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ORIGINAL RESEARCH PAPER

Theoretical study of functionalized single-walled carbon nanotube (5, 5) with Mitoxantrone drug

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ABSTRACT

Objective(s): First principles calculations were performed to study four multiple sclerosis drugs namely, Ampyra, Fingolimod, Mitoxantrone and Eliprodil in gas and liquid phases using Density Functional Theory (DFT). Computational chemistry simulations were carried out to compare calculated quantum chemical parameters for Ampyra, Fingolimod, Mitoxantrone and Eliprodil.

Materials and Methods: All calculations were performed using DMol^3 code which is based on DFT. The Double Numerical basis set with Polarization functions (DNP) was used.

Results: Mitoxantrone has highest HOMO energy, global softness, solvation energy and molecular mass and lowest LUMO energy, energy gap, global hardness and total energy in comparison to Ampyra, Fingolimod and Eliprodil in gas and solvent phases. Calculations were carried out to study the interaction of covalently binding Mitoxantrone to functionalized carbon nanotube. The Mitoxantrone local reactivity was studied through the Fukui indices in order to predict both the reactive centers and the possible sites of nucleophilic and electrophilic attacks. The Mitoxantrone binding energy is calculated to be 6.507 eV in gas phase and -9.943 eV in solvent phase that is a decrease in BE as the drug phase changes from gas to liquid.

Conclusion: The simulation results show Mitoxantrone is quite a reactive drug. The quantum chemical parameters of pristine nanotube and f-SWNT-Mitoxantrone showed that reactivity of f-SWNT-Mitoxantrone increased in comparison to pristine nanotube in both phases.

Keywords: *Density Functional Theory Calculations, Functionalized Carbon Nanotube, Multiple Sclerosis Drugs*

INTRODUCTION

Multiple Sclerosis (MS) is a chronic degenerative disease of the central nervous system that causes inflammation, muscular weakness and a loss of motor coordination [1]. MS affects women more than men and is most commonly diagnosed between ages 20 and 40 but can be seen at any age [2]. It is estimated that 2,500,000 people in the world have MS, MS can progress in different ways [3] . Some people with MS may become seriously disabled. Others may have one or two attacks and then remain symptom-free for the rest of their lives. The frequency and severity of attacks cannot be predicted [4]. Different types of drugs may be prescribed for treatment of different categories of MS. Single-Walled Carbon Nanotubes (SWNTs) with their interesting properties have opened up several fields in nanotechnology since their discovery [5-9]. The SWANTs unique properties have made them useful in different kinds of applications [10-12], in particular their excellent role as carriers of drugs with a highly site-selective delivery and sensitivity [13-15].

SWNTs have the ability to deliver bioactive molecules across cell membranes and even into the cell nuclei because of their very high specific surface areas [16-18]. Because nanotubes can release drugs into the tissue cells without damaging the healthy cells, it is necessary to understand the structural properties of the drug–SWNTs complexes which may lead to accelerate the optimal development of SWNTs as new effective drug transporters. Interaction of anticancer drug molecules like cisplatin [18], carboplatin [19],

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paclitaxel[13], methotrexate [20] and doxorubicin [21, 22] with carbon nanotubes are well reported. It seems that it is necessary to investigate the adsorption properties of MS drugs on SWNT in order to perform further pharmacological studies. The adsorption of mitoxantrone to functionalized multiwall carbon nanotubes (MWCNTs) are represented a comparative analysis of its in vitro suitability as a drug delivery system against cancer and non-neoplastic cells are presented [23]. In this paper, a theoretical study on structural properties and reactivity of four MS drugs are presented. These drugs are Ampyra, Fingolimod, Mitoxantrone and Eliprodil, hereinafter referred to as the four MS drugs. We concluded that the Mitoxantrone is the most reactive drug based on Fukui functions and global reactivity descriptors. The changes in electronic and structural properties of the Mitoxantrone upon its interaction with functionalized SWNTs have been reported in both gas and solvent phases. The calculations were formed based on DFT. DFT method is the standard and the most widely used theoretical techniques for electronic structure calculations. It is the computational method and application in the physical sciences, quantum chemistry, physical sciences and systems of biological.

MATERIALS AND METHODS

Computational methods

All calculations were performed using DMol^3 code[24] which is based on DFT. The Double Numerical basis set with Polarization functions (DNP) was used. This basis set is comparable with the Gaussian 6-31G (d, p). The density function is treated within the generalized gradient approximation with exchange correlation potential parameterized by Wang and Perdew method (GGA-PW91) [25] . The structures and the optimized configurations of the four MS drugs are shown in Fig. 1. Using the optimized geometries, the energy of the Highest Occupied Molecular Orbital (E_{HOMO}), the energy of the Lowest Unoccupied Molecular Orbital (E_{LUMO}), the energy gap, (“E), the Ionization Potential (IP), the Electron Affinity (EA), the global hardness (η), the global softness (Γ), the Chemical Potential (H), the dipole moment (Ό), the Electrophilicity (ω), the fraction of electron transferred (“N) and the Total Negative Charge (TNC) [26, 27] were calculated for the four MS drug molecules and also for functionalized SWNT (f-SWANT) attached to Mitoxantrone drug (see Table 1). Full geometry optimization was performed for each drug in both gas and solvent phases. Table 1 shows the optimized geometries of the four MS drugs. The effect of solvent in water was estimated by the Conductor-like Screening Model (COSMO) [28] .The dielectric constant of water was taken as 78.54 in this model. The dielectric solvation energies of the four MS drugs along with f-SWNT attached to Pyrazinamide anti-tubercular drug was computed.

