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Unexpected formation of 3-chloro-1-hydroxy-2,6-diarylpiperidin-4-ones: Synthesis, antibacterial and antifungal activities

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Abstract

New 3-chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** were synthesized, characterized by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (^{1}H & ^{13}C) spectroscopic data and evaluated for their *in vitro* antibacterial and antifungal activities. All the newly synthesized compounds exerted a wide range of antibacterial activities against the entire tested gram-positive and gram-negative bacterial strains except *Escherichia coli.* Compounds **21 and 22** exerted strong antifungal activities against *Aspergillus flavus, mucor* and *Microsporum gypsuem.* In addition, compound **20** was more potent against *Rhizopus*.

Keywords: *3-chloro-1-hydroxy-2, 6-diarylpiperidin-4-ones,* m-*chloroperbenzoic acid, synthesis, antibacterial activity, antifungal activity*

Introduction

Now-a-days, bioactive heterocyclic ring systems having 2,6-diaryl-piperidine-4-one nucleus with different substituents at 3- and 5-positions of the ring have aroused great interest due to their wide variety of biological properties such as antiviral, antitumour [1,2], central nervous system [3], local anesthetic [4], anticancer [5], and antimicrobial activity [6] and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists [7], analgesic and anti-hypertensive agents [8]. But, only very few reports [9,10] are available with chloro substitution at position 3.

In addition, hydroxylamines have been reported as anti-bacterial, antifungal and antileukemic agents. N-Hydroxy urea was one of the effective antineoplasmic agents [11] and ciclopirox has broad-spectrum antifungal activity [12]. N-hydroxy pyrrolizidine alkaloid intermediate is used for the synthesis of *dl*-retronecine [13], the most widely occurring of the necine bases exhibits marked hepatoxic and antitumour properties.

Due to an increase in the number of immuno-compromised hosts, [14], over the past decades, the incidence of systemic microbial infections has been increasing dramatically. The increasing incidence of bacterial resistance to a large number of antibacterial agents such as glycopeptides (vancomycin, inhibition cell walls synthesis), sulfonamide drugs (inhibitors of tetrahydrofolate synthesis), β-lactam antibiotics (penicillins and cephalosporins), nitroimidazoles and quinolones (DNA inhibitors), tetracyclins, chloramphenicol and macrolides (erythromycin, inhibiting protein synthesis) is becoming a major concern [15]. For the past several years, vancomycin has been considered the last line of defense agent against Gram-positive infections and no alternative drugs for treating diseases that have become resistant to vancomycin [16]. Patients undergoing organ transplants, anticancer chemotherapy or long treatment with antimicrobial agents and patients with AIDS are immuno suppressed

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and very susceptible to life threatening systemic fungal infections like *Candidiasis*, *Cryptococcosis* and *Aspergillosis*. Antifungal azoles, fluconazole and itraconazole which are strong inhibitors of lanosterol 14α-demethylase (cytochrome *P*45014DM) and orally active have been widely used in antifungal chemotherapy. Reports are available on the developments of resistance to currently available antifungal azoles in *Candida spp*., as well as clinical failures in the treatment of fungal infections [17–20]. Furthermore, most of the present antifungal drugs are not effective against invasive *Aspergillosis* and the only drug of choice in such patients is the injectable amphotericin B. These observations places new emphasis on the need of as well as search for alternative new and more effective antimicrobial agents with a broad spectrum.

In the course of broad programme in developing biologically active molecules, we have recently reported the synthesis of 2,6-diarylpiperidin-4-one derivatives and evaluated their biological importance [21–23]. Therefore it was planned to synthesize a system which combines these two biologically active components (3-chloro-piperidin-4-one and hydroxyl amine) together to give a combined structure like the title compound. Inorder to extend our knowledge in structure-activity relationship, all the newly synthesized compounds are tested for their *in vitro* antibacterial and antifungal activities and the influence of some structural variations by varying the substituents at the phenyl ring in the synthesized compounds towards their biological activities is evaluated.

Experimental

Chemistry

TLC was performed to assess the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar–330 FT-IR spectrophotometer and note worthy absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as solvent. The ESI + ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer.

