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Original article

Synthesis, stereochemistry and antimicrobial evaluation of *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-one and its derivatives

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Abstract

In a wide research program toward new and efficient antimicrobial agents, a series of *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-ones (**1**–**7**) were synthesised and tested for their *in vitro* antibacterial and antifungal activities. Also, the structures and their stereochemistry of these synthesised compounds **1**–**7** were characterized by IR, high resolution ^{1}H NMR, ^{13}C NMR and ^{1}H–^{13}C COSY spectra. The analysis of coupling constants of compounds **1**–**5** reveals that they exist in normal chair conformation with equatorial orientations of all the substituents. The spectra of **6** and **7** reveal the presence of two isomers labeled as *E* (carbonyl carbon is *anti* to benzyl group at C-3) and *Z* (carbonyl carbon is *syn* to benzyl group at C-3) in solution and the coupling constants ruled out the possibility of normal chair conformation. From the theoretical studies and coupling constant values the favoured conformation for the *Z*- and *E*-isomers of **6** and **7** was found to be the boat conformations. Their antibacterial activity against *Streptococcus faecalis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and antifungal activity against *Cryptococcus neoformans,* Candida 6, Candida 51, *Aspergillus niger* and *Aspergillus flavus* were also evaluated.

Keywords: Piperidin-4-ones; Theoretical calculation studies; Argus lab; Oximation; Formylation; Stereochemistry; Antibacterial activity; Antifungal activity

1. Introduction

Piperidine heterocycles play an important role in the field of medicinal chemistry. Several 2,6-disubstituted derivatives of this class have been found to possess useful biological activities such as herbicidal, insecticidal, fungicidal, bactericidal, anti-inflammatory, antihistaminic, hypotensive, anticancer, CNS stimulant and depressant and nerve activities. [1–8]. The benzimidazole nucleus is widely accepted for its antiallergic and antiasthmatic activity [9,10] and its derivatives have attracted much attention due to their diverse biological activities such as antiameobic, microfilaricidal, antifungal and antiarylthemic activities. [11–17]. The alkaloid secodihydrocastorazine isolated from the roots of *N. japonicum* has a furan substituent in the 2-position [18]. These observations prompted us to synthesise a system which combines with both biolabile piperidine and furan components together to give a compact structure and to evaluate the *in vitro* antibacterial and antifungal activities. Several substituted analogous have also been synthesised to study structure–activity relationship.

2. Results and discussion

2.1. Synthesis

The general schematic representation describing the routes of synthesis is furnished in Scheme 1. The 3-benzyl-2,6-diarylpiperidine-4-ones **1** and **4** were obtained by the condensation of furfuraldehyde/benzaldehyde, benzyl ketone and ammonium acetate in the ratio of 2:1:1. The piperidinium picrate (**3**) was prepared by mixing equimolar solution of 3-benzylpiperidone (**1**) in ethanol with picric acid in ethanol and stirring the solution for 30 min. The 3-benzyl-2,6-diarylpiperidin-4-one

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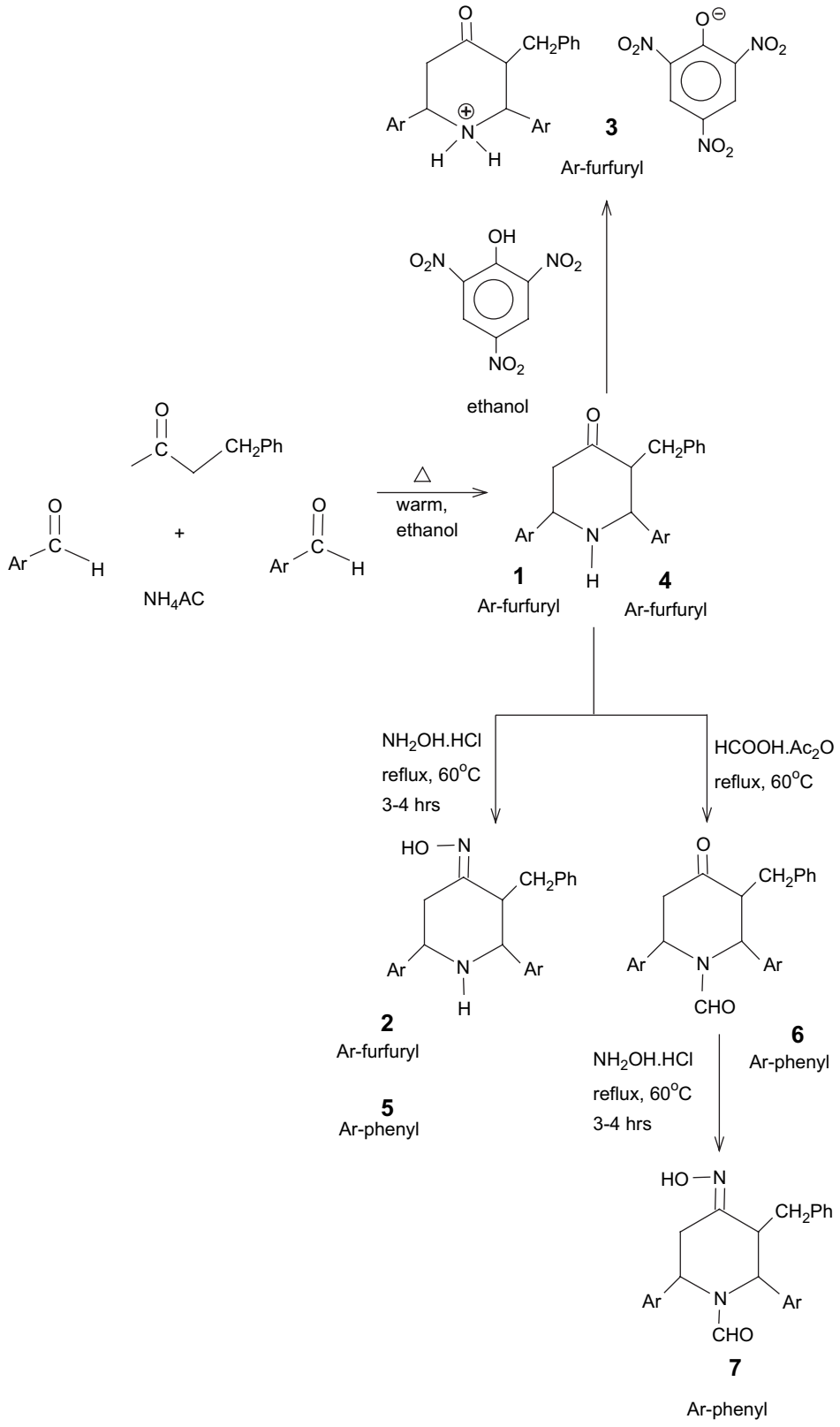


Scheme 1.

oximes **2** and **5** were synthesised by the treatment of 3-benzylpiperidin-4-ones **1** and **4** with hydroxylamine hydrochloride and sodium acetate in 1:1 ratio. *N*-Formyl-*t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one **6** was prepared by the slow addition of cold mixture of formic acid and acetic anhydride to 3-benzylpiperidone **4**. Oximation of **6** was carried out by adding hydroxylamine hydrochloride. The reaction yield, physical constants and elemental analysis of compounds **1**–**7** are

furnished in Table 1. The structures of all the synthesised 3-benzylpiperidones **1** and **4** and their derivatives **2**, **3** and **5**–**7** are established on the basis of ^{1}H NMR, ^{13}C NMR, ^{1}H–^{13}C COSY spectra and IR spectroscopy. The ^{1}H–^{13}C COSY spectrum for compound **7** is shown in Fig. 1.

2.2. Stereochemistry

2.2.1. ^{1}H NMR

The signals in the ^{1}H NMR spectra were assigned based on their positions, multiplicities and integrals. In all these compounds the aromatic protons (furan/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 **1**–**7** are displayed in Table 2. From the chemical shifts, the coupling constants were extracted.

2.2.1.1. 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**–**5** reveals equatorial orientation of benzyl groups at C-3 and aryl rings at C-2 and C-6. Hence, the compounds **1**–**5** exist in normal chair conformation with equatorial orientations of all the substituents. The coupling constants about C(2)–C(3) bond in **1**–**5** are 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 compounds **1**–**5**.

