The 9th International Electronic Conference on Medicinal Chemistry (ECMC 2023)
01–30 November 2023 | Online

Substituted bifunctional Au(III)-2.2'-bipyridine complexes as potential PARP inhibitors

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pharmaceuticals MDPI

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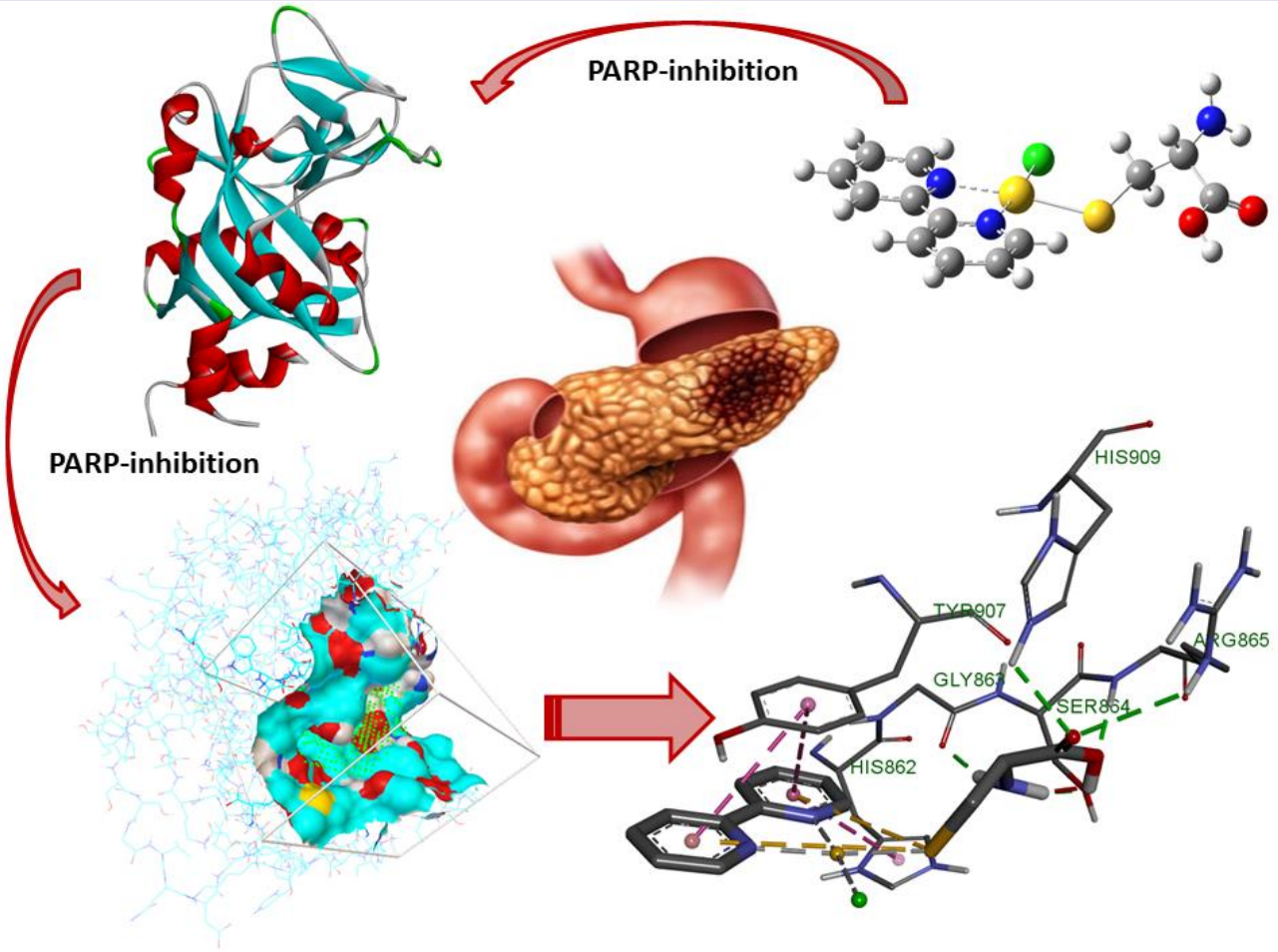

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ABSTRACT:

