Canadian Chemical Transactions

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

Research Article

DOI:10.13179/canchemtrans.2014.02.03.0121

Synthesis and *In Vitro* Antimicrobial Activity of 2,4-Difluorophenyl (piperidin-4-yl)methanone Oxime Derivatives

Lingappa Mallesha[1*] and Kikkeri N. Mohana[2]

[1]*PG Department of Chemistry, JSS College of Arts, Commerce and Science, Ooty Road, Mysore-25, India*
[2]*Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-06, India*

[*]*Corresponding Author, E-mail: mallesha83@gmail.com Phone: 077951-01182*

Received: *April 19, 2014* ***Revised:*** *May 8, 2014* ***Accepted:*** *May 9, 2014* ***Published:*** *May 15, 2014*

Abstract: A series of new 2,4-difluorophenyl(piperidin-4-yl)methanone oxime derivatives **4a-h** and **5a-e** were synthesized by the reaction of 2,4-difluorophenyl(piperidin-4-yl)methanone oxime with various sulfonyl and acid chlorides. The synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and LCMS spectral studies. All compounds were evaluated for *in vitro* antibacterial and antifungal activities. Compounds **4b**, **4g** and **5e** exhibited good antimicrobial activity against tested pathogenic bacterial and fungal strains. Compound **4b** would be a more activity deserves further research.

Keywords: Piperidine; Sulfonyl chlorides; Acid chlorides; Antibacterial; Antifungal

1. INTRODUCTION

Diseases caused by bacterial and fungal infection are a serious menace to the health of mankind and often have connection to some the other diseases, whenever the body system gets debilitated. Developing antimicrobial drugs and maintaining their potency, in opposition to resistance by different classes of microorganisms as well as a broad spectrum of antimicrobial activity are some of the major concern of research in this area. In recent years, considerable interest has been devoted to finding a new methodology for the synthesis of piperidine building blocks.

Piperidine fragment was substituted via variety of synthetic reactions to develop more improved moieties with enhanced activities and to suppress the side effects when taken as medicine for different ailments [1, 2]. Specifically, piperidine based chemical entities with aryl substituents have been documented as potent microbial agents [3, 4]. It is important group of heterocyclic compounds in the field of medicinal chemistry due to their biological activities, including cytotoxic and anticancer properties [5]. Several substituted piperidines display important biological properties like antiviral activity [6], antidepressant effects [7], cytotoxic activity [8] and antibacterial activity [9].

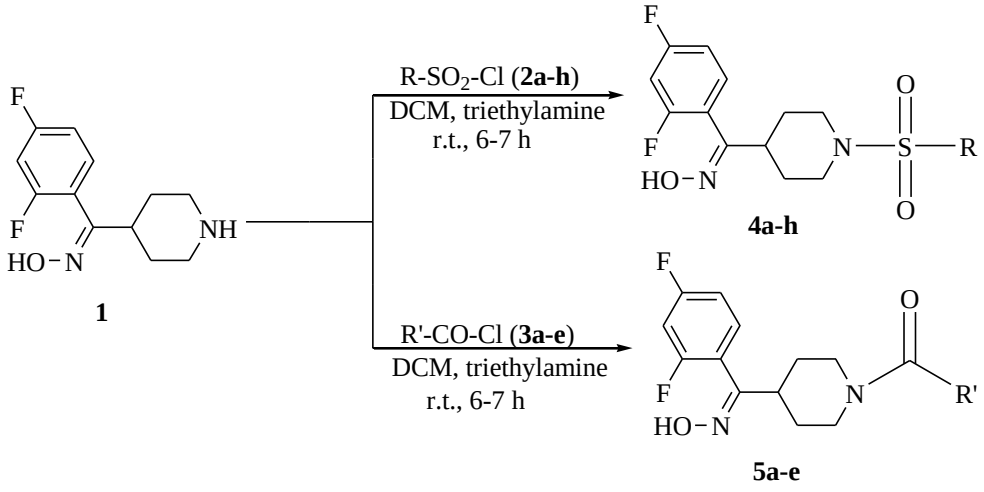
ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

2,4-Difluorophenyl(piperidin-4-yl)methanone oxime (**1**) is an intermediate in the preparation of risperidone. Risperidone contains the functional groups of benzisoxazole and piperidine as part of its molecular structure. The use of risperidone is considered to be important in the treatment of schizophrenia and psychotic disorders helping to manage schizophrenia's "positive symptoms" such as visual and auditory hallucinations, delusions, and thought disturbances. It is believed that its atypical activity profile may be due to its effect on an interaction between the serotonin and dopamine system [10]. The risperidone has combined serotonin and dopamine receptor and plays an important role in the treatment of schizophrenia. This may recur even if the patient has switched to a different antipsychotic [11]. Antimicrobial activity of compounds containing nature of functional linkage [12] and substituted aromatic ring [13] has been reported. In the present study, some new 2,4-difluorophenyl(piperidin-4-yl)methanone oxime derivatives, **4a-h** and **5a-e** have been synthesized and their antimicrobial activity was determined against tested pathogenic microbial strains.

