ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Molecular Docking Studies On Antiviral Activity Of Pyrimidine Contain Novel Indole-2-One Derivatives.

Swaroopa HM, Muvendan C*, Rashmi T, and Naveen K Mathew.

Department of Pharmaceutical chemistry, Bharathi College of Pharmacy, Bharathinagar-571422, Maddur Taluk, Mandya District, Karnataka, India.

ABSTRACT

Molecular docking has become a reliable virtual screening method in the search for compounds that have activity against specific receptors. The current study incorporates the use of Insilco molecular modeling tool Autodock Vina. The three-dimensional structure of Pokeweed Antiviral Protein (PDB ID: 1J1S) was downloaded, the two-dimensional structures of 12 compounds were generated, cleaned and performed 3D optimization then saved in the MDL Molfile format and converted to a PDBQT file format. Molecular docking of pyrimidine contain indole-2-one derivatives against Pokeweed Antiviral Protein (PDB ID: 1J1S), Among the docked ligands, compound 1i, 1e, 1f, 1h & 1g reported lowest binding energy between -8.7 to -8 Kcal/mol. Binding energy of all the compounds ranged from -8.7 to -7.6 Kcal/mol. Compounds 1d & 1i possess three hydrogen bonds each with TYR: 122, ARG: 178 & VAL: 73 amino acids and possess good antiviral activity.

Keywords: molecular docking, antiviral activity, Pokeweed Antiviral Protein (PDB ID: 1J1S), pyrimidine contain indole-2-one derivatives.

https://doi.org/10.33887/rjpbcs/2022.13.4.1

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (e.g., ligand) to another (e.g. Receptor), when both interact each other in order to form a stable complex [1]. The main objective of molecular docking is to attain an optimized docked conformer of both the interacting molecules in furtherance of achieving lessen free energy of the whole system. Final predicted binding free energy (ΔG_{bind}) is modeled in terms of dispersion & repulsion (ΔG_{vdw}), hydrogen bond (ΔG_{hbond}), desolvation (ΔG_{desolv}), electrostatic (ΔG_{elec}), torsional free energy (ΔG_{tor}), final total internal energy (ΔG_{total}) and unbound system's energy (ΔG_{unb}). Therefore, detailed understanding of the general principles that govern predicted binding free energy (ΔG_{bind}) provides auxiliary information about the nature of various kinds of interactions driving the docking of molecules [2]. Viruses are amongst the smallest microorganisms, varying in size from 0.02-0. 08µm1.They are filterable through porcelain filters and can be seen and identified with the help of electron microscope. Freidrich Loffler and Paul Frosch in 1898 found the first clue on viruses. They found evidences that the cause of foot-and-mouth disease in livestock was an infectious particle smaller than bacteria. These are the genetic entities that lie somewhere in the grey area between living and non-living states. Most form of lives-animals, plants and bacteria are susceptible to infection with appropriate viruses [3].

Pokeweed antiviral protein (PAP) was first isolated from the spring-harvested leaves of *Phytolacca Americana* and shown to prevent the replication of a number of plant as well as animal viruses [4]. Furthermore, it was shown that the protein inhibits protein synthesis by inactivating the 60S ribosomal subunit in a similar manner to the ricin A-chain. Subsequent studies found other antiviral proteins, PAP-II [5] and PAP-S [6], from the summer harvested leaves and the seeds, respectively, and showed that they have similar amino acid compositions and N-terminal sequences [7-8] but are immunologically distinct. Recent studies on the catalytic mechanism of PAPs on ribosomes have shown [9] that these proteins, like other ribosome-inactivating proteins including ricin A-chain [10], depurinate the adenine-4324 in the 28S rRNA of rat liver ribosomes, and thereby inactivate 60S ribosomal subunits. In spite of a detailed understanding of the molecular mechanism of PAPs on the ribosome, the functionally and structurally important site of the protein and how PAPs inhibit virus transmission have still been unclear. To provide a structural basis for answering these questions, we have determined the amino acid sequence of PAP-S isolated from- the seeds of *Phytolacca Americana,* and compared this sequence with that of ricin A-chain.

The study on antiviral activity of pyrimidine contains novel indole-2-one derivatives by using *Insilco* molecular docking tool. The compound possess isatin derivatives and pyrimidine moiety.

