Research Article

A FACILE SOLID-STATE SYNTHESIS AND ANTIMICROBIAL ACTIVITY STUDIES ON SOME PIPERIDONE DERIVATIVES

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ABSTRACT

In vitro antibacterial activity of the novel piperidone derivatives synthesised from chalcone in dry media under microwave irradiation through the Michael addition reaction has been represented. It's a comparative study of synthesizing compounds by conventional as well as non-conventional methods of specific greener process. Then the structures of newly synthesized compounds were characterized by FT-IR, UV-Vis, NMR (¹³C, ¹H) and GC-Mass spectrums were investigated. The *in vitro* antimicrobial activities were screened against the standard strains: *Staphylococcus aureus*, *Streptococcus pyogenes* and *Bacillus subtilis* as Gram positive, *Escherichia coli* and *Pseudomonas aeruginosa* as Gram negative. Nitrile group containing piperidone derivative 5d showed better antibacterial activity on *Streptococcus pyogenes*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* than the reference drug Ciprofloxacin.

Keywords: Piperidone, Michael addition, Microwave irradiation, antibacterial activity.

INTRODUCTION

Nitrogen inserted heterocycle have a chief position in organic as well as in medicinal chemistry because of the useful properties of many members of these compounds.¹⁻³ Over the piperidine derivatives are one of the most widely studied class of heterocyclic compounds and have usual attention as a source of new and useful pharmaceuticals and biologically active compounds, Piperidone compounds possess important biological properties, including analgesic,⁴ antioxidant,⁵ antibacterial,⁶ anti-tuberculosis,⁷ antifungal,⁸ anti-inflammatory⁹ and also anticancer.¹⁰⁻¹³ Phenyl ring are substituted piperidone, display a number of exciting pharmacological possessions. Based on the importance of these molecules.¹⁴

Our attention was attracted towards the synthesis of new piperidone derivatives in order to find more potent biologically active molecules.^{15,16} Organic reactions under solvent-free environments involving easily separable solid catalysts are receiving considerable consideration in recent times, particularly from the point of view of green chemistry.¹⁷⁻²⁰ Solvent free solid-state synthetic methods have been shown to be very effectual and favourably coupled with microwave (MW) activation. Hence, we report here the synthesis and characterization of some novel phenyl piperidone derivative compounds. In accumulation, the antimicrobial activities of all synthesized piperidone against different bacteria were evaluated. Among the compounds tested, some of these piperidone were found to be larger compared to the reference drugs in inhibiting all the bacterial and fungal strains.

MATERIALS AND METHODS

Commercially available reagents were purchased from Nice and Fine chemical India and Melting points were measured on an electrothermal apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ¹H NMR, ¹³C NMR spectra were recorded at VIT Vellore, FT-NMR Bruker Avance Ultra Shield Spectrometer. TLC was performed on TLC-grade silica gel-G/UV 254 nm plates.

General Producer for Synthesis of piperidone derivatives

Conventional method

An equal molar mixture of *N*,2-diphenylacetamide or *N*-(2-hydroxyethyl)-2-phenylacetamide with various phenyl substituted chalcones derivatives in dry ethanol (25 ml) was refluxed with added sodium hydride (1.0 g), monitoring the progress of reaction by TLC. The reaction was stopped at the appropriate point 6 h, there action mixture was worked up and subjected to column chromatography over silica gel (60-120 mesh) using 02:98% ethyl acetate in petroleum ether as eluent.

Microwave method

An equal molar mixture of *N*,2-diphenylacetamide or *N*-(2-hydroxyethyl)-2-phenylacetamide with various phenyl substituted chalcones derivatives are dissolved in small amount of DMF and a catalytic amount of sodium hydride is added. Then the reaction mixture is heated for 3 minutes at 140°C in 250 watts. A yellow colour solid is obtained; it is cooled to room temperature then poured into 1000 mL cold water, neutralized with dilute HCl,

filtered, dried and washed with 200 mL of ethyl acetate. It was re-crystallized from ethanol; a pure yellow crystalline powder is obtained with good yield.

4-(4-(dimethylamino) phenyl)-1,3,6-triphenylpiperidin-2-one (5a)

Conventional: Yield 75%; **Microwave:** Yield 90%; m. p. 130-135 °C; 82% yield; IR (KBr, $\nu_{\max}$, cm^{-1}): 3373, 3058, 2888, 2789, 2050, 1672, 1598, 1511, 1258; ^1H NMR (500 MHz, CDCl_3): δ 8.10-7.18 (m, 19H, 4-phenyl ring), 5.10 (t, 1H, $J = 7$ Hz, piperidone- C_6 -H), 4.14 (d, 1H, $J = 7.5$ Hz, piperidone- C_3 -H), 3.65 (t, 1H, piperidone- C_4 -H, benzylic-H), 3.03 (s, 6H, $\text{N}(\text{CH}_3)_2$), 2.47 and 1.80 (d, and t, 2H, piperidone- C_4 -H); ^{13}C NMR (120 MHz, CDCl_3): δ 173.70, 149.22, 138.18, 136.68, 134.65, 131.26, 131.13, 128.97, 128.31, 128.14, 126.47, 112.50, 66.33, 50.88, 43.73, 40.39, 34.96; GC-MS: m/z [M^+] 446.

