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1,3,4-OXADIAZOLE ASSOCIATED 1,3,4-THIADIAZOLES: SYNTHESIS, CHARACTERIZATION AND EVALUATION AS ANTIBACTERIAL AGENTS

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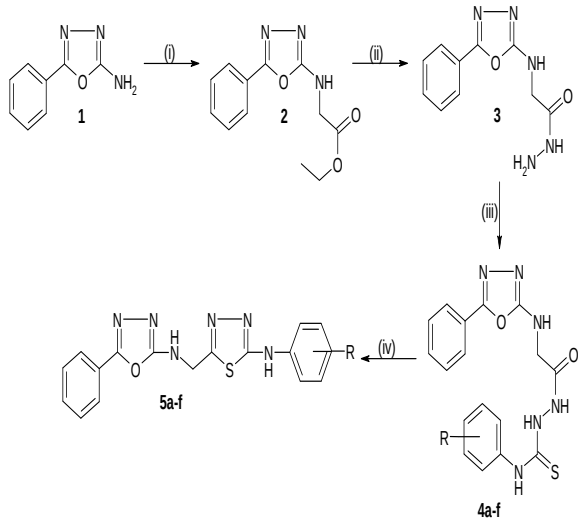
ABSTRACT
A novel series of (5-phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine **(5a)** and its derivatives has been synthesized in good yields by cyclization of *N*-phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazides **(4a-f)** in presence of sulphuric acid. The target compounds have been purified and characterized by using IR, ^{1}H &^{13}C NMR, Mass spectral data and elemental analysis. Further, the title compounds were evaluated for their preliminary *in vitro* antibacterial activity against two representative gram-positive bacteria like *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria such as *Escherichia coli* and *Salmonella typhi*.

KEYWORD:

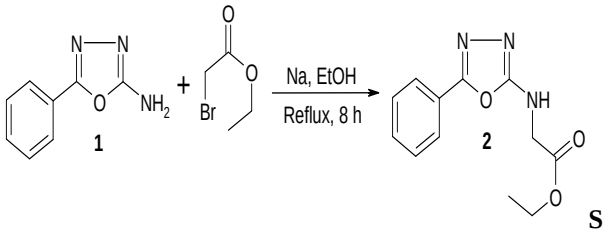


INTRODUCTION
Heterocyclic compounds containing five-membered nucleus possess useful biological effects. 1,3,4-Thiadiazoles exhibit various biological activities, possibly due the present of =N-C-S moiety.[1] In recent years 1, 3, 4-thiadiazoles have received significant attention and have been increasingly investigated due to their diverse range of biological properties such as antifungal[2], antibacterial[3], anticancer[4], anti-inflammatory[5], carbonic anhydrase inhibiting effect[6], anitanxiety, anti-depressant[7], anti-oxidant properties.[8] On the other hand, 1,3,4-oxadiazoles are important because of their versatile biological actions like analgesic[9], antimicrobial[10], antitubercular[11], anticonvulsant[12] and anti-hepatitis B viral activities.[13]

RESULTS AND DISCUSSION
The therapeutic importance of 1,3,4-thiadiazoles and 1,3,4-oxadiazoles prompted us to develop selective molecules with pharmacological activity. In consideration of diverse biological properties of these compounds and in continuation of our interest in the synthesis of biologically active heterocyclics, the aim of the present work was to develop a simple and efficient procedure for the preparation of new 1,3,4-thiadiazole derivatives bearing substituted 1,3,4-oxadiazole. The synthesis of intermediates and target compounds was performed according to the reactions outlined in Scheme 1-4.

Thus, the raw material, 5-phenyl-[1,3,4]oxadiazol-2-ylamine[1] in the initial step, reacts with ethyl bromoacetate and sodium ethoxide under reflux for 8 h with constant stirring furnished the first intermediate, (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester **(2)** in 68% yield (Scheme 1). Analytical and spectroscopic data of compound **2** confirmed this reaction due to the appearance of additional bands and

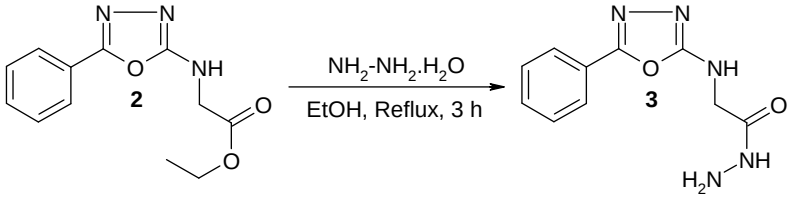
signals derived from the ethyl ester group at the expected values. In the IR spectrum, C=O stretching was observed at 1740 cm^{-1}, which was absent in precursor **1**. The ^{1}H-NMR spectrum shows a signal as singlet at δ 11.12 ppm due to the NH group and the additional signals were identified due to the CH_2-CH_3 group at the expected chemical shift values with equal coupling constant (J = 5.4 Hz). In addition, compound **2** gave relatively stable molecular ion peaks in the corresponding mass spectrum.