2. EXPERIMENTAL

All solvents and reagents were purchased from Sigma Aldrich Chemicals. Melting points were determined on an electrically heated VMP-III melting point apparatus (*Veego*, India). The elemental analyses of the compounds were performed on a Perkin Elmer 2400 Elemental Analyser. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. The NMR spectra were recorded using *Bruker DRX* 400 spectrometer at 400 *MHz* for ^{1}H NMR with tetramethylsilane as the internal standard. Mass spectral data were obtained *by* LC-MSD Trap XCT. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

2,4-Difluorophenyl(piperidin-4-yl)methanone oxime derivatives **4a-h** and **5a-e** were prepared by the method summarized in Scheme 1. The reaction of 2,4-difluorophenyl(piperidin-4-yl)methanone oxime (**1**) with various sulfonyl chlorides (R-SO_2-Cl, **2a–h**) and acid chlorides (R'-CO-Cl, **3a–e**) were carried out in the presence of triethylamine and dry dichloromethane (DCM) as solvent with a good yield ranging from 70-80 % with colorless to yellow solids. These synthesized compounds were characterized by elemental analyses, FT-IR, ^{1}H NMR and LCMS spectral studies.



Scheme 1

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

2.1. General procedure for the synthesis of 2,4-difluorophenyl(piperidin-4-yl)methanone oxime derivatives 4a-h and 5a-e

A solution of 2,4-difluorophenyl(piperidin-4-yl)methanone oxime (**1**) (1.0 eq) in DCM was taken and cooled to 0–5 °C in an ice bath. Triethylamine (3.0 eq) was added to the cold reaction mixture and stirred for 10 min, then different sulfonyl chlorides (**2a–h**)/acid chlorides (**3a–e**) (1.0 eq) were added. The reaction mixture was allowed to stir at room temperature for 6-7 h. The progress of the reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10 % ammonium chloride solution and finally water wash was given to organic layer and dried with anhydrous sodium sulphate. The solvent was evaporated to get crude product which was purified by column chromatography over silica gel (60–120 mesh) using hexane: ethyl acetate (8:2) as an eluent.

2.1.1. (2,4-Difluoro-phenyl)-[1-(toluene-4-sulfonyl)-piperidin-4-yl]-methanone oxime (4a)

FT-IR (KBr, cm^{-1}): 3265 (O-H), 3073 (Ar-H), 1161 (C-N), 1106 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.90 (s, 1H, OH), 7.58 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.40 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.18 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.09 (d, 1H, Ar-H, *J* = 8.3 Hz), 6.91 (s, 1H, Ar-H), 3.58 (d, 4H, *J* = 12.0 Hz), 2.48 (s, 3H, CH_3), 2.30 (d, 4H, *J* = 21.6 Hz), 1.75 (m, 1H). MS (ESI) *m/z*: 394.4. Anal. Calcd. for $C_{19}H_{20}F_2N_2O_3S$ (in %): C, 57.86; H, 5.11; N, 7.10. Found: C, 57.91; H, 5.23; N, 7.15.

2.1.2. (2,4-Difluoro-phenyl)-[1-(2-trifluoromethyl-benzenesulfonyl)-piperidin-4-yl]-methanone oxime (4b)

FT-IR (KBr, cm^{-1}): 3252 (O-H), 3071 (Ar-H), 1170 (C-N), 1107 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.91 (s, 1H, OH), 7.99 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.92 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.38 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.24 (t, 1H, Ar-H, *J* = 12.4 Hz), 7.16 (d, 1H, Ar-H, *J* = 8.1 Hz), 7.08 (t, 1H, Ar-H, *J* = 11.2 Hz), 6.91 (s, 1H, Ar-H), 3.65 (d, 4H, *J* = 12.1 Hz), 2.35 (d, 4H, *J* = 11.8 Hz), 1.78 (m, 1H). MS (ESI) *m/z*: 448.4. Anal. Calcd. for $C_{19}H_{17}F_5N_2O_3S$ (in %): C, 50.89; H, 3.82; N, 6.25. Found: C, 50.79; H, 3.71; N, 6.31.

