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Theoretical investigation of adsorption effects Ciclopirox drug over CNT(6,6-6) nanotube as factor of drug delivery: a DFT study

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Abstract

The main purpose of this study is a better comprehension of the non-bonded interaction between an anticancer drug Ciclopirox and carbon nanotube [CNT(6,6-6)]. The electronic structure and adsorption properties of the molecule Ciclopirox over the surface of CNT were theoretically studied in the solvent phase at the B3LYP/6-31G* level of theory for the first time. The electronic spectra of the Ciclopirox drug, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox in solvent water were calculated by time dependent density functional theory (TD-DFT) for the investigation of adsorption effect. The non-bonded interaction effects of the Ciclopirox drug with CNT(6,6-6) on the chemical shift tensors and natural charge have been also detected. According to the natural bond orbital (NBO) results, the molecule Ciclopirox and CNT(6,6-6) play as both electron donor and acceptor at the complex CNT(6,6-6)/Ciclopirox. On the other hand, the charge transfer is occurred between the bonding, antibonding or nonbonding orbitals in two molecules drug and CNT. As a consequence, CNT(6,6-6) can be considered as a drug delivery system for the transportation of Ciclopirox as anticancer drug within the biological systems.

Keywords Ciclopirox · CNT(6,6-6) · DFT · Charge transfer

1 Introduction

Carbon nanotubes (CNTs) are one of the most tumor-targeted drug delivery systems which are widely used in biology and medicine (Liu et al. 2009; Peretz and Regev

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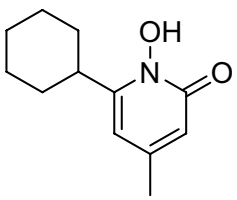
2012; Vashist et al. 2011; Ji et al. 2010; Digge et al. 2012; Chandrasekhar 2018). CNTs can deliver anticancer drugs into target cells through penetrating to cell membranes. Drug molecules can bind to the surface of CNTs as covalently or non-covalently and then are delivered into the cells (Sharma et al. 2016; Mishra 2013). Hence, CNTs are used to improve the pharmaceutical properties and to decrease the taxological effect of delivered drugs (Wilczewska et al. 2012; Lacerda et al. 2006; Parhi et al. 2012). Among the different types of CNTs, single-wall carbon nanotubes (SWCNTs) are suitable as drug carrier to cancer cells (Tripisciano et al. 2009; Panchapakesan et al. 2005; Meng et al. 2012). The diameter of SWCNTs is 2–5 nm, which makes them suitable tools for insertion and slow release of drugs. Moreover, because of their low cytotoxicity, they are potentially used in drug delivery systems (Zhang et al. 2011).

The molecule 6-cyclohexyl-1-hydroxy-4-methylpyridin-2(1H)-on (Fig. 1), which known as Ciclopirox, was synthesized by Dittmar and Lohaus (1975) is an antifungal agent for topical treatment of skin mycoses. It is the most effective against *Tinea versicolor*. The effective of Ciclopirox against a large number of fungus species makes it a broad-spectrum antifungal drug; Ciclopirox also has a wide range of uses as antibacterial and as anti-inflammatory, and has no effect on sterol synthesis, unlike other antifungals (Leem et al. 2003; Niewerth et al. 2003). All the mention above makes the Ciclopirox an interested molecule to be study theoretically. Ciclopirox has a low solubility, and it is used as Ciclopirox ethanolamine salt to increase its polarity.

Density functional theory (DFT) studies can provide more useful information on the interaction between nanotubes and delivered drug molecules (Xu et al. 2018; El Khalifi et al. 2015; Wang and Xu 2016). Recently, we have been studied adsorption anticancer drug Syndros (Sheikhi et al. 2018a), Resveratrol (Sheikhi et al. 2018b) and Alectinib (Sheikhi et al. 2019) over CNTs.

In the present work, the adsorption of Ciclopirox on the sidewall SWCNT has been performed based on the DFT method. We have investigated frontier molecular orbitals, quantum-chemical molecular descriptors, MEP analysis, chemical shift tensors, charge transfer analysis according to NBO analysis and electronic structure and excited states.

Fig. 1 Chemical structure of Ciclopirox



2 Computational methods

In this work, the non-bonded interaction between CNT(6,6-6) with an anticancer drug Ciclopirox in the solvent water was studied. The Polarized Continuum Model (PCM) (Shahab et al. 2017a) was used for the calculations of solvent effect. The quantum chemical calculations have been carried out using the density functional theory (DFT) calculations at the B3LYP/6-31G* level of theory by the Gaussian 09 W program (Frisch et al. 2009) for optimization of the molecule Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox. The adsorption energy (E_{ad}) (Sheikhi et al. 2018a) was calculated using the following equation:

$$E_{ad} = E_{CNT(6,6-6)/Ciclopirox} - \left[E_{Ciclopirox} + E_{CNT(6,6-6)}\right], \quad (1)$$

where $E_{CNT(6,6-6)/Ciclopirox}$, $E_{CNT(6,6-6)}$ and $E_{Ciclopirox}$ are energies of the CNT(6,6-6) with the adsorbed Ciclopirox, CNT(6,6-6) and the compound Ciclopirox, respectively.

The molecular orbital (MO) calculations of the investigated compounds such as E_{HOMO}, E_{LUMO}, energy gap between LUMO and HOMO ($Eg = E_{LUMO} - E_{HOMO}$) were also performed. The optimized molecular structures, HOMO, LUMO and MEP surfaces were visualized using GaussView 05 program (Frisch et al. 2000).

Also, the adsorption effects of the molecule Ciclopirox on CNT(6,6-6), the natural charge and the chemical shielding tensors (Sheikhi et al. 2018a, b) such as chemical shift isotropic (CS^I) and chemical shift anisotropic (CS^A) were calculated at the B3LYP/6-31G* level of theory. The CS^I and CS^A parameters were calculated using following equations, respectively:

$$CS^A(ppm) = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3, \quad (2)$$

$$CS^I(ppm) = \sigma_{33} - (\sigma_{11} + \sigma_{22})/2. \quad (3)$$

The three parameters such as σ_{11}, σ_{22}, σ_{33} show chemical shielding interaction in three dimensions. TD-DFT method (Sheikhi et al. 2018b) was used for the calculation of electronic transitions of the molecule Ciclopirox and the complex CNT(6,6-6)/Ciclopirox. The electronic structure of the mentioned compounds was also studied by using NBO analysis (Sheikhi et al. 2018c) at the B3LYP/6-31G* level in order to understand hyperconjugative interactions and charge delocalization.

