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Anthrarufin and its anionic moieties as potential inhibitors of HIV-1 reverse transcriptase (RT)

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pharmaceuticals MDPI

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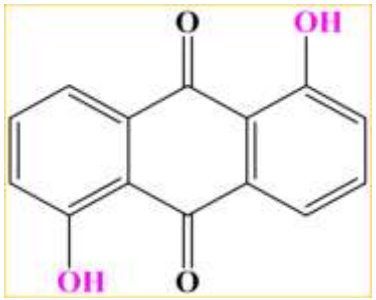
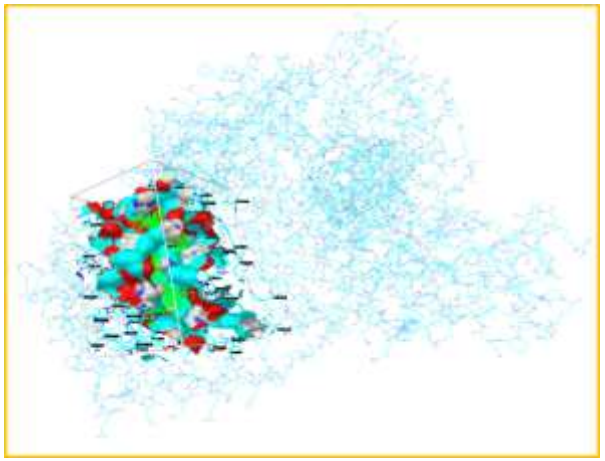
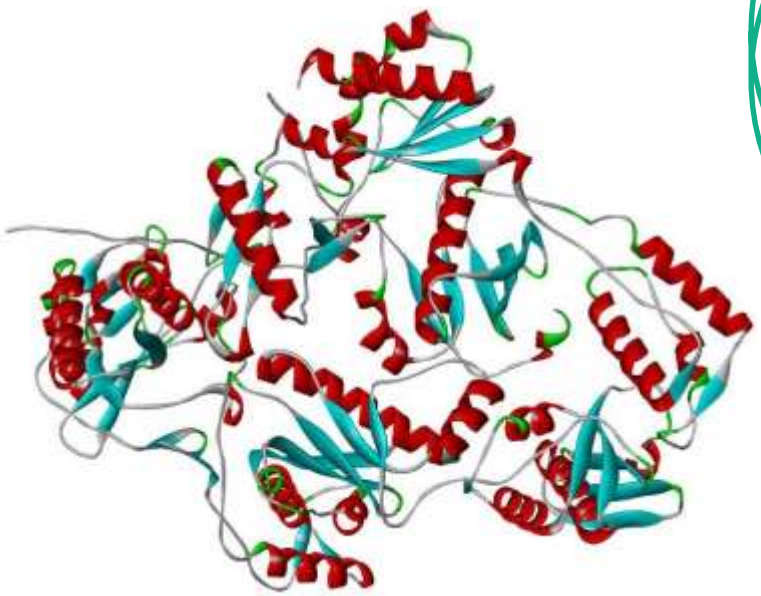
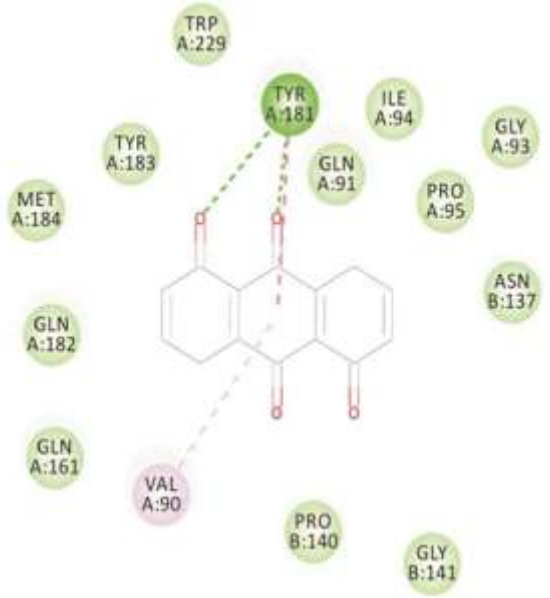
GRAFICAL ABSTRACT:









ABSTRACT:

INTRODUCTION

At the end of the last century, it was revealed that quinones with one, two, and three aromatic rings could inhibit HIV-1 protease, an enzyme crucial for HIV (Human Immunodeficiency Virus) replication. Since HIV-1 protease acts as key target for AIDS medications (Acquired immunodeficiency syndrome), the development of efficient inhibitor of this protein would lead to the increasing of the medical treatment and decreasing of the drug resistance. Later research revealed that simply hydroxyquinones can block HIV-1 protease at the micromolar level, which enabled a direction for the creation of HIV medications. Anthrarufin (1,5-dihydroxy-9,10-anthraquinone) is an anthraquinone that posses a moderate antioxidative capacity and antimalaric activity.

