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Molecular Docking Study of Four Chromene Derivatives as Novel HIV-1 Integrase Inhibitors

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Abstract: Four ligands based on Chromene derivatives have been docked into integrase of prototype foamy virus, which has high structural similarity with that of HIV-1 integrase. The Autodock Vina (Vina) software was used for this purpose. The docking scores for the derivatives are -7.3 kcal/mol, -7.5 kcal/mol, -6.9 kcal/mol, and -7.2 kcal/mol, respectively, which are comparable with that for Raltegravir (-10.7 kcal/mol). The docking results provide a detailed evidence for the interactions of four Chromene derivatives. The results may lead to the design and development of new drug candidates against AIDS.

Keywords: AIDS, chromene derivatives, molecular docking, HIV-1 integrase inhibitors.

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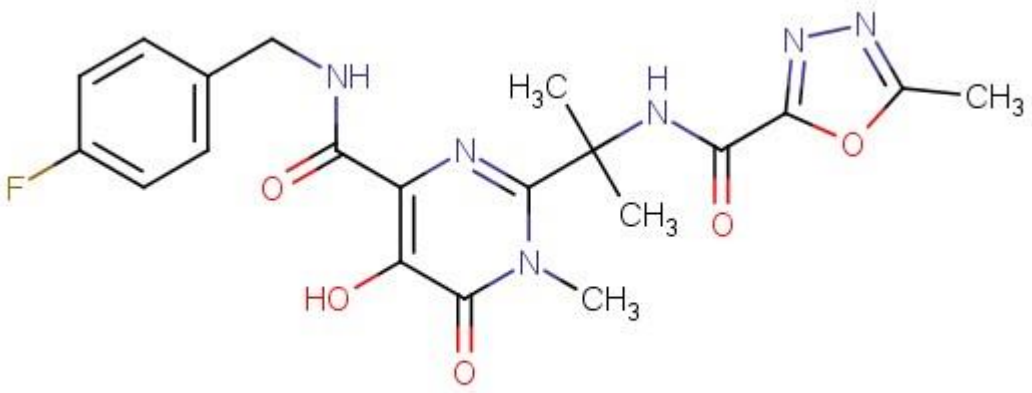
INTRODUCTION

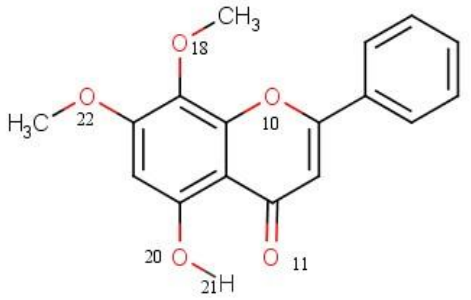
The main reason of the acquired immunodeficiency syndrome (AIDS) is the human immunodeficiency virus type 1 (HIV-1). This is a progressive, sluggish and degenerative disease of the human immune system. HIV-1 belongs to the retrovirus family, which is classified as a lentivirus (1). The HIV replication cycle involves the integration of viral DNA into the host chromosome, which is an essential process conducted by the viral integrase (IN) protein. This protein, together with reverse transcriptase and protease, is one of three enzymes encoded by HIV (2). The current antiviral therapy for treatment of AIDS includes a combination therapy with reverse transcriptase and protease inhibitors with a potential therapeutic capability (3). The integrase is a 32 kDa enzyme composed of three functional domains (catalytic core domain, an N-terminal domain and a less conserved C-terminal domain) (4,5). It does not have sequence homologue or an equivalent counterpart in the human host cell. Therefore, this makes the protein an attractive drug target (6). There are few integrase inhibitors introduced as promising drug candidates for the treatment of AIDS after the authorization of Raltegravir (7). Despite the effective activity of Raltegravir and several other inhibitors against anti-HIV integrase they possess adverse influences on prolonged usage and develop drug resistance. Thus, there is an urgent requirement to investigate new and potential chemical scaffolds for the treatment of AIDS.

Diketo acids (DKA) possess a metal-chelating function and they can simultaneously coordinate two divalent metal ions. Therefore, they are considered as potent inhibiting proteins which bear divalent metals which are involved in the hydrolysis of endonucleolytic phosphodiesters (8-9). Raltegravir is the first efficient anti-HIV drug targeting HIV-1 IN, which is classified as a diketo acid-based derivative. FDA approved it in October 2007. Besides, Elvitegravir is a monoketo acid

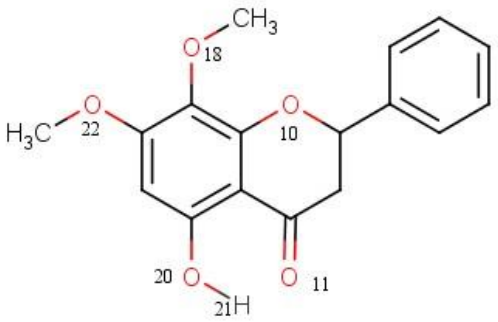
derivative which has two functional groups with only one metal ion binding site. It is identified as a second integrase inhibitor approved in 2012 (10-11).



