Research Article

Chemical Review and Letters
ournal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

Theoretical insights into the intermolecular and mechanisms of covalent interaction of Flutamide drug with COOH and COCl functionalized carbon nanotubes: A DFT approach

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ARTICLE INFO

Article history:
Received 5 January 2020
Received in revised form 3 March 2020
Accepted 3 March 2020
Available online 10 April 2020

Keywords:
Density functional theory
Flutamide drug
Functionalized carbon nanotubes
Covalent and noncovalent functionalization
Reaction mechanisms

ABSTRACT

In this study, it is attempted to scrutinize the noncovalent interaction and two mechanisms of covalent between Flutamide anti-cancer drug (FLU) and functionalized carbon nanotubes (*f*-CNT) employing density functional theory (DFT) calculations regarding their geometries, binding energies and topological features of the electron density in the water solution. For designed noncovalent interactions, binding energies, natural bond orbital (NBO), atom in molecule (AIM) and quantum molecular descriptors analyses were applied for further understanding of the adsorption process. The computed theoretical results confirmed that binding of Flutamide molecule with functionalized CNT is thermodynamically suitable and among two considered systems containing COOH functionalized CNT (NTCOOH) and COCl functionalized CNT (NTCOCl), the NTCOOH revealed more binding energy value which suggests it as a favorable system as a drug delivery within biological and chemical systems (noncovalent). NTCOOH and NTCOCl can bond to the NH group of Flutamide through OH (COOH mechanism) and Cl (COCl mechanism) groups, respectively. Finally, in order to obtain the values of activation energies, the activation enthalpies and the activation Gibbs free energies of two considered pathways different calculations were performed and the results have been compared with each other. Numerical studies for calculating activation parameters related to the COOH mechanism show higher values than those related to the COCl mechanism and therefore COOH mechanism can be suitable for noncovalent functionalization. These results could be generalized to other similar drugs.

1. Introduction

The unique electrical, chemical and one-dimensional structural features of CNTs help them becoming the most significant leading molecular platform in variety of applications such as nano bio sensors devices, nano-electronic applied catalysis and energy storage devices [5]. Moreover, the capability of CNTs in cell's piercing can confirm the capabilities of CNTs as nano-carriers for the delivery of drug molecules [6], proteins [7] and peptides [8].

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Several features of carbon nanotubes such as size, chirality, surface modification, van der Waals forces and dosage play an important role in defining their biocompatibility or cytotoxicity for applying in biomedical systems. Beside these facts, it is shown that individualized CNTs which retain superior intrinsic properties such as high specific surface areas can be more applicable in nano-bio medicine fields, although, pristine CNTs may have toxicity for using in biological systems. Therefore, surface modification is a useful tool for bio-medicine studies. SWCNTs can be surface functionalized and easily coupled with biomolecules through adsorption, chemical conunction or encapsulation.

The advantage of functionalized CNTs for biomedical systems is to change their hydrophobicity characteristics in order to enhance their solubility in biocompatible aqueous media. It has been reported that after hydrophobic functional group attachment, *f*-CNT solubility increased significantly and alters their cellular interaction pathways, resulting in a significant reduction of cytotoxic effects. As a result, bioactive molecules can be delivered into the cell nuclei or passed through the cell membrane by using functionalized SWCNTs [9-11]. Several studies have approved the benefits of applying SWCNTs- drug delivery coupled systems which result in enhanced efficiency in tumor targeting due to an improved permeability and retention effect of the carbon nanotube [12-14].

In addition, using CNTs as a drug delivery system to target the cancerous tissues, has confirmed that the side effects of chemical drug have decreased in several case studies [15–17]. Functionalization of CNTs via covalent and noncovalent interactions (van der Waals and hydrogen bonds interactions) plays a critical role in the yield of systems containing drug delivery [18].

Among different types of cancers, one of the frequent cancers in men in the most of the countries in all over the world is prostate cancer. For curing this type of cancer, Flutamide (FLU) is already one of the best nominate antiandrogen drug which is widely applied [19, 20].

In order to find out the adsorption behavior of the FLU molecule onto the exterior surface of the single-wall carbon nanotube and the mechanism of approaching functionalized Flutamide drug to the surface of the CNTs, density functional theory (DFT) in the water solution has been applied in this study. For better evaluation, quantum theory of atoms in molecules (QTAIM) and natural bond orbital (NBO) are used. To study the electronic properties, using Koopmans' theorem [21,22], quantum descriptors are also calculated. Notwithstanding several computational investigations on CNTs, there are few surveys focusing on the functionalization mechanism.

2. Computational methods

In this theoretical study, the characteristics of Flutamide (FLU) molecule via the adsorption process onto the exterior surface of a functionalized armchair (5,5) single-walled carbon nanotubes has been deeply studied in solution phase.

To elucidate the importance of a functionalization of SWCNT on the strength of FLU adsorption, two functional groups of COOH and COCl are applied to modify the SWCNT surface. In order to simply note, the SWCNT with COOH group is shown the “NTCOOH”, and the other with COCl group is denoted the “NTCOCl”. Figure 1 exhibits the optimized molecular structures of FLU, NTCOOH and NTCOCl in solution phase with their atom labeling. Furthermore, the *f*-CNT/FLU model in which FLU adsorbed into the surface of the NTCOOH is called the “NTCOOH/FLUR” reactant (R), the other in which FLU adsorbed into the surface of the NTCOCl is called the “NTCOCl/FLUR” reactant. The optimized structures of the both *f*-CNT/FLU complexes are shown in Figure 2.

