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Iron-catalyzed aryl-aryl cross coupling route for the synthesis of 1-(2-amino)-phenyl)dibenzo[*b*,*d*]furan-2-ol derivatives and their biological evaluation†

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Naturally occurring dibenzofuran motifs represent promising lead structures for the development of novel antimycobacterial agents. Prompted by our recent development of cross dehydrogenative coupling using iron catalysis, we extended our strategy to synthesize 14 novel anilinodibenzofuranols and they were explored for anti-tubercular and cytotoxic activities. Consistent with our hypothesis, DBF-3, 14 and 16 exhibited promising activity against two strains (*M. tuberculosis* H37Rv and the clinical S, H, R, and E resistant isolate), while DBF-13, 18 exhibited selective inhibitory activity only against the clinical S, H, R and E resistant isolate. However, the compounds DBF-4 and DBF-8 showed promising and selective antitumor activity against the tested cancer cell lines.

Introduction

Tuberculosis (TB), a contagious infectious disease caused by *Mycobacterium tuberculosis*, has affected mankind for over 5000 years, and still continues to be a leading cause of morbidity and mortality.[1] This dreaded disease, accounting for millions of deaths globally for the past few decades, has been acknowledged as a global health problem, by WHO.[2] Now it ranks second, after human immunodeficiency virus (HIV), for the highest number of deaths registered in the recent times.[3] One third of the global population are known to have latent TB, but are asymptomatic. It is very likely that 10% of those latently infected population eventually develop active disease during their life-time. Although most of the *M. tuberculosis*-infected individuals remain asymptomatic, they serve as a reservoir for the pathogen, making control of this disease a significant challenge.[4] With the emergence of HIV, which allows the latent TB to become active and with the emergence of its new virulent strains like multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) that are virtually untreatable with the existing drugs, the epidemic has further surged to alarming levels.[5] Unfortunately most of the standard drugs used to cure this disease today were developed 40 or more years ago. Of late, it was found that self-renewing stem cells in the bone marrow have properties such as natural drug resistance, infrequent division and a privileged immune status that make them resistant to these standard drugs.[6] The challenge of meeting all these facts necessitated an urgent need to the development of fast acting second-line anti-tubercular agents with diverse and unique structural features, and also with the mechanism of action possibly different from that of existing drugs.[7]

In the recent years, structurally diverse new molecules inspired by natural products have played a major role in drug discovery.[8] The lichen dibenzofuran-derived secondary metabolite, usnic acid, seemed to have displayed interesting anti-tubercular activity, but its weak potency had hampered its deployment for the treatment of TB.[9] Later developments in this area showed that dibenzofuran analogues exhibited very good *in vitro* and *in vivo* antimycobacterial activity (Fig. 1). In particular, new hybrid heterocycles with a dibenzofuran ring, such as CGS-35066 and CGS-34043, were developed as potent

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† Electronic supplementary information (ESI) available. Crystal data for **AO80**: $C_{23}H_{23}NO_2$, M = 345.42, colorless needle, 0.18 × 0.11 × 0.08 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.8847(5), b = 11.3771(7), c = 20.8098(13) Å, V = 1866.7(2) Å^3, Z = 4, D_c = 1.229 g cm^{-3}, F_{000} = 736, CCD Area Detector, Mo-Kα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0°, 18068 reflections collected, 1908 unique (R_{int} = 0.0232). Final *GooF* = 1.067, R_1 = 0.0307, wR_2 = 0.0821, R indices based on 1805 reflections with $I > 2\sigma(I)$ (refinement on F^2), 243 parameters, 0 restraints, μ = 0.078 mm^{-1}. Crystallographic data has been deposited for compound **AO80** CCDC 933432. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra43345e

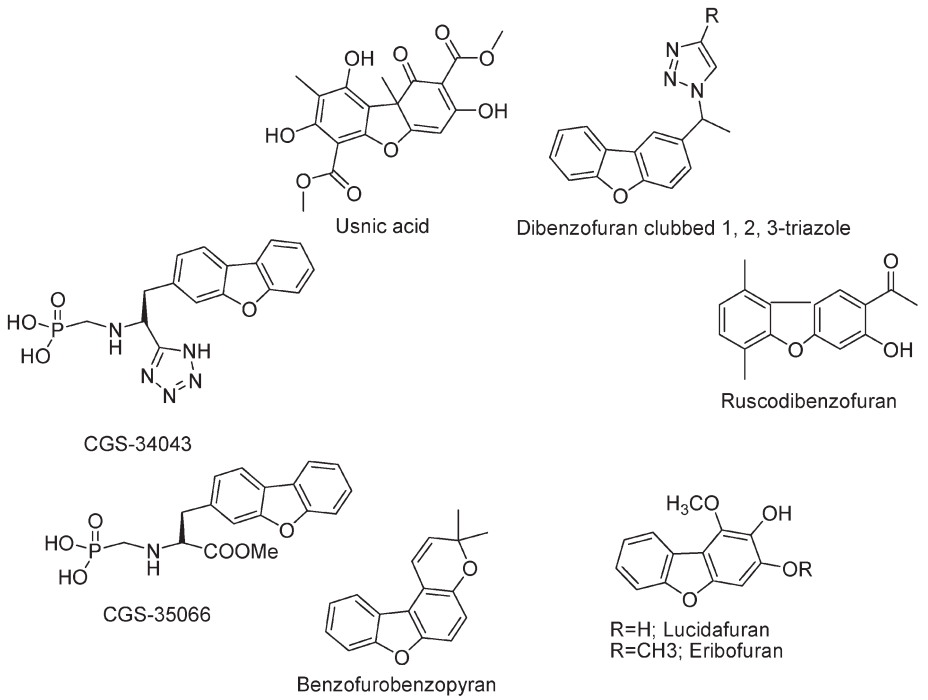


Fig. 1 Bioactive hybrids of dibenzofuran.

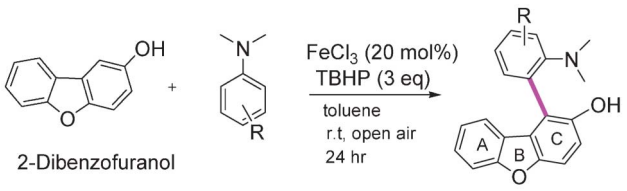
endothelin-converting enzyme (ECE-1) inhibitors.[8b] Better activities resulting from molecular engineering performed on these pharmacophores[9,10] combined with the elegant progress made in these class of compounds for anti-mycobacterial activities in the recent times instilled in us an immense interest to further synthesize various structurally diverse dibenzofuran derivatives and to investigate their biological activities.

