



Original Research article

# Quantum Computations of Interactions of Most Reactive Tricyclic Antidepressant Drug with Carbon Nanotube, Serotonin and Norepinephrin



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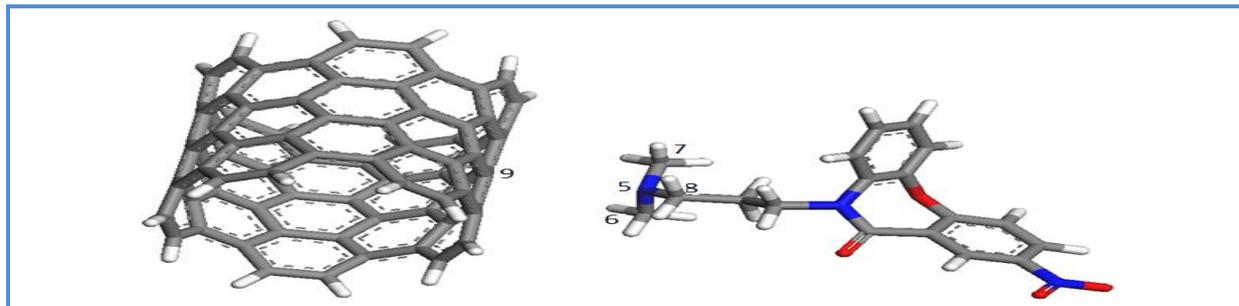
## ABSTRACT

First principles calculations were performed to study the neurotransmitters, tricyclic antidepressant drugs and (5,5) carbon nanotube in the gas phase and solution media for comparison purposes. All calculations were performed using DMol<sub>3</sub> code in materials studio 5.5. The simulation results revealed that, the nitroxazepine is quite a reactive drug, so that it can act as the electron donating specie in its interacting with carbon nanotube. In addition, the nitroxazepine is the electron acceptor and serotonin and norepinephrine is the electron donor. To explain the interaction of the carbon nanotube, serotonin, and norepinephrine with nitroxazepine, their local reactivity was analyzed through Fukui functions. The results show that the hydrogen bonding between oxygen atoms of the nitroxazepine and OH of the serotonin and norepinephrine has been assigned as the dominant interaction. In order to gain a deeper understanding of the interaction between the nitroxazepine with the carbon nanotube, serotonin and norepinephrine, calculations of binding energies, quantum molecular descriptors, the most important modes of the vibrational frequencies and density of states (DOS) have been carried out.

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## Graphical Abstract



## Introduction

Depression is a state of low mood and aversion to activity [1]. Depression is the leading cause of disability all over the world and may be the second leading contributor to the global burden of diseases by 2020 [1]. In general, more women are affected by depression than men. Depression is often the result of experiencing a stressful event such as parental death, loss of a loved one, miscarriages or divorces [2]. There are effective treatments for depression. Many studies have been reported on depression medications and their side effects [2-6]. Tricyclic antidepressants are medicines that relieve mental depression. Tricyclic antidepressants are heterocyclic chemical compounds which contains three rings of atoms. The first tricyclic antidepressants were discovered during the 1950s and they are among the oldest classes of antidepressants which are still used extensively [7]. Although many new antidepressant drugs have been discovered since 1950s, the tricyclic antidepressants still have an important place in the treatment of bipolar disorder where they seem to have a therapeutic advantage over the newer drugs [8]. The tricyclic antidepressants are helpful in the management of chronic pain, especially nerve pain. The therapeutic effectiveness of tricyclic antidepressants drugs has been ascribed to the serotonin-norepinephrine reuptake inhibitors (SNRIs) which are produced by nerve terminals in the brain [9, 10]. Except amineptine, other tricyclic antidepressants have no efficacy compared with dopamine reuptake inhibitors (DRIs) [10]. The tricyclic antidepressants are *in vitro* and competitive antagonists of  $\alpha$  1-adrenergic, muscarinic acetylcholine, histamine H1 and histamine H2 receptors [11, 12]. An overview of the mechanism of actions of some tricyclic antidepressants from the cellular receptor perspective is given in reference [13]. The quantum chemistry computations are widely used to study interactions between different compounds. An important application of quantum chemistry computations is the interaction between drugs and non-drugs. The single-walled carbon nanotubes (SWCNTs) have opened up several new fields in nanotechnology due to their interesting properties [14-16]. The SWCNTs have various applications, in particular as drug carriers [17, 18]. The SWCNTs may be

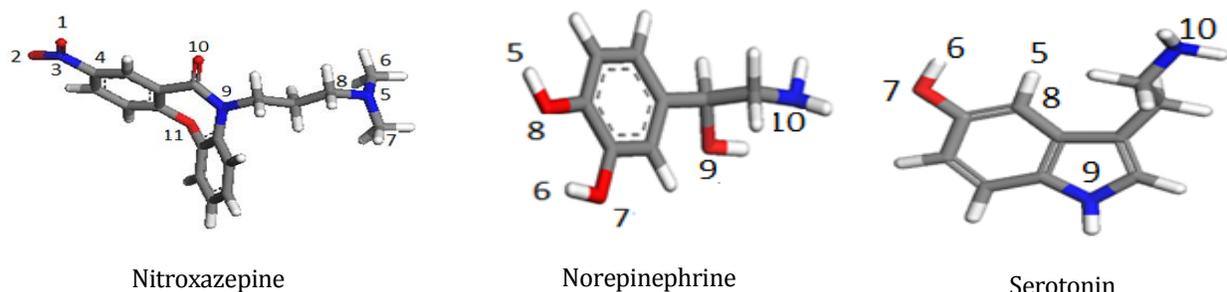
considered to be effective drug transporters because of their high specific surface areas and also their ability to release drugs into the tissue cells without harming the healthy cells [19, 20]. The interaction of drug molecules with carbon nanotubes have been reported by researchers [21-26]. It was also demonstrated that carbon nanotubes are capable of effectively by-passing the blood-tissue barrier and penetrating cells [27]. According to recently published reports, in a review article, Saliev discussed the progress and main fields of bio-medical use of carbon nanotubes [28]. In this research work, we aimed to expand the applications of SWCNTs for drug delivery. A theoretical study on structural properties and reactivity of 28 tricyclic antidepressant drugs was discussed, as well. The tricyclic antidepressants, which were studied, are as follows: amineptine, amitriptyline, amitriptylineoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dosulepin, doxepin, imipramine, imipraminoxide, iprindole, lofepramine, melitracen, metapramine, nitroxazepine, nortriptyline, noxiptiline, opipramol, pipofezine, propizepine, protriptyline, quinupramine, tianeptine and trimipramine. First, the structures of the tricyclic antidepressants were optimized, second, computational chemistry simulations of the optimized drugs were carried out and third, a comparison study was made on quantum chemical parameters of these antidepressants. Based on global reactivity descriptors, nitroxazepine is the most reactive species among these tricyclic antidepressants. Two studies were performed on nitroxazepine. First study was carried out on the adsorption properties of nitroxazepine. The SWCNTs are the most widely used carriers in biomedical and pharmaceutical applications. This fact merits investigation of the structural properties of the nitroxazepine-SWCNTs complexes. Second study was carried out on the electronic and structural properties of the nitroxazepine upon its interaction with neurotransmitters. Neurotransmitters are small molecules which play a prominent role in biological systems. The norepinephrine, serotonin and dopamine function as neurotransmitters in the treatment of depressive disorders. Based on global reactivity descriptors, norepinephrine and serotonin are more reactive than dopamine. Tricyclic antidepressant drugs act as strong inhibitors in the reuptake of both norepinephrine and serotonin. Interactions between nitroxazepine, serotonin and norepinephrine can help to conduct experimental and theoretical studies on drug-ligand interactions. Interaction energies, quantum molecular descriptors, modes of vibrational frequencies and density of states of nitroxazepine complexes were calculated.

