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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activities of N-chloroacetyl-2,6-diarylpiperidin-4-ones

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Abstract An array of new N-chloroacetyl-2,6-diarylpiperidin-4-ones has been synthesised and their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Salmonella typhi*, and antifungal activity against *Cryptococcus neoformans*, *Candida albicans*, *Rhizopus* sp., *Aspergillus flavus*, and *Aspergillus niger* examined. Compounds **14** against *P. aeruginosa*, **15** against *S. typhi*, **16** against *S. aureus*, and **19** against *B. subtilis* showed marked antibacterial activity. Similarly, compounds **15** and **19** against *A. niger* and **19** against *A. flavus* exerted significant antifungal activities.

Keywords Synthesis · Piperidin-4-ones · Chloroacetylation · Antibacterial activity · Antifungal activity

Introduction

In recent years, there has been growing interest in the synthesis of bioactive compounds in the field of heterocyclic chemistry. Among the family of heterocyclic compounds, the nitrogen-containing heterocycles, especially piperidin-4-ones, have gained considerable importance presumably because of their varied biological properties such as antiviral, antitumour (El-Subbagh et al., 2000), analgesic (Jerom and Spencer, 1988), local anaesthetic (Perumal et al., 2001; Hagenbach and Gysin, 1952)antimicrobial, bactericidal, fungicidal, herbicidal, insecticidal, antihistaminic, anti-inflammatory, anticancer, and central nervous system (CNS) stimulant and

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depressant activities (Mobio et al., 1989; Katritzky and Fan, 1968; Ganellin and Spickett, 1965). Lijinsky and Taylor (1975) found that the blocking of α-positions to that of nitrogen in piperidone using alkyl groups provided advantages over unblocked ones in terms of biological activity. Furthermore, the significance of piperidin-4-one as an intermediary in the synthesis of a variety of physiologically active compounds have been reviewed by Prostakov and Gaivoronskaya (1978). The structure of the piperidone nucleus can also be frequently recognised in the molecular framework of most of the naturally occurring alkaloids and synthetic compounds, which are endowed with interesting biological and pharmacological properties.

Similarly, amides are well known for their therapeutic values (Chauhan et al., 2001; Chauhan et al., 1970) . The chemistry of amines with chloroacetyl groups is also fascinating and has received significant attention over the years, resulting in substantial advances both in synthetic and medicinal aspects. N-Benzyl-β-chloropropionamide is a well-proven (Cassel and Kushner, 1951; Kushneret al., 1951) anticonvulsant agent marketed under the trade names Hibicon and Hydrane. Chloroacetyl amides of some amines were found to exert diverse biological properties such as antiepileptic (Kochetkov and Dudykina, 1951), antispasmodic (Kochetkov and Dudykina, 1957), antitumor, anti multidrug resistance (MDR, Eregowda et al., 2000), antimicrobial (Al-Haiza et al., 2003), herbicidal (Gan J et al., 2002), and mild stimulant and depressant activities (Hasan et al., 1971).

Recently, our group has actively engaged in the synthesis (Ramalingan et al., 2003a; 2004a; 2004b; Balasubramanian et al., 2002; 2003; Aridoss et al., 2006a) of 2,6-diarylpiperidin-4-ones with and without substituents at C-3, C-5, and at the heterocyclic nitrogen, and has also explored the existence of a varied degree of *in vitro* antibacterial and antifungal activities (Ramalingan et al., 2003b; 2003c; 2004c; Balasubramanian et al., 2004; 2005; 2006; Aridoss G et al., 2006b; Parthiban P et al., 2006).

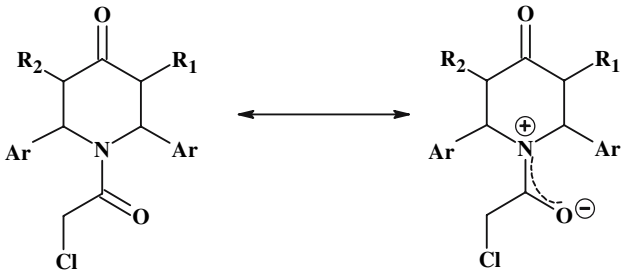
In light of the above observations, it was thought worthwhile to synthesise a system that brings 2,6-diarylpiperidin-4-ones and chloroacetyl chloride together to furnish the corresponding amides **11–20** with the hope of developing some promising antimicrobial agents.

Results and Discussion

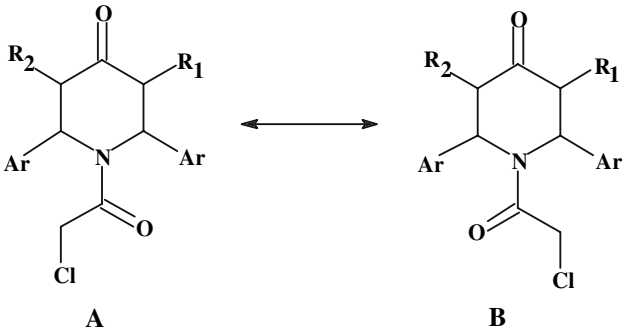
Chemistry

Chloroacetylation of 2,6-diarylpiperidin-4-ones was effected initially by using Na_2CO_3/K_2CO_3 as a base and benzene as a solvent. Only poor yields were achieved. Instead, when triethylamine was used as base the yield of the product improved significantly (i.e., about 80–94%) in stirring mode at about 30–35°C. Furthermore, while using a 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 bifunctional nature of chloroacetyl chloride and also due to the presence of active hydrogens at the C-3 and C-5 positions of piperidin-4-one, which may undergo chloroacetylation besides the secondary

