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One-pot Regioselective Synthesis of Nature Mimicking Dihydronaphthofurans and Dibenzofurans[#]

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Abstract— A regioselective approach for the synthesis of substituted naphthofurans and dibenzofurans has been demonstrated through a ring transformation reaction of suitably functionalized *2H*-pyran-2-ones by reaction with 6,7-dihydro-5*H*-benzofuran-4-one and 7-methoxybenzofuran-3-one, respectively in high yields. The novelty of the procedure lies in the creation of an aromatic ring transformed by 2*H*-pyran-2-one involving the $-COCH_2-$ moiety of a cyclic ketone.

1. Introduction

The chemical and biological potentials of five-membered heterocyclic compounds fused with aromatic nuclei such as indole, benzofuran and their annulated derivatives have attracted the attention of organic and medicinal chemists for several years. Amongst them, the dihydronaphthofuran and dibenzofuran ring systems occupy an important place because they constitute the core skeleton of a family of structurally unique and medicinally important natural products.[1] These natural products mainly belong to sesquiterpene and arylquinone classes of aromatic compounds.[2] Due to the pronounced biological activities of many of the natural 4,5-dihydronaphthofurans such as (±)-laevigatin[3] (**1**), balsaminone[4] A (**2**) and dibenzofurans such as cannabifuran[5] **3**, ruscodibenzofuran[6] **4,** interest in this class of compounds continues to attract the researchers of both academic and pharmaceutical field.

Recently, two novel dibenzofurans, karnatakafurans A (**5**) and B (**6**) have been isolated from Novum *Aspergillus karnatakaensis* Frisvad, which were found active against *Plasmodium falciparum*.[7] A new prenylated dibenzofuran, achyrofuran[8] (**7**) was isolated from an extract of *Achyrocline satureioides* which exhibited glucose lowering activity in *db*/*db* mouse at oral dose of 20 mg/kg q.d. Several synthetic compounds bearing these ring skeleton are associated with diverse biological activities such as antifungal,[9] antibacterial,[10] antiviral,[11] β-adrenolytic,[12] antitumor,[13] and anthelmintic.[14]

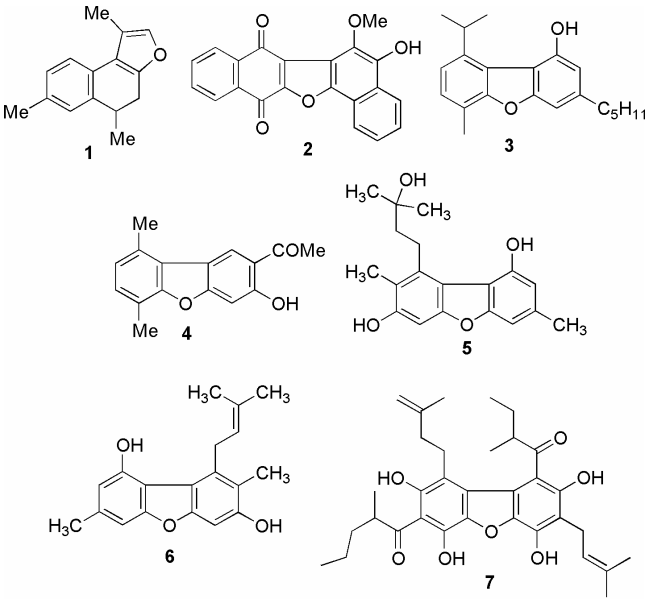


Figure 1. Naturally occurring naphthofuan and dibenzofurans

Common approaches for the synthesis of naphthofurans and dibenzofurans have been reported in the literature.[1] Among them, the metal assisted Dötz benzannulation reaction has received a great deal of attention for preparing diversely functionalized arenes and heteroarenes.[15] Many examples of benzannulation using an array of α,β-unsaturated chromium-carbene complexes and suitably functionalized alkynes have been reported in recent years. Unfortunately the scope of these reactions suffers due to the difficulty in obtaining suitably functionalized organometallic reagents and/or the formation of undesired byproducts.

Several synthetic methodologies[16] are available for the synthesis of 1,2-substituted-naphtho[2,1-*b*]furans but access to 1,2-unsubstituted-naphthofurans shows paucity of references. The general approaches for the synthesis of 1,2-substituted-naphtho[2,1-*b*]furans include reaction of 1-substituted-2-naphthol with either chloroacetone or chloroacetate ester or phenacyl bromides. But the applications of these procedures limit the scope of derivatization simply because of the need of functionalized naphthols such as 1-substituted-2-naphthols, which are not always easily available.

