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Synthesis and Characterization of Novel Pyridine Associated 1,2,4-Triazolo-1,3,4-thiadiazines

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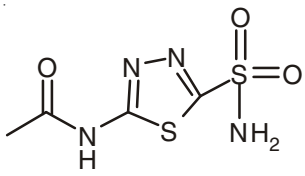
A series of novel 3-(1-methyl-1*H*-pyrazol-4-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine and its derivatives (**8a-f**) were synthesized by using 1-methyl-1*H*-pyrazole-4-carboxylic acid (**3**) as starting material and by involving 1-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (**4**), 1-methyl-1*H*-pyrazole-4-carboxylic acid hydrazide (**5**), 5-(1-methyl-1*H*-pyrazol-4-yl)-[1,3,4]oxadiazole-2-thiol **(6)** and 4-amino-5-(1-methyl-1*H*-pyrazol-4-yl)-4*H*-[1,2,4]triazole-3-thiol **(7)** as intermediate.

Keywords: Pyrazoles, Thiadiazoles, Heterocyclic chemistry.

INTRODUCTION

Several five membered aromatic systems having three heteroatoms at symmetrical positions such as thiadiazoles have been studied extensively owing to their interesting pharmacological activities. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as "hydrogen binding domain" and "two-electron donor system". It also acts as a constrained pharmacophore. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide (**1**), methazolamide (**2**), *etc*.

Thiadiazole can act as the bio-isosteric replacement of thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occured in nature in four isomeric forms *viz*., 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The 1,3,4-thiadiazole isomer of thiadiazole series and its dihydro derivatives provide a bulk of literature on thiadiazole. A glance at the standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers combined. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complex agents. The literature showed that thiadiazole nuclei have antimicrobial [1-8], antiinflammatory [9-14], anticancer [15-19], anticonvulsant [20-24], antidepressant [25,26], antioxidant, radio protective [27-29] and antileishmanial activities [30,31], carbonic anhydrase inhibitors [32,33].



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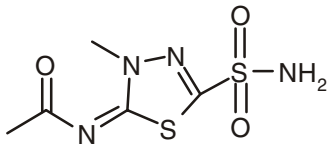

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Chemical properties of 1,3,4-thiadiazole have been reviewed in the last few years. However, the usefulness of 1,3,4-thiadiazole as a privileged system in medicinal chemistry has prompted the advances on the therapeutic potential of this system. A brief summary of the medicinal chemistry of 1,3,4-thiadiazole system and highlights some examples of 1,3,4-thiadiazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 1,3,4-thiadiazole is presented in by generalized synthetic methods. The progress achieved in the synthesis of heterocyclic compounds with biological potential is due to improvement of the methodological study of tested substances too. It is known that many 1,3,4-thiadiazole and derivatives have biological activity, with their antibacterial [34-36], antimycobacterial [37,38], antimycotic [39], antifungal [40,41], antidepression [42] and cardiotonic [43] action being notable. Recent research has also established for these heterocycles as analgesic [44] and anti-inflammatory [45,46] activity. Taking these data into account, in the present study, some new substituted 5-([1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1,3-benzoxazoles have been synthesized.

Five membered heterocyclic compounds show various types of biological activity among them 1,3,4-thiadiazoles are associated with diverse biological activity probably virtue of –N=C–S– grouping. Therapeutic importance of these rings prompted us to develop selective molecules in which substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities. Thiadiazoles have occupied an important place in drug industry *e.g.*, 1,3,4-thiadiazoles have wide applications in many fields. Earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs. Some of other uses are antitumor, anti-inflammatory, pesticides, dyes, lubricants, and analytical reagents [47]. 1,3,4-Thiadiazole derivatives posses interesting biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring [48]. Approach to practice of medicinal chemistry has developed from an empirical one involving synthesis of new organic compounds based on modification of chemical compounds of known biological activities could be better explored. It is well established that slight alteration in the structure of certain compounds are able to bring drastic changes to yield better drug with less toxicity to the host it observed that chemical modification not only alters physico-chemical properties but also pharmacological properties [49,50].

Based on these observations and inspired by the biological profile of pyrazoles, 1,3,4-triazoles and 1,3,4-thiadaizines, we have introduced 1,3,4-triazoles and 1,3,4-thiadaizine moieties into the pyrazole ring which leads to the synthesis of the title compounds with three active pharmacophores in a single molecular frame work for the intensified biological activities. Thus we have designed and synthesized a series of novel 3-(1-methyl-1*H*-pyrazol-4-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine and its derivatives (**8a-f**).

