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Synthesis, Multiparametric Structure Assessment and Biological Evaluation of Some New 1,3,4-Oxadiazoles Containing Piperidine Nucleus

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With an aim to introduce more biologically active compounds, *S*-substituted derivatives of 5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole-2-thiol (**3**) were synthesized through four steps. In the first step, ethyl 1-(4-nitrophenylsulfonyl)piperidine-4-carboxylate (**1**)was synthesized by reacting 4-nitrobenzenesulfonyl chloride (**a**) and ethyl isonipacotate (**b**) in basic medium. In the second step, compound **1** and hydrazine monohydrate were converted to corresponding hydrazide (**2**). In third step, hydrazide (**2**), CS_2 and KOH were refluxed in the presence of MeOH to acquire 5-(1-(4-nitrophenylsulfonyl)piperidin-4-yl)-1,3,4-oxadiazole-2-thiol (**3**). In the last step, alkyl/aralkylhalides (**4a-o**) and **3** were made to react in an aprotic polar solvent to get the final compounds, 2-(substitutedthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (**5a-o**). The synthesized compounds were structurally confirmed by spectroscopic techniques including ^{1}H NMR, EIMS and IR. Finally the synthesized compounds were screened for antibacterial activity against five bacterial strains.

Keywords: Sulfonamide, Ester, 1,3,4-Oxadiazole, Piperidine, Antibacterial activity.

INTRODUCTION

The increasing interest of researchers has been observed to design the oxadiazole system because of its basic application in the formulation of many drugs with a variety of biological activities [1,2]. 1,3,4-Oxadiazole, the five membered heterocyclic compound having two nitrogen atoms at position 3 and 4, exhibits a broad spectrum of biological activities. The production of azoles based drugs has reflected a great achievement in medical field and so serving the humanity against deadly diseases caused by different microbes [3]. Disubstituted 1,3,4-oxadiazole has shown a wide variety of biological activities such as antibacterial, antimycobacterial, antifungal, anti-inflammatory, analgesic, anticonvulsant and anticancer activities [4-7]. Recently it has been found that 1,3,4-oxadiazole has shown the cytotoxity and antiproliferative effect on cancer cell lines [8,9].

Oxadiazole molecule having azinane core is very important in the fields of natural products, pharmaceutical industry and biologically active compounds [10]. A wide variety of compounds having azinane core have been introduced into the preclinical practices since a few decades [11]. This azinane heterocyclic core, piperidine, has been found to possess potential against acetyl cholinesterase enzyme, in the treatment of migraine headaches, in the treatment of schizophrenia and also has great extent of anticonvulsant, anti-inflammatory, antibacterial and antimalarial acivities [12]. In addition to it, piperidine heterocyclic ring has some important features like low toxicity and drugs with water lipid partition coefficient. That's why piperidine nucleus has ability to improve the biological activities of the design drugs system [13,14].

Our research group is already working on derivatives of 1,3,4-oxadiazole. In continuation to our previous work on oxadiazole derivatives having azinane core [15] by the cost effective methods for the synthesis of biologically important compounds, 1,3,4-oxadiazole derivatives bearing piperidine nucleus have been synthesized to combat the vastly resistive pathogens for already available drugs.

EXPERIMENTAL

Different chemicals utilized to achieve our targeted products were availed from Sigma Aldrich and Alfa Aesar (Germany). Purity of synthesized compounds was assured by re-crysta-

llization and thin layer chromatography technique, generated on pre-coated silica gel G-25-UV_{254} aluminum plates, with *n*-hexane and ethyl acetate system and visualized using 254 nm UV lamp. The IR spectra were recorded using KBr pellet method on Jasco-320-A spectrometer. Mass spectra (EI-MS) were recorded on JMS-HX-110 spectrometer.^{1}H NMR spectra were recorded in MeOD solvent on Bruker spectrometer operating at 500 & 600 MHz. Melting points of synthesized compounds were recorded on Griffin and George meting point apparatus using open capillary tube and were uncorrected.

Synthesis of ethyl 1-(4-nitrophenylsulfonyl)piperidin-4-carboxylate (1): 4-Nitrophenyl sulfonyl chloride [0.389 mol; (a)] was reacted with equimolar ethyl isonipecotate (b) in a 250 mL round bottom flask using 100 mL water as solvent. The mixture was stirred at room temperature at 140 rpm for 3 h. The aqueous sodium carbonate solution (18 %) was added to adjust the pH at 9-10. Completion of reaction was confirmed by TLC and then the solution was neutralized using dil. HCl. The reaction mixture was poured into 500 mL beaker having chilled water. The solution was aged until precipitation. The formed precipitates were filtered, washed and dried.

Synthesis of 1-(4-nitrophenylsulfonyl)piperidine-4-carbohydrazide (2): Compound **1** (0.015 mol) was dissolved in methanol (50 mL) in a 250 mL round bottom flask and then hydrazine monohydrate (5 mL) was added. The mixture was refluxed for 4 h. The completion of reaction was confirmed by TLC. The chilled distilled water was added in small amounts along with shaking until precipitation. The precipitates were filtered, washed and dried.

