Canadian Chemical Transactions

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

Research Article

DOI:10.13179/canchemtrans.2014.02.02.0090

Synthesis, Spectral and Structure Activity Relationship Studies of Substituted 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-ones and their Corresponding Oxime Derivatives

Sambandam Savithiri, Govindasamy Rajarajan*, Vengadesan Srividhya, Johnson Jijeesh Venugopal Thanikachalam, Jayaraman Jayabharathi, and Mariadoss Arockia doss

Department of Chemistry, Annamalai University, Annamalainagar 608002, Tamilnadu, India

Corresponding Author, E-mail: jaihari70@yahoo.co.in Cell: +91-9444147388

Received: *January 12, 2014* ***Revised:*** *March 2, 2014* ***Accepted:*** *March 3, 2014* ***Published:*** *March 4, 2014*

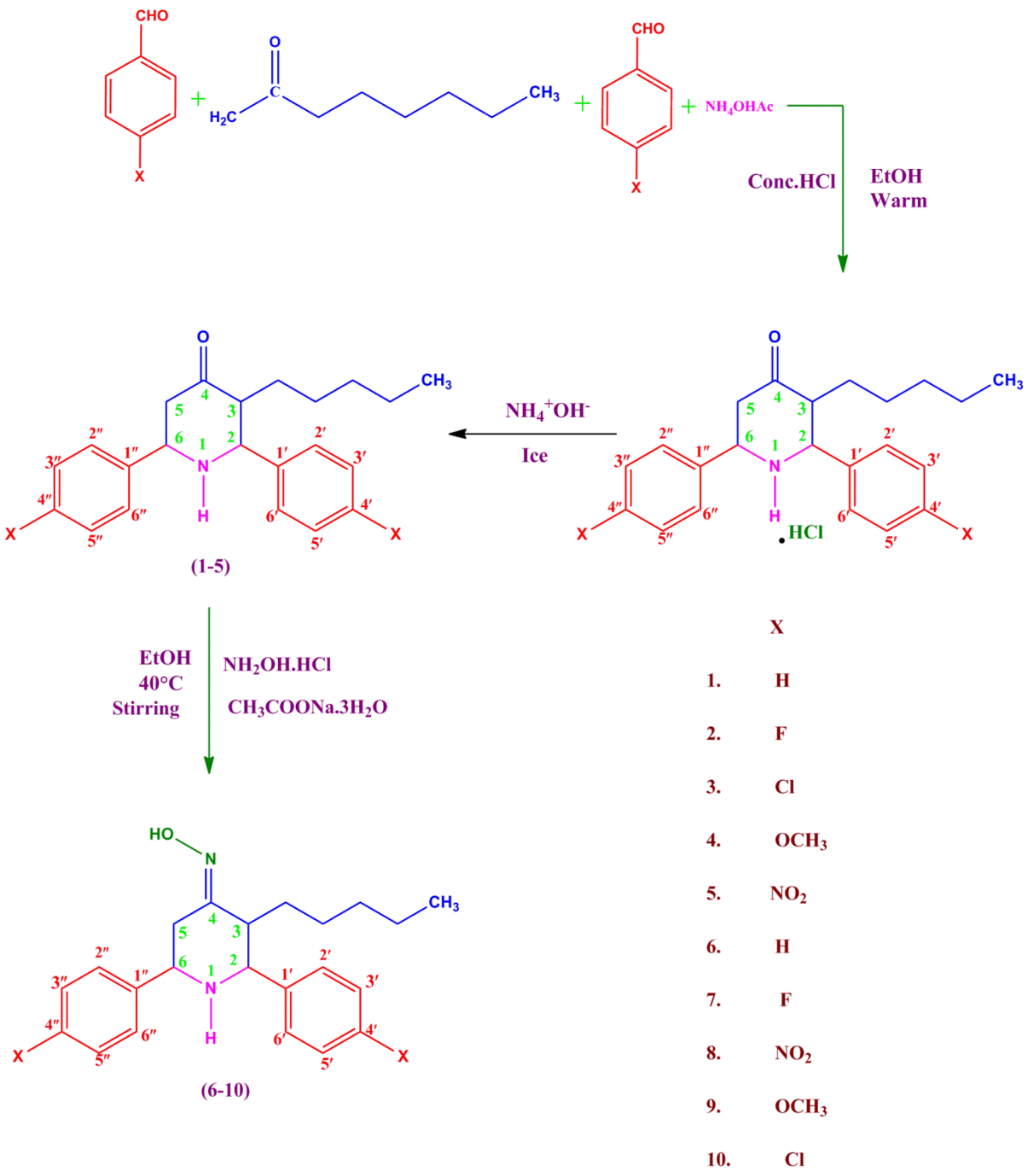
Abstract: Five 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-ones **(1-5)** and their oxime derivatives **(6-10)** (aryl = C_6H_5, *p*-FC_6H_4, *p*-$NO_2C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4) have been synthesized by condensing 2-octanone with the appropriate substituted benzaldehydes and ammonium acetate. For all these compounds, ^{1}H and ^{13}C NMR spectra have been recorded and for certain compounds HOMOCOSY, HSQC, HMBC and Mass spectra have also been recorded. The spectral data suggest that the compounds exist in chair conformation with equatorial orientation of the bulky substituents. Long range coupling is observed between $H(5)_{ax}$ and $H(6)_{(ax)}$ in all the cases suggesting that $H(5)_{ax}$ is anti to C(6)–C(5) bond. To study the structure activity relationship, these compounds were assayed for their antibacterial and antifungal activities via screening them against *Staphylococcus aureus, Escherichia coli, Solmonella typhi, Psedomonas aeruginosa* and *Candida albicans, Aspergillus niger, Mucor, Rhizopus sp* respectively. Among the synthesized compounds *p*-fluoro and *p*- methoxy substituted compounds exhibit better activity against *E.coli, S.typhi* and *A.niger*.

Keywords: Piperidin-4-one, Oxime; Spectral Data; Antimicrobial screening

1. INTRODUCTION

NMR spectroscopy has been used as a powerful tool in studying the conformation of six membered ring compounds in solution [1-4]. Many piperidine derivatives are found to possess pharmacological activity and form an essential part of the molecular structures of important drugs [5-6]. Vicinal proton- proton coupling constants have been widely used in deriving information about the conformation of heterocyclic compounds. 2*r*, 6*c*-diarylpiperidin-4-ones [7-17] and their oximes [18-23] have been shown to exist largely in chair conformation with equatorial orientation of the substituents. In the past two decades, a broad range of biological effects including antiviral, antitumor, bactericidal, fungicidal and antinflammatory activities have been described for these compounds [24-28]. Rajarajan *et al* have investigated the crystal [29] and theoretical studies of compound 3*t*-pentyl-2*r*, 6*c*–diphenylpiperidin-4-one [30] (**1**). In an effort to propose new derivatives of pharmacologically active

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

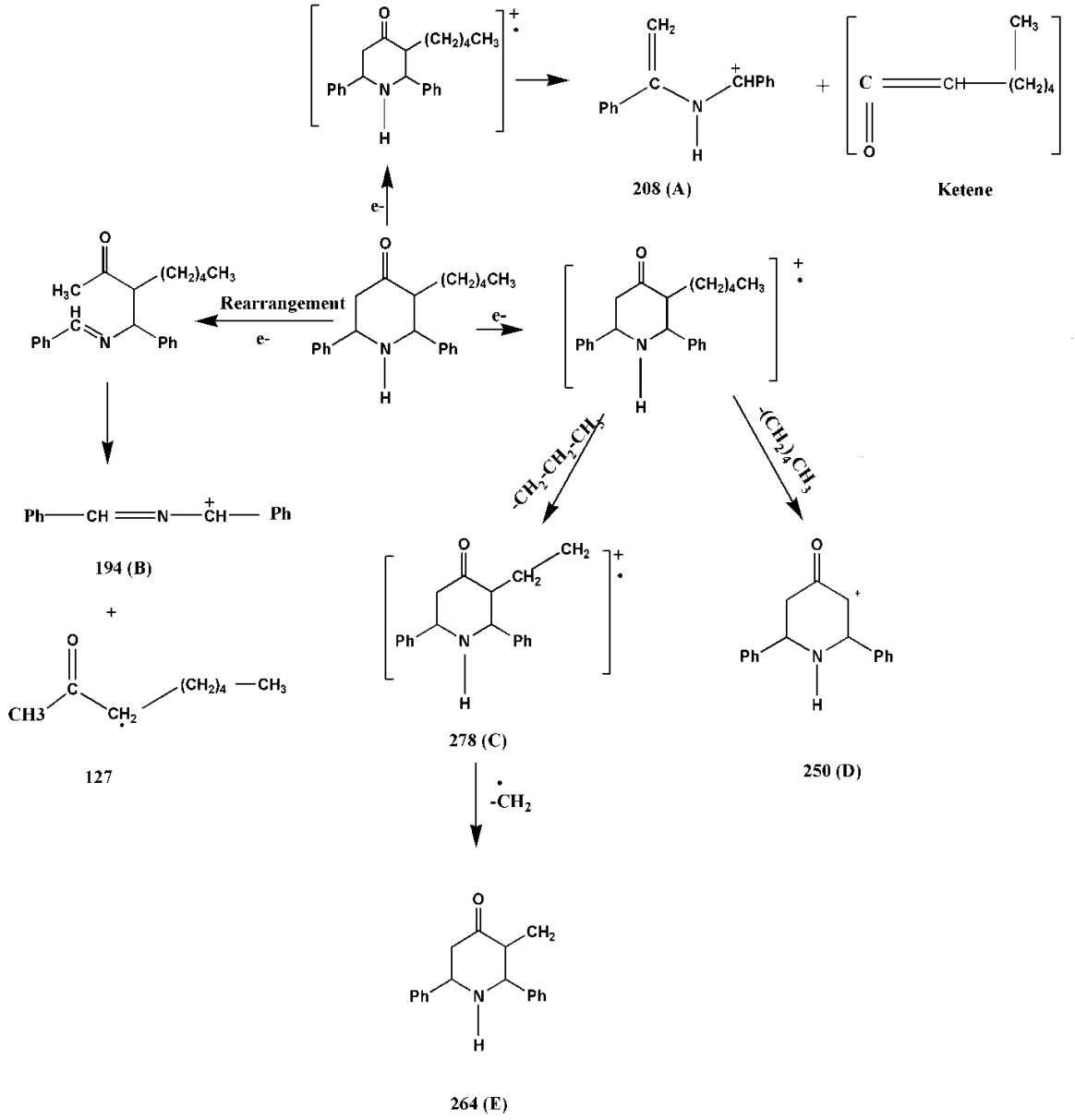


Scheme1. Synthetic route for 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-ones **(1-5)** and their oxime derivatives **(6-10).**

