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SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF 2-ACETAMIDO-4-(5-SUBSTITUTED-PHENYL-4*H*-[1,2,4]TRIAZOL-3-YL) METHYLTHIAZOLES

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Abstract- A new series of 2-acetamido-4-(5-substituted-phenyl-4*H*-[1,2,4]triazol-3-yl)methylthiazole **(5a-m)** were synthesized by the one pot cyclocondensation reaction of 2-(2-acetamido-thiazol-4-yl)acetohydrazide (**3**) with different substituted aromatic/heterocyclic aldehyde (**4a-m**) in presence of ammonium acetate in acetic acid. The structures of new compounds were determined by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR, EIMS) methods and were tested for their antimicrobial activity against three Gram-positive bacteria and four Gram-negative bacteria and against four fungi, using ciprofloxacin and miconazole as standard drug for bacteria and fungi respectively. Bioassay results showed that most of the synthesized compounds exhibited promising activity against tested bacterial and fungal strains.

Keywords- antibacterial, antifungal, acetohydrazide, thiazole, 1,2,4-triazole.

1. Introduction

The thiazole moiety is among the most attractive sulfur containing motifs and present in various natural products e.g. Bacillamide[i], Epothilones[ii], Vitamin B1[iii] and also used in drug development for the treatment of allergies[iv], hypertension[v], inflammation[vi], schizophrenia[vii], bacterial[viii], HIV infections[ix], hypnotics[x] and recently for the treatment of pain[xi] (Figure 1.). Among the nitrogen containing heterocyclic compounds, extensive research has been done on the synthesis of 1,2,4-triazoles due to its immense importance in the field of medicinal chemistry. 1,2,4-Triazole derivatives have shown a wide variety of biological activities such as anticancer[xii,xiii], antibacterial[xiv-xvi], antifungal[xvii,xviii], antituberculous[xix] and hypoglycemic[xx] (Figure 2).

