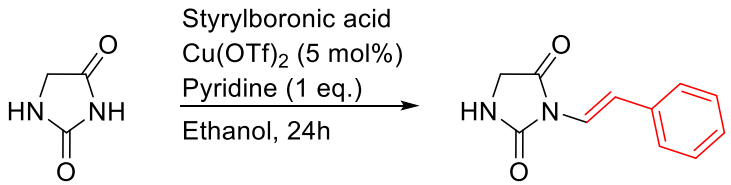
Figure 3.3: ^{1}H NMR (400 MHz, $CDCl_3$) of crude product of the boronic acid reaction synthesizing 3-phenylhydantoin (**2a**). Signal from C-5 in *N*-3-hydantoin marked with blue circle and C-5 in *N,N'*-diphenylhydantoin (**3a**) marked with green square.

With the complications of the boronic acid method and the lower isolated yield, we decided to continue with the diaryliodonium salt method for the synthesis of other *N*-3-arylated hydantoins. This includes the synthetization of **2b**, **2c** and **2d**, with the yields 63, 36 and 71 %, receptively. Compound **2c** gave lower yields than expected, 59 % is reported with the same method.[25] A little amount of the *N,N'*-diarylated product was observed, but this alone cannot explain the low yield. The method of synthesizing was the same.

Compound **2e** was synthesized by the boronic acid method. The reaction has been repeated, and the yield has variated. Both the equivalence of the boronic acid, the temperature and the scale were varied (Table 3.8). It seems like increasing the scale is acceptable in regards to the yield of the reaction. However, the Sandtorv group has

seen a variation in the result of these reactions. We assume this is because of the use of two different batches of the reactant (*E*)-styrylboronic acid. One of the bought (*E*)-styrylboronic acids is undeniably not clean, as seen in the ^{1}H NMR spectrum (Figure 3.4). It is reason to say polymerization of the styrylboronic acid has happened. This is believed to be the reason for the difficulties with the isolation of some of the molecules synthesized from (*E*)-styrylboronic acid. In isolating some of the products, hexane was used in the eluent in column chromatography. The polymer has likely a good solvability in hexane and this could result in the polymer being distributed in the whole column. An extraction of the product was done after the column. The impurity, the polymer can be seen in red in Figure 3.4. The same broad signal is in the (*E*)-styrylboronic acid (green) and as a small impurity in the product of the reaction (blue).

Table 3.8: Yields of reactions synthesizing **2e**.



1a **2e**

#	Eq. of styrylboronic acid	Temperature (ºC)	Scale (mmol)	Yield (%)
1	2	25	0.4	48
2	2	25	0.8	59
3	2	25	1.5	43
4	4	40	0.4	76

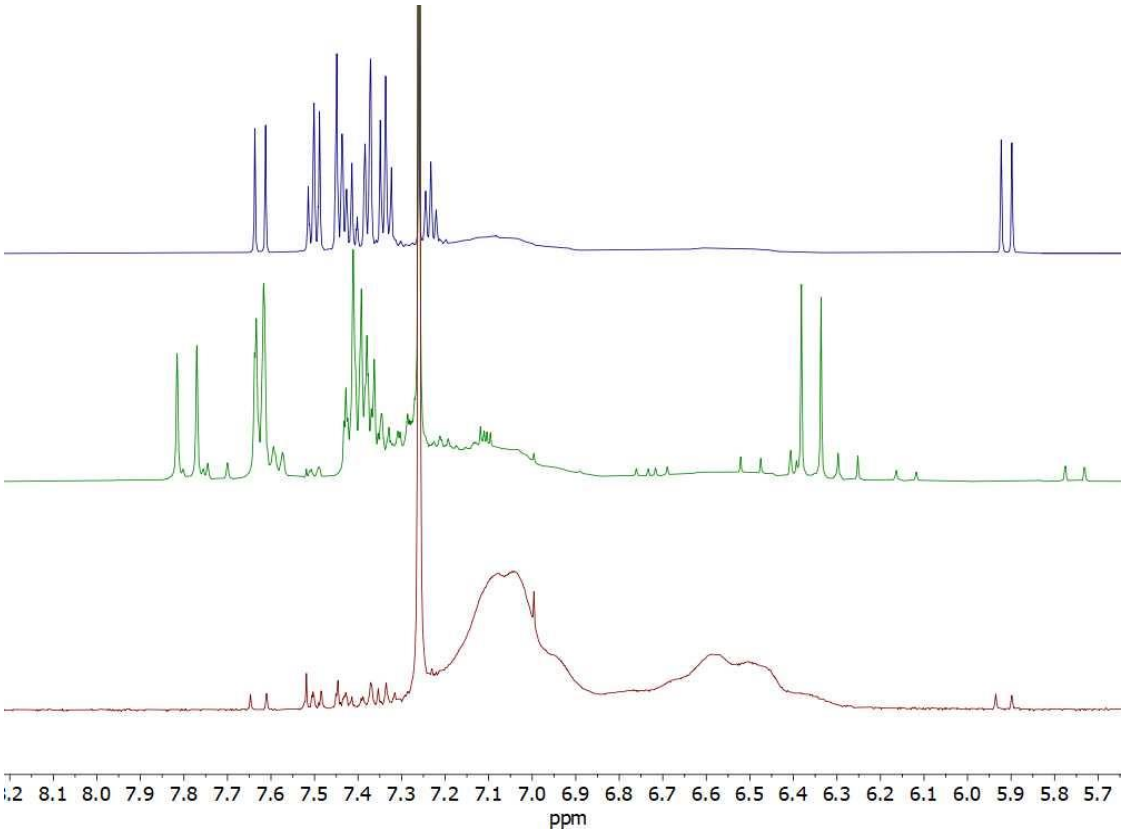
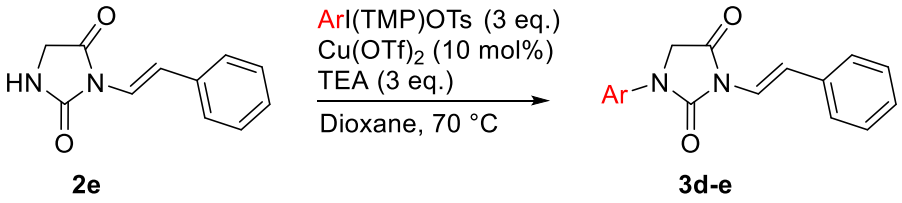


Figure 3.4: ^{1}H NMR (600 MHz, $CDCl_3$) of one of the products syntesized in blue. ^{1}H NMR (400 MHz, $CDCl_3$) of the reactant (*E*)-styrylboronic acid in green. Both spectra contains the polymer: ^{1}H NMR (400 MHz, $CDCl_3$) in red (small amount of product of reaction).

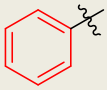
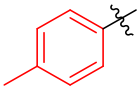
N-1-Functionalization

Functionalization of *N*-1 on hydantoin is more difficult than the *N*-3 position because of the weaker acidity, and we have therefore used more time on this project. With the *N*-1-arylation of **2e**, we wanted to compare different methods. With diaryliodonium salt as the arylation agent, the yield of **3d** was 45 % (Table 3.9). This is tolerable, considering it is a new molecule. Using the same method to synthesize **3e** the yield decreased to 18 %. **3d** and **3e** were not pure after column chromatography, and an additional purification step was needed. This can be part of the reason of the low yields.

Table 3.9: *N*-1-arylation with diaryliodonium salts as arylation agent.

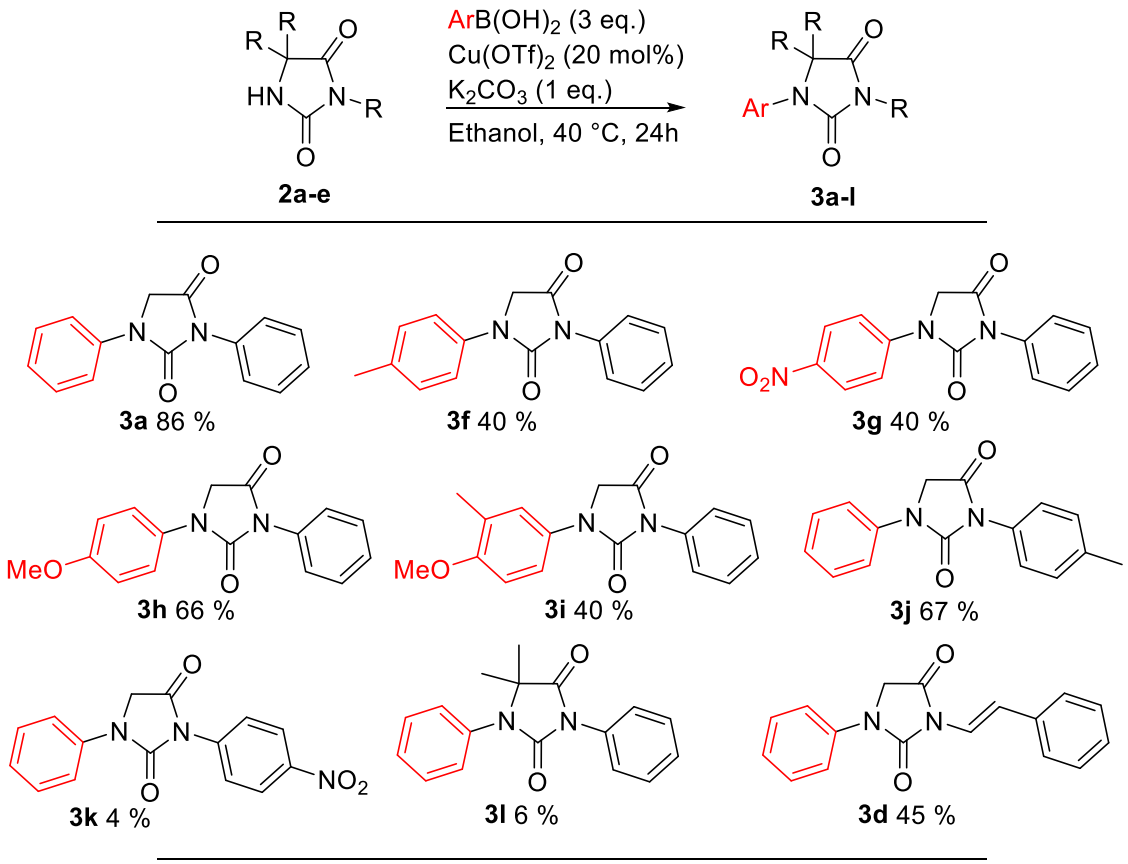


2e **3d-e**

#	"Ar" moiety	Time	Yield (%)
1 (**3d**)		24 h	45
2 (**3e**)		26 h	18

N-1-arylation with boronic acid as the arylating agent was also tried, and a new method developed in the group was used.[50] The method is a copper-catalyzed reaction with 20 mol% copper(II)triflate. This gave the same yield as the diaryliodonium method for synthesizing **3d**, 45 %.

The same method was used to make **3a**, which synthesized the product in 86 % yield. Because of this good yield, investigation of the limitations of the method was done. The result of this can be seen in Scheme 3.8. None of the other molecules were synthesized in as good yields. The desired product was observed in all of the reactions tried, ranging from poor, to moderate to good yields.



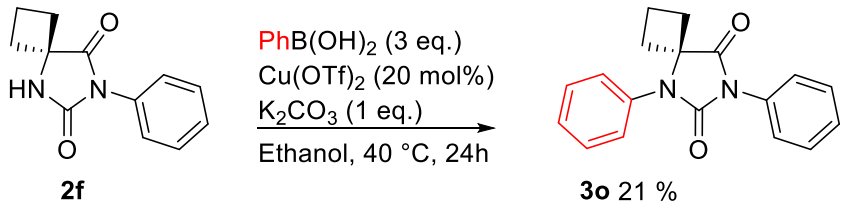
Scheme 3.8: *N*-1-arylation with boronic acid.

If the decomposition of the boronic acid is the critical point of the reaction, the variations of the aryl group will have an impact. Aryl boronic acids can decompose in basic solution, especially *ortho*-substituted and electron deficient groups.[42,43] Arylation of hydantoin (**1a**) has proven to be very difficult with *ortho*-substituted aryl groups.[25,27] This is a general limitation with boronic acids as arylation agent.[33] We have not tested the reaction with *ortho*-substituted aryl groups, but we expect no or little reaction for these molecules. The low stability of electron deficient aryl groups can explain the reduced yield of **3g**. The method seems to tolerate electron rich aryl group, with **3h** as an example. However, we do not have an explanation for the decreased yield of **3i**. The yield of 40 % for the synthesizing the relatively electronically neutral compound **3f** is lower than we expected. We have observed the method to be relatively fragile, working well on only a few molecules.

The very poor yield of **3k** is a mystery. Compared to the synthesis of **3a**, only the starting material, the *N*-3-arylated hydantoin, is different. The acidity of the *N*-1 proton could have affected the reaction at a larger scale. However, it is not likely

that the addition of a nitro group that fare from the reaction site will change the acidity much. Small amount of product was observed in other fractions after the column chromatography. With a better optimized purification, the yield could have been increased, but only by a few percent. Compounds **3a**, **3d**, **3j** and **3k** have all added a phenyl group in the reaction, but have different aryl groups at the *N*-3 positon in the staring materials. The yields of these are varied much, from 4 to 86 %. This means that the substituent on the *N*-3 in hydantoin is of great importance for the outcome of the reaction. We believe that this is because of the relatively mild reaction conditions. A small change in the reaction conditions will give a small difference in the energy barrier. With the energy used in the reaction being as low as it can in the first place, a small difference will have a large impact on the outcome of the reaction.

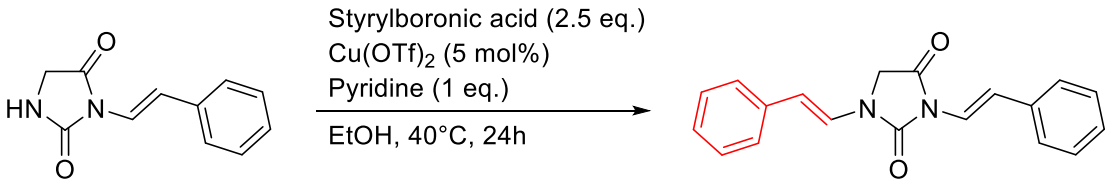
The synthesis of **3l** gave an interesting outcome. Comparing it to the synthesis on **3a**, the reaction is the same except the two methyl groups at the C-5 position of the hydantoin. The decrees of the yield is considerable. The *N*-1-arylation is significantly harder when the C-5 is functionalized. This is in accordance with the result of the *N*-1-arylation of a spiro-hydantoin also tried in the Sandtorv group (Scheme 3.9).[51] This is believed to be because of steric factors, making it harder to correlate to the copper atom and perform the coupling reaction. Boronic acid is a mild arylating agent, and is probably not strong enough to overcome the larger barrier to perform the reaction.



Scheme 3.9: *N*-1-arylation of **2f** to **3o** with the boronic acid method.[51]

Early work in the Sandtorv group has proven that the addition of an oxidant is not necessary for the copper-catalyzed *N*-3-arylation with boronic acids.[52] An important part of the reaction is therefore the presence of air. Known from other copper-catalyzed reactions with boronic acid, is that O_2 is oxidizing and regenerating copper.[33] This is necessary to have a catalytic cycle and it makes the use of only 20 mol% copper(II)triflate possible.

We know the *N*-3-arylation reaction without base is performed to a degree.[32] However, the yield is increased with ether amines or other bases present. Compared to the reaction on the less acidic *N*-1 position, the base is even more important. In the *N*-3-arylation, pyridine in used as the base. This is exchanged for potassium carbonate in the *N*-1-arylation. The combination of air, pyridine and copper can oxidize boronic acids, but this is a slow proses.[53] The believe is that in the *N*-3-functionalization, the proton is acidic enough that the reaction happens before the boronic acid is destroyed. In the *N*-1-functionalization, the proton is less acidic, the reaction is slower and therefore the oxidation of the boronic acid has occurred before the coupling reaction. This theory is strengthened by the low yield of the reaction seen in Scheme 3.10. Here are the combination of copper-catalyst, pyridine and air used to functionalize *N*-1.

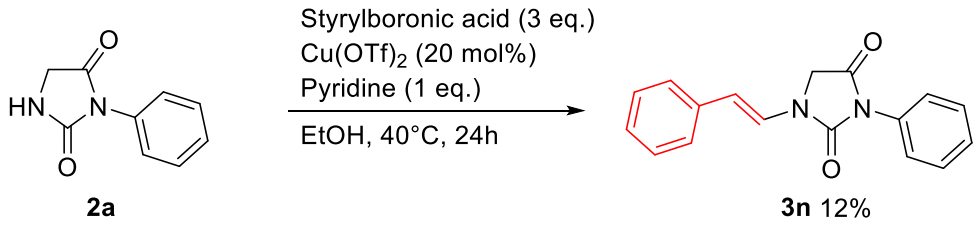


2e **3m** 13 %

Scheme 3.10: Copper catalysed reaction from **2e** to **3m** using pyridine.

The synthesis of **3m** is complex. Pyridine is destroying the reaction, but the use of other bases, as in *N*-1-arylation, is not helping. It is believed that it is the boroxine of the boronic acid, is the active species. With arylboronic acids, the equilibrium is shifted enough against the boroxine that the reaction can proceed. With electron deficient aryl groups, the equilibrium is less towards the boroxine. Adding the pyridine helps stabilizing the boroxine, the equilibrium is shifted, and the reaction can proceed. The same applies for (*E*)-styrylboronic acid, but it is even less of the boroxine originally. The addition of pyridine works well in the *N*-3-functionalisation and is necessary for the reaction of (*E*)-styrylboronic acid. However, this is not the case in the *N*-1-functionalization. This results in the combination of the reaction not being successful ether with or without pyridine. Testing of other boroxine-stabilizing amines have not been done. To stop the decomposition of the boronic acid, but still have pyridine in the reaction, we could have used inert atmosphere. However, since the regeneration of copper is done by oxygen, we presume this would not work without stoichiometric amounts of copper catalyst.

The same type of reaction as for **3m,** was used to synthesize **3n** (Scheme 3.11). A couple of changes were made, the amount of copper catalyst was increased from 5 to 20 mol% and the (*E*)-styrylboronic acid to 3 equivalents. This reaction performed similar to the synthesis of **3m**. We have not tried to do the reaction with boroxine as the staring materiel instead of boronic acid. This can increase the reactivity of the reaction. However, depending on the rate of the equilibrium, the boroxine could be converted to the boronic acid before the coupling reaction starts, resulting in only small differences.



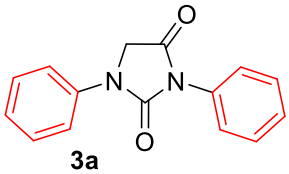
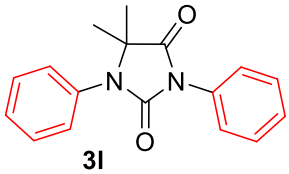
2a **3n** 12%

Scheme 3.11: Copper catalysed reaction from **2a** to **3n** using pyridine.

3.3 Comparison of methods

An overview of the yields of the synthetization of **3a** and **3l**, with different methods used in this thesis compared to the method by Petit, Evano and co-workers[27], is presented in Table 3.10. Starting with C-5-unsubstituted hydantoin and comparing the total yields of **3a,** it is clear that the one-pot (method A) is best. It is a good method when a hydantoin with the same aryl group on the two nitrogen atoms is desired. The method is relatively fragile, with, for example, the yield decreasing with electron deficient aryl groups. Reaction with electron rich aryl group is yet to be tested, it is believed that it could be successful, based on the performance in similar reactions.

Table 3.10: Yields of the different methods synthesizing **3a** and **3l**.[27]

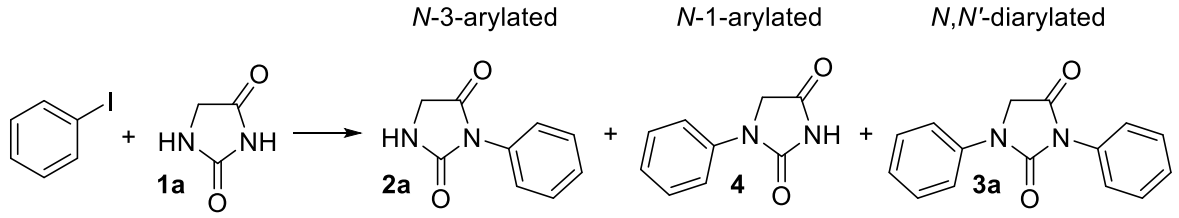
	 **3a**	 **3l**
Method A One-pot	63 %	nd
Method B Two-step	34 %	4 %
Petit, Evano and co-workers[27]	21 %	66 %

The advantage with method B is the possibility for synthesizing hydantoins with different aryl groups on the two nitrogen atoms. The total yield is relatively low and varies much, in the range under 5 % up to 42 %. The low yield is partly acceptable with many of the molecules not being synthesized before. All molecules synthesized with method A, can theoretically also be made with method B. A large advantage of method A is the reduced time. With only one reaction step, instead of two, the time spent purifying is reduced by hours. Low yields of step one in method B, resulted in the first step needed to be repeated to have enough starting material for step two. This makes

the proses even longer. However, performing reactions separately and then do the purification of them combined is a possibility.

The results of Petit, Evano and co-workers *N*-3-arylation method on a bare hydantoin can be seen in Table 3.11. They isolated 21 % of the *N,N'*-diarylated (**3a**) and 31 % of the *N*-1-arylated product (**4**). The absence of **2a** is surprising considering the *N*-3 proton is the most acidic, and is believed to be functionalized first. Tests of the method done by fellow group member L. Neerbye Berntsen have shown *N*-3-arylated hydantoin as a product as well. The ^{1}H NMR of the crude mixture contained *N*-3-arylated (**2a**), *N*-1-arylated (**4**) and *N,N'*-diarylated (**3a**) hydantoin as shown in Table 3.11 and Figure 3.5. Neerbye Berntsen lost the *N*-3-arylated product in the work-up and predicts Petit, Evano and co-workers did the same.[31]

Table 3.11: Yields of the different products in the arylation of bare hydantoin.[27,31]



	N-3-arylated	*N*-1-arylated	*N*,*N*'-diarylated
Petit, Evano and co-workers - isolated yield:		31 %	21 %
Berntsen - relative intensity crude:	24 %	38 %	34 %

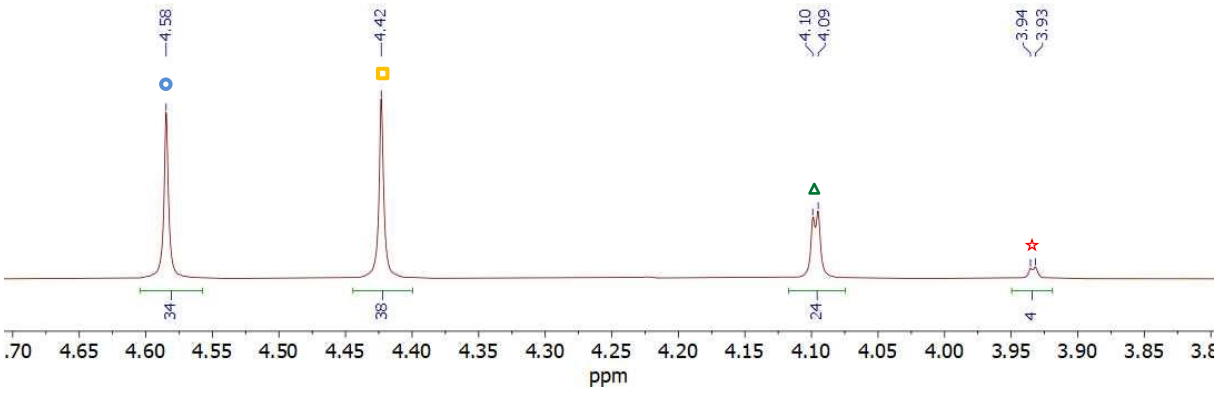


Figure 3.5: ^{1}H NMR (300 MHz, acetone-d_6) Signals of: blue circle – *N,N'*-diarylated (**3a**), yellow sqeare – *N*-1-arylated (**4**), green triangle – *N*-3-arylated (**2a**), red star – starting material –hydantoin (**1a**).[31]

To sum up, the method of Petit, Evano and co-workers is not selective with C-5-unsubstitudet hydantoin (**1a**) as stating material. This results in both reduced yields and a more complex purification because of the additional side products. With the intention of synthesizing C-5-unsubstituted hydantoins the preferred method is ether method A or B, depending on if the aryl groups are the same or not.

Moving on to the C-5-substitited hydantoin **3l** and another outcome. Both method A and B are unsatisfactory. We believe the methods are too mild to overcome the larger energy barrier, compared to C-5-unsubstituted hydantoin. The method of Petit, Evano and co-workers has harder conditions, with both higher temperature and pressure. This makes it easier to promote arylation, hence the total yield of 66 %. The use of aryl iodides, instead of diaryliodonium salts or boronic acids makes it possible to have harder conditions without destroying the arylation agent. However, the use of diaryliodonium salts in method A allows the use of milder conditions. All three methods have therefore their own area of application, method A – C-5-unsibstituted hydantoins with the same aryl groups, method B – C-5-unsubstituted hydantoins with two different aryl groups and the method of Petit, Evano and co-workers – C-5-substituted hydantoins.

3.4 NMR – Structural elucidation

In this chapter, an explanation of the elucidation of the structures synthesized will be presented. Before starting the elucidation, an introduction of the multiplicity system used in this thesis will be given. Many of the structures synthesized have a so-called AA'BB' and/or AA'BB'C system (Figure 3.6).[54] These multiplicity systems have been used because "normal" doublets and triplets cannot be used because of complex correlation, but the AA'BB' and AA'BB'C system can offer more information than simply referring to the signals as multiplets. AA'BB'C is used for phenyl and AA'BB' is used for *para*-substituted phenyl groups. The coupling varies slightly and the multiplicity will therefore also vary. One example of each splitting pattern can be seen in Figure 3.6.

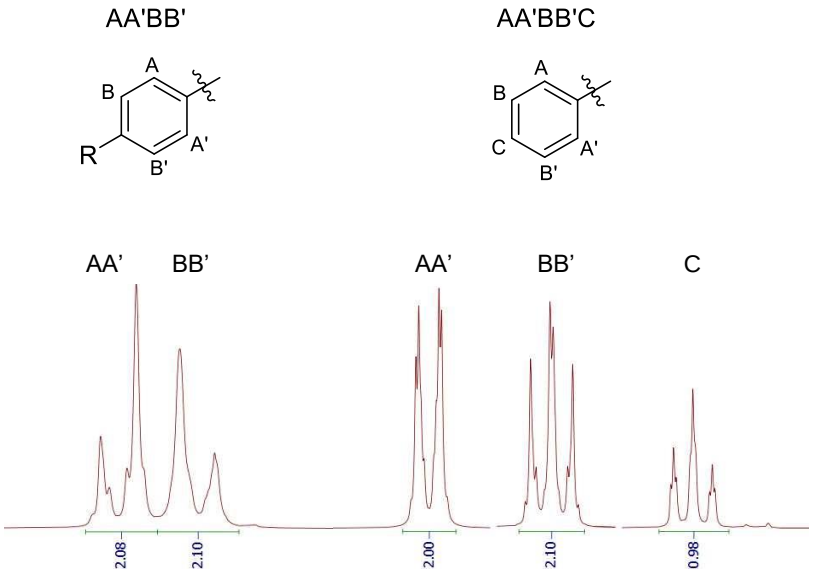


Figure 3.6: AA'BB' and AA'BB'C system with examle of splitting pattern.[54]

1-(4-Nitrophenyl)-3-phenylhydantoin (**3g**) is the molecule used as the example in this elucidation. From the multiplicity in the ^{1}H NMR spectrum of **3g**, a phenyl and a *para*-substituted phenyl is likely (Figure 3.7). Two of the signals overlap slightly, but the integrals are consistent with a phenyl. One of the signals has relatively high chemical shift. This can mean that the group in the *para*-position is the nitro-group, in accordance with the reactant. A signal at 4.56 ppm in the ^{1}H NMR is fitting with the C-5 protons in an *N,N'*-difunctionalized hydantoin. The C-5 protons in hydantoin (**1a**) have the

chemical shift of 4.05 ppm in chloroform, and blocking the NHs results in increase of the shift value.

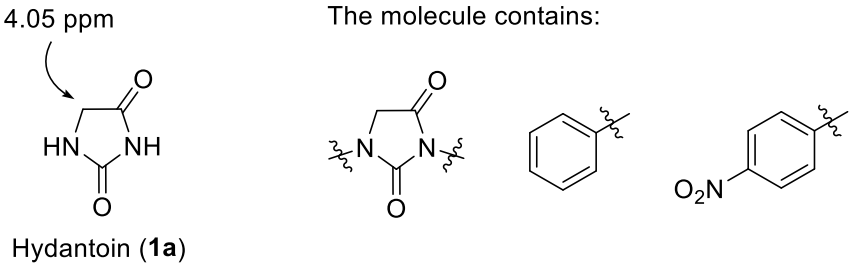


Figure 3.7: The chemical shift of the C-5 protons in hydantoin and the parts of the molecule.

There is a correlation in the NOESY spectrum between the C-5 proton and a signal in the AA'BB' system. This is marked with green circles in Figure 3.8. This means that the 4-nitrophenyl-group is at the *N*-1 position, and the phenyl is at the *N*-3 position. The molecule can be seen in Figure 3.9.

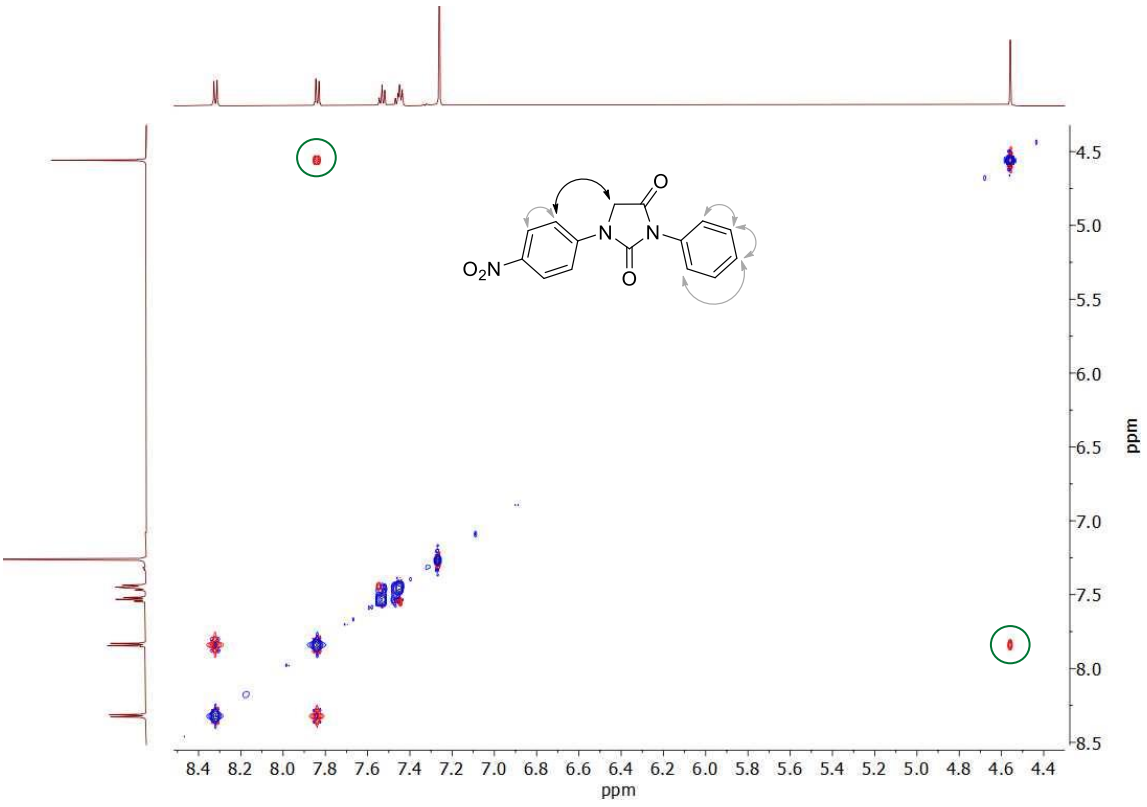
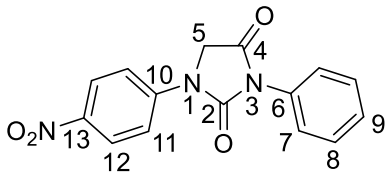


Figure 3.8: NOESY of 1-(4-nitrophenyl)-3-phenylhydantoin (**3g**).



3g

Figure 3.9: illustration of numeration in 1-(4-nitrophenyl)-3-phenylhydantoin (**3g**).

A further elucidation of the atoms in the molecule has been done with a combination of ^{1}H NMR, ^{13}C NMR and the 2D spectra COSY, HSQC and HMBC. The hydrogen and carbon atom elucidation can be seen in Table 3.12 and Table 3.13 receptively.

Table 3.12: Chemical shifts, integrals, multiplicity for hydrogen atoms in 1-(4-nitrophenyl)-3-phenylhydantoin (**3g**).

δ	Integral	Multiplicity	Hydrogen
8.32	2H	BB' in AA'BB'	H12
7.84	2H	AA' in AA'BB'	H11
7.53	2H	BB' in AA'BB'C	H8
7.48-7.42	3H	m	H7 and H9
4.56	2H	s	H5

Table 3.13: Chemical shifts for carbon atoms in 1-(4-nitrophenyl)-3-phenylhydantoin (**3g**).

δ	Carbon
166.2	C4
153.1	C2
143.7	C10/C13
142.9	C10/C13
130.7	C6
129.4	C8
129.0	C9
126.3	C7
125.3	C12
117.7	C11
49.5	C5

The other molecules in the thesis have been elucidated in the same way. The Sandtorv group has not observed the *N*-3-arylated hydantoin reactants to decomposed or rearrange with the environment used in the *N*-1-arylation reactions. This makes us confident the aryl groups are where we intended them to be.

5 Conclusion and further work

The one-pot *N,N'*-diarylation of hydantoin has been investigated in this thesis. We successfully found a new method and used it to synthesize three products. The yields were variating, all below 63 %, but allowed for the synthesis of new molecule. The best reaction conditions were with stoichiometric amounts of copper. The method is limited to C-5-unsubstituted hydantoins and the outcome depends heavily on the aryl group. Even though the method is narrow in scope, it is useful and very time-efficient compared to alternative routes.

The two-step method, first *N*-3- and then *N*-1-functionalization, resulted in a seven new molecules. *N*-3-Arylations with both diaryliodonium salts and boronic acids as coupling partners have been tested, but reproduction of the good yields earlier reported in the Sandtorv group was not entirely successful. A new *N*-1-arylation method was developed in the group, using boronic acid as the arylating agent. As far as we know, this is the first direct arylation of the *N*-1 position in C-5-unsubstituted hydantoins. The limitations of the method have been investigated in this thesis, and it is clear that the method is restricted to C-5-unsubstituted hydantoins. The method is mild and has an easy setup, but is relatively fragile. The yield is highly affected by the aryl groups in both the *N*-3 and *N*-1 positions of hydantoin.

Future work should involve further investigation of the reaction between *N*-3-functionalized hydantoins and (*E*)-styrylboronic acid, as well as the development of a method to alkenylate *N*-1 of hydantoin. Additionally, we think a multivariate regression analysis could be necessary and rewarding to find better conditions for the one-pot *N,N'*-diarylation reaction.

6 Experimental section

General

The chemicals used are from Sigma Aldrich, Flurochem and VWR. NMR-solvents were used as delivered. Hexane and diethyl ether were distilled before use. Toluene was dried using molecular sieves. CH_2Cl_2 was purified using an MB SPS-800 solvent purifier system from MBraun.

Thin layer chromatography was preformed using aluminum plates, 60 F_{254} silica from Merck. Silica 60 (0.040-0.063 mm) was used for manual column chromatography.

^{1}H, ^{13}C and ^{19}F NMR were recorded in $CDCl_3$, DMSO-d_6, CD_3CN or acetone-d_6 using Bruker DPX300 operating at 300 MHz (^{1}H) and 75 MHz (^{13}C), Bruker AVII400, AVIII400 or AVNEO400 operating at 400 MHz (^{1}H) and 101 MHz (^{13}C), Bruker AVI600 or AVII600 operating at 600 MHz (^{1}H) or 151 MHz (^{13}C). All spectra were recorded at 25 ºC. Chemical shift (δ) are given in parts per million (ppm) relative to the solvent used. Reference peaks: $CDCl_3$: 7.24 ppm (^{1}H), 77.0 ppm (^{13}C), DMSO-d_6: 2.50 (^{1}H), 39.5 ppm (^{13}C), CD_3CN: 1.94 ppm (^{1}H), 1.3/118.3 ppm (^{13}C), acetone-d_6: 2.05 (^{1}H), 29.8 ppm (^{13}C) as reported by Gottlieb et al.[55] ^{1}H NMR multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), multiplet (m). ^{13}C NMR signals are singlets, unless marked as q (quartet). Coupling constants (*J*) are reported in hertz (Hz). Resonances that display second order effects are labeled using the appropriate Pople nomenclature.[54] SHSQC and SHMBC with a width of 10 ppm in F2, have been recorded if signals in HSQC and HMBC have overlapped. ^{15}N chemical shifts were obtained indirectly through ^{1}H–^{15}N HMBC experiments.

When enough product was synthesized, FTIR spectra were recorded in ATR (Bruker ATR A225/Q) on a Vertex 80 Bruker infrared spectrophotometer, equipped with a DTGS detector; 32 interferograms (recorded at 4 cm^{-1} resolution) were typically averaged for each spectrum.

High-resolution mass spectra (HRMS) were obtained by electron spray ionization (ESI) on Bruker maXis II ETD QTOF spectrometer by Osama Sekiguchi, Lina Aarsborg, Sverre Løyland and Erlend Steinvik.

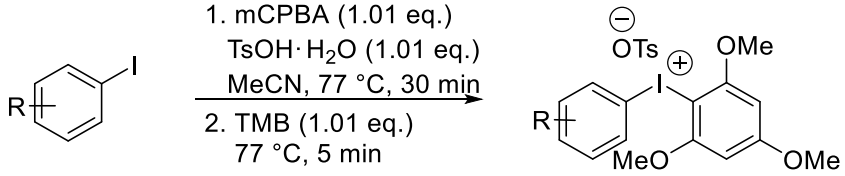
Melting point for crystalline compounds were measured on a Stuart SMP10 melting point apparatus and are reported uncorrected.

5.1 Diaryliodonium salts

Diaryliodonium salts were prepared according to literature procedures.[39-41]

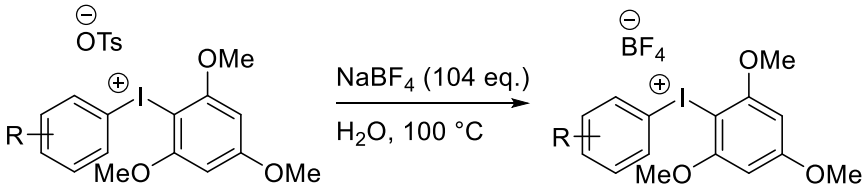
A) Preparation of aryl(2,4,6-trimethoxyphenyl)iodonium tosylates[39]

The experiments were run on a: 5 mmol or b: 10 mmol scale.



Aryl iodide (a: 5 mmol, b: 10 mmol, 1 eq.) and acetonitrile (a: 5 mL, b: 10 mL) were measured and transferred to an a: 50 mL or b: 100 mL round bottom flask. The mixture was stirred with a magnetic stir bar when *p*-toluenesulfonic acid monohydrate (1.01 eq.) and *m*-CPBA (1.01 eq.) were added. A cooler was attached, and the mixture was refluxed on a heating block (77 °C) for 30 minutes. The cooler was removed when 1,3,5-trimethoxybenzene (1.01 eq.) was added, the mixture was refluxed for 5 more minutes (77 °C). The solution was cooled to room temperature and the solvent was removed. The crude product was triturated with diethyl ether (5 mL). The powder was isolated with vacuum filtration and washed with diethyl ether (3 x 5 mL). The product was dried under high vacuum.

B) Preparation of aryl(2,4,6-trimethoxyphenyl)iodonium tetrafluoroborate from diaryliodonium tosylates[39]

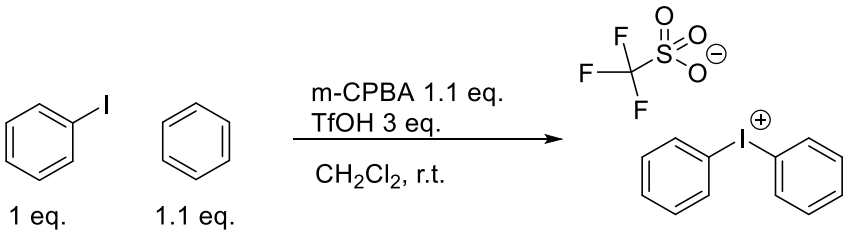


50 mL water was boiled in a beaker and iodonium salt (1 mmol, 1 eq.) was added. The mixture was stirred until the salt was dissolved. The solution was taken of the heat and the salt with desired anion (104 eq.) was added in one portion and stirred for a couple

of minutes. The mixture was cooled to room temperature and further in an ice bath. The mixture was suction filtrated and washed with water (ca. 3 x 30 mL) and diethyl ether (ca. 3 x 30 mL). The product was dried under high vacuum.

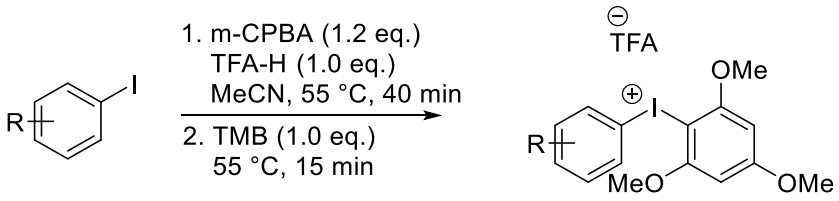
C) Preparation of diphenyliodonium triflate[41]

The experiments were run on a: 2.3 mmol or b: 5.0 mmol scale.



An a: 50 mL or b: 100 mL round bottom flask was dried in an oven for about 30 min before *m*-CPBA was added. It was dried on a vacuum pump for at least an hour. CH_2Cl_2 (a: 10 mL, b: 22 mL) and a magnet was added and a septum was put on. Iodobenzen (a: 2.3 mmol, b: 5.0 mmol, 1 eq.) and benzene (1.1 eq.) were added thru the septum with a syringe. The mixture was cooled to 0 ºC with an ice bath before triflic acid (3 eq.) was slowly added with a syringe thru the septum. After 2 min, the ice bath was removed and the mixture was stirred in r.t. for 10 min. The solvent was removed and (a: 10 mL, b: 15 mL) diethyl ether was added. The mixture was stirred for 10 min before it was placed in a freezer for at least 30 min. The mixture was filtered and washed with diethyl ether.

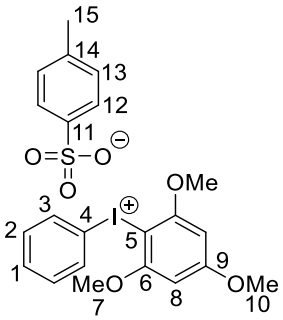
D) Preparation of aryl(2,4,6-trimethoxyphenyl)iodonium trifluoroacetate[40]



Aryl iodide (2 mmol, 1 eq.) and acetonitrile (2 mL) were measured and transferred to a 10 mL round bottom flask. The mixture was stirred with a magnetic stir bar when

m-CPBA (1.2 eq.) was added. Trifluoroacetic acid (1 eq.) was added dropwise. A cooler was attached, and the mixture was refluxed on a heating block (55 °C) for 40 minutes. The cooler was removed, 1,3,5-trimethoxybenzene (1 eq.) was added, and the mixture was refluxed for 15 more minutes (55 °C). The solution was cooled to room temperature and the solvent was removed. The crude product was triturated with diethyl ether (2 mL). The powder was isolated with vacuum filtration and washed with diethyl ether (3 x 2 mL). The product was dried under high vacuum.

Phenyl(2,4,6-trimetoxyphenyl)iodonium tosylate (4a)



[936326-60-2]

4a was prepared according to general procedure A on 10 mmol scale and obtained as a pale, pink solid (5.13 g, 9.47 mmol, 94%).

4a was prepared according to general procedure A on 5 mmol scale and obtained as a pale, pink solid (1.76 g, 3.25 mmol, 65%).

This compound presents a 1: AA'BB'C and 2: AA'BB' system.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (1AA', 2H, H3), 7.61 (1C, 1H, H1), 7.50 – 7.43 (m, 4H, H2 and H12), 7.10 (2BB', 2H, H13), 6.46 (s, 2H, H8), 3.94 (s, 6H, H7), 3.86 (s, 3H, H10), 2.28 (s, 3H, H15).

^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6 (C9), 159.8 (C6), 146.3 (C11), 138.0 (C14), 134.8 (C3), 132.0 (C2), 132.0 (C1), 128.5 (C13), 126.0 (C12), 116.6 (C4), 92.5 (C8), 87.5 (C5), 57.8 (C7), 56.6 (C10), 21.2 (C15).

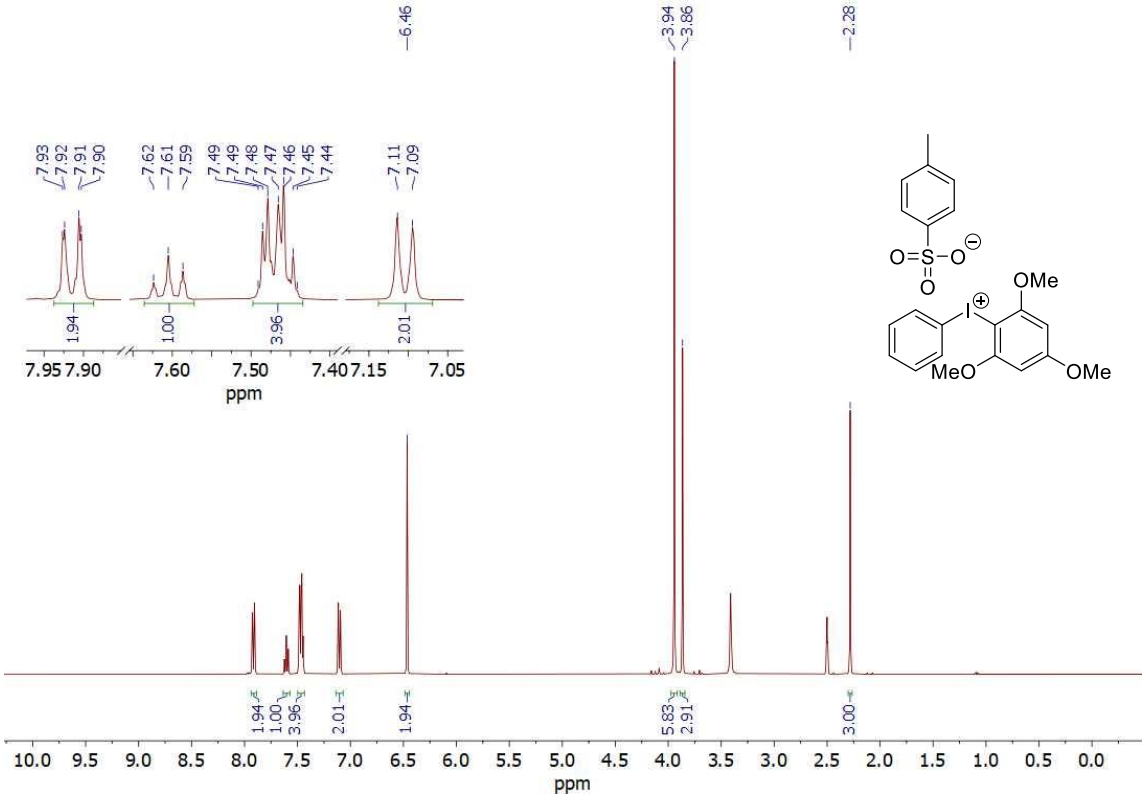
HRMS (ESI) *m/z* [M - OTs]$^{+}$: Calcd. for $C_{15}H_{16}IO_3^{+}$: 371,0139, found: 371,0138.

IR (ATR): ṽ (cm^{-1}) 3089 (w), 2993 (w), 2950 (w), 2841 (w), 1583 (s), 1452 (m, br), 1413 (m), 1342 (m), 1234 (s), 1172 (s, br), 1116 (s), 1008 (s), 908 (m), 840 (m), 811 (s), 740 (s), 675 (s).

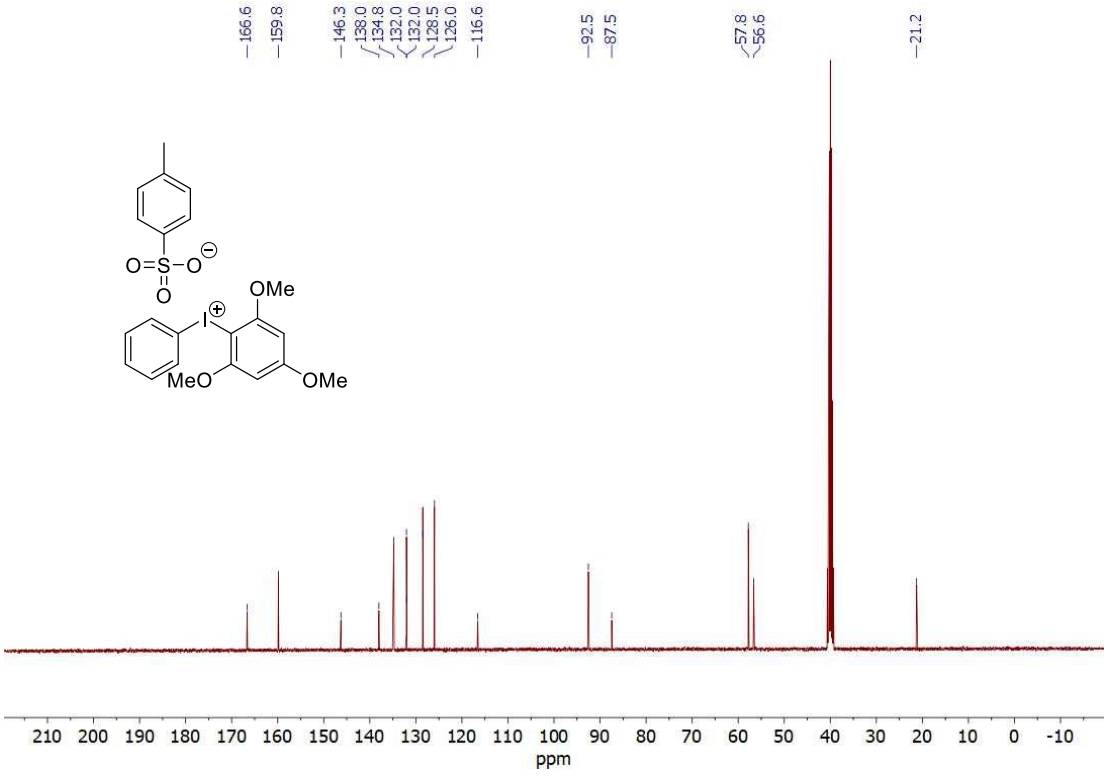
Melting point: 188-200 °C

The spectroscopic data is in accordance with the literature.[39]

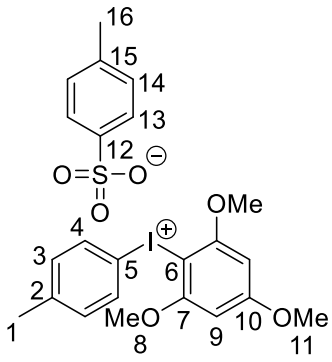
^{1}H NMR spectrum of **4a** (400 MHz, DMSO-d_6)



^{13}C NMR spectrum of **4a** (101 MHz, DMSO-d_6)



4-Tolyl(2,4,6-trimethoxyphenyl)iodonium tosylate (4b)



[1868172-98-8]

4b was prepared according to general procedure A on 10 mmol scale and obtained as a pale, yellow solid (4.99 g, 8.96 mmol, 92 %).

This compound presents an AA'BB' system.

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.79 (AA', 2H, H4), 7.47 (BB', 2H, H13), 7.27 (BB', 2H, H3), 7.10 (AA', 2H, H14), 6.45 (s, 2H, H9), 3.94 (s, 6H, H8), 3.86 (s, 3H, H11), 2.32 (s, 3H, H1), 2.29 (s, 3H, H16).

^{13}C NMR (151 MHz, DMSO-d_6) δ 166.0 (C10), 159.3 (C7), 145.9 (C15), 141.9 (C5), 137.4 (C12), 134.3 (C4), 132.1 (C14), 127.9 (C3), 125.4 (C13), 112.4 (C2), 92.0 (C9), 87.1 (C6), 57.3 (C8), 56.1 (C11), 20.7 (C1), 20.7 C16).

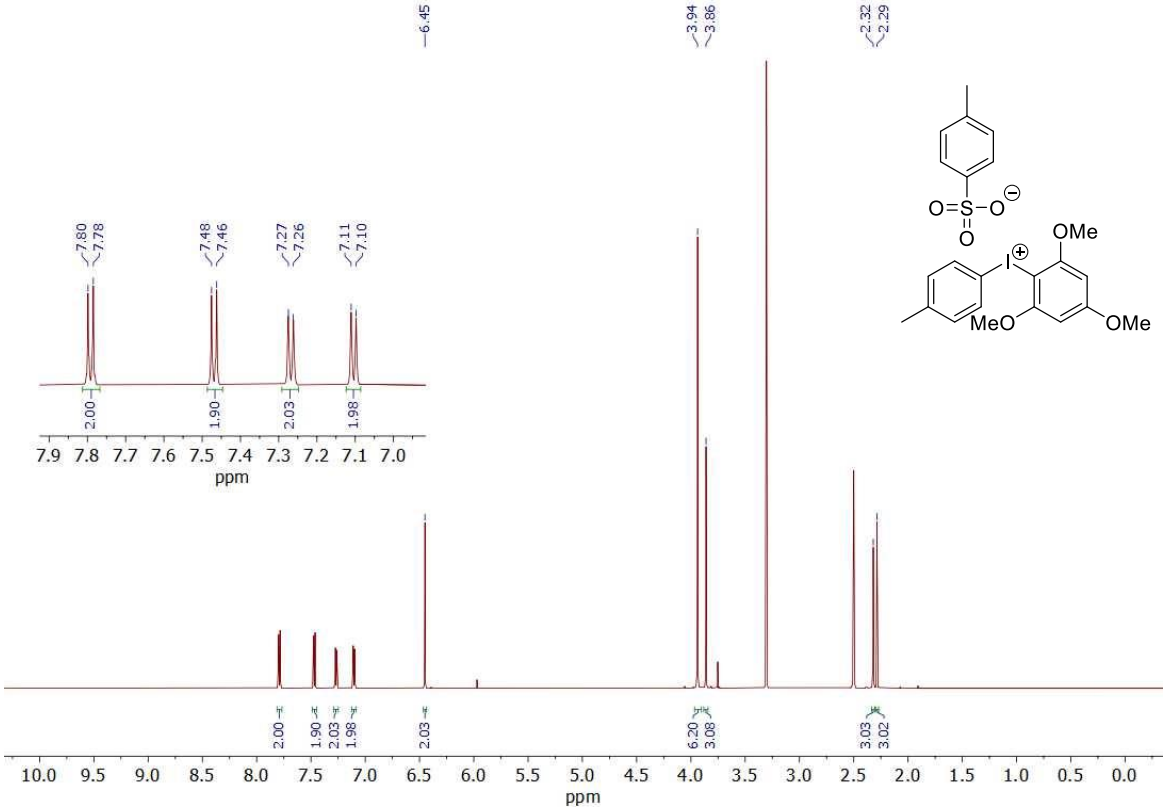
HRMS (ESI) *m/z* [M - OTs]$^{+}$: Calcd. for $C_{16}H_{18}IO_3^{+}$: 385.0295, found: 385.0295.

IR (ATR): ṽ (cm^{-1}) 3093 (w), 2943 (w), 2871 (w), 1583 (s), 1454 (s, br), 1411 (s), 1344 (s), 1222 (s), 1205 (s), 1203 (s), 1174 (s), 1116 (s), 1093 (s), 1031 (s), 1008 (s), 910 (m), 833 (s), 811 (s), 798 (s), 676 (s).

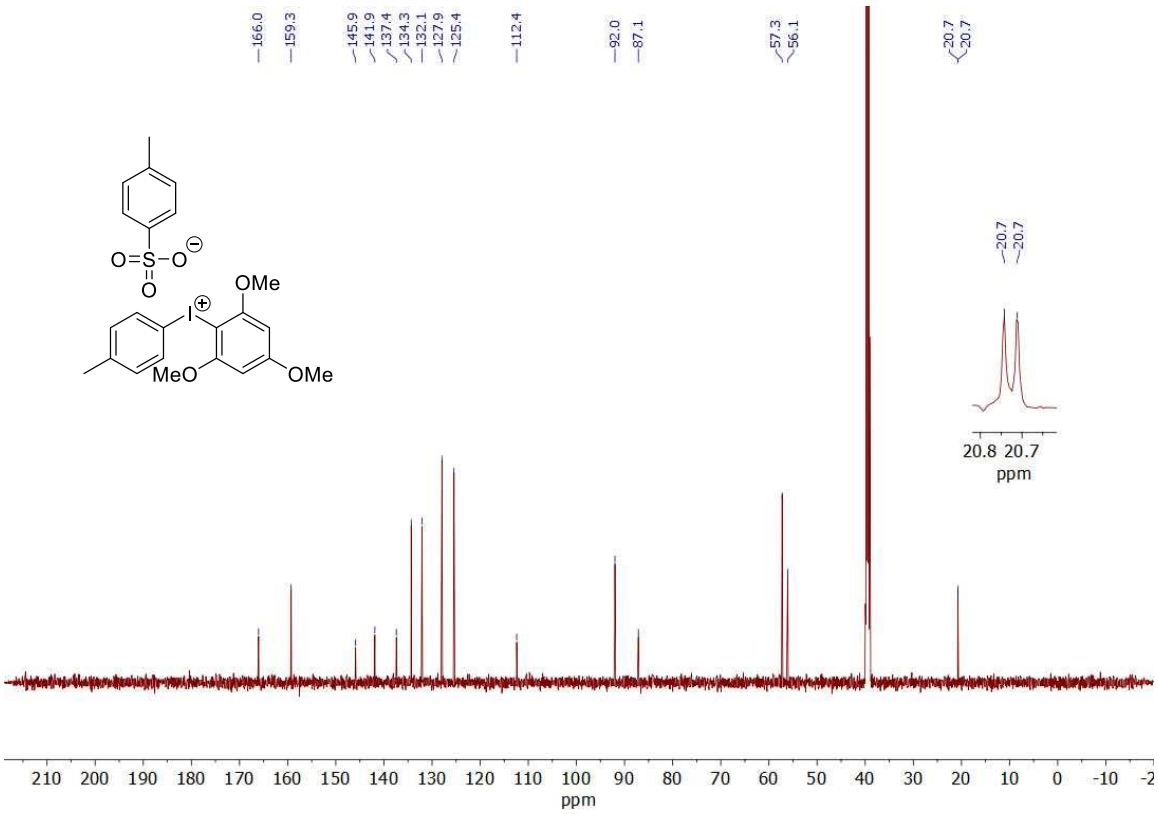
Melting point: 186-191 °C

The spectroscopic data is in accordance with the literature.[39]

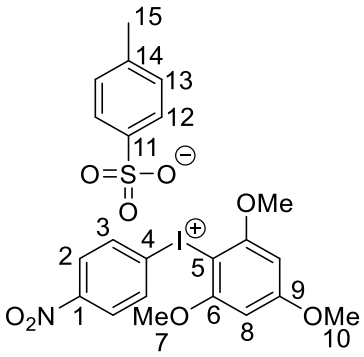
^{1}H NMR spectrum of **4b** (600 MHz, DMSO-d_6)



^{13}C NMR spectrum of **4b** (151 MHz, DMSO-d_6)



4-Nitrophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (4c)



[1868173-17-4]

4c was prepared according to general procedure A on 5 mmol scale and obtained as a pale, yellow solid (2.05 g, 3.49 mmol, 71 %).

This compound presents an AA'BB' system.

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.23 (AA', 2H, H3), 8.14 (BB', 2H, H2), 7.46 (BB', 2H, H12), 7.10 (AA', 2H, H13), 6.49 (s, 2H, H8), 3.94 (s, 6H, H7), 3.88 (s, 3H, H10), 2.28 (s, 3H, H15).

^{13}C NMR (151 MHz, DMSO-d_6) δ 166.6 (C9), 159.4 (C6), 149.1 (C1), 145.8 (C11), 137.5 (C14), 135.4 (C2), 128.0 (C13), 126.1 (C3), 125.5 (C12), 122.3 (C4), 92.2 (C8), 87.1 (C5), 57.4 (C7), 56.3 (C10), 20.8 (C15).

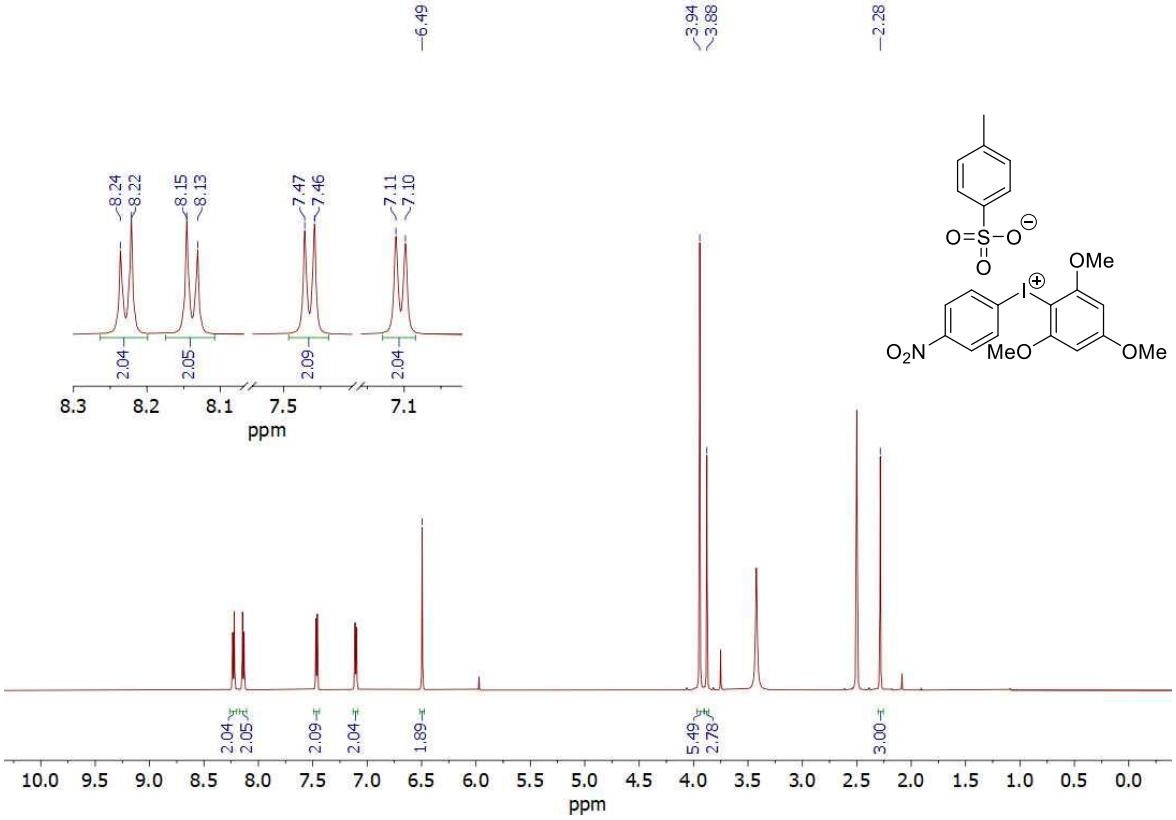
HRMS (ESI) *m/z* [M - OTs]$^{+}$: Calcd. for $C_{15}H_{15}INO_5^{+}$: 425.9989, found: 415.9988.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3016 (w), 2970 (w), 2943 (w), 2358 (m), 2341 (m), 1734 (s), 1587 (m), 1527 (m), 1340 (s), 1226 (s), 1126 (s), 1002 (m), 844 (m), 678 (s).

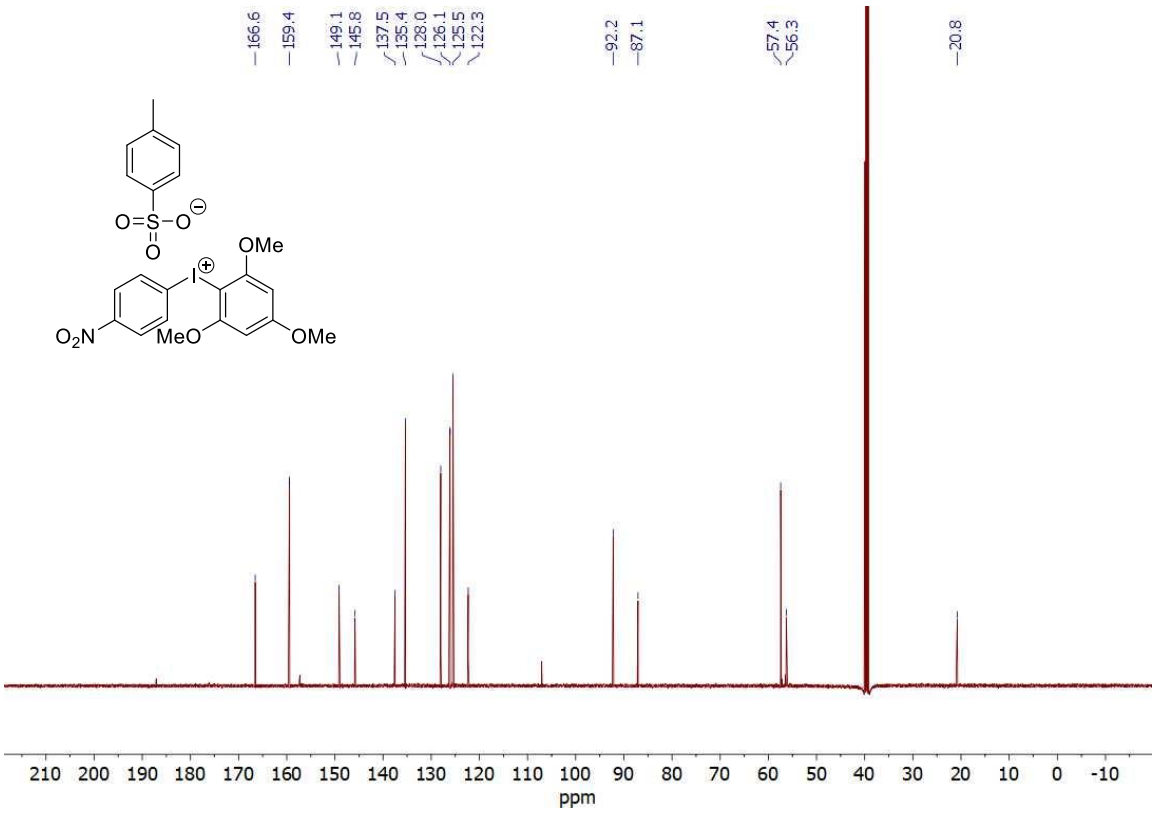
Melting point: 150-155 °C

The spectroscopic data is in accordance with the literature.[39]

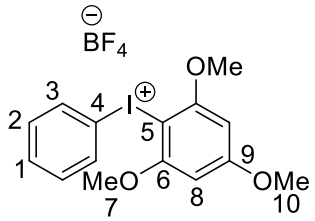
^{1}H NMR spectrum of **4c** (600 MHz, DMSO-d$_6$)



^{1}H NMR spectrum of **4c** (151 MHz, DMSO-d$_6$)



Phenyl(2,4,6-trimetoxyphenyl)iodonium tetrafluoroborate (4d)



[1550166-86-3]

4d was prepared according to general procedure B on 1 mmol scale and obtained as a white solid (0.395 g, 0,863 mmol, 85 %)

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.9 (AA', 2H, H3), 7.6 (C, 1H, H1), 7.5 (BB', 2H, H2), 6.5 (s, 2H, H8), 3.9 (s, 6H, H7), 3.9 (s, 3H, H10).

^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2 (C9), 159.3 (C6), 134.2 (C3), 131.5 (C1, C2), 116.0 (C4), 92.1 (C8), 87.0 (C5), 57.3 (C7), 56.1 (C10).

^{19}F NMR (377 MHz, DMSO-d_6) δ -148.3.

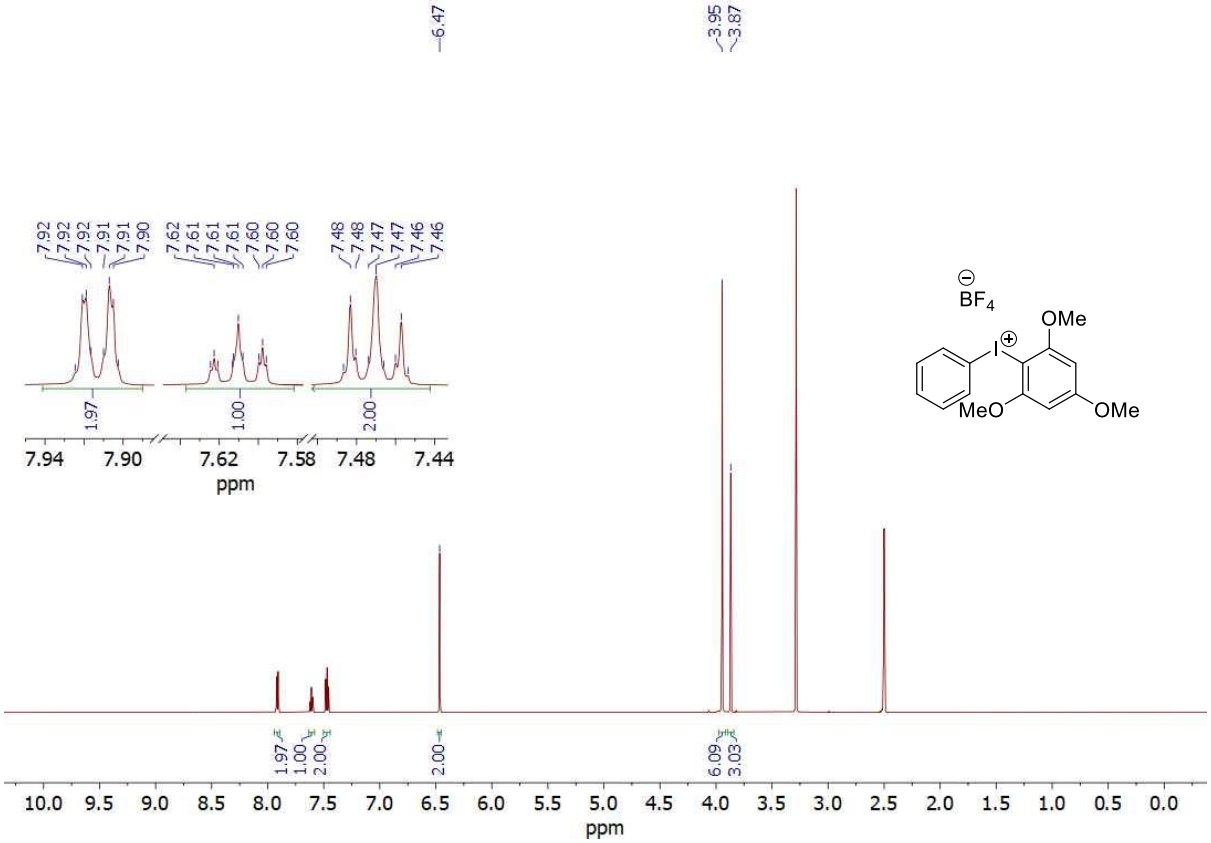
HRMS (ESI) *m/z* $[M - BF_4]^+$: Calcd. for $C_{15}H_{16}IO_3^+$:371.0139, found: 371.0138.

IR (ATR): ṽ (cm^{-1}) 2995 (w), 2947 (w), 1579 (s), 1413 (m), 1348 (m), 1234 (m), 1211 (m), 1116 (m), 1028 (s), 987 (s), 823 (m), 744 (s).

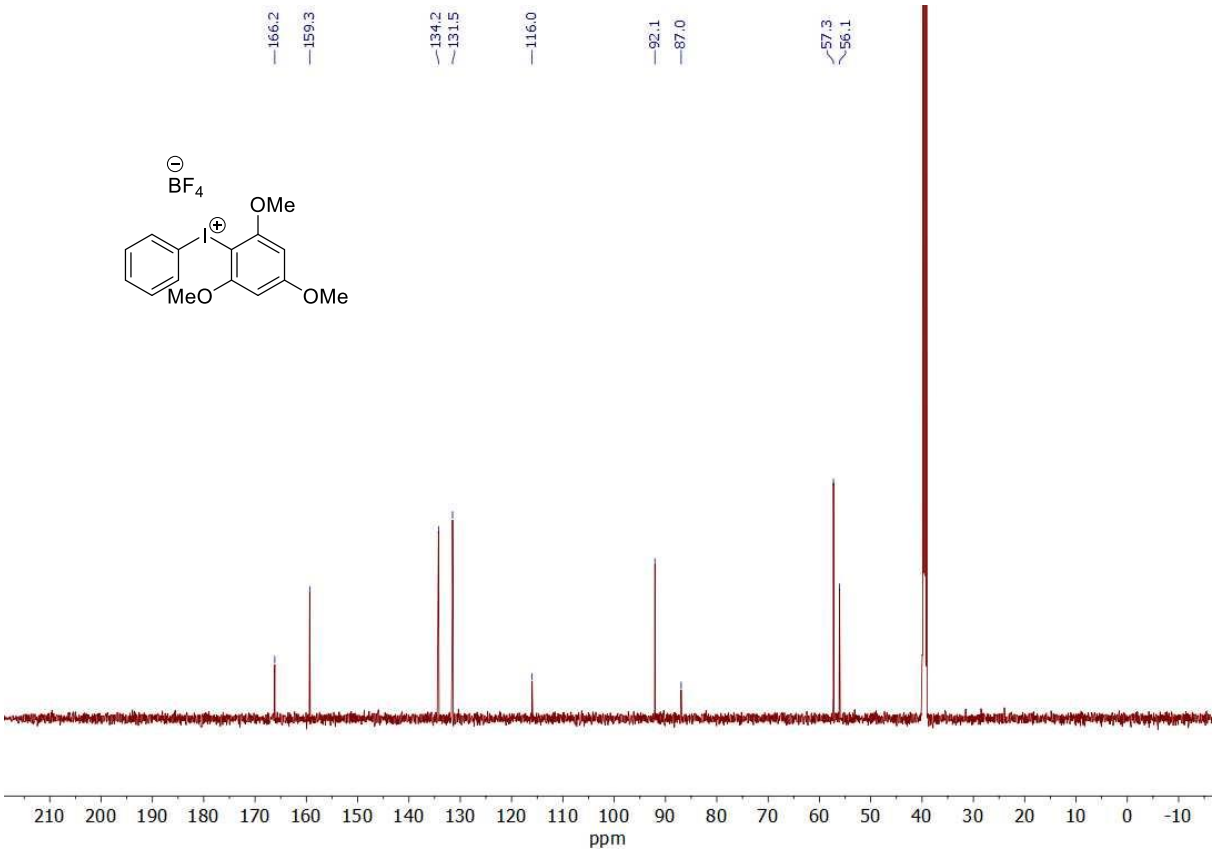
Melting point: 130-132 °C

This compound has been reported in the literature, but without spectroscopic data.[56]

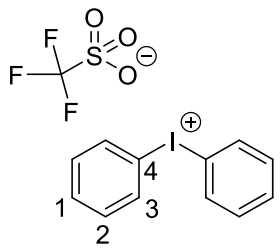
^{1}H NMR spectrum of **4d** (600 MHz, DMSO-d_6)



^{13}C NMR spectrum of **4d** (151 MHz, DMSO-d_6)



Diphenyliodonium triflate (4e)



[66003-76-7]

4e was prepared according to general procedure C on 2.3 mmol scale and obtained as a black solid (0.180 g, 0.546 mmol, 24 %)

4e was prepared according to general procedure C on 5 mmol scale and obtained as a lite brown solid (0.393 g, 0.914 mmol, 18 %)

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.25 (AA', 4H, H3), 7.67 (C, 2H, H1), 7.53 (BB', 4H, H2).

^{13}C NMR (151 MHz, DMSO-d_6) δ 135.1 (C3), 132.1 (C1), 131.8 (C2), 116.5 (C4).

^{19}F NMR (377 MHz, $CDCl_3$) δ -75.29.

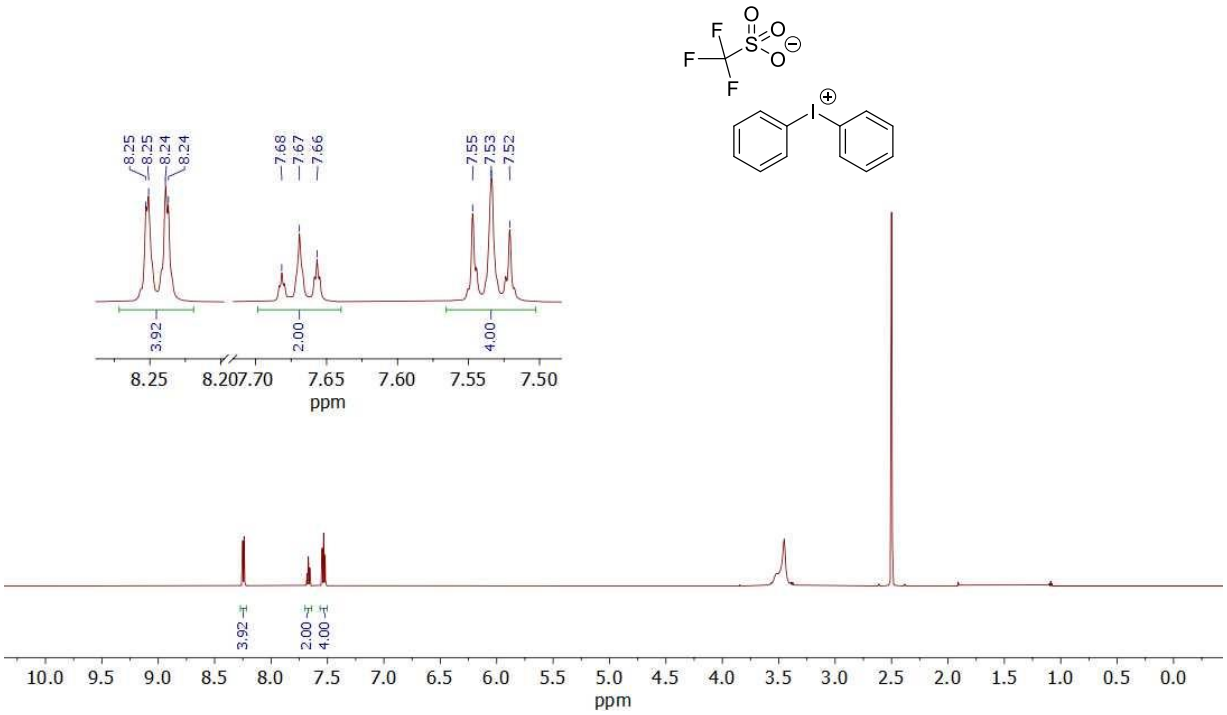
HRMS (ESI) *m/z* [M - OTf]$^{+}$: Calcd. for $C_{12}H_{10}I^{+}$:280.9822, found: 280.9821.

IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3085 (w), 3060 (w), 2358 (w), 1737 (m), 1471 (m), 1442 (m), 1267 (s), 1242 (s), 1218 (s), 1166 (s), 1022 (s) 727 (m), 632 (s).

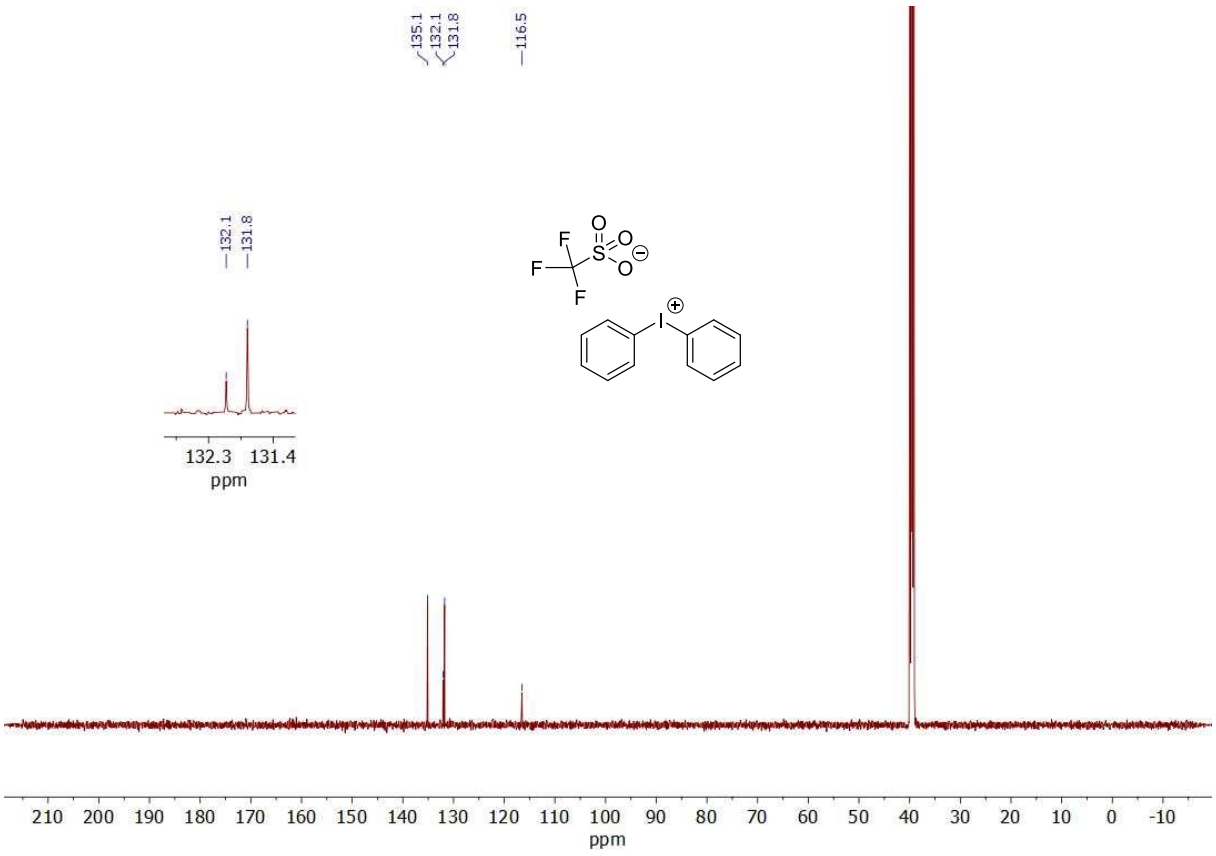
Melting point: 151-156 °C

The spectroscopic data is in accordance with the literature.[41]

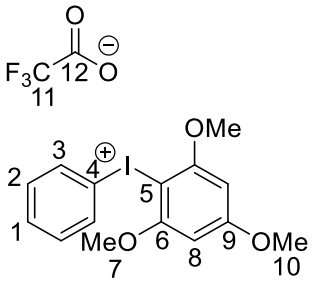
^{1}H NMR spectrum of **4e** (600 MHz, DMSO-d_6)



^{13}C NMR spectrum of **4e** (151 MHz, DMSO-d_6)



Phenyl(2,4,6-trimetoxyphenyl)iodonium trifluoroacetate (4f)



[2057405-75-9]

4f was prepared according to general procedure D on 2 mmol scale and obtained as a yellow solid (0.809 g, 1.67 mmol, 85 %)

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (AA', 2H, H3), 7.49 (C, 1H, H1), 7.35 (BB', 2H, H2), 6.19 (s, 2H, H8), 3.90 (s, 6H, H7), 3.89 (s, 3H, H10).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8 (C9), 161.0 (q, $J_{C\text{-}F}$ = 36.0 Hz, C12), 160.6 (C6), 133.8 (C3), 131.3 (C2), 131.1 (C1), 116.9 (C4), 116.4 (q, $J_{C\text{-}F}$ = 292.3 Hz, C11), 91.5 (C8), 85.7 (C5), 56.7 (C7), 55.8 (C10).

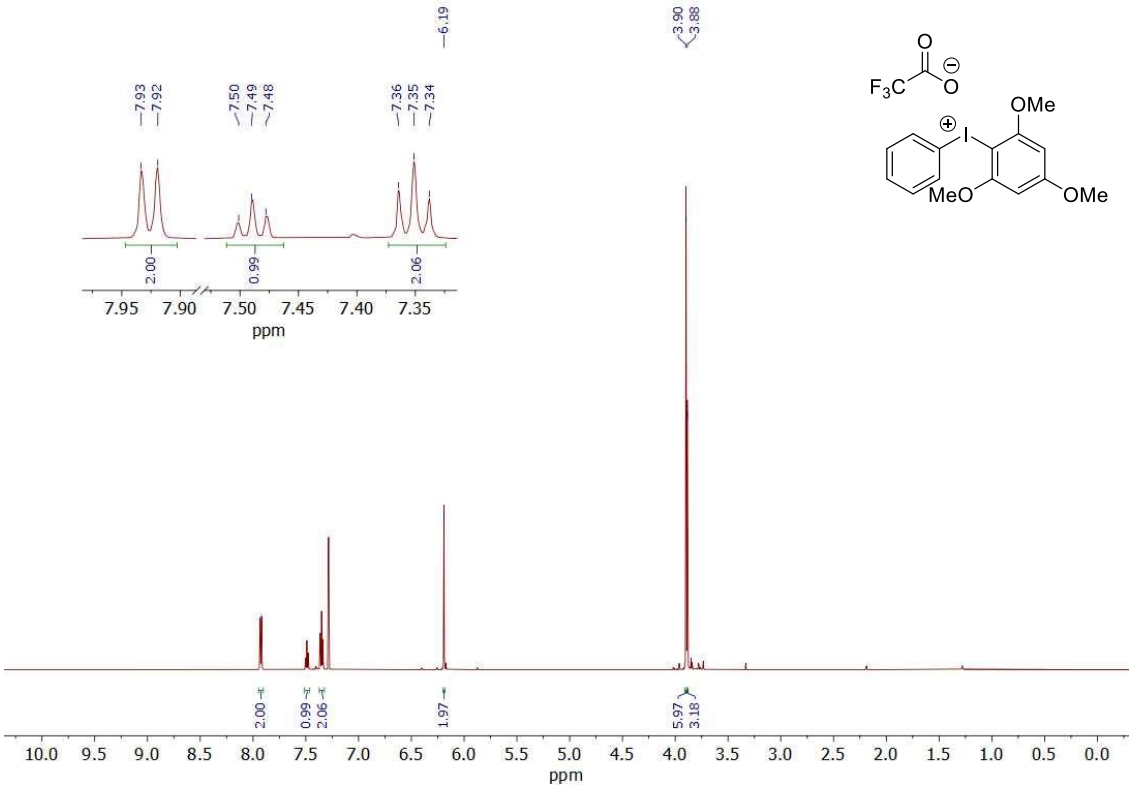
HRMS (ESI) *m/z* [M - TFA]$^{+}$: Calcd. for $C_{15}H_{16}IO_3^{+}$:371.0139, found: 371.0138.

IR (ATR): ṽ (cm^{-1}) 2950 (w), 2852 (w), 2360 (w), 2330 (w), 1716 (m), 1676 (s), 1579 (s), 1463 (m), 1161 (s), 1112 (s), 794 (m), 759 (s).

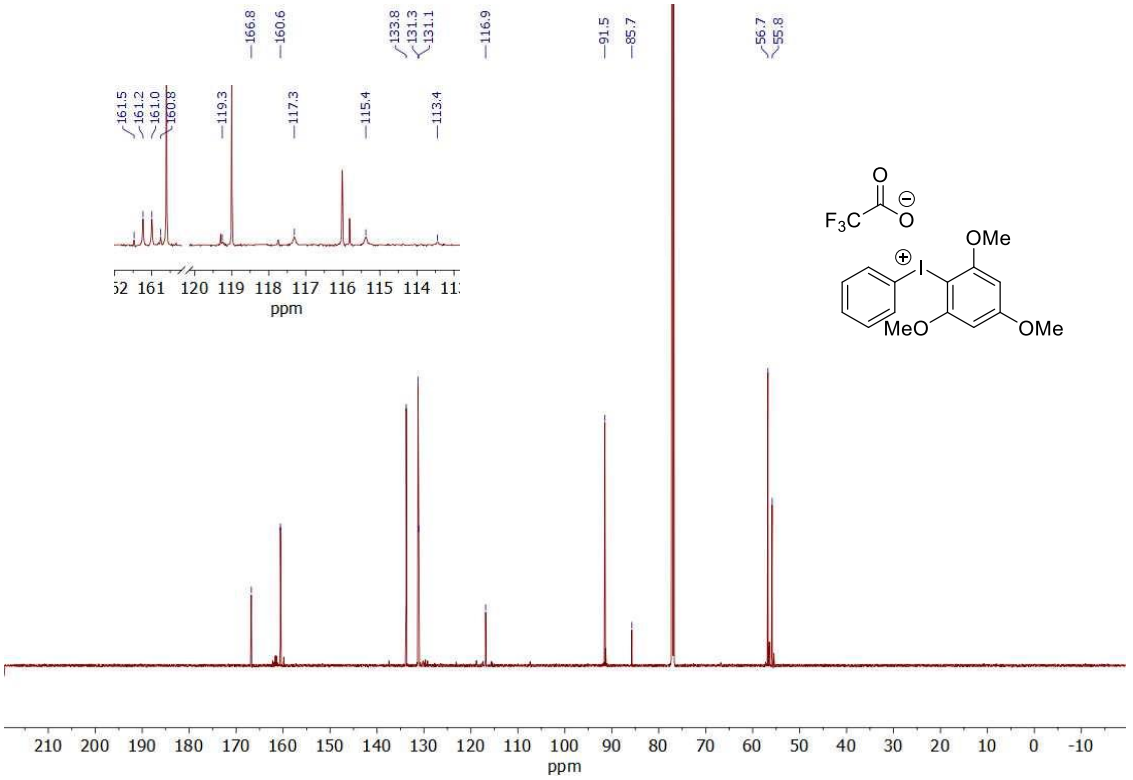
Melting point: 158-163 °C

The spectroscopic data is in accordance with the literature.[40]

^{1}H NMR spectrum of **4f** (600 MHz, $CDCl_3$)

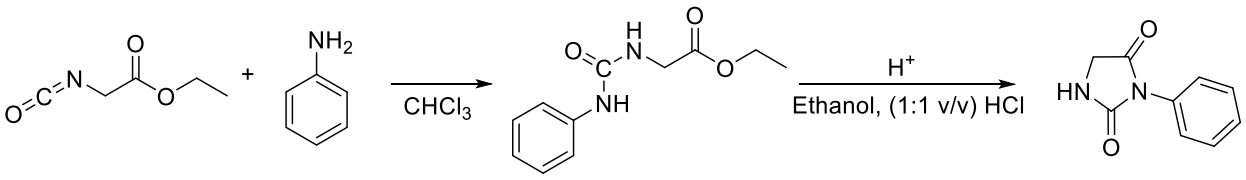


^{13}C NMR spectrum of **4f** (151 MHz, $CDCl_3$)



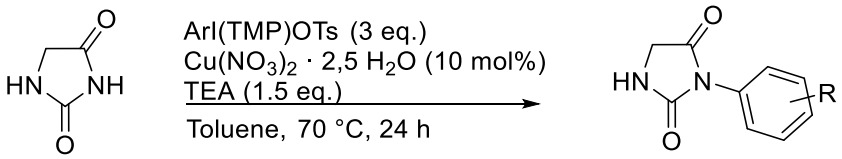
5.2 *N*-3-functionalised hydantoins

E) *N*-3-Phenylhydantoin cyclized[57]



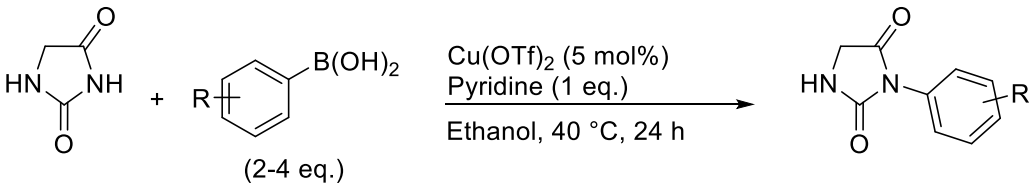
Ethyl isocyanoacetate (4.0 mmol, 1 eq.) was dissolved in 12.5 mL chloroform. Aniline (1.01 eq.) was dissolved in 12.5 mL chloroform and added dropwise to the ethyl isocyanoacetate-solution, while stirred at r.t. The mixture was stirred at r.t. for 4h 45 min, and then refluxed for 30 min. The solvent was evaporated. The remaining crystals were dissolved in 12.5 mL ethanol and 12.5 mL (1:1 v/v) HCl was added dropwise, while stirring. The mixture was refluxed for 3h, before the solvent was evaporated. The solid was triturated with 50 mL hexane and isolated by vacuum filtration. The crystals were dried with a vacuum pump.

F) *N*-3-arylation with diaryliodoniumsalt[25]



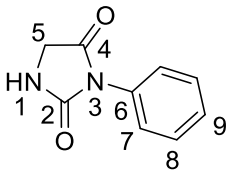
Hydantoin (0.2 mmol, 1 eq.), diaryliodoniumsalt (3 eq.) and $Cu(NO_3)_2 \cdot 2.5\ H_2O$ (10 mol%) were added to a 7 mL vial with a screw cap. The mixture was stirred with a magnetic stirrer. Toluene (2 mL) and TEA (1.5 eq.) were added with a syringe. The vial was placed in a heating block (70 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

G) *N*-3-functionalization with boronic acid[32]



Hydantoin (0.4 mmol, 1 eq.), boronic acid (2-4 eq.) and $Cu(OTf)_2$ (5 mol%) were added to a 5 mL round bottle flask. The mixture was stirred with a magnetic stirrer. Ethanol (2 mL) and pyridine (1 eq.) were added with a syringe. The vial was placed in a heating block (40 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

3-Phenylhydantoin (2a)



[2221-13-8]

2a was prepared according to general procedure E and obtained as a white solid (0.67 g, 3.81 mmol, 94 %).

2a was prepared according to general procedure F and obtained as a white solid (14.1 mg, 0.080 mmol, 39 %). The crude product was purified by column chromatography [hexane:acetone (90:10 % → 70:30 %)]

2a was prepared according to general procedure G with 3 eq. phenylboronic acid and obtained as a white solid (10.6 mg, 0.060 mmol, 15 %). The crude product was dissolved in acetonitrile (2.0 mL), and 0.6 mL 30 % H_2O_2 was added. The mixture was quenched with NaS_2O_5 after 40 minutes of stirring, filtered and the solvent was evaporated under reduced pressure. The product was purified by column chromatography [hexane:chloroform:acetone (45:45:10 % → 40:40:20 %)]

R_f = 0.06 [hexane:acetone (80:20)]

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (BB', 2H, H8), 7.44 – 7.38 (m, 3H, H7 and H9), 6.45 (br s, 1H, H1), 4.10 (s, 2H, H5).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0 (C4), 157.5 (C2), 131.4 (C6), 129.2 (C8), 128.4 (C9), 126.2 (C7), 46.4 (C5).

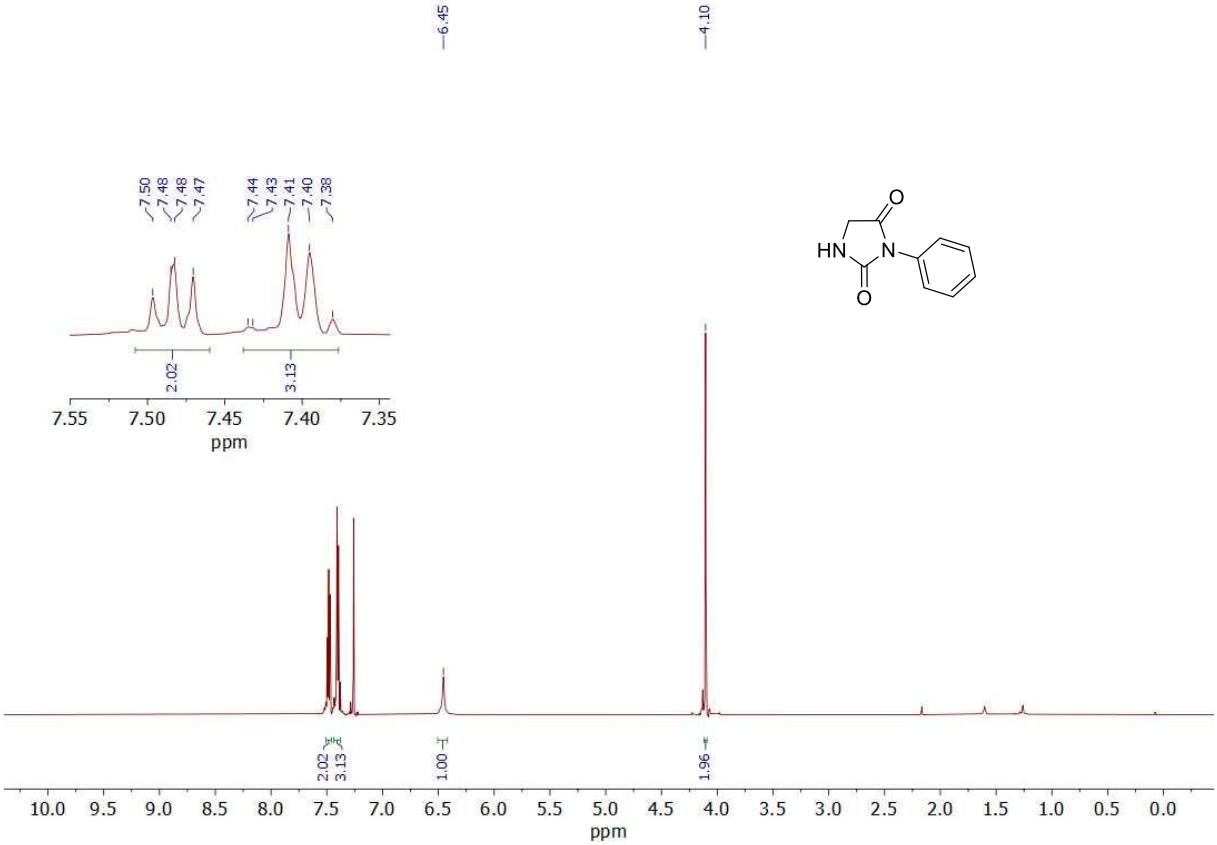
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_9H_8N_2NaO_2^+$:199.0478, found: 199.0478.

IR (ATR): ṽ (cm^{-1}) 3082 (w), 2356 (w), 2335 (w), 1708 (s), 1452 (m), 1429 (s), 1178 (s), 738 (m), 703 (s).

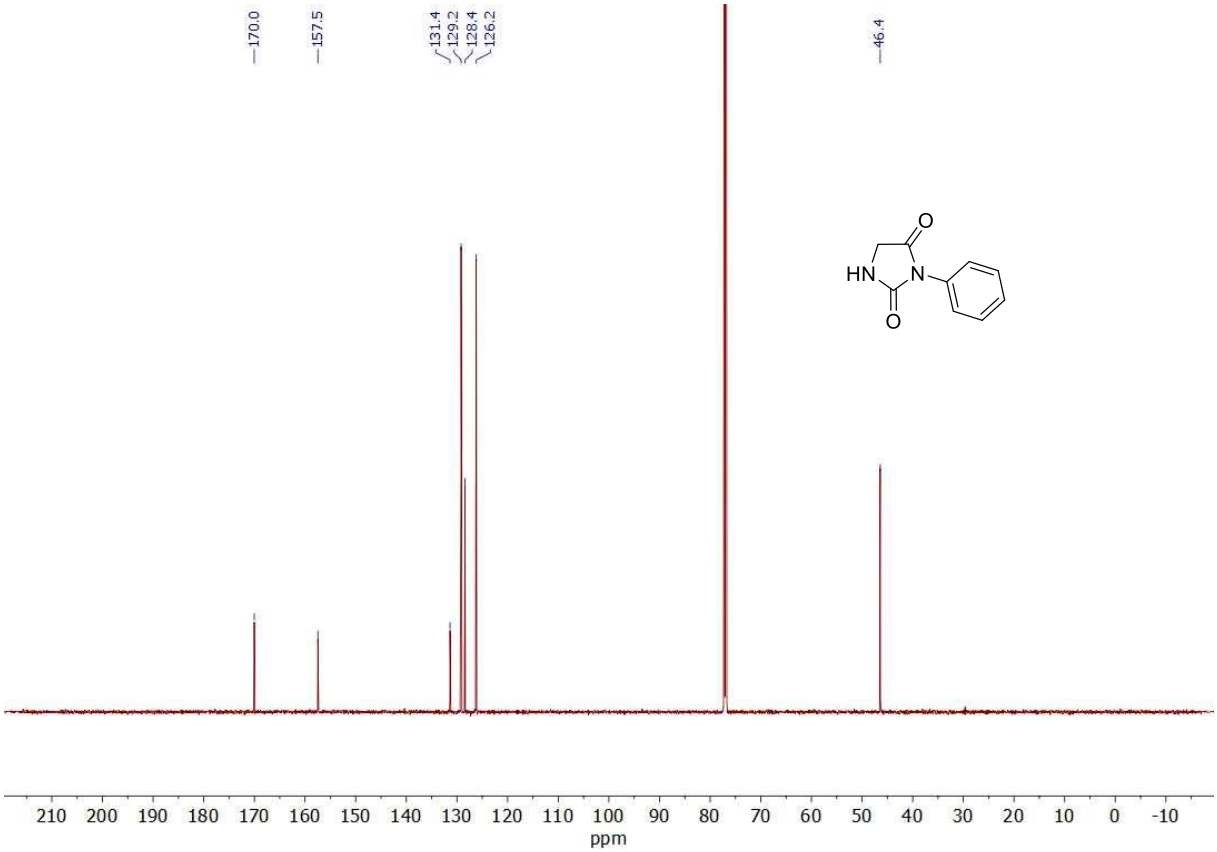
Melting point: 178-180 °C

The spectroscopic data is in accordance with the literature.[58]

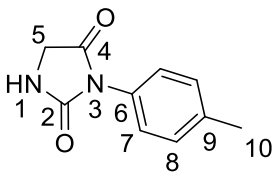
^{1}H NMR spectrum of **2a** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2a** (151 MHz, $CDCl_3$)



3-(4-Tolyl)hydantoin (2b)



[65119-75-7]

2b was prepared according to general procedure F and obtained as a white solid (23.3 mg, 0.123 mmol, 63 %). The crude product was purified by column chromatography [hexane:acetone (90:10 % → 75:25 %)]

R_f = 0.07 [hexane:acetone (80:20)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (m, 4H, H7 and H8), 6.05 (br s, 1H, H1), 4.11 (d, *J* = 1.1 Hz, 2H, H5), 2.38 (s, 3H, H10).

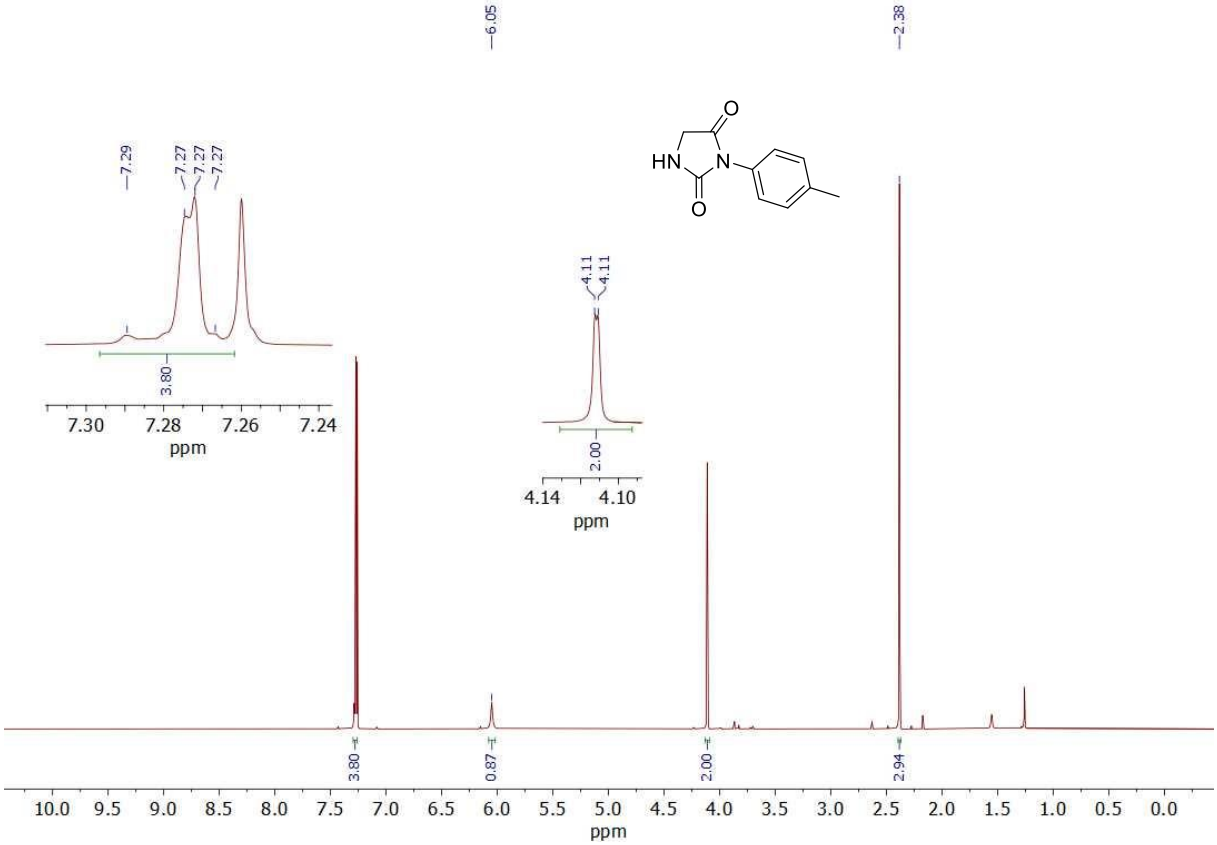
^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1 (C4), 157.4 (C2), 138.5 (C9), 129.8 (C8), 128.7 (C6), 126.1 (C7), 46.4 (C5), 21.2 (C10).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{10}H_{10}N_2NaO_2^+$: 213.0634, found: 213.0635.

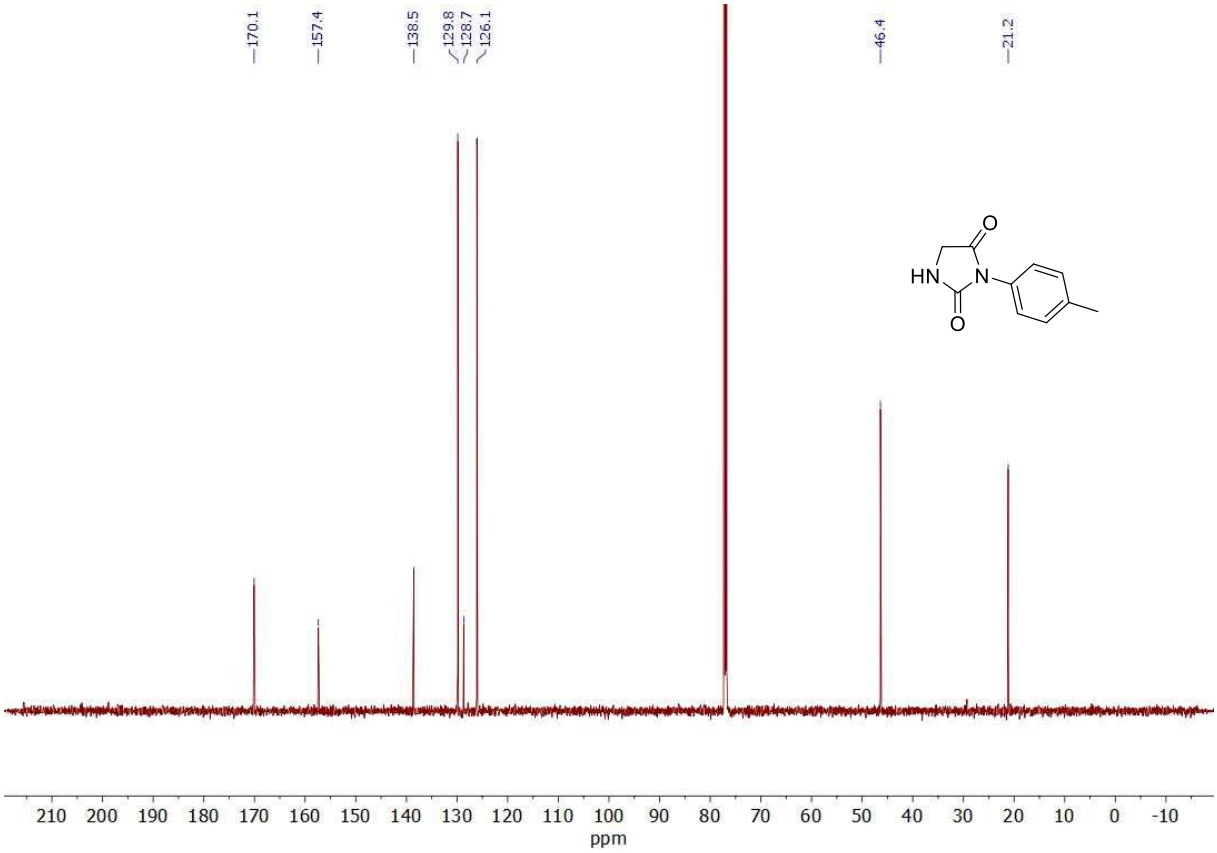
IR (ATR): ṽ (cm^{-1}) 2972 (w), 2358 (w), 2343 (w), 1708 (s), 1517 (m), 1425 (m), 1174 (s), 813 (m), 729 (s), 676 (m).

The spectroscopic data is in accordance with the literature.[59]

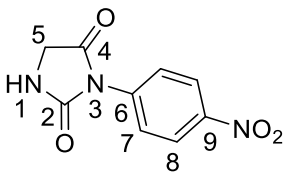
^{1}H NMR spectrum of **2b** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2b** (151 MHz, $CDCl_3$)



3-(4-Nitrophenyl)hydantoin (2c)



[62101-57-9]

2c was prepared according to general procedure F and obtained as a white solid (15.7 mg, 0.071 mmol, 36 %). The crude product was purified by column chromatography [hexane:acetone (80:20 % → 70:30 %)]

R_f = 0.05 (hexane:acetone [80:20])

This compound presents an AA'BB' system.

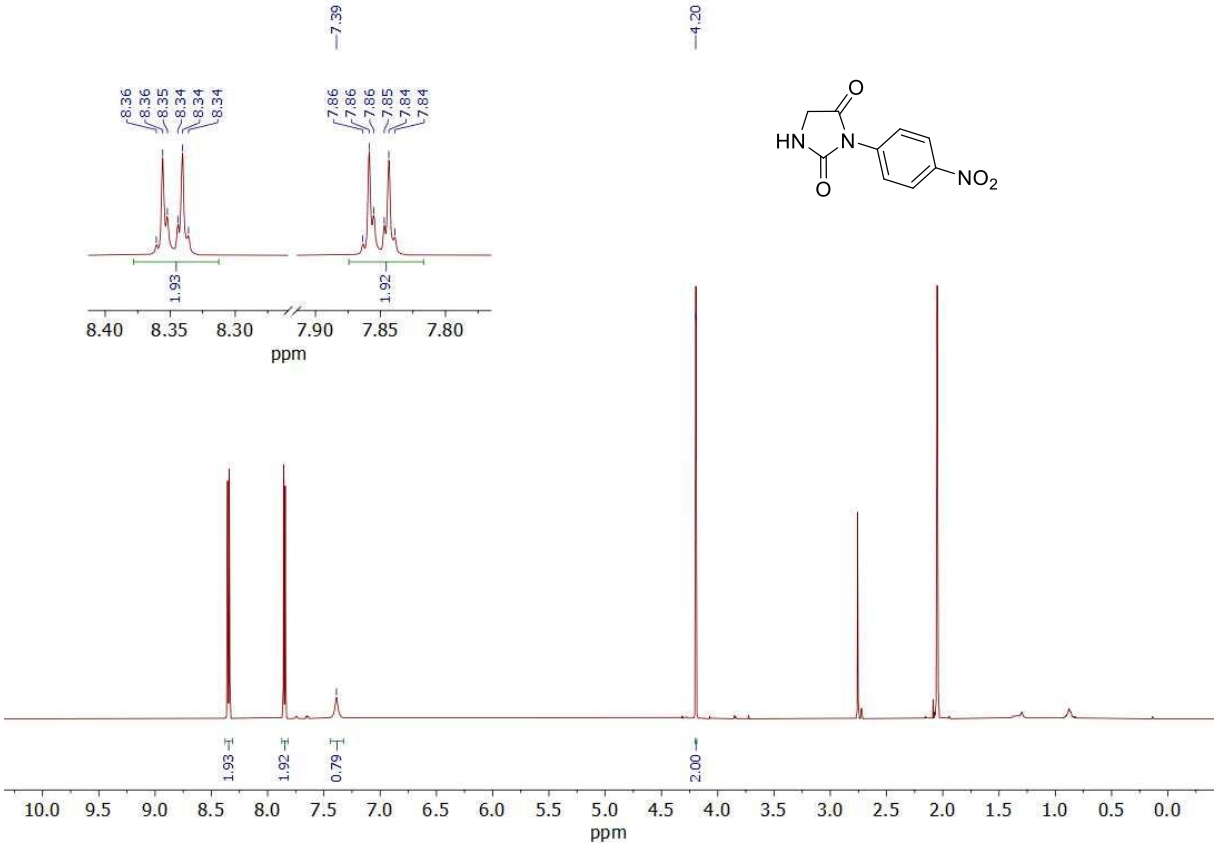
^{1}H NMR (600 MHz, Acetone-d_6) δ 8.35 (BB', 2H, H8), 7.85 (AA', 2H, H7), 7.39 (br s, 1H, H1), 4.20 (s, 2H, H5).

^{13}C NMR (151 MHz, Acetone-d_6) δ 171.1 (C4), 156.6 (C2), 147.1 (C9), 139.6 (C6), 127.1 (C7), 124.7 (C8), 47.0 (C5).

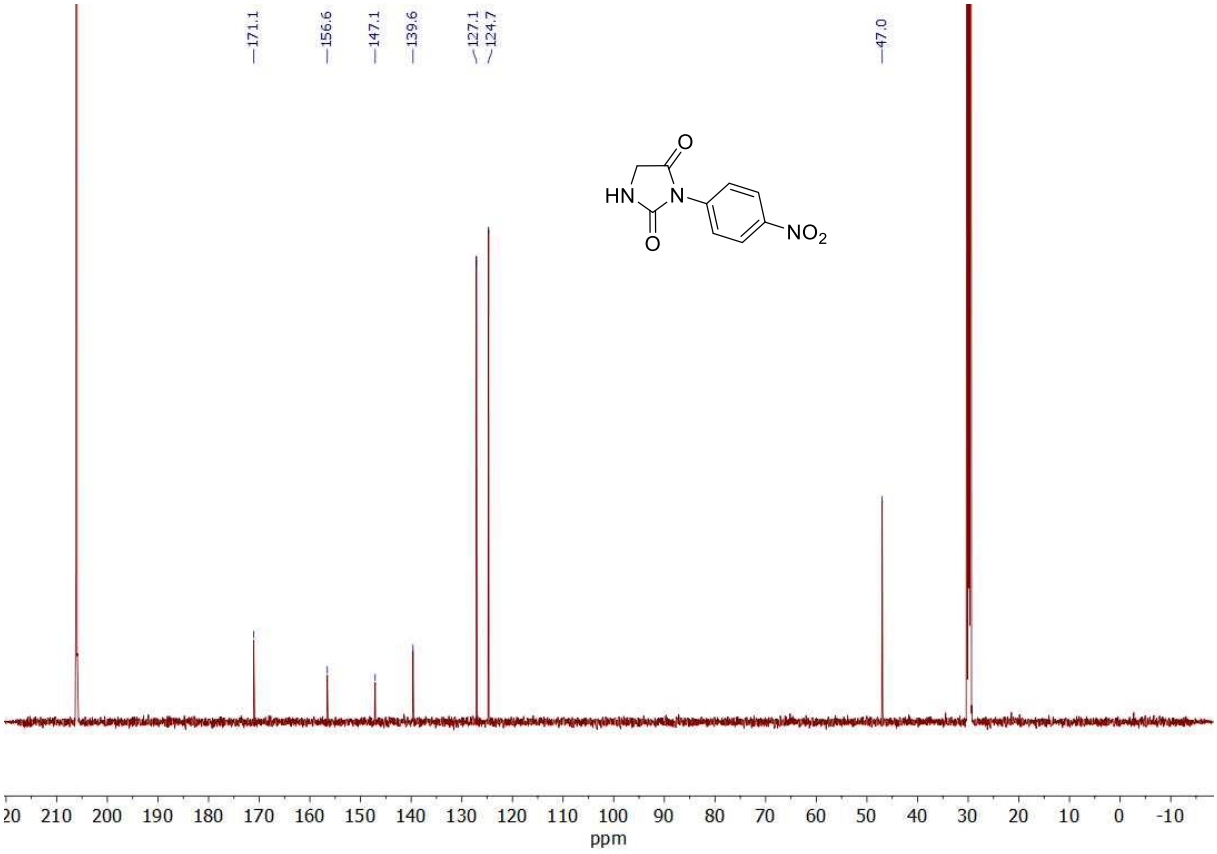
HRMS (ESI) *m/z* $[M - H]^+$: Calcd. for $C_9H_6N_3O_4^+$: 220.0364, found: 220.0365.

The spectroscopic data is in accordance with the literature.[25]

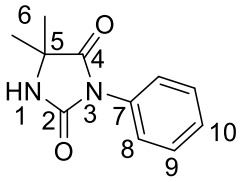
^{1}H NMR spectrum of **2c** (600 MHz, Acetone-d_6)



^{13}C NMR spectrum of **2c** (151 MHz, Acetone-d_6)



5,5-Dimethyl-3-phenylhydantoin (2d)



[70974-10-06]

2d was prepared according to general procedure F and obtained as a white solid (85.2 mg, 0.407 mmol, 71 %). The crude product was purified by column chromatography [hexane:acetone (90:10 % → 70:30 %)]

5,5-dimethylhydantoin (**1b**) (1 eq.), PhI(TMP)OTs (3 eq.), CuI (1 eq.), $NaBF_4$ (10 eq.) and K_2CO_3 (3 eq.) were added to a 7 mL vial with a screw cap. The mixture was stirred with a magnetic stirrer. 1,4-Dioxane (2 mL) and Me_2CyDA (3 eq.) were added with a syringe. The vial was placed in a heating block (70 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure. **2d** was obtained after column chromatography [hexane:acetone (90:10 % →70:30 %)] as a white solid (38.7 mg, 0.189 mmol, 96 %)

R_f = 0.09 (hexane:acetone [80:20])

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (BB', 2H, H9), 7.41 (AA', 2H, H8), 7.37 (C, 1H, H10), 6.69 (br s, 1H, H1), 1.51 (s, 6H, H6).

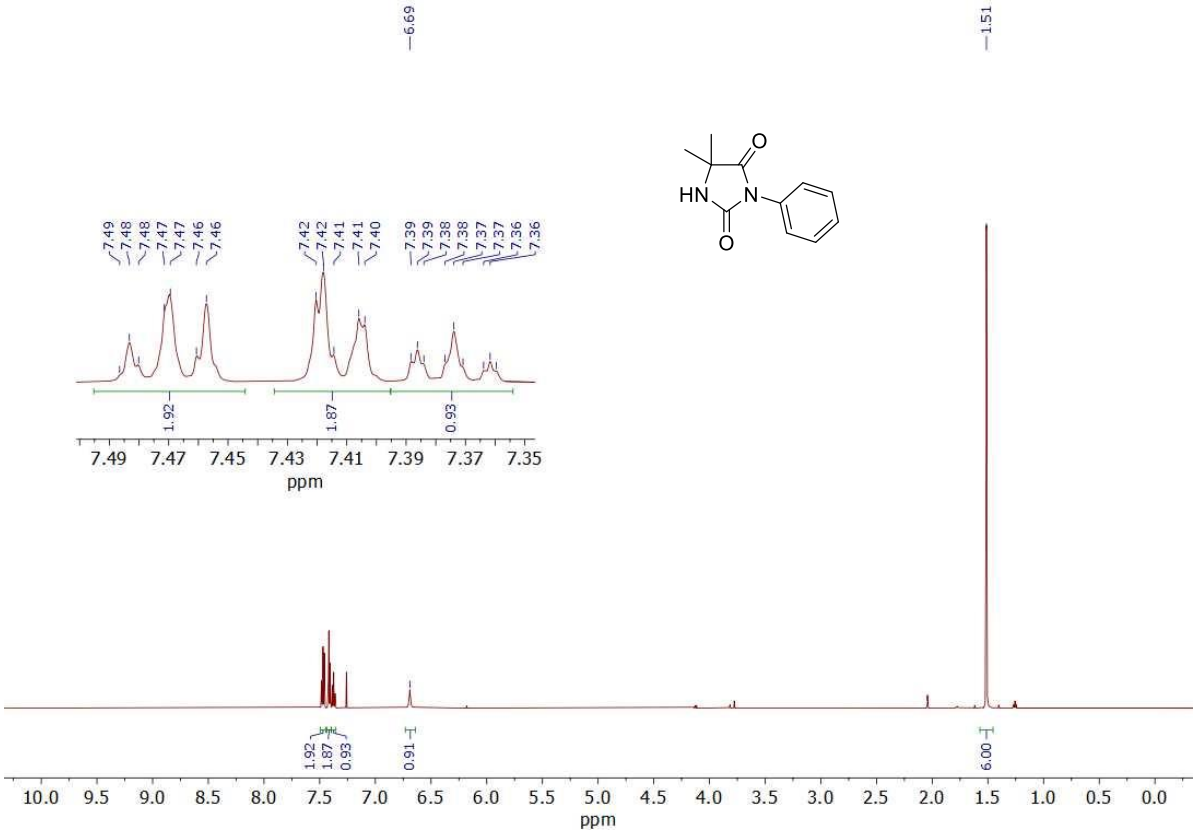
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.2 (C4), 155.6 (C2), 131.6 (C7), 129.0 (C9), 128.1 (C10), 126.1 (C8), 58.6 (C5), 25.1 (C6).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{11}H_{12}N_2NaO_2^+$: 227.0791, found: 227.0800.

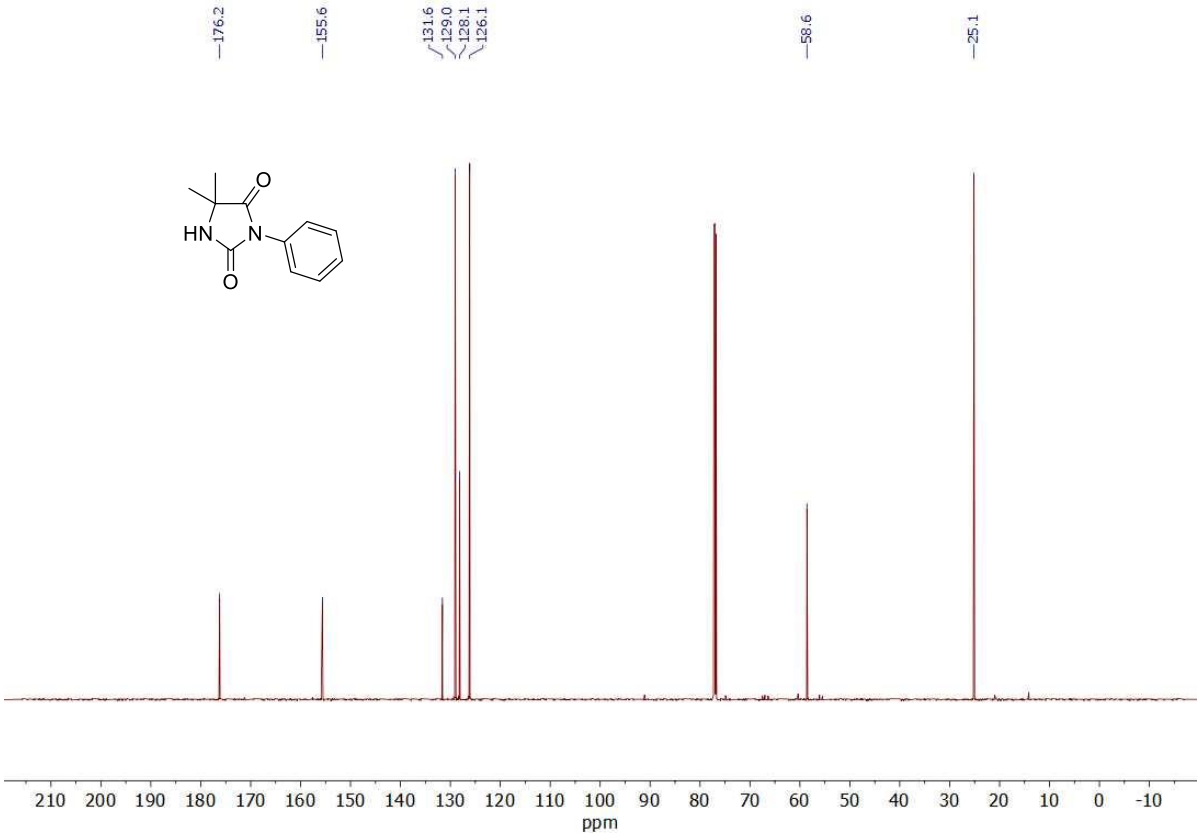
IR (ATR): ṽ (cm^{-1}) 2985 (w), 2358 (w), 2333 (w), 1714 (s), 1425 (m), 1294 (m), 1207 (m), 1145 (m), 862 (m), 707 (m).

The spectroscopic data is in accordance with the literature.[27]

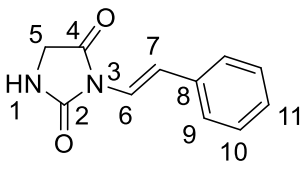
^{1}H NMR spectrum of **2d** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **2d** (151 MHz, $CDCl_3$)



(E)-3-Styrylhydantoin (2e)



[2756091-56-0]

2e was prepared according to general procedure G with 2 eq. of (*E*)-styrylboronic acid and obtained as a white solid (100.5 mg, 0.497 mmol, 59 %) The crude product was purified by column chromatography [chloroform:acetonitrile (9:2)]

R_f = 0.31 (chloroform:acetonitrile [9:2]).

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, DMSO) δ 8.45 (s, 1H, H1), 7.47 – 7.41 (m, 3H, H7 and H9), 7.35 (BB', 2H, H10), 7.25 (C, 1H, H11), 7.09 (d, *J* = 15.2 Hz, 1H, H6), 4.00 (d, *J* = 1.1 Hz, 2H, H5).

^{13}C NMR (151 MHz, DMSO) δ 170.4 (C4), 155.4 (C2), 135.6 (C8), 128.8 (C10), 127.4 (C11), 125.8 (C9), 118.5 (C6), 118.0 (C7), 45.3 (C5).

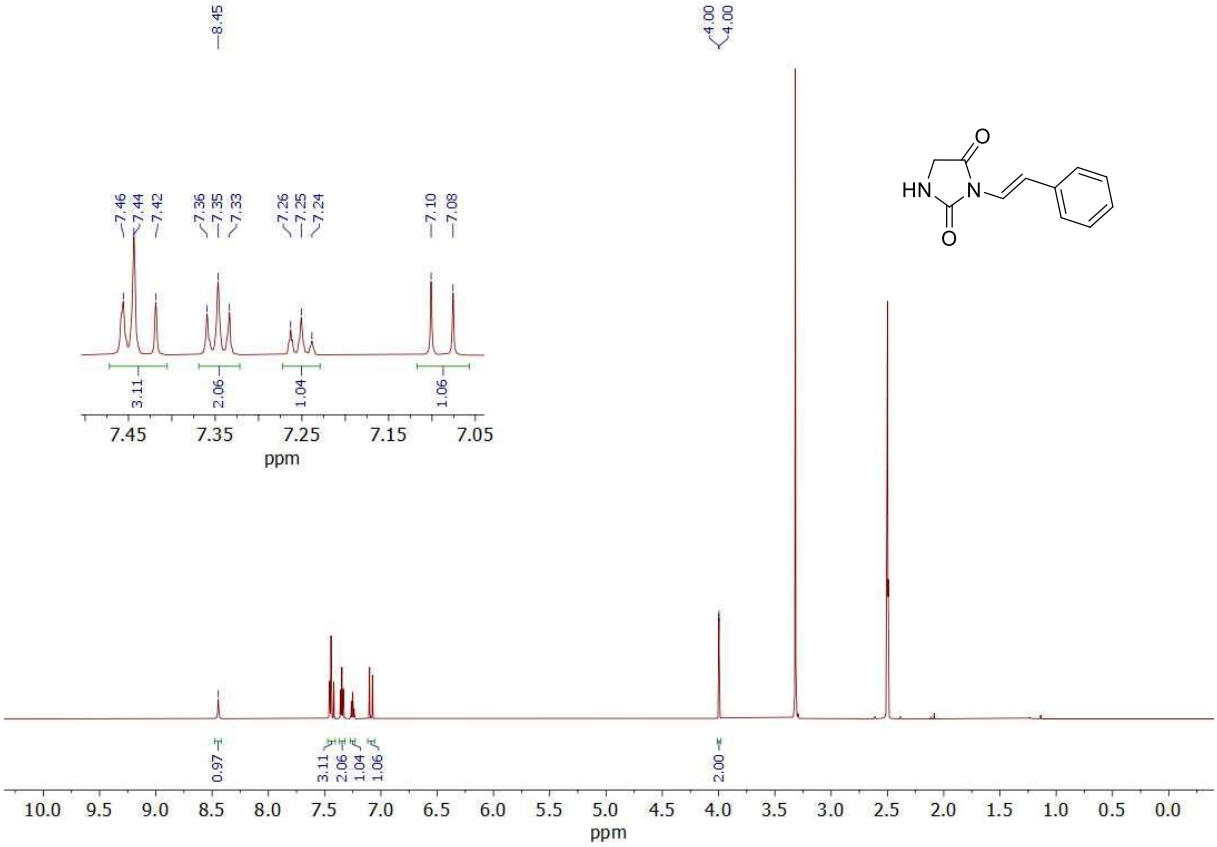
HRMS (ESI) *m/z* [M + Na]$^{+}$: Calcd. for $C_{11}H_{10}N_2NaO_2^{+}$: 225.0634, found: 225.0634.

IR (ATR): ṽ (cm^{-1}) 3226 (w), 3076 (w), 2972 (w). 2364 (w), 2331 (w), 1699 (s), 1411 (m), 1232 (m), 1126 (m), 738 (s), 688 (m).

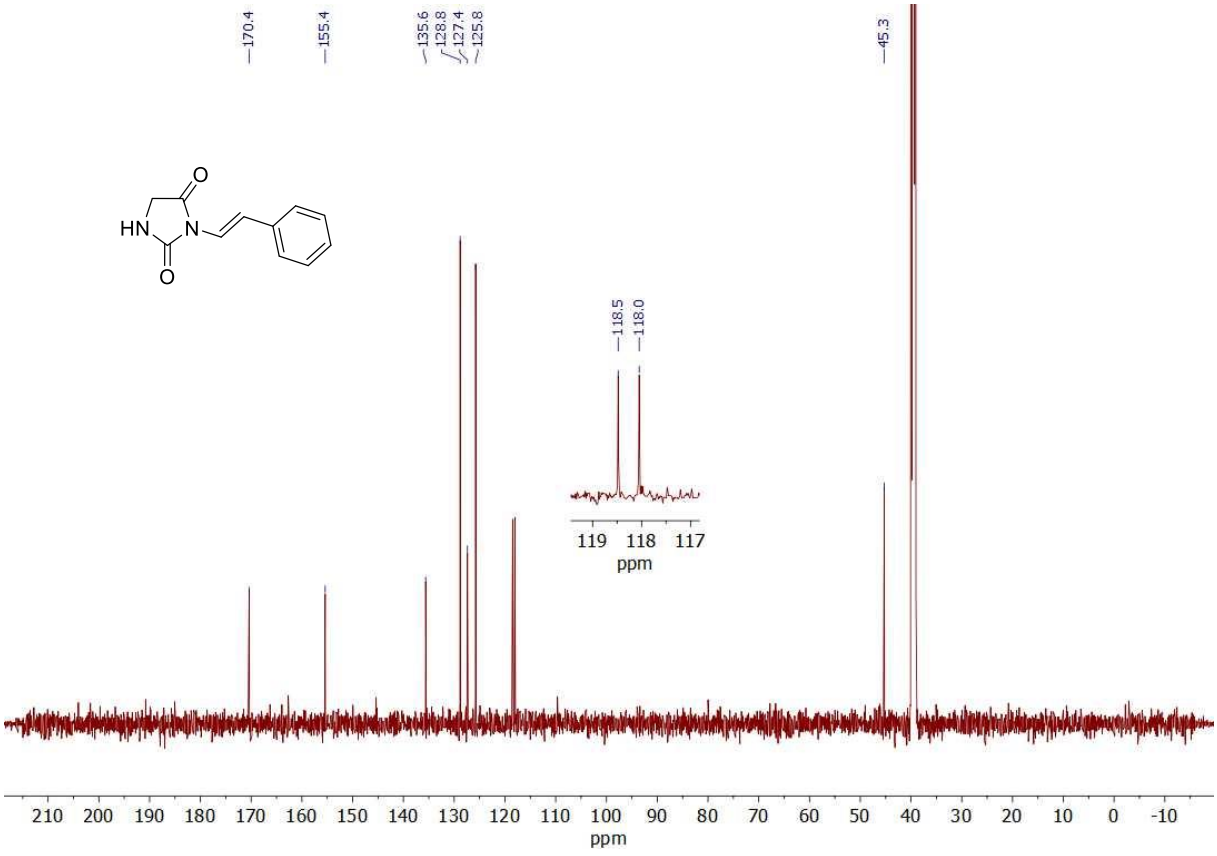
Melting point: 234-240 °C

The spectroscopic data is in accordance with the literature.[32]

^{1}H NMR spectrum of **2e** (600 MHz, DMSO-d_6)

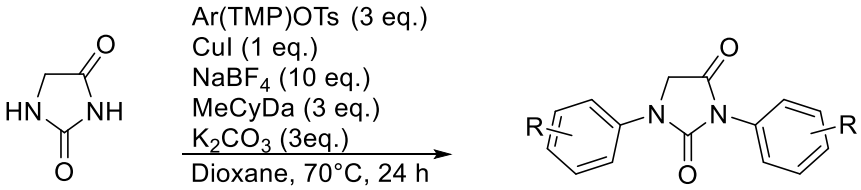


^{13}C NMR spectrum of **2e** (151 MHz, DMSO-d_6)



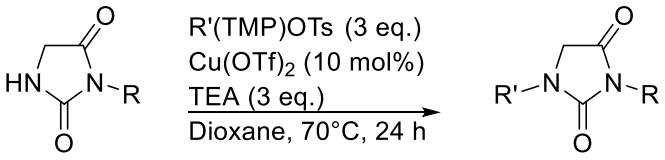
5.3 *N*-1- and *N*-3-functionalized hydantoins

H) *N,N'*-diarylated hydantoin-mediated



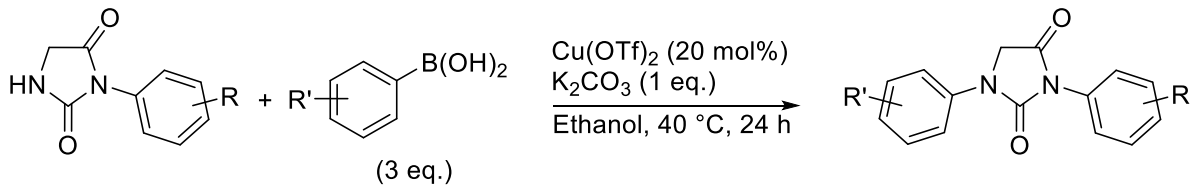
Hydantoin (0.2 mmol, 1 eq.), arylI(TMP)OTs (3 eq.), CuI (1 eq.), $NaBF_4$ (10 eq.) and K_2CO_3 (3 eq.) were added to a 7 mL vial with a screw cap. The mixture was stirred with a magnetic stirrer. 1,4-Dioxane (2 mL) and Me_2CyDA (3 eq.) were added with a syringe. The vial was placed in a heating block (70 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

I) *N*-1-arylation of *N*-3-functionalized hydantoins with diaryliodonium salt



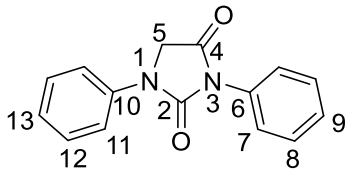
Hydantoin (0.2 mmol, 1 eq.), arylI(TMP)OTs (3 eq.) and $Cu(OTf)_2$ (10 mol%) were added to a 7 mL vial with a screw cap. The mixture was stirred with a magnetic stirrer. 1,4-Dioxane (2 mL) and TEA (3 eq.) were added with a syringe. The vial was placed in a heating block (70 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

J) *N*-1-arylation of *N*-3-arylated hydantoins with boronic acid[50]



Hydantoin (0.4 mmol, 1 eq.), boronic acid (3 eq.), $Cu(OTf)_2$ (20 mol%) and K_2CO_3 (1 eq.) were added to a 5 mL round bottom flask. The mixture was stirred with a magnetic stirrer. Ethanol (2 mL) was added with a syringe. The flask was placed in a heating block (40 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

1,3-Diphenylhydantoin (3a)



[3157-03-7]

3a was prepared according to general procedure H and obtained as a white solid (31.0 mg, 0.123 mmol, 63 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10 %→80:20%)]

3a was prepared according to procedure J and obtained as a white solid (85.5 mg, 0.339 mmol, 85 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10% →80:20 %)]

R_f = 0.26 [hexane:ethyl acetate (80:20)]

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (AA', 2H, H11), 7.49 (BB', 2H, H8), 7.46 (AA', 2H, H7), 7.44 – 7.38 (m, 3H, H12 and H9), 7.19 (C, 1H, H13), 4.42 (s, 2H, H5).

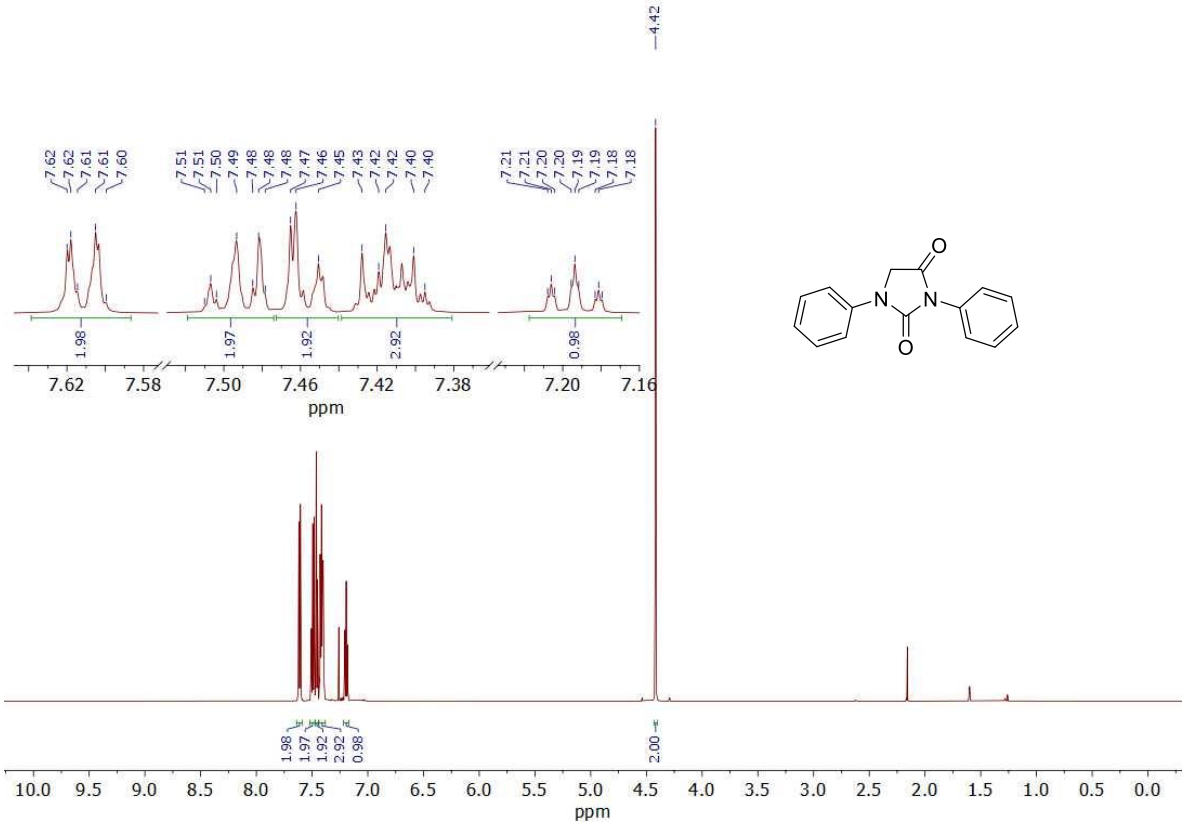
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4 (C4), 153.2 (C2), 137.5 (C10), 131.4 (C6), 129.4 (C8/C12), 129.2 (C8/C12), 128.5 (C9), 126.3 (C7), 124.7 (C13), 118.7 (C11), 49.8 (C5).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{15}H_{12}N_2NaO_2^+$: 275.0791, found: 275.0790.

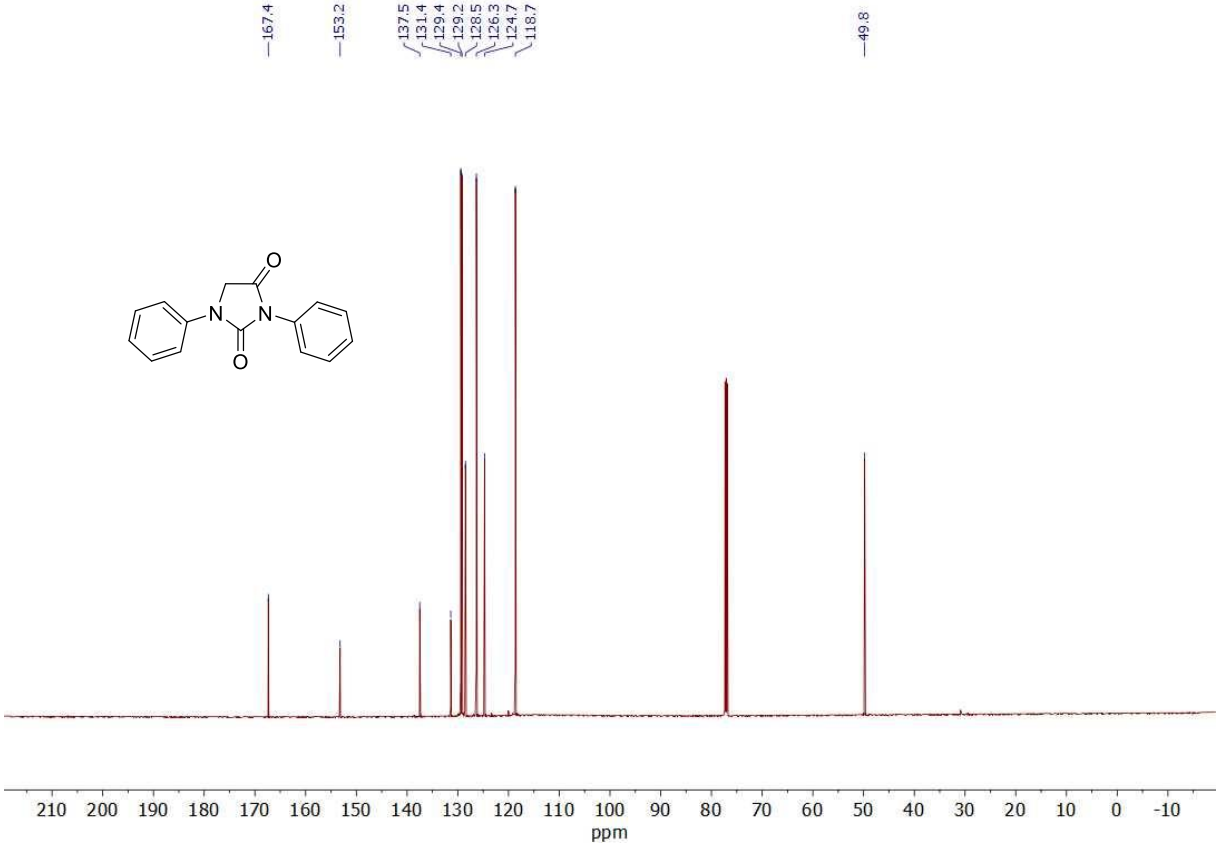
IR (ATR): ṽ (cm^{-1}) 3058 (w), 2958 (w), 2360 (w), 2331 (w), 1776 (m), 1708 (s), 1500 (m), 1371 (s), 1191 (s), 1159 (m), 750 (s), 690 (s).

The spectroscopic data is in accordance with the literature.[60]

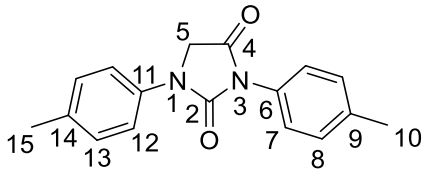
^{1}H NMR spectrum of **3a** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3a** (151 MHz, $CDCl_3$)



1,3-Di(4-tolyl)hydantoin (3b)



[1184640-37-6]

3b was prepared according to general procedure H and obtained as a white solid (25.9 mg, 0.092 mmol, 47 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10 %→80:20 %)]

R_f = 0.33 [hexane:ethyl acetate (80:20)]

This compound presents an AA'BB' system

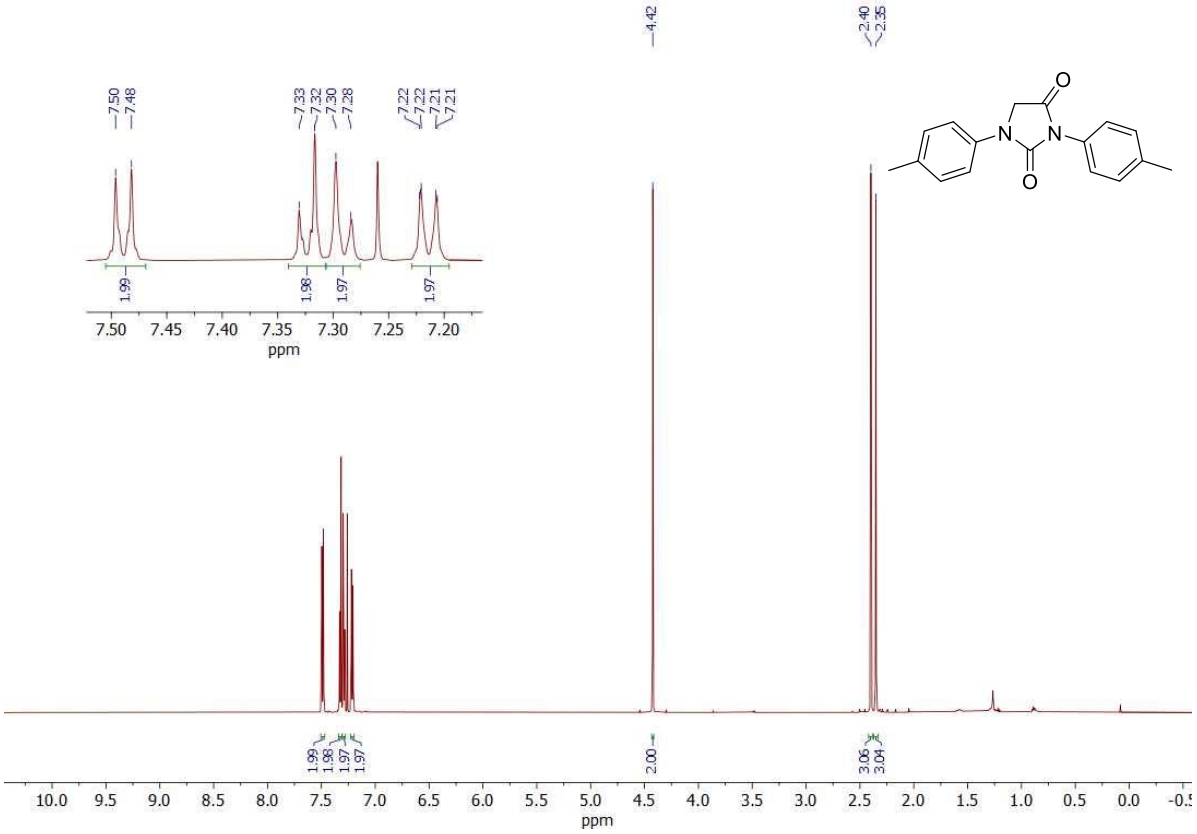
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (AA', 2H, H12), 7.32 (AA', 2H, H7), 7.29 (BB', 2H, H8), 7.21 (BB', 2H, H13), 4.42 (s, 2H, H5), 2.40 (s, 3H, H10), 2.35 (s, 3H, H15).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.6 (C4), 153.3 C2), 138.5 (C9), 135.0 (C11), 134.4 (C14), 129.9 (C13), 129.8 (C8), 128.7 (C6), 126.1 (C7), 118.7 (C12), 49.9 (C5), 21.2 (C10), 20.8 (C15).

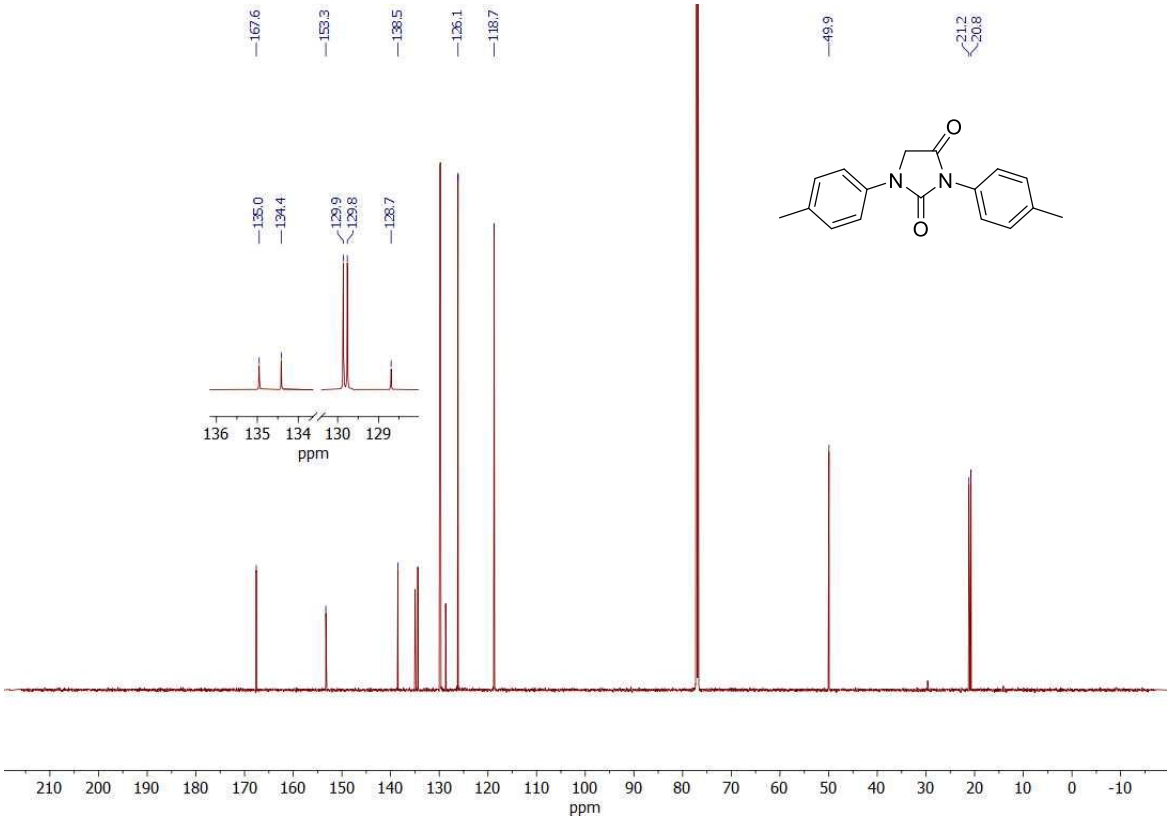
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{17}H_{16}N_2NaO_2^+$: 303.1104, found: 303.1103.

This compound has not been reported in the literature.

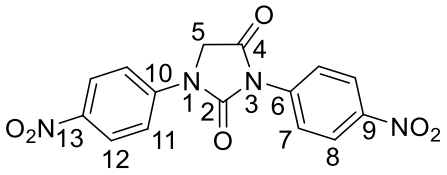
^{1}H NMR spectrum of **3b** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3b** (151 MHz, $CDCl_3$)



1,3-Di(4-nitrophenyl)hydantoin (3c)



[NEW]

3c was prepared according to general procedure H and obtained as a white solid (5.1 mg, 0.015 mmol, 7 %) The crude product was purified by column chromatography [hexane:ethyl acetate (80:20 % →70:30 %)]. The resulting crude was concentrated under reduced pressure and the product was further purified with flash chromatography on a silica plug [hexane:chloroform (50:50 %)]

R_f = 0.09 [hexane:ethyl acetate (80:20)]

This compound presents an AA'BB' system.

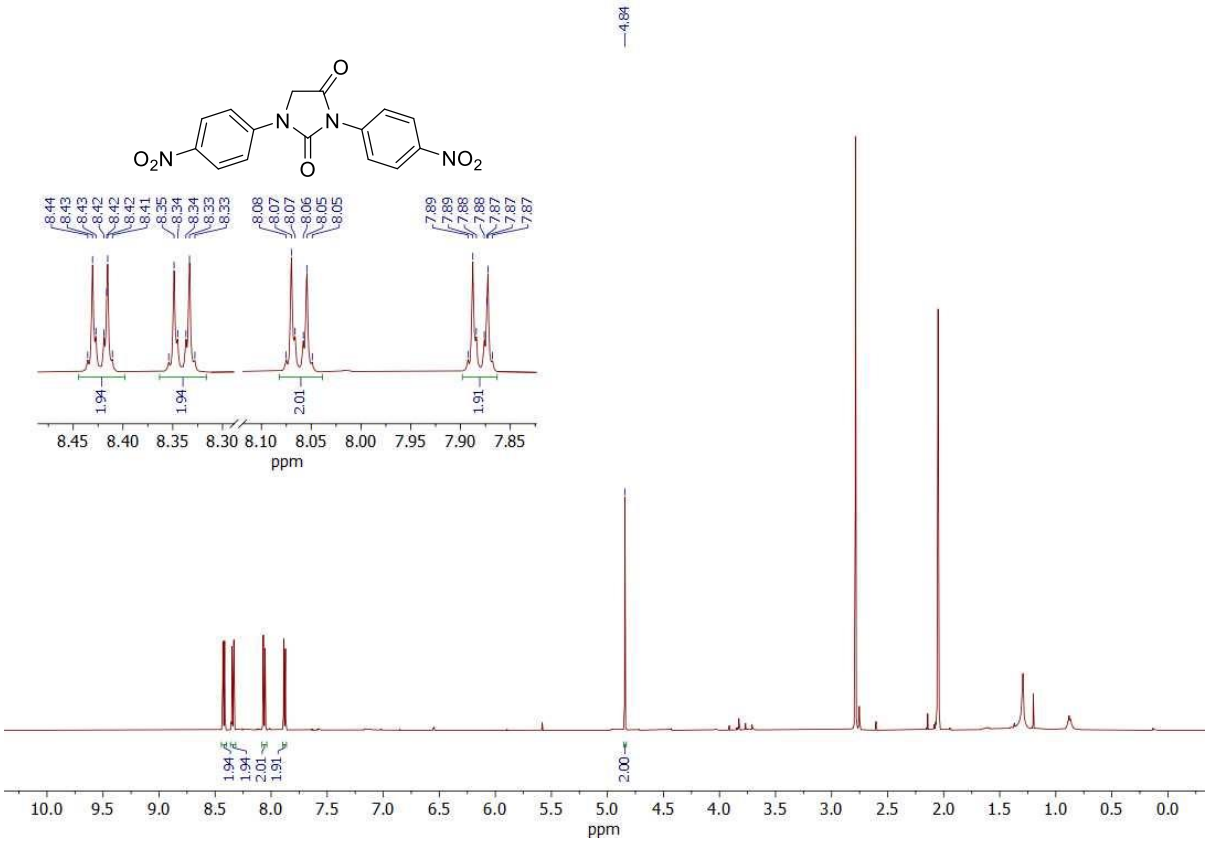
^{1}H NMR (600 MHz, Acetone-d_6) δ 8.42 (AA', 2H, H7), 8.34 (BB', 2H, H12), 8.06 (AA', 2H, H11), 7.88 (BB', 2H, H8), 4.84 (s, 2H, H5).

