Synthesis of Potent Antibacterial Agents Derived from 5-[1-(Phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol

[1] Aziz-Ur-Rehman*, [1] Hira Khalid, [1] Muhammad Athar Abbasi, [1] Samreen Gul,
[2] Khalid Mohammed Khan, [3] Irshad Ahmad and [3] Shafia Arshad
[1]*Department of Chemistry, Government College University, Lahore-54000, Pakistan.*
[2]*H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan.*
[3]*Faculty of Pharmacy and Alternative Medicine; The Islamia University of Bahawalpur, Bahawalpur-63100, Pakistan.*
azizryk@yahoo.com*; rehman@gcu.edu.pk

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Summary: Due to pharmacological importance of 1,3,4-Oxadiazoles, a new series of *S*-substituted derivatives of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol **(4a-v)** was synthesized. The reaction of benzenesulfonyl chloride with ethyl isonipecotate yielded ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate **(1)**, which was further converted into 1-(Phenylsulfonyl) piperidine-4-carbohydrazide **(2)** and 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol **(3)** in the presence of hydrazine hydrate and CS_2 along with KOH respectively. The target compounds (**4a-v)** were synthesized by the reaction of compound **3** with different electrophiles in the presence of DMF and sodium hydride. The structures of all the synthesized compounds were confirmed *via* IR, ^{1}H-NMR & EI-MS spectral data and were evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria. It was observed that the electrophilic substitution influenced significantly for the variation of antibacterial activity from moderate to excellent level.

Keywords: Ethyl isonipecotate, sulfonamide, 1,3,4-Oxadiazole, antibacterial activity.

Introduction

1,3,4-Oxadiazole belongs to the heterocyclic class of compounds and has gained attention for last two decades due to wide variety of biological interactions. These heterocyclic compounds demonstrate antibacterial, anticonvulsant & anticancer activities; and also used to wrestle infections involving AIDS [1-4]. 2,5-disubstituted-1,3,4-Oxadiazoles exhibit remarkable anti-depressive, anticonvulsive, anti-inflammatory, anti-mitotic, hypoglycemic, antifungal, antimicrobial, analgesic, herbicidal, insecticidal and anticancer activities [5-9]. In addition, 1,3,4-Oxadiazole has played a vital role in the improvement of heterocyclic chemistry and also in expansion of organic synthesis. 2,5-disubstituted-1,3,4-Oxadiazole can be expediently synthesized by the treatment of piperidine-4-carbohydrazide with carbon disulfide in strong basic media [10, 11].

This paper reports the synthesis and biological screening of some new 1,3,4-Oxadiazole compounds derived from ethyl isonipecotate. In continuation of our previous work [12-16], we have reported the synthesis of new 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol **(3)** compound bearing a piperidine ring which was subjected to *S*-substitution by reacting with different alkyl/aralkyl halides. Further, *in vitro* antibacterial screening of these synthesized derivatives against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*Shigella sonnei, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhi*) using standard procedure. The research work was a successful effort of fusion of two highly active rings as one unit and to find out biologically active compounds.

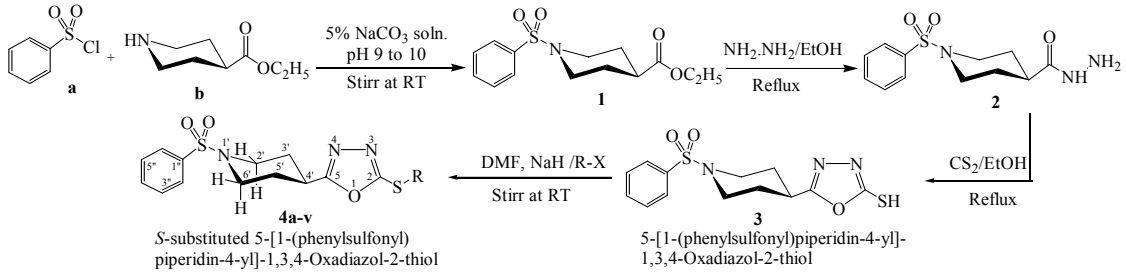
Results and discussion

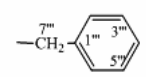
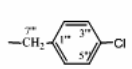
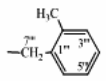
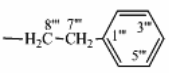
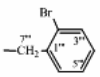
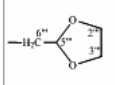
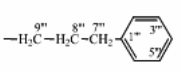
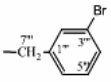
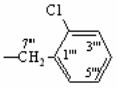
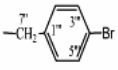
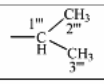
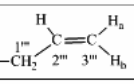
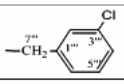
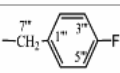
In the undertaken research, *S*-substituted-1,3,4-Oxadiazole derivatives were synthesized in a four step synthesis and all were screened against different Gram-positive and Gram-negative bacteria. In the first step, the starting compound ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate **(1)** was prepared by the stirring of ethyl isonipecotate (**a**) and benzenesulfonyl chloride (**b**) at dynamic pH control in aqueous media for 3-4 hrs [17, 18]. In the second step, the synthesized compound **1** was converted to 1-(phenylsulfonyl)piperidine-4-carbohydrazide **(2)** by refluxing with hydrated hydrazine in methanol as solvent for 5-6 hrs. The compound **2** was then cyclized into 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol **(3)** by refluxing with CS_2 in a basic media utilizing ethanol at the third step in 4-5 hrs. The product **3** was obtained after the addition of acid. The fourth step comprises the synthesis of all