Chemically, Isatin is *1H*-Indole-2, 3-dione, possessing an indole scaffold substituted with carbonyl groups at 2nd and 3rd position. In 1841, "Erdman and Laurent" obtained isatin by nitric and chromic acid oxidation of indigo. It is also known as oxindole and endogenous compound reported to be present in many organisms [11].

Initially isatin was supposed to be synthetic till its presence was not reported in nature. In plants isatin is reported in the genus *isatis*, *"Calanthe (Calanthe discolor Lindl.)" and Couroupita (Couroupita guianensis Aubl)".* Substituted isatin is also found in plant Melochia tomentosa (alkaloids-methoxyphenylpentylisatins), fungi *Streptomyces albus* [6-(3'-methylbuten- 2'-yl) isatin] and *Chaetomium globosum* [5- (3'-methylbuten-2'-yl) isatin] and some marine mollusks. In animal the presence is reported in Bufo frog (secretions from parotid gland) while in human it is a metabolite of adrenaline [12].

Isatin has also been reported as a component of coal tar. Several of its derivatives have been reported to elicit promising pharmacological activity *viz.* antimycobacterial [13], anti inflammatory [14], herpes simplex virus inhibitor [15], antiviral [16], antimicrobial [17-19], anticancer [20-21], and anticonvulsant [22-23] etc.

Pyrimidine is the parent substance of a large group of heterocyclic compounds and plays a vital role in many biological processes, as found in nucleic acids, several vitamins, co-enzymes and purines.

Pyrimidine was first isolated by Gabriel and Colman in 1899 and its chemistry has been widely studied [24-25]. Investigations on new broad-spectrum drugs have attracted a worldwide interest during the past few years. Pyrimidines occupy a distinct and unique place in our life. The pyrimidine derivatives

ISSN: 0975-8585

possessing considerable pharmaceutical significance as antineoplastic, antibacterial, antiviral, anthelmintic, vasodilator, urinary tract infection and anti- parkinsonism.

The current study incorporates the use of *Insilco* molecular modeling tool Autodock Vina. The receptor grid that was generated will helps in locating the protein active site and preparing the grid for the ligands to be docked in the shape and properties of the receptor are represented on a grid by many different sets of fields that provide progressively more precise scoring of the ligand poses. The binding energies of mentioned analogs, further clarify the design of potential drug candidates against Pokeweed Antiviral Protein.

MATERIALS AND MATHODS

Dataset Ligands And Ligand Optimization

The 2D structures of 12 compounds were generated from the ACD/Chemsketch Software. The generated ligands cleaned and performed 3D optimization then saved in the MDL Molfile format. The ligands were then converted to a PDBQT file format using the Open Babel chemistry toolbox.

Molecular Docking Studies

The three-dimensional (3D) structure of Pokeweed Antiviral Protein (PDB ID: 1J1S) was downloaded from Brook heaven Protein Data Bank (https://www.rcsb.org) and saved as a Brookhaven protein data bank file and the structure was optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using AUTODOCK suite of MGL Tools.

Auto dock Vina was used for molecular docking studies. A grid was generated around the co-crystallized ligand. The co-ordinates (x = 32.63, y = 26.25, z = 16.59) were generated with the help of MGL Tools & Pharmit: interactive exploration of chemical space (http://pharmit.csb.pitt.edu/). Prepared pdbqt files for both target & ligands. Created in house batch file of ligands & target and docking performed in the absence of water molecules for all 12 molecules. The molecules were analyzed after docking and visualized in the discovery studio for the interactions with the active site amino acids.

Binding interactions and efficiency of the binding were calculated in terms of dock Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor.

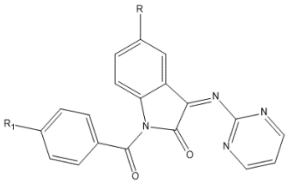


Figure 1: Pyrimidine contain indole-2-one derivatives (1)

Table 1: Ligands used in the study

SLNO	COMPOUND NUMBER	R	R_1
1	1a	H	H
2	1b	CH3	H
3	1c	Cl	H
4	1d	NO2	H
5	1e	H	CH3
6	1f	CH3	CH3
7	1g	Cl	CH3
8	1h	NO2	CH3
9	1i	F	CHJ3
10	1j	Br	CH3
11	1k	Br	H
12	1l	F	H

ISSN: 0975-8585

RESULTS

Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. The potential active site amino acids of 1JIS complex were predicted using CASTp. The target protein and inhibitors were geometrically optimized. All the 12 compounds (table 1) were docked against active site of target protein using AUTODOCK VINA. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About 100 different protein-ligand complex conformations for each docked complex were generated through AUTODOCK suite of MGL Tools, the confirmation with lowest binding energy was displayed as the best binding energy. Binding energy of the dataset ligands were shown in Table 2 along with the interaction amino acids and number of amino acids.

