Docking of Carboplatin towards Chosen Nanostructures

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Abstract: Carboplatin and the closely associated Cisplatin functioning as antitumor agents are among the main platinum-based drugs with wide application in treating various types of cancer. It directly interacts with DNA, which leads to inducing programmed cell death. The theoretical research shows that similar to the nucleobases Adenine or Guanine, Carboplatin and Cisplatin can bind with other chemical compounds, such as B vitamins containing aromatic rings with long pair orbit on the nitrogen atom. It has been proved that vitamins B6 (pyridoxal phosphate) and B3 (niacin) can form complexes with Carboplatin (not only with Cisplatin), which was proven in early theoretical studies. Therefore, creating a drug carrier by complexation Carboplatin with a nanostructure seems appropriate. In this research, the behavior of Carboplatin with Rhombellane homeomorphs and functionalized fullerenes C60 was studied.

Keywords: platinum-based drugs; vitamin B; drug delivery; nanomedicine; nanocarriers; lung cancer treatment.

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1. Introduction

Carboplatin and Cisplatin are antitumor drugs, and their mechanism of action is identical as Guanine and Adenine in DNA.

Figure 1. Structure of Carboplatin. The following colors are assigned to the chemical elements: grey—carbon; dark blue—nitrogen; red—oxygen; white—hydrogen; turquoise —platinum.

This, in turn, the apoptosis in cancer cells by damage of DNA [1–7]. However, B vitamins containing aromatic rings may occur in these interactions [8], which reduce the anticancer effect of Carboplatin or Cisplatin. Based on the conducted clinical interviews [9,10],
it can be stated that such situations are possible during the simultaneous intake of chemotherapy and a diet rich in B vitamins, such as beetroot or carrot juice [9,10]. Therefore, to prevent this competitiveness, an attempt was made to combine Cisplatin and Carboplatin with nanostructures. Two types of nanostructures were used as potential nanocarriers for Carboplatin (Figure 1). The first of these were functionalized C60 fullerene molecules [11] (Figure 2) [12–17], where can be observed increases the binding properties of such nanosystems [18–22], and the second group of structures used was Rhombellanes [12–17] (Figure 3).
C$_{67}$H$_{16}$O$_2$Si; Methyl 9-(2-trimethylsilyl)ethy1 (C60-Ih)[5,6]fullerene-1-carboxylate

CID_16150529

C$_{70}$H$_{20}$N$_2$O$_2$; 1-N,1-N,9-N,9-N-Tetraethyl(C60-Ih)[5,6]fullerene-1,9-dicarboxamide

CID_101382121

C$_{62}$F$_6$; 1,9-Bis(trifluoromethyl)(C60-Ih)[5,6]fullerene

CID_10909337

C$_{66}$HF$_{12}$I; 9-(1,1,2,2,3,3,4,4,5,5,6,6-Dodecafluoro-6-iodohexyl)-1H-(C60-Ih)[5,6]fullerene

Figure 2. The functionalized fullerenes C60.

The second group of nanostructures is molecules invented by prof. M.V. Diudea [15,18,23–28] (Figure 3). Rhombellans are a new class of structures that can become carriers of other drugs and, therefore, can be used in personalized medicine [18]. Because Rhombellane homeomorphs may be bound to other structures, an attempt was made to deposit Carboplatin, as possible nano-drug complexes. The previous studies dedicated to the Cisplatin molecule show important usefulness in immobilizing such molecules as both proposed groups of nanosystems [13].
After the docking procedure and analysis of the structural properties were found many interesting features [15]. The behavior of Carboplatin concerning the new nanosystems was studied. There were found the best values of Carboplatin- nanostructure affinity.

2. Materials and Methods

2.1. Optimization.

The geometries of the study compounds were optimized at the B3LYP/6-31G** level of theory using Gaussian 09 [29], the platinum atoms were described with the use of the lanl2dz basis set, including relativistic effective core potentials necessary in the case of heavy atoms [30]. The Gibbs free energy calculations with entropy corrections (room temperature) were estimated at the same level of theory. The calculations, including solvation effects, were realized with the use of a self-consistent reaction field (SCRF) approach [31] based on accurate numerical solutions of the Poisson-Boltzmann equation [32]. In all computations, including the PCM continuum model, the water dielectric constant 78 and radii Bondi [33] were applied. The chemical affinity was computed by adding contributions of ZPE corrections, thermal corrections to the enthalpy and entropy terms, and continuum solvation free energies.

