NEW TRENDS AND STRATEGIES IN THE CHEMISTRY OF ADVANCED MATERIALS WITH RELEVANCE IN BIOLOGICAL SYSTEMS, TECHNIQUE AND ENVIRONMENTAL PROTECTION
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NATURAL PRODUCTS AS ANTI-HIV AGENTS: AN *IN SILICO* INSIGHT

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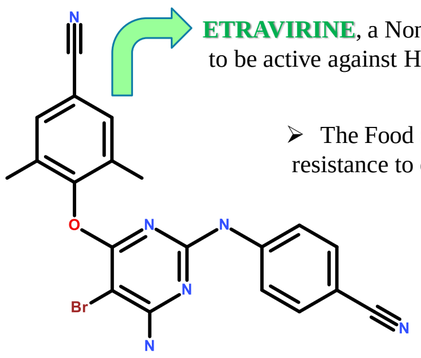
Introduction

In the present work, *in silico* approaches were applied to find natural products (NPs) with similar bioactivity to non-nucleoside reverse transcriptase inhibitors (NNRTIs) but with different chemotypes, as promising candidates to treat human immunodeficiency virus type 1 (HIV-1) infection. The FDA-approved drug, etravirine, was used as reference molecules in a virtual screening experiment. The ZINC15 database of 224205 NPs was screened and filtered using 3D-similarity search, ADMET, and molecular docking simulations. Three NPs having higher docked scores and superior ADMET profile than etravirine were selected for further investigations. For these NPs, hydrogen bonds and hydrophobic interactions with key binding site residues (Lys101, Tyr181, Tyr188, Trp229, and Tyr318), along with free binding energies, argue that ligands can bind to HIV-1 reverse transcriptase. In conclusion, these three compounds were proposed as potential anti-HIV inhibitors. Moreover, our proposed workflow might be helpful to design novel potential NNRTIs from natural sources.

Results and Discussions

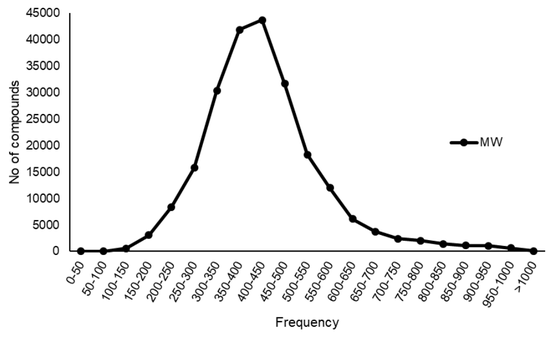
- To expand the chemical space of NPs, the 3D similarity search was employed.
- The FDA-approved drugs, **ETRAVIRINE** was designated as query in the current investigation.

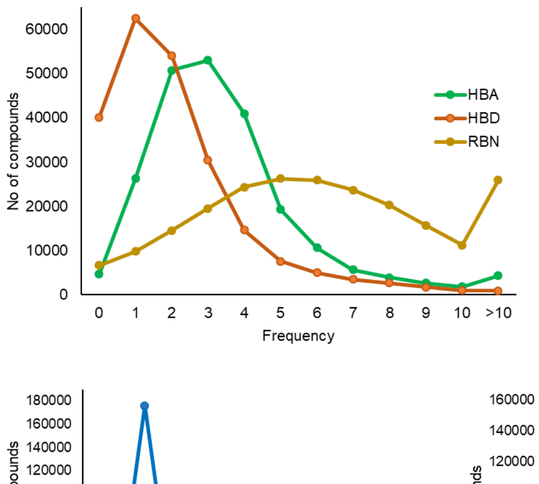


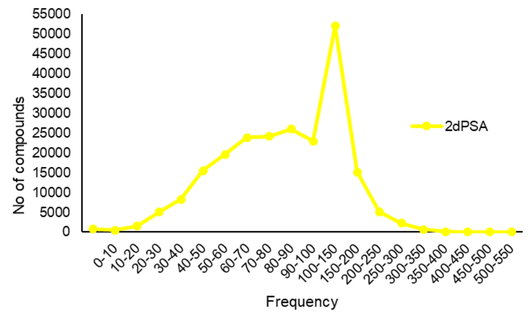
ETRAVIRINE, a Non-nucleoside reverse transcriptase inhibitor (NNRTI), has been designed to be active against HIV1-RT.