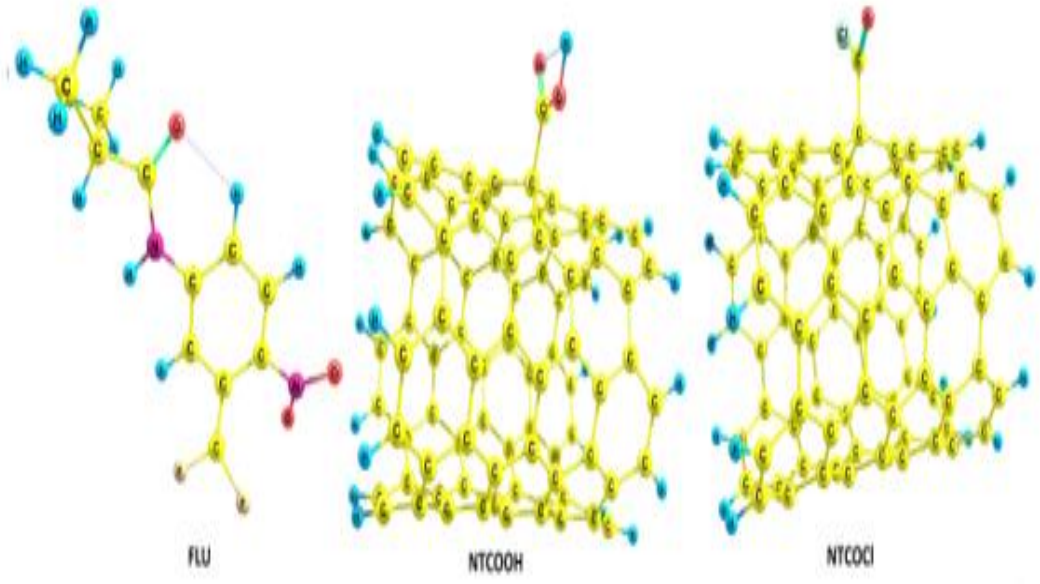


Figure 1. Optimized structures of FLU, NTCOOH and NTCOCl

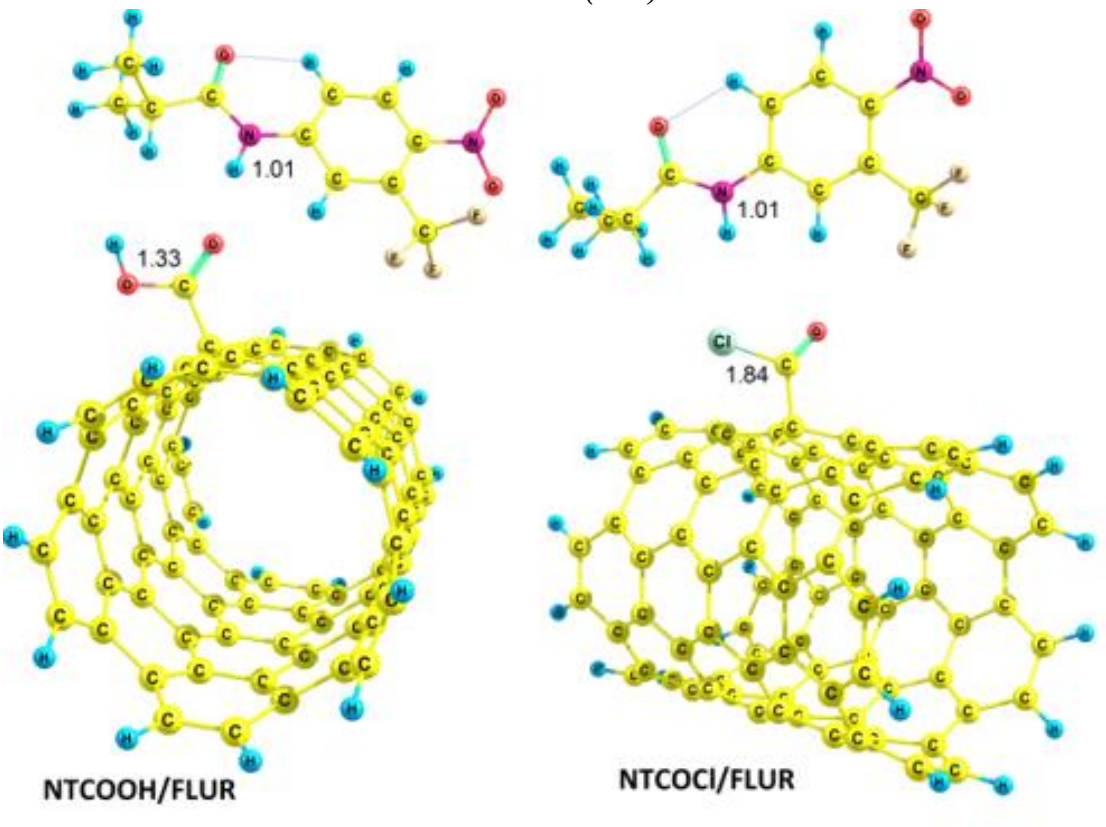


Figure 2. Optimized structures of NTCOOH/FLUR and NTCOCl/FLUR reactants.

All DFT computations are performed using B3LYP functional [23, 24] at 6-31G(d,p) basis set as implemented in the Gaussian 03 program package [25]. The solvent play a crucial role in chemical systems explicitly [26] or implicitly. Water solution was designed by using the SCRF keyword with Tomasi's polarized continuum (PCM) model [27].

In order to figure out the orbital interactions and charge delocalization during the course of the hydrogen bond (H-bond) formation between the drug molecule and the adsorbent surfaces [28], the natural bond orbital (NBO) method is done [29]. The Bather quantum theory of atoms in molecules (QTAIM) methodology were carried out by AIM 2000 [30] program to analyze the electron densities of the considered systems. The molecular orbitals along with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies are examined in order to determine the quantum chemical parameters such as energy gap (Eg), the chemical hardness (η), electronic chemical potential (μ) and global electrophilicity index (ω) according to the Koopmans theorem [31].

The fractional number of electrons transferred, ΔN, which is explained by Pearson is also measured [32]:

$$\Delta N = (\mu_B - \mu_A) / (\eta_B + \eta_A) \quad (1)$$

Where μ and η are the chemical potential and the chemical hardness of donor (B) and acceptor (A), respectively. The negative value of ΔN parameter shows that electron flow is spontaneous from A to B; otherwise, it is in the reverse direction.

In addition, the interaction of FLU molecule and the *f*-CNT on the basis of reactivity descriptors such as the overall stabilization energy ($\Delta E_{SE(AB)}$), the individual energy change of acceptor ($\Delta E_{A(B)}$), the individual energy change of donor ($\Delta E_{B(A)}$) have been explained [33, 34]:

$$\Delta E_{SE(AB)} = \Delta E_{A(B)} + \Delta E_{B(A)} = -(\mu_B - \mu_A)^2 / 2(\eta A + \eta B) \quad (2)$$

$$\Delta E_{B(A)} = \Delta N\,(-\mu_B + 1/2\,\mu_B \Delta N) \quad (3)$$

$$\Delta E_{A(B)} = \Delta N\,(-\mu_A + 1/2\,\mu_A \Delta N) \quad (4)$$

Moreover, GaussSum program [35] has been used to obtain the density of states (DOS). The calculations were done on Flutamide, COOH (in water) and COCl (in DMF) functionalized armchair (5,5) SWCNT comprising 114 atoms (10 Å) with the ends terminated by hydrogen atoms.

3. Results and discussion

3.1. noncovalent interaction

3.1.1. Molecular Geometry and Adsorption Energy

The obtained results in our last investigation by means of density functional theory calculations [36] confirmed the acceptable drug delivery performance of the (5, 5) single walled carbon nanotube with FLU molecule in the both gas phase and water solution. However, screening of the geometries, adsorption energies and topological features of the SWCNT as one of the potential carrier for Flutamide anticancer drug led to this point that some modifications are needed to enhance the activation of the SWCNT surface for efficient adsorption of the FLU molecule. Therefore, this study has been performed to focus on the effect of

functionalized carbon nanotube in the solution media.

It is worth noting that the obtained results in our previous study show that the most stable structure can be constructed when the drug molecule approaches to the surface of SWCNT from the N-H terminal perpendicularly to the z axis of the nanotube. Therefore, in current work, the interaction between FLU molecule and
functionalized CNTs through NH group which forms hydrogen bond has been selected to investigate further.

As it is obvious several key parameters of our investigation such as the binding energy (ΔE), the stretching frequencies (Δν), intermolecular equilibrium distances and the structural properties consisting of the bond lengths, are represented in Tables 1 and S1 (supporting Information) respectively.

Also it is suitable to note that the binding energy discussion is normally an appropriate and useful mean to better understand the interaction between different species in

Table 1. The adsorption energy (ΔE, k/mol), the stretching frequencies (Δν, in cm−1) and the calculated intermolecular distances (Å) of the *f*-CNT… FLU complexes in the water solution.

Model	ΔE	$R_{CNT...FLU}$	Δν
NTCOOH/FLUR	-23.96	O_{112} … H_{134}-N_{121} = 1.99	ν_{N-H}: 3621.32 → 3513.24
NTCOCl/FLUR	-7.73	C_{111}-O_{112} … H_{134} = 2.44 N_{119}-H_{132} … Cl_{143} = 2.87	ν_{N-H}: 3621.63 → 3595.08

considered structures. Furthermore, the binding energies of FLU with NTCOOH (in water) and NTCOCl (in DMF) are defined by the following expression:

$$\Delta E = E_{NTCOOH(NTCOCl)/FLUR} - (E_{NTCOOH(NTCOCl)} + E_{FLU}) \quad (5)$$

It can be easily figured out that the contribution of the binding energy for the selected systems demonstrates the physical and energetic intrinsic of FLU adsorption on the functionalized nanotubes (NTCOOH and NTCOCl) in water and DMF solvent (see Table 1). By comparison of the values of obtained binding energy for two configurations, it can be concluded that the configuration related to NTCOOH is more stable than of NTCOCl configuration.

