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ARTICLE

Synthesis and Antimicrobial Evaluation of Novel Benzene Sulfonamide Pyrazole Linked [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole Derivatives

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ABSTRACT

A novel series of benzene sulfonamide pyrazole linked [1,2,4]-triazolo[3,4-b][1,3,4]thiadiazole derivatives have been synthesized by reaction of 4-(3-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide with different substituted benzoic/pyridinyl/indolyl acids in $POCl_3$, characterized by IR, ^1H NMR, ^{13}C NMR, MS analytical data and evaluated for their antibacterial as well as antifungal activity. Antibacterial activity of compounds **6c**, **6i** and **6k** were found good against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* compared to standard ampicillin. Compounds **6b** and **6e** is having promising antifungal activity against *C. albicans* as compare to standard griseofulvin.

KEYWORDS

Acid hydrazide, Benzene sulfonamide pyrazole, 4-amino-1,2,4-triazole-3-thiol, triazolo-thiadiazole, Antibacterial activity, Antifungal activity.

INTRODUCTION

In recent years, fused derivatives of 1,2,4-triazoles are well known heterocycles for their medicinal, agricultural as well as industrial applications [1]. Now a days young researchers looking towards the 1,2,4-triazoles and their fused derivatives such as triazolothiadiazole as a promising target molecules due to their diverse types of therapeutical applications such as antimicrobial [2-4], anti-inflammatory, analgesic [4,5] antioxidant [5], anticancer [6], anthelmintic [7], anti-HIV, antitumor [8], antitubercular [9], *etc*.

In continuation with our research efforts working on azole derivatives [10] and inspired by the results of clubbed triazole derivatives like triazolothiadiazole, a thought came to develop novel hybrid with triazolothiadiazole and benzenesulfonamide pyrazole moiety in a single scaffold, as benzene sulfonamide is key component of commercially available nonsteroidal anti-inflammatory drugs celecoxib, rofecoxib, valdecoxib and deracoxib. Along with key drug component, benzene sulfonamide pyrazole is also possessing therapeutic properties like anti-inflammatory [11,12], antimicrobial [12,13] and carbonic anhydrase (CA) inhibitors [14,15]. These novel composition

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have been composed and synthesized to gain the advantage of benzene sulfonamide pyrazole and triazolothiadiazole in a single molecule with belief to have new molecule with remarkable antimicrobial activity.

EXPERIMENTAL

Melting points of synthesized compounds were determined using Buchi M-565 melting point analyzer and are uncorrected. Purity of compounds was monitored by TLC on silica gel 60 F_{254} coated aluminium plates (Merck) as adsorbent and visualized under U.V. light and iodine chamber. IR spectra (neat) were recorded using Perkin Elmer Spectrum-100 analyzer. NMR spectra were recorded on a Jeol/bruker operating at 400/200 MHz (^{1}H NMR) and 400/50 MHz (^{13}C NMR) using DMSO as a solvent and TMS as an internal standard (chemical shift in ppm). All the chemicals and solvents used are laboratory reagent grade.

Ethyl-5-(3-fluoro-4-methoxyphenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (3): A mixture of ethyl-4-(3-fluoro-4-methoxyphenyl)-2,4-dioxobutanoate (**2**) (0.01 mol) and 4-sulfonamido phenyl hydrazine hydrochloride (0.03 mol) in ethanol was refluxed for 4-5 h. Reaction progress was examined by TLC. After completion, reaction mass was concentrated under vacuum and the obtained residue was poured over crushed ice. The obtained solid was filtered and washed with water, dried under suction and purified in toluene. Yield 86 %; off white solid; m.p. 230-232 ºC; IR (neat, ν_{max}, cm^{-1}): 3328, 3288 (N-H), 3070 (arom. C-H), 1723 (C=O), 1450 (C=C), 1371, 1162 (S=O), 1281 (C-F); ^{1}H NMR (DMSO-d_6) δ ppm: 1.29-1.33 (m, 3H, -CH3), 3.84 (s, 3H, -OCH_3), 4.31-4.36 (m, 2H, -CH_2-), 7.03 (s, 1H, pyrazole -CH-), 7.14-7.25 (m, 3H, Ar-H), 7.53-7.56 (m, 4H, Ar-H), 7.88-7.90 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 14.23, 56.07, 60.67, 110.22, 113.14, 113.95, 116.39, 116.58, 121.12, 121.20, 125.58, 125.62, 125.91, 126.80, 127.07, 141.34, 143.37, 143.83, 144.04, 147.81, 149.80, 152.30, 161.40; ^{19}F NMR (DMSO-d_6) δ ppm: -134.37 (m, 1F); MS: *m/z*: 420.4 $(M+H)^+$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(hydrazinecarbonyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (4): Ethyl 5-(3-fluoro-4-methoxyphenyl)-1-(4-sulfamoylphenyl)-1*H*-pyrazole-3-carboxylate (**3**) (0.01 mol) was refluxed with hydrazine hydrate (0.03 mol) in ethanol for 8 h. Reaction progress was checked by TLC. After completion, reaction mass was concentrated under vacuum, the obtained residue was poured over crushed ice. The obtained solid was filtered and washed with water, dried under suction and purified in ethanol. Yield 78 %; off white solid; m.p. 238-240 ºC; IR (neat, ν_{max}, cm^{-1}): 3328, 3288, 3520, 3141 (N-H), 3070 (arom. C-H), 1671 (C=O), 1470 (C=C), 1366, 1160 (S=O), 1278 (C-F); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 4.51 (s, 2H, -NH_2), 7.01-7.04 (m, 2H, pyrazole -CH-, Ar-H), 7.17-7.23 (m, 2H, Ar-H), 7.51-7.55 (m, 4H, Ar-H), 7.86-7.88 (m, 2H, -SO_2NH_2), 9.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ ppm: 56.08, 108.20, 114.02, 116.29, 116.48, 121.57, 121.65, 125.59, 126.71, 141.50, 142.86, 143.37, 146.80, 147.63, 149.80, 152.30, 160.52; 19F NMR (DMSO-d_6) δ ppm: 134.35 (m, 1F); MS: *m/z* 406.3 $(M+H)^+$.

