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Synthesis and antimicrobial activity of novel 1*H*-benzo[*d*]imidazole-aryl sulfonamide/amide derivatives

Rahul I Jadhav[a], Nathrao A Kedar*[a,b] & Kamlesh H Chavan[a]

[a] Research Centre and Post Graduate Department of Chemistry, Netaji Subash Chandra Bose Arts Commerce and Science College, Vazirabad, Nanded 431 601, India

[b] Department of Chemistry, Dayanand Science College, Latur 413 512, India

E-mail: dnakedar071@gmail.com

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A series of novel *N*-(6-(propylthio)-1*H*-benzo[*d*]imidazol-2-yl)-aryl sulfonamide and amide derivatives have been synthesized. The structure of all newly synthesized 1*H*-benzo[*d*]imidazole derivatives have been confirmed using spectral analysis and evaluated for antibacterial, antifungal potential. Biological evaluations study reveals that the compounds **2, 3, 5, 7** and **15** are found to have moderate to good antimicrobial activity (MIC range of 10–20 mg/mL) against the bacterial strains *Staphylococcus aureus* ***ATCC 6538*** and *Escherichia coli* ***ATCC 8739*** in comparison to standard Ampicillin as well as fungal strains *Candida albicans* ***ATCC 10231*** and *Aspergillus niger* ***ATCC 6275*** in comparison to Fluconazole. These results suggest that this could be the start of an extensive medicinal chemistry program to identify the 1*H*-benzo[*d*]imidazole-aryl sulfonamide based potent antimicrobial agents.

Keywords: 1*H*-Benzo[*d*]imidazole, sulfonamide, amide, antifungal, antibacterial, MIC

Despite of the advances in the area of antimicrobial drug discovery, the emergence of the multidrug-resistance microbial pathogens is a growing concern. The development of the antibacterial agents such as tetracyclines, streptogramines, quinolones, β-lactams, linezolid, etc. improved life quality of patient suffering from bacterial infections. Despite of the advances in antibacterial drug discovery, the deaths due to the infectious diseases are the foremost reason globally. This urges us to discover the newer class of antibacterial agents[1-4].

Benzimidazole is a privileged scaffold in medicinal chemistry and possess an array of biological activities[5-7] such as anti-inflammatory[8], anti-malarial[9], anti-HIV[10], anti-cancer[11], anti-ulcer[12], anti-hypertensive[13], anti-diabetic[14], anti-anthelmintic[15], anti-tubercular[16,17], anti-microbial[18,19], *etc*. Benzimidazole core containing compounds viz. Albendazole (**B**), Mebendazole (**F**), fenbendazole (**E**), omeprazole (**A**), lansprazole etc. have been reached to market for various clinical applications (Figure 1). The Albendazole (**B**, Figure 1) is an anthelmintic that was recommended by the WHO to treat soil transmitted helminth infections, because of its effectiveness, safety and low price, albendazole is one of the main drugs used in PC programs[20].

Similarly the amide and sulfonamide are important functional groups in the medicinal chemistry with attractive biological activities. The sulfonamide functionality found in many biologically active molecules and more than 112 marketed drugs possess the sulfonamide functionality[21]. The first antibiotics sulfanilamide acts as an antibacterial agent with this functionality and its discovery led to the award of Nobel Prize. The antibacterial activity of the sulfonamide is due to the inhibition of bacterial tetrahydropteroic acid synthetase[22]. Similarly amide is a basic building unit of protein and human body and this functionality found in many marketed drugs and natural products. Moreover the amide and sulfonamides are the bioisosteres of each other[23].

In view of the above mentioned considerations, we designed the novel 1*H*-Benzo[*d*]imidazole derivatives bearing amide and sulphonamide groups (Figure 2). The single molecule containing the privilege 1*H*-Benzo[*d*]imidazole scaffold in antibacterial drug discovery and sulfonamide/ amide groups having potential for inhibition of bacterial tetrahydropteroic acid may be more beneficial for the treatment of the infectious diseases caused by multi-drug resistant strains.