piperidones, the present investigation was undertaken. In this paper, we report the synthesis and detailed ^{13}C, ^{1}H NMR spectral, antibacterial and antifungal studies of 3*t*-pentyl-2*r*, 6*c*-diphenylpiperidin-4-one (**1**), 3*t*-pentyl-2*r*, 6*c*-bis(4-fluorophenyl)piperidin-4-one (**2**), 3*t*-pentyl-2*r*, 6*c*-bis(4-chlorophenyl)piperidin-4-one (**3**), 3*t*-pentyl-2*r*,6*c*-bis(4-methoxyphenyl)piperidin-4-one (**4**), 3*t*-pentyl-2*r*,6*c*-bis(4-nitrophenyl)piperidin-4-one (**5**), 3*t*-pentyl-2*r*, 6*c*-diphenylpiperidin-4-one oxime (**6**), 3*t*-pentyl-2*r*, 6*c*-bis(4-fluorophenyl)piperidin-4-one oxime (**7**), 3*t*-pentyl-2*r*, 6*c*-bis(4-nitrophenyl)piperidin-4-one oxime

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

(**8**) and 3*t*-pentyl-2*r*,6*c*-bis(4-methoxyphenyl)piperidin-4-one oxime (**9**), 3*t*-pentyl-2*r*,6*c*-bis(4-chlorophenyl)piperidin-4-one oxime (**10**).



Scheme 2. Fragmentation pattern of 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-one.

2. EXPERIMENTAL SECTION

2.1 MATERIALS AND METHODS

All the solvents used were spectral grade. The melting points of all the compounds were measured in open capillaries and are uncorrected. IR spectra were recorded on an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz, Bruker, using $CDCl_3$ / DMSO-d_6 as a solvent for all the compounds. Tetramethylsilane (TMS) was used as an internal reference for all NMR spectra, with chemical shifts reported in δ units (parts per million) relative

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

to the standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m). Coupling constants are expressed in Hertz (Hz). Mass spectra were recorded in VARIAN-SASTURAN 2200 GC-MS spectrometry using chemical ionisation and electron impact techniques. Sample was prepared by dissolving about 1 mg in 5ml of methanol. Microanalyses were performed on VarioMicro V2.2.0 CHN analyser. Microbial screening studies recorded for Pondicherry centre for biological sciences in Pondicherry.

2.2 Synthesis

2.2.1 Synthesis of 3t-pentyl-2r,6c-diarylpiperidin-4-one (1-5)

The compounds **1-5** were prepared according to the procedure given in literature for the preparation of 2,6-diarylpiperidin-4-ones [31,32]. A mixture of ammonium acetate (0.05 mol), appropriate substituted benzaldehyde (0.1mol) and 2-octanone (0.05 mol) in distilled ethanol were heated to boiling. After cooling, the viscous liquid obtained was dissolved in ether (200 ml) and shaken with 10 mL concentrated hydrochloric acid, the precipitated hydrochloride of 3*t*-pentyl-2*r*,6*c*-diphenylpiperidin-4-one was removed by filtration and washed first with a mixture of ethanol and ether (1:1) and then with ether to remove most of the coloured impurities. The base was liberated from an alcoholic solution by adding aqueous ammonia and then diluted with water. The products were recrystallized from alcohol. The chemical reactions are shown in **Scheme 1**.

2.2.1.1. 3t-pentyl-2r, 6c–diphenylpiperidin-4-one (1):

Yield 65%., m.p. 69 (ºC), MF: $C_{22}H_{27}NO$: IR (KBr) (cm^{-1}): 3315 (N-H stretching), 3061 (-CH-Ar stretching), 1714 (C=O stretching), 1492 (C=C stretching), 1027 (C-N stretching), 759-698 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):7.26-7.46 (m, Ar-H), 4.06 (d, J_{6a5a}=11.50 Hz, 1H, H6, J_{6a5e}=3.00 Hz, ϕ_{6a5a}=176.1°, ϕ_{6a5e}=56.1°), 3.70 (d, J_{2a3a}=10.50 Hz, 1H, H2,), 2.58-2.65 (m, 1H, $H3_a$), 2.73 (dd, J_{5a5e}=13.00 Hz, 1H, $H5_{ax,}$), 2.58-2.65 (m, 1H, $H5_{eq}$), 0.93-1.65 (m, 8H, CH_2), 0.73 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):209.33 (C=O), 142.83-126.53 (Ar-C), 67.24 C(2), 61.88 C(6), 57.13 C(3), 51.59 C(5), 31.90, 27.38, 24.61, 22.36 (CH_2), 13.95 (CH_3).Mass (m/z): 321 (M^+), 278, 264, 208, 198, 194, 150.

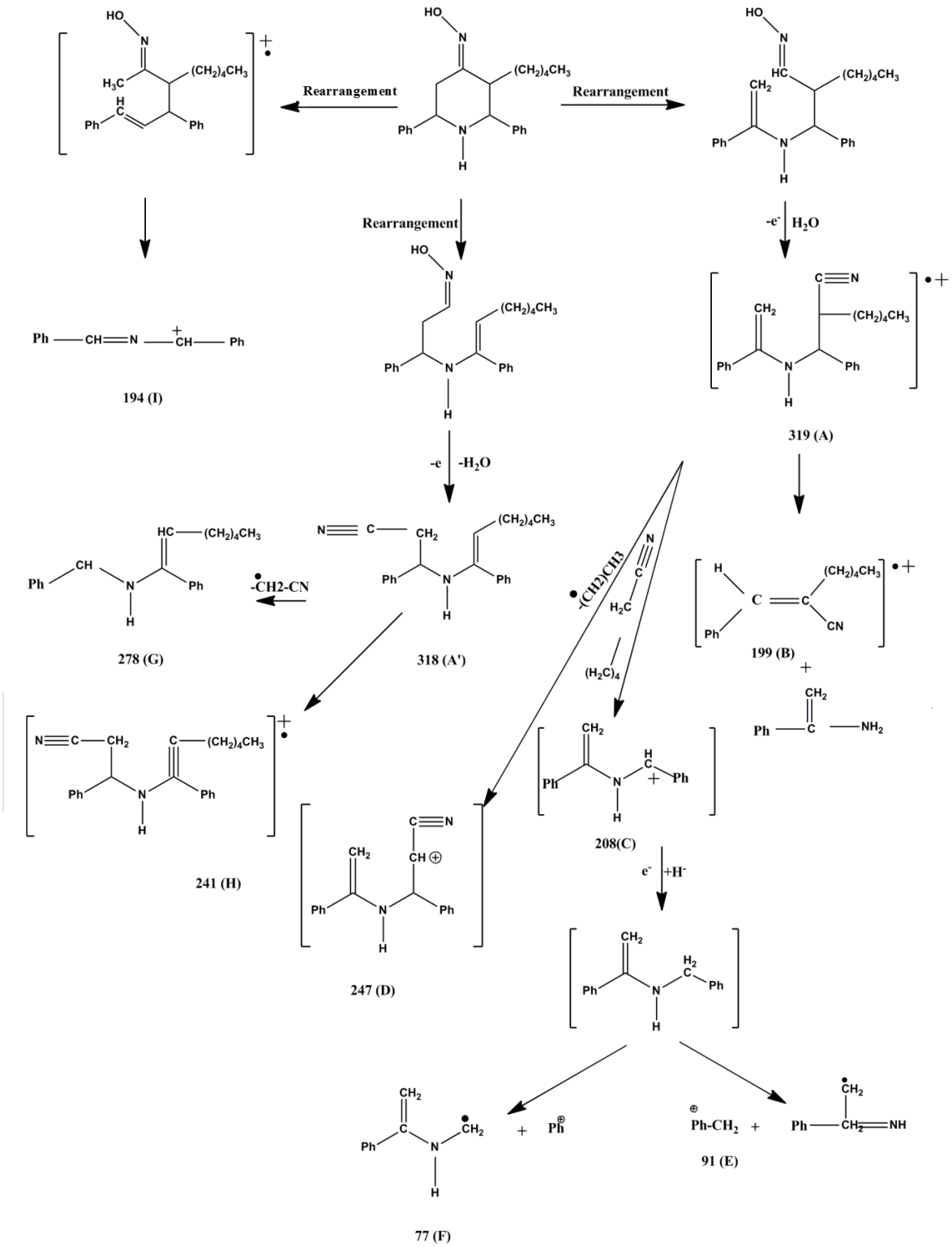
2.2.1.2. 3t-pentyl-2r, 6c–bis(4-fluorophenyl)piperidin-4-one (2):

Yield 70%., m.p. 85 (ºC), MF: $C_{22}H_{25}F_2NO$: IR (KBr) (cm^{-1}): 3414 (N-H stretching), 3063 (-CH-Ar stretching), 1717 (C=O stretching), 1500 (C=C stretching), 1091 (C-N stretching), 757-659 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, DMSO-d_6, δ,(ppm)):6.42-7.21 (m, Ar-H), 4.95 (d, 1H, H6), 4.73 (d, 1H, H2), 2.70(d, 1H, $H3_a$), 3.65 (t, 1H, $H5_{ax}$), 2.51 (m, 1H, $H5_{eq}$), 1.02-1.39 (m, 8H, CH_2), 0.76 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 203.29(C=O), 163.68-115.67 (Ar-C), 62.47 C(2), 58.38 C(6), 44.76 C(3), 31.09 C(5), 30.65-21.57 (CH_2) and 13.63(CH_3).

