EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 11
212-216
Year: 2016

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SOME NOVEL 1,3,4-OXADIAZOLE BASED 1,2,4-TRIAZOL-[3,4-*b*]-[1,3,4]-THIADIAZINES

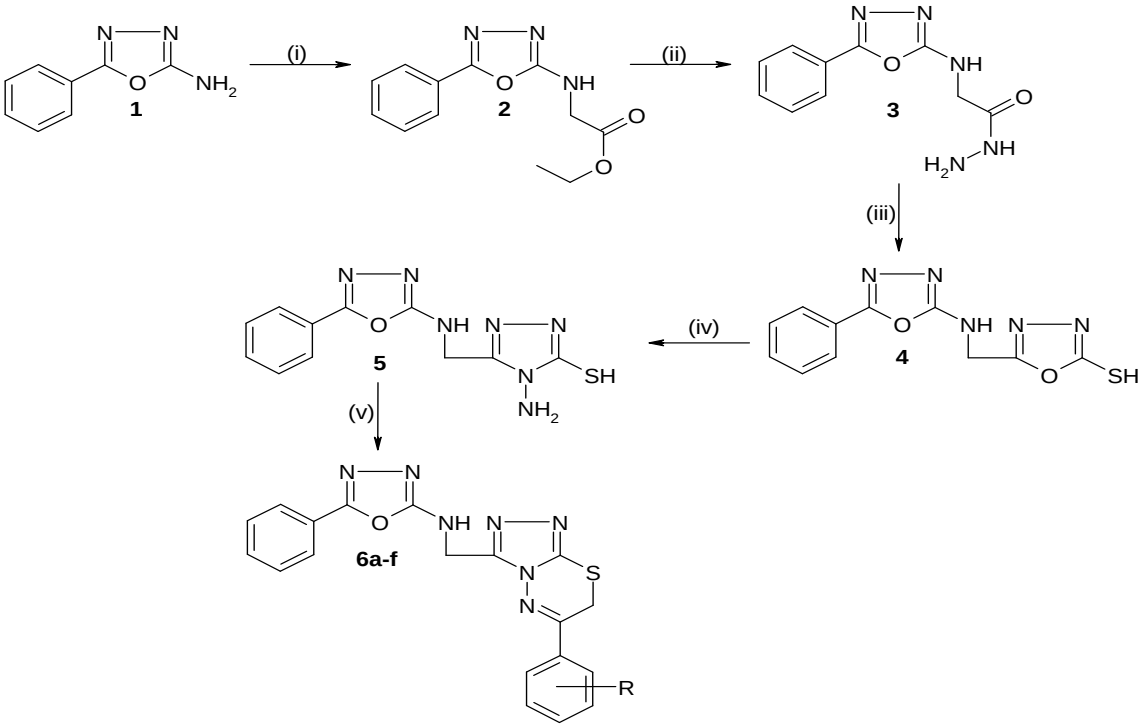
Sri Venkateswarlu Rayudu*[1, 2], Dipankar Karmakar[1] and Pramod Kumar[2]

[1]Department of Research and Development, GVK Bio Sciences Private Limited, 28A, IDA, Nacharam, Hyderabad-500076, Telangana, India.
[2]Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500072, Telangana, India.

*** Corresponding Author: Sri Venkateswarlu Rayudu**
Department of Research and Development, GVK Bio Sciences Private Limited, 28A, IDA, Nacharam, Hyderabad-500076, Telangana, India.

Article Received on 31/08/2016 **Article Revised on 21/09/2016** **Article Accepted on 11/10/2016**

ABSTRACT
In the present study, a novel series of (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amine and its derivatives **(6a-f)** has been developed. These target compounds were achieved by choosing 5-phenyl-[1,3,4]oxadiazol-2-ylamine **(1)** as raw material and by involving (5-phenyl-[1,3,4]oxadiazol-2-ylamine)-acetic acid ester **(2)**, (5-phenyl-[1,3,4]oxadiazol-2-ylamine)-acetic acid hydrazide **(3)**, 5-[(5-phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol **(4)** and 4-amino-5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol **(5)** as intermediates. The chemical structures of all these compounds have been estimated by IR, ^{1}H & ^{13}C NMR, mass spectral data and elemental analysis. Further, the title compounds were evaluated for their preliminary *in vitro* antifungal activity against some fungal strains.

