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MOLECULAR DOCKING STUDIES OF 6-FLUORO-8-HYDROXY-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS

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ABSTRACT

Structure based drug design is one of the key approach for a rational drug design. In the present work, a molecular docking study was implemented to decipher the binding interaction pattern of novel derivatives of 1-cyclopropyl-6,7-difluoro-8methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid against beta-ketoacyl-acp synthase II using Autodock Vina. Beta-ketoacyl-acp synthase II is one of the important target for pathogenic and drug resistant bacteria because it is involved in fatty acid biosynthesis (FAB) in these prokaryotes. The Autodock Vina result showed that out of five derivatives, P5have showed best binding energy (-15.3 Kcal/mol) and it interacted with residues CYS112, ILE156, MET207, VAL212 and ALA246 in the active site of the protein. The lead molecule can be considered for further study.

KEYWORDS: Molecular docking, Quinoline carboxylic acid, beta-ketoacyl-acp synthase II, Autodock Vina, FAB.

INTRODUCTION

The explosion of drug resistant bacteria in recent times poses threat to human health and society. There is an urgency to tackle these drug resistant bacteria by developing novel antibiotics. In recent years, new bacterial targets have been identified and became the interest of research for development new antibacterial agents.

The Fatty acid biosynthesis (FAB) pathway is promising pathway of target of interest as it is vital for the synthesis of fatty acids which forms the cell wall of bacteria, for their growth and survival.[1] Beta-Ketoacyl-acyl carrier protein (ACP) synthase II, also known as FabH or KAS II, is a key enzyme known to play an essential and regulatory role in bacterial FAB.[2,3] The enzyme initiates the fatty acid elongation cycles.[4] It is also involved in the feedback regulation of the biosynthetic pathway via product inhibition.[5]

Quinoline and their derivatives have been used for many years as antibacterial agents and their antibacterial activity are well elucidated in literature.[6]

Molecular docking which is used to predict the binding affinity of small molecules to their target proteins.[7] It is frequently used as a rational approach because synthetic approach would be cost-expensive and time consuming method.[8]

In this present work, the derivatives of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was designed with different R groups to form novel scaffolds and subsequently docked to predict the high binding affinity molecule that could be potential lead for development antibacterial agent.

MATERIALS AND METHODS

Design of derivatives

The derivatives of 1-cyclopropyl-6,7-difluro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid were designed by adding different derivatives substituted in the position of C-7. The core moiety and respective R groups added to it were shown in Fig. 1.The molecules were renamed to code names as P1, P2, P3, P4 and P5 and their Code names, Chemical formula, Molecular weight were shown in Table1.

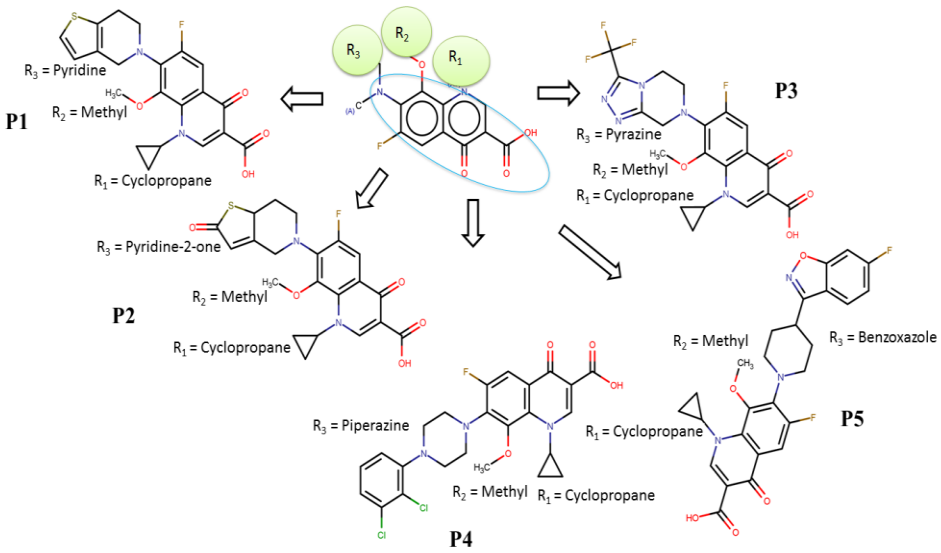


Fig: 1 The derivatives were designed from core moiety highlighted in blue ellipsoid and the respective R groups were highlighted in green and written for all the molecules.

