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

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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 [1].

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.

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).

The inhibition potency of anthrarufin and its anionic species are compared with inhibition potency of Dolutegravir, nevirapine and rilpivirine , a convetional a non-nucleoside inhibitor of estimated protein [2, 3, 4].

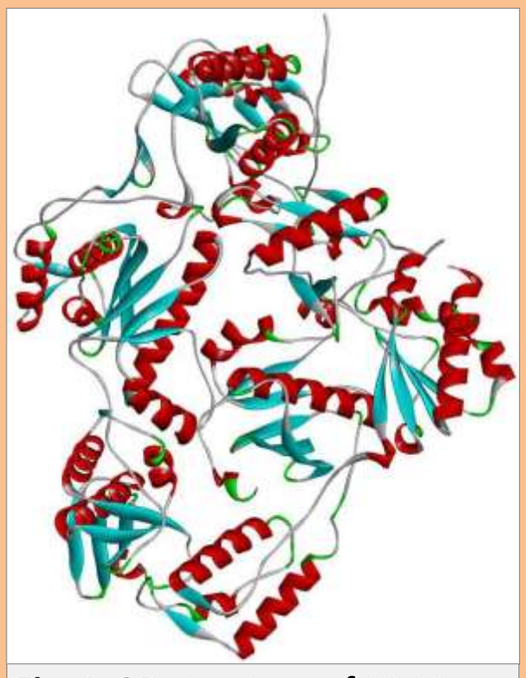

Fig. 1. 3D structure of HIV-1 reverse transcriptase (RT) (PDB ID: 2ZD1)

METHODOLOGY

- **DFT method, M06-2X/6-311++G(d,p)** (Gaussian 09 program package) – optimisation of the structures of terpyridine metal complexes
- **Protein Data Bank** (PDB ID: 2C6W) - three-dimensional (3D) crystal structure of PBP1a protein [5].
- **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 software** – molecular docking simulations [6].
- **BIOVIA Discovery Studio** - analysis of molecular docking simulation results and visualizations of predicted protein-ligand interactions

References:
[1] Brinkworth RL, Fairlie DP (1995) Biochimica et Biophysica Acta, No1253 5-8
[2] McCormack PL.(2014) Drugs, 74 (1) 1241–1252.
[3] Frey KM et al. (2015) J Med Chem, 58 (6) 2737–2745.
[4] Johnson BC et al. (2012) Retrovirology 9, No 99.
[5] Das K et al. (2007) wwPDB, PDB ID : 2ZD1.
[6] Morris GM et al. (2009) J Comput Chem, 30 (16) 2785-2791.

RESULTS AND DISCUSSIONS

Table: The important thermodynamical parameters from molecular docking simulations between RT protein and selected compounds (Fig. 2)

Ligand	ΔG_{bind} (kcal mol^{-1})	K_i (μM)
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	0.161

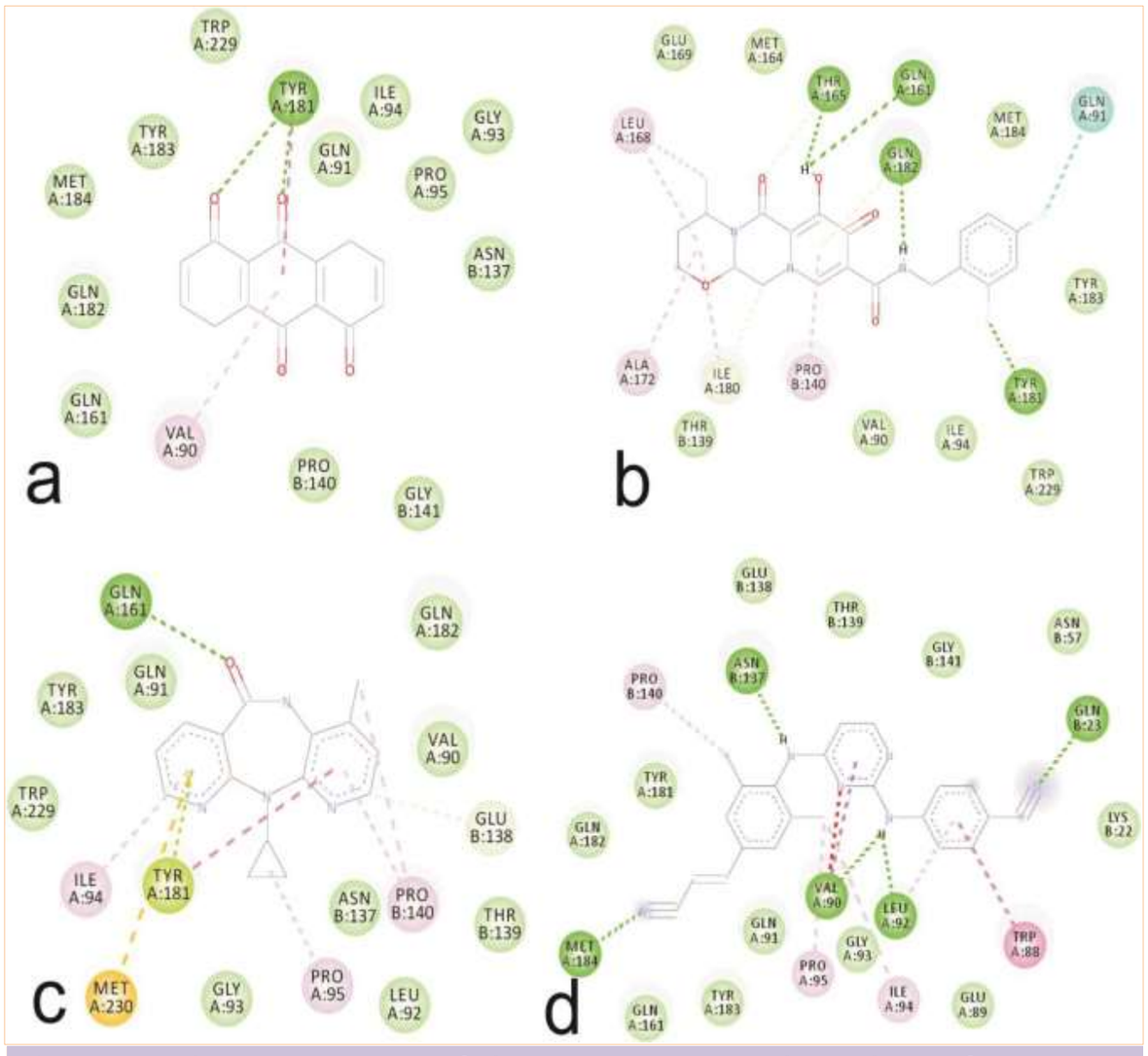

Fig. 2. Docking positions of the RT protein with anthrarufin dianion (a), dolutegravir (b), nevirapine (c) and rilpirivine (d).

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

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