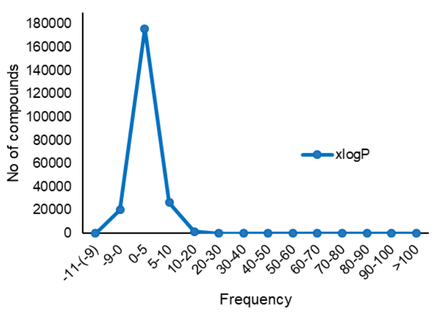
- The Food and Drug Administration (FDA) approved its use for patients with established resistance to other drugs, in January 2008.

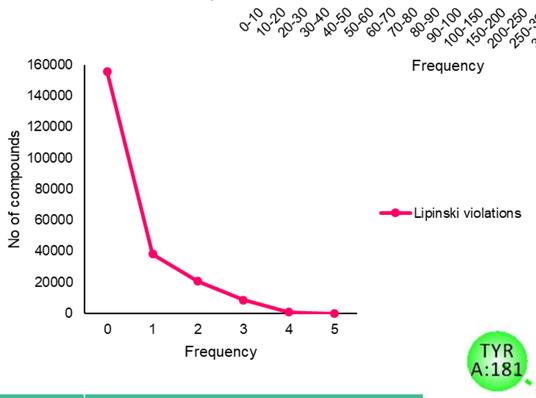
- **Distribution of drug-like properties for the ZINC15 NPs subset.**











Name	Glide score	MM-GBSA ΔG_{bind} (kcal/mol)	Hydrogen Bond*	Hydrophobic interactions
ZINC37538901	-10.656	-63.76	HB: (2) LYS101; TYR181; TYR188 W-HB: HOH470	Alkyl: LYS103; (2) VAL106; (2) LEU234 π-Alkyl: (2) TRP229; (2) TYR188; VAL106; PHE227; TYR318 π-σ: VAL106; LEU234 Attractive charge/Salt bridge: LYS101, LYS103
ZINC67912677	-10.017	-61.98	HB: GLU138; HIS235; (2) LYS101; LYS103; PRO236; π-Donor HB: TYR318 W-HB: HOH470	Alkyl: VAL106; VAL108 π-Alkyl: PHE227 π-π Stacked: TYR188 π-π T-shaped: (2) TRP229 π-σ: (2) TRP229; TYR181
ZINC38321654	-9.917	-64.88	HB: GLU138; HIS235; LYS101; LYS103; PRO236; TYR318 C-HB: LYS101 π-Donor HB: TYR318 W-HB: HOH470	π-Alkyl: VAL106 π-π T-shaped: (2) TRP229 π-σ: TRP229
Etravirine	-9.538	-66.46	HB: GLU138; LYS101 π-Donor HB: TYR318 W-HB: HOH470	Alkyl: VAL106; PRO95; LEU100;VAL179 π-Alkyl: LEU234; (2) LYS103; TRP229; TYR181; VAL106 π-π Stacked: TYR188 π-π T-shaped: (2) TRP229 π-σ: LEU100; VAL179; TRP229

*Conventional Hydrogen Bond – HB; Carbon Hydrogen Bond – C-HB; Water Mediated Hydrogen Bond – W-HB; π-Donor Hydrogen Bond - π-Donor HB