Aryl–aryl bond formation reaction has been practiced for more than a century and is one of the first reactions using a transition metal. Biaryls resulting from these reactions have drawn immense attention for decades, discovering novel molecules that find applications in medicinal and material chemistry.[11] The pressing need to develop non-resistant anti-mycobacterial drugs combined with our expertise in the area of developing structurally varied biaryls by direct oxidative cross coupling of anilines to polynuclear phenols using environmentally benign iron catalyst[12a] and our interest in synthesis of biologically interesting molecules[12b–d] prompted us to discover new anti-mycobacterial scaffolds. This not only extends the scope of our work, but also helps us to solve the medicinal challenges. Thus we successfully coupled 2-dibenzofuranol (DBF) with *N*,*N*-dialkyl anilines and developed novel dibenzofuranol analogues, named anilinodibenzofuranols. These compounds contain diverse structural features and were further tested for different biological activities like anti-tubercular and cytotoxicity. The aforementioned synthetic pathway for the construction of biaryls involved iron(III) as a catalyst and *t*-butyl hydroperoxide (TBHP) (5–6 M in decane) as a co-oxidant (Scheme 1). We synthesized 14 anilinodibenzofuranols, which showed moderate to good anti-mycobacterial activity. Among them, DBF-14 exhibited promising activity against TB. In addition, the compounds DBF-4 and DBF-8 showed promising and selective antitumor activity against the tested cancer cell lines.

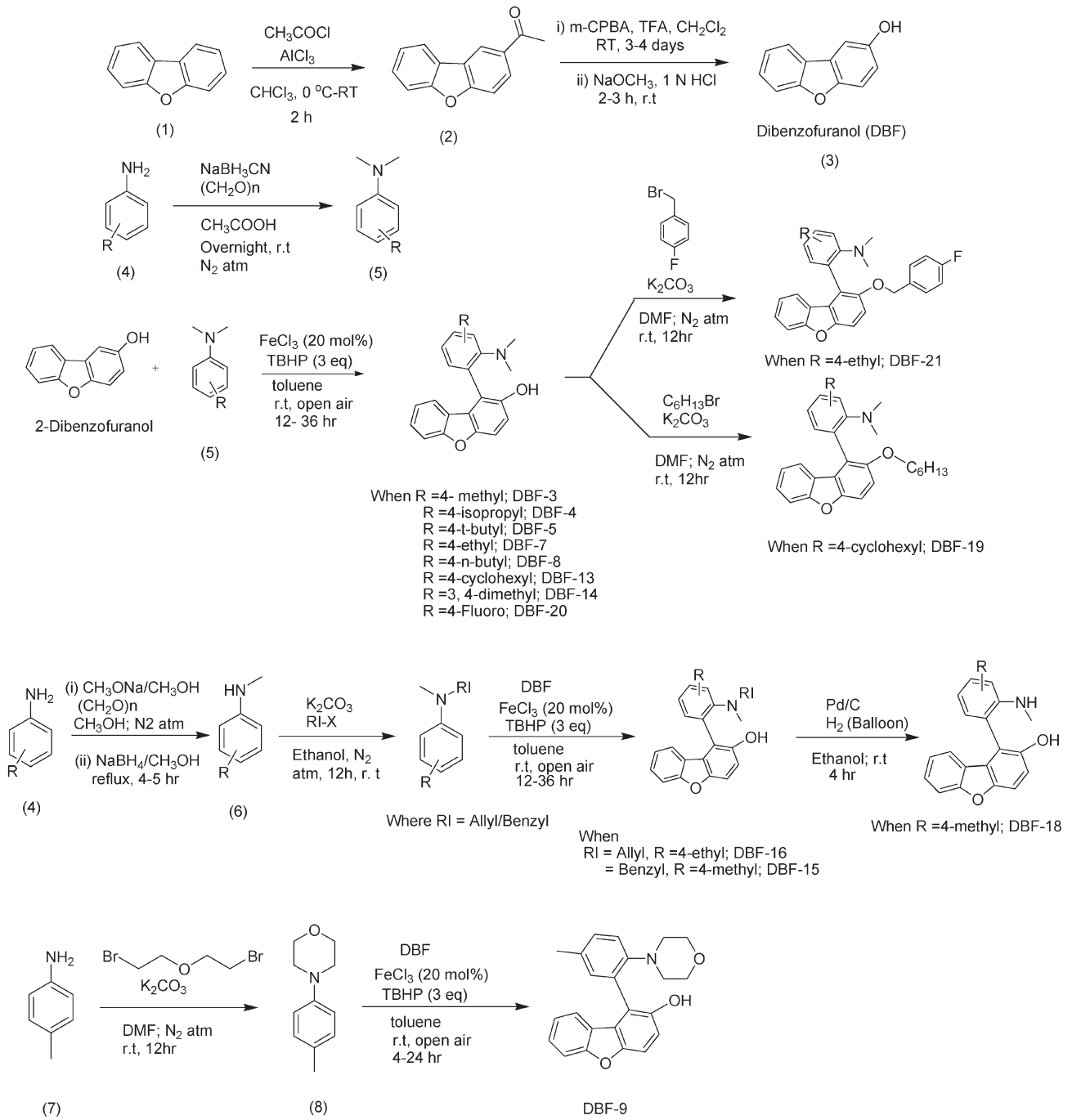
Results and discussion

Chemistry

A toluene solution of 4-methyl *N*,*N*-di methyl aniline, 2-dibenzofuranol, iron(III) catalyst and TBHP (5–6 M in decane) oxidant were stirred for about 24 h under open air atmosphere yielded the desired coupled product. Based on this result, we opted to extend the scope of this work by coupling to various substituted anilines. The starting *N*,*N*-dialkyl anilines were prepared by reductive methylation of anilines whereas the synthesis of 2-dibenzofuranol (DBF) was performed in three step process involving Friedel–Crafts acylation of dibenzofuran, followed by Baeyer–Villiger oxida-



Scheme 1 Aryl–aryl coupling.

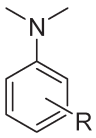
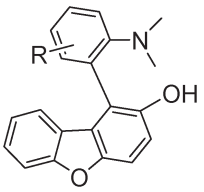
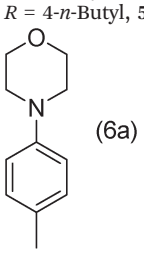
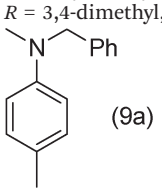
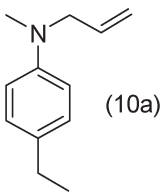


Scheme 2 Synthetic route.

tion and finally basic hydrolysis.[10a] The detailed synthetic route is depicted in Scheme 2.

