Synthesis, spectral investigation and biological evaluation of 3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives

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ABSTRACT

A novel series of heterocyclic compounds 2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)benzamide derivatives 5a–h have been synthesized by the reaction of 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol 3 and 2-((4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)carbamoyl)benzoic acid derivatives 4a–h. Synthesized heterocyclic compounds were characterized by elemental analysis, $^1$H NMR, $^{13}$C NMR, FT–IR and LC-MS spectral studies. Antibacterial activities of all the compounds were studied against gram positive and gram negative bacteria and antifungal activities of all the compounds were studied against various fungi.

Keywords: heterocyclic compound, isonicotinohydrazide, amino-1,2,4-triazoles, triazolothiadiazoles, 4-amino-N-(pyrimidin-2-yl)benzenesulfonamide.

INTRODUCTION

Fused Heterocyclic compounds say triazolothiadiazole derivatives have shown a wide range of pharmacological properties such as antimicrobial [1], anti-inflammatory [2], anticonvulsant [3], anticancer [4], antitubercular [5] and antitumor activities [6]. The sulfa drugs is the Looking to the pharmacological importance, our main concern was to prepare such heterocyclic compounds which possess comparable biological activity by introducing amino-1,2,4-triazoles and triazolothiadiazoles segments together. Literature survey reveals that, not a single report was found in which triazolothiadiazoles containing benzothiazole-amide segment. Hence the initial work pertinent to this in this direction has been carried out by us [7]. In continuation of this the present work comprises the novel 2-(3-(pyridin-4-yl)-[1,2,4] triazolo[3,4-b][1,3,4] thiadiazol-6-yl)-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)benzamide containing benzthiazoloamide segment as shown in Scheme-1.
**Scheme 1: Synthesis of compounds 5a–h**
Where R = As shown in Table-1

**EXPERIMENTAL SECTION**

**Materials and measurements**

All common reagents and solvents including isoniazid used were as analytical grade. Compound 1 and 2 are reported. The 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol (3) was prepared by method reported [8]. 4-amino-N-(pyrimidin-2-yl)benzenesulfonamide and their derivatization with phthalic anhydride was carried out by reported method. [9, 10] (listed in Table-1)

**Table-1**

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Alumina supported pre-coated silica gel 60 F254 thin layer chromatography (TLC) plates were purchased from the E. Merck (India) Limited, Mumbai and were used to check purity of compounds and, to study the progress of the reaction whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I₂ vapors and visualized by spraying with Dragendorff’s reagent. Column chromatography was performed on silica gel (60-120 mesh). LC-MS of all novel samples taken on LCMS 8030 with Nexera UHPLC instrument. Infrared spectra (FT–IR) were obtained from KBr pellets in the range of 4000 –400 cm⁻¹ with a Perkin Elmer spectrometer (FT–IR) instrument. ¹H NMR and ¹³C NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d₆ (residual peak at δ ~2.5 or ~ 39.5 ppm, 300 K) as a solvent as well as TMS an internal reference standard. Micro analytical (C, N, H) data was obtained by using a Perkin–Elmer 2400 CHN elemental analyzer. The melting points were checked by the standard open capillary method and were uncorrected.

**Synthesis of 5a-h**

Compounds 5a-h were synthesized by the general method given below.

An equimolar mixture (0.10 mol) of 4-amino-5-substituted-3-merapto-(4H)-1,2,4-triazoles (2) and 2-((4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)carbamoyl)benzoic acid in phosphorus oxychloride (10 mL) was refluxed for 7 h. The reaction mixture was cooled to room temperature and then gradually poured onto crushed ice with stirring. The mixture was allowed to stand for 5 h. The solid precipitates separated out was filtered, treated with dilute sodium hydroxide solution and washed thoroughly with cold water. The compound obtained was purified by column chromatography, air-dried and recrystallized from ethanol. Products were designated as 5a–h and characterized by elemental, IR, NMR, CMR and LC-MS analyses.
N-(4-(2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-N-(4-(N-(4-methoxypyrimidin-2-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)benzamide (5b)

