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Preparation and Evaluation of Substituted 1-amino dibenzofuran Derivative as Antibacterial and Antifungal Agents

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ABSTRACT

A chain of 1-amino dibenzo[b,d]furan acetamide derivatives were synthesized by reacting through1, 3-dinitrophenol, iodophenolwith 2-chloroacetyl chloride. To understand the chemical structures of the compound ^{1}H NMR,^{13}C NMR spectra were recorded. With the help of the LCMS test the mass of the synthesized compounds was estimated. The FTIR spectral analysis was employed to identify the functional groups present in the title compound. The in vitro antibacterial and antifungal activities of these compounds were also screened for industrial applications.

Keywords: 1-nitro dibenzofuran derivatives;1-amino dibenzo[b,d]furan acetamide; biological activities.

INTRODUCTION

The dibenzofuran was generally isolated from filamentous fungi[1]. The symbiotic association between fungi and algae or cyanobacteria facilitates the biosynthesis of dibenzofurans. A great attention has been gained by dibenzofuran derivatives due to its abundance in lichens and fungi. The dibenzofuran is an important structural motif in many optoelectronic and biological active compounds[2].

Naturally kehokorins A–C, rhodomyrtoxin B, vialinin B, and vanillic acid have dibenzofuran derivatives. These naturally occurring dibenzofurans have shown activity against different types of cancer[3]. In addition to that, natural products possess dibenzofuran moiety exhibit promising biological activities such as anti-inflammatory, antibacterial and inhibit the production of TNF-α.

Not only does the natural dibenzofuran products and also synthetic dibenzofuran derivatives show promising biological activities such as antibacterial, antimycobacterial, antifungal, antiproliferative, potentially anticancer, and anti-inflammatory[4].

The use of dibenzofurans in plants, marine organisms, mushrooms (edible) or myxomycetes has increased the curiosity of researchers to isolate these derivatives from lichens.

Dibenzofuran has been used as an insecticide, a component in heat-transfer oils, a carrier for dyeing and printing textiles, and the synthesis of other compounds. For the study of biodegradation of biaryl ethers and dioxin, these dibenzofuran derivatives have been used as a model compound[5].

The biological activities were evaluated for degradation of dibenzofuran such as *Cunninghamellaelegans, Pseudomonas* sp. strain HH69, *Brevibacterium* sp. Strain DPO 1361, *Sphingomonas* sp. strain RW1, *Pseudomonas aeruginosa*, *Xanthomonas maltophilia*, *Pseudomonas putida* PH-01, and *Terrabacter* sp. strain YK3[6]. The usnic acid possessing dibenzofuran unit shows mycobacterial inhibition. However, it cannot be used as an antitubercular drug because of its myocardial toxicity[7].

A series of dibenzofurans identified as kehokorins A-E have been isolated from two different variants of the slime mould Trichia favoginea[8].

The microbial degradation of dibenzofuran has been studied by several groups. The oxidation was performed cometabolically by bacteria that can grow on other aromatic compounds[9]. The dibenzofuran units make up a major proportion of the macromolecular structure of bituminous coals as evidenced by selective oxidative degradation or thermal treatment used for tar production where the O-heterocyclic compound is released in substantial amount[10].

The aforementioned facts stimulate the scientific community to generate the diversified derivatives of dibenzofuran for pharmacological evaluation[11].

Herein, we report the synthesis of rationale derivatives of 1-amino dibenzofuran. We also presented, its anti-fungal and antibacterial activities.

EXPERIMENTAL

Materials

The Sigma-Aldrich make chemicals 1,3-dinitrobenzene, 2-iodophenol, potassium tert-butoxide, pyridine, 2-chloro acetyl chloride,phenylmethanamine, morpholine, (2,5-dimethoxy phenyl)methanamine,1H-imidazole,2-(methylamino)ethanol, (4-methoxyphenyl) methanamine, 1H-benzo[d]imidazole, piperidin-4-ol, piperidine, (N,N-dimethylethan-1,2-

diamine)and dimethoxyethane were used without purification. Methanol, dichloromethane (DCM), ethyl acetate, hexane,Con.HCl,$SnCl_2$, and triethylamine were also purchased from Sigma-Aldrich. Dry solvents were supplied bySpectrochem.

Instruments and methods

To understand the functional groups that present in the compound, the samples were subjected to FTIR studies using a Perkin- Elmer spectrum 100 series spectrophotometer. The information regarding the presence of protons was obtained from the ^{1}HNMR spectrum recorded on a 400 MHz Varian spectrometer. The presence of carbon was tested by recording^{13} CNMR spectrumwith the help of a 100 MHz Bruker spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded by using Shimadzu mass spectrometer. The melting points were recorded on the SRS Optimelt instrument.

