Docking of Platinum Compounds on Cube Rhombellane Functionalized Homeomorphs

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Received: 19 March 2020; Accepted: 13 April 2020; Published: 6 May 2020

Abstract: Platinum compounds are anti-cancer drugs and can bind to canonical purine bases, mainly guanine, found within double helical DNA. Platinum compounds can be transferred directly to pathologically altered sites in a specific and site-oriented manner by nanocarriers as potential nanocarriers for carboplatin. Two types of nanostructures were used as potential nanocarriers for carboplatin, the first were functionalized C60 fullerene molecules and the second were rhombellanes. The analyzed nanostructures show considerable symmetry, which affects the affinity of the studied nanocarriers and ligands. Thus symmetry of nanostructures affects the distribution of binding groups on their surface. After the docking procedure, analysis of structural properties revealed many interesting features. In all described cases, binding affinities of complexes of platinum compounds with functionalized fullerene C60 are higher compared with affinities of complexes of platinum compounds with rhombellane structures. All platinum compounds easily create complexes with functionalized fullerene C60, CID_16156307, and at the same time show the highest binding affinity. The binding affinities of lobaplatin and heptaplatin are higher compared with oxaliplatin and nedaplatin. The high value of binding affinity and equilibrium constant K is correlated with creation of strong and medium hydrogen bonds or is correlated with forming a hydrogen bond network. The performed investigations enabled finding nanocarriers for lobaplatin, heptaplatin, oxaliplatin and nedaplatin molecules.

Keywords: cube rhombellane homeomorph; lobaplatin; heptaplatin; oxaliplatin; nedaplatin; nanostructure; molecular docking; affinity

1. Introduction

The anticancer activity of cisplatin was discovered for the first time in 1960 by Professor Barnett Rosenberg at the University of Michigan [1,2], however it was Carozzi who showed that cisplatin has anti-cancer effects [3]. After Rosenberg’s first work, several thousand platinum compounds were found, and some of them were synthesized, namely oxaliplatin, nedaplatin, lobaplatin, heptaplatin and carboplatin [4]. This was the reason that the above compounds were chosen for the study. Platinum compounds are anti-cancer drugs and can bind to canonical purine bases, mainly guanine, found within double helical DNA. This in turn causes DNA damage and then apoptosis in cancer cells [5–7].

Platinum compounds can be transferred directly to pathologically altered sites in a specific and site-oriented manner by nanocarriers [8–13]. Two types of nanostructures were used as potential nanocarriers for carboplatin. The first of them were functionalized C60 fullerene molecules, containing numerous active groups on their surface, which significantly increase binding properties of such nanosystems; and the second group of structures was rhombellanes.
The second group of nanostructures used in the study comprises molecules invented by Diudea, [14–22]. Rhombellanes are structures which can become carriers of other drugs, and thus can be used in personalized medicine (Figure 1). An attempt was made to deposit platinum compounds on the surface of rhombellane homeomorphs as possible nanocarrier complexes. In the case of both proposed groups of nanosystems, previous studies dedicated to cisplatin [11] molecules showed their important usefulness in immobilization of such type of molecules.

Many interesting features were found after docking procedures and analysis of structural properties. Behavior of carboplatin in relation to considered nanosystems, in terms of their geometry, energy and topology was studied, and the best values of carboplatin-nanostructure affinity were found.

2. Methods

2.1. Docking Procedure

Two groups of nanostructures, that is, rhombellane structures and functionalized fullerene C60 molecules, were considered in the study. Rhombellane homeomorphs come from the Topo Cluj Group [12,23–27] while functionalized fullerenes were obtained from the PubChem database [28]. AutoDock 4.2 was used to realize the docking procedure [29,30]. Because platinum compounds were used in the study, a modification of parameters was needed; this was obtained from the Autodock website [31]. Another argument for using this program is the quality of the calculations that the applied algorithm provides. A stochastic Lamarckian genetic algorithm was used for computing ligand conformations [32]. Nguyen Thanh Nguyen and co-workers described the accuracy of AutoDock4 results [33]. They demonstrated that AutoDock4 shows a better performance than Vina AD4 for all metrics such as precision, correlation coefficient and success rate over 21 receptors [33]. Therefore the
AutoDock4 approach gives a larger correlation coefficient (R) with experiments than that given by the Vina approach and the AutoDock4 approach is more accurate and precise. AutoDock4 gives a better correlation and a smaller RMSE with respect to experiment. Furthermore, the mean magnitude of docking energy is within the error bar of the experimental value [33], which is why the AutoDock4 results are better than Vina approach in terms of correlation with the experiment. AutoDock4 is also more precise in estimating the hydrogen bonds between ligands and receptors than Vina is [33].

