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One-pot straightforward approach to 2,3-disubstituted benzo/naphtho[*b*]furans via domino annulation of α-oxoketene dithioacetals and 1,4-benzo/naphthoquinone mediated by $AlCl_3$ at room temperature

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ABSTRACT

A versatile and convenient one-pot direct approach to 2,3-disubstituted benzo/naphtho[*b*]furans via domino annulation of α-oxoketene dithioacetals and 1,4-benzo/naphthoquinone has been achieved in the presence of aluminium chloride at room temperature. This protocol represents an extremely simple, straightforward and rapid entry to highly substituted benzo/naphtho[*b*]furans in good yields from easily viable starting materials under mild reaction conditions.

1. Introduction

Benzofuran as a highly valuable molecular motif is not only ubiquitous in the realm of pharmaceutically active agents and in natural products, but also frequently utilized as synthetic block in organic synthesis.[1] Prescribed agents featuring this skeleton include the antidepressant (−)-BPAP[1a] and the antiarrythmic amiodarone.[1b] Some benzofuran derivatives are also known as 5-lipoxygenase inhibitors,[1c] angiotensin II inhibitors,[1d] calcium channel blockers[1e] and antitumour agents.[1f] Benzofuran containing natural products include frondosin B[1g] and the eupomatenoid family.[1h] Further, benzofuran derivatives are also utilized as electroluminescent materials, liquid crystals and organic dyes.[2]

As a consequence, numerous approaches to this scaffold have been disclosed in the literature.[3] Recent approaches have focused on the use of relatively mild transition-metal-catalyzed processes, such as the Heck[4] and Sonogashira[5] reactions. Some other synthetic pathways include palladium/platinum catalyzed cyclization,[6a] Dieckmann condensation of activated methylene,[6b] acid/base catalyzed cyclizations[6c–e] and electrochemical synthesis.[6f] In an alternative approach, conjugate addition and sequential cyclization of quinones with active alkenes provides benzofuran skeleton.[7] Very recently, Q. Liu et al.[8a–c] developed synthesis of benzofurans utilizing quinone and ketene acetals, whereas Zeng et al.[8d] used aminophenol as reaction partner in place of quinone. Zhang et al.[8e] synthesized 2,3-disubstituted benzo[*b*]furans via three-component tandem reactions of 2-hydroxybenzaldehydes, amines and alkynes using recyclable catalytic system. G. Liu et al.[8f] synthesized 2,3-disubstituted benzo[*b*]furans from 2-(2-nitroethenyl)phenols via a hypervalent iodine-induced oxidative cyclization.

Although the aforesaid methods enriched approaches to benzo[*b*]furan derivatives, most of them suffer from one or more limitations, such as poor yield, harsh conditions, limited functional group tolerability, highly toxic reagents and multiple steps with limited structural diversity. Therefore, the development of new methods for efficient construction of highly substituted benzo[*b*]furans is quite desirable. In this paper, we report a facile one-pot synthesis of 2,3-disubstituted benzo[*b*]furans via domino annulation of α-oxoketene dithioacetals and 1,4-benzo/naphthoquinone mediated by $AlCl_3$ at room temperature. $AlCl_3$ is probably the most commonly

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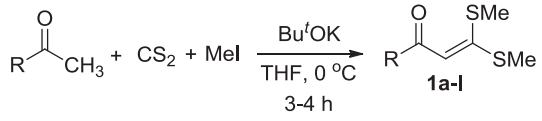
used inexpensive and less toxic Lewis acid, which finds widespread application in a number of industrial processes and chemical reactions, such as Friedel–Crafts reactions, Gatterman–Koch reaction, esterification, isomerization, polymerization and [3+2] cycloaddition etc.[9]

2. Results and discussion

Ketene dithioacetals have been proved to be an important class of versatile intermediates, which have drawn continuous interest in the synthesis of various important scaffolds, such as heterocycles, carbocycles and aromatic compounds.[10,11] In continuation to our interest in α-oxoketene dithioacetals[12] chemistry, we report herein a new domino protocol for the synthesis of 2,3-disubstituted benzo/naphtho[*b*]furans involving α-oxoketene dithioacetals and 1,4-benzo/naphthoquinone. The desired α-oxoketene dithioacetals **1** are prepared in good yields by treating the corresponding aryl/hetaroaryl/aliphatic ketones with carbon disulphide in the presence of potassium *tert*-butoxide followed by alkylation with methyl iodide (Scheme 1).[13]



1a: R= C_6H_5, 60%; **1b:** R= 4-MeC_6H_4, 65%;

1c: R= 4-$MeOC_6H_4$, 74%; **1d:** R= 4-ClC_6H_4, 71%;

1e: R= 4-biphenyl, 65%; **1f:** R= 2-ClC_6H_4, 59%;

1g: R= 1-naphthyl, 60%; **1h:** R= 2-thienyl, 64%;

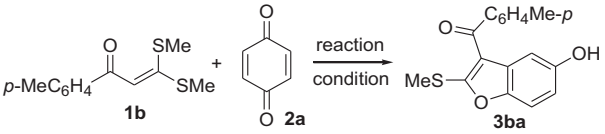
1i: R= 2-furyl, 72%; **1j:** R= 3-pyridyl, 57%;

1k: R= OEt, 45%; **1l:** R= *tert*.-Bu, 69%

Scheme 1. Synthesis of α-oxoketene dithioacetals **1**.