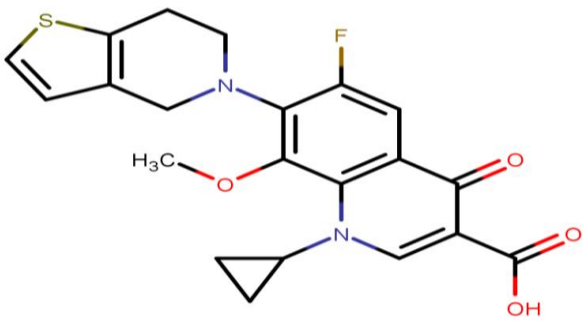
Table1 Ligands with code name, chemical formula and molecular weight

Code Name	Chemical Formula	Molecular Weight
P1	$C_{21}H_{19}FN_2O_4S$	414.45
P2	$C_{21}H_{19}FN_2O_5S$	430.45
P3	$C_{20}H_{17}F_4N_5O_4$	467.38
P4	$C_{24}H_{22}CL_2FN_3O_4$	506.36
P5	$C_{26}H_{23}F_2N_3O_5$	495.47

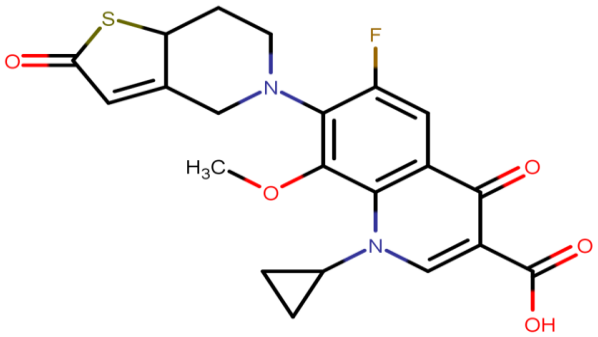
Ligand structure and preparation

The chemical structure of all designed derivatives was drawn by Marvinsketch.[9] The drawn structures with IUPAC name were shown in Fig. 2. The 3D structures of these ligands were optimized by MOPAC program[10] and saved as Triposmol2 format. The mol2 format was then converted to respective pdb formats by Openbable program.[11]

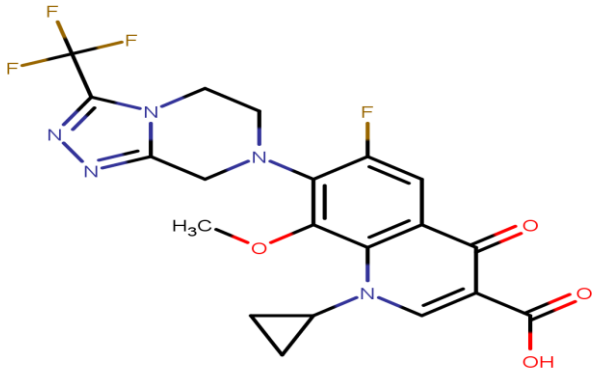
P1: 1-cyclopropyl-7-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.



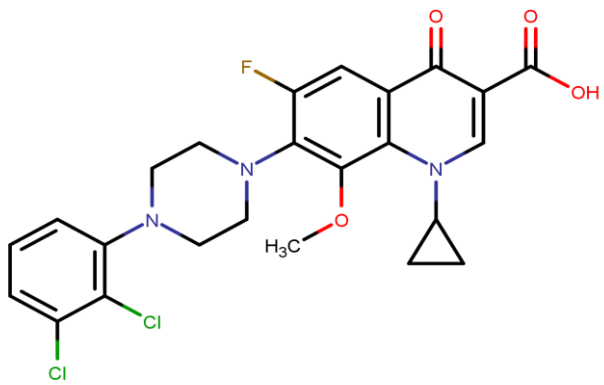
P2: 1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(2-oxo-7,7a-dihydrothieno[3,2-c]pyridin-5(2H,4H,6H)-yl)-1,4-dihydroquinoline-3-carboxylic acid.



P3: 1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1,4-dihydroquinoline-3-carboxylic acid.



P4: 1-cyclopropyl-7-(4-(2,3-dichlorophenyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.



