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Design, synthesis, characterization and bioassay of novel amide derivatives of 2-(benzo[d]thiazol-2-yl)phenol

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ABSTRACT

*A series of new carboxamide derivatives of 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoic acid (**2**) were synthesized by the reaction of 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoyl chloride (**3**) with various bio-potent amines by using 1-methylimidazole as an acid scavenger via Schotten-Baumann reaction. The newly synthesized compounds were characterized by IR, NMR and mass spectral analysis. The title compounds were evaluated for their efficacy as antibacterial and antifungal agents in vitro. Compounds **4e-h** showed high inhibitory activity against both bacteria and fungi.*

Keywords: Carboxamide, 1-methyl imidazole, Schotten-Baumann reaction, antibacterial and antifungal activities

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INTRODUCTION

A continuous effort has been taken up by the synthetic chemist to develop new chemical entities as potent antibacterial and antifungal agents to combat against various bacterial and fungal pathogens with fewer side effects. Among the benzene fused heterocyclic compounds, benzothiazole is a multifunctional nucleus, that has its own importance in pharmaceutical chemistry because of its potent pharmacological activities [1] and industrial applications like vulcanization accelerators, nonlinear optical materials, chemo sensors [2, 3] and dyes [4]. Besides, benzothiazole and its derivatives exhibited varied biological activities such as antimicrobial [5, 6], antituberculotic [7], anti-inflammatory [8], central nervous system (CNS) depressant [9], antiviral [10], antitumor [11] and anthelmintic [12]. Furthermore, derivatives of benzothiazole displayed anti-HIV activity [13] and act as COX inhibitors [14]. From the past10 years the synthesis of anticancer drugs pays much attention by the synthetic chemists. Recent reports revealed that the amide derivatives [15] and piperazine linked benzothiazole derivatives [16] showed promising anticancer activity.

β-Glucuronidase is an exoglycosidase enzyme present in various organs and body fluids such as spleen, bile, kidney and serum respectively. It is responsible for the cleavage of glucoronosyl-O-bonds. Benzothiazole acts as antagonists of different receptors and enzymes. Among them, 2-(benzo[d]thiazol-2-yl)phenol is the one that showed β-glucuronidase activity [17, 18]. Based on the above literature, herein we report design, synthesis and their antibacterial and antifungal activities of new amide derivatives of 2-(benzo[d]thiazol-2-yl)phenol.

MATERIALS AND METHODS

Required chemicals were purchased from Sigma-Aldrich Chemicals. Melting points were determined on Guna digital melting point apparatus and are uncorrected. The FT-IR spectra were recorded using ALPHA (Bruker). ^{1}H and ^{13}C NMR were recorded on Bruker AMX 400 MHz by using DMSO-d_6 as solvent and TMS as an internal standard. Silica gel column chromatography was performed using Merck 7734 silica gel (60-120 mesh) and Merck-

made TLC plates. Liquid chromatography (LC) mass spectra were recorded on a Shimadzu LCMS 2010A. CHN analysis was performed with the Thermo Finnigan Flash EA 1112 instrument at the IICT, Hyderabad, India.

General procedure for the synthesis of 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoic acid (2)
Sodium hydride (0.002 mole) in THF was added to 2-(benzo[d]thiazol-2-yl)phenol (**1**) (0.001 mole) 10 mL of THF, stirred for 1h at 5-20 ˚C. 3-Bromopropanoic acid (0.001 mole) in THF was added dropwise to intermediate anion, stirred for 1h at 10-45 ˚C. It was filtered to get crude compound (**2**) and evaporated the solvent under vacuum, washed with hexane and ethyl acetate.

General procedure for the synthesis of 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoyl chloride (3)
To a stirred solution of acid (**2**) (0.001 mole) in dry THF (10 mL), excess of thionyl chloride (0.0015 mole) was added at 0 ˚C in the presence of Et_3N and stirred for 1 h at 30 ˚C to afford 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoyl chloride **3.** The formed salt Et_3N.HCl was remove by filtration, the solvent and unreacted thionyl chloride was removed in a rotaevaporator.