To expand the substrate scope (see Table 1), the cross-coupling reaction of dibenzofuranol was carried out with 4-alkylated *N*,*N*-dimethyl anilines **1a–5a** and **7a** that proceeded smoothly affording good yields (Table 1, entries 1–5 and 7) of the product. 3, 4-dimethyl *N*,*N*-dimethyl aniline underwent coupling with **8a** at less crowded 6th position, rather than 2nd position (Table 1, entry 8). 4-methoxy *N*,*N*-dimethyl aniline **12a** underwent coupling to give very poor yields of the product and produced complex mixtures (Table 1, entry 15). Unlike 2-naphthol,[12a] which underwent coupling reaction with all halogenated anilines, 2-dibenzofuranol in exception to fluoro aniline **11a** (Table 1, entry 13), failed to couple with other halo substituted *N*,*N*-dialkylanilines. Instead, homo-coupled products were formed, with traces of desired cross-coupled product. It might be the larger size of DBF compared to 2-naphthol, that might have dampened its reactivity. Attempts were made to couple *N*,*N*-dialkyl aniline possessing electron withdrawing nitro group at *para* position **13a** which did not

Table 1 Substrate scope[a]

Entry	Substrate	Reaction time	Product	MP (°C)	Yield (%)
					
1	*R* = 4-Methyl, **1a**	12 h	DBF-3	—	59
2	*R* = 4-Isopropyl, **2a**	24 h	DBF-4	170	55
3	*R* = 4-*t*-Butyl, **3a**	30 h	DBF-5	173	55
4	*R* = 4-Ethyl, **4a**	24 h	DBF-7	134	56
5	*R* = 4-*n*-Butyl, **5a**	24 h	DBF-8	159	58
6	 (6a)	30 h	DBF-9	125	42
7	*R* = 4-Cyclohexyl, **7a**	36 h	DBF-13	163	59
8	*R* = 3,4-dimethyl, **8a**	24 h	DBF-14	147	53
9	 (9a)	12 h	DBF-15	—	45
10	 (10a)	12 h	DBF-16	—	44
11	DBF-15	4 h	DBF-18	—	84
12	DBF-13	12 h	DBF-19	85	88
13	*R* = 4-Fluoro, **11a**	30 h	DBF-20	212	50
14	DBF-7	12 h	DBF-21	—	83
15	*R* = 4-Methoxy, **12a**	12 h	DBF-1	—	trace
16	*R* = 4-Nitro, **13a**	36 h	NR	—	—
17	*R* = 2-Methoxy, **14a**	36 h	NR	—	—

[a] Substituted *N*-alkyl aniline (1 equiv.), 2-naphthol (1 equiv.), TBHP (3 equiv.), and [Fe] (20 mol%): otherwise are mentioned. Reported yields are based on *N*-alkyl aniline. NR = no reaction. TBHP used is a 5–6 M solution in decane.

proceed and the substrate was completely recovered (Table 1, entry 16). Attempts were also made to explore the product variation by altering the substitution at the nitrogen site. Thus the cross coupling reaction of dibenzofuranol with 4-substituted aniline derivatives **6a**, **9a** and **10a** proceeded smoothly to obtain the desired products (Table 1, entries 6, 9 and 10). Keeping in mind the presence of free –NH group in antimicrobial active molecules, we debenzylated the DBF-15 using palladium catalyst, to give DBF-18 (Table 1, entry 11). The efforts made to couple heterocyclic anilines met with failure, as the reaction performed with *N*,*N*-dimethylaminopyridine did not proceed. Treatment of DBF with 2-methoxy *N*,*N*-dimethyl aniline ended up with no reaction, revealing the necessity of the presence of free *ortho* site. O-alkylation and O-benzylation of DBF-13 and DBF-7 using K_2CO_3 as a base afforded DBF-19 and DBF-21, respectively, in very good yields (Table 1, entries 12 and 14). The regioselectivity in the formation of the coupling product is arising from the H-bond between nitrogen of aniline

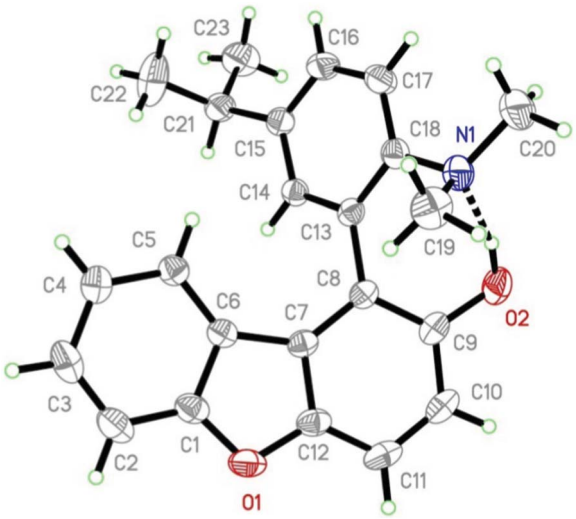


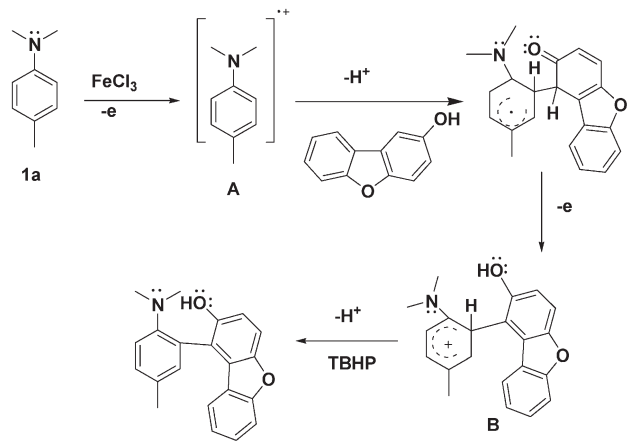
Fig. 2 Ortep diagram of DBF-4.

and oxygen of 2-dibenzofuranol, which is unambiguously confirmed through the crystal structure of DBF-4 (Fig. 2) and also from the broad peaks encountered from IR data. All the newly synthesized compounds were fully characterized by ^{1}H and ^{13}C NMR, mass (ESI-MS), HRMS and IR spectral data.

This reaction is chemoselective, as it selectively underwent coupling at the ring leaving the *N*-methyl site intact.[13] In accordance with the previously suggested mechanism,[11a] it might involve the oxidation of aniline by iron(III) catalyst generating a radical cation, which on coupling to nucleophillic 2-dibenzofuranol generates an adduct. Rearomatization of 2-dibenzofuranol and further oxidation of aniline produces a cation which on deprotonation finally generates cross-coupled product. The reduced iron catalyst is reoxidized back to iron(III) with the help of the co-oxidant TBHP (Scheme 3).

Antimycobacterial activity

Antimycobacterial activity of the synthesized new compounds was evaluated by the luciferase reporter phage (LRP) assay[14] with some modifications against *M. tuberculosis* H37Rv and clinical S, H, R, and E resistant *M. tuberculosis* (MDR-TB) isolate at two different concentrations (25 and 50 μg mL^{-1}) using DMSO as a vehicle solvent. Fifty microliter bacterial suspension equivalent to MacFarlands No.2 standard was added to 400 μl of G7H9 with and without the test compound. For each sample, two drug-free controls and two drug concentrations were prepared and this set up was incubated for 72 h at 37 °C. After incubation 50 μl of the high titer of luciferase reporter phage (phAE129) and 40 μl of 0.1 M $CaCl_2$ were added to all the vials and this setup was incubated at 37 °C for 4 h. After incubation, 100 μl of the mixture was taken from each tube into a luminometer cuvette and equal amount of working D-luciferin (0.3 mM in 0.05 M sodium citrate buffer, pH 4.5) solution was added. The RLU was measured after 10 s of integration in the Luminometer (Monolight 2010). Duplicate readings were recorded for each sample and the mean was calculated. The percentage reduction in the RLU was calculated for each test sample and compared with control. The experiment was repeated when the mean RLU of the control was less than 1000.



Scheme 3 Plausible mechanism.

