Application of 2D-QSAR and Chemical Read-Across Algorithm to Predict the Androgen Receptor Binding Affinity

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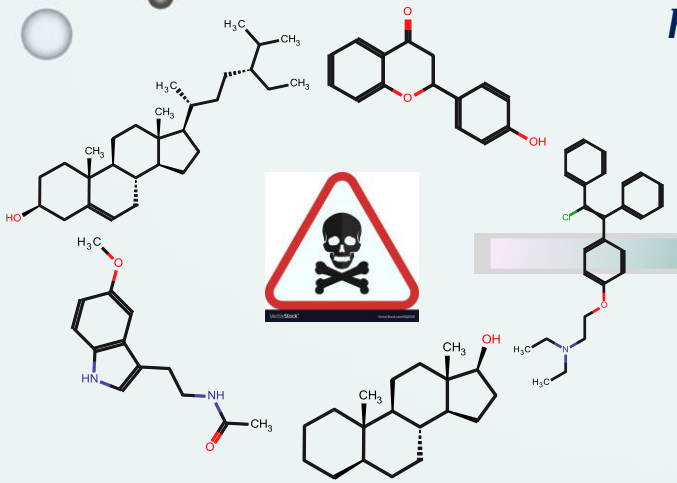
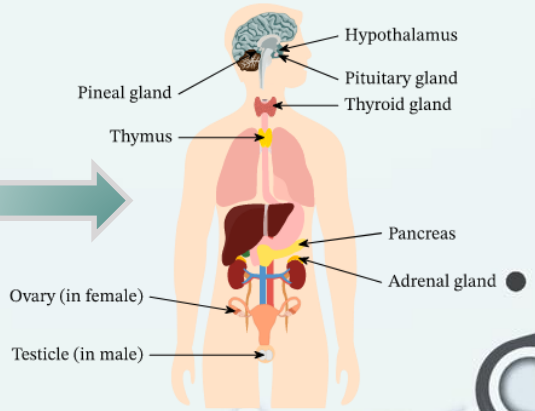
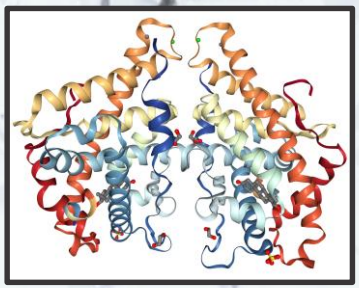