General procedure for the synthesis of carboxamides (4a-h)
The acid chloride (**3**) was reacted with various bioactive amines in the presence of 1-methylimidazole as an acid scavenger and THF as solvent at 10-45 ˚C. The progress of the reaction was monitored by TLC (n-Hexane: Ethyl acetate 3:1). After completion of the reaction, water was added to the stirred mixture, which was extracted with ethyl acetate. The organic layer was washed with 5% HCl solution and 10% $NaHCO_3$ solution in order to remove unreacted amine and acid respectively. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated in a rotaevaporator. The obtained crude product was purified by silica gel column chromatography to obtain respective amides. The physical properties and spectral data of the obtained compounds are given below.

Spectral Data
3-(2-(Benzo[d]thiazol-2-yl)phenoxy)propanoic acid (2)
White solid, yield 75%, mp: 205-206 ˚C. IR (cm^{-1}): 3324 (COOH), 1655 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.60 (t, *J* = 6.4 Hz, 2H, -CH_2), 4.34 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.76-7.22 (m, 4H, Ar-H), 7.64-8.24 (m, 4H, Ar-H), 11.24 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6) *δ:* 33.5, 42.7, 65.3, 112.8, 118.4, 121.5, 123.4, 125.2, 126.3, 128.2, 129.3, 136.4, 153.8, 155.4, 164.5, 175.3. MS: 300 $[M+H]^+$. Anal.Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68. Found C, 64.08; H, 4.12; N, 4.24.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-N-(4-fluorobenzyl)propanamide (4a)
White solid, yield 74%, mp: 210-211 ˚C. IR (cm^{-1}): 3246 (CONH), 1665 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.38 (t, *J* = 6.4 Hz, 2H, -CH_2), 4.10 (t, *J* = 6.4 Hz, 2H, OCH_2), 4.45 (s, 2H, NCH_2), 6.88-7.25 (m, 8H, Ar-H), 7.36-7.72 (m, 4H, Ar-H), 10.24 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6) *δ:* 33.5, 45.2, 65.4, 111.8, 116.6 (2C), 119.8, 121.5, 124.5, 126.8, 127.2(2C), 129.5, 131.4, 132.7, 134.5, 136.1, 139.2, 141.8, 152.6, 153.3, 161.3, 163.7, 171.3. MS: 406 $[M+H]^+$. Anal.Calcd for $C_{24}H_{19}FN_2O_2S$: C, 71.09; H, 4.97; N, 3.45. Found C, 70.85; H, 4.53; N, 3.14.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-N-(2-chlorobenzyl)propanamide (4b)
White solid, yield 78%, mp: 221-222 ˚C. IR (cm^{-1}): 3241 (CONH), 1662 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2. 42 (t, *J* = 6.4 Hz, 2H, -CH_2), 4.22 (t, *J* = 6.4 Hz, 2H, OCH_2), 4.46 (s, 2H, NCH_2), 6.94-7.28 (m, 8H, Ar-H), 7.42-7.86 (m, 4H, Ar-H), 10.12 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6) *δ:* 32.5, 43.7, 64.3, 111.8, 115.5 (2C), 117.4, 120.5, 122.4, 124.7, 125.3, 127.8 (2C), 129.2, 131.4 (2C), 133.3, 136.4, 138.2, 142.5, 144.4, 153.3, 154.4, 173.2. MS: 422 $[M+2]^+$. Anal.Calcd for $C_{24}H_{20}ClN_2O_2S$: C, 68.32; H, 4.78; N, 3.32. Found C, 68.12; H, 4.36; N, 3.15.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-N-((pyridin-4-yl)methyl)propanamide (4c)
