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Theoretical study of anti-HIV medication azidothymidine (Azt) interactions with non-functionalized and functionalized nanotubes

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The current paper investigates Anti-HIV medication Azidothymidine (AZT) interactions with Non-functionalized single-walled nanotube (5 , 5) (NT) and functionalized nanotube NTCOOH using Quantum Mechanics. All calculations were done using a B3LYP hybrid density function and the basic function 6-31G(d,p)in the gas and solution phase and polarization of the continuum model (PCM) was used for solvent effects, also covalent and non-covalent capture of the medicine was studied on the SWNT. Two covalent and two non-covalent configurations were studied in solution phase.Binding energy in non-covalent capture depends on the group on the CNT. The most powerful complex from non-covalent configuration is created when there is an interaction between Zidovudine and SWNT through the NH group. Molecular quantum descriptors likehardness and chemical potential and AIM studies show the nature and absorption of medicine on SWNT.

Keywords: Zidovudine, Azidothymidine, HIV, Non-functionalized nanotubes, Functionalized nanotubes

INTRODUCTION

Research on new methods and effectiveness of drug delivery systems has attracted many researchers in the past decades. Drug delivery systems designed to correct pharmaceutical and therapeutic effects of a medicine. The ability of carbon nanotubes in penetration in biological cells introduced them as a drug carrier to transport low molecular weight drugs. But the low rate of spread as a result of strong Van der Waals intermolecular interactions between the nanotubes and the formation of toxic accumulation of carbon nanotubes are the fundamental problem ahead of their use [1, 2].

Now, functionalized carbon nanotubes (F-CNT) are known as new compounds in nano-carriers equations to deliver drug molecules to the aimed cell [3]. Covalent functionalization of carbon nanotubes and addition of medication molecules to them (anticancer, antiviral and antibacterial), is a new and emerging field of research [4].

Two main classes of carbon nanotubes include:

- Single-walled carbon nanotubes (SWCNT).
- Multi-walled carbon nanotubes (MWCNT).

The discoveries of 1991 mainly included multi-walled nanotubes while the single walled nanotubes remained undiscovered until several years later. Both types of nanotubes length is a few microns. The length and diameter of the nano depends on the metal catalyst used in the synthesis method. Carbon nanotubes are entirely composed of SP2 bonds that lead to their unique strength. Chemical and physical properties of single-walled and multi-walled nanotubes are different due to the difference in the length and diameter [5].

Researchers recently found that a particular form of carbon molecules can penetrate well into the core cell that in the near future can be used in pharmaceuticals and vaccines. Today carbon molecules that are called Nano carbon are used only to carry small peptides to the cell cores, but the researchers hope to be able to use them in cancer therapy, gene therapy, and vaccination. Alberto Bianco from Centre national de la richerchescientifique (CNRS) in French says that the researchers are in the early stages of their research and since it seems that Nano can penetrate into the cell core, this property can be used to carry built genes and medication into the specific part of the cell. Bianco research team heated Nano indimethylformamide for a few days, followed by fitting a shorter ethylene glycol TEG and then small peptide molecules were connected to TEG and when the Nano quickly moved toward core when mixed with discovered human fibroblast cell.

What has empowered carbon nanotubes is the ability to pass through the wall of cell with no damage to the cellular tissue. This is known as nano-needle. The needle-like carbon makes it easily penetrate through the membrane and provide molecular concentrations of medication through nano-needle mechanisms. In addition, the functionalized carbon can be dispersed in water and since are compatible with biological fluids can be excreted through the kidneys quickly and systematically.

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An interaction between biocompatible carbon nanotubes and cells should be created to use carbon Nano-tubes in drug delivery. This will be achieved through functionalization of covalent or non-covalent surface of these structures using water-soluble carrier carbon Nano-tubes. Covalent functionalization of carbon Nano-tubes can be done in two ways: 1) ester or amide oxide Nano-tubes and 2) covalent bond of functional groups to a Nano wall.

Acquired immune deficiency syndrome (AIDS) is the biggest challenge of the 21st century. In recent years HIV-1 integrase (IN) has become an attractive target for the design of antiretroviral drugs. First, IN inhibitor was approved for clinical use, Raltegravir has made IN inhibitors pharmacological viability and signals of new antiretroviral medication generation valid. Raltegravir and other IN inhibitors successful development have influenced the strategy of IN inhibitors design [6, 7]. This has led to the identification of several strong inhibitors in recent years.

Zidovudine is a medicine widely used in the fight against HIV or AIDS. It's combine it with nanotubes is a promising way to overcome the increasing the cellular uptake and internalized by functionalized carbon nanotubes, respectively.

General methods for improving the ability to spread and improve the capabilities of carbon nanotubes are issuing chemical agents on the nanotubes, which allows covalent and non-covalent chemical bonding between nanotubes and provides relevant material. In addition, the use of functionalized nanotubes to deliver anti-cancer, anti-bacterial and anti-viral agents still has not been fully investigated. Developments are regarding the transmission of one or more therapeutic agents as an important factor in the treatment of cancer and infectious diseases of various kinds [8].