## **Experimental**

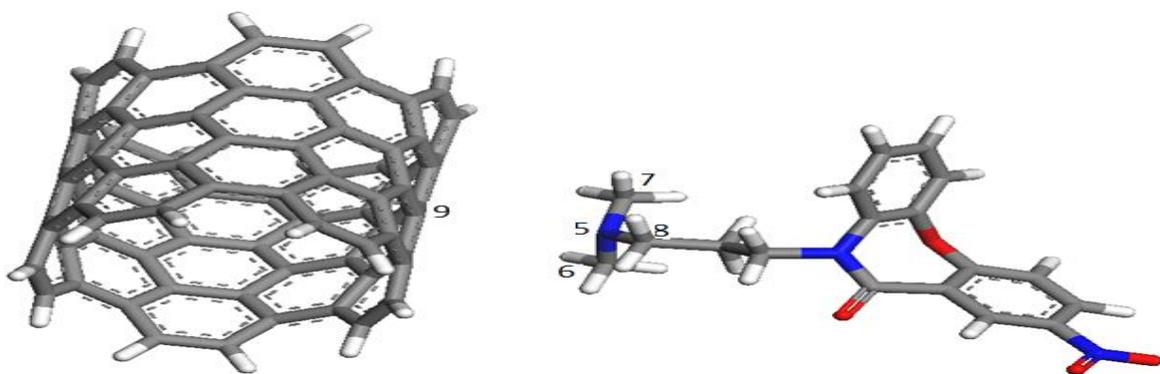
### **Computational methods**

All calculations were performed using DMol<sub>3</sub> code in materials studio 5.5 [29, 30]. The generalized gradient approximation (GGA) [Perdew and Wang 1991 (PW91), Becke-Lee-Yang-Parr (BLYP)] [31-33],

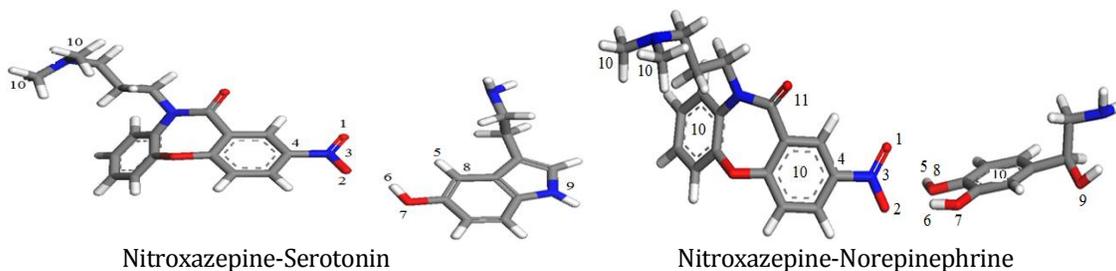
and the double numerical plus polarization function (DNP) were utilized to optimize the structural of the tricyclic antidepressants. Total energy convergence criteria for self-consistent field (SCF) were set to  $10^{-6}$  eV. The structures and the optimized configurations of tricyclic antidepressants drugs, neurotransmitters, SWCNT, drug-SWCNT and drug-neurotransmitters were determined by GGA\BLYP and GGA\PW91 methods. The structures and the optimized configurations of the compounds are shown in Figures S1 and 1-3.



**Figure 1.** The optimized structures of nitroxazepine, serotonin and norepinephrine. The numbers 1 and 2 in nitroxazepine shows sites for nucleophile attack, and the number 5 is site for electrophilic attack. In serotonin site for electrophilic attack is the oxygen atom and the numbers 7 and 8 in norepinephrine indicate sites for electrophilic attack. (Color scheme: gray=carbon, blue=nitrogen, red=oxygen, white=hydrogen).



**Figure 2.** The optimized structures of nitroxazepine-SWCNT by using GGA/BLYP. (Color scheme: gray=carbon, blue=nitrogen, red=oxygen, white=hydrogen)



**Figure 3.** The optimized structures of nitroxazepine-serotonin and nitroxazepine-norepinephrine. (Color scheme: gray=carbon, blue=nitrogen, red=oxygen, white=hydrogen)

The conformers were considered to be minima based on the absence of imaginary frequencies. The effect of the solvent on water was estimated by the conductor-like screening model (COSMO) [34]. The dielectric constant of the solvent was taken to be 78.54. A smearing of 0.005 Hartree and 10 Pulay direct inversion of the interactive subspace (DIIS) [35] were used to improve computational performance in terms of fast SCF convergence. The basis set superposition errors (BSSE) of the DNP basis set have been used for the counterpoise correction of the values of interaction energy [36].

When two molecules react with each other, one molecule will act as a nucleophile and the other molecule will behave as an electrophile. In this study, the intramolecular reactivity has been explained by Fukui indices. Behavior of molecules, as electrophiles or nucleophiles during reactions, depends on how the atomic sites of a molecule react with an approaching reagent. Fukui indices,  $f^+$  or  $f^-$ , permit distinction to be made between the reactive regions of a molecule and determine the nucleophilic and electrophilic behavior of a molecule as well as its chemical reactivity [37]. The maximum of  $f^+$  corresponds to a nucleophilic attack and the maximum of  $f^-$  indicates the preferred sites for adsorption of electrophilic agents [38].

The electrophilic charge transfer (ECT) [39] and fractional number of electrons ( $\Delta N$ ) [40] can be calculated by the following equations (1) and (2).

$$ECT = (\Delta N_{\max})_a - (\Delta N_{\max})_b, (\Delta N_{\max})_a = -\frac{\mu_a}{\eta_a}, (\Delta N_{\max})_b = -\frac{\mu_b}{\eta_b} \quad (1)$$

$$\Delta N = \frac{\chi_a - \chi_b}{2(\eta_a + \eta_b)} \quad (2)$$

Where  $\mu$ ,  $\eta$  and  $\chi$  are electronegativity, chemical potential and global hardness respectively. If  $\Delta N$  and ECT are greater than zero, then charge is transferred from "b" to "a". If ECT is smaller than zero, then charge is transferred from "a" to "b" where "a" and "b" are reactants.