INTRODUCTION

Cancer represents one of the most serious diseases today, with a high mortality rate. Chemotherapy is a primary therapeutic method for the treatment of many cancers. In the middle of the last century, following the discovery that cis-diaminedichloroplatinum (II) (cisplatin) inhibited Escherichia coli (E .coli) cell division, platinum chemotherapeutics played a key role in the treatment of a wide range of malignancies. Although the use of these drugs in chemotherapy has shown success, it has been proven that platinum-based therapy shows many side effects, including severe neurotoxicity. Inhibition of poly(ADP-ribose) polymerase (PARP), a nuclear enzyme activated upon DNA damage, represents one of the basic approaches to cancer treatment by applying targeted therapy. Platinum complexes are also widely used for this purpose. Finding new, less toxic drugs based on metal complexes would make a significant contribution to the treatment of malignancies. In this sense, the potential of the bifunctional Au(III) complexes to inhibit PARP was examined.

METHODOLOGY

In this sense, the potential of the bifunctional Au(III) complexes to inhibit PARP was examined. For that purpose, [AuCl2(bipy)]$^{+}$ (bipy = 2.2'-bipyridine) complex, then complexes in which one and both Cl-atoms are substituted with L-cysteine are examined. The inhibitory activity of these gold complexes was compared with the inhibitory activity of cisplatin and oxyplatinum. Applied molecular docking analysis performed using.

RESULTS AND DISCUSSION

AutoDock 4.0 program indicated that the highest inhibition potency possess monosubstituted Au(III)(bipy) complex (ΔG_{bind}= -8.74 kcal/mol, K_i= 0.40 μM), while somewhat lower inhibition potency has disubstituted Au(III)(bipy) complex (ΔG_{bind}= -7.19 kcal/mol, K_i= 5.40 μM) and initial [$AuCl_2$(bipy)]$^{+}$ complex (ΔG_{bind}= -6.84 kcal/mol, K_i= 9.73 μM). The appropriate thermodynamical parameters that illustrates the inhibition potency of oxyplatinum are ΔG_{bind}= -7.12 kcal/mol, K_i= 6.01 μM, and of cisplatin those are ΔG_{bind}= -4.46 kcal/mol, K_i= 535.61 μM. This indicates that the investigated Au(III) complexes have the potential to be used for targeted therapy and that it would be important to investigate their biological activity *in vitro* and *in vivo* in detail.

KEYWORDS:

Molecular docking, inhibition potential, Au(III)-2.2'-bipyridine complexes, substituted complexes, oxyplatinum, cisplatin.

INTRODUCTION

- **Cancer** represents one of the most serious diseases today, with a high mortality rate. Chemotherapy is a primary therapeutic method for the treatment of many cancers.

- In the middle of the last century, following the discovery that cis-diaminedichloroplatinum (II) (**cisplatin**) inhibited Escherichia coli (*E .coli*) cell division, platinum chemotherapeutics played a key role in the a wide range of malignancies [1].

- Although the use of these drugs in chemotherapy has shown success, it has been proven that platinum-based therapy shows many side effects, including severe **neurotoxicity**.

- Inhibition of poly(ADP-ribose) polymerase (**PARP),** a nuclear enzyme activated upon DNA damage, represents one of the basic approaches to cancer treatment by applying targeted therapy. Platinum complexes are also widely used for this purpose.

- In recent years, a lot of research has been done on gold **complexes** as potential antitumor agents [2.3].

- In this sense, the potential of the **bifunctional Au(III) complexes** to inhibit PARP was examined.

1. C. Zhu, J. Raber, L. A. Eriksson (2005) *J. Phys. Chem B.* **109** (24) 11006.
2. G. Moreno-Alcántar, P. Picchetti, A. Casini (2023) *Angew. Chem. Int. Ed.* **62** (22) e202218000 .
3. S. Yue, M. Luo, H. Liu, S. Wei (2020) *Front. Chem.* **8,** 543.

