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Synthesis and Molecular Docking Studies of 3-Benzylidene-8- Methoxy-6-(prop-1enyl) Chroman-4-One Based Compound against Different HIV Receptors

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Abstract

The Human Immunodeficiency Virus (HIV) infection in human since last three decades is a tremendous issue in the area of infectious diseases. Currently plant based compounds are gaining more interest now-a-days in antiretroviral therpies. HIV replication is a target for the inhibition of HIV infection. The synthesized chroman-4-one based compound recognized as a antireplicative agent. With the synthesized crystals benzene and pyrone ring plays a major role ,molecular structure of the compounds were identified by subjecting the compound to X ray diffraction studies. Anti-HIV effects have been studied by different five viral Proteins. Ligand-protein molecular docking studies using advanced docking tools and minimum binding energies were computed. Comparison was made for better choice of protein ligand interaction

Keywords: Chroman-4-one, HIV, molecular docking, targeted drug delivery

Introduction

The main cause of Acquired Immunodeficiency syndrome (AIDS) is HIV infection worldwide since 1981, a life threatening pandemics has no perfect solution till date, various investigations have been reported in different countries focusing antiretroviral therapies, but till date only two types of the therapies have been studied one is reverse transcriptase and Viral protease, on the other hand the replication has been focusing simultaneously. In addition the chroman-4-one based compound found to be effective and is naturally occurring one[1], Some of the derivatives of the compounds also are found to be antifungal agents[2].

In this study chroman-4-one compound was studied at molecular level, pyrone and benzene rings play an important role in many areas of the medicines, X ray diffraction studies were carried out to identify the details in intermolecular interaction[3]. Current research on RNA dependent DNA polymerase enzyme is still at nascent stage but this chromane4-one was found to be successful in binding the HIV proteins. Five different proteins were retrieved from the Protein data bank and the compound was subjected to docking for binding capacity confirmation studies[4]. Proteins involved in this study are capsid, glycoproteins and mutant polyprotein. Focus of the study to be identifying the binding capacity of the compound to different HIV associated targets so that future drug development can be planned out easily.

Material and Methods

Synthesis of the compounds: 10 mmol of Methyl-2-bromomethyl-3-phenyl-propenoate was treated with 10 mmol of eugenol in the presence of potassium carbonate in acetone at reflux temperature for 3 hrs. The pure ester of methyl-3-phenyl-2 (2-methoxy- 4- prop-2-enyl) phenoxy methyl –prop-2enoate was obtained after silica gel column chromatography (3% EtOAc-hexane) .Hydrolysis of this ester was carried out with KOH in 1,4- Dioxane at room temperature. The reaction mixture was acidified and the precipitated acid was purified by recrystalization. Finally the acid was treated with TFAA and the reaction mixture refluxed in dichloro- methane for 1 hr. It was further purified by column chromatography (silica gel-2% EtOAc-hexane) [5].

X ray diffraction analysis: A single crystal of the title compound with dimensions of 0.18×0.11×0.06mm was chosen for an x-ray diffraction study. The Bruker Kappa APEX-II diffractometer with graphite monochromated Mo-Kα radiation (0.71073 Å) was used for all measurements. The structure was solved by direct methods and refined by full-matrix least squares on F^2 with anisotropic temperatures factor for non-hydrogen atoms. The H atoms were inducted in the right positions and refined with fixed geometry on the their carrier atoms[6]. The structure was solved satisfactorily with reliability index of R=0.068.

Computational Molecular Docking studies: Crystallographic structures of different proteins associated with HIV includes glycoprotein's, envelope proteins, mutant proteins, were retrieved from the RCSB database with PDB ID, computational analysis was done to compute ligand protein binding affinity of the compound, a compound were docked with different five receptor proteins with the help of HEX 6.1 docking tool. In this

docking tool, each molecule is modelled using 3D expansions of real orthogonal spherical polar basis functions to encode both surface shape and electrostatic charge and potential distribution. Fast Fourier transform (FFT) docking methods are very fast than other traditional docking tools[7,8].

The structure of the ligand created charges were adjusted by the Hex tools which was then setup the torsion angles, followed by graphical adjustment to know the exact surface of binding site, after preliminary settings the ligand and protein were docked by considering the electrostatic charges and shape of the molecules.