The binding energies of nitroxazepine-serotonin, nitroxazepine-norepinephrine and nitroxazepine-SWCNT complexes can be calculated by equation (3).

$$\Delta E_{\text{int}}^{\text{BSSE}} = E_{\text{Complex}} - (E_{\text{Serotonin or Norepinephrine or SWCNT}} + E_{\text{Nitroxazepine}}) + \Delta E_{\text{BSSE}} \quad (3)$$

Where E is binding energy and E complex is energy of nitroxazepine-serotonin, nitroxazepine-norepinephrine or nitroxazepine-SWCNT.

The Gibbs free energies, are calculated by equation (4).

$$\Delta G_{int}^{BSSE} = \Delta E_{int}^{BSSE} + \Delta ZPE - TS - T\Delta S + \Delta E_{T/R/V} \quad (4)$$

Where  $\Delta ZPE$  is the change in zero-point vibrational energy,  $T\Delta S$  is the entropy contribution to the change in Gibbs free energy and  $\Delta E_{T/R/V}$  is finite-temperature translational/rotational/vibrational contributions to the total energy [41].

## Results and discussion

### Quantum chemical descriptors of tricyclic antidepressant drugs

The global molecular descriptors of the tricyclic antidepressants were calculated for their optimized geometries by energetic and orbital parameters methods. The descriptors trends are almost similar in gas and liquid phases. Based on quantum chemical descriptors, which are specified in Table 1, nitroxazepine has a low energy gap ( $\Delta E$ ) in comparison to other tricyclic antidepressants drugs. Therefore, electron transfer from the highest occupied molecular orbital (HOMO) of nitroxazepine to its lowest unoccupied molecular orbital (LUMO) occurs more easily than similar electron transfers from other tricyclic antidepressants HOMOs to their LOMOs. The information about the polarity of a molecule is given by the molecular dipole moment. As seen in Table 1, the nitroxazepine has the highest dipole moment. The dipole moments of the tricyclic antidepressants drugs were higher in liquid phase than in gas phase and this is an indication of the polarization effect of the solvent on the drug molecules. The nitroxazepine has the highest electron affinity and the lowest ELUMO (Table S1). The lower the ELUMO of a molecule is, the more probable that molecule would accept electrons. The ELUMO confirmed that, nitroxazepine is an electrophile. The absolute hardness and softness determine molecular stability and reactivity. Table S2 shows nitroxazepine is a soft molecule. The nitroxazepine is more electronegative than other tricyclic antidepressants, Table S3.

Therefore, nitroxazepine molecule is the strongest electrophile among these tricyclic antidepressants. The dielectric solvation energies of tianeptine are -24.19 and -23.93 kcal/mol<sup>-1</sup> in gas and liquid phases respectively and they are the highest among the tricyclic antidepressant drugs.

Tianeptine had the highest solubility in solvent. The ability of a molecule to accept electrons may be described by the electrophilicity index ( $\omega = \chi^2 / 2\eta$ ). Nitroxazepine has the highest electrophilicity and thus is a stronger electrophile than other tricyclic antidepressants. The electrophilicity index, electrodonating ( $\omega = (3I+A) / 16 (I-A)$ ), electroaccepting ( $\omega = (I+3A) / 16 (I-A)$ ) and net electrophilicity ( $\Delta\omega_{\pm} = (\omega_+ + \omega_-)$ ) of tricyclic antidepressants are not included in this study. A large electroaccepting value corresponds to a high capability of accepting charge, whereas a small

electrodonating value makes a system to be a better electron donor. Nitroxazepine has a better capability of accepting charge.

**Table 1.** The energy gap ( $\Delta E$ ) and dipole moment ( $\mu$ ) for 28 tricyclic antidepressants drugs

Compounds	$\Delta E$ (eV)		$\mu$ (D)	
	Gas	Solvent	Gas	Solvent
	PW91	BLYP	PW91	BLYP
Amineptine	4.236	4.227	4.081	4.006
Amitriptyline	3.306	3.341	3.294	3.340
Amitriptylinoxide	2.587	2.611	3.066	3.186
Amoxapine	2.580	2.570	2.669	2.656
Butriptyline	3.741	3.754	3.296	3.345
Clomipramine	3.284	3.275	3.269	3.273
Demexiptiline	2.758	2.800	2.820	2.895
Desipramine	3.437	3.411	3.436	3.415
Dibenzepin	2.821	2.87	2.802	2.868
Dimetacrine	3.335	3.303	3.316	3.284
Dosulepin	2.783	2.821	2.846	2.877
Doxepin	3.148	3.196	3.134	3.192
Imipramine	3.468	3.438	3.438	3.423
Imipraminoxide	3.223	3.204	3.506	3.543
Iprindole	3.550	3.516	3.488	3.459
Lofepramine	1.718	1.700	1.924	1.890
Melitracen	3.042	3.076	3.007	3.060
Metapramine	3.596	3.578	3.548	3.537
Nitroxazepine	1.382	1.320	0.624	0.940
Nortriptyline	3.487	3.529	3.488	3.572
Noxiptiline	2.896	2.785	3.294	2.858
Opipramol	2.494	2.503	2.482	2.487
Pipofezine	2.740	2.732	2.662	2.661
Propizepine	2.381	2.389	2.360	2.350
Protriptyline	2.762	2.834	2.867	2.957
Quinupramine	3.114	3.119	3.146	3.159
Tianeptine	3.909	3.414	3.192	3.187
Trimipramine	3.358	3.379	3.351	3.367

Based on electrophilicity, nitroxazepine is a strong nucleophile. Nitroxazepine molecule has a better capability of accepting charge than other tricyclic antidepressants. Nitroxazepine molecule has highest electron affinity, electronegativity, electroaccepting and net electrophilicity when compared with other tricyclic antidepressants. Therefore, nitroxazepine is an electrophile and can interact with nucleophilic species. On the other hand, nitroxazepine has the lowest LUMO energy, energy gap and global hardness in comparison to other tricyclic antidepressants. Nitroxazepine is a strong reactive drug and can interact with carbon nanotubes in a better way than other tricyclic antidepressants. The SWCNTs can attack the nucleophilic sites as they are electron accepting species [39]. Nitroxazepine can act as an electron donating species when interacting with carbon

nanotubes. This dual behavior of molecules in their global molecular descriptors has been observed in many articles. For example, the interactions of pyrazinamide with carbon nanotubes were studied by N. Saikia *et al.* [42]. They show that pyrazinamide is a reactive and electrophilic drug in comparison to isoniazid and 2-methylheptylisonicotinate drugs. Mitoxantrone drug is also an example of a dual behaving drug, mitoxantrone is quite a reactive and electrophilic drug in comparison to the ampyra, fingolimod and eliprodiol [24]. The interaction of calix [4] arene with polychlorinated dibenzo-*p*-dioxins (PCDDs) shows that PCDD is an electron acceptor and the most reactive drug whereas calix [4] arene acts as an electron donor [43].

### **Interaction of SWCNTs with nitroxazepine**

#### **Local molecular reactivity**

Nitroxazepine acts as an electron donating species when it interacts with carbon nanotubes. The highest  $f^-$  is associated with nitrogen atom of nitroxazepinein, atom 5 in Figure 1. The  $f^-$  Fukui indices of nitroxazepine are listed in Table 2.