The Autodock Tools package was used for preparation of all initial steps. For all nanostructures the grid box with dimensions equal 26 × 26 × 26 Å was used. The center of the grid box was placed in the center of considered nanomolecules. The maximum number of energy evaluations was set to 2,500,000. Twenty runs were performed with a maximum number of 27,000 GA on a single population of 150 individual species. Default values for the operator weights for crossover (0.80), mutation (0.02) and elitism (1.00) parameters were used. The structural analysis of studied complexes was realized with the use of VMD package [34].

2.2. Results and Discussion

The obtained results are presented in the following tables and figures. Tables 1–4 represent values of binding affinity [kcal/mol] of ligand molecule relative to functionalized fullerene C60 molecules and rhombellane structures. Tables 5–8 represent minimum and maximum binding energies and Kmax values.

Among Rbl homeomorphs, lobaplatin has the highest affinity for 308a4 nanostructure with an affinity value of −4.66 kcal/mol, as well as for 308b4 nanostructure with an affinity value of −4.6 kcal/mol (Table 1). Among functionalized structures of C60 fullerene, CID_16156307 has the best binding affinity to lobaplatin with an affinity value of −4.98 kcal/mol, CID_11468612 and CID_101218236 have similar values of binding affinity, that is −4.48 and −4.47 kcal/mol, respectively. In general, binding affinities of lobaplatin-functionalized fullerene C60 complexes are higher compared with affinities of lobaplatin-rhombellane structures complexes.

Table 1. The values of binding free energy (kcal/mol) characterizing complexes of lobaplatin with considered nanocarriers obtained during docking procedure. Binding energy (kcal/mol).

| Name of Nanostructures Title | Binding Energy (kcal/mol) |
|------------------------------|---------------------------|
| CID_71619159                 | −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 |
| CID_53469305                 | −4.31 −4.31 −4.31 −4.31 −4.31 −4.31 −4.31 −4.31 −4.31 −4.31 |
| CID_16156307                 | −4.98 −4.98 −4.98 −4.98 −4.98 −4.98 −4.98 −4.98 −4.98 −4.98 |
| CID_16146387                 | −4.17 −4.12 −4.12 −4.12 −4.12 −4.12 −4.12 −4.12 −4.12 −4.12 |
| CID_11468612                 | −4.48 −4.48 −4.48 −4.48 −4.48 −4.48 −4.48 −4.48 −4.48 −4.48 |
| CID_11332103                 | −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 −4.45 |
| CID_10909337                 | −3.66 −3.64 −3.63 −3.63 −3.63 −3.63 −3.63 −3.63 −3.63 −3.63 |
| CID_101218236                | −4.47 −4.47 −4.47 −4.47 −4.47 −4.47 −4.47 −4.47 −4.47 −4.47 |
| 456                          | −3.8 −3.8 −3.79 −3.79 −3.79 −3.79 −3.79 −3.79 −3.79 −3.79 |
| 444                          | −3.82 −3.82 −3.82 −3.82 −3.82 −3.82 −3.82 −3.82 −3.82 −3.82 |
| 420                          | −3.87 −3.87 −3.87 −3.87 −3.87 −3.87 −3.87 −3.87 −3.87 −3.87 |
| 396                          | −4.02 −4.02 −4.02 −4.02 −4.02 −4.02 −4.02 −4.02 −4.02 −4.02 |
| 372AB                        | −4.08 −4.08 −4.08 −4.08 −4.08 −4.08 −4.08 −4.08 −4.08 −4.08 |
| 360b                         | −4.18 −4.18 −4.17 −4.17 −4.17 −4.17 −4.17 −4.17 −4.17 −4.17 |
| 360a                         | −4.06 −4.06 −4.06 −4.06 −4.06 −4.06 −4.06 −4.06 −4.06 −4.06 |
| 308b4                        | −4.6 −4.6 −4.6 −4.6 −4.6 −4.6 −4.6 −4.6 −4.6 −4.6 |
| 308a4                        | −4.66 −4.66 −4.66 −4.66 −4.66 −4.66 −4.66 −4.66 −4.66 −4.66 |
Table 2. The values of binding free energy (kcal/mol) characterizing complexes of heptaplatin with considered nanocarriers obtained during docking procedure. Binding Energy (kcal/mol).

