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Investigation of Capecitabine and 5-fluorouracil anticancer drugs structural properties and their interactions with single-walled carbon nanotube: insights from computational methods

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ABSTRACT

Nowadays, carbon nanotubes (CNTs) have been highly utilized in medical research as biosensors and drug carriers. In the current study, Single-Walled Carbon Nanotube (SWCNT) with nanotube length of 10 Å, 90 carbon atoms (5,5), and open-end structure has been attached to two chemotherapeutic agents, 5-fluorouracil(5-FU) and its prodrug capecitabine. Subsequently, the NMR, Frequency and thermochemical properties of these structures (5-FU, capecitabine and the attached form of these two molecules at CNT) have been analyzed in different media. The Hyperchem 7.0 and Gaussian 03 software were used. Molecular mechanics and dynamics simulation methods were semi-empirical and ab initio. The quantum mechanics was calculated by B3LYP and Hartree-Fock methods at STO-3G, 6-31G levels of theory. The current study showed the nanotube ameliorates the stability of both compounds; however, 5-FU exhibited more constancy. In conclusion, our findings confirmed that the presence of nanotubes could improve the results of these compounds as anticancer agents.

Keywords: *Capecitabine, 5-Fluorouracil, Nanotube, NMR, Semi-Empirical.*

1. INTRODUCTION

The 5-fluorouracil (5-FU) has been used as a chemotherapeutic agent against breast cancer, colorectal cancer, and a range of solid tumors for many years [1]. Because of its toxic effects on bone marrow, gastrointestinal tract and also its common side effects such as nausea, abdominal pain, stomatitis, and diarrhea, researches were done to solve these existing problems. Findings led to developing a new drug which has overcome the systemic toxicity of 5-FU [1,5]. This new drug is called capecitabine (CAP or Xeloda) which is a prodrug molecule of 5-FU. By enzymatic reactions, consisted of Carboxylesterase, Cytidinedeaminase and Thymidine phosphorylase enzymes, in the liver tissue and at the cancerous cells, it converts to 5-FU (Figure 1) [1]. Metabolizing to 5-dUMP causes deficiency of thymidylate by inhibiting thymidylate synthase (TS) resulting in a reduction of deoxyribonucleic acid (DNA) synthesis and inhibition of cell division by blocking TS, thus a thymidylate deficiency occurs [2]. Capecitabine is currently medically used as an antineoplastic agent to treat colon, metastatic breast malignancy and metastatic colorectal cancers [1,3]. It distributes in all human body tissues in about 3 hours.4over the past 20 years studies triggered to increase our understanding of the mechanism of the action of 5-FU. In turn, these investigations led to the developing of new treatment strategies which improve its antitumor efficacy [6]. Therefore, it seems to be necessary that molecular properties of capecitabine and 5-FU are analyzed to provide a better tool for the theoretical understanding of their molecular behaviours. In this regard, we may be able to find a new perspective to increase the competency of these drugs.

Carbon nanotubes (CNTs) are very common in medical research and have been considered as promising molecules in the fields of biosensing tools for diagnosis and monitoring as well as efficient drug delivery vehicles [7]. Several roles can be determined for CNTs including carriers for a wide range of therapeutic molecules and photothermal destructors of cancer cells according to the possibility of the manipulation of their surfaces and physical dimensions.

CNTs are essentially molecules composed of pure carbon atoms that are made of graphene sheets rolled into a cylinder which have two end structures: open-ended or capped. Single graphene sheets produce a single-walled carbon nanotube (SWCNT) while CNTs made of several graphene sheets form multiwall carbon nanotubes (MWCNTs) [8]. Needle-like CNTs are promising to introduce new carriers in medicine by which both small drug molecules and macromolecules like genes and proteins can be delivered. CNTs can be designed in order to adhere to certain molecules on their surfaces through covalent or noncovalent bonds. By needle-like shape, CNTs make them unable to penetrate cellular membranes and transport the carried therapeutic molecules to the cytoplasm [9,10,11].

CNTs can be defined by their mechanical and electrical properties, extraordinary thermal conductivity, and stability [12,13]. Carbon atoms in nanotube can establish a hexagonal lattice having been rolled up to form a cylinder of thin layers of benzene rings. Arranged in a cylindrical formation, the geometrically perfect nanotube consists of an sp^2-bonded graphene sheet [9,14]. In the current study, the (5,5) SWCNT including 90C atoms has been used [15].

Nanoparticle drug delivery systems have 3-200 nm size. The devices can be formed from a wide variety of materials including polymers (polymeric nanoparticles, micelles, or dendrimers), viruses (viral nanoparticles), lipids (liposomes), viral nanoparticles, and even organometallic compound (nanotubes)

[11]. The main advantages of nanoparticles are their improved bioavailability by enhancing aqueous solubility, their increased resistance half-life in the body for clearance, their increased specificity via their cognate receptors which results in escorting drug to a specific location in the body. These characteristics lead to the reduction along with in the quantity of the drug required and dosage toxicity, providing the safe delivery of toxic therapeutic drugs and protection of non-targeted tissues and cells from predictable side effects [16]. For instance, NPs was used to encapsulate a prodrug analog CAP and demonstrated similar toxicity levels to CAP and significantly lower toxicity levels than 5-FU [18] for carriers capecitabine used nanoparticles PEG–PLGA [19], GNPS [20], PLGA [4] nanoparticles of chitosan (CS) [11].

2. COMPUTATIONAL SECTION

In the current study, the single wall carbon nanotube was used.Our models, Capecitabine and 5-FU, were covalently added to carbon nanotube by (5,5) structure and a length of 10Å[21]. The optimized structure and properties were calculated by Gaussian 03 program [22]. B1LYP and Hartree-Fock (HF) methods at STO-3G, 6-31G levels of theory were performed for each structure [23].Total energy (KJ mol-1), moment dipole (in Debye) and Mulliken atomic charges between nanotube (5,5)- capecitabine and nanotube (5,5)- 5FU were calculated14 by B3LYP/6-31G, b3lyp/Sto-3g, hf/6-31g, hf/Sto-3g[29].The NMR parameters such as isotropy shielding and anisotropy shielding for some of the atoms in the capecitabine and 5-FU before their interaction with SWCNT have been analyzed because they were of importance[15]. Kinetic and thermodynamic parameters were accomplished with Hyperchem 7.0 software. There are three steps in any quantum mechanical calculation in HyperChem 7.0 program package[24].First, the molecule must be prepared by an appropriate starting geometry. Second, a calculation method and its associated (Setup menu) options must be chosen. Third, the type of calculations (single point, geometry optimization, Monte Carlo and vibrational analysis) via the relevant (Compute menu) options must be concerned [25].

