Using artificial intelligence to design BACE1 inhibitors

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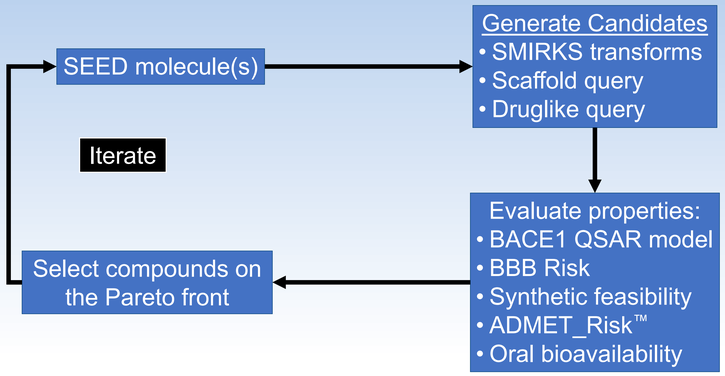
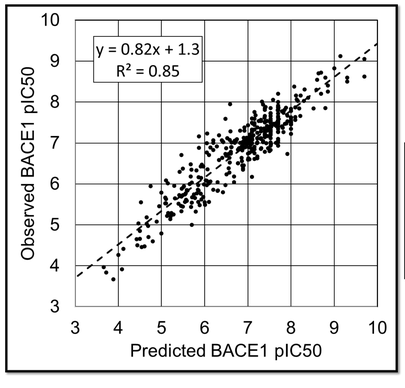
INTRODUCTION

β-secretase 1 (BACE1) is an enzyme involved in production of amyloid-β peptides, which are involved in the pathology of Alzheimer's disease. BACE1 inhibitors have been evaluated in clinical trials for Alzheimer's disease. The AIDD (Artificial Intelligent Drug Design) module in ADMET Predictor® is a compound design technology that generates candidate compounds, scores them using various objective functions, and selects Pareto optimal molecules for the next iteration. The AIDD module was used to design potential BACE1 inhibitors using the scheme below.



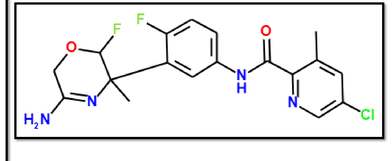
METHODS

All calculations were performed using ADMET Predictor version 10.3.[1] The BACE1 pIC50 QSAR model is an artificial neural network ensemble model trained on a data set of 370 diverse BACE1 inhibitors from the ChEMBL database[2]. A plot of the observed versus predicted values is shown below. The RMSE is 0.42 which represents a 2.6-fold error. Sixteen of the compounds contain an oxazine ring. SAR were extracted from these BACE1 inhibitors and used to formulate the scaffold query used in AIDD.



Seed molecule

The molecule below was used as the starting molecule for AIDD. Its BACE1 IC_{50} value is 6.9 nM.



SMIRKS Transformations

Candidate compounds are generated via SMIRKS string transformations that are medicinal chemistry aware, i.e., unstable, toxic, and non-druglike compounds are avoided. One hundred and one (101) out of ~150 of the standard SMIRKS transformations were used in AIDD.

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METHODS (continued)

The "scaffold query" requires a cyclic amidine "warhead" and two 6 membered aromatic rings linked by an amide. The BBB_Risk model penalizes compounds that are predicted to have low brain to blood concentration ratio, to be Pgp substrates, or to have high fraction of cationic species. ADMET_Risk is a liability score that penalizes compounds with poor predicted ADMET properties like aqueous solubility, logP, permeability, intrinsic clearance, and hERG pIC50. Penalties are applied to predictions that are outside models' applicability domain, to de-prioritize these compounds. ADMET_Risk models were penalized by 1 if an underlying prediction is out of scope. Out of scope BACE1 pIC50 predictions are penalized by subtracting 10 from the prediction. Oral bioavailability is predicted for a 10 mg, immediate release tablet with the HTPK Simulation module of ADMET Predictor.

Capping values on objective function can be used when the predicted value is "good enough". For example, oral bioavailability about 90% is good enough so compounds with higher %Fb are set to 90.

