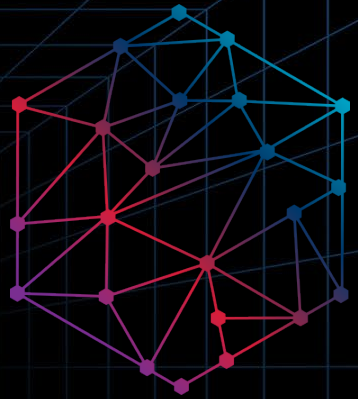
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Designing Novel Compounds with Optimized Target Activity and ADMET Properties Using the AIDD™ Module

Michael S. Lawless, David Miller, and Marvin Waldman

Model-Informed Drug Development
MIDD+
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AIDD Module

Goal – design compounds that have:

- High potency at the primary target
- High synthetic feasibility
- Good ADMET and pharmacokinetic (PK) properties

AIDD Workflow

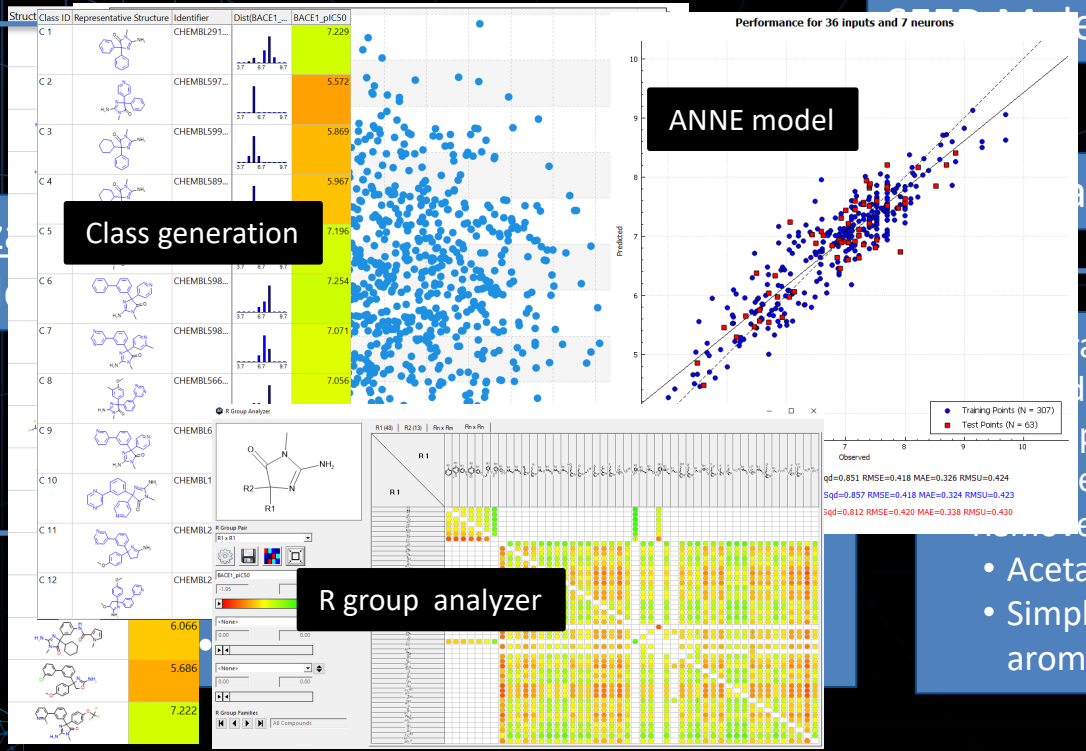
Data Set
- Target Activity

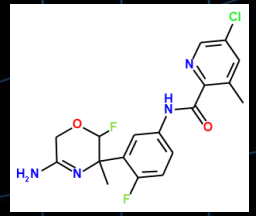
SAR/QSAR

ecule(s)

ndidates

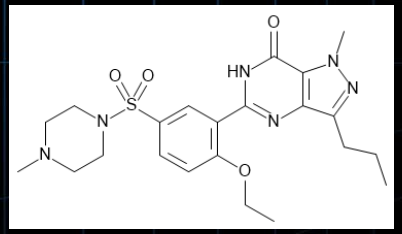
Optimiz
- Pareto sel





ansformations to randomly-
d compounds from the
population
equired substructure
e non-druglike
- Acetals, Michael acceptors
- Simple properties, e.g., ≤ 4 aromatic rings

Generate Molecules Using Transform Rules

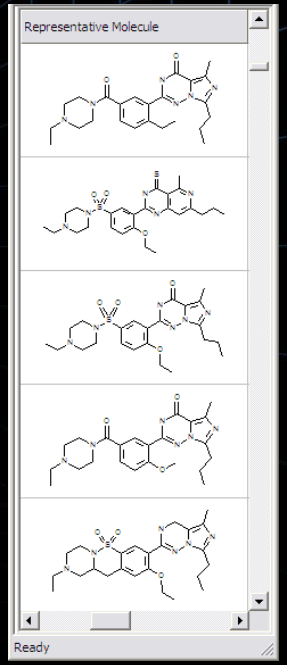


SMIRKS Transforms

- Bioisosteric replacements
- Reactions from literature or in-house expertise
- Chemically-intelligent "mutations"

