Impact of collaborative pKa modelling

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Importance of pKa in Drug Discovery

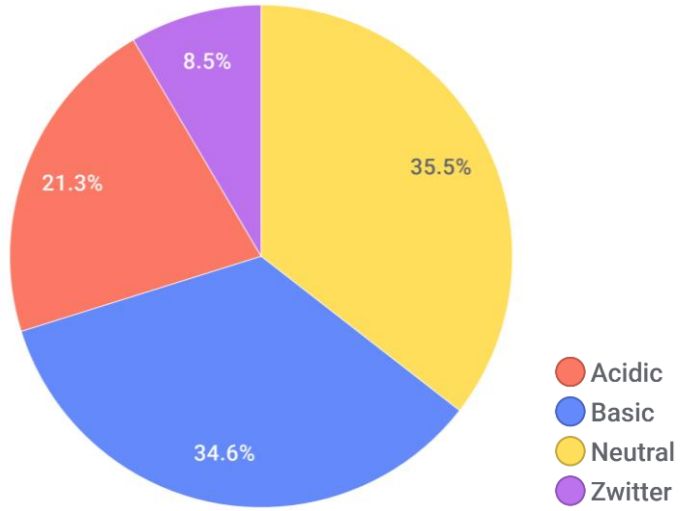
pKa has many impacts in drug discovery, such as:

- Affects absorption, distribution, metabolism and excretion
- Safety profile (off-targets liabilities, e.g. hERG inhibition)
- Binding with membranes, membrane analogs and proteins.
- Can affect drug-receptor binding (salt-bridge formation, desolvation)
- Useful in formulation, manufacturing and process control

pKa is the key parameter for other physchem properties, such as

- Lipophilicity
- Solubility
- Permeability
- Dissolution

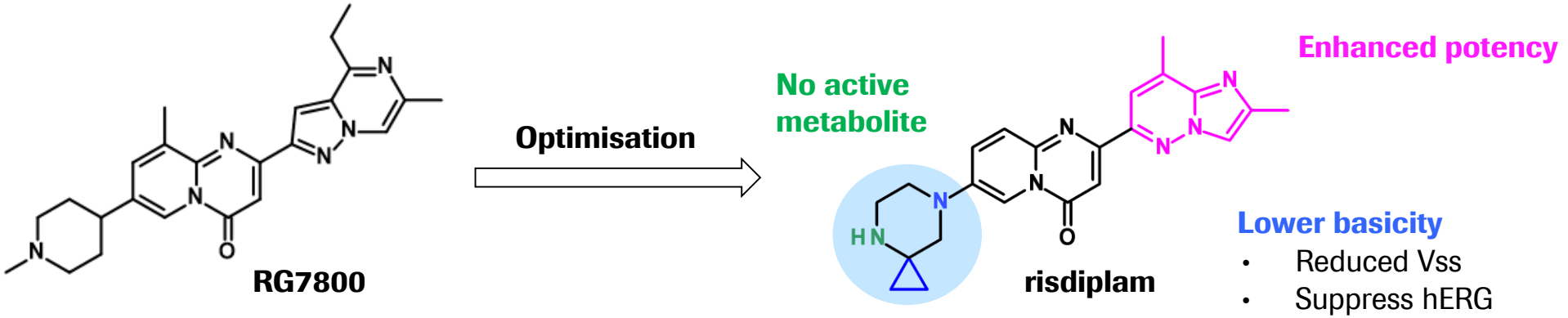
Ionization category of marketed drugs



Based on calculated pKa using AP11

pKa as Crucial Optimization Target

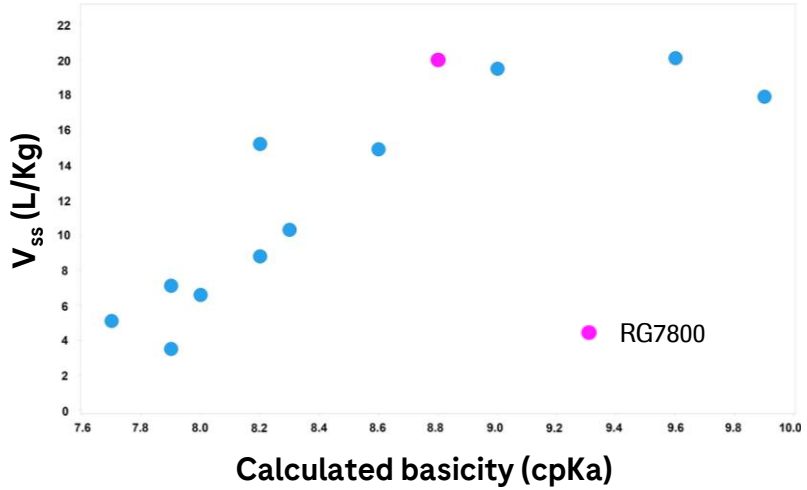
Evrysdi™ (risdiplam) is the first approved small molecule splicing modifier drug to treat spinal muscular atrophy (SMA)