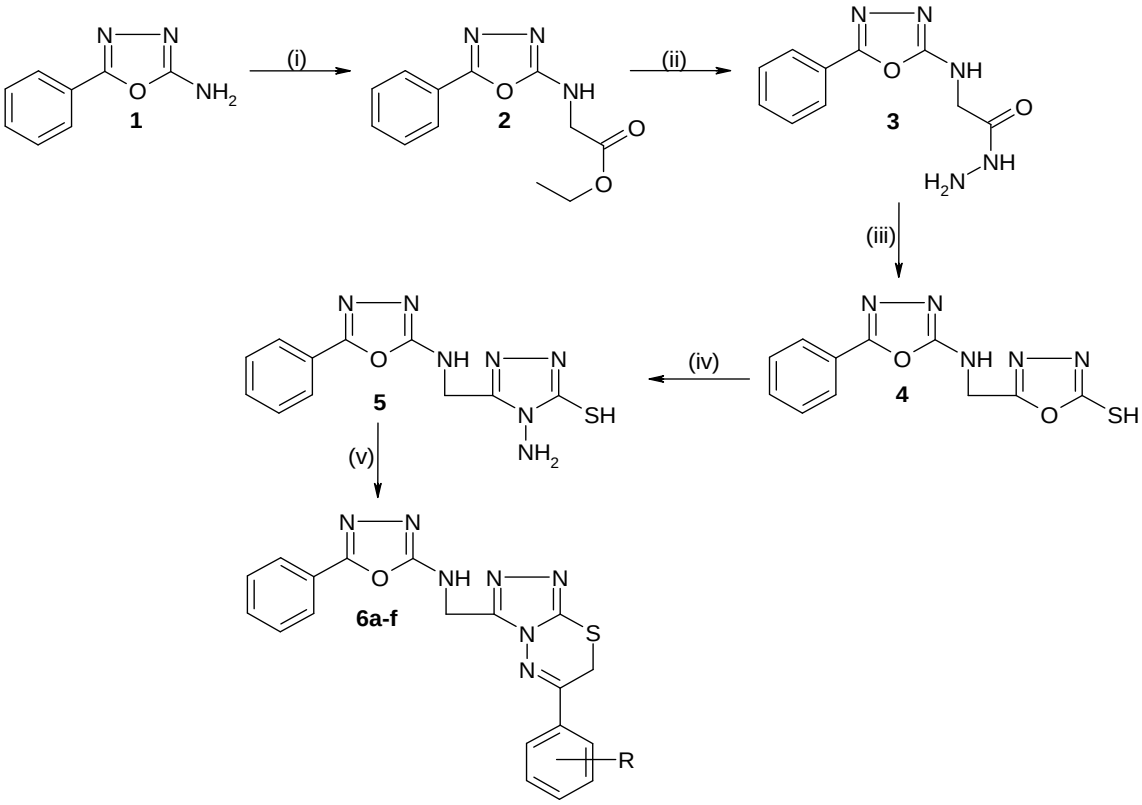


INTRODUCTION
1,3,4-Oxadiazoles constitute an important class of heterocyclic compounds as they have attracted significant interest in medicinal and pesticide chemistry. These compounds have been found to exhibit diverse biological activities such as analgesic[1], anti-inflammatory[2], antimicrobial[3], anti-HIV[4] antimalarial[5], antifungal[6] and other biological properties[7-11]. During the last few decades, a considerable attention has been devoted to synthesis of 1,

2, 4-triazole derivatives, because 1, 2, 4-triazole possess a wide variety of comprehensive bioactivities such as antimicrobial[12], anti-inflammatory[13], analgesic[14], anti-tumor[15], antihypertensive[16] and antiviral[17]. The recent literature survey revealed that 1,2,4-triazolo[3,4-*b*][1, 3, 4]thiadiazine derivatives have promising biological activities such as anti-HIV[18], CNS stimulant[19], antifungal[20], and anti-inflammatory[21]. Studies have also confirmed that triazolothiadiazine derivatives possess anti-Candidal activity[22].

