SAMPL6 pK_a Challenge: Predictions of ionization constants performed by the S+pKa method implemented in ADMET Predictor™ software

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Simulations Plus, Inc.

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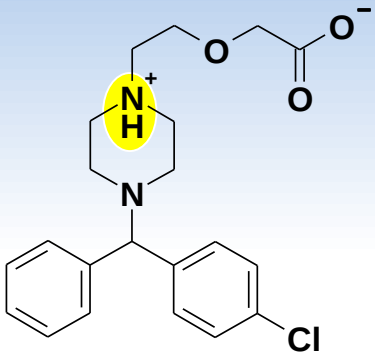
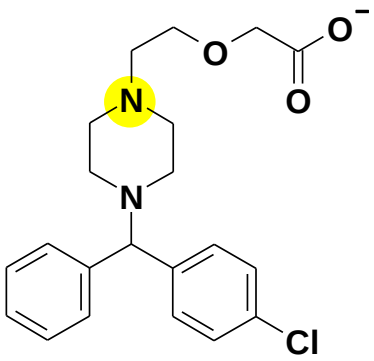
Simplified overview of pK_a modeling

Ionizable atom in a microstate





2D Atomic Descriptors for ionizable atom in its molecular environment

A1
A2
A3
A4
A5
A6
A7
A8
A9
A10
A11
A12
A13
A14
A15

optimal subset from ~130 atomic descriptors

QSPR

Predicted micro pk_a

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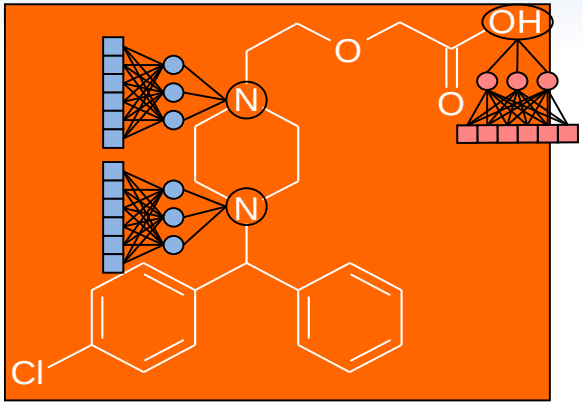
The predictive model, S+pKa

- 10 Artificial Neural Network Ensembles (ANNE);
  one ANNE for each of the following 10 classes of ionizable atoms:
  - (1) Hydroxyacids
  - (2) Acidic amides
  - (3) Acids of aromatic NH
  - (4) Thioacids
  - (5) Carboacids
  - (6) Amines
  - (7) Bases of aromatic N
  - (8) N-oxides
  - (9) Thiones
  - (10) Carbobases (protonatable C in some π–excessive rings)

