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A Theoretical Study of the Separation of Enantiomers of the Drug Modafinil by Nanotubes: Molecular Docking Simulations and Density Functional Theory

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ABSTRACT

The separation of drug enantiomers is crucial in the pharmaceutical industry, as each enantiomer can exhibit different biological activities. Modafinil is a racemic drug, with the R enantiomer being primarily responsible for its pharmacological effects. The main objective of this study was to identify a suitable carbon nanotube (CNT) structure to effectively separate the enantiomers of Modafinil. Molecular docking simulations were performed to investigate the binding of Modafinil enantiomers with various chiral CNTs (7,6), (8,7), (9,8), and (10,9) with lengths ranging from 11 to 15 Angstroms. Molecular docking simulations showed that the CNT (8,7) with a length of 15 Angstroms could effectively separate the S and R enantiomers of Modafinil. The R enantiomer was adsorbed on the surface of the CNT, with a binding energy of -3.49 kcal/mol, while the S enantiomer was located inside the nanotube, with a binding energy of -4.34 kcal/mol. Density functional theory (DFT) calculations at the B3LYP/6-31G level were then employed to optimize the structures and investigate the interactions of the drug enantiomers with the selected CNT. Density functional theory (DFT) calculations revealed that the R enantiomer had a higher binding energy compared to the S enantiomer, indicating better stability upon adsorption on the CNT surface. Further analysis of electronic properties, including frontier orbital energies, reactivity descriptors, Mulliken atomic charges, dipole moments, and molecular electrostatic potentials, provided insights into the differences in the behavior and interactions of the two Modafinil enantiomers with the CNT. In conclusion, this study demonstrates that the chiral carbon nanotube (8,7) with a length of 15 Angstroms can effectively separate the S and R enantiomers of the drug Modafinil, with the R enantiomer being the preferred form for adsorption and separation.

INTRODUCTION

Chirality, the property of an object being non-superimposable on its mirror image, has been a fundamental concept in chemistry and biology for centuries. Enantiomers are a pair of molecules that are non-superimposable mirror images of each other [1,2]. The concept of chirality and the importance of enantiomers have been recognized for centuries, with early discussions dating back to the 19th century work of renowned chemists like Louis Pasteur [3,4].

The discovery of the different biological activities of enantiomers has been a driving force in the field of stereochemistry and has had a profound impact on the pharmaceutical industry.

While enantiomers have identical physical and chemical properties in a non-chiral environment, they can exhibit vastly different behaviors when interacting with optically active (chiral) compounds such as enzymes, receptors, and other biological macromolecules [5,6]. This property of enantiomers is of great importance in the pharmaceutical industry, as the two enantiomers of a chiral drug may have significantly different pharmacological effects, pharmacokinetics, and toxicity profiles [7,8].

The separation and purification of drug enantiomers have been an active area of research for decades. Conventional methods for enantiomer separation, such as chiral chromatography, have limitations like time-

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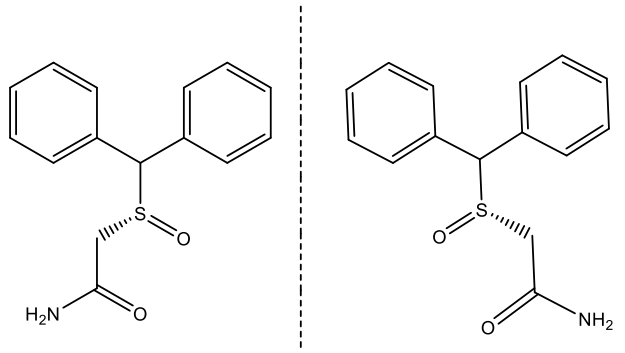
consuming procedures, high costs, and low resolution [9,10].

In recent years, the development of novel chiral separation techniques has gained significant attention [11,12]. One such emerging approach is the use of carbon nanotubes (CNTs) for the enantioselective separation of drug molecules [13,14]. The ability of CNTs to form strong π-π interactions with aromatic compounds, combined with their tunable surface chemistry, makes them promising candidates for chiral recognition and separation [15,16].

Modafinil is a racemic drug, meaning it is a 50:50 mixture of the R and S enantiomers (see Fig.1) [17,18]. Most of the pharmacological activity of modafinil is attributed to the R enantiomer, while the S enantiomer may cause unwanted side effects [19,20]. Therefore, the effective separation and purification of modafinil enantiomers is an important task in the pharmaceutical industry.

In this study, we investigated the ability of several chiral single-walled carbon nanotubes (SWCNTs) with different (n,m) indexes and lengths to separate the enantiomers of the drug modafinil. Molecular docking simulations and density functional theory (DFT) calculations were employed to evaluate the binding and interactions of the drug enantiomers with the selected CNTs.

The results of this work provide valuable insights into the use of chiral CNTs as effective adsorbents for the separation of modafinil enantiomers, which can have important implications for the pharmaceutical industry and drug development processes.



S- Modafinil R- Modafinil

Fig. 1. S and R enantiomers of the drug Modafinil

Computational Details

Molecular Docking Simulations

The binding of the pharmaceutical enantiomers with chiral carbon nanotubes was investigated using the Arguslab molecular docking simulation software [21]. First, single-walled carbon nanotubes (SWCNTs) with different (n,m) indexes, including (7,6), (8,7), (9,8), and (10,9), were designed using the NanoModeler software [22,23]. The lengths of these CNTs were varied between 11 and 15 angstroms.

The interaction of each SWCNT with the S and R enantiomers of the drug modafinil was then evaluated using the Arguslab molecular docking simulation program. The docking method employed an exhaustive search algorithm to identify the lowest energy binding pose of the drug enantiomers with the chiral CNTs. This allowed for the assessment of the ability of these CNTs to effectively separate the enantiomers based on their binding energies and spatial arrangements.

The molecular docking simulations were repeated multiple times and we have consistently derived the same results.

Density Functional Theory Calculations

To further understand the interaction and reactivity of the modafinil enantiomers with the selected CNT, density functional theory calculations were performed. The B3LYP [24] functional with the 6-31G basis set was used to optimize the structures of all the complexes. The Gaussian 03 package [25] was utilized to carry out the quantum chemical calculations.

The binding energy of the drug enantiomers and their complexes with the CNT was calculated to investigate the stability of the systems. The binding energy is defined as follows:

$$\text{Binding Energy} = E_{product} - (E_{CNT} + E_{molecule}) \quad (1)$$

where E_product is the energy of the complex, E_CNT is the energy of the carbon nanotube, and E_molecule is the energy of the drug molecule.

Global reactivity descriptors

Reactivity descriptors were also used to determine the reactivity, electron transfer levels, and stability of the enantiomers. The electron descriptors are directly related to the HOMO-LUMO energy gap. HOMO and LUMO refer to the highest occupied molecular orbital and the lowest unoccupied molecular orbital, respectively. The energy difference between LUMO and HOMO is called the HOMO-LUMO gap. The frontier orbitals provide comprehensive information about the suitable points for nucleophilic and electrophilic attacks and determine the degree of reactivity of the system.

Descriptors of reactivity include ionization energy (I), chemical potential (μ), electron affinity (A), hardness (η), and softness (δ).

