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RESEARCH ARTICLE

Synthesis and *in vitro* antimicrobial activity of novel *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide derivatives of benzothiazole class

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Abstract

In this study, a series of novel 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole (**6a–g**) and 1,3,4-oxadiazole (**7a–g**, **8**) were synthesized from *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide derivatives of benzothiazole class. Antimicrobial properties of the title compound derivatives were investigated against one Gram (+) bacteria (*Staphylococcus aureus*), three Gram (–) bacteria (*Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumoniae*) and five fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus flavus*, *Monascus purpureus* and *Penicillium citrinum)* using serial plate dilution method. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 12.5–100 µg/mL in DMSO. It has been observed that triazolo-thiadiazole derivatives are found to be more active than 1,3,4-oxadiazole derivatives against all pathogenic bacterial and fungal strains.

Keywords: *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide, 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole, 1,3,4-oxadiazole, antimicrobial activity

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Introduction

Antimicrobials reduce or completely block the growth and multiplication of bacteria. This has made them unique for the control of deadly infectious diseases caused by a variety of pathogens. They have transformed our ability to treat infectious diseases such as pneumonia, meningitis, tuberculosis, malaria and AIDS[1]. Although deaths from bacterial and fungal infections have dropped in the developed world, these are still major causes of death in the developing world[2].

According to WHO, each year 1.4 million children died of gut infections and diarrhoea caused by gram-negative bacteria like *Pseudomonas, Salmonella, Shigellae* and gram positive rods like *Corynebacterium diptheriae*[2].Decades of antibiotic use have resulted in the development of widespread resistance to commonly prescribed antibacterial agents[3]. Therefore, there is a need to develop new, potent, fast-acting antimicrobial drugs with low toxicity. In the design of new compounds, development of hybrid molecules through the combination of different pharmacophores in one structure may lead to compounds with increased antimicrobial activity[4].

Despite numerous attempts to develop new structural prototype in the search for more effective antimicrobials, benzothiazole still remain as one of the most versatile class of compounds against microbes and therefore, are useful substructures for further molecular exploration. Benzothiazole's literature is enriched with progressive findings of the moiety in respect of anticonvulsant and antimicrobial activities[5]. Benzothiazole and its derivatives constitute the most versatile and valuable source of antimicrobial compounds. They appear to transcend the chemotherapeutic boundaries of other antiparasitic drugs with a spectrum of activity that includes the majority of fungi, bacteria, protozoa and helminthic species.

Several benzothiazole derivatives were also associated with antitumor[6], antimicrobial[7,8], anticonvulsant[9],

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and anti-inflammatory[7,10] activities. In addition, triazolo-thiadiazoles nucleus constitutes the active part of several biologically active compounds, including antibacterial[11], antifungal[12], antitumor[13], anti-inflammatory[14], analgesic[15] and so on. Moreover, 1,3,4-oxadiazole were also reported to possess significant antimicrobial[16], anti-inflammatory[17] and analgesic activities[18].

A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components-thiosemicarbazide [19,20] and biguanide [21], which often display diverse biological activities. Inspired by these observations a composite system was investigated, which combine these two biolabile components in a ring together to give a compact and planar structure, and screened for their biological activities.

The prime objective for the current study is to develop novel derivatives of benzothiazole moiety and finally screen them against different microbial strains (bacteria and fungi) at variable concentrations. The rationale for the study includes the designing of the derivatives having some common structural features that are important for the compound to exhibit an antimicrobial activity that includes the following:[22–24]

1. A lipohilic bicyclic aromatic ring system.
2. Another bulky lipophilic group (e.g. phenyl, *tert*-butyl) as a side chain.
3. Two lipophilic domain linked by a spacer of appropriate length with polar centre at defined position, for example, Naftifine, Butenafine, Terbinafine, Debacarb, Penicillins and Cephalosporins.

In view of the above mentioned facts and in continuation of our interest in the synthesis of heterocycles containing benzothiazole moiety, to identify new candidates that may be of value in designing new, potent, selective and less toxic antimicrobial agents, we report herein the synthesis and antimicrobial evaluation of some novel structure hybrids incorporating both the benzothiazole moiety with either the triazolo-thiadiazole or oxadiazole ring systems through different linkages. This combination was suggested in an attempt to investigate the influence of such hybridization and structure variation on the anticipated biological activities, hoping to add some synergistic biological significance to the target molecules. The substitution pattern of triazolo-thiadiazole and oxadiazole rings was carefully selected so as to confer different electronic environment to the molecules.

Hence, to discover new and useful agents for treatment of microbial diseases, we have replaced the hydrazide group of *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide with additional heterocycles, which have been found to possess an interesting profile of antimicrobial activity. The heterocycles reported here are triazolo-thiadiazole and 1,3,4-oxadiazole. Thus, the synthesized compounds were investigated against one Gram (+) bacteria (*Staphylococcus aureus*), three Gram (–) bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and five fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus flavus*, *Monascus purpureus* and *Penicillium citrinum)* using serial plate dilution method.

Experimental

Chemistry

Chemicals were purchased from Merck Chemical Company, S.D. Fine (India) and Qualigens (India). Melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on a Nicolet, 5PC FTIR spectrometer (ν_{max} in cm^{-1}) and ^1H NMR spectra were recorded in $CDCl_3$/DM SO-d_6 on a Bruker DRX-300 (300 MHz FT NMR) spectrometer using tetramethylsilane (TMS) as internal reference. Chemical shift (δ) are expressed in parts per million (ppm); coupling constants (*J*) are reported in hertz and refer to apparent peak multiplicities, which may not necessarily be true coupling constants. Mass spectra were recorded using Jeol SR-102 (FAB) mass spectrometer. The purity of various synthesized compounds was checked by TLC and elemental analysis. Spectral data (^1H NMR, IR and mass) of the synthesized compounds were in full agreement with the proposed structures.