Various methods are available in the literature for the synthesis of dibenzofuran skeleton, which include intramolecular cyclization of 2-phenoxybenzene diazonium salt,[17] the acid-catalysed dehydration of 2,2'-dihydroxybiphenyls or their methyl ethers,[1b] photochemical cyclization of 2-phenoxyphenols,[18] and the thermal rearrangement of diquinones.[19] Despite various modifications of the reaction conditions, these cyclization reactions produced low yields of desired compounds, which restricted the applicability of these reactions.[20] Recent approaches to access dibenzofuran ring system include the flash vacuum pyrolysis of 3-(2-furoyl)cinnoline at high temperature,[21] gas-phase condensation of phenoxy radicals at moderately elevated temperature,[22] and the Diels-Alder type cycloaddition of 2-isopropenyl-3-methoxybenzofuran with DMAD.[23]

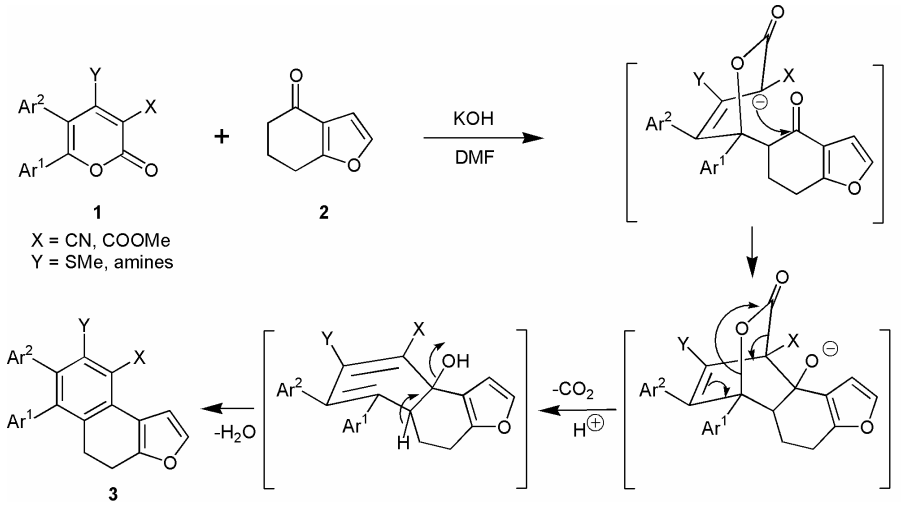
The chemical and the pharmacological potential of substituted naphthofurans and dibenzofurans and the limitations of existing procedures prompted us to develop an expeditious route to their synthesis that could offer flexibility of substituent variations on their molecular scaffold. Herein, we report an elegant route for preparing substituted naphthofurans and dibenzofurans through carbanion-induced ring transformation of 2*H*-pyran-2-ones by 6,7-dihydro-5*H*-benzofuran-4-one and benzofuran-3-one, respectively, in high yields. The advantage of the procedure lies in the construction of a phenyl ring from a lactone in a single step under mild conditions without using any organometallic reagents.

2. Results and discussion

During studies on the chemistry of 2*H*-pyran-2-ones, we found that 4-methylsulfanyl-2-oxo-6-phenyl-2*H*-pyran-3-carboxylic acid methyl esters are susceptible to carbanion attack at position 6 leading to the formation of a benezene ring under mild basic conditions at room temperature.[24] This novel conversion of an α-pyranone ring to a benzene ring (recently termed[25] as 'Lactone Methodology') utilizing methylenecarbonyl compounds under mild basic conditions encouraged us to explore this methodology for preparing various arenes and heteroarenes of particular importance.[26] The unique feature of 2*H*-pyran-2-ones **1** is the presence of three electrophilic centres; C2, C4 and C6, which can be exploited regioselectively by reacting with various *C*-, *N*- and *S*-nucleophiles to generate molecular diversity.[27]

2.1 Synthesis of substituted naphthofurans:

The 2*H*-pyran-2-ones (**1a-n**) used as a parent precursor have been conveniently prepared by the reaction of methyl 2-carbomethoxy/cyano-3,3-dimethylsulfanylacrylate with acetophenone in high yield as described earlier.[28] The presence of three electrophilic centres C2, C4 and C6 in lactone **1,** the latter is highly susceptible to nucleophiles due to the extended conjugation and the presence of the electron withdrawing substitutent at position 3 of the pyranone ring. The synthesis of naphtho[2,1-*b*]furans (**3a-n**) was achieved by stirring of an equimolar mixture of 2*H*-pyran-2-one **1**, 6,7-dihydro-5*H*-benzofuran-4-one **2** and powdered KOH in dry DMF at room temperature for 24-30 hours as shown in Scheme 1.



Scheme 1.

Table 1.

