275 Beyond Filters: ADMET Risk™ for Multi-objective Drug Development

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ABSTRACT

We calculated predictions for over 30 properties relevant to absorption, distribution, metabolism, excretion and toxicity (ADMET) for a large and pharmaceutically pertinent subset of the World Drug Index (WDI)[1], and have identified relevant 10% cutoff thresholds for each of those properties. These thresholds, combined with classification models for over 40 metabolic and toxicological liabilities, enable us to calculate an aggregate risk score (ADMET Risk™)[2,3] for any molecule. ADMET Risk goes beyond the "Rule of 5" formulated by Lipinski et al.[4] by identifying additional potential liabilities - points are added for predicted properties that exceed their threshold values or are classified as problematic. A list of mnemonic codes (ADMET Code™)[3] associated with the numerical score make it easy to identify each "rule" violated by a given compound.

DATA SET

A qualified subset of 2302 drug molecules were extracted from the 2007 version of the WDI using annotation filters similar to those used by Lipinski et al.[4] We removed phosphates, antiseptics, insecticides, emollients, laxatives, etc., as well as any compound that did not have an associated United States Adopted Name (USAN) or International Non-proprietary Name (INN) identifier. Salts were split into their constituent parts and the active ingredient neutralized, after which duplicate structures were removed. This left us with 2302 structures, 8.4% of which violated more than one of the four Rule of 5 criteria.

METHODS

The Rule of 5 only addresses a few of the hurdles a compound must pass before it can become a drug. We calculated a wide range of relevant molecular descriptors and ADMET property predictions that represent potential obstacles to successful compound development as an orally deliverable drug for the focused WDI data set. We identified thresholds for each predicted property such that approximately 10% of the compounds in the data set exceed them (Figure 1a).

Highly correlated criteria (see Figure 1b) were combined into single rules using Boolean operators. Violation of a rule by a structure results in the addition of a point to the customizable ADMET Risk score, with and adding the associated mnemonic ("Sz" in this case) to the ADMET Code™ string.

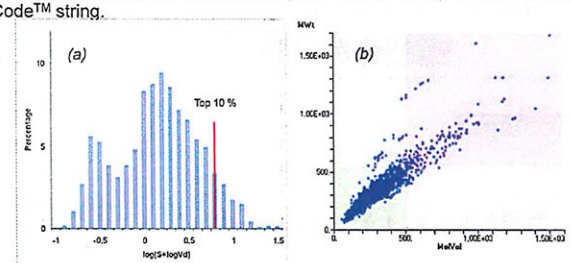

Figure 1. (a) Distribution of volume of predicted distribution (Vd); (b) example of correlated criteria for size: molecular weight (MWt) and volume (MolVol).

Absorption & Distribution Risk rules

Sz: MWt > 550 OR MolVol > 500 OR N_Atoms > 35 OR N_Bonds > 40
ow: S+logP > 5 OR S+logD > 4.1 OR MlogP > 4.1
fu: S+PrUnbnd < 3.5 %
Vd: S+Vd > 5.5
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CYP Metabolism Risk rules

1A: CYP_1A2_Substr = Yes AND MET_1A2_CLint > 30
C9: CYP_2C9_Substr = Yes AND MET_2C9_CLint > 30
D6: CYP_2D6_Substr = Yes AND MET_2D6_CLint > 30
3A: CYP_3A4_Substr = Yes AND MET_3A4_CLint > 30
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Toxicity Risk rules

hE: TOX_hERG > 6
ra: TOX_RAT < 300
Xr: TOX_BRM_Rat < 4
Mu: TOX_MUT_Risk > 2
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Table 1. ADMET Risk rules for calculating risk of absorption and distribution problems; susceptibility to human CYP oxidation metabolism; and toxicity. The overall ADMET Risk includes a total of 24 rules

