Drug-like properties and the causes of poor solubility and poor permeability.

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Drug-like properties and the causes of poor solubility and poor permeability

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Abstract

There are currently about 10 000 drug-like compounds. These are sparsely, rather than uniformly, distributed through chemistry space. True diversity does not exist in experimental combinatorial chemistry screening libraries. Absorption, distribution, metabolism, and excretion (ADME) and chemical reactivity-related toxicity is low, while biological receptor activity is higher dimensional in chemistry space, and this is partly explainable by evolutionary pressures on ADME to deal with endobiotics and exobiotics. ADME is hard to predict for large data sets because current ADME experimental screens are multi-mechanisms, and predictions get worse as more data accumulates. Currently, screening for biological receptor activity precedes or is concurrent with screening for properties related to "drugability." In the future, "drugability" screening may precede biological receptor activity screening. The level of permeability or solubility

needed for oral absorption is related to potency. The relative importance of poor solubility and poor permeability towards the problem of poor oral absorption depends on the research approach used for lead generation. A â€œrational drug designâ€ approach as exemplified by Merck advanced clinical candidates leads to time-dependent higher molecular weight, higher H-bonding properties, unchanged lipophilicity, and, hence, poorer permeability. A high throughput screening (HTS)-based approach as exemplified by unpublished data on Pfizer (Groton, CT) early candidates leads to higher molecular weight, unchanged H-bonding properties, higher lipophilicity, and, hence, poorer aqueous solubility.

Keywords

Chemical diversity; Drug-like; ADME; Absorption; Permeability; Solubility; Clinical candidate; Merck; Pfizer

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