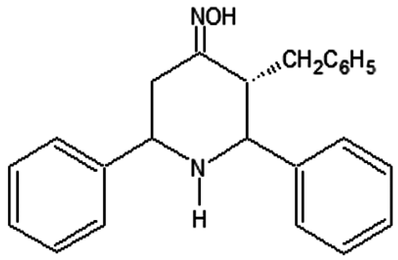
St. Joseph's Journal of Humanities and Science
ISSN: 2347 - 5331
http://sjctnc.edu.in/6107-2/

X-RAY CRYSTAL STRUCTURE, MOLECULAR STRUCTURE, SPECTRAL AND ANTIMICROBIAL ACTIVITY OF t-(3)-BENZYL-r-(2),c-(6)-DIPHENYL PIPERIDIN-4-ONE-OXIME

- R. Arulraj,[a]
- S. Sivakumar,[a,b]*
- K. Rajkumar,[a]
- A. Manimekalai[c]
- A. Thiruvalluvar[d]

Abstract

In the title molecule, C24H24N2O,crystallizes with the monoclinic space group P1 21/c 1, Z=4. From the Spectral data and XRD data, the piperidine ring adopts a chair conformation and the two phenyl groups attached to the piperidine ring at positions 2 and 6 have equatorial orientations. Crystal data: Mr= 356.45 g/mol, a = 19.5024(9) Å, b = 8.7503(4) Å, c = 11.6500(6) Å, β = 100.846(2)°, volume = 1952.58(16) Å3, Z=4, λ =1.54178 Å, T = 296(2) K. The antibacterial and antifungal activities were also evaluated for the title compound.



Keywords: Crystal structure; Piperidin-4-one-oxime; Spectra; Antimicrobial activity.

INTRODUCTION

The piperidine ring is a ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson *et al*[1]asserted that during a recent 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies (Watson *et al.*, 2000)[1]. Piperidine exhibits a wide spectrum of biological activities and forms an essential part

[a] Research and Development Centre, Bharathiar University, Coimbatore 641 046, Tamilnadu, India.
[b] Department of Chemistry, Thiruvalluvar Arts and Science College, Kurinjipadi 607 302, Tamilnadu, India.
[c] Department of Chemistry, Annamalai University, Annamalai Nagar 608 002, Tamilnadu, India.
[d] Postgraduate Research Department of Physics, Rajah Serfoji Government College (Autonomous), Thanjavur 613 005, Tamilnadu, India.
*Corresponding Author - Mobile: 9843693193 , Email: sivakumar.phd2015@gmail.com

of the molecular structures of important drugs. Molecular geometry critically influences biological activity (Venketeshperumal *et al.*, 2001)[2]. Piperidine derivatives are valued heterocyclic compounds in the field of medicinal chemistry. Piperidin-4-ones are reported to possess analgesic, anti-inflammatory, central nervous system (CNS), local anaesthetic, anticancer and antimicrobial activities (Perumal *et al.*, 2001; Dimmock *et al.*, 2001)[3,4] . The crystallographic study of the title compound has been carried out to establish the molecular structure. Jayabharathi *et al.* 2007)[5] have reported the synthesis, stereochemistry and antimicrobial evaluation of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diarylpiperidin-4-one and its derivatives. Recently (Arulraj *et al.* 2016)[6] reported the structure of asymmetric unit of the *t*-(3)-benzyl-*r*-(2),*c*-(6)-diarylpiperidin-4-one, contains two crystallographically independent molecules.

As part of our interest in the identification of bioactive compounds and in our attempt to understand the above reaction mechanisms, we report here the synthesis, x-ray crystal structure, molecular structure , spectral and antimicrobial activity of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenyl piperidin-4-one-oxime (1).

MATERIALS AND METHODS

Preparation of T-(3)-Benzyl-R-(2),C-(6)-Diphenyl Piperidin-4-One-Oxime Compound

Amixture of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenylpiperidin-4-one (0.1 mol, 7.71 g), hydroxilamine hydrochloride (0.1 mol) and sodium acetate trihydrate (0.3 mol) in methanol was refluxed till completion of reaction. After completion of the reaction water was added and extracted with ether, dried with anhydrous sodium sulphate and evaporated. The residue was dissolved in solvent ether to get the solid product. It was recrystallized twice in distilled ethanol. Good-quality single crystals of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenyl piperidin-4-one-oxime (1) were obtained after 2d and a crystal suitable for X-ray diffraction study was selected under an optical microscope. *t*-(3)-benzyl-*r*-(2),c-(6)-diphenyl piperidin-4-one-oxime compound (I) was obtained as a white crystals.