The anti-tubercular activity results of the synthesized compounds are compiled in Table 2. Among the tested compounds, DBF-14, DBF-16, and DBF-3 proved to be good against *M. tuberculosis* H37Rv at both the assayed concentrations, whereas DBF-13, DBF-18, and DBF-9 were effective only at high concentration (50 μg mL^{-1}) against *M. tuberculosis* H37Rv. Eight (DBF-18, DBF-14, DBF-3, DBF-13, DBF-16, DBF-5, DBF-9, and DBF-19) out of 14 tested compounds exhibited promising inhibitory activity against the clinical S, H, R and E resistant isolate when compared with the standard, Isoniazid. It is reported that a relationship exists between % inhibition and *C*log*P*.[15,16] Percentage inhibition increased with increase in *C*log*P*. Lipinski's rule stated that *C*log*P* is an indication of the lipophilicity of molecules, and more lipophilic molecules can easily enter the lipid-enriched mycobacterial cell wall.[17]

Analyzing the structure–activity relationship, we first investigated the effect of substitution pattern on the aryl partner of the aniline. In case of alkyl substitutions (Table 2, entries 1–5, 7 and 8), DBF-14 and DBF-3 exhibited good activity against both the strains with relatively low lipophillicity (Table 2, entries 8 and 1). From this it can be concluded that an elongation of the carbon chain length on aryl ring might dampen its activity, which is probably due to the increased hydrophobicity that makes them ineffective towards the target sites. Surprisingly DBF-13 with cyclohexyl group on the aniline ring was found to be promising at higher concentrations against both the strains, and this discrepancy might be due to the possibility of interaction of these moieties to more than one target site. Keeping electron withdrawing substituents like fluorine in place of alkyl chain was not worthy, as it further deactivated the ring and produced less activity (Table 2, entry 13). Interesting results were observed when one of the methyl groups on nitrogen was replaced by benzyl and allyl groups. Allyl in place of methyl group enhanced the activity, whereas with benzyl substitution, suppressed activity was found (Table 2, entries 9 and 10). The low activity observed with the benzyl substitution was either due to its increased lipophilicity or it might interrupt the hydrophilic –OH group

Table 2 Anti-tubercular activity of the synthesized compounds[a]

		% Reduction in RLU				
		M. tuberculosis H37Rv		Clinical isolate: S, H, R and E resistant *M. tuberculosis*		
S. no	Name of the compound	25 μg mL^{-1}	50 μg mL^{-1}	25 μg mL^{-1}	50 μg mL^{-1}	*Clog*P
1	DBF-3	51.54	62.28	55.47	76.75	5.471
2	DBF-4	00	00	18.50	26.69	6.399
3	DBF-5	32.41	43.09	44.51	64.81	6.798
4	DBF-7	22.96	34.02	16.03	27.59	6.000
5	DBF-8	00	30.83	00	39.10	7.058
6	DBF-9	43.45	55.82	30.24	61.54	5.126
7	DBF-13	46.88	57.43	52.60	63.66	7.592
8	DBF-14	61.52	61.52	58.61	71.98	5.920
9	DBF-15	32.28	42.26	41.60	47.95	7.239
10	DBF-16	64.27	67.99	51.75	58.64	6.774
11	DBF-18	35.36	56.33	56.54	78.12	4.805
12	DBF-19	42.24	54.37	27.30	65.42	10.783
13	DBF-20	34.23	37.10	10.56	38.17	5.303
14	DBF-21	00	00	19.35	44.77	8.457
	isoniazid (0.2 μg ml^{-1})	82.04		38.64		

[a] Antimycobacterial activity is indicated by fifty percent reduction in relative units (RLU) in the presence of compound in comparison with the compound free control. Vehicle solvent used is dimethyl sulfoxide and the method used is luciferase reporter phage (LRP) assay.

through non-bonded interactions. When hydrophilic hydroxyl group of the DBF was protected, decline in the activities were observed, that could be due to the decreased interaction of the moiety towards the hydrophilic partner of the target site (Table 2, entries 12 and 14). From this it is clear that, polar hydrophilic –OH group played a vital role in binding to the target site. Increased activity with increased hydrophilicity was observed in case of DBF-18, when one of *N*-methyl was deprotected, which is a clear indication that this group along with –OH group were binding to the target site (Table 2, entry 11). Though the target site specificity is not clear, it can be concluded from the above results, that the tubercular activity of the compounds obtained by embedding a dialkyl aniline moiety on the C-ring of 2-dibenzofuranol was steered by electronic and steric factors. The moieties are much more promising, when the lipophillicity is maintained normal by not increasing the alkyl chain length and also by enhancing the polarity through appropriate or no substitution on nitrogen, provided the basic –OH group of the 2-dibenzofuranol is kept intact. In brief, DBF-3, 14 and 16 were found to show promising activity against both the strains at both the concentrations, where as DBF-13 and 18 exhibited selective inhibitory activities against the clinical S, H, R and E resistant isolate.

Cytotoxicity assay

Cytotoxicity of all the 14 synthesized compounds was determined on the basis of measurement of *in vitro* growth inhibition of tumor cell lines in 96 well plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals using doxorubicin as a standard. The cytotoxicity as assessed against a panel of four different human tumor cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), HeLa derived from human cervical cancer cells (ATCC No. CCL-2), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) using the MTT assay.[18] The IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose-response curves. IC_{50} values (in μM) are indicated as means $\pm$SD of three independent experiments.

Being aware of the cytotoxicity produced by the dibenzofuran pharmacophores, we also subjected these compounds for antitumor activity.[19,10d] The cytotoxicity of all the synthesized compounds was tested using the MTT assay and the results obtained are shown in Table 3. It was observed that among all the tested compounds, DBF-4 (Table 3, entry 2) showed promising activity against all the aforementioned cell lines. Interestingly, DBF-8 (Table 3, entry 5) showed selective activity against A549 cell line. It is noteworthy to mention that the compounds DBF-4 and DBF-8 with cytotoxicity were inactive towards *M. tuberculosis* whereas the compounds that were most active for anti-mycobacterial activity (Table 2, entries 1, 8, and 10) were inactive towards the cancer cell lines indicating that these compounds showed very specific activity.

