Copper-Catalyzed Cross-Coupling Reaction between Peroxy-benzofuran-2-ones and Phenol Derivatives for the Synthesis of 3-aryl-3-phenyl-benzofuran-2(3*H*)-ones

A Thesis

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by

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Certificate

This is to certify that this dissertation entitled **Copper-Catalyzed Cross-Coupling Reaction between Peroxy-benzofuran-2-ones and Phenol Derivatives for the Synthesis of 3-aryl-3-phenyl-benzofuran-2(3*H*)-ones** towards the partial fulfilment of MSc. Degree programme at the Indian Institute of Science Education and Research, Pune represents study/work carried out by Archita Barma at Indian Institute of Science Education and Research under the supervision of Dr. Boopathy Gnanaprakasam, Associate Professor, Department of Chemistry, during the academic year 2023-2024.

Dr. Boopathy Gnanaprakasam

Committee:

Dr. Boopathy Gnanaprakasam

Prof. Ramakrishna G. Bhat

Declaration

I hereby declare that the matter embodied in the report entitled **Copper-Catalyzed Cross-Coupling Reaction between Peroxy-benzofuran-2-ones and Phenol Derivatives for the Synthesis of 3-aryl-3-phenyl-benzofuran-2(3*H*)-ones** are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Science Education and Research, Pune under the supervision of Dr. Boopathy Gnanaprakasam and the same has not been submitted elsewhere for any other degree.

Archita Barma

Archita Barma

Date: 12.4.24

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Abstract

Peroxides are indispensable functional groups in organic chemistry that are found in a wide range of natural products and pharmaceutical drugs. Peroxides are capable of undergoing a wide range of chemical changes, including rearrangement reactions, because of their weak O-O bond. In general, peroxides are extensively used as oxidants or additives in many chemical transformations. However, it is not explored as a synthetic intermediate for the cross-coupling reaction. Amongst several heterocycles, the 3-phenyl benzofuran-2-one derivatives can easily undergo peroxidation at the tertiary carbon to form 3-*tert* butyl peroxybenzofuranone, which was studied for the rearrangement reaction with various amine derivatives in the absence of the catalyst. Nevertheless, the cross-coupling reaction with these peroxides is not explored for C-C bond formation. Here, we have studied the copper-catalyzed cross-coupling reaction between 3-phenyl benzofuran-2-one with phenol derivatives to produce 3,3-diaryl benzofuranone derivative. Functionalization at the quarternary carbon can be a quite challenging task and many naturally occurring compounds that are biologically active, such as rosmadial, yuccaol contain a derivative of 3,3-diaryl benzofuranone. It can be also be an important framework to synthesize to support structure-activity relationship in drug synthesis. Thus, we have synthesized up to eight substrates using this method with good to moderate yields. In order to look into the plausible mechanism for this coupling reaction, a series of experiments were conducted. These experimental results suggest that this reaction involves radical intermediates, and a justifiable mechanism is proposed for the copper catalysed cross-coupling of benzofuranone peroxide and phenols. All these research findings and experimental results, along with the complete characterization data, were presented in this report.

Acknowledgments

I would like to express my sincere gratitutde to Dr. B. Gnanaprakasam, associate professor, the Department of Chemistry at IISER-Pune, for giving me the chance to work under his supervision. I want to thank him in particular for promoting dialogue and allowing space for individual thought project. Additionally, I want to thank Prof. Ramakrishna Bhat, a member of my TAC, for his valuable suggestions. I want to express my gratitude to our Director, Prof. Sunil. S. Bhagwat, IISER-Pune for providing all the amenities during the course. I am also grateful to my colleagues and lab seniors, Somnath Ghosh, Shankhajit Mondal, Akash Jamdade, Dasharth Sutar, Gokul Londhe, Gourishankar Swami, Padmavathy Nair, Pramod Jadhav, Sonal, former group members, Dr. Nirmala Mohanta, Dr. Akangsha M. Pandey, Dr. Akash Ubale, Dr. Moseen Shaikh and Dr. A Prabu. Their contributions have been essential to the completion of this thesis work. Finally, I would like to thank my family and my friend, Nabarun, Amin and Debasmita for their constant support and encouragement during my academic pursuits. Your love and support have been my source of strength and inspiration. Thank you all for your contribution to this project.

1.Introduction

Heterocyclic compounds are organic compounds that have at least one heteroatom in the ring. The most prevalent heteroatoms are nitrogen, oxygen and sulphur, however heterocycles can be found with more than one heteroatoms in the structure. Pyrrole, furan, pyridine and thiophene are the most well-known examples of simple heterocyclic compounds. They are the interesting and significant class of organic molecules that are widely used in chemistry, biology, and medicine.[1,2] The broad family of heterocyclic compounds has a huge range of chemical structures, each with its own unique properties and reactivity.[3] These interesting applications of heterocycles have driven chemists to develop various synthetic approaches in the past, including catalytic and non-catalytic methods. However, the catalytic methods have several advantages over the non-catalytic conventional approaches, including waste minimization, atom-economy and reduced multi-step operation. Therefore, a number of catalytic processes have been carried out in recent decades in order to generate heterocycles or their derivatives through C-C and C-X bond formation. In literature, cross-coupling reactions were studied largely with an aryl system with/without a directing group. But catalytic cross-coupling reactions with heterocycles are limited and quite challenging due to several reasons. Thus, developing a newer catalytic approach for the cross-coupling reaction among the heterocycles could be fascinating aspect in catalysis. Although several cross-coupling reagents were used in the coupling reaction, very limited studies were done with peroxide as a coupling partner in the literature.

1.1 Overview on organic peroxides and their chemistry

Organic peroxides are formed by reactions involving hydrogen peroxides, molecular oxygen, or the coupling of hydroxyl radicals. The presence of a peroxide functional group (O-O) provides unique properties and reactivity. Peroxides were found as natural products and have been extracted from a broad range of plants and marine species over the last few decades[4]. Many hydroperoxides function as reactive intermediates in natural processes or have bio-active properties. The finding by Chinese researchers of a strong antimalarial activity of sesquiterpene peroxylactone artemisin, isolated from the wild plant *Artemisia annua* L (sweet wormwood), was an event that fundamentally altered many current ideas about natural peroxides[5]. The wider biological activities towards antimalarial[6], anti-HIV[7], anti-cancer[8], etc. are caused by several natural compounds with peroxide functionality (Figure 1.1.1). Due to their widespread use as oxidants, additives, and radical initiators, peroxides play a significant role in organic synthesis. The two most prevalent forms of organic peroxides used in organic synthesis are dialkyl peroxides (R-O-O-R1) and alkyl or aryl hydroperoxides (R-O-O-H). Aryl peroxides, polyperoxides, peroxyesters, alkylidene peroxides, and cyclic peroxides are some kinds of organic peroxides in the literature.[11]

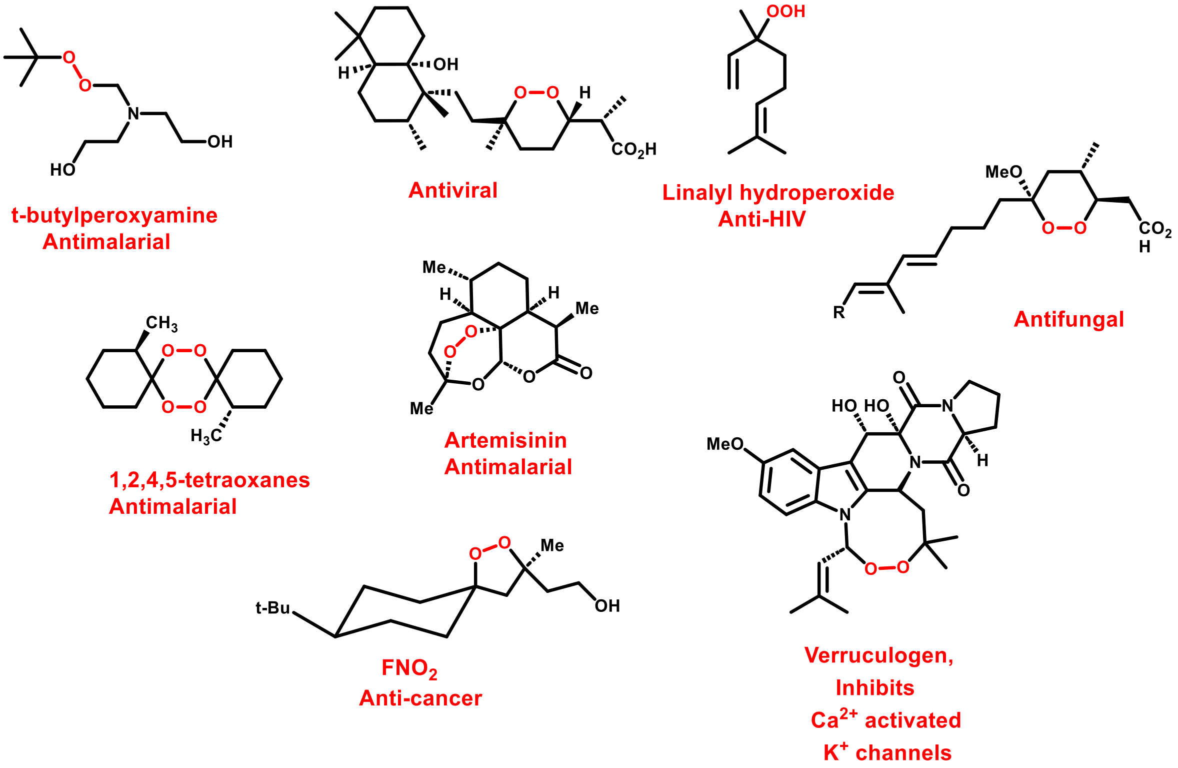


Figure.1.1.1 Bio-active molecules display peroxide linkage.

Due to their weak O-O bond, it can easily undergo homolytic cleavage to produce reactive free radicals.[9] Alkylation of hydrogen peroxide, either by S$_N$2 process or by solvolyses may introduce peroxy groups into organic compounds.[10] Organic peroxides are frequently employed as a free radical source to initiate a variety of addition and polymerization processes.[11] Hydrogen peroxide gets decomposed spontaneously into water and oxygen in the presence of light.[12] Organic peroxides react violently with metals to form metal hydroxides and alkoxy radicals.[13]

$$(CH_3)_3COOH + M^{2+} \longrightarrow (CH_3)_3CO^{\cdot} + {}^{-}OH + M^{3+}$$

Scheme 1.1.1 Reaction of metal with peroxide.[13]

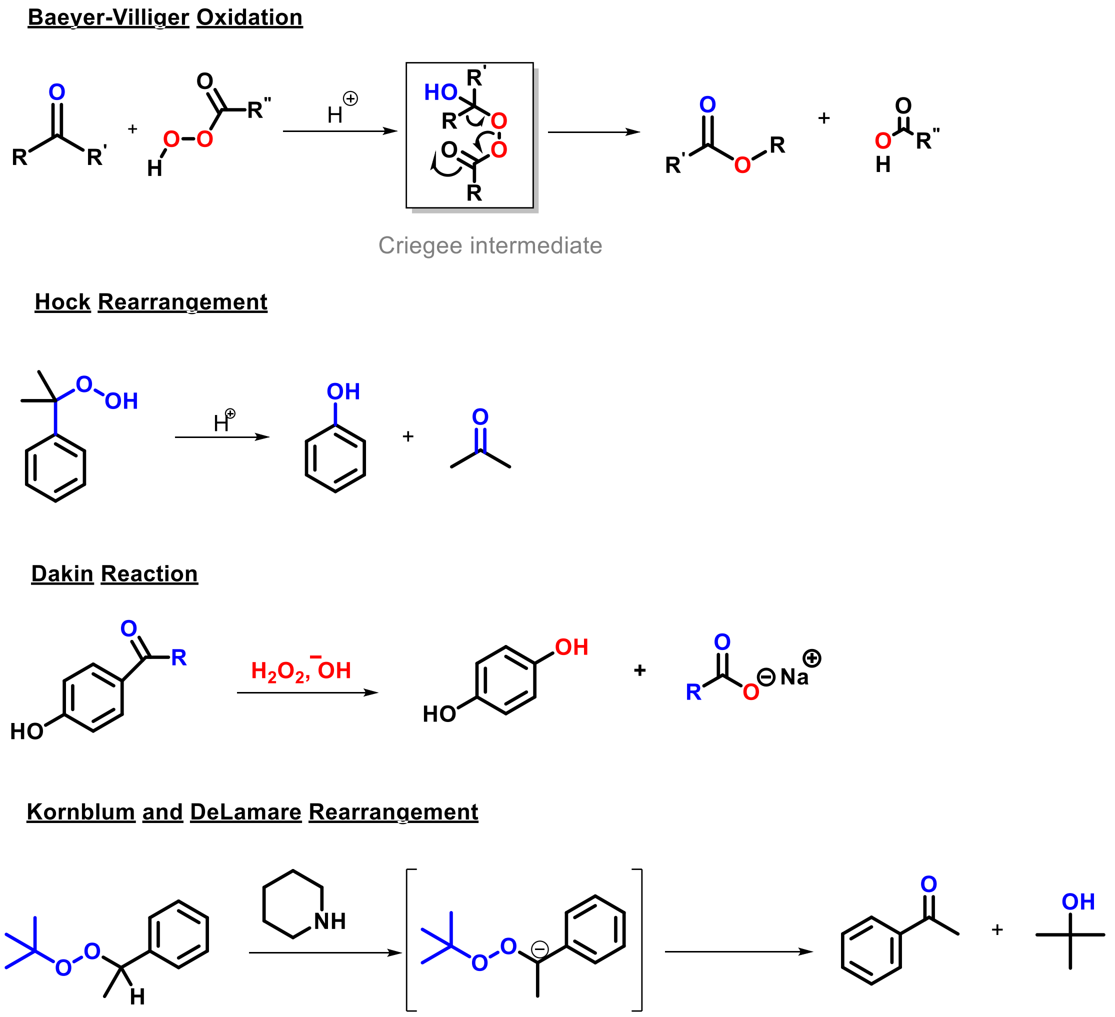
There are many reagents used for oxidation, including peroxidation such as, *tert*-butyl hydroperoxide, *tert*-butyl perbenzoate, dibenzoyl peroxide, cumene hydroperoxide, *meta*-chloroperbenzoic acid etc.

1.2 Rearrangement reactions and chemical transformations using peroxides

Peroxides are well recognized to undergo several chemical transformations or rearrangement reactions. Usually, the rearrangement involves breaking or rearrangement of the peroxide group in the same molecule. The literature lists a number of rearrangement reactions. An important example is Baeyer–Villiger oxidation,[14] which shows a conversion of a ketone to an ester via 1,2 migration. Criegee rearrangement[15] is similar to Baeyer-Villiger reaction, where a hydroperoxide is converted into an ester The Hock process uses peroxides,[16] where phenol is produced from cumene hydroperoxide by the migration of an aryl/alkyl group to an oxygen atom lacking an electron. The Dakin reaction[17] describes the rearrangement reaction of aryl aldehyde or ketone with hydroperoxide to afford benzenediol and carboxylate. Under simple conditions, the Kornblum-DeLamare rearrangement is crucial in organic peroxide for the synthesis of ketones and alcohols.[18]

The conventional rearrangement reaction explored peroxide for the oxidation reaction of various aldehyde, ketones, alkenes, etc, but limited examples are reported for skeletal rearrangement reaction and cross-coupling reactions.

Few research groups have carried out rearrangement reaction utilising organic peroxides. Li and co-workers, for example, reported, acid mediated rearrangement of *tert*-butyl peroxide to produce 2,3-disubstituted furans[19], Recently, Stoltz and co-workers reported, copper-catalyzed C-H peroxidation followed by skeletal rearrangement.[20] In order to create biologically active 1,4-benzooxazin-3-one derivatives, Gnanaprakasam group employed Lewis acid and Bronsted acid to rearrange C3-substituted-2-oxnidole peroxide.[21,22] Another study was covered on the iron-catalyzed rearrangement of aryl peroxyoxindole to furnish 1,3-benzooxazine derivatives.[23-27] Following that, same group conducted a fresh study on peroxidation of benzofuranone followed by skeletal rearrangement using amines under continuous flow conditions.[28] Recently, E. Bosnidou and co-workers reported $InCl_3$ promoted hydroperoxide rearrangements and nucleophilic addition to synthesize benzoxacycles.[29]

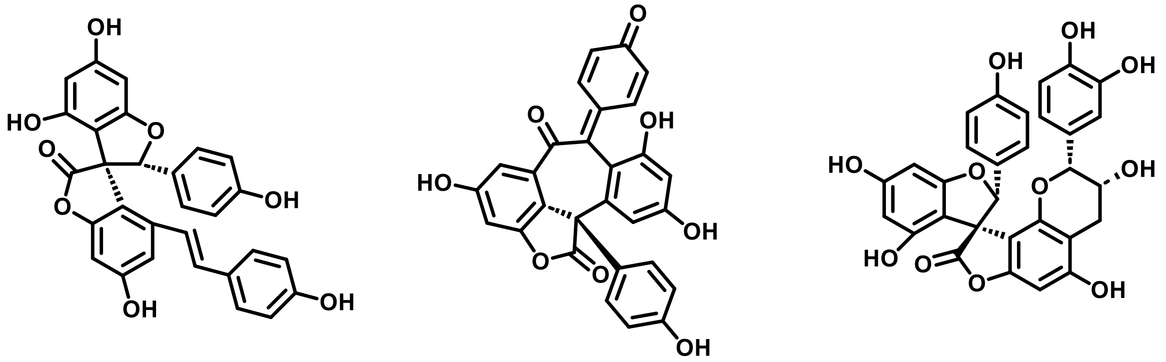


Scheme 1.2.1 Different rearrangement reactions of organic peroxides.[14-18]

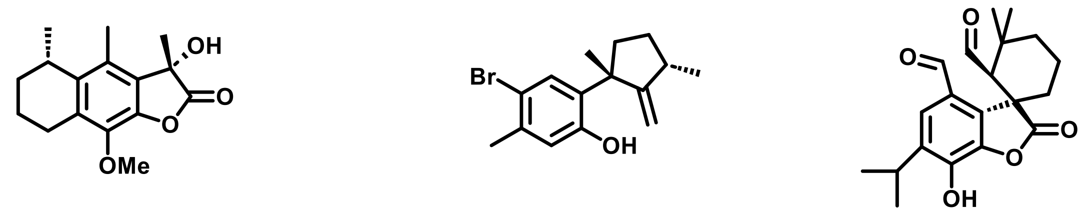
Peroxides are utilised in a number of organic transformations, including amination reactions, arylation or alkylation reactions.[30] Minisci and co-workers described the substitution reaction between cumene peroxide and phenol in 1999.[31] Additionally, peroxide has been extensively employed as an oxidant in cross-dehydrogenative coupling reactions catalysed by transition-metals.[32] But, very limited study uses peroxide as synthetic intermediate for the cross-coupling reaction and there is no report available for direct cross-coupling of benzofuranone peroxide with phenols and other aromatic compounds for the synthesis of 3,3-disubstituted benzofuran-2-(3*H*)-ones.