Semi-Empirical Method. The performing cost of an HF calculation formally scales as the fourth power of the basic functions. This is the result of the number of Semi-empirical methods.To decrease the computational cost, two-electron integrals necessary for constructing the Fock matrix were reduced [26]. All atomic positions and lattice parameters were optimized by the semi-empirical calculations when total energy and atomic forces were minimized. The design was proposed by optimizing parameters such as Total Energy, Binding Energy, Isolated Atomic Energy, Electronic Energy, Core–Core Interaction and Heat of Formation for Capecitabine, 5-FU and nanotubes in which the best relationships has been found [27].The computational methods used in this study were the semi-empirical AM1, MNDO [28].

Molecular Mechanics (Monte Carlo Simulation) and Molecular Dynamics. The Hartree-Fock calculation (abbreviated HF) is the most common type of Ab initio calculations that is called the central field approximation. Quantum Monte Carlo (QMC) is a method that avoids making the HF mistakes in the first place. There are several kinds of QMC variation, diffusion andGreen's function [29,30]. However these calculations are time-consuming, they may be known today as the most accurate method. In general, Ab initio calculations provide good qualitative results and can obtain considerably accurate quantitative results as the proposed molecules become smaller [31]. Hyperchem uses the Metropolis method. In our study, Kinetic, potential and total energy were calculated by Monte Carlo and Molecular Dynamic simulation and time of simulations are 5000 ps [32]. In this research, solvent effects on the relative energies and structural properties of single-walled carbon nanotubes (SWCNT) surrounded by water, methanol and gas were revealed by Monte Carlo simulation [33]. Calculation and geometrical optimization of complex Capecitabine-nanotube in different temperature (290, 294, 298, 302, 306, 310and 314 kelvin) were conducted via Monte Carlo method (Amber, Bio+, MM+ and OPLS) [34].

Formula. The formula used for this study have been as following: In the thermodynamic analysis, Zero-point correction obtains from:

$$E_{tot} = E_{trans} + E_{rot} + E_{vib} + E_{electron}$$

Thermal correction to Energy:

$$H_{corr} = E_{tot} + k_B T$$

$$G_{corr} = H_{corr} - TS_{tot}$$

$\Delta PV = \Delta NRT$ was included in Gibbs free energy to calculate ΔG for a reaction; so $\Delta NRT \approx \Delta PV$ was assumed. By this assumption, ΔG have been computed correctly and changes in the number of moles of gas could be ignored.

ε_0 has been used to calculate total electronic energy:

Sum of electronic and zero-point energies= ε_0 + EZPE

Sum of electronic and thermal energies= ε_0 + Etot

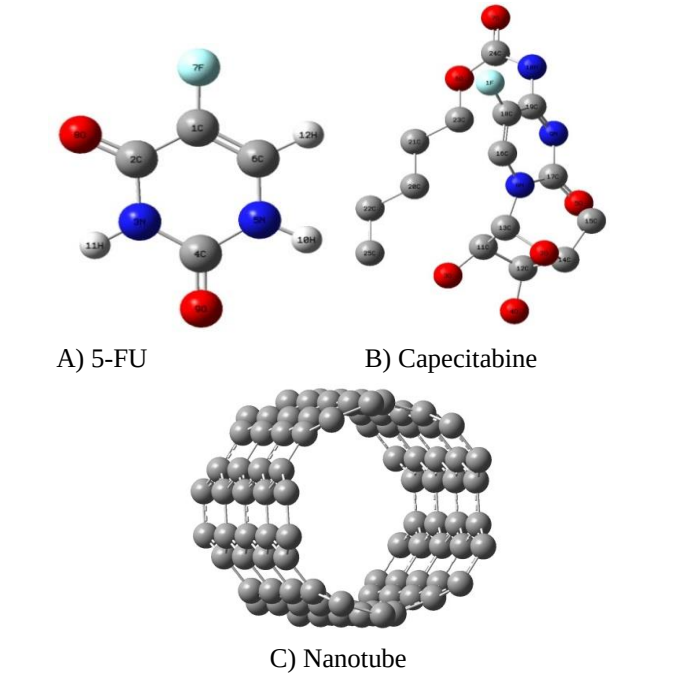
Sum of electronic and thermal enthalpies= ε_0 + Hcorr

Sum of electronic and thermal free energies= ε_0 + Gcorr

3. RESULTS SECTION

To solve existed limitations of 5-FU, capecitabine has been developed. Capecitabine is administered orally and subsequently absorbed fast. In liver tissue and cancerous cells, it is converted to 5-FU through three-step enzymatic reaction [1].

The aim of current study was to theoretically analyze the physical and thermochemical properties of these two drug attached to SWCNTin order to comprehend whether these combinations can be stable in body temperature and solvents or not.



A) 5-FU B) Capecitabine

C) Nanotube

Figure 2. Schematic illustration of 5-5-fluorouracil, Capecitabine, SWCNT.

Solvent effects on NMR parameters. NMR is a technique used in order to exert the magnetic properties of the certain atomic kernel which defines physical and chemical properties of atoms or molecules. This technique relies on the appearance of nuclear magnetic resonance (NMR) and can collect comprehensive information about the structure, chemical and dynamic aspects of molecules. Ab initio calculation of nuclear magnetic shielding has been considered as a method to analyze molecular structure. Hence, NMR is based on the quantum mechanical property of nuclei [26].

The theoretical values of isotropic (σiso) and anisotropic (σaniso) parameters of atoms have been shown in table 1.