S

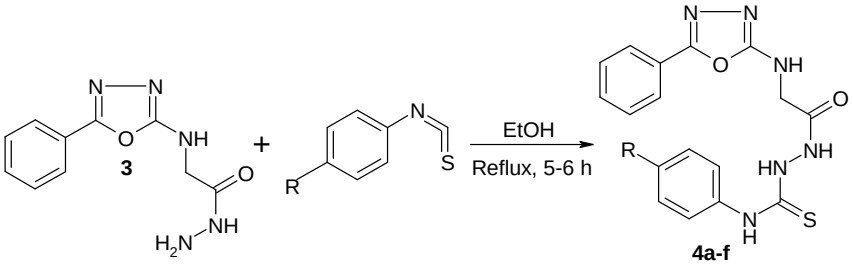
cheme 1

Under reflux of the reaction mixture consisting compound **2** and hydrazine hydrate in ethanol under steady stirring for 3 h yielded the next intermediate, (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide **(3)** in 69% yield (Scheme 2). The spectral and elemental analysis data compound **3** was in accordance with the proposed structure. The IR spectrum showed two additional bands in broad and sharp forms within the range of 3321-3188 cm^{-1} due to the NH_2 and NH groups and these are disappeared in the spectrum of predecessor **2**. Moreover, in the ^{1}H-NMR spectrum, two additional signals as singlet were observed due to the NH_2 and NH group at δ 5.30 ppm (D_2O exchangeable) and δ 11.35 ppm, while the CH_2-CH_3 signals were lost to view. In the MS spectrum, the molecular ion peak at 233 indicated the formation of compounds **3**.



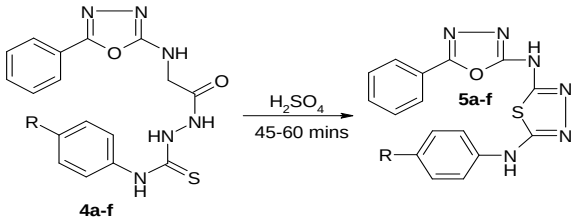
Scheme 2

Reaction of compound **3** with different aryl isothiocyanates in ethanol under reflux on uniform stirring for 5-6 h offered *N*-phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazides **(4a-f)** in 66-73% (Scheme 3). The chemical structures of the series **4a-f** have been established through spectroscopic (IR, ^{1}H &^{13}C-NMR, MS) as well as elemental analysis. In the IR spectra, the stretching band corresponding to the NH_2 group disappeared due to the connection with C=S. In the ^{1}H-NMR spectra, the signal for the new NH group was observed as a singlet between δ 4.48-4.62 ppm along with other signals at anticipated values. The mass spectrum of compounds **4a-f** showed (M^+) peak in agreement with their molecular formulas.



Scheme 3

Finally, the target compounds, (5-phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine **(5a-f)** have been synthesized from the reaction between compound **4a-f** and concentrated H_2SO_4 at room temperature on stable for 45-60 minutes (Scheme 4). The chemical structures of target compounds **5a-f** have been established on the basis IR, ^{1}H & ^{13}C-NMR, MS spectra and elemental analysis. The IR spectra of this series of compounds disclosed the disappearance sharp absorption band corresponding to the C=O of amide group around 1670 cm^{-1}. In the ^{1}H-NMR spectra, no signals of two NH groups and one CH_2 group were recorded at the related δ-chemical shift values due to the participation in cyclization. The MS spectra of the products **5a-f** contained the peaks corresponding to their molecular weights. Eventually, the target compounds were evaluated for their antibacterial activity.