1.3 Overview on 3,3-disubstituted benzofuran-2-(3*H*)-ones

There are significant bio-active natural products which contain two or more stereogenic quaternary carbon centres.[33] 3,3-Diarylbenzofuranones are a difficult synthesis target because of their highly functionalized quaternary carbon centre.Benzofuran-2-(3*H*)-ones can be utilised as building blocks to synthesize sequiterpenes, such as isolaurinterol and aplysins.[34] Additionally, they are also present in a variety of naturally occurring biologically active substances, including yuccaols,[35] rosmadial,[36] (+)-hopeahainol A[37] and abiesinol.[38] It can be also be an important framework to support structure-activity relationship in drug synthesis.



Yuccaol A **(+)-Hopeahainol A** **Abiesinol A**



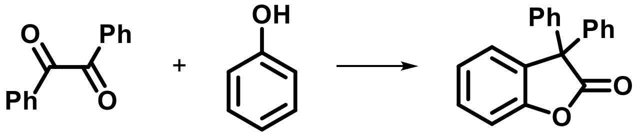
Radulifolin B **Isoalurinterol** **Rosmadial**

Figure1.3.1 Significant bio-active natural products containing 3-substituted-3-aryl-benzofuran-2-(3*H*)-one sekeletons.[35-39]

1.4 Literature background for the synthesis of 3,3-disubstituted benzofuran-2-(3*H*)-one

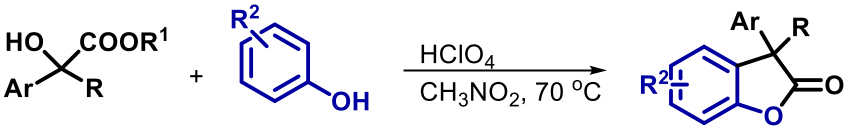
Many methods have been developed to synthesize 3,3-disubstituted benzofuranone including, Friedel Craft alkylation, transition-metal catalysed cross-coupling reactions and functionalization reactions. A few of them are presented here.

In 2009, Ali Sharifi ad co-workers reported a chemo-selective condensation reaction of benzil with phenol using montmorillonite K-10 as a solid support medium to produce 3,3-diphenyl-benzofuran-2-(3*H*)-one. [39]



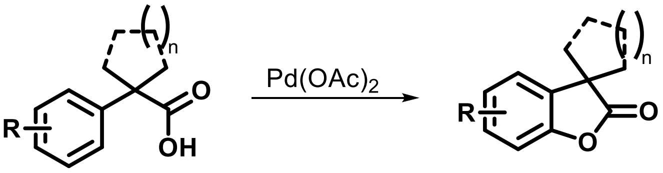
Scheme 1.4.1 Condensation reaction to produce 3,3-diphenyl-benzofuran-2-(3*H*)-one by Ali Sharifi and group.[39]

A sequential lactonization reaction between an α-hydroxy ester and phenols is also an efficient method to synthesize unsymmetrically substituted benzofuran-2-ones. [40]



Scheme 1.4.2 Jian Zhou's approach for the Friedel-crafts reaction to synthesize unsymmetrically substituted benzofuran-2-ones.[40]

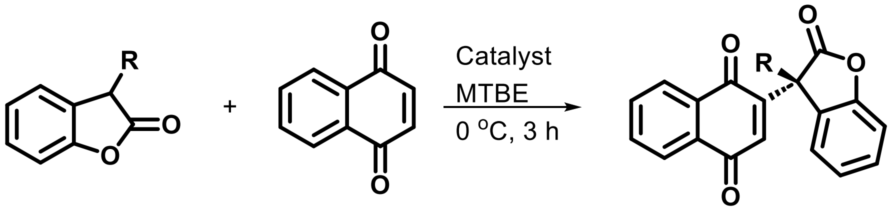
Another way to synthesize such moiety is by transition-metal catalytic intra or intermolecular heteroannulation of pre-functionalized substrates. Zhang-Jie Shi and group studied a Palladium-catalyzed direct lactonization of 2-arylacetic acid to synthesize functionalized benzofuranone derivatives.[41]



Scheme 1.4.3 Transition-metal catalytic lactonization reaction by Shi and coworkers.[41]

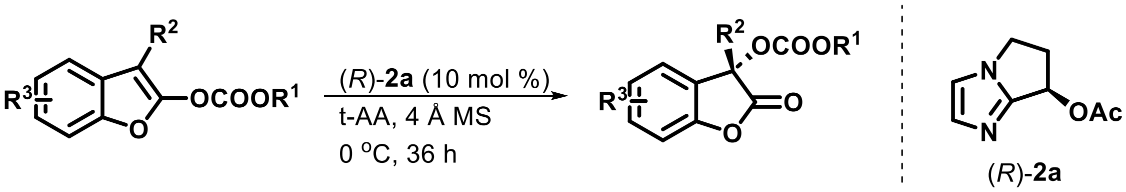
In the recent decades, several methods have been established for the asymmetric synthesis of 3-susbstituted benzofuran-2-ones. Pre-constructed heterocyclic rings can be rearranged and modified by chiral catalyst to produce enantioselective 3,3-disubstituted benzofuran-2-(3*H*)-ones

Jiang group reported an organocatalytic asymmetric reaction of benzofuran-2-(3*H*)-one with naphthoquinones by cooperative visible-light photocatalysis.[42]



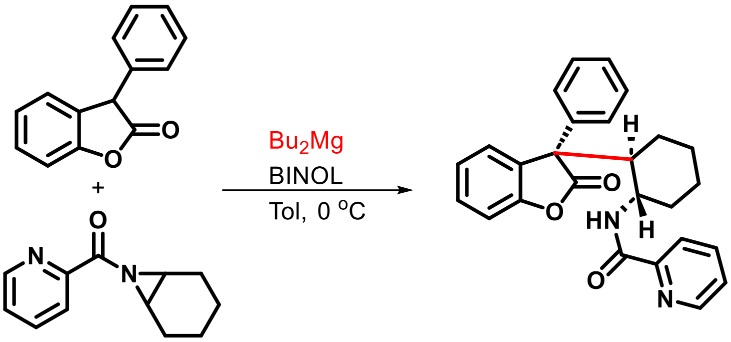
Scheme 1.4.4 Visible light mediated synthesis of chiral 3,3-diaryl-substituted-benzofuran-2-ones.[42]

Wanbin Zhang and group reported an enantioselective *Black* rearrangement through carbonyl migration of benzofuran-2-(3*H*)-ones by employing a chiral bicyclic imidazole.[43]



Scheme 1.4.5 *Black* rearrangement using chiral bicyclic imidazole by Zhang and co-workers.[43]

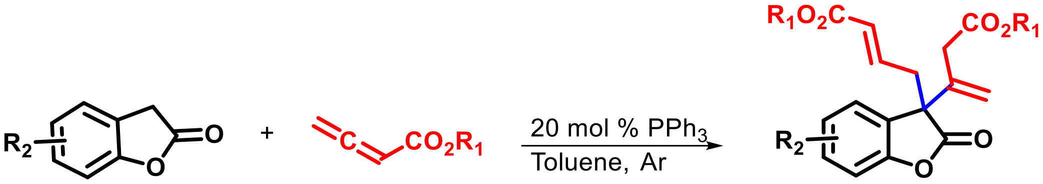
Asymmetric ring opening reaction of *meso*-aziridines with benzofuran-2(3*H*)-ones by in situ generated magnesium catalysis furnishes enantioselective 3,3-disubstituted benzofuran-2-(3*H*)-ones.[44]



Scheme 1.4.6 Catalytic ring opening reaction of aziridines with benzofuran-2-(3*H*)-ones reported by Wang and co-workers.[44]

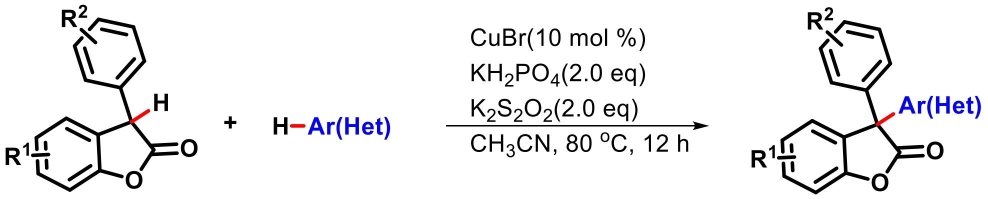
It can be challenging to synthesize unsymmetrical 3,3-disubstituted-benzofuran-2-(3*H*)-one directly from benzofuran-2-(3*H*)-one.

Nucleophilic Phosphine is observed to be an excellent catalyst for addition reaction. Using this method, benzofuranone reacts with alleonates to form unsymmetrical disubstituted benzofuran by a tandem β-umplolang/ γ-umpolang process.[45]



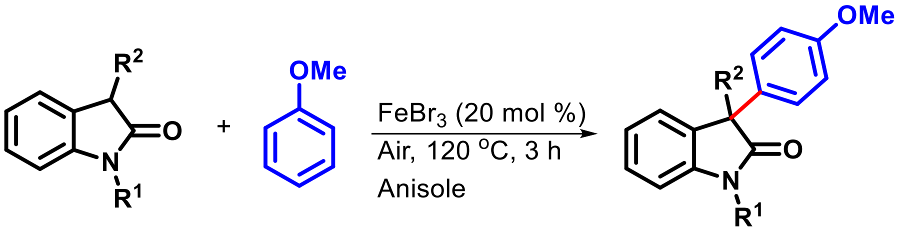
Scheme 1.4.7 Phosphine-catalyzed domino process to synthesize unsymmetrically substituted benzofuranones by Zhou and co-workers.[45]

Cross-dehydrogenative coupling can be a straightforward strategy for C-C bond formation. For coupling reactions, activated sp^3 C-H compounds produce stabilised quaternary carbon centers, and typically, carbon radicals are chosen as a substrate for cross coupling reactions. Kambe and group reported a copper-catalyzed cross-dehydrogenative coupling of benzofuranones with different heterocyclic moieties producing 3,3- diaryl benzofuranones.[46]



Scheme 1.4.8 CDC reactions of benzofuran-2-(3*H*)-ones with heteroarenes.[46]

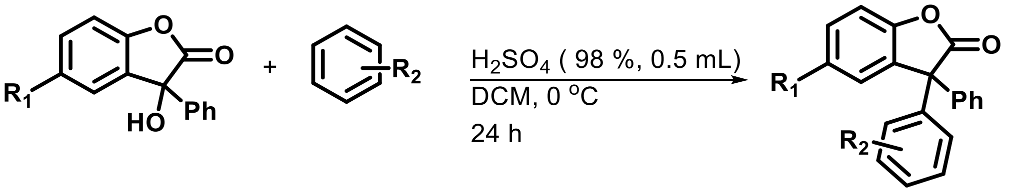
Similarly, Jun Li and co-workers reported a Fe^{II} catalyzed cross-dehydrogenative arylation between oxindoles and arenes. [47]



Scheme 1.4.9 Li's approach of CDC reactions between oxindoles and arenes.[47]

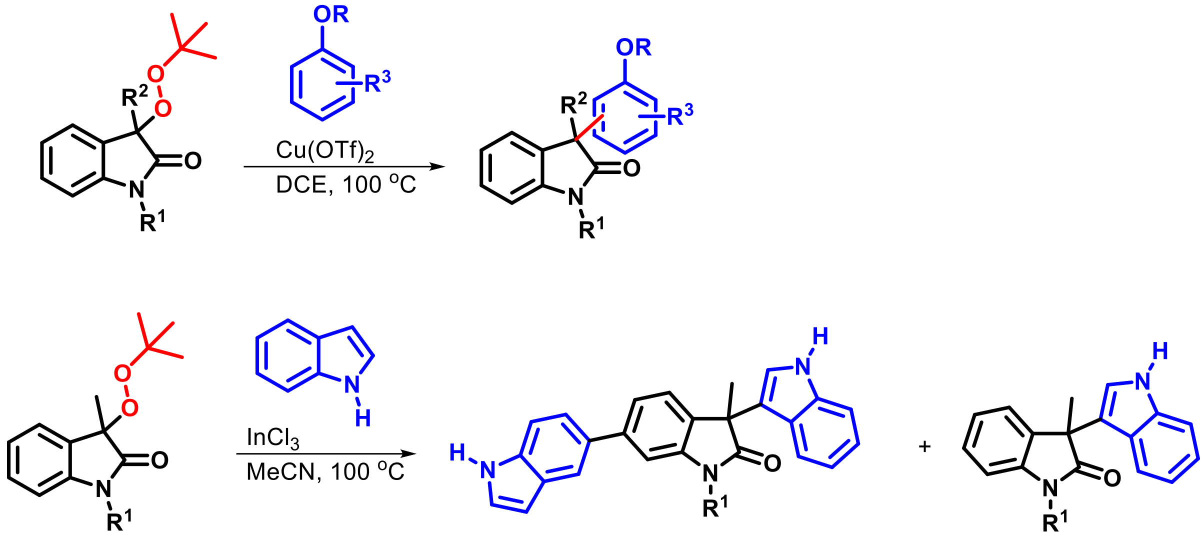
Very recently, C. Kozlowski and group reported Copper catalyzed oxidative arylation of teriary carbon centres in benzouranones. [48]

Furthermore, 3-aryl-3-hydroxy-benzofuran-2(3*H*)-ones are an ideal starting material for the synthesis of 3,3-diarylbenzofuranones by dehydrative substitution of the alcohol. The hydroxy group can be activated and subsequent nucleophilic substitution using arenes leads to the formation of unsymmetrically 3-substituted-3-phenyl-benzofuran-2-(3*H*)-one.[49]



Scheme 1.4.10 Acid-mediated dehydrative substitution for the synthesis of functionalized 3-substituted-3-arylbenzofuran-2(3*H*)-ones by Goswami and group.[49]

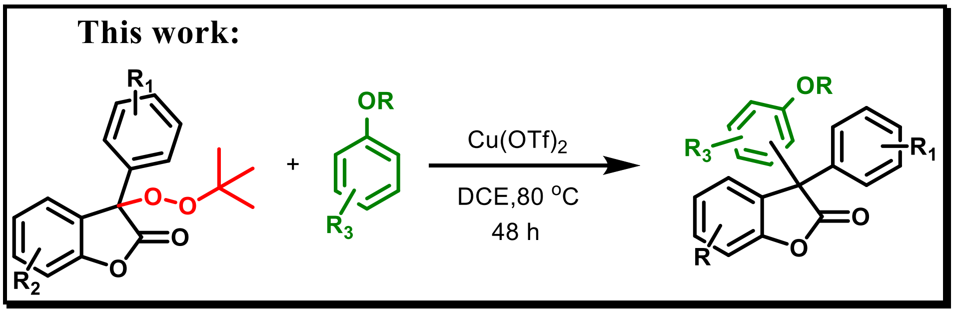
Nucleophilic substitution of a pi activated alcohol using a catalytic Bronsted acid has been reported previously. Then we thought that, the direct reaction of phenol derivatives with peroxybenzofuranone can be an interesting study as it can eliminate the additional step for the formation of 3-hydroxybenzofuranone. Chen and colleagues previously reported, an oxidative coupling rearrangement to functionalize tetrahydro-β-carboline peroxides.[50] Gnanaprakasam group also reported a regiospecific coupling reaction of phenols with peroxyoxindoles.[21,22]



Scheme 1.4.10 Lewis-acid catalyzed functionalization reaction of peroxyoxindoles reported by Gnanaprakasam group.[21,22]

Objective of thesis

3,3-disubstituted benzofuran-2(3*H*)-one framework is a significant structural motif found in many bio-active natural products and pharmaceutically relevant compounds, making it's synthesis extremely desirable. There is additional difficulty in synthesizing it because of its sterically demanding quaternary carbon core. Numerous methods have been studied in this field; however, these methods necessitate the pre-functionalization or modification of substrates, which can be a time-consuming process and costly due to the demand for expensive catalysts. Therefore, new advancements in the construction of scaffolds with functionalized benzofuranones are quite intriguing. Hence, we hypothesized to utilize 3-*tert*-butylperoxy-3-arylbenzofuran-2-(3*H*)-one as one of the substrates. The peroxidation of benzofuranone moiety is an attractive scaffold owing to its important biological properties. Cleavage of the weak O-O bond can result in distinct functionalization and rearrangement reactions. This thesis work is proposed to investigate the functionalization of quaternary carbon centres by using benzofuran-2-(3*H*)-one peroxides to prepare unsymmetrically substituted 3,3-diaryl-benzofuran-2-(3*H*)-one derivatives. Through this study, we were able to use a variety of C-nucleophiles with different molecular skeletons, to establish a new way to construct C-C bonds and construct quaternary stereo-centres.



