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The love story of physchem data and oral bioavailable bRo5 drug candidates

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The beyond-rule-of-5 (bRo5) chemical space is anticipated to hold a wealth of effective agents for challenging drug targets. However, the widespread utilization of bRo5 compounds in drug discovery is currently hindered by a few obstacles, with DMPK (Drug Metabolism and Pharmacokinetics) limitations being the most significant concern. This is primarily attributed to the substantial size and flexibility of bRo5 molecules, leading to limited understanding of a) the array of essential experimental physicochemical descriptors crucial for *in vitro* ADME (Absorption, Distribution, Metabolism, and Excretion) and b) the preferred conformations in nonpolar, membrane-like, and aqueous environments.
As conventional strategies employed to design or optimize drugs compliant with the Rule of 5 (Ro5) may not adequately apply to bRo5, a specialized property-based drug design approach must be integrated into the bRo5 drug discovery process. The focus of this presentation centers on the recent advancements in establishing a set of physicochemical determinants tailored specifically for bRo5. Notably, the discussion centers on lipophilicity, polarity, and chameleonicity descriptors, which play crucial roles in solubility and permeability modeling and prediction.
Moreover, computational endeavors aimed at creating a permeable bRo5 (membrane-like and aqueous environments) chemical space and predicting chameleonicity and other properties from scratch will also be explored.