White solid, yield 73%, mp: 208-209 ˚C. IR (cm^{-1}): 3243 (CONH), 1660 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.44 (t, *J* = 6.4 Hz, 2H, -CH_2), 4.26 (t, *J* = 6.4 Hz, 2H, OCH_2), 4.48 (s, 2H, NCH_2), 6.92-7.38 (m, 6H, Ar-H), 7.38-7.74 (m, 4H, Ar-H), 8.45 (d, *J* = 8.0 Hz, 2H, Ar-H, Py-H), 10.24 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6) *δ:* 32.5, 43.7, 64.3, 111.8, 115.5 (2C), 117.4, 120.5, 122.4, 124.7 (2C), 125.3, 127.8 (2C), 129.2, 131.4 (2C), 142.5, 144.4, 148.3, 153.6, 155.4, 172.4. MS: 389 $[M+H]^+$. Anal.Calcd for $C_{23}H_{20}N_3O_2S$: C, 71.11; H, 5.19; N, 7.21. Found C, 70.88; H, 4.92; N, 7.12.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-1-(indolin-1-yl)propan-1-one (4d)
White solid, yield 68%, mp: 232-233 ˚C. IR (cm^{-1}): 1663 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.56 (t, *J* = 6.4 Hz, 2H, -CH_2), 2.64 (t, *J* = 6.4 Hz, 2H, -CH_2), 3.62 (t, *J* = 6.4 Hz, 2H, -CH_2) 4.24 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.86-7.18 (m, 8H, Ar-H), 7.25-7.84 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6) *δ:* 26.4, 32.5, 46.8, 66.2, 110.8, 115.5 (2C), 117.4, 120.5, 122.4, 124.7 (2C), 125.3, 127.8 (2C), 129.2, 131.4 (2C), 136.3, 141.5 (2C), 143.4, 146.3, 152.8, 154.5, 171.5. MS: 400 $[M+H]^+$.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-1-(4-(4-nitrophenyl)piperazin-1-yl)propan-1-one (4e)
Yellow solid, yield 80%, mp: 254-255 °C. IR (cm^{-1}): 1658 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.52 (t, *J* = 6.4 Hz, 2H, -CH_2), 3.32-3.64 (m, 8H, 4xCH_2), 4.35 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.18-7.15 (m, 6H, Ar-H), 7.28-7.78 (m, 4H, Ar-H), 8.14 (d, *J* = 8.0 Hz, 2H, Ar-H). ^{13}C NMR (DMSO-d_6) *δ:* 33.7, 44.8 (2C), 48.8 (2C), 64.3, 112.8, 114.5 (2C), 120.5, 122.8 (2C), 124.7 (2C), 125.3, 127.8, 129.2, 131.4, 136.3, 140.5 (2C), 143.4, 146.3, 151.8, 153.7, 156.4, 172.5. MS: 488 $[M+H]^+$.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-1-(4-(4-fluorophenyl)piperazin-1-yl)propan-1-one (4f)
White solid, yield 75%, mp: 261-262 °C. IR (cm^{-1}): 1661 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.65 (t, *J* = 6.4 Hz, 2H, -CH_2), 3.28-3.56 (m, 8H, 4xCH_2), 4.30 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.82-7.18 (m, 8H, Ar-H), 7.92-8.22 (m, 4H, Ar-H). ^{13}C NMR (DMSO-d_6) *δ*: 33.5, 43.8 (2C), 47.8 (2C), 65.3, 111.8, 114.5 (2C), 116.3 (2C), 120.5, 122.8, 124.7 (2C), 125.3, 127.8, 129.2, 131.4, 136.3, 146.3, 152.8, 155.7, 156.5, 164.2, 170.8. MS: 462 $[M+H]^+$. Anal.Calcd for $C_{26}H_{24}FN_4O_2S$: C, 67.66; H, 5.24; N, 9.10. Found C, 67.22; H, 5.10; N, 8.92.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)propan-1-one (4g)
White solid, yield 70%, mp: 243-244 °C. IR (cm^{-1}): 1656 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.55 (t, *J* = 6.4 Hz, 2H, -CH_2), 3.24-3.48 (m, 8H, 4xCH_2), 4.42 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.36 (dd, *J* = 7.2, 16.0 Hz, 1H, Pyrimidine-H), 6.78-7.16 (m, 4H, Ar-H), 7.76-8.14 (m, 4H, Ar-H), 8.24 (d, 2H, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) *δ*: 34.5, 44.8 (2C), 48.5 (2C), 65.3, 111.8, 114.5, 121.8, 123.7 (2C), 124.6, 126.3, 128.5, 131.4, 135.5, 151.7, 154.6, 157.3 (2C), 161.4, 163.2, 172.4. MS: 446 $[M+H]^+$.