Interaction of anticancer drugs such as Cisplatin, Carboplatin, Paclitaxel, and Methotrexate and anti-corruption medications as Nimesulide with nanotubes have been studied and published. In addition, theoretical studies on energy, structure and electronic properties of interactions between the nanotubes and Nifedipine, cholesterol and nucleic bases suggested that carbon nanotubes be used for the transmission of such medications [9, 10].Thus, the understanding of nanotube interactions with Zidovudine can be a good guide to better understanding of drug interactions with nanotubes and evaluate changes to improve effectiveness or reduce its toxicity.

COMPUTATIONAL DETAILS

Density functional theory (DFT) was used in the current study to evaluate the interactions and all calculations were performed using Gaussian 09 software. Calculations were performed using the B3LYP level of theory and basis set6-31G(d,p) molecule drugs (Zidovudine), single walled carbon nanotubes (CNT) and functionalized nanotubes (f-CNT) for all configurations. All configurations have been tested. All configurations in the gas-solvent phase (water) were applied with the Polarizable Continuum Modulation (PCM) method. This section examines the interaction of single-walled carbon nanotubes (5 , 5) with the medication Zidovudine. This section applies ZIDO goes for the medication Zidovudine, CNT goes for pure carbon nanotubes and f-CNT goes for functionalized carbon nanotubes with COOH [11, 12].

RESULTS AND DISCUSSION

Structures optimization

For the calculation of the interaction of zidovudine with functionalized carbon nanotubes (5, 5) the optimal structure of each is separately required. Zidovudine, carbon nanotubes (5,5) and functionalized nanotubes in the gas phase and solvent phase are individually optimized. Five configurations were considered to investigate the interaction of nanotubes with Zidovudine. optimized configuration structure include CNT-ZIDO1, CNT-ZIDO2, CNT-ZIDO3, f-CNT-ZIDO1 and f-CNT-ZIDO2 in gas and solvent (water) phase, in each of these configurations Zidovudine interacts from Deoxythymidine ring with π-π interaction; RCH2OH groups oxygen and van der Waals interactions from the N3 group with natural carbon nanotubes (CNT), and also has covalent binding from alcohol group and deoxythymidine ring. Table 1 shows the absolute energy values for these configurations.

Binding energy (BE) for each Complex and to determine their relative stability, taking into account the interaction of nanotubes with medication is calculated as follows:

Equation 1:

$$BE = E_{CNT-ZIDO} - (E_{CNT} + E_{ZIDO})$$

Table 1- Absolute energy values related to medicine and nanotubes and different configurations according to Harter in the gas phase and solvent phase.

	E	BE	E_HOMO	E_LUMO	E gap
		GAS			
ZIDO	-963.5187801		-6.65133	-1.32194	5.329392
CNT	-3428.46649		-4.77509	-3.73262	1.042476
CNT-ZIDO1	-4391.987482	-5.80295	-4.85972	-3.81534	1.044381
CNT-ZIDO2	-4391.988709	-9.01984	-4.75387	-3.71003	1.043837
CNT-ZIDO3	-4391.986759	-3.90596	-4.62434	-3.53179	1.092546
FCNT	-3617.605573		-4.69182	-3.36798	0.91431
FCNTZIDO1	-4504.662065		-4.61019	-3.29587	0.913493
FCNTZIDO2	-4504.699969		-4.78298	-3.46458	0.914582
		PCM			
ZIDO-PCM	)63.538022		-6.5120	-1.0825	5.4295
CNT-PCM	-3428.470560		-4.6559	-3.6270	1.0289
CNT-ZIDO1PCM	-4392.009467	-2.3214	-4.6652	-3.6360	1.0291
CNT-ZIDO2PCM	-4392.010411	-4.7959	-4.6597	-3.6306	1.0291
CNT-ZIDO3PCM	-4392.008811	-0.6010	-4.6532	-3.6251	1.0281
FCNT-PCM	-3617.614438		-4.5884	-3.2695	1.3189
FCNTZIDO1-PCM	-4504.685053		-4.5941	-3.2765	1.3176
FCNTZIDO2-PCM	-		-	-	-

Where,$E_{CNT-ZIDO}$ is the electron energy of the whole medication placed on pure nanotube or functionalized nanotube, E_{CNT} and $E_{ZIDO}$are the total carbon nanotubes optimized electron energy and the total optimized medicine electron energy, respectively. BE can be obtained for configurations with van der Waals interactions and relative stability of this configuration to be determined using the above formula and energy values in Table 1, so that the more negative BE, the configuration is more stable [13, 14].