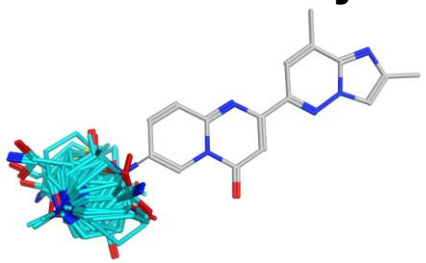
Ratni et al., J. Med. Chem. 2018, 61, 15, 6501−6517

pKa as Crucial Optimization Target

- Correlation of Volume of Distribution (Vss) and calculated basicity was observed in compound series
- Used *in silico* profiling to quickly assess library of basic amines
- Risdiplam was among the identified 40 compounds with optimal balance of basicity and lipophilicity



***In silico* library**



***In silico* profiling**

pka: 6.7 - 8.5
LogD: 1.5 - 3.0
MW: < 500

> 6,000 possible molecules

Prioritized 100 virtual compounds

Only 40 compounds were synthesized and characterized

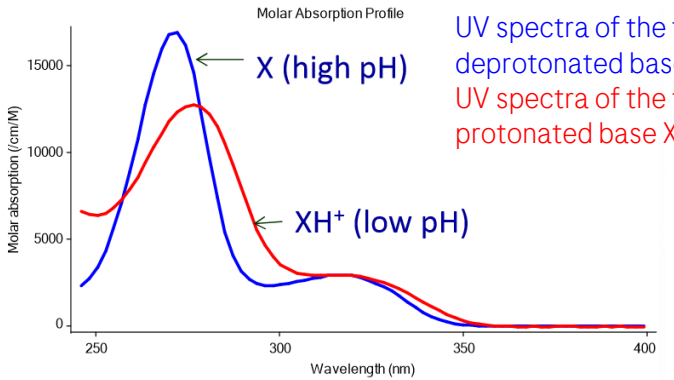
Ratni et al., J. Med. Chem. 2018, 61, 15, 6501−6517

Experimental setup at Roche

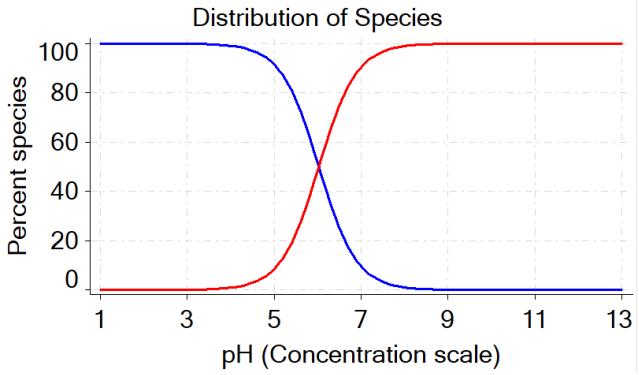
- pKas are routinely measured in **photometric titration** experiments with Pion Sirius T3 instrument
- **Global charge changes** (apparent pKa constants or macroconstants) are determined by this method

Photometric Titration

- Fast method for pKa values between 2 and 12
- Very little sample required (3µL of 10mM stock solution)
- High precision (repeatability within 0.03 pKa units)
- Sample must have a **pH-active chromophore**



UV spectra of the fully deprotonated base X
UV spectra of the fully protonated base XH^+