A change of conformation of nitroxazepine-SWCNT complex was considered in response to nitrogen atom interaction with SWCNT, Figure 2. The conformational change was optimized by GGA/BLYP and GGA/PW91 methods. The interaction distances and the bond lengths of nitroxazepine-SWCNT and nitroxazepine are shown in Table 3. The bond lengths and the interaction distances of nitroxazepine-SWCNT are approximately equal in both gas and liquid phases. The optimized configuration of nitroxazepine-SWCNT complex indicates that the interaction between nitroxazepine and pristine carbon nanotube has a physical adsorption nature. The evidence for the weak interaction between nitroxazepine and pristine carbon nanotube is the close proximity of C6-N5, C7-N5 and C8-N5 bond lengths of nitroxazepine-nanotube complex to their corresponding bond lengths of free nitroxazepine and the interaction distance between nitroxazepine and nanotube falls in the weak range of 3.720-3.682 Å. A further evidence for this weak interaction is the existence of small binding energies between SWCNT and nitroxazepine (Table 4). The weak interaction implied that nitroxazepine was physically adsorbed on the SWCNT. The negative binding energies indicate that absorption process is exothermic. Adsorption process was not spontaneous at room temperature because Gibbs free energy is positive. Positive Gibb free energy revealed that, the nature of adsorption was physical [44]. The binding energy of the nitroxazepine-SWCNT complex increased as its physical state changed from gas to liquid.

**Table 2.** Calculated Fukui function (f) for nitroxazepine

Distance (Å)	Nitroxazepine-SWCNT				Nitroxazepine			
	PW91		BLYP		PW91		BLYP	
	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent
C6-N5	1.460	1.461	1.474	1.474	1.468	1.474	1.455	1.510
C7-N5	1.455	1.455	1.468	1.468	1.467	1.473	1.454	1.510
C8-N5	1.455	1.456	1.468	1.468	1.473	1.479	1.460	1.509
C9-N5	3.682	3.689	3.779	3.720	-	-	-	-

**Table 3.** The calculated interaction distance and the bond length of the nitroxazepine-SWCNT and the nitroxazepine

Nitroxazepine- SWCNT	Molecular descriptors			
	Gas		Solvent	
	PW91	BLYP	PW91	BLYP
$\Delta E_{int}$	-2.877	-0.430	-0.568	-0.407
$\Delta E_{BSSE}$	0.387	0.136	0.219	0.129
$\Delta E_{int}^{BSSE}$	-2.490	-0.294	-0.349	-0.278
$\Delta ZPE$	0.972	0.275	0.514	0.193
$T\Delta S$	-15.447	-13.248	-17.217	-12.085
$\Delta G_{Corr}^{BSSE}$	17.330	14.833	18.858	14.296

**Table 4.** The binding energies and Gibbs free energies of the nitroxazepine-SWCNT (all energy terms are given in kcal/mol<sup>-1</sup>)

Atom	PW91				BLYP			
	Gas		Solvent		Gas		Solvent	
	Muliken	Hirshfeld	Muliken	Hirshfeld	Muliken	Hirshfeld	Muliken	Hirshfeld
O1	0.012	0.011	0.003	0.003	0.011	0.011	0.041	0.039
O2	0.018	0.017	0.004	0.004	0.018	0.017	0.042	0.039
N3	0.003	0.004	0.001	0.002	0.002	0.003	0.022	0.027
C4	0.006	0.008	0.000	0.002	0.005	0.007	0.005	0.008
N5	0.209	0.242	0.257	0.270	0.210	0.240	0.209	0.021
C6	-0.057	0.050	-0.021	0.041	-0.055	0.050	-0.024	0.048
N9	-0.007	0.000	0.003	0.006	-0.013	-0.002	-0.005	0.001
O10	0.012	0.011	0.010	0.007	0.013	0.014	0.010	0.011
O11	-0.003	-0.003	-0.003	-0.003	0.001	0.000	0.004	0.007

### Quantum chemical parameters

Table 5. shows the quantum chemical parameters of (5,5)-SWCNT compound and SWCNT-nitroxazepine complex. When nitroxazepine is physisorbed on SWCNT to form nitroxazepine-SWCNT complex, the complex band gap decreases in both gaseous and liquid phases but more significantly in liquid phase. The decrease in the band gap is due to the weak interaction. The global hardness and ionization potential of nitroxazepine-SWCNT complex also decrease. This implies that reactivity of nitroxazepine-SWCNT complex increases. The increase in dipole moments of nitroxazepine-SWCNT complex induces significant polarizability within SWCNT. In addition, the dipole moment of the complex is higher in liquid phase than in gas phase and this is an indication of the polarization effect of the solvent on the complex. The increase in electrophilicity of nitroxazepine-SWCNT complex suggests an

increase in its reactivity. The dielectric solvation energies of nitroxazepine-SWCNT complex are high which implies that the complex has a high solubility in solvents.

**Table 5.** The Quantum molecular descriptors for the nitroxazepine-SWCNT and SWCNT

Nitroxazepine-SWCNT	SWCNT	Parameter				Molecular descriptors			
		Gas		Solvent		Gas		Solvent	
		PW91	BLYP	PW91	BLYP	PW91	BLYP	PW91	BLYP
$\Delta E$ (eV)	-	0.939	0.941	0.931	0.931	0.921	0.923	0.756	0.664
Ionization Potential (IP)(eV)	Energetic Orbital	5.577 3.309	5.311 3.993	4.586 4.443	4.295 4.161	5.331 4.300	5.079 4.065	4.382 4.427	4.120 4.159
Electron Affinity (EA)(eV)	Energetic Orbital	2.100 4.248	1.842 3.052	3.392 3.512	3.101 3.230	2.639 3.379	2.413 3.142	3.717 3.671	3.480 3.495
Global hardness ( $\eta$ )(eV)	Energetic Orbital	1.738 0.469	1.735 0.471	0.597 0.466	0.597 0.466	1.346 0.460	1.333 0.462	0.333 0.378	0.320 0.332
electronegativity ( $\chi$ )(eV)	Energetic Orbital	3.838 3.778	3.576 3.523	3.989 3.978	3.698 3.695	3.985 3.840	3.746 3.603	4.050 4.049	3.800 3.827
Electrophilicity ( $\omega$ )(eV)	Energetic Orbital	4.237 15.210	3.686 13.186	13.321 16.991	11.458 14.665	5.899 16.012	5.265 14.066	24.652 21.686	22.552 22.054
Electrodonating ( $\omega^-$ )(eV)	Energetic Orbital	6.374 17.157	5.691 15.006	15.390 19.038	13.381 16.571	8.060 17.989	7.305 15.925	26.718 23.758	24.492 24.009
Electroaccepting ( $\omega^+$ )(eV)	Energetic Orbital	2.535 13.379	2.115 11.483	11.401 15.060	9.683 12.876	4.074 14.149	3.558 12.322	22.668 19.709	20.692 20.182
net electrophilicity ( $\Delta\omega_{\pm}$ )(eV)	Energetic Orbital	8.909 30.537	7.806 26.489	26.791 34.098	23.065 29.446	12.134 32.139	10.863 28.247	49.386 43.467	45.184 44.191
Dipole moment ( $\mu$ )(D)	-	0.003	0.003	0.004	0.004	8.719	9.576	15.835	19.281
Solvation energy (kcal/mol <sup>-1</sup> )	-	-	-	-19.68	-17.15	-	-	-35.87	-35.23