RESULTS

1. The Absorption and Distribution Risk (S+AD_Risk) includes ten rules based on descriptors and predicted physicochemical and bio-pharmaceutical properties. It exceeds 3 for about 10.4% of our qualified WDI subset (Figure 2a).
2. CYP_Risk includes rules based on a combination of substrate classification models and predicted intrinsic clearances for five different human cytochrome P450s as well as predicted inhibition of CYP 3A4. It exceeds 1 for 10% of the qualified WDI (Figure 2b).
3. TOX_MUT_Risk is a "virtual Ames test" summarizing the mutagenicity expected for five strains of *Salmonella typhimurium* with and without microsomal activation. TOX_Risk model consists of seven rules, one of which is based on TOX_MUT_ Risk. It exceeds 2 for 13% of our qualified WDI subset (Figure 2c).
4. The global ADMET_Risk model combines the rules and mnemonics from S+AD_Risk. CYP_Risk and TOX_Risk. There are total 24 different rules that contribute to the ADMET_Risk, more than 6 of which are broken by 9% of the qualified WDI (Figure 2d).

The customizable ADMET Risk™ and its associated ADMET Code™ together provide a compact yet highly multidimensional view of the potential problems represented by any particular candidate structure. We believe this will be a powerful tool for guiding the multi-objective optimization process involved in developing a successful new drug or other biologically active molecule. An example of the application of ADMET Risk is shown in Figure 3.

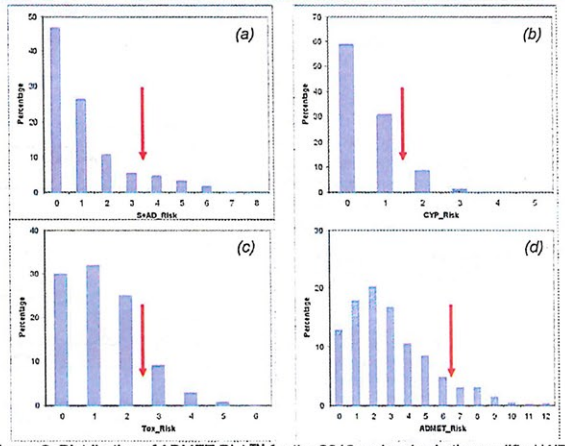

Figure 2. Distribution of ADMET Risk™ for the 2316 molecules in the qualified WDI data set: (a) Absorption & Distribution Risk; (b) CYP Risk; (c) Toxicity Risk; and (d) Overall ADMET Risk. Red arrows indicate thresholds exceeded by about 10% of the qualified WDI data set.

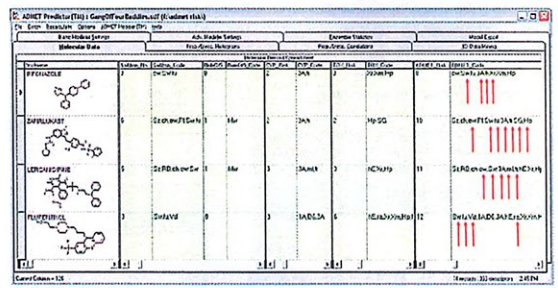

Figure 3. Four of the worst ADMET Risk offenders in the qualified WDI data set not flagged by the Rule of 5. Potential liabilities confirmed by literature reports are indicated by red arrows.

REFERENCES

1. World Drug Index 2007/04; Thomson Reuters; http://thomsonreuters.com/products_services/science/science_products/a-z/world_drug_index/
2. ADMET Predictor™ is distributed by Simulations Plus, Inc., Lancaster CA USA: http://www.simulations-plus.com.
3. M.B. Bolger, R. Fraczkiewicz & V. Lukacova. "Simulation of absorption, metabolism, and bioavailability." In: Drug Bioavailability. Estimation of Solubility, Permeability and Bioavailability; H. Van de Waterbeemd & B. Testa, eds.; Wiley-VCH, Weinheim, 2009.
4. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3-25.

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