EXPERIMENTAL

All the reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^{1}H NMR and 100 MHz for ^{13}C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

1-Methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (4): To the solution of 1-methyl-1*H*-pyrazole-4-carboxylic acid **(3)** (0.01 mol) in absolute ethyl alcohol (15 ml), conc. H_2SO_4 (2 mL) was added. The mixture was refluxed for 5 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the obtained residue was recrystallized with petroleum ether to get pure 1*H*-indole-4-carboxylic acid ethyl ester (**4**).

1-Methyl-1*H*-pyrazole-4-carboxylic acid hydrazide (5): A mixture of 1-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (**4**) (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (20 mL) was refluxed for 6 h. After completion of the reaction (observed by TLC), the mixture was cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give 1*H*-indole-4-carboxylic acid hydrazide (**5**) in pure form.

5-(1-Methyl-1*H*-pyrazol-4-yl)-[1,3,4]oxadiazole-2-thiol (6): A mixture of 1-methyl-1*H*-pyrazole-4-carboxylic acid hydrazide (**5**) (0.01 mol), potassium hydroxide (0.02 mol) and carbon disulfide (0.03 mol) in ethanol (100 mL) was heated under reflux with stirring for 12 h. After accomplishment of the reaction (watched by TLC), the solvent was distilled *in vacuo*, the residual mass was poured over crushed ice and neutralized the alkaline solution with 10 % hydrochloric acid. The precipitated crude product was filtered, washed with water, dried and recrystallized from ethanol to get the pure compound 5-(1*H*-indole-4-yl)-[1,3,4]oxadiazole-2-thiol (**6**).

4-Amino-5-(1-methyl-1*H*-pyrazol-4-yl)-4*H*-[1,2,4]-triazole-3-thiol (7): To a warm solution of 5-(1-methyl-1*H*-pyrazol-4-yl)-[1,3,4]oxadiazole-2-thiol **(6)** (0.01 mol) in ethanol (20 mL), 80 % hydrazine hydrate (0.03 mol) was added drop wise and the reaction mixture was heated under reflux for 8 h. After achievement of the reaction (examined by TLC), the solvent was distilled off *in vacuo,* cooled and the solid separated were filtered, washed with cold ethanol and recrystallized from chloroform to give pure compound 4-amino-5-(1*H*-indol-4-yl)-4*H*-[1,2,4]-triazole-3-thiol (**7**).

3-(1-Methyl-1*H*-pyrazol-4-yl)-6-phenyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadaizines (8a-f): A mixture of 4-amino-5-(1-methyl-1*H*-pyrazol-4-yl)-4*H*-[1,2,4]triazole-3-thiol (**7**) (0.01 mol) and corresponding phenacyl bromide (0.02 mol) in absolute ethanol (20 mL) was refluxed for 10-12 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated and cooled to room temperature, and the remaining solvent was removed under reduced pressure, then diethyl ether (25 mL) was added and the reaction mixture was left at 0 °C for overnight. The precipitated solid was filtered off. The crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford pure 3-(1*H*-indole-4-yl)-6-aryl-7*H*-[1,2,4]-triazolo-[3,4-*b*][1,3,4]-thiadiazines (**8a-f**).

Physical and spectral data

1-Methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (4): Yellow solid; yield 78 %; m.p. 185-187 °C; IR (KBr, ν_{max}, cm^{-1}): 3024 (=C-H), 2962 (C-H, CH_3), 1742 (C=O), 1699 (C=N), 1588 (C=C), 1135 (C-O); ^{1}H NMR ($CDCl_3$) δ: 7.52 (s, 1H, pyrazole H), 7.42 (s, 1H, pyrazole H), 4.00 (q, 2H, J = 5.6 Hz, CH_2), 3.24 (s, 3H, N-CH_3), 1.24 (t, 3H, J = 5.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 166.5, 136.4, 131.2, 106.8, 61.5, 41.4, 14.7; MS *m/z*: 154 (M^+); Elemental analysis calculated for $C_7H_{10}N_2O_2$: C-54.54, H-6.54, N-18.17. Found: C-52.98, H-6.32, N-17.84.