As it can be found out from Figure 2, drug molecule has the capability of performing an interaction in a vast range of intermolecular conventional (N-H…O and N-H…Cl) and nonconventional (C-H…O) hydrogen bonds with the functionalized CNTs.

Considering NTCOOH/FLUR stable configuration, the interaction of H_{134} atom of the FLU drug with the O_{112} atom of COOH group of the CNT results in forming hydrogen bond at the situation of perpendicular FLU molecule existence to the surface of the nanotube which shows the value of intermolecular O…H distance being equal to 1.99 Å in the aqueous media. Furthermore, it can be claimed that in the N–H···O hydrogen bond in this system FLU drug acts as a proton donor and the oxygen atom of the carboxylic group of the NTCOOH behaves as a proton acceptor.

Based on our theoretical calculations, the weakest interaction between FLU molecule and the functionalized CNT has been appeared in NTCOCl/FLUR reactant with the O_{112}…H_{134} distance being equal to 2.44 Å in the DMF solvent. In this reactant, the hydrogen atom of the drug molecule as Lewis acids interact with oxygen atom of the functionalized group of the nanotube as a Lewis base and lead to C–H···O containing HB complexes.

Moreover, the interaction of the H atom of the adsorbed FLU as proton-accepting center with the Cl atom of the -COCl group of CNT as proton-donating molecule resulted in the N–H···Cl interaction with a distance of 2.87 Å is obtained in the NTCOCl/FLUR reactant.

Several studies have been confirmed that the HB distances can play a critical role in determination of the hydrogen bond strength. Close inspection of Table 1 reveals that less intermolecular hydrogen bond length in NTCOOH/FLUR reactant results in a stronger interaction within the NTCOCl/FLUR reactant. Moreover, the conventional hydrogen bond in NTCOOH/FLUR reactant is shorter than the nonconventional HB in NTCOCl/FLUR reactant. Consequently, it can be confirmed that this kind of intermolecular hydrogen bond has more strength than the other HB which exists in the NTCOCl/FLUR structure.

Based on the obtained results, no notable changes on the structural parameters of the adsorbed drug has been detected in the intermolecular interaction between FLU molecule and functionalized nanotubes (see Table S1, supporting information). For instance, within the NTCOOH/FLUR stable structure, the N–H bond length of FLU drug has been changed from 1.01 to 1.02 Å, thus, it can be revealed that *f*-CNT can act as a structurally stable drug carrier.

In addition, in order to better clarify the hydrogen bond strength, for both two reactants depicted in Table 1, vibrational frequencies are calculated. It is understood that mainly based on the formation of intermolecular HB between *f*-CNT and FLU molecule, the N–H stretching mode shift from 3621.32 (3621.63 cm^{-1}) in FLU drug to the low bands 3513.24 (3595.08 cm^{-1}) in NTCOOH/FLUR (NTCOCl/FLUR) reactant. Especially, it can be mentioned that the largest shift value of N–H vibrational frequency in NTCOOH/FLUR reactant indicates the high interaction ability between FLU molecule and the exterior surface of functionalized nanotube.

3.1.2. Electronic properties

Several definitions can be presented for better expressing the performance of a suitable drug delivery system, but the verified expression is the ability of delivering the drugs into the cells without any significant change in its intrinsic properties during the delivering process. Subsequently, theoretical analysis has been performed in this study to obtain the influence of the FLU molecule adsorption on the behavior of nanotubes.

Thus, first, the frontier orbitals of CNTs and the FLU molecule are calculated to predict the effects of FLU molecule and nanotubes are analyzed. Figure 3 represents the iso-surfaces of the frontier orbitals of FLU molecule, *f*-CNT and the nanotubes which are interacted with the FLU molecule. It can be elicited that the HOMO and LUMO of the isolated FLU are both distributed mainly over the whole molecule. Considering the NTCOOH/FLUR model which contains the FLU attached functionalized CNT, the HOMO are mainly located on the NTCOOH while the LUMO are mainly distributed on the FLU molecule, indicating *f*-CNT is an electron donor species and the FLU molecule is an electron accepting one in this reactant. This proposes a charge transfer from the HOMO to the LUMO (see Figure 3a). Furthermore, it is interesting to see that both frontier orbitals are distributed over the surface of nanotube at the NTCOCl/FLUR reactant (see Figure 3b).the pristine functionalized nanotubes (see Figure 4). The DOS of a system demonstrates the number of states per interval of energy at each level of energy that are available to be occupied by electrons. According to Figure 4 and comparing the Eg (difference between LUMO and HOMO) values, it can be found that after the adsorption of FLU molecule on NTCOOH and NTCOCl, the HOMO–LUMO energy gap of nanotube has been not changed moderately. Considering the analysis of the DOS plots, it can be revealed that both their valence and conduction levels altered very slightly by about 0.01eV which is negligible, and thus, the DOS plots of FLU-adsorbed functionalized nanotubes are close to that of the pristine nanotubes. As well, it can be suggested that *f*-CNT can carry FLU drug. Furthermore, the density of state (DOS) is plotted for two studied complexes and compared with that of In order to have a better understanding of the intrinsic of interaction between FLU and *f*-CNT, we have investigated the chemical reactivity and stability of the considered complexes. Three DFT based chemical descriptors, μ, η and ω for FLU (H_2O and DMF), NTCOOH, NTCOCl, NTCOOH/FLUR and NTCOCl/FLUR are tabulated in Table 2. In these quantities, μ is analyzed as the average of HOMO and LUMO energies. η shows the resistance of one molecule against the change in its electronic structure and it is calculated as the half of the differences between the HOMO and LUMO energies. Decrease in η causes a depletion in the reactivity and an enhancement in stability. The electrophilicity index which is mentioned above can be calculated according to the equation:

