DESIGN, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF NOVEL MANNICH BASE

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ABSTRACT

In this work we describe a simple method to synthesis of some novel piperidine derivative. The Structures of the newly synthesized compound were supported by means of FTIR, CHN elemental analysis, and NMR (^{1}H, ^{13}C) spectroscopic analysis. The synthesized compounds were evaluated for their in vitro antibacterial activity against Escherichia coli, Staphylococcus aureus, Aspergillus niger and Mucor. The inhibition zones were measured, expressed in mm, and the minimum inhibitory concentration (MIC) is reported in μg/mL. The results show that compound have a significant antimicrobial activity with the highest MIC value against all tested bacteria. The comparative molecular docking studies revealed better insights into binding mechanisms.

Keywcords: Mannich Base, Piperidine derivative, Antimicrobial activity and MDS.

INTRODUCTION

Heterocyclic compounds represent an important class of biologically active molecules. A deep study of literature review showed that the study of reaction like Claisen-Schimt, Mannich[1] and aldol condensation. Owing to their pharmacological activity of such as antibacterial[2], antifungal[3], anti-inflammatory[4,14], antimalaria, cytotoxity and anticancer[5,7,8]

activities. In the present study we have reported for its antibacterial, antifungal activities. It has been planned in this work to synthesis a novel type of compounds using cyclic ketones, aldehydes, and amines.

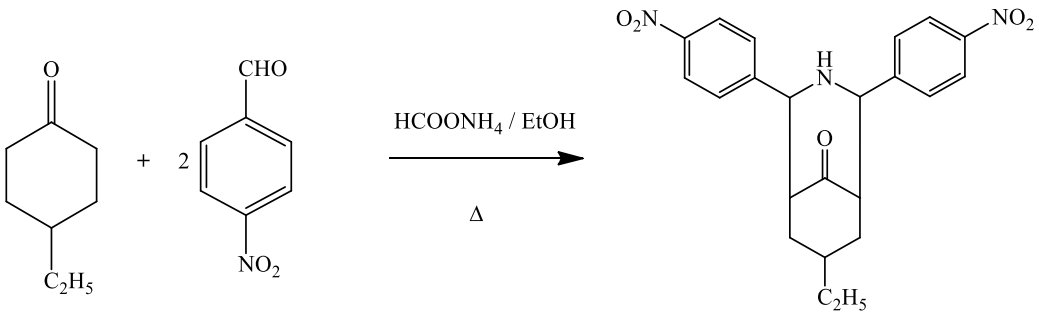
EXPERIMENTAL

Melting points were determined with open capillary and are uncorrected. Proton NMR spectra were taken in DMSO and recorded at 400 MHz in Burker and ^{13}C NMR spectra were taken in DMSO and recorded in 300 MHz in Burker. Chemical shifts were measured in ppm with respect to TMS. FTIR spectra recorded on instrument Simadzu 2100 S and Perkin Elmer BX.

MATERIALS AND METHODS

4-ethylcyclohexanone (0.01mol), ammonium formate (0.01mol), 4-nitrobenzaldehyde (0.02mol) in a RB flask containing ethanol (10ml). The mixture is refluxed at 60-70 °C in a water bath with occasional shaking until the colour changes into red orange. The solution is cooled, and then ether (50ml) is added. The filtered solution is transfer into conical flask. The yellow colour precipitate formed is filtered and dried. Then the product is recrystallised with ethanol and crystal form of product obtained is dried. The melting point is 160°C.

(4-ethylcyclohexanone and ammonia formate supplied by E.merck were used as such. 4-methoxybenzaldehyde were supplied by BDH. Ethanol was distilled twise to get maximum alcohol content. Silicagel.G supplied by BDH was used to prepare TLC plates)



SCHEME – I

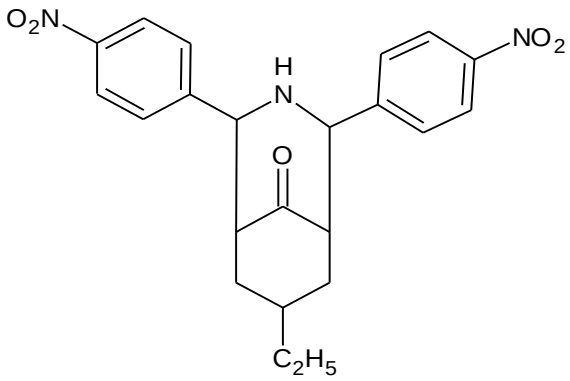
RESULT AND DISCUSSION

SPECTRAL DATA

IR (KBr): 3059 cm^{-1}(NH), 2997 cm^{-1} (aromatic C-H), 2924 cm^{-1} (aliphatic C-H), 1664 cm^{-1} (C=O), 1145 cm^{-1} (C-O-C); ^{1}H NMR (400 MHz, DMSO): δ 7.53-7.50 and 7.04-7.01 (8H, aromatic proton), δ 2.50 (1H NH proton); ^{13}C NMR (DMSO): Chemical shift value 159 ppm (C=O), 135 ppm (Ipso carbon), 133 ppm (carbons of phenyl ring) and 34 ppm (C_7).

