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Docking study and result conclusion of heterocyclic derivatives having urea and acyl moiety.

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Abstract

In the field of molecular modeling, Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules. In this study a series of synthesized compounds were evaluated for focusing on binding modes, potential interactions and specific binding sites. Chemically compounds bear both the moiety acyl as well as urea and their interaction by using in silico study was investigated with beta tubulin protein that interferes with the tubulin-microtubule equilibrium, crucial for cellular mitosis. In silico studies revealed that synthesized and tested compounds show 1-7 no. of interactions with amino acids of tubulin protein. Docking study was done by using Autodock, it was found that among different synthesized compound some shows the highest and best scoring pose (lowest energy) which was -2.94 Kcal/mole between N (11) and Leucine (113) and -3.09 between N (11) and Alanine (149). Compounds with amino, hydroxy, methyl, methoxy, trimethoxy and dimethoxy substitution in derivatives of acyl urea gave an idea that urea and acyl when used in combination in different synthesized compounds show good antitumor activity.

Keywords: Docking, Urea, Acyl, Tubulin, Autodock.

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Introduction

Computer-aided docking is an important tool for gaining understanding of the binding interactions between a ligand and its target receptor (mainly, a protein). Multistep docking strategies have also been employed for flexible ligand docking [1-5]. Some common docking programs that utilize such fragment-based approaches include Molegro, Auto Dock, LUDI, FlexX, Growmol, Hook, Q-fit and Surflex [6-8] (Figure 1).

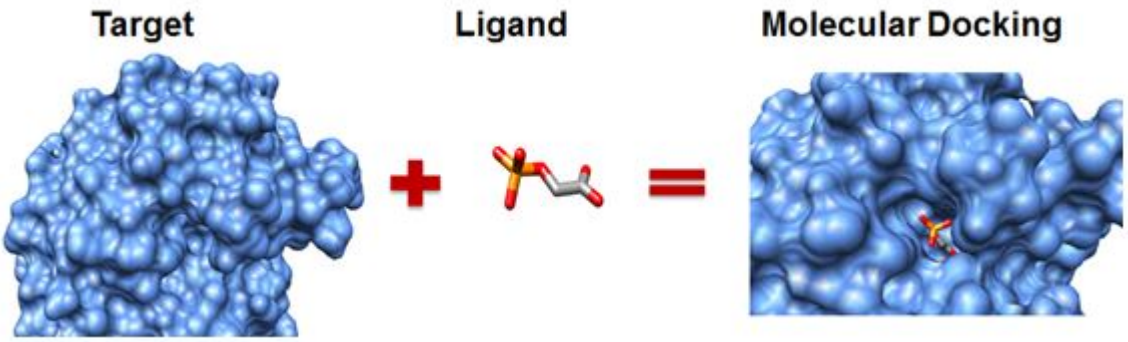

Figure 1. *Docking of ligand and recptor [9].*

It was therefore considered of interest to synthesize a variety of cinnamic acid derivatives wherein substituted cinnamoyl chlorides were reacted with urea to obtain acyl urea's. These new compounds possess features similar to above mentioned series of compounds and are expected to exhibit similar pattern

of pharmacological activities which in this case are anti-tumor activity sedative- hypnotic, smooth muscle relaxant activities.

Methodology

The structure of tubulin was obtained from the Protein Data Bank (www.pdb.org). Compound structures were built with ChemBio Draw Ultra 11.0 and their geometry optimization was performed using the MMFF94 method in the program and saved as MRV format [9,10]. The test compound were placed into binding site of tubulin molecule by import method to the reference ligand ACO201(A), MES(137), MES(148) which are selective inhibitor against tubulin The binding affinity between ligand (synthesized compounds) and enzyme (docking score) was predicted using MolDock Score, plant score using algorithm of iterated complex and mole dock optimizer [11-15] (Figures 2 and 3).

