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

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Summary: Due to pharmacological importance of 1,3,4-Oxadiazole derivatives, a new series of *S*-substituted derivatives, **4a-v**, of 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol (**1**) was synthesized. The reaction of benzenesulfonyl chloride with ethyl isonipecotate yielded ethyl 1-(phenylsulfonyl)piperidin-4-carboxylate (**1**), which was further converted into 1-(Phenylsulfonyl) piperidin-4-carbohydrazide (**2**) by hydrazine hydrate and then **2** into 5-[1-(phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol (**3**) in the presence of CS_2 along with KOH. The target compounds (**4a-v**) were synthesized by treating **3** with various electrophiles in DMF and NaH. The proposed structures of compounds, **4a-v**, were corroborated through IR, ^{1}H-NMR & EI-MS spectral data. Further these were evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria. It was observed that the substitution at sulfur of thiol group influenced the antibacterial activity significantly and so varied from moderate to excellent level.

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

Introduction

1,3,4-Oxadiazole, a heterocycle, bearing compounds have gained attention for last twenty years 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]. The substituted 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 demonstrated a vital function to improve heterocyclic and organic synthesis. This heterocyclic ring has been expediently synthesized through treatment of a carbohydrazide with carbon disulfide in strong basic media [10, 11].

This paper reports the synthesis and biological activity results of a series of 1,3,4-Oxadiazole bearing compounds derived from ethyl isonipecotate. In continuation of our previous work [12-16], we have reported the synthesis of a new molecule 5-[1-(Phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol (**3**) bearing a piperidine ring which was subjected to *S*-substitution by reacting with different alkyl/aralkyl halides. Furthermore, the molecules were evaluated for *in vitro* antibacterial activity against different bacterial strains of Gram-positive and Gram-negative bacteria by a reported method using ciprofloxacin and ampicillin as reference standard. The research work was a successful effort of fusion of two highly active heterocyclic rings as one unit and to find out the valuable biologically active compounds.