Synthesis of 5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (3): Compound **2** (0.0304 mol) was dissolved in 100 mL ethanol in a 250 mL round bottom flask along with KOH (0.0304 mol) and set to reflux till complete dissolution of KOH. After this, CS_2 (0.0608 mol) was added at room temperature and then again refluxed for 5 h. TLC was used to confirm the completion of reaction. Excess distilled water was added and the pH was adjusted to 5-6. The mixture was aged for 5 h to acquire maximum yield and formed precipitates were filtered, washed and dried.

General procedure for the synthesis of target compounds (5a-o): Compound **3** (0.5 mmol) was taken in 50 mL round bottom flask along with 10 mL of *N,N*-dimethyl formamide. Then LiH was added as an activator and mixture was set to stirrer for 30 min. Equimolar amount of aralkyl/aralkyl halides (**4a-o**) were added and the reaction mixture was stirred for 3-4 h at room temperature. TLC was performed to confirm the completion of reaction. The excess chilled water was added on vigorous shaking and the mixture was aged for 1 h for precipitation. The precipitates were filtered, washed and dried. Some compounds were extracted by chloroform.

Antibacterial activity assay: The synthesized compounds were screened for the antibacterial activity by the reported method [16].

Spectral characterization of the synthesized compounds

Ethyl 1-(4-nitrophenylsulfonyl)piperidin-4-carboxylate (1): Off white amorphous solid; Yield: 90 %; m.p.: 142-145 °C; m.f.: $C_{14}H_{18}N_2O_6S$; molecular mass: 342.37 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3079 (Ar C-H), 1723 (C=O), 1610 (Ar C=C), 1519 (N=O), 1455 (S=O), 1176 (C-N); ^{1}H NMR ($CDCl_3$, 600 MHz, δ (ppm)): 8.39 (d, *J* = 8.8 Hz, 2H, H-3'', H-5''), 7.95 (d, *J* = 8.8 Hz, 2H, H-2'', H-6''), 4.11 (q, *J* = 7.14 Hz, 2H, CH_2), 3.64 (dt, *J* = 4.2, 12.1 Hz, 2H, H_{eq}-2', H_{eq}-6'), 2.62 (dt, *J* = 3.0, 8.9 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.32-2.28 (m, 1H, H-4'), 2.02-2.00 (m, 2H, H_{eq}-3', H_{eq}-5'), 1.99-1.97 (m, 2H, H_{ax}-3', H_{ax}-5'), 1.22 (t, *J* = 7.14 Hz, 3H, CH_3); EI-MS (*m/z*): 342 [M]$^+$, 269, 185, 122.

1-(4-Nitrophenylsulfonyl)piperidin-4-carbohydrazide (2): Light red amorphous solid; Yield: 85 %; m.f.: $C_{12}H_{16}N_4O_5S$; molecular mass: 328.34 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3098 (Ar C-H), 1635 (C=O), 3279 (N-H), 1608 (Ar C=C), 1515 (N=O), 1395 (S=O), 1085 (C-N); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.45 (d, *J* = 8.6 Hz, 2H, H-3'', H-5''), 6.73 (d, *J* = 8.7 Hz, 2H, H-2'', H-6''), 4.60 (s, 2H, N-H), 3.72-3.68 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.29 (dt, *J* = 3.5, 11.6 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.12-2.09 (m, 1H, H-4'), 1.82-1.75 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 328 [M]$^+$, 269, 185, 122.

5-[1-(4-Nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (3): Light green amorphous solid; Yield: 77 %; m.p.: 176-177 °C; m.f.: $C_{13}H_{14}N_4O_5S_2$; molecular mass: 370.40 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3075 (Ar C-H), 2567 (S-H), 1678 (C=N), 1596 (Ar C=C), 1523 (N=O), 1435 (S=O), 1222, 1039 (C-O-C), 1076 (C-N), 605 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.43 (d, *J* = 8.7 Hz, 2H, H-3'', H-5''), 6.75 (d, *J* = 8.7 Hz, 2H, H-2'', H-6''), 3.68-3.64 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.51 (dt, *J* = 11.6,11.3 Hz, 2H, H_{ax}-2',H_{ax}-6'), 2.15-2.11 (m, 1H, H-4'), 1.85-1.79 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 370 [M]$^+$, 311, 297, 295, 269, 185, 122.

2-(Ethylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole(5a): Sticky greenish solid; Yield: 82 %; m.f.: $C_{15}H_{18}N_4O_5S_2$; molecular mass: 398.46 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3132 (Ar C-H), 1678 (C=N), 1584 (Ar C=C), 1518 (N=O), 1426 (S=O), 1226, 1028 (C-O-C), 1148 (C-N), 628 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.73 (d, *J* = 8.2 Hz, 2H, H-3'', H-5''), 7.05 (d, *J* = 8.1 Hz, 2H, H-2'', H-6''), 3.74-3.72 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.24 (q, *J* = 7.3 Hz, 2H, H-1'''), 2.66 (dt, *J* = 11.6 Hz, 2H, H_{ax}-2',H_{ax}-6'), 1.44 (t, *J* = 7.2 Hz, 3H, H-2'''); EI-MS (*m/z*): 398 [M]$^+$, 311, 297, 295, 269, 185, 122.