4-(3-(4-Amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (5): Carbon disulphide (0.20 mol) was slowly added to the mixture of compound **4** (0.1 mol) and KOH (0.15 mol) in ethanol (75 mL) under stirring. The reaction mixture was refluxed for 6 h. Completion of the reaction was monitored by TLC using dichloromethane (DCM) and methanol (9.5:0.5) as mobile phase. After completion the reaction mass was cooled to room temperature. Reaction mass containing dithiocarbazinate potassium in ethanol was as such treated with hydrazine hydrate (0.3 mol) at reflux temperature for 12 h. Evolution of H_2S gas with change in colour of the reaction mass to greenish, reaction completion was monitored by TLC using DCM and methanol (9.5:0.5) as mobile phase. After completion, reaction mass was cooled to room temperature, diluted with cold water and neutralized by concentrated hydrochloric acid. The obtained solid was filtered under vacuum, washed with water, dried under suction and purified in methanol. Yield 69 %; white solid; m.p. 249-251 ºC; IR (neat, ν_{max}, cm^{-1}): 3309, 3242 (NH_2), 2960 (arom. C-H), 1620 (C=N), 1498 (C=C), 2600 (SH), 1275 (C-F); ^{1}H NMR (DMSO-d_6) ppm: 3.85 (s, 3H, -OCH_3), 5.27 (s, 2H, NH_2), 7.01-7.04 (m, 2H, pyrazole -CH-, Ar-H), 7.17-7.23 (m, 3H, Ar-H), 7.51-7.55 (m, 4H, Ar-H), 7.86-7.88 (m, 2H, -SO_2NH_2), 13.29 (s, 1H, SH); ^{13}C NMR (DMSO-d_6) δ ppm: 56.08, 108.20, 114.02, 116.48, 121.57, 121.65, 125.59, 126.71, 141.50, 142.86, 143.37, 146.80, 147.63, 149.80, 152.30, 165.52; MS: *m/z* 462.0 $(M+H)^+$.

General synthesis of benzene sulfonamide pyrazole triazolothiadiazole derivatives (6a-l): A mixture of 4-(3-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (**5**) (0.1 mol) and substituted benzoic/pyridinyl/indolyl acid (0.11 mol) in $POCl_3$ (10 mL) was refluxed for 8-10 h. Completion of the reaction was monitored by TLC using hexane and ethyl acetate (1:1) as mobile phase. After completion, reaction mass was cooled to room temperature, quenched over crushed ice with stirring. The obtained solid was stirred filtered, washed with water, then treated with 10 % aqueous sodium bicarbonate solution and again washed with water, dried under suction and purified using appropriate solvents.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6a): Yield 67 %; off white solid; m.p. 273-275 ºC; IR (neat, ν_{max}, cm^{-1}): 3432 (N-H), 2912 (arom. C-H), 1606 (C=N), 1491 (C=C), 1361, 1180 (S=O), 1267 (C-F), 699 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85-3.99 (m, 6H, -OCH_3), 7.06-7.08 (m, 1H, pyrazole -CH-), 7.13-7.23 (m, 4H, Ar-H), 7.26-7.32 (m, 3H, Ar-H), 7.54-7.59 (m, 4H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.10, 56.59, 108.14, 114.00, 114.70, 116.63, 120.90, 125.64, 125.67, 125.81, 126.84, 129.63, 137.65, 141.18, 143.89, 147.96, 149.80, 150.86, 152.32, 156.08, 160.30, 165.88; MS: *m/z* 577.1 $(M)^+$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(2-methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6b): Yield 74 %; light yellow solid; m.p. 275-277 ºC; IR (neat, ν_{max}, cm^{-1}): 3422 (N-H), 2918 (arom. C-H), 1621 (C=N), 1495 (C=C), 1377, 1178 (S=O), 1259 (C-F), 700 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.74-3.88 (m, 6H, -OCH_3), 7.09 (s, 1H, pyrazole -CH-), 7.21-7.27 (m, 4H, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.53-7.59 (m, 4H, Ar-H),

7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.10, 56.62, 108.20, 114.00, 114.72, 116.44, 116.65, 120.89, 121.02, 121.87, 122.42, 125.65, 125.68, 125.83, 126.83, 128.63, 137.63, 141.17, 143.92, 147.96, 149.79, 152.32, 160.35, 163.16; MS: *m/z* 576.9 $(M-H)^-$.

