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The QSAR and docking calculations of fullerene derivatives as HIV-1 protease inhibitors

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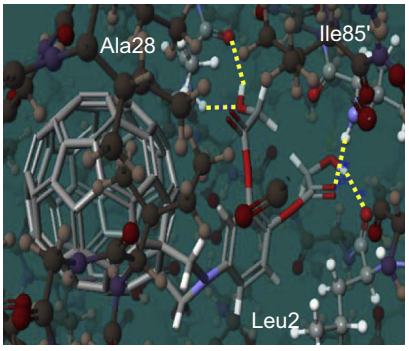
HIGHLIGHTS

- Fullerene derivatives as HIV-1 protease inhibitors.
- Quantitative Structure Activity Relationship (QSAR).
- Docking calculations.

GRAPHICAL ABSTRACT

The fullerene diameter is similar to the diameter of HIV-1 protease and form good hydrophobic interaction with the hydrophobic residues in HIV-1 protease. Unfortunately, the fullerene is insoluble in biological system. In this study some fullerene derivatives are modified to increase the solubility and inhibitory properties. These properties studied through QSAR and docking calculations. According to this study the fullerene derivative with two O atoms + HMC groups has good HIV-1 protease inhibitory properties. This result is benefit to improve the treatment of AIDS.



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ABSTRACT

The inhibition of HIV-1 protease is considered as one of the most important targets for drug design and the deactivation of HIV-1. In the present work, the fullerene surface (C_{60}) is modified by adding oxygen atoms as well as hydroxymethylcarbonyl (HMC) groups to form 6 investigated fullerene derivative compounds. These compounds have one, two, three, four or five O atoms + HMC groups at different positions on phenyl ring. The effect of the repeating of these groups on the ability of suggested compounds to inhibit the HIV protease is studied by calculating both Quantitative Structure Activity Relationship (QSAR) properties and docking simulation. Based on the QSAR descriptors, the solubility and the hydrophilicity of studied fullerene derivatives increased with increasing the number of oxygen atoms + HMC groups in the compound. While docking calculations indicate that, the compound with two oxygen atoms + HMC groups could interact and binds with HIV-1 protease active site. This is could be attributed to the active site residues of HIV-1 protease are hydrophobic except the two aspartic acids. So that, the increase in the hydrophilicity and polarity of the compound is preventing and/or decreasing the hydrophobic interaction between the compound and HIV-1 protease active site.

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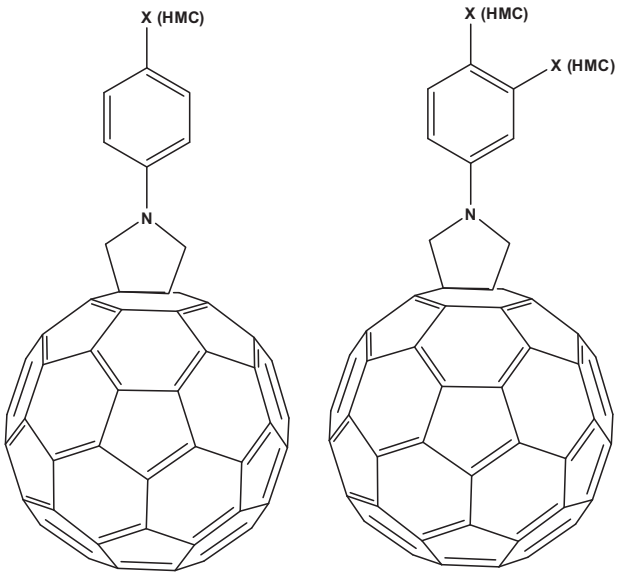
Introduction