2.2.1.3. 3t-pentyl-2r, 6c–bis (4-chlorophenyl)piperidin-4-one (3):

Yield 75%., m.p.82 (ºC), MF: $C_{22}H_{25}Cl_2NO$: IR (KBr) (cm^{-1}): 3430 (N-H stretching), 3035 (-CH-Ar stretching), 1720 (C=O stretching), 1493 (C=C stretching), 1091 (C-N stretching), 730-680 (Aromatic C-H out of plane bending vibration);^{1}H NMR (400 MHz, DMSO-d_6 , δ,(ppm)):7.48-7.78 (m, Ar-H), 4.93 (d, 1H, H6), 4.70 (d, 1H, H2), 3.38(m, 1H,$H3_a$), 3.51 (t, 1H, $H5_{ax}$), 2.69 (d, 1H, $H5_{eq}$), 1.38-1.00 (m, 8H, -CH_2-), 0.62 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 203.08(C=O), 134.29-128.53 (Ar-C), 62.56 C(2), 58.50 C(6), 50.51 C(3), 44.66 C(5), 31.10-21.61(CH_2) and 13.64(CH_3).

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220



Scheme 3. Fragmentation pattern of 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-one oxime.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

2.2.1.4. 3t-pentyl-2r, 6c–bis(4-methoxyphenyl)piperidin-4-one (4):

Yield 65%., m.p.82 (ºC), MF: $C_{24}H_{31}NO_3$: IR (KBr) (cm^{-1}): 3302 (N-H stretching), 3068 (-CH-Ar stretching), 1714 (C=O stretching), 1445 (C=C stretching), 1028 (C-N stretching), 748-646 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):6.85-7.34 (m, Ar-H), 4.00 (d, J_{6a5a}=11.2 Hz, 1H, H6, 3.89 (d, 6H, OCH_3), 3.63 (d, J_{2a3a}=10.0 Hz, 1H, H2,), 2.57(t, 1H,$H3_a$), 2.70 (t, J_{5a5e}=12.4 Hz, 1H, $H5_{ax}$,), 2.57 (t, 1H, $H5_{eq}$), 0.98-1.66 (m, 8H, - CH_2-), 0.79(t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 209.73(C=O), 159.24-113.85 (Ar-C), 66.60 C(2), 61.25 C(6), 57.30 C(3), 51.77 C(5), 31.98-22.44(CH_2) and 14.02(CH_3).

2.2.1.5. 3t-pentyl-2r, 6c–bis (4-nitrophenyl)piperidin-4-one (5):

Yield 65%., m.p.76 (ºC), MF: $C_{22}H_{25}N_3O_5$: IR (KBr) (cm^{-1}): 3307 (N-H stretching), 3115 (-CH-Ar stretching), 1715 (C=O stretching), 1455 (C=C stretching), 1012 (C-N stretching), 750-698 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):7.27-8.27 (m, Ar-H), 4.25 (d, 1H, H6), 3.89 (d, 1H, H2), 2.68(m, 1H,$H3_a$), 2.68 (m, 1H, $H5_{ax}$), 2.68 (m, 1H, $H5_{eq}$), 0.92-1.60 (m, 8H, CH_2), 0.78(t, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl3, δ, ppm): 207.12(C=O), 149.35-123.88 (Ar-C), 66.18 C(2), 61.10 C(6), 56.76 C(3), 51.02 C(5), 31.83-22.35(CH_2) and 13.94(CH_3).

2.2.2 Synthesis of 3t-pentyl-2r,6c-diarylpiperidin-4-one oxime (6-10)

The compounds **6-9** were prepared according to the procedure given in literature for the preparation of 2,6-diarylpiperidin-4-one oximes [10] 3*t*-pentyl-2r, 6*c*-diarylpiperidin-4-one (0.05 mol) and sodium acetate trihydrate (0.15 mol) were dissolved in boiling ethanol and hydroxylamine hydrochloride (0.06 mol) was added. The mixture was heated to 40ºC and stirred for 3-4 h and then poured into crushed ice. The separated solid was filtered off and recrystallized from ethanol. The chemical reactions are shown in (**Scheme 1**).

2.2.2.1.3t-pentyl-2r, 6c–diphenylpiperidin-4-one oxime (6):

Yield 78%., m.p.89 (ºC), MF: $C_{22}H_{28}N_2O$: IR (KBr) (cm^{-1}):3435 (OH stretching), 3320 (N-H stretching), 3265 (-CH-Ar stretching), 1605 (C=N stretching), 1458 (C=C stretching), 1113(C-N stretching), 943 (N-O stretching), 752-700 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):8.25 (s,1H,OH), 7.23-7.47 (m, Ar-H), 3.90 (d, J_{6a5a}=11.57 Hz, 1H, H6, J_{6a5e}=2.60 Hz, ϕ_{6a5a}=178.6°, ϕ_{6a5e}=58.6°), 3.65 (d, J_{2a3a}=10.58 Hz 1H, H2,), 2.49(m, 1H,$H3_a$), 2.03 (dd, J_{5a5e}=13.12 Hz, 1H, $H5_{ax}$), 3.65 (m, 1H, $H5_{eq}$), 0.83-1.63 (m, 8H, CH_2), 0.77 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):159.54(C=N), 143.67-126.69 (Ar-C), 68.03 C(2), 60.92 C(6), 48.52 C(3), 34.13 C(5), 31.96, 26.94, 25.78, 22.43 (CH_2) and 13.98 (CH_3). Mass (m/z): 336 (M^+), 319, 278, 247, 241, 220, 208, 199, 198, 194, 158, 91, 77.

2.2.2.2. 3t-pentyl-2r, 6c–bis(4-fluorophenyl)piperidin-4-one oxime (7):

Yield 75%., m.p.130 (ºC), MF: $C_{22}H_{26}F_2N_2O$: IR (KBr) (cm^{-1}):3424 (OH stretching), 3298(N-H stretching), 3002 (-CH-Ar stretching), 1603 (C=N stretching), 1507 (C=C), 1091(C-N stretching),939 (N-O stretching), 772-723 (Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):8.66 (s,1H,OH), 6.99-7.44 (m, Ar-H), 3.87 (d, J_{6a5a}=11.2 Hz, 1H, H6), 3.61 (t, J_{2a3a}=9.2 Hz, 1H, H2), 2.42(t, 1H, $H3_a$), 1.97 (t, J_{5a5e}=12.4 Hz, 1H, $H5_{ax}$), 3.61 (t, 1H, $H5_{eq}$), 1.07-1.57 (m, 8H, CH_2), 0.78 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 161.13(C=N), 139.38-115.23 (Ar-C), 67.16 C(2), 60.19 C(6), 48.67 C(3), 34.31 C(5), 22.47-31.97 (CH_2), and14.03(CH_3).

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

Table 1. Analytical data of compound (**1-10**).

Compd	m.p (°C)	Yield	Molecular Formula	Elemental analysis (%)			
				C	H	N	O
				Found (Calcd)	Found (Calcd)	Found (Calcd)	Found (Calcd)
1	69	65	$C_{22}H_{27}NO$	80.20 (82.32)	8.47 (8.48)	4.36 (4.36)	4.98 (4.98)
2	85	70	$C_{22}H_{25}F_2NO$	73.93 (74.02)	7.05 (7.06)	3.92 (3.92)	4.48 (4.48)
3	82	75	$C_{22}H_{25}Cl_2NO$	67.69 (67.75)	6.46 (6.46)	3.59 (3.59)	4.10 (4.10)
4	82	65	$C_{24}H_{31}NO_3$	75.56 (75.46)	8.19 (8.18)	3.67 (3.67)	12.58 (12.57)
5	76	65	$C_{22}H_{25}N_3O_5$	64.22 (64.29)	6.12 (6.13)	10.21 (10.22)	19.44 (19.46)
6	89	78	$C_{22}H_{28}N_2O$	78.53 (78.64)	8.39 (8.40)	8.33 (8.34)	4.76 (4.76)
7	130	75	$C_{22}H_{26}F_2N_2O$	70.94 (71.03)	7.04 (7.04)	7.52 (7.53)	4.30 (4.30)
8	110	78	$C_{22}H_{26}N_4O_5$	61.96 (62.03)	6.15 (6.15)	13.14 (13.15)	18.79 (18.78)
9	172	80	$C_{24}H_{32}N_2O_3$	72.70 (72.61)	8.13 (8.12)	7.06 (7.06)	12.10 (12.09)
10	106	75	$C_{22}H_{25}Cl_2NO$	65.19 (65.18)	6.46 (6.46)	6.91 (6.91)	3.95 (3.95)

2.2.2.3. 3t-pentyl-2r, 6c–bis(4-nitrophenyl)piperidin-4-one oxime (8):

Yield 78%., m.p.110 (ºC), MF: $C_{22}H_{26}N_4O_5$: IR (KBr) (cm^{-1}):3424 (OH stretching), 3254(N-H stretching), 3150 (-CH-Ar stretching), 1600 (C=N stretching), 1517 (C=C stretching), 1005 (C-N stretching), 944 (N-O stretching), 7.49-6.69 (Aromatic C-H out of plane bending vibration); ^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):10.66 (s,1H,OH), 7.88-8.18 (m, Ar-H), 4.06 (d, J_{6a5a}=11.2 Hz, 1H, H6), 4.06 (d, J_{2a3a}=8.4 Hz, 1H, H2), 2.49 (t, 1H, $H3_a$), 1.95 (t, J_{5a5e}=13.2 Hz, 1H, $H5_{ax}$), 3.60 (d, 1H, $H5_{eq}$), 1.61 (m, 8H, -CH_2-), 0.77 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.83 (C=N), 146.89-123.09 (Ar-C), 66.17 C(2), 59.25 C(6), 47.24 C(3), 32.88 C(5), 21.86-31.39 (-CH_2-) and 13.61(CH_3).

