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In Silico Designing of Biologically Active Dihydropyrimidinone N-Mannich

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ABSTRACT

Despite the recent advances in medicine, antimicrobial chemotherapy still remains a major problematic in most under-developed and developed countries. An Anti-microbial agent is a substance which kills or inhibits the growth of microorganisms such as bacteria, fungi or protozoans. N- Mannich Bases of 3, 4-dihydropyrimidine -2(1H)-one (DHPMs) derivatives belong to an interesting class of heterocyclic compounds which has attracted considerable attention of medicinal chemists. N- Mannich Bases of DHPMs have been considered for a variety of biological activities such as antitumor, antiviral and antioxidant activities. The main objective of molecular docking is to predict the biological activity of given ligand. The Molecular Docking study was done by using Maestro 11.5 Schrodinger software to find the interaction between active Dihydropyrimidinone Mannich bases with DNA Gyrase ***(PDB ID: 1KZN)*** *and Sterol 14α-demethylase* ***(PDB ID: 1EA1)****enzymes. Molecular docking studies showed that Novel Dihydropyrimidinone N-Mannich bases has shown formation of hydrogen bond and good binding affinity with some amino acid residues. Hence Dihydropyrimidinone N-Mannich Bases may inhibit the activity of enzyme Topoisomerase II DNA Gyrase and Sterol 14α-Demethylaseby binding at its active site. The compounds ((****DHPM-01, DHPM-03, DHPM-13))*** *were showed potent against the DNA Gyraseas compared with standard Chloramphenicol. The compounds (****DHPM-03, DHPM-05, DHPM-08, and DHPM-16)*** *were showed more potent against the Sterol 14α-demethylase as compared with standard Fluconazole. On the basis of docking result N-Mannich bases of DHPMs may be good Antimicrobial agents.*

Keywords: Dihydropyrimidinone, Mannich bases, Topoisomerase II DNA Gyrase, Sterol 14α-demethylase, Molecular docking, Anti-microbial.

INTRODUCTION

Antimicrobial is an agent that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic). Antimicrobial drugs have generated a dramatic change not only of the treatment of infectious diseases but of a destiny of humanity.1If an inappropriate antimicrobial agent happens to be preferred for the treatment of infection with drug-resistant microorganisms, the therapy may not attains an beneficial effect, and furthermore, may shows to a poor prognosis.2 Special focus on the history of human diseases, infectious diseases have measured for a very large proportion of diseases.3Recent focus in the antimicrobial drug research is on the development of agents inhibiting the enzyme targets involved

in potential role in the life cycle of the pathogen.4DNA gyrase is a subclass of Type II topoisomerases is one of the key enzymes involved in the microbial DNA production cycle and has been considered as a capable target in antibacterial screening.5,6 Similarly, Lanosterol 14α-demethylase (CYP51A1) is a cytochrome P450 enzyme. In the formation of cholesterol in human, demethylated products of the CYP51 reaction play an active role. Ergosterol in fungi, and other types of sterols in plants, hence it should be the capable target in the antifungal screening.7 Competitive and non-competitive inhibition of both DNA gyrase and Lanosterol 14α-demethylase are considered as antimicrobial drugs. Docking was performed against DNA gyrase protein enzyme (PDB ID: 1KZN)9 and Lanosterol 14α-demethylase protein enzyme (PDB ID: 1EA1)10 using the GLIDE molecular docking tool implemented in the Schrodinger software.

MATERIALS AND METHODS

Docking protocol

Molecular docking study on Dihydropyrimidinone derivatives was carry out by software Maestro11.5 from Schrödinger in order to develop selective antimicrobial agents. The docking study of eighteen substituted N-Mannich bases of Dihydropyrimidinone Derivatives was carried out using GLIDE (Grid Based Ligand Docking and Energetics) module of Maestro 11.5 Schrodinger software. The molecule were docked on the *DNA gyrase*protein enzyme (PDB ID: 1KZN) and *Lanosterol 14α-demethylase* protein enzyme (PDB ID: 1EA1) retrieved from the Protein Data Bank (www.rscb.org).

The steps are involved in molecular docking studies:-

Ligand Preparation

The 3D Ligand structures of eighteen Substituted N-Mannich bases of Dihydropyrimidinone derivatives were drawn in MAESTRO workspace using build panel. The Schrödinger ligand preparation was done by using LigPrep panel application and optimize the structure by minimizing its energy through OPLS-3 force field.