2-(*n*-Propylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5b): Light green amorphous solid; Yield: 82 %; m.p.: 111-112 °C; m.f.: $C_{16}H_{20}N_4O_5S_2$; molecular mass: 412 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3098 (Ar C-H), 1654 (C=N), 1594 (Ar C=C), 1523 (N=O), 1446 (S=O), 1238, 1042 (C-O-C), 1168 (C-N), 642 (C-S); ^{1}H NMR (MeOD, 600MHz, δ (ppm)): 7.48 (d, *J* = 8.8 Hz, 2H, H-3'', H-5''), 6.75 (d, *J* = 6.7 Hz, 2H, H-2'',H-6''), 3.67-3.65 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.22 (t, *J* = 7.2 Hz, 2H, H-1'''), 2.52 (dt, *J* = 2.7, 12.2 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.16-2.14 (m, 1H, H-4'), 1.89-1.86 (m, 4H, H-3', H-5'), 1.80 (sex, *J* = 7.4 Hz, 2H, H-2'''), 1.05 (t, *J* = 7.3 Hz, 3H, H-3'''); EI-MS (*m/z*): 412 [M]$^+$, 311, 297, 295,269, 185, 122.

2-(Isopropylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5c): Dark brown sticky solid; Yield: 78 %; m.f.: $C_{16}H_{20}N_4O_5S_2$; molecular mass: 412.38 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3062 (Ar C-H), 1668 (C=N), 1615 (Ar C=C),

1549 (N=O), 1398 (S=O), 1215, 1021 (C-O-C), 1096 (C-N), 643 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.40 (d, *J* = 8.6 Hz, 2H, H-3", H-5"), 6.72 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 3.68-3.62 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.75-2.65 (m, 1H, H-1'"), 2.59-2.49 (m, 2H, H_{ax}-2', H_{ax}-6'), 2.12-2.07 (m, 1H, H-4'), 1.95-1.94 (m, 4H, H-3', H-5'), 1.87 (d, *J* = 7.2 Hz, 6H, H-2'", H-3'"); EI-MS (*m/z*): 412 $[M]^+$, 311, 297, 295,269, 185, 122.

2-(*n*-Butylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5d): Light brown amorphous solid; Yield: 83 %; m.p.: 85-86 °C; m.f.: $C_{17}H_{22}N_4O_5S_2$; molecular mass: 426.51 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3068 (Ar C-H), 1662 (C=N), 1610 (Ar C=C), 1543 (N=O), 1368 (S=O), 1218, 1024 (C-O-C), 1096 (C-N), 646 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.47 (d, *J* = 9.8 Hz, 2H, H-3", H-5"), 6.75 (d, *J* = 8.8 Hz, 2H, H-2", H-6"), 3.68-3.65 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.23 (t, *J* = 7.3 Hz, 2H, H-1'"), 2.54 (dt, *J* = 2.7, 8.9 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.16-2.14 (m, 1H, H-4'), 1.91-1.84 (m, 4H, H-3', H-5'), 1.75 (qui, *J* = 7.3 Hz, 2H, H-2'"), 1.50 (sex, *J* = 7.5 Hz, 2H, H-3'"), 0.97 (t, *J* = 6.3 Hz, 3H, H-4'"); EI-MS (*m/z*): 426 $[M]^+$, 311, 297, 295,269, 185, 122, 57.

2-(*sec*-Butylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5e): Light brown amorphous solid; Yield: 81 %; m.p.: 122-123 °C; m.f.: $C_{17}H_{22}N_4O_5S_2$; molecular mass: 426.51 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3038 (Ar C-H), 1642 (C=N), 1590 (Ar C=C), 1513 (N=O), 1395 (S=O), 1168, 1044 (C-O-C), 1066 (C-N), 626 (C-S); ^{1}H NMR (MeOD, 600MHz, δ (ppm)): 7.48 (d, *J* = 8.7 Hz, 2H, H-3", H-5"), 6.74 (d, *J* = 6.7 Hz, 2H, H-2", H-6"), 3.74-3.72 (m, 1H, H-1'"), 3.72-3.65 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.55 (dt, *J* = 2.6, 8.9 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.17-2.14 (m, 1H, H-4'), 1.91-1.85 (m, 4H, H-3', H-5'), 1.68 (qui, *J* = 7.3 Hz, 2H, H-2'"), 1.47 (d, *J* = 7.9 Hz, 3H, H-4'"), 0.97 (t, *J* = 7.3 Hz, 3H, H-3'"); EI-MS (*m/z*): 426 $[M]^+$, 311, 297, 295,269, 185, 122, 57.