1, 3	Ar^1	Ar^2	X	Y	Yield (%)
a	C_6H_5	H	COOMe	SMe	68
b	4-ClC_6H_4	H	COOMe	SMe	64
c	4-FC_6H_4	H	COOMe	SMe	69
d	4-BrC_6H_4	H	COOMe	SMe	71
e	3,4-$Cl_2C_6H_4$	H	COOMe	SMe	68
f	2-thienyl	H	COOMe	SMe	63
g	4-ClC_6H_4	H	CN	SMe	54
h	4-BrC_6H_4	H	CN	SMe	59
i	thienyl	H	CN	SMe	53
j	4-$OMeC_6H_4$	H	CN	SMe	51
k	4-MeC_6H_4	H	CN	SMe	48
l	4-ClC_6H_4	H	CN	4-methylpiperidine	82
m	3,4-$CH_2O_2C_6H_3$	H	CN	piperidine	73
n	C_6H_5	C_6H_5	COOMe	SMe	28

The reaction is initiated by attack of the carbanion generated in situ from 6,7-dihydro-5*H*-benzofuran-4-one **2** at position C6 of the pyran-2-one, followed by cyclization involving carbonyl group and C3 of the pyran ring to form a bicyclic intermediate. This intermediate on decarboxylation, protonation and dehydration furnished naphtho[2,1-*b*]furans in good yields. The beauty of the reaction lies in the insertion of two carbon atoms of methylenecarbonyl group of **2** into cyclic dieneone **1** without affecting any functional groups present on the substrate. Due to the flexibility of substituent variation, this methodology can be applied to the synthesis of various natural products bearing dihydronaphtho[2,1-*b*]furan ring skeleton. It is worth mentioning that among the presence of three electrophilic positions on 2*H*-pyran-2-one, reaction took place predominantly at position 6 and no side products were obtained.

The ^{1}H NMR spectrum of **3a** showed two sharp singlets at δ 2.46 and 7.11 for a methylsulfanyl group and a C7 proton, respectively. Two multiplets at 2.75-2.79 and 2.86-2.92 for two methylene groups and two multiplets at 7.26-7.32 and 7.40-7.45 for six aromatic protons and a singlet at 3.99 for a methoxycarbonyl group protons were in agreement with the proposed structure. The presence of the carbonyl peak at ν 1720 cm^{-1} in IR spectrum and the molecular ion peak m/z at 351 in the mass spectrum confirmed the structure as 8-methylsulfanyl-6-phenyl-4,5-dihydro-naphtho[2,1-b]furan-9-carboxylic acid methyl ester. Similarly, all the synthesized compounds were characterized by spectroscopic analysis. The structure of one of the naphthofurans **3b** was unambiguously confirmed by a single crystal X-ray diffraction analysis. The conformation of **3b** along with the atom-numbering scheme is shown in Fig. 2.

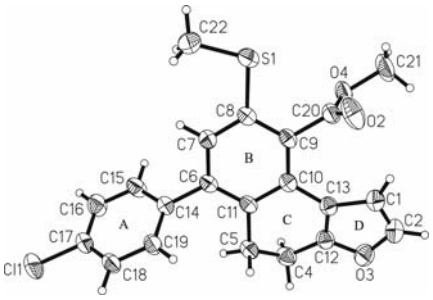
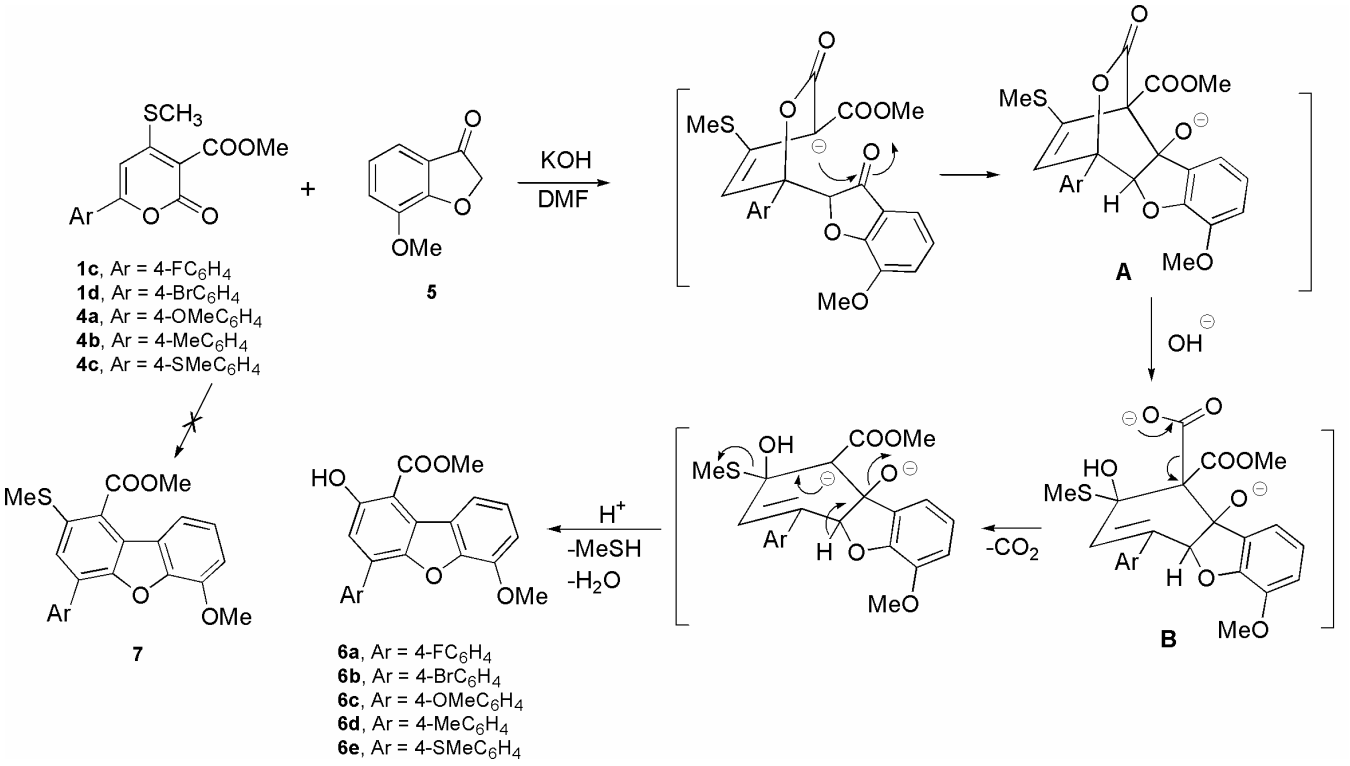