Scheme 4

Antibacterial activity: The antibacterial activity of the newly prepared compounds has been carried out with cup plate method[14] by using nutrient agar medium against two representative gram-positive bacteria viz., *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria viz., *Escherichia coli* and *Salmonella typhi*. Ampicillin sodium was employed as reference for antibacterial study. The test solution was prepared by dissolving 10 mg of compound in 10 ml of DMF. The nutrient agar medium (peptone-5.0 gm, sodium chloride-5.0 gm, beef extract-1.5 gm, yeast extract-1.5 gm, agar-15.0 gm, distilled water up to-1000 ml, pH-7.4 ± 0.2) s sterilized by autoclaving at 121 ^{0}C for 15 mins. The petri plates, tube and flasks plugged with cotton were sterilized in hot-air oven at 160^{0}C for 60 mins. The diameter of zone of inhibition surrounding each of the cups was measured after incubation of the plates at 37 ± 1^{0}C for 24 h. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The zone of inhibition produced by each compound was measured in mm and the results are reported in Figure 1. According to the results, all the tested compounds exhibited significant antibacterial activity with a degree of alteration. Against all the bacterial strains, compounds **5b**, **5c** and **5d** towards *S. aureus* and product **5a** in the direction *E. coli*, **5d** so as to near *B. subtilis* and **5f** close to *S. typhi* disclosed highest activity. Compounds **5a**, **5b** and **5f** have been performed activity with equal potential against *S. aureus*, *E. coli* and *B. subtilis* respectively. Title compound **5d** showed against both strains *S. aureus* and *S. typhi* with same strength. Amid all the target compounds against all microorganisms, compound 5a against *B. subtilis* revealed poor activity. Remaining all the tested compounds showed notable antibacterial activity.

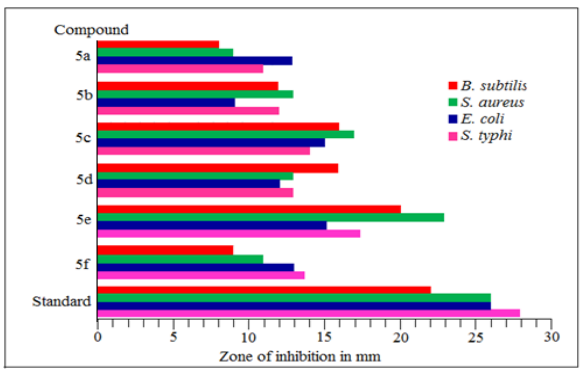


Figure 1: Antibacterial activity of the tested compounds 5a-f

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 (0.03 mol) 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, 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 *N*-phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazides (4a-f)

An aryl isothiocyanate (0.01 mol) was added to a solution of (5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide **(3)** in ethanol (20 ml) and resulted reaction mixture was refluxed with steady stirring for about 5-6 h. After fulfilment of the reaction (scanned by the TLC), reaction mixture was cooled to room temperature to get a solid residue and it was filtered, washed with cold water, dried and recrystallized from ethyl acetate to obtain *N*-phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazides **(4a-f)** in pure form.

Preparation of (5-phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amines (5a-f)

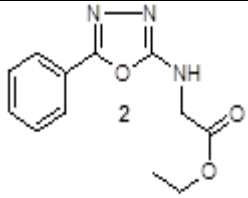
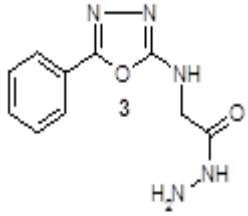
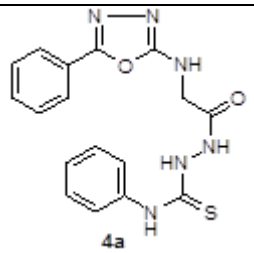
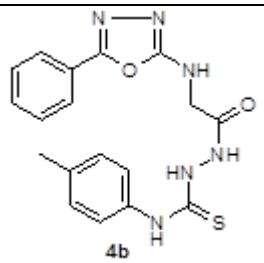
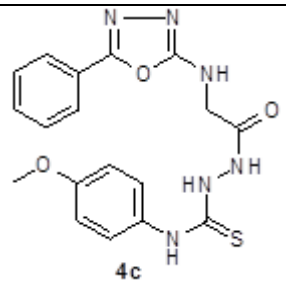
A mixture of *N*-phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazides **(4a-**