By adopting the literature precedent [9], 3-chloro-2,6-diarylpiperidin-4-ones were prepared **13–17**.

*Synthesis of 3-chloro-1-hydroxy-2,6-diphenylpiperidin-4-one **18:*** A solution of 3-chloro-2,6-diphenylpiperidin-4-one **13** (0.001 mol) and *m*-chloroperbenzoic acid (0.001 mol) in 50 mL of dichloromethane was stirred for 1 h at (0–5)°C and kept aside for overnight at 20°C. Then the mixture was extracted with dichloromethane and washed with 10% sodium bicarbonate solution. The dichloromethane layer was dried over anhydrous sodium sulphate and distilled off under reduced pressure. Purifications by silica gel column chromatography with ethyl acetate: petroleum ether (bp60–80) 2:8 mixture yielded the product 3-chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18**. IR (KBr) (cm^{-1}): 3492, 3033, 2922, 2852, 1729, 753, 698; ^1H NMR (δ ppm): 2.80–2.88 (m, 1H, H_{5a}); 2.95–3.01 (m, 1H, H_{5e}), 3.99 (d, 1H, H_{2a}, J = 11.3), 4.07–4.36 (m, 1H, H_{6a}), 4.55 (s, 1H, H_1), 4.72 (d, 1H, H_{3a}, J = 11.0), 7.26–7.51 (m, 10H, H_{arom}); ^{13}C NMR (δ ppm): 46.7 C-5, 65.7 C-3, 67.6 C-6, 70.1 C-2, 128.1–128.9 –C_{arom}, 139.0, 140.63 *ipso*-C, 196.7 C-4.

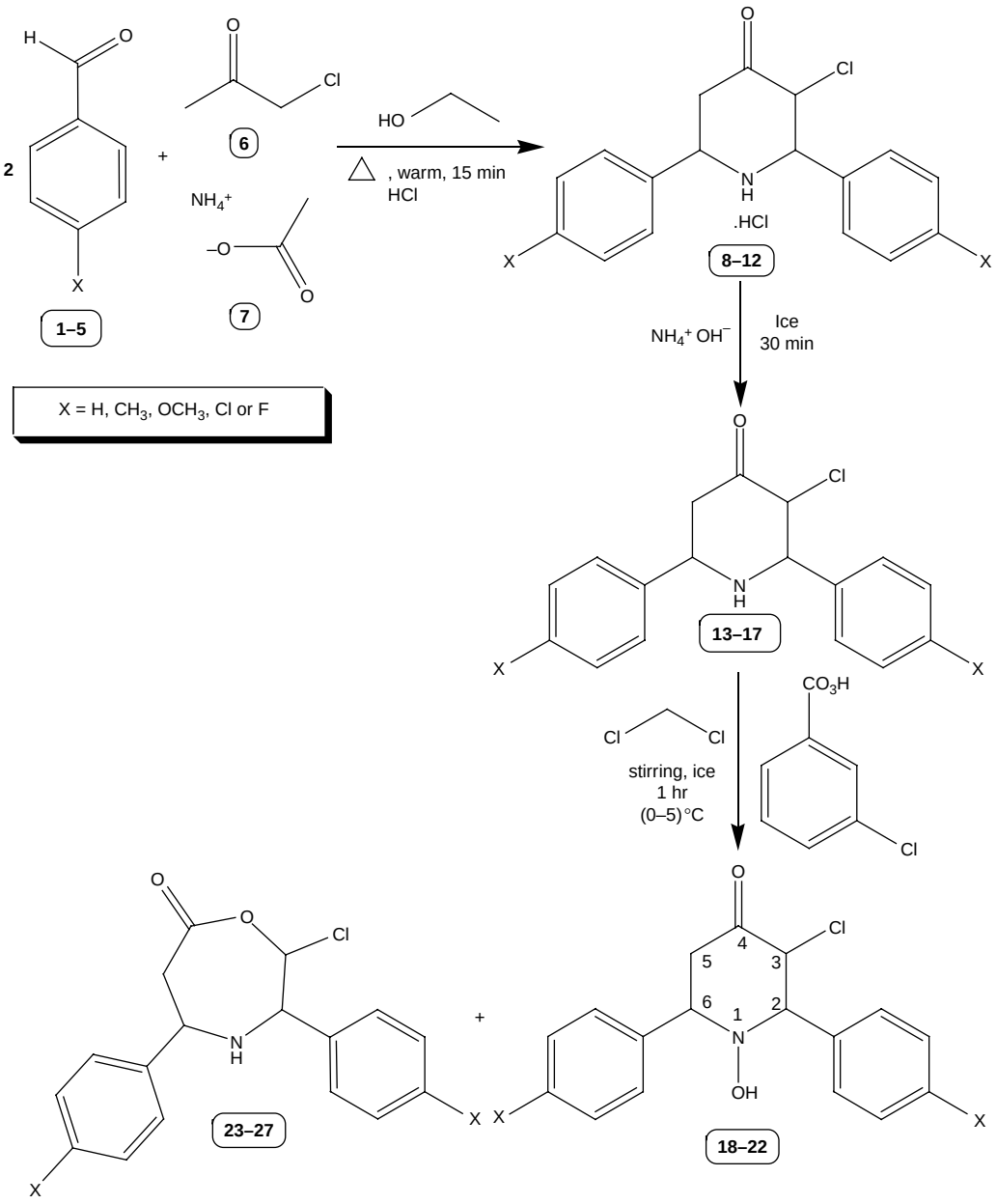
The compounds **19–22** were synthesized similarly.

