Afyon Kocatepe Üniversitesi Fen ve Mühendislik Bilimleri Dergisi
Afyon Kocatepe University – Journal of Science and Engineering
https://dergipark.org.tr/tr/pub/akufemubid

Araştırma Makalesi / Research Article
e-ISSN: 2149-3367
DOI: https://doi.org/10.35414/akufemubid.1691954
AKÜ FEMÜBİD **25** (2025) 061203 (1308-1315)
AKU J. Sci. Eng. **25** (2025) 061203 (1308-1315)

Dakin Oxidation of 4,6-Dimethoxybenzofuran-7-Carbaldehydes: Synthesis of Benzofuran-7-ols

Makale Bilgisi / Article Info
Alındı/Received: 06.05.2025
Kabul/Accepted: 03.07.2025
Yayımlandı/Published: 03.12.2025

4,6-Dimetoksibenzofuran-7-Karbaldehitlerin Dakin Oksidasyonu: Benzofuran-7-ol Bileşiklerinin Sentezi

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Abstract

The conversion of 4,6-dimethoxybenzofuran-7-carbaldehydes to the 6-methoxy-benzofuran-4,7-quinones via Dakin oxidation was reported by us. In the current work, we explored the effect of varying amounts of hydrogen peroxide (H_2O_2) on the outcome of the Dakin oxidation reaction. By optimizing the reaction conditions, benzofuran-7-ol derivatives were successfully synthesized in yields ranging from 18% to 39%. The results provide insight into the influence of H_2O_2 quantity on product selectivity, contributing to the development of efficient synthetic strategies for benzofuran derivatives. The structures of the synthesized 4,6-dimethoxy-benzofuran-7-ols were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR and mass spectral analyses. Additionally, the structures of compounds with suitable crystalline forms were further characterized.

Keywords: *Heterocyclic; Synthesis; Benzofuran; Dakin Oxidation; Phenolic Compounds.*

Öz

Dakin oksidasyonu ile 4,6-dimetoksibenzofuran-7-karbaldehitlerin 6-metoksi-benzofuran-4,7-kinonlara dönüşümü daha önce tarafımızdan rapor edilmiştir. Bu çalışmada ise, Dakin oksidasyon yönteminde kullanılan hidrojen peroksit (H_2O_2) miktarının reaksiyon üzerindeki etkisi araştırılmıştır. Reaksiyon koşullarının optimize edilmesi sonucunda, benzofuran-7-ol türevleri 18% ile 39% arasında değişen verimlerle başarıyla elde edilmiştir. Elde edilen sonuçlar, H_2O_2 miktarının ürün seçiciliği üzerindeki etkisini ortaya koymakta ve benzofuran türevlerinin verimli sentez stratejilerinin geliştirilmesine katkı sağlamaktadır. Sentezlenen 4,6-dimetoksibenzofuran-7-ol yapıların karakterizasyonu, ^{1}H NMR, ^{13}C NMR, FT-IR ve kütle spektrum analizleri kullanılarak gerçekleştirilmiştir. Ayrıca, uygun kristal yapıya sahip bileşiklerin yapıları X-ışını kırınım analizi ile de doğrulanmıştır.

Anahtar Kelimeler : *Heterosiklik; Sentez; Benzofuran; Dakin Oksidasyon; Fenolik Bileşikler.*

1. Introduction

Heterocyclic compounds are important motifs in medicinal chemistry, playing a crucial role in biological processes by interacting with the functional units of the human body. These interactions occur through intermolecular interactions, namely Van der Waals forces, hydrogen bonding, and hydrophobic interactions. Based on the heteroatoms present in their structures, heterocyclic compounds can be categorized into three groups such as nitrogen-, oxygen-, and sulfur-containing heterocycles (Bendi *et. al.* 2024). A great number of FDA-approved drugs contain oxygen-containing heterocyclic compounds, highlighting their importance in pharmaceutical development (Ceyhan *et. al.* 2024).

Among the oxygen-containing heterocycles, the benzofuran structure is of particular significance. Benzofuran compounds are planar, bicyclic aromatic molecules formed by the fusion of benzene and furan rings (Bendi *et. al.* 2024, Deorha and Gupta 1963, Black *et. al.* 2002). These compounds, which can be isolated from plants, marine organisms, bacterial or fungal metabolites, or synthesized artificially, possess a wide range of biological and pharmacological properties. Due to these properties, they are considered valuable in medicinal chemistry. Benzofuran derivatives, such as moracins, ribisins, stemofurans, and gramnifenols, show various pharmaceutical properties including antiviral, antibacterial, anti-inflammatory, and anti-mitotic effects (Sivaraman *et. al.* 2019, He *et. al.* 2019). Additionally, both synthetic and natural benzofuran derivatives have demonstrated cytotoxic properties, making them promising candidates for cancer treatments (Miao *et. al.* 2019). Phenolic compounds, which include at least one aromatic ring and one hydroxyl group, are another important class of compounds with significant biological properties (De la Rosa *et. al.* 2019, Ojha *et. al.* 2018). Due to their chemical properties, phenolic compounds exhibit