4-(3-(6-(2-Chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6c): Yield 69 %; off white solid; m.p. 307-309 ºC; IR (neat, ν_{max}, cm^{-1}): 3407 (N-H), 2910 (arom. C-H), 1621 (C=N), 1496 (C=C), 1375, 1182 (S=O), 1271 (C-F), 689 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.08 (m, 1H, pyrazole -CH-), 7.12-7.18 (m, 3H, Ar-H), 7.21-7.33 (m, 4H, Ar-H), 7.53-7.68 (m, 4H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.09, 108.15, 113.99, 114.78, 116.44, 116.63, 120.89, 122.42, 125.67, 125.81, 126.83, 127.96, 128.73, 131.58, 137.65, 141.17, 143.89, 147.96, 149.79, 150.43, 152.32, 163.97, 166.84; MS: *m/z* 580.9 $(M-H)^-$.

4-(3-(6-(3-Chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6d): Yield 71 %; off white solid; m.p. 250-252 ºC; IR (neat, ν_{max}, cm^{-1}): 3417 (N-H), 2913 (arom. C-H), 1622 (C=N), 1503 (C=C), 1375, 1180 (S=O), 1277 (C-F), 703 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.08 (m, 1H, pyrazole -CH-), 7.18-7.27 (m, 4H, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.54-7.59 (m, 4H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.10, 108.16, 114.00, 115.12, 116.44, 116.64, 120.90, 121.55, 123.17, 125.64, 125.68, 125.82, 126.84, 128.17, 130.77, 133.51, 137.65, 141.18, 143.89, 147.96, 149.80, 152.30, 164.09; MS: *m/z* 583.2 $(M+H)^+$.

4-**(3-(6-(4-Chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6e):** Yield 78 %; off white solid; m.p. 255-257 ºC; IR (neat, ν_{max}, cm^{-1}): 3426 (N-H), 2918 (arom. C-H), 1623 (C=N), 1503 (C=C), 1369, 1187 (S=O), 1276 (C-F), 703 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.08-7.33 (m, 4H, pyrazole -CH-, Ar-H), 7.55-7.95 (m, 10H, Ar-H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.12, 108.27, 114.03, 116.46, 116.62, 120.80, 120.92, 125.82, 126.86, 129.00, 129.51, 130.12, 133.58, 133.90, 141.34, 143.83, 144.04, 147.81, 149.80, 152.32, 163.52; MS: *m/z* 581.0 $(M-H)^-$.

4-(3-(6-(2,4-Dichlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6f): Yield 73 %; off white solid; m.p. 263-265 ºC; IR (neat, ν_{max}, cm^{-1}): 3401 (N-H), 2910 (arom. C-H), 1623 (C=N), 1495 (C=C), 1383, 1183 (S=O), 1272 (C-F), 700 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.07-7.12 (m, 1H, pyrazole -CH), 7.19-7.33 (m, 6H, Ar-H), 7.55-7.60 (m, 4H, Ar-H), 7.90-7.92 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.12, 108.19, 114.02, 116.69, 120.92, 125.83, 126.73, 126.87, 128.48, 128.70, 129.35, 130.50, 132.65, 135.26, 136.33, 137.69, 141.21, 143.92, 147.63, 149.80, 152.30, 163.91, 167.40; MS: *m/z* 619.0 $(M+2)^+$.

