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Molecular docking study on the interaction of Rhodopsin-like receptor with tetra-coordinated gold(III) complex

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ИНСТИТУТ ЗА ИНФОРМАЦИОНЕ ТЕХНОЛОГИЈЕ КРАГУЈЕВАЦ
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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 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 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 (ΔGbind in kJ/mol).

Keywords:

Rhodopsin-like receptor; gold(III) complex; molecular

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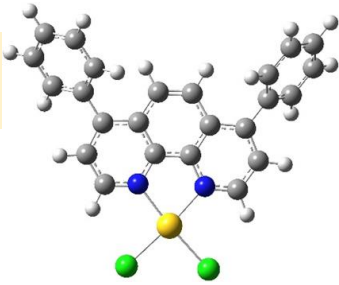
Introduction:



- ✓ In the last decade, gold complexes have received increased attention due to the variety of their applications
- ✓ Encouraging results for *in vivo* and *in vitro* investigations were obtained after the utilization of gold(III) complexes.
- ✓ Change of Au(III) to Au(I) species, responsible for further interaction with different biomolecules, DNA/BSA, proteins, and enzymes.
- ✓ Au(III) and Au(I) compounds can undergo ligand exchange reactions in the presence of thiol-containing enzymes, including thioredoxin reductase.
- ✓ However, the stability of gold(III) complexes can be improved with the appropriate choice of inert ligands
- ✓ Stability of Gold(III) complexes were reached using the nitrogen-donor ligands, such as pyridine, bipyridine, terpyridine, phenanthroline, macrocyclic ligands, and porphyrins

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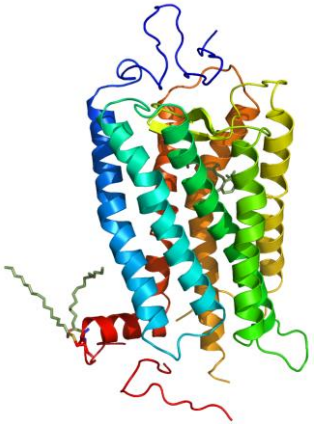
Introduction:



- ✓ 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
- ✓ 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

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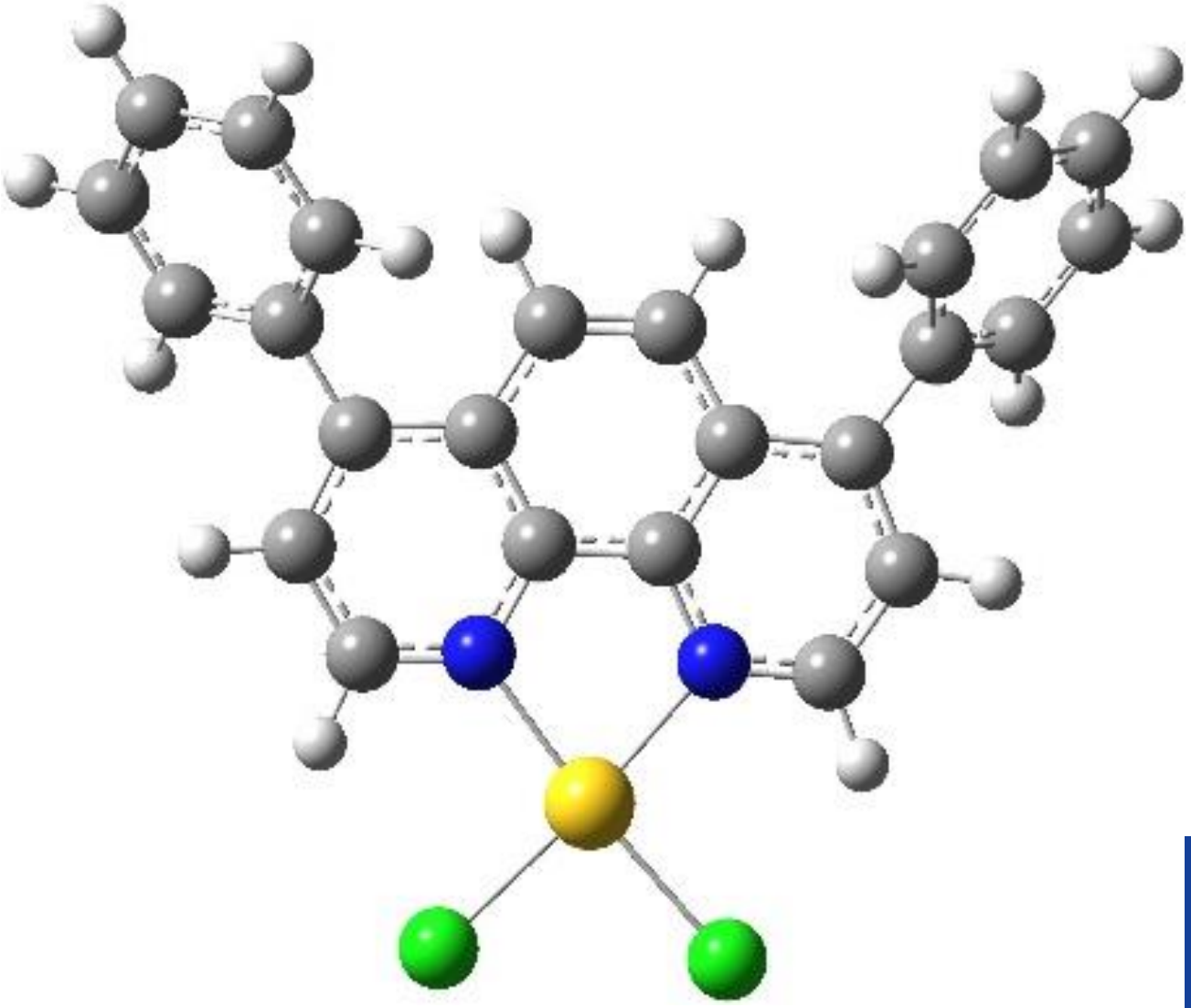
Optimized structures of gold(III) complex ($[Au(DPP)Cl_2]_+$