Compound 5b (M. Wt. 569.62g) was obtained in 62% yield as a dark brown color solid; mp > 250 °C (dec); 1H NMR: δ 4.07 (s, 1H, -NH-), 9.17 (s, 1H, -NH-), 7.97, 8.73 (m, 4H, pyridine), 7.56-8.07 (m, 4H, Ar-H), 7.83, 7.95 (m, 4H, Ar-H), 8.54 (s, 2H, pyrimidine), 2.36 (s, 3H, -CH3); 13C NMR: δ 174.7 (-N=C=S-), 167.5 (-N=C=S-), 164.8 (-C=O), 151.3 (-N=C-N-), 167.4 (-N=N-C-N-), 149.6 (-N=C=C-Py), 121.2, 134.7, 149.6 (Pyridine), 127.2, 127.8, 128.6, 131.8, 132.3, 135.6 (Ar-H), 117.5, 157.2, 167.4 (Pyrimidine), 17.4 (-CH3), 118.7, 129.6, 135.4, 141.3 (Ar-H); FT-IR: ν 3075 (-C=H=Aromatic stretching), 1682 (-C=O stretching), 1531 (-C=C- stretching), 1237 (-N=N-C- stretching), 692 (-C=S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 569.11[M–H]+, (M=569.62); Anal. Calcd for C₂₉H₁₉N₃O₂S₂: C 54.04, H 3.08, N 22.69, S 11.54% Found: C 54.02, H 3.06, N 22.67, S 11.52%.

N-(4-(2,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl]benzamide (5c)

Compound 5c (M. Wt. 583.64g) was obtained in 64% yield as a dark brown color solid; mp > 250 °C (dec); 1H NMR: δ 4.02 (s, 1H, -NH-), 9.18 (s, 1H, -NH-), 7.95, 8.76 (m, 4H, pyridine), 7.51-8.03 (m, 4H, Ar-H), 7.82, 7.99 (m, 4H, Ar-H), 6.34 (s, 1H, pyrimidine), 2.37 (s, 3H, -CH3), 2.43 (s, 3H, -CH3); 13C NMR: δ 174.2 (-N=C=S-), 167.6 (-N=C=S-), 164.4 (-C=O), 151.7 (-N=C-N-), 162.3 (-N=C=N-), 149.5 (-N=C=C-Py), 121.4, 134.6, 149.5 (Pyridine), 127.1, 127.9, 128.4, 131.6, 132.4, 135.2 (Ar-H), 104.7, 158.2, 162.3, 164.3 (Pyrimidine), 24.5 (-CH3), 24.9 (-CH3), 118.2, 129.5, 135.6, 141.7 (Ar-H); FT-IR: ν 3073 (-C=H=Aromatic stretching), 1681 (+C=O stretching), 1538 (-C=C- stretching), 1239 (-N=N-C- stretching), 694 (-C=S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 583.12[M–H]+, (M=583.64); Anal. Calcd for C₂₉H₁₉N₃O₂S₂: C 55.56, H 3.63, N 21.60, S 10.99%; Found: C 55.54, H 3.61, N 21.59, S 10.97%.

N-(4-(4-methoxypyrimidin-2-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl]benzamide (5d)

Compound 5d (M. Wt. 585.62g) was obtained in 66% yield as a dark brown color solid; mp > 250 °C (dec); 1H NMR: δ 4.08 (s, 1H, -NH-), 9.12 (s, 1H, -NH-), 7.92, 8.74 (m, 4H, pyridine), 7.57-8.05 (m, 4H, Ar-H), 7.84, 7.95 (m, 4H, Ar-H), 5.86, 7.47 (d, 2H, pyrimidine), 3.85 (s, 3H, -OCH3); 13C NMR: δ 174.5 (-N=C=S-), 167.8 (-N=C=S-), 164.2 (-C=O), 151.4 (-N=C-N-), 167.3 (-N=C=N-), 149.4 (-N=C=C-Py), 121.5, 134.3, 149.4 (Pyridine), 127.4, 127.7, 128.5, 131.3, 132.6, 135.7 (Ar-H), 98.4, 161.8, 167.3, 167.6 (Pyrimidine), 54.2 (-OCH3), 118.3, 129.7, 135.6, 141.4 (Ar-H); FT-IR: ν 3071 (-C=H=Aromatic stretching), 1688 (-C=O stretching), 1539 (-C=C- stretching), 1235 (-N=N=C- stretching), 697 (-C=S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 585.10[M–H]+, (M=585.62); Anal. Calcd for C₂₉H₁₉N₃O₂S₂: C 53.32, H 3.27, N 21.53, S 10.95%; Found: C 53.31, H 3.26, N 21.51, S 10.93%.

