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Original Article

# DESIGN, BINDING AFFINITY STUDIES AND *IN SILICO* ADMET PREDICTIONS OF NOVEL ISOXAZOLES AS POTENTIAL ANTI-BACTERIAL

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**ABSTRACT**

**Objective:** The objective of the study is to design novel isoxazole derivatives, predicting their interactions with the selected target proteins and determining the ADMET properties of potent molecules using recent computational methods.

**Methods:** With the intent to discover potent novel antibacterial, we have designed a set of compounds containing the isoxazole nucleus by using software tools like Discovery studios, PyRx, PyMOL, SWISSPDB. ADMET studies were carried out by using SWISS ADMET and pkCSM. Molecular docking studies were carried out on the target proteins of both gram-positive and gram negative bacteria in order to assesses binding affinity for the proteins.

**Results:** Designed scaffold was designed by Benzene Derivatives Tethered with 5(4-chloro-3-nitro phenyl-1-yl) isoxazole. All the derivatives were docked against the three proteins, namely DNA Ligase (PDB ID: 3PN1), Topoisomerase (PDB ID: 3TTZ), Sterol demethylase (PDB ID: 5FSA), The compound JJC3F has shown best binding score against DNA ligase, sterol demethylase protein. Further, compound JJC3A has shown a better binding affinity towards topoisomerase than the standard drugs.

**Conclusion:** Molecular Docking study indicates that isoxazole derivatives may be effective inhibitors for the different microbial proteins. Additionally, *in silico* ADMET studies predicts drug-like features. Hence, these compounds may be considered as leads and further investigation of their analogues may help in development of novel drugs for the treatment of microbial diseases.

**Keywords**: Molecular docking, DNA ligase, Topoisomerase, Glutamate racemase, Sterol Demethylase, Isoxazole, ADMET, SWISSPDB, PyMOL


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## INTRODUCTION

Drug discovery is a method and time-thorough process which is aimed at developing new drug candidates. By using the aid of computational means in the pre-clinical phase of drug discovery. Computer-aided drug design (CADD) is defined as discover, develop, and analyse drug and active molecules with similar biochemical properties by using computational approaches. Some of them are Homology modelling; molecular docking, virtual screening (VS) or virtual high-throughput screening (vHTS), quantitative structure reactivity relationship (QSAR) and three-dimensional (3D) pharmacophore mapping generally, are the main constituents of CADD. Among these techniques, it seems that virtual screening is the major contributor to CADD and it has become somewhat a proven and well-appreciated computational method, which stands as a contemporary to the experimental high-throughput screening for hit identification and optimization, This computational method is mainly based upon the improvements in computing algorithms, considerable development of computers processing power and as well as in the vast knowledge of structural and physico-chemical properties of compounds in libraries and databases like pubchem etc., and the increased knowledge of the structural and functional properties of protein molecules. This computational method can be applied to screen for chemical compounds (natural and synthesized), peptides or proteins [1].

Molecular docking is used to find out the hit molecule from numerous compounds to a particular protein 3d structure is available. Lock and key, induced work and ensemble are the three categories of docking; Docking methodology are following rigid ligand and rigid receptor docking; flexible ligand and rigid receptor docking; and flexible ligand and flexible receptor docking. Docking software's are available in-house and out-house for use [2].

The main aim of docking is to find the ligand which is fitting into the binding site of the receptor results like binding affinity, force-field, empirical etc., are useful to find out the best conformation between ligand and receptor [2].

Microbial diseases are becoming global threat because of the effective decrease in the potential activity of anti-microbial therapies and also bacteria's like *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* theses families of organism becomes serious threat to the society because of change in the pathology of these organisms [3, 4].

Microbial organisms are adapting to the condition and evolving their nature and acquiring resistance to the available anti-microbial drugs. So that there is need for developing novel anti-microbial agents [5].

Based on the need for novel microbial agents we designed a set of isoxazole contains compounds by using this computational software's.

Isoxazole is a five-membered ring with two hetero atoms like oxygen and nitrogen, which are present adjacent to each other, isoxazole are most widely used against insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic agents [6].