Protein Preparation and its Minimization

Protein for ligand docking was prepared by using protein preparation Wizard which was used to import, refine and minimize the energy of the *DNA Gyrase* and *Lanosterol 14-α-Demethylase*. The protein preparation prior to docking is necessary as the protein retrieved from the Protein Data Bank, Vendors, and other sources often have missing hydrogen, partial charges, side chain, and completely loop regions.

Receptor Grid Generation

Grid generation required to be performing prior to running a virtual screen with glide. The shape and properties of the receptor has represented in a grid by field that provides progressively more accurate scoring of the ligand poses.

Validation of Protein

Ramachandran plot is used for the validation *DNA Gyrase* and *Lanosterol 14-α-Demethylase* receptor has performed to test the reliability and reproducibility of the docking protocols for the study.

Protein-Ligand Docking

The ligand docking was done flexibly using Standard Precision (SP) mode of GLIDE module and further refinement was done by using extra precision (XP) mode. The ligand docking process helps to predict ligand conformation and orientation within a targeted binding site and thus results in an accurate structural modeling and correct prediction of activity of ligands.

RESULT and DISCUSSION

All the compounds were docked into the binding site of the receptor (PDB ID- 1KZN and 1EA1), docking result shows that binding of ligand to protein was done independently as per applied constrains with interaction in preferred manner as shown in table 1. Best docking score of the compound were compared using docking score and glide docking energy. Compound DHPM-03 showing the best docking score for which is comparable with the standard (Chloramphenicol) as shown in table 2. Similarly, Compound DHPM-08 showing the best docking score which is comparable with the standard (Fluconazole) as shown in table 3.

Table 1. Showing various substituted Mannich base of DHPMs derivatives

Sr No	Code	Aromatic aldehyde	Code	Aromatic aldehyde
1.	DHPM-01	Benzaldehyde	DHPM-10	4-Bromomethylbenzaldehyde
2.	DHPM-02	4-aminobenzaldehyde	DHPM-11	4-(trifluro 4-hydroxy methylbenzaldehyde
3.	DHPM-03	3-nitrobenzaldehyde	DHPM-12	2,4 Dimethoxybenzaldehyde
4.	DHPM-04	2-hydroxyaldehyde	DHPM-13	4-Flurobenzaldehyde
5.	DHPM-05	4-methylbenzaldehyde	DHPM-14	2,4 Dibromobenzaldehyde
6.	DHPM-06	2-Hydroxy 3,5- dinitro benzaldehyde	DHPM-15	4-Methoxybenzaldehyde
7.	DHPM-07	4-Nitrobenzaldehyde	DHPM-16	4-Bromobenzaldehyde
8.	DHPM-08	2-Chlorobenzaldehyde	DHPM-17	2-Methoxybenzaldehyde
9.	DHPM-09	3,5-Dinitrobenzaldehyde	DHPM-18	2,4 Dichlorobenzaldehyde

Table 2. Docking results for Antibacterial study

Sr. No.	Compound Code	Glide Docking Score	Glide Docking Energy	No. of Hydrogen Bonds
1.	DHPM-01	-5.228	-40.027	1
2.	DHPM-02	-4.215	-52.94	0
3.	DHPM-03	-5.966	-45.378	3
4.	DHPM-04	-4.072	-35.891	0
5.	DHPM-05	-5.309	-55.472	1
6.	DHPM-06	-4.264	-50.213	0
7.	DHPM-07	-3.444	-41.413	0
8.	DHPM-08	-4.524	-42.067	0
9.	DHPM-09	-2806	-39.885	0
10.	DHPM-10	-4.856	-45.355	0
11.	DHPM-11	-4.284	-42.39	0
12.	DHPM-12	-4.479	-47.773	0
13.	DHPM-13	-6.797	-45.95	0
14.	DHPM-14	-3.821	-40.022	2
15.	DHPM-15	-2.238	-43.538	0
16.	DHPM-16	-5.031	-53.56	0
17.	DHPM-17	-3.473	-40.04	2
18.	DHPM-18	-4.616	-41.65	0
19.	Standard (Chloramphenicol)	-5.11	-56.205	2