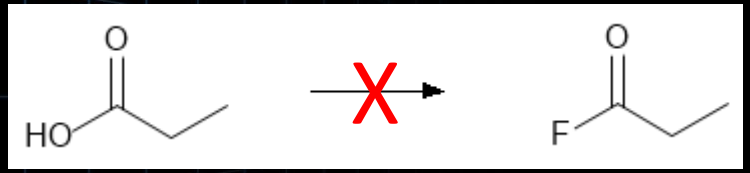
Users can modify the default rules

Generated analogs



Chemically Intelligent Transforms

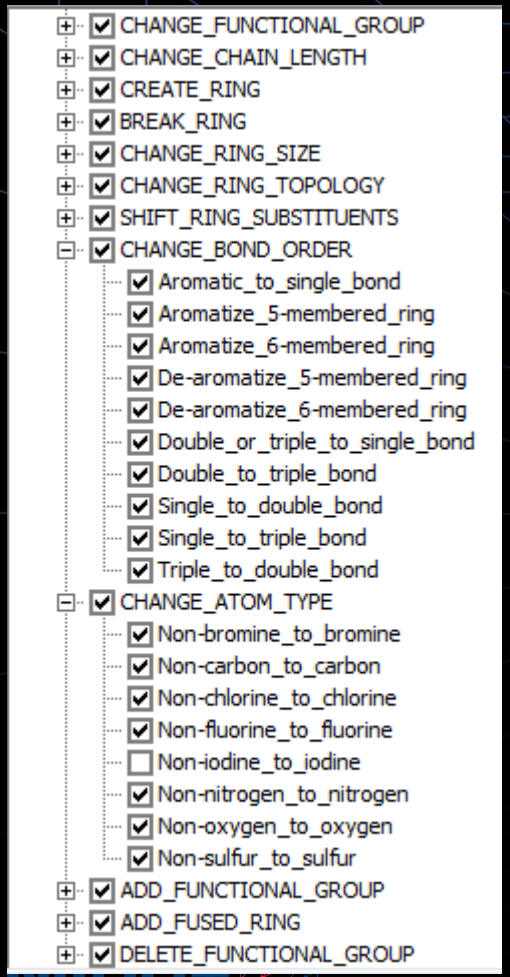
- Example: Convert Non-fluorine to fluorine
  - Simple version: [!#9:1;D1_S]>>[#9:1]
  - Problem (Need to avoid)