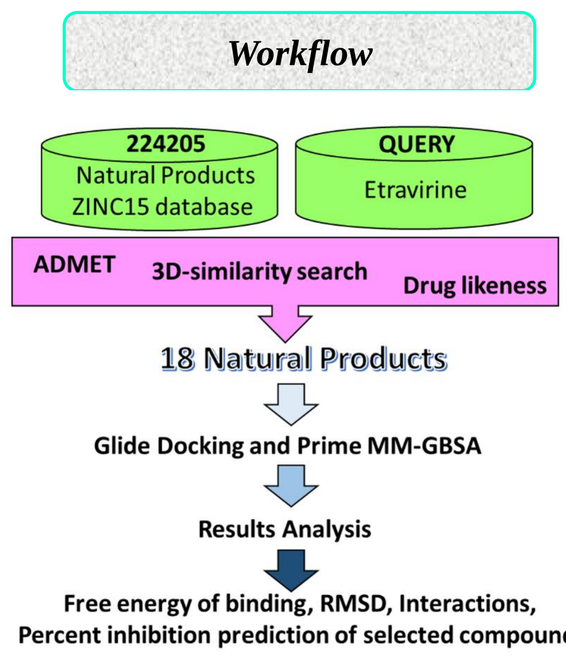
Known therapeutic benefits of the proposed natural products

✓ **ZINC37538901** is a natural derivative of β-D-glucopyranoside type known to develop anticancer, anti-inflammatory, antiseptic and many other activities.

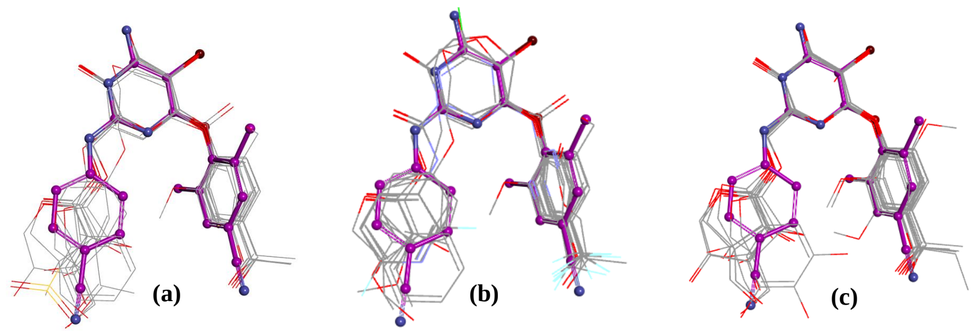
✓ **Canthoside D** (**ZINC038321654**), a phenolic compound isolated from aerial parts of *Salsola tetragona* specie, is known to possess anticancer, antimicrobial, anti-inflammatory, antioxidant, antidepressant, and antihypertensive activities.

✓ **Geoside** (**ZINC67912677**), one out of more than 30 steviol glycosides, is a natural sweetness compound extracted from *Stevia rebaudiana* leaves. The steviol glycosides are used in food industry, especially as sweeteners in fruit juices. They also exhibit antinflammatory, antibacterial, antiviral, antitumor, antihyperglycemic, antioxidant activities, etc. In short, stevia has zero calories, many benefits. Like most natural compounds, they are safe for human health and could be consumed without restriction by diabetics.