BE Values, for configuration CNT-ZIDO 1, CNT-ZIDO 2 and CNT-ZIDO 3, , for a gaseous state is 5.80295kJ / mol-, -9.01984kJ / mol, -3.90596kJ / mol, respectively. According to energies calculated in Table 1 and BE values, the most stable configuration in the gas phase for van der Waals interactions is CNT-ZIDO 2.

By changing the solvent or by changing the dielectric environment sustainability trends will be similar to the values for the configuration CNT-ZIDO1PCM, CNT-ZIDO2PCM and CNT-ZIDO3PCM, as 2.3214kJ / mol-, -4.7959kJ / mol, -0.6010kJ / mol, respectively.But by comparing values for two phases we observe that interaction is weaker in the solvent phase with lower interaction energy levels.

According to Table (1) it seems that f-CNT-ZIDO1 configuration in the solvent phase has more stability than that of f-CNT-ZIDO2, so that the f-CNT-ZIDO2 configuration lacks anoptimal structure.

Review the overall reactive descriptors

To evaluate the overall reactive descriptors, first the overall descriptors; Electrophilicity ω, electronic chemical potential μ, η hardness and softness S of reactive molecules is calculated and then the data is compared. The calculation of all reactive descriptors is possible using density functional theory such as Electrophilicity ω, electronic chemical potential μ, η hardness and softness S. The following equation was used to calculate the quantum molecular descriptors that Table 2 shows all configuration values.

$$\mu = -\frac{(1+A)}{z} \quad (2)$$

$$\chi = -\mu \quad (3)$$

$$\eta = \frac{1-A}{2} \quad (4)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

$$E_{gap} = E_{LUMO} - E_{HOMO} \quad (6)$$

Where, in the above equations, μ is the chemical potential and χ is negative chemical potential that represents Electronegativity. η or hardness can be estimated from Koopman theory because$I = -E_{HOMO}$is the ionization energy and $A = -E_{LUMO}$is the amount of molecule Electron Affinity [47, 74-71]. HOMO and LUMO energy difference isobtained from Eq. (6) that is called energy gap (Egap). The more energy gap the more stable structure will be. E_gap represents less reactivity or instability of complex [15].

According to Table (2) pure Zidovudine E_gap in the gaseous phase is 5.3294 eV, which is more compared to the CNT-ZIDO1, CNT-ZIDO2, f-CNTZIDO1 and f-CNTZIDO2 configurations; it seems that the position of Zidovudine on carbon nanotubes increases reactivity, with exposure to solvent phase E_gap amount of Zidovudine increases to9.649 kJ / mol, which states Zidovudine structure stability increase and reduced reactivity.

The E_gap for CNT-ZIDO1, CNT-ZIDO2, f-CNTZIDO1 and f-CNTZIDO2 configurations in the gas phase is 1.0444 eV, 1.0438 eV,1.0925eV, 0.9135 eV, 0.9146 eV, respectively. These values show, f-CNTZIDO1 and f-CNTZIDO2 configurations are more responsive than the van der Waals three configurations. But compared to ZIDO, it seems that configurations are more active.

According to the data in Table 2, Zidovudine ω in the gas phase is equal to 2.98 and Electrophilicity reduces by changing the dielectric environment and will be almost constant at about 2.66, the value for the CNT-ZIDO1, CNT -ZIDO2, CNT-ZIDO3, f-CNT-ZIDO1 and f-CNT-ZIDO2 configurations is 18.01, 17.16, 15.22, 11.89 and 12.90, respectively in the gas phase, which reactivity increases with increasing ω for configurations.

The increased reactivity for configuration is as follows:

$$\begin{aligned} CNT-ZID\,1 > CNT-ZIDO2 > CNT-ZIDO3 \\ > f-CNT-ZIDO2 \\ > f-CNT-ZIDO1 \end{aligned}$$

It seems that the Zidovudine place on carbon nanotubes increases reactivity. E_gap data show that f-CNT-ZIDO1, unlike other complexes; is more stable, with more electron affinity and less ionization energy than other configurations when exposed to solvent phase.

As mentioned, we functionalize carbon nanotubes to reduce toxicity of and prevent the accumulation. Now, if we consider it toxic with ω limit of pure carbon nanotubes that is 17.36 in the gas phase and 16.67 in the solvent phase we can go on that toxicity is reduced with the functionalization of nanotubes (ω = 11.89) and stability increased (E_gap = 0.9135) compared to than non-functionalized carbon nanotubes. So f-CNT-ZIDO1 in the gas phase is more volatile than three covalent complexes, but the ω value for CNT-ZIDO 2 configuration is less than the amount of nanotubes, which indicates decreased toxicity of configuration as a result of covalent bond. On the other hand, f-CNT-ZIDO1, being in solvent phase is more stable than three other Van der Waals complexes with little changes in reactivity compared to the other complexes.

As discussed, in the f-CNT-ZIDO1 configuration the ω is less than the natural carbon nanotubes and is about functionalized nanotubes, which is equal to 11.75. This means that, for drug delivery by the nanotubes, the best way is to connect the drug to functionalized nanotubes.