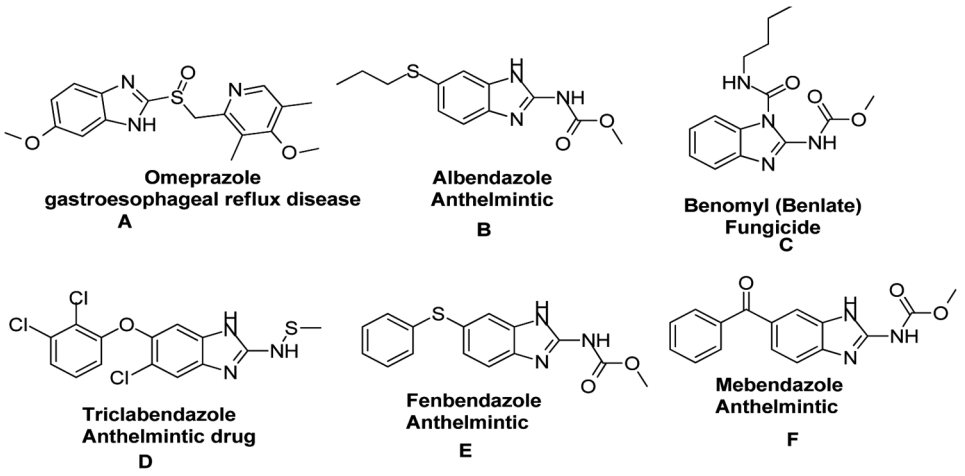
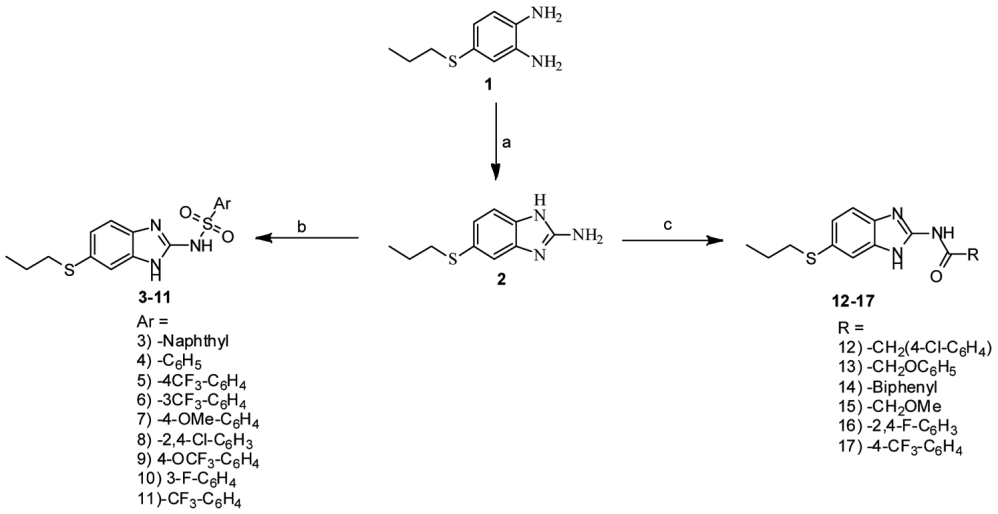


Figure 1 — Molecular structure of representative marketed 1*H*-benzo[*d*]imidazoles



Reagents and conditions: (a) *S*-Methylthiourea hemisulfate, AcOH, EtOAc, 55-60°C, 8 h; (b) $ArSO_2Cl$, triethylamine, DCM, RT, 1-2 h; (c) RCOCl, triethylamine, DCM, RT, 1-2 h

Scheme I — Synthesis of novel benzo[*d*]imidazole derivatives bearing sulfonamides **3-11** and amides **12-17**

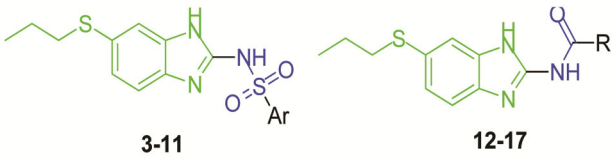


Figure 2 — Molecular structure of the designed benzo[*d*]imidazole derivatives bearing amide **12-17** and sulphonamide groups **3-11**

Results and Discussion

Chemistry

The synthesis of a designed novel series of 1*H*-benzo[*d*]imidazole derivatives bearing sulfonamide (3 -11) and amide (12-17) functionalities is outlined in Scheme I. The key intermediate of 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (**2**) was synthesized as per the reported procedure[24]. The reaction of the *S*-methylthiourea hemisulphate with 4-(propylthio) benzene-1,2-diamine in presence of the acetic acid in ethyl acetate at 55-60 °C produces 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (**2**). The required *S*-methylthiourea hemi sulphate was obtained by reaction of thiourea (1.0 Eq.), water (0.7 vol.), and dimethylsulphate DMS (0.55 Eq.) after heating at 85-90 °C for 24 h. The designed novel benzo[*d*]imidazoles derivatives bearing sulfonamides (**3-11**) and amides (**12-17**) were prepared by coupling of 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (**2**) and suitable sulfonyl chloride/acid chloride in presence of triethylamine in dichloromethane at

ambient temperature. The structures of all novel 1H-benzo[d]imidazoles (2-17) were confirmed by spectral analysis: IR, NMR ^{1}H, ^{13}C and Mass Spectrometry.

Biology

Antimicrobial potential of the newly synthesized 6-(propylthio)-1*H*-benzo[*d*]imidazole (**2-17**) were evaluated against selected bacterial strains (*Staphylococcus aureus- **ATCC 6538***, *Escherichia coli- **ATCC 8739**)*, and fungal strains (*Candida albicans- **ATCC 10231***, *Aspergillus niger- **ATCC 6275)*** by the Agar well diffusion procedure with little modifications**.** The results of biological activity were illustrated in Table I and Table II.

