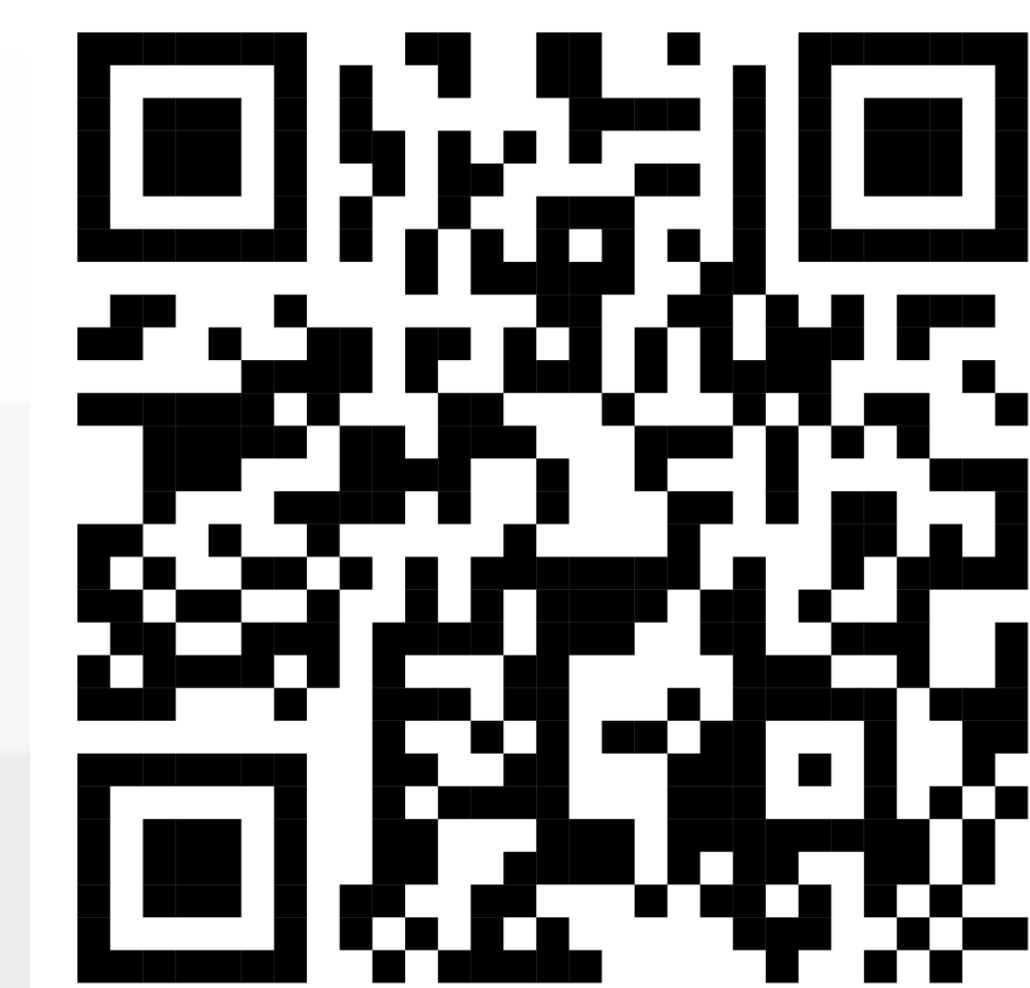


Novel Descriptors and Models for More Accurate ADME and PK Predictions of Beyond Rule of Five Molecules