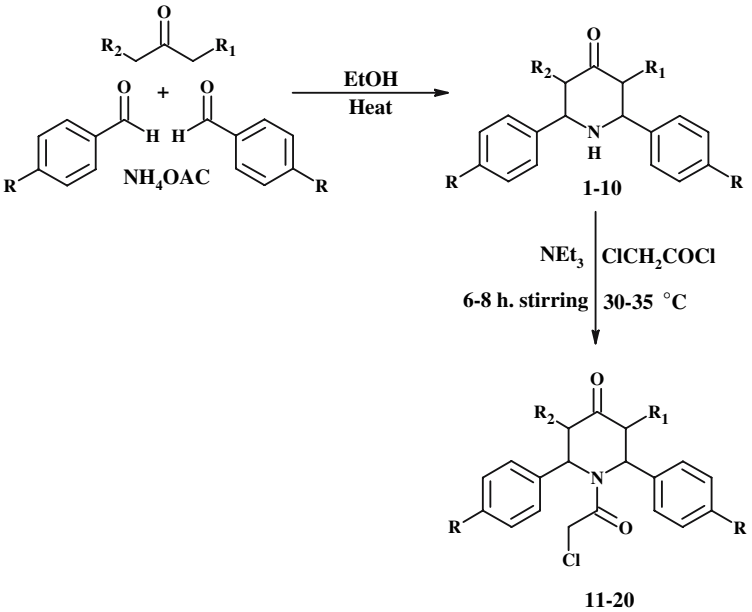
nitrogen. Generally, the attachment of an electron-withdrawing acyl group (-COR) at the nitrogen site of the 2,6-diarylpiperidin-4-one ring is known to exert a major change in the ring conformation and the chemical shifts of ring carbons and attached protons (Krishnapillai et al., 2000; Krishnakumar and Krishnapillai 1996). These conformational and chemical-shift changes are attributed to the involvement of the lone pair of electrons on the ring nitrogen in conjugation with the -COR function (Chow et al., 1968; Lunazzi et al., 1982; Lunazzi et al., 1980; Ravindran et al., 1991; Senthilkumar et al., 1992; Krishnakumar and Krishnapillay, 1996; Krishnakumar and Krishnapillay, 1992; Krishnapillay et al., 2000; Gdaniec et al., 1995; Rubiralta et al., 1989). Hence, this kind of conjugation creates partial double-bond character about the N–CO bond in **11–20,** which in turn leads to restricted rotation about this bond as shown in Scheme 1. Existence of restricted rotation in the molecule is also confirmed by the broadening of the signal of the benzylic protons (H_2 and H_6) at room temperature. If rotation about the N–CO bond is slow (i.e., restricted rotation) on the nuclear magnetic resonance (NMR) time scale due to its high energy barrier, two sets of signals can be expected for the corresponding two rotomers **A** and **B** (Scheme 2) in its NMR spectrum. Despite the restricted rotation, two separate spectra were not obtained for the compounds **11–20** pertaining to the two rotomers **A** and **B**. Instead, we have only the average NMR spectra for these compounds at room temperature. Hence, it can be assumed that these two rotomers undergo interconversion at a faster rate than the NMR time scale.



Scheme 1



Scheme 2



Compound	R_1	R_2	R
1, 11	H	H	H
2, 12	CH_3	H	H
3, 13	$CH(CH_3)_2$	H	H
4, 14	CH_3	H	Cl
5, 15	CH_2CH_3	H	Cl
6, 16	CH_3	CH_3	Cl
7, 17	CH_3	H	OCH_3
8, 18	CH_3	CH_3	OCH_3
9, 19	CH_3	H	CH_3
10, 20	CH_3	CH_3	CH_3

Scheme 3

The schematic representation and analytical data for the synthesised compounds **11–20** are furnished in Scheme 3 and Table 1, respectively. Condensation of respective ketones, aldehyde, and ammonium acetate in the ratio of 1:2:1 respectively afforded the formation of 2,6-diarylpiperidin-4-ones **1–10**. N-Chloroacetylation of the piperidin-4-ones was achieved by using triethylamine as catalyst.

Table 1 Analytical data of compounds **11–20**

Entry	Yield (%)	Melting point (°C)	Molecular formula	Elemental analysis (observed)*		
				C (%)	H (%)	N (%)
11	84	120–122	$C_{19}H_{18}NO_2Cl$	69.57	5.53	4.28
12	94	131	$C_{20}H_{20}NO_2Cl$	70.28	5.91	4.10
13	89	102	$C_{22}H_{24}NO_2Cl$	71.40	6.52	3.78
14	82	159	$C_{20}H_{18}NO_2\ Cl_3$	58.45	4.41	3.40
15	80	Semisolid	$C_{21}H_{20}NO_2Cl_3$	59.35	4.75	3.29
16	84	128	$C_{21}H_{20}NO_2Cl_3$	59.31	4.74	3.29
17	83	108–110	$C_{22}H_{24}NO_4Cl$	65.73	6.03	3.48
18	80	162–164	$C_{23}H_{26}NO_4Cl$	66.40	6.31	3.36
19	81	118–120	$C_{22}H_{24}NO_2Cl$	71.43	6.55	3.78
20	88	158–160	$C_{23}H_{26}NO_2Cl$	71.91	6.82	3.65

* The observed microanalysis values for C, H, and N were within ± 0.4% of the theoretical values

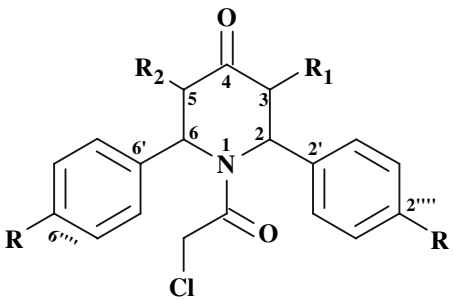


Fig. 1 Target compound numbering

To get a clear idea about the structure–activity relationship results for the synthesised compounds, numberings of the target compound are done as shown in Fig. 1.

