International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 130-134, Jan-Mar 2012

A Study on the Geometrical and Physicochemical Properties of Daidzein–Daunomycin Conjugate Using Density functional theory and Hartree–Fock

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Abstract: Daunomycin (or daunorubicin) is a well known anti-cancer agent. It is an anthracycline antibiotic**.** The use of daunomycin against neoplasms is limited due to its severe cardiotoxicity. The cytotoxicity of daunomycin can be minimized by linking it to an affinity tag. In this report, the Molecular Structure, Binding Energy (BE), Dipole Moment (DM), Gibbs Free Energy of Solvation ($\Delta G_{(solvation)}$) and some physicochemical properties of Daidzein–Daunomycin conjugated complex were investigated using the Density Functional Theory (DFT) and Hartree Fock (HF) calculations. Our results indicate that the above mentioned complex can be used to improve the anti-cancer activity and water-solubility of Daunomycin.
Keywords: Anti-cancer drug, DFT and HF calculations, Daidzein and Daunomycin.

1. Introduction

Experimental studies carried out by several researchers have illustrated that although anthracycline antibiotics (e.g., daunomycin, adriamycin, etc.) are highly effective chemotherapeutic agents, the cardiotoxicity of these drugs limits their therapeutic potential. In addition, the concentration needed to kill tumor cells is close to the drug levels which produce severe toxicity in normal cells of the body. To circumvent some of these problems, anthracycline antibiotics have been conjugated to carriers such as peptide or steroidal hormones which are recognized by homologous - either membranal or nuclear associated - steroid receptors present in tumor cells (1–6). Although some of the receptor-mediated cytotoxic-drug conjugates appeared promising in vitro, their use in vivo was generally ineffective. More recently, Nanoparticle Drug Delivery Systems such as lipid or polymer based nanoparticles were designed to improve the pharmacological and therapeutic properties of cytotoxic drugs (7-9). In this study, we intend to show some of the characteristics of Daunorubicin or Daidzein–Daunomycin mentioned above and obtained by other researchers experimentally through predictable computational calculations, including, molecular energy, binding energy, Dipole Moment, ΔG (solvation), Distance Bound and a Angle Bound (10). This complex was synthesized by Fortune Kohen and colleagues (11). The conjugation scheme can be seen as follows, in Figure1.

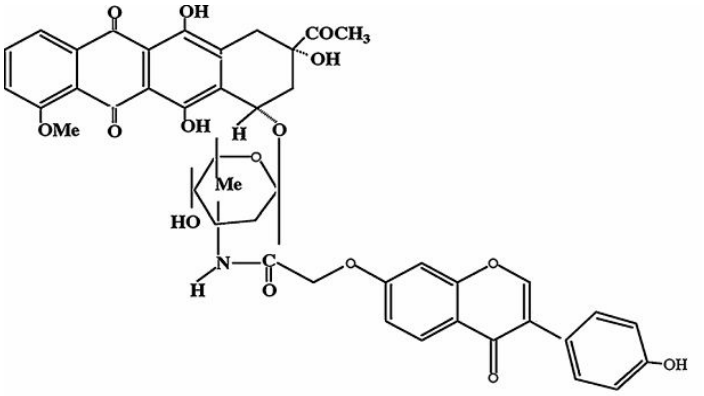

Figure 1: Structure of 7-(*O*)-Carboxymethyl daidzein–Daunomycin conjugate

2. Results and Discussion

2.1. Structural Optimization of Daunomycin and

Daidzein

In this study, Density functional Theory (DFT) and Hartree Fock (HF) calculations were used to optimize the molecular geometries of Daunomycin and Daidzein. Geometric parameters were established and optimized in this fashion.

2.1.1. Daunomycin

The optimized Daunomycin structures obtained from the Density Functional Theory B3LYP/6-31G* method and from the ab initio HF/6-31G* method were identical (Figure 2).

Molecular geometries of Daunomycin (Figure 2) was optimized using the Hartree–Fock (HF) and B3LYP procedure employing the 6-31G* basis set. It was not possible to employ a more sophisticated basis set due to the large sizes of the molecules. The molecular structure of Daunomycin is shown in Figure 2. The geometry of this molecule was optimized using the 6-31G* basis set at the RHF and B3LYP levels presented in **Table 1.** Experimental X-ray crystallographic values of bond lengths and bond angles of Daunomycin (12) are included in Table 1 for the sake of comparison with the calculated results.