4-(3-(6-(3,4-Dichlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6g): Yield 69 %; off white solid; m.p. 269-271 ºC; IR (neat, ν_{max}, cm^{-1}): 3416 (N-H), 2917 (arom. C-H), 1623 (C=N), 1494 (C=C), 1375, 1180 (S=O), 1275 (C-F), 700 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.08-7.33 (m, 4H, pyrazole -CH, Ar-H), 7.55-7.59 (m, 7H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.11, 108.23, 114.02, 116.47, 116.67, 119.54, 120.91, 125.71, 125.85, 126.77, 126.86, 129.76, 130.24, 132.54, 134.48, 135.39, 137.61, 141.19, 143.95, 147.98, 149.80, 152.30, 163.33; MS: *m/z* 614.9 $(M-H)^-$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(2-fluorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6h): Yield 73 %; cream coloured solid; m.p. 276-278 ºC; IR (neat, ν_{max}, cm^{-1}): 3400 (N-H), 2917 (arom. C-H), 1619 (C=N), 1493 (C=C), 1351, 1184 (S=O), 1276 (C-F), 700 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.08 (m, 1H, pyrazole -CH), 7.18-7.27 (m, 4H, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.57-7.59 (m, 4H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.10, 108.16, 114.00, 114.87, 116.44, 116.64, 120.97, 122.21, 124.88, 125.69, 125.80, 126.86, 128.76, 130.27, 137.67, 141.18, 143.87, 147.98, 149.81, 152.00, 158.28, 164.12, 166.78; MS: *m/z* 567.2 $(M+2)^+$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(4-fluorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6i): Yield 68 %; off white solid; m.p. 267-269 ºC; IR (neat, ν_{max}, cm^{-1}): 3408 (N-H), 2904 (arom. C-H), 1619 (C=N), 1496 (C=C), 1371, 1187 (S=O), 1277 (C-F), 699 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.08 (m, 1H, pyrazole -CH), 7.19-7.28 (m, 4H, Ar-H), 7.30-7.34 (m, 3H, Ar-H), 7.55-7.59 (m, 4H, Ar-H), 7.90-7.92 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.12, 108.19, 114.02, 116.44, 116.64, 118.39, 120.97, 124.90, 125.69, 125.80, 126.86, 127.19, 130.59, 137.67, 141.19, 143.87, 147.88, 149.80, 152.30, 160.31, 164.12; MS: *m/z* 565.0 $(M-H)^-$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(*m*-tolyl)-[1,2,4]-triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)-benzenesulfonamide (6j): Yield 72 %; cream colored solid; mp 259-261 ºC; IR (neat, ν_{max}, cm^{-1}): 3419 (N-H), 2912 (arom. C-H), 1620 (C=N), 1496 (C=C), 1352, 1184 (S=O), 1276 (C-F), 702 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H, -CH_3), 3.85 (s, 3H, -OCH_3), 7.08-7.33 (m, 4H, pyrazole -CH-, Ar-H), 7.55-7.59 (m, 8H, Ar-H), 7.89-7.91 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 21.33, 56.12, 108.19, 114.02, 116.47, 116.69, 120.80, 120.92, 125.72, 125.83, 126.62, 126.73, 126.87, 128.48, 128.70, 137.69, 139.18, 141.21, 143.83, 143.92, 147.63, 149.80, 152.30, 163.91; MS: *m/z* 561.0 $(M)^+$.

4-(5-(3-Fluoro-4-methoxyphenyl)-3-(6-(pyridin-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6k): Yield 63 %; brown solid; m.p. 272-274 ºC; IR (neat, ν_{max}, cm^{-1}): 3415 (N-H), 2926 (arom. C-H), 1621 (C=N), 1496 (C=C), 1352, 1185 (S=O), 1274 (C-F), 700 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.12 (m, 4H, pyrazole -CH-, Ar-H), 7.19-7.33 (m, 4H, Ar-H), 7.55-7.59 (m, 4H, Ar-H), 7.90-7.92 (m, 2H, -SO_2NH_2); ^{13}C NMR (DMSO-d_6) δ ppm: 56.12, 108.27, 114.03, 116.46, 120.92, 125.82, 126.86, 128.46, 128.68, 129.51, 133.58, 137.00, 141.34, 143.83, 144.04, 147.63, 147.81, 149.80, 152.32, 155.22, 163.52, 167.41; MS: *m/z* 548.1 $(M)^+$.

4-(3-(6-(1*H*-Indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (6l): Yield 75 %; light brown solid;

m.p. 279-281 ºC; IR (neat, ν_{max}, cm^{-1}): 3417 (N-H), 2925 (arom. C-H), 1621 (C=N), 1496 (C=C), 1346, 1184 (S=O), 1274 (C-F), 697 (C-S-C); ^{1}H NMR (DMSO-d_6) δ ppm: 3.85 (s, 3H, -OCH_3), 7.06-7.12 (m, 5H, pyrazole -CH-, Ar-H), 7.19-7.33 (m, 4H, Ar-H), 7.55-7.59 (m, 4H, Ar-H), 7.90-7.92 (m, 2H, -SO_2NH_2), 11.62 (s, 1H, -NH); ^{13}C NMR (DMSO-d_6) δ ppm: 56.12, 99.87, 108.19, 114.02, 116.47, 116.69, 120.78, 120.90, 125.72, 125.83, 126.62, 126.73, 126.87, 128.48, 128.70, 137.69, 139.18, 141.21, 143.83, 143.92, 147.63, 149.80, 152.30, 163.91, 166.85; MS: *m/z* 585.9 $(M-H)^-$.

Antimicrobial screening: The antibacterial activity was evaluated against *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688), *Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442) and antifungal activity was evaluated against *Candida albicans* (MTCC-227), *Aspergillus niger* (MTCC-282) and *Aspergillus clavatus* (MTCC-1323). These strains were provided by Institute of Microbial Technology (IMT), Chandigarh, India. Mueller Hinton Broth was used as Nutrient Medium to grow and dilute the drug suspension for the test bacteria. This agar media was sterilized (autoclaved at 120 ºC for 30 min), poured at uniform depth of 5 mm and allowed to solidify. The microbial suspension (10^5 CFU/mL) was streaked over the surface of media using sterile cotton swab to ensure even growth of the organisms. The tested compounds were dissolved in dimethyl sulfoxide to give the solutions of 3.12-1000 µg/mL. Sterile filter paper discs measuring 6.25 mm in diameter, previously soaked in a known concentration of the respective test compound in dimethyl sulfoxide were placed on the solidified nutrient agar medium that has been incubated with the respective microorganism and plates were incubated at (37 ± 1) ºC for 24 h (bacteria) and 72 h (fungi). A control disc impregnated with an equivalent amount of dimethyl sulfoxide without any sample was also used and did not produce any inhibition. Ampicillin and griseofulvin were used as control drugs for antibacterial and antifungal activity, respectively.