The Antibacterial activities Zone of Inhibition (ZOI) data is represented in Table I and Minimum Inhibitory Concentration (MIC) data for the compounds showing activity in terms of zone of inhibitions are represented in Table II. All the tested newly synthesized benzo[*d*]imidazole derivatives possess moderate to good microbial activity in terms of the zone of inhibition. From the series of the tested benzo[*d*]imidazole derivatives, **2, 3, 5, 7** and **15** exhibit moderate to good antimicrobial activity in terms of zone of inhibition, in comparison to the reference compounds ampicillin and fluconazole. While the inhibitors **4, 6, 8, 9, 10** showed moderate to good antibacterial activity, however, did not show antifungal potential. The compounds **11, 12, 14, 16, 17** were found inactive towards the tested antibacterial and antifungal strains. If we compare the activity of newly synthesized amide (**12-17**) and sulfonamide (**3-11**), most of the compounds in the sulfonamide series exhibit the antibacterial and antifungal potential. However, in the amide series only the compound **15** bearing CH_2OCH_3 substitution possesses the antibacterial and antifungal activity. If we compare the activity trend among the sulfonamide derivatives, the interesting trends in Structure Activity Relationship (SAR) is observed, where the inhibitor **2** bearing -2-Naphtyl sulfonamide showed good antibacterial activity but moderate activity towards the tested antifungal stain. The inhibitor **5** bearing 4-trifluoromethyl-benzenesulfonamide and **7** having 4-OMe-benzenesulfonamide showed good activity against both antifungal and antibacterial strains. While the compound **6** bearing $-CF_3$ at meta position of benzene ring *and* compound **9** bearing $–OCF_3$ at para position of benzene ring of sulfonamide showed low potency against *Staphylococcus aureus **ATCC 6538*** but comparable potency against *Escherichia coli **ATCC 8739.***

Table I — Antimicrobial activities Zone of Inhibition (mm) of novel 1*H*-benzo[*d*]imidazole-aryl sulfonamide/amide derivatives [ZOI (mm) [a] values 20 mg/mL against Ampicillin (35 mm) and Flucanozole (32.5 mm)][a]

Compd	Zone of Inhibition (mm)			
	Bacterial Strains		Fungal Strains	
	Staphylococcus aureus *ATCC 6538*	*Escherichia coli* *ATCC 8739*	*Candida albicans* *ATCC 10231*	*Aspergillus niger* *ATCC 6275*
2	16.0	17.0	12.0	10.0
3	12.0	15.0	3.4	1.0
4	2.0	5.0	–	–
5	9.0	10.0	11.8	7.0
6	4.0	11.0	–	–
7	10.0	12.0	6.0	8.0
8	1.0	1.0	–	–
9	3.0	9.0	–	–
10	5.0	6.0	–	–
11	–	–	–	–
12	–	–	–	–
13	3.4	–	–	–
14	–	–	–	–
15	21.0	16.8	9.2	3.4
16	–	–	–	–
17	–	–	–	–

Values are the average of 3 readings. Activity was seen up to 20 mg/mL.

Table II — Antimicrobial activities MIC values (mg) of novel 1*H*-benzo[*d*]imidazole-aryl sulfonamide/amide derivatives. [MIC values (mg)[b] values 20 mg/mL against Ampicillin (0.25 mg) and Flucanozole (0.20 mg)]

Compd	MIC values (mg/mL)			
	Bacterial Strains		Fungal Strains	
	Staphylococcus aureus ATCC 6538	*Escherichia coli ATCC 8739*	*Candida albicans ATCC 10231*	*Aspergillus niger ATCC 6275*
2	10	10	15	15
3	15	15	20	20
4	20	20	–	–
5	15	15	20	20
6	15	15	–	–
7	10	10	15	15
8	20	20	–	–
9	20	20	–	–
10	20	20	–	–
13	15	–	–	–
15	10	10	15	15

Activity was seen up to 20 mg/mL, Values are the average of 3 readings

The sulfonamide analogous bearing C_6H_5 , -3CF_3-C_6H_4 , -2,4-Cl-C_6H_3, 4-OCF_3-C_6H_4, 3-F-C_6H_4 and CF_3-C_6H_4 were moderate inhibitors of *Staphylococcus aureus* ***ATCC 6538*** but exhibited comparable potency against *Escherichia coli* ***ATCC 8739*****,** however, inactive against the tested antifungal stain. No activity was observed in the case of amide analogues 12, 14, 16 and 17 up to a concentration of 20 mg/mL against mentioned bacteria.

From the results of the biological activities (Table I and Table II), it is also clear that the designed modification have potential against the bacterial and fungal strains. Hence, this can be considered as the good start for the extensive medicinal chemistry programme in order to find out the potent antimicrobial agent.

Experimental section

Materials and Methods

All the reagents, chemicals and solvents were procured from Sigma Aldrich, Spectrochem, Combiblocks and finar unless otherwise mentioned and used as such without any purifications. The TLC used the pre-coated silica gel 60 F_{254} plates from Merck and visualised under UV light or using the TLC stains. The IR were recorded on (Perkin-Elmer FT-IR), Bruker AVANCE NMR instrument were used to record the NMR with frequency of 300 MHz or 400 MHz and Tetramethylsilane is used as internal reference, J values expressed in Hz, and d value expressed in ppm. Purification was performed using the silica gel (100-200#) column chromatography using the EtOAc in *n*-hexane as elute. The mass spectra recorded on the Thermo Finnigan-TSQ Quantum Ultra (triple Quad).