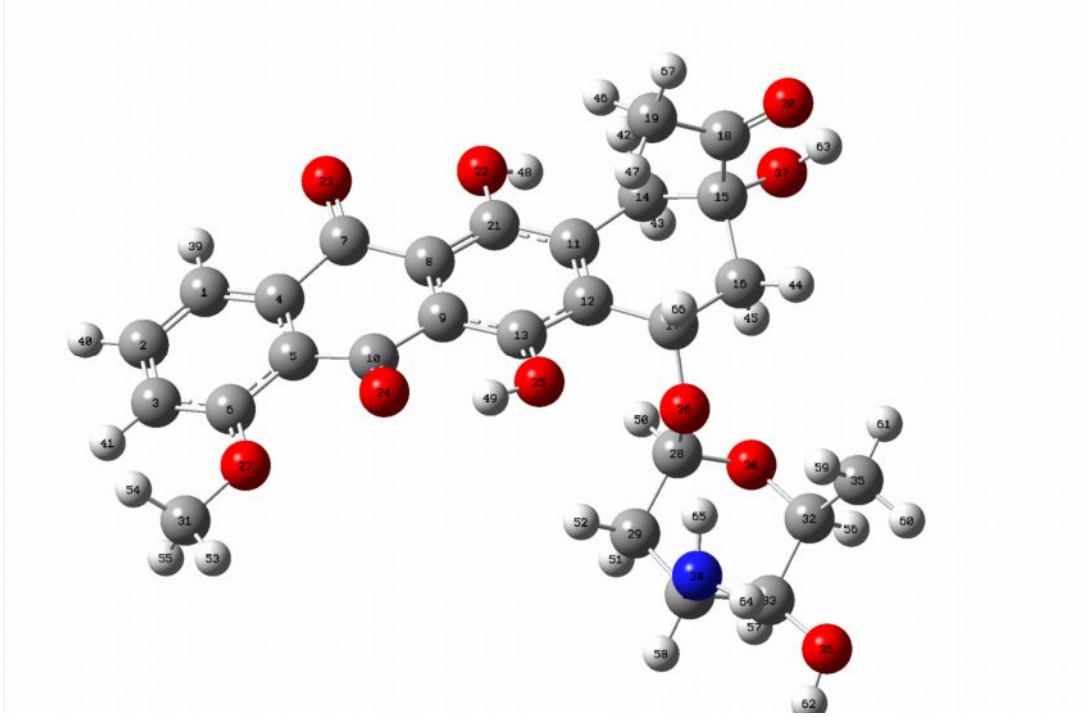

Figure 2: Optimized structure of Daunomycin

Table 1: Geometric parameters of optimized Daunomycin structure

Geometrical parameters (Bond lengths (Å) and Bond angles (°))	HF/6-31G*	B3LYP/6-31G*	Experimental[a]
O_{22}-C_{28}	1.397	1.423	1.39
C_{28}-H_{50}	1.081	1.095	1.02
C_{28}-O_{30}	1.390	1.414	1.43
O_{30}-C_{32}	1.420	1.445	1.45
C_{32}-H_{56}	1.082	1.095	1.01
C_{32}-C_{35}	1.526	1.530	1.56
C_{35}-H_{59}	1.082	1.093	1.08
C_{35}-H_{60}	1.078	1.089	0.99
C_{35}-H_{61}	1.084	1.094	1.03
C_{32}-C_{33}	1.532	1.541	1.50
C_{33}-H_{57}	1.089	1.103	1.00
C_{33}-O_{36}	1.406	1.428	1.41
O_{36}-H_{62}	0.947	0.970	0.97
C_{33}-C_{34}	1.535	1.545	1.52
C_{34}-H_{58}	1.089	1.103	.98
C_{34}-N_{38}	1.451	1.463	1.50
N_{38}-H_{64}	1.000	1.018	1.00
N_{38}-H_{65}	0.999	1.017	0.98
C_{34}-C_{29}	1.529	1.534	1.54
C_{29}-C_{28}	1.525	1.532	1.50
C_{29}-H_{51}	1.086	1.096	1.06
C_{29}-H_{52}	1.082	1.094	1.00
Bond angles			
C_{28}-O_{30}-C_{32}	120.072	118.617	113.5
O_{30}-C_{32}-C_{35}	113.194	113.258	105.3
O_{30}-C_{32}-C_{33}	109.481	109.818	110.3
C_{32}-C_{33}-C_{34}	114.609	114.493	109.5
C_{33}-C_{34}-C_{29}	108.007	108.218	108.8
C_{34}-C_{29}-C_{28}	112.981	112787	112.3
C_{33}-O_{36}-H_{62}	109.412	107.388	104.8
H_{58}-C_{34}-N_{38}	106.903	107.106	110.2
H_{64}-N_{38}-H_{65}	108.681	107.972	109.7
C_{32}-C_{35}-H_{59}	108.691	109.118	108.6
C_{32}-C_{35}-H_{60}	109.405	109.294	108.6
C_{33}-C_{35}-H_{61}	113.266	112.682	112.7

[a]Data obtained from (12)

2.1.2. Daidzein.

The optimized daidzein structures obtained from Density Functional Theory B3LYP/6-31G* method and from the ab initio HF/6-31G* method were identical (Figure 3).

The relevant geometric structural parameters from each method are given in **Table 2.**

The optimized structure is used as a starting point for subsequent calculations, such as dipole moment, ΔG (solvation), distance bound and angle bound (13).

