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Research Article

SYNTHESES, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF NOVEL 2,6-DI SUBSTITUTED PIPERIDINE-4-ONE DERIVATIVES

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ABSTRACT

Piperidine and its derivatives have high impact on medical field due to its wide variety of pharmacological action. Piperidine derivatives are formed by the reaction between acetone, ammonium acetate and substituted aromatic aldehyde in the presence of ethanol. In the present investigation, an attempt to synthesize some novel biologically active piperidine derivatives was made. The structures of the newly synthesized compounds were characterized by spectral data. The compounds synthesized were screened for anti-microbial activity. Compounds **4b**, **4d**, **4e**, **4f** and **4g** were found to possess potent anti-bacterial activity.

INTRODUCTION

Various strategies are currently being employed to develop novel antibiotics and to improve the effectiveness of established antimicrobial compounds. For example therapeutics are being investigated that target bacterial mRNA, lipopolysaccharide synthesis and bacterial adhesion molecules. In order to improve the efficacy of known antibiotics, siderophore-antibiotic conjugates and efflux pump inhibitors are being studied. An additional attractive approach for the development of antibacterial agents is the preparation of compounds that target bacterial membranes. Bacterial membrane is highly conserved among most species of gram-negative and gram-positive bacteria. Mutations leading to gross changes in bacterial membrane structures are typically not stable because they can cause changes in membrane permeability potentially increasing susceptibility to hydrophobic antibiotics.

Piperidine is very important pharmacophore because of its presence in numerous alkaloids, pharmaceuticals, agrochemicals and as synthetic intermediates. Biologically active alkaloids of substituted piperidines ring system have been targeted for their total or partial synthesis [1]. Piperidines are known to have CNS depressant action at low dosage levels and stimulant activity with increased doses. In addition, the nucleus also possesses analgesic, ganglionic blocking and anesthetic properties as well [2, 3].

Piperidine was first isolated from the alkaloid piperine, which occurs in black pepper (*Piper nigrum*). Piperidine itself is present in small amounts in black pepper and tobacco,

but it is abundant in *Psyclocoulon absimile*, an American toxic plant [4]. The synthesis of piperidine is easy, economic and less time consuming. The parent molecule is flexible in nature and hence various derivatives can be easily prepared by altering its substituent [5].

The present study is an attempt to synthesize various piperidine derivatives and evaluate for antimicrobial activity.

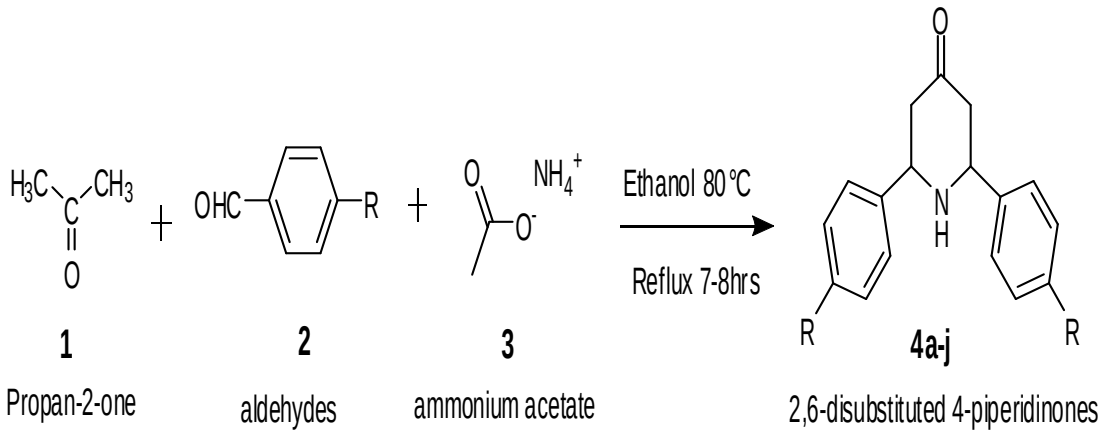
MATERIALS AND METHODS

General

The melting points were determined by open capillary tube method and are uncorrected (Table 1). IR Spectra were recorded on Shimadzu FTIR 8400S Spectrophotometer by using KBr technique (Table 2). Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC spectrometer. Progress of the reactions was monitored by TLC and spots were detected in iodine chamber. All the synthesized compounds were purified by recrystallization. The purity of the synthesized compounds was confirmed by getting single spot in TLC which was run precoated silica gel G plates using methanol and chloroform (1:9) as the solvent system.