2.1.3. [1-(4-Chloro-benzenesulfonyl)-piperidin-4-yl]-(2,4-difluoro-phenyl)-methanone oxime (4c)

FT-IR (KBr, cm^{-1}): 3212 (O-H), 3054 (Ar-H), 1168 (C-N), 1107 (C-F), 721 (C-Cl). ^{1}H NMR (DMSO-d_6) δ ppm: 10.91 (s, 1H, OH), 7.71 (d, 2H, Ar-H, *J* = 2.4 Hz), 7.70 (d, 2H, Ar-H, *J* = 2.0 Hz), 7.24 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.18 (d, 1H, Ar-H, *J* = 7.9 Hz), 7.04 (s, 1H, Ar-H), 3.60 (d, 4H, *J* = 17.2 Hz), 2.37 (d, 4H, *J* = 20.6 Hz), 1.76 (m, 1H). MS (ESI) *m/z*: 414.8. Anal. Calcd. for $C_{18}H_{17}ClF_2N_2O_3S$ (in %): C, 52.11; H, 4.13; N, 6.75. Found: C, 52.02; H, 4.21; N, 6.71.

2.1.4. (1-Benzenesulfonyl-piperidin-4-yl)-(2,4-difluoro-phenyl)-methanone oxime (4d)

FT-IR (KBr, cm^{-1}): 3223 (O-H), 3061 (Ar-H), 1169 (C-N), 1109 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.90 (s, 1H, OH), 7.70-7.58 (m, 5H, Ar-H), 7.24 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.09 (d, 1H, Ar-H, *J* = 7.8 Hz), 6.90 (s, 1H, Ar-H), 3.60 (d, 4H, *J* = 4.8 Hz), 2.34 (d, 4H, *J* = 18.3 Hz), 1.76 (m, 1H). MS (ESI) *m/z*: 380.4. Anal. Calcd. for $C_{18}H_{18}F_2N_2O_3S$ (in %): C, 56.83; H, 4.77; N, 7.36. Found: C, 56.69; H, 4.57; N, 7.41.

2.1.5. (2,4-Difluoro-phenyl)-(1-methanesulfonyl-piperidin-4-yl)-methanone oxime (4e)

FT-IR (KBr, cm^{-1}): 3262 (O-H), 3029 (Ar-H), 1158 (C-N), 1111 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.90 (s, 1H, OH), 7.21 (d, 1H, Ar-H, *J* = 7.3 Hz), 7.02 (d, 1H, Ar-H, *J* = 7.5 Hz), 6.92 (s, 1H, Ar-H), 2.92 (d, 4H, *J* = 4.8 Hz), 2.83 (s, 3H, CH_3), 2.24 (d, 4H, *J* = 18.3 Hz), 1.75 (m, 1H). MS (ESI) *m/z*: 318.3. Anal. Calcd. for $C_{13}H_{16}F_2N_2O_3S$ (in %): C, 49.05; H, 5.07; N, 8.80. Found: C, 49.21; H, 5.20; N, 8.77.

2.1.6. (2,4-Difluoro-phenyl)-[1-(2-nitro-benzenesulfonyl)-piperidin-4-yl]-methanone oxime (4f)

FT-IR (KBr, cm^{-1}): 3219 (O-H), 3070 (Ar-H), 1545 (NO_2), 1175 (C-N), 1109 (C-F). ^{1}H NMR

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

(DMSO-d_6) δ ppm: 10.90 (s, 1H, OH), 8.50-7.84 (m, 4H, Ar-H), 7.16 (d, 1H, Ar-H, *J* = 12.2 Hz), 6.97 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.91 (s, 1H, Ar-H), 3.64 (d, 4H, *J* = 12.0 Hz), 2.34 (d, 4H, *J* = 11.8 Hz), 1.75 (m, 1H). MS (ESI) *m/z*: 425.4. Anal. Calcd. for $C_{18}H_{17}F_2N_3O_5S$ (in %): C, 50.82; H, 4.03; N, 9.88. Found: C, 50.71; H, 4.13; N, 9.81.

2.1.7. [1-(2,5-Dichloro-benzenesulfonyl)-piperidin-4-yl]-(2,4-difluoro-phenyl)-methanone oxime (4g)

FT-IR (KBr, cm^{-1}): 3358 (O-H), 3050 (Ar-H), 1169 (C-N), 1104 (C-F), 722 (C-Cl). ^{1}H NMR (DMSO-d_6) δ ppm: 10.90 (s, 1H, OH), 7.78 (s, 1H, Ar-H), 7.40 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.28 (d, 1H, Ar-H, *J* = 8.1 Hz), 7.15 (d, 1H, Ar-H, *J* = 4.8 Hz), 7.09 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.91 (s, 1H, Ar-H), 3.58 (d, 4H, *J* = 11.4 Hz), 2.30 (d, 4H, *J* = 18.6 Hz), 1.74 (m, 1H). MS (ESI) *m/z*: 449.3. Anal. Calcd. for $C_{18}H_{16}Cl_2F_2N_2O_3S$ (in %): C, 48.12; H, 3.59; N, 6.23. Found: C, 48.03; H, 3.53; N, 6.37.

