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REVIEW: ACTIVITY PREDICTION,MOLECULAR DOCKING AND IR INTERPRITATION OF CIPRFLOXACIN

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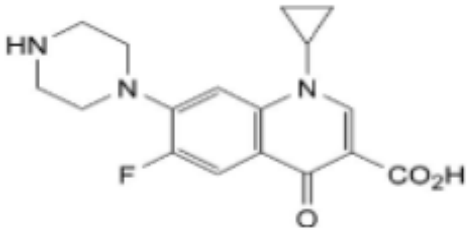
ABSTRACT :

Heterocyclic compounds considered one of the vital classes of organic compounds, which are used in many biological fields, due to it is activity in multiple illnesses. Quinoline is six membered unsaturated nitrogen containing heterocyclic compound. Quinoline derivatives play a crucial role in medicinal chemistry due to their diverse biological activities and therapeutic potential. Quinoline nucleus occurs in several natural compounds, which exhibit wide range of biological activity such as anti-inflammatory, Antimalarial, HIV-1 replication inhibitors, antituberculosis and anthelmintic. Ciprofloxacin is a good candidate and displayed better in silico activity against Staphylococcus aureus DNA gyrase (2XCT- protein).The best affinity target is selected for final docking based on docking score. CHEMINFO.ORG.IR website used to predict the infrared spectrum of ciprofloxacin.

INTRODUCTION :

Ciprofloxacin is an antibiotic agent in the fluoroquinolone class used to treat bacterial infections such as urinary tract infections and pneumonia



MECHANISM:

- DNA Gyrase Inhibition
- Topoisomerase IV Inhibition

SIDE EFFECT:

- Vomiting, Stomach pain , Nausea, Diarrhea.

TO PREDICT BIOACTIVITY USING MOLINSPIRATION :

Molinspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfileconversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches.

Molinspiration supports internet chemistry community by offering free on-line services for calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors).

Molinspiration molecule viewer allows visualization of collection of molecules encoded as SMILES or SDfile. SMILES is automatically transformed into molecule 2D representation by our depiction engine. Display of associated data, selection of molecules, built-in substructure search and export of selected molecules is supported.

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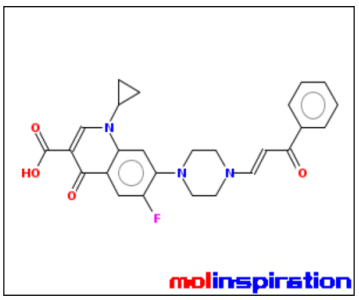
miSMILES: O=C(O)c5cn(C1CC1)c4cc(N3CCN(C=CC(=O)c2ccccc2)CC3)c(F)cc4c5=O



Molinspiration bioactivity score v2022.08

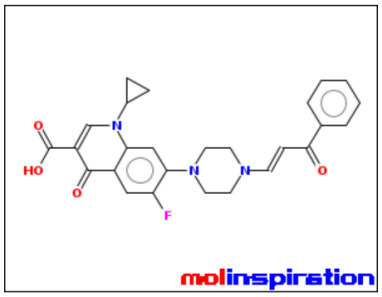
GPCR ligand	-0.01
Ion channel modulator	-0.19
Kinase inhibitor	-0.26
Nuclear receptor ligand	-0.33
Protease inhibitor	-0.26
Enzyme inhibitor	0.20

Get data as text (for copy / paste).

Get 3D geometry BETA

molinspiration

miSMILES: O=C(O)c5cn(C1CC1)c4cc(N3CCN(C=CC(=O)c2ccccc2)CC3)c(F)cc4c5=O

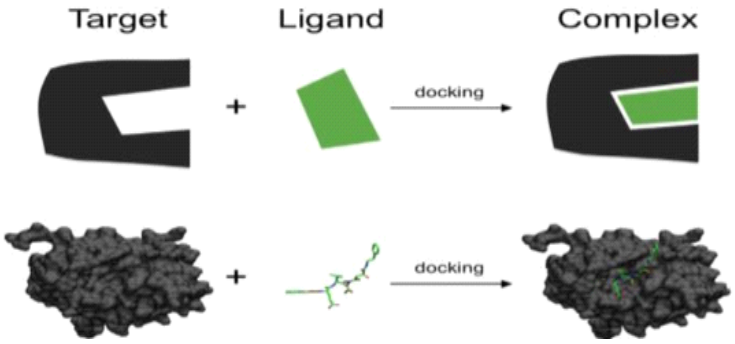


Molinspiration property engine v2022.08

miLogP	1.22
TPSA	82.85
natoms	34
MW	461.49
nON	7
nOHNH	1
nviolations	0
nrotb	6
volume	403.65