In simulation studies, the four MS drugs were attached covalently to functionalized Carbon Nanotubes (f-CNTs). The C (5, 5) pristine carbon nanotubes, which were used in the carbon nanotube functionalization, contain 80 carbon atoms and 20 hydrogen atoms ($C_{80}H_{20}$). The C (5, 5) carbon nanotubes is the most reactive nanotube [29] .In this COSMO model, the four MS drugs were also attached to functionalized nanotubes. Based on a previous Fukui indices analysis of electrophilic sites, we determined the attaching sites of the drugs to the f-CNTs.

RESULTS AND DISCUSSION

Drugs

The structures and the optimized configurations of the four MS drugs have been illustrated in Fig. 1. The drugs conformers were considered to be minima based on the absence of imaginary frequencies. Table 1 shows the significant bond lengths and bond angles of the studied drugs in both gas and solvent phases.

The Fukui indices permit the distinction of the reactive regions and the nucleophilic and electrophilic behavior of a molecule, as well as its chemical reactivity. For a finite system, when a molecule is accepting electrons, it has the Fukui index for nucleophilic attack, f^+, and when the molecule is donating electrons, it has the Fukui index for electrophilic attack, f^-. Therefore HOMO and LUMO are related to negative and positive Fukui indices, respectively. The Fukui functions allows prediction where the most electrophilic and nucleophilic sites of the drug molecules are. The HOMO, LUMO and the Fukui functions (Mulliken) for the studied drugs in the gas and solvent phases are shown in Fig.s 2 and 3, respectively.

Ampyra

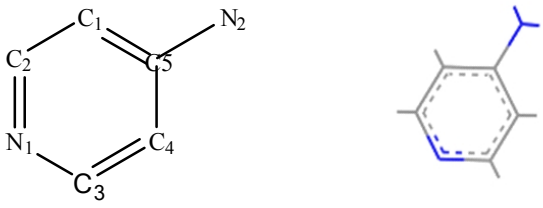
Ampyra (also called dalfampridine or fampridine) (IUPAC name: Pyridin-4-amine) is a drug that has been found to improve walking in patients with MS. This improvement was demonstrated by an increase in walking speed. Table 1 shows the bond lengths and the bond angles of the four MS drugs in the gas phase

are approximately equal to their corresponding bond lengths and bond angles in solvent phase. We have noticed that the differences between the nitrogen bond lengths and bond angles in the two phases are greater than non-nitrogen bond lengths and bond angles. The difference between the C5-N2 bond lengths in the two phases is 0.01 Å but this difference for the C5-C1 is 0.004 Å. A possible explanation for this phenomenon is that the solvent has more influence on the polarization of nitrogen atoms than the other atoms.

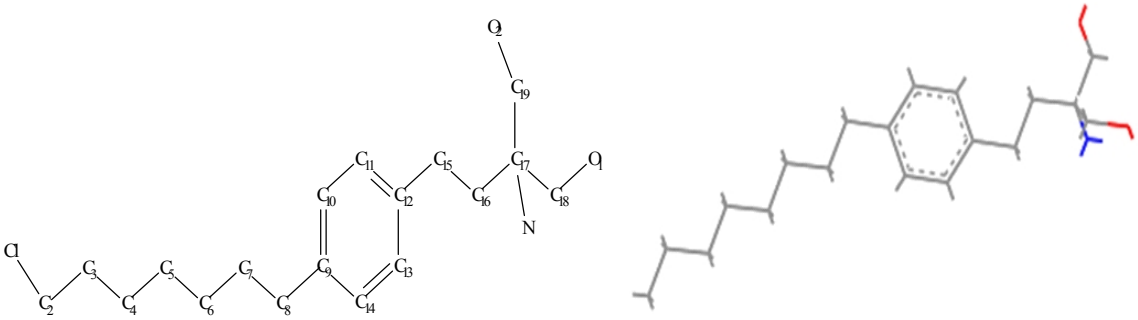
Fig. 2 shows that the HOMO is almost distributed throughout the entire Ampyra molecule, while the LUMO has an anti-bonding character and are strongly distributed across this molecule with the exception of the NH_2 group in the gas and solvent phases. In Fig. 3, the C2, C4, C5, N1 and N2 atoms are nucleophilic sites of the Ampyra molecule in gas phase and the Fukui indices (f^-) are almost throughout the entire Ampyra molecule in solvent phase. This Fig. show that the Fukui indices (f^+) are almost throughout the entire Ampyra molecule in both phases. The N1 and C2 atoms have the highest nucleophilic electron density and the highest electrophilic electron density in gas phase. The N2 and C2 atoms have the highest nucleophilic electron density and the highest electrophilic electron density in solvent phase.