Figure 2. ORTEP diagram of **3b** with 50% probability

The structural analysis showed the presence of intermolecular C-H...π interaction [C19-H19…X1D, Centroid distance 2.66 Å], (symmetry codes: x, -1+y, z). The crystal packing further revealed the formation of intra- and intermolecular C-H...O interactions [H2...O2 = 2.59Å, <C2-H2-O2 = 129°, C2-O2 = 3.2516 Å; H6B...O2 = 2.57 Å, <C6-H6B-O2 = 155°, C6-O2 = 3.471 Å and H17...O3 = 2.55 Å, <C17-H17-O3 = 169°, C17-O3 = 3.4709Å], (symmetry codes: -x, -0.5+y, 0.5-z; -x, 1-y, -z). The crystal packing analysis revealed the presence of C-H...Cl short contact [H21B...Cl1 = 2.917 Å, <C21-H21B-Cl1 = 144.92°, C21-Cl1 = 3.743 Å], (symmetry code: 0.5+x, -0.5-y, 0.5-z).

2.2 Synthesis of substituted dibenzofurans:

It was envisaged that the reaction of 2*H*-pyran-2-one with benzofuran-3-one would analogously furnish dibenzofurans following same reaction mechanism as described for the synthesis of naphtho[2,1-*b*]furans. Thus, diversely substituted dibenzofurans (**6a-e**) were prepared by stirring an equimolar mixture of the 2*H*-pyran-2-one (**1c,d, 4a-c**), 7-methoxybenzofuran-3-one **5** and powdered KOH in dry DMF in an inert atmosphere at ambient temperature for 4-6 hours as shown in Scheme 2. The spectroscopic analysis of a ring transformed product **6a** revealed that the reaction of 6-(4-fluorophenyl)-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-ones (**1c**) with 7-methoxybenzofuran-3-one **5** afforded 2-hydroxy-6-methoxy-4-aryl-dibenzofuran-1-carboxylic acid methyl ester (**6a**) instead of corresponding 2-methylsulfanyl derivatives (**7**). The ^{1}H NMR spectrum of **6a** showed two sharp singlets at δ 4.02 and 4.19 for a methoxy group and the methoxycarbonyl group protons, respectively. Two multiplets in the range of 7.22-7.28 and 7.86-7.94 for six protons were assigned for methine protons. The absence of a singlet in the range of 2.4-2.6 for a



Scheme 2

methylsulfanyl group and the presence of a peak at 11.29 for a hydroxyl group was in agreement with the proposed structure. The presence of the carbonyl peak at ν 1653 cm^{-1} and hydroxyl peak at 3436 cm^{-1} in IR spectrum and the molecular ion peak m/z at 367 in the mass spectrum confirmed the proposed structure as 4-(4-fluorophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester..The mechanism, depicted in Scheme 2, implies that the reaction is initiated by attack of the carbanion generated in situ from benzofuran-3-one **6** at position C6 of the 2*H*-pyran-2-one, followed by intramolecular cyclization involving the carbonyl group of benzofuran-3-one and C3 of the pyranone to form a diene intermediate **A**. The intermediate A is electrophilic in nature and hydroxide may attack at this position to form intermediate **B**, followed by decarboxylation, protonation and elimination of methyl mercaptan and water yield **6a-e** in high yields. All the synthesized compounds were similarly characterized by spectroscopic analyses. The structure of the compound **6d** was further unambiguously confirmed by a single X-ray diffraction analysis.