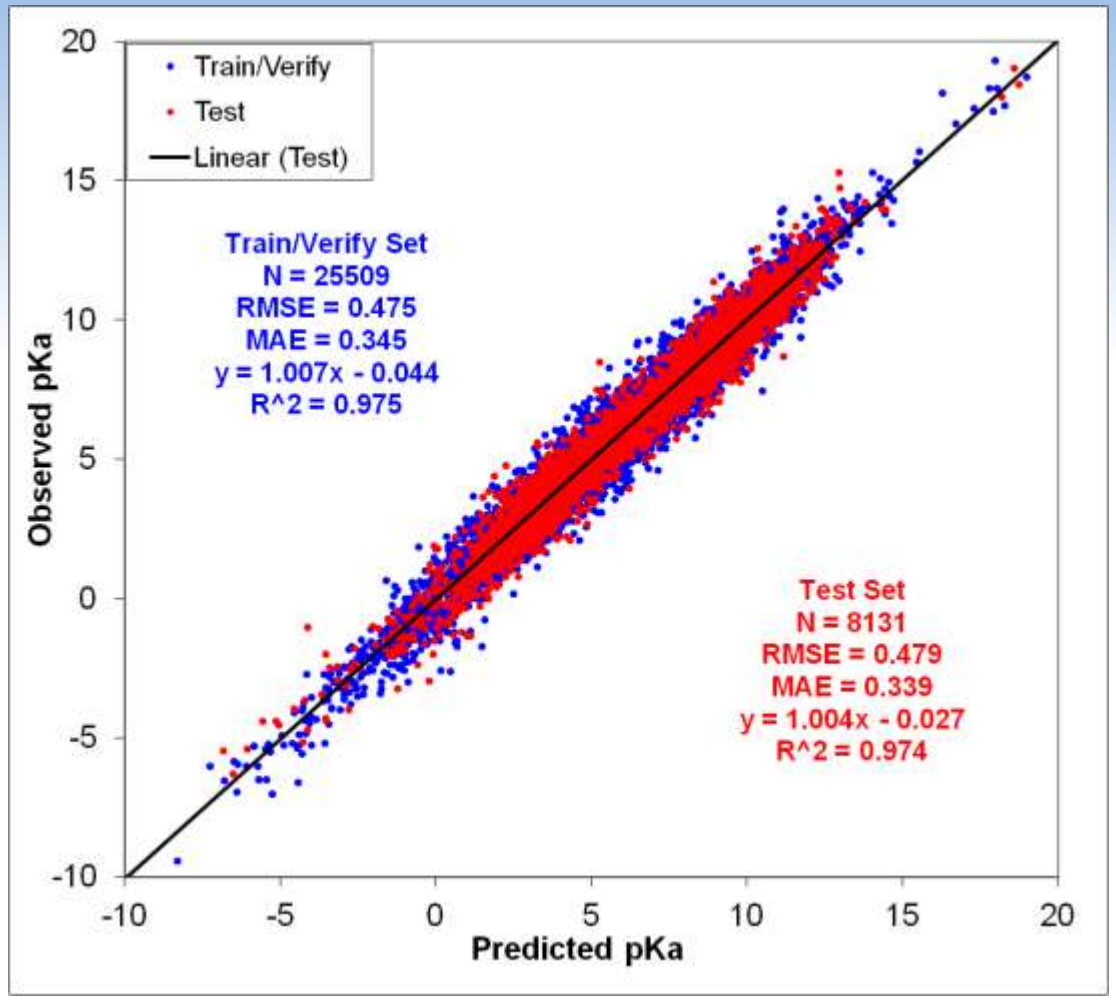
The main factor determining an atom's ionization is its type, followed by its local molecular environment



- ANNEs use localized atomic descriptors as inputs
- ANNEs predict ionization microconstants (micro pK_a)
- Macroconstants calculated with microequilibria theory

Fraczkiewicz, R.; Lobell, M.; Göller, A. H.; Krenz, U.; Schoenneis, R.; Clark, R. D.; Hillisch, A. "Best of Both Worlds: Combining Pharma Data and State of the Art Modeling Technology To Improve in Silico pKa Prediction." *Journal of Chemical Information and Modeling* **2014**, *55*, 389-397.

Model training and initial testing with internal test set*



Details of data split:

Training pool: 25509 pK_a values

- 10594 from public sources
- 14915 from Bayer Pharma

Internal test set: 8131 pK_a values

- 3582 from public sources
- 4549 from Bayer Pharma

Internal test set prediction statistics:

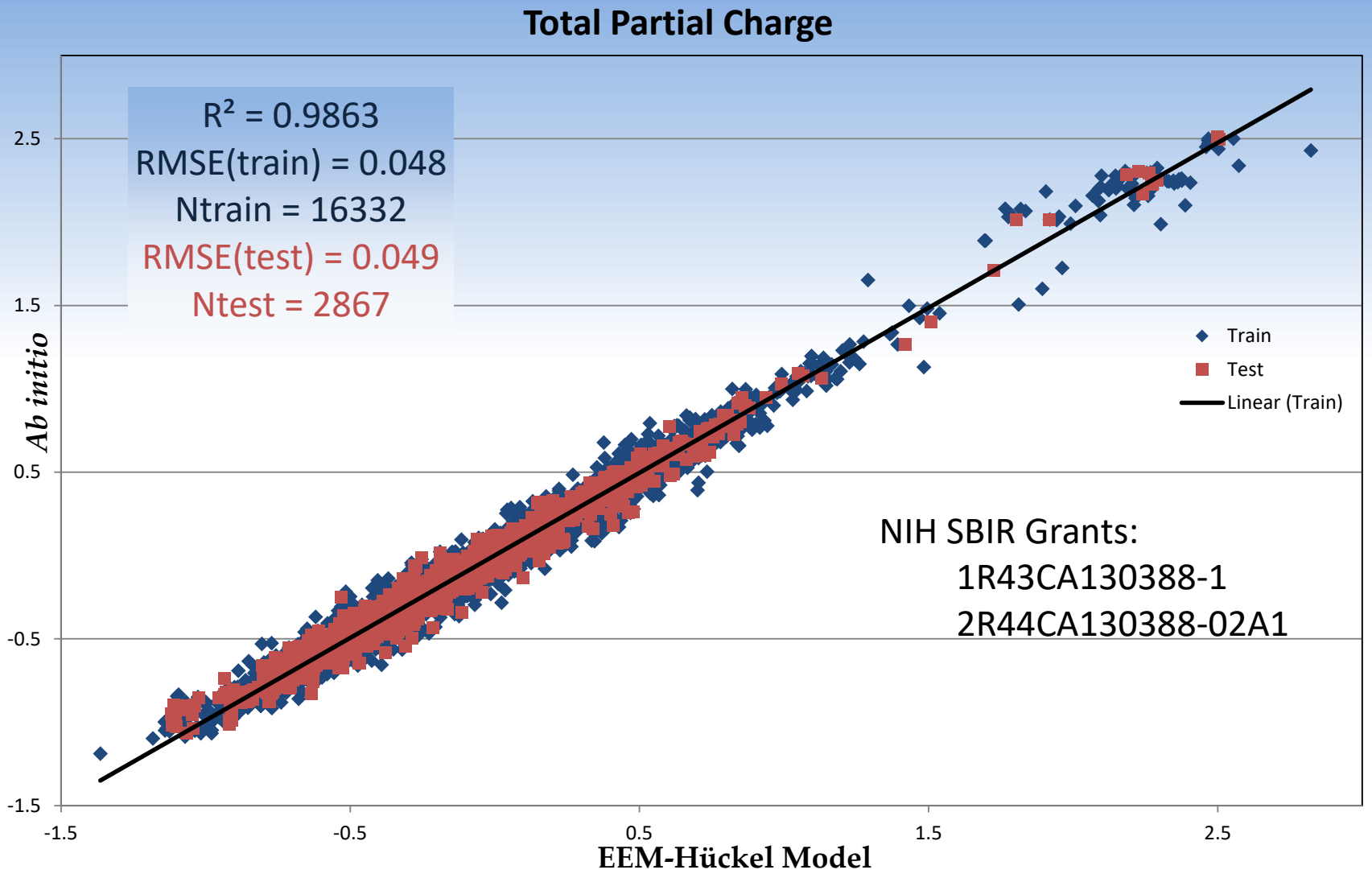
MAE = 0.34

RMSE = 0.48

R^2 = 0.97

* Internal test set compounds have not been used for model training but have been used to select the 10 ANNEs to appear in the final model