Accordingly, the solvent can have a direct impact on the stability and toxicity of configurations and affect the proper configuration for drug delivery on the nanotubes.

HOMO and LUMO orbital review in configurations

Given that the effect of solvents on the configuration is not so that can be comparable in figures, thus the configurations in the gas phase and solvent phase (water solvent) will be reviewed. Fig. 1 to 18 show HOMO and LUMO orbital for different configurations.

the HOMO orbital of CNT-ZIDO 1 configuration in the gas phase in Fig. 1 show, HOMO orbital focus on Zidovudine is more on two groups of NH and C = O groups. This indicates that the two groups to focus on interact with the nanotubes, the group C = O has a more interaction share considering that orbital focus on the O93 atomic is greater.

According to Fig. 2 LUMO orbital focus is on the same chain which refer to that enabled LUMO orbital on the N97, indicates that this group plays the role of the recipient due to the electrons giving of those chain to aromatic interactions between the nanotubes and Zidovudine.

Table 2. the values of molecular descriptors differ in different dielectrics that all values are expressed in eV

	I	A	μ	η	χ	ω
			GAS			
ZIDO	6.6513	1.3219	-3.9866	2.6647	3.9866	2.98
CNT	4.7751	3.7326	-4.2539	0.5212	4.2539	17.36
CNT-ZIDO1	4.8597	3.8153	-4.3375	0.5222	4.3375	18.01
CNT-ZIDO2	4.7539	3.7100	-4.2319	0.5219	4.2319	17.16
CNT-ZIDO3	4.6243	3.5318	-4.0781	0.5463	4.0781	15.22
FCNT	4.6918	3.3680	-4.0299	0.6619	4.0299	12.27
FCNTZIDO1	4.6102	3.2959	-3.9530	0.6572	3.9530	11.89
FCNTZIDO2	4.7830	3.4646	-4.1238	0.6592	4.1238	12.90
			PCM			
ZIDO-PCM	6.5120	1.0825	-3.7972	2.7148	3.7972	2.66
CNT-PCM	4.6559	3.6270	-4.1415	0.5144	4.1415	16.67
CNT-ZIDO1PCM	4.6652	3.6360	-4.1506	0.5146	4.1506	16.74
CNT-ZIDO2PCM	4.6597	3.6306	-4.1451	0.5146	4.1451	16.70
CNT-ZIDO3PCM	4.6532	3.6251	-4.1392	0.5140	4.1392	16.67
FCNT-PCM	4.5884	3.2695	-3.9289	0.6595	3.9289	11.70
FCNTZIDO1-PCM	4.5941	3.2765	-3.9353	0.6588	3.9353	11.75
FCNTZIDO2-PCM	-	-	-	-	-	-

Fig. 11, 12 depict HOMO and LUMO orbital and CNT-ZIDO 1 configuration in the water phase with dielectric of78.35. Increased dielectric activates the interactions between carbon nanotubes and Zidovudine. Increased interaction intensity reflects the fact that, interactions greatly increased by increasing the environment dielectric. It seems that by increasing this effect, the group NH (with Atom N97) is more under the effect of the carbon nanotube electron donor properties.

Fig. 3 displays the HOMO orbital concentration in CNT-ZIDO 2 configuration in the gas phase, indicating the interaction between alcohol groups O92, O91 erupted five-member ring and Pyrimidine ring. HOMO orbital more focus on the O93 atom represents electron donor property of 093 atoms compared to 092 atoms. As is known, Pyrimidine ring chain -C105-C107-C108-N97-C106-N95- is also in interaction with carbon nanotubes. Fig. 4 shows the LUMO orbital focus with the Pyrimidine ring is of the most focus of the orbital; on the other hand LUMO orbital focus on the 091 atoms of erupted ring represents more Electrophilicity than 092. The effect of solvent intensifies interactions and electron donor or receiver nature of Zidovudine (Fig. 13,14).

Fig. 5 shows HOMO orbital focus on CNT-ZIDO3 configuration. The orbital display indicates two interacting of O93 atoms and on interaction between functionalized nanotubes and N3. It seems that the interaction between the N3 and nanotubes is stronger than the interaction of O93 atom of the pyrimidine ring and carbon nanotubes. Fig. 6 shows that, C106 = O93 has to interact with carbon nanotubes, which acts as the electron receiver. The significant point is that adding a solvent effect (Fig. 15, 16), increases the interaction of N3groups. But it seems that the C106 = O93 group interaction lowers

solvent effect and it can be concluded that the dominant interaction is the interaction of N3 group.

Covalent F-CNT-ZIDO1 configuration (Fig. 7, 8) focus is on carbon and nitrogen atoms in the Pyrimidine ring junction with Zidovudine, It seems that in f-CNT-ZIDO1 configuration The effect of solvent in handling a large share HOMO and LUMO orbitals electron transfer within the structure and load in the configuration (Fig. 17,18).