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redox activities, including hydrogen atom transfer and electron transfer, leading to various biological effects such as antioxidant activity. Natural phenolic compounds have been shown to play a crucial role in cancer prevention and therapy due to their ability to interrupt the cell cycle, induce apoptosis, inhibit cell proliferation and differentiation, and block signaling pathways. These characteristics confer chemo-preventive properties to phenolic compounds (De la Rosa *et. al.* 2019, Ojha *et. al.* 2018, Mercado-Mercado *et. al.* 2020)

In the current work, we aimed to synthesize the novel benzofuran bearing a hydroxyl group starting from benzofuran-7-carbaldehydes. To achieve this goal, we employed the Dakin oxidation reaction, a well-known method for synthesizing phenolic compounds from aryl aldehydes or aryl ketones in the presence of hydrogen peroxide and acid catalysis (Uslu Ucar *et. al.* 2025). The Dakin oxidation provides a valuable synthetic route for the functionalization of aromatic systems, offering potential for the development of a variety of biologically active phenolic derivatives. Previously, we successfully synthesized 6-methoxy-benzofuran-4,7-quinones from benzofuran-7-carbaldehydes via Dakin oxidation (Uslu Ucar *et. al.* 2025). Building upon this, we modified the reaction conditions to synthesize 4,6-dimethoxy-benzofuran-7-ol derivatives in this study. The structures of the targeted compounds were identified utilizing various spectroscopic techniques.

2. Materials and Methods

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. The deuterated solvent $CDCl_3$ and DMSO-d_6 for NMR spectroscopy was obtained from Merck. Measurements IR spectra were recorded between 4000 and 650 cm^{-1} using a Perkin Elmer Spectrum 100 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian 500 MHz spectrophotometer. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) measurements were performed on a Bruker Daltonics microTOF. Unit cell measurements and intensity data collection was performed on a Bruker APEX II QUAZAR three-circle diffractometer using monochromatized Mo Kα X-radiation (λ = 0.71073 Å).

2.1 General Procedure: Preparation of benzofuran-7-ol (5a-c)

The benzofuran-7-carbaldehyde derivatives (1 mmol) were dissolved by heating in a solvent mixture of methanol/tetrahydrofuran (5/5). After cooling to room temperature, a drop of HCl was added to the solution, and the reaction mixture was stirred for 5 minutes. Hydrogen peroxide (30 mmol) was then slowly added to the reaction mixture, which was stirred at room temperature for 2 hours. After the reaction, the mixture was poured into an ice-water mixture. The resulting solid was filtered, collected, dried, and purified using column chromatography with a solvent system of DCM/hexane (2/8).

2.2 2-(4-Chlorophenyl)-4,6-dimethoxybenzofuran-7-ol (5a)

Red solid (0.04 g, %33). M.p.: 168-170 °C. IR: υmax 3539, 1517, 1234, 1104, 900, 835, 787. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H, aryl H), 7.38 (d, *J* = 8.7 Hz, 2H, aryl H), 7.03 (s, 1H, aryl H), 6.41 (s, 1H, aryl H), 3.96 (s, 3H, OMe), 3.92 (s, 3H, OMe). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.74, 145.73, 144.13, 143.56, 133.78, 128.98, 128.94, 125.86, 125.79, 114.84, 99.43, 92.12 (aryl C), 57.57, 56.22 (OMe). Maldi (TOF): m/z $C_{16}H_{13}ClO_4$ $[M]^+$: calculated: 304.050; found: 304.248.

2.3 4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-7-ol (5b)

Red solid (0.06 g, %18). M.p.: 162-164 °C. IR: υmax 3394, 1501, 1245, 1231, 1105, 828, 781. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.9 Hz, 2H, aryl H), 6.95 (d, J = 8.9 Hz, 2H, aryl H), 6.90 (s, 1H, aryl H), 6.41 (s, 1H, aryl H), 3.94 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.85 (s, 3H, OMe). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.66, 155.05, 145.41, 143.60, 143.34, 126.10, 125.94, 123.40, 114.17, 97.23, 92.23 (aryl C), 57.66, 56.28, 55.36 (OMe). Maldi (TOF): m/z $C_{17}H_{16}O_5$ $[M-H]^+$: calculated: 299.092; found: 299.059.

