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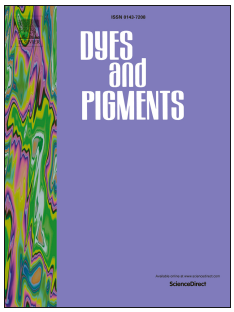

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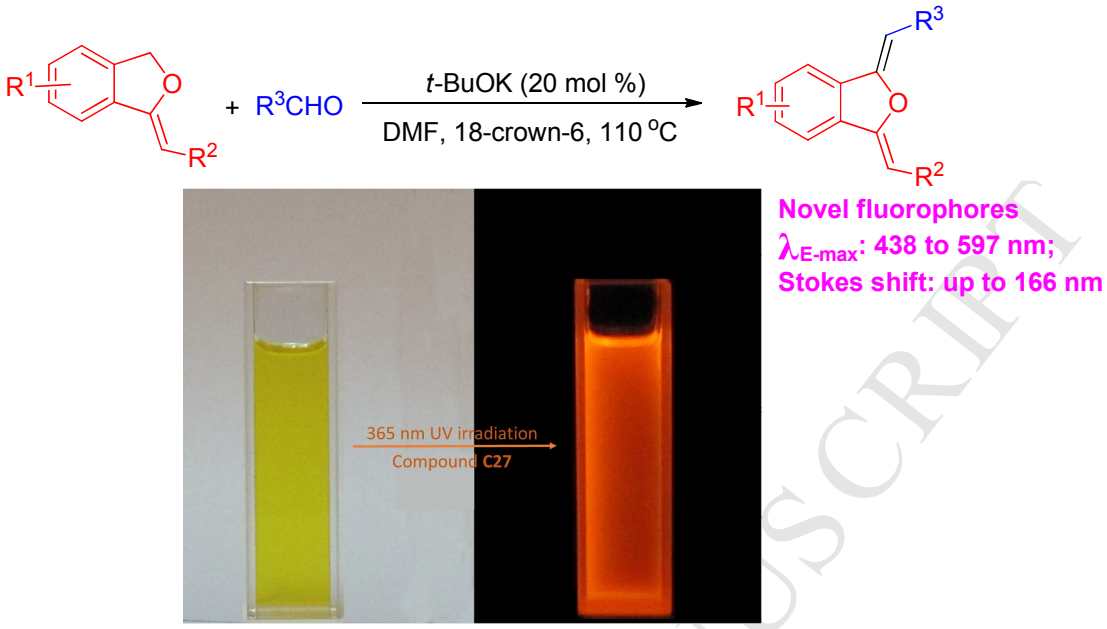
Graphical Abstract



A concise synthesis of tunable fluorescent 1,3-dihydroisobenzofuran derivatives as new fluorophores

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Abstract: A convenient potassium *tert*-butoxide catalyzed addition-elimination reaction has been achieved using *exo*-cyclic enol ethers and aryl aldehydes as the starting materials. The transition-metal free reaction proceeded smoothly to afford 1,3-dihydroisobenzofuran derivatives with good to excellent yields. More importantly, the resulting products were discovered as novel fluorophores with good fluorescence properties and remarkable Stokes shifts. Changing the nature of the substituents in 1,3-dihydroisobenzofurans derivatives allowed the maximum emission wavelengths to be tuned between 438 and 597 nm and the Stokes shifts varied between 63 and 166 nm. In particular, derivative **C27** containing a piperidyl and a cyano group showed the maximum emission wavelength of 597 nm and a Stokes shift of 166 nm.

Keywords: Addition-elimination, 1,3-dihydroisobenzofuran, fluorescence, Stokes shift, tunable

1. Introduction

Fluorescent molecules have recently attracted significant attention because of their extensive applications in the dyeing industry and in various fields of research [1-3]. Efficient, high-yield strategies to synthesize fluorescent scaffolds are therefore quite desirable [4-7], particularly methods of generating "smart" fluorophores with tunable fluorescent emission [8-24]. These fluorescent scaffolds typically have a core with extended π-conjugated aryl-(hetero)aryl motifs. Extending such π-conjugated systems by introducing a vinyl or aromatic group can yield high-emission fluorophores that are particularly useful for bioimaging [25-32].

Despite significant progress in this area, efficiently generating small useful organic fluorophores in biological applications remains a challenge. One class of compounds with substantial potential as tunable fluorophores are 1,3-dihydroisobenzofuran derivatives, a new type of vinylogous analogues of benzalphthalide [33], which can be served as a potential medical intermediate. Little is known about how the structure of these derivatives influences their fluorescence, which is a crucial question since it is possible that substituting the 1,3-dihydroisobenzofuran core may generate a diverse library of fluorophores with large Stokes shifts.

Synthesis of 1,3-dihydroisobenzofuran derivatives requires functionalizing benzylic methylene, which typically relies on reactions catalyzed by transition metal salts or complexes [34-39]. This functionalization has also been achieved using metal-free catalysts such as diphenyl phosphate [40], MsOH [41], chiral phosphoric acids [42] and ammonium salts [43, 44], in which oxidant was usually needed. Another alternative is direct benzylic C-H

activation by photoredox catalysis [45]. We recently reported a novel method for synthesizing a new type of 1,3-dihydroisobenzofuran derivatives **C** by reacting *exo*-cyclic enol ethers with imines in the presence of stoichiometric potassium *tert*-butoxide (*t*-BuOK, 1.2 equivalent) [46].

Here we improve on that approach by reacting *exo*-cyclic enol ethers with aldehydes directly, instead of with imines, in the presence of a catalytic amount of *t*-BuOK (20 mol%). This method is much more efficient because it does not require the preparation of imines from aldehydes and it does not release amine as a by-product. More importantly, this approach allows the concise generation of structurally diverse 1,3-dihydroisobenzofuran derivatives as novel fluorophores with fluorescence emission wavelengths varying from 438 to 597 nm and remarkable Stokes shifts of up to 166 nm.

2. Results and discussion

2.1. Reaction optimization

As shown in Table 1, we used (*Z*)-1-benzylidene-1,3-dihydroisobenzofuran (**A1**) and 4-methoxybenzaldehyde (**B1**) as the model substrates to investigate the reaction of *exo*-cyclic enol ether with aldehyde. Firstly, we screened several kinds of bases for the reaction of **A1** and **B1** in DMF, and found that the reaction proceeded to afford the product **C1** after 10 h in 46% yield at 80 ^{o}C in the presence of 20 mol% *t*-BuOK (entry 1). Other bases such as KHMDS and KOH also gave similar results, but NaH gave only 24% yield (entries 2-4). When DBU and K_2CO_3 were used, no reaction was observed due to the weak basicity (entries 5 and 6). Interestingly, adding 18-crown-6 (30 mol%) to the reaction substantially increased

the yield of **C** to 80% after only 4.5 h at 80 ^{o}C (entry 7). Increasing the reaction temperature to 110 ^{o}C led to a complete reaction with 82% yield within 2 h (entry 8). The effect of organic solvents was also examined, and it is noteworthy that DMSO used in the reaction of *exo*-cyclic enol ethers with imines[15] was ineffective in the reation of *exo*-cyclic enol ethers with aldehydes and product **C1** was not detected (entry 9). The reactions in THF or toluene gave substantially decreased yields and the reactions in acetonitrile or dichloroethane (DCE) led to no desired product (entries 10-13). The amount of catalyst proved crucial to the reaction of **A1** with **B1**, and **C1** was not generated when the amount of *t*-BuOK was decreased to 10 mol% (entry 14).

<Table 1>

2.2. Substrate scope

Next, we studied the scope of the reaction using a series of aldehydes and various *exo*-cyclic enol ethers (Table 2). The reaction was examined in DMF at 110 ^{o}C, using 20 mol% of *t*-BuOK as the catalyst and 30 mol% of 18-crown-6 as the additive. A series of benzaldehydes with *para*-substituted electron-donating groups, such as methoxy, methylthio, *t*-butyl and methyl groups, readily reacted with 1,3-dihydroisobenzofuran **A** to give the products **C1**-C**4** in moderate to high yields, and the methoxy group gave the best yield of 81%. The fact suggests that the stronger electron-donating ability of methoxy group contributes to the higher yield. Notably, when more strongly electron-donating *N*,*N*-dimethylamino, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl were used as the *para*-substituents of benzaldehyde, the reactions of **A** with them proceeded smoothly to afford the products **C5-C8**

in excellent 88-99% yields. In contrast, 2-methoxy and 3,4-dimethoxy substituted benzaldehydes were tested in the reactions with **A**, only 52% and 53% yields were observed for the products **C9** and **C10**, respectively. Nevertheless, 2,4-dimethoxy benzaldehyde reacted with **A** to give product **C11** in 90% yield. The different yields between **C10** and **C11** reveals that the electron-donating ability in ortho-position is stronger than that in meta-position. It is noteworthy that benzaldehyde, benzaldehydes containing electron-withdrawing substituents, naphthaldehydes or alkylaldehydes were ineffective in this catalytic reaction.

Subsequently, we tested the reactions of a series of *exo*-cyclic enol ethers with 4-(dimethylamino)benzaldehyde. *Exo*-cyclic enol ethers in which R^2 was a phenyl ring *para*-substituted with electron-donating methoxy and methyl groups or electron-withdrawing chloro, trifluoromethyl, and cyano groups reacted well to afford the desired products **C12**-**C16** in 83-89% yields. If R^2 of *exo*-cyclic enol ethers was changed to 2-methoxyphenyl, 2-chlorophenyl, 3-chlorophenyl or 2-naphthyl, the reactions of *exo*-cyclic enol ethers with 4-(dimethylamino)benzaldehyde also proceeded smoothly to afford the products **C17**-**C20** in 75%-93% yields. Substituting the R^1 position of *exo*-cyclic enol ethers with methyl or chloro group gave products **C21** and **C22** in 89% and 98% yield, respectively. The *exo*-cyclic enol ether carrying two methoxy groups at R^1 and 4-methoxyphenyl at R^2 gave product **C23** in only 53% yield, while the *exo*-cyclic enol ether carrying a fluoro atom at R^1 and 4-fluorophenyl at R^2 afforded product **C24** in decreased 34% yield. Finally, we used 4-(piperidin-1-yl)benzaldehyde to react with the *exo*-cyclic enol ethers containing 4-hydroxymethylphenyl, 4-cyanophenyl at R^2 or a cyano group at R^1, the reactions produced **C25**-**C27** in 63-82% yields.

<Table 2>

2.3. Reaction Mechanism

Based on the experimental results, we proposed the reaction mechanism of *exo*-cyclic enol ethers **A** and aldehydes **B** (Scheme 1). First, deprotonation of exo-cyclic enol ethers **A** in the presence of *t*-BuOK affords intermediate **D**, which adds to aldehydes **B** to produce **E**. The oxygen anion B traps a proton, leading to the key intermediate **F**. Then, deprotonation of **F** gives **G** which undergoes an E2 elimination to afford the desired product **C**.

<Scheme 1>

2.4. Photophysical properties

After the facile preparation of these 1,3-dihydroisobenzofuran derivatives, we then examined their photophysical properties. The UV absorption spectra of compounds **C1-C27** in dichloromethane are shown in Fig. 1. As shown in Fig. 1a-1e, we can see that the maximum absorption wavelength of each product has little difference. In general, the products **C1-C4** and **C9-C11** bearing MeO, SMe, *t*-Bu or Me groups have similar absorption spectra and their absorption peaks are located around 380 nm in the range of 350 and 450 nm, which suggests that the above substituents possess the similar electron-donating ability. In contrast, when piperidyl, *N*,*N*-dimethyl, pyrrolidyl and morpholinyl were introduced to form products **C5-C8** and **C12-C27**, the absorption peaks are all red-shifted. The results are ascribed to the stronger electron-donating ability of N atom than O, S and C atoms. In particular, compounds **C16** and **C26-C27** containing *N*,*N*-dimethyl or piperidyl in combination with strong electron-withdrawing cyano group obviously red-shift absorption peaks to 438 and 431 nm.

Such D-π-A molecules may contribute to electron transfer from donor to acceptor and thus making the absorption peaks red-shift. In the range from 350 to 500 nm, we calculated the maximum molar absorption coefficient of each product and the results were recorded in Table 3. Among all of the products, **C5** shows the best light absorption ability.

<Fig. 1>

In order to study the solvent effect on the absorption spectra of our target products, we took compound **C16** for example and found that the absorption spectra have nearly no difference in solvents with different polarity (Fig. 2). The absorbance of **C16** in toluene is smaller than that in other solvents. The spectra in CH_2Cl_2, EtOAc, THF and dioxane are nearly overlapped. When the test was studied in DMF and DMSO, the absorption peaks are slightly red-shifted.

<Fig. 2>

Subsequently, we tested the fluorescence property of products **C1-C27**. The fluorescence spectra were depicted in Fig. 3a-3e and the maximum emission wavelengths ($\lambda_{E\text{-}max}$) of each product were listed in Table 3. The Stokes shift was accordingly obtained from $\lambda_{E\text{-}max}$ and $\lambda_{A\text{-}max}$ and the fluorescence quantum yield (Φ_F) of each product was calculated by using Rhodamine 6G as the standard (0.88 in ethanol) [47]. The corresponding calculation equations are presented in Supporting Information. As shown in Table 3, the compounds **C1-C4** and **C9-C11** which carry methoxy, methylthio, *t*-butyl or methyl groups on one benzene ring showed poor fluorescence quantum yields, with the maximum emission

wavelengths ($\lambda_{E\text{-}max}$) ranging from 438 to 473 nm. In contrast, compounds **C5**-**C8** carrying dimethylamine, pyrrolidine, piperidine or morpholine substituent on one benzene ring showed stronger fluorescence in CH_2Cl_2 (enhanced Φ_F compared with those of **C1**-**C4** and **C9**-**C11** in Table 3), which are consistent with those reported by You for 1,2-disubstituted benzimidazole fluorescent scaffolds [48]. Moreover, compounds **C5**-**C8** also exhibited large Stokes shifts ranging from 108 to 126 nm and red-shifted $\lambda_{E\text{-}max}$ values ranging from 505-523 nm. The results obtained further demonstrate the stronger electron-donating ability of N atom than O, S and C atoms, which helps to electron transition from ground state to excitation state upon irradiation by light.

<Fig. 3>

Analysis of the compound series **C12**-**C20** and **C21**-**C24** reflected that substitution with electron-donating nitrogen atom red-shifted $\lambda_{E\text{-}max}$ and increased the Stokes shift. In the case of compounds **C12**-**C20,** which carry *N*,*N*-dimethylamino group on one benzene ring, attaching OMe, Me, Cl, CF_3 or CN groups to the other benzene ring increased $\lambda_{E\text{-}max}$ and the Stokes shift. For example, compound **C15** with a *para*-trifluoromethyl group showed an $\lambda_{E\text{-}max}$ of 550 nm and a Stokes shift of 142 nm; compound **C16** with a *para*-cyano group showed an $\lambda_{E\text{-}max}$ of 582 nm and a Stokes shift of 144 nm. A similar trend was found in the compound series **C21**-**C24**, in which the 1,3-dihydroisobenzofuran core was substituted by methyl, chloro, methoxy or fluoro group. To our surprise, compound **C24** which carries two fluoro groups, gave the highest fluorescence quantum yield in our experiment scope (Φ_F: 0.15). In comparison with compounds **C12** and **C17**, we can see that the position of methoxy

exerts influences on fluorescent properties in which **C17** has a lower Φ_F but a red-shifted emission wavelength than **C12**. Further introduction of two methoxy groups on the 1,3-dihydroisobenzofuran core of **C12** decreases Φ_F and induces slight blue-shift of $\lambda_{E\text{-}max}$. Nevertheless, compounds **C13** and **C21** have no obvious change in fluorescent properties (Table 3). When *N*,*N*-dimethyl and methyl in **C13** were replaced by piperidyl and hydroxymethyl, the resulting compound **C25** has the same Φ_F and 18 nm red-shift of $\lambda_{E\text{-}max}$ compared with those of **C13**. The influence of substituent position on fluorescent properties was further investigated on compounds **C14**, **C18** and **C19** in which chlorine atom was *para*-, *ortho*- and *meta*-substituted. As shown in Table 3, we can see that they have a similar $\lambda_{E\text{-}max}$ and **C18** has a smaller Φ_F but a large Stokes shift than **C14** and **C19**. When chlorine atom was substituted on the 1,3-dihydroisobenzofuran core to form **C22**, the fluorescence quantum yield and Stokes shift are both increased due to the short D-π-A structure. Optimizing the donor-acceptor structure also allowed us to red-shift $\lambda_{E\text{-}max}$ and increase the Stokes shift. For instance, compounds **C15** and **C16** containing trifluoromethyl or cyano group have longer $\lambda_{E\text{-}max}$ and remarkable Stokes shifts due to the strong electron-withdrawing ability of the substituents. Changing the substitution on the benzene ring from *N*,*N*-dimethylamino to piperidinyl and attaching a cyano group to the other benzene ring afforded compound **C27,** which exhibited the longest $\lambda_{E\text{-}max}$ in our experiment (597 nm) and an impressive Stokes shift of 166 nm. The $\lambda_{E\text{-}max}$ and Stokes shift are sharply decreased upon change of the position of cyano group, taking **C26** for example, the two values are decreased by 44 and 51 nm, respectively. The superior fluorescence properties of **C27** are attributed to the substantial contribution of an intramolecular charge transfer (ICT) from the electron donor (piperidinyl)

to the electron acceptor (CN) upon excitation by light [17, 18].

<Table 3>

3. Experimental

3.1. Materials and instruments

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. DMF was distilled under reduced pressure from calcium hydride. THF and toluene were distilled under nitrogen from sodium-benzophenone. Acetonitrile and 1,2-dichloroethane were distilled under nitrogen from calcium hydride. DMSO was dried with activatory 4Å molecular sieves before used. *t*-BuOK (1 M in THF) and KHMDS (0.91 M in THF) used in the catalytic reactions were purchased from a commercial source. The *exo*-cyclic enol ethers, 4-(piperidin-1-yl)benzaldehyde, 4-(pyrrolidin-1-yl)benzaldehyde and 4-morpholinobenzaldehyde were prepared according to literature methods [49-54]. Other chemicals were obtained from commercial sources, and were used without further purification.

^{1}H NMR and ^{13}C NMR were recorded on Bruker 400 MHz spectrometer. HRMS were obtained on a Waters LCT Premier XE spectrometer with acetonitrile or methanol as solvent. The UV absorption and fluorescence spectra were tested using UV-Vis spectrophotometer and fluorescence spectrophotometer provided by Varian. Chemical shifs (δ, ppm) in the ^{1}H NMR spectra were recorded using TMS as internal standard. Chemical shifs in ^{13}C{^{1}H } NMR spectra were internally referenced to $CHCl_3$ (δ = 77.16 ppm).

3.2. Synthesis route

Typical Procedure for the Preparation of 1,3-Dihydroisobenzofuran Derivatives . A flame-dried sealed tube equipped with *exo*-cyclic enol ether (0.3 mmol) and 18-crown-6 (23.8 mg, 0.09 mmol) was pumped to vacuum and exchanged with nitrogen for three times. Aldehyde (0.45 mmol), solution of *t*-BuOK in THF (60 μL) and DMF (1 mL) were then added successively under nitrogen atmosphere. The mixture was stirred at 110 ^{o}C and the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and concentrated aqueous solution of NH_4Cl was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 and the organic phase was washed with concentrated brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was passed through column chromatography on silica gel to afford the desired product **C**.

(1Z,3Z)-1-Benzylidene-3-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (C1) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a light green solid (79.5 mg, 81% yield). Mp: 112-115.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.90 (d, J = 7.40 Hz, 2H), 7.87 (d, J = 8.80 Hz, 2H), 7.62-7.68 (m, 2H), 7.40-7.46 (m, 5H), 6.98 (d, J = 8.84 Hz, 2H), 6.18 (s, 1H), 6.16 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 158.5, 152.0, 150.5, 135.3, 134.1, 133.6, 129.9, 129.3, 128.9, 128.7, 128.4, 127.9, 126.5, 120.0, 119.7, 114.2, 99.6, 99.2, 55.5; HRMS (ESI, TOF) calcd for $C_{23}H_{19}O_2^+$ $[M+H]^+$: 327.1380, found: 327.1389.

(1Z,3Z)-1-Benzylidene-3-(4-(methylthio)benzylidene)-1,3-dihydroisobenzofuran (C2). Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a light yellow-green solid (54.0 mg, 53% yield). Mp: 123.8-126.8 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.89 (d, J = 7.88 Hz, 2H), 7.84 (d, J = 8.28 Hz, 2H), 7.63-7.68 (m, 2H),

7.41-7.46 (m, 4H), 7.28-7.33 (m, 3H), 6.20 (s, 1H), 6.15 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 151.9, 151.6, 136.7, 135.1, 133.9, 133.9, 132.1, 129.3, 129.3, 128.9, 128.7, 128.5, 126.8, 126.7, 120.0, 119.9, 99.8, 99.4, 16.1; HRMS (ESI, TOF) calcd for $C_{23}H_{19}OS^+$ $[M+H]^+$: 343.1151, found: 343.1151.

(1Z,3Z)-1-Benzylidene-3-(4-(tert-butyl)benzylidene)-1,3-dihydroisobenzofuran (C3). Column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) on silica gel gave a light green solid (59.7 mg, 56% yield). Mp: 134.0-137.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.92 (d, J = 7.88 Hz, 2H), 7.85 (d, J = 8.28 Hz, 2H), 7.65-7.67 (m, 2H), 7.40-7.47 (m, 7H), 6.19 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 152.0, 151.4, 149.8, 135.2, 134.1, 133.9, 132.3, 129.3, 129.1, 128.7, 128.6, 128.4, 126.6, 125.6, 120.0, 119.9, 99.8, 99.6, 34.8, 31.5; HRMS (ESI, TOF) calcd for $C_{26}H_{25}O^+$ $[M+H]^+$: 353.1900, found: 353.1880.

(1Z,3Z)-1-Benzylidene-3-(4-methylbenzylidene)-1,3-dihydroisobenzofuran (C4). Column chromatography (eluent = petroleum ether/ethyl acetate 100:1 v/v) on silica gel gave a grass-green solid (46.4 mg, 50% yield). Mp: 110.2-113.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.91 (d, J = 7.56 Hz, 2H), 7.81 (d, J = 8.08 Hz, 2H), 7.63-7.67 (m, 2H), 7.40-7.46 (m, 5H), 7.23-7.28 (m, 2H), 6.18 (s, 1H), 6.18 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 152.0, 151.3, 136.6, 135.2, 134.1, 133.8, 132.3, 129.4, 129.3, 129.1, 128.7, 128.5, 128.5, 126.6, 120.0, 119.9, 99.9, 99.5, 21.5; HRMS (ESI, TOF) calcd for $C_{23}H_{19}O^+$ $[M+H]^+$: 311.1430, found: 311.1434.

4-((Z)-((Z)-3-Benzylideneisobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C5) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (100.4 mg, 99% yield). Mp: 145.6-148.2 ^{o}C; ^{1}H NMR (400 MHz,

$CDCl_3$, 25 °C) δ 7.92 (d, J = 7.84 Hz, 2H), 7.82 (d, J = 8.72 Hz, 2H), 7.59-7.65 (m, 2H), 7.34-7.49 (m, 5H), 6.79 (d, J = 8.68 Hz, 2H), 6.14 (s, 2H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.3, 149.3, 135.6, 134.4, 133.3, 129.8, 129.2, 128.6, 128.4, 126.2, 123.5, 119.9, 119.4, 112.5, 100.5, 98.5, 40.6; HRMS (ESI, TOF) calcd for $C_{24}H_{22}NO^+$ $[M+H]^+$: 340.1696, found: 340.1705.

