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Molecular Docking Study on the Interaction of Rhodopsin-like Receptor with tetra-coordinated gold(III) Complex †

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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 active binding sites of the Rhodopsin-like receptor (RLR) and synthesized gold(III) complex ($[Au(DPP)Cl_2]^+$ where DPP=4,7-diphenyl-1,10-phenanthroline) were investigated by molecular docking simulations. The crystal structure of investigated receptor RLR (PDB ID: 4A4M) was extracted from RCSB Protein Data Bank in PDB format. The native bound ligand (11-*cis*-retinal) was extracted from receptor and binding pocket analysis was performed. Re-docking was performed with the gold(III) complex to generate the same docking pose as found in co-crystallized form of receptor. The binding energy of gold(III) complex to RLR was found to be -35.35 kJ/mol, as opposed to 11-*cis*-retinal which of about -40.5 kJ/mol. The obtained results of revealed that gold(III) complex binds at the same binding pockets to RLR, as well as native bound ligand, by weak non-covalent interactions. The most prominent interactions are hydrogen bonds, alkyl-π, and π-π interactions. The preliminary results suggest that gold(III) complex showed good binding affinity against RLR, as well as 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

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 utilization of gold(III) complexes [4]. The main problem of the biological development and usage of these compounds is poor stability in aqueous solutions. Also, gold(III) complexes are unstable under physiological conditions due to the intracellular redox reactions with biologically relevant reducing agents [5–8]. This kind of reduction involves a change of 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 of 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 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) ion generally prefer binding to the nitrogen or oxygen, because of "hard-soft" Lewis theory [11]. The high physiological stability of some mononuclear and dinuclear gold(III) complexes were reached using the nitrogen-donor ligands, such as pyridine, bipyridine, terpyridine, phenanthroline, macrocyclic ligands and porphyrins [12,13]. The G protein-coupled receptors (GPCR) belong to seven-transmembrane helix proteins. They have a role in the coupled binding of extracellular ligands to conformational changes and 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 [14–16].

In this paper, the binding affinities previously synthesized and investigated gold(III) complex (**C1)** [17] (Figure 1) and 11-*cis*-retinal to the Rhodopsin-like receptor (RLR) were investigated by the Molecular Docking simulations.

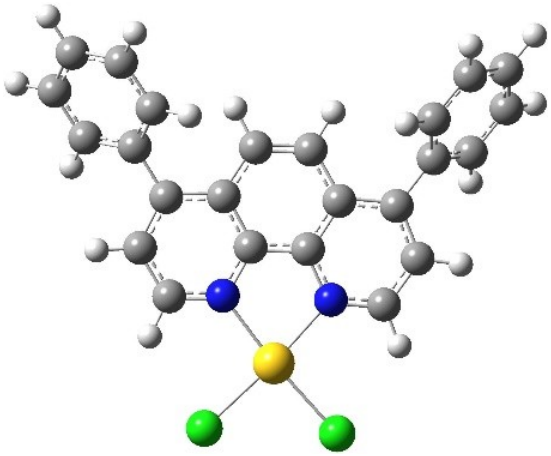

Figure 1. Optimized structures of gold(III) complex ($[Au(DPP)Cl_2]^+$ where DPP=4,7-diphenyl-1,10-phenanthroline, **C1**).

2. Materials and Methods

The binding affinity of the title compound (**C1**), as well as 11-*cis*-retinal, was estimated using the molecular docking. For this purpose, the AutoDock 4.0 software was used [18]. The X-Ray structure of human RLR was extracted from RCSB Protein Data Bank (PDB ID: 4A4M, [19]. The native bound ligand (11-*cis*-retinal) was extracted from receptor and binding pocket analysis was performed. Re-docking was performed with the gold(III) complex and 11-*cis*-retinal to generate the same docking poses as found in co-crystallized form of receptor. The pockets and binding sites of RLR were determined by the AutoGridFR (AGFR) program. The Discovery Studio 4.0 [20] was used for the preparation of protein for docking by removing the co-crystallized ligand, water molecules and co-factors. The AutoDockTools (ADT) graphical user interface was used to calculate Kollman charges and to add polar hydrogen. Title molecule **C1** (Figure 1) were prepared for docking by minimizing their energy using B3LYP-D3 in combination with the 6-311G(d,p) basis set for C, N, S, Cl, and H, and LAN2DZ basis set for Au. The protein - ligand flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method[21]. The grid center with dimensions 10.988 × 45.838 × 35.362 $Å^3$ in *-x*, *-y*, and *-z* directions of human RLR was used in order to cover the protein binding sites and accommodate ligands to move freely. The biding affinity of title molecules were investigated and discussed. The AutoDock program calculate the free energy of binding values according to the following equation, Eqn 1:

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

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

3. Results and discussion

In this study, the molecular interactions between active binding sites of RLR receptors and analyzed compounds were investigated by molecular docking simulations. Before molecular docking, the pockets and binding sites of targeted receptor were determined. For this purpose, the AGFR software was applied to configure and computing affinity maps for a receptor molecule to be used for AutoDock4. The native bound ligand (11-*cis*-retinal) was extracted from RLR, and binding pocket analysis was performed. After that, re-docking was performed with the **C1** to generate the same docking pose as found in its co-crystallized form. The same protocol was done for the co-crystallized form of RLR where the 11-*cis*-retinal ligand was used. This step was performed to compare the theoretical binding affinity of **C1** with 11-*cis*-retinal [22]. The position and orientation of ligand inside protein receptor and the interactions with amino acids bound to the ligand were analyzed and visualized with Discovery Studio 4.0 and AutoDockTools.