While the maximum and minimum amounts of 5-FU molecule's σiso have been obtained, respectively, on the basis setHF/STO-3G =435.9 for 7F atom and HF/6-31G = -239.14 for 8O;for capecitabine, the maximum amount of σisowas related to 1F atoms on the basis set HF/STO-3G =446.08 and the minimum amount was related to 9N atoms and obtained by HF/6-31G =-120.61basis set. In regard to σaniso, the maximum and minimum amounts for capecitabine have been obtained for 7O atom on the basis set HF/STO-3G =671.62 and for 25C atom on the basis set HF/6-31G =10.13, respectively.These obtained amounts for 5-FU were related to 8O atoms on the basis set HF/STO_3G =1000.89 and to 5N atom on the basis set HF/6 -31G = 44.81 obtained.

The raw zero-point energy correction and the thermal corrections to the total energy, enthalpy, and Gibbs free energy (all of which include the zero-point energy) are listed, followed by the corresponding corrected energy. The analysis uses the standard expressions for an ideal gas in the canonical ensemble[42].

Thermal correction to Enthalpy = 0.082202

Thermal correction to Gibbs Free Energy = 0.055064

The related data on the effects of various temperatures and different media on thermochemical parameters have been presented in table 3 for both 5-FU and capecitabine. In table 3, it has been observed that the most negative value of ΔG (Gibbs free energy) for capecitabine was -813827 which was obtained from the B3LYP/Sto-3G method. But this amount was -322403 for 5-FU according to the B3LYP/6-31G method.The highest total energy (E_{tot}) of capecitabine was computed by HF/Sto-3G basis set and the calculated amount was 307.1238(Kcal/mol). Similar results have been observed for the 5-FU drug as well by 57.2414 (Kcal/mol).

Table 1. Optimized NMR/GIAO parameters of Capecitabine at B3LYP and HF levels by various basis sets.

Methods	HF						b3lyp					
Atomic Label	sto-3g			6-31g			sto-3g			6-31g		
	Atomic charge	σ_{iso}	σ_{aniso}	Atomic charge	σ_{iso}	σ_{aniso}	Atomic charge	σ_{iso}	σ_{aniso}	Atomic charge	σ_{iso}	σ_{aniso}
1F	-0.13318	446.0893	144.7558	-0.42584	418.0534	69.4954	-0.07323	377.6901	199.6129	-0.29819	370.4297	104.0297
2O	-0.25711	338.7648	41.1301	-0.57853	214.7119	40.6868	-0.20961	279.0291	38.5355	-0.40065	155.0278	65.3328
3O	-0.13588	386.8459	65.2229	-0.33916	295.7531	110.7198	-0.11173	350.5514	80.71	-0.26025	267.675	125.9688
4O	-0.12422	383.7618	68.0906	-0.31119	330.4103	67.2195	-0.09315	352.2735	68.611	-0.21072	306.5025	63.5189
5O	-0.28853	375.8741	82.0532	0.744683	343.3778	70.1124	-0.24324	352.2081	77.4847	0.713015	303.3702	71.9951
6O	-0.27665	321.1797	104.8076	-0.6967	208.5328	165.6427	-0.21108	266.8732	115.9206	-0.47357	168.8287	136.5882
7O	-0.31393	11.9501	671.6222	-0.57539	-13.1933	501.1734	-0.2688	44.4374	537.3586	-0.41959	-2.2905	428.7024
8N	-0.30819	303.2258	111.3005	-0.84117	222.7428	120.9923	-0.25209	265.8839	156.5868	-0.49868	178.4632	164.4769
9N	-0.23299	-2.6854	468.5544	-0.37465	-120.6118	518.1396	-0.24347	23.9684	413.9959	-0.25318	-83.88	473.8024
10N	-0.17466	274.6685	104.9205	-0.4544	188.7628	109.3955	-0.12615	251.3576	101.6741	-0.27642	171.1853	113.3155
11C	0.113988	193.6836	25.55	0.343642	147.6738	21.4002	0.081526	177.7533	27.4514	0.227417	130.9246	19.5281
12C	0.058372	192.3055	35.6285	0.247718	152.4422	32.786	0.035271	178.7034	41.2152	0.12929	136.1737	38.3624
13C	0.249045	168.2236	24.6736	0.508015	117.1636	10.6123	0.205869	152.8972	28.9795	0.298206	96.4442	13.8937
14C	0.101053	177.7856	35.9711	0.19464	115.6394	12.5809	0.080386	162.0142	41.6567	0.112928	98.0207	13.1933
15C	0.572869	204.0406	47.9457	-0.46999	158.8958	77.6017	0.51357	196.0447	39.8734	-0.393	145.3379	71.6401
16C	0.12692	123.7313	97.7544	0.489602	68.1467	118.1708	0.074387	125.3887	68.5487	0.30642	67.1547	89.6769
17C	0.092418	110.7476	148.6242	0.351144	92.2548	153.5788	0.107203	102.955	149.7804	0.186992	77.185	145.6164

18C	0.07153	125.0214	88.39	0.329037	60.3001	88.8834	0.037177	120.6974	63.0281	0.269611	52.8194	70.2112
19C	0.185042	124.6723	87.4001	0.29403	60.2188	120.9919	0.154955	125.5969	57.5698	0.135374	60.9712	87.6822
20C	0.016527	203.4763	13.1101	0.006464	160.8551	16.7766	0.020196	189.1617	14.7474	0.063469	143.032	18.4678
21C	0.017029	213.9305	18.0286	0.075136	169.5933	29.8998	0.013613	199.8557	19.4029	0.031827	152.3746	29.5566
22C	0.029311	216.3893	15.0674	0.067073	182.574	16.2873	0.027291	203.2861	16.1603	0.064974	166.3076	16.6418
23C	0.156098	185.6195	26.8551	0.395123	139.5201	30.4974	0.129569	171.1019	32.7742	0.294312	119.5241	31.4959
24C	0.437609	124.6157	111.0625	1.031432	48.0416	98.4597	0.323664	134.8105	104.0099	0.649974	53.1451	89.8839
25C	0.017532	213.0197	11.4455	-0.01072	180.633	10.1313	0.027871	201.8148	11.3041	0.000423	168.1138	11.5067

Table2. Optimized NMR/GIAO parameters of 5-FU at B3LYP and HF levels by various basis sets