2.Materials and Methods

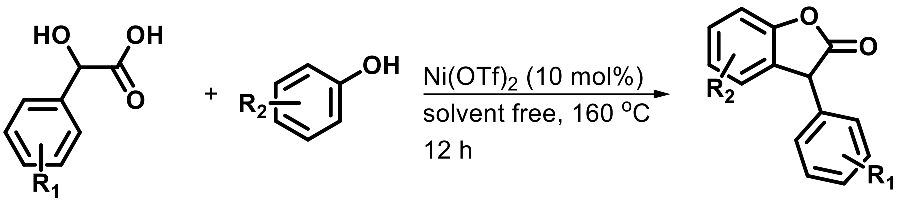
2.1 Material and instrumentation:

All experiments with metal complexes were carried out maintaining a nitrogen environment. Purchased from Sigma-Aldrich, the starting material included phenols, mandelic acid, and *tert*-butyl hydroperoxide (TBHP) 5.0-6.0 M in decane solution. All reactions were carried out in dry solvents. Silica gel (60-120 mesh) was used for column chromatography. Bruker 400 MHz spectrometers were used to record the ^{1}H and ^{13}C NMR spectra at 400 and 100 MHz, respectively. Abbreviations used in NMR follow-up experiments: bs = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The coupling constants were reported in Hz, and all chemical shifts were recorded in ppm. High-resolution mass spectra were recorded by using ionization (ESI-TOF). Single-crystal diffraction analysis data were collected at 100 K with a Bruker APEX-II CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo $K\alpha$ radiation.

2.2 Synthetic procedures:

2.2.1 Preparation of the 3-aryl benzofuran-2(3*H*)-ones: According to the literature, derivatives of 3-aryl benzofuran-2(3*H*)-ones were prepared. [51]

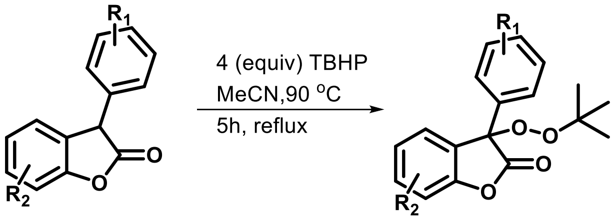
To a 20 mL oven-dried seal tube with a magnetic stirring bar, Mandelic acid (2.7 mmol, 2.0 equiv.), phenol (1.3 mmol, 1.0 equiv), and $Ni(OTf)_2$ (0.27 mmol, 10 mol %) were added. The mixture was stirred vigorously at 160 ℃ for 12 hours under N_2 atmosphere vacuum, and then it was cooled to room temperature. Following the addition of 15 mL of water, the resulting mixture was subjected to extraction with EtOAc (15 mL ×3). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuum. Further purification using flash column chromatography on silica gel and eluting with ethyl acetate/n-hexane (10:90) was required to achieve the pure product of 3-phenyl benzofuran-2(3*H*)-ones.



Scheme 2.2.1 Synthesis of 3-phenyl benzofuran-2(3*H*)-ones.[51]

2.2.2 General procedure for C-H peroxidation of 3-aryl benzofuran-2(3*H*)-ones:[28]

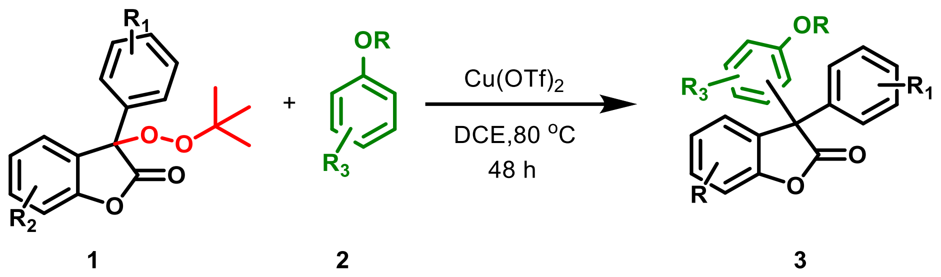
In a 50mL round bottom flask was added 3-arylbenzofuran-2(3*H*)-one (3.51 mmol,1 equiv) in acetonitrile (10mL). 5.0–6.0 M TBHP in decane solution (14.04 mmol, 4 equiv) was added gradually without maintaining any specific parameters, such as an inert environment. The reaction mixture was refluxed for 5 hours at 90℃ in an oil bath. It became, a yellow sticky liquid, which was concentrated under vacuum once the reaction was finished. By using silica gel column chromatography, the residue was immediately purified by using EtOAc/n-hexane (5:95).



Scheme 2.2.2 Peroxidation of 3-aryl benzofuran-2(3*H*)-ones.[29]

2.2.3 General procedure for synthesis of 3-substituted-3-phenylbenzofuran-2(3*H*)-one:

In a sealed tube 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **1** (0.25 mmol, 1 equiv) was added along with the phenol derivative **2** (0.75mmol,3 equiv) in 1,2 dichloroethane solvent. Cu(OTf)$_2$ (0.050 mmol, 0.2 equiv) was then added to it. It was heated at 80 °C for a duration of 48 hours. Finally, the reaction mixture was purified by silica gel column chromatography using ethyl acetate/n-hexane (20:80).



Scheme 2.2.3 Synthesis of 3-substituted-3-phenylbenzofuran-2(3*H*)-one.

2.2.4 Radical quenching experimental procedure:

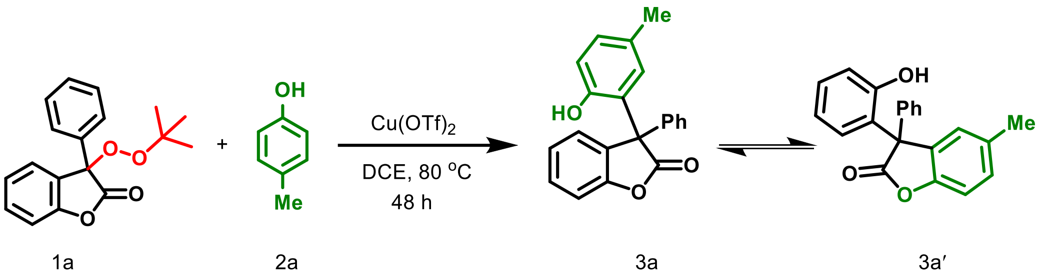
In a resealable vial 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one (0.25 mmol, 1 equiv.), *p*-cresol (0.75 mmol, 3 equiv), $Cu(OTf)_2$ (0.050 mmol, 0.2 equiv), and finally TEMPO (0.75 mmol, 3 equiv) or BHT (0.75 mmol, 3 equiv) were added. Further, DCE was added and the reaction mixture was stirred at 80 °C for 48 hours in a preheated oil bath.

2.2.5 Detection of *iso*-butylene gas using ^1H NMR:

Peroxy-benzofuran-2-one **1a** (20 mg, 0.07mmol, 1 equiv), *p*-cresol **2a** (22 mg, 0.20 mmmol, 3 equiv), $Cu(OTf)_2$ (5 mg, 0.01 mmol, 0.2 equiv) were added to an NMR tube in $CDCl_3$ solvent. A cap was used to properly seal the tube. The reaction mixture was heated at 80 ℃ for 12 hours. Finally, the NMR tube was cooled and subjected to ^1H NMR analysis.

3. Results and Discussion

3.1 Optimization of reaction



Scheme 3.1.1 Reaction of peroxybenzofuran-2-one with *p*-cresol.

Initially, we examined the reaction conditions by using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one and *p*-cresol by taking a 1:1 equivalent as a model substrate. A control experiment was conducted at 80 ℃ in the absence of a catalyst for 24 hours, but no reaction occurred. The cross-coupling product **3a and 3a'** was formed in the presence of catalytic $Cu(OTf)_2$ with 30 % yield.

Further, to improve the yield of product, we have optimized this reaction by varying the amount of catalyst, *p*-cresol, temperature, different catalysts, and solvents. It must be noted that, all the yields shown in the below tables are isolated yields.

Table 3.1.1: Optimization by changing the equivalent of reactants:

Entry	Reactant 1a (Equivalent)	Reactant 2a (Equivalent)	Catalyst amount (mg)	Yield
1	1	1	18	29 %
2	1	2	18	50 %
3	1	3	18	63 %

As it is seen from the observation, using 3 equivalents of *p*-cresol afforded the highest yield when the catalyst is used at 20 mol %. Then, we optimized the reaction by varying the amount of catalyst.

Table 3.1.2: Optimization by changing the amount of catalyst:

Entry	Reactant 1a (Equivalent)	Reactant 2a (Equivalent)	Catalyst amount (mg)	Yield
1	1	3	9	52 %
2	1	3	18	63 %
3	1	3	27	55 %

Product **3a** was obtained with 52 % yield when 10 mol % catalyst was used. An increase in the amount to 20 mol % produces a 63 % yield of the product. However, increasing the concentration to 30 mol% allowed for a cross-coupling product **3a** with a 55 % yield. Therefore, it was determined that the ideal catalyst concentration for this functionalization procedure is 20 mol % $Cu(OTf)_2$.

Table 3.1.3: Temperature optimization:

Entry	Reactant 1 (Equivalent)	Reactant 2 (Equivalent)	Catalyst amount (mg)	Temperature (℃)	Yield
1	1	3	18	RT	No reaction
2	1	3	18	40	No reaction
3	1	3	18	60	31 %
4	1	3	18	80	63 %
5	1	3	18	100	64 %

At room temperature, no product formed from the reaction. 31% yield was obtained by raising the temperature to 60 ℃. Conversely, raising the temperature to 80 ℃ and 100 ℃ produced the product with yields 63 % and 64 % respectively. Thus, 80 ℃ was selected as the ideal temperature.

Table3.1.4: Solvent optimization:

Entry	Catalyst amount (mg)	Temperature	Solvent	Yield
1	18	80	DCE	63 %
2	18	80	ACN	12 %

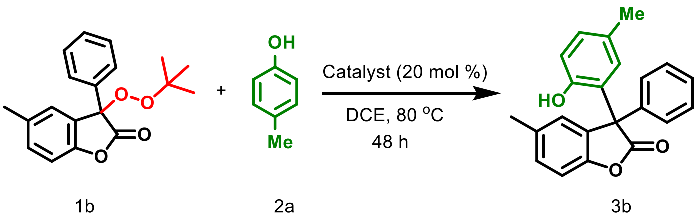
Initially, 1,2 dichloroethane was used as a solvent, which afforded a 61 % yield of the product. A significant decrease in yield was observed when acetonitrile was utilised as a solvent.

Table 3.1.5: Time study:

Entry	Catalyst amount (mg)	Temperature (℃)	Time (h)	Yield
1	18	80	12	12 %
2	18	80	24	35 %
3	18	80	48	63 %

The reaction was continuously stirred for 12 hrs, 24 hrs, and 48 hrs. After 12 hours, 12 % yield was observed; rising to 35 % after 24 hours, and finally 63 % yield was furnished after 48 hours.

Next, we carried out the screening of different catalysts to verify the reaction route, increase in yield, and product formation while maintaining the optimized conditions.



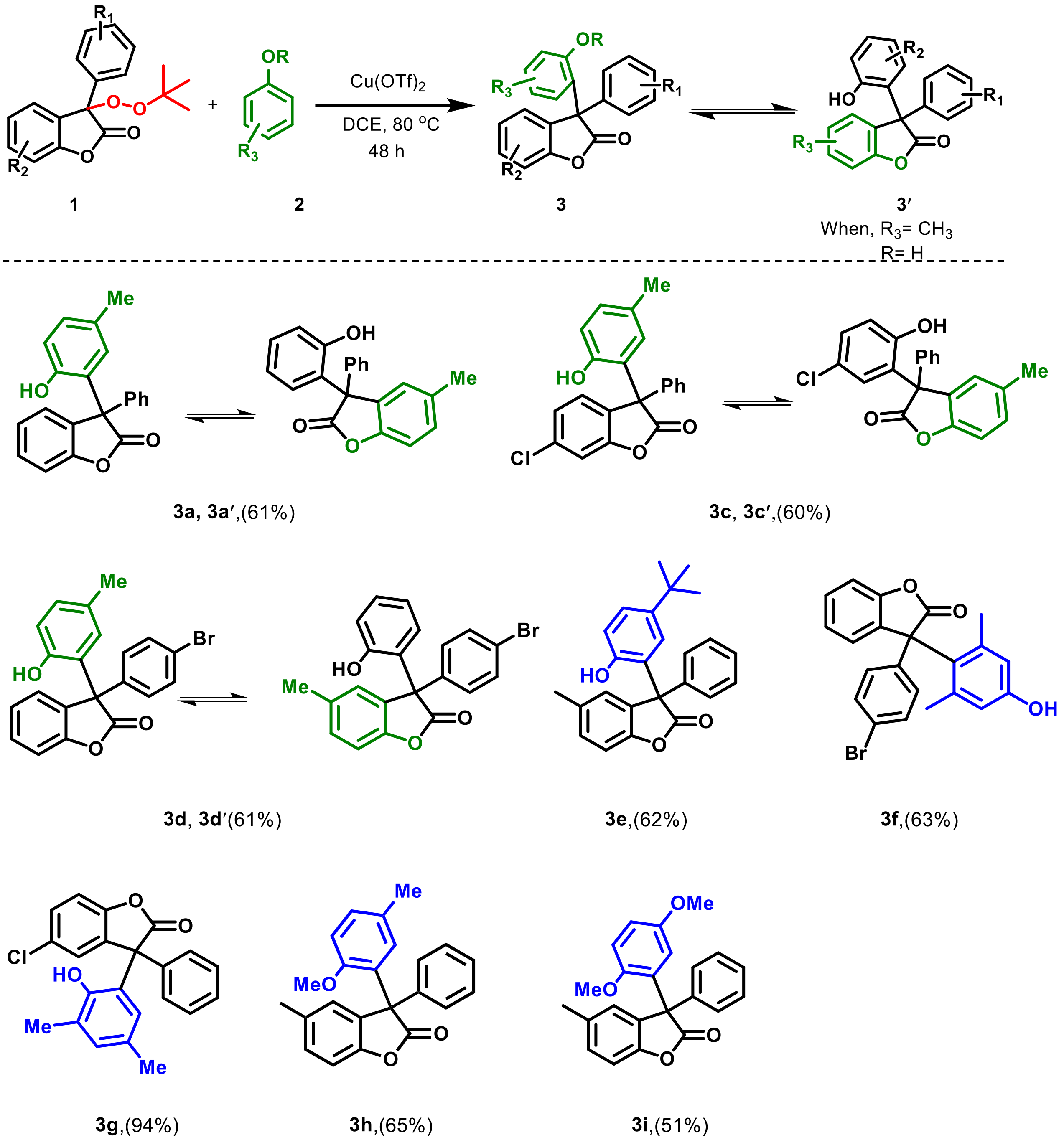
Scheme 3.1.2 Synthesis of 3-substituted-3-phenylbenzofuran-2(3*H*)-one.

Table 3.1.6: Screening of different catalyst:

Entry	Catalyst	Solvent	Temperature	Yield (%)
1.	$In(OTf)_3$	DCE	80 ℃	34 %
2.	$InCl_3$	DCE	80 ℃	33 %
3.	$Cu(OTf)_2$	DCE	80 ℃	70 %
4.	CuI	DCE	80 ℃	26 %
5.	$Sc(OTf)_3$	DCE	80 ℃	37 %
6.	$Sn(OTf)_2$	DCE	80 ℃	46 %
7.	AgOTf	DCE	80 ℃	47 %
8.	$Mn(OTf)_2$	DCE	80 ℃	10 %
9.	$Zn(OTf)_2$	DCE	80 ℃	Trace
10.	Ni(OTf)	DCE	80 ℃	No reaction

For the screening of catalysts, 3-(*tert*-butylperoxy)-5-methyl-3-phenyl benzofuran-2(3*H*)-one **1b** (1 equiv) and *p*-cresol **2a** (3 equiv) was heated to 80 ℃ in DCE solvent. The results showed that, $In(OTf)_3$, and $InCl_3$ afforded 34 % and 33 % product **3b** (entry no. 1,2). Whereas, $Sc(OTf)_3$, $Sn(OTf)_2$ and AgOTf gave 37 %, 46 % and 47 % yield respectively (entry no. 5-7). The highest yield was observed with $Cu(OTf)_2$ (entry no. 3). Alternatively, very trace amounts of product **3b** were generated when $Mn(OTf)_2$ and $Zn(OTf)_2$ were utilized (entry no. 8,9). There was no reaction with $Ni(OTf)_2$ (entry no. 10).

3.2 Substrate scope:



Scheme 3.2.1 Substrate scope for copper-catalyzed cross-coupling between peroxybenzofuran-2-one and phenol derivatives.

Reaction conditions: For 48 hours, a combination of $Cu(OTf)_2$ (20 mol %), compound **1** (0.25 mmol), phenol derivatives (0.75 mmol), and dichloroethane (2mL) was stirred 80 ℃. The yields that have been mentioned are isolated yields.

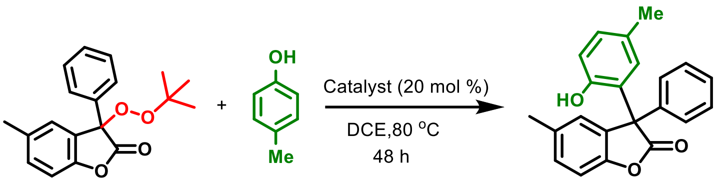
We investigated the range of the reactions with several peroxybenzofuranone compounds at the optimized conditions. The reaction of *p*-cresol with substituted benzofuranones gave good to moderate yield. 5-methyl-3-phenyl benzofuran-2(3*H*)-one gave 70 % yield whereas, 5-chloro-3-phenyl benzofuran-2(3*H*)-one, 5,7-dimethyl-3-phenyl benzofuran-2(3*H*)-one and 3-(4-bromophenyl) benzofuran-2(3*H*)-one afforded 60 %, 60% and 61 % respectively. In the case of **3a**,**a'-3d**,**d'** an inseparable mixture of products were obtained, which is formed from **3a-d**, via the attack of the hydroxy group of *p*-cresol to the carbonyl carbon of the benzofuranone ring, followed by a ring opening process to get **3a'-d'**. An equilibrium has been established between the two products and it can be observed from the ^{1}H and ^{13}C NMR spectra (**figure 7.1-7.8**). The structure of the rearranged product has been confirmed by single-crystal diffraction data (**figure 7.19**).

