Using AI-driven Drug Design to Shorten Your Drug Development Process

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Overview

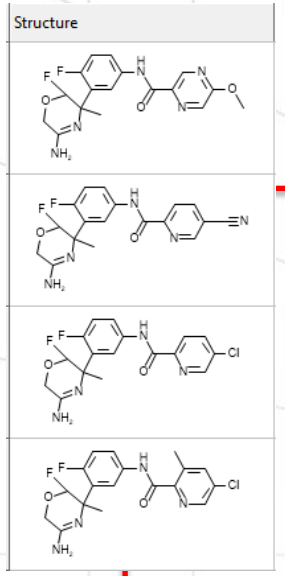
- How our AI-driven Drug Design module works
- Example internal project: PPARγ inhibitors
- Early Drug Discovery Partnerships

De novo drug design at SLP

- Simulations Plus (SLP) is well known for our user-friendly software and providing expert consulting to support drug discovery, clinical development research, and regulatory submissions.
  - GastroPlus®: Our mechanistically based simulation software package that simulates IV, oral, ocular, inhalation, dermal, subQ, and IM absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals.
  - ADMET Predictor®: Our flagship machine learning platform for ADMET modeling and property estimation. It is also the home of the AI-driven drug design (AIDD) module.

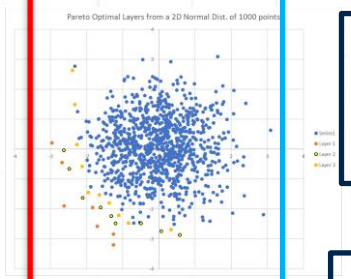
- The AIDD module integrates the predictions from AP and GastroPlus into the generative chemistry process.
  - These best-in-the-industry predictions set us apart from other de novo design platforms
  - Useful for hit discovery, hit-to-lead, and lead optimization projects

Automating the de novo drug design process: AIDD



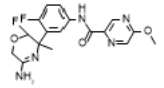
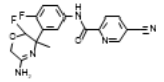
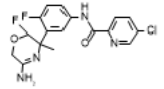
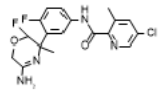
Initialize with K randomly generated analogs using chemical transforms starting from initial seed molecules

Evaluate properties:
ADMET_Risk
SynthDiff
Activity(s)
HT-PK
3D shape matching



Prune molecules using Pareto optimal layers

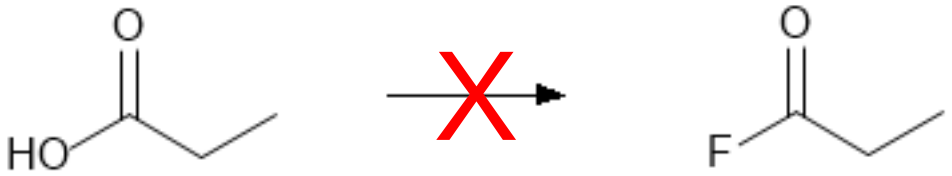
Generate M more analogs using chemical transforms and randomly selected molecules from current population

Structure	ADMET_Risk	S+logP	S+logD	S+Peff	S+Sw
	0.961	2.309	2.272	2.231	0.349
	0.930	2.705	2.667	2.687	0.023
	1.558	3.569	3.533	3.379	0.026
	1.110	3.793	3.748	3.462	0.022

Repeat N times

Generating Analogs

- Uses a library of chemically “intelligent” SMIRKS transforms
  - Example: Non-fluorine_to_fluorine
    - Simple version: [!#9:1]>>[#9:1]
    - Problem (Need to avoid)



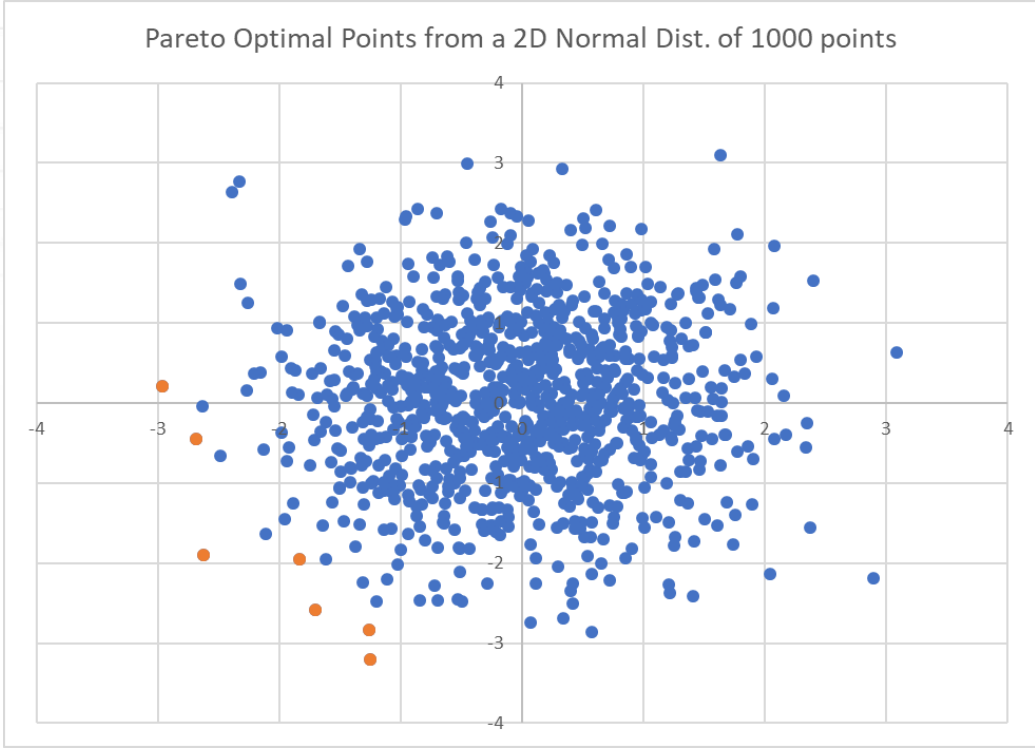
Highly reactive acid halide

    - Improved SMIRKS: [!#9;D1_S$(*~[#6])!$(*C=[O,N,S]):1]>>[#9:1]
    - Currently ~200 transforms

https://www.simulations-plus.com/resource/delivering-on-the-promise-of-ai-driven-drug-discovery-with-admet-predictor-10-apx-background-and-applications-examples/

Multi-parameter optimization

- Based on Pareto front calculations
  - 1000 normally distributed points
    - 2-dim: 7 Pareto optimal points
    - 5-dim: ~100 Pareto optimal points



- Typically optimize using 4-5 parameters
  - Typical parameters:
    - Activity (QSAR model)
    - Docking Score
    - ADMET Risk
    - Synthetic Accessibility
    - HT-PK
    - 3D shape matching

ADMET Risk™

Identifier	Weight	Rule logic
Size	1.0	MWt > 450{500} OR N_Atoms > 30{35} OR MolVol > 470{520} OR N_Bonds > 35{40}
RotB	1.0	N_FrRotB > 8{10}
HBD	1.0	HBDH > 3{5} AND HBDch > 1.5{2.0}
HBA	1.0	HBA > 7{10} AND HBAch < -6.0{-5.0}
ch	1.0	NPA_ABSQ > 19{21} OR T_PSA > 120{140}
Kow	1.0	S+logP > 4.5{5.0} OR S+logD > 3.5{4.0} OR MlogP > 3.5{4.0}
Peff	1.0	S+Peff < 0.40{0.60} OR S+MDCK < 10{25}
Sw	1.0	S+Sw < 0.005{0.010}
fu	1.0	hum_fup% < 4{6}
Vd	1.0	Vd > 4{5}
hERG	1.0	hERG_Filter = Yes AND hERG_pIC50 > 5.5{6.0}
rat	1.0	Rat_Acute < 200{300}
Xr	1.0	Rat_TD50 < 2.5{5.0}
Xm	1.0	Mouse_TD50 < 25{40}
HEPX	1.0	Ser_AST = Elevated AND Ser_ALT = Elevated AND Ser_LDH = Elevated
MUT	1.0	MUT_Risk > 1
1A2	1.0	(CYP1A2_CLint > 20{40} AND CYP1A2_Substr = Yes)
2C9	1.0	(CYP2C9_CLint > 10{20} AND CYP2C9_Substr = Yes)
2C19	1.0	(CYP2C19_CLint > 10{20} AND CYP2C19_Substr = Yes)
2D6	1.0	(CYP2D6_CLint > 10{20} AND CYP2D6_Substr = Yes)
3A4	1.0	(CYP3A4_CLint > 20{50} AND CYP3A4_HLM_CLint > 30{75} AND CYP3A4_Substr = Yes)
CL	1.0	CYP_HLM_CLint > 90{150} OR HEP_hCLint > 60{90}

Absorption

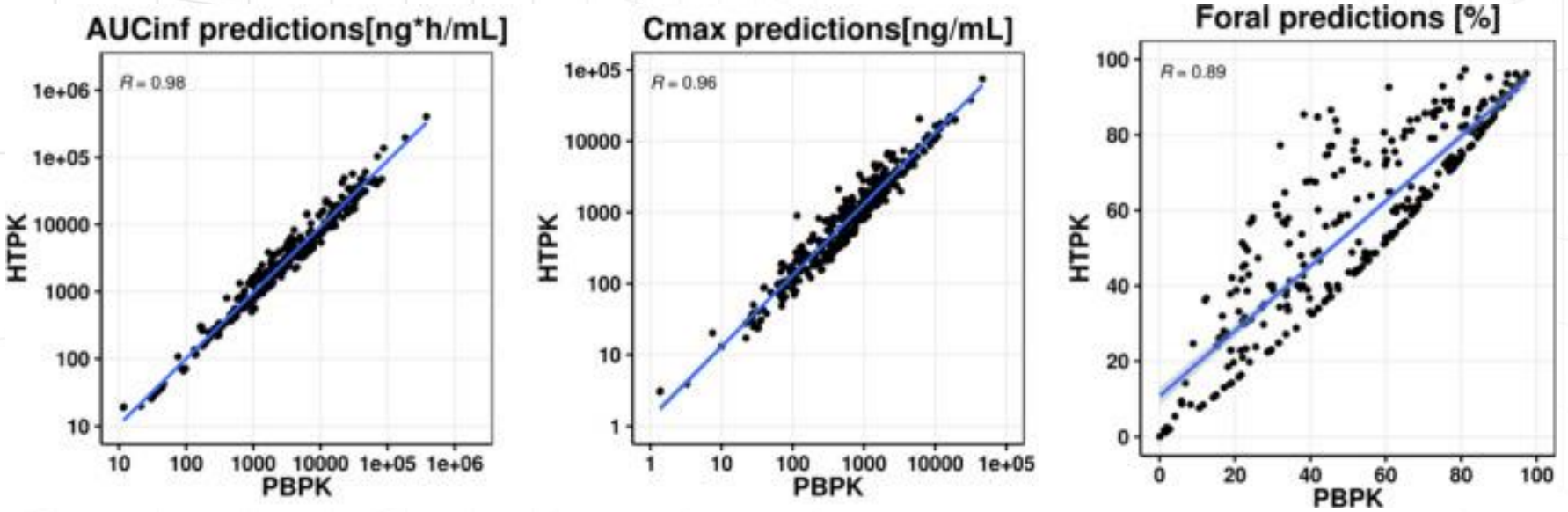
Distribution

Toxicity

Metabolism

High-Throughput Physiologically Based Pharmacokinetic (HT-PBPK) Predictions

- The algorithm uses our top-rated Advanced Compartmental Absorption and Transit (ACAT™) model from GastroPlus to simulate dissolution, transit, and absorption in the GI tract.
- In a real-world trial, the HT-PBPK approach produced comparable results to the full PBPK modeling approach for a range of molecules, but reduced the simulation time from hours to seconds



Pure *in silico* simulation
No exptl properties required
Extremely rapid, multi-threaded

Scatter plots comparing AUC_{inf}, C_{max}, and F_{oral} predictions of the back-calculated clearance scaling method using the PBPK module (*x*-axis) vs the HTPK module (*y*-axis). Blue solid line and shaded gray area represent the linear regression and its 95% confidence interval, respectively.

Mol Pharm. 2022 Jul 4; 19(7): 2203–2216.

