PK-Cast: Free Webtool for Triaging Compounds with Undesired Pharmacokinetic Properties

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Despite the crucial role of pharmacokinetics (PK) in ensuring the safety and efficacy of therapeutic agents, inadequate PK profiles account for 16% of drug failures in Phase I clinical trials. Computational models that predict PK properties, such as those related to drug absorption, metabolism, distribution, and excretion, are therefore critical to flagging compounds with inadequate PK profiles that are found active in high-throughput screening (HTS) campaigns. We have collected, curated and integrated a database of fifteen major PK endpoints containing more than 9,000 compounds after curation. Then, we succeeded to develop predictive quantitative structure-activity relationship (QSAR) models for nine out of 15 PK endpoints, including hepatic stability, renal clearance, blood-brain barrier permeation, and microsomal intrinsic clearance. In contrast to many publicly available QSAR models, those developed herein followed best practices with respect to data curation and model validation. We present a case study where we used our models to predict the PK properties of all DrugBank compounds, as well as only those compounds targeting SLC6A4, ADRB2, HMGCR, and CaSR. Across all analyses, we found that almost all compounds have a half-life of greater than 30 minutes at the subcellular level in the liver and are metabolized 50% or more within 60 minutes in the liver. We also found that among all DrugBank compounds, half have a half-life of 30 minutes or greater in the liver tissue; half have a renal clearance of 0.5 ml/min/kg or greater; and half permeate the blood-brain barrier, whereas each group of compounds targeting different receptors show different trends. This confirms that desired PK properties should be considered within the context of the compound's indication. Thus, we propose that medicinal chemists use the developed models to prioritize HTS hit compounds with desired PK profiles for respective indications.