Recording of Spectra

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 MHz .Solutions were prepared by dissolving 10 mg (^{1}H) and 50 mg (^{13}C) of the compound in 0.5 ml of solvent ($CDCl_3$). The NMR spectra measurements were made in 5 mm NMR tube.

Recording of XRD

Bruker Kappa APEXIII CCD area-detector diffractometer	10617 independent reflections
Radiation source: fine-focus sealed tube	6350 reflections with $I > 2\sigma(I)$
Detector resolution: 8.3333 pixels mm^{-1}	$R_{int} = 0.078$
φ and ω scans	$\theta_{max} = 29.7°$, $\theta_{min} = 1.8°$
Absorption correction: multi-scan (SADABS; Bruker, 2015)	h = −13→13
$T_{min} = 0.81$, $T_{max} = 0.99$	k = −42→42
58653 measured reflections	l = −14→17

RESULTS AND DISCUSSION

^{1}H NMR Analysis

The signals in the ^{1}H NMR spectra were assigned based on their positions, multiplicities and integrals. In all these compounds the aromatic protons (phenyl ring protons) absorb around 7.4- 6.2 ppm. The signals in the range 3.1- 4.2 ppm are due to H(2) and H(6) protons. Methylene and methine protons appear in the region 2.2-3.6 ppm . The signals around 2.4-3.7 ppm are due to methylene protons of the benzyl group at C(3). The ^{1}H NMR data of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenyl piperidin-4-one-oxime are displayed in Table 1. From the chemical shifts, the coupling constants were extracted.

Table 1 : The ^{1}H NMR spectral data of *t*-(3)-benzyl-*r*-(2),*c*-(6)- diphenyl piperidin-4-one-oxime

S.No	Protons	H[1] NMR data(ppm)
1	H(2)	3.74
2	H(3)	2.85
3	H(5)	1.99(axial) ,
4	H(5)	3.62(eq)
5	H(6)	3.92
6	$C_6H_5CH_2$	3.07 , 2.39
7	Aromatic protons	7.47-7.45
		7.34-7.25
		7.14-6.99

^{13}C NMR Analysis

The aromatic carbons could be readily distinguished by their characteristic absorption above 100 ppm. Assignments for the heterocyclic ring carbons and benzylic carbons have been made on the basis of known effects of alkyl substituents in six-membered ring compounds. The assignment of the signals in *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one oxime (1) was made as follows. In compound (1) the chemical shift of C-2 is greater than that of C-6. From the other isomer based on intensities. The ^{13}C chemical shifts are displayed in Table 2.

Table 2: ^{13}C NMR Spectral Data of *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenyl piperidin-4-one-oxime

S.No	Carbon	^{13}C NMR data
1	C(2)	68.46
2	C(3)	50.43
3	C(4)	159.22
4	C(5)	34.28
5	C(6)	61.04
6	$C_6H_5CH_2$	31.36
7	Aromatic protons	143.67 ,142.29 ,141.46 ,128.93 ,128.55 ,128.35 ,128.05 ,127.83 ,127.62 ,126.70 ,125.37

Analysis of Coupling Constants

The observation of one large and one small coupling about C(5)-C(6) bond and one large coupling about C(2)-C(3) bond in **1** reveals equatorial orientation of benzyl groups at C-3 and aryl rings at C-2 and C-6. Hence, the compound **1** exist in normal chair conformation with equatorial orientations of all the substituents. The coupling constants about C(2)-C(3) bond in **1** is considerably lower than the *trans* couplings about C(5)-C(6) bond. This can be explained as follows. The benzyl group at C-3 experiences severe *gauche* interaction with phenyl group at C-2 and in order to avoid this *gauche* interaction, the ring is flattened about C(2)-C(3) bond. This flattening is responsible for lowering of the magnitude of $J_{2a,3a}$ relative to $J_{6a,5a}$ in compound(**1**).