The reaction of 3-(4-bromophenyl)-3-(*tert*-butylperoxy)-benzofuran-2(3*H*)-one with 3,5-dimethyl phenol afforded **3f** in 62 % yield, while interestingly, reacting with 2,4 - dimethyl phenol produced **3g** in 94 % yield. Further, 4-methyl anisole afforded 65 % yield of product **3h** and the yield decreased to 51 % when 4-dimethoxybenzene is reacted with **1a** to afford **3i**.

3.3 Mechanistic studies:

Several control experiments were carried out to further explain the process of the functionalization at the quaternary center of benzofuran-2-one systems and to gain insight into the reaction pathway.

i) When three equivalents of TEMPO was added, the reaction was completely suppressed, and the yield of **3b** significantly decreased when BHT was employed, indicating that the reaction took a radical path.



1a 2a 3a

Radical Scavenger(2.0 eq)	Yield
BHT	Trace
TEMPO	No Reaction

Scheme 3.3.1 Radical quenching experiment.

ii) Notable peaks were observed at 4.83 ppm (brs) and 1.71 (brs) when the NMR tube containing the reaction mixture was subjected to ^{1}H NMR (see experiment **2.2.5**), which indicates the presence of isobutylene gas (**figure 3.3.1**). The paramagnetic nature of copper accounts for the observed broad singlet peak.

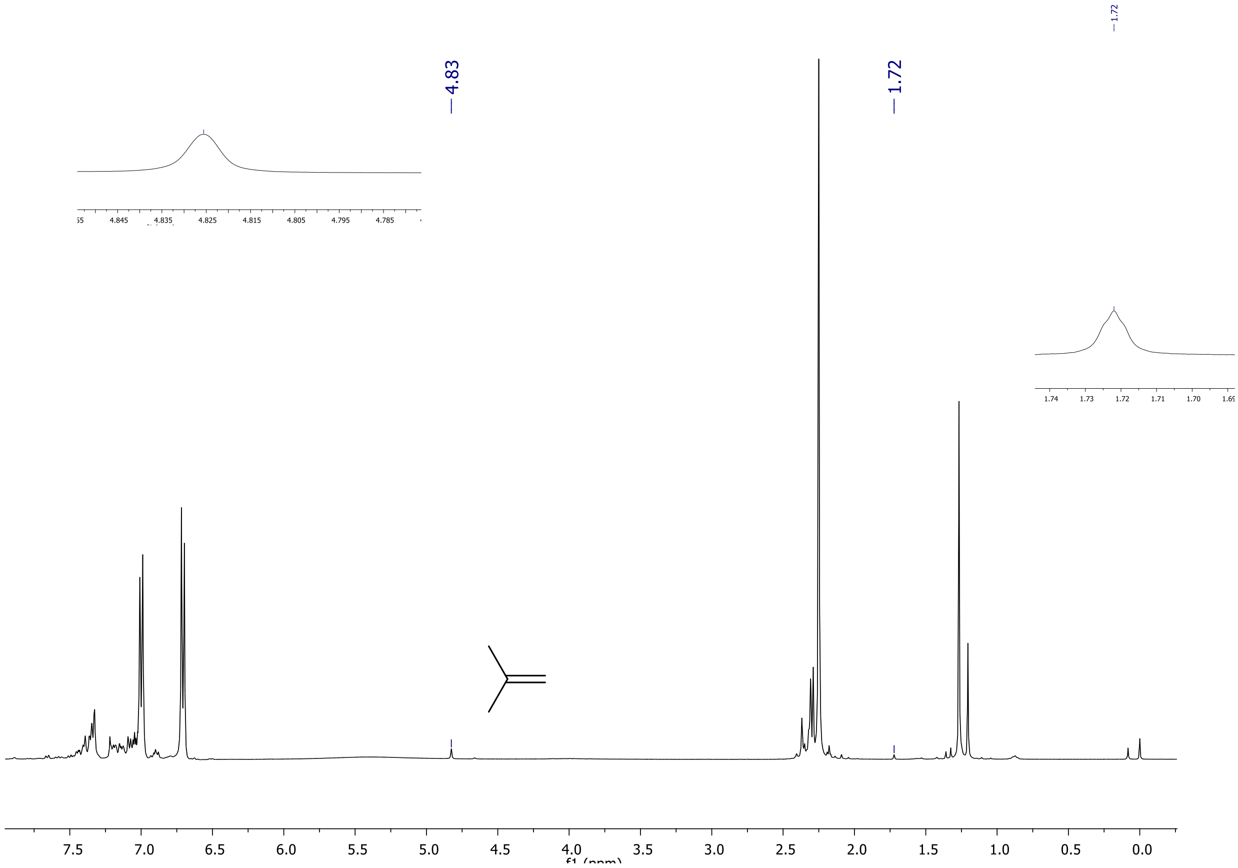
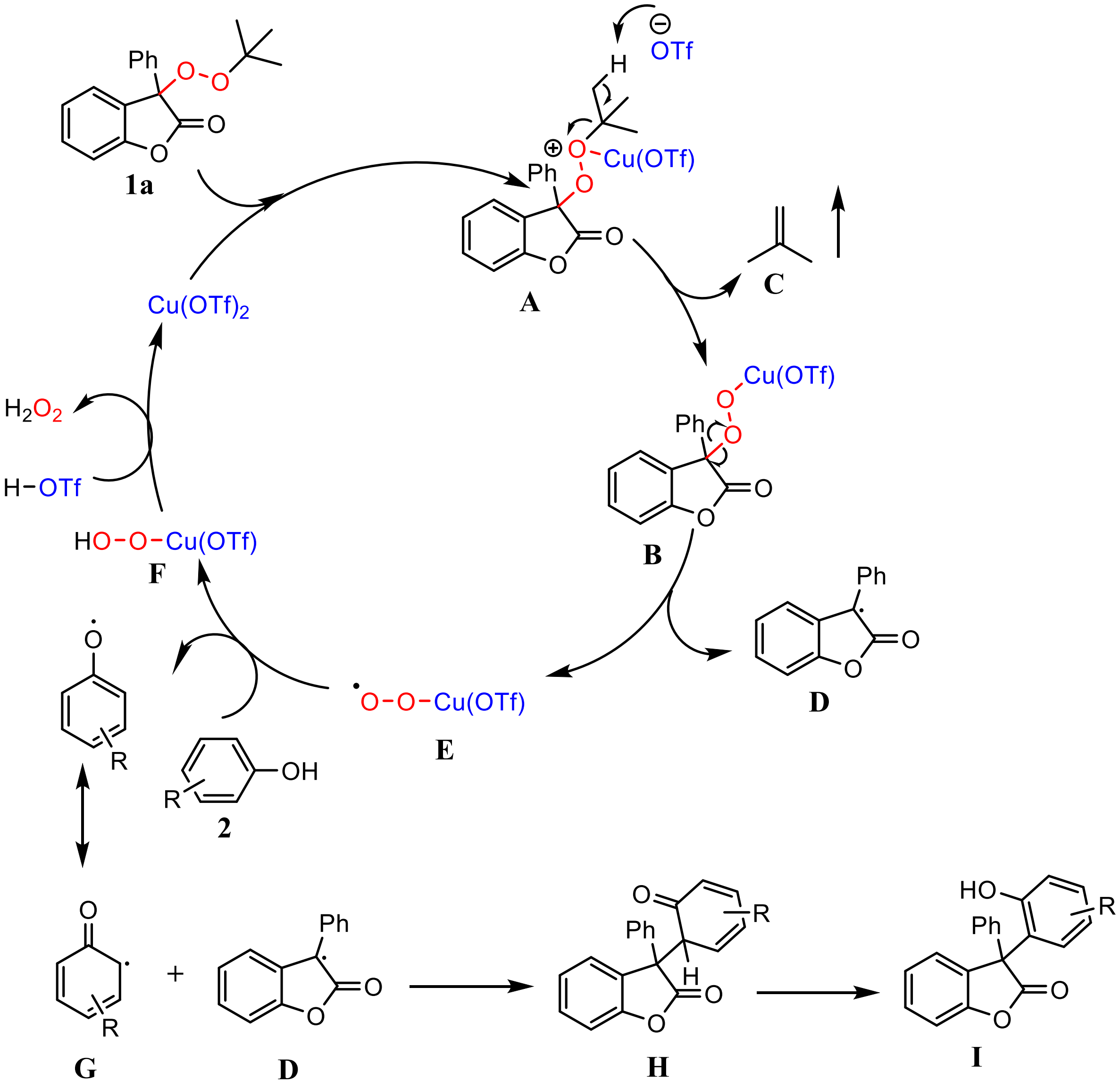


Figure 3.3.1 Detection of iso-butylene gas

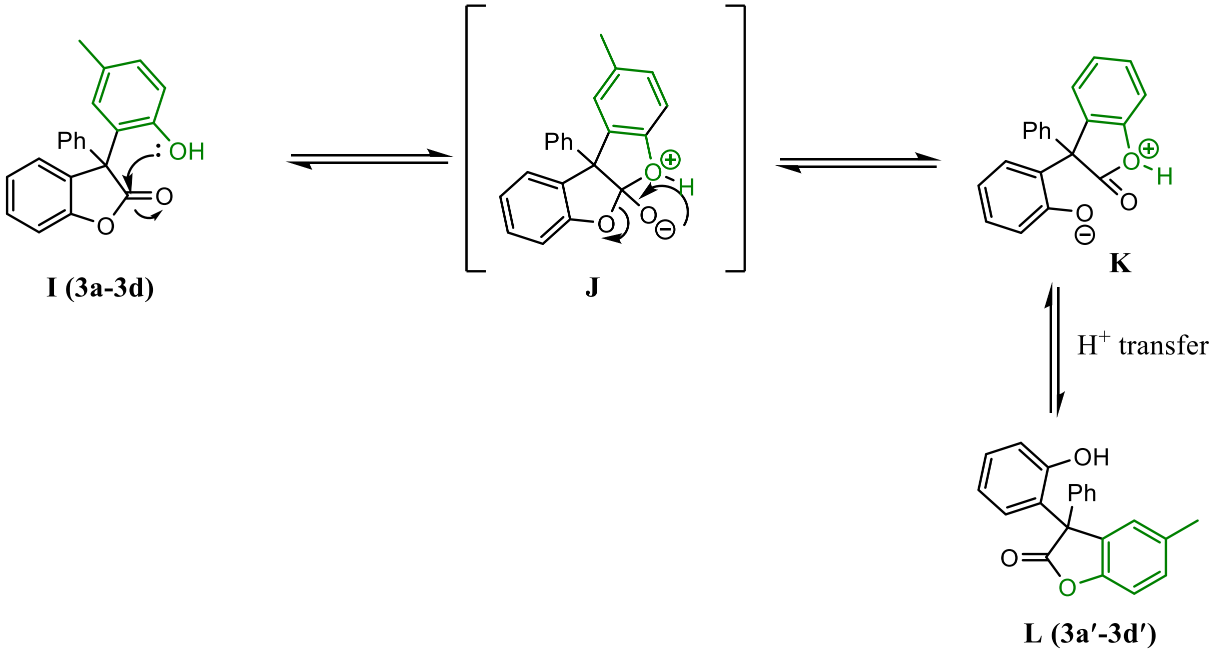
3.4 Plausible reaction mechanism:

After performing few mechanistic studies and going through literature a plausible mechanism was depicted. The reaction was suppressed in presence of TEMPO which proves it follows a radical path. $Cu(OTf)_2$ can facilitate single electron transfer and expand it’s coordination sphere by one.[52] The lactone ring exhibits unusual radical stabilization and it is unreactive toward oxygen.[53] Therefore, complex **A** is formed in the first step when $Cu(OTf)_2$ coordinates with the peroxy oxygen in compound **1a**. Subsequently, the trifluoromethane sulfonate anion abstracts one proton, releasing isobutylene gas **C** and producing complex **B**. One can prove the liberation of isobutylene using ^{1}H NMR spectra. Then, the C-O bond of the peroxy group was homolytically cleaved with a generation of a copper(II) peroxy radical **E** and radical **D**. The stability of radical **D** can be explained by the co-planarity of the attached aromatic ring which maximizes the delocalization of unpaired electrons on to the system. The addition of a phenol derivative **2** causes it to oxidise, producing a phenoxyl radical **G**. The proton is transferred to the Copper(II) peroxy radical, resulting in the production of Copper(II) hydroperoxide. In order to produce the desired product, the phenoxyl radical participates in cross-coupling with **D** to form **H**, which subsequently gains aromaticity by forming **I**. The final step involves the regeneration of catalyst the Copper(II) hydroxide species **F** reacts combines with triflic acid to release H_2O_2.



Scheme 3.3.1 Plausible reaction pathway.

Now, In case of **3a,a'-3d,d'**, inseperable mixture of products are obtained (**scheme 3.2.1**).One possible explanation is that, copper triflate coordinates with the carbonyl oxygen in the cross-coupled product **I** produced when peroxybenzofuranone interacted with *p*-cresol, causing the carbon centre to become electron deficient. The carbonyl carbon is subsequently attacked by the lone pair of the hydroxy group of *p*-cresol, forming a tetrahedral intermediate **J**. Further, the intermediate undergoes rearrangement, which causes the benzofuranone ring to open **K**. Ultimately, there is a proton transfer that forms **L**. The ring opening process is reversible and thus, an equilibrium is established between product **I** and **L** (for **3a,a'-3d,d')**. The formation of **L** has been confirmed by single crystal X-ray diffraction data (**figure 7.19**).

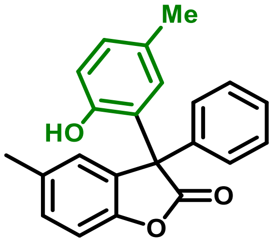


Scheme 3.3.2 Plausible reaction mechanism for the formation of **3a'-3d'**.

4. Conclusion

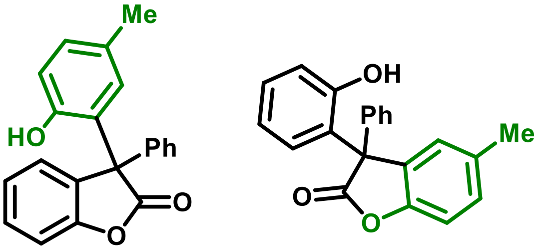
In summary, we have developed a cross-coupling reaction between peroxy benzofuranone and the phenol derivatives to deliver an unsymmetrically substituted, biologically active 3,3-disubstituted benzofuran-2(3*H*)-one derivative. We have optimized several parameters such as catalyst, concentration, solvents, and temperature and found that copper catalyst was found to be the best catalyst at 80 °C in DCE solvent. All the products were characterized by NMR and mass analysis. Further, the structure of the product was supported by X-ray crystallography. Furthermore, the attained optimized reaction condition performed well with a range of substrates in moderate to excellent yield. Additional control experiments and literature reviews were conducted to investigate the mechanism. The reaction goes via the generation of a C3 radical and phenoxy radical, followed by recombination of these radicals to form 3,3-disubstituted benzofuran-2(3*H*)-one derivatives.

5. Analytical Data of Products



3b

3-(2-hydroxy-5-methylphenyl)-5-methyl-3-phenylbenzouran-2(3*H*)-one (3b): Prepared according to general procedure **2.2.3**, using 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzouran-2(3*H*)-one **1b** (78 mg, 0.25 mmol), and *p*-cresol (81 mg, 0.75 mmol) to afford 3-(2-hydroxy-5-methylphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **3b** (57 mg, 70% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 20:80). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (s, 1H), 7.45 – 7.38 (m, 4H), 7.16 (d, *J* = 3.7 Hz, 2H), 6.94 (d, *J* = 5.6 Hz, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.47 (d, *J* = 1.5 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 177.1, 152.2, 151.0, 137.2, 133.2, 130.0, 129.4, 129.2, 128.7, 128.6, 128.3, 128.2, 127.3, 126.1, 115.3, 109.9, 57.5, 20.6, 20.4; HRMS (ESI-TOF); m/z calculated for $C_{22}H_{19}O_3$ $(M+H)^+$ 331.1334, found: 331.1333.

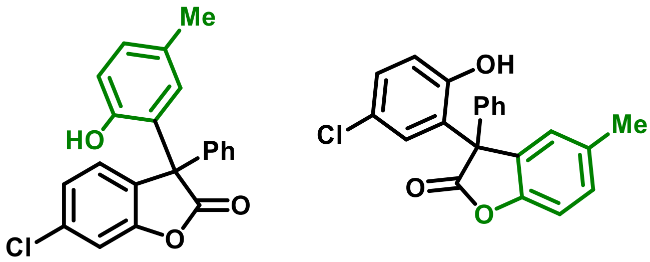


(Inseperable mixture)

3a, 3a′

3-(2-hydroxy-5-methylphenyl)-3-phenylbenzofuran-2(3*H*)-one (3a)

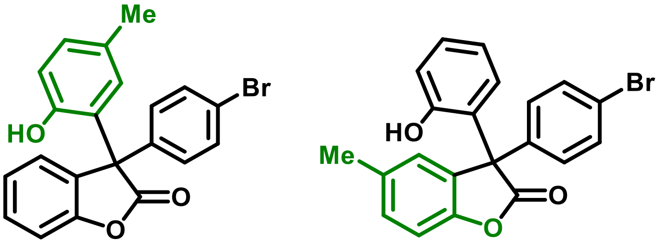
3-(2-hydroxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one (3a'): Prepared according to general procedure **2.2.3**, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **1a** (74 mg, 0.25 mmol) and *p*-cresol (81 mg, 0.75 mmol) to afford 3-(2-hydroxy-5-methylphenyl)-3-phenylbenzofuran-2(3*H*)-one **3a** and 3-(2-hydroxy-5-methylphenyl)-3-phenylbenzofuran-2(3*H*)-one **3a'** (53 mg, 63% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 20:80); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.00 (s, 1H), 9.76 (s, 1H), 7.45 – 7.35 (m, 9H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.11 (m, 5H), 6.98 – 6.90 (m, 2H), 6.78 – 6.62 (m, 4H), 6.48 (d, *J* = 1.6 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 177.4, 177.2, 154.9, 153.4, 152.6, 151.4, 137.5, 137.5, 133.6, 130.6, 130.3, 129.9, 129.8, 129.7, 129.2, 129.4, 129.3, 129.1, 129.1, 129.0, 128.9, 128.7, 128.6, 127.7, 126.5, 126.4, 124.4, 119.3, 115.8, 115.7, 110.6, 110.3, 21.0, 20.8; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}O_3$ $(M+H)^+$ 317.1178, found: 317.1172.