Hence, the present study focuses on designing of novel isoxazole derivatives, predicting their interactions with the selected target proteins and determining the ADMET properties of potent molecules using recent computational methods.

## MATERIALS AND METHODS

In this study, three protein targets were selected, namely DNA ligase, Topoisomerase, 14-$\alpha$ Sterol demethylase proteinand their X-Ray Diffraction structures were taken from RCSB Protein Data Bank in PDB ID: 3PN1 [6], 3TTZ [7], in PDB format respectively. Preparation

of protein was done on swisspdb after downloading the protein from protein data bank in pdb format and it was opened in swisspdb. It will automatically arrange all the missing amino acids and remove water molecule and add hydrogen bonds to it and save it in pdb format. Designed ten ligands structure were drawn by using chemsktech and saved in SDF format. All the ligands were then converted to cluster file in SDF format using Discovery Studio 2021 Client. Standard drugs Ciprofloxacin, Moxifloxacin were selected for docking on the same targets in order for comparison of docking scores. The structures of the standards were downloaded from Pubchem and saved in 3D conformer as SDF format. The structure of protein was loaded in PyRx software where the Kollmann and Gasteiger charges were assigned. The proteins were then converted to PDBQT file format. Then the ligands were loaded into PyRx, energy minimised and converted to PDBQT file format. Finally specific protein and ligands were selected for docking and grid box was assigned in the protein structure. Molecular docking was performed in PyRx software after assigning grid dimensions. Docking of the ligands at the active site of the respective proteins was carried out. The docking scores and binding energy analysis were downloaded in the CVS format. The ligand which gave best score compared to standard drugs against the proteins was chosen it will be opened along with protein in pymol for envisioning the 3D interaction. The multiple files will be compressed into a single file and its docking interactions were visualised in 2D conformation using Discovery Studio 2021 Client.

**Table 1: ADMET studies using pkCSM [8]**

| **Physic-chemical properties** | **Compounds** | |
|---|---|---|
| | **JJC3A** | **JJC3F** |
| **Descriptor** | **Value** | **Value** |
| Molecular Weight | 318.716 | 337.162 |
| LogP | 3.5708 | 4.5186 |
| Rotatable Bonds | 3 | 3 |
| Acceptors | 5 | 4 |
| Donors | 2 | 1 |
| Surface Area | 130.256 | 135.765 |

## RESULTS AND DISCUSSION

Designed compound shows better binding affinity and also all the designed compounds are following Lipinski rule of five which means the designed may show potent activity towards selected targets docking results revealed that Substitution of OH group at 2nd position show better activity against DNA gyrase, moreover compound JJC3A shows better activity against topoisomerase. The structure of scaffold is given in figure. Total Ten derivatives of the designed scaffold were prepared using ChemDraw 20.0 and their structures are given in figure.