RESULTS AND DISCUSSION

These initial reports stimulated us to integrate 1,2,4-triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amine moiety with 1,3,4-oxadiaol frame work, since these systems possess well documented biological activity. The easily accessible 5-phenyl-[1,3,4]oxadiazol-2-ylamine **(1)** was chosen as starting material for the synthesis of title compounds, (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amine and its derivatives **(6a-f)** and the general strategy for the synthesis is summarized in schemes 1. Thus The initial intermediate, (5-phenyl-[1,3,4]oxadiazol-2-ylamine)-acetic acid ester **(2)** has been prepared through substitution in good yield by boiling of a mixture of 5-phenyl-[1,3,4]oxadiazol-2-ylamine **(1)**, ethyl bromoacetate and sodium ethoxide in ethanol for 7 h. Then compound **2** was treated with hydrazine hydrate in ethanol at reflux temperature for 4 h to get the next intermediate, (5-phenyl-[1,3,4]oxadiazol-2-ylamine)-acetic acid hydrazide **(3)**. Further, the next intermediate, 5-[(5-phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol **(4)** has been was prepared by the cyclization of compound **3** with carbon disulfide and potassium hydroxide in ethanol solvent under reflux for 11 h. Further, the final intermediate, 4-amino-5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol **(5)** was synthesized in moderate yield by the substitution method of compound **4** with hydrazine hydrate in presence of in ethanol at reflux temperature for 6 h. Finally, the intermediate **5** has been condensed successively with a variety of phenacyl bromide in ethyl alcohol under reflux for 7-8 h to get the title compounds, (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amine and its derivatives **(6a-f)** in moderate to good yields. The chemical structures of the newly synthesized compounds have been established by IR, ^{1}H & ^{13}C-NMR, Mass spectral data and elemental analysis. Further, all the synthesized target compounds were tested to evaluate their affinity against some fungal strains.



Scheme 1: *Reagents and conditions:* (i) Ethyl bromoacetate, Na, EtOH, reflux, 7 h; (ii) NH_2-NH_2.H_2O, ethanol, reflux, 4 h; (iii) CS_2, KOH, EtOH, reflux, 11 h; (iv) NH_2–NH_2. H_2O, EtOH, reflux, 6 h; (v) $ArCOCH_2Br$, EtOH, reflux, 7-8 h. **6 R** = a) H; b) 4–OH ; c) 4–OCH_3; d) 4–Cl; e) 4–Br; f) 4–NO_2;

Antifungal activity

All the newly synthesized target compounds, (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amines **(6a-f)** were screened for antifungal activity against four fungal strains *viz*., *Candida albicans*, *Aspergillus fumigatus*,

Trichophyton rubrum, and *Trichophyton mentagrophytes* in dimethyl sulfoxide by broth dilution method[23] and using Aamphotericin B as standard drug. The minimum inhibitory concentration (MIC, µg/mL) was measured and the results are reported in tables 1. As per the screening results, compound **6a** is performed high activity against both fungal organisms i.e *C. albicans* and *A. fumigates*. The elevated activity towards *C. albicans* is executed by product **6b** which bearing OH group at *para* position of aromatic ring. Title compound **6c** with methoxy group at *para* position is displayed good activity against *T. Rubrum*. Product **6d** carrieng 4-chloro derivative is showed appreciated activity averse to three fungal organisms such as *C. albicans*, *T. rubrum*, and *T. Mentagrophytes*. Both compounds **6e** with 4-bromo group and **6f** with 4-nitro moiety are disclosed prominent activity against only *A. fumigates*. All the compounds in this series exhibited moderate to poor activity and none of the compounds is inactive against any one of the fungal organisms.

Table 1: *In vitro* antifungal activity of compounds 6a-f (MIC in µg/mL)

Compound	*C. Albicans*	*A. Fumigatus*	*T. Rubrum*	*T. Mentropyhte*
6a	12.5	6.25	25.5	25.0
6b	12.5	25.0	25.0	25.0
6c	50.0	25.0	6.25	12.5
6d	12.5	12.5	6.25	6.25
6e	25.0	6.25	12.5	25.0
6f	25.0	6.25	12.5	12.5
Amphotericin B	6.25	3.12	3.12	3.12

Experimental section

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a PerkinElmer BX series FT-IR 5000 spectrometer using KBr pellet. ^{1}H & ^{13}C-NMR spectra were recorded on a Varian 300 MHz & 100 MHz spectrometers respectively. 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.

