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New two carrier-Taxol as drug delivery system: A computational chemistry study

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ABSTRACT

The physicochemical properties of a novel amphiphilic polymer–paclitaxel conjugate monomethoxy-poly(ethylene glycol)-b-poly(lactide) (MPEG-PLA) and a cyclic small peptide c(RADfK)-paclitaxel containing the arginyl-glycyl-aspartic acid (RGD) amino acid sequence have been evaluated using Density Functional Theory (DFT) and Hartree Fock (HF) calculations. In the both complexes the linking positions are 2'- and 7-OH groups of taxol. Our investigation include: geometrical parameters of paclitaxel complexs, Gibbs free energy of solvation ($\Delta G_{solvation}$), binding energy (BE) and Dipole Moment (DM) of prodrugs, beside some other properties such as partition coefficient, polarizibility, hydration energy and etc. Our results indicate that these carrier-paclitaxel complexes mentioned above can be used to improve anti cancer activity and water-solubility of paclitaxel.

INTRODUCTION

The diterpenoid paclitaxel (Taxol,Fig.1), originally isolated from the Pacific yew (Taxus brevifolia Nutt.) in 1971, exhibited remarkably high cytotoxicity and strong antitumor activity against different tumors resistantly treated by existing anticancer drugs. It has been approved for the treatment of advanced ovarian and breast cancers non-small cell lung cancer, head and neck carcinomas [1–5].

The structure-activity relationships of paclitaxel have been explored extensively with the aim of preparing water-soluble prodrugs. It has been established that the 2'- or 7-hydroxy group of paclitaxel is suitable for structure modification [14,15]. A lot of attempts have been made to connect low-molecular-weight solubilizing moieties at the C2' or C7 position. These prodrugs are mainly ester derivatives including succinate, sulfonic acid, and amino acid and phosphate derivatives [6,7,8]. Although these derivatives possess adequate aqueous solubility, some of them have no antitumor activity because they are too stable to release the parent drug, and several of them are not suitable for i.v. injection because of their instability in aqueous solution at neutral pH.

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 polymer and peptide based transporters [9,10] 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 the present work a series of theoretical treatments were carried out to understand the effect of some carrier-Taxol conjugates on overcoming or improvement of pure Taxol drawbacks. Two carrier that were usaed in this article are monomethoxy-poly(ethylene glycol)-b-poly(lactide) (MPEG-PLA) [9] and a small cyclic peptide *c(RADfK)-paclitaxel* [10] containing the arginyl-glycyl-aspartic acid(RGD) amino acid sequence, both connected to Taxol via 2'- and 7-OH groups of taxol(see fig. 1).

The presence of the glutamic acid residue makes *c(RADfK)* an ideal ligand for further chemical conjugation with diagnostic or therapeutic agents.

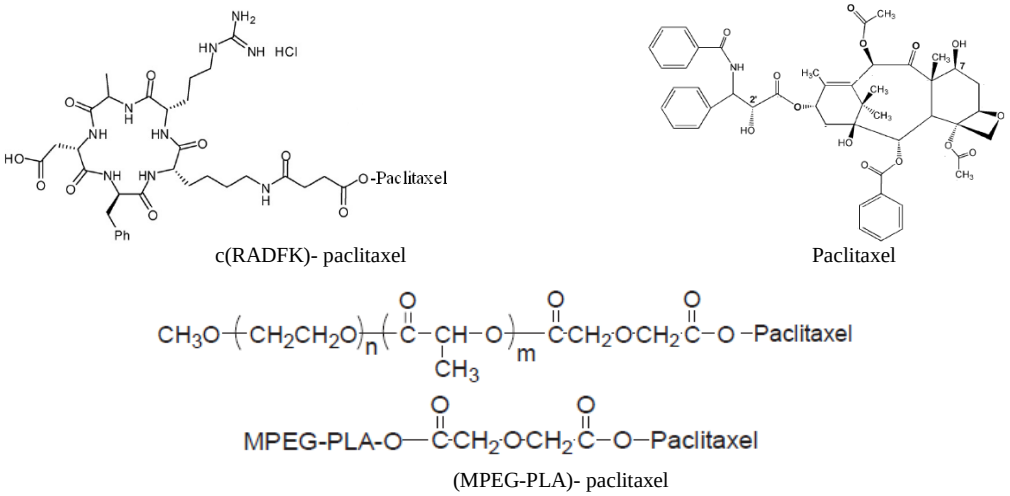

Fig.1. Structures of paclitaxel , c(RADFK)- paclitaxel and (MPEG-PLA)- paclitaxel.