Table 2: Binding energy, number of H-bonds, interacting amino acids and H-bond length of the ligand dataset

Compound No	Binding Energy (Kcal/mol)	No of H-bonds	Interacting amino acids	H-bond lengths (Å)
1a	-7.6	1	ASN:70, TYR: 72	2.17
1b	-7.8	1	TYR: 72 ARG: 178	2.38
1c	-7.8	0	ASN:70, TYR: 122	---
1d	-7.8	3	LEU:71, TYR: 122, ARG: 178	1.79, 1.29, 2.53,
1e	-8.4	1	ARG: 178, TRP: 207	2.49
1f	-8.3	1	ARG: 178, TRP: 207	2.56
1g	-8	1	ARG: 178, TRP: 207	2.68
1h	-8.2	1	ARG: 178	2.30
1i	-8.7	3	TYR: 122, ARG: 178, VAL: 73	1.69, 2.08, 2.04
1j	-7.7	0	ASN:70, TYR: 122	---
1k	-7.8	0	ASN:70, TYR: 122	---
1l	-7.8	1	ARG: 178	2.45

Among the docked ligands, compound 1i, 1e, 1f, 1h & 1g reported lowest binding energy between -8.7 to -8 Kcal/mol. Binding energy of all the compounds ranged from -8.7 to -7.6 Kcal/mol. Compounds 1d & 1i possess three hydrogen bonds each with TYR: 122, ARG: 178 & VAL: 73 amino acids. Compounds 1g, 1k, 1c had no hydrogen bond interaction.

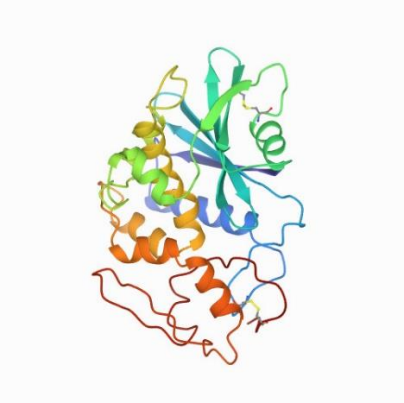
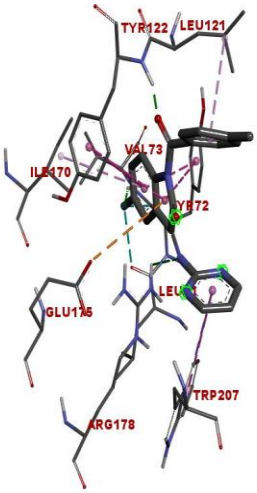
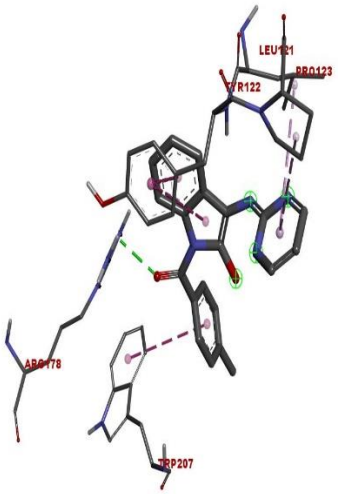


Figure 2: 3D structure of Pokeweed Antiviral Protein (PDB ID: 1J1S)

