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ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis, Antimicrobial and *In-Silico* Studies of 3-Benzyl-2,6-Diphenylpiperidin-4-One

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ABSTRACT
Piperidin is an important class of heterocyclic compounds which play a vital role in the field of medicinal chemistry. Several 2,6-disubstituted derivatives of these compounds are found to posses biological activities such as herbicidal, fungicidal, anticancer, anaesthetic etc. The synthesis of substituted piperidin-4-one derivatives using 4-Phenyl-2-butanone, benzaldehyde and ammonium acetate or ammonium formate (amine) in ethanol medium under reflux-free condition is described. The characterized by FT-IR, [1]HNMR, [13]CNMR, biological and Molecular docking studies.
***KEYWORDS**: FT-IR, [1]HNMR, [13]CNMR, biological and Molecular docking studies.*

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INTRODUCTION

The synthesis and structures of Mannich Bases have attracted much attention in biology and chemistry due to their model character and practical application. Mannich base piperidin-4-one have remained an important and popular area of research due to simple synthesis, adaptability, and diverse range of applications. Heterocyclic compound with a piperidone skeleton are attractive target for organic synthesis and there is found to be significant in compound possessing aromatic substitution in 2 and 6th position in the piperidone rings [1-3].

Literature reports show that a wide range of 2,6 disubstituted piperidin-4-one [4-6]. Amoung the piperidin derivatives, piperidones are important intermediates in several synthetic sections [7]. Due to the known therapeutic properities of piperidones and the presence of keto functional group that facilitates the introduction of other substituted derivatives of this class compounds have been found the possess biological activities such as herbicidal insecticidal, fungicidal, anti-inflammatory, anesthetic, anticancer activity.

The antimicrobial activity was performed by the Disc diffusion technique method, using different concentrations (50µg, 100 µg, 500µg and 1000µg). The sterile Muller hinton agar and Sabouraud dextrose agar were used for bacteria and fungi respectively. Two Gram positive, two Gram negative and two fungal strains were used to study the antimicrobial activity. All these strains were obtained from Pune. (NCIM-National collection of Industrial microbes) The watt-man Number 2 filter paper of 6mm diameter was loaded with 100µl of the diluted sample placed at equal intervals over the uniformly inoculated plate along with a standard disc Ciprofloxacin 5mcg/disc for bacteria and Nystatin 100units/disc for fungi were also placed along with sample to maintain quality control [8-12].

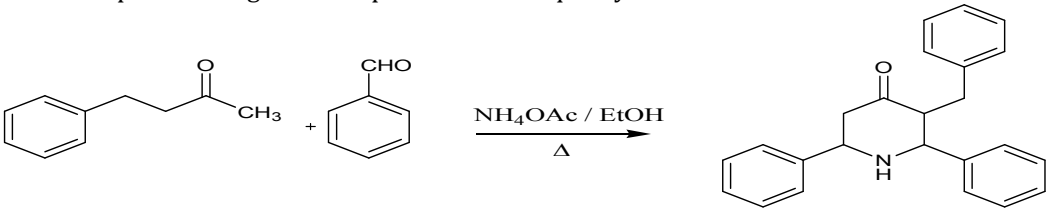

Figure 1. Scheme-1 of synthesis

MATERIAL AND METHODS

4-Phenyl-2-butanone (1.3g; 0.1mol), ammonium acetate (4g; 0.1mol) and benzaldehyde (2.1.ml; 0.02mol) were taken in a RB flask containing ethanol (10ml). The mixture was refluxed in a water bath with occasional shaking until the colour changed into red orange. The solution was cooled, and then ether (50ml) was added. The filtered solution was transferred into conical flask and Con.HCl (5ml) was added. A white precipitate was formed. The precipitate was washed with 5:1 ethanol:ether mixture and dried. Acetone (10ml), liquid ammonia (5ml), and excess of coldwater were added. The precipitate formed was filtered and dried. Then the product was recrystallized with etanol. The product was dried, m.p 222-224^{0}C.

RESULTS AND DISCUSSION

Spectral characterization

3-benzyl-2,6-diphenylpiperidin-4-one Yield: 86-92%; mp: 222-224ºC .**FT-IR** (KBr): 3392 (υN-H), 3023(υaromatic-CH), 2901 (υaliphatic-CH), 1704 (υC=O), 1588, 1430 (υC C) cm-^{1}, **^{1}H-NMR** (300MHz, DMSO-d6, δ in ppm); 8.562-8.555 (d, 2H, pyridine –**H**); 7.51-7.45(t, 6H,pyridine-H); 7.16- 6.87(m, 12H, aromatic-H); 4.77-4.69(t, 2H, benzylic-**H** (C3 and C5 protons); 4.40-4.36(d, 2H, benzylic-**H** (C2 and C6 protons); 3.37(hump,1H,N**H**).

^{13}C-NMR (100 MHz, DMSO- d6, δ in·ppm) 206.2(>C=O), 158.9, 149.1, 136.2, 129.7,127.5, 126.2, 123.0, 122.4, 66.9, 63.4.

