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SYNTHESIS, SPECTRAL, THERMAL AND ANTIMICROBIAL ACTIVITY ANALYSIS OF AMINO SUBSTITUTED DIBENZOFURAN DERIVATIVES

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Abstract: The derivatives of 1-amino dibenzo[b,d]furan by alkyl and aryl substitution were synthesised via 1,3-dinitrophenol with iodophenol compound. With the help of ^{1}H NMR, ^{13}C NMR the chemical structures of the compound were elucidated. The LCMS test was employed to estimate the mass of the synthesized compounds. From the recorded FTIR spectrum, the various functional groups present in the title compound were revealed and the same were confirmed by elemental analysis. To ascertain the pharmaceutical application of these compounds, they were also screened for in vitro antibacterial an antifungal activity.
Keywords: 1-nitro dibenzofuran; 1-amino dibenzofuran; antimicrobial activities.

Introduction:

Many pharmaceutical compounds are based on dibenzofurans and now a days they draw the attention of chemical and pharmaceutical researchers for its new kind medicines[I]. The dibenzo furan analogues were found to be in-vitro inhibitors on microbial growth which enables to design anti tuberculosis medicines[II]. It is also used as multidentate ligand in catalysis, chemo sensor and organic electronics[III]. Its influence on the bacterial structural changes and the transition of catabolic genes were also studied[IV].

The dibenzofuran scaffolds are present naturally in kehokorins A–C, rhodomyrtoxin B, vialinin B, and vanillic acid. They have cytotoxic, anti-infammatory, antibacterial activities and inhibit production of TNF-a[V]. Also, they have been isolated from the Pyrinae. The dibenzofuran phytoalexins were also found in the leaves of Eriobotrya japonica plants[VI-X].

In this work an attempt is made to synthesis the derivatives of 1-amino dibenzo[b,d]furan by alkyl and aryl substitution via 1,3-dinitrophenol with iodophenol compound. The spectral, thermal and antimicrobial activity of the synthesized compounds were carried out and the discussion of the result are presented.

Experimental:

Materials

The 1,3-dinitrobenzene, 2-iodophenol, potassium tert-butoxide, pyridine and dimethoxyethane were purchased from Sigma-Aldrich, India and were used without purification. Methanol, dichloromethane (DCM), ethyl acetate, hexane, Con.HCl, $SnCl_2$ and triethylamine were purchased from Sigma-Aldrich. Dry solvents were supplied by Spectrochem. Reagent and solvent were purchased from commercial sources and used without further purification unless otherwise noted.

Instruments and methods

The melting points were recorded on SRS Optimelt and are uncorrected. ^{1}HNMR spectra were recorded on a 400 MHz Varian spectrometer and ^{13}CNMR spectra were recorded on a 100 MHz Bruker spectrometer with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded by using Shimadzu mass spectrometer. The FT-IR spectra were recorded by KBr pellet technique with the help of a Perkin- Elmer spectrum 100 series spectrophotometer. Column chromatography was performed with silica gel in 60-120 mesh. All the reactions were monitored by thin layer chromatography (TLC) plates and their spots were visualized by exposing them to UV lamp, $KMnO_4$ or iodine chamber. The elemental analysis has been obtained using a Varian instrument VARIO EL3 series analyzer.

Synthesis and characterization of the compounds

Synthesis of 1-nitro dibenzo[b,d]furan (3)

In 1,3-dinitrobenzene (1) (5 g, 29.74 mmol, 1 eq), 2-iodophenol (2) (6.5 g, 29.74 mmol, 1 eq) was added and stirred well. Now dimethoxyethane (20 mL) and Pyridine (10 mL) were added and stirred again by keeping the temperature at 25°C. The reaction mixture was stirred for 10 min and then potassium tertiary butoxide (6.7 g, 59.48 mmol, 2 eq) was added and heated to 100° C for 16 hrs. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and quenched with cold water and extracted with ethyl acetate (2*50 mL), the organic layer was dried (MgSO4) and concentrated. The residue was purified by column chromatography to get 1-nitrodibenzo [b,d]furan (**3**) (3 g, yield 47%, LCMS: 95.5% purity), m.pt.124-129°C. IR (KBr, cm^{-1}): ν_{max} 1518 (N=O), 1690, 1441-1630 (C=C), 973-1150 (C-O, C-N). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): δ 8.84 (t, 1H, *J*=8.1Hz, Ar-CH), 8.53 (d, 1H, *J*=7.6Hz, Ar-CH), 8.52-8.25 (m, 3H, Ar-3CH), 7.99-7.58 (m, 2H, Ar-2CH). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 112.52, 118.16, 119.09, 120.42, 120.57, 124.36, 125.86, 128.20, 129.86, 130.62, 132.08, 143.02. For $C_{12}H_7NO_3$, calculated: 67.61% C, 3.31% H, 6.57% N and 22.51% O. found: 67.40% C, 3.39% H, 6.86% N, and 22.18% O. LCMS $[M+1]^+$: m/z 214.19.