The ionization energy is inversely related to the HOMO and is defined as:

$$(I) = (-HOMO) \quad (2)$$

The electron-seeking behavior is inversely proportional to the LUMO energy and tends to attract electrons. The electron-demand relationship is equal to:

$$(A) = (-LUMO) \quad (3)$$

Hardness is another electron descriptor directly related to the energy gap. The higher the HOMO-LUMO energy gap, the higher the hardness. Hardness can be defined as:

$$(\eta) = (I-A)/2 \quad (4)$$

Softness is the opposite of hardness and is defined as:

$$(\delta) = 1/\eta \quad (5)$$

Chemical potential is released or received during chemical reactions. The more negative the chemical potential, the better the absorption. The chemical potential relationship is as follows:

$$(\mu) = (I+A)/2 \quad (6)$$

Mulliken atomic charge, dipole moment, and MEP are other parameters of computational chemistry used to investigate the charge density of atoms, charge transfer, intramolecular interactions, and charge distribution of molecules, which are calculated using density functional theory [26-32].

RESULTS AND DISCUSSIONS

Docking

Considering that drug enantiomers act differently when dealing with chiral compounds, it is expected that the enantiomers of the drug Modafinil will have different energy and properties after being absorbed inside and outside the nanotubes. However, some properties of nanotubes, such as small length and inappropriate dimensions for drug placement, led nanotubes with a length of 11 to 14 both enantiomers to choose one position (both outside or both inside). As a result, in this case, the energy of both enantiomers was almost close to each other, which was not suitable for drug separation. The nanotubes longer than 15 angstroms are ineffective in separating R and S isomers. This is due to both isomers being accommodated within the nanotube, resulting in identical absorption energies for each. For the optimal separation of medicinal isomers, the S and R enantiomers should have a minimum energy difference of 0.1 kcal/mol or 0.004 electron volts. The absorption energy of medicinal enantiomers with carbon nanotubes of the mentioned dimensions are presented in Table 1. Drug enantiomers adsorbed on the nanotube surface had higher energy values than those absorbed inside the nanotube. More negative energy values show that the enantiomers absorbed inside the nanotubes are more stable. In general, it can be inferred from the values given in Table 1 that the tendency of both enantiomers to enter the nanotube is very high. In nanotubes with n and m (6 and 7) and length 11 to 15, both enantiomers could not enter the nanotube due to the small length of the nanotube and were forced to settle on the carbon nanotube. In nanotubes (8,7), (9,8), and (10,9) with dimensions of 11 to 15, the length of the nanotube was suitable for the entry of both enantiomers. For this reason, except for the state (8,7) with a length of 15, the rest of the states show the establishment of both enantiomers inside the nanotube, and the energy values in Table 1 are a clear proof to prove this matter. In addition, after examining the appearance of drug docking with nanotubes of different dimensions, it was found that some enantiomers were located at the entrance edge of the nanotube, and due to the small dimensions of the nanotube, they were not able to enter the nanotube. Table 1 lists the binding energy values of S and R enantiomers with carbon nanotubes in terms of (kcal/mol). The results of this research showed that S and R enantiomers have a significant energy difference after absorption in the outer and inner parts of carbon nanotubes (8,7) with a length of 15. The R enantiomer was placed on the nanotube and its energy was equal to -3.48589 kcal/mol. But the S enantiomer was absorbed inside the nanotube and its energy was equal to -4.34 kcal/mol. The energy difference between the two enantiomers was approximately 0.85 kcal/mol. This amount of energy difference is quite suitable for the separation of medicinal enantiomers. The results of the docking process show that the S enantiomer has less energy than the R enantiomer after being absorbed inside the nanotube. The docking energy diagram of modafinil drug enantiomers with CNTs is presented in Fig.2. The obtained docking poses are shown in Fig.3.

Table 1
Docking values of R and S enantiomers with carbon nanotube of different dimensions in terms of kcal/mol.

(n, m, nanotube length)	Energy	
	R-Enantiomer	S_Enantiomer
(7,6,11)	-3.64	-3.62
(8,7,11)	-4.47	-4.24
(9,8,11)	-4.53	-4.52
(10,9,11)	-4.35	-4.36
(7,6,12)	-4.01	-3.88
(8,7,12)	-4.12	-4.23
(9,8,12)	-4.62	-4.62
(10,9,12)	-4.41	-4.41
(7,6,13)	-3.68	-3.65
(8,7,13)	-4.08	-4.22
(9,8,13)	-4.67	-4.54
(10,9,13)	-4.45	-4.44
(7,6,14)	-3.29	-3.33
(8,7,14)	-4.11	-4.21
(9,8,14)	-4.68	-4.67
(10,9,14)	-4.45	-4.49
(7,6,15)	-3.26	-3.28
(8,7,15)	-3.48	-4.33
(9,8,15)	-4.69	-4.68
(10,9,15)	-4.50	-4.50

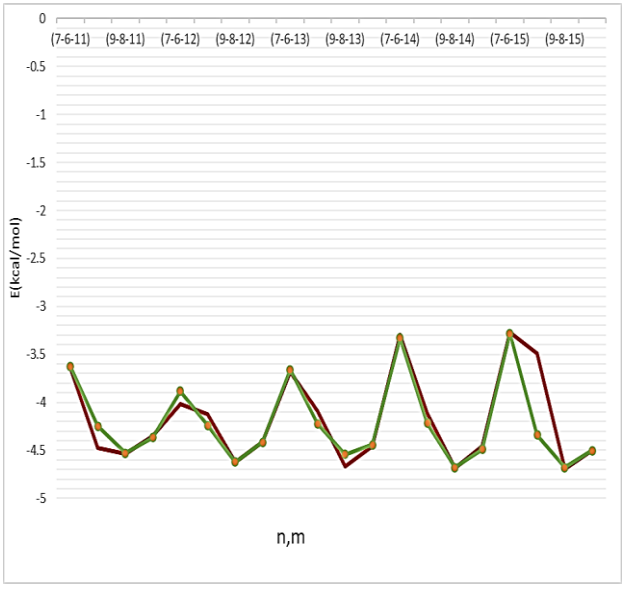


Fig. 2. diagram of docking energy changes of the S and R enantiomers of the drug Modafinil with carbon nanotubes

DFT results and optimization

First, the geometrical structure of medicinal enantiomers and its binding energy with nanotubes were investigated. The main goal of this study was to achieve a configuration with high stability and proper interaction. Therefore, in the first step, drug optimization was done by density functional theory method at the B3LYP/6-31G theoretical level. The structural properties of the drug, including bond length, dihedral angle, and dihedral angle, were then investigated. The values related to the structural properties of the drug are presented in Table 2. The length the nanotube before absorption is equal to 10.353 Å and after absorption was equal to 10.206 Å in R enantiomer and 10.672 Å in S enantiomer. Examining the structural parameters and its analysis showed that the length and angle of the dihedral bond in the R enantiomer attached to the nanotube is constant and no significant change was observed. The non-change of the molecular geometry of the R enantiomer after adsorption on the nanotube indicates that this nanotube is a suitable carrier for protecting the drug structure and separating it from the S enantiomer. On the contrary, structural properties of S enantiomer showed changes after adsorption inside the nanotubes. This enantiomer is more affected by the charge potential of CNTs because of its placement on the inner surface of the nanotube. The dihedral angle of the R enantiomer before and after adsorption on the nanotube is almost constant, and the bond angles at the location of the key atoms do not show much change. While some S enantiomer angles have decreased after absorption inside the nanotubes. The values of bond angle changes are listed in Table 2. The R enantiomer has approached the nanotube only from the side of some special atoms such as hydrogen attached to nitrogen, oxygen, and some atoms of the phenyl ring. The S enantiomer is completely inside the nanotube. Inside the nanotube, there is not enough space to change the position of the S enantiomer. Also, some dihedral angles were affected by the nanotubes and were compressed more than the R enantiomer. The dihedral angle of both R and S enantiomers was changed after adsorption. The biggest change of dihedral angle is observed at the sites of functional groups such as carbonyl and oxygen attached to sulfur. All calculations were done in the water phase, and no significant changes were observed between the gas and liquid phases. The bond lengths and angles slightly decreased or increased under the influence of the water environment. But the amount of changes was small and negligible. The optimized structures of R and S enantiomers before and after nanotube adsorption are shown in Fig .4and Fig .5.

