Identification of In Silico Structural Alerts for Liver Steatosis Induced by Nuclear Receptor Agonists

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Introduction and Aims

- In silico models are fundamental to the development of integrated alternative methods to identify organ level toxicity and lead the replacement of animal testing. These models include (Quantitative) Structure-Activity Relationships (Q)SARs and the identification of structural alerts associated with defined toxicological effects.
- Structural alerts are both able to predict toxicity directly and assist in the formation of categories to facilitate read-across. They assist in deciphering the myriad mechanisms of action that result in organ level toxicity.
- Nuclear receptor (NR) agonists and the mechanistic pathways they influence are known inducers of liver steatosis and many other toxic effects. There are few structural alerts currently developed for nuclear receptors relating to liver toxicity.
- The aim of this study was to develop structural alerts for nuclear receptor agonists that are associated with hepatic steatosis. The alerts were developed on the basis of in vitro data and entered into KNIME workflows.

Approach

- NR agonists were identified from the ChEMBL database.
- Literature data were examined revealing NR associated hepatic steatosis pathways.
- Information on NR agonists and associated data were entered into a spreadsheet.
- PyMOL v1.3 and the PDB were used to study the interactions between the NR and agonist.
- The chemical structure and physico-chemical properties where also studied.

Results

- More than 60 structural alerts were developed.
- These alerts have been compiled into 8 workflows (see figure below).
- These are within the domain rules for AHR agonists.
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- Red highlighting shows when the chemical matched to AHR structural alert.
- YES / NO decision sent to output file.

Conclusions

- NR agonists have been linked to the onset of liver steatosis.
- More than 60 new structural alerts for NR agonists that induce liver steatosis were developed and form the basis of KNIME workflows.
- KNIME workflows allow for the identification of nuclear receptor agonists.
- The structural alerts and workflows could be used to enhance product development through the elimination of toxic fragments and risk assessment.

References

1. Moya M et al., 2010, Chemico-Biological Interactions, 184, p 376–387

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