$$\omega = \mu^2/2\eta \quad (6)$$

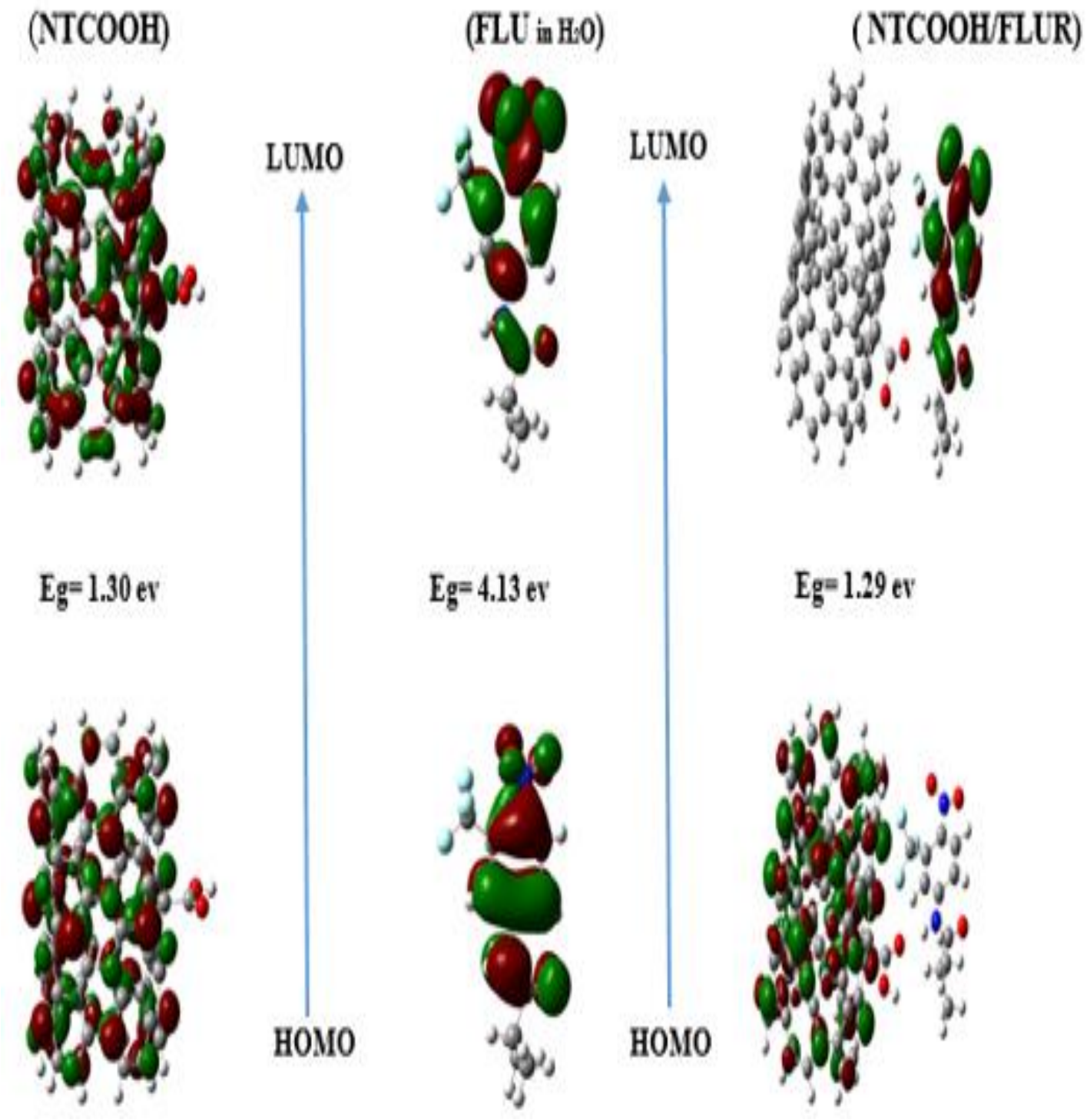
The ω is a useful tool in predicting the reactivity of the molecule. It has been found that there is a correlation between the electrophilic index of various chemical compounds and the rate of reaction in the biochemical system. Analyzing the obtained results, η and Eg related to the FLU drug are higher than those of NTCOOH/FLUR and NTCOCl/FLUR, an indication of the FLU stability reduction in the presence of COOH (COCl) functionalized SWCNT and an enhancement in its reactivity. The electronic chemical potential displays the direction of electron flow. As can be seen in Table 2, the functionalized SWCNT has the higher chemical potential (μ) compared to FLU. Hence, the transfer of electrons from the nanotube to drug because electron flows from high chemical potential to low chemical potential. Also, the value of ω for FLU has been in increased in the presence of COOH (COCl) functionalized SWCNT, showing that FLU acts as electron acceptor. Consequently, for noncovalent interactions, a deep look to COOH and COCl functionalized CNTs suggests that applying the COOH containing complex can be more acceptable based on a stronger interaction between FLU and CNTCOOH.

3.1.3. AIM analysis

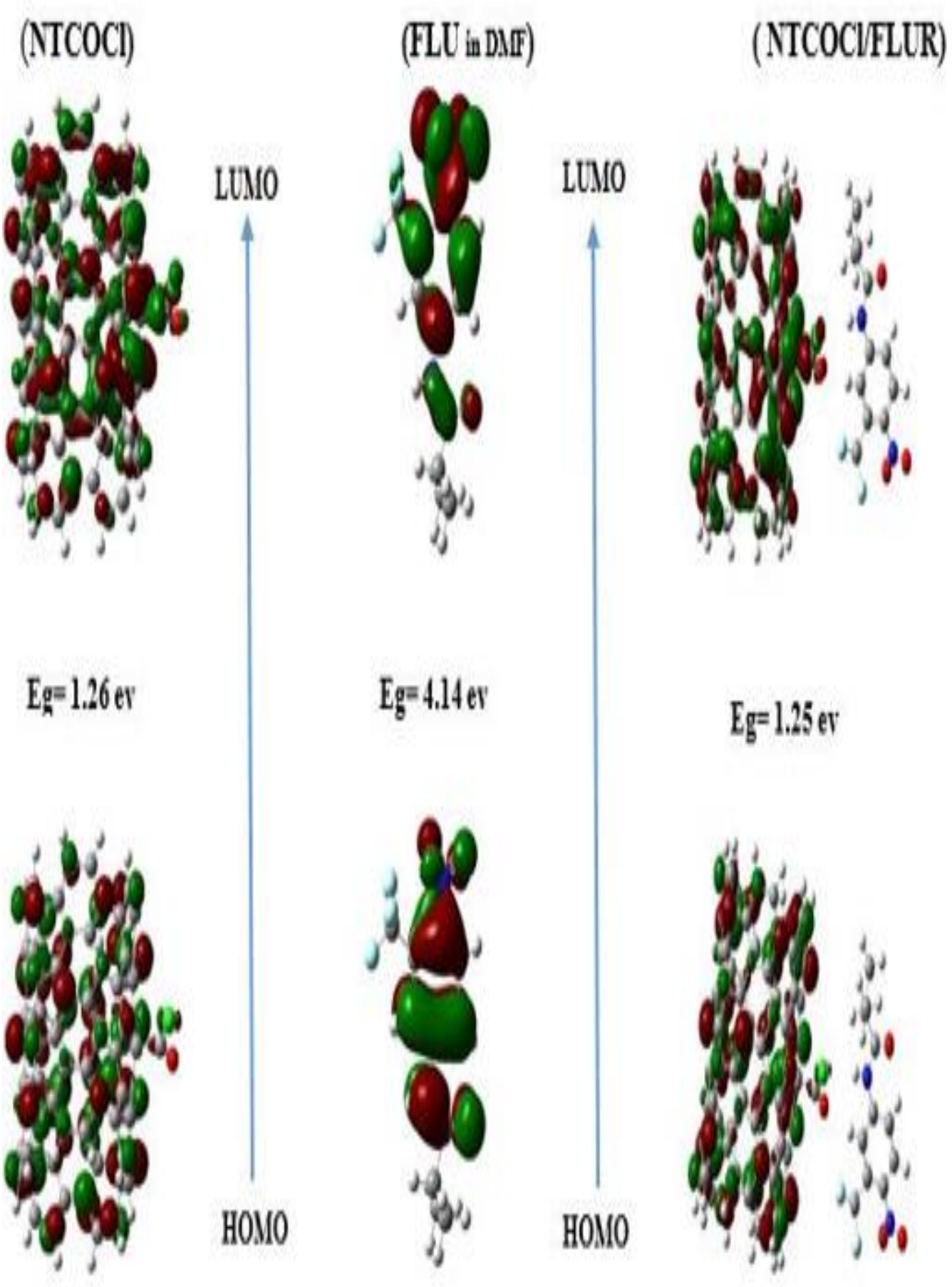
In order to have further understanding into the intrinsic of the intermolecular hydrogen-bonds in the considered complexes, the topological characteristics of electron charge density are analyzed by theory of AIM [37, 38]. The molecular graphs are represented in Figure 5, in which the positions of all bond critical points (BCPs) between the drug and functionalized nanotubes are indicated. The formation of chemical bond between pairs of interacting atoms can be interpreted by the existence of BCPs. Moreover, it can be seen in Figure 5 that there are CO···HC, CO···HN and CCl···HN intermolecular interaction in the selected complexes. In the both reactants, hydrogen bonds can be detected between the two interacting atoms. The values of electron density (ρ), Laplacian ($\nabla^2\rho$), kinetic energy

density (G), potential energy density (V) and total energy density (H) are given in Table 3. The QTAIM theory and with respect to these parameters provide information about the bonds at bond critical points. The electronic energy density (H) is the sum of G and V parameters and helps more accurate descriptions of the nature of bonds. According to

Rozas et al. [39], positive $\nabla^2\rho$ and H values denote the weak interactions (electrostatic), negative $\nabla^2\rho$ and H values refer to strong interaction (covalent bond), and medium strength ($\nabla^2\rho$ >0 and H<0) is defined as partially covalent. Moreover, the intermolecular interactions have lower ρ and positive $\nabla^2\rho_{BCP}$ (see Table 3) with respect to the calculated electron density and laplacian properties in the considered complexes. These properties are typical for the closed-shell interactions. On the other hand, negative



(a)



(b)

Figure 3. HOMO and LUMO in functionalized CNT with (a) –COOH (b) COCl groups.