Our literature survey at this stage revealed that various toxic and expensive catalysts, co-catalysts and hypervalent iodine involving multiple steps have been used for the synthesis of benzo[*b*]furans from α-oxoketene dithioacetals.[8] It is hypothesized that Lewis/Bronsted acids can induce this reaction by activation of the carbonyl groups of both the substrates α-oxoketene dithioacetas and quinones. In our initial studies, we choose 3,3-bis-methylthio-1-(4-methylphenyl)-propen-1-one **1b** and 1,4-benzoquinone **2a** as model substrates. Reaction of **1b** (1.0 mmol) with **2a** (1.2 mmol) in 5 ml of acetonitrile in the presence of 20 mol % of $AlCl_3$ at room temperature was carried out. The reaction proceeded smoothly and the desired product 3-(4-methylbenzoyl)-5-hydroxy-2-methylthio benzofuran (**3ba**) was obtained in 76% yield within 2.5 h (Table 1, entry 1). Motivated by the above result, the model reaction was performed with various Lewis and Bronsted acids at room temperature under different solvents and the results are tabulated in Table 1. $InCl_3$, $FeCl_3$, $TiCl_4$, *p*-TSA, $SiO_2{\cdot}H_2SO_4$ and $SiO_2{\cdot}HClO_4$ did catalyze the reaction albeit in low yields (Table 1, entries 2–7). Notably, CuI and LiBr were found to be completely ineffective and did not catalyze the reaction even after 24 h of stirring (Table 1, entries 8 and 9). Next, we intended to optimize the $AlCl_3$ loading and it was found that either increasing or decreasing the amount of $AlCl_3$ did not improve the outcome of the reaction in terms of yield and reaction time (Table 1, entries 10 and 11). Thus, 20 mol % of $AlCl_3$ was found to be the optimum loading. To increase the yield of the reaction, the effect of solvents on the model reaction was further examined. Among the solvent tested dichloromethane and acetone provided the desired product in 40% and 44% yields, respectively, while ethanol was found to be completely ineffective (Table 1, entries 12–14). A blank reaction was also performed, which did not afford the desired product even in trace after 24 h of stirring at room temperature (Table 1, entry 15). Thus, from the above screening it was found that 20 mol % of $AlCl_3$ in acetonitrile at room temperature was found to be the best condition for this reaction (Table 1, entry 1).

Table 1
Optimization of the reaction conditions for the synthesis of **3ba**[a]



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	$AlCl_3$ (20)	CH_3CN	2.5	76
2	$InCl_3$ (20)	CH_3CN	24	24
3	$FeCl_3$ (20)	CH_3CN	24	60
4	$TiCl_4$ (20)	CH_3CN	6	52
5	*p*-TSA (20)	CH_3CN	24	32
6	$SiO_2{\cdot}H_2SO_4$ (20)	CH_3CN	24	48
7	$SiO_2{\cdot}HClO_4$ (20)	CH_3CN	24	50
8	CuI (20)	CH_3CN	24	NR[c]
9	LiBr (20)	CH_3CN	24	NR[c]
10	$AlCl_3$ (25)	CH_3CN	2.5	75
11	$AlCl_3$ (15)	CH_3CN	4	62
12	$AlCl_3$ (20)	CH_2Cl_2	4	40
13	$AlCl_3$ (20)	CH_3COCH_3	4	44
14	$AlCl_3$ (20)	EtOH	24	NR[c]
15	No catalyst	CH_3CN	24	NR[c]

[a] Reaction condition: 1.0 mmol of **1b** and 1.2 mmol of **2a** at rt in 5 ml of solvent.
[b] Isolated pure yields.
[c] No reaction.

Under the optimized reaction conditions, the scope and generality of the reaction were systematically investigated. The results listed in Table 2 demonstrate that the corresponding target products were obtained in good yields for most substrates. To check the effect of substituents R at α-oxoketene dithioacetals **1** various aryl/hetaryl/alkyl motifs at this position were converted to the desired products **3** in satisfactory yields. To further discover the scope and to add structural diversity, the procedure was extended to 1,4-naphthoquinone **2b** as another quinone counterpart. Compound **2b** was treated with various α-oxoketene dithioacetals **1** under optimized reaction conditions and afforded the desired naphtho[*b*]furans **3** in good yields (Table 2, entries 13–20). Compared with the reported multi-step synthesis, this domino reaction in one-pot could enhance the efficiency of preparing the target products from simple starting materials, avoid the separation of intermediates and reduce the amount of pollutant waste emission. The structures of all the newly synthesized compounds were deduced from their satisfactory spectral (IR, ^1H, ^{13}C NMR and HRMS) studies. Finally, the structures of two representative compounds **3ba** and **3ia** were explicitly confirmed by X-ray single crystal diffraction analysis (Fig. 1).[14]

Although we have not established the mechanism of the reaction experimentally, on the basis of above experimental results and the literature evidence, a plausible reaction pathway for the formation of benzo/naphtho[*b*]furans mediated by $AlCl_3$ is formulated in Scheme 2. α-Oxoketene dithioacetals **1** are polarized alkenes (polarization flows from two electron-donating alkylthio groups on C-1 to electron-withdrawing carbonyl group on C-2), showing C-1 electrophilic and C-2 nucleophilic characteristics. It is assumed that initially $AlCl_3$ activates both the substrates **1** and **2** by coordinating with their carbonyl oxygens forming a complex **A**. Then complex **A** is believed to undergo Michael-type addition to give an open chain intermediate **B**,