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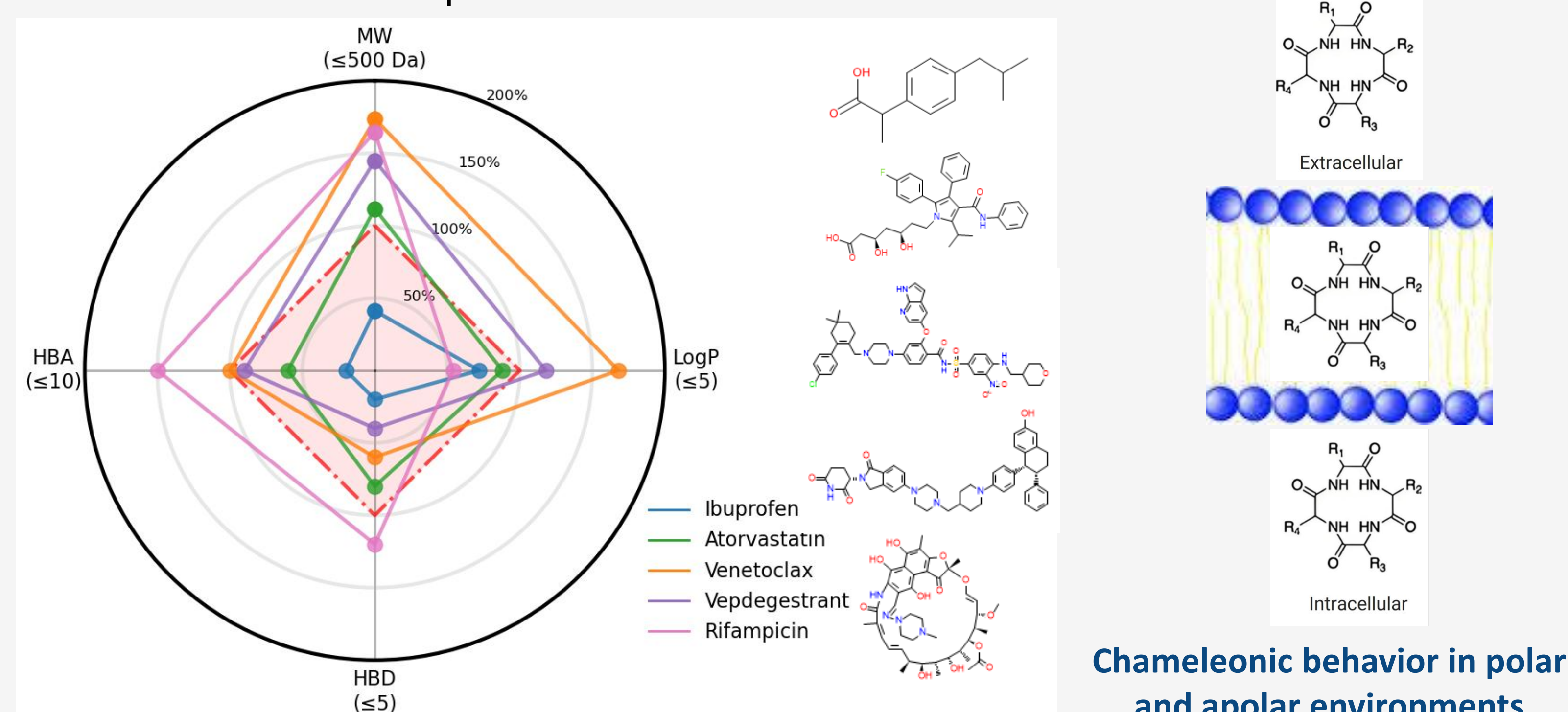


ABSTRACT

This study addresses the critical need for improved physicochemical descriptors and predictive models tailored to beyond Rule of Five (bRo5) compounds, including PROTACs and cyclic peptides. By integrating experimental parameters such as EPSA¹, ChromLogD², and ChameLogK³ with computationally derived features of molecular chameleonicity, we aim to establish new structure-property relationships that better capture the dynamic polarity and conformational adaptability of these complex molecules. The resulting models are designed to enhance the prediction of key in vitro ADME and in vivo pharmacokinetic (PK) endpoints, ultimately providing a more reliable framework for the design and optimization of developable bRo5 therapeutics. Case studies demonstrate the contribution of these new descriptors to model building as well as improvements in predicting key in vivo endpoints for this challenging chemical space.