3 Results and discussion

3.1 Optimized structures

At first, we have investigated eight states for interaction between the Ciclopirox drug with the CNT(6,6-6) in order to specify the most stable configuration. In the investigated configurations, Ciclopirox is placed in various positions around of the CNT(6,6-6). The six configurations (**A**–**F**) were calculated by PM6 method (Fig. 2). The calculated values of energy (HF) for the six structures **A**–**F** using PM6 method are reported in Table 1. The lowest energy value was observed for configuration **E**; therefore, it is the most stable complex CNT(6,6-6)/Ciclopirox.

Table 1 The energy parameters for the various configurations CNT(6,6-6)/Ciclopirox complex optimized by PM6 method

Systems	HF (Hartree)
A	0.53395400285
B	0.53253549881
C	0.53363132615
D	0.53277846824
E	0.52994942989
F	0.53054864461

In the next step, we have considered the interaction between the Ciclopirox drug and the CNT(6,6-6) at the

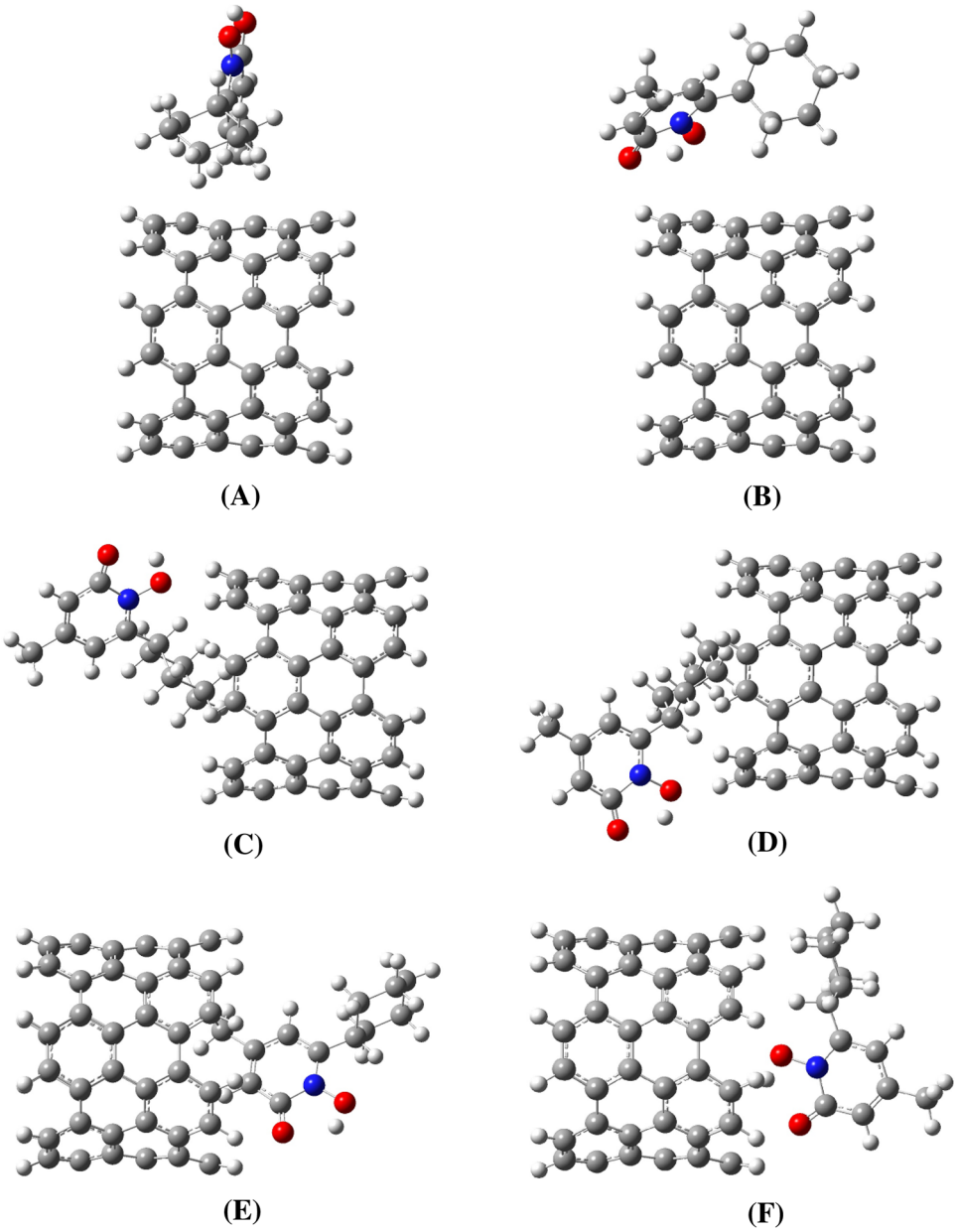


Fig. 2 The various configurations of CNT(6,6-6)/Ciclopirox complex optimized by PM6 method

configuration **E** and have optimized using B3LYP/6-31G* level of theory in a solvent water. The optimized structures of the compounds Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox are shown in Fig. 3.

The calculated thermochemical parameters with B3LYP/6-31G* level of theory for the molecules Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox (state **E**) are shown in Table 2.

According to the summarized results in Table 2, with the adsorption of the molecule Ciclopirox on CNT(6,6-6), the Thermal, Gibbs and Enthalpy energies values decrease. Energy values reflect the reduced reactivity and increase the stability of Ciclopirox drug in non-bonded reaction with CNT(6,6-6).