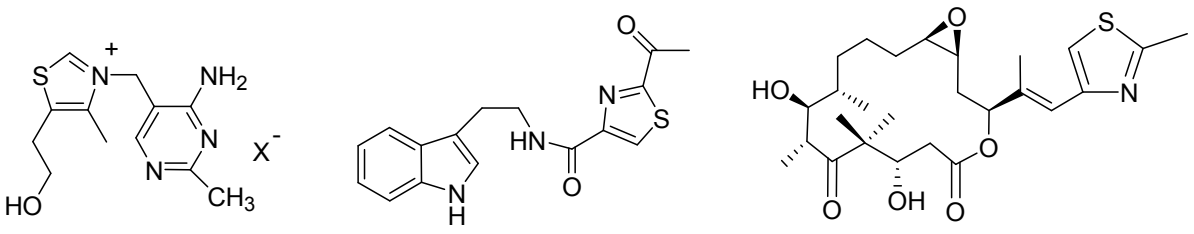


Figure 1. Some biologically important thiazoles

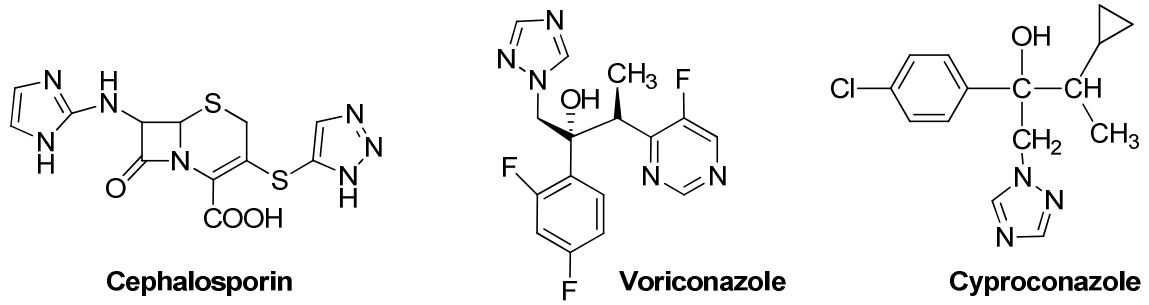


Figure 2. Some biologically important 1,2,4-triazoles

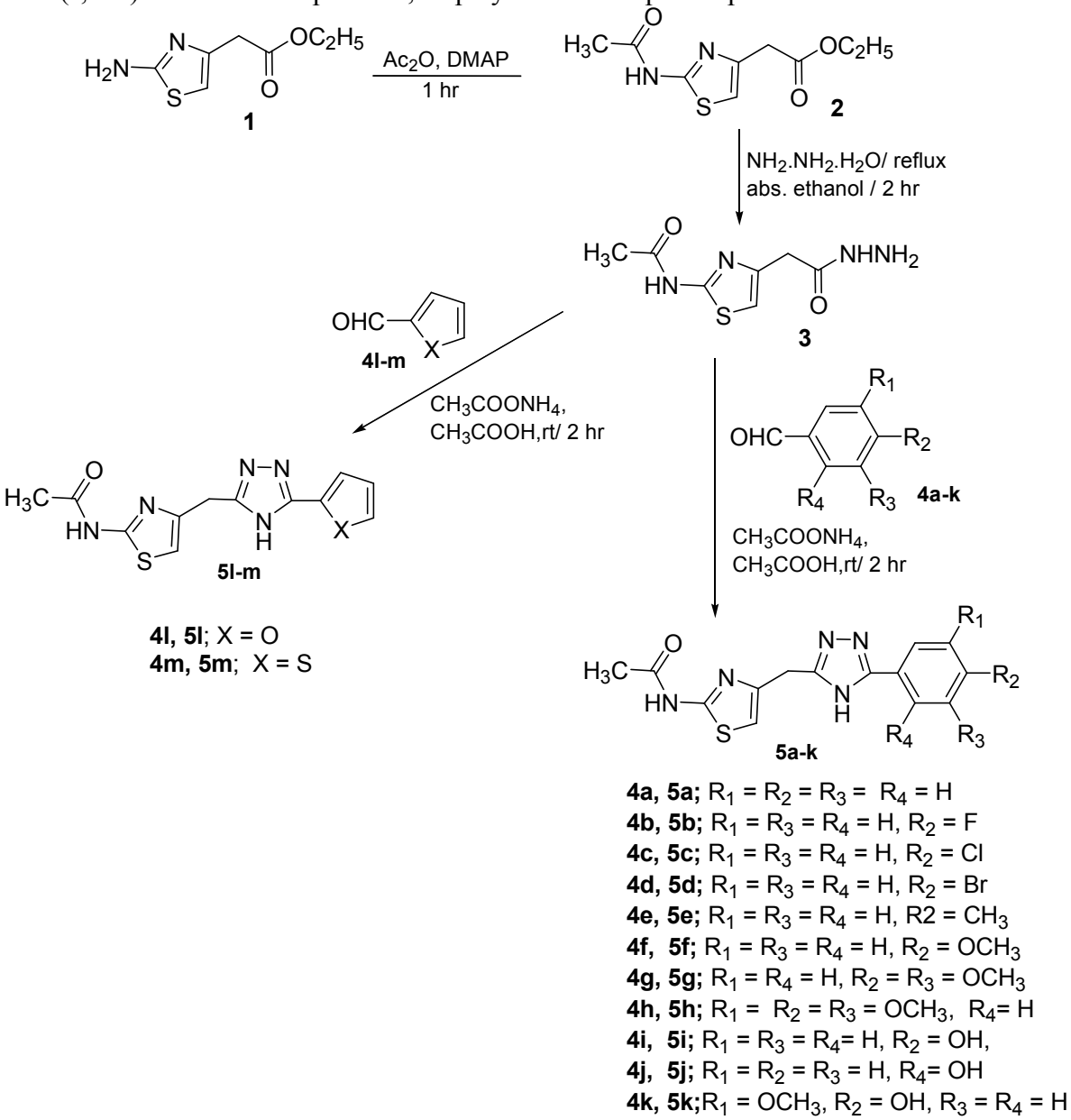
Thus the molecular hybridization assumption (the coupling of two different bioactive moieties used in the development of drugs) encouraged us to design and synthesize a new series of compounds containing both triazole and thiazole *viz.* triazolylthiazoles, on the promise that the two pharmacophores, present in tandem will contribute significantly to the biological activity. There were few reports in literature where compounds containing both triazole and thiazole moietites, have shown promising biological activities such as antitubercular and antimicrobial activities.[xxi,xxii] Therefore, in view of the highly important status of thiazole and triazole entities in medicinal chemistry we herein wish to report a simple and an efficient method for the synthesis of new triazolylthiazoles in excellent yields. The compounds were synthesized as shown in Scheme-I. All the newly synthesized compounds gave satisfactory elemental analysis and were screened for their antibacterial and antifungal activities against three Gram-positive bacteria, two Gram-negative bacteria and against four fungal strains. The results of such studies are discussed in this paper.