derivatives **4a-v** from the compound **3** with different electrophiles in the presence of DMF and sodium hydride (NaH) as shown in scheme-1. Complete conversion was achieved within 2-3 hours by stirring at room temperature. The products were isolated by adding cold water in the reaction mixture and subsequently through filtration or solvent extraction by *n*-butanol. The structure of the synthesized compounds **1**, **2**, **3** and *S*-substituted derivatives **4a-v** of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (**3**) were corroborated by IR, ^{1}H-NMR & EI-MS spectral data as described in experimental section. The mass fragmentation pattern of 4-[5-(benzylthio)-1,3,4-oxadiazol-2-yl]-1-(phenylsulfonyl)piperidine (**4k**) is clearly elaborated in Fig. 1. Parent compound **3** was synthesized as a white powder solid with 88% yield and having a melting point 210-213^{o}C. The molecular formula $C_{13}H_{15}N_3O_3S_2$ was established by molecular ion peak at *m/z* 325 in EI-MS and by counting the number of protons in its ^{1}H-NMR spectrum. The infrared spectrum showed absorption bands at 3035 cm^{-1}, 2250 cm^{-1}, 1593 cm^{-1} and 1326 cm^{-1} which were assigned to C-H (aromatic stretching), S-H (stretching), C=N (stretching) and -SO_2 (stretching of sulfonyl group) respectively. The EI-MS gave characteristic peaks at *m/z* 224 and 77 which were attributed to the loss of (phenylsulfonyl)piperidine and phenyl groups respectively. Base peak was appeared at *m/z* 156 characteristic of benzenesulfamoyl group. In the ^{1}H-NMR spectrum, the signals in the aromatic region appeared at □7.80 (dd, *J* = 7.8, 1.8 Hz, 2H, H-2" & 6") and 7.67-7.65 (m, 3H, H-3" to 5") which were assigned to the protons of monosubstituted benzenesulfonyl ring. In the aliphatic region of the ^{1}H-NMR spectrum, singles resonated at □3.75 (t, *J* = 3.6 Hz, 2H, H_{eq}-2' & 6'), 3.71 (t, *J* = 3.6 Hz, 2H, H_{ax}-2' & 6'), 2.80-2.75 (m, 1H, H-4') and 1.80-1.76 (m, 4H, H-3', 5') which were assigned to the protons of piperidine nucleus. The ^{13}C-NMR spectrum (both broad band and distorsionless enhancement by polarization transfer) showed nine carbon signals; three quaternary carbons, four methine carbons and two methylene carbons. Downfield signals appeared at δ_C (ppm) 180.3, 168.3 and 137.3 which were assigned to the two quaternary carbons, C-2 and C-5 of Oxadiazole ring and one quaternary carbon, C-1" of aromatic ring respectively. The signals appeared at δ_C (ppm) 130.4 and 128.7 with double intensities and at δ_C (ppm) 134.2 with single intensity were allotted to methine carbons, C-3" & C-5" and C-2" & C-6" and C-4" respectively. Further, the two upfield signals appeared at δ_C (ppm) 46.3 and 29.1 with double intensities were designated for C-2' & C-6' and C-3' & C-5' respectively for the piperidine ring while the methine carbon signal with single intensity appeared at δ_C (ppm) 33.6. On the basis of above mentioned cumulative evidences, the structure of **3** was assigned 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol. Likewise, the structures of other compounds were characterized.

Antibacterial Activity

All the synthesized compounds were screened against Gram-positive bacteria (*B. subtilis, S. aureus*) and Gram-negative bacteria (*S. sonnei, E. coli, P. aeruginosa* and *S. typhi*) using Ampicillin and Ciprofloxacin as reference standard. All compounds showed varying degree of antimicrobial activity as given in Table-1. It is clearly evident from MIC values that some of the compounds were found to be more potent than Ciprofloxacin and Ampicillin, the reference standards. A close observation of these MIC values revealed that overall the compounds **4b**, **4d**, **4e**, **4g**, **4k**, **4l**, **4n**, **4o**, **4p**, **4q**, **4r** and **4u** showed good inhibitory potential against all the strains of Gram-positive and Gram-negative bacteria. Other compounds also showed moderate inhibitory potential. Compound **4t** was found to be inactive against all bacterial strains probably due the presence of fluorine at para position of the aromatic ring which attracts the electronic density of benzene ring towards it being the most electronegative element of halogen series. For Gram-positive bacteria, compounds **4b**, **4k**, **4l**, **4n**, **4q**, **4r** and **4u** were more active than the reference standard Ampicillin against both *B. subtilis* and *S. aureus*. Among these, **4b** and **4k** showed same inhibition behavior as that for the reference standard Ciprofloxacin against both Gram-positive bacteria but **4q** and **4u** showed same behavior against *B. subtilis* only. *S. aureus* was efficiently inhibited by **4n** and **4u** with respect to both Ampicillin and Ciprofloxacin. Likewise, *B. subtilis* was expeditiously inhibited by **4r** only relative to both reference standards. The compounds **1**, **2**, **4f** and **4j** were active against *B. subtilis* only and **4v** was active against *S. aureus* only. **4h**, **4i** and **4t** remained inactive against both Gram-positive bacteria. For Gram-negative bacteria, the most of the synthesized compounds showed inhibitory action. **4b**, **4l**, **4r** and **4u** were more active against *P. aeruginosa* than both the reference standards. Some of the synthesized compounds were inactive like **2** and **4m** against *E. coli*, **2** and **4a** against *S. sonnei* etc. These observations revealed us that alkyl and ortho halo-substitutions favored the antibiotic activities. The new drug candidates submitted in this study would be the remarkable contribution in the field of antibiotics.



C. No.	R	C. No.	R	C. No.	R	C. No.	R	C. No.	R
4a	$-CH_3$	4f	$-CH_2-CH_2-CH_2-CH_3$	4k		4p		4u	
4b	$-CH_2-CH_3$	4g	$-CH(CH_3)-CH_2-CH_3$	4l		4q		4v	
4c	$-CH_2-CH_2-Br$	4h	$-CH_2-CH_2-CH_2-CH_2-CH_3$	4m		4r			
4d	$-CH_2-CH_2-CH_3$	4i	$-CH_2-CH_2-CH_2-CH_2-CH(CH_3)-CH_3$	4n		4s			
4e		4j		4o		4t			

Scheme-1: Outline for the synthesis of *S*-substituted derivatives of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole-2-thiol (4a-v).

Experimental

General

Melting points of the synthesized compounds were recorded on a Griffin and George melting point apparatus by open capillary tube and were uncorrected. Purity was checked on thin layer chromatography (TLC) on pre-coated silica gel G-25-UV_{254} plates with different polarity solvent systems using ethyl acetate and *n*-hexane giving single spot. Identification of spots was carried out at 254 nm UV Lamp, and by ceric sulphate reagent. Elemental analysis was done on EAGER 300 for EA 1112 with K factor method. The I.R. spectra were recorded in KBr pellet method on a Jasco-320-A spectrophotometer (wave number in cm^{-1}). Nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Bruker spectrometers operating at 300 MHz. ^{13}C-NMR spectra were recorded at 75 MHz. Chemical shifts are given in ppm. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer, with a data system. Elemental analyses were carried out on a Perkin–Elmer-2400 model CHN analyzer.

Preparation of ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate in aqueous media **(1)**

Ethyl isonipecotate (20.0 mL, 10.0 mmol; **a**) was suspended in 50 mL water and the pH was maintained at 9.0 by adding basic aqueous solution of Na_2CO_3 (5) at 0-5^{o}C. Then, benzenesulfonyl chloride (29.0 mL; 10.0 mmol; **b**) was added in the reaction mass slowly over 10-15-minutes. After that the temperature of the reaction mixture was allowed to rise slowly to 30 °C (RT). The reaction mixture was stirred and monitored with TLC for the completion. At the end of reaction, conc. HCl (2 mL, 11M) was added slowly to adjust the pH to 2.0 to washout the undesirable contents of reaction mixture. The reaction mass was cooled to RT and the off-white precipitates were filtered and washed with distilled water to afford the title compound **1** on drying.

