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Investigation of possible release mechanisms for flurbiprofen and ifosfamide drugs using multi-silicon decorated fullerene-C_{60}: Computational insights

Çoklu silikon katkılı fulleren-C_{60} kullanılarak flurbiprofen ve ifosfamid ilaçları için olası salınım mekanizmalarının incelenmesi: Hesaplamalı edinimler

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Abstract

Invention and production of new nano-based versatile materials make it possible to design new drug carriers and sensors. In the scope of this work, one of the famous members of fullerene family, C_{60}, was taken as a reference structure and its multi-silicon modified form was investigated as possible drug delivery vehicles towards flurbiprofen and ifosfamide drug molecules. The results suggest that by replacing carbon atoms from the surface of fullerene-C_{60} with silicon dopants, it is possible to increase the numbers of loaded drugs over the surface of C_{60} with changing structural, electronic and vibrational properties. Calculations of desorption characteristics via the interpretation of recovery times also showed that the release of flurbiprofen tend to occur faster than that of the release of ifosfamide drug molecule making the selective drug delivery applications possible.

Keywords: DFT, Fullerene, Multi-drug interactions, Multi-silicon doping

Öz

Yeni nano tabanlı çok yönlü malzemelerin keşfi ve üretimi, yeni ilaç taşıyıcıları ve sensörlerin tasarlanmasını mümkün kılmaktadır. Bu çalışma kapsamında, fulleren ailesinin çok kullanılan yapılarından biri olan C_{60} referans yapı olarak alınmış ve çoklu silikon atomu katkılı formunun flurbiprofen ve ifosfamid ilaç moleküllerine yönelik olası ilaç taşıma aracı olarak kullanımı araştırılmıştır. Sonuçlar, fulleren C_{60}'ın yüzeyindeki karbon atomlarının silikon katkı atomları ile değiştirilmesinin yapısal, elektronik ve titreşimsel özelliklerini değiştirerek C_{60} yüzeyine yüklenen ilaçların sayısını artırmanın mümkün olduğunu göstermektedir. Salınım sürelerinin yorumlanması yoluyla desorpsiyon özelliklerinin hesaplanması da flurbiprofen salınımının ifosfamid ilaç molekülünün salınımından daha hızlı gerçekleşme eğiliminde olduğunu ve kontrollü ilaç dağıtım uygulamalarının mümkün olabileceğini göstermiştir.

Anahtar kelimeler: *YFT, Fulleren, Çoklu ilaç etkileşimi, Çoklu silikon katkılama*

1. Introduction

Recent developments in material science and the vast application possibilities of carbon-based nanostructured systems such as fullerenes and carbon nanotubes have received considerable attention among the scientists working particularly in the field of drug design and drug delivery (Rezaian et al., 2018). In order to provide an effective treatment for patients, the controlled drug delivery appears as an important factor to minimize the possible side effects of the drugs (Liu, 2013; Singh et al., 2021). Furthermore, the treatment with a single drug towards a potential receptor is considered as an outdated approach for the management of complex diseases. Instead, as a more effective alternative for the treatrment of various health issues, taking the advantage of combined drugs with predefined ratios could be preferred (Rahaman et al., 2025). Furthermore, the capacity, physical and chemical properties of the combined drug sytems and their course of interactions have been determined extensively using computational approaches (Kunjie et al., 2021). The investigations of fullerene-based materials as possible drug delivery instruments have been received increasing attention due to versatile and easy to manipulate chemical and physical properties of fullerenes (Qiang et al., 2024; Talaei et al., 2025).

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In previous publications, it was shown that some drawbacks of fullerenes such as low solubility and difficult processibility can be enhanced by impurity doping and taking the advantage of computational based pre-evaluation strategies (Apebende et al., 2023; Moumivand et al., 2025).

Along with the increasing capacity of computer systems, computational methods have taken their places as indispensable tools for the simulation of experimental works before going into expensive and time required laboratory studies. In this way, it seems possible to follow a more object-oriented workflow and effective handling of the time. Among the computational approaches, density functional theory (DFT) stands out with its many practical aspects as an important method used in many ways such as prediction of spectral, electronic and structural characteristics of different types of molecular systems expanding from small molecules, dimeric systems to large clusters (Parlak & Alver, 2017; Wu & Kumar, 2020; Nouraliei et al., 2023; Hasannezhad et al., 2025). In recent years, particularly, in the field of drug development, drug delivery and for the investigation of multiple drug interactions DFT method has been widely used to make beforehand evaluations (Naz et al., 2025; Almansour et al., 2025).