Geometrical parameters play an important role to interpret the attachment of drug to CNT in drug delivery systems. The computed bond lengths of optimized Ciclopirox, CNT(6,6-6), and CNT(6,6-6)/Ciclopirox complex at the binding sites are reported in Table 3. As can be seen from Table 3, some geometrical parameters of Ciclopirox and

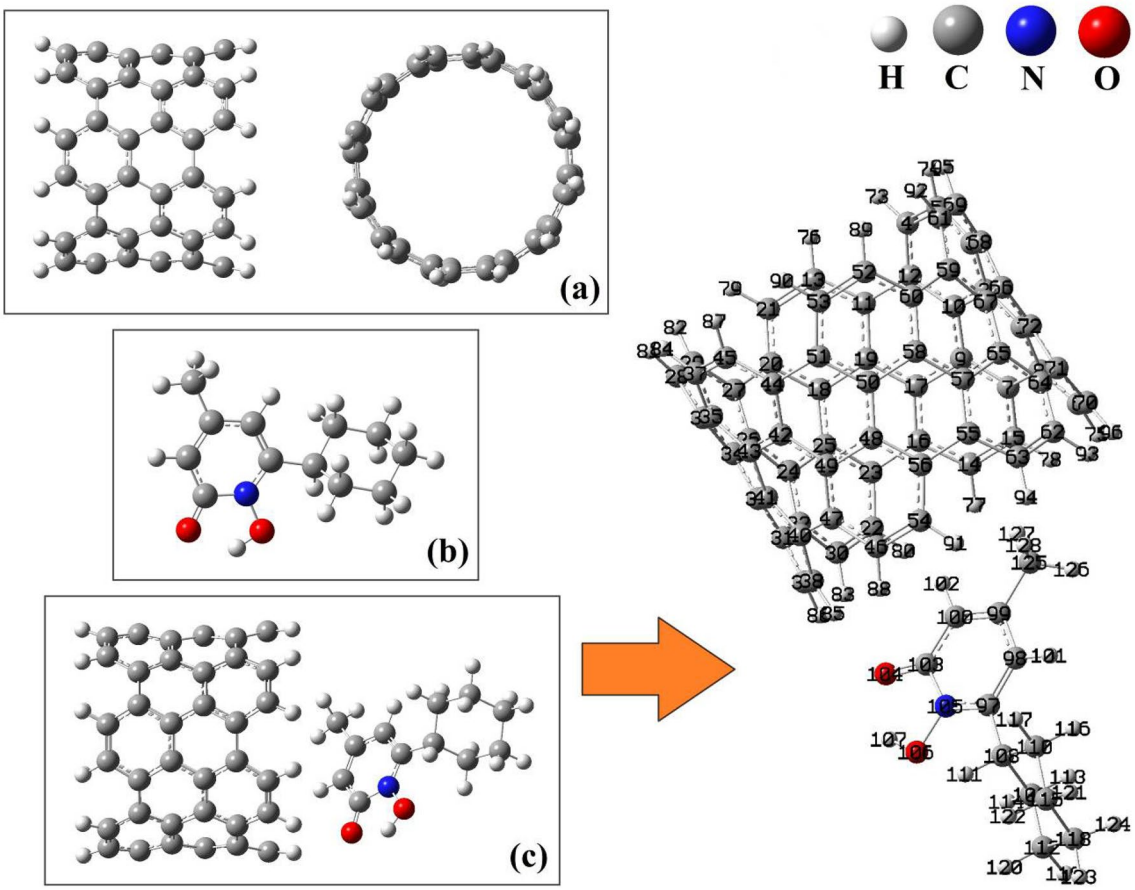


Fig. 3 The optimized geometry of the molecules Ciclopirox and the CNT(6,6-6) using B3LYP/6-31G* level of theory

Table 2 The thermochemical parameters of the molecules Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox and relative values of energies calculated by B3LYP/6-31G* level of theory

Parameter	Ciclopirox	CNT(6,6-6)	CNT(6,6-6)/Ciclopirox
E + G (kcal/mol)	− 421,976.102	− 1,730,432.443	− 2,152,400.487
E + H (kcal/mol)	− 421,941.394	− 1,730,369.193	− 2,152,312.030
E + T (kcal/mol)	− 421,941.987	− 1,730,369.786	− 2,152,312.622
S (cal/mol K)	116.411	212.141	296.687
$\Delta G_{adsorption}$	–	–	8.058
$\Delta H_{adsorption}$	–	–	− 1.443
$\Delta E_{adsorption}$	–	–	− 0.849
$\Delta S_{adsorption}$	–	–	31.865

Table 3 The calculated bond length (Å) of the molecule Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox using B3LYP/6-31G* method in a solvent water and the distance of the intermolecular hydrogen bonds (Å)

Bond length	CNT(6,6-6)	Ciclopirox	CNT(6,6-6)/ Ciclopirox
C15–C7	1.418	–	1.417
C14–C15	1.387	–	1.384
C14–C16	1.418	–	1.417
C22–C23	1.418		1.416
C22–C30	1.387	–	1.385
C46–C54	1.387	–	1.384
C62–C63	1.387	–	1.384
C46–C47	1.418	–	1.416
C14–H77	1.089	–	1.085
C22–H80	1.089	–	1.085
C30–H83	1.089	–	1.085
C38–H85	1.089	–	1.085
C46–H88	1.089	–	1.085
C54–H91	1.089	–	1.085
C63–H94	1.089	–	1.085
C98–C99	–	1.418	1.417
C99–C100	–	1.382	1.382
C100–H102	–	1.085	1.084
C100–C103	–	1.422	1.420
C103–O104	–	1.254	1.259
C103–N105	–	1.404	1.401
N105–O106	–	1.386	1.385
O106–H107	–	1.000	0.999
C99–C125	–	1.508	1.508
C125–H126	–	1.096	1.096
C125–H127	–	1.093	1.093
C125–H128	–	1.096	1.097