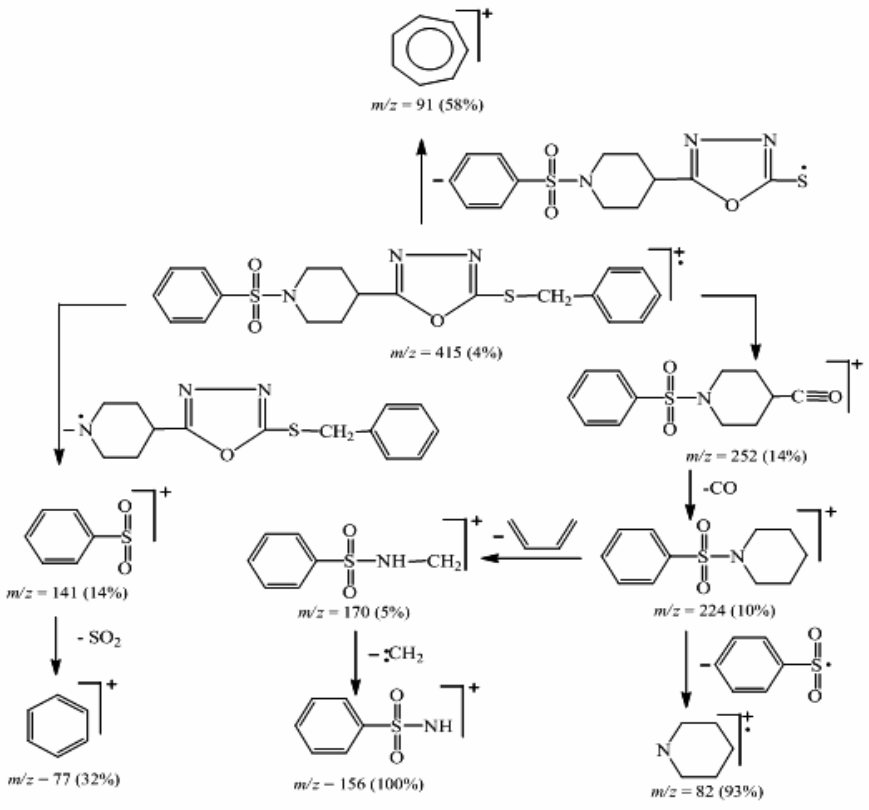


Fig. 1: MS pattern of 4-[2-(Benzylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (4k).

Table-1: Results of Antibacterial activity of the tested compounds.

Compound	MIC (µg/mL)					
	***B. subtilis* (+)**	***S. aureus* (+)**	***E. coli* (-)**	***S. sonnei* (-)**	***S.typhi* (-)**	***P. aureginosa* (-)**
1	19.83±0.04	-	14.28 ±0.06	18.67±0.03	11.7 ±0.32	14.66 ±0.23
2	18.36±0.37	-	-	-	18.06±0.70	16.08 ±0.11
3	14.16±0.27	13.50 ±0.22	13.57 ±0.27	15.58±0.11	-	15.33 ±0.31
4a	16.33±0.11	13.49±0.11	19.19 ±0.44	-		-
4b	9.53±0.44	9.63±0.10	10.47±0.1	8.74±0.25	11.11±0.12	10.22 ±0.07
4c	11.36±0.20	12.52±0.21	13.08 ±0.11	16.72±0.31	12.53±0.22	-
4d	15.34±0.22	12.52±0.73	18.00 ±0.16	14.08 ±0.21	11.86±0.55	12.52 ±0.11
4e	11.16±0.01	13.59±0.01	11.76 ±0.16	14.29±0.31	13.34±0.12	13.19 ±0.02
4f	16.15±0.11	-	13.19 ±0.28	17.75±0.42	-	-
4g	13.16±0.51	17.43±0.24	12.11 ±0.27	13.19±0.27	11.24±0.25	17.43 ±0.13
4h	-	-	16.23 ±0.14	14.29±0.41	-	-
4i	-	-	14.79 ±0.25	15.55±0.53	14.99±0.34	-
4j	12.62±0.19	-	13.92 ±0.19	15.06±0.41	-	-
4k	8.84±0.41	9.47±0.02	10.49±0.51	10.19 ±0.37	10.55±0.02	10.47 ±0.52
4l	11.19±0.42	11.46±0.22	7.70 ±0.12	11.38±0.33	10.40±1.23	9.80±0.01
4m	13.11±0.11	10.78±0.09	-	14.00 ±0.29	14.49±0.41	10.78 ±0.46
4n	10.86±0.12	7.51±0.06	9.76 ±0.11	9.08±0.09	11.22±0.50	11.51 ±0.31
4o	16.43±0.21	15.33±0.11	16.32±0.53	15.28±0.43	13.98±0.90	15.33 ±0.32
4p	18.09±0.83	17.40±0.28	17.40 ±0.29	12.89 ±0.20	14.52±0.24	17.40 ±0.00
4q	8.47±0.07	10.33±0.21	17.77 ±0.20	7.48±0.11	14.36±1.15	20.57 ±0.18
4r	7.74±0.12	10.10±0.29	11.36 ±0.00	8.412±0.18	10.07±0.43	9.10 ±0.11
4s	10.81±0.17	14.28±0.24	10.53 ±0.10	15.38±0.14	12.20±0.31	-
4t	-	-	-	-	-	-
4u	9.11±0.08	7.52±0.00	8.57 ±0.31	9.74 ±0.27	10.05±0.52	8.52 ±0.09
4v	-	12.11±0.19	16.13 ±0.57	13.92±0.52	-	-
Ampicillin	**14.92±0.29**	**14.69 ±0.31**	**11.32±0.13**	**15.92±0.16**	**-**	**16.86±0.31**
Ciprofloxacin	**8.36 ± 0.12**	**9.42 ± 0.11**	**8.21 ± 0.02**	**7.31 ± 0.08**	**7.59 ± 0.11**	**11.03 ± 0.10**

Note: MIC (minimum inhibitory concentration) values of compounds were calculated using EZ–Fit Perella Scientific Inc. Amherst, USA

Preparation of 1-(phenylsulfonyl) piperidine-4-carbohydrazide **(2)**

Ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate (0.03 mol, 10 g; **1**) was dissolved in 50 mL of methanol in the round bottom flask and mixture was cooled to 0-5°C. 80% Hydrazine hydrate (30 mL) was added drop wise in reaction mixture and the solution was stirred for 5-6 hrs at temperature 0-5°C. Reaction completion was monitored by TLC. At the end of reaction excess solvent was removed from reaction mixture by distillation to get white crystalline product **2** which was filtered off and washed with *n*-hexane.

Preparation of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol **(3)**

Carbohydrazide (8.0 g, 0.028 mol; **2**) was dissolved in absolute ethanol (30 mL) in a 500 mL round bottom flask. Carbon disulfide (12.0 mL, 0.15 mol) was then added to the solution followed by the addition of excess potassium hydroxide (4.0 g, 0.88 mol). This reaction mixture was properly stirred and refluxed for 4-5 hours. Color of solution was changed from yellow to milky white with the progress of reaction. Hydrogen sulfide gas was evolved during this reaction. After the formation of precipitates, the mixture was diluted with distilled water (50 mL) and acidified with dilute hydrochloric acid to pH 2-3 to remove the unwanted mixture contents. The precipitates of product **3** were filtered, washed with water and re-crystallized from ethanol.