Raltegravir



5-hydroxy-7,8-dimethoxy-2-phenyl-4H-chromen-4-one



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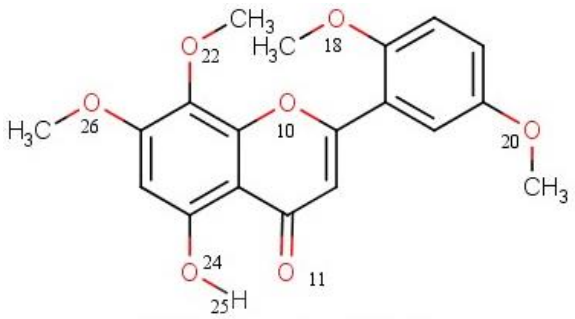
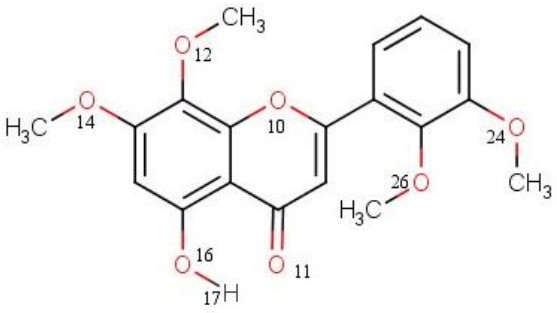


2-(2,5-dimethoxyphenyl)-5-hydroxy-7,8-dimethoxy-4H-chromen-4-one



2-(2,3-dimethoxyphenyl)-5-hydroxy-7,8-dimethoxy-4H-chromen-4-one

Figure 1. Structures of ligands used for molecular docking. (The atoms in interaction with protein or DNA labelled by number in structure file.).

The computational methods have occupied a significant place in drug discovery. These methods are collectively termed pharmacoinformatics. They include virtual screening, structure activity relationship (SAR), pharmacophore and molecular docking. These approaches have widely been employed in the pharmaceutical industry for identification and optimization including several groups who have identified IN inhibitors for HIV therapy (12–17). The current research involves exploring the binding choice of the inhibitory molecules of HIV IN according to virtual screening and space modelling study together with molecular docking. Chromene derivatives (Figure 1), (L01), (L02), (L03) and (L04) were used as ligands. The structure of the HIV-1 IN has not yet been experimentally determined. Nevertheless, it is known that INs have a high level of conservation especially within their active sites (6, 8, 9, 17) (Calculated catalytic core residues identity between 1BL3.pdb and 3OYA.pdb with Chimera is 25%) and the catalytic triad DDE motif which interacts with both target and viral DNA. Recently an X-ray

structure of prototype foamy virus (PFV) IN has been resolved and thus it can provide a basis for structural explorations of HIV INs (18, 19). HIV-1 lacks only Ser217 residue in the immediate vicinity of the catalytic carboxylates of PFV IN. Nevertheless, this residue is not directly involved in the interaction of IN with integrase strand transfer inhibitors (INSTIs) (6).

MATERIAL AND METHOD

Preparing of Receptor Structure

We obtained the crystallographic structure of full-length (3OYA.pdb) PFV Integrase from the Protein Data Bank (www.rcsb.org). This structure includes a DNA fragment and Raltegravir. After removing all ligands and water molecules from crystal structure, receptor and ligand files were separately saved by DS Visualizer software. MGL Tools (Version 1.5.7rc1) was used for creating pdbqt files of receptor and ligands needed for docking with Autodock Vina (Vina) (Version 1.1.2).

Preparing of Ligand Structures

2D structures of ligands were drawn with Chemaxon Marvin Sketch program and also saved as 3D structure file in mol2 file format. Structures were then optimized with semi-empirical PM6 method with Gaussian 09 (18) program. Charges were derived by antechamber module of AMBER 14 (19) suite software. Ptbqt files of ligands were prepared with MGL Tools by keeping charges obtained from the antechamber.