*3-Chloro-1-hydroxy-2,6-bis(p-methylphenyl)piperidin-4-one **19:*** IR (KBr) (cm^{-1}): 3485, 3026, 2921, 2859, 1728, 787, 677; ^1H NMR (δ ppm): 2.35 (s, 6H, CH_3 at phenyl rings), 2.80–2.91 (m, 1H, H_{5a}); 2.95–2.98 (m, 1H, H_{5e}), 3.93 (d, 1H, H_{2a}, J = 11.1), 3.98–4.29 (m, 1H, H_{6a}), 4.50 (s, 1H, H_1), 4.69 (d, 1H, H_{3a}, J = 11.1), 7.18–7.40 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 21.0 CH_3 at phenyl rings, 46.7 C-5, 67.2 C-3, 69.8 C-6, 70.5 C-2, 126.7–129.3 –C_{arom}, 129.5, 136.01, 137.89, 138.2 *ipso*-C, 196.8 C-4.

*3-Chloro-1-hydroxy-2,6-bis(p-methoxyphenyl)piperidin-4-one **20:*** IR (KBr) (cm^{-1}): 3495, 3006, 2964, 2934, 2840, 1727, 745, 671; ^1H NMR (δ ppm): 2.80–2.91 (m, 1H, H_{5a}); 2.95–2.98 (m, 1H, H_{5e}), 3.80 (s, 6H, OCH_3 at phenyl rings), 3.90 (d, 1H, H_{2a}, J = 11.1), 3.95–4.14 (m, 1H, H_{6a}), 4.47 (s, 1H, H_1), 4.67 (d, 1H, H_{3a}, J = 11.1), 7.26–7.53 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 46.7 C-5, 53.40, 55.27 OCH_3 at phenyl rings, 66.0 C-3, 67.0 C-6, 70.2 C-2, 128.03–130.4 –C_{arom}, 131.0, 132.6, 159.3, 159.5 *ipso*-C, 196.8 C-4.

*3-Chloro-1-hydroxy-2,6-bis(p-chlorophenyl)piperidin-4-one **21:*** IR (KBr) (cm^{-1}): 3483, 2983, 2923, 2874, 1736, 826, 803, 666; ^1H NMR (δ ppm): 2.82–2.85 (m, 1H, H_{5a}); 2.88–2.95 (m, 1H, H_{5e}), 3.96 (d, 1H, H_{2a}, J = 11.0), 4.01–4.07 (m, 1H, H_{6a}), 4.53 (s, 1H, H_1), 4.64 (d, 1H, H_{3a}, J = 11.3), 7.26–7.48 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 46.7 C-5, 65.7 C-3, 67.6 C-6, 70.1 C-2, 126.9–128.5 –C_{arom}, 128.6, 128.9, 139.0, 140.6 *ipso*-C, 196.7 C-4.