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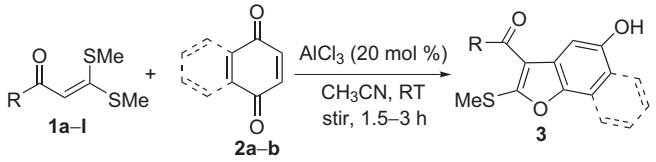
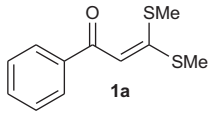
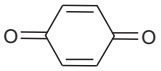
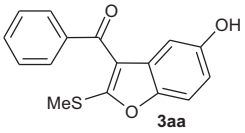
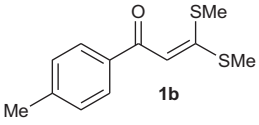
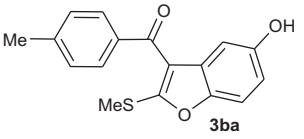
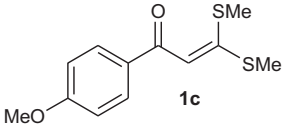
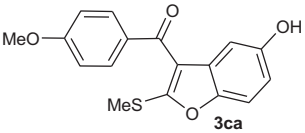
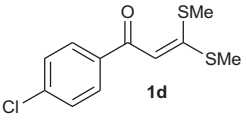
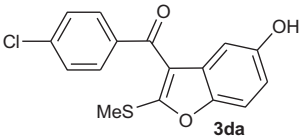
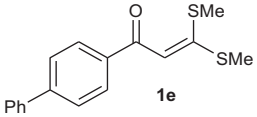
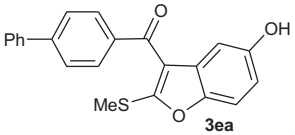
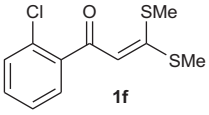
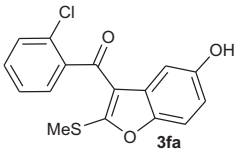
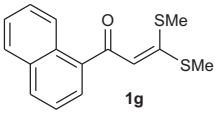
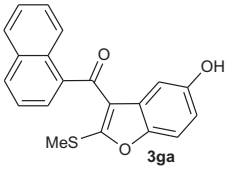
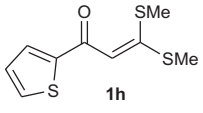
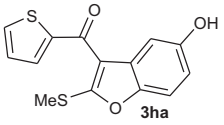
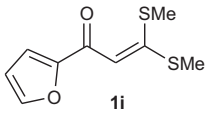
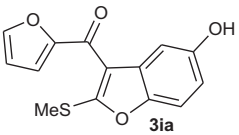
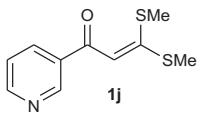
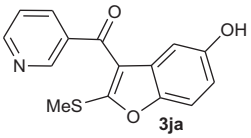
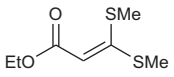
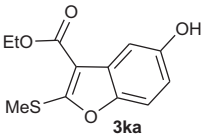
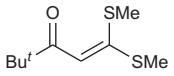
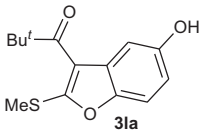
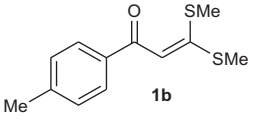
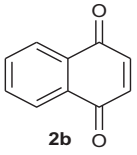
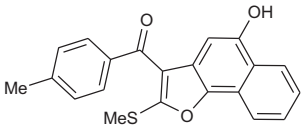
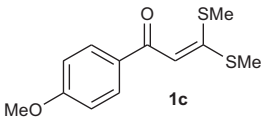
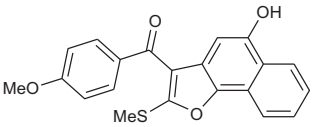
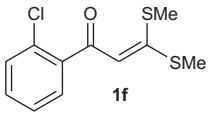
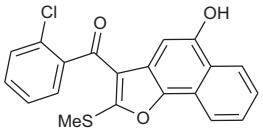
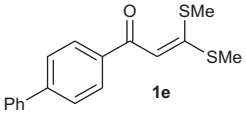
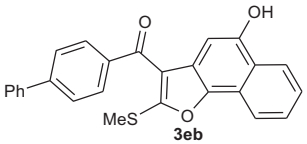
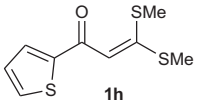
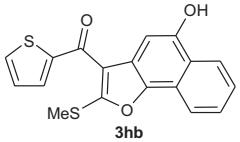
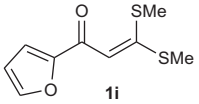
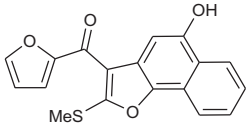
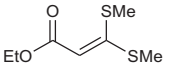
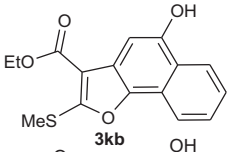
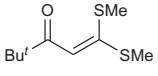
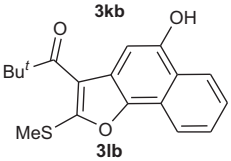
Table 2
Synthesis of 3-substituted-5-hydroxy-2-methylthio benzo/naphthofuran derivatives



Entry	α-Oxoketene dithioacetals (**1**)	Quinone (**2**)	Product (**3**)	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	 **3aa**	3.0	69
2	 **1b**	**2a**	 **3ba**	2.5	76
3	 **1c**	**2a**	 **3ca**	2.5	78
4	 **1d**	**2a**	 **3da**	2.7	72
5	 **1e**	**2a**	 **3ea**	2.5	75
6	 **1f**	**2a**	 **3fa**	2.8	70
7	 **1g**	**2a**	 **3ga**	3.0	70
8	 **1h**	**2a**	 **3ha**	2.2	77
9	 **1i**	**2a**	 **3ia**	2.2	77
10	 **1j**	**2a**	 **3ja**	3.0	74

(*continued on next page*)

Table 2 (*continued*)

Entry	α-Oxoketene dithioacetals (**1**)	Quinone (**2**)	Product (**3**)	Time (h)	Yield[a] (%)
11	 **1k**	**2a**	 **3ka**	1.5	86
12	 **1l**	**2a**	 **3la**	3.0	80
13	 **1b**	 **2b**	 **3bb**	3.3	72
14	 **1c**	**2b**	 **3cb**	3.3	70
15	 **1f**	**2b**	 **3fb**	3.5	68
16	 **1e**	**2b**	 **3eb**	3.2	67
17	 **1h**	**2b**	 **3hb**	3.0	74
18	 **1i**	**2b**	 **3ib**	3.0	72
19	 **1k**	**2b**	 **3kb**	2.0	75
20	 **1l**	**2b**	 **3lb**	2.4	72

[a] Isolated pure yield.

which isomerizes to **C**. Intermediate **C** is ready to undergo an intramolecular attack on the carbon bearing thiomethyl groups by the phenolic oxygen to give **D**, which undergoes dethiomethylation to furnish the desired product **3**. This operationally simple and two-component domino process concomitantly created one new C–C and one C–O bond leading to furan ring.