2.2.2.4.3t-pentyl-2r, 6c–bis (4-methoxyphenyl) piperidin-4-one oxime (9):

Yield 80%., m.p.172 (ºC), MF: $C_{24}H_{32}N_2O_3$: IR (KBr)(cm^{-1}):3457 (OH stretching), 3247(N-H stretching), 3002 (-CH-Ar stretching), 1610 (C=N stretching), 1513 (C=C stretching), 1032(C-N stretching),940 (N-O stretching), 756-641(Aromatic C-H out of plane bending vibration);^{1}H NMR(400 MHz, $CDCl_3$, δ,(ppm)):8.57 (s, 1H, OH), 6.59-7.56 (m, Ar-H), 3.80 (d, 6H, OCH_3)3.61 (d, 1H, H6), 3.61 (d, 1H, H2), 2.44 (t, 1H, $H3_a$), 2.17(t, 1H, $H5_{ax}$), 2.62 (t, 1H, $H5_{eq}$), 1.08-1.39 (m, 8H, -CH_2-), 0.78 (t, 3H,

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 159.12 (C=N), 134.72-113.75 (Ar-C), 67.36 C(2), 60.32 C(6), 55.30 C(3), 48.57 C(5), 22.53-34.19 (-CH_2-), and 14.03 (CH_3).

Table 2. IR spectral data of compound (**1-10**).

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Assignment
3315	3414	3307	3302	3430	3320	3298	3254	3247	3298	ν_{N-H}
-	-	-	-	-	3435	3424	3424	3457	3428	ν_{OH}
3061	3063	3115	3068	3035	3265	3002	3150	3002	3183	ν_{C-H}
3030		2952	3037	2953	3030	2947	2924	2922	3066	
1714	1717	1715	1714	1720	-	-	-	-	-	$\nu_{C=O}$
-	-	-	-	-	1605	1603	1600	1610	1620	$\nu_{C=N}$
1492	1500	1455	1445	1493	1458	1507	1517	1513	1495	$\nu_{C=C}$
1456	1445	1405	1343	1406	1432	1437	1459	1443	1403	
1027	1091	1012	1028	1091	1113	1091	1005	1032	1236	ν_{C-N}
-	-	-	-	-	943	939	944	940	1030	ν_{N-O} Oxime
759	757	750	748	730	752	772	749	756	762	Aromatic C-H Out Of Plane Bending Vibrations
698	652	698	646	680	700	723	696	641	700	
611	529	635	657	518	603	623	613	615	597	Aromatic Plane Bending Vibrations

2.2.2.5. 3t-pentyl-2r, 6c–bis(4-chlorophenyl)piperidin-4-one oxime (10):

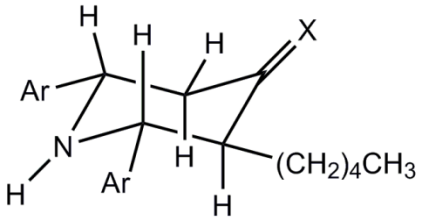
Yield 75%., m.p.106 (ºC), MF: $C_{22}H_{26}Cl_2N_2O$: IR (KBr) (cm^{-1}):3428 (OH stretching), 3298(N-H stretching), 3183 (-CH-Ar stretching), 1620 (C=N stretching), 1495 (C=C), 1236(C-N stretching),1030 (N-O stretching), 762-700 (Aromatic C-H out of plane bending vibration); ^1H NMR(400 MHz, $CDCl_3$, δ,(ppm)):7.78 (s, 1H, OH), 7.29-7.38 (m, Ar-H), 3.86 (d, 1H, H6), 3.60 (d, 1H, H2), 2.39 (t, 1H, $H3_a$), 1.93(t, 1H, $H5_{ax}$), 3.60 (t, 1H, $H5_{eq}$), 1.06-1.67 (m, 8H, -CH_2-), 0.78 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 158.74 (C=N), 142.51-121.41 (Ar-C), 67.20 C(2), 60.22 C(6), 48.46 C(3), 34.11 C(5), 22.51-31.97 (-CH_2-), and 14.05 (CH_3).

2.3 Antibacterial Activity by Disc Diffusion Method

Nutrient agar plates were prepared under sterile conditions and incubated overnight to detect contamination. About 0.2ml of working stock culture was transferred into separate nutrient agar plates and spread thoroughly using a glass spreader. Whatmann No.1 discs (6 mm in diameter) were

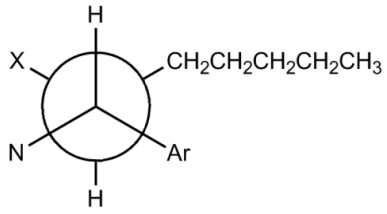
ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

impregnated in the test compounds dissolved in DMSO (200 mg/ml) for about half an hour. Commercially available drug disc *(Ciprofloxacin* 10 µg/disc) was used as positive reference standard. Negative controls were also prepared by impregnating the disc of same size in DMSO solvent. The discs were placed on the inoculated agar plates and incubated at 37 ± 1°C for about 18-24 h. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism.



	X	Ar
1.	O	Phenyl
2.	O	*p*-Fluorophenyl
3.	O	*p*-Chlorophenyl
4.	O	*p*-Methoxyphenyl
5.	O	*p*-Nitrophenyl
6.	NOH	Phenyl
7.	NOH	*p*-Fluorophenyl
8.	NOH	*p*-Nitrophenyl
9.	NOH	*p*-Methoxyphenyl
10.	NOH	*p*-Chlorophenyl

Figure 1. Chair conformation of 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-ones **(1-5)** and their oxime derivatives **(6-10)**.



	X	Ar
1.	O	Phenyl
2.	O	*p*-Fluorophenyl
3.	O	*p*-Chlorophenyl
4.	O	*p*-Methoxyphenyl
5.	O	*p*-Nitrophenyl
6.	NOH	Phenyl
7.	NOH	*p*-Fluorophenyl
8.	NOH	*p*-Nitrophenyl
9.	NOH	*p*-Methoxyphenyl
10.	NOH	*p*-Chlorophenyl

Figure 2. *Gauche* interaction of 3*t*-pentyl-2*r*, 6*c*–diarylpiperidin-4-ones **(1-5)** and their oxime derivatives **(6-10)**.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

2.4 Antifungal Activity by Disc Diffusion Method

Sabouraud's dextrose agar (SDA) medium was used for the growth of fungi and testing was done in Sabouraud's dextrose broth (SDB) medium. The subculture and the viable count were carried out by the same procedure used for in antibacterial studies except the temperature, which should be maintained at 28 ± 1°C for about 72 h. Similarly for disc diffusion method, the petridishes were incubated at 28 ± 1°C for about 72 h. The same concentration of the test compound, solvent (DMSO) and *Amphotericin B* (standard) prepared previously were used for the antifungal studies.

2.5 Minimum Inhibitory Concentration (MIC)

The lowest concentration of the test compounds which caused apparently the inhibition of growth of organism, was taken as the minimum inhibitory concentration (MIC). The minimum inhibitory concentration was recorded by visual observation after 24 h (bacteria) and 72-96 h (fungi) of incubation. The sterile distilled water and DMSO did not show any inhibition.

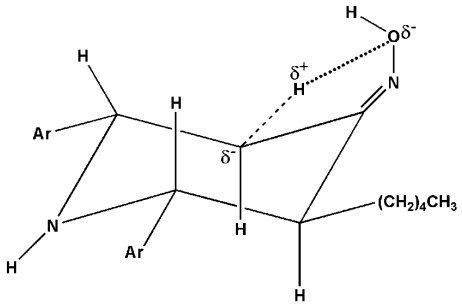


Figure 3. Interaction between the N-O bond and C-H bond.

3. RESULTS AND DISCUSSION

3.1 Synthesis

The evident synthetic pathway that leads to the title compounds (**1-10**) is represented in scheme 1. By adopting 3*t*-pentyl-2*r*, 6*c*- diphenylpiperidin-4-ones (**1-5**) [31,32] were obtained by the condensation reaction of *para* substituted benzaldehyde, 2-octanone and ammonium acetate in 2: 1: 1 ratio. Oximes (**6-10**) were obtained by treatment of 3*t*-pentyl-2*r*, 6*c*- diphenylpiperidin-4-one with hydroxylamine hydrochloride in the presence of sodium acetate trihydrate in absolute ethanol in good yield [10]. They are soluble in DMSO, $CHCl_3$, methanol, ethanol, ethyl acetate and benzene and are insoluble in petroleum ether and hexane.

3.1 Elemental Analysis

The C, H, N and O data of the compounds **1-10** are given in **Table 1**. These values are in good agreement between experimental and calculated values. The elemental analysis provides further support to the assignment structure.

Structures of all synthesised compounds were established on the basis of IR, ^{1}H and ^{13}C NMR spectral data.

3.2 FT-IR Spectra

Formation of the synthesized compounds **1-5** are confirmed by the observed carbonyl stretching in IR spectra of these compounds at 1700 cm^{-1} and compounds **6-10** are confirmed by the absence of

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

carbonyl stretching vibration and the presence of C=N stretching frequency around 1600 cm^{-1} due to oximation (**Table 2**).

