Abstract #383: Accelerated discovery of novel RORγT modulators using an AI-driven platform integrating generative chemistry and mechanistic PK simulation

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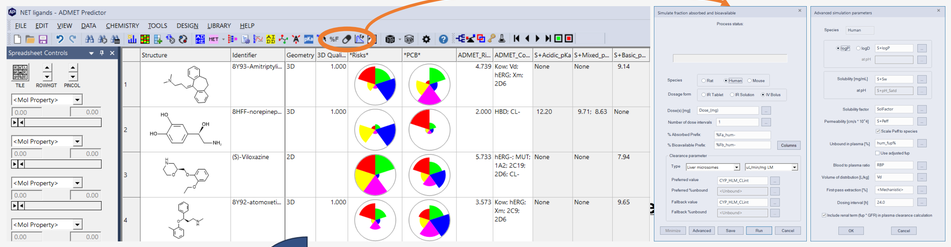
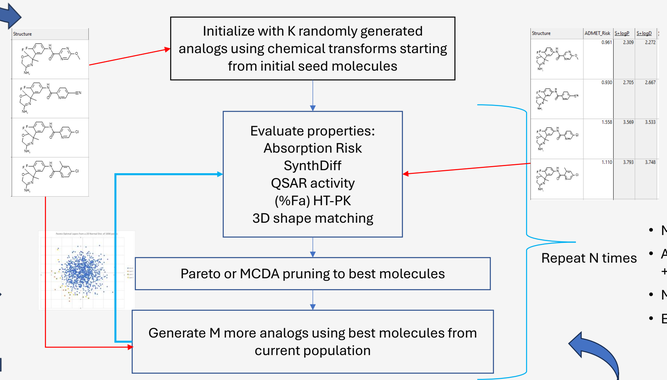
THE AI-DRIVEN DRUG DESIGN (AIDD) PLATFORM

Advanced ML models with ADMET Predictor

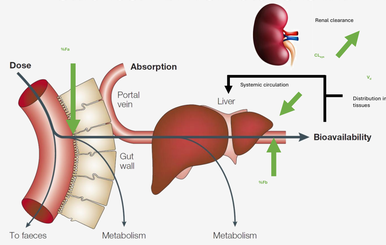


About ADMET Predictor

- >450 ML models built on highly-curated data
- Physchem properties, metabolism, transporters, tox, and synthesizability
- No black boxes: model applicability domains, confidence indicators, sensitivity analysis tools



Ultra-fast PBPK simulations with HTPK



Gut clearance and active transport (efflux/influx) are **not** considered

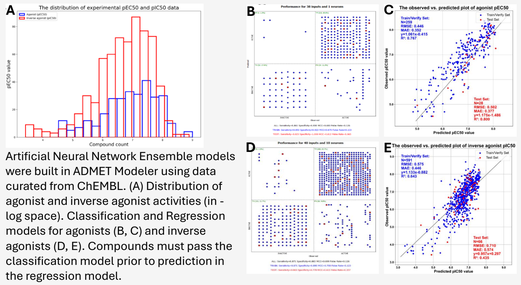
About HTPK

- Modified version of the full ACAT model available in GastroPlus
- Mechanistically simulate the in vivo PK of thousands of compounds in minutes[2]
- Uses measured data and/or AP model predictions for input (solubility, clearance)
- Produces full Cp-time profiles along with important endpoints (%Fa, %Fb, AUC, Thalf)
- Species: human, monkey, dog, rat, mouse

About AIDD

- Molecular generative engine + Multi-Parameter Optimization (MPO)[3].
- AP and user models + chemical validity + synthetic feasibility + HTPK + 3D shape matching integrated into point of design
- MPO options: Pareto or Multi-Criteria Decision Analysis[4] algorithms
- Enables rapid design–test cycles in silico

QSAR model building with ADMET Modeler



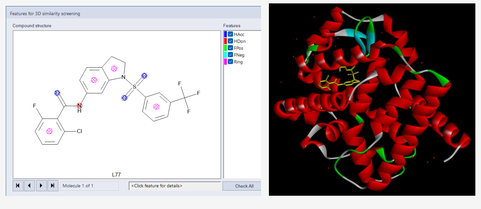
Artificial Neural Network Ensemble models were built in ADMET Modeler using data curated from ChEMBL. (A) Distribution of agonist and inverse agonist activities (in -log space). Classification and Regression models for agonists (B, C) and inverse agonists (D, E). Compounds must pass the classification model prior to prediction in the regression model.

About ADMET Modeler

- Regression or classification models with seamless deployment in ADMET Predictor
- ML algorithms available: artificial neural network ensembles (ANNE), novel linear boost networks, XGboost, random forest, and more
- Built-in tools for cross-validation, external test sets, applicability domain analysis, and performance metrics to ensure model robustness and reliability

3D volume/pharmacophore similarity within AP

$$V = \sum_{i,j} p_{ij}\, e^{-k_{ij} R_{ij}^2}$$



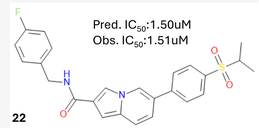
- Various RORγ ligands from crystal structures, both agonists and inverse agonists, were used in their crystal structure pose for 3D volume/pharmacophore similarity optimization within AIDD.
- Shown here is an agonist from PDB:6NWS as well as a 2D representation showing the recognized pharmacophore features. The formula for Gaussian volumetric overlap for similarity scoring is also shown.