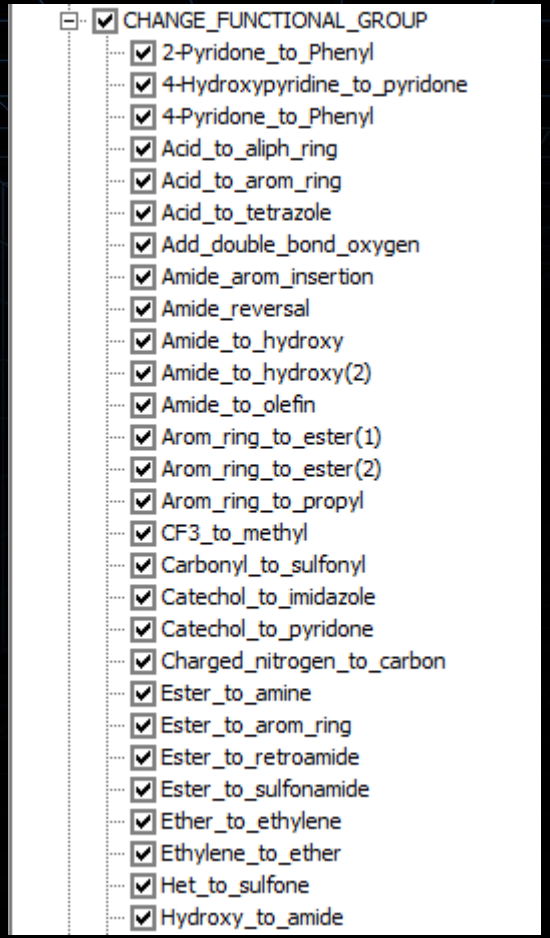


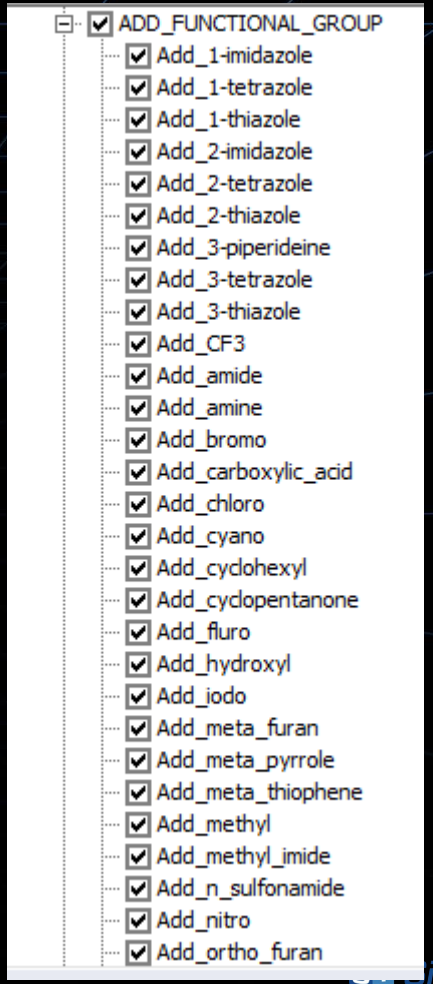
Highly reactive acid halide

  - Improved SMIRKS: [!#9;D1_S$(*~[#6])!$(*C=[O,N,S]):1]>>[#9:1]
  - Currently ~150 transforms

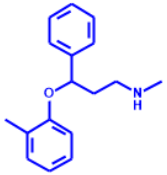
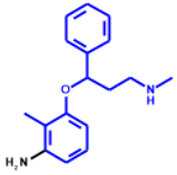
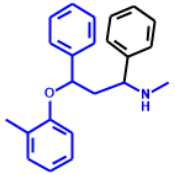
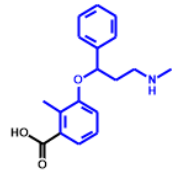
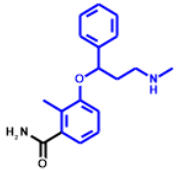
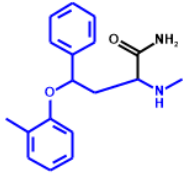
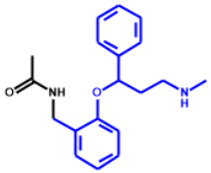
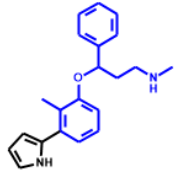
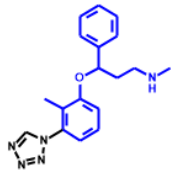
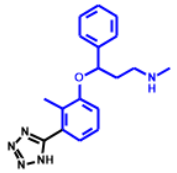
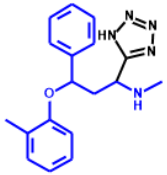
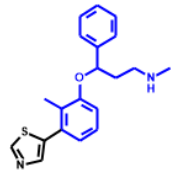
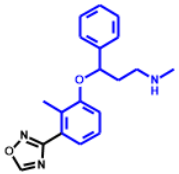
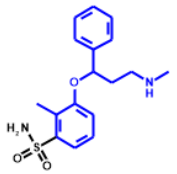
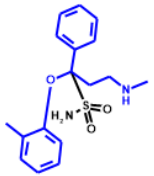
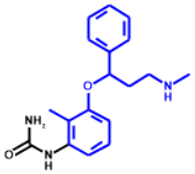
Transforms


CHANGE_FUNCTIONAL_GROUP
CHANGE_CHAIN_LENGTH
CREATE_RING
BREAK_RING
CHANGE_RING_SIZE
CHANGE_RING_TOPOLOGY
SHIFT_RING_SUBSTITUENTS
CHANGE_BOND_ORDER
Aromatic_to_single_bond
Aromatize_5-membered_ring
Aromatize_6-membered_ring
De-aromatize_5-membered_ring
De-aromatize_6-membered_ring
Double_or_triple_to_single_bond
Double_to_triple_bond
Single_to_double_bond
Single_to_triple_bond
Triple_to_double_bond
CHANGE_ATOM_TYPE
Non-bromine_to_bromine
Non-carbon_to_carbon
Non-chlorine_to_chlorine
Non-fluorine_to_fluorine
Non-iodine_to_iodine
Non-nitrogen_to_nitrogen
Non-oxygen_to_oxygen
Non-sulfur_to_sulfur
ADD_FUNCTIONAL_GROUP
ADD_FUSED_RING
DELETE_FUNCTIONAL_GROUP


CHANGE_FUNCTIONAL_GROUP
2-Pyridone_to_Phenyl
4-Hydroxypyridine_to_pyridone
4-Pyridone_to_Phenyl
Acid_to_aliph_ring
Acid_to_arom_ring
Acid_to_tetrazole
Add_double_bond_oxygen
Amide_arom_insertion
Amide_reversal
Amide_to_hydroxy
Amide_to_hydroxy(2)
Amide_to_olefin
Arom_ring_to_ester(1)
Arom_ring_to_ester(2)
Arom_ring_to_propyl
CF3_to_methyl
Carbonyl_to_sulfonyl
Catechol_to_imidazole
Catechol_to_pyridone
Charged_nitrogen_to_carbon
Ester_to_amine
Ester_to_arom_ring
Ester_to_retroamide
Ester_to_sulfonamide
Ether_to_ethylene
Ethylene_to_ether
Het_to_sulfone
Hydroxy_to_amide