2-(*n*-Pentylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5f): Orange sticky solid; Yield: 76 %; m.f.: $C_{18}H_{24}N_4O_5S_2$; molecular mass: 440.54 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3084 (Ar C-H), 1672 (C=N), 1606 (Ar C=C), 1518 (N=O), 1386 (S=O), 1234, 1027 (C-O-C), 1064 (C-N), 628 (C-S); ^{1}H NMR (MeOD, 600MHz, δ (ppm)): 7.40 (d, *J* = 8.9 Hz, 2H, H-3", H-5"), 6.74 (d, *J* = 8.6 Hz, 2H, H-2", H-6"), 3.68-3.65 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.23 (t, *J* = 7.3 Hz, 2H, H-1'"), 2.54 (dt, *J* = 2.8, 9.0 Hz, 2H, H_{ax}-2',H_{ax}-6'), 2.16-2.14 (m, 1H, H-4'), 1.91-1.87 (m, 4H, H-3', H-5'), 1.78 (qui, *J* = 7.4 Hz, 2H, H-2'"), 1.47-1.43 (m, 2H, H-3'"), 1.37 (sex, *J* = 7.6 Hz, 2H, H-4'"), 0.95 (t, *J* = 7.1 Hz, 3H, H-5'"); EI-MS (*m/z*): 440 $[M]^+$, 311, 297, 295,269, 185, 122, 71.

2-(*n*-Heptylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5g): Dark brown sticky solid; Yield: 86 %; m.f.: $C_{20}H_{28}N_4O_5S_2$; molecular mass: 468.59 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3124 (Ar C-H), 1664 (C=N), 1596 (Ar C=C), 1512 (N=O), 1446 (S=O), 1185, 1047 (C-O-C), 1164 (C-N), 618 (C-S); ^{1}H NMR (MeOD, 500 MHz, δ (ppm)): 7.44 (d, *J* = 9.0 Hz, 2H, H-3", H-5"), 6.71 (d, *J* = 9.0 Hz, 2H, H-2", H-6"), 3.65-3.62 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.19 (t, *J* = 7.0 Hz, 2H, H-1'"), 2.96-2.91 (m, 1H, H-4'), 2.50 (dt, *J* = 2.5, 12.0 Hz, 2H, H_{ax}-2',H_{ax}-6'), 2.12 (dd, *J* = 3.5,13.5 Hz, 2H, H_{eq}-3',H_{eq}-5'), 1.86 (dq, *J* = 4.0, 9.5 Hz, 2H, H_{ax}-3',H_{ax}-5'), 1.75 (qui, *J* = 7.5 Hz, 2H, H-2'"), 1.42 (qui, *J* = 8.0 Hz, 2H, H-3'"), 1.38-1.27 (m, 6H, H-4'" to H-6'"), 0.89 (t, *J* = 7.0 Hz, 3H, H-7'"); EI-MS (*m/z*): 468 $[M]^+$, 311, 297, 295,269, 185, 122, 99.

2-(Benzylthio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (5h): Yellow sticky solid; Yield: 86 %; m.f.: $C_{20}H_{20}N_4O_5S_2$; molecular mass: 460.53 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3132 (Ar C-H), 1678 (C=N), 1584 (Ar C=C), 1518 (N=O), 1426 (S=O), 1226, 1028 (C-O-C), 1148 (C-N), 628 (C-S); ^{1}H NMR (MeOD, 500 MHz, δ (ppm)): 7.43 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.38 (d, *J* = 7.0 Hz, 2H, H-2'", H-6'"), 7.33-7.26 (m, 3H, H-3'"to H-5'"), 6.70 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 4.42 (s, 2H, H-7'"), 3.67-3.58 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.98 (br.s, 1H, H-4'), 2.54-2.49 (m, 2H, H_{ax}-2',H_{ax}-6'), 2.16-2.13 (m, 2H, H_{eq}-3', H_{eq}-5'), 1.83-1.80 (m, 2H, H_{ax}-3', H_{ax}-5'); EI-MS (*m/z*): 460 $[M]^+$, 311, 297, 295,269, 185, 122, 91,65.

2-(2-Methylbenzylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5i): Sticky brown solid; Yield: 85 % m.f.: $C_{21}H_{22}N_4O_5S_2$; molecular mass: 474.55 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3090 (Ar C-H), 1658 (C=N), 1598 (Ar C=C), 1545 (N=O), 1397 (S=O), 1242, 1023 (C-O-C), 1127 (C-N), 625 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.45 (d, *J* = 8.8 Hz, 2H, H-3", H-5"), 7.23-7.11 (m, 4H, H-3'"to H-6'"), 6.68 (d, *J* = 7.8 Hz, 2H, H-2", H-6"), 4.74 (s, 2H, H-7'"), 3.70 (br.s, 2H, H_{eq}-2', H_{eq}-6'), 2.43 (br.s, 2H, H_{ax}-2',H_{ax}-6'), 2.37 (s, 3H, CH_3-2'"), 2.28-2.26 (m, 1H, H-4'), 1.68-1.81 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 474 $[M]^+$, 311, 297, 295,269, 185, 122, 105.