Furthermore, to illustrate the broad synthetic utility of our developed methodology, functionalization of the desired product was

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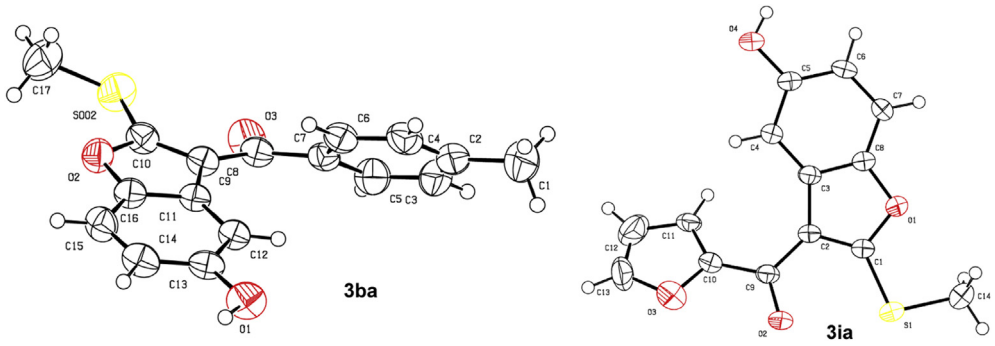
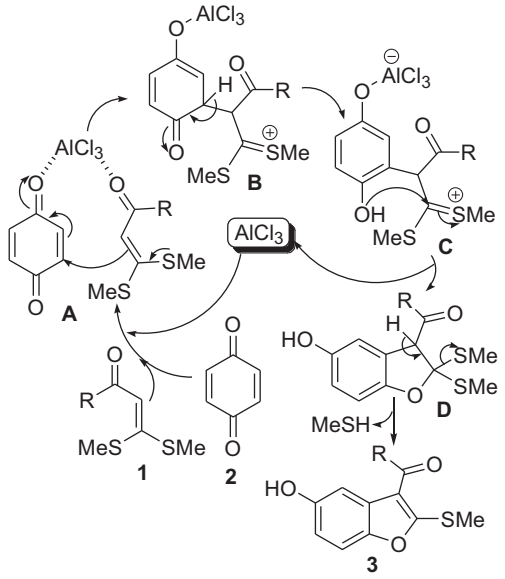
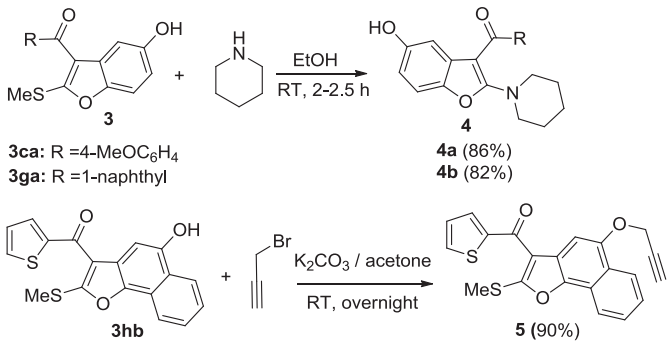


Fig. 1. ORTEP diagrams of **3ba** and **3ia**.



Scheme 2. A plausible reaction mechanism for the formation of **3**.

carried out to add more structural diversity on to benzofuran frameworks. In this regard, 2-methylthio group of **3ca** and **3ga** was substituted by piperidine to give 2-piperidine substituted benzofurans **4a** and **4b**, respectively, in high yield (Scheme 3). Next, when benzofuran derivative **3hb**, was treated with propargyl bromide in the presence of potassium carbonate, the 5-hydroxy group was functionalized to give 5-(prop-2-ynyloxy) substituted benzofuran **5** in 90% yield, which could further be converted into benzofuran/benzopyran-3/4-one moieties under suitable conditions.[15]



Scheme 3. Functionalization of product **3** to **4** and **5**.

3. Conclusion

In conclusion, we have developed a facile and efficient one-pot protocol for the synthesis of functionalized benzo/naphtho[*b*]furans via domino coupling of α-oxoketene dithioacetals and 1,4-benzo/naphthoquinones mediated by $AlCl_3$ at room temperature in good yields. Importantly, for the first time, cheap and easily available $AlCl_3$ has been utilized for the construction of benzo/naphtho[*b*]furan frameworks. The easy accessibility of starting materials, simplicity of execution and mild reaction conditions make this new strategy highly demanding for academic research and realistic applications.

4. Experimental

4.1. General

All the commercially available reagents were purchased from Merck, Aldrich and Fluka, and were used as received. All ^1H and ^{13}C NMR spectra were recorded on JEOL AL 300 FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on Perkin–Elmer Spectrum Version 10.03.05 FT-IR spectrophotometer. Mass spectra were recorded on an Agilent Q-TOF and Waters-Q-Tof Premier-HAB213 instrument. X-ray diffraction was measured on Xcalibur Oxford CCD Diffractometer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck $60F_{254}$) using UV light for visualization. Melting points were determined with Büchi B-540 melting point apparatus and are uncorrected. Solvents were dried and purified by standard procedures.

4.2. General procedure for the synthesis of 3-substituted-5-hydroxy-2-methylthio-benzo/naphtho[*b*]furans (3)

A mixture of α-oxoketene dithioacetal **1** (1.0 mmol) and 1,4-benzoquinone **2a** (1.2 mmol) or 1,4-naphthoquinone **2b** (1.2 mmol) in 5 ml of dry acetonitrile in the presence of $AlCl_3$ (20 mol %) was stirred at room temperature for the stipulated period of time (Table 2). After completion of the reaction (monitored by TLC) the solvent was evaporated under vacuum and the residue thus obtained was diluted with water (15 ml) and extracted with ethyl acetate (2×15 ml). The combined organic extract was washed with water (2×20 ml) followed by brine (1×20 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography over silica gel using ethyl acetate/*n*-hexane (1:10) as eluent to give the desired product in excellent purity. The physical and spectral data of the synthesized compounds are as follows.

*4.2.1. 3-Benzoyl-5-hydroxy-2-methylthio-benzofuran (**3aa**).* Yellow solid; mp: 212–213 °C (lit.[8c] 212–214 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.33 (s, 1H, OH, D_2O exchangeable); 7.68–7.63 (m, 3H, ArH); 7.54 (t, *J*=7.5 Hz, 2H, ArH); 7.42 (d, *J*=9.0 Hz, 1H, ArH); 6.68 (dd, *J*=8.7 and 1.8 Hz, 1H, ArH); 6.52 (d, *J*=2.4 Hz, 1H, ArH); 2.62 (s, 3H, SMe); ^{13}C NMR (75 MHz, DMSO-d_6): δ 189.6, 163.1, 154.2, 148.8, 139.0, 132.2, 128.6, 128.0, 126.9, 115.6, 112.3, 111.2, 105.0, 13.4; IR (KBr): ν 3263, 2925, 2852, 1604, 1457, 1364, 1220, 1152 cm^{-1}.

