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Original article

Synthesis, stereochemistry and antimicrobial evaluation of some *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones

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Abstract

In a search for new leads towards potent antimicrobial agents, an array of novel *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones has been synthesized and their in vitro antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi* and antifungal activity against *Candida albicans*, *Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus* were evaluated. Structure and stereochemistry of all the *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones have been analyzed using ^{1}H and ^{13}C NMR spectroscopic techniques. In all the cases, amide N–C=O group is preferentially in coplanar orientation with respect to the dynamically averaged plane of the piperidone ring. Further, all the symmetrically substituted compounds **19**, **23**, **24**, **26** and **27** are expected to adopt half boat conformations while other compounds **20**–**22** and **25** adopt twist-boat conformations. Structure–activity relationship results for these nine compounds have shown that compounds **26** and **27** exerted excellent antibacterial activity against all the bacterial strains used except **27** against *S. aureus*. Against *C. albicans* and *A. flavus*, compound **24** recorded excellent antifungal activities while against *Rhizopus* sp., compound **25** showed potent activities. The obtained results may be used as key step for the building of novel chemical compounds with interesting antimicrobial profiles comparable to that of the standard drugs.

Keywords: Piperidin-4-one; Chloroacetylation; Conformation; Morpholine; Antibacterial activity; Antifungal activity

1. Introduction

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Among the family of heterocyclic compounds, nitrogen containing heterocycles especially piperidin-4-ones presumably gaining considerable importance owing to their varied biological properties such as antiviral, antitumour [1], analgesic [2], local anaesthetic [3,4], antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, CNS stimulant and depressant activities [5–7]. Lijinsky and Taylor [8] reported that blocking of α-positions to that of nitrogen in piperidone by alkyl group had good advantages over unblocked one in improving the biological activity. Furthermore, significance of piperidin-4-ones as intermediates in the synthesis of a variety of physiologically active compounds has been reviewed by Prostakov and Gaivoronskaya [9]. The skeletal ring of piperidine nucleus can also be often found in the molecular framework of many synthetic and natural medicaments [10].

Similarly, amides are well known for their therapeutic values [11]. The chemistry of amides having a chloroacetyl group is also very fascinating and has received significant attention through the years resulting in substantial advances both in the synthetic and medicinal aspects. *N*-Benzyl-β-chloropropionamide is a well-proven anticonvulsant agent [12] and is marketed under the trade name Hibicon and Hydrane. Chloroacetyl derivatives of some amines were found to exert diverse biological properties such as antiepileptic [13], antipasmodic [14], antitumor, anti-MDR [15],

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antimicrobial [16], herbicidal [17], mild stimulant and depressant activities [18].

Furthermore, many *N*-functionalized morpholines have found to possess diverse pharmacological activities. They are reported to exert a number of important physiological activities such as antidiabetic [19,20], antiemetic [21,22], platelet aggregation inhibitors, antihyperlipoproteinemics [19], bronchodilators, growth stimulants [23] and antidepressants [19,23,24]. These were also used in the treatment of inflammatory diseases, pain, migraine and asthma [22].

It is known from Scheme 1 that some clinically useful compounds contain morpholine moiety in addition to 'N' containing heterocycles which are separated by one or more number of carbon atoms than linking directly.

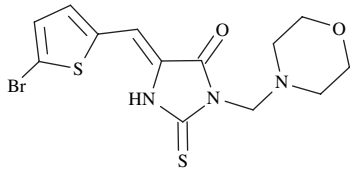
Al-Obaid et al. [25] reported that compounds **1a** and **1b** are potential broad-spectrum antitumor agents based on the anticancer screening data obtained from the National Cancer Institute (NCI) antitumor drug discovery screen. Medicines derived from morpholine-incorporated compounds include dextromoramide (**1c**), a narcotic analgesic and doxapram·HCl (**1d**), a respiratory stimulant. Latter compound is frequently employed in the treatment of respiratory depression following anaesthesia.

In continuation of our earlier work on the synthesis of 2,6-diarylpiperidin-4-ones with relatively bulkier group at the heterocyclic ring [26] which were found to posses multifarious biological activities [27], we thought it is worthwhile to synthesize a system that unite 2,6-diarylpiperidin-4-ones, chloroacetyl chloride and morpholine moieties together to furnish a new series of compounds **19–27** with the hope to develop some promising antimicrobial agents.

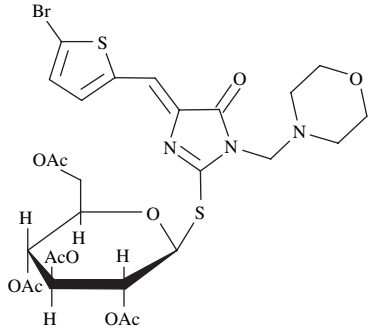
2. Results and discussion

2.1. Chemistry

When chloroacetylation of 2,6-diarylpiperidin-4-ones was effected by using Na_2CO_3 or K_2CO_3 as base and benzene as solvent, appreciable yields were not obtained. But significant improvement in yield (i.e., about 85–94%) was achieved with triethylamine as base in stirring mode itself at about 30–35 °C. Furthermore, while using more basic catalyst such as NaOH, KOH and pyridine individually to effect chloroacetylation, undesired products were obtained along with the expected product. This may be ascribed to the bi-functional



1a



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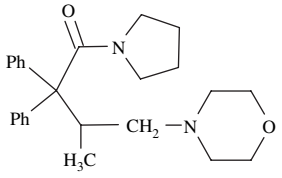
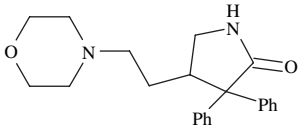
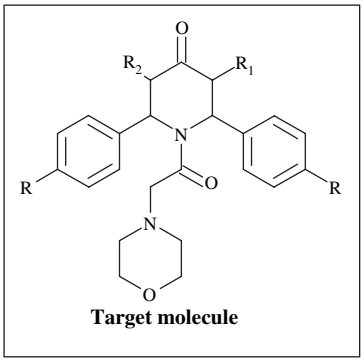