Synthesis of 6-(propylthio)-1*H*-benzo[d] imidazol-2-amine, 2

Dimethylsulphate (0.55 mmol) was slowly added to a stirred solution of Thiourea (1.0 mmol), in H_2O (0.7 vol.) at 25 – 30 °C. Resulting reaction mixture was stirred at 85-90 °C for 24 h. The reaction mixture was cooled to rt and diluted with water. 25% aqueous NaOH was added slowly until pH of the reaction mixture is 7.0 to 7.5. Ethyl acetate was added and stirred for 10 min, the layer was separated, and aqueous layer was extracted back with ethyl acetate (2 x 100 mL). The water and brine wash was given to combined organic layers. Anhydrous sodium sulphate was used for drying of organic layers; sodium sulphate was removed by filtration to get the ethyl acetate solution of *S*-methylthiourea hemisulphate. To this 1, 4-(propylthio) benzene-1, 2-diamine (0.59 mmol) and acetic acid (1.8 mmol) were added at rt. The resulting reaction mixture at 55-60 °C for 8 h, the reaction mixture was cooled to rt and stirred for 1 h. The precipitated solid was collected by filtration and suck dried to get crude product. Purification was done by using hot water (15 vol.) slurry at 55-60 °C for 3 h filtration. The solid is dried under vacuum at 55-60 °C to get a 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (2) as an Off-white solid, yield 82%, mp. 39-40 °C ; IR (KBr) λmax/cm^{-1} 3374 (N–H), 3046 (C–H), 1558 (C=C), 1441 (N-H bend), 1114 (C–H), 804 (C–N); ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 0.86-0.91 (t, J = 7.3 Hz, 3H), 1.42-1.50 (m, J = 7.4 Hz,2H), 2.71-2.76 (t, J = 7.4 Hz, 2H), 6.18 (s, 2H), 6.85-6.88 (d, J = 8.0

Hz, 1H), 6.98-7.00 (d, *J* = 8.0 Hz, 1H), 7.09-7.10 (s, *J* = 1.5 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.51, 22.59, 37.81, 112.21, 115.29, 123.45, 139.11, 156.42; MS (APCI): m/z 207.3[M+H]$^+$.

General procedure for the synthesis of compounds 3-11

Substituted sulfonyl chloride (1.1 eq.) was dropped slowly to a stirred mixture of 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (1 eq.) and triethylamine (1.1 eq.) in DCM (10 mL). The reaction mixture was stirred at room temperature for 1-2 h and the reaction progress was monitored by TLC. The reaction mixture was diluted with DCM and washed with water. Organic layer was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and filtered. Filtrate was evaporated under vacuum to get crude product, the crude was chromatographed using silica gel (100–200 #) and elute used is 0-30% ethyl acetate in petroleum ether.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d] imidazol-2-yl) naphthalene-1-sulfonamide, 3: Off-white solid, Yield 85 %, mp 49-50 °C; IR (KBr) λmax/cm^{-1} 3159 (N–H), 2922 (C–H), 1586 (C=C), 1458 (N-H bend), 1261 (SO_2NH), 1113 (C–H), 796 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.81-0.90 (t, *J* = 7.3 Hz, 3H), 1.32-1.60 (m, *J* = 7.5 Hz, 2H), 2.61-2.80 (t, *J* = 7.1 Hz, 2H), 7.30-7.36 (d, *J* = 8.0 Hz, 1H), 7.55-7.60 (d, *J* = 7.7 Hz, 1H), 7.65 (s, *J* = 1.5 Hz, 1H), 8.75-8.78 (d, *J* = 8.4 Hz, 1H), 8.26-8.29 (d, *J* = 7.1 Hz, 1H), 8.08-8.11 (d, *J* = 8.1 Hz, 1H), 7.98-8.00 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.36, 22.44, 30.27, 107.17, 111.85, 1119, 124.89, 126.37, 126.86, 127.07, 127.78, 128.34, 129.05, 130.37, 131.83, 133.28, 134.29, 138.65, 139.03, 150.84; MS (APCI): m/z 397.5[M+H]$^+$.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d] imidazol-2-yl) benzenesulfonamide, 4: Off-white solid, Yield 88%, mp 48-49 °C; IR (KBr) λmax/cm^{-1} 3143 (N–H), 2998 (C–H), 1555 (C=C), 1451 (N-H bend), 1366 (SO_2NH), 1172 (C–H), 819 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.88-0.92 (t, *J* = 6.9 Hz, 3H), 1.41-1.48 (m, *J* = 7.0 Hz, 2H), 2.78-2.83 (t, *J* = 6.9 Hz, 2H), 6.96 (s, 1H), 7.03-7.06 (d, *J* = 7.8 Hz, 1H), 7.12-7.14 (d, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 7.57 (s, *J* = 1.5 Hz, 1H), 7.97-7.99 (d, *J* = 7.2 Hz, 2H), 7.71-7.74 (t, *J* = 6.8 Hz, 1H), 7.61-7.64 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.47, 22.43, 37.17, 114.85, 116.84, 126.94, 127.20, 128.41, 130.58, 131.0, 135.95, 136.91, 142.45, 152.88; MS (APCI): m/z 347.5[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d] imidazol-2-yl)-4-(trifluoromethyl) benzenesulpho namide, 5: Light brown solid, Yield 82%, mp 54-55 °C; IR (KBr) λmax/cm^{-1} 3141 (N–H), 2922 (C–H), 1631 (C=C), 1461 (N-H bend), 1318 (SO_2NH), 1124 (C–H), 1062 (C-F), 801 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.87-0.92 (t, *J* = 7.3 Hz, 3H), 1.41-1.48 (m, *J* = 7.2 Hz, 2H), 2.79-2.84 (t, *J* = 7.1 Hz, 2H), 7.06-7.08 (d, *J* = 8.2 Hz, 1H), 7.14 (s, 1H), 7.17 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 1H) , 7.57 (s, *J* = 1.3 Hz, 1H), 8.18-8.21 (d, *J* = 8.3 Hz, 2H), 8.02-8.04 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.55, 22.39, 35.43, 113.02, 116.71, 122.09, 124.05, 125.25, 128.76, 131.26, 132.35, 133.0, 137.99, 144.13, 152,93; MS (APCI): m/z 403.6[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d] imidazol-2-yl)-3-(trifluoromethyl) benzene sulphonamide, 6: Off-white solid, Yield 80%, mp 132-134 °C; IR (KBr) λmax/cm^{-1} 3127 (N–H), 2948 (C–H), 1554 (C=C), 1465 (N-H bend), 1320 (SO_2NH), 1132 (C–H), 1054 (C-F), 819 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.86-0.91 (t, *J* = 7.3 Hz, 3H), 1.42-1.54 (m, *J* = 7.3 Hz, 2H), 2.82-2.87 (t, *J* = 7.1 Hz, 2H), 6.96-6.99 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 1H), 7.07 (s, 1H), 7.32 (s, *J* = 1.3 Hz, 1H) , 7.59-7.62 (d, *J* = 8.4 Hz, 1H), 8.36 (s, *J* = 1.5 Hz, 1H), 8.25-8.28 (d, *J* = 8.1 Hz, 1H), 8.13-8.16 (d, *J* = 7.8 Hz, 1H), 7.84-7.89 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.54, 22.40, 35.49, 113.03, 116.76, 122.13, 124.03, 125.25, 128.78, 130.71, 131.25, 132.34, 132.62, 133.03, 138.02, 144.14, 152.94; MS (APCI): m/z 415.5[M+H]+.