MOLEULAR DOCKING :

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design.Predicting the main binding mode(s) of a ligand with a protein that has a known three-dimensional structure is the aim of ligand-protein docking. Effective docking techniques use a scoring system that appropriately rates candidate dockings and efficiently explore high-dimensional spaces. Docking is a helpful tool for lead optimization since it can be used to virtually screen huge compound libraries, rank the results, and suggest structural ideas about how the ligands block the target. It can occasionally be difficult to interpret the outcomes of stochastic search techniques, and configuring the input structures for the docking is just as crucial as the docking process itself. This chapter covers the history and principles of molecular.



Types of docking: -

Docking study can be of three types, namely rigid docking, flexible-rigid docking, and flexible docking (based on the flexibility of the interacting molecules, receptor, and ligand).

Rigid docking: -

In rigid type docking, both ligand and receptor molecules are considered rigid. Their coformation is not changed and thus the internal geometry of each molecule is kept fixed. The lock-and-key principle can be applied in this method

Flexible-rigid docking: -

It is a semi-flexible docking method. In this case, either ligand or receptor is taken as a rigid body. Usually, the shape of the receptor is kept fixed, and the conformation of the ligand is varied. This method gives more accurate and better reliable results than the rigid docking method and is thus frequently used.

Flexible (soft) docking: -

It is a fully flexible docking method, in which both ligand and receptor are considered as flexible bodies, i.e., an enumeration of rotations of the molecules (both receptor and ligand) is done to search for optimized conformation and orientation of the molecules to interact with each other. The

molecule's shape can be varied by changing the torsion angles and rotatable bonds. This method results in the prediction of docked conformation with high accuracy that most probably resembles experimental results but may require heavy computational calculation and time.
In both semi-flexible and fully flexible docking methods, the induced-fit principle can be implemented, and the docking process becomes complicated when the interacting molecule has many conformational degrees of freedom.

Applications of Molecular Docking

Lead optimization
Hit identifications
Drug-DNA interaction

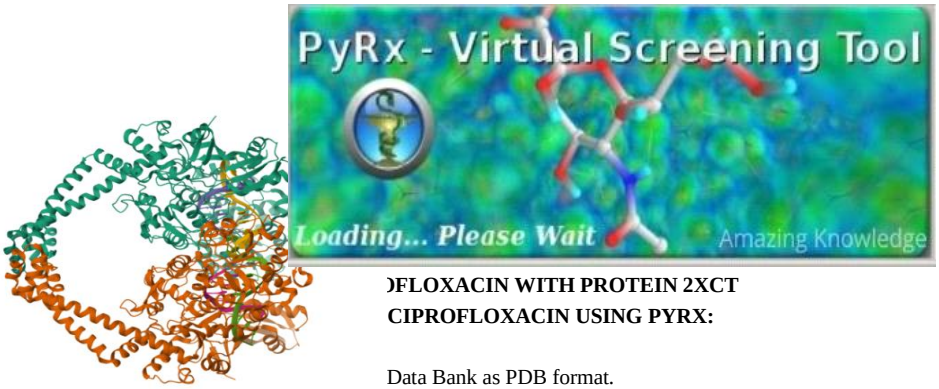
SOFTWARES USED IN MOLECULAR DOCKING

- AUTO DOCK
- SCHRODINGER'S GLIDE
- AUTODOCK VINA
- GOLD
- SURFLEX –DOCK

MOLECLAR DOCKING OF CIPROFLOXACIN BY USING PyRXSOFTWARE:

Here the molecular docking done between 2XCT(target protein) and the ciprofloxacin(lignd) done by using pyrex software.
PyRx is a Virtual Screening software for Computational Drug Discovery.
PyRx is using a large body of established open source software including:

- *AutoDock 4 and AutoDockVina are used as a docking software.
- AutoDockTools, used to generate input files.
- Python as a programming scripting language.
- Open Babel for importing SDF files, removing salt and energy minimization.



