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Theoretical investigation of Glucuronide-Taxol conjugates as a useful delivery system for Taxol anti cancer agent

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ABSTRACT

The physicochemical properties of three new glucuronide paclitaxel prodrugs have been evaluated using Hartree fock (HF) and Density Functional Theory (DFT) calculations. Linked to the 2'-OH of the drug by a carbonate function, they include a self-immolative spacer bearing an arylnitro or arylamino group between the drug and the glucuronic acid residue. Our investigation include: geometrical parameters of glucuronide-paclitaxel conjugates, Gibbs free energy of solvation ($\Delta G_{solvation}$), binding energy and Dipole Moment (DM) of prodrugs, beside some properties such as partition coefficient, polarizibility, hydration energy and etc. Our results indicate that the glucuronide-paclitaxel conjugates mentioned above can be used to improve anticancer activity and water-solubility of paclitaxel.

INTRODUCTION

Despite recent progress in cancer therapy, two major challenges remain to increase antitumour selectivity of cytotoxic drugs and their water solubility. Indeed, the lack of selectivity and sufficient water solubility of such drugs is a serious drawback typically associated with severe side-effects, insufficient drug concentrations that would completely eradicate the tumour and, for most of them, emergence of drug resistance after prolonged treatment. Among different ways to overcome these problems, one is to use non-cytotoxic prodrugs designed to locally deliver the antitumour agent by specific activation [1-3]. According to this strategy called ‘tumour activated prodrug’ (TAP), [4-6] some prodrugs have reached the preclinical or clinical trial steps [7].This tumour-specific activation may occur by hypoxic environment of solid tumours, by localization to tumour antigen, by tumour-associated proteases (PSA, PSMA) or by enzyme selectively present in the tumour. In the case of tumour-associated enzyme activation, the active enzyme may be present in the tumour, like in PMT [8,9] strategies, or targeted to the tumour site, as in ADEPT, GDEPT, or VDEPT approaches [10-13,6].

Paclitaxel (Taxol) is potent anticancer agents that are currently used for the treatment of patients with ovarian, breast, non-small cell lung (NSCL) and prostate cancers. They possess a unique mechanism of action by binding to tubulin and promoting stable and non-functional microtubule formation [14,15] which finally leads to disrupted mitosis and cell death. Recent findings have shown that paclitaxel initiates apoptosis through multiple mechanisms [16,17]. However, the clinical usefulness of these drugs is particularly hampered by their poor water solubility, along with the aforementioned general problems, that is, lack of selectivity and development of multidrug resistance in clinic. [18,19] Therefore, it remains of interest to improve their use, at least to gain in solubility and selectivity, by preparing water-soluble prodrugs selectively activable in tumour areas [28,29]. Since endogenous extracellular β-D-glucuronidase [20-23] is highly present in necrotic tumours, glucuronide prodrugs fulfill these two requirements and can be used in prodrug monotherapy (PMT).

Three prodrugs were well detoxified and easily cleaved in the presence of β-D-glucuronidase with fast removal of the spacer, releasing paclitaxel. The arylamino spacer-containing prodrug is more stable than the corresponding nitro analogue [24].

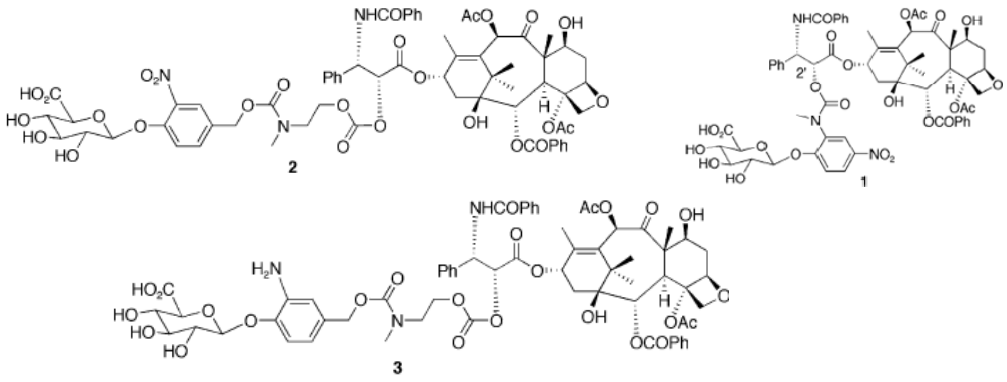

Figure 1. Structures of glucuronide-paclitaxel prodrugs.