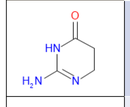
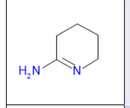
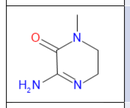
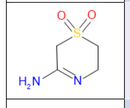
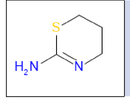
The table below lists the five objective functions that were optimized.

Objective	Direction	Capping Value
Oral bioavailability	Maximize	90
BACE1_Model	Maximize	10
ADMET_Risk	Minimize	0.9
Synthetic difficulty	Minimize	2.5
BBB_Risk	Minimize	

50 iterations of AIDD were performed, 500 molecules were generated each iteration except for the first iteration where 1,000 molecules were generated. The run took only 9 minutes.

RESULTS

The run generated 450 Pareto optimal molecules. The most potent compound had a predicted BACE1 pIC50 value of 0.11 nM. The table below shows replacements for the oxazine scaffold and average properties of the objective functions for each chemotype.

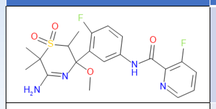
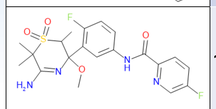
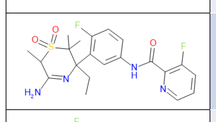
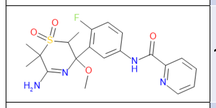
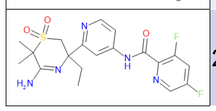
	Class Size	Average %Fb	Average ADMET_Risk	Average BACE1_pIC50	Average BBB_Risk	Average SynthDiff+
	3	82	1.2	5.6	2.3	2.8
	4	85	1.3	6.9	0.5	3.0
	20	90	1.2	8.2	0.0	3.3
	401	86	2.1	9.4	1.0	4.1
	18	89	1.7	7.5	0.6	3.1

RESULTS

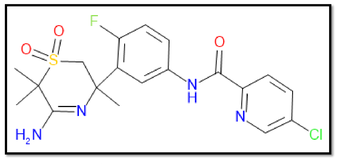
43 molecules met the criteria below:

- OBJ_BACE1_Model 8 – 9.98
- OBJ_ADMET_Risk 0.9 – 1.9
- OBJ_BBB_Risk 0 – 0.1
- OBJ_SynthDiff+ 2.73 – 4.0

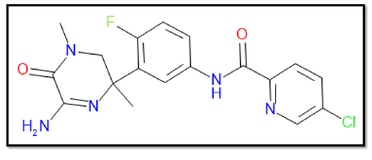
These molecules have predicted BACE1 IC_{50} values at or below 10 nM, very low ADMET liability score, good synthetic feasibility, and predicted oral bioavailability greater than 85%. The 5 compounds in the table below had the lowest predicted BACE1 IC_{50} values.

	ID	%Fb	ADMET_Risk	BACE1_pIC50	BBB_Risk	SynthDiff+
	9818	90	1.7	9.6	0	4.0
	17916	90	1.7	9.6	0	3.9
	4968	90	1.6	9.5	0.1	3.9
	13366	90	1.5	9.5	0	3.8
	22940	90	1.9	9.4	0	3.8

The two compounds shown below are exact matches of known BACE1 inhibitors.



Compound 9660 is an exact match of known Merck BACE1 inhibitor.[4]



Compound 14025 is an exact match of a known Janssen BACE1 inhibitor.[5]

CONCLUSIONS

The AIDD module of ADMET Predictor was used to generate candidates with high predicted BACE1 activity, good ADMET properties, high oral bioavailability, and synthetic feasibility.

REFERENCES

[1]Simulations Plus, Inc. Lancaster CA USA 93534.
[2]Gaulton et al. *Nucleic Acids Res.*, **2017,** 45(D1) D945-D954.
[3]Ertl and Shuffenhauer, *J. Cheminfo,* **2009**, 1, 8.
[4]Wu et al. WO 2012 139425.
[5]Tresadern et al. *Bioorg. Med. Chem. Lett.* **2011**, 21, 7255.