2-(4-Fluorobenzylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5j): Brown sticky solid; Yield: 78 %; m.f.: $C_{20}H_{19}N_4O_5S_2F$; molecular mass: 478.52 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3120 (Ar C-H), 1678 (C=N), 1610 (Ar C=C), 1543 (N=O), 1437 (S=O), 1192, 1043 (C-O-C), 1157 (C-N), 629 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.47 (d, *J* = 8.8 Hz, 2H, H-3", H-5"), 7.29 (d, *J* = 8.7 Hz, 2H, H-3'", H-5'"), 7.06 (d, *J* = 8.8 Hz, 2H, H-2'", H-6'"), 6.74 (d, *J* = 8.8 Hz, 2H, H-2", H-6"), 4.45 (s, 2H, H-7'"), 7.67 (br.s, 2H, H_{eq}-2', H_{eq}-6'), 2.53-2.51 (m, 2H, H_{ax}-2', H_{ax}-6'), 2.15-2.12 (m, 1H, H-4'), 1.84-1.80 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 478 $[M]^+$, 311, 297, 295, 269, 185, 122, 109, 65.

2-(2-Chlorobenzylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5k): Light brown sticky liquid; Yield: 80 %; m.f.: $C_{20}H_{19}ClN_4O_5S_2$; molecular mass: 494.97 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3115 (Ar C-H), 1639 (C=N), 1605 (Ar C=C), 1527 (N=O), 1447 (S=O), 1225, 1027 (C-O-C), 1155 (C-N), 637 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.49 (d, *J* = 8.8 Hz, 1H, H-6'"), 7.4 (d, *J* = 6.8 Hz, 2H, H-3", H-5"), 7.31 (d, *J* = 9.0 Hz, 2H, H-2", H-6"), 7.29-7.24 (m, 3H, H-3'" to H-5'"), 4.49 (s, 2H, H-7'"), 3.85-3.83 (m, 2H,H_{eq}-2', H_{eq}-6'), 3.01 (br.s, 2H,H_{ax}-2', H_{ax}-6'), 2.27-2.10 (m, 1H, H-4'), 1.85-1.75 (m, 4H, H-3', H-5'); EIMS (*m/z*): 496 $[M+2]^+$, 494 $[M]^+$, 311, 297, 295, 269, 185, 125, 122.

2-(4-Chlorobenzylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5l): Greenish sticky product; Yield: 81 %; m.f.: $C_{20}H_{19}ClN_4O_5S_2$; molecular mass: 494.97 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3116 (Ar C-H), 1634 (C=N), 1606 (Ar C=C), 1530 (N=O), 1442 (S=O), 1228, 1027 (C-O-C), 1135 (C-N), 638 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)):7.42 (d, *J* = 8.5 Hz, 2H, H-3", H-5"), 7.34 (d, *J* = 8.7 Hz, 2H, H-2'", H-6'"), 7.33 (d, *J* = 8.4 Hz, 2H, H-3'", H-5'"),

6.74 (d, *J* = 8.8 Hz, 2H, H-2", H-6"), 4.44 (s, 2H, H-7'"), 3.67 (br.s, 2H,H_{eq}-2', H_{eq}-6'), 2.58-2.51 (m, 2H,H_{ax}-2', H_{ax}-6'), 2.15-2.11 (m, 1H, H-4'), 1.89-1.81 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 496 $[M+2]^+$, 494 $[M]^+$, 311, 297, 295,269, 185, 125, 122.

2-(4-Bromobenzylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5m): Yellow amorphous solid; Yield: 77 %; m.p.: 99-101 °C; m.f.: $C_{20}H_{19}N_4O_5S_2Br$; molecular mass: 538.42 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3064 (Ar C-H), 1658 (C=N), 1612 (Ar C=C), 1542 (N=O), 1398 (S=O), 1245, 1036 (C-O-C), 1155 (C-N), 607 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)): 7.48 (d, *J* = 7.02 Hz, 2H, H-3", H-5"), 7.36 (d, *J* = 8.4 Hz, 2H, H-2'", H-6'"), 7.30 (d, *J* = 8.5 Hz, 2H, H-3'", H-5'"), 6.70 (d, *J* = 8.2 Hz, 2H, H-2", H-6"), 4.58 (s, 2H, H-7'"), 3.66-3.59 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.58-2.54 (m, 2H,H_{ax}-2', H_{ax}-6'), 2.20-2.10 (m, 1H, H-4'), 1.30 (br.s, 4H, H-3', H-5'); EI-MS (*m/z*): 540 $[M+2]^+$, 538 $[M]^+$, 311, 297, 295, 269, 185, 169, 122, 65.

