Indian Journal of Chemistry
Vol. 60B, July 2021, pp. 1022-1026

Synthesis, characterization and antimicrobial activity of some novel 1-amino dibenzofuran derivatives

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Received 29 October 2019; accepted (revised) 10 March 2021

A series of novel 1-amino dibenzo[b,d]furan derivatives have been synthesised *via* 1,3-dinitrophenol with iodophenol compound. The chemical structures of the compound have been elucidated by ^{1}H and ^{13}C NMR. The mass of the synthesized compounds has been estimated by LCMS. The functional groups present in the title compound are revealed from FT-IR and confirmed by elemental analysis. These compounds have also been screened for *in vitro* antibacterial and antifungal activities.

Keywords: 1-Nitrodibenzofuran, 1-aminodibenzofuran, antimicrobial activities

The use of metal complexes for biomedical applications is an important one. In this process, the macrocycles were used as chelating agents for metal ions. They play a vital role as fluorescent sensors and neuroimaging agents. One among them is benzofuran which is a fluorescent molecule that has attracted the attention of researchers as it is able to bind to the amyloid plaques formed during Alzheimer's disease. Dibenzofuran bearing compounds, an analog of benzofuran ring, have been reported to exhibit a great variety of biological effects, including thrombosis and anticholinesterase activity[1,2]. Isolation of several Gram-negative or Gram-positive bacteria able to mineralize non-halogenated dibenzofuran was reported earlier[3]. Lichen secondary metabolite isolated from C*ladonia substellata*, a derivative of dibenzofuran, shows antimycobacterial activity. However, it cannot be used as a drug because of its weak potency. Synthetic analogue derived from dibenzo[b,d]furan possesses good inhibitory activity against *M. tuberculosis*[4-6].

In most of the naturally occurring molecules, there is a lack of biological activity and also the isolation is a tedious procedure. Structure activity relationship (SAR) studies showed the vital role of dibenzo[b,d]furan moiety on their pharmacological properties[7,8]. Therefore it is envisaged to synthesize a library (series) of small triazolyl derivatives of dibenzo[b,d]furan by Huisgen's1,3-dipolar cycloaddition reaction and a view to study their anti-mycobacterial and immune modulatory activity[9,10].

Experimental Section

The 1,3-dinitrobenzene, 2-iodophenol, potassium tert-butoxide, pyridine and dimethoxyethane were purchased from Sigma-Aldrich, India and 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.

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) 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 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

A solution of 1,3-dinitrobenzene **1** (5 g, 29.74 mmol, 1 eq) and 2-iodophenol **2** (6.5 g, 29.74 mmol, 1 eq) was prepared. 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.124-135°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, reaction 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.85-117°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.

Representative procedure to prepare amide derivative, 5a-e

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 drop-wise 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-e**.

Synthesis of N-(dibenzo[b,d]furan-1-yl)acetamide, 5a

Yield: 80 mg, 65%, off-white solid, LCMS: 95.3% (purity), m.pt.197-212°C. IR (KBr, cm^{-1}): ν_{max} 3257 (amide N-H), 1650 (C=O), 1474-1418 (C=C), 1199-1047 (C-O, C-N). ^{1}HNMR (400MHz, DMSO-d_6, ppm) : δ 10.15 (s, 1H, N-H), 7.94 (d, 1H, *J*=8.4Hz, Ar-CH), 7.71 (d, 1H, *J*=7.2Hz, Ar-CH), 7.50-7.40 (m, 3H, Ar-3CH), 7.42 (t, 1H, *J*=7.2Hz, Ar-CH), 7.35 (d, 1H, *J*=8Hz, Ar-CH), 2.23 (s, 3H, CO-CH_3). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.34, 40.60, 106.11, 107.12, 111.70, 116.22, 123.29, 123.40, 124.60, 127.75, 127.86, 134.12, 145.62, 168.51. For $C_{14}H_{11}NO_2$, calculated: 74.65% C, 4.92% H, 6.22% N and 14.21% O. found: 74.75% C, 4.96% H, 6.27% N and 14.20% O. LCMS $[M+1]^+$: m/z 226.25.