Table 1. Comparison of the bond length and bond angles in gas and solvent phases for species of the studies compounds

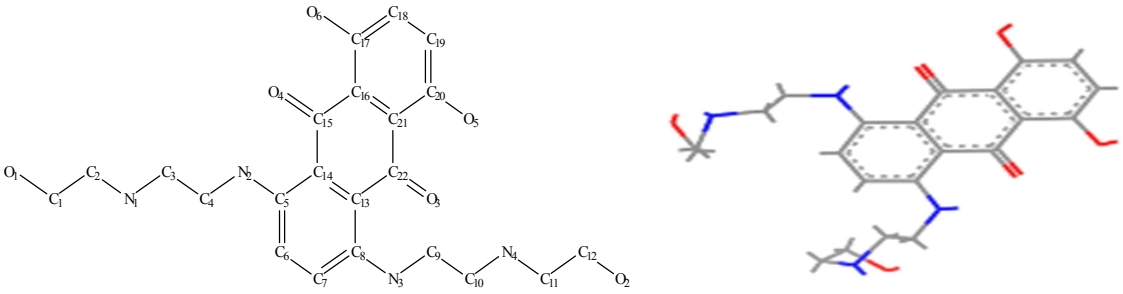
Ampyra			Fingolimod		
Bond lengths(Å)	Gas	Solvent	Bond lengths(Å)	Gas	Solvent
C1-C2	1.390	1.388	C1-C2	1.520	1.521
C2-N1	1.343	1.350	C4-C5	1.519	1.519
C3-C4	1.389	1.387	C7-C8	1.520	1.520
C1-C5	1.404	1.408	C9-C10	1.399	1.400
C5-N2	1.382	1.372	C12-C13	1.398	1.399
Bond angles(°)			C13-C14		
C1-C2-N1	124.661	124.681	C12-C15	1.507	1.507
N1-C3-C4	124.699	124.735	C15-C16	1.521	1.522
C1-C5-N2	121.451	121.552	C17-C19	1.526	1.526
			C17-C18	1.537	1.535
Mitoxantrone			C17-N	1.471	1.474
Bond lengths(Å)	Gas	Solvent	C19-O2	1.431	1.434
C1-O1	1.417	1.429	C18-O1	1.429	1.434
C2-N1	1.465	1.467	Bond angles(°)		
C3-C4	1.534	1.533	C17-C18-O1	112.599	112.610
C4-N2	1.442	1.446	C17-C19-O2	109.941	110.959
C5-C6	1.419	1.423	C12-C15-C16	114.603	114.697
C7-C8	1.419	1.423	C14-C9-C10	117.964	117.919
C8-N3	1.360	1.356	C1-C2-C3	112.466	112.363
C10-N4	1.456	1.462	C4-C5-C6	113.989	113.784
C12-O2	1.431	1.438	C6-C7-C8	113.553	113.216
C13-C14	1.429	1.436	Eliprodil		
C14-C15	1.459	1.453	Bond lengths(Å)	Gas	Solvent
O4-C15	1.257	1.266	F-C1	1.365	1.374
C16-C21	1.429	1.434	C1-C6	1.388	1.388
O3-C22	1.257	1.266	C5-C4	1.399	1.400
C16-C17	1.415	1.415	C2-C3	1.394	1.395
C17-O6	1.365	1.366	C7-C8	1.533	1.533
C18-C19	1.381	1.379	C9-C10	1.515	1.515
C20-O5	1.365	1.366	C10-N	1.464	1.469
Bond angles(°)			N-C13	1.456	1.517
C1-C2-N1	O-C14	1.444	O-C14	1.444	1.459
C3-C4-N2	C19-C20	1.391	C19-C20	1.391	1.449
C6-C7-C8	C18-Cl	1.747	C18-Cl	1.747	1.391
N3-C9-C10	N-C13	112.752	Bond angles(°)		
C11-C12-O2	O-C14	111.750	F-C1-C6	118.960	118.729
C5-C14-C13	120.028	119.884	C5-C4-C7	121.099	121.063
O4-C15-C16	119.809	119.835	C9-C10-N	112.162	112.179
C16-C21-C20	119.386	119.115	N-C13-C14	115.211	115.773
C18-C17-O6	118.396	117.751	O-C13-C15	58.036	58.325
O5-C20-C21	121.927	122.186	C16-C17-C18	119.117	118.807
O5-C20-C19	118.377	117.731	Cl-C18-C19	119.480	119.232