Synthesis of 1-amino dibenzo[b,d]furan (4)

Stannous chloride (4 g, 21.12mmol, 1.5eq) was added to a stirred solution compound (3) (3 g, 14.08 mmol) in Conc.HCl (25 mL) at 0° C, in portions wise. Reaction was stirred for 4hrs at 0° C. The progress of the reaction was monitored by TLC. After the completion, it was quenched with ice water. Reaction mixture was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. Crude residue was purified by column chromatography to get 1-amino dibenzo[b,d]furan(**4**) (2 g, yield : 77.8%). LCMS: 95.7% (purity), m.pt.85-89°C. IR (KBr, cm^{-1}): ν_{max} 3368 (NH_2), 1430-1577 (C=C), 1352-1197 (C-O, C-N). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): δ 8.27 (t, 1H, *J*=8.4Hz, Ar-CH), 7.61 (d, 1H, *J*=8Hz, Ar-CH), 7.43-7.39 (m, 2H, Ar-2CH), 7.22 (t, 1H, *J*=8Hz, Ar-CH), 6.85 (d, 1H, *J*=7.6Hz, Ar-CH), 6.64 (d, 1H, *J*=8Hz, Ar-CH), 5.87 (s, 2H, NH_2). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 99.14, 108.63, 109.52, 111.10, 122.03, 122.99, 124.20, 125.85, 128.74, 144.92, 154.81, 157.35. For $C_{12}H_9NO$, calculated:

78.67% C, 4.95% H, 7.65% N and 8.73% O. found: 78.70% C, 4.79% H, 7.86% N and 8.58% O. LCMS [M+1] $^{+}$: m/z 184.21.

N-(dibenzo[b,d]furan-1-yl) aminoethane (4a)

Yield: 95mg, 60%, white solid, LCMS: 94.5% (purity), m.pt.65-70°C. IR (KBr, cm^{-1}): ν_{max} 1024.49(C-O), 1181.03(C-N), 1457.51(C=C). ^{1}HNMR (400 MHz, DMSO-d$_6$, ppm) : δ 8.30 (t, 2H, *J*=7.6Hz, Ar-2CH), 7.62 (d, 2H, *J*=8Hz, Ar-2CH), 7.43 (t, 1H, *J*=3.2Hz, -NH), 6.91 (t, 1H, *J*=8.6Hz, Ar-CH), 6.50 (d, 2H, *J*=8.4Hz, Ar-2CH), 2.93 (t, 3H, *J*=8.2Hz, -CH_3), 2.51 (q, 2H, -CH_2).^{13}CNMR (100 MHz, DMSO-d$_6$, ppm): δ 30.62, 39.55, 40.18, 99.58, 103.59, 109.50, 111.64, 122.99, 123.31, 123.49, 126.90, 128.63, 145.85, 157.02. LCMS [M+1] $^{+}$: m/z 211.10

Scheme 1:

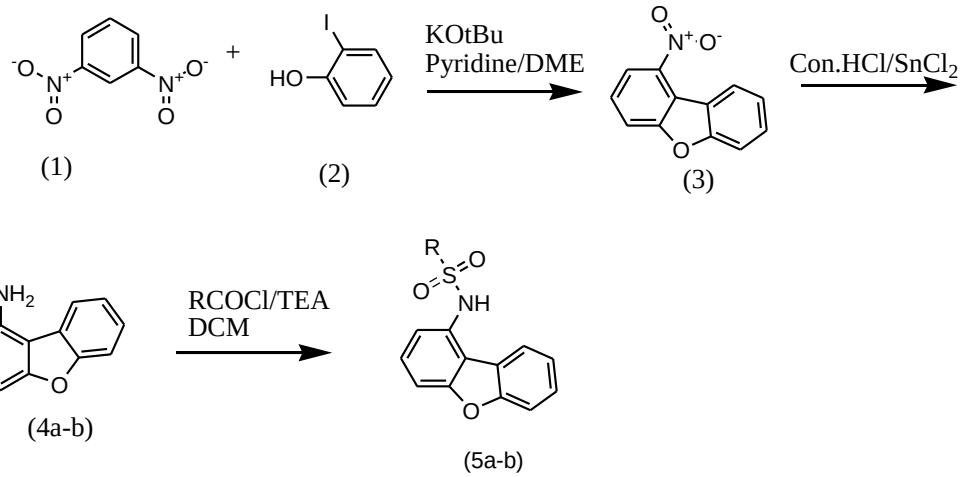
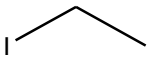
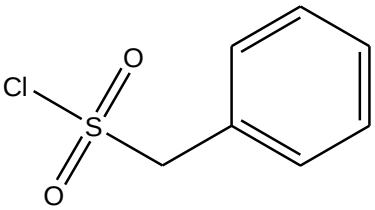
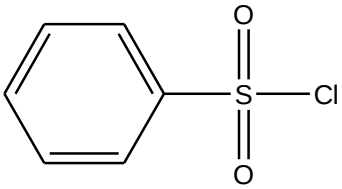