The conformation of **6d** along with the atom-numbering scheme is shown in Fig. 3. The structural analysis shows the presence of intermolecular C-H... π (C21-H21A…X1D, centroid distance = 2.79 Å); (symmetry code: 0.5-x, -0.5+y, 0.5-z) and π…π interaction (centroid separation X1B…X1B = 3.847, X1B… X1A =3.7572, X1A… X1C = 3.6767 Å);

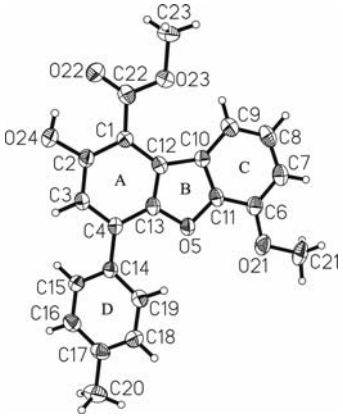


Figure 3. ORTEP diagram of compound **6d** with 50% probability.

(symmetry code: -x, 1-y, -z). The crystal packing further revealed the formation of intermolecular O-H...O dimer formation [H24...O22 = 2.53Å, <O24-H24-O22= 135°, O24-O22 = 3.1696 Å], (symmetry code: -1-x, 1-y, -z) and intramolecular O-H...O and C-H...O interactions [H24...O22 = 1.83 Å, <O24-H24-O22 = 144°, O24-O22 = 2.54 Å, H9...O23 = 2.22 Å, <C9-H9-O23 = 125°, C9-O23 = 2.8565Å and H19...O5 = 2.44 Å, <C19-H19-O5 = 111°, C19-O5 = 2.9004Å]. These non-covalent interactions play an important role in designing ligands for particular receptors.

4. Conclusion

In summary, we have developed a one-pot regioselective synthesis of diversely functionalized naphtho[2,1-*b*]furans and substituted dibenzofurans in high yields. The reaction of 2*H*-pyran-2-one with 6,7-dihydrobenzofuran-4-one afforded naphtho[2,1-b]furans while reaction with 7-methoxy-benzofuran-3-one furnished dibenzofurans in high yields. These dibenzofurans and naphthofurans with hydroxyl, methoxy and ester functionalities are structurally similar to naturally occurring ruscodibenzofurans and achyrofurans. Therefore, this methodology can be applied to the synthesis of benzofuran-based natural products. The potential of the procedure lies in the creation of C-C bond through carbanion-induced ring transformation of 2*H*-pyran-2-one in a single step from easily accessible precursors without using any organometallic reagents.

4. Experimental

4.1 General

^{1}H NMR spectra were taken on a Bruker WM-200 at 200MHz. $CDCl_3$ was taken as the solvent. Chemical shift are reported in parts per million shift (δ-value) from Me_4Si (δ 0 ppm for ^{1}H) as an internal standard. Signal pattern are indicate as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Coupling constant (J) are given in hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer AX-1 spectrophotometer in KBr disc and reported in wave number (cm^{-1}). Fast-atomic bombardment (FAB) spectrometer was used for mass spectra analysis. HRMS spectra was recorded on JEOL-MSroute JMS-600H spectrometer. Melting points were measured with Buchi-530 melting point apparatus and are uncorrected. All the reactions were carried out under anhydrous conditions and were monitored by TLC; visualization was done with UV-light (254 nm).

General procedure for the synthesis of compounds (3a-l):

A mixture of 3-carbomethoxy-4-methylsulfanyl-6-aryl-2*H*-pyran-2-one (1 mmol), 6,7-dihydro-5*H*-benzofuran-4-one **2** (0.14 g, 1 mmol) and powdered KOH (84 mg, 1.5 mmol) in dry DMF (10 mL) was stirred at room temperature for 24-26 h. After completion of reaction, the mixture was poured onto crushed ice with vigorous stirring, then neutralised with 10% HCl. The precipitate thus obtained was filtered off, washed with water, dried and purified by silica gel column chromatography using hexane as an eluent.