CNT are changed due to the formation of intermolecular bonds. The length of C15–C7, C14–C15, C14–C16, C22–C23, C22–C30, C46–C54, C62–C63, C46–C47 bonds of CNT(6,6-6) is 1.418 Å, 1.387 Å, 1.418 Å, 1.418 Å, 1.387 Å, 1.387 Å, 1.387 Å, 1.418 Å and after the adsorption of Ciclopirox drug on CNT(6,6-6) changes to 1.417 Å, 1.384 Å, 1.417 Å, 1.416 Å, 1.385 Å, 1.384 Å, 1.384 Å, 1.416 Å, respectively (see Table 3). Furthermore, the length bonds of C–H in the open end of CNT(6,6-6) change after adsorption of Ciclopirox over CNT. For instance, the length of C14–H77, C22–H80, C30–H83, C38–H85, C46–H88, C54–H91, C63–H94 bonds of the CNT is 1.089 Å and after the intermolecular interaction with Ciclopirox drug changes to 1.085 Å. The optimized structure of Ciclopirox has the C98–C99, C100–H102, C100–C103, C103–O104, C103–N105, N105–O106, O106–H107, C125–H128 bond length 1.418 Å, 1.085 Å, 1.422 Å, 1.254 Å, 1.404 Å, 1.386 Å, 1.000 Å, 1.096 Å, whereas after adsorption process change to 1.417 Å, 1.084 Å, 1.420 Å, 1.259 Å, 1.401 Å, 1.385 Å, 0.999 Å, 1.097 Å, respectively. The results show that the geometry of the molecules Ciclopirox and CNT(6,6-6) change after the intermolecular interaction two molecules and the formation of the complex, although these changes are not significant.

3.2 NBO analysis

NBO analysis is an important method for studying intra- and inter-molecular bonding and interaction between bonds in molecular systems (Shahab et al. 2017b). The electron delocalization from donor orbitals (full NBOs) to acceptor orbitals (empty NBOs) describes a conjugative electron transfer process between them (Shahab et al. 2017b). For each donor orbital (*i*) and acceptor orbital (*j*), the stabilization energy $E^{(2)}$ associated with the delocalization $i \rightarrow j$ is computed (Weinhold and Landis 2001):

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i} \tag{4}$$

The stabilization energy ($E^{(2)}$) describes the amount of the participation of electrons in the resonance between atoms of the molecular system (Shahab et al. 2017b). The bigger $E^{(2)}$, the more donation tendency from electron donors to electron acceptors (Sheikhi et al. 2018c). The NBO analysis for complex CNT(6,6-6)/Ciclopirox has been carried out by B3LYP/6-31G* level of theory and the results are reported in Table 4. According to results of NBO analysis, the $\pi \rightarrow \sigma^*$ transitions from CNT(6,6-6) to Ciclopirox take place as σ(C22-C30) → σ*(C100-H102) and σ(C62-C63) → σ*(C125-H128) interactions with stabilization energies ($E^{(2)}$) about 0.36 and 0.14 kcal/mol, respectively. The $n \rightarrow \sigma^*$ and $\pi^* \rightarrow \pi^*$ transitions from Ciclopirox to CNT(6,6-6) also occur in complex CNT(6,6-6)/Ciclopirox. According to results, lone pairs (n) of the oxygen atom (O104) in the compound Ciclopirox overlaps with the anti-bonding orbitals σ* of CNT(6,6-6) that are including n1 (O104) → σ*(C30–H83), n1 (O104) → σ*(C39–H86), n2 (O104) → σ*(C30–H83), n2 (O104) → σ*(C39–H86), n3 (O104) → σ*(C39–H86) with stabilization energies ($E^{(2)}$) of 0.94, 0.56, 1.38, 0.16, 1.40 kcal/mol, respectively. The obtained results indicated that n2 (O104) → σ*(C30–H83) and π*(C99–C10) → π*(C22–C30) in complex have the maximum stabilization energies ($E^{(2)}$) 1.38, 1.40 kcal/mol, respectively. So, they are the most important donor–acceptor interactions between the Ciclopirox and CNT. Thus, Ciclopirox and CNT(6,6-6) acts as both electron donor and electron acceptor; therefore, charge transfer takes place between Ciclopirox and CNT(6,6-6) in the complex CNT(6,6-6)/Ciclopirox.

Table 4 The donor–acceptor interactions and second-order perturbation energies ($E^{(2)}$, kcal/mol) related to charge transfer between Ciclopirox and CNT(6,6-6) in complex calculated using the B3LYP/6-31G* method

Donor (i)	Acceptor (j)	$E^{(2)a}$ (kcal/mol)	$E(j)-E(i)^b$ (a.u.)	$F(i, j)^c$ (a.u.)
π (C22–C30)	σ* (C100–H102)	0.36	0.74	0.016
π (C62–C63)	σ* (C125–H128)	0.14	0.71	0.010
n1 (O104)	σ* (C30–H83)	0.94	1.19	0.030
	σ* (C39–H86)	0.56	1.19	0.023
n2 (O104)	σ* (C30–H83)	1.38	0.76	0.030
	σ* (C39–H86)	0.16	0.76	0.010
n3 (O104)	σ* (C39–H86)	1.40	0.74	0.032
π* (C99–C10)	π* (C22–C30)	0.08	0.01	0.002

[a]$E^{(2)}$ energy of hyperconjucative interactions

[b]Energy difference between donor and acceptor i and j NBO orbitals

[c]F(i, j) Is the Fock matrix element between i and j NBO orbitals

3.3 Electronic properties

The frontier molecular orbitals (FMO) including HOMO and LUMO are indicated as significant parameters for the chemical reactions (Weinhold and Landis 2001). The HOMO and LUMO energies represent the ability to donate an electron and obtain an electron respectively. The molecular orbitals have a significant role in charge transfer phenomenon in molecular systems. The energy gap between HOMO and LUMO orbitals is an important factor in determining electrical transport properties in molecular systems (Sheikhi et al. 2018a). We have investigated the non-bonded intermolecular interaction effects between Ciclopirox drug and CNT(6,6-6) on the electronic properties. The calculated results are reported in Table 5.

The adsorption energy (E_{ad}) of the molecule Ciclopirox over the CNT(6,6-6) has a negative value of about −2.823 eV; therefore, the reaction is exothermic (Table 5).

Figure 4a shows that the electron density of HOMO orbital in the molecule Ciclopirox is mainly situated on the double bonds (–C=C–) of pyridine ring, nitrogen and oxygen atoms, whereas the LUMO is localized on double bonds (–C=C–) of pyridine ring, cyclohexane ring, nitrogen and oxygen atoms (Fig. 4a). Therefore, the most of the charge transfer from the HOMO to LUMO in the Ciclopirox drug is due to the contribution of pi (π) bonds and lone pairs. The HOMO and LUMO orbitals of the CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox mainly focus on double bonds (–C=C–) (see Fig. 4b, c).