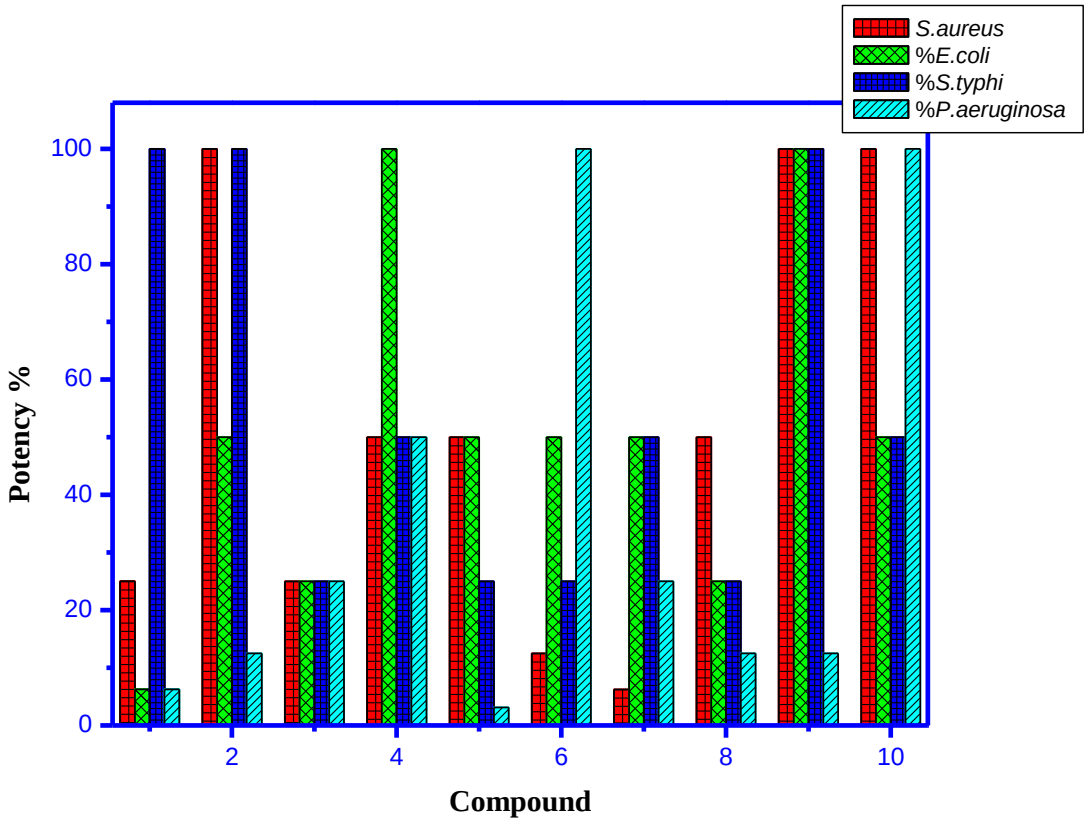


Figure 4. Comparison of antibacterial potency of compounds **1-10** with *Ciprofloxacin*.

3.3 NMR Spectra

The numbering of carbon atoms is shown in **Scheme 1**. The protons of the piperidine ring are given the numbers of the carbons to which they are attached. The methylene protons at C(5) are denoted as $H(5)_{ax}$ and $H(5)_{eq}$ representing the axial and equatorial hydrogens, respectively.

The benzylic protons at C(6) give rise to a doublet of doublet due to their coupling with adjacent methylene protons. The two coupling constants are found to be about 11.5 and 3 Hz, respectively, indicating a diaxial and an axial- equatorial coupling. However, in compounds **1, 4, 5, 6, 7** and **8**, the benzylic proton at C(2) appears as a doublet with a *J* value of about 10 Hz. The above observations are in accordance with the chair conformation for these compounds with the aryl and alkyl groups occupying the equatorial positions (**Figure 1**). A possible explanation is that in the 3-alkyl compounds the ring may be flattened about C(2)–C(3) bond. This flattening occurs probably due to decrease in the phenyl-alkyl *gauche* interaction as shown in **Figure 2** and this causes an increase in the distance between the nitrogen lone pair and the *ortho* proton. Such a distortion may also cause a change in the relative orientation of the nitrogen lone pair with respect to the *ortho* protons. However, the net effect is probably a decrease in the deshielding of the *ortho* protons by the lone pair. The pentyl group at C(3) influences the chemical shift of the benzylic proton significantly in compounds **1-5**. The benzylic proton at C(6)

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

appears in the same position. i.e. around 4.0 ppm. However, the chemical shift of the benzylic proton at C(2) decreases. Thus, the axial proton at C(2) carbon is shielded by the equatorial pentyl group. In the compounds **3, 4, 5, 6, 7** and **8** the piperidone ring is in the chair conformation with equatorial orientation of the substituents which is confirmed by the almost identical carbon chemical shifts of the benzylic carbons in the *p*-substituted compounds. The methylene protons of the pentyl group gave three multiplets in the region 0.92-1.65 ppm. The aromatic protons appear in the region 6.42 - 8.27 ppm. The ^{1}H chemical shift values are given in **Table S1** (supporting information).

In compound **1,** one doublet of doublet and a doublet are observed at 4.06 and 3.70 ppm, respectively. These signals are obviously due to benzylic protons at C(6) and C(2), respectively. The axial methylene proton at C(5) is observed at 2.73 ppm. The signals for the equatorial methylene proton at C(5) and the proton at C(3) overlapped and appeared in the region around 2.58-2.65 ppm. The four multiplets around the region 0.93-1.65 ppm are assigned to the methylene protons of the pentyl side chain at C(3) (integral value corresponds to eight protons). The upfield triplet at 0.78 ppm is assigned to methyl proton of the pentyl side chain. Comparison of the chemical shifts of pentyl compound (**1**) with the corresponding *p*-F(**2**), *p*-Cl(**3**), *p*-OCH_3(**4**) and *p*-NO_2(**5**) compounds show that *p*-substituent de-shield the heterocyclic ring protons markedly due to inductive and mesomeric effect.

The ^{1}H NMR study of oximes shows with the difference in chemical shifts of the two *α*-hydrogens. It has been generally observed in six- membered ring oximes that the chemical shift difference between the equatorial *α*-hydrogen and the axial α hydrogen is approximately 1 ppm. In all the oximes **(6-10),** the *syn*- α equatorial proton appears in the low field compared to the *syn*- α proton. The present study shows that the *β*-hydrogen *syn* to the OH group is shielded by 0.16 ppm relative to its *anti* counterpart. The *syn α* –axial protons and *syn β*-protons are shielded due to the transfer of the negative charge on the *syn α*-carbon to the axial *α*-proton and to the *syn β*-proton through the *syn β*-carbon. In compounds **6-10,** the *syn α*-axial protons are observed at 2.03, 1.97, 1.95 and 2.17 ppm and the *anti α*-protons at 2.49, 2.42, 2.49 and 2.41 ppm, respectively. The chemical shift of C(5) axial proton is, however, much less than that of the C(5) equatorial proton of compounds **6-10**, hence, the *syn α*-(C-H) bond is neither equatorial nor axial. The negative charge on the *syn α* –carbon C(5) is transmitted to *syn α* –axial hydrogen to some extent. Therefore, axial hydrogen at C(5) is shielded whereas equatorial hydrogen is deshielded due to oxime formation. Oximation slightly shields the H(2), H(6) and methine H(3) protons. There is no appreciable change in the chemical shifts of methyl protons of pentyl group at C(3) due to the oximation.

The aromatic carbons could be readily distinguished by their characteristic absorption around 120 ppm. The *ipso* carbons should absorb at (~ 140 ppm) downfield compared to other aromatic carbons. The upfield signal around 14 ppm is assigned to methyl carbon of pentyl group at C(3). In 3*t*-pentyl-2*r*, 6*c*-diphenylpiperidin-4-one (**1**) the signals for the heterocyclic ring carbons appeared at 67.24, 57.13, 209.33, 51.59, 61.88 and 31.90, 27.38, 24.61 and 22.36 ppm. The most downfield signal at 209.3 ppm is obviously due to carbonyl carbon *i.e.,* C(4). The upfield signals at 31.90, 27.38, 24.61 and 22.36 ppm are due to four methylene carbons of the pentyl group at C(3). The downfield signal at 67.24 ppm is assigned to C(2) based on the known de-shielding *β*-effect of the pentyl group. The other downfield signal at 61.88 ppm is obviously due to C(6). Among the remaining signals, at 57.13 and 51.59 ppm, the one at downfield 57.13 ppm is assigned to C(3) based on known *α*-effect of the pentyl group at C(3) and the signal at 51.59 ppm is assigned to C(5). The ^{13}C chemical shift values are summarized in **Table S2**.

The chemical shifts of the heterocyclic ring carbons in **1-5** are assigned by comparison with the corresponding phenyl piperidone and *p*-substituted phenyl piperidones and also by considering the effect of the pentyl substituents on the chemical shifts of the heterocyclic ring carbons. The benzylic carbon

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

appears at a lower field than the methylene and methine carbon. In **1**, pentyl substitution at C(3) causes downfield shift of 7.10 ppm for the pentyl-bearing carbon (α- carbon). However, it is known that both the steric and the electronic interactions between the pentyl group and the substituents on adjacent carbons cause a decrease in the magnitude of the C-α parameter. The unusually small α effect of the pentyl group in **1** is due to the summed interaction of the pentyl group with the neighbouring carbonyl, NH and phenyl groups, which are surprisingly high in comparison with the corresponding phenyl substituted compounds. The chemical shift of the β-carbon at C(2) shows a large downfield in the pentyl substituted compounds, and the magnitude of this in **1** is 6.2 ppm. In compounds which bear *p*-substituted phenyl moiety at C(2) instead of phenyl group, the β-effect of the pentyl group is reduced, thus compounds **2, 3, 4** and **5** show upfield shifts of 4.7, 1.0, 0.6 and 4.7 ppm, respectively.

