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A theoretical study on the physicochemical and geometrical properties of the five anti-cancer drug using density functional theory for understanding their biological and anti-cancer activities

S. M. Hassani[1], S. Bagheri[2*] and H. Ghahremani[3]

[1]Department of Chemical Engineering, Shahrood Branch, Islamic Azad University, Shahrood, Iran
[2]Department of Chemistry, Quchan Branch, Islamic Azad University, Quchan, Iran
[3]Young Researchers Club, Quchan Branch, Islamic Azad University, Quchan, Iran

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ABSTRACT

Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen are anti-cancer drugs. In this report, the physicochemical properties of these drugs have been evaluated using Density functional Theory (DFT) calculations. Our investigation include the: geometrical parameters of the mentioned drugs, Gibbs free energy of solvation ($\Delta G_{(solvation)}$), binding energy and Dipole Moment (DM) of complexes, beside other properties such as partition coefficient, polarizibility, hydration energy, etc.

Keywords: Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen, DFT.

INTRODUCTION

Temozolomide is a cytotoxic prodrug that, when hydrolyzed, inhibits DNA replication by methylating nucleotide bases. In preclinical testing, temozolomide has shown a broad spectrum of antineoplastic activity[1].

Methotrexate was originally developed and continues to be used for chemotherapy either alone or in combination with other agents. It is effective for the treatment of a number of cancers including: breast, head and neck, leukemia, lymphoma, lung, osteosarcoma, bladder, and trophoblastic neoplasms.

Methotrexate is thought to affect cancer and rheumatoid arthritis by two different pathways. For cancer, methotrexate allosterically inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis. The affinity of methotrexate for DHFR is about one thousand-fold that of folate. DHFR catalyses the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the de novo synthesis of the nucleoside thymidine, required for DNA synthesis. Also, folate is needed for purine base synthesis, so all purine synthesis will be inhibited. Methotrexate, therefore, inhibits the synthesis of DNA, RNA, thymidylates, and proteins[2-7].Methotrexate acts specifically during DNA and RNA synthesis, and thus it is cytotoxic during the S-phase of the cell cycle.

BiCNU (Carmustine for injection) is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1,3-bis(2-chloroethyl)-1-nitrosourea. It is in the form of sterile lyophilized pale yellow flakes or a congealed mass with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. It is generally agreed that carmustine alkylates DNA and RNA are not cross-resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins[8-10].

Tamoxifen is an antagonist of the estrogen receptor in breast tissue via its active metabolite, hydroxytamoxifen. In other tissues such as the endometrium, it behaves as an agonist; hence, tamoxifen may be characterized as a mixed agonist/antagonist. Tamoxifen is the usual endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre-menopausal women, and it is also a standard in post-menopausal women although, aromatase inhibitors are also frequently used in that setting[11].

Some breast cancer cells require estrogen to grow. Estrogen binds to and activates the estrogen receptor in these cells. Tamoxifen is metabolized into compounds that also bind to the estrogen receptor but do not activate it. Because of this competitive antagonism, tamoxifen acts like a key broken off in the lock that prevents any other key from being inserted, preventing estrogen from binding to its receptor. Hence breast cancer cell growth is blocked.

RESULTS AND DISCUSSION

2.1. Structural optimization of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen.

In this study, Density functional Theory (DFT) calculations were used to optimize the molecular geometries of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen. The geometric parameters were considered and optimized in the below fashion.

2.1.1. Methotrexate

The optimized Methotrexate structures obtained from Density Functional Theory B3LYP/6-31G* method (Figure 1).

Fig. 1: Optimized structure of Methotrexate

The molecular geometries of Methotrexate (Fig. 1) were optimized using the B3LYP procedure employing the 6-31G* basis set. The molecular structure of Methotrexate is shown in Fig. 1. The geometries of this molecule optimized using the 6-31G* basis set at the B3LYP level are presented[12] in Table 1.