For *N*-formylpiperidin-4-one **6** and its oxime **7**, normal chair conformations with equatorial orientations of phenyl groups at C-2 and C-6 and benzyl group at C-3 are not favoured, since in the normal chair conformation severe $A^{1,3}$ strain exists between *N*-formyl group and equatorial phenyl groups at C-2 and C-6. Moreover, observation of one large and one small coupling about C(5)–C(6) bond in one of the isomers (7.19 and 3.62 Hz) and the large total width (12.40 Hz) for H(6) signal in the other isomer and the singlet for H(2) in both the isomers (approximately coupling is less than 1 Hz) of **7** ruled out the possibility of existing in normal chair conformation with equatorial orientations of all the substituents. In order to relieve the $A^{1,3}$ strain the compound may exist either in the alternate chair form (flipped chair) or boat form. Several examples in literature reveal that forms without allylic strain are favoured. The possible conformations for the two rotameric forms (*Z* and *E*) of *N*-formyl-3-benzylpiperidin-4-one **6** and its oxime **7** (Fig. 2) are shown in Schemes 2 and 3, respectively.

For the *Z*-isomer allylic strain exists in the conformations **CE**, $\mathbf{B_3}$ and $\mathbf{B_6}$ and hence these conformations are ruled out in the present study. In alternate chair conformation **CA** 1,3-diaxial interaction exists between phenyl groups at C-2 and C-6 and between benzyl group and axial methylene proton at C-5 and hence this form is also not stabilized and hence ruled out in the present study. Moreover in the alternate chair form **7 CA** where $A^{1,3}$ strain is completely relieved the large total width observed for H(6) signal (12.40, 10.81 Hz) cannot be accounted and hence ruled out. Therefore the compound **7** may exist in any one of the boat conformations $\mathbf{B_1}$, $\mathbf{B_2}$, $\mathbf{B_4}$ and $\mathbf{B_5}$ in which $A^{1,3}$ strain is completely relieved.

The boat conformation $\mathbf{B_2}$ is not favoured since in this conformation the total width of the H(6) signal is expected to be around 6–7 Hz and large coupling is expected about C(2)–C(3) bond. However, the observation of large total width of H(6) signal (12.04 Hz) and singlet for H(2) (coupling $\approx$1 Hz) ruled out the possibility of **7** existing in boat conformation $\mathbf{B_2}$. Molecular mechanics calculations of several *N*-formyl-3-alkyl-2,6-diphenylpiperidin-4-ones [19] have shown that the boat conformation $\mathbf{B_4}$ in which the alkyl group at C-3 is in flagpole position is having higher energy when compared to the boat conformations $\mathbf{B_1}$ and $\mathbf{B_5}$ and hence the boat conformation $\mathbf{B_4}$ can also be excluded. Therefore, the compound **7** may exist either in the boat conformation $\mathbf{B_1}$ or $\mathbf{B_5}$ or as an equilibrium mixture of $\mathbf{B_1}$ and $\mathbf{B_5}$.

For *E* isomer allylic strain exists in the conformations **CE**, $\mathbf{B_4}$ and $\mathbf{B_6}$ and hence these conformations are ruled out in the present study. The alternate chair form **11CA** is also ruled out based on the large total width observed for H(6) signal. The observation of singlet for H(2) ($J_{2,3}$ is very small $\approx$1 Hz) ruled out the possibility of existing in boat conformations $\mathbf{B_2}$

Table 1
Physical and analytical data

Compound	M.P (°C)	Yield (%)	M.F.	Elemental analysis		
				C	H	N
1	190	70	$C_{20}H_{19}NO_3$	73.23 (74.75)	5.80 (5.96)	5.00 (4.36)
2	198	65	$C_{20}H_{20}N_2O_3$	71.12 (71.41)	5.82 (5.99)	8.20 (8.33)
3	>200	80	$C_{26}H_{22}N_4O_{10}$	55.65 (56.73)	3.98 (4.03)	9.99 (10.18)
4	96	70	$C_{23}H_{29}NO$	85.28 (85.88)	6.86 (6.97)	3.20 (3.34)
5	180	80	$C_{24}H_{24}N_2O$	79.99 (80.87)	6.29 (6.79)	7.18 (7.86)
6	88	68	$C_{25}H_{23}NO_2$	81.00 (81.27)	6.10 (6.27)	3.13 (3.79)
7	65	70	$C_{25}H_{24}N_2O_2$	77.86 (78.10)	6.08 (6.29)	7.40 (7.29)

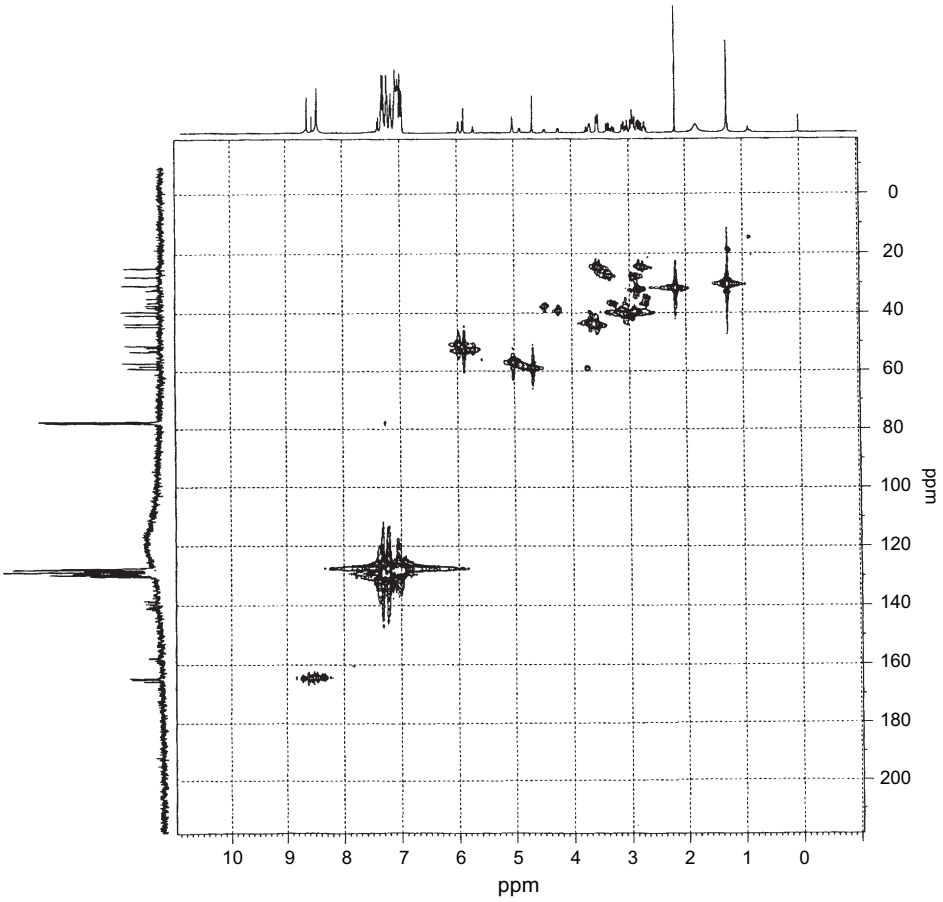


Fig. 1. $^{1}H-^{13}C$ COSY spectrum of **7**.

and $\mathbf{B_3}$. Therefore the compound **7***E* exists either in boat conformation $\mathbf{B_1}$ or $\mathbf{B_5}$, similar to the *Z* form of **7**.

Molecular geometrics were calculated by Universal Force Field (UFF) method [20–22] (Argus Lab Version 4.01) and optimization of the conformers shown in Schemes 2 and 3 was carried out. The relative steric energies of the conformers corresponding to the calculated energy minima are displayed in Table 3. The chair form **CE** has higher energy which reveals the importance of $A^{1,3}$ strain in destabilizing the **CE** conformers. The relative energies of various conformers indicate that both *Z* and *E* rotamers of **6** and **7** prefer distorted boat conformation $\mathbf{B_1}$ only. Thus the geometrics predicted from spectral data are in agreement with those calculated using UFF method in **6** and **7**.