Synthesis of 4-methoxy-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) benzene sulphonamide, 7: Light brown solid, Yield 84%, mp 67-68 °C; IR (KBr) λmax/cm^{-1} 3138 (N–H), 2961 (C–H), 1592 (C=C), 1464 (N-H bend), 1376 (SO_2NH), 1116 (C–H), 1024 (C-O), 802 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.88-0.93 (t, *J* = 7.3 Hz, 3H), 1.46-1.54 (m, *J* = 7.2 Hz, 2H), 2.83-2.88 (t, *J* = 7.1 Hz, 2H), 3.76-3.78 (s,3H), 7.14-7.18 (d, *J* = 8.3 Hz, 1H), 7.24 (s, 1H), 7.46 (s, 1H), 7.49-7.54 (d, *J* = 7.05 Hz, 1H), 7.59-7.60 (s, *J* = 1.0 Hz, 1H), 8.60 (d, *J* = 8.3 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 6.80-6.85 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.52, 22.41, 35.41, 36.20, 112.98, 116.66, 122.06, 125.33, 126.80, 127.87, 128.35, 130.94, 133.09, 140.57, 144.11, 151.13, 152.94; MS (APCI): m/z 377.5[M+H]+.

Synthesis of 2, 4-dichloro-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) benzene sulphonamide, 8: White solid, Yield 88%, mp 68-70 °C; IR (KBr) λmax/cm^{-1} 3122 (N–H), 2945 (C–H), 1552 (C=C), 1448 (N-H bend), 1373 (SO_2NH), 1113 (C–H), 812 (C–N), 641(C-Cl); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.87-0.91 (t, *J* = 7.3 Hz, 3H), 1.43-1.55 (m, *J* = 7.4 Hz, 2H), 2.81-2.86 (t, *J* = 7.2 Hz, 2H), 6.84-6.87 (d, *J* = 8.4 Hz, 1H), 7.73-7.77 (d, *J* = 8.7 Hz, 1H), 7.92-7.93 (s, *J* = 2.1 Hz, 1H), 8.26-8.29 (d, *J* = 8.6 Hz, 1H), 7.14 (s, J *J* =2.2 Hz 1H), 7.11-7.13 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.57, 22.41, 37.41, 112.37, 116.81, 121.73, 128.83, 128.99, 132.63, 132.93, 133.55, 134.06, 141.43, 143.62, 153.32; MS (APCI): m/z 416.3[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl)-4-(trifluoromethoxy) benzene sulphonamide, 9: White solid, Yield 85%, mp 49-50 °C; IR (KBr) λmax/cm^{-1} 3102 (N–H), 2922 (C–H), 1553 (C=C), 1463 (N-H bend), 1375 (SO_2NH), 1254 (C-O), 1164 (C–H), 1045 (C-F), 813 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.86-0.91 (t, *J* = 7.2 Hz, 3H), 1.45-1.52 (m, *J* = 7.3 Hz, 2H), 2.82-2.86 (t, *J* = 7.2 Hz, 2H), 7.07 (s, 1H), 7.25 (s, 1H), 7.54-7.57 (d, *J* = 8.4 Hz, 1H), 7.60-7.63 (d, *J* = 8.6 Hz, 1H), 7.68 (s, *J* = 1.5 Hz, 1H) 8.12-8.37 (d, *J* = 8.8 Hz, 2H), 6.95-6.98 (d, *J* = 8.4 Hz, 1H), 7.15-7.18 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.52, 22.42, 35.46, 112.94, 116.68, 118.43, 120.72, 122.05, 122.47, 125.24, 128.10, 128.81, 130.53, 132.90, 135.55, 144.09, 152.96; MS (APCI): m/z 431.5[M+H]+.