2. Result and discussion

2.1. Chemistry

2-Amino-4-(carboethoxymethyl)thiazole **(1)** was reacted with acetic anhydride in presence of DMAP to obtain compound **2** which on further treatment with hydrazine hydrate gave 2-(2-acetamido-thiazol-4-yl)acetohydrazide (**3**). 2-acetamido-4-(5-phenyl-4*H*-[1,2,4]triazol-3-yl)methylthiazole (**5a)** was synthesized *via* cyclocondensation reaction of compound **3** with benzaldehyde (**4a)** in presence of ammonium acetate using acetic acid as solvent. Compound **5a** displayed a molecular ion peak M^++1 at m/z 300.231 in TOF ES+, corresponding to the molecular formula $C_{14}H_{13}N_5OS$ thereby indicating that the cyclocondensation has occurred. This was fully supported by its ^{1}H NMR spectrum which exhibited a singlet at δ 4.06 for two protons of -CH_2- which confirmed the linkage of **3** with benzaldehyde *via* triazole ring formation.^{1}H NMR also displayed characteristic broad singlets at δ 11.85 and 11.17 for two D_2O exchangeable protons for NH. NH stretching band at 3302 cm^{-1} was also observed in its IR spectrum. Further, six aromatic protons of the

thiazole and phenyl nucleus appeared at δ 7.63 (m, 2H), 7.54 (m, 2H), 7.36 (m, 1H) and 6.71 (s, 1H). Its ^{13}CNMR spectrum, displayed all the expected peaks for aromatic carbons.



Scheme. The synthesis of compounds (**5a-m**)

2.2. Antimicrobial activity

The biological activity data analysis suggests that all the synthesized compounds showed moderate to significant activity against different bacterial strains. Compounds **5l** and **5m** showed significant activity against *Staphylococcus aureus* and *Escherichia coli* whereas against *Pseudomonas aeruginosa* both these compounds showed moderate activity. Compounds **5b**, **5c**, **5f** and **5g** showed weak to moderate activity against most of the bacterial pathogens. Above results indicates that the substitution with furan and thiophene moiety showed better activity as compared to those containing substituted phenyl group. Compounds **5c, 5d, 5h, 5l** and **5m** showed promising activity against all the fungal pathogens. Compound **5l** was found to be most active against *Candida albicans* and showed activity comparable to standard drug Miconazole. The results obtained recommend

that since some of the synthesized compounds can be taken up further for detailed biological experiments.

3. Materials and methods

3.1. Chemistry

Melting points were determined on an electronic apparatus and are uncorrected. Thin layer chromatography (TLC) were carried out on precoated silica gel plates (F_{254} Merck).^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) and ^{13}C NMR spectra were recorded on Bruker Advance (100 MHz) using trimethylsilane (TMS) as an internal standard and $CDCl_3$/$DMSOd_6$ as solvent. TOF ES+ Mass spectra (m/z) were recorded on Micromass Autospec LCTKC455. Infrared (FTIR) spectra were determined on a Perkin Elmer-2000 Spectrophotometer instrument. Elemental analyses were performed on a Perkin Elmer series 11, CHNS/O analyzer 2400. The chemicals used in this work were purchased from Merck and used without further purification. 2-Amino-4-(carboethoxymethyl)thiazole was synthesized according to the literature procedure[xxiii].

3.1.1 2-Acetamido-4-(carboethoxymethyl)thiazole[xxiv] (2).