STEP 1 - Auto Dock / Molegro software was opened

Clicked on file

- Molecule of protein taken from protein database was imported
- Cofactor water, ligands were removed
- Protein molecule was imported

Clicked on preparation

- Prepared molecule of protein
- Detected cavities than click on OK

Again clicked on file

- Followed same step as A but only import ligand now

Again repeated step B of preparation

Clicked on file, saved workspace

Clicked on docking

Docking wizard was opened

Ligands were chosen

Plant score, mole dock score was used using mole dock complex algorithm

Results were obtained and saved

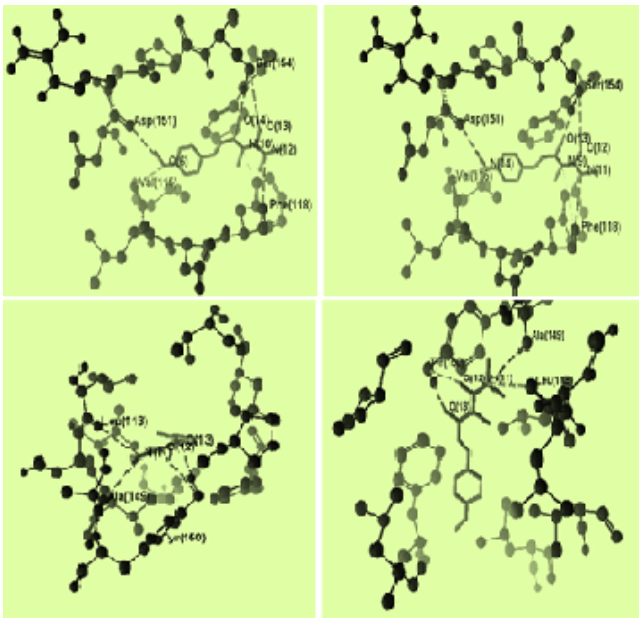

Figure 2. *Shows binding of acyl urea derivatives with tubulin molecules [10-13].*

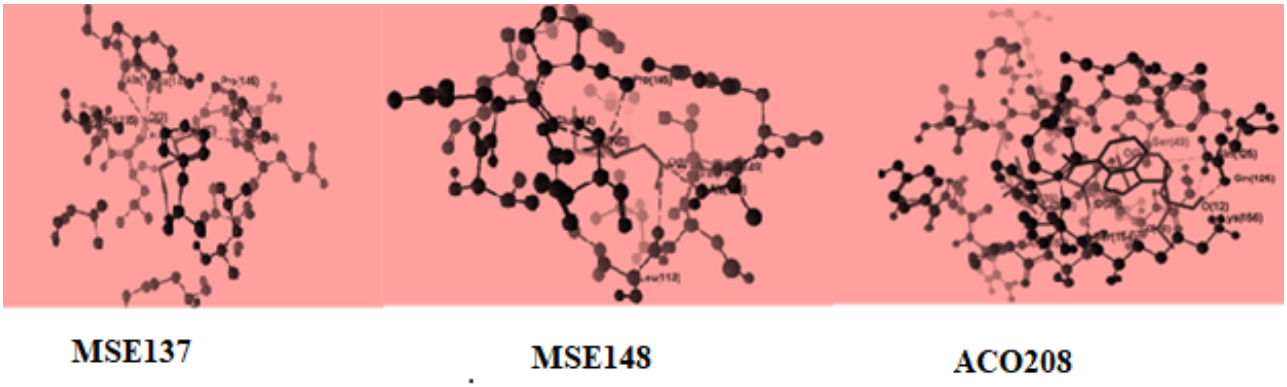

Figure 3. *Shows binding of tubulin molecules to reference ligands having good binding affinity [14-16].*

Result and Discussion

Newly synthesized acyl urea derivatives were evaluated for their antitumor activity by using Autodock software program. By using Autodock software values of different parameters like no of interactions, bond length and bond energy were obtained. All the measured values are compared with three reference compounds.