General procedure for the synthesis of 6-chloro-1,3-benzothiazole-2-amines (1)

A mixture of aniline (0.01 mol) and potassium thiocyanate (0.01 mol) in glacial acetic acid (10%) was cooled and stirred. To this solution bromine (0.01 mol) was added dropwise at such a rate as to keep the temperature below 10°C throughout the addition. Stirring was continued for an additional 3 h and the separated hydrochloride salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralized with aqueous ammonia solution (25%), filtered, washed with water and dried, recrystallized with benzene to obtain 6-chloro-1,3-benzothiazole-2-amines.

1. IR (KBr) ν_{max} (cm^{-1}): 817 (C-Cl), 1570 (C = N), 3480 (NH); ^1H NMR (300 MHz) (DMSO-d_6) δ (ppm) 6.12 (2H, s, NH_2), 6.61–6.64 (3H, *J* = 9 Hz, m, Ar-H).

General procedure for the synthesis of 1-(6-chloro-1,3-benzothiazol-2-yl) urea (2)

To the solution of sodium cyanate in minimum quantity of water, glacial acetic acid (5 mL) was added. This solution was heated with 2-amino-6-chloro-benzothiazole **1** (0.01 mol) in alcohol till the contents of mixture become turbid and volume remained half of the original volume. The contents were added to ice cool water. The solid obtained was filtered off and dried.

2. IR (KBr) ν_{max} (cm^{-1}): 830 (C-Cl), 1560 (C = N), 1628 (C = O), 3310 (NH); ^1H NMR (DMSO-d_6) (300 MHz) δ (ppm) 6.34 (2H, s, NH_2), 6.68–6.70 (3H, *J* = 6 Hz, m, Ar-H), 8.10 (1H, s, NHC = O).

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General procedure for the synthesis of N-(6-chlorobenzo[d] thiazol-2-yl)hydrazine carboxamide (3)

To the warm hydrazine hydrate solution of compound **2** in alcohol, conc. NaOH was added and refluxed for 6 h. Reaction mixture was poured into crushed ice and solid obtained was filtered off and dried. The solid collected out was recrystallized from suitable solvent to get the compound *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide.

(**3**). IR (KBr) ν_{max} (cm^{-1}): 657 (C-S-C), 817 (C-Cl), 1588 (C=N), 1660 (C=O), 3300 (NH); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.28 (1H, s, $NHNH_2$), 7.70–7.74 (3H, J = 12 Hz, m, Ar-H), 9.12 (1H, s, NHC=O).

General procedure for the synthesis of potassium dithiocarbazinate (4)

Potassium hydroxide (0.03 mol) was dissolved in absolute ethanol (50 mL). The solution was cooled in ice bath and acid hydrazide (**3**; 0.02 mol) was added with stirring. To this carbon disulphide (0.025 mol) was added in small portions with constant stirring. The reaction mixture was agitated continuously for 12 h at room temperature. The precipitated potassium dithiocarbazinate was collected by filtration, washed with anhydrous ether (100 mL) and dried in vacuum. The potassium salt thus obtained was in quantitative yield and was used in the next step without further purification.

General procedure for the synthesis of 4-amino-5-(6-chlorobenzo[d]thiazol-2-ylamino)-4H-1,2,4-triazole-3-thiol (5)

A suspension of potassium dithiocarbazinate (**4**; 0.02 mol) in water (50 mL) and hydrazine hydrate (99%,0.04 mol) was refluxed for 18–20 h with occasional shaking. The colour of the reaction mixture changed to green, with evolution of hydrogen sulphide gas. A homogenous reaction mixture was obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with water (20 mL). On acidification with acetic acid, the required triazole was precipitated out. It was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol. Purity of the compound was checked by TLC using silica gel-G coated plates by using toluene: ethyl acetate:formic acid (T:E:F); (5:4:1) as solvent system, and observed in UV light.

5. IR (KBr) ν_{max} (cm^{-1}): 635 (C-S-C), 817 (C-Cl), 1528 (C=N), 2518 (SH), 3338 (NH_2); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm): 5.15(s, 2H, NH_2), 7.28–7.32 (3H, J = 12 Hz, Ar-H), 9.29 (1H, s, NH),13.18 (1H, br s, SH).

General procedure for the synthesis of 6-chloro-N-(6-substituted-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl) benzo[d] thiazol-2-amine (6a–g)

An equimolar mixture (0.10 mol) of 4-amino-5-(6-chlorobenzo[*d*]thiazol-2-ylamino)-4H-1,2,4-triazole-3-thiol (**5**) and aromatic acids in phosphorus oxychloride (10 mL) was refluxed for 5 h. The reaction mixture was cooled to room temperature and then gradually poured on to crushed ice with stirring. The mixture was allowed to stand overnight and the solid separated out was filtered, treated with dilute sodium hydroxide solution and washed thoroughly with cold water. The compound so obtained was dried and recrystallized from ethanol.