3-(2-(Benzo[d]thiazol-2-yl)phenoxy)-1-(4-(pyridin-2-yl)piperazin-1-yl)propan-1-one (4h)
White solid, yield 74%, mp: 236-237 °C. IR (cm^{-1}): 1657 (C=O). ^{1}H NMR (DMSO-d_6) *δ:* 2.52 (t, *J* = 6.4 Hz, 2H, -CH_2), 3.26-3.40 (m, 8H, 4xCH_2), 4.45 (t, *J* = 6.4 Hz, 2H, OCH_2), 6.46-7.12 (m, 3H, Py-H), 6.82-7.18 (m, 4H, Ar-H), 7.66-8.10 (m, 4H, Ar-H), 8.15 (d, 1H, *J* = 8.0 Hz, Py-H). ^{13}C NMR (DMSO-d_6) *δ*: 34.8, 44.2 (2C), 48.8 (2C), 66.2, 108.4, 112.8, 115.5, 119.4, 121.3 (2C), 122.5, 123.7, 124.6, 126.3, 128.5, 131.4, 137.5, 146.3, 151.7, 153.6, 154.5, 164.2, 171.8. MS: 445 $[M+H]^+$.

Pharmacology
Anti-microbial activity
Bacterial cultures were prepared in Nutrient Agar Medium (NAM) and for fungal test Potato Dextrose Agar (PDA) medium was used. 10 mL of distilled water was used to scrape conidia from 10 days culture and the spores were collected after filtration. The spores were resuspended in sterile distilled water and were used as inoculum. For bacterial culture plates a 100 µL of the cell suspension (10^6 cells/ mL) was used to prepare bacterial lawn. Anti-microbial tests were done by disc diffusion technique [31, 32]. Discs were prepared with Whatman No.1 filter paper (6 mm diameter) and was impregnated with 100 µg/ disc of each compound and placed on the inoculated microbial plates. And all the plates were subjected to incubation at 37 ˚C for 24 hours. Chloramphenicol was used as positive control and was placed in the center of all the plates for bacterial cultures and nystatin was used as positive control for fungal cultures. Anti-microbial activity was evaluated by measuring the Zone of inhibition against the tested organisms and the results are summarized in **Table 2** (antibacterial) and **Table 3** (antifungal). Each test was carried out three times and average values are taken.

Minimum inhibitory concentration
Minimum inhibitory concentration was evaluated using micro-broth dilution assay method [33]. MIC was determined by taking the minimum concentration at which there were observed no visually detectable bacterial/ fungal growth. Specifically, 0.1 mL of standardized inoculum (1.2x 10^7 c.f.u/mL) was added to each test tube. The tubes were incubated aerobically at 37 ˚C for 24 h for bacterial activity and 48-72 h for fungal activity. Control was maintained for each test sample. The lowest concentration (highest) of test compound that produced no visible signs of microbial growth (no turbidity) when compared with the control tubes were regarded as MICs (**Tables 2** and **3**).

Antimicrobial activity was evaluated by measuring the zone of inhibition against the tested organisms and the results are summarized in **Table 1** (antibacterial) and **Table 2** (antifungal). All the target compounds exhibited promising antibacterial and antifungal activities. The title compounds were dissolved in DMSO at 100 µg/mL and each test was carried out three times and mean values of inhibition zone diameter are taken. All the synthesized compounds were screened for their *in vitro* antibacterial activity against the following bacterial strains: Gram negative bacteria *Escherichia coli* and *Klebsiella pneumoniae*, Gram positive bacteria: *Bacillus subtilis* and *Staphylococcus aureus*. Moderate to excellent antibacterial activity was displayed by the synthesized compounds.

Table 1. Antibacterial activity of synthesized compounds 4a-h

Entry	Product	Gram negative				Gram positive			
		E. coli		*K. pneumoniae*		*B. subtilis*		*S. aureus*	
		IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
1	**4a**	24	6.45	17	6.65	25	9.65	24	18.42
2	**4b**	22	7.75	20	9.55	22	14.84	22	19.15
3	**4c**	20	12.25	26	10.24	20	16.65	18	20.35
4	**4d**	22	10.15	22	5.25	24	11.15	20	17.85
5	**4e**	28	4.25	24	9.45	30	8.75	26	8.45
6	**4f**	30	3.35	25	4.35	32	6.15	28	6.15
7	**4g**	26	8.15	20	12.44	28	12.35	24	14.15
8	**4h**	25	10.65	18	16.16	26	15.35	22	16.25
9	**Std**	32	5.15	26	8.45	34	10.25	30	12.35

E. coli: Escherichia coli, K. pneumoniae: Klebsiella pneumoniae, B. subtilis: Bacillus subtilis, S. aureus: Staphylococcus aureus, Std: Chloramphenicol
IZ: Inhibition zone in (mm), MIC: Minimum inhibitory concentration (in µg/mL).