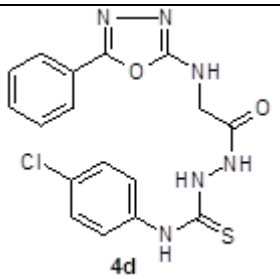
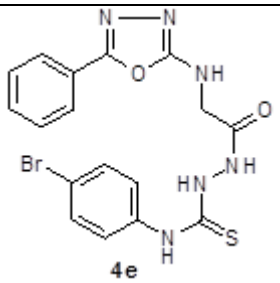
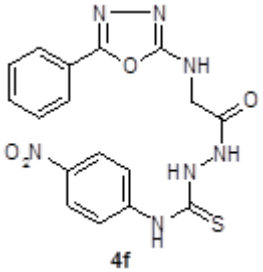
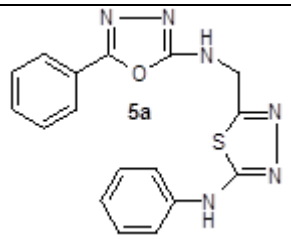
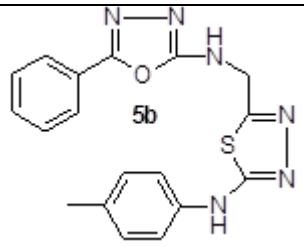
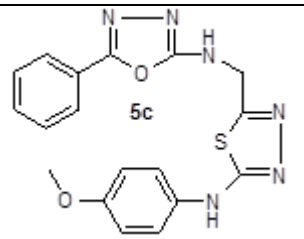
f) (0.01 mol) and cold con. sulfuric acid (20 ml) was stirred at room temperature for 45- 60 minutes. After realization of the reaction (investigated by the TLC), the acquired solution was poured in ice-cold water and neutralized with 10% NaOH to get solid crude and it was filtered, washed with ice-cold water and recrystallized from ethanol to get corresponding pure (5-phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amines **(5a-f)**.

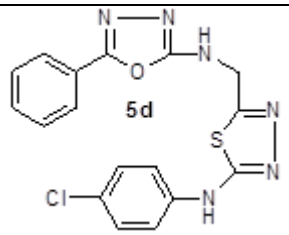
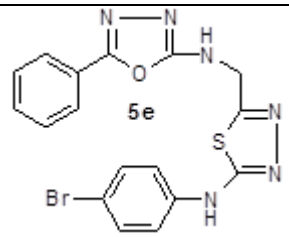
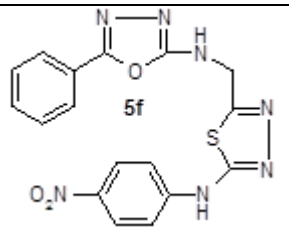
CONCLUSION

In conclusion, a series of new (5-phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine **(5a-f)** was synthesized. The antibacterial activity of the newly synthesized compounds against different bacterial strains has been investigated. All the tested compounds revealed moderate to good antibacterial activity with a degree of variation.