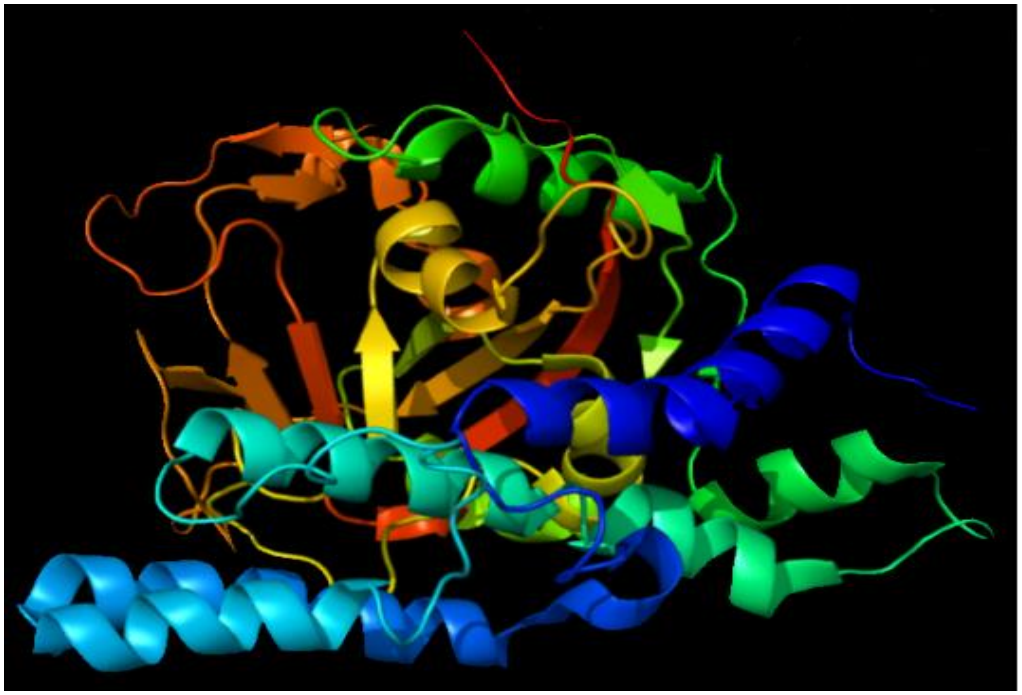


Figure 1. *poly(ADP-ribose) polymerase (PARP)*

- Inhibition of **poly(ADP-ribose) polymerase (PARP**), a nuclear enzyme activated upon DNA damage, represents one of the basic approaches to cancer treatment by applying targeted therapy [4,5].

4. A. Chen (2011) *Chin J. Cancer*. **30** (7) 463–471.
5. J. S. Brown, B. O'Carrigan, S. P. Jackson, T. A. Yap (2017) *Cancer Discov*. **7** (1), 20–37.

