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Synthesis and biological evaluation of 3-benzyl/piperazino-methyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione

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Abstract: A new series of 3-benzyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **8(a-d)** and 3-piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **9(a-e)** has been synthesized from 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,3-thiazole-2-thione **7**. Chemical structures of all the new compounds were established by IR, ^{1}H, ^{13}C NMR, MS and elemental data. The compounds **8(a-d)** and **9(a-e)** were evaluated for their antibacterial activity against human pathogenic organisms *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus typhi.* The investigation of antibacterial screening data reveal that, compounds in the series of **8** which contain 4-chlorobenzyl, 4-nitrobenzyl moiety on the thiadiazole and compounds in series of **9** containing *N*-methylpiperazine moiety on the thiadiazole, displayed good antibacterial activity against all the organisms. Compounds **8c** and **9a** were highly active against *B. subtilis* and *S. typhi*. Most of these new compounds showed appreciable activity against test bacteria and emerged as potential molecules for further development.

Keywords: Antibacterial Synthesis; 1,2,3-Triazole; 1,3,4-Thiadiazole-2-thione; Antibacterial activity.

1. Introduction

The development of 1,2,3-triazoles for drug discovery and industrial use has been shown to be very versatile. The uses for triazoles have been found in various areas and are continuously growing. The applications of these triazoles are increasingly found in all aspects of drug discovery, ranging from cutting edge research through combinatorial chemistry and target-templated *in situ* chemistry, to proteomics and DNA research using bioconjugation reactions[1]. These triazole products are more than just passive linkers; they readily associate with biological targets, through hydrogen bonding and dipole interactions[1]. Derivatives of 1,2,3-triazole have been found to have anti-HIV,[2] anti-allergenic,[3] cytostatic,[4] virostatic[5] and anti-inflammatory[6] activities. Triazoles are also being studied for the treatment of obesity[7] and osteoarthritis.[8] The increased interest in the 1,2,3-triazole is due to it being non-toxic, benign and stable. Triazoles are particularly interesting for medicinal use because they are more likely to be water soluble than normal aromatic compounds, and are stable in biological systems.[9] The triazole antifungal drugs include fluconazole,[10] isavuconazole,[11] itraconazole,[12] voriconazole,[13] pramiconazole,[14] and posaconazole.[15] The triazole plant protection fungicides include epoxiconazole,[16] triadimenol,[17] propiconazole,[18] metconazole,[19] cyproconazole,[20] tebuconazole,[21] flusilazole[22] and paclobutrazol.[23] This allows for the applications of 1,2,3-triazoles to grow exponentially due to their reliability, tolerance to a wide variety of functional groups, regiospecificity and the readily available starting materials.

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Further, thiadiazole is a heterocyclic compounds featuring both two nitrogen atoms and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1,3,4-thiadiazole. They occur in nature in four isomeric forms as 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. 1,3,4-Thiadiazole are important because of their versatile biological actions. In particular, compounds bearing the 1,3,4-thiadiazole nucleus is known to have unique antibacterial[24] and anti-inflammatory activities.[25] Differently substituted thiadiazole moieties have also been found to have other interesting activities such as analgesic,[26] antimicrobial,[27] antitubercular,[28] anticonvulsant[29] and anti-hepatitis B viral activities.[30]

Based on the wide spectrum of biological profile of triazole, thiadiazole and their increasing importance in pharmaceutical and biological field and in continuation of our on going research on biologically active heterocycles,[31-35] it was thought of interest to accommodate triazole and thiadiazole moieties in a single molecular frame work to synthesize some new heterocyclic compounds with potential biological activity. The present investigation deals with the synthesis of some new 3-benzyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **8(a-d)** and 3-piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **9(a-e)** from 5-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,3-thiazole-2-thione **7**. The antibacterial activities of the compounds **8** and **9** have also been evaluated.