bRo5 COMPOUNDS AND CHAMELEONICITY

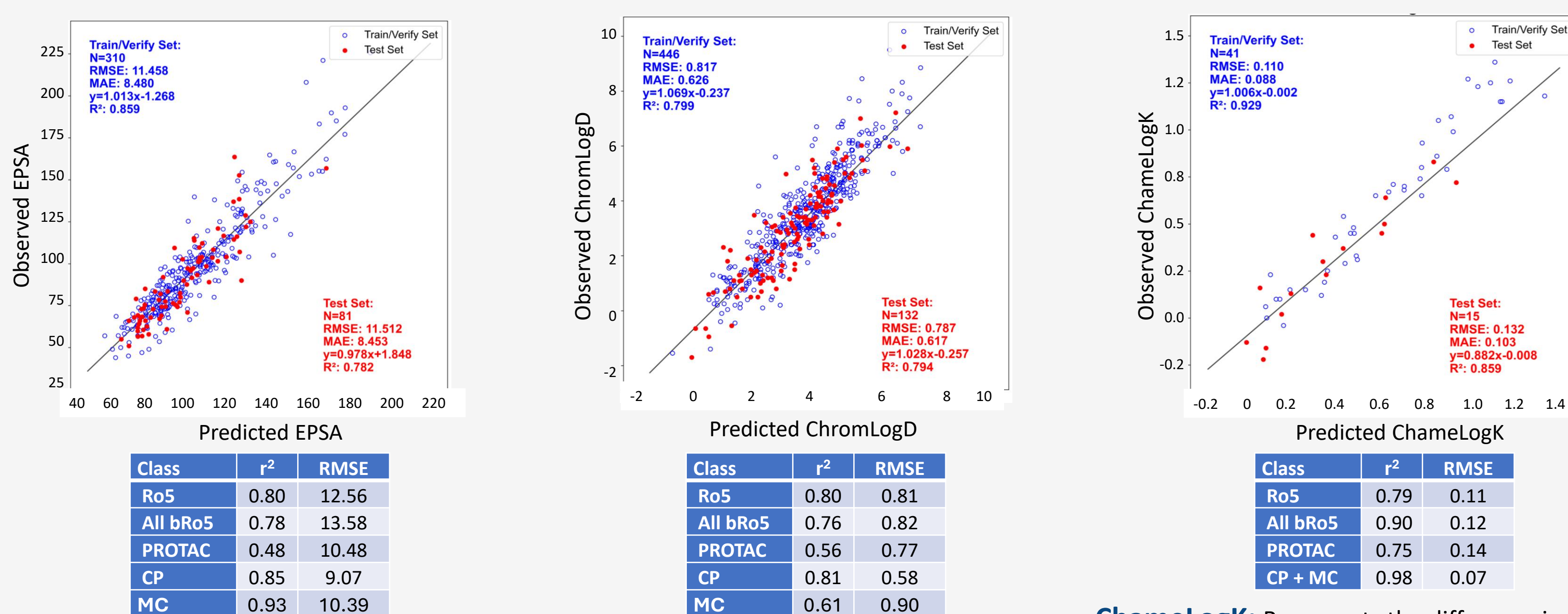
- Lipinski's Rule of Five⁴ has traditionally guided small-molecule drug development, but it does not adequately describe beyond Rule of Five (bRo5) compounds such as PROTACs, macrocycles, and cyclic peptides.
- bRo5 molecules expand therapeutic possibilities by enabling novel target engagement, yet their large size, flexibility, and polarity challenge conventional ADME and PK assumptions.



- A key property of many bRo5 compounds is **chameleonicity**, allowing them to dynamically adjust conformation and polarity to balance solubility and membrane permeability.
- Because static descriptors like logP and TPSA fail to capture this behavior, new dynamic descriptors and predictive models (e.g., EPSA, ChameLogK, ChromLogD) are needed to better predict bRo5 ADME and PK properties.