Table 1: Geometric parameters of optimized Methotrexate structure

Methotrexate			
	Bond lengths		**Bond angles**
N_8-H_9	1.008	H_9-N_8-H_{10}	119.001
N_8-H_{10}	1.008	N_{14}-C_7-N_{15}	128.505
N_8-C_7	1.362	C_7-N_{15}-C_2	115.331
C_7-N_{15}	1.332	N_{15}-C_2-C_3	122.282
C_7-N_{14}	1.365	C_2-C_3-C_6	116.292
N_{14}-C_6	1.321	C_3-C_6-N_{14}	121.202
C_6-N_{11}	1.348	H_{12}-N_{11}-H_{13}	121.196
N_{11}-H_{12}	1.008	H_{52}-O_{51}-C_{49}	106.051
N_{11}-H_{13}	1.008	O_{51}-C_{49}-O_{50}	122.653
C_6-C_3	1.446	H_{47}-C_{46}-H_{48}	105.304
C_3-C_2	1.420	H_{44}-C_{43}-H_{45}	106.561
N_{16}-C_2	1.465	C_{49}-C_{46}-C_{43}	112.121
C_{49}-O_{50}	1.210	C_{46}-C_{43}-C_{37}	114.133
C_{49}-O_{51}	1.356	H_{42}-O_{41}-C_{39}	106.394
O_{51}-H_{52}	0.975	O_{40}-C_{39}-O_{41}	123.103
C_{49}-C_{46}	1.514	O_{34}-C_{33}-N_{35}	120.249
C_{46}-C_{43}	1.530	H_{38}-C_{37}-C_{39}	108.414

2.1.2. Carmustine.

The optimized Carmustine structures obtained from Density Functional Theory B3LYP/6-31G* method (Figure 2).

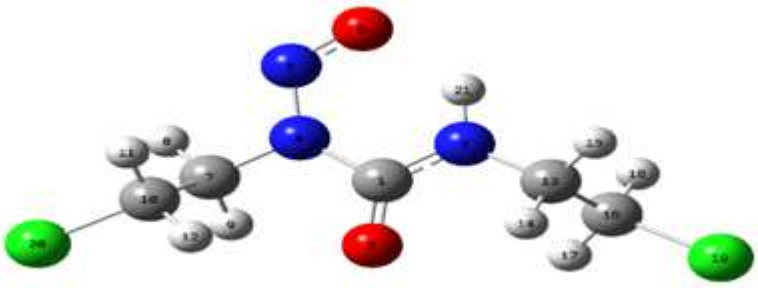

Fig. 2: Optimized structure of Carmustine

Molecular geometries of Carmustine (Fig. 2) were optimized using the B3LYP procedure employing the 6-31G* basis set. The molecular structure of Carmustine is shown in Fig. 2. The geometries of this molecule optimized using the 6-31G* basis set at the B3LYP level are presented in Table 2.

Table 2: Geometric parameters of optimized Carmustine structure

Carmustine			
Bond lengths		**Bond angles**	
CL_{20}-C_{10}	1.809	CL_{20}-C_{10}-C_7	109.604
C_{10}-C_7	1.528		
C_7-N_4	1.471		
N_4-N_5	1.358	C_{10}-C_7-N_4	111.307
N_5-O_6	1.224	N_4-N_5-O_6	117.597
N_4-C_1	1.454		
C_1-O_2	1.221	N_4-C_1-N_3	116.244
C_1-N_3	1.350	C_1-N_3-H_{21}	117.674
N_3-C_{13}	1.458		
C_{13}-C_{16}	1.530	O_2-C_1-N_3	125.458
C_{16}-C_{19}	1.811		
C_{10}-H_{11}	1.091		
C_{10}-H_{12}	1.089	C_1-N_3-C_{13}	120.533
C_7-H_8	1.090		
C_7-H_9	1.090		
N_3-H_{21}	1.015	N_3-C_{13}-C_{16}	111.308
C_{13}-H_{15}	1.092		
C_{13}-H_{14}	1.092		
C_{16}-H_{18}	1.091	C_{13}-C_{16}-CL_{19}	110.136
C_{16}-H_{17}	1.090		

2.1.3. Temozolomide.

The optimized Temozolomide structures obtained from Density Functional Theory B3LYP/6-31G* method were identical (Figure 3).