Conclusion

We have successfully synthesized hither to unknown novel anilinodebenzofuranols, using iron(III) catalyzed cross-dehydrogenative C–C coupling. The products were assayed for their anti-tubercular and cytotoxic activities. These moieties produced moderate to good activity and were very specific. The results obtained in this platform spur a quest in us in developing reliable methods of C–C bond formation, leading to products that have promising biological applications. To the

Table 3 Cytotoxicity evaluation of the synthesized compounds on different cancer cell lines[a]

S. no.	Test compound	IC_{50} in μM			
		A549	HeLa	MDA-MB-231	MCF-7
1	DBF-3	—[b]	—	—	—
2	DBF-4	0.91 ± 0.021	1.81 ± 0.025	1.95 ± 0.032	2.75 ± 0.021
3	DBF-5	14.89 ± 0.054	16.79 ± 0.048	44.79 ± 0.065	33.91 ± 0.052
4	DBF-7	—	—	—	—
5	DBF-8	5.44 ± 0.027	—	—	—
6	DBF-9	—	17.89 ± 0.032	36.79 ± 0.044	14.91 ± 0.036
7	DBF-13	36.00 ± 0.045	—	—	—
8	DBF-14	15.90 ± 0.039	30.90 ± 0.052	—	—
9	DBF-15	—	—	—	—
10	DBF-16	15.78 ± 0.038	78.91 ± 0.069	22.89 ± 0.047	14.71 ± 0.043
11	DBF-18	—	—	—	—
12	DBF-19	—	—	33.98 ± 0.058	38.91 ± 0.062
13	DBF-20	—	—	—	—
14	DBF-21	19.97 ± 0.046	—	—	—
15	Doxorubicin	0.459 ± 0.021	0.509 ± 0.011	0.91 ± 0.021	1.07 ± 0.026

[a] A549–Human alveolar adenocarcinoma cell line; HeLa–human cervical cancer cell line; MCF-7 human breast adenocarcinoma cell line; MDA-MB-231–human breast adenocarcinoma cell line. [b] ''—'' Indicates no activity.

best of our knowledge, there have been no previous reports of anilinodibenzofuranols as anti-tubercular agents and further studies on the structure–activity relation of these compounds would give more insight into the design of more active candidates. In view of the specificity showed by most of these active compounds towards anti-tubercular activity as well as cytotoxicity, further studies are under way.

Experimental section

General considerations

All commercially-available chemicals were used as received. *t*-BuOOH in 5–6 M in decane was purchased from Sigma-Aldrich Chemicals. Thin-layer chromatography plates were visualized by exposure to ultraviolet light (UV)/Iodine and/or by immersion in an acidic staining solution of phosphomolybdic acid followed by heating on a hot plate. ^{1}H spectra were obtained on 300 MHz, 500 MHz spectrometers and ^{13}C NMR spectra were obtained on 75 MHz and 100 MHz spectrometers with tetramethylsilane and chloroform-d1, respectively, as the internal standard. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data for ^{1}H NMR were reported as follows: chemical shift (multiplicity, coupling constant, number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). IR spectra were recorded on a Perkin-Elmer 1800 series FTIR spectrometer and samples were analyzed as thin films on KBr plates. Mass spectra were carried out using Quattro LC triple-quadrupole mass spectrometer (Micromass, Manchester, UK). High-resolution mass spectra were determined using Quadrupole time-of-flight (Q-TOF) mass spectrometer (QSTARXL, Applied Biosystems/MDS Sciex, Foster city, USA).

General procedure for CDC reaction of *N*,*N*-dialkyl anilines with 2-dibenzofuranol

A 10 mL round bottomed flask was charged with *N*,*N*-dialkyl aniline (1.0 mmol), dibenzofuranol (1.0 mmol) and toluene. To the resulting mixture was then added $FeCl_3{\cdot}6H_2O$ (20 mol%) and TBHP (3.0 mmol) *via* syringe drop wise under atmospheric air. The resulting solution was allowed to stir at room temperature under open air for 24 h. The resulting mixture obtained was celite filtered, washed with ethyl acetate and water. The combined organic layers were dried over Na_2SO_4 (s) and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (100–200/60–120 mesh) using hexane-ethyl acetate as eluent to afford the product.

General procedure for the synthesis of *N*,*N*-dimethyl anilines from various substituted anilines

Ex: Synthesis of *N*,*N*,4-trimethylaniline (**1a**): To a solution of *p*-toluidine (1.00 g, 9.33 mmol) in glacial acetic acid (50 mL) under inert atmosphere was added paraformaldehyde (2.74 g, 91.43 mmol) and sodium cyanoborohydride (2.75 g, 43.86 mmol). The addition of sodiumcyanoborohydride caused vigorous bubbling. After stirring overnight, the reaction mixture was poured into a water/ice mixture (~100 mL) containing NaOH (40 g). The addition was exothermic, and more ice was added to bring the total volume of the quench mixture to ~300 mL. This mixture which had a pH of 14 was extracted with CH_2Cl_2 (350 mL). The combined organic layers were dried over Na_2SO_4 (s), filtered, and concentrated under reduced pressure, and was purified by column chromatographic technique to yield a yellowish liquid (1.06 g, 7.85 mmol, 84%).

General procedure for the synthesis of 2-dibenzofuranol

To a solution of dibenzofuran (**1**) (5.0 g, 29 mmol) in chloroform (50 mL), was added a mixture of $AlCl_3$ (4.76 g,

35.7 mmol) and acetyl chloride (2.80 g, 35.6 mmol) in chloroform (50 mL). After stirring the reaction mixture for 45 min at room temperature, it was poured into ice water (100 mL) and 1N HCl (50 mL). The aqueous layer was washed with chloroform (2 × 30 mL); combined organic layer was dried over Na_2SO_4 (s) and concentrated under vacuum. The crude residue was purified over silica gel column chromatography to yield 2-acetyldibezofuran **2** (5.90 g, 95%) as white solid.

2-Acetyldibezofuran (**2**) (1.0 g, 4.7 mmol) in CH_2Cl_2 (20 ml) at 0 °C was added trifluoroacetic acid (1.47 mL, 19.1 mmol) and m-CPBA (1.64 g, 9.5 mmol) slowly at 0 °C. After stirring at room temperature for 3 days, the reaction mixture was quenched with ferrous sulphate, washed with water; organic layer was separated, dried over Na_2SO_4 (s) and concentrated over rotary evaporator. The crude residue was dissolved in methanol (15 mL); sodium methoxide (0.76 g, 14.1 mmol) was added and stirred at room temperature for one hour. The reaction mixture was quenched with 2.0 N HCl (5 mL) and solvent was removed under vacuum. It was then treated with water, extracted with chloroform (2 × 30 mL), combined organic layers was dried over anhyd. Na_2SO_4 and concentrated under vacuum. Purification of residue over silica gel column chromatography yielded compound 2-dibenzofuranol (**3**) (0.69 g, 79%) as pale yellow solid.

Procedure for the synthesis of DBF-19

A 10 mL round bottomed flask equipped with mechanical stirrer, was charged with 3 mL of *N*,*N*-dimethylformamide and 0.107 g (0.78 mmol) of anhydrous potassium carbonate. To the rapidly stirred mixture was then added 0.100 g. (0.259 mmol) of DBF-13 followed by the addition of 0.064 g (0.39 mmol) of 1-bromohexane. The mixture was stirred for 12 h.; after the addition was completed, the mixture was poured into ice water, extracted with ethyl acetate, and dried over Na_2SO_4 (s). The solvent was removed on a rotary evaporator, affording 0.120 g (88%) of colorless liquid.

Procedure for the synthesis of DBF-21

A 10 mL round bottomed flask equipped with mechanical stirrer, was charged with 3 mL of *N*,*N*-dimethylformamide and 0.124 g (0.90 mmol) of anhydrous potassium carbonate. The rapidly stirred mixture was then added 0.100 g (0.3 mmol) of DBF-7 followed by the addition of 0.048 mL (0.39 mmol) of 4-fluoro benzyl bromide. The mixture was then stirred for 12 h; after the addition was completed, the mixture was poured into ice water, extracted with ethyl acetate, and dried over Na_2SO_4 (s). The solvent was removed on a rotary evaporator, affording 0.109 g (83%) of colorless liquid.