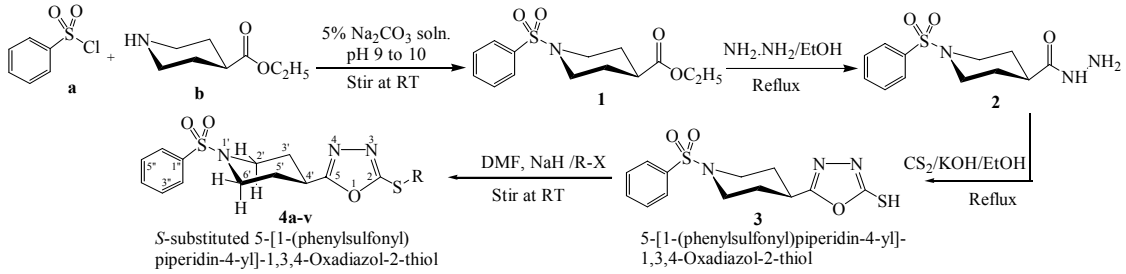
Results and discussion

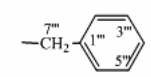
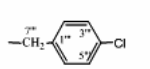
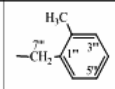
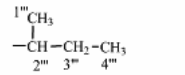
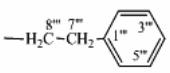
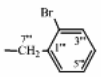
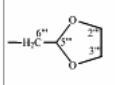
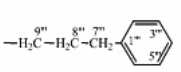
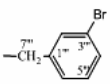
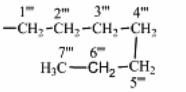
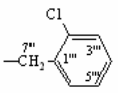
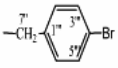
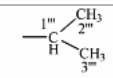
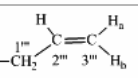
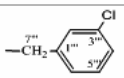
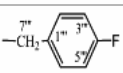
The undertaken research revealed the synthesis of valuable bioactive compounds through *S*-substitution of 1,3,4-Oxadiazole. The four step synthesis was carried out to yield the various compounds, **4a-v**. First of all, benzenesulfonyl chloride (**a**) and ethyl isonipecotate (**b**) were stirred under definite pH in water to yield ethyl 1-(phenylsulfonyl)piperidin-4-carboxylate (**1**) [17, 18]. In the second step, the synthesized compound **1** was refluxed with hydrazine in ethanol to acquire 1-(phenylsulfonyl)piperidin-4-carbohydrazide (**2**). The cyclization of **2** into 1,3,4-Oxadiazol-2-thiol, **3**, was efficiently achieved on refluxing **2** with CS_2 in a basic media utilizing ethanol at the third step. The product **3** was obtained after the addition of acid. The fourth step comprises the synthesis of all the derivatives **4a-v** on stirring different electrophiles with **3** in DMF & NaH as shown in scheme-1. The so obtained products were separated after addition of cold water and subsequently through filtration or solvent extraction by *n*-butanol. The proposed

structure of all the synthesized molecules including starting compound and derivatives of **3**, that is, **1**, **2**, **3** and **4a-v** were well 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**) was clearly elaborated in Fig. 1 for the readers. The parent compound **3** was acquired as powdered white solid having promising yield of 88% and m.p. of 210-213 ^{o}C. The molecular formula $C_{13}H_{15}N_3O_3S_2$ was elucidated by molecular ion peak, $[M]^+$, at *m/z* 325 by EI-MS spectrum along with the integration for protons in the proton NMR spectrum. The absorption bands in infra-red spectrum with definite stretching frequencies absorbed at 3035, 2250, 1593 and 1326 relative to aromatic C-H, S-H, C=N of 1,3,4-Oxadiazole and S=O of sulfamoyl group respectively. The other characteristic peaks erecting in EI-MS spectrum were at *m/z* 224 (attributed to the fragment obtained after the loss of (phenylsulfonyl)piperidine from molecular ion fragment) and at *m/z* 77 because of phenyl group. The base peak with 100% intensity appeared at *m/z* 156 because of cationic fragment of benzene sulfamoyl group, its formation is elucidated in Fig.1. The proton NMR spectrum affirmed the presence of phenyl ring by resonating two signals at δ 7.80 (dd, J = 7.8, 1.8 Hz, 2H, H-2" & 6") and 7.67-7.65 (m, 3H, H-3" to 5") for five protons of ring. The four singles resonated at δ 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') for nine 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 attributed 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 nucleus while the methine carbon signal with single intensity appeared at δ_C (ppm) 33.6. All the mentioned manifests collectively supported the whole structure of the compound **3** which was named 5-[1-(Phenylsulfonyl)piperidin-4-yl]-1,3,4-Oxadiazol-2-thiol according to IUPAC rules. Likewise, the structures of other synthesized molecules were well characterized, elucidated and named, given in experimental section.

Antibacterial Activity

The synthesized molecules were also demonstrated for their MIC (Minimum Inhibitory Concentration) results of screening against certain bacterial strains of Gram-positive and Gram-negative bacteria using Ampicillin and Ciprofloxacin as reference standard. All compounds showed varying degree of antimicrobial activity as given in Table-1. The MIC values demonstrated 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-e**, **4g**, **4k-l**, **4n-r** and **4u** executed promising inhibition potential for the bacterial strains taken into account. The other molecules also showed moderate inhibitory potential. Compound **4t** remained inactive at all against all the bacterial strains probably due to 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 +ve bacteria. For the Gram -ve bacteria, the most of the molecules exhibited 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		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		4n		4s			
4e		4j		4o		4t			

Scheme-1: Outline for the synthesis of *S*-substituted derivatives of **3** (**4a-v**)