P5: 1-cyclopropyl-6-fluoro-7-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

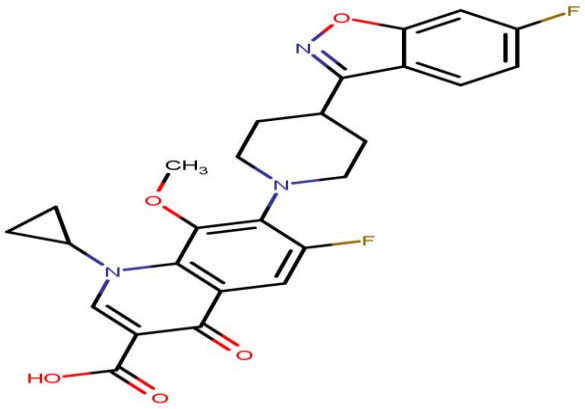


Fig: 2. The chemical structures of ligands with IUPAC name.

Preparation of protein

The crystal structure of protein was retrieved from Protein Data Bank (PDB id: 1HNJ). Water molecules, bound ligands were removed and missing residues were corrected from the crystal structure by UCSF Chimera.[12]

Molecular docking

The prepared ligands and protein were converted to respective pdbqt formats by AutoDock tools from MGLTOOLS suite.[13]Autodock Vina[14] was employed for performing docking calculation because of its fast screening algorithm the vina provides. The grid box size of 68 x 92 x 88 was generated for all ligands.Ligands were docked at the active site of protein as shown in Fig. 3. The exhaustiveness of vina was set to default, 8, due computational constraint. All these parameters were written to the configuration file of vina for calculation. Post docking calculation for visualization and interaction Pymol[15-16] was used.

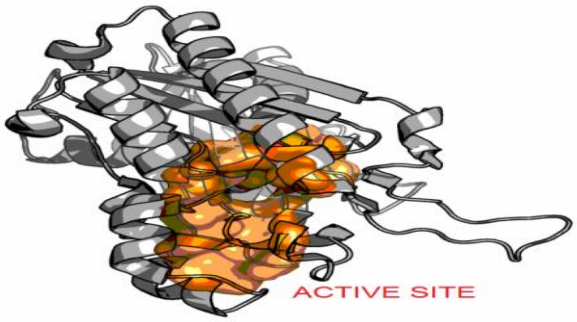


Fig. 3 Protein (PDB: 1HNJ) represented in cartoon (grey) and the active site illustrated as surface (orange) where the ligands were docked.

RESULT AND DISCUSSION

Docking results were analysed on binding energy and hydrogen bond. The average binding energy of all ligands was shown in Table 2. Among five ligands, P5 showed highest binding energy with binding energy -15.3 Kcal/mol.

Table: 2 Average binding energy of ligands with respective code name.

Code name	Binding energy (Kcal/mol)
P5	-15.3
P4	-14.6
P3	-14.6
P2	-13.1
P1	-13.1

The molecule formed van der waal interaction with GLY305. The quinonline ring of the molecule formed a weak Pi bond with VAL212, ALA246, ILE156 and CYS112 of the active site. Residue MET207 exhibited Pi-sulfur interaction. Van der waal and weak Pi bonds helped ligand to be in correct conformation for interaction between ligand and active site residues. All the interactions of P5 molecule is shown as 2D representation and 3D illustration of docked P5 molecule in the active site of protein is shown in Fig. 4.

