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Der Pharma Chemica, 2014, 6(4):223-232
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antibacterial activity of 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine

Ravi G.^{1*}, Ravinder Nath A.¹, Nagaraj A.², Damodhar S.¹ and Nageshwara Rao G.²

¹Department of Biotechnology & Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India

²Department of Chemistry, Telangana University, Nizamabad, Telangana, India

ABSTRACT

A new series of novel 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **10(a-j)** in good to excellent yield by the reaction of 4-amino-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazol-3-ylhydrosulfide with a variety of phenacylbromides. The compounds of all the novel new compounds were established by IR, ¹H, ¹³C NMR, MS and elemental data. The compounds **10(a-j)** were evaluated for their antibacterial activity against four human pathogenic bacteria viz. *Escherichiacoli*, *Klebseillapneumoniae*, *Shigelladysenteriae* and *shigella flexnei*. Amongst them, compounds containing (4-methylphenyl) moiety **10b**, (4-methoxyphenyl) moiety **10c**, (4-chlorophenyl) moiety **10d**, (4-dichlorophenyl) moiety **10f**, showed significant antibacterial activity, almost equal/more than the activity of the standard drug Sterptomycin and Neomycin. All the compounds displayed significant activity against *E.coli*. Most of the novel new compounds showed appreciable activity against test bacteria as potential molecules for further development.

Keywords: Synthesis, 4-amino-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazol-3-ylhydrosulfide, 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine, Anti bacterial activity.

INTRODUCTION

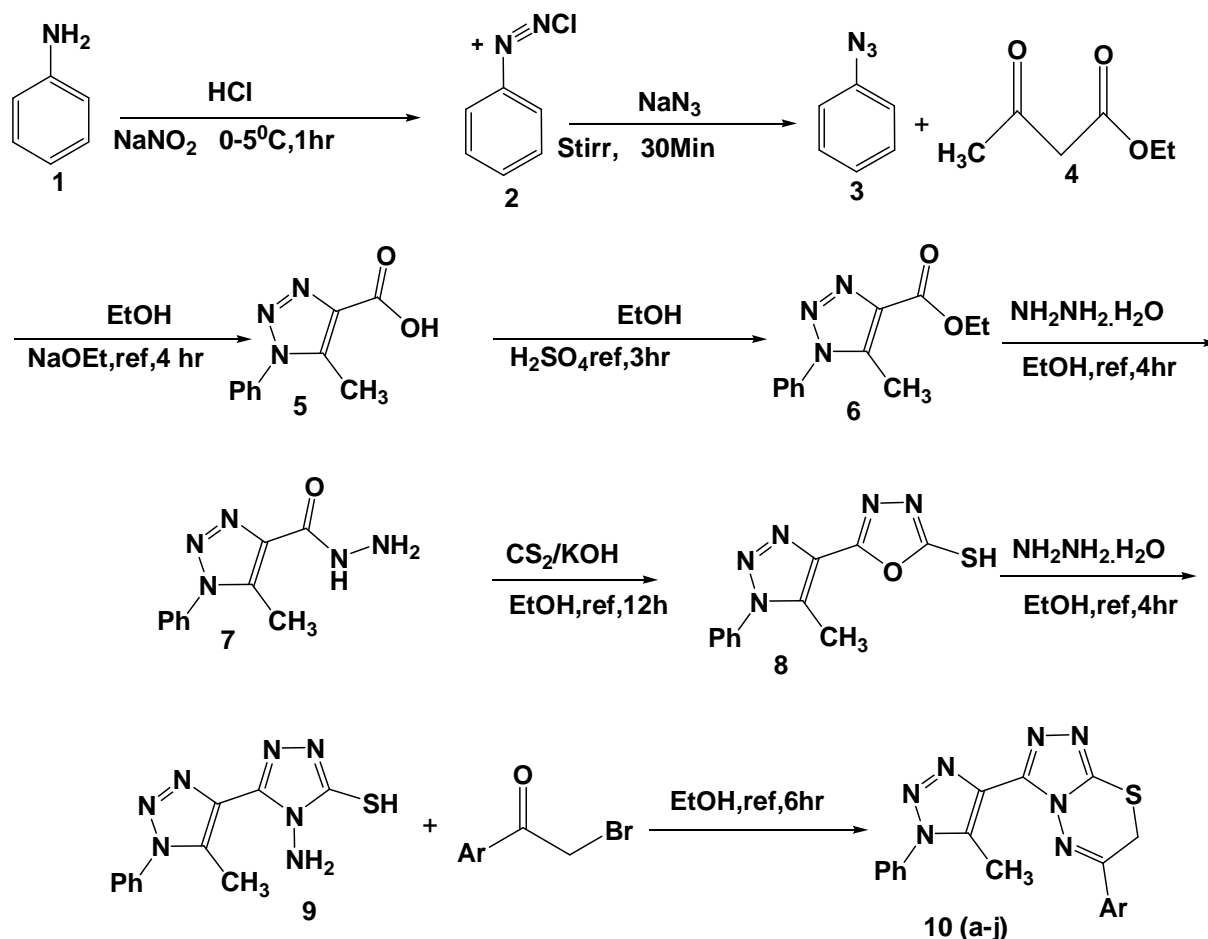
The development of 1,2,3-triazoles for drug discovery and industrial use has been shown to be very versatile. The uses for triazoles have been found in various areas and are continuously growing. The applications of these triazoles are increasingly found in all aspects of drug discovery, ranging from cutting edge research through combinatorial chemistry and target-templated *in situ* chemistry, to proteomics and DNA research using bioconjugation reactions. 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], anti-inflammatory[4] and anti-bacterial[5] activities. Triazoles are also being studied for the treatment of obesity[6] and osteoarthritis[7]. The increased interest in the 1,2,3-triazole is due to it being non-toxic, benign and stable in biological systems[8].