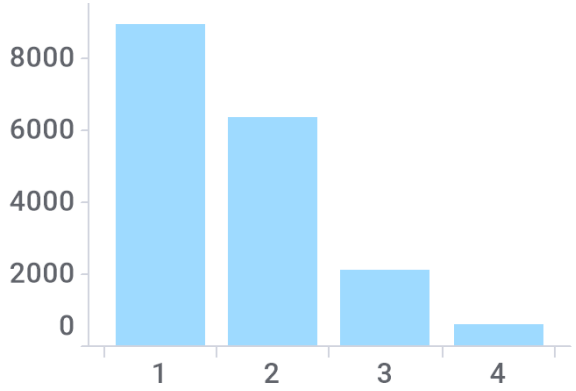


pH 2 to pH 12: UV change from red to blue:
pH at **50%** is reached is equal to pK_a

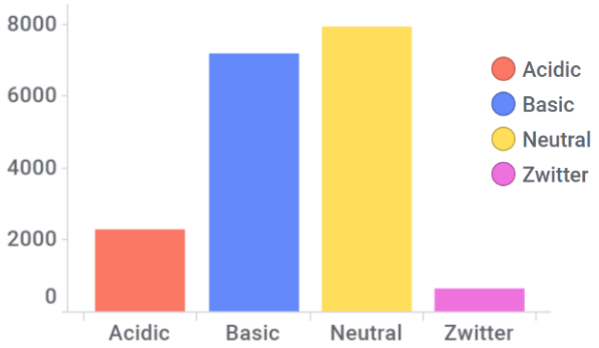
Overview collaboration pKa dataset

- Shared dataset contains more than **18’000 compounds** with over **30’000 pKa values**
- Includes pKa values measured with same photometric method to ensure consistent input for pKa model building
- Many compounds are **multiprotic** with potentially complex ionization behavior