(**6a**). IR (KBr) ν_{max} (cm^{-1}): 610 (C-S-C benzothiazole), 674 (C-S-C triazolo-thiadiazole), 837 (C-Cl), 1269 (N-N=C triazolo-thiadiazole), 1416 (C-N benzothiazole), 1518 (C=C aromatic), 3084 (C-H aromatic), 3314 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm): 7.41–7.44 (8H, J = 9 Hz, m, Ar-H), 8.06 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3,121.2, 125.8, 128.7, 129.2, 129.8, 130.9, 132.3, 133.5, 143.3, 151.3, 157.2, 167.6, 174.5; Mass (*m/z*): 384 (M^+). Analysis for $C_{16}H_9ClN_6S_2$ (384.87); Calcd: C; 49.96, H; 2.40, N; 21.88, S; 16.69. Found: C; 49.93, H; 2.36, N; 21.84, S; 16.66.

(**6b**). IR (KBr) ν_{max} (cm^{-1}): 616 (C-S-C benzothiazole), 688 (C-S-C triazolo-thiadiazole), 821 (C-Cl), 1274 (N-N=C triazolo-thiadiazole), 1422 (C-N benzothiazole), 1524 (C=C aromatic), 3114 (C-H aromatic), 3318 (N-H);^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.36–7.40 (7H, J = 12 Hz, m, Ar-H), 8.01 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 127.3, 128.9, 129.3, 129.8, 130.1, 132.2, 132.3, 136.9, 151.3, 157.2, 167.6, 174.1, 174.5; Mass (*m/z*): 419 (M^+). Analysis for $C_{16}H_8Cl_2N_6S_2$ (419.31); Calcd: C; 45.86, H; 1.94, N; 20.07, S; 15.31. Found: C; 45.83, H; 1.92, N; 20.04, S; 15.29.

(**6c**). IR (KBr) ν_{max} (cm^{-1}): 614 (C-S-C benzothiazole), 686 (C-S-C triazolo-thiadiazole), 822 (C-Cl), 1275 (N-N=C triazolo-thiadiazole), 1424 (C-N benzothiazole), 1526 (C=C aromatic), 3112 (C-H aromatic), 3317 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.40–7.44 (6H, *J* = 12 Hz, m, Ar-H), 8.03 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 127.4, 129.8, 130.3, 130.9, 132.3, 133.6, 135.0, 135.7, 151.3, 157.2, 167.6, 174.1, 174.5; Mass (*m/z*): 453 (M^+). Analysis for $C_{16}H_{17}Cl_3N_6S_2$ (453.76); Calcd: C; 42.37, H; 1.58, N; 18.56, S; 14.15. Found: C; 42.35, H; 1.55, N; 18.52, S; 14.13.

(**6d**). IR (KBr) ν_{max} (cm^{-1}): 618 (C-S-C benzothiazole), 691 (C-S-C triazolo-thiadiazole), 829 (C-Cl), 1281 (N-N=C triazolo-thiadiazole), 1427 (C-N benzothiazole), 1531 (C=C aromatic), 3119 (C-H aromatic),3319 (N-H);^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 2.34(3H, S, CH_3), 7.35–7.37 (6H, *J* = 6 Hz, m, Ar-H), 8.07 (1H, s, NH); ^{13}C NMR δ (ppm): 18.7,118.3, 121.2, 125.8, 126.2, 127.4, 128.6,129.5, 129.8, 132.3, 136.9, 137.2, 151.3, 157.2, 167.6, 174.1, 174.5; Mass (*m/z*): 398 (M^+). Analysis for $C_{16}H_{17}Cl_3N_6S_2$ (398.89); Calcd: C; 51.21, H; 2.82, N; 21.10, S;16.12. Found: C; 51.19, H; 2.78, N; 21.07, S; 16.08.

(**6e**). IR (KBr) ν_{max} (cm^{-1}): 626 (C-S-C benzothiazole), 684 (C-S-C triazolo-thiadiazole), 817 (C-Cl), 1267 (N-N=C triazolo-thiadiazole), 1436 (C-N benzothiazole), 1527 (C=C aromatic), 3106 (C-H aromatic), 3324 (N-H);^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 2.51(3H, s, $OCOCH_3$), 7.24–8.28 (7H, *J* = 12 Hz, m, Ar-H),8.10 (1H, s, NH); ^{13}C NMR δ (ppm): 20.3,118.3, 121.2, 123.2, 125.8, 126.0, 127.9, 129.1, 129.4,129.8, 132.3, 151.1, 151.3, 157.2, 167.6, 169.0, 174.1, 174.5; Mass (*m/z*): 442 (M^+). Analysis

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for $C_{18}H_{11}ClN_6O_2S_2$ (442.90); Calcd: C; 48.84, H; 2.52, N; 18.99, S; 14.51. Found: C; 48.81, H; 2.50, N; 18.97, S; 14.48.

(**6f**). IR (KBr) ν_{max} (cm^{-1}): 626 (C-S-C benzothiazole), 692 (C-S-C triazolo-thiadiazole), 836 (C-Cl), 1274 (N-N=C triazolo-thiadiazole), 1434 (C-N benzothiazole), 1532 (C=C aromatic), 3123 (C-H aromatic), 3318 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.29–7.31 (m, J=6 Hz,8H, Ar-H), 8.10 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 122.7, 124.6, 125.8, 129.7, 129.8, 132.3, 151.3, 155.2, 157.2, 167.6, 174.5; Mass (*m/z*): 400 (M^+). Analysis for $C_{16}H_9ClN_6OS_2$ (400.87); C; 47.97, H; 2.30, N; 20.98, S; 16.04. Found: C; 47.94, H; 2.26, N; 20.96, S; 16.00.

