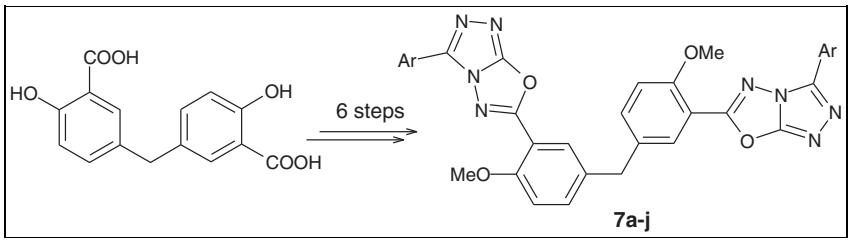
# Synthesis and Biological Evaluation of Novel Bis[1,2,4]triazolo[3,4-b][1,3,4]oxadiazoles

Ch. Sanjeeva Reddy,[a,*] M. Vani Devi,[a] G. Rajesh Kumar,[a] M. Sunitha,[a] and A. Nagaraj[b]

[a]Department of Chemistry, Kakatiya University, Warangal 506 009, India
[b]Department of Pharmaceutical Chemistry, Telangana University, Nizamabad 503 175, India
*E-mail: chsrkuc@yahoo.co.in

Received January 13, 2011
DOI 10.1002/jhet.1528
Published online 18 May 2013 in Wiley Online Library (wileyonlinelibrary.com).




A series of novel 6-2-methoxy-5-[4-methoxy-3-(3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl)benzyl] phenyl-3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles **7a–j** has been synthesized and characterized *via* IR, $^{1}$H NMR, $^{13}$C NMR, MS, and elemental analyses. Compounds **7a–j** were also screened for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), and *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39), and *Chromobacterium violaceum* (MTCC 2656). The antibacterial screening reveal that the presence of 2,4-difluorophenyl (**7e**) or 4-nitrophenyl (**7f**) of 2-pyrazyl (**7i**), or 2-furyl (**7j**) on the triazole moiety exhibited potent inhibitory activity comparable with the standard drug streptomycin, at the tested concentrations, and emerged as potential molecules for further development.

*J. Heterocyclic Chem*., **50**, 557 (2013).

## INTRODUCTION

Heterocyclics represent one of the most active classes of compounds possessing a wide spectrum of biological activities, including antibacterial, antifungal, and other biological activities [1–6]. The 1,2,4-triazole derivatives and their *N*-bridged heterocyclic analogs have been widely investigated as antitumor [7], antiviral [8], anti-inflammatory [9], analgesic [10], and antidepressant [11]. 1,2,4-triazole system is also an important starting material in the synthesis of biologically active heterocycles, which constitute an important class of organic compounds with diverse biological activities, including antiparasitic, analgesic, antibacterial, and anti-inflammatory activities [12–15]. The triazole system fused to another heterocyclic ring has attracted with a wide spectrum of biological activities such as antibacterial, antidepressant, antiviral, antitumoral, and anti-inflammatory agents, pesticides, herbicides, dyes, lubricant, and also analytical reagents [16]. The commonly known triazole fused to other heterocyclic systems is triazole-pyridines [17], triazolo-pyridazines [18], triazolo-pyrimidines [19], triazolo-pyrazines [20], triazolo-triazines [21], and triazolo-thiadiazines [22]. Although there are not many triazole fused to oxadiazole, even the number of them are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities. Further, there is no report on the triazolefused oxadiazole of bis-heterocyclic systems. On the other hand, 1,3,4-oxadiazole derivatives were reported to possess significant antibacterial [23], anti-inflammatory [24], tyrosinase inhibitory [25], antiviral [26], antihypertensive [27], cortical muscarinic receptor agonists [28], herbicidal [29], $Ca^{+2}$ channel blocker [30], antitumour [31], anticonvulsant [32], anti-elmintic [33], and antioxidant activities [34].

In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities [35–38], including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties. Further, recent reports [39] indicate that bis-heterocyclic compounds displayed much better antibacterial activity than the mono heterocyclic compounds.

Owing to the immense importance and varied bioactivities exhibited by triazolo-oxadiazole and in continuation of our ongoing research on biologically active bis-heterocyclics [40–45], it was thought of interest to accommodate triazole and oxadiazole moieties in a single molecular framework and to obtain new bis-heterocyclic compounds with potential biological activity. In the present study, we performed the synthesis and biological evaluation of some new bis-triazolo-oxadiazoles.