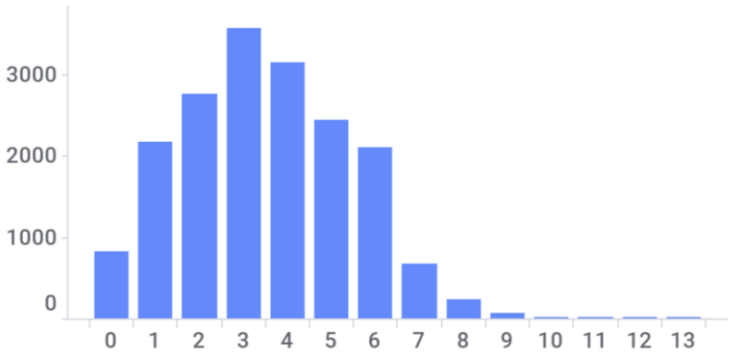
Number measured pKas per compound



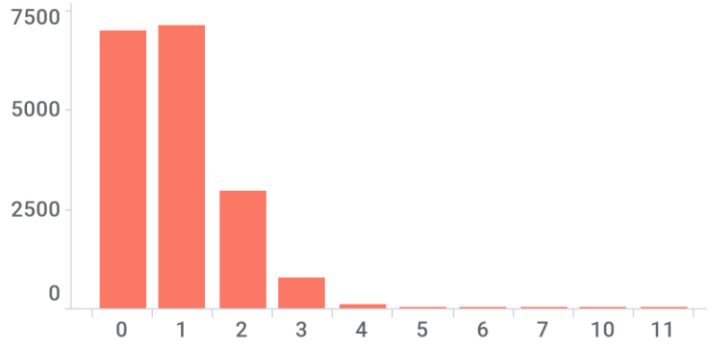
Ionization Category (pH 7.4) *



Number basic groups *



Number acidic groups *

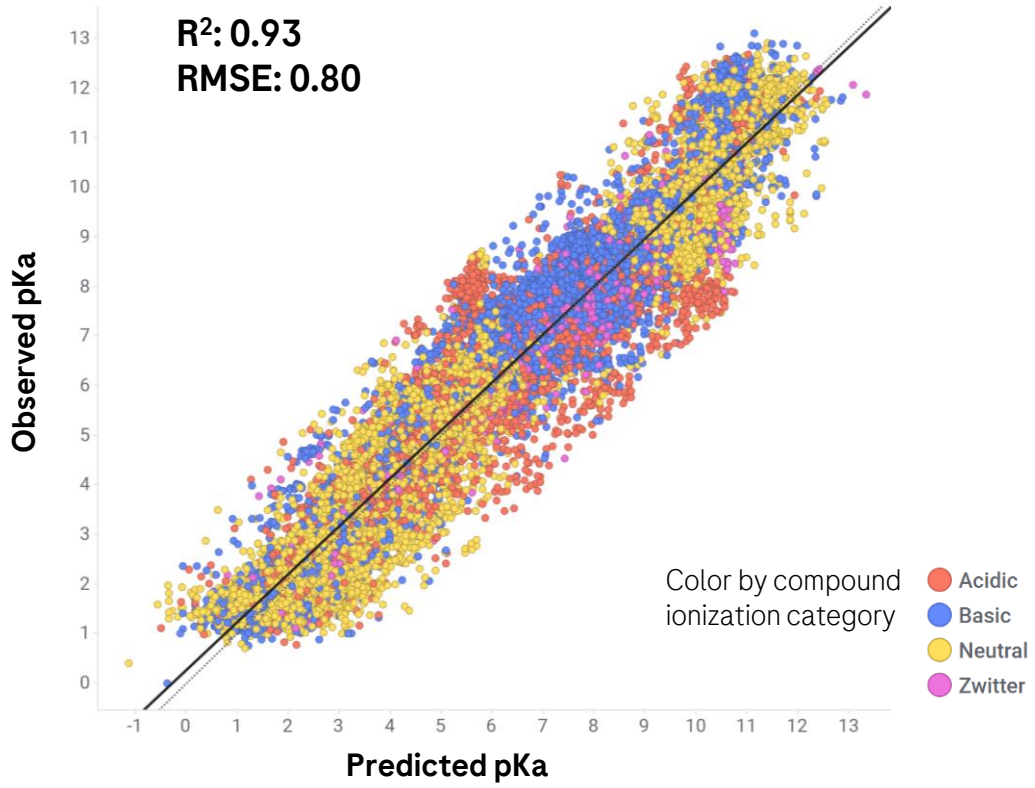


* Calculated values using ADMET Predictor 11

In silico pKa performance

Model performance prior to collaboration

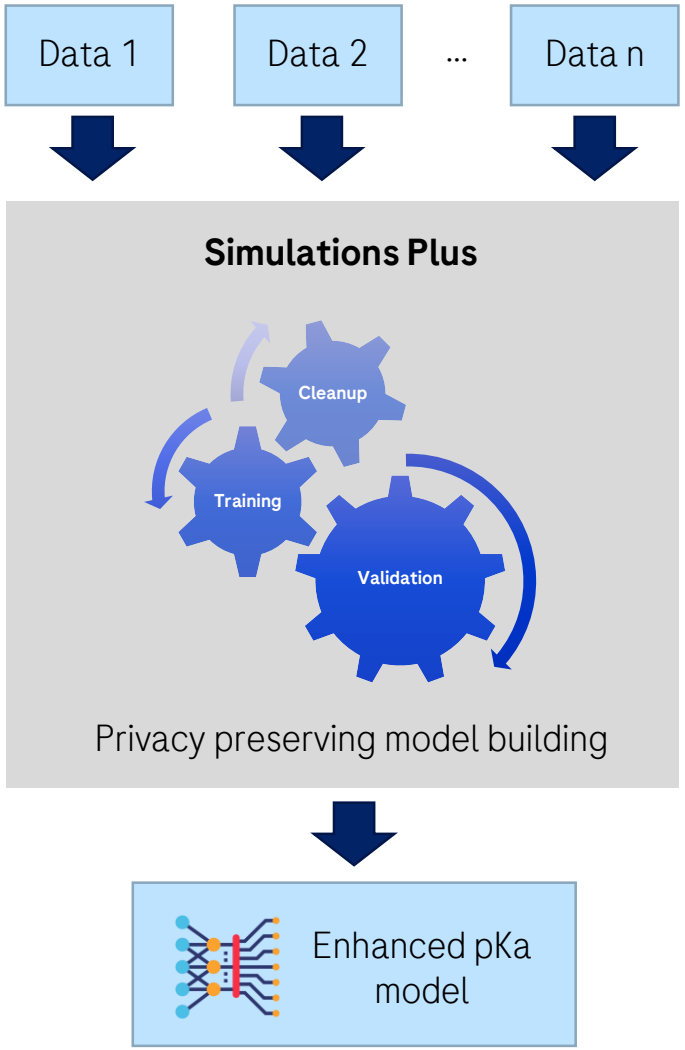
Prediction of full dataset with ADMET Predictor 10



- Proprietary chemical space unknown to the model
- For each compound experimental pKas are mapped to predicted pKas to generate global performance plot
- Overall good performance observed, 230 pKa values could not be mapped
- Groups of outliers indicated a **potential for improvement** with inclusion of the data into the model