The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole. The triazole plant protection fungicides include epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol [9-22].

On the industrial side, 1,2,3-triazoles are found in hydraulic fluids, agrochemicals, and photochemical products[23,24]. They have also been used as herbicides, light stabilizers, fluorescent whiteners, optical brightening agents, pigments and corrosion retardants[25-27]. 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. Through this, 1,2,3-triazoles are very attractive to use and apply in many fields.

Yan Zouet al[28], prepared a series of triazoles. The *in vitro* antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi, which showed the best antifungal activity. Zahra Rezaeiet al.[29] synthesized 1,2,4-triazole and 1,2,3-benzotriazole and evaluated for their antifungal activity. A novel class of cationic anthraquinone analogs has been synthesized[30]. Among these compounds synthesized, some exhibit broad antibacterial activity including MRSA and vancomycin resistant *Enterococcus faecalis* (VRE), which is comparable to other commercially available cationic antiseptic chemicals. A series of novel sulphanilamide derived 1,2,3-triazole compounds has been synthesized and screened *in vitro* for their antibacterial and anti-inflammatory activities[31].

The present investigation deals with the synthesis A new series of novel 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **10(a-j)** in good to excellent yields by the reaction of 4-amino-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazol-3-ylhydrosulfide with a variety of phenacyl bromides. The antibacterial activities of the compounds **10a-j** have also been evaluated.



9: Ar = (a) C_6H_5 ; (b) $4-CH_3-C_6H_4$; (c) $4-CH_3O-C_6H_4$; (d) $3-CH_3O-C_6H_4$; (e) $4-Cl-C_6H_4$; (f) $4-(Cl)_2-C_6H_4$; (g) $4-Br-C_6H_4$; (h) $4-NO_2-C_6H_4$; (i) $3-NO_2-C_6H_4$; (j) $4-OH-C_6H_4$

