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International Journal of Current Research in Life Sciences
Vol. 07, No. 06, pp.2183-2186, June, 2018

ISSN: 2319-9490

RESEARCH ARTICLE

MOLECULAR DOCKING STUDIES OF BENZOCYCLOHEPTENONE DERIVATIVES AS ANTI-PROLIFERATIVE AGENTS

[1]CH. B. Praveena Devi, [1*]Vijay, K. and [2]Vijjulatha, M.

[1]Department of Pharmaceutical Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur - 522510, India
[2]Department of Chemistry, Osmania University, Hyderabad, Telangana

Received 20th April, 2018; Accepted 26th April, 2018; Published 12th June, 2018

ABSTRACT

The computational technique, Molecular docking studies has been performed to design benzocycloheptanone derivatives. Docking is an automated computer algorithm that determines how a compound will bind in the active site of a protein. In the present studies, docking has been carried out using glide version 5.6 method of Schrodinger suite. Docking studies were performed on the series of compounds along with Doxorubicin and Paclitaxel into the active site. From the Docking studies we have observed the compound 3 showed hydrogen bonding interaction with only Gly 149 and Gly 150. Regression analysis was performed to validate the correlation between experimental anti-tumour activity and dock scores. The derivatives were also checked for their pharmacokinetic properties by making use of Qikprop 4.0. All the molecules docked were in agreement with Lipinski rule.

Key words: Molecular Docking, Benzocycloheptenones, Glide, Qikprop.

Citation: CH. B. Praveena Devi , Vijay, K. and Vijjulatha, M. 2018. "Molecular docking studies of benzocycloheptenone derivatives as anti proliferative agents" *International Journal of Current Research in Life Sciences*, 7, (06), 2183-2186.

INTRODUCTION

Computer-aided drug design involves using the biochemical information of ligand-receptor interaction in order to postulate ligand refinements. The best possible starting point is an X-ray crystal structure of the target site. If the molecular model of the binding site is precise enough, one can apply docking algorithms that simulate the binding of drugs to the respective receptor site, like GOLD, FRED and Autodock (Morris *et al*., 1998).The program will try a set of different conformers of the ligand in order to obtain the best disposition of the atoms of the molecule for maximizing the scoring function that quantifies ligand receptor interaction. Docking is an automated computer algorithm that determines how a compound will bind in the active site of a protein. This includes determining the orientation of the compound, its conformational geometry, and the scoring (scoring may be a binding energy, free energy). There are two key components of a docking program namely the search algorithm and the scoring function. The search algorithm automatically tries to generate many different orientations and conformations of the compound in the active site, followed by computing a score for each. The identified orientations are sampled further through energy minimization to obtain the optimal conformations.

Corresponding author: **Vijay, K.,**
Department of Pharmaceutical Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur - 522510, India.

The choice of the search algorithm determines the thoroughness of the program in checking the possible positions of the molecule and time taken. The scoring function is responsible for determining if the orientations chosen by the search algorithm are energetically the most favourable, and is responsible for computing the binding energy. In the present study docking studies have been carried out using the (Grid-based Ligand Docking with Energetic) Glide (Friesner *et al*., 2004; Halgren *et al*., 2004; Schrödinger, 2010; Schrodinger, 2010) method of Schrodinger suite.

MATERIALS AND METHODS

Ligand structure: The chemical structure of each ligand was drawn using build module of maestro.

Ligand preparation: LigPrep (Schrodinger, 2010) was used to add hydrogen, converts 2D structures to 3D, generates stereoisomer and optionally neutralizes charged structures or determines the most probable ionization state at user-defined pH. All the structures are ionized at neutral pH 7. Conformers for each ligand are generated using Conf Gen by applying OPLS-2005 force field method (Kaminski *et al*., 2001).

Protein preparation: The typical structure file from the PDB is not suitable for immediate use in molecular modelling calculations.

A typical PDB structure file consists of only heavy atoms and may include a co-crystallized ligand, water molecules, metal ions, and cofactors. According to the requirement Protein is prepared using Protein Preparation Wizard where the protein is preprocessed, optimized and minimized with force field of OPLS2005 and RMSD of 0.30 Å.

Receptor Grid Generation: Receptor grid generation requires a "prepared" structure; an all atom structure with appropriate bond orders and formal charges. Glide searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. A grid area was generated around the binding site of the receptor with receptor van der Waals scaling for non-polar atoms as 0.9.

