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Theoretical study on physicochemical properties of 7-Glycolylpaclitaxel 2''-O-α-glucooligosaccharides, novel taxol (paclitaxel) prodrugs of ester-linked oligosaccharide series compounds

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ABSTRACT

The physicochemical properties of 7-Glycolylpaclitaxel 2''-O-α-glucooligosaccharides, novel taxol (paclitaxel) prodrugs of ester-linked oligosaccharide series compounds, have been evaluated using Hartree Fock (HF) calculations. Our investigation include: geometrical parameters of saccharide-paclicaxel 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 saccharide-paclitaxel mentioned above can be used to improve anti cancer activity and water-solubility of paclitaxel.

INTRODUCTION

Taxol (paclitaxel), which is a taxane diterpenoid isolatedfrom Taxus brevifolia, shows cytotoxic activity against leukemia cells and inhibitory action against a variety of tumors such as ovarian, breast cancers, and has been recognized as one of the most effective and widely used anticancer agents. [1] That paclitaxel was hailed by National Cancer Institute as the most significant advance in chemotherapy of the 20 years [2]. But, its low water-solubility (0.25 μg/mL) [3] requires coinjection in a vehicle composed of 1:1 blend of Cremophor EL® (polyethoxylated castor oil) and ethanol, which was proved to cause hypersensitivity reactions, and the patients receiving this drug require premedication [4].

It present shortcoming such as low solubility in water and drug selectivity toward tumor cells. Paclitaxel prodrugs, which incorporate acids or aminoacids, have attracted considerable attention, because ester and amide linkages improve the water-solubility of paclitaxel and can be hydrolyzed by hydrolytic enzymes in the living body [5]. To improve drug selectivity toward tumor cells, many efforts to chemically synthesize paclitaxel prodrugs designed containing a

transport system have been made. An interesting approach for drug delivery is the use of saccharide based transporters [6,7] and there have been several reports on the synthesis of paclitaxel–sugar conjugates In addition, saccharide conjugation drastically enhances the water-solubility of aglycone molecule.

In order to understand the biological and anti cancer activity of prodrug, it is inevitable to study the physicochemical properties of paclitaxel–sugar conjugates. Therefore we used HF calculations via Gaussian 03 [8] to study these properties.

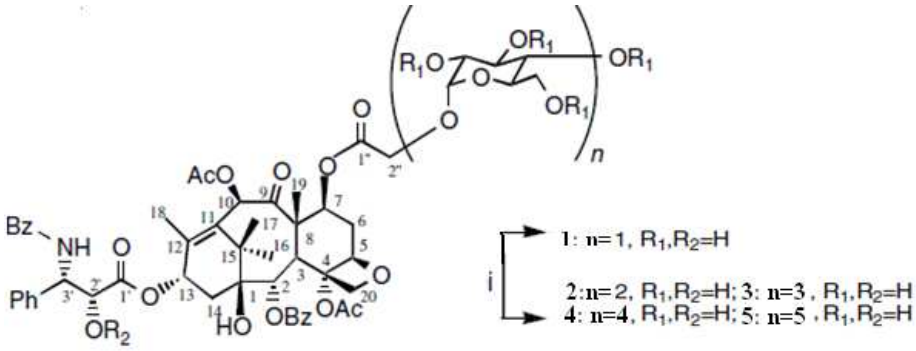

Fig 1. paclitaxel–sugar conjugates conjugates 1-5 structure[20]

RESULTS AND DISCUSSION

The geometry structure of these five complexes was 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. Table 1 presents the geometrical parameters of five different complexes mentioned above around linking position (ester group), see also Fig 2.

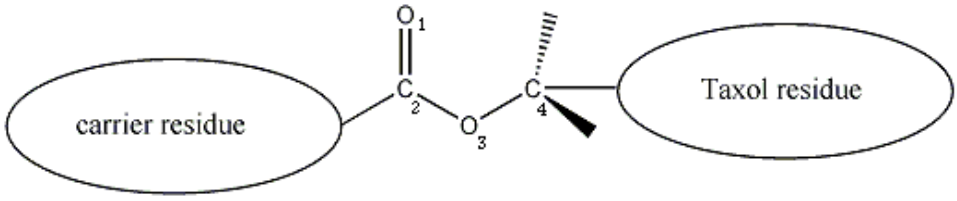

Fig 2. Structure of linking position in sugar-paclitaxel complexes.

Table 1. Geometrical parameter of complexes around linking position

Prodrug	$R(C_2=O_1)$ (Å)	$R(C_2-O_3)$ (Å)	$R(C_4-O_3)$ (Å)	$C_2-O_3-C_4$ (°)
TX-Sugar 1	1.193	1.365	1.445	126.99
TX-Sugar 2	1.191	1.369	1.443	127.24
TX-Sugar 3	1.191	1.371	1.442	127.42
TX-Sugar 4	1.191	1.371	1.443	127.32
TX-Sugar 5	1.191	1.371	1.443	127.31

Table 2. shows some physicochemical properties of sugar-paclitaxel conjugates 1-5 such as Refrectivity, polarizability, Log p, polarizability, Hydration energy.

Table 2. Some calculated physicochemical properties of sugar-paclitaxel conjugates 1-5

Prodrug	Refrectivity[a]	polarizability[a]	Log p[a]	Hydration energy[a]	Surface area[a] ($Å^2$)
TX-Sugar 1	264.54	103.95	1.75	-29.13	956.48
TX-Sugar 2	296.95	117.37	0.54	-36.72	1063.98
TX-Sugar 3	329.36	130.79	0.68	-43.54	1180.74
TX-Sugar 4	361.77	144.21	1.9	-51.94	1287.1
TX-Sugar 5	394.19	157.63	3.11	-59.68	1394.66

[a] Data were calculated using HyperChem 8 software[10]

Some calculated physicochemical properties of sugar-paclitaxel conjugates (1-5) 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* level of theory.

Prodrug	BE (kcal/mol)	IC_{50}[d] (nM)	Water solubility[c] (μM)	Dipole moment(Debye)	ΔG_{solv} (kcal/mol)[a]
TX-Sugar 1	-5.879	170	21	11.680	-5.22
TX-Sugar 2	-5.034	855	3.0×10^2	14.143	-18.86
TX-Sugar 3	-4.228	1320	7.6×10^2	17.297	-31.61
TX-Sugar 4	-2.438	1906	1.6×10^3	24.034	-41.28
TX-Sugar 5	-3.033	2152	2.7×10^3	27.556	-52.32

[c] Data are obtained from [9]
[d] Data are obtained from [9]

CONCLUSION

Hartree Fock calculation was applied to study some physicochemical properties of sugar-paclitaxel conjugates 1-5. The water-solubility and Gibbs free energy of solvation (ΔG_{solv}) of paclitaxel–sugar conjugates increased in the order 1, 2, 3, 4, and 5. C-7 modification of paclitaxel with a longer oligosaccharide chain, decreased the in vitro cytotoxicity of paclitaxel[11]. Our results indicate that Taxol conjugated with this oligosaccharide can be utilized to improve the biological and anti cancer activity of Taxol.

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