## RESULTS AND DISCUSSION

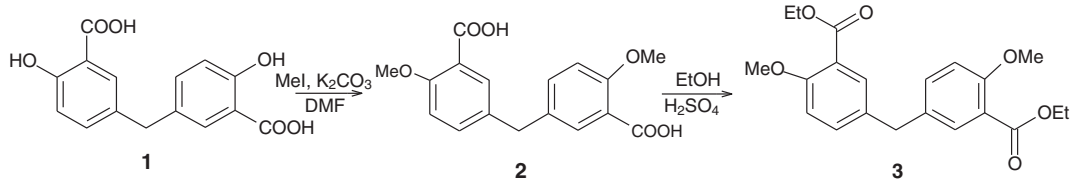
Compound **1**, required for the synthesis of the title compounds, was prepared according to the procedure described

in literature [46]. Compound **1** on reaction with methyl iodide, in the presence of $K_2CO_3$ in DMF at room temperature for 12 h, furnished the 5-(3-carboxy-4-methoxybenzyl)-2-methoxybenzoic acid **2** in 74% yield. Compound **2** on reaction with absolute ethyl alcohol in the presence of a catalytic amount of conc. $H_2SO_4$ at reflux for 3 h, gave the ethyl-5-[3-(ethoxycarbonyl)-4-methoxybenzyl]-2-methoxybenzoate **3** in 69% yield (Scheme 1).

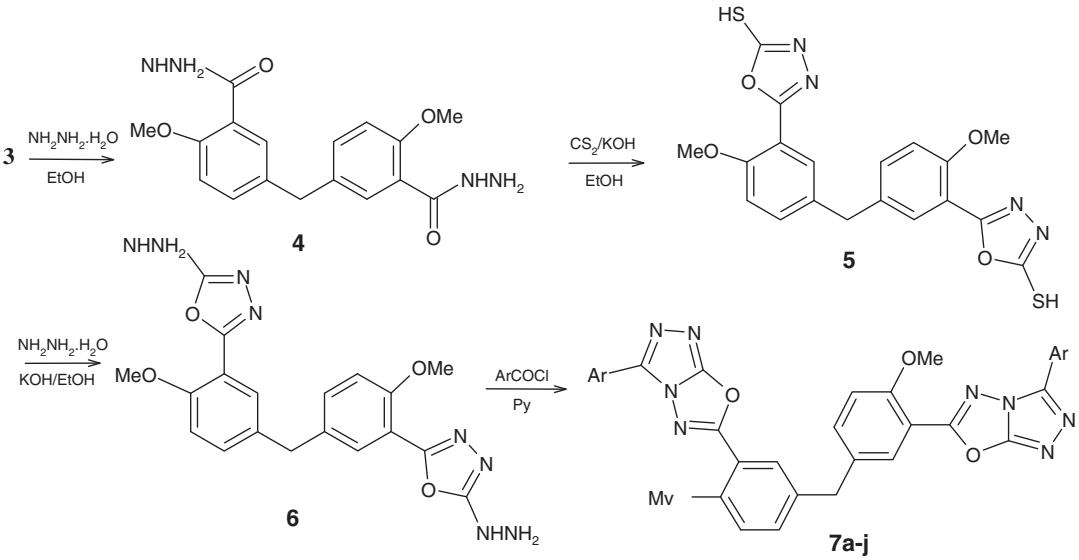
The structure of compound **3** was confirmed by its IR, $^1H$, $^{13}C$ NMR MS, and elemental analyses. The IR spectrum of compound **3** showed two absorption bands in the region of 1696 and 1229 $cm^{-1}$, assigned to C=O and O-Et groups, provides a strong evidence for the formation of ester. Its $^1H$ NMR spectrum showed two signals at δ 1.27 and 4.32 parts per million (ppm) corresponding to $CH_3$ and $CH_2$ of ethyl protons, respectively. The aromatic protons appeared in the region δ 6.69, 7.36, and 7.56 ppm are in accord with its structure. $^{13}C$ NMR spectrum showed signals at δ 16.7 and 62.0 ppm corresponding to the $CH_3$, $CH_2$ of ethyl group, respectively. The other signals observed were at the expected chemical shifts and integral values. In addition, elemental analysis is also consistent with the structure proposed for compound **3**.

The intermediate, 5-[3-(hydrazinocarbonyl)-4-methoxybenzyl]-2-methoxy-1-benzenecarbohydrazide **4**, was prepared on hydrazinolysis of **3** with hydrazine hydrate, in ethyl alcohol at reflux for 4 h, with 70% of yield. The compound **4** on reaction with carbon disulfide in the presence of potassium hydroxide, in ethanol at reflux for 12 h, followed by acidification afforded the 5-2-methoxy-5-[4-methoxy-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzyl] phenyl-1,3,4-oxadiazole-2-thiol **5** in 72% yield. Compound **5** on reaction with the hydrazine hydrate, in the presence of potassium hydroxide, in ethanol at reflux for 8 h, produced 1-(5-5-[3-(5-hydrazino-1,3,4-oxadiazol-2-yl)-4-methoxybenzyl]-2-methoxyphenyl-1,3,4-oxadiazol-2-yl)hydrazine **6** in 79% yield. The one-pot cyclo-condensation of compound **6** with different aroyl/heteroyl chlorides in the presence of pyridine at reflux temperature resulted the new series of 6-2-methoxy-5-[4-methoxy-3-(3-aryl[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl)benzyl]phenyl-3-aryl[1,2,4] triazolo[3,4-*b*][1,3,4]oxadi-azoles **7a–j** (Scheme 2). The

**Scheme 1**




**Scheme 2**



structures of the newly synthesized compounds were confirmed by their IR, $^1$H, $^{13}$C NMR MS, and elemental analyses.