Covalent f-CNT-ZIDO2 configuration, as mentioned before, has a more stable structure in the gas phase in term of energy, but solvent phase configuration has no optimal point. Fig. 9 clearly shows the orbital accumulation on the C121-O92 link says that plays no significant role in electron transfer within the structure despite good strong bond. This can be a main reason for that transfer from Alcohol Group is never possible. Fig. 10 shows LOMO orbitals on F-CNT-ZIDO2 configuration in the gas phase.

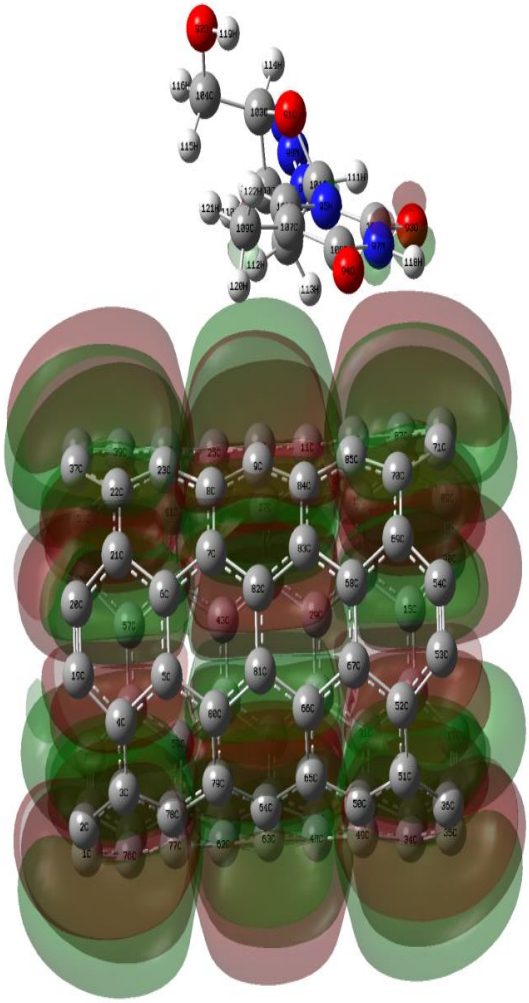

Fig. 1- HOMO orbitals on CNT-ZIDO1 configuration in the gas phase.

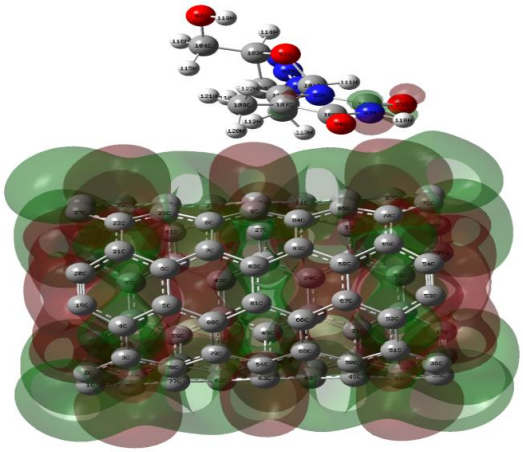

Fig. 2- LOMO orbitals on CNT-ZIDO1 configuration in the gas phase.