The energy gaps between LUMO and HOMO (Eg) in the Ciclopirox is 5.01 eV, whereas after the adsorption Ciclopirox on CNT(6,6-6) (complex) decreases to 1.66 eV. Therefore, this result shows a significant increase in electrical conductivity of system complex compared with the isolated Ciclopirox drug and CNT. DOS plots (Sheikhi and Sheikh 2014) in Fig. 6 also show the energy gaps of the title systems. The quantum molecular descriptors for Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox consist of ionization potential (I), electron affinity (A), global hardness (η), electronegativity (χ), electronic chemical potential (μ), electrophilicity (ω) and

Table 5 The calculated electronic properties of the Ciclopirox drug, CNT(6,6-6) and the complex CNT(6,6-6)/Ciclopirox at the B3LYP/6-31G* level of theory in the solvent water

Property	Ciclopirox	CNT(6,6-6)	CNT(6,6-6)/Ciclopirox
Dipole moment (Debye)	5.57	0.00	5.81
E (Hartree)	−672.6973023	−2758.2691446	−3430.9709933
E_{HOMO} (eV)	−5.91	−4.41	−4.40
E_{LUMO} (eV)	−0.90	−2.75	−2.74
E_g (eV)	5.01	1.66	1.66
E_{ad} (eV)	–	–	−2.823
I (eV)	5.91	4.41	4.40
A (eV)	0.90	2.75	2.74
χ (eV)	3.40	3.58	3.57
η (eV)	2.50	0.83	0.83
μ (eV)	−3.40	−3.58	−3.57
ω (eV)	2.31	7.72	7.68
S (eV)	0.20	0.60	0.60

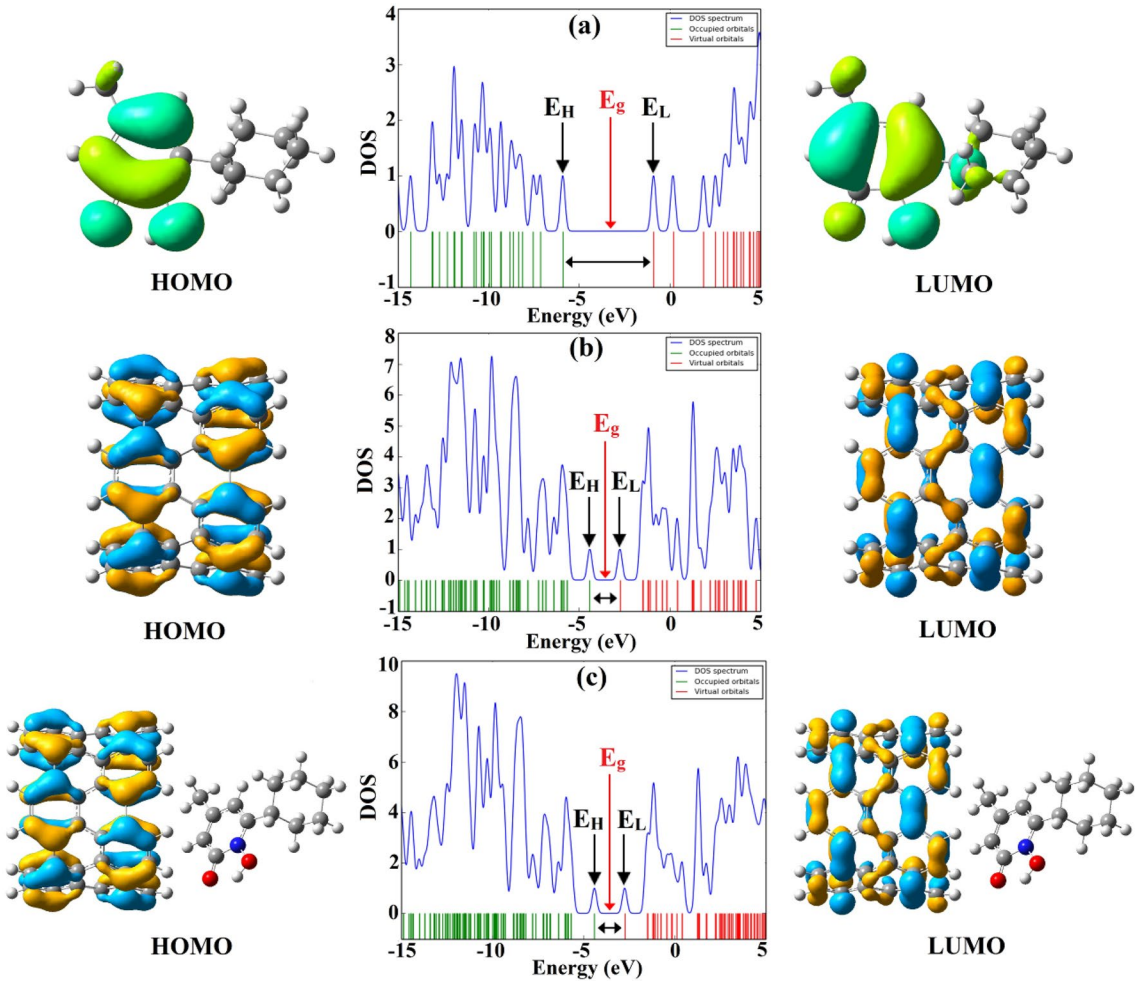


Fig. 4 The calculated HOMO, LUMO orbitals and DOS plot of the Ciclopirox drug at the B3LYP/6-31G* level of theory

chemical softness (S) are calculated according to follows equations, respectively (Sheikhi et al. 2016):

$$I = -E_{HOMO} \tag{5}$$

$$A = -E_{LUMO} \tag{6}$$

$$\eta = I - A/2 \tag{7}$$

$$\chi = I + A/2 \tag{8}$$

$$\mu = -(I + A)/2 \tag{9}$$

$$\omega = \mu^2/2\eta \tag{10}$$

$$S = 1/2\eta \tag{11}$$

that reported in Table 5. As can be seen from Table 5, the quantum molecular descriptors of Ciclopirox are changed with the adsorption process over CNT. The stability of the molecular systems is related to hardness which is a tool to understand chemical reactivity (Shayan and Nowroozi 2018). The hardness and electronic chemical potential of the complex will be decreased, while electrophilicity and softness will be increased compared with isolated Ciclopirox drug. Therefore, the complex has a high chemical activity, low chemical stability and it is a soft system. Thus, it is found that the adsorption of the molecule Ciclopirox on CNT(6,6-6) in the solvent water changes electronic properties of the complex.