(Inseperable mixture)

3c, 3c′

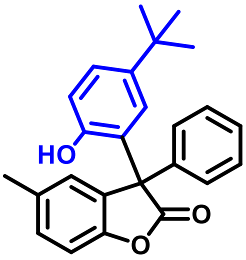
6-chloro-3-(2-hydroxy-5-methylphenyl)-3-phenylbenzofuran-2(3*H*)-one (3c):
3-(5-chloro-2-hydroxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one(3c')
Prepared according to general procedure **2.2.3**, using 3-(*tert*-butylperoxy)-5-chloro-3-phenylbenzofuran-2(3*H*)-one (83 mg, 0.25 mmol) and *p*-cresol (81 mg, 0.75 mmol) to afford 6-chloro-3-(2-hydroxy-5-methylphenyl)-3-phenylbenzofuran-2(3*H*)-one **3c** and 3-(5-chloro-2-hydroxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **3c'** (52 mg, 60% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 15:85 to 20:80). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.39 (s, 1H), 9.86 (s, 1H), 7.47 – 7.38 (m, 6H), 7.27 – 7.14 (m, 3H), 7.02 (s, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 2.28 (s, 3H), 2.08 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 177.1, 152.2, 151.0, 137.2, 133.2, 130.0, 129.4, 129.2, 128.7, 128.6, 128.3, 128.2, 127.3, 126.1, 115.3, 109.9, 57.5, 20.6, 20.4; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{16}ClO_3$ (M+H)$^+$ 351.0788, found: 351.0789.



(Inseperable mixture)

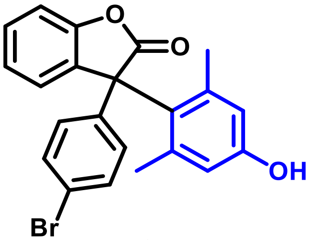
3d, 3d′

3-(4-bromophenyl)-3-(2-hydroxy-5-methylphenyl)benzofuran-2(3*H*)-one (3d)
3-(4-bromophenyl)-3-(2-hydroxyphenyl)-5-methylbenzofuran-2(3*H*)-one (3d'):
Prepared according to general procedure **2.2.3**, using 3-(4-bromophenyl)-3-(*tert*-butylperoxy)benzofuran-2(3*H*)-one (94 mg, 0.25 mmol) and *p*-cresol (81 mg, 0.75 mmol) to afford 3-(4-bromophenyl)-3-(2-hydroxy-5-methylphenyl)benzofuran-2(3*H*)-one **3d** and 3-(4-bromophenyl)-3-(2-hydroxyphenyl)-5-methylbenzofuran-2(3*H*)-one **3d'** (57 mg, 61% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 15:85 to 20:80); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.06 (s, 1H), 9.82 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 3H), 7.41 – 7.13 (m, 10H), 6.93 (s, 1H), 6.79 – 6.62 (m, 4H), 6.49 (s, 1H), 2.27 (s, 3H), 2.10 (s, 2H).; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 176.6, 176.4, 154.2, 152.8, 151.9, 150.8, 136.5, 133.3, 131.4, 130.7, 129.4, 129.2, 129.0, 128.8, 127.9, 127.6, 127.4, 125.9, 125.7, 124.1, 121.7, 118.9, 115.3, 110.2, 109.9, 57.0, 56.9, 20.4, 20.2; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{16}BrO_3$ (M+H)$^+$ 395.0283, found: 395.0283.



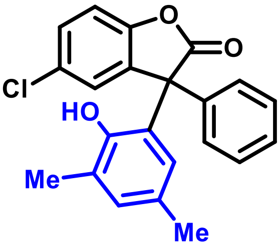
3e

3-(5-(*tert*-butyl)-2-hydroxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one (3e): Prepared according to general procedure **2.2.3**, using 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzouran-2(3*H*)-one **1b** (78 mg, 0.25 mmol), and 4-(*tert*-butyl)phenol (112 mg, 0.75 mmol) to afford 3-(5-(*tert*-butyl)-2-hydroxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **3e** (57 mg, 62% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 15:75); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (s, 1H), 7.40 (d, *J* = 4.0 Hz, 4H), 7.20 – 7.10 (m, 4H), 6.96 – 6.89 (m, 1H), 6.66 (dd, *J* = 16.5, 7.9 Hz, 2H), 6.51 (s, 1H), 2.28 and 2.08 (s, 3H), 1.23 (s, 3H),1.08 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 177.1, 152.1, 152.1, 151.0, 150.9, 146.0, 140.7, 137.2, 133.1, 130.0, 129.7, 129.5, 129.2, 128.7, 128.6, 128.6, 128.4, 128.2, 128.2, 128.1, 127.7, 127.2, 126.1, 125.6, 125.5, 122.3, 115.3, 114.8, 109.9, 109.6, 57.7, 34.4, 33.7, 31.3, 31.2, 20.6, 20.4; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{24}O_3Na$ (M+Na)$^+$ 395.1622, found: 395.1629.



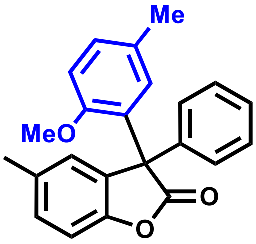
3f

3-(4-bromophenyl)-3-(4-hydroxy-2,6-dimethylphenyl)benzofuran-2(3*H*)-one (3f): Prepared according to general procedure **2.2.3** using, 3-(4-bromophenyl)-3-(*tert*-butylperoxy)benzofuran-2(3*H*)-one (94 mg, 0.25 mmol) and 3,5-dimethylphenol (122 mg, 0.75 mmol) to afford 3-(4-bromophenyl)-3-(4-hydroxy-2,6-dimethylphenyl) benzofuran-2(3*H*)-one **3f** (62 mg, 63% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 20:80); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.02 (s, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.22 – 7.14 (m, 2H), 6.96 (s, 1H), 6.88 – 6.83 (m, 1H), 6.76 (dd, *J* = 17.1, 8.3 Hz, 3H), 2.32 (s, 3H), 1.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 177.4, 155.2, 153.8, 139.6, 135.8, 135.6, 132.1, 130.7, 129.7, 127.4, 126.5, 124.2, 122.4, 118.9, 116.0, 109.0, 57.8, 21.5, 18.1; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{18}BrO_3$ (M+H)$^+$ 409.0439, found: 409.0435.



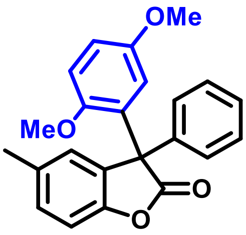
3g

5-chloro-3-(2-hydroxy-3,5-dimethylphenyl)-3-phenylbenzofuran-2(3*H*)-one (3g): Prepared according to general procedure **2.2.3**, using 3-(*tert*-butylperoxy)-5-chloro-3-phenylbenzofuran-2(3*H*)-one (83 mg, 0.25 mmol) and 2,4-dimethyl phenol (122 mg, 0.75 mmol) to afford 5-chloro-3-(2-hydroxy-3,5-dimethylphenyl)-3-phenylbenzofuran-2(3*H*)-one **3g** (85 mg, 94% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 20:80); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.44 (s, 1H), 7.40 (d, *J* = 3.2 Hz, 3H), 7.19 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.01 (s, 1H), 6.80 – 6.72 (m, 3H), 6.56 (d, *J* = 2.4 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 176.5, 153.6, 149.6, 136.5, 133.2, 131., 130.61, 129.0, 128.9, 128.8, 128.7, 128.6, 123.6, 122., 119.53, 117.1, 57, 20.6, 14.7; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{18}ClO_3$ (M+H)$^+$ 365.0944, found: 365.0943.



3h

3-(2-methoxy-5-methylphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one (3h): Prepared according to general procedure 2.2.3, using 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzouran-2(3*H*)-one (78 mg, 0.25 mmol) and 1-methoxy-4-methylbenzene (91 mg, 0.75 mmol) to afford 3-(2-methoxy-5-methylphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **3h** (55 mg, 65 % yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 20:80); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (s, 1H), 7.38 – 7.34 (m, 3H), 7.26 (s, 1H), 7.09 (ddd, *J* = 17.2, 11.9, 4.7 Hz, 3H), 6.87 (d, *J* = 1.1 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 3.60 (s, 3H), 2.32 (s, 3H), 2.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 178.1, 154.9, 151.7, 137.6, 133.8, 131.5, 130.4, 130.3, 130.2, 129.6, 129.4, 129.3, 128.5, 128.2, 126.4, 112.5, 110.1, 58.0, 56.1, 21.3, 20.9; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{21}O_3$ (M+H)$^+$ 317.1177, found: 317.1531.



3i

3-(2, 5-dimethoxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one (3i): Prepared according to general procedure 2.2.3, using 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzouran-2(3*H*)-one (78 mg, 0.25 mmol) and 1,4-dimethoxybenzene (103 mg, 0.75 mmol) to afford 3-(2, 5-dimethoxyphenyl)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **3i** (44 mg, 51% yield) as a white solid after purification by silica gel column chromatography (EtOAc: n-hexane= 15:75); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.35 (dt, *J* = 4.8, 3.1 Hz, 3H), 7.13 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.80 (d, *J* = 2.4 Hz, 2H), 6.46 – 6.45 (m, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.6, 153.6, 151.4, 151.0, 137.0, 133.2, 132.9, 129.9, 129.3, 129.2, 128.4, 128.1, 126.2, 116.6, 113.4, 112.7, 110.0, 77.2, 57.8, 56.4, 55.5, 21.1; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{20}O_4Na$ $(M+Na)^+$ 383.1259, found: 382.1259.

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7. Appendix

Copies of 1H and 13C{1H} NMR spectra of representative compounds.

Entry	**Figure no.**	**NMR Data**	**Page no**
3b	7.1 & 7.2	^{1}H & ^{13}C{^{1}H}	42
3a, 3a'	7.3 & 7.4	^{1}H & ^{13}C{^{1}H}	43
3c, 3c'	7.5 & 7.6	^{1}H & ^{13}C{^{1}H}	44
3d, 3d'	7.7 & 7.8	^{1}H & ^{13}C{^{1}H}	45
3e	7.9 & 7.10	^{1}H & ^{13}C{^{1}H}	46
3f	7.11 & 7.12	^{1}H & ^{13}C{^{1}H}	47
3g	7.13 & 7.14	^{1}H & ^{13}C{^{1}H}	48
3h	7.15 & 7.16	^{1}H & ^{13}C{^{1}H}	49
3i	7.17 & 7.18	^{1}H & ^{13}C{^{1}H}	50
3a'	7.19	Crystal structure	51