3D Shape Matching

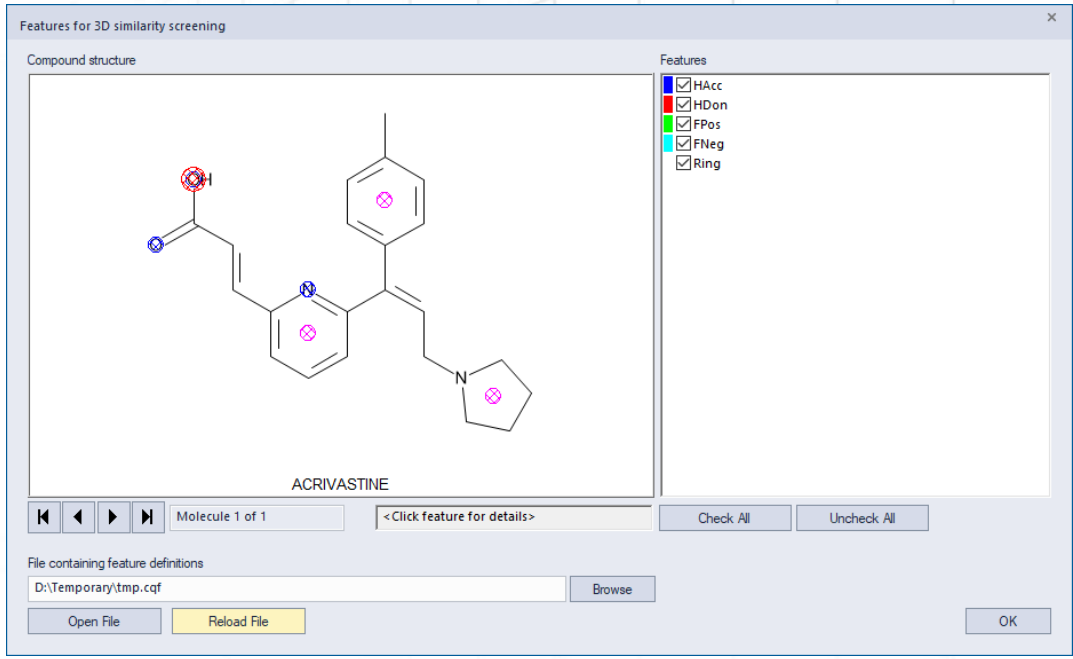
- Generates 100 conformations of each molecule produced in AIDD and compares to reference ligand structure (X-ray or model)
  - Can also screen a virtual 3D database instead of AIDD

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

- Similarity scores consist of a shape term based on overlap volume and (optionally) a feature term based on the alignment of pharmacophore features; users can adjust the relative importance of the two terms

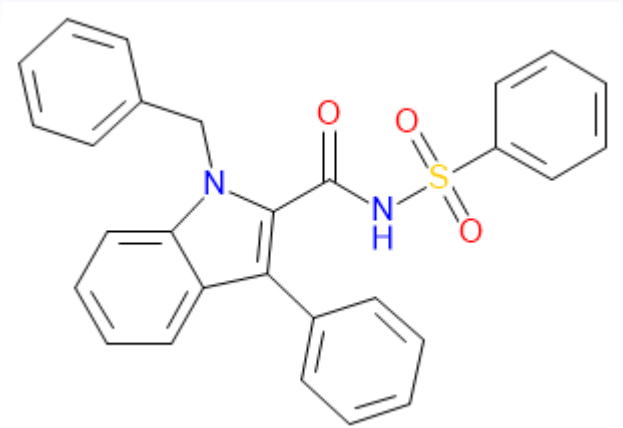
- Overlap volumes are computed using atom-centered gaussian functions; these allow fast computation and are convenient for gradient based optimization

- For each database conformer and each of several starting alignments, BFGS optimization is used to find the alignment maximizing the similarity score

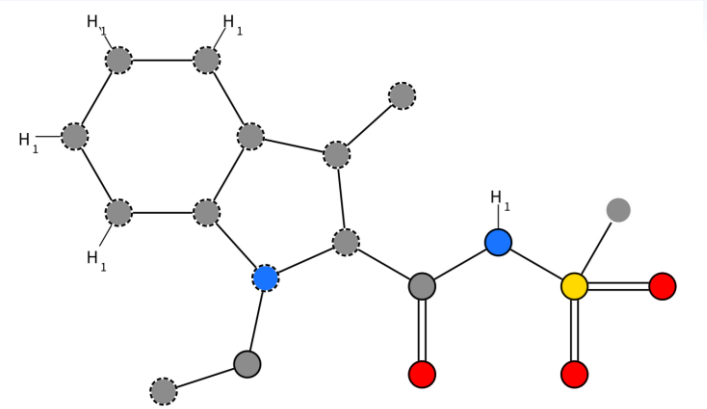


Features can be modified and visualized

Demonstration Time!



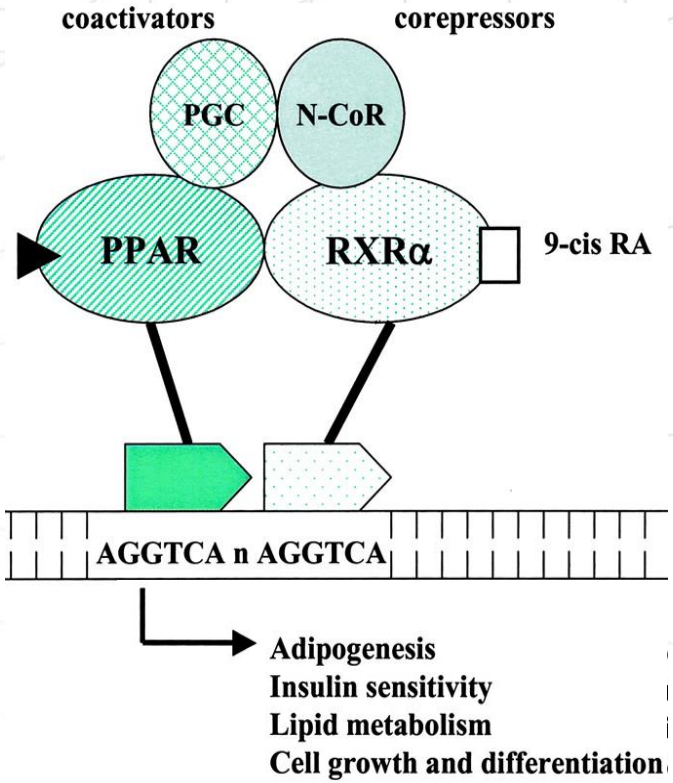
Seed



Query Scaffold

Using AIDD to design PPARγ inhibitors

- Background:
  - Peroxisome proliferator activated receptor gamma (PPARγ) is a member of the Nuclear Receptor class of transcription factors.
  - Best known for regulating fatty acid metabolism, adipocyte differentiation, and inflammatory responses.
    - PPARγ agonists (glitazones) have been used to treat Type II diabetes
  - Recently identified as an oncogene in bladder cancer.
    - 20-30% of advanced bladder cancers have PPARγ pathway alterations
    - PPARγ inhibitors may be useful in treating advanced cancers.



- Goal: Design high potency inhibitors with good ADMET/PK properties

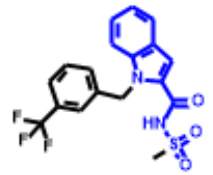
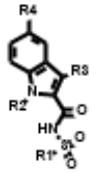
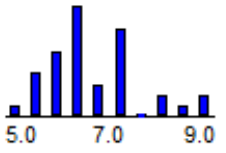
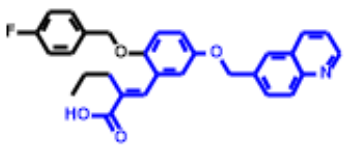
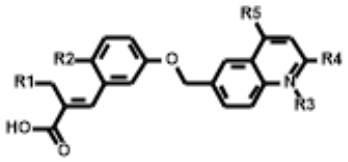
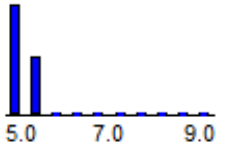
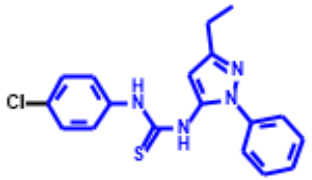
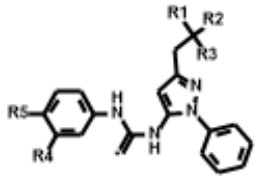
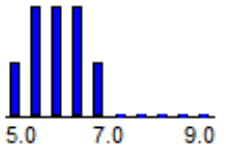
- Hoping you'll see how easy this software is to use as a tool to guide the drug design process

Project Goals and Strategy

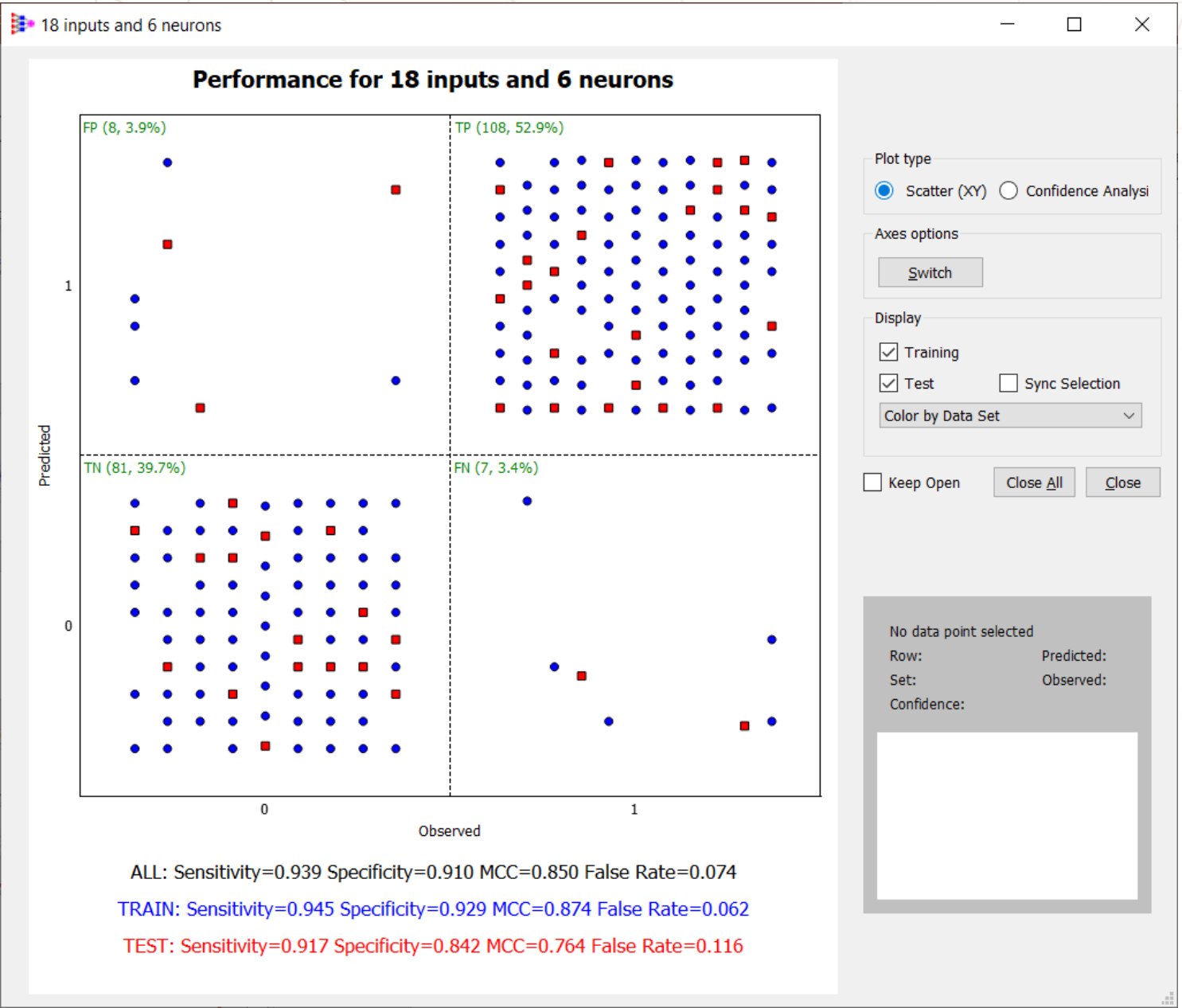
- Goals:
  - Design high potency inhibitors with good ADMET/PK properties
  - Pareto optimize: Activity (pIC_{50}), ADMET risk, %Fb, SynDiff, 3D shape matching
- Strategy:
  - First build QSAR models to predict activity using ADMET Modeler
    - Identify useful data: ensure all data come from similar assays and that benchmark compounds have similar values
    - Use classification model as determining descriptor for regression model
  - Try several AIDD approaches
    - Modify side chains from best class (indole sulfonamides)
    - Scaffold hopping (hold 3 best side chains constant and replace the core)
    - 3D shape matching
  - Compile best compounds from various runs and select compounds to synthesize & test
    - Generate classes, assess additional drug-like properties, determine novelty and commercial availability
    - Rank with a multi-criteria decision tool

PPARγ inhibitor dataset

- Classification model (Yes/No)
  - 210 (127 mine) data points with categorical data (inhibit PPARγ activity <> 10uM)
  - 90 (43%) neg, 120 (57%) pos
- Regression model (predict IC_{50})
  - 113 (62 mine) data points with reliable IC_{50} data
- Dominated by 2-3 classes
  - Indole sulfonamides (ours), Quinoline ether (lit), (thio)urea (ours)

Representative Structure	Identifier	R Tables	Class Size	Dist(PPARG_pIC...
	4j		37	
	CHEMBL4440578		20	
	B166		8	

Classification model



Using ADMET Modeler, I built many ANNE models using random stratified sampling to divide the data and tested reproducibility with random seeds. The best model was chosen for its high sensitivity and specificity in both the training and test sets.