ADD_FUNCTIONAL_GROUP
Add_1-imidazole
Add_1-tetrazole
Add_1-thiazole
Add_2-imidazole
Add_2-tetrazole
Add_2-thiazole
Add_3-piperideine
Add_3-tetrazole
Add_3-thiazole
Add_CF3
Add_amide
Add_amine
Add_bromo
Add_carboxylic_acid
Add_chloro
Add_cyano
Add_cyclohexyl
Add_cyclopentanone
Add_fluro
Add_hydroxyl
Add_iodo
Add_meta_furan
Add_meta_pyrrole
Add_meta_thiophene
Add_methyl
Add_methyl_imide
Add_n_sulfonamide
Add_nitro
Add_ortho_furan

- Starting structure is atomoxetine
- Use transformations from "ADD_FUNCTIONAL_GROUP"
- Creates 403 compounds
- A few diverse compounds are shown on the right

atomoxetine	CombiTrans_24	CombiTrans_73	CombiTrans_76
			
CombiTrans_88	CombiTrans_98	CombiTrans_104	CombiTrans_149
			
CombiTrans_197	CombiTrans_209	CombiTrans_219	CombiTrans_309
			
CombiTrans_369	CombiTrans_381	CombiTrans_386	CombiTrans_393
			

Synthetic Feasibility Assessment

Based on method from Ertl and Shuffenhauer, *J. Cheminfo,* **2009**, 1, 8.

Score = fragmentScore – complexityPenalty

Fragment frequencies

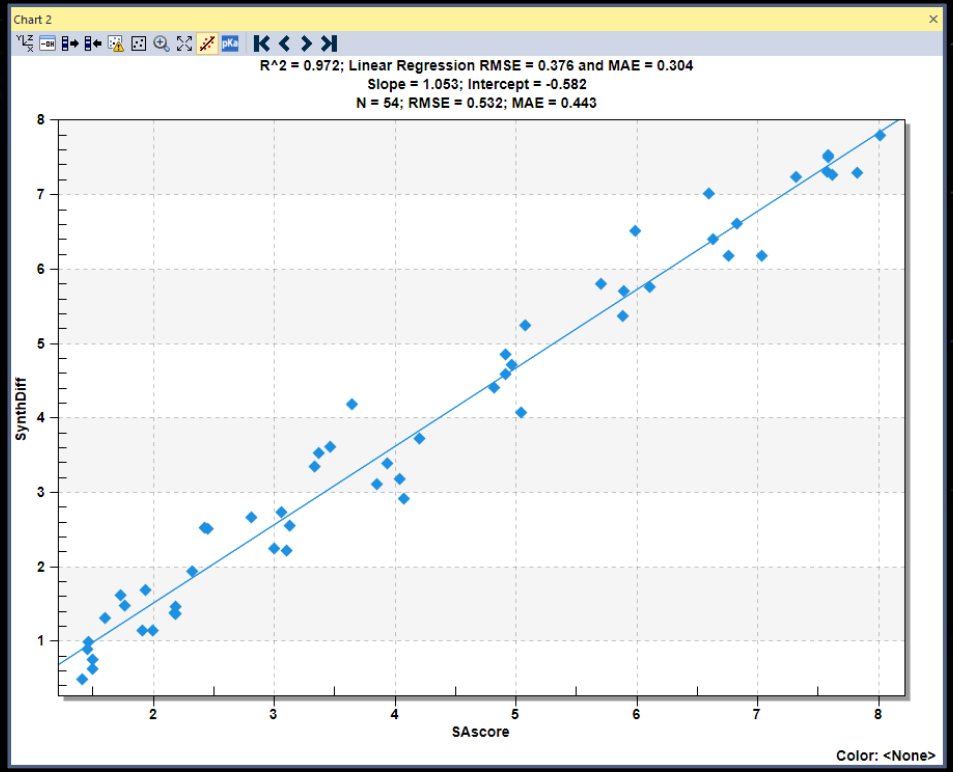
- ECFP of PubChem compounds
- Does the proposed compound contain fragments of compounds that have been synthesized?