Methods	**HF**						**b3lyp**					
Atomic Label	**sto-3g**			**6-31g**			**sto-3g**			**6-31g**		
	Atomic charge	**σ_{iso}**	**σ_{aniso}**	**Atomic charge**	**σ_{iso}**	**σ_{aniso}**	**Atomic charge**	**σ_{iso}**	**σ_{aniso}**	**Atomic charge**	**σ_{iso}**	**σ_{aniso}**
1C	0.078305	126.7301	87.9562	0.301522	67.2425	87.6062	0.05349	121.6875	71.7459	0.288945	57.9051	75.0942
2C	0.286461	112.066	118.1195	0.694642	32.1003	123.4432	0.213652	119.9523	98.1488	0.425227	37.4262	86.9956
3N	-0.162885	242.8927	94.6448	-0.479674	136.9444	95.7918	-0.105429	208.0004	116.3183	-0.292593	113.2427	105.4369
4C	0.403214	116.0517	141.8496	0.946696	39.3596	115.9477	0.314943	124.6651	123.3014	0.607849	43.8907	105.8098
5N	-0.138055	258.3151	50.2414	-0.515822	173.3712	70.62	-0.077026	228.3561	62.0455	-0.305944	146.3912	71.0825
6C	0.139243	127.2222	113.6057	0.445128	74.0098	137.9608	0.078748	129.2794	94.5971	0.277119	77.5540	114.2954
7F	-0.130386	435.9062	130.3866	-0.41401	408.6772	44.8131	-0.06443	354.3792	197.1325	-0.29197	351.6871	84.2406
8O	-0.235003	-199.277	1000.8947	-0.498098	-239.1443	914.8905	-0.208258	-126.3526	814.5867	-0.36701	-177.3366	770.2916
9O	-0.240896	-145.588	886.0905	-0.480384	-209.25	787.5774	-0.20569	-94.8907	716.9771	-0.341624	-169.3437	667.8893

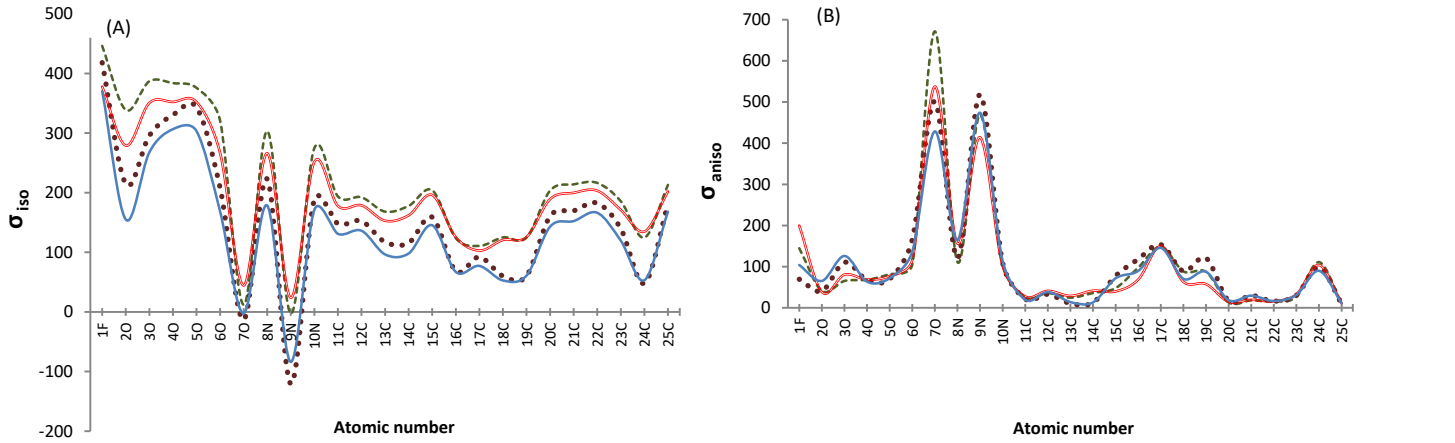


Figure 3. NMR parameters of (A) isotropic and (B) anisotropic shielding for Capecitabine in gas phases at the HF/6-31G, HF/STO-3G and B3LYP/6-31G, B3LYP/STO-3G basis sets. hf/sto-3g , b3lyp/sto-3g , hf/6-31g , b3lyp/6-31g.

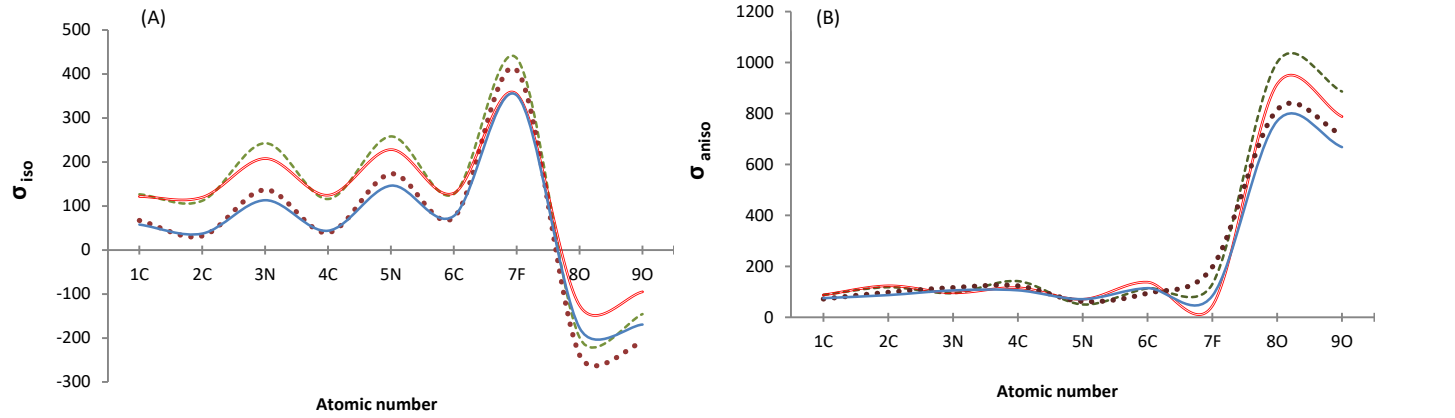


Figure 4. NMR parameters of (A) isotropic and (B) anisotropic shielding for 5-FU in gas phases at the HF/6-31G, HF/STO-3G and B3LYP/6-31G, B3LYP/STO-3G basis sets. hf/sto-3g , b3lyp/sto-3g , hf/6-31g , b3lyp/6-31g.