Pharmacology

In vitro antibacterial and antifungal activity

The *in vitro* antimicrobial activities of the compounds were tested in Sabouraud's dextrose broth (SDB, Hi-media, Mumbai) for fungi and nutrient broth (NB, Hi-media, Mumbai) for bacteria by the twofold serial dilution method (Dhar et al., 1968). The test compounds were dissolved in dimethylsulphoxide (DMSO) to obtain 1 mg/mL stock solutions. Seeded broth (broth containing microbial spores) was prepared in NB from 24-hour-old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 24-hour- to 7-day-old Sabouraud's agar slant cultures were suspended in SDB. The colony-forming units (cfu) of the seeded broth were determined by the plating technique and adjusted in the range

10^4–10^5 cfu/mL. The final inoculum size was 10^6 cfu/mL for the antibacterial assay and $1.1–1.5 \times 10^2$ cfu/mL for the antifungal assay. Testing was performed at pH 7.4 ± 0.2. Exactly 0.2 mL of the solution of test compound was added to 1.8 mL of seeded broth to form the first dilution. One mL of this was diluted with a further 1 mL of the seeded broth to give the second dilution and so on until 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 hours (for bacteria) and 72–96 hours (for fungi) of incubation. Streptomycin and ciprofloxacin were used as standards for bacterial study while amphotericin B was used as a standard for the fungal study.

Structure–activity relationship results

Antibacterial activity

All the synthesised novel N-chloroacetyl-2,6-diarylpiperidin-4-ones (**11–20**) were assessed to elicit their antibacterial activity *in vitro* against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*. Against *Mycobacterium tuberculosis*, streptomycin was the first antibiotic used and also found importance for years in monotherapy regimens, leading to the emergence of resistance. Apart from its other antibiotic properties, it is one of the most widely used agents for dermatological reasons (Le Gall et al., 2005; Ruiz et al., 2002). Therefore, the antibacterial potency of the synthesised compounds was compared with broad-spectrum antibiotics, namely streptomycin and ciprofloxacin, and their minimum inhibitory concentration values are summarised in Table 2.

A close survey of the MIC values indicates that all the compounds exhibited a varied range (12.5–200 μg/mL) of antibacterial activity against all the tested bacterial strains except **11,** which did not show activity against *B. subtilis* and *E. coli* even at a maximum concentration of 200 μg/mL. The compounds without any substituent at the *para* position of the phenyl groups at the C-2 and C-6 positions of the heterocyclic ring (**11–20**) showed antibacterial activity in the range of 50–200 μg/mL.

Compound **11**, which was inactive against *B. subtilis* and *E. coli*, became active with the introduction of a methyl (compound **12**) or isopropyl (compound **13**) group at the C-3 position and showed MICs, respectively, of 100 and 200 μg/mL. Likewise, against *S. aureus*, this substitution improved the activity by about 50% compared to **11**. But, against *P. aeruginosa*, 50% decreased activity was noted in **12** and **13** compared to the unsubstituted one (compound **11**).

Replacement of phenyl groups present at the C-2 and C-6 positions of compound **12** by *p*-chlorophenyl groups (compound **14**) registered a two- to fourfold increase in activity against all the tested organisms but *S. typhi*, for which a onefold decreased activity was noted while the same activity was retained towards *B.*

Table 2 *In vitro* antibacterial activity of compounds 11–20

Entry	Minimum inhibitory concentration (MIC) in μg/mL				
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*S. typhi*
11	200	-	-	100	50
12	100	100	100	200	50
13	100	200	200	200	100
14	50	100	25	12.5	100
15	25	25	50	50	12.5
16	12.5	100	50	100	25
17	25	200	100	50	100
18	50	50	100	100	25
19	100	12.5	25	100	50
20	200	100	50	200	100
Streptomycin	25	12.5	50	50	25
Ciprofloxacin	25	50	25	12.5	50

-, no inhibition even at a higher concentration of 200 μg/mL

subtilis. This phenyl group modification (i.e., in compound **14)** was found to be remarkable against *P. aeruginosa* as it showed a fourfold increased activity while against *E. coli* the activity was enhanced by only twofold compared to **12**.

Moreover, the introduction of an ethyl group in place of methyl function in **14** (compound **15**) exhibited appreciable inhibition potency towards the tested bacteria at a minimum concentration between 12.5 and 50 μg/mL. A well-pronounced effect (i.e., two- to threefold increased activity) was noted against *B. subtilis* and *S. typhi*. However, owing to the introduction of another methyl group at the C-5 position in **14** (compound **16**), twofold improvement in the antibacterial potency was found against *S. aureus* and *S. typhi*, while against the rest of the organisms, an appreciable decrease in activity was noted compared to **14**.

Substitution of the *p*-methoxyphenyl group in place of *p*-chlorophenyl function of **14** and **16** (compounds **17** and **18**) suppressed the activity against all the tested organisms except *S. aureus* and *B. subtilis* against which compounds **17** and **18**, respectively registered 50% improved activity. However, these compounds (**17** and **18**) exhibited greater activity than the compounds **11–13** in which the N-chloroacetamide is flanked by a phenyl group only (having no substitution at the *para* position).