1c



1d



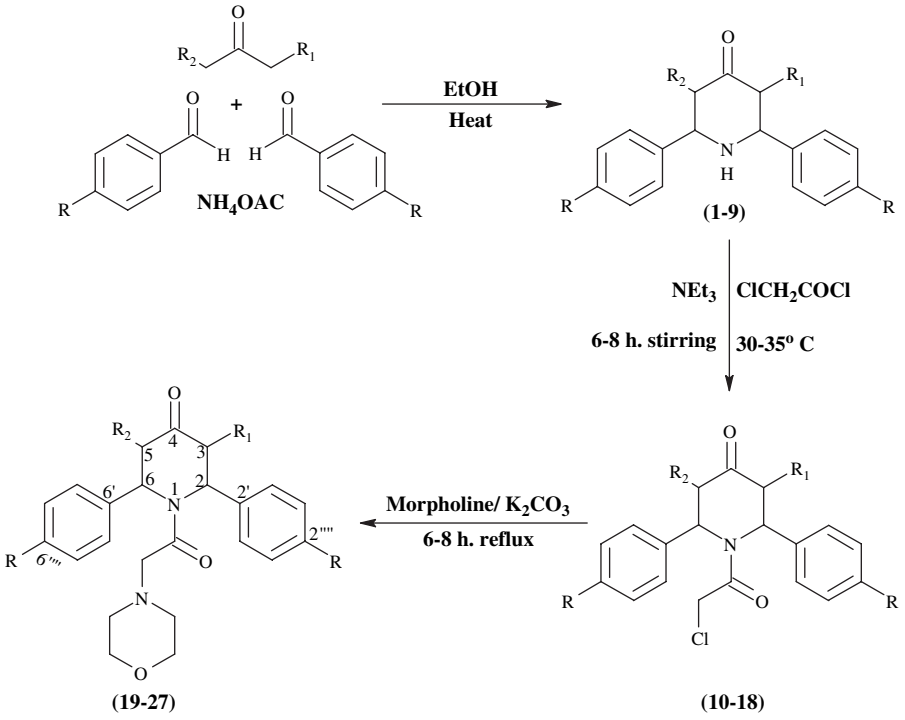
Target molecule

Scheme 1.

nature of chloroacetyl chloride and also due to the presence of active hydrogens at C-3 and C-5 positions of piperidin-4-one besides the secondary nitrogen.

A three-step synthetic route furnished the target compounds **19–27** in good yields. A general schematic representation is given in Scheme 2 while yields and melting points are reproduced in Table 1. Through the pathway involving Mannich reaction, 2,6-diarylpiperidin-4-ones (**1–9**) were prepared in one pot by condensing ketone, aldehyde and ammonium acetate in 1:2:1 ratio using ethanol as solvent. Chloroacetylation of piperidin-4-ones was achieved by treating with chloroacetyl chloride using triethylamine as base. Then, condensation of compounds **10–18** with morpholine in the presence of K_2CO_3 furnished the novel target compounds **19–27**.

Formation of the synthesized compounds **19–27** are confirmed by the observed amide carbonyl stretching in IR spectra



Entry			R_1	R_2	R
1	**10**	**19**	H	H	H
2	**11**	**20**	Me	H	H
3	**12**	**21**	Et	H	H
4	**13**	**22**	i-Pr	H	H
5	**14**	**23**	Me	Me	H
6	**15**	**24**	Me	Me	Cl
7	**16**	**25**	Me	H	OMe
8	**17**	**26**	Me	Me	OMe
9	**18**	**27**	Me	Me	Me

Scheme 2.

Table 1
Analytical data for compounds **10**–**27**

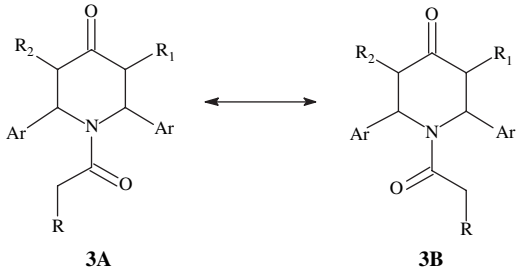
Compound	Yield (%)	M.p. (°C)	Elemental analysis					
			Observed (%)			Calculated (%)		
			C	H	N	C	H	N
10	84	120–122	69.60	5.56	4.29	69.59	5.54	4.27
11	94	131	70.28	5.91	4.10	70.25	5.90	4.09
12	88	118–120	70.86	6.22	3.92	70.85	6.24	3.94
13	89	102	71.42	6.55	3.80	71.41	6.54	3.79
14	91	192	70.84	6.24	3.95	70.85	6.24	3.94
15	80	159	59.32	4.73	3.29	59.34	4.75	3.29
16	83	128–129	65.73	6.01	3.50	65.72	6.02	3.49
17	80	108–110	66.41	6.31	3.37	66.39	6.30	3.37
18	81	162–164	71.94	6.83	3.64	71.93	6.83	3.65
19	76	Semi solid	73.01	6.91	7.40	72.98	6.93	7.40
20	89	146–148	73.45	7.16	7.13	73.43	7.19	7.14
21	80	139	73.84	7.45	7.00	73.85	7.44	6.89
22	84	134	74.30	7.67	6.67	74.24	7.68	6.66
23	83	139	73.86	7.43	6.88	73.85	7.44	6.89
24	77	185–187	63.15	5.92	5.88	63.13	5.94	5.89
25	80	Semi solid	69.03	7.11	6.19	68.99	7.13	6.19
26	77	178	69.51	7.33	6.01	69.49	7.35	6.01
27	75	108–110	74.66	7.87	6.46	74.61	7.89	6.45

of these compounds at around 1650 cm^{-1} and C–O–C asymmetric stretching of morpholine at about 1115 cm^{-1}. Besides, the preferred conformations of the synthesized compounds are also deduced based on their ^1H and ^{13}C NMR spectral data.

2.2. NMR analysis and stereochemistry

In all the synthesized compounds, signal due to benzylic protons (H_2 and H_6) is broadened instead of getting multiplicities as in their parent compounds [28]. Earlier reports [29] reveal that broadening of benzylic signal at room temperature is mainly due to the existence of restricted rotation about N–CO bond in the molecule. Further, it is also obvious from this NMR study that such line broadening is possible only if we visualize coplanar orientation of acetyl moiety to that of dynamically averaged plane of the piperidone ring and is also confirmed by X-ray studies in the case of *N*-phenylcarbomoyl [30] and *N*-benzoyl [31] derivatives of 2,6-diarylpiperidin-4-ones. This prediction of coplanarity of acetyl moiety is also supported by Lunazzi et al. [32] who have stated that perpendicular orientation does not bring about the said line broadening. Despite the restricted rotation of N–CO group in the molecule, we have got only one set of signals for the ring protons instead of getting two sets of signals corresponding to two rotomers **3A** and **3B** (Scheme 3) arising out of restricted rotation. Hence, the obtained average ^1H NMR spectra for the compounds **19**–**27** may be due to the fact that the two rotomers undergo interconversion at a faster rate on the NMR time scale.