Collaborative data sharing

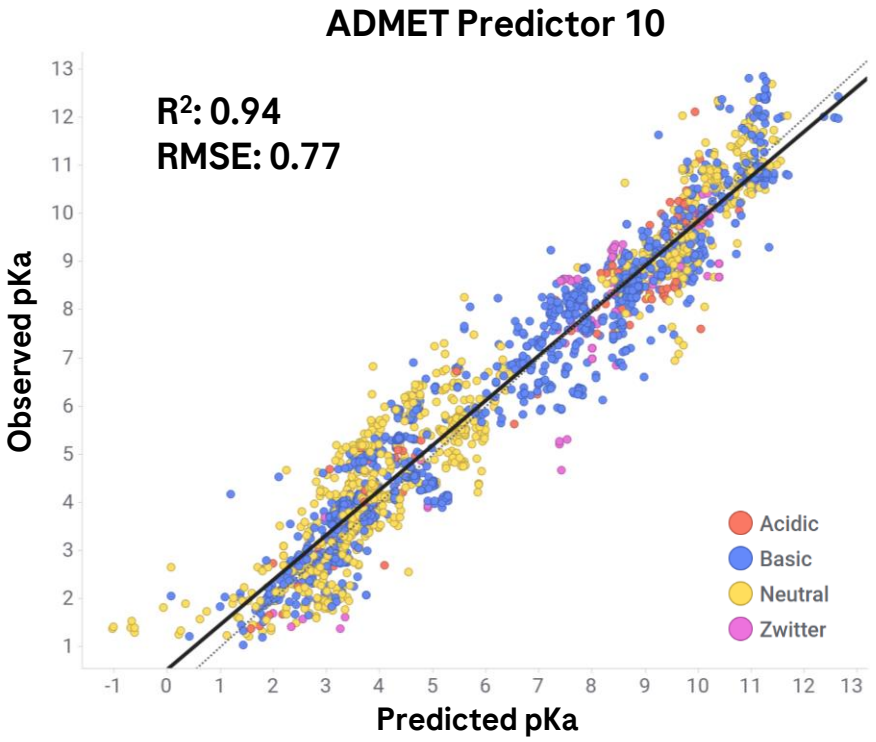
- Opportunity to enhance the pKa model with data covering our proprietary chemical space
- Iterative data curation to ensure data integrity
  - Discover data inconsistencies e.g. based on “pKa cliffs”
  - Collaborator feedback on problematic data to guide data inclusion
  - Early feedback on new model versions using not shared holdout external test sets performance
- Feedback about incompatible data can be used to flag data internally