Acetic anhydride (20 mL) was added in small portions to a mixture of 2-amino-4-(carboethoxymethyl)thiazole **(1)** (1.86 g, 10 mmol) and DMAP (20 mg, 0.16 mmol) on stirring and heated the contents on an oil bath at 70 °C for 1 hour. Afterwards the contents were poured into ice cold water. The compound that separated out was filtered and crystallized from ethanol and obtained as a white solid. Yield 95 %, m.p. 152 °C; R_f: 0.57 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3173, 3067, 2983, 1731, 1660, 1559, 1409, 1305, 1163, 1021, 732, 690. ^{1}H NMR (δ, $CDCl_3$, 300 MHz): 10.06 (s, 1H, NH, D_2O exchangeable), 6.84 (s, 1H), 4.20 (q, 2H, OCH_2), 3.73 (s, 2H, CH_2), 2.26 (s, 3H, $COCH_3$), 1.28 (t, 3H, CH_3). MS, TOF ES+ *m/z* (%): 229 (M^++1).

3.1.2 Synthesis of 2-(2-acetamido-thiazol-4-yl)acetohydrazide[xxiv] (3).

A mixture of compound **2** (2.28 g, 10 mmol) and hydrazine hydrate (0.6 g, 12.19 mmol) in ethanol was refluxed for a period of 2 hour. The solid that separated out on cooling was filtered and recrystallized from ethanol. Yield 79 %, m.p. 169 °C; R_f: 0.42 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3311, 3206, 3100, 2926, 1661, 1576, 1521, 1418, 997, 751. ^{1}H NMR (δ, $CDCl_3$, 300 MHz): 12.04 (s, 1H, NH, D_2O exchangeable), 9.17 (s, 1H, NH, D_2O exchangeable), 6.82 (s, 1H), 4.21 (brs, 2H, NH_2, D_2O exchangeable), 3.37 (s, 2H, CH_2), 2.08 (s, 3H, $COCH_3$). ^{13}C NMR (δ, $CDCl_3$, 75.5 MHz): 170.3, 168.5, 157.3, 144.9, 109.4, 36.4, 22.3. MS, TOF ES+ *m/z* (%): 215 (M^++1).

3.1.3 General procedure for the synthesis of 2-acetamido-4-(5-subsitituted-phenyl-4H-[1,2,4]triazol-3-yl)methylthiazole (5a-m).

In a 100 mL round bottom flask, 2-(2-acetamido-thiazol-4-yl)acetohydrazide **(3)** (0.215g, 1.0 mmol) was dissolved in glacial acetic acid (10 mL). To the above contents substituted aromatic/heterocyclic aldehydes (1.0 mmol) **(4a-m)** and ammonium acetate were added and reaction mixture was stirred at room temperature for 2 hours. The progress of the reaction was monitored on TLC. After completion of the reaction, the reaction mixture was poured into ice cold water and neutralized with ammonium hydroxide solution. The white solid that separated out was filtered and crystallized from ethanol.

3.1.3.1 2-Acetamido-4-(5-phenyl-4H-[1,2,4]triazol-3-yl)methylthiazole (5a).

90% yield; m.p. 228 °C; R_f: 0.50 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3302, 2981, 1717, 1618, 1523, 1333, 1235, 1181, 710. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 11.85 (s, 1H, NH, D_2O exchangable proton), 11.17 (1H, >NH, D_2O exchangable proton),

7.63 (m, 2H), 7.54 (m, 2H), 7.36 (m, 1H), 6.71 (s, 1H), 4.06 (s, 2H, CH_2), 2.10 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.1, 168.3, 165.3, 157.6, 146.3, 144.8, 142.7, 134.2, 129.9, 128.8, 127.0, 109.7, 38.6, 22.4. MS, TOF ES+ *m/z* (%): 300.231 (M^++1), Anal. Calcd for: $C_{14}H_{13}N_5OS$: C, 56.17; H, 4.38; N, 23.40%. Found: C, 56.21; H, 4.32; N, 23.38%.

3.1.3.2 2-Acetamido-4-(5-(4-fluorophenyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5b).