2.2.1.2. Conformation of benzyl group. There are three possible conformations **A**, **B** and **C** for the benzyl group at C(3) in compounds **1**–**5** as shown in Fig. 3. 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 $J_{H(3),CH_2}$ are expected to be around 3–4 Hz. However, in conformations **A** and **C** one coupling *i.e.*, $J_{H(3),CH_2}$ is expected to be around 10–12 Hz and the other coupling is expected to be around 3–4 Hz. In 3-benzylpiperidone (**1**) the couplings are 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) with the furfuryl ring at C(2) 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. 4. 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)–CH_2 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

Table 2
^{1}H NMR chemical shifts for compounds **1**–**7**

Compound		H(2)	H(3)	H(5)	H(6)	$C_6H_5CH_2$	NH	Others	Aromatic
1		3.96	3.16	2.83 (ax), 2.72 (eq)	4.16	3.06, 2.48	2.31	–	7.39–7.40, 7.01–7.21, 6.23–6.51
2		3.91	3.04–3.14	2.20 (ax), 3.69 (eq)	4.00	2.52, 3.04–3.14	1.90	–	7.32–7.40, 7.08–7.26, 6.20–6.36
3		4.24	3.56	3.29 (ax), 2.83 (eq)	4.43	3.73, 3.56	–	9.03 (Picryl ring protons)	7.01–7.37, 6.29–6.43
4		3.77	3.04	2.72 (ax), 2.60 (eq)	4.08	3.04, 2.30	2.10	–	6.94–6.96, 7.07–7.14, 7.24–7.50
5		3.74	2.89	1.99 (ax), 3.62 (eq)	3.92	3.07, 2.39	–	–	7.47–7.45, 7.34–7.25, 7.14–6.99
6	*E*	4.83	3.05	3.05, 2.88	5.95	2.88, 3.47	–	8.38 (H–C=O)	7.29–7.23, 7.17–7.12, 7.50
	Z	5.90	3.05	3.05, 2.88	5.10	2.88, 3.47		8.52 (H–C=O)	
7	*E*	4.66	3.63–3.67	3.36, 2.90–2.97	5.97	4.22 3.03–3.11	–	8.61 (H–C=O)	7.15–7.12
	Z	5.86	3.50–3.57	2.77–2.82, 3.50–3.57	5.01	2.90–2.97 3.03–3.11		7.64 (N–OH)	7.07–6.95

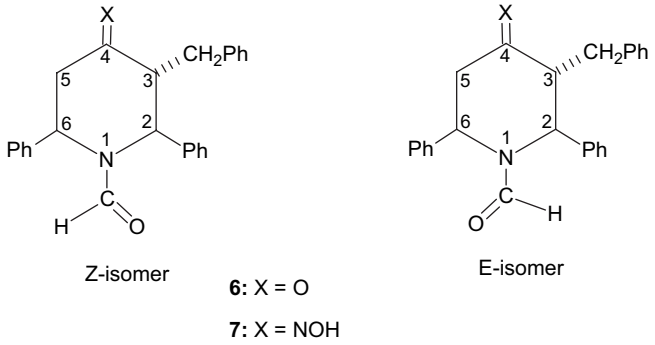


Fig. 2.

is not favoured in compounds **1**–**5**. Thus, the favoured conformation of phenyl ring of benzyl group is established as in conformation **B′**.

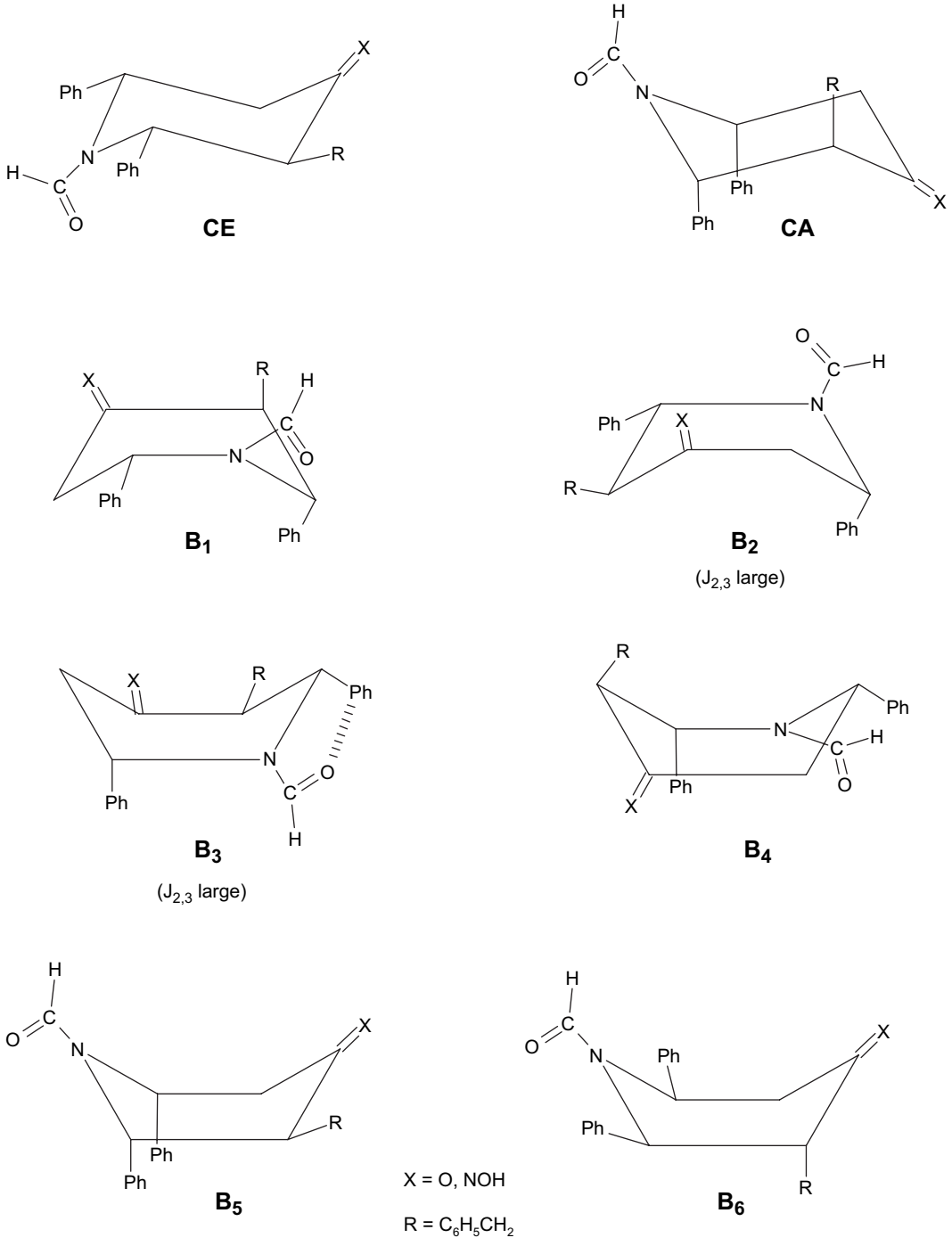
2.2.1.3. Analysis of chemical shifts. In order to study the effect of oximation on ^{1}H chemical shift, the chemical shifts of 3-benzylpiperidone oximes **2** and **5** have been compared with those of the corresponding 3-benzylpiperidones **1** and **4**. Conversion of piperidone to oxime shields all the protons except H_{5e}. The deshielding magnitude observed on H_{5e} can be explained as follows.

In 3-benzylpiperidone oximes **2** and **5** 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.

Comparison of chemical shifts of 3-benzyl piperidinium picrate **3** with those of 3-benzylpiperidone **1** reveals that all the heterocyclic ring protons and benzylic protons at C-3 are deshielded due to conversion of piperidone into its picrate. The deshielding magnitude observed on H(2) and H(6) is considerably greater than those observed on other protons. It is explained as follows.

In the benzyl piperidinium picrate **3** the two protons at nitrogen occupy axial and equatorial orientations. The magnetic anisotropic effect of the axial N–H bond is responsible for the deshielding magnitude observed on H(6) and H(2).

