Expanding ADMET Predictor®'s Chemical Space: Enhanced bRo5 and Chameleon Molecule Predictions for HTPK

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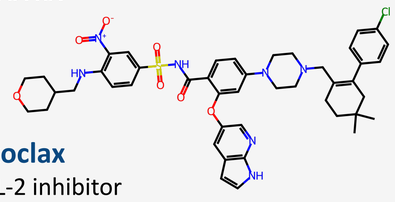
ABSTRACT

ADMET Predictor has been enhanced to accurately predict properties of beyond Rule-of-Five (**bRo5**) molecules, including macrocycles and PROTACs. We introduce new descriptors for molecular chameleonicity and three specialized models: **EPSA**[1] (Experimental Polar Surface Area), **ChromLogD**[2], and **ChameLogK**[3] (Chromatographic Chameleonicity), which serve as advanced molecular features for core ADMET predictions. These new descriptors improve predictive capabilities for various HTPK-input models, such as liver microsome/hepatocyte clearance, fraction unbound in plasma, and blood-to-plasma ratio. This subsequently enhances overall HTPK modeling accuracy. Validation on novel molecules demonstrates significant performance improvements for bRo5 compounds. Case studies reveal substantial improvements in predicting key *in vivo* endpoints for challenging chemical space, supporting modern drug discovery.

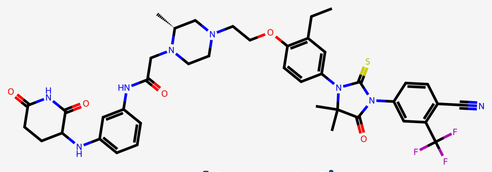
BRO5 COMPOUNDS AND CHAMELEONICITY

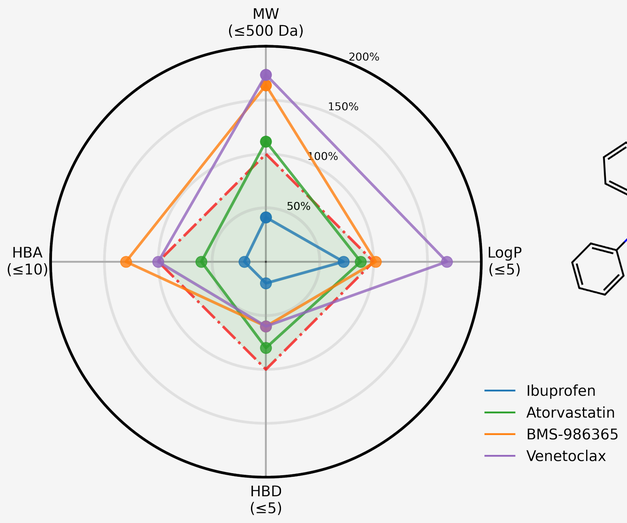
Lipinski's **Rule of Five** effectively filters drug-like molecules for good absorption but fails to account for molecular **chameleonicity**—the ability of molecules to dynamically shield polar groups and adopt different conformations in lipophilic versus aqueous environments—which enables many **bRo5** molecules to maintain good absorption despite apparent violations.



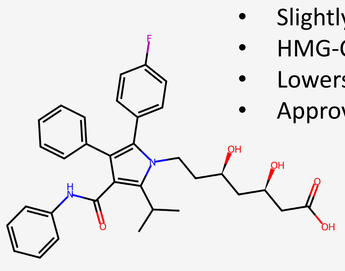
Venetoclax
- BCL-2 inhibitor
- Well beyond RO5 space
- Approved by FDA in 2016

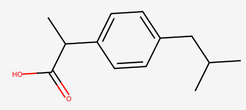
BMS-983665
- PROTAC degrader
- Targeting Androgen Receptor
- Significant *in vivo* potency
- Phase III clinical trials





Atorvastatin
- Slightly beyond RO5 space
- HMG-CoA inhibitor
- Lowers cholesterol level
- Approved by FDA in 1996





