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Theoretical study of some physicochemical properties of paclitaxel esters of malic acid as Prodrugs with Improved Water Solubility

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ABSTRACT

The physicochemical properties of paclitaxel esters of malic acid are studied. Novel taxol (paclitaxel) prodrugs of ester-linked series compounds have been evaluated using Hartree Fock (HF) and Density Functional Theory (DFT) calculations. Our investigation include: Some physicochemical properties of malic acid-paclitaxel conjugates, such as Gibbs free energy of solvation ($\Delta G_{solvation}$) and Dipole Moment (DM) of prodrugs, beside some properties such as partition coefficient, polarizibility, refractivity, hydration energy and etc. Our results indicate that the malic acid-paclitaxel mentioned above can be used to improve anti cancer activity and water-solubility of paclitaxel.

INTRODUCTION

Paclitaxel (Taxol) is a potent anticancer agent used clinically to treat advanced ovarian, breast and non small cell lung cancer. Although paclitaxel has demonstrated to be a unique antitumour agent it has several disadvantages. One of the major problems is its poor water solubility. Paclitaxel is administered in a vehicle containing ethanol and Cremophor EL[1], which is considered to cause some hypersensitivity reactions [2]. In addressing the solubility problems, many research groups have reported syntheses and biological evaluations of water soluble paclitaxel derivatives. These analogues have polar substituents coupled to paclitaxel either at the C2' or at the C7-hydroxyl group [21,22]. The solubilising moieties can be (salts of) carboxylic acids [3-5], phosphates [6-8], sulphonates [9], amines[10,11], sugar derivatives [12,13], or polyethylene glycol [14-16]. In most cases these moieties are coupled to paclitaxel via an ester or carbonate linkage.

In order to understand the water-solubility and anti cancer activity of paclitaxel prodrugs, it is inevitable to study the physicochemical properties of them. Therefore we used DFT and HF

calculations via Gaussian 03 [17] to study these properties. The structure of paclitaxel ester of malic acid complex utilized in this paper is presented in Fig1.

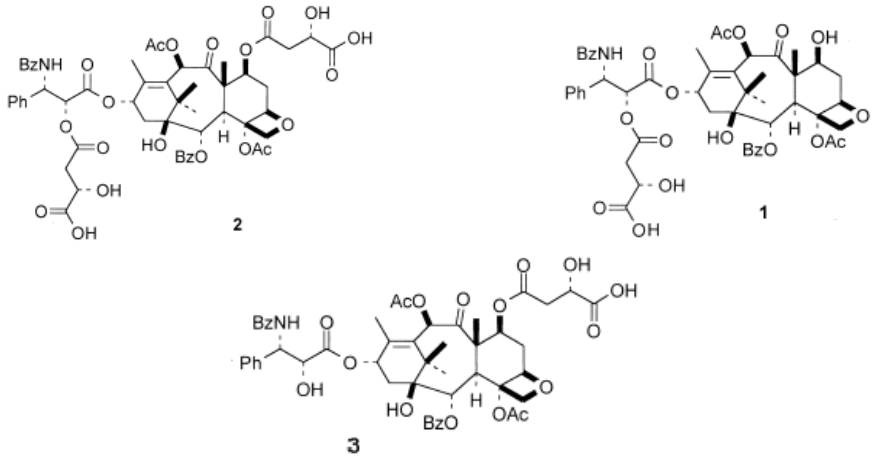

Figure 1. (1): 2'-Malyl-TX, (2): 2',7-Bis(malyl)-TX, (3): 7-Malyl-TX

RESULTS AND DISCUTION

The structure of paclitaxel prodrugs were optimized at HF/6-31g* level of theory and then the physicochemical properties of them were calculated at b3lyp/6-31g* level of theory. Table 1 and Table 2 show some physicochemical properties of Taxol complexes such as Dipole moment, Logp, polarizability, Hydration energy, etc.

As one can clearly see from table 1, the partition coefficient of these complexes are in more proper situation relative to pure taxol with experimental logp equal to 6.9 [20].

Table 1. Some physicochemical properties of malic acid paclitaxel derivatives[a]

Taxol derivatives	Refractivity	Polarizabilitya	Log p	Hydration energy (kcal/mol)	Volume ($Å^3$)	Surface area($Å^2$)
2'-Malyl-TX	234.21	91.73	3.16	-21.98	2224.18	948.37
2',7-Bis(malyl)-TX	253.85	99.25	2.61	-29.64	2458.45	1068.67
7-Malyl-TX	234.21	91.73	3.16	-22.23	2219.97	940.26

[a]*Data were calculated using HyperChem 7 software[18]*

.

Table 2. Some calculated physicochemical properties of prodrugs

Taxol derivatives	Water solubility[a] (mg/mL)	IC_{50}[a] (ng/mL)	ΔG_{solv}[b] (kcal/mol)	Dipole moment[b](Debye)
Taxol	0.01	< 3	7.38	4.8
2'-Malyl-TX	0.2	< 3	-0.8	5.216
2',7-Bis(malyl)-TX	0.5	69	-5.3	4.92
7-Malyl-TX	0.3	390	-2.3	6.06

[b]*Data are obtained from [19]*

[c]*Data were calculated using Gaussian 03 [17] software.*

CONCLUSION

Hartree Fock (HF) and Density Functional Theory (DFT) calculations were applied to study some physicochemical properties of malic acid-paclitaxel conjugates 1-3. The water-solubility and Gibbs free energy of solvation (ΔG_{solv}) of paclitaxel–malic acid conjugates increased in the order 1, 2 and 3. Our results indicate that Taxol conjugated with this malic acid can be utilized to improve the water-solubility and anti cancer activity of Taxol.

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