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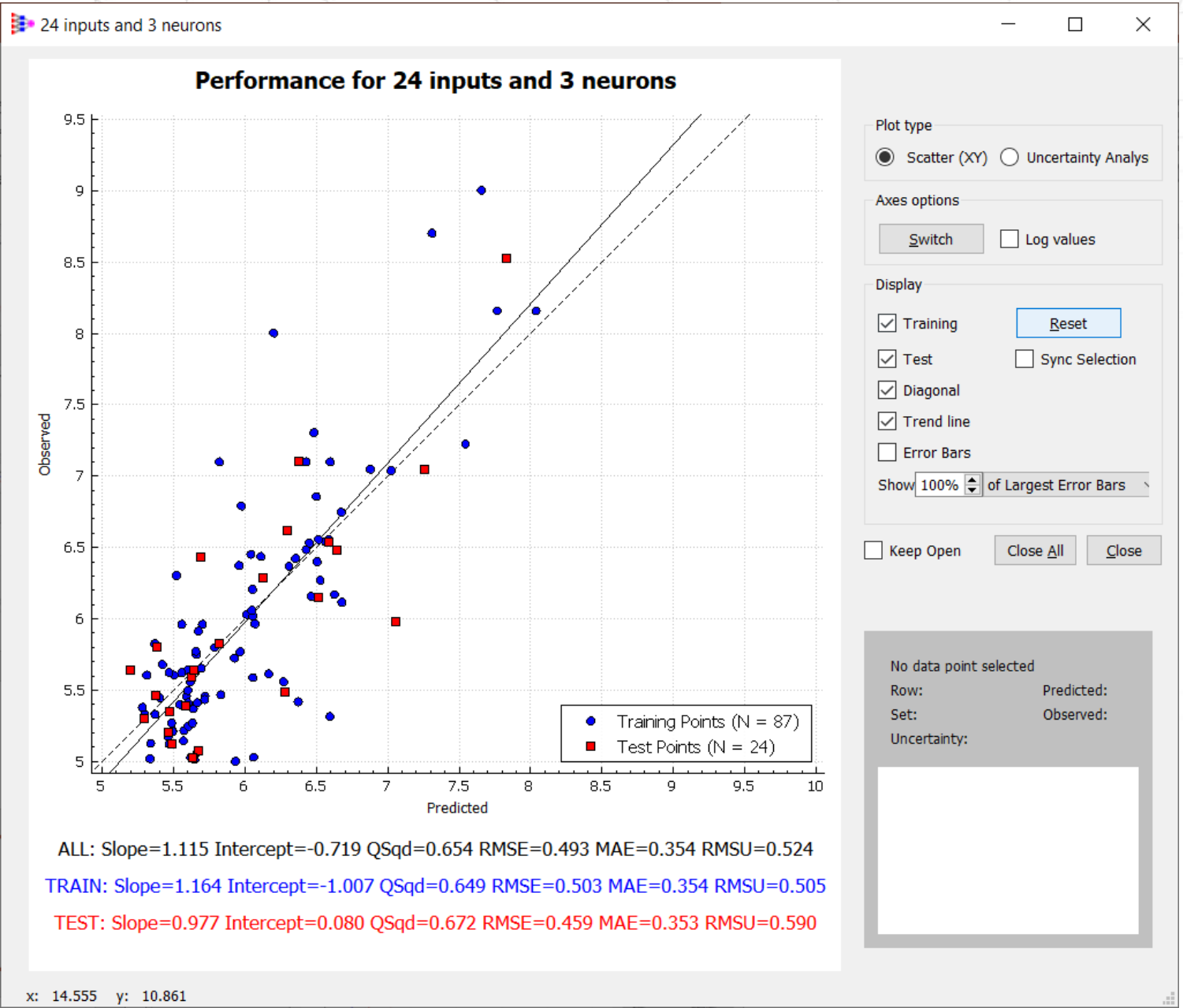
Regression Model



Using ADMET Modeler, I built many ANNE models using random stratified sampling to divide the data and tested reproducibility with random seeds. The best model was chosen for its high r^2 and low RMSE scores in both the training and test sets.

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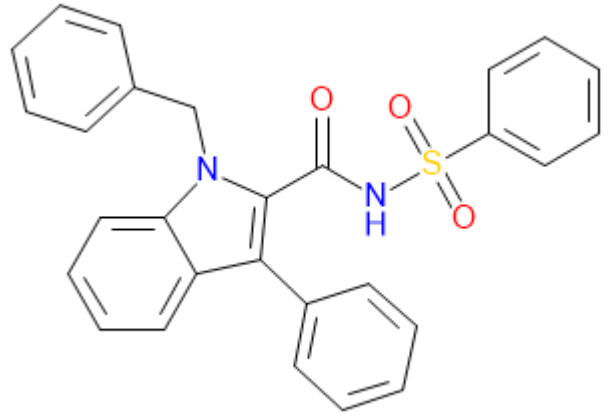
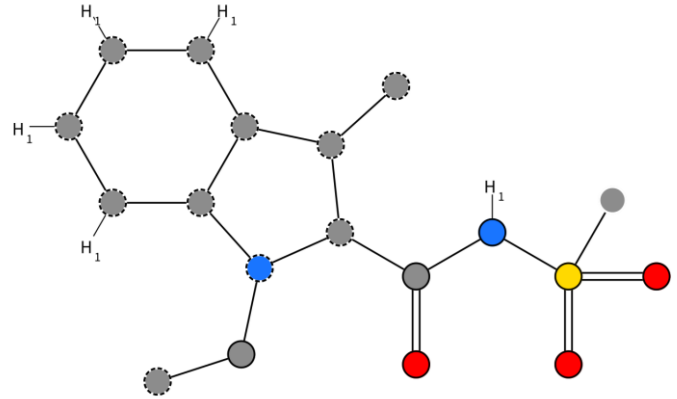
Time to Design Some Molecules!

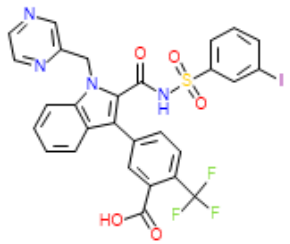
- Goals:
  - In general, derive novel, high potency inhibitors with good ADMET/PK properties
  - Pareto optimize: Activity (pIC_{50}), ADMET risk, %Fb, SynDiff, 3D shape matching
- Strategy: Try several AIDD approaches
  - Modify side chains from best class (indole sulfonamides)
  - Scaffold hopping (hold 3 best side chains constant and replace the core)
  - 3D shape matching
- Typical settings for builds:
  - 50 generations, 25 molecules/gen, except 1st gen = 50, 100 min size; pare down to best with filters

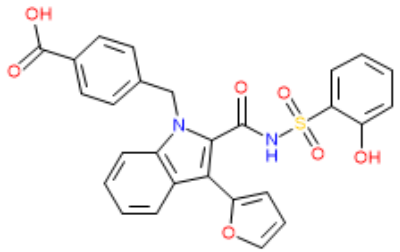
Strategy 1: Directed side chain optimization

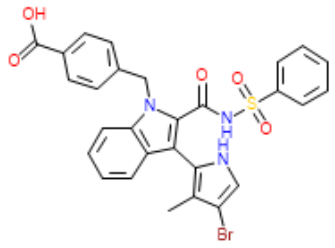


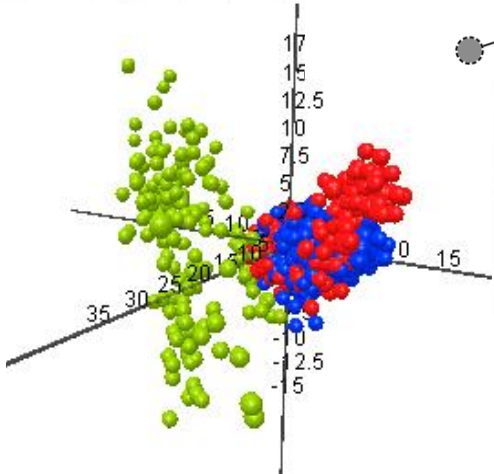
- Seed molecule: core scaffold of sulfonamide + aromatic substituted indole
- Query: Scaffold that forces aromatic substitutions on the indole N (with 1 C linker) and C2, allows any C substitution on sulfur
- Optimization Parameters:
  - ADMET risk (0.9), %Fb (95%), syn diff (2.5), S+Sw (10), PPARGi_pIC$_{50}$ (9.5)
- Results:
  - Variety of new side chains
  - Perform additional AIDD rounds with best molecules from this run
  - Use Principal Component Analysis to examine change in chemical space
  - AIDD generated novel compounds (blue, red) compared to compounds used to construct the QSAR model (green)











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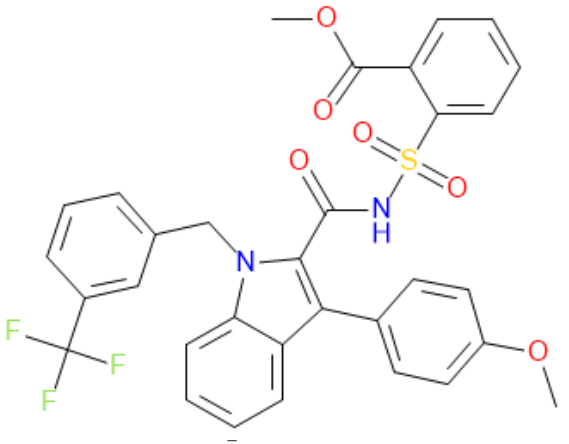
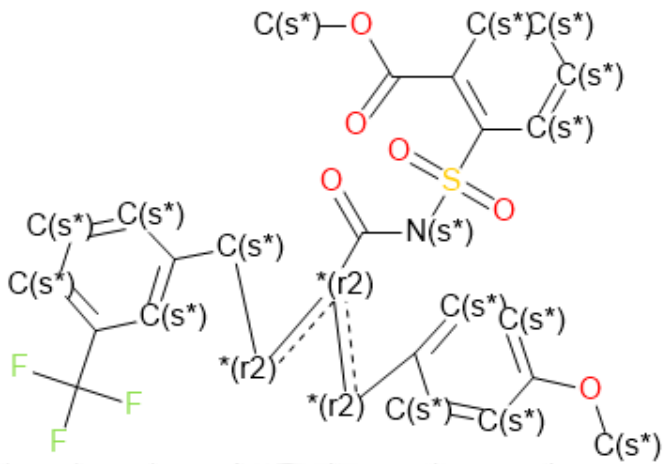
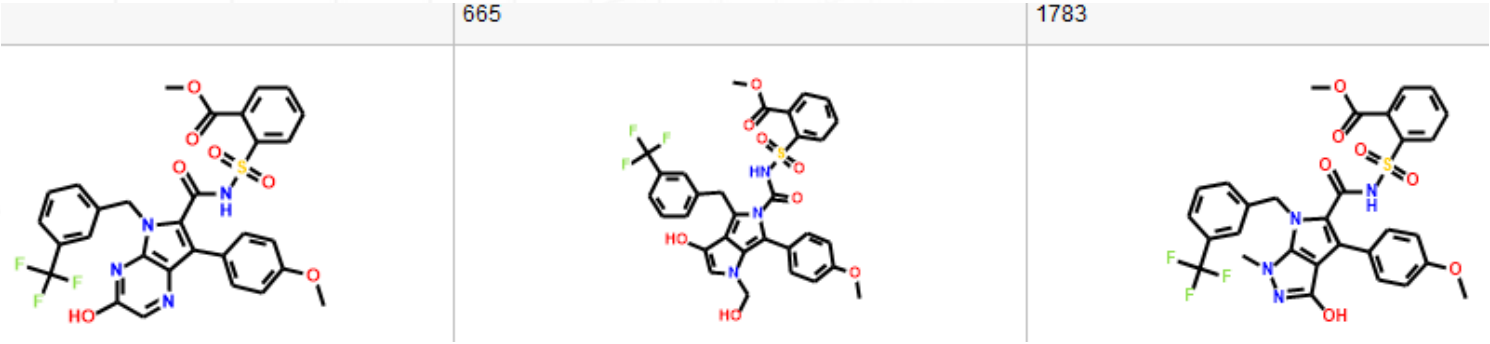
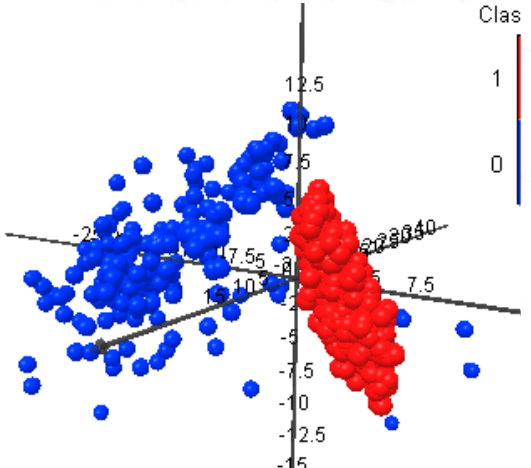
Strategy 2: Scaffold hopping

- Seed molecule: most potent indole sulfonamide
- Query: Scaffold that forces aromatic ring to maintain orientation of side chains (SMARTS string or use MedChem Designer)
- Optimization Parameters:
  - ADMET risk (0.9), %Fb (95%), syn diff (2.5), S+Sw (10), PPARGi_pIC$_{50}$ (9.5)
- Results:
  - Variations of aromatic ring cores
  - Principal Component Analysis demonstrates novel chemical space
  - Perform additional AIDD rounds with best molecules from this run