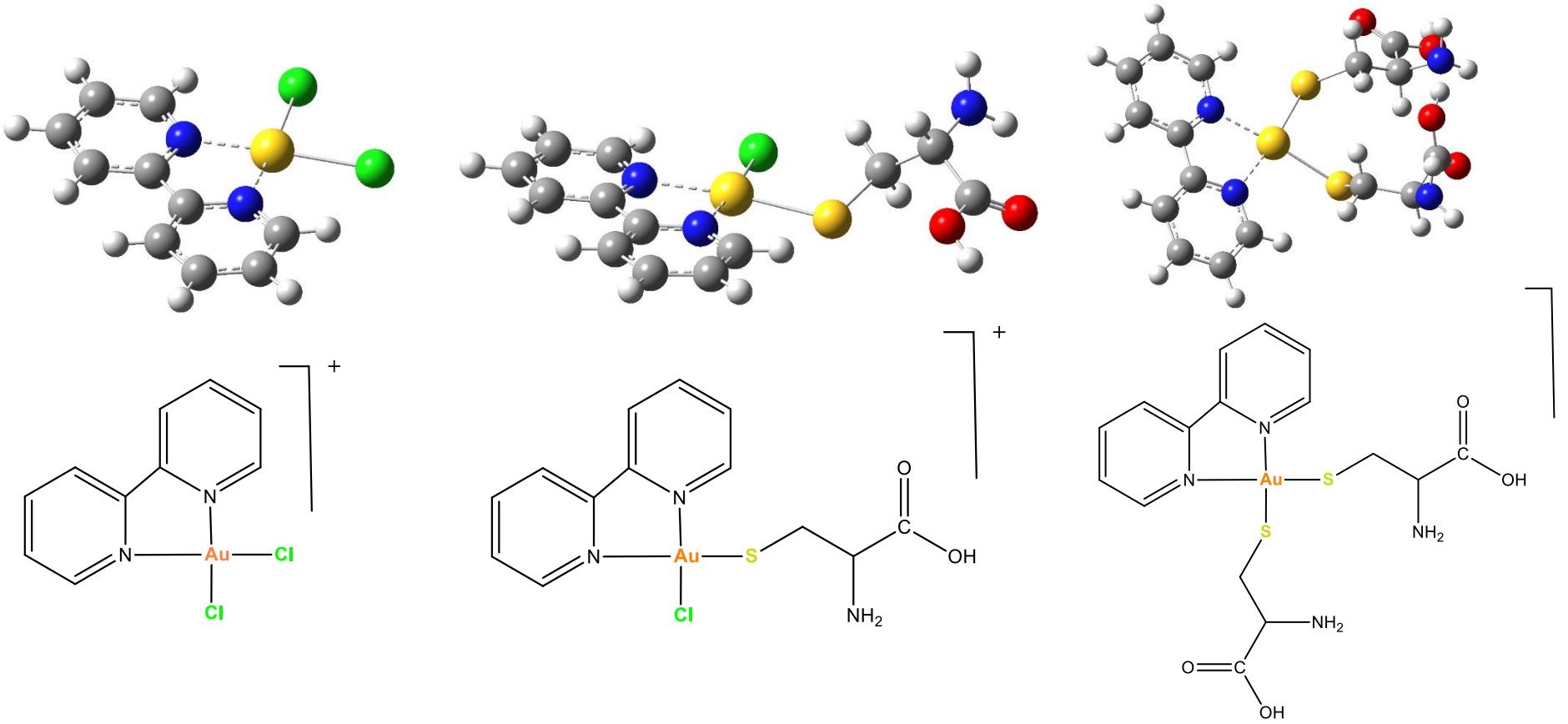
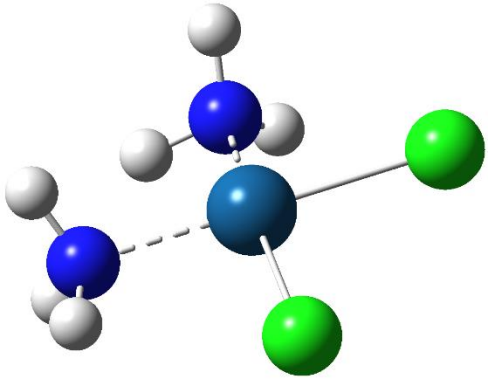
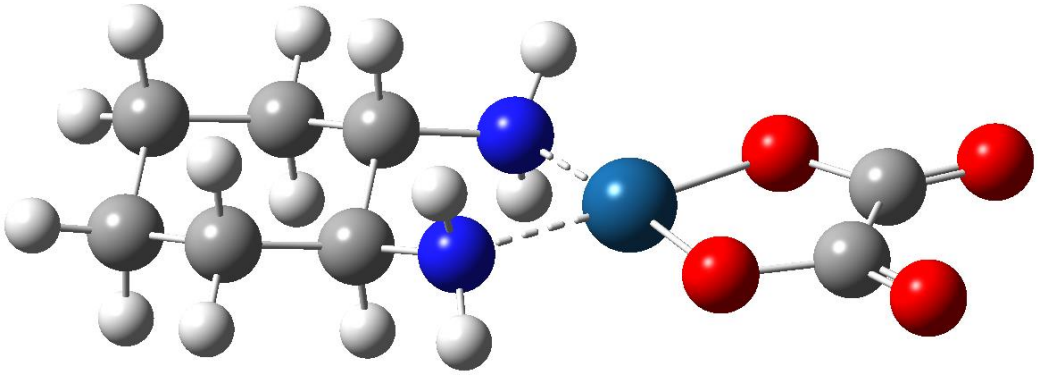
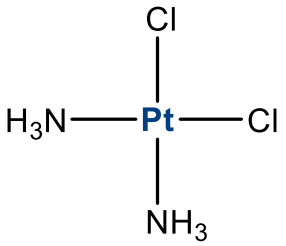
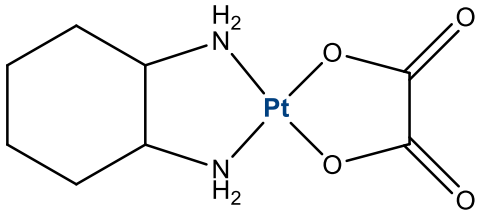