*4.2.2. 5-Hydroxy-3-(4-methylbenzoyl)-2-methylthio-benzofuran (**3ba**).* Yellow solid; mp: 188–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J*=7.8 Hz, 2H, ArH); 7.32–7.25 (m, 3H, ArH); 6.94 (d, *J*=2.4 Hz, 1H, ArH); 6.75 (dd, *J*=9.0 and 2.1 Hz, 1H, ArH); 5.36 (s, 1H, OH, D_2O exchangeable); 2.63 (s, 3H, SMe); 2.44 (s, 3H, ArMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 189.8, 162.5, 153.7, 149.3, 142.4, 136.3, 128.7, 128.5, 127.1, 116.7, 112.0, 110.4, 105.6, 21.3, 13.6; IR (KBr): ν 3201, 2923, 2852, 1597, 1447, 1372, 1224, 1161 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{17}H_{14}O_3S$: 299.0742, found 299.0744.

*4.2.3. 5-Hydroxy-3-(4-methoxybenzoyl)-2-methylthio-benzofuran (**3ca**).* Yellow solid; mp: 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (dd, *J*=8.7 and 4.2 Hz, 2H, ArH); 7.26 (d, *J*=3.0 Hz, 1H, ArH); 6.97 (d, *J*=8.4 Hz, 1H, ArH); 6.71 (s, 3H, ArH); 4.48 (s, 1H, OH, D_2O exchangeable); 3.89 (s, 3H, OMe); 2.63 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 189.5, 162.8, 153.8, 149.7, 131.0, 115.8, 113.4, 112.2, 110.6, 105.7, 55.2, 13.9; IR (KBr): ν 3218, 2929, 2843, 1590, 1453, 1360, 1264, 1151 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{17}H_{14}O_4S$: 315.0691, found 315.0696.

*4.2.4. 3-(4-Chlorobenzoyl)-5-hydroxy-2-methylthio-benzofuran (**3da**).* Brown solid; mp: 183–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.1 Hz, 2H, ArH); 7.46 (d, *J*=8.4 Hz, 2H, ArH); 7.32 (d, *J*=8.7 Hz, 1H, ArH); 6.78 (dd, *J*=8.4 and 2.1 Hz, 1H, ArH); 6.74 (d, *J*=2.4 Hz, 1H, ArH); 5.00 (s, 1H, OH, D_2O exchangeable); 2.66 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 164.5, 152.9, 150.2, 138.5, 137.5, 130.0, 128.8, 127.5, 116.4, 112.3, 111.1, 106.0, 14.0; IR (KBr): ν 3214, 2925, 2854, 1600, 1456, 1358, 1240, 1133 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{16}H_{11}ClO_3S$: 319.0196, found 319.0192.

*4.2.5. 3-(Biphenyl-4-carbonyl)-5-hydroxy-2-methylthio-benzofuran (**3ea**).* Yellow solid; mp: 191–192 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.1 Hz, 2H, ArH); 7.71 (d, *J*=8.1 Hz, 3H, ArH); 7.67 (d, *J*=7.5 Hz, 2H, ArH); 7.50–7.31 (m, 4H, ArH); 6.89 (d, *J*=2.4 Hz, 1H, ArH); 5.04 (s, 1H, OH, D_2O exchangeable); 2.66 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 178.6, 170.7, 157.1, 155.3, 137.1, 135.0, 134.5, 133.0, 129.3, 128.9, 127.2, 127.1, 122.7, 99.9, 14.0; IR (KBr): ν 3418, 2926, 1598, 1464, 1370, 1244, 1190, 1165 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{22}H_{16}O_3S$: 361.0898, found 361.0890.

*4.2.6. 3-(2-Chlorobenzoyl)-5-hydroxy-2-methylthio-benzofuran (**3fa**).* Yellow solid; mp: 157–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.38 (m, 3H, ArH); 7.28 (d, *J*=8.7 Hz, 1H, ArH); 6.85 (s, 1H, ArH); 6.75 (d, *J*=2.4 Hz, 1H, ArH); 6.72 (d, *J*=5.1 Hz, 1H, ArH); 5.36 (s, 1H, OH, D_2O exchangeable); 2.64 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 188.2, 165.4, 154.2, 149.6, 149.4, 139.7, 130.7, 130.1, 129.7, 127.7, 127.0, 115.7, 112.0, 110.4, 105.4, 13.3; IR (KBr): ν 3160, 2997, 1584, 1470, 1380, 1271, 1163 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{16}H_{11}ClO_3S$: 319.0196, found 319.0190.

*4.2.7. 5-Hydroxy-2-methylthio-3-(1-naphthoyl)-benzofuran (**3ga**).* Yellow solid; mp: 164–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (s, 1H, OH, D_2O exchangeable); 8.15 (d, *J*=6.6 Hz, 1H, ArH); 8.06 (d, *J*=7.8 Hz, 1H, ArH); 7.83 (d, *J*=8.1 Hz, 1H, ArH); 7.64–7.52 (m, 5H, ArH); 7.41 (d, *J*=8.7 Hz, 1H, ArH); 6.64 (dd, *J*=9.0 and 2.4 Hz, 1H, ArH); 2.62 (s, 3H, SMe); ^{13}C NMR (75 MHz, DMSO-d_6): δ 190.5, 165.0, 149.6, 148.8, 137.7, 133.2, 130.6, 129.0, 128.5, 127.2, 126.7, 126.5, 125.3, 124.4, 116.5, 112.0, 111.1, 104.9, 13.1; IR (KBr): ν 3190, 2980, 2706, 1604, 1460, 1378, 1209, 1170 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{20}H_{14}O_3S$: 335.0742, found 335.0745.