About 3D conformer generation and shape matching

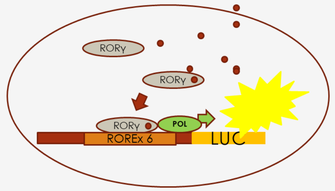
- Fast (GPU enabled), customizable, and accurate conformer generation
  - Generate 3D conformer databases from internal compounds or commercial libraries
- Shape Matching: shape (based on overlap volume) + alignment of pharmacophore features
- Ideal for scaffold hopping and lead expansion, and virtual screening of ultra-large libraries.

NOVEL CLASSES OF RORγ INHIBITORS IDENTIFIED

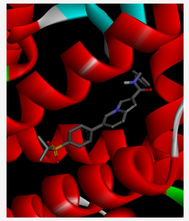
- Multiple AIDD runs were performed with varying parameters; results were combined and AIDD-generated compounds were identified in the Enamine REAL and WuXi GalaXi synthesis-on-demand libraries[5].
- Initial results were used to rebuild QSAR models and a second round of AIDD was performed and compounds identified in synthesis-on-demand libraries.
- In all, 69 molecules were synthesized and tested.



Lead class typified by linear molecules with a terminal sulfone



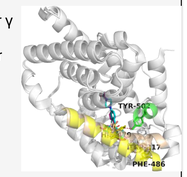
Primary assay: Luciferase activity driven by RORγ response element (RORE)-containing promoter; both in agonist and inverse agonist (inhibitor) modes

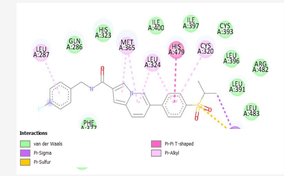


- Of 27 compounds in initial set, 70% demonstrated ≥ 25% luciferase inhibition
- Multiple chemotypes, none of which have > 0.30 Tanimoto similarity to known RORγ ligands
- 2nd round, focusing on lead class, identified 14/19 (74%) active compounds with 4 having improved potency

THE TARGET: RORγ

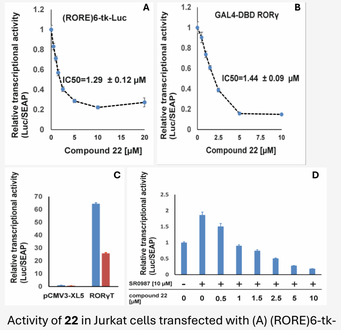
- Retinoic acid receptor-related orphan receptor γ
- γT isoform is the master regulator of Th17 cells[1]
- Inhibitors for autoimmune diseases
- Agonists for ex-vivo activation of CART cells.



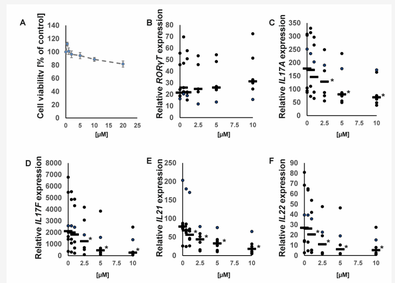


SMINA docking of **22** to RORγ predicts interactions with HIS479 and TRP317, known to be important for activity.

IN VITRO ANALYSIS OF BEST COMPOUND (22) FROM FIRST DMTA CYCLE



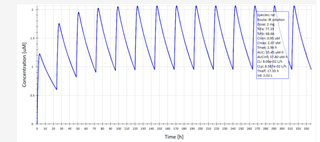
Activity of **22** in Jurkat cells transfected with (A) (RORE)6-tk-Luc ROR reporter plasmid, (B) GAL4-DBD RORγ fusion + UAS-luc, (C) RORγT over-expression plasmid + (RORE)6-tk-Luc, (D) (RORE)6-tk-Luc in the presence of agonist SR0987.



Effect on Th17 cells. CD4+ T cells were isolated from buffy coats and treated to differentiate them into Th17 lymphocytes. Increasing concentrations of **22** did not significantly affect cell viability (A) or RORγT mRNA levels (B) but did reduce the expression of IL17A (C), IL17F (D), IL21 (E), and IL22 (F) compared to controls.

Property	Predicted	Observed
logP	4.99	4.82
Thermodynamic solubility (ug/mL)	0.30	30.6
MDCK A-B (10^{-6} cm/s)	14.87	7.69
MDCK B-A (10^{-6} cm/s)	No model	8.63
Efflux ratio	No model	1.12

Predicted and observed ADME values for **22**



Using HTPK, the optimal dose to reach the IC_{50} (1.5uM) of **22** in rats was calculated and then that dose was used to create a Cp-time curve using once daily oral dosing.

CONCLUSIONS

- AIDD integrates ADMET property prediction, HTPK simulation, QSAR models and 3D shape matching at point of design
- AIDD was used to identify novel RORγ ligands with a >70% hit rate, representing multiple chemotypes, all wholly distinct from known RORγ ligands
- In vitro predictions were mostly accurate for **22** and in silico PK simulations promising, suggesting a great starting point for lead class exploration
- Future Directions:
  - Further exploration of lead class
  - Nuclear receptor selectivity profiling
  - Development of gut restricted inhibitor to treat colitis
  - Development of an agonist to prime ex-vivo T cells

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[5] Bachorz RA, et al,. ACS Med Chem Lett. 2025 Jul 10;16(7):1272-1281. doi: 10.1021/acsmedchemlett.4c00595