N-(4-(2,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl]benzamide (5e)

Compound 5e (M. Wt. 585.62g) was obtained in 61% yield as a dark brown color solid; mp > 250 °C (dec); 1H NMR: δ 4.08 (s, 1H, -NH-), 9.11 (s, 1H, -NH-), 7.95, 8.77 (m, 4H, pyridine), 7.56-8.08 (m, 4H, Ar-H), 7.82, 7.98 (m, 4H, Ar-H), 5.75 (s, 2H, pyrimidine), 3.86 (s, 3H, -OCH3); 13C NMR: δ 174.2 (-N=C=S-), 167.7 (-N=C=S-), 164.3 (-C=O), 151.7 (-N=C-N-), 160.7 (-N=C=N-), 149.9 (-N=C=C-Py), 121.7, 134.1, 149.9 (Pyridine), 127.5, 127.9, 128.8, 131.2, 132.7, 135.4 (Ar-H), 140.6, 143.4, 160.7 (Pyrimidine), 55.5 (-OCH3), 118.5, 129.7, 135.1, 141.7 (Ar-H); FT-IR: ν 3077 (-C=H=Aromatic stretching), 1689 (-C=O stretching), 1533 (-C=C- stretching), 1227 (-N=N=C- stretching), 695 (-C=S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 585.10[M–H]+, (M=585.62); Anal. Calcd for C₂₉H₁₉N₃O₂S₂: C 53.32, H 3.27, N 21.53, S 10.95%; Found: C 53.30, H 3.24, N 21.51, S 10.93%.

N-(4-(4-methoxypyrimidin-2-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl]benzamide (5f)

Compound 5f (M. Wt. 615.64g) was obtained in 65% yield as a dark brown color solid; mp > 250 °C (dec); 1H NMR: δ 4.08 (s, 1H, -NH-), 7.93, 8.76 (m, 4H, pyridine), 7.54-8.01 (m, 4H, Ar-H), 7.82, 7.97 (m, 4H, Ar-H), 5.93...
(s, 1H, pyrimidine), 3.82 (s, 3H, -OCH₃), 3.87 (s, 3H, -OCH₃); 13C NMR: δ 174.8 (-N=C=S-), 167.3 (-N=C-S-), 164.8 (-C=O), 151.7 (-N=C-N-), 171.7 (-N=C-N-), 149.2 (-N=C-Py), 121.8, 134.6, 149.2 (Pyridine), 127.1, 127.7, 128.5, 131.4, 132.8, 135.7 (Ar-H), 82.6, 162.3, 164.7 (Pyrimidine), 54.3 (-OCH₃), 54.8 (-OCH₃), 118.2, 129.7, 135.6, 141.8 (Ar-H); FT-IR: υ 3066 (-C-H=Aromatic stretching), 1686 (-C=O stretching), 1525 (-C=C-stretching), 1232 (-N-N=C-stretching), 696 (-C-S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 615.11[M-H]+, (M=615.64); Anal. Calc'd for C₂₇H₁₉N₅O₆S₂: C 52.67, H 3.44, N 20.48, S 10.42%. Found: C 52.65, H 3.42, N 20.46, S 10.40%.

N-(4-(5,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)benzamide (5g) Compounds 5g (M. Wt. 615.64g) was obtained in 66% yield as a dark brown color solid; mp > 250 °C (dec); ¹H NMR: δ 4.07 (s, 1H, -NH-), 9.12 (s, 1H, -NH-), 7.94, 8.77 (m, 4H, pyridine), 7.58-8.03 (m, 4H, Ar-H), 7.81, 7.97 (m, 4H, Ar-H), 8.34 (s, 1H, pyrimidine), 3.87 (s, 1H, -OCH₃), 4.09 (s, 1H, -OCH₃); 13C NMR: δ 174.6 (-N=C-S-), 167.7 (-N=C-S-), 164.4 (-C=O), 151.8 (-N=C-N-), 153.5 (-N=C-N-), 149.7 (-N=C-Py), 121.7, 134.5, 149.7 (Pyridine), 127.1, 127.7, 128.3, 131.7, 132.5, 135.9 (Ar-H), 130.6, 154.3, 161.8 (Pyrimidine), 54.7 (-OCH₃), 118.2, 129.7, 135.9, 141.4 (Ar-H); FT-IR: υ 3063 (-C-H=Aromatic stretching), 1681 (-C=O stretching), 1524 (-C=C-stretching), 1236 (-N-N=C-stretching), 693 (-C-S-C- = triazolo-thiadiazole) cm⁻¹; LC-MS m/z 615.11[M-H]+, (M=615.64); Anal. Calc'd for C₂₇H₁₉N₅O₆S₂: C 52.67, H 3.44, N 20.48, S 10.42%. Found: C 52.65, H 3.42, N 20.46, S 10.40%.