General procedure for the synthesis of S-substituted-1,3,4-oxadiazole derivatives **(4a-v)**

The calculated amount of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (0.032g, 0.1 mmol; **3**) was taken in a round bottom flask (50 mL). *N,N*-dimethyl formamide (DMF, 10 mL) was added to dissolve it, followed by the addition of sodium hydride (0.002g, 0.1 mmol) to the mixture. The mixture was stirred for 30 minutes at room temperature (30 °C) and then the alkyl/aralkyl halides were added slowly. The solution was further stirred for 2-3 hours. The progress of reaction was monitored *via* TLC till single spot. Distilled water was added to the flask and the products **4a-v** was recovered by filtration or solvent extraction.

Spectral Characterization of the synthesized compounds

Ethyl 1-(phenylsulfonyl)piperidine-4-carboxylate (**1**)

Creamy white powder solid; yield 90%; m.p: 60-62; Molecular formula: $C_{14}H_{19}NO_4S$; Mol. Wt. 297; IR (KBr, cm^{-1}) ν_{max}: 3015, 2925, 1531, 1329, 1760, 1640; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.78 (dd, J = 7.8, 1.8 Hz, 2H, H-2', 6'), 7.68-7.63 (m, 1H, H-4'), 7.62 (dd, J = 7.5, 1.8 Hz, 2H, H-3', 5'), 4.11 (q, J = 7.2 Hz, 2H, O-CH_2), 3.64 (t, J = 3.6 Hz, 2H, H_{eq}-2 & 6), 3.59 (t, J = 3.6 Hz, 2H, H_{ax}-2 & 6), 2.13-2.00 (m, 1H, H-4), 1.75-1.70 (m, 4H, H-3, 5), 1.20 (t, J = 6.9 Hz, 3H, CH_3); EIMS *m/z* (%): 297 (M^+, 7), 224 (10), 156 (90), 141 (14), 77 (32), 82 (100); Anal. Calcd for $C_{14}H_{19}NO_4S$: C 56.55, H 6.44, N 4.71, S 10.78; found C 56.21, H 6.22, N 5.12, S 11.78.

1-(Phenylsulfonyl)piperidine-4-carbohydrazide (**2**):

White Crystals; Yield 80%; m.p: 119; Molecular formula: $C_{12}H_{19}N_3O_3S$; Mol. Wt. 283; IR (KBr, cm^{-1}) ν_{max}: 3310, 3018, 2926, 1529, 1325, 1630; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.85 (s, NH-CO), 7.78 (dd, J = 7.8, 1.8 Hz, 2H, H-2', 6'), 7.66-7.63 (m, 3H, H-3' to 5'), 3.79 (t, J = 3.6 Hz, 2H, H_{eq}-2 & 6), 3.75 (t, J = 3.6 Hz, 2H, H_{ax}-2 & 6), 2.12-1.99 (m, 1H, H-4), 1.79-1.75 (m, 4H, H-3, 5); EIMS *m/z* (%): 283 (M^+, 13), 252 (10), 224 (12), 156 (100), 141 (12), 77 (30); Anal. Calcd for $C_{12}H_{19}N_3O_3S$: C 50.87, H 6.05, N 14.83, S 11.32; found C 51.21, H 6.01, N 14.12, S 11.15.

5-[1-(Phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (**3**):

White powder solid; Yield 88%; m.p: 210-213; Molecular formula: $C_{13}H_{15}N_3O_3S_2$; Mol. Wt. 325; IR (KBr, cm^{-1}) ν_{max}: 3035, 2250, 1593, 1326; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.80 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.67-7.65 (m, 3H, H-3" to 5"), 3.75 (t, J = 3.6 Hz, 2H, H_{eq}-2' & 6'), 3.71 (t, J = 3.6 Hz, 2H, H_{ax}-2' & 6'), 2.80-2.75 (m, 1H, H-4'), 1.80-1.76 (m, 4H, H-3', 5'); EIMS *m/z* (%): 325 (M^+, 8), 252 (14), 224 (10), 157 (14), 156 (100), 141 (14), 82 (93), 77 (31), 55 (12); Anal. Calcd for $C_{13}H_{15}N_3O_3S_2$: C 46.14, H 4.52, N 13.45, S 20.53; found C 41.28, H 4.42, N 13.22, S 24.16.

4-[2-(Methylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4a**):

White powder; Yield 75%; m.p: 88-90; Molecular formula: $C_{14}H_{17}N_3O_3S_2$; Mol. Wt. 339; IR (KBr, cm^{-1}) ν_{max}: 3033, 2955, 1570, 1598, 1329; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.78 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 3.72 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.69 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.53 (s, 3H, CH_3), 2.13-2.10 (m, 1H, H-4'), 1.99-1.96 (m, 4H, H-3', 5'); EIMS *m/z* (%): 339 (M^+, 7), 252 (11), 224 (13), 156 (100), 141 (20), 77 (29); Anal. Calcd for $C_{14}H_{17}N_3O_3S_2$: C 49.54, H 5.05, N 12.38, S 18.89; found C 48.45, H 4.98, N 12.11, S 19.98.

4-[2-(Ethylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4b**):

Off white powder; Yield 78%; m.p: 174-176; Molecular formula: $C_{15}H_{19}N_3O_3S_2$; Mol. Wt. 353; IR (KBr, cm^{-1}) ν_{max}: 3034, 2918, 1597, 1330; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.62-7.58 (m, 3H, H-3" to 5"), 3.71 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.68 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 3.24 (q, J = 7.5 Hz, 2H, H-1'"), 2.14-2.11 (m, 1H, H-4'), 1.98-1.95 (m, 4H, H-3', 5'), 1.46 (t, J = 7.5 Hz, 3H, H-2'"); EIMS *m/z* (%): 353 (M^+, 10), 252 (14), 224 (10), 156 (50), 141 (14), 77 (27), 29 (100); Anal. Calcd for $C_{15}H_{19}N_3O_3S_2$: C 50.92, H 5.70, N 13.20, S 15.11; found C 50.29, H 5.07, N 13.02, S 16.53.

4-[2-{(2-Bromoethyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4c**):

Mustard viscous liquid; Yield 77%; Molecular formula: $C_{15}H_{18}BrN_3O_3S_2$; Mol. Wt. 432; IR (KBr, cm^{-1}) ν_{max}: 3035, 1577, 1631, 1328; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.77 (dd, J = 6.9,1.8 Hz, 2H, H-2", 6"), 7.58-7.55 (m, 3H, H-3" to 5"), 3.71 (t, J = 2.1 Hz, 2H, H-2'"), 3.60 (t, J = 2.1 Hz, 2H, H-1'"), 2.89 (t, J = 2.1 Hz, 2H, H_{eq}-2' & 6'), 2.63 (t, J = 2.1 Hz, 2H, H_{ax}-2' & 6'), 2.13-1.99 (m, 1H, H-4'), 1.95-1.90 (m, 4H, H-3', 5'); EIMS *m/z* (%): 432 (M^+, 6), 252 (11), 224 (12), 107 (100), 156 (59),

141 (21), 77 (22). Anal. Calcd for $C_{15}H_{18}BrN_3O_3S_2$: C 45.31, H 4.93, N 11.16, S 13.44; found C 45.29, H 4.87, N 11.02, S 13.53.