**Antibacterial assay.** All the newly synthesized compounds **7a–j** were screened for their antibacterial activity against Gram-positive bacteria *viz. Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), and *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria *viz. Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39), and *Chromobacterium violaceum* (MTCC 2656) by disc diffusion method [47]. For the antibacterial assay, standard inoculums ($1–2 \times 10^7$ c.f.u/mL 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6.26 mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37°C. The inhibition zones were measured and compared with the standard drug streptomycin, and zone of inhibition are presented in Table 1.

The antibacterial screening data reveal that all the tested compounds **7a–j** showed moderate to good inhibition towards all the tested strains. Compounds **7e**, **7f**, **7i**, and **7j** exhibited potent inhibitory activity compared with standard drug at the tested concentrations. The results also reveal that the presence of 2,4-difluorophenyl (**7e**) or 4-nitrophenyl (**7f**) or 2-pyrazyl (**7i**), or 2-furyl (**7j**) on triazole ring might be the reason for the significant inhibitory activity. The presence of 2,4-difluorophenyl moiety in the molecules would enhance the inhibitory activity as shown by **7e**. However, the presence of 4-bromophenyl (**7c**) and 2-chloro-3-pyridyl (**7h**) did not show significant inhibition. Further, comparison of inhibition zones (in mm) of the selected compounds **7** and standard drug streptomycin against *B. subtilis* is presented in Figure 1.

In conclusion, a series of novel 6-2-methoxy-5-[4-methoxy-3-(3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl)benzyl] phenyl-3-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadi- azoles **7a–j** has been synthesized and evaluated for their antibacterial activity against various Gram-positive and Gram-negative bacteria. Most of the bis compounds showed good antibacterial activity. Among them, compounds **7e**, **7f**, **7i**, and **7j** were found to be most active against all the microorganisms employed. Further, the presence of 2,4-difluorophenyl moiety in the molecule enhanced the inhibitory activity.

## EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purities of the compounds were checked using precoated TLC plates. IR spectra were recorded on a Perkin-Elmer FTIR 5000 spectrometer using KBr pellets. $^1$H, $^{13}$C NMR spectra in DMSO-$d_6$ were recorded on a Varian Gemini 300 MHz spectrometer (Fall River, MA) and the chemical shifts were reported as parts per million (δ ppm) down field using TMS as an internal standard. Mass spectra were obtained

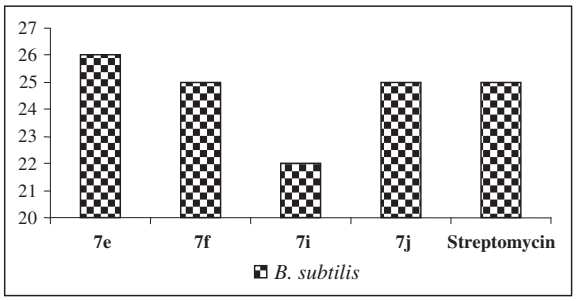



**Figure 1.** Comparison of inhibition zone (mm) of the selected compounds **7** and standard drug against *Bacillus subtilis*.

**Table 1**

Antibacterial activity of compounds **7a–j**.

| | Zone of inhibition at 50 μg/mL (mm) | | | | | |
|---|---|---|---|---|---|---|
| Compound | *Bacillus subtilis* | *Bacillus sphaericus* | *Staphylococcus aureus* | *Pseudomonas aeruginosa* | *Klobsinella aerogenes* | *Chromobacterium violaceum* |
| **7a** | 12 | 14 | 12 | 15 | 10 | 12 |
| **7b** | 10 | 12 | 10 | 12 | 11 | 18 |
| **7c** | 14 | 10 | 14 | 10 | 14 | 16 |
| **7d** | 15 | 14 | 16 | 10 | 12 | 14 |
| **7e** | 26 | 28 | 28 | 29 | 25 | 30 |
| **7f** | 25 | 24 | 24 | 26 | 24 | 28 |
| **7g** | 10 | 10 | 13 | 10 | 10 | 18 |
| **7h** | 10 | 12 | 12 | 12 | 10 | 14 |
| **7i** | 22 | 26 | 28 | 30 | 24 | 29 |
| **7j** | 25 | 28 | 28 | 28 | 25 | 26 |
| Streptomycin | 25 | 30 | 30 | 30 | 25 | 30 |

on a VG micromass 7070H spectrometer. Elemental analyses were performed on a Perkin-Elmer CHN elemental analyzer. All the solvents and chemicals were purchased from Sigma-Aldrich chemical company and used without further purification.