RESULTS AND DISCUSSION

In order to understand the biological and anti cancer activity of prodrug, it is inevitable to study the physicochemical properties of paclitaxel–carrier conjugates. Therefore we were used Hartree-Fock (HF) and Density Functional Theory (DFT) calculations via Gaussian 03 [12] to study these properties.

The ONIOM2 method was applied to optimize the geometry of both carrier-Paclitaxel complexes. In this method we were used B3lyp/6-31g* and HF/6-31g* for high layer (linking position) and low layer (other parts of complexes), respectively. Table 1 presents the geometrical parameters of four different complexes mentioned above around linking position, see also Fig 2.

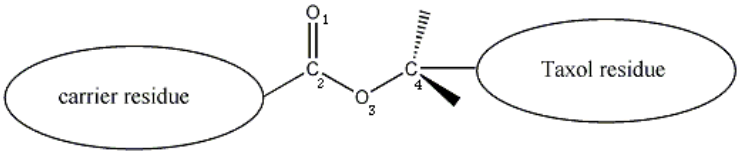

Fig 2. Structure of linking position in polymer-paclitaxel complexes.

The geometry structure of these four complexes were optimized and then the Gibbs free energy of solvation ($\Delta G_{solvation}$) were calculated at HF/6-31g* level of theory using Gaussian 03. Some calculated physiochemical properties of complexes such as logp, binding energies (BE), Gibbs free energy of solvation (ΔG solv), Dipole moment (DM) hydration energy are listed in table 2 and 3. As one can clearly see from table 2, the partition coefficient of four complexes are in more proper situation relative to pure taxol with experimental logp equal to 6.9 [13].

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)	$C_2-O_3-C_4$ (°)
MPEG-PLA-TX 2'	1.2	1.37	1.42	116.5
MPEG-PLA-TX 7	1.21	1.36	1.45	118.5
c(RADFK)-TX 2 '	1.218	1.35	1.43	117.7
c(RADFK7)-TX 7	1.219	1.35	1.46	128.8

Table 2. Some physicochemical properties of prodrugs[a]

Prodrug	Polarizability	Log p	Hydration energy(kcal/ mol)	Volume ($Å^3$)	Surface area ($Å^2$)
MPEG-PLA-TX 2'	138.89	2.46	-25.05	3593.19	1806.78
MPEG-PLA-TX 7	138.26	2.59	-25.89	3507.43	1707.76
c(RADFK)-TX 2'	157.98	0.79	-29.87	3492.24	1592.09
c(RADFK7)-TX 7	156.68	0.5	-35.14	3555.58	1659.17

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

Table 3. Some calculated physicochemical properties of prodrugs

Prodrug	BE (kcal/mol)	ΔG_{solv} (kcal/mol)	Dipole moment(Debye)
MPEG-PLA-TX 2'	-8.55	-12.12	12.637
MPEG-PLA-TX 7	-13.62	-2.38	7.302
c(RADFK)-TX 2 '	-22.11	-5.17	4.035
c(RADFK7)-TX 7	-17.12	-4.99	2.619

CONCLUSION

Hartree Fock(HF) and Density Functional Theory (DFT) calculations were applied to study some physicochemical properties of carrier-paclitaxel conjugates. The water-solubility and Gibbs free energy of solvation (ΔG_{solv}) of carriers increased in the order C-2' ,C-7 modification of paclitaxel. Our results indicate that these prodrugs can be utilized to improve the biological and anti cancer activity of Taxol.

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