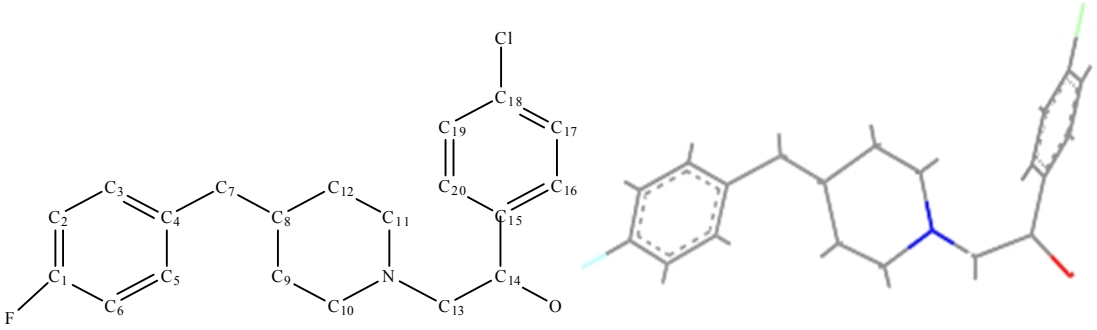
Ampyra



Fingolimod



Mitoxantrone



Eliprodil

Fig.1. The structures and the optimized geometries of the drugs under study

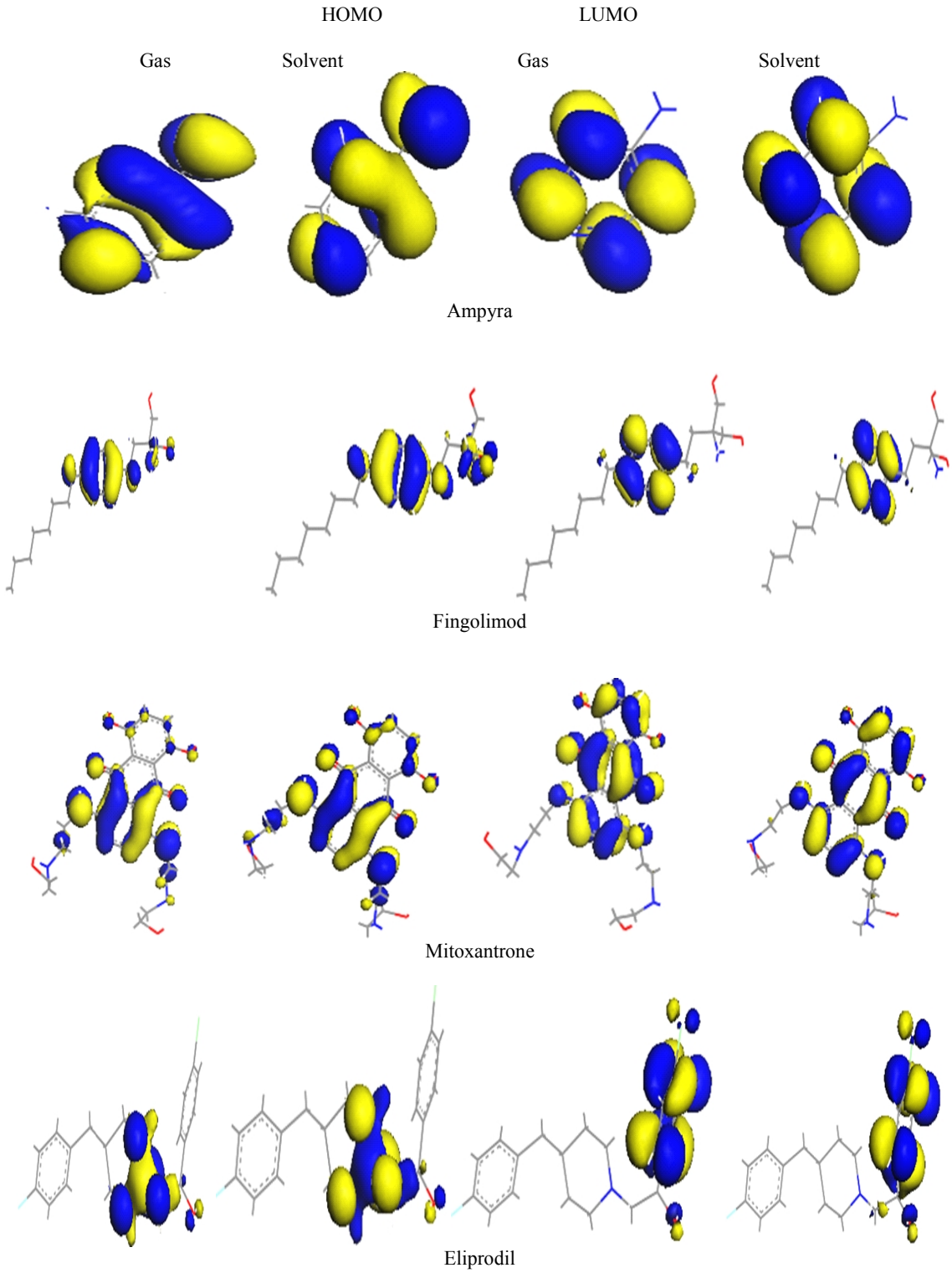


Fig. 2. The HOMO and the LUMO for the studied drugs in gas and solvent

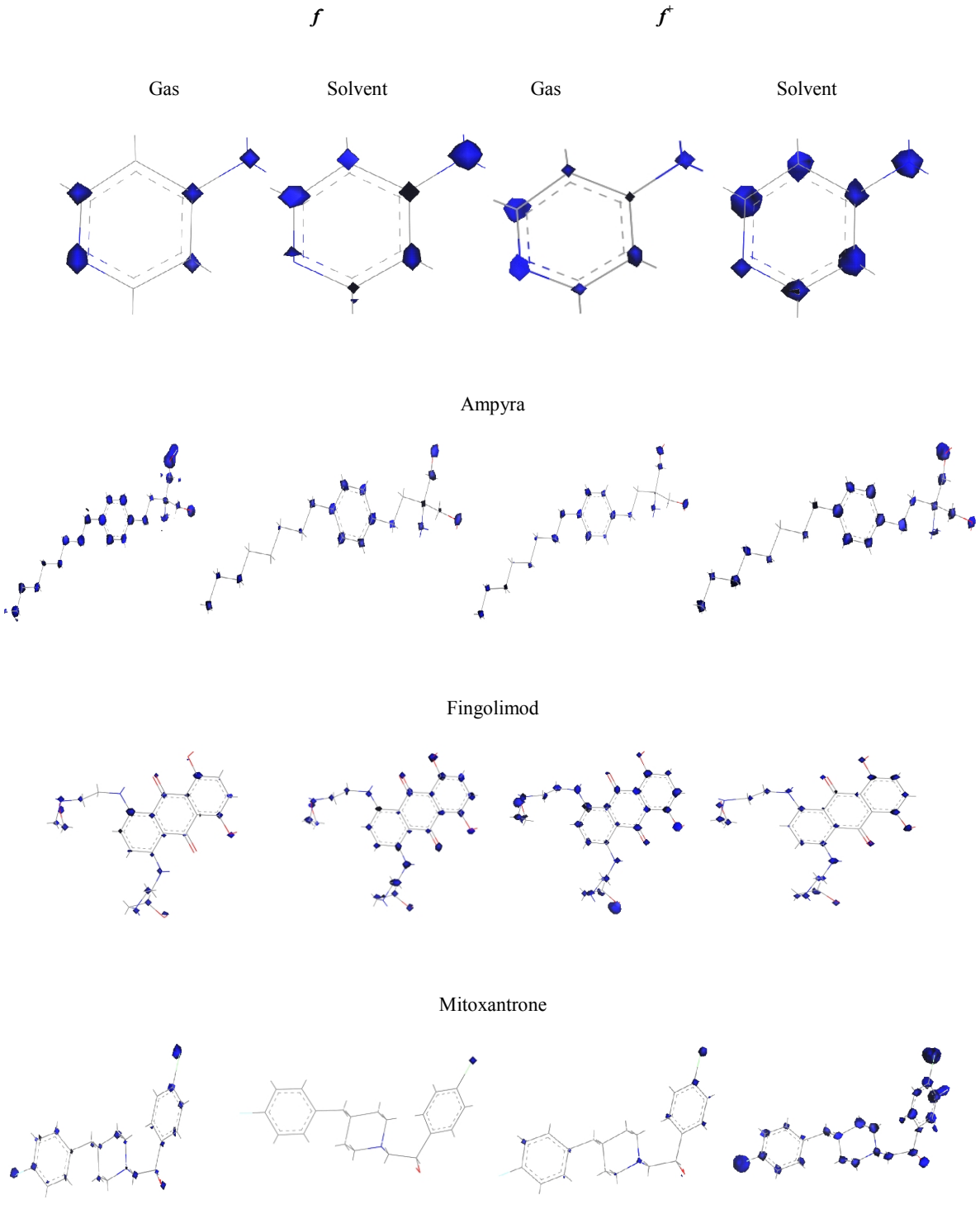


Fig. 3. The Fukui functions for the studied drugs in gas and solvent

Fingolimod

Fingolimod (also called FTY720) (IUPAC name: 2-amino-2-[2-(4-octylphenyl) ethyl] propane-1, 3-diol) belongs to a class of medications called sphingosine l-phosphate receptor modulators. It is used to treat the relapsing-remitting form of MS. It works by decreasing the action of immune cells that may cause nerve damage.

A comparison between the differences in bond lengths and the bond angles of the Fingolimod in gas and solvent phases reveals the fact that the differences related to oxygen and nitrogen atoms are greater than those differences associated with other atoms. The difference between the C18-O1 bond lengths in the two phases is 0.005 Å but this difference in the C17-C18 bond lengths is 0.002 Å. This is because oxygen and nitrogen atoms are more polarized in solvent phase.

In the Fingolimod, Fig. 2, the HOMO densities are concentrated on the carbon ring, C8, C15, O1 and NH_2 group, the LUMO is delocalized on the carbon ring and the carbon skeletal chain of the molecules appears to have no contribution towards the donor-acceptor interactions in both phases. Fig. 3 shows active sites of the Fingolimod molecule in both phases. The electron density is almost distributed throughout this molecule and the Fukui indices indicate that O atoms and C atoms in ring have the highest electron density in both phases.

Mitoxantrone

Mitoxantrone (also known as Mitozantrone or Mitoxantrone) (IUPAC name: 1, 4-dihydroxy-5, 8-bis [2-(2-hydroxyethylamino) ethyl amino]-anthracene-9, 10-Dione) is an anti-cancer chemotherapy drug. This medication is classified as an antitumor antibiotic. This drug works by suppressing the immune system to lessen its attack on the myelin sheath that surrounds nerves. It can slow down increases in disability and reduce the relapse rate in people with worsening forms of relapsing-remitting, progressive-relapsing, and secondary-progressive MS.