Atomic Partial Charge Descriptors



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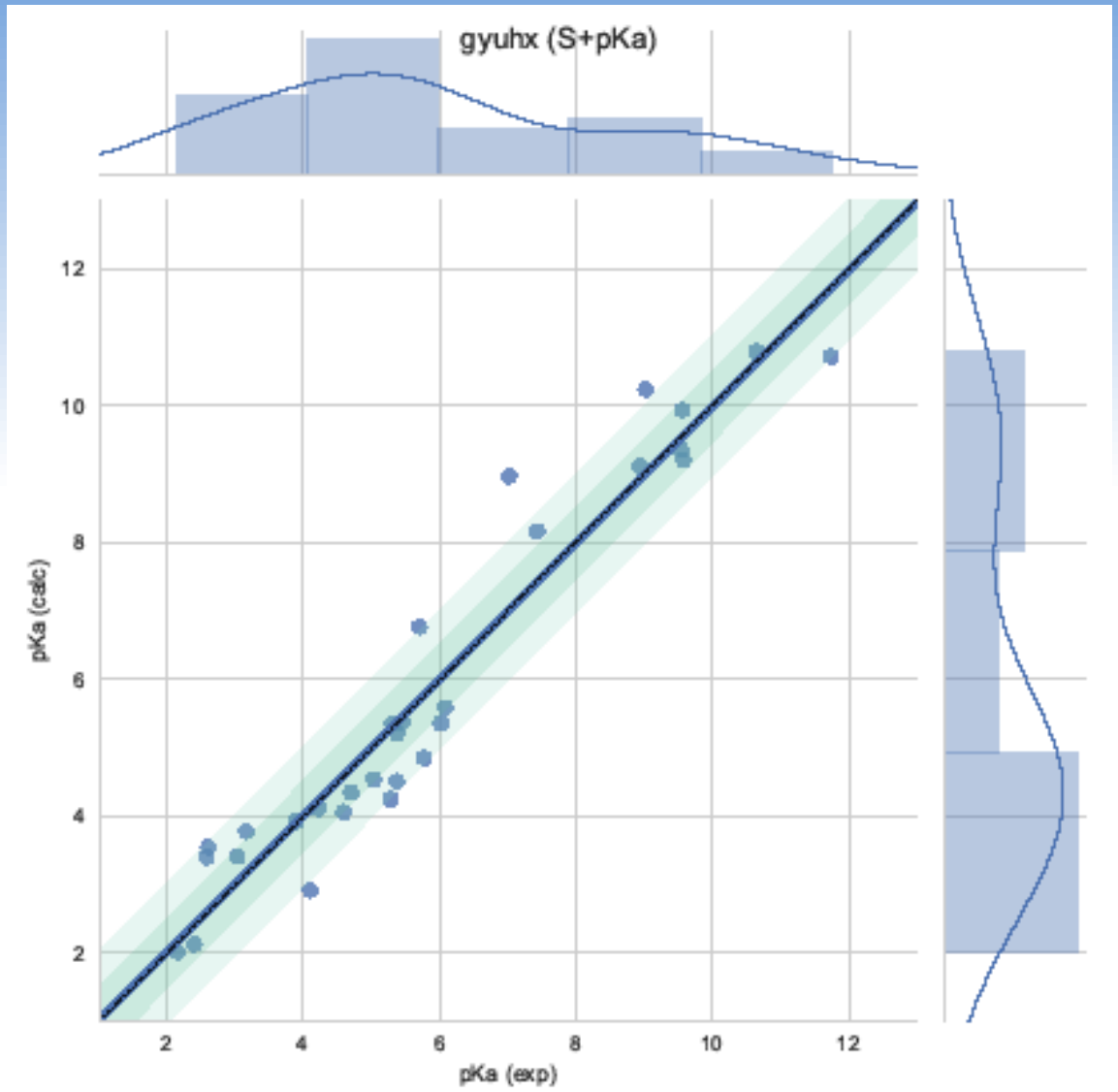
SAMPL6 pK_a challenge results



