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A Computational study on the Physicochemical and Geometrical properties of Daunorubicin-GA3, Daunorubicin-mGA3, DOX-GA3 and DOX-mGA3

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Abstract: Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well known anti-cancer agents. They are anthracycline antibiotics and are commonly used in the treatment of a wide range of cancers**.** 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 DOX-GA3 (glucuronide - prodrug of doxorubicin), DOX-mGA3 (methylester of the glucuronide prodrug), daunorubicin - GA3(glucuronide prodrug of daunorubicin) and daunorubicin - mGA3(methylester of the glucuronide prodrug) conjugated complexes were investigated using Density functional Theory (DFT) and Hartree Fock (HF) calculations. Our results indicate that these complexes mentioned above can be used to improve the anti-cancer activity and the water-solubility of Doxorubicin and Daunorubicin.
Keywords: Anti-cancer drugs, DFT and HF calculations, Doxorubicin, GA3, mGA3, Daunorubicin.

Introduction:

Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well known anti-cancer agents. Biochemical evidence suggests that these drugs make complexes with DNA and thus block the processes of replication and transcription (1–4). Adriamycin has a wide spectrum of anti-cancer activity and has been used to treat acute lymphoblastic and myeloblastic leukemia, malignant lymphomas of both Hodgkin's and non-Hodgkin's types as well as carcinoma of different parts of the human body, e.g. breast, lung, bladder, thyroid, ovary, etc.(5–13).

Daunomycin is particularly useful to treat leukemia in human beings. The structures of adriamycin and daunomycin are only slightly different, but their activities are appreciably diverse (Fig. 1).

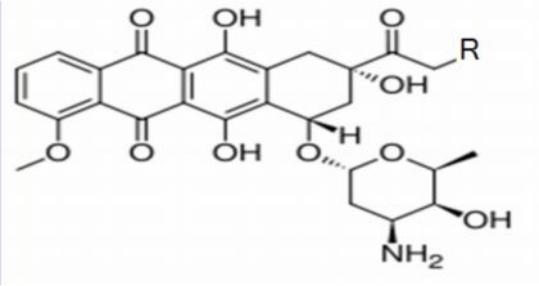

Fig. 1: Structures of adriamycin (R = OH) and daunomycin (R = H).

Experimental

In experimental studies carried out by some other researchers, it has been illustrated that an important metabolic route in the liver is the generation of glucuronide drugs, which are biologically or chemically less reactive and exhibit higher polarity and excretability than the corresponding parent aglycones. In fact, such metabolites could be useful as prodrugs. These naturally occurring glucuronide prodrugs are less toxic than their parent compounds due to increased hydrophilicity, thus resulting in decreased cellular uptake (14). They can be selectively activated in the tumor by b-glucuronidase, which is released in the necrotic tumor areas. An example of a naturally occurring glucuronide prodrug is the metabolite of aniline mustard. Efficacy of treatment with aniline mustard has directly been related to the level of b-glucuronidase in mouse tumors (15). Since doxorubicin generation in the heart tissue after DOX-mGA3 as well as after DOX-GA3 (16) was proportionally lower than that in usual tumor tissues, we expect that this prodrug will be less cardiotoxic than what is normally associated with doxorubicin treatment. Treatment with DOX-mGA3 and daunorubicin - mGA3 is hampered by their low solubility and preclude effective doses being administered. Lipophilic DOX-mGA3 and daunorubicin - mGA3 are not soluble in aqueous solutions such as water, phosphate buffer or ethanol and the lipophilicity of DOX-mGA3 and daunorubicin -mGA3 is higher than that of DOX-GA3 and daunorubicin - GA3 (16). The DOX-mGA3 and DOX-GA3 complexes were synthesized by Epie Boven and colleagues (16). The conjugation scheme is illustrated in Fig. 2.