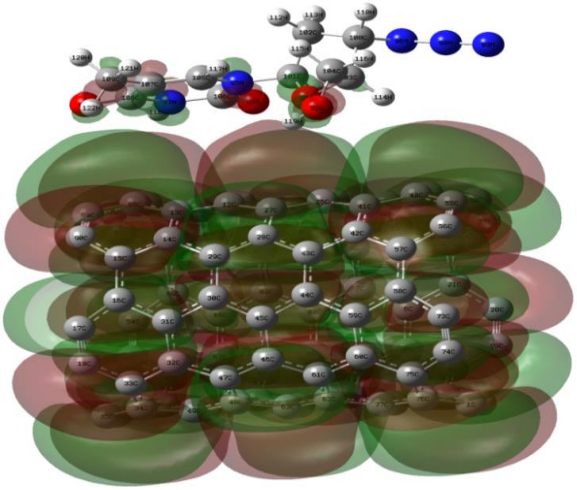

Fig. 3- HOMO orbitals on CNT-ZIDO2 configuration in the gas phase

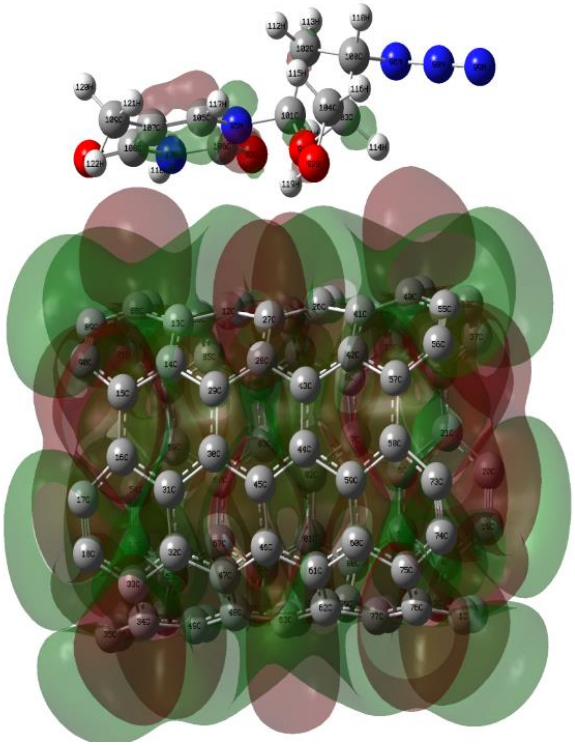

Fig. 4- LOMO orbitals on CNT-ZIDO2 configuration in the gas phase

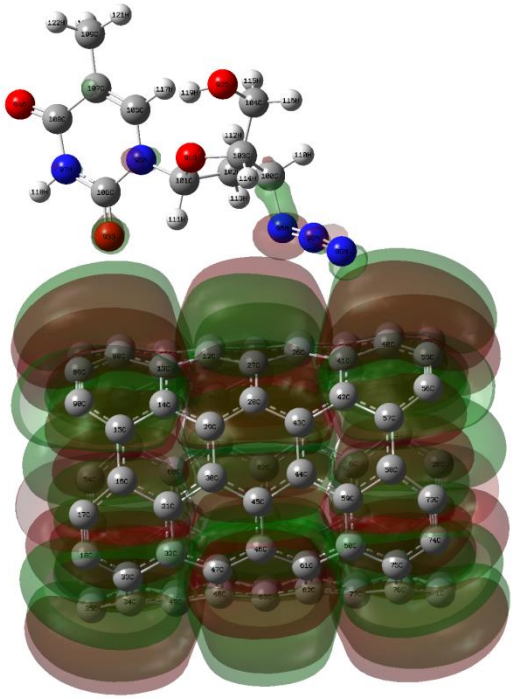

Fig. 5- HOMO orbitals on CNT-ZIDO3 configuration in the gas phase.

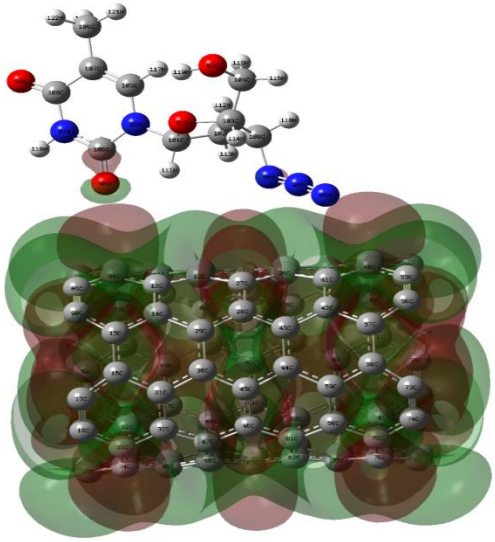

Fig. 6- LOMO orbitals on CNT-ZIDO3 configuration in the gas phase.

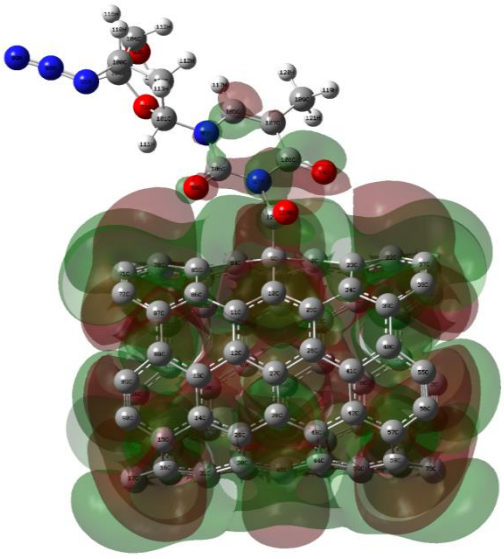

Fig. 7- HOMO orbitals on F-CNT-ZIDO1 configuration in the gas phase.

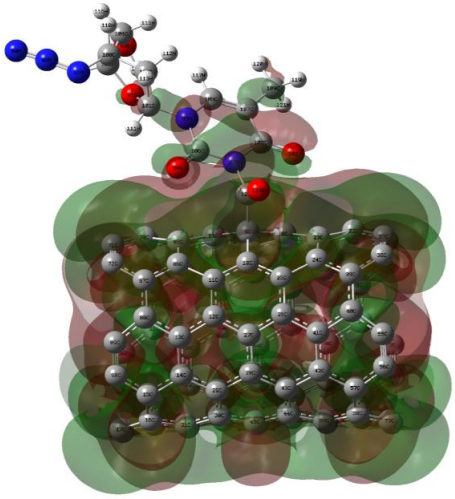

Fig. 8- LOMO orbitals on F-CNT-ZIDO1 configuration in the gas phase.