METHODOLOGY

In this study, molecular docking simulations were used to examine the molecular interactions between anthrarufin, its monoanion and dianion as ligands, and the HIV-1 reverse transcriptase (HIV-1 RT) as target protein. Using AGFR software, the binding site of the HIV-1 RT is identified. The three-dimensional crystal structure of HIV-1 RT is downloaded from the Protein Data Bank (PDB ID: 2ZD1). Dolutegravir, nevirapine, anthrarufin, anthrarufin-anion and anthrarufin-dianion are used as ligands in the molecular docking simulations together with rilpivirine (TMC278), a non-nucleoside inhibitor of estimated protein. The AutoDock 4.0 program is used for molecular docking simulations.

RESULTS AND DISCUSSION

Anthrarufin, its monoanion and dianion can be considered as a potential HIV-1 RT inhibitors because they have similar inhibitory potency to other ligands under consideration, according to the results of the free energy of binding (ΔG_{bind}) and inhibition constant (K_i) values.

Keywords: Reverse transcriptase (RT), Anthrarufin, molecular docking, HIV-1 .

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INTRODUCTION

- ✓ At the end of the last century, it was revealed that quinones with one, two, and three aromatic rings could inhibit HIV-1 protease, an enzyme crucial for HIV (Human Immunodeficiency Virus) replication.
- ✓ Since HIV-1 protease acts as key target for AIDS medications (Acquired immunodeficiency syndrome), the development of efficient inhibitor of this protein would lead to the increasing of the medical treatment and decreasing of the drug resistance.
- ✓ Later research revealed that simply hydroxyquinones can block HIV-1 protease at the micromolar level, which enabled a direction for the creation of HIV medications.
- ✓ Polyhydroxy anthraquinones can bind to proteins in different ways, both due to hydroxyl groups and due to the polycyclic aromatic π-electron structure. It is believed that those binding interactions are responsible for the detected inhibition of HIV-1 proteinase by anthraquinones.

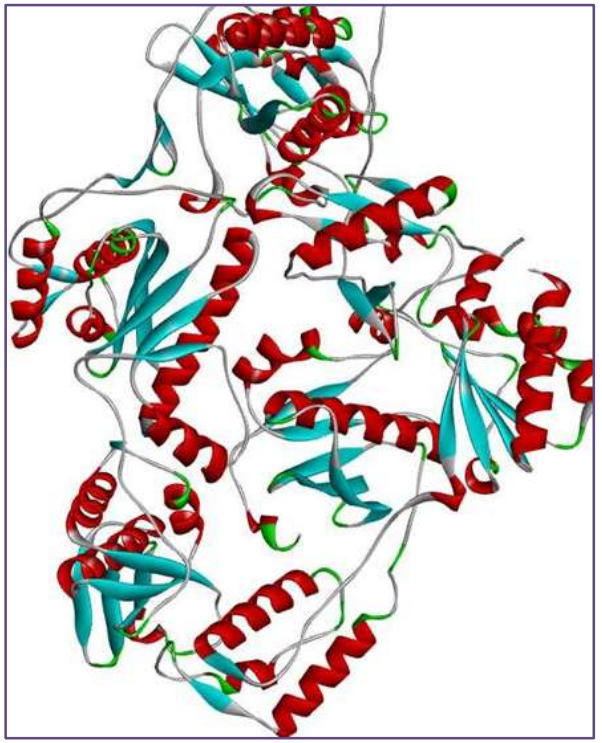

***Fig. 1**. 3D structure of HIV-1 reverse transcriptase (RT) (PDB ID: 2ZD1)*

Brinkworth, R.L., Fairlie, D.P. (1995), *Biochimica et Biophysica Acta,* No1253 5-8

- ✓ In this study, molecular docking simulations were used to examine the molecular interactions between anthrarufin, its monoanion and dianion as ligands, and the HIV-1 reverse transcriptase (HIV-1 RT) as target protein (**Fig. 1 and Fig.2**).
- ✓ Recently, integrase chain inhibitors, especially dolutegravir, have shown significantly higher safety and efficacy and have become the main agents of choice in HIV therapy. Dolutegravir is an antiretroviral drug belonging to the class of HIV integrase strand transfer inhibitors (ISTIs).
- ✓ The inhibition potency of anthrarufin and its anionic species are compared with inhibition potency of dolutegravir, nevirapine and rilpivirine, a conventional a non-nucleoside inhibitor of estimated protein.