Temperature and solvent effects on thermochemical parameters. The raw zero-point energy correction and the thermal corrections to the total energy, enthalpy, and Gibbs free energy (all of which include the zero-point energy) are listed, followed by the corresponding corrected energy. The analysis uses the standard expressions for an ideal gas in the canonical ensemble[42].

Thermal correction to Enthalpy = 0.082202

Thermal correction to Gibbs Free Energy = 0.055064

The related data on the effects of various temperatures and different media on thermochemical parameters have been presented in table 3 for both 5-FU and capecitabine. In table 3, it has been observed that the most negative value of ΔG (Gibbs free energy) for capecitabine was -813827 which was obtained from the B3LYP/Sto-3G method. But this amount was -322403 for 5-FU according to the B3LYP/6-31G method. The highest total energy (E_{tot}) of capecitabine was computed by HF/Sto-3G basis set and the calculated amount was 307.1238(Kcal/mol). Similar results have been observed for the 5-FU drug as well by 57.2414 (Kcal/mol).

Table3. Energy Parameters (kcal/mol) of capecitabine and 5-FU at B3LYP and HF levels computed by STO-3G and 6-31G basis sets by Freq methods.

Methods / Parameters/Energy	HF		B3LYP	
	STO-3G	6-31G	STO-3G	6-31G
Capecitabine				
E_{ZPE}	298.8332	275.8908	256.9005	271.9532
E_{tot}	307.1238	284.7085	266.0853	280.6617
H_{corr}	307.7162	285.3009	266.6783	281.2541
G_{corr}	273.5652	250.1641	231.1814	246.6721
$E_0 = \varepsilon_0 + E_{ZPE}$	-798670	-803125	-813801	-808932
$E = \varepsilon_0 + E_{tot}$	-798662	-803116	-813792	-808923
$H = \varepsilon_0 + H_{corr}$	-798661	-803116	-813791	-808923
$G = \varepsilon_0 + G_{corr}$	-798695	-803151	-813827	-808957
5-FU				
E_{ZPE}	53.5152	51.5367	49.011	47.5263
E_{tot}	57.2414	55.8226	52.8726	51.6377
H_{corr}	57.8337	56.4149	53.465	52.2301
G_{corr}	34.0549	31.6107	29.4935	27.8971
$E_0 = \varepsilon_0 + E_{ZPE}$	-316520	-320619	-318128	-322384
$E = \varepsilon_0 + E_{tot}$	-316517	-320615	-318124	-322380
$H = \varepsilon_0 + H_{corr}$	-316516	-320614	-318124	-322379
$G = \varepsilon_0 + G_{corr}$	-316540	-320639	-318148	-322403

To obtain molecular mechanics data, the calculations were performed in three different media including gas, water and methanol at various temperatures. The energy values in the gas phase were the highest among four force fields.In this study, the favorable temperatures were 298°K and 310°K. Although, in 298°K, in other words, environment temperature, the least stability and the most energy have been observed for capecitabine and Nanotube complex in Gas phase, more stability has been seen in 310°K. similar results did not obtain for 5-Fu and Nanotube complex. the most stable state for 5-FU was related to MM+ force field at 298°K. the calculated results of water medium were equal to 223.8 Kcal/mol, while The most stable state of capecitabine attached to nanotube complex belonged to Bio force field at 290°K in Methanol solvent (table 4 and 5)[25].

Table 4. Calculated optimized energy parameter(kcal/mol) of 5-FU and Capecitabine binding to nanotube in different temperatures and force fields by molecular mechanics method (Monte Carlo).

	Capecitabine- nanotube											
	AM0BER			BIO			MM+			OPLS		
	Gas	Water	Methanol	Gas	Water	Methanol	Gas	Water	Methanol	Gas	Water	Methanol
290	1326.5	469.14	494.23	1329	280.24	274.03	1076.27	280.72	285.15	982.49	305.39	331.3
294	1031.92	483.86	471.73	1121.55	284.55	285.42	1189.79	275.14	294.32	963.55	321.53	356.59
298	1326.49	490.82	502.05	1328.99	279.09	280.52	1189.79	281.38	287.29	963.55	346.11	345.35
302	1031.92	499.29	510.83	1121.55	289.17	280.58	1189.79	302.89	293.16	960.45	364.8	331.48
306	1031.92	472.29	483.56	1121.55	291.83	280.41	1189.79	296.24	304.24	960.45	356.12	359.79
310	1031.92	498.61	496.22	1121.55	283.35	289.29	1189.79	299.71	296	960.45	334.75	353.79
314	1031.92	486.09	477.50	1121.55	296.17	294.68	1189.79	285.68	298.97	961.25	352.96	343.04
	5-FU- nanotube											
290	1474.51	483.14	452.16	1379.86	237.89	246.79	1302.77	244.9	248.17	1046.7	304.2	326.43
294	1177.99	459.08	468.2	1261.1	249.34	250.51	1348.95	230.31	241.80	1087.86	315.44	320.08
298	1134.27	472.5	449.37	1268.59	234.12	233.06	1314.48	223.80	226.61	1083.78	321.37	364.13
302	1186.83	482.72	472.13	1281.01	232.39	250.44	1330.91	240.66	246.16	1097.91	323.26	346.25
306	1175.23	470.67	467.9	1275.31	253.97	253.71	1323.55	238.64	245.13	1094.55	331.89	354.15
310	1178.46	465.26	467.59	1284.75	254.66	249.45	1331.77	226.94	243.6	1094.81	319.31	363.51
314	1192.45	467.20	467.2	1283.74	250.69	246.76	1359.95	242.98	238.16	1101.35	317.38	323.32

Table 5. Calculated optimized energy parameter(kcal/mol) of 5-FU and Capecitabine binding to nanotube in MM+force field by molecular dynamics method