In the framework of this study, as a continuation of our previous interest, two model drugs, flurbiprofen (Flurb), an effective anti-inflammatory agent and an analgesic, and ifosfamide (IFO) having a broad spectrum of activities against various cancer types such as sarcomas and lung cancers, were selected as model samples and their interactions with multi-silicon (Si) doped fullerene-C_{60} were examined based on the DFT method (Hirabayashi & Okada, 1993; Scinto et al., 1999; Valentovic, 2007; Çatal et al., 2023; Kolsuz et al., 2024). The interaction energies, partial charge behavior, electronic and structural properties together with some important molecular vibrational bands of the interacted systems were examined. Different from our previous studies, in this work, the possibility of multiple interaction, combined application and controlled delivery trials of Flurb and IFO drug molecules were examined. All the findings of the work were discussed and explained.

2. Computational details

As a first step, six carbon atoms on the equatorial line of C_{60} were replaced by six silicon atoms and the resultant structure was optimized. The optimized structure can be seen in Figure 1. The separation of adjacent Si atoms was calculated as 4.40 Å. To leave a suitable space between the drug molecules and to avoid space interactions, the related distances were not shortened by inserting additional Si atoms which can be the subject of another study.

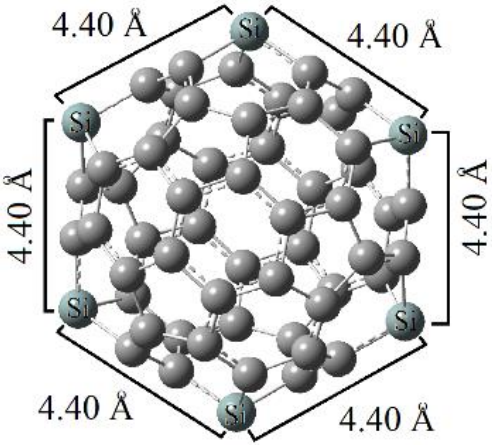

Figure 1. Optimized structure of $C_{54}Si_6$.

To make it clear for the optimization sequence, the steps followed for the structural optimization procedures were shown in Figure 2. According to the information given in Figure 2, only one drug molecule was let to be interacted with the fullerene cage at once and additional drug interactions were carried out one by one. Interaction sites were labelled as site-I, site-II and site-III, correspondingly (Figure 2). After the determination of the optimized structure for the interaction between Flurb and $C_{54}Si_6$, the calculations were carried out by the creation and optimization of additional interactions as given in Figure 2. All the optimization steps were carried out together with vibrational frequency calculations to make sure that none of the vibrations contains negative frequencies.

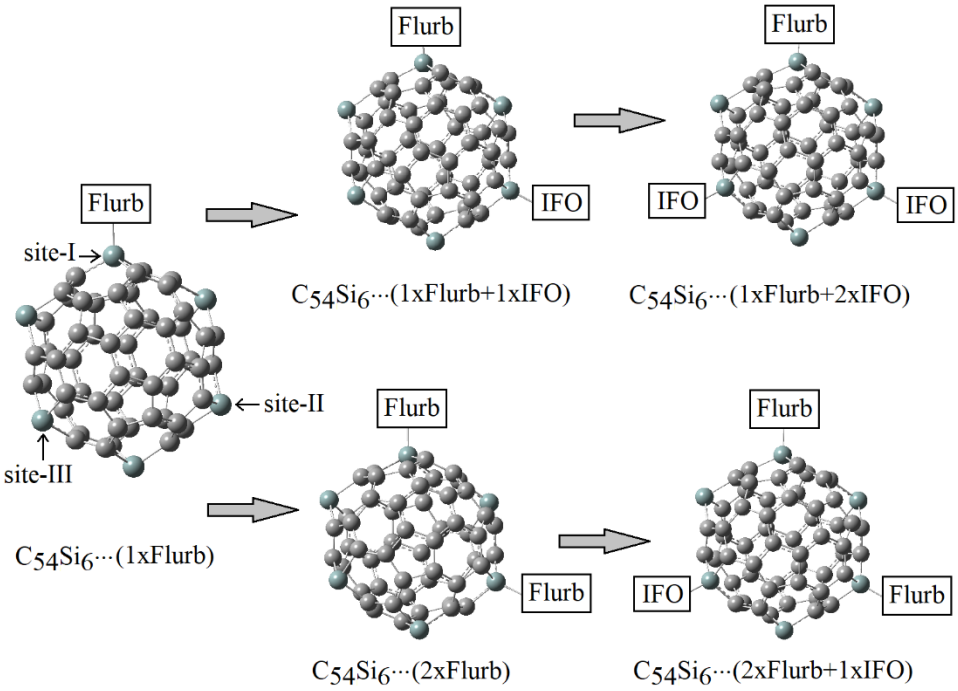

Figure 2. Optimization protocol of the examined systems.