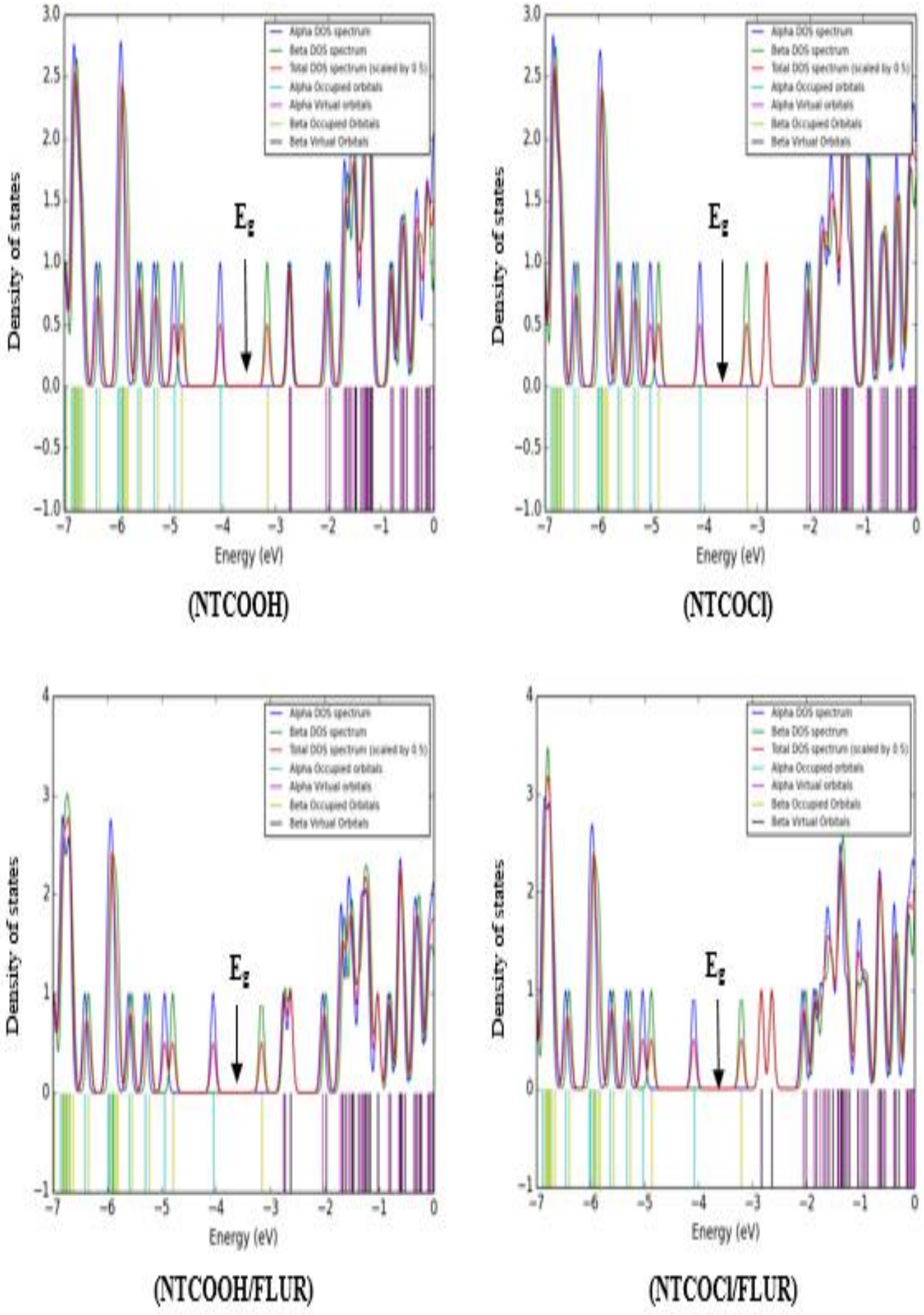


Figure 4. DOS plots for the functionalized CNTs and studied complexes.

Table 2. The values of the highest occupied molecular orbital energies (E_{HOMO}), the lowest unoccupied molecular orbital energies (E_{LUMO}), energy gap (Eg), the chemical potential (μ), chemical hardness (η), and electrophilicity index (ω) (all in eV) for FLU, the pristine NTCOOH, NTCOCl and the studied complexes in the water solution.

Model	E_{HOMO}	E_{LUMO}	Eg	μ	η	ω
FLU (H_2O)	-6.81	-2.68	4.13	-4.74	2.06	5.45
FLU (DMF)	-6.81	-2.67	4.14	-4.74	2.07	5.43
NTCOOH	-4.04	-2.74	1.30	-3.39	0.65	8.86
NTCOCl	-4.07	-2.82	1.26	-3.45	0.63	9.45
NTCOOH/FLUR	-4.05	-2.76	1.29	-3.40	0.65	8.96
NTCOCl/FLUR	-4.08	-2.83	1.25	-3.46	0.63	9.55

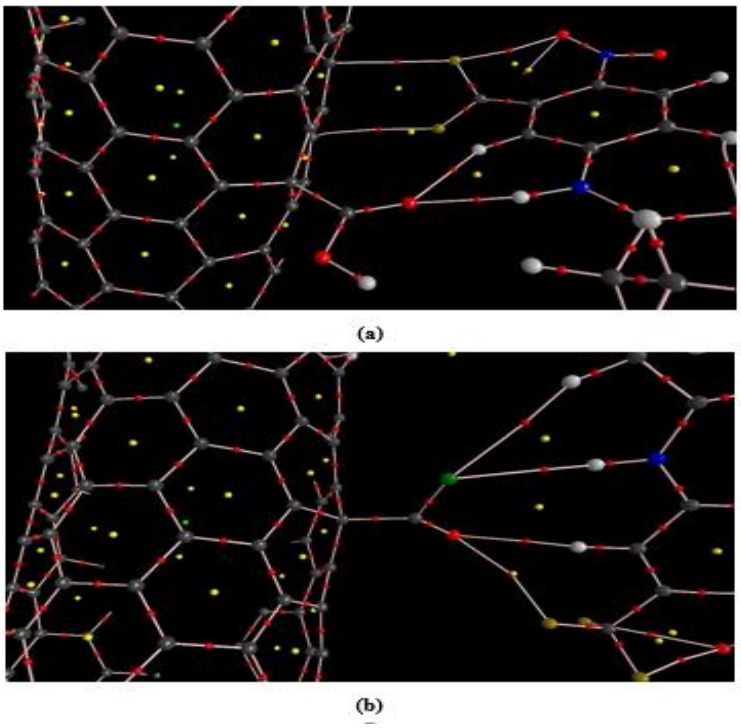


Figure 5. The molecular graph of a) NTCOOH/FLUR and b) NTCOCl/FLUR complexes

Table 3. The density of the total energy of electrons (H) and its two components, the kinetic (G) and potential (V) electron energy, the topological parameters of intermolecular interactions densities (all in a.u.) between FLU drug and *f*-CNT for the studied complexes in the water solution.