Preparation of (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester (2)

The solution of 5-phenyl-[1,3,4]oxadiazol-2-ylamine **(1)** (0.01 mol) and an equivalent amount of sodium in absolute ethanol (15 ml) was refluxed for 2 h and then ethyl bromoacetate (0.01 mol) was added and the mixture was refluxed for another 6 h on constant stirring. After completion of the reaction (monitored by the TLC), the solvent was evaporation under reduced pressure. The generated solid was filtered, washed with cold-water, dried and recrystallized from ethanol to offer pure 5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester **(2)**.

Preparation of (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide (3)

A mixture of 5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester **(2)** (0.01 mol) and hydrazine hydrate in ethanol (20 ml) was refluxed with uniform stirring for 3 h. After realization of the reaction (examined by the TLC), the reaction mixture was cooled to room temperature, then poured in ice-cold water and the resulted solid was filtered, dried and recrystallized from ethyl acetate to give (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide **(3)** in pure form.

Preparation of 5-[(5-phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol (4)

A mixture of (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide **(3)** (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 11 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 5-[(5-phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol **(4)**.

Preparation of 4-amino-5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol (5)

To a warm solution of 5-[(5-phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol **(4)** (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 6 h. 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-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol **(5)**.

Preparation of (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]-thiadiazin-3-ylmethyl)-amines (6a-f)

A mixture of 4-amino-5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol **(5)** (0.01 mol) and corresponding phenacyl bromide (0.01 mol) in absolute ethanol (20 mL) was refluxed for 7-8 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 ^{o}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 (5-phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]-thiadiazin-3-ylmethyl)-amines **(6a-f)**.

Physical spectral data

(5-Phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester (2)

Yellow solid, Yield: 68%, mp: 132-135; IR (KBr, cm^{-1}): 3248 (N-H), 3048 (C–H, Ar), 2965 (C-H, CH_3), 1740 (C=O), 1656 (C=N), 1665, (C=C, Ar), 1125 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.12 (s, 1H, NH), 7.65-7.25 (m, 5H, Ar–H), 4.00 (q, 2H, CH_2), 3.85 (s, 2H, NCH_2), 1.24 (t, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 153.5, 141.4, 132.8, 127.3, 125.8, 123.7, 120.5, 66.3, 52.7, 23.2; MS: *m/z* 247 (M^+); Elemental analysis: Calculated for $C_{12}H_{13}N_3O_3$: C-58.29, H-5.30, N-16.99, O-19.41. Found: C-57.89, H-5.29, N-16.78, O-19.32.

(5-Phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide (3)

White solid, Yield: 69%, mp: 120-122; IR (KBr, cm^{-1}): 3321 (N-H, NH_2), 3188 (N-H), 3047 (C–H Ar), 2968 (C–H, CH_2), 1672 (C=O), 1655 (C=N), 1650 (C=C, Ar), 1135 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.35 (s, 1H, $NHNH_2$), 11.06 (s, 1H, $NHCH_2$), 7.77-7.32 (m, 5H, Ar–H), 5.30 (s, 2H, NH_2), 3.85 (s, 2H, NCH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 154.8, 142.2, 135.2, 130.2, 128.1, 126.8, 118.8, 62.2; MS: *m/z* 233 (M^+); Elemental analysis: Calculated for $C_{10}H_{11}N_5S_2$: C-51.50, H-4.75, N-30.03, S-13.72. Found: C-50.89, H-4.73, N-29.91, S-13.66.

5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-[1,3,4]oxadiazole-2-thiol (4)

Brown solid; yield 73%; mp 139-141 °C; IR (KBr) cm^{-1}: 3229 (N-H), 3033 (C-H, Ar), 2629 (S-H), 1652 (C=N), 1552 (C=C), 1155 (C-O); ^{1}H-NMR ($CDCl_3$) *δ*: 11.24 (s, 1H, NH), 7.58-7.32 (m, 5H, Ar-H), 3.83 (s, 1H, SH), 2.85 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$) *δ*: 155.7, 143.5, 136.7, 131.2, 127.5, 125.6, 122.7, 117.5, 61.8; MS *m/z*: 289 (M^+); Elemental analysis calculated for $C_{11}H_9N_5O_2S$: C-47.99, H-3.30, N-25.44, O-11.62, S-11.65. Found: C-47.22, H-3.29, N-25.29, O-11.52, S-11.59.