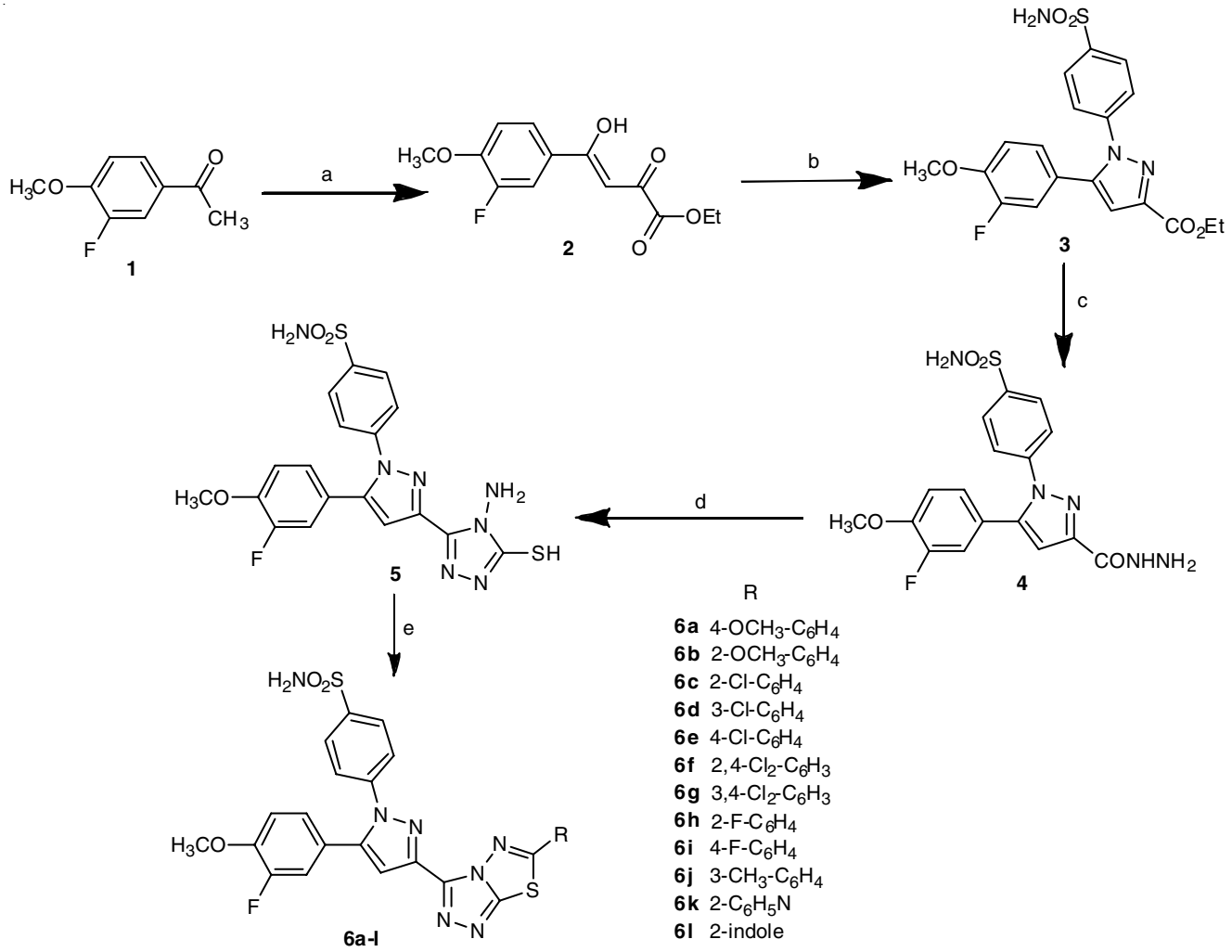
MIC of compound was determined by agar streak dilution method [16]. A stock solution of the synthesized compounds in dimethyl sulfoxide was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar for the evaluation of antibacterial and Sabouraud dextrose agar for antifungal activity, respectively. The medium containing test compound was poured into a petri dish at depth of 4-5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism of approximately 10^5 CFU/mL was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.12-1000 µg/mL in dimethyl sulfoxide and incubated at (37 ± 1) ºC for 24 h (bacteria) and 72 h (fungi). Test run was triplicated, the lowest concentration of substance that prevents the development of visible growth is considered to be the MIC value.