4-[2-(Propylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4d**):

White granules; Yield 78%; m.p: 168-170; Molecular formula: $C_{16}H_{21}N_3O_3S_2$; Mol. Wt. 367; IR (KBr, cm^{-1}) ν_{max}: 3028, 2920, 1579, 1620, 1330; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.62-7.49 (m, 3H, H-3" to 5"), 3.67 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.64 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 3.10 (t, J = 2.5 Hz, 2H, H-1'"), 2.13-2.00 (m, 1H, H-4'), 1.98-1.96 (m, 4H, H-3', 5'), 1.41 (sex, J = 5.7 Hz, 2H, H-2'"), 0.90 (t, J = 2.0 Hz, 3H, H-3'"); EIMS *m/z* (%): 367 (M^+, 8), 252 (45), 224 (40), 156 (100), 141 (11), 77 (21), 41 (31); Anal. Calcd for $C_{16}H_{21}N_3O_3S_2$: C 52.29, H 5.76, N 11.43, S 17.45; found C 51.29, H 5.56, N 11.63, S 18.00.

4-[2-(Isopropylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4e**):

Light yellow crystals; Yield 73%; m.p: 106-108; Molecular formula: $C_{16}H_{21}N_3O_3S_2$; Mol. Wt. 367; IR (KBr, cm^{-1}) ν_{max}: 3026, 2887, 1575, 1623, 1327; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.61-7.58 (m, 3H, H-3" to 5"), 3.67 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.64 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.88-2.85 (m, 1H, H-1'"), 2.11-1.98 (m, 1H, H-4'), 1.95-1.92 (m, 4H, H-3', 5'), 1.21 (s, 6H, H-2'", 3'"); EIMS *m/z* (%): 367 (M^+, 12), 252 (35), 224 (30), 156 (40), 141 (14), 77 (31), 41(100); Anal. Calcd for $C_{16}H_{21}N_3O_3S_2$: C 52.29, H 5.76, N 11.43, S 17.45; found C 51.25, H 5.55, N 11.68, S 17.70.

4-[2-(Butylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4f**):

Peachy pink crystals; Yield 72%; m.p: 122-124; Molecular formula: $C_{17}H_{23}N_3O_3S_2$; Mol. Wt. 381; IR (KBr, cm^{-1}) ν_{max}: 3028, 2930, 1565, 1618, 1326; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.62-7.57 (m, 3H, H-3" to 5"), 3.67 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.64 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 3.10 (t, J = 2.5 Hz, 2H, H-1'"), 2.14-2.10 (m, 1H, H-4'), 1.97-1.94 (m, 4H, H-3', 5'), 1.41-1.38 (m, 4H, H-2'", 3'"), 0.90 (t, J = 2.0 Hz, 3H, CH_3-4'"); EIMS *m/z* (%): 381 (M^+, 12), 252 (15), 224 (20), 157 (14), 156 (100), 141 (24), 77 (36), 58 (23); Anal. Calcd for $C_{17}H_{23}N_3O_3S_2$: C 53.52, H 6.08, N 11.01, S 16.81; found C 53.25, H 6.05, N 10.89, S 16.70.

4-[2-(sec-Butylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4g**):

Lemon yellow sticky solid; Yield 71%; Molecular formula: $C_{17}H_{23}N_3O_3S_2$; Mol. Wt. 381; IR (KBr, cm^{-1}) ν_{max}: 3018, 2889, 1575, 1628, 1328; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.8, 1.8 Hz, 2H, H-2", 6"), 7.60-7.55 (m, 3H, H-3" to 5"), 3.67 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.64 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.69 (m, 1H, H-2'"), 2.13-2.11 (m, 1H, H-4'), 1.96-1.93 (m, 4H, H-3', 5'), 1.69 (sex, J = 2.5 Hz, 2H, H-3'"), 1.25 (d, J = 6.9 Hz, 3H, H-1'") 0.90 (t, J = 7.2 Hz, 3H, H-4'"); EIMS *m/z* (%): 381 (M^+, 12), 252 (13), 224 (30), 156 (54), 141 (14), 77 (31), 58 (100); Anal. Calcd for $C_{17}H_{23}N_3O_3S_2$: C 53.51, H 6.08, N 11.01, S 16.81; found C 53.22, H 6.03, N 10.99, S 16.78.

4-[2-(Pentylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4h**):

Lemon yellow sticky solid; Yield 78%; Molecular formula: $C_{18}H_{25}N_3O_3S_2$; Mol. Wt. 395; IR (KBr, cm^{-1}) ν_{max}: 3038, 2931, 1571, 1622, 1320; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 7.2, 1.2 Hz, 2H, H-2", 6"), 7.62-7.53 (m, 3H, H-3" to 5"), 3.74 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.18 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.59 (t, J = 2.5 Hz, 2H, H-1'"), 2.11-1.99 (m, 1H, H-4'), 1.97-1.94 (m, 4H, H-3', 5'), 1.82 (q, J = 7.2 Hz, 2H, H-2'"), 1.48 (br-s, 4H, H-3'", 4'"), 1.04 (t, J = 7.2 Hz, 3H, H-5'"); EIMS *m/z* (%): 395 (M^+, 12), 252 (11), 224 (13), 156 (60), 141 (24), 71 (100); Anal. Calcd for $C_{18}H_{25}N_3O_3S_2$: C 54.66, H 6.37, N 10.62, S 16.21; found C 54.25, H 6.35, N 10.59, S 16.90.

4-[2-(Heptylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4i**):

Off-white granules; Yield 77%; m.p: 116-118; Molecular formula: $C_{20}H_{29}N_3O_3S_2$; Mol. Wt. 423; IR (KBr, cm^{-1}) ν_{max}: 3031, 2935, 1565, 1621, 1329; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (d, J = 7.6 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 3.74 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.64 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 3.10 (t, J = 2.5 Hz, 2H, H-1'"), 2.14-2.11 (m, 1H, H-4'), 2.00-1.97 (m, 4H, H-3', 5'), 1.65-1.62 (m, 2H, H-2'"), 1.42-1.39 (m, 2H, H-3'"), 1.31-1.27 (m, 2H, H-6'"), 1.25-1.22 (m, 4H, H-4'", 5'"), 0.88 (t, J = 2.0 Hz, 3H, H-7'"); EIMS *m/z* (%): 423 (M^+, 12), 252 (15), 224 (10), 156 (50), 141 (44), 100 (100), 77 (40); Anal. Calcd for $C_{20}H_{29}N_3O_3S_2$: C 56.71, H 6.90, N 9.92, S 15.14; found C 56.52, H 6.53, N9.59, S 15.20.