)FLOXACIN WITH PROTEIN 2XCT
CIPROFLOXACIN USING PYRX:

Data Bank as PDB format.

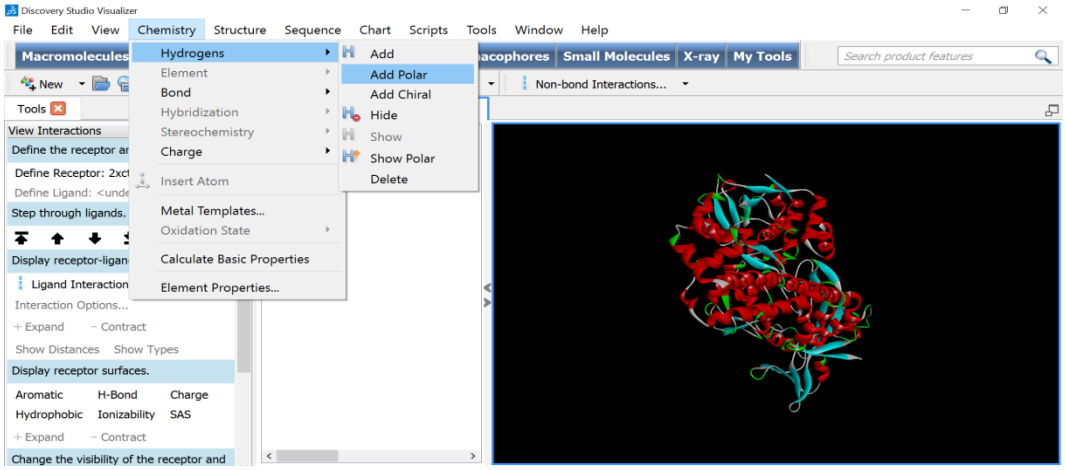
b) DOWNLOAD THE LIGAND CIPROFLOXACIN

The ligand ciprofloxacin was downloaded from pubchem as 3D SDF (structure data file)format.

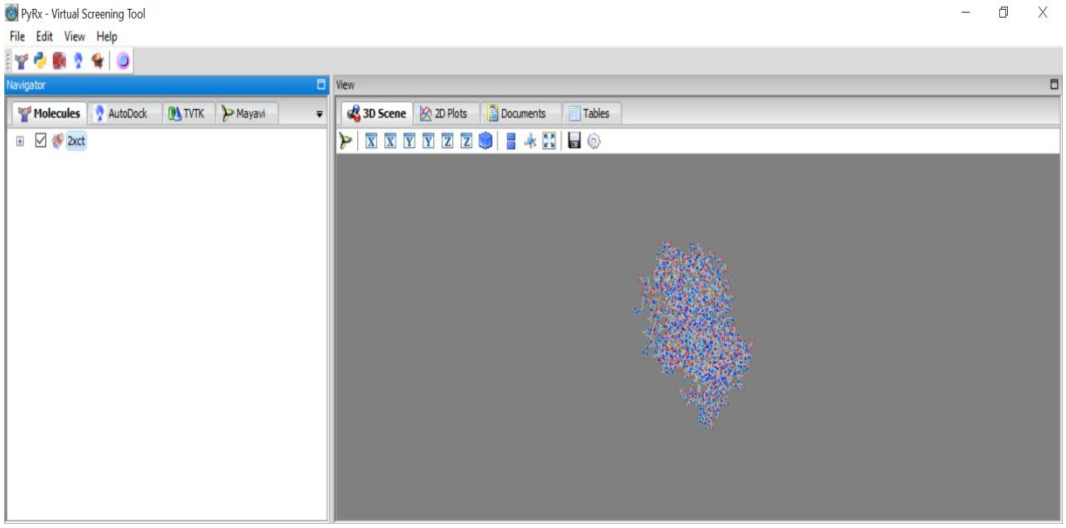
c) PROTEIN PREPERATION

protein preparation carried out in Biovia Discovery Studio.