Table 1: Characterization data of synthesized compounds

Compound	Physical, spectral and elemental characterization data
	*(5-Phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid ethyl ester* **(2)**: Yield: 68%, mp: 132-135 °C; IR (KBr, cm^{-1}): 3248 (N-H), 3048 (C–H, Ar), 2965 (C-H, CH_3), 1740 (C=O), 1665, (C=C, Ar), 1456 (C=N), 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, J = 5.4 Hz), 3.85 (s, 2H, NCH_2), 1.24 (t, 3H, CH_3, J = 5.4 Hz); ^{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)**: Yield: 69%, mp: 120-122 °C; IR (KBr, cm^{-1}): 3321 (N-H, NH_2), 3188 (N-H), 3047 (C–H Ar), 2968 (C–H, CH_2), 1672 (C=O), 1650 (C=C, Ar), 1455 (C=N), 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 $C_{10}H_{11}N_5O_2$: C-51.50, H-4.75, N-30.03, O-13.72. Found: C-50.89, H-4.73, N-29.91, O-13.66.
	*N-Phenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4a)**: Yield: 70%, mp: 141-143 °C; IR (KBr, cm^{-1}): 3321 (N-H), 3047 (C–H Ar), 2968 (C–H, CH_2), 1672 (C=O), 1650 (C=C, Ar), 1462 (C=N),1210 (C=S), 1135 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.38 (s, 1H, NH), 10.95 (s, 1H, NH), 7.77-7.23 (m, 10H, Ar–H), 5.26 (s, 1H, NH), 4.55 (s, 1H, NH), 3.82 (s, 2H, NCH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 175.6, 161.2, 145.3, 142.7, 138.3, 135.2, 132.0, 128.6, 126.5, 125.3, 123.7, 120.6, 66.2; MS: *m/z* 368 (M^+); Elemental analysis: Calculated for $C_{17}H_{16}N_6O_2S$: C-55.42, H-4.38, N-22.81, O-8.69, S-8.70. Found: C-54.86, H-4.35, N-22.69, O-8.60, S-8.66.
	*N-(4-Methylphenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4b)**: Yield: 71%, mp: 119-121 °C; IR (KBr, cm^{-1}): 3336 (N-H), 3042 (C–H Ar), 2972 (C–H, CH_2), 1675 (C=O), 1645 (C=C, Ar), 1458 (C=N), 1222 (C=S), 1141 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.26 (s, 1H, NH), 10.85 (s, 1H, NH), 7.73-7.33 (m, 5H, Ar–H), 7.55 (d, 2H, J = 7.2 Hz, Ar-H), 7.40 (d, 2H, J = 7.2 Hz, Ar-H), 5.22 (s, 1H, NH), 4.58 (s, 1H, NH), 3.79 (s, 2H, NCH_2), 2.15 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 172.1, 160.3, 144.0, 142.0, 137.0, 135.0, 132.1, 129.4, 128.0, 123.0, 120.0, 118.63, 65.7, 23.6; MS: *m/z* 382 (M^+); Elemental analysis: Calculated for $C_{18}H_{18}N_6O_2S$: C-56.53, H-4.74, N-21.97, O-8.37, S-8.38. Found: C-55.98, H-4.72, N-21.65, O-8.35, S-8.35.
	*N-(4-Methoxyphenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4c)**: Yield: 66%, mp: 136-138 °C; IR (KBr, cm^{-1}): 3318 (N-H), 3055 (C–H Ar), 2972 (C–H, CH_2), 1668 (C=O), 1644 (C=C, Ar), 1462 (C=N), 1222 (C=S), 1141 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.22 (s, 1H, NH), 10.89 (s, 1H, NH), 7.70-7.38 (m, 5H, Ar–H), 7.58 (d, 2H, J = 7.0 Hz, Ar-H), 7.43 (d, 2H, J = 7.0 Hz, Ar-H), 5.33 (s, 1H, NH), 4.62 (s, 1H, NH), 3.81 (s, 2H, NCH_2), 2.58 (s, 3H, OCH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 174.6, 161.6, 145.5, 142.4, 137.1, 135.0, 132.9, 129.7, 128.1, 126.4, 124.7, 122.7, 67.6, 43.4; MS: *m/z* 398 (M^+); Elemental analysis: Calculated for $C_{18}H_{18}N_6O_3S$: C-54.26, H-4.55, N-21.09, O-12.05, S-8.05. Found: C-53.85, H-4.53, N-20.95, O-11.96, S-8.01.

