**Characterization of a QSAR Model for Phospholipidosis Using a Hierarchical Scaffold Tree of Significant Molecular Features**

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[The views expressed here are those of the authors, who are not an official FDA guidance or policy statement.]

**Abstract**

Drug-induced phospholipidosis (PL) continues to be a safety concern for pharmaceutical companies and regulatory agencies, which has prompted the FDA/CDER Phospholipidosis Working Group to investigate the development of a novel QSAR model. The model will enable pharmaceutical companies to optimize the PL-inducing potential of new drug candidates and regulatory agencies to identify PL-related safety concerns during drug development. The QSAR model described here is a hierarchical scaffold tree that utilizes a novel chemistry-focused methodology, which enables the model to be sensitive to local structural features that, while small, can contribute to the PL-inducing potential of a compound.

**Methods and Materials**

**QSAR Model**

The QSAR model is a hierarchical scaffold tree that assesses PL-inducing potential by considering contributions from multiple molecular features simultaneously, including negative contributions from mitigating features. The model is built using the software (Figure 2).

**Results and Discussion**

**Proposed Exceptions**

Aromatic amines are not independently predictive of PL. Substituted halide groups are thought to increase PL potency by enhancing lipophilicity.

**Linker Length = 0 (Aromatic Amines)**

There are 213 compounds in the database that are aromatic amines, of which 94 are positive and 119 are negative. In this dataset, aromatic amines are not independently predictive of PL.

**Linker Length = 1 Atom**

5) Aromatic Nitrogen and Carboxamide Exceptions

Proposed exceptions are that nitrogen must not be part of a carboxamide, aromatic ring, or aromatic amine.

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**References**


**Legend**

Node color: green = scaffold present; red = scaffold absent; white = unknown scaffold.

Node size: small = scaffold not used; medium = scaffold used in 2-5% of compounds; large = scaffold used in >20% of compounds.

Scaffold color: yellow = scaffold not used; green = scaffold used in 2-5% of compounds; blue = scaffold used in >20% of compounds.

Node text: the number indicates the number of compounds containing the scaffold; the percentage indicates the percentage of compounds containing the scaffold.

Figure 2. Scaffolds depicting all structural features in the QSAR model positively correlated with PL.