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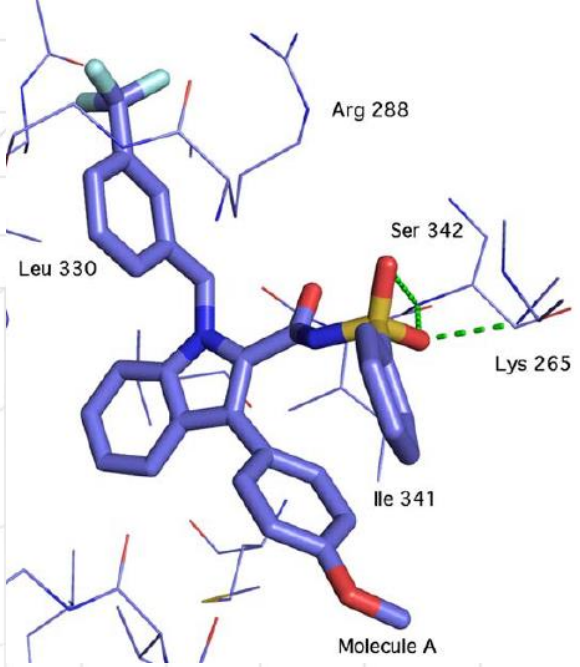
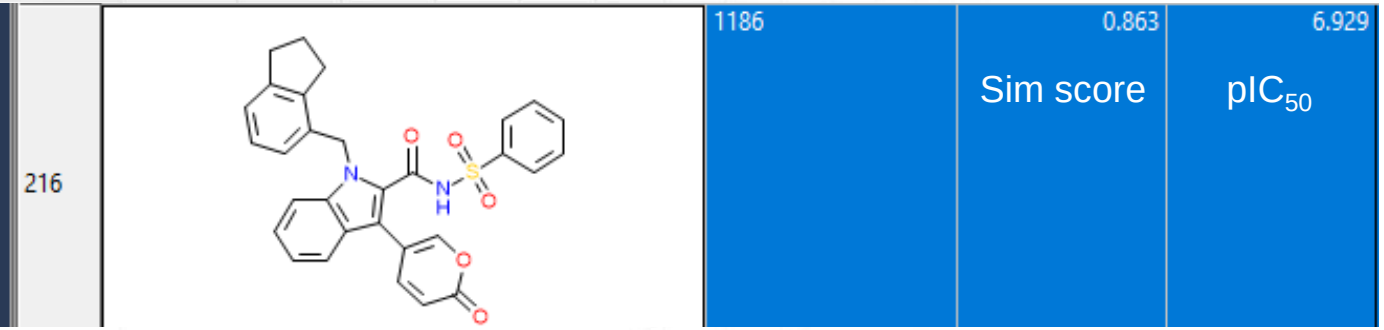
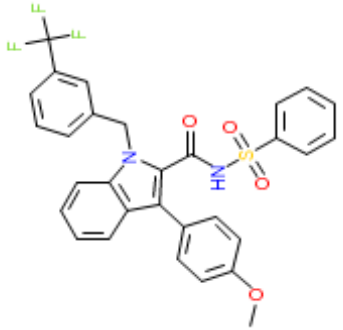
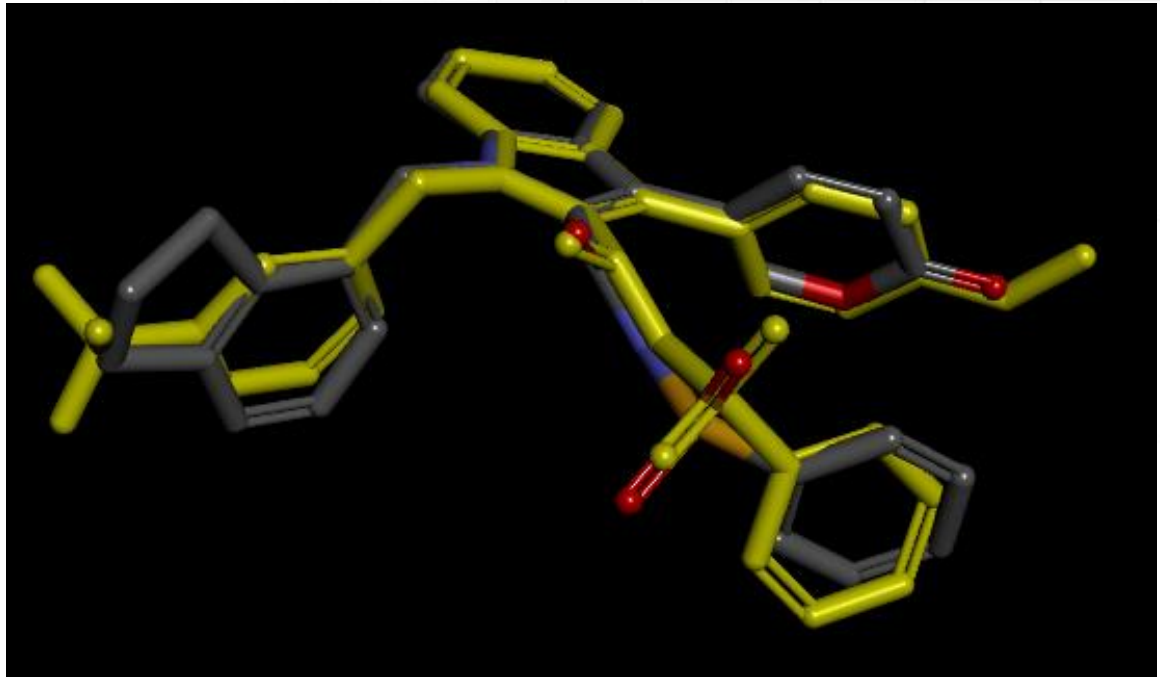
Strategy 3: 3D shape matching

- Reference ligand: Indole sulfonamide from PDB:2HFP
- Various indole sulfonamide seed, no query molecule
- Optimization Parameters:
  - 3D Tanimoto similarity (0.9), ADMET risk (0.9), %Fb (95%), syn diff (2.5), PPARGi_pIC50 (9.5)
- Results:
  - Very good results in terms of similarity, activity, and ADMET/PK properties
  - Automatically generates 3D overlay
  - Some unique chemical space and novel scaffolds: alternative method of scaffold hopping









Selecting compounds for study

- Overall goal:
  - Derive novel, high potency inhibitors with good ADMET/PK properties
- Process:
  - Combine compounds from all AIDD runs that meet the following criteria into one file:
    - pIC_{50}>6 (IC_{50}< 1uM), ADMET risk < 6, bioavailability > 40% , solubility > 0.05mg/mL, SynthDiff < 5.5
    - 181 compounds
  - Perform docking studies and add docking scores
  - Separate into classes:
    - Helps to understand potential SAR and select diverse candidates
  - Search novelty and commercial availability
    - Currently post-hoc, but working to integrated into optimization parameters
  - Use multi-criteria decision algorithm to prioritize compounds based on:
    - pIC_{50}, 3D shape similarity, novelty, and to a lesser extent, docking score
    - Ideal “drug-like measures”: LLE (pIC_{50}-LogP) > 4, LipMetE (logD-CL) = 0-4, LE (pIC_{50}*1.4/# of heavy atoms) > .2, LogP = 0-5
  - Order available compounds and discuss other candidates with synthetic chemistry team
  - Test novel compounds, rebuild QSAR models, and proceed to the next stage of optimization

Success stories are on the way!

Large pharma company collaboration

- The partner company entrusted Simulations Plus with compound structure and activity data from one of their ongoing drug discovery programs. We worked with the partner's team to define the multi-objective parameters against which the lead molecule(s) needed to be optimized and used their existing SAR data to build neural network QSAR activity models.
- The company synthesized and tested 70 compounds selected by their "traditional in-house" med chem approach and 23 compounds selected by our AIDD campaign.
- A significantly higher fraction of AIDD-designed compounds met the company's success criteria (a mixture of activity and ADMET properties) compared to the "in-house" compounds.
- We also generated follow-on libraries of virtual compounds with optimal predicted combinations of these properties for further screening and analysis. We hope to publish these results in the near future.

https://www.simulations-plus.com/resource/simulations-plus-partners-with-large-pharmaceutical-company-to-validate-ai-driven-drug-design-capabilities-in-admet-predictor/

Two new drug discovery partnerships

Simulations Plus Enters New Strategic Collaboration to Discover Anticancer Therapies Through Its AI-Driven Drug Design Technology

Drug discovery services partnership with Sino-American Cancer Foundation focuses on the development of actionable hits against the MTHFD2 target

March 28, 2023 08:30 AM Eastern Daylight Time

LANCASTER, Calif.--(BUSINESS WIRE)--Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation software and services for pharmaceutical safety and efficacy, today announced that it established a strategic research collaboration with the Sino-American Cancer Foundation (SACF). This collaboration will leverage Simulations Plus' staff and Artificial Intelligence-driven Drug Design (AIDD) technology in the ADMET Predictor® software platform to support the discovery and design of novel inhibitors of methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), an emerging cancer target.

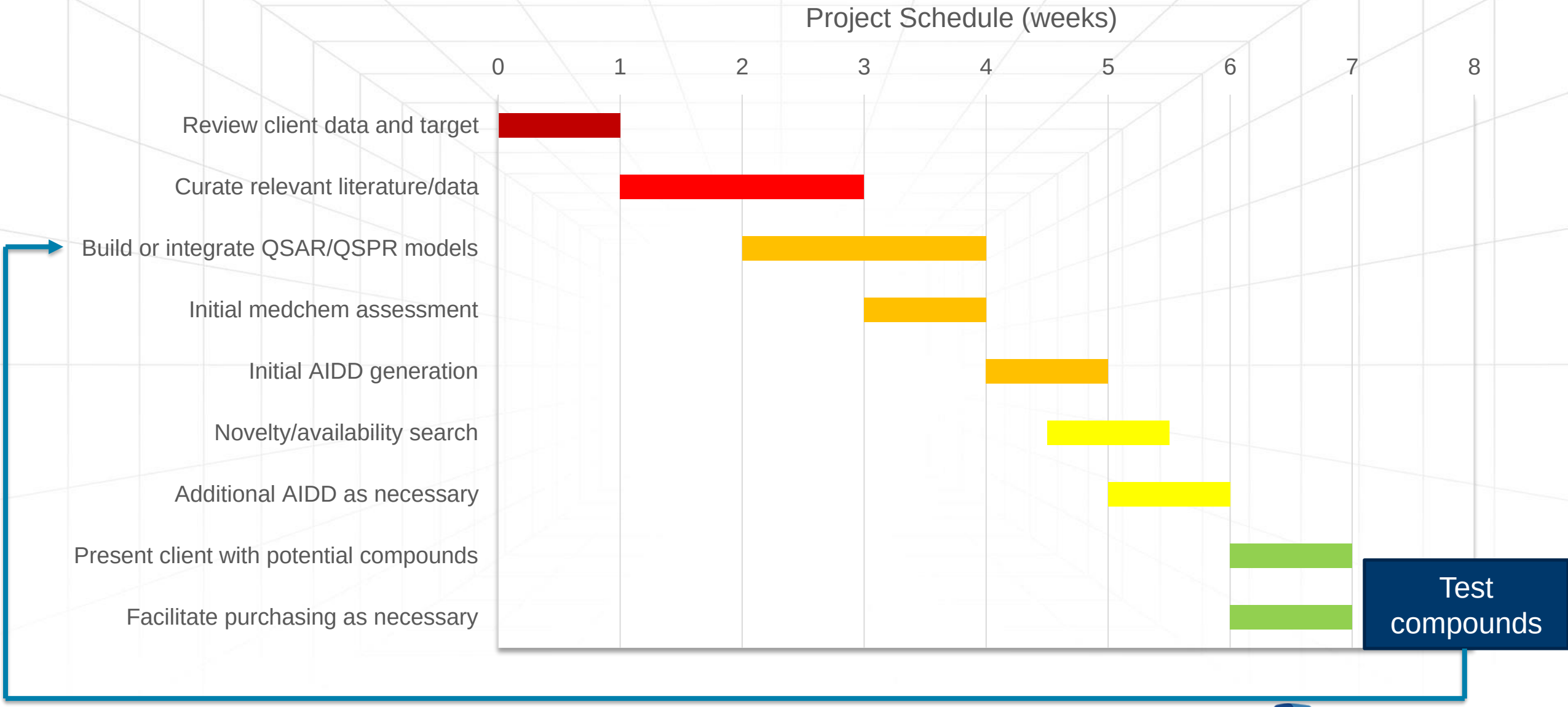
Simulations Plus Enters Partnership to Apply AI/ML Technologies to Design Novel Compounds

Promising intellectual property resulting from the collaboration with Polish Academy of Sciences will be jointly owned for further development opportunities

March 15, 2023 08:30 AM Eastern Daylight Time

LANCASTER, Calif.--(BUSINESS WIRE)--Simulations Plus, Inc. (Nasdaq: SLP), a leading provider of modeling and simulation software and services for pharmaceutical safety and efficacy, today announced that it entered into a collaborative research agreement with the Institute of Medical Biology of the Polish Academy of Sciences (IMB PAS) to jointly design new compounds for the RORγ/RORγT nuclear receptors using its cutting-edge artificial intelligence (AI) / machine learning (ML) technology in the ADMET Predictor® software platform.

What does a typical discovery project look like?