| Name of Nanostructures Title | Binding Energy (kcal/mol) |
|------------------------------|--------------------------|
| CID_101218232                | -4.97                    |
| CID_101218236                | -4.67                    |
| CID_1090937_C                | -4.06                    |
| CID_11332103                 | -4.82                    |
| CID_11468612                 | -4.93                    |
| CID_16146387                 | -4.62                    |
| CID_16150529                 | -4.48                    |
| CID_16156307                 | -5.85                    |
| 308a4                       | -4.76                    |
| 308b4                       | -4.43                    |
| 360a                        | -4.41                    |
| 360b                        | -3.87                    |
| 372AB                       | -3.93                    |
| 396                         | -4.51                    |
| 420                         | -4.44                    |
| 444                         | -3.95                    |
| 456                         | -3.83                    |
| CID_10909337                | -3.41                    |
| CID_11332103                 | -3.79                    |
| CID_11468612                 | -3.7                     |
| CID_16146387                 | -3.64                    |
| CID_16150529                 | -3.55                    |
| CID_16156307                 | -4.61                    |
| CID_53469305                 | -3.39                    |
| CID_71619159                 | -2.59                    |
| CID_10909337                 | -3.56                    |
| CID_11468612                 | -3.17                    |
| CID_16146387                 | -3.94                    |
| CID_16150529                 | -3.76                    |
| CID_101218232                | -3.82                    |
| CID_101218236                | -3.39                    |
| CID_10266715                 | -3.44                    |
| CID_10382121                 | -2.59                    |
| 456                         | -3.65                    |
| 444                         | -3.66                    |
| 420                         | -3.51                    |
| 396                         | -3.59                    |
| 372AB                       | -3.85                    |
| 360b                        | -3.65                    |
| 360a                        | -4.05                    |
| 308b4                       | -4.08                    |
| 308a4                       | -4                      |

Table 3. The values of binding free energy (kcal/mol) characterizing complexes of oxaliplatin with considered nanocarriers obtained during docking procedure. Binding energy (kcal/mol).

| Name of Nanostructures Title | Binding Energy (kcal/mol) |
|------------------------------|--------------------------|
| CID_11332103                 | -3.79                    |
| CID_11468612                 | -3.7                     |
| CID_16146387                 | -3.64                    |
| CID_16150529                 | -3.55                    |
| CID_16156307                 | -4.61                    |
| CID_53469305                 | -3.56                    |
| CID_71619159                 | -3.17                    |
| CID_10909337                 | -3.94                    |
| CID_16146387                 | -3.76                    |
| CID_101218232                | -3.82                    |
| CID_101218236                | -3.39                    |
| CID_10266715                 | -3.44                    |
| CID_10382121                 | -2.59                    |
| 456                         | -3.65                    |
| 444                         | -3.66                    |
| 420                         | -3.51                    |
| 396                         | -3.59                    |
| 372AB                       | -3.85                    |
| 360b                        | -3.65                    |
| 360a                        | -4.05                    |
| 308b4                       | -4.08                    |
| 308a4                       | -4                      |
The values of binding free energy (kcal/mol) characterizing complexes of nedaplatin with considered nanocarriers obtained during docking procedure. Binding Energy (kcal/mol).

| Name of Nanostructures | Binding Energy (kcal/mol) |
|------------------------|--------------------------|
| CID_10909337           | 4.45                     |
| CID_11332103           | 4.31                     |
| CID_114668612          | 4.98                     |
| CID_16146387           | 4.48                     |
| CID_16150529           | 4.47                     |
| CID_16156307           | 4.45                     |
| CID_53469305           | 4.31                     |
| CID_71618962           | 4.45                     |
| CID_71619055           | 4.47                     |
| CID_71619159           | 4.48                     |
| CID_101218232          | 4.47                     |
| CID_101266715          | 4.45                     |
| CID_101382121          | 4.47                     |

Table 4. The values of binding free energy (kcal/mol) characterizing complexes of nedaplatin with considered nanocarriers obtained during docking procedure. Binding Energy (kcal/mol).