4-[2-(Allylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4j**):

Mustard liquid; Yield 77%; Molecular formula: $C_{16}H_{19}N_3O_3S_2$; Mol. Wt. 365; IR (KBr, cm^{-1}) ν_{max}: 3077, 3038, 1565, 1601, 1324; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.75 (dd, J = 7.2, 1.5 Hz, 2H, H-2", 6"), 7.70-7.67 (m, 3H, H-3" to 5"), 5.99 (m, 1H, H-2'"), 5.33 (dd, J = 15.9, 1.2 Hz, 1H, H_a-3'"), 5.17 (dd, J = 15.9, 1.2 Hz, 1H, H_b-3'"), 3.80 (d, J = 7.2 Hz, 2H, H-1'"), 3.72 (t, J = 3.3 Hz, 2H, H_{eq}-2' & 6'), 3.65 (t, J = 3.3 Hz, 2H, H_{ax}-2' & 6'), 3.24 (q, J = 7.5 Hz, 2H, H-1'"), 2.15-2.13 (m, 1H, H-4'), 1.97-1.94 (m, 4H, H-3', 5'); EIMS *m/z* (%): 365 (M^+, 12), 252 (21), 224 (16), 156 (35), 141 (16), 77 (38), 42 (100); Anal. Calcd for $C_{16}H_{19}N_3O_3S_2$: C 52.58, H 5.24, N 11.50, S 17.55; found C 52.52, H 5.23, N 11.49, S 17.75.

4-[2-(Benzylthio)-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4k**):

Brown viscous liquid; Yield 79%; Molecular formula: $C_{20}H_{21}N_3O_3S_2$; Mol. Wt. 415; IR (KBr, cm^{-1}) ν_{max}: 3040, 1567, 1605, 1325; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 6.9, 1.8Hz, 2H, H-2", 6"), 7.61-7.58 (m, 3H, H-3" to 5"), 7.33-7.29 (m, 5H, H-2'" to 6'"), 4.40 (s, 2H, H-7'"), 3.81 (t, J = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.69 (t, J = 2.7 Hz, 2H, H_{ax}-2' & 6'), 2.09-2.03 (m, 1H, H-4'), 1.94-1.92 (m, 4H, H-3', 5'); EIMS *m/z* (%): 415 (M^+, 4), 252 (14), 224 (10), 170 (5), 156 (100), 141 (14), 91 (58), 82 (93), 77 (32); Anal. Calcd for $C_{20}H_{21}N_3O_3S_2$: C 57.81, H 5.09, N 10.11, S 15.43; found C 57.89, H 5.05, N 10.19, S 15.55.

4-[2-{(2-Phenethyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4l**):

Bright white solid; Yield 80%; m.p: 104-106; Molecular formula: $C_{21}H_{23}N_3O_3S_2$; Mol. Wt. 429; IR (KBr, cm^{-1}) ν_{max}: 3042, 1569, 1610, 1330; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.77 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.63-7.60 (m, 3H, H-3" to 5"), 7.32-7.29 (m, 5H, H-2"' to 6"'), 3.45 (t, J = 7.2 Hz, 2H, H-7"'), 3.10 (t, J = 7.2 Hz, 2H, H-8"'), 2.87 (t, J = 2.7 Hz, 2H, H_{eq}-2' & 6'), 2.82 (t, J = 2.7 Hz, 2H, H_{ax}-2' & 6'), 2.15-2.13 (m, 1H, H-4'), 1.97-1.95 (m, 4H, H-3', 5'); EIMS *m/z* (%): 429 (M^+, 14), 252 (16), 224 (17), 157 (11), 156 (60), 141 (19), 91 (45), 77 (100); Anal. Calcd for $C_{21}H_{23}N_3O_3S_2$: C 58.72, H 5.40, N 9.78, S 14.93; found C 58.87, H 5.45, N 9.89, S 15.12.

4-[2-{(3-Phenpropyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4m**):

Mustard viscous liquid; Yield 82%; Molecular formula: $C_{22}H_{25}N_3O_3S_2$; Mol. Wt. 443; IR (KBr, cm^{-1}) ν_{max}: 3032, 1515, 1614, 1326; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 6.9,1.8 Hz, 2H, H-2", 6"), 7.62-7.59 (m, 3H, H-3" to 5"), 7.25-7.22 (m, 5H, H-2"' to 6"'), 3.71 (t, J = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, J = 2.7 Hz, 2H, H_{ax}-2' & 6'), 3.19 (t, J = 5.7 Hz, 2H, H-7"'), 2.93 (t, J = 5.7 Hz, 2H, H-9"'), 2.73-2.70 (m, 2H, H-8"'), 2.11-2.09 (m, 1H, H-4'), 1.93-1.90 (m, 4H, H-3', 5'); EIMS *m/z* (%): 443 (M^+, 12), 252 (14), 224 (10), 157 (14), 156 (100), 141 (12), 91 (21), 77 (30), 44 (14); Anal. Calcd for $C_{22}H_{25}N_3O_3S_2$: C 59.57, H 5.68, N 9.47, S 14.46; found C 59.75, H 5.61, N 9.29, S 14.82.

4-[2-{(2-Chlorobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4n**):

White powder; Yield 76%; m.p: 192-194; Molecular formula: $C_{20}H_{20}ClN_3O_3S_2$; Mol. Wt. 449; IR (KBr, cm^{-1}) ν_{max}: 3035, 1555, 1616, 1319; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 7.38 (dd, J = 6.0, 1.5 Hz, 1H, H-3"'), 7.25-7.21 (m, 2H, 3H, H-4"' to 6"'), 4.50 (s, 2H, H-7"'), 3.71 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.12-2.09 (m, 1H, H-4'), 1.96-1.93 (m, 4H, H-3', 5'); EIMS *m/z* (%): 449 (M^+, 12), 252 (14), 224 (10), 157 (14), 156 (33), 141 (12), 113 (100), 91 (41), 77 (20); Anal. Calcd for $C_{20}H_{20}ClN_3O_3S_2$: C 53.38, H 4.48, N 9.34, S 14.25; found C 53.45, H 4.51, N 9.28, S 14.22.

4-[2-{(3-Chlorobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4o**):

White powder; Yield 71%; m.p: 158-160; Molecular formula: $C_{20}H_{20}ClN_3O_3S_2$; Mol. Wt. 449; IR (KBr, cm^{-1}) ν_{max}: 3038, 1557, 1619, 1328; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 6.9, 1.8Hz, 2H, H-2", 6"), 7.65-7.62 (m, 3H, H-3" to 5"), 7.37 (br s, 1H, H-2"'), 7.55 (dd, J = 6.0, 1.5Hz, 1H, 2H, H-4"'), 7.24-7.21 (m, 2H, H.5"', 6"'), 4.35 (s, 2H, H-7"'), 3.72 (t, J = 3.9 Hz, 2H, H_{eq}-2' & 6'), 3.66 (t, J = 3.9 Hz, 2H, H_{ax}-2' & 6'), 2.09-2.05 (m, 1H, H-4'), 1.93-1.89 (m, 4H, H-3', 5'); EIMS *m/z* (%): 449 (M^+, 10), 252 (18), 224 (11), 157 (10), 156 (28), 141 (10), 113 (100), 91 (14), 77 (20); Anal. Calcd for $C_{20}H_{20}ClN_3O_3S_2$: C 53.38, H 4.48, N 9.34, S 14.25; found C 53.47, H 4.57, N 9.38, S 14.27.