Docking Method and Method Validation

Autodock Vina uses an efficient quasi-Newton and Broyden-Fletcher-Goldfarb-Shanno (BFGS) methods for local optimization (20). Ligands were docked to binding site cavity using x=-38.7 Å, y=29.9 Å, and z=-20.2 Å Cartesian coordinates which take catalytic site in. The grid box dimensions used for search space were 28 Å x 28 Å x 28 Å. Docking calculations were performed with exhaustiveness option of 8 (average accuracy) and an energy range of 3. The Vina gives docking scores as predicted inhibition constants (K_i), which is derived from Gibbs free energy of binding calculated by following equations,

$$\Delta G = -RT(lnK_i) \quad \text{Eq. 1}$$

$$K_i = e^{\frac{-\Delta G}{RT}} \quad \text{Eq. 2}$$

where R (gas constant) is 1.98 cal/mol.K, and T is 298.15 K.

Validation of docking method was performed by re-docking Raltegravir to the crystal structure. Binding mode of Raltegravir to the protein structure is shown in Fig. 2 which shows the ligand is located in a similar mode with its original location.

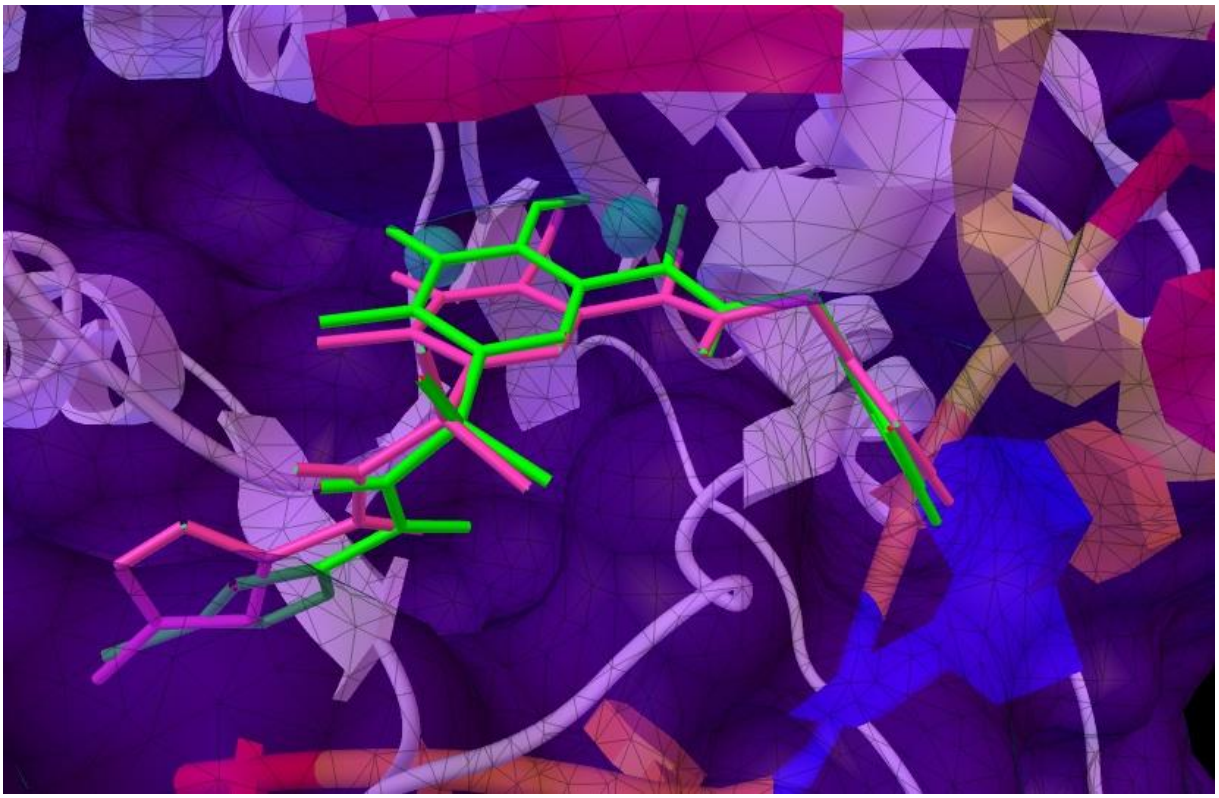


Figure 2. Validation of docking with Autodock Vina (pink: original coordinates, green: docking mode of Raltegravir with Vina)

RESULTS AND DISCUSSION

On one hand, the prediction of some properties of molecules is important for their consideration as drug candidates. These are defined by the Lipinski's rules. (21). Analyses demonstrate that all the ligands follow the Lipinski's rule of five and they show moderate water solubility (Table 1)

Table 1. Molecular properties of ligands according to Lipinski's rules.