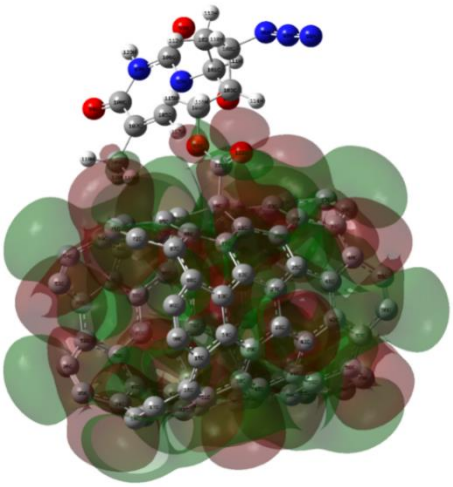

Fig. 9- HOMO orbitals on F-CNT-ZIDO2 configuration in the gas phase.

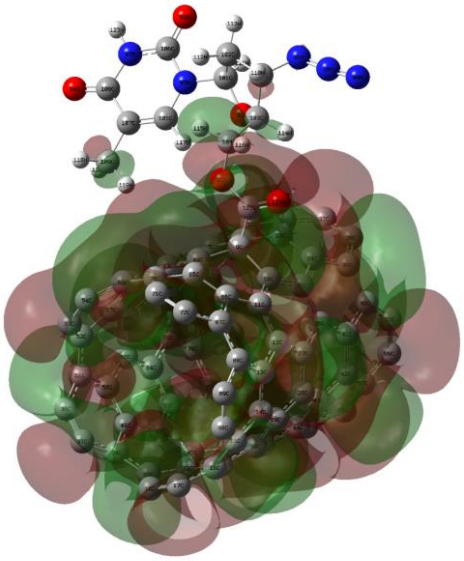

Fig. 10- LOMO orbitals on F-CNT-ZIDO2 configuration in the gas phase.

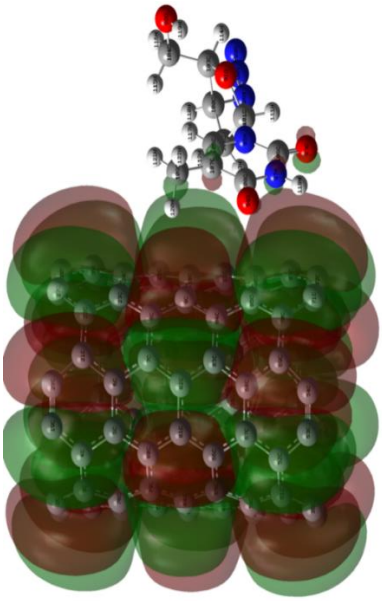

Fig. 11- HOMO orbitals on CNT-ZIDO1 configuration in water $\boldsymbol{\varepsilon = 78.35}$

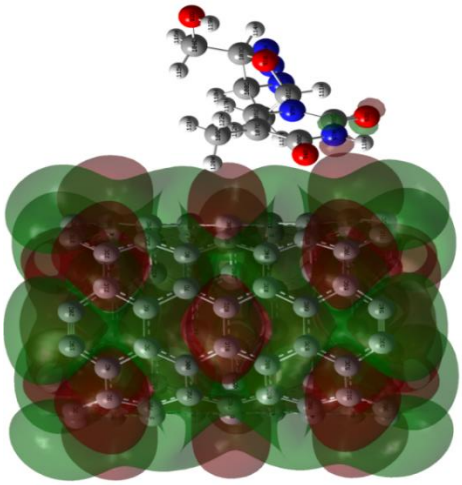

Fig. 12- LOMO orbitals on CNT-ZIDO1 configuration in water $\boldsymbol{\varepsilon = 78.35}$.

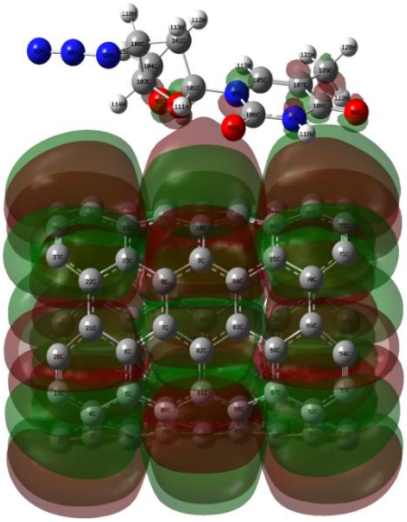

Fig. 13- HOMO orbitals on CNT-ZIDO2 configuration in water $\boldsymbol{\varepsilon = 78.35}$.