Acquired Immune Deficiency Syndrome (AIDS) is considered the terminal stage of Human Immunodeficiency Virus (HIV) infections. HIV is one of the dreaded infectious diseases of the late 20th century, having claimed more than 25 million lives over the past three decades [1–5]. The most widely spread type of HIV is HIV-1 type [6]. There are two keys prevent the reducing the incidence of new infections. The first one is the reducing the number of people living with HIV who do not know their serologic status. The other is the reducing the time between infection and diagnosis [7]. Many drugs are getting ineffective due to resistance offered by the mutation-prone HIV. Hence, there is an urgent need for developing new drugs with greater potential [8]. Two factors are crucial for understanding the underlying principles of drug resistance. First, HIV has a very high reproduction rate. Secondly, the high error rate of the reverse transcriptase when transcribing viral RNA to DNA results in a large number of mutated forms of the virus being produced [9]. The three essential enzymes of HIV-1 virus are HIV-1 protease (PR), HIV-1 reverse transcriptase (RT), and HIV-1 integrase (IN) [8,10]. HIV-1 protease and HIV-1 reverse transcriptase are considered the important target sites for HIV-fighting drugs [11,12]. The HIV-1 protease can recognize Phe-Pro or Tyr-Pro sequences as the retrovirus-specific cleavage sites and its essential activity is the cleavage of the junctions between the gag and gag–pol polyproteins [12,13]. The HIV-1 protease is a homodimer with C2 symmetry. The homodimeric protein is composed of two chemically identical subunits of 99 amino acid subunits, each containing one catalytic aspartic acid Asp25 and Asp25′. The C2-symmetric active site is located at the dimer interface and each subunit contributes one catalytic aspartic acid residue present in a tripeptide sequence, Asp25, 25′–Thr26, 26′–Gly27, 27′. The protease subunit fold consists of a compact structure of β-strands with a short α-helix near the C-terminus [13–15].

There are two specific characters for HIV-1 protease. The first one, the cavity of HIV-1 protease active site is about 10 Å in diameter. The second one, all amino acids of HIV-1 protease active site are hydrophobic except two hydrophilic aspartic acids (Asp25 and Asp25′) [16]. Due to these HIV-1 protease active site characters, the fullerene C_{60} is considered a good inhibitor of the activity of HIV-1 protease. This is because (a) the diameter of fullerene C_{60} close to the diameter of HIV-1 protease active site cavity. (b) The fullerene C_{60} is more stable and not easily degradable like as other fullerenes types. (c) Its hydrophobic surface provide strong van der Waals interaction between fullerene C_{60} and HIV-1 protease active site [16,17]. There are many fullerene C_{60} derivatives studied to use as HIV-1 protease inhibitors [16–24].



Scheme 1. The general structure of previous study suggested compounds. Where X atom is O, S or Se and HMC is the hydroxymethylcarbonyl group.

In previous study the modified fullerene systems were investigated by utilizing both molecular modeling and QSAR descriptors [9,24,25]. These modified fullerene compounds had pyrrolidine ring to form fulleropyrrolidine in addition to O, S or Se atom and hydroxymethylcarbonyl (HMC) groups at para position on phenyl ring or at para and meta position on phenyl ring (Scheme 1). The compounds with O atoms indicated the best biological activity. In the present study, the O atom with HMC group is repeated at different position on phenyl ring to investigate the effect of this repeatation on the ability of compound to act as HIV-1 protease inhibitor. This effect is studied by calculating the QSAR properties and docking simulation.

Computational details

The investigated compounds which are selected as a target for this study are built by HyperChem 7.5 program [26].

QSAR calculations

The Quantitative Structure Activity Relationship (QSAR) is quantitative correlation between the physicochemical properties of molecules and their biological activities. The calculations of QSAR properties are performed using the HyperChem 7.5 program [26]. The geometries of the studied compounds are optimized at semi-empirical quantum mechanical PM3 level of calculations [27], using the restricted Hartree–Fock (RHF) procedure [28]. The Polak–Ribier algorithm [29] is used for the optimization, with the termination condition being a root mean square (RMS) of <0.001 kcal mol^{-1}. The optimized structures are confirmed by calculating IR spectra of compounds at the same semi-empirical PM3 level to confirm that the obtained structures are corresponding to real structures not corresponding to transitions states.

The QSAR calculated descriptors include total energy, heat of formation, dipole moment, hydration energy, log*p*, refractivity, surface area (grid) and volume.

Docking calculations

The docking molecular simulation is calculated by SCIGRESS 3.0 program [30]. The origin of HIV-1 protease which used for this calculation is the Protein Data Bank (PDB code: 4DJO) [31]. After preparing the protein structure by adding the hydrogen atoms, the optimized geometry of HIV-1 protease is calculated using MM3 force field which is better than the MM2 force field [32]. The conserved catalytic triad residues of HIV-1 protease active site Asp25–Thr26–Gly27 (for first monomer of HIV-1 protease) and Asp25′–Thr26′Gly27′ (for second monomer of HIV-1 protease) are selected as a group to be ready for docking calculation. By performing the genetic algorithm, the both FASTDOCK and PMF04 scoring function [33–36] are used to fit the ligand into the selected HIV protease active site residues. The optimization of best score docking systems is recalculated for docking systems at MM3 force field.

Result and discussion

Building the model molecules

In previous study of our research group, the calculated electronic and QSAR properties of some modified fullerene based