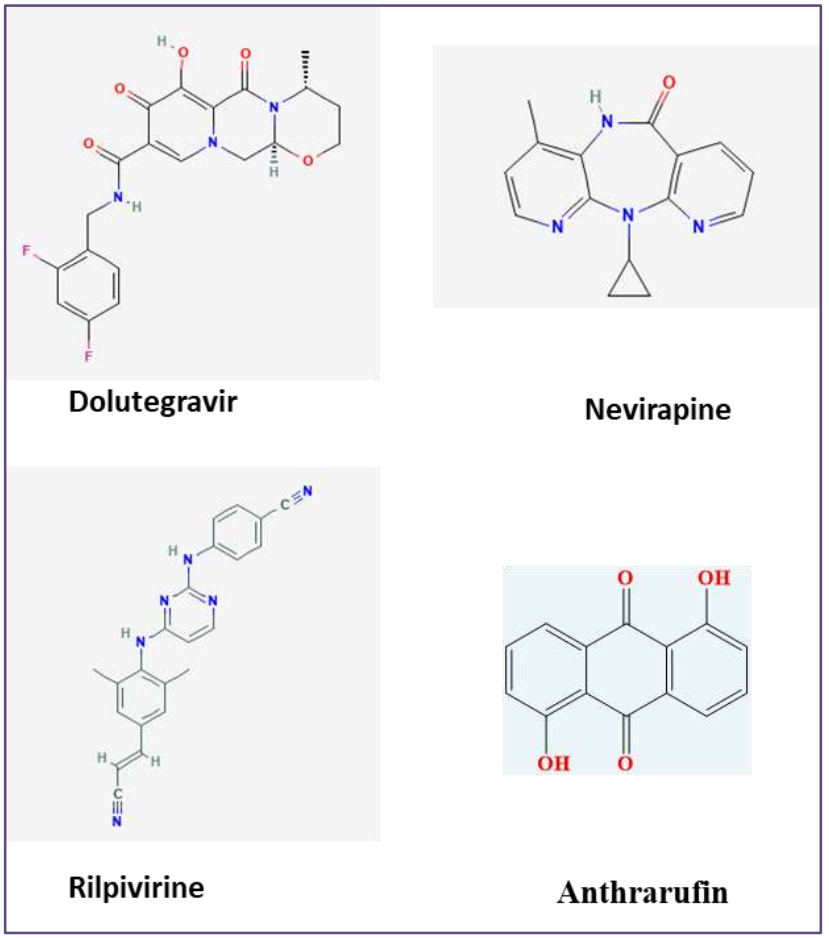

***Fig. 2**. The structural formulas of the investigated compounds*

McCormack PL.(2014), *Drugs*, Vpl.74, 1241–52.

METHODOLOGY

- ✓ **DFT method, M06-2X/6-311++G(d,p)** (Gaussian 09 program package) – optimization of the structures of terpyridine metal complexes
- ✓ **Protein Data Bank (PDB ID: 2C6W)1** - three-dimensional (3D) crystal structure of PBP1a protein
- ✓ **Discovery Studio 4.0** - protein is released from the co- crystallized ligand, water molecules, and co factors.
- ✓ **AGFR (AutoGridFR) software** – establishing of the affinity maps of the target protein
- ✓ **AutoDock 4.0 software2** – molecular docking simulations
- ✓ **BIOVIA Discovery Studio** - analysis of molecular docking simulation results and visualizations of predicted protein- ligand interactions

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RESULTS AND DISCUSSION

✓ In **Fig. 3**. are presented interactions achieved in all molecular docking simulations. The obtained interactions are of different types of interactions. The most represented of them are formations of hydrogen bonds.