Time (ps)	EKIN	EPOT 5-FU	ETOT	EKIN	EPOT Capecitabine	ETOT	EKIN	EPOT 5-FU-nanotube	ETOT	EKIN	EPOT Capecitabine- nanotube	ETOT
0	0.435273	23.53954	23.97481	1.833882	1462.279	1464.113	6.805579	1692.709	1699.515	4.577791	1189.786	1194.363
250	11.51277	12.40684	23.91961	736.1778	729.0955	1465.273	342.6836	1360.955	1703.639	87.54605	1105.277	1192.823
500	9.046402	15.11074	24.15714	739.1516	726.4972	1465.649	335.8882	1370.826	1706.714	94.30952	1098.101	1192.411
750	12.53409	11.48241	24.0165	688.1977	775.0061	1463.204	363.6315	1347.237	1710.868	91.63306	1102.764	1194.397
1000	12.69026	11.14132	23.83158	750.237	714.6619	1464.899	385.1509	1331.075	1716.226	84.88881	1110.727	1195.616
1250	9.701339	13.97143	23.67277	809.2965	656.3915	1465.688	381.0512	1339.412	1720.463	88.79414	1106.744	1195.538
1500	9.222206	14.67656	23.89877	771.1146	694.8578	1465.972	384.9697	1334.929	1719.898	91.62683	1104.428	1196.055
1750	11.5387	11.97601	23.51471	770.2374	696.4554	1466.693	383.0986	1339.022	1722.12	86.42908	1110.657	1197.086
2000	13.03714	10.3926	23.42974	816.851	650.6493	1467.5	354.4333	1374.501	1728.935	88.85529	1107.412	1196.268
2250	6.783873	16.86681	23.65068	677.1317	791.1591	1468.291	357.8257	1374.232	1732.057	91.85741	1105.214	1197.071
2500	11.86358	11.56938	23.43296	762.7803	705.2628	1468.043	374.0545	1362.285	1736.34	88.53404	1108.766	1197.3
2750	10.37026	12.8007	23.17096	780.3838	683.4929	1463.877	366.5442	1371.44	1737.984	89.7009	1108.558	1198.259
3000	10.72914	12.58422	23.31336	830.9589	634.1893	1465.148	404.6671	1332.607	1737.274	89.41801	1108.155	1197.573
3250	9.774435	13.52801	23.30245	698.4677	765.5278	1463.995	397.7307	1341.672	1739.403	94.96388	1103.042	1198.006
3500	10.72745	12.61232	23.33977	786.3748	677.6229	1463.998	415.0638	1331.214	1746.278	89.00207	1109.501	1198.503
3750	9.451792	14.28172	23.73351	731.1136	733.0598	1464.173	371.3126	1377.262	1748.574	91.39265	1107.43	1198.823
4000	9.436295	14.0139	23.4502	742.0494	722.1522	1464.202	390.6037	1361.78	1752.384	93.71478	1105.997	1199.711
4250	12.61293	10.89297	23.5059	718.0377	747.0092	1465.047	387.8416	1362.291	1750.133	94.98817	1104.348	1199.336
4500	10.85498	12.66736	23.52234	728.8066	735.411	1464.218	412.286	1339.683	1751.969	94.34403	1105.055	1199.399
4750	8.805444	14.69861	23.50406	702.7976	763.0629	1465.86	368.9507	1386.12	1755.071	88.83543	1111.701	1200.537
5000	9.619734	14.03336	23.65309	765.0812	702.5014	1467.583	391.9431	1366.014	1757.957	91.62843	1109.408	1201.036