2.4 4,6-Dimetoksi-2-(p-tolil)benzofuran-7-ol (5c)

Red Solid (0.14 g, %39). M.p: 153-155 °C. IR: υmax 3438, 1521, 1338, 1277, 1230, 1100, 1056, 902, 787. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H, aryl H), 7.23 (d, *J* = 8.1 Hz, 2H, aryl H), 6.99 (s, 1H, aryl H), 6.41 (s, 1H, aryl H), 3.95 (s, 3H, OMe), 3.92 (s, 3H, OMe), 2.38 (s, 3H, Me). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.19, 145.54, 143.75, 143.43, 138.09, 129.40, 127.75, 125.94, 124.58, 115.09, 98.14, 92.19 (aryl C), 57.65, 56.27 (OMe), 21.36 (Me). Maldi (TOF): m/z $C_{17}H_{16}O_4$ $[M]^+$: calculated: 284.105; found: 284.268.

3. Results and Discussions

3.1 Synthesis and Characterization

The Dakin oxidation is widely recognized as an effective method for converting aryl aldehydes or aryl ketones into phenolic compounds through oxidation with hydrogen peroxide. This reaction enables the efficient

transformation of carbonyl-containing aromatic compounds into their corresponding phenols, with the use of hydrogen peroxide as an oxidizing agent. In this current work, 4,6-dimethoxy-2-phenylbenzofuran-7-carbaldehydes **3a-c** were converted to 4,6-dimethoxy-2-phenylbenzofuran-7-ols **5a-c** via Dakin oxidation method. We have previously reported the synthesis of benzofuran-7-carbaldehydes **3a-c** (Uslu Ucar *et al.* 2025). In the previously reported method, 2-arylbenzofurans **2a-c** were successfully obtained from the reaction of 3,5-dimethoxyphenol **1** and commercially available α-bromoacetophenones **2a-c** in the presence of alumina in xylene at 140°C (Figure 1). 2-Arylbenzofurans **3a-c** were then subjected to the Vilsmeier-Haack reaction using phosphoryl chloride ($POCl_3$) and dimethylformamide (DMF), leading to the formation of the desired benzofuran-7-carbaldehydes **3a-c** (Figure 1). The successful synthesis of benzofuran-7-carbaldehydes **3a-c** provided an opportunity for the preparation of the target compounds. This method offers an efficient and straightforward approach to synthesize functionalized benzofuran derivatives, which are of significant interest in medicinal chemistry due to their broad range of biological activities.

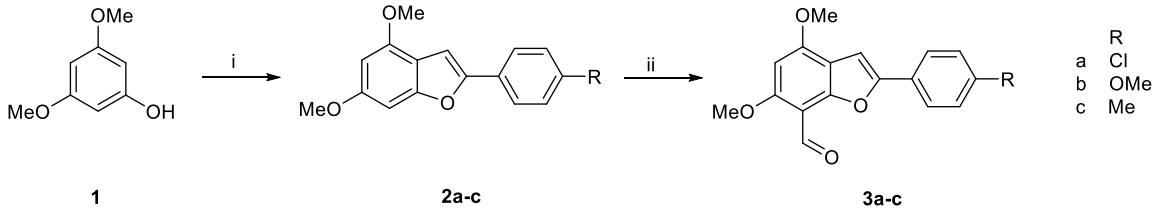


Figure 1. Reagents and conditions: i) α-Bromoacetophenones, xylene, Al_2O_3, 140 ˚C, ii) DMF, $POCl_3$, 50 ˚C, 2h

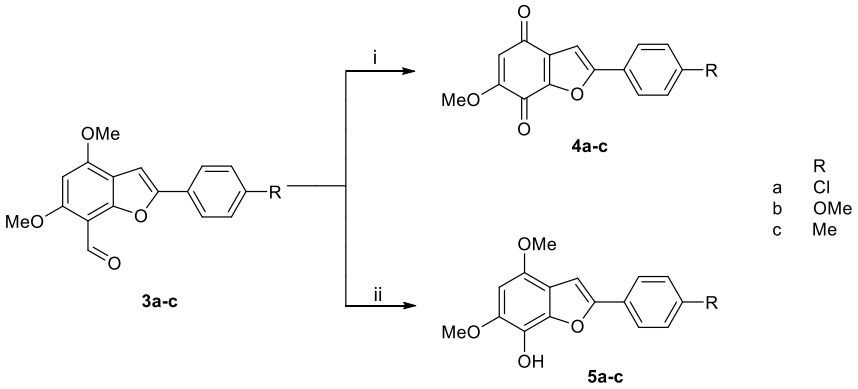
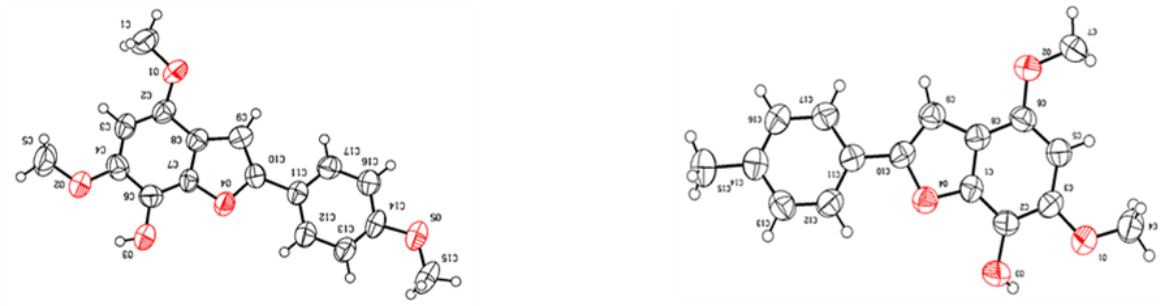