The values of dipole moment of CNT(6,6-6), Ciclopirox and complex CNT(6,6-6)/Ciclopirox are 0.00, 5.57, 5.81 Debye, respectively (Table 5). After adsorption process, the value of dipole moment of the Ciclopirox decreases from 5.57 to 5.81 Debye and the value of dipole moment of the CNT increases from 0.00 to 5.81. The change of dipole moment after adsorption of Ciclopirox drug on CNT(6,6-6) indicates a charge transfer between Ciclopirox drug and CNT(6,6-6). The atomic charges have a significant role

on physical properties such as molecular polarizability, dipole moment, electronic structure and related properties of molecular systems (Sheikhi et al. 2019). The charge distributions (NBO charges) for equilibrium geometry of the CNT(6,6-6), Ciclopirox and complex were calculated using B3LYP/6-31G* level of theory. The calculated natural charges for selected atoms in these three molecular systems are reported in Table S1 (atoms are numbered according to Fig. 3). The natural charges of the C4, C7, C22, C23, C30, C38, C46, C54, C62, C63, H80, H83, H85 atoms at the CNT(6,6-6) are − 0.028e, − 0.209e, − 0.209e, − 0.209e, − 0.028e, − 0.209e, − 0.209e, − 0.028e, − 0.209e, − 0.209e, − 0.209e, 0.248e, 0.248e, 0.248e while with adsorption of Ciclopirox on the CNT(6,6-6) change to − 0.029e, − 0.210e, − 0.210e, − 0.214e, − 0.029e, − 0.216e, − 0.210e, − 0.029e, − 0.210e, − 0.211e, − 0.212e, 0.247e, 0.260e, 0.246e, respectively. The most significant changes observed for C22, C23, H83 atoms because of pyridine ring of Ciclopirox drug in the complex CNT(6,6-6)/Ciclopirox is close to these atoms in the nanotube. Also, the natural charges of the selected atoms in the molecule Ciclopirox before and after non-bonded interaction with CNT(6,6-6) are reported. The natural charges of the C99, C100, H102, C103, O104, N105, O106, H107, C125, H126, H127, H128 atoms of the molecule Ciclopirox are 0.027e, − 0.344e, 0.256e, 0.590e, − 0.717e, − 0.070e, − 0.569e, 0.512e, − 0.694e, 0.254e, 0.246e, 0.254e, respectively; whereas after adsorption of Ciclopirox on CNT(6,6-6), the natural charges change to 0.030e, − 0.339e, 0.257e, 0.588e, − 0.725e, − 0.066e, − 0.567e, 0.514e, − 0.695e, 0.252e, 0.247e, 0.256e, respectively. The C100 and O104 atoms exhibit main changes because of they are close to CNT(6,6-6). The change of the atomic charges induces a dipole moment in the complex. Thus, it shows a charge transfer and non-bonded interaction between Ciclopirox drug and CNT(6,6-6).

3.4 NMR analysis

We have calculated the NMR parameters such as chemical shift isotropic (CS^I) and chemical shift anisotropic (CS^A) for selected atoms in molecule Ciclopirox, CNT(6,6-6) and complex CNT(6,6-6)/Ciclopirox using the B3LYP/6-31G* level of theory. The electronic density affects the electrostatic properties of atoms. The adsorption of Ciclopirox drug on CNT(6,6-6) changes the electronic densities of atoms and NMR parameters. The results of the chemical shift tensors (ppm) are summarized in Table S1. The calculated results show that the values of the CS^I for the C30, C38, C46, C54, C62, C63, H80, H85, H88 atoms of the CNT(6,6-6) are 74.23, 74.34, 74.94, 74.18, 74.23, 74.26, 22.31, 22.30 ppm, respectively, whereas after the adsorption of Ciclopirox drug on CNT(6,6-6) was estimated about 71.77, 74.06, 75.18, 74.55, 74.44, 74.63, 22.10, 22.61 ppm, respectively. The title atoms exhibit the main changes because Ciclopirox drug in complex CNT(6,6-6)/Ciclopirox is close to these atoms in CNT. For the molecule Ciclopirox, the CS^I values of the C99, C100, H102, C103, O104, C125, H127 atoms are 46.60, 84.16, 26.17, 41.14, 91.15, 167.51, 30.41 ppm, respectively, but these values after the adsorption of Ciclopirox over CNT(6,6-6), change to 43.95, 80.94, 23.04, 38.73, 95.85, 164.69, 27.69 ppm, respectively.

3.5 Molecular electrostatic potential (MEP) analysis

Molecular electrostatic potential (MEP) maps display the electronic density in the molecular systems and they are utilized to detect positions of positive and negative electrostatic potentials surfaces with different colors (Sheikhi and Sheikh 2014; Sheikhi et al. 2016). In MEPs, the negative sites with the high electron density have red, orange or yellow colors that were related to electrophilic reactivity, whereas the positive regions with low electron density have blue color and they were related to nucleophilic reactivity and green color was used for neutral regions. The MEPs of the molecule Ciclopirox and complex CNT(6,6-6)/Ciclopirox were obtained by theoretical calculations using the B3LYP/6-31G* level of theory (Fig. 5) and the charge distribution was studied by MEP calculations. As seen from the MEP maps of the Ciclopirox drug, the O_a atom with red color has the highest electron density. Whereas after adsorption of the molecule Ciclopirox on nanotube, the O_a in complex CNT(6,6-6)/Ciclopirox has the orange color with lower electron density compared with Ciclopirox.

3.6 Electronic structure and excited states

In order to investigation of adsorption effect of Ciclopiroxd over CNT(6,6-6) on the λ_{max}, we have calculated the UV/Vis spectra of Cicloripox and the complex CNT(6,6-6)/Ciclopirox in the solvent water using TD-DFT calculations at B3LYP/6-31G* method with considering 20 excited states which is represented in Tables S2 and S3 and Fig. 6. Tables S2 and S3 indicates the λ_{max}, oscillator strength (f), and excitation energies (E).