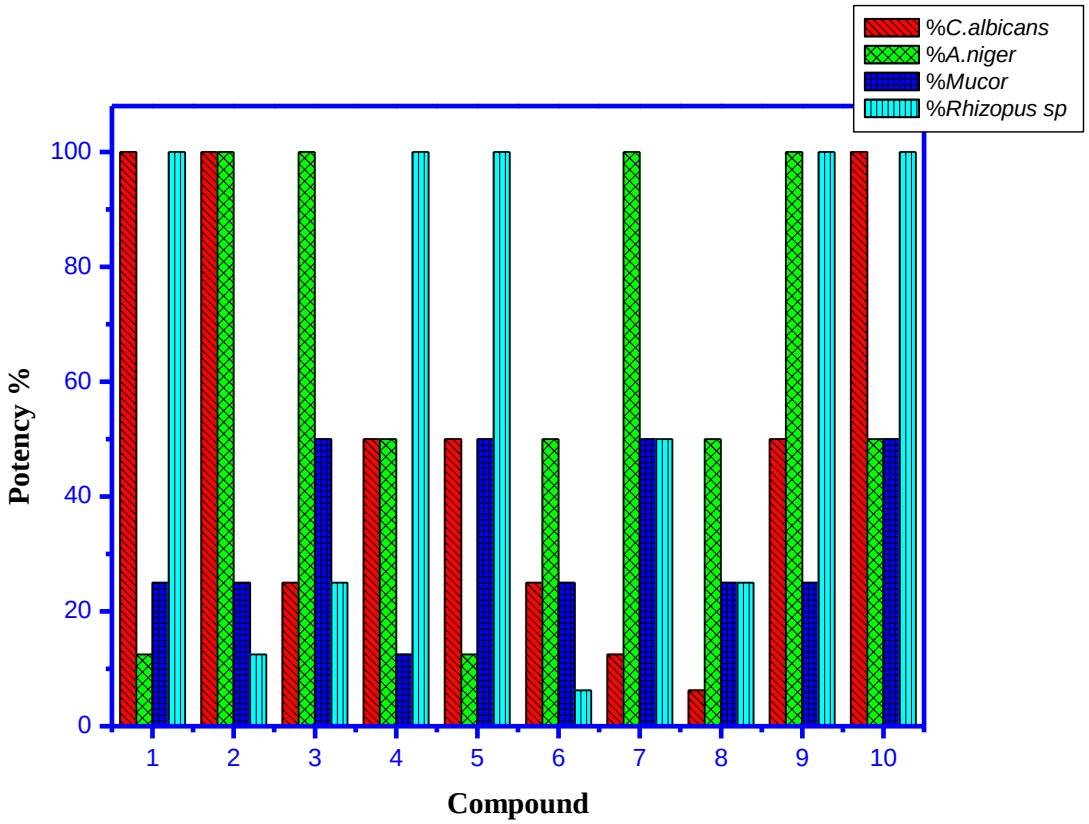


Figure 5. Comparison of antifungal potency of compounds **1-10** with *Amphotericin-B.*

A comparison of the chemical shifts of *p*-methoxyphenyl compounds **4** and **9** with those of parent compounds **1** and **6** reveal that the *p*-methoxy group shields the heterocyclic ring carbons except the carbonyl carbon on which it produces a slight deshielding. The benzylic carbons appear at a lower field than the carbons adjacent to the carbonyl group. In the *p*-methoxyphenyl compounds, apart from the *ipso* and methoxy bearing carbons, the other carbons appear in two distinct positions around 128 and 113 ppm. The methoxy bearing carbon appears around 159 ppm and the signal around 135 ppm is due to *ipso*

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

carbon. The signal around 128 ppm is due to carbons *meta* to the methoxy group and that around 113 ppm is due to carbons *ortho* to the methoxy group. By comparing the chemical shift of the aromatic carbons in **1** and **4**, it becomes apparent that *ortho* carbons are shielded about 13 ppm and the *ipso* carbons about 6 ppm by the methoxy group. Thus, carbons *ortho* to methoxy are shielded to a greater extent than those *para* to it. This is due to the fact that the *ortho* carbons are shielded by both steric and mesomeric effects whereas the *para* carbons shielded only by mesomeric effect.

In the *p*-methoxy compounds, two equivalent orientations are possible. In each orientation, the methyl group interacts with one of the two *ortho*-hydrogens. Thus, both the *ortho* hydrogens feel an average steric interaction and both the *ortho* carbons are shielded equally which reveals that the methoxy group must be coplanar with the benzene ring in order to have an effective conjugation between oxygen lone pair and π-electrons of the benzene ring. The effects of *p*-chloro and *p*-fluro substituents are, therefore found to be nearly the same for C(4) but very different for C(2) and C(3), which indicates that the shielding of C(2) and C(3) are largely steric in nature, whereas C(4) is influenced by field effects.

Oximation shields all the ring carbons except the *anti* β-carbons of **6-10**. The oximation reduces the electronegativity of C(4). As a result C(3), C(4) and C(5) are shielded in oximes relative to the corresponding ketones (**Table S3**).

Furthermore, in oxime there is an interaction between the N-O and one of the C-H bonds in the *syn* side. Due to this interaction the C-H bond gets polarised. So that the hydrogen gets a slight positive charge and the carbon gets a negative charge (**Figure 3**). This de-shields the hydrogen but shields the corresponding carbon. In chair conformation, this interaction can occur only with the equatorial C-H bond and the equatorial methylene hydrogen is deshielded whereas the methylene carbon at C(5) and the axial methylene hydrogen are shielded. The negative charge on C(5) induces a slight negative charge on C(6) and due to this effect C(6) and H(6) are slightly shielded.

Generally in oxime, the *syn* α-carbon is more shielded than the *anti* α-carbon, probably the chemical shift difference between the α-carbons varying by 13-12 ppm depending on the structure of the oxime (**Table S4**).The two dimensional NMR Spectral assignments of compounds **1** and **6** were confirmed unambiguously by HOMOCOSY, HSQC and HMBC spectra. The chemical shift values are given in **Table S5**. In the HOMOCOSY spectrum of compound **1,** the doublet at 3.70 ppm shows cross peak with a multiplet in the region 2.58-2.65 ppm for H(3). This clearly exhibits that doublet at 3.70 ppm is due to H(2) proton. A multiplet and a triplet observed in the region 2.58 -2.65 ppm and at 2.73 ppm, respectively, for methylene protons at C(5) reveal cross peaks with the signal at 4.06 ppm. Obviously this signal is due to H(6).

In the HOMOCOSY spectrum of compound **6,** the doublet at 3.90 ppm shows correlation with methylene protons at 2.03 ppm and equatorial methylene proton in the region 3.61-3.66 ppm should be due to H(6) proton. The signal at 2.03 ppm and 3.61-3.66 ppm should be due to $H(5)_{ax}$ and $H(5)_{eq}$, respectively. The multiplet in the region of 3.61-3.66 shows cross peak with the signal for H(3) at 2.49 ppm. This clearly reveals that signals in the region of 3.61-3.66 ppm are due to H(2) proton.

In the HMBC spectrum of compound **1,** signals at 67.24 and 61.88 ppm show correlation with the benzylic protons. The signals at 67.24 ppm and 61.88 ppm correlate with the benzylic proton signals at 3.70 and 4.06 ppm, respectively. It is obvious that the proton signals at 3.70 and 4.06 ppm are due to H(2) and H(6), respectively. Also the ^{13}C the signal at 67.24 ppm and 61.88 ppm should be due to C(2) and C(6), respectively. The other two signals at 57.13 and 51.59 ppm show correlation with the methine and methylene protons in the region 2.58-2.65 and at 2.73 ppm, respectively. Hence, the signals must be due to methine carbon at C(3) and methylene carbon at C(5). Equatorial methylene proton at C(5) and methine proton at C(3) overlapped and appeared in the region 2.58-2.65. The proton signals in the region

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

2.58-2.65 are due to H(3) and $H(5)_{eq}$ and the signal at 2.73 ppm is due to $H(5)_{ax}$ protons. The signals at

Table 3. Antibacterial activity of compounds **1-10**.

Compounds	Minimum inhibitory concentration in (µg/ml)			
	S.aureus	*E.coli*	*S.typhi*	*P.aeruginosa*
1	25	100	6.25	100
2	6.25	12.5	6.25	50
3	25	25	25	25
4	12.5	6.25	12.5	12.5
5	12.5	12.5	25	200
6	50	12.5	25	6.25
7	100	12.5	12.5	25
8	12.5	25	25	50
9	6.25	6.25	6.25	50
10	6.25	12.5	12.5	6.25
Ciprofloxacin	6.25	6.25	6.25	6.25

31.90, 27.38, 24.61 and 22.36 ppm show correlations with the methylene proton in the region 1.05-1.15, 1.25-1.32, 0.99-1.01 and 1.56-1.65 ppm, respectively. It is obvious that the carbon signals at 31.90, 27.38, 24.61 and 22.36 ppm are due to methylene carbons of the pentyl group at C(3) position, respectively.