Synthesis of 2,6-disubstituted-piperidine-4-one derivatives (4a-j)

Acetone (**1**) (0.01 mol), substituted benzaldehydes (**2**) (0.02 mol) and ammonium acetate (**3**) (0.01 mol) were taken in a 500 ml round bottom flask. Further ethanol (25 ml) was added to the flask and mixed well, so as to make a homogenous mixture. Then this mixture was refluxed at 80°C for 7-8 hours. Once the reaction was completed, the mixture was poured over crushed ice. The crude product obtained was filtered and the solid product was collected and washed with cold water. Dried the product at room temperature and recrystallized from ethanol to get the title compounds (**4a-j**) [6].



SCHEME 1. Synthetic route of the title compounds

***In–Vitro* Antibacterial activity**

Cup plate method

(Agar Diffusion Method of Assay)

The antibacterial activity of the synthesized compounds was studied systematically against four different strains of bacteria *Staphylococcus aureus, Bacillus subtillis* (Gram-positive), and *Escherichia coli, Pseudomonas aerugenosa* (Gram-negative), by using the agar diffusion method of assay [7-12]. The organisms were subcultured using nutrient agar medium. The tubes containing sterilized media were inoculated with respective bacterial strain. After incubation at 37 ± 1°C for 24 hr, they were stored in a refrigerator. Bacterial inocula were prepared by transferring a loopful of stock culture to nutrient broth (100ml) in a clean and sterilized conical flask (250 ml). Solutions of the test compounds were prepared by dissolving 10 mg of each in 10 ml of dimethylsulfoxide (DMSO) (10%v/v). Ciprofloxacin 100µg/ml was used as standard. In each plate, four cups of 4 mm diameter were made with a sterile borer. Then, 0.02 ml of the test solution was added to the cups, aseptically and labeled, accordingly. The plates were kept undisturbed for at least 2 hrs at room temperature to allow diffusion of the solution properly, into nutrient agar medium. After incubation of the plates at 37 ± 1°C for 24 hr the diameter of the zone of inhibition surrounding each of the cups was measured with the help of an 'antibiotic zone reader'. 10%v/v DMSO was used as control (Table 3).

RESULTS AND DISCUSSION

Title compounds were synthesized by reaction of propan-2-one with various aldehydes in presence of ammonium acetate. The compounds obtained in good yields were subjected to physical (table 1) and spectral characterization (table 2). Absorption bands observed in IR spectra of the compounds exhibited characteristic absorption bands (cm^{-1}) at approximately 3228 (O-H), 3390 (N-H), 1670 (C=O), 1191(C-F), 1330 (C-N) and 760 (C-CI). Further, the success of synthesis was confirmed by appearance of molecular ion peak as $M^{+}+1$ in the mass spectra of compounds. The newly synthesized compounds were evaluated for antibacterial activity at concentration of 100-1000 $\mu g/ml$ by using the agar diffusion method of assay wherein ciprofloxacin was used as standard (Table 3). The test compounds were found to be active against both gram positive and gram-negative organisms. Among these, compounds **4a**, **4b**, **4d**, **4e**, **4f** and **4g** emerged as potent anti bacterial compounds.