79% yield; m.p. 169 °C; R_f: 0.54 (98:2 chloroform: methanol, v/v);IR ν (KBr, cm^{-1}): 3340, 3154, 2970, 1663, 1611, 1529, 1398, 1184, 984. ^1H NMR (δ, DMSO-d_6, 400 MHz): 12.08 (s, 1H, NH, D_2O exchangable), 11.55 (s, 1H, >NH, D_2O exchangable), 7.72 (d, 2H, *J*= 8.7 Hz), 7.30 (d, 2H, *J*= 8.7 Hz), 6.93 (s, 1H), 4.00 (s, 2H, CH_2), 2.11 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 172.0, 168.3, 165.4, 157.62, 145.3, 144.5, 141.6, 139.7, 130.8, 129.2, 116.0, 109.7, 38.6, 21.0. MS, TOF ES+ *m/z* (%): 318.451 (M^++1), Anal. Calcd for: $C_{14}H_{12}FN_5OS$: C, 52.99; H, 3.81; N, 22.07%. Found: C, 52.89; H, 3.78; N, 22.10%.

3.1.3.3 2-Acetamido-4-(5-(4-chlorophenyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5c).

92% yield; m.p 198 °C; R_f: 0.53 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3350, 3202, 2926, 1685, 1560, 1388, 1317, 1011, 820, 721. ^1H NMR (δ, DMSO-d_6, 400 MHz): 11.93 (s, 1H, NH, D_2O exchangable), 11.42 (s,1H, >NH, D_2O exchangable), 7.62 (d, 2H, *J*= 8.2 Hz), 7.31 (d, 2H, *J*= 8.2 Hz), 6.69 (s, 1H), 3.99 (s, 2H, CH_2), 2.07 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.2, 168.3, 165.4, 157.6, 145.1, 144.5, 141.4, 134.4, 133.1, 128.6, 116.0, 109.7, 38.6, 22.3. MS, TOF ES+ *m/z* (%): 334.512 (M^++1), Anal. Calcd for: $C_{14}H_{12}ClN_5OS$: C, 50.38; H, 3.62; N, 20.98%. Found: C, 50.31; H, 3.59; N, 20.10%.

3.1.3.4 2-Acetamido-4-(5-(4-bromophenyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5d).

94% yield; m.p. 230 °C; R_f: 0.55 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3202, 2972,1684, 1610, 1560, 1388, 1137, 1087, 820. ^1H NMR (δ, DMSO-d_6, 400 MHz): 11.86 (s, 1H, NH, D_2O exchangable), 11.25 (s, 1H, >NH, D_2O exchangable), 7.55 (d, 2H, *J*= 8.1 Hz), 7.01 (d, 2H, *J*= 8.1 Hz), 6.99 (s, 1H), 3.99 (s, 2H, CH_2), 2.09 (s, 3H, $COCH_3$). MS, TOF ES+ *m/z* (%): 379.550 (M^++1), Anal. Calcd for: $C_{14}H_{12}BrN_5OS$: C, 44.46; H, 3.20; N, 18.52%. Found: C, 44.40; H, 3.22; N, 18.51%.

3.1.3.5 2-Acetamido-4-(5-(4-methylphenyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5e).

90% yield; m.p. 218 °C; R_f: 0.53 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3430, 3170, 2966, 1654, 1549, 1396, 1307, 1276, 1235, 1019, 788. ^1H NMR (δ, DMSO-d_6, 400 MHz): 11.93 (s, 1H, NH, D_2O exchangable proton), 11.29 (s, 1H, >NH, D_2O exchangable proton), 7.50 (d, 2H, *J*= 8.2 Hz), 7.13 (d, 2H, *J*= 8.2 Hz), 6.74 (s, 1H), 4.14 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.07 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.9, 168.3, 165.2, 157.5, 146.4, 144.8, 142.8, 139.7, 131.5, 129.3, 126.9, 109.6, 37.3, 22.3, 21.0. MS, TOF *m/z* ES+ (%): 314.232 (M^++1), Anal. Calcd for: $C_{15}H_{15}N_5OS$: C, 57.49; H, 4.82; N, 22.35%. Found: C, 57.46; H, 4.81; N, 22.38%.

3.1.3.6 2-Acetamido-4-(5-(4-methoxyphenyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5f).