Table 5. The energetic characteristic of lobaplatin complexes created with nanomolecules. Kmax represents the values of binding constants based on the most favorable values of binding free energies estimated for complexes.

| Name of Nanostructures | MAX Binding Energy | MIN Binding Energy | AVERAGE | SD | Binding Constant [Kmax] |
|------------------------|-------------------|-------------------|---------|----|------------------------|
| CID_71619159           | −4.45             | −4.45             | −4.45   | 9 × 10⁻¹⁶ | 1827.7                 |
| CID_53469305           | −4.31             | −4.29             | −4.298  | 9 × 10⁻³  | 1443.0                 |
| CID_16156307           | −4.98             | 4.81              | −4.946  | 7 × 10⁻²  | 4470.8                 |
| CID_16146387           | −4.17             | −4.11             | −4.121  | 2 × 10⁻²  | 1139.3                 |
| CID_114668612          | −4.48             | −4.48             | −4.48   | 9 × 10⁻¹⁶ | 1922.6                 |
| CID_11332103           | −4.45             | −4.45             | −4.45   | 9 × 10⁻¹⁶ | 1827.7                 |
| CID_10909337           | −3.66             | −3.59             | −3.625  | 2 × 10⁻²  | 481.7                  |
| CID_101218236          | −4.47             | −4.23             | −4.446  | 7 × 10⁻²  | 1890.4                 |
| CID_101218232          | −4.37             | −4.37             | −4.37   | 9 × 10⁻¹⁶ | 1596.8                 |
| 456                    | −3.8              | −3.75             | −3.788  | 1 × 10⁻²  | 610.2                  |
| 444                    | −3.82             | −3.81             | −3.818  | 4 × 10⁻³  | 631.1                  |
| 420                    | −3.87             | −3.85             | −3.866  | 7 × 10⁻³  | 686.7                  |
| 396                    | −4.02             | −3.98             | −4.01   | 1 × 10⁻²  | 884.5                  |
| 372AB                  | −4.08             | −3.95             | −4.05   | 5 × 10⁻²  | 978.8                  |
| 360b                   | −4.18             | −4.16             | −4.168  | 7 × 10⁻³  | 1158.7                 |
| 360a                   | −4.06             | −3.96             | −4.004  | 5 × 10⁻²  | 946.3                  |
| 308b4                  | −4.6              | −4.6              | −4.6    | 9 × 10⁻¹⁶ | 2354.2                 |
| 308a4                  | −4.66             | −4.48             | −4.625  | 7 × 10⁻²  | 2605.1                 |
The energetic characteristic of heptaplatin complexes created with nanomolecules.

Table 6. The energetic characteristic of heptaplatin complexes created with nanomolecules. Kmax represents the values of binding constants based on the most favorable values of binding free energies estimated for complexes.

| Name of Nanostructures | MAX Binding Energy | MIN Binding Energy | AVERAGE | SD | Binding Constant [K_{max}] |
|------------------------|-------------------|--------------------|---------|----|---------------------------|
| CID_101218232          | -4.97             | -4.83              | -4.932  | 0.038678 | 4396.0                    |
| CID_101218236          | -4.67             | -4.38              | -4.605  | 0.09426  | 2649.4                    |
| CID_10909337_C         | -4.06             | -3.85              | -3.976  | 0.070456 | 946.3                     |
| CID_11332103           | -4.82             | -4.4               | -4.664  | 0.184076 | 3412.8                    |
| CID_114686612          | -4.93             | -4.89              | -4.922  | 0.014    | 4109.0                    |
| CID_16146387           | -4.62             | -4.47              | -4.577  | 0.042438 | 2435.0                    |
| CID_16150529           | -4.48             | -4.39              | -4.445  | 0.022913 | 1922.6                    |
| CID_16156307           | -5.85             | -5.35              | -5.551  | 0.238095 | 19413.6                   |
| CID_53469305           | -4.33             | -4.11              | -4.155  | 0.062968 | 1492.6                    |
| CID_71619159           | -4.62             | -4.55              | -4.606  | 0.020591 | 2435.0                    |
| 308a4                  | -4.76             | -4.11              | -4.312  | 0.23731  | 3084.1                    |
| 308b4                  | -4.43             | -4.04              | -4.164  | 0.096974 | 1767.0                    |
| 360a                   | -4.41             | -3.9               | -4.073  | 0.179279 | 1708.3                    |
| 360b                   | -3.87             | -3.77              | -3.817  | 0.024104 | 686.7                     |
| 372AB                  | -3.93             | -3.85              | -3.898  | 0.023152 | 759.9                     |
| 396                    | -4.51             | -3.89              | -4.202  | 0.253567 | 2022.4                    |
| 420                    | -4.44             | -3.82              | -4.19   | 0.242899 | 1797.1                    |
| 444                    | -3.95             | -3.73              | -3.873  | 0.075637 | 785.9                     |
| 456                    | -3.83             | -3.65              | -3.784  | 0.052192 | 641.8                     |