Ligands	Molecular Mass	Hydrogen bond donor	Hydrogen bond acceptor	LogP	Molar Refractivity
L01	298.29	1	5	2.81	82.93
L02	300.11	1	5	2.61	80.51
L03	358.34	1	7	2.83	95.91
L04	358.34	1	7	2.79	95.91

Four ligands were successfully docked to PFV IN by Autodock Vina. Raltegravir gave the best docking score which was used for validation of docking method with a score of -10.7 kcal/mol. L01, L02, L03, and L04 have a docking score of -7.3 kcal/mol, -7.5 kcal/mol, -6.9 kcal/mol, and -7.2 kcal/mol, respectively. The ligands have quite similar docking scores with comparable magnitude to that of Raltegravir.

X-ray structure of PNV IN (22) demonstrates that Tyr212 (corresponding Tyr 143 in HIV-1 Integrase) is involved in a face-to-face π–π stacked interaction with the oxadiazole ring of Raltegravir. Raltegravir also forms two hydrogen bonds with Tyr212, and two water molecules coordinated with the metal ions. The other important interaction between Raltegravir and receptor (protein and DNA) involves π–π stacking with DC16 (DNA cytosine), DA17 (DNA adenine), Gln215 and Pro214. The electrostatic interaction with both Mg ions is of course one of the most significant interactions (Figure 3).

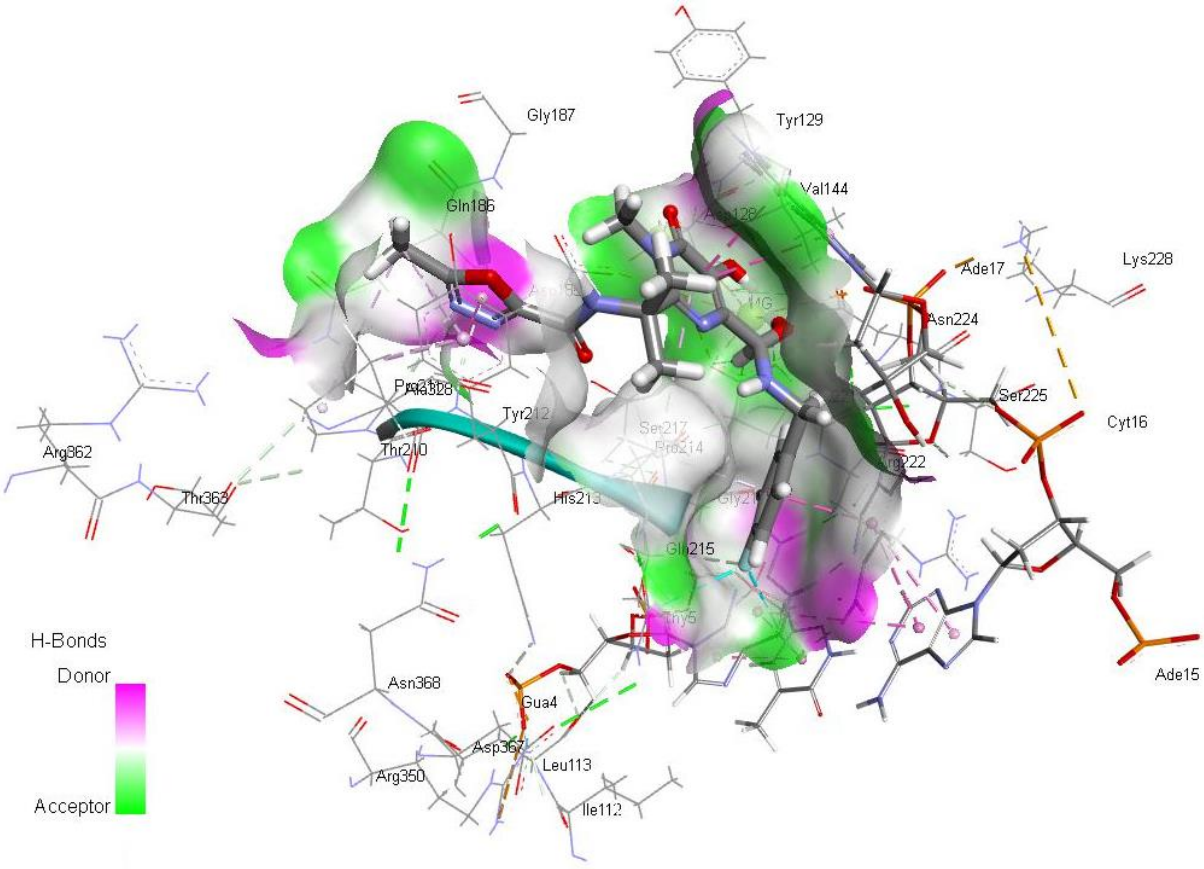


Figure 3. Interaction mode of RAL with IN obtained from docking results.