**5-(3-Carboxy-4-methoxybenzyl)-2-methoxybenzoic acid (2)**. To a solution of **1** (0.01 mol) and $K_2CO_3$ (0.04 mol) in DMF (16 mL), MeI (0.03 mol) was added. The reaction mixture was stirred for 12 h at room temperature (TLC, EtOAc: Pet-ether, 2:1). The mixture was poured in water (30 mL) and extracted with $Et_2O$ (3 × 20 mL). Washing the organic phase with 2*N* NaOH solution, dried over $Na_2SO_4$ and evaporation of solvent gave compound **2** as white solid; Yield 74%, mp 194–96°C; IR (KBr) ν: 3300–3200, 3037, 1698, 1070 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.82 (s, 6H, $OCH_3$), 3.91 (s, 2H, $CH_2$), 6.60 (d, $J$ = 8.7 Hz, 2H, ArH), 7.72 (d, $J$ = 8.7 Hz, 2H, ArH), 7.87 (s, 2H, ArH), 10.7 (s, 2H, COOH); $^{13}C$ NMR (DMSO-$d_6$): δ 41.2, 54.2, 122.0, 122.8, 131.9, 133.0, 134.3, 156.1, 170.1; MS *m/z*: 316 ($M^+$). *Anal*. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.50; H, 5.03.

**Ethyl-5-[3-(ethoxycarbonyl)-4-methoxybenzyl]-2-methoxy benzoate (3)**. To the solution of **2** (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 afford the compound **3** as pink solid; Yield 69%, mp 249–51°C; IR (KBr) ν: 3041, 1696, 1229, 1067 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.27 (t, 6H, $CH_3$), 3.83 (s, 6H, $OCH_3$), 3.90 (S, 2H, $CH_2$), 4.32 (q, 4H, $CH_2$), 6.69 (d, $J$ = 8.9 Hz, ArH), 7.36 (d, $J$ = 8.9 Hz, 2H, ArH), 7.56 (s, 2H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 16.7, 41.2, 53.7, 62.0, 116.8, 121.6, 128.0, 128.7, 132.5, 156.7, 170.2; MS: *m/z* 372 ($M^+$). *Anal*. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.69; H, 6.52.

**5-[3-(Hydrazinocarbonyl)-4-methoxybenzyl]-2-methoxy-1-benzenecarbohydrazide (4)**. A mixture of compound **3** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (50 mL) was refluxed for 4 h, cooled at room temperature and filtered. The crude product was recrystallized from ethanol to give new intermediate **4** as white crystal; Yield 70%, mp 141–43°C; IR (KBr) ν: 3300–3200, 3065, 1680, 1072 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.82 (s, 6H, $OCH_3$), 4.21 (s, 2H, $CH_2$), 5.49 (s, 4H, $NH_2$), 6.87 (d, $J$ = 8.4 Hz, 2H, ArH), 7.20 (s, 2H, ArH), 7.47 (d, $J$ = 8.4 Hz, 2H, ArH), 8.20 (s, 2H, NH); $^{13}C$ NMR (DMSO-$d_6$): δ 41.6, 54.6, 119.4, 124.2, 126.3, 130.9, 133.2, 157.6, 168.6; MS: *m/z* 345 ($M^+$ +1). *Anal*. Calcd. for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85. Found: C, 59.23; H, 5.80.

**5-2-Methoxy-5-[4-methoxy-3-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzyl]phenyl-1,3,4-oxadiazole-2-thiol (5)**. A mixture of compound **4** (0.01 mol), potassium hydroxide (0.02 mol), and carbon disulfide (0.03 mol) in ethanol (150 mL) was heated under reflux, stirring for 12 h and 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 give pure compound **5** as yellow solid; Yield 72%, mp 187–89°C; IR (KBr) ν: 3030, 2902, 1601, 1570, 1067, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.84 (s, 6H, $OCH_3$), 3.98 (s, 2H, $CH_2$), 6.76 (d, $J$ = 8.9 Hz, 2H, ArH), 7.38 (d, $J$ = 8.9 Hz, 2H, ArH), 8.21 (s, 2H, ArH), 11.20 (s, 2H, NH/SH); $^{13}C$ NMR (DMSO-$d_6$): δ 40.9, 54.1, 114.8, 115.4, 128.7, 131.0, 133.3, 154.7, 163.5, 172.2; MS: *m/z* 429 ($M^+$ +1). *Anal*. Calcd. for $C_{19}H_{16}N_4O_4S_2$: C, 53.26; H, 3.76; N, 13.08. Found: C, 53.22; H, 3.78; N, 13.00.