2. Results and discussion

The diazotization of aniline **1** by nitrous acid at 0-5 ^{0}C in the presence of HCl for 1 h, led to the formation of aryldiazonium chloride **2**, which on reaction with sodium azide at stirring for 30 min. produced arylazides **3** in 76% yield. It was reported that the azide compound can be cyclized using ethyl acetoacetate to furnish 1,2,3-triazole derivative. In a similar fashion the azide **3** was cyclized with ethyl acetoacetate in the presence of sodium ethoxide at reflux for 4 h, to afford 5-methyl-1-[aryl]-1,2,3-triazole-4-carboxylic acid **4** in 68% yield[36]. The compounds **4** was reacted with absolute ethyl alcohol in the presence of catalytic amount of conc. H_2SO_4 at reflux for 3 h, to get the ethyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate **5** in 72% yield. Hydrazinolysis of compound **5** with hydrazine hydrate, in ethyl alcohol at reflux for 4 h afforded, 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide **6** in 70% of yield. Further, the condensation of compound **6** with carbon disulphide in ethanolic potassium hydroxide at room temperature, yield potassium salt, which was liberated and simultaneously dehydrated by the action of concentrate sulphuric acid at room temperature for 24 h, to yield the intermediate, 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2,3-dihydro-1,3-thiazole-2-thione **7** in good overall yield (**Figure 1**).

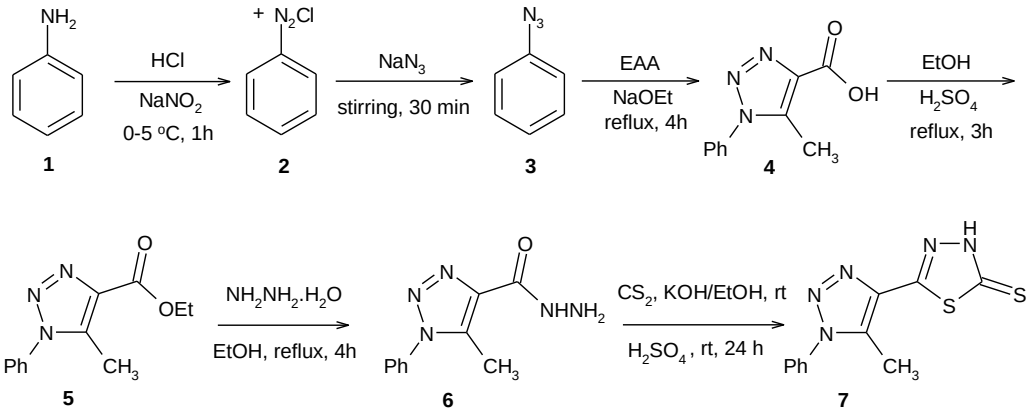
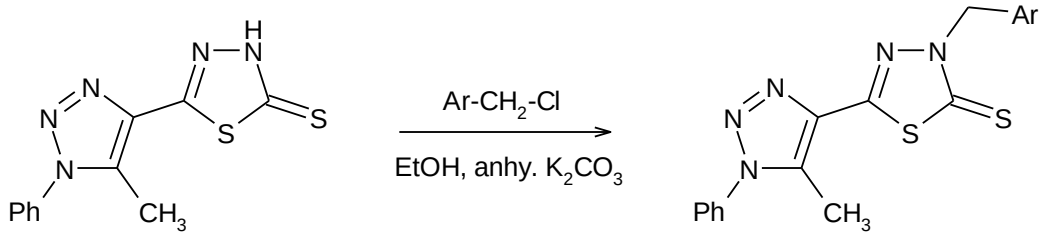


Figure 1. Synthetic pathways for compound **7**

The structure of the compound **7** was confirmed by its IR, ^{1}H, ^{13}C NMR and Mass spectra. The proton NMR spectrum of **7** showed the aromatic protons at δ 7.22-7.35 ppm as multiplet for five protons, methyl protons at δ 2.37 as singlet and the NH proton of thiadiazole ring appear as singlet at δ 6.92 ppm. The ^{13}C NMR spectra of compound **7** showed the signals corresponding to the carbons of thiadiazole C-5 at δ 133.4 and the C=S at 159.6 ppm and the triazole carbons at δ 124.9 and 144.5 ppm. The IR spectrum of **7** showed absorption bands at 3341 cm^{-1} (N-H), 1394 and 1605 cm^{-1} (C=N).