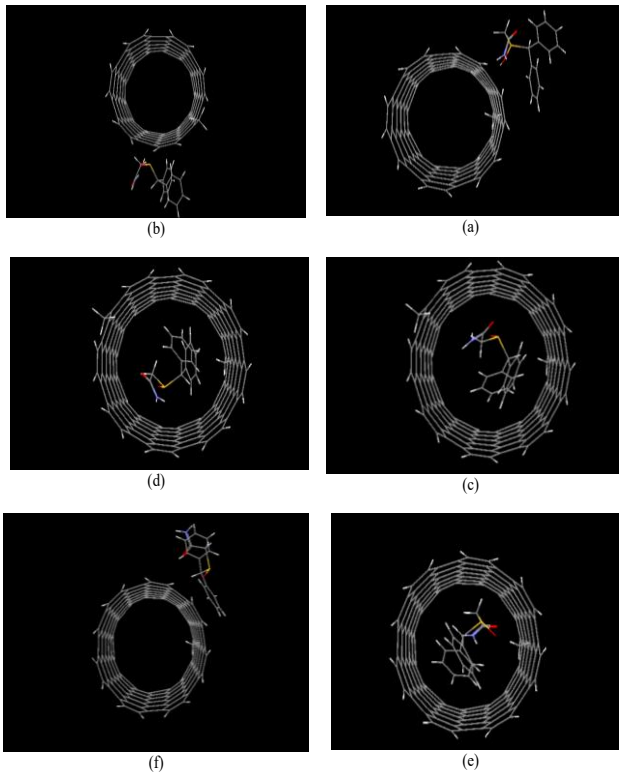


Fig. 3. Different states of placement of S and R enantiomers of the drug on the outer and inner surface of the nanotube with different dimensions
(a) The placement of S enantiomer on nanotube (6,7) with length of 14
(b) The placement of R enantiomer on nanotube (6,7) with length of 14
(c) The placement of S enantiomer on nanotube (8,9) with length of 15
(d) The placement of R enantiomer on nanotube (8,9) with length of 15
(e) The placement of S enantiomer on nanotube (7,8) with length of 15
(f) The placement of R enantiomer on nanotube (7,8) with length of 15.

Table 2
Structural characteristics (bond length, dihedral angle) of some modafinil drug atoms before adsorption with CNT in gas and water phases.

		Gas phase				Water phase		
structure	R-Enantiomer		S-Enantiomer		R-Enantiomer		S-Enantiomer	
Bond-length label	Before ads	After ads	Before ads	After ads	Before ads	After ads	Before ads	After ads
H34-N18	1.03	1.03	1.03	1.01	1.03	1.03	1.03	1.01
N18-C17	1.36	1.36	1.36	1.37	1.35	1.35	1.35	1.36
C16-S8	1.93	1.93	1.93	1.94	1.92	1.93	1.93	1.93
Bond angle label								
N18-C17-O19	124.90	125.00	124.9	121.70	124.50	124.80	124.50	121.78
S8-C16-C17	113.20	113.00	115.30	121.60	113.60	116.78	113.20	123.26
S8-C16-H31	105.90	107.20	107.00	100.90	106.10	105.82	106.40	100.71
Dihedral-angle label								
H34-N18-C17-O19 H31-C16-S8-O15 O19-C17-C16-H31	175.30	175.50	173.20	175.90	175.74	177.47	176.10	175.00

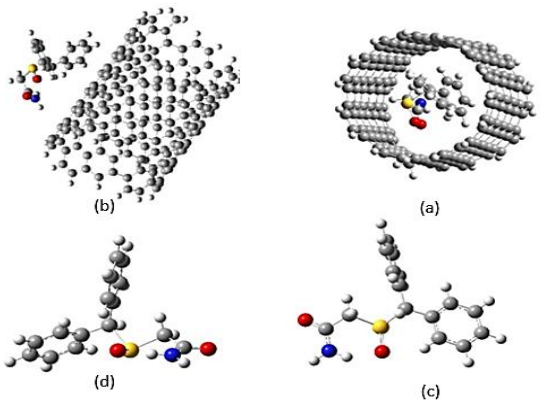


Fig. 4. Optimized structure of drug and CNT enantiomers before and after adsorption with nanotube in gas phase ((a): S-CNT, (b): R-CNT, (c): S-Enantiomer, (d): R-Enantiomer)

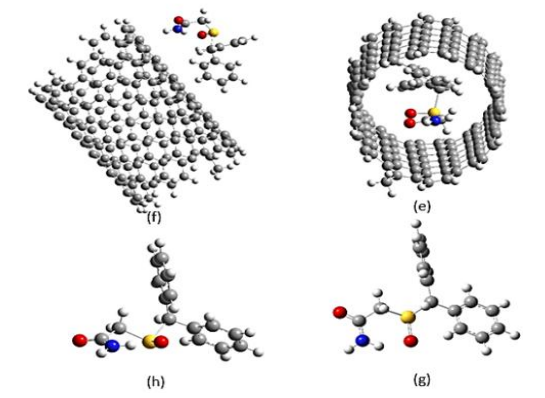


Fig. 5. Optimized structure of drug and CNT enantiomers before and after adsorption with nanotubes in water phase ((e): -CNT, (f): R-CNT, (g): S-Enantiomer, (h): R-Enantiomer

Binding Energy

Table 3 shows the binding energy of S and R enantiomers after adsorption with nanotubes in gas and water phases. The findings showed that the binding energy of R-CNT in the gas phase is equal to -3.66 Kcal/mol and the binding energy of S-CNT in the same phase is equal to 36.77 Kcal/mo. In the water phase, the binding energy of the R-CNT complex is increased and is equal to -2 Kcal/mol. The binding energy of S-CNT also increased to 39.64 Kcal/mo. The results showed that the absorption of S enantiomer inside the nanotube is weaker than the absorption of R enantiomer on the nanotube. The results of optimization of the structures show that the low level of binding energy has caused pharmaceutical enantiomers not to stick to the surface of the nanotubes. Based on the optimization structures, the enantiomers are only adsorbed on the CNTs and do not directly bind. The lowest binding energy in the gas phase is related to the R-CNT complex. The R enantiomer after adsorption on the chiral carbon nanotube is more stable than the S enantiomer after adsorption inside the nanotube. The R enantiomer has a good and stable interaction with the carbon nanotube and is well placed on them. The S enantiomer is in a more unstable.

Table 3
Binding energy of enantiomers of modafinil drug before and after adsorption with nanotube in gas and water phase at B3LYP level.