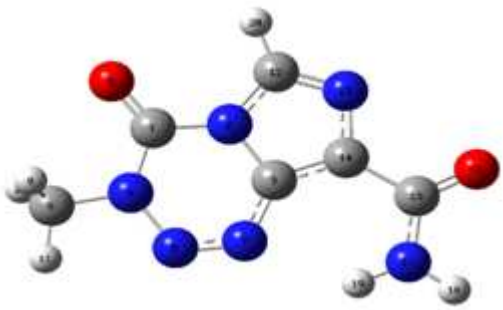

Fig. 3: Optimized structure of Temozolomide.

Molecular geometries of Temozolomide (Fig. 3) were optimized using the B3LYP procedure employing the 6-31G* basis set. The molecular structure of Temozolomide is shown in Fig. 3. The geometries of this molecule optimized using the 6-31G* basis set at the B3LYP level are presented in Table 3.

Table 3: Geometric parameters of optimized Temozolomide structure

Temozolomide			
Bond lengths		**Bond angles**	
C_8-H_9	1.092	H_9-C_8-H_{10}	108.889
C_8-H_{10}	1.092	H_9-C_8-H_{11}	110.421
C_8-H_{11}	1.089	H_{11}-C_8-H_{10}	110.425
C_8-N_4	1.463	C_8-N_4-C_1	118.016
N_4-N_6	1.386	N_4-C_1-O_5	124.698
N_6-N_7	1.268	N_4-C_1-N_2	110.639
N_7-C_3	1.364	C_1-N_2-C_3	121.729
N_2-C_1	1.399	N_2-C_3-N_7	121.367
C_1-O_5	1.211	C_3-N_7-N_6	120.065
N_2-C_{12}	1.371	N_7-N_6-N_4	119.073
C_{12}-N_{13}	1.314	N_2-C_{12}-N_{13}	111.343
N_{13}-C_{14}	1.371	H_{20}-C_{12}-N_{13}	126.763
C_{14}-C_3	1.390	C_{12}-N_{13}-C_{14}	107.224
C_{14}-C_{15}	1.499	N_{13}-C_{14}-C_3	109.194
C_{15}-O_{16}	1.220	C_{14}-C_3-N_2	105.661
C_{15}-N_{17}	1.365	C_{14}-C_{15}-O_{16}	121.770
N_{17}-H_{19}	1.012	O_{16}-C_{15}-N_{17}	123.807
N_{17}-H_{18}	1.009	H_{18}-N_{17}-H_{19}	119.794

2.1.4. Tamoxifen and Hydroxifen

The optimized Tamoxifen and Hydroxifen structures obtained from Density Functional Theory B3LYP/6-31G* method were identical (Figures 4 and 5).

Fig. 4: Optimized structure of Tamoxifen

Molecular geometries of Tamoxifen (Fig. 4) were optimized using the B3LYP procedure employing the 6-31G* basis set. The molecular structure of Tamoxifen is shown in Fig. 4. The geometries of this molecule optimized using the 6-31G* basis set at the B3LYP level are presented in Table4.