- ✓ DPP=4,7-diphenyl-1,10-phenanthroline, C1

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Material and Metods

- ✓ The pockets and binding sites of RLR were determined by the AutoGridFR (AGFR) program
- ✓ The Discovery Studio 4.0 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
- ✓ The protein - ligand flexible docking were done using the Lamarckian Genetic Algorithm (LGA) method
- ✓ The grid center with dimensions 10.988 × 45.838 × 35.362 Å3 in -x, -y, and -z directions of human RLR was used
- ✓ The AutoDock program calculate the free energy of binding values according to the following equation, Eqn 1:

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

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Results and Discussion

- ✓ 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.

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

Estimated free energy of binding (ΔG_{bind}) in kcal/mol, estimated inhibition constant (*Ki*) (μM) of best position of C1 against RLR protein

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Results and Discussion

- ✓ The pockets and binding sites of RLR were determined by the AutoGridFR (AGFR) program
- ✓ The binding energies of gold(III) complex and 11-*cis*-retinal to RLR were found to be -35.4 and -40.5 kJ/mol

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**

Estimated free energy of binding (ΔG_{bind}) in kcal/mol, estimated inhibition constant (*Ki*) (μM) of best position of 11-*cis*-retinal against RLR protein.

- ✓ 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

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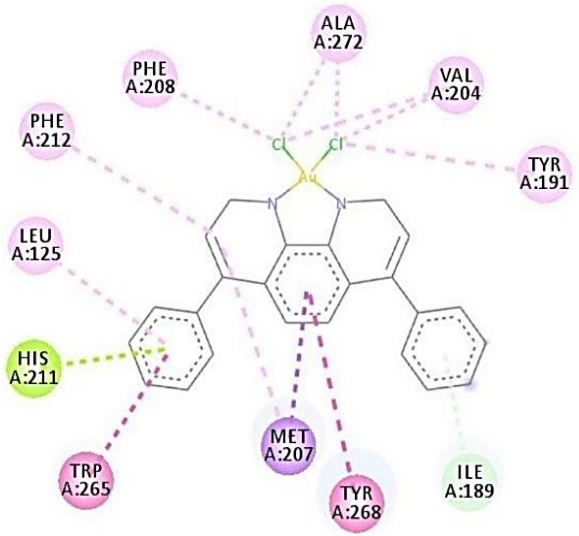
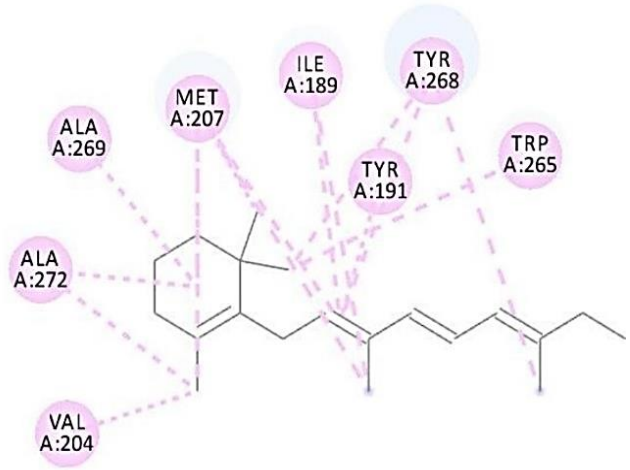
Results and Discussion

- ✓ The position The most prominent interactions are π-donor H-bonds, alkyl-π, π-lone pair and π-π interactions
- ✓ HIS, MET, ALA, ILE, TYR, TRP and TYR in the primary structure of RLR have a predominant role as the active site of this receptor regarding ligands





- ✓ 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 .

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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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