Compound **7** was aralkylated *via* reaction with benzyl- or substituted benzyl chloride, in ethanol, in the presence of anhydrous potassium carbonate to yield the corresponding 3-benzyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **8(a-d)**. Although the alkylation of 1,2,4-triazole-3-thiols were reported to yield a mixture of the *S*- and *N*-alkyl derivatives, the *N*-alkyl derivatives were reported to be the sole product of alkylation of 1,3,4-oxadiazole-2-thiols. The reaction of **7** with benzyl- or 4-substituted benzyl chloride yielded only one product as proved by thin layer chromatography (TLC) which was identified to be the *N*-arylmethyl derivatives (**Figure 2**).

The IR spectra of these compounds **8** showed common characteristic absorption peaks at 3065 and 3182 cm^{-1} (Ar C-H), 2942 cm^{-1} (CH_3 and CH_2 C-H) and 1413-1656 cm^{-1} (C=N). The ^1H NMR spectra are characterized by the presence of the aromatic protons as multiplet at δ 7.20-7.30 ppm (8H) and doublet at δ 7.09 ppm (2H). The methyl and benzylic CH_2 were shown as singlets at δ 2.56 and 5.17 ppm respectively. The ^{13}C NMR spectra are characterized by the presence of the benzylic CH_2 carbons at δ 52.4 ppm. The C-5 and C=S carbons of thiadiazole were shown at δ 148.9 and 168.5 ppm respectively.

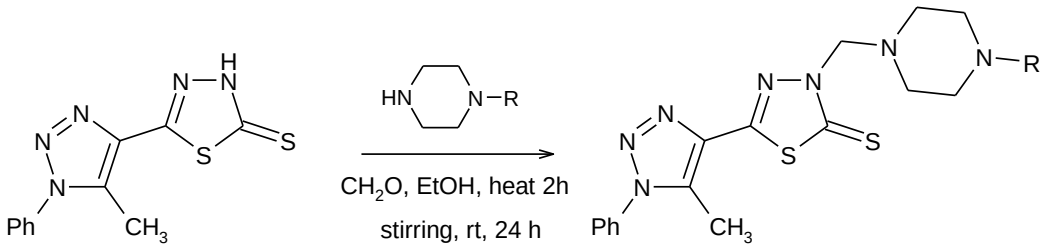


7 **8 (a-d)**

8: Ar = ***a***) phenyl; ***b***) 4-fluorophenyl; ***c***) 4-chlorophenyl; ***d***) 4-nitrophenyl

Figure 2. Synthetic pathways for compounds **8a-d**

Further, the compound **7** was reacted with formalin solution and monosubstituted piperazines, in ethanol, by heating for 2 h, then stirring at room temperature for 24 h yielded the *N*-Mannich bases of 3-piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **9(a-e)** relatively low yields (36-52%), **(Figure 3)**.



7 **9 (a-e)**

9: R = ***a***) methyl; ***b***) ethyl; ***c***) phenyl; ***d***) 2-methoxyphenyl; ***e***) 2-pyrimidinyl

Figure 3. Synthetic pathways for compounds **9a-e**

The IR spectra of compound **9** showed common characteristic absorption at 3152 cm^{-1} for the aromatic C-H, 2921 cm^{-1} (NCH_2N, piperazine and alkyl C-H) and 1401-1675 cm^{-1} (C=N). The ^1H NMR spectra are characterized by the presence of the aromatic and aliphatic protons as singlets at δ 7.35-7.40 (5H). The piperazine (8H) appeared as multiplets at δ 2.42 and 2.69 ppm. The NCH_2N protons appeared as singlet at δ 5.18 ppm. The ^{13}C NMR spectra are characterized by the presence of the piperazine carbon as two peaks at δ 50.7 and 53.9 ppm, while the NCH_2N carbons appeared at δ 67.2 ppm. The C-5 and C=S carbons of thiadiazole ring were shown at δ 152.8 and 171.3 ppm, respectively. In summary, all the synthesized compounds exhibited satisfactory spectral data consistent with their structures.

3. Antibacterial activity

The compounds **8(a-d)** and **8(a-e)** were assayed for their antibacterial activity against human pathogenic organisms *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus typhi*. The zone of inhibition in mm at concentration 500 μg was determined using the cup plate method.[37] DMF was used as solvent control. Norfloxacin was used as antibacterial standard and the results are given in **Table 1**. It has been observed that the compounds exhibited interesting biological activity however, with a degree of variation. The investigation of antibacterial screening data reveal that, compounds in the series of **8** which contain 4-chlorobenzyl, 4-nitrobenzyl moiety on the thiadiazole and in compounds **9** containing *N*-methylpiperazine moiety on the thiadiazole, displayed good antibacterial activity against all the organisms. Compounds **8c** and **9a** were highly active against *B. subtilis* and *S. typhi*. The remaining compounds showed moderate to good activity against all the organisms employed.

