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MOLECULAR DOCKING STUDIES ON CARBAZOLE DERIVATIVES

Prafulla M. Sabale*[1], Potey Lata[1], Kadkanje Sandip[1]

[1*]Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440033, Maharashtra, India.

ABSTRACT

Carbazole is one of the most important nitrogen containing fused heterocyclic moiety in various chronic as well as other diseases. The main objective of molecular docking is to predict the biological activity of given ligand. This work has been focus on the carbazole moiety as anti-microbial agents, present work emphasize the flexible and extra precision docking simulation on eighteen different Carbazole substituted derivatives in order to evaluate their affinity to bacterial proteins for antibacterial and antifungal activity against *DNA gyrase* (PDB:1KZN) and *Lanosterol 14-α-Demethylase* (PDB:1EA1) enzymes respectively by Maestro 11.5 Schrodinger software in order to choose the derivatives which shows good interactions with target protein. All the compound shows best docking results compared to Chloramphenicol and Fluconazole as standard drugs. Compound C_{16} shows -5.373 docking score as standard Chloramphenicol itself shows -5.110 docking score against *DNA Gyrase* enzyme for anti-bacterial agents. Whereas in anti-fungal study, the compound Ca_1 gives -9.869 docking score as standard Fluconazole gives -7.789 docking score against *Lanosterol 14-α-Demethylase* enzyme. The results may conclude that Carbazole may serve as useful hits in the development of clinically useful anti-microbial agents.

KEYWORDS

Carbazole, DNA *gyrase* enzyme, *Lanosterol 14-α-Demethylase* enzyme, Molecular docking studies and Anti-microbial activity.

Author for Correspondence:
Prafulla M. Sabale,
Department of Pharmaceutical Sciences,
Rashtrasant Tukadoji Maharaj Nagpur University,
Nagpur, Maharashtra, India.

Email: prafullasable@yahoo.com

INTRODUCTON

The antimicrobial agents are the substances 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[1]. If an inappropriate antimicrobial

agent happens to be chosen for the treatment of infection with drug-resistant microorganisms, the therapy may not attains an advantageous effect, and furthermore, may shows to a poor prognosis[2]. Special focus on the history of human diseases, infectious diseases have considered for a very large proportion of diseases as a whole[3]. Recent 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[4]. *DNA gyrase*, the class of topoisomerase and 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 promising target in antibacterial screening[5,6]. Similarly, *Lanosterol 14α-demethylase* (CYP51A1) is a cytochrome P450 enzyme. The demethylated products of the CYP51 reaction are vital intermediates in pathways leading to the formation of cholesterol in humans, ergosterol in fungi, and other types of sterols in plants, hence it should be the promising 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)[8] and *Lanosterol 14α-demethylase* protein enzyme (PDB ID: 1EA1)[9] using the GLIDE molecular docking tool implemented in the Schrodinger software.

MATERIAL AND METHODS

Docking protocol

Molecular docking study on Carbazole derivatives was carried out by Schrödinger software Maestro11.5v in order to develop selective antimicrobial agents. The docking study of eighteen thiazolidine substituted Carbazole compounds 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) imported from the Protein Data Bank (www.rscb.org).

The steps are involved in molecular docking studies:-

Ligand Preparation

The 2D Ligand structures of eighteen Thiazolidine substituted Carbazole derivatives were drawn in MAESTRO workspace using build panel. The Schrödinger ligand preparation was done by using LigPrep panel application and optimize the structure to 3D by minimizing its energy through OPLS-3 force field.

Protein Preparation and its Refinement

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 obtained from the PDB, 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

Ramchandran 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

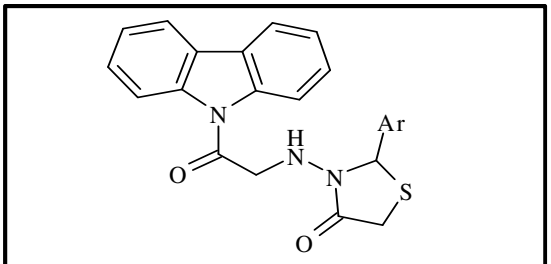
The ligand docking was done flexibly using Standard Precision (SP) mode of GLIDE module and further refinement was done by using extra precision (XP) mode. The ligand docking process helps to predict ligand conformation and orientation (posing) within a targeted binding site and thus results in an accurate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