1-Methyl-1*H*-pyrazole-4-carboxylic acid hydrazide (5): Brown solid; yield 81 %; m.p. 166-168 °C; IR (KBr, ν_{max}, cm^{-1}): 3318 (N-H, NH_2), 3218 (N-H, NH), 3047 (=C-H), 2984 (C-H, CH_3), 1674 (C=O), 1645 (C=N), 1548 (C=C); ^{1}H NMR ($CDCl_3$) δ: 11.06 (s, 1H, NH), 7.58 (s, 1H, pyrazole H), 7.48 (s, 1H, pyrazole H), 5.30 (s, 2H, NH_2), 3.27 (s, 3H, N-CH_3);

^{13}C NMR ($CDCl_3$) δ: 167.4, 136.2, 128.7, 103.5, 47.6; MS *m/z*: 140 (M^+); Elemental analysis calculated for $C_5H_8N_4O$: C-42.85, H-5.75, N-39.98. Found: C-41.23, H-5.56, N-38.28.

5-(1-Methyl-1*H*-pyrazol-4-yl)-[1,3,4]oxadiazole-2-thiol (6): Pale yellow solid; yield 72%; m.p. 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 3028 (=C-H), 2978 (C-H, CH_3), 2610 (S-H), 1648 (C=N), 1559 (C=C), 1155 (C-O); ^{1}H NMR ($CDCl_3$) δ: 7.51 (s, 1H, pyrazole H), 7.42 (s, 1H, pyrazole H), 3.81 (s, 1H, SH), 3.31 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$) δ: 152.3, 148.5, 138.4, 132.0, 108.7, 44.2; MS *m/z*: 182 (M^+); Elemental analysis calculated for $C_6H_6N_4OS$: C-39.55, H-3.32, N-30.75, S-17.60. Found: C-38.54, H-3.21, N-29.45, S-16.98.

4-Amino-5-(1-methyl-1*H*-pyrazol-4-yl)-4*H*-[1,2,4]-triazole-3-thiol (7): White solid; yield 70 %; m.p. 161-163 °C; IR (KBr, ν_{max}, cm^{-1}): 3248 (N-H), 3018 (=C-H), 2968 (C-H, CH_3), 2648 (S-H), 1662 (C=N), 1552 (C=C); ^{1}H NMR ($CDCl_3$) δ: 7.61 (s, 1H, pyrazole H), 7.44 (s, 1H, pyrazole H), 3.85 (s, 2H, NH_2), 3.65 (s, 1H, SH), 3.31 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$) δ: 151.5, 147.3, 135.2, 131.0, 107.8, 43.2; MS *m/z*: 196 (M^+); Elemental analysis calculated for $C_6H_8N_6S$: C-36.72, H-4.11, N-42.83, S-16.34. Found: C-35.23, H-4.05, N-41.58, S-15.98.

3-(1-Methyl-1*H*-pyrazol-4-yl)-6-phenyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadaizine (8a): Pink solid; yield 70 %; m.p. 135-137 °C; IR (KBr, ν_{max}, cm^{-1}): 3018 (Ar-H), 2965 (C-H, CH_3), 1638 (C=N), 1548 (C=C), 680 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.74-7.41 (m, 5H, Ar-H), 7.63 (s, 1H, pyrazole H), 7.51 (s, 1H, pyrazole H), 3.33 (s, 3H, N-CH_3), 1.86 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 164.2, 147.1, 145.6, 138.4, 132.4, 131.0, 129.4, 127.4 (2), 126.2 (2), 104.8, 42.6, 35.1; MS *m/z*: 296 (M^+); Elemental analysis calculated for $C_{14}H_{12}N_6S$: C-56.74, H-4.08, N-28.36, S-10.82. Found: C-55.36, H-3.98, N-27.85, S-10.12.

6-(4-Methoxy-phenyl)-3-(1-methyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine (8b): Pale yellow solid; yield 68 %; m.p. 122-124 °C; IR (KBr, ν_{max}, cm^{-1}): 3025 (Ar-H), 2948 (C-H, CH_3), 1644 (C=N), 1568 (C=C), 1142 (C-O), 688 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.59 (s, 1H, pyrazole H), 7.48 (s, 1H, pyrazole H), 7.32 (d, 2H, *J* = 7.0 Hz, Ar-H), 3.39 (s, 3H, N-CH_3), 2.85 (s, 3H, OCH_3), 1.78 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 164.2, 162.3, 146.8, 143.1, 135.8, 132.5, 130.4, 126.8, 125.7 (2), 123.5 (2), 106.2, 44.8, 38.1; MS *m/z*: 326 (M^+); Elemental analysis calculated for $C_{15}H_{14}N_6OS$: C-55.20, H-4.32, N-25.75, S-9.82. Found: C-53.98, H-4.32, N-24.84, S-9.24.