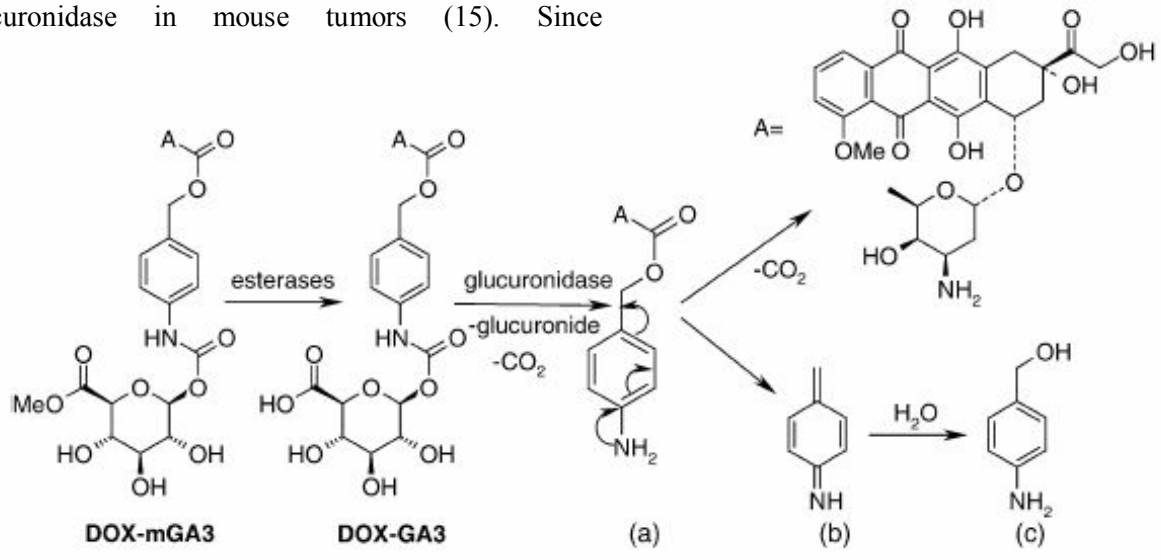

Fig. 2: The methyl glucuronate prodrug will be hydrolyzed first to liberate its glucuronide by esterases. The formed acid should be further cleaved by b-glucuronidase and spontaneous release of CO2 to the drug-spacer molecule (a). the electron-releasing free amino-group will trigger the 1,6-elimination process and second molecule of CO2 resulting in release of the parent antracycline and iminoquinone methide (b). transition state that it is rapidly hydrolyzed to the nontoxic 4-aminobenzyl alcohol (c) (16).

In this study, we intend to show some of the characteristics of doxorubicin, daunorubicin, DOX-GA3, DOX-mGA3, daunorubicin - GA3 and daunorubicin - mGA3 which have been mentioned above and have been obtained by other researchers experimentally through predictable computational calculations, including, molecular energy, binding energy, dipole moment, $\Delta G_{(solvation)}$, partition coefficient (logP), distance bound and angle bound(17,18).

Results and Discussion

The geometrical structure of DOX-GA3, DOX-mGA3, daunorubicin - GA3 and daunorubicin -mGA3 were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation ($\Delta G_{(solvation)}$) was calculated at B3LY/6-31g* level of theory using Gaussian 03 (19). **Table 1** presents the geometrical parameters of four different complexes, mentioned above, around linking position (amide group). See also Fig 3.

Table 1: Geometrical Parameter of complexes around linking position

Complex	R(C2=O1) (Å)	R(C2-N3) (Å)	R(N3-H4) (Å)	C2-N3-H4 (°)
DOX-GA3	1.214	1.354	1.010	115.315
DOX-mGA3	1.214	1.354	1.009	114.870
Daunorubicin -GA3	1.216	1.358	1.012	115.671
Daunorubicin- mGA3	1.226	1.356	1.009	123.036