*3-Chloro-1-hydroxy-2,6-bis(p-fluorophenyl)piperidin-4-one **22:*** IR (KBr) (cm^{-1}): 3482, 3044, 2923, 2874, 1735, 755, 676; ^1H NMR (δ ppm): 2.82–2.85 (m, 1H, H_{5a}); 2.90–2.97 (m, 1H, H_{5e}), 3.96 (d, 1H, H_{2a}, J = 11.6), 4.00–4.14 (m, 1H, H_{6a}), 4.50 (s, 1H, H_1), 4.65 (d, 1H, H_{3a}, J = 11.1), 7.06–7.48 (m, 8H, H_{arom});^{13}C NMR (δ ppm): 46.6 C-5, 66.8 C-3, 68.0 C-6, 68.3 C-2, 128.2-129.7 –C_{arom}, 131.0, 134.6, 163.7, 163.8 *ipso*-C, 196.0 C-4.



Scheme 1. Reaction route for the synthesis of 3-chloro-l-hydroxy-2,6-diarylpiperidin-4-one.

Microbiology

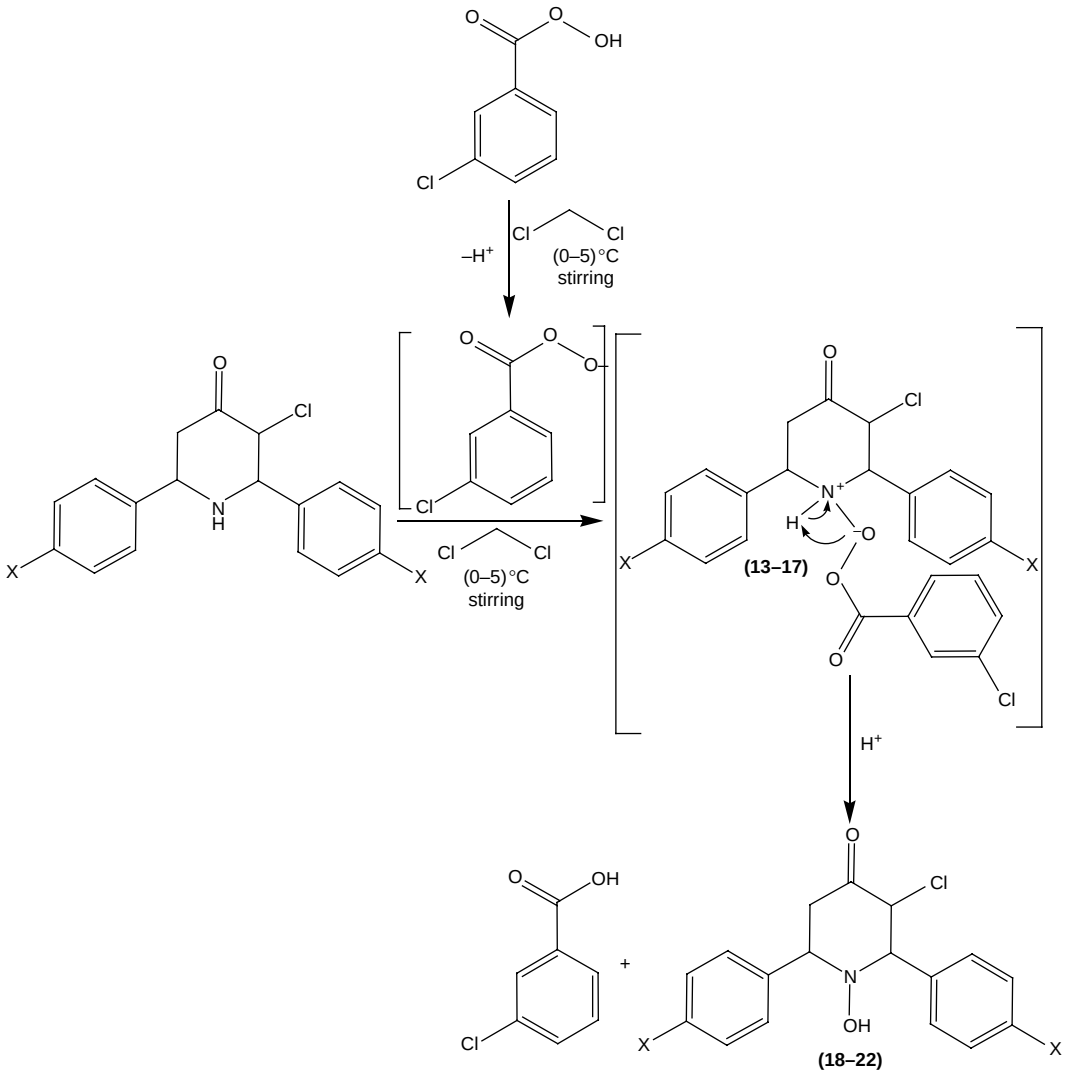
Materials. All the bacterial strains namely *Staphylococcus aureus*, *β-Haemolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhii*, *Shigella felxneri*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas* and fungal strains namely *Aspergillus flavus*, *Mucor*, *Rhizopus* and *Microsporum gypsuem* were obtained from Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