(**6g**). IR (KBr) ν_{max} (cm^{-1}): 621 (C-S-C benzothiazole), 689 (C-S-C triazolo-thiadiazole), 830 (C-Cl), 1280 (N-N=C triazolo-thiadiazole), 1369 (NO_2), 1429 (C-N benzothiazole), 1527 (C=C aromatic), 3118 (C-H aromatic), 3320 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.39–7.41 (7H, J=6 Hz, m, Ar-H), 8.12 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 124.4, 125.8, 128.4,129.8, 132.3, 139.6, 143.3, 147.9, 151.3, 157.2, 167.6, 174.1, 174.5; Mass (*m/z*): 429 (M^+). Analysis for $C_{16}H_{17}Cl_3N_6S_2$ (429.86): C; 48.84, H; 2.52, N; 18.99, S; 14.51. Found: C; 48.81, H; 2.50, N; 18.97, S; 14.48.

General procedure for the synthesis of N-(6-Chlorobenzo[d] thiazol-2-yl)-5-phenyl-1,3,4-oxadiazol-2-amine (7a)

Compound **3** (0.001 mol) and appropriate aromatic acid (0.001 mol) was dissolved in phosphorus oxychloride and refluxed for 20 h. The reaction mixture was slowly poured over crushed ice and kept overnight. The solid thus separated out was filtered, washed with water, dried and recrystallized from ethanol.

(**7a**). IR (KBr) ν_{max} (cm^{-1}): 622 (C-S-C benzothiazole), 1454 (C-N benzothiazole), 1488 (C-O-C oxadiazole), 1518 (C=C aromatic), 3318 (N-H),. ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.24–7.28 (8H, J=12 Hz, m, Ar-H), 8.10 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 126.1, 127.5, 128.7, 129.2, 129.8, 132.3, 151.3, 164.5, 169.3, 174.5; Mass (*m/z*): 328 (M^+). Analysis for $C_{15}H_9ClN_4OS$ (328.78): C; 54.82, H; 2.78, N; 17.08, S; 9.77. Found: C; 54.80, H; 2.76, N; 17.04, S; 9.75.

(**7b**). IR (KBr) ν_{max} (cm^{-1}): 624 (C-S-C benzothiazole), 821 (C-Cl), 1456 (C-N benzothiazole), 1491 (C-O-C oxadiazole), 1512 (C=C aromatic), 3317 (N-H).^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.22–7.26 (7H, J=12 Hz, m, Ar-H), 8.14 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 127.3, 128.9, 129.3, 129.8, 130.1, 132.2,132.3, 136.9, 151.3, 164.5, 169.3, 174.5; Mass *m/z*: 363 (M^+). Analysis for $C_{15}H_8Cl_2N_4OS$ (363.22): C; 49.64, H; 2.24, N; 15.45, S; 8.85. Found: C; 49.60, H; 2.22, N; 15.42, S;8.83.

(**7c**). IR (KBr) ν_{max} (cm^{-1}): 628 (C-S-C benzothiazole), 826 (C-Cl), 1461 (C-N benzothiazole), 1497 (C-O-C oxadiazole), 1516 (C=C aromatic), 3321 (N-H). ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.26–7.30 (6H, J=12 Hz, m, Ar-H), 8.20 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 128.8, 129.8, 130.2, 130.3, 130.7, 132.3, 132.9, 138.3, 151.3, 164.5, 169.3, 174.5; Mass (*m/z*): 397 (M^+).Analysis for $C_{15}H_7Cl_3N_4OS$ (397.67): C; 45.32, H; 1.79, N; 14.11, S; 8.08. Found: C; 45.30, H; 1.77, N; 14.09, S; 8.06.

(**7d**). IR (KBr) ν_{max} (cm^{-1}): 632 (C-S-C benzothiazole), 812 (C-Cl), 1467 (C-N benzothiazole), 1496 (C-O-C oxadiazole), 1514 (C=C aromatic), 3331 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 2.21(3H, s, CH_3), 7.64–7.68 (7H, J=12 Hz, m, Ar-H), 8.12 (1H, s, NH); ^{13}C NMR δ (ppm): 18.7, 118.3, 121.2, 125.8, 126.2, 127.4, 128.6, 129.5, 129.8, 132.3, 136.9, 137.2, 151.3, 164.5, 169.3, 174.5; Mass (*m/z*): 342 (M^+).Analysis for $C_{16}H_{11}ClN_4OS$ (342.80): C; 56.06, H; 3.23, N; 16.34, S; 9.35. Found: C; 56.10, H; 3.25, N; 16.36, S; 9.37.

(**7e**). IR (KBr) ν_{max} (cm^{-1}): 638 (C-S-C benzothiazole), 824 (C-Cl), 1468 (C-N benzothiazole), 1489 (C-O-C oxadiazole), 1517 (C=C aromatic), 3336 (N-H). ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 2.59 (3H, s, $OCOCH_3$), 7.24–7.28 (7H, *J*=12 Hz, m, Ar-H),8.16 (1H, s, NH); ^{13}C NMR δ (ppm): 20.3, 117.8, 118.3, 121.2, 123.2, 125.8, 126.0, 129.1, 129.8, 132.3, 137.1, 151.1, 151.3, 164.5, 169.0, 169.3, 174.5; Mass (*m/z*): 386 (M^+). Analysis for $C_{17}H_{11}ClN_4O_3S$ (386.81): C; 52.79, H; 2.87, N; 14.48, S; 8.29. Found: C; 52.81, H; 2.88, N; 14.51, S; 8.32.