2.2. Docking procedure.

The structures of considered nanostructures, namely Rhombellane homeomorphs were found by the Topo Cluj Group [34,35], while the functionalized fullerenes come from the PubChem Database [36]. AutoDock 4.2 was used in the docking procedure [37,38]. Its parameter file was modified by a set of necessary parameters for platinum obtained from the Autodock website [39]. A stochastic Lamarckian genetic algorithm was employed for computing ligand conformations [40]. All initial steps related to the preparation of the initial files were realized utilizing the Autodock Tools package. The grid box with equal dimensions, 26x26x26 Å, was used for all nanostructures. The grid box center was placed in the center of the considered nanomolecules. Each of twenty runs was performed with a 27000 GA on a single population, the following values of operator weights for crossover (0.80), mutation (0.02), and elitism (1.00) parameters were used. The structural analysis of the studied complexes was realized using the VMD package [11].
3. Results and Discussion

The following Table and Figures show the results given after the study. The atom number of Rhombellane structures creates their names.

**Table 1.** The values of Binding Affinity, kcal mol$^{-1}$ of Carboplatin towards chosen nanostructures representing Cube Rhombellane homeomorphs and C60 derivatives.

| Nanostructure | Binding Affinity, kcal mol$^{-1}$ | K MAX |
|---------------|----------------------------------|-------|
|               | MAX | MIN | AVERAGE | SD  |       |
| 1             | 360b | -4.01 | -3.60 | -3.84 | 0.13 | 869.70 |
| 2             | 372  | -3.79 | -3.26 | -3.61 | 0.17 | 599.90 |
| 3             | 396  | -4.22 | -3.85 | -3.97 | 0.13 | 1239.70 |
| 4             | 420  | -3.95 | -3.55 | -3.82 | 0.12 | 785.90 |
| 5             | 444  | -3.95 | -3.67 | -3.87 | 0.09 | 785.90 |
| 6             | 456  | -4.02 | -3.49 | -3.82 | 0.16 | 884.50 |
| 7             | 308a4 | -4.59 | -3.84 | -4.19 | 0.21 | 2314.80 |
| 8             | 308b4 | -4.42 | -3.74 | -4.00 | 0.19 | 1737.40 |
| 9             | 360a  | -3.69 | -3.51 | -3.60 | 0.05 | 506.80 |
| 10            | stf114 | -3.20 | -2.95 | -3.05 | 0.08 | 221.60 |
| 11            | CID_11332103 | -4.31 | -3.76 | -4.10 | 0.20 | 1443.00 |
| 12            | CID_11468612 | -4.16 | -3.95 | -4.09 | 0.07 | 1120.30 |
| 13            | CID_16146387 | -3.96 | -3.83 | -3.89 | 0.04 | 799.30 |
| 14            | CID_16150529 | -3.96 | -3.64 | -3.82 | 0.10 | 799.30 |
| 15            | CID_16156307 | -5.01 | -4.62 | -4.83 | 0.13 | 4703.00 |
| 16            | CID_53469305 | -3.91 | -3.47 | -3.70 | 0.13 | 734.60 |
| 17            | CID_71619159 | -4.03 | -3.78 | -3.91 | 0.07 | 899.60 |
| 18            | CID_101218232 | -4.41 | -3.38 | -4.16 | 0.28 | 1708.30 |
| 19            | CID_101218236 | -4.64 | -4.24 | -4.53 | 0.13 | 2518.60 |
| 20            | CID_10909337_C | -3.65 | -3.47 | -3.57 | 0.06 | 473.70 |

**Figure 4.** The values of Binding Affinity in kcal mol$^{-1}$ of ligand Carboplatin molecule to Rhombellane and functionalized structures of C60 fullerene.

Carboplatin has the highest affinity for the 308a4 nanostructure with an affinity value of -4.19 kcal mol$^{-1}$ and 308b4 nanostructure with an affinity value of -4.00 kcal mol$^{-1}$, among Rbl homeomorphs. The 396 nanostructure occupies the third position with an affinity value of -3.97 kcal mol$^{-1}$. The best affinity is shown by CID_16156307, next CID_101218236, and CID_101218232 with affinity values equal to: -4.83, -4.53, and -4.16 kcal mol$^{-1}$, among the functionalized structures of C60 fullerene (Table 1, Figure 4). To sum up, in the case of the C60 functionalized fullerene, the examined structures show a significantly larger affinity than in the case of the Rbl home morphs. Furthermore, all values of affinities are much larger than in the case of complexes with Cisplatin [9].

https://biointerfaceresearch.com/
Figure 5. The $K_{\text{max}}$ values of ligand Carboplatin molecule relative to Rhombellane and functionalized structures of C60 fullerene.