6-(4-Chloro-phenyl)-3-(1-methyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine (8c): Brown solid; yield 770 %; m.p. 150-152 °C; IR (KBr, ν_{max}, cm^{-1}): 3032 (Ar-H), 2955 (C-H, CH_3), 1640 (C=N), 1554 (C=C), 677 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.58 (s, 1H, pyrazole H), 7.48 (s, 1H, pyrazole H), 7.33 (d, 2H, *J* = 7.2 Hz, Ar-H), 3.41 (s, 3H, N-CH_3), 1.98 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 166.7, 148.4, 146.2, 139.4, 133.1, 130.4, 128.4, 125.6 (2), 123.7 (2), 109.4, 46.7, 38.1; MS *m/z*: 330 (M^+); Elemental analysis calculated for $C_{14}H_{11}N_6SCl$: C-50.83, H-3.35, Cl-10.72, N-25.41, S-9.69. Found: C-49.26, H-3.28, Cl-9.97, N-24.87, S-9.12.

6-(4-Bromo-phenyl)-3-(1-methyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine (8d): Yellow solid; yield 74 %; m.p. 160-162 °C; IR (KBr, ν_{max}, cm^{-1}): 3025 (Ar-H), 2948 (C-H, CH_3), 1646 (C=N), 1551 (C=C), 676 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.69 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.54 (s, 1H, pyrazole H), 7.47 (s, 1H, pyrazole H), 7.32 (d, 2H, *J* = 7.4 Hz, Ar-H), 3.41 (s, 3H, N-CH_3), 1.92 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 160.6, 144.8, 142.6, 135.8, 130.2, 128.6, 126.7, 125.4 (2), 123.7 (2), 108.6, 45.7, 38.3; MS *m/z*: 375 (M^+); Elemental analysis calculated for $C_{14}H_{11}N_6SBr$: C-44.81, H-2.95, Br-21.29, N-22.40, S-8.55. Found: C-43.12, H-2.84, Br-20.26, N-21.58, S-8.12.

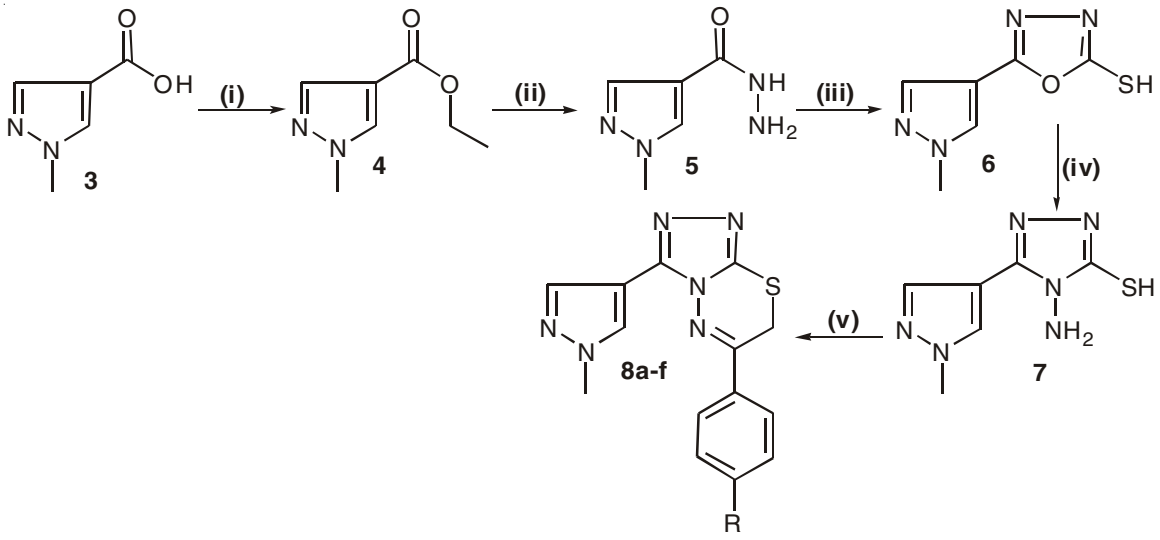
6-(4-Nitro-phenyl)-3-(1-methyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine (8e): White solid; yield 76 %; m.p. 144.146 °C; IR (KBr, ν_{max}, cm^{-1}): 3022 (Ar-H), 2938 (C-H, CH_3), 1646 (C=N), 1552 (C=C), 1530 (N=O), 688 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.71 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.58 (s, 1H, pyrazole H), 7.45 (s, 1H, pyrazole H), 7.36 (d, 2H, *J* = 7.3 Hz, Ar-H), 3.40 (s, 3H, NCH_3), 1.74 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 166.3, 149.8, 147.5, 141.2, 136.8, 133.1, 129.7, 126.2 (2), 121.7 (2), 109.4, 48.7, 38.3; MS *m/z*: 341 (M^+); Elemental analysis calculated for $C_{14}H_{11}N_7O_2S$: C-49.26, H-3.25, N-28.72, S-9.39. Found: C-48.26, H-3.12, N-27.45, S-9.05.