1-(4-((Z)-((Z)-3-Benzylideneisobenzofuran-1(3H)-ylidene)methyl)phenyl)pyrrolidine (C6) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a dark yellow solid (100.2 mg, 91% yield). Mp: 195.8-199.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.92 (d, J = 7.44 Hz, 2H), 7.82 (d, J = 8.72 Hz, 2H), 7.59-7.65 (m, 2H), 7.33-7.46 (m, 4H), 7.21-7.26 (m, 1H), 6.64 (d, J = 8.36 Hz, 2H), 6.15 (s, 1H), 6.14 (s, 1H), 3.38 (br s, 4H), 2.04 (t, J = 6.52 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 152.4, 148.8, 146.8, 135.6, 134.6, 133.2, 129.9, 129.1, 128.6, 128.3, 128.2, 126.1, 122.4, 119.9, 119.3, 111.8, 100.9, 98.3, 47.7, 25.6; HRMS (ESI, TOF) calcd for $C_{26}H_{24}NO^+$ $[M+H]^+$: 366.1852, found: 366.1860.

1-(4-((Z)-((Z)-3-Benzylideneisobenzofuran-1(3H)-ylidene)methyl)phenyl)piperidine (C7) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow-green solid (109.4 mg, 96% yield). Mp: 142.0-146.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.91 (d, J = 7.48 Hz, 2H), 7.82 (d, J = 8.80 Hz, 2H), 7.60-7.66 (m, 2H), 7.37-7.46 (m, 4H), 7.22-7.26 (m, 1H), 7.00 (d, J = 8.04 Hz, 2H), 6.16 (s, 1H), 6.14 (s, 1H), 3.26 (t, J = 5.32 Hz, 4H), 1.75 (br s, 4H), 1.60-1.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 152.2, 150.7, 149.9, 135.4, 134.3, 133.5, 129.6, 129.2, 128.6, 128.4, 126.3, 125.7, 119.9, 119.5, 116.1, 100.2, 98.8, 50.3, 25.9, 24.5; HRMS (ESI, TOF) calcd for $C_{27}H_{26}NO^+$

$[M+H]^+$: 380.2009, found: 380.2017.

4-(4-((Z)-((Z)-3-Benzylideneisobenzofuran-1(3H)-ylidene)methyl)phenyl)morpholine (C8) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave a yellow-green solid (100.5 mg, 88% yield). Mp: 189.6-192.2 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 7.91 (d, J = 6.52 Hz, 2H), 7.85 (d, J = 8.68 Hz, 2H), 7.61-7.67 (m, 2H), 7.39-7.45 (m, 5H), 6.97 (d, J = 8.68 Hz, 2H), 6.17 (s, 1H), 6.14 (s, 1H), 3.90 (t, J = 4.80 Hz, 4H), 3.25 (t, J = 4.88 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC) δ 152.1, 150.3, 149.8, 135.4, 134.2, 133.6, 129.6, 129.2, 128.8, 128.6, 128.4, 126.8, 126.4, 120.0, 119.6, 115.5, 99.8, 99.1, 67.0, 49.1; HRMS (ESI, TOF) calcd for $C_{26}H_{24}NO_2^+$ $[M+H]^+$: 382.1802, found: 382.1803.

(1Z,3Z)-1-Benzylidene-3-(2-methoxybenzylidene)-1,3-dihydroisobenzofuran (C9). Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a light yellow-green solid (50.7 mg, 52% yield). Mp: 173.4-176.4 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 8.47 (dd, J_1 = 1.48 Hz, J_2 = 7.80 Hz, 1H), 7.90 (d, J = 7.52 Hz, 2H), 7.72-7.75 (m, 1H), 7.64-7.67 (m, 1H), 7.38-7.43 (m, 4H), 7.22-7.26 (m, 2H), 7.10 (t, J = 7.48 Hz, 1H), 6.94 (d, J = 8.16 Hz, 1H), 6.66 (s, 1H), 6.18 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC) δ 156.3, 152.0, 151.9, 135.2, 134.3, 133.8, 129.3, 129.2, 129.1, 128.7, 128.5, 127.9, 126.5, 124.0, 120.9, 120.2, 119.9, 110.5, 99.5, 93.5, 55.7; HRMS (ESI, TOF) calcd for $C_{23}H_{19}O_2^+$ $[M+H]^+$: 327.1380, found: 327.1329.

(1Z,3Z)-1-Benzylidene-3-(3,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (C10) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave a light green solid (57.0 mg, 53% yield). Mp: 164.8-166.6 ^oC; ^1H NMR (400 MHz,

$CDCl_3$, 25 °C) δ 7.89 (d, J = 7.32 Hz, 2H), 7.62-7.67 (m, 3H), 7.35-7.43 (m, 4H), 7.29-7.31 (m, 1H), 7.21-7.25 (m, 1H), 6.92 (d, J = 8.36 Hz, 1H), 6.18 (s, 1H), 6.16 (s, 1H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 152.1, 150.5, 149.1, 148.2, 135.3, 134.1, 133.7, 129.3, 129.0, 128.6, 128.4, 128.2, 126.6, 121.9, 119.9, 119.6, 111.3, 111.2, 100.0, 99.3, 56.3, 56.0; HRMS (ESI, TOF) calcd for $C_{24}H_{21}O_3^+$ $[M+H]^+$: 357.1485, found: 357.1495.

(1Z,3Z)-1-Benzylidene-3-(2,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (C11). Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave a yellow-green solid (96.1 mg, 90% yield). Mp: 123.8-127.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.40 (d, J = 8.64 Hz, 1H), 7.89 (d, J = 7.44 Hz, 2H), 7.68-7.71 (m, 1H), 7.63-7.66 (m, 1H), 7.38-7.44 (m, 4H), 7.21-7.26 (m, 1H), 6.64 (dd, J_1 = 2.40 Hz, J_2 = 8.68 Hz, 1H), 6.58 (s, 1H), 6.52 (d, J = 2.44 Hz, 1H), 6.15 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 159.9, 157.6, 152.2, 150.6, 135.5, 134.5, 133.6, 130.0, 129.2, 128.7, 128.6, 128.4, 126.3, 119.9, 119.8, 117.1, 104.9, 98.9, 98.4, 93.5, 55.7, 55.6; HRMS (ESI, TOF) calcd for $C_{24}H_{21}O_3^+$ $[M+H]^+$: 357.1485, found: 357.1488.

4-((Z)-((Z)-3-(4-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C12) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave a yellow solid (92.1 mg, 83% yield). Mp: 156.4-159.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.86 (d, J = 8.80 Hz, 2H), 7.82 (d, J = 8.80 Hz, 2H), 7.58-7.62 (m, 2H), 7.35-7.38 (m, 2H), 6.98 (d, J = 8.88 Hz, 2H), 6.82 (br s, 2H), 6.12 (s, 1H), 6.11 (s, 1H), 3.88 (s, 3H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 158.1, 150.9, 149.5, 149.2, 134.2, 133.6, 129.6, 128.8, 128.4, 123.7, 119.6, 119.4, 114.1, 112.6, 99.9, 98.3, 55.5, 40.7; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO_2^+$ $[M+H]^+$: 370.1802, found: 370.1810.

N,N-Dimethyl-4-((Z)-((Z)-3-(4-methylbenzylidene)isobenzofuran-1(3H)-ylidene)methyl)aniline (C13) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (91.2 mg, 86% yield). Mp: 164.6-168.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.82 (d, J = 8.32 Hz, 4H), 7.58-7.63 (m, 2H), 7.35-7.38 (m, 2H), 7.23-7.26 (m, 2H), 6.80 (d, J = 8.32 Hz, 2H), 6.12 (s, 2H), 3.03 (s, 6H), 2.40 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C): δ 151.7, 149.4, 149.3, 136.0, 134.4, 133.5, 132.7, 129.7, 129.4, 129.0, 128.4, 128.3, 123.6, 119.8, 119.4, 112.6, 100.2, 98.6, 40.7, 21.5; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO^{+}$ $[M+H]^{+}$: 354.1852, found: 354.1855.

4-((Z)-((Z)-3-(4-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C14) [55]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave an orange-yellow solid (99.8 mg, 89% yield). Mp: 179.2-181.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.84 (d, J = 8.60 Hz, 2H), 7.78 (d, J = 8.84 Hz, 2H), 7.60-7.64 (m, 2H), 7.37-7.41 (m, 4H), 6.80 (d, J = 8.28 Hz, 2H), 6.16 (s, 1H), 6.09 (s, 1H), 3.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 152.7, 149.4, 149.2, 134.5, 134.2, 133.1, 131.4, 129.8, 129.4, 129.4, 128.7, 128.4, 123.3, 119.9, 119.4, 112.6, 100.9, 97.3, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ $[M]^{+}$: 373.1233, found: 373.1230.

N,N-Dimethyl-4-((Z)-((Z)-3-(4-(trifluoromethyl)benzylidene)isobenzofuran-1(3H)-ylidene)methyl)aniline (C15). Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a dark yellow solid (100.6 mg, 82% yield). Mp: 207-208.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.99 (d, J = 8.20 Hz, 2H), 7.79 (d, J = 8.88 Hz, 2H), 7.61-7.66 (m, 4H), 7.36-7.46 (m, 2H), 6.80 (d, J = 8.92 Hz, 2H), 6.19 (s, 1H), 6.14 (s, 1H), 3.05 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 154.0, 149.6, 149.0, 139.2, 134.8, 132.8,

129.9, 129.8, 128.5, 128.1, 127.6, 127.2, 126.0, 125.5 (q, *J* = 3.81 Hz), 123.3, 122.9, 120.2, 119.5, 112.5, 101.6, 97.0, 40.6; HRMS (EI, TOF) calcd for $C_{25}H_{20}F_3NO$ $[M]^+$: 407.1497, found: 407.1499.

4-((Z)-((Z)-3-(4-(Dimethylamino)benzylidene)isobenzofuran-1(3H)-ylidene)methyl)benzonitrile (C16). Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave an orange solid (92.1 mg, 84% yield). Mp: 199.2-202.2 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 7.96 (d, *J* = 8.32 Hz, 2H), 7.77 (d, *J* = 8.72 Hz, 2H), 7.62-7.68 (m, 4H), 7.37-7.47 (m, 2H), 6.79 (d, *J* = 8.76 Hz, 2H), 6.22 (s, 1H), 6.11 (s, 1H), 3.06 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC) δ 154.9, 149.7, 148.8, 140.4, 134.9, 132.5, 132.3, 130.1, 130.0, 128.5, 128.3, 122.7, 120.3, 119.7, 119.5, 112.4, 108.4, 102.3, 96.8, 40.5; HRMS (EI, TOF) calcd for $C_{25}H_{20}N_2O$ $[M]^+$: 364.1576, found: 364.1577.

4-((Z)-((Z)-3-(2-Methoxybenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C17) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave a yellow solid (91.2 mg, 80% yield). Mp: 187.4-190.2 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 8.50 (d, *J* = 7.72 Hz, 1H), 7.81 (d, *J* = 8.56 Hz, 2H), 7.71 (d, *J* = 6.88 Hz, 1H), 7.58-7.61 (m, 1H), 7.35-7.38 (m, 2H), 7.21-7.24 (m, 1H), 7.09-7.14 (m, 1H), 6.93 (d, *J* = 8.20 Hz, 1H), 6.78 (d, *J* = 8.60 Hz, 2H), 6.59 (s, 1H), 6.12 (s, 1H), 3.92 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC): δ 156.3, 152.4, 149.4, 149.3, 134.4, 133.8, 129.7, 129.2, 129.0, 128.3, 127.3, 124.6, 123.7, 120.9, 120.2, 119.3, 112.6, 110.6, 100.2, 92.2, 55.8, 40.6; HRMS (ESI, TOF) calcd for $C_{25}H_{24}NO_2^+$ $[M+H]^+$: 370.1802, found: 370.1775.

4-((Z)-((Z)-3-(2-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethy

laniline (C18) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (84.2 mg, 75% yield). Mp: 154.2-157.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 8.55 (d, J = 7.92 Hz, 1H), 7.71-7.80 (m, 3H), 7.61 (d, J = 7.52 Hz, 1H), 7.33-7.44 (m, 4H), 7.11-7.19 (m, 1H), 6.76 (d, J = 8.68 Hz, 2H), 6.55 (s, 1H), 6.16 (s, 1H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 153.6, 149.4, 149.0, 134.6, 133.4, 133.2, 132.4, 129.8, 129.7, 129.6, 128.5, 127.1, 126.8, 123.2, 120.4, 119.4, 112.5, 101.2, 94.0, 40.6; HRMS (ESI, TOF) calcd for $C_{24}H_{21}ClNO^{+}$ $[M+H]^{+}$: 374.1306, found: 374.1306.

4-((Z)-((Z)-3-(3-Chlorobenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethy laniline (C19) [55]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave an orange solid (101.3 mg, 90% yield). Mp: 118.6-120.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 8.22 (t, J = 1.68 Hz, 1H), 7.82 (d, J = 8.88 Hz, 2H), 7.61-7.64 (m, 2H), 7.52 (d, J = 7.76 Hz, 1H), 7.29-7.42 (m, 3H), 7.20 (dd, J_1 = 1.00 Hz, J_2 = 7.96 Hz, 1H), 6.84 (d, J = 8.80 Hz, 2H), 6.19 (s, 1H), 6.08 (s, 1H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 153.3, 149.5, 149.0, 137.4, 134.6, 134.5, 132.9, 129.8, 129.7, 129.5, 128.4, 127.8, 126.5, 126.0, 123.1, 120.1, 119.4, 112.7, 101.3, 97.1, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ $[M]^{+}$: 373.1233, found: 373.1229.

N,N-Dimethyl-4-((Z)-((Z)-3-(naphthalen-2-ylmethylene)isobenzofuran-1(3H)-ylidene) methyl)aniline (C20) [46]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave an orange-yellow solid (108.5 mg, 93% yield). Mp: 178.5-180.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 8.55 (s, 1H), 7.90-7.94 (m, 4H), 7.82-7.87 (m, 2H), 7.67-7.69 (m, 1H), 7.62-7.64 (m, 1H), 7.38-7.50 (m, 4H), 6.86 (d, J = 8.84 Hz, 2H), 6.29 (s, 1H), 6.19 (s, 1H), 3.06 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 151.7, 148.4, 148.3,

133.4, 133.0, 132.3, 132.1, 131.2, 128.8, 128.2, 127.4, 127.1, 126.9, 126.7, 126.2, 125.7, 125.1, 124.5, 122.5, 118.9, 118.4, 111.5, 99.7, 97.6, 39.6; HRMS (ESI, TOF) calcd for $C_{28}H_{24}NO^+$ $[M+H]^+$: 390.1852, found: 390.1861.

4-((Z)-((Z)-3-Benzylidene-5-methylisobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C21) [55]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (94.6 mg, 89% yield). Mp: 163.0-166.0 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 7.91 (d, J = 7.84 Hz, 2H), 7.81 (d, J = 8.72 Hz, 2H), 7.40-7.51 (m, 4H), 7.20-7.26 (m, 2H), 6.79 (d, J = 8.64 Hz, 2H), 6.11 (s, 1H), 6.08 (s, 1H), 3.02 (s, 6H), 2.45 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC) δ 152.3, 149.5, 149.2, 138.6, 135.7, 133.7, 132.2, 130.6, 129.6, 128.6, 128.4, 126.1, 123.8, 120.0, 119.2, 112.7, 99.7, 98.3, 40.7, 21.8; HRMS (EI, TOF) calcd for $C_{25}H_{23}NO$ $[M]^+$: 353.1780, found: 353.1781.

4-((Z)-((Z)-3-Benzylidene-5-chloroisobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C22) [55]. Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (109.5 mg, 98% yield). Mp: 175.5-178.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC) δ 7.89 (d, J = 7.60 Hz, 2H), 7.79 (d, J = 8.76 Hz, 2H), 7.60 (s, 1H), 7.51 (d, J = 8.28 Hz, 1H), 7.44 (t, J = 7.56 Hz, 2H), 7.32-7.35 (m, 1H), 7.23-7.28 (m, 1H), 6.78 (d, J = 8.72 Hz, 2H), 6.11 (s, 2H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^oC) δ 151.1, 149.5, 148.5, 135.1, 134.9, 134.2, 133.0, 129.8, 129.5, 128.7, 128.5, 126.6, 123.2, 120.5, 119.9, 112.5, 101.1, 99.6, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{20}ClNO$ $[M]^+$: 373.1233, found: 373.1234.

4-((Z)-((Z)-5,6-Dimethoxy-3-(4-methoxybenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N,N-dimethylaniline (C23). Column chromatography (eluent = petroleum ether/ethyl

acetate 40:1 v/v) on silica gel gave a brown-yellow solid (68.2 mg, 53% yield). Mp: 179.6-182.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.84 (d, J = 8.56 Hz, 2H), 7.79 (d, J = 8.60 Hz, 2H), 6.96-7.01 (m, 4H), 6.81 (d, J = 8.28 Hz, 2H), 5.96 (s, 1H), 5.94 (s, 1H), 3.99 (s, 6H), 3.87 (s, 3H), 3.02 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 157.9, 151.1, 150.8, 149.7, 149.1, 129.3, 128.6, 127.4, 126.7, 124.0, 114.1, 112.7, 101.1, 100.9, 98.4, 96.8, 56.3, 55.5, 40.7; HRMS (EI, TOF) calcd for $C_{27}H_{27}NO_4$ $[M]^+$: 429.1940, found: 429.1937.

4-((Z)-((Z)-5-Fluoro-3-(4-fluorobenzylidene)isobenzofuran-1(3H)-ylidene)methyl)-N, N-dimethylaniline (C24). Column chromatography (eluent = petroleum ether/ethyl acetate 80:1 v/v) on silica gel gave a yellow solid (37.9 mg, 34% yield, 0.12 mmol *t*-BuOK and 0.18 mmol 18-crown-6 were used). Mp: 190.8-193.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.84-7.89 (m, 2H), 7.75 (d, J = 8.48 Hz, 2H), 7.53-7.57 (m, 1H), 7.24-7.26 (m, 1H), 7.10-7.14 (m, 3H), 6.78 (d, J = 8.40 Hz, 2H), 6.07 (s, 1H), 6.05 (s, 1H), 3.03 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 164.4, 162.7, 162.0, 160.3, 151.0, 149.4, 148.5, 135.0 (d, $J_{C\text{-}F}$ = 9.55 Hz), 131.4, 131.3, 130.5, 130.0 (d, $J_{C\text{-}F}$ = 7.85 Hz), 129.6, 123.2, 121.1 (d, $J_{C\text{-}F}$ = 9.08 Hz), 117.4 (d, $J_{C\text{-}F}$ = 24.7 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.4 Hz), 112.5, 106.2 (d, $J_{C\text{-}F}$ = 24.4 Hz), 100.3, 98.4, 40.6; HRMS (EI, TOF) calcd for $C_{24}H_{19}F_2NO$ $[M]^+$: 375.1435, found: 375.1443.

(4-((Z)-((Z)-3-(4-(Piperidin-1-yl)benzylidene)isobenzofuran-1(3H)-ylidene)methyl)phenyl)methanol (C25). Column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v) on silica gel gave a yellow solid (99.0 mg, 81% yield, 0.12 mmol *t*-BuOK and 0.18 mmol 18-crown-6 were used). Mp: 196.6-198.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.91 (d, J = 8.00 Hz, 2H), 7.81 (d, J = 8.64 Hz, 2H), 7.63 (t, J = 8.12 Hz, 2H), 7.44 (d, J = 8.12 Hz, 2H), 7.37-7.41 (m, 2H), 7.00 (d, J = 8.48 Hz, 2H), 6.15 (s, 2H), 4.74 (s, 2H), 3.26 (t, J = 4.84 Hz,

4H), 1.73-1.75 (m, 4H), 1.61-1.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 152.3, 150.8, 149.9, 138.8, 135.0, 134.4, 133.5, 129.6, 129.2, 128.6, 128.5, 127.4, 125.7, 119.9, 119.5, 116.2, 100.3, 98.5, 65.5, 50.3, 25.9, 24.5; HRMS (EI, TOF) calcd for $C_{28}H_{27}NO_2$ $[M]^+$: 409.2042, found: 409.2039.

(1Z,3Z)-3-Benzylidene-1-(4-(piperidin-1-yl)benzylidene)-1,3-dihydroisobenzofuran-5-carbonitrile (C26) Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave an orange-yellow solid (77.0 mg, 63% yield). Mp: 236.6-239.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.88-7.91 (m, 3H), 7.81 (d, J = 8.80 Hz, 2H), 7.60-7.68 (m, 2H), 7.43-7.48 (m, 2H), 7.28-7.31 (m, 1H), 6.98 (d, J = 8.84 Hz, 2H), 6.24 (s, 1H), 6.20 (s, 1H), 3.27-3.31 (m, 4H), 1.74 (br s, 4H), 1.63-1.65 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 151.2, 150.4, 148.3, 137.7, 134.6, 133.9, 132.1, 130.2, 128.8, 128.6, 127.1, 124.4, 124.2, 120.2, 118.8, 115.7, 111.6, 103.7, 100.7, 49.8, 25.8, 24.5; HRMS (EI, TOF) calcd for $C_{28}H_{24}N_2O$ $[M]^+$: 404.1889, found: 404.1890.

4-((Z)-((Z)-3-(4-(Piperidin-1-yl)benzylidene)isobenzofuran-1(3H)-ylidene)methyl)benzonitrile (C27). Column chromatography (eluent = petroleum ether/ethyl acetate 60:1 v/v) on silica gel gave an orange-yellow solid (99.5 mg, 82% yield). Mp: 227.8-230.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C) δ 7.95 (d, J = 8.28 Hz, 2H), 7.76 (d, J = 8.68 Hz, 2H), 7.62-7.68 (m, 4H), 7.38-7.48 (m, 2H), 6.99 (d, J = 8.56 Hz, 2H), 6.21 (s, 1H), 6.12 (s, 1H), 3.27-3.31 (m, 4H), 1.74-1.76 (m, 4H), 1.63-1.67 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C) δ 154.8, 151.0, 149.3, 140.3, 134.7, 132.7, 132.3, 130.1, 129.8, 128.8, 128.3, 124.8, 120.3, 119.7, 119.6, 115.8, 108.5, 101.9, 97.1, 50.0, 25.8, 24.5; HRMS (EI, TOF) calcd for $C_{28}H_{24}N_2O$ $[M]^+$: 404.1889, found: 404.1891.

4. Conclusions

In summary, we have developed a facile method to synthesize 1,3-dihydroisobenzofuran derivatives using *t*-BuOK as the catalyst. The resulting compounds proved to be served as tunable fluorophores, for which the maximum emission wavelengths ranged from 438 to 597 nm and the Stokes shift reached up to 166 nm. The results might open a gate for the further application of the readily available 1,3-dihydroisobenzofuran framework as the novel chromophore in electronic devices and fluorescence probes.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/.