CONCLUSION

Result of present study demonstrates that, a new class of piperidine derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized heterocyclics exhibited promising antibacterial activity at low and high concentration. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

Table 1: Physicochemical data of piperidine derivatives

Comp. Code	R	Molecular formula	Colour	State	M.P. (°C)	Solubility
4a	4-Cl	$C_{17}H_{15}Cl_2NO$	Pale yellow	Solid	176-180	$CHCl_3$,MeOH
4b	4-OCH_3	$C_{19}H_{21}NO_3$	brown	Oily	-	$CHCl_3$,MeOH
4c	4-F	$C_{17}H_{15}F_2NO$	Light yellow	Solid	150-152	$CHCl_3$,MeOH
4d	3-OC_2H_5, 4-OH	$C_{21}H_{25}NO_5$	Light brown	Solid	68-72	$CHCl_3$,MeOH
4e	3-OCH_3, 4-OH	$C_{19}H_{21}NO_5$	Brown	Solid	76-78	$CHCl_3$,MeOH
4f	$N(CH_3)_2$	$C_{21}H_{27}N_3O$	Orange	Solid	74-76	$CHCl_3$,MeOH
4g	3-NO_2	$C_{17}H_{15}N_3O_5$	Yellow	Solid	272-276	$CHCl_3$,MeOH
4h	2-NO_2	$C_{17}H_{15}N_3O_5$	Brown	Solid	260-268	$CHCl_3$,MeOH
4i	3-Cl	$C_{17}H_{15}Cl_2NO$	Brown	Solid	110-112	$CHCl_3$,MeOH
4j	2-Ar	$C_{25}H_{21}NO$	Brown	Oily	-	$CHCl_3$,MeOH

Table 2: Characteristics IR absorption bands and Mass spectra

Comp. Code	C=O	N-H	C-N	C-NO_2	C-Cl	C-F	OH	Mol. Wt.	M^++1 peak
4a	1685.67	3413.77	1321.15	-	761.83	-	-	320	321.2
4b	1665.50	3398.44	1345.23	-	-	-	-	311	312.3
4c	1652.88	3421.48	1238.21	-	-	1191.93	-	287	288.3
4d	1670.50	3390.11	1311.23	-	-	-	3228.55	371	372.1
4e	1666.38	3398.34	1300.67	-	-	-	3180.40	343	344.3
4f	1658.67	3397.80	1313.43	-	-	-	-	337	338.4
4g	1690.00	3413.77	1274.86	1525.59, 1350	-	-	-	341	342.3
4h	1648.30	3421.48	1238.1	1523.6, 1320.1	-	-	-	341	342.3
4i	1654.81	3345.32	1193.85	-	794.62	-	-	320	321.2
4j	1648.00	3266.77	1326.70	-	-	-	-	351	352.2

Table 3: Antibacterial activity of synthesized compounds (4a-4j)

COMP. CODE	Zone of inhibition (diameter in mm)																							
	B. subtillis (conc. in µg/ml)						*S. aureus* (conc. in µg/ml)						*P. aerugenosa* (conc. in µg/ml)						*E. Coli* (conc. in µg/ml)					
	100	200	400	600	800	1000	100	200	400	600	800	1000	100	200	400	600	800	1000	100	200	400	600	800	1000
4a	-	-	8	10	13	17	-	-	11	11	15	20	-	5	9	10	12	14	-	-	8	12	12	15
4b	-	-	-	10	12	13	-	-	9	11	11	12	-	6	9	14	14	16	-	-	6	10	16	16
4c	-	-	-	-	-	13	-	-	8	11	15	16	-	-	-	-	8	12	-	-	-	8	8	8
4d	6	8	9	11	13	15	-	8	10	12	14	15	-	6	9	12	13	16	-	7	8	12	14	14
4e	-	6	8	10	11	14	-	6	8	14	17	20	-	-	-	8	10	15	8	10	10	12	13	16
4f	-	7	8	8	12	16	6	8	12	14	18	18	7	9	10	12	15	16	-	-	8	10	12	14
4g	-	-	7	10	13	14	-	8	10	13	16	18	-	6	9	11	13	15	-	6	8	8	8	10
4h	-	-	-	-	-	-	-	-	-	6	8	8	-	-	-	-	-	6	-	-	6	8	9	11
4i	-	-	-	-	-	-	-	-	-	-	-	7	-	-	-	6	7	7	-	-	-	7	9	8
4j	-	-	6	7	7	10	-	-	-	7	8	9	-	-	-	8	8	7	-	-	-	-	6	6
Control	Nil						Nil						Nil						Nil					
Ciprofloxacin	20						22						18						16					

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