*4.2.8. 5-Hydroxy-2-methylthio-3-(thien-2-carbonyl)-benzofuran (**3ha**).* Yellow solid; mp: 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=3.6 Hz, 1H, ArH); 7.69 (d, *J*=5.1 Hz, 1H, ArH); 7.31 (d, *J*=9.0 Hz, 1H, ArH); 7.15–7.12 (m, 1H, ArH); 7.07 (d, *J*=2.1 Hz, 1H, ArH); 6.78 (dd, *J*=9.0 and 2.4 Hz, 1H, ArH); 6.23 (s, 1H, OH, D_2O exchangeable); 2.64 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 181.3, 161.2, 153.8, 149.6, 144.0, 133.0, 127.5, 126.7, 117.2, 115.6, 112.5, 110.5, 105.4, 14.0; IR (KBr): ν 3069, 2924, 2850, 1586, 1467, 1344, 1232, 1139 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{14}H_{10}O_3S_2$: 291.0150, found 291.0158.

*4.2.9. 3-(Furan-2- carbonyl)-5-hydroxy-2-methylthio-benzofuran (**3ia**).* Yellow solid; mp: 167–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H, ArH); 7.34–7.31 (m, 2H, ArH); 6.78 (dd, *J*=8.7 and 2.4 Hz, 1H, ArH); 6.71 (s, 2H, ArH); 5.08 (s, 1H, OH, D_2O exchangeable); 2.65 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 184.1, 153.7, 149.5, 145.8, 126.3, 118.2, 115.6, 112.2, 111.9, 110.4, 105.8, 13.7; IR (KBr): ν 3309, 2925, 1584, 1465, 1376, 1247, 1174 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{14}H_{10}O_4S$: 275.0378, found 275.0375.

*4.2.10. 5-Hydroxy-2-methylthio-3-(pyridyl-3-carbonyl)-benzofuran (**3ja**).* Brown solid; mp: 128–129 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.31 (s, 1H, OH, D_2O exchangeable); 9.15 (s, 1H, ArH); 8.73 (d, *J*=3.9 Hz, 1H, ArH); 8.30 (d, *J*=7.8 Hz, 1H, ArH); 7.53 (dd, *J*=7.5 and 4.8 Hz, 1H, ArH); 6.93–6.89 (m, 1H, ArH); 6.79–6.70 (m, 1H, ArH); 6.57–6.55 (m, 1H, ArH); 2.69 (s, 3H, SMe); ^{13}C NMR (75 MHz, DMSO-d_6): δ 182.8, 167.9, 152.2, 150.1, 148.8, 145.5, 135.2, 133.9, 123.7, 117.0, 116.0, 115.6, 114.7, 109.0, 14.4; IR (KBr): ν 3418, 3090, 2950, 1626, 1590, 1465, 1384, 1204, 1117 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{15}H_{11}NO_3S$: 286.0538, found 286.0538.

*4.2.11. 3-Carboethoxyl-5-hydroxy-2-methylthio-benzofuran (**3ka**).* - White solid; mp: 152–153 °C (lit.[8c] 156–158 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H, ArH); 6.72 (dd, *J*=8.7 and 2.4 Hz, 1H, ArH); 4.81 (s, 1H, OH, D_2O exchangeable); 4.40 (q, *J*=7.2 Hz, 2H, OCH_2); 2.68 (s, 3H, SMe); 1.43 (t, *J*=6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 163.3, 152.9, 150.0, 127.7, 111.6, 110.8, 109.9, 106.1, 103.3, 60.6, 14.4, 13.2; IR (KBr): ν 3289, 2926, 1662, 1593, 1496, 1346, 1268, 1134 cm^{-1}.

*4.2.12. 3-(2,2-Dimethylpropionyl)-5-hydroxy-2-methylthio-benzofuran (**3la**).* Brown solid; mp: 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J*=8.7 Hz, 1H, ArH); 7.18 (d, *J*=2.4 Hz, 1H, ArH); 6.75 (dd, *J*=9.0 and 2.4 Hz, 1H, ArH); 4.75 (s, 1H, OH, D_2O exchangeable); 2.60 (s, 3H, SMe); 1.40 (s, 9H, 3× CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.3, 173.3, 165.2, 152.0, 150.5, 126.3, 116.8, 111.5, 111.2, 107.7, 43.3, 26.1, 14.3; IR (KBr): ν 3330, 2926, 1599, 1451, 1354, 1287, 1185 cm^{-1}; HRMS [ESI, (M+H)$^+$] calcd for $C_{14}H_{16}O_3S$: 265.0898, found 265.0896.

*4.2.13. 5-Hydroxy-3-(4-methylbenzoyl)-2-methylthio-naphtho[1,2-b]furan (**3bb**).* Yellow solid; mp: 165–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H, OH, D_2O exchangeable); 8.29 (d, *J*=8.4 Hz, 1H, ArH); 8.17 (d, *J*=8.1 Hz, 1H, ArH); 7.76 (d, *J*=7.8 Hz, 2H, ArH); 7.59 (t, *J*=7.8 Hz, 1H, ArH); 7.47 (t, *J*=7.8 Hz, 1H, ArH); 7.30 (d, *J*=7.8 Hz, 2H, ArH); 6.94 (s, 1H, ArH); 2.72 (s, 3H, SMe); 2.45 (s, 3H, ArMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 192.7, 178.8, 174.3, 168.5, 155.7, 150.0, 136.1, 128.7, 128.6, 126.5, 123.8, 123.0, 120.3, 118.8, 99.6, 21.3, 14.3; IR (KBr): ν 3196, 2930, 1589, 1432, 1348, 1249,

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1147 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{21}H_{16}O_3S$: 349.0898, found 349.0895.

*4.2.14. 5-Hydroxy-3-(4-methoxybenzoyl)-2-methylthio-naphtho[1,2-b]furan (**3cb**).* Yellow solid; mp: 217–218 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H, OH, D_2O exchangeable); 8.29 (d, *J*=8.1 Hz, 1H, ArH); 8.17 (d, *J*=8.1 Hz, 1H, ArH); 7.86 (d, *J*=8.4 Hz, 2H, ArH); 7.59 (t, *J*=7.5 Hz, 1H, ArH); 7.46 (t, *J*=7.5 Hz, 1H, ArH); 6.99 (d, *J*=8.7 Hz, 2H, ArH); 6.91 (s, 1H, ArH); 3.90 (s, 3H, OMe); 2.72 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 188.9, 162.8, 157.5, 150.1, 145.0, 131.5, 131.1, 126.6, 123.9, 123.2, 122.9, 122.6, 120.5, 119.3, 118.9, 113.4, 99.8, 55.1, 14.6; IR (KBr): ν 3182, 2924, 2852, 1583, 1486, 1348, 1267, 1146 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{21}H_{16}O_4S$: 365.0848, found 365.0845.