RMSE = 0.73

MAE = 0.579

ME = -0.009

R^2 = 0.925

Slope = 0.929

Computation time (wall clock) for all pK_a in all 24 compounds:

Under 2 seconds*

* This includes 145 other properties and ~400 molecular descriptors

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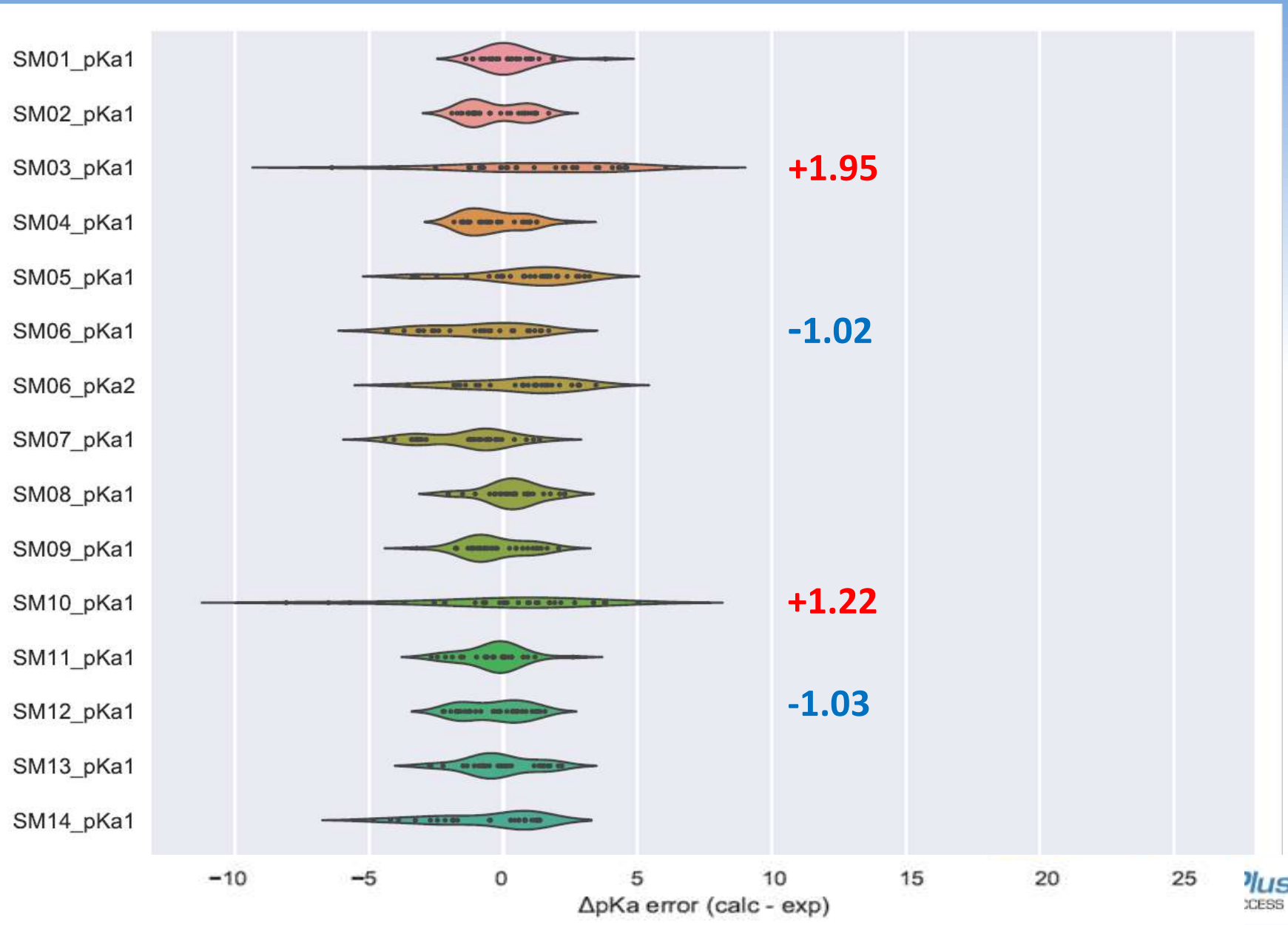