Table: I Antibacterial activity

S.No	Name of the Microorganisms	Zone of inhibition in mm					
		50mcg	100mcg	500mcg	1000mcg	Solvent Control	standard
1	*Staphylococcus aureus* (NCIM2079)	16	18	20	20	-	35
2	*Basillus subtilis* (NCIM2063)	18	20	20	21	-	40
3	*Klebsiella aerogenes* (NCIM2098)	12	16	18	19	-	30
4	E.coli (NCIM2065)	16	18	20	24	-	38
5	*Aspergillus niger* (NCIM2105)	16	18	18	20	-	35
6	*Candida albicans* (NCIM3102)	16	16	17	20	-	32

Standard-Ciprofloxacin 5µg/disc for bacteria: Nystatin 100units/disc for fungi.Solvent-DMSO

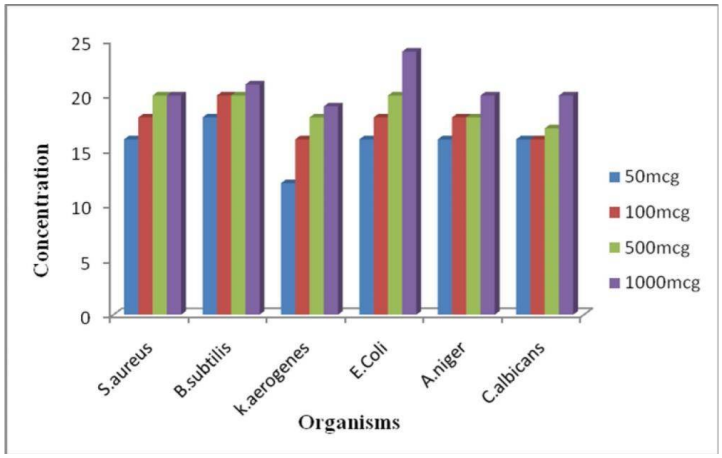

Figure-2: Graphical chart of Inhibition

Followed by incubation at 37ºC for 24hrs and 25ºC for two days for bacteria and fungi were observed for zone of inhibition. The zone of inhibition was measured by using a standard scale. The diameter of the zone of inhibition directly proportional to the amount of active constituent present in the sample. The

compound were found to be effective against Gram positive (*Staphylococcus aureus* and *Basillus subtilis).* Among these two Gram positive the effect was found to be remarkable at low concentration (100µl) towards *Basillus subtilis* and more effective against Gram negative *E.coli* and *Klebsiella aerogenes.* In the compound showed better response towards fungal strains *Aspergillus niger* and *Candida albicans* [Fig 2, Table1].

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 heterostate 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 ligands 3-benzyl-2,6-diphenylpiperidin-4-one of EGFR tyrosine kinase. The two dimensional structures of ligands were drawn by using the Maestro 8.5. The ligands 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 ligands did not show the formation of any tautomers or isomers after ligprep and macromodel multiple energy minimizations. The ligands' docking was performed with Xtra precision mode (XP) which is employed in GLIDE 5.0 module implemented in the Schrodinger LLC.

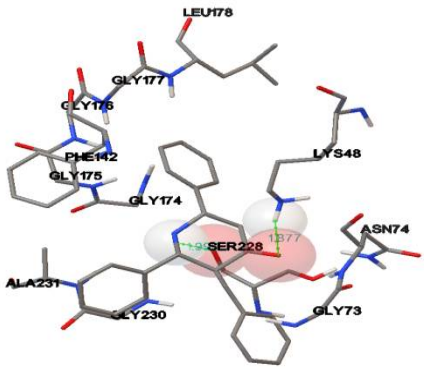

Figure – 4: Glide extra – Precision (XP) result for use of Schrodinger LLC

Table.2 Details of Bonding

Binding Energy (Kcal/mol)	No.of.Hydrogen Bond Interaction	Interacting Residues	Distance (A^0)
-8.17	2	LYS 48, SER 228	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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REFERENCES

1. C.Noller ;V.Baliah, (1948). The Preparation of Some Piperidine Derivatives by the Mannich Reaction, J. Am. Chem.Soc.,70,3853
2. Baliah V, Ekambaram A, Govindarajan T. S, (1954).Synthesis and Characterization of new Spiro Heterocyles, Curr. Sci,1954; 23: 264.

3. Baliah V, Jeyaraman R, Chandrasekaran L. (1983). Synthesis, Characterization And Biological Studies Of N-(2,4-Dinitro-Phenyl)-N'-(2,3,5,6-Tetraphenylpiperidin- 4-Ylidine)-Hydrazine, *J.* Am. Chem. Soc*,Rev.* Vol.83, 379-423.
4. R. Jeyaraman and S. Avila,(1981). Cytotoxic and Antioxidant Activity of a Set of Hetero Bicylic Methylthiadiazole Hydrazones: A Structure-Activity Study, Chem. Rev., 81, 1499.
5. Silverstein, Bassler and Morrill, (2008). Spectrometric Identification of Organic Compounds.4thEdn. John Wiley &Sons.
6. Seeni Mubarak M, et al., (2011). Synthesis and Characterisation of new Spiro Heterocyles Oriental J. Chem., 27(1): 333.
7. Ramani Devi R, Kathirvel R, Seeni Mubarak M, Mohamed Rabeek S, Fazal Mohamed M.I, (2014). Synthesis, 2DNMR and Crystal Structure Analysis of Piperidin - 4 - one Derivatives, International J.ITEE., 3: 1-4.
8. Kitchen D B, Decornez H, Furr J R and Bajorth J, (2002). Docking and scoring in virtual screening for drug discovery, Methods and applications, Nat Rev Drug Discovery, 3, 935-949.
9. Schneider G and Bohm H J, (2002). Virtual screening and fast automated docking methods, Drug Discovery Today, 7, 64-70.
10. Protein Preparation Wizard Maestro New York: Schrodinger LLC, 2013.
11. Qikprop, (2013). The Advantages of ADME Properties Prediction, Version 3.7., LLC, New York, 2013.
12. Hardy L W, Malikayil A, (2003). The impact of structure-guided drug design on clinical agents, Cure Drug Discovery, 3, 15-20.

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