Take home messages

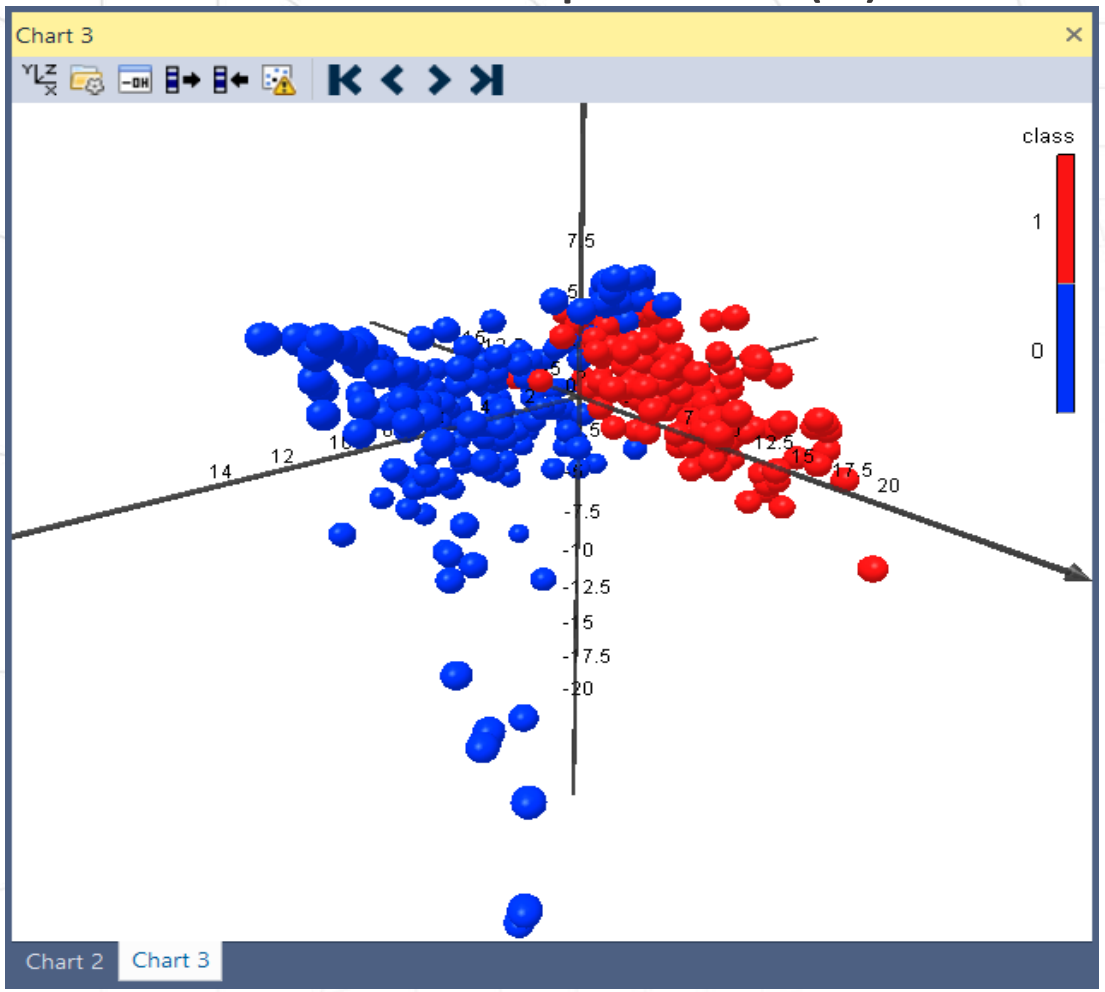
- AI approaches can accelerate the drug discovery and optimization process.
- The results are only as good as the data and models on which they're built.
- The Simulations Plus AIDD module within the ADMET Predictor platform is a user-friendly, end-to-end drug discovery and optimization tool.
  - Studies can also be performed with the help of our experts.
- Drug discovery is still an intensely a human activity and will remain so for the foreseeable future.
  - AI drug discovery platforms won't replace experts, but instead are a tool to help with decision making.
  - We hope to prompt a mix of responses, including "Of course!"; "That makes sense"; "Well, maybe…"; and "Now *that's* interesting…"

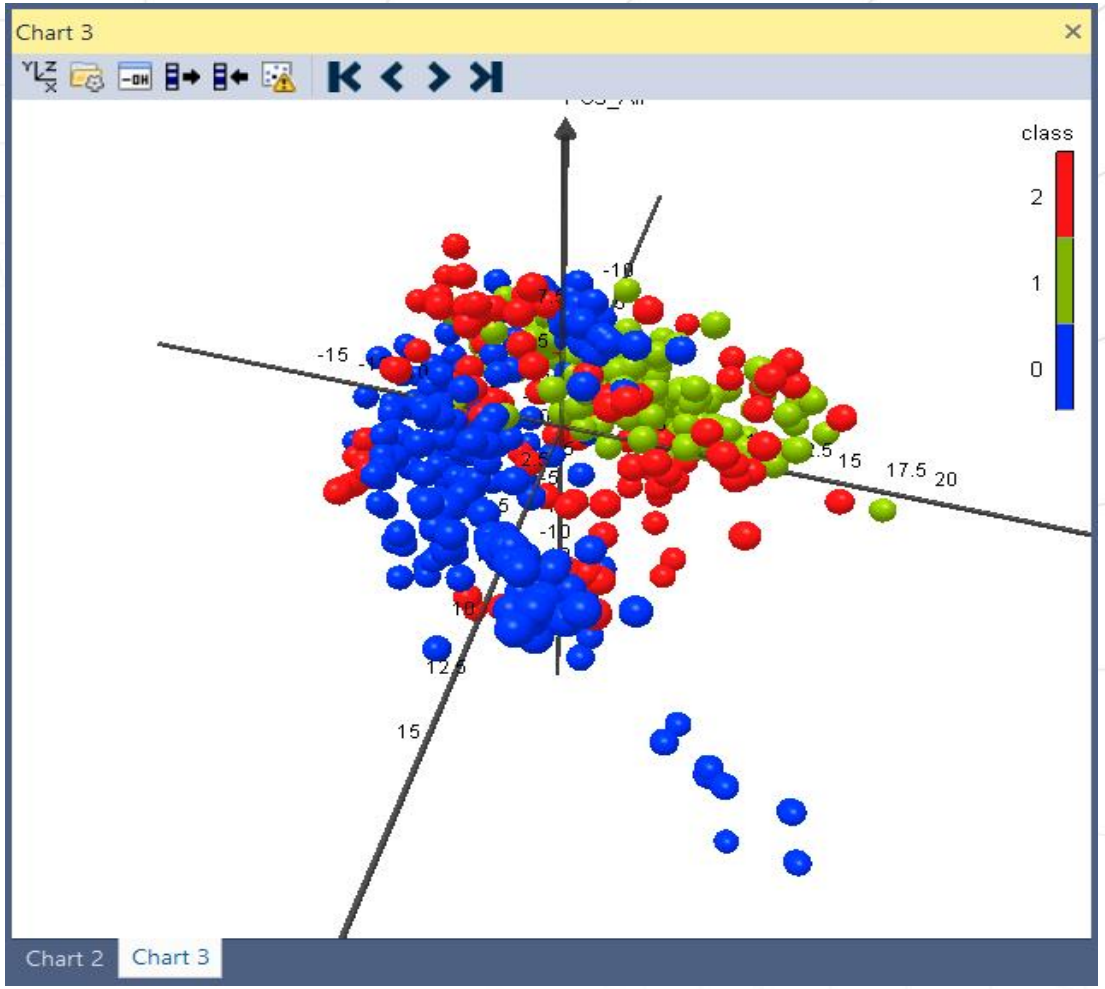
TENA KOUTOU KATOA!

- Michael Lawless
- David Miller
- Rafal Bachorz
- Cheminformatics Team

SimulationsPlus
Cognigen | DILIsym Services | Lixoft

PCA of model compounds (0) vs this 3DSM run (1) vs “best 126” (2)



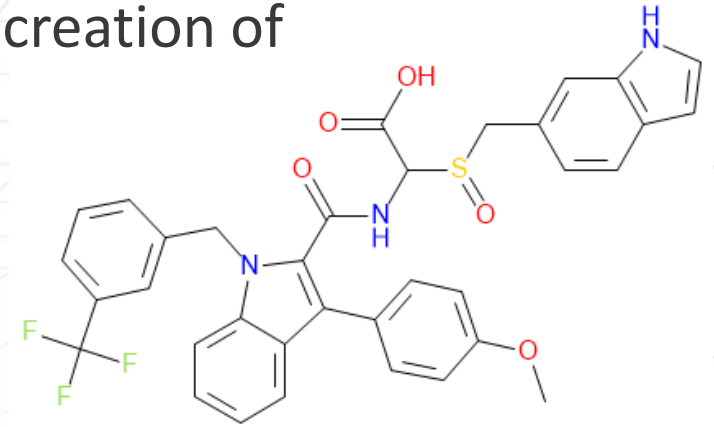


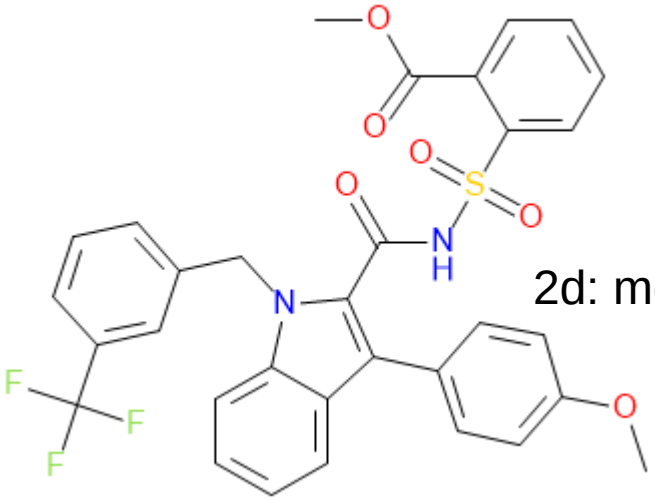
Compiled a list of 253 “best” compounds from all AIDD runs

- Only 2 duplicates!
- pIC50>6, ADMET risk <7, %Fb>80, syndiff<5, S+Sw>.005

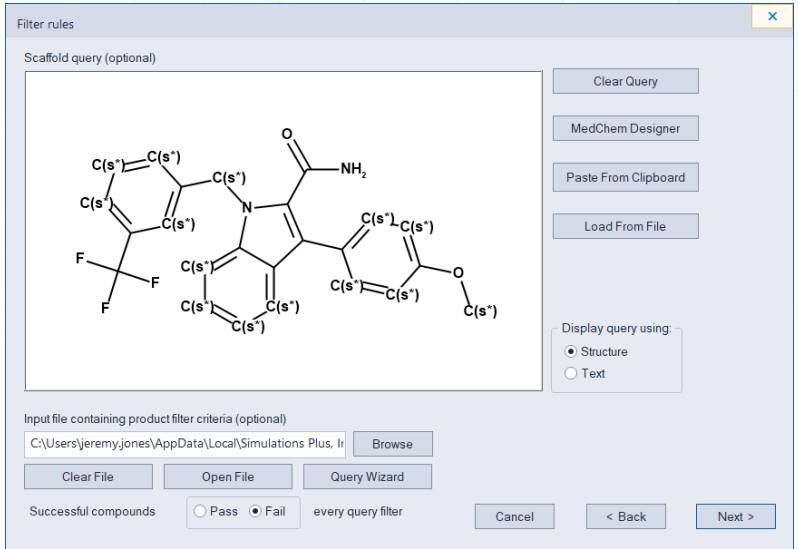
PLS similarity model results

- As Michael suspected, current rules don't appear to allow creation of sulfonamide
  - Edit rules: Jeremy_moleculeTransforms.crf
    - REACTIONNAME Add_SO2C
    - REACTIONCLASS ADD_FUNCTIONAL_GROUP
    - SMK [N;_H1:1]>>[N:1]S(=O)(=O)C
    - $$$$
  - We do get phenyl added directly to S
- Although I will say the "double indole" is interesting to me
  - Structures predicts 2:1 stoichiometry with both indoles making important



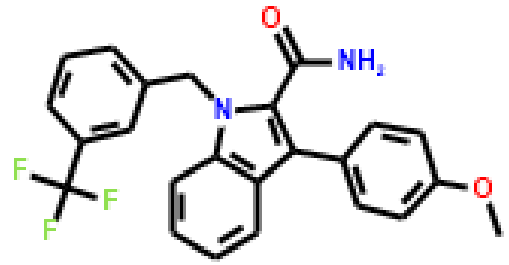


2d: most potent



PLS similarity model results

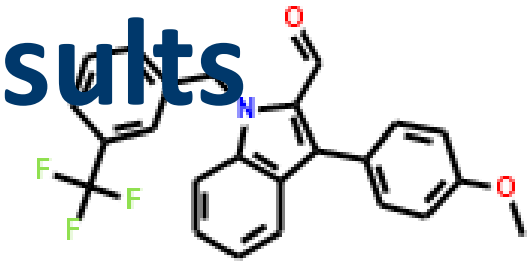
- New rule allows desired addition
- AIDD now produces something very similar to best compounds
  - 2-8-23Similar2



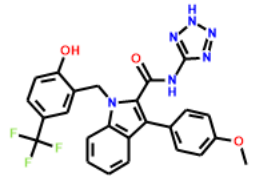
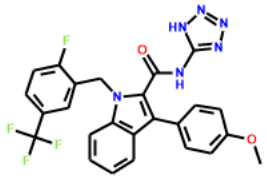
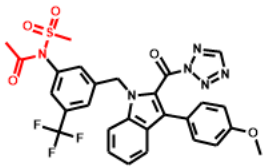
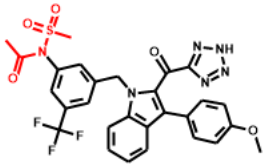
Structure	Identifier	OBJ_PPAR_si...	OBJ_ADMET_...	OBJ_SynthDif...	Generation	RxnCount
	13059	1405.184	6.658	2.721	26.000	15.000
	15245	1000.000	6.965	2.746	30.000	16.000
	13772	1335.310	7.873	2.724	27.000	12.000
	9230	1000.000	8.337	2.670	18.000	12.000
	24905	1000.000	5.467	2.913	49.000	17.000
	20835	1000.000	5.395	2.934	41.000	15.000
	22026	1000.000	6.608	2.903	44.000	16.000
	20151	1231.912	8.763	2.618	40.000	15.000

	Structure	Identifier	Pair Count	OBJ_PPAR_si...	OBJ_ADMET_...	OBJ_SynthDif...	Ge
1		2d	190				
2		13772	0	1335.310	7.873	2.724	
3		20357	0	1327.970	7.675	2.744	
4		20835	0	1000.000	5.395	2.934	
5		34779	0	1000.000	7.062	2.925	

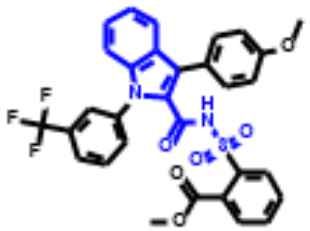
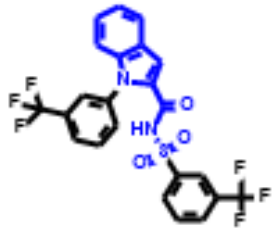
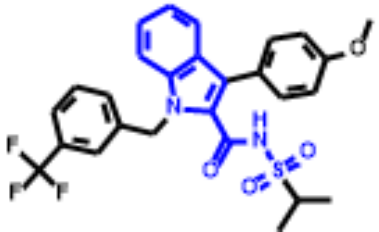
PLS similarity model results



- Pare back to C to see if N + sulfone +phenyl added
  - Did not find entire addition, and not where I wanted it
  - Did get carbonyl + N + sulfone, in a different place

	Structure	Identifier	OBJ_PPAR_si...	OBJ_ADMET_...	OBJ_SynthDif...	Generation	RxnCount	ADM
143		1163	20993.772	4.614	2.895	46.000	11.000	
144		970	21963.784	5.625	2.903	38.000	9.000	
145		1021	2251.574	6.327	3.565	40.000	7.000	
146		650	2630.489	6.298	3.506	25.000	6.000	

- Corey began by tinkering with substitutions on the S of the sulfonamide (series 2) then dropped the indole phenyl ether and tinkered further with S-substitution (early series 4) and N-indole substitution (late series 4) for novelty's sake.
- With me, brought back phenyl ether and focused on indole N substitutions (KVA-E series)

Structure	Identifier	PPARG_pIC50
	2d	9.000
	4d	7.097
	KVA-E-74A	7.036

In general, 2>4>KVA BUT KVA not built with optimal sulfonamide substitution.