Heavy Atoms
Macrocycles
Stereocenters
Spiro centers
Bridges

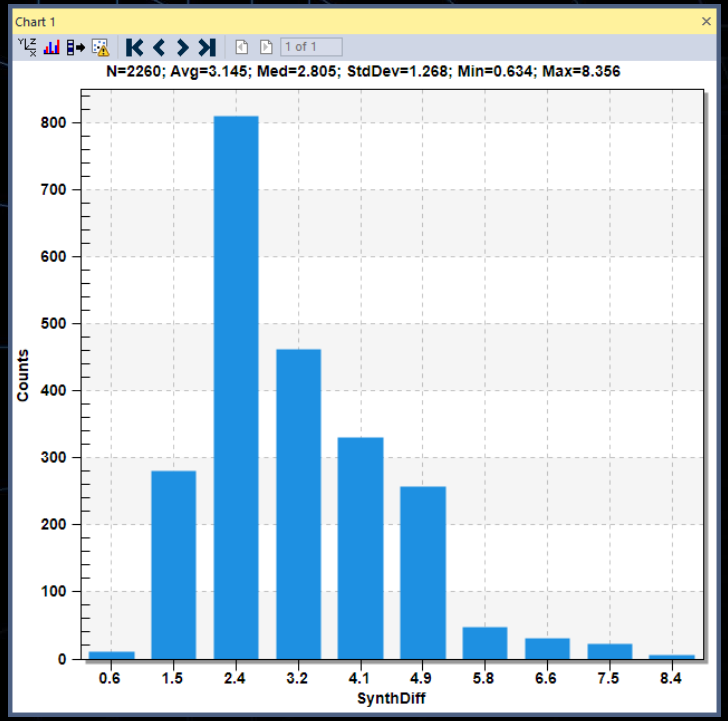
Synthetic Accessibility/Difficulty

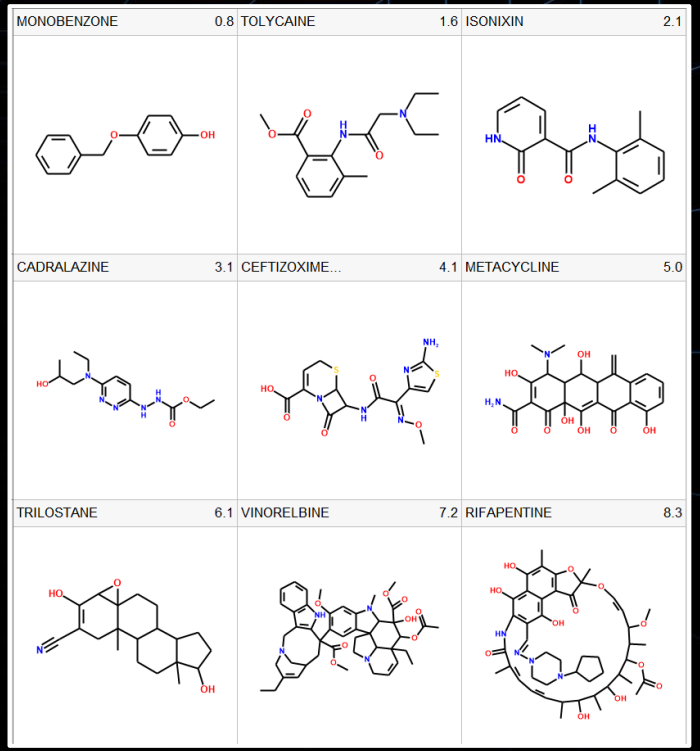
	SA Ertl[1]	SynthDiff[2]
Training	~1 million	~47 million
Outer Layer	Any	aromatic vs. aliphatic
Complexity	Same	Same
Range	1-10	0-10

[1]Ertl and Shuffenhauer, *J. Cheminfo,* **2009**, **1,** 8.
[2]Implemented in ADMET Predictor