Experimental

General

M.P. of the synthesized molecules were recorded on Griffin-George apparatus using capillary tube opened at one side (uncorrected). Purity of compound and the reaction progress was checked out on thin layer chromatography (TLC) which was prepared by silica gel G-25-UV_{254} coated on aluminum plates and run by using different compositions of AcOEt and *n*-C_6H_{14} giving single spot. The spots of run TLC were observed under UV lamp operated at 254 nm. Elemental analysis was done on EAGER 300 for EA 1112 with K factor method. All the compounds were characterized by I.R. spectra (performed by KBr pellet method using Jasco-320-A spectrophotometer), NMR spectra (proton and ^{13}C-NMR in $CDCl_3$ using Bruker spectrometers at 300 and 75 MHz respectively) and EIMS (using JMS-HX-110 spectrometer). The synthetic grade chemicals were got through local suppliers and employed without distilling them. The solvents used were also of synthetic grade.

Preparation of ethyl 1-(phenylsulfonyl)piperidin-4-carboxylate **(1)**

Ethyl isonipecotate (11.0 mmol; **b**) was introduced in a 100 mL round bottom (RB) flask followed by 30 mL distilled water. To this suspension, benzenesulfonyl chloride (11.0 mmol; **a**) was poured gradually over a time duration of five minutes on stirring. The temperature of the system was at room temperature (RT). The reaction mixture was set to stir for 4-5 hrs and the pH was kept constant at 9-10 during the whole reaction by the addition of 5% sodium carbonate solution. The reaction progress was monitored with TLC taken after certain time interval. After completion, concentrated HCl (1 mL, 11M) was added gradually with shaking to adjust the pH of 4-5 and to washout the undesirable contents of reaction mixture. The reaction mass was aged for 15 minutes to acquire the off-white precipitates which were isolated through filtration, washed with distilled water and dried to afford the title compound.

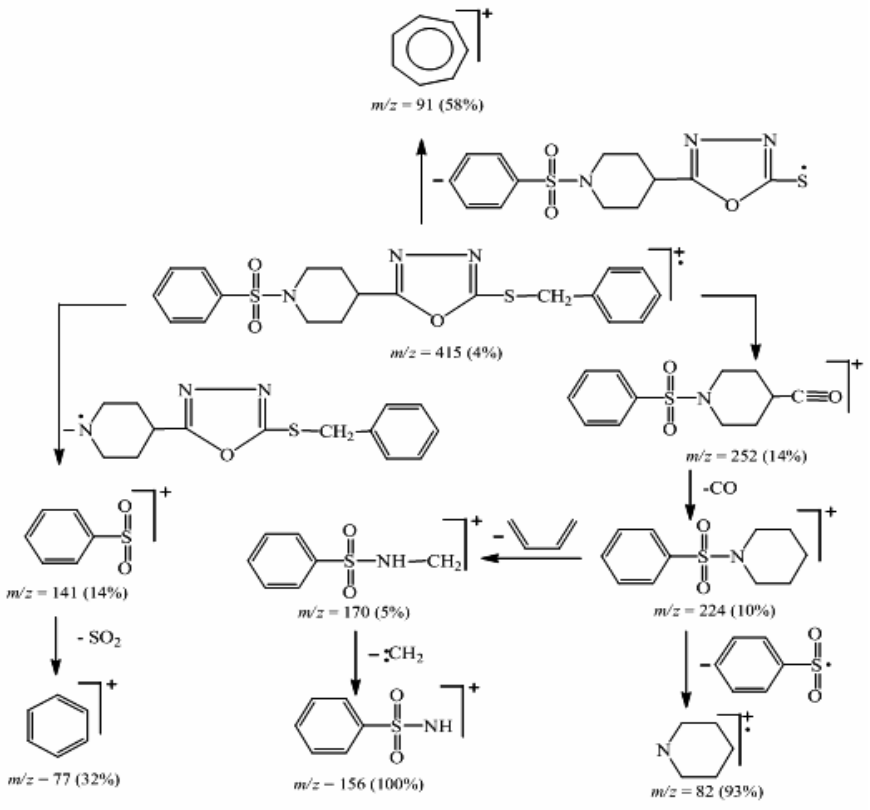


Fig. 1: MS pattern of 4-[2-(Benzylthio)-1,3,4-Oxadiazol-5-yl]-1-(phenylsulfonyl)piperidine (**4k**)