Figure 2. *Optimized 3D structures (up) and 2D structures (down) of the evaluated gold-based ligands*









cisplatin

oxyplatinum

Figure 3. *Optimized 3D structures (up) and 2D structures (down) of the evaluated platinum-based ligands*

METHODOLOGY

- **The DFT method M06-2X/6-311++G(d,p)** (Gaussian 09 program package) is used for the optimization of the ligand structures [6].
- **Protein Data Bank (PDB ID: 6NTU)** - three-dimensional (3D) crystal structure of human PARP-1 polymerase [7].
- **Discovery Studio Visualizer 4.0** - protein is released from the co-crystallized ligand, water molecules, and co-factors.[8].
- **AGFR (AutoGridFR) software** – establishing the affinity maps of the target protein [9].
- **AutoDock 4.0 software** – molecular docking simulations [10].
- **BIOVIA Discovery Studio** - analysis of molecular docking simulation results and visualizations of predicted protein-ligand interactions [7].

6. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, et al. (2010) Gaussian 09. Revision C.01, Gaussian Inc, Wallingford.
7. L. Zandarashvili, M.F. Langelier, U.K. Velagapudi, M.A. Hancock, J.D. Steffen, et al. (2020) *Science* **368** (6486) 46.
8. D. S. Biovia (2017) Discovery studio modeling environment.
9. Y. Zhang, S. Forli, A. Omelchenko, M. F. Sanner (2019*) J. Comput. Chem.* **40** (32) 2882–2886.
10. G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, et al. (2011) *J. Comput. Chem.* **30** (2009) 2785-2791.

RESULTS AND DISCUSSIONS

Table 1. *Thermodynamic parameters corresponding to the most stable conformation of the protein-ligand complex obtained by docking analysis. The inhibition constant values (K_i) are presented in micromolars (μM), while all energy values are presented in kcal/mol (ΔG_{bind} - free energy of binding; ΔG_{inter}- final intermolecular energy; $\Delta G_{vdw+hbond+desolv}$- sum of energy of dispersion and repulsion, hydrogen-bond energy, and desolvation energy; ΔG_{tor}- torsional free energy).*

PARP-ligand complex	ΔG_{bind}	K_i	ΔG_{inter}	$\Delta G_{vdw+hbond+desolv}$	ΔG_{tor}
PARP-$[AuCl_2(bipy)]^+$	-6.84	9.73	-6.84	-6.80	0.00
PARP-$[AuCl(bipy)(Cys)]^+$	-8.74	0.40	-10.53	-9.63	1.79
PARP-$[Au(bipy)(Cys)_2]^+$	-7.19	5.40	-10.77	-9.86	3.58
PARP-cisplatin	-4.46	535.61	-5.06	-2.84	0.60
PARP-oxyplatinum	-7.12	6.01	-7.12	-6.69	0.00

- AGFR software predicted box with dimensions 98.799Å x 35.214Å x 55.068Å in -x, -y, and -z directions, and with spacing of 0.375 Å
- AutoDock4 calculations: ten different conformations of protein-ligand complexes are set for molecular docking simulations.
- A different number of conformations has been achieved at the final protein-ligand complex depending of the ligand rigidity.
- The complete rigidity of the cisplatin structure gives only one complex conformation.