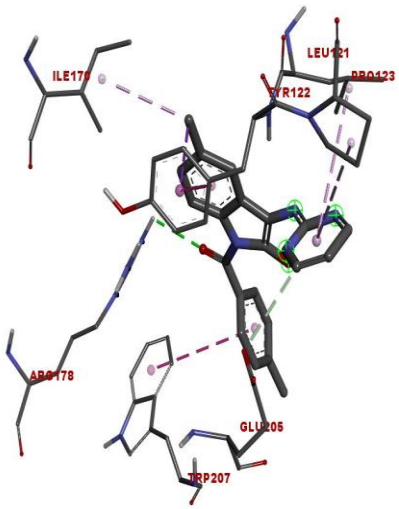
ISSN: 0975-8585



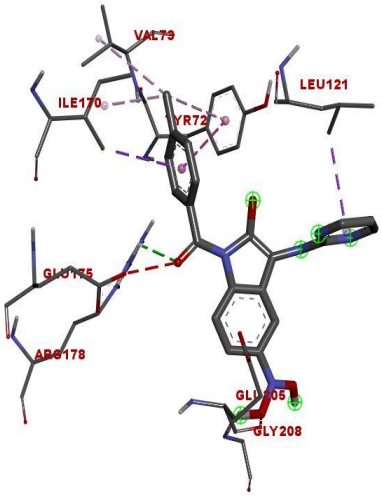
1i-3D



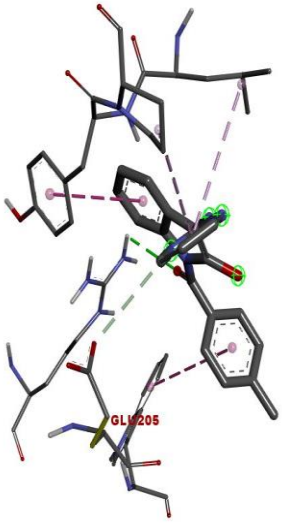
1e-3D



1f-3D



1h-3D



1g-3D

Figure 3: 3D interaction of ligand with target protein

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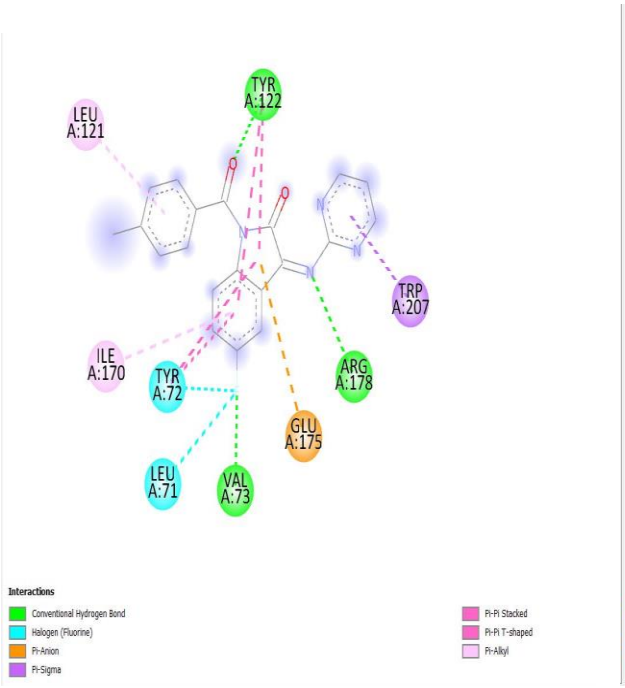
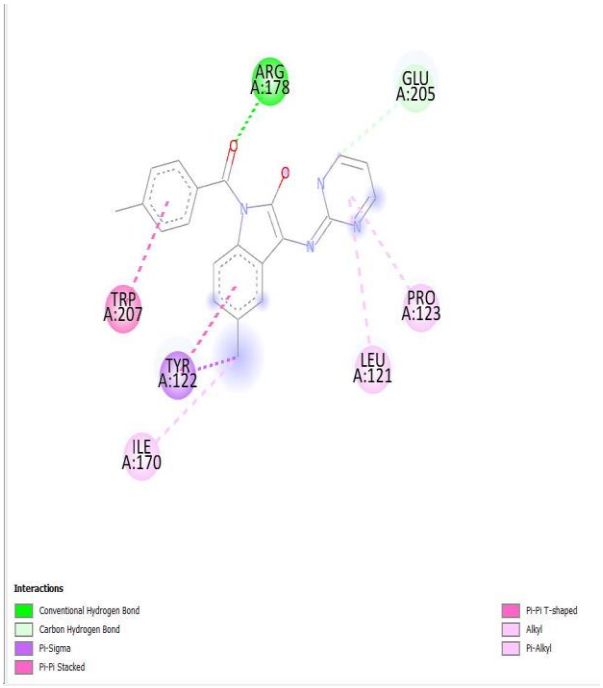
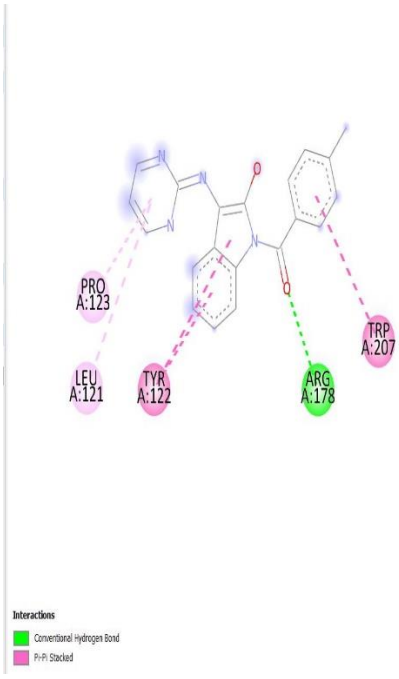