Modafinil Enantiomers	Gas		Water	
	E(kcal/mol)	E Binding	E(kcal/mol)	E Binding
R-Enantiomer	-742801.62	------	-742813.86	-----
S-Enantiomer	-742802.14	-----	-742814.00	-----
CNT	-4483314.63	-----	-4483327.65	-----
R_CNT	-5226119.91	-3.66	-5226144.00	-2.00
S_CNT	-5226080.00	36.76	-5226102.00	39.64

State under the influence of the inner space of the nanotube. Also, the energy level of both enantiomers decreased significantly after absorption. The binding energy of the R enantiomer after adsorption on the nanotube is more negative than that of the S enantiomer. Therefore, the R enantiomer has better interaction and binding with CNTs. The binding energy of both R-CNT and S-CNT complexes were higher in the water phase than in the gas phase. The binding energy of R-CNTs in the water phase is negative as in the gas phase and the binding energy of S-CNT in the water phase is positive. It seems that the complexity of the reaction in the liquid phase due to the presence of water molecules led to an increase in the energy level in the water phase. Therefore, enantiomer adsorption by nanotubes is more favorable in the gas phase than in the water phase. Also, the negative binding energy in the R-CNT complex in both phases indicates that the adsorption process is exothermic and spontaneous.

Table 4
HOMO-LUMO values and energy gap of enantiomers of modafinil drug before and after adsorption with nanotubes in gas and water at B3LYP/6-31G level.

structure	Gas			Water		
	E_{HOMO} (ev)	E_{LUMO} (ev)	GAP	E_{HOMO} (ev)	E_{LUMO} (ev)	GAP
R-Enantiomer	-6.21	-1.50	4.72	-6.34	-1.55	4.80
S-Enantiomer	-6.19	-1.53	4.67	-6.36	-1.50	4.86
CNT	-4.51	-2.73	1.79	-4.66	-2.87	1.80
R_CNT	-4.53	-2.75	1.79	-4.66	-2.87	1.80
S_CNT	-4.48	-2.71	1.77	-4.65	-2.87	1.79

Electronic Properties
Energy Gap

To investigate the reactivity and stability of R-CNT and S-CNT complexes, frontier orbitals and energy gaps were investigated. The frontier orbitals include the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) and provide useful information about electron transfer or electron acceptance. This information is useful for investigating biochemical reactions and drug reactivity. The energy gap shows the maximum range of electron transfer between the highest and lowest unoccupied molecular orbitals. From frontier orbitals and DFT calculations, many useful reactivity parameters, such as chemical potential, electron affinity, hardness, and softness, can be evaluated [33]. The frontier orbital and energy gap information are presented in Table 4. The largest energy gap in the gas phase, corresponding to the R enantiomer before adsorption on the nanotube, is equal to 4.719 ev. Both enantiomers have a larger energy gap before CNT adsorption. After adsorption with nanotubes, the energy gap significantly decreased and reached 1.787 eV in the R-CNT complex and 1.768 ev in the S-CNT complex . Due to the reduction of the energy gap after absorption, the reactivity and conductivity in both complexes increased. Also, the probability of electron transfer after the enantiomers are attached to the carbon nanotubes is high.

Then, before the attachment. As a result, electrons move from the highest occupied molecular orbital to the lowest unoccupied molecular orbital at a faster rate. R-CNT complex has a higher energy gap than S-CNT and its stability and conductivity level is lower. This finding can also be seen in the water phase and the energy gap between the enantiomers decreased after absorption. Unlike the gas phase, the S enantiomer has a higher energy gap than the other enantiomers before absorption. Of course, the energy gap difference between the two enantiomers before absorption in the water phase is negligible.

HOMO and LUMO are expressed as follows:

The results show that the highest HOMO corresponds to the S enantiomer after carbon nanotube adsorption. As a result, it is the most Nucleophile system. This complex tends to participate in electrophilic reactions and is attacked by electrophiles. The HOMO energy in both enantiomers increases after adsorption because of their interaction with CNTs. The comparison of the two enantiomers after absorption shows that S-CNT complex has higher HOMO energy values than R-CNT.

HOMO and LUMO images of drug enantiomers before and after nanotube adsorption in both gas and water phases are shown in Figures 6, 7, and 8. These images have red and green dots that show the negative and positive charges of the atoms, respectively [34]. The HOMO orbital in the R enantiomer is located on the bonds and the remaining parts of the molecule, except for the carbonyl functional group. The LUMO orbital is uniformly covered throughout the molecule. In the S enantiomer, the HOMO orbitals are on the pi bonds (except for the carbonyl functional group) and some sigma bonds. The LUMO orbital of the S enantiomer is covered throughout the molecule (on Π and sigma bonds). There is no difference between the HOMO-LUMO images in gas and water phase and the results are similar in both phases. The HOMO and LUMO orbitals are non-uniformly placed on the upper and lower walls of the nanotube. The distribution of the HOMO and LUMO

orbitals in one of the CNT walls is more than the other, and this applies to both gas and water phases. The HOMO and LUMO orbitals in the R-CNT and S-CNT complexes are on the nanotube wall. In the S enantiomer, the nanotube is closer to the drug from the side where the distribution of HOMO-LUMO orbitals is less. HOMO-LUMO distribution is the same in both complexes in gas and water phases. HOMO-LUMO energy pictures of R and S enantiomers before and after adsorption with nanotubes are shown in figure (6), (7) and (8). Also, the diagrams (DOS) of R and S enantiomers before and after adsorption with nanotubes are presented in Fig.9.