If the bond lengths and angles of Mitoxantrone in the gas phase are compared with those in solvent phase, it can be seen that not only differences in bond lengths and angles of nitrogen and oxygen atoms in the two phases are greater than the other bond lengths and bond angles but also demonstrates the fact that the smaller the space barrier is the more the bonds are polarized. The difference between the O5-C20-C19 bond angles in the two phases is 0.646 degrees, but this difference for the O5-C20-C21 is 0.256 degrees. This is due to more space barrier in the latter case.

In both phases, the HOMO energy levels include carbon rings and N_2 i N_3 i O_3 and O_4 atoms of the Mitoxantrone molecule and the LUMO is delocalized on carbon rings and on N2, N3, O3, O4, O5 and O6 atoms (see Fig. 2). Fig. 3 shows that the Mitoxantrone molecule has many nucleophilic and electrophilic sites. The negative Fukui indices indicate that O2 and O1 atoms in gas phase and O1, O2, O3 and O6 atoms in solvent phase have the highest electron density. The positive Fukui indices suggest that O3, N3 and C20 in solvent phase and C5 atom in gas phase have the high electron density.

Eliprodil

Eliprodil (SL-82.0715) (IUPAC name: 1-(4-chlorophenyl) -2-[4-[(4-fluorophenyl) methyl] piperidin-1-yl] ethanol) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist which acts at the polyamine modulatory site. Eliprodil is reported to act as a neuroprotective.

The differences between the nitrogen, oxygen and chlorine bond lengths and bond angles in the gas phase of Eliprodil and those of its solvent phase are greater than the differences between its carbon and hydrogen bond lengths and bond angles in gas phase and those of its solvent phase. The differences between the N-C13-C14 and O-C13-C15 bond angles in the two phases of Eliprodil are 0.562 and 0.289 degrees respectively but this difference for C5-C4-C7 is 0.036 degrees. This may be due to the greater solvent polarization effect on the nitrogen, oxygen and chlorine atoms.