• Biovia discovery studio > view> hierarchy >(a side window will open contain the details ofprotein; delete water molecule hetero atom and chains other than main chain containingbinding site) chemistry> hydrogen>add polar only> file>save> with extention .pdb.



PyRx > file> load molecule> select the protein(right click the mouse)> display >molecularsurface view.

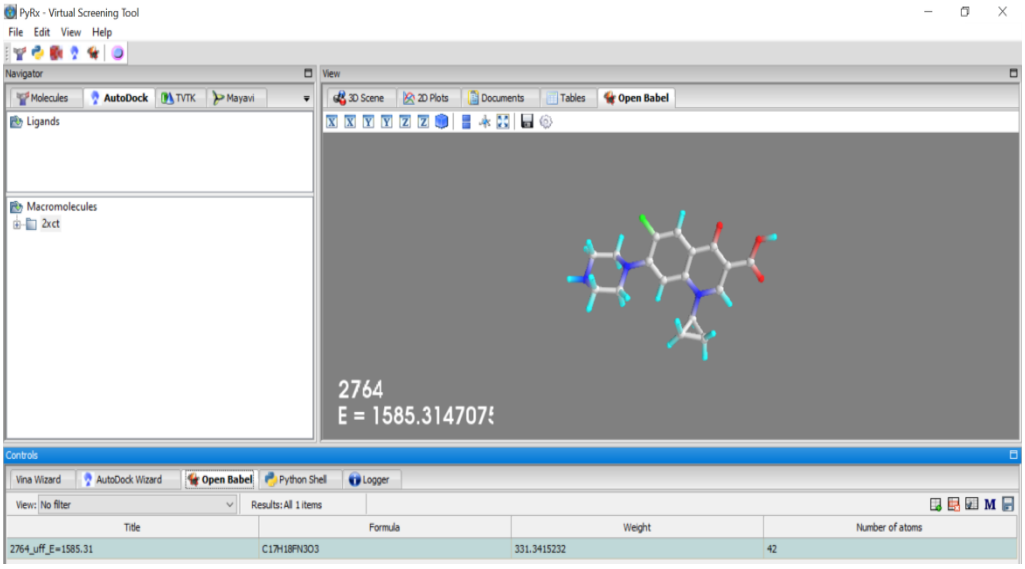


• Select the protein(right click the mouse) >auto dock>macromolecule.

a) LIGAND PREPARATION

Ligand preparation is carried out in open babel ,which is already present in PyRx.

• Open Babel >insert new one>select the ligand>open>select ligand (right click the mouse)minimize selected> conert selected to autodock ligand pdbqt.



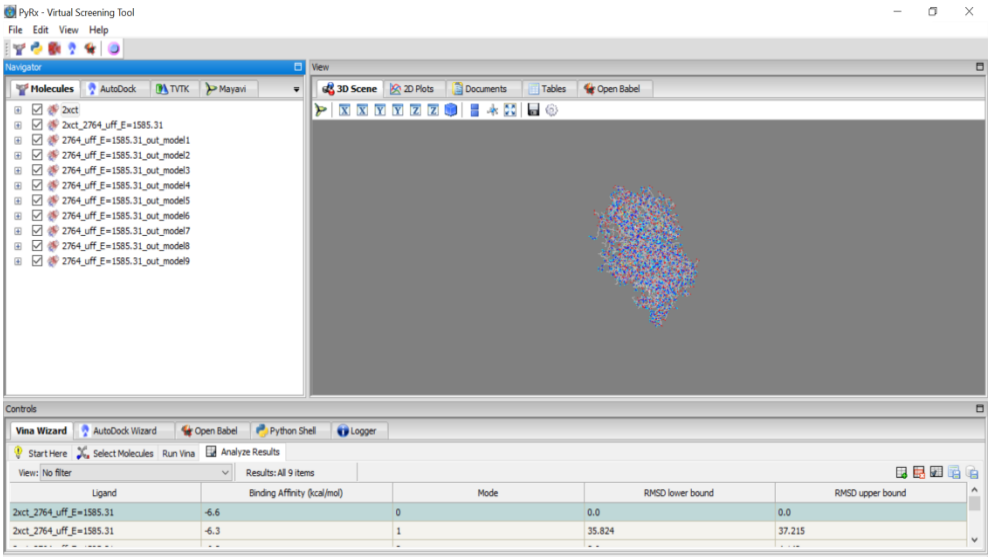
b) SELECTION OF BEST DOCKING SCORE

It can be carried out in vina wizard present in PyRx.