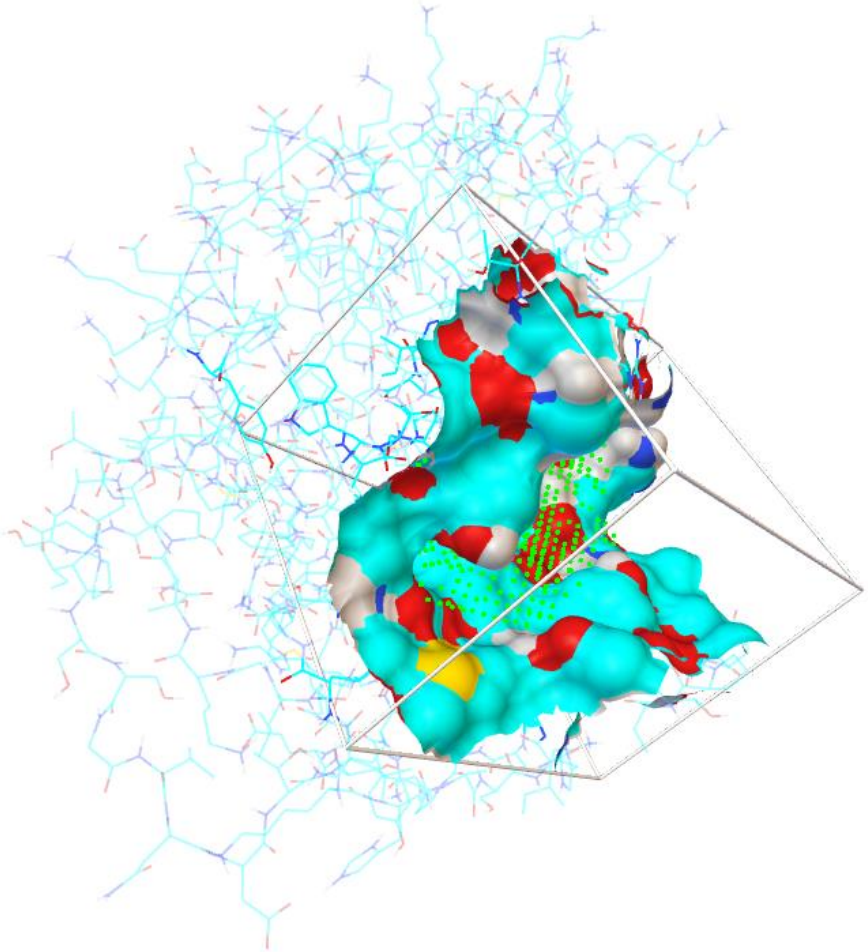


Figure 4. *The location of the most probable binding site of PARP for all estimated ligands*

- That the highest inhibition potency possesses monosubstituted **[AuCl(bipy)(Cys)]$^+$** complex (ΔG_{bind} = -8.74 kcal/mol, K_i = 0.40 μM). It is the consequence of the strong intamolecular bonds (ΔG_{inter} = -10.53 kcal/mol)

- Somewhat lower inhibition potency has been achieved with the disubstituted **[Au(bipy)(Cys)$_2$]$^+$** complex (ΔG_{bind} = -7.19 kcal/mol, Ki = 5.40 μM). The reason for the decrease in inhibitory activity is steric distraction, which is reflected in the increase in torsional energy (ΔG_{tor} = 3.58 kcal/mol).

- **[AuCl$_2$(bipy)]$^+$** and **oxyplatinum** are rigid ligands, which is why they have a lower possibility of stabilizing the resulting complex by intramolecular bonds.

- **PARP-cisplatin** is the weakest complex, and cisplatin is the weakest inhibitor of all considered here. This is due to the fact that in the case of the formation of the PARP-cisplatin complex, the smallest contribution to the stabilization of the complex comes from the energy of intramolecular interactions (ΔG_{inter} = -5.06 kcal/mol), as well as from the sum of energy of dispersion and repulsion, hydrogen-bond energy, and desolvation energy ($\Delta G_{vdw + hbond + desolv}$ = -2.84 kcal/mol). The calculated values of the mentioned energies are most likely a consequence of the rigidity of cisplatin, and the inability of this molecule to take any more favorable conformation that would allow for stronger intramolecular interactions to occur.