Workflow

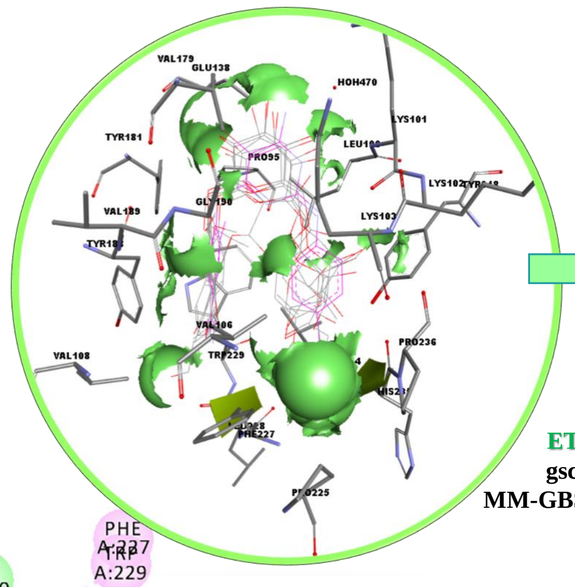


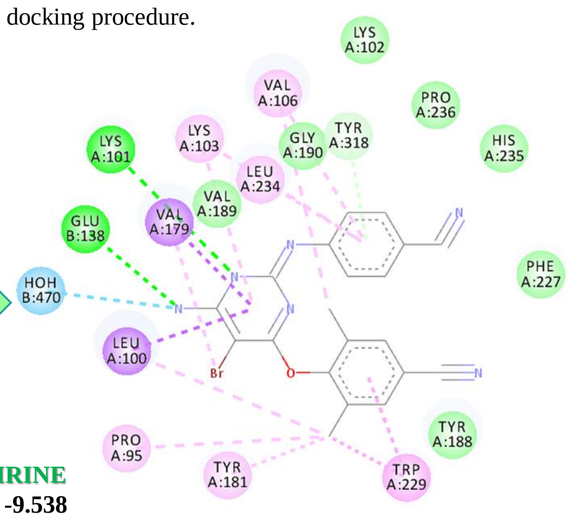
- The TanimotoCombo (TC), ShapeTanimoto (ShT), and ComboScore (CS) were selected as scoring parameters to rank NPs with respect to etravirine.
- The top ten molecules aligned by ROCS using the criteria: TC values (a), ShT values (b), CS values (c)



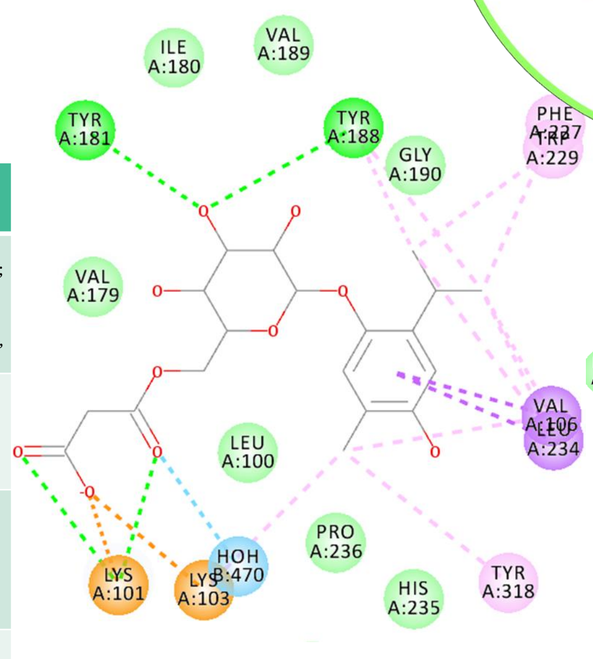
3D structure of Etravirine is depicted in magenta

- The RMSD between the best docking pose of Etravirine and its X-ray structure coordinates, was calculated.
- The very low RMSD value of 0.695Å validates the docking procedure.