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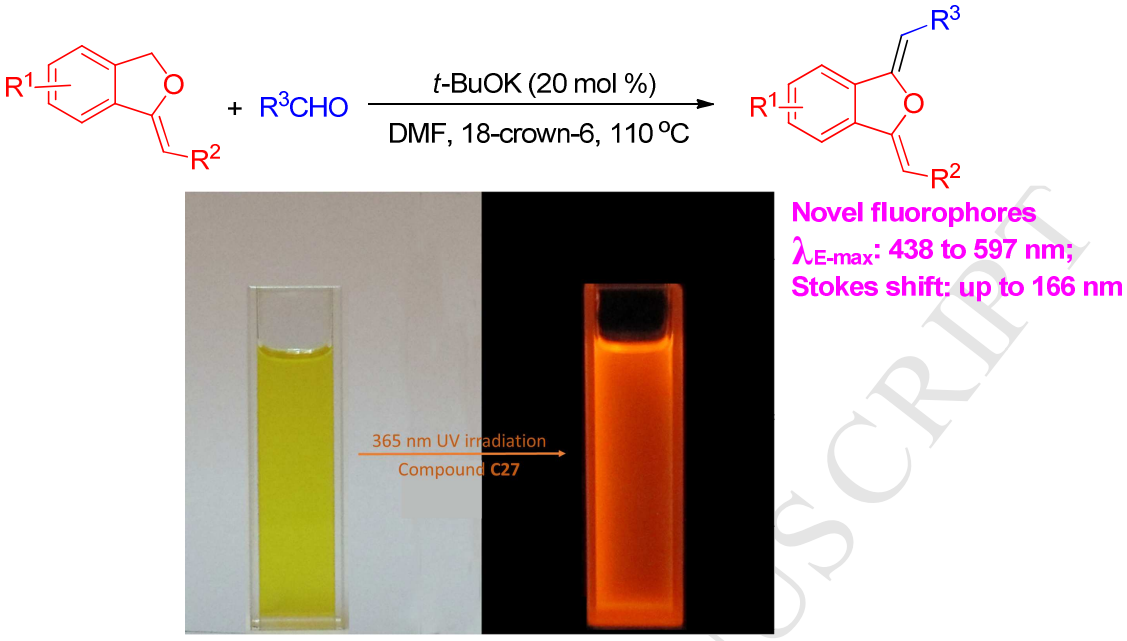
Graphical Abstract



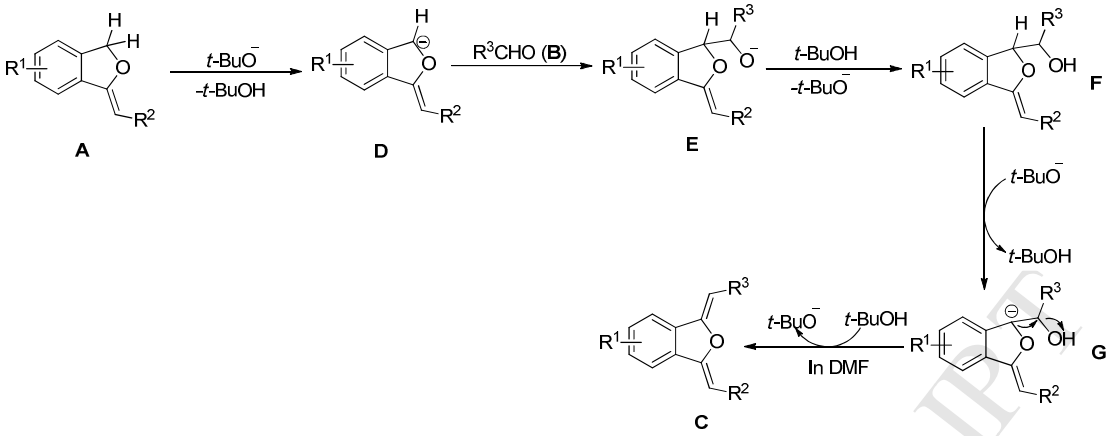
Scheme and Figure captions

Scheme 1. Reaction mechanism of *t*-BuOK catalyzed *exo*-cyclic enol ethers **A** and aldehydes **B**.

Fig. 1. UV-vis absorption spectra of compounds **C1**-**C27** in CH_2Cl_2 (10^{-5} M) at 25 ^oC.

Fig. 2. UV-vis absorption spectra of compound **C16** in different solvents (10^{-5} M) at 25 ^oC.

Fig. 3. Fluorescence spectra of compounds **C1**-**C27** in CH_2Cl_2 (10^{-5} M) at 25 ^oC. $\lambda_{A\text{-}max}$ of each product was chosen as the excitation wavelength.



Scheme 1.

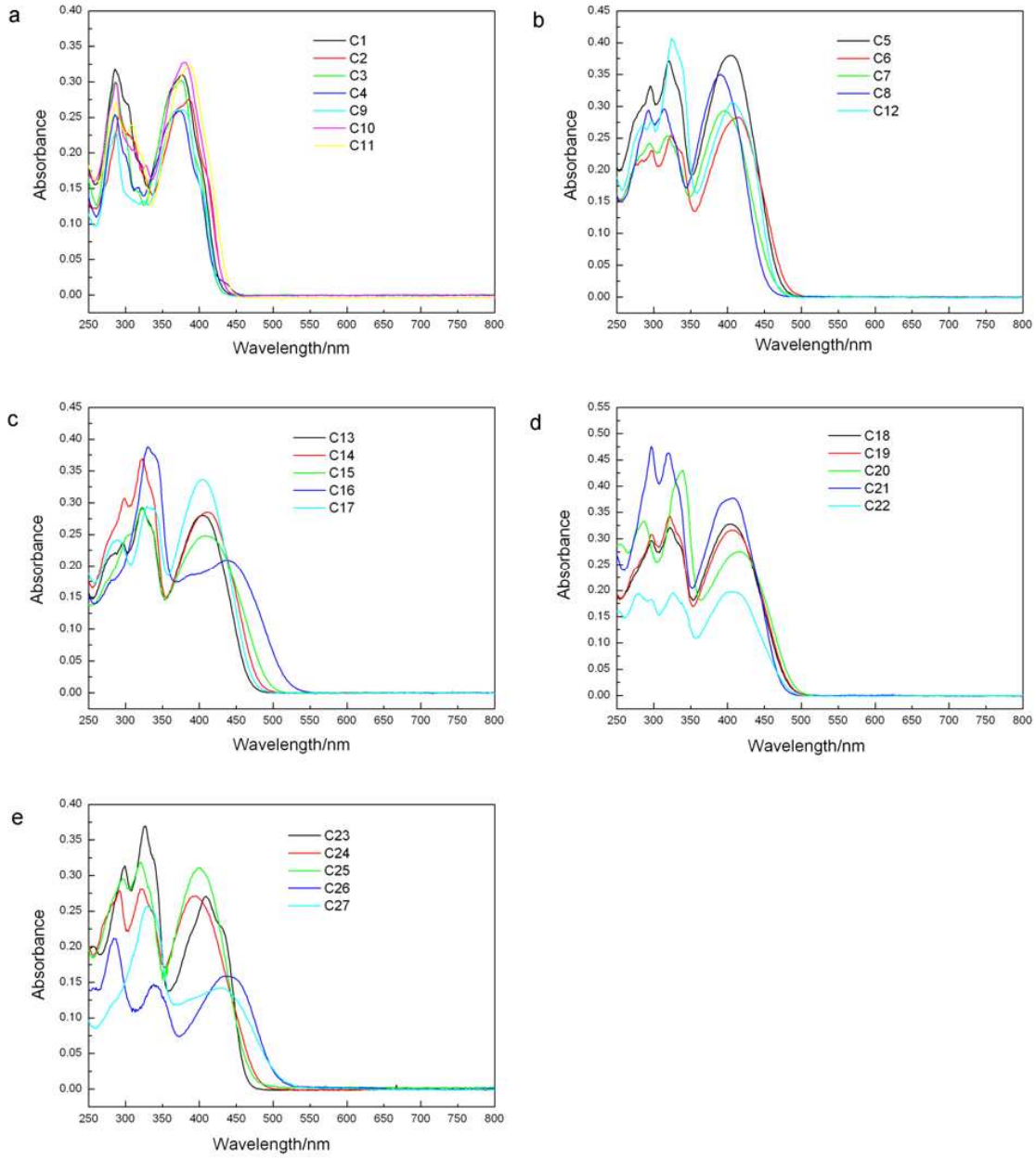

a
Absorbance
Wavelength/nm
C1
C2
C3
C4
C9
C10
C11
b
Absorbance
Wavelength/nm
C5
C6
C7
C8
C12
c
Absorbance
Wavelength/nm
C13
C14
C15
C16
C17
d
Absorbance
Wavelength/nm
C18
C19
C20
C21
C22
e
Absorbance
Wavelength/nm
C23
C24
C25
C26
C27

Fig. 1.

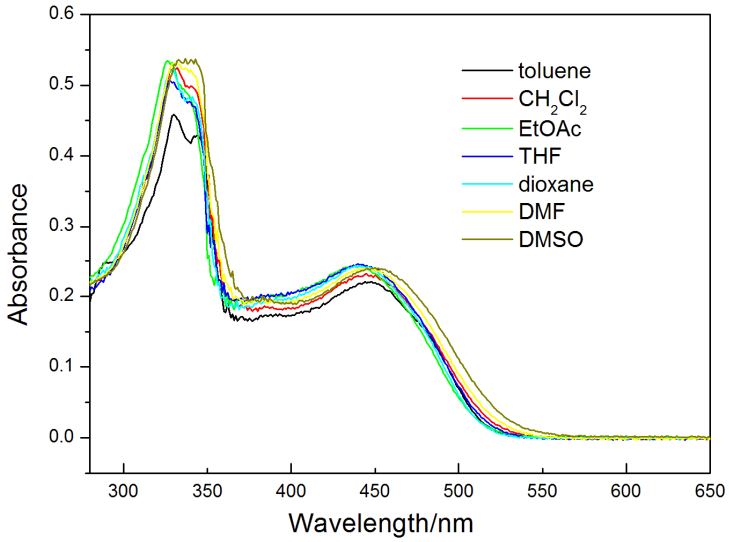


Fig. 2.

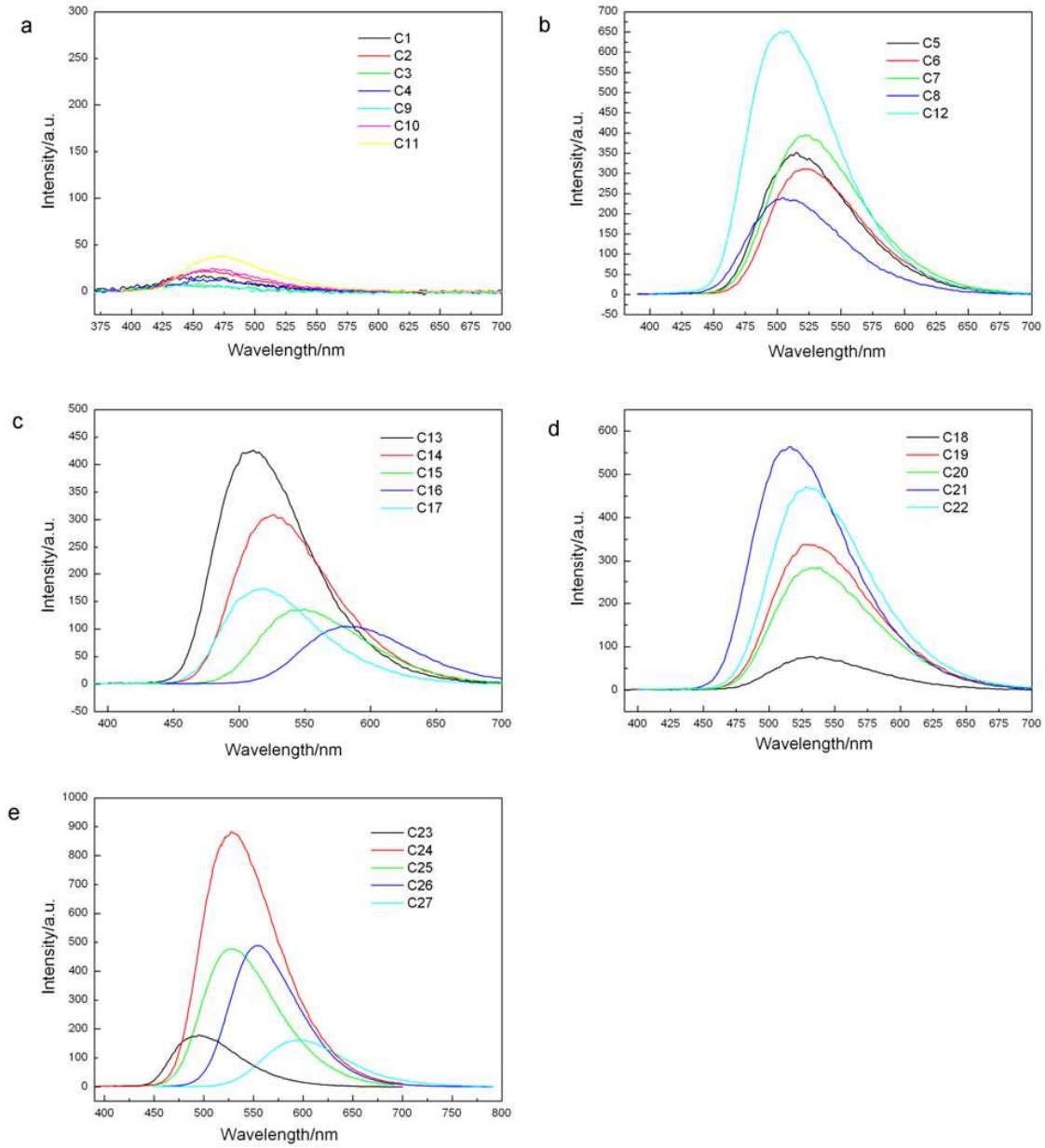
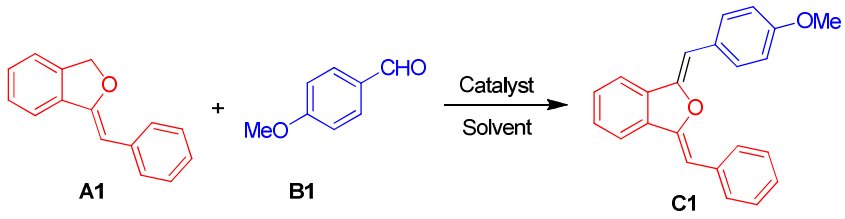

a
Intensity/a.u.
Wavelength/nm
C1
C2
C3
C4
C9
C10
C11
b
Intensity/a.u.
Wavelength/nm
C5
C6
C7
C8
C12
c
Intensity/a.u.
Wavelength/nm
C13
C14
C15
C16
C17
d
Intensity/a.u.
Wavelength/nm
C18
C19
C20
C21
C22
e
Intensity/a.u.
Wavelength/nm
C23
C24
C25
C26
C27

Fig. 3.

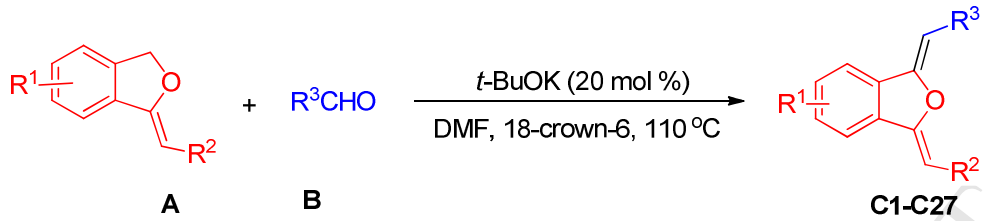
Table 1. Optimization of conditions for the reaction of **A1** with **B1**.[a]



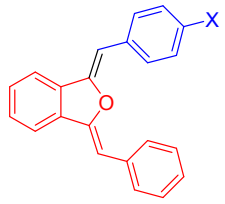
entry	catalyst	solvent	temp (^{o}C)	time (h)	yield (%)[b]
1	*t*-BuOK	DMF	80	10	46
2	KHMDS	DMF	80	10	44
3	KOH	DMF	80	10	43
4	NaH	DMF	80	10	24
5	DBU	DMF	80	10	n.d.
6	K_2CO_3	DMF	80	10	n.d.
7[c]	*t*-BuOK	DMF	80	4.5	80
8[c]	*t*-BuOK	DMF	110	2	82
9[c]	*t*-BuOK	DMSO	110	2	n.d.
10[c]	*t*-BuOK	THF	110	2	45
11[c]	*t*-BuOK	toluene	110	2	14
12[c]	*t*-BuOK	MeCN	110	2	n.d.
13[c]	*t*-BuOK	DCE	110	2	n.d.
14[d]	*t*-BuOK	DMF	110	10	n.d.

[a]Reaction conditions: **A1** (0.2 mmol), **B1** (0.3 mmol), catalyst (0.04 mmol), solvent (1.0 mL), unless otherwise noted. [b]Determined by ^{1}H NMR using $PhSiMe_3$ as the internal standard. [c]30 mol% of 18-crown-6 was added. [d]10 mol% of *t*-BuOK and 15 mol% of 18-crown-6 were used, n.d. = not detected.

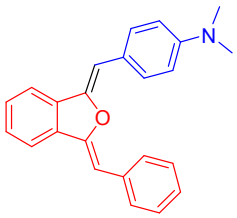
Table 2. Reaction of *exo*-cyclic enol ethers with aldehydes using *t*-BuOK as the Catalyst.[a]



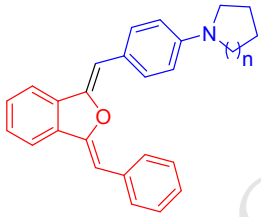
A **B** **C1-C27**



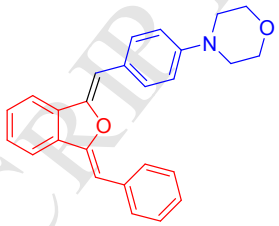
X = OMe, 2 h, **C1**, 81%
X = SMe, 5 h, **C2**, 53%
X = *t*-Bu, 5 h, **C3**, 56%
X = Me, 3 h, **C4**, 50%



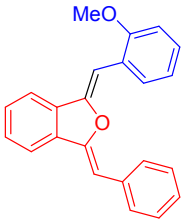
2 h, **C5**, 99%



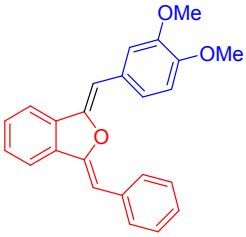
n = 1, 5 h, **C6**, 91%
n = 2, 2 h, **C7**, 96%



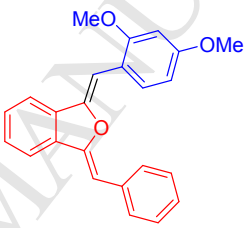
2 h, **C8**, 88%



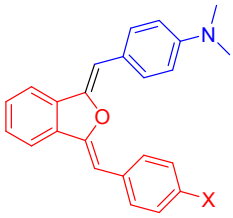
2 h, **C9**, 52%



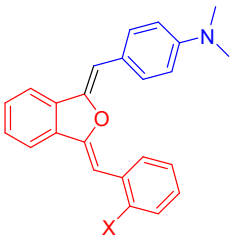
2 h, **C10**, 53%



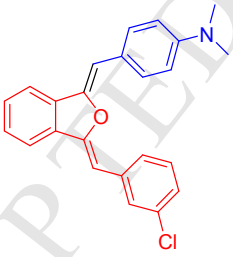
2 h, **C11**, 90%



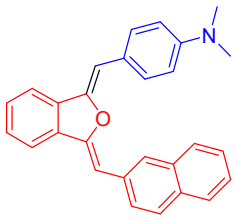
X = OMe, 3 h, **C12**, 83%
X = Me, 2 h, **C13**, 86%
X = Cl, 3 h, **C14**, 89%
X = CF_3, 3 h, **C15**, 82%
X = CN, 2 h, **C16**, 84%



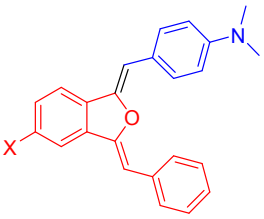
X = OMe, 8 h, **C17**, 80%
X = Cl, 7 h, **C18**, 75%



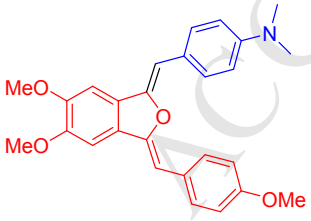
3 h, **C19**, 90%



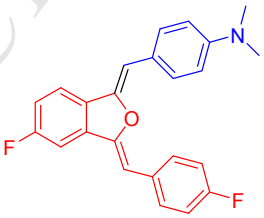
2.5 h, **C20**, 93%



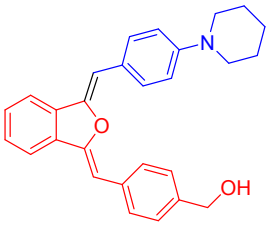
X = Me, 6 h, **C21**, 89%
X = Cl, 2 h, **C22**, 98%



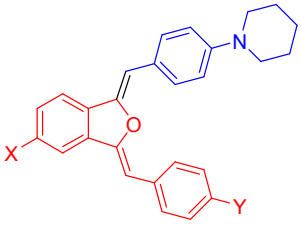
4 h, **C23**, 53%



9 h, **C24**, 34%[b]



3 h, **C25**, 81%[b]



X = CN, Y = H, 3 h, **C26**, 63%
X = H, Y = CN, 3 h, **C27**, 82%

[a]Reaction conditions: *exo*-cyclic enol ethers **A** (0.3 mmol), aryl aldehydes **B** (0.45 mmol), *t*-BuOK (0.06 mmol), 18-crown-6 (0.09 mmol), DMF (1.0 mL), 110 °C. [b]0.12 mmol of *t*-BuOK and 0.18 mmol of 18-crown-6 were used. Isolated yields are shown.

Table 3. UV absorption and fluorescence emission properties of compounds **C1**-**C27**.[a]

product	ε_{max} ($10^4 \cdot M^{-1} \cdot cm^{-1}$)	$\Phi_F \times 100$	$\lambda_{A\text{-}max}$ (nm)	$\lambda_{E\text{-}max}$ (nm)	Stokes shift (nm)
C1	3.10	0.21	376	448	72
C2	2.75	0.30	386	450	64
C3	3.02	0.081	375	438	63
C4	2.59	0.20	373	472	99
C5	3.80	4.31	404	515	111
C6	2.83	5.06	414	522	108
C7	2.93	5.52	397	523	126
C8	3.50	2.90	390	505	115
C9	2.61	0.070	376	448	72
C10	3.27	0.29	380	466	86
C11	3.23	0.43	386	473	87
C12	3.06	9.36	407	508	101
C13	2.80	6.37	405	511	106
C14	2.85	4.31	413	527	114
C15	2.48	2.43	408	550	142
C16	2.10	2.25	438	582	144
C17	3.36	2.53	406	521	115
C18	3.28	1.12	402	532	130

C19	3.16	4.77	407	525	118
C20	2.75	4.49	417	539	122
C21	3.77	6.18	407	516	109
C22	1.98	10.3	406	533	127
C23	2.71	2.62	409	496	87
C24	2.71	15.0	396	528	132
C25	3.11	6.37	400	529	129
C26	1.59	11.7	438	553	115
C27	1.42	5.24	431	597	166

[a] Spectral properties of compounds **C1**-**C27** in CH_2Cl_2 solution (10^{-5} M) at 25 ^{o}C.