94% yield; m.p. 223 °C; R_f: 0.52 (98:2 chloroform: methanol, v/v); IR ν(KBr, cm^{-1}): 3317, 3190, 2967, 1665, 1608, 1563, 1407, 1373, 1248, 962, 828, 758. ^1H NMR (δ, DMSO-d_6, 400 MHz): 12.06 (s, 1H, NH, D_2O exchangable), 11.42 (s, 1H, >NH, D_2O exchangable), 7.64 (d, 2H, *J*= 8.4 Hz), 7.00 (d, 2H, *J*= 8.4 Hz), 6.89 (s, 1H), 3.99 (s, 2H, CH_2), 3.86(s, 3H, OCH_3), 1.89 (s, 3H, $COCH_3$). MS, TOF ES+ *m/z* (%): 330 (M^++1), Anal. Calcd for: $C_{15}H_{15}N_5O_2S$: C, 54.70; H, 4.59; N, 21.26%. Found: C, 54.68; H, 4.52; N, 21.22%.

3.1.3.7 2-Acetamido-4-(5-(3,4-dimethoxyphenyl)-4H-[1,2,4]triazol-3-yl)methyl thiazole (5g).

95% yield; m.p. 227 °C; R_f: 0.54 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3319, 3199, 2929, 1674, 1541, 1270, 1241, 1025, 746. ^1H NMR (δ, DMSO-d_6, 400 MHz): 12.12 (s, 1H, NH, D_2O exchangable), 11.48 (s, 1H, >NH, D_2O exchangable), 7.29 (s, 1H),

7.17 (d, 1H, *J*= 8.1 Hz), 7.02 (d, 1H, *J*= 8.1 Hz), 6.92 (s, 1H), 4.00 (s, 2H, CH_2), 3.79 (s, 6H, 2x OCH_3), 1.88 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.8, 168.2, 165.0, 157.4, 150.5, 144.9, 142.6, 126.8, 121.5, 111.3, 109.5, 108.1, 55.4, 38.5, 22.3. MS, TOF ES+ *m/z* (%): 360.362 (M^++1), Anal. Calcd for: $C_{16}H_{17}N_5O_3S$: C, 53.47; H, 4.77; N, 19.49%. Found: C, 53.46; H, 4.71; N, 19.47%.

3.1.3.8 2-Acetamido-4-(5-(3,4,5-trimethoxyphenyl)-4H-[1,2,4]triazol-3-yl) methyl thiazole(5h).

94% yield; m.p. 233 °C; R_f: 0.54 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3358, 3238, 2969, 1678, 1581, 1326, 1278, 1124, 747. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.12 (s, 1H, NH, D_2O exchangable), 11.57 (s, 1H, >NH, D_2O exchangable), 6.99 (s, 2H), 6.93 (s, 1H), 4.01 (s, 2H, CH_2), 3.82 (s, 6H, 2x OCH_3), 3.69 (s, 3H, OCH_3), 2.11 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 75.47 MHz): 170.0 (>C=O), 168.3, 165.3, 157.6, 153.1, 146.4, 145.0, 142.5, 139.1, 129.7, 109.6, 103.8, 60.0 (2x OCH_3), 55.9 (OCH_3), 38.9 (CH_2), 22.4 ($COCH_3$). MS, TOF *m/z* ES+ (%): 390.108 (M^++1), Anal. Calcd for: $C_{17}H_{19}N_5O_4S$: C, 52.43; H, 4.92; N, 17.98%. Found: C, 52.41; H, 4.93; N, 17.99%.

3.1.3.9 2-Acetamido-4-(5-(4-hydroxyphenyl)-4H-[1,2,4]triazol-3-yl) methylthiazole (5i).

88% yield; m.p. 219 °C; R_f: 0.51 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3430, 3170, 2966, 1707, 1654, 1549, 1396, 1276, 788. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.02 (s, 1H, NH, D_2O exchangeable), 11.24 (s, 1H, >NH, D_2O exchangable), 9.60 (s, 1H, OH, D_2O exchangable), 7.48 (d, 2H, *J*= 7.9 Hz), 6.80 (d, 2H, *J*= 7.9 Hz), 6.76 (s, 1H), 4.03 (s, 2H, CH_2), 2.13 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 170.8, 168.3, 159.3, 146.7, 144.8, 146.7, 144.9, 143.0, 128.7, 125.2, 115.6, 109.4, 38.6, 22.4. MS, TOF ES+ *m/z* (%): 316.129 (M^++1), Anal. Calcd for: $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.16; N, 22.21%. Found: C, 53.29; H, 4.11; N, 22.20%.

3.1.3.10 2-Acetamido-4-(5-(2-hydroxyphenyl)-4H-[1,2,4]triazol-3-yl)methyl thiazole (5j).