The energetic characteristic of oxaliplatin complexes created with nanomolecules.

Table 7. The energetic characteristic of oxaliplatin complexes created with nanomolecules. Kmax represents the values of binding constants based on the most favorable values of binding free energies estimated for complexes.

| Name of Nanostructures | MAX Binding Energy | MIN Binding Energy | AVERAGE | SD | Binding Constant [K_{max}] |
|------------------------|-------------------|--------------------|---------|----|---------------------------|
| CID_10909337           | -3.41             | -3.41              | -3.41   | 0.00 | 315.9                     |
| CID_11332103           | -3.79             | -3.76              | -3.78   | 0.01 | 599.9                     |
| CID_11468612           | -3.70             | -3.69              | -3.69   | 0.00 | 515.4                     |
| CID_16146387           | -3.64             | -3.64              | -3.64   | 0.00 | 465.8                     |
| CID_16150529           | -3.55             | -3.52              | -3.54   | 0.01 | 400.1                     |
| CID_16156307           | -4.61             | -4.60              | -4.60   | 0.00 | 2394.3                    |
| CID_53469305           | -3.56             | -3.51              | -3.55   | 0.01 | 406.9                     |
| CID_71618962           | -3.17             | -3.16              | -3.17   | 0.00 | 210.7                     |
| CID_71619055           | -3.94             | -3.94              | -3.94   | 0.00 | 772.8                     |
| CID_71619159           | -3.76             | -3.73              | -3.75   | 0.01 | 570.3                     |
| CID_101218232          | -3.82             | -3.80              | -3.81   | 0.01 | 631.1                     |
| CID_101218236          | -3.39             | -3.36              | -3.38   | 0.01 | 305.4                     |
| CID_101266715          | -3.44             | -3.42              | -3.43   | 0.01 | 332.3                     |
| CID_101382121          | -2.59             | -2.56              | -2.57   | 0.01 | 79.2                      |
| 456                    | -3.65             | -3.37              | -3.49   | 0.12 | 473.7                     |
| 444                    | -3.66             | -3.36              | -3.42   | 0.08 | 481.7                     |
| 420                    | -3.51             | -3.48              | -3.49   | 0.01 | 374.0                     |
| 396                    | -3.59             | -3.54              | -3.57   | 0.01 | 428.1                     |
| 372AB                  | -3.85             | -3.77              | -3.80   | 0.03 | 663.9                     |
| 360b                   | -3.65             | -3.60              | -3.63   | 0.02 | 473.7                     |
| 360a                   | -4.05             | -4.00              | -4.02   | 0.02 | 930.4                     |
| 308b4                  | -4.08             | -4.06              | -4.07   | 0.01 | 979.8                     |
| 308a4                  | -4.00             | -3.99              | -4.00   | 0.00 | 855.1                     |
Table 8. The energetic characteristic of nedaplatin complexes created with nanomolecules. Kmax represents the values of binding constants based on the most favorable values of binding free energies estimated for complexes.