^{13}C NMR (151 MHz, Acetone-d_6) δ 167.8 (C4), 153.9 (C2), 147.8 (C6), 144.7 (C10), 144.4 (C13), 138.6 (C9), 128.1 (C8), 125.8 (C12), 125.0 (C7), 119.1 (C11), 50.9 (C5).

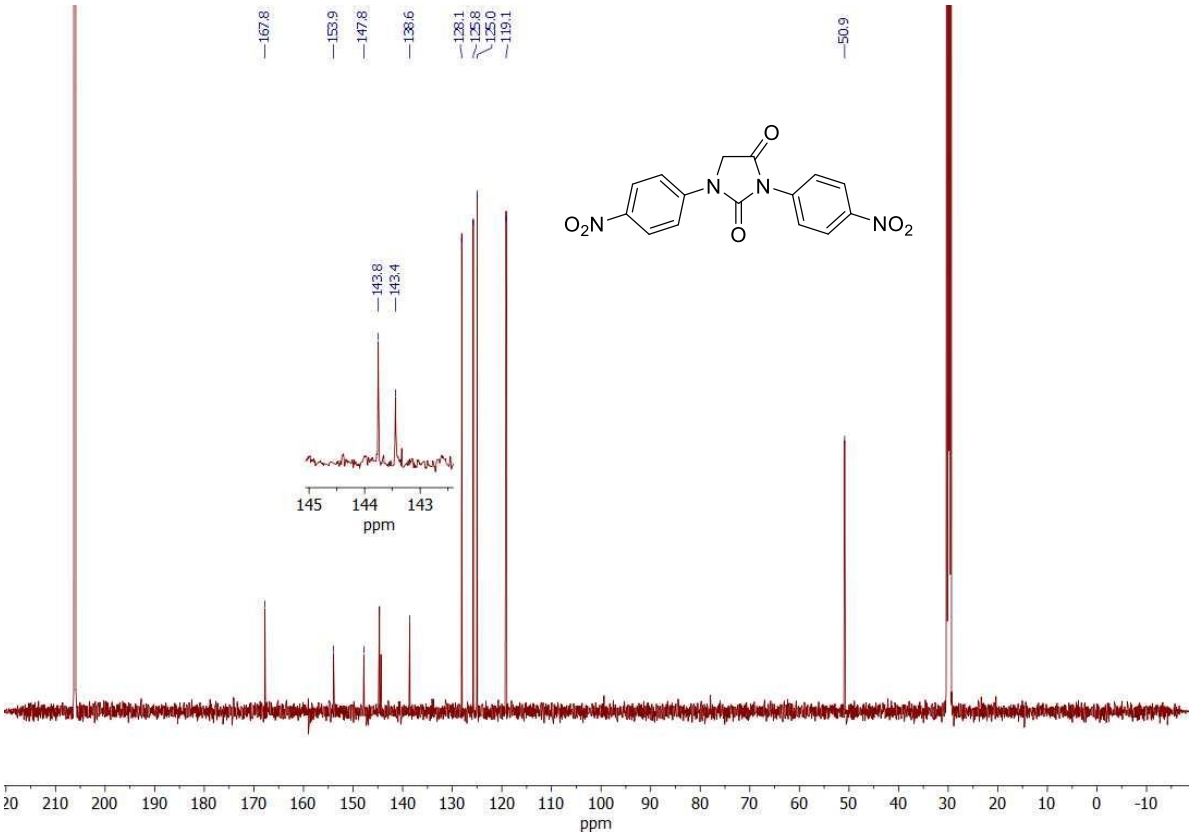
HRMS (ESI) *m/z* $[M - H]^+$: Calcd. for $C_{15}H_9N_4O_6^+$: 341.0528, found: 341.0528.

This compound has not been reported in the literature.

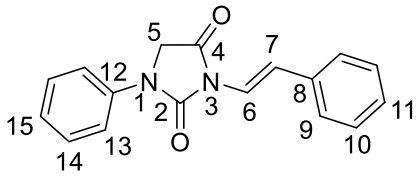
^{1}H NMR spectrum of **3c** (600 MHz, Acetone-d_6)



^{13}C NMR spectrum of **3c** (151 MHz, Acetone-d_6)



(E)-1-Phenyl-3-styrylhydantoin (3d)



[NEW]

3d was prepared according to general procedure I and obtained as a white solid (24.6 mg, 0.088 mmol, 45 %). The crude product was purified by column chromatography [hexane:chloroform (30:70 %)]. The resulting crude was concentrated under reduced pressure and triturated with acetone and methanol.

3d was prepared according to general procedure J on 0.2 mmol scale and obtained as a white solid (24.4 mg, 0.088 mmol, 45 %). The crude product was purified by column chromatography [hexane:chloroform (2:4→2:5)].

R_f = 0.36 [hexane:chloroform (30:70)]

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 15.1 Hz, 1H, H7), 7.60 (AA', 2H, H13), 7.46 – 7.42 (m, 4H, H9 and H14), 7.35 (BB', 2H, H10), 7.27 (m, 1H, H11(overlap with $CDCl_3$)), 7.23 – 7.20 (m, 2H, H6 and H15 (overlap with vinylic proton)), 4.37 (s, 2H, H5).

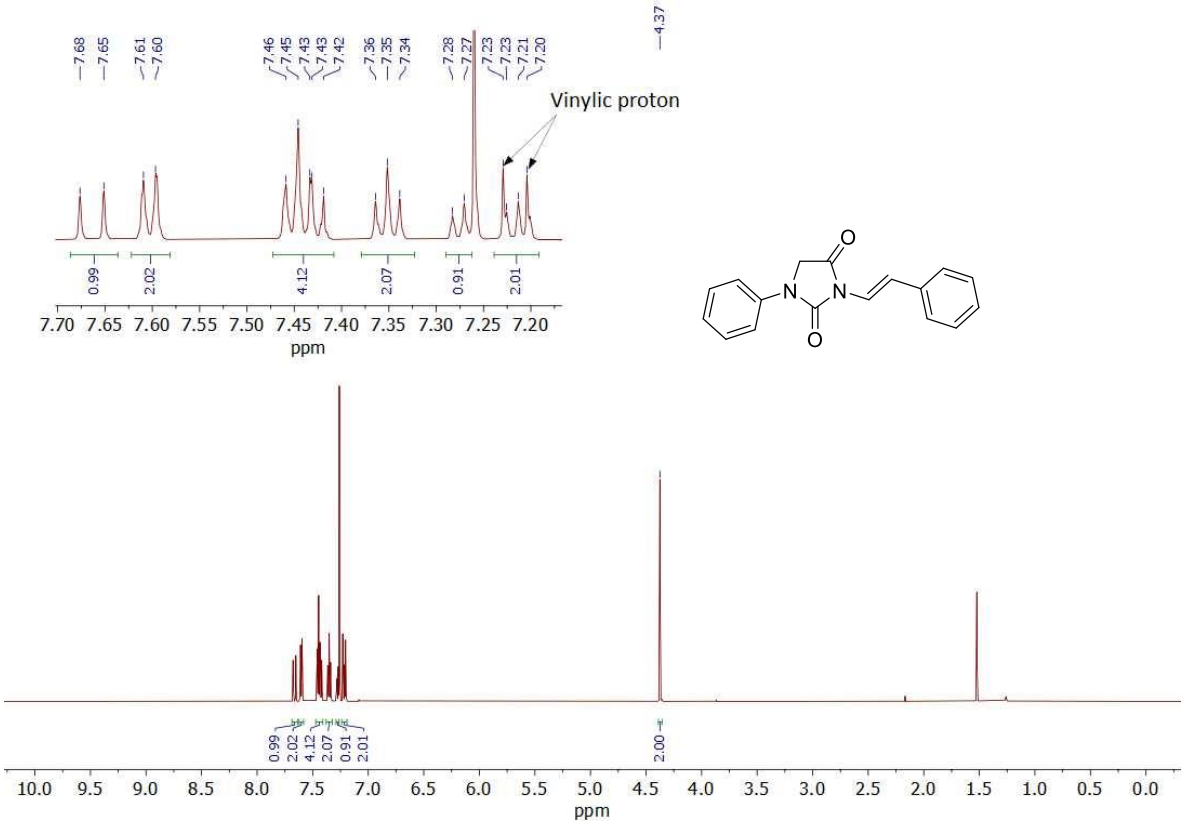
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3 (C4), 152.3 (C2), 137.2 (C12), 135.6 (C8), 129.5 (C14), 128.8 (C10), 127.8 (C11), 126.3 (C9), 125.0 (C15), 121.1 (C7), 118.8 (C13), 117.7 (C6), 49.3 (C5).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{17}H_{14}N_2NaO_2^+$:301.0947, found: 301.0947.

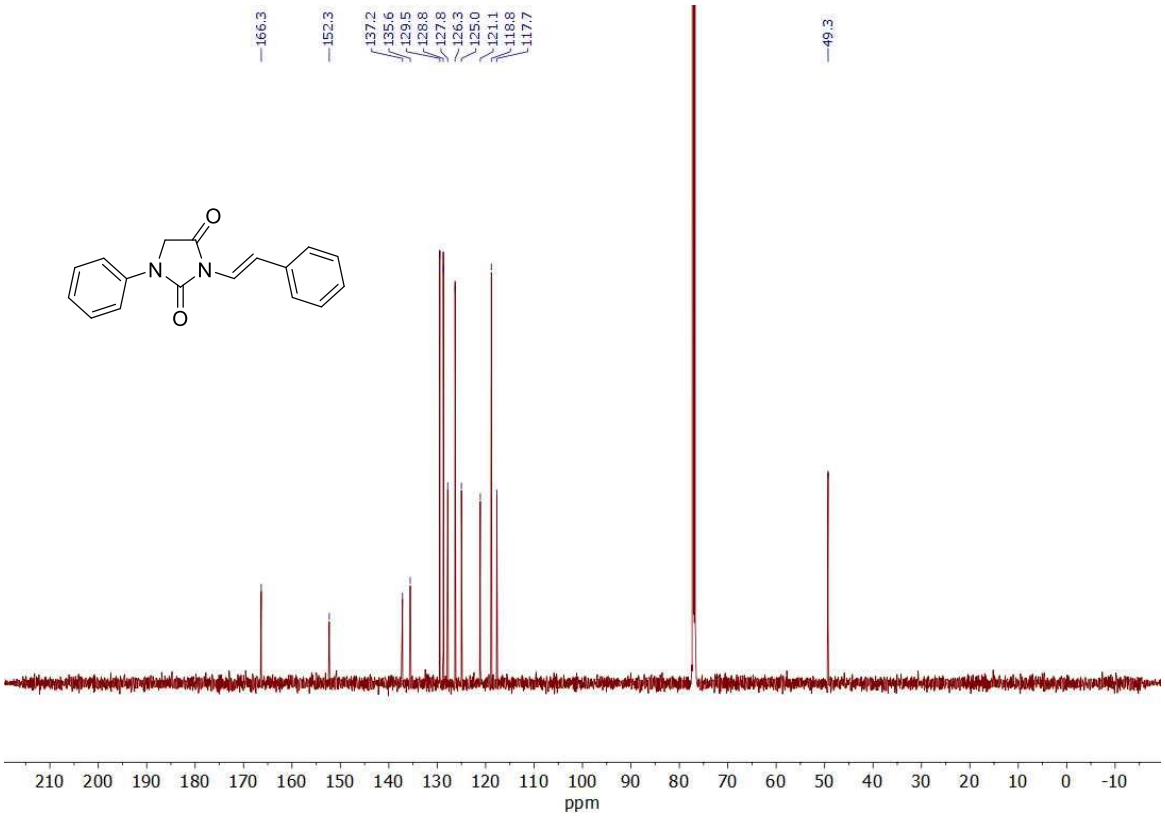
IR (ATR): ṽ (cm^{-1}) 3030 (w), 2935 (w), 2358 (w), 2331 (w), 1739 (s), 1697 (s), 1380 (s), 1375 (s), 742 (m), 686 (m).

This compound has not been reported in the literature.

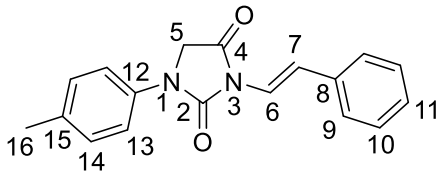
^{1}H NMR spectrum of **3d** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3d** (151 MHz, $CDCl_3$)



(E)-3-Styryl-1-(4-tolyl)hydantoin (3e)



[NEW]

3e was prepared according to general procedure I and obtained as a white solid (10.5 mg, 0.036 mmol, 18 %) The crude product was purified by column chromatography [hexane:chloroform:acetone (6:2:1)] The resulting crude was concentrated under reduced pressure and triturated with methanol.

R_f = 0.44 [hexane:chloroform:acetone (6:2:1)]

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 15.1 Hz, 1H, H7), 7.48 – 7.43 (m, 4H, H9 and H13), 7.35 (BB', 2H, H10), 7.26 (C, 1H, H11), 7.24 – 7.19 (m, 3H, H6 and H14), 4.34 (s, 2H, H5), 2.36 (s, 3H, H16).

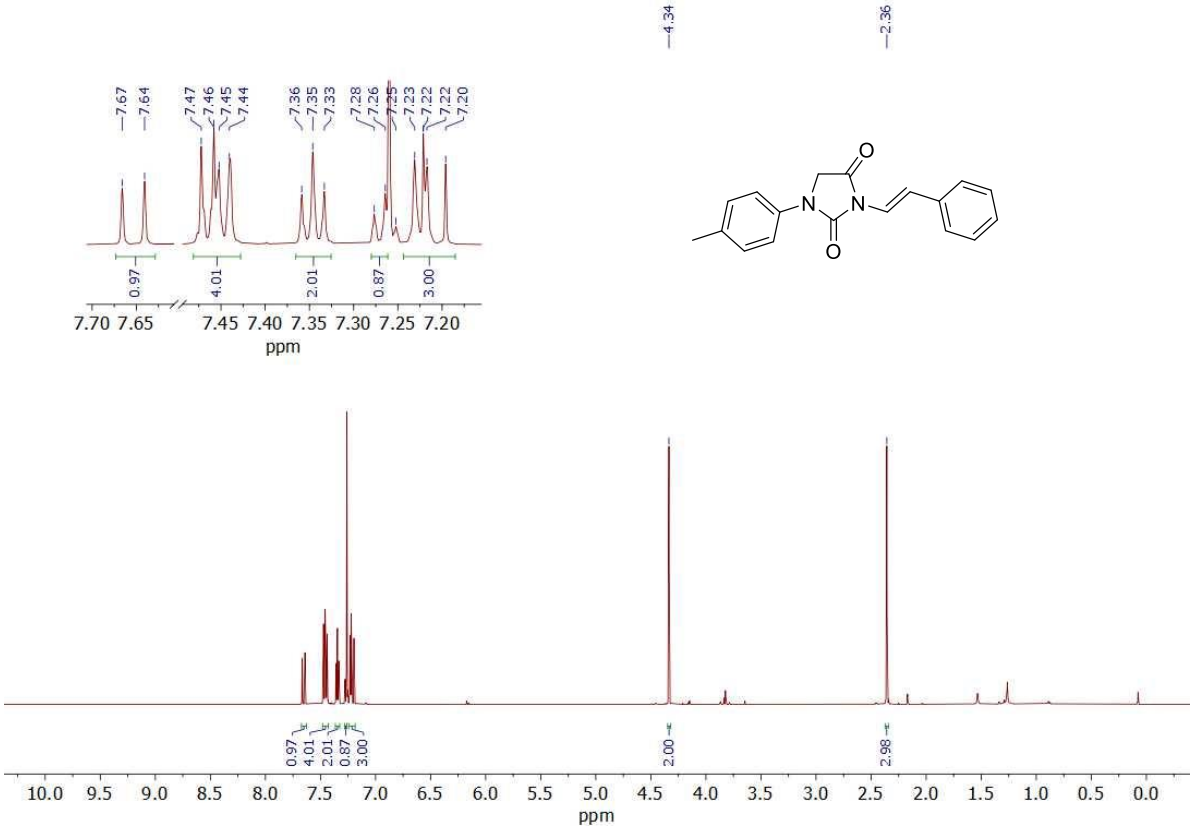
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5 (C4), 152.3 (C2), 135.6 (C8), 134.9 (C12), 134.6 (C15), 130.0 (C14), 128.7 (C10), 127.8 (C11), 126.3 (C9), 120.9 (C7), 119.0 (C13), 117.8 (C6), 49.4 (C5), 20.8 (C16).

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

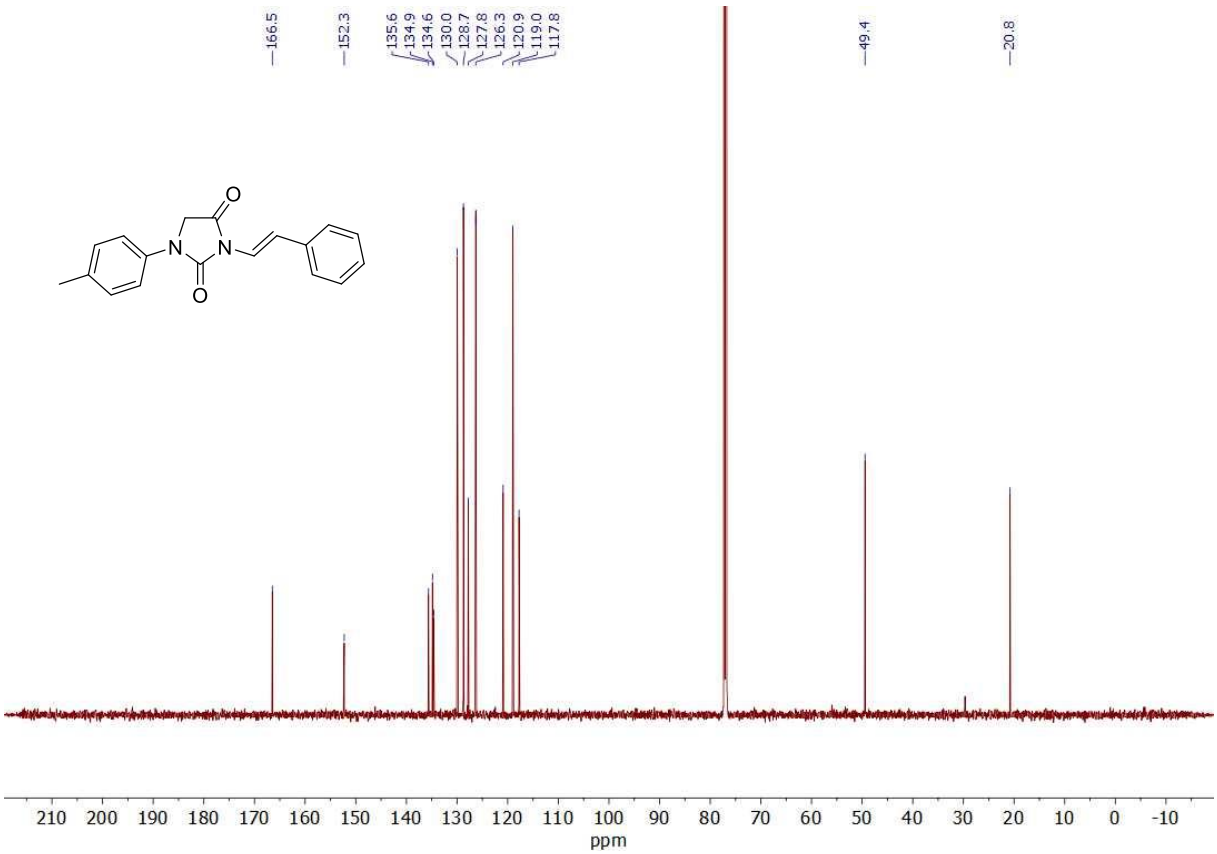
IR (ATR): ṽ (cm^{-1}) 2360 (s), 2339 (s), 1708 (m), 1442 (m), 1406 (m), 1153 (m), 1056 (br s), 813 (m), 742 (m).

This compound has not been reported in the literature.

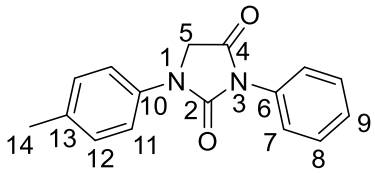
^{1}H NMR spectrum of **3e** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3e** (151 MHz, $CDCl_3$)



3-Phenyl-1-(4-tolyl)hydantoin (3f)



[15355-74-5]

3f was prepared according to general procedure J and obtained as a white solid (42.3 mg, 0.159 mmol, 40 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10→80:20 %)]

R_f = 0.28 [hexane:ethyl acetate (80:20)]

This compound presents a 1: AA'BB'C and a 2: AA'BB' system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 4H, H8 and H12), 7.46 (1AA', 2H, H7), 7.40 (1C, 1H, H9), 7.22 (2AA', *J* = 8.3 Hz, 2H, H11), 4.44 (s, 2H, H5), 2.36 (s, 3H, H14).

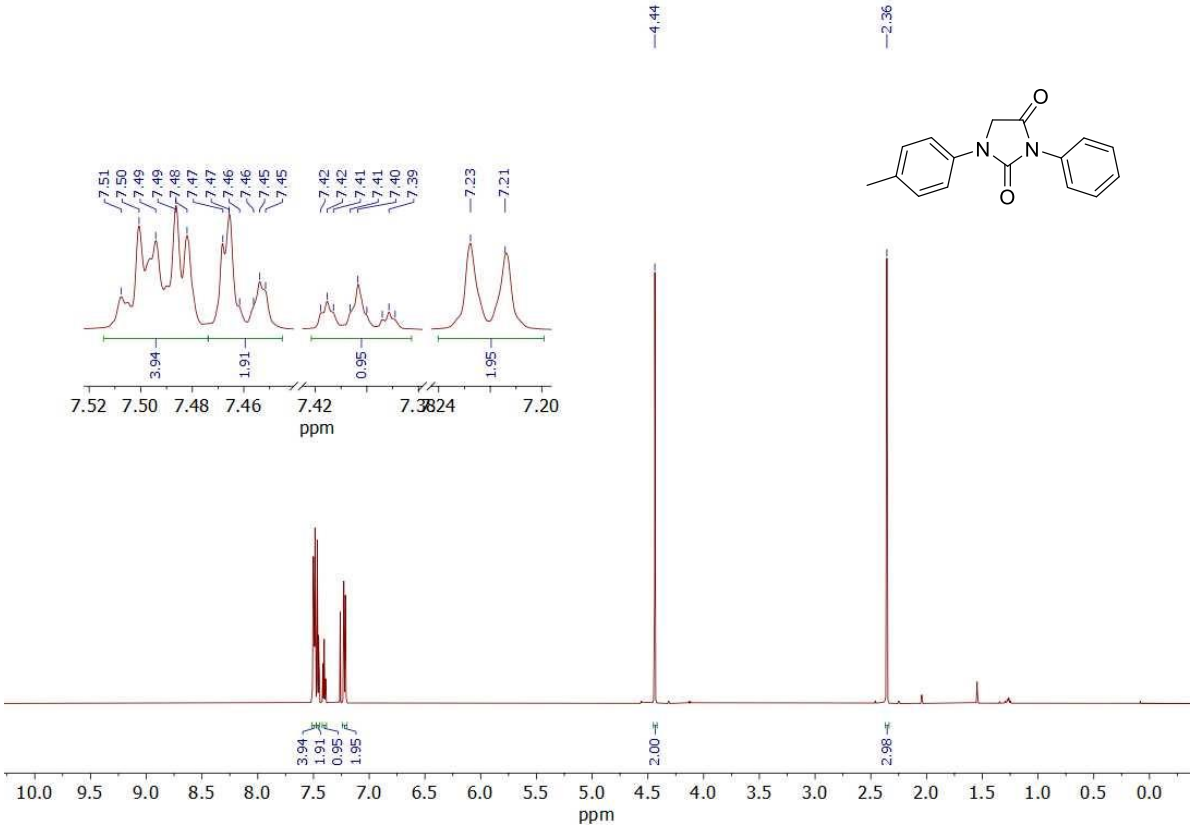
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5 (C4), 153.2 (C2), 134.9 (C10/C13), 134.5 (C10/C13), 131.4 (C6), 129.9 (C11), 129.1 (C8), 128.4 (C9), 126.3 (C7), 118.8 (C12), 50.0 (C5), 20.8 (C14).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{16}H_{14}N_2NaO_2^+$: 289.0947, found: 289.0947.

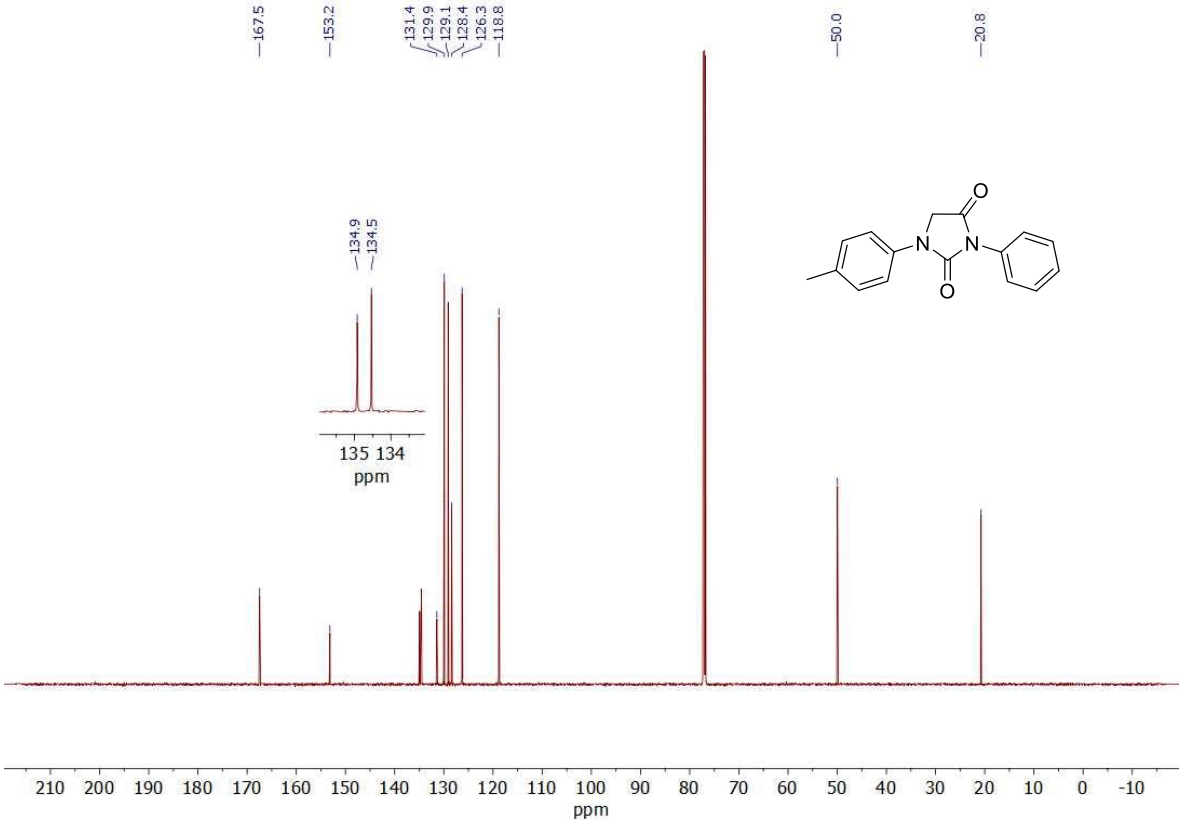
IR (ATR): ṽ (cm^{-1}) 2970 (w), 2918 (w), 2358 (w), 2339 (w), 1737 (s), 1716 (s), 1371 (s), 1217 (m), 810 (m), 692 (m).

This compound has been reported in the literature.[61]

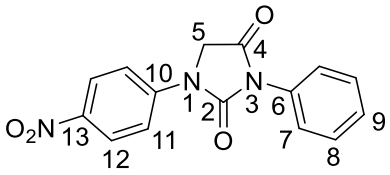
^{1}H NMR spectrum of **3f** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3f** (151 MHz, $CDCl_3$)



1-(4-Nitrophenyl)-3-phenylhydantoin (3g)



[NEW]

3g was prepared according to general procedure J and obtained as a white solid (52.9 mg, 0.178 mmol, 40 %) The crude product was purified by column chromatography [hexane:ethyl acetate (80:20→70:30 %)]

R_f = 0.12 [hexane:ethyl acetate (80:20)]

This compound presents a 1: AA'BB'C and a 2: AA'BB' system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (2BB', 2H, H12), 7.84 (2AA', 2H, H11), 7.53 (1BB', 2H, H8), 7.48 – 7.42 (m, 3H, H7 and H9), 4.56 (s, 2H, H5).

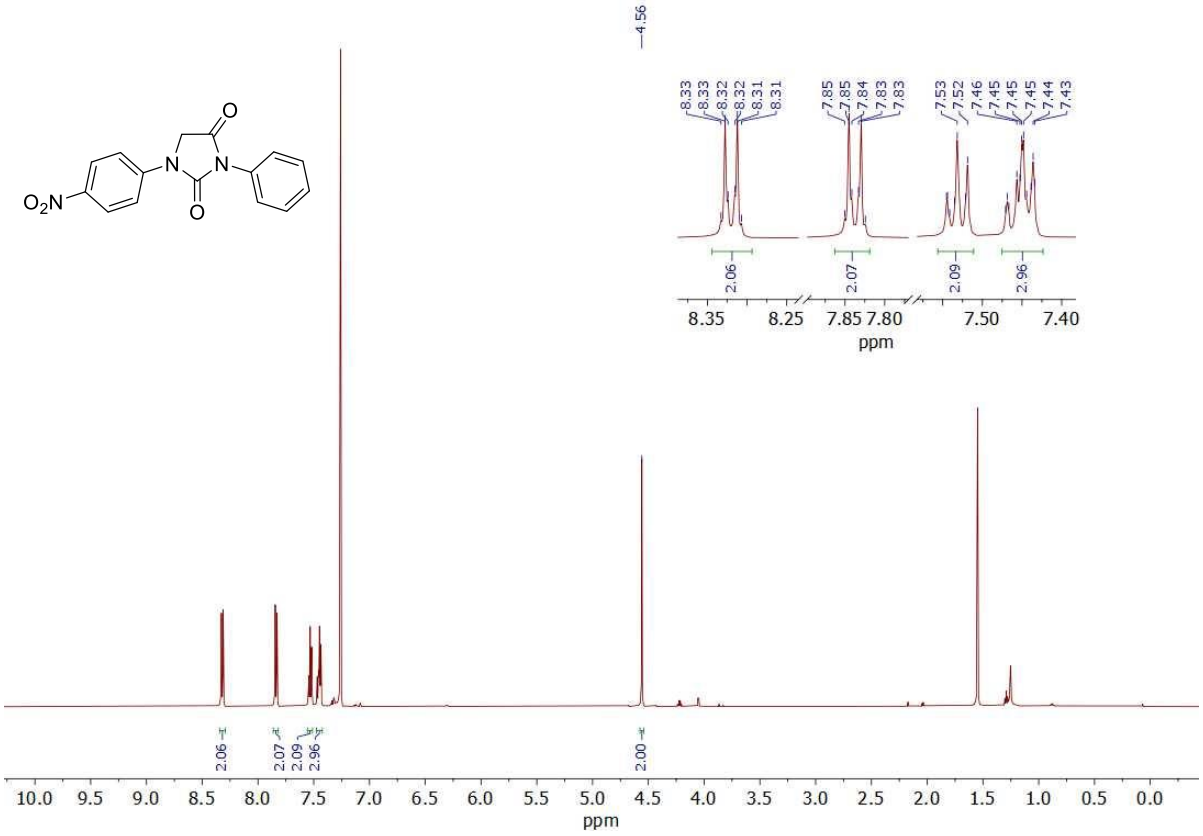
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2 (C4), 153.1 (C2), 143.7 (C10/C13), 142.9 (C10/C13), 130.7 (C6), 129.4 (C8), 129.0 (C9), 126.3 (C7), 125.3 (C12), 117.7 (C11), 49.5 (C5).

HRMS (ESI) *m/z* $[M - H]^+$: Calcd. for $C_{15}H_{10}N_3O_4^+$: 296.0677, found: 296.0676.

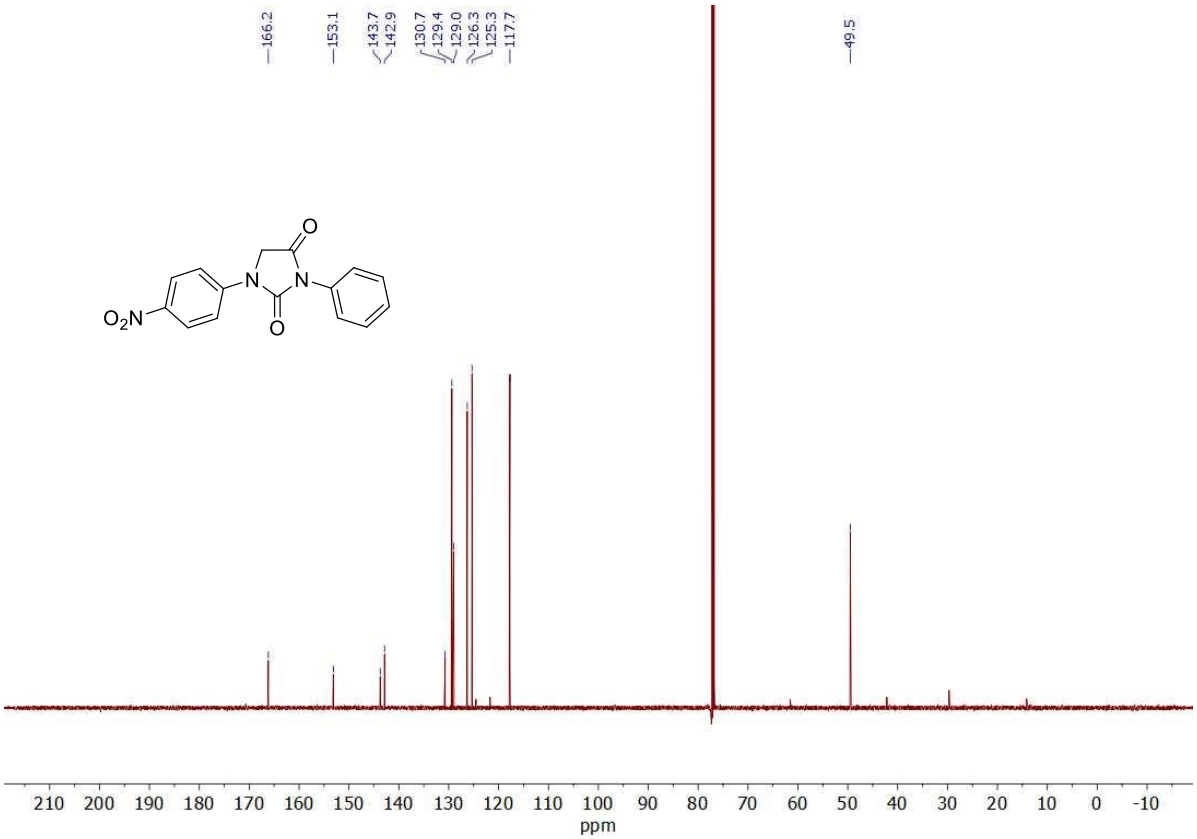
IR (ATR): ṽ (cm^{-1}) 2922 (w), 2358 (w), 2329 (w), 1778 (m), 1718 (s), 1492 (s), 1323 (s), 1184 (s), 1107 (m), 821 (m), 694 (m).

This compound has not been reported in the literature.

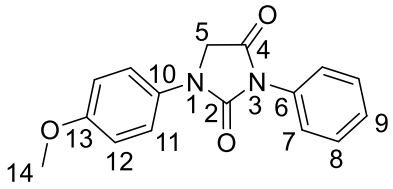
^{1}H NMR spectrum of **3g** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3g** (151 MHz, $CDCl_3$)



1-(4-Methoxypenyl)-3-phenylhydantoin (3h)



[14486-57-8]

3h was prepared according to general procedure J and obtained as a white solid (75.2 mg, 0.266 mmol, 66 %) The crude product was purified by column chromatography [hexane:ethyl acetate (80:20 %)]

R_f = 0.15 [hexane:ethyl acetate (80:20)]

This compound presents a 1: AA'BB'C and a 2: AA'BB' system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 4H, H8 and H11), 7.45 (1AA', 2H, H7), 7.40 (1C, 1H, H9), 6.95 (2BB', 2H, H12), 4.43 (s, 2H, H5), 3.82 (s, 3H, H14).

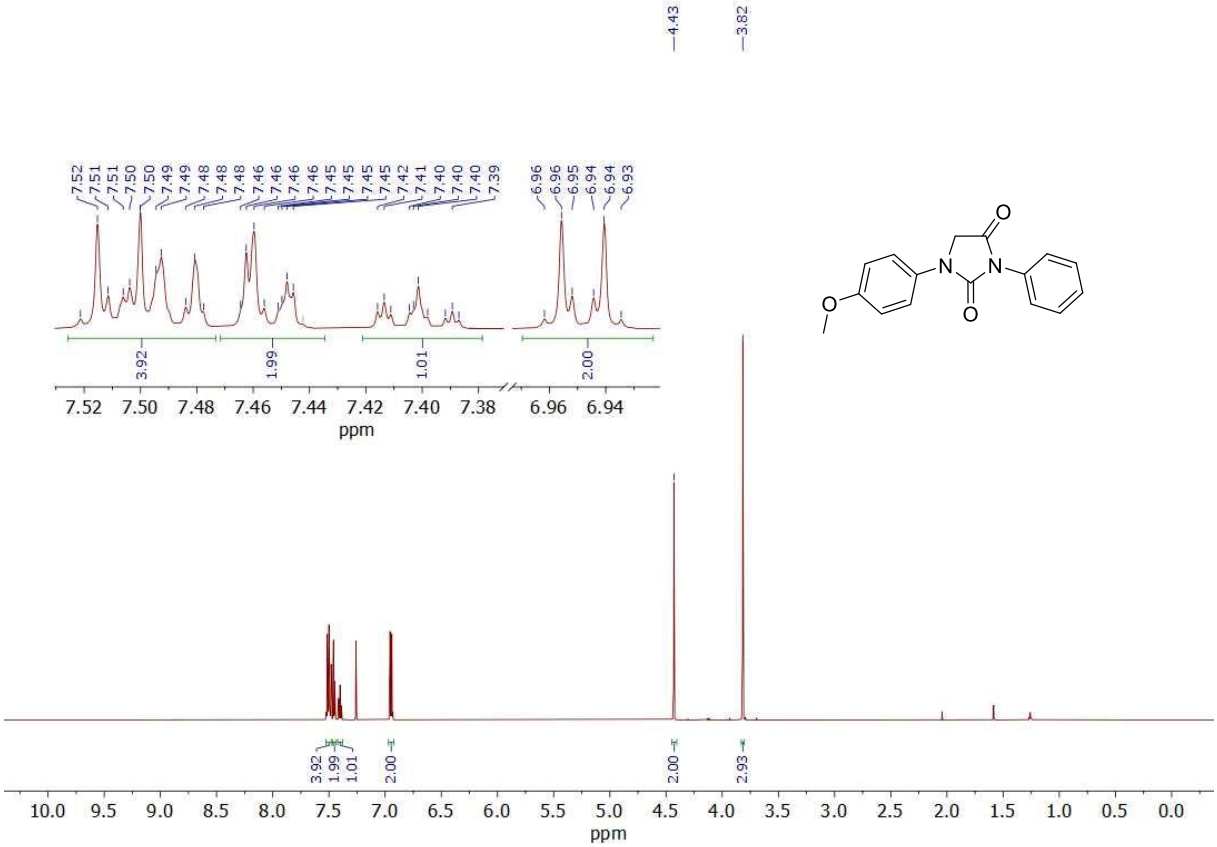
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5 (C4), 156.8 (C13), 153.2 (C2), 131.4 (C6), 130.4 (C10), 129.1 (C8), 128.4 (C9), 126.2 (C7), 120.8 (C11), 114.5 (C12), 55.5 (C14), 50.3 (C5).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{16}H_{14}N_2NaO_3^+$: 305.0897, found: 305.0896.

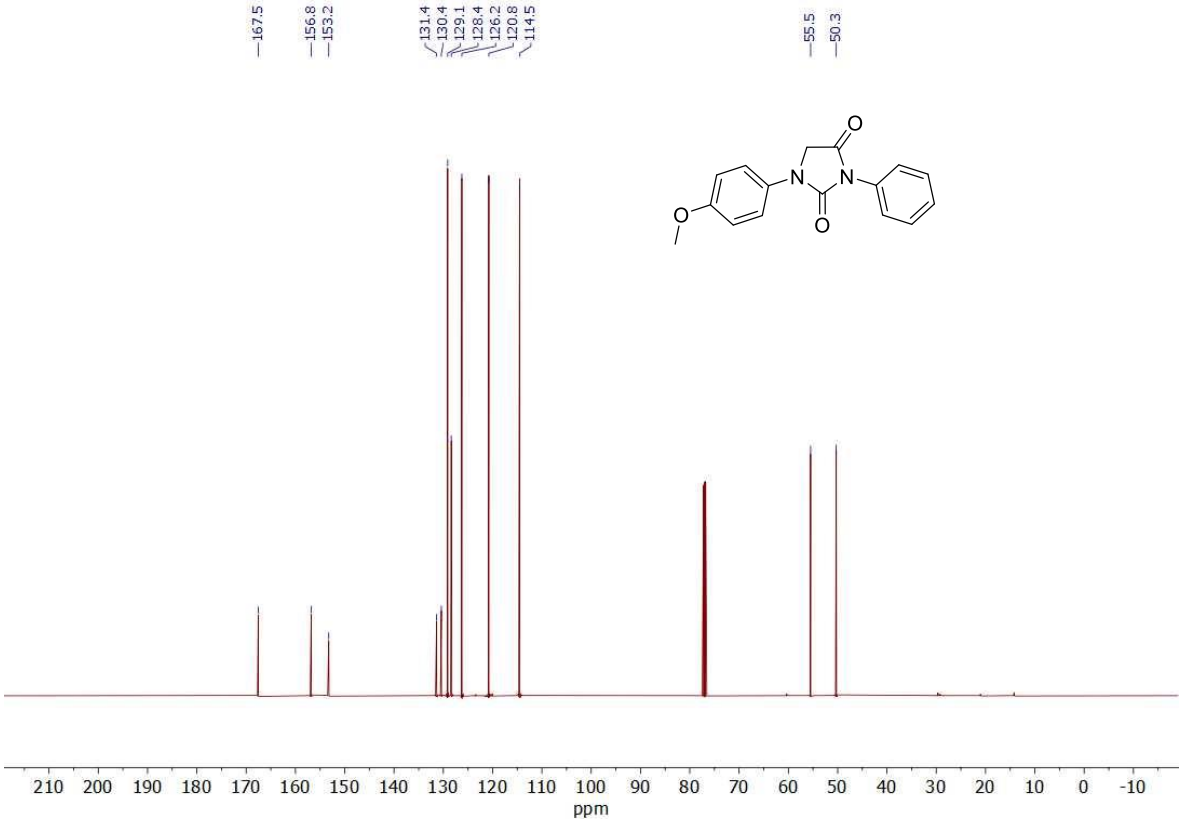
IR (ATR): ṽ (cm^{-1}) 2929 (w), 2839 (w), 2360 (m), 2331 (m), 1776 (m), 1704 (s), 1515 (m), 1444 (m), 1413 (m), 1253 (s), 1157 (s), 831 (m), 756 (m), 692 (m).

The spectroscopic data is in accordance with the literature.[20]

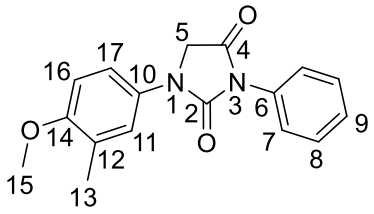
^{1}H NMR spectrum of **3h** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3h** (151 MHz, $CDCl_3$)



1-(4-Methoxy-3-methylphenyl)-3-phenylhydantoin (3i)



[NEW]

3i was prepared according to general procedure J and obtained as a white solid (47.2 mg, 0.159 mmol, 40 %) The crude product was purified by column chromatography [hexane:ethyl acetate (80:20 %)]

R_f = 0.15 [hexane:ethyl acetate (80:20)]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 4H, H7 and H8), 7.41 – 7.37 (m, 2H, H9 and H11), 7.34 (dd, *J* = 8.7, 2.9 Hz, 1H, H17), 6.85 (d, *J* = 8.8 Hz, 1H, H16), 4.42 (s, 2H, H5), 3.84 (s, 3H, H15), 2.25 (s, 3H, H13).

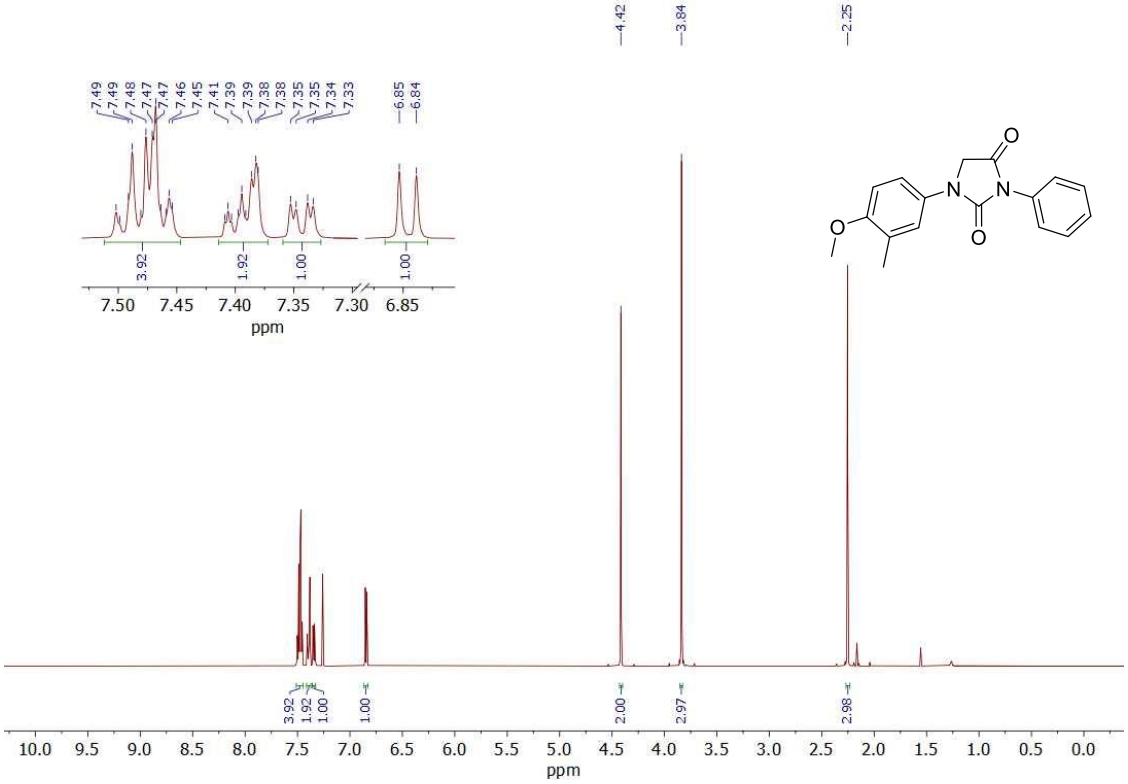
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.6 (C4), 155.2 (C14), 153.3 (C2), 131.5 (C6), 129.9 (C10), 129.1 (C8), 128.3 (C9), 127.8 (C12), 126.2 (C7), 122.3 (C11), 118.1 (C17), 110.4 (C16), 55.6 (C14), 50.5 (C5), 16.4 (C13).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{17}H_{16}N_2NaO_3^+$: 319.053, found: 319.1053.

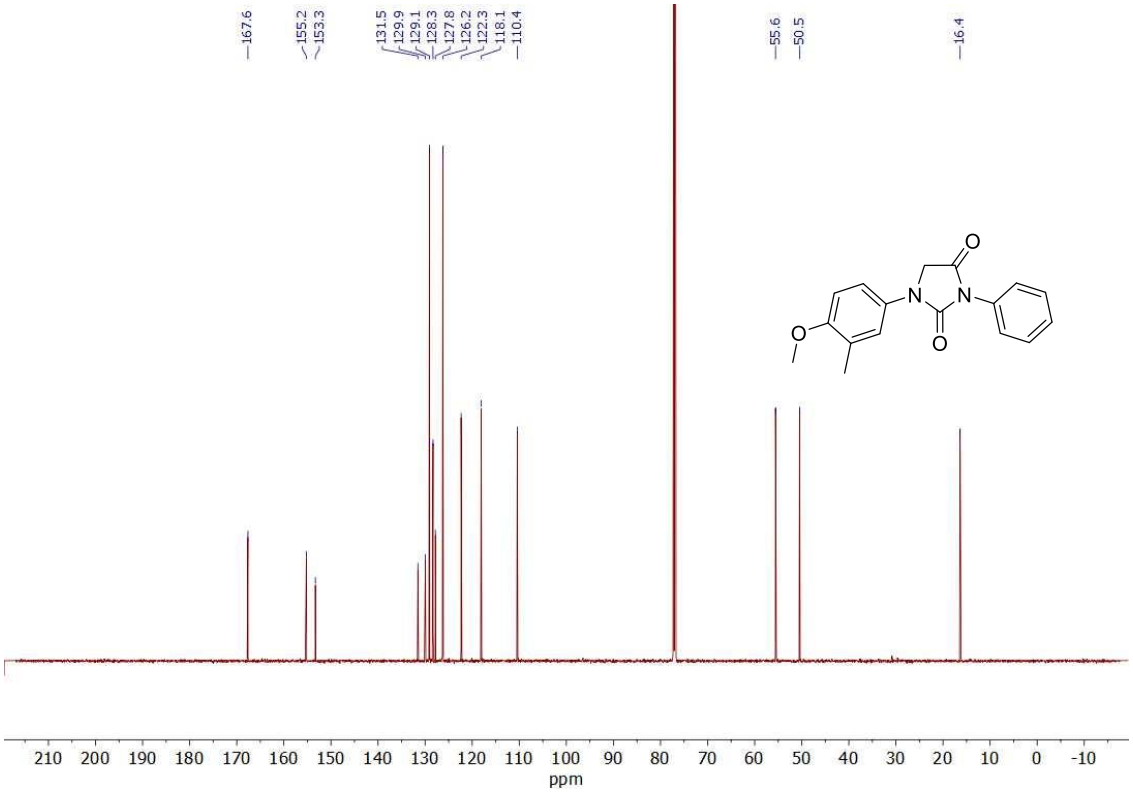
IR (ATR): ṽ (cm^{-1}) 2970 (w), 2839 (w), 2358 (w), 2329 (w), 1728 (s), 1710 (s), 1367 (m), 1226 (m), 754 (m), 692 (m).

This compound has not been reported in the literature.

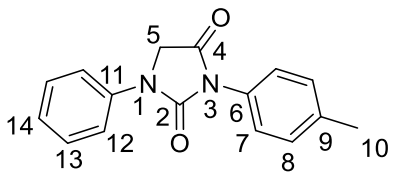
^{1}H NMR spectrum of **3i** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3i** (151 MHz, $CDCl_3$)



1-Phenyl-3-(4-tolyl)hydantoin (3j)



[58532-68-6]

3j was prepared according to general procedure J on 0.27 mmol scale and obtained as a white solid (47.9 mg, 0.180 mmol, 67 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10 %→80:20 %)]

R_f = 0.23 [hexane:ethyl acetate (80:20)]

This compound presents a 1: AA'BB'C and a 2: AA'BB' system.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (1AA', 2H, H12), 7.42 (1BB', 2H, H13), 7.33 (2AA', 2H, H7), 7.30 (2BB', 2H, H8), 7.19 (1C, 1H, H14), 4.44 (s, 2H, H5), 2.40 (s, 3H, H10).

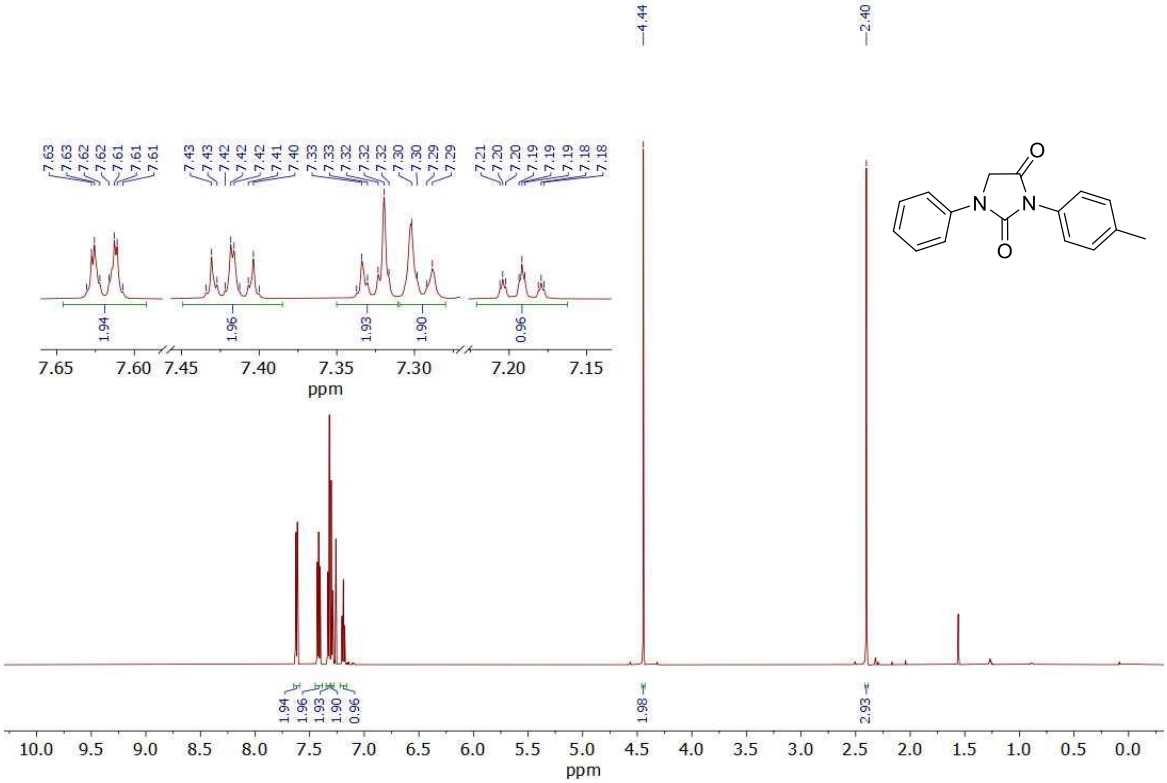
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4 (C4), 153.3 (C2), 138.6 (C9), 137.5 (C11), 129.8 (C8), 129.4 (C13), 128.7 (C6), 126.2 (C7), 124.6 (C14), 118.6 (C12), 49.8 (C5), 21.2 (C10).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{16}H_{14}N_2NaO_2^+$: 289.0947, found: 289.0949.

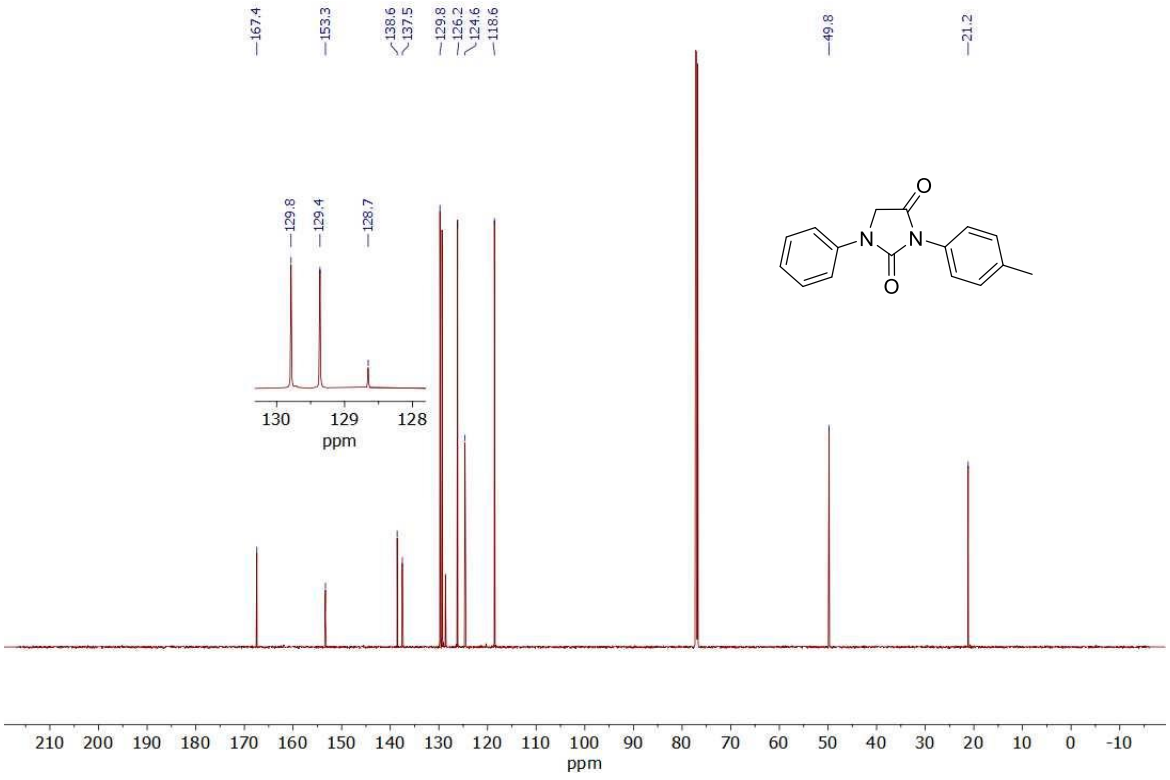
IR (ATR): ṽ (cm^{-1}) 2970 (w), 2918 (w), 2358 (w), 2335 (w), 1722 (m), 1710 (s), 1375 (s), 1153 (m), 752 (m).

The spectroscopic data is in accordance with the literature.[62]

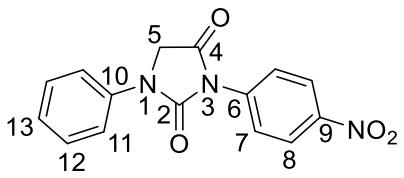
^{1}H NMR spectrum of **3j** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3j** (151 MHz, $CDCl_3$)



3-(4-Nitrophenyl)-1-phenylhydantoin (3k)



[NEW]

3k was prepared according to general procedure J on 0.18 mmol scale and obtained as a white solid (2.0 mg, 0.0067 mmol, 4 %) The crude product was purified by column chromatography [hexane:ethyl acetate (80:20 % →70:30 %)]

R_f = 0.15 [hexane:ethyl acetate (80:20)]

This compound presents a 1: AA'BB'C and a 2: AA'BB' system.

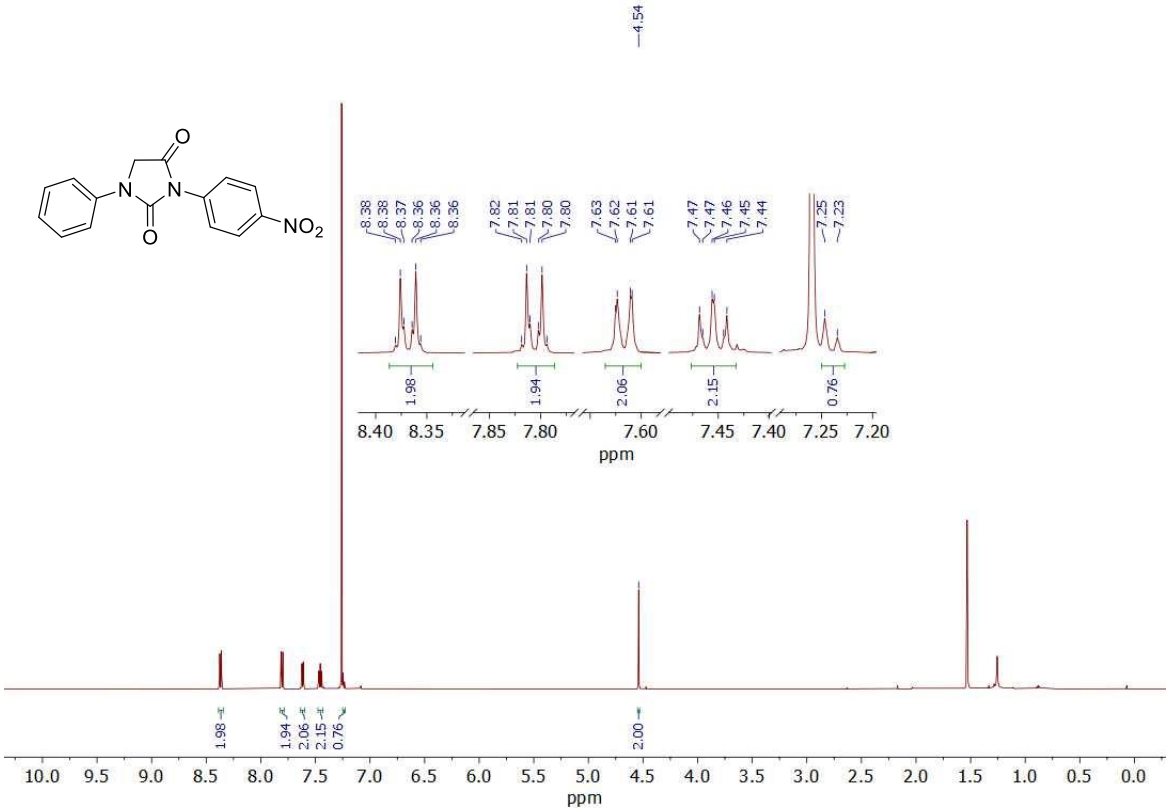
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (2BB', 2H, H8), 7.81 (2AA', 2H, H7), 7.62 (1AA', 2H, H10), 7.46 (1BB', 2H, H12), 7.24 (1C, 1H, H13), 4.54 (s, 2H, H5).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6 (C4), 152.1 (C2), 146.7 (C6), 137.0 (C9), 136.9 (C10), 129.6 (C12), 126.2 (C7), 125.4 (C13), 124.4 (C8), 119.0 (C11), 49.9 (C5).

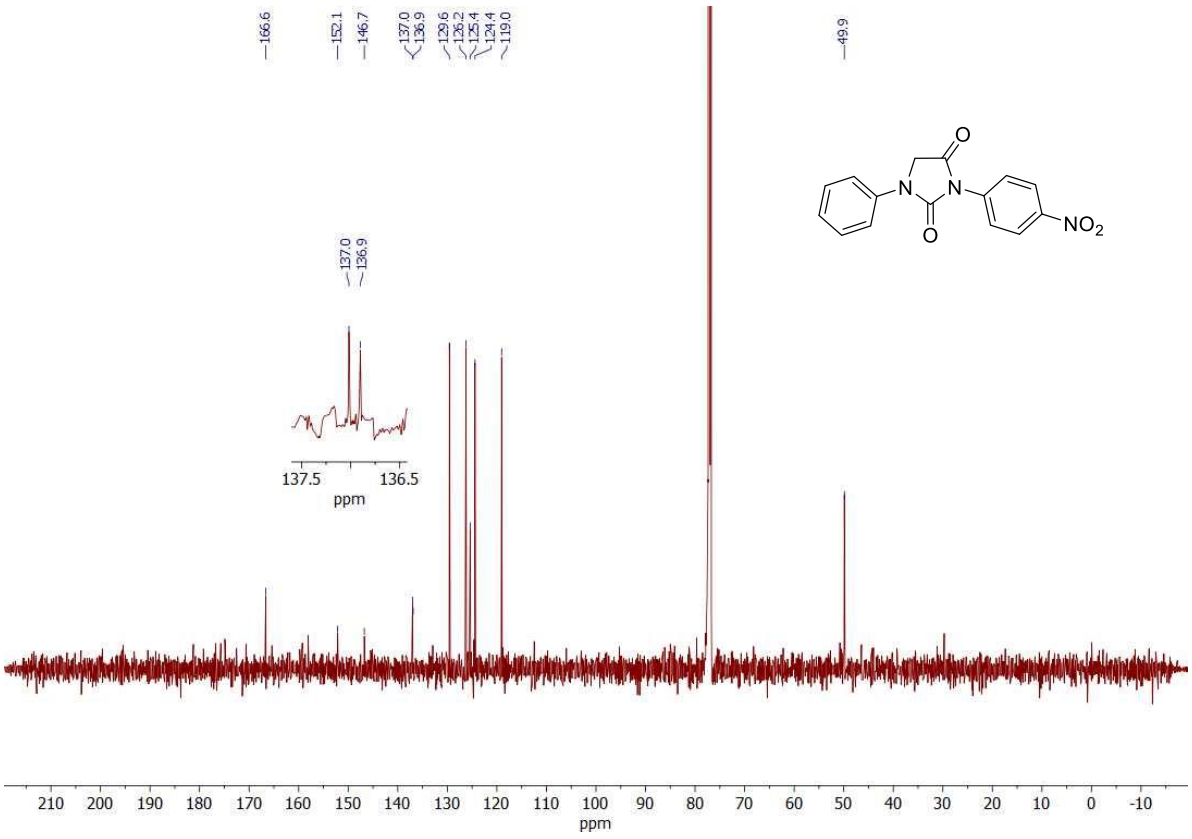
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{15}H_{11}N_3NaO_4^+$: 320.0642, found: 320.0641.

This compound has not been reported in the literature.

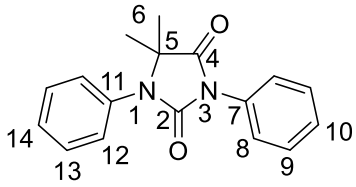
^{1}H NMR spectrum of **3k** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3k** (151 MHz, $CDCl_3$)



5,5-Dimethyl-1,3-diphenylhydantoin (3l)



[87976-13-4]

3l was prepared according to general procedure J on 0.31 mmol scale and obtained as a white solid (5.3 mg, 0.0189 mmol, 6 %) The crude product was purified by column chromatography [hexane:ethyl acetate (90:10 % → 80:20 %)]. The resulting crude was concentrated under reduced pressure and the product was further purified with flash chromatography on a silica plug [hexane:ethyl acetate (80:20 %)].

R_f = 0.24 [hexane:ethyl acetate (80:20)]

This compound presents an AA'BB'C system.

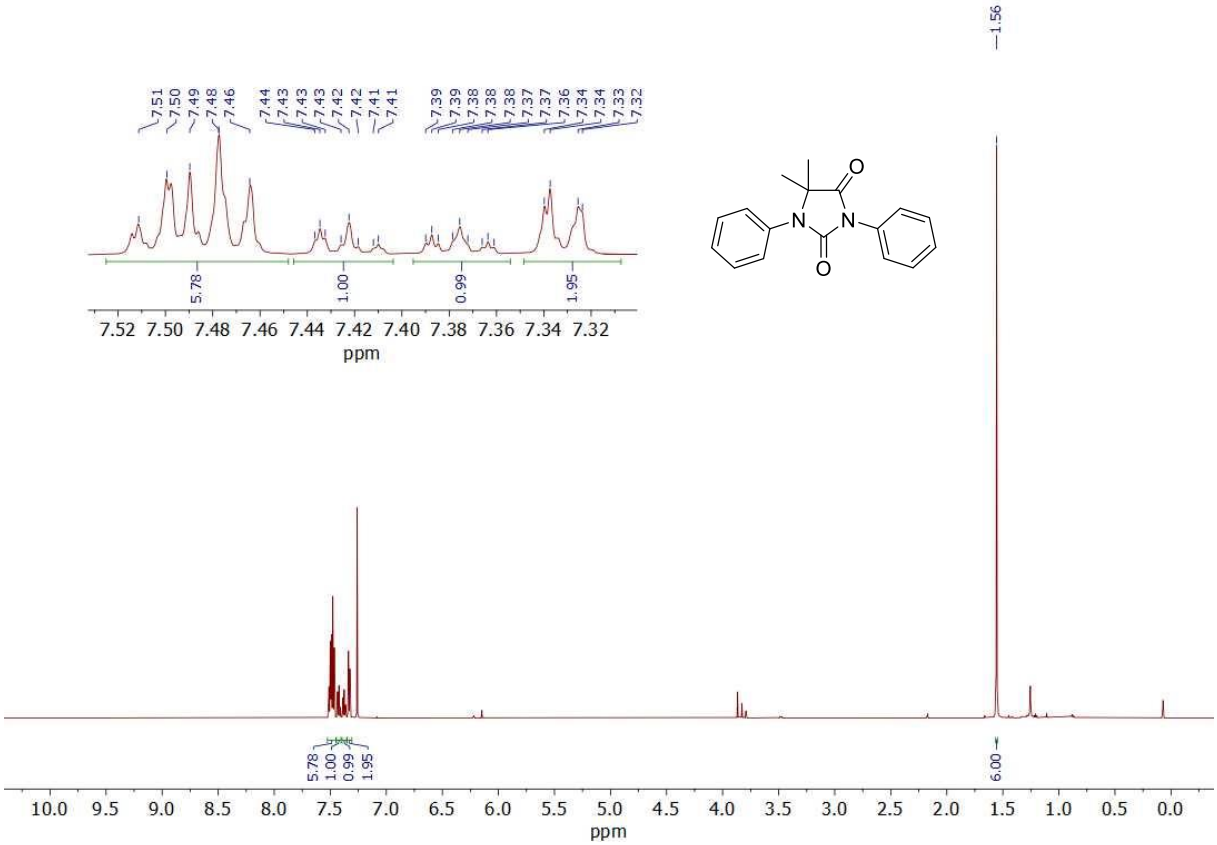
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 6H, H8, H9 and H13), 7.42 (C, 1H, H14), 7.37 (C, 1H, H10), 7.33 (AA', 2H, H12), 1.56 (s, 6H, H6).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.2 (C4), 153.9 (C2), 134.0 (C11), 131.7 (C7), 129.6 (C13), 129.0 (C9, C12), 128.6 (C14), 128.1 (C10), 126.1 (C8), 63.4 (C5), 24.1 (C6).

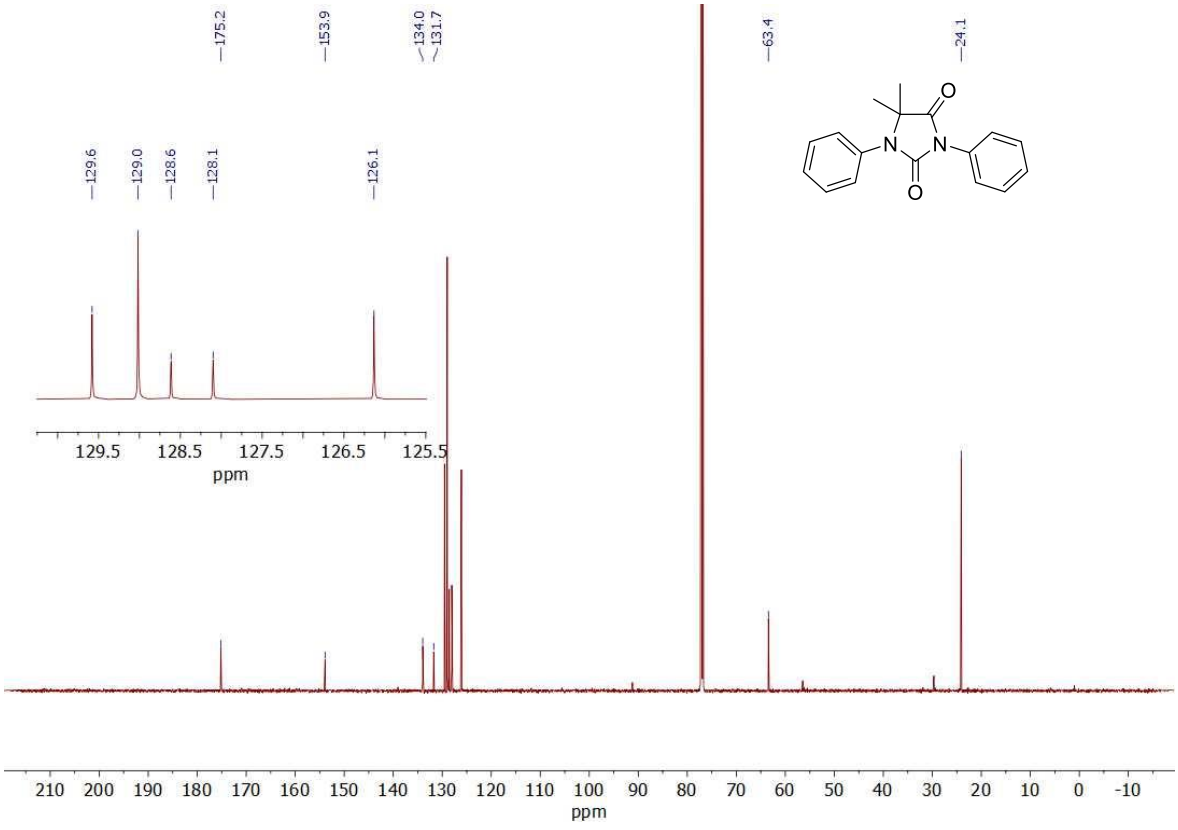
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{17}H_{16}N_2NaO_2^+$: 303.1104, found: 303.1103.

The spectroscopic data is in accordance with the literature.[63]

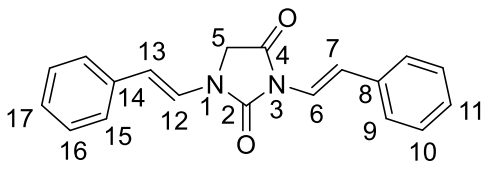
^{1}H NMR spectrum of **3l** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3l** (151 MHz, $CDCl_3$)



(*E,E*)-1,3-Distyrylhydantoin (3m)



[NEW]

3m was prepared according to general procedure J on 0.36 mmol scale, with pyridine (1 eq.) instead of K_2CO_3, and 20 mol% $Cu(OTf)_2$. The product was obtained as a white solid (14.6 mg, 0.048 mmol, 13 %) The crude product was purified by column chromatography [hexane:acetone (90:10 % →80:20)].

R_f = 0.20 [hexane:acetone (80:20)]

This compound presents an AA'BB'C system.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 15.1 Hz, 1H, H7), 7.58 (d, *J* = 14.8 Hz, 1H, H12), 7.44 (AA', 2H, H9), 7.39 – 7.31 (m, 6H, H10, H15, H16), 7.29 – 7.27 (m, 1H, H11), 7.23 (C, 1H, H17), 7.17 (d, *J* = 15.1 Hz, 1H, H6), 5.89 (d, *J* = 14.7 Hz, 1H, H13), 4.19 (s, 2H, H5).

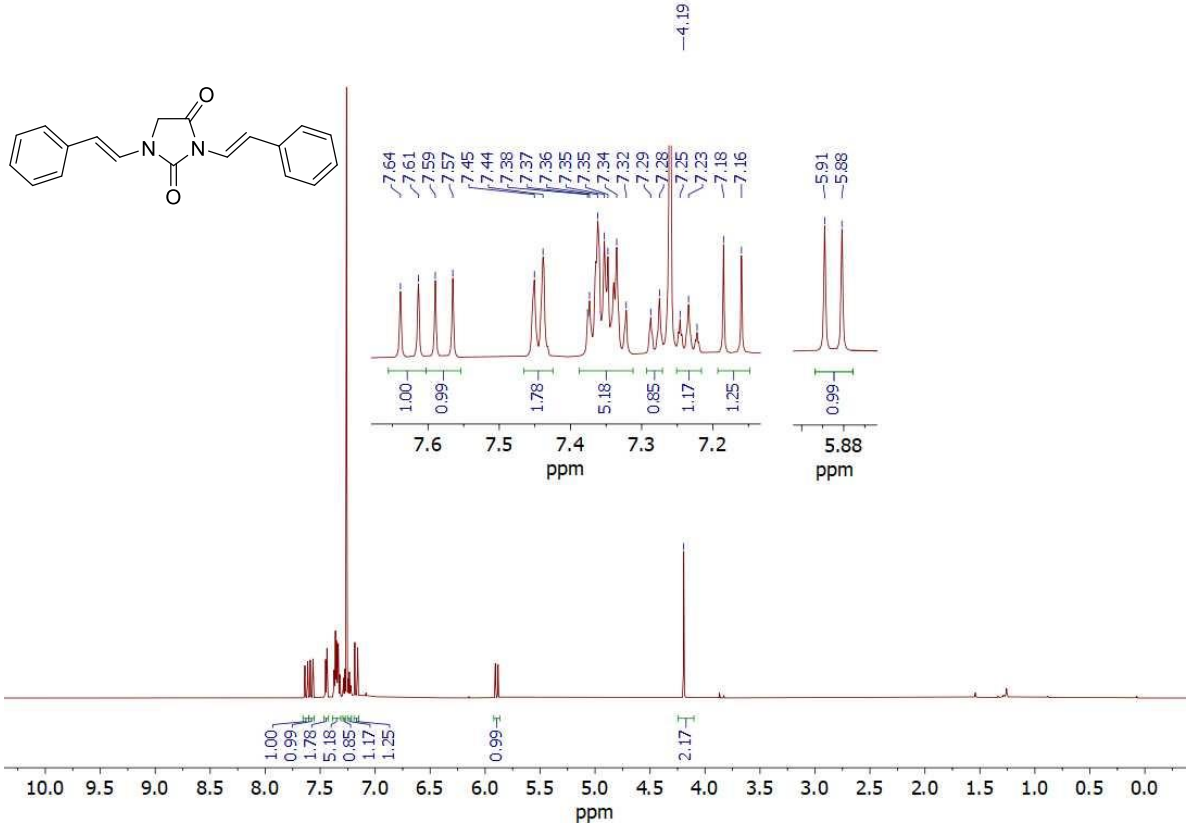
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.3 (C4), 152.1 (C2), 135.4 (C14/8), 135.2 (C14/8), 128.9 (C16/10), 128.8 (C16/10), 127.9 (C11), 127.2 (C17), 126.3 (C9), 125.7 (C15), 121.4 (C12/7), 121.1 (C12/7), 117.4 (C6), 112.0 (C13), 47.2 (C5).

HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{19}H_{16}N_2NaO_2^+$: 327.1104, found: 327.1103.

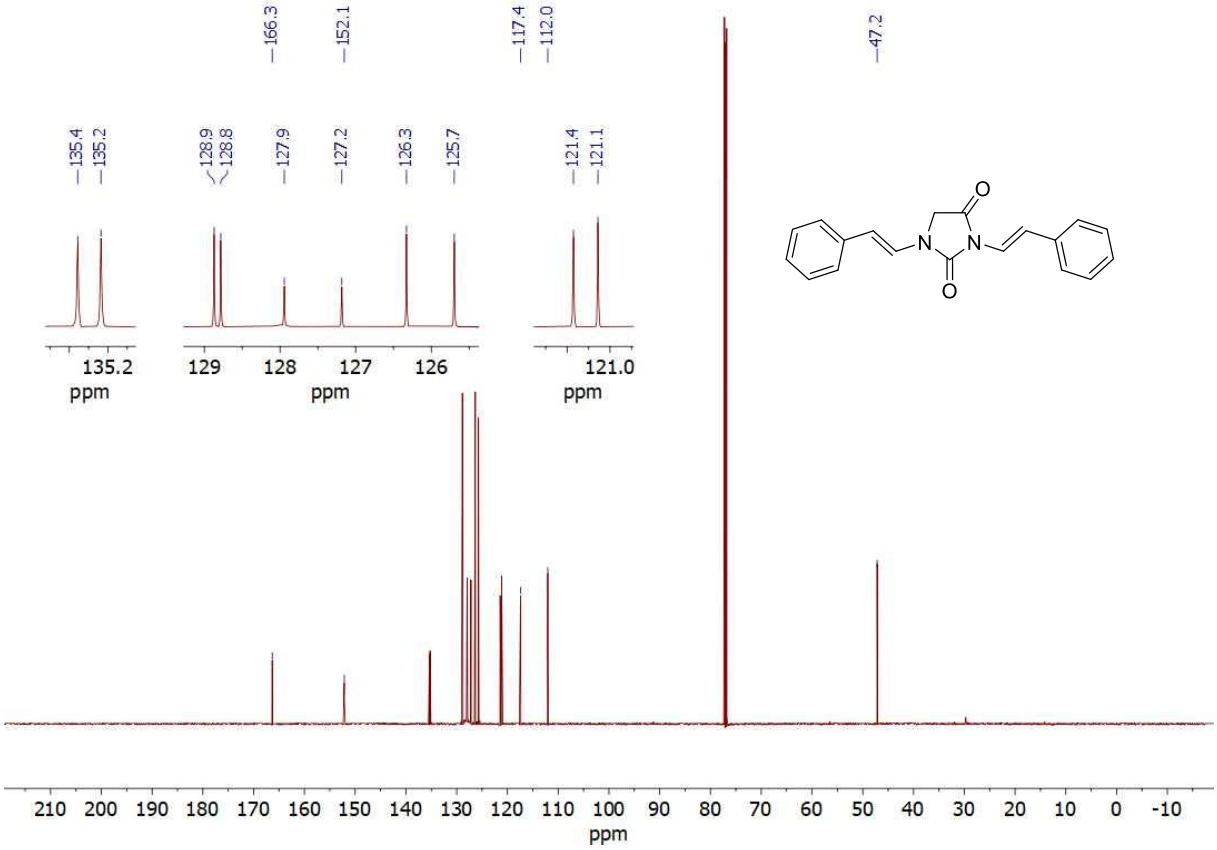
IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3026 (w), 2925 (w), 2358 (m), 2337 (m), 1739 (s), 1716 (s), 1450 (m), 1365 (m), 1217 (m), 740 (m), 694 (s).

This compound has not been reported in the literature.

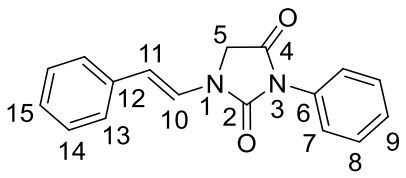
^{1}H NMR spectrum of **3m** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3m** (151 MHz, $CDCl_3$)



(*E*)-3-Phenyl-1-styrylhydantoin (3n)



[NEW]

3n was prepared according to general procedure J, with pyridine (1 eq.) instead of K_2CO_3 and obtained as a white solid (13.3 mg, 0.048 mmol, 12 %) The crude product was purified by column chromatography [hexane:chloroform (2:4 →2:5)]. The resulting crude was concentrated under reduced pressure and the product was further purified with flash chromatography on a silica plug [hexane:chloroform (2:4)]

R_f = 0.38 [hexane:chloroform (30 :70)]

This compound presents a AA'BB'C system

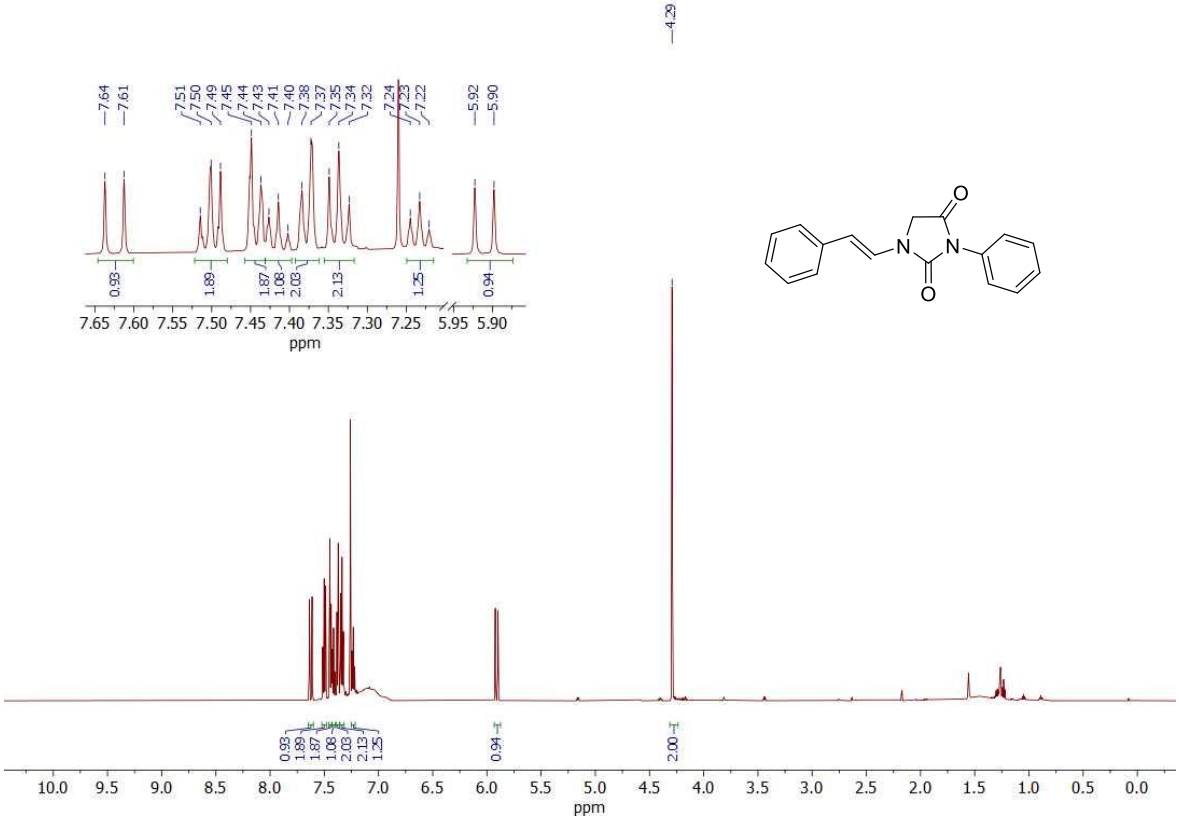
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 14.8 Hz, 1H, H10), 7.50 (BB', 2H, H8), 7.44 (AA', 2H, H7), 7.41 (C, 1H, H9), 7.37 (AA', 2H, H13), 7.34 (BB', 2H, H14), 7.23 (C, 1H, H15), 5.91 (d, *J* = 14.8 Hz, 1H, H11), 4.29 (s, 2H, H5).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4 (C4), 153.1 (C2), 135.4 (C12), 131.2 (C6), 129.2 (C8), 128.9 (C14), 128.6 (C9), 127.1 (C15), 126.1 (C7), 125.7 (C13), 121.8 (C10), 111.7 (C11), 47.7 (C5).

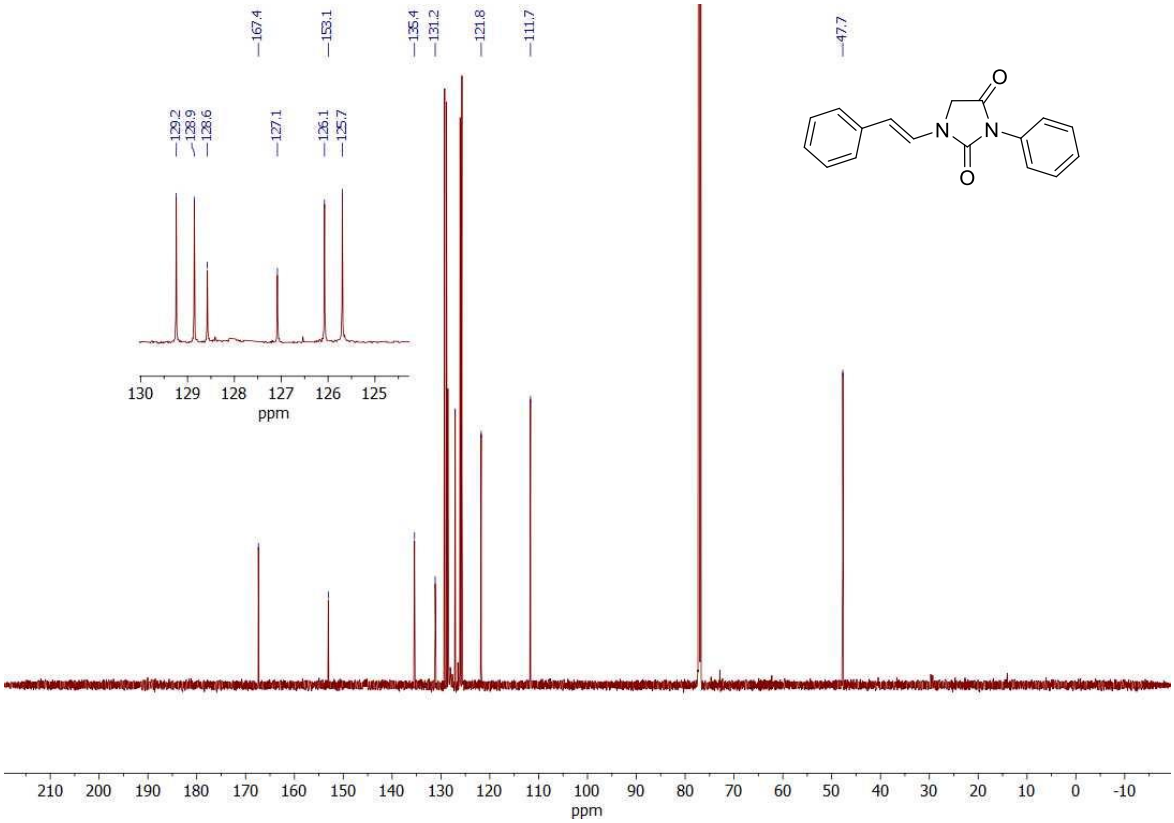
HRMS (ESI) *m/z* $[M + Na]^+$: Calcd. for $C_{17}H_{14}N_2NaO_2^+$: 301.0947, found: 301.0947

This compound has not been reported in the literature.

^{1}H NMR spectrum of **3n** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **3n** (151 MHz, $CDCl_3$)

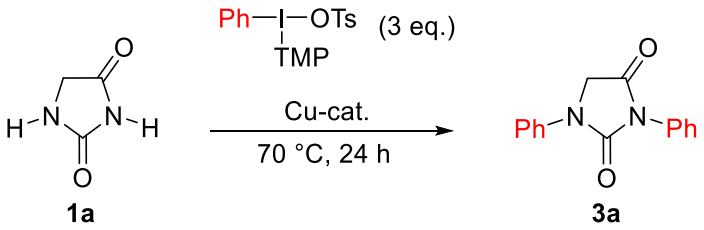


5.4 Controls and optimization data

One-pot – Method A

Hydantoin (0.2 mmol, 1 eq.), ArI(TMP)OTs (3 eq.), Cu-cat. (10 mol%), NaX (10 eq.) and base (3 eq.) were added to a 7 mL vial with a screw cap. The mixture was stirred with a magnetic stirrer. Solvent (2 mL) and amine (3 eq.) were added with a syringe. The vial was placed in a heating block (70 ºC) and stirred for 24 h or as specified.

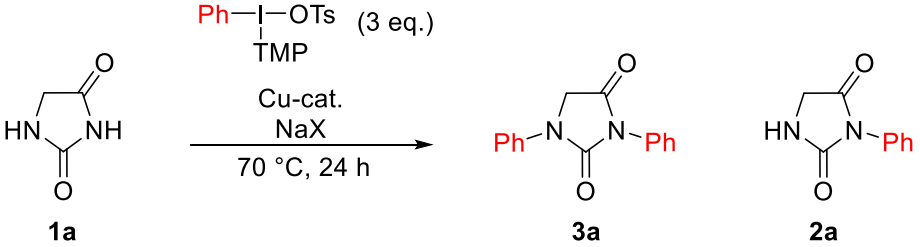
Study 1:



#	Catalyst (10 mol%)	Base / Ligand (3 eq.)	Solvent	Yield [a] **3a** (%)
1	$Cu(OTf)_2$	TEA	Toluene	72[b]
2	$Cu(OTf)_2$	TEA	Toluene	40
3	$Cu(NO_3)_2 \cdot 2.5\ H_2O$	TEA	Toluene	29
4	CuI	TEA	Toluene	44
5	$Cu(OTs)_2$	TEA	Toluene	6
6	$Cu(OTf)_2$	TEA	1,4-dioxane	51
7	$Cu(OTf)_2$	K_3PO_4	Toluene	nd
8	$Cu(OTf)_2$	Pyridine	Toluene	nd
9	$Cu(OTf)_2$	TMA	Toluene	11
10	$Cu(OTf)_2$	DMEDA	Toluene	2
11	$Cu(OTf)_2$	DBU	Toluene	9

[a] Yield measured with mesitylene as internal standard in ^1H NMR analysis of crude.
[b] Result by Neerbye Berntsen.

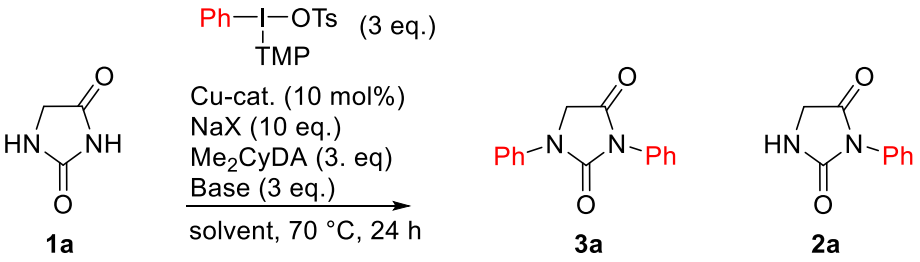
Study 2:



#	Solvent	Catalyst (10 mol%)	Ligand (3 eq.) / Base (3 eq.)	X (10 eq.)	Yield[a] **3a** (%)	Yield[a,b] **2a** (%)
1	Toluene	CuI	TEA	-	44	NM
2	Toluene	CuI	$Me_2CyDA + K_2CO_3$	-	51	42
3	Toluene	CuI	$TEA + K_2CO_3$	-	10	NM
4	Toluene	$Cu(OTf)_2$	TEA	-	40	NM
5	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	-	30	nd
6	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	-	6	NM
7	Toluene	CuI	TEA	BF_4	26	NM
8	Toluene	CuI	$Me_2CyDA + K_2CO_3$	BF_4	nd	nd
9	Toluene	CuI	$TEA + K_2CO_3$	BF_4	42	NM
10	Toluene	$Cu(OTf)_2$	TEA	BF_4	18	NM
11	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	BF_4	3	66
12	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	BF_4	32	NM
13	Toluene	CuI	TEA	I	nd	NM
14	Toluene	CuI	$Me_2CyDA + K_2CO_3$	I	nd	nd
15	Toluene	CuI	$TEA + K_2CO_3$	I	nd	NM
16	Toluene	$Cu(OTf)_2$	TEA	I	nd	NM
17	Toluene	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	I	nd	nd
18	Toluene	$Cu(OTf)_2$	$TEA + K_2CO_3$	I	nd	NM
19	1,4-dioxane	CuI	TEA	-	13	NM
20	1,4-dioxane	CuI	Me2CyDA + K_2CO_3	-	30	30
21	1,4-dioxane	CuI	$TEA + K_2CO_3$	-	a: 35 b: 60	8 NM
22	1,4-dioxane	$Cu(OTf)_2$	TEA	-	51	NM
23	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	-	45	37
24	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	-	42	NM
25	1,4-dioxane	CuI	TEA	BF_4	40	NM
26	1,4-dioxane	CuI	$Me_2CyDA + K_2CO_3$	BF_4	35	4
27	1,4-dioxane	CuI	$TEA + K_2CO_3$	BF_4	a: 52 b: 56, 35[c]	13 6
28	1,4-dioxane	$Cu(OTf)_2$	TEA	BF_4	16	NM
29	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	BF_4	27	NM
30	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	BF_4	47	5
31	1,4-dioxane	CuI	TEA	I	3	nd
32	1,4-dioxane	CuI	$Me_2CyDA + K_2CO_3$	I	nd	nd
33	1,4-dioxane	CuI	$TEA + K_2CO_3$	I	7	nd
34	1,4-dioxane	$Cu(OTf)_2$	TEA	I	nd	nd
35	1,4-dioxane	$Cu(OTf)_2$	$Me_2CyDA + K_2CO_3$	I	nd	nd
36	1,4-dioxane	$Cu(OTf)_2$	$TEA + K_2CO_3$	I	1	nd

[a] Yield measured with mesitylene as internal standard in ^1H NMR analysis of crude.
[b] NM – not measurable.
[c] Isolated yield.

Study 3:

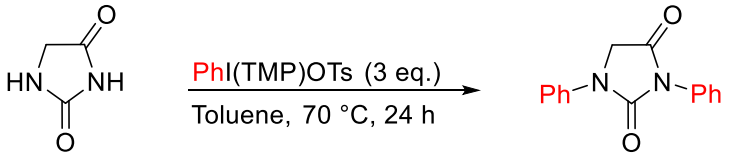


1a **3a** **2a**

#	Catalyst	Base	Iodoniumsalt	X	Solvent	Yield[a] **3a** (%)	Yield[a,e] **2a** (%)
1	CuI	K_2CO_3	PhI(TMP)OTs	BF_4	1,4-dioxane	a: 35 b: 29	a: 4 b: 7
2	$Cu(OTf)_2$	K_2CO_3	PhI(TMP)OTs	BF_4	1,4-dioxane	27	2
3	CuI	-	PhI(TMP)OTs	BF_4	1,4-dioxane	6	NM
4	CuI	tBuOK	PhI(TMP)OTs	BF_4	1,4-dioxane	29	nd
5	CuI	NaOH	PhI(TMP)OTs	BF_4	1,4-dioxane	65, 8[b]	22
6	CuI	$LiOC(CH_3)_3$	PhI(TMP)OTs	BF_4	1,4-dioxane	8	nd
7	CuI	$NaHCO_3$	PhI(TMP)OTs	BF_4	1,4-dioxane	19	NM
8	CuI	K_3PO_4	PhI(TMP)OTs	BF_4	1,4-dioxane	a: 108 b: 106, 5[b] c: 53, 8[b]	a: 8 b: 4 c: 5
9	CuI	K_3PO_4	PhI(TMP)OTs	-	1,4-dioxane	31	4
10	CuI	K_2CO_3	PhI(TMP)BF_4	-	1,4-dioxane	32	4
11	CuI	K_2CO_3	PhI(TMP)OTs	-	1,4-dioxane	34	5
12	CuI	K_2CO_3	PhI(TMP)TFA	-	1,4-dioxane	43	7
13	CuI	K_2CO_3	PhIPhOTf	-	1,4-dioxane	43	10
14	CuI	K_2CO_3	PhI(TMP)OTs	OTf	1,4-dioxane	a: 4 b: 36[c]	NM NM
15	CuI	K_2CO_3	PhI(TMP)OTs	BF_4	Toluene	nd	nd
16	CuI	K_2CO_3	PhI(TMP)OTs	BF_4	Acetonitril	10	nd
17	CuI	K_2CO_3	PhI(TMP)OTs	BF_4	Acetic acid	nd	nd
18	CuI[d]	K_2CO_3	PhI(TMP)OTs	-	1,4-dioxane	53	10
19	CuI[d]	K_2CO_3	PhI(TMP)OTs	BF_4	1,4-dioxane	95, 63[b]	NM

[a] Yield measured with 2,4,6-trimehoxybenzealdehyde as internal standard in ^1H NMR analysis of crude.
[b] Isolated yield.
[c] 3 eq. NaOTf instead of 10 eq.
[d] 1 eq. of catalyst.
[e] NM – not measurable.

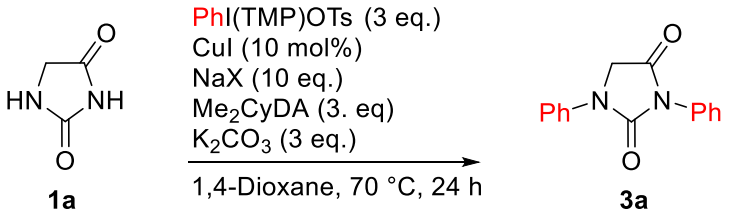
Study of reaction time:



#	Catalyst (10 mol%)	Reaction time	Amin (3 eq.) / Base (3 eq.)	Yield[a] **3a** (%)
1	$Cu(OTf)_2$	24 h	TEA	40
2	$Cu(OTf)_2$	7 days	TEA	40
3	$Cu(OTf)_2$	7 days	TEA + K_2CO_3	37
4	CuI	24 h	TEA	44
5	CuI	7 days	TEA	40

[a] Yield measured with mesitylene as internal standard in ^1H NMR

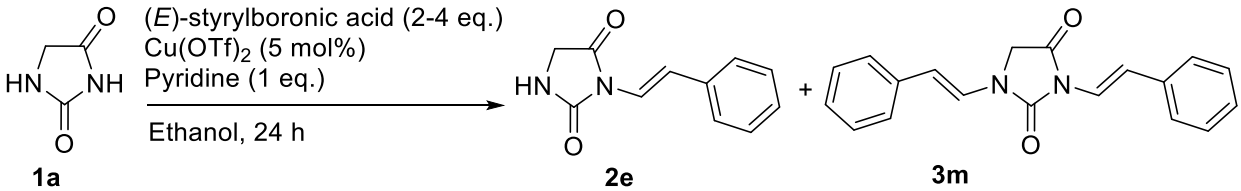
Other anions:



#	X	Yield **3a** (%)
1	NaBARF[a,b]	8
2	$NaPF_6$	11

[a] BARF = Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
[b] 6.8 eq. was used.

Coupling reaction between (*E*)-styrylboronic acid and hydantoin



Hydantoin (1 eq.), (*E*)-styrylboronic acid (2-4 eq.) and $Cu(OTf)_2$ (5 mol%) were added to a round bottle flask. The mixture was stirred with a magnetic stirrer. Ethanol (2-3 mL) and pyridine (1 eq.) were added with a syringe. The vial was placed in a heating

block (25-80 ºC) and stirred for 24 h. The mixture was concentrated under reduced pressure and purified with column chromatography.

	Eq. of bronic acid	Comment	Temperature (ºC)	Scale (mmol)	Yield **2e** (%)	Yield **3m** (%)
1	2		25	0.4	48	nd
2	2		25	0.8	59	nd
3	2		25	1.5	43	nd
4	4		40	0.4	76	5[a]
5	4		80	0.4	61	nd
6	4	2 eq. of K_2CO_3[b]	40	0.4	<5[a]	nd
7	2.5	**2e** as reactant[c]	40	0.35		13

[a] Calculated
[b] K_2CO_3 was added in addition
[c] (*E*)-*N*-3-styrylhydantoin (**2e**) was used as reactant instead of hydantoin. Amount unreacted reactant not calculated.

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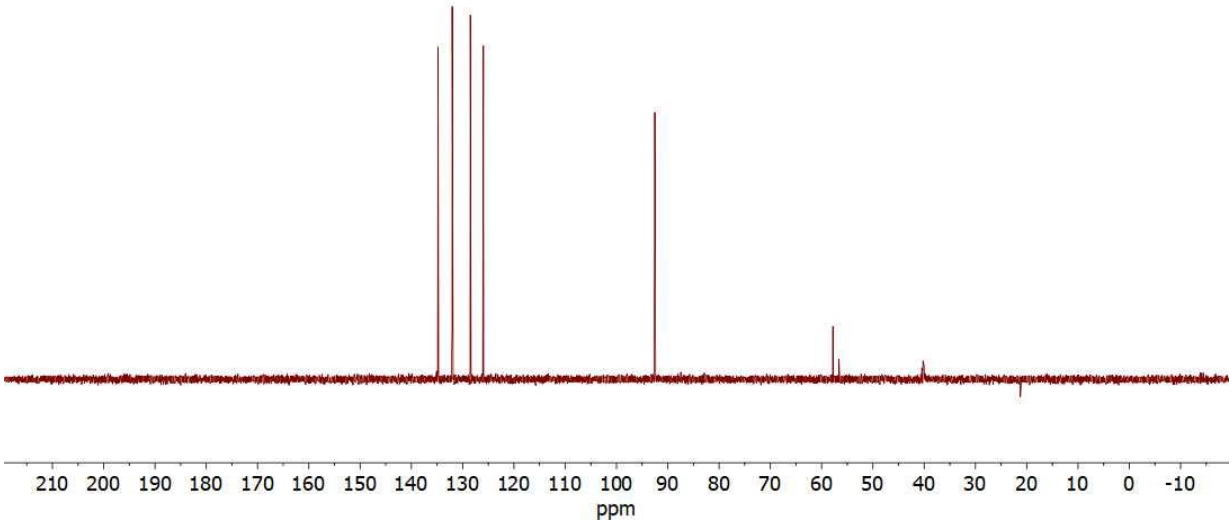
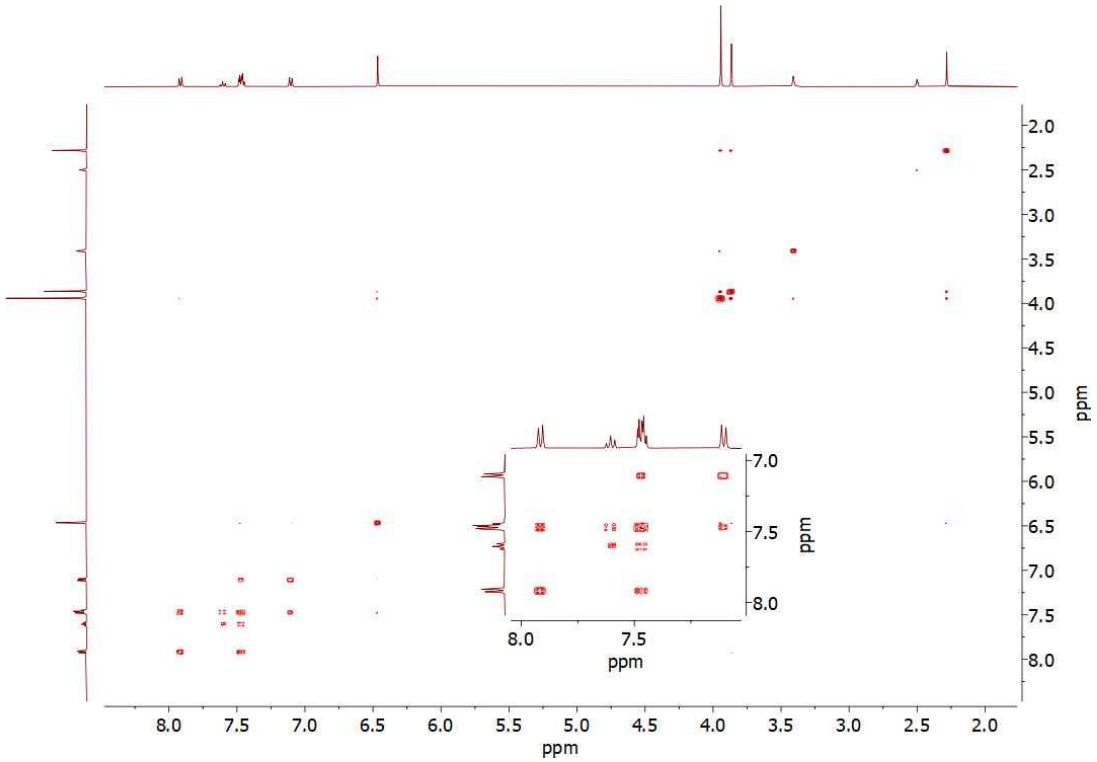
8 Appendix

7.1 Phenyl(2,4,6-trimetoxyphenyl)iodonium tosylate (4a)

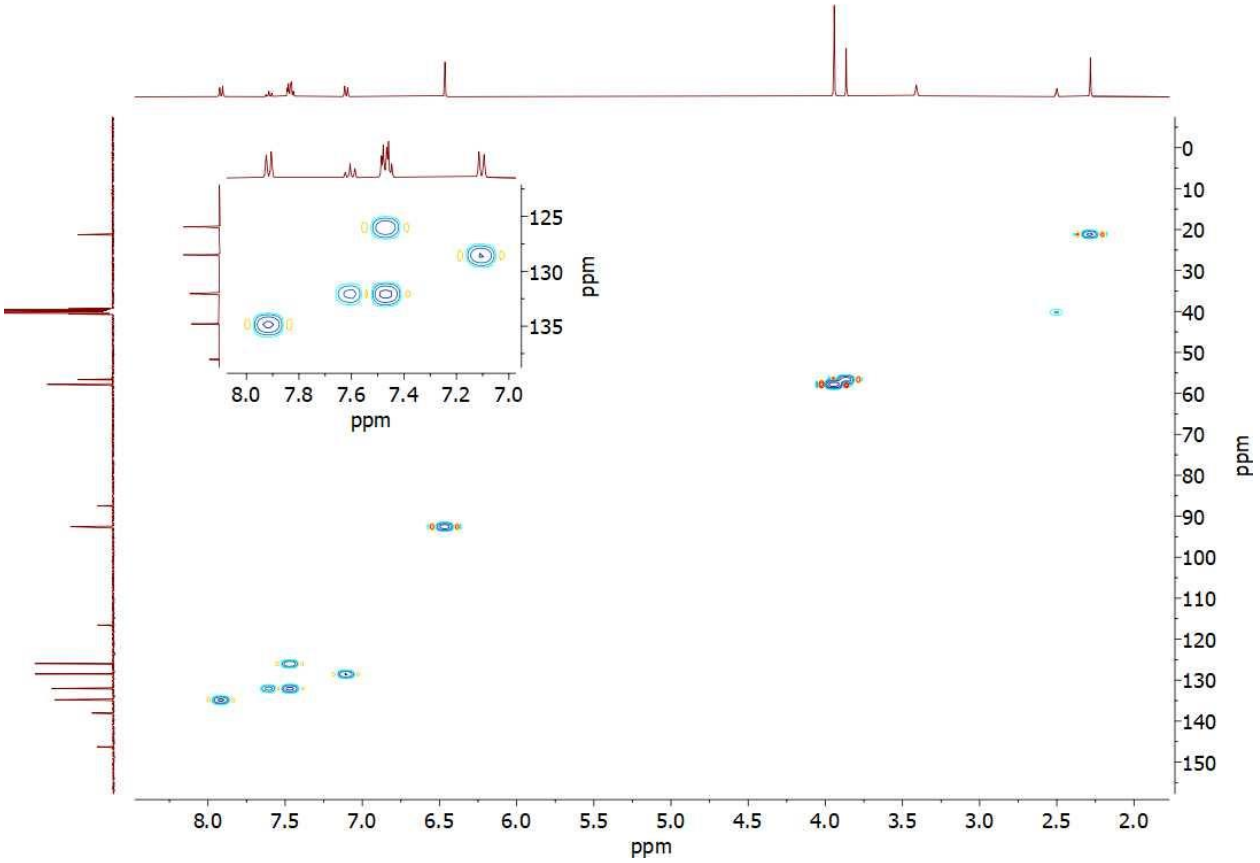
DEPT90 of **4a** (100 MHz, DMSO-d_6)



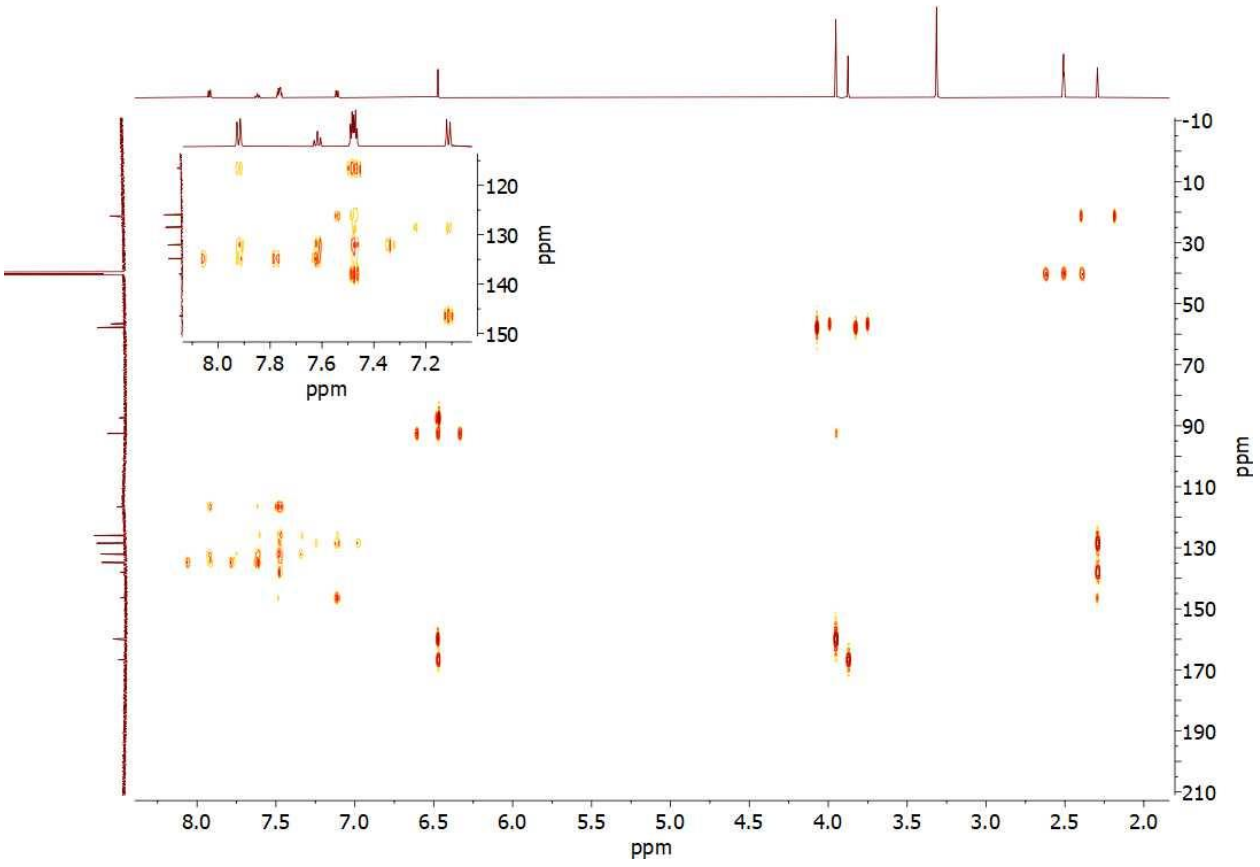
COSY of **4a** (400 MHz, DMSO-d_6)



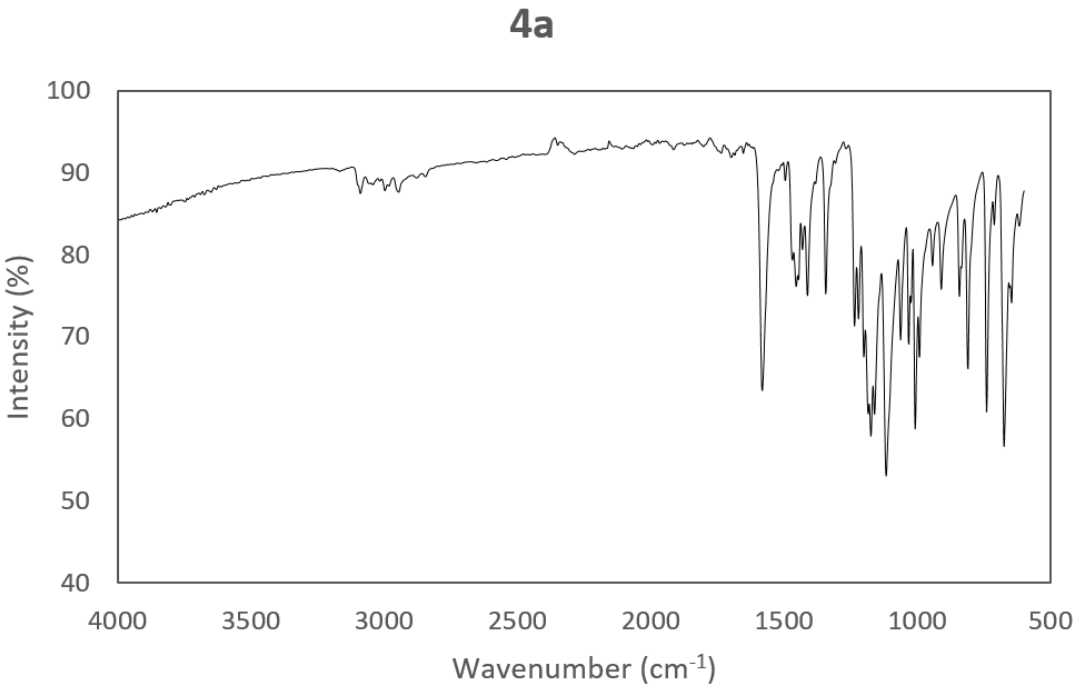
HSQC of **4a** (400 MHz, DMSO-d_6)



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

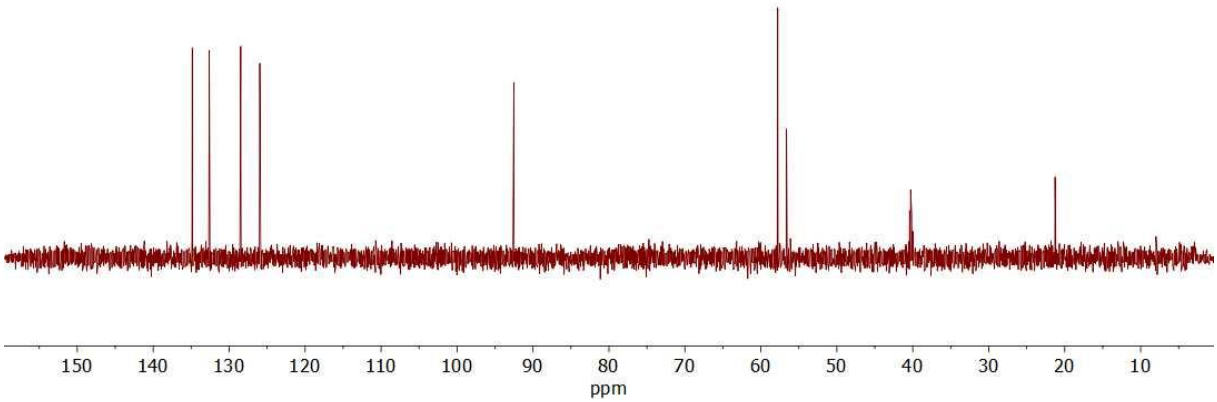


IR spectrum of **4a**

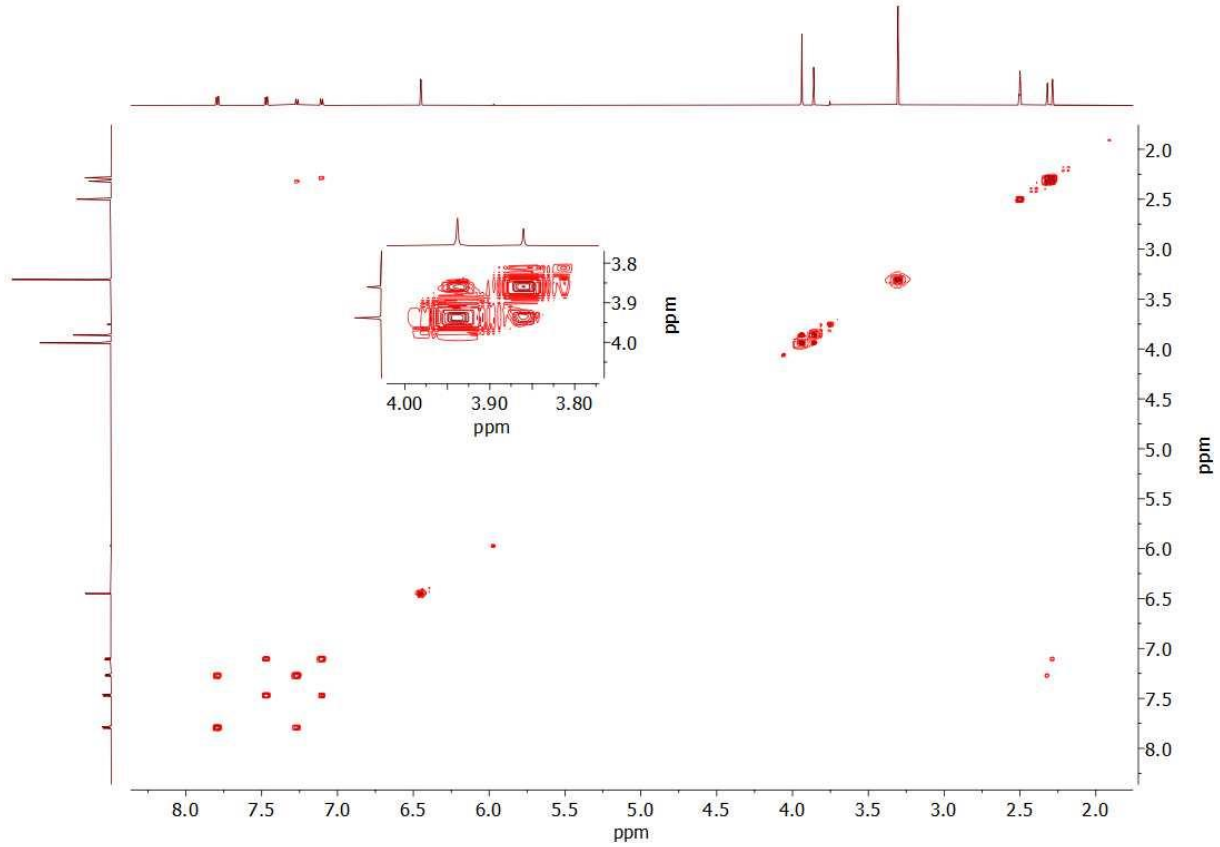


7.2 4-Tolyl(2,4,6-trimetoxyphenyl)iodonium tosylate (4b)

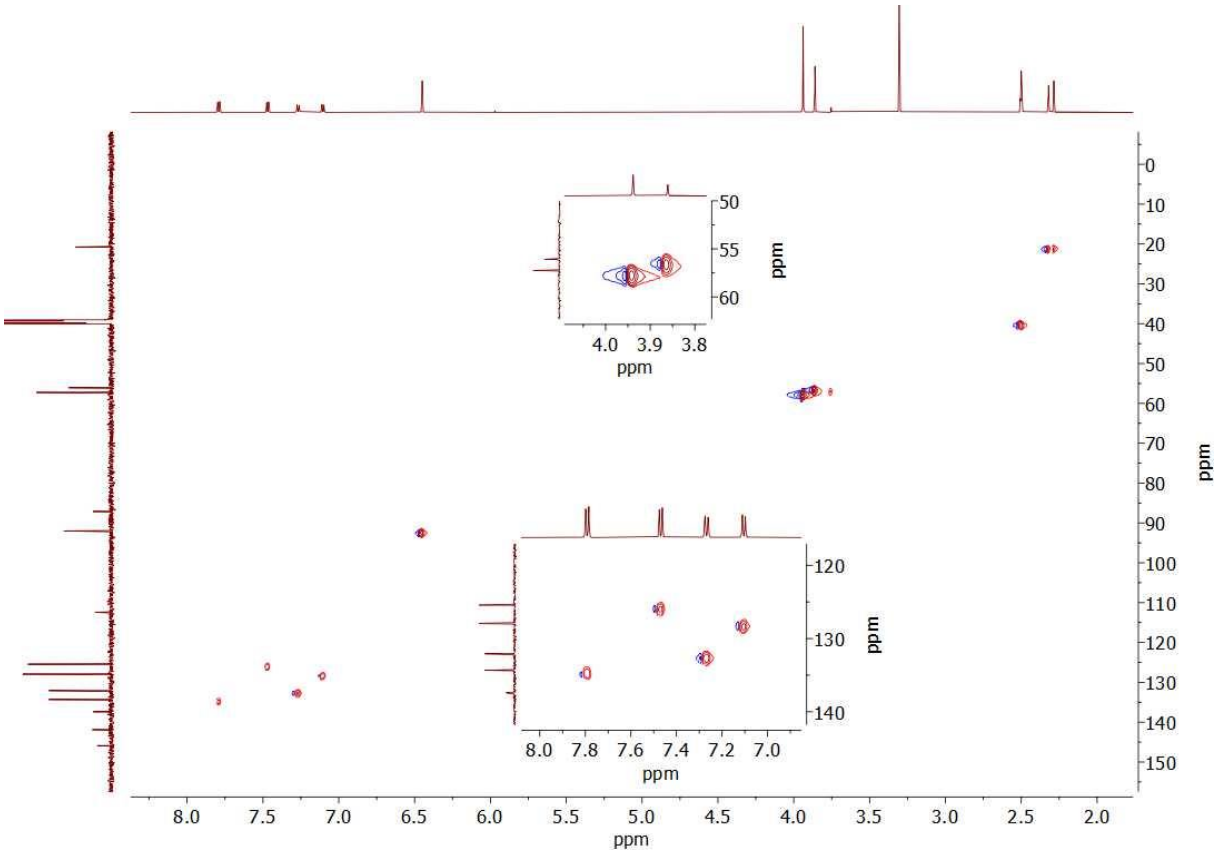
DEPT135 of **4b** (151 MHz, DMSO-d_6)



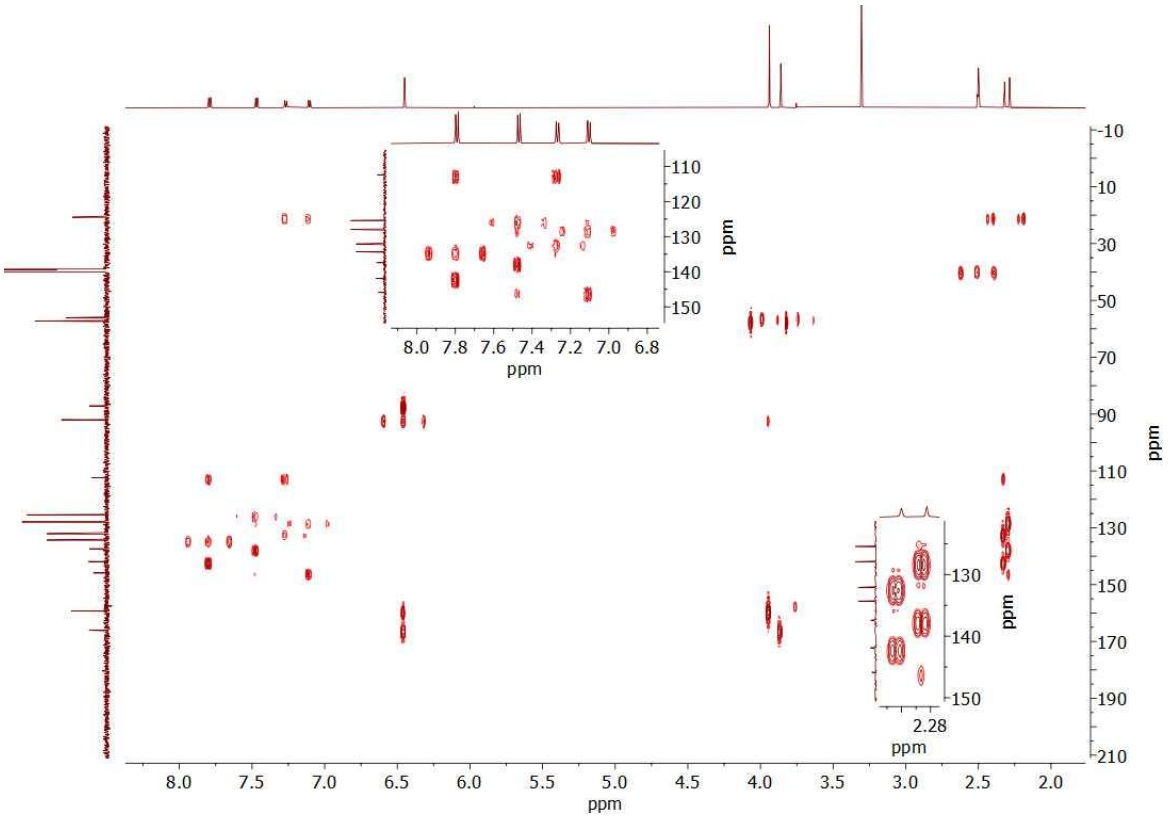
COSY of **4b** (600 MHz, DMSO-d_6)



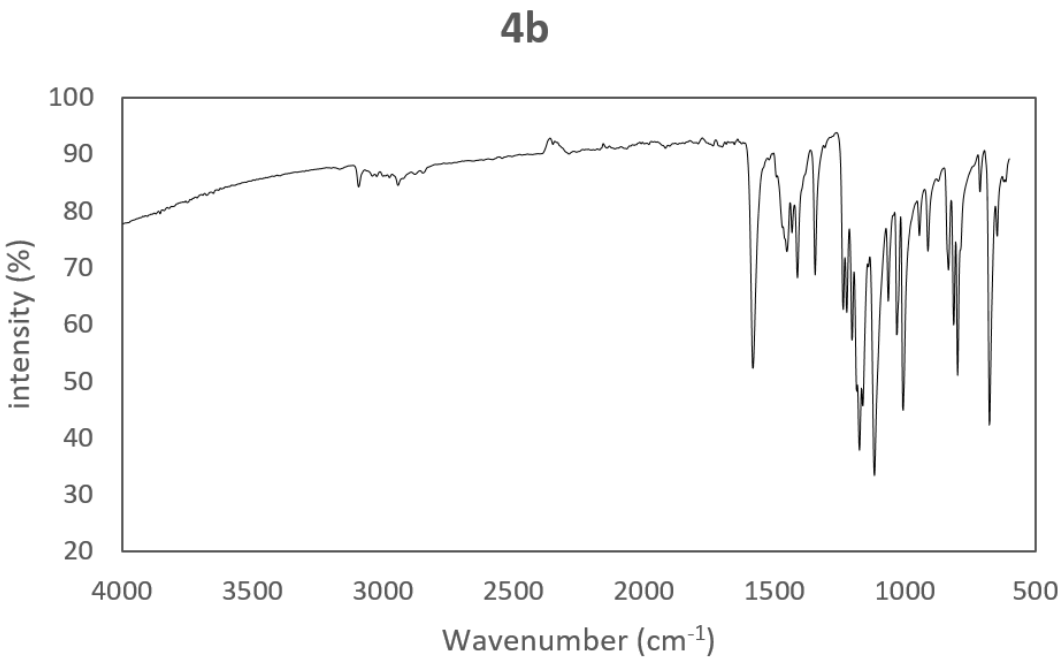
HSQC of **4b** (600 MHz, DMSO-d_6)



HMBC of **4b** (600 MHz, DMSO-d_6)

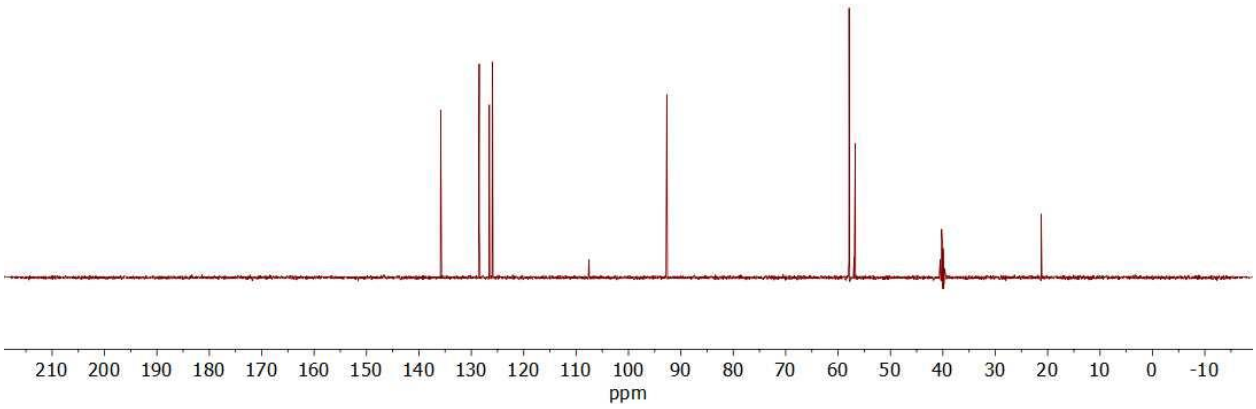


IR spectrum of **4b**

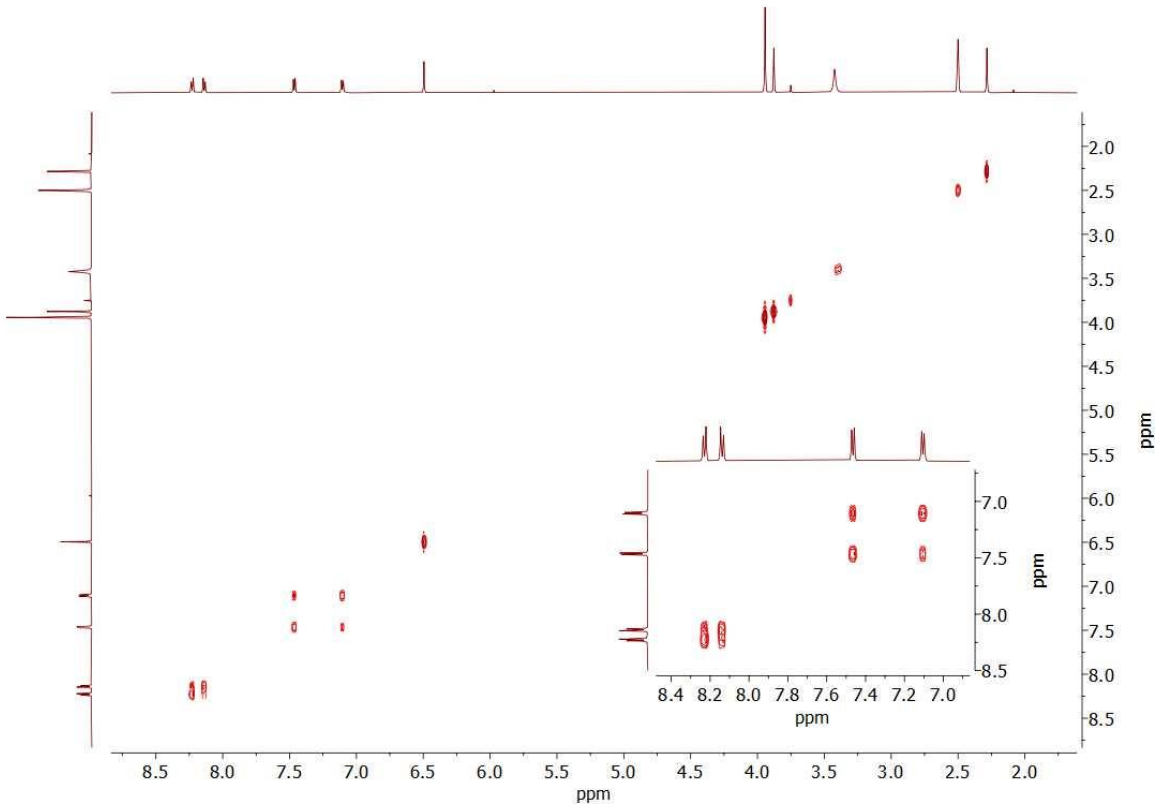


7.3 4-Nitrophenyl(2,4,6-trimethoxyphenyl)iodonium tosylate (4c)

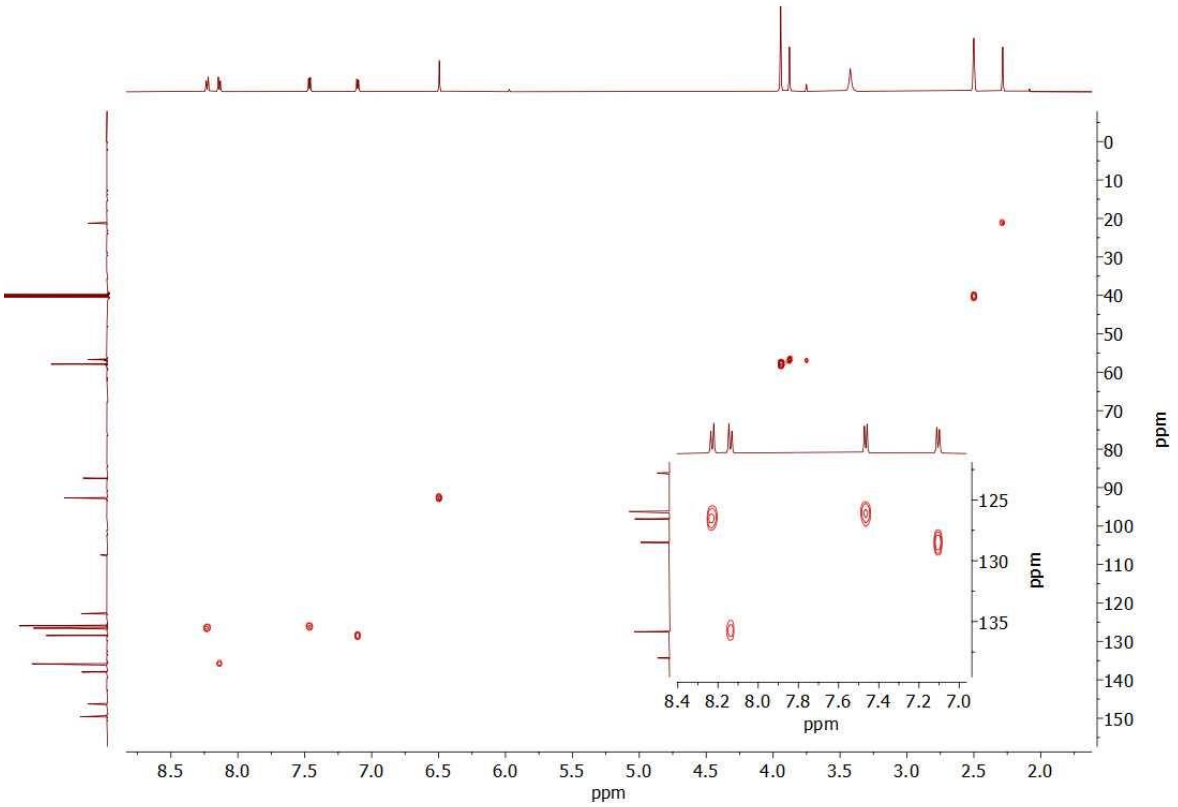
DEPT135 of **4c** (151 MHz, DMSO-d_6)



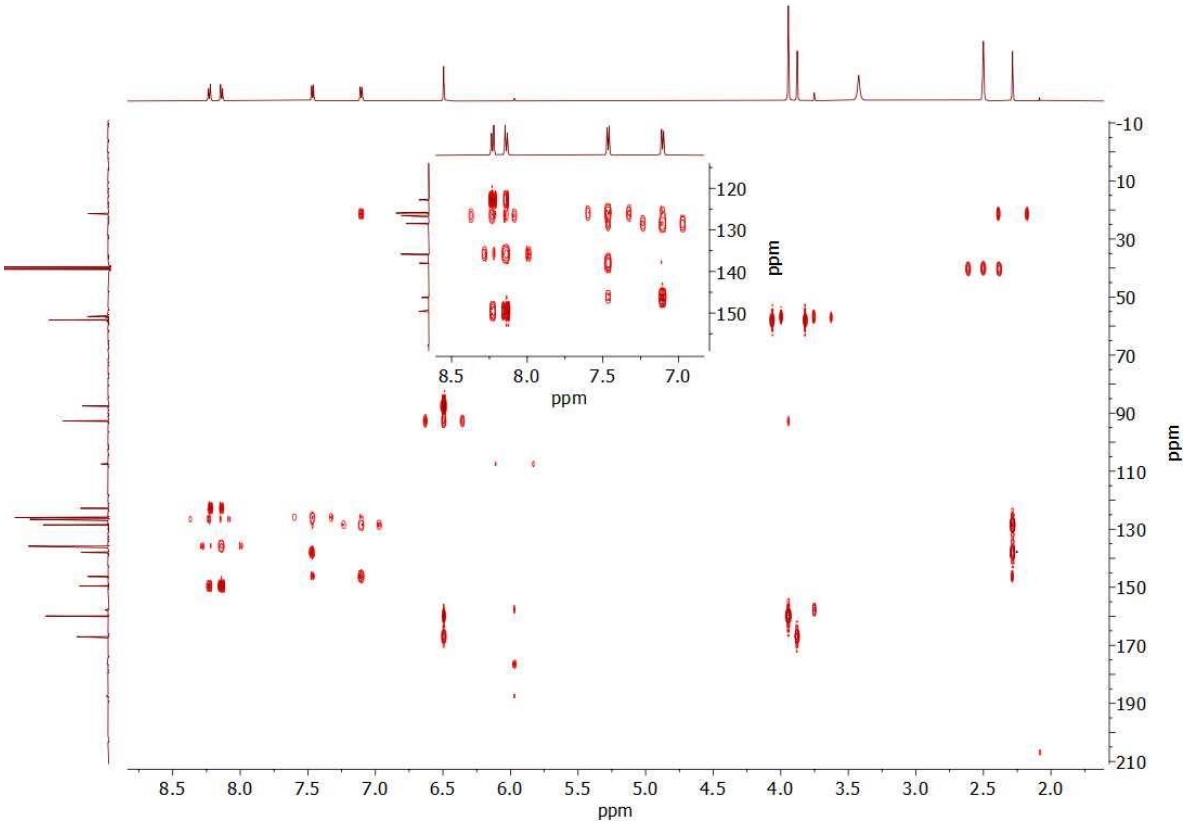
COSY of **4c** (600 MHz, DMSO-d_6)



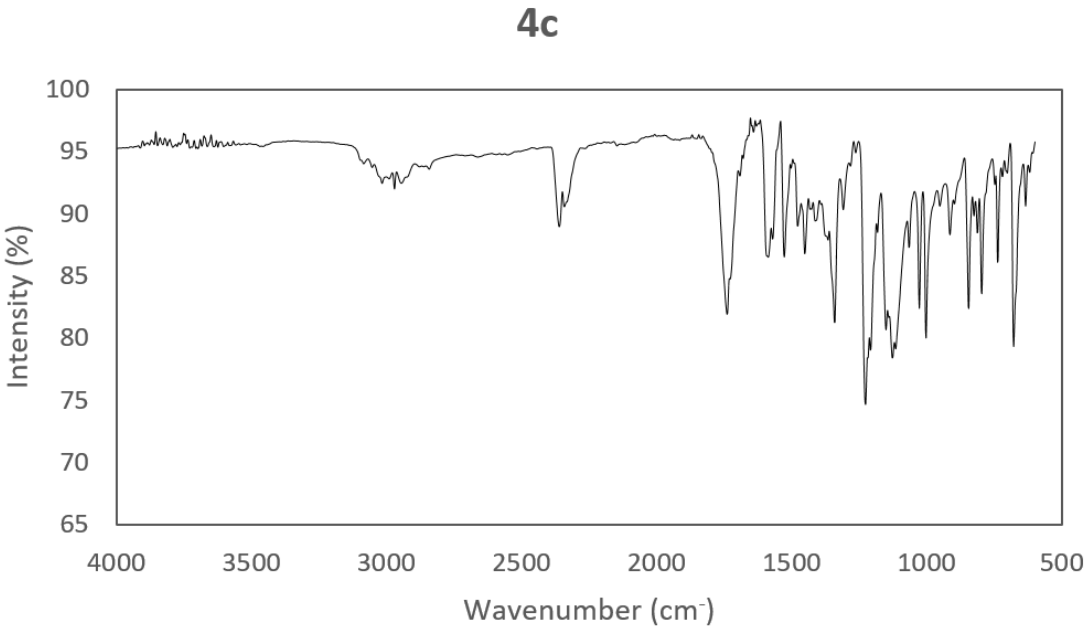
HSQC of **4c** (600 MHz, DMSO-d_6)



HMBC of **4c** (600 MHz, DMSO-d_6)

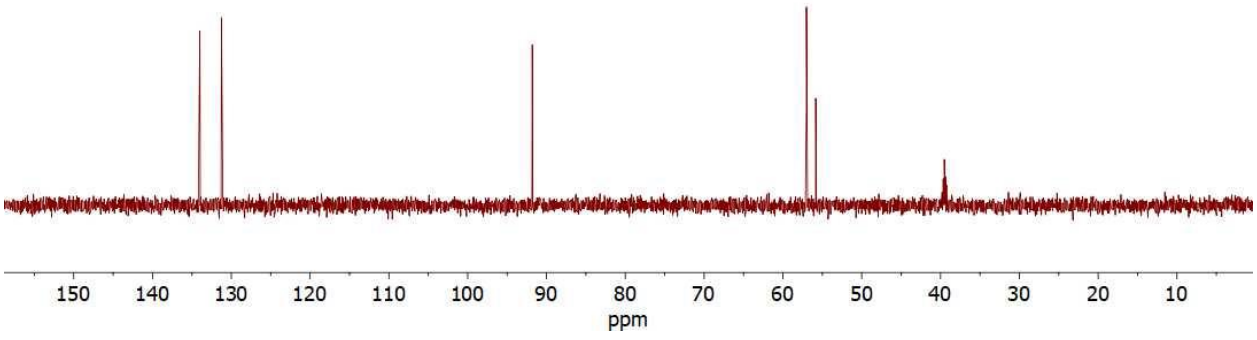


IR spectrum of **4c**

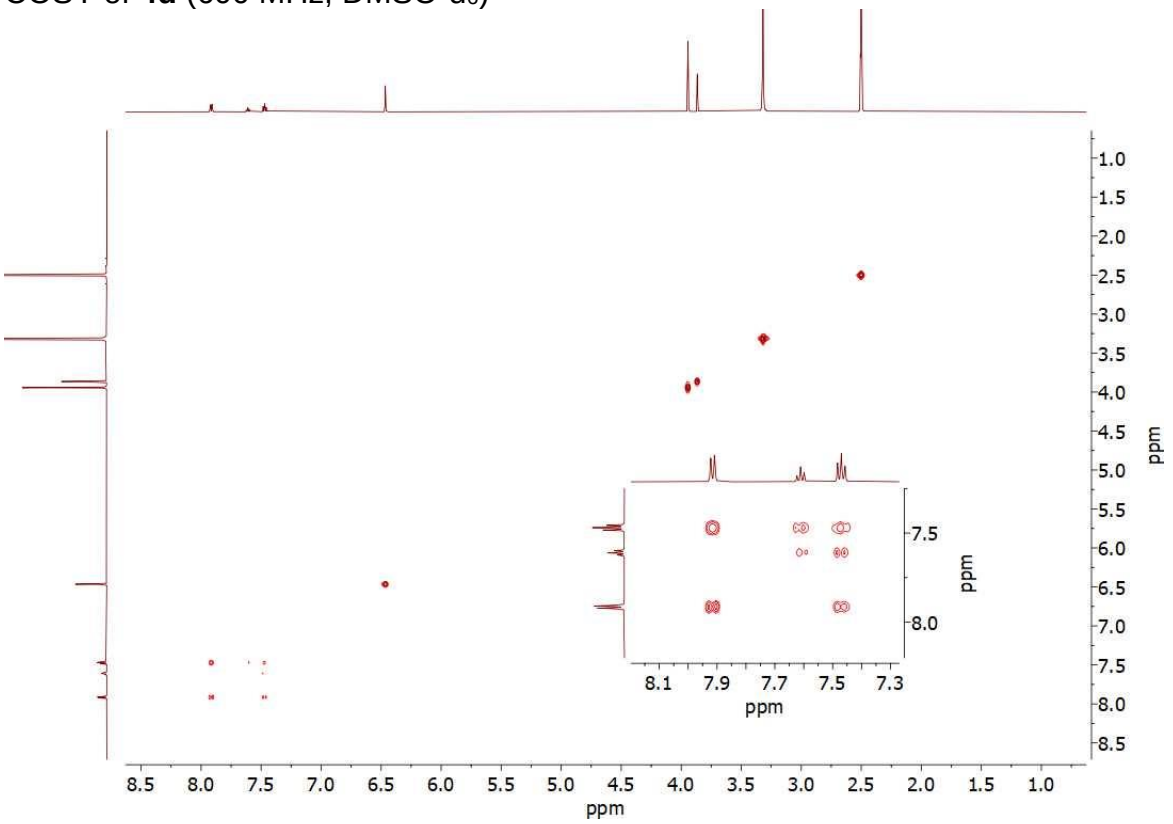


7.4 Phenyl(2,4,6-trimetoxyphenyl)iodonium tetrafluoroborate (4d)

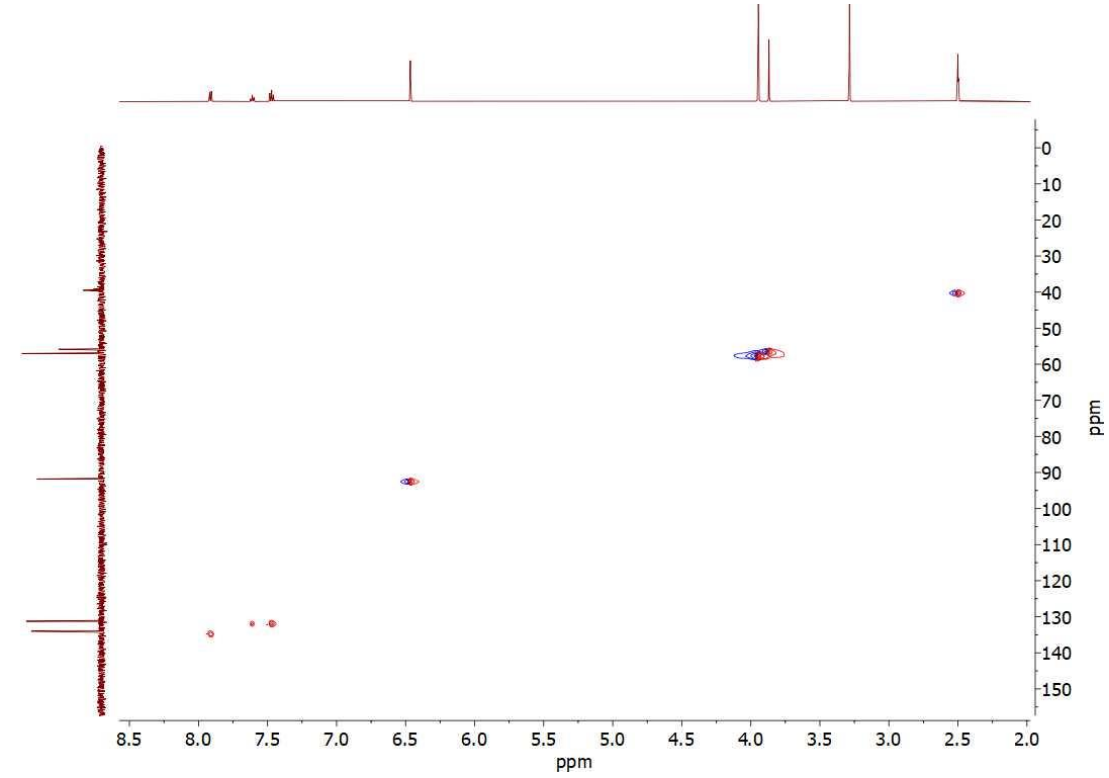
DEPT135 of **4d** (151 MHz, DMSO-d_6)



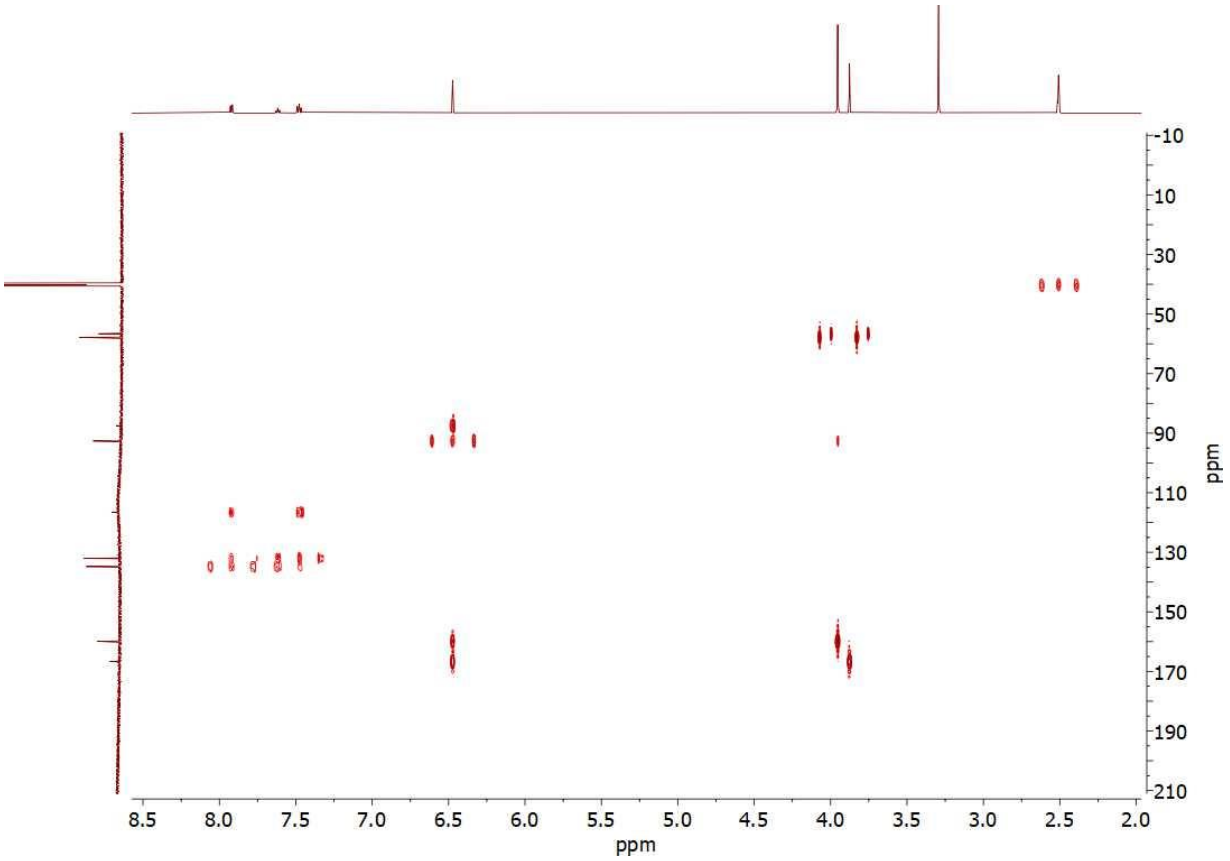
COSY of **4d** (600 MHz, DMSO-d_6)



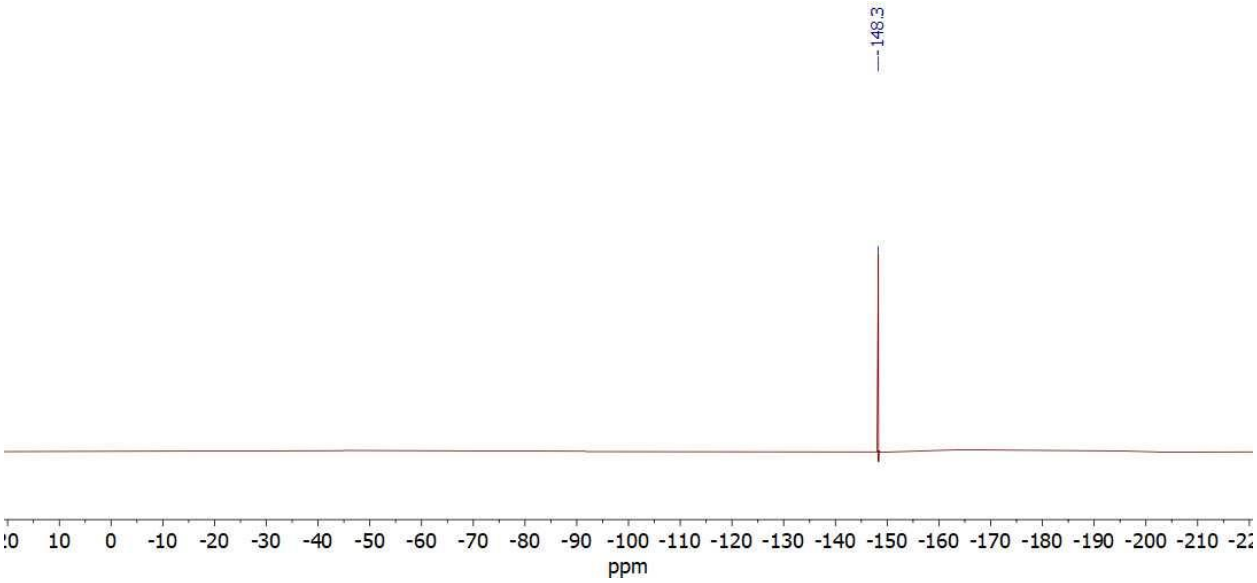
HSQC of **4d** (600 MHz, DMSO-d_6)