Among the synthesized amides **4e-h** showed high antibacterial activity against the growth of *E. coli* and *B. subtilis* than that of others compared to that of standard chloramphenicol. When we compare the antibacterial activity of the compounds, it is observed that the effect of substitution plays major role in inhibition of the growth of the bacterial strains. The antibacterial activity of the compounds **4e-h** against tested bacterial strains is as follows, **4h<4g<4e<4f**. Compounds **4a-b** displayed more antibacterial activity than **4c** due to the presence of substitution in the former ones and lacks in the latter compound. Substitutions like halogens (Cl, F), and nitro groups at 2, 4 positions on the benzene ring in the compounds **4a-b** and *p*-position on the phenyl ring in the case of compound **4f** enhances the zone of inhibition. Compound **4f** showed high antibacterial activity with MIC **(**3.35 µg/mL**)** than **4e (**4.25µg/mL**)**, due to fluorine substitution [34] which enhances the activity against *E. coli*. Similar trend is observed in the case of **4a-d** analogs, **4c<4b<4a<4d**.

Table 2. Antifungal activity of synthesized compounds 4a-h

Entry	Product	*A. niger*		*T. viride*		*A. flavus*		*P. chrysogenum*	
		IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
1	**4a**	15	9.45	18	14.45	16	14.45	16	20.45
2	**4b**	12	16.75	12	18.75	10	18.26	14	22.25
3	**4c**	14	12.85	16	16.14	14	15.65	12	24.35
4	**4d**	16	11.15	20	13.64	18	12.25	17	18.25
5	**4e**	22	5.15	26	7.25	24	8.15	22	10.25
6	**4f**	24	3.25	28	6.15	26	6.35	24	8.24
7	**4g**	20	8.45	24	9.25	22	10.35	20	12.34
8	**4h**	18	10.55	22	12.36	20	14.45	18	16.48
9	**Std**	26	5.25	30	10.25	28	8.45	26	10.15

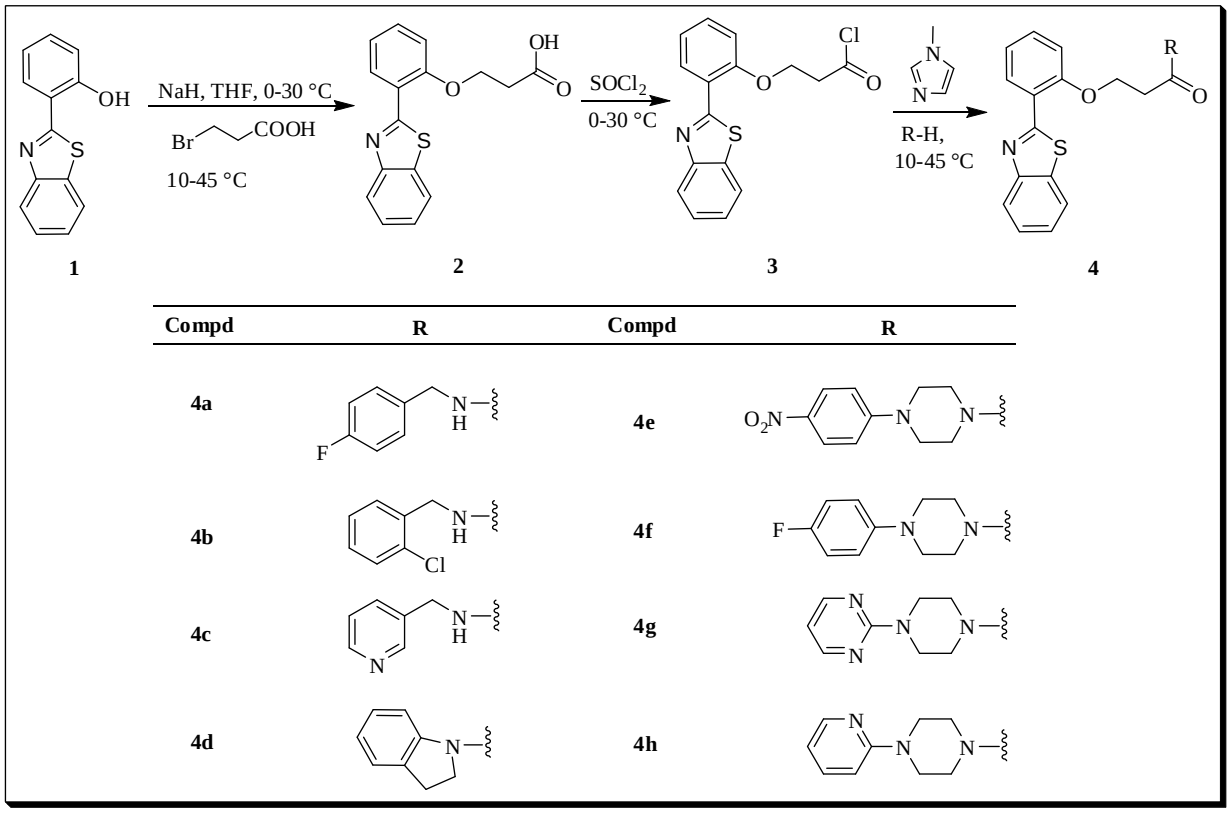
A. niger: Aspergillus niger, T. viride: Trichoderma viride, A. flavus: Aspergillus flavus, P. chrysogenum: Penicillium chrysogenum, Std: Nystatin
IZ: Inhibition zone in (mm), MIC: Minimum inhibitory concentration (in µg/mL).