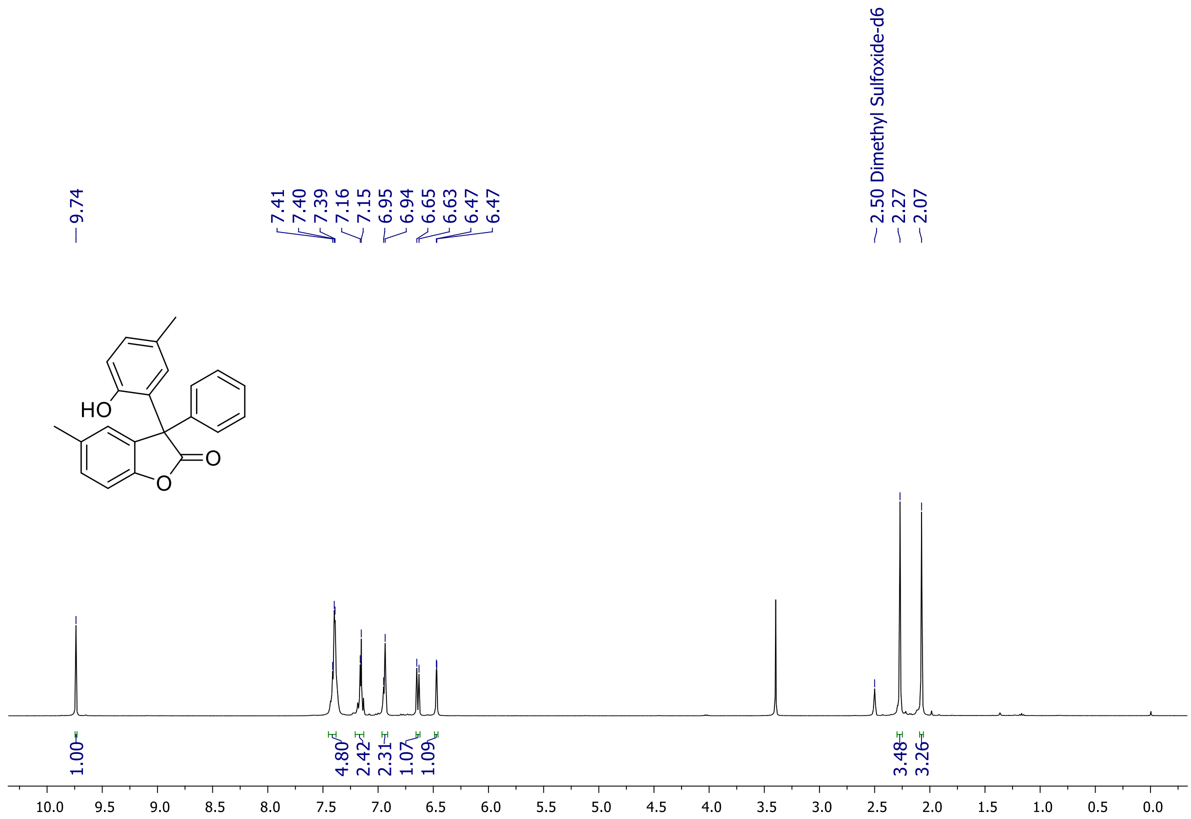

Figure 7.1. ^{1}H NMR of **3b**, 400 MHz, DMSO-d_6

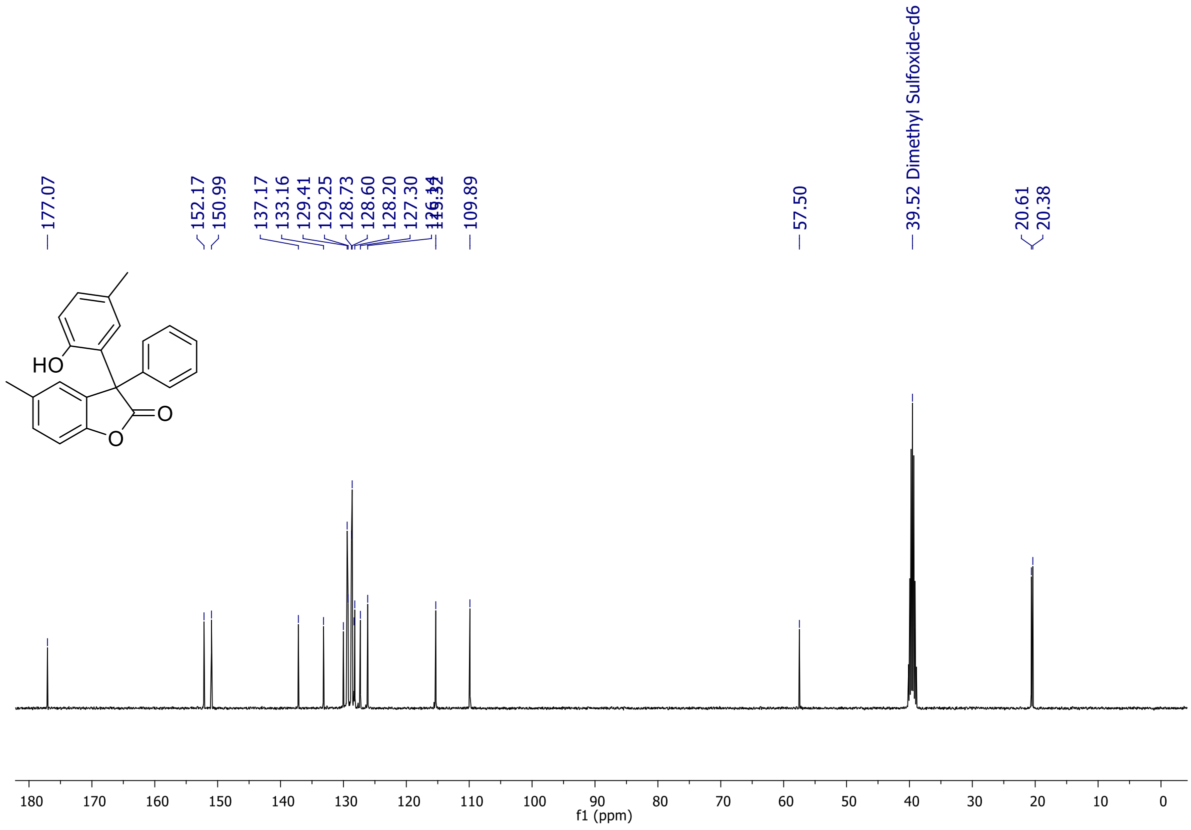

Figure 7.2. ^{13}C{^{1}H} NMR of **3b**, 100 MHz, DMSO-d_6

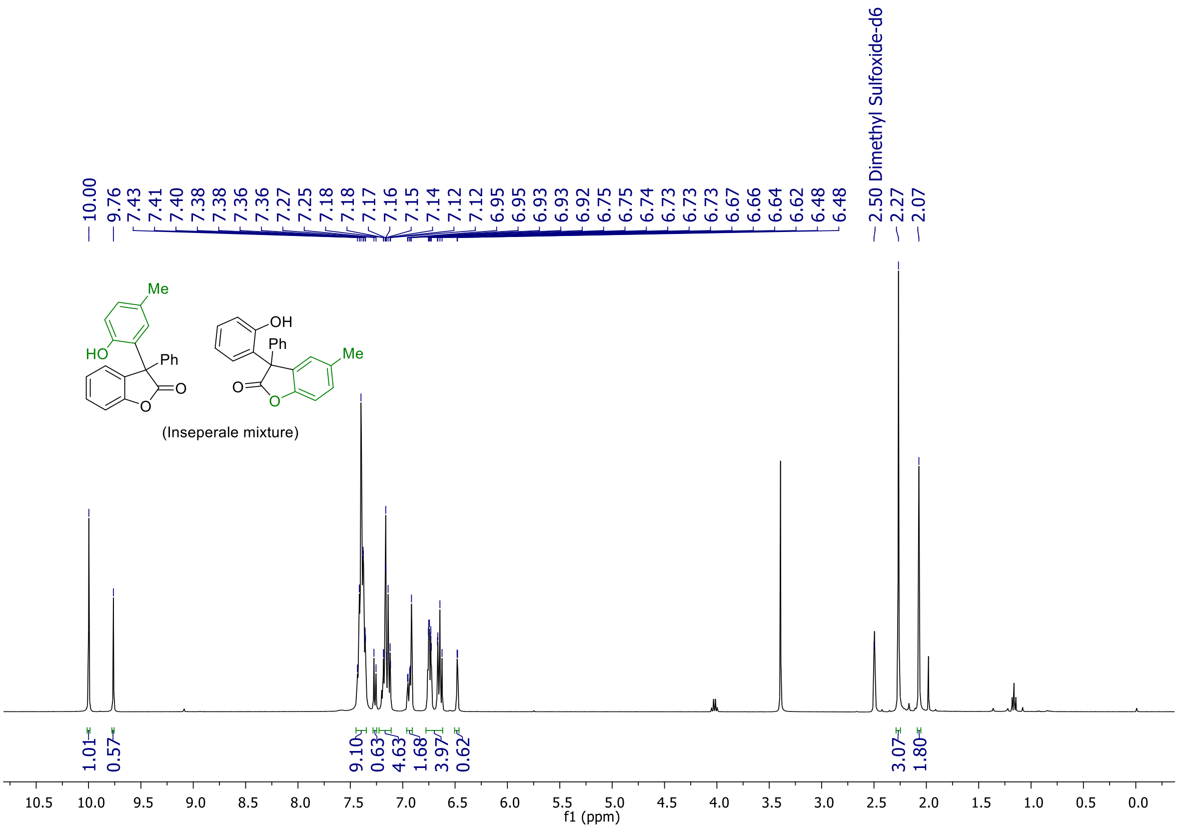

Figure 7.3. ^{1}H NMR of **3a**, 400 MHz, DMSO-d$_6$

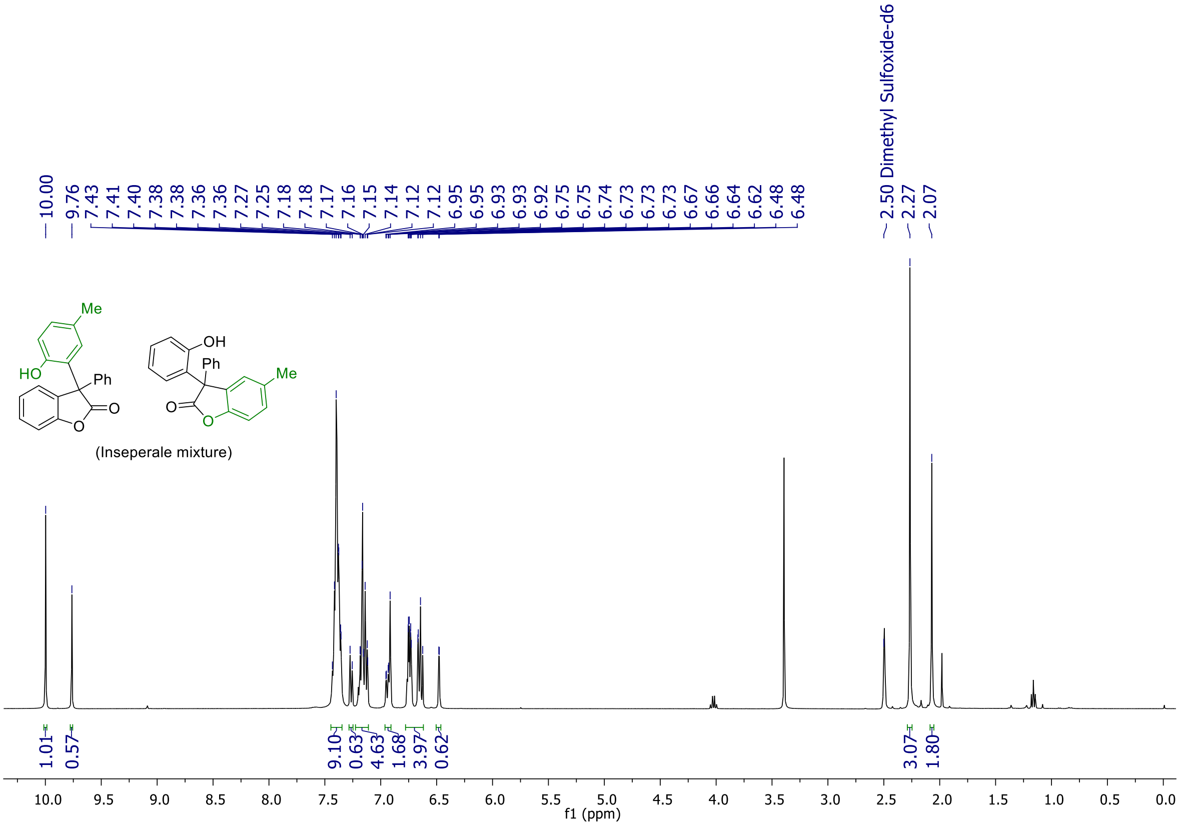

Figure 7.4. ^{13}C{^{1}H} NMR of **3a**, 100 MHz, DMSO-d$_6$

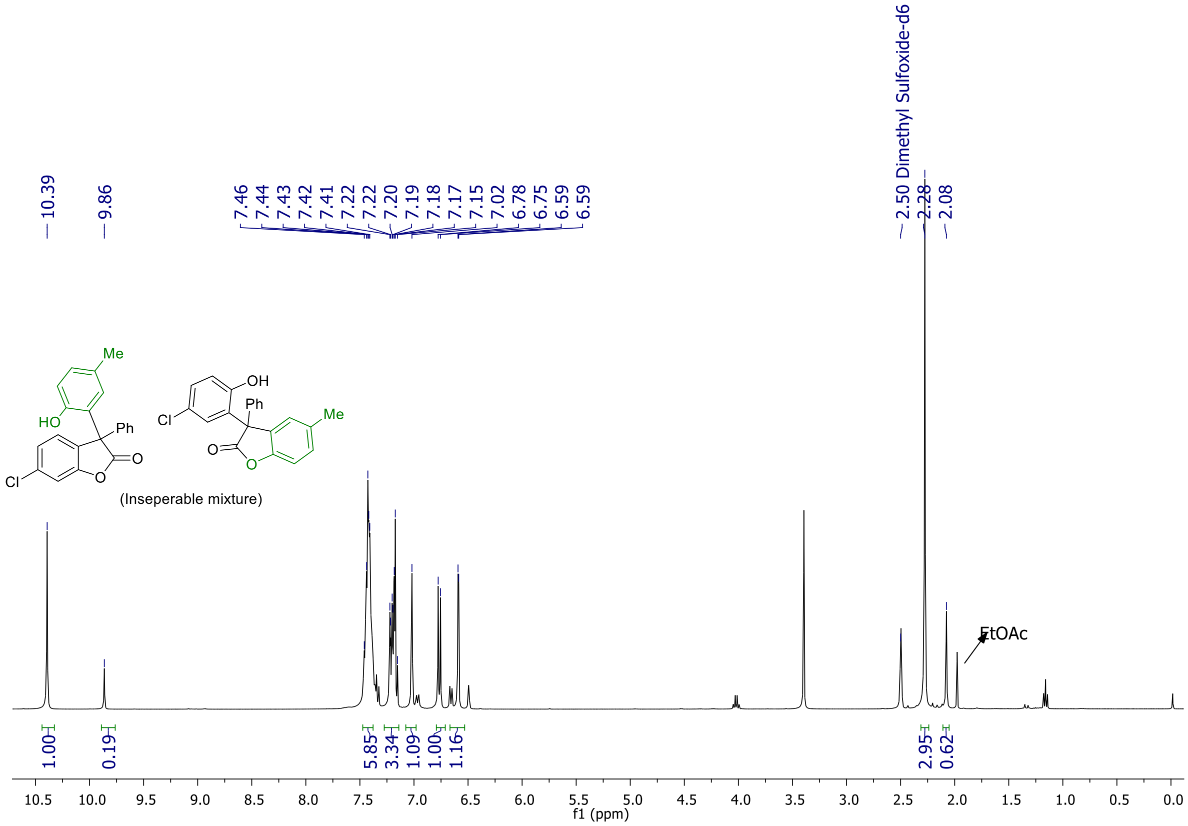

Figure 7.5. ^{1}H NMR of **3c**, 400 MHz, DMSO-d$_6$

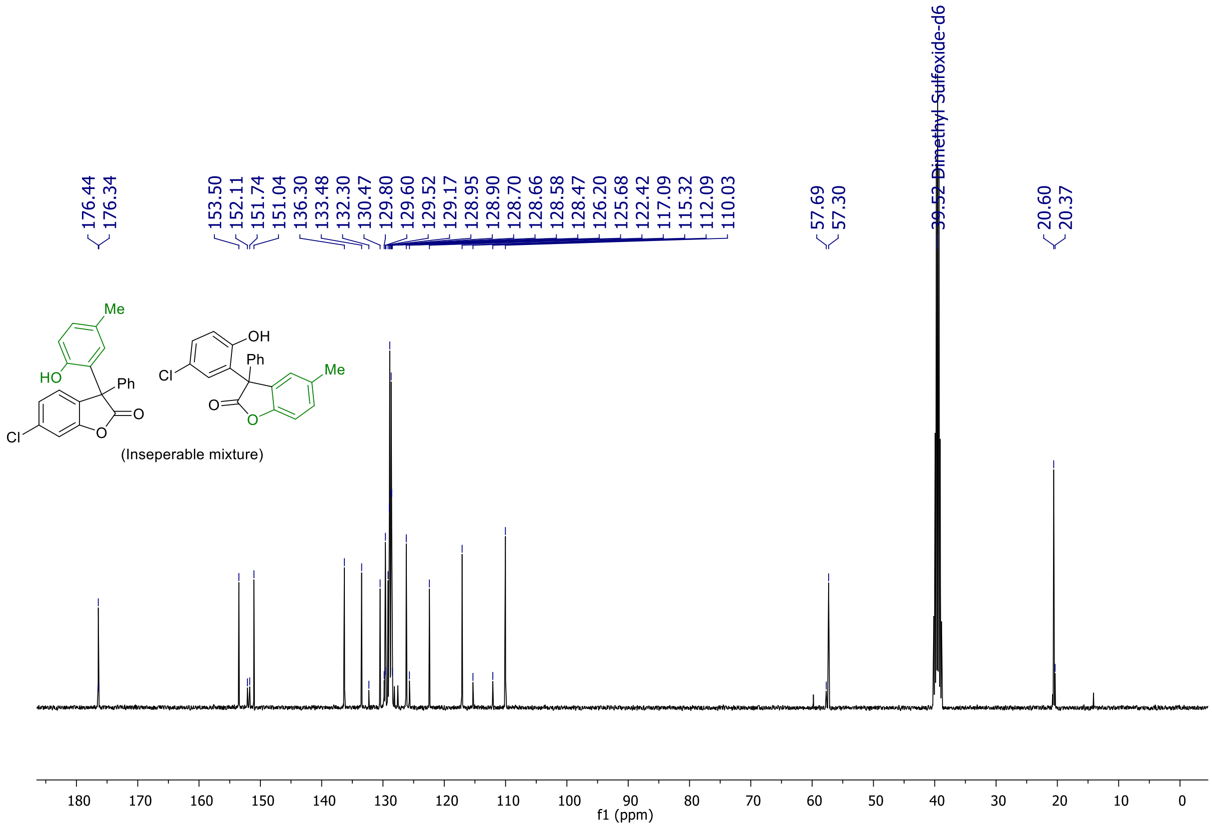

Figure 7.6. ^{13}C{^{1}H} NMR of **3c**, 100 MHz, DMSO-d$_6$

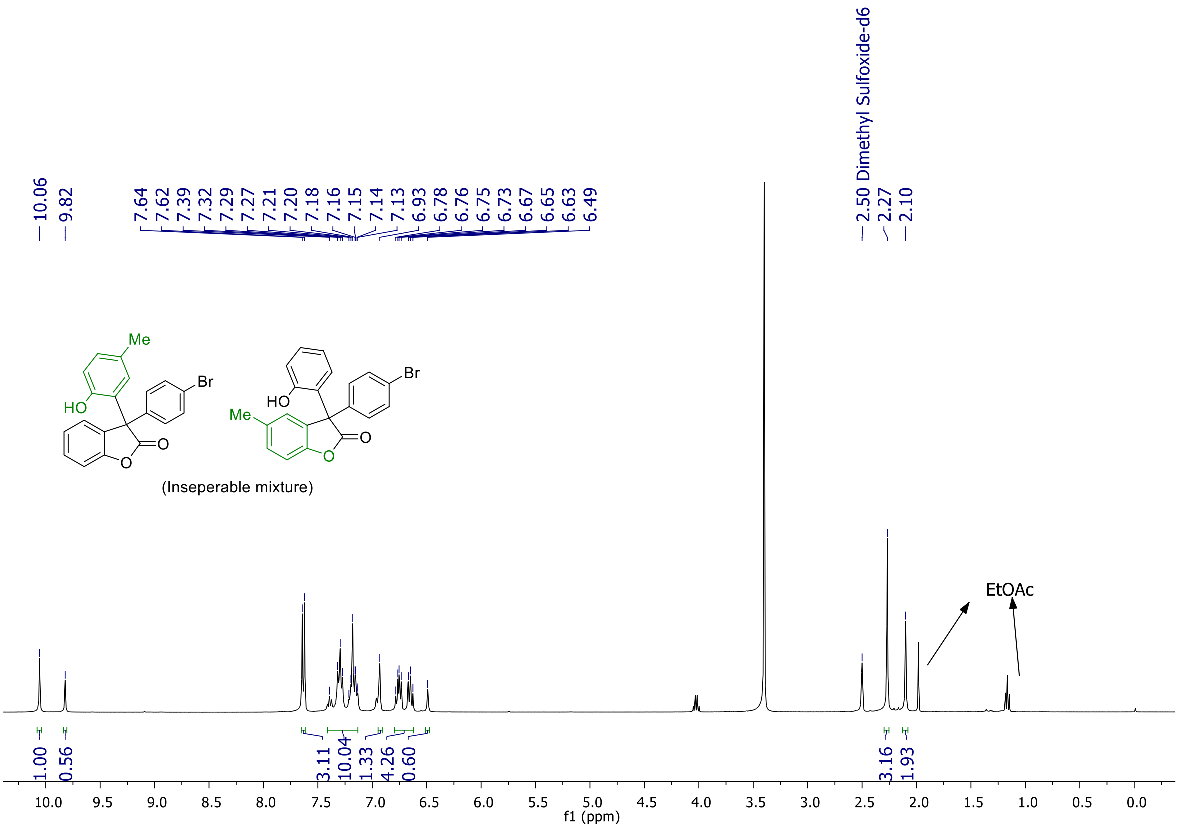

Figure 7.7. ^{1}H NMR of **3d**, 400 MHz, DMSO-d$_6$

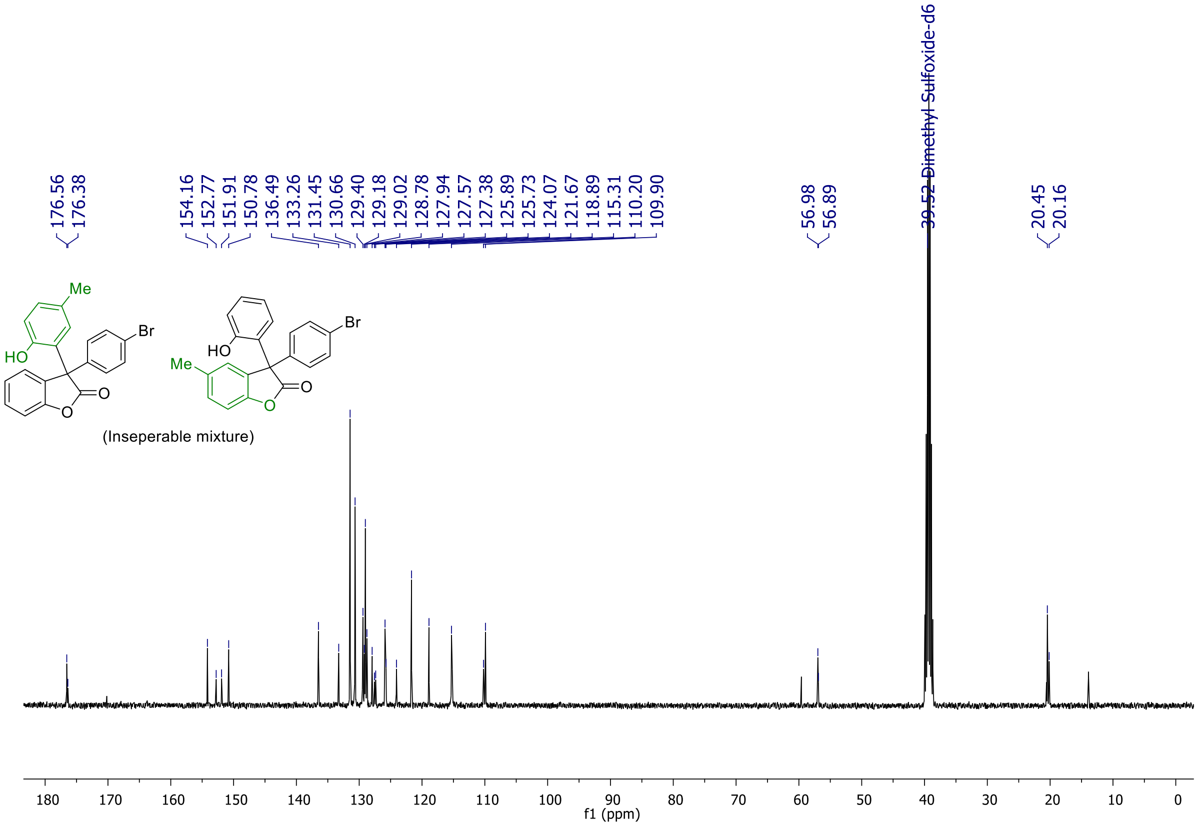

Figure 7.8. ^{13}C{^{1}H} NMR of **3d**, 100 MHz, DMSO-d$_6$

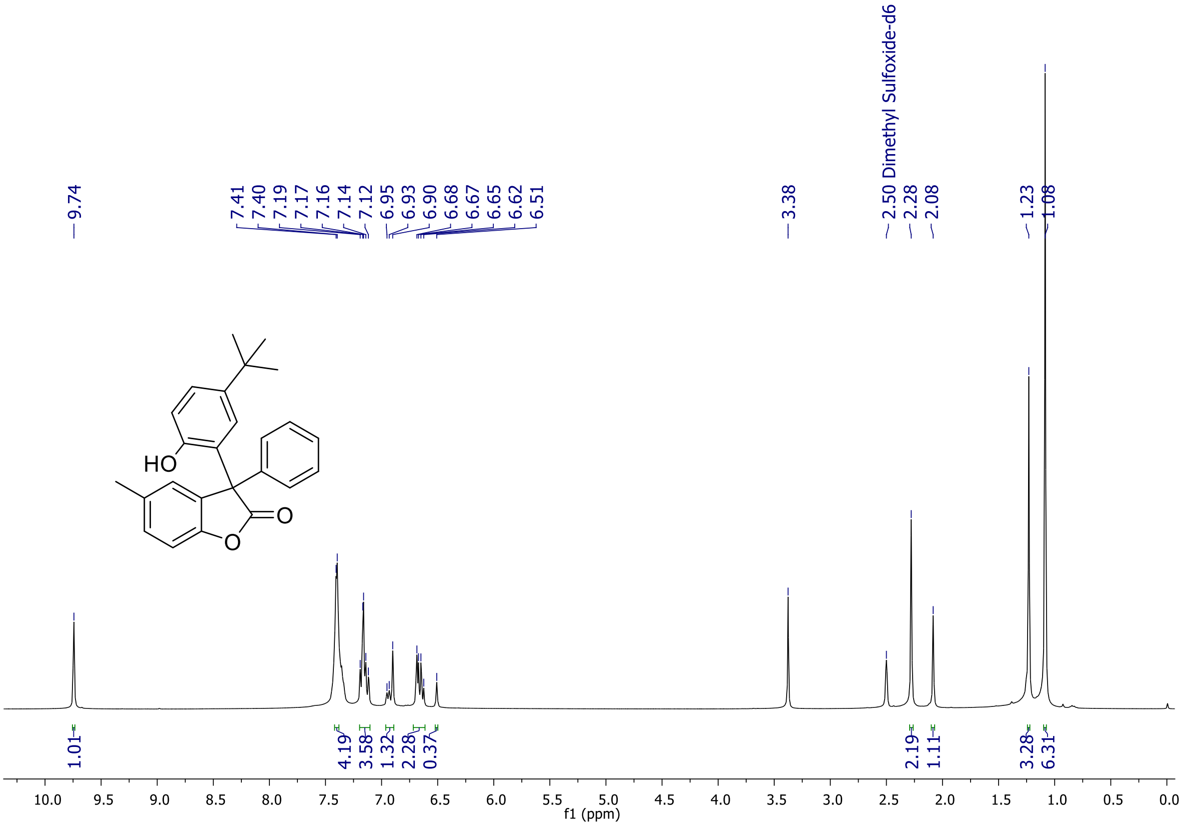

