Molecular Docking Study on the Interaction of Rhodopsin-like Receptors with Tetracoordinated Gold(III) Complexes[†]

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Abstract: The pharmacologic properties of gold compounds have been known since the end of the 19th century. In the last decade gold complexes have received increased attention due to the variety of their applications. Rhodopsin-like receptors are a family of proteins that belong to the largest group of G-protein-coupled receptors (GPCRs). In this paper the molecular interactions between the active binding sites of rhodopsin-like receptors (RLRs) and synthesized gold(III) complexes ($[\text{Au}(\text{DPP})\text{Cl}_2]^+$, where DPP = 4,7-diphenyl-1,10-phenanthroline) were investigated through molecular docking simulations. The crystal structure of investigated RLRs (PDB ID: 4A4M) was extracted from the RCSB Protein Data Bank in a PDB format. The native bound ligand (11-*cis*-retinal) was extracted from receptors and a binding pocket analysis was performed. Redocking was performed with gold(III) complexes to generate the same docking pose as found in the cocrystallized form of receptors. The binding energy of gold(III) complexes to RLRs was found to be -35.35 kJ/mol, as opposed to 11-*cis*-retinal, where it was about -40.5 kJ/mol. The obtained results revealed that gold(III) complexes bind at the same binding pockets to RLRs, as well as native bound ligands, via weak noncovalent interactions. The most prominent interactions are hydrogen bonds, alkyl- π and π - π interactions. The preliminary results suggest that gold(III) complexes showed good binding affinity against RLRs as well as the native bound ligand 11-*cis*-retinal, as evident from the free binding energy (ΔG_{bind} in kJ/mol).

Keywords: rhodopsin-like receptor; gold(III) complex; molecular

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1. Introduction

Gold compounds have been used for different studies, even though they are usually used for the treatment of arthritis. In the last decade gold complexes have received increased attention due to the variety of their applications [1,2]. Primary, they have been investigated as potential anticancer and chemotherapeutic agents. It is well-known that gold(III) complexes are very similar to platinum(II) compounds, so they could exhibit prospective anticancer, cytotoxic and antitumor properties [3]. Indeed, encouraging results for in vivo and in vitro investigations were obtained after the utilization of gold(III) complexes [4]. The main problem of the biological development and usage of these compounds is their poor stability in aqueous solutions. Additionally, gold(III) complexes are unstable under physiological conditions due to intracellular redox reactions with biologically relevant reducing agents [5–8]. This kind of reduction involves a change in Au(III) to Au(I) species, responsible for further interaction with different biomolecules, DNA/BSA, proteins and enzymes. Additionally, both Au(III) and Au(I) compounds can undergo ligand exchange reactions in the presence of thiol-containing enzymes, including thioredoxin reductase. Furthermore, the change in the geometry of complexes during the reduction, from

square planar to linear, is accompanied by the release of free ligands from the coordination sphere of the starting Au(III) complex, which can also be biologically active [9]. However, the stability of gold(III) complexes can be improved with the appropriate choice of inert ligands [10]. Gold(III) ions generally prefer binding to nitrogen or oxygen, because of “hard-soft” Lewis theory [11]. The high physiological stability of some mononuclear and dinuclear gold(III) complexes was reached using nitrogen-donor ligands, such as pyridine, bipyridine, terpyridine, phenanthroline, macrocyclic ligands and porphyrins [10,12]. The G-protein-coupled receptors (GPCRs) belong to seven transmembrane helix proteins. They have a role in the coupled binding of extracellular ligands to conformational changes as well as the activation of intracellular G proteins and GPCR kinases. Rhodopsin is activated by light-induced isomerization in the native membranes due to the covalently binding inverse agonist 11-*cis* retinal to the all-*trans*-retinal within a very tight binding pocket [13–15].

In this paper the binding affinities of the previously synthesized and investigated gold(III) complex (C1) [16] (Figure 1) and 11-*cis*-retinal to rhodopsin-like receptors (RLRs) were investigated through molecular docking simulations.

