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Molecular docking studies of novel Carbazole tethered pyrrole derivatives as potent inhibitors of *Mycobacterium tuberculosis*

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Abstract
Recent focus in the tubercular drug research is on the development of agents inhibiting the enzyme targets involved in potential role in the life cycle of the pathogen. Inh A, the enoyl acyl carrier protein reductase from *Mycobacterium tuberculosis* is one of the key enzymes involved in the mycobacterial fatty acid elongation cycle and has been considered as a promising target in antitubercular screening. Inhibition of Inh A disrupts the biosynthesis of the mycolic acids that are central constituents of the mycobacterial cell wall. In the present research work the docking studies was performed on the human pathogenic bacterial enzyme InhA from its parent domain *Mycobacterium Tuberculosis.* In this present study, the flexible and extra precision docking simulation were performed on twenty new carbazole tethered pyrrole derivative against InhA by using Glide v5.6. All the derivatives were considered and docked as well as bound to ligand binding domain EAcCPR. All the compounds show good Glide score as compared to isoniazid as standard drug. Compound MA8 showing highest glide score (-9.518). The result obtain were valuable for synthesis and thereafter biological screening of promising hits and it could be useful for development of new anti- tubercular agents.

Keywords: molecular docking studies, potent inhibitors, *Mycobacterium tuberculosis*

Introduction
Tuberculosis (TB) is a highly dangerous infectious disease caused by the bacterial pathogen Mycobacterium tuberculosis (Mtb). Amongst the worldwide health threats, TB continued to remain as second leading cause of mortality from a single infectious disease. In 2012 alone, nearly 1.3 million fatalities are due to TB and over 95% of them are occurred in low- and middle income countries. Further TB threat has acquired a new dimension with the emergence of both multidrug- resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Recent focus in the tubercular drug research is on the development of agents inhibiting the enzyme targets involved in potential role in the life cycle of the pathogen. Inh A, the enoyl acyl carrier protein reductase from Mycobacterium tuberculosis is one of the key enzymes involved in the mycobacterial fatty acid elongation cycle and has been considered as a promising target in antitubercular screening. Inhibition of Inh A disrupts the biosynthesis of the mycolic acids that are central constituents of the mycobacterial cell wall. Docking was performed against enoyl acyl carrier protein reductase protein (PDB ID: 4TZK) and enoyl acyl carrier protein reductase transpeptidase (PDB ID: 2H7M) using the GLIDE molecular docking tool implemented in the Schrodinger software.

Objective: The objective of the present research is to perform docking studies of novel carbazole tethered pyrrole derivatives as potent inhibitors of mycobacterium tuberculosis.

Experimental method
Docking protocol
The docking study of twenty compounds was carried out using GLIDE (Grid Based Ligand Docking and Energetics) module of Schrodinger Suite 2010. The molecule were docked on the enoyl acyl carrier protein reductase protein (PDB ID: 4TZK) and enoyl acyl carrier protein reductase transpeptidase (PDB ID: 2H7M) taken from the Protein Data Bank (www.rscb.org).

Preparation of protein
The protein was prepared by running the protein preparation wizard.

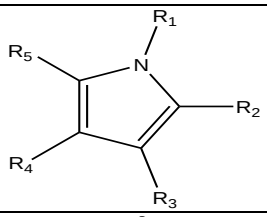
The protein preparation was carried out in two steps:-
1. Preparation
2. Refinement

Ligand preparation
The 3D Ligand structure of twenty carbazole conjucted pyyrole were drawn in MAESTRO workspace using build panel. It was then prepared for using lig Prep (3.2) application. The initial geometry of the structure was optimized using the OPLS-2005 force field.

Receptor grid generation
Grids were generated by receptor Grid Generation Panel which defines receptor structure by excluding any co-crystallized ligand that may be present, determines the position and size of the active sites as it will be represented by receptor grids, and set up glide constrains.

Docking simulation
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. Hydrogen bond interaction, docking scores, emodal energy and RMSD between c-alpha atoms of derivatives with respect to references ligand carbazole.