### IR spectra part one

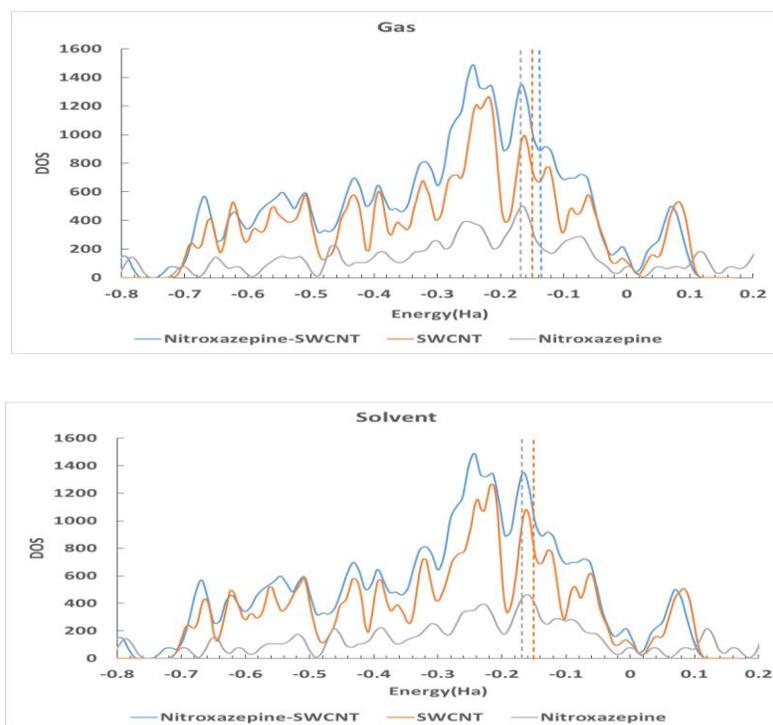
The sharp bands, which are assigned to the characteristic asymmetric deformation modes of nitroxazepine-SWCNT complex, occurred in the regions of 1237 cm<sup>-1</sup>, 1132 cm<sup>-1</sup> and 1211 cm<sup>-1</sup> (Figure S2). The most intense band and the highest frequency in the infrared spectra of SWCNT are related to the C-H stretching vibrations. The wavenumbers which are assigned to the deformation modes of SWCNT are 3152 cm<sup>-1</sup> and 3186 cm<sup>-1</sup> in gas phase and 3158 cm<sup>-1</sup> and 3189 cm<sup>-1</sup> in liquid phase. Asymmetric deformation mode of SWCNT at 1238 cm<sup>-1</sup> has the highest intensity in liquid phase. The C-H stretching vibrations of SWCNT have been assigned to the regions 3152-3123 cm<sup>-1</sup> and 3186-3151 cm<sup>-1</sup> in gas phase and the regions 3158-3133 cm<sup>-1</sup> and 3190-3156 cm<sup>-1</sup> in liquid phase. In addition, the C-H stretching vibration modes of SWCNT in gaseous nitroxazepine-SWCNT occur in the region 3157-3148 cm<sup>-1</sup>. When the nitroxazepine-SWCNT is in its liquid phase, these modes occur at two different regions, 3158-3141 cm<sup>-1</sup> and 3164-3137 cm<sup>-1</sup>. The number of C-H stretching modes of carbon nanotubes are

higher than nitroxazepine-SWCNT modes. This indicates that the frequencies of the C-H stretching of carbon nanotubes decrease as a result of interaction between SWCNT and nitroxazepine. The highest frequency of nitroxazepine-SWCNT is assigned to the characteristic C-H stretching vibrations in rings of nitroxazepine. These modes occur in the region 3191-3159  $\text{cm}^{-1}$  in gas phase and in the regions 3187-3159  $\text{cm}^{-1}$  and 3191-3161  $\text{cm}^{-1}$  in liquid phase. The highest frequency of nitroxazepine is assigned to the characteristic C-H stretching vibrations of rings. These modes have been assigned to wavenumbers, 3184-3135  $\text{cm}^{-1}$ , 3192-3143  $\text{cm}^{-1}$ , 3200-3156  $\text{cm}^{-1}$  and 3236-3164  $\text{cm}^{-1}$ . The C-H stretching frequencies related to rings in nitroxazepine are slightly lower than nitroxazepine-SWCNT complex which implies that the frequencies of the C-H stretching of nitroxazepine rings increase as a result of the interaction between SWCNT and nitroxazepine. The asymmetric deformation modes of nitroxazepine occur at 1242  $\text{cm}^{-1}$  (BLYP) or 1318  $\text{cm}^{-1}$  (PW91) in gas phase and at 1238  $\text{cm}^{-1}$  (BLYP) or 1284  $\text{cm}^{-1}$  (PW91) in liquid phase. These modes have maximum intensity. In nitroxazepine-SWCNT complex, the C-N stretching mode is assigned to the region 988-1033  $\text{cm}^{-1}$  in gas phase and the regions 982-1035  $\text{cm}^{-1}$  and 981-1034  $\text{cm}^{-1}$  in liquid phase. For nitroxazepine, C-N stretching mode was assigned to the regions 994-1043  $\text{cm}^{-1}$  and 975-1059  $\text{cm}^{-1}$  in gas phase and 988-1048  $\text{cm}^{-1}$  and 972-1041  $\text{cm}^{-1}$  in liquid phase. The C-N stretching vibrations of nitroxazepine-SWCNT are slightly different from free nitroxazepine. Vibrational frequencies of the fundamental modes of SWCNT and nitroxazepine indicate that the interaction between these compounds has a physical adsorption nature. Figure S2 shows that all IR frequencies are stronger in liquid phases than in gas phases.