In vitro *antibacterial and antifungal activity*. The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by two-fold serial dilution method [26]. The respective test compounds **18–22** were dissolved in dimethylsulfoxide to obtain 1 mg ml^{-1} stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) 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 10^5cfu/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 a pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of test compound was added to

Table I. Physical and analytical data of 3-chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22**.

Compound	Yield (%)	m.p° C	Elemental analysis (%) C Found (calculated)	H Found (calculated)	N Found (calculated)	m/z ($M^{+\cdot}$) Molecular formula
18	65	149–151	67.65 (67.69)	5.27 (5.30)	4.62 (4.64)	302 $C_{17}H_{16}NO_2Cl$
19	60	160–162	69.20 (69.22)	6.07 (6.09)	4.22 (4.25)	330 $C_{19}H_{20}NO_2Cl$
20	65	169–171	63.07 (63.10)	5.51 (5.53)	3.84 (3.87)	362 $C_{19}H_{20}NO_4Cl$
21	55	168–170	55.07 (55.10)	3.77 (3.78)	3.75 (3.78)	371 $C_{17}H_{14}NO_2Cl_3$
22	70	160–162	60.45 (60.48)	4.11 (4.14)	4.13 (4.15)	338 $C_{17}H_{14}NO_2ClF_2$

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. The tubes were incubated in BOD incubators at 37 ± 1°C for bacteria and 72–96 h 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 was used as standard for bacteria studies and Fluconazole was used as standards for fungal studies.



Scheme 2. Probable reaction meachanism for the synthesis of target molecules.

Table II. *In vitro* antibacterial activities (MIC) values for compounds **18–22**.

Micro organisms	Minimum inhibitory concentration (MIC) in μg/mL					
	Compound **18**	Compound **19**	Compound **20**	Compound **21**	Compound **22**	Ciprofloxacin
S.aureus	100	12.5	100	12.5	12.5	25
β-H. streptococcus	100	100	200	12.5	25	50
V. cholerae	50	50	50	25	25	50
S. typhii	50	50	200	100	6.25	50
S. felxneri	100	200	12.5	50	50	25
E. coli	200	200	200	100	100	25
K. pneumonia	100	100	12.5	50	50	50
Pseudomonas	200	100	100	12.5	6.25	25