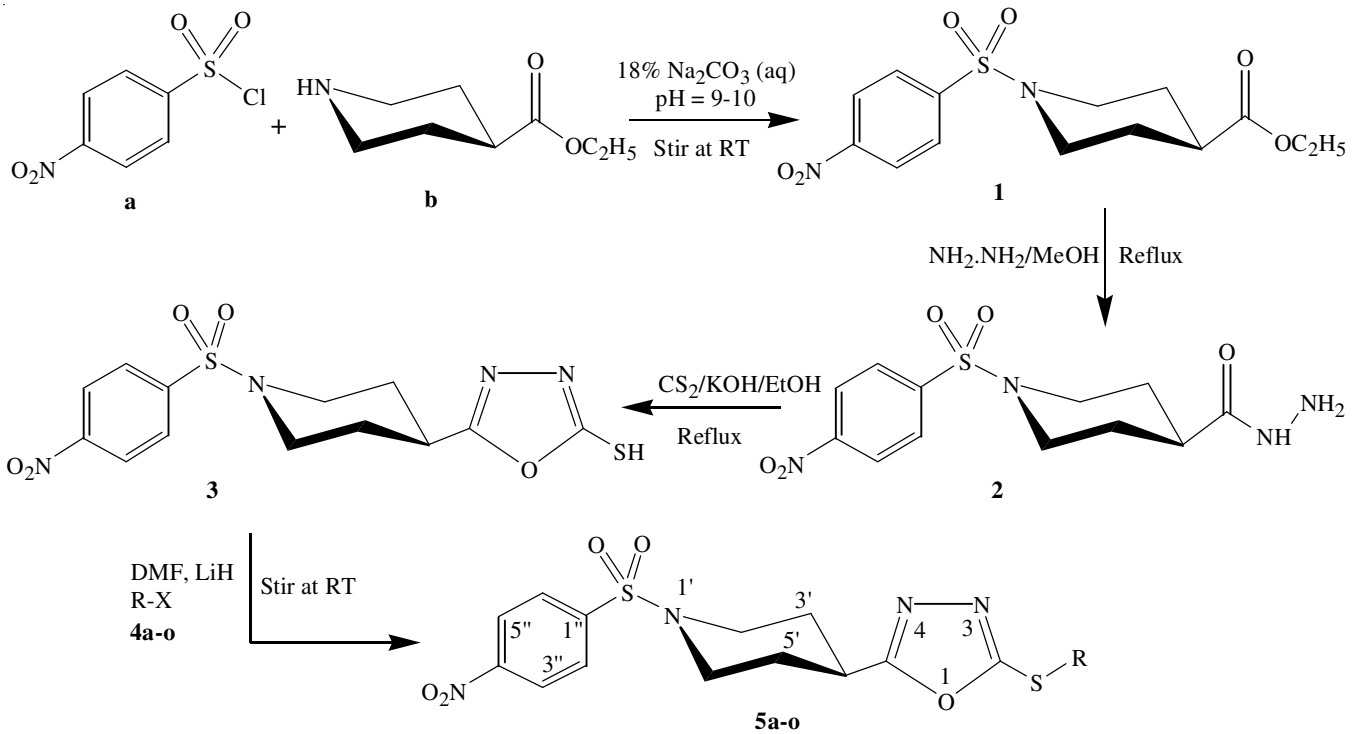
2-(2-Bromoethylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5n): Yellow amorphous solid; Yield: 83 %; m.p.: 186-187 °C; m.f.: $C_{15}H_{17}N_4O_5S_2Br$; molecular mass: 476.35 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3132 (Ar C-H), 1678 (C=N), 1584 (Ar C=C), 1518 (N=O), 1426 (S=O), 1226, 1028 (C-O-C), 1148 (C-N), 628 (C-S); ^{1}H NMR (MeOD, 500 MHz, δ (ppm)): 7.45 (d, *J* = 8.2 Hz, 2H, H-3", H-5"), 6.71 (d, *J* = 8.5 Hz, 2H, H-2", H-6"), 5.70 (t, *J* = 9.5 Hz, 2H, H-2'"), 3.65-3.62 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.45 (t, *J* = 6.5 Hz, 2H, H-1'"), 2.85 (br.s, 1H, H-4'), 2.51 (dt, *J* = 2.5, 12 Hz, 2H, H_{ax}-2',H_{ax}-6'), 2.13 (dd, *J* = 3.5, 13.5 Hz, 2H, H-2'"), 1.89-1.81 (m, 4H, H-3', H-5'); EI-MS (*m/z*): 478 $[M+2]^+$, 476 $[M]^+$, 311, 297, 295, 269, 185, 122, 107.

2-(3-Bromopropylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole (5o): Light brown amorphous solid; Yield: 84 %; m.p.: 142-143 °C; m.f.: $C_{16}H_{19}N_4O_5S_2Br$; molecular mass: 491.38 g mol^{-1}; IR (KBr, ν_{max}, cm^{-1}): 3125 (Ar C-H), 1675 (C=N), 1610 (Ar C=C), 1533 (N=O), 1445 (S=O), 1168, 1024 (C-O-C), 1128 (C-N), 634 (C-S); ^{1}H NMR (MeOD, 600 MHz, δ (ppm)); 7.51 (d, *J* = 8.7 Hz, 2H, H-3", H-5"), 6.83 (d, *J* = 8.6 Hz, 2H, H-2", H-6"), 3.69-3.67 (m, 2H, H_{eq}-2', H_{eq}-6'), 3.16 (t, *J* = 5.8 Hz, 2H, H-1'"), 2.32 (dt, *J* = 6.6 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.22 (qui, *J* = 6.5 Hz, 2H, H-2'"), 2.13-2.11 (m, 1H, H-4'), 1.91-1.83 (m, 4H, H-3', H-5'), 0.92 (t, *J* = 6.9 Hz, 2H, H-3'"); EI-MS (*m/z*): 491 $[M]^+$, 311, 297, 295, 269, 185, 122, 121.