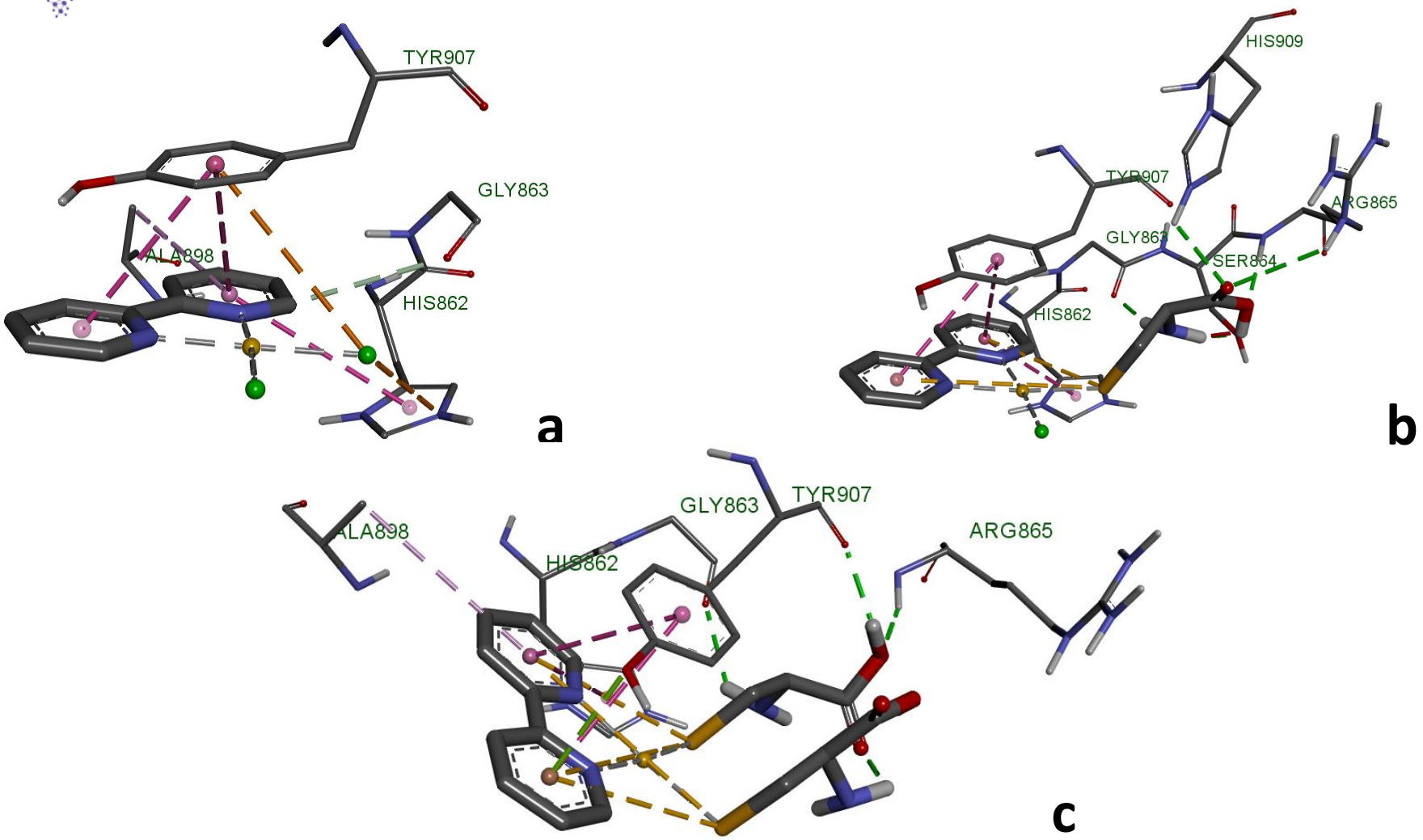
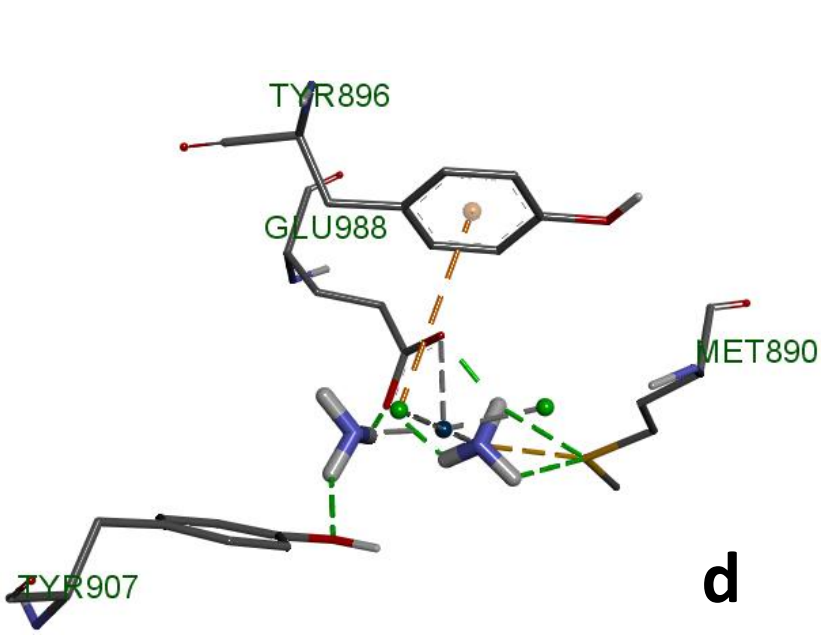
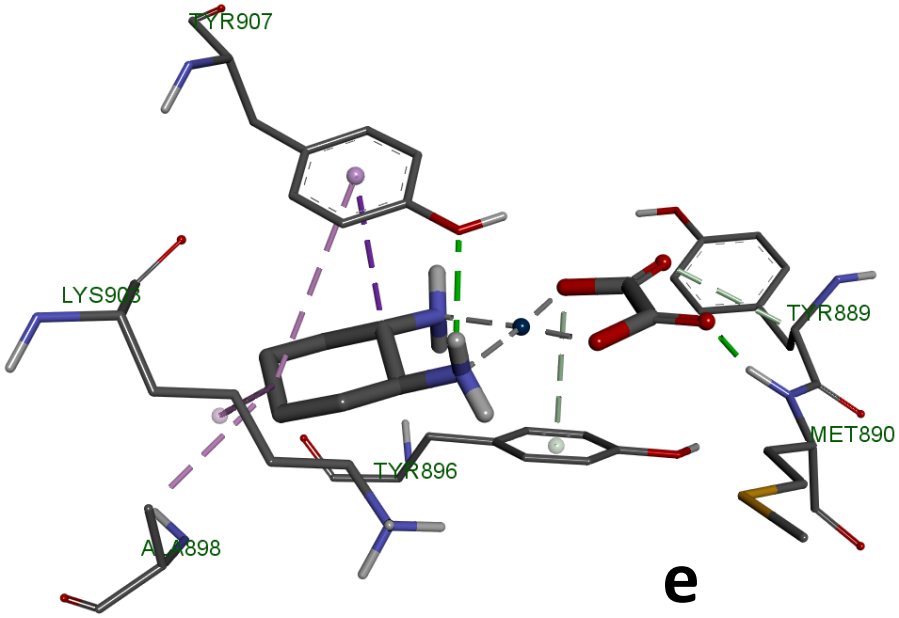