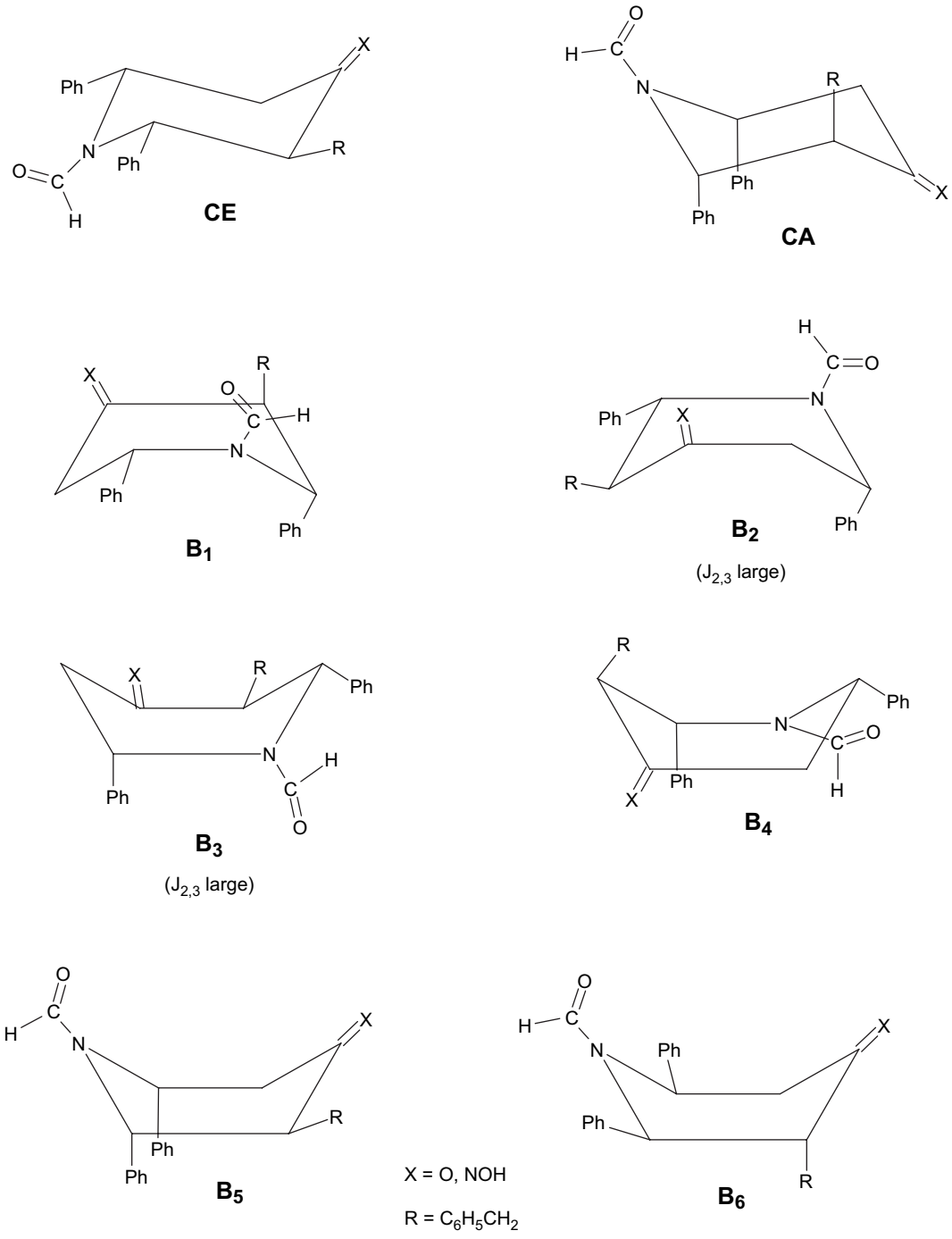
It is also evident from Table 2 that protonation deshields the axial protons at C(3) *i.e.*, H(3) and C(5) *i.e.*, H_{5a} to a greater extent than equatorial methylene proton (H_{5e}). The proton at C(3) *i.e.*, H(3) is deshielded by 0.40 ppm and axial proton at C(5) *i.e.*, H_{5a} is deshielded by 0.46 ppm due to N-protonation. The equatorial methylene proton *i.e.*, H_{5e} is deshielded only by 0.13 ppm. It is because the axial N–H bond experiences severe *syn* 1,3-diaxial interaction with axial hydrogens at C(3) *i.e.*, H(3) and C(5) *i.e.*, H_{5a} (Fig. 5) and due to these



Scheme 2. Possible conformations for *Z*-isomer of **6** and **7**.

interactions the axial protons are deshielded and corresponding carbons are shielded.

*2.2.1.4. Boat conformation for compounds **6** and **7**.* The benzylic protons H(2) and H(6) resonate considerably at downfield in *N*-formyl-3-benzylpiperidin-4-one **6** compared to 3-benzylpiperidin-4-one **4**. The deshielding magnitude has been found to be 1.06 and 2.13 ppm for H(2) and 1.87 and 1.02 ppm for H(6). Similar deshielding magnitude has also been observed in **7** due to N-formylation. In piperidine derivatives existing in normal chair conformation the deshielding magnitude due to the replacement of N–H by *N*-acyl group is expected to be greater for equatorial protons compared to axial protons, since equatorial protons lie in the same plane of –N–C═O moiety. The higher magnitude of deshielding observed on H(2) and H(6) in *N*-formyl-3-benzylpiperidin-4-one **6** and its oxime **7** suggests that these protons should lie in the same plane of –N–C═O moiety. Therefore, this observation ruled out the possibility of existing in normal chair conformation where the benzylic protons are in axial



Scheme 3. Possible conformations for *E*-isomer of **6** and **7**.

orientation and moreover severe pseudoallylic $A^{1,3}$ strain exists between *N*-formyl group and equatorial phenyl groups at C-2 and C-6. Therefore, the observed deshielding magnitude of H(2) and H(6) in **6** and **7** also supports the boat conformation in which H(2) and H(6) lie in the same plane of N–C═O moiety.

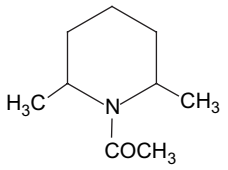
Comparison of chemical shifts of H(3) in **4** and **6** reveals that there is no appreciable change in the chemical shifts due to N-formylation. Similar comparison of chemical shifts of methylene protons at C-5 reveals that one of the methylene protons at C-5 is deshielded to a considerable extent (0.3–0.4 ppm) due to N-formylation. The methylene protons of the benzyl group are also deshielded due to N-formylation. Comparison of chemical shifts of **5** with that of **7** reveals that H(3) and H_{5a} are deshielded due to N-formylation and the observed deshielding also supports the boat conformation of **6** and **7**. This is based on the following observations.

Comparison of chemical shifts of H(3) in *N*-acetylpiperidine [23] (1.52 ppm) and piperidine (1.46 ppm) reveals that N-acetylation causes no significant change in the chemical

Table 3
Relative steric energies (kcal/mol) of the conformers calculated by the UFF method

Compound		CE	CA	B_1	B_2	B_3	B_4	B_5	B_6
6	*E*	5.32	3.83	0	6.50	6.80	3.64	5.11	2.47
	Z	4.86	1.73	0	6.14	7.50	2.24	3.76	3.97
7	*E*	12.78	6.05	0	10.80	5.15	3.38	8.40	2.48
	Z	13.87	3.78	0	10.28	4.36	1.35	7.64	4.06

shifts of β-protons in the normal chair conformation. However, in *N*-acetyl-*cis*-2,6-dimethylpiperidine (**8**) which exists in alternate chair form considerable deshielding (+0.36 ppm) has been noted on the β-hydrogens due to N-acetylation. This deshielding is not probably due to N-acetylation but may be due to the axial conformation of the methyl group which is expected to deshield the nearby axial proton. Thus, the observed deshielding of H(5) in **6** and H(3) and H(5) in **7** due to the replacement of −NH by −N−CHO group is probably due to change in the conformation *i.e*., boat conformation only.