RESULTS AND DISCUSSION

All the compounds were docked into the binding site of the enzymes (PDB ID- 1KZN and 1EA1), docking result shows that binding of ligand to protein occur as pre applied constrains with

interaction in preferred manner as shown in Table No.1. Best biological activity was predicted on the basis of highest docking score and glide docking energy. Compound C_{16} has shown good antibacterial activity against *DNA Gyrase* enzyme with highest docking score (-5.373) and Glide docking energy (-51.560) which is comparable with the standard Chloramphenicol with docking score (-5.110) and glide docking energy (-56.205) as shown in Table No.2. Similarly, Compound Ca_1 has shown good antifungal activity against *Lanosterol 14α-demethylase* enzyme with highest docking score (-9.869) and Glide docking energy (-40.599) which is comparable with the standard Fluconazole with docking score (-7.789) and glide docking energy (-45.801) as shown in Table No.3. Hydrogen bonding was observed with oxygen of 4-hydroxyl group for compound (Ca_1) and the hydrogen of amino group for compound (C_{16}), which indicates that both the compounds bind with the active site in a similar way as the natural substrate which is shown in figure 1 and 2. Compound (C_{16}) has shown the non bonding interactions with GLU 50, ARG 76, ASP 49, ASP 101, ILE 90, PRO 79 and ILE 78 active amino acid residues in binding pocket of *DNA Gyrase* enzyme and the compound (Ca_1) shown interactions with MET 433, ARG 96, PHE 83, PHE 78, MET 79, TYR 76, MET 99, SER 252 and GLN 72 amino acid residues in binding pockets of *Lanosterol 14α-demethylase* enzyme, shown in Figure No.1 and 2. Compound C12 and Ca_{11} have shown less binding affinity with *DNA Gyrase* and *Lanosterol 14α-demethylase* enzyme respectively with least docking and glide energy scores it could be because of its inauspicious positioning in contrast to the other active compounds and natural substrate androstenedione in the active site.

Table No.1: Thiazolidine substituted Carbazole derivatives



Thiazolidine Substituted Carbazole Derivatives

S.No	For Antibacterial		For Antifungal	
1	**Code**	**Ar**	**Code**	**Ar**
2	C_1	Benzaldehyde	Ca_1	4-Hydroxybenzaldehyde
3	C_2	3-methoxybenzaldehyde	Ca_2	4-Methylbenzaldehyde
4	C_3	3-Methylbenzaldehyde	Ca_3	3-Bromobenzaldehyde
5	C_4	Salicylaldehyde	Ca_4	Benzaldehyde
6	C_5	4-Dimethylaminobenzaldehyde	Ca_5	3-Methylbenzaldehyde
7	C_6	2,4-Dimethoxybenzaldehyde	Ca_6	4-Chlorobenzaldehyde
8	C_7	4-Trifluoromethylbenzaldehyde	Ca_7	3-methoxybenzaldehyde
9	C_8	4-Chlorobenzaldehyde	Ca_8	2,3-Dimethoxybenzaldehyde
10	C_9	2,4-Dichlorobenzaldehyde	Ca_9	4-Dimethylaminobenzaldehyde
11	C_{10}	2-Methoxybenzaldehyde	Ca_{10}	3-Chlorobenzaldehyde
12	C_{11}	3-Bromobenzaldehyde	Ca_{11}	2,4-Dimethoxybenzaldehyde
13	C_{12}	2-Nitrobenzaldehyde	-	-
14	C_{13}	3-Chlorobenzaldehyde	-	-

15	C_{14}	4-Nitrobenzaldehyde	-	-
16	C_{15}	2,3-Dimethoxybenzaldehyde	-	-
17	C_{16}	4-Hydroxybenzaldehyde	-	-
18	C_{17}	4-Methylbenzaldehyde	-	-
19	C_{18}	4-Methoxybenzaldehyde	-	-
20	Standard	Chloramphenicol	Standard	Fluconazole

Table No.2: Docking results for Antibacterial study

S.No	Compound Code	Glide Docking Score	Glide Docking Energy	No. of Hydrogen Bonds
1	C_1	-4.625	-48.027	1
2	C_2	-4.660	-47.940	1
3	C_3	-4.446	-43.378	0
4	C_4	-4.801	-49.891	0
5	C_5	-4.760	-50.472	0
6	C_6	-3.467	-51.213	0
7	C_7	-4.643	-49.413	1
8	C_8	-2.559	-47.067	0
9	C_9	-4.499	-45.885	0
10	C_{10}	-4.418	-47.355	1
11	C_{11}	-4.552	-47.390	0
12	C_{12}	-1.852	-42.773	0
13	C_{13}	-2.574	-41.950	1
14	C_{14}	-4.028	-45.022	0
15	C_{15}	-4.243	-43.538	0
16	C_{16}	-5.373	-51.560	2
17	C_{17}	-4.720	-49.040	1
18	C_{18}	-4.667	-47.650	1
19	Standard	-5.110	-56.205	2