Table 1. Antibacterial Activity of Compounds **8(a-d)** and **9(a-e)**

Compound	zone inhibition in mm		
	B. subtilis	*E. coli*	*S. typhi*
8a	17	20	18
8b	21	17	23
8c	26	28	26
8d	24	24	24
9a	26	26	24
9b	24	18	20
9c	19	21	15
9d	18	19	20
9e	20	21	22
Norfloxacin	26	28	26

Note: <16mm, inactive; 17-23mm, moderately active; 23-26mm, highly active

4. Experimental Section

Reagents were of commercial grade and were used as supplied or were prepared according to procedures described in literature. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck, and compounds visualized either by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR, ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer, were within ± 0.4% of theory.

4.1. Ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (5):

To the solution of **4** (0.01 mol) in absolute ethyl alcohol (25 mL), conc. H_2SO_4 (2 mL) was added. The mixture was refluxed for 3 h. After completion of the reaction (TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed with 10% $NaHCO_3$ solution, dried and recrystallized from ethyl alcohol to get pure product **5** in 72% of yield, m.p. 158-160 ^{o}C; IR (KBr): *v* 3010, 2943, 1698, 1621, 1513, 1249, 1034 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.24 (t, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.17 (q, 2H, CH_2), 7.30-7.40 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6): δ 15.7, 16.4, 59.7, 125.4, 128.0, 128.9, 129.1, 134.5, 140.2, 160.1; MS: *m/z* 231 (M^+). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.29; H, 5.61; N, 18.11.

4.2. 5-*Methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (6):*
A mixture of compound **5** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (20 mL) was refluxed for 4 h, cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give the new intermediate **6** in 70% of yield, m.p. 168-169 ^{o}C; IR (KBr): *ν* 3270, 1630, 1610, 1395, 741 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.30 (s, 3H, CH_3), 5.27 (s, 2H, NH_2), 7.25-7.35 (m, 5H, ArH), 7.69 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): *δ* 13.5, 119.2, 125.6, 128.7, 129.7, 138.7, 151.9, 158.7; MS: *m/z* 217 (M^+). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.21; H, 5.04; N, 32.19.

4.3. 5-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3-thiazole-2-thione (7):
To the compound **6** (0.1 mol) 98% sulphuric acid (25 mL) was added portion-wise, and the resulted clear solution was stirred at room temperature for 24 h. The mixture was cautiously added to crushed ice, stirred for 3 h, refrigerated for 2 h, and the separated precipitate was filtered, washed with water, dried and crystallized from ethanol to give compound **7** in 60% yield; IR (KBr): *ν* 3341, 3084, 1696, 1605, 1394, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.37 (s, 3H, CH_3), 6.92 (s, 1H, NH), 7.35-7.40 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6): *δ* 10.8, 123.5, 124.9, 126.5, 128.7, 133.4, 140.2, 144.5, 159.6; MS: *m/z* 274 (M^+). Anal. Calcd for $C_{12}H_{10}N_4S_4$: C, 52.53; H, 3.67; N, 20.42. Found: C, 52.48; H, 3.60; N, 20.60.

4.4. General procedure for the synthesis of 3-benzyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione 8a-d:
A mixture of compound 7 (0.01 mol), the appropriate benzyl- or substituted benzyl chloride (0.01 mol) and anhydrous potassium carbonate (0.01 mol), in ethanol (25 mL) was heated under reflux for 6 h, and the solvent was distilled off under reduced pressure. Water (25 mL) was added to the residue and the separated crude product was filtered, washed with water, dried and crystallized to give the pure compounds 8(a-d) in 59-64% yields. All the products were characterized by IR, ^{1}H, ^{13}C NMR, MS and elemental analyses.