Table 1: Physical constants of 4 (a-b) and 5(a-b)

Compounds	Aryl/Alkyl substituents(-R)	m.p (ºC)	R_f
4a		**65-70**	**0.59**
4b		**62-66**	**0.63**
5a		**112-115**	**0.58**
5b		**102-105**	**0.61**

N-(dibenzo[b,d]furan-1-yl) aminomethane (4b)
Yield: 90mg, 58%, 0ff-white solid, LCMS: 95.3% (purity), m.pt.62-66°C. IR (KBr, cm^{-1}): ν_{max} 1048.57(C-O), 1156.36(C-N), 1351.83(-$NHSO_2$), 1451.97(C=C). ^{1}HNMR (400 MHz, DMSO-d_6, ppm) : δ 8.22 (d, 1H, *J*=7.2Hz, Ar-CH), 7.93 (d, 1H, *J*=7.6Hz, Ar-CH), 7.80 (d, 1H, *J*=8.4Hz, Ar-CH), 7.67 (d, 1H, *J*=8Hz, Ar-CH), 7.64 (t, 1H, *J*=7.8Hz, Ar-CH), 7.62 (t, 1H, *J*=7.4Hz, Ar-CH), 7.51 (t, 1H, *J*=7.4Hz, Ar-CH), 5.75 (s, 1H, -NH), 2.50 (s, 3H, -CH_3).^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.34, 43.59, 112.47, 114.47, 121.88, 123.03, 124.15, 124.76, 127.30, 127.84, 128.24, 129.07, 156.51. LCMS [M+1] $^+$: m/z 197.08.

Representative procedure to prepare amide derivative *(5 a-b)*
To a solution of 1-amino dibenzo[b,d]furan(4) (100 mg, 0.546 mmol) in DCM (2mL), TEA (0.5 mL, 1.09 mmol, 2 eq) was added. At 0°C, corresponding acid chloride was added dropwise and stirred for 5hrs. The progress of the reaction was monitored by TLC. After the completion, ice water was added then the organic layer was separated, dried ($MgSO_4$) and concentrated. The crude residue was recrystallized from diethyl ether to give compound (**5a-b**).
N-(dibenzo[b,d]furan-1-yl)phenyl methane sulfonamide (5a)
Yield: 120mg, 65%, white solid, LCMS: 95.3% (purity), m.pt.112-143°C. IR (KBr, cm^{-1}): ν_{max} 3429 (amide N-H), 1496-1429 (C=C), 1264-1162 (sulfonamide), 1054-844 (C-O, C-N). ^{1}HNMR (400 MHz, DMSO-d_6, ppm) : δ 8.24 (d, 2H, *J*=8Hz, Ar-CH), 7.60 (d, 1H, *J*=8.4Hz, Ar-CH), 7.42 (t, 2H, *J*=7.6Hz, Ar-CH), 7.35 (t, 2H, *J*=7.2Hz, Ar-CH), 7.20 (t, 2H, *J*=7.8Hz, Ar-CH), 6.83 (d, 2H, *J*=8Hz, Ar-CH), 6.61 (d, 1H, *J*=8Hz, Ar-CH), 5.84 (s, 2H, -CH_2), 5.32 (s, 1H, -NH). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.97, 40.60, 59.55, 99.14, 108.64, 111.10, 157.35. LCMS [M+1] $^+$: m/z 337.05.
N-(dibenzo[b,d]furan-1-yl)phenyl sulfonamide (5b)
Yield: 95mg, 61%, white solid, LCMS: 95.8% (purity), m.pt.109-113°C. IR (KBr, cm^{-1}): ν_{max} 1054.37(C-O), 1104.63(C-N), 1264.52(-$NHSO_2$), 1429.09(C=C). ^{1}HNMR (400 MHz, DMSO-d_6, ppm) : δ 8.25 (d, 2H, *J*=8.4Hz, Ar-CH), 7.57 (d, 1H, *J*=7.6Hz, Ar-CH), 7.42 (t, 2H, *J*=7.2Hz, Ar-CH), 7.36 (t, 2H, *J*=7.6Hz, Ar-CH), 7.21 (t, 2H, *J*=8Hz, Ar-CH), 6.84 (d, 2H, *J*=8.8Hz, Ar-CH), 6.62 (d, 1H, *J*=8.4Hz, Ar-CH), 5.94 (s, 1H, -NH). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.33, 39.54, 39.75,39.96, 40.17, 40.38, 40.58, 45.85, 125.93, 128.11, 128.73, 128.88, 130.11. LCMsS [M+1] $^+$: m/z 323.06.