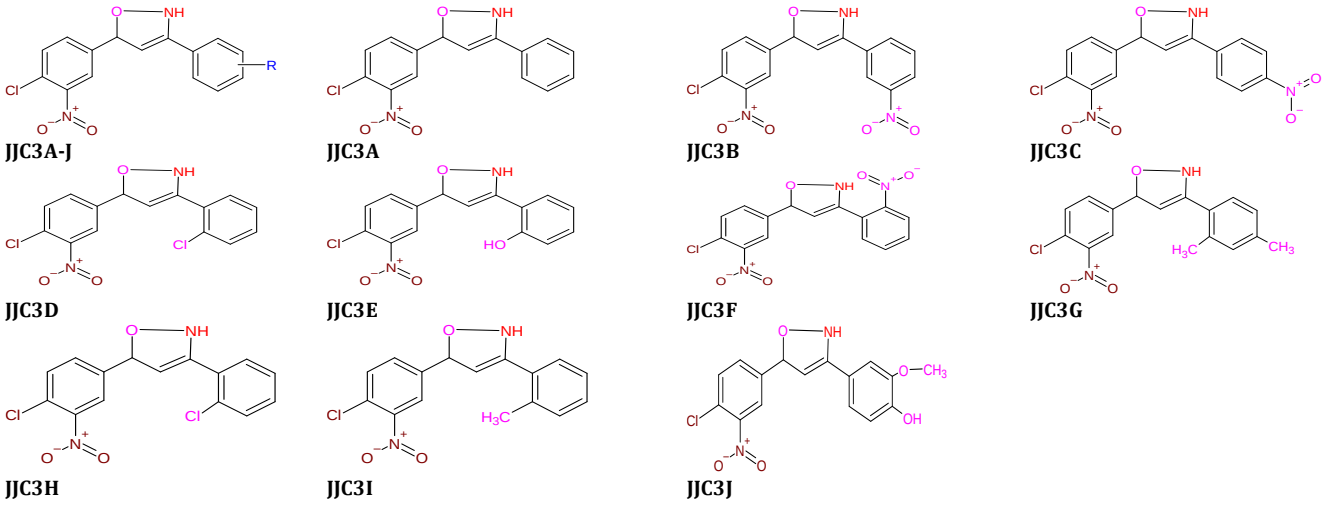


**Fig. 1: Benzene derivatives tethered with 5(4-chloro-3-nitro phenyl-1-yl)isoxazole**

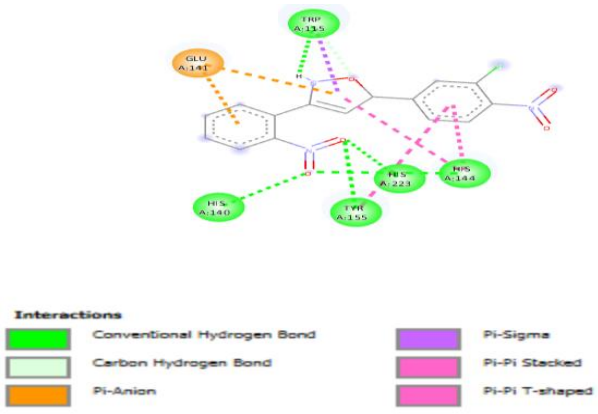


**Fig. 2: 2D interaction of compound JJC3F with DNA ligase**

**Molecular docking studies**

Molecular docking is the computational method of drug discovery which is use for prediction of interaction between the ligand and protein The interaction energy includes van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding were calculated for each minimized complex. The residues thus predicted are energetically important for ligand binding inside the binding site via hydrophobic, hydrogen bond interactions in almost all complexes.

**Table 1: Docking scores of ligands against selected target proteins**

| S. No. | Ligand | Docking score | |
|---|---|---|---|
| | | DNA ligase (3PN1) | Topoisomerase (3TTZ) |
| 1. | JJC3A | 9.2 | -9.3 |
| 2. | JJC3B | 9.6 | -8 |
| 3. | JJC3C | 9.0 | -86 |
| 4. | JJC3D | 8.8 | -8.8 |
| 5. | JJC3E | 8.7 | -9 |
| 6. | JJC3F | 10.1 | -8.1 |
| 7. | JJC3G | 9.9 | -8.8 |
| 8. | JJC3H | 9.5 | -8.6 |
| 9. | JJC3I | 9.6 | -8.7 |
| 10. | JJC3J | 9.9 | -8.6 |
| S1 | Ciprofloxacin | -8.9 | -7.6 |
| S2. | Moxifloxacin | -9.9 | -7.1 |

All the ligands were docked against the selected proteins. Among them compound JJC3F has shown the best binding score against DNA ligase. Further, compound JJC3A has shown a better binding affinity towards topoisomerase than the standard drugs. The 2D interactions of potent molecules with the target proteins are shown in below fig. 1-3.