Figure 2. Reagents and conditions: i) MeOH, THF, H_2O_2 (excess), HCl, room temperature, 2h ii) MeOH, THF, H_2O_2 (30 eq), HCl, room temperature, 2h

Furobenzquinones **4a-c** were previously synthesized using the Dakin oxidation reaction method (Uslu Ucar *et. al.* 2025). During the synthesis of furobenzquinones, various reaction conditions were employed to improve reaction completion, increase yields, and establish ideal conditions. Notably, altering the amount of H_2O_2 in the reaction medium led to changes in the number of products formed. For instance, when the amount of H_2O_2 was increased 20-fold compared to the equivalent amount of the aldehydes **3a-c**, extensive product formation was observed in thin-layer chromatography (TLC) analysis. However, no specific product could be isolated from this complex reaction mixture. In another reaction where H_2O_2 was used in 30-fold excess, in addition to the oxidation products of the benzofuran-7-carbaldehyde **3a-c**, the formation of compounds **5a-c** was also detected (Figure 2). The identity of the targeted benzofuran-7-ols **5a-c** were confirmed by spectroscopic analysis. Compound **5b** was representative of analogues **5a-c**. Upon examination of ^{1}H NMR spectrum of the compound **5b**, the absence of the aldehyde peak around 10 ppm, which is present in the starting material, serves as a key indication that the reaction has successfully proceeded. The ^{1}H NMR spectrum also exhibited three singlets at 3.85, 3.92, and 3.94 ppm, corresponding to the methoxy groups of benzofuran and phenyl rings, respectively. Similarly, the disappearance of the characteristic aldehyde peak around 186 ppm in the starting compound, along with the appearance of carbon peaks for the methoxy groups at 55.3, 56.2, and 57.6 ppm, is another factor that supports the proposed structure **5b**. Additionally, a broad peak at 3393 cm^{-1} in the IR spectrum, corresponding to the OH functional group, further confirms the structure of the compound. The molecular ion m/z at 304.299 in the MALDI mass spectra supports the formation of the compounds **5a-c**, respectively. For advanced analysis, single crystals of compounds **5b** and **5c** were grown in chloroform, and X-

ray crystallography was performed. The X-ray analysis definitively determined the structures of benzofuran-7-ol derivatives **5b** and **5c** (Figure 3). It is noteworthy that, in previous studies involving 4,6-dimethoxyindoles and 4,6-dimethoxy-benzofurans, the reactions predominantly afforded indoloquinones and furoquinone derivatives rather than the expected alcohol products (Alamgir *et al.* 2008., Uslu Uçar *et al*. 2025). In contrast, the present study successfully yielded the anticipated 4,6-dimethoxy-benzofuran-7-ol derivatives from the corresponding 4,6-dimethoxybenzofurans.