4.4.1.3-benzyl-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (8a): Yield 61%, m.p. 176-178 ^{o}C; IR (KBr): *ν* 3182, 3065, 2942, 1692, 1605, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.56 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 7.09 (d, 2H, ArH), 7.20-7.30 (m, 8H, ArH); ^{13}C NMR (DMSO-d_6): *δ* 14.2, 52.4, 125.0, 127.6, 128.1, 128.9, 129.0, 130.6, 132.0, 135.4, 136.5, 141.4, 148.9, 168.5; MS: *m/z* 365 (M^+). Anal. Calcd for $C_{18}H_{15}N_5S_2$: C, 59.16, ; H, 4.14; N, 19.16. Found: C, 59.10; H, 4.10; N, 19.10.

4.4.2.3-(4-fluorobenzyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (8b): Yield 64%, m.p. 179-181 ^{o}C; IR (KBr): *ν* 3182, 3065, 1692, 1605, 1413, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.52 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 7.20-7.35 (m, 7H, ArH), 7.56 (d, 2H, ArH); MS: *m/z* 383 (M^+). Anal. Calcd for $C_{18}H_{14}FN_5S_2$: C, 56.38; H, 3.68; N, 18.26. Found: C, 56.30; H, 3.60; N, 18.19.

4.4.3.3-(4-chlorobenzyl)-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (8c): Yield 60%, m.p. 188-190 ^{o}C; IR (KBr): *ν* 3184, 3067, 2942, 1692, 1605, 1413, 1067, 686 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.51 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.20-7.35 (m, 7H, ArH), 7.48 (d, 2H, ArH); MS: *m/z* 399 (M^+). Anal. Calcd for $C_{18}H_{14}ClN_5S_2$: C, 54.06; H, 3.53; N, 17.51. Found: C, 54.00; H, 3.48; N, 17.42.

4.4.4. 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-3-(4-nitrobenzyl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (8d): Yield 59%, m.p. 180-182 ^{o}C; IR (KBr): *ν* 3182, 3062, 2945, 1695, 1602, 1413, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): *δ* 2.50 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 7.20-7.30 (m, 5H, ArH), 7.51 (d, 2H, ArH), 7.77 (d, 2H, ArH); MS: *m/z* 410 (M^+). Anal. Calcd for $C_{18}H_{14}N_6S_2$: C, 52.67; H, 3.44; N, 20.47. Found: C, 52.60; H, 3.40; N, 20.41.

4.5. General procedure for the synthesis of 3-piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione 9a-e:

A mixture of compound 7 (0.01 mol), the *N*-substituted piperazine (0.02 mol) and 37% formaldehyde solution (2 mL), in ethanol (20 mL), was heated under reflux for 2 h and stirred at room temperature for 24 h. The crude product was separated in case of compound **9c**, while in case of compounds **9a** and **9b** it was necessary to add water (5 mL) to precipitate the products. The crude products were filtered, washed with water, dried and crystallized to give the pure compounds 9(a-e) in 55-60% yields. All the products were characterized by IR, ^{1}H, ^{13}C NMR, MS and elemental analyses.

4.5.1. 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-3-[(4-methylpiperazino)methyl]-2,3-dihydro-1,3,4-thiadiazole-2-thione (9a): Yield 55%, m.p. 192-194 ^{o}C; IR (KBr): *v* 3152, 2921, 1675, 1637, 1602,1401, 1067 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.42 (m, 4H, CH_2), 2. 60 (s, 3H, CH_3), 2.69 (m, 4H, CH_2), 5.18 (s, 2H, CH_2), 7.35-7.40 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6): δ 11.4, 41.7, 42.0, 50.6, 53.2, 69.7, 118.4, 121.7, 127.5, 129.2, 132.5, 134.3, 143.1, 151.6, 165.8, 184.3; MS: *m/z* 387 (M^+). Anal. Calcd for $C_{17}H_{21}N_7S_2$: C, 52.69; H, 5.46; N, 25.30. Found: C, 52.60; H, 5.40; N, 25.22.

4.5.2. 3-[(4-ethylpiperazino)methyl]-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (9b): Yield 59%, m.p. 189-191 ^{o}C; IR (KBr): *v* 3154, 2927, 1672, 1640, 1605, 1401, 1062 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, CH_3), 2. 39 (s, 3H, CH_3), 2.69 (q, 2H, CH_2), 2.86 (m, 4H, CH_2), 2.70 (m, 4H, CH_2), 5.18 (s, 2H, CH_2), 7.35-7.40 (m, 5H, ArH); MS: *m/z* 401 (M^+). Anal. Calcd for $C_{18}H_{23}N_7S_2$: C, 53.84; H, 5.77; N, 24.42. Found: C, 53.78; H, 5.70; N, 24.36.