Due to the substitution of morpholinoacetyl moiety at the heterocyclic nitrogen, a significant change in chemical shift and coupling constant values of piperidone ring protons is observed compared to the corresponding protons in their parent compounds. On the basis of coupling constant values (as in Table 2), a rigid chair conformation has been proposed for the parent piperidin-4-one moiety with equatorial orientation of phenyl groups at C-2/C-6 besides the substituents at C-3 or C-3/C-5 positions. But, such rigid chair conformation could not be offered for the compounds **19**–**27** as the acetyl moiety is in coplanar orientation. Due to this coplanarity, there may exists severe allylic strain ($A^{1,3}$) between carbonyl group of acetyl moiety and phenyl groups at C-2 and C-6. In order to avoid this and to account for the appreciable change in chemical shift and coupling constant values of compounds **19**–**27**, the most probable nonchair conformations are proposed. Moreover, as the extracted coupling constant values of chloroacetyl derivatives (Table 2) and morpholinoacetyl derivatives are in close proximity with the one reported earlier for *N*-phenylcarbomoyl [30] and *N*-benzoyl [31] derivatives of 2,6-diarylpiperidin-4-ones, we may also propose similar kind of conformations for compounds **19**–**27** wherein the said $A^{1,3}$ strain is very minimum.



Where R = Cl / Morpholine

Scheme 3.

From the coupling constant values of chloroacetyl (Table 2) and morpholinoacetyl derivatives, it is clear that vicinal coupling constant values are decreased remarkably compared to their parent piperidones. In order to account for the lower $^3J_{2a,3a}$ (5.15 Hz) value, Ramalingam et al. [33] have suggested a sofa conformation for compound **28** (Fig. 1) and was also confirmed by single crystal X-ray diffraction studies. Therefore, an equilibrium between chair and half boat conformations **4A** and **4B** (Scheme 4) is assumed to be most probable

Table 2
Vicinal and geminal coupling constants (Hz) of compounds (**10**–**18**) and parent 2,6-diarylpiperidin-4-ones (**1**–**5**)

Compound	$^3J_{2a,3a}$	$^3J_{2a,3e}$	$^2J_{3a,3e}$	$^2J_{5a,5e}$	$^3J_{5a,6a}$	$^3J_{5e,6a}$
10	6.24	5.52	17.54	17.54	6.24	5.52
11	7.01	–	–	18.22	6.10	5.91
12	3.49	–	–	17.32	9.31	5.57
13	1.50	–	–	17.00	9.50	6.00
14	6.71	–	–	–	6.71	–
15	6.90	–	–	18.15	5.46	6.02
16	6.75	–	–	–	6.75	–
17	6.99	–	–	18.35	5.59	6.01
18	6.78	–	–	–	6.78	–
1	9.96	4.47	–	–	9.96	4.47
2	10.36	–	–	–	11.85	2.83
3	10.51				11.75	2.83
4	10.51	–	–	–	11.67	3.03
5	10.35	–	–	–	10.35	–

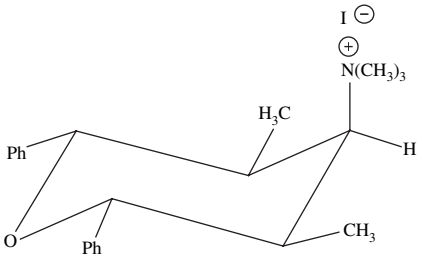
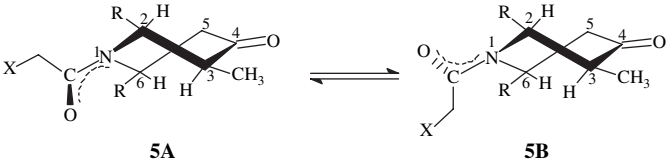


Fig. 1.



5A 5B

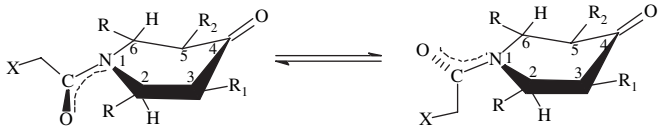
X		Substituent
Cl	Morpholine	R
11	**20**	Ph
16	**25**	Ph (*p*-OCH_3)

Scheme 5.

and stable one for compound **19**. In these proposed conformations, the ring becomes flattened appreciably at nitrogen end and consequently benzylic protons get into the planar region of acetyl moiety. In spite of this, benzylic protons are deshielded appreciably as they lie in the deshielding region of amide plane (on the basis of the model proposed by Paulson and Todt [34] for anisotropic effect of amides). Since the compounds **23**, **24**, **26** and **27** are symmetrically substituted by methyl group at C-3 and C-5, we may offer similar kind of conformations **4A** and **4B** for these compounds too. However, shielding of benzylic protons of **23**, **24**, **26** and **27** by about 0.4–0.6 ppm and increase in $^3J_{2a,3a}$ coupling constant values nearly about 0.8–0.9 ppm compared to **19** suggests that flattening of the ring at nitrogen is lowered slightly in conformations **4A** and **4B** for these compounds thereby decreases the ''in plane'' nature of benzylic protons.

In the case of compounds **20** and **25** (bearing methyl group at C-3), the extent of deshielding experienced by the benzylic proton at C-2 is considerably lower than that of compound without methyl group (i.e. compound **19**). Moreover, in parent piperidone **2**, the ring is reported to be flattened about C(2)–C(3) bond in order to minimize the phenyl–methyl *gauche* interaction [28]. Thus, introduction of methyl group at C-3 position in conformations **4A** and **4B** may increase phenyl–methyl *gauche* interaction. Hence, to avoid this *gauche* interaction, the ring in **20** and **25** is puckering about C(2)–C(3) and C(5)–C(6) bonds compared to **19** to result in highly twisted conformations **5A** and **5B** as in Scheme 5. Indeed, its consequence in $^3J_{2a,3a}$ value for the compounds **20** and **25** could not be noted as the signals for H_{3a}, H_{5a} and $-COCH_2$ protons are merged together to appear as multiplet. However, it is clearly reflected on their corresponding chloroacetyl derivatives **11** and **16** (refer Table 2).