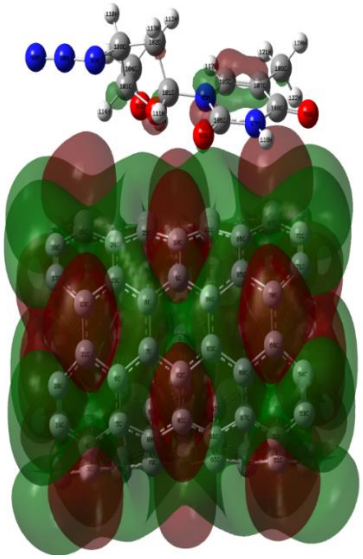

Fig. 14- LOMO orbitals on CNT-ZIDO2 configuration in water $\boldsymbol{\varepsilon = 78.35.}$

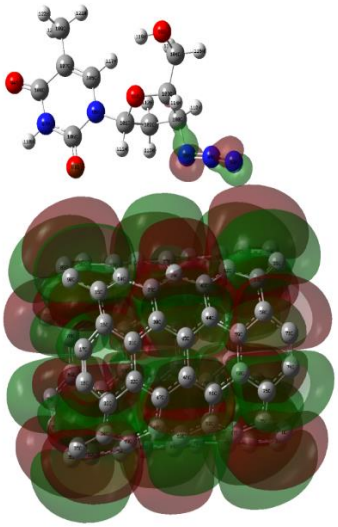

Fig. 15- HOMO orbitals on CNT-ZIDO3 configuration in water $\boldsymbol{\varepsilon = 78.35}$

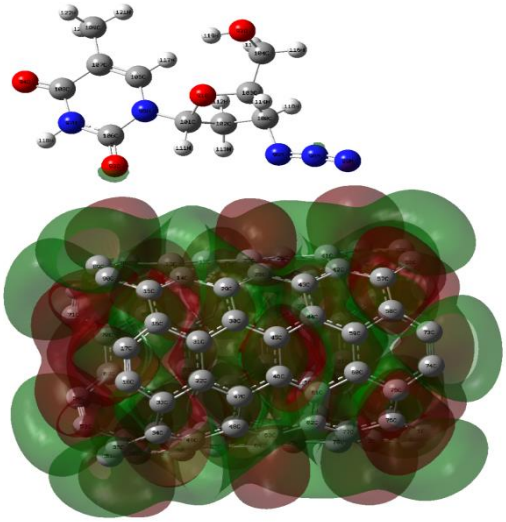

Fig. 16- LOMO orbitals on CNT-ZIDO3 configuration in water $\boldsymbol{\varepsilon = 78.35}$

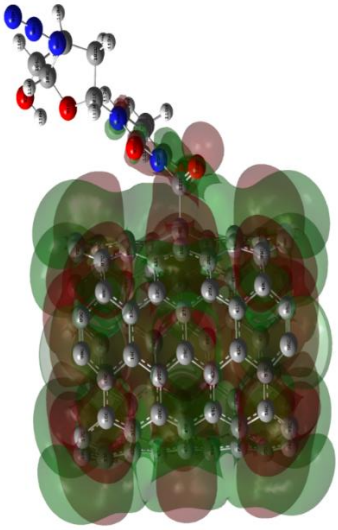

Fig. 17- HOMO orbitals on CNT-Dap1 configuration in water $\boldsymbol{\varepsilon = 78.35}$

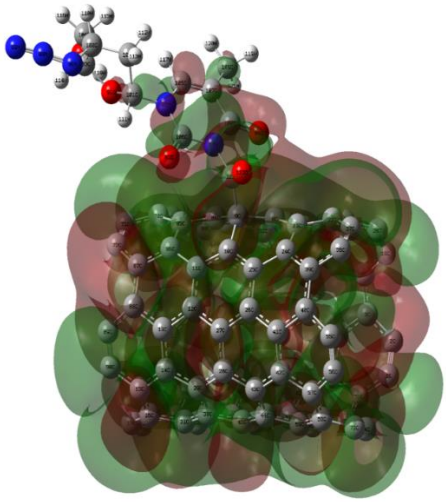

Fig. 18- LOMO orbitals on CNT-Dap1 configuration in water $\boldsymbol{\varepsilon = 78.35.}$

CONCLUSION

We can conclude that configurationsthat usenon-functionalized carbon nanotubes show direct effect of the solvent and the interaction between the nanotubes and Zidovudine is under the effect of solvent. On the other hand the interaction between functionalized nanotubes and Zidovudine in a covalent bond of Zidovudine and functional groups on the nanotubes shows that the best type of Zidovudine and nanotubes bond is covalent. It should be noted as a conclusion that the presence of 2 ketones in the Pyrimidine – 2 structures in $f - CNT - ZIDO1$ covalent structure leads to increased electron affinity of nitrogen in NH group in the ring with more acidic property than other hydrogen contents. Generally, it can be predicted that the binding of medication occurs through NH- group of Pyrimidine ring-2,4-dionne.

It should be noted that in HOMO and LUMO orbitals the green color indicates a negative charge and the red indicates a positive charge.

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