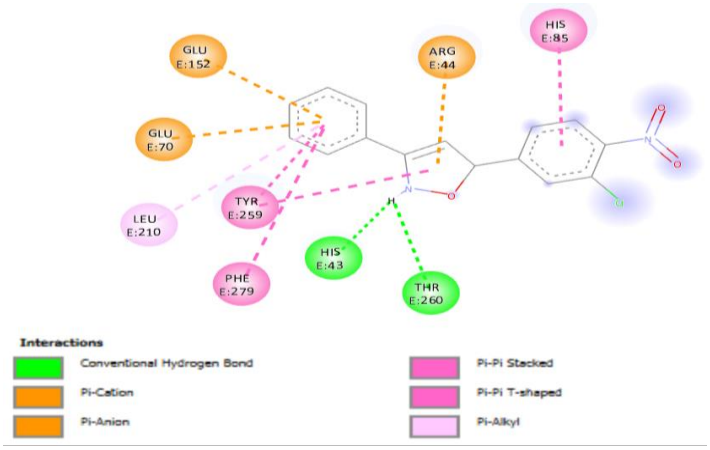


**Fig. 3: 2D interaction of compound JJC3A with topoisomerase**

**CONCLUSION**

Molecular Docking study indicates that Benzene Derivatives Tethered with 5(4-chloro-3-nitro phenyl-1-yl) isoxazole may be effective inhibitors for selected bacterial proteins. Additionally, *in silico* ADMET studies predicts drug-like features. Therefore, these compounds can be considered as leads for further investigation in development of novel, effective antibacterial.

**AUTHORS CONTRIBUTIONS**

The study protocol was designed by Judy Jays and has coordinated the overall project. Molecular docking was performed by G. Chaitanya Sai and ADMET studies were computed by Burhanuddin Madriwala.

**FUNDING**

The data used to support the findings of this study are available with the corresponding author upon request.

**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICTS OF INTERESTS**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

**REFERENCES**

1. Sabe VT, Ntombela T, Jhamba LA, Maguire GEM, Govender T, Naicker T. Current trends in computer-aided drug design and a highlight of drugs discovered via computational techniques: a review. Eur J Med Chem. 2021;224:113705. doi: 10.1016/j.ejmech.2021.113705, PMID 34303871.
2. Joseph L, George M. Anti-bacterial and *in vitro* anti-diabetic potential of novel isoxazole derivatives. Br J Pharm Res. 2016;9(4):1-7. doi: 10.9734/BJPR/2016/21926.
3. Aktas DA, Akinalp G, Sanli F, Yucel MA, Gambacorta N, Nicolotti O. Design, synthesis and biological evaluation of 3,5-diaryl isoxazole derivatives as potential anticancer agents. Bioorg Med Chem Lett. 2020;30(19):127427. doi: 10.1016/j.bmcl.2020.127427, PMID 32750679.
4. Shahinshavali S, Sreenivasulu R, Guttikonda VR, Kolli D, Rao MVB. Synthesis and anticancer activity of amide derivatives of 1,2-isoxazole combined 1,2,4-thiadiazole. Russ J Gen Chem. 2019;89(2):324-9. doi: 10.1134/S1070363219020257.
5. Bhardwaj S, Bendi A, Singh L. A study on synthesis of chalcone derived-5-membered isoxazoline and isoxazole scaffolds. Curr Org Synth. 2022;19. doi: 10.2174/1570179419666220127143141.
6. Bi F, Ma R, Ma S. Discovery and optimization of NAD$^+$-dependent DNA ligase inhibitors as novel antibacterial com-

pounds. Curr Pharm Des. 2017;23(14):2117-30. doi: 10.2174/1381612822666161025145639, PMID 27784238.

7. Sherer BA, Hull K, Green O, Basarab G, Hauck S, Hill P. Pyrrolamide DNA gyrase inhibitors: optimization of antibacterial activity and efficacy. Bioorg Med Chem Lett. 2011;21(24):7416-20. doi: 10.1016/j.bmcl.2011.10.010, PMID 22041057.
8. Pires D; 2022. Biosig.unimelb.edu.au. Available from: http://biosig.unimelb.edu.au/pkcsm/theory. [Last accessed on 23 May 2022]
9. Shaik A, Bhandare RR, Palleapati K, Nissankararao S, Kancharlapalli V, Shaik S. Antimicrobial, antioxidant, and anticancer activities of some novel isoxazole ring containing chalcone and dihydro pyrazole derivatives. Molecules. 2020;25(5):1047. doi: 10.3390/molecules25051047, PMID 32110945.