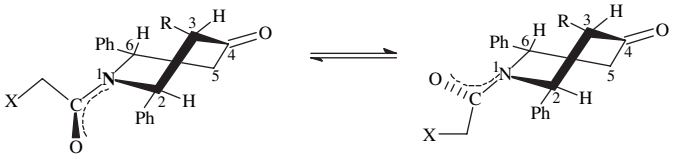
In morpholinoacetyl derivatives of 3-ethyl (**21**) and 3-isopropyl (**22**) compounds, H_2 protons are deshielded markedly compared to H_6 proton. Here also, $^3J_{2a,3a}$ coupling constant values could not be extracted as their signals appear as multiplet. Therefore, conformations of these compounds are established by taking into account the observed coupling constants of their precedent chloroacetyl derivatives **12** and **13**, respectively. In these molecules also deshielding of H_2 is greater than H_6. This reveals that the ring of conformers **4A** and **4B** may be flattened about C(2)–C(3) bond and puckering about C(5)–C(6) bond. This is also reflected in the coupling constant values of **12** and **13** (in Table 2) wherein $^3J_{2a,3a}$ values are decreased whereas $^3J_{5a,6a}$ values are increased remarkably from the corresponding values in **10**. Thus, the compounds **12** and **13** are assumed to adopt twisted conformations **6A** and **6B** (Scheme 6). As there is no appreciable change in chemical shifts of piperidone ring protons in *N*-morpholinoacetyl derivatives **21** and **22** compared to **12** and **13**, we may propose the same conformations **6A** and **6B** to **21** and **22** also. However in **22**, a substantial deshielding of H_2 proton is noted compared to the corresponding proton in **21**. This suggests that C(2)–C(3) bond in conformations **6A** and **6B** may be flattened further in **22**.



4A 4B

X		Substituent		
Chlorine	Morpholine	R_1	R_1	R
10	**19**	H	H	Ph
14	**23**	CH_3	CH_3	Ph
15	**24**	CH_3	CH_3	Ph (*p*-Cl)
17	**26**	CH_3	CH_3	Ph (*p*-OCH_3)
18	**27**	CH_3	CH_3	Ph (*p*-CH_3)

Scheme 4.



6A 6B

X		Substituent
Cl	Morpholine	R
12	**21**	Et
13	**22**	i-Pr

Scheme 6.

In all the cases, ^{13}C NMR shows two signals in the regions 209–211 ppm and 170–172 ppm. These are characteristic for ring carbonyl carbon at C-4 and amide carbonyl carbon attached to the heterocyclic nitrogen, respectively. The signals in the region 113–159 ppm are due to aromatic carbons. The heterocyclic ring carbons and acetyl methylene carbon appear in the range 43–67 ppm.

Due to coplanar orientation of acetyl moiety at the 'N' site with the plane of the ring, it would induce different charge densities at α (C-2/C-6), β (C-3/C-5) and γ (C-4) carbons in the proposed conformations and consequently shield or deshields the same differently. However, the marked shielding effect observed with ring carbon chemical shifts may not be explained on the basis of electronic effect alone. Instead, it would have also been explained on the basis of steric interactions and conformational distortions arising out of the substituent at nitrogen site.

Among α, β and γ carbons, α carbons are shielded significantly compared to β and γ carbons. This shielding effect of α carbons in **19–27** is noted by about 6–10 ppm compared to the corresponding carbons in their parent piperidones due to the substitution of morpholinoacetyl group.

Hence, irrespective of the various conformations, which the heterocyclic ring adopts in order to avoid various strain energies, the atoms such as N, C-2, C-6 and CO of morpholinoacetyl moiety lie in the same plane. Therefore, in all the cases, γ-eclipsing interactions exists between CO (of substituent) and N–C(2)/N–C(6). Owing to this γ-eclipsing interaction, C-2 and C-6 carbons are shielded to a greater extent in all the compounds compared to the corresponding carbons in their parent compounds. But, the shielding effects observed with β and γ carbons are not more significant compared to α carbons.

2.3. Antimicrobial evaluation (structure–activity relationship)

2.3.1. Antibacterial activity

In vitro antibacterial activities of the variously substituted *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones **19–27** against a group of bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi* have recorded a minimum inhibitory concentration (MIC μg/ml) and is reproduced in Table 3. Here, ciprofloxacin was taken as a reference drug. A close survey of the MIC values in Table 3 indicates that all the compounds exhibit a varied range (6.25–200 μg/ml) of antibacterial potency against the tested bacterial strains except compounds **19** and **20**, which did not show antibacterial activity against *E. coli* and *Sa. typhi*, respectively, even at a maximum concentration of 200 μg/ml. The compound **19**, which was inactive against *E. coli* become potent by the incorporation of methyl group at C-3 position (compound **20**) whereas against *Sa. typhi*, this methyl group modification has no effect even at 200 μg/ml. However, replacement of methyl function in **20** by ethyl group at C-3 (compound **21**) has regained the activity against *Sa. typhi* whose growth was controlled at 100 μg/ml.

Table 3
In vitro antibacterial activities of compounds **19–27**

Compound	Minimum inhibitory concentration (MIC) in μg/ml			
	S. aureus	*E. coli*	*P. aeruginosa*	*Sa. typhi*
19	200	–[a]	100	100
20	200	100	50	–[a]
21	50	50	25	100
22	100	100	50	200
23	50	100	25	50
24	25	25	50	100
25	50	100	25	50
26	6.25	12.5	12.5	25
27	50	25	6.25	6.25
Ciprofloxacin	25	25	12.5	50

[a] – No inhibition even at higher concentration i.e., at 200 μg/ml.

Introduction of bulkier isopropyl group at C-3 position of **19** (compound **22**) increased the activity by 50% against *S. aureus* and *P. aeruginosa* while against *Sa. typhi* 50% decreased activity was noted. But, replacement of each one of the protons from C-3 and C-5 positions in **19** by methyl group (compound **23**) have considerable impact on antibacterial activity i.e., a two-fold enhanced activity was registered against *S. aureus* and *P. aeruginosa* while against *Sa. typhi* only 50% was improved. However, its activity is at par with the potency of 3-ethyl analogue (compound **21**) against *S. aureus* and *P. aeruginosa* whereas against *Sa. typhi* and *E. coli*, the activity was enhanced and decreased, respectively, by one-fold rate.

Among the compounds having no substitution at the *para* position of phenyl groups (i.e. compounds **19–23**), **21** and **23** only exerted moderate activities against all the used strains.

In the case of compounds **24–27** with *para* substituted phenyl groups at C-2 and C-6 positions, MIC values for these organisms are recorded in the range 6.25–100 μg/ml. These modifications at the *para* position of phenyl groups have appreciable implication over the antibacterial potency. Substitution of *p*-chlorophenyl groups in place of phenyl groups at C-2 and C-6 positions in **23** (compound **24**) has fairly improved the activity against *E. coli* and *S. aureus* while against rest of the strains, 50% decreased activity was noted.