5b **5c**

Figure 3. Crystal structures of compounds **5b** and **5c**

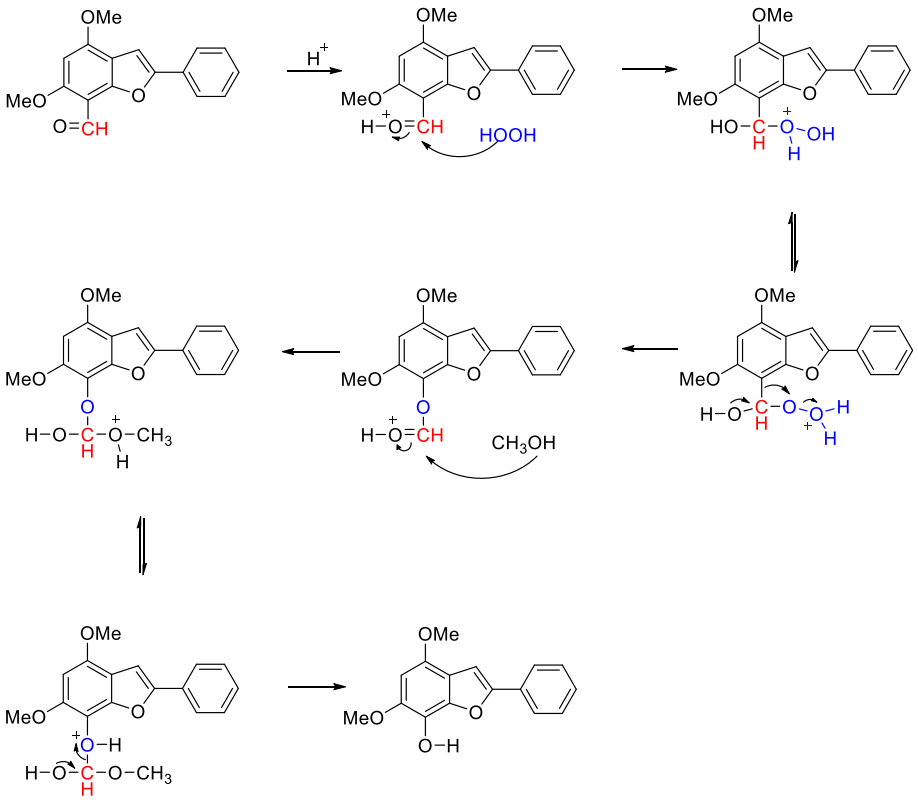


Figure 4. A proposed mechanism for the formation of benzofuran-7-ols **5a-c**

The proposed mechanism for the formation of benzofuran-7-ol is outlined in Figure 4. The reaction is believed to be initiated with the nucleophilic addition of a hydroperoxide ion to the carbonyl carbon, resulting in the formation of a tetrahedral intermediate. This intermediate then undergoes 1,2-aryl migration, followed by hydroxide elimination and the creation of a phenyl ester. The phenyl ester is subsequently hydrolyzed: a hydroxide ion from the solution nucleophilically adds to the ester carbonyl carbon, generating a second tetrahedral intermediate. These intermediate collapses, releasing a phenoxide ion and forming carboxylic acid. Finally, the phenoxide ion abstracts an acidic hydrogen from the carboxylic acid, leading to the formation of the targeted benzofuran-7-ols **5a-c** (Figure 4).

4. Conclusions

The 4,6-dimethoxybenzofuran derivatives synthesized from 3,5-dimethoxyphenol underwent a Vilsmeier-Haack reaction to yield 4,6-dimethoxybenzofuran-7-

carbaldehyde compounds. In the Dakin oxidation of these 4,6-dimethoxybenzofuran-7-carbaldehyde derivatives, a deviation from previous studies was observed. Specifically, when 30 equivalents of H_2O_2 were used relative to the aldehyde, 4,6-dimethoxybenzofuran-7-ol derivatives were obtained. Unlike previous studies, this work successfully yielded the expected benzofuran-7-ol derivatives from 4,6-dimethoxybenzofurans. This work adds to the existing knowledge on the synthesis of benzofuran derivatives and highlights the flexibility of this synthetic route for producing bioactive compounds.

Declaration of Ethical Standards

The authors declare that they comply with all ethical standards.

This study is derived from doctorate thesis (thesis number: 915722) under the supervision of Prof. Dr. Hakan Kandemir by Tuğçe Nur Uslu Uçar on date of 09.01.2025 titled. The authors declare that they comply with all ethical standards.

Credit Authorship Contribution Statement

Author-1: Data curation, Visualization Conceptualization, Methodology, Software, Validation.

Author-2: Writing- original draft, Writing- review and editing, Investigation.

Author-3: Data curation, Visualization Conceptualization, Methodology, Software, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

Supplementary data was given as Supporting Information. Additional crystallographic data with CCDC reference numbers 2427132 **(5b)** and 2427134 **(5c)** have been deposited within the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/deposit.

Acknowledgement

This study was supported by Scientific and Technological Research Council of Turkey (TUBITAK) under the Grant Number 122Z598. The authors thank TUBITAK for their support.