NEW DESCRIPTORS AND bRo5 MODELS

- High-quality descriptors are critical for accurate ML models, often outweighing the choice of algorithm, as demonstrated in a recent J&J paper using ADMET Predictor descriptors⁵. To better capture **chameleonic** behavior, new descriptors capturing **macrocyclic** structure and **long-range intramolecular hydrogen bonding** were developed and incorporated into updated and new models.
- These descriptors were used to train models that can quickly detect PROTACs and cyclic peptides with > 99% sensitivity and specificity, as well as models that predict EPSA, ChromLogD, and ChameLogK.



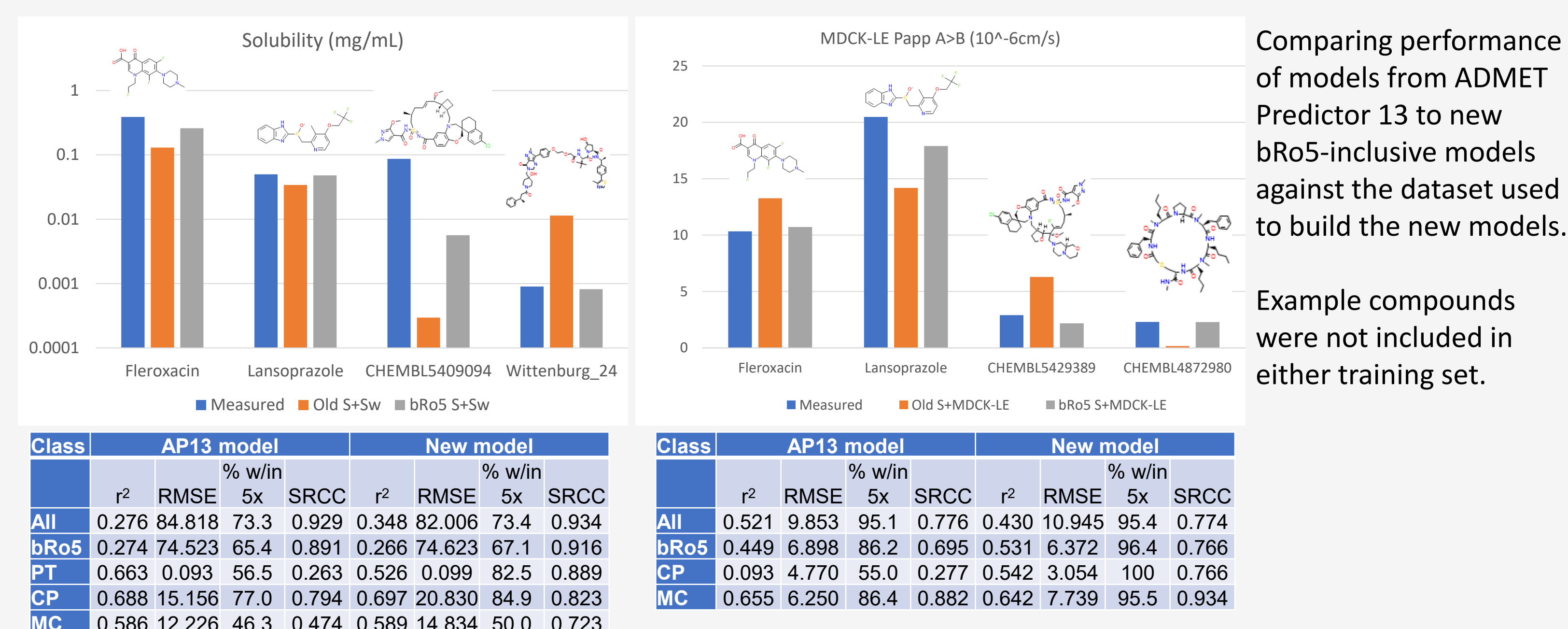
EPSA: Supercritical fluid chromatography technique that quantifies the experimentally accessible polarity of a molecule

