Modelling Studies to Support the Prediction of Molecular Initiating Events for Liver Steatosis: LXR and PPARγ Binding

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Introduction and Aims

This study summarises the applications of different in silico approaches (including molecular modelling) to study two particular nuclear receptors that could play a role in the mode of action leading to liver steatosis, namely liver X receptor (LXR) and peroxisome proliferator-activated receptor γ (PPARγ). The work includes: (i) characterisation of the developed binders databases (ii) development and validation of different models to predict receptor binding potential (iii) integration of the different models within consensus/data fusion strategy (iv) in silico screening of liver toxicity databases for LXR and PPARγ binding using the developed models to prioritise compounds of potential concern for liver toxicity.

Methods

- Molecular modelling (MM)
  - Pharmacophore modelling
  - Ensemble Docking
  - 3D QSAR modelling

- Classical (Q)SAR modelling
  - PLS-DA classification Q SAR
  - KNIME workflow (WF) for nuclear receptors (NR) - mediated liver steatosis alerts

Results

- Several MM methodologies, including both ligand- and structure-based methods, were employed and combined by consensus/data fusion methods to predict LXR binding potential:
  - ED = Ensemble docking
  - eP = e-Pharmacophore
  - FP = fingerprints-based similarity

- A validation dataset of 356 LXR binders and 1000 decoys was used to assess the ability (in terms of EF - Enrichment Factor) of the MM methods and consensus models to identify LXR binders (Fig. 1).

- QSAR Classification model (PLS-DA method) was developed for predicting LXR binding affinity and implemented in KNIME.

- Screening of liver toxic datasets by applying an integrated in silico strategy, which combines MM methods, QSAR and alerts.

- Development of PPARγ agonists dataset (currently 410 structures) to be used in the subsequent in silico analyses.

- Development of pharmacophore model of the PPARγ full agonists (Fig. 2).

- Development of two-steps virtual screening procedure to screen databases for PPARγ full agonists:
  2. Filtering of the generated poses based on the pharmacophore model.

- Screening of the JRC case-study dataset using the developed virtual screening procedure -> four positives (based on experimental evidence that they cause hepatotoxicity) retrieved as hits:

- Development of 3D QSAR (CoMSIA) models (Fig. 3).

Conclusions and Future Perspectives

- Molecular modelling plays an important role in the AOP framework by working in synergy with other in silico (QSAR, chemotypes, alerts) and in vitro approaches.

- Literature search is being planned to collect data on LXR/PPARγ binding and activation, and liver steatosis-related effects for the prioritised chemicals from the liver toxic datasets analysed in this work.

- The proposed in silico strategy should be complemented by in chemico, in vitro and in vivo (where available) data to relate LXR/PPARγ binding/activation and liver steatosis.

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