Likely room for improvement in activity and definitely drug-like props

Protein-ligand interaction

- Compound 2a was co-crystallized with the ligand-binding domain of the protein (PPAR-c LBD) and the co-activator peptide fragment (SRC-1) and subjected to X-ray structure determination (PDB-id, 2HFP).
- Interestingly, two molecules of compound 2a were seen to span the binding pocket. Such a 2:1 stoichiometry of binding is n
- One molecule of 2a (molecul bonds with His449 through t the close proximity to Tyr473 although no distinct interacti
- The second molecule of com molecule occupied the area i methylaminopyridine portio carbonyl and sulfonyl oxygen productive hydrophobic inte two bound ligand molecules

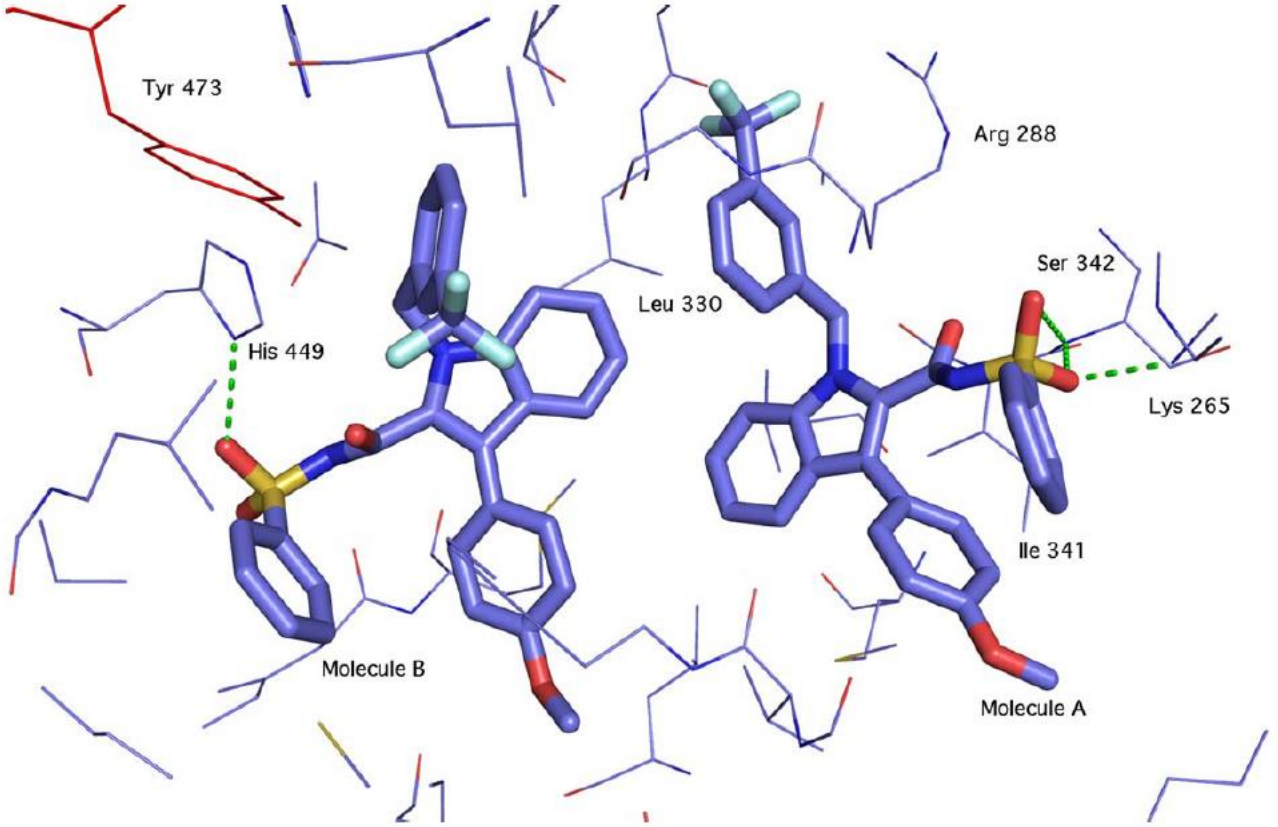
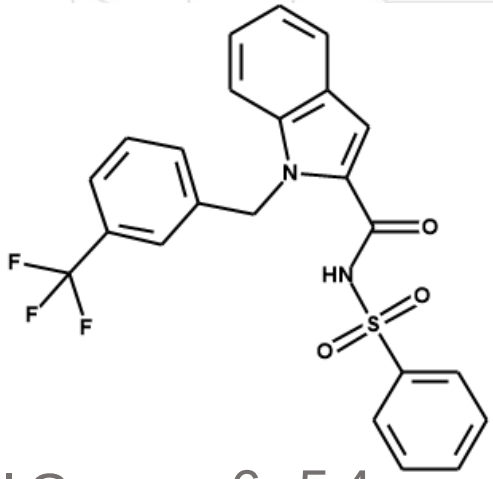
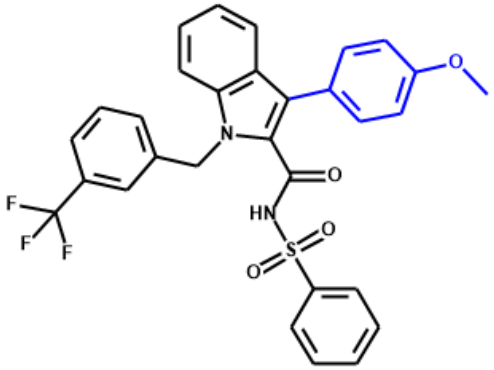


Figure 1. X-ray crystal structure of compound **2a** co-crystallized with PPAR-γ LBD and SRC-1. Ligands and relevant protein residues are shown as thick and thin sticks, respectively. The important Tyrosine 473 is highlighted in red; hydrogen bonds are represented by green dashes.

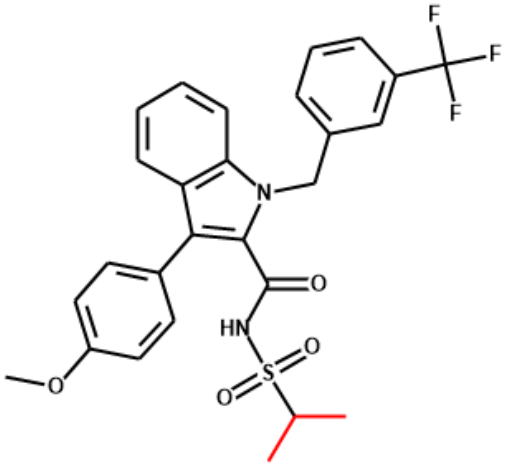
Activity cliffs

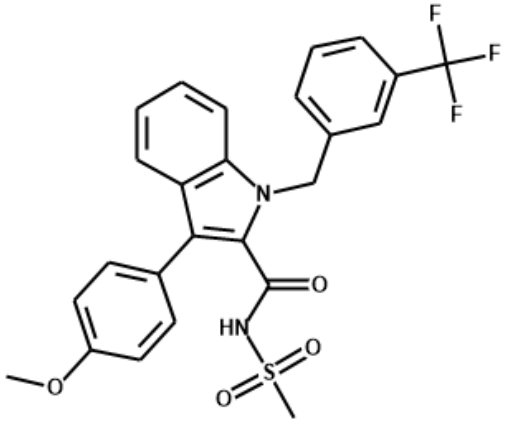




pIC_{50}	6.54	8.52
	4a	2a

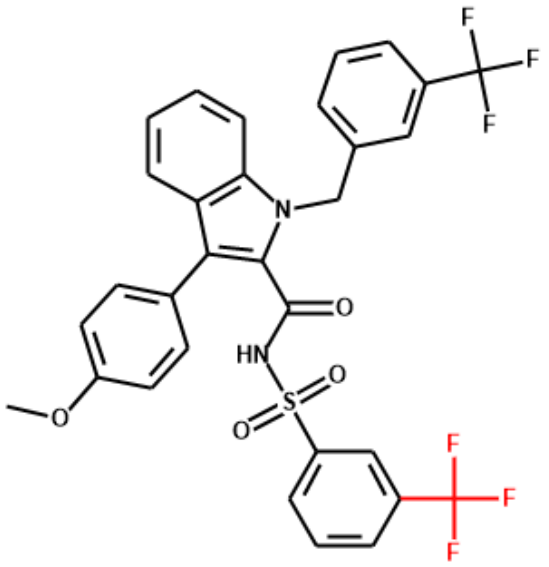
Phenyl ether is important





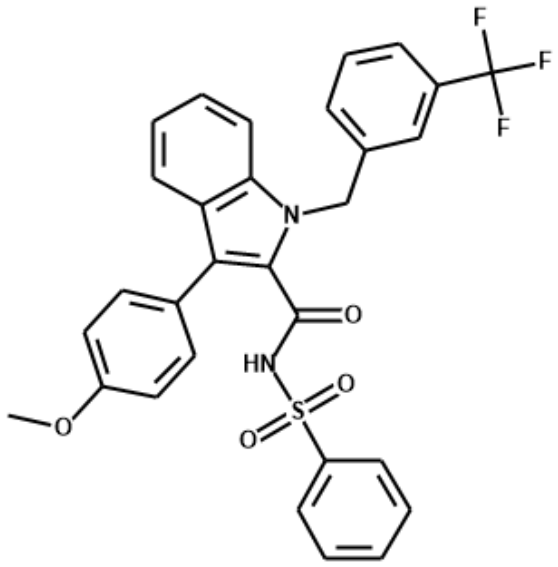
	7.04	8.70
	KVA-E-74A	2f

I suspect differences are due to lab assay variance (show same trend with other substitutions)



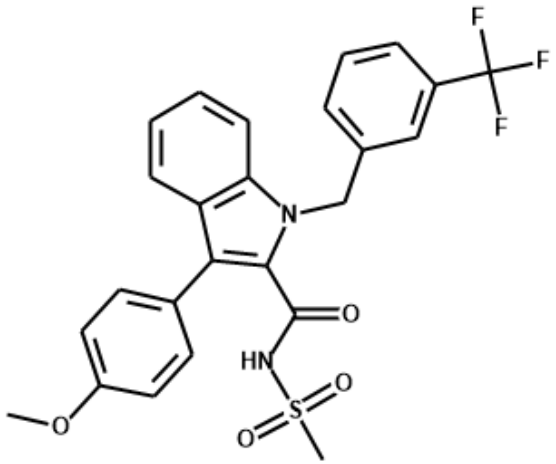
2c

7.222



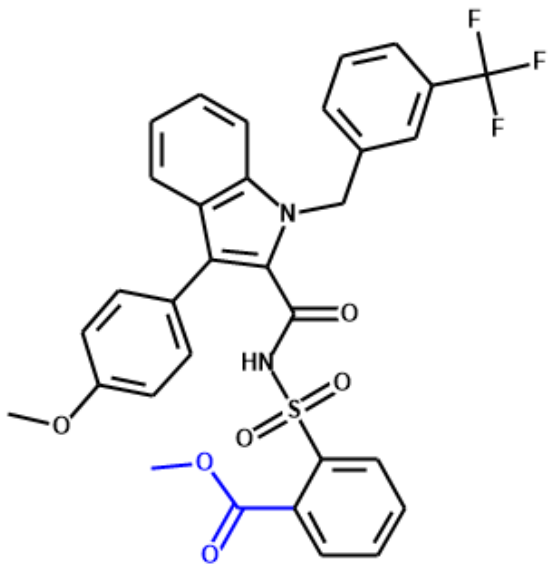
2a

8.523



2f

8.699



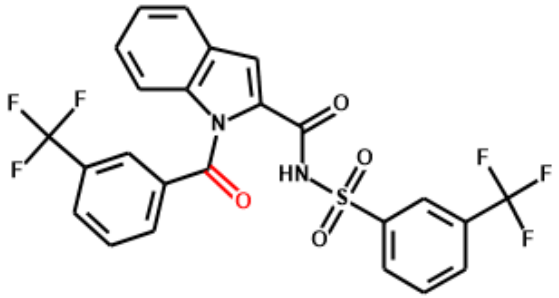
2d

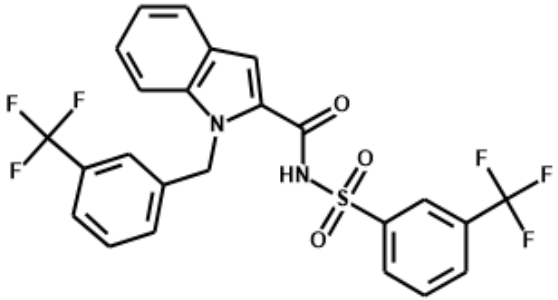
9.0

Corey's thought was that only meta substituted phenyl really affected activity.