Results and discussion

Chemistry

Target molecules, 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** were synthesized as a result of a three-step synthetic strategy. One of the direct synthetic route for the formation of 3-chloro-2,6-diarylpiperidin-4-ones **13–17** is as follows: A mixture of chloroacetone **6**, appropriate benzaldehyde **1–5** and ammonium acetate **7** in the ratio of 1:2:1, was warmed for 15 min. and hydrochloric acid was added to afford 3-chloro-2,6-diaryl-piperidin-4-ones hydrochloride **8–12**, which upon neutralization with aqueous ammonia at 0°C gave the respective 3-chloro-2,6-diarylpiperidin-4-ones **13–17**. Cyclic ketones normally undergo Baeyer-Villeger oxidation (oxygen insertion reaction) to yield lactones upon treatment with peracids [24,25]. But, when 3-chloro-2,6-diarylpiperidin-4-ones **13–17** were subjected to Baeyer-Villeger type of reaction by using *m*-chloroperbenzoic acid, 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** resulted instead of lactones **23–27**. The schematic representation and the analytical data of compounds **18–22** are given in Scheme 1 and Table I, respectively. Their proposed mechanism of formation is shown in Scheme 2. The structure of the newly synthesized compounds **18–22** was confirmed by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (^{1}H & ^{13}C) spectroscopic data.

Antibacterial activity

Novel 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** were tested for their antibacterial activity *in vitro* against *S.aureus*, β-*H.streptococcus, V.cholerae, S.typhii, S.felxneri, E.coli, K.pneumonia* and *Pseudomonas*. Ciprofloxacin was used as standard drug. Minimum inhibitory concentration (MIC) in μg/mL values is shown in Table II. All the synthesized 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** exerted potent antibacterial activity *in vitro* against the tested gram-positive and gram-negative bacterial strains except *E.coli*. Moreover, compounds **21** and **22** exerted strong antibacterial activities against *S.aureus, β-H.streptococcus, V.cholerae, S.typhii* and *Pseudomonas*.

Antifungal activity

The *in vitro* antifungal activity of the synthesized novel heterocyclic compounds, **18–22** was studied against the fungal strains viz., *A.flavus, Mucor, Rhizopus* and *M.gypsuem*. Fluconazole was used as a standard drug. Minimum inhibitory concentration (MIC) in μg/mL values is shown in Table III. Compounds **21** and **22** exerted strong antifungal activities against all the tested fungal strains. In addition, compound **20** was the most potent against *Rhizopus*.

Conclusion

A close inspection of the *in vitro* antibacterial and antifungal activity profile in differently electron donating (CH_3 and OCH_3) as well as electron withdrawing (Cl,F) functional group substituted phenyl rings of novel 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones **18–22** against the tested bacterial strains *viz*. *S.aureus*, β-*H.streptococcus, V.cholerae, S.typhii, E.coli, K.pneumonia, Pseudomonas* and the

Table III. *In vitro* antifungal activities (MIC) values for compounds **18–22**.

Micro organisms	Minimum Inhibitory Concentration (MIC) in μg/mL					
	Compound 18	Compound **19**	Compound **20**	Compound **21**	Compound **22**	Fluconazole
A. flavus	100	200	100	25	25	50
Mucor	200	100	50	25	12.5	50
Rhizopus	200	50	6.25	12.5	25	25
M. gypsuem	200	50	50	12.5	12.5	25

fungal strains viz., *A.flavus, Mucor, Rhizopus* and *M.gypsuem* respectively, provides a better structure activity relationship correlate, which may be summarized as follows: Results of this study show that the nature of substituents on the phenyl ring viz., methyl, methoxy, chloro, fluoro functions at the *para* positions of the aryl moieties are determinant for the nature and extent of the anti-bacterial activity of the synthesized compounds, which might have influences on their inhibiting mechanism of actions. Compounds **21 and 22,** which contain chloro and fluoro moieties exerted strong antifungal activities against *A.flavus, Mucor* and *M.gypsuem*. The presence of electron donating methoxy functional moiety in compound **20** is most potent against *Rhizopus*. Further development of this group of 3-Chloro-1-hydroxy-2,6-diarylpiperidin-4-ones may lead to compounds with better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to come to blow bacterial and fungal infections.

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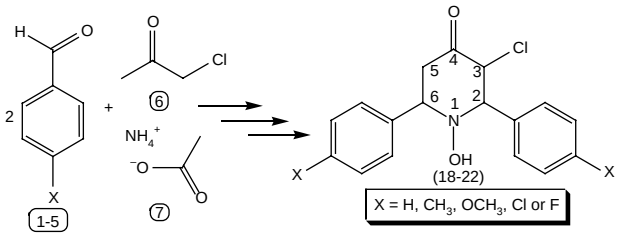

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