2.1.8. [1-(4-tert-Butyl-benzenesulfonyl)-piperidin-4-yl]-(2,4-difluoro-phenyl)-methanone oxime (4h)

FT-IR (KBr, cm^{-1}): 3284 (O-H), 3024 (Ar-H), 1165 (C-N), 1115 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.93 (s, 1H, OH), 7.58 (d, 2H, Ar-H, *J* = 8.2 Hz), 7.41 (d, 2H, Ar-H, *J* = 8.3 Hz), 7.15 (d, 1H, Ar-H, *J* = 8.3 Hz), 7.00 (d, 1H, Ar-H, *J* = 7.3 Hz), 6.90 (s, 1H, Ar-H), 3.53 (d, 4H, *J* = 11.3 Hz), 2.32 (d, 4H, *J* = 16.2 Hz), 1.74 (m, 1H), 1.35 (s, 9H, $3CH_3$). MS (ESI) *m/z*: 436.5. Anal. Calcd. for $C_{22}H_{26}F_2N_2O_3S$ (in %): C, 60.53; H, 6.00; N, 6.42. Found: C, 60.37; H, 6.05; N, 6.43.

2.1.9. (2,4-Difluoro-phenyl)-[1-(3-methoxy-benzoyl)-piperidin-4-yl]-methanone oxime (5a)

FT-IR (KBr, cm^{-1}): 3282 (O-H), 3055 (Ar-H), 1644 (C=O), 1162 (C-N), 1139 (C-O), 1113 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.91 (s, 1H, OH), 7.33-7.22 (m, 3H, Ar-H), 7.13 (d, 1H, Ar-H, *J* = 8.0 Hz), 6.97 (s, 1H, Ar-H), 6.95 (d, 1H, Ar-H, *J* = 7.3 Hz), 6.84 (s, 1H, Ar-H), 3.78 (s, 3H, OCH_3), 3.55 (d, 4H, *J* = 11.0 Hz), 1.79 (d, 4H, *J* = 16.2 Hz), 1.75 (m, 1H). MS (ESI) *m/z*: 374.3. Anal. Calcd. for $C_{20}H_{20}F_2N_2O_3$ (in %): C, 64.16; H, 5.38; N, 7.48. Found: C, 64.21; H, 5.53; N, 7.37.

2.1.10. [1-(4-tert-Butyl-benzoyl)-piperidin-4-yl]-(2,4-difluoro-phenyl)-methanone oxime (5b)

FT-IR (KBr, cm^{-1}): 3279 (O-H), 3060 (Ar-H), 1645 (C=O), 1165 (C-N), 1115 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.91 (s, 1H, OH), 7.42 (d, 2H, Ar-H, *J* = 8.12 Hz), 7.29 (d, 2H, Ar-H, *J* = 8.3 Hz), 7.12 (d, 1H, Ar-H, *J* = 8.1 Hz), 7.10 (d, 1H, Ar-H, *J* = 4.3 Hz), 7.08 (s, 1H, Ar-H), 2.73 (d, 4H, *J* = 10.3 Hz), 2.48 (d, 4H, *J* = 16.2 Hz), 1.96 (m, 1H), 1.31 (s, 9H, $3CH_3$). MS (ESI) *m/z*: 400.4. Anal. Calcd. for $C_{23}H_{26}F_2N_2O_2$ (in %): C, 68.98; H, 6.54; N, 7.00. Found: C, 68.82; H, 6.44; N, 6.94.

2.1.11. (2,4-Difluoro-phenyl)-[1-(3,5-dinitro-benzoyl)-piperidin-4-yl]-methanone oxime (5c)

FT-IR (KBr, cm^{-1}): 3341 (O-H), 3075 (Ar-H), 1644 (C=O), 1536 (NO_2), 1171 (C-N), 1073 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 11.03 (s, 1H, OH), 8.99-8.96 (s, 3H, Ar-H), 7.30 (d, 1H, Ar-H, *J* = 9.2 Hz), 7.15 (d, 1H, Ar-H, *J* = 9.1 Hz), 6.95 (s, 1H, Ar-H), 3.22 (d, 4H, *J* = 11.7 Hz), 2.88 (d, 4H, *J* = 10.3 Hz), 1.86 (m, 1H). MS (ESI) *m/z*: 434.3. Anal. Calcd. for $C_{19}H_{16}F_2N_4O_6$ (in %): C, 52.54; H, 3.71; N, 12.90. Found: C, 52.38; H, 3.40; N, 12.82.