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Synthesis of 4,6-dimethoxy-2-phenylbenzofuran-7-ols from 4,6-dimethoxy-2-phenylbenzofuran-7-carbaldehydes via Dakin Oxidation

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SUPPLEMENTARY FILES

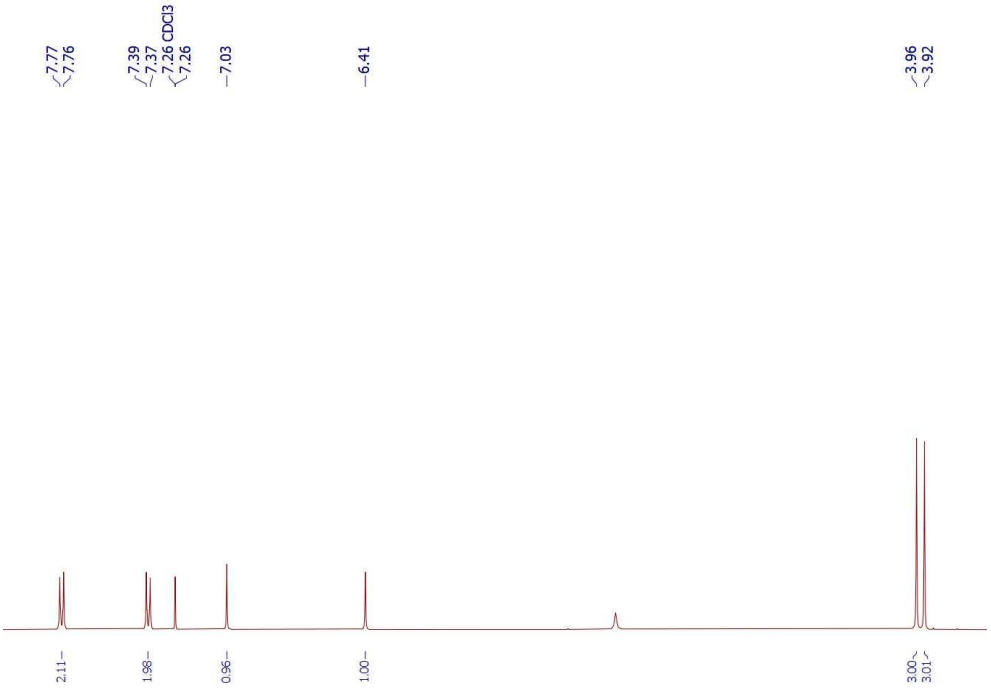


Figure S1. ^{1}H NMR spectrum of 2-(4-chlorophenyl)-4,6-dimethoxybenzofuran-7-ol **5a**

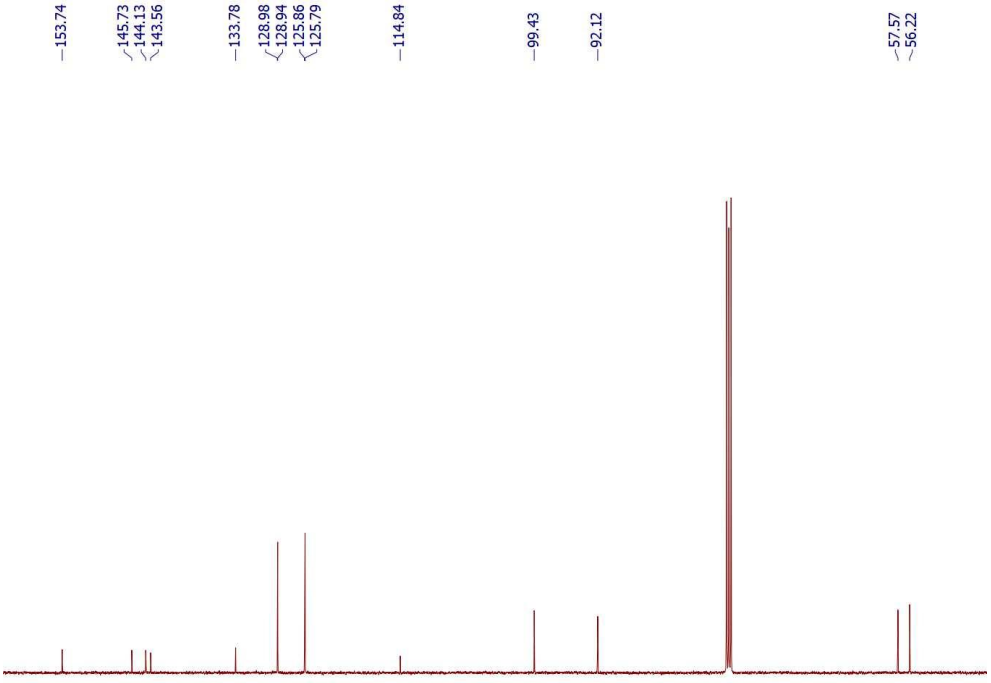


Figure S2. ^{13}C NMR spectrum of 2-(4-chlorophenyl)-4,6-dimethoxybenzofuran-7-ol **5a**