Supporting Information

A concise synthesis of tunable fluorescent 1,3-dihydroisobenzofuran derivatives as new fluorophores

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1. Calculation equations for fluorescence quantum yield Φ_F

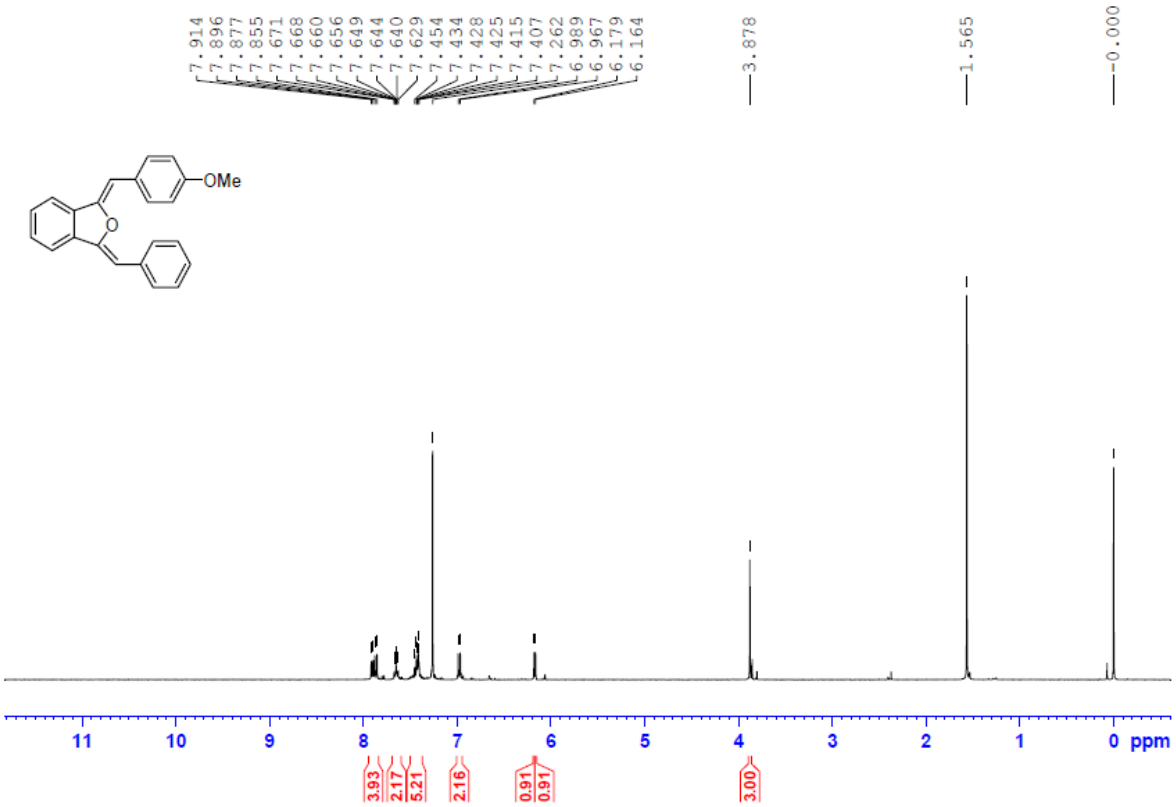
The fluorescence quantum yield (Φ_F) was calculated using the following equation [1, 2]:

$$\Phi_F = \Phi_s \times \frac{A_s}{A_r} \times \frac{n_r^2}{n_s^2} \times \frac{F_r}{F_s} \qquad (2)$$

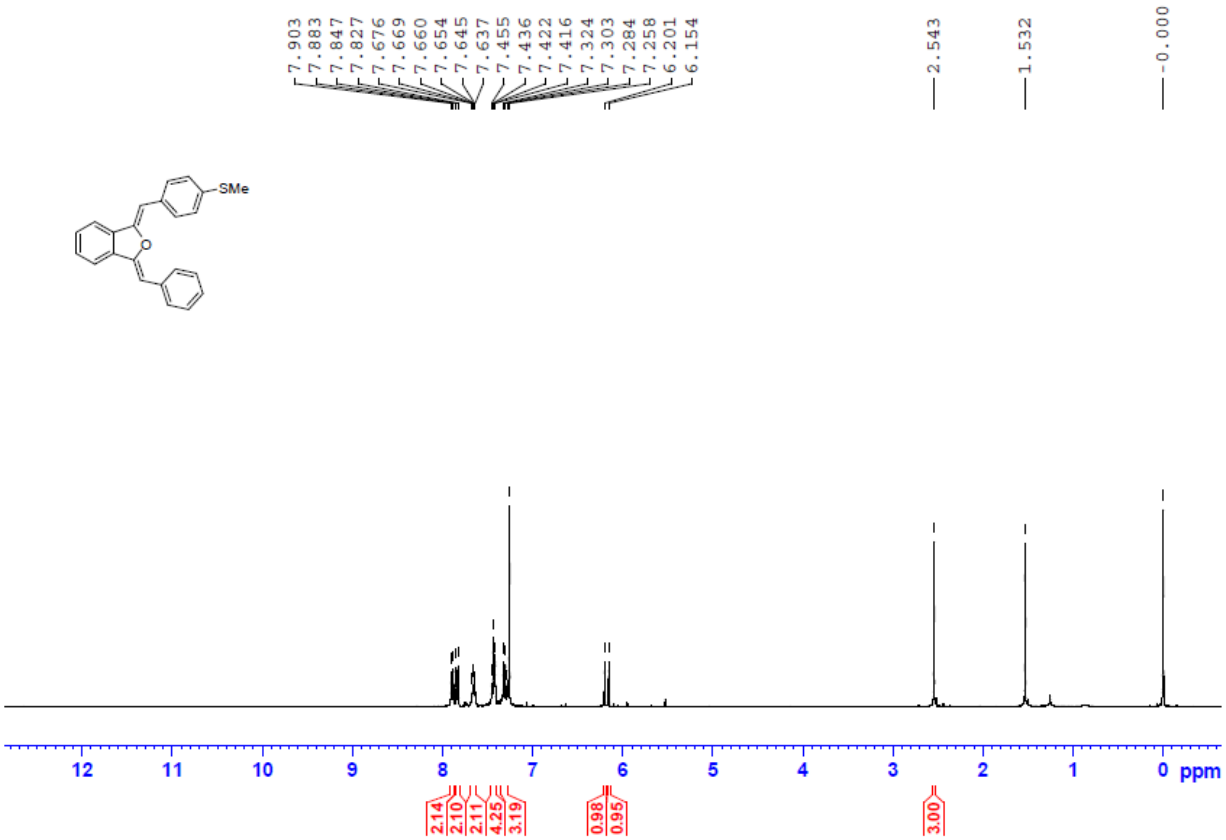
Where Φ_s is the standard fluorescence quantum yield (Rhodamine 6G, $\Phi_s = 0.88$), A_r and A_s are the respective absorbance of the samples and standard at the excitation wavelengths, n_r and n_s are the the refractive index of CH_2Cl_2 and EtOH, F_r and F_s are the areas under the fluorescence emission curves of samples and the standard, respectively.

2. Copies of ^{1}H and ^{13}C NMR Spectra

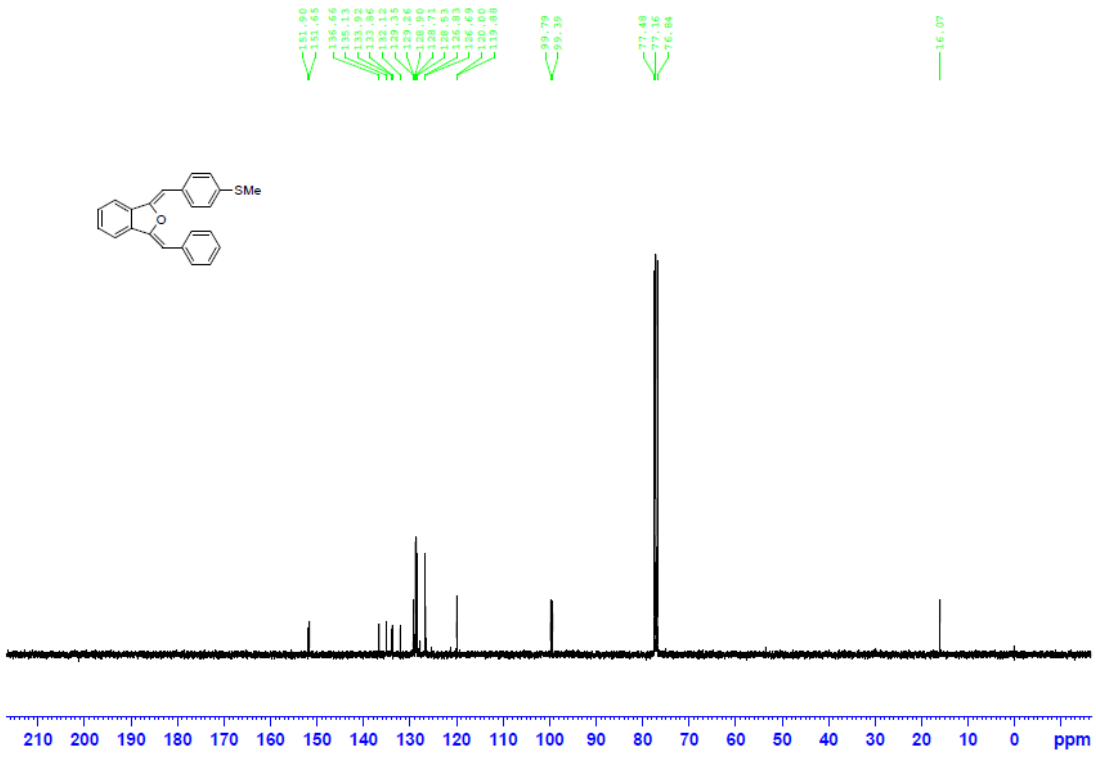
^{1}H NMR of (1Z,3Z)-1-benzylidene-3-(4-methoxybenzylidene)-1,3-dihydroisobenzofuran (**C1**)



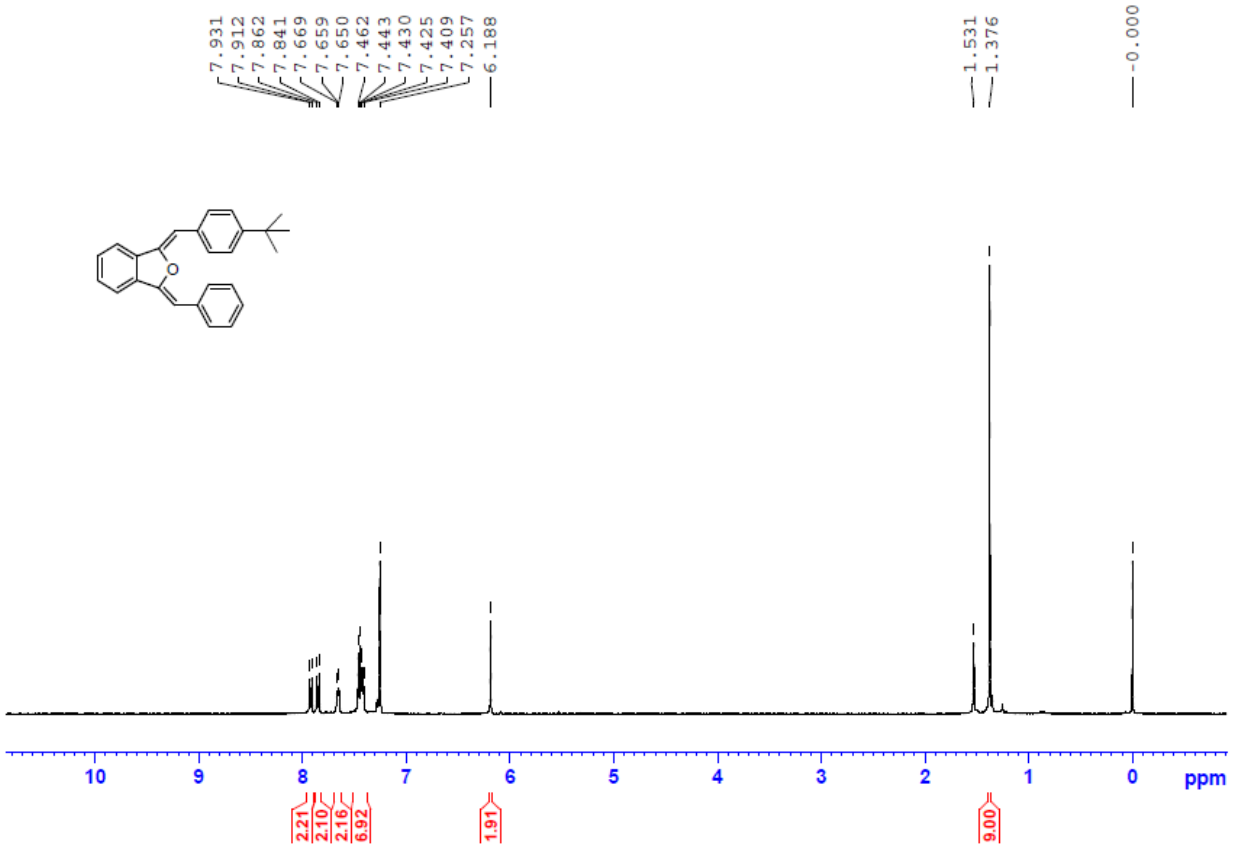
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-(methylthio)benzylidene)-1,3-dihydroisobenzofuran (**C2**)



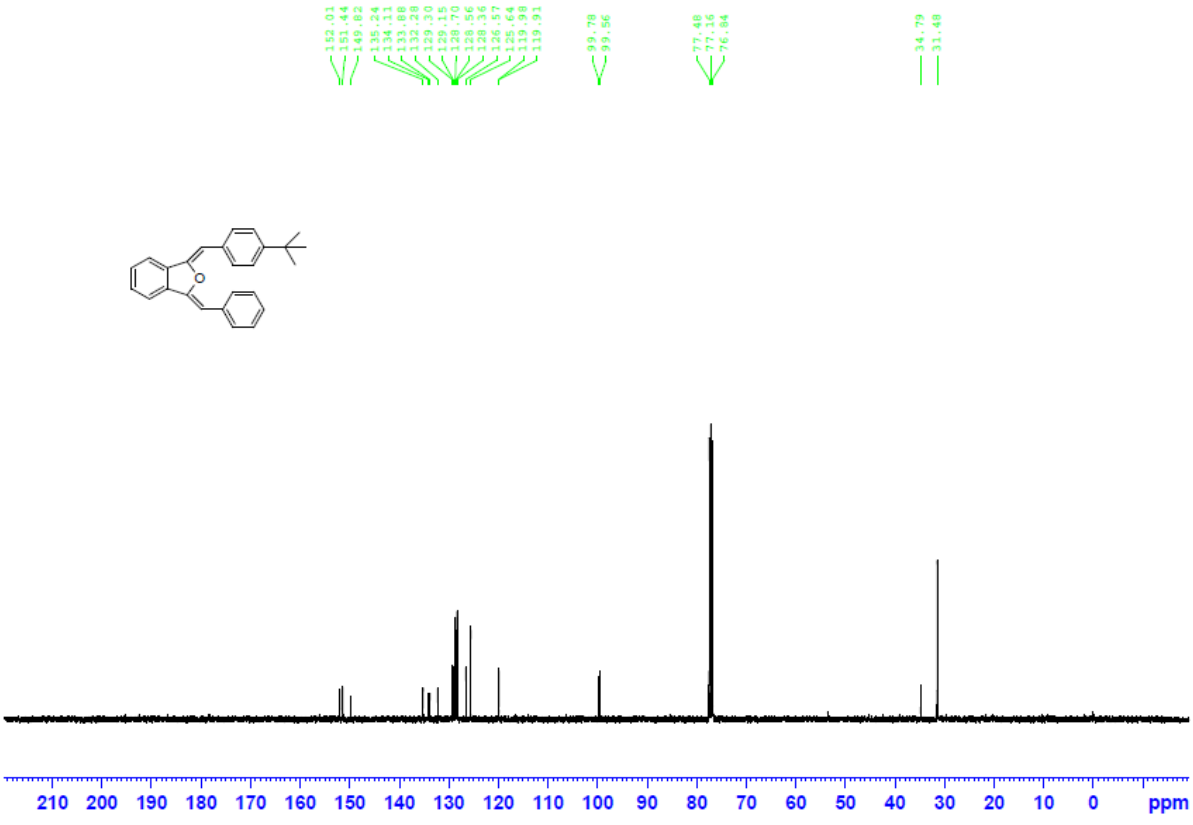
^{13}C NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-(methylthio)benzylidene)-1,3-dihydroisobenzofuran (**C2**)



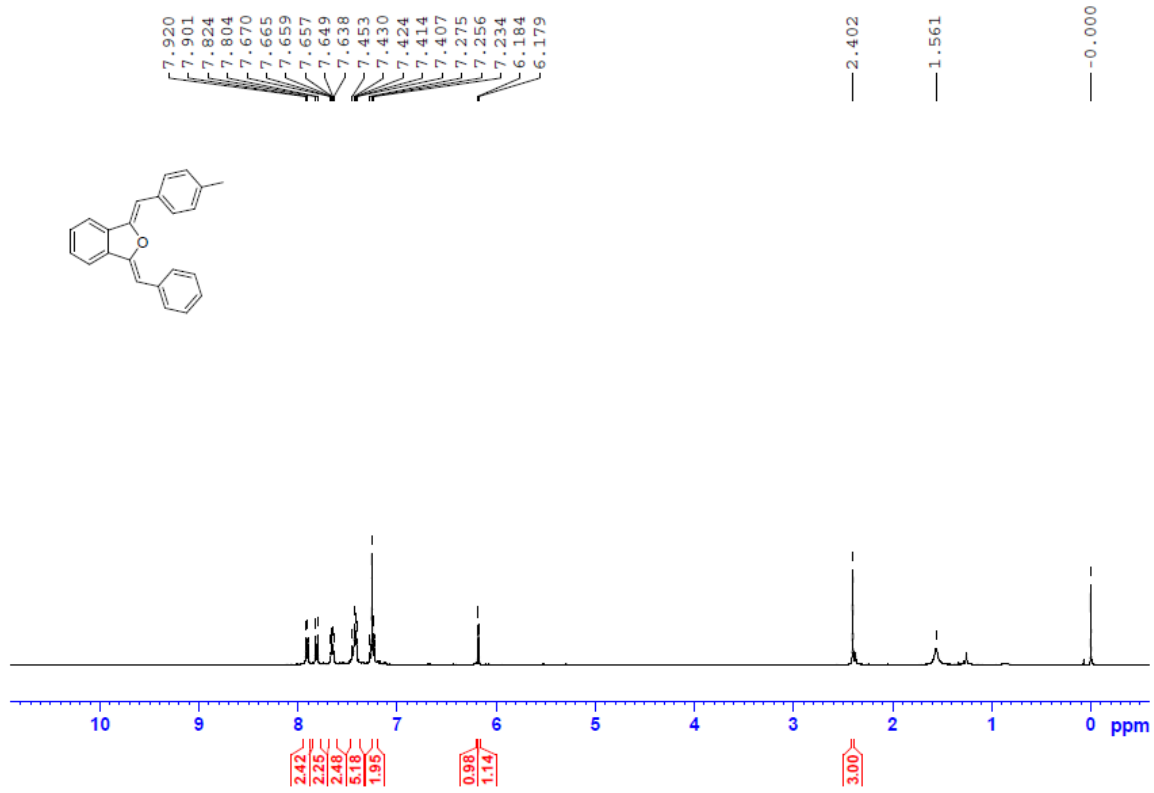
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-(tert-butyl)benzylidene)-1,3-dihydroisobenzofuran (**C3**)



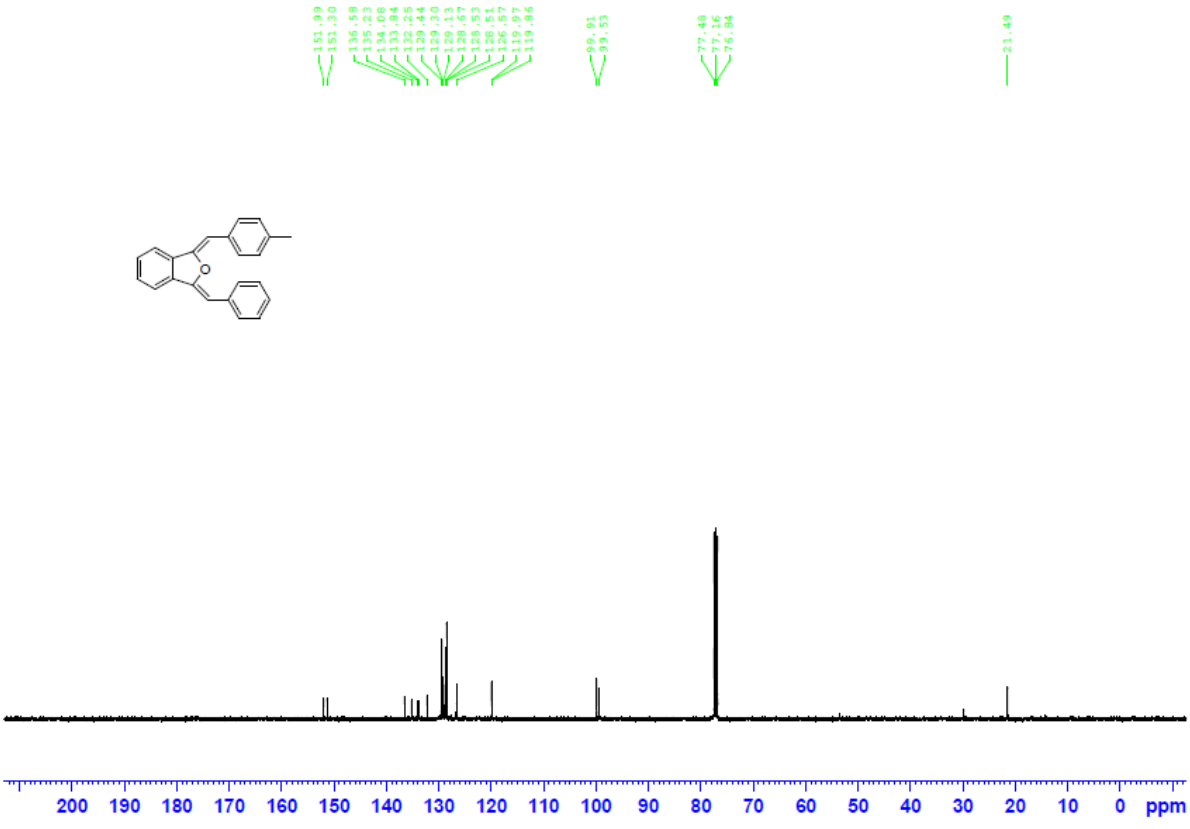
^{13}C NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-(tert-butyl)benzylidene)-1,3-dihydroisobenzofuran (**C3**)