Figure 7.9. ^{1}H NMR of **3e**, 400 MHz, DMSO-d$_6$

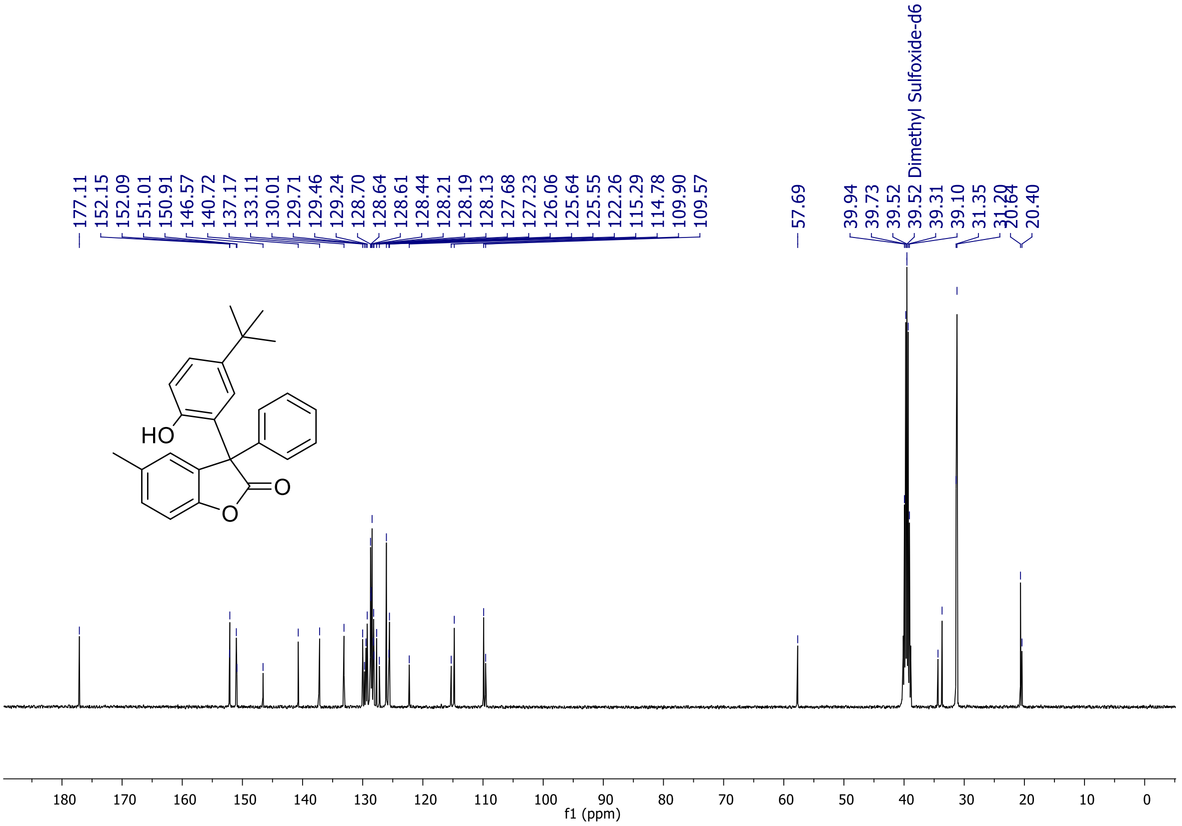

Figure 7.10. ^{13}C{^{1}H} NMR of **3e**, 100 MHz, DMSO-d$_6$

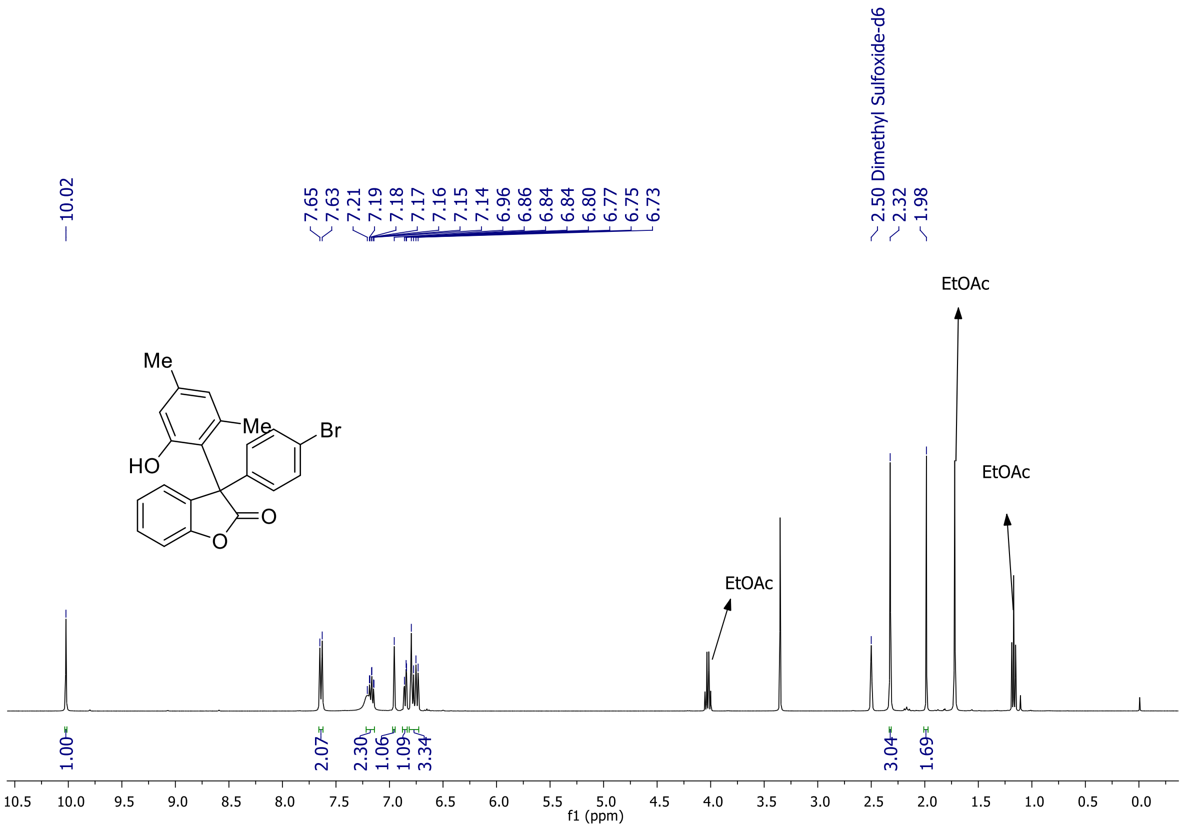

Figure 7.11. ^{1}H NMR of **3f**, 400 MHz, DMSO-d_6

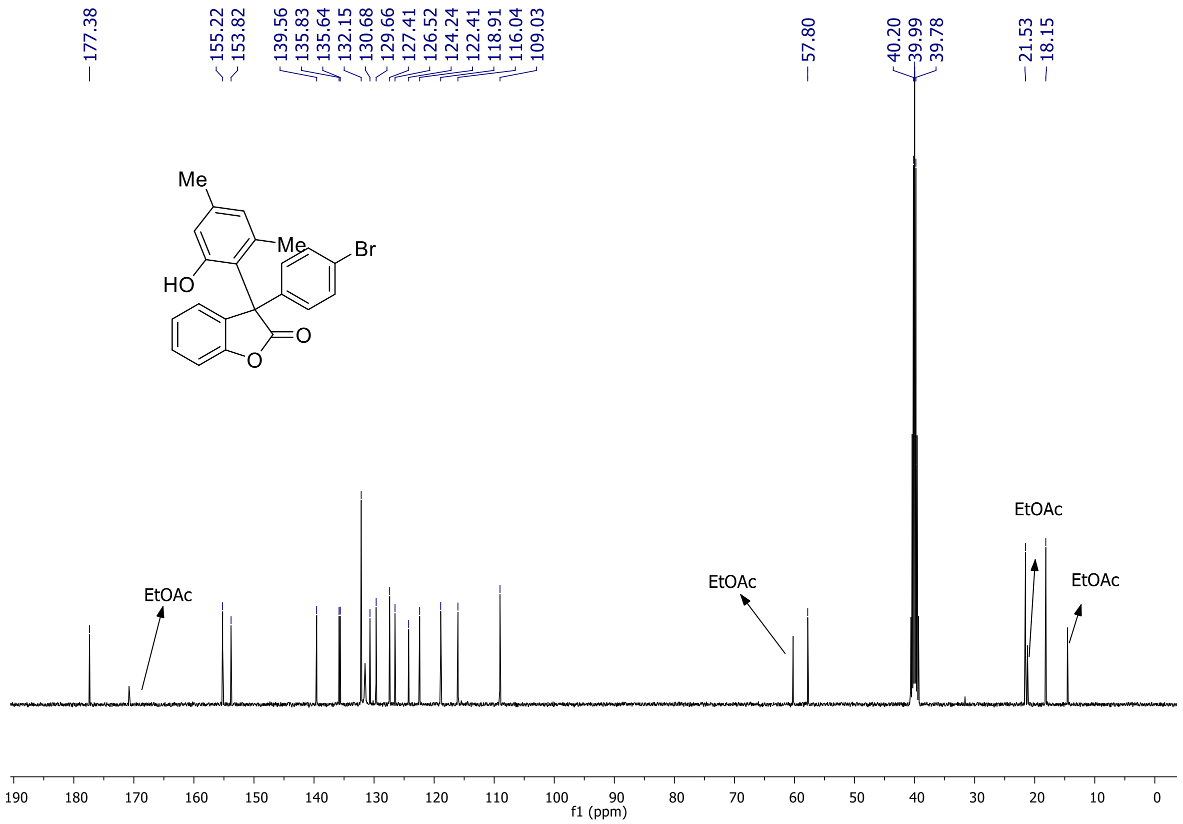

Figure 7.12. $^{13}C\{^{1}H\}$ NMR of **3f**, 100 MHz, DMSO-d_6

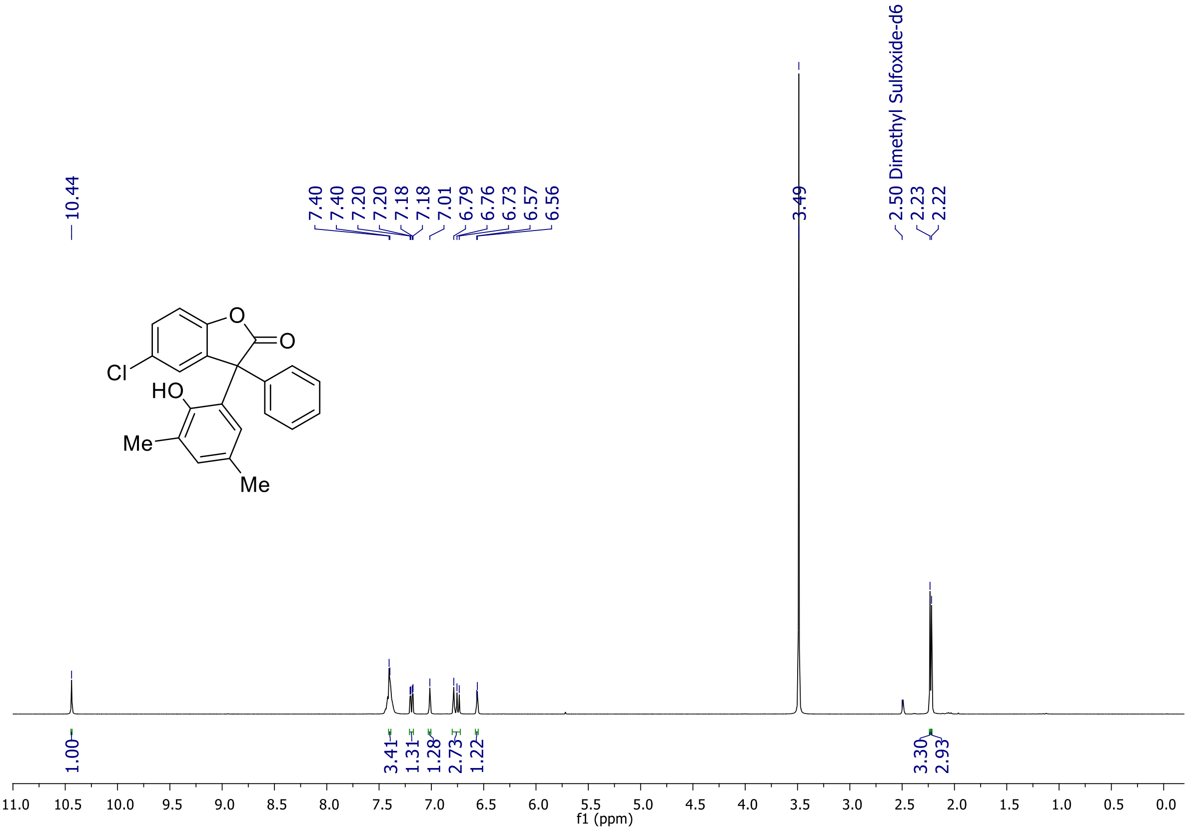

Figure 7.13. ^{1}H NMR of **3g**, 400 MHz, DMSO-d$_6$

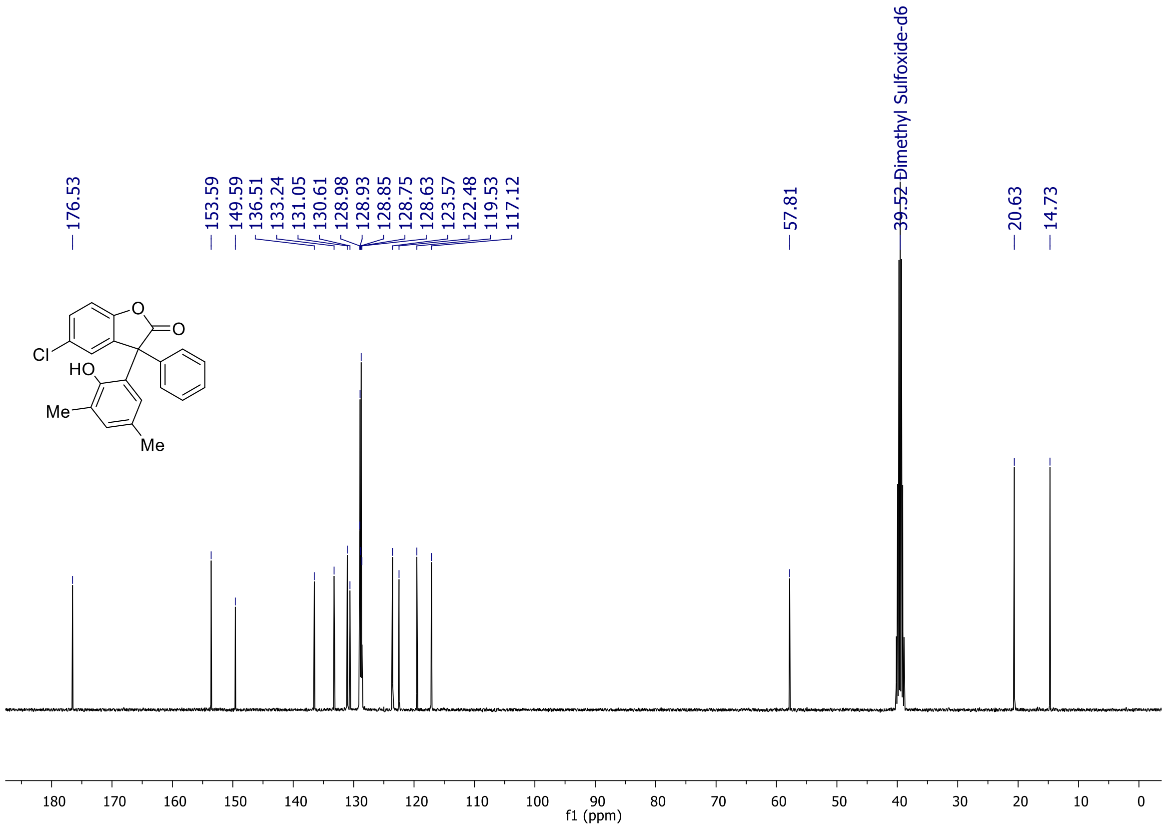

Figure 7.14. ^{13}C{^{1}H} NMR of **3g**, 100 MHz, DMSO-d$_6$

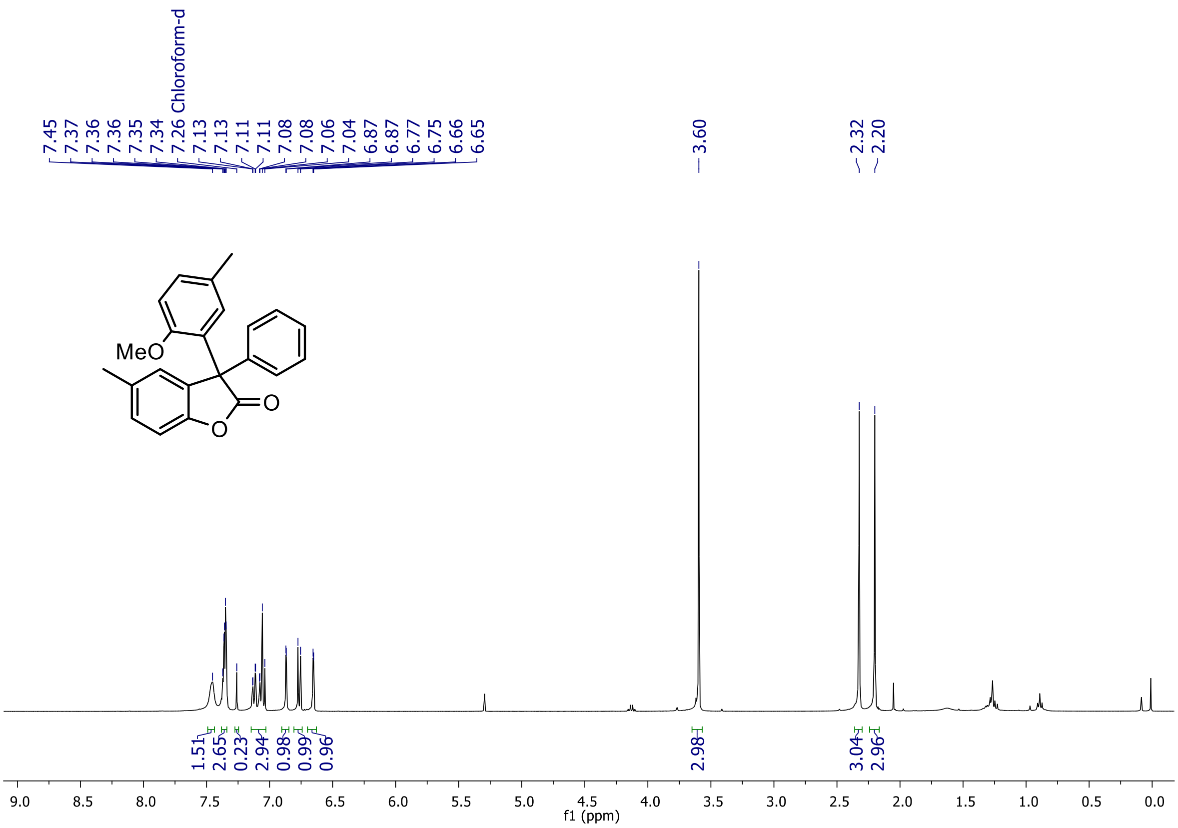

Figure 7.15. ^{1}H NMR of **3h**, 400 MHz, CDCl$_3$

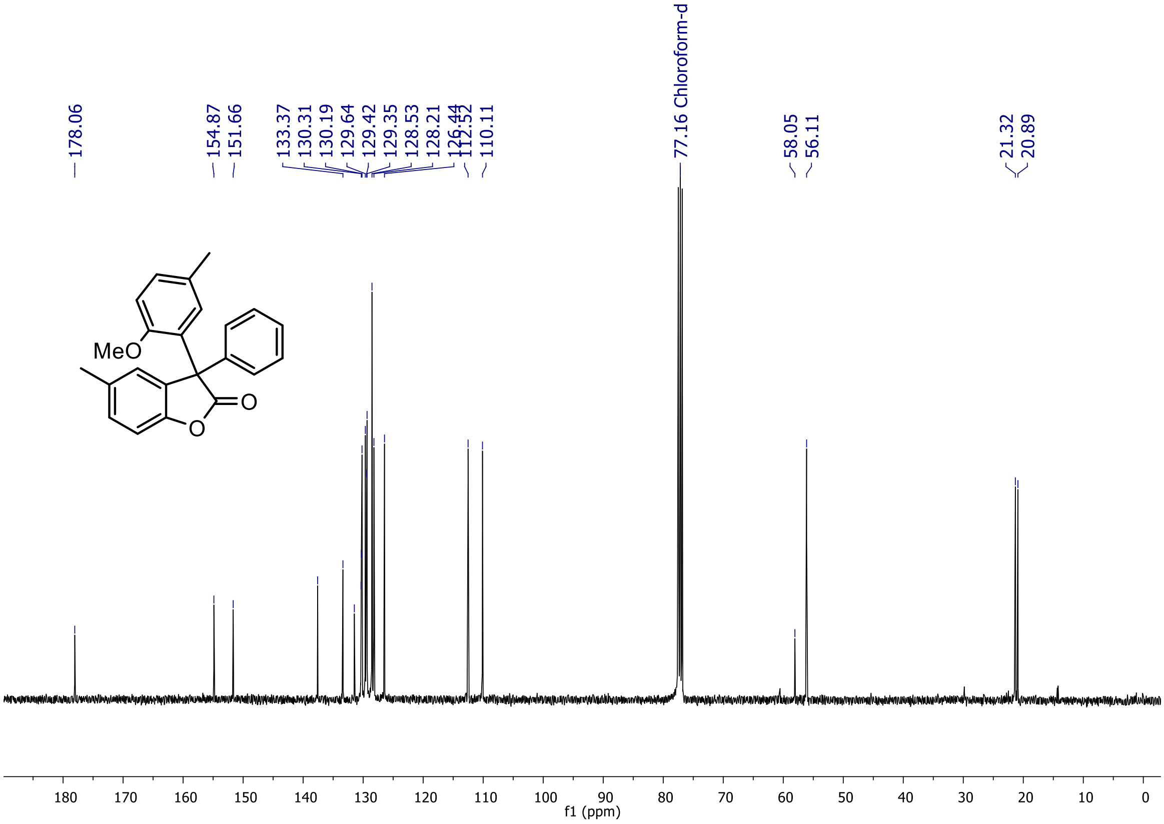

Figure 7.16. ^{13}C{^{1}H} NMR of **3h**, 100 MHz, CDCl$_3$

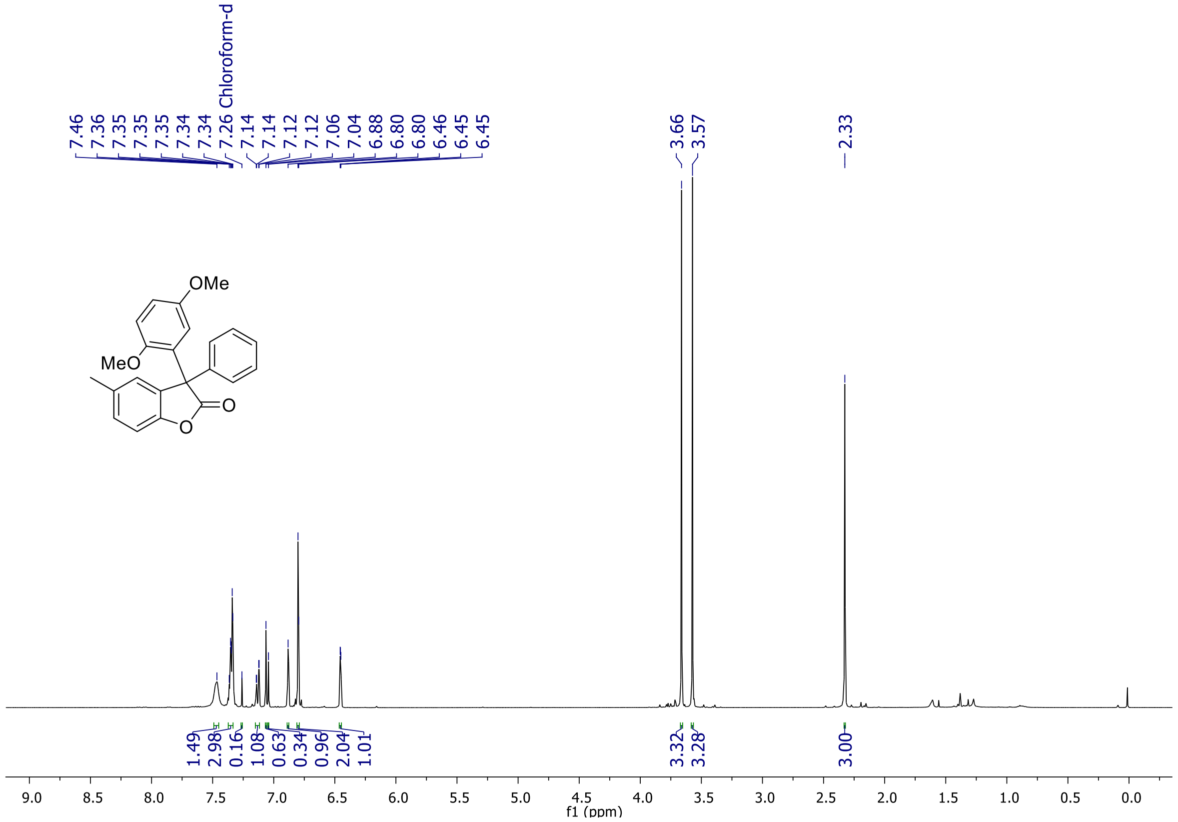

Figure 7.17. ^{1}H NMR of **3i**, 400 MHz, CDCl$_3$