Looking back, not sure why we didn't use the ester substituted phenyl for KVA class optimization.

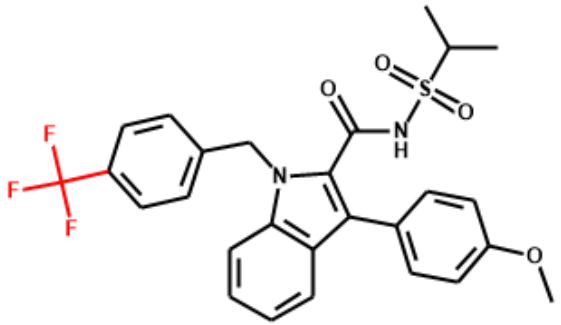
Activity cliffs





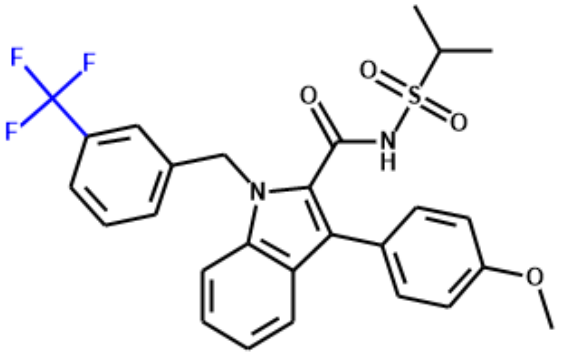
pIC_{50}	5.03	7.10
	4n	4d

KVA-E series SAR



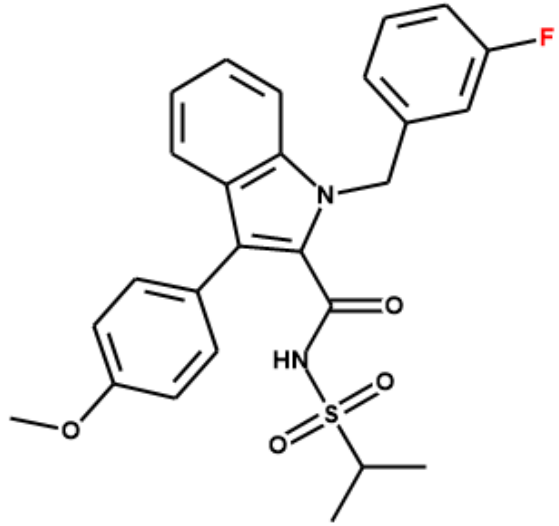
KVA-E-74G

5.973



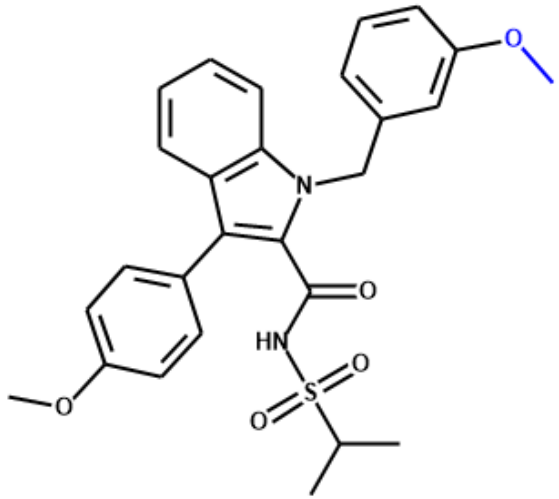
KVA-E-74A

7.036



KVA-E-74D

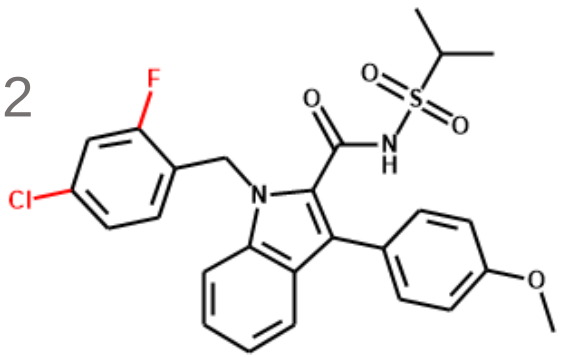
5.416



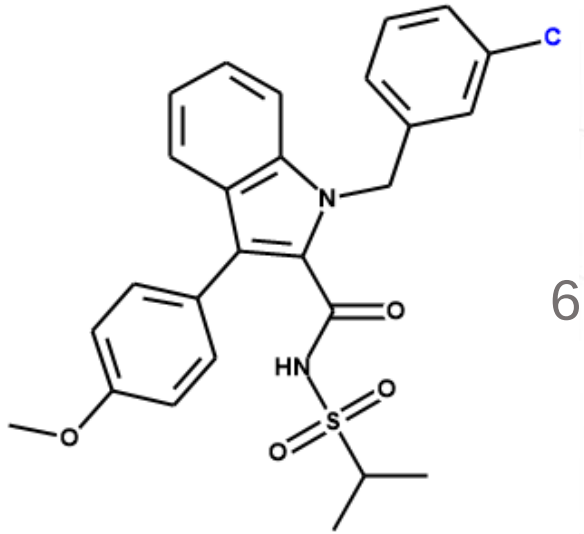
KVA-E-74B

6.614

5.482



KVA-E-74I



KVA-E-74E

6.529

Meta >> para

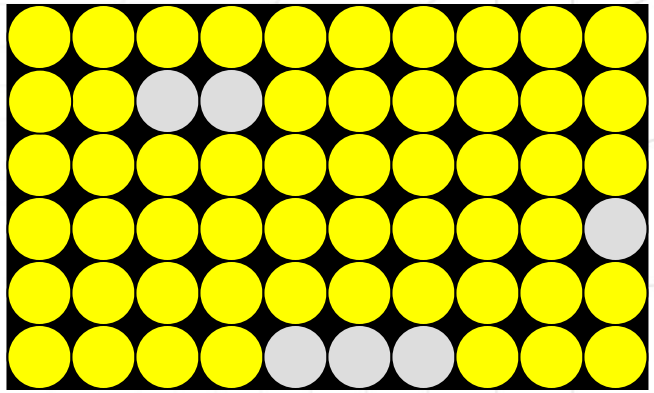
CF3 > OCH3~CH3 > Halogen(s)

History of targeting PPARs

- PPAR gamma agonists have long been used to treat Type II diabetes
  - Exactly how they work is not completely understood, but it involves increased lipid storage in fat depots, which helps regulate blood sugar and insulin sensitization
  - Several were approved by the FDA and other regulatory agencies, but most have been removed from use due to side-effects (rosiglitazone, pioglitazone)
  - These include weight gain, fluid retention, bone loss, congestive heart failure, and increased risk of myocardial infarction and bladder cancer
- PPAR dual/pan agonists are *still* in development for diabetes
  - It is thought that activating alpha/delta will ameliorate AEs of gamma agonists
- PPAR alpha: agonists (fibrates) to treat hyperlipidemia and cardiovascular disease
  - Antagonist for immune adjuvant: Tempest phase Ib
- No clinical development of any PPAR gamma antagonists to date

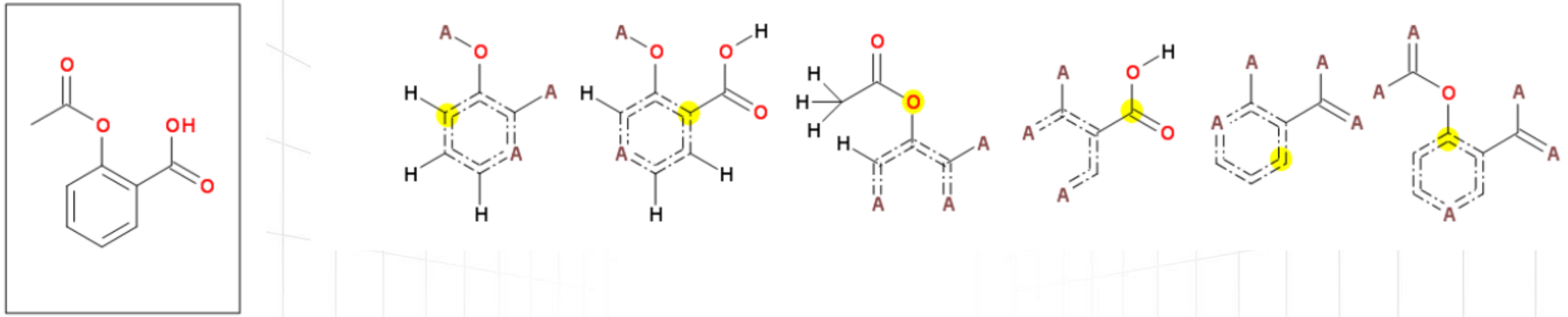
Screening strategy

- Started by screening targeted collections from collaborators
- Quantified activity/selectivity against PPAR A/G/D using luciferase reporter assays
- Determined effects against relevant cancer models in culture
- Confirmed effects against endogenous genes in cancer cells
- Tested efficacy, and toxicity in mouse models



	Antag	Agonist
PPARG	☑	X
PPARD	X	X
PPARA	X	x

Synthetic Accessibility/Difficulty



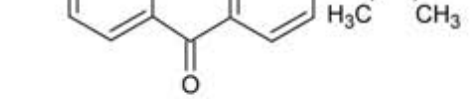
Score = fragment_Score – complexity_Penalty

Fragment frequencies

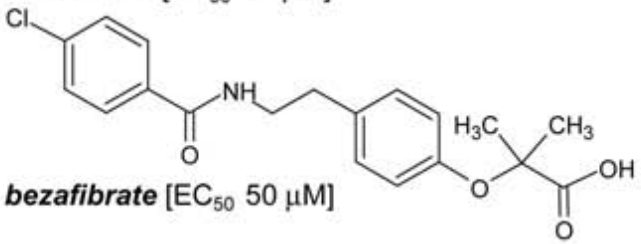
Heavy Atoms
Macrocycles
Stereocenters
Spiro centers
Bridges

	SA Ertl	Synth Diff
Training	~1 million	~47 million
Outer Layer	Any	aromatic vs. aliphatic
Complexity	Same	Same
Range	1-10	0-10

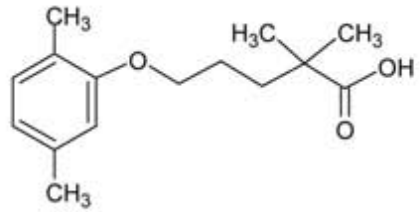
Ertl and Shuffenhauer, J Cheminf, 2009, doi:10.1186/1758-2946-1-8



fenofibrate [EC_{50} 30 μM]

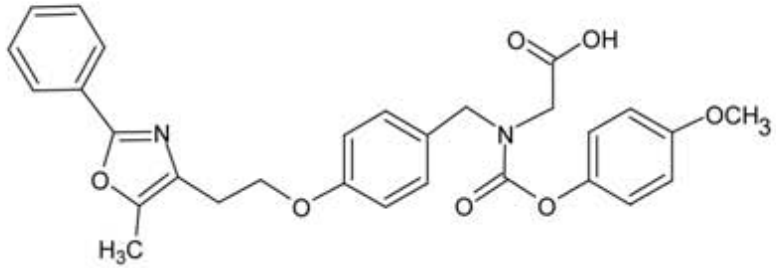


bezafibrate [EC_{50} 50 μM]

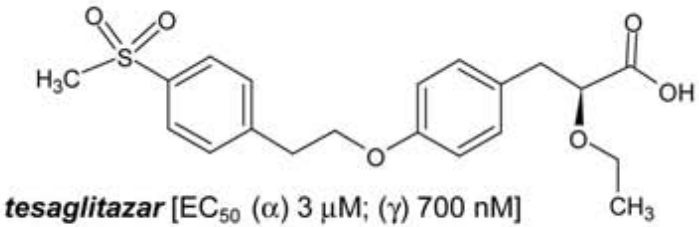


gemfibrozil [EC_{50} 190 μM]

PPARα/PPARγ dual agonists

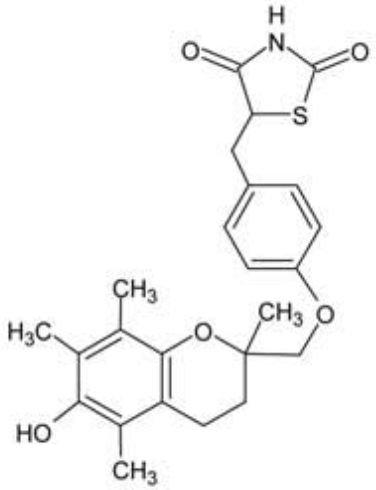


muraglitazar [EC_{50} (α) 4 μM; (γ) 150 nM]

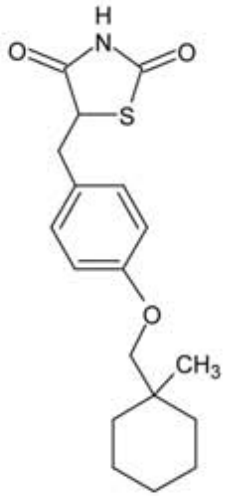


tesaglitazar [EC_{50} (α) 3 μM; (γ) 700 nM]

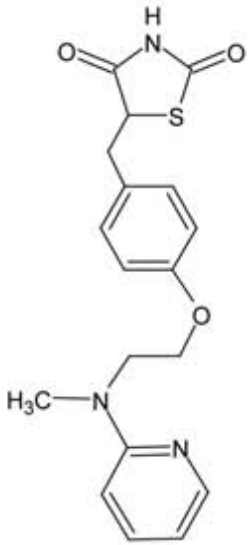
PPARγ agonists



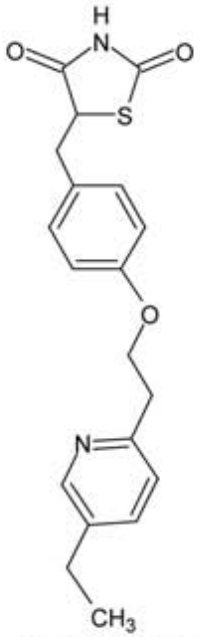
troglitazone
[EC_{50} 550 nM]