Synthesis of 3-fluoro-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) benzene sulphonamide, 10: White solid, Yield 87%, mp 94-95 °C; IR (KBr) λmax/cm^{-1} 3455 (N–H), 2918 (C–H), 1552 (C=C), 1434 (N-H bend), 1366 (SO_2NH), 1167 (C–H), 1035 (C-F), 786 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.88-0.93 (t, *J* = 7.3 Hz, 3H), 1.42-1.49 (m, *J* = 7.3 Hz, 2H), 2.80-2.85 (t, *J* = 7.1 Hz, 2H), 7.05-7.07 (d, *J* = 8.1 Hz, 1H), 7.13-7.17 (d, *J* = 8.2 Hz, 1H), 7.25 (s, 2H), 7.60 (s, *J* = 1.3 Hz,1H) , 7.94-7.96 (d, *J* = 8.2 Hz, 1H), 7.80-7.83 (d, *J* = 7.4 Hz, 1H), 7.73 (s, *J* = 1.5 Hz, 1H), 7.64-7.67 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO-d_6, δ ppm): 13.43, 22.42, 37.17, 114.45, 114.89, 116.93, 123.12, 123.49, 127.16, 128.60, 133.24, 138.62, 142.44, 152.70, 160.54, 163.85; MS (APCI): m/z 365.4[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl)-2-(trifluoromethyl) benzene sulphonamide, 11: Off-white solid, Yield 82%, mp 62-63 °C; IR (KBr) λmax/cm^{-1} 3471 (N–H), 3078 (C–H), 1554 (C=C), 1453 (N-H bend), 1377 (SO_2NH), 1133 (C–H), 1049 (C-F), 778 (C–N); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.87-0.92 (t, *J* = 7.4 Hz, 3H), 1.47-1.54 (m, *J* = 7.2 Hz, 2H), 2.83-2.88 (t, *J* = 7.2 Hz, 2H), 6.88-6.92 (d, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 7.14-7.17 (d, *J* = 7.5 Hz, 1H), 7.19 (s, 1H),7.23 (s, *J* = 1.3 Hz,1H), 8.09-8.11 (d, *J* = 7.5 Hz, 1H), 7.90-7.93 (t, *J* = 8.0 Hz, 1H), 7.85-7.89 (t, *J* = 8.1 Hz, 1H), 7.48-7.51 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.58, 22.41, 35.38, 112.58, 116.87, 121.98, 126.58, 127.02, 129.44, 130.00, 130.53, 133.0, 134.84, 135.84, 136.30, 143.49, 153.37; MS (APCI): m/z 415.5[M+H]+.

General procedure for the synthesis of synthesize compounds 12-17

Added triethylamine (1.1 mmol.) a stirred solution of 6-(propylthio)-1*H*-benzo[*d*]imidazol-2-amine (1 eq.) in DCM (10 mL) at 25 – 30 °C followed by added substituted acetyl chloride (1.1 eq.). Resulting reaction mixture stirred at for 1-2 h at rt. Reaction mixture was diluted with DCM, and water. Organic layer was separated and washed with brine. Organics was dried over anhydrous Na_2SO_4 and filtered, evaporated filtrate to get crude product. Crude was chromatographed using the silica gel (100–200 #) and 0-30% ethyl acetate in petroleum ether is used as eluent to yield amide analogues **12-17.**

Synthesis of 2-(4-chlorophenyl)-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) acetamide, 12: White solid, Yield 83%, mp 82-83 °C; IR (KBr) λmax/cm^{-1} 3483 (N–H), 2965 (C–H), 1680 (CONH), 1573 (C=C), 1418 (N-H bend), 1284 (C–O), 1195 (C–H), 811 (C–N), 659 (C-Cl); ^{1}H NMR (300 MHz, DMSO- d_6, δ ppm): 0.87-0.92 (t, *J* = 7.2 Hz, 3H), 1.42-1.52 (m, *J* = 7.1 Hz, 2H), 2.78-2.83 (t, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 7.06-7.08 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.41 (s, *J* = 1.3 Hz,1H), 11.80 (s, 1H), 12.00 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.51, 22.50, 36.89, 46.03, 66.74, 114.80, 115.0, 121.65, 124.68, 127.87, 129.98, 147.52, 158.20, 168.88, 171.44; MS (APCI): m/z 359.9[M+H]+.