However, introduction of *p*-methoxyphenyl groups at C-2 and C-6 positions in **20** (compound **25**) has marked improvement against *S. aureus*, *P. aeruginosa* and *Sa. typhi* while against *E. coli*, the activity is at par with each other. But, introduction of another methyl group at C-5 position in **25** (compound **26**) has

significant antibacterial activity against all the tested organisms. Moreover, the activity is maximum against *S. aureus* (6.25 μg/ml), *E. coli* (12.5 μg/ml) and *P. aeruginosa* (12.5 μg/ml) while against *Sa. typhi*, the MIC value is noted at 25 μg/ml. Besides, its activity is also superior than **23** having phenyl groups (without *para* substituent) at C-2 and C-6 positions.

Compound **27**, which has *p*-methylphenyl function instead of phenyl groups has registered excellent activity against *P. aeruginosa* and *Sa. typhi* (i.e., MIC at 6.25 μg/ml each) while against *E. coli* and *S. aureus*, the MIC was recorded at 25 and 50 μg/ml, respectively. From the MIC values, it is very clear that the antibacterial activity of compounds **26** and **27** was remarkable and their activity is also comparatively more than that of the reference drug used.

2.3.2. Antifungal activity

Table 4 exhibits the in vitro antifungal activities of compounds **19**–**27**. Here, amphotericin-B was chosen as standard drug on a list of fungal strains such as *Candida albicans*, *Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus* whose potencies were measured as minimum inhibitory concentration (MIC, μg/ml).

Among the compounds, which bear phenyl groups at C-2 and C-6 positions (i.e., compounds **19**–**23**), compound **19** did not exert antifungal activity even at 200 μg/ml against *C. albicans* and *A. flavus*. Further, introduction of methyl group at C-3 in **19** also did not promote activity against *C. albicans* even at 200 μg/ml while against *A. flavus*, it has registered maximum activity (i.e., at 50 μg/ml). Also, this methyl group modification has marked antifungal activity against *A. niger* too. But, replacement of methyl group by ethyl group was found to be excellent in improving the activity against *C. albicans* to which compounds **19** and **20** became inactive even at all concentrations used. However, against rest of the strains, activity of **21** is decreased by 50% compared to **20**.

Due to the incorporation of isopropyl group at C-3 in **19**, there was a marked improvement in activity against all the organisms used.

However, symmetrical substitution of methyl group at both C-3 and C-5 positions in **19** (compound **23**) has pronounced antifungal potency against *Rhizopus* sp. and *A. niger*, respectively, at 12.5 and 25 μg/ml. Thus, among the compounds **19**–**23** having no substitution at the *para* position of phenyl groups at C-2 and C-6, compound **23** was found to be better in enhancing the antifungal activity against all the strains.

However, substitution of chlorine at the *para* position of phenyl groups in **23** (compound **24**) exerted remarkable activity against *C. albicans* and *A. flavus* each of which showing MIC at 6.25 μg/ml. However, this introduction did not show any improvement against *Rhizopus* sp. and *A. niger*.

Among the compounds in which the heterocyclic nitrogen is flanked by *p*-methoxyphenyl groups, compound **25** only produced marked potency against *Rhizopus* sp. at a MIC of 6.25 μg/ml while against *A. flavus*, it is about 12.5 μg/ml.

Likewise, substitution of *p*-methylphenyl function at C-2 and C-6 positions of piperidone ring in **23** (compound **27**) failed to enhance the activity well against all the strains except towards *A. flavus* for which it has registered 50% increased activity.

From the Table 4, it is obvious that compound **24** has recorded excellent antifungal activity against all the tested fungal strains. Further, its activity is at par with the standard amphotericin-B against *Rhizopus* sp. while against rest of the strains, compound **24** was found to be superior to the standard.

Table 4
In vitro antifungal activities of compounds **19**–**27**

Compound	Minimum inhibitory concentration (MIC) in μg/ml			
	C. albicans	*Rhizopus* sp.	*A. niger*	*A. flavus*
19	–[a]	100	200	–[a]
20	–[a]	100	50	50
21	100	200	100	100
22	50	25	50	100
23	50	12.5	25	50
24	6.25	25	25	6.25
25	25	6.25	50	12.5
26	100	50	50	100
27	50	25	50	25
Amphotericin-B	25	25	50	50

[a] – No inhibition even at higher concentration i.e., at 200 μg/ml.

3. Conclusion

The ^{1}H and ^{13}C NMR spectral studies indicate that *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones adopt nonchair conformations unlike rigid chair conformation proposed for the parent 2,6-diarylpiperidin-4-ones. Besides, owing to the coplanarity of acetyl moiety, the $C-H_2/C-H_6$ bonds get polarized by amide carbonyl group, which in turn may develop fractional positive and negative charges over the respective protons and carbons. As a result of this, resonance of those carbons is shielded while the attached protons are deshielded significantly.

Moreover, the microbiological screening studies carried out to evaluate the antibacterial and antifungal potencies of the compounds are clearly known from Tables 3 and 4, respectively.

Among the compounds tested for antibacterial activity, compounds with methyl group at C-3 and C-5 positions were found to exert remarkable antibacterial response towards the entire tested organisms. In particular, compound **27** has registered significant activity against *P. aeruginosa* and *Sa. typhi* while **26** against *S. aureus*. From this study, it is concluded that modifications at the *para* position of the phenyl groups at C-2 and C-6 positions of piperidone ring in addition to the methyl groups at C-3 and C-5 positions were found to be important in eliciting good antibacterial activity.

Similarly, among the antifungal profile of the compounds tested, compounds which have symmetrical substitution at C-3/C-5 by methyl groups and at C-2/C-6 by phenyl groups exert promising activity. However, introduction of *p*-chlorophenyl groups in place of phenyl groups at C-2 and C-6 positions have promoted the activity and showed its MIC at 6.25 μg/ml against *C. albicans* and *A. flavus*. Similarly,

compound **25** which has *p*-methoxyphenyl groups at C-2 and C-6 positions and methyl group at C-3 only recorded a marked potency particularly against *Rhizopus* sp.