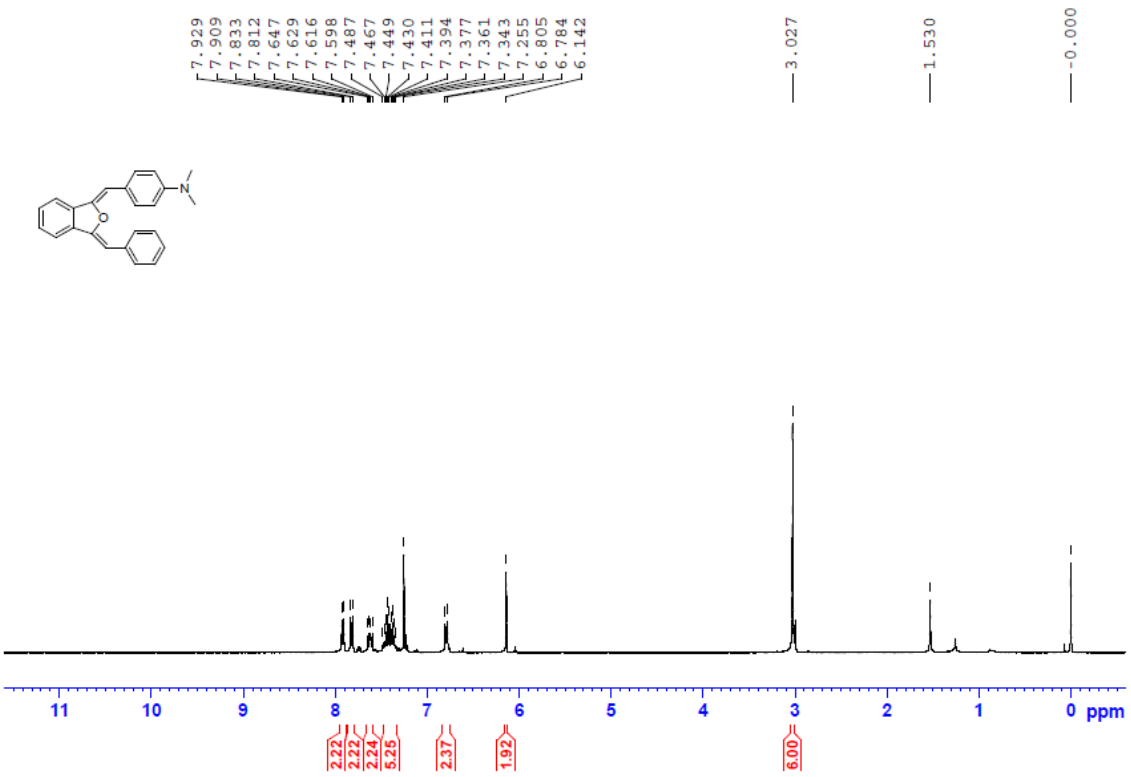
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-methylbenzylidene)-1,3-dihydroisobenzofuran (**C4**)



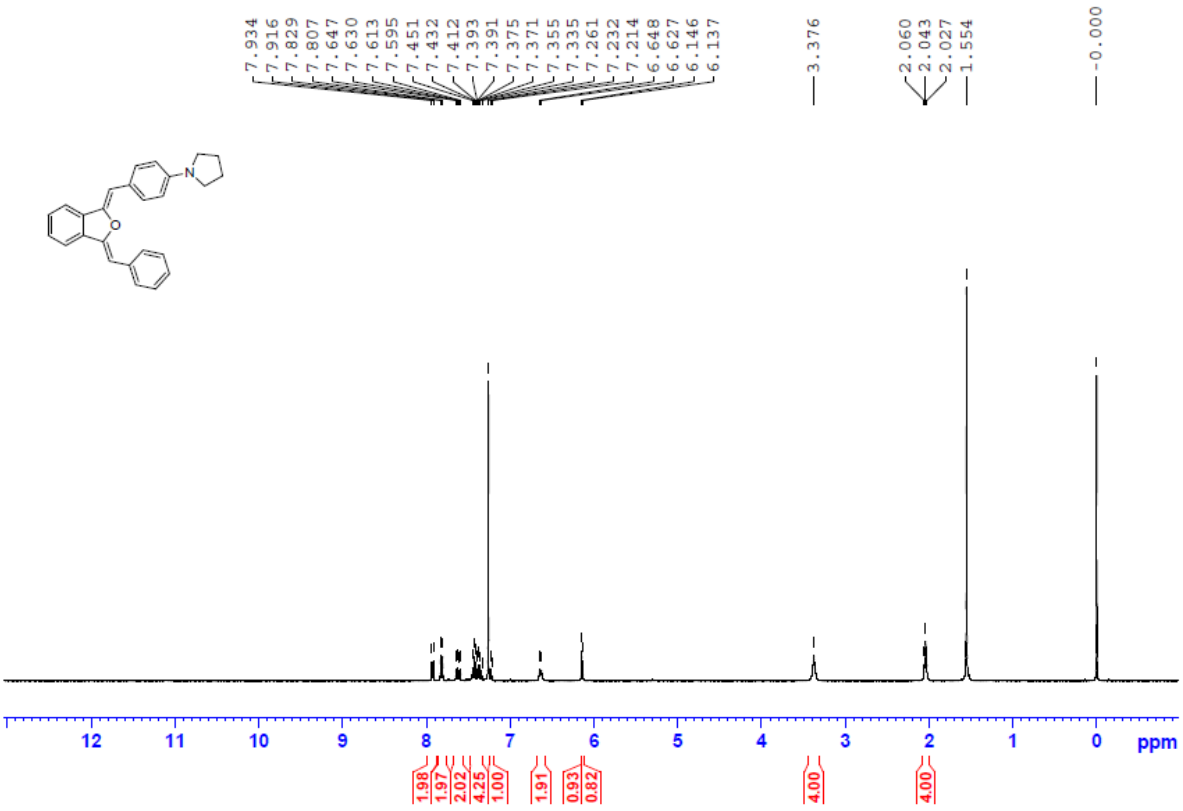
^{13}C NMR of (1*Z*,3*Z*)-1-benzylidene-3-(4-methylbenzylidene)-1,3-dihydroisobenzofuran (**C4**)



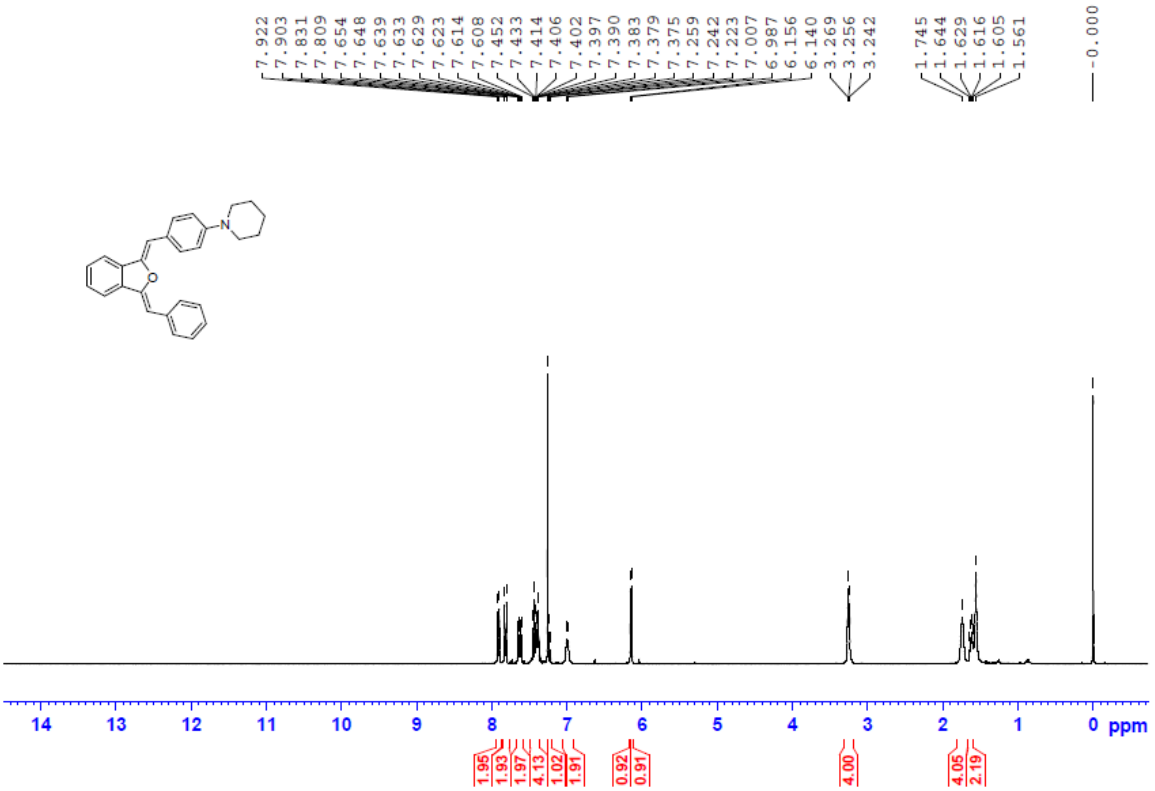
^{1}H NMR of 4-((*Z*)-((*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C5**)



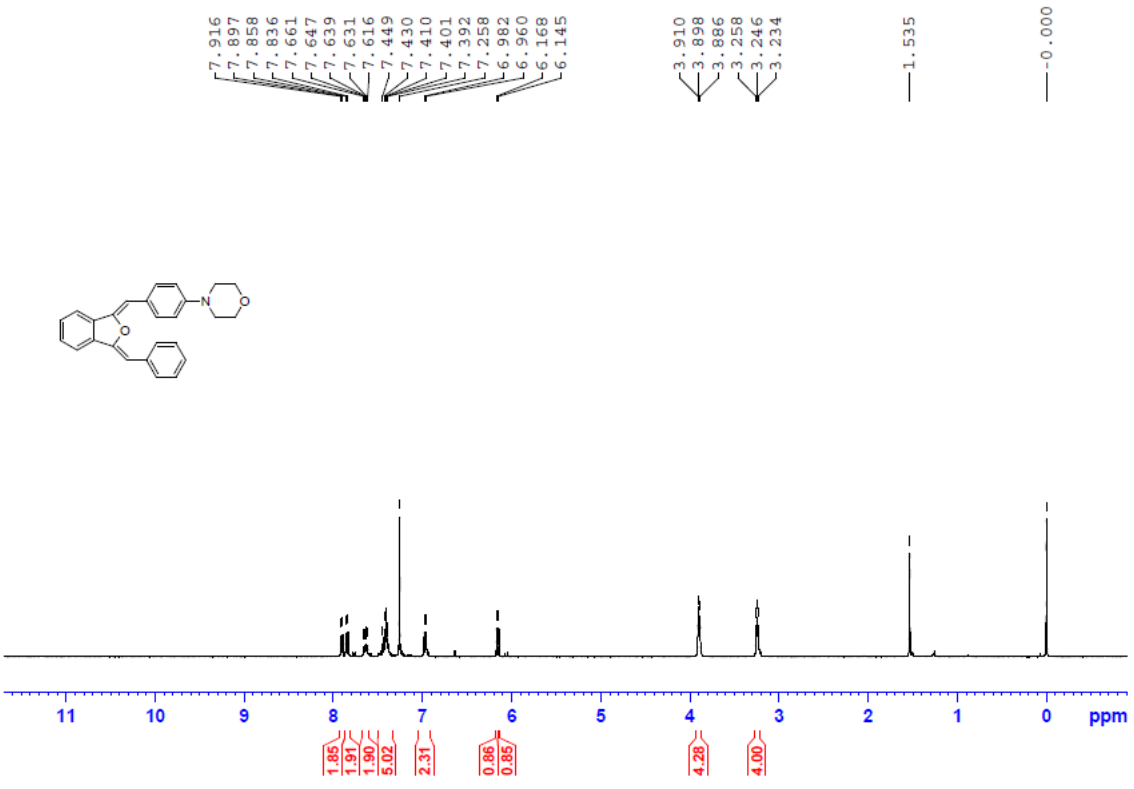
^{1}H NMR of 1-(4-((*Z*)-((*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene)methyl)phenyl)pyrrolidine (**C6**)



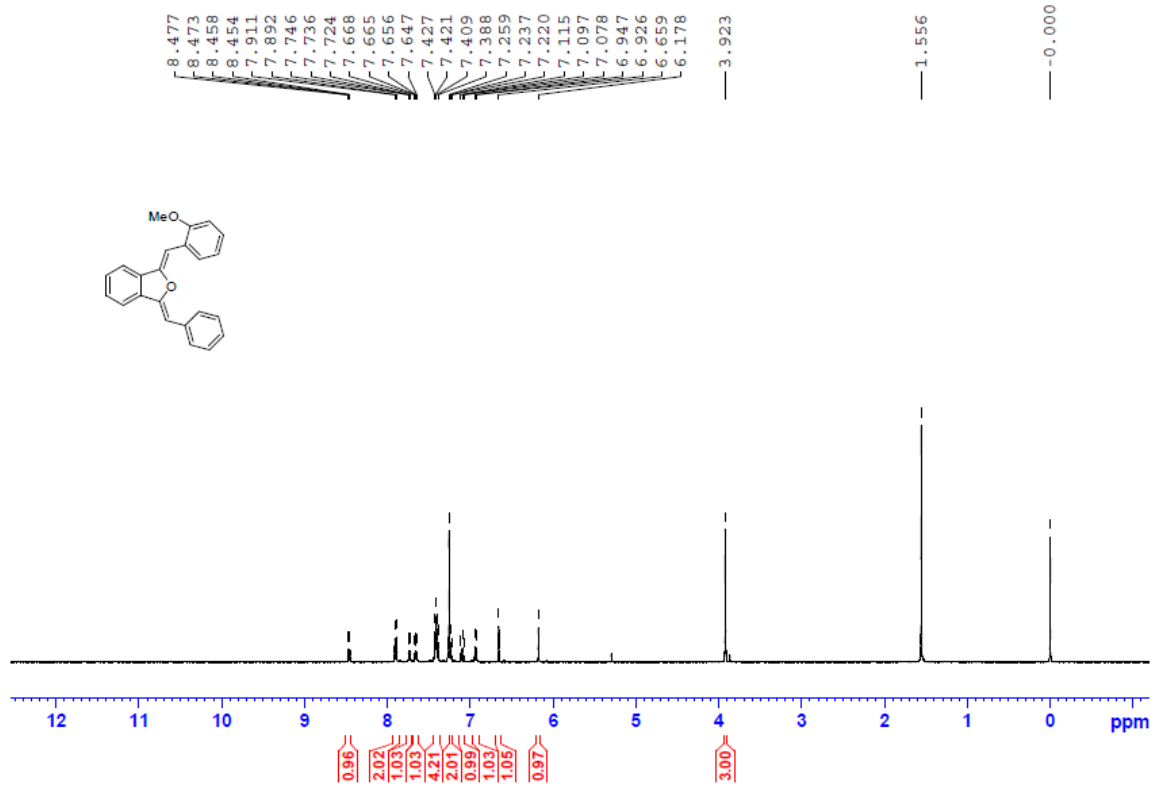
^{1}H NMR of 1-(4-((*Z*)-((*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene)methyl)phenyl)piperidine (**C7**)



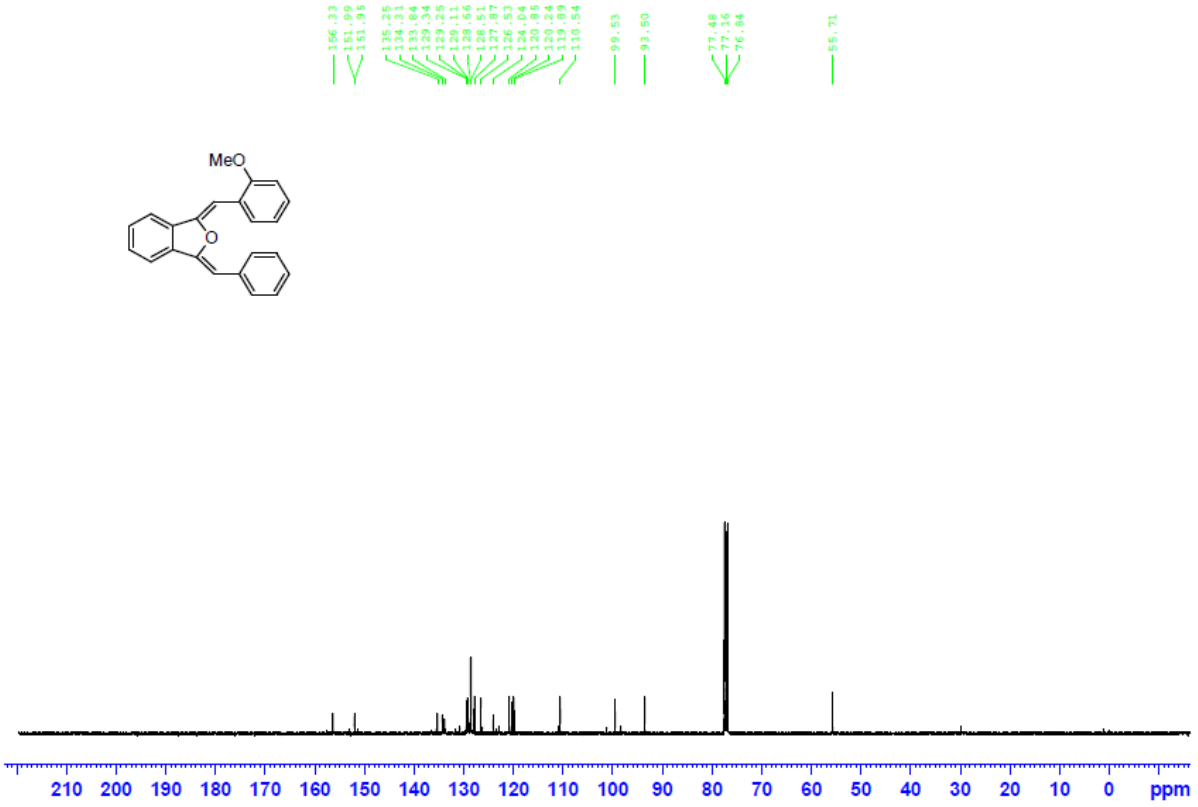
^{1}H NMR of 4-(4-((*Z*)-((*Z*)-3-benzylideneisobenzofuran-1(3*H*)-ylidene)methyl)phenyl)morpholine (**C8**)



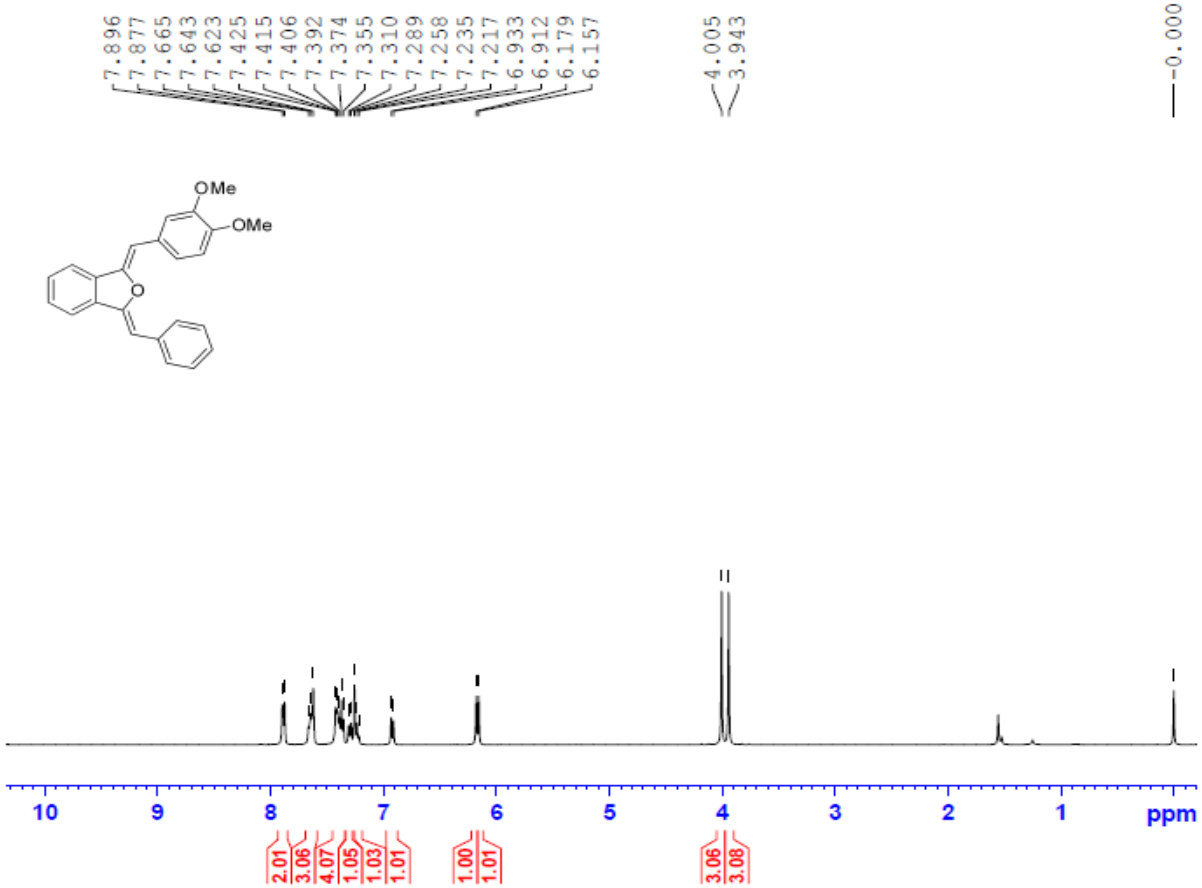
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(2-methoxybenzylidene)-1,3-dihydroisobenzofuran (**C9**)



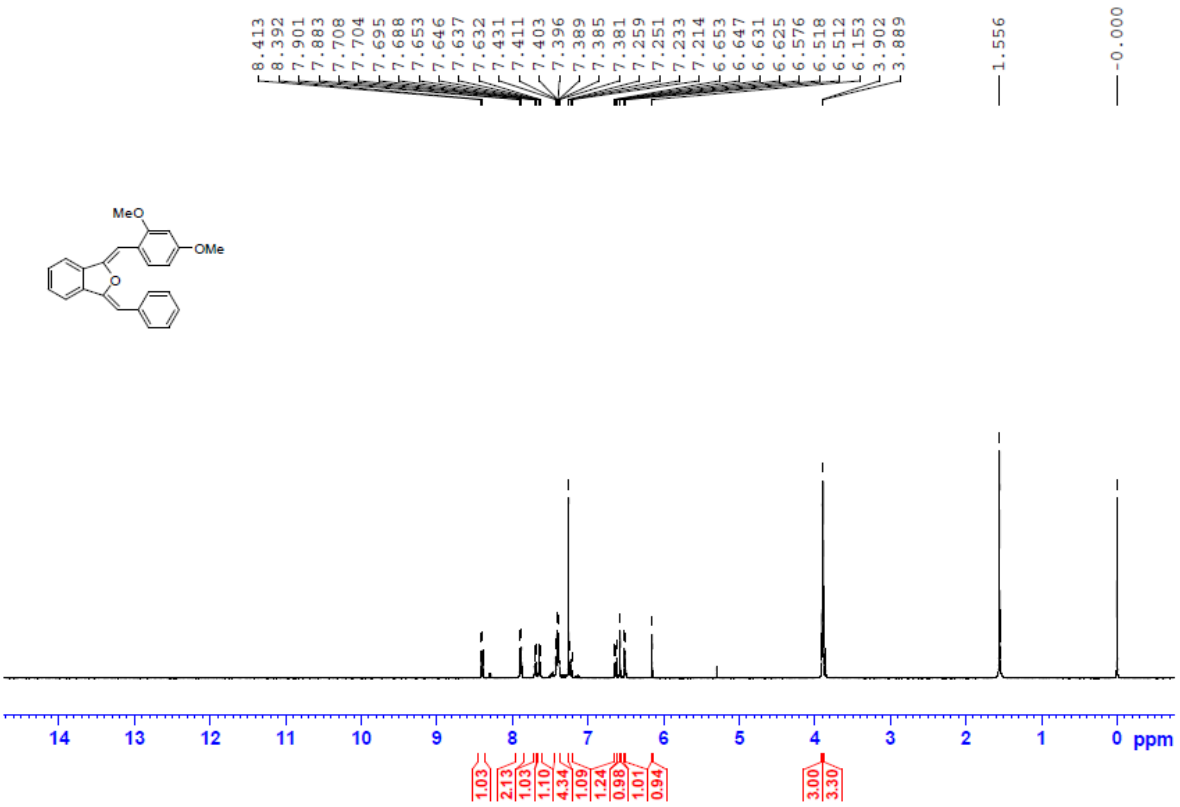
^{13}C NMR of (1*Z*,3*Z*)-1-benzylidene-3-(2-methoxybenzylidene)-1,3-dihydroisobenzofuran (**C9**)