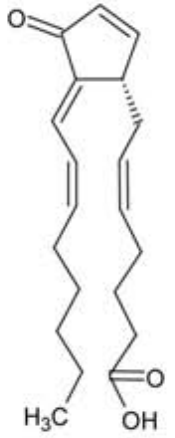
ciglitazone
[EC_{50} 3 μM]



pioglitazone
[EC_{50} 580 nM]

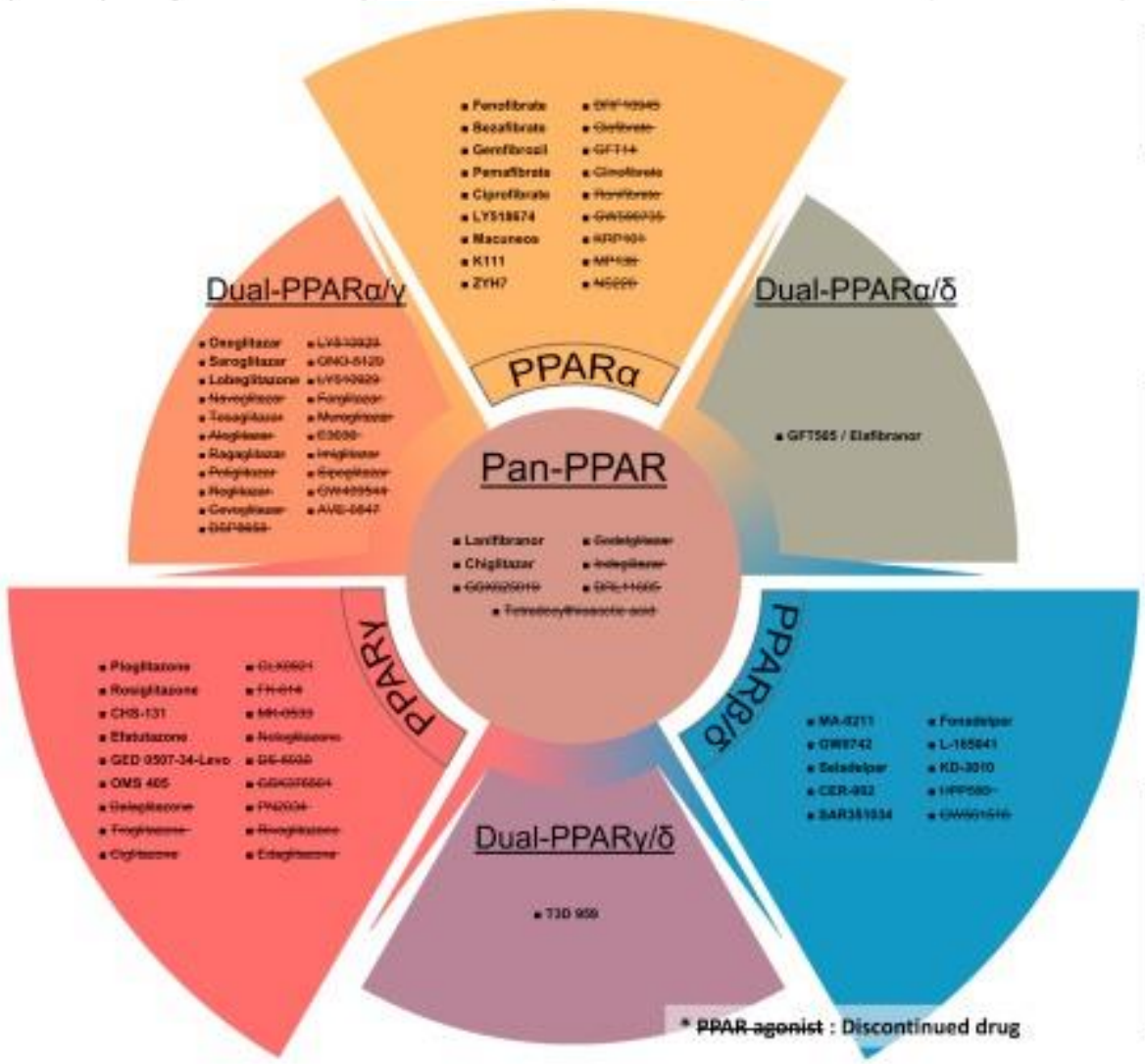


rosiglitazone
[EC_{50} 43 nM]



15d-PGJ2
[EC_{50} 2 μM]

History of targeting PPARs



Preclinical
- GW0742
- L-165041

Phase I
- MA-0211
- KD-3010
- CER-002
- SAR351034
- Oxeglitazar

Phase II
- LY518674
- ZYH7
- K111
- Macuneos
- Efatutazone
- CHS-131
- OMS 405
- GED 0507-34-Levo
- T2D 959
- Lanifibranor

Phase III
- Seladelpar
- Fonadelpar
- Elafibranor
- Chiglitazar

Approved
- Gemfibrozil
- Ciprofibrate
- Bezafibrate
- Fenofibrate
- Pemafibrate (in Japan)
- Rosiglitazone
- Pioglitazone
- Lobeglitazone (in South Korea)
- Saroglitazar (in India)

Cheng, et al 2019

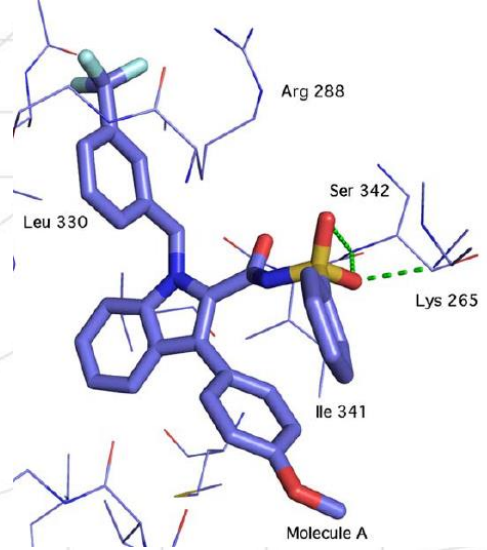
PPARG pathway activation in bladder cancer

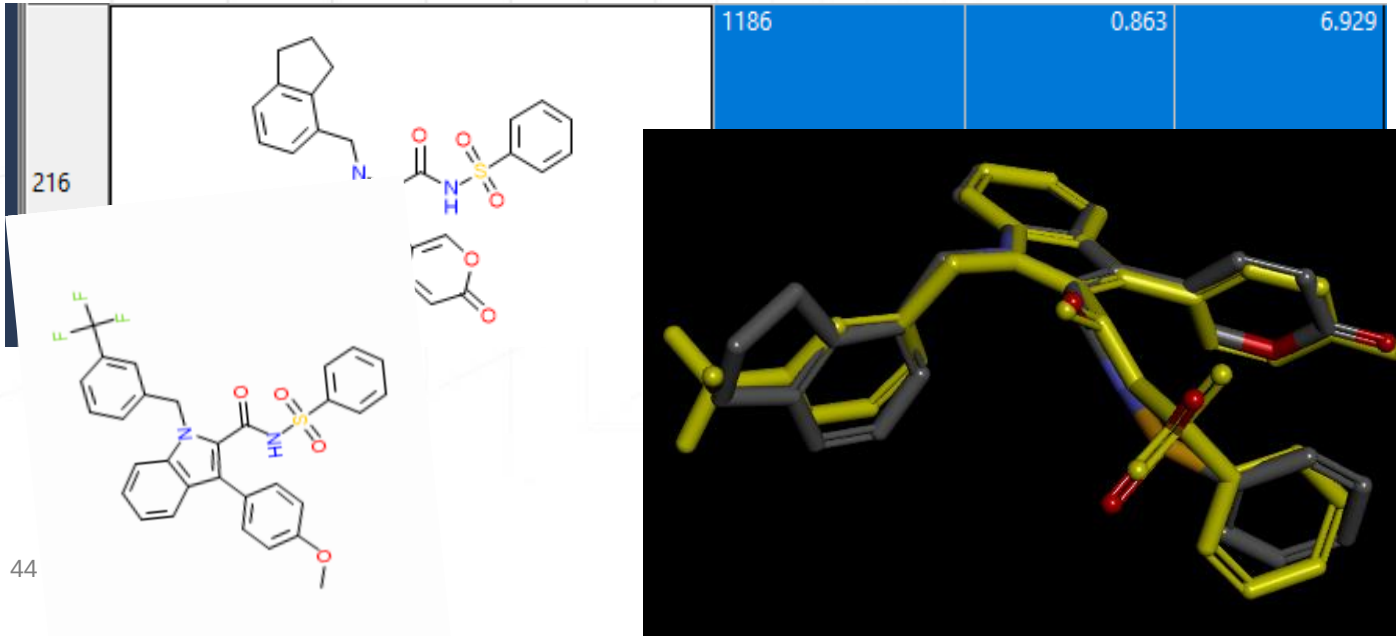
20-30% of advanced bladder cancers have PPARγ pathway alterations.

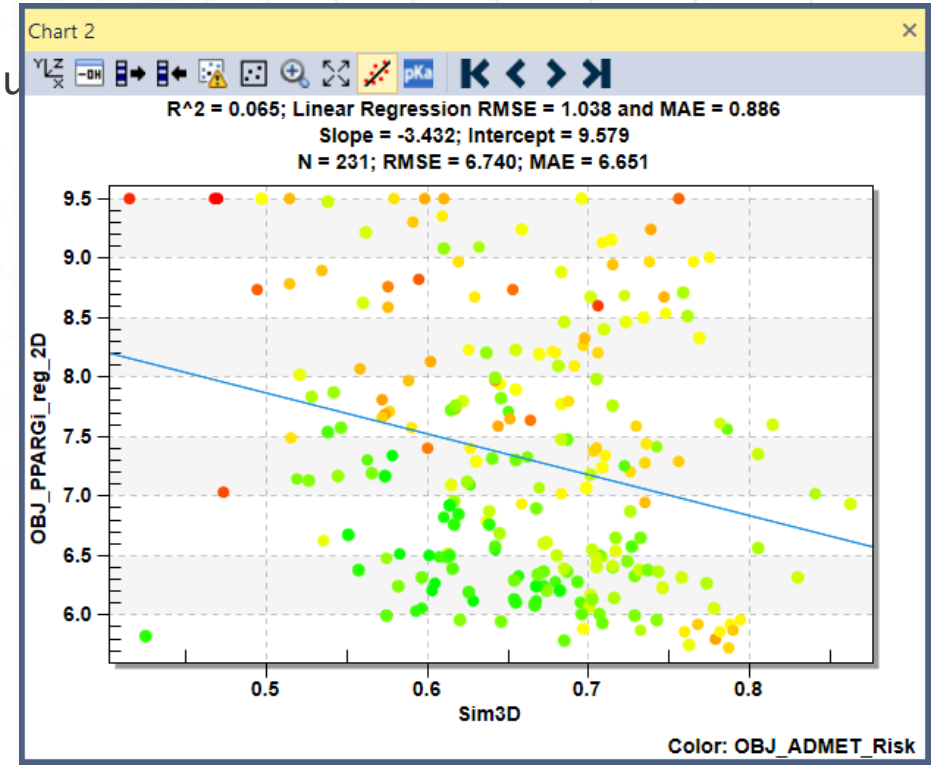
- Biton, Cell Reports (2017)
  - In silico analysis of BlCa transcriptomes reveals PPARG as a major driver of luminal cancers.
- Halstead eLIFE (2017)
  - TCGA analysis suggests that hyperactive PPAR signaling, either due to PPARG chromosomal amplification (~10-15%) or RXRA hot-spot mutation (S427F/Y, 6-7%) is involved in >20% of muscle invasive bladder cancers (MIBC).
  - RXRA mutation allosterically regulates PPARG AF2, activating it.
  - PPARG activity or RXRA mut sufficient to drive growth of bladder organoids; reversible by inhibition.
- Goldstein, Cancer Research (2017)
  - Activating alterations of PPARG or RXRA lead to a specific gene expression signature in bladder cancers.
  - Reducing PPARG activity, whether by pharmacologic inhibition or genetic ablation, inhibited proliferation of PPARG-activated bladder cancer cells.
- Rochel, Nature Communications (2019)
  - Mutations in PPARG (3-4% of pts) also cause pathway activation and drive bladder cancer growth.

Strategy 4: 3D shape matching

- Reference ligand: Indole sulfonamide from PDB:2HFP
- No Query molecule:
- Optimization Parameters:
  - 3D Tanimoto similarity (0.9), ADMET risk (0.9), %Fb (95%), syn diff (2.5), PPARGi_pIC50 (9.5)
- Results:
  - Very good results in terms of similarity, activity, and ADMET/PK properties
  - Some unique chemical space and novel scaffolds: alternative method of scaffold hopping
  - Little correlation between PPARGi activity and Sim3D?
  - Compounds with high Sim3D/low PPARGi are interesting because they wou







Background

- History of Computer-Aided *De Novo* Drug Design
  - Early 1990's
    - Structure (Receptor) Based
    - Ludi, MCSS/Hook, Sprout
  - Late 1990's – Rule of 5, ADMET, Drug Design is multi-objective
    - "It ain't just activity anymore"
  - Early to late 2000's
    - Multi-objective ligand and structure-based design
    - Typically multi-objective "combined" into a single function
    - EA-Inventor, Muse, in-house Pharma programs
  - In the last decade
    - Pareto-based optimization
    - Deep Learning Generative algorithms