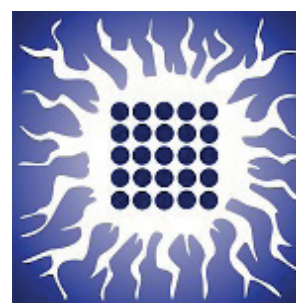


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Inhibitor potential of some Au(III) complexes against SARS-CoV-2 Spike Glycoprotein: A Molecular Docking Study

Žiko Milanović^{1*}, Ana Kesić¹, Dejan Milenković¹, Edina Avdović¹ and Zoran Marković¹

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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. Square planar Au(III) complexes are suitable candidates for biological investigation because of useful substances with a good stability profile. Some Au(III) complex could be significantly stabilized, even at neutral pH, with the appropriate choice of the inert ligands, preserving its peculiar biological properties. In this paper, the molecular interactions between active binding sites of SARS-CoV-2 Spike Glycoprotein and analyzed compounds, Au(III) complexes ([Au(terpy)Cl]₂⁺ (C1) and [Au(bipy)Cl]₂⁺ (C2)), hydroxychloroquine and chloroquine, were investigated by molecular docking simulations. The crystal structure of investigated receptor (PDB ID: 6VSB) was extracted from RCSB Protein Data Bank in PDB format. The binding affinity of investigated compounds was examined by the AutoDock 4.2 software. AutoDockTools was used to calculate the Kollman partial charges and addition polar hydrogens. The flexibility of the ligands was considered, while the protein kept on as the rigid structure in the ADT. The Lamarckian Genetic Algorithm (LGA) method was used for protein-ligand flexible docking. The parameters for the LGA method were determined as follows: a maximum number of energy evaluations is 250,000, a maximum number of generations is 27,000, and mutation and crossover rates are 0.02 and 0.8, respectively. The pockets and binding sites of the target receptor were determined by the AutoGridFR program. The binding energies of the docked compounds of C1 and C2 against SARS-CoV-2 Spike Glycoprotein were found to be in the range between -28.5 and -23.5 kJ/mol, as opposed to hydroxychloroquine and chloroquine which are -34.5 and -35.8 kJ/mol, respectively. The obtained results revealed that C1 and C2 bind at the same binding pockets to SARS-CoV-2 Spike Glycoprotein, as well as hydroxychloroquine and chloroquine, by weak non-covalent interactions. The most prominent interactions are hydrogen bonds, alkyl- π , and π - π interactions. The preliminary results suggest that Au(III) complexes showed good binding affinity against SARS-CoV-2 Spike Glycoprotein, as evident from the free binding energy (ΔG_{bind} in kJ/mol) and that might exhibit inhibitory activity against SARS-CoV-2 Spike Glycoprotein.

Keywords:

Au(III) complex, terpyridine, bipyridine, molecular docking, SARS-CoV-2 Spike Glycoprotein

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INTRODUCTION

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. Square planar Au(III) complexes are suitable candidates for biological investigation because of useful substances with a good stability profile. Some Au(III) complex could be significantly stabilized, even at neutral pH, with the appropriate choice of the inert ligands, preserving its peculiar biological properties.

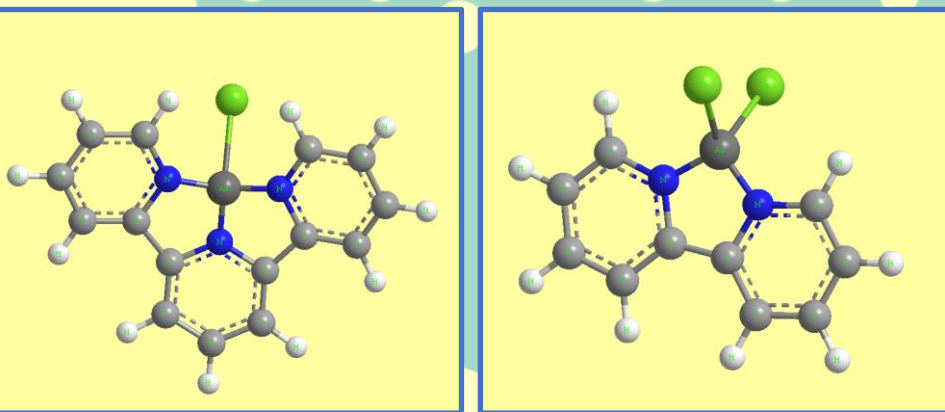


Figure 1. The structure of studied gold(III) complexes ([Au(terpy)Cl]²⁺, **C1** (left) and [Au(bipy)Cl₂]⁺, **C2** (right)