Biological activity Antibacterial activity (in vitro) Compounds (5a–h) were screened for in vitro antibacterial activity against Gram-positive bacterial strains (Bacillus subtilis [BS] and Staphylococcus aureus [SA]) and Gram-negative bacterial strains (Salmonella typhimurium [ST] and Escherichia coli [EC]) utilizing the agar diffusion assay [11,12]. The wells were dug in the media with the help of a sterile metallic borer. Recommended concentration (100 µl) of the test sample (1 mg/mL in DMSO) was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug, ciprofloxacin were served as negative and positive controls, respectively. The plates were incubated immediately at 37°C for 24 hours. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO and they showed no activity against any bacterial strains.

Antifungal activity (in vitro) Compounds (5a–h) were also examined for antifungal activity against different fungal strains, i.e. Penicillium expansum [PE], Botryodiplodia theobromae [BT], Nigrospora sp. [NS], Trichothecium sp. [TS]. The antifungal drug, ketoconazole was used as a positive control. Antifungal screening for compounds (5a–h) and positive control was performed at a recommended concentration. The fungal strains were grown and maintained on potato dextrose agar plates. The cultures of the fungi were purified by single spore isolation technique. Each compound (5a–h) in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated at 25± 2°C for 48 h. The plates were then observed and the diameters of the zone of inhibition (in mm) were measured. The percentage inhibition for fungi was calculated after five days using the formula given below:

\[
\text{Percentage of inhibition} = \frac{100(X-Y)}{X}
\]

Where, X = Area of colony in control plate
Y = Area of colony in test plate
RESULTS AND DISCUSSION

Synthesis of compounds 5a–h
To the best of our knowledge, compounds 5a–h has not been reported previously. The characterization of the reaction product provided the first unambiguous proof of the successful synthesis of 2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-N-(4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)benzamide derivatives.

Elemental analysis of all compounds was in good agreement with proposed structures as mentioned in scheme 1. The structures of all compounds were consistent with the FT–IR, $^1$H NMR, $^{13}$C NMR and LC-MS.

IR spectral features provide valuable information regarding the nature of functional group attached [13]. In order to study the bonding mode of compound 3 to the compound 5a-h, the IR spectrum of compound 3 was compared with the spectra of compound 5a-h. Considerable differences to be expected were observed. The FT–IR spectrum of 5a–h showed the most relevant peaks of triazolo-thiadiazole ring. The band around 1680 cm$^{-1}$ and 1533 cm$^{-1}$ corresponding respectively to –C=N stretching and –C=C– stretching. The band around 1230 cm$^{-1}$ and 688 cm$^{-1}$ corresponding respectively to –N–N=C– banding and –C–S–C– banding indicating the formation of triazolo-thiadiazole derivatives.

Inspection of IR spectra of 5a-h, 3 and 4a-h reveals discernible differences. The important band due to –COOH group of 4a-h appeared [13] at 1680 cm$^{-1}$ almost disappeared in IR spectra of 5a-h. The bands due to –NH$_2$ and –SH groups observed [13] in the spectrum of 3 are almost vanished in the IR spectra of 5a-h.

In the 1H NMR spectroscopy, the signals at 7.9 and 8.8 ppm were ascribed to the protons of the pyridine ring. The singlet at about 9.13 ppm was ascribed to the protons of –N-H bond. Which was further confirmed by 13C NMR value i.e. δ 164 is attributed to (carbonyl carbon), 174 and 167 are attributed to –N=C–S–, 152 and 170 are attributed to –N=C–N– and 149 is attributed to –N=C–C–. The expected structure was thus clearly verified by the spectroscopic analysis which indicated moreover the absence of any detectable impurity, particularly of the two reagents used to prepare 5a–h. which again supported by the LC–MS Spectral features. Other detail data of each compound are presented in experimental section. All the data suggest the predicted structure shown in scheme-1.

The expected structure was thus clearly verified by the spectroscopic analysis which indicated moreover the absence of any detectable impurity, particularly of the two reagents used to prepare 5a–h. which again supported by the LC-MS Spectral features.