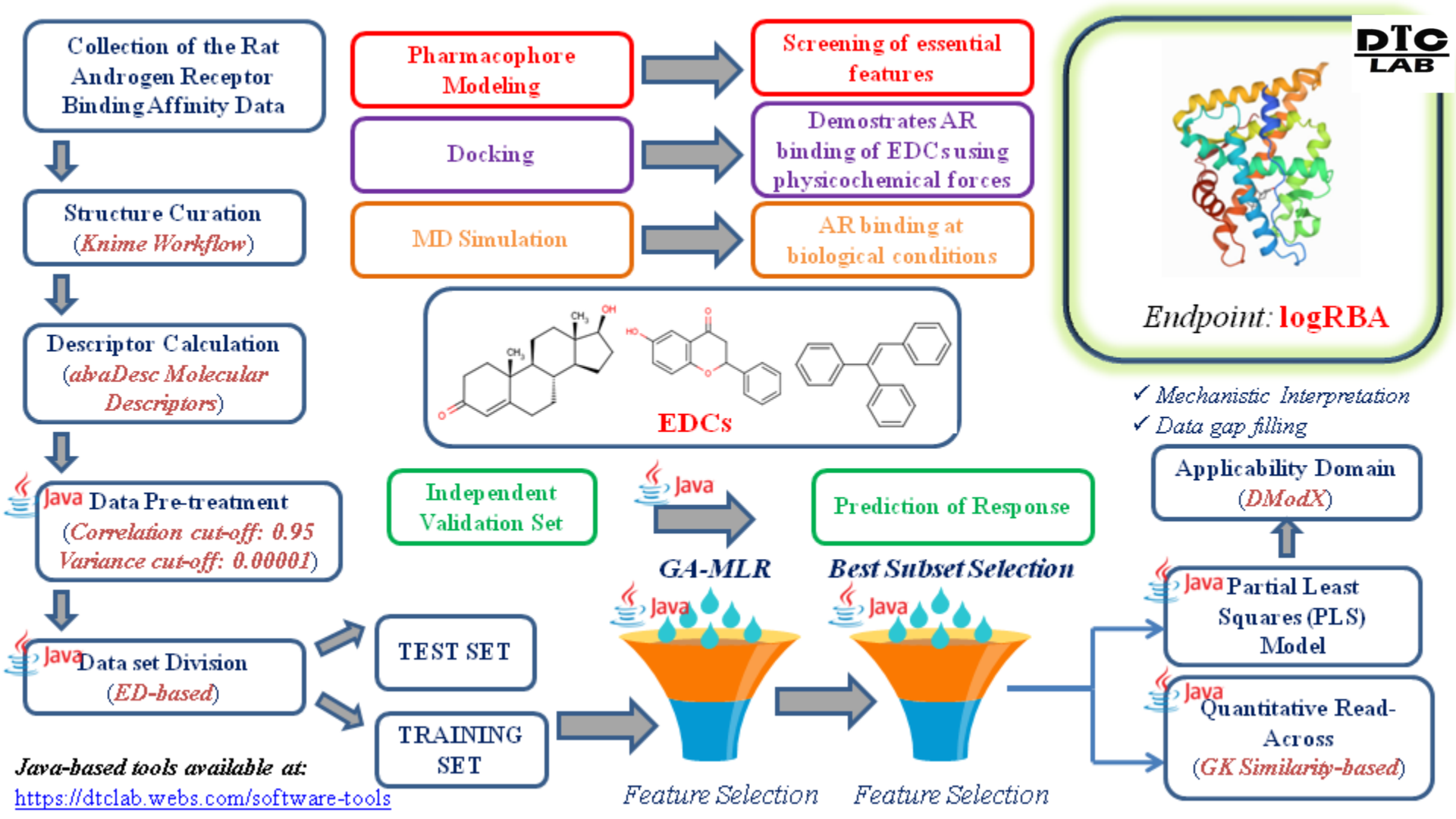
Introduction

- ✓ Endocrine Disruptors (EDCs) promote adverse modification in hormonal regulation
- ✓ They show various neurological, reproductive and cardiovascular adverse effects by interfering with the synthesis, transport, metabolism and release of hormones
- ✓ Among these, certain compounds mimic Androgen, which is responsible for male sexual characters

This study models and predict androgen receptor binding affinity using 2D-QSAR and Chemical Read-Across approaches



Schug, T.T., Janesick, A., Blumberg, B., Heindel, J.J., 2011. J. Ster. Biochem. Mol. Bio.. 127, 204-215


Collection of the Rat Androgen Receptor Binding Affinity Data
Structure Curation (Knime Workflow)
Descriptor Calculation (alvaDesc Molecular Descriptors)
Java Data Pre-treatment (Correlation cut-off: 0.95 Variance cut-off: 0.00001)
Java Data set Division (ED-based)
TEST SET
TRAINING SET
Pharmacophore Modeling
Screening of essential features
Docking
Demostrates AR binding of EDCs using physicochemical forces
MD Simulation
AR binding at biological conditions
EDCs
Endpoint: logRBA
DTC LAB
✓ Mechanistic Interpretation
✓ Data gap filling
Independent Validation Set
Java
Prediction of Response
GA-MLR
Best Subset Selection
Java
Java
Feature Selection
Feature Selection
Applicability Domain (DModX)
Java Partial Least Squares (PLS) Model
Java Quantitative Read-Across (GK Similarity-based)
Java-based tools available at:
https://dtclab.webs.com/software-tools

Software tools used for 2D-QSAR & Read-Across

✓ DTC-QSAR v1.0.5 available at https://dtclab.webs.com/software-tools

✓ BestSubsetSelection_v2.1 available at https://dtclab.webs.com/software-tool

✓ PLS_SingleY_1.0 available at https://dtclab.webs.com/software-tools

✓ Read-Across-v3.1 available at https://sites.google.com/jadavpuruniversity.in/dtc-lab-software/home

✓ PRI Tool_PLSversion available at https://dtclab.webs.com/software-tool

Software used for Pharmacophore Modeling, Docking and Molecular Dynamics Simulation