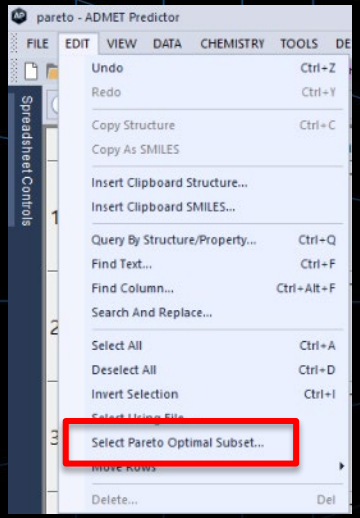
Distribution of SynthDiff Scores

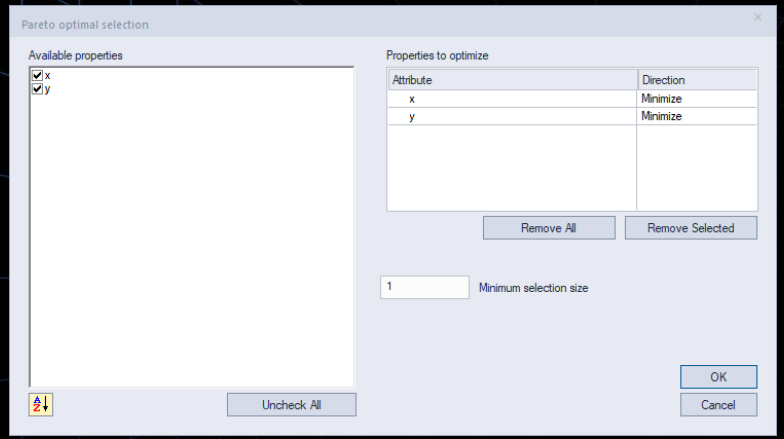


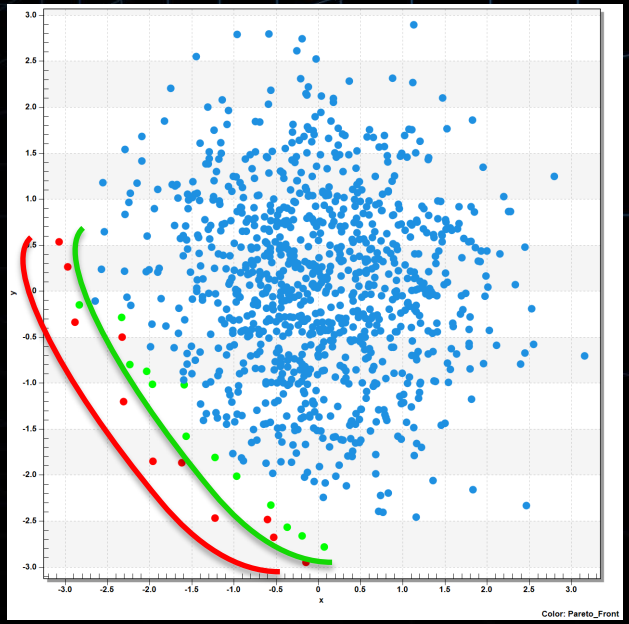


Pareto Optimal Selection

- AIDD Module uses Pareto algorithm to select best molecules
- Pareto selection tool is also available in ADMET Predictor



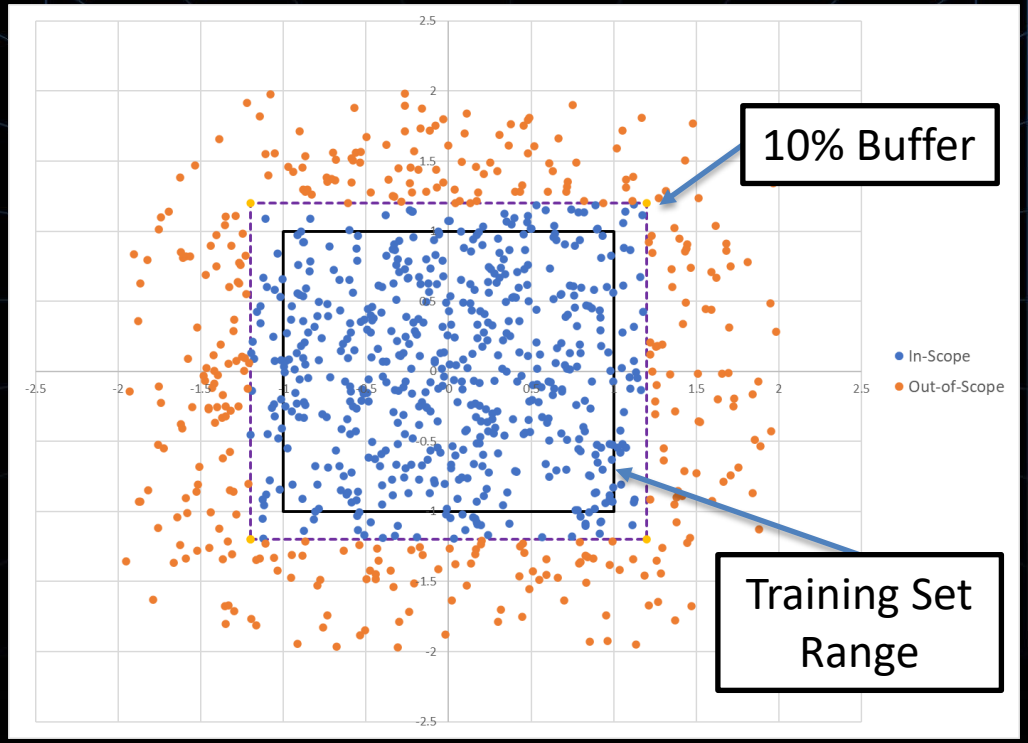




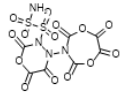
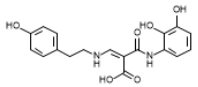
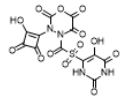
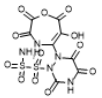
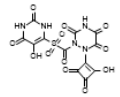
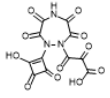
- Red points – 1st Pareto front
- Green points – 2nd Pareto front

Applicability Domain

Apply penalty to predictions that are outside the scope of the model

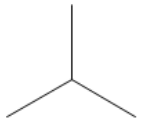
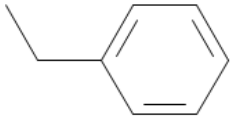


After Applying “Penalties”

	Structure	OBJ_HIVI-ST	ADMET_Risk	SynthDiff	HIVI-ST	HIVI-ST+	ADMET_Risk+	SynthDiff+
1		12.799	3.000	4.256	12.799	2.799	14.000	8.253
2		6.525	3.956	2.313	6.525	-3.475	11.956	6.312
3		12.248	3.500	4.181	12.248	2.248	13.500	7.897
4		12.163	6.000	4.132	12.163	2.163	15.000	7.848
5		11.952	4.000	4.082	11.952	1.952	15.000	6.848
6		11.051	1.694	3.674	11.051	1.051	13.404	7.674

The out of scope penalty results in deprioritization of molecules that are outside the applicability domain of the model.