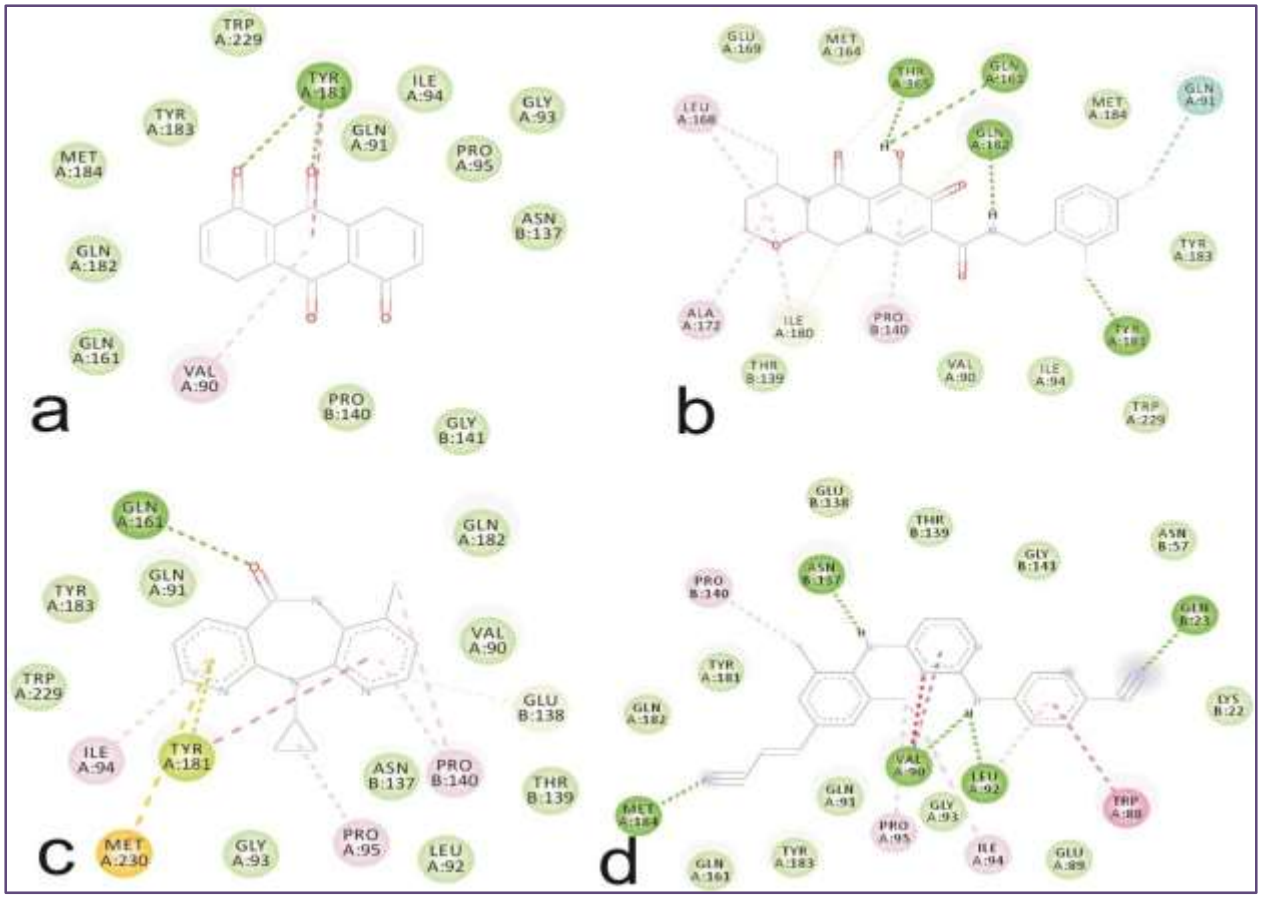

***Fig. 3 D**ocking positions of the RT protein with anthrarufin dianion (a), dolutegravir (b), nevirapine (c) and rilpirivine (d).*

✓ The inhibitory potency of preferred compounds can be estimated based on the thermodynamical parameters obtained from molecular docking simulations: free energy of binding (ΔG_{bind}) and inhibition constant (K_i).

Table1: *The important thermodynamical parameters from molecular docking simulations between RT protein and selected compounds (Fig. 3)*

Ligand	ΔG_{bind} (kcalmol^{-1})	K_i (nM)
Anthrarufin	-7.44	3.53
Anthrarufin anion	-7.43	3.57
Anthrarufin dianion	-7.78	1.97
Dolutegravir	-9.01	0.248
Nevirapine	-6.41	20.17
Rilpivirine	-9.27	0.167

CONCLUSIONS

- ✓ Anthrarufin dianion has higher inhibition potency than anthrarufin anion and anthrarufin
- ✓ Anthrarufin and both of their anionic species have lower inhibition potency than dolutegravir and rilpirivine , but higher inhibition potency than nevirapine.
- ✓ All six estimated inhibitors interact with RT protein over three comon aminoacids: Pro140, Gln 161 and Gln182.
- ✓ Among the most important interactions are conventional hydrogen bonds, and interactions involving π–electrons from aromatic rings.
- ✓ Anthrarufin, its monoanion and dianion can be considered as a potential HIV-1 RT inhibitors

ACKNOWLEDGMENTS

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