Conformation of Benzyl Group

There are three possible conformations **A, B** and **C** for the benzyl group at C(3) in compound **1** as shown in Fig. 1. In conformation **B** H(3) is *gauche* with respect to both the methylene protons of the benzyl group at C(3) and hence both the coupling constants $J_{H(S),CH2}$ are expected to be around 3-4 Hz. However, in conformations **A** and **C** one coupling *i.e.*, $J_{H(S),CH2}$ is expected to be around 10-12 Hz and the other coupling is expected to be around 3-4 Hz. In 3-benzylpiperidone oxime (**1**) the couplings are in 2.23 and 8.28 Hz. The former corresponds to *gauche* coupling and other value falls in between those for a *gauche* and *anti* coupling. This large coupling suggests that the major conformer may be either **A** or **C**. Drieding model reveals that in conformation **C** there will be severe interaction between phenyl ring of the benzyl group at C(3) and hence this conformation is ruled out in the present study. Therefore the favoured conformation of benzyl group is predicted to be **A**. In conformation **A** the large and small couplings are expected to be 10 and 3 Hz. However the observed couplings 8.28 and 2.23 Hz suggest that a small amount of another conformer *i.e.*, the conformation **B** may also be present in solution in addition to the major conformation **A**. Thus the conformation of benzyl group is found to be an equilibrium mixture of conformations **A** (major) and **B** (minor).There are two possible conformations for phenyl ring of benzyl group at C(3) as shown in Fig. 2. In conformation **A**' the phenyl group prefers to

be oriented in such a way that phenyl ring is parallel to C(3)-CH_2 bond. In conformation **B'** the phenyl ring prefers to be oriented in such a way that the phenyl ring is perpendicular to C(3)-H_{3a} bond i.*e*., parallel for C(3)-H_{3a} bond. The conformation **A'** is destabilized due to severe interaction between the *ortho* protons of the phenyl ring with carbonyl group in conformation **A** and with the $H_{(2)}$ and in conformation **B**. Therefore this conformation is not favoured in compound **1**. Thus, the favoured conformation of phenyl ring of benzyl group is established as in conformation **B'**.

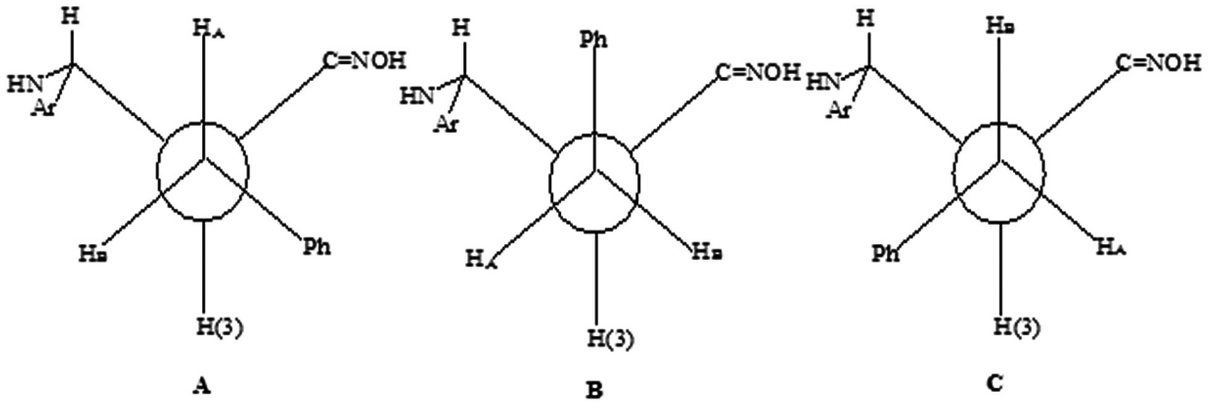


Figure 14.1

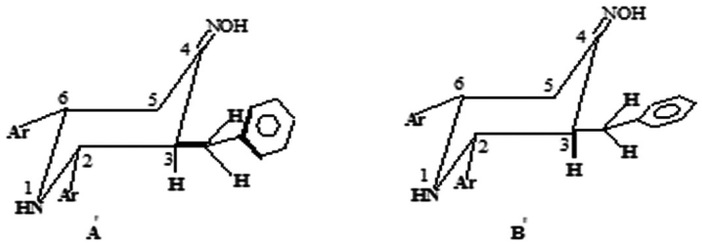


Figure 14.2

Analysis of Chemical Shifts

In order to study the effect of oximation on ^{1}H chemical shift, the chemical shifts of 3-benzylpiperidone oximes (**1**) have been compared with those of the corresponding 3-benzylpiperidones[7]. Conversion of piperidone to oxime shields all the protons except H_{5e}. The deshielding magnitude observed on H_{5e} can be explained as follows. In 3-benzylpiperidone oximes 1 severe interaction exists between N-O bond and *syn* equatorial α-(C-H)bond. Due to this interaction the *syn* equatorial α-(C-H)bond is said to be polarised and *syn* α-equatorial hydrogen acquires a slight positive charge and the *syn* α-carbon acquires a slight negative charge. 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.