RESULTS AND DISCUSSION

The proposed hybrids were synthesized after five steps as per synthetic route outlined in **Scheme-I**. Intermediate **2** was synthesized as per reported process [17,18] and the synthesized intermediates were confirmed with the reported data. Intermediate **2** on reacting with 4-sulfonamido phenyl hydrazine hydrochloride in ethanol at reflux temperature afforded pyrazole ester **3**. IR spectrum of intermediate **3** showed stretching band at 1723 cm^{-1} belongs to ester -C=O group. Pyrazole proton as a singlet at δ 7.03, NH_2 protons of sulfonamide at δ 7.88-7.91 and ethyl protons at δ 4.31-4.36 (-CH_2) and 1.29-1.33 (-CH_3) in ^{1}H NMR confirmed the formation of intermediate **3**. Ester intermediate **3** on reacting with hydrazine hydrate in ethanol at reflux temperature afforded respective acid hydrazide **4**. In IR spectrum of intermediate **4**, amide -C=O strong band observed at 1671 cm^{-1}. According to ^{1}H NMR spectra of acid hydrazide **4**, absence of ethyl protons and presence of hydrazide protons at δ 4.51 (NH_2) and δ 9.63 (NH) confirmed the formation of acid hydrazide **4**. Pyrazole carbohydrazide **4** was processed with CS_2 and ethanolic KOH under reflux condition for 6 h to get corresponding dithiocarbazinate potassium. Completion of reaction was observed on TLC, then obtained dithiocarbazinate potassium salt was *in situ* processed with hydrazine hydrate at reflux temperature for 12 h to get the compound **5** with good yield. Formation of compound **5** proved by its IR, ^{1}H NMR, MS analysis and structure related studies [19,20] described thiol-thione tautomeric equilibrium of heterocyclic thione derivatives. IR spectra demonstrated two absorption bands at 3309-2600 cm^{-1}, indicate presence of NH_2 and SH groups. Along with this two other absorption bands have been observed at 1633-1513 cm^{-1} indicates -C=N vibrations, which clearly indicate cyclization and formation of triazole ring. ^{1}H NMR spectrum showed free NH_2 protons at δ 5.27 and SH proton at δ 13.29. One proton from pyrazole ring appeared at δ 7.01-7.04 and other aromatic protons appeared at δ 7.17-7.88 which correlates the structure of compound **5**. In ^{13}C NMR spectra signals appeared at δ 146.80 and 165.52 indicates 3rd and 5th carbon of triazole moiety respectively, other signals were appeared at the presupposed chemical shifts. Compound **5** was reacted with substituted benzoic/pyridinyl/indolyl acids in $POCl_3$ at reflux temperature for 8-10 h to get 4-(5-(3-fluoro-4-methoxyphenyl)-3-(6-substituted-phenyl)-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamides (**6a-l**).

NH_2 and SH stretching vibrations are absent in the IR spectra as well as NH_2 and SH protons are absent in ^{1}H NMR, which confirms the conversion of 4-(3-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)-5-(3-fluoro-4-methoxyphenyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (**5**) to 4-(5-(3-fluoro-4-methoxyphenyl)-3-(6-substituted phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazol-3-yl)-1*H*-pyrazol-1-yl)benzenesulfonamide (**6**). All other aromatic protons are in the range of δ 7.06-7.91 ppm which supports the structures.

Antimicrobial activity: The antibacterial activity of benzene sulphonamide pyrazole clubbed triazolo-thiadiazole hybrids (**6a-l**) was appraised against *S. pyogenes*, *P. aeruginosa*, *S. aureus* and *E. coli* using ampicillin as standard drugs. Minimum bacterial inhibitory concentration (MIC) values was resolved by Broth dilution technique. Dimethyl sulfoxide was used as diluent. MIC values of the appraised compounds are summarized in Table-1. Most of the synthesized compounds except **6b**, **6d**, **6f**, **6h** and **6l** displayed excellent antibacterial activity than standard drug ampicillin with all the tested bacterial strains.



Scheme-I: Synthetic scheme for title compounds **6a-l**. Reagents and conditions: (a) toluene, NaH, diethyl oxalate, RT, 8 h, (b) ethanol, 4-$SO_2NH_2C_6H_4NH_2NH_2$·HCl, reflux, 4-5 h, (c) ethanol, $NH_2NH_2·H_2O$, reflux, 8 h, (d) (i) ethanol, CS_2, KOH, reflux, 6 h, (ii) $NH_2NH_2·H_2O$, reflux, 10-12 h, (e) RCOOH, $POCl_3$, reflux, 8-10 h

TABLE-1
ANTIMICROBIAL ACTIVITY DATA

Compd. No.	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
6a	100	125	200	500	500	1000	1000
6b	250	200	250	200	250	500	500
6c	100	125	100	100	1000	> 1000	> 1000
6d	250	250	100	125	500	1000	1000
6e	100	200	250	250	250	500	500
6f	500	500	250	250	1000	> 1000	> 1000
6g	200	100	125	125	500	1000	1000
6h	125	200	250	250	1000	1000	500
6i	62.5	100	200	125	1000	> 1000	> 1000
6j	100	100	250	250	500	500	500
6k	125	62.5	100	100	500	250	250
6l	200	125	200	200	1000	500	500
Ampicillin	100	100	250	100	–	–	–
Griseofulvin	–	–	–	–	500	100	100
DMSO	–	–	–	–	–	–	–