(**7f**). IR (KBr) ν_{max} (cm^{-1}): 634 (C-S-C benzothiazole), 824 (C-Cl), 1464 (C-N benzothiazole), 1492 (C-O-C oxadiazole), 1518 (C=C aromatic), 3326 (N-H). ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.25–7.28 (8H, J=9 Hz, m, Ar-H), 8.14 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 122.7, 124.6, 125.8, 129.7, 129.8, 132.3, 151.3, 155.2, 158.7, 169.3, 174.5; Mass (*m/z*): 344 (M^+).Analysis for $C_{15}H_9ClN_4O_2S$ (344.78): C; 52.25, H; 2.63, N; 16.25, S; 9.30. Found: C; 52.22, H; 2.61, N; 16.23, S; 9.27.

(**7g**). IR (KBr) ν_{max} (cm^{-1}): 637 (C-S-C benzothiazole), 828 (C-Cl), 1378 (NO_2), 1468 (C-N benzothiazole), 1496 (C-O-C oxadiazole), 1521 (C=C aromatic), 3336 (N-H). ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.21–7.24 (7H, *J*=9 Hz, m, Ar-H), 8.16 (1H, s, NH); ^{13}C NMR δ (ppm): 118.3, 121.2, 122.8, 123.9, 125.8, 127.0, 129.8, 130.1, 132.3, 133.6, 148.4, 151.3, 164.5, 169.3, 174.5; Mass (*m/z*): 373 (M^+). Analysis for $C_{15}H_8ClN_5O_3S$ (373.77); C; 48.20, H; 2.16, N; 18.74, S; 8.58. Found: C; 48.23, H; 2.18, N; 18.76, S; 8.60.

General procedure for the synthesis of 5-(6-Chlorobenzo[d] thiazol-2-ylamino)-1,3,4-oxadiazole-2-thiol (8)

A mixture of **3** (0.005 mol), KOH (0.005 mol) and carbon disulphide (5 mL) in ethanol (50 mL) was refluxed on a steam bath for 12 h. The solution was then concentrated, cooled and acidified with dilute HCl. The solid mass that separated out was filtered, washed with ethanol, dried and recrystallized from ethanol.

(**8**). IR (KBr) ν_{max} (cm^{-1}): 614 (C-S-C benzothiazole), 826 (C-Cl), 1421 (C-N), 1505 (C-O-C oxadiazole), 1514 (C=C), 1614 (C=O), 2516 (SH), 3316 (N-H); ^{1}H NMR (DMSO-d_6) (300 MHz) δ (ppm) 7.17–7.19 (3H, *J*=6 Hz, m, Ar-H), 8.05 (1H, s, NH), 10.41(1H, s, SH); ^{13}C NMR δ (ppm): 118.3, 121.2, 125.8, 129.8, 132.3, 151.3, 169.3, 174.5; Mass (*m/z*): 284 (M^+). Analysis for $C_9H_5ClN_4OS_2$ (284.75): C; 37.98, H; 1.80, N; 19.71, S; 22.56. Found: C; 37.96, H; 1.77, N; 19.68, S; 22.52.

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Antimicrobial activity

Antibacterial activity of the synthesized compounds were determined *in vitro* by using serial plate dilution method[25,26] against *E. coli* (ATCC-25922), *S. aureus* (ATCC-25923), *P. aeruginosa* (ATCC-27853) and *K. pneumoniae* (ATCC-700603) at 100 µg/mL, 50 µg/mL, 25 µg/mL and 12.5 µg/mL concentrations, respectively, in the nutrient agar media. Standard antibiotic ofloxacin was used as reference drug at 25 µg/mL, 12.5 µg/mL and 6.25 µg/mL concentrations.

Newly synthesized compounds were screened *in vitro* against pathogenic fungal strains *C. albicans* (ATCC 2091), *A. niger* (MTCC 281), *Aspergillus flavus* (MTCC 277), *M. purpureus* (MTCC 369) and *P. citrinum* (NCIM 768) by serial plate dilution method[27,28] at 100 µg/mL, 50 µg/mL, 25 µg/mL and 12.5 µg/mL concentrations in sabouraud dextrose medium. Ketoconazole was used as standard drug at 25 µg/mL, 12.5 µg/mL and 6.25 µg/mL concentrations. Solutions of required concentrations of test compounds were prepared by dissolving the compounds in DMSO. The minimum inhibitory concentration (MIC) obtained for the test compounds and reference drugs are reported in Tables 2 and 3. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the compounds that inhibited visible growth of microorganisms on the plate.

Results and discussion

Chemistry

6-substituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole (**6a–g**) and 1,3,4-oxadiazole (**7a–g**, **8**) were prepared according to the procedure outlined in Schemes 1 and 2. The required dithiocarbazinate (**4**) was synthesized by reacting *N*-(6-chlorobenzo[*d*]thiazol-2-*yl*) hydrazine carboxamide with carbon disulfide and potassium hydroxide in ethanol. This salt underwent ring closure with an excess of 99% hydrazine hydrate to give the 4-amino-5-(6-chlorobenzo[*d*] thiazol-2-ylamino)-4*H*-1,2,4-triazole-3-thiol (**5**). Hence resulted triazole (**5**) was then further converted to the 6-chloro-*N*-(6-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)benzo[*d*] thiazol-2-amine (**6a–g**) in a one-pot reaction, by condensation with aromatic acids in the presence of $POCl_3$. Phosphorus oxychloride was necessary for this condensation, which activate the carbonyl group of aromatic acids and increases its electrophilicity to enhance the addition of triazole to it. The synthesis of compounds (**7a–g**) was accomplished in a single step by reacting the benzothiazole carboxamide with aromatic acids in the presence of $POCl_3$ and compound (**8**) by reacting with carbon disulfide and potassium hydroxide in ethanol, respectively. The structure of synthesized compounds was confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, Mass).