4.1.1 8-Methylsulfanyl-6-phenyl-4,5-dihydro-naphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3a)

white solid; mp: 123-124 ^{o}C; MS (FAB): m/z 351 (M^+ +1); IR (KBr) 1720 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.75-2.79 (m, 2H, CH_2), 2.86-2.92 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, *J* = 2.0 Hz, CH), 7.11 (s, 1H, ArH), 7.26-7.32 (m, 3H, ArH), 7.40-7.45 (m, 3H, ArH); HRMS (EI) *m/z* calcd. for $C_{21}H_{18}O_3S$ 350.0977, Found 350.0975.

4.1.2 6-(4-Chlorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3b)

white solid; mp: 141-142 ^{o}C; MS (FAB): m/z 385 (M^+ +1); IR (KBr) 1728 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.72-2.79 (m, 2H, CH_2), 2.86-2.93 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, *J* = 2.0 Hz, CH), 7.07 (s, 1H, ArH), 7.22 (d, 2H, *J* = 8.4 Hz, ArH), 7.31 (d, 1H, *J* = 2.0 Hz, CH), 7.44 (d, 2H, *J* = 8.4 Hz, ArH); HRMS (EI) *m/z* calcd. for $C_{21}H_{17}O_3SCl$ 384.0587, Found 384.0588.

4.1.3 6-(4-Fluorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3c)

white solid; mp: 147-148 ^{o}C; MS (FAB): m/z 369 (M^+ +1); IR (KBr) 1726 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.74-2.79 (m, 2H, CH_2), 2.85-2.90 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, *J* = 2.0 Hz, CH), 7.08 (s, 1H, ArH), 7.12-7.17 (m, 2H, ArH), 7.21-7.26 (m, 2H, ArH), 7.31 (d, 1H, *J* = 2.0 Hz, CH).

4.1.4 6-(4-Bromophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3d)

white solid; mp: 138-140 ^{o}C; MS (FAB): m/z 429 (M^+ +1); IR (KBr) 1728 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 2.74-2.79 (m, 2H, CH_2), 2.85-2.90 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, *J* = 2.0 Hz, CH), 7.06 (s, 1H, ArH), 7.16 (d, 2H, *J* = 8.4 Hz, ArH), 7.31 (d, 1H, *J* = 2.0 Hz, CH), 7.57 (d, 2H, *J* = 8.4 Hz, ArH); HRMS (EI) *m/z* calcd. for $C_{21}H_{17}O_3SBr$ 428.0082, Found 428.0099.

4.1.5 6-(3,4-Dichlorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3e)

white solid; mp: 176-177 ^{o}C; MS (FAB): m/z 419 (M^+ +1); IR (KBr) 1719 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.77-2.80 (m, 2H, CH_2), 2.85-2.87 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, *J* = 2.0 Hz, CH), 7.05 (s, 1H, ArH), 7.12

(dd, 1H, *J* = 8.4 Hz & 2.0 Hz, ArH), 7.32 (d, 1H, *J* = 2.0 Hz, CH), 7.39 (s, 1H, ArH), 7.51 (d, 1H, *J* = 8.4 Hz, ArH).

4.1.6 8-Methylsulfanyl-6-thiophen-2-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3f)

white solid; mp: 139-140 ^{o}C; MS (FAB): m/z 357 (M^{+} +1); IR (KBr) 1729 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.74-2.78 (m, 2H, CH_2), 2.87-2.91 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.45 (d, 1H, *J* = 2.0 Hz, CH), 7.12 (s, 1H, ArH), 7.26-7.31 (m, 2H, CH), 7.39-7.46 (m, 2H, CH).

4.1.7 6-(4-Chlorophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3g)

white solid; mp: 181-182 ^{o}C; MS (FAB): m/z 351 (M^{+}); IR (KBr) 2228 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.74-2.84 (m, 4H, $2CH_2$), 6.84 (s, 1H, ArH), 7.15 (d, 2H, *J* = 8.6 Hz, ArH), 7.33 (d, 1H, *J* = 2.0 Hz, CH), 7.36-7.41 (m, 3H, ArH & CH).

4.1.8 6-(4-Bromophenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3h)

white solid; mp: 204-206 ^{o}C; MS (ESI): m/z 397, 395 (M^{+}); IR (KBr) 2230 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, SCH_3), 2.79-2.88 (m, 4H, $2CH_2$), 6.91 (s, 1H, ArH), 7.16 (d, 2H, *J* = 8.4 Hz, ArH), 7.40 (d, 1H, *J* = 2.0 Hz, CH), 7.47 (d, 1H, *J* = 2.0 Hz, CH), 7.60 (d, 2H, *J* = 8.4 Hz, ArH); HRMS (EI) *m/z* calcd. for $C_{20}H_{14}NOSBr$ 394.9979, Found 394.9982.