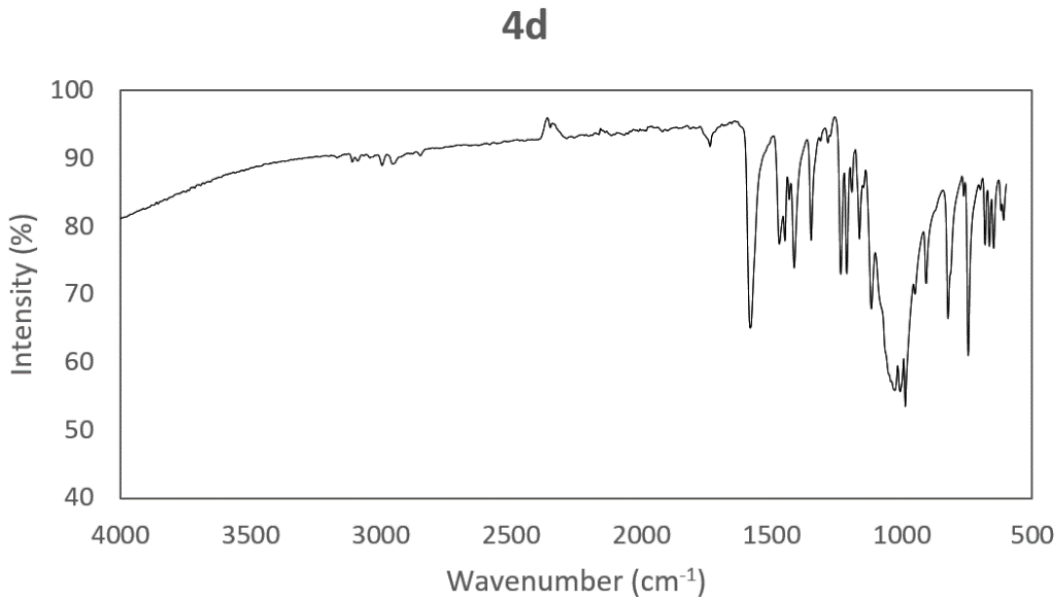
HMBC of **4d** (600 MHz, DMSO-d_6)



^{19}F NMR spectrum of **4d** (377 MHz, DMSO-d_6)

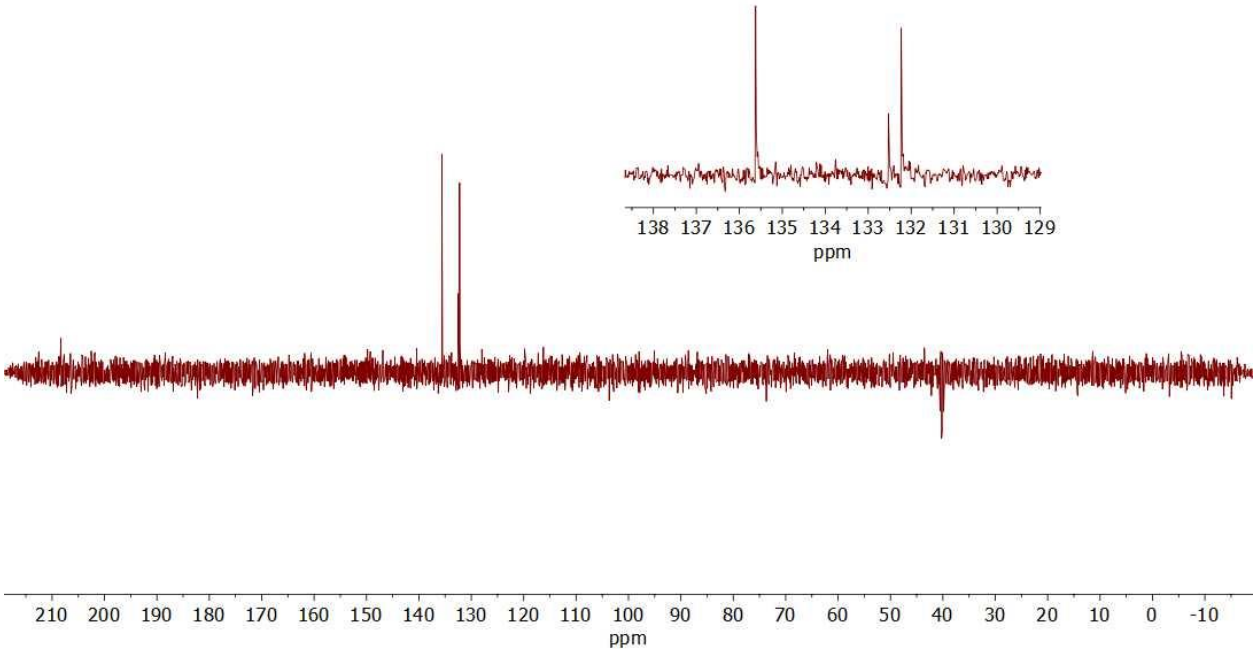


IR spectrum of **4d**

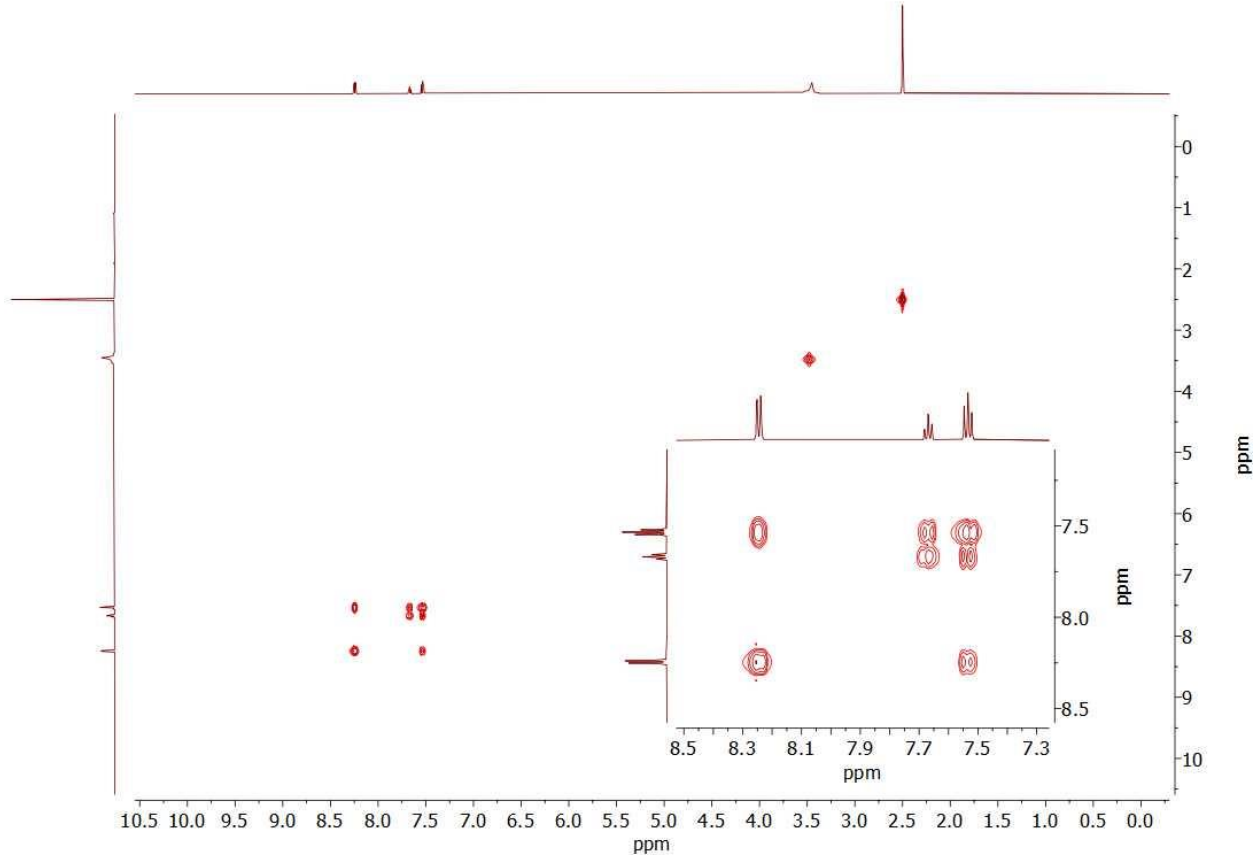


7.5 Diphenyliodonium triflate (4e)

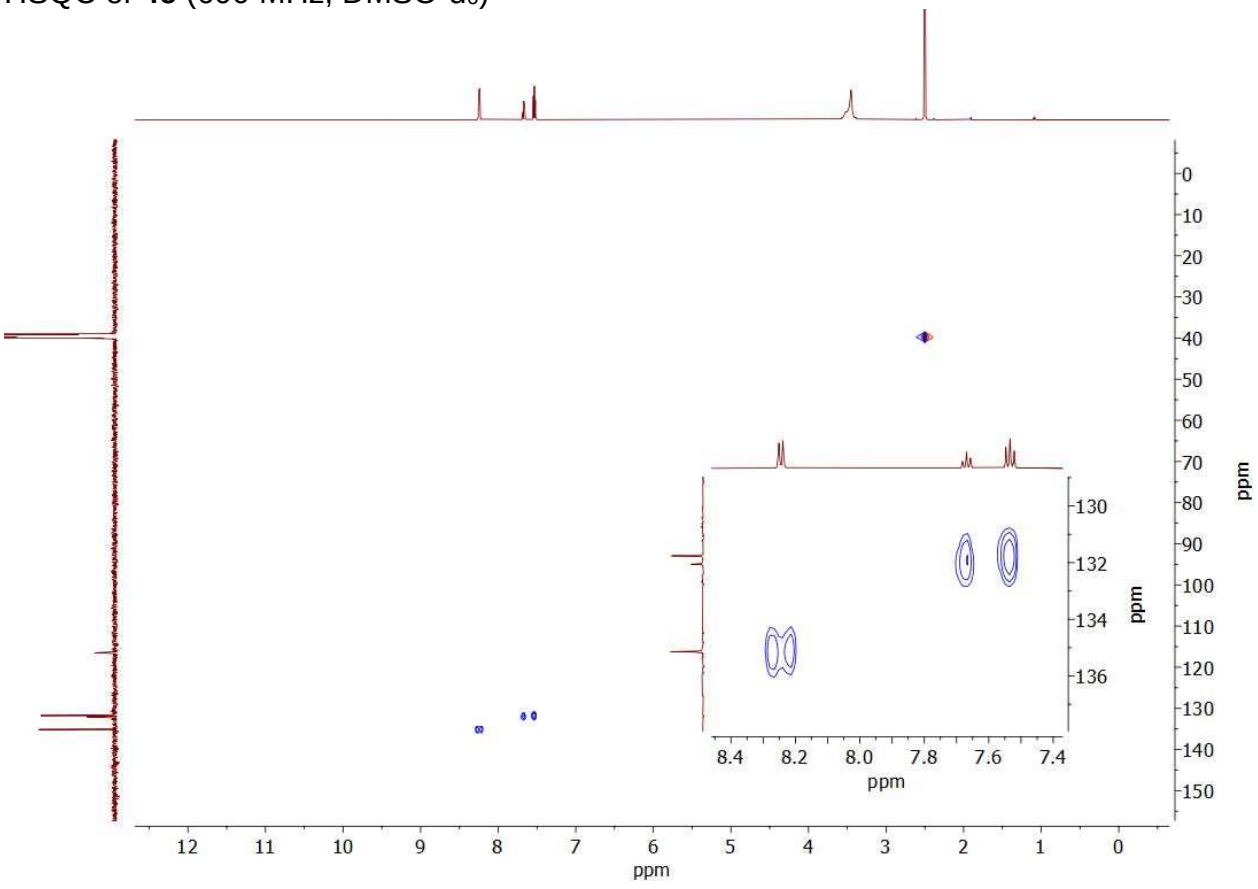
DEPT135 of **4e** (151 MHz, DMSO-d_6)



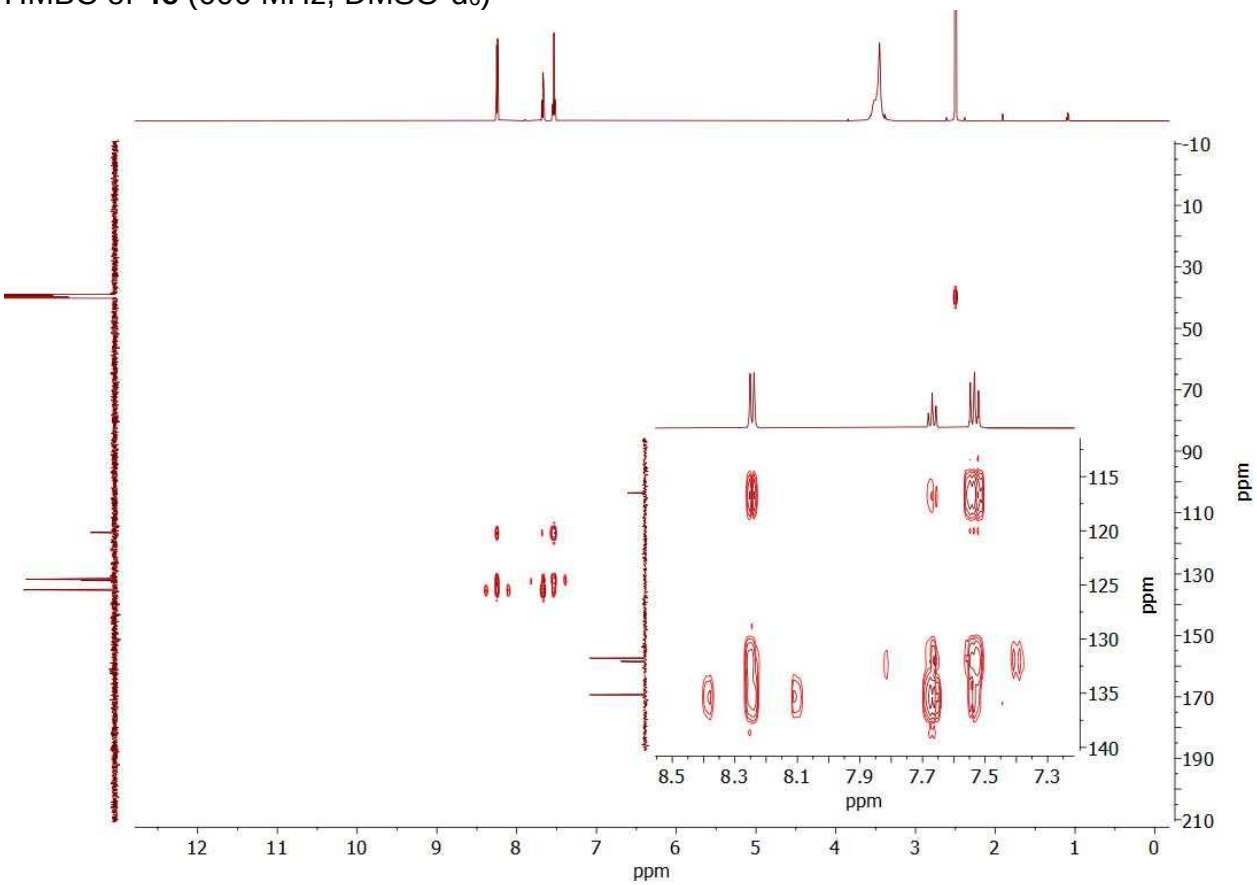
COSY of **4e** (600 MHz, DMSO-d_6)



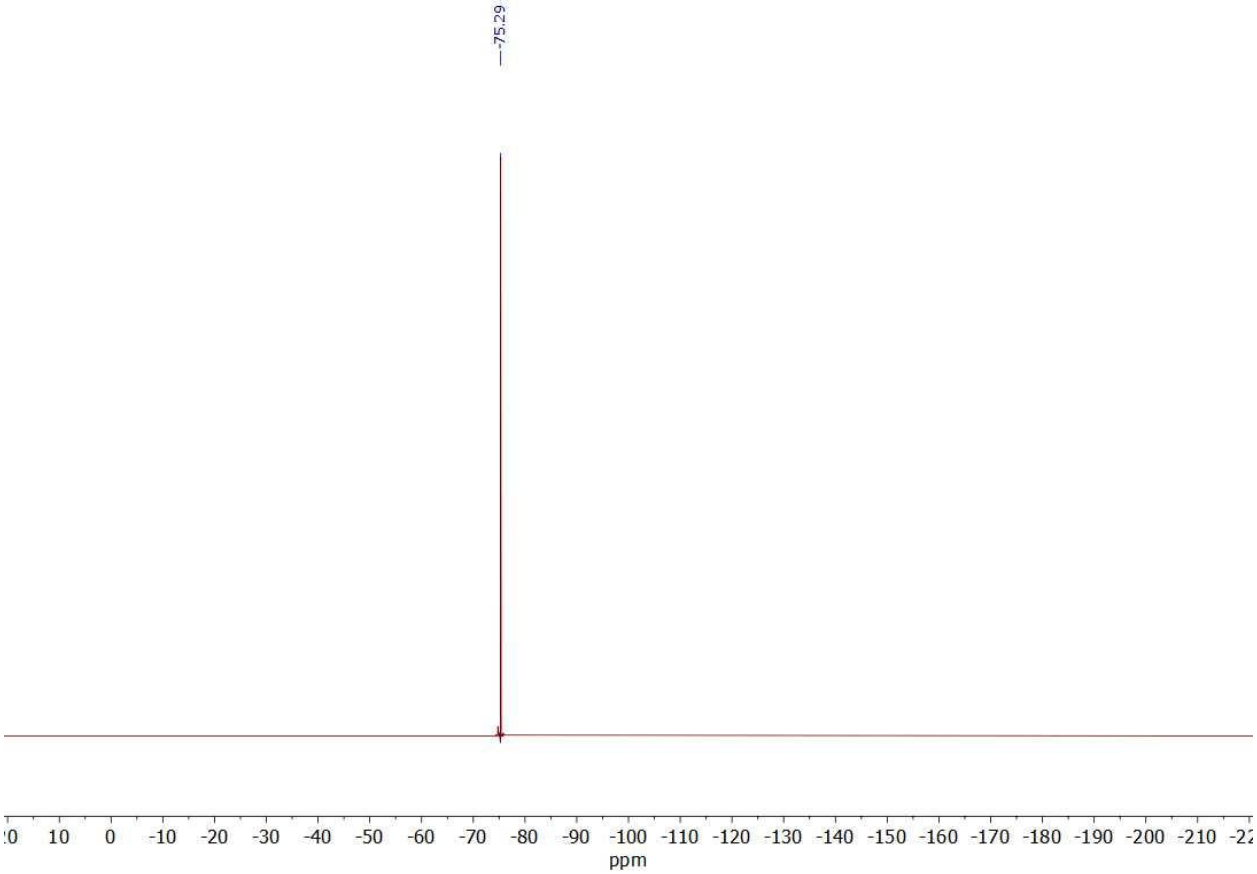
HSQC of **4e** (600 MHz, DMSO-d_6)



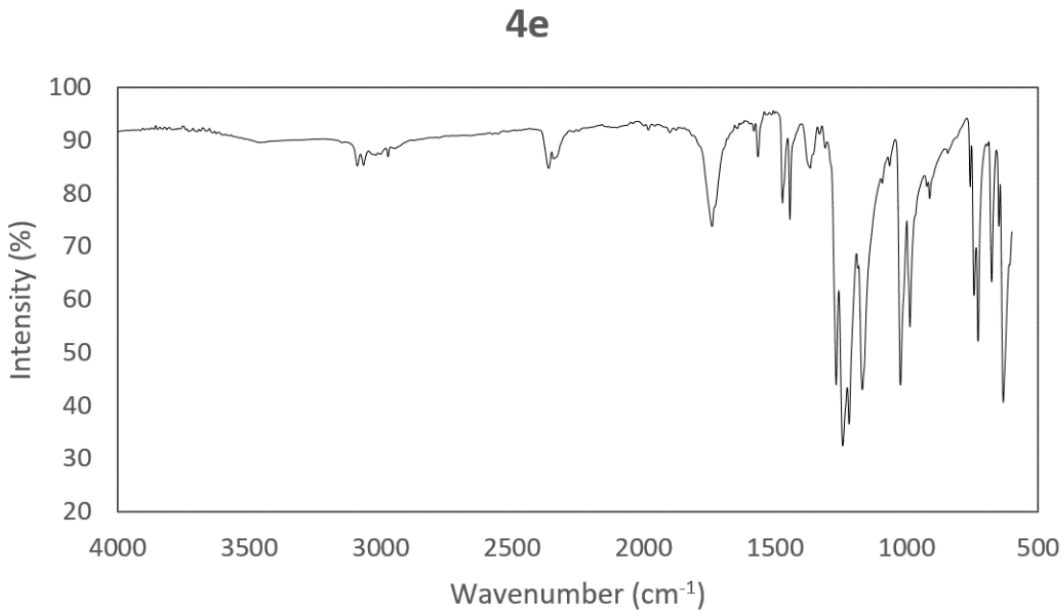
HMBC of **4e** (600 MHz, DMSO-d_6)



^{19}F spectrum of **4e** (377 MHz, $CDCl_3$)

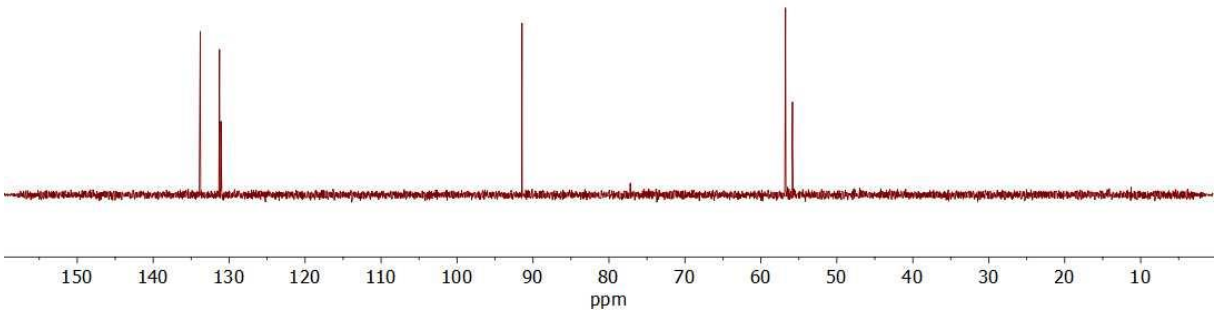


IR spectrum of **4e**

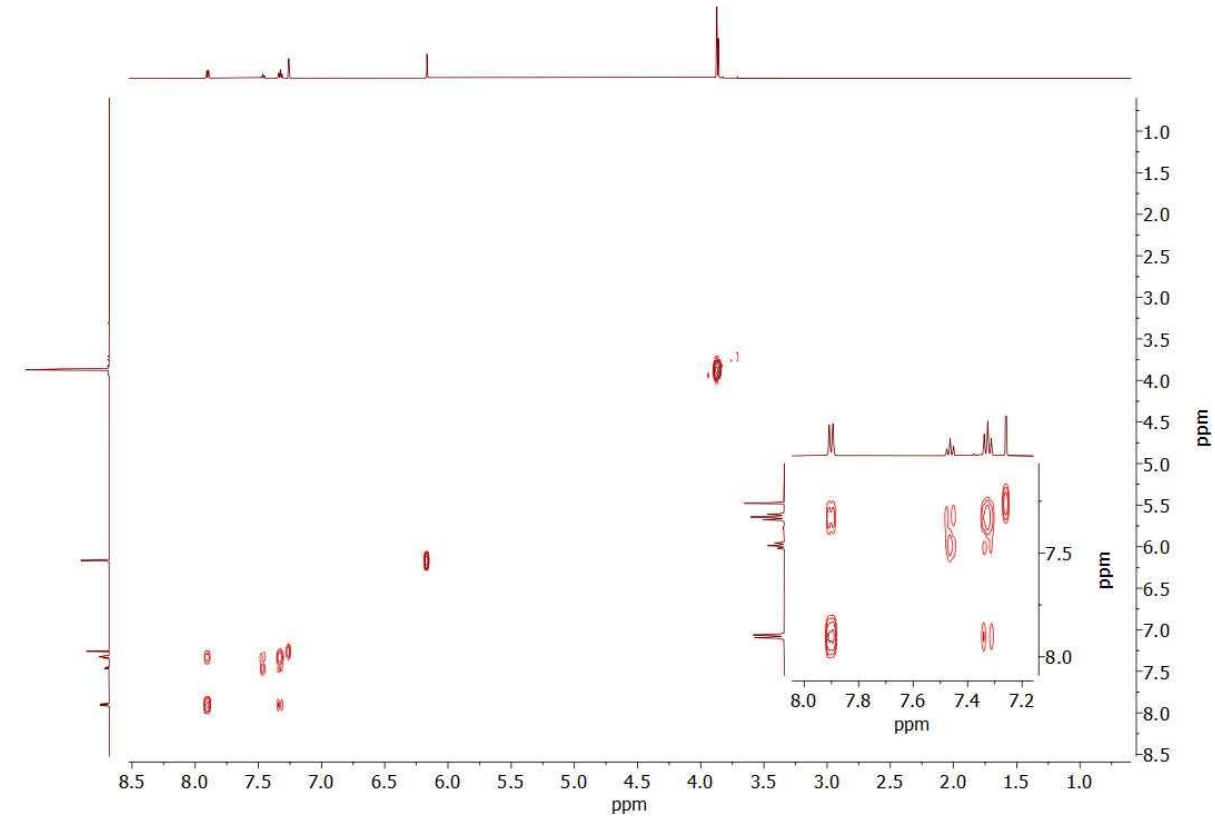


7.6 Phenyl(2,4,6-trimetoxyphenyl)iodonium trifluoroacetate (4f)

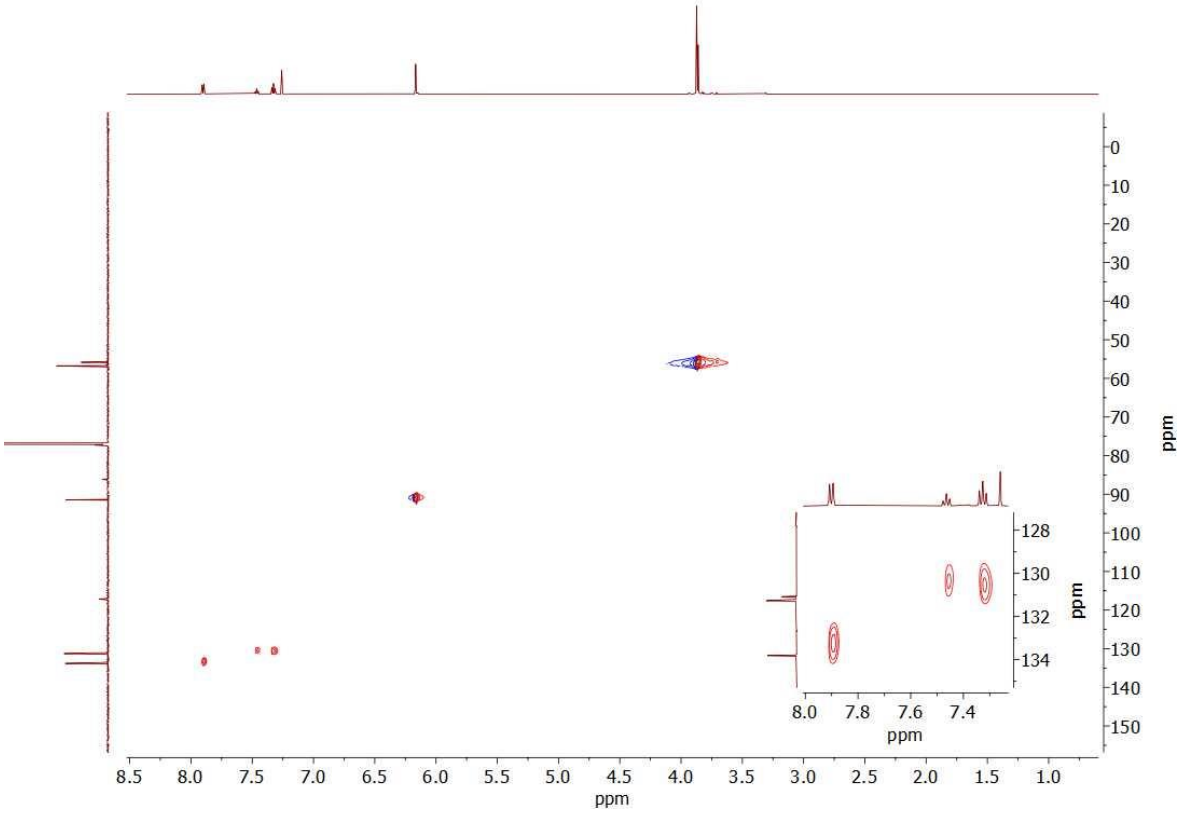
DEPT135 of **4f** (151 MHz, $CDCl_3$)



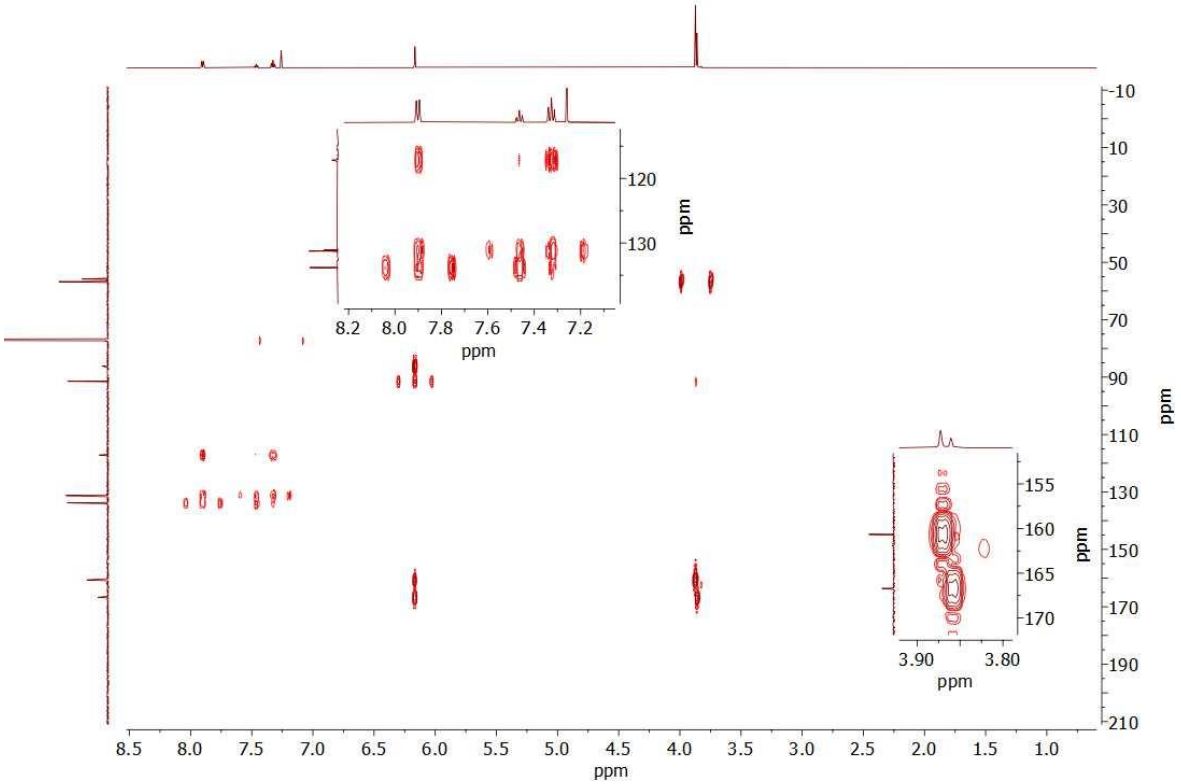
COSY of **4f** (600 MHz, $CDCl_3$)



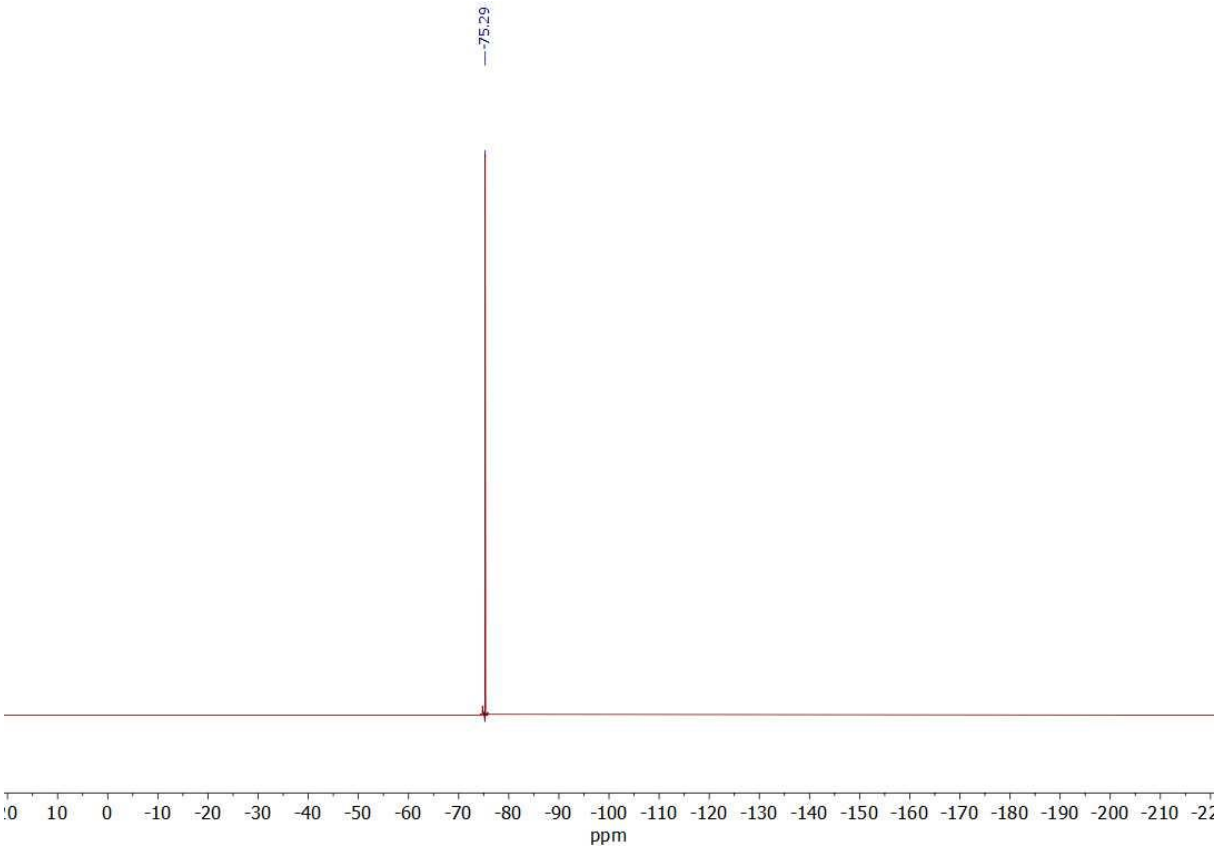
HSQC of **4f** (600 MHz, $CDCl_3$)



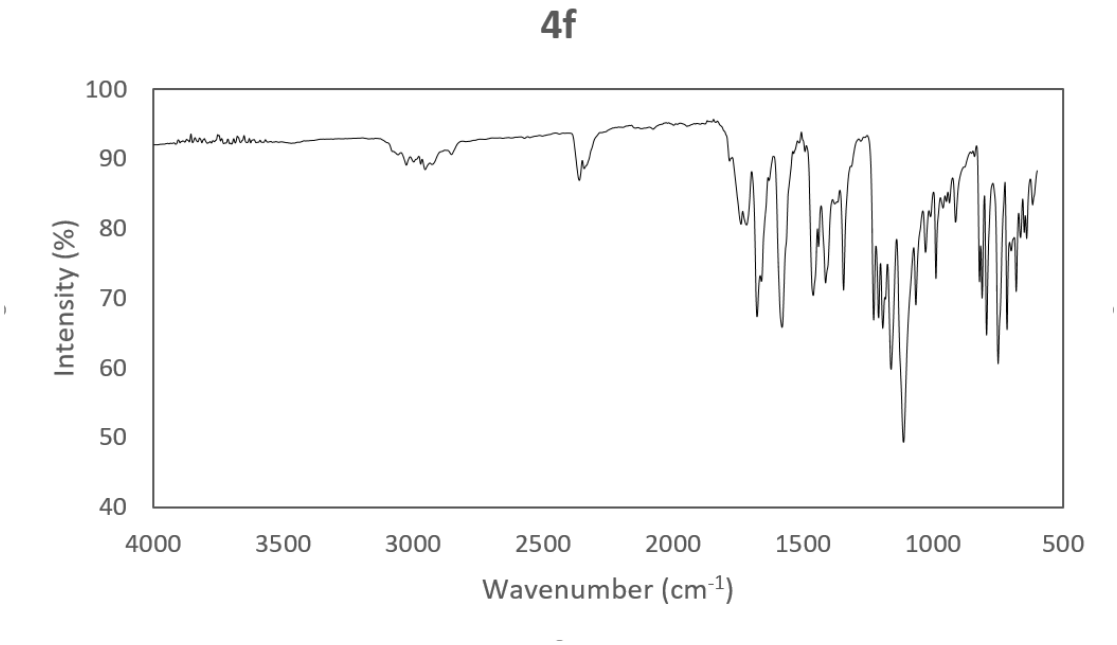
HMBC of **4f** (600 MHz, $CDCl_3$)



^{19}F spectrum of **4f** (377 MHz, $CDCl_3$)

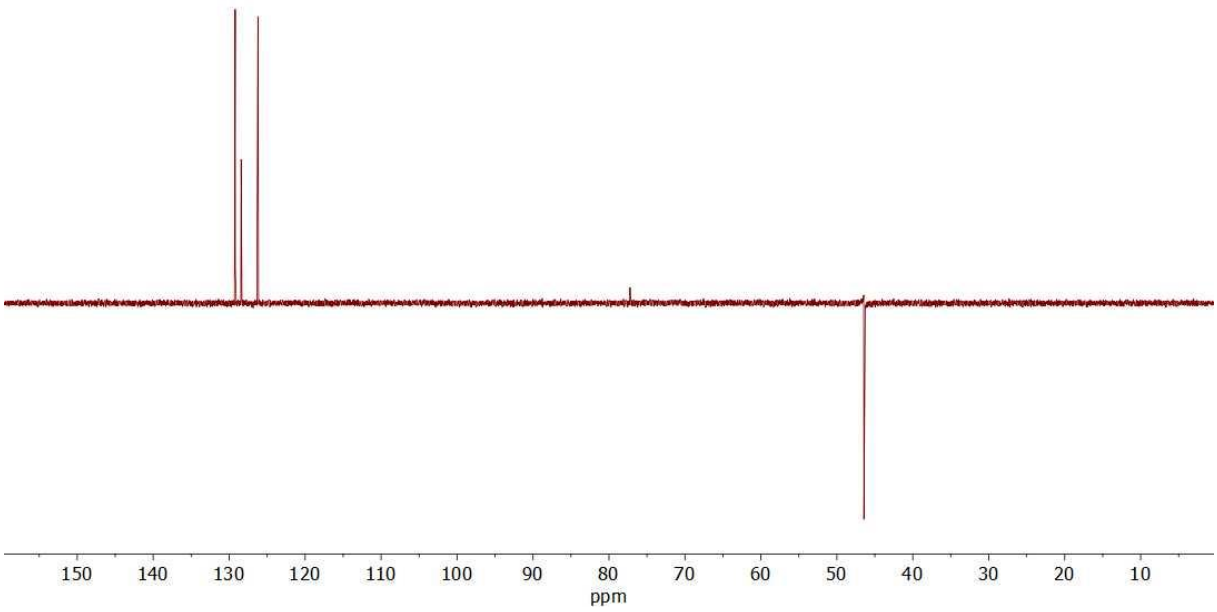


IR spectrum of **4f**

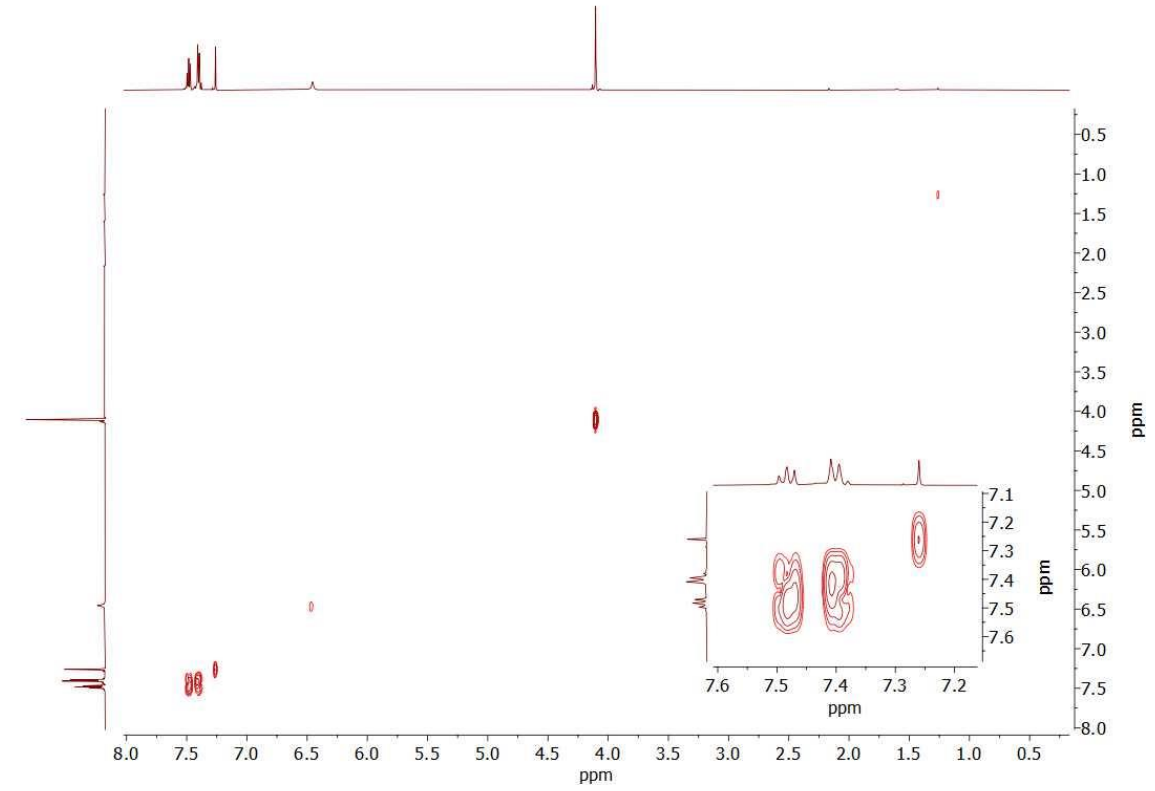


7.7 3-Phenylhydanotin (2a)

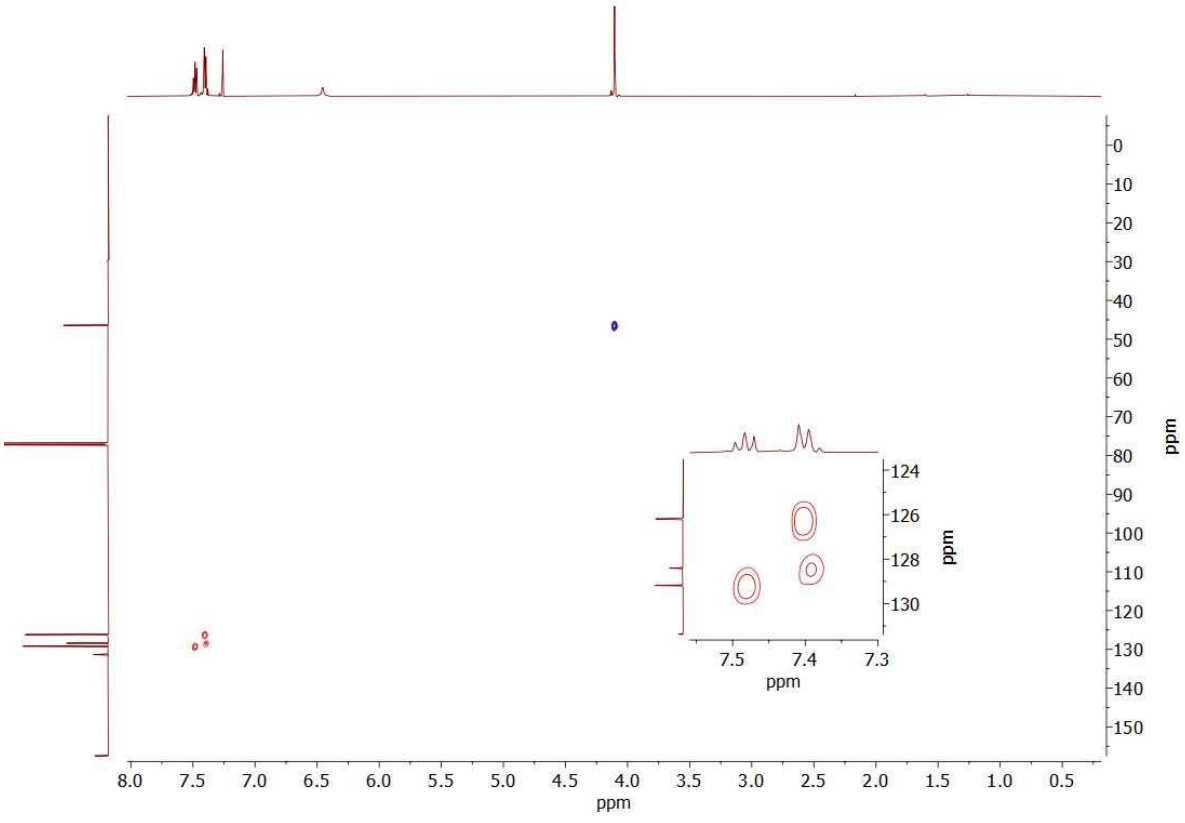
DEPT135 of **2a** (151 MHz, $CDCl_3$)



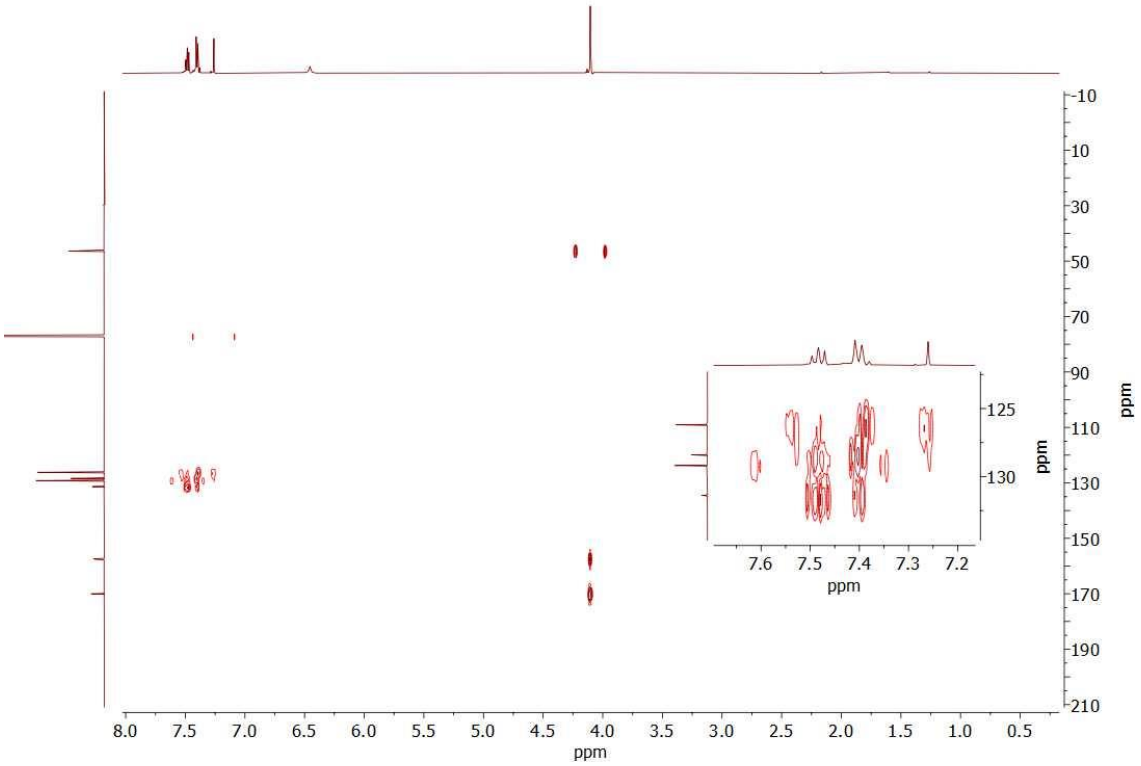
COSY of **2a** (600 MHz, $CDCl_3$)



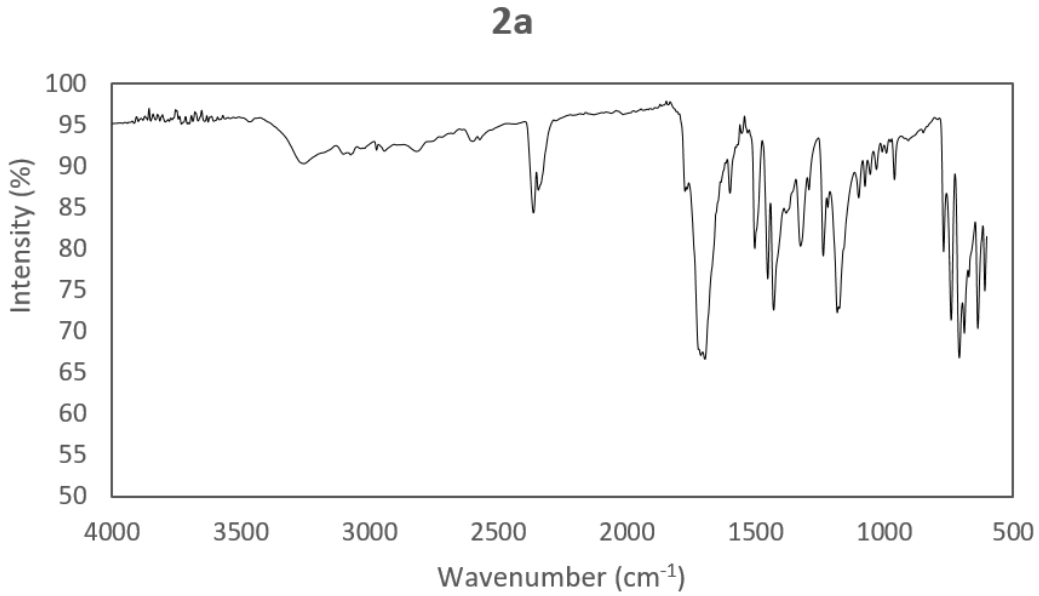
HSQC of **2a** (600 MHz, $CDCl_3$)



HMBC of **2a** (600 MHz, $CDCl_3$)

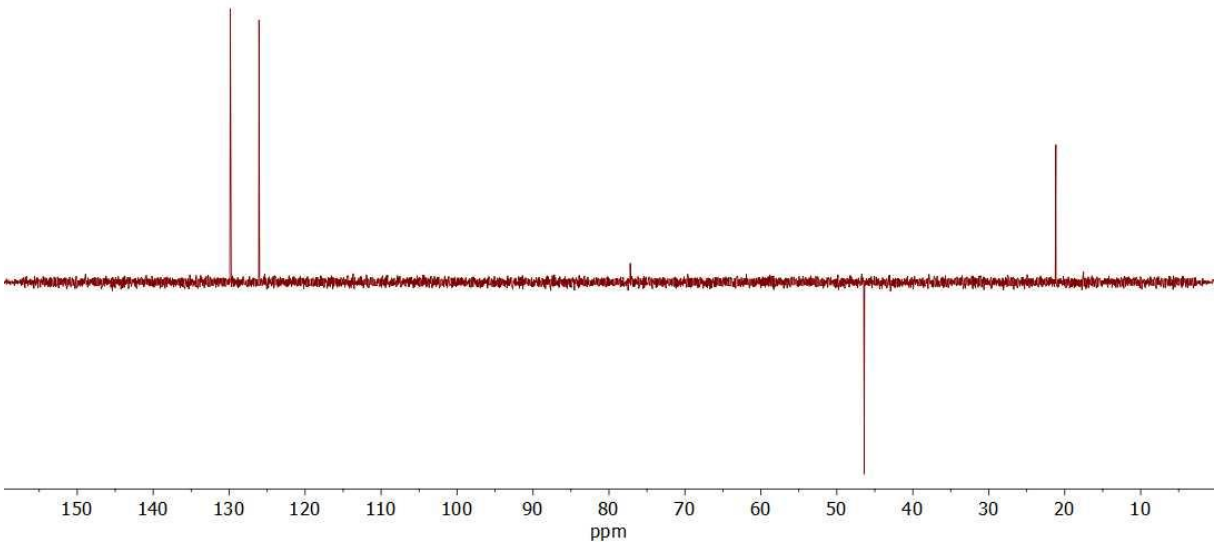


IR spectrum of **2a**

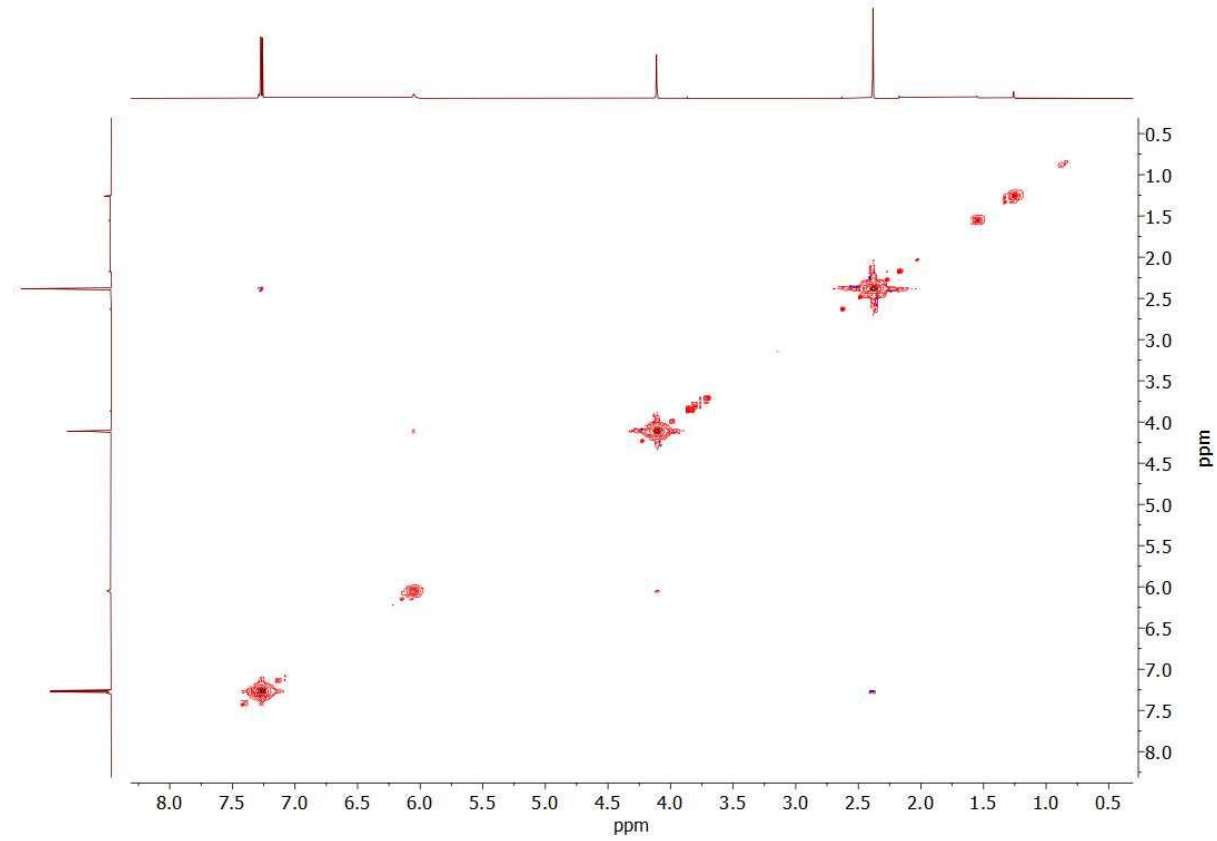


7.8 3-(4-Tolyl)hydantoin (2b)

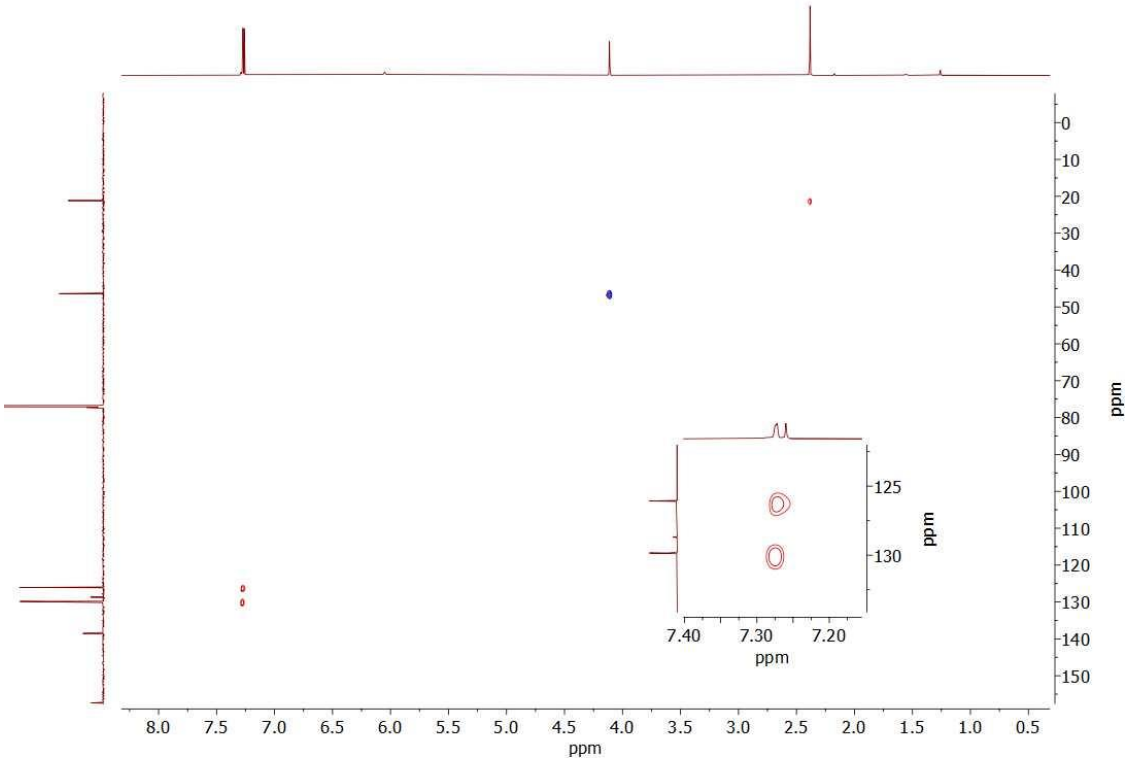
DEPT135 of **2b** (151 MHz, $CDCl_3$)



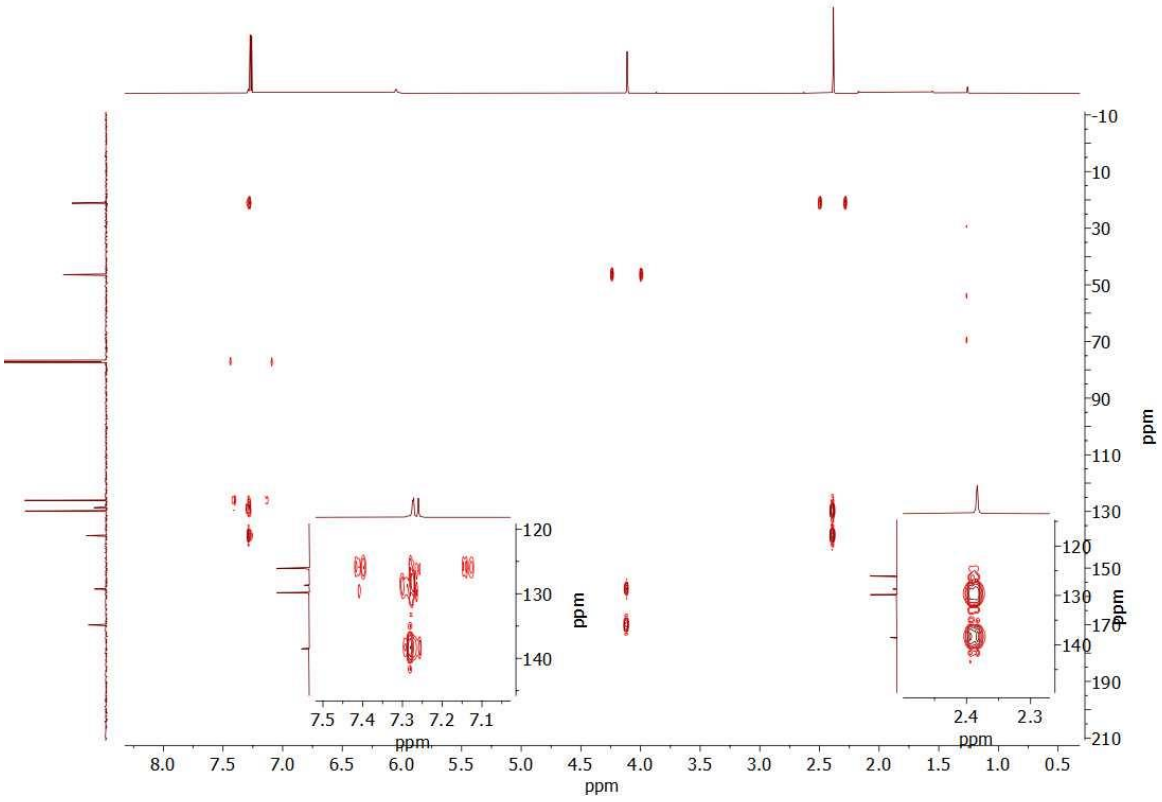
COSY of **2b** (600 MHz, $CDCl_3$)



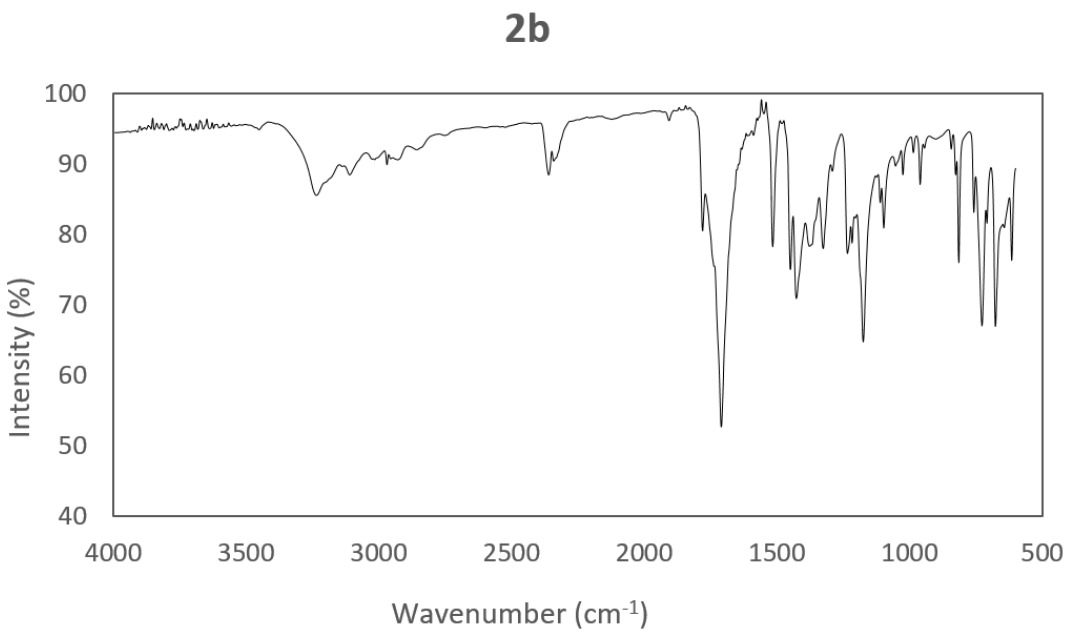
HSQC of **2b** (600 MHz, $CDCl_3$)



HMBC of **2b** (600 MHz, $CDCl_3$)

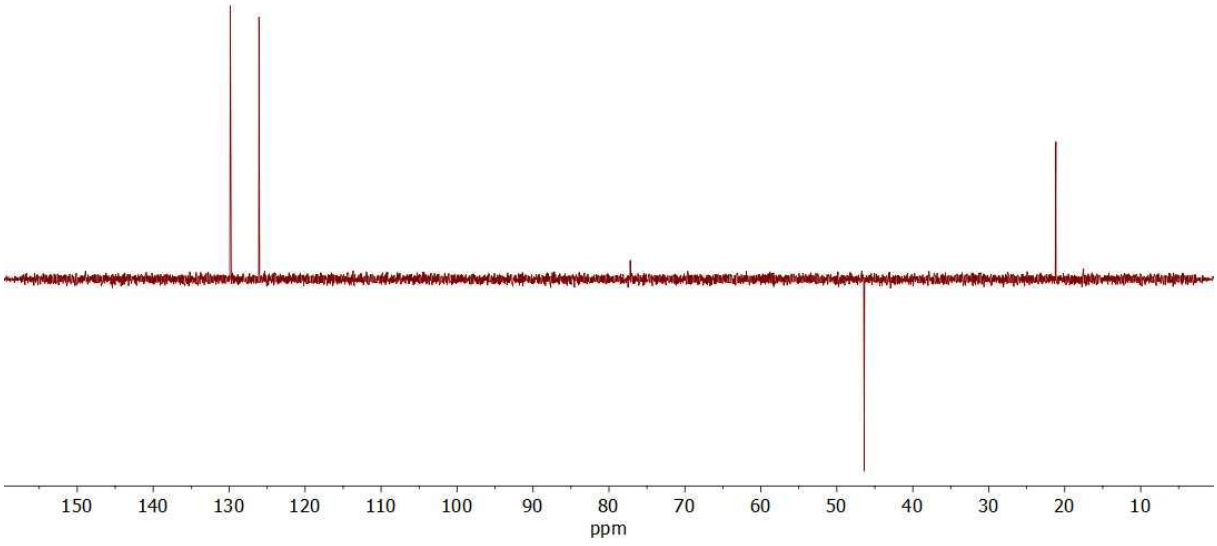


IR spectrum of **2b**

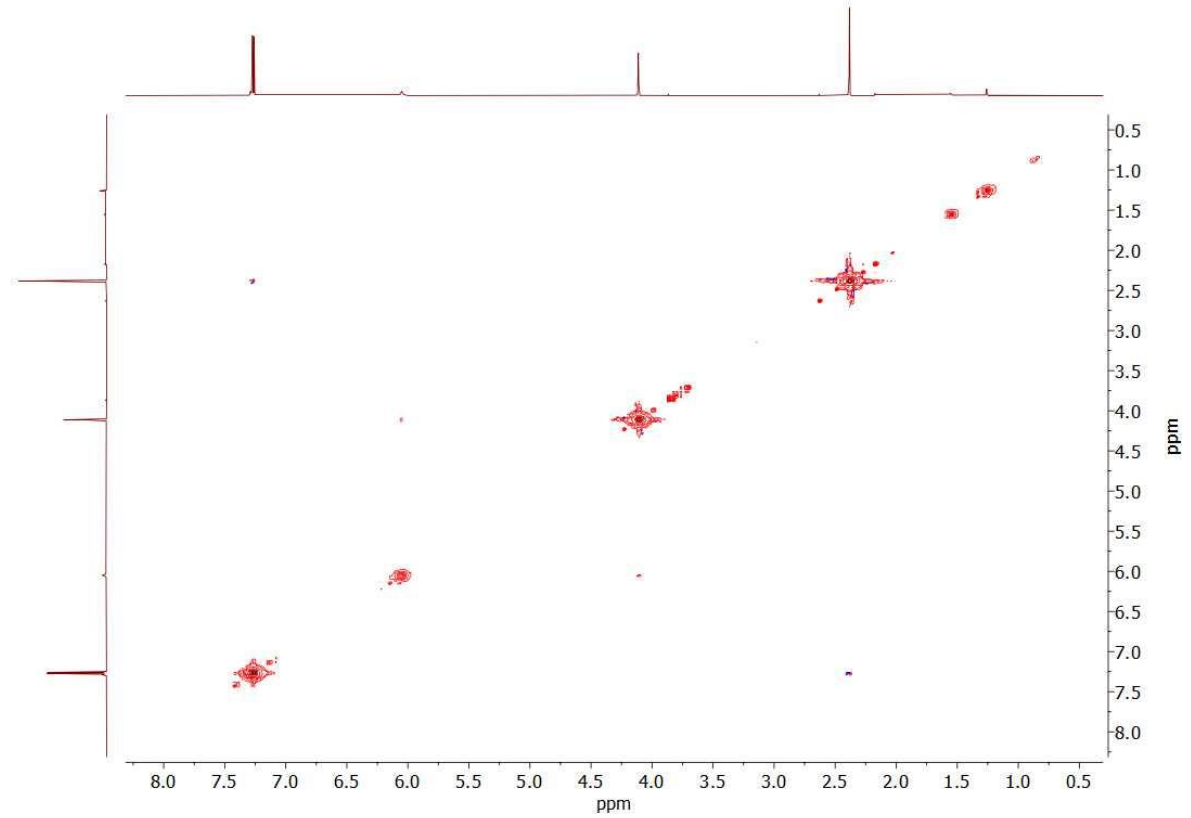


7.8 3-(4-Nitrophenyl)hydantoin (2c)

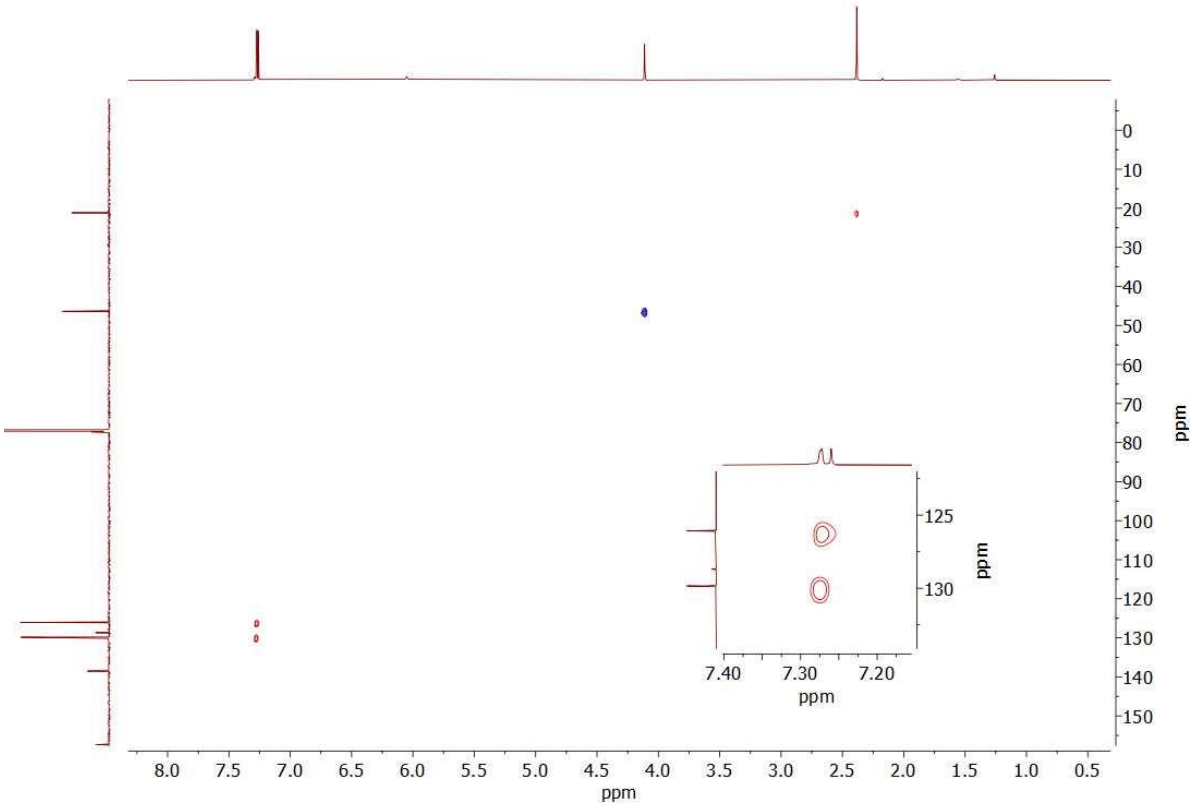
DEPT135 of **2c** (151 MHz, $CDCl_3$)



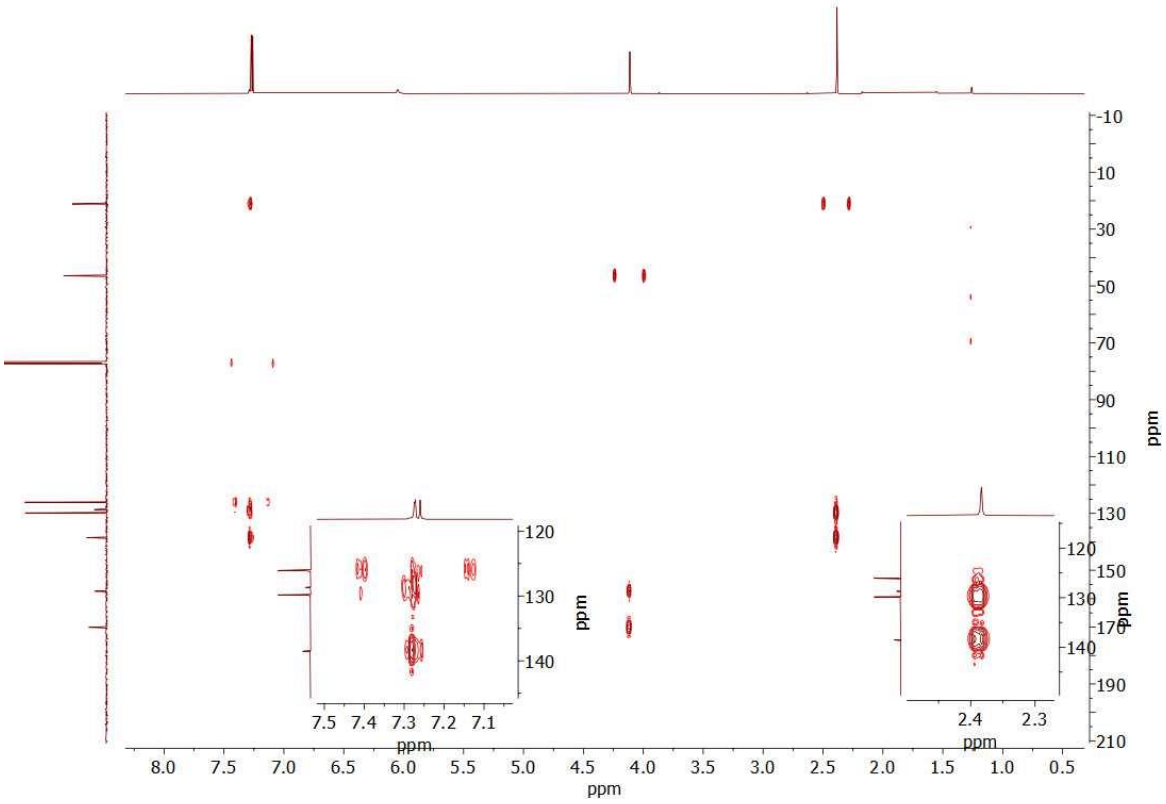
COSY of **2c** (600 MHz, $CDCl_3$)



HSQC of **2c** (600 MHz, $CDCl_3$)

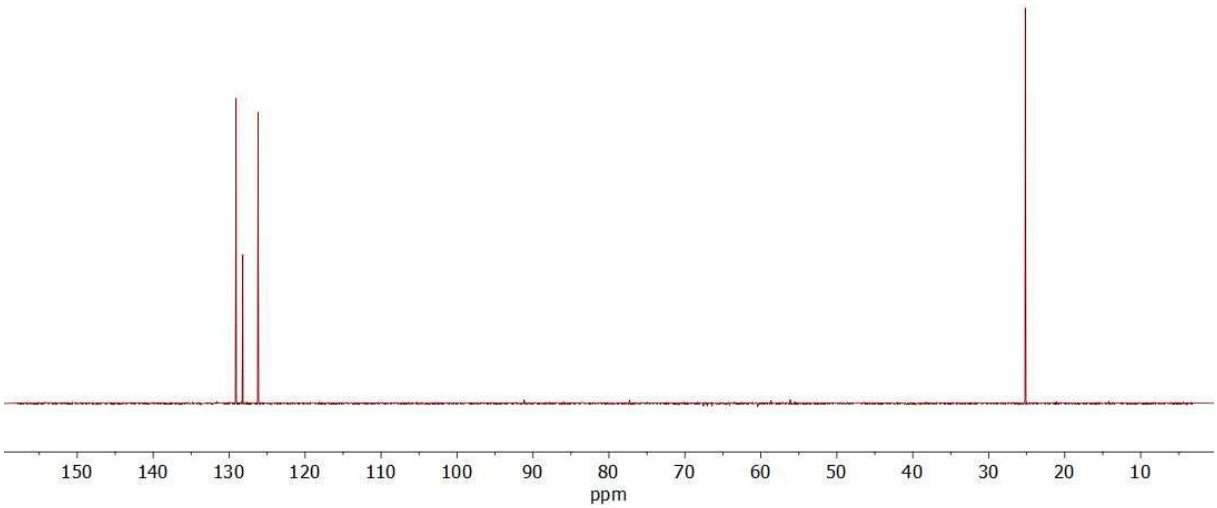


HMBC of **2c** (600 MHz, $CDCl_3$)