Physicochemical data for the *N*-(6-chlorobenzo[*d*] thiazol-2-*yl*) hydrazine carboxamide derivatives (**6a–g**, **7a–g**, **8**) is given in Table 1. The synthetic route for the title compounds is shown in Schemes 1 and 2.

Antimicrobial activity

The newly synthesized compounds were screened for their antimicrobial activity. The results of antimicrobial effect of all the tested compounds were reported as minimal inhibitory concentrations (MICs, µg/mL).The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **6a–g**, **7a–g** and **8** showed moderate to good inhibition at 12.5–100 µg/mL in DMSO.

The compounds **6c**, **6d**, **6g**, **7a**, **7c**, **7f** and **8** showed comparatively good activity against all the bacterial strains (Table 2). The good activity is attributed to the presence of pharmacologically active 2,4-dichloro (**6c**), methyl (**6d**), 4-nitro (**6g**) substituent attached to phenyl group at position 6 of the triazolo-thiadiazole ring (MIC 12.5 µg/mL & 25 µg/mL), whereas phenyl (**7a**), 2,4-dichlorophenyl (**7c**), phenoxy groups (**7f**) and mercapto (**8**), attached at second position of 1,3,4-oxadiazole moiety (MIC 12.5 µg/mL & 25 µg/mL). When this group was replaced by 2-chlorophenyl (**6b** and **7b**) and acetyl groups (**6e** and **7e**) it caused sharp decrease in activity against most of the strains (MIC 100 µg/mL). The compounds **6a**, **6f**, **7d** and **7g**, exhibited moderate activity compared to that of standard against all the bacterial strains (MIC 25 µg/mL & 50 µg/mL). Further, the result also shows that gram-negative (*E. coli, P. aeruginosa, K. pneumoniae*) exhibited better activity than gram positive (*S. aureus*) organisms.

The compounds **6c**, **6d**, **6f**, **7e**, **7g** and **8** showed comparatively good activity against all the fungal strains (Table 3). The structure of these compounds contains biologically active 2,4-dichloro phenyl, methyl phenyl and phenoxy group attached at position 6 of the triazolo-thiadiazole ring (MIC 12.5 µg/mL & 25 µg/mL) and mercapto, acetyl and 4-nitro phenyl group attached at second position of oxadiazole ring (MIC 12.5 µg/mL & 25 µg/mL), respectively. The compounds **6a**, **6g**, **7a**, **7c** and **7d** showed moderate activity compared to that of standard (6.25 µg/mL) against all the fungal strains (MIC 25 µg/mL & 50 µg/mL). It has been observed that triazolo-thiadiazole derivatives are found to be more active than 1,3,4-oxadiazole derivatives against all pathogenic bacterial and fungal strains.

The antimicrobial activity study revealed that all the compounds tested showed good to moderate antibacterial and antifungal activities against all pathogenic strains (MIC 12.5 µg/mL, 25 µg/mL and 50 µg/mL). Structure and biological activity relationship of title compounds showed that the presence of 2,4-dichloro phenyl, methyl phenyl,4-nitro phenyl group at sixth position of triazolo-thiadiazole (MIC 12.5 µg/mL and 25 µg/mL) and 2-mercapto, phenyl, 2,4-dichlorophenyl and phenoxy group at second position of oxadiazole nucleus (MIC 12.5 µg/ mL and 25 µg/mL) are responsible for good antibacterial activity.

Similarly, presence of 2,4,-dichloro phenyl, methyl phenyl and phenoxy group attached at sixth position of triazolo-thiadiazole (MIC 12.5 µg/mL and 25 µg/mL),

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Table 1. Physicochemical data of *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide derivatives (**6a–g, 7a–g, 8**).

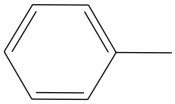
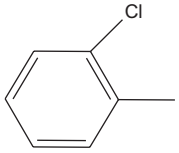
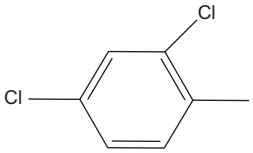
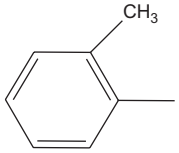
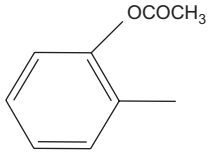
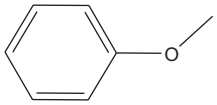
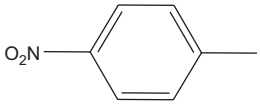
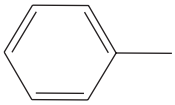
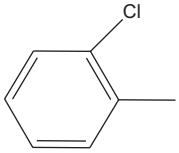
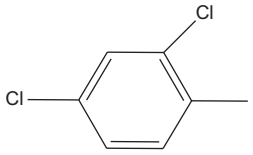
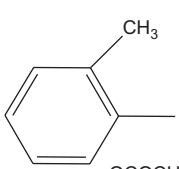
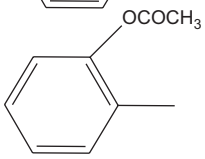
Comp.	R	Yield (%)	M.P. (°C)	Molecular Weight	Molecular Formula	R_f
6a		74	240	384.87	$C_{16}H_9ClN_6S_2$	0.7
6b		71	254	419.31	$C_{16}H_8Cl_2N_6S_2$	0.6
6c		68	248	453.76	$C_{16}H_{17}Cl_3N_6S_2$	0.9
6d		71	282	398.89	$C_{16}H_{17}Cl_3N_6S_2$	0.8
6e		66	288	442.90	$C_{18}H_{11}ClN_6O_2S_2$	0.7
6f		76	218	400.87	$C_{16}H_9ClN_6OS_2$	0.6
6g		63	116	429.86	$C_{16}H_{17}Cl_3N_6S_2$	0.7
7a		67	262	328.78	$C_{15}H_9ClN_4OS$	0.8
7b		64	234	363.22	$C_{15}H_8Cl_2N_4OS$	0.6
7c		66	249	397.67	$C_{15}H_7Cl_3N_4OS$	0.7
7d		65	232	342.80	$C_{16}H_{11}ClN_4OS$	0.8
7e		64	246	386.81	$C_{17}H_{11}ClN_4O_3S$	0.7