### **Density of states (DOS) part one**

The DOS was calculated to study the adsorption properties of nitroxazepine-SWCNT complex. The DOS spectra of nitroxazepine, SWCNT and nitroxazepine-SWCNT are plotted in Figure 3. There is a small difference between the DOSs of nitroxazepine-SWCNT and SWCNT. The energy gap of SWCNT is slightly reduced after interaction with nitroxazepine. There is a relationship between the DOS and the energy gap. The trend of the DOS is similar to the energy gap. The Fermi energies of SWCNT and nitroxazepine-SWCNT are further away from their highest peaks. This implies that many states available for occupation are near Fermi level. Nitroxazepine-SWCNT peak is higher than the peaks of SWCNT and nitroxazepine. Nitroxazepine has the lowest peak in the DOS spectra. Fermi energy of SWCNT is the same as its HOMO energy. Fermi energy of nitroxazepine-SWCNT is located between its HOMO and LUMO energies. The interaction of SWCNT with nitroxazepine caused a slight shift in the DOS spectra of nitroxazepine-SWCNT complex. The small shift indicates that the interaction process does not significantly change the DOS spectra of nitroxazepine-SWCNT complex. Therefore, we may conclude

that nitroxazepine molecule is weakly bounded to SWCNT and thus nitroxazepine-SWCNT interaction can be classified as a physisorption process. DOSs of SWCNT, nitroxazepine and nitroxazepine-SWCNT were calculated to determine the sensitivity of SWCNT to nitroxazepine molecule. One can see that the DOS plot of nitroxazepine-SWCNT changes whereas the DOS plot of SWCNT does not. Our results show that the SWCNT was able to detect the nitroxazepine molecule. Therefore, SWCNT can be a proper sensor for nitroxazepine molecule.



**Figure 4.** The density of states (DOS) for nitroxazepine, SWCNT and nitroxazepine-SWCNT in both gaseous and aqueous phases and by using GGA/BLYP. The dashed lines indicate the position of the Fermi level

## Interaction of neurotransmitters with nitroxazepine

### Quantum chemical descriptors of neurotransmitters

Table S4 presents the quantum chemical descriptors of serotonin, norepinephrine and dopamine. The serotonin and norepinephrine have highest LUMO, energy gap and global hardness but with the lowest electron affinity, electronegativity, electroaccepting, global softness, net electrophilicity and dipole moment. The serotonin and norepinephrine are nucleophiles. Nitroxazepine is an electrophile and can interact with serotonin and norepinephrine. Equations 1 and 2 were used to calculate the charge transfer between the nitroxazepine, serotonin and norepinephrine. "a" in Equations 1 and 2 is nitroxazepine and "b" is serotonin or norepinephrine. The charge transfer calculations are given in Table 6.  $\Delta N$  and ECT are greater than zero and therefore charge flows from serotonin and

norepinephrine to nitroxazepine. We can conclude that serotonin and norepinephrine act as electron donors (nucleophiles) and nitroxazepine acts as an electron acceptor (electrophile).

**Table 6.** Calculated ECT and  $\Delta N$  using B3LYP and PW91

Molecular descriptors	Parameter	Nitroxazepine-serotonin				Nitroxazepine-norepinephrine			
		Gas		Solvent		Gas		Solvent	
		PW91	BLYP	PW91	BLYP	PW91	BLYP	PW91	BLYP
ECT	Energetic	0.724	0.718	2.129	2.301	0.791	0.754	2.301	2.451
	Orbital	4.387	4.527	11.464	7.269	4.634	4.721	11.685	7.459
$\Delta N$	Energetic	0.095	0.096	0.181	0.186	0.086	0.081	0.162	0.157
	Orbital	0.249	0.259	0.232	0.279	0.227	0.220	0.187	0.222

### Local molecular reactivity

Serotonin and norepinephrine are suitable for electrophilic attack whereas nitroxazepine has sites for adsorption of nucleophile agents. The maximum  $f^+$  is associated with oxygen atoms of nitroxazepine, atoms 1 and 2 in Figure 1. Oxygen atoms of serotonin and norepinephrine provide the sites for electrophilic attack, atoms 7 and 8 in Figure 1. The key Fukui indices of the nitroxazepine, serotonin and norepinephrine are listed in Table S5. Conformational isomers of nitroxazepine-serotonin and nitroxazepine-norepinephrine complexes were determined. These conformers were optimized using PW91 and BLYP codes. It has been observed that the interactions between nitroxazepine, norepinephrine and serotonin are mainly due to hydrogen bonding, Figure 3.

**Table 7.** The calculated bond lengths and interaction distance of the nitroxazepine, norepinephrine, serotonin, nitroxazepine-norepinephrine and nitroxazepine-serotonin

Distance (Å)	Norepinephrine				Serotonin			
	PW91		BLYP		PW91		BLYP	
	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent
O7-H6	0.975	0.977	0.977	0.978	0.971	0.974	0.973	0.976
C8-H5	-	-	-	-	1.091	1.091	1.091	1.090
O8-H5	0.970	0.974	0.973	0.976	-	-	-	-
Distance (Å)	Nitroxazepine-norepinephrine				Nitroxazepine-serotonin			
	PW91		BLYP		PW91		BLYP	
	Gas	Solvent	Gas	Solvent	Gas	Solvent	Gas	Solvent
O1-N3	1.234	1.239	1.245	1.250	1.252	1.240	1.261	1.236
O2-N3	1.247	1.251	1.258	1.262	1.267	1.250	1.247	1.250
C4-N3	1.467	1.457	1.477	1.465	1.463	1.456	1.473	1.461
O2-H6	2.027	1.956	2.041	1.991	1.923	1.973	1.982	1.967
O1-H5	4.153	4.118	4.238	4.288	3.820	3.738	3.755	3.742
O7-H6	0.983	0.986	0.984	0.987	0.986	0.980	0.981	0.979
C8-H5	-	-	-	-	1.089	1.091	1.089	1.091
O8-H5	0.970	0.974	0.973	0.976	-	-	-	-
Distance (Å)	Nitroxazepine							
	PW91				BLYP			
	Gas		Solvent		Gas		Solvent	
	O1-N3		1.235		1.242		1.245	
	O2-N3		1.237		1.242		1.248	
	C4-N3		1.475		1.461		1.487	

**Table 8.** The binding energies and Gibbs free energies for nitroxazepine-serotonin and nitroxazepine-norepinephrine all energy terms are given in kcal/mol<sup>-1</sup>)

Nitroxazepine - norepinephrine	Nitroxazepine-serotonin				Molecular descriptors			
	Gas		Solvent		Gas		Solvent	
	PW91	BLYP	PW91	BLYP	PW91	BLYP	PW91	BLYP
$\Delta E_{int}$	-5.875	-5.066	-2.276	-3.037	-4.259	-3.106	-2.437	-2.069
$\Delta E_{BSSE}$	0.431	0.389	0.205	0.189	0.328	0.148	0.187	0.118
$\Delta E_{int}^{BSSE}$	-4.444	-4.677	-2.071	-2.848	-3.931	-2.958	-2.250	-1.951
$\Delta ZPE$	0.748	0.957	0.456	0.789	1.167	1.215	0.171	0.623
$T\Delta S$	-12.874	-10.399	-9.771	-9.460	-14.606	-11.518	-13.309	-10.239
$\Delta G_{Corr}^{BSSE}$	13.823	12.326	10.977	11.008	16.662	9.388	14.227	11.535

Table 7. shows that the bond lengths and the interaction distances of the compounds in their gas phase are approximately equal to their corresponding values in their liquid phase. O2-N3 bond lengths of the complexes are slightly lengthened whereas C4-N3 bond lengths are slightly shortened. The C8-H5 bond length of serotonin is close to C8-H5 bond length of nitroxazepine-serotonin complex. The C8-H5 bond length of nitroxazepine-norepinephrine complex is the same as C8-H5 bond length of norepinephrine. Our results show that optimized structures of nitroxazepine-serotonin and nitroxazepine-norepinephrine complexes have a physisorb nature.