Introduction of *p*-methylphenyl groups instead of *p*-methoxyphenyl moieties in **17** and **18** (compounds **19** and **20**) exhibited an elevated antibacterial potency against *B. subtilis* and *E. coli* while against the rest of the strains a decreased activity was observed. Besides, the activity of **19** against *B. subtilis*, *E.coli* and *S. typhi* respectively exerted four-, two- and onefold improved activity compared to **17** whereas against *E. coli*, compound **20** produced a 50% increased activity compared to **18**. Moreover, the observed potencies of **19** and **20** were also found to be better than **11–13**.

Table 3 *In vitro* antifungal activity of compounds **11–20**

Entry	Minimum inhibitory concentration (MIC) in μg/mL				
	C. *neoformans*	*C. albicans*	*Rhizopus sp.*	*A. niger*	*A. flavus*
11	-	200	-	-	100
12	100	200	100	200	200
13	200	50	100	100	-
14	100	100	25	50	25
15	50	100	50	12.5	25
16	50	200	100	50	100
17	100	100	25	50	50
18	100	100	100	25	50
19	25	50	50	12.5	12.5
20	50	50	25	100	50
Amphotericin B	25	25	25	50	50

-, no inhibition even at a higher concentration of 200 μg/mL

Antifungal activities

The *in vitro* antifungal activities of the novel compounds **11–20** were examined against the five fungal strains *Cryptococcus neoformans*, *Candida albicans*, *Rhizopus* sp., *Aspergillus niger*, and *Aspergillus flavus*. Here, amphotericin B was used as standard drug. The MIC values of the tested compounds and the standard are illustrated in Table 3.

The compounds **11–13** without any substituents at the *para* position of phenyl groups present at the carbon atoms adjacent to the heterocyclic nitrogen exhibited antifungal activity in the region 50–200 μg/mL. However, compound **11** against *C. neoformans*, *Rhizopus* sp., and *A. niger* and **13** against *A. flavus* did not show antifungal activity even at a maximum concentration of 200 μg/mL. Moreover, methyl group incorporation at the C-3 position in **11** (compound **10**) improved the activity considerably against *C. neoformans*, *Rhizopus* sp., and *A. niger* and recorded MIC values in the range 100–200 μg/mL for the respective organisms. Likewise, 50% improved activity was noted in compound **12** against *A. flavus* compared to **11**.

Replacement of the methyl group in **12** by an isopropyl group (compound **13**) registered two- and onefold improved activites against *C. albicans* and *A. niger*, respectively, while against *Rhizopus* sp. the activity was retained as such. However, this modification decreased the activity against *C. neoformans* by 50% and became inactive against *A. flavus*.

If the heterocyclic nitrogen of compound **12** was flanked by *p*-chlorophenyl groups (compound **14**) instead of phenyl groups, a marked improvement in activity was noted. The increased activity was significant against *Rhizopus* sp. and *A. niger* (i.e., twofold increased activity) while against *C. albicans* and *A. flavus*, the activity was improved by 50%. However, substitution of the ethyl group in place of methyl

function in compound **14** (compound **15**) registered further improvement in inhibitory activity against *C. neoformans* and *A. niger* while against *C. albicans* and *A. flavus* the activity was retained. Introduction of another methyl group at C-5 position in **14** resulted in a notable decrease in activity against all the tested organisms except against *A. niger*, which retained the activity at the same MIC.

Due to the introduction of a methoxy group in place of the chloro function present at the *para* position of the phenyl groups (i.e., compound **17**), there is no improvement in antifungal potency against the tested organisms except against *A. flavus* for which a 50% decrease in activity was noted. Even after the incorporation of another methyl group at the C-5 position in **17** (compound **18**), there was no indication of enhancement of activity against *C. neoformans*, *C. albicans*, and *A. flavus* whereas against *A. niger*, the activity was improved by 50%. Furthermore, against *Rhizopus* sp. a twofold decreased activity was achieved.

Replacement of *p*-methoxyphenyl groups in **17** and **18** (compounds **19** and **20**) had a marked impact over the antifungal activity against the panel of organisms under study. Compound **19** showed a twofold increased activity against *C. neoformans* and *A. flavus* while against the rest of the strains a 50% improved activity was noted. However, introduction of another methyl group at the C-5 position in **19** (compound **20**) was found to decrease the activity against all the organisms except *C. albicans* for which the same activity was retained at the same MIC.

However, it is very clear from Table 3 that compounds **17** and **20** registered better activity than compounds **11–13,** which bear phenyl groups at the C-2 and C-6 positions of heterocyclic ring (i.e., without any substituents at the *para* position).

Conclusion

A comparison of potency of the compounds **11–20** is given in the form of Figs. 2–4 by employing the following the equation.

$$\text{Potency}\ (\%) = \frac{\text{MIC}\ (\mu g/ml)\ of\ reference\ compound}{\text{MIC}\ (\mu g/ml)\ of\ \text{tested}\ compound} \times\ 100$$

A close survey of the *in vitro* antibacterial and antifungal activity profile of the new N-chloroacetyl-2,6-diarylpiperidin-4-ones against the tested bacterial and fungal organisms gives a clear picture about the structure–activity correlations among compounds **11–20** under study. Compounds **14–20** with chloro, methoxy, or methyl functions at the *para* positions of the aryl groups present at the C-2 and C-6 positions of the piperidone moiety along with and without alkyl substituent at the C-3 and C-5 positions exerted a varied range of biological activities, while the activity was not significant for compounds **11–13** without any substituent at the *para* position of phenyl groups.