Thus, the close examination of in vitro antibacterial and antifungal activity profiles for the novel *N*-morpholinoacetyl-2,6-diarylpiperidin-4-ones against the tested bacterial and fungal strains clearly indicates that presence of methyl groups at C-3 and C-5 positions of piperidone ring is considered to be beneficial besides the presence of different substituent at the *para* position of phenyl groups at C-2 and C-6 positions. Furthermore, the observed marked antibacterial and antifungal activities may be considered as key steps for the building of novel chemical framework with comparable pharmacological profile to that of standard drugs.

4. Experimental

All the reported melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimeters) are listed. ^{1}H NMR spectra were recorded at 400 MHz on Bruker AMX 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz on Bruker AMX 400 MHz spectrometer in $CDCl_3$. The tubes used for recording NMR spectra are of 5 mm diameter. Mass spectra were recorded on Jeol SX-102 (EI) and microanalyses were performed on Heraeus Carlo Erba 1108 CHN analyzer. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. All the solvents were distilled prior to use.

All the parent 2,6-diarylpiperidin-4-ones were prepared by the literature precedent of Noller and Baliah [35].

*4.1. Synthesis of N-chloroacetyl-2,6-diphenylpiperidin-4-ones (**10**)*

To a well-stirred solution of 2,6-diphenylpiperidin-4-one **1** (0.005 mol) and triethylamine (0.005 mol) in benzene, chloroacetyl chloride (0.005 mol) in benzene was added in dropwise for about half an hour. Stirring was continued with mild heating (30–35 °C). After the completion of reaction, it was poured into water and extracted with ether. The collected ether extracts were then washed well with 3% sodium bicarbonate solution and dried over anhydrous sodium sulphate. This upon evaporation afforded the compound **10** in good yield. The compounds **11**–**18** were synthesized similarly.

*4.2. Synthesis of N-morpholinoacetyl-2,6-diphenylpiperidin-4-one (**19**)*

A mixture of *N*-chloroacetyl-2,6-diphenylpiperidin-4-one **10** (0.005 mol), K_2CO_3 (0.01 mol) and morpholine (0.005 mol) in toluene was refluxed for about 6–8 h. After the completion of reaction, K_2CO_3 was removed by filtration and excess of solvent was removed under reduced pressure. The obtained residue was column chromatographed on silica gel using benzene–ethyl acetate (1:1) mixture as an eluent which afforded the product **19** in good yield.

IR (KBr) (cm^{-1}): 3060, 3031, 2961, 2921, 2853, 2809 (C–H stretching), 1722 (C=O stretching), 1646 (N–C=O stretching), 1496, 1452, 1413, 1265, 1226, 1116, 1072, 1014, 908, 866, 809, 699, 649, 588, 539, 482. ^{1}H NMR (δ ppm): 3.67 [t, 4H, O–$(CH_2)_2$ methylene protons α to oxygen atom of morpholine], 2.42 [bs, 4H, N–$(CH_2)_2$ methylene protons α to nitrogen atom of morpholine], 3.03 [dd, $^2J_{3a,3e} = {}^2J_{5a,5e} = 17.39$ Hz; $^3J_{2a,3a} = {}^3J_{5a,6a} = 5.89$ Hz, 4H (merged), H_{3a}, H_{5a} and N–$COCH_2$], 2.69 (dd, $^2J_{3a,3e} = {}^2J_{5a,5e} = 17.34$ Hz; $^3J_{2a,3e} = {}^3J_{5e,6a} = 5.88$ Hz, 2H, H_{3e} and H_{5e}), 5.99 (bm, 2H, H_2 and H_6), 7.13–7.26 (m, 10H, aryl protons). ^{13}C NMR (δ ppm): 43.963 (C-3 and C-5), 53.608 [N–$(CH_2)_2$], 54.471 (C-2 and C-6), 62.331 (N–$COCH_2$), 66.641 [O–$(CH_2)_2$], 126.626, 127.404, 128.532 (aryl carbons), 140.885 (C-2′ and C-6′ *ipso*), 170.650 (N–*C*O), 206.947 (*C*=O at C-4).

The compounds **20**–**27** were synthesized similarly.

*4.3. N-Morpholinoacetyl-3-methyl-2,6-diphenylpiperidin-4-one (**20**)*

Mass: *m*/*z* 393 $(M+1)^+$ (100%) (M.F: $C_{24}H_{28}N_2O_3$), 344, 275, 233, 202, 171, 131, 119, 100, 77, 57. IR (KBr) (cm^{-1}): 3060, 3028, 2973, 2835, 2853, 2815 (C–H stretching), 1719 (C=O stretching), 1651 (N–C=O stretching), 1493, 1459, 1393, 1290, 1225, 1176, 1115 (C–O–C asymmetric stretching), 1072, 1006, 929, 864, 815, 766, 706, 651, 591, 520, 460. ^{1}H NMR (δ ppm): 3.71 [t, 4H, O–$(CH_2)_2$], 2.41–2.48 [m, 4H, N–$(CH_2)_2$], 2.99–3.15 [m, 4H (merged), H_{3a}, H_{5a} and N–$COCH_2$], 2.76 (dd, $^2J_{5a,5e} = 18.04$ Hz; $^3J_{5e,6a} = 5.94$ Hz, 1H, H_{5e}), 5.54 (bm, 1H, H_2), 5.99 (bm, 1H, H_6), 7.06–7.29 (m, 10H, aryl protons), 1.07 (d, 3H, CH_3 at C-3). ^{13}C NMR (δ ppm): 13.939 (CH_3 at C-3), 43.183 (C-5), 45.847 (C-3), 53.797 [N–$(CH_2)_2$], 54.384 (C-6), 60.930 (C-2), 62.462 (N–$COCH_2$), 66.696 [O–$(CH_2)_2$], 126.682, 127.670, 128.206, 128.445, 128.807 (aryl carbons), 140.959 (C-6′ *ipso*), 141.326 (C-2′ *ipso*), 170.988 (N–*C*=O), 209.245 (*C*=O at C-4).