*4.2.15. 3-(2-Chlorobenzoyl)-5-hydroxy-2-methylthio-naphtho[1,2-b]furan (**3fb**).* Yellow solid; mp: 132–133 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J*=8.4 Hz, 1H, ArH); 8.15 (d, *J*=8.1 Hz, 1H, ArH); 7.61 (t, *J*=7.5 Hz, 1H, ArH); 7.52–7.41 (m, 5H, ArH); 6.80 (s, 1H, ArH); 5.32 (s, 1H, OH, D_2O exchangeable); 2.75 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 187.7, 161.8, 150.1, 144.1, 139.1, 130.3, 129.4, 129.1, 127.3, 126.5, 126.2, 123.3, 122.6, 121.9, 121.4, 119.6, 118.1, 116.8, 98.8, 13.0; IR (KBr): ν 3437, 2924, 2854, 1554, 1457, 1295, 1250, 1122 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{20}H_{13}ClO_3S$: 369.0352, found 369.0350.

*4.2.16. 3-(Biphenyl-4-carbonyl)-5-hydroxy-2-methylthio-naphtho[1,2-b]furan (**3eb**).* Yellow solid; mp: 241–242 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J*=8.4 Hz, 1H, ArH); 8.20 (d, *J*=8.1 Hz, 1H, ArH); 7.91 (d, *J*=7.8 Hz, 2H, ArH); 7.76–7.61 (m, 5H, ArH); 7.54–7.40 (m, 4H, ArH); 6.98 (s, 1H, ArH); 5.83 (s, 1H, OH, D_2O exchangeable); 2.75 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 190.1, 160.0, 150.3, 145.2, 144.5, 139.7, 137.8, 129.5, 128.8, 128.0, 126.9, 126.7, 124.2, 123.3, 122.8, 122.4, 120.7, 119.1, 99.9, 14.3; IR (KBr): ν 3443, 2926, 1585, 1429, 1365, 1248, 1350, 1147 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{26}H_{18}O_3S$: 411.1055, found 411.1052.

*4.2.17. 5-Hydroxy-2-methylthio-3-(thien-2-carbonyl)-naphtho[1,2-b]furan (**3hb**).* Yellow solid; mp: 174–175 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 10.19 (s, 1H, OH, D_2O exchangeable); 8.21 (dd, *J*=7.8 and 3.3 Hz, 2H, ArH); 8.13 (d, *J*=4.5 Hz, 1H, ArH); 7.84 (d, *J*=3.0 Hz, 1H, ArH); 7.68 (t, *J*=7.5 Hz, 1H, ArH); 7.53 (t, *J*=7.5 Hz, 1H, ArH); 7.31 (t, *J*=4.2 Hz, 1H, ArH); 7.00 (s, 1H, ArH); 2.75 (s, 3H, SMe); ^{13}C NMR (75 MHz, DMSO-d_6): δ 181.0, 157.5, 150.3, 144.2, 143.4, 135.2, 134.3, 128.5, 127.4, 124.7, 123.2, 122.5, 122.1, 120.2, 119.2, 119.0, 98.9, 14.6; IR (KBr): ν 3280, 2928, 2854, 1560, 1464, 1384, 1248, 1115 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{18}H_{12}O_3S_2$: 341.0306, found 341.0301.

*4.2.18. 3-(Furan-2-carbonyl)-5-hydroxy-2-methylthio-naphtho[1,2-b]furan (**3ib**).* Brown solid; mp: 194–195 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J*=8.4 Hz, 1H, ArH); 8.20 (d, *J*=8.1 Hz, 1H, ArH); 7.72 (s, 1H, ArH); 7.63 (t, *J*=7.5 Hz, 1H, ArH); 7.53 (t, *J*=7.5 Hz, 1H, ArH); 7.36 (d, *J*=3.3 Hz, 1H, ArH); 7.26 (d, *J*=5.1 Hz, 1H, ArH); 6.63 (d, *J*=1.8 Hz, 1H, ArH); 5.83 (s, 1H, OH, D_2O exchangeable); 2.74 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 175.9, 158.6, 151.8, 149.9, 145.9, 144.6, 126.3, 123.7, 122.8, 122.4, 121.4, 120.1, 118.6, 118.3, 118.1, 111.7, 99.5, 14.2; IR (KBr): ν 3284, 2924, 2851, 1586, 1467, 1391, 1232, 1071 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{18}H_{12}O_4S$: 325.0535, found 325.0531.

*4.2.19. 3-Carboethoxyl-5-hydroxy-2-methylthio-naphtho[1,2-b]furan (**3kb**).* White solid; mp: 210–212 °C (lit.[8c] 208–210 °C); ^1H NMR (300 MHz, $CDCl_3$): δ 9.10 (s, 1H, OH, D_2O exchangeable); 8.31 (d, *J*=8.4 Hz, 1H, ArH); 8.11 (d, *J*=8.1 Hz, 1H, ArH); 7.57 (t, *J*=7.5 Hz, 1H, ArH); 7.43 (br s, 2H, ArH); 4.42 (q, *J*=7.2 Hz, 2H, OCH_2); 2.79 (s, 3H, SMe); 1.47 (t, *J*=7.2 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 138.6, 134.3, 133.8, 133.2, 132.1, 131.7, 126.7, 126.5, 126.3, 61.6, 14.0, 12.0; IR (KBr): ν 3312, 2922, 1670, 1605, 1526, 1356, 1256, 1118 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{16}H_{14}O_4S$: 303.0691, found 303.0692.