Fig. 2 shows that the HOMO energy levels include the carbon ring attached to N and O atoms and the LUMO is delocalized on the carbon ring attached to the chlorine atom and on Cl and O atoms of the Eliprodil molecule in both phases. As shown in Fig. 3, in phase solvent the Eliprodil molecule has only one nucleophilic site, Cl, but has many nucleophilic sites in gas phase. In this phase, Cl is the nucleophilic electrophilic and has the highest electron density.

This Fig. shows that the Eliprodil molecule has many electrophilic sites in solvent phase, but Cl has the highest electron density (most electrophilic) in both phases.

Because the four MS drugs have different structures, their electronic distributions of HOMO and LUMO are

different and therefore we selected the drug which can be best attached to the f-SWANT and delivered to its target.

Calculations of quantum chemical parameters of the drugs in gas and solvent phases

Table 2 shows the quantum chemical parameters for Ampyra, Fingolimod, Mitoxantrone and Eliprodil. These parameters give information on the chemical reactivity of the studied molecules in the gas and solvent phases. The trends of the quantum chemical parameters are almost similar in both gas and solvent phases. A higher E_{HOMO} suggests a lower capability of accepting electrons because this energy describes the electron donating ability of the molecule. The energy of LUMO indicates the ability of a molecule to accept electrons. Thus the lower the value of E_{LUMO} is, the more probable that the molecule would accept electrons. The binding ability of the four MS drugs to the f-SWNT increases with increasing HOMO and decreasing LUMO energy values. Based on quantum molecular descriptors, as given in Table 2, Mitoxantrone has a high E_{HOMO} and a low E_{LUMO} in comparison to Ampyra, Fingolimod and Eliprodil in gas and solvent phases. The gap between the HOMO and LUMO energy levels is an important function of reactivity of a molecule. The calculations indicate that the Mitoxantrone has a low energy gap in the gas and solvent phases. Thus, moving an electron from the HOMO of the Mitoxantrone to its LUMO is easier than in other three drugs. This means that this drug could have a better performance as f-SWNT. The E_{HOMO}, E_{LUMO} and "E of the Mitoxantrone in solvent phase are only slightly different from their corresponding values in the gas phase.

Ionization potential is a basic descriptor of the chemical reactivity of atoms and molecules. Low ionization potential indicates low stability. Table 2 shows that Mitoxantrone ionization energies using both orbital and energy modes in gas and solvent phases are low compared with the other three MS drugs. Chemical potential is a measure of molecular capability of accepting electrons.

Absolute hardness and softness are important properties to measure the molecular stability and reactivity. Table 2 shows that Fingolimod has the lowest electronegativity and Mitoxantrone has the lowest hardness and the highest softness. The ability of molecules to accept electrons may be described by the electrophilicity index. It is a measure of a system's energy stabilization after the system accepts the additional amount of electron charge from its environment. In our study, Ampyra has the lowest value of electrophilicity calculated by energy mode in the gas phase.

Therefore, the Ampyra molecule is the strongest nucleophile in the gas phase, but Fingolimod is the strongest nucleophile in solvent phase because it has the lowest value of electrophilicity calculated by orbital mode in solvent phase. The calculations show that Mitoxantrone has the highest value of the TNC in comparison to Ampyra, Fingolimod and Eliprodil. This property expresses the capability of a molecule's donating electrons.

The adsorption of the drugs onto the f-SWNT surface is enhanced at higher TNC values. The TNC of the Mitoxantrone molecule is higher in water solution than in the gas phase. The dielectric solvation energy of Mitoxantrone is the highest (-39.89 kcal/mol) which suggests that it has the highest solubility in water compared to Ampyra, Fingolimod and Eliprodil. The polarity of a molecule describes its dipole moment. Table 2 shows Ampyra has the highest value of dipole moment in gas and solvent phases and Mitoxantrone has the highest molecular mass.

The high molecular mass of Mitoxantrone causes an increase of drug adsorption onto the f-SWNT and hence increases the efficiency uptake of the drug. It is clear from Table 2 that the dipole moments of the four MS drugs are higher in water solution than in the gas phase and this is an indication of the polarization effect of the solvent on the drug molecules. From the computed results in gas and solvent phases (Table 2), we can easily notice the stabilization effect of solvent on the significant decrease of the Total Energy (TE) values of the four MS drugs.

Table 2 shows Mitoxantrone has highest HOMO energy, global softness, TNC, solvation energy and molecular mass and lowest LUMO energy, energy gap, global hardness and TE in comparison to Ampyra, Fingolimod and Eliprodil in gas and solvent phases. Therefore, Mitoxantrone will exhibit better adsorption onto the f-SWNT surface and is more reactive than the other three drugs. The SWNTs are electron accepting species which can attack the nucleophilic sites of the drug molecules [30].