The 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 exposingthem to UV lamp in$KMnO_4$or iodine chamber. A Varian instrument VARIO EL3 series analyzer was used for elemental analysis.

Synthesis and characterization of the compounds

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

In a round bottom flask,dimethoxyethane (20 mL) and pyridine (10 mL) were taken and1,3-dinitrobenzene (1)(5g, 29.74mmol, 1eq),2-iodophenol(2)(6.5g, 29.74mmol, 1eq) wereadded and the solution was stirred it for 10 min at 25°C. Now potassium tertiarybutoxide(6.7g, 59.48mmol, 2eq) was added and heated to 100° C for 16 hrs. The progress of the reaction was monitored by TLC. The reaction mixture was quenched with cold water and cooled to room temperature.Then it was extracted with ethyl acetate (2 x 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 (400MHz, 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)

The stannous chloride (4 g, 21.12mmol, 1.5eq) was added with thestirred solution of compound (3) (3g, 14.08mmol) in conc.HCl (25 mL) at 0° C, in portionswise. The reaction was stirred for 4hrs at 0° C and the reaction was monitored by TLC. Now it was quenched with ice water. The reaction mixture was extracted with ethyl acetate. The moisture content was removed and dried with the help of $MgSO_4$ and concentrated. The crude residue was purified by column chromatography to get 1-amino dibenzo[b,d]furan(**4**) (2g, 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 (400MHz, 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. obtained:78.70% C, 4.79% H, 7.86% Nand 8.58%O. LCMS $[M+1]^+$:m/z 184.21.

Synthesis of 2-chloro-N-(dibenzo[b,d]furan-1-yl)acetamide (5)

The compound-4 (2g, 10.86mmol, 1eq)was dissolved in DCM (2mL) andcooled to 0°C. Then the solution was added to chloro acetyl chloride (2.2g, 19.46mmol, 1.1 eq) and stirred for 4hrs. After completion of reaction, ice water was added and extracted with DCM. The organic layer was washed with water, brine solution, dried and concentrated. The crude was purified by column chromatography to get 2-chloro-N-(dibenzo[b,d]furan-1-yl)acetamide (5) (1g, Yield: 57.5%).LCMS: 95.3% (purity), m.pt.180-188°C. IR (KBr, cm^{-1}): ν_{max} 3246 (amide N-H), 1664 (C=O), 1453-1592 (C=C), 1195-1277(C-O, C-N), 716 (C-Cl).^{1}HNMR (400MHz, DMSO-d_6, ppm): δ8.60 (s,1H,-CONH),8.20-8.08 (m, 3H, Ar-CH),8.08-8.06 (d, 4H, *J*=8.4Hz,Ar-CH),4.66 (s, 2H, -CH_2).^{13}CNMR (100MHz, DMSO-d_6, ppm): δ 40.61, 43.67, 109.69, 111.80, 119.12, 120.27, 122.75, 123.40, 123.91, 127.99, 132.22, 155.65, 156.44, 165.79.For $C_{14}H_{10}ClNO_2$, calculated: 64.75% C, 3.88% H, 13.65% Cl, 5.39% N and 12.32% O,obtained: 64.70% C, 3.96% H, 13.60% N and 12.26% O.LCMS $[M+1]^+$:m/z 259.69.

Representative procedure to prepare amide derivative*(6a-e)*

To a stirred solution of compound (5) (100 mg, 3.85 mmol) in DCM (2mL), TEA (0.5 mL, 1.09 mmol, 2 eq) was added and stirred for 15minutes.The substituted amines (1.2eq) were added dropwise, heated to 70°C and maintained for 4hours. After completion of the reaction, quenched with ice water and cooled to room temperature.It was extracted with DCM. The organic layer was dried and concentrated. Finally, the residue was purified by column chromatography to get the desired product (**6a-e**).The scheme of synthesis of the N-(dibenzo[b,d]furan-1-yl) substituted amides (6a-e) was carried out as shown in Figure 1.