Procedure for the synthesis of DBF-18

Palladium (Pd), 5% on carbon, 0.108 g (10 mol%) was placed in a 10 ml round bottomed flask under N_2 and carefully wetted with 3 ml of denatured ethanol (EtOH). A slurry of 0.200 g of DBF-15 (0.51 mmol) in denatured EtOH (3 mL) was also added. After the system was purged with nitrogen–hydrogen (N_2/H_2), the reaction was stirred at room temperature for 4 h. The catalyst was then filtered over a Celite pad and rinsed with ethanol (EtOH). The filtrate was concentrated under reduced pressure and dried to afford 0.130 g (84%) of the product as a colorless liquid.

General procedure for the monomethylation of anilines (6)

Sodium methoxide (5.0 mol) was made into a paste with methanol. To this aniline (**5**) (1.0 mol), dissolved in methanol, was added and the resulting hot solution poured into a suspension of paraformaldehyde (1.5 mol) in methanol (20 mL). The mixture was stirred under inert atmosphere at room temp for 5 h and then $NaBH_4$ (1.0 mol) was added. The resulting solution was heated under reflux for 2–3 h. The crude then obtained was concentrated under reduced pressure to remove methanol, followed by quenching with cold aq. NH_4Cl gives residue, which on extraction with ethyl acetate, drying over Na_2SO_4 (s), followed by column purification yields the desired product (**6**) in good yields.

Procedure for the synthesis of *N*-allyl/benzyl, *N*-methyl aniline from various substituted *N*-methyl anilines (6)

To the ethanolic solution of the aniline (**6**) (1.0 mol), K_2CO_3 (3.0 mol), allyl/benzyl bromide (1.2 mol) were added at room temperature and the resulting mixture was allowed to stir for 12 h at room temperature under inert atmosphere. The resulting mixture thus obtained was first ethanol concentrated, and then extracted with ethyl acetate and was purified by column chromatographic technique.

Procedure for the synthesis of 4-*p*-tolylmorpholine (8)

A 100 ml round bottomed flask equipped with mechanical stirrer, was charged with 30 mL of *N*, *N*-dimethylformamide and 3.87 g (28.05 mmol) of anhydrous potassium carbonate. To the rapidly stirred mixture was then added 1.0 g (9.35 mmol) of *p*-toluidine (**7**) followed by the addition of 2.60 g (11.22 mmol) of 1-bromo-2-(2-bromoethoxy) ethane. The mixture was stirred for 12 h.; after the addition was completed, the mixture was poured into ice water, extracted with ethyl acetate, and dried Na_2SO_4 (s). The solvent was removed on a rotary evaporator, affording 1.30 g (79%) of brown colored solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (d, J = 8.50 Hz, 2H), 6.85 (d, J = 8.50 Hz, 2H), 3.88–3.84 (m, 4H), 3.12–3.09 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (75 MHz,$CDCl_3$) δ: 149.1, 129.6, 129.5, 116.0, 66.9, 49.9, 20.4.

Characterization data of the compounds

1-(2-(Dimethylamino)-5-methylphenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-3). Isolated by column chromatography. The title compound was a red colored liquid (138 mg, 59% Yield). FTIR (cm^{-1}): 3339, 2980, 2929, 1674, 1633, 1497, 1445, 1389, 1363, 1303, 1261, 1183, 1070, 861, 752; ^{1}H NMR (ppm) δ: 7.57–7.54 (m, 1H), 7.49–7.46(m, 2H), 7.42–7.35 (m, 2H), 7.20–7.07 (m, 3H), 6.92–6.88 (m, 1H), 2.70 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (ppm) δ: 151.3, 134.5, 129.6, 128.8, 126.5, 122.1, 121.7, 118.6, 118.0, 111.6, 111.5, 43.9, 26.3 MS(ESI) m/z: 318 $(M + H)^+$, 319; HRMS (ESI) calcd. for $C_{21}H_{20}NO_2$ $(M + H)^+$: 318.14886; found: 318.14840.

1-(2-(Dimethylamino)-5-ethylphenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-7). Isolated by column chromatography. The title compound was a cream colored solid (124 mg, 56% Yield); mp 134 °C. FTIR (cm^{-1}): 3450, 2955, 2866, 2796, 1605, 1496,

1496, 1469, 1439, 1412, 1300, 1259, 1209, 1182, 1155, 929, 888, 834, 805, 748, 734, 611; ^{1}H NMR (ppm) δ: 7.56–7.47 (m, 3H), 7.42–7.28 (m, 3H), 7.24–7.21 (m, 1H), 7.18–7.15 (m, 1H), 7.10–7.05 (m, 1H), 2.71(s, 6H), 2.66–2.58 (q, J = 7.55, 2H), 1.23–1.18jb (t, J = 7.55, 3H); ^{13}C NMR (ppm) δ: 156.9, 151.3, 150.5, 147.0, 139.4, 133.6, 130.0, 128.5, 126.5, 124.5, 122.2, 121.6, 118.5, 118.0, 111.5, 111.4, 43.9, 28.1, 15.6; MS (ESI) m/z: 332 (M + H)$^+$, 333; HRMS (ESI) calcd. for $C_{22}H_{22}NO_2$ (M + H)$^+$: 332.16451; found: 332.16382.

1-(5-Iso-propyl-2-(dimethylamino)phenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-4). Isolated by column chromatography. The title compound was a colorless solid (116 mg, 55% Yield); mp 170 °C. FTIR (cm^{-1}): 3445, 2958, 2870, 1623, 1498, 1468, 1442, 1409, 1303, 1261, 1213, 1187, 932, 890, 810, 751, 625; ^{1}H NMR (ppm) δ: 7.56–7.47 (m, 3H), 7.41–7.31 (m, 3H), 7.25–7.15 (m, 2H), 7.09–7.04 (m, 1H), 2.95–2.85 (m, 1H), 2.72 (s, 6H), 1.24–1.20 (m, 6H); ^{13}C NMR (ppm) δ: 156.9, 151.3, 150.5, 147.2, 143.7, 132.2, 129.9, 127.1, 126.6, 124.5, 122.5, 122.4, 122.2, 121.5, 118.5, 117.9, 111.5, 111.4, 43.9, 33.5, 24.0, 23.7; MS (ESI) m/z: 346 (M + H)$^+$, 347; HRMS (ESI) calcd. for $C_{23}H_{24}NO_2$ (M + H)$^+$: 346.18016; found: 346.17993.