Table 3. Docking results for Antifungal study

Sr. No.	Compound Code	Glide Docking Score	Glide Docking Energy	No. of Hydrogen Bonds
1.	DHPM-01	-6.524	-25.027	0
2.	DHPM-02	-6.215	-20.94	0
3.	DHPM-03	-7.845	-30.378	1
4.	DHPM-04	-5.321	-40.891	0
5.	DHPM-05	-8.53	-35.472	3
6.	DHPM-06	-6.23	-21.213	0
7.	DHPM-07	-6.452	-20.413	0
8.	DHPM-08	-9.79	-21.067	4
9.	DHPM-09	-7.012	-23.885	1
10.	DHPM-10	-5.846	-40.599	0
11.	DHPM-11	-7.125	-31.761	1
12.	DHPM-12	-6.945	-32.155	0
13.	DHPM-13	-6.797	-30.077	0
14.	DHPM-14	-6.895	-24.933	2
15.	DHPM-15	-5.125	-32.802	0
16.	DHPM-16	-8.031	-21.407	3
17.	DHPM-17	-6.012	-19	0
18.	DHPM-18	-7.124	-27.512	1
19.	Standard (Fluconazole)	-7.789	-31.949	2

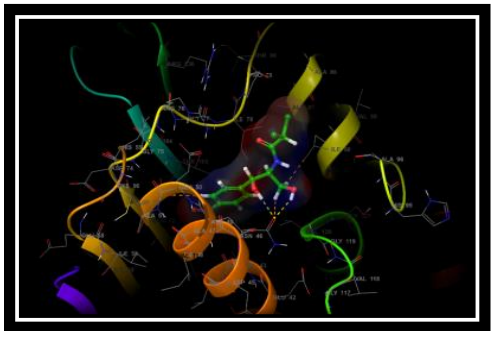

Fig.1 : Best binding pose of compound Chloramphenicol

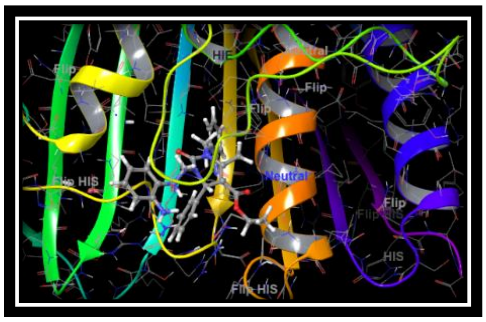

Fig.2 : Best binding pose of compound DHPM- 03

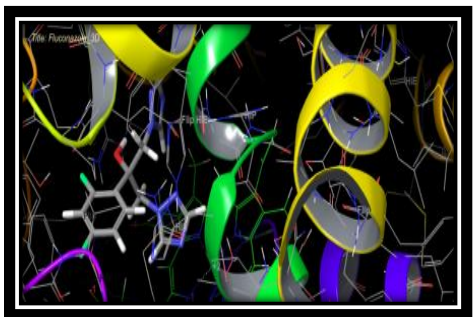

Fig.3 : Best binding pose of compound Fluconazole

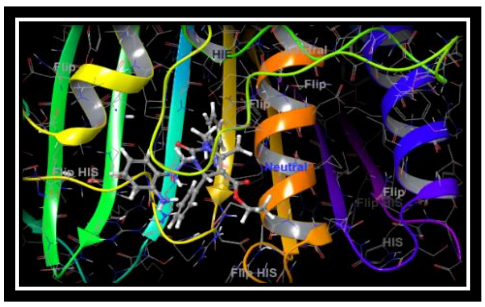

Fig.4 : Best binding pose of compound DHPM-08

CONCLUSION

Molecular docking studies concluded that compounds (**DHPM-01, DHPM-03, DHPM-13**) possessed higher G-score and have shown good hydrogen bond interaction with DNA gyrase enzyme as compared to Standard Chloramphenicol (-5.110) which are Most Active for antibacterial Activity. The molecular docking studies revealed that the Compounds (**DHPM-03, DHPM-05, DHPM-08, DHPM-16**) possessed higher G-score and have shown good hydrogen bond interaction with Sterol 14 alpha demethylase enzyme as compared to standard Fluconazole (-7.789) which are most active for Antifungal Activity. Therefore, it was decided to synthesis above six Mannich Bases of DHPMs derivatives. On the basis of result of molecular docking of these compounds could be selected as a lead compounds for further development of antimicrobial agents.

Conflict of Interest

Authors declared that we have no conflict of interest.

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CONFLICTING INTEREST

The authors declare that they have no competing interests.

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