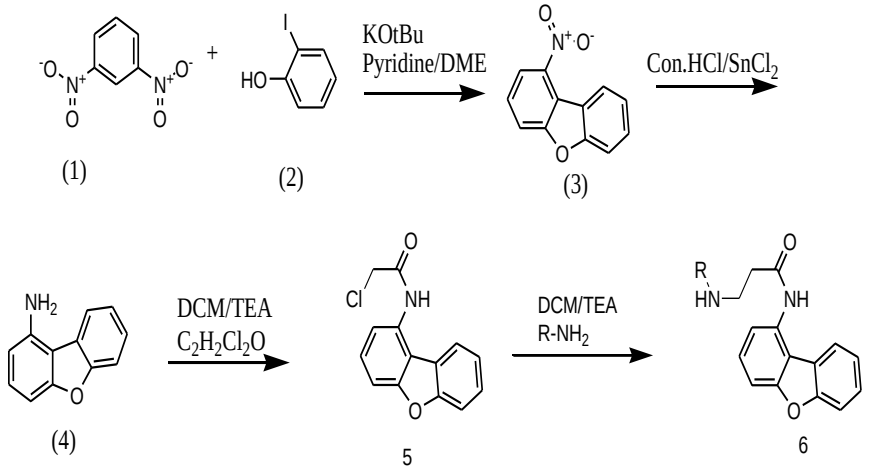
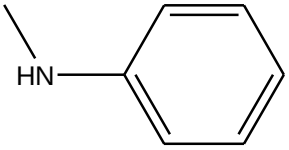
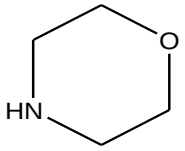
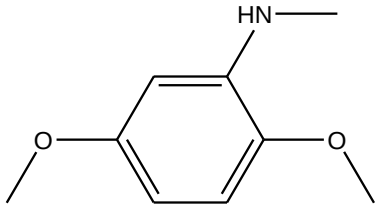
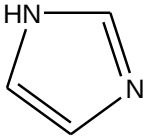
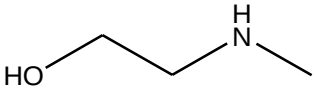


Fig.1. Scheme of the reactions

Table-1 Physical constants of 6(a-e)

Product	Aryl/alkyl Substituents (-RX)	m.p (°C)	R_f
6a		100-105	0.52
6b		163-167	0.58
6c		102-125	0.61
6d		130-152	0.63
6e		122-130	0.54

Synthesis of 2-(benzylamino)-N-(dibenzo[b,d]furan-1-yl)acetamide(6a)

Yield: 85 mg, 65%, white solid, LCMS: 95.5% (purity), m.pt.100-105°C. IR (KBr, cm^{-1}): ν_{max} 3296 (amide N-H), 1669 (C=O), 1591-1410 (C=C), 1247-1049(C-O, C-N).^{1}HNMR (400MHz, DMSO-d_6, ppm):δ8.03 (s, 1H, -CONH), 7.94-7.92 (d, 2H, *J*=6.8Hz,Ar-CH), 7.74-7.72 (d, 2H, *J*=8Hz,Ar-CH), 7.55-7.50 (m, 2H, Ar-CH), 7.48-7.44 (t, 2H, *J*=6.8Hz,Ar-CH), 7.39-7.35 (t, 2H, *J*=7.4Hz,Ar-CH),7.31-7.25 (m, 2H, Ar-CH),3.90 (s, 2H, -CH_2),3.46 (d, 2H, -CH_2), 2.50 (m, 1H, -NH).^{13}CNMR (100 MHz,DMSO-d_6,ppm):δ39.98, 40.19, 40.40, 40.61, 52.57, 53.45, 107.93,112.10,115.79,122.44, 122.57, 123.48, 127.38,127.73,128.61,128.80,133.49,140.43,155.43, 156.34,170.82.For $C_{21}H_{18}N_2O_2$, calculated: 76.34% C, 5.49% H, 8.48% Nand 9.69%O,obtained:76.40% C,5.40% H,8.44% Nand 9.68%O.LCMS $[M+1]^+$:m/z 330.38.

Synthesis ofN-(dibenzo[b,d]furan-1-yl)-2-morpholino acetamide (6b)

Yield: 80mg, 60% off white solid, LCMS: 95.3% (purity). m.pt.163-167°C. IR (KBr, cm^{-1}): ν_{max} 3297 (amide N-H), 1683 (C=O), 1594-1413 (C=C), 1240-1169 (C-O, C-N).^{1}HNMR (400MHz, DMSO-d_6, ppm) :δ 8.04 (s, 1H, -CONH), 7.94-7.93 (d, 1H, *J*=7.2Hz,Ar-CH), 7.75-7.73 (d, 1H, *J*=8.4Hz,Ar-CH), 7.57-7.47 (m, 5H, Ar-CH), 7.37-7.29 (m, 4H, Ar-CH), 3.83-3.74 (t, 2H, *J*=8.3Hz, -CH_2), 3.46 (s, 2H, -CH_2), 2.51-2.50 (t, 2H, *J*=1.6Hz, -CH_2). ^{13}CNMR (100MHz, DMSO-d_6, ppm): δ 40.61, 52.85, 55.39,55.53, 107.90,112.10, 115.70, 122.41,122.58,123.53,127.74, 129.88, 132.32, 133.50, 155.44, 156.34,158.77, 170.86.For $C_{18}H_{18}N_2O_3$, calculated: 69.66% C, 5.85% H, 9.03% Nand 15.47%O,obtained:69.67% C, 5.80% H, 9.10% N and 15.41% O.LCMS $[M+1]^+$:m/z 310.35.