Table No.3: Docking results for Antifungal study

S.No	Compound Code	Glide Docking Score	Glide Docking Energy	No. of Hydrogen Bonds
1	Ca_1	-9.869	-40.599	1
2	Ca_2	-9.433	-37.761	0
3	Ca_3	-9.266	-36.155	0
4	Ca_4	-8.881	-32.077	0
5	Ca_5	-8.492	-27.933	0
6	Ca_6	-8.299	-33.802	0
7	Ca_7	-6.398	-26.407	0
8	Ca_8	-5.437	-1.000	0
9	Ca_9	-4.618	-8.512	0
10	Ca_{10}	-3.951	-31.949	0
11	Ca_{11}	-3.778	-30.039	0
12	Standard	-7.789	-45.801	0

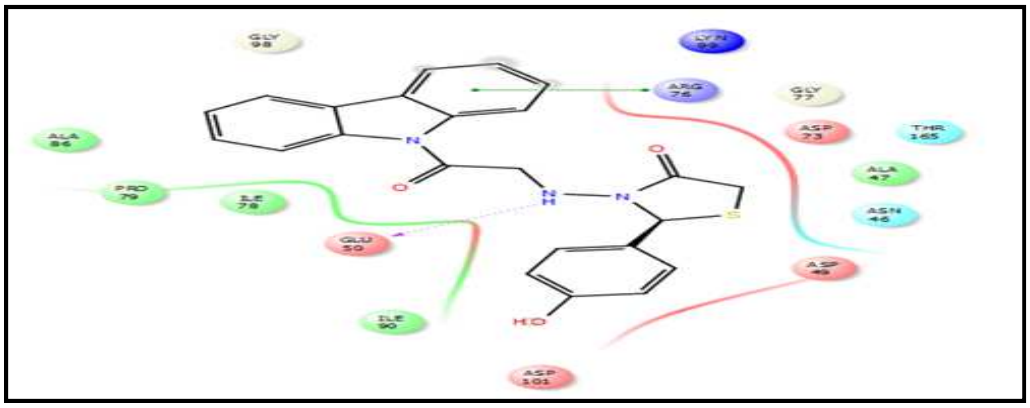


Figure No.1: Docked conformations of compound C_{16} along with important amino acid residues of *DNA gyrase* (PDB: 1KZN) enzyme as antibacterial

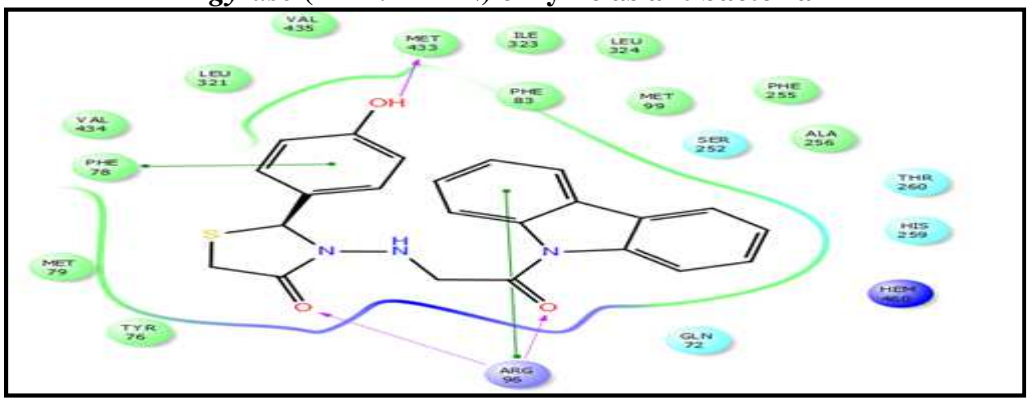


Figure No.2: Docked conformations of compound Ca_1 along with important amino acid residues of *Lanosterol 14α-demethylase* (PDB: 1EA1) enzyme as antifungal

CONCLUSION

Results of docking study clearly demonstrated that the selected thiazolidine substituted Carbazole derivatives have better binding sites and interactions with selected proteins. The highly précised binding protein interactions leads to greater field interaction with crystallized domain. This can be valuable for synthesis and thereafter biological screening of promising hits.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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