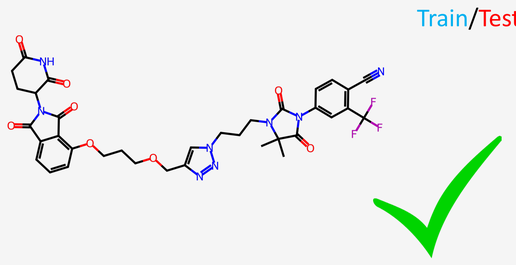
Ibuprofen
- Well within RO5 space
- Widely used nonsteroidal anti-inflammatory drug
- Discovered in the 1960s

NEW DESCRIPTORS AND FILTER MODELS

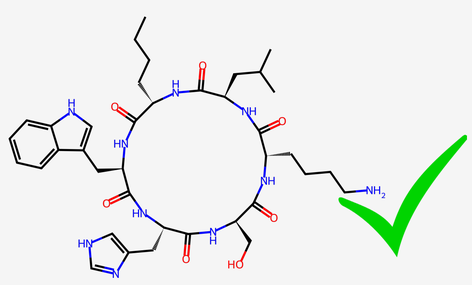
To enhance the predictive capabilities of ADMET Predictor, we developed new descriptors designed to capture the **chameleonic** behavior of compounds. They detect the presence of large **macrocycle** and describe various aspects of **long-range intra-molecular hydrogen bonds**. To further improve the ADMET models, we also trained two filter models: **PROTAC** and **CyclicPeptide**. Both have excellent performance and leverage our new descriptors.

PROTAC filter
- Trained on 59792 compounds (6456 PROTACs)
- Sensitivity: 1.00/1.00
- Specificity: 1.00/1.00

Train/Test



CyclicPeptide filter
- Trained on 59792 compounds (6456 cyclic peptides)
- Sensitivity: 1.00/0.996
- Specificity: 1.00/1.00



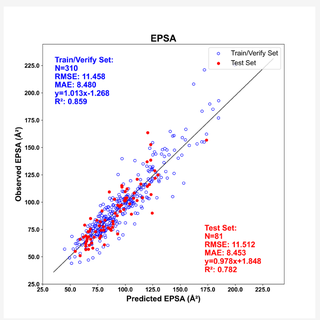
DEDICATED MODELS

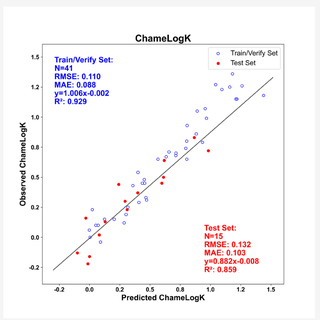
EPSA, ChamelogK, and ChromLogD are complementary experimental tools that provide key insights into the drug-likeness of beyond rule of five compounds, where traditional metrics often fall short.

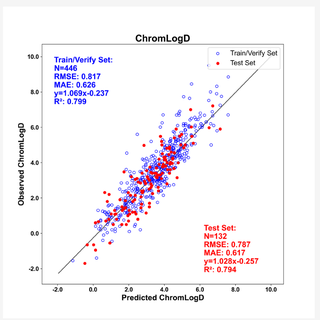
EPSA: Experimental Polar surface area
- Supercritical fluid chromatography technique that quantifies the experimentally accessible polarity of a molecule
- Captures conformational shielding effects
- Rationalizes permeability in large or flexible molecules

ChameLogK
- Chromatographic chameleonicity metric measuring deviation from expected retention behavior at 100% acetonitrile
- Threshold of 0.6 distinguishes chameleon from non-chameleon molecules
- Predicts oral bioavailability potential for bRo5 compounds

ChromLogD
- Replaces traditional shake flask LogD measurements which are only accurate up to ~4.5
- Provides accurate lipophilicity values for bRo5 molecules that typically exceed LogD 4.5
- Widely adopted for development and prioritization of PROTACs and other beyond RO5 molecules