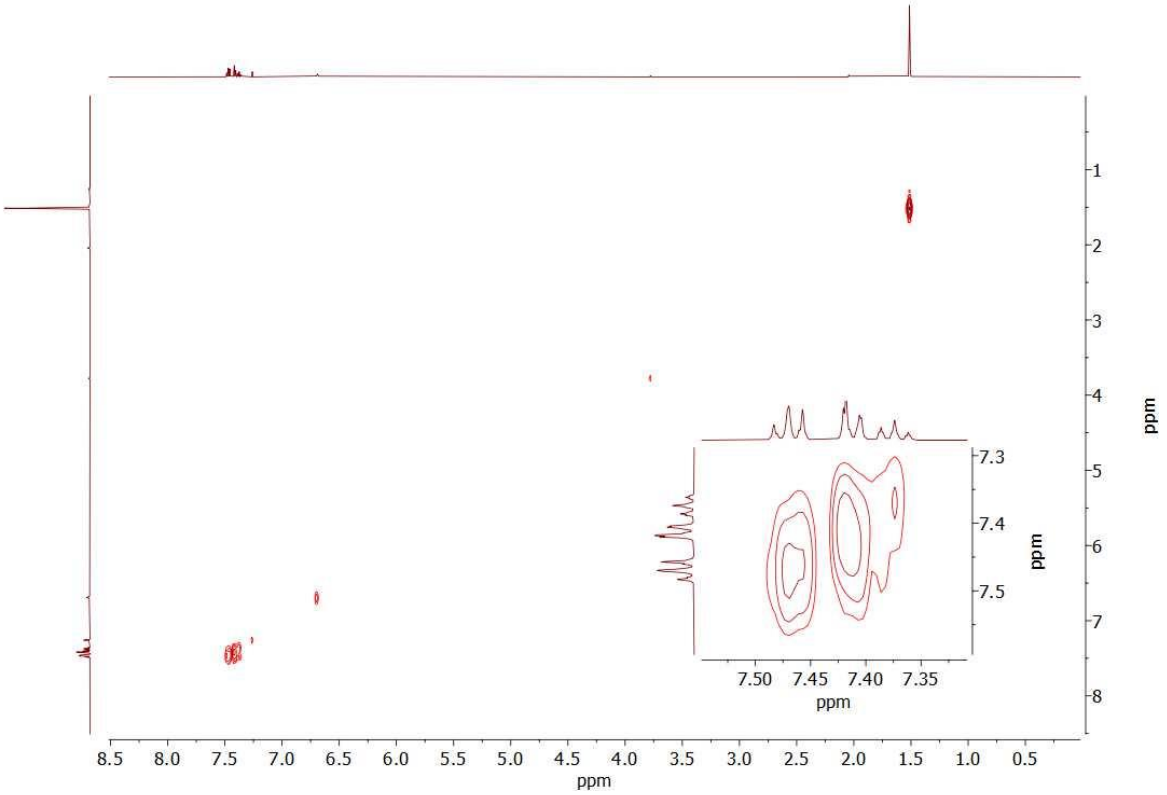


7.9 5,5-Dimethyl-3-phenylhydantoin (2d)

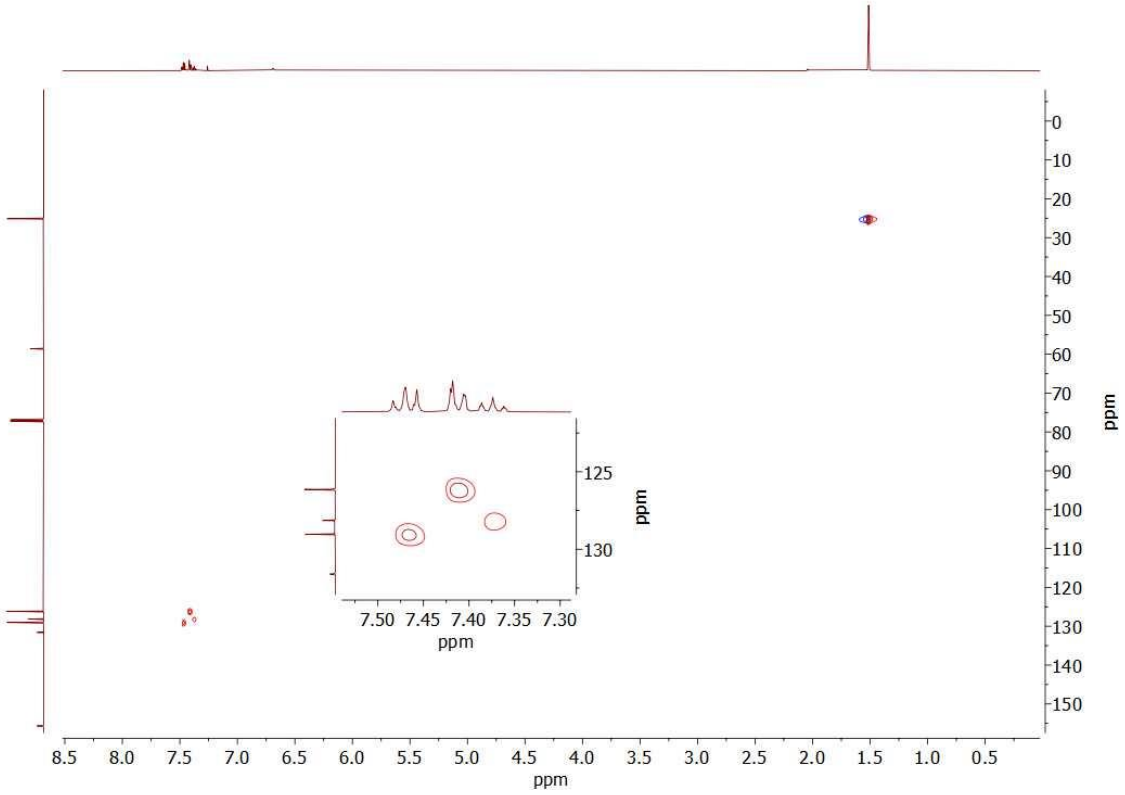
DEPT135 of **2d** (151 MHz, $CDCl_3$)



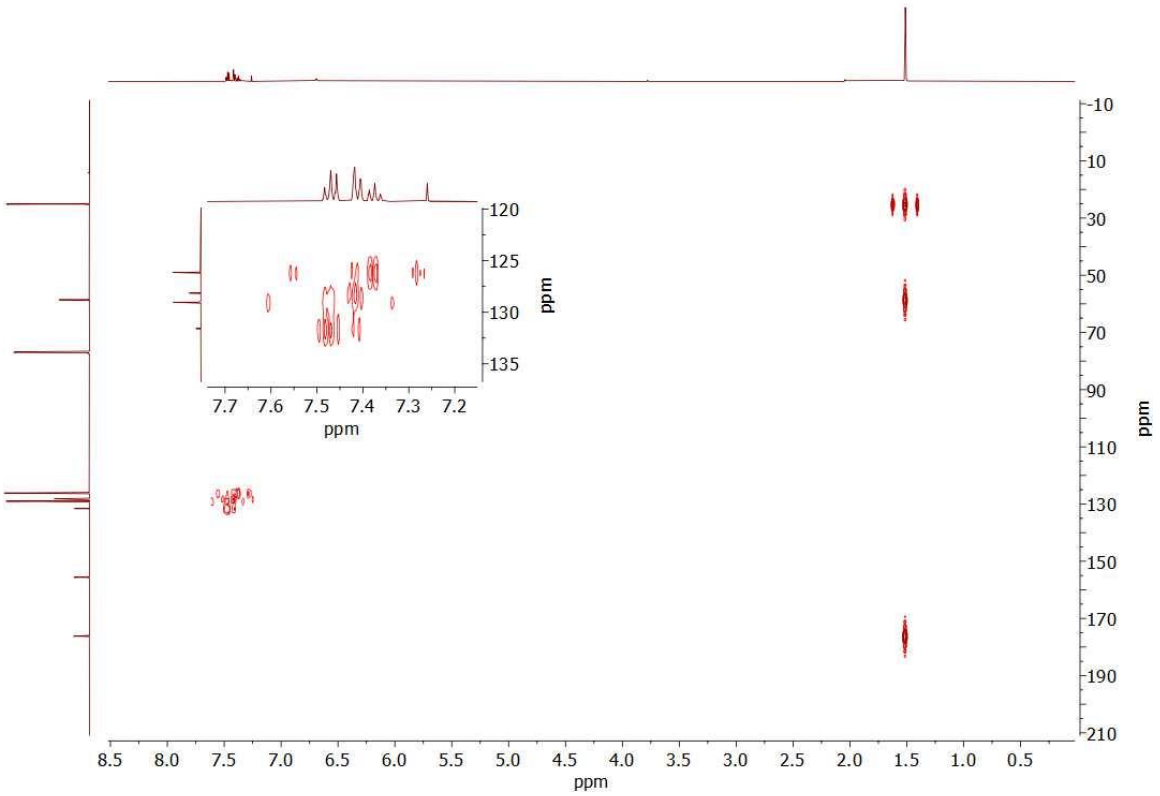
COSY of **2d** (600 MHz, $CDCl_3$)



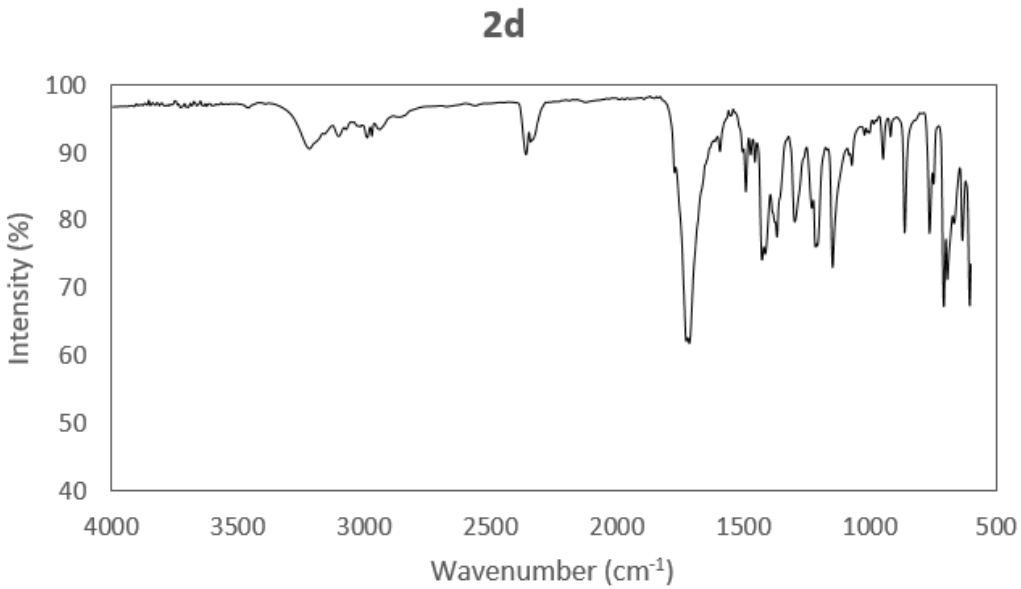
HSQC of **2d** (600 MHz, $CDCl_3$)



HMBC of **2d** (600 MHz, $CDCl_3$)

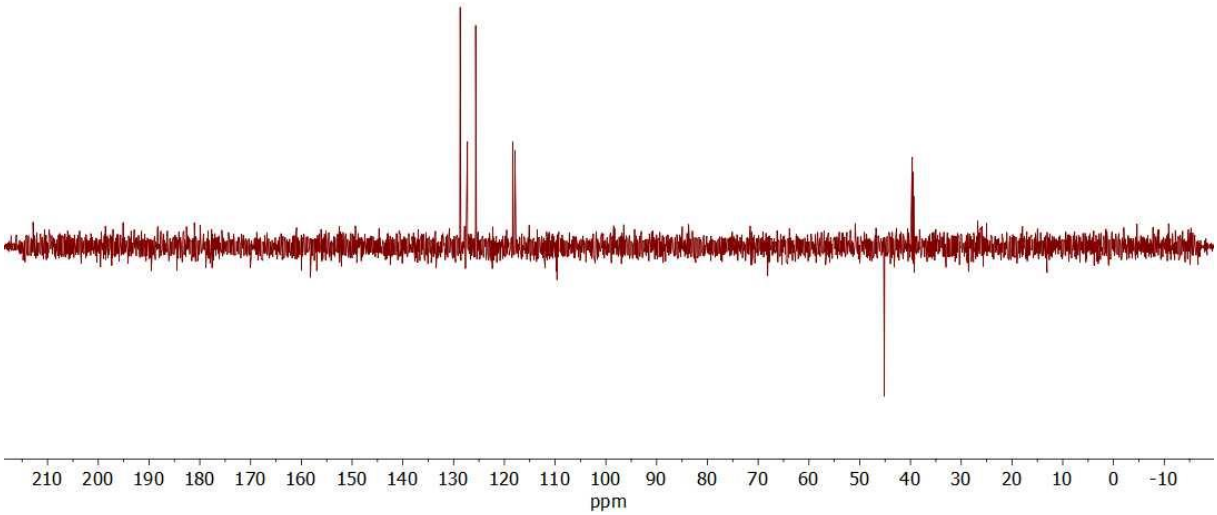


IR spectrum of **2d**

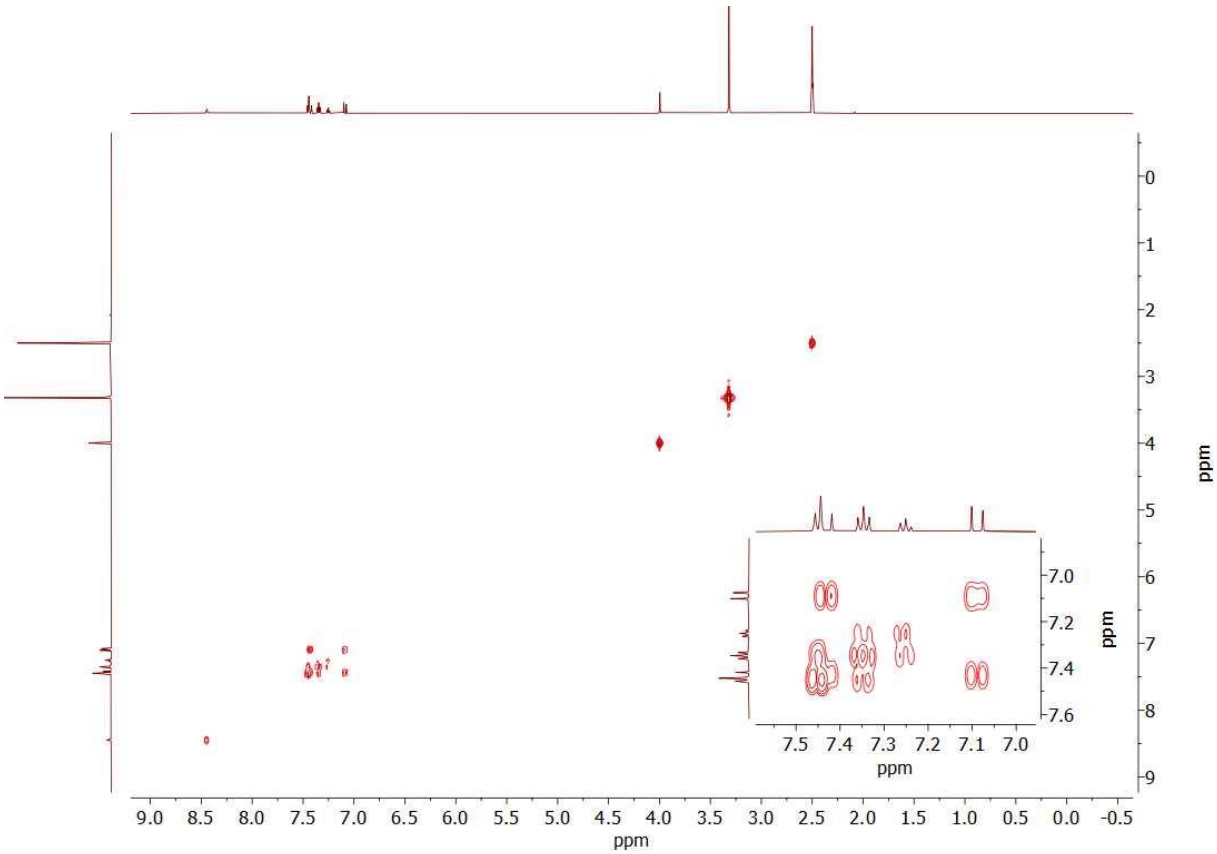


7.10 *(E)*-3-Styrylhydantoin (2e)

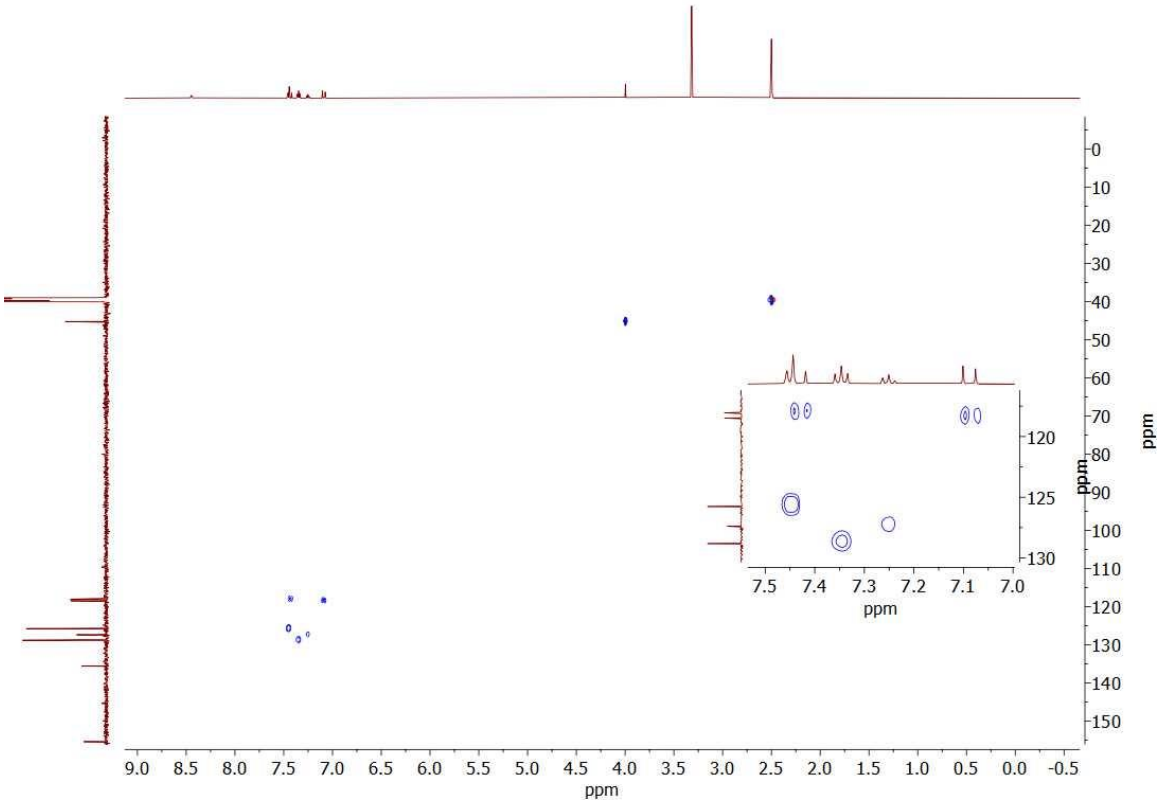
DEPT135 of **2e** (151 MHz, $CDCl_3$)



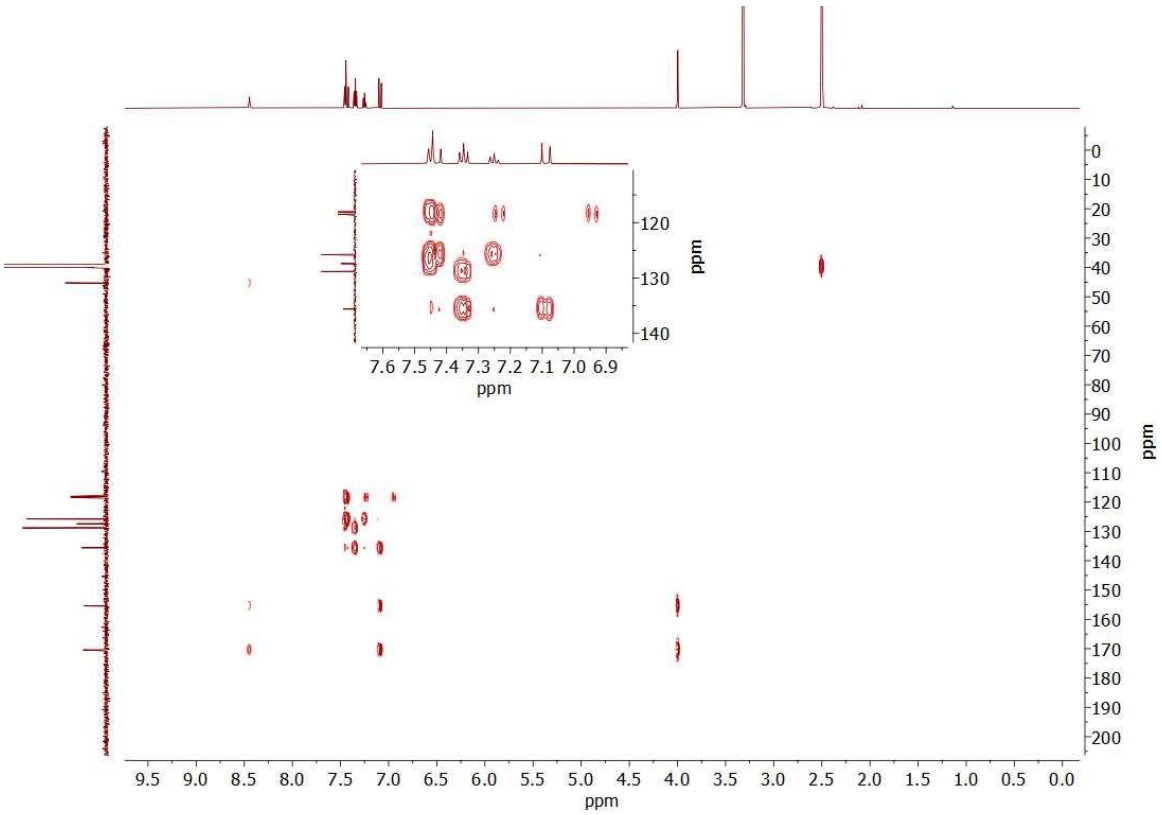
COSY of **2e** (600 MHz, $CDCl_3$)



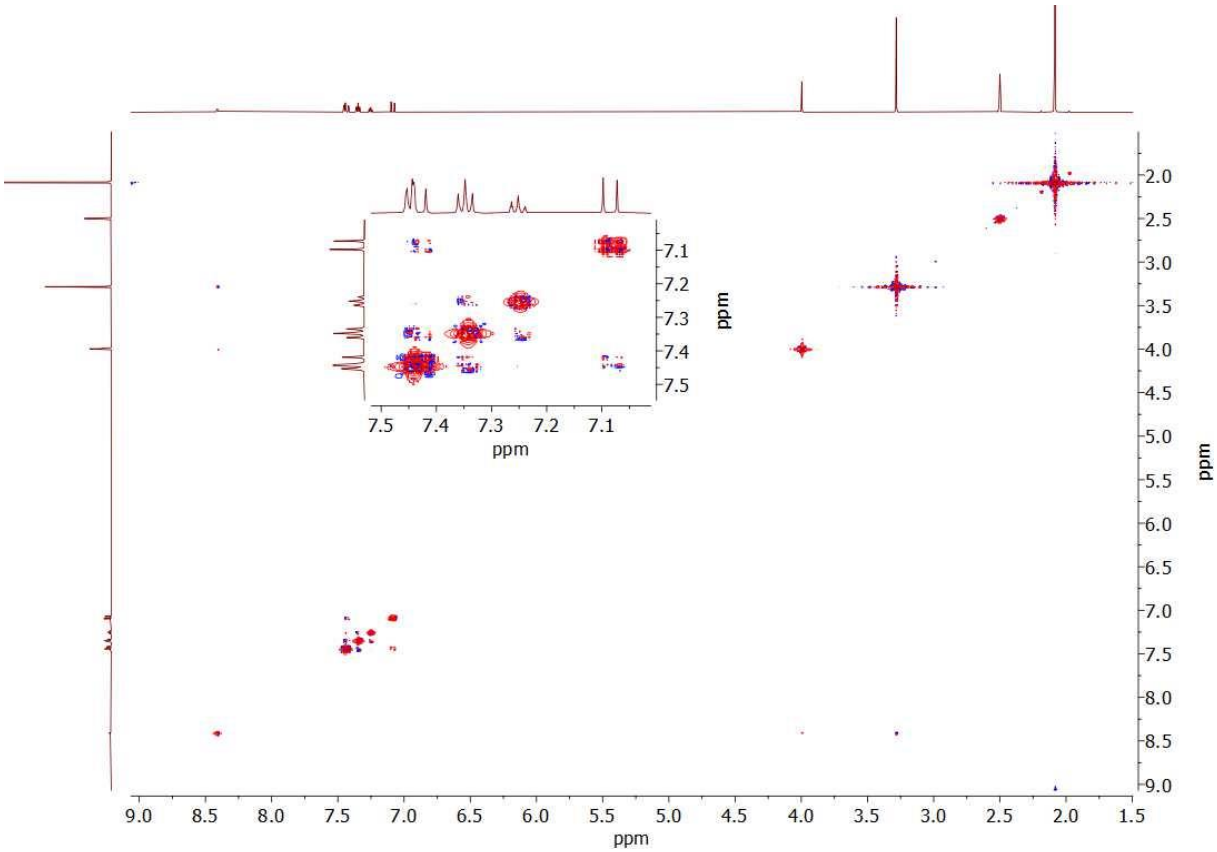
HSQC of **2e** (600 MHz, $CDCl_3$)



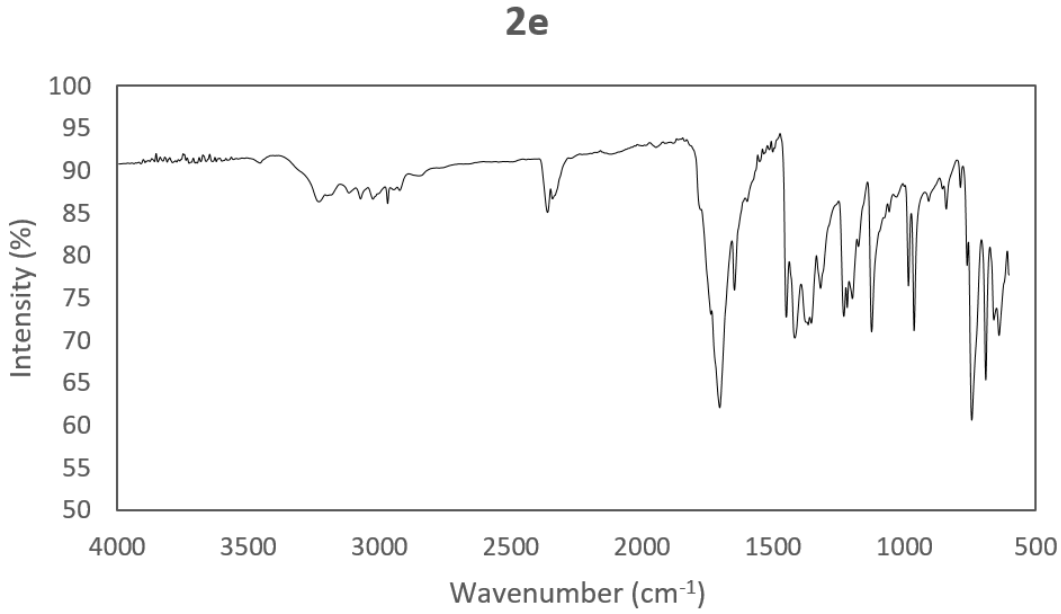
HMBC of **2e** (600 MHz, $CDCl_3$)



NOESY of **2e** (600 MHz, $CDCl_3$)

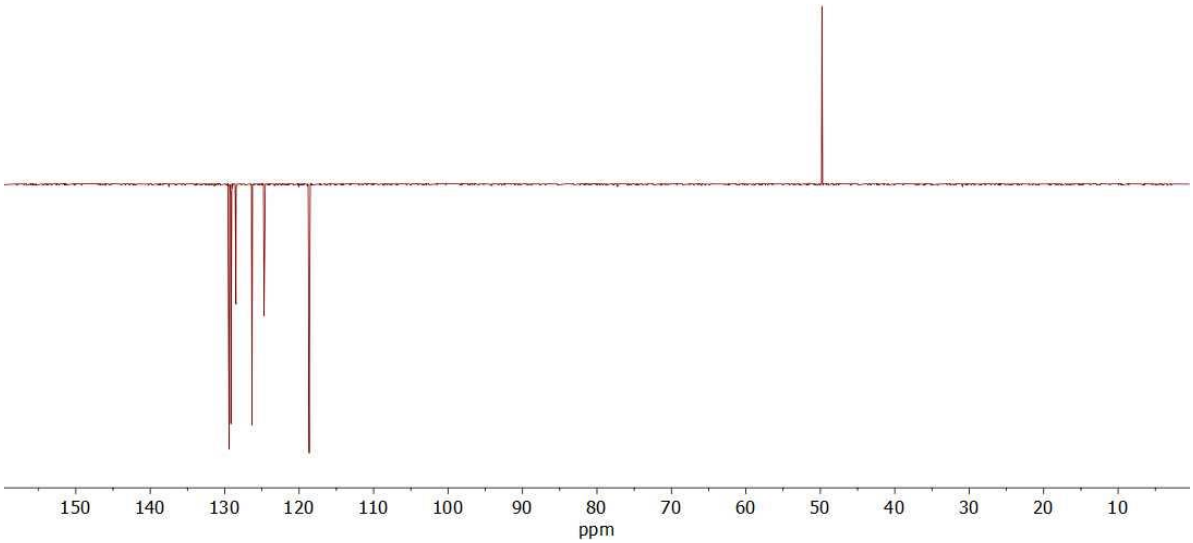


IR spectrum of **2e**

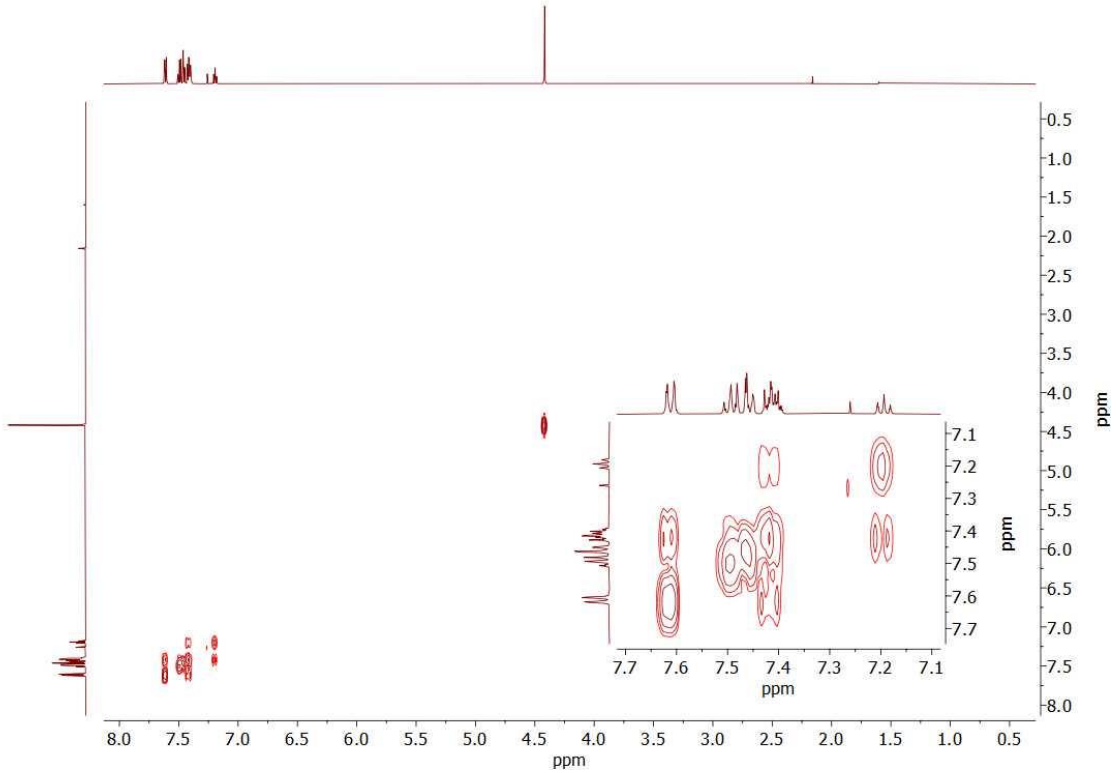


7.11 1,3-Diphenylhydantoin (3a)

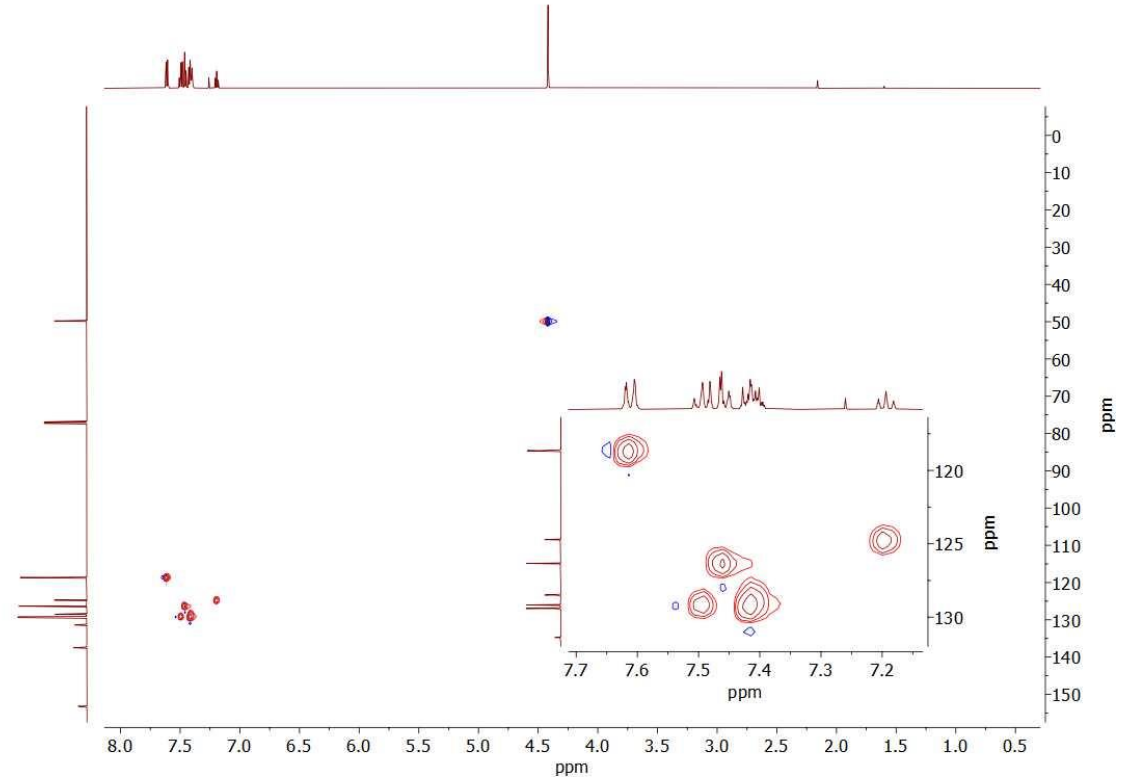
DEPT135 of **3a** (151 MHz, $CDCl_3$)



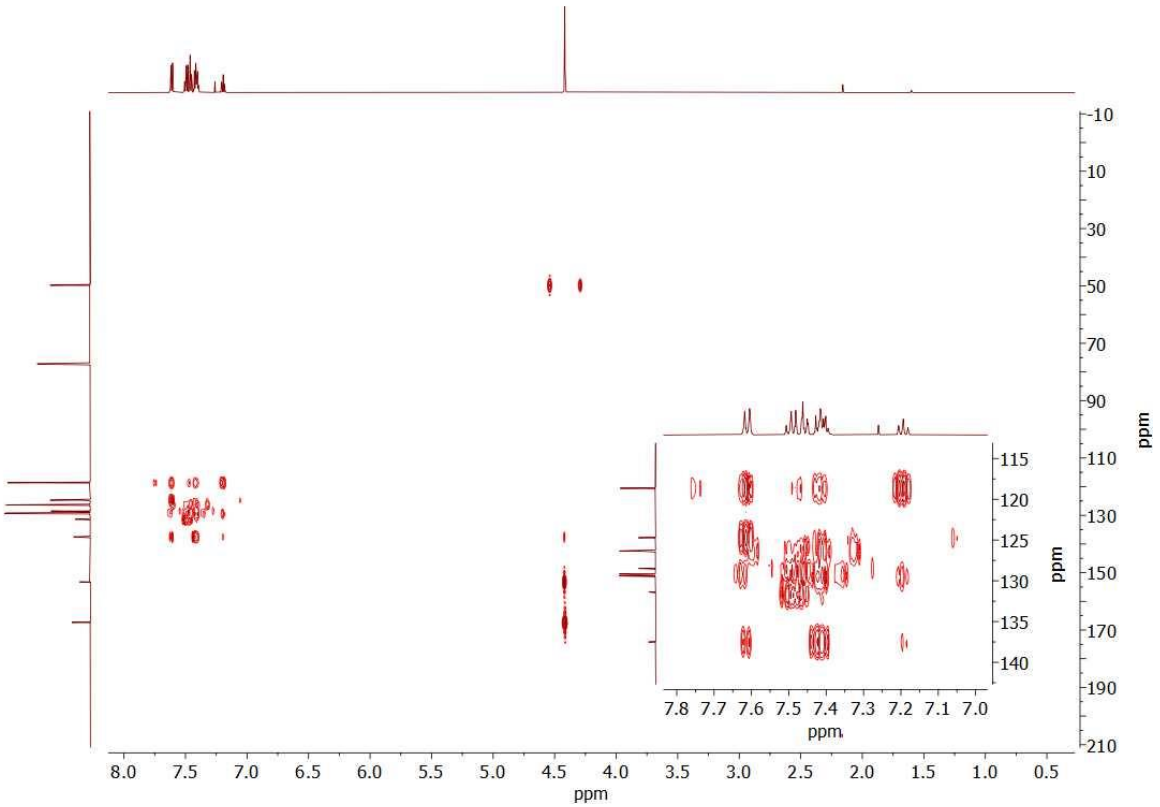
COSY of **3a** (600 MHz, $CDCl_3$)



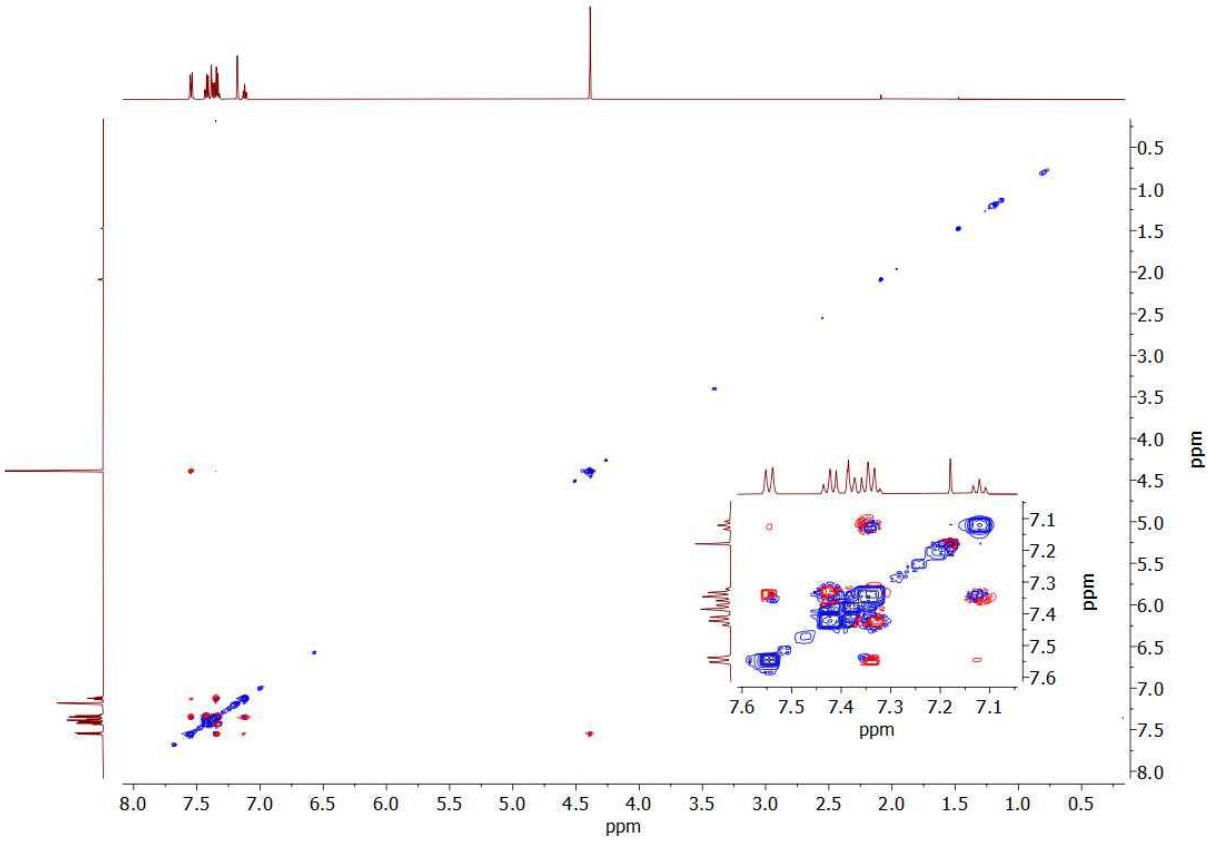
HSQC of **3a** (600 MHz, $CDCl_3$)



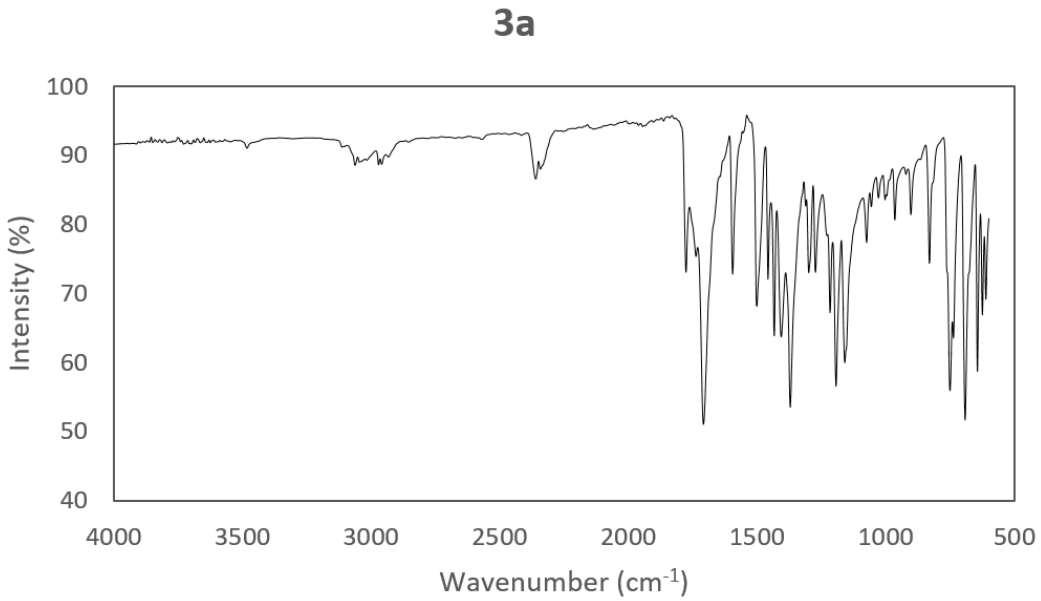
HMBC of **3a** (600 MHz, $CDCl_3$)



NOESY of **3a** (600 MHz, $CDCl_3$)

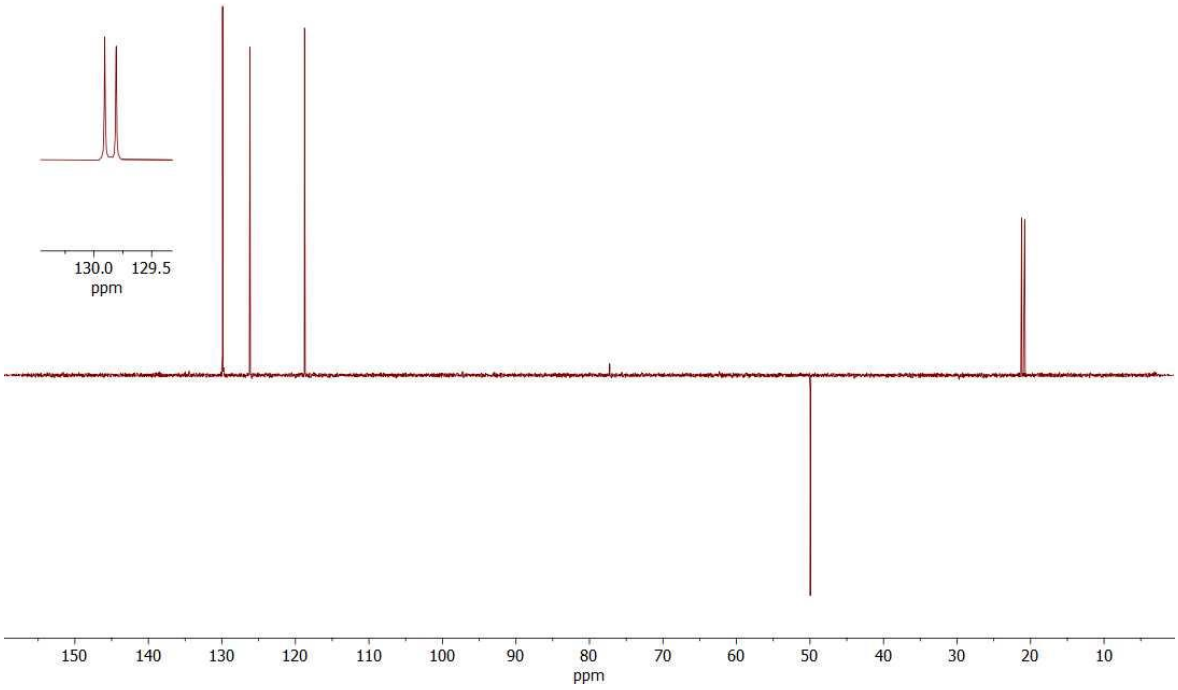


IR spectrum of **3a**

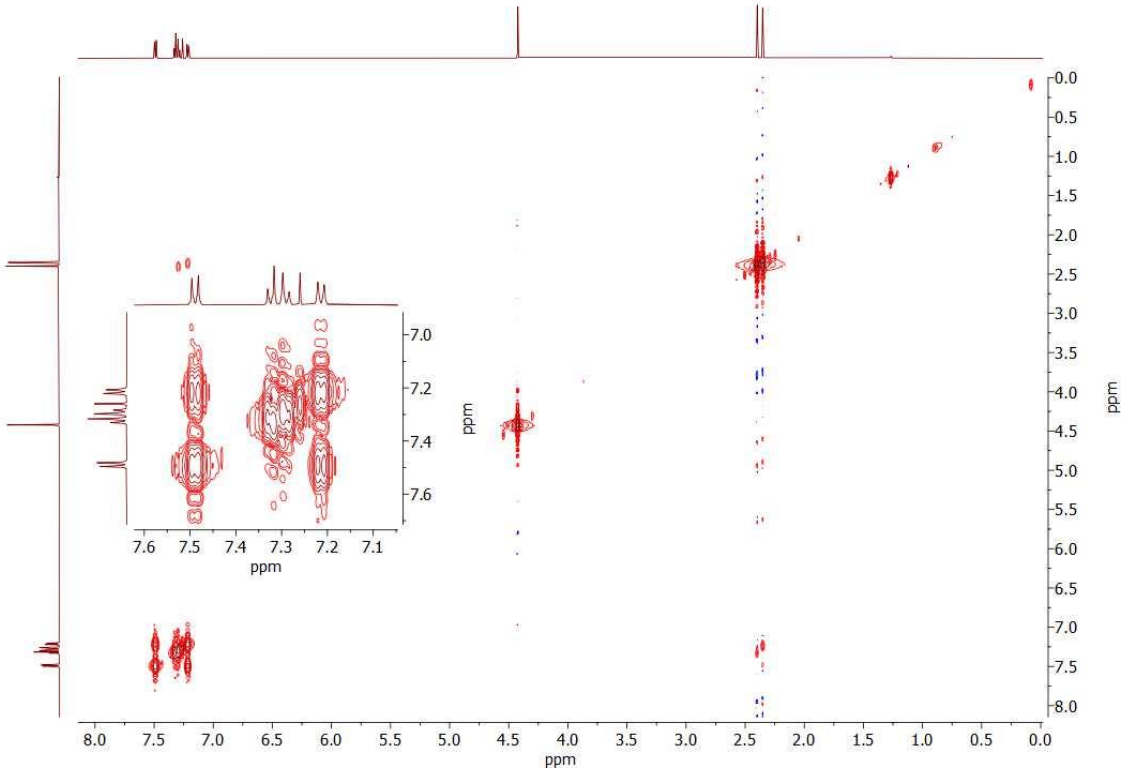


7.12 1,3-Di(4-tolyl)hydantoin (3b)

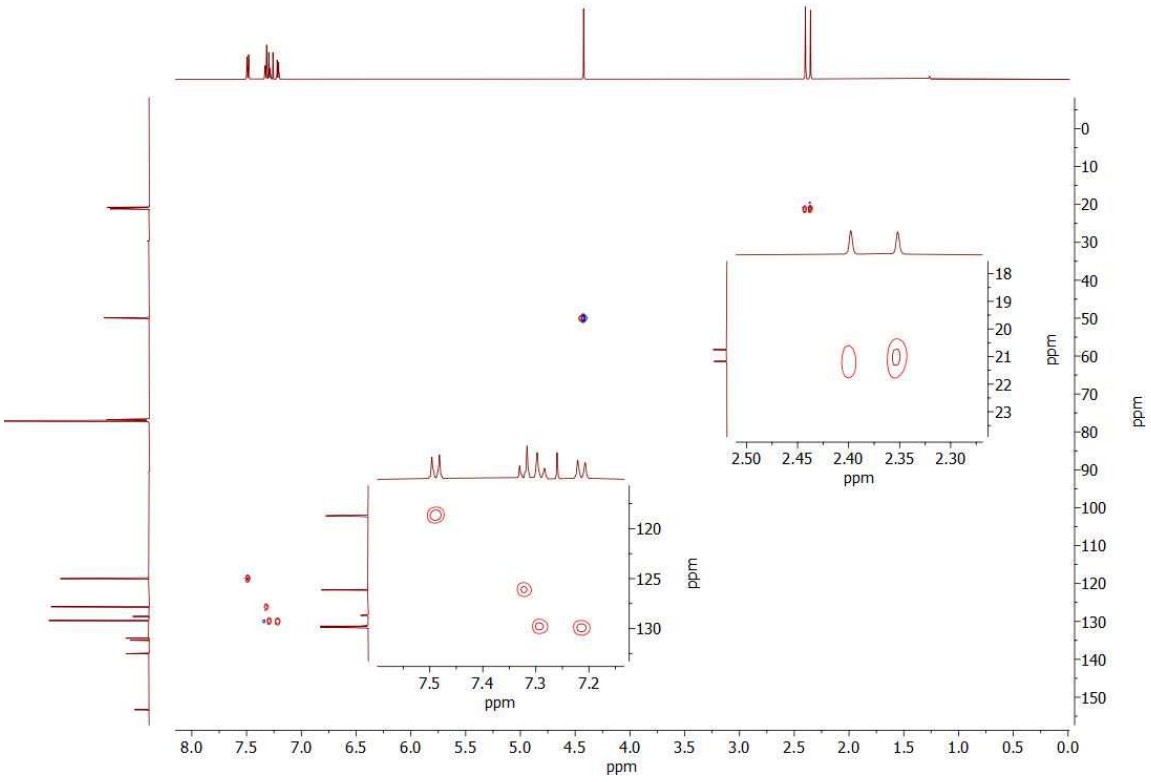
DEPT135 of **3b** (151 MHz, $CDCl_3$)



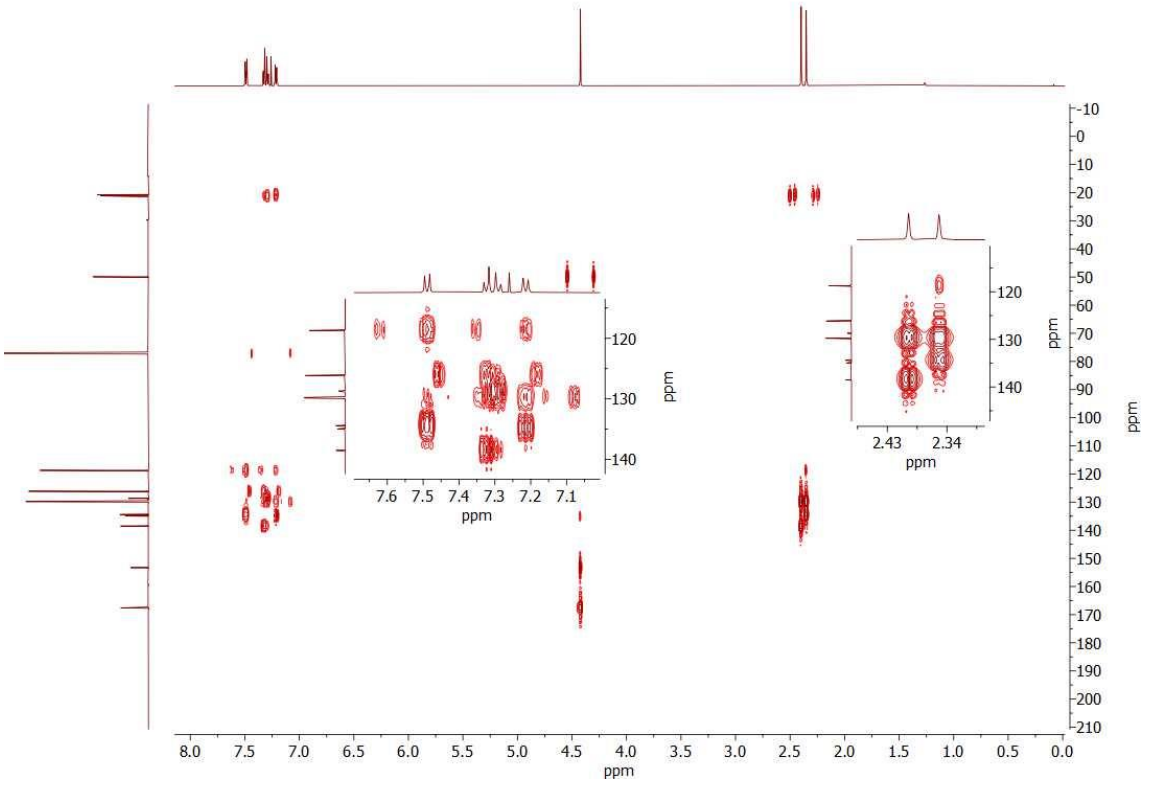
COSY of **3b** (600 MHz, $CDCl_3$)



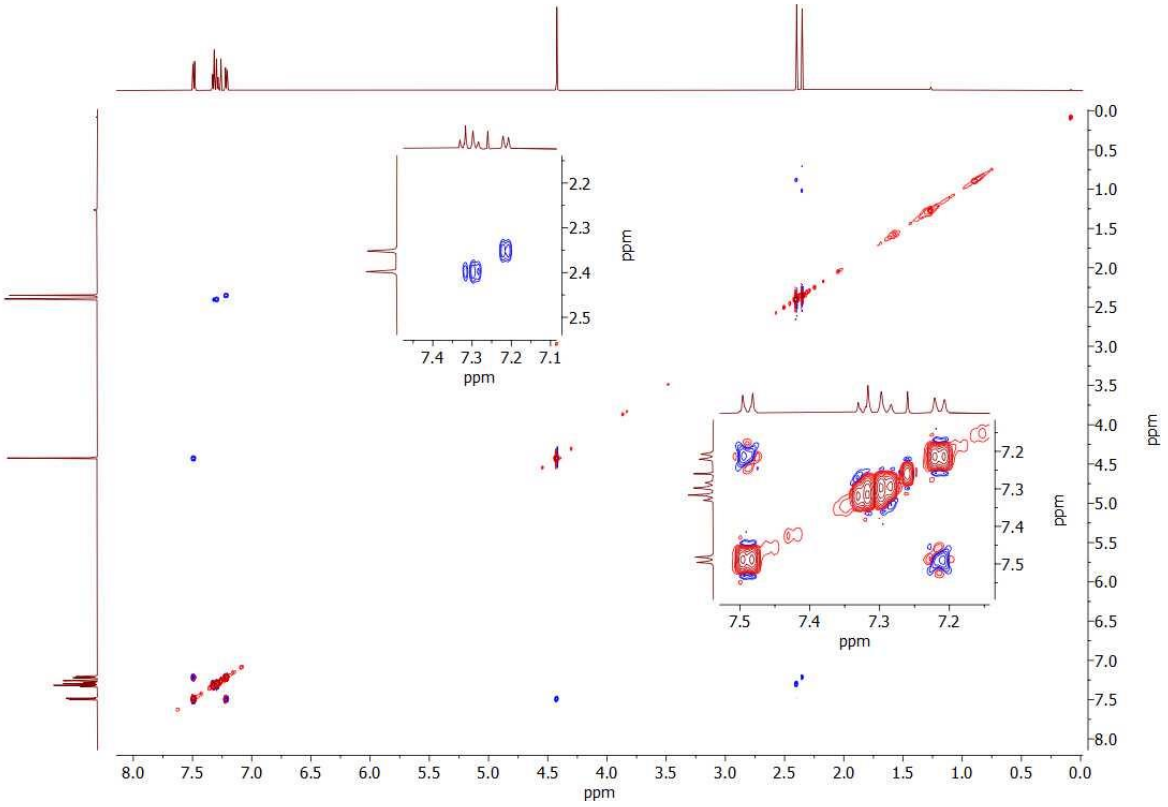
HSQC of **3b** (600 MHz, $CDCl_3$)



HMBC of **3b** (600 MHz, $CDCl_3$)

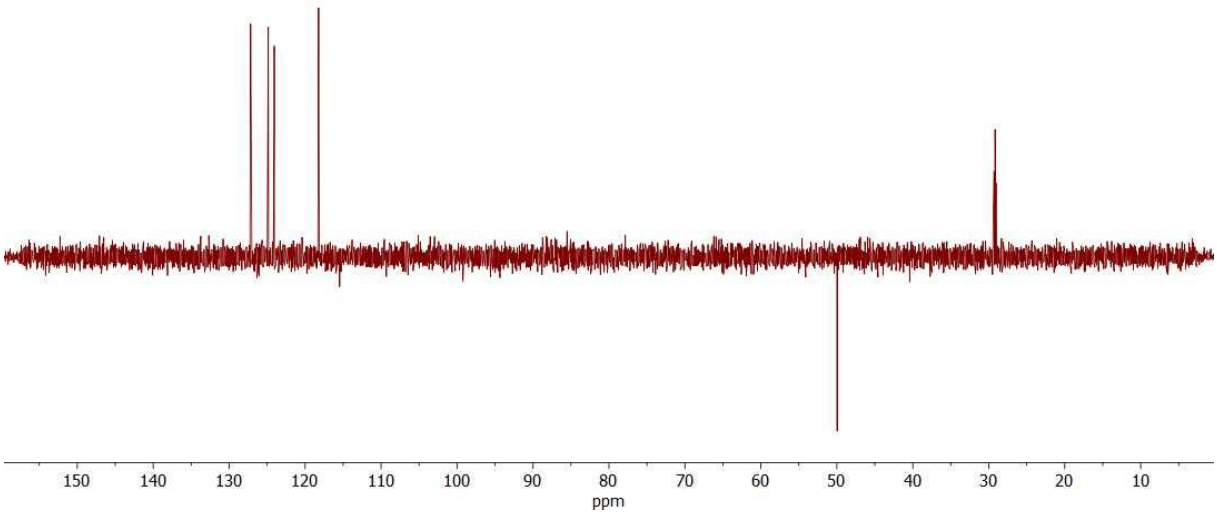


NOESY of **3b** (600 MHz, $CDCl_3$)

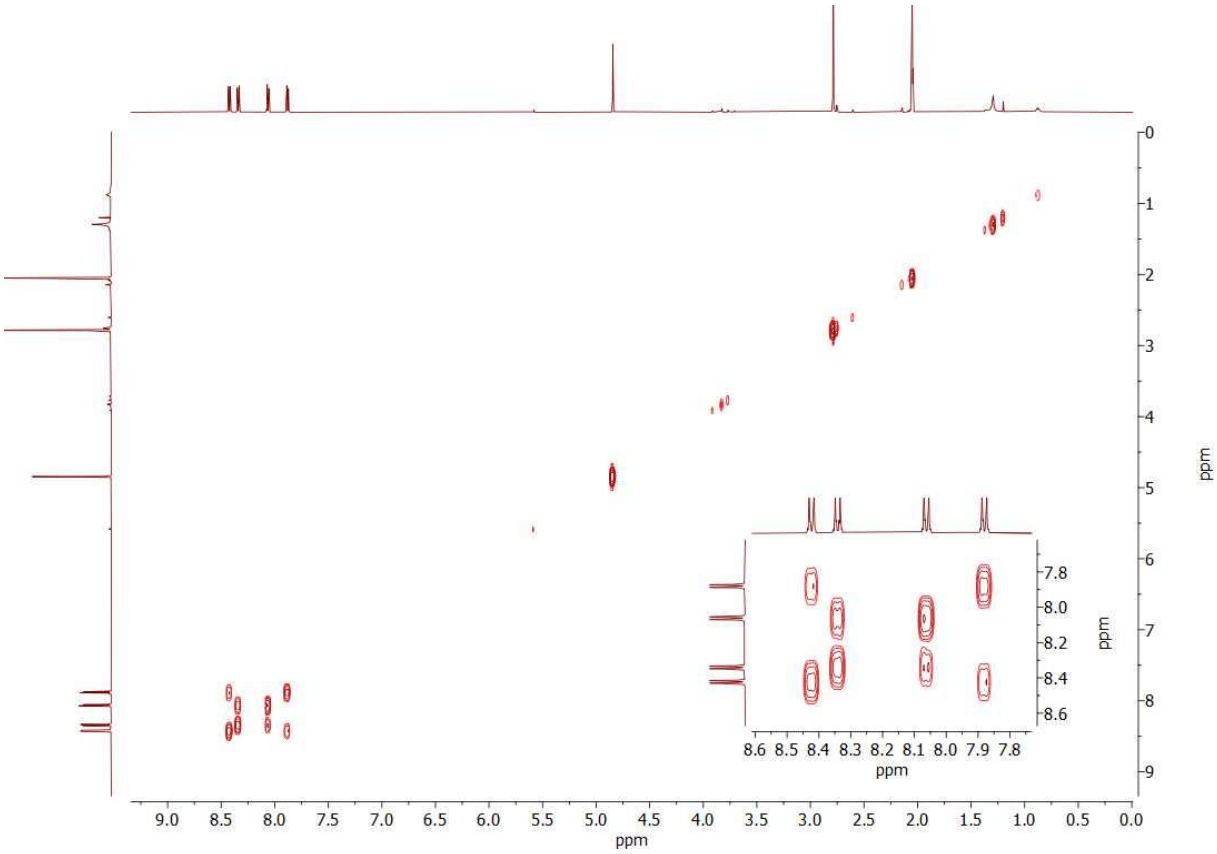


7.13 1,3-Di(4-nitrophenyl)hydantoin (3c)

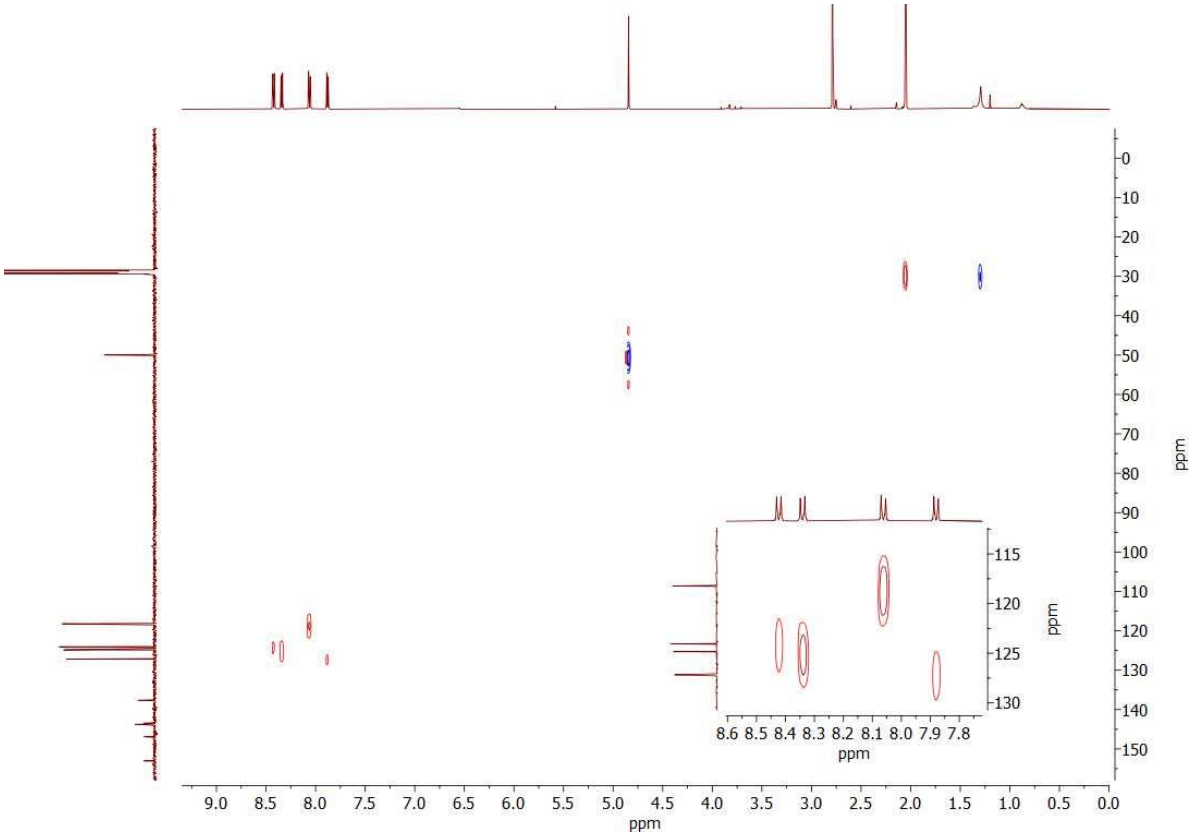
DEPT135 of **3c** (151 MHz, Acetone-d_6)



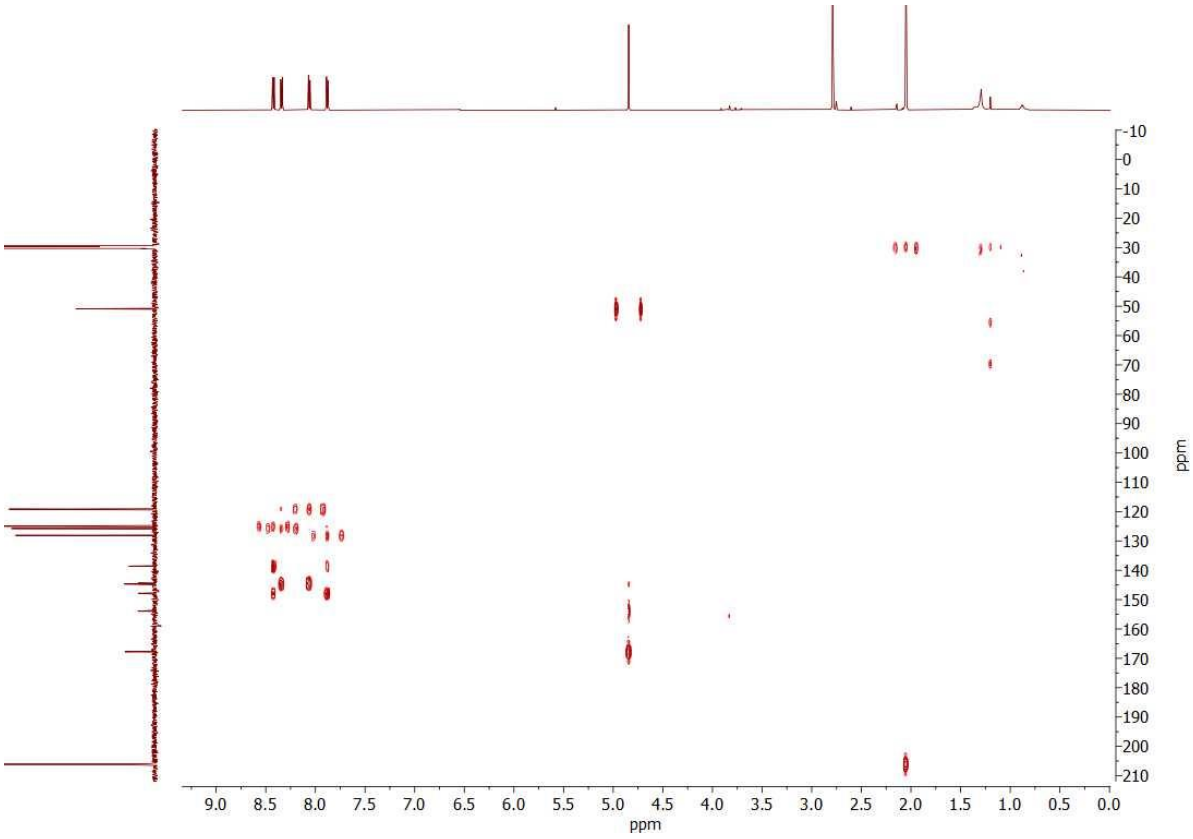
COSY of **3c** (600 MHz, Acetone-d_6)



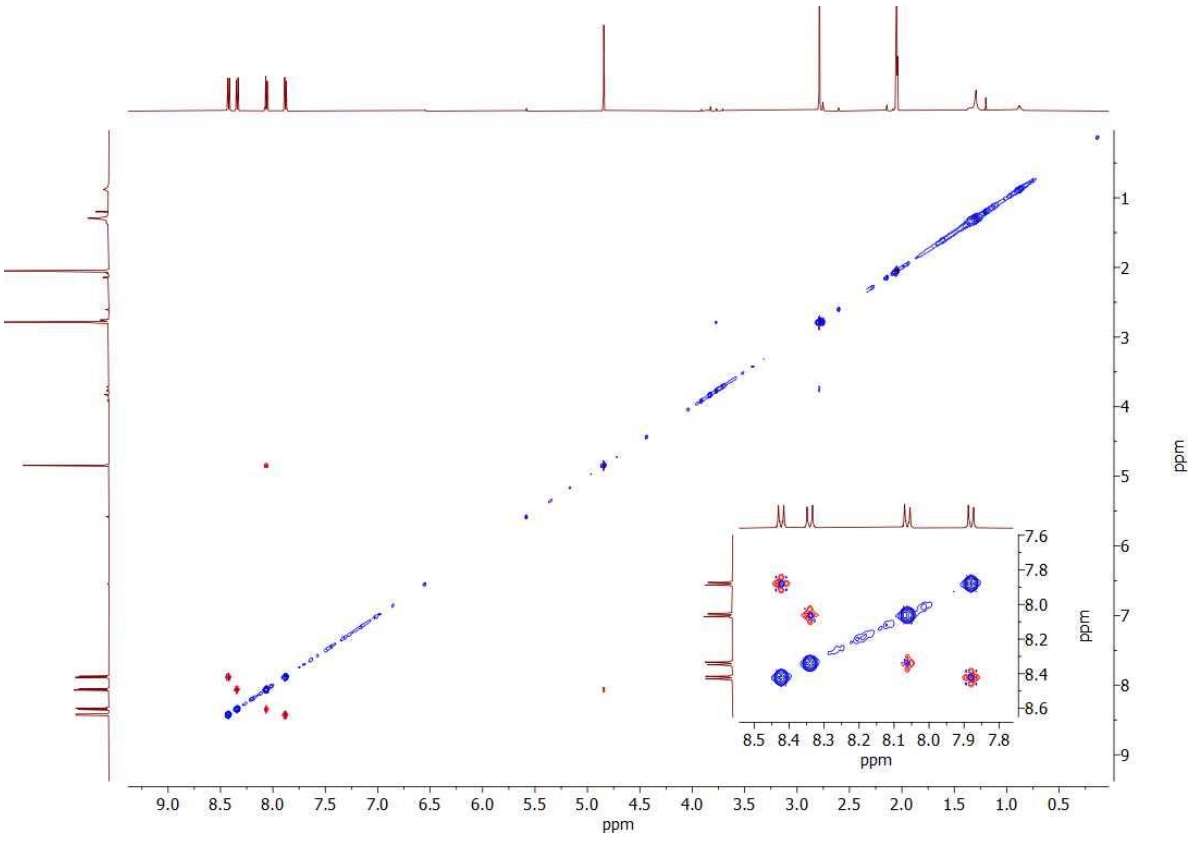
HSQC of **3c** (600 MHz, Acetone-d_6)



HMBC of **3c** (600 MHz, Acetone-d_6)

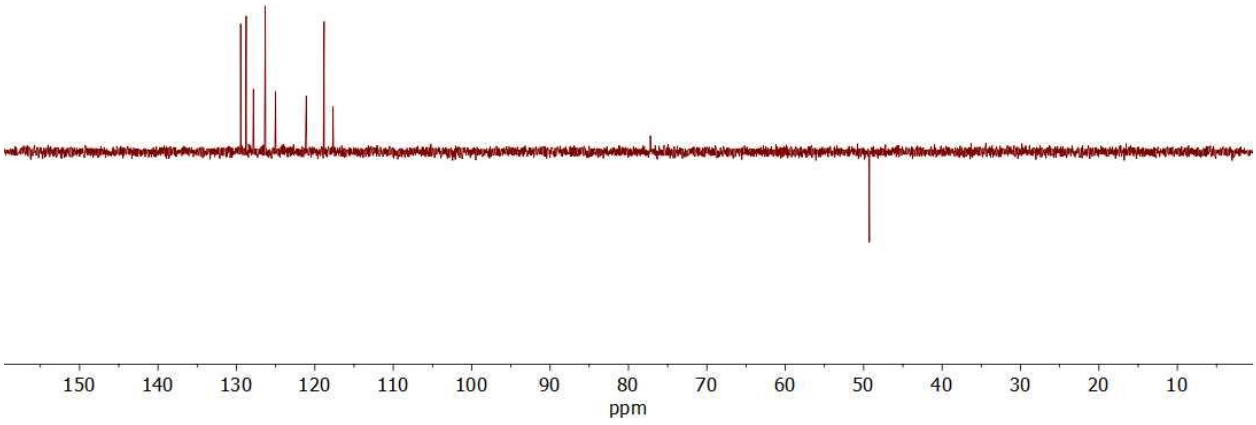


NOESY of **3c** (600 MHz, Acetone-d_6)

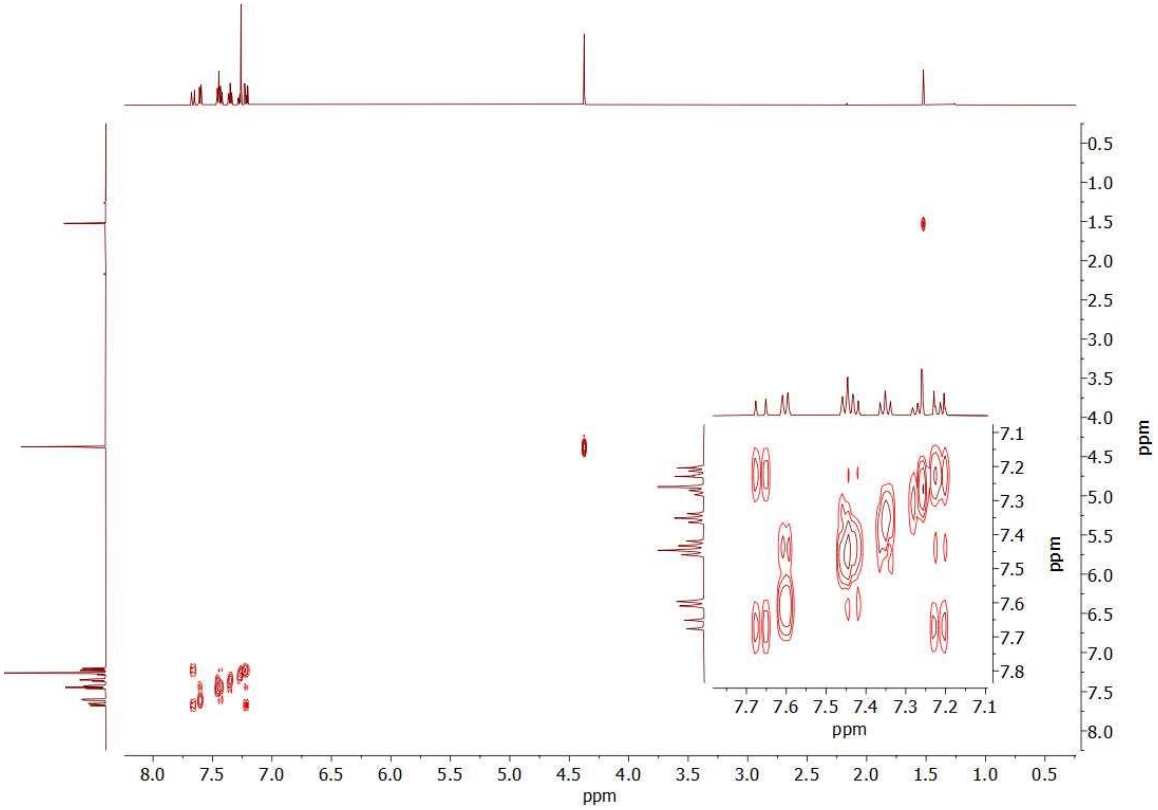


7.14 (*E*)-1-Phenyl-3-styrylhydantoin (3d)