In the result it was found that some acyl urea derivatives are having bond energy and bond length which was of significance when compared with reference compounds used such as ACO201(A), MES(137) and MES(148). It was found that compound 1a (acyl urea derivative) have binding energy of -0.27589 Kcal/mole which was similar and comparable to reference compounds binding energy with tubulin protein. It was also observed in the result that in all acyl urea derivatives, nitrogen atom of urea have the best binding energy score when

checked for binding with tubulin protein. All the compounds are having 4-6 no of interactions which reflects that the binding poses of the docked acyl urea compound ensures favourable and valid potential binding modes with tubulin protein

Table 1: *Binding affinity between ligand and tubulin protein [17].*

Docking of protein (Tubulin) with ligands						
S. No	**Compound Name**	**No of Interactions**	**Protein residue name**	**Compound residue name**	**Bond Length (A°)**	**Bond Energy (Kcal/mole)**
1	1a	6	Phe(118)	N(12)	2.86065	-2.5
			Ser(154)	O(14)	2.78873	-2.5
			Phe(118)	N(10)	3.25137	-0.2759
			Ser(154)	O(13)	3.09957	-2.5
			Asp(151)	O(6)	3.10001	-2.5
			Val(115)	O(6)	3.10001	-2.4999
2	2a	6	Phe(118)	N(11)	2.88065	-2.5
			Ser(154)	O(12)	3.09991	-2.5
			Phe(118)	N(9)	3.25537	0.26664
			Ser(154)	O(13)	2.79341	-2.5
			Asp(151)	N(14)	3.10011	-2.4995
			Val(115)	N(14)	3.10008	-2.4996
3	3a	4	Tyr(150)	O(13)	2.9897	-7.5
			Tyr(150)	O(12)	3.13828	-7.4008
			Leu(113)	N(11)	2.93669	-7.1
			Ala(149)	N(11)	3.09969	-7.2
4	4a	4	Tyr(150)	O(13)	2.9709	-2.5
			Tyr(150)	O(12)	3.12009	-7.3995
			Leu(113)	N(11)	2.94296	-2.943
			Ala(149)	N(11)	3.09964	-3.0996
a)	ACO201(A)	8	Arg(152)	N(39)	3.34554	-0.6456
			Arg(152)	O(36)	2.84055	-2.5
			Gln(53)	N(39)	3.57519	0.37031
			Gln(53)	O(36)	3.0643	-2.5
			Ser(49)	O(24)	2.40575	-0.8813
			Ser(154)	O(16)	3.22297	-1.8852
			Lys(156)	O(12)	1.96771	-2.8895
			Gln(125)	O(12)	2.96183	-2.3273
b)	MES(137)	5	Glu(144)	N(0)	3.07233	-2.5
			Pro(145)	N(0)	3.10014	-2.4993
			Val(115)	O(3)	3.26753	-0.7544
			Leu(113)	O(3)	2.83785	-2.5
			Ala(149)	O(3)	3.10025	-2.4988

			Ala(149)	O(3)	2.62258	-2.5
c)	MES(148)	6	Glu(144)	N(0)	3.09915	-2.5
			Pro(145)	N(0)	3.08851	-2.5
			Val(115)	O(3)	2.87091	-2.5
			Leu(113)	O(3)	3.25601	-0.7973
			Ala(149)	O(3)	3.10042	-2.4979
			Ala(149)	O(3)	2.59975	-2.4979

Conclusion

The molecular docking study of acyl urea derivatives with tubulin protein revealed that acyl urea's are having good interaction in favourable pose with tubulin which was explained by lowest binding energy, strong bond length and 4-6 no of interactions with active site of tubulin molecule Thus it can be concluded that some acyl urea derivatives could be used as a template for the future development through modification or derivatization to design more potent therapeutic agents. Compounds synthesized if properly changed into therapeutic agent can be used for antitumor action.

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