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

Compound	MIC (□g/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)piperidin-4-carbohydrazide **(2)**

The molecule **1** (0.03 mol) was mixed with 30 mL ethanol in a 100 mL RB flask followed by the addition of 80% hydrazine hydrate (30 mL) drop wise. The reaction mixture was stirred for 5-6 hrs at RT. One drop glacial AcOH can be used as catalyst. Reaction completion was based on single spot by TLC. After single spot by TLC, two third of solvent was distilled from reaction mixture. The mixture was cooled to get the white crystalline product **2**, collected through filtration, washed with *n*-hexane and dried for next step.

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

The molecule **2** (0.021 mol) was added to 25 mL ethanol in a 100 mL RB flask followed by the addition of KOH (0.021 mol) and refluxed for 0.5 hr. Then mixture was cooled to RT and CS_2 (0.042 mol) was added to the solution. This reaction contents were properly stirred to homogenize them and refluxed for 4-5 hrs. Color of solution medium gradually varied from yellow to milky white along with the emission of rotten egg smell H_2S. After single spot on TLC, the contents were diluted by excess of distilled water followed by acidification by concentrated HCl to adjust pH of 5-6 to remove the unwanted mixture contents and also bounce back acidic form of 1,3,4-Oxadiazol-2-thiol. The obtained precipitates of product **3** were isolated through filtration and subjected to washing by water and re-crystallizion from ethanol.

General procedure for preparation of S-substituted-1,3,4-Oxadiazole derivatives **(4a-v)**

The calculated amount of **3** (0.11 mmol) was introduced to a 50 mL RB flask and stirred with 12 mL DMF and NaH (0.11 mmol) for 0.5 hr at RT to activate the molecule **3** for further reaction. Then the alkyl/aralkyl halides were added and the solution was kept to stir for further 2-3 hours. The reaction movement was checked out through TLC until single spot. Excess of distilled water was introduced to the flask along with gentle shaking and the products, **4a-v**, were isolated by filtration or solvent extraction as per nature of product.

Spectral Characterization of the synthesized compounds

Ethyl 1-(phenylsulfonyl)piperidin-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)piperidin-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 antimicrobial activity was assayed by the known method. The sterilized 96-wells microplates were employed for analysis but under sterile condition. The basic principle of the applied method was to observe the absorbance which is directly related to log phase growth of bacterial cells [19, 20]. The list of bacterial strains includes *Bacillus subtilis* and *Staphylococcus aureus* as two gram-positive bacteria; and *Shigella sonnei, Escherichia coli, Pseudomonas aeroginosa* and *Salmonella typhi* as four gram-negative. The given formula was used to calculate the percent inhibition:

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

where
Control = Absorbance in control
Test = Absorbance in test sample

Ciprofloxacin and ampicillin were adopted as standard drugs for comparison of the synthesized molecules. The minimum inhibitory concentration (MIC) was calculated after suited dilutions ranging 5-30 µg/well and the results were recorded using EZ-Fit Perrella Scientific Inc. Amherst USA software. All the deduced results were mean of triplicate (n=3, ± SEM).

Statistical Analysis

All the results have been presented as mean ± SEM after performing statistical analysis on ME 2010. The calculations are based on triplicate measurements.

Conclusion

The projected structural formulae of the synthesized molecules were well corroborated through spectroscopic data analysis. The MIC data for antibacterial activity revealed that the compounds exhibited talented to moderate activity for different *S*-substitutions on **3**. 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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