• Vina wizard > start> select protein and ligand >forward>grid box.

The dimension of grid box can be changed,Here in blind docking entire surface of protein isconsidered and grid is formed in such a way that entire protein come inside the grid box.

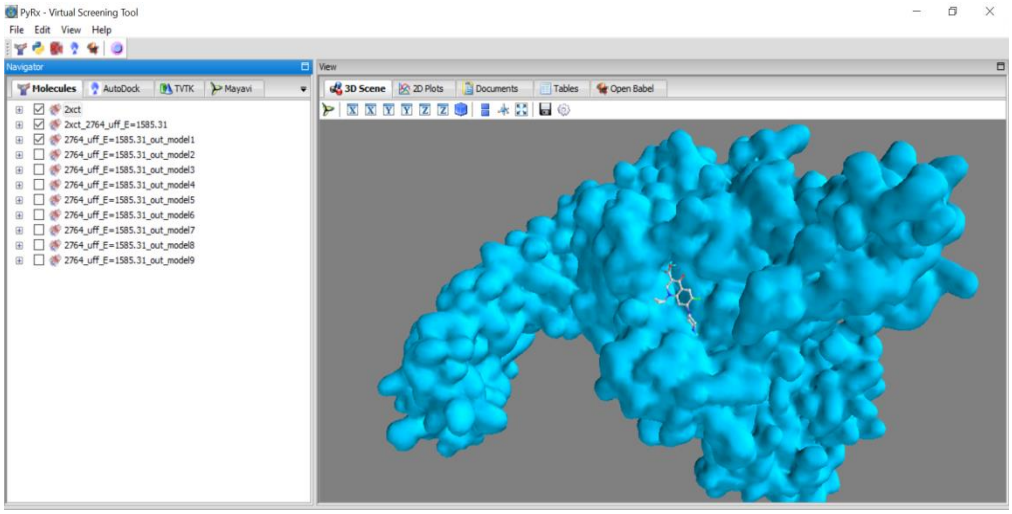
• After forming grid box click forward,then scoring function will run.



• Select the ligand with highest docking score>display

All the confirmations of ligand will be displayed

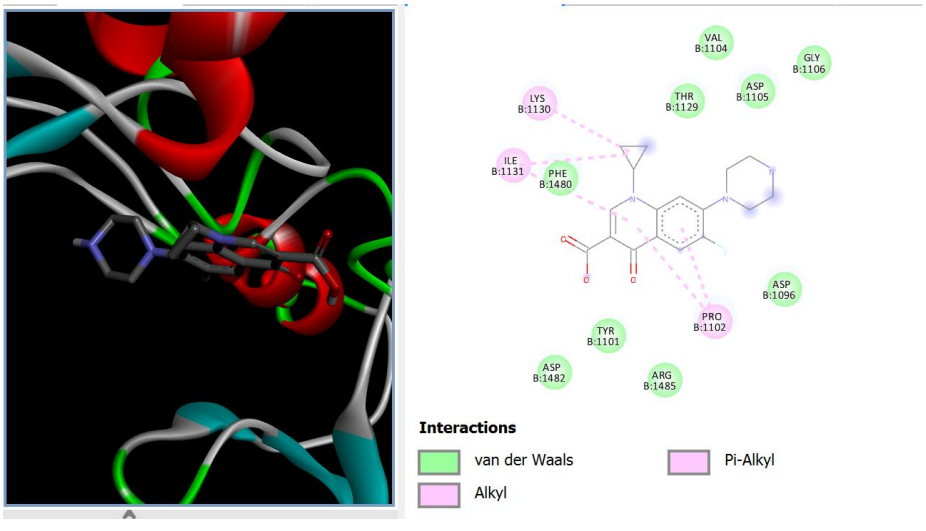
• select one confimation with best docking score>display>macromolecule>save as pdb



c) STRUCTURE VISUALIZATION OF DOCKED

The docked structure can be visualized in Biovia Discovery Studio

• Biovia discovery studio> file>open > model 1.pdb>view>hierarchy>copy>file>open>prepared protein>view>hierarchy>paste.



d) ANALYSIS OF INTERACTION

To analyze the docked pose of the lowest binding free energy conformer with the DNA gyrase protein, we use Biovia Discovery Studio .Which ensured that the ligands were binding to the correct protein binding pocket after docking.