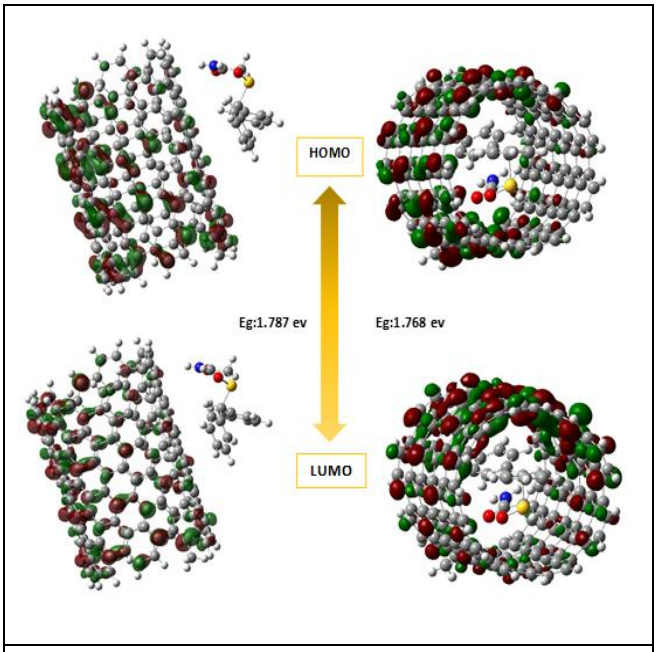


Fig. 6. HOMO-LUMO energy diagram in R-CNT and S-CNT complex in gas phase

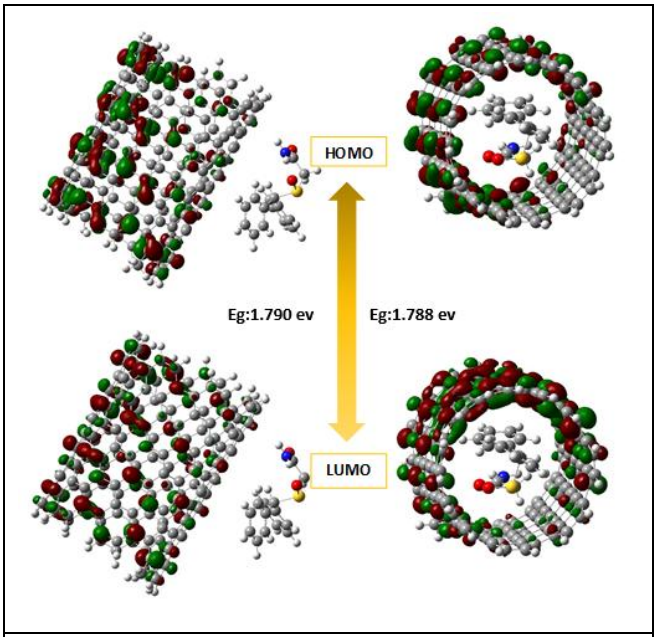


Fig. 7. HOMO-LUMO energy diagram in R-CNT and S-CNT complex in water phase

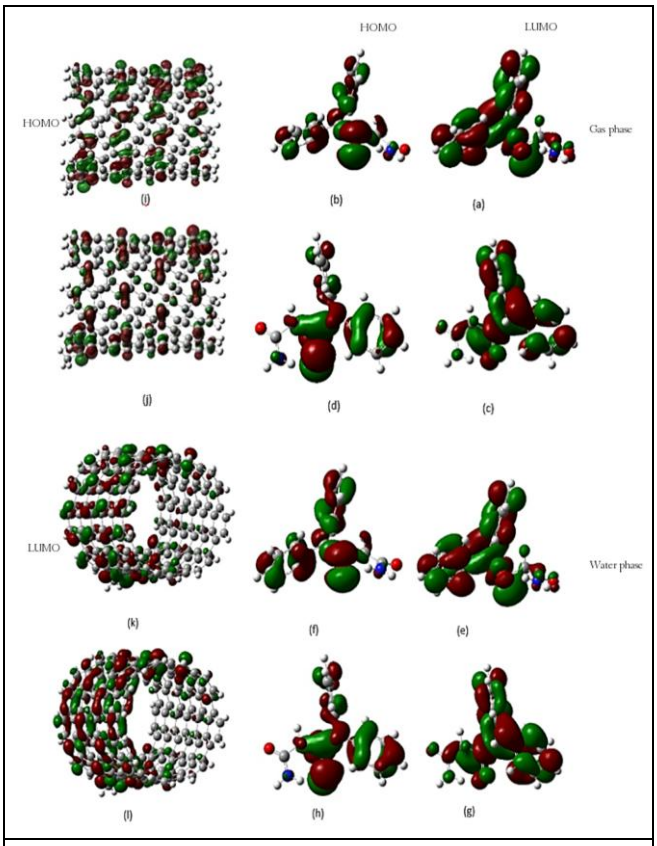


Fig. 8. HOMO-LUMO energy diagram of the enantiomers of the drug Modafinil and CNT in gas and water phase (a, b, e, f): R-Enantiomer, (c,d,g,h): S-Enantiomer, (i,j) ,k,l): CNT

Also, comparing the two enantiomers before absorption shows that the HOMO energy of the S enantiomer is higher than that of the R enantiomer. The LUMO energy decreased after binding with carbon nanotubes. So that the lowest LUMO energy corresponds to the R enantiomer after CNT adsorption. This enantiomer is the most electrophilic system and is attacked by nucleophiles. A comparison of the two complexes after absorption shows that the R enantiomer has a lower LUMO energy than the S enantiomer. The lowest LUMO energy before absorption corresponds to the S enantiomer, which is equal to -1.529 ev. After binding of enantiomers to CNTs, the tendency of R enantiomer to participate in nucleophilic reaction is greater than that of the S enantiomer. The opposite is observed before absorption. The HOMO and LUMO energies were investigated in the water phase. The findings show that the energy values of the frontier orbitals have increased numerically. After adsorption, the enantiomers exhibited the same performance as the gas phase. As observed in the gas phase, the highest HOMO corresponds to the S enantiomer and the lowest LUMO corresponds to the R enantiomer after bonding with CNT. Both enantiomers have a completely different state before absorption compared to the gas phase. In contrast to the gas phase and before bonding with CNTs, the HOMO energy of the R enantiomer is higher than that of the other enantiomers. The LUMO energy level of the S enantiomer is higher than that of the R enantiomer.

Electron Descriptors

Table 5
Values of electron descriptors of enantiomers of modafinil drug before and after adsorption with nanotubes in gas and water

	Gas					Water				
structure	(I)	(A)	(μ)	(η)	(δ)	(I)	(A)	(μ)	(η)	(δ)
R-Enantiomer	6.21	1.50	-3.86	2.36	0.42	6.34	1.55	-3.95	2.40	0.42
S-Enantiomer	6.19	1.53	-3.86	2.33	0.43	6.35	1.50	-3.92	2.43	0.41
CNT	4.51	2.73	-3.62	0.89	1.12	4.66	2.87	-3.76	0.90	1.12
R_CNT	4.53	2.75	-3.64	0.89	1.12	4.66	2.87	-3.77	0.90	1.12
S_CNT	4.48	2.71	-3.59	0.88	1.13	4.65	2.87	-3.76	0.89	1.12

Ionization energy is the amount of energy required to separate an electron from a gaseous atom and transform it into a gaseous ion. In general, the higher the HOMO energy, the easier it is to detach the electron and the lower the ionization energy. A high level of ionization energy indicates that the system is more stable and less reactive. The highest ionization energy corresponds to the R enantiomer before attachment to the CNTs. Both enantiomers exhibited higher ionization energy before binding with nanotubes than after adsorption. After connecting, the reactivity and instability of the system increased. Table.5 shows electronic descriptors for enantiomers and complexes. The lowest ionization energy and the highest instability is related to the S-CNT complex, which is equal to 4.4770.

The R-CNT complex is more stable than the other two complexes. The electron affinity represents the amount of energy released when an electron is added to a neutral atom or molecule in the gas phase. Electron withdrawal is inversely related to the LUMO energy. In other words, electron-seeking behavior shows the desire to attract electrons. The highest electron affinity and lowest LUMO are related to R-CNTs. The electron withdrawal level increases after enantiomers are attached to CNTs. Before absorption, the S enantiomer is slightly more electron-demanding than the other enantiomers. Chemical potential is a type of potential energy received or released during a chemical reaction. A more negative chemical potential indicates better absorption. The chemical potential of both enantiomers before adsorption was more negative than after binding with nanotubes. After adsorption onto CNTs, the chemical potential of R-CNTs was more negative than that of S-CNTs. This problem shows that R enantiomer has better adsorption on carbon nanotubes. Hardness and softness are inversely related to each other and are related to the HOMO-LOMO gap. The higher the energy gap, the higher the hardness and the lower the softness and conductivity. The energy gap of both enantiomers is larger before binding to the nanotubes. As a result, the hardness is higher, and the conductivity and softness before absorption is lower. The lowest hardness and the highest softness are related to the connection of enantiomers to CNTs. Therefore, the conductivity of enantiomers increases after absorption. Chiral carbon nanotubes are highly effective in increasing the conductivity level.