Synthesis of N-(dibenzo[b,d]furan-1-yl)benzamide, 5b

Yield: 85 mg, 51%, white solid, LCMS: 95.4% (purity), m.pt.162-171°C. IR (KBr, cm^{-1}): ν_{max} 3245 (amide N-H), 1690 (C=O), 1521-1425 (C=C), 1268-1125 (C-O, C-N). ^{1}HNMR (400 MHz, DMSO-d_6, ppm): δ 7.86 (d, 1H, *J*=8Hz, Ar-CH), 7.82 (t, 1H, *J*=6.8Hz, Ar-CH), 7.83-7.77 (m, 5H, Ar-5CH), 7.71 (d, 1H, *J*=8.4Hz, Ar-CH), 7.56 (t, 1H, *J*=7.2Hz, Ar-CH), 7.50 (d, 1H, *J*=8Hz, Ar-CH), 7.44 (t, 1H, *J*=7.6Hz, Ar-CH), 7.42 (t, 1H, *J*=7.8Hz, Ar-CH), 7.34 (d, 1H, *J*=8Hz, Ar-CH). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 40.60, 112.29, 112.62, 121.90, 124.29, 126.45, 127.65, 128.66, 128.89, 129.04, 129.27,

129.33, 129.73, 132.21, 133.35, 134.30, 145.08, 156.03, 173.03. For $C_{19}H_{13}NO_2$, calculated: 79.43% C, 4.56% H, 4.88% N and 11.14% O. found: 79.40% C, 4.59% H, 4.88% N and 11.18% O. LCMS $[M+1]^+$: m/z 287.32.

Synthesis of N-(dibenzo[b,d]furan-1-yl)-[1,1'-biphenyl]-4-carboxamide, 5c

Yield: 120mg, 60% white solid, LCMS: 95.3% (purity). m.pt. 65-72°C. IR (KBr, cm^{-1}): ν_{max} 3369 (amide N-H), 1651 (C=O), 1594-1306 (C=C), 1264-996 (C-O, C-N). ^{1}HNMR (400 MHz, DMSO-d_6, ppm) :δ 8.25 (d, 2H, *J*=7.2Hz, Ar-2CH), 7.60 (d, 2H, *J*=8.4Hz, Ar-2CH), 7.42-7.38 (t, 2H, *J*=7Hz, Ar-2CH), 7.35-7.31 (t, 2H, *J*=7.6Hz, Ar-2CH), 7.20-7.16 (t, 2H, *J*=7.8Hz, Ar-CH), 6.83-6.81 (d, 1H, *J*=8Hz, Ar-CH), 6.61-6.59 (d, 2H, *J*=8Hz, Ar-2CH), 5.84(s, 4H). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.97, 40.60, 99.14, 108.64, 109.52, 111.10, 122.03, 122.99, 124.21, 124.88, 125.85, 126.01, 127.34, 127.90, 128.21, 128.74, 129.02, 129.40, 129.54, 131.11, 134.34, 136.05, 144.92, 157.35, 164.13. For $C_{25}H_{17}NO_2$, calculated: 82.63% C, 4.72% H, 3.85% N and 8.81% O. found: 82.67% C, 4.70% H, 3.87% N and 8.83% O. LCMS $[M+1]^+$: m/z 363.42.

Synthesis of N-(dibenzo[b,d]furan-1-yl)methane sulphonamide, 5d

Yield: 95mg, 67%, 0ff-white solid, LCMS: 95.3% (purity), m.pt.158-162°C. IR (KBr, cm^{-1}): ν_{max} 3019 (amide N-H), 1451 (C=C), 1361-1156 (sulfonamide) 1048-877 (C-O, C-N). ^{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 39.97, 43.70, 112.47, 114.47, 121.88, 123.03, 124.76, 127.30, 127.84, 128.24, 129.07, 139.12, 156.51. For $C_{13}H_{11}NO_3S$, calculated: 59.76% C, 4.24% H, 5.36% N, 18.37% O and 12.27% S. found: 59.66% C, 4.28% H, 5.39% N, 18.39% O and 12.28% S. LCMS $[M+1]^+$: m/z 261.30.