4.5.3. 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-3-[(4-phenylpiperazino)methyl]-2,3-dihydro-1,3,4-thiadiazole-2-thione (9c): Yield 60%, m.p. 187-189 ^{o}C; IR (KBr): *v* 3150, 2922, 1667, 1637, 1607, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.86 (m, 4H, CH_2), 2.92 (m, 4H, CH_2), 5.18 (s, 2H, CH_2), 7.35-7.40 (m, 10H, ArH); MS: *m/z* 449 (M^+). Anal. Calcd for $C_{22}H_{23}N_7S_2$: C, 58.77; H, 5.16; N, 21.81. Found: C, 58.70; H, 5.09; N, 21.76.

4.5.4. 3-[4-(2-methoxyphenyl)piperazino]methyl-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione (9d): Yield 59%, m.p. 191-193 ^{o}C; IR (KBr): *v* 3150, 2922, 1667, 1637, 1607, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.84 (m, 4H, CH_2), 2.92 (m, 4H, CH_2), 3.89 (s, 3H, OCH_3) 5.18 (s, 2H, CH_2), 6.70-6.80 (m, 3H, ArH), 7.35-7.40 (m, 5H, ArH); MS: *m/z* 479 (M^+). Anal. Calcd for $C_{23}H_{25}N_7OS_2$: C, 57.60; 5.25; N, 20.44. Found: C, 57.54; H, 5.20; N, 20.39.

4.5.5. 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-3-[4-(2-pyrimidinyl)piperazino]methyl-2,3-dihydro-1,3,4-thiadiazole-2-thione (9e): Yield 55%, m.p. 182-183 ^{o}C; IR (KBr): *v* 3150, 2922, 1667, 1637, 1607, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 2.92 (m, 4H, CH_2), 3.11 (m, 4H, CH_2), 5.18 (s, 2H, CH_2), 6.90 (m, 1H, ArH), 7.35-7.40 (m, 5H, ArH), 8.30 (m, 2H, ArH); MS: *m/z* 451 (M^+). Anal. Calcd for $C_{20}H_{21}N_9S_2$: C, 53.20; H, 4.69; N, 27.92. Found: C, 53.16; H, 4.60; N, 27.86.

5. Conclusion

In conclusion, a series of novel 3-benzyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **8(a-d)** and 3-piperazinomethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1,3,4-thiadiazole-2-thione **9(a-e)** were prepared. The antibacterial activity of these compounds was evaluated against various bacteria. The compounds showed variable degree of antibacterial activity. Among the screened compounds, **8c** and **9a** were found to be the most active against all the microorganisms employed for antibacterial activity. With this set of analogues, we are now in a position to investigate the multiple biological activities of these compounds.

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References

[1] Hartmuth, C. K.; Barry, S. The growing impact of click chemistry on drug discovery, *Drug Discovery Today*, **2003**, *8*, 1128-1137.

[2] Lazrek, H. B.; Taourirte, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. Synthesis and anti-HIV activity of new modified 1,2,3-triazole acyclonucleosides, *Nucleosides Nucleotides Nucleic Acids*, **2001**, *20*, 1949-1960.

[3] Buckle, D. R.; Rockell, C. J.; Smith, H.; Spicer, B. A. Studies on 1,2,3-triazoles: synthesis and antiallergic properties of 9-oxo-1*H*, 9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazoles and their S-oxides, .*J. Med. Chem*. **1984**, *27*, 223-227.

[4] De las Heras, F. G.; Alonso, R.; Alonso, G. Alkylating nucleosides: synthesis and cytostatic activity of *N*-glycosyl(halomethyl)-1,2,3-triazoles. A new type of alkylating agent, *J. Med. Chem*. **1979**, *22*, 496-501.

[5] El-Etrawy, A. Sh.; Abdel-Rahman, A. A.-H. Synthesis and antiviral evaluation of 1,3-dimethyl-6-(1*H*-1,2,3-triazol-1-yl)pyrimidine-2,4(1*H*, 3*H*)-dione derivatives, *Chem. Heterocycl. Comp.* **2010**, *46*, 1105-1108.