2.1.12. (2,4-Difluoro-phenyl)-[1-(2-fluoro-benzoyl)-piperidin-4-yl]-methanone oxime (5d)

FT-IR (KBr, cm^{-1}): 3293 (O-H), 3073 (Ar-H), 1645 (C=O), 1159 (C-N), 1117 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 11.43 (s, 1H, OH), 8.47-7.35 (m, 4H, Ar-H), 7.22 (d, 1H, Ar-H, *J* = 11.4 Hz), 7.12 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.07 (s, 1H, Ar-H), 3.82 (d, 4H, *J* = 11.3 Hz), 2.86 (d, 4H, *J* = 9.8 Hz), 1.85 (m, 1H). MS (ESI) *m/z*: 362.3. Anal. Calcd. for $C_{19}H_{17}F_3N_2O_2$ (in %): C, 62.98; H, 4.73; N, 7.73. Found: C, 62.82; H, 4.51; N, 7.61.

2.1.13. [1-(3,4-Dichloro-benzoyl)-piperidin-4-yl]-(2,4-difluoro-phenyl)-methanone oxime (5e)

FT-IR (KBr, cm^{-1}): 3244 (O-H), 3075 (Ar-H), 1645 (C=O), 1141 (C-N), 1070 (C-F). ^{1}H NMR (DMSO-d_6) δ ppm: 10.82 (s, 1H, OH), 7.54 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.48 (d, 1H, Ar-H, *J* = 9.0 Hz), 7.26-7.20 (s, 3H, Ar-H), 7.11 (s, 1H, Ar-H), 3.41 (d, 4H, *J* = 8.7 Hz), 1.96 (d, 4H, *J* = 10.3 Hz), 1.47 (m,

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

1H). MS (ESI) *m/z*: 413.2. Anal. Calcd. for $C_{19}H_{16}Cl_2F_2N_2O_2$ (in %): C, 55.22; H, 3.90; N, 6.78. Found: C, 55.33; H, 3.77; N, 6.85.

2.2. Antibacterial activity

Antibacterial activity of the synthesized compounds was determined against Gram-positive bacteria (*Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 7443) and Gram-negative bacteria (*Xanthomonas campestris MTCC 7908 and Escherichia coli* MTCC 7410) in DMF by disc diffusion method on nutrient agar medium [14]. The sterile medium (Nutrient Agar Medium, 15 ml) in each petriplates was uniformly smeared with cultures of Gram positive and Gram negative bacteria. Sterile discs of 10 mm diameter (Hi-Media) were made in each of the petriplates, to which 50 µl (1 mg/ml i.e., 50 µg/disc) of the different synthesized compounds were added. The treatments also included 50 µl of DMF as negative, bacteromycin and gentamycin as positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at 25 ± 2 ºC for 24 h and the size of the resulting zone of inhibition, if any, was determined.

2.3. Antifungal activity

The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* MTCC 2480 in DMF by poisoned food technique [15]. Potato Dextrose Agar (PDA) media was prepared and about 15 ml of PDA was poured into each petriplate and allowed to solidify. 5 mm disc of seven days old culture of the test fungi was placed at the center of the petriplates and incubated at 26 °C for 7 days. After incubation the percentage inhibition was measured and three replicates were maintained for each treatment. Nystatin was used as standard. All the synthesized compounds were tested (at the dosage of 500 µl of the novel compounds/petriplate, where concentration was 0.1 mg/ml) by poisoned food technique.

3. RESULTS AND DISCUSSION

3.1. Chemistry

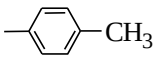
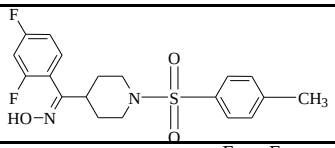
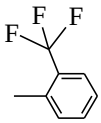
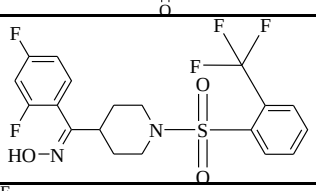
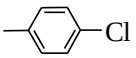
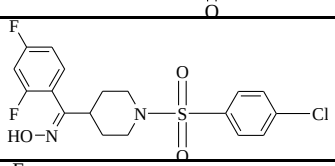
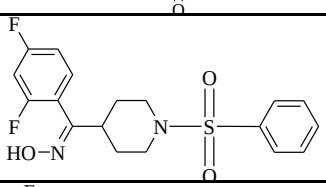
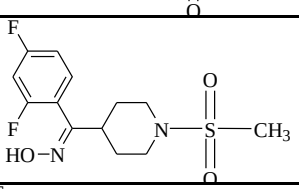
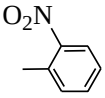
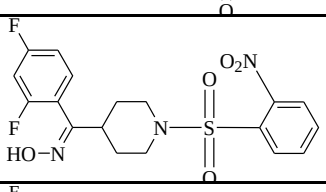
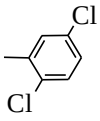
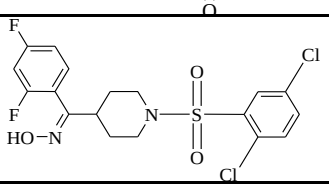
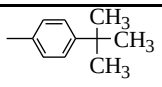
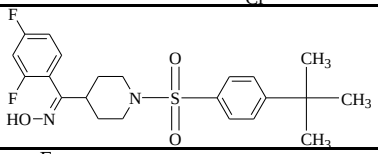
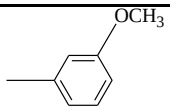
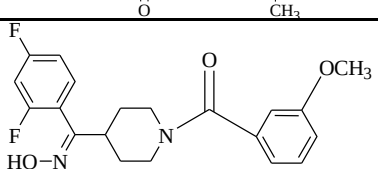
In the present work, a series of thirteen new compounds were synthesized. Structure of the synthesized compounds was established on the basis of FT-IR, ^{1}H NMR and mass spectral data. The chemical structure and physical data of novel compounds are given in Table 1. The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ± 0.4 %.