Mulliken Atomic Charge

The Mulliken atomic charge is an important concept in chemistry. The best method for calculating atomic charge is Mulliken population analysis, which is still widely used in the scientific community. The Mulliken atomic charge provides complete information about the charge density of atoms. Mulliken atomic charge values related to key drug atoms are presented in Table 5. In general, no significant change was observed in the Mulliken charge values of carbon nanotube atoms before and after binding with the drug enantiomers. But the amount of atomic charge was changed in the place of the functional groups and key atoms of both enantiomers.

The maximum negative charge corresponds to the O15 atom in the S enantiomer. The charge of this atom is -0.745 and it is attacked by electrophiles. In general, the O15 atom has a more negative charge than the rest of the drug atoms and is more electron-donating than the R enantiomer with an atomic charge of -0.695. Unlike the R enantiomer, the electron-donating level of the O15 atom in the S enantiomer increases after absorption. After the O15 atom, the N18, C7, and O19 atoms and some C atoms of the phenyl ring have the highest electron donor, respectively. Charge transfer from the drug to the nanotube occurs at the location of these atoms. The maximum positive charge corresponds to the S8 atom in the S enantiomer. This atom has a charge of 1.034 and is attacked by a nucleophile. After binding to the nanotubes, the atomic charge of S8 in the S enantiomer is higher than that of the R enantiomer. As a result, this part of the drug can be a good place to participate in nucleophilic reactions and receive electrons. In addition to the S8 atom, the hydrogen atoms of the drug have a great

tendency to receive electrons. The atomic charge values in the water phase were also investigated, and no significant change was observed in the atomic charge of the enantiomers before and after binding. However, the atomic charge of O15 in the R enantiomer increased slightly in the water phase (-0.695 in the gas phase and -0.743 in the water phase). But its value is still more positive than that of the S enantiomer.

Dipole Moment

Table 6
Atomic charge values of some atoms of modafinil drug before and after adsorption with nanotubes in gas and water phases.

	Gas				Water			
atoms	R-Enantiomer	R - CNT	S-Enantiomer	S-CNT	R-Enantiomer	R-CNT	S-Enantiomer	S-CNT
7C	-0.63	-0.66	-0.62	-0.65	-0.63	-0.66	-0.62	-0.65
8S	0.97	0.99	0.95	1.03	0.97	0.99	0.95	1.03
9C	0.14	0.08	0.12	0.11	0.13	0.08	0.12	0.10
15 O	-0.73	-0.70	-0.74	-0.75	-0.77	-0.74	-0.77	-0.76
18 N	-0.70	-0.69	-0.70	-0.69	-0.70	-0.69	-0.70	-0.70
19 O	-0.42	-0.40	-0.42	-0.45	-0.48	-0.45	-0.48	-0.46

The difference in the electronegativity of chemically bonded atoms ultimately leads to an unequal electron distribution and the creation of a dipole moment. The higher the dipole moment, the greater is the intramolecular interaction and charge transfer. The values related to the dipole moments of the drug enantiomers before and after their connection with nanotubes are presented in Table 6. Findings show in the gas phase, the lowest dipole moments and charge transfers are related to the CNT and S-CNT complex. The highest dipole moment and the highest charge transfer related to R-CNT complex is equal to 8.162. The dipole moments of pharmaceutical enantiomers and CNTs before and after binding in the water phase was also investigated.

The results show that the lowest dipole moment and charge transfer are related to CNT. Like the gas phase, the highest dipole moments and charge transfers are related to the R-CNTs. However, the dipole moments of both complexes were significantly greater in the water phase than in the gas phase. Therefore, the charge transfer rate was higher in the water phase than in the gas phase.

Molecular Electrostatic Potential (MEP)

To determine the electrostatic effect at different points of Molecular electrostatic potential (MEP). Electrostatic potential maps, known as electrostatic potential energy maps or molecular electric potential surfaces, show the charge distribution of molecules in three dimensions. This map allows the researcher to visualize the regions of variable charge of molecules. MEP also represents electron density and is a useful descriptor for understanding electrophilic attack sites, nucleophilic reactions, and hydrogen bonding interactions. In this map, areas with negative electron density (red color) are related to electrophilic reactions, and areas with positive electron density (blue color) are related to molecular nucleophilic reactions .In general, in electrostatic potential maps, negative sites with high electron density are colored red, orange, or yellow. The positive regions with low electron density have blue and green colors for neutral. The green color of CNTs indicates that this part of the molecular structure has no desire to participate in the reaction and is completely neutral in terms of reactivity. The highest negative electron density was observed for oxygen atoms attached to sulfur and carbonyl oxygen atoms of the drug enantiomers. The red and orange colors of these regions indicate that oxygen atoms are suitable places for electrophilic attack and tend to participate in electrophilic reactions. This matter applies to both enantiomers before and after connection with the nanotube. The highest positive electron density was observed in the place of phenyl rings and amino groups of drug enantiomers. These regions are blue in color and are suitable places for nucleophilic attack.