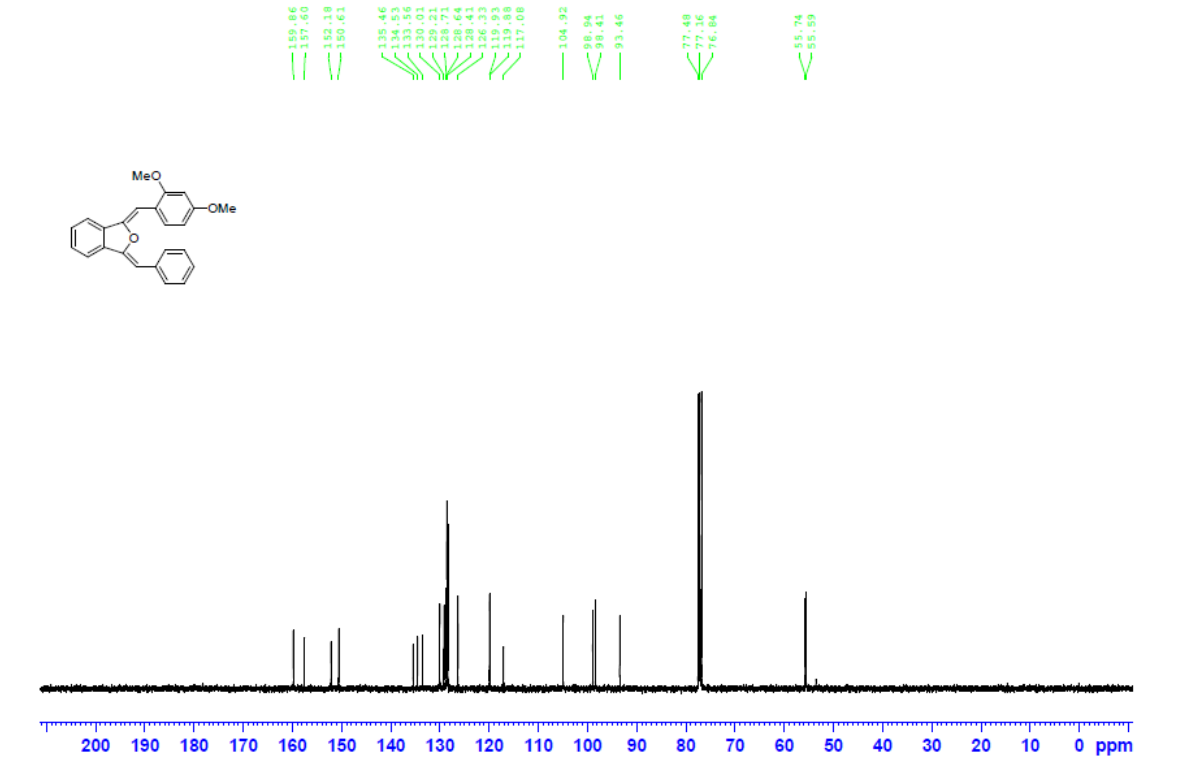
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(3,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (**C10**)



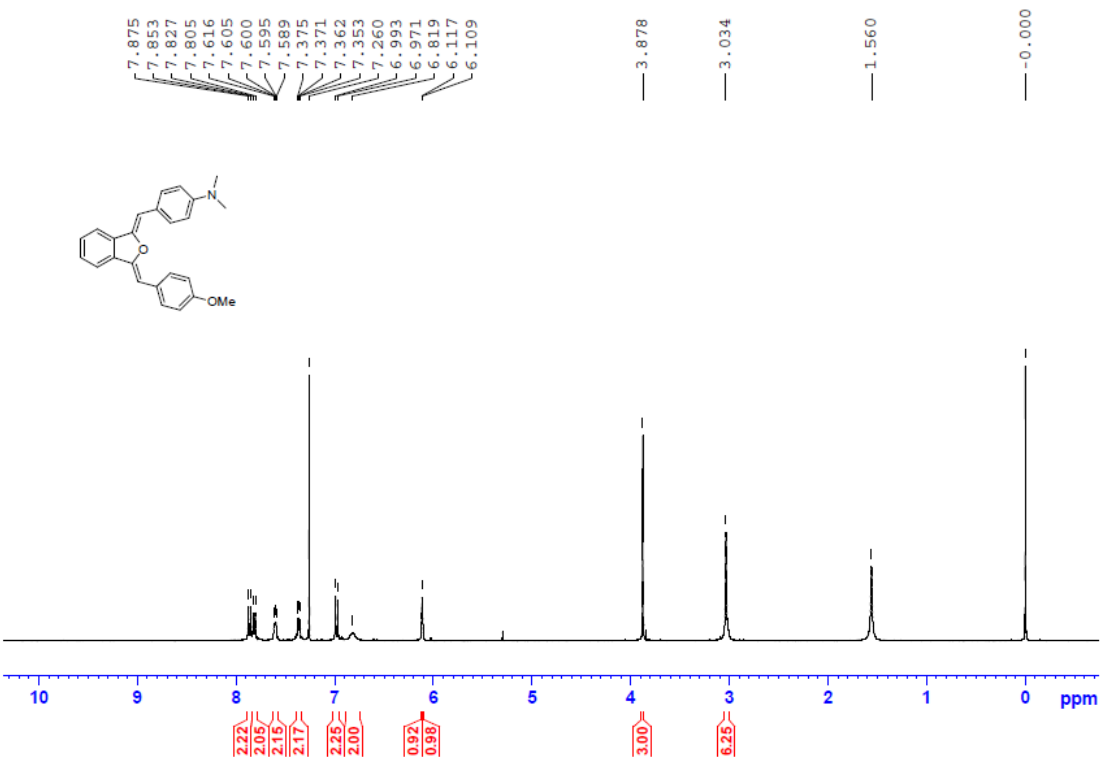
^{1}H NMR of (1*Z*,3*Z*)-1-benzylidene-3-(2,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (**C11**)



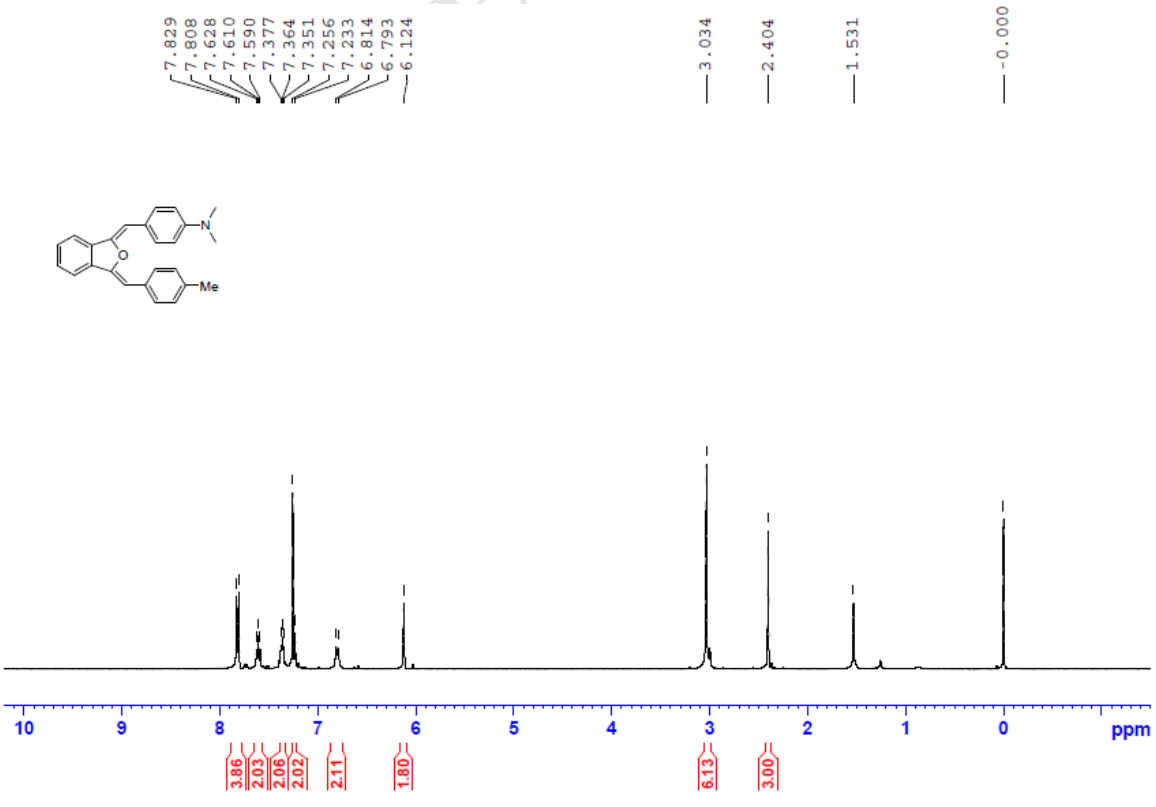
^{13}C NMR of (1*Z*,3*Z*)-1-benzylidene-3-(2,4-dimethoxybenzylidene)-1,3-dihydroisobenzofuran (**C11**)



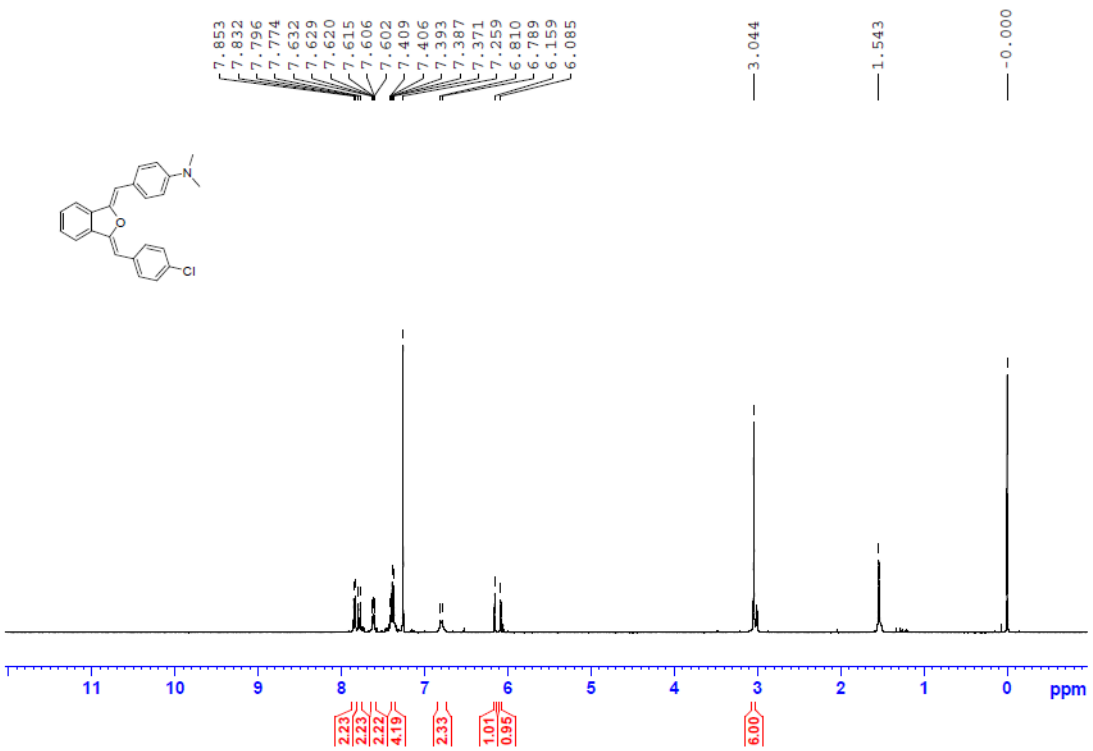
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(4-methoxybenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C12**)



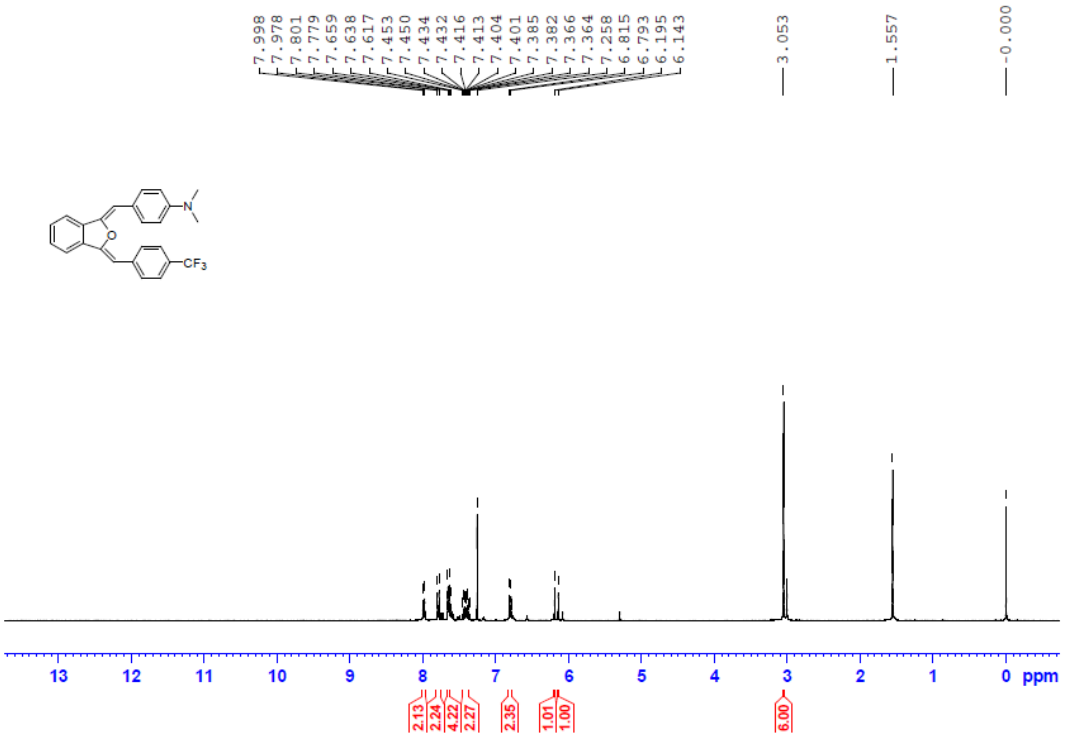
^{1}H NMR of *N*,*N*-dimethyl-4-((*Z*)-((*Z*)-3-(4-methylbenzylidene)isobenzofuran-1(3*H*)ylidene)-methyl)aniline (**C13**)



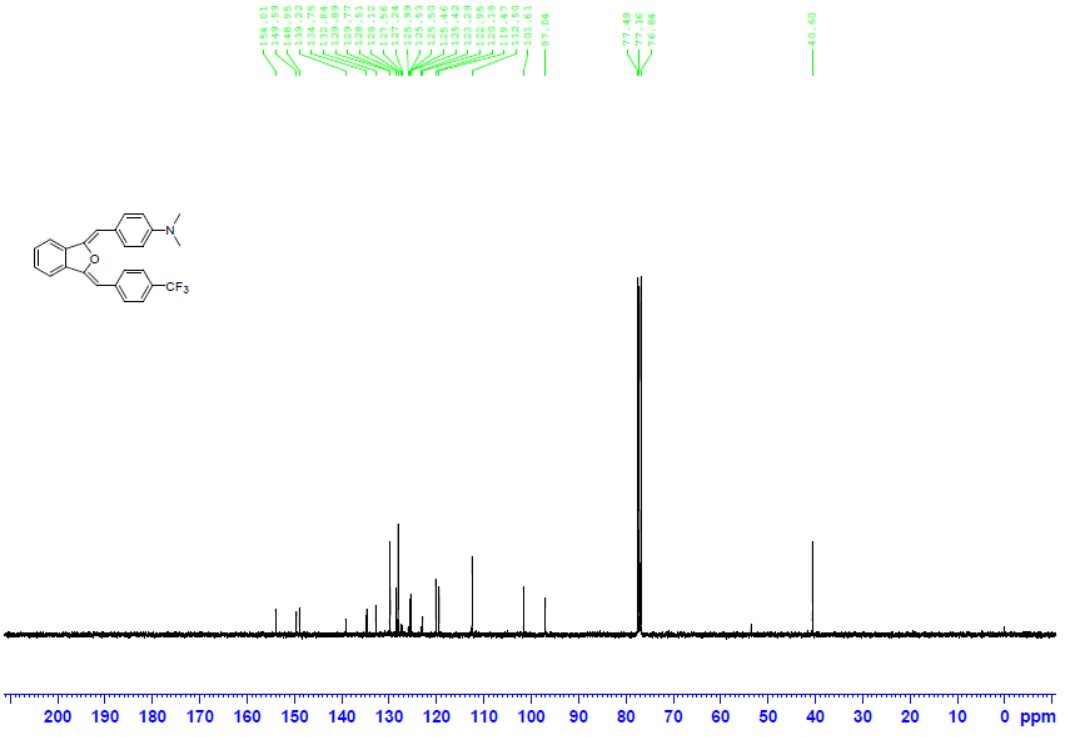
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(4-chlorobenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C14**)



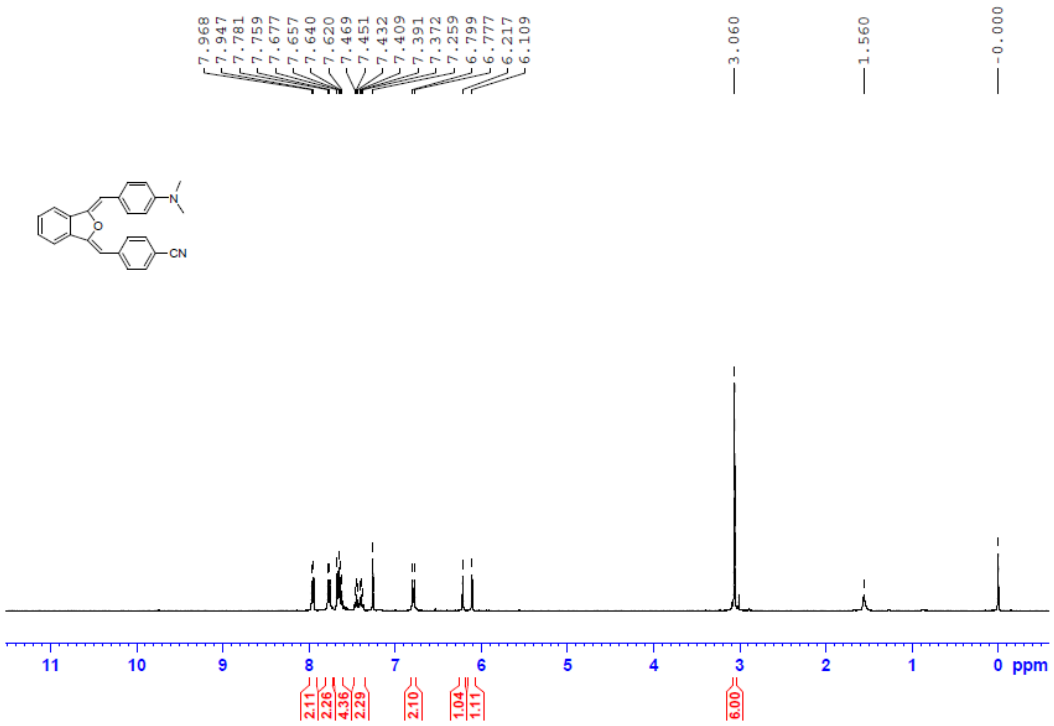
^{1}H NMR of *N*,*N*-dimethyl-4-((*Z*)-((*Z*)-3-(4-(trifluoromethyl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)aniline (**C15**)



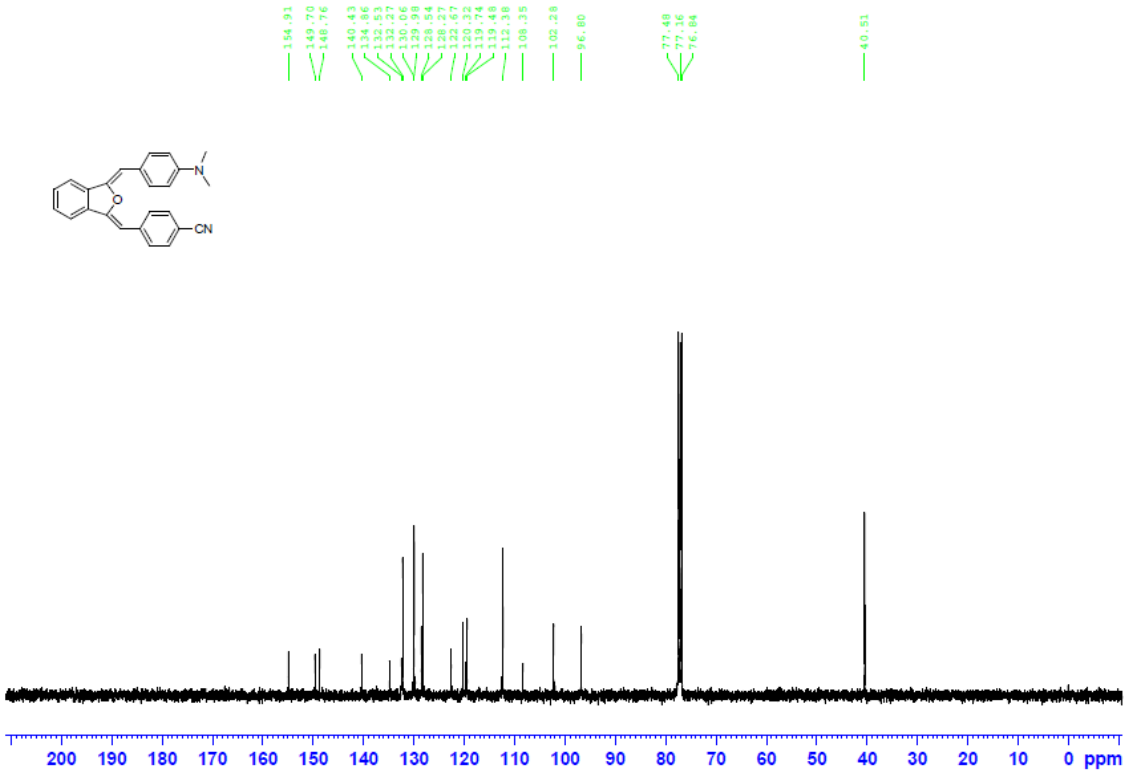
^{13}C NMR of *N*,*N*-dimethyl-4-((*Z*)-((*Z*)-3-(4-(trifluoromethyl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)aniline (**C15**)