*4.4. N-Morpholinoacetyl-3-ethyl-2,6-diphenylpiperidin-4-one (**21**)*

IR (KBr) (cm^{-1}): 3063, 3029, 2963, 2857, 2811 (C–H stretching), 1715 (C=O stretching), 1649 (N–C=O stretching), 1494, 1454, 1391, 1367, 1318, 1272, 1221, 1113, 1077, 1007, 864, 766, 739, 706, 651, 517, 459. ^{1}H NMR (δ ppm): 3.69–3.73 [m, 4H, O–$(CH_2)_2$], 2.46 [t, 4H, N–$(CH_2)_2$], 2.67 (dd, $^2J_{5a,5e} = 17.17$ Hz; $^3J_{5e,6a} = 5.74$ Hz, 1H, H_{5e}), 2.89 (dd, $^2J_{5a,5e} = 17.22$ Hz; $^3J_{5a,6a} = 9.01$ Hz, 1H, H_{5a}), 2.99–3.04 (m, 2H, H_{3a} and N–COC*H*H), 3.16 (d, 1H, N–COCH*H*), 6.19 (bm, 1H, H_2), 5.72 (bm, 1H, H_6), 7.03–7.26 (m, 10H, aryl protons), 1.63–1.74 (m, 2H, CH_2CH_3 protons at C-3), 1.04 (t, 3H, CH_2CH_3 protons at C-3). ^{13}C NMR (δ ppm): 11.903 (CH_2CH_3 at C-3), 23.326 (CH_2CH_3 at C-3), 44.426 (C-5), 52.456 (C-3), 55.256 (C-6), 53.959 [N–$(CH_2)_2$], 56.110 (C-2), 62.490 (N–$COCH_2$), 66.790 [O–$(CH_2)_2$],

127.069, 127.566, 127.703, 128.169, 128.543, 128.851 (aryl carbons), 141.154 (C-6′ *ipso*), 141.680 (C-2′ *ipso*), 171.272 (N–C=O), 209.479 (*C*=O at C-4).

4.5. N-Morpholinoacetyl-3-isopropyl-2,6-diphenylpiperidin-4-one (**22**)

IR (KBr) (cm^{-1}): 3064, 3031, 2973, 2847, 2814, 2758 (C–H stretching), 1703 (C=O stretching), 1644 (N–C=O stretching), 1499, 1452, 1413, 1349, 1271, 1228, 1116, 1037, 1007, 864, 749, 698. ^{1}H NMR (δ ppm): 3.71–3.74 [m, 4H, O–(CH_2)$_2$], 2.49 [bs, 4H, N–(CH_2)$_2$], 2.79–2.88 [m, 2H (merged), H_{3a} and H_{5a}], 2.73 (dd, $^2J_{5a,5e} = 16.71$ Hz; $^3J_{5e,6a} = 6.28$ Hz, 1H, H_{5e}), 3.26 (d, 1H, N–COC*H*H), 3.01 (bs, 1H, N–COCH*H*), 6.54 (bm, 1H, H_2), 5.66 (bm, 1H, H_6), 6.86-7.26 (m, 10H, aryl protons), 2.00–2.06 [m, 1H, *CH*(CH_3)$_2$ at C-3], 1.12 {d, 3H, [CH(*CH*$_3$′)(CH_3″)] at C-3}, 1.05 {d, 3H, [CH(CH_3′)(*CH*$_3$″)] at C-3}. ^{13}C NMR (δ ppm): 20.366 [CH(*C*H$_3$′)(CH_3″) at C-3], 21.625 [CH(CH_3′)(*C*H$_3$″) at C-3], 28.831 [*C*H(CH_3)$_2$ at C-3], 44.396 (C-5), 53.944 (C-3), 53.944 [N–(*C*H$_2$)$_2$], 56.601 (C-6), 58.112 (C-2), 62.350 (N–CO*C*H$_2$), 66.739 [O–(*C*H$_2$)$_2$], 126.238, 127.670, 128.324, 128.621 (aryl carbons), 141.177 (C-2′ and C-6′ *ipso*), 170.970 (N–*C*=O), 209.389 (*C*=O at C-4).

4.6. N-Morpholinoacetyl-3,5-dimethyl-2,6-diphenylpiperidin-4-one (**23**)

Mass: *m/z* 407 (M^+) (M.F: $C_{25}H_{30}N_2O_3$), 381, 353, 289, 233, 171, 129, 100 (100%), 91, 77. IR (KBr) (cm^{-1}): 3062, 3028, 2968, 2933, 2853, 2891 (C–H stretching), 1715 (C=O stretching), 1645 (N–C=O stretching), 1494, 1454, 1389, 1299, 1268, 1209, 1117, 1009, 866, 762, 705, 657, 529, 435. ^{1}H NMR (δ ppm): 3.69 [t, 4H, O–(*CH*$_2$)$_2$], 2.43 [bs, 4H, N–(*CH*$_2$)$_2$], 3.09–3.15 [m, 2H, H_{3a} and H_{5a}], 2.99 (s, 2H, N–COCH$_2$), 5.51 (bm, 2H, H_2 and H_6), 7.18–7.29 (m, 10H, aryl protons), 1.06 (d, 6H, CH_3 at C-3 and C-5). ^{13}C NMR (δ ppm): 14.085 (CH_3 at C-3, C-5), 45.394 (C-3 and C-5), 53.852 [N–(*C*H$_2$)$_2$], 60.786 (C-2 and C-6), 62.269 (N–CO*C*H$_2$), 66.632 [O–(*C*H$_2$)$_2$], 127.655, 128.609, 129.048 (aryl carbons), 171.403 (N–*C*=O), 141.242 (C-2′ and C-6′ *ipso*), 211.181 (*C*=O at C-4).

4.7. N-Morpholinoacetyl-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one (**24**)

IR (KBr) (cm^{-1}): 2979, 2936, 2878, 2806 (C–H stretching), 1716 (C=O stretching), 1654 (N–C=O stretching), 1595, 1492, 1439, 1403, 1344, 1138, 1093, 1013, 933, 832, 722, 550, 521. ^{1}H NMR (δ ppm): 3.62–3.66 [m, 4H, O–(*CH*$_2$)$_2$], 2.37 [bs, 4H, N–(*CH*$_2$)$_2$], 2.95–3.05 [m, 4H (merged), H_{3a}, H_{5a} and N–COCH$_2$], 5.38 (bm, 2H, H_2 and H_6), 7.05 (d, 4H, aryl protons *meta* to chlorine), 7.23 (d, 4H, aryl protons *ortho* to chlorine), 0.99 (d, 6H, CH_3 at C-3 and C-5). ^{13}C NMR (δ ppm): 14.101 (CH_3 at C-3), 45.372 (C-3 and C-5), 53.816 and 53.919 [N–(*C*H$_2$)$_2$], 60.286 (C-2 and C-6), 62.458 (N–CO*C*H$_2$), 66.622 and 66.741 [O–(*C*H$_2$)$_2$], 133.851 (C-2‴ and C-6‴ *ipso*),139.501 (C-2′ and C-6′ *ipso*), 128.944 and 130.396 (aryl carbons), 171.301 (N–*C*=O), 210.907 (*C*=O at C-4).