RESULTS AND DISCUSSION

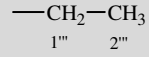
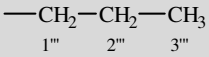
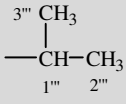
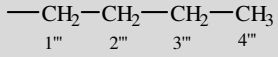
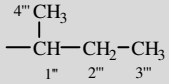
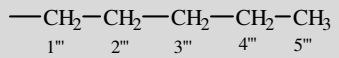
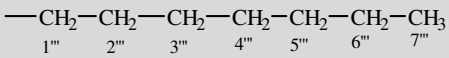
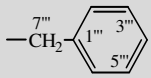
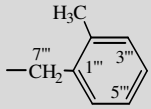
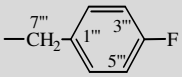
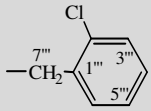
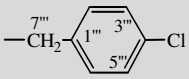
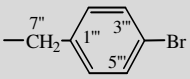
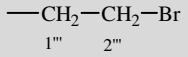
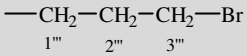
Resistivity of microbes against existing drugs prompted us to synthesize some new *S*-substituted-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole.All the compounds were characterized by IR, ^{1}H NMR and EIMS. The protocol for synthesis is given in **Scheme-I** and the varying groups are given in Table-1.

Compound **5b** has been considered for single compound discussion. It was obtained in the form of light green amorphous solid having melting point of 111-112 °C. Its molecular formula was found to be $C_{16}H_{20}N_4O_5S_2$ with molecular mass of 412 g mol^{-1} erected from mass spectrum data and the integration curves of protons in ^{1}H NMR spectrum. In IR spectrum, the stretching absorption peaks appeared at 3098 cm^{-1} for aromatic C-H of benzene ring chloride, at 1654 for C=N of oxadiazole ring, at 1594 for aromatic C=C of benzene ring, at 1523 for N=O of nitro group, at 1446 for S=O of sulfonyl group, at 1238, 1042 for C-O-C of oxadiazole ring, at 1168 for C-N bond and at 642 for C-S bond. In ^{1}H NMR spectrum, the aromatic protons of 4-nitrobenzenesulfonyl appeared at d 7.48 (d, *J* = 8.8 Hz, 2H, H-3", H-5") and 6.75 (d, *J* = 6.7 Hz, 2H, H-2", H-6"). The piperidine ring presented signals at 3.67-3.65 (m, 2H, H_{eq}-2', H_{eq}-6'), 2.52 (dt, *J* = 2.7 Hz, 2H, H_{ax}-2', H_{ax}-6'), 2.16-2.14 (m, 1H, H-4') and 1.89-1.86 (m, 4H, H-3',



Scheme-I: Synthesis of 2-(substituted thio)-5-[1-(4-nitrophenylsulfonyl)piperidin-4-yl]-1,3,4-oxadiazole (**5a-o**)

TABLE-1
DIFFERENT ALKYL/ARALKYL GROUPS

Compound	R
5a	
5b	
5c	
5d	
5e	
5f	
5g	
5h	
5i	
5j	
5k	
5l	
5m	
5n	
5o	

H-5'). The signals due to substitution at heteroatom 'S' were 3.22 (t, *J* = 7.2 Hz, 2H, H-1'''), 1.80 (sex, *J* = 7.4 Hz, 2H, H-2''') and 1.05 (t, *J* = 7.3 Hz, 3H, H-3''') for *n*-propyl group. In the EI-MS spectral data, the fragment at 311 confirmed the formation of 1,3,4-oxadiazole ring. This fragment was further converted into small fragments of 297, 295, 269, 185 and 122. The above mentioned spectroscopic evidences corroborated the structure of 2-(*n*-propylthio)-5-[1-(4-nitrophenylsulfonyl)-piperidin-4-yl]-1,3,4-oxadiazole. The structures of other synthesized derivatives were also confirmed by the spectroscopic data given in the experimental section.

Biological activity: All the compounds were screened for their antibacterial activity and the results are mentioned as % inhibition in Table-2. Ofloxacin was used as reference standard. The most of the compounds remained efficient against *E. coli*, *S. aureus* and *S. typhi* but one or two compounds showed inhibition against *P. aeruginosa* and *B. subtilis*. The inhibition potential demonstrated the least bioactivity of these synthesized compounds against all the bacterial strains. The compound **5e** remained inactive at all against the bacterial strains. Against *B. subtilis*, the compounds, **5c** and **5l**, were active with % inhibition of 35.04 and 30.49 with respect to that of ofloxacin with % inhibition of 95.60. Against *S. aureus*, **5m** was the most active with % inhibition of 19.49. The compound **5g** was the best inhibitor of *E. coli* bacterial strain. Against *S. typhi*, **5g** was the most active inhibitor. The best activity of **5c**, **5l**, **5m** and **5g** might be attributed to the presence of isopropyl, 4-chlorobenzyl, 4-bromobenzyl and *n*-heptyl groups respectively.