Model	*f*-CNT…FLU	ρ	$\nabla^2\rho$	G	V	H	E_{HB}
NTCOOH/FLUR	O_{112} - H_{134}	0.02103	0.06804	0.00176	-0.00778	-0.00602	-10.22
	O_{112} - H_{136}	0.00730	0.02584	-0.00029	-0.00104	-0.00133	-1.36
NTCOCl/FLUR	O_{112} - H_{134}	0.00952	0.02996	-0.00002	-0.00183	-0.00185	-2.40
	Cl_{143}-H_{132}	0.00588	0.02067	-0.00031	-0.00067	-0.00098	-0.88
	Cl_{143}-H_{133}	0.00463	0.01474	-0.00024	-0.00043	-0.00068	-0.56

The electron densities at BCP of X⋯H contact are well correlated with the hydrogen bond energies strength (E_{HB}) which are calculated by Espinosa method [40, 41]. This method reveals the relationship between HB energy (E_{HB}) and the potential energy density at the bond critical point (V_{BCP}) as E_{HB}=1/2 V_{BCP}. All E_{HB} energies which are calculated from the potential energy densities of the intermolecular HB contacts are also included in Table 3. The strong hydrogen bond is found to be related with maximum electron density at bond critical point and higher stability, which is observed

for the conventional to $O_{112}\cdots H_{134}–N_{121}$ at the NTCOOH/FLUR reactant.

The reduced density gradient (RDG) analysis can be determined more details about the nature of intermolecular interaction between the drug and the carrier molecules. The RDG plot allows us to identify the interacting regions as well as assessment of the type of interaction. From the color-filled RDG iso-surface, different interactions can be identified based their color. In this plot the blue region implies the strong attractive interactions such as HB interaction, green region relates to weaker attractive interaction and the strong steric effects are represented in red [42]. The RDG plot for complex NTCOOH/FLUR was calculated by Multiwfn program and shown in Figure S1(supporting information). The intermolecular HB between the drug and the carrier clearly identified in this Figure (blue color). Moreover, the interaction in blue region is related to interactive interaction, approving hydrogen bond between H atom with oxygen atom of COOH group of nanotube. Another distinctive feature of RDG plot is that a wide red region in positive values of sign $(\lambda_2)\rho$, which can be related to intramolecular steric effects in NTCOOH.

3.1.4. NBO analysis

The NBO analysis is a useful tool for applying in better understanding intra and intermolecular interactions in addition to prepare a good foundation for finding out charge transfer (CT) in the molecular systems [43, 44]. The NBO second-order perturbation stabilization energy ($E^{(2)}$) for all investigated complexes provided from NBO calculations and included in Table 4.

Including data from the NBO, it can be easily found that the oxygen lone pair (LP) of the NTCOOH overlaps with the LP* hydrogen atom of NH terminal of the FLU drug molecule at the NTCOOH/FLUR reactant. This overlap has been resulted in a transfer of electronic charge from the LP O112 to LP* H134 with the second order perturbation energy ($E^{(2)}$) value of 4.58 kcal/mol. As interparticular viewpoint of interaction, the oxygen atom of -COOH functional group of the nanotube acts as a proton donor and NH terminal of the drug molecule acts as a proton acceptor in the NTCOOH/FLUR reactant.

Table 4. The electron donors, electron acceptors, and the corresponding second-order perturbation energy ($E^{(2)}$, kcal/mol) in the water solution.

Model	Donor	Acceptor	$E^{(2)}$
NTCOOH/FLUR	LP (1) O_{112}	LP* (1) H_{134}	4.58
NTCOCl/FLUR	LP (1) Cl_{143}	LP* (1) H_{132}	1.06

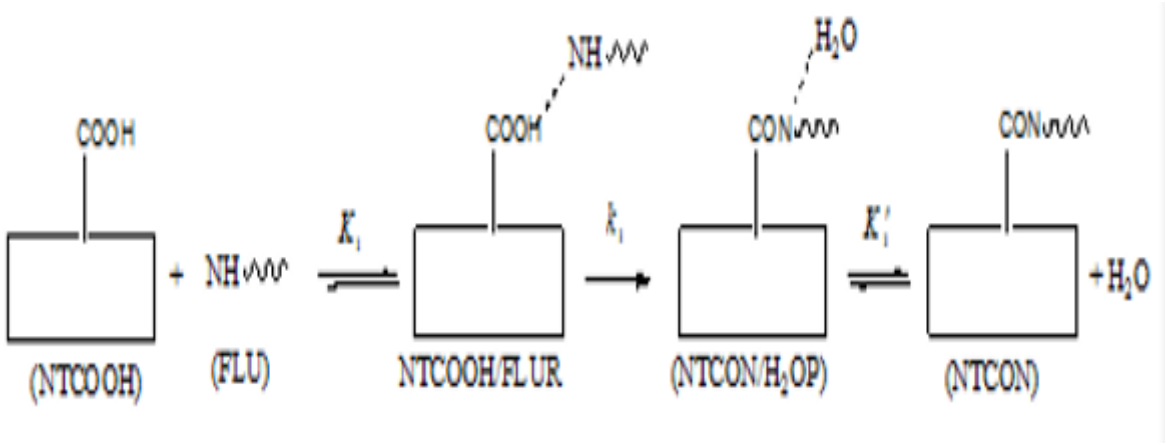
It can be obvious that from the obtained data given in Table 4, the electron is transferred from the NTCOCl to FLU, in which electrons are provided by interacting of the LP (1) Cl_{143} of the NTCOCl with LP*(1) H_{132} of FLU molecule with $E^{(2)}$ energy value of 1.06 kcal/mol. Furthermore, the maximum $E^{(2)}$ value can make the NTCOOH/FLUR reactant more stable than the NTCOCl/FLUR reactant. The NBO analysis data approve that the intermolecular interaction of this reactant is stronger than the other reactant mainly due to more total charge transfer energy. Also, it is found that the greatest stabilization energy for NTCOOH/FLUR reactant is accordance with the shortest interaction distance (see Tables 1 and 4). Results indicate that in the both reactants, the charge transfer occurred from nanotube to drug. In order to confirm this result, the fractional number of electron transferred between the FLU molecule and *f*-CNT is evaluated. The FLU molecule acts as an electron acceptor/donor when ΔN has positive/negative value. The positive value of ΔN confirms that the charge is transferred from *f*-CNT to FLU drug (see Table S2).

Parameters such as positive energy component ($\Delta E_{B(A)}$), negative energy component ($\Delta E_{A(B)}$) and the stabilization energy ($\Delta E_{SE(AB)}$) are computed to compare the interaction between drug and *f*-SWCNT and ordered in Table S2. Analyzing the data from listed parameters in this Table shows that the positive value of $\Delta E_{B(A)}$ means that the process is favorable from the energetic viewpoint, while a negative value of $\Delta E_{A(B)}$ specifies that the f-SWCNT/ FLU complex is more stable than the f-SWCNT and free drug molecule. Moreover, $\Delta E_{SE(AB)}$ is negative, meaning that the studied complexes are stable (see Table S2, Supplementary data).