Figure 5. *Docking positions of the PARP with $[AuCl_2(bipy)]^+$ (**a**), $[AuCl(bipy)(Cys)]^+$ (**b**), and $[Au(bipy)(Cys)_2]^+$ (**c**) as ligands*



d



e

Figure 6. *Docking positions of the PARP with* ***cisplatin*** *(**d**), and* ***oxyplatinum*** *(**e**) as ligands*

- **The most important types of interactions are:**
  - **Attractive charges**
  - **Conventional hydrogen bonds**
  - **Carbon hydrogen bonds**
  - **π – π stacking**
  - **π – anion interaction**
- The number of ligand-protein interactions is not the only parameter that affects the strength of inhibition, but it is also the type of interactions (hydrogen bonds, and interactions that include π - electrons).

CONCLUSIONS

- AutoDock 4.0 program indicated that the highest inhibition potency possesses **monosubstituted Au(III)(bipy) complex** (ΔG_{bind} = -8.74 kcal/mol, K_i = 0.40 μM), while somewhat lower inhibition potency has **disubstituted Au(III)(bipy) complex** (ΔG_{bind} = -7.19 kcal/mol, K_i = 5.40 μM) and initial $[AuCl_2(bipy)]^+$ complex (ΔG_{bind} = -6.84 kcal/mol, K_i = 9.73 μM).

- The appropriate thermodynamical parameters that illustrate the inhibition potency of **oxyplatinum** are ΔG_{bind} = -7.12 kcal/mol, K_i = 6.01 μM, and of **cisplatin**, those are ΔG_{bind} = -4.46 kcal/mol, K_i = 535.61 μM.

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ACKNOWLEDGMENTS

The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement **No. 451-03-47/2023-01/200252, No. 451-03-47/2023-01/200378,** and **No. 451-03-47/2023-01/200122).**

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