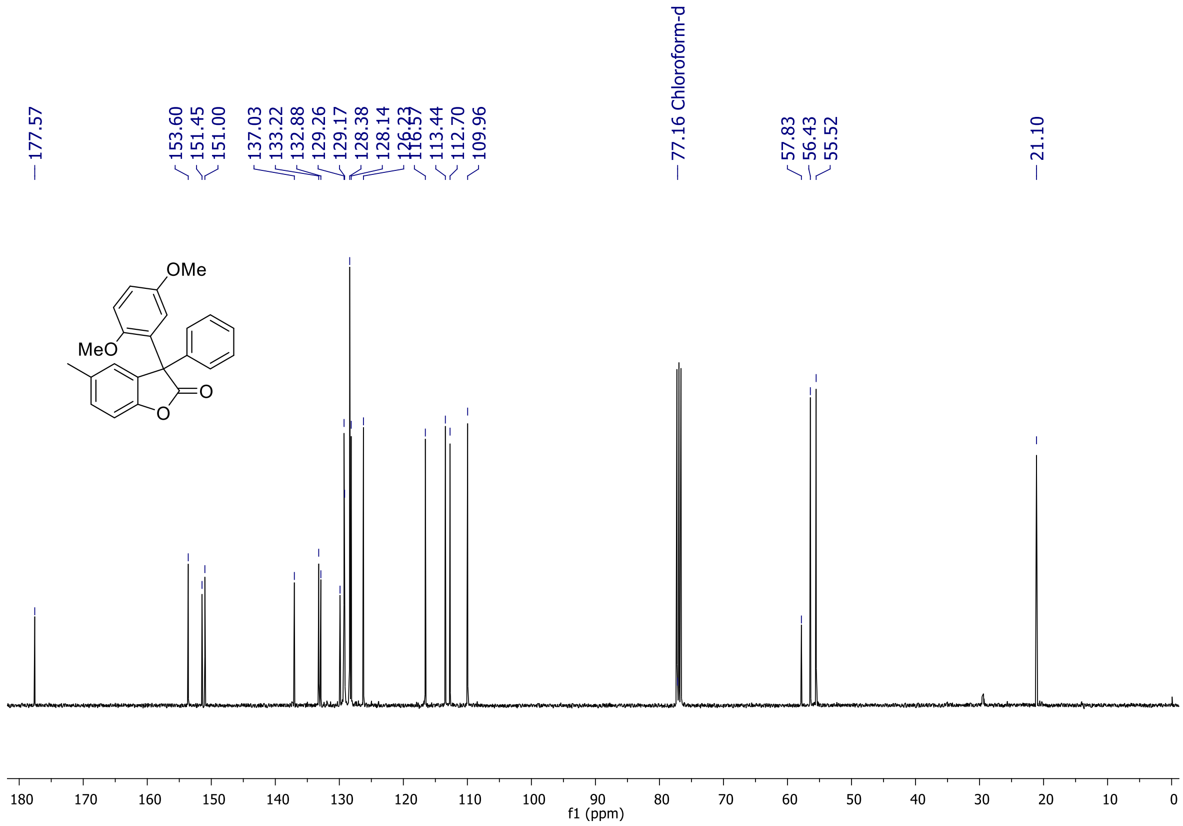

Figure 7.18. ^{13}C{^{1}H} NMR of **3i**, 100 MHz, CDCl$_3$

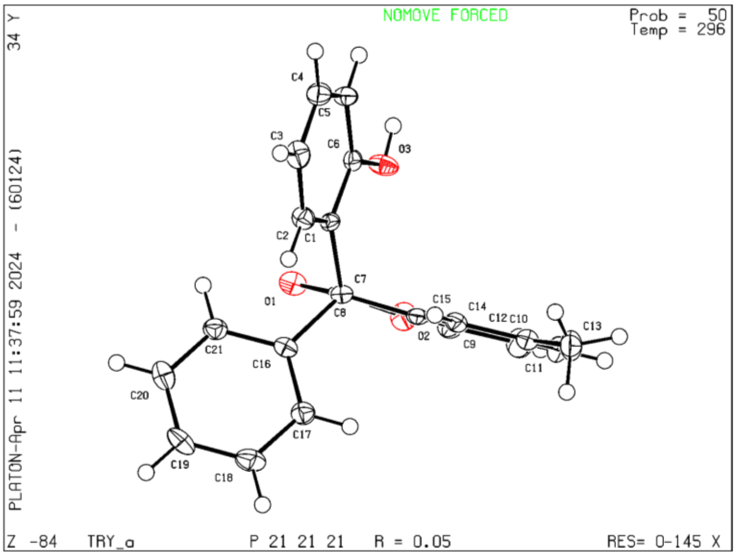

Figure 7.19 ORTEP crystal structure of **3a'** showing thermal ellipsoids at the 50 % probability level.

Crystallographic parameters of **3a'**:

Parameters	**3a'**
Empirical formula	$C_{21}H_{16}O_3$
Formula Mass/g mol	316.34
Experimental crystal description	Plate
Colour	White
Dcalcd/g cm^{-3}	1.355
Crystal system	Orthorhombic
Space group	P 21 21 21
a/ Å	8.595 (4)
b/ Å	9.4436(5)
c/ Å	19.1017(9)
α/ deg	90
β/ deg	90
/ deg	90
V/Å^3	1550.59(13)
Z	4
T / K	296(2)
Diffraction Source	MoK\a
Diffraction radiation wavelength/ Å	0.71073
Diffraction reflection theta full	25.242
Reflection number total	3871
Reflection number gt	3207
μ/mm-1	0.090
F(000)	664.0
R_1,wR_2 [I>2σ(I)]	0.0479 0.1055
R_1,wR_2(all data)	0.0671 0.1055
GoF	1.032