90% yield; m.p. 225 °C; R_f: 0.50 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3441, 3317, 3216, 2975, 1670, 1719, 1522, 1342, 1263, 750. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 11.78 (s, 1H, NH, D_2O exchangable), 11.40 (s, 1H, >NH, D_2O exchangable), 10.15 (s, 1H, OH, D_2O exchangable), 7.19 (d, 1H, *J*=8.2 Hz), 6.83 (d, 1H, *J*= 7.7 Hz), 6.79 (m, 2H), 6.69 (s, 1H), 3.88 (s, 2H, CH_2), 2.09 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 172.0, 168.3, 155.9, 144.9, 138.5, 130.6 127.6, 125.0, 123.2, 120.6, 118.1, 102.9, 38.6, 21.0. MS, TOF ES+ *m/z* (%): 316.213 (M^++1), Anal. Calcd for: $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.16; N, 22.21%. Found: C, 53.29; H, 4.20; N, 22.23%.

3.1.3.11 2-Acetamido-4-(5-(4-hydroxy,3-methoxyphenyl)-4H-[1,2,4]triazol-3-yl)methyl thiazole (5k).

86% yield; m.p. 229 °C; R_f: 0.51 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3493, 3213, 2925, 1706, 1669, 1595, 1517, 1130, 1077, 854. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 11.90 (s, 1H, NH, D_2O exchangable), 11.10 (s, 1H, >NH, D_2O exchangable), 8.63 (s, 1H, OH, D_2O exchangable), 6.93 (s, 1H), 6.74 (d, 1H, *J*=8.1 Hz), 6.75 (d, 1H, *J*=8.1 Hz), 6.65(s, 1H), 4.08 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.16 (s,3H,$COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 170.8, 168.3, 165.0, 148.8, 145.0, 143.1, 125.6, 121.9, 115.4, 109.6, 55.5, 38.6, 22.4. MS, TOF ES+ *m/z* (%): 346.246 (M^++1), Anal. Calcd for: $C_{15}H_{15}N_5O_3S$: C, 52.16; H, 4.38; N, 20.21%. Found: C, 52.10; H, 4.42; N, 20.31%.

3.1.3.12 2-Acetamido-4-(5-(2-furanyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5l).

88% yield; m.p.204 °C; R_f: 0.55 (98:2 chloroform: methanol, v/v);IR ν (KBr, cm^{-1}): 3487, 3199, 2924, 1679, 1601, 1543, 1465, 1270, 997, 745. ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 11.79 (s, 1H, NH, D_2O exchangable), 11.13 (s, 1H, >NH, D_2O exchangable), 7.52 (d, 1H,

J=7.9 Hz), 6.67 (d, 1H, *J*=7.9 Hz), 6.51 (m, 1H), 6.40 (s, 1H), 4.04 (s, 2H, CH_2), 2.17 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 170.9, 168.3, 157.6, 149.3, 145.1, 136.3, 133.0, 113.4, 112.1, 109.8, 37.3, 22.4. MS, TOF ES+ *m/z* (%): 290.233 (M^++1), Anal. Calcd for: $C_{12}H_{11}N_5O_2S$: C, 49.82; H, 3.83; N, 24.21%. Found: C, 49.85; H, 3.80; N, 24.19%.

3.1.3.13 2-Acetamido-4-(5-(2-thienyl)-4H-[1,2,4]triazol-3-yl)methylthiazole (5m).

84% yield; m.p. 211 °C; R_f: 0.53 (98:2 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3199, 3044, 2925, 2857, 1663, 1597, 1551, 1374,1085, 982, 855, 716. ^1H NMR (δ, DMSO-d_6, 400 MHz): 11.97 (s, 1H, NH, D_2O exchangable), 11.35 (s, 1H, >NH, D_2O exchangable), 7.39 (d, 1H, *J*= 7.8 Hz), 7.45 (d, 1H, *J*= 7.8 Hz), 7.21 (m, 1H), 6.73(s, 1H), 4.02 (s, 2H, CH_2), 2.12 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 170.1, 168.2, 165.2, 157.5, 144.6, 141.6, 139.0, 130.7, 128.1, 109.5, 38.6, 22.4. MS, TOF ES+ *m/z* (%): 306.234 (M^++1), Anal. Calcd for: $C_{12}H_{11}N_5OS_2$: C, 47.20; H, 3.63; N, 22.93%. Found: C, 47.18; H, 3.64; N, 22.91.