The FT-IR spectra of **4a-h** and **5a-e** were recorded using KBr pellets in the range of 4000-400 cm^{-1}. The absorption bands at 1644-1645 cm^{-1} are due to the presence of C=O stretch. The absorption band at 3368 cm^{-1} is due to the N-H stretch in compound **1**. The absence of N-H absorption bands in **4a-h** and **5a-e** confirmed the synthesized compounds. The strong bands at 1323-1327 cm^{-1} and 1156-1170 cm^{-1}, attributed to SO_2 (asym. stretch) and SO_2 (sym. stretch), respectively.

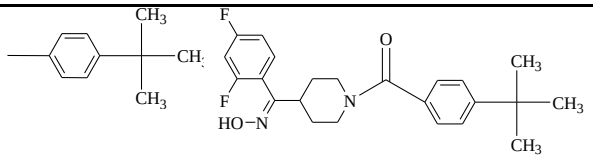
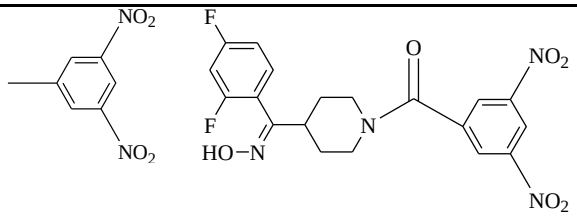
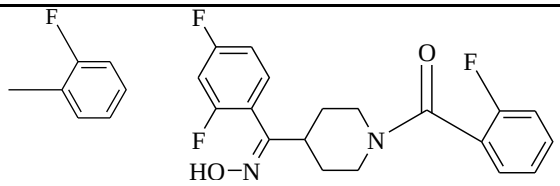
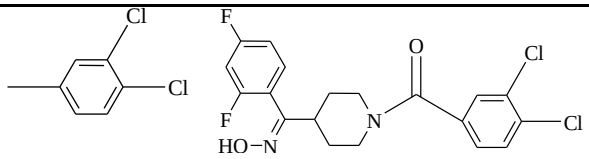
The characteristic resonance peaks in ^{1}H NMR for the new compounds were reported using DMSO. The expected resonances were assigned by their peak multiplicity and integration. The integration of spectra shows good agreement with the synthesized compounds. The proton NMR spectral data of NH in **1** show single resonance at δ 9.20 ppm, which is absent in the spectra of **4a-h** and **5a-e**, indicating the replacement of the sulfonamide series. In addition, the resonance appearing in the range of δ 8.99-6.84 ppm as a singlets, doublets, triplets and multiplates is attributed to the aromatic protons. The piperadine protons were resonated at δ 3.78-1.31 ppm. The proton spectral data agree with respect to the number of protons and their chemical shifts with the proposed structures.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

Table 1. Chemical structure and physical data of 2,4-difluorophenyl(piperidin-4-yl)methanone oxime derivatives **4a-h** and **5a-e**.

Compound	R	R'	Structure	Yield (%)	m.p. (°C)
4a		-		75	146-148
4b		-		74	141-142
4c		-		78	144-146
4d		-		71	129-131
4e		-		70	118-120
4f		-		77	139-141
4g		-		73	127-130
4h		-		74	137-139
5a	-			76	104-106

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

5b	-		74	135-137
5c	-		65	148-150
5d	-		65	126-128
5e	-		70	120-122

The synthesized compounds were further confirmed by the appearance of molecular ion peak in mass spectra. Mass spectra of all the newly synthesized compounds showed M^+ fragmentation peak in agreement with their molecular formula.

3.2. Antimicrobial activity

The antimicrobial activities of the piperidine derivatives **4a-h** and **5a-e** were determined against various microbial types. The experimental result of antimicrobial activity indicated variable degree of efficacy of the compounds against different microbial strains (Table 2). All the piperidine derivatives had antimicrobial effect against both Gram-positive and Gram-negative bacteria used. The results revealed that few of the synthesized compounds exhibited good antimicrobial activity comparable to some antibiotics such as bacteromycin, gentamycin and nystatin against all of the tested microorganisms.