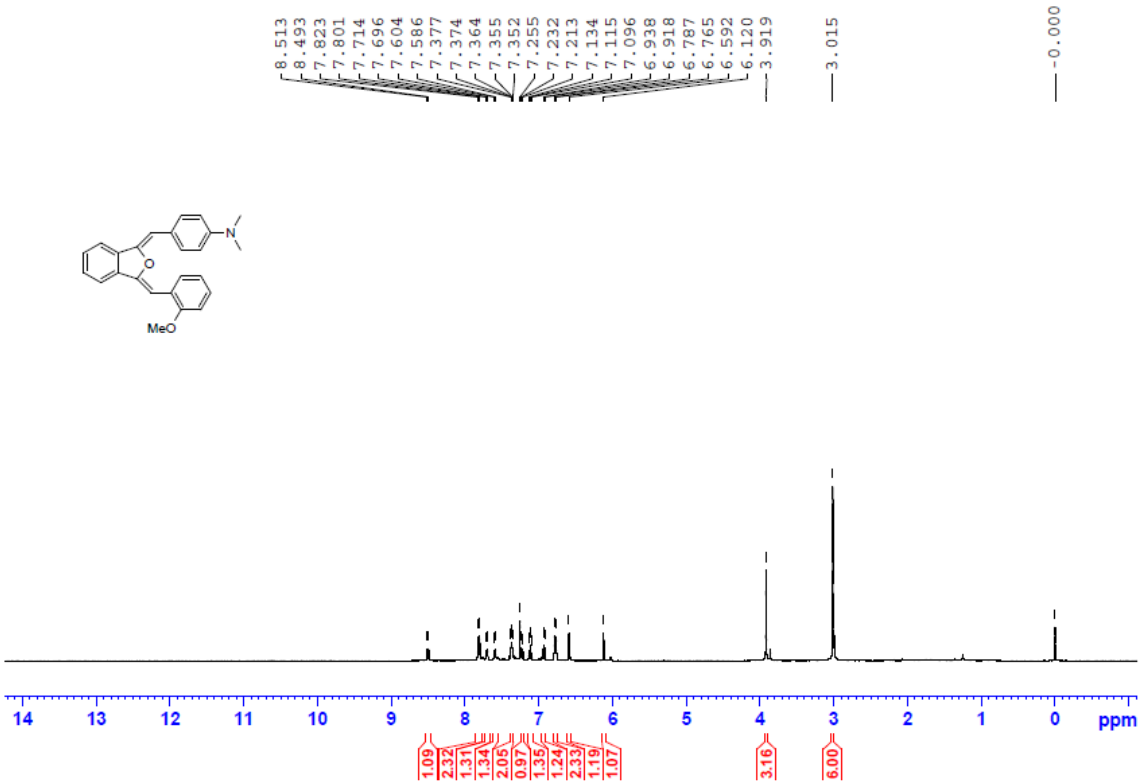
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(4-(dimethylamino)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)benzonitrile (**C16**)



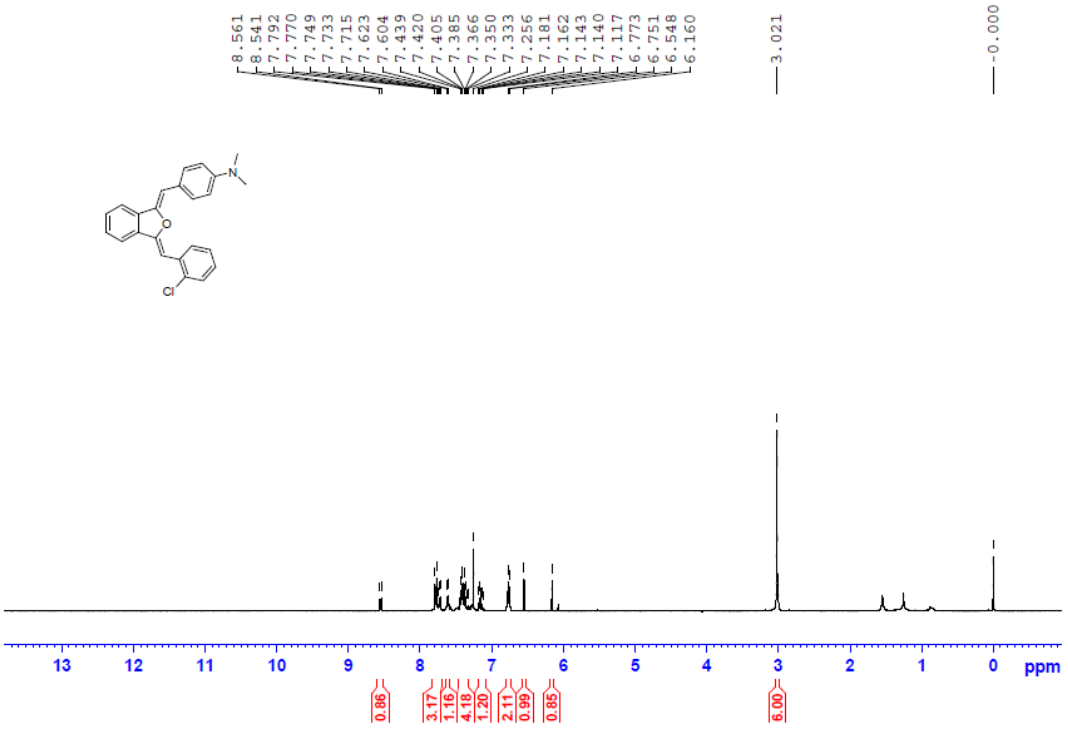
^{13}C NMR of 4-((*Z*)-((*Z*)-3-(4-(dimethylamino)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)benzonitrile (**C16**)



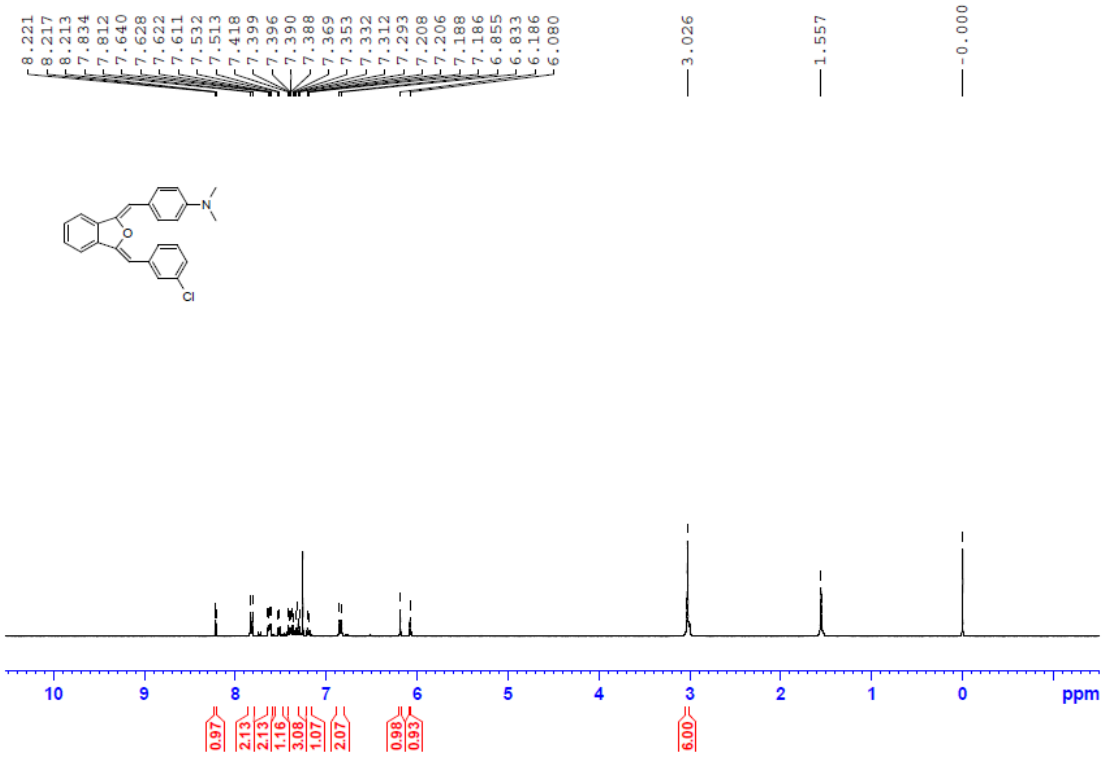
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(2-methoxybenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C17**)



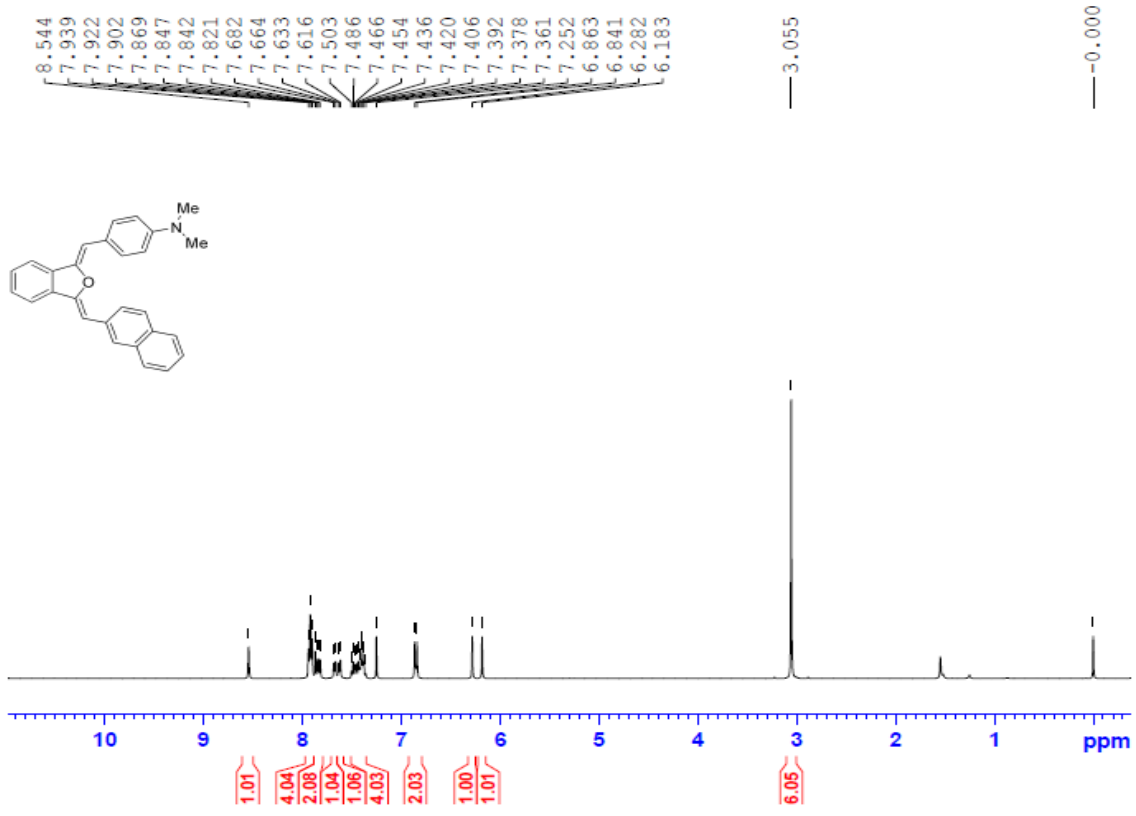
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(2-chlorobenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C18**)



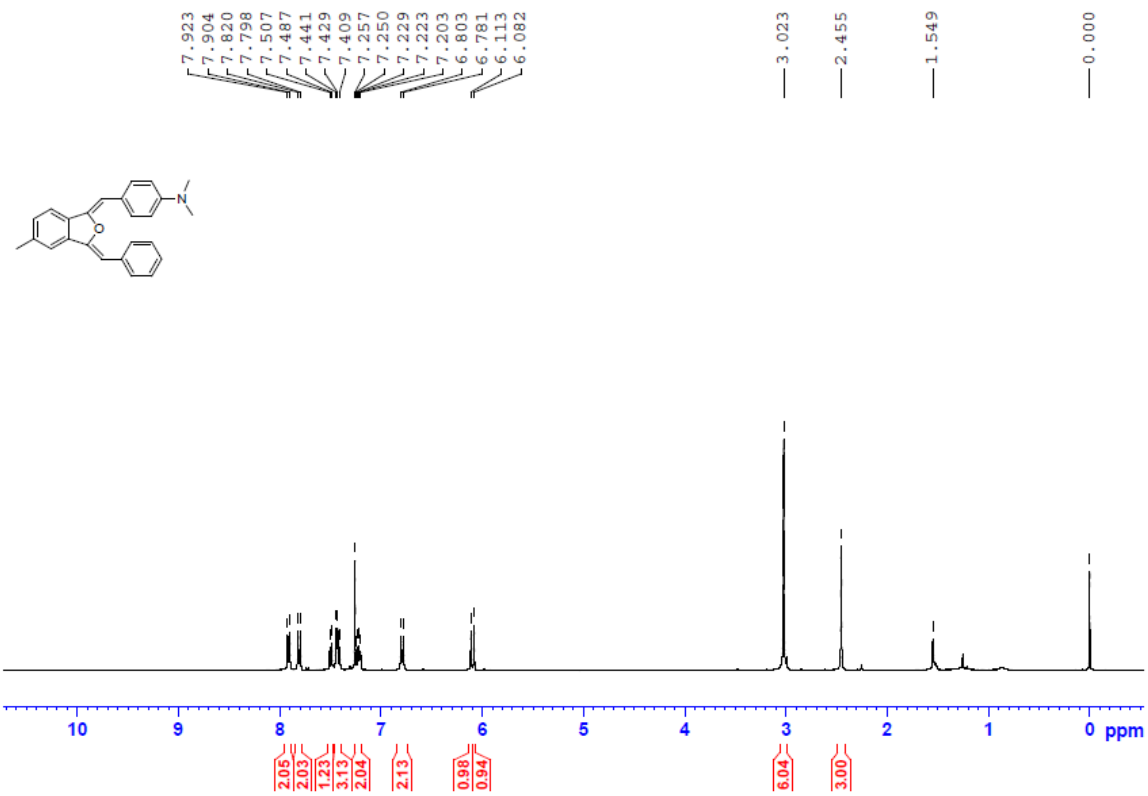
^{1}H NMR of 4-((*Z*)-((*Z*)-3-(3-chlorobenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C19**)



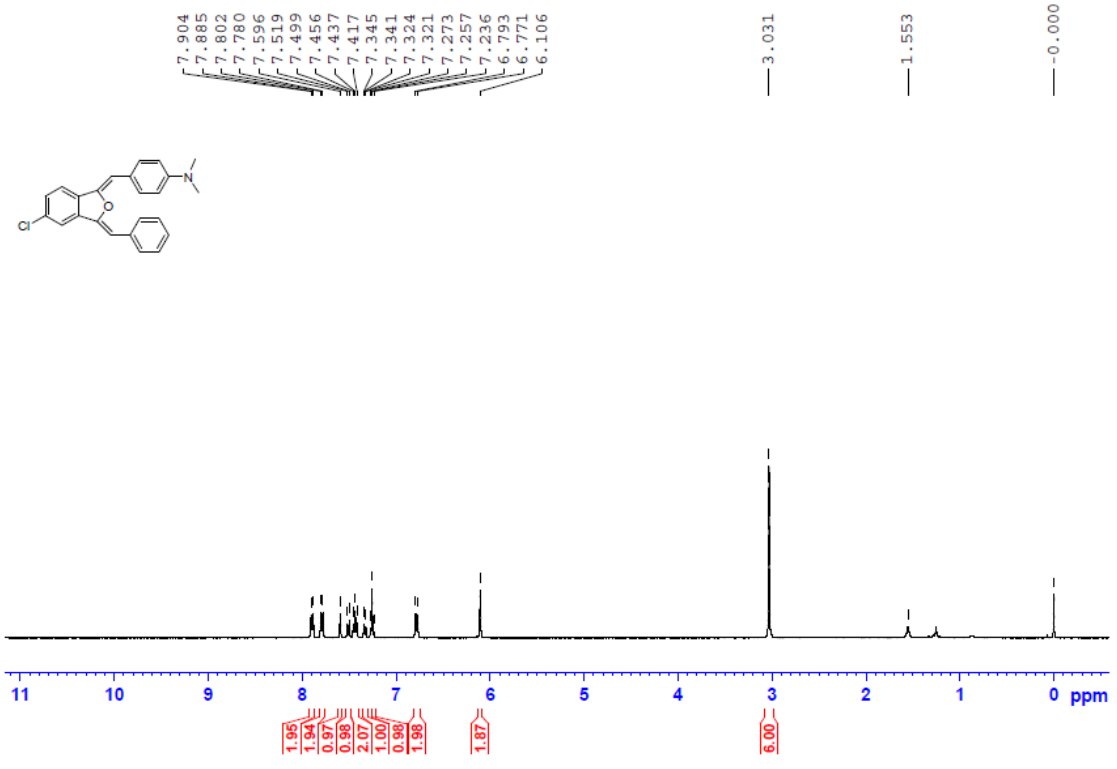
^{1}H NMR of *N*,*N*-dimethyl-4-((*Z*)-((*Z*)-3-(naphthalen-2-ylmethylene)isobenzofuran-1(3*H*)-ylidene)methyl)aniline (**C20**)



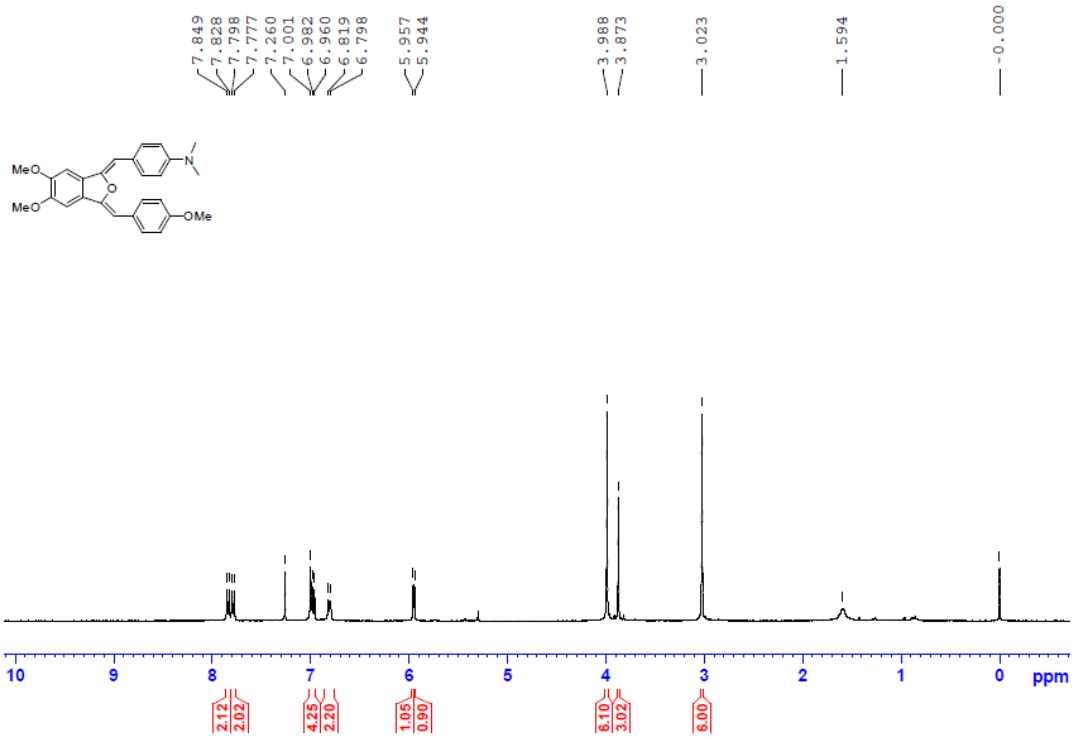
^{1}H NMR of 4-((*Z*)-((*Z*)-3-benzylidene-5-methylisobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C21**)



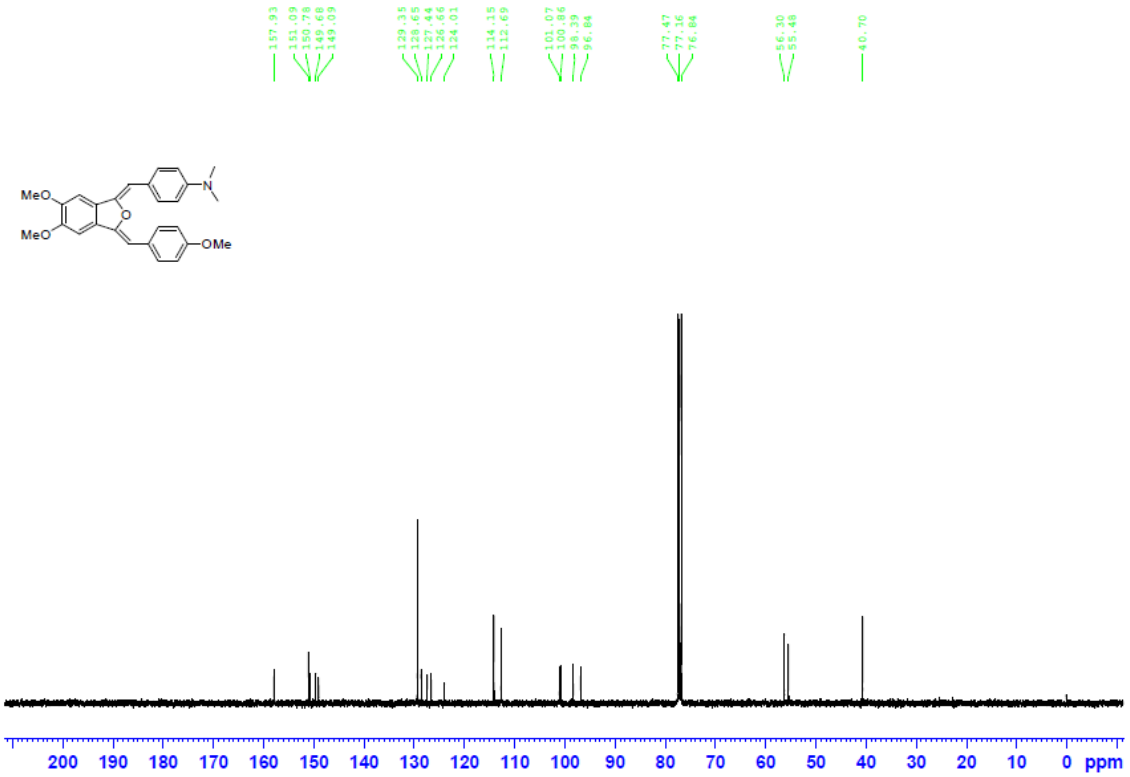
^{1}H NMR of 4-((*Z*)-((*Z*)-3-benzylidene-5-chloroisobenzofuran-1(3*H*)-ylidene)methyl)-N,N-dimethylaniline (**C22**)