1-(5-*tert*-Butyl-2-(dimethylamino)phenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-5). Isolated by column chromatography. The title compound was a cream colored solid (111 mg, 55% Yield); mp 173 °C. FTIR (cm^{-1}): 3447, 2959, 2904, 2870, 1623, 1499, 1470, 1441, 1422, 1395, 1260, 1193, 932, 894, 811, 753, 617; ^{1}H NMR (ppm) δ: 7.68–7.67 (d, J = 2.45 Hz, 1H), 7.56–7.53 (m, 1H), 7.51–7.50 (m, 1H), 7.48–7.47 (m, 1H), 7.40–7.34 (m, 2H), 7.23–7.16 (m, 2H), 7.08–7.04 (m, 1H), 2.72 (s, 6H), 1.28 (s, 9H); ^{13}C NMR (ppm) δ: 156.8, 151.3, 150.5, 146.7, 145.9, 131.4, 129.5, 126.6, 125.8, 124.4, 122.6, 122.4, 122.2, 121.4, 118.5, 117.7, 111.5, 111.4, 43.8, 34.3, 31.2; MS (ESI) m/z: 360 (M + H)$^+$, 361; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$ (M + H)$^+$: 360.19581; found: 360.19559.

1-(5-Butyl-2-(dimethylamino)phenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-8). Isolated by column chromatography. The title compound was a colorless solid (117 mg, 58% Yield); mp 159 °C. FTIR (cm^{-1}): 3445, 2955, 2928, 2853, 2794, 1624, 1583, 1497, 1471, 1439, 1410, 1300, 1259, 1209, 1184, 1039, 1012, 889, 833, 748, 734, 681, 611; ^{1}H NMR (ppm) δ: 7.57–7.54 (m, 1H), 7.50–7.46 (m, 2H), 7.41–7.35 (m, 2H), 7.30–7.27 (m, 1H), 7.26–7.21 (m, 1H), 7.19–7.16 (m, 1H), 7.09–7.04 (m, 1H), 2.73 (s, 6H), 2.61–2.55 (m, 2H), 1.63–1.59 (m, 2H), 1.39–1.33 (m, 2H), 0.93–0.88 (m, 3H); ^{13}C NMR (ppm) δ: 156.9, 151.3, 150.5, 147.0, 143.1, 132.5, 129.8, 127.5, 126.5, 124.5, 122.4, 122.2, 121.5, 118.5, 117.9, 111.5, 111.4, 60.3, 43.8, 34.5, 34.0, 26.7., 25.9, 20.9, 14.1; MS (ESI) m/z: 360 (M + H)$^+$, 361, 362; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$ (M + H)$^+$: 360.19581; found: 360.19568.

1-(2-(Dimethylamino)-4,5-dimethylphenyl)dibenzo[*b*,*d*]-furan-2-ol (DBF-14). Isolated by column chromatography. The title compound was a cream colored solid (118 mg, 53% Yield); mp 147 °C. FTIR (cm^{-1}): 2923, 1847, 1729, 1611, 1500, 1447, 1393, 1258, 1190, 1039, 875, 805, 757; ^{1}H NMR (ppm) δ: 7.56–7.53 (m, 1H), 7.47–7.35 (m, 4H), 7.17–7.06 (m, 3H), 2.70 (s, 6H), 2.39 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (ppm) δ: 152.9, 150.5, 147.0, 134.8, 127.3, 127.1, 126.7, 122.2, 121.6, 118.4, 111.5, 111.1, 43.9, 19.9, 18.7; MS (ESI) m/z: 332 (M + H)$^+$, 333; HRMS (ESI) calcd. for $C_{22}H_{22}NO_2$ (M + H)$^+$: 332.16451; found: 332.16354.

1-(5-Cyclohexyl-2-(dimethylamino)phenyl)dibenzo[*b*,*d*]-furan-2-ol (DBF-13). Isolated by column chromatography. The title compound was a colorless solid (111 mg, 59% Yield); mp 163 °C. FTIR (cm^{-1}): 3418, 3016, 2920, 2865, 2792, 1589, 1459, 1401, 1330, 1298, 1234, 1202, 1149, 922, 819, 752, 669, 621; ^{1}H NMR (ppm) δ: 7.57–7.54 (m, 1H), 7.50–7.47 (m, 2H), 7.41–7.36 (m, 2H), 7.33–7.29 (m, 1H), 7.26–7.23 (m, 1H), 7.19–7.16 (m, 1H) 7.09–7.04 (m, 1H), 2.72 (s, 6H), 2.55–2.44 (m, 1H), 1.90–1.66 (m, 6H), 1.41–1.25 (m, 4H); ^{13}C NMR (ppm) δ: 156.9, 151.3, 150.5, 147.0, 143.1, 132.5, 129.8, 127.5, 126.5, 124.5, 122.4, 122.2, 121.5, 118.5, 117.9, 111.5, 111.4, 60.3, 43.8, 34.5, 34.0, 26.7., 25.9, 20.9, 14.1; MS (ESI) m/z: 386 (M + H)$^+$, 387; HRMS (ESI) calcd. for $C_{26}H_{28}NO_2$ (M + H)$^+$: 386.21146; found: 386.21140.

1-(2-(Dimethylamino)-5-fluoro phenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-20). Isolated by column chromatography. The title compound was a colorless solid (115 mg, 50% Yield); mp 210 °C. FTIR (cm^{-1}): 3424, 3067, 2970, 2873, 2791, 1855, 1733, 1494, 1471, 1406, 1338, 1302, 1262, 1207, 1182, 1144, 1115, 817, 757; ^{1}H NMR (ppm) δ: 7.57–7.49 (m, 2H), 7.43–7.34 (m, 3H), 7.29 (s, 1H), 7.21–7.10 (m, 3H), 2.71 (s, 6H); ^{13}C NMR (ppm) δ: 159.5, 157.0, 151.4, 150.5, 145.7, 132.2, 126.8, 124.0, 122.0, 121.0, 120.5, 120.3, 119.5, 118.8, 115.6, 115.5, 112.2, 111.7, 44.1; MS (ESI) m/z: 322 (M + H)$^+$, 344 (M + Na)$^+$; HRMS (ESI) calcd. for $C_{20}H_{17}NO_2F$ (M + H)$^+$: 322.12378; found: 322.12387.

1-(2-(Benzyl(methyl)amino)-5-methylphenyl)dibenzo[*b*,*d*]-furan-2-ol (DBF-15). Isolated by column chromatography. The title compound was a red colored liquid (83 mg, 45% Yield). FTIR (cm^{-1}): 3409, 2922, 2853, 1632, 1446, 1260, 1215, 1178, 1113, 1068, 920, 812, 752; ^{1}H NMR (ppm) δ: 7.56–7.49 (m, 3H), 7.43–7.36 (m, 2H), 7.22–7.09 (m, 5H), 6.99–6.96 (m, 2H), 6.92–6.88 (d, J = 10.19, 1H), 6.25–6.20 (d, J = 10.19, 1H), 3.97–3.85 (m, 2H), 2.69 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (ppm) δ: 151.4, 150.2, 146.4, 135.5, 134.4, 133.2, 130.1, 129.7, 129.5, 129.3, 128.8, 128.2, 127.5, 126.6, 122.6, 122.3, 121.9, 121.8, 119.5, 118.5, 111.6, 61.8, 38.8, 26.2; MS (ESI) m/z: 394 (M + H)$^+$, 395; HRMS (ESI) calcd. for $C_{27}H_{24}NO_2$ (M + H)$^+$: 394.18016; found: 394.18052.