The binding energies (E_b) for the interacted systems were calculated using the following relations:

For the interaction energy between Flurb and $C_{54}Si_6$ system:

$$E_b(site-I) = E_{C_{54}Si_6\ldots 1xFlurb} - (E_{C_{54}Si_6} + E_{Flurb}) \quad (1)$$

For the interaction energy between IFO and $C_{54}Si_6$…1xFlurb system:

$$E_b(site-II) = E_{C_{54}Si_6\ldots 1xFlurb+1xIFO} - (E_{C_{54}Si_6\ldots 1xFlurb} + E_{IFO}) \quad (2)$$

For the interaction energy between IFO and $C_{54}Si_6$…1xFlurb+1xIFO system:

$$E_b(site-III) = E_{C_{54}Si_6\ldots 1xFlurb+2xIFO} - (E_{C_{54}Si_6\ldots 1xFlurb+1xIFO} + E_{IFO}) \quad (3)$$

For the interaction energy between Flurb and $C_{54}Si_6$…1xFlurb system:

$$E_b(site-II) = E_{C_{54}Si_6\ldots 2xFlurb} - (E_{C_{54}Si_6\ldots 1xFlurb} + E_{Flurb}) \quad (4)$$

For the interaction energy between IFO and $C_{54}Si_6$…2xFlurb system:

$$E_b(site-III) = E_{C_{54}Si_6\ldots 2xFlurb+1xIFO} - (E_{C_{54}Si_6\ldots 2xFlurb} + E_{IFO}) \quad (5)$$

In order to evaluate the sensitivity of the $C_{54}Si_6$ towards the Flurb and IFO drug molecules, the following relation was used (Li, 2006):

$$\sigma\ \alpha\ \exp\left(-E_g/2K_BT\right) \quad (6)$$

In the given equation, E_g represents the energy difference between lowest unoccupied molecular orbitals (LUMOs) and highest occupied molecular orbitals (HOMOs). Further, σ, K_B and T indicate the conductivity, Boltzmann constant and temperature, respectively. From the given relation, it is seen that smaller E_g for a given temperature leads to a higher electric conductivity.

Desorption phenomena or the understanding of how quickly the interacted drugs can be released from the surface of the fullerene cage were evaluated by examining the reversibility of the interaction via the calculation of recovery times (τ) with the following equation (Hadipour et al., 2015):

$$\tau = \upsilon^{-1}\exp\left(-E_b/K_BT\right) \quad (7)$$

In equation (7), E_b and υ show the binding energy and attempted frequency, respectively. The determination of attempt frequency can vary depending on the working conditions. In present study it was chosen as 10^{12} Hz.

Water was chosen as the solvent for all calculations and the effect of solvent was simulated using the polarizable continuum model (Tomasi et al., 2005). Literature survey reflects that B3LYP functional when used with 6-31G(d) basis set yields acceptable outcomes for the calculations of geometric parameters, spectroscopic and electronic properties of different types of molecular systems when compared to experimental findings (Jasiński et al., 2009; Rafik et al., 2024). Therefore, B3LYP functional with 6-31G(d) basis set was used for the calculations carried out in the scope of present work. Additionally, to include basis set superposition error (BSSE), the counterpoise correction method was employed (Gutowski & Chalasinski, 1993). For the computational work, visualization, interpretation of structural and electronic parameters, Gaussian and GaussView programs were used (Dennington et al., 2008; Frisch et al., 2009).