| Name of Nanostructures | MAX Binding Energy | MIN Binding Energy | AVERAGE | SD | Binding Constant [Kmax] |
|------------------------|-------------------|--------------------|---------|----|------------------------|
| CID_10909337           | −1.30             | −1.24              | −1.28   | 0.02 | 9.0                    |
| CID_11332103           | −2.81             | −2.45              | −2.70   | 0.11 | 114.8                  |
| CID_11468612           | −2.88             | −2.74              | −2.79   | 0.04 | 129.1                  |
| CID_16146387           | −2.31             | −2.12              | −2.23   | 0.06 | 49.3                   |
| CID_16150529           | −2.26             | −2.14              | −2.22   | 0.04 | 45.4                   |
| CID_16156307           | −4.14             | −3.38              | −3.75   | 0.23 | 1083.1                 |
| CID_53469305           | −2.26             | −2.07              | −2.17   | 0.06 | 45.4                   |
| CID_71618962           | −2.20             | −2.14              | −2.17   | 0.02 | 41.0                   |
| CID_71619055           | −2.40             | −2.36              | −2.39   | 0.01 | 57.4                   |
| CID_71619159           | −2.24             | −2.17              | −2.22   | 0.02 | 43.8                   |
| CID_101218232          | −3.04             | −2.93              | −2.98   | 0.03 | 169.2                  |
| CID_101218236          | −3.09             | −3.00              | −3.03   | 0.03 | 184.1                  |
| CID_101266715          | −1.59             | −1.52              | −1.56   | 0.03 | 14.6                   |
| CID_101382121          | −1.12             | −1.03              | −1.09   | 0.02 | 6.6                    |
| 456                    | −2.96             | −2.70              | −2.84   | 0.09 | 147.8                  |
| 444                    | −2.90             | −2.61              | −2.77   | 0.08 | 133.6                  |
| 420                    | −2.57             | −2.45              | −2.53   | 0.04 | 76.5                   |
| 396                    | −2.75             | −2.39              | −2.56   | 0.08 | 103.7                  |
| 372AB                  | −2.61             | −2.45              | −2.54   | 0.06 | 81.9                   |
| 360b                   | −2.58             | −2.50              | −2.54   | 0.03 | 77.8                   |
| 360a                   | −3.02             | −2.56              | −2.84   | 0.13 | 163.6                  |
| 308b4                  | −2.72             | −2.36              | −2.55   | 0.11 | 98.6                   |
| 308a4                  | −2.79             | −2.29              | −2.57   | 0.15 | 110.9                  |

The values of binding energy are correlated with values of the Kmax constant and among rhombellanes the highest values are obtained in the case of 308a4 and 308b4 nanostructures (Table 5, Figure 2), however, it is one of functionalized structures of C60 fullerene, namely CID_16156307, which is characterized by the highest Kmax value among all studied structures.

Lobaplatin and functionalized fullerenes C60 easily form strong hydrogen bonds between them (Figure 3).

The complex of nanostructure CID_11468612 and lobaplatin creates one strong hydrogen bond with the length of 1.86 Å between the hydrogen atom of lobaplatin and the oxygen atom of phosphate group of nanostructure. Similarly, a strong hydrogen bond is created in the case of CID_16156307 and lobaplatin with 1.99 Å bond length between the hydrogen bond of lobaplatin and the oxygen atom of nanostructure. Strong hydrogen bond is also created in the case of Rbl structure 308b4 (hydrogen atom) and lobaplatin (oxygen atom), where the bond length is 1.88 Å. However, rhombellane structure 308a4 forms a hydrogen bond network with medium and week strength of 2.03 Å, 2.96 Å and 3.30 Å, all of them between hydrogen atoms of lobaplatin and oxygen atoms of nanostructure.

Table 2 represents the values of binding affinity (kcal/mol) of heptaplatin molecule ligand relative to functionalized fullerene C60 and rhombellane structures. Between functionalized fullerenes C60, the highest affinity to heptaplatin is shown by CID_16156307 with value of −5.08 kcal/mol, next by CID_101218232 and finally by CID_11468612, with values equal −4.97 kcal/mol and −4.93 kcal/mol, respectively. Generally, it can be said that the values of binding affinities of heptaplatin to functionalized fullerenes C60 are higher than to rhombellane structures. Thus, the highest affinity of heptaplatin molecule ligand to a particular rhombellane is obtained for 308a4 structure, and next to 396 and 420 structures with affinity values of −4.76 kcal/mol, −4.51 kcal/mol and −4.44 kcal/mol, respectively.
Figure 2. Graphic representation of functionalized fullerenes C60.
Table 2. The values of binding free energy (kcal/mol) characterizing complexes of heptaplatin with considered nanocarriers obtained during docking procedure.