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2.2.2. Analysis of ^{13}C NMR

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. For example, the assignment of the signals in *t*(3)-benzyl-r(2),*c*(6)-di-2′-furylpiperidin-4-one (**1**) was made as follows.

In **1** the signals for the heterocyclic carbons and benzylic carbon appeared at 59.42, 54.22, 206.74, 47.13, 57.23 and 30.85 ppm. The most downfield signal at 206.74 ppm is obviously due to carbonyl carbon *i.e*, C(4). The upfield signal at 30.85 ppm is due to methylene carbon of benzyl group at C(3). Among the remaining signals the downfield signal at 59.42 ppm is assigned to C(2) carbon based on the known deshielding β-effect of the benzyl group. The other downfield signal at 57.23 ppm is obviously due to C(6). Among the remaining signals at 54.22 and 47.13 ppm, the one at downfield (54.22 ppm) is assigned to C(3) based on known α-effect of the benzyl group at C(3). Obviously the remaining signal at 47.13 ppm is due to C(5).

In similar manner the assignments were made for compounds **2**–**5**. The ^{13}C chemical shifts are displayed in Table 4.

In *N*-formylpiperidin-4-one **6** the α-carbon which is *syn* to the carbonyl group is expected to resonate at upfield when compared to *anti* α-carbon. In the parent compound **4** the chemical shift of C-2 is greater than that of C-6. Therefore in the *E*-isomer of *N*-formyl-3-benzylpiperidin-4-one **6** C-6 carbon is expected to appear at upfield when compared to C-2 carbon. In **6** among the benzylic carbon signals at 59.16, 57.06, 52.73 and 51.64 ppm the most downfield signal at 59.16 ppm and upfield signal at 51.64 ppm are obviously due to C-2 and C-6 carbons of the *E*-isomer. The remaining signals at 57.06 and 52.73 ppm are due to C-2 and C-6 carbons of the *Z*-isomer, respectively. The signals in the region around 52 and 42 ppm in the ring are due to C-3 and C-5 carbons, respectively. The signal for one isomer can be easily differentiated from the other isomer based on intensities.

In ^{13}C NMR spectrum of *N*-formyl-3-benzyl-2,6-diphenylpiperidin-4-one oxime (**7**) 19 peaks for the heterocyclic ring carbons and methylene carbon of the benzyl group at C-3 and three signals for formyl and four signals for C(4) carbons are observed. This confirms the presence of four isomers in solution. In order to assign the signals for the *Z*- and *E*-isomers of **7** (Fig. 2) the substituent-induced chemical shifts for the oxime group were added to the chemical shifts of heterocyclic ring carbons in **6**.

For C-2 carbon oximation parameter for C(2) (0.9 ppm) was added to the C-2 chemical shift in the *Z*-isomer of *N*-formyl-3-benzylpiperidin-4-one **6** (52.73 ppm). Thus, the value is calculated to be 53.66 ppm. For C-3 carbon the substituent parameter −10 ppm was added to the C-3 chemical shift in **6** (52.73 ppm) and it is found to be 42.73 ppm. Similarly for C-6, C-5 and C-4 carbons the oximation effects (−0.4, −17,

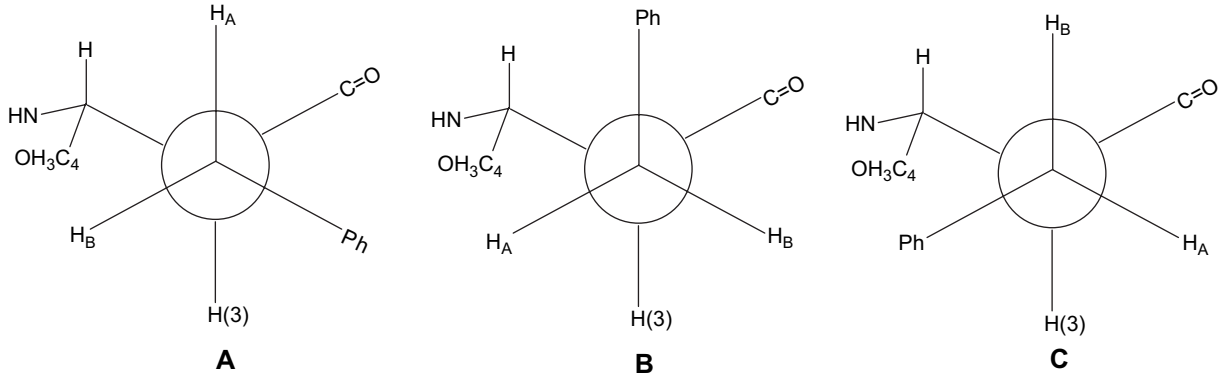

Fig. 3.

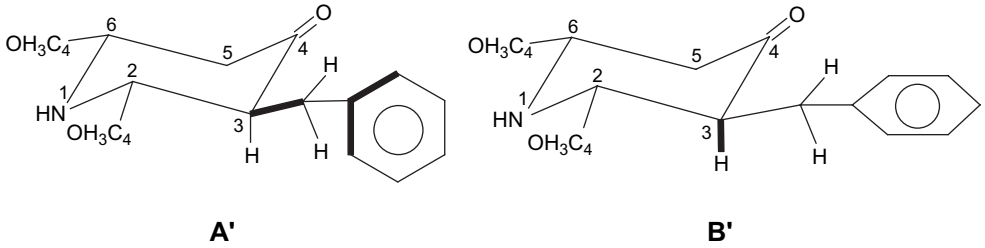

Fig. 4.

−49.9 ppm) were added, respectively, to the chemical shifts of C-6 (57.00 ppm), C-5 (43.77 ppm) and C-4 (208.16 ppm) carbons in **6**. The values are calculated to be 56.66 (C-6), 26.77 (C-5) and 158.26 ppm (C-4).

Similarly for the *E*-isomer of **7** the chemical shifts were calculated and compared with the observed values. The calculated values are closer to the high intense signals observed in the ^{13}C spectrum (Table 5). The calculated values are in agreement with those of high intense signals for C(3), C(4) and C(5) carbons. For the α-carbons C(2) and C(6) the calculated values are slightly higher than observed values. It has been previously reported that the substituent parameters are greatly modified due to *gauche* interaction and the value decreases as the number of *gauche* interaction increases [24].

The *gauche* interaction between the formyl group and phenyl group probably decreases the substituent effect of the phenyl group on α-carbons *i.e.*, C(2) and C(6). The higher calculated values for C(2) in the *E*-isomer (60.06 ppm) and C(6) in the *Z*-isomer (53.13 ppm) are closer to the high intense signals observed in the ^{13}C NMR spectrum. Obviously, the other two high intense signals at 56.47 and 50.49 ppm are due to C(2) and C(6) carbons in the *Z*- and *E*-isomer, respectively. Therefore, the major intense signals correspond to the *Z*- and *E*-isomers of *N*-formyl-*t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one oxime (**7**). The less intense signals in ^{13}C NMR spectrum may be due to the epimerised forms *i.e.*, *N*-formyl-*c*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one oxime (**7′**).

2.2.2.1. Analysis of ^{13}C chemical shifts. It is seen from Table 5 that the conversion of *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-ones (**1** and **4**) into its corresponding oximes **2** and **5** shields all heterocyclic ring carbons except C-2 and methylene carbon of benzyl group at C-3 where slight deshielding has been observed. This can be explained as follows.

It is well established that increase in the electronegativity of a group in the ring skeleton deshields α-carbon but shields

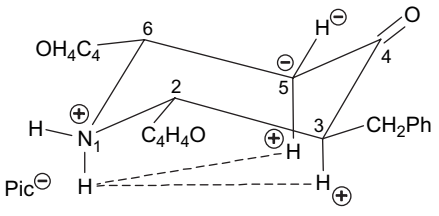

Fig. 5.

β and γ carbons [25]. The electronegativity of oxime group should be less than that of >C=O group since >C=N bond is less polar than >C=O bond. Based on the electronegativity effect one can expect shielding of α-carbons (C-3 and C-5) and deshielding of β-carbons (C-2 and C-6) due to oxime formation. The observed downfield resonance of *anti* β-carbon (C-2) in **2** and **5** relative to the 3-benzylpiperidones **1** and **4** is in accordance with this expectation.