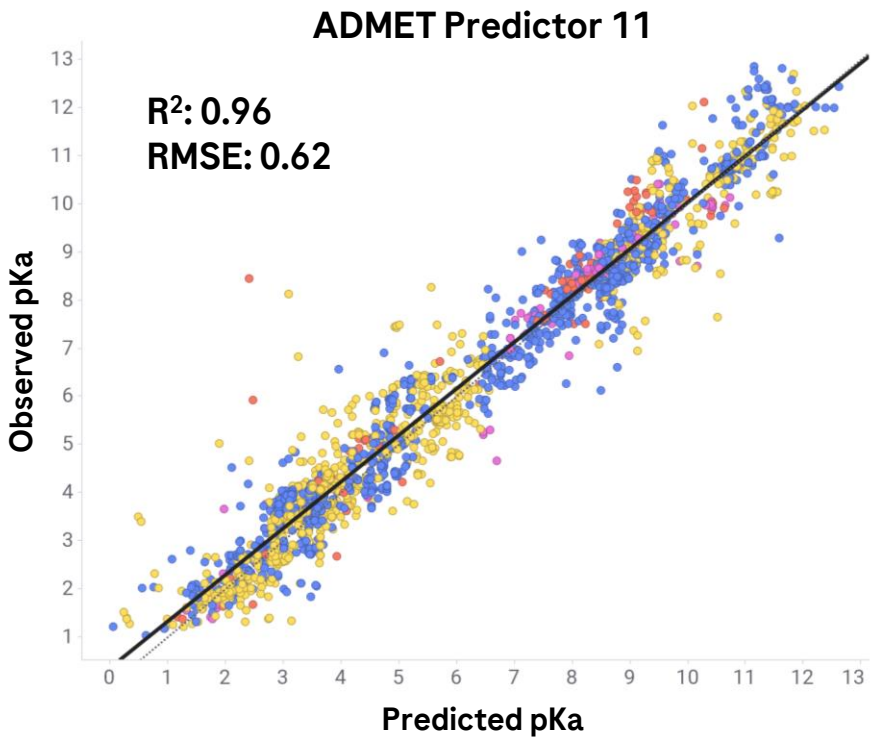


Performance Evaluation

Holdout Test Set

- Historic compounds that were not part of shared collaboration dataset (**1184 cpds** with **2605 pKa** values)