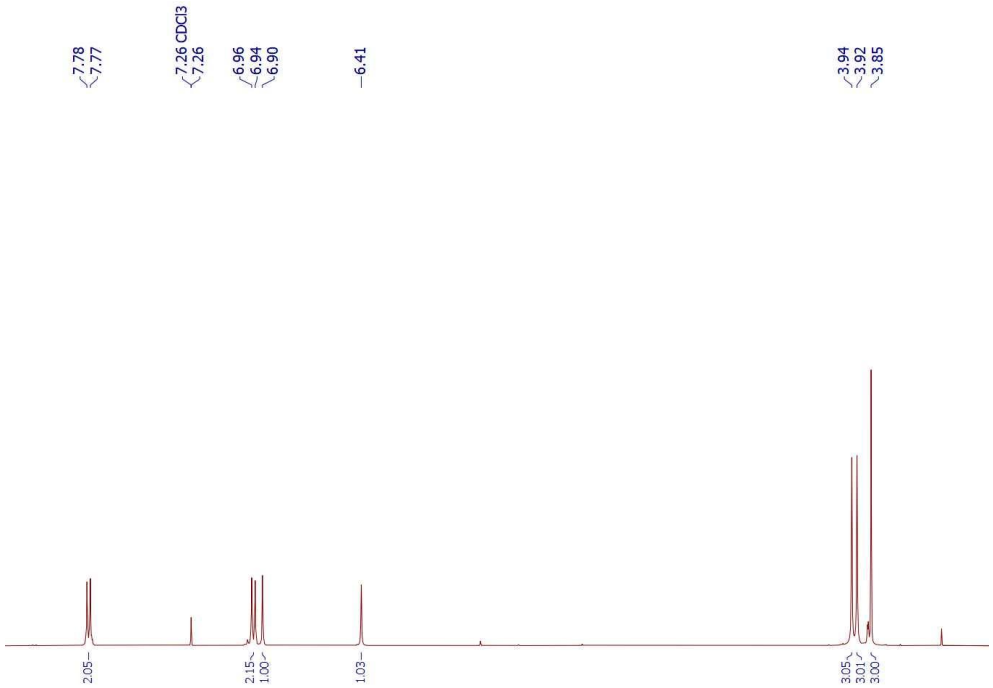


Figure S3. [1]H NMR spectrum of 4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-7-ol **5b**

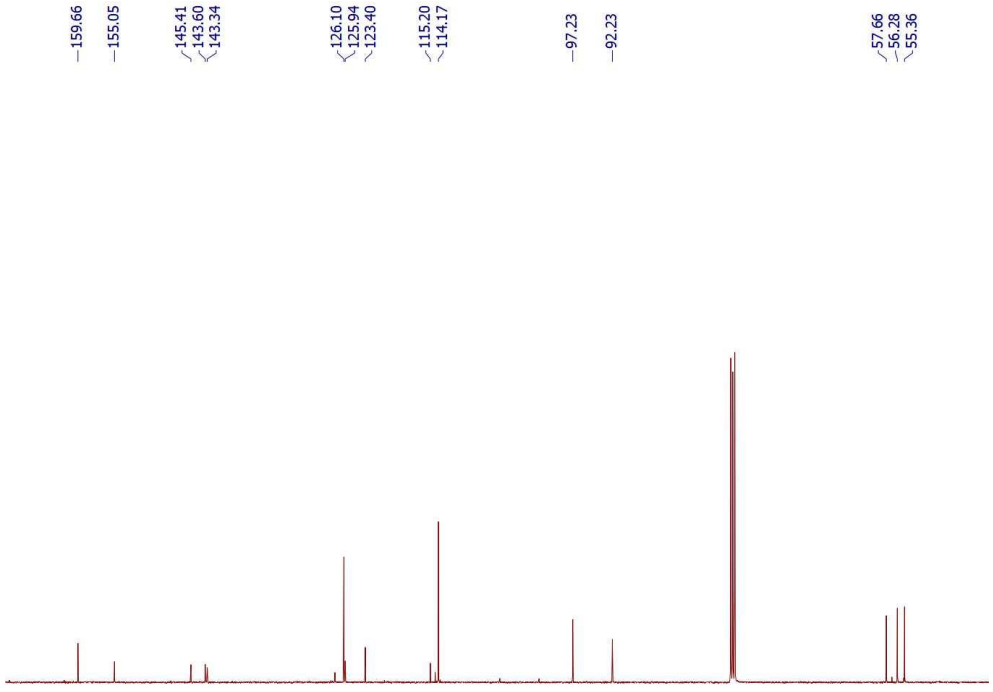


Figure S4. [13]C NMR spectrum of 4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-7-ol **5b**