ChromLogD: Replaces traditional shake flask LogD measurements which are only accurate up to ~4.5

ChameLogK: Represents the difference in measured log k' (chromatographic capacity factors) of a compound under different mobile phase conditions (aqueous vs. more lipophilic)

IMPROVED ADME MODEL PERFORMANCE

New regression models including bRo5 data were trained for thermodynamic water solubility, in vitro permeability (PAMPA, MDCK1, MDCK-LE, MDCK-MDR1, Caco-2, and effective permeability in human jejunum (S+Peff) – a model that scales various datasets to human jejunal perfusion experiments from Lennernas et al⁸, and in five species (human, monkey, dog, rat, mouse) liver microsome and hepatocyte intrinsic clearance, blood-to-plasma ratio, and fractions unbound in plasma, microsomes and hepatocytes. Models were either ensembles of neural networks or XGBoost.

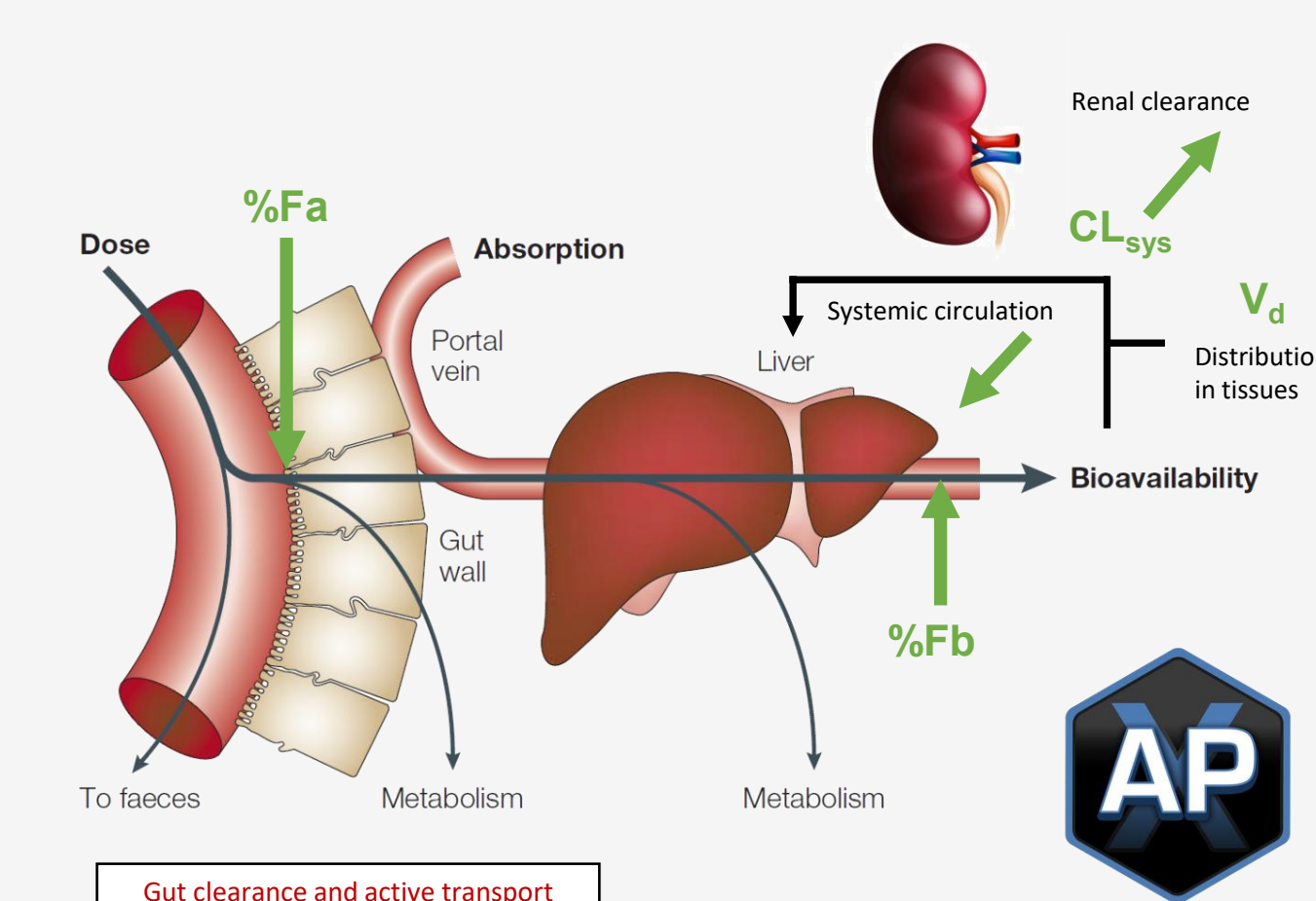


Comparing performance of models from ADMET Predictor 13 to new bRo5-inclusive models against the dataset used to build the new models. Example compounds were not included in either training set.