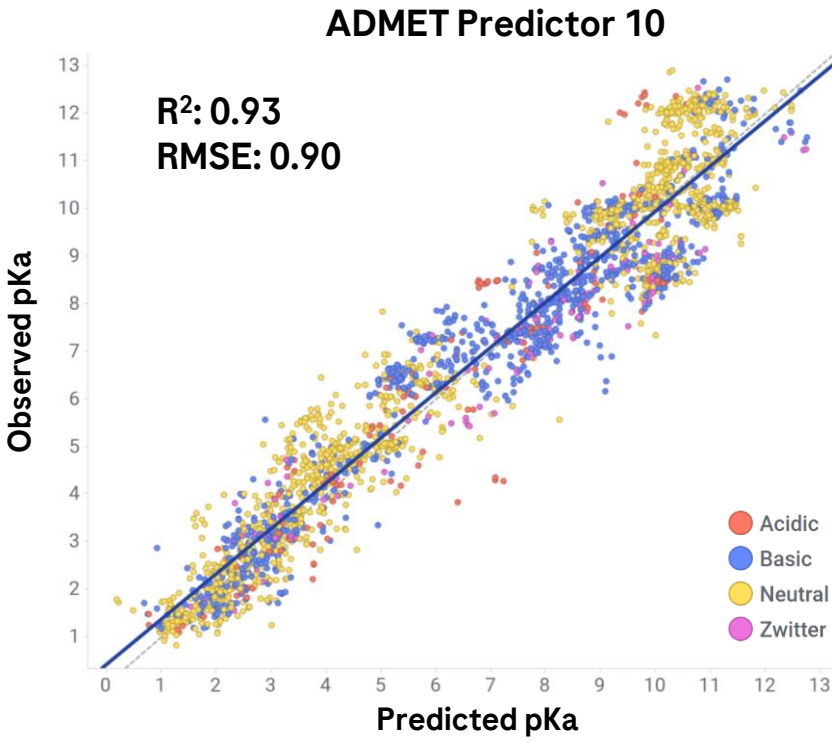


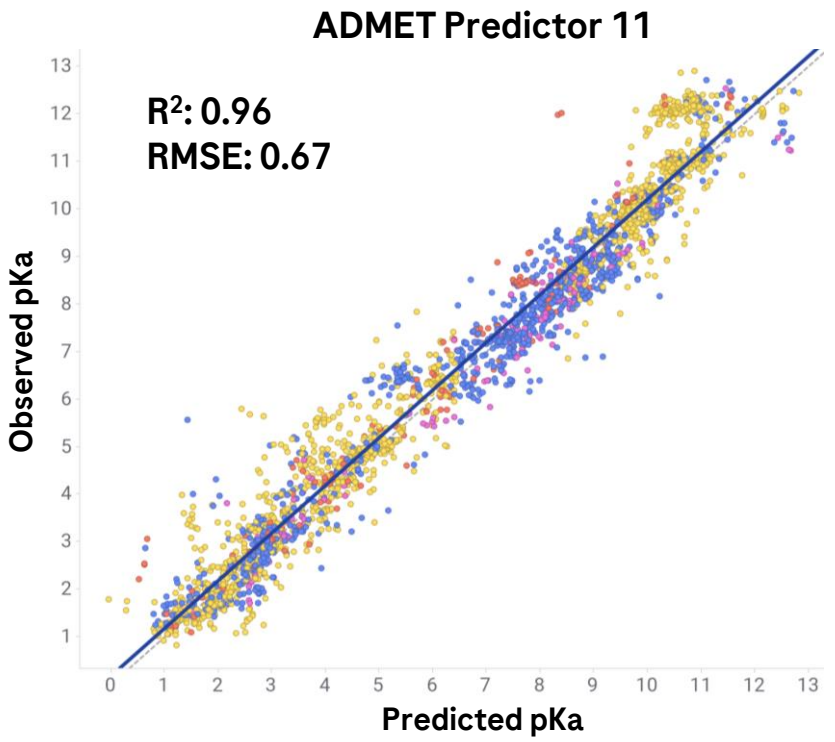


Performance Evaluation

Temporal Test Set

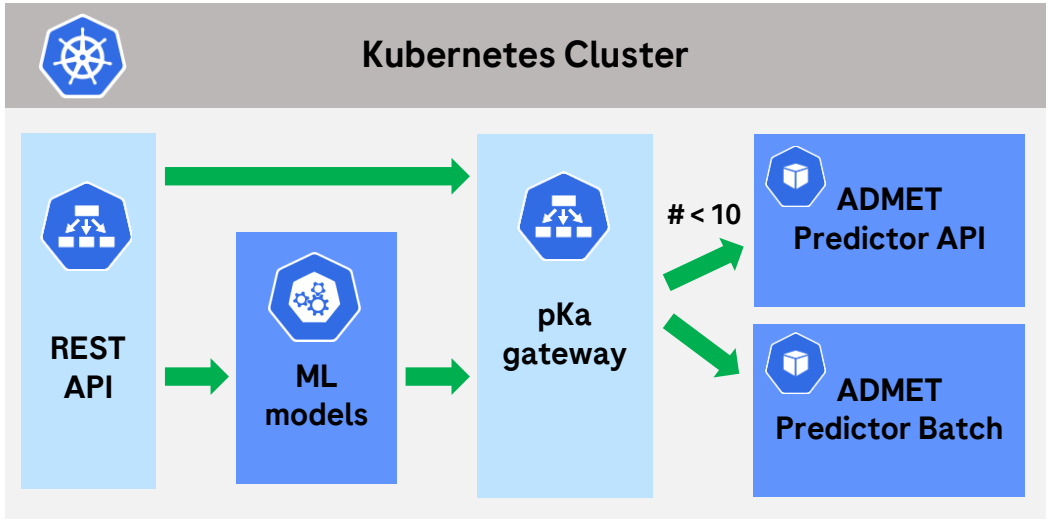
- Prospective analysis on temporal dataset (**1615 cpds** with **2942 pKa** values) reveals substantial improvements