[6] Erhan, P.; Gülay, Ş.; Pelin, K.; Tuğba, D.; Gülçin, A. Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones, *Il Farmaco*, **2002**, *57*, 101-107.

[7] Poulsen, S. A.; Wilkinson, B. L.; Innocenti, A. Inhibition of human mitochondrial carbonic anhydrases VA and VB with para-(4-phenyltriazole-1-yl)-benzene sulphonamide derivatives, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4624-4627.

[8] Joshua, S. T.; John C Van, R.; Michael, G. Natchus.; Michael, P. C.; Biswanath, De.; Lily, C. H.; Michael, J. J. The development of new triazole based inhibitors of tumor necrosis factor-α (TNF-α) production, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1609-1838.

[9] Kaval, N.; Ermolat'ev, D.; Appukkuttan, P.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. The application of "click chemistry" for the decoration of 2(1*H*)-pyrazinone scaffold: generation of templates, *J. Comb. Chem.* **2005**, *7*, 490-502.

[10] Yi, Xu.; Yan, W.; Lan, Y.; Rong-Mei, L.; Bao-Di, D.; Ren-Jie, T.; Ping-Hui, G.; Yuan-Ying, J. Proteomic analysis reveals a synergistic mechanism of fluconazole and berberine against fluconazole-resistant *Candida albicans*: Endogenous ROS Augmentation, *J. Proteome Res.* **2009**, *8*, 5296-5304.

[11] Pasqualotto, A. C.; Denning, D. W. New and emerging treatments for fungal infections, *J. Antimicrob. Chemother.* **2008**, 61, i19- i30.

[12] Alexander, A.; Tom, P.; Caremans, Jan, V.; Guy Van den, M.; Johan, A. M.; Patrick, A. Growth of itraconazole nanofibers in supersaturated simulated intestinal fluid randy mellaerts, *Molecular Pharmaceutics* , **2010**, *7*, 905- 913.

[13] Smith, J.; Safdar, N.; Knasinski, V.; Simmons, W.; Bhavnani, S. M.; Ambrose, P. G.; Andes, D. Voriconazole therapeutic drug monitoring, *Antimicrob. Agents Chemother*. **2006**, *50*, 1570—1572.

[14] Geria, A. N.; Scheinfeld, N. S. Pramiconazole, a triazole compound for the treatment of fungal infections, *Drugs* **2008**; *11*, 661-670.

[15] Schiller, D. S.; Fung, H. B. Posaconazole: an extended-spectrum triazole antifungal agent, *Clin. Ther*. **2007**, *29*, 1862-86.

[16] Xu, X. M.; Nicholson, P.; Ritieni, A. Effects of fungal interactions among fusarium head blight pathogens on disease development and mycotoxin accumulation, *Int. J. Food Microbio*. **2007**, ***119***, 67-71.

[17] Clark, T.; Deas, A. H. B. GC separation of enantiomers, *J. Chromatogr.* **1985**, *329*, 181-186.

[18] Toribio, L.; del Nozal, M. J.; Bernal, J. L.; Jiménez, J.J.; Alonso, C. Chiral separation of some triazole pesticides by supercritical fluid chromatography, *J. Chromatogr. A.* **2004**, *1046*, 249-253.

[19] Terence Grayson, B.; Sarah, L. B.; Alan, J. S.; Jeremy, N. D.; David, W. Effect of adjuvants on the performance of the new cereal fungicide, metconazole. I glasshouse trials, *Pesticide Science* **1995**, *45*, 153-160.