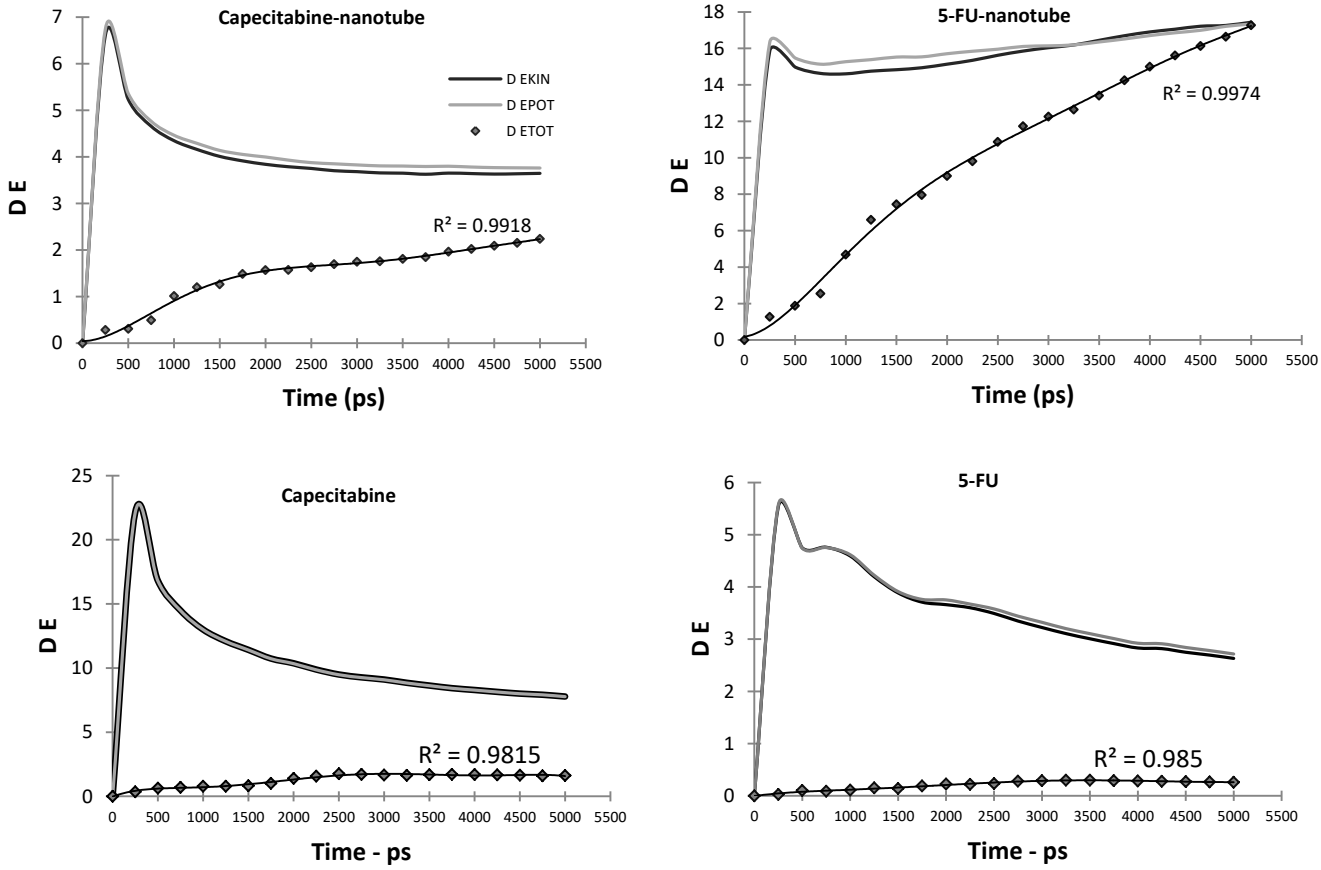


Figure 5. Calculated deviation of the total energy (D ETOT) and deviation of the kinetic energy (D EKIN) and deviation of the potential energy (D EPOT) for 5-FU and Capecitabine binding to Nanotube in MM+ force field by molecular dynamics method

We use deviation of the total energy (D ETOT) and deviation of the kinetic energy (D EKIN) and deviation of the potential energy (D EPOT) in a simulation that is shown in figure 5.

The comparison of four molecules was shown in table6 which has been investigated by two methods: AM1 and MNDO. There have been four compositions: 5-FU, capecitabine, 5-FU-nanotube and Capecitabine-nanotube and calculations were performed in three media of gas (vacuum), water and methanol.The most negative total energy obtained from AM1 was of the capecitabine-nanotube complex in a vacuum (-422276 Kcal/mol) and it has been followed by 5-FU-nanotube in the gas phase (-347568 Kcal/mol).But in MNDO method, capecitabine-nanotube complex in gas phase had the most negative total energy (-423098 Kcal/mol) and it is followed by 5-Fu-nanotube complex in a gas phase (-350560 Kcal/mol).The obtained results for capecitabine-nanotube and 5-FU-nano complexes via different

parameters in water and methanol phases by both methods, AM1 and MNDO, were significant. They have been presented in table 6.

Table 6. Optimized parameters of total energy, binding energy, isolated atomic energy, electronic energy, core–core interaction and heat of formation(Kcal/mol) for 5-fu, Capecitabine, 5-fu_nanotube and Capecitabine_nanotubeinvarious solvents by AM1and MNDO calculations.

Molecules	Solvent	Total Energy	Binding Energy	Isolated Atomic Energy	Electronic Energy	Core-Core Interaction	Heat of Formation
AM1 calculation							
5-FU	Gas	-48243	-1274	-46969	-178323	130078	-70
	Water	-200872	-5414	-195458	-1070359	869487	-1098
	Methanol	-159879	-2864	-157014	-754733	594854	718
Capecitabine	Gas	-119698	-3261	-116437	-951487	831788	1163
	Water	-232229	-6379	-225849	-1983093	1750864	337
	Methanol	-194499	-3238	-191261	-1306297	1111798	1883
5-FU-Nanotube	Gas	-347568	-20937	-326630	-7637588	7290020	1377
	Water	963809	1412543	-448734	-6484267	7448077	1432357
	Methanol	987588	1398772	-411183	-5906146	6893734	1418412
Capecitabine-Nanotube	Gas	-422276	-25127	-397148	-9510989	9088712	616
	Water	1557030	2028901	-471871	-6499949	8056979	2050061
	Methanol	1579914	2025081	-445167	-5886332	7466247	2046208
MNDO calculation							
5-FU	Gas	-48223	-1287	-46935	-178478	130255	-84
	Water	-202128	-5482	-196646	-1072942	870814	-1167
	Methanol	-159901	-2587	-157314	-754829	594928	995
Capecitabine	Gas	-119741	-3027	-116713	-952534	832793	1397
	Water	-233185	-6159	-227026	-1985904	1752719	558
	Methanol	-194613	-3067	-191546	-1306797	1112183	2055
5-FU-Nanotube	Gas	-350560	-20545	-330015	-7692633	7342073	1941
	Water	970453	1416923	-446470	-6378515	7348969	1436567
	Methanol	863567	1274549	-410982	-6031052	6894619	1294189
Capecitabine-Nanotube	Gas	-423098	-24986	-398112	-9514806	9091708	758
	Water	1083294	1767400	-684106	-7260382	8343676	1788560
	Methanol	1202693	1647632	-444940	-6264310	7467003	1668760

Results gathered in Figure 6 has presented R2≅0.99 for the heat formation and R2≅0.90 for binding energy, electronic energy and core-core interaction. In normal mode diagram that four compositions have been investigated. Figure 7 has been shown the frequency in which a good overlap for all four compositions has been observed and it revealed that, by a very close and equal approximation, both (capecitabine and 5-FU) were similar in their vibration movement and displacement; while 5-FU composition expressed a better approximation.