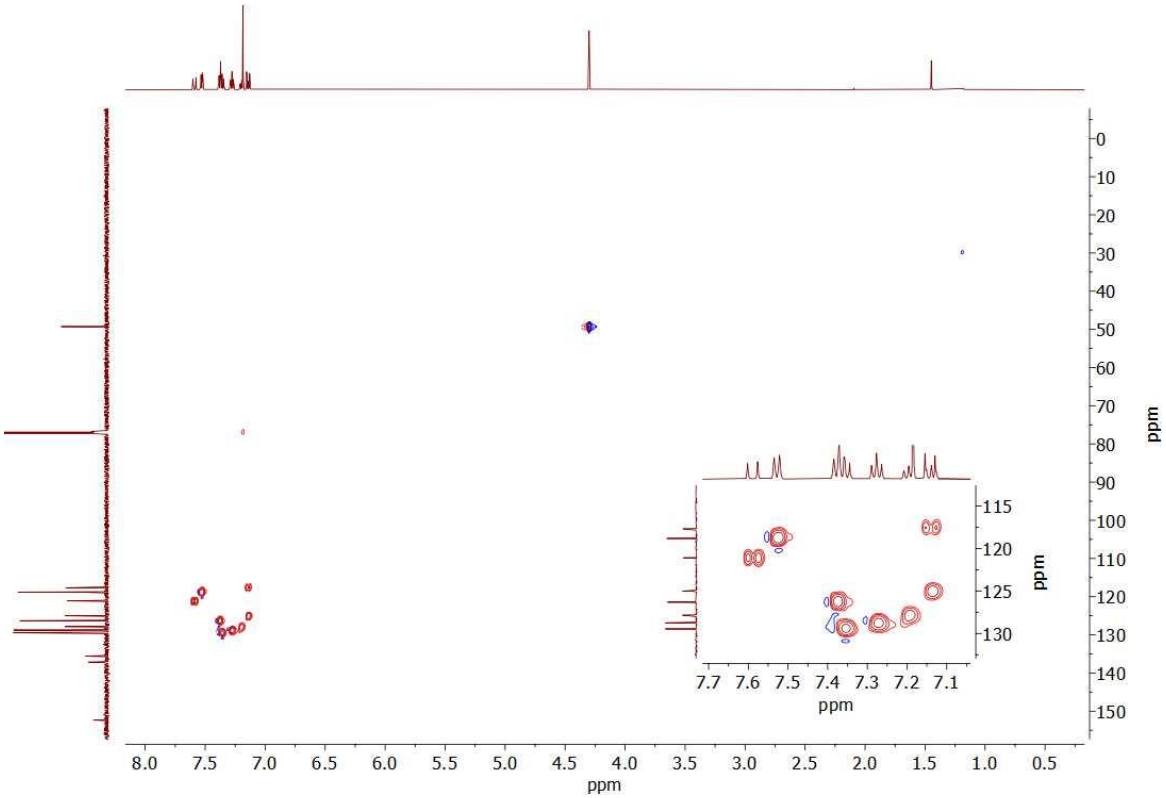
DEPT135 of **3d** (151 MHz, $CDCl_3$)



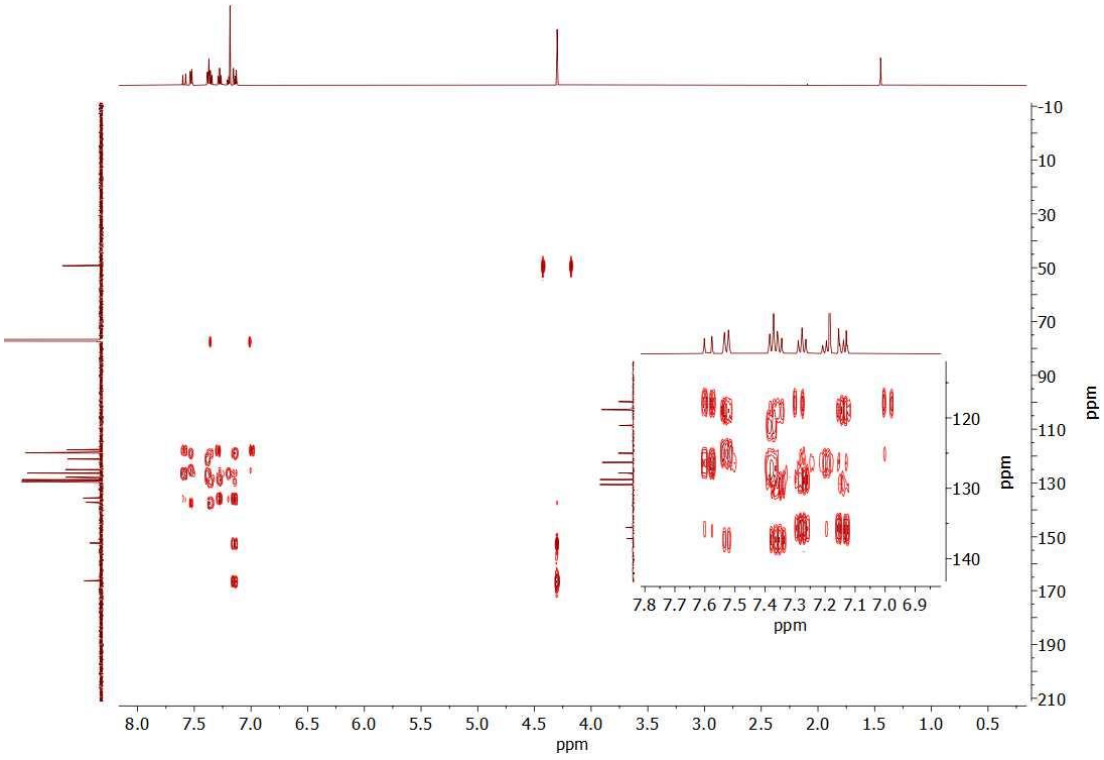
COSY of **3d** (600 MHz, $CDCl_3$)



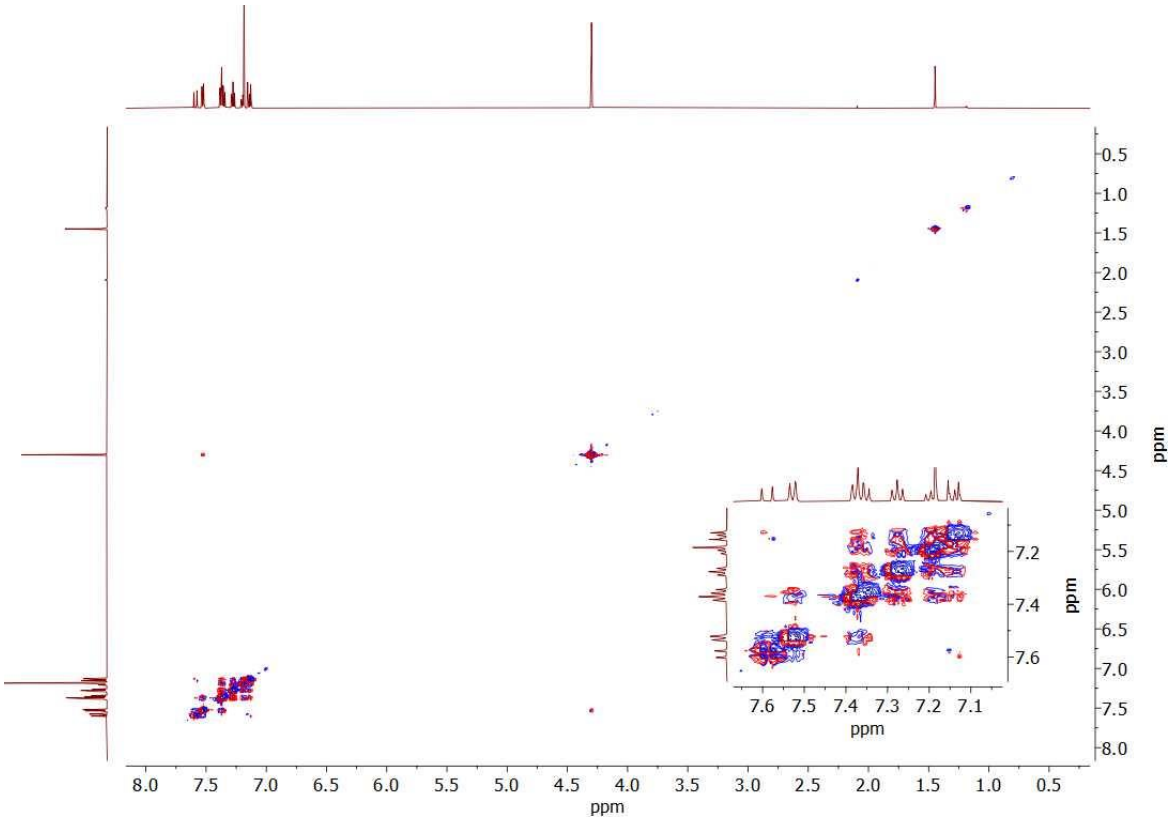
HSQC of **3d** (600 MHz, $CDCl_3$)



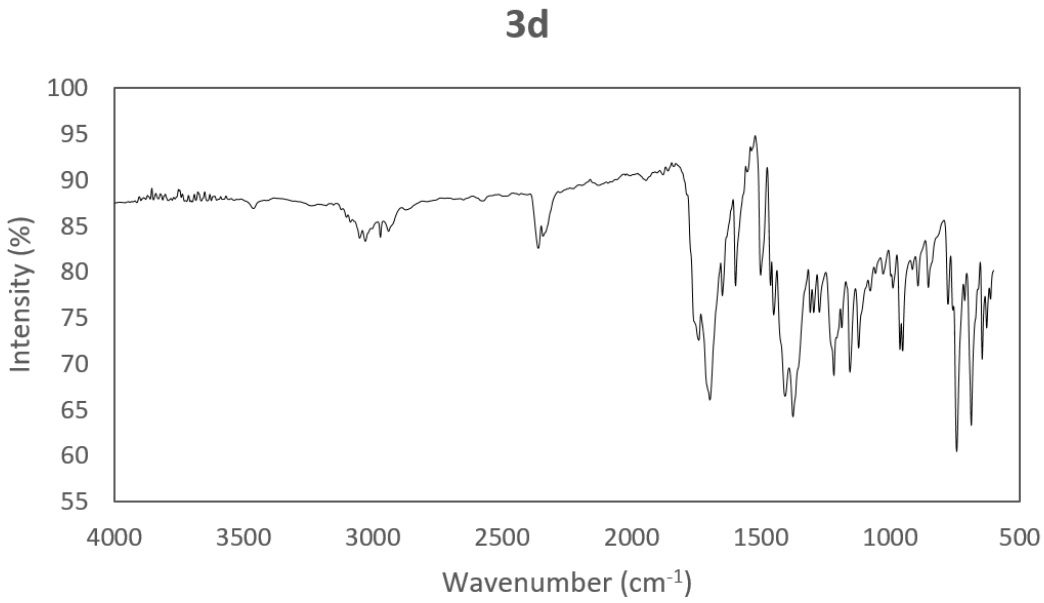
HMBC of **3d** (600 MHz, $CDCl_3$)



NOESY of **3d** (600 MHz, $CDCl_3$)

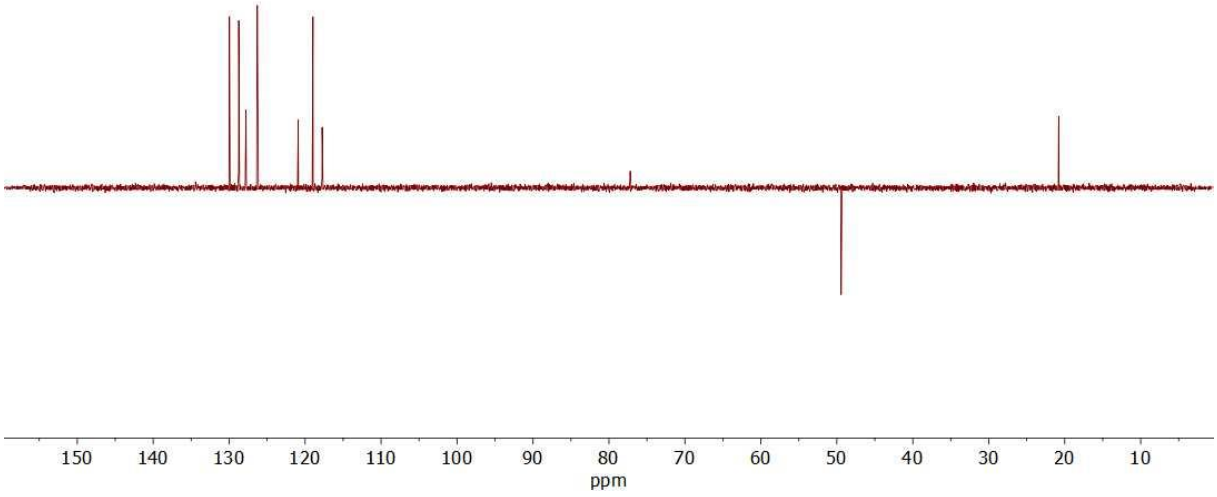


IR spectrum of **3d**

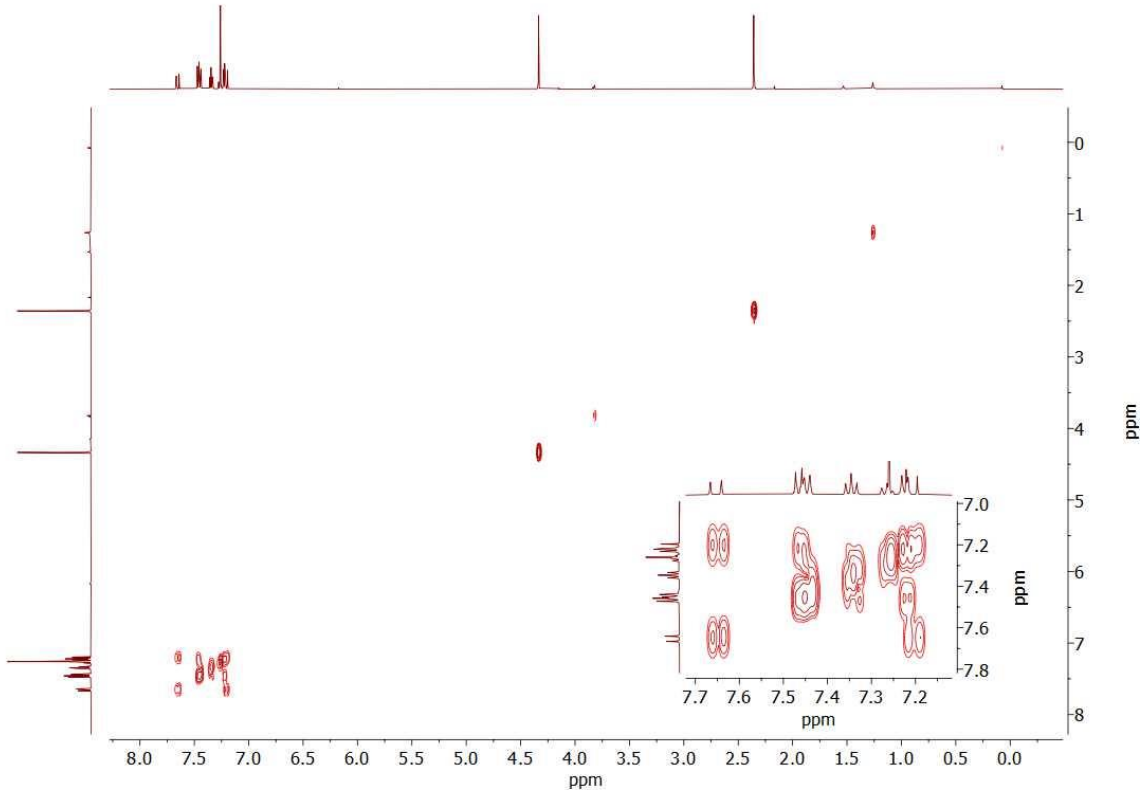


7.15 (*E*)-3-Styryl-1-(4-tolyl)hydantoin (3e)

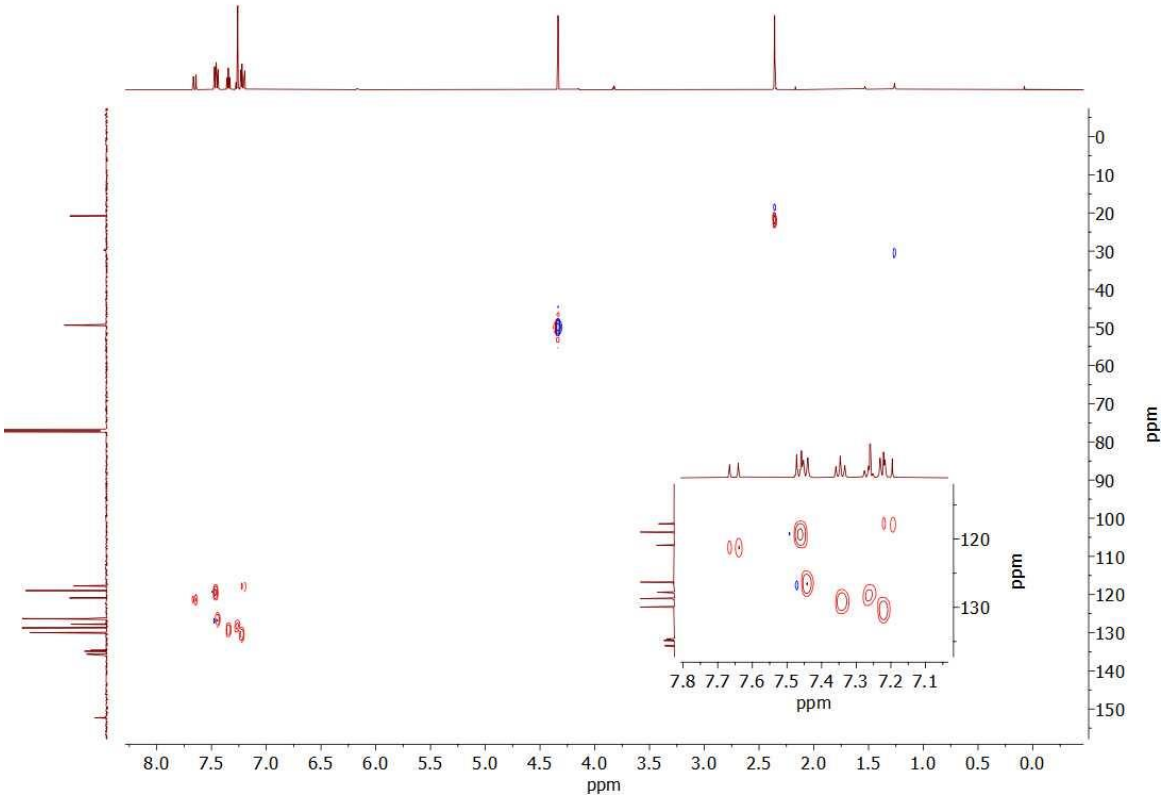
DEPT135 of **3e** (151 MHz, $CDCl_3$)



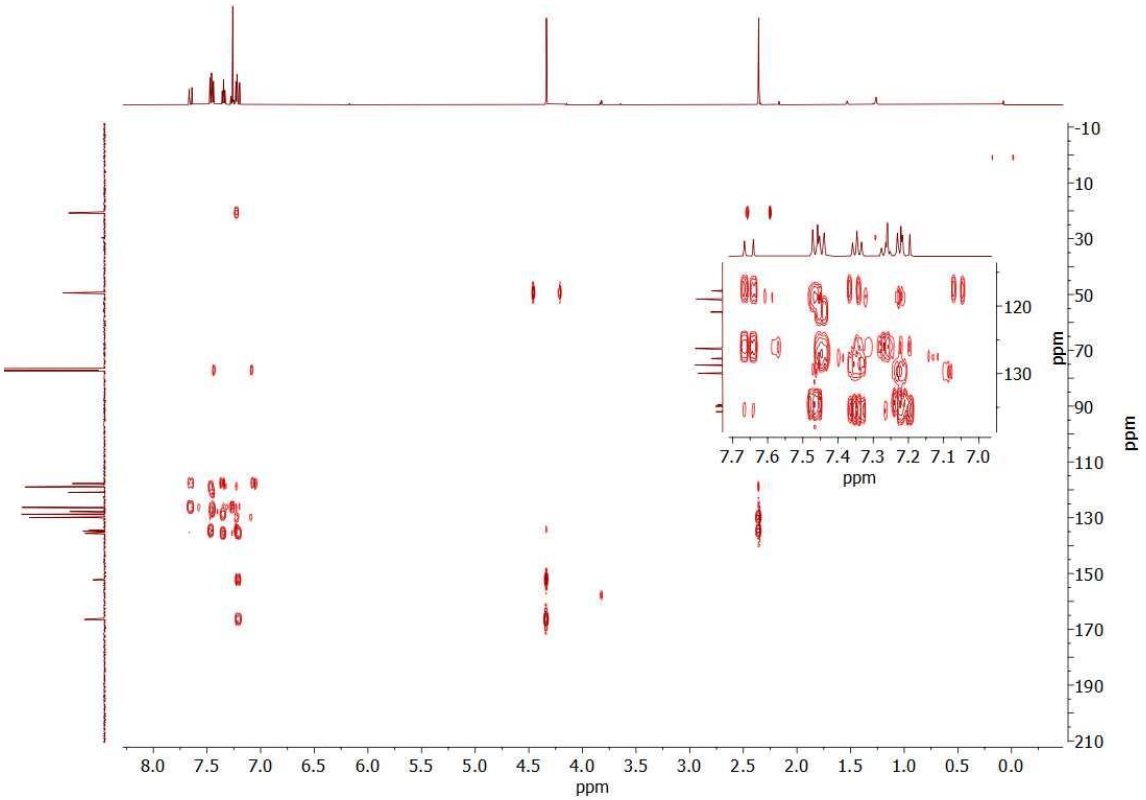
COSY of **3e** (600 MHz, $CDCl_3$)



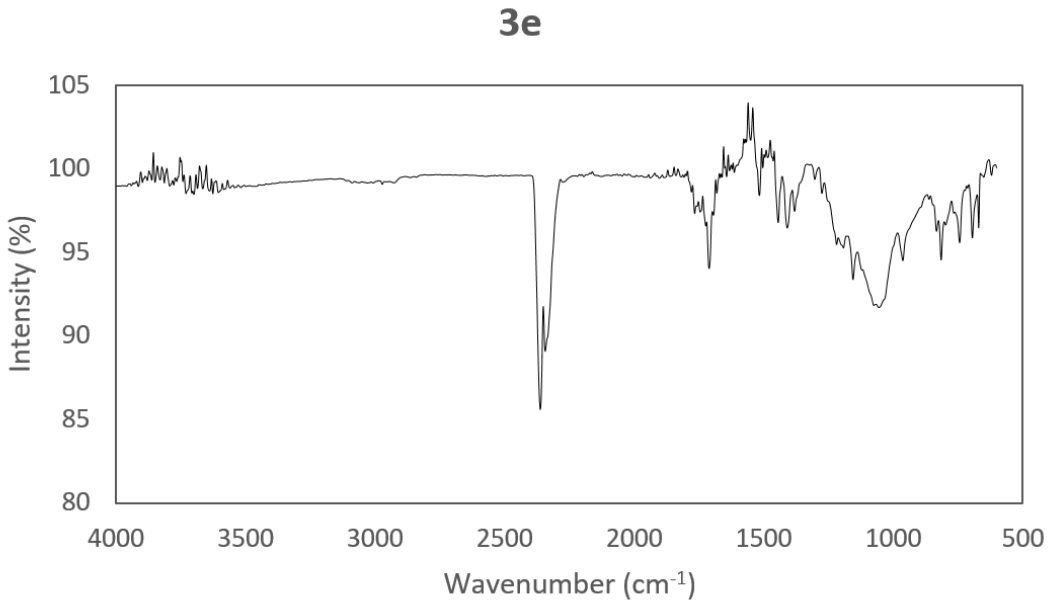
HSQC of **3e** (600 MHz, $CDCl_3$)



HMBC of **3e** (600 MHz, $CDCl_3$)

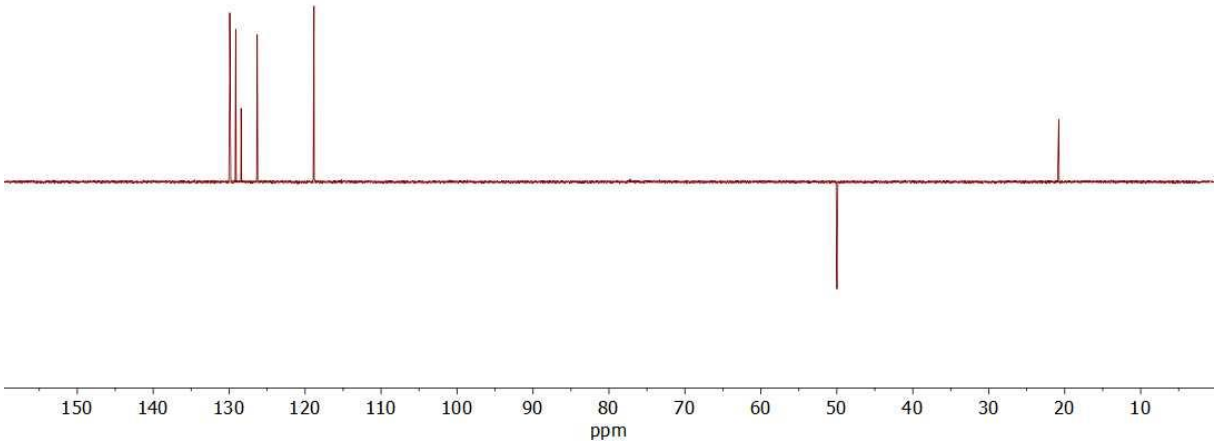


IR spectrum of **3e**

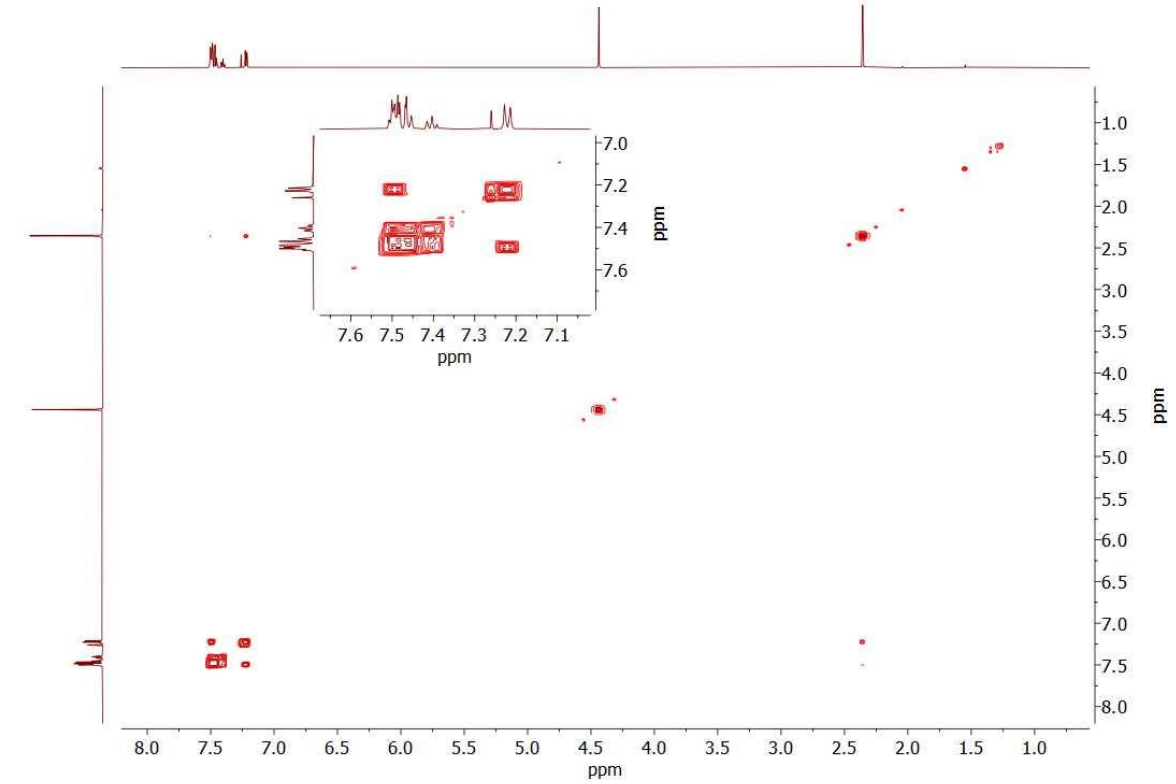


7.16 3-Phenyl-1-(4-tolyl)hydantoin (3f)

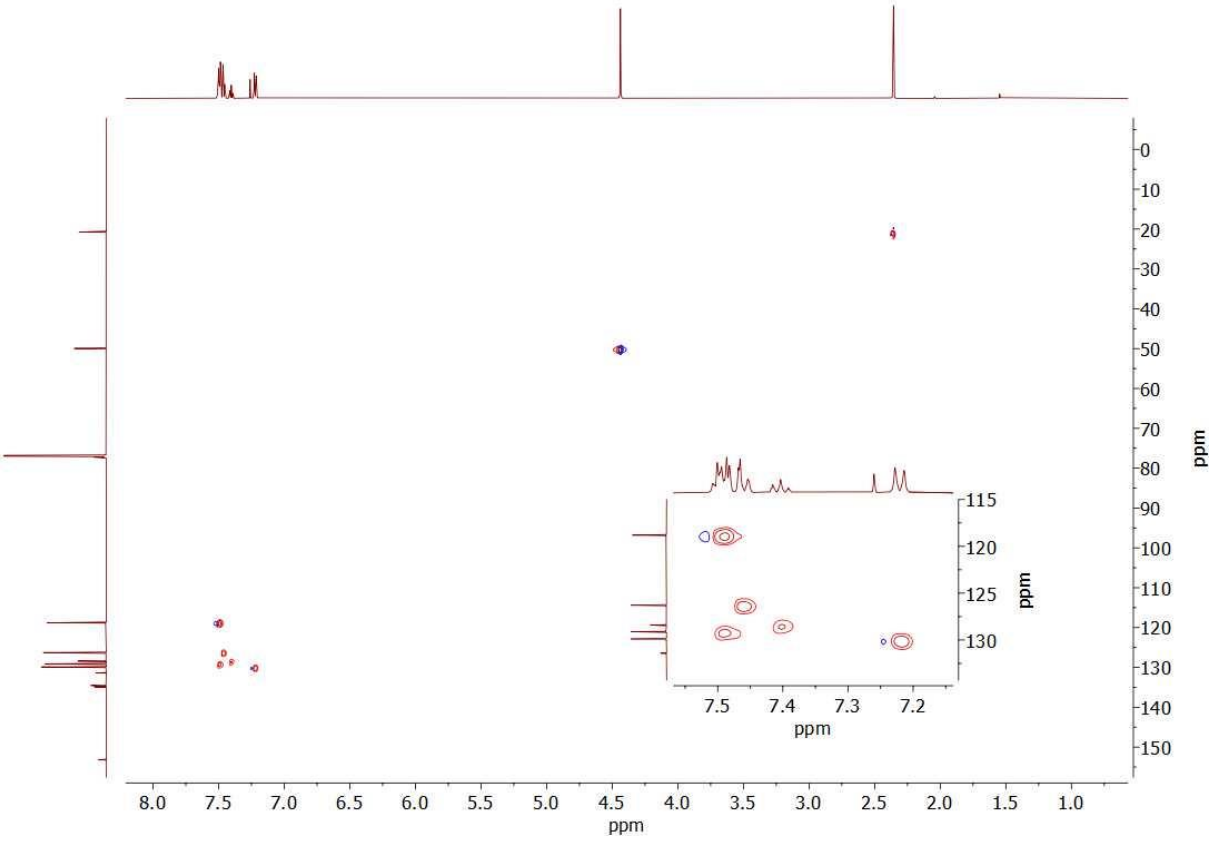
DEPT135 of **3f** (151 MHz, $CDCl_3$)



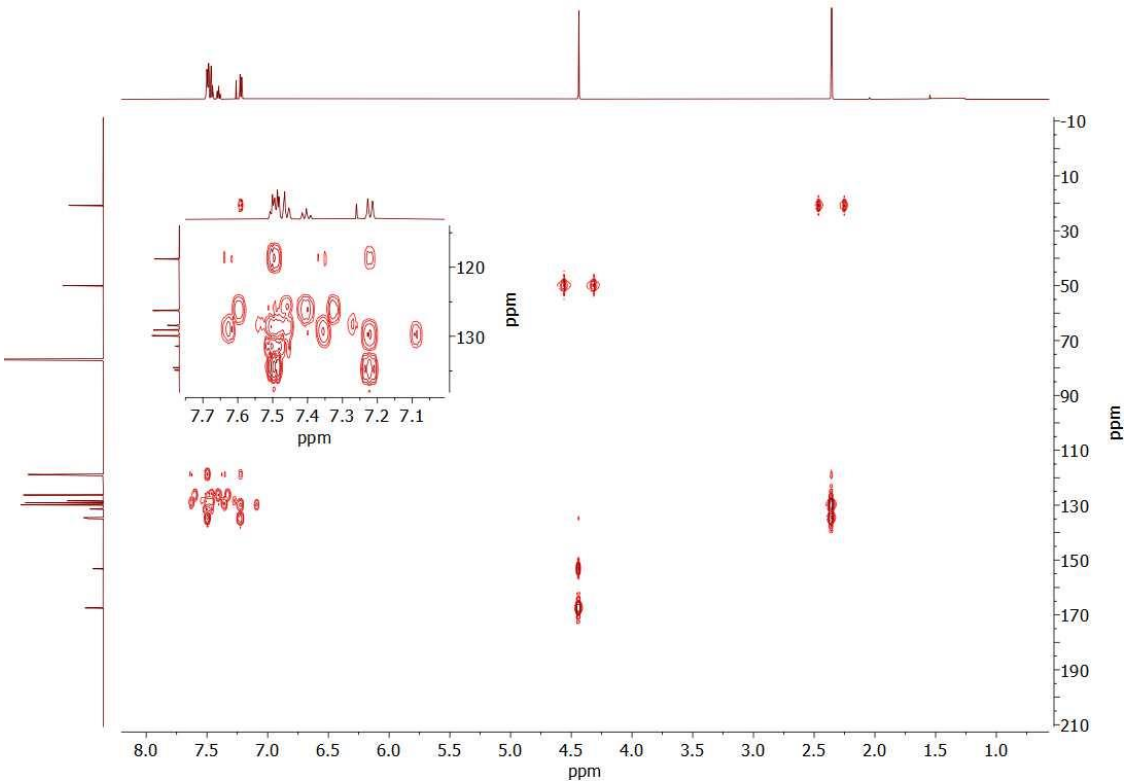
COSY of **3f** (600 MHz, $CDCl_3$)



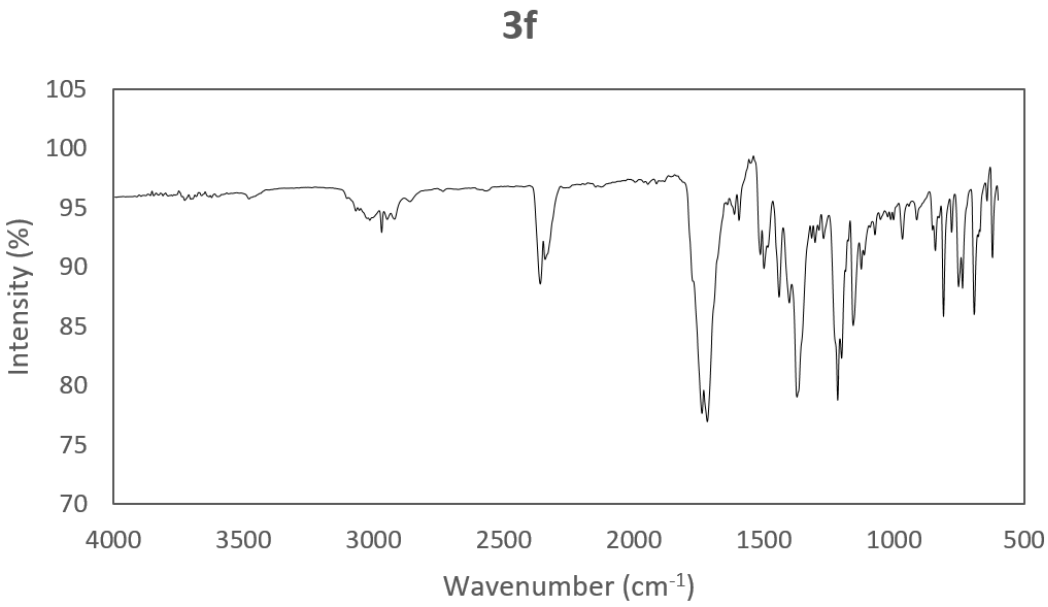
HSQC of **3f** (600 MHz, $CDCl_3$)



HMBC of **3f** (600 MHz, $CDCl_3$)

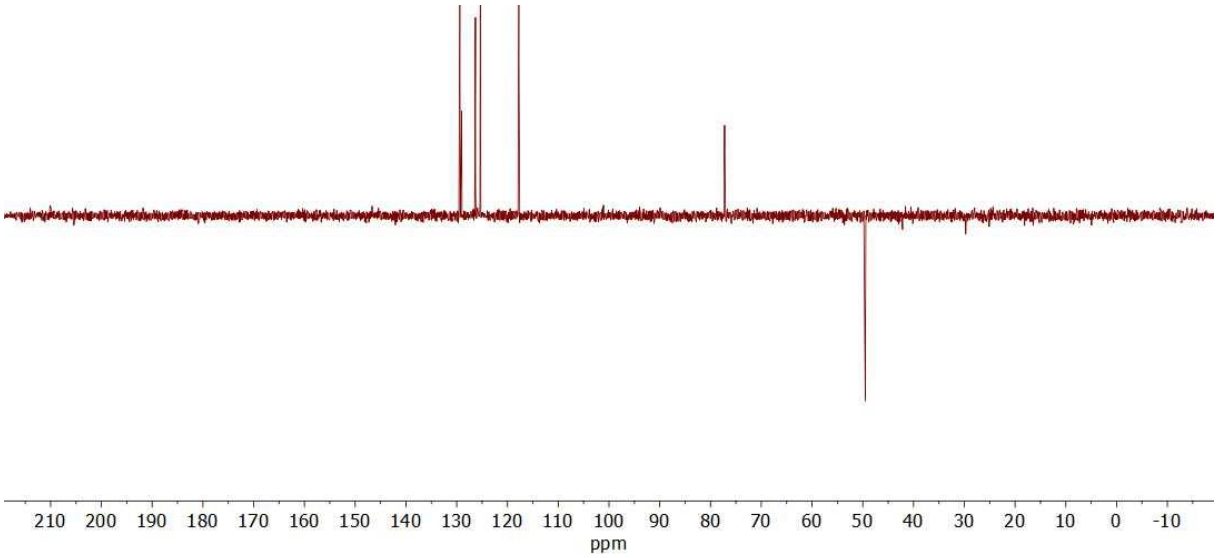


IR spectrum of **3f**

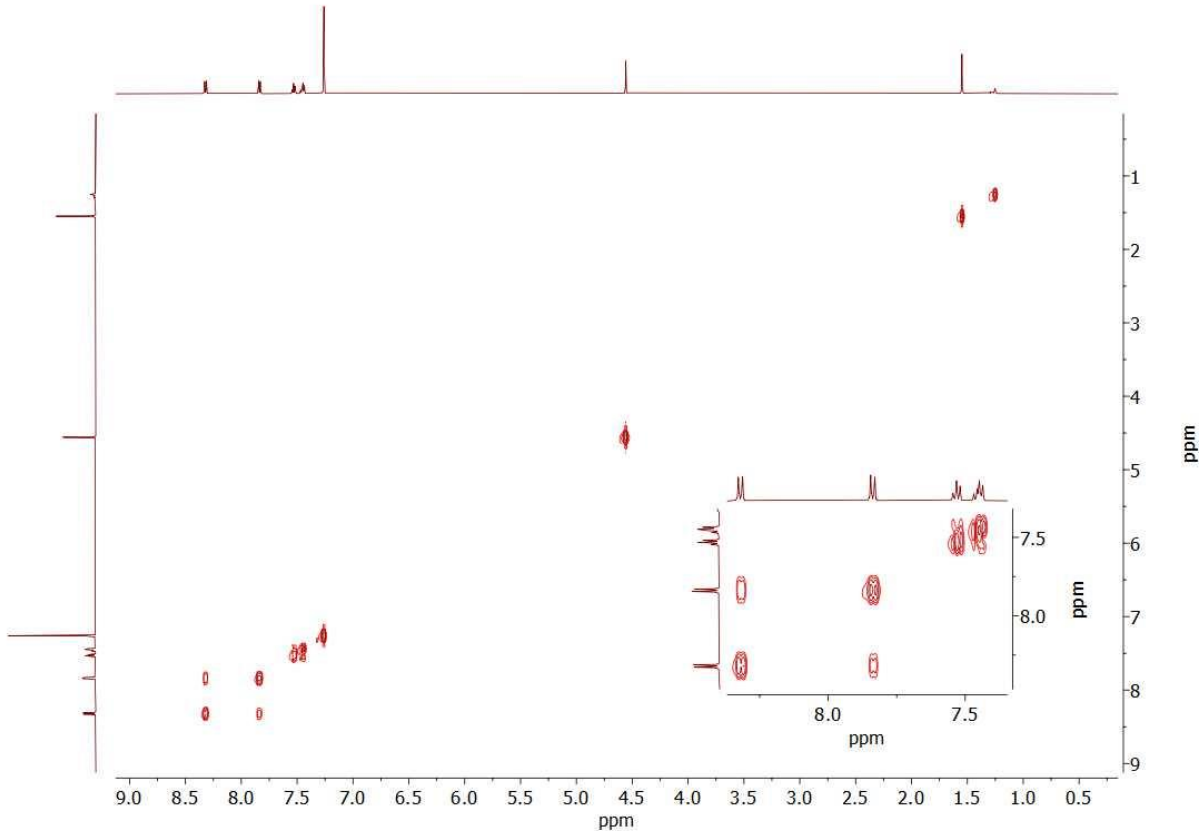


7.17 1-(4-Nitrophenyl)-3-phenylhydantoin (3g)

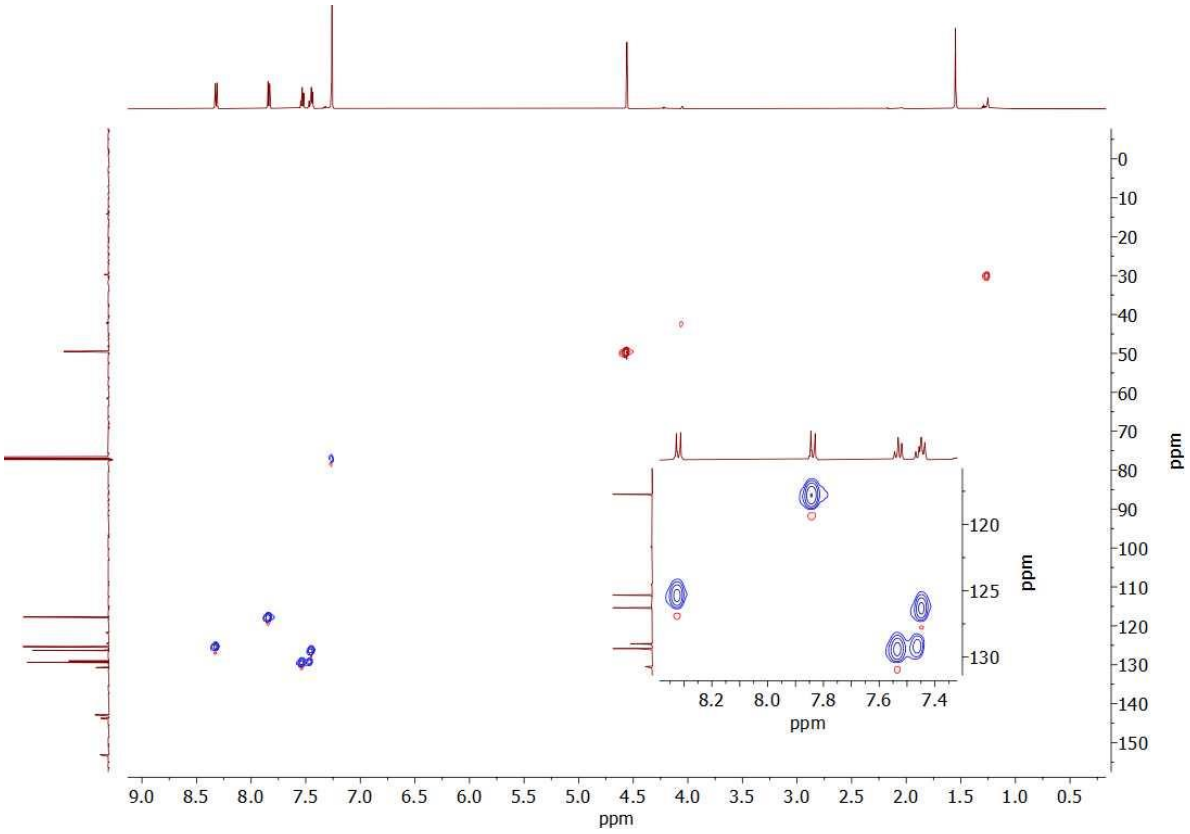
DEPT135 of **3g** (151 MHz, $CDCl_3$)



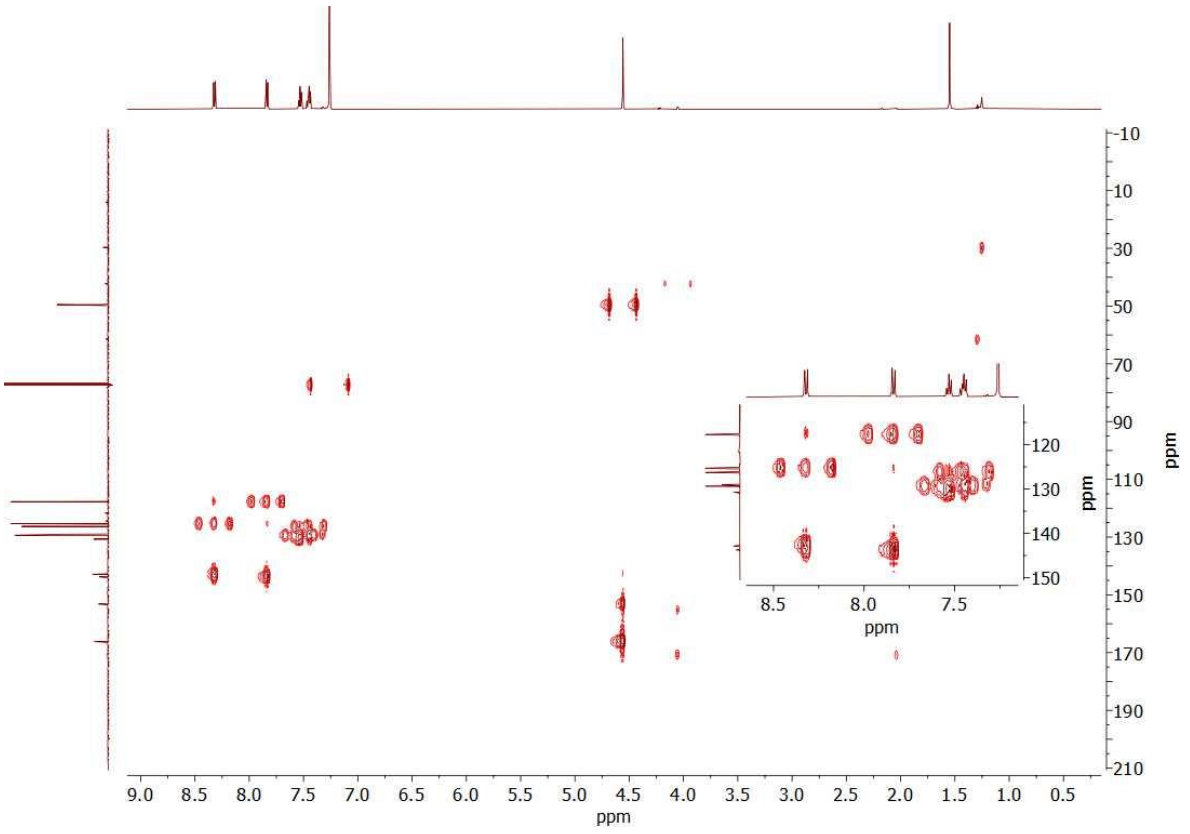
COSYof **3g** (600 MHz, $CDCl_3$)



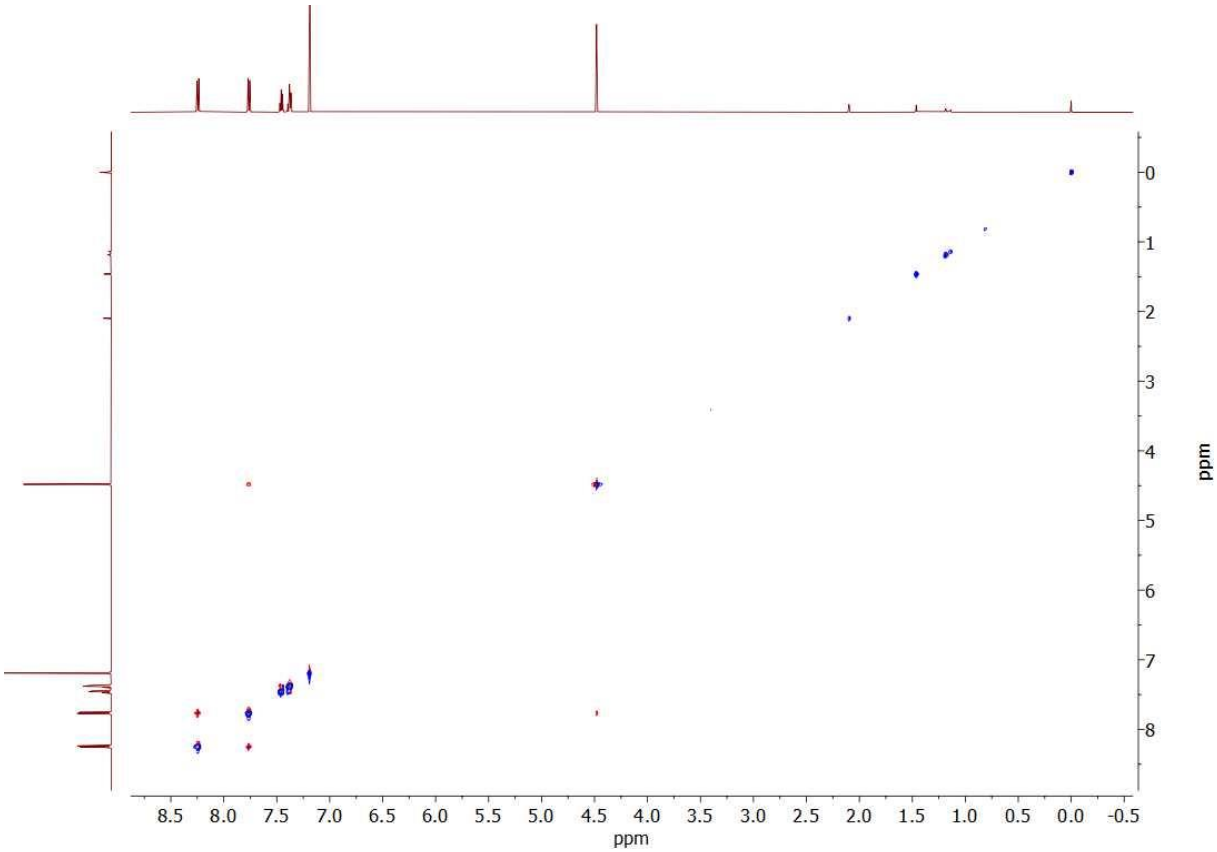
HSQC of **3g** (600 MHz, $CDCl_3$)



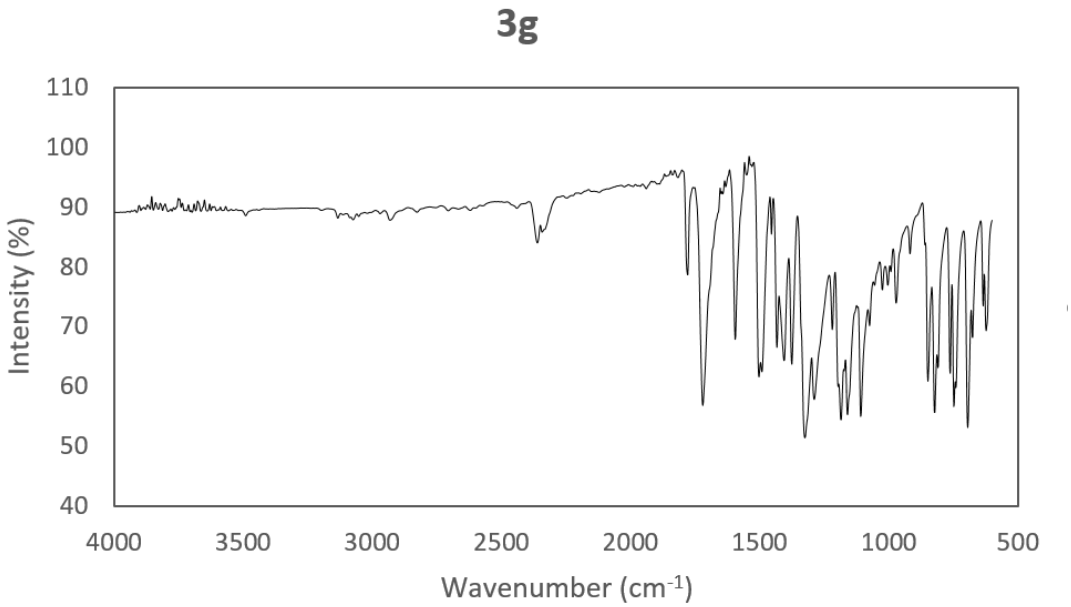
HMBC of **3g** (600 MHz, $CDCl_3$)



NOESY of **3g** (600 MHz, $CDCl_3$)

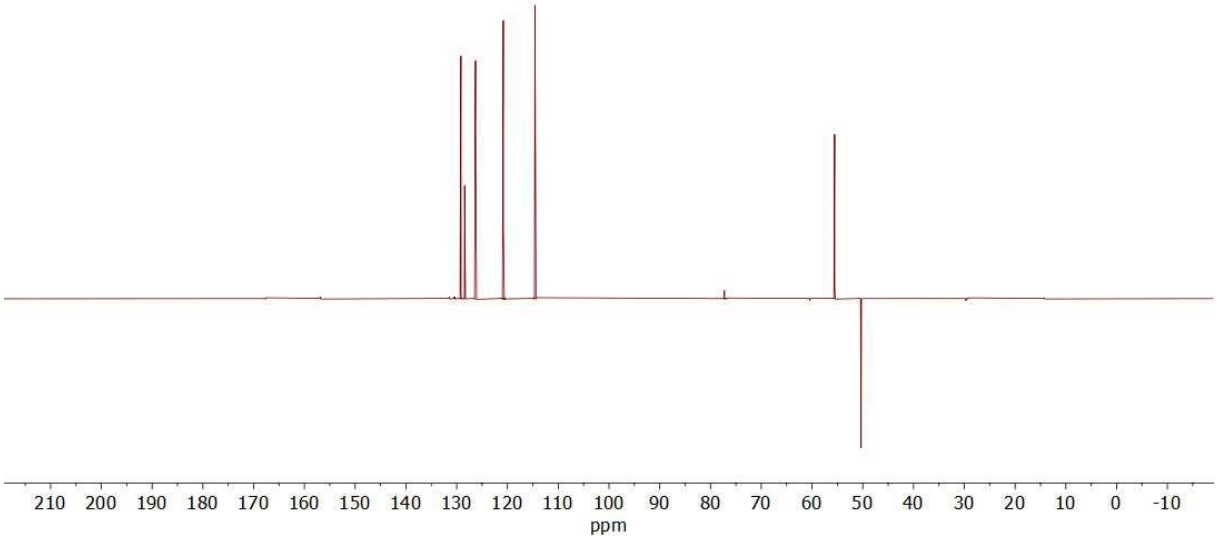


IR spectrum of **3g**

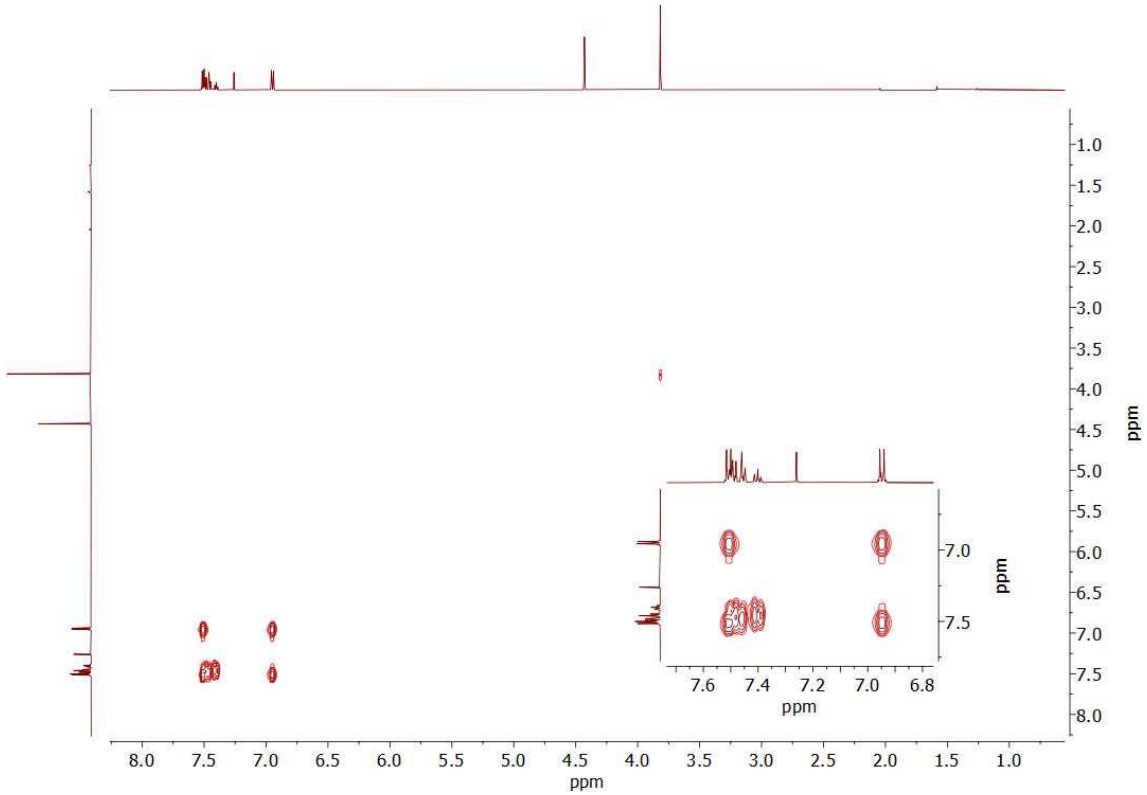


7.18 1-(4-Methoxypenyl)-3-phenylhydantoin (3h)

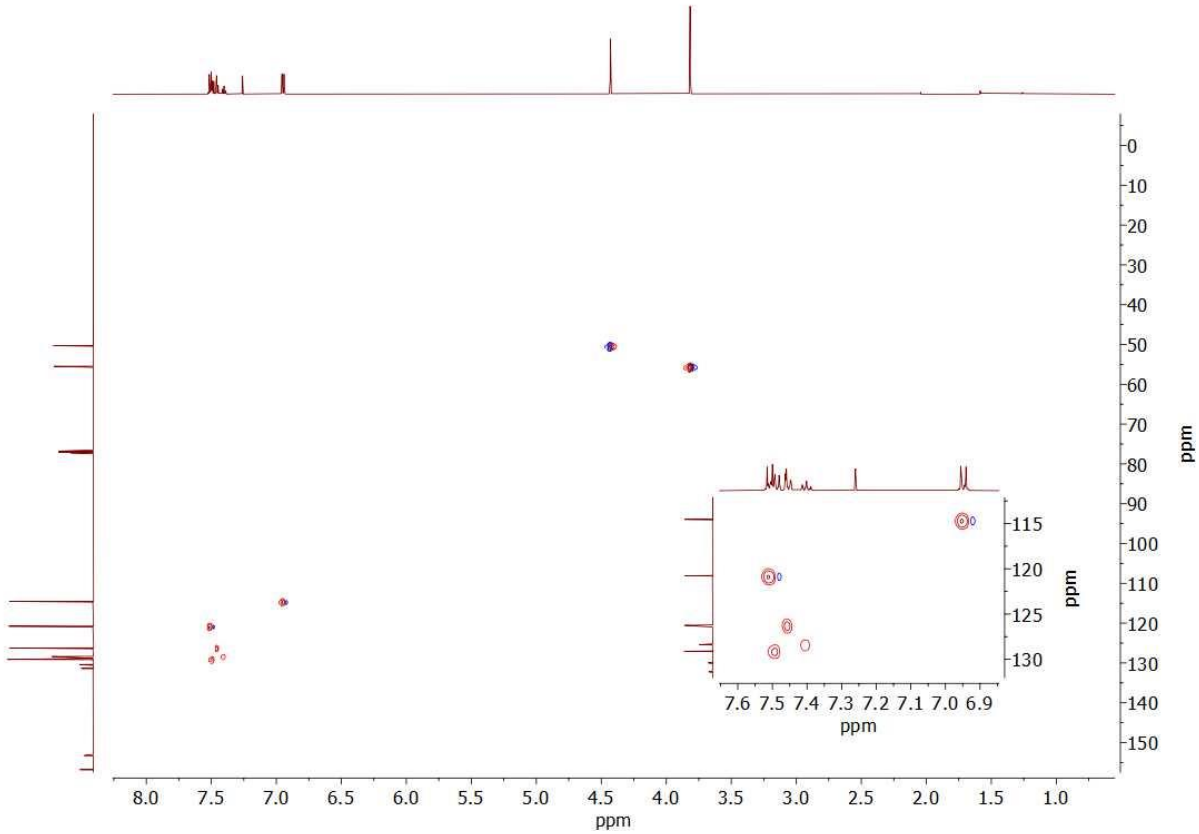
DEPT135 of **3h** (151 MHz, $CDCl_3$)



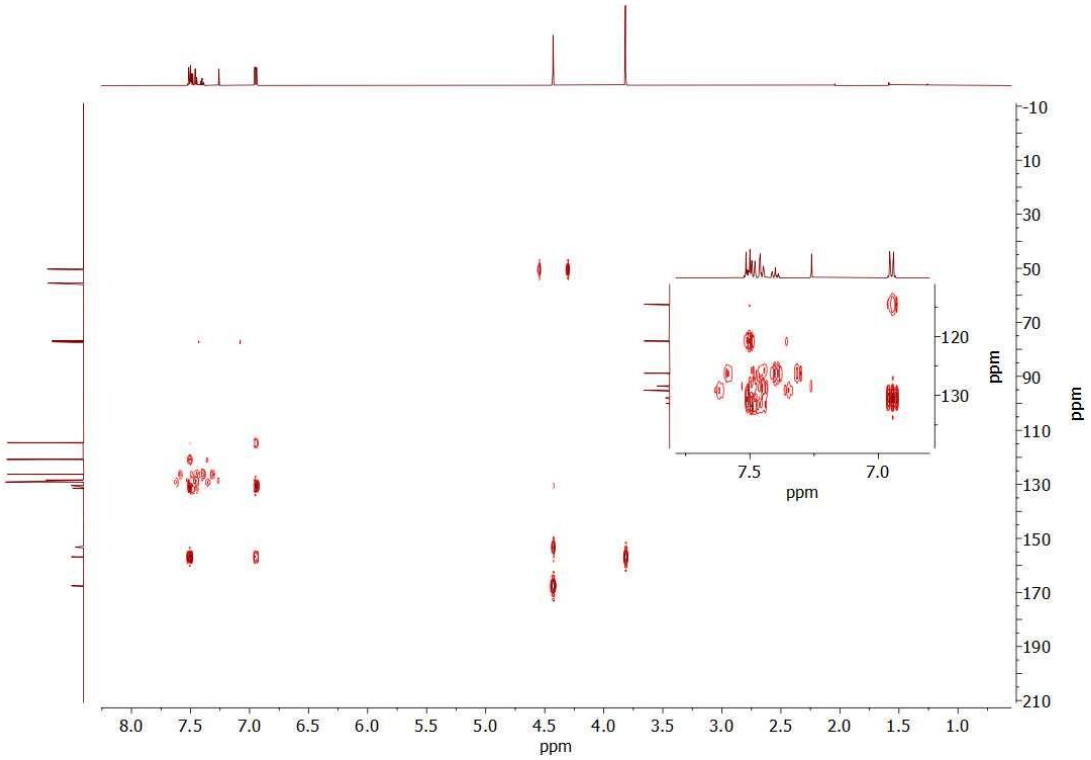
COSY of **3h** (600 MHz, $CDCl_3$)



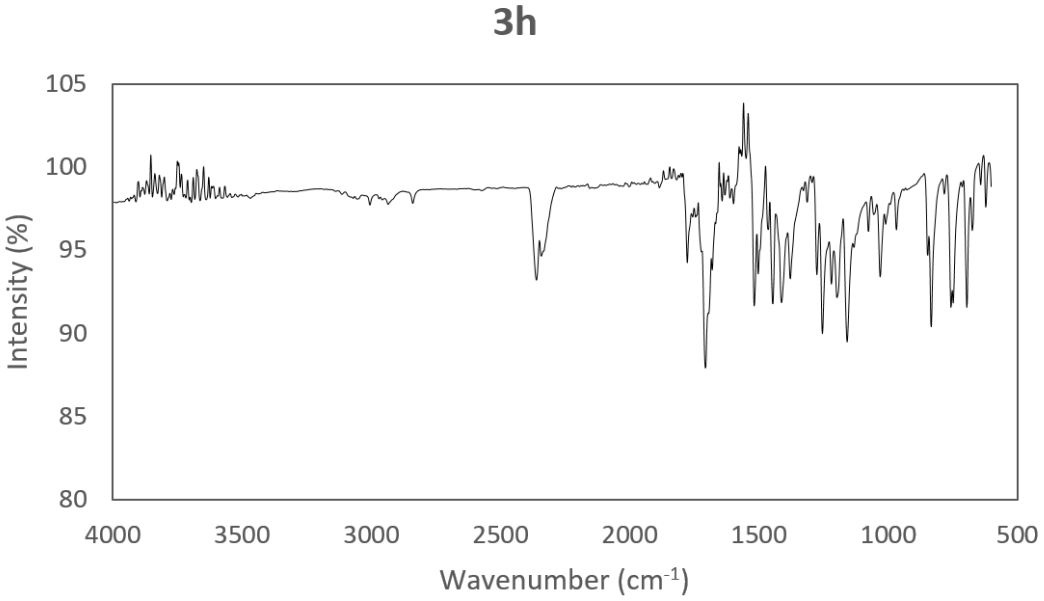
HSQC of **3h** (600 MHz, $CDCl_3$)



HMBC of **3h** (600 MHz, $CDCl_3$)

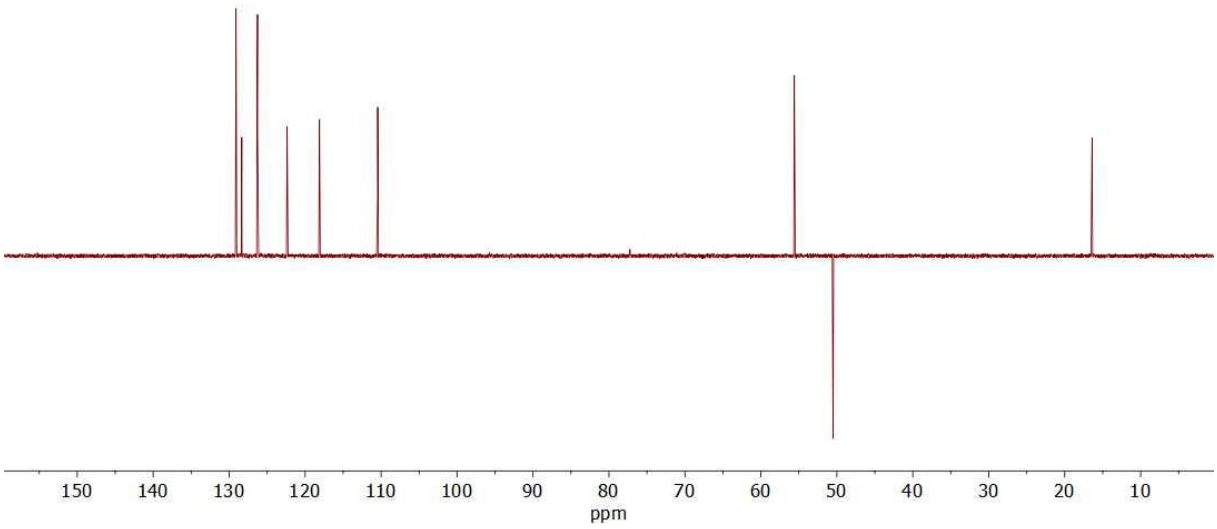


IR spectrum of **3h**

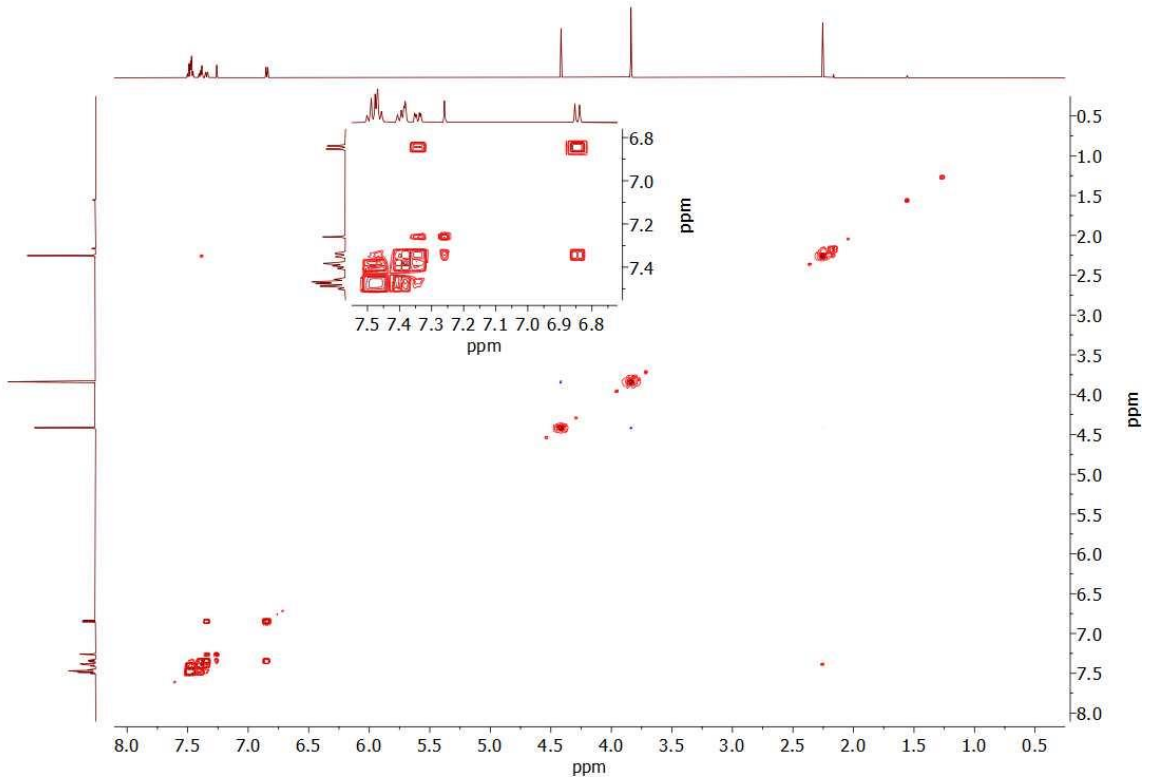


7.19 1-(4-Methoxy-3-methylphenyl)-3-phenylhydantoin (3i)

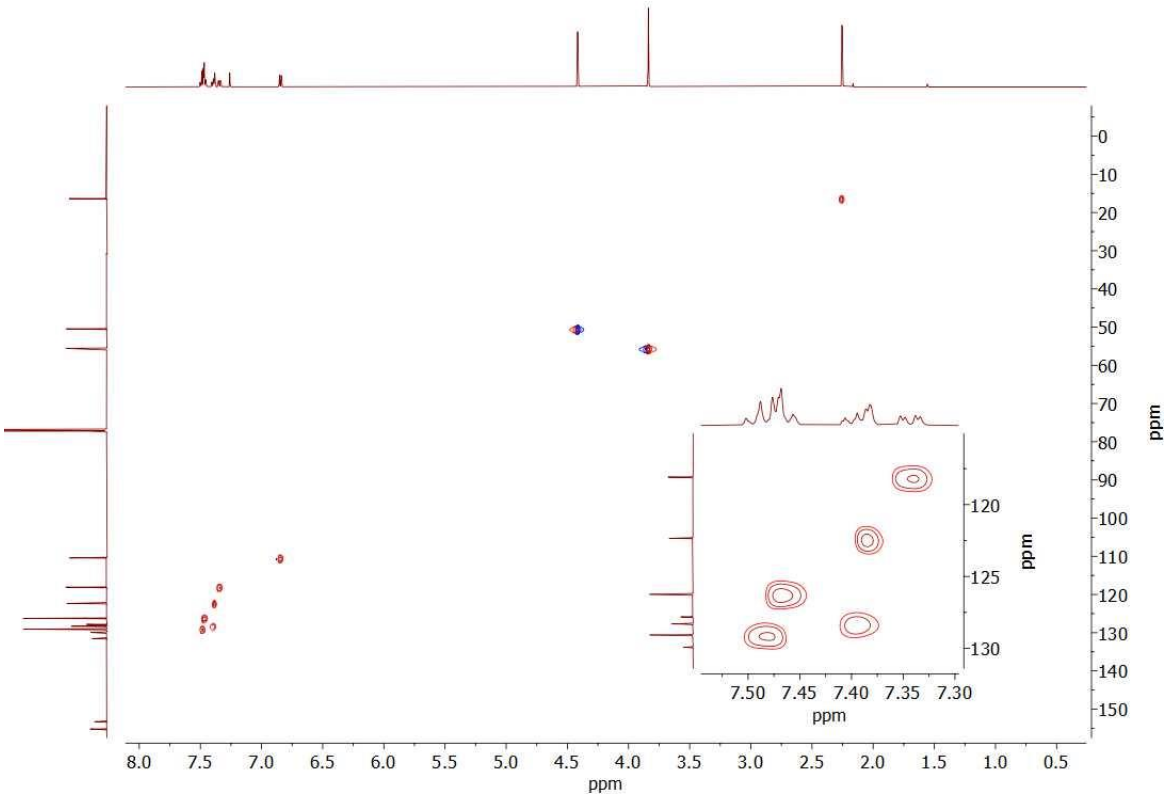
DEPT135 of **3i** (151 MHz, $CDCl_3$)



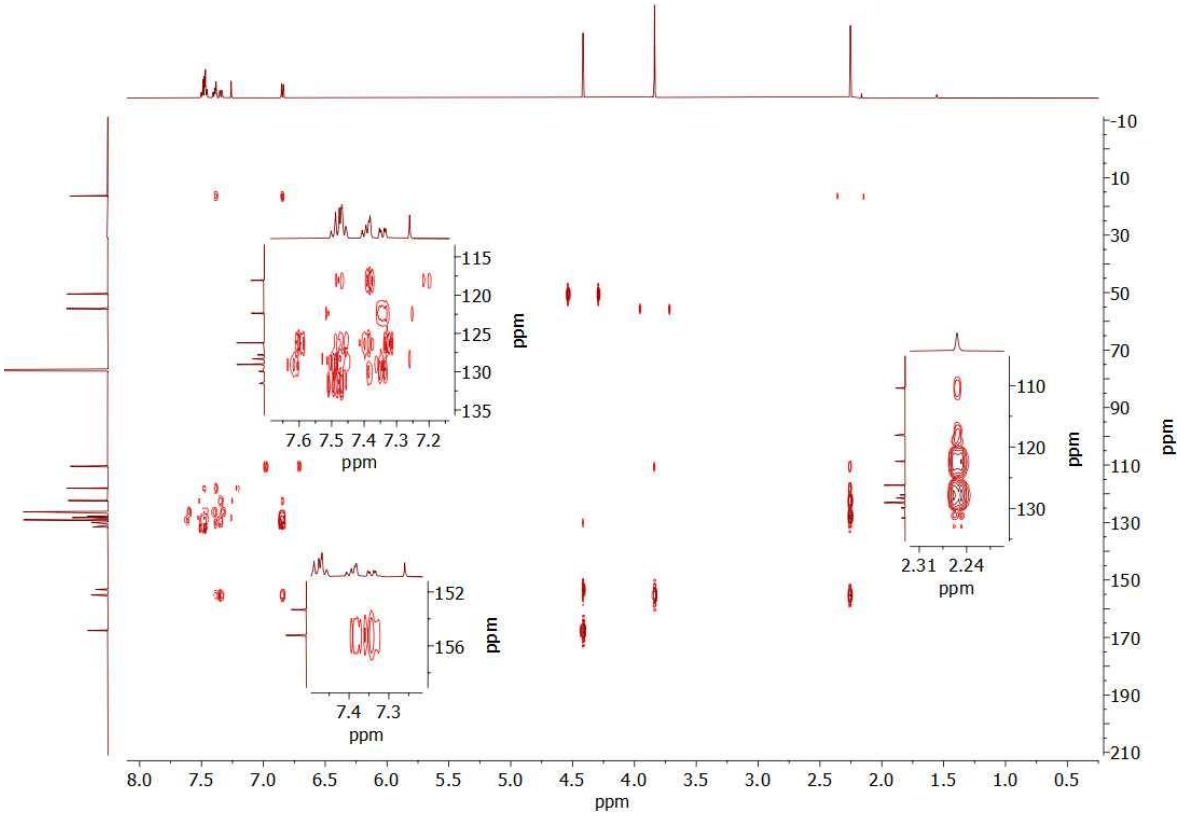
COSY of **3i** (600 MHz, $CDCl_3$)