4-Amino-5-[(5-Phenyl-[1,3,4]oxadiazol-2-ylamine)-methyl]-4*H*-[1,2,4]triazole-3-thiol (5)

Brownish yellow solid; yield 74%; mp 130-132 °C; IR (KBr) cm^{-1}: 3256 (N-H), 3025 (C-H, Ar), 2632 (S-H), 1652 (C=N), 1563 (C=C, Ar), 1139 (C-O); ^{1}H-NMR ($CDCl_3$) *δ*: 11.29 (s, 1H, NH), 7.62-7.30 (m, 5H, Ar-H), 3.88 (s, 1H, SH), 3.82 (2H, s, NH_2), 2.82 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$) *δ*: 153.8, 145.8, 137.2, 133.7, 126.2, 124.7, 123.7, 119.5, 63.7; MS *m/z*: 289 (M^+); Elemental analysis calculated for $C_{11}H_{11}N_7OS$: C-45.67, H-3.83, N-33.89, O-5.53, S-11.08. Found: C-45.58, H-3.82, N-33.79, O-5.52, S-11.01.

(5-Phenyl-[1,3,4]oxadiaol-2-yl)-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl)-amine (6a)

Yellow solid; yield 72%; mp 118-120 °C; IR (KBr) cm^{-1}: 3262 (N-H), 3022 (C-H, Ar), 2975 (C-H, CH_2), 1644 (C=N), 1555 (C=C, Ar), 1123 (C-O), 1245 (C–S); ^{1}H-NMR ($CDCl_3$) *δ*: 10.97 (s, 1H, NH); 7.75-7.33 (m, 108H, Ar-H), 3.82 (s, 2H, NCH_2), 1.85 (s, 2H, SCH_2); ^{13}C-NMR ($CDCl_3$) *δ*: 158.2, 146.3, 143.7, 137.3, 136.2, 133.0, 129.6, 128.6, 126.3, 124.7, 123.2, 121.6, 67.2, 58.6; MS: *m/z* 389 (M^+); Elemental analysis: Calculated for $C_{19}H_{15}N_7OS$: C-58.60, H-3.88, N-25.18, O-4.11, S-8.23. Found: C-57.95, H-3.87, N-25.05, O-4.10, S-8.22.

4-{3-[(5-Phenyl-[1,3,4]oxadiaol-2-yaminol)-methyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-phenol (6b)

Brown solid; yield 70%; mp 133-135 °C; IR (KBr) cm^{-1}: 3256 (N-H), 3152 (O-H), 3030 (C-H, Ar), 2981 (C-H, CH_2), 1636 (C=N), 1562 (C=C, Ar), 1131 (C-O), 1250 (C–S); ^{1}H-NMR ($CDCl_3$) *δ*: 10.92 (s, 1H, NH); 7.71-7.35 (m, 5H, Ar-H), 7.38 (d, 2H, d, *J* = 7.0 Hz, Ar-H), 7.28 (d, 2H, *J* = 7.0 Hz, Ar-H), 5.08 (s, 1H, OH), 3.85 (s, 2H, NCH_2), 1.89 (s, 2H, SCH_2);); ^{13}C-NMR ($CDCl_3$) *δ*: 156.7, 145.2, 144.7, 136.5, 135.8, 134.2, 128.2, 127.1, 124.3, 122.1, 121.0, 120.7, 68.5, 57.2; MS: *m/z* 405 (M^+); Elemental analysis: Calculated for $C_{19}H_{15}N_7O_2S$: C-56.29, H-3.73, N-24.18, O-7.89, S-7.91. Found: C-56.01, H-3.72, N-24.02, O-7.88, S-7.90.

[6-(4-Methoxy-phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl]-(5-phenyl-[1,3,4]oxadiaol-2-yl)-amine (6c)