**1-(5-5-[3-(5-Hydrazino-1,3,4-oxadiazol-2-yl)-4-methoxybenzyl]-2-methoxyphenyl-1,3,4-oxadiazol-2-yl)hydrazine (6)**. To a mixture of compound **5** (0.01 mol) and potassium hydroxide (0.02 mol) in ethanol (50 mL), 80% hydrazine hydrate (0.03 mol) was added drop wise, and the reaction mixture was heated under reflux for 8 h. The solvent was distilled off *in vacuo*, cooled and the crystals separated were filtered, washed with cold ethanol, and recrystallized from alcohol to give the pure compound **6** as yellow solid; Yield 79%, mp 156–58°C; IR (KBr) ν: 3300–3200, 3047, 1600, 1062, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.84 (s, 6H, $OCH_3$), 4.01 (s, 2H, $CH_2$), 5.32 (s, 4H, $NH_2$), 6.76 (d, $J$ = 8.6 Hz, 2H, ArH), 7.38 (d, $J$ = 8.6 Hz, 2H, ArH), 8.10 (s, 2H, NH), 8.22 (s, 2H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 41.2, 55.1, 113.9, 116.4, 127.4, 131.6, 133.2, 154.7, 157.8, 165.5; MS: *m/z* 424 ($M^+$). *Anal*. Calcd. for $C_{19}H_{20}N_8O_4$: C, 53.77; H, 4.75; N, 26.40. Found: C, 53.72; H, 4.71; N, 26.44.

**6-2-Methoxy-5-[4-methoxy-3-(3-aryl[1,2,4]triazolo[3,4-b][1,3,4]oxadiazol-6-yl)benzyl]phenyl-3-aryl[1,2,4]triazolo[3,4-b] [1,3,4]oxadiazoles (7a–j)**. To a solution of compound 6 (0.01 mol) in dry pyridine (25 mL), the corresponding acid chlorides (0.02 mol), was added in drops. The reaction mixture was stirred at room temperature for 2 h and then heated for 2 h in a steam bath. It was then poured onto crushed ice. The solid products obtained by filtration were crystallized from the appropriate solvents to furnish the pure compounds **7a–j**, which were characterized by $^1H$, $^{13}C$ NMR, IR, MS, and elemental analyses.

**6-2-Methoxy-5-[4-methoxy-3-(3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl)benzyl]phenyl-3-phenyl[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazole (7a)**. This compound was obtained as brown solid; Yield 74%; mp 166–68°C; IR (KBr) ν: 3037, 1590, 1070, 1024 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.47 (s, 2H, $CH_2$), 3.66 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.30–7.40 (m, 12H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 117.2, 119.2, 126.5, 128.3, 130.2, 131.6, 132.3, 133.0, 134.5, 151.6, 156.5, 159.1, 160.4; MS: *m/z* 596 ($M^+$). *Anal*. Calcd. for $C_{33}H_{24}N_8O_4$: C, 66.44; H, 4.05; N, 18.78. Found: C, 66.40; H, 4.01; N, 18.71.

**3-(4-Chlorophenyl)-6-(5-3-[3-(4-chlorophenyl)[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxyphe- nyl) [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7b)**. This compound was obtained as yellow solid; Yield 71%; mp 170–72°C; IR (KBr) ν: 3041, 1592, 1580, 1064, 1032, 685 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.46 (s, 2H, $CH_2$), 3.66 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.30–7.40 (m, 6H, ArH), 8.31 (d, $J$ = 8.6 Hz, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.6, 54.5, 117.2, 119.2, 127.4, 131.3, 132.5, 133.0, 133.6, 134.9, 136.2, 151.4, 156.3, 159.1, 160.1; MS: *m/z* 666 ($M^+$). *Anal*. Calcd. for $C_{33}H_{22}Cl_2N_8O_4$: C, 59.56; H, 3.33; N, 16.84. Found: C, 59.51; H, 3.30; N, 16.79.

**3-(4-Bromophenyl)-6-(5-3-[3-(4-bromophenyl)[1,2,4]triazo lo [3,4-*b*] [1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxy phenyl) [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7c)**. This compound was obtained as white solid; Yield 76%; mp 159–61°C; IR (KBr): ν 3033, 1594, 1570, 1067, 1027, 586 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.47 (s, 2H, $CH_2$), 3.67 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.40–7.50 (m, 6H, ArH), 7.71 (d, $J$ = 8.3 Hz, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.1, 54.7, 117.2, 119.6, 126.6, 128.1, 130.8, 131.6, 132.5, 133.8, 134.5, 151.3, 156.5, 159.4, 160.7;

MS: *m/z* 754 ($M^+$). *Anal*. Calcd. for $C_{33}H_{22}Br_2N_8O_4$: C, 52.54; H, 2.94; N, 14.85. Found: C, 52.49; H, 2.95; N, 14.80.