Synthesis of 2-phenoxy-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) acetamide, 13: White solid, Yield 78%, mp 77-78 °C; IR (KBr) λmax/cm^{-1} 3436 (N–H), 2955 (C–H), 1690 (CONH), 1567 (C=C), 1480 (N-H bend), 1230 (C–O), 1163 (C–H), 793 (C–

N);[1]H NMR (300 MHz, DMSO- d_6, δ ppm): 0.88-0.93 (t, J = 7.3 Hz, 3H), 1.46-1.50 (m, J = 7.2 Hz, 2H), 2.73-2.84 (t, J = 7.1 Hz, 2H), 4.82 (s, 2H), 6.63 (s, 1H), 7.02-7.08 (d, J = 8.1 Hz, 1H), 7.33-7.36 (d, J = 8.2 Hz, 1H), 7.42-7.43 (s, J = 1.1 Hz,1H), 11.82 (s, 1H), 7.21-7.29 (t, J = 8.7 Hz, 2H), 6.92-6.96 (t, J = 8.1 Hz, 1H), 6.84-6.86 (d, J = 8.2 Hz, 2H) ; [13]C NMR(300 MH_Z , DMSO-d_6, δ ppm): 14.31, 38.95, 45.94, 51.30, 95.63, 122.38, 127.23, 128.24, 129.53, 134.84, 139.72, 140.20, 141.82, 148.45, 151.83, 169.48; MS (APCI): m/z 341.4[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl)-[1,1'-biphenyl]-4-carboxamide, 14: White solid, Yield 85%, mp 98-100 °C; IR (KBr) λmax/cm^{-1} 3345 (N–H), 2903 (C–H), 1680 (CONH), 1596 (C=C), 1389 (N-H bend), 1286 (C–O), 1023 (C–H), 840 (C–N); [1]H NMR (300 MHz, DMSO- d_6, δ ppm): 0.86-0.90 (t, J = 7.3 Hz, 3H), 1.39-1.51 (m, J = 7.3 Hz, 2H), 2.72-2.77 (t, J = 7.1 Hz, 2H), 6.46 (s, 2H), 6.88-6.91 (d, J = 8.1 Hz, 1H), 7.01-7.04 (d, J = 8.0 Hz, 1H), 7.12 (s, J = 1.4 Hz,1H), 7.97-7.99 (d, J = 8.4 Hz, 2H), 7.72-7.75 (d, J = 8.3 Hz, 2H), 7.67-7.69 (d, J = 7.2 Hz, 2H), 7.43-7.48 (t, J = 7.6 Hz, 2H), 7.43-7.48 (t, J = 7.2 Hz, 1H); [13]C NMR(300 MH_Z , DMSO- d_6, δ ppm): 15.73, 24.79, 39.93, 114.42, 117.34, 125.72, 126.82, 129.45, 129.63, 130.94, 131.76, 132.63, 132.68, 141.75, 146.84, 158.42, 170.04; MS (APCI): m/z 387.5[M+H]+.

Synthesis of 2-methoxy-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) acetamide, 15: White solid, Yield 82%, mp 134-135 °C; IR (KBr) λmax/cm^{-1} 3249 (N–H), 2969 (C–H), 1672 (CONH), 1566 (C=C), 1421 (N-H bend), 1316 (C–O), 1107 (C–H), 791 (C–N); [1]H NMR (300 MHz, DMSO- d_6, δ ppm): 0.87-0.92 (t, J = 7.3 Hz, 3H), 1.41-1.53 (m, J = 7.3 Hz, 2H), 2.73-2.78 (t, J = 7.2 Hz, 2H), 3.25 (s, 3H), 3.84 (s, 2H), 6.78 (s, 1H), 6.90-6.93 (d, J = 8.1 Hz, 1H), 7.02-7.05 (d, J = 8.1 Hz, 1H), 7.12 (s, J = 1.5 Hz, 1H), 9.90 (s, 1H); [13]C NMR(300 MH_Z , DMSO-d_6, δ ppm): 13.51, 22.53, 37.42, 58.60, 69.94, 112.15, 114.64, 123.80, 125.63, 136.52, 137.95, 155.63, 173.11; MS (APCI): m/z 279.4[M+H]+.