All the ligands are placed in catalytic center of integrase and they all interact with both Mg ions. In L01, O11 and O20 atoms form electrostatic interactions with Mg ions while O5 atom forms a hydrogen bond with HN atom of DA17. Chromene ring of L01 also forms π-anion, π/CH interaction with Glu221, and Pro214, respectively (Figure 4). L02, which differs from L01 by lacking the double bond between C8 and C9 atoms of chromene, has a similar binding mode compared to that of L01 (Figure 5).

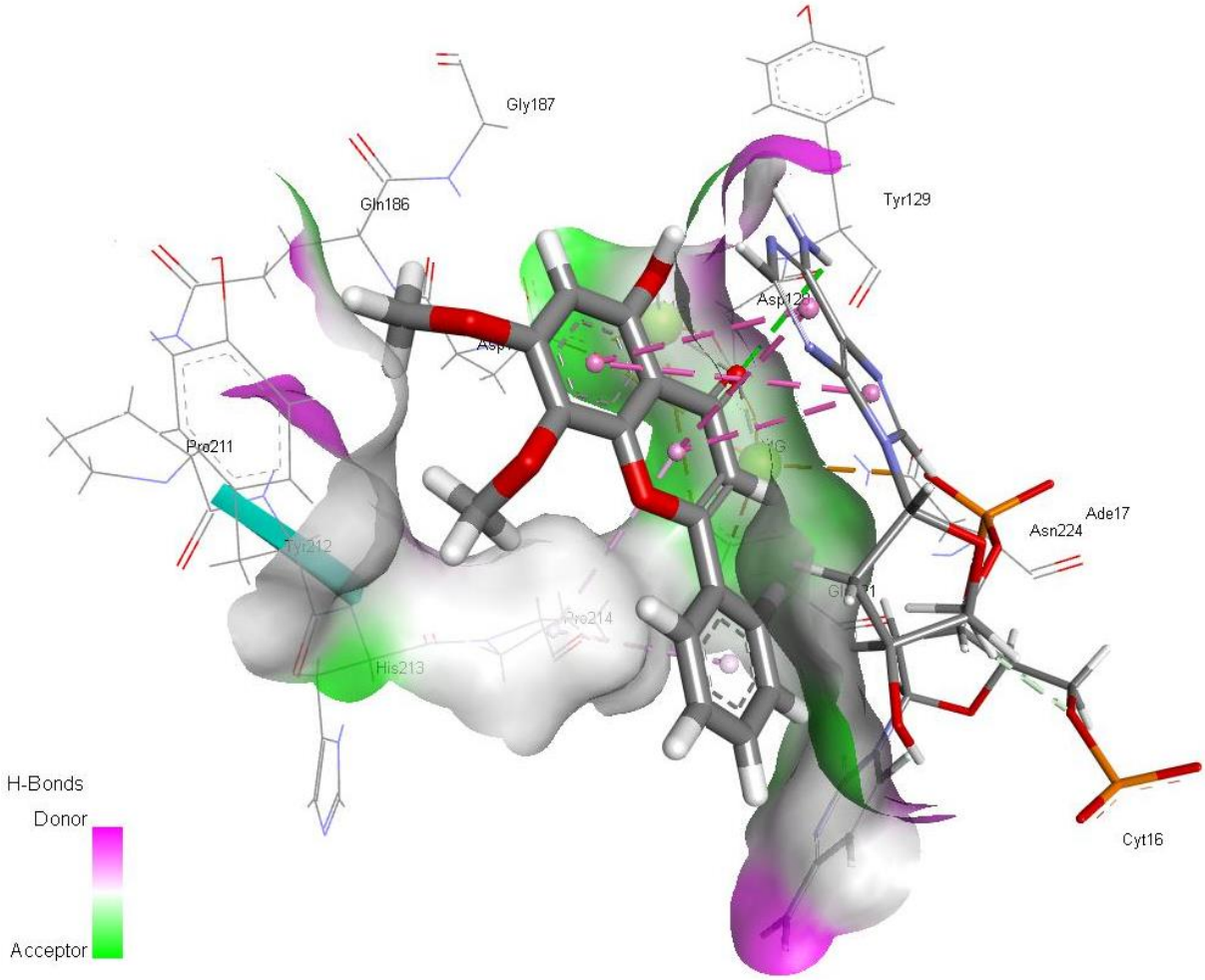


Figure 4. Interaction mode of L01 with IN obtained from docking results.