Synthesis of N-(dibenzo[b,d]furan-1-yl)-2-((2,4-dimethoxybenzyl)amino)acetamide(6c)

Yield: 95mg, 67%, white solid, LCMS: 95.4% (purity), m.pt.102-125°C. IR (KBr, cm^{-1}): ν_{max} 3256 (amide N-H),1683 (C=O), 1414-1594(C=C), 1285-1170 (C-N, C-O), 1027 (C-O-C).^{1}HNMR (400MHz, DMSO-d_6, ppm): δ8.00 (s, 1H, -CONH), 7.99-7.97(t, 1H, *J*=7.6Hz, Ar-CH), 7.73-7.50 (d, 2H, *J*=8Hz,Ar-CH), 7.55-7.48 (m, 5H, Ar-CH), 7.29-7.23 (m, 3H, Ar-CH), 6.50-6.49 (d, 3H, *J*=6.4Hz, Ar-CH), 3.77-3.57 (s, 6H, -2CH_3), 2.50 (m, 1H, -NH).^{13}CNMR (100MHz, DMSO-d_6, ppm): δ 39.98, 40.19, 40.40, 40.61, 52.41, 52.85, 55.39, 55.53, 107.90, 112.10, 114.19, 115.70, 122.41, 122.58, 123.53, 127.74, 128.48, 129.88, 132.32, 133.50, 155.44, 156.34, 158.77.For $C_{23}H_{22}N_2O_4$, calculated: 70.75% C, 5.68% H, 7.17% N, 16.39% O,obtained:70.72% C, 7.18% H, 7.19% N, and 16.33%O.LCMS $[M+1]^+$:m/z 390.43.

Synthesis of N-(dibenzo[b,d]furan-1-yl)-2-(1H-imidazol-1-yl)acetamide (6d)

Yield: 120mg, 65%, white solid, LCMS: 95.2% (purity), m.pt.130-152°C. IR (KBr, cm^{-1}): ν_{max}3306 (amide N-H), 1679 (C=O), 1590-1409 (C=C),1236-1113 (C-N, C-O).^{1}HNMR (400MHz, DMSO-d_6, ppm) : δ 8.16 (s, 1H, -CONH), 7.85-7.83 (t, 3H, *J*=8.8Hz,Ar-CH), 7.77-7.75 (d, 2H, *J*=8.4Hz, Ar-CH), 7.59-7.55 (m, 2H, Ar-CH), 7.52-7.47

(m, 3H, N-CH), 5.76 (s, 2H, -CH_2). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 39.35,39.56,39.77, 39.98,40.19, 40.40, 40.61, 53.90, 62.63, 66.76, 112.19, 122.60, 123.51, 127.85, 128.38, 129.12, 129.45. For $C_{17}H_{13}N_3O_2$, calculated: 70.09% C, 4.50% H, 14.42% N,10.98%O, obtained:70.07% C, 4.43% H, 14.43% N,10.95%O.LCMS $[M+1]^+$:m/z 291.30.

Synthesis of N-(dibenzo[b,d]furan-1-yl)-2-((2-hydroxyethyl)(methyl)amino)acetamide (6e)

Yield: 80mg, 65%, white solid, LCMS: 95.7% (purity), m.pt.130-152°C. IR (KBr, cm^{-1}): ν_{max}3374 (-OH), 3255 (amide N-H), 1677 (C=O), 1591-1413 (C=C), 1244-1114 (C-N, C-O). ^{1}HNMR (400MHz, DMSO-d_6, ppm) : δ 8.18 (s, 1H, -CONH),7.98-7.96 (d, 2H, *J*=7.2Hz,Ar-CH),7.78-7.76 (d, 2H, *J*=8Hz, Ar-CH), 7.60-7.52 (m, 1H, Ar-CH), 7.50-7.46 (t, 2H, *J*=7.6Hz, Ar-CH), 3.60-3.57 (m, 2H, -CH_2), 3.34 (s, 2H, N-CH_2), 2.93-2.90 (t, 2H, *J*=5.8Hz, N-CH_2), 2.50 (s, 3H, N-CH_3), 2.43-2.38 (t, 1H, *J*=9.8Hz, -OH). ^{13}CNMR (100 MHz, DMSO-d_6, ppm): δ 40.61, 55.38, 62.49, 65.92, 107.89, 112.29, 115.15, 115.52, 122.16, 122.59, 123.50, 127.82, 128.55, 133.54, 155.45, 156.34, 169.41. For $C_{17}H_{18}N_2O_3$, calculated: 68.44% C, 6.08% H, 9.39% N, 16.09% O,obtained:68.40% C, 6.03% H, 9.43% N, 16.15% O.LCMS $[M+1]^+$:m/z 298.34.