6-(4-Hydroxy-phenyl)-3-(1-methyl-1*H*-pyrazol-4-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadaizine (8f): Yellow solid; yield 78 %; m.p. 150-152 °C; IR (KBr, ν_{max}, cm^{-1}): 3412 (O-H), 3024 (Ar-H), 2946 (C-H, CH_3), 1652 (C=N), 1547 (C=C), 675 (C-S); ^{1}H NMR ($CDCl_3$) δ: 7.64 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.58 (s, 1H, pyrazole H), 7.47 (s, 1H, pyrazole H), 7.31 (d, 2H, *J* = 7.2 Hz, Ar-H), 3.41 (s, 3H, NCH_3), 1.74 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 166.3, 145.3, 143.7, 140.2, 136.4, 133.2, 130.4, 129.7 (2), 125.2 (2), 108.1, 48.7, 36.2; MS *m/z*: 312 (M^+); Elemental analysis calculated for $C_{14}H_{12}N_6OS$: C-53.83, H-3.87, N-26.91, S-10.27. Found: C-51.58, H-3.65, N-25.87, S-9.74.

RESULTS AND DISCUSSION

The initial intermediate, 1-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (**4**) has been prepared through esterification by boiling of a mixture of 1-methyl-1*H*-pyrazole-4-carboxylic acid (**3**) and ethanol in presence of sulfuric acid for 5 h. Formation of the compound **4** was confirmed by its spectral analysis. The IR spectrum of compound **4** showed absorption bands at 3024 (=C-H), 2962 (C-H, CH_3), 1742 (C=O), 1699 (C=N), 1588 (C=C) and 1135 (C-O) cm^{-1}. The proton NMR spectrum of intermediate **4** showed a signal at δ 7.52 ppm as a singlet integrating for one proton is assigned to pyrazole H. The other pyrazole H appeared as singlet for one proton at δ 7.42 ppm. The resonance frequency at δ 4.00 ppm for two protons as quartet is allotted to CH_2 group. The singlet signal performed at δ 3.24 ppm for three protons corresponding to N-CH_3 group. The signal at δ 1.24 ppm as triplet integrating for three protons is assigned to the CH_3 group. The ^{13}C NMR spectrum of this compound showed the signals at different δ-chemical shifts such as 166.5, 136.4, 131.2, 106.8, 61.5, 41.4 and 14.7 ppm. Mass spectrum showed molecular ion peak at *m/z* 154 (M^+), thus confirming the structure of compound **4**.

The compound **4** was reacted with hydrazine hydrate in absolute ethyl alcohol under reflux temperature for 6 h to get



8: Ar = a) H; b) 4–OCH_3; c) 4–Cl; d) 4–Br; e) 4–NO_2; f) 4–OH

Scheme-I: (i) EtOH, H_2SO_4, reflux, 5 h; (ii) NH_2–NH_2·H_2O, EtOH, reflux, 6 h; (iii) CS_2, KOH, EtOH, reflux, 12 h; (iv) NH_2–NH_2·H_2O, EtOH, reflux, 8 h; (v) $ArCOCH_2Br$, EtOH, reflux, 10-12 h

the next intermediate, 1-methyl-1*H*-pyrazole-4-carboxylic acid hydrazide (**5**). Formation of the compound **5** is confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. The IR spectrum of compound **5** showed the bands at 3318 (N-H, NH_2), 3218 (N-H, NH), 3047 (=C-H), 2984 (C-H, CH_3), 1674 (C=O), 1645 (C=N) and 1548 (C=C) cm^{-1}. In the ^{1}H NMR spectrum, the precessional frequency at δ 11.06 ppm as singlet for one proton is associated with NH group. The singlet signal for one proton of pyrazole CH group linked with δ 7.58 ppm. The resonance frequency at δ 7.48 ppm as singlet for one proton is related to another pyrazole CH group. Two protons of NH_2 group as singlet is appeared at δ 5.30 ppm. The δ-chemical shift at 3.27 ppm as singlet for three protons is corresponding to N-CH_3 group. The ^{13}C NMR spectrum of this compound exhibited the signals at various δ-chemical shifts such as 167.4, 136.2, 128.7, 103.5 and 47.6 ppm. The mass spectrum of the compound **5** displayed a molecular ion peak at *m/z* 140 (M+).