3.2. The covalent functionalization mechanisms

For the covalent functionalization, NH group attacks the carbon atom of COOH or COCl to transfer its protons to

the OH (Cl) group. We studied these two possible mechanisms for NTCOOH(Cl)/FLUR. Scheme 1 shows the mechanism for the formation of covalent bond between FLU and NTCOOH (COOH mechanism) where k_1 is rate constant and K_1 and K_1' are equilibrium constants. In this mechanism, NTCOOH/FLUR is converted into the product NTCON by losing H_2O.



Scheme 1. COOH Mechanism of covalent functionalization.

According to the Scheme 1, in COOH mechanism, OH from NTCOOH is substituted by N from FLU to give product NTCON. The optimized structure of product NTCON/H_2OP has been shown in Figure 6.

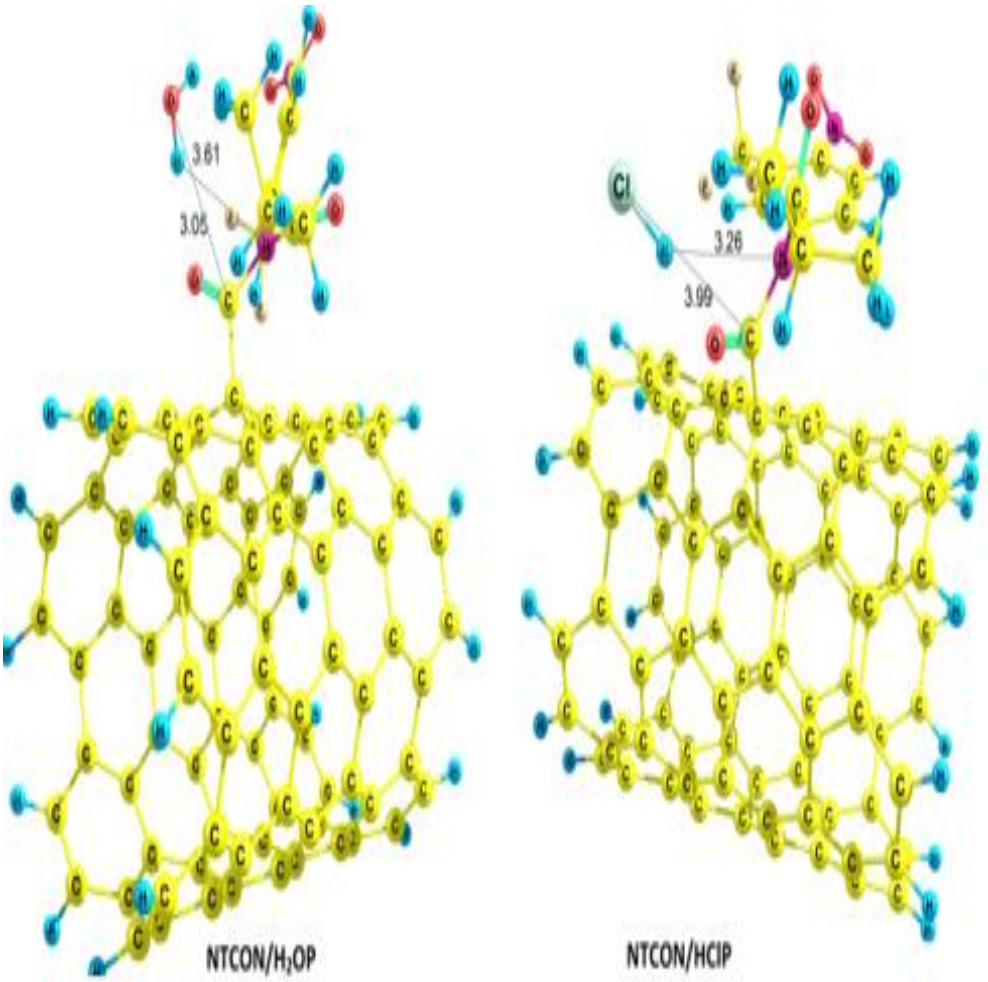


Figure 6. Optimized structures of products NTCON/H_2OP and NTCON/HClP

Using reactant NTCOOH/FLUR and product NTCON/H_2OP, the transition state of k_1 step was optimized which we call TS_{k1} (Figure 7). Considering Figures 2, 6 and 7, the N-H and C-O bond lengths increase (decrease) from 1.01 Å and 1.33 Å (3.61 Å and 3.05 Å) for NTCOOH/FLUR (NTCON/H_2OP) to 1.62 Å and 1.84Å for TS_{k1}, respectively.

Relative energies for optimized structures in all pathways have been calculated in Table 5 by considering electronic plus zero point energy (E), enthalpy (H) and Gibbs free energy (G) of reactants (NTCOOH+FLU) equal to zero [45].

The activation energy (E_a), activation enthalpy ($\Delta H^{\ddagger}$) and activation Gibbs free energy ($\Delta G^{\ddagger}$) for k_1 step are 206.62 k mol^{-1}, 204.24 k mol^{-1} and 217.47 k mol^{-1}, respectively. The total rate constant for overall reaction (COOH pathway) is equal to $k_1 \times K_1$, so the total activation energy the total activation enthalpy and total activation Gibbs free energy can be calculated by equations:

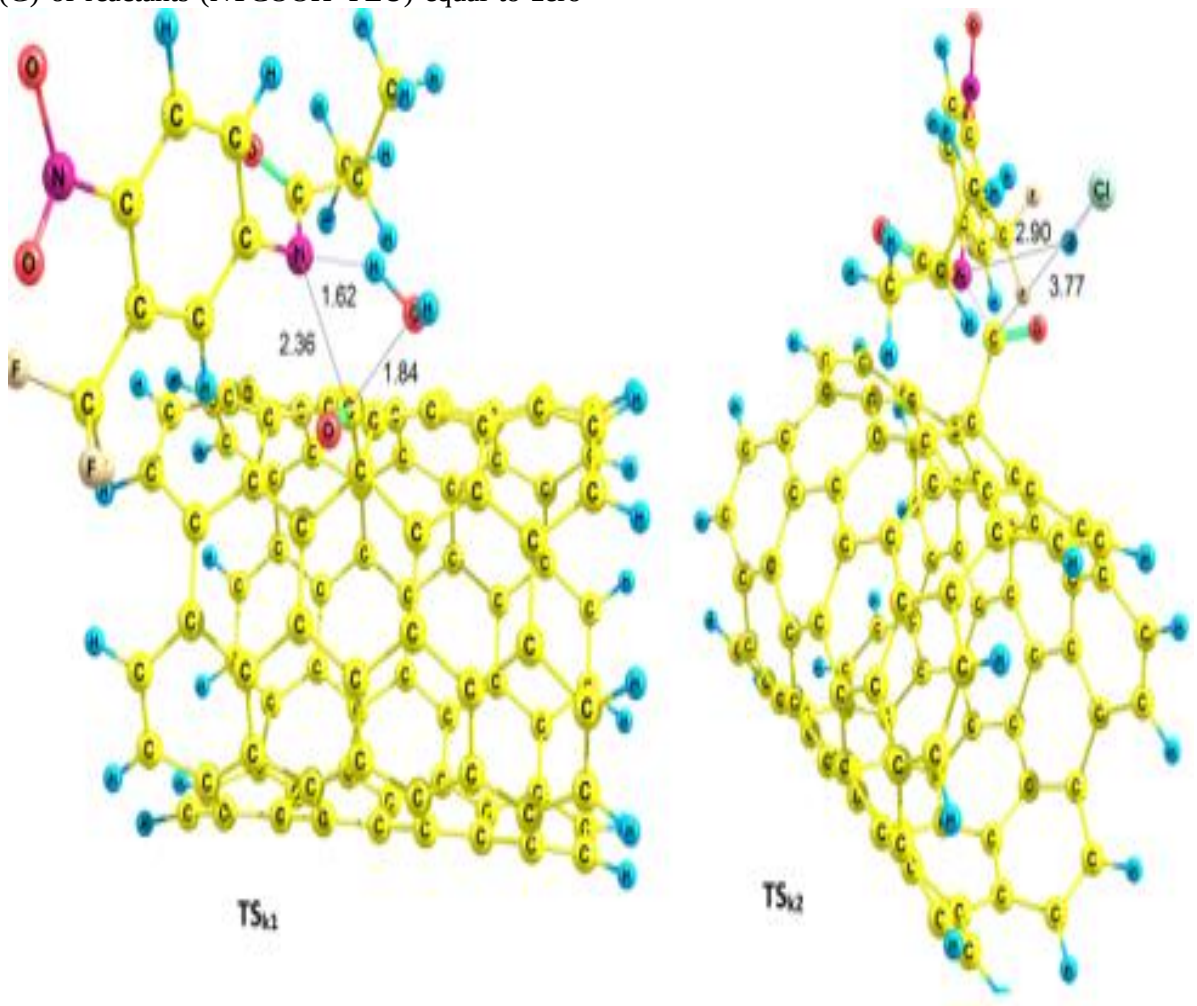


Figure 7. Optimized structures of TS_{k1}, TS_{k2}.

$$(E_a = E_a(k_1 \text{ step}) + \Delta E(K_1 \text{ step})) \quad (7)$$

$$(\Delta H^{\ddagger} = \Delta H^{\ddagger}(k_1 \text{ step}) + \Delta H(K_1 \text{ step})) \quad (8)$$

$$(\Delta G^{\ddagger} = \Delta G^{\ddagger}(k_1 \text{ step}) + \Delta G(K_1 \text{ step})) \quad (9)$$

The mentioned parameters for COOH mechanism are 184.31 k mol^{-1}, 187.93k mol^{-1} and 236.58 k mol^{-1}, respectively (Table 5).The other reaction for the covalent functionalization of FLU onto COCl functionalized carbon nanotube is shown in Scheme 2 (COCl mechanism).In this reactions, NTCOOH was firstly converted into alkyl chloride using $SOCl_2$ (NTCOCl) in DMF. FLU then reacts with NTCOCl to form covalent bond. COCl mechanism begins with the attack of NH of FLU to Cl in the NTCOCl to form products NTCON/HClP (Figure 6).

Table 5. Relative energies (k/mol) for different species in COOH and COCl mechanisms. E, H and G are electronic plus zero-point energy, enthalpy and Gibbs free energy, respectively.

species	E	H	G
In water	COOH mechanism		
NTCOOH+FLU	0	0	0
NTCOOH/FLUR	-23.96	-16.31	19.13
TS_{k1}	184.31	187.93	236.58
NTCON/H_2OP	106.06	113.67	157.03
In DMF	COCl mechanism		
NTCOCl+FLU	0	0	0
NTCOCl/FLUR	-6.1	0.33	28.59
TS_{k2}	56.22	59.53	108.74
NTCON/HClP	23.14	28.4	71.24

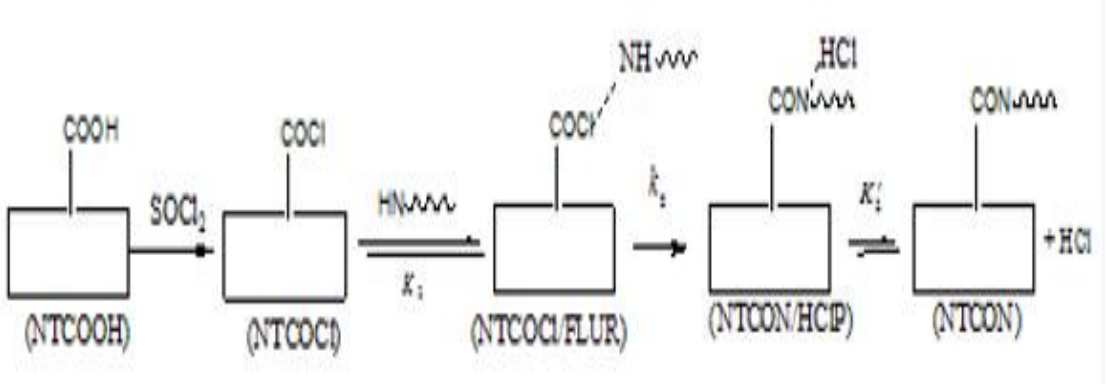
Using NTCOCl/FLUR and NTCON/HClP, a transition state is optimized which we call TS_{k2} (Figure 7). Considering Figures 2, 6 and 7, the C-Cl and N-H bond lengths increase (decrease) from 1.84 Å and 1.01 Å (3.99 Å and 3.26 Å) for NTCOCl/FLUR (NTCON/HClP) to 3.77 Å and 2.90 Å for TS_{k2}, respectively. Ea, $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ for k_2 step are 62.32 k mol^{-1}, 59.20 k mol^{-1} and 80.17 k mol^{-1}, respectively. The total activation energy, the total activation enthalpy and the total activation Gibbs free energy for COCl mechanism are 56.22 k mol^{-1}, 59.53 k mol^{-1} and 108.74 k mol^{-1}, respectively (Table 5).

The total activation energy, the total activation enthalpy and the total activation Gibbs free energy for COCl mechanism are lower than COOH mechanism by 128.09 k mol^{-1}, 128.38 k mol^{-1} and 127.84 k mol^{-1}, respectively.

Both mechanisms (COOH and COCl) are nucleophilic substitution reactions. Generally, these reactions proceed through a tetrahedral intermediate. We designed a tetrahedral intermediate as input and ultimately a structure was optimized which is similar to reactant NTCOCl/FLUR. This means that tetrahedral intermediate could not be existed, being probably due to electronic and steric effects carbon nanotubes.

4. Conclusion

In summary, the noncovalent interaction of FLU drug molecule on functionalized nanotube surface



Scheme 2. COCl Mechanism of covalent functionalization.

with COOH and COCl functional groups is investigated using density functional theory. Several useful and applicable computational tools such as the geometrical and electronic properties, NBO and AIM were applied to study the details of the interaction. With respect to our calculations, the negative binding energy values illustrate and confirm the favorable interaction between FLU drug and *f*-CNT at the considered complexes. Also, the amount of the binding energy related to NTCOOCl is lower than that related to NTCOOH, indicating NTCOOH/FLUR reactant is stabilized. The obtained information from AIM calculations confirmed the presence of the partial covalence interaction between FLU drug and *f*-CNT. In addition, it can be approved that the functionalized nanotube has the role of an electron donor and the FLU acts as an electron acceptor at the investigated complexes by the NBO analysis. The global hardness and HOMO-LUMO energy gap of NTCOOH/FLUR reactant are higher than those of NTCOCl/FLUR reactant, indicating the reactivity of the FLU increases in the presence of NTCOCl and its stability decreases. In addition, covalent functionalization of drug Flutamide onto NTCOOH (COOH mechanism) and NTCOCl (COCl mechanism) have been investigated in detail. The obtained information shows that the activation parameters related to COOH mechanism are higher than those related to next mechanism. Consequently, for covalent functionalization, comparison between COOH and COCl functionalized CNT shows that using the second one is more suitable due to a lower activation energy.

Acknowledgement

We thank the Research Center for Animal Development Applied Biology for allocation of computer time.

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How to Cite This Article

maedeh kamel; ali morsali; Heidar Raissi; Kamal Mohammadifard. "Theoretical insights into the intermolecular and mechanisms of covalent interaction of Flutamide drug with COOH and COCl functionalized carbon nanotubes: A DFT approach". Chemical Review and Letters, 3, 1, 2020, 23-37. doi: 10.22034/crl.2020.221149.1039