The magnitude of shielding observed on C(5) *i.e.*, *syn* α-carbon (17.21 ppm) due to oxime formation is greater than that observed on C-3 *i.e.*, *anti* α-carbon (9.19 ppm). Severe interaction exists between the N−O bond and the *syn* α-(C−H) equatorial bond and due to this interaction α-(C−H) bond is said to be polarised. As a result of polarisation *syn* α-equatorial hydrogen acquires a slight positive charge and *syn* α-carbon acquires a slight negative charge. Due to this *syn* α-carbon (C-5) is shielded to a greater extent than *anti* α-carbon (C-3). The negative charge on the *syn* α-carbon (C-5) is transmitted to C-6 *i.e.*, *syn* β-carbon to small extent. Based on polarisation one can expect shielding on C-6 but deshielding is expected due to lower electronegativity of oxime group on the same carbon. The shielding due to polarisation is more than that due to electronegativity factor. This is the reason for the shielding observed on C-6 carbon due to oxime formation.

Comparison of chemical shifts of **4** with those of the corresponding *N*-formylpiperidin-4-one **6** (Table 6) reveals that there is a drastic change in the chemical shifts of benzylic (C-2 and C-6), methylene (C-5) and methine carbons (C-3) due to the replacement of −NH by −N−CHO group. All the carbons are shielded due to this conversion. There is no appreciable change in the chemical shifts of C-4 carbon due to N-formylation. However, methylene carbon of benzyl group at C-3 is deshielded due to N-formylation. Similar comparison of chemical shifts of **5** and **7** also reveals that all the carbons are shielded except the methylene carbon of the benzyl group at C-3 where considerable deshielding has been observed on this carbon due to N-formylation. The observed shielding magnitude of the heterocyclic ring carbons also supports the boat conformation for **6** and **7** of *E*- and *Z*-isomers of **6**.

3. Structural activity

3.1. Antibacterial activity

The synthesised compounds **1**–**7** were tested for their antibacterial activity *in vitro* against *Streptococcus faecalis*,

Table 4
^{13}C NMR chemical shifts for compounds **1**–**7**

Compound		C(2)	C(3)	C(4)	C(5)	C(6)	$C_6H_5CH_2$	Others	Aromatic
1		59.42	54.22	206.74	47.13	57.23	30.85	–	154.24, 153.32, 142.30, 142.10, 140.38, 129.16, 128.06, 125.75–105.79 (phenyl carbons)
2		60.05	47.85	157.49	32.13	53.39	29.71	–	157.49, 154.91, 153.73, 142.17, 141.94, 140.66, 128.97–125.62
3		57.10	51.71	201.36	41.95	52.91	30.72	–	156.77, 146.71, 145.96, 144.26, 133.97, 137.71, 134.25, 129.35–111.02
4		67.48	59.62	208.11	51.49	61.95	30.38	–	142.61, 141.46, 141.07, 129.02, 128.66, 128.18, 128.00, 127.85, 126.51, 125.59
5		68.46	50.43	159.22	34.28	61.04	31.36	–	143.67, 142.29, 141.46, 128.93, 128.55, 128.35, 128.05, 127.83, 127.62, 126.70, 125.37
6	*E*	59.16	208.16	208.16	41.92	51.64	34.99	163.87 [O; H–C–]	139.88, 137.17, 128.65, 127.97, 127.33, 126.88, 126.73
	Z	52.73	208.16	208.16	43.77	57.06	36.77	163.86 [O; H–C–]	
7	*E*	58.43	42.80	157.01	24.20	50.49	38.72	163.94 [O; H–C–]	140.48, 140.21, 139.85, 138.87, 138.27, 137.79, 129.52, 128.98, 128.65
	Z	52.48	43.75	156.86	27.08	56.47	39.97	164.37 [O; H–C–]	128.12, 127.98, 127.22, 127.08, 126.98, 126.90

Bacillus subtilis, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Streptomycin was used as standard drug whose minimum inhibitory concentration values are furnished in Table 7.

The antibacterial screening put in evidence that all the synthesised novel *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-ones (**1**–**7**) exhibited a wide spectrum of antibacterial profile *in vitro* against the tested organisms except **4** against *P. aeruginosa*. Compounds **1**–**3** and **5**–**7** exhibited antibacterial activity *in vitro* at 6.25–60 μg/ml against all the tested strains, *t*(3)-benzyl-r(2),*c*(6)-di-2′-furylpiperidin-4-one (**1**) and its derivatives **2** and **3** exhibited good antibacterial activity against all the tested strains. Compound **3** exhibited remarkable antibacterial activity against all the tested organisms.

3.2. Antifungal activity

The *in vitro* antifungal activity of *t*(3)-benzyl-r(2),*c*(6)-diaryl-piperidin-4-ones (**1**–**7**) 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 8.

The antifungal spectrum of 3-benzylpiperidones **1** and **4** and their derivatives **2**, **3** and **5**–**7** falls in the region of 6.25–100 μg/ml except compound **4** against *C. neoformans*. Compounds **1**–**3** and **5**–**7** exhibited moderate antifungal activity at 25–100 μg/ml against all the tested strains. Compounds **1**–**3** exerted improved *in vitro* antifungal activity against all the tested organisms.

4. Conclusion

Several substituted 3-benzylpiperidones and their derivatives were synthesised starting with benzaldehyde/furfuraldehyde for (**4/1**), benzyl ketone and ammonium acetate through the pathway involving Mannich reaction followed by oximation and formylation. The nuclear magnetic resonance studies clearly furnish the conformations that compounds **1**–**5** exist in normal chair conformation with equatorial orientation of all substituents. In addition to ^{1}H and ^{13}C NMR, ^{1}H–^{13}C COSY spectra revealed the presence of two isomers namely *E* and *Z* for **6** and **7** which arises due to restricted rotation about N–C bond of the formyl group. Molecular geometrics of **1**–**7** were calculated by Universal Force Field (UFF) method. From the theoretical studies it revealed that **6** and **7** adopted a boat conformation $\mathbf{B_1}$.

A minute examination of *in vitro* antibacterial and antifungal spectra of novel *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-one and its derivatives (**1**–**7**) against the tested bacterial and fungal strains provide a better structure activity which is summarized below *t*(3)-benzyl-r(2),*c*(6)-di-2′-furylpiperin-4-one (**1**) and its derivatives **2** and **3**, influence the antimicrobial properties. Thus in future these compounds may be used as templates to generate better drug to fight against bacterial and fungal infections.

Table 5
Comparison of calculated and observed values of *Z*- and *E*-isomers of **7**

	N-Formyl-3-benzyl-2,6-diphenyl-piperidin-4-one oxime (**7***E*)		*N*-Formyl-3-benzyl-2,6-diphenyl-piperidin-4-one oxime (**7***Z*)	
	Calculated	Observed	Calculated	Observed
C(2)	60.06	58.43	53.63	52.73
C(3)	42.43	42.80	42.73	43.75
C(4)	158.26	157.01	158.26	156.86
C(5)	24.92	24.20	26.77	27.08
C(6)	52.04	50.49	56.66	57.06

5. Experimental

5.1. ^{1}H NMR spectra

Proton spectra were recorded on a Bruker AMX-400 NMR instrument operating at 400 MHz. Samples were prepared by dissolving 10 mg of the substance in 0.5 ml of $CDCl_3$ containing 1% TMS. The spectral parameters used are number of scans, 32; number of data points, 32 K; and spectral sweep width, 4000 Hz.

5.2. ^{13}C NMR spectra

Proton decoupled ^{13}C NMR spectra were recorded on a Bruker AMX-400 NMR instrument operating at 100 MHz. Solutions for the measurement of spectra were prepared by dissolving 0.5 g of the sample in 2.5 ml of $CDCl_3$ containing few drops of TMS as internal reference. The solvent chloroform-*d* also provided the internal field frequency lock signal. The spectral parameters used are number of scans, 5000; number of data points, 32 K; pulse width, 6 μs (45°); and spectral sweep width, 22 000 Hz.