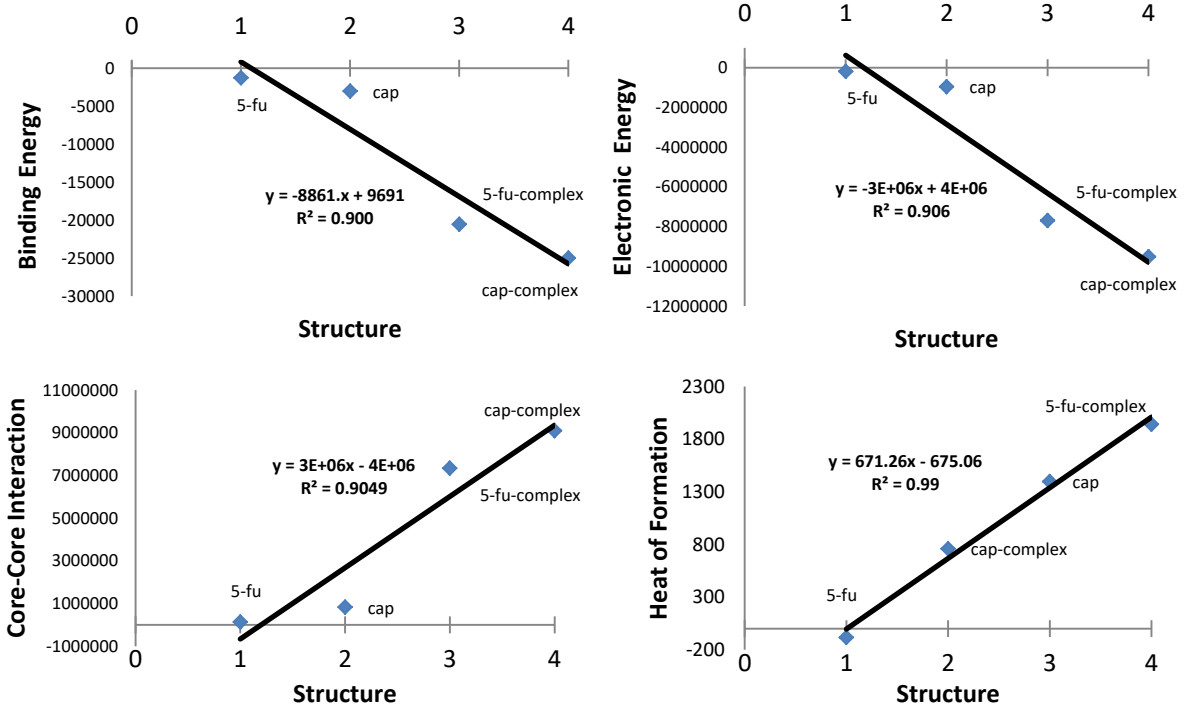


Figure 6. Optimized parameters of total energy, binding energy, isolated atomic energy, electronic energy, core–core interaction and heat of formation(Kcal/mol) for 5fu, Capecitabine, 5fu-nanotube and Capecitabine-nanotube in the gas phase by MNDO calculation.

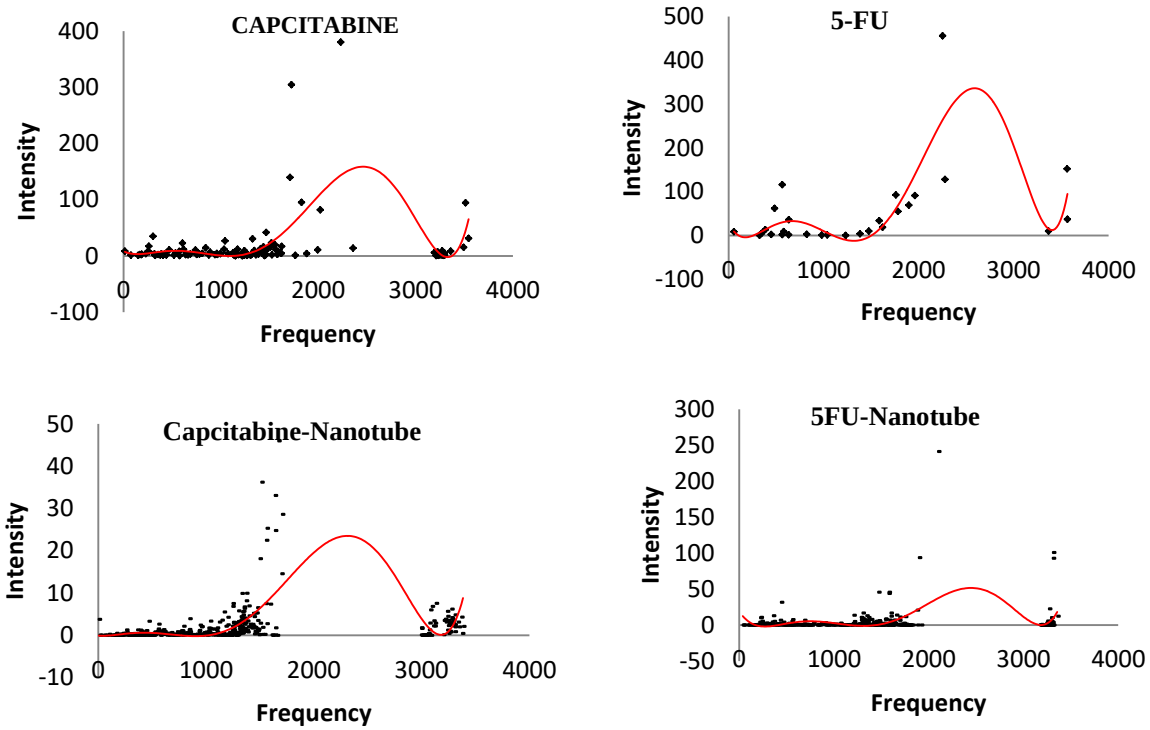


Figure 7. The natural logarithms frequency (cm−1) and intensity (km/mol) of 5fu, capecitabine, 5fu-nanotube and capecitabine-nanotube by MNDO calculation.

4. CONCLUSIONS

Capecitabine and 5-Fluorouracil are anticancer reagents utilized in catabolism and anabolism processes. The influence of nanotubes on these two is very interesting. First, the ab initio method through 2 basis sets (NMR and frequency) has been used. The results of NMR has been analyzed by σiso and σaniso parameters; also frequency has been assessed by zero-point energy correction, enthalpy, and Gibbs free energy. The results could shed light on the structural characteristics in absence of nanotubes leading to better understanding of their capacity.

In the semi-empirical method, AM1 and MNDO were performed. By which total energy, binding energy, isolates atomic energy, electronic energy, core-core interaction and heat of formation of gas, water and methanol phases have been calculated. The results confirmed the findings of primary observation.

Current study elaborated that the nanotube interaction by 2 compounds has had a distinguished energy order for binding energy, electronic energy, and core-core interaction parameters; however, for the heat of formation, this order is different. In Mont-Carlo method the best-assessed force field was MM+. Hence, this force field was chosen for molecular mechanics method. The obtained results were in accordance with molecular mechanic's finding and they were promising.

According to obtain studies, Capecitabine is more stable and active rather than 5-FU in the presence of CNT. because the binding energy of Capecitabine/SWCNT complex is more than 5-FU in water and methanol phases. These results are confirmed to Experimental results.

The results followed one defined and similar procedure. For clinical trials of capecitabine and 5-FU, use of more stable carbonic nanotube can be suggested. Our results were in accordance with laboratory findings. In another word, theoretical and practical results confirm each other.

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