**3-(2-Fluorophenyl)-6-(5-3-[3-(2-fluorophenyl)[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxyphenyl) [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7d)**. This compound was obtained as yellow solid; Yield 70%; mp 171–73°C; IR (KBr): ν 3065, 1590, 1575, 1062, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.48 (s, 2H, $CH_2$), 3.64 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.30–7.40 (m, 8H, ArH), 8.22 (d, $J = 7.9$ Hz, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 116.8, 117.2, 119.2, 121.4, 125.2, 129.7, 131.6, 132.8, 133.0, 134.5, 151.6, 156.5, 159.1, 160.4, 162.7; MS: *m/z* 632 ($M^+$). *Anal*. Calcd. for $C_{33}H_{22}F_2N_8O_4$: C, 62.66; H, 3.51; N, 17.71. Found: C, 62.60; H, 3.47; N, 17.75.

**3-(2,4-Difluorophenyl)-6-(5-3-[3-(2,4-difluorophenyl)[1,2,4] triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxyphenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7e)**. This compound was obtained as brown solid; Yield 68%; mp 187–89°C; IR (KBr): ν 3064, 1597, 1581, 1063, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.46 (s, 2H, $CH_2$), 3.65 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.20–7.30 (m, 6H, ArH), 7.91 (d, $J = 8.2$ Hz, 2H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.3, 54.4, 108.1, 114.9, 115.1, 117.1, 119.5, 129.9, 131.6, 133.2, 134.6, 151.6, 156.0, 156.7, 159.1, 160.6, 172.2; MS: *m/z* 668 ($M^+$). *Anal*. Calcd. for $C_{33}H_{22}F_4N_8O_4$: C, 59.29; H, 3.02; N, 16.76. Found: C, 59.22; H, 3.37; N, 16.70.

**6-(2-Methoxy-5-4-methoxy-3-[3-(4-nitrophenyl)[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl]benzylphenyl)-3-(4-nitrophenyl) [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7f)**. This compound was obtained as brown solid; Yield 75%; mp 184–186°C; IR (KBr): ν 3032, 1590, 1580, 1565, 1370, 1061 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.47 (s, 2H, $CH_2$), 3.66 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.34 (s, 2H, ArH), 8.14 (d, $J = 8.7$ Hz, 4H, ArH), 8.82 (d, $J = 8.7$ Hz, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 117.2, 119.2, 127.6, 131.6, 132.4, 133.0, 134.0, 134.8, 149.3, 151.6, 156.5, 159.1, 160.4; MS: *m/z* 686 ($M^+$). *Anal*. Calcd. for $C_{33}H_{22}N_{10}O_8$: C, 57.73; H, 3.23; N, 20.40. Found: C, 57.70; H, 3.17; N, 20.41.

**6-(2-Methoxy-5-4-methoxy-3-[3-(3-pyridyl)[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl]benzylphenyl)-3-(3-pyridyl)[1,2,4] triazolo[3,4-*b*][1,3,4]oxadiazole (7g)**. This compound was obtained as yellow solid; Yield 73%; mp 139–41°C; IR (KBr): ν 3049, 1595, 1580, 1550, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.47 (s, 2H, $CH_2$), 3.65 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.60–7.70 (m, 6H, ArH), 8.34 (d, $J = 7.9$ Hz, 2H, ArH), 8.80 (s, 2H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.2, 54.1, 117.6, 119.2, 123.9, 125.3, 131.1, 132.8, 133.5, 134.4, 150.7, 151.8, 152.7, 156.9, 159.1, 160.4; MS: *m/z* 598 ($M^+$). *Anal*. Calcd. for $C_{31}H_{22}N_{10}O_4$: C, 62.20; H, 3.70; N, 23.40. Found: C, 62.16; H, 3.62; N, 23.33.

**3-(2-Chloro-3-pyridyl)-6-(5-3-[3-(2-chloro-3-pyridyl)[1,2,4] triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxyphenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (7h)**. This compound was obtained as yellow solid; Yield 70%; mp 144–46°C; IR (KBr): ν 3031, 1595, 1070, 1026, 689 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.46 (s, 2H, $CH_2$), 3.66 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.42 (s, 2H, ArH), 7.80–7.90 (m, 4H, ArH), 8.34 (d, $J = 8.0$ Hz, 2H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 117.2, 119.2, 125.1, 126.7, 131.6, 133.0, 134.5, 135.3, 146.1, 151.6, 156.5, 157.0, 159.1, 160.4; MS: *m/z* 668 ($M^+$). *Anal*. Calcd. for $C_{31}H_{20}Cl_2N_{10}O_4$: C, 55.78; H, 3.02; N, 20.98. Found: C, 55.71; H, 3.00; N, 20.94.