Among compounds **14–20**, **15–17** against *S. aureus*, **15** and **19** against *B. subtilis*, **14** and **19** against *E. coli*, **14** against *P. aeruginosa*, and **15**, **16**, and **18** against *S. typhi* were shown to be significant in their antibacterial potency at 12.5 and 25 μg/mL. Furthermore, their activity was also on a par with the standard drugs used and

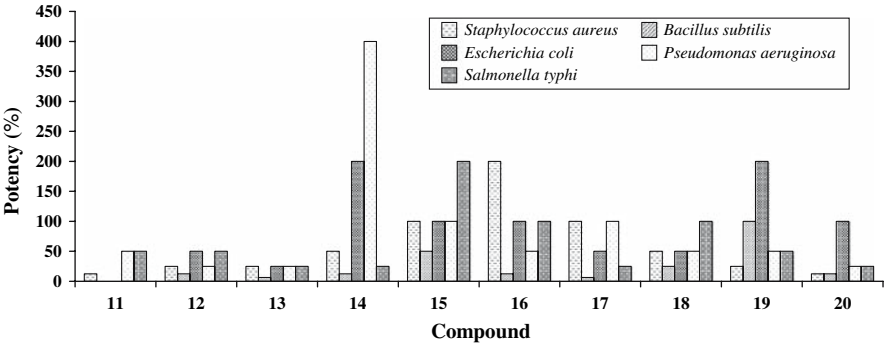


Fig. 2 Comparison of potency of compounds **11–20** with streptomycin (as standard) against bacterial strains from serial dilution method

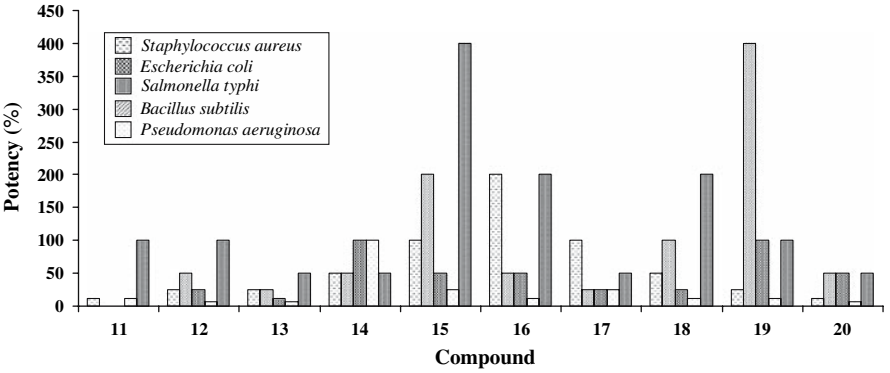


Fig. 3 Comparison of potency of compounds **11–20** with ciprofloxacin (as standard) against bacterial strains from serial dilution method

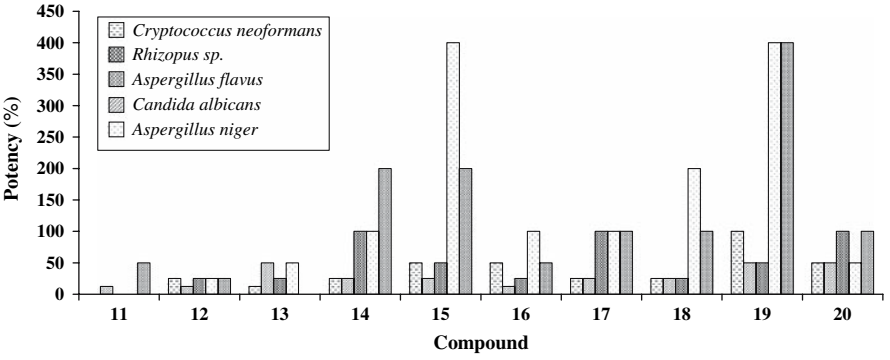


Fig. 4 Comparison of potency of compounds **11–20** with streptomycin B (as standard) against fungal strains from serial dilution method

for some compounds was even higher than the activity of the standard drugs. Though most of the compounds studied exhibited moderate to significant antibacterial activity, compound **15** (with an ethyl group at C-3 and a *p*-chlorophenyl group at the C-2 and C-6 positions) was found to exert a pronounced effect against all the tested organisms.

Similarly, against the tested fungal strains, compound **19** against *C. neoformans*, **14** and **17** against *Rhizopus* sp., **15**, **18**, and **19** against *A. niger*, and **14**, **15**, and **19** against *A. flavus* recorded enhanced activity at 12.5 and 25 μg/mL. However, the activity of compound **19** against all the tested organisms was found to be superior to the other compounds and with an even higher activity than the standard against *A. niger* and *A. flavus*.

From this study, it is clear that presence of an alkyl group at the C-3 or C-3/C-5 positions of the piperidone ring is considered to be advantageous as well as the presence of either chloro or methoxy functions at the *para* positions of phenyl groups present at C-2 and C-6 positions for elevated antimicrobial activity. Furthermore, the observed marked antibacterial and antifungal activities may be considered as key steps for the building of novel chemical entities with comparable pharmacological profiles to that of the standard drugs after considering results from toxicology studies.

Experimental

Thin-layer chromatography (TLC) was carried out to monitor the course of the reaction and the purity of the product. Melting points were recorded in open capillaries and are uncorrected. Infrared (IR) spectra were recorded in an AVATAR-330 Fourier-transform (FT)-IR spectrophotometer (Thermo Nicolet) and only noteworthy absorption levels (reciprocal centimeters) are listed. ^{1}H-NMR spectra were recorded at 400 MHz on a BRUKER AMX 400 MHz spectrometer using $CDCl_3$ as the solvent and trimethyl silane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded at 100 MHz on a BRUKER AMX 400 MHz spectrometer in $CDCl_3$. Mass spectra were recorded on a Jeol SX-102 (EI) and microanalyses were performed on an Heraeus Carlo Erba 1108 CHN analyser. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. All solvents were distilled prior to use.