The molecular docking of ciprofloxacin with targeted protein 2CXT is done by using pyrx software. The best affinity target is selected for final docking based on highest –ve docking score.

The ligand ciprofloxacin formed a hydrogen bonds with a polar residues (amino acid) PHE 1480 of 2XCT protein. It also formed alkyl interaction with LYS 1130, ILE 1131 and PRO 1102.

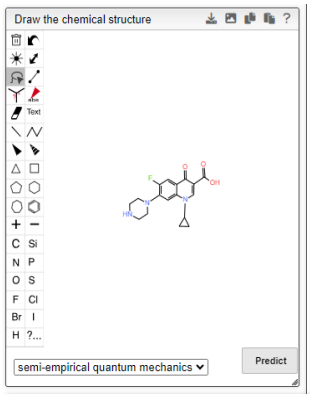
Ciprofloxacin is a good candidate and displayed better in silico activity against Staphylococcus aureus DNA gyrase (2XCT- protein).

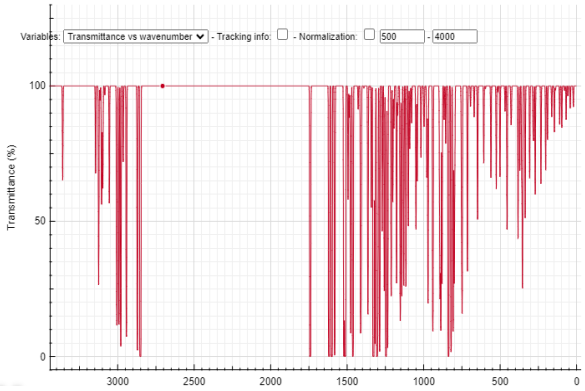
CHEMINFO.ORG.IR :

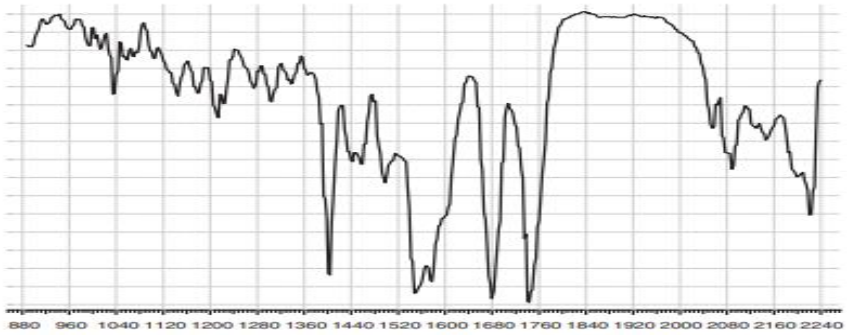
It is website used to predict the infrared spectrum of any compound from its structure.

IR spectroscopy is a technique used to analyze and identify chemical compounds based on their absorption of IR radiation.

It used to identify functional group of a compound.







The camparison between the observed and experimented ir peak value is done and the below table shows the ranges.

FUNCTIONAL GROUPS	RANGE	OBSERERVED RANGE
O-H	3490	3500
N-H	3320	3350
N-C	2930	2900
C-O of carboxyl group	1696	1700
C-O of quinoline group	1605	1600
C-N	1480,1435	1450,1420

- 3490 O–H stretch
- 3320 N–H stretch of piperazinyl moiety
- 2930 Aliphatic C–H stretch
- 2840 N–C stretch
- 1696 C¼O stretch of carboxyl group

- 1605 C¼O stretch of quinoline
- 1480, 1435 C–N stretch

Ciprofloxacin is a good candidate and displayed better in silico activity against Staphylococcus aureus DNA gyrase (2XCT- protein) . After analyzing all parameters, like bioactivity using molinspiration , functional groups using cheminfo.org.ir . The study was concluded on the basis of various studies done by molinspiration , cheminfo.org.ir, PyRx software.

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