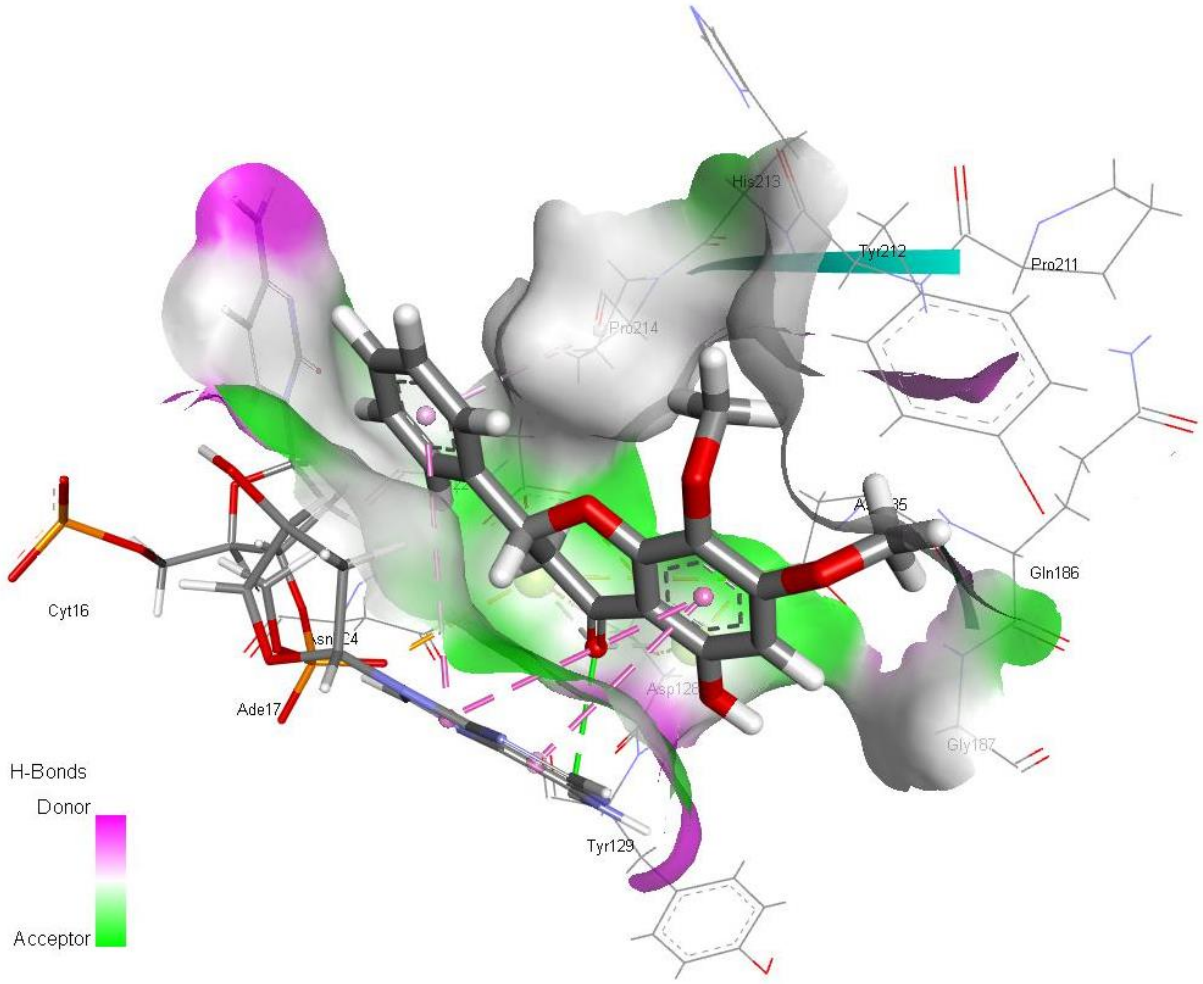


Figure 5. Interaction mode of L02 with IN obtained from docking results.

Unlike other three ligands, L03 forms electrostatic interaction with only Mg 397 atom. The distances between ligand oxygen atoms and Mg atoms are shown in Table 2. The other interactions of L03 with the receptor include the π-π stacking between chromene and DA17 and π/CH interactions between chromene and Pro214 (Figure 6). On the other hand, L04 ligand has two hydrogen bonds, one is between O24 in the ligand and the amide NH of Tyr212 and the other is between H6 in the ligand and OE1 of Glu221 residue. Besides, there are electrostatic interactions of oxygen atoms in the ligand with Mg atoms and π/CH interaction with Pro214 residue (Figure 7).