✓ **BIOVIA Discovery Studio Client 4.1**

✓ **GROMACS 2021.4**

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Results & Discussion

Partial Least Squares Equation

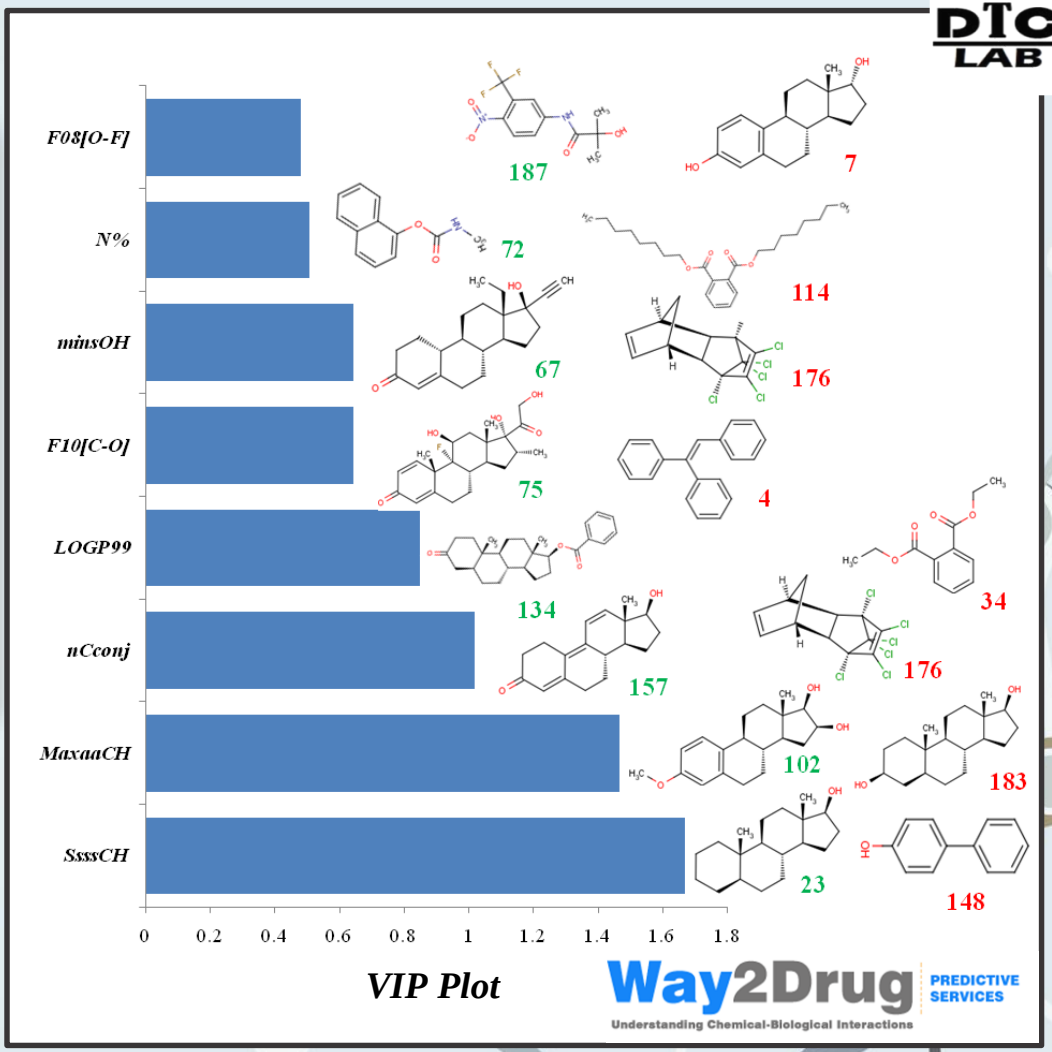
$$LogRBA = -3.23 + 0.49 \times SsssCH - 0.41 \times MaxaaCH + 0.23 \times nCconj + 0.35 \times LogP99 - 0.17 \times F10[C-O] + 0.06 \times minsOH + 0.06 \times N\% + 0.67 \times F08[O-F]$$

R^2 (Train) :0.737 Q^2 (LOO) :0.680
Q^2F1 :0.582 Q^2F2 :0.582

Read-Across: Q^2F1 : 0.635 Q^2F2 : 0.635
(Gaussian-Kernel Similarity)

Wold S, Sjöström M, Eriksson L, 2001, Chemom. Intell. Lab. Sys., 58, 109-130.