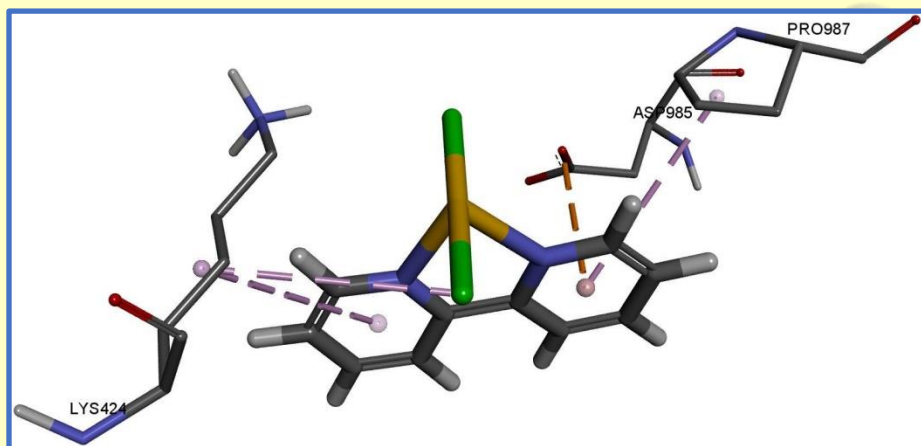
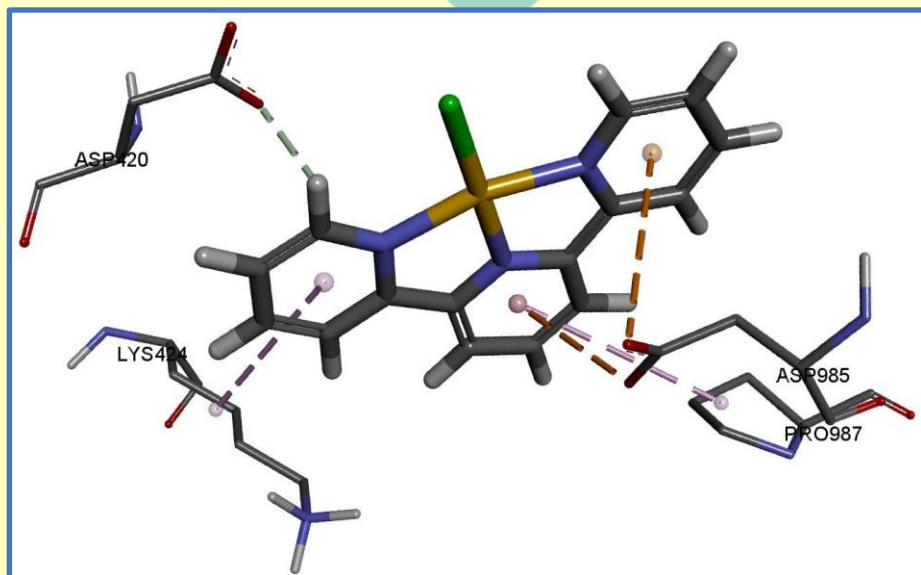


Figure 2. 3D representation of noncovalent interactions between protein and transition metal complexes

METHODOLOGY

In this paper, the molecular interactions between active binding sites of SARS-CoV-2 Spike Glycoprotein and analyzed compounds, Au(III) complexes ([Au(terpy)Cl]²⁺ (**C1**) and [Au(bipy)Cl₂]⁺ (**C2**)), hydroxychloroquine and chloroquine, were investigated by molecular docking simulations. The crystal structure of investigated receptor (PDB ID: 6VSB) was extracted from RCSB Protein Data Bank in PDB format. The binding affinity of investigated compounds was examined by the AutoDock 4.2 software. AutoDockTools was used to calculate the Kollman partial charges and addition polar hydrogens. The flexibility of the ligands was considered, while the protein kept on as the rigid structure in the ADT. The Lamarckian Genetic Algorithm (LGA) method was used for protein-ligand flexible docking. The parameters for the LGA method were determined as follows: a maximum number of energy evaluations is 250,000, a maximum number of generations is 27,000, and mutation and crossover rates are 0.02 and 0.8, respectively. The pockets and binding sites of the target receptor were determined by the AutoGridFR program.

Table 1. Thermodynamic data obtained by docking simulation of tested compounds with SARS-CoV-2 M^{pro}

Compounds:	ΔG_{bind} (kcal mol ⁻¹)	K _i (uM)
C1	-6.81	10.21
C2	-5.75	60.70
Hydroxychloroquine	-8.24	0.91
Chloroquine	-8.55	0.54

RESULTS

The binding energies of the docked compounds of **C1** and **C2** against SARS-CoV-2 Spike Glycoprotein were found to be in the range between -6.81 and -5.75 kcal mol⁻¹, as opposed to hydroxychloroquine and chloroquine which are -8.24 and -8.55 kcal mol⁻¹, respectively. The obtained results revealed that **C1** and **C2** bind at the same binding pockets to SARS-CoV-2 Spike Glycoprotein, as well as hydroxychloroquine and chloroquine, by weak non-covalent interactions. The most prominent interactions are hydrogen bonds, alkyl- π , and π - π interactions.

CONCLUSION

The preliminary results suggest that Au(III) complexes showed good binding affinity against SARS-CoV-2 Spike Glycoprotein.

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