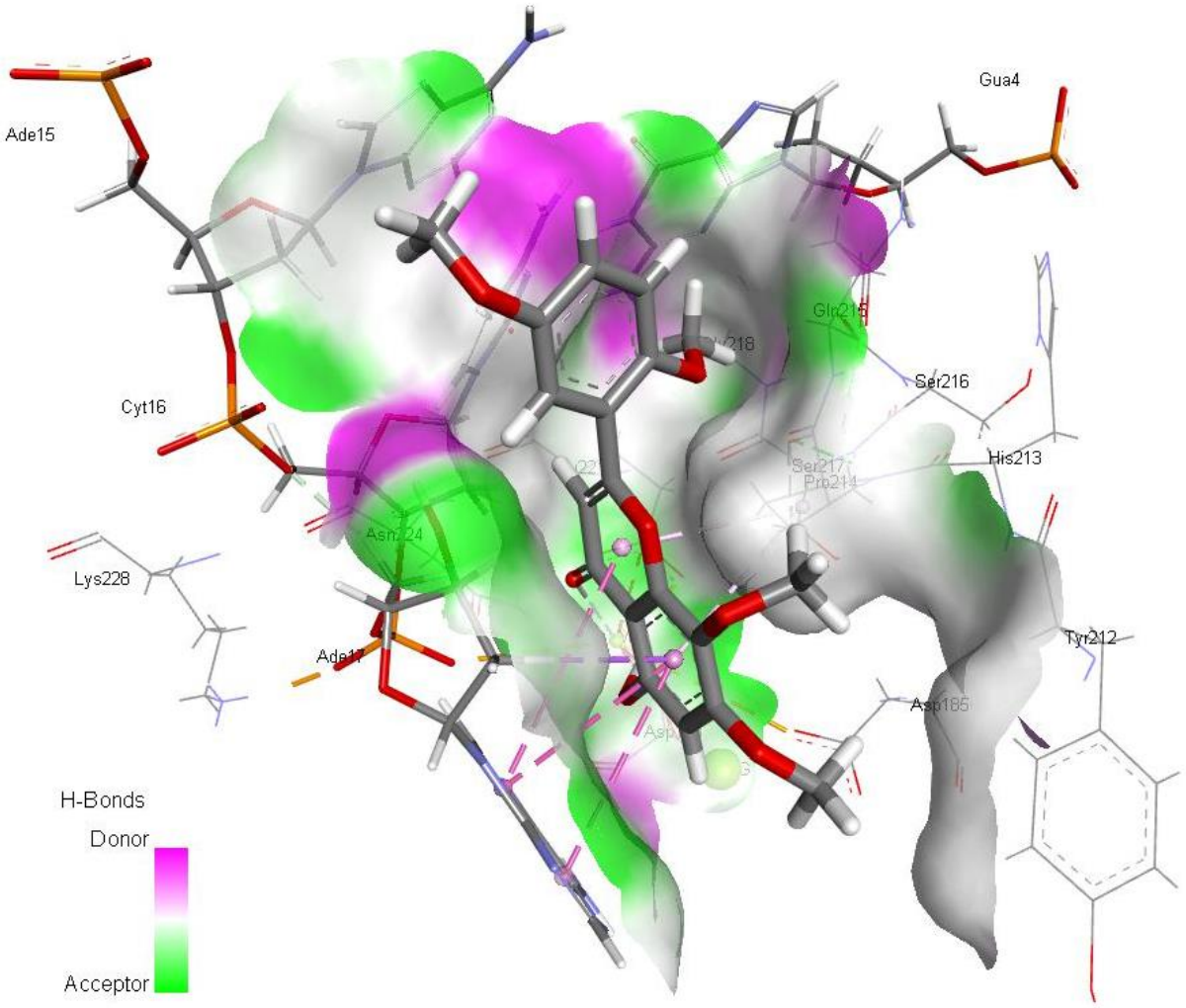


Figure 6. Interaction mode of L03 with IN obtained from docking results.