Chatterjee, M., Banerjee, A., De, P., Gajewicz, A., Roy, K., 2022. Environ. Sci.: Nano. 9, 189-203.



Interpretation

logP

Aliphatic CH group count

Bulkiness

Hydrophobicity

Electron richness & polarity

Aromaticity

Polar groups

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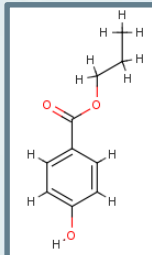
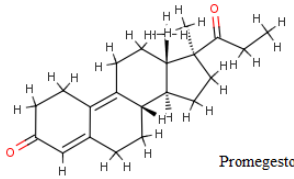


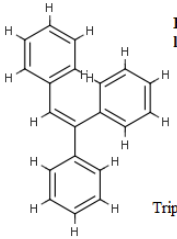
log P99 = 1.96
log RBA = -3

n-Propyl 4-hydroxybenzoate



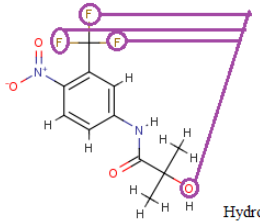
log P99 = 5.18
log RBA = -0.64

Promegestone



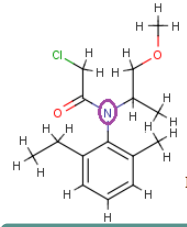
F08[O-F] = 0
log RBA = -1.98

Triphenylethylene



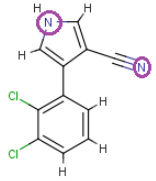
F08[O-F] = 3
log RBA = +0.23

Hydroxyflutamide



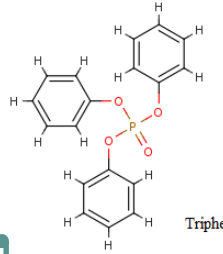
N% = 2.44
log RBA = -2.61

Metolachlor



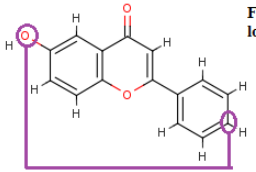
N% = 9.52
log RBA = -1.61

Fenpiclonil



F10[C-O] = 0
log RBA = -1.69

Triphenyl phosphate



F10[C-O] = 1
log RBA = -2.77

6-Hydroxyflavone

Zhou W et al. 2018, Genom. Proteom. Bioinform. 16, 416-427

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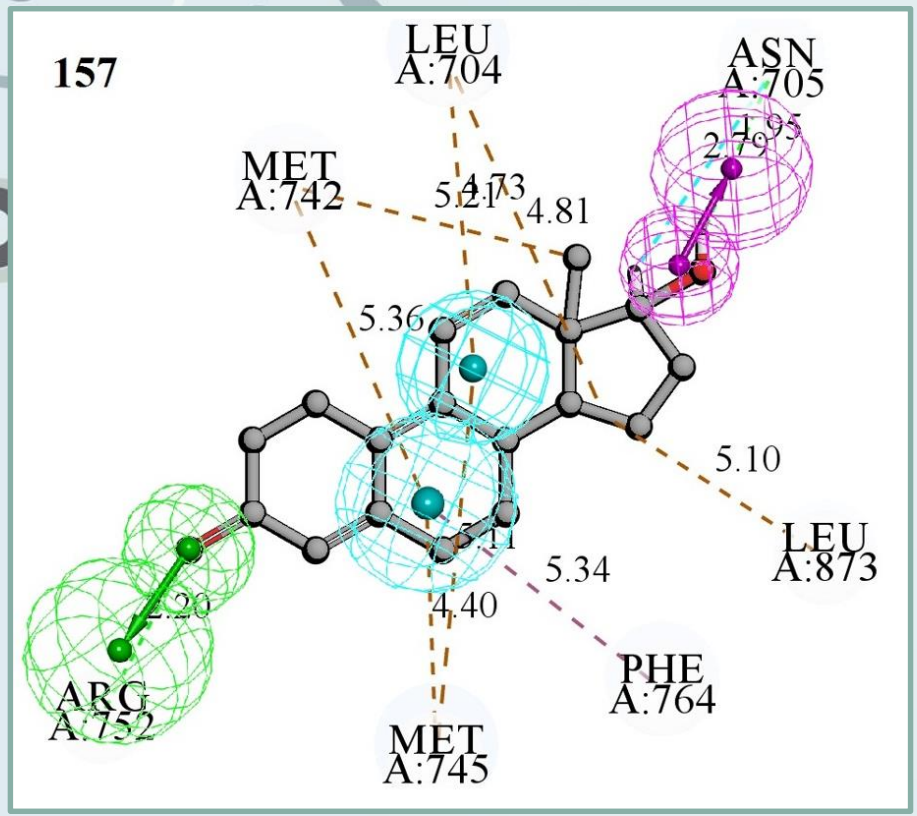
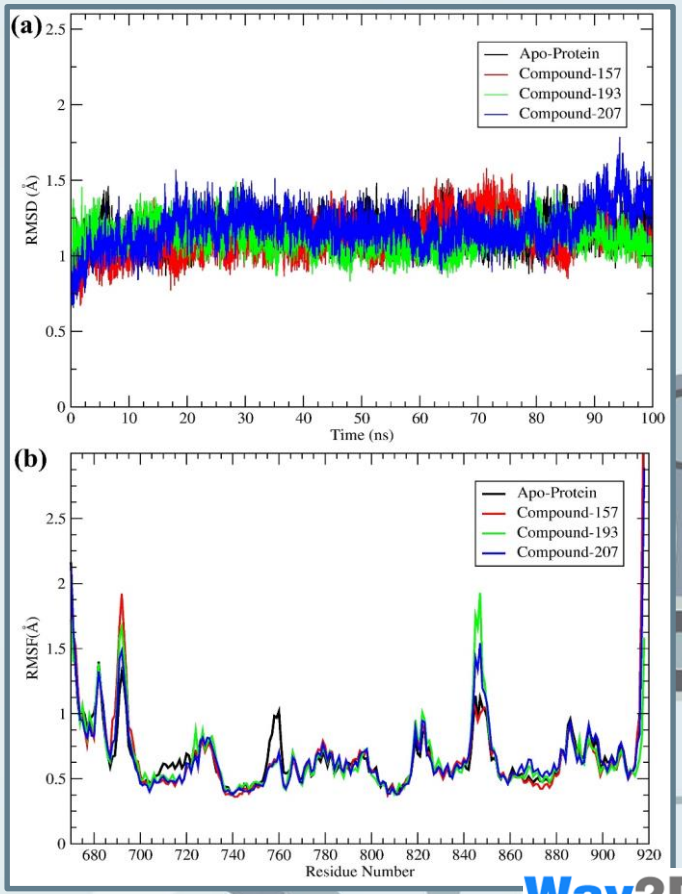
Pharmacophore modeling, Docking and Molecular Dynamics Simulation