Some physicochemical properties (Dipole Moment and ΔG (solvation), Surface Area, Hydration Energy and Polarizability) have been obtained from the optimal structure, and are listed in **Table 3.**

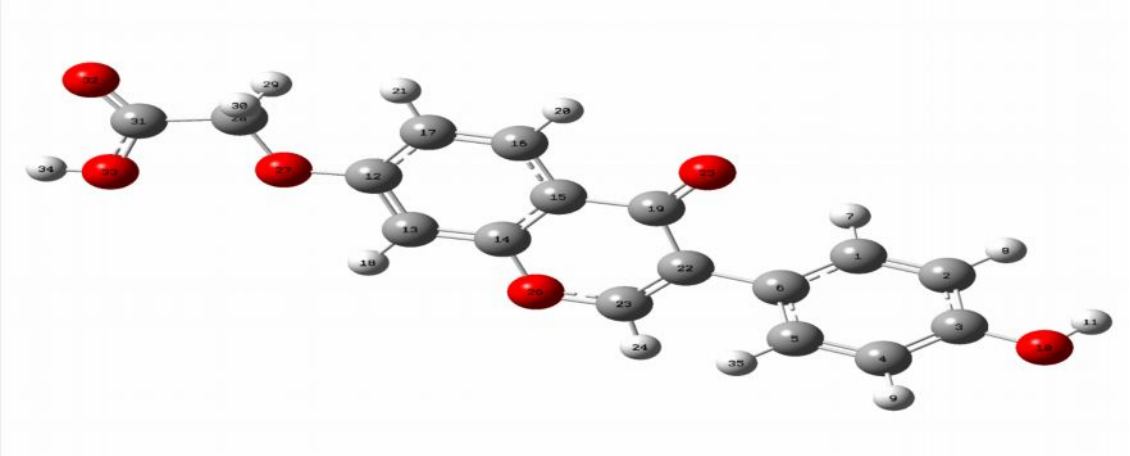

Figure 3: Optimized structure of Daidzein.

Table 2: Geometrical Parameters of Optimized Daidzein Structure.

Geometrical parameters (Bond lengths (Å) and Bond angles(°))	HF/6-31G*	B3LYP/6-31G*
H_{35}-O_{34}	0.952	0.976
O_{34}-C_{32}	1.316	1.343
C_{32}-O_{33}	1.187	1.210
C_{32}-C_{29}	1.512	1.519
C_{29}-H_{30}	1.083	1.098
C_{29}-H_{31}	1.084	1.098
C_{29}-O_{28}	1.391	1.412
O_{28}-C_{18}	1.344	1.363
C_{18}-C_{17}	1.382	1.395
C_{18}-C_{13}	1.400	1.410
C_{13}-C_{14}	1.375	1.386
C14-C_{15}	1.393	1.402
C_{15}-C_{16}	1.388	1.403
C_{16}-C_{17}	1.382	1.391
Bond angles		
H_{35}-O34-C_{32}	107.924	105.813
O34-C_{32}-O_{33}	123.901	124.231
O_{33}-C_{32}-C_{29}	120.922	121.527
O_{32}-C_{29}-H_{30}	106.989	107.185
C_{32}-C_{29}-H_{31}	106.912	107.167
H_{30}-C_{29}-H_{31}	108.211	107.602
C_{29}-O_{28}-C_{18}	120.270	118.674

Table 3: Some calculated physicochemical properties of Daidzein–Daunomycin and Daunomycin

Physicochemical Properties	Daidzein–Daunomycin		Daunomycin	
	HF/6-31G*	B3LYP/6-31G*	HF/6-31G*	B3LYP/6-31G*
Refrectivity[a]	211.21	208.18	133.80	132.24
polarizability[a]	80.28	81.01	51.18	51.27
Hydration energy[a]	-20.53	-28.85	-17.87	-19.09
Surface area[a](Å2)	832.53	838.10	-542.54	542.54
ΔG (solvation) (kcal/mol)		-21.34		-16.88
Dipole moment(Debye)	7.0591	6.677	6.006	4.727
BE (ev/mol)	-1082.102	-1071.581	-	-

[a]Data were calculated by using Hyper Chem 8 software (14)

Conclusion

The Density Functional Theory (DFT) and the Hartree Fock (HF) calculation were applied to study some physicochemical properties of Daidzein–Daunomycin and Daunomycin. As can be seen in table 1, there is a good concurrence between the computed geometrical parameters and the experimental results (X-ray crystallographic data). Regarding the calculation of results, the Hydrophilicity of Daidzein–Daunomycin was found to be higher than that of Daunomycin. This fact can be verified through the Gibbs Free Energy of Solvation (ΔGsolvation) obtained for Daidzein–Daunomycin and Daunomycin using Gaussian 03. It is also predictable that, based on Dipole Moment rates, a higher solubility exists in Daidzein–Daunomycin compared to Daunomycin, which in turn is higher than the former in lipophilicity. Our results indicate that the mentioned complex can be used to improve the anti-cancer activity and the water-solubility in Daunomycin.

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