The computed analysis of the UV spectrum for the molecule Ciclopirox exhibits λ_{max} at 199 nm (f = 0.45) (see Table S2). The charge transfer at λ_{max} = 199 nm is related to the excited state $S_0 \rightarrow S_4$ with three electron configurations such as [H − 3 → L (14%), H − 1 → L (48%), H → L + 1 (34%)] in which the main transition is involved with the transition from HOMO − 1 to LUMO [H − 1 → L (48%)]. The molecular orbitals that are involved in formation of electron transition at λ_{max} = 199 nm are shown in Fig. 6. As can be seen from Fig. 6, HOMO − 1 orbital of the molecule Ciclopirox mainly focused on the double bonds C=C of pyridine ring and nitrogen atom and oxygen atoms of carbonyl

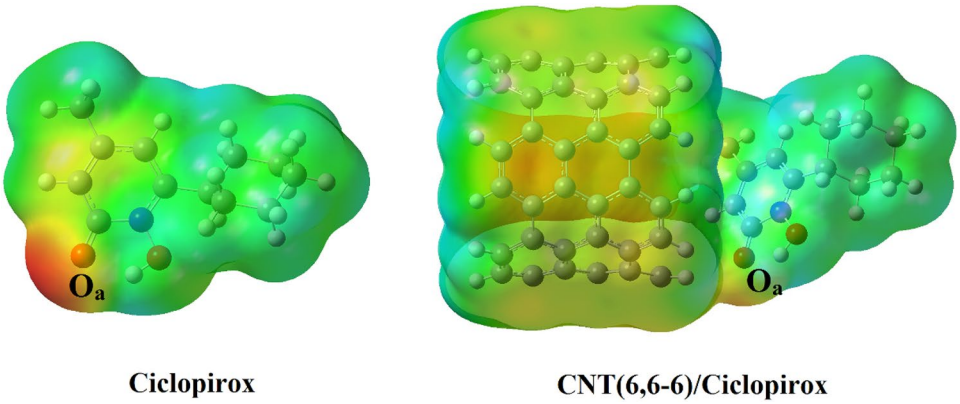


Fig. 5 MEP maps of the molecule Ciclopirox and complex CNT(6,6-6)/Ciclopirox

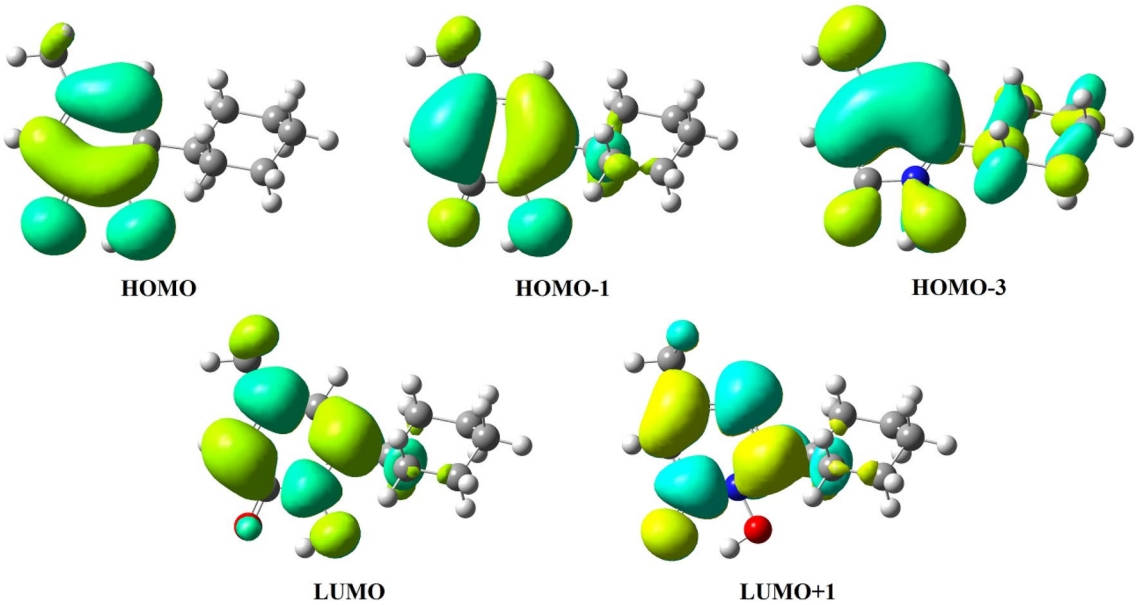


Fig. 6 Shape of the MO involved in formation of absorption spectrum of the compound Ciclopirox at λ_{max} = 199 nm calculated by B3LYP/6-31G* method

and hydroxyl groups, while the LUMO orbital localized on double bonds C=C of pyridine ring, nitrogen atom and oxygen atom of hydroxyl group. The excited states of $S_0 \rightarrow S_8$ and $S_0 \rightarrow S_4$ at 186 nm (f = 0.25) and 168 nm (f = 0.32) are also the other important excited states in the UV spectrum of Ciclopirox. The other excited states of Ciclopirox drug have very small intensity and do not play any role in the formation of electron spectrum of the title compound (Table S2). The calculated electronic absorption spectrum of Ciclopirox drug in the solvent water is shown in Fig. 7a.

After the adsorption of Ciclopirox on the CNT(6,6-6), λ_{max} appear at 461 nm (f = 0.63). The charge transfer at λ_{max} = 461 is related to the excited state $S_0 \rightarrow S_9$ and is defined by four configurations including [H − 2→L (29%), H − 1 → L (28%), H → L + 1 (24%), H → L + 2 (13%)] (Table S3). The major contribution to the absorption maxima related to HOMO − 2 → LUMO, which contributes about 29% of the total excitations. The shape of molecular orbitals involving at λ_{max} = 461 nm is shown in Fig. 8. As can be seen from Fig. 8, the electron density of HOMO and LUMO is significantly focused on the double bonds C=C of nanotube. The excited states of $S_0 \rightarrow S_{10}$ and $S_0 \rightarrow S_{16}$ at 460 nm (f = 0.62) and 405 nm (f = 0.39) are also the other important excited states in the UV/Vis spectrum of complex CNT(6,6-6)/Ciclopirox. The other excited states of the title compound have very small intensity (f ≈ 0) that is nearly forbidden by orbital symmetry considerations (Table S3). Figure 7b shows the calculated UV/Vis is the spectrum of CNT(6,6-6) in the solvent water.