In the Tables 1 and 2, the values of the estimated free energy of binding and the inhibition constant (*K*i) for the investigated ligands in three different conformations are given. The lower value of *Ki* and the more negative value of ΔG_{bind} indicate better binding ligand to receptor.

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 protein.

Conformations of Ligand	ΔG_{bind} (kJ/mol)	K_i (nM)	Hydrogen Bond	Hydrophobic Contact
1	-35.44	$6.2x10^2$	A:ILE189:HN	A:MET207 A:TRP265 A:TYR268 A:TYR191 A:ALA272 A:TYR191 A:PHE208 A:ILE189 A:LEU125
2	-35.44	$6.2x10^2$	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	$6.4x10^2$	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 protein.

Conformations of Ligand	ΔG_{bind} (kJ/mol)	K_i (μM)	Hydrogen Bond	Hydrophobic Contact
1	-40.50	$8.1x10^1$	/	A:MET207 A:ALA269 A:ALA272 A:ILE189 A:VAL204 A:TYR191 A:TRP265 A:TYR268
2	-40.46	$8.1x10^1$	/	A:MET207 A:ALA269 A:ALA272 A:ILE189 A:VAL204 A:TYR191 A:TRP265

				A:TYR268
3	-40.38	8.4x10[1]	/	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, the **C1** binds at the same active site of RLR protein as its native ligand, 11-*cis*-retinal, by weak non-covalent interactions (Tables 1, 2 and Figure 2). The binding energies of gold(III) complex and 11-*cis*-retinal to RLR were found to be -35.4 and -40.5 kJ/mol. The obtained results indicate that the ligands strongly bind to RLR receptor. The docking analyses of investigated molecules revealed that several non-covalent interactions existed between investigated molecules and target receptor. The most prominent interactions are π-donor H-bonds, alkyl-π, π-lone pair and π-π interactions (Figure 2). HIS, MET, ALA, ILE, TYR, TRP and TYR in positions 211, 207, 272, 189, 191, 265, 268 in the primary structure of RLR have a predominant role as the active site of this receptor regarding ligands, gold(III) complex and 11-*cis*-retinal. The preliminary results suggest that gold(III) complex showed good binding affinity against RLR, as well as native bound ligand, 11-*cis*-retinal, as evident from the free binding energy (ΔG_{bind} in kJ/mol).

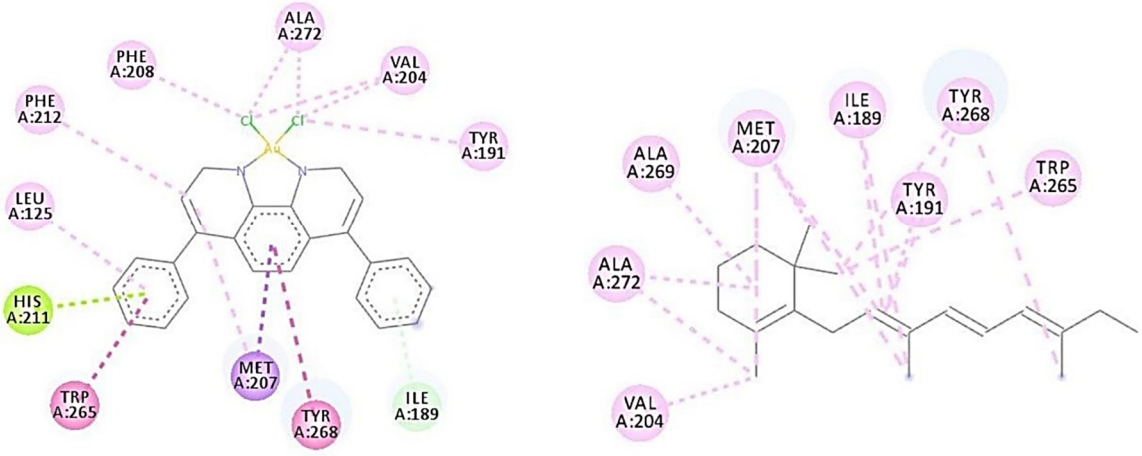

Figure 2. Picture showing interaction between **C1** and 11-*cis*-retinal (conformations **1**, the lowest *K*i) and amino acids in RLR (left) and (right).

4. Conclusions

To evaluate the binding affinity of investigated gold (III) complex to Rhodopsin-like receptor (RLR), the molecular docking study was performed. According to the results of the molecular docking study, the investigated ligand form stable complexes with RLR as evident from the free binding energy (ΔG_{bind} is -40.5 kJ/mol for C1), as well as achieve 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 the RLR receptor.

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