Table 4: Geometric parameters of optimized Tamoxifen structure

Geometrical parameters (Bond lengths (Å) and Bond angles(°)) of Tamoxifen			
Bond lengths		**Bond angles**	
C_1-C_2	1.405	C_1-C_2-C_3	117.906
C_2-C_3	1.405		
C_3-C_4	1.393	C_2-C_3-C_4	121.078
C_4-C_5	1.396	C_3-C_4-C_5	120.290
C_5-C_6	1.395		
C_6-C_1	1.395	C_4-C_5-C_6	119.393
C_2-C_{12}	1.496	C_5-C_6-C_1	120.230
C_{12}-C_{13}	1.360		
C_{12}-C_{14}	1.521	C_6-C_1-C_2	121.092
C_{14}-C_{17}	1.538	C_2-C_{12}-C_{13}	122.450
C_{13}-C_{21}	1.495		
C_{21}-C_{23}	1.408	C_{12}-C_{14}-C_{17}	114.167
C_{23}-C_{26}	1.387	C_{12}-C_{13}-C_{21}	123.554
C_{26}-C_{28}	1.402		
C_{28}-C_{24}	1.399	C_{21}-C_{22}-C_{24}	121.986
C_{24}-C_{22}	1.395	C_{22}-C_{24}-C_{28}	119.601
C_{22}-C_{21}	1.402	C_{24}-C_{28}-C_{26}	119.334

C_{28}-O_{42}	1.365		
O_{42}-C_{43}	1.424	C_{28}-C_{26}-C_{23}	120.305
C_{43}-C_{46}	1.027	C_{26}-C_{23}-C_{21}	121.458
C_{46}-N_{49}	1.461		
N_{49}-C_{50}	1.457	C_{23}-C_{21}-C_{22}	117.297
N_{49}-C_{54}	1.458	C_{28}-O_{42}-C_{43}	118.740
C_{13}-C_{31}	1.498		
C_{31}-C_{32}	1.405	O_{42}-C_{43}-C_{46}	106.645
C_{32}-C_{34}	1.393		
C_{34}-C_{38}	1.397		
C_{38}-C_{36}	1.395		
C_{36}-C_{33}	1.396	C_{50}-N_{49}-C_{54}	110.670
C_{33}-C_{31}	1.404		

Fig. 5: Optimized structure of Hydroxifen

The geometry structures of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen were optimized at B3LYP/6-31g* level of theory and then the Gibbs free energy of solvation (ΔG (solvation)) was calculated at B3LY/6-31g* level of theory using Gaussian 03[13].

Some physicochemical properties of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen, such as, Refractivity, polarizability, Log p, Hydration energy, Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) were obtained from the optimal structure and have been shown in Table 5 and 6.

Table 5: Some calculated physicochemical properties of Methotrexate, Carmustine, Temozolomide

Physicochemical properties	Methotrexate	Carmustine	Temozolomide
Refractivity[a]	111.30	41.77	40.39
Polarizability	45.65	17.93	17.52
Hydration energy[a] (Kcal/mol)	-29.17	-5.50	-8.68
Surface area[a] (Å2)	535.65	393.31	268.08
Dipole moment (Debye)	7.14	1.848	5.89
ΔG solvation(Kcal/mol)	-29.77	-6.27	-12.35

[a] Data was calculated using HyperChem 8 software[14]

Table 6: Some calculated physicochemical properties of Tamoxifen, Hydroxifen

Physicochemical properties	Tamoxifen	Hydroxifen
Refractivity[a]	119.26	120.95
Polarizability	46.23	46.87
Hydration energy[a] (Kcal/mol)	-2.69	-8.75
Surface area[a] (Å2)	616.67	631.31
Dipole moment (Debye)	1.42	1.805
$\Delta G_{solvation}$ (Kcal/mol)	1.12	-3.81

[a] Data was calculated using HyperChem 8 software[14]

CONCLUSION

B3LYP calculations were applied to study some physicochemical properties of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen. Density functional Theory (DFT) calculation were applied to study

some geometrical properties of Methotrexate, Carmustine, Temozolomide, Tamoxifen and Hydroxifen. With regards to the calculations carried out and the amount of $\Delta G_{solvation}$, the solvation of Methotrexate was seen to be higher than the other four types under study. As can be seen in the experimental results, Carmustine is poorly soluble in water where as its highly soluble in lipids and alcohol; $\Delta G_{solvation}$ =-6.27 calculated for this chemical confirms the same. Further, $\Delta G_{solvation}$ =-29.77 for Methotrexate confirms its higher solubility in water than the other types. In this research, we have been able to identify the physicochemical properties of five anti-cancer drugs through calculations.

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