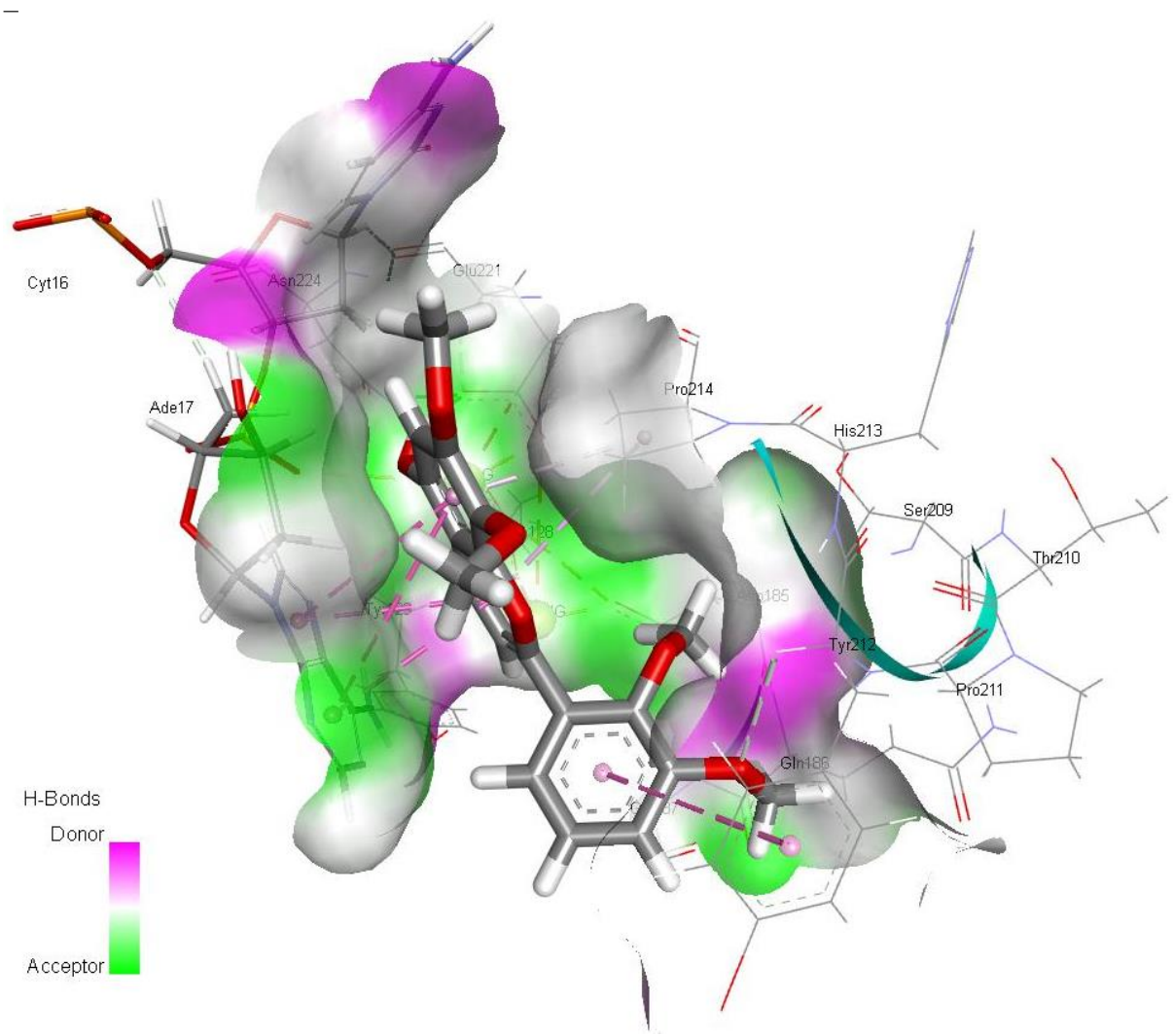


Figure 7. Interaction mode of L04 with IN obtained from docking results.

The binding role and importance of metal ions which are contained in the enzyme is well known (23). Table 2 details the distances between Mg^{2+} ions and related ligand atoms. Hereunder, except L03-O24/Mg396 ligands have an acceptable interaction distance with Mg^{2+} ions and while all other ligands make an interaction with both Mg^{2+} ions by one oxygen atom, L03 is in interaction with one Mg^{2+} ion per oxygen atom (L03-O11/Mg397, L03-O24/Mg397). L03-O24/Mg396 interaction is weak (4.03 Å) when comparing with other ligands' equivalent oxygen atoms-Mg interactions.

Table 2. Interaction distances between the oxygen atoms in the ligands with Mg atoms.

Ligand Atoms	MG396	MG397
L01-O11	2.51 Å	2.60 Å
L01-O20	2.41 Å	-
L02-O11	2.43 Å	2.66 Å
L02-O20	2.47 Å	-
L03-O11	-	2.75 Å
L03-O24	4.03 Å	2.76 Å
L04-O6	-	2.27 Å
L04-O11	2.98 Å	2.26 Å

CONCLUSIONS

The docking results provide a detailed evidence for the interactions of four Chromene derivatives. Docking scores and interactions of ligands with catalytic core residues and Mg ions encourage hope for a new ligand group in HIV-1 drug design studies. Also, we note that these ligands need some improvements by adding or removing some fragments. This information may be used for the design and development of new drug candidates against AIDS.

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