TABLE-2
% INHIBITION OF ANTIBACTERIAL ACTIVITY

Compd.	Inhibition (%)				
	B. subtilis (+)	*S. aureus* (+)	*E. coli* (–)	*P. aeruginosa* (–)	*S. typhi* (–)
5a	–	–	9.39	–	–
5b	–	–	5.20	–	–
5c	35.04	–	15.21	–	12.78
5d	–	3.6	17.52	–	–
5e	–	–	–	–	–
5f	–	14.09	3.50	–	–
5g	–	7.36	22.04	4.68	15.29
5h	–	–	9.41	–	3.42
5i	–	3.38	7.49	–	–
5j	–	6.92	6.56	–	–
5k	–	4.85	11.67	–	14.62
5l	30.49	–	–	–	–
5m	–	19.49	6.31	–	–
5n	–	9.19	6.59	–	–
5o	–	–	8.17	–	–
Ofloxacin	95.60	95.43	93.98	94.28	92.75

Conclusion

All the compounds were obtained in notable yields and were well corroborated by spectral data. The antibacterial activity evaluation demonstrated lowantibacterial potential of these compounds except a few ones.

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REFERENCES

1. F. Macaev, G. Rusu, S. Pogrebnoi, A. Gudima, E. Stingaci, L. Vlad, N. Shvets, F. Kandemirli, A. Dimoglo and R. Reynolds, *Bioorg. Med. Chem.*, **13**, 4842 (2005); https://doi.org/10.1016/j.bmc.2005.05.011.
2. M. Al-Ghorbani, V. Vigneshwaran, V.L. Ranganatha, B.T. Prabhakar and S.A. Khanum, *Bioorg. Chem.*, **60**, 136 (2015); https://doi.org/10.1016/j.bioorg.2015.04.008.
3. D.D. Gaikwad, A.D. Chapolikar, C.G. Devkate, K.D. Warad, A.P. Tayade, R.P. Pawar and A.J. Domb, *Eur. J. Med. Chem.*, **90**, 707 (2015); https://doi.org/10.1016/j.ejmech.2014.11.029.
4. E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu and G. Altinok, *Farmaco*, **57**, 101 (2002); https://doi.org/10.1016/S0014-827X(01)01176-4.
5. M. Amir and K. Shikha, *Eur. J. Med. Chem.*, **39**, 535 (2004); https://doi.org/10.1016/j.ejmech.2004.02.008.

6. A. Zarghi, S.A. Tabatabai, A. Faizi, P. Ahadian, V. Navabi, A. Zanganeh and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **15**, 1863 (2005); https://doi.org/10.1016/j.bmcl.2005.02.014.
7. J.J. Bhat, B.R. Shah, H.P. Shah, P.B. Trivedi, N.K. Undavia and N.C. Desai, *Indian J. Chem.*, **33B**, 189 (1994).
8. H.D. Gurupadaswamy, V. Girish, C.V. Kavitha, S.C. Raghavan and S.A. Khanum, *Eur. J. Med. Chem.*, **63**, 536 (2013); https://doi.org/10.1016/j.ejmech.2013.02.040.
9. H.D. Gurupadaswamy, P. Thirusangu, B.R. Vijay Avin, V. Vigneshwaran, M.V. Prashanth Kumar, T.S. Abhishek, V.L. Ranganatha, S.A. Khanum and B.T. Prabhakar, *J. Biomed. Pharmacother.*, **68**, 791 (2014); https://doi.org/10.1016/j.biopha.2014.07.004.
10. P.A. Clarke, A.V. Zaytzev and A.C. Whitwood, *Tetrahedron Lett.*, **48**, 5209 (2007); https://doi.org/10.1016/j.tetlet.2007.05.141.
11. K. Kamei, N. Maeda, R. Katsuragi-Ogino, M. Koyama, M. Nakajima, T. Tatsuoka, T. Ohno and T. Inoue, *Bioorg. Med. Chem. Lett.*, **15**, 2990 (2005); https://doi.org/10.1016/j.bmcl.2005.04.059.
12. M. Misra, S.K. Pandey, V.P. Pandey, J. Pandey, R. Tripathi and R.P. Tripathi, *Bioorg. Med. Chem.*, **17**, 625 (2009); https://doi.org/10.1016/j.bmc.2008.11.062.
13. Z.C. Wu, X. Wang, W. Wei and X. Chin, *J. Synth. Chem.*, **22**, 429 (2014).
14. D.H. Jiang and M. Huang, *Chem. Reagents*, **34**, 797 (2012).
15. Aziz-ur-Rehman, H. Khalid, M.A.Abbasi, S.Gul, I. Ahmad and S. Arshad, *J. Chem. Soc. Pak.*, **36**, 131 (2014).
16. M. Kaspady, V.K. Narayanaswamy, M. Raju and G.K. Rao, *Lett. Drug Des. Discov.*, **6**, 21 (2009); https://doi.org/10.2174/157018009787158481.