Pale yellow solid; yield 71%; mp 141-143 °C; IR (KBr) cm^{-1}: 3244 (N-H), 3023 (C-H, Ar), 2978 (C-H, CH_2), 1641 (C=N), 1571 (C=C, Ar), 1140 (C-O), 1242 (C–S);); ^{1}H-NMR ($CDCl_3$) *δ*: 10.89 (s, 1H, NH); 7.75-7.30 (m, 5H, Ar-H), 7.32 (d, 2H, d, *J* = 7.2 Hz, Ar-H), 7.25 (d, 2H, *J* = 7.2 Hz, Ar-H), 5.12 (s, 1H, OH), 3.90 (s, 2H, NCH_2), 1.92 (s, 2H, SCH_2), 1.28 (s,3H, CH_3); ^{13}C-NMR ($CDCl_3$) *δ*: 155.3, 147.8, 146.2, 137.1, 136.1, 135.2, 127.5, 125.2, 124.0, 123.2, 122.7, 121.0, 65.6, 56.7, 36.7; MS: *m/z* 419 (M^+); Elemental analysis: Calculated for $C_{20}H_{17}N_7OS$: C-57.27, H-4.09, N-23.37, O-7.63, S-7.64. Found: C-57.03, H-4.08, N-23.26, O-7.62, S-7.63.

[6-(4-Chloro-phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl]-(5-phenyl-[1,3,4]oxadiaol-2-yl)-amine (6d)

Yellow solid; yield 75%; mp 122-124 °C; IR (KBr) cm^{-1}: 3232 (N-H), 3030 (C-H, Ar), 2969 (C-H, CH_2), 1638 (C=N), 1565 (C=C, Ar), 1136 (C-O), 1239 (C–S); ^{1}H-NMR ($CDCl_3$) *δ*: 10.87 (s, 1H, NH); 7.79-7.38 (m, 5H, Ar-H), 7.37 (d, 2H, d, *J* = 7.3 Hz, Ar-H), 7.28 (d, 2H, *J* = 7.3 Hz, Ar-H), 5.18 (s, 1H, OH), 3.95 (s, 2H, NCH_2), 1.97 (s, 2H, SCH_2); ^{13}C-NMR ($CDCl_3$) *δ*: 158.3, 149.7, 148.2, 139.1, 138.2, 137.1, 129.2, 127.5, 125.2, 123.7,

122.9, 120.7, 68.5, 59.3; MS: *m/z* 423 (M^+); Elemental analysis: Calculated for $C_{19}H_{14}ClN_7OS$: C-53.84, H-3.33, Cl-8.36, N-23.13, O-3.77, S-7.56. Found: C-53.51, H-3.32, Cl-8.35, N-23.01, O-3.76, S-7.55.

[6-(4-Bromo-phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl]-(5-phenyl-[1,3,4]oxadiaol-2-yl)-amine (6e)

Brown solid; yield 69%; mp 135-137 °C; IR (KBr) cm^{-1}: 3245 (N-H), 3042 (C-H, Ar), 2975 (C-H, CH_2), 1648 (C=N), 1573 (C=C, Ar), 1152 (C-O), 1255 (C–S); ^{1}H-NMR ($CDCl_3$) δ: 10.93 (s, 1H, NH); 7.72-7.35 (m, 5H, Ar-H), 7.33 (d, 2H, d, J = 7.1 Hz, Ar-H), 7.25 (d, 2H, J = 7.1 Hz, Ar-H), 5.15 (s, 1H, OH), 3.93 (s, 2H, NCH_2), 1.95 (s, 2H, SCH_2); ^{13}C-NMR ($CDCl_3$) δ: 153.6, 145.2, 144.1, 135.7, 134.7, 133.2, 126.8, 124.7, 122.8, 121.7, 120.7, 119.8, 65.3, 58.6; MS: *m/z* 467 (M^+); Elemental analysis: Calculated for $C_{19}H_{14}BrN_7OS$: C-48.73, H-3.01, Br-17.06, N-20.94, O-3.42, S-6.85. Found: C-48.52, H-3.00, Br-16.89, N-20.82, O-3.41, S-6.84.

[6-(4-Nitro-phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-ylmethyl]-(5-phenyl-[1,3,4]oxadiaol-2-yl)-amine (6f)

Yellow solid; yield 71%; mp 147-149 °C; IR (KBr) cm^{-1}: 3252 (N-H), 3049 (C-H, Ar), 2985 (C-H, CH_2), 1655 (C=N), 1563 (C=C, Ar), 1552 (N=O), 1138 (C-O), 1262 (C–S); ^{1}H-NMR ($CDCl_3$) δ: 10.96 (s, 1H, NH); 7.78-7.39 (m, 5H, Ar-H), 7.37 (d, 2H, d, J = 7.5 Hz, Ar-H), 7.28 (d, 2H, J = 7.5 Hz, Ar-H), 5.19 (s, 1H, OH), 3.95 (s, 2H, NCH_2), 1.98 (s, 2H, SCH_2); ^{13}C-NMR ($CDCl_3$) δ: 157.2, 145.2, 144.3, 138.7, 135.2, 133.7, 125.7, 124.2, 122.8, 121.2, 120.7, 119.5, 67.8, 54.7; MS: *m/z* 434 (M^+); Elemental analysis: Calculated for $C_{19}H_{14}N_8O_3S$: C-52.53, H-3.25, N-25.79, O-11.05, S-7.38. Found: C-52.27, H-3.24, N-25.62, O-10.98, S-7.37.