Result and Discussion

X ray Diffraction analysis: Crystal and Experimental Data: Chemical formula: $C_{20}H_{18}O_3$, Formula weight = 306.34, T = 293 K, Crystal system: Monoclinic Space group: $P2_1/c$, a = 10.0763(8) Å, b = 6.9018(7) Å, c = 22.1841(18) Å, β=98.690(7), V = 1525.1(2) Å^3 Z = 4, Dx = 1.334 Mgm^{-3}, Radiation: Mo $K\alpha$ (λ = 0.71073 Å), F000 = 648, Crystal size = 0.18×0.11×0.06 mm, No. of reflections collected = 11793, No. of Independent reflections = 3177, θ range for data collection: 1.9° to 27.2°, Data/Restraints/Parameters = 3177/0/210, Final R indices [I>2σ (I)] R1 = 0.068, Goodness-of-fit on F^2 =0.92,

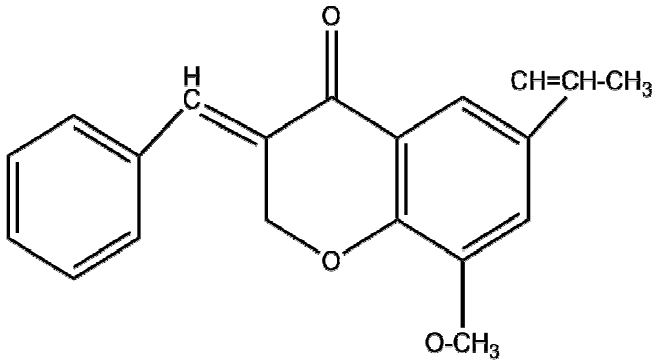

Figure-1
Ligand (3-Benzylidene-8-methoxy-6-(prop-1-enyl) chroman-4-one)

Molecular docking Studies: The structures of the ligands were drawn using tool Chembiodraw 11.0. Figure-1 and converted into PDB format using Molecular conversion tool VCC lab online server[9,10]. The five HIV protein receptors retrieved from PDB were docked with ligand and docking score was compared (PDB ID: 1A8O, 1TAM, 3DNN, 3P7K, 3UF3)[11,12,13,14] this clearly depicted in the docking figure-2, 3, 4, 5, 6.

Among the total five protein receptors three are showing efficient docked score viz. in the range of Emin.= -161 to -215, which is considered as a good score in ligand- protein interactions. These two proteins such as 3P7K is a (gp41) subunit of the envelope protein complex of retroviruses, including (HIV) which involves in fusion process and various target findings are still under process. In such a case binding affinity is an important aspect of discovering the drug. Indirectly it has impacts on replication of virus particles, while on the other hand the remaining protein 3UF3 is mutant polyprotein of antibiotic resistant HIVstrain, possibly it also suggests the targets

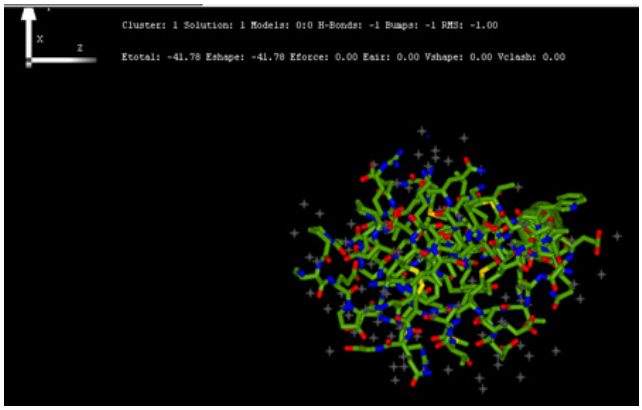

Figure-2
Docked ligand Receptor (1A8O)

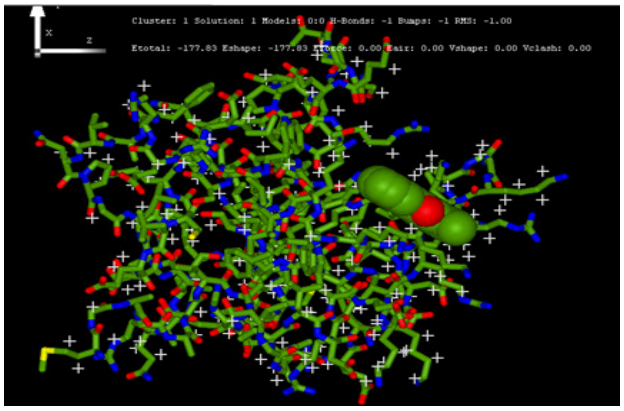

Figure-3
Docked Ligand receptor (1TAM)