 4d	*N-(4-Chlorophenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4d)**: Yield: 68%, mp: 145-147 °C; IR (KBr, cm^{-1}): 3332 (N-H), 3035 (C–H Ar), 2975 (C–H, CH_2), 1668 (C=O), 1647 (C=C, Ar), 1460 (C=N), 1222 (C=S), 1139 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.18 (s, 1H, NH), 10.80 (s, 1H, NH), 7.75-7.28 (m, 5H, Ar–H), 7.62 (d, 2H, J = 7.4 Hz, Ar-H), 7.45 (d, 2H, J = 7.4 Hz, Ar-H), 5.29 (s, 1H, NH), 4.57 (s, 1H, NH), 3.77 (s, 2H, NCH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 171.2, 160.7, 148.4, 143.2, 136.1, 134.9, 131.9, 129.4, 127.1, 125.3, 124.5, 119.5, 64.4; MS: *m/z* 402 (M^+); Elemental analysis: Calculated for $C_{17}H_{15}ClN_6O_2S$: C-50.68, H-4.75, Cl-8.80, N-20.86, O-7.94, S-7.96. Found: C-49.81, H-4.73, Cl-8.72, N-20.65, O-7.90, S-7.91.
 4e	*N-(4-Bromophenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4e)**: Yield: 70%, mp: 155-157 °C; IR (KBr, cm^{-1}): 3315 (N-H), 3050 (C–H Ar), 2975 (C–H, CH_2), 1677 (C=O), 1663 (C=C, Ar), 1466 (C=N), 1220 (C=S), 1147 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.23 (s, 1H, NH), 10.72 (s, 1H, NH), 7.70-7.35 (m, 5H, Ar–H), 7.60 (d, 2H, J = 7.3 Hz, Ar-H), 7.42 (d, 2H, J = 7.3 Hz, Ar-H), 5.25 (s, 1H, NH), 4.53 (s, 1H, NH), 3.77 (s, 2H, NCH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 172.0, 161.8, 147.2, 144.7, 142.0, 135.4, 132.7, 130.5, 128.3, 125.0, 122.4, 116.4, 62.2; MS: *m/z* 446 (M^+); Elemental analysis: Calculated for $C_{17}H_{15}BrN_6O_2S$: C-45.65, H-3.38, Br-17.86, N-18.79, O-7.15, S-7.17. Found: C-45.16, H-3.37, Br-17.78, N-18.70, O-7.14, S-7.16.
 4f	*N-(4-Nitrophenylcarbamothioyl)-5-phenyl-[1,3,4]oxadiazol-2-ylamino)-acetic acid hydrazide* **(4f)**: Yield: 73%, mp: 143-135 °C; IR (KBr, cm^{-1}): 3328 (N-H), 3039 (C–H Ar), 2971 (C–H, CH_2), 1680 (C=O), 1658 (C=C, Ar), 1461 (C=N), 1545 (N=O), 1223 (C=S), 1129 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.13 (s, 1H, NH), 10.52 (s, 1H, NH), 7.73-7.31 (m, 5H, Ar–H), 7.65 (d, 2H, J = 7.1 Hz, Ar-H), 7.38 (d, 2H, J = 7.1 Hz, Ar-H), 5.20 (s, 1H, NH), 4.48 (s, 1H, NH), 3.81 (s, 2H, NCH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 171.3, 163.2, 145.3, 143.1, 137.1, 134.9, 131.2, 128.4, 126.9, 125.0, 122.6, 116.2, 63.2; MS: *m/z* 413 (M^+); Elemental analysis: Calculated for $C_{17}H_{15}N_7O_4S$: C-49.39, H-3.66, N-23.72, O-15.48, S-7.76. Found: C-48.92, H-3.65, N-23.58, O-15.41, S-7.75.
 5a	*5-Phenylamino-[1,3,4]thiadiazol-2-ylmethyl)-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5a)**: Yield: 73%, mp: 131-133 °C; IR (KBr, cm^{-1}): 3185 (N-H), 3066 (C–H Ar), 2972 (C-H, CH_2), 1575 (C=C, Ar), 1441 (C=N), 1241 (C–S), 1158 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.23 (s, 1H, NH), 7.68-7.35 (m, 10H, Ar–H), 4.85 (s, 1H, NH), 3.95 (s, 2H, CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): δ: 142.1, 138.5, 136.6, 135.6, 132.0, 129.2, 128.2, 126.8, 125.5, 123.7, 120.8, 116.3, 45.3; MS: *m/z* 350 (M^+); Elemental analysis: Calculated for $C_{17}H_{14}N_6OS$: C-58.27, H-4.03, N-23.98, O-4.57, S-9.15. Found: C-57.83, H-4.02, N-23.65, O-4.55, S-9.10.
 5b	*5-(4-Methyl-phenylamino)-[1,3,4]thiadiazol-2-ylmethyl]-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5b)**: Yield: 70 %, mp: 146-148 °C, IR (KBr, cm^{-1}): 3172 (N-H), 3055 (C–H Ar), 2975 (C-H, CH_2), 1578 (C=C, Ar), 1445 (C=N), 1244 (C–S), 1162 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.26 (s, 1H, NH), 7.61-7.39 (m, 5H, Ar–H), 7.52 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.38 (d, 2H, *J* = 7.0 Hz, Ar-H), 4.77 (s, 1H, NH), 3.91 (s, 2H, CH_2), 2.25 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 143.7, 139.7, 137.6, 133.4, 129.7, 127.2, 125.3, 123.7, 122.4, 121.8, 117.1, 113.6 46.8, 25.8; MS: *m/z* 364 (M^+); Elemental analysis: Calculated for $C_{18}H_{16}N_6OS$: C-59.32, H-4.43, N-23.06, O-4.39, S-8.80. Found: C-59.02, H-4.42, N-22.89, O-4.38, S-8.78.
 5c	*[5-(4-Methoxy-phenylamino)-[1,3,4]thiadiazol-2-ylmethyl]-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5c)**: Yield: 71 %, mp: 138-140 °C, IR (KBr, cm^{-1}): 3180 (N-H), 3062 (C–H Ar), 2968 (C-H, CH_2), 1571 (C=C, Ar), 1438 (C=N),1238 (C–S), 1155 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H, NH), 7.66-7.36 (m, 5H, Ar–H), 7.45 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.36 (d, 2H, *J* = 7.3 Hz, Ar-H), 4.69 (s, 1H, NH), 3.95 (s, 2H, CH_2), 2.52 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.2, 138.4, 137.2, 135.6, 134.7, 128.7, 126.3, 124.3, 121.8, 120.7, 117.4, 115.6, 46.8, 44.2; MS: *m/z* 380 (M^+); Elemental analysis: Calculated for $C_{18}H_{16}N_6O_2S$: C-56.83, H-4.24, N-22.09, O-8.41, S-8.43. Found: C-5612, H-4.23, N-21.89, O-8.39, S-8.41.