In HSQC spectrum, proton chemical shifts are plotted *vs* carbon chemical shifts. Correlation peaks are obtained between carbon and hydrogen which are involved in direct one bond coupling. From the HSQC spectra of compounds **1** and **6,** the signals of all carbons containing hydrogen could be assigned unambiguously. In the HSQC spectrum of compound **1**, 67.24 ppm shows correlation with the signal at 3.70 ppm. Therefore, this signal should be due to C(2). The signal at 61.88 ppm shows correlation with 4.06 ppm and is assigned to C(6). The signal at 57.13 ppm has correlation with the signal in the region 2.58-2.65 ppm and it is assigned to C(3). The signal at 51.59 ppm has correlation with 2.73 ppm and it is assigned to C(5). The signals at 24.61, 27.38, 32.61 and 22.36 ppm have correlations with the signals in the regions 1.56-1.65, 1.25-1.32 and 1.05-1.15 ppm and they are assigned to four methylene carbon of pentyl groups at C(3). The signal at 13.95 ppm has correlation with the signal at 0.78 ppm and it is assigned to methyl carbon of pentyl group at C(3). In the HSQC spectrum of compound **6**, the signals at 60.92, 48.52, 34.13 and 13.98 ppm have correlation with the signals at 3.90, 2.49, 2.03 and 0.77 ppm and they are assigned to C(6), C(3), C(5) the carbons of piperidone ring and methyl carbon in pentyl

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

group at C(3), respectively.

Table 4. Antifungal activity of compounds **1-10**.

Compounds	Minimum inhibitory concentration in (μg/ml)			
	C.albicans	*A.niger*	*Mucor*	*Rhizopus sp*
1	12.5	100	50	12.5
2	12.5	12.5	50	100
3	50	12.5	25	50
4	25	25	100	12.5
5	25	100	25	12.5
6	50	25	50	200
7	100	12.5	25	25
8	200	25	50	50
9	25	12.5	50	12.5
10	12.5	25	25	12.5
Amphotericin-B	12.5	12.5	12.5	12.5

3.4 Mass Spectra

The mass spectra of compounds **1** and **6** were recorded and the possible fragmentation patterns are given in **Scheme 2** and **Scheme 3**.The presence of peaks at m/e 321 and 336 are due to the molecular ion peaks of compounds **1** and **6**. The characteristic peak at m/e 208 (A) is formed from the 3*t*-pentyl-2r, 6*c*–diphenylpiperidin-4-one by the removal of ketene. The ion with mass 194 (B) represented as the substituted benzylic cation or substituted tropylium cation. The peaks at m/e 278 (C), 250 (D) are from the 3*t*-pentyl-2*r*, 6*c* -diphenylpiperidin-4-one (**1**) by the elimination of (i) $-CH_2-CH_2-CH_3$ and pentyl radical. The peak at m/e 264 (E) is formed due to the elimination of methylene radical from (C).

In compound **6**, the characteristic peak at m/e 319 is due to formation of nitrile (A or A') obtained by rearrangement and followed by the elimination of water molecule. The nitrile (A) eliminates (i) Ph-C-NH_2, (ii) Hexylnitrile and Hydrogen radical and (iii) pentyl radical producing peaks at m/e 199 (B), 208 (C) and 247 (D), respectively. The carbonium ion (C) forms (i) tropylium cation (E) after abstracting hydride ion and (ii) pentyl cation with m/e 91 and 77 readily. The peaks at m/e 278 (G) and 241 (H) are formed from the nitrile (A') by the elimination of (i) acetonitrile radical and (ii) benzene, respectively. The ion with mass 194 (I) represented as the substituted benzylic cation or substituted tropylium cation is formed from the 3*t*-pentyl-2r, 6*c*-diphenylpiperidin-4-one oxime by rearrangement followed by the elimination of 3*t*-alkyl-2*r*, 6*c*-diphenylpiperidin-4-one oxime. Similar fragmentation pattern was reported previously by Ganapathy *et.al* [33].

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

3.5 Structure Activity Relationship

The structure activity relationship was undertaken to establish the relationship between the antimicrobial activity of the synthesized compounds and their molecular descriptors.

3.5.1 Antibacterial Activity

In *vitro* antibacterial activities of the various substituted 3*t*-pentyl-2*r*,6*c*-diarylpiperidin-4-one **1-5** and their oximes **6-10** against a group of bacterial strains such as *Staphylococcus aureus, Escherichia coli, Solmonella typhi* and *Psedomonas aeruginosa* were used for a minimum inhibitory concentration (µg/mL) and are listed in **Table 3**. *Ciprofloxacin* was used as a reference drug.

Antibacterial studies of the compounds **1** and **6** with unsubstituted phenyl group at C(2) and C(6) revealed that the compound **1** against *S.typhi* and *S.aureus* and compound **6** against *E.coli, S.typhi, P. aeruginosa* exhibited better activity. But the compound **1** against *E.coli* and *P. aeruginosa*, and **6** against *S.aureus* registered poor activity. A close survey of **Table 3** revealed that compounds **2** and **7** with *p*-fluoro substituted phenyl groups at C(2) and C(6) positions of piperidone ring were found to show better activity against all the tested strains except **7** against *S.aureus* for which no change in activity was noted. Compound **3** obtained due to the replacement of phenyl groups in **1** by *para*-chlorophenyl group produced moderate activity against all the tested strains at MIC of 25 µg/mL except aginst *S.typhi*. Substitution of *p*- methoxyphenyl groups instead of phenyl ring in **1** and **6** (compounds **4** and **9**) showed better activity against all the tested bacterial 6.25-12.5 µg/mL and **9** showed moderate activity against *E.coli*, *S.typhi* and *P.aeruginosa*. Introduction of *p*- nitrophenyl groups at C(2) positions of piperidone ring in **1** and **6** (compounds **5** and **8**) are significant in inhibiting the growth of all the tested bacterial strains. Particularly **5** and **8** against *S.aureus, E.coli* and *S.typhi* showed better activity and their potencies fall in between 12.5 and 25 µg/mL. For **4** and **8** very poor activities were noted against *P.aeruginosa.*

The *p*-methoxyphenyl substituted compounds **4** and **9** exhibited excellent activity against all the tested bacterial strains in the range of 6.25- 50 µg/mL. This is due to the mesomeric effect of methoxy group in phenyl ring. Introduction of chloro phenyl group instead of phenyl group in **6** (compound **10)** showed excellent activity against all the tested bacterial strains in the range 6.25-12.5. The compounds **2, 3, 5, 7** and **8** exhibited excellent activity against *E.coli* and *S.typhi*. The compound **7** against *S.aureus* and **5** against *P.aeruginosa* showed poor activity. The other compounds exhibited excellent activity against all the tested bacterial strains due to the presence of electron withdrawing substituted in the phenyl ring at C(2) and C(6) positions. This reduces the electron density in the piperidone ring.

The percentage of antimicrobial potency of the tested compounds compared with reference standard was calculated by adopting the following equation

Antimicrobial potency (%)

$$= \frac{\text{MIC(µg/mL) of reference compound}}{\text{MIC(µg/mL) of test compound}} \text{ X } 100$$

3.5.2 Antifungal Activity

In vitro antifungal activity of compounds **1-10** was studied against fungal strains such as *Candida albicans, Aspergillus niger* and *Mucor, Rhizobus sp* with *amphotericin B* as the standard drug **Table 4**. Among the synthesized compounds, **1** and **6** having no substitution at the *para* position of phenyl groups at C(2) and C(6) revealed that the compound **1** exhibited enhancing the antifungal activity against

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

C.albicans and *Rhizopus.sp* while the activity was reduced against *A.niger* and *Mucor*. The compound **6** showed less activity against all the tested fungi strains. Introduction of *p*-fluorophenyl groups at C(2) and C(6) positions of piperidone ring system in **1** and **6** (compounds **2** and **7**) showed better activity against *A.niger* and **2** against *C.albicans*. While poor activity was noted against all other tested organisms. Substitution of *p*-chlorophenyl groups at C(2) and C(6) positions in **1** (compound **3**) has fairly improved the activity against *A.niger* and *mucor* while less activity was noted against rest of the strains. However, introduction of *p*-methoxyphenyl group in the place of phenyl groups at C(2) and C(6) positions in **1** and **6** (compounds **4** and **9**) have fairly improved the activity against *A.niger* and did not promote activity against *C.albicans* and *mucor*. The substitution of chlorophenyl group at C(2) and C(6) position of piperidone ring in **6** (compound **10**) showed excellent activity against *C.albicans* and *Rhizopus sp* and has better activity against *A.niger* and *Mucor.*

Likewise, substitution of *p*-nitrophenyl group at C(2) and C(6) positions of piperidone ring in **1** and **6** (compound **5** and **8**) showed less activity against all the fungal strains. The compounds **2, 3** and **7** showed better activity against *A.niger* due to electron withdrawing group attached in the phenyl group at C(2) and C(6) positions. The results suggest that the antibacterial and antifungal activities are markedly influenced by substituent in phenyl ring (**Figure 4** and **Figure 5**).

Narayanan *et al* [34] and Jayabharathi *et al* [35] have studied on antimicrobial evaluation of some N-protected 2,6-diarylpiperidin-4-one and its derivatives. Comparison of antimicrobial activities of 3-pentyl-2,6-diphenylpiperidine-4-one and their oxime derivatives with N-prodected-2,6-diphenyl piperidine-4-one and their derivatives, reveal that former compounds show excellent activity against all the tested antibacterial and antifungal strains.

4. CONCLUSION

The NMR spectral data of all the synthesized compounds (**1-10)** suggest that the compound adopt chair conformation with equatorial orientation of all the substituents. The oximation shielded all carbons except carbon at C(2) in the heterocyclic ring. The observed deshielding and shielding on $H(5)_{eq}$ and $H(5)_{ax}$, respectively can be explained on the basis of steric polarisation effect. All the compounds were screened for their preliminary antibacterial and antifungal activities. Most of the compounds show good antibacterial and antifungal activities. However, antibacterial and antifungal activities are significantly influenced by the substituents in the phenyl ring.

ACKNOWLEDGMENT

One of the authors G. Rajarajan is thankful to UGC, New Delhi for financial support in the form of major research project. Ms. S. Savithri is grateful to UGC for the award of UGC-BSR fellowship.

SUPPORTING INFORMATION

Table S1-S5, NMR and mass spectra are included in the supporting information.

REFERENCES AND NOTES

[1] Harris, R.K.; Spragg, R.A. NMR studies of N-nitrosamines. III. Saturated dinitrosamines. *J. Mol. Spec.* **1969**, *30*, 77-95.