RESULTS AND DISCUSSION

The geometry structure of these three prodrugs were optimized at HF/3-21g* level of theory and then the Gibbs free energy of solvation ($\Delta G_{solvation}$) were calculated at HF/6-31g* level of theory using Gaussian 03[25]. Table.1 presents the optimized geometrical parameters of five different complexes mentioned above around linking position, see also Fig 2.

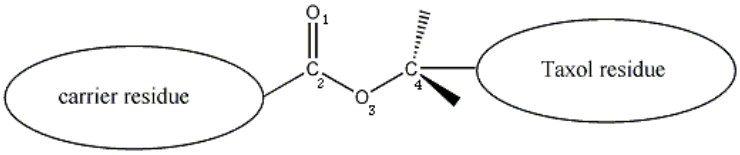

Table 1. Geometrical parameter of complexes around linking position

Prodrugs	$R(C_2=O_1)$ (Å)	$R(C_2-O_3)$ (Å)	$R(C_4-O_3)$ (Å)	$C_2-O_3-C_4$ (°)
Prodrug 1	1.228	1.357	1.443	115.7
Prodrug 2	1.233	1.362	1.435	119.7
Prodrug 3	1.223	1.325	1.434	122.7

Table 2 shows some physicochemical properties of glucuronide -paclitaxel conjugates 1-3 such as Surface area, polarizability, Log p and hydration energy. As one can see in table 2, the partition coefficient of these three prodrugs exist in absolutely better conditions relative to pure taxol with experimental log p equal 6.9 [27]

Table 2. Some calculated physicochemical properties of glucuronide-paclitaxel prodrugs [a]

Prodrug	Refractivity	Polarizability	Log p	Hydration energy (kcal/mol)	Volume ($Å^3$)	Surface area ($Å^2$)
Prodrug 1	303.65	117.65	2.28	-34.27	2689.43	1119.5
Prodrug 2	325.67	128.57	2.14	-33.73	2992.79	1248.87
Prodrug 3	321.52	124.98	3.46	-27.6	2788.28	1058.96

[a] *Data were calculated using HyperChem 8 software. [26]*

Some calculated physicochemical properties of glucuronide-paclitaxel conjugates such as binding energies (BE), Gibbs free energy of solvation (ΔG_{solv}) and Dipole moment (DM) are summarized in Table 3. The Binding energy values for each complexes were calculated at b3lyp/6-31g(d) level of theory.

Table 3. Some calculated physicochemical properties of glucuronide-paclitaxel prodrugs [a]

Prodrug	BE (kcal/mol)	ΔG_{solv} (kcal/mol)	Dipole moment(Debye)
Prodrug 1	-12.195	-6.59	7.99
Prodrug 2	-17.357	-14.28	9.76
Prodrug 3	-12.96	-14.51	7.72

[a] *Data were calculated using Gaussian 03 software package [25].*

CONCLUSION

Hartree Fock (HF) and Density Functional Theory (DFT) calculations were applied to study some physicochemical properties of glucuronide-paclitaxel conjugates. The partition coefficients and Gibbs free energies of solvation (ΔG_{solv}) of prodrugs emphasis the importance of conjugation in order to improve the anti cancer agents drawbacks. Our results indicate that glucuronide-paclitaxel prodrugs qualify to utilize for improvement of water-solubility and anti cancer activity of Taxol.

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