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Molecular Docking Study of Coumarin Derivatives Binding to Caspase-7, a Key Player in the Apoptosis Pathway

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Abstract

This study is focused on analysis of inhibitory activity of novel molecules in the active site of human caspase-7. Caspase inhibition is an approach for treating multiple diseases such as Osteoarthritis, Alzheimer's disease, Parkinson's disease and Cisplatin induced renal injury. The caspase family of proteins, particularly activated caspase 3, 7 and 8, is widely implicated in cisplatin induced tubular cell apoptosis. Caspase-7 is a popular drug target for Cisplatin induced renal injury. Coumarins are a family of natural compounds with anti-cancer, anti-inflammatory, anti-oxidant and many more therapeutic properties. Coumarin derivatives were used as the ligands for the caspase-7 receptor using a molecular docking approach. The crystal structure of caspase-7 was obtained from the protein data bank, entry 4FDL, and a set of coumarin derivatives were docked in to the pre-equilibrated protein structure using AutoDockVina and Gold software. The interaction diagrams were obtained using BIOVIA discovery studio. Hydrogen bonds and pi-stacking interactions were considered favorable for stabilizing the ligand in the active site. Results revealed that there are favorable interactions with coumarin derivatives used in this study and caspase-7. The coumarin derivatives with high binding affinity may be developed as potential drug candidates.

Keywords: Caspase-7 protein • Coumarin derivatives • Inhibitory activity

Introduction

The mechanisms which are possibly involved in cisplatin induced nephrotoxicity could directly affect the renal tubular epithelial cells [1]. Also it induces apoptosis, deregulate cell cycle proteins and cause inflammation [2]. *Hydrangea paniculata* is a medicinal plant with anti-inflammatory activity which has the ability to reduce renal injury through inhibition of caspase 3 and 7 proteases [3]. Caspase-7 is selected for the study because activation of Caspase-7 may prove to be very useful in conditions where excessive cell death or inflammation causes diseases [4]. *Hydrangea paniculata* has many coumarin derivatives as functional constituents and it contains high amounts of coumarin glycosides [5]. Skimmin and Apiosylskimmin coumarins are the major constituents present along with other coumarin glycosides. Research has shown that these coumarins inhibit the cisplatin induced apoptosis and reduce acute kidney damage caused by cisplatin. Skimmin and apiosylskimmin coumarin inhibition of caspase-7 was compared with the coumarin derivatives investigated in this study using molecular docking.

Although caspase inhibitors have been developed with some degree of specificity, most of them are peptide based molecules with low effectiveness, and are quickly destroyed *in vivo*. In this study coumarin derivatives were selected as ligands in the inhibition process and their binding interactions with caspase-7 are compared with that of the standard molecules (Figure 1) [6].

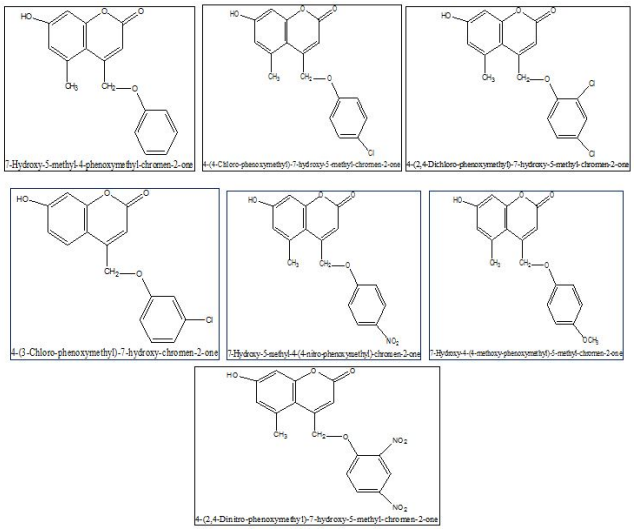

Figure 1. Structures of the coumarin derivatives.

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Materials and Methods

Methodology

Ligand preparation: The coumarin derivative structures and the standard ligands were prepared using Spartn'14 software [7]. After sketching the molecules energy was minimized and final molecules were obtained by applying density functional/B3LYP/6-31G** level to obtain the most stable structures.

Protein preparation: PDB ID 4FDL protein structure was obtained from the protein data bank and prepared using Chimera 1.9 software [8]. The solvents and ligands present were deleted and H atoms and charges were added.

Molecular docking: The crystal structure of protein PDB ID 4FDL was docked with a set of coumarin ligands using AutoDockVina in PyRx Version 0.9.4 and GOLD 5.3.01 in both rigid and flexible options [9-11].

In Auto Dock Vina software the search space box for the 4FDL protein was set by marking Tyr223, Cys290, Glu216, Phe221, Val292 and Met294 residues. When flexible docking option was used the above mentioned residues were made flexible [12]. Exhaustiveness and the number of modes were set as 100 and 10 respectively. In GOLD 5.3.0 software the binding site was defined by entering the above mentioned amino acid residues and the cavity radius was set as 10Å. The scoring function applied was ChemPLP. The number of genetic algorithm runs was set as 30 and the residues were made flexible when flexible docking was performed [13].

The docking results obtained from the Auto Dock Vina were visualized using BIOVIA discovery studio 2016 client and the interaction diagrams were obtained for each of the ligand protein interactions [14].