Table 2. Quantum chemical descriptors for the studied compounds

Molecular descriptors	Parameter	Ampyra=A		Fingolimod=F		Mitoxantrone=M		Eliprodil=E		Comments	
		Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent
HOMO(eV)	-	-5.568	-5.621	-5.563	-5.763	-4.338	-4.616	-5.194	-5.253	M>E>F>A	M>E>A>F
LUMO(eV)	-	-1.133	-1.309	-0.945	-1.178	-3.111	-3.412	-1.725	-1.666	F>A>E>M	F>A>E>M
? E(eV)	-	4.435	4.312	4.618	4.585	1.227	1.204	3.469	3.587	F>A>E>M	F>A>E>M
Ionization Potential(IP) IP=[E(+1)-E(0)]	Energetic	8.412	6.221	7.301	5.901	6.039	4.799	7.141	5.722	A>F>E>M	A>F>E>M
IP=-E_{HOMO}	Orbital	5.568	5.621	5.563	5.763	4.338	4.616	5.194	5.253	A>F>E>M	F>A>E>M
Electron Affinity(EA) EA=[E(0)-E(-1)]	Energetic	-1.545	0.835	-1.004	0.737	1.394	3.180	0.199	1.535	M>E>F>A	M>E>A>F
EA=-E_{LUMO}	Orbital	1.133	1.309	0.945	1.178	3.111	3.412	1.725	1.666	M>E>A>F	M>E>F>A
Global hardness(η) (I-A)/2η=	Energetic	4.978	2.693	4.152	2.582	2.322	0.809	3.471	2.093	A>F>E>M	A>F>E>M
	Orbital	2.217	2.156	2.309	2.292	0.613	0.602	1.734	1.793	F>A>E>M	F>A>E>M
Electronegativity (χ) (I+A)/2χ=	Energetic	3.433	3.528	3.148	3.319	3.716	3.990	3.670	3.628	M>E>A>F	M>E>A>F
	Orbital	3.350	3.465	3.254	3.470	3.724	4.014	3.459	3.459	M>E>A>F	M>F>A>E
Global softness(σ) =1/ησ	Energetic	0.201	0.3713	0.241	0.387	0.430	1.236	0.288	0.477	M>E>F>A	M>E>F>A
	Orbital	0.451	0.464	0.433	0.436	1.631	1.661	0.576	0.558	M>E>A>F	M>E>A>F
Electrophilicity(ω) ω=χ^2/2η	Energetic	1.184	2.311	1.193	2.133	2.973	9.839	1.940	3.144	M>E>F>A	M>E>A>F
	Orbital	2.531	2.784	2.293	2.627	11.312	13.382	3.450	3.336	M>E>A>F	M>E>A>F
Total Negative Charge(TNC)	-	-0.981	-1.108	-3.275	-3.592	-5.296	-5.76	-2.518	-2.816	M>F>E>A	M>E>A>F
Solvation energy (kcal/mol)	-	-	-12.21	-	-17.04	-	-39.89	-	-13.68	M>>F>E>A	-
Dipole moment(μ)(D)	-	4.096	5.915	1.128	1.912	3.489	4.334	1.127	0.988	A>M>F>E	A>M>F>E
Molecular mass(amu)	-	94.1146	-	307.471	-	444.486	-	347.86	-	M>E>F>A	-
ET_I(a.u)	-	-303.65	-303.66	-949.05	-949.07	-1525.59	-1525.64	-1465.99	-1466.01	A>F>E>M	A>F>E>M

Calculation of interaction energy

There are many chemical compounds that may be used to functionalize the SWNTs in order to decrease the cellular toxicity and increase the dissolution of the SWNTs. Azomethine ylide is a nitrogen-based 1, 3-dipole that has been used to deliver the drugs to their targets[31].

The HOMO and the LUMO of the (5, 5)-SWNT, azomethine ylide, and f-SWNT-Mitoxantrone in both phases are shown in Fig. 4. In mono-functional SWNT with Mitoxantrone, HOMO orbital is more localized throughout the framework of the SWNT with no distribution of the side chain. LUMO orbital is delocalized on rings of Mitoxantrone. A comparison between the HOMO and the LUMO of our f-SWNT-Mitoxantrone and those reported by Saikia et al [30]] and Gallo et al [14] proves that the HOMO and the LUMO energy distributions depend on the drug's chemical structure. Many electronic properties of chemical structures are directly related to the HOMO and LUMO levels, thus the energy gap depends on the energy geometric structure of the molecule.Tables 3 shows the quantum chemical parameters of (5, 5)-SWNT and SWNT functionalized with azomethine ylide chain terminated with Mitoxantrone drug molecule in both gas and solvent phases. Some of these quantum chemical parameters are different in gas and liquid phases and some of the same type parameters obtained by orbital method are different from those obtained by energy method. The energy gap and Ionization Potential of f-SWNT-Mitoxantrone decreased in comparison to pristine nanotube in both phases. This showed that the reactivity of f-SWNT-Mitoxantrone increases. Table 3 shows electrophilicity of f-SWNT-Mitoxantrone increased in comparison to pristine nanotube in both phases (except for values obtained by energy parameter method in gas phase), which suggests an increase in charge transfer from Mitoxantrone to carbon nanotube. The absolute hardness and softness are important properties for

measuring a molecular stability and reactivity. Table 3 shows that the absolute hardness of f-SWNT-Mitoxantrone decreased in comparison to pristine nanotube in both phases (except for values obtained by energy parameter method in gas phase), which reflect the high reactivity of f-SWNT-Mitoxantrone as compared with pristine nanotube.

The binding energy (BE) between a drug molecule and an f-SWNT is evaluated by the equation:

$$BE = E_{(SWNT/addend)} - (E_{(SWNT)} + E_{(addend)})$$

Where $E_{(SWNT/addend)}$ is the total electronic energy of f-SWNT loaded with Mitoxantrone after full geometry optimization. $E_{(SWNT)}$ is the electronic energy of SWNT without any functional group attached and $E_{(addend)}$ is the electronic energy of azomethine ylide side chain attached to Mitoxantrone.