MATERIALS AND METHODS

The diazotization of aniline **1** by nitrous acid at 0-5 °C lead to the formation of aryldiazonium chloride **2**, which on reaction with sodium azide 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 azide compound **3** was cyclized with ethyl acetoacetate **4** in the presence of sodium ethoxide to afford another intermediate, 5-methyl-1-[aryl]-1,2,3-triazole-4-carboxylic acid **5** in 68% yield. 5-methyl-1-[aryl]-1,2,3-triazole-4-carboxylic acid **5** was reacted with absolute ethyl alcohol in the presence of catalytic amount of conc. H₂SO₄ at reflux for 3 h, to get the ethyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate **6** in 72% yield. The intermediate, 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide **7** was prepared on hydrazinolysis of compound **6** with hydrazine hydrate, in ethyl alcohol at reflux for 4 h, with 70% of yield. The 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide **7** was reacted with carbon disulfide in the presence of potassium hydroxide, in ethanol at reflux for 12 h, followed by acidification gave the 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-ylhydrosulfide **8** in 71% of yield. Compound **8** when reacted with hydrazine hydrate, in ethanol at reflux for 6 h, resulted the 4-amino-5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-4*H*-1,2,4-triazol-3-ylhydrosulfide **9** in 68% of yield. Further, the 4-amino-5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-4*H*-1,2,4-triazol-3-ylhydrosulfide **9** has been condensed successively with a variety of phenacyl- bromides in ethyl alcohol under reflux for 6 h to get the title compounds, 3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **10 (a-j)**.

2.1. Antibacterial Activity

The 3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **10(a-j)** were screened for their antibacterial activity against four human pathogenic bacteria viz., *Escherichia coli*, *Klebsiella pneumoniae*, *Shigella dysenteriae* and *Shigella flexneri*. The zone of inhibition in mm at concentration 100 µg/mL was determined using the cup-plate method. Standard antibacterial agents such as streptomycin and neomycin, were also screened under similar conditions for comparison and the results are presented in **Table 1**.

Table 1: Antibacterial activity of 10(a-j)

| Compound | zone of inhibition in mm at 100 µg/mL | | | |
|-----------------------|---------------------------------------|----------------------|-----------------------|--------------------|
| | <i>E. coli</i> | <i>K. pneumoniae</i> | <i>S. dysenteriae</i> | <i>S. flexneri</i> |
| 10^a | 22 | 18 | 18 | 20 |
| 10^b | 23 | 22 | 21 | 26 |
| 10^c | 28 | 27 | 28 | 27 |
| 10^d | 24 | 20 | 25 | 20 |
| 10^e | 20 | 21 | 22 | 22 |
| 10^f | 21 | 22 | 23 | 24 |
| 10^g | 15 | 18 | 19 | 12 |
| 10^h | 18 | 16 | 14 | 13 |
| 10ⁱ | 16 | 17 | 16 | 13 |
| 10^j | 19 | 13 | 18 | 16 |
| Streptomycin | 30 | 30 | 30 | 30 |
| Neomycin | 20 | 20 | 20 | 20 |

Note: <16 mm, inactive; 17-20 mm, moderately active; 20-27mm, highly active.

The antibacterial screening data of the compounds **10(a-j)** showed that the compounds **10b**, **10c**, **10d**, **10e** and **10f** were highly active against all the organism employed. Compound **10c** is highly active against all the test organisms employed and the zone of inhibition is more than the standard drug Neomycin, and almost equal to the standard drug streptomycin. The other compounds showed moderate to good activity against these organisms employed. All the compounds displayed significant activity against *E. coli*.

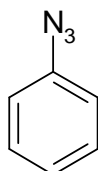
Experimental

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 F254 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 ¹H NMR, ¹³C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ¹H and 75 MHz for ¹³C). Chemical shifts are reported in δppm 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 $\pm 0.4\%$ of theory.

4.1. Synthesis of phenylazide (3)

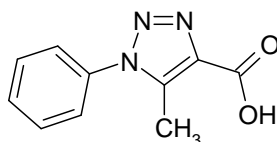
To a solution of aniline **1** (10 mmol) in hydrochloric acid (25 mL), sodium nitrite solution was added drop wise at 0-5 °C and stirred for one hour to afford the diazonium chloride **2** and then cooled, stirred solution, a solution of sodium azide (25 mL) was added and stirring was continued for 30 min and the resulting solid was filtered and recrystallized from ethanol as yellow crystals.



IR (KBr): ν_{\max} 3110, 2949, 2230, 1610 cm^{-1} .; **$^1\text{H NMR}$** (CDCl_3 , 300 MHz): δ 7.10-7.20 (m, 5H, ArH).; **$^{13}\text{C NMR}$** (CDCl_3 , 75 MHz): δ 117.3, 122.9, 130.1, 140.2.; **MS**: m/z 119 (M^+).; **Anal. Calcd.** for $\text{C}_6\text{H}_5\text{N}_3$: C, 60.50; H, 4.23; N, 35.27. Found: C, 60.45; H, 4.18; N, 35.21.