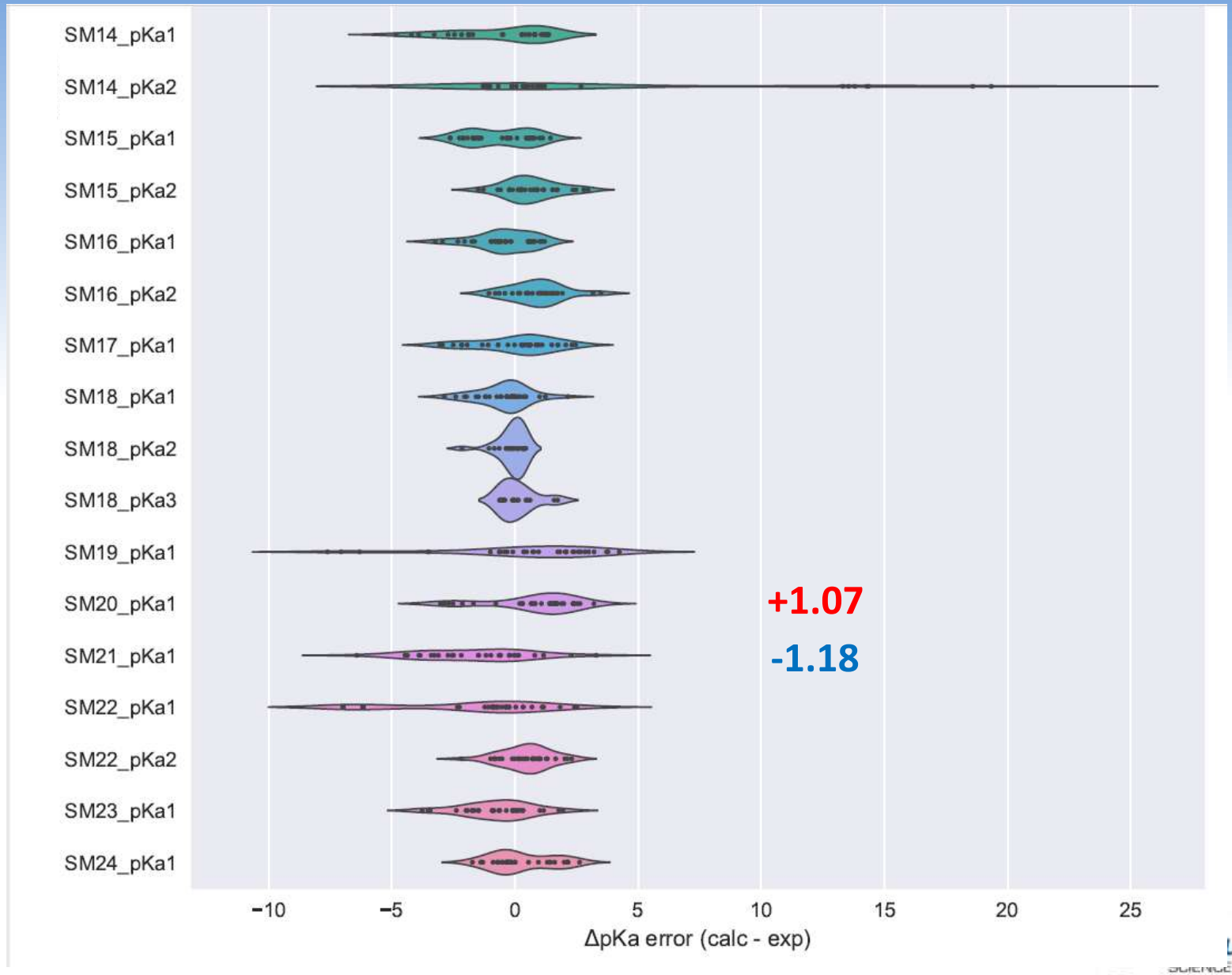
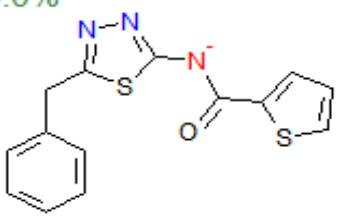
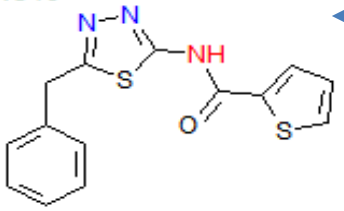
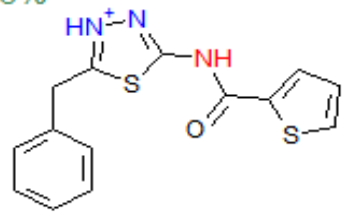
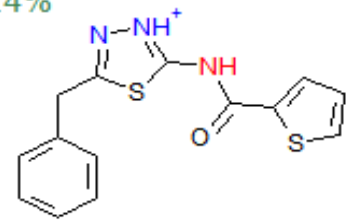
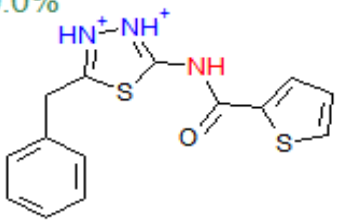
Deviations above 1 log unit