By employing the literature precedent of Noller and Baliah (1948), all the parent 2,6-diarylpiperidin-4-ones were prepared by the condensation of appropriate ketones, aldehydes, and ammonium acetate in a 1:2:1 ratio using ethanol as a solvent.

Synthesis of N-chloroacetyl-2,6-diphenylpiperidin-4-one (11)

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 dropwise for about half an hour. Stirring was continued with mild heating (30–35°C) using a magnetic stirrer. After the completion of the 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 sulfate. This upon evaporation afforded the compound **11** in good yield.

IR (KBr) (cm^{-1}): 3059, 3029, 2953, 2912 (C–H stretching), 1723 (C=O stretching), 1633 (N–C=O stretching), 1495, 1449, 1391, 1358, 1241, 1146, 1083, 1023, 947, 844, 781, 701, 596, 544, 482, 427. **^{1}H NMR (δ ppm):** 3.08 (dd, $^2J_{3a,3e}$= $^2J_{5a,5e}$ =17.44 Hz; $^3J_{2a,3a}$= $^3J_{5a,6a}$ = 6.24 Hz, 2H, H_{3a} and H_{5a}), 2.78 (dd, $^2J_{3a,3e}$= $^2J_{5a,5e}$ = 17.64 Hz; $^3J_{2a,3e}$ = $^3J_{5e,6a}$ = 5.52 Hz, 2H, H_{3e} and H_{5e}), 3.93 (s, 2H, CH_2Cl), 5.88 (bs, 2H, H_2 and H_6), 7.19–7.30 (m, 10H, aryl protons). **^{13}C NMR (δ ppm):** 55.360 (C-2 and C-6), 44.062 (C-3 and C-5), 206.331 (C=O at C-4), 168.656 (N–C=O), 140.796 (C-2′ and C-6′ *ipso*), 129.110, 128.046, 126.569 (other aryl carbons), 42.676 (CH_2Cl).

The compounds **12**–**20** were prepared similarly.

N-Chloroacetyl-3-methyl-2,6-diphenylpiperidin-4-one (12)

IR (KBr) (cm^{-1}): 3077, 3057, 3028, 2971, 2937, 2886 (C–H stretching), 1721 (C=O stretching), 1651 (N–C=O stretching), 1495, 1453, 1386, 1323, 1253, 1199, 1116, 1079, 1027, 931, 855, 784, 744, 704, 607, 529, 405. **Mass (*m/z*):** 342 $(M)^+$ (100%, molecular formula: $C_{20}H_{20}NO_2Cl$), 316, 301, 288, 249, 238, 224, 182, 149, 131, 119, 105, 91, 77. **^{1}H NMR (δ ppm):** 3.17 (dd, $^2J_{5a,5e}$ = 18.22 Hz; $^3J_{5a,6a}$ = 6.10 Hz, 1H, H_{5a}), 2.83 (dd, $^2J_{5a,5e}$ = 18.22 Hz; $^3J_{5e,6a}$ = 5.91 Hz, 1H, H_{5e}), 3.06 (t, 1H, H_{3a}), 3.88, 3.93 (two d, 2H, CH_2Cl), 5.39 (bs, 1H, H_2), 5.92 (bs, 1H, H_6), 7.11–7.36 (m, 10H, aryl protons), 1.06 (d, J = 6.62 Hz, 3H, CH_3 at C-3). **^{13}C NMR (δ ppm):** 61.846 (C-2), 54.730 (C-6), 46.141 (C-3), 42.975 (C-5), 208.610 (C=O at C-4), 168.942 (N–C=O), 140.920 (C-6′ *ipso*), 140.653 (C-2′ *ipso*), 129.208, 128.932, 128.133, 127.528, 126.662 (other aryl carbons), 42.730 (CH_2Cl), 13.628 (CH_3 at C-3).

N-Chloroacetyl-3-isopropyl-2,6-diphenylpiperidin-4-one (13)

IR (KBr) (cm^{-1}): 3082, 3044, 3028, 2984, 2962, 2924, 2897, 2869 (C–H stretching), 1718 (C=O stretching), 1648 (N–C=O stretching), 1494, 1454, 1383, 1263, 1216, 1137, 1105, 1031, 993, 931, 764, 701, 627, 518. **^{1}H NMR (δ ppm):** 2.82 [dd, J =18.51 Hz; J = 8.91 Hz, 2H(merged), H_{5a} and H_{3a}], 2.72 (dd, $^2J_{5a,5e}$ =17.03 Hz; $^3J_{5e,6a}$ = 6.02 Hz, 1H, H_{5e}), 3.91, 4.04 (two d, 2H, CH_2Cl), 6.45 (bs, 1H, H_2), 5.43 (bs, 1H, H_6), 6.98–7.30 (m, 10H, aryl protons), 2.08–2.16 (m, 1H, H_7 at C-3), 1.13 (d, J = 6.53 Hz, 3H, CH_3), 1.07 (d, J = 6.68 Hz, 3H, CH_3). **^{13}C NMR (δ ppm):** 57.772 (C-2), 57.189 (C-6), 54.942 (C-3), 44.639 (C-5), 208.374 (C=O at C-4), 168.635 (N-C=O), 140.888 (C-2′ and C-6′ *ipso*), 128.988, 128.496, 128.281, 127.775, 127.549, 127.448, 125.894 (other aryl carbons), 42.406 (CH_2Cl), 28.562 (C-7), 21.282 (CH_3), 20.402 (CH_3).