The intermediate, 5-(1-methyl-1*H*-pyrazol-4-yl)-[1,3,4]-oxadiazole-2-thiol (**6**) for the synthesis of title compounds was prepared by the cyclization of compound **5** with carbon disulphide in the presence of potassium hydroxide in ethanol at reflux for 12 h followed by acidification. Emergence of the compound **6** is established by its different spectral study. The IR spectrum of compound **6** display the bands at 3028 (=C-H), 2978 (C-H, CH_3), 2610 (S-H), 1648 (C=N), 1559 (C=C) and 1155 (C-O) cm^{-1}. In the ^{1}H NMR spectrum, the singlet signal for one proton of pyrazole CH group linked with δ 7.51 ppm. The precessional frequency at δ 7.42 ppm as singlet for one proton is associated with another pyrazole CH group. One proton of SH group as singlet is appeared at δ 3.81 ppm. The resonance frequency at δ 3.31 ppm as singlet for three protons is related to the N-CH_3 group. The ^{13}C NMR spectrum of this compound displayed the signals at various δ-chemical shifts such as 152.3, 148.5, 138.4, 132.0, 108.7 and 44.2 ppm. The mass spectrum of the compound **6** exhibited a molecular ion peak at *m/z* 182 (M^+).

Further the compound **6** when reacted with hydrazine hydrate in ethanol at reflux for 8 h resulted final intermediate, 4-amino-5-(1-methyl-1*H*-pyrazol-4-yl)-4*H*-[1,2,4]triazole-3-thiol (**7**). Compound **7** is identified by IR, ^{1}H NMR, ^{13}C NMR and mass spectral examination. The IR spectrum of compound **7** showed the bands at 3248 (N-H), 3018 (=C-H), 2968 (C-H, CH_3), 2648 (S-H), 1662 (C=N) and 1552 (C=C) cm^{-1}. In the ^{1}H NMR spectrum, the precessional frequency at δ 7.61 ppm as singlet for one proton is associated with pyrazole CH group. The resonance frequency at δ 7.44 ppm as singlet for one proton is related to another pyrazole CH group. The δ-chemical shift at 3.85 ppm as singlet for two protons is corresponding to NH_2 group. The singlet signal for one proton of SH group linked with δ 3.65 ppm. Three protons of N-CH_3 group as singlet are appeared at δ 3.31 ppm. The ^{13}C NMR spectrum of this compound showed the signals at various δ-chemical shifts such as 151.5, 147.3, 135.2, 131.0, 107.8 and 43.2 ppm. The mass spectrum of the compound **7** performed a molecular ion peak at *m/z* 196 (M^+).

Finally, the compound **7** has been condensed successively with a variety of phenacyl bromides in ethyl alcohol under reflux for 10-12 h to get the title compounds, 3-(1-methyl-1*H*-pyrazol-4-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadaizine and its derivatives (**8a-f**). Evolution of the compound **8a** is confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral investigation. The IR spectrum of compound **8a** exhibited the bands at 3018 (Ar-H), 2965 (C-H, CH_3), 1638 (C=N), 1548 (C=C) and 680 (C-S) cm^{-1}. In the ^{1}H NMR spectrum, the only one multiplet signal of all five aromatic protons is appeared on δ-scale between 7.74-7.41 ppm. The signal appeared at δ 7.63 ppm as singlet for one proton connected with pyrazole CH group. Another one proton of pyrazole CH group as singlet is appeared at δ 7.51 ppm. The singlet signal for three protons of N-CH_3 group linked with δ 3.33 ppm. The resonance frequency at δ 1.86 ppm as singlet for two protons is related to CH_2 group. The ^{13}C NMR spectrum of this compound disclosed the signals at various δ-chemical shifts

such as 164.2, 147.1, 145.6, 138.4, 132.4, 131.0, 129.4, 127.4 (2), 126.2 (2), 104.8, 42.6 and 35.1 ppm. The mass spectrum of the compound **8a** showed a molecular ion peak at *m/z* 296 (M^+). The chemical structures of the different com-pounds (**8b-f**) of this order are evaluated with same strategy. Further the title compounds have been used to evaluate their antimicrobial activity.

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