Biological activity

Antibacterial activity

Based on the data from the antibacterial studies against both Gram–positive and Gram–negative bacterial strains (Figure 1), the following observations can be made. All compounds (5a–h) exhibited antibacterial activity against both Gram–positive and Gram–negative bacterial strains with zones of inhibition (ZOI) ranging from 29 mm to 46 mm (Figure 2). Among the analogs 5a–h, compound 5f (ZOI$_{[BS]}$ = 44 mm, ZOI$_{[SA]}$ = 45 mm, ZOI$_{[ST]}$ = 43 mm, ZOI$_{[EC]}$ = 46 mm) and compound 5g (ZOI$_{[BS]}$ = 42 mm, ZOI$_{[SA]}$ = 43 mm, ZOI$_{[ST]}$ = 42 mm, ZOI$_{[EC]}$ = 44 mm) was identified as a potent antibacterial agent against all Gram–positive and Gram–negative bacterial strains. Compound 5h (ZOI$_{[BS]}$ = 41 mm, ZOI$_{[SA]}$ = 41 mm, ZOI$_{[ST]}$ = 40 mm, ZOI$_{[EC]}$ = 42 mm) and compound 5d (ZOI$_{[BS]}$ = 39 mm, ZOI$_{[SA]}$ = 38 mm, ZOI$_{[ST]}$ = 37 mm, ZOI$_{[EC]}$ = 39 mm) had good antibacterial activity against bacterial strains. Compound 5e (ZOI$_{[BS]}$ = 37 mm, ZOI$_{[SA]}$ = 36 mm, ZOI$_{[ST]}$ = 34 mm, ZOI$_{[EC]}$ = 36 mm) and compound 5c (ZOI$_{[BS]}$ = 35 mm, ZOI$_{[SA]}$ = 36 mm, ZOI$_{[ST]}$ = 34 mm, ZOI$_{[EC]}$ = 36 mm) also had comparable antibacterial activity against bacterial strains. Compounds 5b and 5a exhibited less antibacterial activity. Compounds 5a–h exhibited less antibacterial activity as compare to standard antibiotic drug, ciprofloxacin (ZOI$_{[BS]}$ = 45 mm, ZOI$_{[SA]}$ = 46 mm, ZOI$_{[ST]}$ = 45 mm, ZOI$_{[EC]}$ = 47 mm).
Antifungal activity
Based on the screening data from the antifungal studies (Figure 3), the following observations can be made. All compounds (5a–h) exhibited antifungal activity against different fungal strains (Figure 4). Among the analogs 5a–h, compound 5f (ZOI_{PE} = 39 mm, ZOI_{BT} = 41 mm, ZOI_{NS} = 40 mm, ZOI_{TS} = 38 mm) and Compound 5g (ZOI_{PE} = 37 mm, ZOI_{BT} = 38 mm, ZOI_{NS} = 38 mm, ZOI_{TS} = 36 mm) was found more active against all fungal strains. Compound 5h (ZOI_{PE} = 34 mm, ZOI_{BT} = 36 mm, ZOI_{NS} = 35 mm, ZOI_{TS} = 34 mm) and compound 5d (ZOI_{PE} = 31 mm, ZOI_{BT} = 34 mm, ZOI_{NS} = 33 mm, ZOI_{TS} = 32 mm) also had good antifungal activity against fungal
strains. Compound 5e (ZOI[PE] = 29 mm, ZOI[BT] = 32 mm, ZOI[NS] = 30 mm, ZOI[TS] = 31 mm) and compound 5c (ZOI[PE] = 28 mm, ZOI[BT] = 30 mm, ZOI[NS] = 28 mm, ZOI[TS] = 29 mm) also had comparable antifungal activity against bacterial strains. Compounds 5b and 5a exhibited less antifungal activity. All compounds (5a–h) exhibited less antifungal activity as compare to standard antibiotic drug, ketoconazole (ZOI[PE] = 40 mm, ZOI[BT] = 42 mm, ZOI[NS] = 41 mm, ZOI[TS] = 39 mm).

Figure 3: Antifungal activity of compounds 5a–h

Figure 4: Comparative Antifungal activity of compounds 5a–h
CONCLUSION

A novel series of heterocyclic compounds 2-(3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-N-(4-(N- (pyrimidin-2-yl)sulfamoyl)phenyl)benzamide derivatives 5a–h have been duly synthesized and characterized. Antibacterial activities were studied against gram positive and gram negative bacteria and antifungal activities of all the compounds were studied against various fungi. All the compounds were found biologically active.

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