4-(4-(dimethylamino)phenyl)-6-ethyl-1,3-diphenylpiperidin-2-one (5b)

Conventional: Yield 75%; **Microwave:** Yield 90%; m. p. 130-131 °C; 82% yield; IR (KBr, $\nu_{\max}$, cm^{-1}): 3398, 3252, 3135, 3059, 2920, 2852, 1654, 1596, 1548, 1162, 751; ^1H NMR (500 MHz, CDCl_3): δ 8.10-7.37 (m, 14H, 3-phenyl ring), 4.87 (d, 1H, $J = 7$ Hz, piperidone- C_3 -H), 4.19-4.15 (m, 1H, piperidone- C_5 -H), 3.52 (q, 1H, $J = 6.5$, piperidone- C_4 -H), 2.99 (s, 6H, $\text{N}(\text{CH}_3)_2$), 1.37 and 1.30 (t, and d, 2H, piperidone- C_4 -H), 1.12 (q, 2H, $-\text{CH}_2-$), 0.99 (t, 3H, $-\text{CH}_3$); ^{13}C NMR (120 MHz, CDCl_3): δ 180.70, 148.12, 137.98, 135.20, 134.65, 128.98, 128.60, 128.36, 128.29, 128.14, 126.77, 112.59, 66.33, 50.11, 43.45, 43.91, 25.96, 10.34; GC-MS: m/z [M^+] 398 (29 %).

6-(4-(dimethylamino)phenyl)-1-(2-hydroxyethyl)-3,4-diphenylpiperidin-2-one (5c)

Yellow crystal, m. p. 110°C; 52% yield; IR (KBr, $\nu_{\max}$, cm^{-1}): 3361, 3160, 2958, 2889, 1698, 1649, 1483, 1426, 1209, 961; ^1H NMR (500 MHz, CDCl_3): δ 7.53-6.96 (unresolved m, 14H, phenyl-H), 6.18 (bs, 1H, O-H), 4.77 (t, 1H, piperidone C_4 -H), 4.40 (t, 1H, piperidone C_5 -H), 4.07 (t, 1H, piperidone C_2 -H), 3.01 (s, 6H, $\text{N}-\text{CH}_3$) 2.19 and 2.16 (2d, 2H, $J=2$ MHz piperidone C_3 -H); ^{13}C NMR (125 MHz, CDCl_3): δ 207.88, 149.54, 149.48,

146.22, 139.47-112.70, 57.58, 47.18, 46.28, 40.77, 40.59, 31.92, 29.69; GC-MS: m/z [$\text{M}+1$] 415.

6-(4-(dimethylamino)phenyl)-1-(2-hydroxyethyl)-2-oxo-4-phenylpiperidine-3-carbonitrile (5d)

Yellow crystal, m. p. 130°C; 62% yield; IR (KBr, $\nu_{\max}$, cm^{-1}): 3423, 2954, 2921, 2850, 1647, 1615, 1461, 1445, 1423, 1117, 1018; ^1H NMR (500 MHz, CDCl_3): δ 7.92-6.76 (unresolved m, 9, phenyl-H), 6.57 (bs, 1H, O-H), 3.59 (t, 1H, piperidone C_4 -H), 3.04 (t, 1H, piperidone C_2 -H), 2.07 (t, 1H, piperidone C_5 -H), 3.01 (s, 6H, $\text{N}-\text{CH}_3$) 2.14 and 2.28 (2d, 2H, $J=2$ MHz piperidone C_3 -H); ^{13}C NMR (125 MHz, CDCl_3): δ 207.02, 159.05, 155.33, 151.10-112.18, 64.06, 45.82, 40.81, 40.59, 40.33, 40.27, 34.67, 31.59; GC-MS: m/z [$\text{M}+1$] 364.

Biological activity

Anti-bacterial activity

Anti-bacterial activity of the newly synthesized piperidone derivatives compounds were resolute *in vitro* for anti-bacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus pyogenes* by paper disc diffusion method with DMF as solvent control nutrient agar was employed as culture media. After 24 hours hot incubation at 37°C the zone of inhibition was measured in mm.