Table 1. continued on next page

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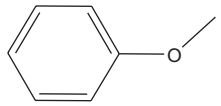
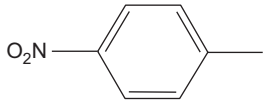
Table 1. Continued.

Comp.	R	Yield (%)	M.P. (°C)	Molecular Weight	Molecular Formula	R_f
7f		73	261	344.78	$C_{15}H_9ClN_4O_2S$	0.8
7g		67	223	373.77	$C_{15}H_8ClN_5O_3S$	0.6
8	—	74	234	284.75	$C_9H_5ClN_4OS_2$	0.8

Elemental analysis were found to be within ± 0.4% of theoretical values.

Table 2. Antibacterial activity of the title compounds (**6a–g**, **7a–g** and **8**).

	MIC in μg/mL and zone of inhibition in mm			
Compounds	*Escherichia coli*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
6a	25 (16–20)	50 (11–15)	50 (11–15)	50 (11–15)
6b	100 (<10)	100 (<10)	100 (<10)	100 (<10)
6c	12.5 (21–25)	25 (16–20)	12.5 (21–25)	12.5 (21–25)
6d	12.5 (21–25)	25 (16–20)	12.5 (21–25)	12.5 (21–25)
6e	100 (<10)	100 (<10)	100 (<10)	100 (<10)
6f	25 (16–20)	25 (16–20)	50(11–15)	25 (16–20)
6g	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	25 (16–20)
7a	12.5 (21–25)	25 (16–20)	25 (16–20)	25 (16–20)
7b	100 (<10)	100 (<10)	100 (<10)	100 (<10)
7c	12.5 (21–25)	25 (16–20)	12.5 (21–25)	12.5 (21–25)
7d	25 (16–20)	50 (11–15)	50 (11–15)	50 (11–15)
7e	100 (<10)	100 (<10)	100 (<10)	100 (<10)
7f	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	25 (16–20)
7g	25 (16–20)	50 (11–15)	50 (11–15)	50 (11–15)
8	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)
Ofloxacin	6.25 (26–30)	6.25 (26–30)	6.25 (26–30)	6.25 (26–30)

The figures in the table show the MIC (Minimum Inhibitory Concentration) values in μg/mL and the corresponding zone of inhibition in mm.

Table 3. Antifungal activity of the title compounds (**6a–g**, **7a–g** and **8**).

	MIC in μg/mL and zone of inhibition in mm				
Compounds	*Candida albicans*	*Aspergillus niger*	*Aspergillus flavus*	*Monascus purpureus*	*Penicillium citrinum*
6a	50 (11–15)	25 (16–20)	50 (11–15)	50 (11–15)	50 (11–15)
6b	100 (<10)	100 (<10)	100 (<10)	100 (<10)	100 (<10)
6c	12.5 (21–25)	25 (16–20)	12.5 (21–25)	25 (16–20)	12.5 (21–25)
6d	12.5 (21–25)	25 (16–20)	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)
6e	100 (<10)	100 (<10)	100 (<10)	100 (<10)	100 (<10)
6f	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	25 (16–20)	25 (16–20)
6g	50 (11–15)	50 (11–15)	25 (16–20)	25 (16–20)	50 (11–15)
7a	25 (16–20)	50 (11–15)	25 (16–20)	25 (16–20)	50 (11–15)
7b	100 (<10)	100 (<10)	100 (<10)	100 (<10)	100 (<10)
7c	50 (11–15)	25 (16–20)	25 (16–20)	50 (11–15)	50 (11–15)
7d	50 (11–15)	50 (11–15)	50 (11–15)	25 (16–20)	50 (11–15)
7e	12.5 (21–25)	12.5 (21–25)	25 (16–20)	25 (16–20)	12.5 (21–25)
7f	100 (<10)	100 (<10)	100 (<10)	100 (<10)	100 (<10)
7g	25(16–20)	25 (16–20)	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)
8	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)	12.5 (21–25)
Ketoconazole	6.25 (26–30)	6.25 (26–30)	6.25 (26–30)	6.25 (26–30)	6.25 (26–30)

The figures in the table show the MIC (minimum inhibitory concentration) values in μg/mL and the corresponding zone of inhibition in mm.