Deviations above 1 log unit



SM03 prediction

pKa	Macrostates	Microstates
	M^-	100.0% 
8.97		
	HM	100.0% 
0.20		
	H_2M^+	58.6%  41.4% 
-2.65		
	H_3M^{+2}	100.0% 

Experimental pKa = 7.02
UV-metric psKa,
with Yasuda-Shedlovsky
extrapolation

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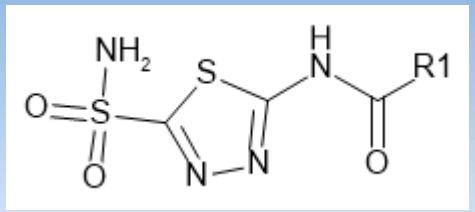
SM03 prediction- Training set analogs



All analogs in training set contain sulfonamide group and have reported pKa's ranging from 4.8-9.3

pKa	Macrostates	Microstates
	M^{-2}	100.0%
9.27		
	HM^{-}	57.2% / 42.8%
8.19		
	H_2M	100.0%
-1.92		
	H_3M^{+}	99.3%
-6.19		
	H_4M^{+2}	100.0%

Example:
First acidic dissociation
Is a mixture of two
Microstates.

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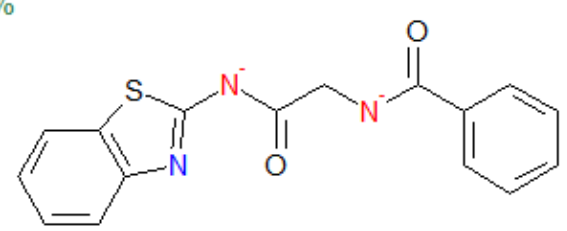
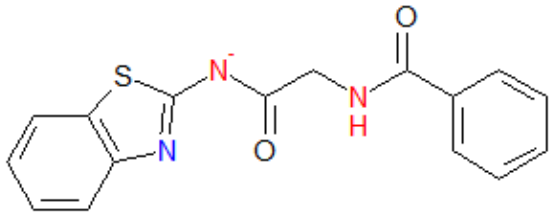
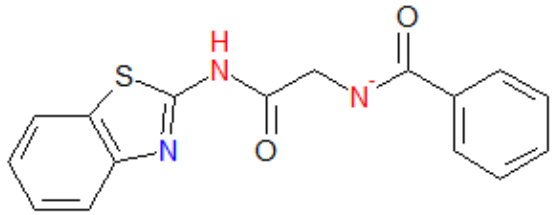
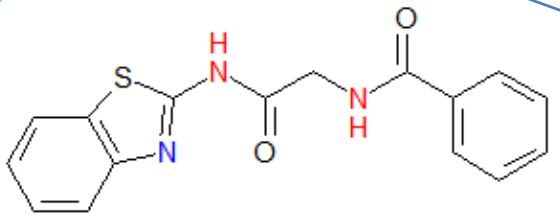
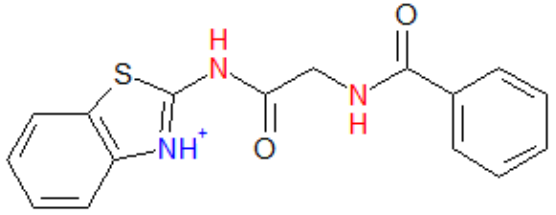
SM10 prediction

pKa	Macrostates	Microstates
	M^{-2}	100.0% 