**6-(2-Methoxy-5-4-methoxy-3-[3-(2-pyrazinyl)[1,2,4]triazolo [3,4-*b*][1,3,4]oxadiazol-6-yl]benzylphenyl)-3-(2-pyrazinyl)[1,2,4] triazolo[3,4-*b*][1,3,4]oxadiazole (7i)**. This compound was obtained as brown solid; Yield 68%; mp 152–154°C; IR (KBr): ν 3032, 2972, 1590, 1070, 1025 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.45 (s, 2H, $CH_2$), 3.65 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 7.41 (s, 2H, ArH), 8.21 (d, $J = 8.7$ Hz, 2H, ArH), 8.20–8.30 (m, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 117.2, 119.2, 131.6, 133.0, 134.5, 141.2, 145.7, 146.9, 148.5, 151.6, 156.5, 159.1, 160.4; MS: *m/z* 600 ($M^+$). *Anal*. Calcd. for $C_{29}H_{20}N_{12}O_4$: C, 58.00; H, 3.36; N, 27.99. Found: C, 57.94; H, 3.31; N, 27.92.

**3-(2-Furyl)-6-(5-3-[3-(2-furyl)[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol-6-yl]-4-methoxybenzyl-2-methoxyphenyl)[1,2,4]lo[3,4-*b*] [1,3,4]oxadiazole (7j)**. This compound was obtained as brown solid; Yield 69%; mp 167–69°C; IR (KBr): ν 3072, 2961, 1590, 1030 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.46 (s, 2H, $CH_2$), 3.68 (s, 6H, $OCH_3$), 6.70–6.90 (m, 4H, ArH), 6.50–6.60 (m, 4H, ArH), 7.40–7.50 (m, 4H, ArH); $^{13}C$ NMR (DMSO-$d_6$): δ 42.7, 54.7, 113.1, 117.2, 119.2, 121.5, 131.6, 133.0, 134.5, 134.9, 145.3, 151.6, 156.5, 159.1, 160.4; MS: *m/z* 576 ($M^+$). *Anal*. Calcd. for $C_{29}H_{20}N_8O_6$: C, 60.42; H, 3.50; N, 19.44. Found: C, 60.36; H, 3.45; N, 19.39.

**Acknowledgments.** The authors are grateful to the Director, Indian Institute of Chemical Technology, Hyderabad, India, for providing NMR and mass spectral data. Financial assistance from the UGC SAP (Phase-I)DRS Programme, New Delhi, India, is greatly acknowledged.

## REFERENCES AND NOTES

[1] Colak, A. T.; Colak, F.; Atar, N. Acta Chim Slov 2010, 57, 212.
[2] Gaber, H. M.; Hafiz, I. S. A.; EISawy, K. M. Acta Chim Slov 2010, 57, 230.
[3] Rohini, R.; Reddy, P. M.; Shanker, K. Acta Chim Slov 2009, 56, 900.
[4] Kotb, E. R.; EI-Hashash, M. A.; Salama, M. A. Acta Chim Slov 2009, 56, 908.
[5] Anderluh, P. S.; Vilfan, G.; Prezelj, A. Acta Chim Slov 2009, 56, 669.
[6] EI-Gazzar, A. R. B. A.; Hafez, H. N. Acta Chim Slov 2008, 55, 359.
[7] Kohn, E. C.; Liotta, L. A. U.S. Patent 637145; Chem Abstr 1991, 115, 248099.
[8] Srivatava, A. J.; Swarup, S.; Saxena, V. K. J Indian Chem Soc 1991, 68, 103.
[9] Udupi, R. H. G.; Suresh, V.; Setty, S. R.; Bhat, A. R. J Indian Chem Soc 2000, 77, 303.
[10] Turan, Z. G.; Kaplancikli, Z. A.; Erol, K. F. S. Il Farmaco 1999, 54, 218.
[11] Kane, M. J.; Wdudley, M.; Sorensen, S. M.; Miller, F. P. J Med Chem 1988, 31, 1253.
[12] Hovsepian, T. R.; Dilanian, E. R.; Egoyan, A. P.; Melik-Ohanjaian, R. G. J Chem Heterocycl Compds 2004, 40, 1194.
[13] Cansiz, A.; Koparir, M.; Demirdag, A. Molecules 2004, 9, 204.
[14] Li-Xue, A.; An-Jian, Z.; Xian-Xin, C.; Xin-Xiang, L.; Xiang Yun, N.; Dong-Yung, C.; Zhang, Z. Molecules 2002, 7, 681.
[15] Wasfy, A. A. F. J Chem Res 2003, 8, 457.
[16] Holla, B. S.; Akberali, P. M.; Shivananda, M. K. Il Farmaco 2001, 56, 919.
[17] Yao, G.; Haque, S.; Sha, L.; Kumaravel, G.; Wang, J.; Enger, T. M.; Whalley, T. M.; Conlon, P. R.; Chang, H.; Kiesman, F. W.; Petter, R. C. Bioorg Med Chem Lett 2005, 15, 511.