The Mitoxantrone BE was calculated to be 6.507 eV in gas phase and -9.943 eV in solvent phase that is a decrease in BE as the drug phase changes from gas to liquid.

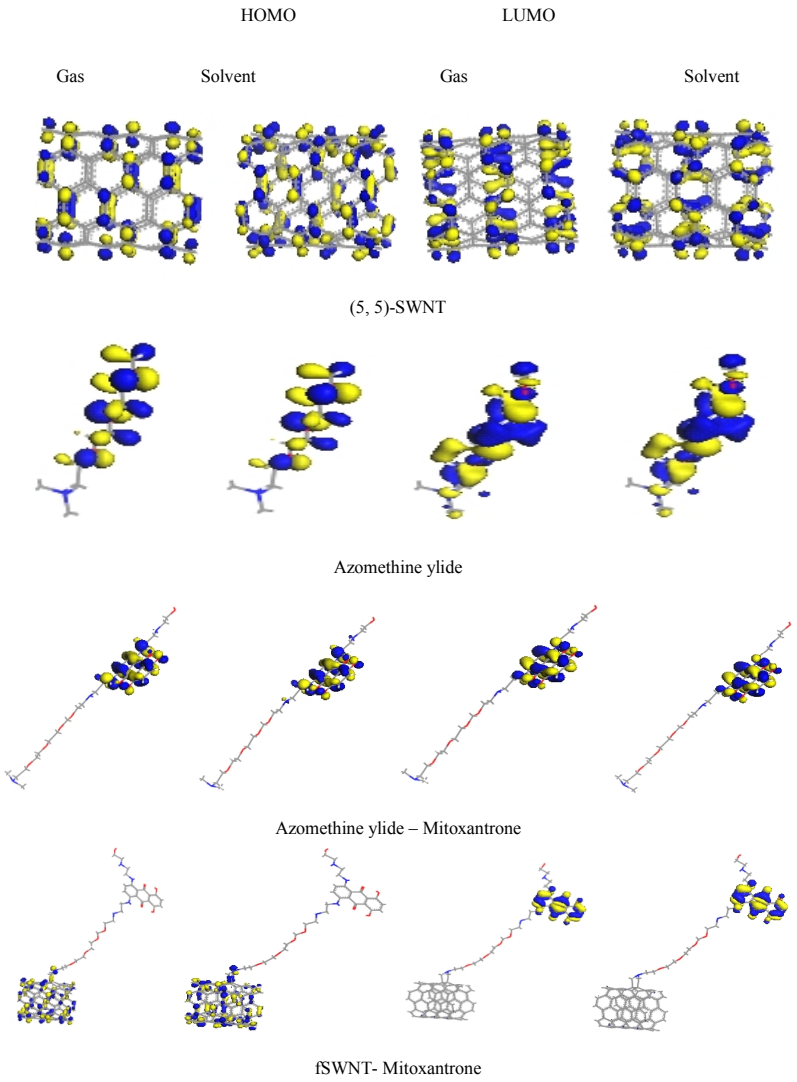


Fig. 4. The HOMO and the LUMO for (5, 5)-SWNT, Azomethine ylide, Azomethine ylide- Mitoxantrone, and fSWNT- Mitoxantrone in gas and solvent

Table 3. Quantum chemical descriptors for the studied compounds

Molecular descriptors	Parameter	(5, 5)-SWNT		fSWNT- Mitoxantrone	
		Gas	Solvent	Gas	Solvent
HOMO(eV)	-	-4.243	-4.419	-4.246	-4.079
LUMO(eV)	-	-3.323	-3.507	-3.502	-3.344
? E(eV)	-	0.920	0.912	0.744	0.735
Ionization Potential(IP)	Energetic				
IP=[E(+1)-E(0)]	Orbital	5.396	4.384	4.246	3.937
$IP=-E_{HOMO}$		4.243	4.419	4.246	4.079
Electron Affinity(EA)	Energetic				
EA=[E(0)-E(-1)]	Orbital	2.294	3.572	-1.004	3.287
$EA=-E_{LUMO}$		3.323	3.507	3.502	3.344
Global hardness(η)	Energetic	1.551	0.405	4.152	0.325
(I-A)/2η=	Orbital	0.460	0.456	0.372	0.368
Chemical potential(χ)	Energetic	3.845	3.977	3.148	3.612
(I+A)/2χ=	Orbital	3.783	3.963	3.874	3.711
Global softness(σ)	Energetic	0.645	2.465	0.241	3.077
=1/ησ	Orbital	2.175	2.192	2.688	2.721
Electrophilicity(ω)	Energetic	4.767	19.505	1.193	20.069
$\omega=\chi^2/2\eta$	Orbital	15.564	17.222	20.173	18.738

CONCLUSION

In this work, first principles calculations were performed to study four multiple sclerosis drugs namely Ampyra, Fingolimod, Mitoxantrone and Eliprodil in gas and aqueous phases using density functional theory (DFT). Computational chemistry simulations were carried out by comparing calculated quantum chemical parameters for Ampyra, Fingolimod, Mitoxantrone and Eliprodil that these results showed Mitoxantrone to be a quite reactive drug. Thus calculations were carried out to study the interaction of covalently binding Mitoxantrone to functionalized carbon nanotube.

The binding energy between a Mitoxantrone molecule and an f-SWNT showed that this energy decreases from 6.507 eV in gas phase to -9.943 eV in solvent phase.

The quantum chemical parameters of pristine nanotube and f-SWNT-Mitoxantrone showed that reactivity of f-SWNT-Mitoxantrone increased in comparison to pristine nanotube in both phases.

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