Triplicated test run, minimum inhibitory concentrations (MIC, µg/mL)

As compared to ampicillin against *E. coli*, compounds **6a**, **6c**, **6e** and **6j** displayed equivalent activity whereas compound **6i** displayed promising activity. Compounds **6g**, **6i** and **6j** showed similar activity whereas compound **6k** was found promising activity in comparison to ampicillin against *P. aeruginosa*. All the compounds shows equivalent to better antibacterial activity

against *S. aureus*. Compounds **6a**, **6b**, **6e**, **6f**, **6h**, **6i**, **6j** and **6l** displayed equivalent to moderate activity whereas compounds **6c**, **6d**, **6g** and **6k** exhibited encouraging activity as compared to ampicillin against *S. aureus*. Only compounds **6c** and **6k** are having better activity as compared to ampicillin against *S. pyogenes*. Overall the compounds **6c**, **6i** and **6k** displayed encouraging activity against all tested species as compared to ampicillin as standard drug.

The antifungal activity of benzene sulphonamide pyrazole linked triazolo-thiadiazole derivatives (**6a-l**) was appraised against *A. niger*, *A. clavatus* and *C. albicans* using griseofulvin as standard drug. Broth dilution method was used to calculate the minimum fungal inhibitory concentration (MIC) values. Dimethyl sulfoxide was used as diluent. MIC values of the appraised compounds are shown in Table-1. All the synthesized compounds had shown less activity than standard drug griseofulvin against *A. Niger* and *A. clavatus* strains. But when the same compounds were screened against *C. albicans*, compounds **6a**, **6b**, **6d**, **6e**, **6g**, **6j** and **6k** displayed good to moderate activity as compared with standard drug griseofulvin. Compounds **6c**, **6f**, **6h**, **6i** and **6l** showed less antifungal activity with all tested species. Compounds **6a**, **6d**, **6g**, **6j** and **6k** showed good activity as equivalent to griseofulvin as a standard drug against *C. albicans*. Compounds **6b** and **6e** is having promising antifungal activity against *C. albicans* as compare to standard griseofulvin.

Conclusion

In this study, a series of novel benzene sulfonamide pyrazole triazolothiadiazole derivatives were proposed, produced and preliminary biological evaluation of antibacterial and antifungal activity indicated that compounds **6c** (2-Cl), **6i** (2-F) and **6k** (2-pyridyl) were found active against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* as compared to standard ampicillin. Compounds bearing halo (Cl, F) group at *ortho* position and 2-pyridyl are more effective to inhibit bacterial strains. Compounds **6b** (2-MeO) and **6e** (4-Cl) is having promising antifungal activity against *C. albicans* as compare to standard griseofulvin. Thus, there are the new opportunities for the possible modification as per the pharmaceutical requirement in future.