Ligand Docking: This is carried out using GLIDE. Glide searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The initial filters test the spatial fit of the ligand to the defined active site and examine the complementarily of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore function. Poses that passed these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA non bonded ligand-receptor interaction energy. Final scoring is then carried out on the energy-minimized poses. Generally, Glide outputs three scores, the GlideScore/GScore, Docking Score, and Glide Emodel, along with associated terms. GlideScore is based on the empirical scoring function ChemScore (Eldridge *et al*., 1997), but includes also terms for steric clashes, buried polar groups, and terms that penalise electrostatic mismatches:

Glide Score

$$GScore = 0.065 * vdW + 0.130 * Coul + Lipo + HB + Metal + BuryP + RotB + Site$$

where vdW represents van der Waals energies, Coul represents Coulomb energies, Lipo is a hydrophobic term, HB is a hydrogen bonding term, Metal rewards anionic interactions with metal cations, BuryP is for buried polar groups, RotB is a penalty for frozen rotatable bonds, and Site rewards polar but non-hydrogen bonding atoms in a hydrophobic region. In the Docking Score additional penalties from Epik (an application used to estimate pKa values of ligands) (Schrödinger, 2009) are added to the GScore. These penalties are associated with high-energy states of the ligand. The model energy score, Emodel, combines the energy grid score, the GScore binding affinity, and a measure for the internal strain energy. The energy grid score is a measure of how well the ligand fits the binding site grid. Prior to the molecular docking simulation the protein binding site is analysed in terms of shape and properties, and mapped onto a grid. Glide uses the OPLS_2005 force field. Various molecular docking procedures:

Glide SP: Standard Precision (SP) is the default method of docking in Glide. Glide SP is a multistep procedure using a funnelling approach to filter out models that do not fit to the binding site. Initially, a large pool of conformations is generated for each ligand. The ligand conformations are then fitted to the binding site in the form of the generated grid. In the first two steps of docking, ligand conformations are filtered through a shape match-like procedure.

Next, ligands are scored in the binding site by a Greedy score, i.e. it is evaluated if the ligand interacts adequately in terms of e.g. hydrogen bonds. The best scoring poses (typically 100-400 poses) are further minimised and rescored by the Glide scoring functions.

Glide XP

The extra precision (XP) mode uses a more stringent scoring function than Glide SP. Glide XP was designed for redocking of good ligand poses only, and was intended to sort out false-positives and provide a better correlation between good poses and good scores. Glide XP uses the initial docking poses from Glide SP, from which the ligand is re-grown from an anchor fragment. Glide version 5.6 of Schrödinger was used as a platform to perform molecular docking studies. Crystal structure of oxidised quinine reductase 2 in complex with doxorubicin (DNA intercalating agent) (PDB ID: 4ZVM) was retrieved from protein data bank. Refinement of protein was made by withholding unwanted water molecules and appending hydrogen atoms. The binding site was identified with the aid of the crystal structure ligand (pdb id: 4zvm). Through Ligprep all possible conformers for themolecules were generated applying OPLS force fields. Docking has been carried out enclosing the grid around the crystallised ligand.

RESULTS AND DISCUSSION

DNA intercalation is unanimous mechanism targeted by most anti-tumour drugs. The key function of intercalation is primarily achieved by forming grooves in the DNA.

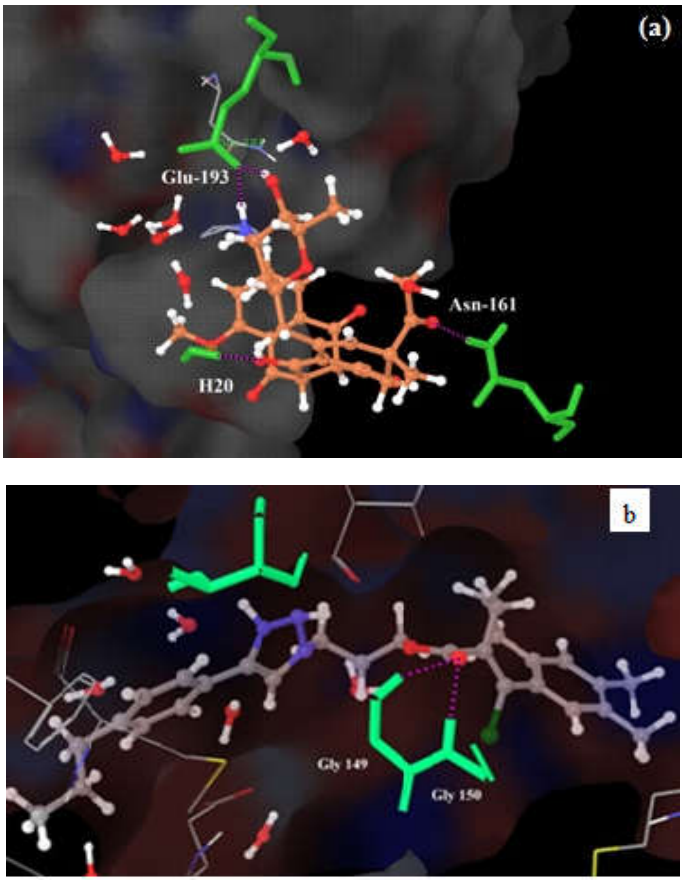

Fig. A. Dock poses of Doxorubicin (a) and 3 (c) with its interaction in the active site