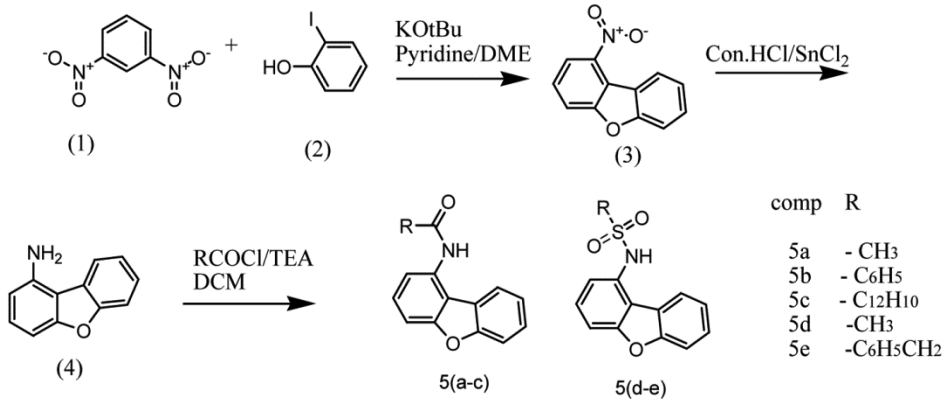
Synthesis of N-(dibenzo[b,d]furan-1-yl)phenyl methane sulphonamide, 5e

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, 122.03, 122.99, 124.21, 125.85, 128.74, 129.12, 129.45, 133.01, 134.11, 144.92, 145.8, 154.35, 157.35. For $C_{19}H_{15}NO_3S$, calculated: 67.64% C, 4.48% H, 4.15% N, 14.23% O, 9.50% S. found: 67.67% C, 4.43% H, 4.13% N, 14.25% O, 9.53% S. LCMS $[M+1]^+$: m/z 337.05.

Results and Discussion

Chemistry aspect

The synthesis of the N-(dibenzo[b,d]furan-1-yl) substituted amides **5a-e** 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**



Scheme I

Table I — *In vitro* antibacterial and antifungal activity of synthesized compounds using agar diffusion

Organism	Zone of inhibition in mm							
	Bacteria							
	3	**4**	**5a**	**5b**	**5c**	**5d**	**5e**	Ciprofloxacin
Salmonella typhi	13	7	−	8	9	8	−	20
Staphylococcus aureus	−	10	7	−	11	−	11	15
Bacillus cereus	−	9	8	8	9	−	7	12
	Fungi							
Aspergillus niger	9	8	8	7	10	9	−	Amphotericin B 10
Candida albicans	5	9	7	6	11	5	12	12
Candida kefyr	−	8	12	10	10	−	6	15

was then refluxed. The amine derivatives in dichloromethane (DCM), triethylamine (TEA) with an added acid chloride to get desired compounds **5a-e**.

In the IR 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, $CO\text{-}CH_3$, and NH protons respectively. M+1 peaks in mass spectra were agreed with the calculated molecular weight of the title compounds **5a-e**. The weight percentage of C, H and N elements obtained from elemental analysis agree with theoretically calculated values of the compounds. According to LCMS analysis, purity ratio was found greater than 95% for all compounds.

Biological aspect

Collection of microorganisms

The microorganisms such as *Bacillus cereus*, *Salmonella typhi*, *Staphylococcus aureus* (*S. aureus*) and fungal development of *Aspergillus niger*, *Candida albicans*, *Candida kefyr* were obtained from Micro lab, Institute of Research and Technology, Arcot, Vellore, Tamil Nadu, India. In the present study, antimicrobial organisms were used for testing microbial activities. The bacteria were maintained on nutrient broth (NB) at 37°C and fungus was maintained on potato dextrose agar (PDA) at 28°C.

Antimicrobial activity

The synthesized N-(dibenzo[b,d]furan-1-yl)acetamide **5a**, N-(dibenzo[b,d]furan-1-yl)benzamide **5b**, N-(dibenzo[b,d]furan-1-yl)-[1,1'-biphenyl]-4-carboxamide **5c**, N-(dibenzo [b,d]furan-1-yl)methanesulfonamide **5d** and N-(dibenzo[b,d]furan-1-yl)phenyl methanesulfonamide **5e** compounds are subjected to *in vitro* antibacterial and antifungal activity using agar diffusion (Table I). 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.

Conclusions

A series of novel 1- amino dibenzo[b,d]furan derivatives were synthesised from the preparation of 1,3-dinitrophenol with 2-iodophenol compound. The functional groups were identified by FT-IR spectral analysis. The ^{1}HNMR and ^{13}CNMR establish the chemical structures of the synthesized compound. Among the series of synthesized compounds, compound 5c shows better antibacterial and antifungal activities. Hence compound 5c can be used for further studies and pharmacological applications.

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