| Name of Nanostructures | Binding Energy (kcal/mol) |
|------------------------|---------------------------|
| CID_101218232          | -4.97                     |
| CID_101218236          | -4.67                     |
| CID_10909337           | -4.06                     |
| CID_11332103           | -4.82                     |
| CID_11468612           | -4.93                     |
| CID_16146387           | -4.62                     |
| CID_16150529           | -4.48                     |
| CID_16156307           | -5.85                     |
| CID_53469305           | -4.33                     |
| CID_71619159           | -4.62                     |
| 308a4                  | -4.76                     |
| 308b4                  | -4.43                     |
| 360a                   | -4.41                     |
| 360b                   | -3.87                     |
| 372AB                  | -3.93                     |
| 396                    | -4.51                     |
| 420                    | -4.44                     |
| 444                    | -3.95                     |
| 456                    | -3.83                     |

Lobaplatin and functionalized fullerenes C60 easily form strong hydrogen bonds between them (Figure 3).

Figure 3. Graphic representation of lobaplatin complexes with chosen nanostructures obtained during docking stage.

Because binding affinity is correlated with binding constant $K_{max}$, the highest value can be found for CID_16156307 and by analogy for CID_101218232 and CID_11468612. Again, $K_{max}$ values for complexes of heptaplatin with rhombellane structures are lower. The highest value is obtained for 308a4 structure and next for 396 and 420 Rbl structures.

In the case of heptaplatin, for all described complexes a hydrogen bond network can be seen (Figure 4). CID_11468612 forms one strong hydrogen bond with the length of 1.98 Å between the hydrogen atom of nitrogen group of heptaplatin and the oxygen atom of CID_11468612. The rest of the hydrogen bonds of this network are rather weak. CID_16156307 forms four hydrogen bonds with heptaplatin: one strong, two medium and one weak, all between hydrogen atoms of the nitrogen group of heptaplatin and the oxygen atom of nanostructure, with lengths of 1.74 Å, 2.03 Å, 2.09 Å and 3.49 Å, respectively. Similarly, CID_101218232 creates four hydrogen bonds with heptaplatin: one strong (1.97 Å), two medium (2.09 Å and 2.19 Å) and one weak (3.58 Å). Rhombellane structures 308a4 and 396 create the largest hydrogen bond network. All hydrogen bonds are created between hydrogen atoms of nitrogen groups of heptaplatin and oxygen atoms of rhombellanes. In the case of 308a4, the bond lengths of hydrogen bonds are from 1.74 Å to 3.37 Å, while in the case of the 396 structure there are from 2.03 Å to 3.76 Å. Only for heptaplatin-396 complex there are three hydrogen bonds, strong (1.93 Å), medium (2.28 Å) and weak (3.35 Å).
Figure 4. Graphic representation of heptaplatin complexes which chosen nanostructures obtained during docking stage.
The binding affinities of oxaliplatin and nedaplatin molecules relative to spherical nanosystems are much smaller compared to lobaplatin and heptapl ain. Again, complexes with functionalized fullerenes C60 have higher bond affinity compared to rhombellane structures. Among all structures, the best binding affinity was found for the CID_16156307-nedaplatin complex (Table 3) with a value of \(-4.61\) Å.

Because $K_{\text{max}}$ value is closely correlated with the value of binding affinity, this is why once more the best binding constant is observed for CID_16156307 structure.

Oxaliplatin creates two hydrogen bonds with CID_16156307 between the hydrogen atom of nitrogen group of oxaliplatin and the oxygen atom of nanostructure with values of 1.90 Å and 2.36 Å (Figure 5).

![Figure 5](image.png)

**Figure 5.** Graphic representation of oxaliplatin complexes which chosen nanostructure (CID_16156307) obtained during docking stage.

Again, CID_16156307 creates complex with nedaplatin with the best binding affinity, equal to \(-4.14\) kcal/mol, between all nanostructures.