3. Results and discussions

Optimized and interacted structures with some important structural, vibrational, and natural bond orbital (NBO shown in rectangles) charge parameter are given in Figure 3. E_b energy, Si…O interatomic distance, vibrational frequency of OH group and NBO charges of Si&O atoms (in a.u.) at the interaction site (site-I) were calculated as -16.19 kcal/mol, 1.800Å, 3133 cm^{-1} and 1.986 & -0.740, respectively, for $C_{54}Si_6$…(1xFlurb) system. It was observed that for additional Flurb or IFO drug molecules over $C_{54}Si_6$…(1xFlurb) system resulted longer Si…O bond length, smaller vibrational frequency of OH group, less positive and less negative Si and O atoms at the site I, correspondingly as can be seen in Figure 3. Particularly, for the dopant Si atom at the interaction site, it was observed that upon additional interaction with Flurb or IFO drug molecules some number of electrons flow towards the dopant atom making it less positive. E_b energies between $C_{54}Si_6$…(1xFlurb) and IFO drug and between $C_{54}Si_6$…(1xFlurb) and Flurb drug were computed as -28.26 and -14.08 kcal/mol. Furthermore, E_b energies between $C_{54}Si_6$…(1xFlurb+1xIFO) and IFO drug and between $C_{54}Si_6$…(2xFlurb) and IFO drug were computed as -22.66 and -24.66 kcal/mol. Calculations of recovery times as indicators of the reversibility of the adsorption or interaction process were calculated in compliance with the previously reported methods in the literature (Hadipour et al., 2015; Kolsuz et al., 2024). The approximate values of the recovery times for the interactions between $C_{54}Si_6$ & 1xFlurb, $C_{54}Si_6$…(1xFlurb) & IFO, $C_{54}Si_6$…(1xFlurb) & Flurb, $C_{54}Si_6$…(1xFlurb+1xIFO) & IFO, $C_{54}Si_6$…(2xFlurb) & IFO were computed as $7x10^{-1}$, $4x10^{8}$, $2x10^{-2}$, $4x10^{4}$ and $1x10^{6}$ s. The results suggest that while the desorption of Flurb drug tends to occur very quickly, the release of IFO requires extended period of times.

Overall NBO analyses indicate that Si-dopant at the interaction site of IFO is more positive when compared to Si-dopant at the interaction site of Flurb drug molecule. Similarly, O-atom at the interaction site of IFO appears as more negative compared to O-atom of Flurb for the related interaction edge. The obtained values correlate well with the resulting E_b values since the interaction of IFO with $C_{54}Si_6$ fullerene cage was found stronger than the interaction of Flurb drug molecule which further suggest that desorption of Flurb from the surface of $C_{54}Si_6$ can be expected to happen before the IFO drug molecule. It was also observed that OH stretching vibration of Flurb is more sensitive to the structural alterations when compared to NH vibration of IFO molecule by yielding larger vibrational shifts upon each interaction.