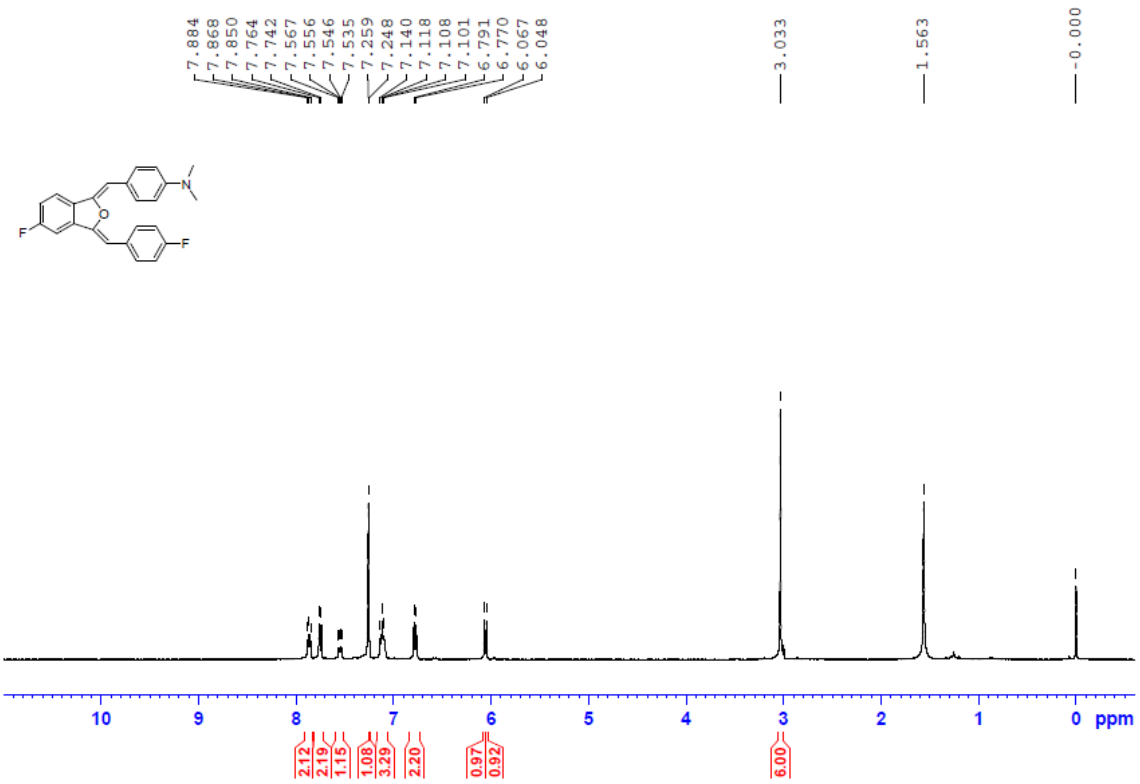
^{1}H NMR of 4-((*Z*)-((*Z*)-5,6-dimethoxy-3-(4-methoxybenzylidene)isobenzofuran-1(3*H*)-ylidene)-methyl)-*N*,*N*-dimethylaniline (**C23**)



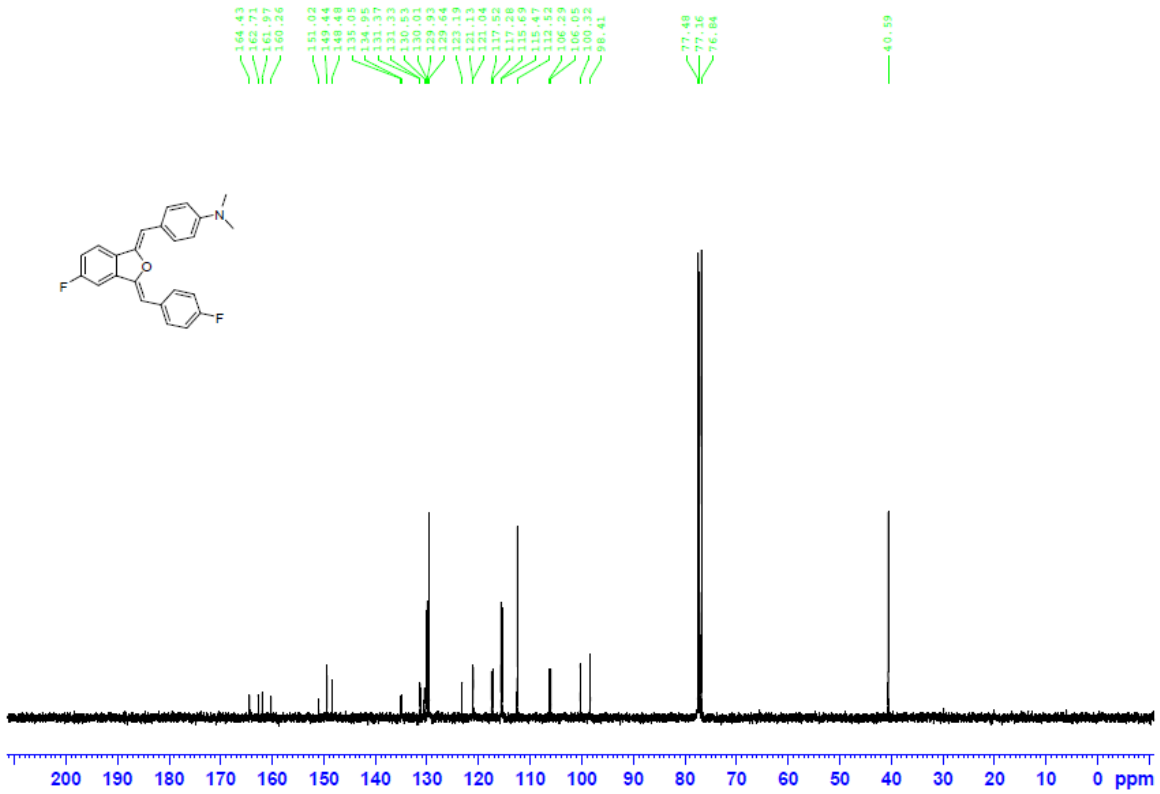
^{13}C NMR of 4-((*Z*)-((*Z*)-5,6-dimethoxy-3-(4-methoxybenzylidene)isobenzofuran-1-(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C23**)



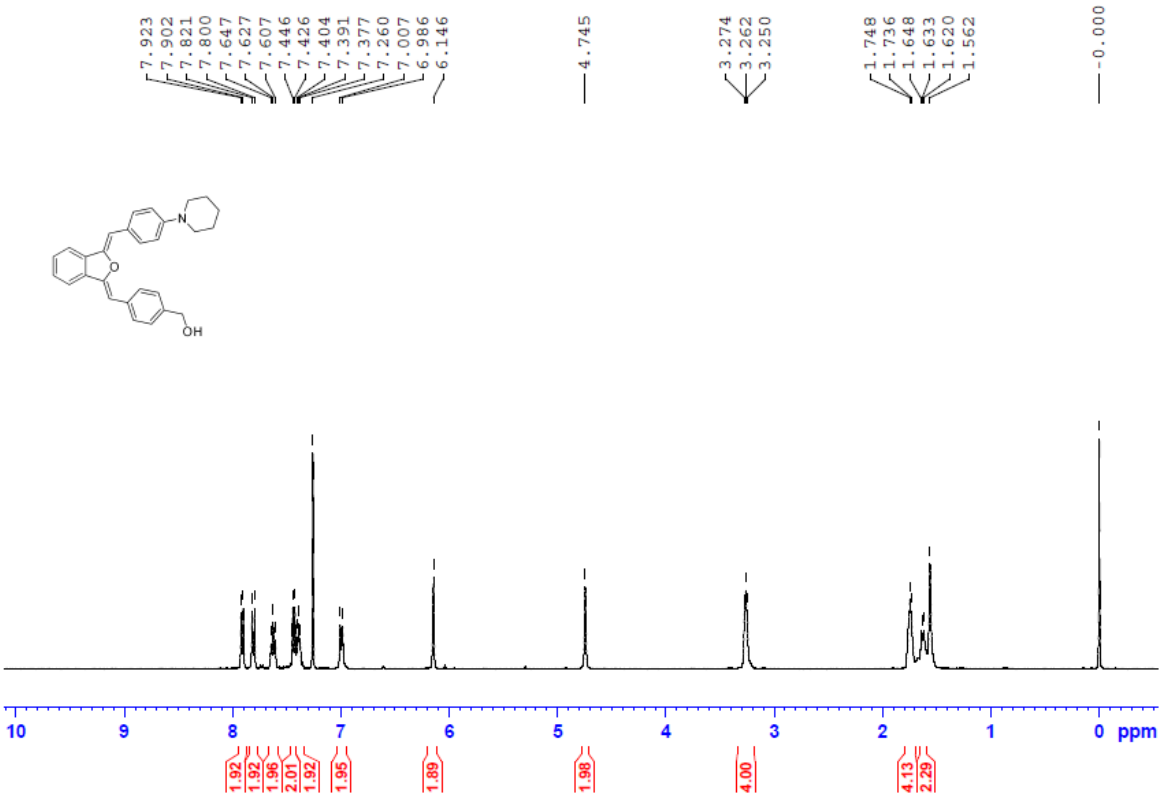
^{1}H NMR of 4-((*Z*)-((*Z*)-5-fluoro-3-(4-fluorobenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C24**)



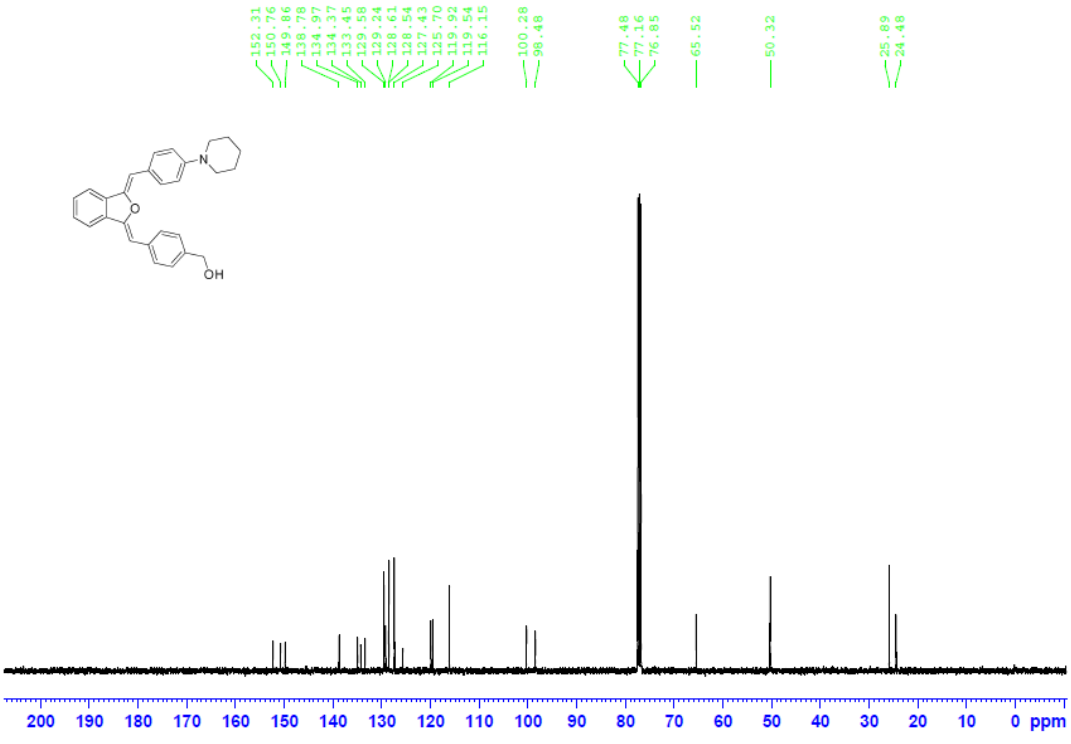
^{13}C NMR of 4-((*Z*)-((*Z*)-5-fluoro-3-(4-fluorobenzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-*N*,*N*-dimethylaniline (**C24**)



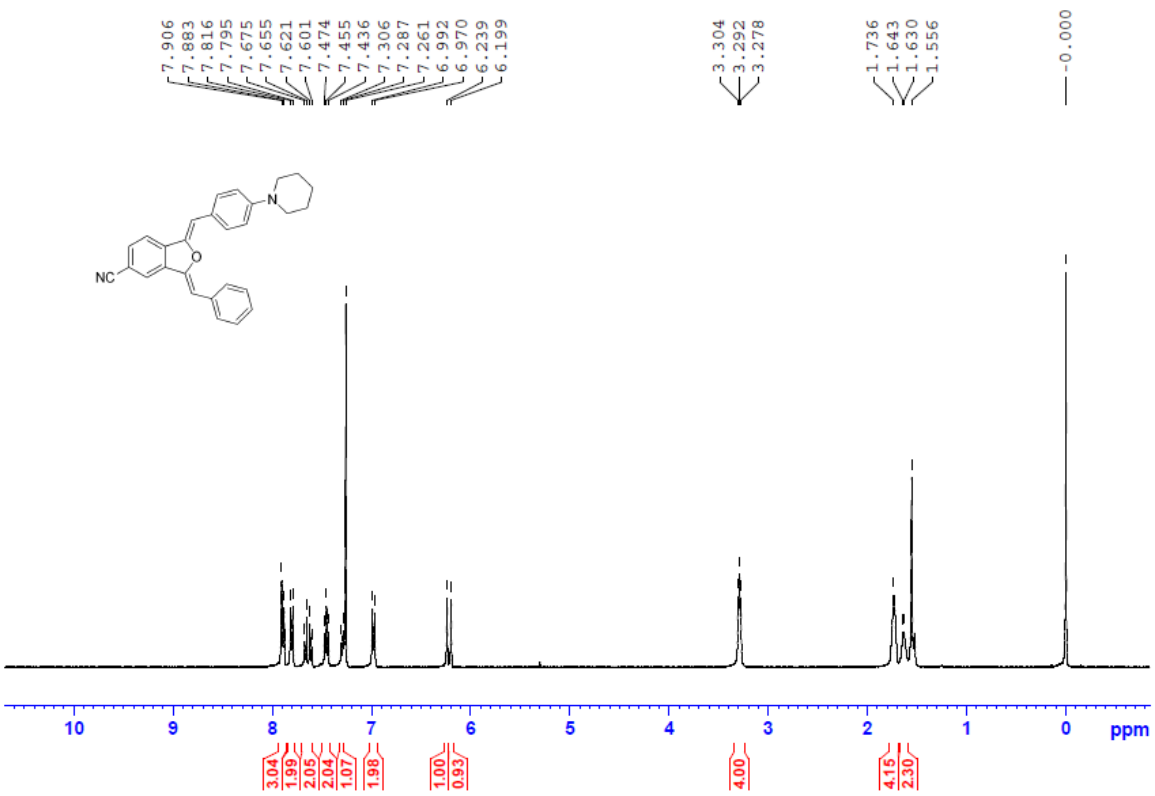
^{1}H NMR of (4-((*Z*)-((*Z*)-3-(4-(piperidin-1-yl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-phenyl)methanol (**C25**)



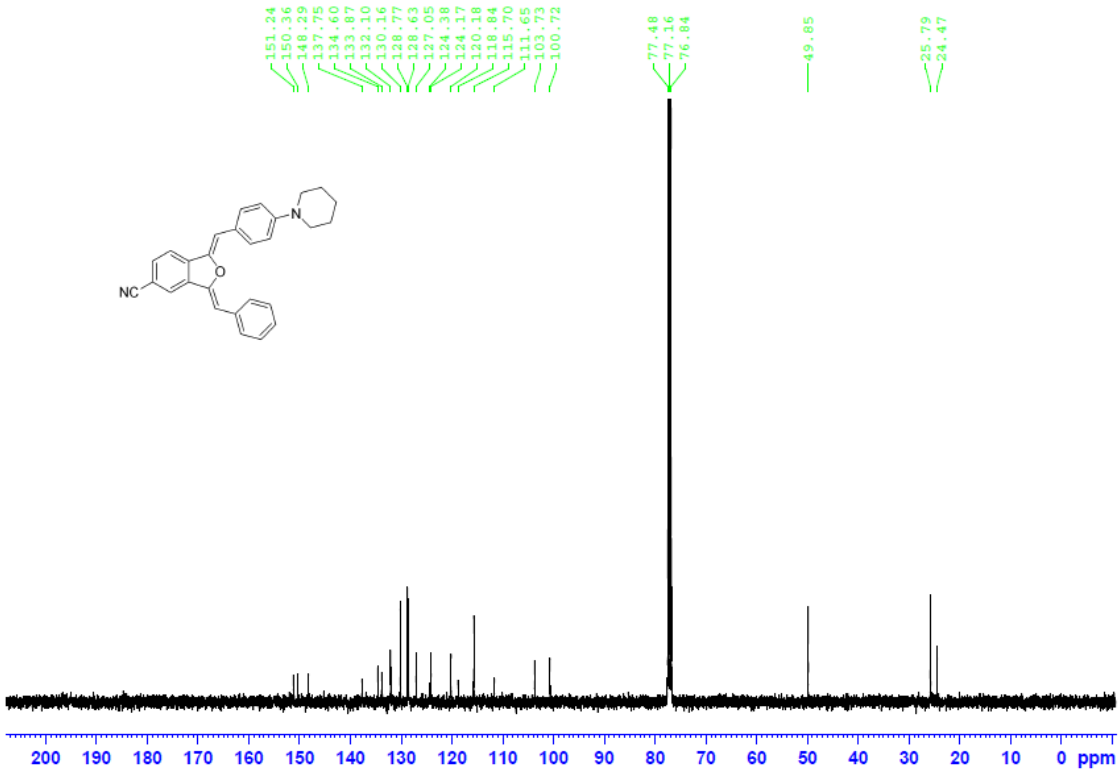
^{13}C NMR of (4-((*Z*)-((*Z*)-3-(4-(piperidin-1-yl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)-phenyl)methanol (**C25**)



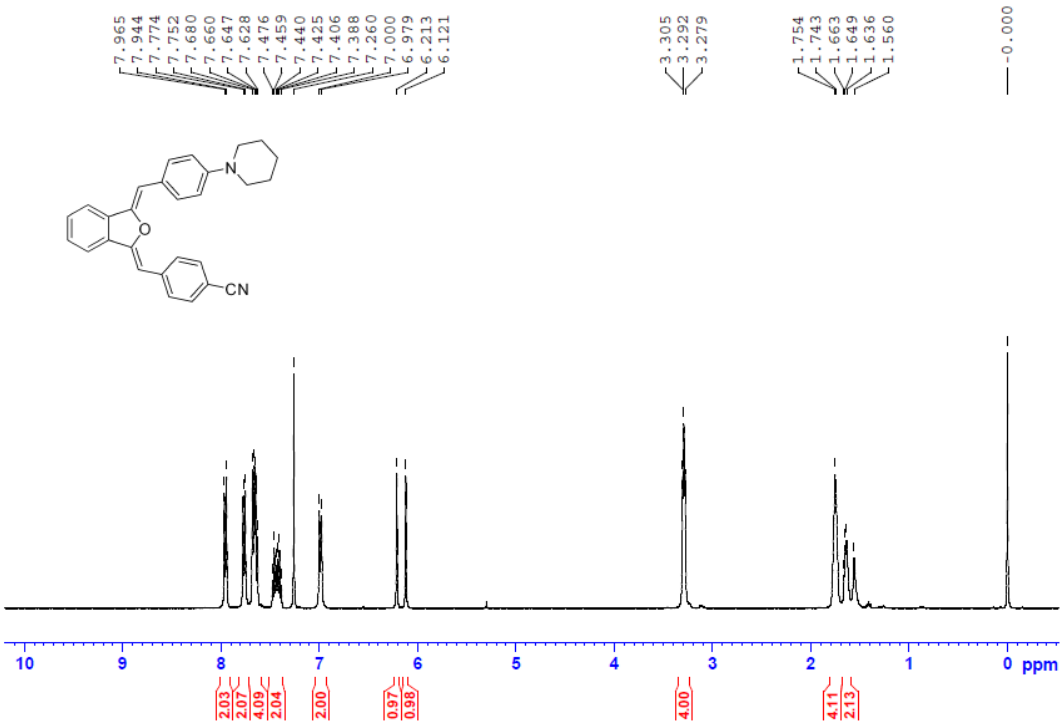
^{1}H NMR of (1*Z*,3*Z*)-3-benzylidene-1-(4-(piperidin-1-yl)benzylidene)-1,3-dihydroisobenzofuran-5-carbonitrile (**C26**)



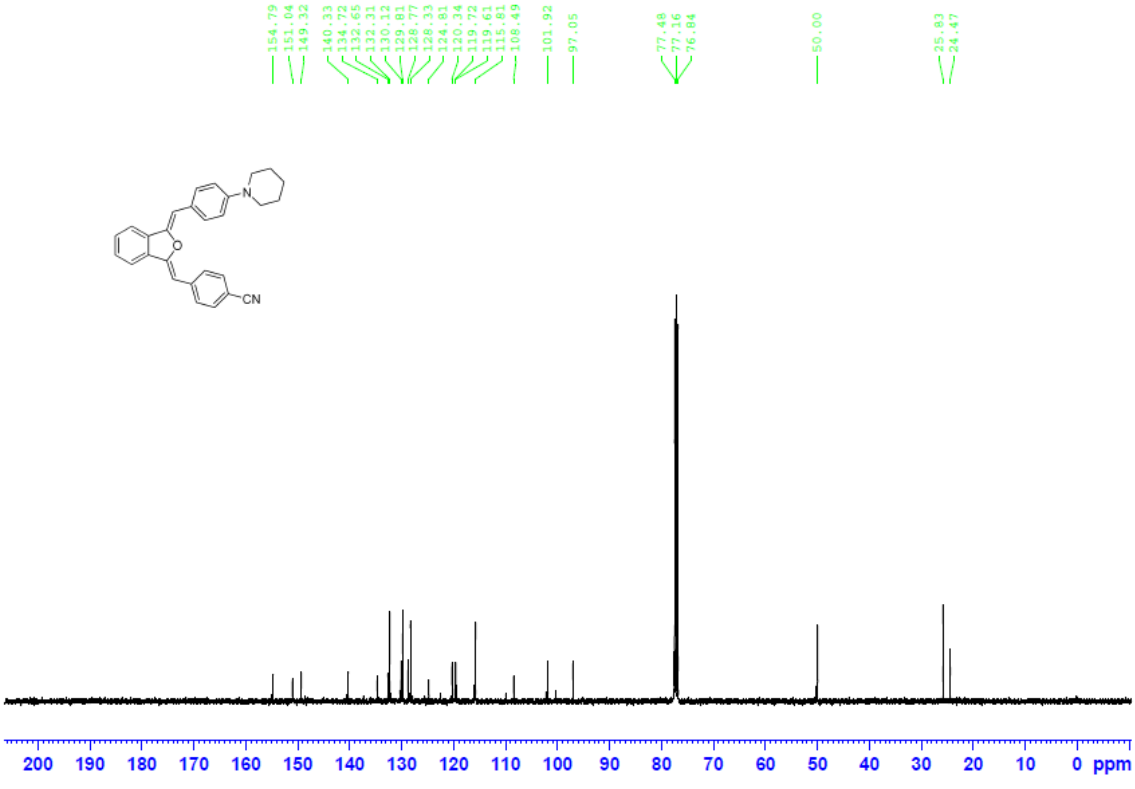
^{13}C NMR of (1*Z*,3*Z*)-3-benzylidene-1-(4-(piperidin-1-yl)benzylidene)-1,3-dihydroisobenzofuran-5-carbonitrile (**C26**)



^{1}H NMR of 4-((*Z*)-((*Z*)-3-(4-(piperidin-1-yl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)benzonitrile (**C27**)



^{13}C NMR of 4-((*Z*)-((*Z*)-3-(4-(piperidin-1-yl)benzylidene)isobenzofuran-1(3*H*)-ylidene)methyl)benzonitrile (**C27**)



3. References

[1] Çoşut B. Highly efficient energy transfer in BODIPY-epyrene decorated cyclotriphosphazene. Dyes Pigm 2014; 100: 11-6.

[2] Didier P, Ulrich G, Mély Y, Ziessel R. Improved push-pull-push *E*-Bodipy fluorophores for two-photon cell-imaging. Org Biomol Chem 2009; 7: 3639-42.