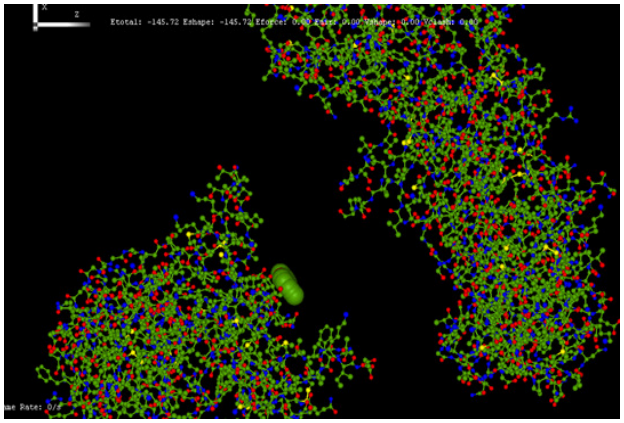

Figure-4
Docked ligand Receptor (3DNN)

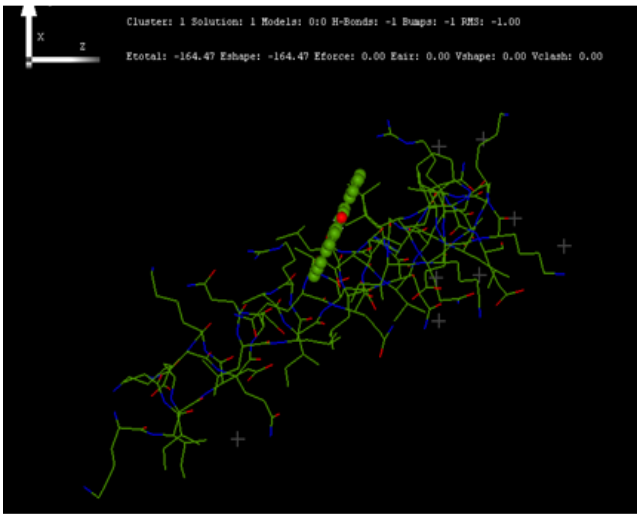

Figure-5
Docked ligand Receptor (3P7K)

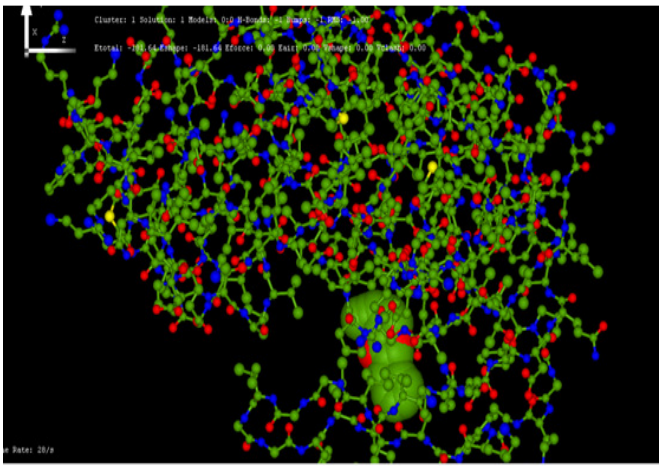

Figure-6
Docked ligand Receptor (3UF3)

Table-1
Energy values of docked 3-Benzylidene-8-methoxy-6-(prop-1enyl) chroman-4-one ligand with different receptors

Receptors (PDBID)	Emax	Emin
3UF3	-146.34	-181.64
3P7K	-132.43	-164.47
1TAM	-118.69	-215.72
3DNN	-72.32	-124.33
1A8O	-18.78	-42.0

Conclusion

Docking studies are the presently promising tool towards the drug development. In present study, it is clear that glycoprotein and mutant protein of antibiotic resistance strain of HIV can be treated with the ligand showing good pose result. Among the three (3P7K, 3UF3, 1TAM) 1TAM is found to be more suitable target receptor. This interaction plays a significant role in structure based drug designing. The study of comparative docking score will surely explain positive correlation between the docked ligand and receptor by perfect score. In future such a comparative study need to be done to explore more research Insilco it is to be concluded that the synthesized compound was found to be effective. The result show that three proteins ligand interactions are good and have agreeable values

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