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Structural and electronic properties of new fullerene derivatives and their possible application as HIV-1 protease inhibitors

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ABSTRACT

Density functional theory (DFT) calculations have been carried out at the hybrid Becke 3-Lee–Yang–Parr; B3LYP/3-21G** level of theory to study two series of hydroxy-chalca-acetic acid-(4-pyrrolidin-1-yl-phenyl) ester [C_{60}-C_2H_4N-(4-XCOCH$_2$OH)C_6H_4] and hydroxy-chalcoacetic acid-[2-(2-hydroxy-acetylchalcanyl)-4-pyrrolidin-1-yl-phenyl] ester[C_{60}-C_2H_4N-(3,4-XCOCH$_2$OH)C_6H_4]. The X atom is O, S or Se for the two series. The vibrational spectra, physical, chemical, thermodynamics and Quantitative Structure Activity Relationship (QSAR) properties of the studied molecules are calculated and discussed. We have evaluated these molecules as HIV-1 protease inhibitors based on the hydrogenation interaction between the hydroxymethylcarbonyl (HMC) groups and the two aspartic acid of the HIV-1 protease active site. Results show that some of the investigated fullerene-based derivatives can be considered promising as HIV-1 protease inhibitors.

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1. Introduction

Fullerenes and their derivatives have been the center of attraction of many studies during the past decade. Most of these investigations have demonstrated unique applications for such systems in material science and to some extent in the biological field [1–8].

However, the low solubility of fullerenes greatly restricts their applications. Several efforts have been performed to carry out synthesis of new C_{60}-based molecules, in which C_{60} is covalently to polar organic groups. These groups have led to significant improvements in their physical, biological and chemical properties [9–12]. Fulleropyrrolidine is among the most important fullerene derivatives that have been used for a wide range of biological and material applications [13]. This starting product can be formed easily by 1,3-dipolar cycloaddition reactions with azomethane and thereby attach to the fullerene [14,15]. The compounds produced from such mechanisms are of more practical application.

Organochalca compounds, which contain O, S and Se, frequently possess unique chemical reactivities and biological activities [16]. Additionally, many trials have been carried out to evaluate their possible applications as therapeutic agents in the treatment of several diseases such as cancer and AIDS [16–18].

The majority of these organochalca compounds are polar and therefore soluble in biological systems. They can then form networks of hydrogen bonding complexes, in addition to van der Waals attractions and chemical bonds with other systems [19] that can also occur. Thus, the covalent binding of fullerene to these compounds may lead to the improvement of its dissolvability as well as its biocompatibility profile.

The three essential enzymes of HIV-1 virus are HIV-1 protease (PR), HIV-1 reverse transcriptase (RT), and HIV-1 integrase (IN) [20]. Many compounds target to inactivate the HIV-1 protease while others target to inhibit both the HIV-1 protease and HIV-1 reverse transcriptase. The latter is called cocktail therapy or Highly Active Antiretroviral Therapy (HAART).

The cavity of HIV-1 protease active site is about 10 Å in diameter. This is close to the diameter of fullerene C_{60} [21,22]. All amino acids in HIV-1 protease active site are hydrophobic except two aspartic acids (Asp25 and Asp125) which are hydrophilic [22]. The stability of fullerene C_{60} and its hydrophobic surface provide strong van der Waals interaction between fullerene C_{60} and HIV-1 protease active site [22]. The addition of polar groups to fullerene C_{60} is expected to cause an increase in the probability of interaction with aspartic acid. Some studies show that the HMC group interacted excellently with the aspartic acid carboxyl groups of the HIV-1 protease active site [17,23]. We use

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the advantages and properties of fulleropyrrolidine, chalcogene atoms and HMC group to build our compounds which may have potential use as effective HIV-1 protease inhibitors. Accordingly, we have investigated two series of hydroxy-chalca-acetic acid-(4-pyrrolidin-1-yl-phenyl) ester[C_{60}-C_2H_4N-(4-XCOCH$_2$OH)C_6H_4] and hydroxy-chalcoacetic acid-[2-(2-hydroxy-acetylchalcanyl)-4-pyrrolidin-1-yl-phenyl] ester [C_{60}-C_2H_4N-(3,4-XCOCH$_2$OH)C_6H_4] where X atom = O, S or Se for the two series. Vibrational spectra have been carried out using DFT at the B3LYP/3-21G** level of the theory. Also, their possible applications as HIV-1 protease inhibitors have been theoretically investigated via calculation of their interaction with the aspartic acid of the HIV-1 protease active site.