Table-1. Synthesised molecules with their activity (IC_{50}) and Dock scores (pIC_{50})

Compound	HeLa		MIAPACA		MDA MB 231		IMR 32	
	IC_{50}	pIC_{50}	IC_{50}	pIC_{50}	IC_{50}	pIC_{50}	IC_{50}	pIC_{50}
1	0.97±0.06	6.0132	59.2±0.5	4.2277	2.0±0.06	5.699	>100	4
2	5.7±0.51	5.2441	>100	4	20.4±0.1	4.6904	1.4±0.07	5.8539
3	0.3±0.01	6.5229	10±0.3	5	0.71±0.02	6.1487	0.3±0.02	6.5229
4	9.2±0.8	5.0362	0.7±0.01	6	0.29±0.02	6.5376	26.5±0.08	4.5768
5	9.8±0.25	5.0088	14.0±0.9	4.8539	4.8±0.06	5.3188	3.0±0.09	5.5229
Doxorubicin	0.09±0.002	7.0458	0.086±0.03	7.0655	0.087±0.001	7.0605	0.03±0.008	7.5229
Paclitaxel	0.035±0.005	7.4559	0.09±0.001	7.0458	0.084±0.002	7.0757	0.083±0.003	7.0809

Table 2. QikProp data with dock score values and membrane bound surface energies

Compounds	Dock scores	Prime MMGBSA	Mol.Wt	Donor H.B	Acceptor H.B	QP log o/w	QP log S
1	-5.221	-51.494	437.968	2	3	6.648	-8.779
2	-3.419	-53.315	451.995	2	3	6.897	-9.401
3	-5.856	-81.551	480.048	2	3	7.696	-10.320
4	-4.465	-50.551	494.075	2	3	8.064	-10.029
5	-3.778	-60.865	467.994	2	3	6.695	-9.043

MMGBSA-membrane bound generalised surface area energies, Mol.Wt- Molecular weights, H.B- Hydrogen- Bond, QP log o/w- predicted Octanol-water partition coefficients, QP log S- predicted aqueous solubility in mol/litre.