Flip Side of the Coin: Capping Values

	Structure	OBJ_HIVI-ST	ADMET_Risk	SynthDiff
1		3.645	1.000	0.000
2		3.676	1.000	0.000
3		3.846	1.000	0.000
4		3.506	0.431	0.131
5		3.173	1.000	0.243
6		3.250	1.000	0.384

Properties to optimize

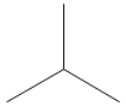
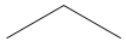
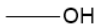
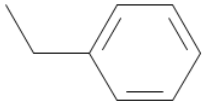
Name	Direction	Capping Value
<Synthetic_Difficulty+>	Minimize	2.5
ADMET_Risk	Minimize	
<Fraction bioavailable (%Fb)>	Maximize	90

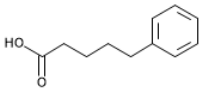
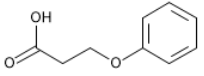
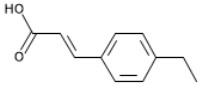
Modify Selected | Remove Selected | Remove All

Trivially Simple Molecules:
Very easy to make
Very good in one objective

Assigning a capping value tends to filter out such molecules.
The capping value is assigned as the result when the actual result is “better”, because this value is “good enough”.

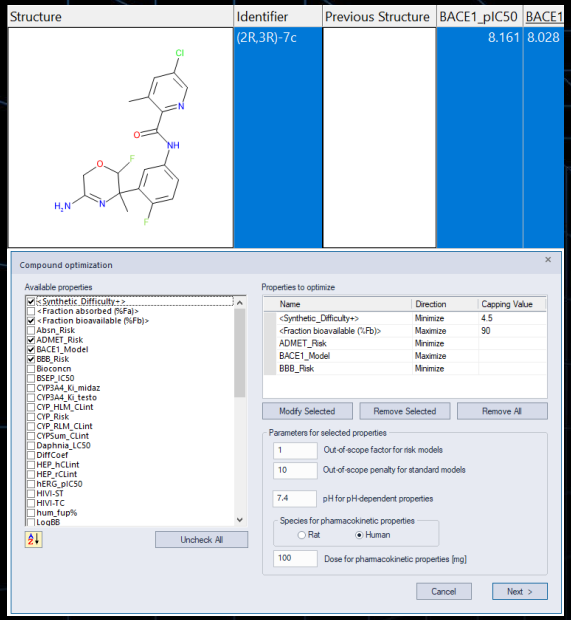
Applying Capping Values: Example

	Structure	OBJ_HIVI-ST	ADMET_Risk	SynthDiffCap
1		3.645	1.000	2.500
2		3.676	1.000	2.500
3		3.846	1.000	2.500
4		3.506	0.431	2.500
5		3.173	1.000	2.500
6		3.250	1.000	2.500

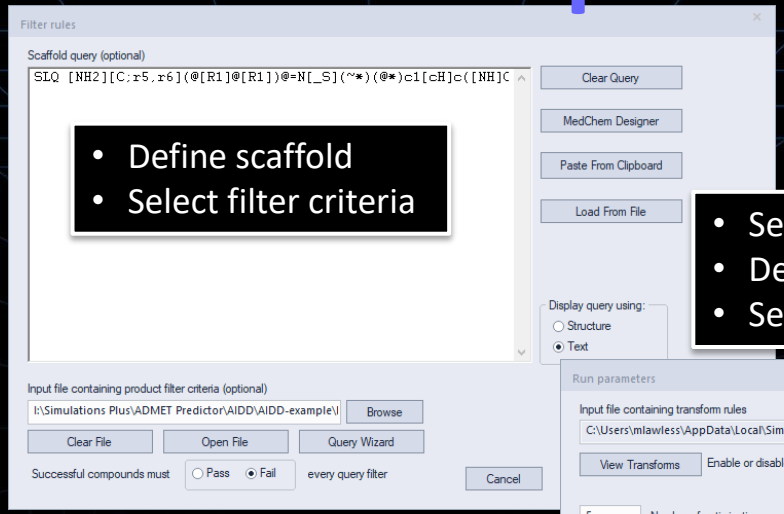
	Structure	OBJ_HIVI-ST	ADMET_Risk	SynthDiff+	SynthDiffCap
1		4.524	0.000	1.880	2.500
2		4.228	0.000	1.907	2.500
3		4.701	0.000	2.356	2.500

Molecules on right “dominate” molecules on left after applying capping to SynthDiff

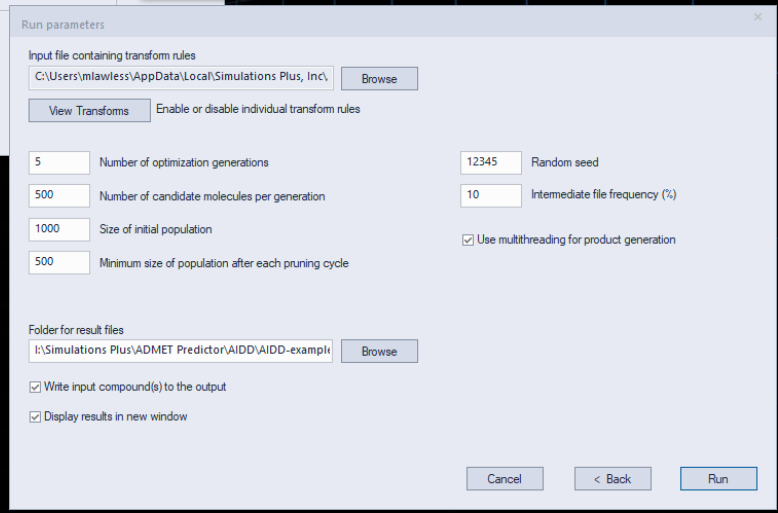
AIDD Setup



- Select seed molecule(s)
- Select properties to optimize
- Define capping values