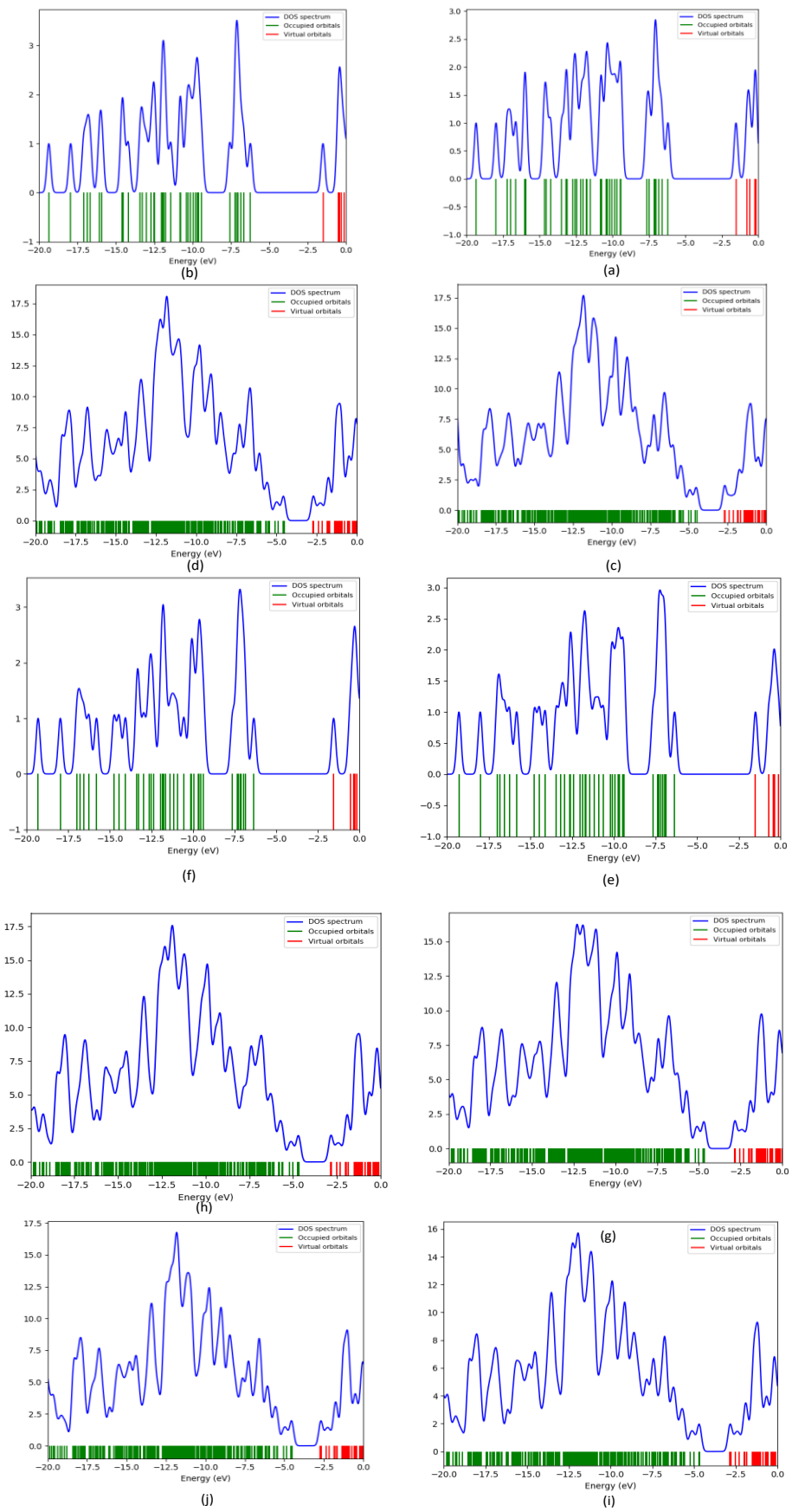


Fig. 9. Total electron density (DOS) diagrams of enantiomers of modafinil drug before and after adsorption with nanotubes in gas phase ((a): S-Enantiomer, (b): R-Enantiomer, (c): S-CNT, (d): R-CNT, (j): CNT) and in the water phase (((e): S-Enantiomer, (f): R-Enantiomer, (g): S-CNT, (h): R-CNT, (I): CNT)

Participation in nucleophilic reactions. This problem applies to both enantiomers before and after absorption. Although the central part of the chiral carbon nanotube is completely green, the side of the end atoms of the CNT is observed to be blue. As a result, these places can also be suitable places for nucleophilic attacks. The molecular electrostatic potential in the water phase was also investigated, and no difference was observed between the water and gas phases. The images (MEP) of R and S enantiomers before and after nanotube adsorption are shown in Fig.10.

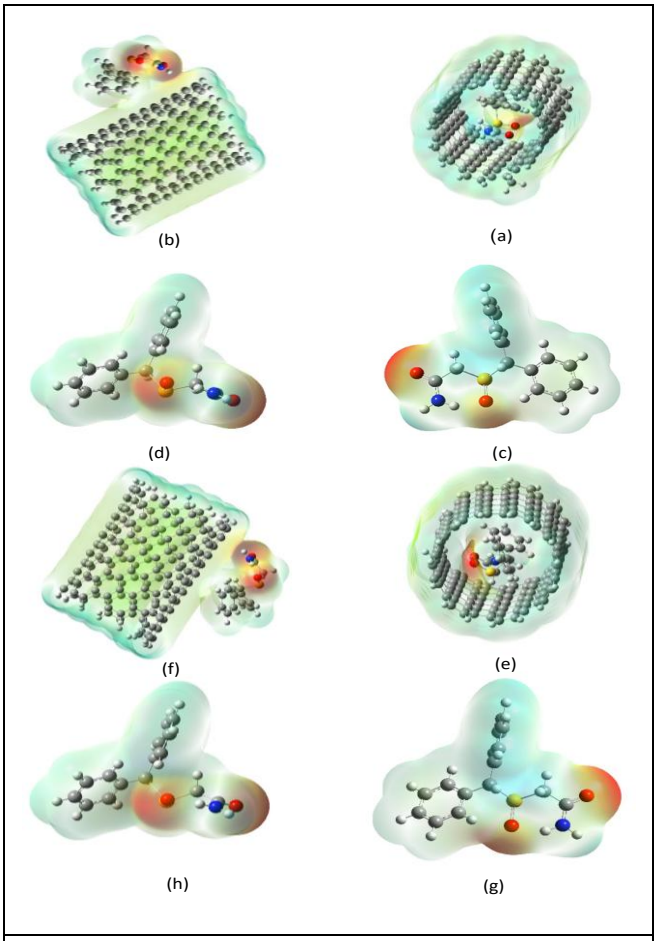


Fig. 10. Molecular electrostatic potential (MEP) diagram of the enantiomers of the drug modafinil before and after adsorption with nanotubes in the gas phase ((a) S-CNT (b) R-CNT (c) S-enantiomer (d) R-enantiomer) and in water phase ((e) S-CNT (f) R-CNT (g) S-enantiomer (h) R-enantiomer).

The findings of this study demonstrate the significant potential of chiral carbon nanotubes in the effective separation of drug enantiomers, which is a critical task in the pharmaceutical industry. The ability to efficiently separate the R and S enantiomers of modafinil using the (8,7) CNT with a length of 15 Å highlights the novelty and importance of this work. Compared to conventional chromatographic techniques, the use of chiral CNTs as adsorbents offers several advantages, including higher selectivity, faster separation times, and the potential for scalability.

The combination of molecular docking simulations and DFT calculations employed in this study provides a comprehensive computational framework to understand the adsorption mechanisms and interactions of the drug enantiomers with the selected CNT structure. This integrated approach allows for the elucidation of the electronic properties, reactivity, and charge distribution of the drug-CNT complexes, which is crucial for the rational design and optimization of enantiomer separation systems [35].

Furthermore, the insights gained from this research can have broader implications for the separation of enantiomers of other chiral drugs and the development of novel drug delivery systems utilizing chiral CNTs. The ability to selectively adsorb and isolate specific enantiomers can significantly impact the pharmaceutical industry, leading to improved therapeutic efficacy and reduced side effects.

CONCLUSION

This study provides a comprehensive investigation of the separation of enantiomers of the drug modafinil using chiral carbon nanotubes (CNTs). The geometric analysis revealed that the R enantiomer maintained a more stable conformation upon adsorption on the CNT surface, while the S enantiomer exhibited slight structural changes when located inside the nanotube.

The binding energy calculations showed that the R enantiomer had a higher binding energy compared to the S enantiomer, indicating better stability and stronger adsorption on the CNT. This was further supported by the reactivity descriptor analysis, which demonstrated that the R-CNT complex had the lowest ionization energy and chemical potential, suggesting improved adsorption and electron-donating abilities compared to the S-CNT complex.

The Mulliken atomic charge analysis identified the oxygen and nitrogen atoms, as well as the phenyl ring carbons, as the most electron-donating regions in the drug enantiomers. The sulfur atom and hydrogen atoms, on the other hand, exhibited a greater tendency to accept electrons. These insights into the charge distribution and reactivity of the enantiomers provide a deeper understanding of their interactions with the chiral CNT.

The dipole moment and molecular electrostatic potential (MEP) analyses revealed that the R-CNT complex had the highest dipole moment and charge transfer, indicating stronger intramolecular interactions. The MEP maps further highlighted the electronegative regions, such as the carbonyl and sulfur-oxygen groups, as potential sites for electrophilic attack, while the phenyl rings and amino groups were identified as favorable locations for nucleophilic interactions.

Overall, the results of this study demonstrate that the chiral carbon nanotube (8,7) with a length of 15 Å can effectively separate the S and R enantiomers of the drug modafinil, with the R enantiomer exhibiting better adsorption and stability on the CNT surface compared to the S enantiomer. These findings highlight the potential of chiral CNTs as efficient adsorbents for the separation and purification of drug enantiomers, which is crucial in

the pharmaceutical industry for improving therapeutic efficacy and reducing adverse effects.