4-[2-{(4-Chlorobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4p**):

White powder; Yield 73%; m.p: 196-198; Molecular formula: $C_{20}H_{20}ClN_3O_3S_2$; Mol. Wt. 449; IR (KBr, cm^{-1}) ν_{max}: 3035, 1545, 1620, 1321; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.78 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.66-7.69 (m, 3H, H-3" to 5"), 7.34 (d, J = 8.4 Hz, 2H, H-3"', 5"'), 7.27 (d, J = 8.4 Hz, 2H, H-2"', 6"'), 4.35 (s, 2H, H-7"'), 3.72 (t, J = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.66 (t, J = 2.7 Hz, 2H, H_{ax}-2' & 6'), 2.11-2.08 (m, 1H, H-4'), 1.98-1.95 (m, 4H, H-3', 5'); EIMS *m/z* (%): 449 (M^+, 15), 252 (14), 224 (10), 157 (14), 156 (25), 141 (12), 113(100), 91 (16), 77 (30); Anal. Calcd for $C_{20}H_{20}ClN_3O_3S_2$: C 53.38, H 4.48, N 9.34, S 14.25; found C 53.49, H 4.60, N 9.40, S 14.32.

4-[2-{(2-Bromobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4q**):

Orange sticky liquid; Yield 77%; Molecular formula: $C_{20}H_{20}BrN_3O_3S_2$; Mol. Wt. 494; IR (KBr, cm^{-1}) ν_{max}: 3037, 1535, 1619, 1318; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.78 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.67-7.65 (m, 3H, H-3" to 5"), 7.44 (d, J = 8.4 Hz, 1H, H-3"'), 7.28 (dd, J = 8.4, 2.3 Hz, 1H, H-6"'), 7.23 (dt, J = 6.8, 1.8 Hz, 1H, H-5"'), 7.12 (dt, J = 6.8, 1.8 Hz, 1H, H-4"'), 4.34 (s, 2H, H-7"'), 3.71 (t, J = 3.3 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, J = 3.3 Hz, 2H, H_{ax}-2' & 6'), 2.86-2.83 (m, 1H, H-4'), 2.00-1.97 (m, 4H, H-3', 5'); EIMS *m/z* (%): 494 (M^+, 13), 252 (22), 157 (100), 156 (40), 141 (16), 91 (14), 77 (32). Anal. Calcd for $C_{20}H_{20}BrN_3O_3S_2$: C 51.58, H 4.98, N 10.50, S 10.97; found C 53.51, H 5.00, N 11.46, S 9.72.

4-[2-{(3-Bromobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4r**):

White powder; Yield 74%; m.p: 170-172; Molecular formula: $C_{20}H_{20}BrN_3O_3S_2$; Mol. Wt. 494; IR (KBr, cm^{-1}) ν_{max}: 3038, 1545, 1623, 1320; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.79 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 7.55 (dd, J = 8.4, 1.5 Hz, 2H, H-4"'), 7.37 (br s, 1H, H-2"'), 7.29-7.25 (m, 2H, H-5"' to 6"'), 4.34 (s, 2H, H-7"'), 3.71 (t, J = 3.3 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, J = 3.3 Hz, 2H, H_{ax}-2' & 6'), 2.85-2.82 (m, 1H, H-4'), 2.02-2.00 (m, 4H, H-3', 5'); EIMS *m/z* (%): 494 (M^+, 11), 252 (25), 224 (18), 157 (100), 156 (30), 141 (17), 91 (15), 77 (32); Anal. Calcd for $C_{20}H_{20}BrN_3O_3S_2$: C 51.58, H 4.98, N 10.50, S 10.97; found C 53.57, H 5.05, N 11.49, S 9.82.

4-[2-{(4-Bromobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4s**):

White powder; Yield 74%; m.p: 176-178; Molecular formula: $C_{20}H_{20}BrN_3O_3S_2$ Mol. Wt. 493; IR (KBr, cm^{-1}) ν_{max}: 3058, 1575, 1621, 1328; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.76 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 7.43 (d, J = 8.4 Hz, 2H, H-3"', 5"'), 7.28 (d, J = 8.4 Hz, 2H, H-2"', 6"'), 4.34 (s, 2H, H-7"'), 3.71 (t, J = 3.3 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, J = 3.3 Hz, 2H, H_{ax}-2' & 6'), 2.81-2.77 (m, 1H, H-4'), 2.03-1.98 (m, 4H, H-3', 5'); EIMS *m/z* (%): 494 (M^+, 13), 252 (24), 224 (10), 157 (100), 156 (35), 141 (12), 91 (16), 77 (44); Anal. Calcd for $C_{20}H_{20}BrN_3O_3S_2$: C 51.58, H 4.98, N 10.50, S 10.97; found C 53.56, H 5.03, N 11.50, S 9.77.

4-[2-{(4-Flourobenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4t**):

Orange viscous liquid; Yield 80%; Molecular formula: $C_{20}H_{20}BrN_3O_3S_2$; Mol. Wt. 433; IR (KBr, cm^{-1}) ν_{max}: 3018, 1577, 1614, 1319, 1023; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.80 (dd, J = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.68-7.65 (m, 3H, H-3" to

5"), 7.55 (d, *J* = 7.8 Hz, 2H, H-3"', 5"'), 6.98 (d, *J* = 8.7 Hz, 2H, H-2"', 6"'), 4.37 (s, 2H, H-7"'), 3.71 (t, *J* = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.67 (t, *J* = 2.7 Hz, 2H, H_{ax}-2' & 6'), 2.07-2.03 (m, 1H, H-4'), 1.93-1.89 (m, 4H, H-3', 5'); EIMS *m/z* (%): 433 (M^+, 12), 252 (14), 224 (13), 157 (24), 156 (55), 141 (17), 91 (11), 96 (100), 77 (30); Anal. Calcd for $C_{20}H_{20}FN_3O_3S_2$: C 55.41, H 4.65, N 9.69, S 14.79; found C 55.51, H 4.56, N 9.86, S 14.72.

4-[2-{(2-Methylbenzyl)thiol}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4u**):

Creamy white solid; Yield 79%; m.p: 174-176; Molecular formula: $C_{21}H_{23}N_3O_3S_2$; Mol. Wt. 429; IR (KBr, cm^{-1}) ν_{max}: 3020, 1575, 1618, 1320; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.66 (dd, *J* = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.59-7.55 (m, 3H, H-3" to 5"), 7.32 (d, *J* = 7.2 Hz, 1H, H-6"'), 7.19-7.15 (m, 2H, H.4"', 5"'), 6.81 (d, *J* = 8.4 Hz, 1H, H-3"'), 4.42 (s, 2H, H-7"'), 3.70 (t, *J* = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.66 (t, *J* = 2.7 Hz, 2H, H_{ax}-2' & 6'), 2.34 (s, 3H, H-2"'), 2.16-2.13 (m, 1H, H-4'), 2.01-1.97 (m, 4H, H-3', 5'); EIMS *m/z* (%): 429 (M^+, 12) $[M]^+$, 252 (16), 224 (10), 157 (14), 156 (43), 141 (12), 91 (100), 77 (23); Anal. Calcd for $C_{21}H_{23}N_3O_3S_2$: C 58.72, H 5.40, N 9.78, S 14.93; found C 58.51, H 5.46, N 9.66, S 14.75.