Ring Conformations

The observation of one large and one small coupling about C(5)–C(6) bond and large coupling about C(2)–C(3) bond in the piperidin-4-one oxime (**1**) reveals that the compound adopts normal chair conformation with the equatorial orientations of phenyl rings at C(2) and C(6) and benzyl group at C(3). For **(1)** single crystal measurements were also made [10]. The single crystal measurements also reveal normal chair conformation with equatorial orientations of all substituents. The molecule belongs to the Monoclinic crystal system

and (P 1 21/c 1) space group. The ORTEP structure of piperidin-4-one oxime (**1**) is given in Figure 3**.** The crystal data of piperidin-4-one oxime (**1**) is displayed in Table 3.

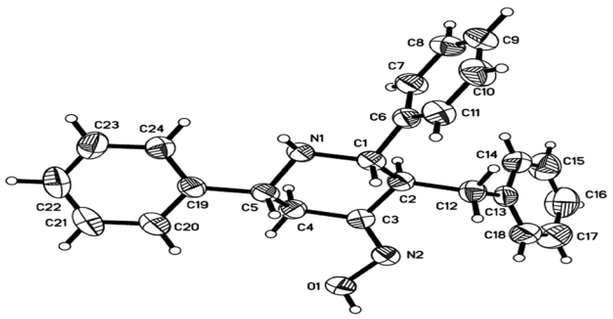


Figure 14.3 : The ORTEP Structure of Piperidin-4-One Oxime (1)

Table 3. The Crystal Data of Piperidin-4-One Oxime (1)

Chemical formula	$C_{24}H_{24}N_2O$	
Formula weight	356.45 g/mol	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal size	0.040 x 0.100 x 0.220 mm	
Crystal habit	colorless plate	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 19.5024(9) Å	α = 90°
	b = 8.7503(4) Å	β = 100.846(2)°
	c = 11.6500(6) Å	γ = 90°
Volume	1952.58(16) $Å^3$	
Z	4	
Density (calculated)	1.213 g/cm^3	
Absorption coefficient	0.578 mm^{-1}	
F(000)	760	

ANTIMICROBIAL ACTIVITY

Antibacterial Activity

The synthesized *t*-(3)-benzyl-*r*-(2), *c*-(6) - diphenyll piperidin-4-one-oxime (1) compound was tested for their antibacterial activity in vitro against Streptococcus faecalis, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumoniae*. Ciprofloxacin was used as standard drug whose minimum inhibitory concentration values are furnished in Table 4.The antibacterial screening put in evidence that the synthesized *t*-(3)-benzyl-*r*-(2),*c*-(6)-diphenylpiperidin-4-one(1) exhibited a wide spectrum of antibacterial profile in vitro against the tested organisms. *t*(3)-benzyl-*r*(2),*c*(6)-diphenyllpiperidin-4-one-oxime (1) exhibited good antibacterial activity against all the tested strains.The Measured zone of inhibition (in mm) against the growth of bacterial for the compound 1 is shown in Figure.4.

Table 4. *In VITRO* Antibacterial Activity of (1)

Compound	Streptococcus faecalis	Bacillus subtilis	Escherichia coli	Klebsiella pneumoniae
(1)	25	50	25	25
Ciprofloxacin	50	25	50	50