The binding energies and Gibbs free energy of norepinephrine-nitroxazepine and nitroxazepine-serotonin complexes were calculated (Table 8). Table 8. shows that, the absorption process for formation of these complexes is an exothermic process as the binding energies are negative. Interaction energy of nitroxazepine-norepinephrine complex is higher than nitroxazepine-Serotonin. The binding energies of complexes increase as phase changes from gas to liquid. The binding energies of the complexes are in the range 2.069-5.875 kcal/mol<sup>-1</sup> (negative values) which suggests interactions between nitroxazepine, norepinephrine and serotonin have a physisorb nature. Bond lengths also imply that the interactions are physisorb. It should be noted that the adsorption process of norepinephrine- nitroxazepine and nitroxazepine-serotonin complexes is not spontaneous at room temperature.

### Quantum chemical descriptors of complexes

The quantum molecular descriptors of the complexes are listed in Table 9. In the presence of a solvent, the energy gap of nitroxazepine-norepinephrine complex is slightly lower which points to an increase in its solubility. The dipole moments of the two complexes are higher in liquid phase than in gas phase and this is an indication of the polarization effect of the solvent on the complexes. The  $\mu$  values of nitroxazepine-serotonin complex are lower than the corresponding  $\mu$  values of

nitroxazepine-norepinephrine complex. This demonstrates that the polarization effect of solvent on nitroxazepine-norepinephrine molecule is more than its effect on nitroxazepine-serotonin complex. Norepinephrine has three oxygen atoms and one nitrogen atom but serotonin has one oxygen atom and two nitrogen atoms. The dielectric solvation energy of nitroxazepine-norepinephrine complex is the lowest and that is the reason it has the highest solubility in solvent. The negative solvation energy indicates that the solvation is spontaneous. The energy gap, ionization potential and global hardness of nitroxazepine-norepinephrine and nitroxazepine-serotonin complexes are lower than norepinephrine and serotonin. Electrophilicity of these two complexes are higher than norepinephrine and serotonin which suggests an increase in reactivity. The dipole moments of these two complexes are higher than their neurotransmitters due to the increasing number of oxygen and nitrogen atoms. The dielectric solvation energies of nitroxazepine-norepinephrine and nitroxazepine-serotonin complexes are the highest which suggest that these complexes have the highest solubility in solvent.

### **IR spectra part two**

Figure S3 shows that the first sharp band in the region of  $3572\text{ cm}^{-1}$  can be assigned to the characteristic N-H stretching mode of nitroxazepine-serotonin, band 9 in Figure 3, the second sharp band in the region of  $1133\text{ cm}^{-1}$  can be assigned to asymmetric deformation modes of the methyl groups, band 10 in Figure 3, and the third sharp band in the region of  $3193\text{ cm}^{-1}$  can be assigned to C-H stretching vibrations in rings of nitroxazepine. The highest intensity occurs at  $1160\text{ cm}^{-1}$  (BLYP) or  $1163\text{ cm}^{-1}$  (PW91) in gas phase and  $1152\text{ cm}^{-1}$  (BLYP) or  $1159\text{ cm}^{-1}$  (PW91) in liquid phase. These frequencies are assigned to the asymmetric deformation modes of serotonin. The N-H stretching modes of nitroxazepine-serotonin complex are assigned to highest wavenumbers in gas phase and  $3557\text{ cm}^{-1}$  (BLYP) or  $3583\text{ cm}^{-1}$  (PW91) in liquid phase.

The O-H stretching mode of nitroxazepine-serotonin complex are  $3540\text{ cm}^{-1}$  (BLYP and PW91) in gas phase and  $3427\text{ cm}^{-1}$  (BLYP) or  $3544\text{ cm}^{-1}$  (PW91) in liquid phase, band 7 in Figure 3. O-H stretching modes of serotonin are  $3672\text{ cm}^{-1}$  (BLYP) or  $3716\text{ cm}^{-1}$  (PW91) in gas phase and  $3648\text{ cm}^{-1}$  (BLYP) or  $3689\text{ cm}^{-1}$  (PW91) in liquid phase. The O-H stretching modes have maximum frequency. O-H stretching modes of serotonin are slightly higher than nitroxazepine-serotonin complex. This demonstrates that the interaction between serotonin and nitroxazepine decreased the frequency of O-H stretching. Vibrational frequencies suggest a physisorption interaction between nitroxazepine and serotonin.

The most intense band in the infrared spectra of gaseous nitroxazepine-norepinephrine occurs at 1627 cm<sup>-1</sup> (BLYP) or 1659 cm<sup>-1</sup> (PW91) in a symmetric stretching mode of the carbonyl group, band 11 in Figure 3. Asymmetric deformation modes of the methyl groups and rings, band 10 in Figure 3, occur at 1132 cm<sup>-1</sup> (BLYP) and asymmetric deformation modes of complex occur at 1263 cm<sup>-1</sup> in liquid phase. The greatest intensity of norepinephrine occurs at 1256 cm<sup>-1</sup> (BLYP) or 1286 cm<sup>-1</sup> (PW91). Asymmetric deformation modes and O-H stretching vibrations, band 9 in Figure 3, occur at 3503 cm<sup>-1</sup> (BLYP) or 3525 cm<sup>-1</sup> (PW91) in gas phase. Wagging vibrations of O-H at 276 cm<sup>-1</sup> and O-H stretching vibrations, band 9 in Figure 4, at 3425 cm<sup>-1</sup> and 3381 cm<sup>-1</sup>, band 9 in Figure 3, (PW91) have maximum intensity. However, the O-H stretching vibrations modes of nitroxazepine-norepinephrine, band 9 in Figure 4, occur at 3508 cm<sup>-1</sup> (BLYP) or 3535 cm<sup>-1</sup> (PW91) in gas phase and 3474 cm<sup>-1</sup> (BLYP) or 3520 cm<sup>-1</sup> (PW91) in liquid phase. The highest frequency of nitroxazepine-norepinephrine is assigned to the characteristic O-H stretching vibrations, band 8 in Figure 4, which occurs at 3686 cm<sup>-1</sup> (BLYP) or 3736 cm<sup>-1</sup> (PW91) in gas phase and 3656 cm<sup>-1</sup> (BLYP) or 3700 cm<sup>-1</sup> (PW91) in liquid phase. For norepinephrine, these modes have been calculated to occur at 3690 cm<sup>-1</sup> (BLYP) or 3735 cm<sup>-1</sup> (PW91) in gas phase and 3654 cm<sup>-1</sup> (BLYP) or 3693 cm<sup>-1</sup> (PW91) in liquid phase. For nitroxazepine-norepinephrine, the BLYP calculations assign 3497 cm<sup>-1</sup> to O-H stretching vibrations, band 7 in Figure 4, in gas phase and 3439 cm<sup>-1</sup> in liquid phase. However, the PW91 method assigns 3511 cm<sup>-1</sup> to O-H stretching vibrations in gas phase and 3439 cm<sup>-1</sup> in liquid phase. For norepinephrine, these modes occur at 3638 cm<sup>-1</sup> (BLYP) or 3677 cm<sup>-1</sup> (PW91) in gas phase and 3614 cm<sup>-1</sup> (BLYP) or 3646 cm<sup>-1</sup> (PW91) in liquid phase.