On the other hand, study of the antifungal activity of the synthesized compounds revealed that all the analogs exhibited substantial growth inhibitory activity against *Trichoderma viride*, *Aspergillus niger*, *Aspergillus flavus* and *Penicillium chrysogenum* by disc diffusion method at 100 µg/mL concentration. Nystatin was used as a standard antifungal agent. The analogs showed high activity towards *Trichoderma viride* and *Aspergillus flavus*. In particular, compounds **4e** and **4f** (MIC 5.15 and 3.25 µg/mL) displayed the highest zone of inhibition when compared to standard antifungal agent against *Trichoderma viride*.

RESULTS AND DISCUSSION

Chemistry

The synthetic protocol to the target compounds **4a-h** is sketched in **Scheme 1**. In brief, commercially available 2-(benzo[d]thiazol-2-yl)phenol (**1**) was taken as starting material. It was converted into acid (**2**) by the reaction of sodium hydride followed by 3-bromopropanoic acid in THF. Acid chloride was synthesized by reacting the acid (**2**) with thionyl chloride, which in turn reacted with various bio-active amines in the presence of acid scavenger, 1-methylimidazole [19-21] in THF as solvent at 10-45 $^{\circ}$C.



Scheme 1. Synthesis of carboxamide derivatives

The reaction of different amines with the acid chloride 3-(2-(benzo[d]thiazol-2-yl)phenoxy)propanoyl chloride (**3**) gave moderate yields in the presence of triethylamine as an acid scavenger but with 1-methylimidazole as catalyst gave high yields [22]. All the newly synthesized compounds were characterized by IR, NMR and mass spectral analysis. Amide carbonyl group stretching band is observed in the region 1657–1665 cm^{-1}. A band in the region 3241-3246 cm^{-1} corresponds to the amide NH stretching for the compounds **4a-c** and no absorption band is observed in this region for the compounds **4d-h** due to lack of NH bond in that compounds. [23-26] In ^{1}H NMR, a signal at δ 2.42-4.48 indicates the methylene protons and signals due to amide NH protons were observed in the region δ 10.96-11.25 [27-30] for the compounds **4a-c**. In ^{13}C NMR spectra, signals δ 34.2-38.5 confirmed the presence of methylene carbons and peaks in the region at δ 169.6-173.7 indicate the carbonyl group of amide. EIMS were recorded for a few representative compounds; they gave M+H ions at their respective molecular masses. CHN analysis was obtained for a few title compounds and the data confirmed their elemental composition.

CONCLUSION

In conclusion, we have described the design and synthesis of new carboxamide derivatives of 2-(benzo[d]thiazol-2-yl)phenol in the presence of 1-methylimidazole with augmenting yields and screened for their antioxidant and antimicrobial activities. By summarizing the antimicrobial results, it can be seen that the pharmacological efficacy of the synthesized compounds showed good inhibitory activity. Particularly the compounds **4c-h** displayed pronounced activity against tested strains. From the antimicrobial activity results, it can be concluded that, a combination of two different heterocyclic motifs namely benzothiazole, piperazine and pyrimidine exhibited augmented biological properties. Hence, derivatives of this scaffold are ideally suitable for the further modifications which will contribute varied pharmacological activities.

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