Anti-fungal activity

The compounds were screened for their anti-fungal activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium oxysporum*, *Trichoderma viride* by paper disc diffusion methods at concentration of 2 and 5 mg/mL with DMF as solvent control and nutrient agar was employed as culture media. After 48 hours incubation at 25°C the zone of inhibition was measured in mm.

RESULTS AND DISCUSSION

We first synthesized novel chalcone 3 for this a Claisen-Schmidt condensation reaction of Dimethylamino benzaldehyde with variety of ketone produced the corresponding chalcones already reported.²¹

Scheme 1: Synthesis of Novel piperidone Derivatives 5a-d

In the current research investigation, we were synthesised piperidone derivative compounds 3 (Scheme 1). We chose acetamide derivative (*N*, 2-diphenylacetamide or *N*-(2-hydroxyethyl)-2-phenylacetamide or 2-cyano-*N*-(2-

hydroxyethyl)acetamide) as a starting precursor since we have this prepared in bulk,¹⁴⁵ dissolved in ethanol with an equivalent amount of chalcones 3. A catalysts amount of sodium hydride was added to initiate the reaction and then the mixture was refluxed.

The anti-microbial activity of synthesized compounds 5 (a-d) were studied in the concentrations of 100 mg / ml against five pathogenic bacterial strains (Figure 1). All the bacterial strains were selected for the basis of its application purpose of further formulation study. Anti-microbial potential of test samples was assessed in terms of zone of inhibition of bacterial growth and the results were compared with standard (Ciprofloxacin). The results of the anti-microbial activities are presented in Table 1.

The test samples dose at 100 mg revealed reasonable anti-microbial activity with zone of inhibition ranging from 2.0 to 11.0 mm and had shown to all pathogens. These observations may be due to the nature of biological active component of active constituent that are responsible for anti-bacterial activities. Standard Ciprofloxacin (30 mg) shows moderate anti-microbial activity with zone of inhibition ranging from 12.0 to 22.0 mm and had shown to all pathogens. It may be due to the occurrence of broad spectrum of anti-microbial compounds in the synthesised of selected four piperidone derivatives compounds 5 (a-d). On the origin of the results reached in the extant investigation, the compounds 5a showed considerable inhibitory activity against *Streptococcus pyogenes*, *Bacillus subtilis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Our results indicate the potential

utility of isolated compounds, in the treatment of various bacterial infections.

The *in vitro* antibacterial activity of newly synthesized piperidone compounds 5a was determined by well disk dilution method. The antibacterial screening exposed that some of the tested compounds showed good inhibition against several tested bacterial strains. The result indicated that among the tested compounds, 5a showed excellent activity against *Bacillus subtilis* at concentrations of 1 and 0.5 mg/mL compared to standard drug streptomycin. 5a showed similar activity as that of standard, against *Staphylococcus aureus* at 1 and 0.5 mg/mL concentrations. Results of antibacterial studies have been presented in Table 2.

As favours the dealings between the structure of the heterocyclic support and the detected antibacterial properties, it showed diverse biological activity. Compound 5a has N-dimethylamine moiety on piperidone ring, which is accounted for the improved antibacterial activity. However, in the 5d compounds showed moderate antimicrobial activity. However, the presence of other cyano substituents is responsible for the varied biological activity of the compounds.

Table 1: Antibacterial activity of the piperidone compounds 5

S. No.	Micro organisms	Zone of inhibition mm in diameter (M ± SD)				
		Isolated Compounds (100 mg)				Standard Ciprofloxacin (30 mg)
1	<i>Streptococcus pyogenes</i>	6	07	06	04	18
2	<i>Bacillus subtilis</i>	14	-	11	01	16
3	<i>Staphylococcus aureus</i>	18	06	03	02	21
4	<i>Escherichia coli</i>	-	02	07	03	12
5	<i>Pseudomonas aeruginosa</i>	10	10	-	-	22

Figure 1: Anti-microbial activity of piperidone compounds 5 by disc diffusion method

Figure 2: Anti-microbial activity of piperidone compounds 5 by disc diffusion method

CONCLUSION

In summary novel piperidone derivatives containing amino-aryl moiety have been synthesized through the conventional and microwave irradiation method. This synthetic strategy allows the construction of piperidone ring system by Michael addition protocol; Microwave reduced the reaction time from 6 hours to 3

minutes and enhanced the yield considerably. It can be determined from anti-microbial screening against a panel of human pathogens, antibacterial activity of these piperidone derivatives compounds was examined using culture of bacteria and the results showed that the N-methyl amino containing piperidone derivative 5a increased the antibacterial activity. Among the entire four compounds, Nitrile group containing

piperidone derivative 5d showed better antibacterial activity on *Streptococcus pyogenes*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* than the reference drug Ciprofloxacin.

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