N-Chloroacetyl-3-methyl-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one (14)

IR (KBr) (cm^{-1}): 3071, 3044, 2981, 2929, 2869 (C–H stretching); 1723 (C=O stretching); 1658 (N–C=O stretching); 1492, 1433, 1401, 1342, 1302, 1263, 1130, 1093, 1013, 942, 834, 735, 670, 585, 543, 499, 448; **^{1}H NMR (δ,ppm):** 3.11 (dd, $^2J_{5a,5e}$ = 18.13 Hz; $^3J_{5a,6a}$ = 5.46 Hz, 1H, H_{5a}); 2.87 (dd, $^2J_{5a,5e}$ = 18.17 Hz; $^3J_{5e,6a}$ = 6.02 Hz, 1H, H_{5e}); 2.96 (t, 1H, H_{3a}); 3.94 (t, 2H, CH_2Cl); 5.35 (bs, 1H, H_2); 5.86 (bs, 1H, H_6); 7.03, 7.15 (two d, 4H, aryl protons *meta* to chlorine); 7.25, 7.32 (two d, 4H, aryl protons *ortho* to chlorine); 1.06 (d, J = 6.63 Hz, 3H, CH_3 at C-3); **^{13}C NMR (δ, ppm):** 61.256 (C-2); 54.343 (C-6); 46.117 (C-3); 42.477 (C-5); 207.687 (C=O at C-4); 168.711 (N–C=O); 138.996 (C-6′ *ipso*); 138.818 (C-2′ *ipso*); 134.310 (C-6′′′′ *ipso*); 134.186 (C-2′′′′ *ipso*); 129.403, 129.114, 128.892, 128.047 (other aryl carbons); 42.330 (CH_2Cl); 13.753 (CH_3 at C-3).

N-Chloroacetyl-3-ethyl-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one (15)

IR (KBr) (cm^{-1}): 3094, 3066, 3035, 2967, 2934, 2876 (C–H stretching); 1720 (C=O stretching); 1655 (N–C=O stretching); 1595, 1492, 1407, 1341, 1254, 1220, 1092, 1143, 1013, 963, 827, 680, 548,498; **^{1}H NMR (δ, ppm):** 2.65–2.88 (m, 3H, H_{5a}, H_{5e} and H_{3a}); 3.96, 4.0 (two d, 2H, CH_2Cl); 5.90 (bs, 1H, H_2); 5.50 (bs, 1H, H_6); 6.89–7.1 (m, 8H, aryl protons); 1.59 (m, 2H, CH_2CH_3 at C-3); 0.89 (t, 3H, CH_2CH_3 at C-3); **^{13}C NMR (δ, ppm):** 56.693 (C-2); 55.871 (C-6); 52.585 (C-3); 43.492 (C-5); 208.047 (C=O at C-4); 168.851 (N–C=O); 139.024 (C-6′ *ipso*); 138.862 (C-2′ *ipso*); 134.185 (C-6′′′′ *ipso*); 133.980 (C-2′′′′ *ipso*); 129.353, 128.974, 128.911, 127.696 (other aryl carbons); 42.183 (CH_2Cl); 23.382 (CH_2CH_3 at C-3); 11.728 (CH_2CH_3 at C-3).

N-Chloroacetyl-3,5-dimethyl-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one (16)

IR (KBr) (cm^{-1}): 3010, 2983, 2938, 2872 (C–H stretching); 1717 (C=O stretching); 1652 (N–C=O stretching); 1492, 1386, 1335, 1258, 1206, 1091, 1014, 836, 788, 652; **^{1}H NMR (δ, ppm):** 3.03–3.09 (m, 2H, H_{3a} and H_{5a}); 3.89 (s, 2H, CH_2Cl); 5.42 (bs, 2H, H_2 and H_6); 7.12 (d, 4H, aryl protons *meta* to chlorine); 7.33 (d, 4H, aryl protons *ortho* to chlorine); 1.09 (d, J = 6.91 Hz, 6H, CH_3 at C-3 and C-5); **^{13}C NMR (δ, ppm):** 60.731 (C-2 and C-6); 45.509 (C-3 and C-5); 209.762 (C=O at C-4); 169.301 (N–C=O); 139.204 (C-2′ and C-6′ *ipso*); 134.348 (C-2′′′′ and C-6′′′′ *ipso*); 129.321, 128.812 (other aryl carbons); 42.381 (CH_2Cl); 14.137 (CH_3 at C-3 and C-5).

N-Chloroacetyl-3-methyl-2,6-*bis*(*p*-methoxyphenyl)piperidin-4-one (17)

IR (KBr) (cm^{-1}): 3060, 3006, 2968, 2831 (C–H stretching); 1714 (C=O stretching); 1646 (N–C=O stretching); 1610, 1512, 1463, 1389, 1306, 1252, 1179, 1116, 1029, 930, 870, 848, 787, 662, 553, 411; **^{1}H NMR (δ, ppm):** 3.15 (dd, $^2J_{5a,5e}$ = 18.32 Hz;

$^{3}J_{5a,6a}$ = 5.59 Hz, 1H, H_{5a}); 2.80 (dd, $^{2}J_{5a,5e}$ = 18.38 Hz; $^{3}J_{5e,6a}$ = 6.01 Hz, 1H, H_{5e}); 3.03 (t, 1H, H_{3a}); 3.89, 3.94 (two d, 2H, CH_2Cl); 5.30 (bs,1H, H_2); 5.86 (bs, 1H, H_6); 6.79, 6.86 (two d, 4H, aryl protons *ortho* to methoxy group); 7.01, 7.15 (two d, 4H, aryl protons *meta* to methoxy group); 3.81, 3.78 (two s, 6H, OCH_3 at C-2′′′′ and C-6′′′′), 1.03 (d, J = 5.17 Hz, 3H, CH_3 at C-3); **^{13}C NMR (δ, ppm):** 61.443 (C-2); 54.197 (C-6); 46.351 (C-3); 43.058 (C-5); 208.771(C=O at C-4); 168.755 (N–C=O); 159.351 (C-6′′′′ *ipso*); 159.277 (C-2′′′′ *ipso*); 132.983 (C-6′ *ipso*); 132.776 (C-2′ *ipso*); 128.731, 127.939, 114.510, 114.248 (other aryl carbons); 55.325, 55.274 (OCH_3 at C-2′′′′ and C-6′′′′); 42.672 (CH_2Cl); 13.588 (CH_3 at C-3).