2. Computational details

Semiempirical quantum mechanical calculations were performed using the Hyperchem version 7.5 program [24], which was used to analyze the initial potential energy surface (PES). The geometry of the studied series was optimized by performing the semiempirical molecular orbital theory at the PM3 level [25], using the restricted Hartree–Fock (RHF) procedure [26]. The Polak–Ribier algorithm [27] was used for the optimization, with the termination condition being a root mean square (RMS) of <0.001 kcal mol^{-1}. We have implemented the use of the scf = tight Keywords: for all optimizations due to the sensitive nature of the PES. Theoretical calculations of QSAR properties were performed using the Hyperchem.

For vibrational spectra calculations DFT-B3LYP was performed with 3-21G** basis set, using the Gaussian 03 program system [28]. The hybrid Becke 3-Lee–Yang–Parr (B3LYP) exchange correlation functional was applied for DFT calculations [29–31].

Due to computational limitations, we were unable to perform higher level optimizations and frequencies on the systems. Nevertheless, this level of calculation is suitable for new compounds and the size of molecules. Also this level is satisfactory and produces good results which are expected to be very close to experimental data.

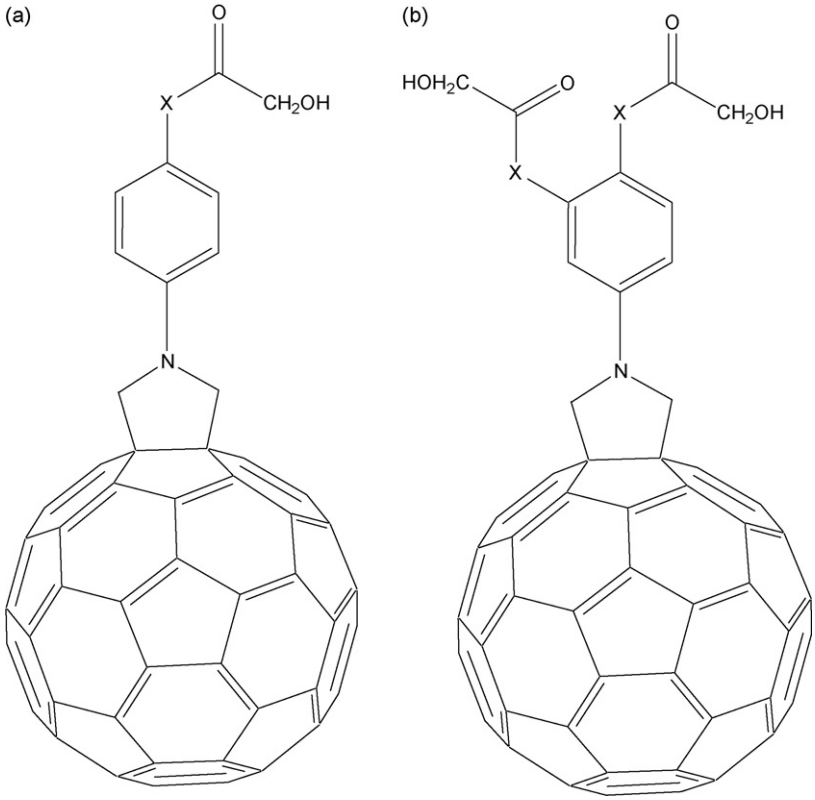
3. Results and discussion

3.1. Structural properties

Scheme 1 depicts a graphical representation of the chalcanthrenes-C_{60} complexes described in this work whereby, X = O, S or Se. Fig. 1 displays the optimized geometrical structures of the systems calculated at the B3LYP/3-21G** level of theory. These optimized structures are essential to study the geometrical parameters of compounds and give information about their point groups. The optimization of structures is an essential step to proceed with other meaningful calculations.

3.2. Electronic properties

Table 1 shows the calculated energy values obtained by PM3 method for the studied systems. Some of calculated energy values of the studied molecules according to the BLYP/3-21G** level are listed in Table 2. The highest occupied and the lowest unoccupied molecular orbital energies (HOMO and LUMO, respectively), and the frontier molecular orbital energy gap (HOMO–LUMO energy difference, ΔE) with the calculated dipole moment value of the considered systems are also given in Table 2. As shown in this table, the change in the chalcogene atom led to slight change in the HOMO and LUMO levels for the two series. According to the BLYP/3-21G** calculation, for the two series, the selenium molecules have the smallest optimization energy. When the relative energy with respect to the O and S molecules in the first series is computed,



Scheme 1. The general structures of (a) hydroxy-chalca-acetic acid-(4-pyrrolidin-1-yl-phenyl) ester and (b) hydroxy-chalcoacetic acid-[2-(2-hydroxy-acetylchalcanyl)-4-pyrrolidin-1-yl-phenyl] ester.

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