Compound **4b** exhibit good antimicrobial activity against *bacillus subtilis*, *staphylococcus aureus*, *xanthomonas campestris*, *escherichia coli* and *fusarium oxysporum* with zone of inhibition at 25 mm, 23 mm, 21 mm, 22 mm and percentage inhibition at 78.5, respectively. Similarly **4g** and **5e** were effective against all the tested bacterial and fungal strains. Compounds **4c**, **4f**, **5c** and **5d** showed moderate inhibitory activity. Compounds **4a**, **4d**, **4e**, **4h**, **5a** and **5b** showing weak activity in comparison to standard drugs.

The initial structure activity relationship (SAR) can be drawn for the compounds **4a-h** and **5a-e**. In the present study, different electron withdrawing and electron donating groups attached to phenyl ring as substituent which is linked to sulfonyl and carbonyl groups were studied for antimicrobial and antioxidant efficacy. These modifications result in changes in potency and antimicrobial activity profile of the synthesized compounds. In this contrast, first keeping the same substituent at the same position on the phenyl ring of the series (**4h**, **5b**) the carboxamide functionalized derivatives show relatively more

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

Table 2. *In Vitro* Antibacterial and Antifungal Activities of **4a-h** and **5a-e**.

Compound	Zone of inhibition in diameter (mm)				% Inhibition
	Bs	Sa	Xc	Ec	Fo
4a	11	12	11	12	41.5
4b	25	23	21	22	78.5
4c	19	18	16	17	68.6
4d	12	13	11	13	45.4
4e	11	13	11	12	43.2
4f	15	16	14	15	68.7
4g	24	21	20	21	70.5
4h	11	12	11	12	43.0
5a	13	14	12	14	57.1
5b	12	13	12	13	53.2
5c	17	18	15	16	65.4
5d	17	17	14	16	63.0
5e	20	20	18	20	70.2
Bacteromycin	NI	NI	29	NI	NA
Gentamycin	30	28	NI	30	NA
Nystatin	NA	NA	NA	NA	100

Abbrevations: Bs - *Bacillus subtilis*; Sa - *Staphylococcus aureus*; Xc - *Xanthomonas campestris*; Ec- *Escherichia coli*; Fo - *Fusarium oxysporum*, NI- no inhibition, NA- not applicable.

antibacterial activity. Secondly, changing the substituents on the phenyl ring in the same position (**4b**, **5d**) reveals that sulfonamide functionalized derivatives show relatively significant antimicrobial activity. In third SAR study, introducing the same substituents (**4f**, **5c**) and (**4c**, **5e**) emphasizes that the electron withdrawing group increases the potency of the compound and showed carboxamide functionalized derivatives are relatively shown more antimicrobial activity. Finally, changing substituent on the phenyl ring (**4a**, **5a**) reveals that the carboxamide functionalized derivatives show relatively more antimicrobial activity. The above four SAR correlation studies reveals that, the nature of the functional linkage (-SO_2 or

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

–CO-) and substituent on phenyl ring influences the antibacterial activity [16, 17].

4. CONCLUSION

Series of new 2,4-difluorophenyl(piperidin-4-yl)methanone oxime derivatives **4a-h** and **5a-e** were synthesized and their antimicrobial activity have been evaluated. Trifluoromethyl group in **4b** produced significant changes in activity against Gram-positive and Gram-negative bacteria. The SAR studies revealed that, the nature of functional linkage (-SO_2- and –CO-) and substituent (electron withdrawing and electron donating groups) on phenyl ring are responsible for the antimicrobial activity. Hence, there is the need for further investigations to clarify the features underlying the antibacterial and antifungal activities of these new piperidine derivatives.

ACKNOWLEDGEMENTS

The authors thank Dr. S. Satish, Department of Microbiology, University of Mysore, India to carryout antimicrobial studies.

REFERENCES

[1] Petukhov, P. A.; Zhang, J.; Wang, C. Z.; Ye, Y. P.; Johnson, K. M.; Kozikowski, A. P. Synthesus molecular modeling and biological studies of novel piperidine based analogues of cocaine. *J. Med. Chem.*, **2000**, *47*, 3009-3018.

[2] Wong, H.; Ethel, C; Garnier, A.; Lanny, S. L. Organometallic enantiomeric scaffolding: A strategy for the enantiocontrolled construction of regio- and sterodivergent trisubstituted piperidines. *J. Am. Chem. Soc*., **2011**, *133*, 7517-7527.

[3] Balasubramanian, S.; Ramalingan, C.; Aridoss, G.; Kabilan, S. Synthesis and study of antibacterial and antifungal activities of novel 8-methyl-7,9-diaryl-1,2,4,8-tetraazaspiro[4.5]decan-3-thiones. *Eur. J. Med. Chem*., **2005**, *40*, 694-700.