Results and Discussion

In the allosteric active site of caspase-7 the binding pocket is situated away from the catalytic active site Cys186, and placed in the dimer interface [15]. According to previous studies it has proved that this binding site has a high affinity for small ligands and the docking results of the ligands in order of highest binding affinity are listed in Table 1. Coumarin derivatives were compared with the standard ligands, FICA, DICA, 1-methyl-5-nitroisatin which have previously shown high affinity towards the allosteric binding site of caspase-7 and have shown successful inhibition of caspase-7 [16]. Skimmin and Apiosyl skimmin coumarins present in *H. paniculata* plant extracts were the other two standards [17].

Ligand	Name	Binding Affinity (kcal mol^{-1}) (AutoDock Vina)	Score (Gold 5.3.0)
Coumarin 1	7-Hydroxy-5-methyl-4-phenoxymethyl-chromen-2-one	-6.6	64.96
Coumarin 2	4-(4-Chloro-phenoxymethyl)-7-hydroxy-5-methyl-chromen-2-one	-6.8	66.37
Coumarin 3	4-(2,4-Dichloro-phenoxymethyl)-7-hydroxy-5-methyl-chromen-2-one	-7	67.89
Coumarin 4	4-(3-Chloro-phenoxymethyl)-7-hydroxy-chromen-2-one	-6.6	73.59
Coumarin 5	7-Hydroxy-5-methyl-4-(4-nitro-phenoxymethyl)-chromen-2-one	-6.9	73.67
Coumarin 6	7-Hydroxy-4-(4-methoxy-phenoxymethyl)-chromen-2-one	-6.6	74.33
Coumarin 7	4-(2,4-Dinitro-phenoxymethyl)-7-hydroxy-chromen-2-one	-7.1	75.64
Std 1	FICA 5-Fluoro-1H-indole-2-carboxylic acid (2-mercapto-ethyl)-amide	-5.1	55.86
Std 2	DICA 2-(2,4-Dichlorophenoxy)-N-(2-mercapto-ethyl)-acetamide	-4.5	54.7
Std 3	1-methyl-5-nitroisatin	-5.5	44.97
Std 4	7-(3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy)-chromen-2-one	-6.3	59.4
Std 5	7-[6-(3,4-Dihydroxy-4-hydroxymethyl-tetrahydro-furan-2-yloxymethyl)-3,4,5-trihydroxy-tetrahydro-pyran-2-yloxy]-chromen-2-one	-6.7	73.82

Table 1. Binding affinities of ligands in the caspase dimer interface from Auto Dock Vina and SCORE values obtained from GOLD software.

According to flexible docking results, all coumarin derivatives show a higher binding affinity when compared to standard ligands 1, 2, 3 and 4. Coumarin derivatives, ligands 2, 3, 5 and 7 gave higher

binding affinity with respect to reference ligand 5, Apiosylskimmin which has the highest binding affinity out of the standard ligands. When considering the Gold results, all the 7 coumarin structures gave a higher score compared to the standard ligands 1, 2, 3 and 4.

Ligands 6 and 7 gave scores of 74.33 and 75.64 respectively, which is greater than the score of Apiosyl skimming, 73.84, which is the highest score among the standard ligands.

According to both the Auto Dock Vina and GOLD score values, coumarin 7 had the highest binding affinity out of all the coumarins and it is greater than that of Apiosyl skimming (Figure 2).

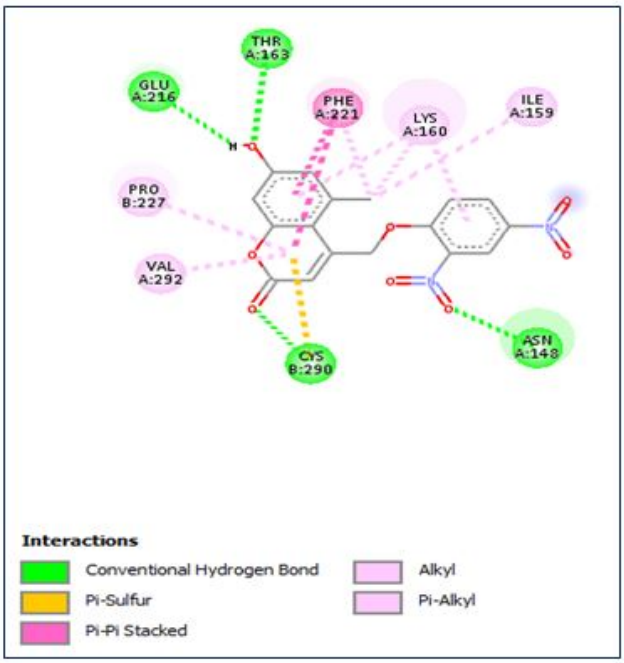

Figure 2. 2D interaction diagram of ligand 7 with caspase-7.

Conclusion

Computational studies were conducted to determine potency of coumarin derivatives as candidates for development of inhibitors to caspase-7. Docking studies were performed using Auto Dock Vina and GOLD software. Ligand 7 4-(2, 4-Dinitro-phenoxymethyl)-7-hydroxy-chromen-2-one, showed the highest binding affinity and GOLD score value. The ligand is stabilized in the active site by forming H bond interactions with the protein, and also Pi-Pi stacking interactions with the aromatic rings. Effective interactions with the residues CYS290, GLU216, PHE221, VAL292 of the dimerization interface in the allosteric binding site were formed which showed evidence for the enhanced stability of the ligand in the active site. Therefore, coumarin derivative ligand 7, (4-(2, 4-Dinitro-phenoxymethyl)-7-hydroxy-chromen-2-one, can be considered as a potential drug target for the inhibition of caspase-7.

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