4.8. N-Morpholinoacetyl-3-methyl-2,6-bis(p-methoxyphenyl)piperidin-4-one (**25**)

IR (KBr) (cm^{-1}): 3071, 2968, 2929, 2847 (C–H stretching), 1719 (C=O stretching), 1644 (N–C=O stretching), 1514, 1458, 1415, 1299, 1254, 1179, 1115, 1032, 934, 866, 832, 559, 464. ^{1}H NMR (δ ppm): 3.68 [s, 4H, O–(*CH*$_2$)$_2$], 2.44 [bs, 4H, N–(*CH*$_2$)$_2$], 3.03 (bs, 4H, H_{3a}, H_{5a} and N–COCH$_2$), 5.40 (bm, 1H, H_2), 5.89 (bm, 1H, H_6), 6.76 (d, 4H, aryl protons *ortho* to methoxy group), 7.04 (d, 4H, aryl protons *meta* to methoxy group), 1.01 (bs, 3H, CH_3 at C-3), 3.73 and 3.74 (two s, 6H, OCH_3 at C-2‴ and C-6‴). ^{13}C NMR (δ ppm): 13.809 (CH_3 at C-3), 43.167 (C-5), 46.009 (C-3), 53.705 (C-6), 53.705 [N–(*C*H$_2$)$_2$], 55.139 and 55.197 (OCH_3 carbons at C-2‴ and C-6‴), 60.898 (C-2), 62.323 (N–CO*C*H$_2$), 66.612 [O–(*C*H$_2$)$_2$], 128.826, 127.926, 114.089, 113.730 (aryl carbons), 133.232 (C-2′ *ipso*), 132.968 (C-6′ *ipso*), 158.885 and 158.762 (C-2‴ and C-6‴ *ipso*), 170.824 (N–*C*=O), 209.722 (*C*=O at C-4).

4.9. N-Morpholinoacetyl-3,5-dimethyl-2,6-bis(p-methoxyphenyl)piperidin-4-one (**26**)

IR (KBr) (cm^{-1}): 3071, 2969, 2940, 2897, 2854, 2814 (C–H stretching), 1711 (C=O stretching), 1643 (N–C=O stretching), 1609, 1513, 1459, 1416, 1298, 1248, 1179, 1116, 1029, 926, 869, 835, 771, 741, 630, 559. ^{1}H NMR (δ ppm): 3.70 [t, 4H, O–(*CH*$_2$)$_2$], 2.44 [bs, 4H, N–(*CH*$_2$)$_2$], 3.06–3.13 (m, 2H, H_{3a} and H_{5a}), 3.00 (s, 2H, N–COCH$_2$), 5.43 (bm, 2H, H_2 and H_6), 6.82 (d, 4H, aryl protons *ortho* to methoxy group), 7.08 (d, 4H, aryl protons *meta* to methoxy group), 3.79 (s, 6H, OCH_3 at C-2‴ and C-6‴), 1.05 (d, 6H, CH_3 at C-3 and C-5). ^{13}C NMR (δ ppm): 14.087 (CH_3 at C-3 and C-5), 45.577 (C-3 and C-5), 53.863 [N–(*C*H$_2$)$_2$], 55.210 (O*C*H$_3$ carbons at C-2‴ and C-6‴), 60.210 (C-2 and C-6), 62.350 (N–CO*C*H$_2$), 66.650 [O–(*C*H$_2$)$_2$], 113.913 and 128.828 (aryl carbons), 133.312 (C-2′ and C-6′ *ipso*), 158.953 (C-2‴ and C-6‴ *ipso*), 171.329 (N–*C*=O), 211.561 (*C*=O at C-4).

4.10. N-Morpholinoacetyl-3,5-dimethyl-2,6-bis(p-methylphenyl)piperidin-4-one (**27**)

IR (KBr) (cm^{-1}): 2978, 2932, 2899, 2859, 2835, 2810 (C–H stretching), 1711 (C=O stretching), 1647 (N–C=O), 1511, 1395, 1299, 1266, 1208, 1116, 1035, 978, 863, 819, 804, 727, 652, 576, 517, 488, 437. ^{1}H NMR (δ ppm): 3.69 [t, 4H, O–(*CH*$_2$)$_2$], 2.44 [bs, 4H, N–(*CH*$_2$)$_2$], 3.07–3.12 [m, 2H, H_{3a} and H_{5a}], 2.99 (s, 2H, N–COCH$_2$), 5.46 (bm, 2H, H_2 and H_6), 7.09 (t, 8H, aryl protons), 2.33 (s, 6H, CH_3 at C-2‴ and C-6‴), 1.04 (d, 6H, CH_3 at C-3 and C-5). ^{13}C NMR (δ ppm): 14.067 (CH_3 at C-3 and C-5), 20.911 (CH_3 carbons at C-2‴ and C-6‴), 45.458 (C-3 and C-5), 53.872 [N–(*C*H$_2$)$_2$], 60.522 (C-2 and C-6), 62.323 (N–CO*C*H$_2$), 66.661

[O–(CH_2)$_2$], 127.572 and 129.227 (aryl carbons), 137.363 (C-2′ and C-6′ *ipso*), 138.291 (C-2′′′′ and C-6′′′′ *ipso*), 171.369 (N–*C*=O), 211.551 (*C*=O at C-4).

5. Pharmacology

In vitro activities of the compounds were tested in Sabourauds dextrose broth (SDB, Hi-media, Mumbai) for fungi and in nutrient broth (NB, Hi-media, Mumbai) for bacteria by two-fold serial dilution method [36]. The test compounds were dissolved in dimethylsulphoxide (DMSO) to obtain 1 mg/ml stock solutions. Seeded broth (broth containing microorganisms) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1 °C while fungal spores from 24 h − 7 days old Sabourauds agar slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4–10^5 cfu/ml. The final inoculums size was 10^5 cfu/ml for antibacterial assay and $1.1–1.5 \times 10^2$ cfu/ml for antifungal assay. Testing was performed at pH 7.4 ± 0.2 for bacteria (NB) and at pH 5.6 for fungi (SDB). Exactly 0.4 ml of the solution of test compound was added to 1.6 ml of seeded broth to form the first dilution. One milliliter of this was diluted with a further 1 ml of seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control and likewise solvent controls were also run simultaneously. The tubes were incubated in BOD incubators at 37 ± 1 °C for bacteria and 28 ± 1 °C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. ciprofloxacin and amphotericin-B were used as standards for bacterial and fungal studies, respectively.

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