Figure 1. Optimized structures of gold(III) complexes ($[\text{Au}(\text{DPP})\text{Cl}_2]^+$, where DPP = 4,7-diphenyl-1,10-phenanthroline, C1).

2. Materials and Methods

The binding affinity of the title compound (C1), as well as 11-*cis*-retinal, was estimated using molecular docking. For this purpose, AutoDock 4.0 software was used [17]. The X-ray structure of human RLRs was extracted from the RCSB Protein Data Bank (PDB ID: 4A4M) [18]. The native bound ligand (11-*cis*-retinal) was extracted from receptors, and a binding pocket analysis was performed. Redocking was performed with the gold(III) complex and 11-*cis*-retinal to generate the same docking poses found in the cocrystallized form of receptors. The pockets and binding sites of RLRs were determined by the Auto-GridFR (AGFR) program. Discovery Studio 4.0 [19] was used for the preparation of protein for docking by removing the cocrystallized ligand, water molecules and cofactors. The AutoDockTools (ADT) graphical user interface was used to calculate Kollman charges and add polar hydrogen. Title molecule C1 (Figure 1) was prepared for docking by minimizing its energy using B3LYP-D3 in combination with the 6-311G(d,p) basis set for C, N, S, Cl and H, in addition to the LAN2DZ basis set for Au. The protein–ligand flexible docking was conducted using the Lamarckian genetic algorithm (LGA) method [20]. The grid center with dimensions of $10.988 \times 45.838 \times 35.362 \text{ \AA}^3$ in the -x, -y and -z directions of human RLRs was used in order to cover the protein binding sites and accommodate ligands to move freely. The binding affinity of title molecules was investigated and discussed. The AutoDock program calculated the free energy of the binding values according to the following equation, Equation (1):

$$\Delta G_{\text{bind}} = \Delta G_{\text{vdw+hbond+desolv}} + \Delta G_{\text{elec}} + \Delta G_{\text{total}} + \Delta G_{\text{tor}} - \Delta G_{\text{unb}} \quad (1)$$

where ΔG_{bind} is the estimated free energy of binding and $\Delta G_{\text{vdw+hbond+desolv}}$ denotes the sum of the energies of dispersion and repulsion (ΔG_{vdw}), hydrogen bonds (ΔG_{hbond}) and desolvation (ΔG_{desolv}). ΔG_{total} represents the final total internal energy, ΔG_{tor} is the torsional free energy, ΔG_{unb} is the unbound system's energy and ΔG_{elec} is the electrostatic energy.

3. Results and Discussion

In this study the molecular interactions between the active binding sites of RLRs and analyzed compounds were investigated through molecular docking simulations. Before molecular docking the pockets and binding sites of the targeted receptor were determined. For this purpose the AGFR software was applied to configure and compute affinity maps for a receptor molecule to be used for AutoDock4. The native bound ligand (11-*cis*-retinal) was extracted from RLRs, and a binding pocket analysis was performed. After that, redocking was performed with C1 to generate the same docking pose as found in its cocrystallized form. The same protocol was utilized for the cocrystallized form of RLRs, where the 11-*cis*-retinal ligand was used. This step was performed to compare the theoretical binding affinity of C1 with 11-*cis*-retinal [20]. The position and orientation of ligands inside the protein receptors and the interactions with amino acids bound to the ligand were analyzed and visualized with Discovery Studio 4.0 and AutoDockTools.

In Tables 1 and 2 the values of the estimated free energy of binding in addition to the inhibition constant (K_i) for the investigated ligands in three different conformations are given. Lower values of K_i and more negative values of ΔG_{bind} indicate the better binding of ligands to receptors.

Table 1. Estimated free energy of binding (ΔG_{bind}) in kJ/mol, estimated inhibition constant (K_i) (μM) of different poses of C1 against RLR proteins.