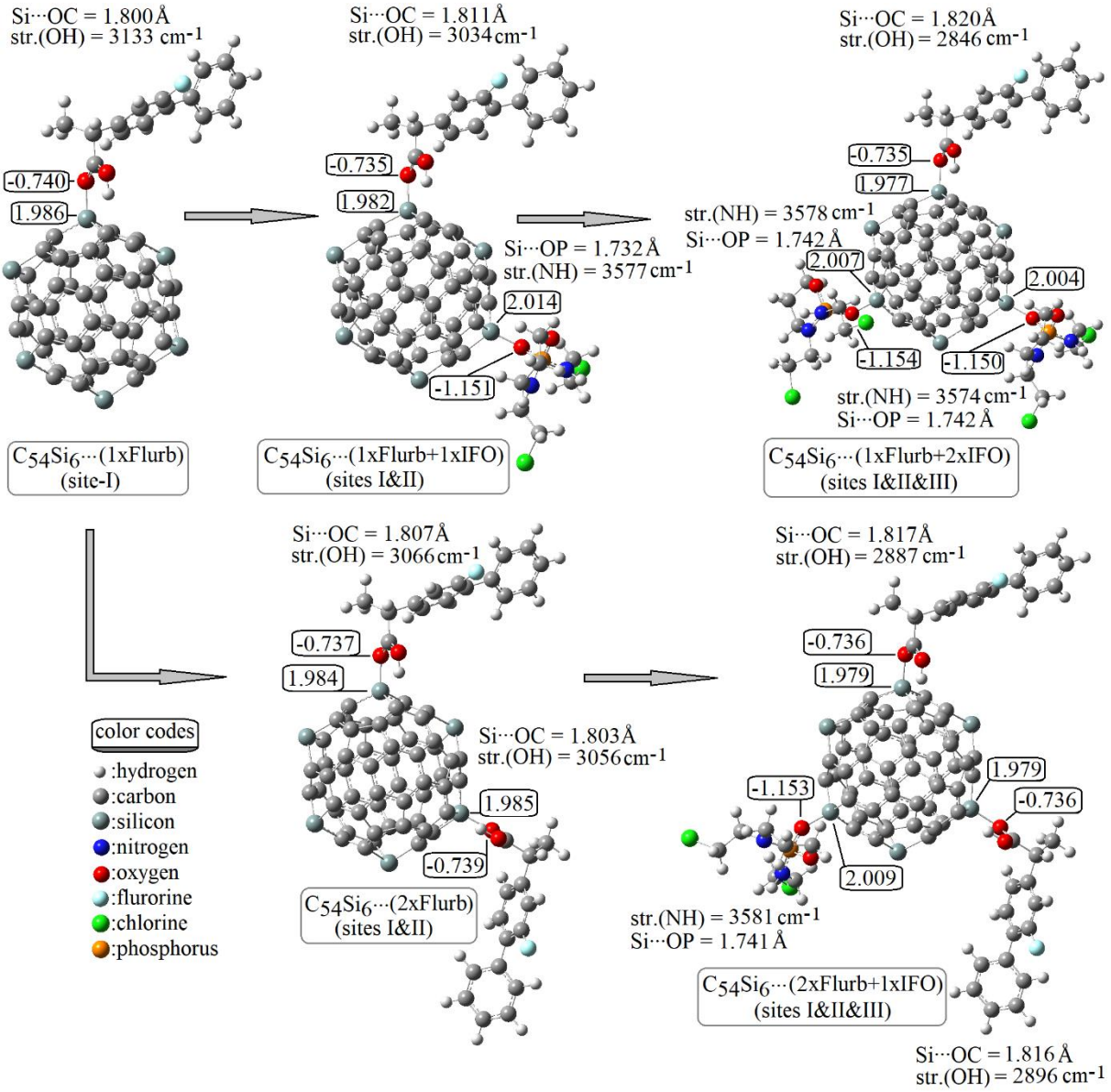

Figure 3. Interacted structures with some important parameters of the examined systems.

The HOMO and LUMO diagrams can be used to identify electron accepting and donating parts of a given molecular system (Fukui, 1982). HOMO-LUMO distributions of the examined systems can be seen in Figure 4. At first glance a quick examination of Figure 4 reveals that electron acceptance or electron donation mainly tend to occur over fullerene cage rather than drug molecules. E_g energy of isolated $C_{54}Si_6$ was computed as 1.85 eV. It was observed from the sequence given in Figure 4 that up to two drug molecules loaded on the $C_{54}Si_6$, E_g values tend to decrease which refers that $C_{54}Si_6$ is sensitive the additional drug molecules up to two numbers of drugs. However, further addition of IFO drug molecule to build a triple interacted system causes an increase in E_g value which refers that double drug interacted $C_{54}Si_6$ is not sensitive to the presence of a third IFO molecule. In other words, it can be concluded that among the investigated structures shown in Figure 4, having the smallest E_g values, double drug interacted systems appear as the most reactive systems. The magnitudes of E_{HOMO} and E_{LUMO} of $C_{54}Si_6$ indicating the ionization potential (IP) and electron affinity (EA) of the related system (Frenking & Shaik, 2014; Danish et al., 2021) were calculated as 5.47 and 3.62 eV. As for the drug interacted fullerene cages, the highest E_{HOMO} and E_{LUMO} values in magnitudes were calculated as 4.88 and 3.48 eV which further refers that $C_{54}Si_6$…(1xFlurb) system has the highest IP and EA. On the other hand, the lowest E_{HOMO} and E_{LUMO} values as indicators of the lowest IP and EA in magnitudes were found for $C_{54}Si_6$…(1xFlurb+2xIFO) system with respective values of 4.19 and 2.64 eV.