3.2. Antimicrobial activity

Among all, compounds **5a–m** were tested for their *in vitro* antimicrobial activity against three Gram-positive bacteria (*S. aureus* MTCC 096, *Bacillus subtilis* MTCC 441 and *Staphylococcus epidermis* MTCC 435), four Gram-negative bacteria (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 424, *Salmonella typhi* MTCC 733, and *Klebsiella pneumoniae* MTCC 432) as well as four fungal strain (*Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus flavus* MTCC 277, and *Candida albicans* MTCC 227) using Cup plate method[xxv-xxvi] at 100 μg/mL concentration where Muller-Hinton agar was used for bacterial and Sabouraud dextrose agar used for fungi and were poured on to the sterilized petri dishes (25 mL: each petri dish). The poured material was allowed to set (0.5 h) and thereafter the 'CUPS' (08 mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution (0.1 mL) was added with the help of a micro pipette. The plates were incubated at 37 °C for 16 h for bacteria and 34 h for fungi and the results were recorded. The test solution was prepared using DMSO as solvent. Clinically antimicrobial drugs Ciprofloxacin and Miconazole were used as the positive control and DMSO solution was used for blank. The results for antimicrobial studies depicted in **Tables 1** revealed that the tested compounds displayed variable inhibitory effects against the bacterial and fungal strains.

Table 1 Antimicrobial activity data of compounds **5a-m**.[a]

Compd.	*Sa*	*Bs*	*Se*	*Ec*	*Pa*	*St*	*Kp*	*An*	*Af*	*Afl*	*Ca*
5a	11	10	12	11	12	12	10	12	--	12	12
5b	13	14	13	14	14	12	11	12	13	13	13
5c	13	14	12	13	14	12	10	12	14	12	12
5d	12	13	13	14	13	12	10	12	13	13	14
5e	11	11	11	11	12	11	11	10	--	13	12
5f	13	13	12	13	13	13	10	13	--	10	10
5g	13	13	12	13	14	12	11	12	13	13	12
5h	12	10	10	10	12	10	10	13	14	12	13
5i	11	12	12	10	13	10	11	12	12	10	--
5j	11	10	11	10	13	12	10	13	13	13	10
5k	12	11	10	10	12	12	11	10	--	12	12

5l	14	10	10	14	15	12	10	10	14	13	15
5m	15	12	11	14	16	12	11	10	13	13	14
Cip.	17	18	17	16	18	17	18	--	--	--	--
Mic.	--	--	--	--	--	--	--	14	15	15	16

[a] *Values represent zone of inhibition; (--) means no activity.*

Sa: *Staphylococcus aureus* MTCC 096, Bs: *Bacillus subtilis* MTCC 441, Se: *Staphylococcus epidermis* MTCC 435, Ec: *Escherichia coli* MTCC 443, Pa: *Pseudomonas aeruginosa* MTCC 424, St: *Salmonella typhi* MTCC 733, Kp: *Klebsiella pneumoniae* MTCC 432, An: *Aspergillus niger* MTCC 282, Af: *Aspergillus fumigatus* MTCC 343, Afl: *Aspergillus flavus* MTCC 277, Ca: *Candida albicans* MTCC 227, Cip.: Ciprofloxacin, Mic.: Miconozole.

4. Conclusion

A series of thirteen 2-acetamido-4-(5-subsitituted-phenyl-4*H*-[1,2,4]triazol-3-yl) methyl thiazoles (**5a-m**) were synthesized using a simple methodology in excellent yields. Synthesized 1,2,4-triazole derivatives are obtained in high purity without employing column chromatography. The compounds were screened for their antimicrobial activity against seven strains of bacteria and four strains of fungi by determining of zone of inhibition. In general, compounds were found to exhibit promising activity against most of the bacterial pathogens while moderate to good activity was displayed against the various fungal pathogens. Compounds substituted with furan and thiophene moieties showed significant antibacterial as well as antifungal activity. It is also suggested that triazolylthiazoles are conceivable for further investigations with hope to get more selective and potential antimicrobial agents.

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