4.1.9 8-Methylsulfanyl-6-thiophen-2-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3i)

white solid; mp: 177-176 ^{o}C; MS (FAB): m/z 323 (M^{+}); IR (KBr) 2213 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 3H, SCH_3), 2.83 (t, 2H, *J* = 7.8 Hz, CH_2), 3.10 (t, 2H, *J* = 7.8 Hz, CH_2), 7.04-7.15 (m, 3H, 2CH & ArH), 7.39-7.46 (m, 3H, 3CH).

4.1.10 6-(4-Methoxyphenyl)-8-methylsulfanyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3j)

white solid; mp: 154-156 ^{o}C; MS (FAB): m/z 347 (M^{+}); IR (KBr) 2215 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, SCH_3), 2.80 (t, 2H, *J* = 7.6 Hz, CH_2), 2.97 (t, 2H, *J* = 7.6 Hz, CH_2), 3.87 (s, 3H, OCH_3), 6.96 (s, 1H, ArH), 6.99 (d, 2H, *J* = 8.9 Hz, ArH), 7.22 (d, 2H, *J* = 8.9 Hz, ArH), 7.39 (d, 1H, *J* = 2.0 Hz, CH), 7.47 (d, 1H, *J* = 2.0 Hz, CH).

4.1.11 8-Methylsulfanyl-6-*p*-tolyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3k)

white solid; mp: 182-184 ^{o}C; MS (FAB): m/z 331 (M^{+}); IR (KBr) 2215 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 2.79 (t, 2H, *J* = 7.6 Hz, CH_2), 2.94 (t, 2H, *J* = 7.6 Hz, CH_2), 6.96 (s, 1H, ArH), 7.16-7.30 (m, 4H, ArH), 7.29 (d, 2H, *J* = 7.0 Hz, ArH), 7.39 (d, 1H, *J* = 2.0 Hz, CH), 7.48 (d, 1H, *J* = 2.0 Hz, CH); HRMS (EI) *m/z* calcd. for $C_{21}H_{17}NOS$ 331.1031, Found 331.1038.

4.1.13 6-(4-Chlorophenyl)-8-(4-methyl-piperidin-1-yl)-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3l)

Mp: 166-168 ^{o}C; MS (ESI): *m/z* 403 (M^{+}+1); IR (KBr) 2215 cm^{-1} (CN); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 3H, CH_3), 1.47-1.60 (m, 3H, CH & CH_2), 1.70-1.81 (m, 2H, CH_2), 2.70-2.86 (m, 6H, $3CH_2$), 3.45-3.58 (m, 2H, CH_2), 6.64 (s, 1H, ArH), 7.22 (d, 2H, *J* = 8.4 Hz, ArH), 7.38 (d, 1H, *J* = 2.0 Hz, CH), 7.42 (d, 2H, *J* = 8.4 Hz, ArH), 7.48 (d, 1H, *J* = 2.0 Hz, CH); HRMS (EI) *m/z* calcd. for $C_{25}H_{23}N_2OCl$ 402.1499, Found 402.1446.

4.1.14 6-Benzo[1,3]dioxol-5-yl-8-piperidin-1-yl-4,5-dihydronaphtho[2,1-*b*]furan-9-carbonitrile (3m)

Mp: 185-187 ^{o}C; MS (ESI): *m/z* 399 (M^{+}+1); IR (KBr) 2207 cm^{-1} (CN); ^{1}H NMR (200 MHz, $CDCl_3$), δ 1.54-1.62 (m, 2H, CH_2), 1.72-1.81 (m, 4H, $2CH_2$), 2.70-2.81 (m, 2H, CH_2), 2.83-2.96 (m, 2H, CH_2), 3.04-3.14 (m, 4H, $2CH_2$), 6.02 (s, 2H, OCH_2O), 6.67 (s, 1H, ArH), 6.70-6.76 (m, 2H, ArH), 6.88 (d, 1H, *J* = 7.8 Hz, ArH), 7.38 (d, 1H, *J* = 2.0Hz, CH), 7.48 (d, 1H, *J* = 2.0 Hz, CH); HRMS (EI) *m/z* calcd. for $C_{25}H_{22}N_2O_3$ 398.1631, Found 398.1583.

4.1.15 8-Methylsulfanyl-6,7-diphenyl-4,5-dihydronaphtho[2,1-*b*]furan-9-carboxylic acid methyl ester (3n)

Mp: 222-224 ^{o}C; MS (ESI): *m/z* 426 (M^{+}); IR (KBr) 1733 cm^{-1} (CO), ^{1}H NMR (200 MHz, $CDCl_3$): 1.98 (s, 3H, SMe), 2.75 (s, 4H, $2CH_2$), 3.99 (s, 3H, OMe), 6.47 (d, 1H, *J* = 2.0 Hz, CH), 6.85-7.01 (m, 4H, ArH), 7.03-7.15 (m, 6H, ArH), 7.29 (d, 1H, *J* = 2.0 Hz, CH); HRMS (EI) *m/z* calcd. for $C_{27}H_{22}O_3S$ 426.1290, Found 426.1238.