Synthesis of 2,4-difluoro-N-(6-(propylthio)-1*H*-benzo[d]imidazol-2-yl) benzamide, 16: White solid, Yield 85%, mp 148-150 °C; IR (KBr) λmax/cm^{-1} 3363 (N–H), 2962 (C–H), 1665 (CONH), 1583 (C=C), 1418 (N-H bend), 1288 (C–O), 1144 (C–H), 1092 (C-F), 874 (C–N); [1]H NMR (300 MHz, DMSO-d_6, δ ppm): 0.89-0.94 (t, J = 7.2 Hz, 3H), 1.45-1.57 (m, J = 7.2 Hz, 2H), 2.82-2.86 (t, J = 7.5 Hz, 2H), 7.11-7.14 (d, J = 8.3 Hz, 1H), 7.33-7.37 (d, J = 7.9 Hz, 1H) , 7.43 (s, J = 1.3 Hz,1H), 12.22 (s, 2H), 7.81-7.89 (d, J = 8.3 Hz, 1H), 7.39-7.40 (s, J = 2.3 Hz, 1H), 7.19-7.21 (d, J = 8.2 Hz, 1H); [13]C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.53, 22.49, 36.75, 105.27, 112.05, 112.34, 114.75, 115.72, 121.18, 124.80, 128.75, 132.81, 148.47, 159.15, 162.55, 165.15, 166.04; MS (APCI): m/z 347.4[M+H]+.

Synthesis of N-(6-(propylthio)-1*H*-benzo[d] imidazol-2-yl)-4-(trifluoromethyl) benzamide, 17: Light brown solid, Yield 87%, mp 79-80 °C; IR (KBr) λmax/cm^{-1} 3389 (N–H), 2987 (C–H), 1675 (CONH), 1579 (C=C), 1428 (N-H bend), 1315 (C–O), 1129 (C–H), 1060 (C-F), 846 (C–N); [1]H NMR (300 MHz, DMSO- d_6, δ ppm): 0.86-0.94 (t, J = 7.4 Hz, 3H), 1.43-1.58 (m, J = 7.3 Hz, 2H), 2.83-2.87 (t, J = 7.1 Hz, 2H), 7.13-7.16 (d, J = 8.2 Hz, 1H), 7.35-7.37 (d, J = 8.3 Hz, 1H) , 7.42-7.43 (s, J = 1.1 Hz, 1H), 8.3 (s, 1H), 12.06 (s, 1H), 8.26-8.29 (d, J = 8.1 Hz, 2H), 7.82-7.85 (d, J = 8.3 Hz, 2H); [13]C NMR(300 MH_Z , DMSO- d_6, δ ppm): 13.53, 22.50, 36.66, 45.77, 113.79, 114.70, 124.96, 125.70, 129.0, 129.92, 131.18, 133.74, 139.87, 150.97, 155.13, 169.30; MS (APCI): m/z 379.4[M+H]+.

Biological assay

Synthesized 1H-benzo[d]imidazole-aryl sulfonamide/amide were evaluated for their antimicrobial potential against selected Gram-positive organisms viz. *Staphylococcus aureus* ATCC 6538 and Gram-negative organisms viz. *Escherichia coli* ATCC 8739 bacterial strains as per the Agar well diffusion procedure with little modifications. The bacterial suspensions were adjusted with sterile saline to a concentration of 1.0 x 107 CFU/ml. The inocula were prepared and stored at 4 °C until use. Dilutions of the inocula were cultured on solid medium to verify the absence of contamination and to check the validity of the inoculum.

Newly synthesized compounds were screened for their antifungal activity against selected *Aspergillus niger* ATCC 6275 and *Candida albicans* ATCC 10231 fungal strains by the Agar well diffusion method with little modifications. The fungal spores were washed from the surface of agar plates with sterile 0.85% saline containing 0.1% Tween 80 (v/v). The spore suspension was adjusted with sterile saline to a concentration of approximately 1.0 X 107. The inocula were stored at 4 °C for further use. Dilutions

of the inocula were cultured on solid potato dextrose agar to verify the absence of contamination and to check the validity of the inoculum.

Agar well-diffusion method was performed to assess the Antimicrobial activity of the samples. Nutrient agar (NA) and Potato Dextrose Agar (PDA) plates were swabbed (sterile cotton swabs) with respective bacterial and fungal suspensions. Well (10mm diameter) was made in each of these plates using sterile cork borer. Stock solution of each sample was prepared at a concentration of 20 mg/ml in 5 % DMSO. About 100 µl of different concentrations of the stock solution were added using micropipette into the wells and allowed to diffuse at room temperature for 2 hrs. Control experiments comprising inoculums without samples were set up. The plates were incubated at 37°C for 18-24 h for bacterial organisms and at 28°C for 48 hours for fungal organisms. The diameter of the inhibition zone (mm) was measured and the activity was reported (Table I). The compounds showing good inhibition zone was taken as minimum inhibitory concentration (MIC) (Table II).

Conclusion

Herein, we have presented the synthesis and antimicrobial activity of novel *N*-(6-(propylthio)-1*H*-benzo[*d*]imidazol-2-yl)- aryl sulfonamide and amide derivatives. Structure of all the newly synthesized compounds were fully characterized using the spectral analysis. All the compounds from the sulfonamide series exhibit the anti-microbial and antifungal activity against the tested strain, while one of the amide derivative possesses the anti-microbial potential. The inhibitor **3**, **5, 7** and **15** found to be more active form of the synthesized analogues.

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