DECLARATIONS

Ethical Approval

Not applicable.

Competing interests

The authors declare no competing interest.

Authors' contributions

Kosar Mohammadi writing; Dr. Hossein Nikofard writing, review and editing; Dr. Mohsen Sargolzaei writing, review and editing and submitting.

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References

[1] Xie Z, Gao L, Li C, et al. Chiral separation of racemic drugs using functionalized carbon nanotubes. Nanoscale. 2020;12(21):11585-11593.
[2] Tanaka M, Watanabe K, Tsukahara T. Enantioselective adsorption of ibuprofen on chiral carbon nanotubes. ACS Appl Nano Mater. 2021;4(3):2644-2651.
[3] Bayat P, Shukla R, Barrow CJ, Loon A, Dunstan DE. Chiral carbon nanotubes for enantioselective separations and sensing. Small. 2020;16(22):1907359.
[4] Zhang X, Zhang Y, Ren X, et al. Chiral carbon nanotubes for enantioselective adsorption and separation of pharmaceutical drugs. ACS Appl Mater Interfaces. 2022;14(33):37762-37771.
[5] Qi Z, Xu J, Liu C, Hou J, Liu Y. Functionalized carbon nanotubes for chiral recognition and enantioseparation. New J Chem. 2020;44(23):9920-9937.
[6] Wang Y, Li Y, Wang Z, Tang Z. Chiral carbon nanotubes: synthesis, properties and applications. Nanoscale. 2022;14(3):790-810.
[7] Silvestri IP, Colbon PJ. The growing importance of chirality in 3D chemical space exploration and modern drug discovery approaches for Hit-ID: Topical Innovations. ACS Med Chem Lett. 2021;12(8):1220-1229.
[8] Banik SD, Nandi N. Chirality and protein biosynthesis. In: Queisser G, ed. Biochirality: Origins, Evolution and Molecular Recognition. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013:255-305.
[9] Nguyen LA, He H, Pham-Huy C. Chiral drugs: an overview. Int J Biomed Sci. 2006;2(2):85.
[10] Inaki M, Liu J, Matsuno K. Cell chirality: its origin and roles in left–right asymmetric development. Philos Trans R Soc B Biol Sci. 2016;371(1710):20150403.
[11] Williams K, Lee E. Importance of drug enantiomers in clinical pharmacology. Drugs. 1985;30(4):333-354.
[12] McConathy J, Owens MJ. Stereochemistry in drug action. Prim Care Companion J Clin Psychiatry. 2003;5(2):70.
[13] Kim D. Practical use and risk of modafinil, a novel waking drug. Environ Health Toxicol. 2012;27:e2012007.
[14] Murillo-Rodríguez E, Barciela Veras A, Barbosa Rocha N, Budde H, Machado S. An overview of the clinical uses, pharmacology, and safety of modafinil. ACS Chem Neurosci. 2018;9(2):151-158.
[15] Ikai T, Okamoto Y. Structure control of polysaccharide derivatives for efficient separation of enantiomers by chromatography. Chem Rev. 2009;109(11):6077-6101.
[16] Bereznitski Y, Thompson R, O'Neill E, Grinberg N. Thin-layer chromatography—a useful technique for the separation of enantiomers. J AOAC Int. 2001;84(4):1242-1251.
[17] Kim D. Practical use and risk of modafinil, a novel waking drug. Environ Health Toxicol. 2012;27:e2012007.
[18] Murillo-Rodríguez E, Barciela Veras A, Barbosa Rocha N, Budde H, Machado S. An overview of the clinical uses, pharmacology, and safety of modafinil. ACS Chem Neurosci. 2018;9(2):151-158.
[19] Darwish M, Kirby M, Hellriegel ET, Robertson P. Armodafinil and modafinil have substantially different pharmacokinetic profiles despite having the same terminal half-lives: analysis of data from three randomized, single-dose, pharmacokinetic studies. Clin Drug Investig. 2009;29:613-623.
[20] Power TD, Skoulidas AI, Sholl DS. Can chiral single walled carbon nanotubes be used as enantiospecific adsorbents. J Am Chem Soc. 2002;124(9):1858-1859.
[21] Mark A. Argus Lab 4.0.1. Seattle, WA: Thompson, Planaria Software LLC; 2002.
[22] Melchor S, Dobado JA. An algorithm for connecting two arbitrary carbon nanotubes. J Chem Inf Comput Sci. 2004;44(5):1639-1646.
[23] Johnson JE, Speir JA. Quasi-equivalent viruses: a paradigm for protein assemblies. J Mol Biol. 1997;269(5):665-675.
[24] Becke AD. Density-functional thermochemistry. III. The role of exact exchange. J Chem Phys. 1993;98(7):5648-5652.
[25] Frisch MJ, Trucks GW, Schlegel HB, et al. GAUSSIAN 03, Revision C.02. Wallingford, CT: Gaussian, Inc.; 2004.
[26] Pearson RG. Chemical hardness and the electronic chemical potential. Inorg Chim Acta. 1992;198-200:781-786.
[27] Demircioğlu Z, Kaştaş ÇA, Büyükgüngör O. Theoretical analysis (NBO, NPA, Mulliken Population Method) and molecular orbital studies (hardness, chemical potential, electrophilicity and Fukui function analysis) of (E)-2-((4-hydroxy-2-

methylphenylimino)methyl)-3-methoxyphenol. J Mol Struct. 2015;1091:183-195.
[28] Kumar SA, Bhaskar BL. Preliminary investigation of drug impurities associated with the anti-influenza drug Favipiravir–An in silico approach. Comput Theor Chem. 2021;1204:113375.
[29] Saikia N, Deka RC. A comparison of the effect of nanotube chirality and electronic properties on the π–π interaction of single-wall carbon nanotubes with pyrazinamide antitubercular drug. Int J Quantum Chem. 2013;113(9):1272-1284.
[30] Pandey AK, Dwivedi A, Mishra AK, Tiwari SN, Vuai SA, Singh V. Quantum chemical study of effect on adsorption properties of antituberculosis drug N-Cyclopentylidenepyridine-4-carbohydrazide interaction with CNT (C56H16). J Indian Chem Soc. 2023;100(1):100851.
[31] Ravikumar N, Rajendran A, Sivalingam A. Computational study on the adsorption mechanism of telmisartan drug on pristine and functionalized single-walled carbon nanotube as a drug delivery system. Struct Chem. 2022;33(1):293-303.
[32] Xu H, Li L, Fan G, Chu X. DFT study of nanotubes as the drug delivery vehicles of Efavirenz. Comput Theor Chem. 2018;1131:57-68.
[33] Choudhary V, Bhatt A, Dash D, Sharma N. DFT calculations on molecular structures, HOMO–LUMO study, reactivity descriptors and spectral analyses of newly synthesized diorganotin (IV) 2-chloridophenylacetohydroxamate complexes. J Comput Chem. 2019;40(27):2354-2363.
[34] Karthick V, Kumari KV. Computational study on the adsorption behavior of atazanavir drug on pristine and functionalized single-walled carbon nanotubes as a drug delivery system. Struct Chem. 2022;33(2):1019-1030.
[35] Mathew B, Suresh J, Mathew GE. Novel benzothiazole derivatives as antioxidants and cholinesterase inhibitors: A computational study. J Mol Struct. 2020;1209:127891.