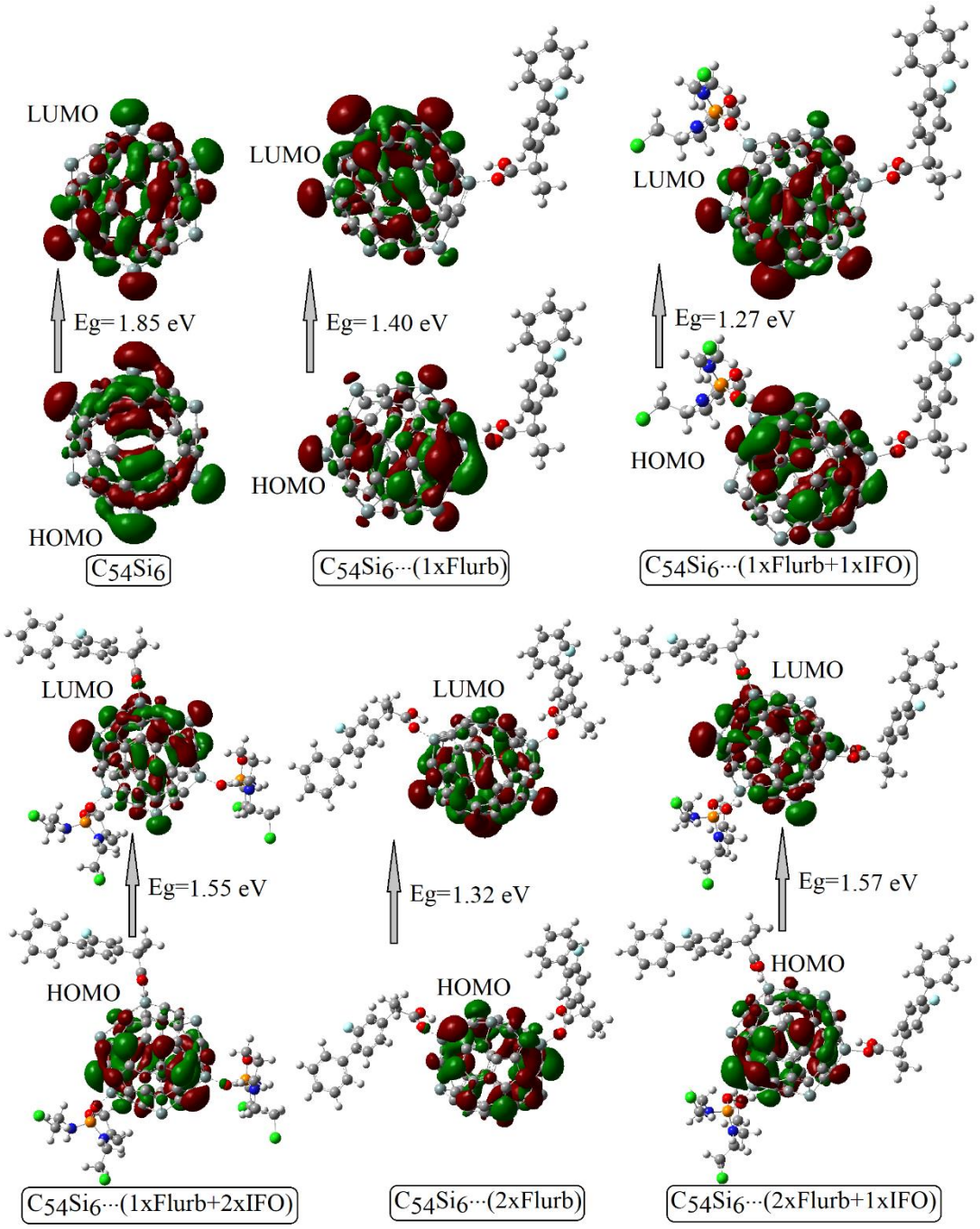

Figure 4. HOMO-LUMO distributions with related E_g values of the examined systems.

4. Conclusions

In the scope of present study, fullerene-C_{60} doped with six numbers of Si impurity atoms and its interacted forms with Flurb and IFO drug molecules have been analyzed using DFT method. In summary following remarks can be drawn from the findings of the undertaken study:

i. It is possible to replace six carbon atoms over the surface of C_{60} with six Si-atoms without causing a serious structural distortion of fullerene cage and up to three drugs (1xFlurb+2xIFO or 2xFlurb+1xIFO), it is possible to build stable complex systems with $C_{54}Si_6$.
ii. From the E_g energy analyses it was found that while the single Flurb interacted $C_{54}Si_6$ is sensitive to the presence of additional Flurb or IFO drug, the double drug interacted $C_{54}Si_6$ is not sensitive to the presence of an addition IFO drug molecule.
iii. It was observed that the release of Flurb tend to occur faster than that of the release of IFO drug molecule.

iv. The results also suggest that by using different numbers of impurity atoms such as silicon used in this study, it is possible to load multiple drugs over the fullerene cage for selective delivery purposes.

The overall examinations of the obtained results suggest that using different types and numbers of dopant atoms and interacted drug molecules, it seems possible to build drug delivery vehicles with fullerene-C_{60} by building stable complexes with various interaction energies.

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Author contribution

The authors contributed to all sections. The authors read and approved the last version of the manuscript.

Declaration of ethical code

The authors of this article declare that the materials and methods used in this study do not require ethics committee approval and/or legal-special permission.

Conflicts of interest

The authors declare that there is no conflict of interest.

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