N-Chloroacetyl-3,5-dimethyl-2,6-*bis*(*p*-methoxyphenyl)piperidin-4-one (18)

IR (KBr) (cm^{-1}): 3021, 3015, 3000, 2973, 2962, 2935, 2902, 2836 (C–H stretching); 1713 (C=O stretching); 1658 (N–C=O stretching); 1609, 1513, 1458, 1388, 1289, 1252, 1180, 1110, 1029, 974, 886, 838, 809, 722, 586, 542; **^{1}H NMR (δ, ppm):** 3.12 (t, 2H, H_{3a} and H_{5a}); 3.90 (s, 2H, CH_2Cl); 5.39 (bs, 2H, H_2 and H_6); 6.85 (d, 4H, aryl protons *ortho* to methoxy group); 7.09 (d, 4H, aryl protons *meta* to methoxy group); 3.81 (s, 6H, OCH_3 at C-2′′′′ and C-6′′′′); 1.08 (d, J = 6.66 Hz, 6H, CH_3 at C-3 and C-5); **^{13}C NMR (δ, ppm):** 60.679 (C-2 and C-6); 45.638 (C-3 and C-5); 210.813 (C=O at C-4); 169.174 (N–C=O); 159.241 (C-2′′′′ and C-6′′′′ *ipso*); 132.920 (C-2′ and C-6′ *ipso*); 128.594, 114.238 (other aryl carbons); 42.585 (CH_2Cl); 55.198 (OCH_3 at C-2′′′′ and C-6′′′′), 14.030 (CH_3 at C-3 and C-5)

N-Chloroacetyl-3-methyl-2,6-*bis*(*p*-methylphenyl)piperidin-4-one (19)

IR (KBr) (cm^{-1}): 3066, 3000, 2967, 2934, 2835 (C–H stretching); 1713 (C=O stretching); 1646 (N–C=O stretching); 1611, 1512, 1461, 1388, 1305, 1252, 1179, 1117, 1030, 929, 837, 785, 549; **^{1}H NMR (δ, ppm):** 3.15 (dd, $^{2}J_{5a,5e}$ = 18.03 Hz; $^{3}J_{5a,6a}$ = 5.59 Hz, 1H, H_{5a}); 2.79 (dd, $^{2}J_{5a,5e}$ = 18.25 Hz; $^{3}J_{5e,6a}$ = 5.62 Hz, 1H, H_{5e}); 3.03 (t, 1H, H_{3a}); 3.85–3.96 (m, 2H, CH_2Cl); 5.34 (bs,1H, H_2); 5.87 (bs, 1H, H_6); 7.00–7.35 (m, 8H, aryl protons); 2.34, 2.31 (two s, 6H, CH_3 at C-2′′′′ and C-6′′′′), 1.03 (d, 3H, CH_3 at C-3); **^{13}C NMR (δ, ppm):** 61.611 (C-2); 54.449 (C-6); 46.099 (C-3); 43.027 (C-5); 208.595 (C=O at C-4); 168.743 (N–C=O); 137.708, 137.981 and 137.488 (C-2′′′′, C-6′′′′ and C-2′, C-6′ *ipso* carbons); 129.654, 129.400, 127.364, 126.509 (other aryl carbons); 20.845 (CH_3 at C-2′′′′ and C-6′′′′); 42.634 (CH_2Cl); 13.462 (CH_3 at C-3).

N-Chloroacetyl-3,5-dimethyl-2,6-*bis*(*p*-methylphenyl)piperidin-4-one (20)

IR (KBr) (cm^{-1}): 3028, 2983, 2941, 2875 (C–H stretching), 1718 (C=O stretching), 1649 (C=O stretching), 1514, 1454, 1383, 1256, 1185, 1120, 1026, 972, 926, 881, 823, 793, 719, 658, 585, 521, 423. **^{1}H NMR (δ ppm):** 3.12 (t, 2H, H_{3a} and H_{5a}), 3.89 (s, 2H, -CH_2Cl), 5.41 (broad s, 2H, H_2 and H_6 benzylic protons), 7.06 (d, 4H,

aryl protons *ortho* to methoxy group), 7.3 (d, 4H, aryl protons *meta* to methoxy group), 2.33 (s, 6H, at C-2′′′′ and C-6′′′′), 1.07 (d, J= 6.47 Hz, 6H, CH_3 at C-3 and C-5). **^{13}C NMR (δ ppm):** 60.947 (C-2 and C-6), 45.507 (C-3 and C-5), 210.851 (C=O at C-4), 169.244 (N–C=O), 137.768 (C-2′ and C-6′ *ipso*), 137.919 (C-2′′′′ and C-6′′′′ *ipso*), 127.345, 129.505 (aryl carbons), 42.652 (–CH_2–Cl), 20.881 (CH_3 at C-2′′′′ and C-6′′′′), 14.035 (CH_3 at C-3 and C-5).

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