In the UV spectrum of the isolated Ciclopirox, λ_{max} is observed at 199 nm, while after adsorption of the Ciclopirox over the nanotube it is enhanced to 461 nm. Thus, we found

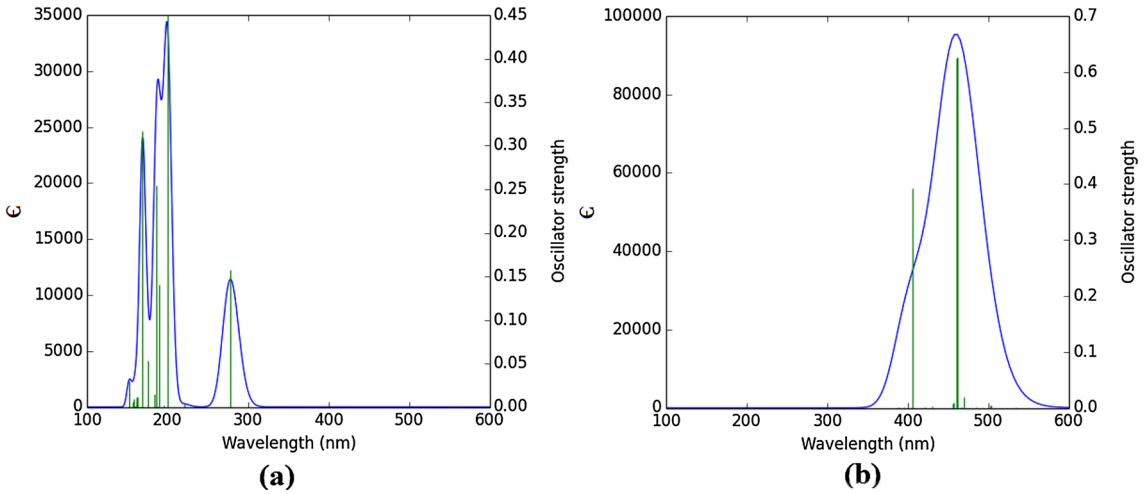


Fig. 7 UV spectrum of the Ciclopirox drug (**a**) and complex CNT(6,6-6)/Ciclopirox (**b**) calculated by TDB3LYP/6-31G* method

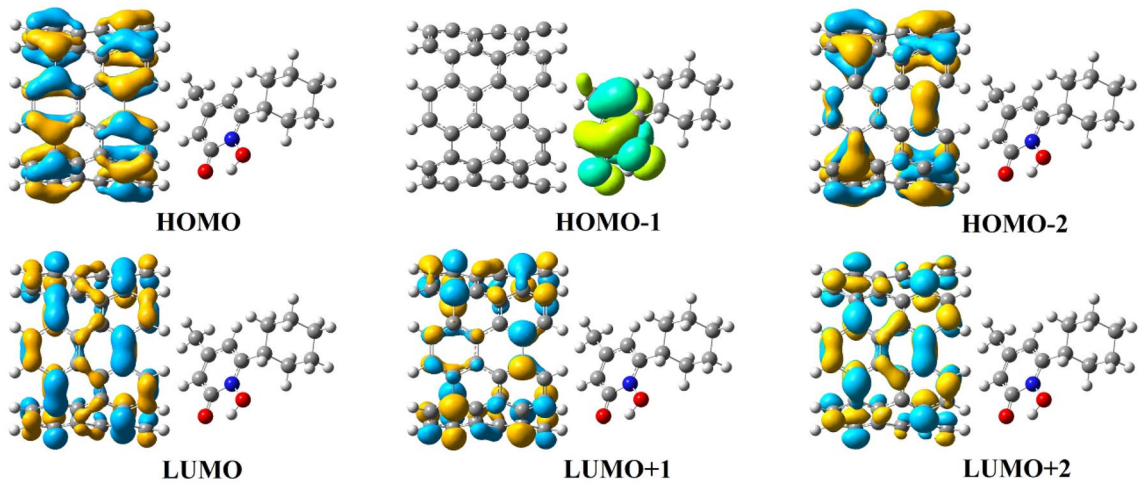


Fig. 8 Shape of the MO involved in formation of absorption spectrum of the molecule CNT(6,6-6) at λ_{max} = 461 nm calculated by B3LYP/6-31G* method

that adsorption of the Ciclopirox over the CNT(6,6-6) nanotube change the value of λ_{max} and it can be considered as a bathochromic shift.

4 Conclusion

In this study, the adsorption of the Ciclopirox drug on the CNT(6,6-6) was investigated at the B3LYP/6-31G* level of theory. Some interesting outcomes of theoretical calculations are as follows:

1. According to the obtained results adsorption of Ciclopirox drug on the CNT(6,6-6) is an exothermic process and CNT(6,6-6)/Ciclopirox is a stable complex.
2. It is found that some geometrical parameters of Ciclopirox and CNT are changed after adsorption process due to the formation of intermolecular non-bonded interaction.
3. NBO analysis predicted a charge transfer from the molecule Ciclopirox to nanotube and from nanotube to Ciclopirox.
4. The energy gaps between LUMO and HOMO in Ciclopirox increase after the adsorption Ciclopirox on CNT(6,6-6). This result indicates a significant increase in electrical conductivity of complex compared with the isolated Ciclopirox drug and CNT.
5. The electronic properties, natural charges and chemical shift tensors are changed after adsorption of the Ciclopirox on the CNT(6,6-6).

6. As a result, the quantum molecular descriptors are changed at adsorption process. The hardness and electronic chemical potential of the complex will be decreased, while electrophilicity and softness will be increased.
7. Non-bonded interaction between the compound Ciclopirox and CNT(6,6-6) is changed the value of λ_{max}.

We hope that our results of the adsorption properties of Ciclopirox with CNT(6,6-6) can be used as in the adsorbent enhancing drugs delivery of the cancer cells and to support decreased drug interaction with healthy tissue.

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