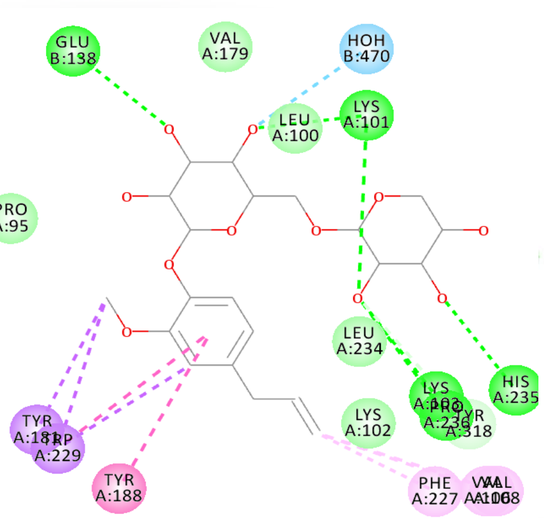




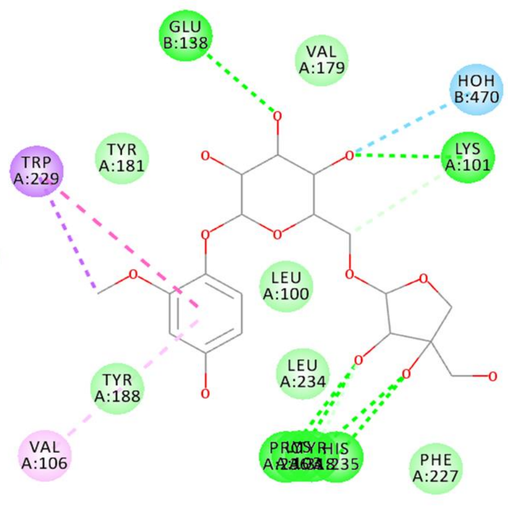
ETRAVIRINE
gscore = -9.538
MM-GBSA(ΔG_{bind})=-66.46



ZINC37538901
gscore = -10.656
MM-GBSA(ΔG_{bind})=-63.76



ZINC67912677
gscore = - 10.017
MM-GBSA(ΔG_{bind})=-61.98



ZINC38321654
gscore = - 9.917
MM-GBSA(ΔG_{bind})=-64.88

Conclusions

- **3D-similarity search, ADMETox, molecular docking, and MM-GBSA simulations were performed within 224205 natural compounds of the ZINC15 database to identify potential new antiviral agents against HIV-1 RT.**
- **The *in-silico* analysis revealed that three (ZINC37538901, ZINC67912677, and ZINC38321654) out of twenty five selected natural products fulfilled all the parameters investigated such as 3D-similarity coefficients, ADMETox parameters, the IC50/percent inhibition of HIV RT protein, docking scores, and free binding energies.**
- **Docking outcomes suggested that residues Lys101, Tyr181, Tyr188, Trp229, and Tyr318, involved in essential hydrogen bonding and π-π stacked interaction which stabilized ZINC NP in HIV-1 RT active site, played essential roles for anti-HIV activity.**
- **Concerning the antiviral activity evaluated by HIVprotI, all ZINC NPs were predicted to show activity against HIV-1 RT with an IC50 range of 2-99.86μM and 27.65-52.46% inhibition.**

References

- Crisan, L., Bora, A., *Life* 2021, 11(7), 722; https://doi.org/10.3390/life11070722
- OMEGAv.2.5.1.4 OpenEye Scientific Software Inc. Santa Fe NM, USAwww.eyesopen.com
- Hawkins PCD, Nicholls A (2012). J Chem Inf Model 52:2919– 2936
- ROCS v 3.2.1.4 OpenEye Scientific Software Inc Santa Fe NM, USA wwweyesopencom.
- Hawkins P.C.D., Skillman A.G., Nicholls A., *J. Med. Chem.* 50 (2007) 74-82.
- RCSB Protein Data Bank, RCSB PDB, https://www.rcsb.org/structure/3MEC
- Halgren, T.A.; Murphy, R.B.; Friesner, R.A.; Beard, H.S.; Frye, L.L.; Pollard, W.T.; Banks, J.L. Glide: A new approach for rap-id, accurate docking and scoring. 2. Enrichment factors in database screening. *J. Med. Chem.* 2004, 47, 1750–1759.
- Qureshi, A.; Rajput, A.; Kaur, G.; Kumar, M. HIVprotI: An integrated web based platform for prediction and design of HIV proteins inhibitors. *J. Cheminform*. 2018, *10*, 1213.
- Hwang, S.J.; Lee, H.J. Phenyl-β-D-Glucopyranoside exhibits anti-inflammatory activity in lipopolysaccharide-activated RAW 264.7 cells. *Inflammation* 2015, *38*, 1071–1079.
- Ghorab, H.; Khettaf, A.; Lehbili, M.; Kabouche, A.; Magid, A.A.; Harakat, D.; Voutquenne-Nazabadioko, L.; Kabouche, Z. A new cardenolide and other compounds from Salsola tetragona. *Nat. Prod. Comm*. 2017, *12*, 3–5.
- Dassault Systèmes BIOVIA, Discovery Studio Visualizer v. 19.1.0 Dassault Systèmes, San Diego, www.3dsbiovia.com

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