Results and discussion:
Chemistry aspect
The synthesis of the N-(dibenzo[b,d]furan-1-yl) substituted amides 4(a-b) & (5a-b) were carried out as shown in Scheme-I. The starting materials were 1, 3-dinitrobenzene and 2-iodophenol in dimethoxyethane (DME). The obtained intermediate product 1-nitro dibenzo[b,d]furan (3) and 1-amino dibenzo[b,d]furan (4) was then refluxed. The amine derivatives in dichloromethane (DCM), triethylamine (TEA) with an added acid chloride to get desired compounds 4(a-b)&(5a-b).
In the FTIR spectra, the characteristic N–H bands and amide functions were observed at in the range 3245–3369 cm^{-1}. In the NMR spectra, peaks at about 2.22–3.62 ppm, 2.50–2.54 ppm and 10.15–10.17 ppm were seen assigning to CH_3, CO-CH_3, and NH protons respectively. M+1 peaks in mass spectra were agreed with the calculated molecular weight of the title compounds 4(a-b) & (5a-b). The weight percentage of C, H and N elements were obtained from elemental analysis and also calculated theoretically. Both the values are agree with each other and the values are presented in Table.1. According to LCMS analysis, purity ratio was found greater than 95% for all compounds.

Table. 1: Elemental analysis of the synthesized compounds (4a-b) & (5a-b)

Compound Code	Mol. Formula	Appearance	Elemental Analysis		
			% C Calcd (found)	% H Calcd (found)	% N Calcd (found)
4a	$C_{14}H_{13}NO$	white solid	79.59 (79.62)	6.20 (6.30)	6.63 (6.67)
4b	$C_{13}H_{11}NO$	0ff-white solid	79.16 (79.10)	5.62 (5.66)	7.10 (7.17)
5a	$C_{19}H_{15}NO_3S$	white solid	67.64 (67.67)	4.48 (4.43)	4.15 (4.13)
5b	$C_{18}H_{13}NO_3S$	white solid	66.86 (66.76)	4.05 (4.13)	4.33 (4.30)

Biological aspect:

Antimicrobial activity

The synthesized N-(dibenzo[b,d]furan-1-yl) aminoethane *(4a),* N-(dibenzo[b,d]furan-1-yl) aminomethane *(4b),* N-(dibenzo[b,d]furan-1-yl)phenyl methane sulfonamide *(5a)* and N-(dibenzo[b,d]furan-1-yl)phenyl sulfonamide *(5b)* compounds are subjected to *in-vitro* antibacterial and antifungal activity using agar diffusion. A 20 mL of nutrient agar and PDA medium are used for each sterile Petri plate (90 mm). It is left for solidification. And then 100 µL of bacterial apprehension was spread on the plates. After 5 minutes, a sterile filter paper disc (6 mm) containing 5 µL of the compound was placed on the surface of each plate. Now the plates were incubated at 37°C for 24 h bacterial development and at 28°C for 48 h for fungal production. The antimicrobial activities of various compounds are examined by measuring the diameter of the inhibition zone (DIZ) in mm. *ciprofloxacin* and *amphotericin B* were served as reference. The results are tabulated in Table.2.

Table-2: Biological activity of the compounds

Organism	Zone of inhibition in mm						
	Bacterial						
	Com3	Com4	4-a	4-b	5-a	5-b	*Ciprofloxacin*
Salmonella typhi	13	7	11	-	10	7	20
Staphylococcus aureus	-	10	-	8	11	6	15
Escherichia coli	-	9	9	9	7	6	12
Fungi							
Aspergillus nigar	9	8	10	-	8	-	***Amphotericin B*** 10
Candida albicans	5	9	-	7	12	5	12
Candida kefyr	-	8	8	8	8	8	15

Conclusion:

The derivatives of 1- amino dibenzo[b,d]furan were synthesised from the preparation of 1,3-dinitrophenol with 2-iodophenol compound. The different functional groups present in the compounds were identified by FT-IR spectral analysis. The ^{1}HNMR and ^{13}CNMR spectral result shows the chemical structures of these compounds. From the biological studies, it is observed that the compound 5a shows better antibacterial and antifungal activities among others. Hence compound 5a can be used for pharmacological applications.

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