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REFERENCES

1. S.C. Holm and B.F. Straub, Synthesis of N-Substituted 1,2,4-Triazoles. A Review, *Org. Prep. Proced. Int*., **43**, 319 (2011); https://doi.org/10.1080/00304948.2011.593999.
2. S. Desai, U. Laddi, R. Bennur and S. Bennur, Synthesis and Antimicrobial Activities of Some New 1,2,4-Triazole Derivatives, *Indian J. Chem.*, **52B**, 1176 (2013).
3. S. Swamy, B. Basappa, B.S. Priya, B. Prabhuswamy, B.H. Doreswamy, J.S. Prasad and K.S. Rangappa, Synthesis of Pharmaceutically Important Condensed Heterocyclic 4,6-Disubstituted-1,2,4-Triazolo-1,3,4-Thiadiazole Derivatives as Antimicrobials, *Eur. J. Med. Chem.*, **41**, 531 (2006); https://doi.org/10.1016/j.ejmech.2005.12.009.
4. M. Akhter, M. Hassan and M. Amir, Synthesis and Pharmacological Evaluation of 3-Diphenylmethyl-6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles: A Condensed Bridgehead Nitrogen Heterocyclic System, *Arab. J. Chem.*, **7**, 955 (2014); https://doi.org/10.1016/j.arabjc.2014.05.036.
5. N. Chidananda, B. Poojary, V. Sumangala, N.S. Kumari, P. Shetty and T. Arulmoli, Facile Synthesis, Characterization and Pharmacological Activities of 3,6-Disubstituted 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles and 5,6-Dihydro-3,6-disubstituted-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles, *Eur. J. Med. Chem.*, **51**, 124 (2012); https://doi.org/10.1016/j.ejmech.2012.02.030.
6. A. Husain, M. Rashid, R. Mishra, S. Parveen, D. Shin and D. Kumar, Benzimidazole Bearing Oxadiazole and Triazolo-Thiadiazoles Nucleus: Design and Synthesis as Anticancer Agents, *Bioorg. Med. Chem. Lett.*, **22**, 5438 (2012); https://doi.org/10.1016/j.bmcl.2012.07.038.
7. S. El-Khawass, M. Khalil, A. Hazzaa, H. Bassiouny and N. Loutfy, Synthesis of Some 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles as Potential Anthelmintics, *Farmaco*, **44**, 703 (1989).
8. Y.A. Al-Soud, N.A. Al-Masoudi, R. Loddo and P. La Colla, *in vitro* Anti-HIV and Antitumor Activity of New 3,6-Disubstituted [1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazoles and Thiadiazine Analogues, *Arch. Pharm.*, **341**, 365 (2008); https://doi.org/10.1002/ardp.200700272.
9. M. Karthikeyan, B. Holla, B. Kalluraya and N. Kumari, Biological Studies of Some 2,4-Dichloro-5-fluorophenyl Containing Triazolothiadiazoles, *Monatsh. Chem.*, **138**, 1309 (2007); https://doi.org/10.1007/s00706-007-0718-y.
10. R. Shingare, Y. Patil, S. Gadekar, J. Sangshetti and B. Madje, Synthesis and Antibacterial Screening of Novel 1,3,5-Triaryl-4, 5-dihydro-1*H*-pyrazole Derivatives, *Moroc. J. Chem.*, **5**, 177 (2017).
11. H.A. Abdel-Aziz, K.A. Al-Rashood, K.E.H. ElTahir and G.M. Suddek, Synthesis of N-benzenesulfonamide-1*H*-pyrazoles Bearing Arylsulfonyl Moiety: Novel Celecoxib Analogs as Potent Anti-Inflammatory Agents, *Eur. J. Med. Chem.*, **80**, 416 (2014); https://doi.org/10.1016/j.ejmech.2014.04.065.
12. P. Khloya, P. Kumar, A. Mittal, N.K. Aggarwal and P.K. Sharma, Synthesis of Some Novel 4-Arylidene Pyrazoles as Potential Antimicrobial Agents, *Org. Med. Chem. Lett.*, **3**, 9 (2013); https://doi.org/10.1186/2191-2858-3-9.
13. A.A. Bekhit, H.M.A. Ashour, A.E.-D.A. Bekhit, H.M. Abdel-Rahman and S.A. Bekhit, Synthesis of Some Pyrazolyl Benzenesulfonamide Derivatives as Dual Anti-Inflammatory Antimicrobial Agents, *J. Enzyme Inhib. Med. Chem.*, **24**, 296 (2009); https://doi.org/10.1080/14756360802188404.
14. H.S. Ibrahim, S.M. Abou-Seri, M. Tanc, M.M. Elaasser, H.A. Abdel-Aziz and C.T. Supuran, Isatin-Pyrazole Benzenesulfonamide Hybrids Potently Inhibit Tumor-Associated Carbonic Anhydrase Isoforms IX And XII, *Eur. J. Med. Chem.*, **103**, 583 (2015); https://doi.org/10.1016/j.ejmech.2015.09.021.
15. T. Rogez-Florent, S. Meignan, C. Foulon, P. Six, A. Gros, C. Bal-Mahieu, C.T. Supuran, A. Scozzafava, R. Frederick, B. Masereel, P. Depreux, A. Lansiaux, J.F. Goossens, S. Gluszok and L. Goossens, New Selective Carbonic Anhydrase IX Inhibitors: Synthesis and Pharmacological Evaluation of Diarylpyrazole-Benzenesulfonamides, *Bioorg. Med. Chem.*, **21**, 1451 (2013); https://doi.org/10.1016/j.bmc.2012.10.029.
16. P.M. Hawkey and D.A. Lewis, Medical Bacteriology-A Practical Approach, Oxford University Press, United Kingdom (1994).
17. H.N. Raundal, R.P. Jadhav, A.A. Patil and V.D. Bobade, Synthesis and Biological Screening of Novel Pyrazole and Isoxazole Derivatives, *Indian J. Chem.*, **54B**, 979 (2015).
18. H.N. Raundal, R.P. Jadhav, A.A. Patil and V.D. Bobade, Synthesis and Biological Activity of Novel Derivatives of 2-(5-(3-Fluro-4-methoxy phenyl)-1*H*-pyrazol-3-yl)-5-aryl-1,3,4-oxadiazole, *Indian J. Chem.*, **55B**, 892 (2016).
19. A. Cansiz, A. Cetin, P. Kutulay and M. Koparir, Synthesis of Tautomeric Forms of 5-(2-Hydroxyphenyl)-4-substituted-3H-1,2,4-triazole-3-thione, *Asian J. Chem.*, **21**, 617 (2009).
20. S. Ozturk, M. Akkurt, A. Cansiz, M. Koparir, M. Sekerci, F.W. Heinemann, 4-(4-Chloro-phenyl)-3-(furan-2-yl)-1H-1,2,4-triazole-5(4H)-thione, *Acta Cryst.,* **E60**, o425 (2004); https://doi.org/10.1107/S1600536804003721.