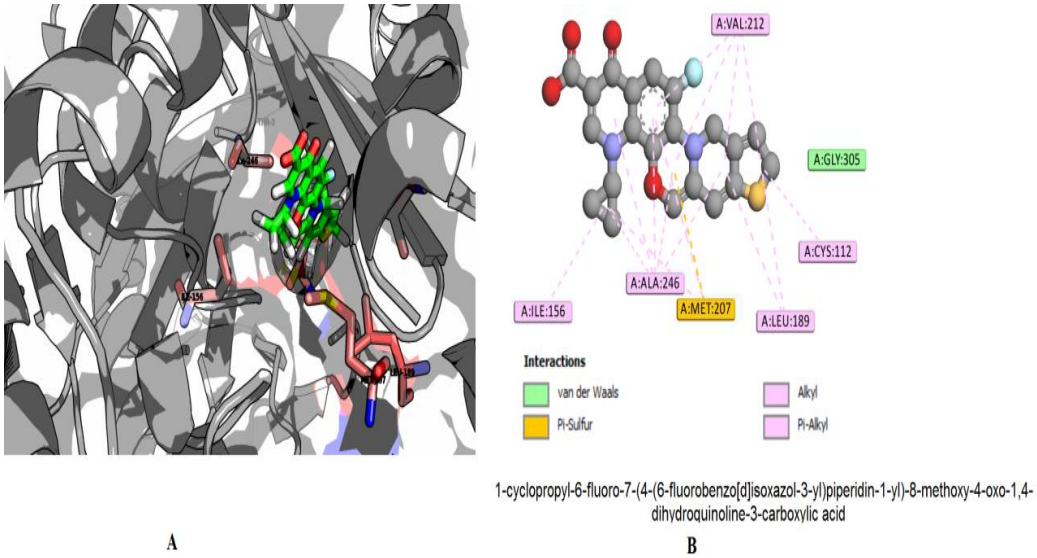


Fig: 4 (A) 3d representation of highest binding affininity docked molecule P5 and (B) Interaction profile of the molecule with IUPAC name.

CONCLUSION

Molecular docking study provides virtual screening approach to filter large molecule databases and to predict the strongest binding ligands. This study tries to identify the

strongest binder of beta-ketoacyl-acp synthase II from the derivatives of 1-cyclopropyl-6,7-difluro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid as novel antibacterial agent. P5 or 1-cyclopropyl-6-fluoro-7-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid has shown highest binding energy in docking and can act as a lead molecule towards the development of beta-ketoacyl-acp synthase II inhibitors though further research is needed.

REFERENCES

1. Hoang, Tung T., et al. "β-Ketoacyl acyl carrier protein reductase (FabG) activity of the fatty acid biosynthetic pathway is a determining factor of 3-oxo-homoserine lactone acyl chain lengths." *Microbiology*, 2002; 148.12: 3849-3856.
2. Khandekar, Sanjay S., Robert A. Daines, and John T. Lonsdale. "Bacterial β-ketoacyl-acyl carrier protein synthases as targets for antibacterial agents." Current Protein and Peptide Science, 2003; 4.1: 21-29.
3. Heath, Richard J., and Charles O. Rock. "The Claisen condensation in biology." Natural product reports, 2002; 19.5: 581-596.
4. Martz, Françoise, et al. "Contribution of omega-3 fatty acid desaturase and 3-ketoacyl-ACP synthase II (KASII) genes in the modulation of glycerolipid fatty acid composition during cold acclimation in birch leaves." Journal of experimental botany, 2006; 57.4: 897-909.
5. Heath, Richard J., and Charles O. Rock. "Regulation of fatty acid elongation and initiation by acyl-acyl carrier protein in Escherichia coli." Journal of Biological Chemistry, 1996; 271.4: 1833-1836.
6. Kharb, R., M. Shahar Yar, and P. C Sharma. "New insights into chemistry and anti-infective potential of triazole scaffold." Current medicinal chemistry, 2011; 18.21: 3265-3297.
7. Taylor, Richard D., Philip J. Jewsbury, and Jonathan W. Essex. "A review of protein-small molecule docking methods." Journal of computer-aided molecular design, 2002; 16.3: 151-166.
8. Jorgensen, William L. "The many roles of computation in drug discovery." Science, 2004; 303.5665: 1813-1818.
9. Chem Axon, L. L. C. "Marvin Sketch, 2012; 5.11: 4.".
10. Stewart, James JP. "MOPAC: a semiempirical molecular orbital program." Journal of computer-aided molecular design, 1990; 4.1: 1-103.

11. O'Boyle, Noel M., et al. "Open Babel: An open chemical toolbox." Journal of cheminformatics, 2011; 3.1: 1.
12. Pettersen, Eric F., et al. "UCSF Chimera—a visualization system for exploratory research and analysis." Journal of computational chemistry, 2004; 25.13: 1605-1612.
13. Huey, Ruth, and Garrett M. Morris. "Using Auto Dock 4 with Auto Docktools: a tutorial." The Scripps Research Institute, USA, 2008; 54-56.
14. Trott, Oleg, and Arthur J. Olson. "Auto Dock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading." Journal of computational chemistry, 2010; 31.2: 455-461.
15. DeLano, Warren L. "The Py MOL molecular graphics system." 2002.
16. Betty Daneial, Devashish das, Jacob V J Paul, Guruprasad R. Establishing wonder oil, Solanesol, as a novel inhibitor for Focal Adhesive Kinase by in silico strategies. doi: http://dx.doi.org/10.1101/086660.