	*[5-(4-Chloro-phenylamino)-[1,3,4]thiadiazol-2-ylmethyl]-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5d)**: Yield: 69 %, mp: 129-131 °C, IR (KBr, cm^{-1}): 3192 (N-H), 3073 (C–H Ar), 2978 (C-H, CH_2), 1582 (C=C, Ar), 1446 (C=N), 1246 (C–S), 1165 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (s, 1H, NH), 7.70-7.39 (m, 5H, Ar–H), 7.48 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.39 (d, 2H, *J* = 7.5 Hz, Ar-H), 4.72 (s, 1H, NH), 3.88 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.3, 139.4, 136.2, 134.2, 132.5, 128.4, 125.7, 122.0, 121.7, 120.5, 119.1, 116.2, 43.9; MS: *m/z* 384 (M^+); Elemental analysis: Calculated for $C_{17}H_{13}ClN_6OS$: C-53.06, H-3.40, Cl-9.21, N-21.84, O-4.16, S-8.33. Found: C-52.95, H-3.39, Cl-9.19, N-21.62, O-4.15, S-8.32.
	*5-(4-Bromo-phenylamino)-[1,3,4]thiadiazol-2-ylmethyl]-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5e)**: Yield: 66 %, mp: 133-135 °C, IR (KBr, cm^{-1}): 3180 (N-H), 3061 (C–H Ar), 2968 (C-H, CH_2), 1570 (C=C, Ar), 1437 (C=N), 1236 (C–S), 1154 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.30 (s, 1H, NH), 7.66-7.32 (m, 5H, Ar–H), 7.45 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.36 (d, 2H, *J* = 7.2 Hz, Ar-H), 4.70 (s, 1H, NH), 3.85 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.7, 138.2, 136.4, 134.2, 131.2, 128.5, 126.2, 121.4, 120.2, 119.8, 118.7, 117.3, 43.0; MS: *m/z* 428 (M^+); Elemental analysis: Calculated for $C_{17}H_{13}BrN_6OS$: C-47.56, H-3.05, Br-18.61, N-19.58, O-3.73, S-7.47. Found: C-47.12, H-3.04, Br-18.49, N-19.38, O-3.72, S-7.44.
	*[5-(4-Nitro-phenylamino)-[1,3,4]thiadiazol-2-ylmethyl]-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine* **(5f)**: Yield: 71 %, mp: 122-124 °C, IR (KBr, cm^{-1}): 3189 (N-H), 3070 (C–H Ar), 2977 (C-H, CH_2), 1582 (C=C, Ar), 1545 (N=O), 1446 (C=N),1245 (C–S), 1162 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.25 (s, 1H, NH), 7.60-7.37 (m, 5H, Ar–H), 7.49 (d, 2H, *J* = 7.0 Hz, Ar-H), 7.40 (d, 2H, *J* = 7.0 Hz, Ar-H), 4.66 (s, 1H, NH), 3.80 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.7, 139.7, 136.2, 134.2, 131.3, 128.4, 125.6, 122.2, 120.7, 119.2, 117.3, 116.7, 44.2; MS: *m/z* 395 (M^+); Elemental analysis: Calculated for $C_{17}H_{13}N_7O_3S$: C-51.64, H-3.31, N-24.80, O-12.14, S-8.11. Found: C-51.25, H-3.30, N-24.68, O-12.09, S-8.10.

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