[18] Vu, C. B.; Shields, P.; Peng, B.; Kumaravel, G.; Jin, X.; Phadke, D.; Wang, J.; Engber, T.; Ayyub, E.; Petter, R. C. Bioorg Med Chem Lett 2004, 14, 4835.

[19] Sadana, K. A.; Mirza, Y.; Aneja, K. R.; Prakash, O. Eur J Med Chem 2003, 38, 533.

[20] Bussolari, J. C.; Panzica, R. P. Bioorg Med Chem 1999, 7, 2373.

[21] Zafer, A. K.; Gulhan, T. Z.; Ahmet, O.; Gilbert, R. Eur J Med Chem 2005, 43, 155.

[22] Vennerstrom, J. L.; Maklet, M. T.; Angerhofer, C. K.; Williams, J. A. Antimicrob Agents Chemother 1995, 39, 2671.

[23] Kucukguzel, S. G.; Oruc, E. E.; Rollas, S. Eur J Med Chem 2002, 37, 197.

[24] Amir, M.; Shikla, K. Eur J Med Chem 2004, 39, 535.

[25] Lam, K. W.; Syahida, A.; Ul-Haq, Z.; Abdul Rahman, M. B.; Lajis, N. H. Bioorg Med Chem Lett 2010, 20, 3755.

[26] Srivastava, P. C.; Robins, R. K. J Med Chem 1981, 24, 1172.

[27] Tyrkov, A. G.; Tyurenkov, I. N.; Tmchenko, M. V.; Perfilova, V. N. Pharm Chem J 2006, 40, 240.

[28] Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B. J Med Chem 1990, 33, 2690.

[29] Zhao, O.; Liu, S.; Li, Y.; Wang, O. J Agric Food Chem 2009, 57, 2849.

[30] Schlecker, R.; Thieme, P. C. Tetrahedron, 1988, 44, 3289.

[31] Savariz, F. C.; Formagio, A. S. N.; Barbosa, V. A.; Foglio, M. A.; Duarte, M. C. T.; Filhoc, B. P. D.; Sarragiotto, M. H. J Braz Chem Soc 2010, 21, 288.

[32] Bhat, M. A.; Siddiqui, N.; Khan, S. A. Acta Poloniae Pharm Drug Res 2008, 65, 235.

[33] Srinivas, K.; Kumar, K. P. Int J Biopharm 2010, 1, 14.

[34] Rajasekaran, S.; Rao, G. K.; Vedavathy, J. J. Chem Pharm Res 2010, 2, 101.

[35] Kritsanida, M.; Mouroutsou, A.; Marakos, P.; Pouli, N.; Papakonstantinou-Garoufalias, S.; Pannecouque, C.; Witvouw, M.; De Clercq, E. Il Farmaco 2002, 57, 253.

[36] Holla, B. S.; Sarojini, B.; Rao, S. B.; Akberali, P. M.; Kumari, N. S.; Shetty, V. Il Farmaco 2001, 56, 565.

[37] Turan-Zitouni, G.; Kaplancikli, Z. A.; Erol, K.; Kilic, F. S. Il Farmaco 1999, 54, 218.

[38] Holla, B. S.; Gonsalves, R.; Shenoy, S. Il Farmaco 1998, 53, 574.

[39] Onca, S.; Punar, M.; Erakosy, H. Chemotherapy, 2004, 50, 98.

[40] Srinivas, A.; Nagaraj, A.; Sanjeeva Reddy, C. Eur J Med Chem 2010, 45, 2353.

[41] Sanjeeva Reddy, C.; Srinivas, A.; Nagaraj, A. Chem Pharm Bull 2010, 58, 805.

[42] Sanjeeva Reddy, C.; Sanjeeva Rao, L.; Vani Devi, M.; Kumar, G. R.; Nagaraj, A. Chin Chem Lett 2010, 21, 1045.

[43] Sanjeeva Reddy, C. Sanjeeva Rao, L.; Kumar, G. R.; Nagaraj, A. Chem Pharm Bull 2010, 58, 1328.

[44] Sanjeeva Reddy, C.; Sanjeeva Rao, L.; Nagaraj, A. Acta Chim Slov 2010, 57, 726.

[45] Sanjeeva Reddy, C.; Vani Devi, M.; Sunitha, M.; Nagaraj, A. Chem Pharm Bull 2010, 58, 1622.

[46] Clemmensen, E.; Heitman, A. H. C. J Am Chem Soc 1911, 33, 733.

[47] National Committee for Clinical Laboratory Standards (NCCLS). Standard methods for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically. Nat Comm Lab Stands Villanova, 1982, pp. 242.