[4] Balasubramanian, S.; Ramalingan, C.; Aridoss, G.; Parthiban, P.; Kabilan, S. Synthesis and microbial evaluation of novel [N-acetyl-2,6-diaylpiperidin-4-yl]-5-spiro-4-acetyl-2-(acetylamino)-D2-1,3,4-thiadiazoline. *Med. Chem. Res.*, **2004**, *13*, 297-311.

[5] Dimmock, J. R.; Padmanilayam, M. P.; Puthucode, R. N.; Nazarali, A. J.; Motaganahalli, N. L.; Zello, G. A.; Quail, J. W.; Oloo, E. O.; Kraatz, H. B.; Prisciak, J. S.; Allen, T.; Santos, C. L.; Balsarini, J.; Clercq, E. D.; Manavathu, E. K. A conformational and structure-activity relationship study of cytotoxic 3,5-bis(arylidene)-4-piperidones and related N-acryloyl analogues. *J. Med. Chem*., **2001**, *44*, 586-593.

[6] Finke, P. E.; Oates, B.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; Demartino, J. A.; Carella, A.; Carver, G.; Holmes, K.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Schleif, W. A.; Emini, E. A. Antagonists of the human CCR5 receptor as anti-HIV-1 agents. Part 4: Synthesis and structure-activity relationships for 1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-2-(phenyl)-4-(4-(*N*-(alkyl)-*N*-(benzyloxycarbonyl)amino)piperidin-1-yl)butanes. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2475-2479.

[7] Trabaco, A. A.; Aerts, N.; Alvarez, R. M.; Andres, J. I.; Boeckx, I.; Fernandez, J.; Gomez, A.; Janssens, F. E.; Leenaerts. J. E.; Lucas, A. I. D.; Matesanz, E.; Steckler, T.; Pullan, S. 4-Phenyl-4-[1h-imidazol-2-yl]-piperidine derivatives as non-peptidic selective δ-opioid agonists with potential anxiolytic/antidepressant properties. *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 3860-3863.

[8] (a) Kobayashi, J.; Ishibashi, M. Sphingosine-related marine alkaloids: Cyclic amino alcohols. *Heterocycles*, **1996**, *42*, 943-970.
(b) Ninomiya, I.; Kiguchi, T.; Naito, T. ChemInform Abstract: Pseudodistomins: Structure, Synthesis, and Pharmacology. *Alkaloids*, **1998**, *50*, 317-342.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 3 | Page 343-352

[9] Saify, Z. S.; Vaid, F. I. M. Synthesis and anti-microbial screening of some piperidine derivatives. *Pak. J. Pharm. Sci.*, **1998**, *11*, 15-21.
[10] Enrique, R.; Christian, F. Conformationally constrained butyrophenones. Synthesis and evaluation as antipsychotics. *Curr. Med. Chem.*, **2001**, *1*, 43-62.
[11] Szarfman, A.; Tonning, J. M.; Levine, J. G.; Doraiswamy, P. M. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. *Pharmacotherapy*, ***2006***, 26, *748-758.*
[12] Malík, I.; Bukovsky, M.; Andriamainty, F.; Galisinova jk, J. Antimicrobial activity of meta-alkoxyphenylcarbamates containing substituted N-phenylpiperazine fragment, *Braz. J. Micro*., ***2012***, 15, *959-965*.
[13] Alsughayer, A.; Elassar, A. A.; Mustafa, S.; Sagheer, F. A. Synthesis, structure analysis and antibacterial activity of new potent sulfonamide derivatives. *J. Biomater. Nanobiotech*., ***2011***, 2, *144-149.*
[14] Jorgensen, J. H.; Ferraro, M. J. Antibiotic susceptibility testing: A review of general principles and contemporary practices. Clin. Infect. Dis., **2009**, *49*, 1749-1755.
[15] Satish, S.; Mohana, D. C.; Raghavendra, M. P.; Raveesha, K. A. Antifungal activity of some plant extracts against important seed borne pathogens of *Aspergillus* sp. *J. Agric. Technol.* **2007**, *3*, 109-119.
[16] Venkateshwarlu, T.; Ravinder Nath, A.; Prasad Chennapragada, K. Synthesis and antimicrobial activity of novel benzo[b]furan derivative. *Der Pharma Chemica*, **2013**, *5*, 229-234.
[17] Mallesha, L.; Mohana, K. N. Synthesis, antimicrobial and antioxidant activities of 1-(1,4-benzodioxane-2-carbonyl)piperazine derivatives. *Eur. J. Chem*., **2011**, *2*, 193-199.

The authors declare no conflict of interest

© 2014 By the Authors; Licensee Borderless Science Publishing, Canada. This is an open access article distributed under the terms and conditions of the Creative Commons Attribution license http://creativecommons.org/licenses/by/3.0/