*4.2.20. 3-(2,2-Dimethylpropionyl)-5-hydroxy-2-methylthio-naphtho[1,2-b]furan (**3lb**).* Yellow solid; mp: 183–184 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J*=8.4 Hz, 1H, ArH); 8.13 (d, *J*=8.1 Hz, 1H, ArH); 7.59 (t, *J*=7.8 Hz, 1H, ArH); 7.48 (t, *J*=7.5 Hz, 1H, ArH); 7.13 (s, 1H, ArH); 6.17 (s, 1H, OH, D_2O exchangeable); 2.67 (s, 3H, SMe); 1.39 (s, 9H, 3× Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 158.5, 148.4, 146.0, 127.3, 124.9, 122.7, 122.1, 121.0, 120.8, 119.7, 102.0, 43.9, 26.4, 15.3; IR (KBr): ν 3450, 1670, 1645, 1554, 1336, 1295, 1251, 1123 cm^{-1}; HRMS [ESI, $(M+H)^+$] calcd for $C_{18}H_{18}O_3S$: 315.1055, found 315.1051.

4.3. General procedure for the synthesis of 3-substituted-5-hydroxy-2-piperidino-benzofuran (4)

A mixture of **3** (0.5 mmol) and piperidine (0.6 mmol) in 3 ml of ethanol was stirred at room temperature for 2–2.5 h. After completion of the reaction (monitored by TLC) the solvent was evaporated under reduced pressure and the residue was treated with water (15 ml) followed by extraction with ethyl acetate (2×10 ml). The organic layer was washed with water (2×15 ml), brine (1×20 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product, which was purified by column chromatography over silica gel (100–200 mesh) using ethyl acetate/*n*-hexane (1:19) as eluent.

*4.3.1. 5-Hydroxy-3-(4-methoxybenzoyl)-2-piperidino-benzofuran (**4a**).* Brown solid; mp: 216–217 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H, OH, D_2O exchangeable); 7.78 (d, *J*=8.7 Hz, 2H, ArH); 7.01 (d, *J*=8.7 Hz, 1H, ArH); 6.94 (d, *J*=8.4 Hz, 2H, ArH); 6.60 (d, *J*=2.4 Hz, 1H, ArH); 6.52 (dd, *J*=8.4 and 2.7 Hz, 1H, ArH); 3.88 (s, 3H, OMe); 3.40 (s, 4H, 2× CH_2); 1.60 (s, 6H, 3× CH_2); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 188.8, 163.6, 162.2, 153.2, 142.5, 133.1, 130.7, 130.1, 113.2, 109.1, 108.7, 105.1, 55.1, 49.0, 25.1, 23.6; IR (KBr): ν 3417, 2924, 2852, 1617, 1544, 1442, 1300, 1221, 1180, 1020 cm^{-1}; HRMS [ESI, $(M+H)^+$/$(M+Na)^+$] calcd for $C_{21}H_{21}NO_4$: 352.1549/374.1368, found 352.1540/374.1363.

*4.3.2. 5-Hydroxy-3-(1-naphthoyl)-2-piperidino-benzofuran (**4b**).* Yellow solid; mp: 195–196 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J*=8.1 Hz, 1H, ArH); 7.97 (d, *J*=8.1 Hz, 1H, ArH); 7.90 (d, *J*=7.5 Hz, 1H, ArH); 7.64 (d, *J*=7.2 Hz, 1H, ArH); 7.53–7.49 (m, 4H, ArH); 7.03 (d, *J*=8.4 Hz, 1H, ArH); 6.47–6.40 (m, 1H, ArH); 5.86 (s, 1H, OH, D_2O exchangeable); 3.55 (s, 4H, 2× CH_2); 1.62 (s, 6H, 3× CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 170.6, 168.4, 152.0, 141.6, 140.1, 138.8, 134.3, 133.2, 129.6, 128.2, 126.5, 125.0, 120.8, 112.9, 111.4, 105.6, 49.8, 25.5, 22.8; IR (KBr): ν 3428, 2970, 2813, 1610, 1523, 1440, 1324, 1215, 1165, 1055 cm^{-1}; HRMS [ESI, $(M+H)^+$/$(M+Na)^+$] calcd for $C_{24}H_{21}NO_3$: 372.1600/394.1419, found 372.1592/394.1414.

4.4. General procedure for the synthesis of 2-methylthio-5-(prop-2-ynyloxy)-3-(thien-2-carbonyl)-naphtho[1,2-*b*]furan (5)

A mixture of **3hb** (170 mg, 0.5 mmol), propargyl bromide (0.04 ml, 0.6 mmol) and potassium carbonate (83 mg, 0.6 mmol), in 5 ml of acetone was stirred at room temperature overnight. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the residue was treated with water (10 ml) followed by extraction with ethyl acetate (2×10 ml). The organic layer was washed with water (2×15 ml), brine (1×20 ml) and dried over anhydrous Na_2SO_4. The solvent was

evaporated under vacuum to give crude product, which was purified by column chromatography over silica gel (100–200 mesh) using ethyl acetate/*n*-hexane (1:19) as eluent.

*4.4.1. 2-Methylthio-5-(prop-2-ynyloxy)-3-(thien-2-carbonyl)-naphtho[1,2-b]furan (**5**).* Yellow solid; mp: 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J=8.4 Hz, 1H, ArH); 8.20 (d, J=8.1 Hz, 1H, ArH); 7.79–7.72 (m, 2H, ArH); 7.65–7.60 (m, 1H, ArH); 7.54–7.48 (m, 2H, ArH); 7.15–7.13 (m, 1H, ArH); 4.82 (d, J=2.4 Hz, 2H, CH_2); 2.72 (s, 3H, SMe); 2.52 (t, J=2.4 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 157.9, 150.6, 146.3, 144.4, 133.9, 133.6, 127.7, 127.4, 125.2, 123.7, 123.2, 121.7, 120.9, 120.1, 119.5, 98.4, 78.3, 75.6, 56.5, 15.3; IR (KBr): ν 3248, 2924, 2853, 1608, 1436, 1416, 1367, 1278, 1101 cm^{-1}; HRMS [ESI, $(M+H)^+/(M+Na)^+$] calcd for $C_{21}H_{14}O_3S_2$: 379.0463/401.0282, found 379.0461/401.0296.

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Supplementary data

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