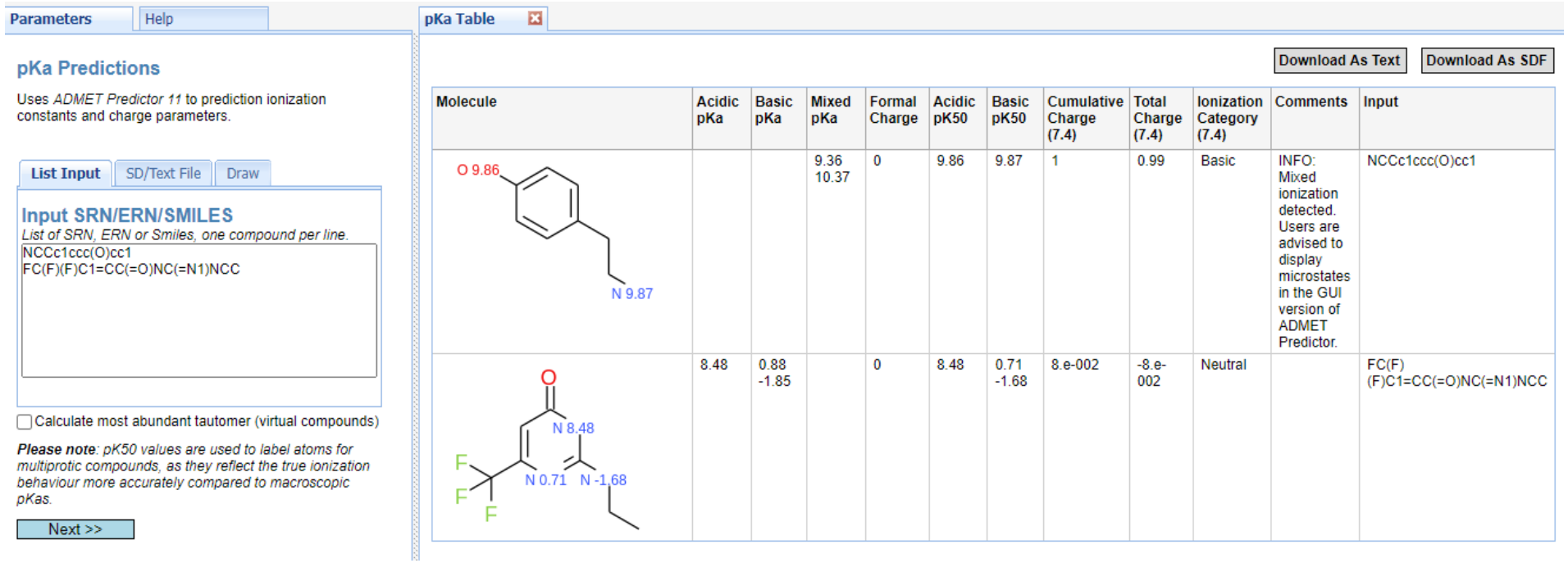


Technical deployment

- **REST API gateway**
  - Integrations with frontend systems (e.g. D360, DesignHub, MOE)
  - Focus on fast ad-hoc calculations
- **Linux client (on HPC cluster)**
  - Data science / cheminformatics
  - Library work
- **Windows client**
  - Available for all scientists
  - Detailed analysis of microstates etc.



Pipeline Pilot Web Interface



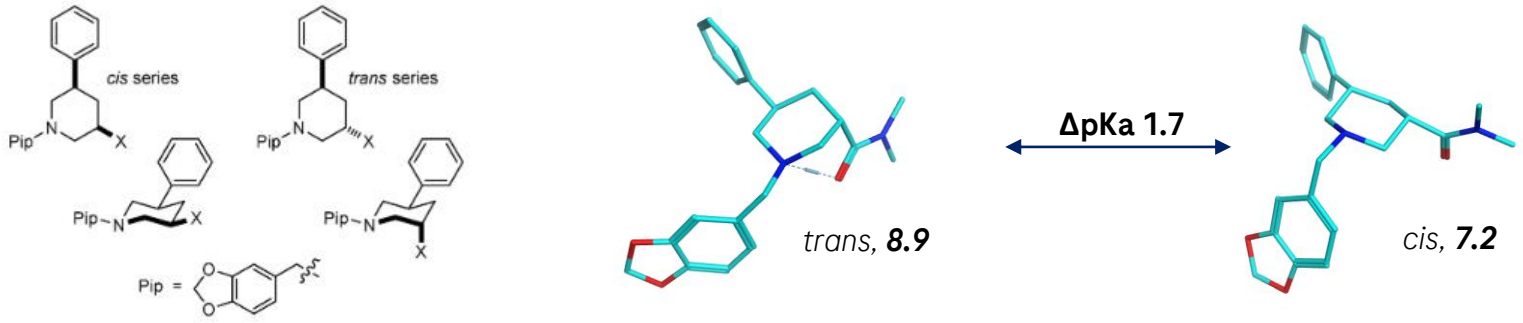
Molecule	Acidic pKa	Basic pKa	Mixed pKa	Formal Charge	Acidic pK50	Basic pK50	Cumulative Charge (7.4)	Total Charge (7.4)	Ionization Category (7.4)	Comments	Input
			9.36 10.37	0	9.86	9.87	1	0.99	Basic	INFO: Mixed ionization detected. Users are advised to display microstates in the GUI version of ADMET Predictor.	NCCc1ccc(O)cc1
	8.48	0.88 -1.85		0	8.48	0.71 -1.68	8.e-002	-8.e-002	Neutral		FC(F)(F)C1=CC(=O)NC(=N1)NCC

- Web interface for registered and virtual compounds for quick access to pKa predictions
- Input options:
  - Lists of corporate IDs or Smiles strings
  - SDF / SMILES text files
  - Interactive Biovia Draw sketcher
- Assignment of pK_{50} values to individual atoms in output molecules

Impact of Predicted pKa in Projects

- Utilize pKa predictions during the design stage,
  before synthesis, to prioritize most promising compounds
- Use predicted pKa values for experimental setup and validity checks
- Focus lab experiments on challenging pKa contributions:

Conformational effect of equatorial or axial position on amine pKa



Schnider et al., Chembiochem. 2020, 21, 212-234

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- Heiner Straumann

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