[20] Fuller, M. S.; Robertson, R. W.; Gisi, U. Effects of the sterol demethylase inhibitor, cyproconazole, on hyphal tip cells of *Sclerotium rolfsii*. III. Cell wall chemistry. *Pestic. Biochem. Physiol*. **1990**, *36*, 115-126.
[21] Johannes, Kaulen. The enantiomers of the azole fungicide HWG-1608—asymmetric synthesis of a 2-hydroxyethyl azole fungicide, *Angewandte. Chemie. Int. Ed*. **1989**, 462-463.
[22] Eckert, M. R.; Rossall, S.; Selley, A.; Fitt, B. D. Effects of fungicides on *in vitro* spore germination and mycelial growth of the phytopathogens Leptosphaeria maculans and L. biglobosa, *Pest. Management Science*, **2010**, *66*, 396-405.
[23] Malgorzata, B.; Zlatko, Z. Physiological response and yield of paclobutrazol treated tomato plants, *Plant Growth Regulation*, **2000**, *30*, 117-123.
[24] Thomasco, L. M.; Gadwood, R. C.; Weaver, E. A.; Ochoada, J. M.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Schaadt, R. D.; Yagi, B. H. The synthesis and antibacterial activity of 1,3,4-thiadiazole phenyl oxazolidinone analogues, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 4193-4196.
[25] Shiv, K. G.; Sharma, P. K. Synthesis and anti-inflammatory activity of disubstituted 1,3,4-thiadiazole, *Int. J. Drug Formul. Res*. **2011**, *2*, 344-350.
[26] Silvia, S.; Chiara, B.; Olga, B.; Francesco, B.; Angelo, R.; Walter, F.; Barbara, R.; Annalisa, C.; Giuseppe, F. New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities, *Bioorg. Med. Chem*. **2006**, *14*, 1698-1705.
[27] Kallur, H. J.*;* Prabhudev. S. M.*;* Kishore Singh, Ch.*;* Siddanna, A. D.*;* Hariprasanna, R. C.*;* Mohammad, Y. Synthesis and *a*ntimicrobial *a*ctivity of some 1, 3, 4-*t*hiadiazole *d*erivatives, *Am. J. PharmTech Res*. **2012**, *2*, 680-693.
[28] Talath, *S,;* Gadad, *A. K.* Synthesis, antibacterial and antitubercular activities of some 7-[4-(5-amino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl]fluoroquinolonic derivatives, *Eur. J. Med. Chem.* **2006**, *41*, 918-924.
[29] Stillings, M. R.*;* Welbourn, A. P.*;* Walter, D. S. Substituted 1,3,4-thiadiazoles with anticonvulsant activity*: a*minoalkyl derivatives, *J. Med. Chem.* **1986**, *29*, 2280-*228*4.
[30] Ahmad S. S. 1,3,4-Thiadiazoles of pharmacological interest: *r*ecent trends in their synthesis *via* tandem 1,3-dipolar cycloaddition: Review, *J. Adv. Res.* **2014**, *5*, 1-17.
[31] Sanjeeva Reddy, Ch.*;* Vani Devi, M.*;* Rajesh Kumar, G.*;* Sunitha, M.*;* Nagaraj, A. Synthesis and biological evaluation of novel bis[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles, *J. Heterocycl. Chem.* **2013**, *50*, 557-562.
[32] Sanjeeva Reddy, Ch.; Sanjeeva Rao, L.; Vani Devi, M.; Nagaraj, A. Synthesis and antimicrobial activity of linked heterocyclics containing pyrazole and oxadiazoles, *J. Heterocycl. Chem.* **2012**, *49*, 1038-1043.
[33] Sanjeeva Reddy, Ch.; Rajesh Kumar, G.; Vani Devi, M.; Nagaraj, A. Synthesis of novel linked pyrazolyl-thiazolidinone heterocycles as potent antibacterial agents, *Acta. Chim. Slov*. **2011**, *58*, 576-581.
[34] Sanjeeva Reddy, Ch.; Vani Devi, M.; Rajesh Kumar, G.; Sanjeeva Rao, L.; Nagaraj, A. Synthesis and antimicrobial activity of linked heterocyclics containing pyrazole-pyrimidine rings**,** *Indian J. Chem.* **2011**, *50B*, 1181-1186.
[35] Sanjeeva Reddy, Ch.; Chandrashekar Rao, D.; Yakub, V.; Nagaraj, A. Synthesis and antimicrobial study of bis-[thiadiazol-2-yl-tetrahydro-2*H*-pyrazolo[3,4-*d*][1,3]thiazole]methanes, *Org. Commun.* **2010**, *3*, 57-69.
[36] Nazariy, P.; Olga, S.; Vasyl, M. Synthesis of 1,2,3-triazole derivatives and evaluation of their anticancer activity, Sci. Pharm. **2013**, 81, 663-676.
[37] Collins, A. H. in: *Microbiological Methods*, second ed. Butterworth, London, **1976**.