1-(2-(Allyl(methyl)amino)-5-ethylphenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-16). Isolated by column chromatography. The title compound was a red colored liquid (89 mg, 44% Yield). FTIR (cm^{-1}): 3450, 2964, 2928, 2858, 1671, 1632, 1453, 1366, 1259, 1197 1102, 1063, 1008, 752; ^{1}H NMR (ppm) δ: 7.55–7.53 (d, J = 8.23, 1H), 7.48–7.47 (m, 2H), 7.38–7.36 (m, 2H), 7.29–7.28 (m, 1H), 7.21–7.16 (m, 2H), 7.08–7.05 (m, 1H), 5.69–5.59 (m, 1H), 5.07–5.06 (d, J = 9.26, 1H), 5.01–4.98(m, 1H), 3.45–3.34 (m, 2H), 2.77 (s, 3H), 2.65–2.60 (m, 2H), 1.22–1.19 (m, 3H); ^{13}C NMR (ppm) δ: 156.9, 150.4, 146.4, 139.3, 133.5, 132.9, 129.9, 128.4, 126.5, 122.2, 121.6, 119.4, 119.0, 118.6, 111.5, 80.0, 71.9, 60.4, 37.4, 29.3, 26.3, MS (ESI) m/z: 358 (M + H)$^+$; HRMS (ESI) calcd. for $C_{24}H_{24}NO_2$ (M + H)$^+$: 358.18016; found: 358.18044.

1-(5-Methyl-2-(methylamino)phenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-18). Isolated by column chromatography. The title compound was a colorless liquid (64 mg, 84% Yield). FTIR (cm^{-1}): 3363, 2963, 2926, 2858, 1709, 1602, 1570, 1451, 1305,

1261, 1183, 1062, 1012, 955, 882, 813, 750; ^{1}H NMR (ppm) δ: 7.56–7.54 (d, J = 7.99, 1H), 7.49–7.46 (m, 2H), 7.39–7.36 (m, 1H), 7.33–7.29 (m, 3H), 7.20–7.18 (d, J = 7.99, 1H), 7.09–7.06 (m, 1H), 2.83 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (ppm) δ: 156.8, 151.7, 150.7, 146.6, 129.7, 127.3, 127.0, 124.8, 124.2, 122.3, 120.5, 115.3, 113.3, 111.9, 111.6, 106.2, 31.3, 20.3; MS (ESI) m/z: 304 $(M + H)^+$; HRMS (ESI) calcd. for $C_{20}H_{18}NO_2$ $(M + H)^+$: 304.13321; found: 304.13367.

4-Cyclohexyl-2-(2-(hexyloxy)dibenzo[*b*,*d*]furan-1-yl)-*N*,*N*-dimethylaniline (DBF-19). Isolated by column chromatography. The title compound was a greenish solid (107 mg, 88% Yield); mp 85 °C. FTIR (cm^{-1}): 2924, 2853, 2777, 1604, 1504, 1467, 1422, 1250, 1190, 1142, 1097, 1605, 1013, 943, 867, 795, 747, 622; ^{1}H NMR (ppm) δ: 7.50–7.31(m, 5H), 7.15–6.91 (m, 4H), 4.02–3.89 (m, 2H), 2.44 (s, 7H), 1.90–1.68 (m, 6H), 1.38–1.22 (m, 12H), 0.86–0.81 (m, 3H); ^{13}C NMR (ppm) δ: 151.9, 150.9, 130.4, 129.0, 128.6, 127.2, 126.6, 122.5, 122.3, 121.9, 117.5, 113.5, 111.1, 111.0, 110.6, 109.8, 70.2, 43.6, 34.6, 34.5, 31.4, 29.4, 26.8, 26.1, 25.6, 22.5, 13.9, 0.9; MS (ESI) m/z: 470 $(M + H)^+$; HRMS (ESI) calcd. for $C_{32}H_{40}NO_2$ $(M + H)^+$: 470.30536; found: 470.30447.

4-Ethyl-2-(2-(4-fluoro benzyloxy)dibenzo[*b*,*d*]furan-1-yl)-*N*,*N*-dimethylaniline (DBF-21). Isolated by column chromatography. The title compound was a colorless liquid (110 mg, 83% Yield). FTIR (cm^{-1}): 2962, 2932, 2865, 2828, 2779, 1605, 1508, 1419, 1252, 1225, 1191, 1066, 823, 748; ^{1}H NMR (ppm) δ: 7.52–7.45 (m, 2H), 7.38–7.33 (m, 2H), 7.22–6.93(m, 9H), 5.06 (s, 2H), 2.66–2.59 (m, 2H), 2.44 (s, 6H), 1.246–1.19 (m, 3H); ^{13}C NMR (ppm) δ: 158.9, 151.3, 131.6, 131.4, 129.8, 128.7, 128.6, 127.6, 122.3, 122.2, 122.1, 115.2, 115.0, 114.2, 111.2, 71.3, 43.7, 29.6, 15.8; MS (ESI) m/z: 440 $(M + H)^+$; HRMS (ESI) calcd. for $C_{29}H_{27}NO_2$ F $(M + H)^+$: 440.20203; found: 440.20087.

1-(5-Methyl-2-morpholinophenyl)dibenzo[*b*,*d*]furan-2-ol (DBF-9). Isolated by column chromatography. The title compound was a brown colored solid (85 mg, 42% Yield); mp 125 °C. FTIR (cm^{-1}): 3417, 2922, 2852, 1446, 1260, 1215, 1178, 1113, 1068, 920, 812, 751; ^{1}H NMR (ppm) δ: 7.57–7.30 (m, 6H), 7.21–7.07 (m, 3H), 3.77–3.65(m, 4H), 3.14–2.89 (m, 4H), 2.42 (s, 1H), 2.33 (s, 2H); ^{13}C NMR (ppm) δ: 156.9, 149.6, 145.9, 134.6, 133.6, 130.0, 129.8, 126.7, 122.7, 122.2, 122.0, 121.8, 120.6, 118.6, 118.1, 112.0, 106.1, 66.7, 52.4, 20.5; MS (ESI) m/z: 360 $(M + H)^+$, 361; HRMS (ESI) calcd. for $C_{23}H_{22}NO_3$ $(M + H)^+$: 360.15942; found: 360.15973.

X-ray data

The intensity data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo–Kα radiation (λ = 0.71073 Å) by the ω-scan method [1]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 8434 reflections in the range of $2.65 < \theta < 26.90^\circ$. Integration and scaling of intensity data were accomplished using the program SAINT [1]. The structures were solved by direct methods using SHELX97 [2] and refinement was carried out by full-matrix least-squares technique using SHELXL97 [2]. Anisotropic displacement parameters were calculated for all non-hydrogen atoms. The O-bound H atom was located in a difference Fourier density map and refined isotropically. All other H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H = 0.93–0.96 Å, and with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H and $1.2U_{eq}(c)$ for other H atoms.

HPLC procedure

The chromatographic separation was achieved on Inertsil-ODS3V-C_{18} (4.6 mm × 250 mm i.d.; particle size 5 μm) analytical column using different compositions of acetonitrile and 20 mM ammonium acetate as a mobile phase in an isocratic elution mode at a flow rate 1.0 mL min^{-1} at 25 °C. The column effluents were monitored by a photo diode array detector.

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