5.3. IR spectra

IR spectra were recorded on a NICOLET AVATAR 360 FT-IR spectrometer. The sample was mixed with KBr and the pellet technique was adopted to record the spectra.

5.4. Two-dimensional spectra

$^{1}H-^{13}C$ COSY spectra were obtained on a DRX-500 NMR spectrometer using standard parameters: the number of scans, 32; number of data points, 2048; acquisition time, 0.17 s and spectral width, 6009 Hz.

5.5. t(3)-Benzyl-r(2),c(6)-diarylpiperidin-4-ones **1** and **4**

These compounds were prepared according to the following procedure. A mixture of ammonium acetate (0.01 mol), redistilled benzaldehyde/furfuraldehyde (0.02 mol) for (**4/1**) and benzylacetone (0.01 mol) in distilled ethanol was heated to boiling. The mixture was cooled and 10 ml hydrochloric acid was added. The precipitated 3-benzyl-2,6-diarylpiperidin-4-one hydrochlorides were treated with aqueous ammonia

Table 6
Comparison of ^{13}C chemical shifts (ppm) of *t*(3)-benzylpiperidones (**4** and **6**) and *t*(3)-benzylpiperidin-4-one oximes (**5** and **7**)

Compound		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl	Others	Aromatic carbons
4		67.48	59.62	208.11	51.49	61.95	30.38	–	142.61; 141.46; 141.07; 129.02; 128.66; 128.18; 128.00; 127.85; 126.51; 125.59
6	*E*	59.16	52.43	208.16	41.92	51.64	34.99	163.87 [O; H–C–]	139.88; 137.17; 128.65; 127.97; 127.33; 126.88; 126.73
	Z	52.73	52.73	208.16	43.77	57.06	36.77	163.87 [O; H–C–]	
5		68.46	50.43	159.22	34.28	61.04	31.36	–	143.67; 142.29; 141.46; 128.93; 128.55; 128.35; 128.05; 127.83; 127.62; 126.70; 125.37
7	*E*	58.43	42.80	157.01	24.20	50.49	38.72	163.94 [O; H–C–]	140.48; 140.21; 139.85; 138.87; 138.27; 137.79; 129.52; 128.98; 128.65; 128.12; 127.98; 127.22; 127.08; 126.98; 126.90
	Z	52.48	43.75	156.86	27.08	56.47	39.97	164.37 [O; H–C–]	

Table 7
In vitro antibacterial activity of compounds **1**–**7**

Compound	Minimum inhibitory concentration (MIC) in μg/ml				
	S. faecalis	*B. subtilis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
1	12.5	50	12.5	25	12.5
2	12.5	25	12.5	12.5	6.25
3	6.25	6.25	12.5	6.25	6.25
4	50	12.5	12.5	–	100
5	25	25	12.5	25	12.5
6	25	25	25	12.5	6.25
7	25	25	25	50	6.25
Streptomycin	50	12.5	12.5	25	25

and diluted with water. The 3-benzylpiperidones **1** and **4** were chromatographed.

5.6. *t*(3)-Benzyl-r(2),*c*(6)-diarylpiperidin-4-one oximes **2** and **5**

About 0.05 mol of *t*(3)-benzyl-r(2),*c*(6)-diarylpiperidin-4-ones **1** and **4** 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 40 °C and stirred for 3–4 h. It was allowed to stand overnight and then poured into crushed ice. The separated solid was filtered off and recrystallized from ethanol.

5.7. *N*-Formyl-*t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one (**6**)

Formic acid 85% (5 ml) was added slowly to cold acetic anhydride (10 ml) and kept at about 5 °C in a 50 ml round bottom flask. After the addition was over, the mixture was heated to 60 °C and then maintained at 50–60 °C for 1 h. The solution was then cooled to 5 °C and added drop wise to a cold solution of *t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one **4** (5 mmol) in dry benzene (50 ml) taken in a 250 ml round bottom flask. The reaction mixture was stirred at 25 °C for 8 h. The solution was poured into water. The benzene layer was separated and the aqueous layer was extracted with 50 ml portions of chloroform. The organic extracts were combined, dried over anhydrous Na_2SO_4, partially evaporated and left for crystallization. The crystals thus separated were recrystallized from ethanol.

Table 8
In vitro antifungal activity of compounds **1**–**7**

Compound	Minimum inhibitory concentration (MIC) in μg/ml against fungi				
	C. neoformans	Candida 6	Candida 51	*A. niger*	*A. flavus*
1	25	25	25	50	50
2	6.25	25	12.5	6.25	25
3	6.25	25	6.25	6.25	12.5
4	–	50	50	100	50
5	25	50	12.5	100	50
6	12.5	25	12.5	50	25
7	6.25	12.5	12.5	25	12.5
Amphotericin B	25	25	25	50	50

5.8. *N*-Formyl-*t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one oxime (**7**)

About 0.01 mol of *N*-formyl-*t*(3)-benzyl-r(2),*c*(6)-diphenylpiperidin-4-one (**7**) and 0.02 mole of sodium acetate trihydrate were dissolved in boiling ethanol and hydroxylamine hydrochloride (0.02 mol) was added. The mixture was heated to 40 °C for 3–4 h. It was allowed to stand overnight and then poured into crushed ice. The separated solid was filtered off and recrystallized from ethanol.

5.8.1. *t*(3)-Benzyl-r(2),*c*(6)-di-2′-furylpiperidin-4-one (**1**)

IR KBr (cm^{-1}): 3322, 3142, 3022, 1708, 1505, 1484, 1149, 1013, 757, 698, 598. Mass: 321 (M^+) *m/e* 316, 303, 287, 238, 222, 208, 194, 183, 165, 148, 132, 1022, 105, 77, 65. ^{1}H NMR: 4.16 ppm H(6) (dd, $J_{6a,5a} = 12.11$ Hz, $J_{6a,5e} = 2.76$ Hz), 3.96 ppm H(2) (d, $J_{2a,3a} = 10.72$ Hz), 2.83 ppm H_{5a}, 2.72 ppm H_{5e} (dd, $J_{5a,5e} = 13.37$ Hz), 3.16 ppm H(3) ($J_{H(3),CH_2} = 2.23$, 8.28 Hz), 3.06, 2.48 ppm CH_2Ph ($J_{CH_2Ph}(J_{gem}) = 13.84$, 13.83 Hz), 2.31 ppm NH (br s) and aromatic protons: 7.39–7.40, 7.01–7.21 and 6.23–6.51 ppm. ^{13}C NMR: 59.24 C(2), 54.22 C(3), 206.74 C(4), 47.13 C(5), 57.23 C(6), 30.85 CH_2Ph. Aromatic carbons: 154.24, 153.32, 142.30, 142.10, 140.38, 129.16, 128.06, 125.75–105.79.

5.8.2. *t*(3)-Benzyl-r(2),*c*(6)-di-2′-furylpiperidin-4-one oxime (**2**)

IR KBr (cm^{-1}): 3317, 3366, 3235, 2916, 1601, 1495, 1453, 1151, 1017, 919, 739, 702, 601. Mass: 336 (M^+) *m/e* 292, 276, 239, 203, 185, 166, 153, 138, 125, 111, 107, 91, 78, 77, 65. ^{1}H NMR: 4.00 ppm H(6) (dd, $J_{6a,5a} = 11.53$ Hz, $J_{6a,5e} = 2.71$ Hz), 3.91 ppm H(2) (d, $J_{2a,3a} = 9.67$ Hz), 3.04–3.14 ppm H(3) (m), 2.20 ppm H_{5a} (br t), 3.69 ppm H_{5e} (dd, $J_{5a,5e} = 13.75$ Hz), 2.52, 3.04–3.14 ppm CH_2Ph ($J_{CH_2Ph}(J_{gem}) = 11.74$ Hz). Aromatic protons: 7.32–7.40, 7.08–7.26 and 6.20–6.36 ppm. ^{13}C NMR: 60.05 C(2), 47.85 C(3), 157.49 C(4), 32.13 C(5), 53.39 C(6), 29.71 CH_2Ph. Aromatic carbons: 157.49, 154.91, 153.73, 142.17, 141.94, 140.66, 128.97–125.62.