REFERENCES

1. Jayashankar B, Rai KML, Baskaran N, Sathish HS, *Eur. J. Med. Chem*., 2009; 44: 3898.
2. Alam MM, Shaharyar M, Hamid H, Nazreen S, Haider S, Alam MS, *Med. Chem*., 2011; 7: 663.
3. Padmaja A, Muralikrishna A, Rajasekhar C, Padmavathi V, *Chem. Pharm. Bull*., 56, 2011, 1509.
4. El-Emam AA, Al-Deeb OA, Al-Omar M, Lehmann J, *Bioorg. Med. Chem*., 2004; 12: 5107.
5. Zareef M, Rashid I, De Dominguez NG, Rodrigues J, Zaidi JH, Arfan M, Supuran CT, *J. Enzym. Inhib. Med. Chem*., 2007; 22: 301.
6. Xu W, He J, He M, Han F, Chen X, Pan Z, Wang J, Tong M, *Molecules*, 2011; 16: 9129.
7. Kashaw SK, Gupta V, Kashaw V, Mishra P, Stables JP, Jain NK, *Med. Chem. Res*., 2010; 19: 250.
8. Kotaiah Y, Harikrishna N, Nagaraju K, Rao CV, *Eur. J. Med. Chem*., 2012; 58: 340.
9. Oliveira CS, Lira BF, Barbosa-Filho JM, Lorenzo JGF, Athayde-Filho PF, *Molecules*, 2012; 17: 10192.
10. Rajak H, Thakur BS, Singh A, Raghuvanshi K, Sah AK, Veerasamy R, Sharma PC, Pawar RS, Kharya MD, *Bioorg. Med. Chem. Lett*., 2013; 23: 864.
11. Zhang S, Luo Y, He L-Q, Liu Z-J, Jiang A-Q, Yang Y-H, Zhu H-L, *Bioorg. Med. Chem*., 2013; 21: 3723.
12. Gulerman NN, Dogan HN, Rollas S, Johansson C, Celik C, *II Farmaco*., 2001; 56: 953.
13. Maxwell JR, Wasdahl DA, Wolfson AC, *J. Med. Chem*., 1984; 27: 1565.
14. Turan-Zitouni G, Kapalancikli ZA, Erol K, Kilic FS, *II Farmaco*., 1999; 54: 218.
15. Demirbas N, Ugurluoglu R, Demirbas A, *Bioorg. Med. Chem*., 2002; 10: 3717.
16. Paulvannan K, Chen T, Hale R, *Tetrahedron*., 2000; 56: 8071.
17. Kritsanida M, Mouroutsou A, Marakos P, Pouli N, Papakonstantinou GS, Pannecouque C, Witvrouw M, Clercq ED, *II. Farmaco*., 2002; 57: 253.
18. Al-Masoudi IA, Al-Soud YA, Al-Salihi NJ, Al-Masoudi NA, *Chem. Heterocyclic Comp*., 2006; 42: 1377.
19. Turan-Zitouni G, Kaplancikli ZA, Erol K, Kilic FS, *IL Farmaco*, 1999; 54: 218.
20. Karabasanagouda T, Adhikari AV, Shetty NS, *Eur. J. Med. Chem*., 2007; 42: 521.
21. Bhalla M, Hitkari A, Gujrati VR, Bhalla TN, Shanker K, *Eur. J. Med. Chem*., 1994; 29: 713.
22. Badr SMI, Barwa RM, *Bioorg. Med. Chem*., 2011; 19: 4506.
23. Winter CA, Risley EA, Nus GN, Carrageenin-induced edema in hind paw of the rat as assay for anti-inflammatory drugs, *Proc. Soc. Exp. Biol. Med*., 1962; 111: 544.