Banerjee A, De P, Kumar V, Kar S, Roy K. 2022. ChemRxiv

Comparison with previous models

Hong H et al. 2003. SAR QSAR. Environ. Res. 14, 373-388

- CoMFA
- nTrain=146
- nTest=8
- R^2=0.902
- Q^2=0.571
- Q^2_F1=Not reported
- Q^2_F2=Not reported

Not robust, Not reproducible

Our Work

- 2D-QSAR
- nTrain=103
- nTest=44
- R^2=0.737
- Q^2(LOO)=0.680
- Q^2_F1=0.582
- Q^2_F2=0.582

Robust, Predictive, Reproducible

Waller C. L. et al. 1996. Toxicol. Appl. Pharmacol. 137, 219-227

- CoMFA
- nTrain=21
- nTest=7
- R2=0.989
- Q2=0.792
- Q2_F1=Not reported
- Q2_F2=Not reported

Less robust, Less compounds, Not reproducible

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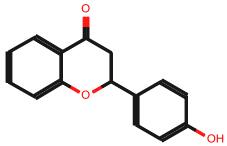
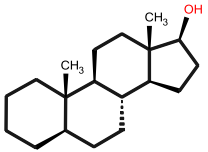


Conclusion



✓A regression-based 2D-QSAR Model was developed which is robust, predictive and avoids 3D descriptor computation and conformational complexity

✓ The model generated should be an useful tool to quickly and efficiently predict the quantitative binding affinity of EDCs for the Androgen Receptor

✓ Chemical Read-Across was also tried, and the prediction results obtained were even better.

✓ The 2D-QSAR model was supported by the results of Pharmacophore modeling, Docking and MD Simulation

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Thank you