Nedaplatin creates hydrogen networks with nanostructures (Figures 6 and 7). In the case of CID_16156307 there are medium and weak hydrogen bonds with lengths from 2.14 to 3.45 Å. In the case of Rbl structure, two strong hydrogen bonds also appear with lengths of 1.65 Å and 1.89 Å.

![Figure 6](image.png)

**Figure 6.** Graphic representation of nedaplatin complexes which chosen nanostructure (CID_16156307) obtained during docking stage.
The high value of binding affinity is correlated with the appearance of additional cyclic systems and with the quantity of hydrogen bond donors. The high value of binding affinity and equilibrium constant K is correlated with creation of strong and medium hydrogen bonds or is correlated with forming hydrogen bond network. The conducted research allowed finding the most important. The binding capabilities of considered platinum complexes are strictly correlated with their chemical structure. The observed increase of this property, starting from nedaplatin through oxaliplatin to lobaplatin and heptaplatin, correlates with expansion of their chemical structure which is in turn related to the appearance of additional cyclic systems and with the quantity of hydrogen bond donors.

Many interesting features were demonstrated after a detailed analysis of structural properties. In all described cases, binding affinities of platinum compounds with functionalized fullerene C60 complexes are higher compared with affinities of platinum compounds with rhombellane structure complexes. The binding affinities of oxaliplatin and nedaplatin molecules relative to spherical nanosystems are much smaller compared to lobaplatin and heptaplatin. The two former ones easily form complexes with studied nanostructures. Additionally, all platinum compounds readily create complexes with functionalized fullerene C60 CID_16156307 and at the same time show the highest binding affinity. Behavior of lobaplatin is the same as heptaplatin; while oxaliplatin behavior is similar to nedaplatin. Among all considered complexes, the highest binding affinity is observed for systems created by functionalized fullerenes which contain hydrogen bond donors localized near fullerene surface in the structure of their active group. Such chemical structure ensures the possibility of the appearance of additional hydrophobic contributions stabilizing the structure of created complexes. Such phenomenon is pronouncedly observed in the case of platinum complexes with more complex chemical structure. Among all functionalized fullerenes C60, three of them have the best binding affinity and equilibrium constant K towards lobaplatin and heptaplatin, namely CID_16156307, CID_11468612 and CID_101218236 with affinity values from −5.85 to −4.47 kcal/mol. For oxaliplatin and nedaplatin, the best binding affinity values with CID_16156307 are −4.61 kcal/mol and −4.14 kcal/mol, respectively. Among rhombellane structures, 308a4 creates complexes with lobaplatin, heptaplatin and oxaliplatin with the highest values of binding affinity (−4.6 kcal/mol, −4.76 kcal/mol, −4.0 kcal/mol) and equilibrium constant K. However, 308b4, 360a, 396 and 420 nanostructures also seem to be very important. The binding capabilities of considered platinum complexes are strictly correlated with their chemical structure. The observed increase of this property, starting from nedaplatin through oxaliplatin to lobaplatin and heptaplatin, correlates with expansion of their chemical structure which is in turn related to the appearance of additional cyclic systems and with the quantity of hydrogen bond donors. The high value of binding affinity and equilibrium constant K is correlated with creation of strong and medium hydrogen bonds or is correlated with forming hydrogen bond network. The conducted

3. Conclusions

Behavior of four platinum compounds: lobaplatin, heptaplatin, oxaliplatin and nedaplatin with respect to functionalized fullerenes C60 and rhombellane homeomorphs, was studied in terms of their (interacting) geometry, energy and topology. AutoDock 4.2 was used to realize the study. Many interesting features were demonstrated after a detailed analysis of structural properties. During docking stage. Figure 7. Graphic representation of nedaplatin complexes which chosen nanostructure (360a) obtained during docking stage.
research allowed finding the most promising nanocarriers, such as functionalized C60 fullerenes and rhombellane structures for lobaplatin, heptaplatin, oxaliplatin and nedaplatin molecules.

**Author Contributions:** conceptualization, B.S. and P.C.; methodology, B.S. and P.C.; validation B.S. and P.C.; formal analysis, B.S.; investigation, B.S.; resources, B.S.; data curation, B.S.; writing—original draft preparation, B.S.; writing—review and editing, B.S.; visualization, B.S.; supervision, B.S.; project administration, B.S.; funding acquisition, B.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

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