Conformations of Ligand	ΔG_{bind} (kJ/mol)	K_i (nM)	Hydrogen Bond	Hydrophobic Contact
1	−35.44	6.2×10^2	A:ILE189:HN	A:MET207 A:TRP265 A:TYR268 A:TYR191 A:ALA272 A:TYR191 A:PHE208 A:ILE189 A:LEU125
2	−35.44	6.2×10^2	A:ILE189:HN	A:MET207 A:HIS211 A:TRP265 A:TYR268 A:TYR191 A:ALA272 A:TYR191 A:PHE208 A:ILE189 A:LEU125
3	−35.35	6.4×10^2	A:ILE189:HN	A:MET207 A:HIS211 A:TRP265 A:TYR268 A:TYR191 A:ALA272 A:TYR191 A:PHE208 A:ILE189 A:LEU125

Table 2. Estimated free energy of binding (ΔG_{bind}) in kcal/mol, estimated inhibition constant (K_i) (μM) of different poses of 11-*cis*-retinal against RLR proteins.

Conformations of Ligand	ΔG_{bind} (kJ/mol)	K_i (μM)	Hydrogen Bond	Hydrophobic Contact
1	−40.50	8.1×10	/	A:MET207 A:ALA269 A:ALA272 A:ILE189 A:VAL204 A:TYR191 A:TRP265 A:TYR268
2	−40.46	8.1×10	/	A:MET207 A:ALA269 A:ALA272 A:ILE189 A:VAL204 A:TYR191 A:TRP265 A:TYR268
3	−40.38	8.4×10	/	A:MET207 A:ALA269 A:ALA272 A:ILE189 A:VAL204 A:TYR191 A:TRP265 A:TYR268

The lowest values of ΔG_{bind} and K_i are found for conformation 1 (Tables 1 and 2). As can be seen, when analyzing the position of active amino acids C1 binds at the same active site of RLR proteins as its native ligand, 11-*cis*-retinal, through weak noncovalent interactions (Tables 1 and 2, in addition to Figure 2). The binding energies of gold(III) complexes and 11-*cis*-retinal to RLRs were found to be −35.4 and −40.5 kJ/mol, respectively. The obtained results indicate that the ligands strongly bind to RLRs. The docking analyses of the investigated molecules revealed that several noncovalent interactions existed between the investigated molecules and target receptors. The most prominent interactions are π -donor H-bonds, alkyl- π , π -lone pair and π - π interactions (Figures 2 and 3). The most stable docking conformations of the investigated compound are presented in Figure 3. HIS, MET, ALA, ILE, TYR, TRP and TYR in positions 211, 207, 272, 189, 191, 265 and 268, respectively, in the primary structure of RLRs have a predominant role as the active site of this receptor regarding ligands, gold(III) complexes and 11-*cis*-retinal. The preliminary results suggest that gold(III) complexes showed a good binding affinity against RLRs as well as the native bound ligand, 11-*cis*-retinal, as evident from the free binding energy (ΔG_{bind} in kJ/mol).

Figure 2. Picture showing interaction between C1 and 11-*cis*-retinal (conformations 1, the lowest K_1) and amino acids in RLR (left) and (right).

Figure 3. The docking interactions of the most stable conformation of ligand (Au(III) complex) with RLRs.

4. Conclusions

To evaluate the binding affinity of the investigated gold(III) complexes to rhodopsin-like receptors (RLRs), a molecular docking study was performed. According to the results of the molecular docking study, the investigated ligand forms stable complexes with RLRs, as evident from the free binding energy (ΔG_{bind} is -40.5 kJ/mol for C1), as well as achieves a more effective interaction with the target receptor. The most important interactions are π -donor H-bonds, alkyl- π , π -lone pair and π - π interactions. The obtained preliminary results suggest that the gold(III) complex might exhibit strong binding activity to RLRs.

Supplementary Materials: The supplementary are available online at <https://www.mdpi.com/article/10.3390/ECB2021-10264/s1>.

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