4.2. Synthesis of 5-methyl-1-[aryl]-1,2,3-triazole-4-carboxylic acid(5)

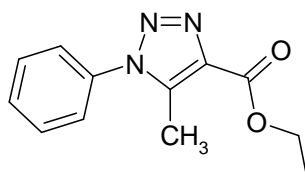
A mixture of azide **3** (0.1 mol) and ethyl acetoacetate **4** (0.1 mol) in absolute ethanol (40 mL), and sodium ethoxide solution (20 mL) was refluxed for 4 h, the white solid which formed on heating was filtered and recrystallized from ethanol.



IR (KBr): ν_{\max} 3450-3500, 3198, 2980, 2230, 1610 cm^{-1} .; **$^1\text{H NMR}$** ($\text{DMSO-}d_6$, 300 MHz): δ 2.47 (s, 3H, CH_3), 7.60-7.60 (m, 5H, ArH), 10.5 (s, 1H, COOH).; **$^{13}\text{C NMR}$** (CDCl_3 , 75 MHz): δ 126.3, 128.2, 129.6, 131.3, 134.3, 138.1, 168.8.; **MS**: m/z 203 (M^+).; **Anal. Calcd.** for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.01; H, 4.41; N, 20.62.

4.3. Ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (6)

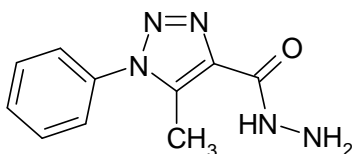
To the solution of **6** (0.01 mol) in absolute ethyl alcohol (25 mL), conc. H_2SO_4 (2 mL) was added. The mixture was refluxed for 3 h. After completion of the reaction (TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed with 10% NaHCO_3 solution, dried and recrystallized from ethyl alcohol to get pure product **6** with 72% of yield, m.p. 158-60°C.



IR (KBr): ν_{\max} 3010, 2943, 1698, 1621, 1513, 1249, 1034 cm^{-1} .; **$^1\text{H NMR}$** ($\text{DMSO-}d_6$, 300 MHz): 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).; **$^{13}\text{C NMR}$** ($\text{DMSO-}d_6$, 75 MHz): δ 15.7, 59.7, 125.4, 128.0, 128.9, 129.1, 134.5, 160.1.; **MS**: m/z 231 (M^+).; **Anal. Calcd.** for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.29; H, 5.61; N, 18.11.

4.4. 5-Methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (7)

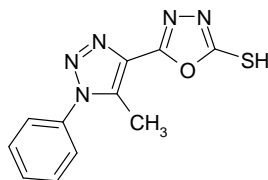
A mixture of compound **6** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (20 mL) was refluxed for 4 h, cooled to room temperature and filtered. The crude product was recrystallized from ethanol to give the new intermediate **7** in 70% of yield, m.p. 168-69°C.



IR (KBr): ν_{\max} 3270, 1630, 1610, 1395, 741 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.30 (s, 3H, CH₃), 5.27 (s, 2H, NH₂), 7.25-7.35 (m, 5H, ArH), 7.69 (s, 1H, NH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 13.5, 119.2, 125.6, 129.7, 138.7, 151.9, 158.7.; **MS**: m/z 217 (M⁺).; **Anal. Calcd.** for C₁₀H₁₁N₅O: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.21; H, 5.04; N, 32.19.

4.5. Synthesis of 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1,3,4-oxadiazol-2-ylhydrosulfide (8)

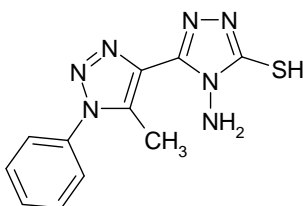
A mixture of compound **7** (0.01 mol), potassium hydroxide (0.02 mol) and carbon disulfide (0.03 mol) in ethanol (100 mL) was heated under reflux with stirring for 12 h. The solvent was distilled *in vacuo*, the residual mass was poured over crushed ice and neutralized the alkaline solution with 10% hydrochloric acid. The precipitated crude product was filtered, washed with water, dried and recrystallized from ethanol to get the pure compound **8** in 71% yield, m.p. 146-48 °C.