[2] Gurumani,V.; Pandiarajan,K.; Swaminathan, M. Conformational studies of some 1-hetero-2,6-diphenylcyclohexan-4-one oxime using NMR spectrum–Evidence for boat form contributions to trans-2,6-diphenyl systems. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 29-35.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

[3] Pandiarajan, K.; Manimekalai, A.; Kalaiselvi, N. Conformational studies of some t(4)-acetoxy-r(2), c(6)-diphenyl-N-acetylpiperidines using ^{1}H NMR spectra evidence for contribution of boat forms with a substituent in the flagpole position. *Magn. Reson. Chem.* **1997**, *35*, 372-378.

[4] Rubiralta, M.; Giralt, E.; A. Diel. Piperidine structure, preparation and synthetic applications of piperidine and its derivatives. Elsevier. Amsterdam. **1991**, pp 225-312.

[5] Amirthaganesan, S.; Sabapathy Mohan, R.T.; Murugavel,K.; Muthukumaran, G.; Pandiarajan, K. Synthesis and ^{1}H and ^{13}C NMR spectral study of some t(3)-aryl-r(2)-C(4)dicarbalkoxy-C(5)-hydroxy-t(5)-methylcyclohexanones and their oximes. *Indian J. Chem.* **2007**, *46B*, 1004-1013.

[6] Kim, D.G.; Tulemisova, G.B. Reduction of 3-hydroxymethyl-3-methyl-2,6-diphenyl- piperidin-4-one. *Russian J. Org. Chem.* **2002**, *38*, 136-136.

[7] Perumal, S.; Manonmani,V.; Vijayabaskar, V.; Selvaraj, S.; Lycka , A. Synthesis and NMR study of the stereochemistry of *r*(2),*c*(6)-diaryl-c(3)-chloropiperidin-4-ones. *Indian J. Chem*. **2004**, *43B*, 2147-2151.

[8] Rameshkumar,N.; Veena, A.; Ilavarasan,R.; Adirja, M.; Shanmugapandian,P.; Sridhar,S. K. Synthesis and biological activities of 2,6-diaryl-3-methyl-4-piperidone derivatives. *Biol. Pharm. Bull.* **2003**, *26*, 188-193.

[9] Jayabharathi, J.; Thangamani,A.; Balamurugan,S.; Thiruvalluvar, A.; Linden, A. *t*-3-Benzyl-*r*-2,*c*-6-bis(4-methoxyphenyl)piperidin-4-one. *Acta Cryst. E*. **2008**, *64*, 1181.

[10] Pandiarajan, K.; Sabapathy Mohan, R.T.; Hasan , M.U. ^{13}C and ^{1}H NMR spectral studies of some piperidin-4-one oximes. *Magn. Reson. Chem.* **1986**, *24*, 312-316.

[11] Karthick, N.; Nithiya, S.; Jayabharathi, J. Novel piperidone derivatives: synthesis, spectral and evaluation of antioxidant activity. *J. Int. J. Drug Dev. Res.* **2011**, *3*, 122-127.

[12] Pandey, P.; Chawla,P. Synthesis characterization and biological activity of novel 2,6-disubstituted piperidine -4-one derivatives. *Int. J. Pharm. Chem. Bio. Sci.* **2012**, *2*, 305-309.

[13] Ajaykumar, K.; Pavithra, G.; Renuka, N.; Vasanthkumar, G. Piperidone analogs: Synthesis and their diverse biological applications. *Int. Res. J. Pharm. App. Sci.* **2012**, *2*, 145-154.

[14] Kirankumar, K.; Sridharbabu, G.; Naresh, B.; Kishorekumar, S.; Preaveenkumar Jampana. Microwave mediated synthesis of some diaryl piperidine -4-one derivatives. *Int. J. Bio. Pharm. Res. **2012**, 3*, 48-50.

[15] Manikandan, D.; Krishnaraj, K.; Nanjan, MJ. Synthesis and biological evaluation some substituted 4-piperidones. *Int. J. Chem. Tech. Res.* **2012**, 532-538.

[16] Venkateshvaramoorthi, R.; Krishnasamy, K. Synthesis, spectral characterisation, antimicrobial studies of some 3-substituted piperidine -4-one derivatives. *Int. J. Rec. Sci. Res.* **2013**, *4*, 45-49.

[17] Senthil, A.; Sureshkumar, P.; Narasimha Raju, CH.; Mohindeen BH, S.; Navaneetha Krishnan, S. Synthesis, characterisation, pharmacological screening antimicrobial activity of 3-methyl-1,2-phenyl (3,4-dihydroxy)6-phenyl piperidine 4-one. *Int. J. Prec. Pharma. Res.* **2011**, *2*, 22-25.

[18] Jayabharathi, J.; Sivakumar, R.; Praveena, A. Synthesis and antimicrobial evaluation of some *t*(3)-alkyl and *t*(3), *t*(5)- dimethyl-*r*(2), *c*(6)-di-(furfuryl)piperidin-4-one and its derivatives. *Med. Chem. Res.* **2005**, *14*, 198-210.

[19] Jayabharathi, J.; Thangamani,A.; Balamurugan,S.; Thiruvalluvar, A.; Linden, A. *t*-3-Benzyl-*r*-2,*c*-6-bis(4-methoxyphenyl)piperidin-4-one oxime**.** *Acta. Cryst. E.* **2008**, *64*, 1211.

[20] Kappe, C.O. 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron* **1993**, *49*, 6937-6963.

[21] Premalatha, B.; Elavarasan, S.; Bhakiaraj,D.; Chellakili, B.; Gopalakrishnan, M. Synthesis, antimicrobial and antioxidant activity of novel 2,6-diphenyl-1-3-alkyl piperidine-4-one-o-(2,4,6-tritertiary butyl- cyclo hexa -2,5-dienon-4-yl) oximes. *J. Appl. Chem.* **2013**, *2*, 1509-1515.

[22] Kanagarajan, V.; Sureshkumar, P.; Gopalakrishnan, M. Strange formation of N-hydroxy-3,3-dimethyl 2,6-diaryl piperidine 4-one and its oxime derivatives- Synthesis, stereochemistry, antibacterial anti fungal activity. *Eur. Rew. Med. Pharm. Sci.* **2010**, *14*, 597-604.

[23] Gopalakrishnan, M.; Thanusu, J.; Kanagarajan, V. J. A simple and efficient grindstone chemistry solid state reaction procedure for the synthesis of heterocyclic oximes in dry media. *J. Korean Chem. Soc.* **2008**, *52*, 523-529.

ISSN 2291-6458 (Print), ISSN 2291-6466 (Online)
Year 2014 | Volume 2 | Issue 2 | Page 201-220

[24] Kappe, C.O. Biologically active dihydropyrimidones of the Biginelli-type - a literature survey. *Eur. J. Med. Chem.* **2000**, *35*, 1043-1052.
[25] Parthipan, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S Synthesis, spectral, crystal and antimicrobial studies of biologically potent oxime ethers of nitrogen, oxygen and sulfur heterocycles. *BioOrg. Med. Chem. Lett.* **2009**, *19*, 2981-2985.
[26] Parthipan, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. Synthesis, stereochemistry and antimicrobial studies of novel oxime ethers of aza/diazabicycles. *BioOrg. Med. Chem. Lett.* **2009**, *19*, 6981-6985.
[27] Parthipan, P.; Rathika, P.; Ramkumar, V.; Se Mo Son. Yeon Taejcong. Stereospecific synthesis of oximes and oxime ethers of 3-azabicycles: A SAR study towards antimicrobial agents. *BioOrg. Med. Chem. Lett.* **2010**, *20*, 1642-1647.
[28] Ramalingam, C.; Park, Y.T.; Kabilan, S. Synthesis, Stereochemistry and antimicrobial evolution of substituted piperidine-4-one oxime ethers. *Eur. J. Med. Chem.* **2006**, *41*, 683-696.
[29] Gayathri, P.; Jayabharathi, J.; Rajarajan, G.; Thiruvalluvar, A.; Butcher, R.J. *t*-3-Pentyl -*r*-2,*c*-6-diphenylpiperidin-4-one. *Acta Cryst. E.* **2009**, *65*, 3083.
[30] Subashchandrabose, S.; Saleem, H.; Erdogdu, Y.; Rajarajan, G.; Thanikachalam, V. FT-Raman, FT-IR spectra and total energy distribution of 3*t*-pentyl-2*r*,6*c*-diphenylpiperidin-4-one: DFT method, *Spectrochim. Acta A* **2011**, *82*, 260-269.
[31] Noller, C.R.; Balliah, V. The preparation of some piperidine derivatives by the Mannich reaction. *J. Amer. Chem. Soc.* **1948**, *70*, 3853-3855.
[32] Thennarasu, S.; Perumal, P.T. An Efficient Preparation of 1,2-Diamino-1-phenylheptane, Molecules **2002**, 7, 487-493.
[33] Ganapathy, K.; Gopalakrishnan, V.; Pandiarajan, K.; Jeyaraman, R. Electron impact mass spectral fragmentation of some piperidine derivative. *Indian J. Hetrocycl. Chem.* **1993**, *2*, 159-164.
[34] Narayanan, K.; Shanmugam, M.; Jothivel, S.; Kabilan, K. Design, synthesis, spectral and biological evaluation of novel 1-allyl substituted-2,6-diphenylpiperidin-4-ones and its derivatives of oxime/oxime ethers. *BioOrg. Med. Chem. Lett.* **2012**, *22*, 6602-6607.
[35] Jayabharathi, J.; Manimekalai. A.; Padmavathy, M. Syhthesis, spectral, theoretical and antimicrobial of some heterocyclic oximes. *Med. Chem. Res.* **2011**, *20*, 981-995.

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/