IMPROVED HIGH THROUGHPUT PK SIMULATIONS

About HTPK

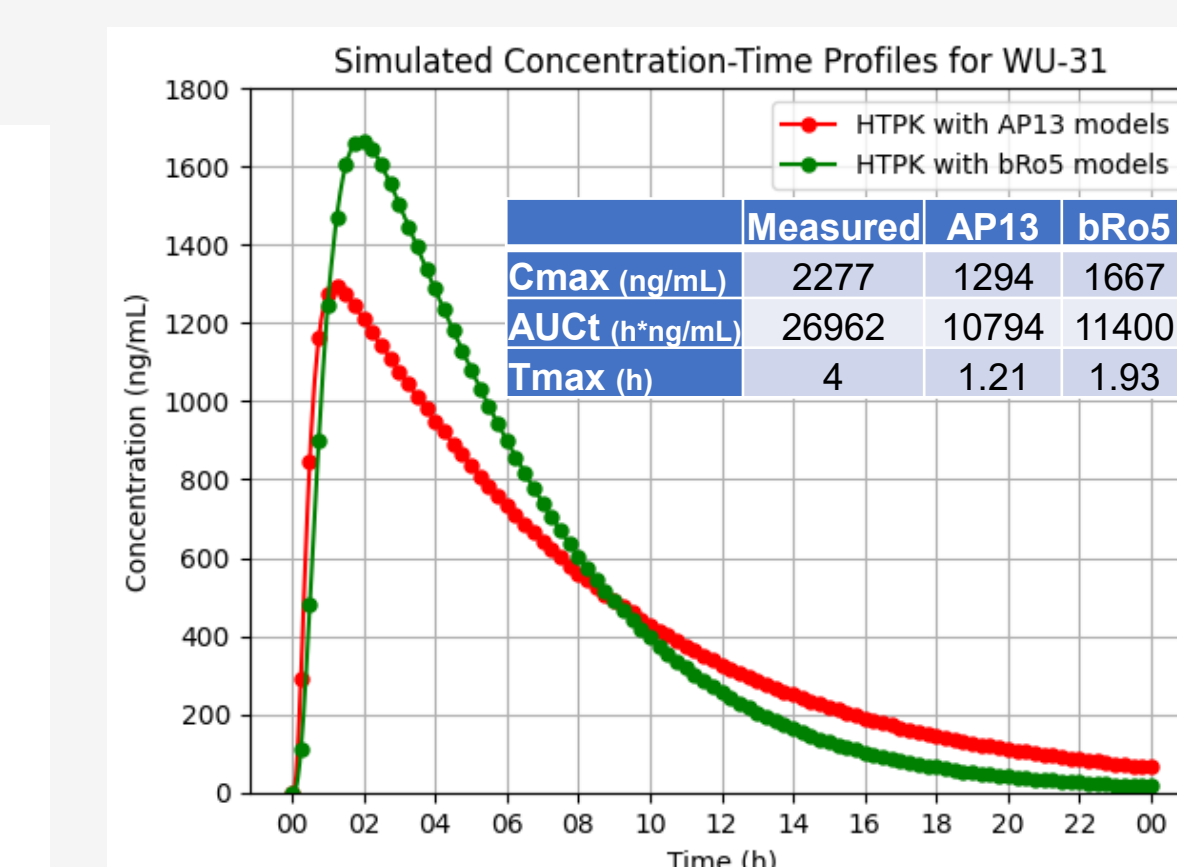
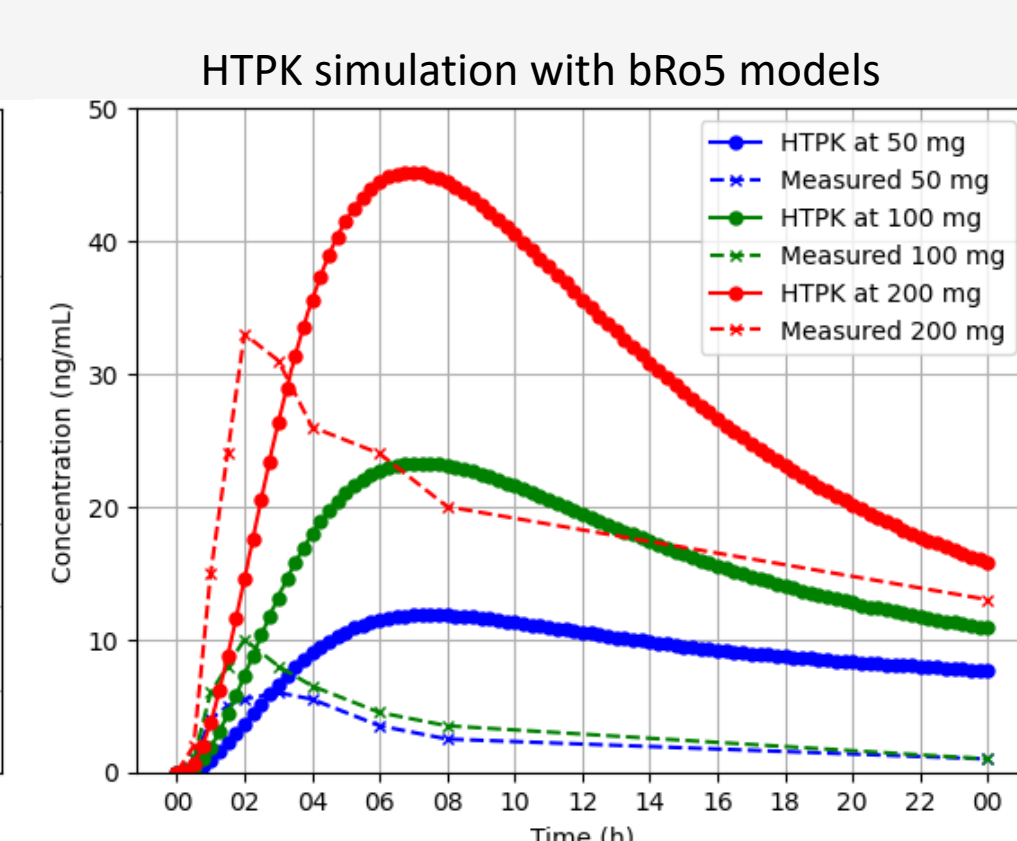
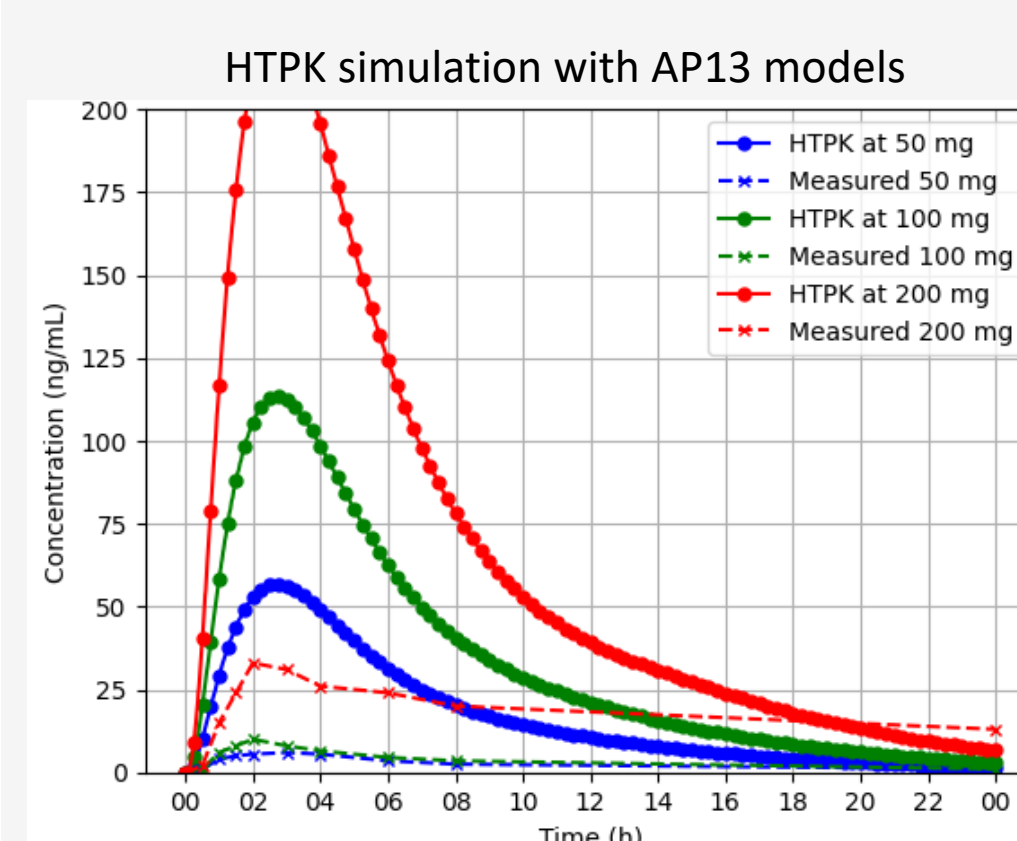
- Modified version of the full ACAT model available in GastroPlus designed to mechanistically simulate the in vivo PK of thousands of compounds in minutes⁷
- Uses measured data and/or AP model predictions for input (solubility, permeability, microsome clearance, fraction unbound in plasma, etc)
- Produces full Cp-time profiles along with important endpoints (%Fa, %Fb, AUC, Tmax, Thalf, etc.)
- Calculates optimal dose and schedule
- Species: human, monkey, dog, rat, mouse



HTPK was performed on PROTACs using either ADMET Predictor 13 or new bRo5-inclusive models

BTK degrader

- Bruton's tyrosine kinase (BTK) PROTAC NX-5948 (bexobrutideg) with 1st-in human Cp time curves⁸
- HTPK using new bRo5 models as inputs produced simulations more similar to those reported



SUMMARY

Expanding the descriptor space and retraining models with explicit inclusion of bRo5 chemistry leads to substantial improvements in ADME and PK predictions by better capturing the dynamic behavior of large, flexible, chameleonic molecules. These advances enable more accurate prediction of developability for PROTACs and related modalities, supporting a necessary shift toward bRo5-specific modeling frameworks in modern drug discovery.

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