IR (KBr): ν_{\max} 3030, 2902, 2843, 1601, 1569, 1412, 1070 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.52 (s, 3H, CH₃), 7.30-7.40 (m, 5H, ArH), 9.7 (s, 1H, SH/NH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.5, 125.4, 125.9, 128.1, 129.4, 136.4, 141.7, 152.1, 169.7.; **MS**: m/z 259 (M⁺).; **Anal. Calcd.** for C₁₁H₉N₅OS: C, 50.96; H, 3.50; N, 27.01. Found: C, 50.85; H, 3.45; N, 26.97.

4.6. Synthesis of 4-amino-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazol-3-ylhydrosulfide (9)

To a warm solution of compound **8** (0.01 mol) in ethanol (50 mL), 80% hydrazine hydrate (0.03 mol) was added drop wise and the reaction mixture was heated under reflux for 6 h. The solvent was distilled off *in vacuo*, cooled and the crystals separated were filtered, washed with cold ethanol and recrystallized from chloroform to give pure compound **9**, in 68% yield, m.p. 167-69 °C.

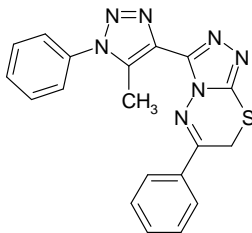


IR (KBr): ν_{\max} 3343, 3068, 1663, 1460, 1030 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 1.37 (bs, 2H, NH₂), 2.52 (s, 3H, CH₃), 7.30-7.40 (m, 5H, ArH), 9.7 (s, 2H, SH/NH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.3, 123.6, 125.3, 128.7, 131.4, 139.0, 144.0, 144.7, 150.2. ; **MS**: m/z 273 (M⁺).; **Anal. Calcd.** for C₁₁H₁₁N₇S: C, 48.34; H, 4.06; N, 35.87. Found: C, 48.29; H, 4.00; N, 35.80.

4.7. General procedure for the synthesis of 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 10(a-j):

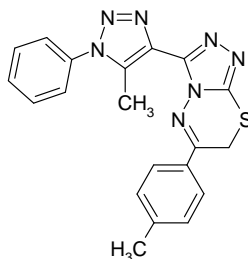
A mixture of compound **9** (0.01 mol) and corresponding phenacylbromide (0.02 mol) in absolute ethanol (20 mL), was refluxed for 6 h. The reaction mixture was concentrated and cooled to room temperature, and the remaining solvent was removed under reduced pressure, then diethyl ether (25 mL) was added 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 compounds **10(a-j)** in 62-72% of yields.

4.7.1 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine(10a):



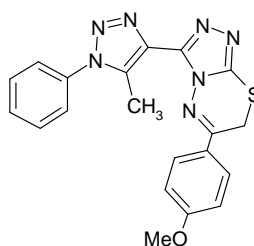
IR (KBr): ν_{\max} 3031, 1624, 1590, 1457 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 5H, ArH), 7.40-7.50 (m, 5H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.9, 125.4, 128.0, 128.6, 129.9, 130.1, 131.4, 131.7, 132.4, 132.9, 137.3, 142.1, 145.3, 156.3.; **MS**: m/z 373 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{15}\text{N}_7\text{S}$: C, 61.11; H, 4.05; N, 26.26. Found: C, 61.07; H, 4.00; N, 26.20.

4.7.2.6-(4-methylphenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10b):



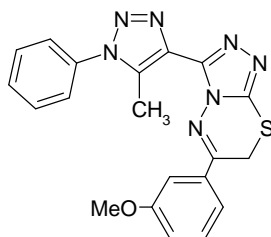
IR (KBr): ν_{\max} 3032, 1610, 1591, 1530, 1032, 746 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.24 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 7H, ArH), 7.85 (d, $J = 7.9$ Hz, 2H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 22.3, 35.7, 123.9, 125.4, 128.6, 129.0, 129.9, 130.1, 131.4, 131.9, 132.4, 137.3, 139.2, 142.1, 145.3, 156.3. ; **MS**: m/z 387 (M^+).; **Anal. Calcd.** for $\text{C}_{20}\text{H}_{17}\text{N}_7\text{S}$: C, 62.00; H, 4.42; N, 25.30. Found: C, 61.92; H, 4.36; N, 25.26.