11.31		
	HM^{-}	89.9%  10.1% 
10.24		
	H_2M	100.0% 
1.79		
	H_3M^{+}	100.0% 

Experimental pKa = 9.02
UV-metric psKa,
with Yasuda-Shedlovsky
extrapolation

SimulationsPlus
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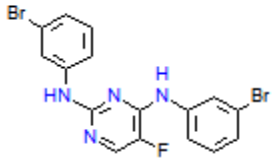
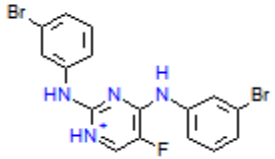
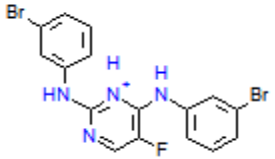
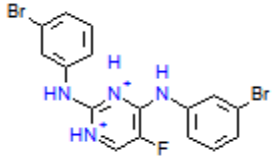
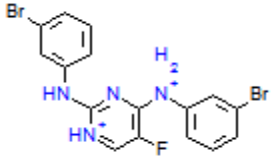
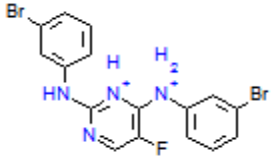
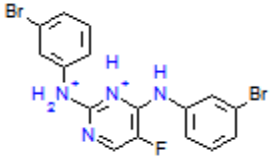
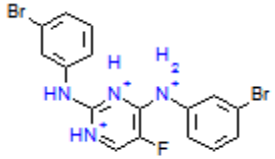
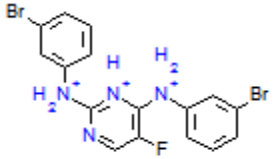
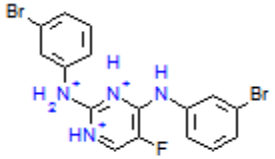
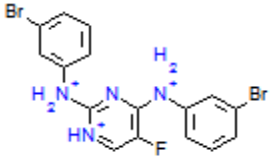
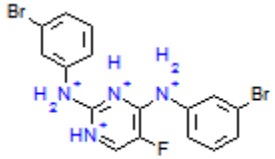
SM21 prediction

pKa	Macrostates	Microstates
	M	100.0% 
2.92		
	HM^{+}	86.2%  13.6% 
-0.43		
	H_2M^{+2}	47.8%  46.1%  3.5%  1.7% 
-1.69		
	H_3M^{+3}	72.4%  11.7%  8.6%  7.3% 
-2.83		
	H_4M^{+4}	100.0% 

Experimental pKa = 4.1
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