**Table 9.** The quantum molecular descriptors for nitroxazepine-serotonin and nitroxazepine-norepinephrine

Molecular descriptors	Parameter	Nitroxazepine-serotonin				Nitroxazepine-norepinephrine			
		Gas		Solvent		Gas		Solvent	
		PW91	BLYP	PW91	BLYP	PW91	BLYP	PW91	BLYP
$\Delta E$ (eV)	-	0.900	0.868	1.015	0.922	1.017	0.999	1.011	0.970
Ionization potential (IP)(eV)	Energetic	5.819	5.624	4.935	5.191	6.045	5.865	5.137	4.957
	Orbital	4.427	4.249	4.894	4.715	4.587	4.429	4.914	4.743
Electron affinity (EA)(eV)	Energetic	1.507	1.359	3.286	3.185	1.483	1.330	3.271	3.134
	Orbital	3.528	3.381	3.879	3.793	3.570	3.430	3.903	3.773
Global hardness ( $\eta$ )(eV)	Energetic	2.156	2.133	0.825	1.003	2.281	2.267	0.933	0.912
	Orbital	0.450	0.434	0.508	0.461	0.508	0.499	0.506	0.485
electronegativity ( $\chi$ )(eV)	Energetic	3.663	3.492	4.111	4.188	3.764	3.597	4.204	4.046
	Orbital	3.978	3.815	4.387	4.254	4.078	3.929	4.409	4.258
Electrophilicity ( $\omega$ )(eV)	Energetic	3.111	2.858	10.246	8.742	3.105	2.854	9.470	8.975
	Orbital	17.587	16.773	18.955	19.623	16.356	15.462	19.222	18.695
Electrodonating ( $\omega^-$ )(eV)	Energetic	5.212	4.870	12.405	10.961	5.273	4.936	11.689	11.111
	Orbital	19.632	18.735	21.212	21.807	14.381	17.489	21.490	20.885
Electro accepting ( $\omega^+$ )(eV)	Energetic	1.549	1.379	8.294	6.773	1.509	1.339	7.485	7.066
	Orbital	15.654	14.920	16.826	17.553	14.381	13.559	17.081	16.626
Netelectrophilicity ( $\Delta\omega^\pm$ )(eV)	Energetic	6.761	6.249	20.698	17.734	6.781	6.275	19.173	18.177
	Orbital	35.286	33.655	38.038	39.360	32.840	31.048	38.571	37.511

Dipole moment ( $\mu$ )(D)	-	4.246	4.246	6.950	7.546	9.810	9.988	15.443	15.889
Solvation energy (kcal/mol <sup>-1</sup> )	-	-	-	-31.32	-31.6	-	-	-34.52	-34.92

The O-H stretching vibrations show that there are slight difference between nitroxazepine-norepinephrine complex and norepinephrine. Vibrational frequencies indicate that the interaction between nitroxazepine and norepinephrine is a physisorption process. Figure S3 shows that all IR frequencies are stronger in liquid phase than in gas phase.

### DOS part two

The DOSs were calculated to study interactions of nitroxazepine with serotonin and norepinephrine. The DOS spectra of nitroxazepine, serotonin, norepinephrine, nitroxazepine-norepinephrine and nitroxazepine-serotonin are plotted in Figure S4. The DOSs of complex systems are higher than nitroxazepine, serotonin and norepinephrine. This implies that the energy gaps of serotonin and norepinephrine will decrease after interaction with nitroxazepine. The complex systems have the highest peaks whereas serotonin and norepinephrine have the lowest peaks. The Fermi energy of nitroxazepine is closer to its highest peak. The highest peak of serotonin has the same energy level as the Fermi energy. The Fermi energy of norepinephrine is slightly less than its highest peak in gas phase but further from the highest peak in liquid phase. The highest peaks of nitroxazepine-serotonin and nitroxazepine-norepinephrine are closer to their Fermi energies in liquid phase when compared with their highest peaks in gas phase. The Fermi energy of nitroxazepine is equal to the Fermi energy of serotonin and is slightly more negative than nitroxazepine. The Fermi energies of neurotransmitters are the same as their HOMO energies. The Fermi energies of complex systems are located between their HOMO and LUMO energies. The DOS of neurotransmitters shifts upward by any amount in the range 0.019-0.046 eV as a result of interaction of neurotransmitters with nitroxazepine. This shift does not cause any significant charge transfer between nitroxazepine, serotonin and norepinephrine. These weak interactions are characterized as physisorption processes.

### Conclusions

The quantum chemical parameters provided information about the chemical reactivity of the tricyclic antidepressant drugs. Nitroxazepine is the most reactive tricyclic antidepressant. In this work, the Fukui functions were used to predict the reactivity of sites on drug molecules. Nitroxazepine can act as a nucleophile when interacting with carbon nanotubes. The highest  $f^-$  of nitroxazepine is associated with nitrogen atom. Serotonin and norepinephrine are nucleophile and

the maximum  $f^-$  of these compounds are suitable for electrophilic attack. In contrast, nitroxazepine is electrophile and the maximum  $f^+$  of this compound shows sites for adsorption of nucleophile agents. The highest  $f^+$  of nitroxazepine is associated with oxygen atoms. Serotonin and norepinephrine sites for electrophilic attack are the OH groups. The hydrogen bonding between oxygen atoms of nitroxazepine and OH of serotonin and norepinephrine has been identified as the dominant interaction site. In general, nitroxazepine is weakly bounded to pristine carbon nanotube, norepinephrine and serotonin through van der Waals type interactions. Thus, these interactions can be classified as physisorption interactions. The small binding energy, large adsorption distance, density of states and IR spectra are consistent with physical adsorption and interactions of nitroxazepine molecule with norepinephrine, serotonin and SWCNT.

### Supporting information

All the additional information on chemical structure and optimized geometries of tricyclic antidepressants drugs (Figure S1), IR spectrum of nitroxazepine, SWCNT and nitroxazepine-SWCNT, serotonin, norepinephrine, nitroxazepine-serotonin and nitroxazepine-norepinephrine (Figures S2, S3), the DOS spectra of nitroxazepine, serotonin, norepinephrine, nitroxazepine-norepinephrine and nitroxazepine-serotonin (Figure S4), quantum chemical descriptors for 28 tricyclic antidepressants drugs (Tables S1-S3), quantum chemical descriptors for serotonin, norepinephrine and dopamine (Table S4) and the calculated Fukui functions for norepinephrine, serotonin and nitroxazepine (Table S5) are provided in the supporting information available [www.chemmethod.avicenna.pub](http://www.chemmethod.avicenna.pub).

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