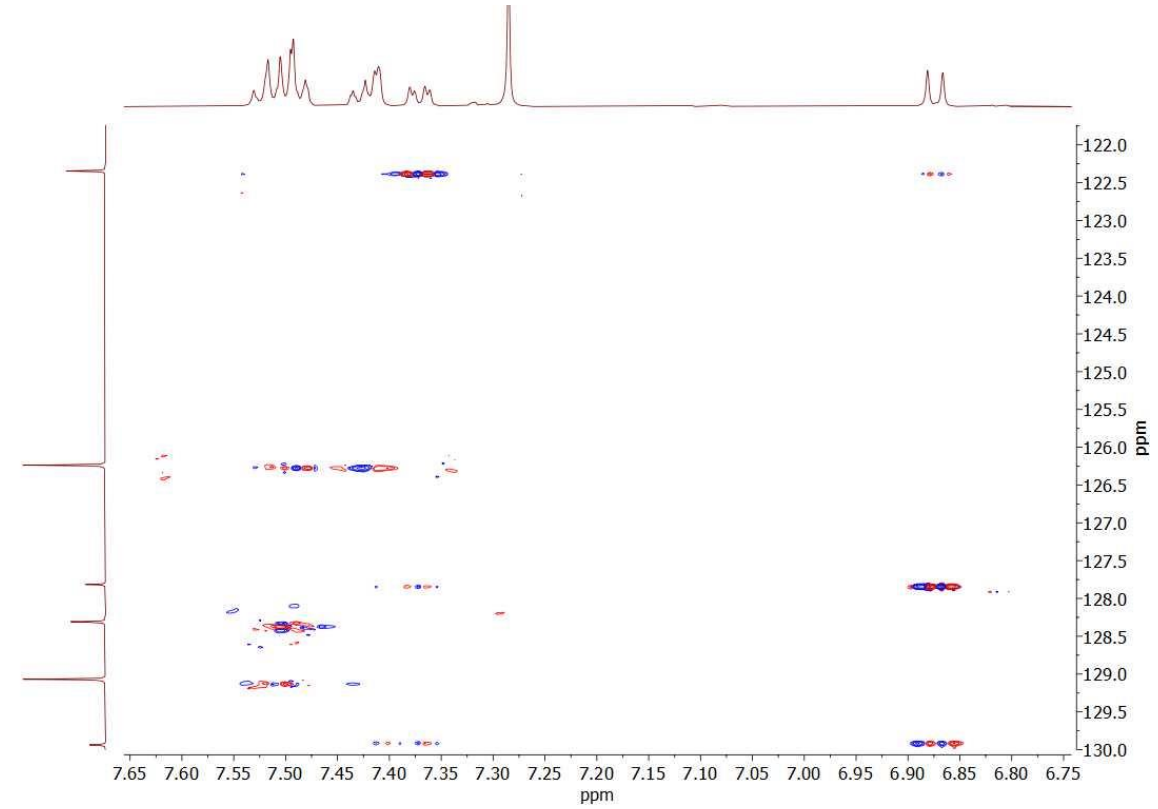
HSQC of **3i** (600 MHz, $CDCl_3$)



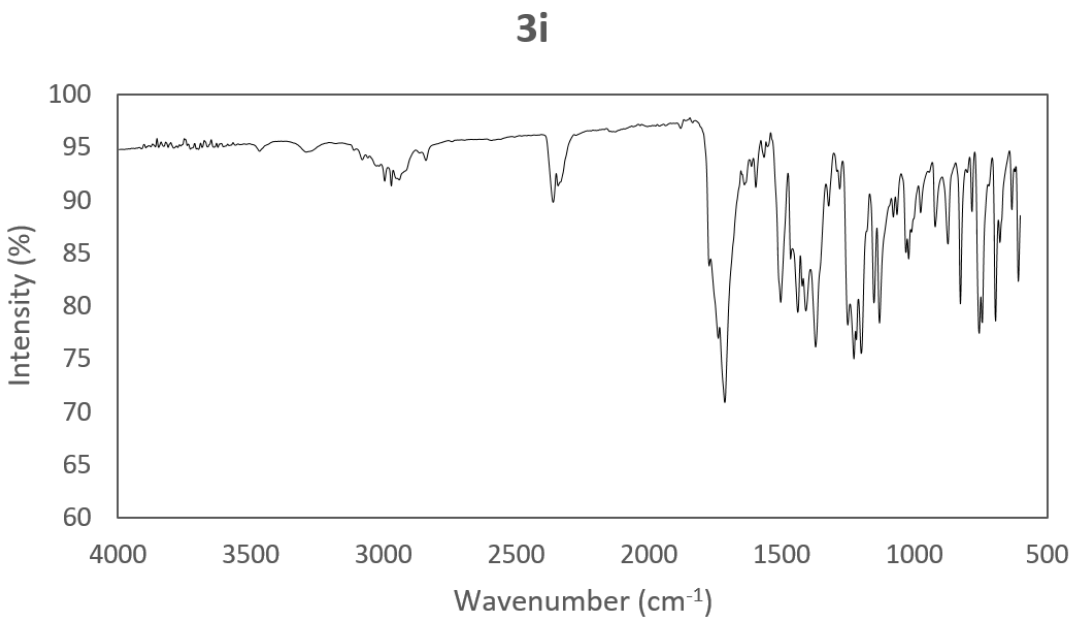
HMBC of **3i** (600 MHz, $CDCl_3$)



SHMBC of **3i** (600 MHz, $CDCl_3$)

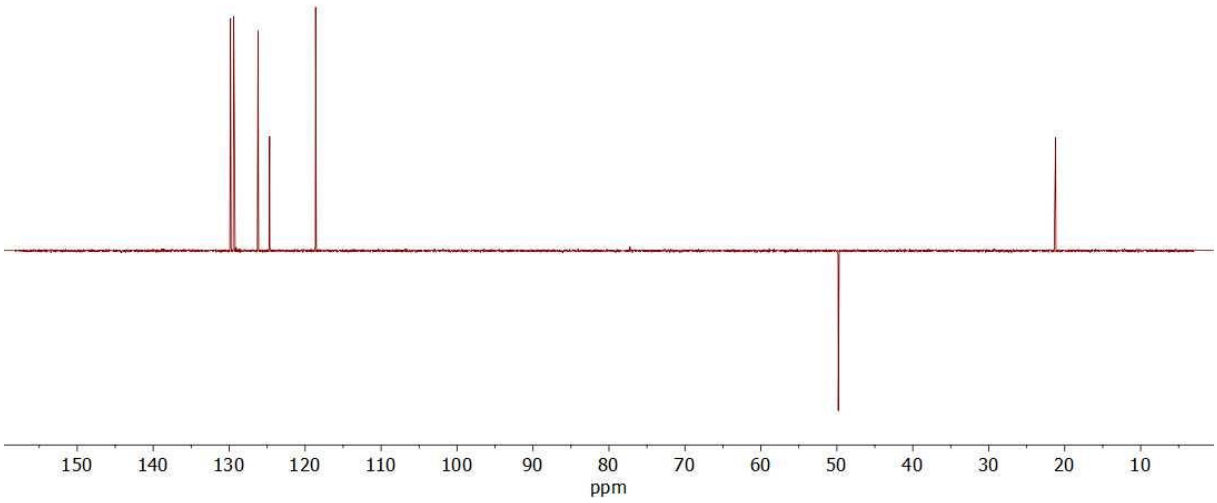


IR spectrum of **3i**

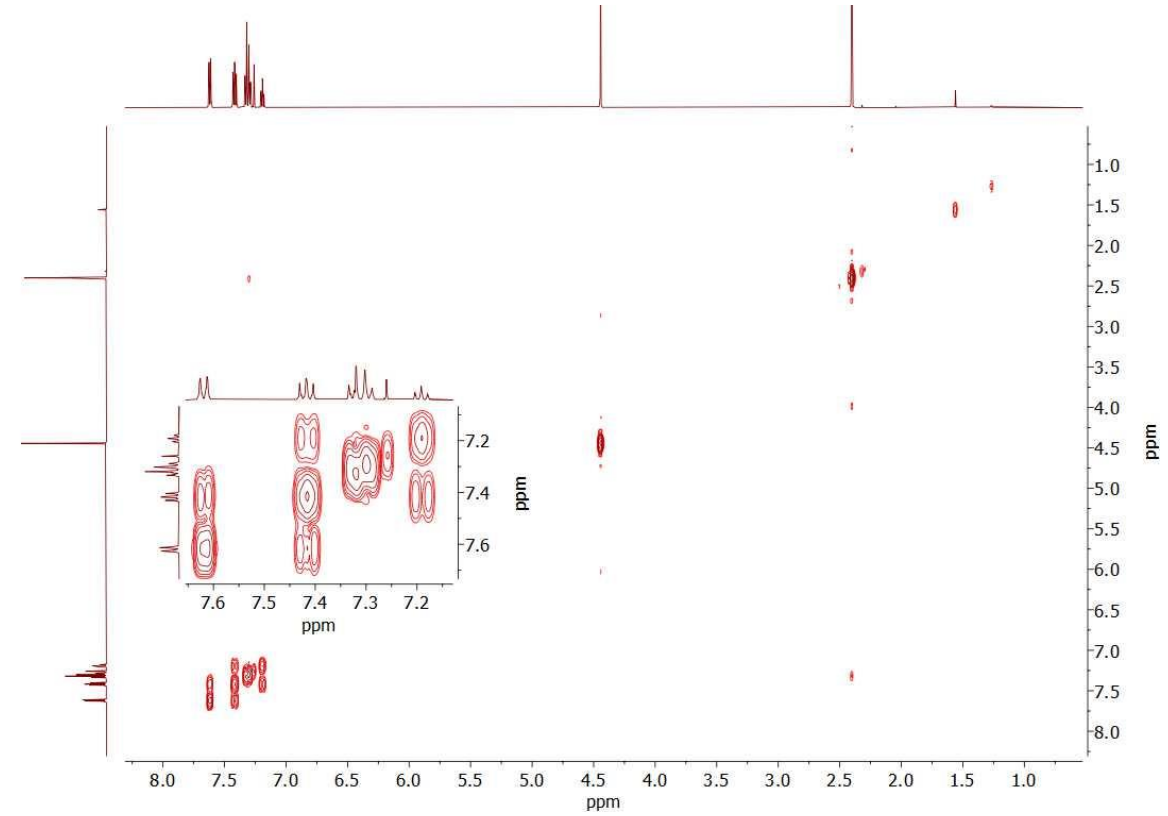


7.20 1-Phenyl-3-(4-tolyl)hydantoin (3j)

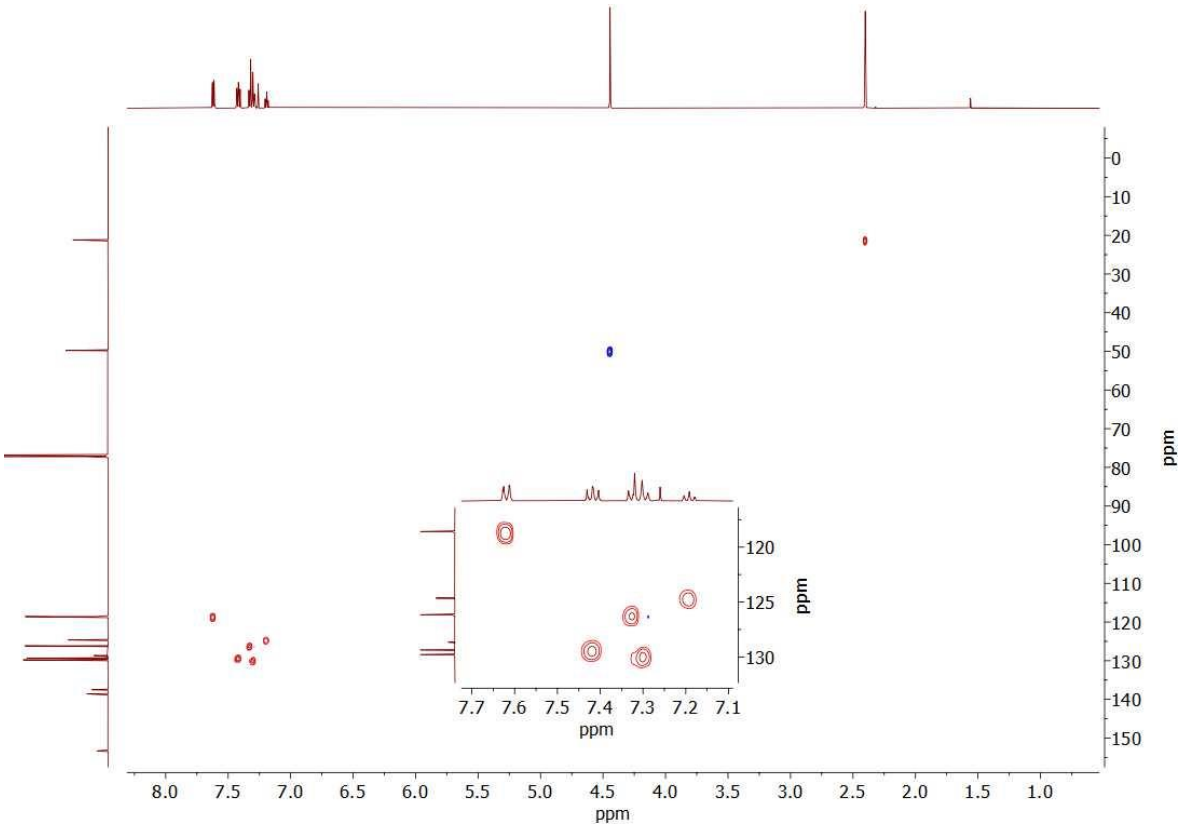
DEPT135 of **3j** (151 MHz, $CDCl_3$)



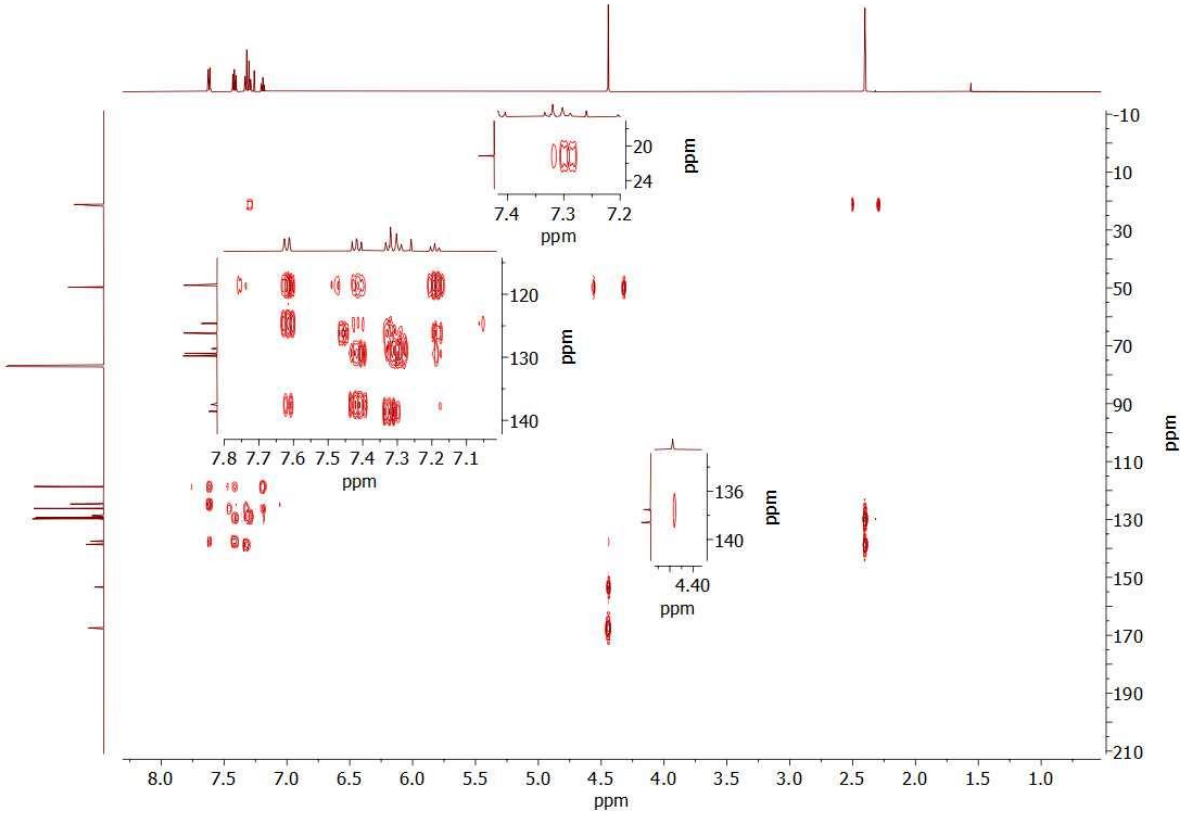
COSY of **3j** (600 MHz, $CDCl_3$)



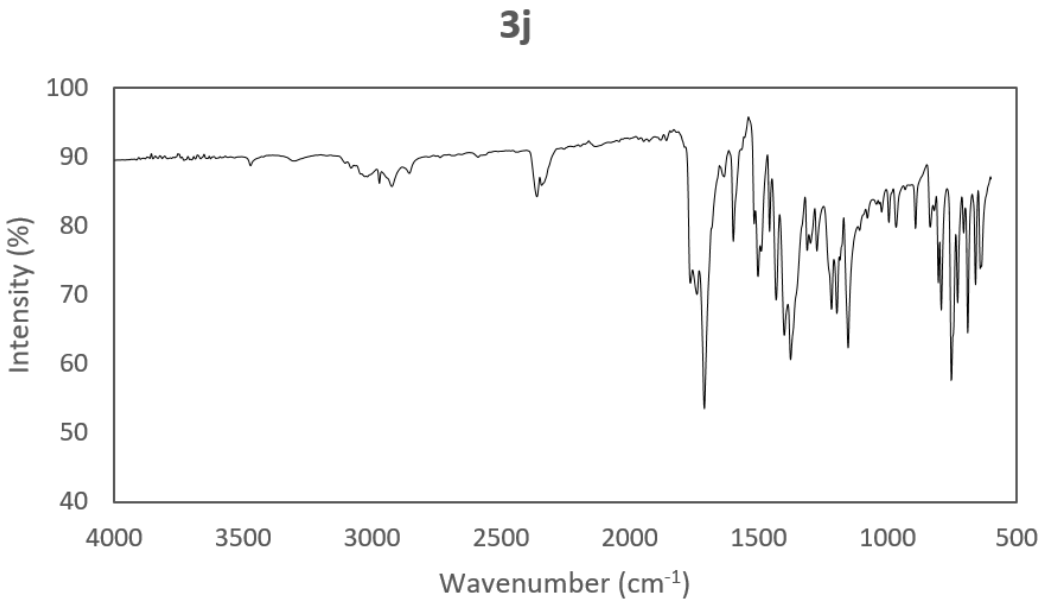
HSQC of **3j** (600 MHz, $CDCl_3$)



HMBC of **3j** (600 MHz, $CDCl_3$)

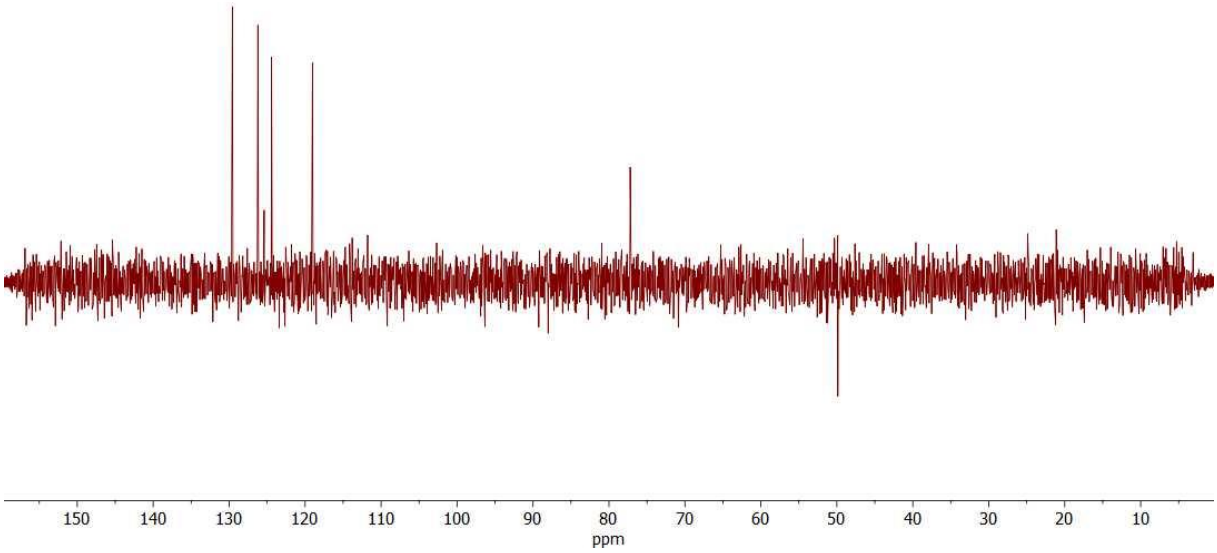


IR spectrum of **3j**

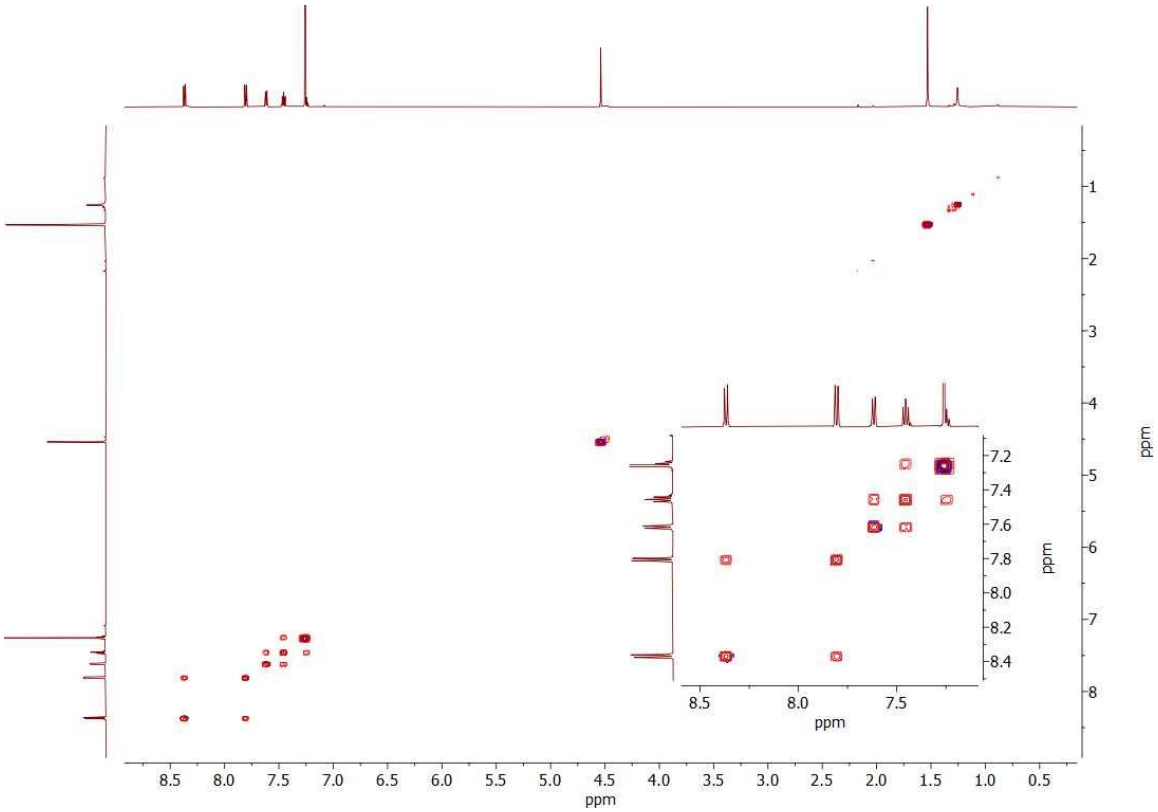


7.21 3-(4-Nitrophenyl)-1-phenylhydantoin (3k)

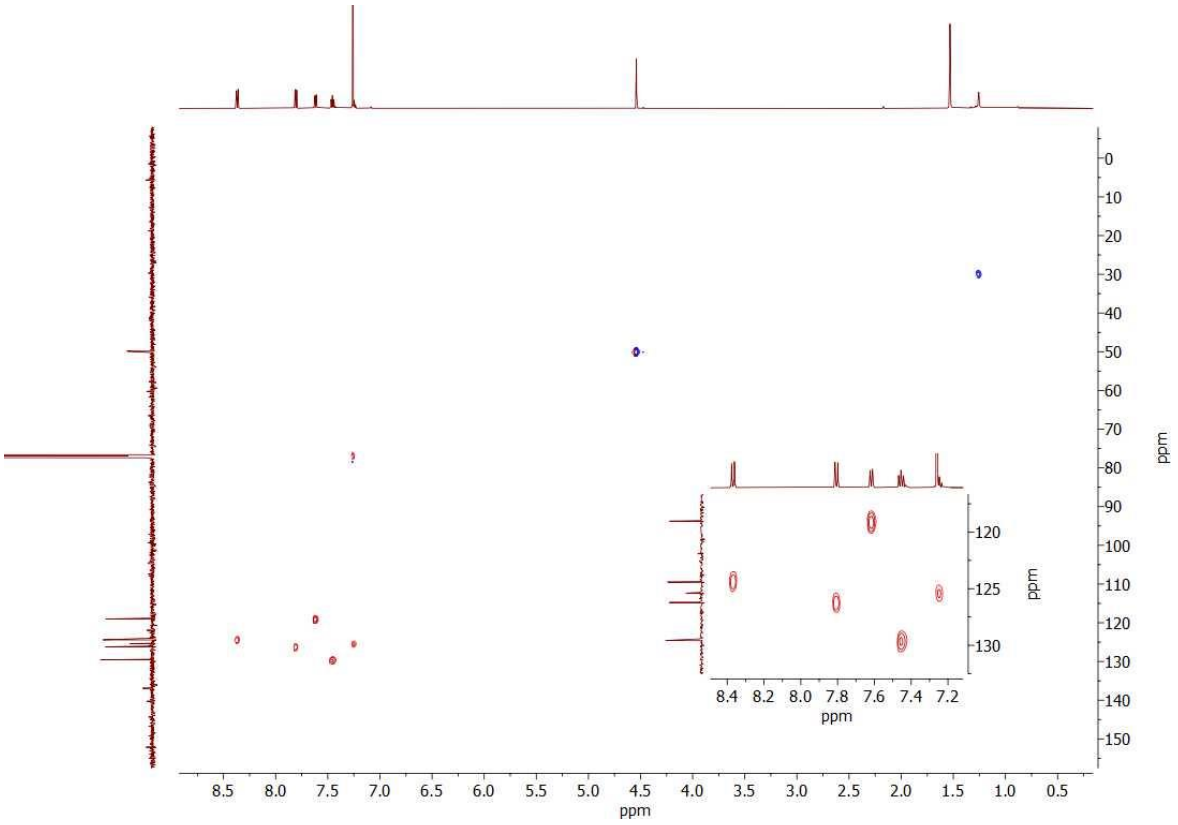
DEPT135 of **3k** (151 MHz, $CDCl_3$)



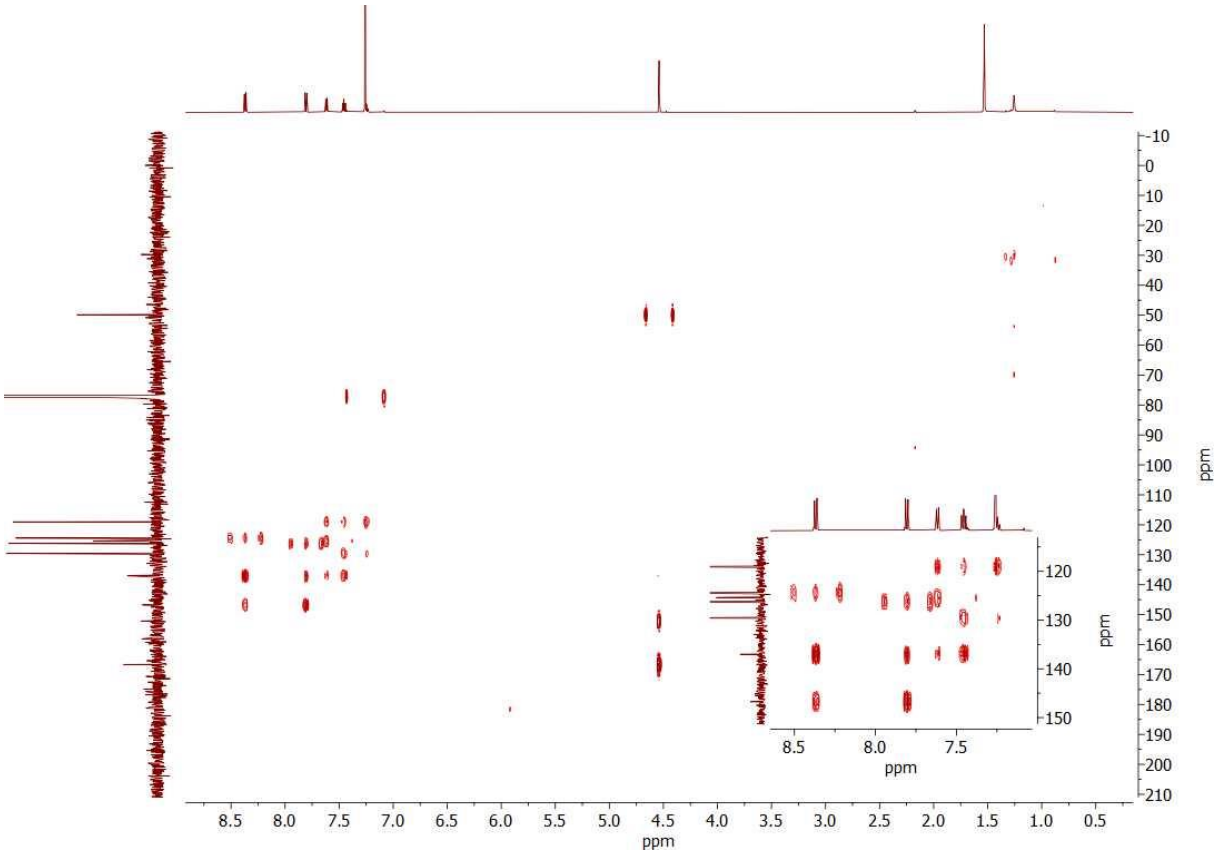
COSY of **3k** (600 MHz, $CDCl_3$)



HSQC of **3k** (600 MHz, $CDCl_3$)

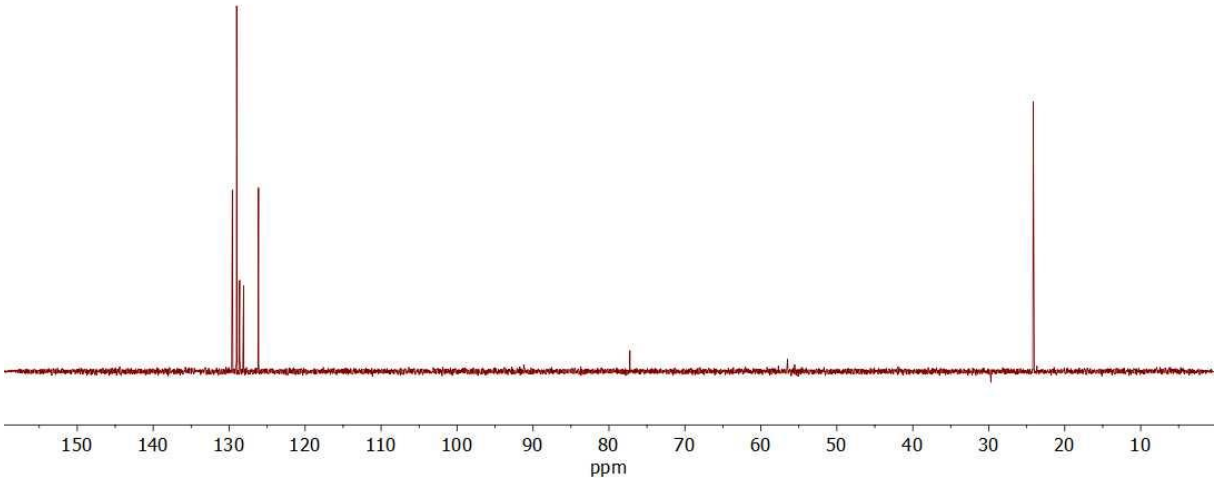


HMBC of **3k** (600 MHz, $CDCl_3$)

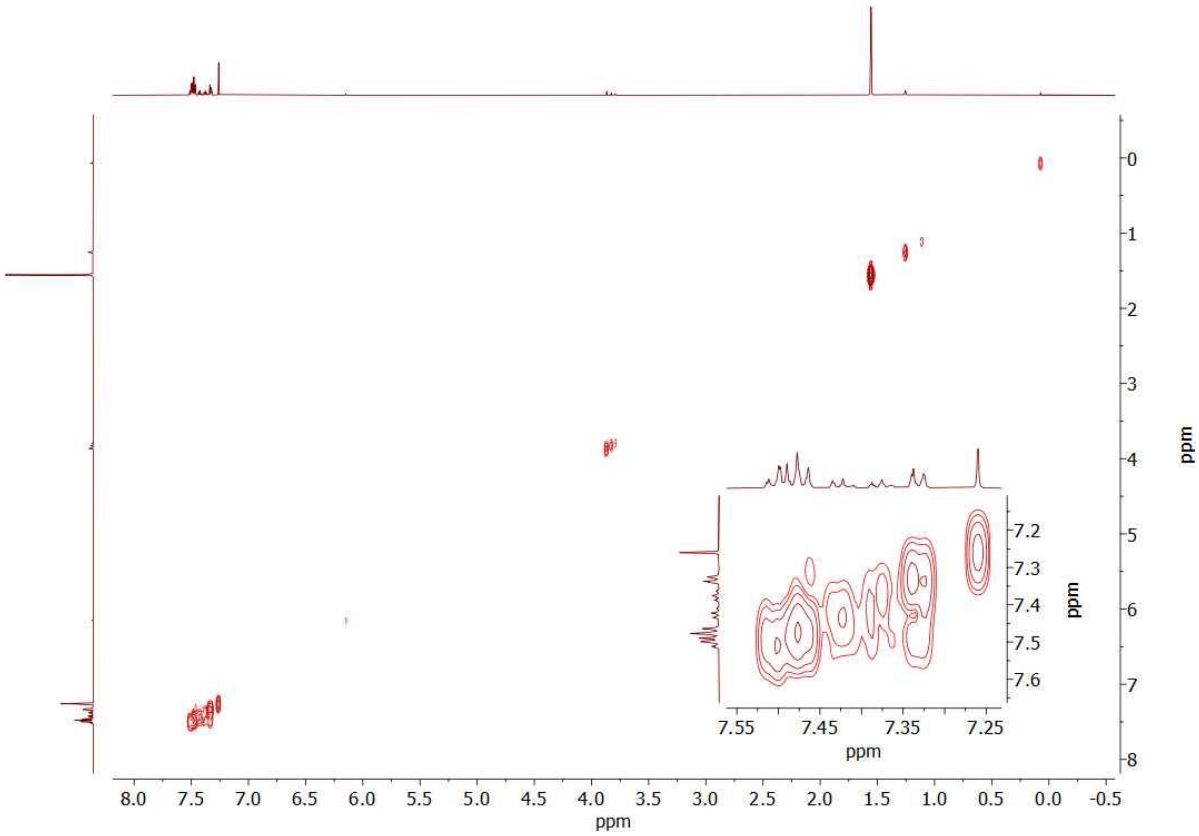


7.22 5,5-Dimethyl-1,3-diphenylhydantoin (3l)

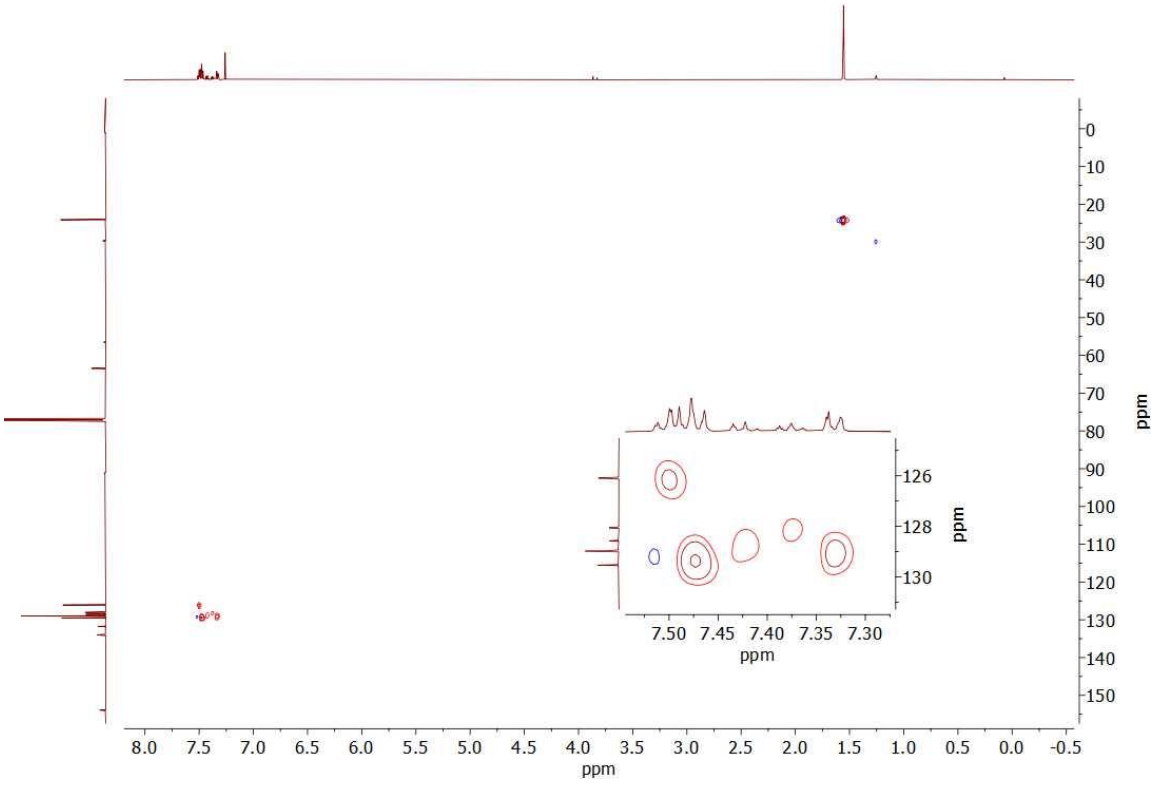
DEPT135 of **3l** (151 MHz, $CDCl_3$)



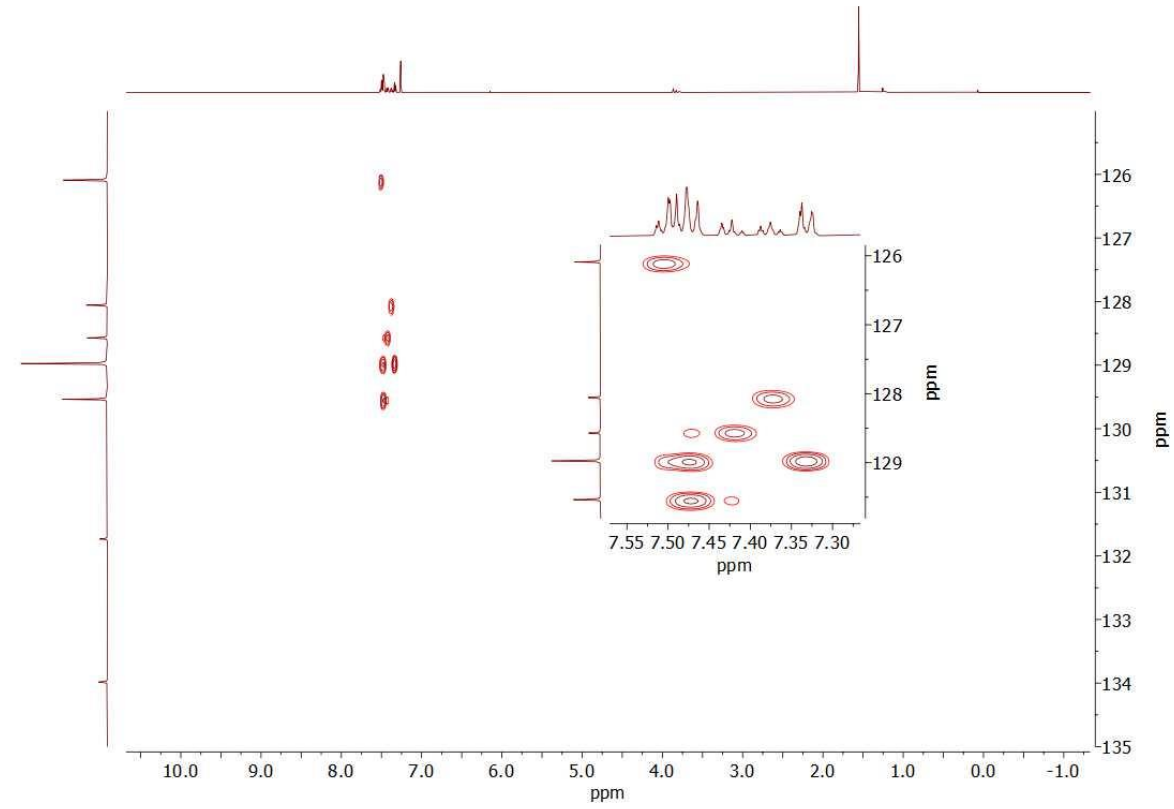
COSY of **3l** (600 MHz, $CDCl_3$)



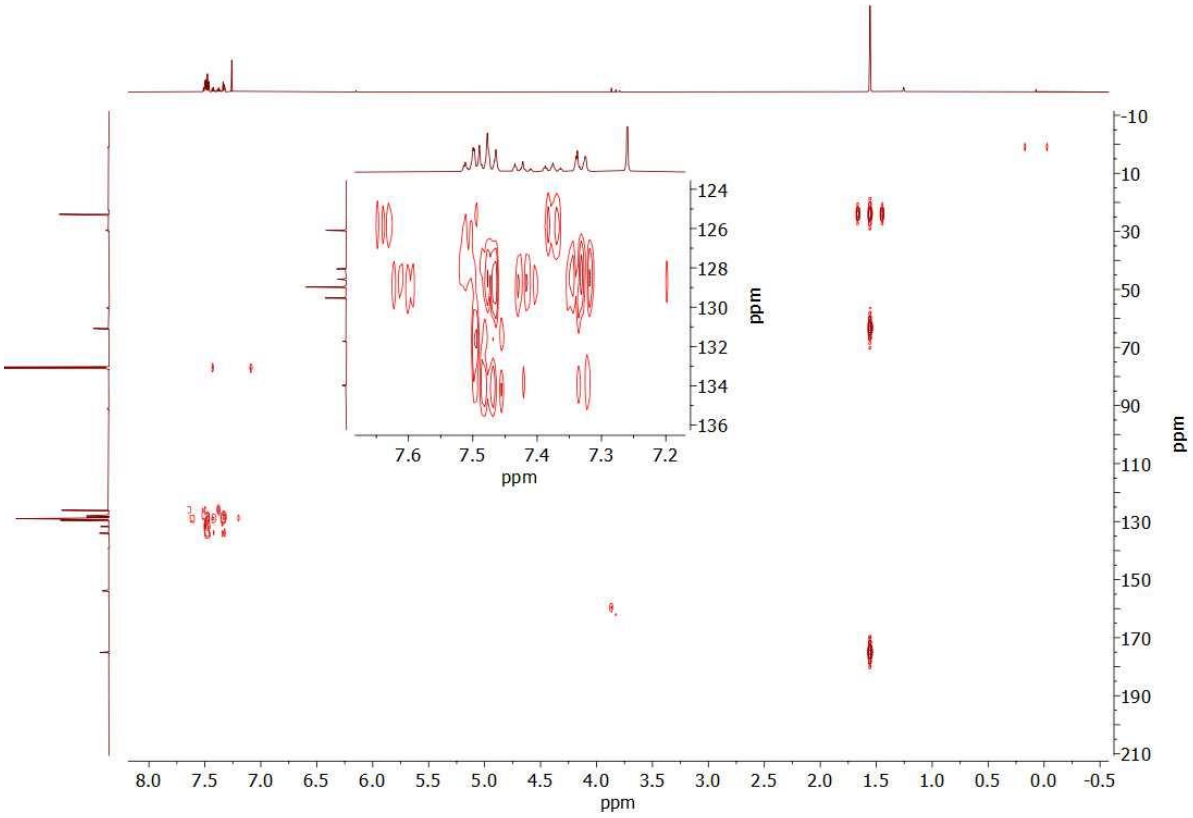
HSQC of **3l** (600 MHz, $CDCl_3$)



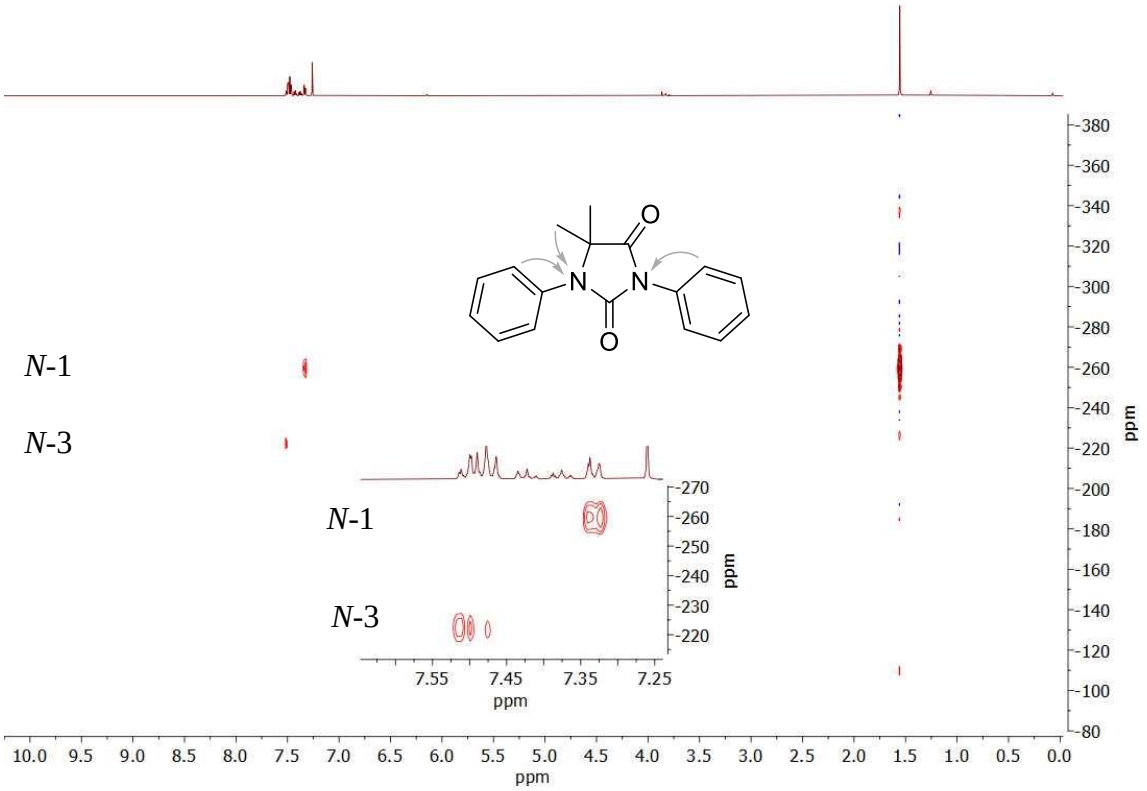
SHSQC of **3l** (600 MHz, $CDCl_3$)



HMBC of **3l** (600 MHz, $CDCl_3$)

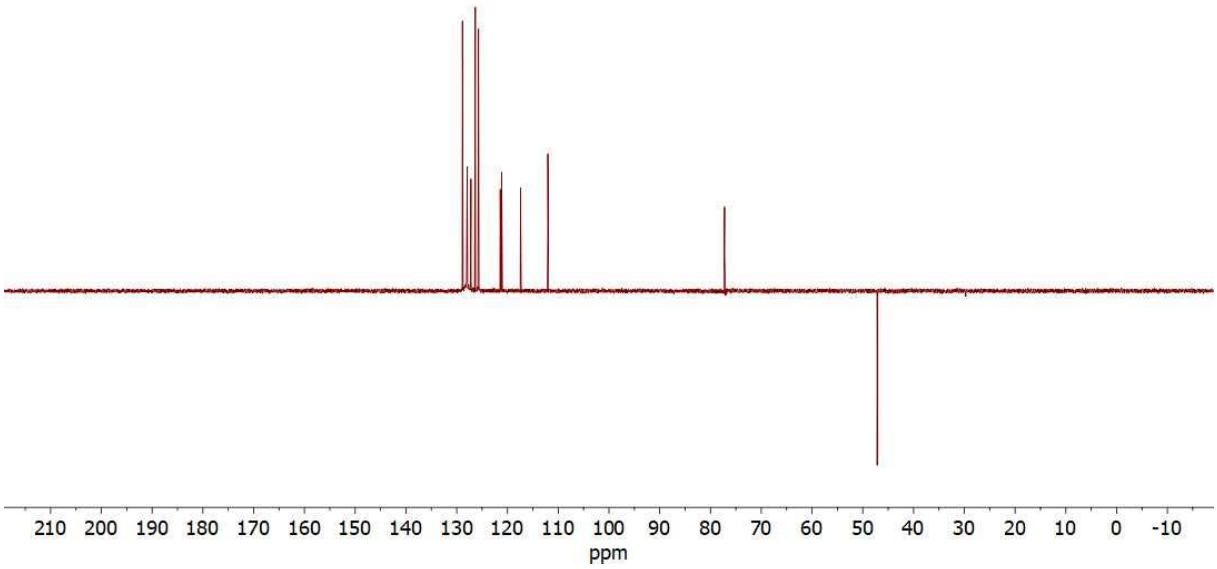


^{1}H–^{15}N HMBC of **3l** (600 MHz, $CDCl_3$)

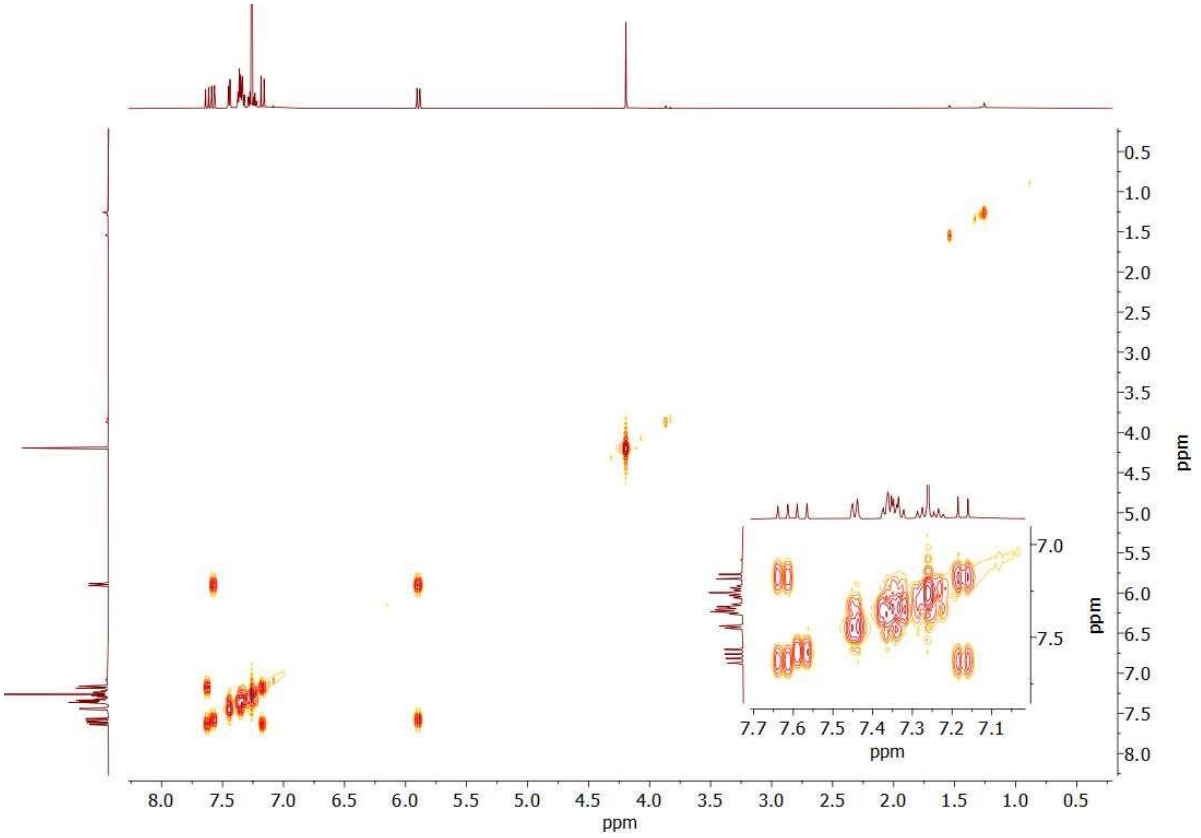


7.23 (*E,E*)-1,3-Distyrylhydantoin (3m)

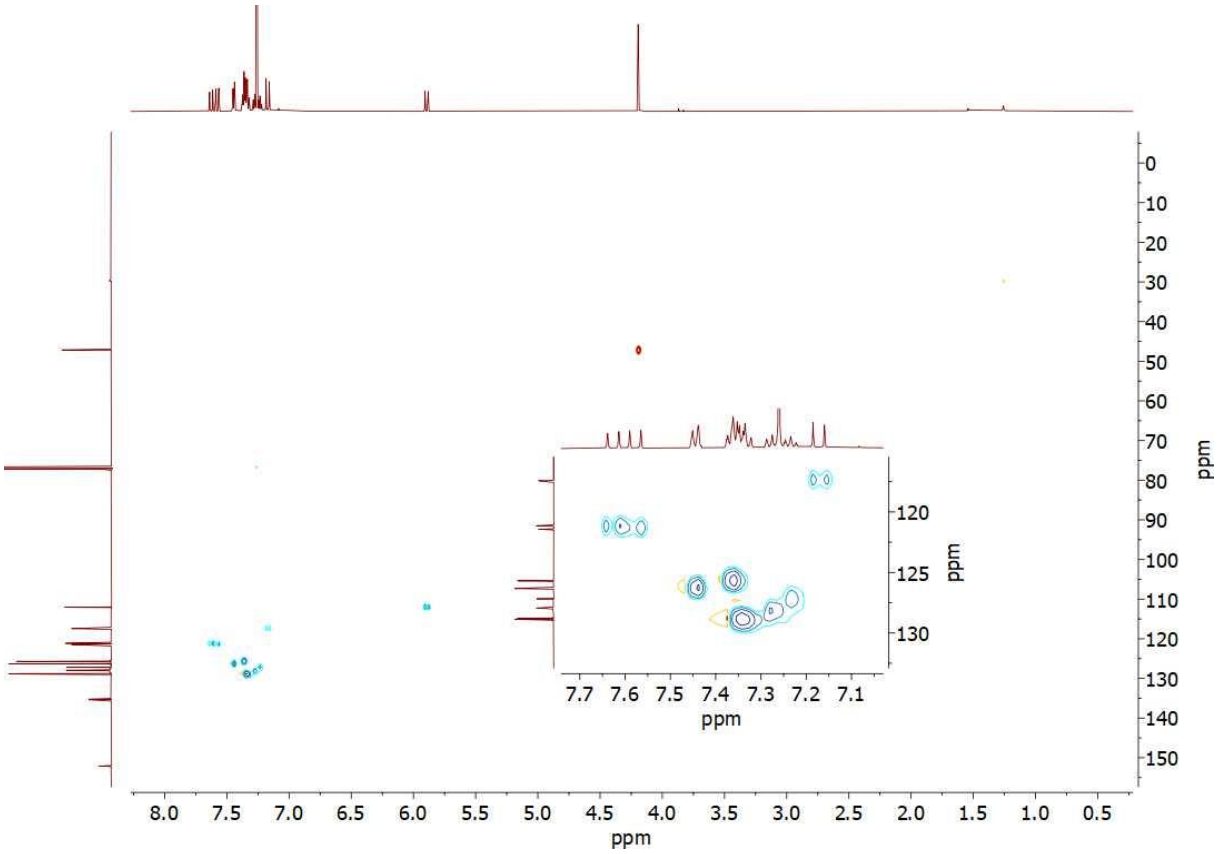
DEPT135 of **3m** (151 MHz, $CDCl_3$)



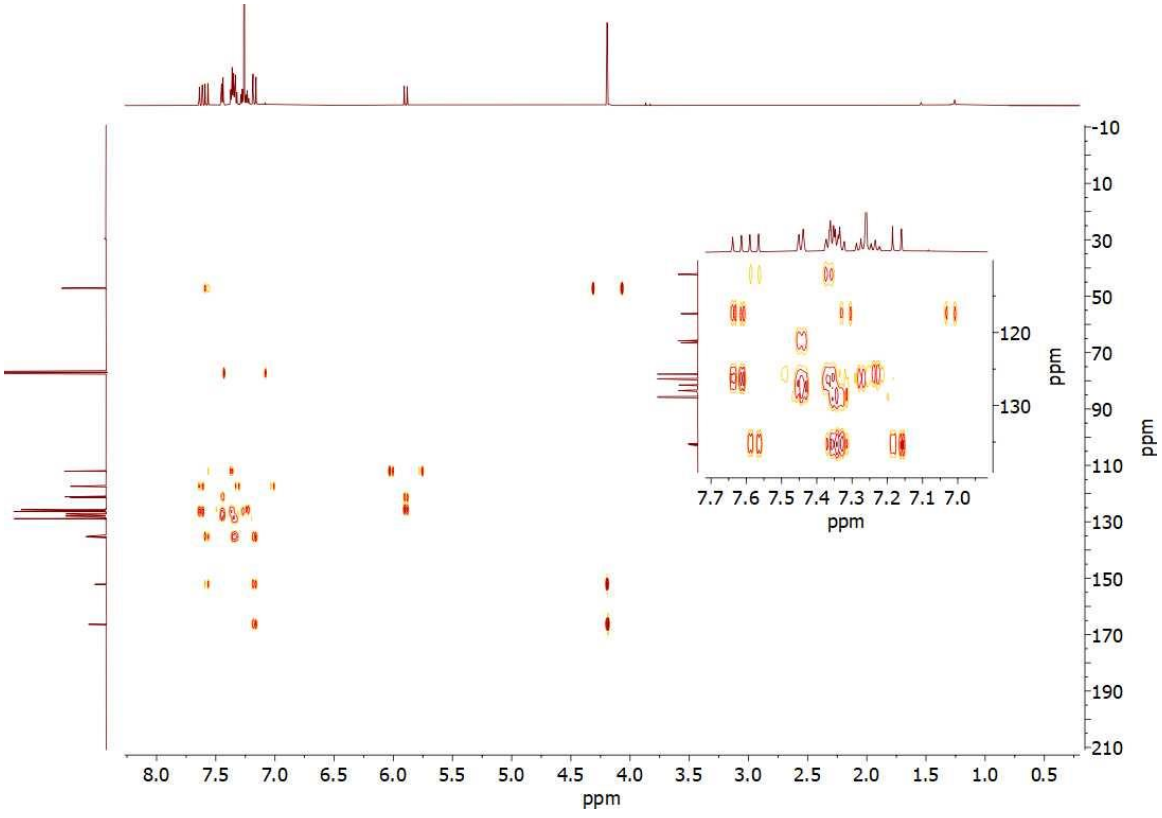
COSY of **3m** (600 MHz, $CDCl_3$)



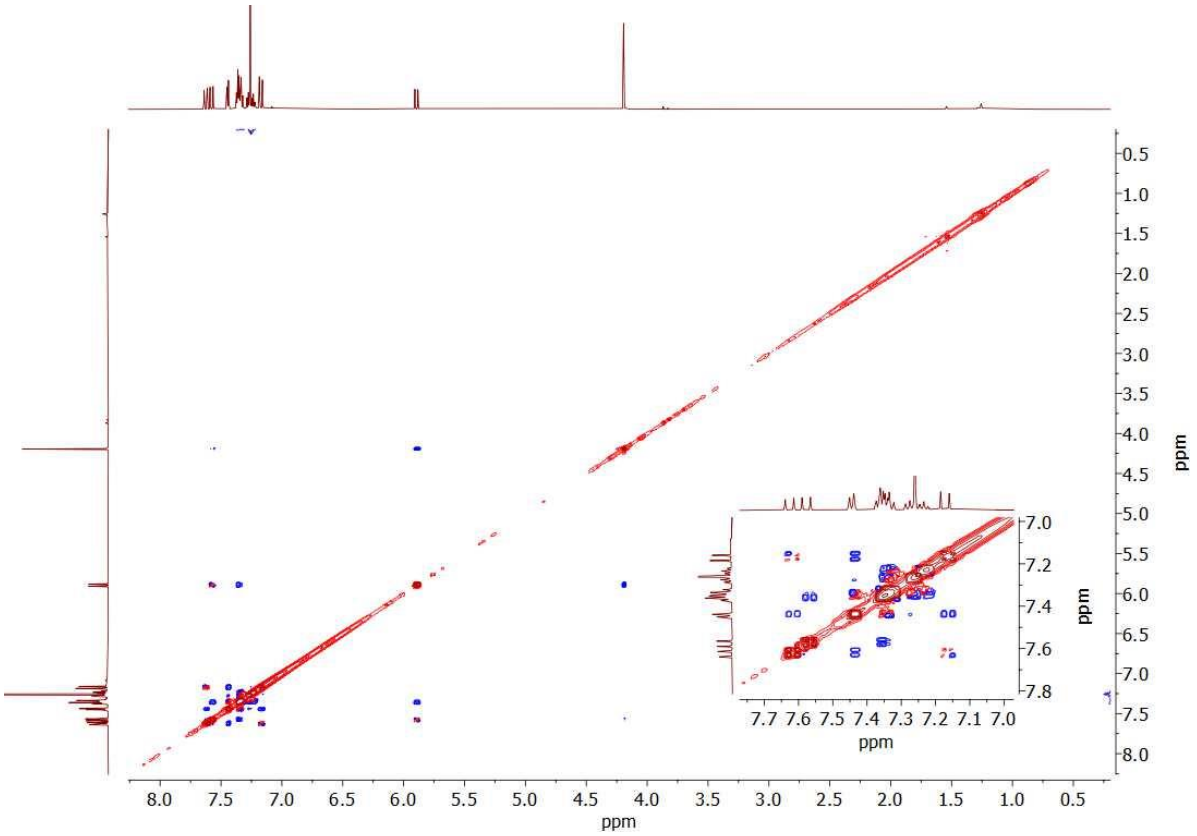
HSQC of **3m** (600 MHz, $CDCl_3$)



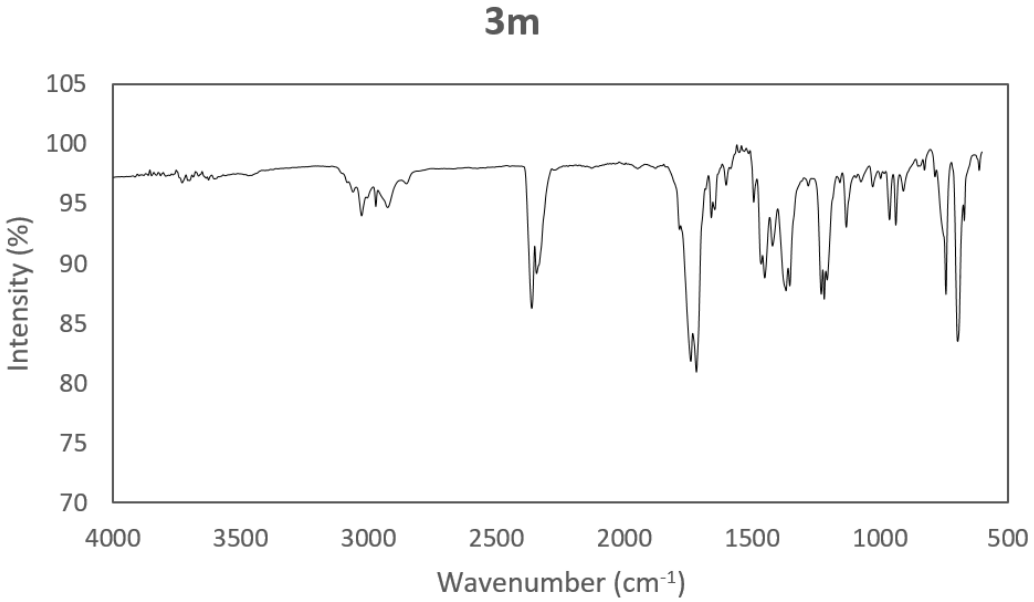
HMBC of **3m** (600 MHz, $CDCl_3$)



NOESY of **3m** (600 MHz, $CDCl_3$)

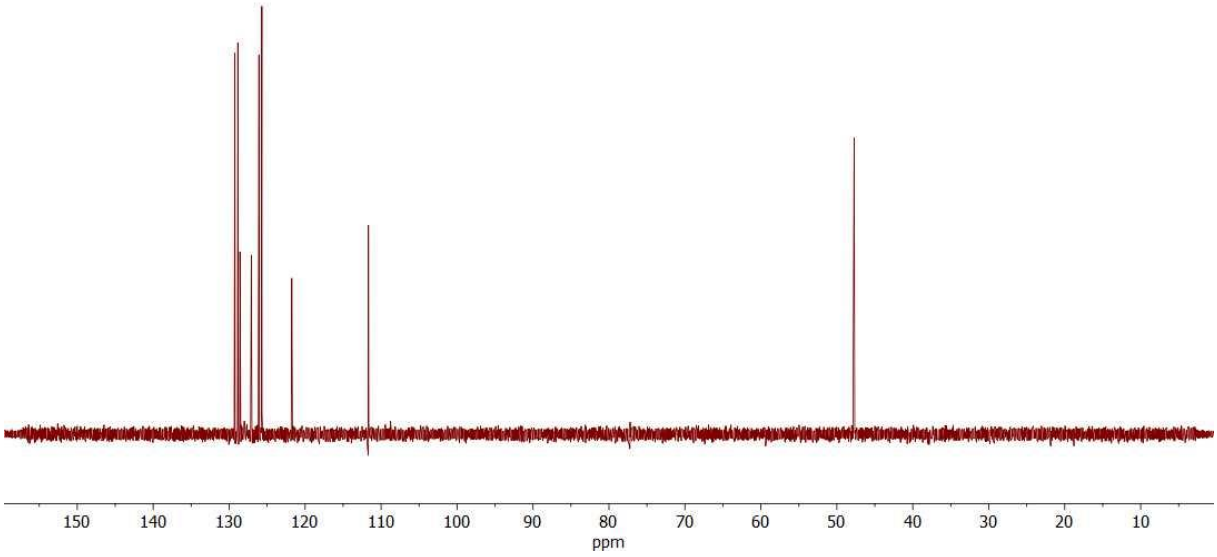


IR spectrum of **3m**

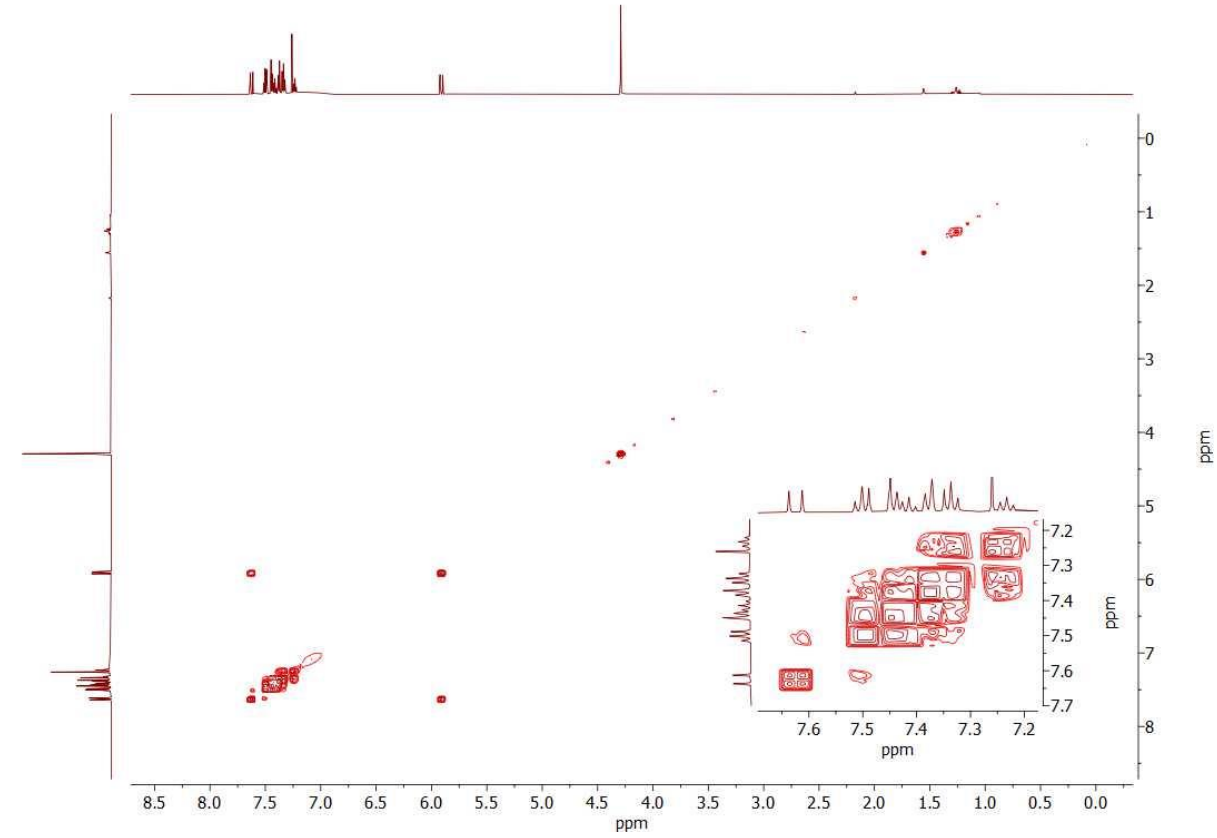


7.24 (*E*)-3-Phenyl-1-styrylhydantoin (3n)

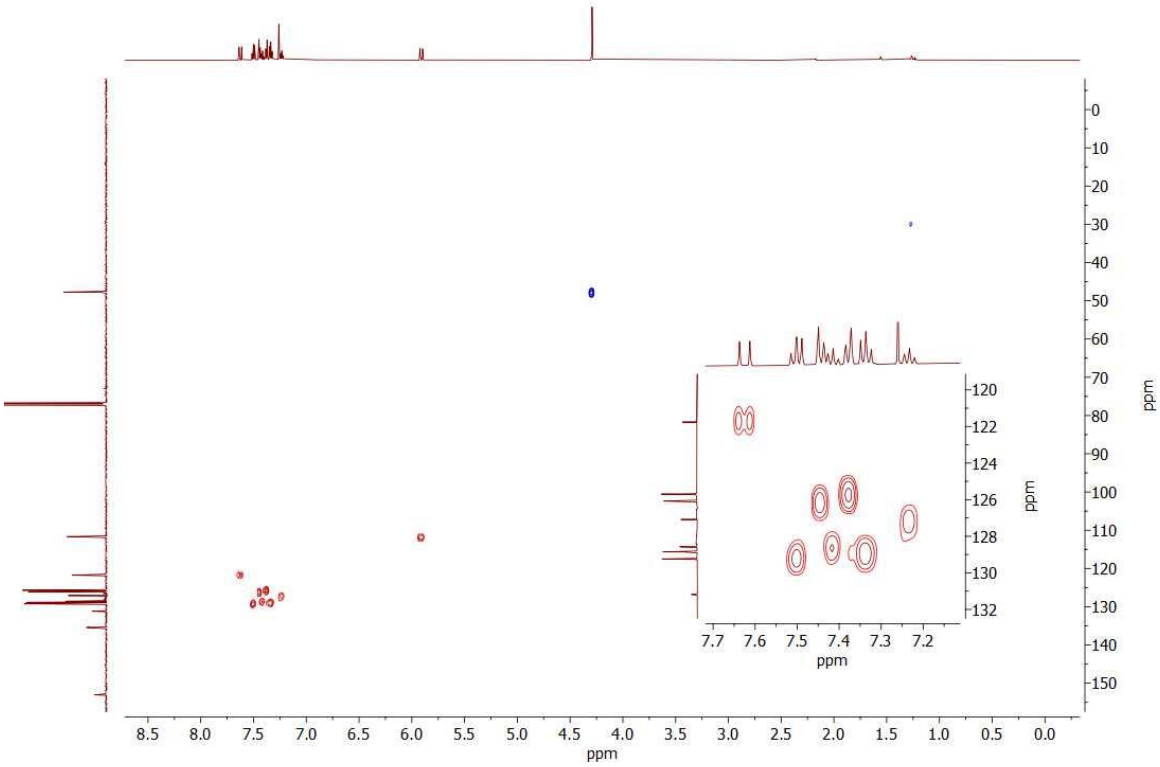
DEPT135 of **3n** (151 MHz, $CDCl_3$)



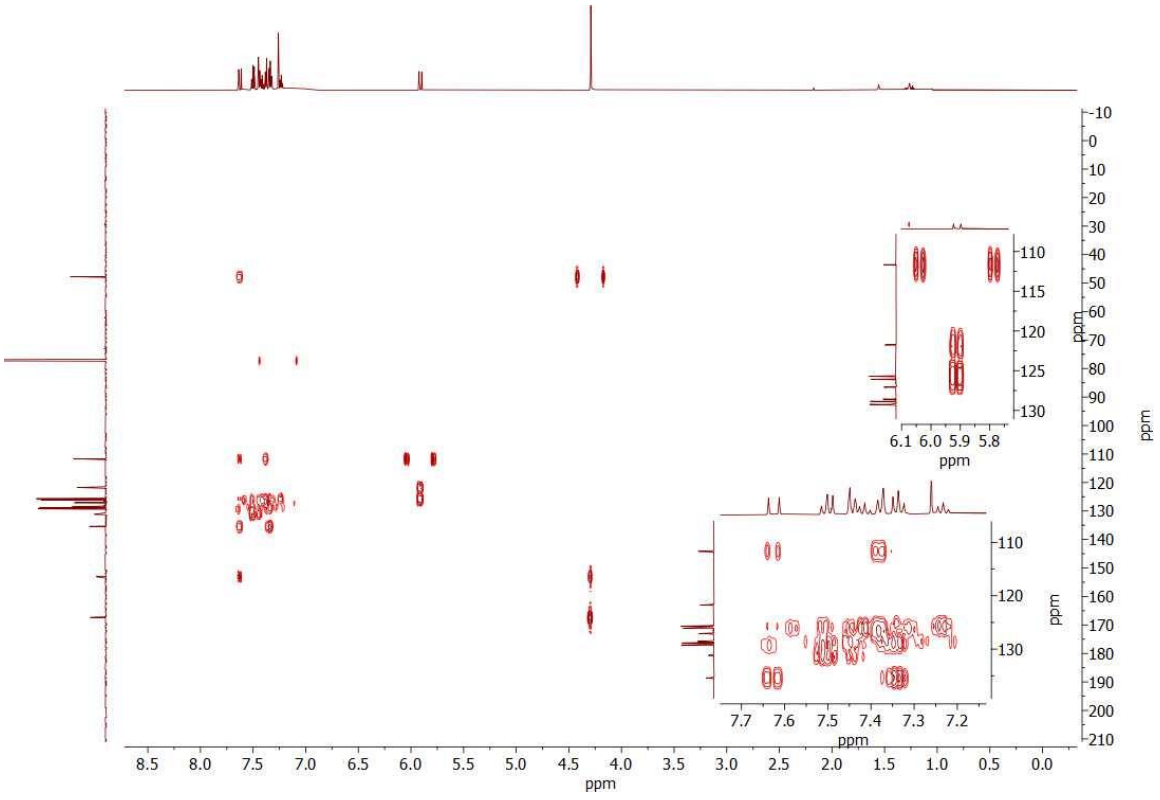
COSY of **3n** (600 MHz, $CDCl_3$)



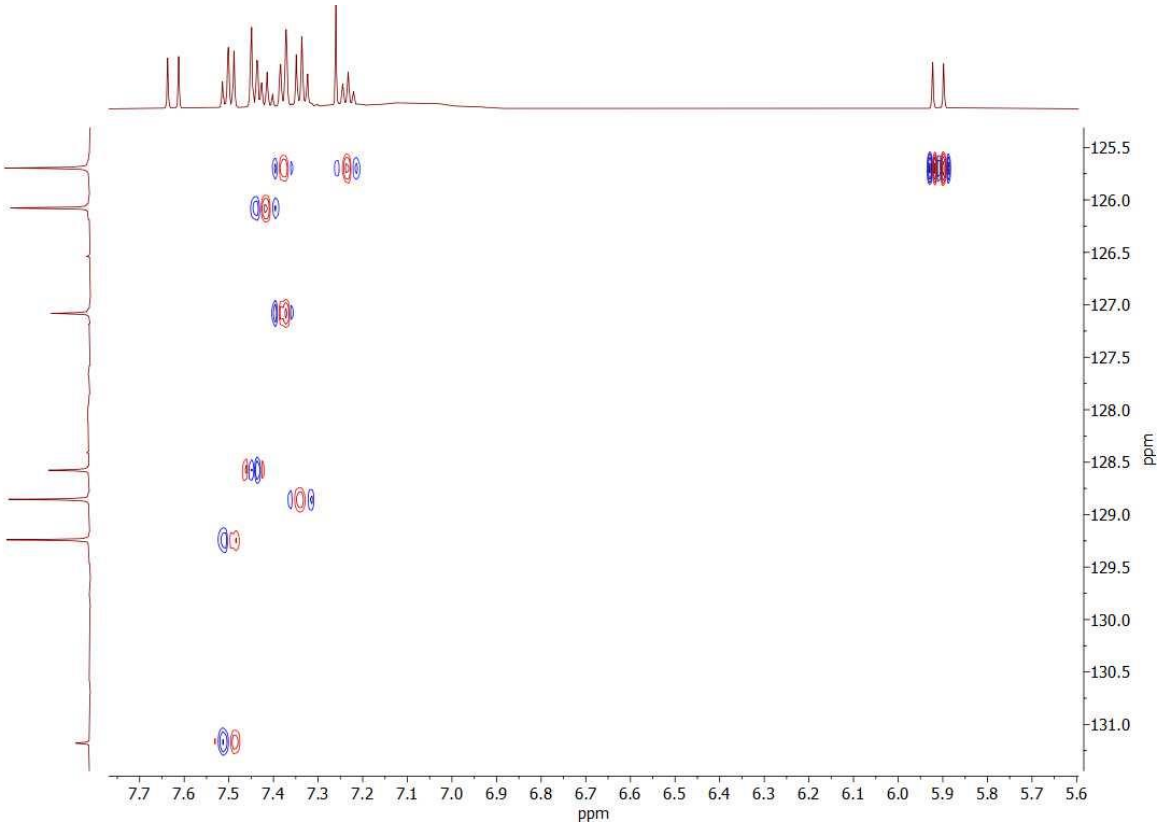
HSQC of **3n** (600 MHz, $CDCl_3$)



HMBC of **3n** (600 MHz, $CDCl_3$)



SHMBC of **3n** (600 MHz, $CDCl_3$)



NOESY of **3n** (600 MHz, $CDCl_3$)