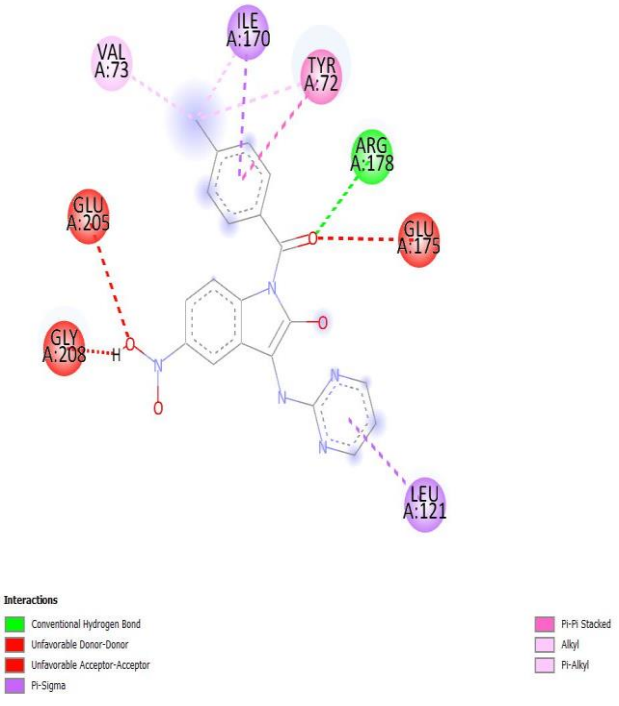
1i-2D



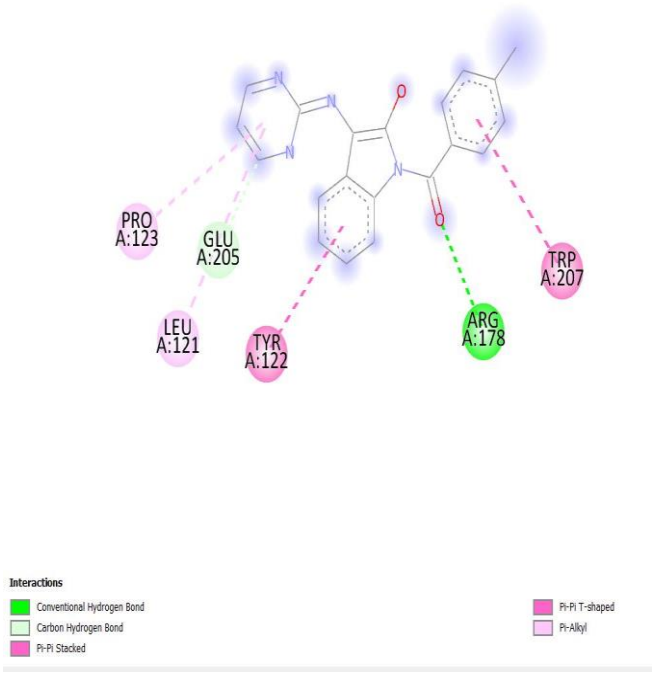
1e-2D



1f-2D



1h-2D



1g-2D

Figure 4: 2D interaction of ligands with target protein

CONCLUSION

Molecular docking of pyrimidine contain indole-2-one derivatives against Pokeweed Antiviral Protein (PDB ID: 1J1S), compound 3i, 3e, 3f, 3h & 3g reported lowest binding energy between -8.7 to -8 Kcal/mol and which possess good antiviral activity.

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