4-[2-{(1,3-Dioxolan-2-yl)methylthio}-1,3,4-oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4v**):

White powder; Yield 78%; m.p: 118-120; Molecular formula: $C_{17}H_{21}N_3O_5S_2$; Mol. Wt. 411; IR (KBr, cm^{-1}) ν_{max}: 3023, 1535, 1611, 1311, 1270; ^{1}H-NMR (300 MHz, $CDCl_3$ δ / ppm): 7.69 (dd, *J* = 6.9, 1.8 Hz, 2H, H-2", 6"), 7.60-7.57 (m, 3H, H-3" to 5"), 5.17 (t, *J* = 3.5 Hz, 1H, H-5"'), 4.06-4.03 (m, 4H, $2CH_2$, H.2"', 3"'), 3.70 (t, *J* = 2.7 Hz, 2H, H_{eq}-2' & 6'), 3.66 (t, *J* = 2.7 Hz, 2H, H_{ax}-2' & 6'), 3.23 (d, *J* = 2.5 Hz, 2H, CH_2-6"'), 2.18-2.15 (m, 1H, H-4'), 2.03-1.99 (m, 4H, H-3', 5'); EIMS *m/z* (%): 411 (M^+; 8), 252 (14), 224 (15), 157 (16), 156 (100), 141 (17), 77 (30), 54 (11). Anal. Calcd for $C_{17}H_{21}N_3O_5S_2$: C 49.62, H 5.14, N 10.21, S 15.58; found C 49.61, H 5.16, N 10.19, S 16.05.

Anti-bacterial Activity Assay

The antibacterial activity was performed in sterile 96-wells microplates under aseptic environments. The method is based on the principle that microbial cell number increases as the microbial growth proceeds in a log phase of growth which results in increased absorbance of broth medium [19, 20]. Clinically isolated, two gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and four gram-negative (*Shigella sonnei, Escherichia coli, Pseudomonas aeruginosa and Salmonella typhi*) were included in the study. The organisms were maintained on stock culture agar medium. The test samples with suitable solvents and dilutions were pipette out into wells (20 µg/well). Overnight maintained fresh bacterial culture after suitable dilution with fresh nutrient broth was poured into wells (180 µL). The initial absorbance of the culture was strictly maintained between 0.12-0.19 at 540 nm. The total volume in each well was kept to 200 µL. The incubation was done at 37°C for 16-24 hours with lid on the micro plate. The absorbance was measured at 540 nm using micro plate reader, before and after incubation and the difference was noted as an index of bacterial growth. The percent inhibition was calculated using the formula:

$$\text{Inhibition (\%)} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

where Control = Absorbance in control with bacterial culture

Test = Absorbance in test sample

Results are mean of triplicate (n=3, ± sem). Ciprofloxacin and ampicillin were taken as standard. Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software, and data expressed as MIC.

Statistical Analysis

All the measurements were performed in triplicate and statistical analysis was performed by Microsoft Excel 2010. Results are presented as mean ± sem.

Conclusion

The projected structures of the synthesized compounds are well supported by spectroscopic data. From the antibacterial data (Table-1), it is obvious that the compounds exhibit talented to moderate antibacterial activity with different *S*-substitutions on 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol. The present study is an interesting demonstration for the influence of substitutions on pharmacological activities of oxadiazole ring. In this way, the compounds could be potential target in the drug discovery and drug development program.

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References

1. A. O. Maslat, M. Abussaud, H. Tashtoush and M. Al. Talib, *Polish Journal of Pharmacology,* **54,** 55 (2002).
2. N. Bhardwaj, S. K. Saraf, P. Sharma and P. Kumar, *European Journal of Chemistry,* **6,** 1133 (2009).
3. A. Husain and M. Ajmal, *Acta Pharmaceutica,* **59,** 223 (2009).
4. Nagaraj, K. C. Chaluvaraju, M. S. Niranjan and S. Kiran, *International Journal of Pharmacy and Pharmaceutical Sciences,* **3,** 9 (2011).
5. F. A. Omar, N. M. Mahfouz and M. A. Rahman, *European Journal of Medicinal Chemistry,* **31,** 819 (1996).
6. L. Jin, J. Chen, B. Song, Z. Chen, S. Yang, Q. Li, D. Hu and R. Xu, *Bioorganic and Medicinal Chemistry Letter,* **16,** 5036 (2006).
7. D. Kumar, S. Sundaree, E. O. Johnson and K. Shah, *Bioorganic and Medicinal Chemistry Letter,* **19,** 4492 (2009).
8. T. M. Chin Tan, Y. Chena, K. H. Kong, J. Bai, Y. Li, S. G Lim, T. H Ang and Y. Lam, *Antiviral Research,* **71,** 7 (2006).
9. H. L. Yale and K. Losee, *Journal of Medicinal Chemistry,* **9,** 478 (1966).
10. S. Ebrahimi, *European Journal of Medicinal Chemistry,* **1,** 322 (2010).
11. Aziz-ur-Rehman, S. Z. Siddiqui, N. Abbas, M. A. Abbasi, K. M. Khan, M. Shahid, Y. Mahmood, N. M. Akhtar and N. H. Lajis, *International*

Journal of Pharmacy and Pharmaceutical Sciences, **4,** 676 (2012).

12. Aziz-ur-Rehman, K. Nafeesa, M. A. Abbasi, H. Khalid, K. M. Khan, M. Ashraf, I. Ahmad and S. A. Ejaz, *Asian Journal of Pharmaceutical Health Sciences,* **2,** 370 (2012).
13. H. Khalid, Aziz-ur-Rehman, M. A. Abbasi and K. M. Khan, *International Journal of Pharmacy and Pharmaceutical Sciences,* **4,** 443 **(**2012).
14. Aziz-ur-Rehman, A. Fatima, M. A. Abbasi, S. Rasool, A. Malik, M. Ashraf, I. Ahmad and S. A. Ejaz, *Journal of Saudi Chemical Society* (2013), doi: http://dx.doi.org/10.1016/j.jscs.2013.02.006
15. Aziz-ur-Rehman, A. Fatima, N. Abbas, M. A. Abbasi, K. M. Khan, M. Ashraf, I. Ahmad and S. A. Ejaz, *Pakistan Journal of Pharmaceutical Sciences,* **26**, 345 (2013).
16. H. Khalid, Aziz-ur-Rehman, M. A. Abbasi, A. Malik, S. Rasool, K. Nafeesa, I. Ahmad and S. Afzal. *Journal of Saudi Chemical Society* (2013), doi: http://dx.doi.org/10.1016/j.jscs.2013.05.001
17. X. Deng and N. S. Mani, *Green Chemistry,* **8,** 835 (2006).
18. M. Jafarpour, A. Rezaeifard and T. Golshani, *Journal of Phosphorous, Sulfur, and Silicon.* **186,** 140 (2011).
19. M. Kaspady, V. K. Narayanaswamy, M. Raju and G. K. Rao, *Drug Design and Discovery,* **6,** 21 (2009).
20. C. R. Yang, Y. Zang, M. R. Jacob, S. I. Khan, Y. J. Zhang and X. C. Li, *Antimicrobial Agents Chemotherapy,* **50,** 1710 (2006).