The values of the $K_{\text{max}}$ constant are correlated with the values of binding energy values. The highest values are obtained in the case of CID_16156307, which means the more the reaction proceeds towards the formation of the complex, the functionalized C60 fullerene; in the Rhombellane group of nanostructures, the highest values are shown by the 308a4 molecule (Table 1, Figure 5).
Carboplatin and functionalized fullerene C₆₀ easily form hydrogen bonds between them with strong and medium strength (Figure 6).

The criterion for classification of the strength of these hydrogen bonds was described by Grabowski [41].

The nanostructure CID_11332103 with Carboplatin creates one strong hydrogen bond with a length of 1.74 Å between the amino group of Carboplatin and the oxygen atom of the phosphate group of the nanostructure. The second amino group of Carboplatin forms four medium hydrogen bonds; the first one with the oxygen atom of the side chain phosphate group of fullerene with a value of 2.29 Å; the second one with the fluorine atom of the second side chain of fullerene with a value of 2.38 Å; the third one with the next fluorine atom with the value of 2.69 Å, and the fourth hydrogen bond is created with an oxygen atom of the trifluoro ethoxy group (Figure 6). The distance of Carboplatin relative to the fullerene surface is 3.22 Å. In the case of CID_11468612, each of the amino groups of Carboplatin forms one hydrogen bond with oxygen atoms from the phosphate group from the side chain of fullerene with lengths of 1.79 Å and 2.08 Å. The distance between Carboplatin and the fullerene surface is 3.29 Å.

The complex of nanostructure CID_16156307 and Carboplatin creates two medium hydrogen bonds. Both amino groups of Carboplatin form one hydrogen bond with an oxygen atom from the side chain functional group of nanostructure with distances equal 2.04 Å and 2.29 Å, respectively. The distance of Carboplatin the fullerene surface is 3.28 Å. For CID_101218232, each of the Carboplatin amino groups forms two hydrogen interactions; one with the oxygen atom of the trifluoro ethoxy group from the fullerene, the other with the fluorine atom of the nanostructure. In the case of the first amino group, the appropriate distances are equal to 1.91 and 2.42 Å, while in the case of the second amino group, they are equal to 2.81 and 2.41 Å. The distance of Carboplatin the fullerene surface is 3.46 Å. Carboplatin, during the interaction with CID_101218236 creates one hydrogen bond of the first of the amino groups of Carboplatin with oxygen from the methoxy group on the side chain, with a distance equal 2.21 Å. The distance of Carboplatin in relation to the fullerene surface is 3.50 Å. In the case of 396 nanostructure, both amino groups of Carboplatin are involved in the formation of hydrogen bonds; the first of them creates one hydrogen bond with an oxygen atom from the ester group with a distance equal 2.45 Å, the second amine group creates two hydrogen bonds with another oxygen atom from the ester group on the surface with a distance equal to 2.14 Å and 2.30 Å, respectively. Both Carboplatin amino groups form a hydrogen bond network with oxygen atoms from the outer shell of Rhombellane 308a4; the first amino group forms two hydrogen bonds formed by two hydrogen atoms with distance values equal to 2.41 Å and 1.96 Å; the second amino group forms three hydrogen bonds formed by two hydrogen atoms, the first with a bond length of 2.14 Å, and the second with 2.22 Å and 2.83 Å. Both
amino groups of Carboplatin form a hydrogen bond network with oxygen atoms from the outer shell of Rhombellane 308b4; the first amino group forms two hydrogen bonds formed by two hydrogen atoms with bond length values of 2.18 Å and 2.27 Å; the second amino group forms two hydrogen bonds formed by two hydrogen atoms with bond length values of 2.11 Å and 2.37 Å. The structures of the formed complexes are presented in Figure 6.

4. Conclusions

Because vitamin B3 and B6 can form complexes with Carboplatin, like Cisplatin, it seems appropriate to form a Carboplatin complex with a nanostructure as a drug carrier. The behavior of Carboplatin, functionalized fullerenes C60 and Rhombellane homeomorphs in terms of their (interacting) geometry, energy and topology were studied. AutoDock 4.2 was used to realize the docking procedure. Many interesting features were shown after the docking procedure. The complexation with C60 functionalized fullerene of study structures shows a significantly larger affinity than in the case of Rbl homeomorphs, and all the values of affinities are much larger than in the case of Cisplatin. Again, the highest values of the $K_{\text{max}}$ constant were obtained for the fullerene structures of C60. The study nanostructures easily created complexes with Carboplatin, and that’s why they could be used as nanocarriers for Carboplatin molecules.

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Conflicts of Interest

The authors declare no conflict of interest.

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