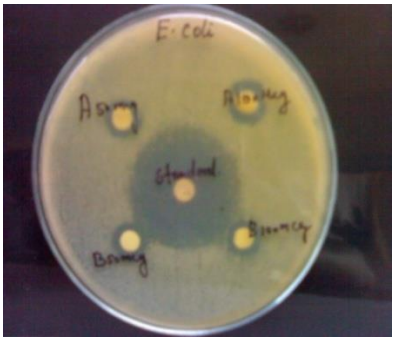
Based on the above spectral data the compound is identified as

7-ethyl-2,4-bis(4-nitro-phenyl)-3-aza-bicyclo[3.3.1]nonan-9-one

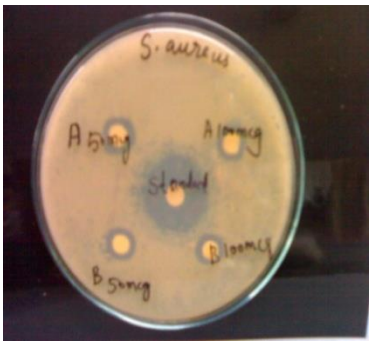


ANTIMICROBIAL ACTIVITY

The compound was dissolved in DMSO. The filter paper disks were soaked with different solution of the compound dried and then placed in petri dish previously seeded with test organism *E-coli, S-aureus, A-nigar* and *mucor*. The plates were incubated for 24h at 37 °C and incubation zone around each disc was measured the biological activities of the synthesized compound was studied against the *E-coli, S-aureus, A-nigar* and *mucor* using agar plates technique at concentration of 1mg/ml in DMSO. The compound show inhibition zone diameter ranges between 10-15 mm as shown in table. The compound show greater antimicrobial activity towards *E-coli* and antifungal activity towards *A.nigar* while all other showed moderate activity against all the bacterial and fungal cultures.

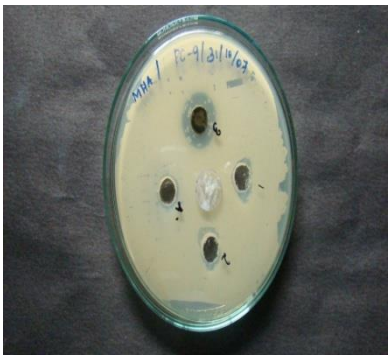


E-Coli



S-aureus

A.nigar



Mucor

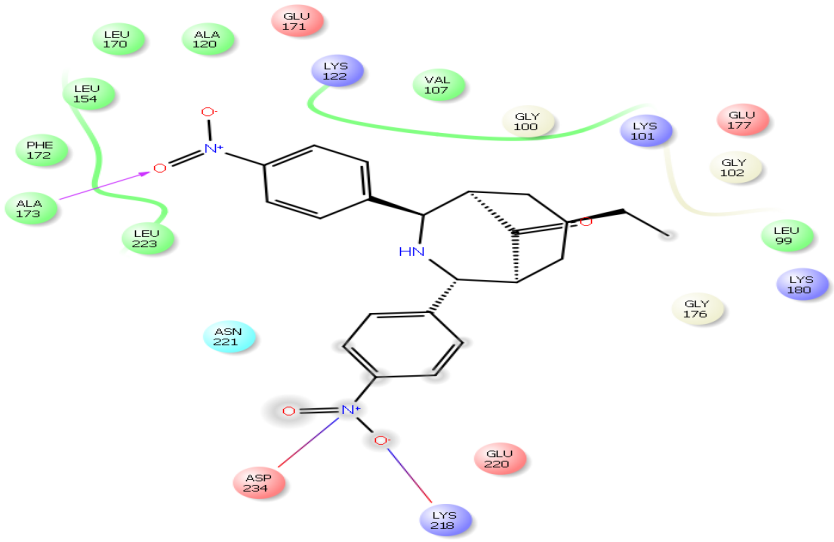
Table No.1: Results of Antimicrobial Activity

Antimicrobial		Antifungal	
E-coli	*S-aureus*	*A.nigar*	*Mucor*
38	35	35	32

(Reference standard Ciprofloxin 5µ/g disk for bacteria; Nystain 100 µ/g disk for fungi)

MOLECULAR DOCKING STUDIES

X-ray crystal structure of EGFR tyrosine kinase (PDB: 2J5F) was downloaded from www.rcsb.org. The active site of 2J5F is well established with hydrophobic active site containing irreversible inhibitor and molecular docking simulations were performed in order to distinguish the basic receptor-ligand interactions. The X-ray crystal structure of EGFR tyrosine kinase domain had the resolution of 3.00Å. The protein was prepared by using the Protein Preparation Wizard, pre-processed and hetero state for co-crystallized ligand was generated using Epik; protonation state and optimization of H bonding of the protein side chains were assigned using Protassign, energy minimized (impref minimization) using OPLS2001 force field. Receptor grid has been prepared with default parameters and without any constrains. Site was specified around the reference ligand 7-ethyl-2,4-bis(4-nitro-phenyl)-3-aza-bicyclo[3.3.1]nonan-9-one of EGFR tyrosine kinase. The two dimensional structures of ligand were drawn by using the Maestro 8.5. The ligand were prepared by using Ligprep utility of Schrodinger Suite with default parameters, the ligand energy minimized by using OPLS 2005 (Macromodel multiple minimization) and water as solvent. The ligand did not show the formation of any tautomers or isomers after ligprep and macromodel multiple energy minimizations. The ligand docking was performed with Xtra precision mode (XP) which is employed in GLIDE 5.0 module implemented in the Schrodinger LLC.



Glide extra – Precision (XP) result for use of Schrodinger LLC

Table:II

Binding Energy (Kcal/mol)	No.of.Hydrogen Bond Interaction	Interacting Residues	Distance (A^0)
-3.20	**2**	**LYS 210, ALA 173**	**1.877, 1.998**

CONCLUSION

A simple and elegant method for the synthesis of the compound described in this work. Nitrogen containing piperidine-4-ones are obtained, when more convenient ammonium acetate is employed instead of the deliquescent ammonium formate. The synthesized compound was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, biological and Molecular docking activity. After studying the docking poses and binding modes of the docked compound, the necessity of hydrogen bond formation for enhancing the activity of this class of compound can be highly advocated.

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