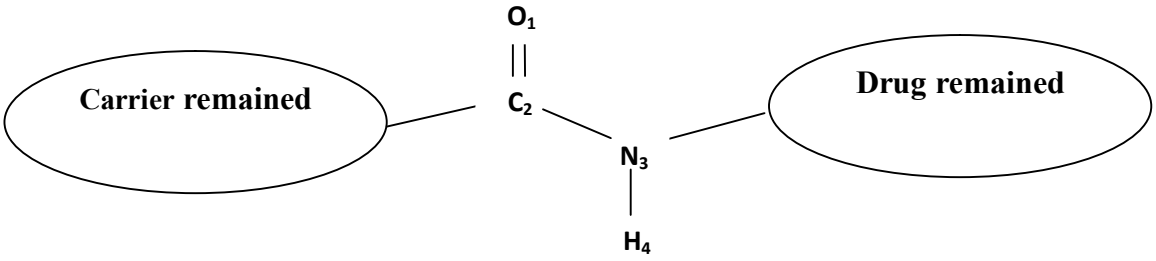

Fig. 3: Structure of linking position in DOX-GA3, DOX-mGA3, daunorubicin - GA3 and daunorubicin - mGA3 complexes

Table 2. Some calculated physicochemical properties of DOX-GA3, DOX-mGA3 and Doxorubicin

Physicochemical properties	DOX-GA3	DOX-mGA3	Doxorubicin
Refrectivity[a]	211.29	215.31	135.50
Polarizability	82.71	84.64	52.00
Log p[a]	-0.83	-0.54	0.110
Log p [b]	-0.15	1.27	0.52
Hydration energy[a]	-39.18	-35.80	-24.03
Surface area[a] (Å2)	831.56	911.01	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-24.54	-25.86	-18.08
Dipole moment(Debye)	15.416	6.720	6.848
BE (ev/mol)	2.616	-1.962	

[a]Data were calculated using HyperChem 8 software(21)
[b] Experimental Data obtained from (16)

Table 3: Some calculated physicochemical properties of Daunorubicin -GA3, Daunorubicinm-GA3 and Daunorubicin

Physicochemical properties	Daunorubicin –GA3	Daunorubicin-mGA3	Daunorubicin
Refrectivity[a]	207.29	212.13	132.24
polarizability	82.36	84.28	51.27
Log p[a]	0.30	0.51	0.55
Log p [b]	-	-	0.766
Hydration energy[a](kcal/mol)	-38.95	-29.81	-19.09
Surface area[a](Å2)	924.35	855.58	542.54
$\Delta G_{(solvation)}$ (kcal/mol)	-34.90	-16.23	-16.88
Dipole moment(Debye)	5.781	6.472	4.722
BE (ev/mol)	0.545	-0.763	

[a]Data were calculated using HyperChem 8 software(21)
[b] Experimental Data obtained from (23)

Some physicochemical properties of DOX-GA3, DOX-mGA3, Doxorubicin, daunorubicin - GA3, Daunorubicin - mGA3 and Daunorubicin Conjugates, such as, Refrectivity, Polarizability, Log p, Hydration energy, Binding Energies (BE), Gibb's Free Energy of Solvation (ΔG solvation) and Dipole moment (DM) are obtained from the optimal structure (20) and have been noted in **Table 2 and Table 3.**

With regards to the experimental results, Hydrophilic DOX-GA3 had a relatively low value of -0.15 as compared to 0.52 of Doxorubicin. These values were similar to those reported before (22). The log P of DOX-mGA3 was 1.27 and considerably higher than that of doxorubicin demonstrating the very lipophilic nature of this prodrug (16).

Conclusion

The Density Functional Theory (DFT) and Hartree Fock (HF) calculations were applied to study some physicochemical properties of Daunorubicin -GA3, Daunorubicin-mGA3, DOX-GA3, DOX-mGA3, Daunorubicin and Doxorubicin. In relation with the calculations carried out, we have drawn this significant conclusion that computational chemistry is closely consistent with experimental results. Regarding the experimental results, lipophilicity of DOX-mGA3 and daunorubicin-mGA3 is higher than that of DOX-GA3 and Daunorubicin -GA3; this fact can be verified through the logP obtained for DOX-mGA3, Daunorubicin-mGA3 and DOX-GA3, Daunorubicin - GA3 using HyperChem 8 software. Our results indicate that Doxorubicin and Daunorubicin conjugated with this carrier (mGA3) can be utilized to improve the biological anti-cancer activity and water-solubility of Doxorubicin and Daunorubicin.

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