Table 1: showing various substitutionson pyrole ring



R^1	R^2	R^3	R^4	R^5
H	H	H	H	H
Methyl	H	H	H	H
Methyl	Methyl	H	H	H
Ethyl	H	H	H	H
Methyl	H	H	Methyl	H
Ethyl	H	4-Methyl	H	H
Methyl	H	4-Methyl	H	H
Ethyl	Ethyl	H	H	H
t-Butyl	H	3-CI	H	H
Methyl	H	3,4-Methylenedioxy	H	H
Ethyl	H	3,4-Methylenedioxy	H	H
{pyrrolidino}		H	H	H
{pyrrolidino}		4-Methyl	H	H
{pyrrolidino}		4-MeO	H	H
{pyrrolidino}		4-Methyl	Propyl	H
{pyrrolidino}		4-Methyl	Ethyl	H
{pyrrolidino}		4-Methyl	Methyl	H
{pyrrolidino}		4-Methyl	H	Methyl
{pyrrolidino}		3,4-Methylenedioxy	H	H
{pyrrolidino}		3,4-Methylenedioxy	Ethyl	H

Table 2: coupound code, docking score, Glide Emodel energy, RMSD

S. No	Compound Code	Glide Docking Score	Glide Emodel Energy	RMSD
1	MA1	-8.2704	-39.8266	0.3156
2	MA2	-8.0861	-36.4803	0.0452
3	MA3	-8.7528	-39.5468	0.3872
4	MA4	-7.8685	-40.3519	1.0682
5	MA5	-8.1373	-34.495	0.6437
6	MA6	-8.5838	-38.7973	1.3056
7	MA7	-8.3759	-38.9353	1.6985
8	MA8	-9.5187	-45.0566	0.3511
9	MA9	-8.5079	-44.8770	2.1361
10	MA10	-8.2199	-37.6536	1.8003
11	MA11	-8.3513	-38.6739	0.8520
12	MA12	-8.7111	-37.1584	0.9836
13	MA13	-8.3634	-38.1594	1.4976
14	MA14	-9.3464	-54.2946	0.2456
15	MA15	-8.4692	-44.5972	0.4559
16	MA16	-8.7518	-34.5849	0.4685
17	MA17	-9.4861	-47.3497	1.2459
18	MA18	-6.3479	-46.1645	0.1254
19	MA19	-7.4621	-47.3565	0.7864
20	MA20	-7.7964	-51.5846	1.2465

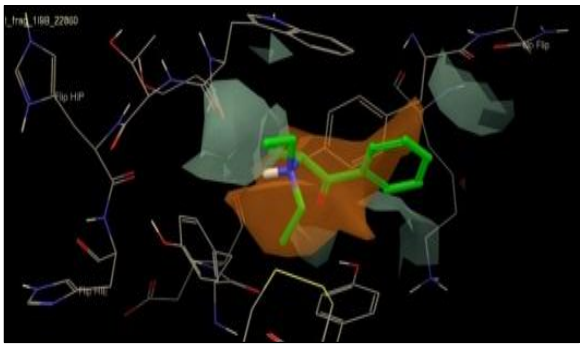


Fig 1a: Best binding pose of compound standard

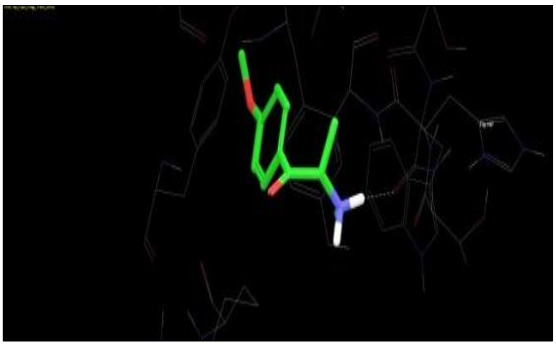


Fig 1b: best binding pose of compound MA8

Result and discussion

Molecular docking simulation

- All the compounds were docked into the binding site of the receptor (PDB ID- 4ZTK) using Grid Based Ligand Docking with Energetics (Glide) software.
- After preparation of ligand and protein, protein grid was generated by setting grid box of size 12×12×12 A to define the size if grid box in which ligand were expected to dock.
- Docking result shows that binding of ligand to protein occur as pre applied constrains with interaction in preferred manner as shown in table 1.
- Best docking score of the compound were compared using docking score and emodel energy. Compound V8 showing the best glide score (-95187) and Glide emodel energy (-45.0566) which is comparable with the standard (Carbazole) as shown in table 2.
- From the binding pose the best docked compound (*RS*)-2-diethylamino-1-phenylpropan-1-one as shown in figure 1a and 1b it is clear that the compound bound to ligand binding domain EAcCPR.

Conclusion

These results clearly indicate that the selected carbazole tethered pyyrole derivatives have better binding sites and interactions with mycobacterium cell wall protein. The highly précised binding protein interactions leads to greater field interaction with crystalized domain. This can be valuable for synthesis and thereafter biological screening of promising hits.

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