4.2 General procedure for the synthesis of compounds (6a-e):

A mixture of 6-aryl-3-carbomethoxy-4-methylsulfanyl-6-aryl-2*H*-pyran-2-one (**1c,d, 4a-c,** 1 mmol), 7-methoxybenzofuran-3-one **5** (0.152 g, 1

mmol) and powdered KOH (84 mg, 1.5 mmol) in dry DMF (6 mL) was stirred at room temperature for 24-26 h. After completion of reaction, the mixture was poured onto crushed ice with vigorous stirring, then neutralised with 10% HCl. The precipitate thus obtained was filtered off, washed with water, dried and purified by silica gel column chromatography using 2% ethyl acetate in hexane as an eluent.

4.2.1 4-(4-Fluorophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (6a):
white solid; mp: 214-215 ^{o}C; MS (FAB): *m/z* 367 (M^{+} +1); IR (KBr) 1653 (CO), 3436 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.02 (s, 3H, OCH_3), 4.19 (s, 3H, $COOCH_3$), 7.02 (d, 2H, *J* = 8.0 Hz, ArH), 7.22-7.28 (m, 3H, ArH), 7.86-7.94 (m, 3H, ArH), 11.29 (s, 1H, OH); HRMS (EI) *m/z* calcd. for $C_{21}H_{15}FO_5$ 366.0903, Found 366.0897.

4.2.2 4-(4-Bromophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (6b):
white solid; mp: 226-227 ^{o}C; MS (FAB): *m/z* 427 (M^{+} +1); IR (KBr) 1654 (CO), 3428 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.03 (s, 3H, OCH_3), 4.20 (s, 3H, $COOCH_3$), 7.03 (d, 1H, *J* = 8.0 Hz, ArH), 7.23-7.26 (m, 2H, ArH), 7.68 (d, 2H, *J* = 8.6 Hz, ArH), 7.80 (d, 2H, *J* = 8.6 Hz, ArH), 7.98 (d, 1H, *J* = 8.0 Hz, ArH), 11.29 (s, 1H, OH); HRMS (EI) *m/z* calcd. for $C_{21}H_{15}BrO_5$ 426.0103, Found 426.0113.

4.2.3 2-Hydroxy-6-methoxy-4-(4-methoxyphenyl)-dibenzofuran-1-carboxylic acid methyl ester (6c):
white solid; mp 168-169 ^{0}C; MS (FAB) 379 (M^{+}+1); IR (KBr) 1658 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 7.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.08 (d, *J* = 8.8 Hz, 2H, ArH), 7.21-7.30 (m, 2H, ArH), 7.90 (d, *J* = 8.8 Hz, 2H, ArH), 7.98 (d, *J* = 8.0 Hz, 1H, ArH), 11.31 (s, 1H, OH); HRMS (EI) *m/z* calcd. for $C_{22}H_{18}O_6$ 378.1103, Found 378.1103.

4.2.4 2-Hydroxy-6-methoxy-4-*p*-tolyl-dibenzofuran-1-carboxylic acid methyl ester (6d):
white solid; mp 164-165 ^{0}C; MS (ESI) 362 (M^{+}); IR (KBr) 1663 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H CH_3), 4.03 (s, 3H, OCH_3), 4.19 (s, 3H, OCH_3), 7.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.21-7.31 (m, 2H, ArH), 7.36 (d, *J* = 8.1 Hz, 2H, ArH), 7.83 (d, *J* = 8.1 Hz, 2H, ArH), 8.00 (d, *J* = 8.0 Hz, 1H, ArH), 11.30 (s, 1H, OH); HRMS (EI) *m/z* calcd. for $C_{22}H_{18}O_5$ 362.1154, Found 362.1149.

4.2.5 2-Hydroxy-6-methoxy-4-(4-methylsulfanyl-phenyl)-dibenzofuran-1-carboxylic acid methyl ester (6e):
white solid; mp 163-164 ^{0}C; MS (ESI) 394 (M^{+}); IR (KBr) 1663 cm^{-1} (CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56 (s, 3H , SCH_3), 4.03 (s, 3H, OCH_3), 4.19 (s, 3H, OCH_3), 7.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.21-7.31 (m, 2H, ArH), 7.42 (d, *J* = 8.6 Hz, 2H, ArH), 7.87 (d, *J* = 8.6 Hz, 2H, ArH), 7.98 (d, *J* = 8.0 Hz, 2H, ArH), 11.30 (s, 1H, OH); HRMS (EI) *m/z* calcd. for $C_{22}H_{18}O_5S$ 394.0875, Found 394.0873.

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References and Notes

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