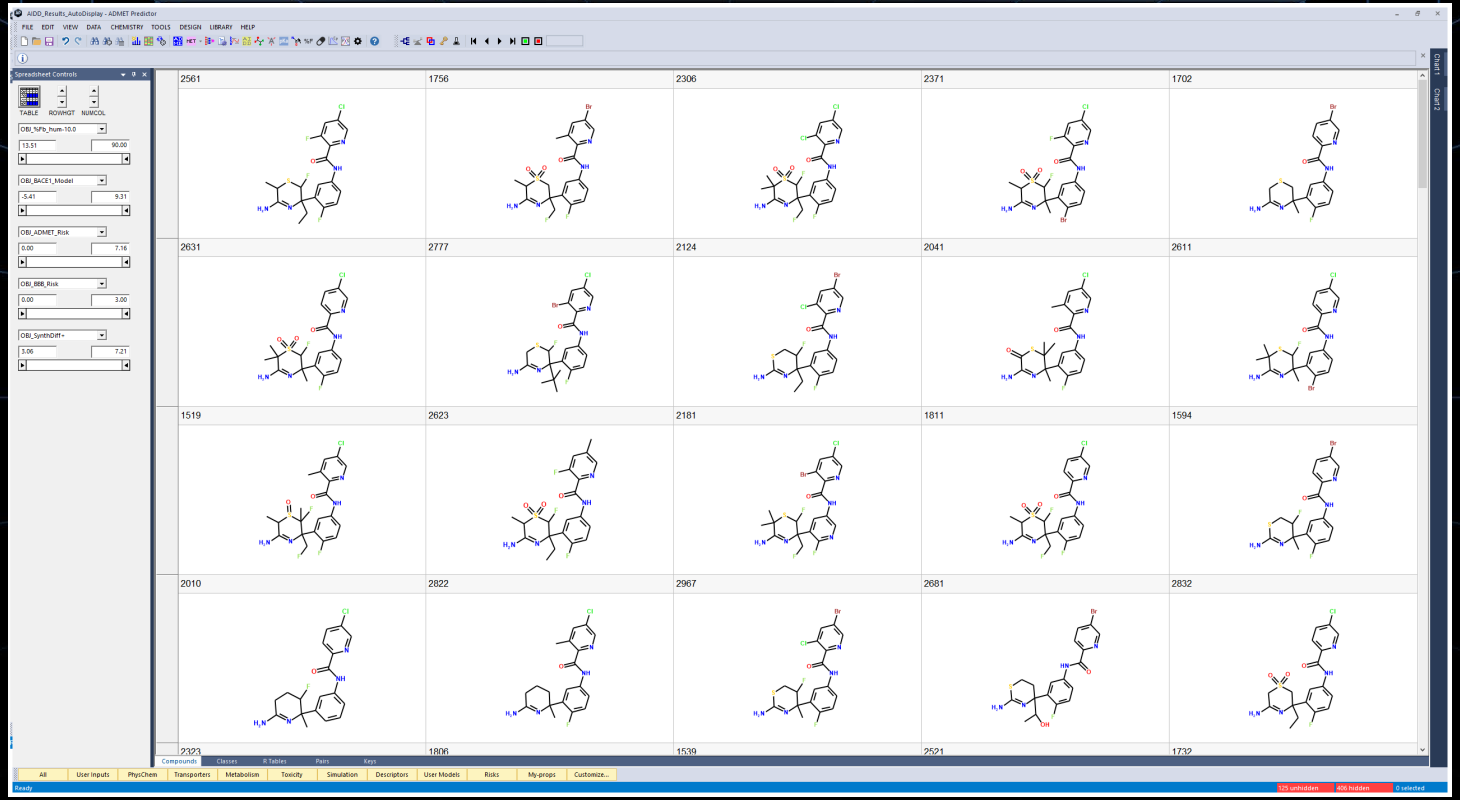


- Define scaffold
- Select filter criteria



- Select transform rules
- Define no. of optimization cycles
- Select output folder

A Few Results



AIDD Module

Goal – design compounds that have:

- High activity based on a QSAR model
  - Penalizes out of scope predictions
- High synthetic feasibility
  - Based on fragment counts of PubChem compounds
- Good ADMET and PK properties
  - Incorporates absorption, CYP metabolism, toxicity, and oral bioavailability

Q&A

Questions & Answers

Model-Informed Drug Development

MIDD+

2021 Virtual Conference

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