In Silico Modelling of Phospholipidosis: Improving Predictive Performance Through the Use of Structural Fragments

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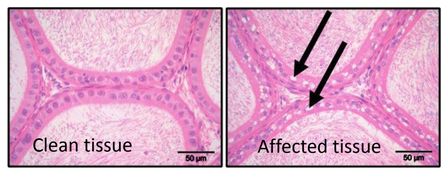
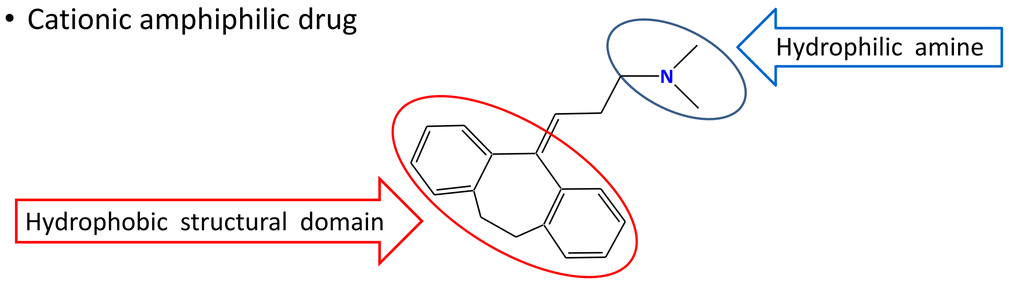
Introduction

- Drug-induced phospholipidosis (PLD) is characterised by the excessive accumulation of phospholipids and the administrated drug in lysosomes after short-term or chronic treatment with cationic amphiphilic drugs (CADs).



- Cationic amphiphilic drug



- Although, there is no strong evidence that drug-induced PLD is harmful to human health, it is important to identify potential PLD inducers at an early stage of drug development to ensure the drug safety.
- A number of *in silico* methods have been developed to evaluate PLD-inducing potential:

PLOEMEN MODEL	$(\log P)^2 + (pK_a)^2 > 90$	with $\log P > 1$ and $pK_a > 8$
PELLETIER MODEL	$(\log P)^2 + (pK_a)^2 > 50$	with $\log P > 2$ and $pK_a > 6$
HANUMEGOWDA MODEL	$(pK_a \times \log P \times V_d) \geq 180$	with $\log P \geq 2$

- These models are generated many false positives when applied to predominantly basic, lipophilic drugs.

Aims

- To investigate the relationship between the structure and PLD inducing potential of 450 compounds.
- To develop molecular fragments for PLD in the form of structural alerts.
- To assess previously published models predicting PLD potential.

Methods

Data

- 450 chemicals, 93 positive PLD inducers and 357 non-inducers were obtained from Kruhlak et al.[1]
- A reduced dataset of 135 chemicals possessing measured V_d (45 positive inducers and 90 non-inducers) was created to test the Hanumegowda model.
- A validation set of 67 compounds (16 positive PLD-inducers and 51 non-inducers) was compiled from the literature.

Descriptors

- More than one hundred descriptors, representing the physicochemical, structural and topological properties of each molecule, were calculated.

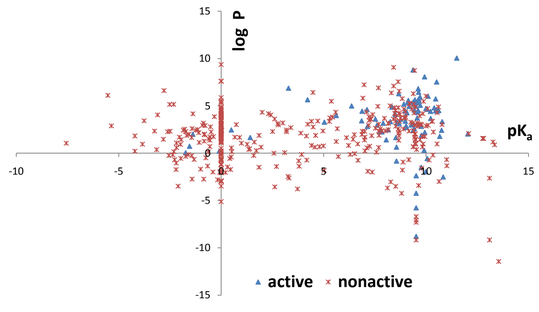
Structural alerts

- Structural features and fragments associated with the induction of PLD were captured using SMARTS (SMiles ARbitrary Target Specification) strings. Based on the presence of a hydrophobic ring system and a hydrophilic amine group, a set of 32 most characteristic and desirable SMARTS patterns was created. The SMARTS strings were divided into five main chemical groups, those for: primary amines, secondary amines, tertiary amines, cyclic amines and aromatic systems. Additionally, a group of SMARTS patterns assigning the presence of ring systems, and a set of undesirable SMARTS patterns: a carboxylic acid and nitro group were also developed to help differentiate the PLD inducers from non-inducers.

QSAR model

- Linear discriminant analysis was performed using the MINITAB for Windows.