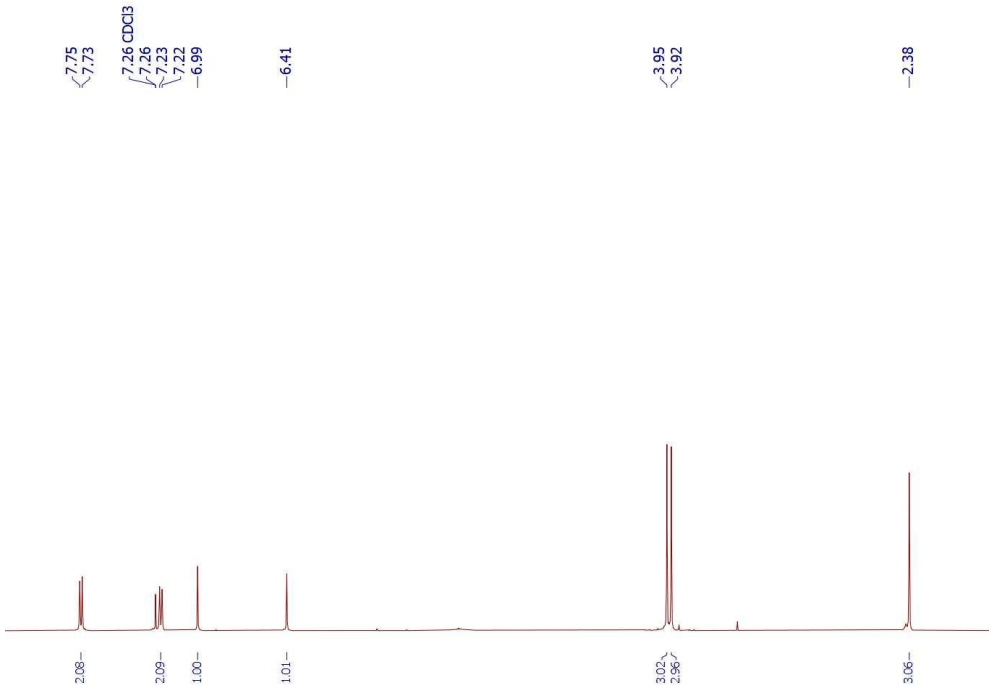


Figure S5. [1]H NMR spectrum of 4,6-dimethoxy-2-(p-tolyl)benzofuran-7-ol **5c**

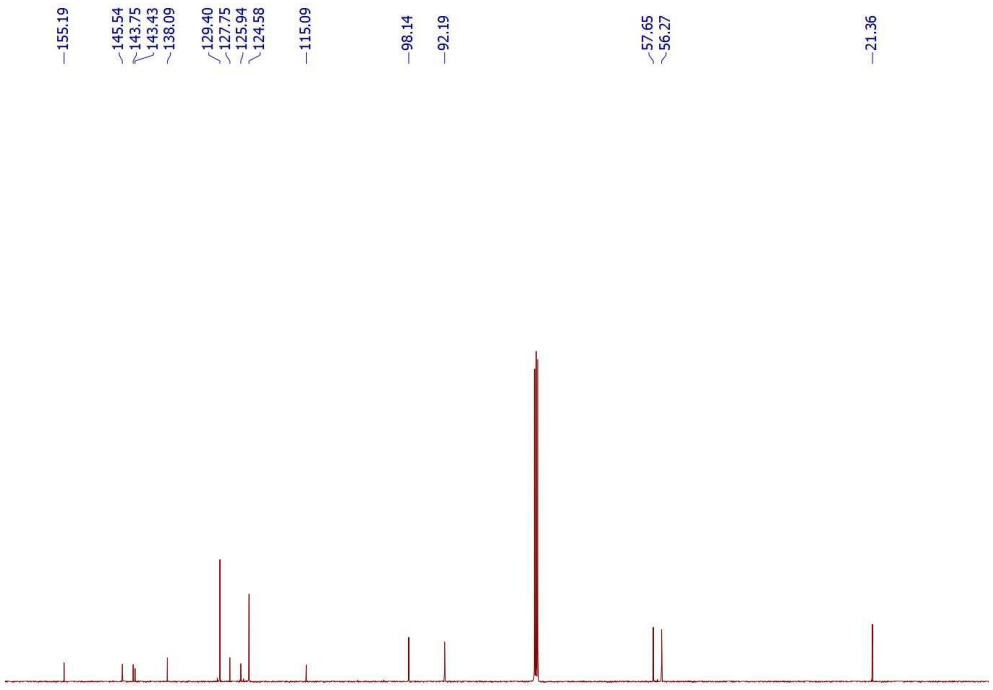


Figure S6. [13]C NMR spectrum of 4,6-dimethoxy-2-(p-tolyl)benzofuran-7-ol **5c**