LipMetE (Lipophilic Metabolism Efficiency) as a Simple Guide for Half-Life and Dosing Regimen Prediction of Oral Drugs

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The in vivo half-life is a key property of every drug molecule, as it determines dosing regimens, peak-to-trough ratios and often dose. However, half-life optimization can be challenging due to its multifactorial nature, with in vitro metabolic turnover, plasma protein binding and volume of distribution all impacting half-life. We here propose that the medicinal chemistry design parameter Lipophilic Metabolism Efficiency (LipMetE) can greatly simplify half-life optimization of neutral and basic compounds. Using mathematical transformations, examples from preclinical GABAA projects and clinical compounds with human pharmacokinetic data, we show that LipMetE is directly proportional to the logarithm of half-life. As the design parameter LipMetE can be swiftly calculated using the readily available parameters LogD, intrinsic clearance and fraction unbound in human liver microsomes or hepatocytes, this approach enables rational half-life optimization from the early stages of drug discovery projects.

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