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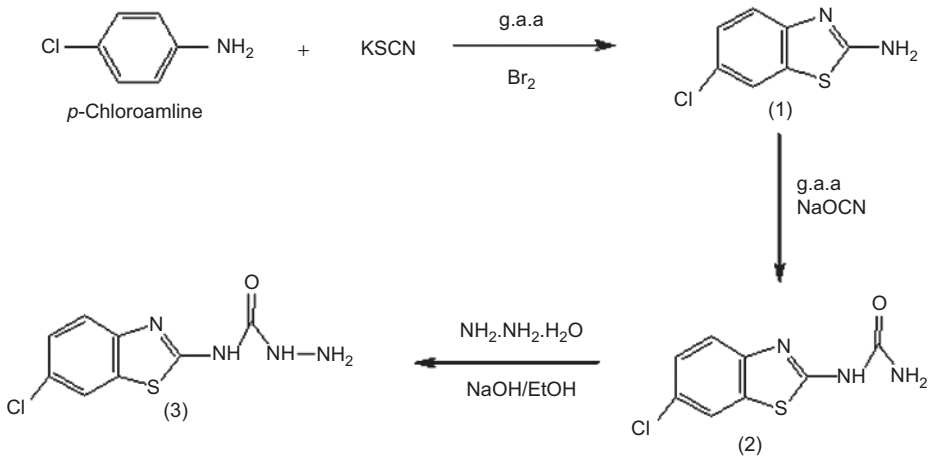
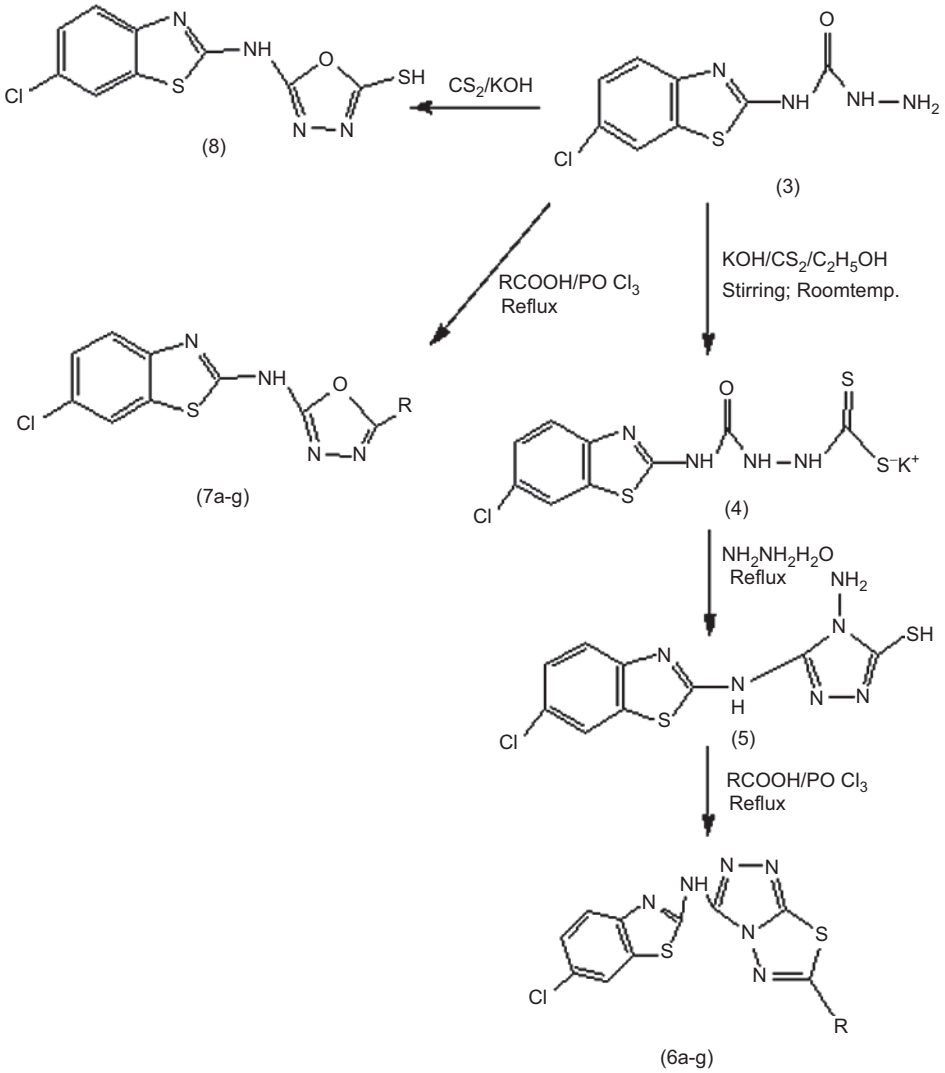


Scheme 1. Synthetic pathways to *N*-(6-chlorobenzo[*d*]thiazol-2-yl) hydrazine carboxamide.



Scheme 2. Synthetic route for the title compounds.

whereas mercapto (–SH), acetyl and 4-nitro phenyl attached at second position of oxadiazole nucleus (MIC 12.5 µg/mL and 25 µg/mL) are responsible for good antifungal activity.

Thus, various triazolo-thiadiazole (**6a–g**) and oxadiazole (**7a–g**, **8**) derivatives of benzothiazole hydrazine carboxamide were prepared with the objective of developing better antimicrobial agents. The triazolo-thiadiazole and oxadiazole derivatives were found to have a promising class of compounds with an interesting pharmacological profile. Further, it is clear from structure

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activity relationship (SAR), that the triazolo-thiadiazole derivatives were found to be more active than oxadiazole derivatives.

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Declaration of interest

The authors report no conflict of interest.

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