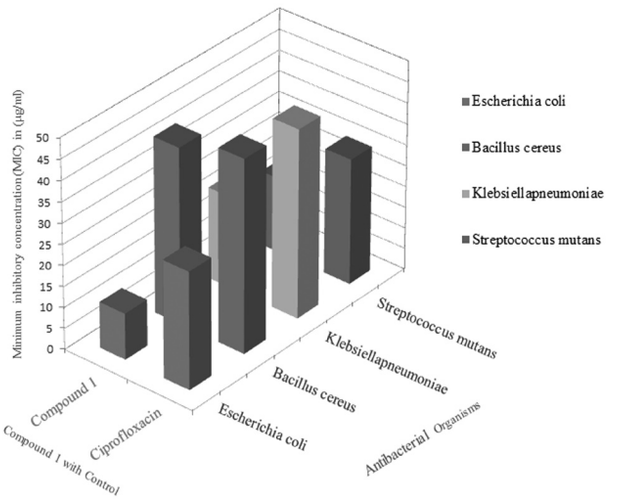


Fig. 14.4: Measured Zone of Inhibition (In Mm) Against the Growth of Bacterial for the Compound 1

Antifungal Activity

The in vitro antifungal activity of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one-oxime (**1**) was examined against the fungal strains viz., Aspergillus niger, Candida 6, Candida 51 and Aspergillus flavus. Amphotericin B was used as standard drug whose minimum inhibitory concentration values are furnished in Table 5. The Measured zone of inhibition (in mm) against the growth of fungal for the compound 1 is shown in Figure 5.

Table 5. *In VITRO* Antifungal Activity of (1)

Compound	Aspergillus niger	Candida 6	Candida 51	Aspergillus flavus
(1)	25	25	50	50
Amphotericin B	25	25	25	50

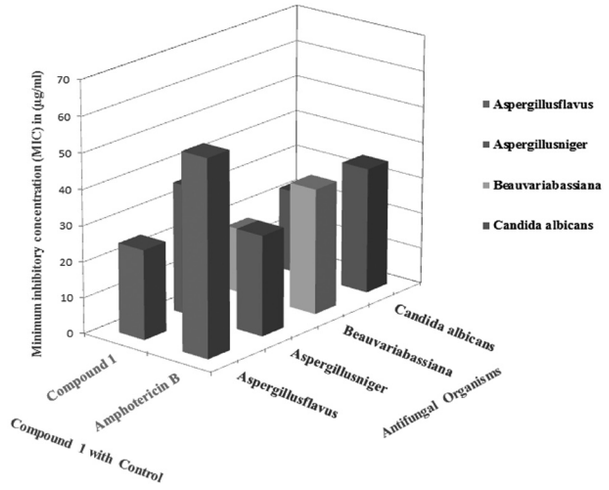


Fig: 5 Measured Zone of Inhibition (In Mm) Against the Growth of Fungal for the Compound 1

CONCLUSION

Spectral studies and single crystal studies also reveals the presence of the *t*(3)-benzyl-*r(*2),*c(*6)-diphenylpiperidin-4-one-oxime (**1**). From the coupling constants and the ^{1}H and ^{13}C chemical shift data of Compound (**1**) exist in normal chair conformation with equatorial orientation of all substituents. A minute examination of in vitro antibacterial and antifungal spectra of *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one-oxime (**1**) against the tested bacterial and fungal strains provide a better structure activity which is *t*(3)-benzyl-*r*(2),*c*(6)-diphenylpiperidin-4-one-oxime (**1**) influence the antimicrobial properties. Thus in future this compound may be used as templates to generate better drug to fight against bacterial and fungal infections.

Acknowledgment

We are grateful to the Chairman Mr R. Sattanathan and Treasurer Mr T. Ramalingam of Thiruvalluvar Arts and Science College for giving permission to carry out research work in the Chemistry laboratory.

REFERENCES

1. S.Watson, B.Jiang, B. Scott, Org. Lett. 2000, 2, 3679–3681.
2. Venketeshperumal, R., Adiraj, M. & Shanmugapandian, P. (2001). Indian Drugs, 38, 167–169.
3. Perumal, R. V., Adiraj, M. & Shanmugapandiyan, P. (2001). Indian Drugs, 38, 156–159.
4. Dimmock, J. R., Padmanilayam, M. P., Puthucode, R. N., Nazarali, A. J.
5. Jayabharathi, J., Manimekalai, A., Consalata Vani, T. &Padmavathy, M.(2007). Eur. J. Med. Chem. 42, 593–605.
6. R.Arulraj, S.Sivakumar, A.Thiruvalluvar, A.Manimekalai, IUCrData, 2016, 1, x160188.
7. Arulraj, S.Sivakumar, A.Thiruvalluvar, A.Manimekalai, *Chem Sci Rev Lett* 2016, 5(18), 99-105.