RESULTS AND DISCUSSION

Chemistry aspect

The starting materials were 1, 3-dinitrobenzene and 2-iodophenol in dimethoxyethane (DME). The obtained intermediate product 1-nitro dibenzo[b,d]furan(3) , 1-amino dibenzo[b,d]furan(4), and 2-chloro-N-(dibenzo[b,d]furan-1-yl)acetamide (5)was then refluxed. Theamine derivatives in dichloromethane (DCM), triethylamine (TEA) with an added acid chloride to get desired compounds (6a-e).

In the IR spectra, the characteristic N–H bands and amide functions were observed in the range 3245–3369 cm^{-1}. In the NMR spectra, peaks at about δ2.22–3.62 ppm, δ 2.50–2.54 ppm and δ 10.15–10.17 ppm were seen assigning to CH_3, CO-CH_3, and NH protons respectively. The M+1 peak in mass spectra were agreedwith the calculated molecular weight of the title compounds (6a-e). The weight percentage of C, H and N elements obtained from elemental analysis agree with the 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*, *Escherichia coli*,*Staphylococcus aureus* and fungal strains of *Aspergillus niger*, *Candida albicans*, *Candida tropicalis* were obtained fromMicro lab, Institute of Research and Technology,Arcot, Vellore,Tamilnadu,

India and were used for testingmicrobial 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 2-(benzylamino)- N-(dibenzo[b,d]furan-1-yl)acetamide (6a),N-(dibenzo[b,d]furan-1-yl)-2-morpholino acetamide (6b), N-(dibenzo[b,d]furan-1-yl)-2-((2,4-dimethoxybenzyl)amino)acetamide(6c), N-(dibenzo[b,d]furan-1-yl)-2-(1H-imidazol-1-yl) acetamide (6d), N-(dibenzo[b,d]furan-1-yl)-2-((2-hydroxyethyl)(methyl)amino)acetamide (6e), compounds are subjected to *in-vitro* antibacterial and antifungal activities using agar diffusion.The nutrients agar and PDA medium (20 mL)are used for each sterile Petri dish (90 mm) and then left for solidification. After this, 100 μL of bacterial apprehension was loaded on the plates.

Five minutes later, a sterile filter paper disc (6 mm) containing 5 μL of the compound was loaded 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.The *ciprofloxacin* and *ketoconazole* were served as standard. The obtained results were presented in Table.1.

From the table, the compound 6(C) shows better antibacterial and antifungal activities. The fundamental chemistry behind this is the free radicals are inhibiting the normal metabolism of the bacteria or fungi by damaging the cell organelles and causes cell death. The presence of oxy radicals, which are active radicals, is responsible for the better performance of the compound 6 (c).

Table.1. Antibacterial and fungus activities of the compounds

Organism	Zone of inhibition in mm						
	Bacterial						
	Com5	6A	6B	6C	6D	6E	*Ciprofloxacin*
Staphylococcus aureus	***8.4***	**-**	***10.6***	***8.6***	**-**	**-**	**20.5**
Escherichia coli	***9.7***	**-**	***10.5***	***10.7***	**-**	**-**	**21.6**
Bacillus cereus	***8.6***	***9.4***	***9.7***	***11.5***	**-**	**-**	**23.8**
	Fungi						
Aspergillus niger	**-**	**-**	**-**	***10.6***	**-**	**-**	***Ketoconazole*** ***12.3***
Candida albicans	***9.5***	***10.4***	***10.5***	***10.5***	**-**	**-**	**11.6**
Candida tropicalis	***7.4***	***8.6***	***8.5***	***12.4***	**-**	**-**	**15.5**

CONCLUSIONS

A series of novel 1- amino dibenzo[b,d]furan derivatives were synthesized 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, compounds 6d-e showed no activity on the microbes used and compound 6c shows better antibacterial and antifungal activities. Hence compound 6c can be used for further studies and pharmacological applications.

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