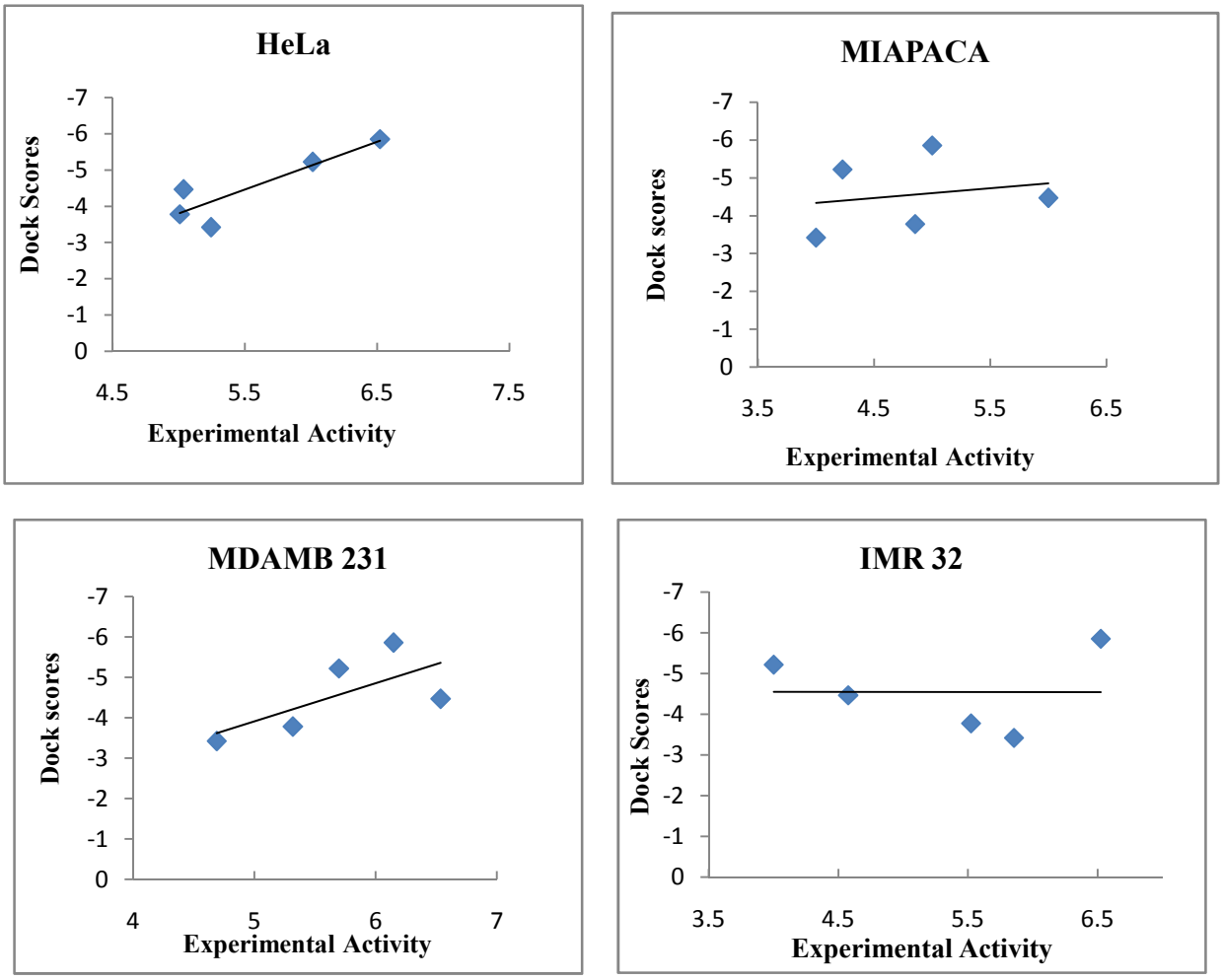

Fig. B. Experimental activity VS dock scores

While the secondary mechanism suggests that they also act by alteration of fluidity and ion transport which helps in maintenance of cell shape upon interacting with cell membrane, that is identical to anti mitotic affect. Hence there is a need to develop Novel anti-cancer drugs that target DNA intercalation as well as microtubule formation. Doxorubicin an anthracycline anti-tumour drug mainly functions by inhibiting Topoisomerase enzyme which aid in repairing of damaged DNA there by acting as DNA intercalating agent.

While, Paclitaxel a drug of choice is used to inhibit microtubule formation by exhibiting anti mitotic affect. Therefore in the current studies we have docked the series of compounds along with Doxorubicin and Paclitaxel in to the active site to understand probable binding interactions. From the Docking studies we have observed that doxorubicin has shown hydrogen bond interactions with carbonyl of Glu 193 of B chain, amine function of Asn 161 in A chain and with water molecule as depicted in figure (A). It has also shown π - π

stacking interaction with Phe 128 of B chain. The compound 3 showed hydrogen bonding interaction with only Gly 149 and Gly 150. Fig: A represents the dock poses of Doxorubicin (a), 3 (c) in the active site of DNA intercalating agent. The IC_{50} and pIC_{50} values were tabulated in Table 1. From the above results we have observed that the potent compounds have shown common hydrogen boning interaction with Gly 149 and Gly 150 which are in agreement with experimental anti proliferative activity. The membrane bound generalised surface area (MMGBSA) energies were calculated for all the molecules. The experimental activity (IC_{50}) versus dock score (pIC_{50}) for four different cell lines were compared in the Fig.B The newly synthesised molecules were checked for their Pharmacokinetic properties (ADME) by making use of QikProp 4.0. It is imperative to calculate drug like properties which should not surpass Lipinski rule of five. The Dock score values, surface energies and ADME properties data are tabulated in Table-2. We have found that all the synthesised molecules were in agreement with Lipinski rule.

Conclusion

The computational techniques, Molecular docking studies have been performed. From the Docking studies we have observed that doxorubicin has shown hydrogen bond interactions with carbonyl of Glu 193 of B chain, amine function of Asn 161 in A chain and with water molecule. It has also shown π - π stacking interaction with Phe 128 of B chain. The compound **3** showed hydrogen bonding interaction with only Gly 149 and Gly 150. From the above studies, we can conclude that the docking studies for the molecules were becoming giving a scope for synthesising many novel benzocycloheptanone derivatives which can be used as potential anti-proliferative agents.

Acknowledgement: We are thankful to the Principal, University college of Pharmaceutical sciences, Guntur for extending her support.

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