4.7.3.6-(4-methoxyphenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10c):



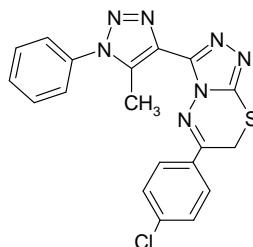
IR (KBr): ν_{\max} 3035, 1620, 1596, 1535, 1070, 1030, 747 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 6.94 (d, $J = 7.6$ Hz, 2H, ArH), 7.20-7.30 (m, 7H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 48.2, 112.6, 123.9, 124.1, 125.4, 128.6, 129.9, 131.4, 132.0, 132.4, 137.3, 142.1, 145.3, 156.3, 160.0.; **MS**: m/z 433 (M^+).; **Anal. Calcd.** for $\text{C}_{20}\text{H}_{17}\text{N}_7\text{S}$: C, 59.54; H, 4.25; N, 24.30. Found: C, 59.50; H, 4.21; N, 24.24.

4.7.4.6-(3-methoxyphenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10d):



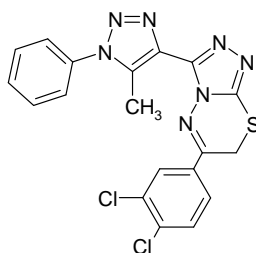
IR (KBr): ν_{\max} 3034, 1617, 1592, 1541, 1070, 1032, 745 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.30-7.40 (m, 9H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 54.8, 114.5, 117.8, 123.9, 125.4, 126.0, 128.6, 129.9, 130.1, 130.9, 131.4, 132.4, 134.9, 137.3, 142.1, 145.3, 156.3, 159.7. ; **MS**: m/z 4.3 (M^+).; **Anal. Calcd.** for $\text{C}_{20}\text{H}_{17}\text{N}_7\text{OS}$: C, 59.54; H, 4.25; N, 24.30. Found: C, 59.50; H, 4.21; N, 24.22.

4.7.5.6-(4-chlorophenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10e):



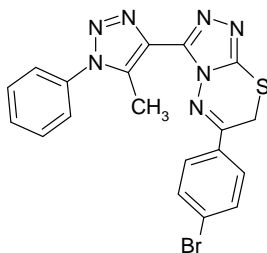
IR (KBr): ν_{\max} 3030, 1610, 1591, 1547, 1030, 686 cm^{-1} . ; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 7H, ArH), 7.82 (d, $J = 8.3$ H, 2H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.9, 125.4, 128.6, 128.9, 129.0, 129.9, 131.4, 132.4, 132.9, 134.8, 137.3, 142.1, 145.3, 156.3. ; **MS**: m/z 4.7 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{14}\text{ClN}_7\text{S}$: C, 55.95; H, 3.46; N, 24.04. Found: C, 55.89; H, 3.40; N, 24.00.

4.7.6.6-(3,4-dichlorophenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10f):



IR (KBr): ν_{\max} 3035, 1618, 1590, 1532, 1030, 750, 680 cm^{-1} . ; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 6H, ArH), 7.70-7.80 (m, 2H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.9, 125.4, 128.0, 128.0, 128.6, 129.0, 129.5, 129.9, 131.4, 132.4, 132.9, 133.0, 136.5, 137.3, 142.1, 145.3, 156.3. **MS**: m/z 4.42 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{13}\text{Cl}_2\text{N}_7\text{S}$: C, 51.59; H, 2.96; N, 22.17. Found: C, 51.53; H, 2.90; N, 22.11.

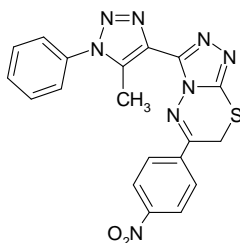
4.7.7.6-(4-bromophenyl)-3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (10g):



IR (KBr): ν_{\max} 3030, 1611, 1586, 1530, 1030, 586 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 5H, ArH), 7.70-7.80 (m, 4H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.0, 123.9, 125.4, 128.6, 129.0, 129.9, 131.4, 132.4, 133.0, 134.1, 137.3, 142.1, 145.3, 156.3.; **MS**: m/z 452 (M^+).

Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{BrN}_7\text{S}$: C, 50.45; H, 3.12; N, 21.68. Found: C, 50.40; H, 3.06; N, 21.60.

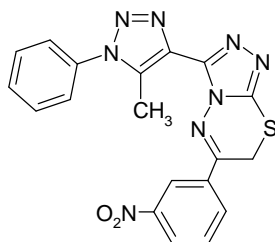
4.7.8.3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-(4-nitrophenyl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazine (10h):



IR (KBr): ν_{\max} 3035, 1618, 1595, 1532, 1370, 1030, 749 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 5H, ArH), 7.87 (d, $J = 8.2$ Hz, 2H, ArH), 8.32 (d, $J = 8.2$ Hz, 2H, ArH).

$^{13}\text{C NMR}$ (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.9, 125.4, 127.8, 128.6, 129.9, 131.4, 131.9, 132.4, 135.7, 137.3, 142.1, 145.3, 146.5, 156.3. ; **MS**: m/z 418 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{14}\text{N}_8\text{O}_2\text{S}$: C, 54.54; H, 3.37; N, 26.78. Found: C, 54.49; H, 3.31; N, 26.70.

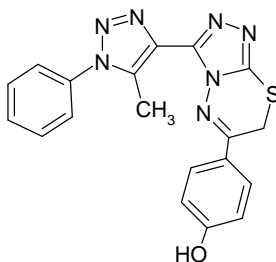
4.7.9.3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-(3-nitrophenyl)-7H-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazine (10i):



IR (KBr): ν_{\max} 3035, 1614, 1590, 1520, 1370, 1030, 746 cm^{-1} .; **$^1\text{H NMR}$** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 7.20-7.30 (m, 5H, ArH), 7.90-8.00 (m, 4H, ArH).; **$^{13}\text{C NMR}$** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 123.9, 125.4, 126.3, 127.0, 128.6, 128.9, 129.9, 130.2, 131.4, 132.4, 137.3, 138.0, 142.1, 145.3, 148.9, 156.3.

MS: m/z 418 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{14}\text{N}_8\text{O}_2\text{S}$: C, 54.54; H, 3.37; N, 26.78. Found: C, 54.48; H, 3.30; N, 26.70.

4.7.10. 4-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thia diazin-6-yl]phenol (10j)



IR (KBr): ν_{\max} 3310, 3035, 1618, 1596, 1030, 746 cm^{-1} .; **^1H NMR** (DMSO- d_6 300 MHz): δ 2.46 (s, 3H, CH_3), 3.96 (s, 2H, $\text{CH}_2\text{-S}$), 5.32 (s, 1H, OH), 7.00-7.10 (m, 2H, ArH), 7.20-7.30 (m, 7H, ArH).; **^{13}C NMR** (DMSO- d_6 75 MHz): δ 12.4, 35.7, 116.1, 123.9, 124.0, 125.4, 128.6, 129.9, 131.4, 132.4, 135.7, 137.3, 142.1, 145.3, 156.3, 162.1. **MS**: m/z 389 (M^+).; **Anal. Calcd.** for $\text{C}_{19}\text{H}_{15}\text{N}_7\text{OS}$: C, 58.60; H, 3.88; N, 25.18. Found: C, 58.54; H, 3.80; N, 25.13.

CONCLUSION

In conclusion, we have described the synthesis of novel 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **10(a-j)** in good to excellent yields by the reaction of 4-amino-5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazol-3-ylhydrosulfide **9** and corresponding phenacyl bromide. Some of these compounds exhibit excellent antibacterial activities and can be evaluated as antibacterial agents.

Acknowledgements

The authors are grateful thanks to the Director, Indian Institute of Chemical Technology, Hyderabad, India, for providing NMR and Mass spectral data. Biological evaluation from the Department of Biotechnology, Telangana University, Nizamabad, India, is greatly acknowledged.

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