5.8.3. *t*(3)-Benzyl-r(2),*c*(6)-di-2′-furylpiperidinium picrate (**3**)

IR KBr (cm^{-1}): 3420, 3082, 2978, 1716, 1627, 1559, 1443, 1156, 913, 749, 707, 600. Mass: 550 (M^+) *m/e* 492, 476, 463, 398, 384, 269, 255, 223, 165, 148, 135, 119, 108, 103, 91, 77, 65. ^{1}H NMR: 4.43 ppm H(6) (dd, $J_{6a,5a} = 12.86$ Hz, $J_{6a,5e} = 3.13$ Hz), 4.24 ppm H(2) (d, $J_{2a,3a} = 11.73$ Hz), 3.56 ppm H(3) ($J_{H(3),CH_2} = 2.67$, 7.62 Hz), 3.29 ppm H_{5a} (br s), 2.85 ppm H_{5e} (dd, $J_{5a,5e} = 14.47$ Hz), 3.73, 3.56 ppm CH_2Ph ($J_{CH_2Ph}(J_{gem}) = 14.17$, 14.21 Hz), 9.03 ppm picryl proton. Aromatic protons: 7.01–7.37, 6.29–6.43 ppm. ^{13}C NMR: 57.10 C(2), 51.77 C(3), 201.36 C(4), 41.95 C(5), 52.91 C(6), 30.72 CH_2Ph. Aromatic carbons: 156.77, 146.71, 145.96, 144.26, 133.97, 137.11, 134.25, 129.35–111.02 ppm.

*5.8.4. t(3)-Benzyl-r(2),c(6)-diphenylpiperidin-4-one (**4**)*

IR KBr (cm^{-1}): 3434, 3037, 2924, 1706, 1495, 1454, 758, 699. Mass: 419 (M^+) *m/e* 418, 402, 355, 344, 339, 324, 280, 266, 222, 208, 194, 179, 177, 162, 135, 132, 117, 107, 105, 91, 77, 65. ^{1}H NMR: 4.08 ppm H(6) (d, $J_{6a,5a} = 10.74$ Hz), 3.77 ppm H(2) (d, $J_{2a,3a} = 9.27$ Hz), 2.72 ppm H_{5a} (t), 2.60 ppm H_{5e} (d, $J_{5a,5e} = 11.72$ Hz), 3.04 and 2.30 ppm CH_2Ph, 3.04 ppm H_{3a}, NH = 2.10 ppm (br s). Aromatic protons: 6.94–6.96, 7.07–7.14 and 7.24–7.50 ppm. ^{13}C NMR: 67.48 C(2), 59.62 C(3), 208.11 C(4), 51.49 C(5), 61.95 C(6), 30.38 CH_2Ph. Aromatic carbons: 142.61, 141.46, 141.07, 129.62, 128.66, 128.18, 128.00, 127.85, 126.51, 125.59.

*5.8.5. t(3)-Benzyl-r(2),c(6)-diphenylpiperidin-4-one oxime (**5**)*

IR KBr (cm^{-1}): 3400, 3847, 3022, 2924, 1656, 1493, 1449, 1241, 930, 755, 700. Mass: 356 (M^+) *m/e* 346, 301, 282, 268, 254, 227, 174, 147, 134, 119, 107, 91, 77, 65. ^{1}H NMR: 3.92 ppm H(6) (d, $J_{6a,5a} = 10.74$ Hz), 3.74 ppm H(2) (d, $J_{2a,3a} = 9.77$ Hz), 3.62 ppm H_{5e} (d, $J_{5a,5e} = 13.67$ Hz), 1.99 ppm H_{5a} (br t), 307, 2.39 ppm CH_2Ph, 2.89 ppm H_{3a}. Aromatic proton: 7.47–7.45, 7.34–7.25 and 7.14–6.99 ppm. ^{13}C NMR: 68.46 C(2), 50.43 C(3), 159.22 C(4), 34.28 C(5), 61.04 C(6), 31.36 CH_2Ph. Aromatic carbons: 143.67, 142.29, 141.46, 128.93, 128.55, 128.35, 128.05, 127.83, 127.62, 126.70, 125.37.

*5.8.6. N-Formyl-t(3)-benzyl-r(2),c(6)-diphenylpiperidin-4-one (**6**)*

IR KBr (cm^{-1}): 3027, 2924, 1718, 1672, 1503, 1454, 754, 710. Mass: 369 (M^+) *m/e* 362, 346, 301, 282, 268, 254, 227, 174, 147, 134, 119, 107, 103, 91, 77, 65. ^{1}H NMR: *E*-isomer (major): 8.38 ppm H–C(=O)– (br s), 5.95 ppm H(6) (s), 4.83 H(2) (s), 3.05, 2.88 ppm H(5) ($J_{5a,5e} = 15.10$ Hz) 3.05 ppm H(3) (br d), 2.88, 3.47 ppm CH_2Ph. Aromatic protons: 7.29–7.23, 7.17–7.12, 7.05 ppm. ^{13}C NMR: 59.16 C(2), 52.43 C(3), 208.16 C(5), 41.92 C(5), 51.64 C(6), 34.99 CH_2Ph, 163.87 H–C(=O)–. Aromatic carbons: 139.88, 137.17, 128.65, 127.97, 127.33, 126.88, 126.73. *Z*-isomer: 5.10 ppm H(6) (s), 5.90 ppm H(2) (s) 3.05, 2.88 ppm H_5 (d, $J_{5a,5e} = 15.10$ Hz), 3.05 ppm H(3) (br d), 2.88, 3.46 ppm CH_2Ph. Aromatic protons: 7.29–7.23, 7.17–7.12 and 7.05 ppm. ^{13}C NMR: 52.73 C(2), 52.73 C(3), 208.16 C(4), 43.77 C(5), 57.06 C(6), 36.77 CH_2Ph, 136.87 H–C(=O)–. Aromatic carbons: 139.88, 137.17, 128.65, 127.97, 127.33, 126.88, 126.73.

*5.8.7. N-Formyl-t(3)-benzyl-r(2),c(6)-diphenylpiperidin-4-one oxime (**7**)*

IR KBr (cm^{-1}): 3268, 3030, 2920, 1655, 1495, 1450, 1244, 938, 749, 698. Mass: 384 (M^+) *m/e* 370, 354, 338, 292, 276, 239, 203, 185, 166, 153, 138, 125, 111, 107, 104, 91, 77, 65. ^{1}H NMR: *E*-isomer (major): 5.97 ppm H(6) (dd, $J_{5,6} = 3.62$, 7.19 Hz), 4.66 ppm H(2) (s), 3.63–3.67 ppm H(3) (m), 3.36, 2.90–2.97 ppm H(5) (m, $J_{5,5} = 16.68$ Hz), 4.22, 3.03–311 CH_2Ph, 8.43 ppm H–C(=O)–(S), 7.52 ppm NO*H* (br s). Aromatic protons: 7.33–7.29, 7.27–7.18, 7.15–7.12 and 7.07–6.95 ppm. ^{13}C NMR: 58.43 C(2), 42.80 C(3), 157.01 C(4), 24.20 C(5), 50.49 C(6), 38.72 CH_2Ph, 163.94, H–C(=O)–, *Z*-isomer (minor): ^{1}H NMR: 5.01 ppm H(6) (t, $J_{5,6} = 6.20$ Hz), 5.86 ppm H(2) (s), 3.50–3.57 H(3) (m), 2.77–2.82, 3.50–3.57 H(5) (m), 2.90–2.97, 3.03–3.11 ppm CH_2Ph, 8.61 ppm H–C(=O)–(S), 7.64 N–OH (br s). Aromatic protons: 140.48, 140.21, 139.85, 138.87, 138.27, 137.79, 129.52, 128.98, 128.65, 128.12, 127.98, 127.22, 127.08, 126.98, 126.90. ^{13}C NMR: 52.48 C(2), 43.75 C(3), 156.88 C(4), 27.08 C(5), 56.47 C(6), 39.97 CH_2Ph 164.37 H–C(=O)–. Aromatic carbons: 140.48, 140.21, 139.85, 138.87, 138.27, 137.79, 129.52, 128.98, 128.65, 128.12, 127.98, 127.22, 127.08, 126.98, 126.90.

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