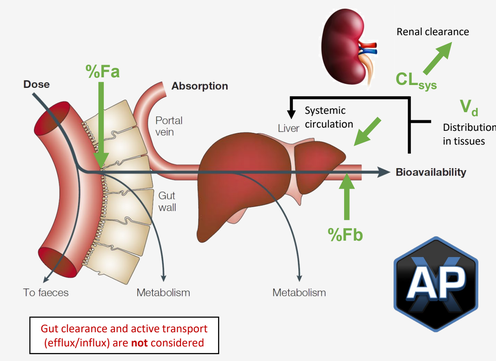




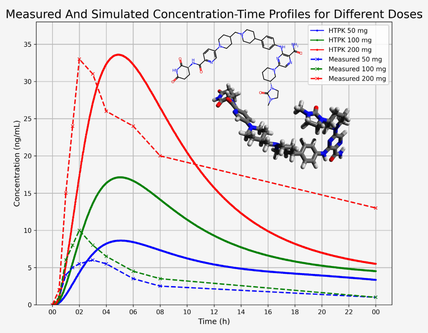


HIGH THROUGHPUT PHARMACOKINETICS

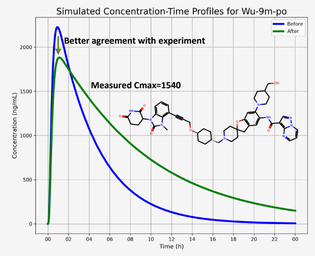
About HTPK
- Cp-time profiles
- Fraction absorbed, fraction bioavailable (%Fa, %Fb)
- Optimal dose
- Volume of distribution
- Static PK endpoints: AUC, Tmax, Thalf, etc.
- Tissue partition coefficients
- Species: human, monkey, dog, rat, mouse
- Administration routes: IR tablet, IR solution, IV bolus
- ACAT™ model (Advanced Compartmental Absorption and Transit)
- Part of ADMET Predictor

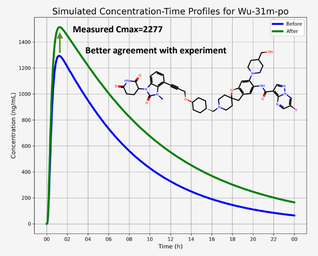


BTK degrader
- Bruton's tyrosine kinase (BTK) inhibitors are widely used in the treatment of patients with B-cell malignancies
- NX-5948: Selective BTK degrader, PROTAC
- First-in-human PK data[4]
- New **bRo5** models: solubility, RBP
- Optimized S+Peff (Effective permeability) at 0.08 [10^{-4} cm/s]
- Good agreement with the experiment



IRAK degraders
- Interleukin-1 receptor-associated kinase 4
- Key regulator of inflammatory diseases
- Mouse PK data[5]
- New **bRo5** models: solubility, RBP, Fraction unbound in plasma, Microsomal clearance
- Improved agreement with the experimental static PK endpoints





Property	Measured[5]	Old	New
Cmax [ng/mL]	1540	2226	**1881**
AUCt [h*ng/mL]	14793	10386	**17480**
Tmax [h]	2	0.93	**1.11**

Property	Measured[5]	Old	New
Cmax [ng/mL]	2277	1294	**1515**
AUCt [h*ng/mL]	26962	10794	**15640**
Tmax [h]	4	1.21	**1.26**

SUMMARY

ADMET Predictor has been enhanced with new descriptors and specialized models to accurately predict properties of **bRo5** molecules including macrocycles and PROTACs by capturing molecular chameleonicity. These improvements enhance predictions for critical HTPK-input parameters like clearance, fraction unbound, and blood-to-plasma ratio, enabling comprehensive PK profile simulations. Validation with NX-5948, a selective BTK degrader, showed good agreement between simulated and experimental first-in-human PK data using the new bRo5-optimized models.

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