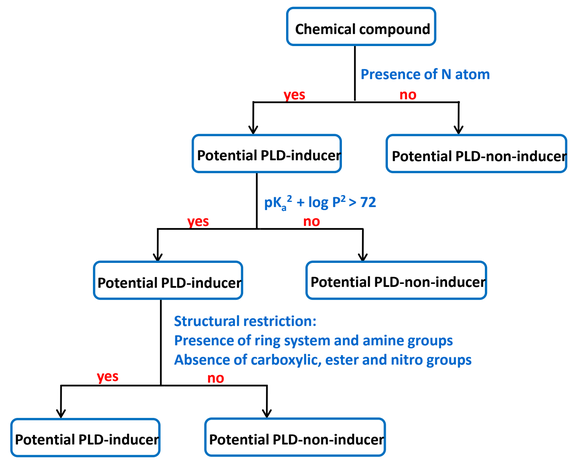
Results



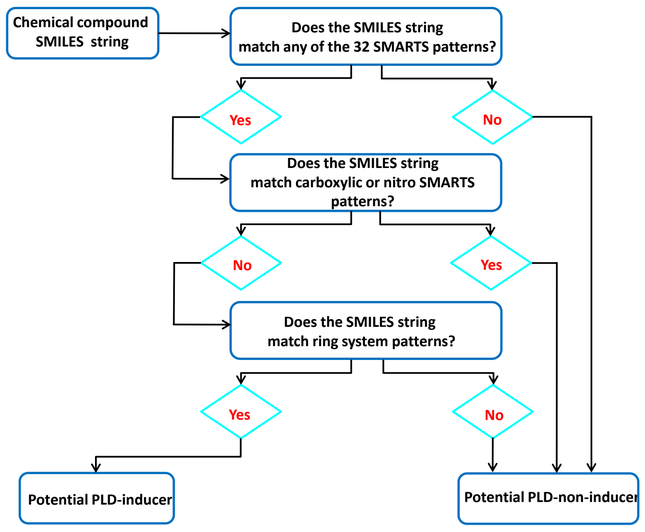
Distribution of log P and pK_a for 93 PLD-inducers and 357 non- inducers

These results are described in more detail by Przybylak and Cronin (2011).[2]

MODIFIED MODEL



SMARTS MODEL



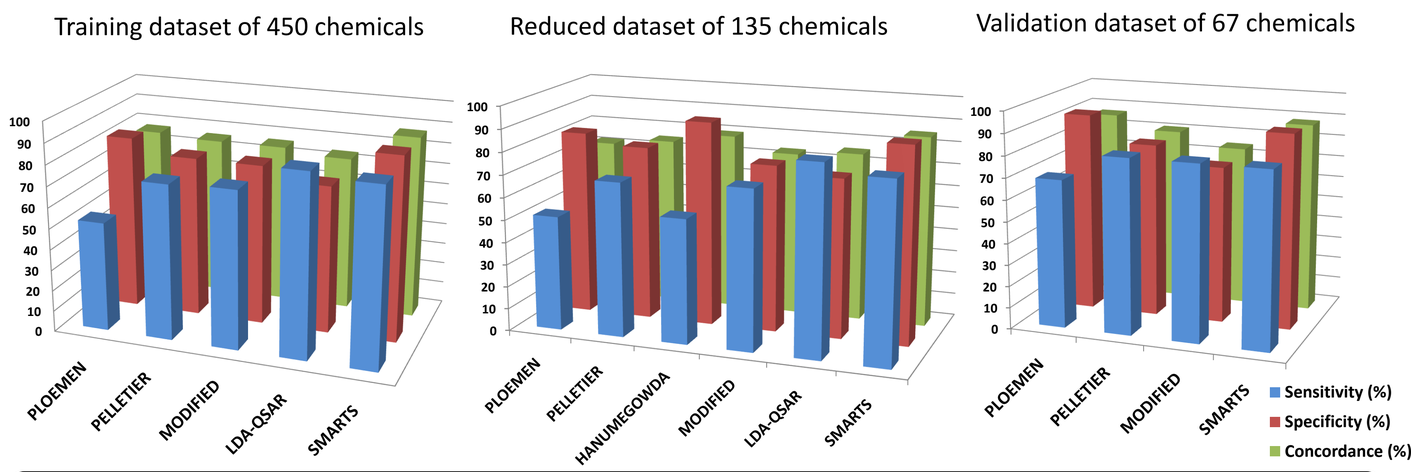
LINEAR DISCRIMINANT ANALYSIS (LDA)

$$P_{ni} = -2.15 + 0.619 \log P + 0.226\, pK_a + 18.077\, {}^5\chi_R^V + 0.436\, N_{HBD} + 0.983\, S_{HBD}$$

$$P_i = -4.58 + 0.963 \log P + 0.426\, pK_a + 7.864\, {}^5\chi_R^V + 1.156\, N_{HBD} - 0.077\, S_{HBD}$$

${}^5\chi_R^V$ - the fifth order valence-corrected molecular connectivity index
N_{HBD} - number of H-bond donors
S_{HBD} - H-donor strength

PREDICTIVE STATISTICS OF THE STUDIED *IN SILICO* MODELS



Conclusions

- *In silico* methods based only on simple physicochemical properties, log P and pK_a, appear to be insufficient to differentiate PLD inducers from non-inducers.
- Introduction of the pharmacokinetic parameter- volume of distribution (V_d) improves the specificity, but significantly decrease the sensitivity of the prediction.
- Phospholipidosis is linked directly to molecular (sub-)structure(s).
- The structural patterns have been developed to reflect meaningful molecular fragments associated with PLD: hydrophobic, cyclic moieties with peripheral, amine groups. These could be used in the early screening of potential PLD-inducers.

References

1. N. L. Kruhlak, S. S. Choi, J. F. Contrera, J. L. Weaver, J. M. Willard, K. L. Hastings, and L. F. Sancilio, *Toxicol. Mech. Methods* **2008**, 18, 217–227.
2. K. R. Przybylak and M.T. D. Cronin, *Mol. Inf.* **2011**, 30, 415 – 429.

Acknowledgements

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