EUTOXRISK

Beyond Simple Chemical Structure Similarity Assessment - Moving Towards Quantitative Chemical and Metabolic Reaction Similarity.

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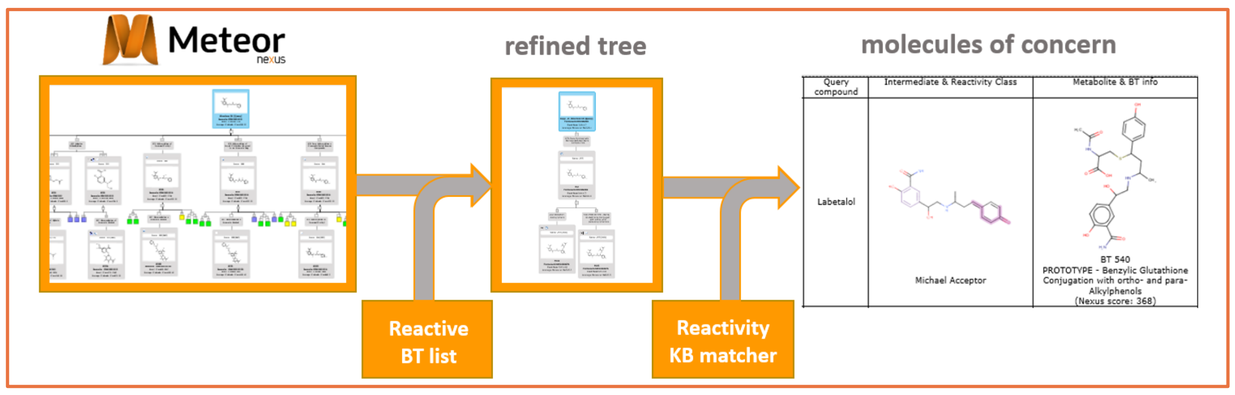
INTRODUCTION

There is a recognised need for read-across approaches to move beyond grouping chemicals based purely on the similarities of their molecular structures. Lhasa has developed three approaches (two general and one specific) that could be deployed to group chemicals based on similarity in their predicted metabolic biotransformation profiles.

METHOD 1.

Towards a Reactive Metabolite Profiler in the Toxicity Assessment of Analogue Groups.

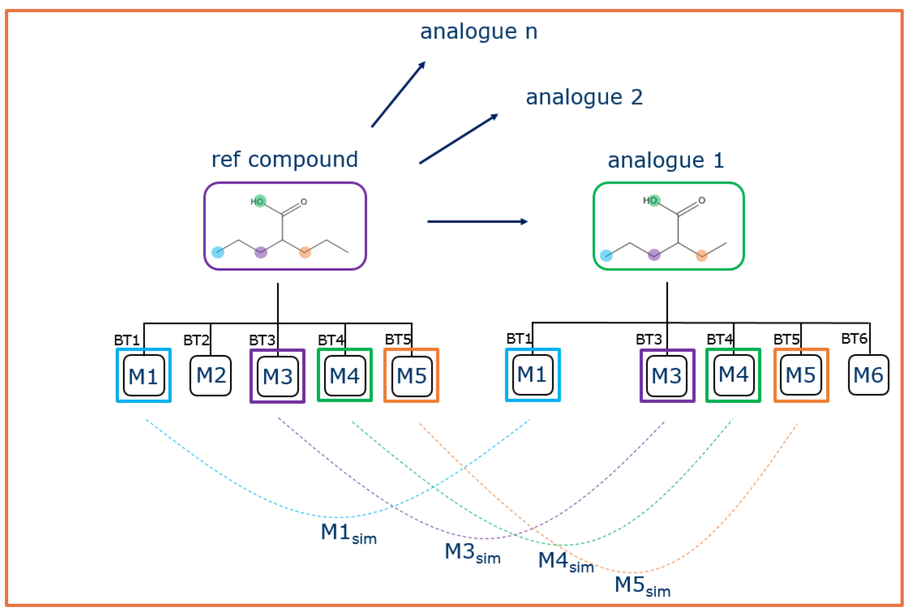
In this general method, molecules are profiled in terms of predicted biotransformations that express the formation of electrophilic intermediates and metabolites. Characterisation of predicted pathways includes biotransformation intermediate reactivity classification (quinone, Michael acceptor, iminium ion etc.) and biotransformation scores. The biotransformation scoring function is based on an assessment of site of metabolism similarities for nearest neighbours and indicates a likelihood that the biotransformations will occur. This method will enable comparison of metabolic profiles for similar compounds within a chemical class. Uncommon intermediates and pathways of activation can be identified and this is important as these represent potential activity-cliffs within a chemical series.

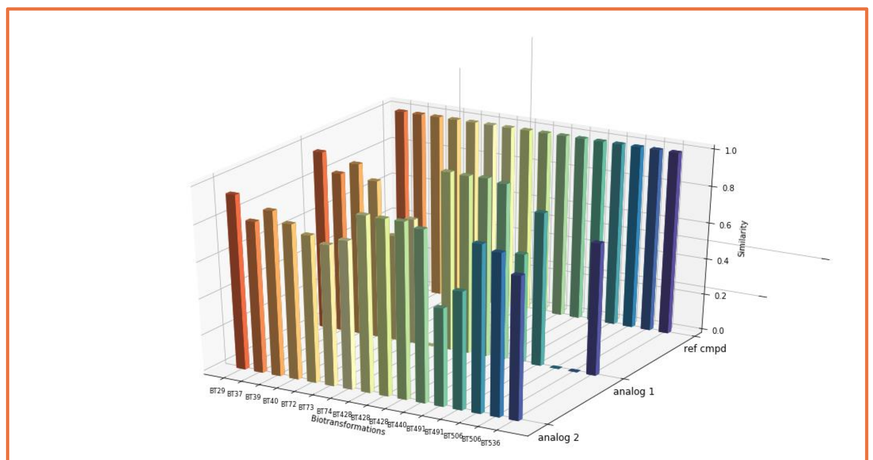


METHOD 2.

Quantitation of Concordant Biotransformation Pathways - Understanding the Metabolic Behaviour of Analogues.

In this general method, structural similarities of concordant (predicted) metabolites for closely related analogues are assessed based on the dichotomous data Tanimoto method using extended circular fingerprints as the choice of molecular descriptors. Concordant metabolites are defined here as those arising via the same biotransformation occurring at equivalent positions on the maximum subgraph common to both analogues. The similarity of the entire metabolic tree (in our investigations to date, only the first generation of metabolites have been considered) can then be assessed based on the continuous data Tanimoto method using the computed similarities (a number between zero and one) for each concordant pair.





$$\textit{Tanimoto Similarity (binary data)} = \frac{C}{A + B - C}$$

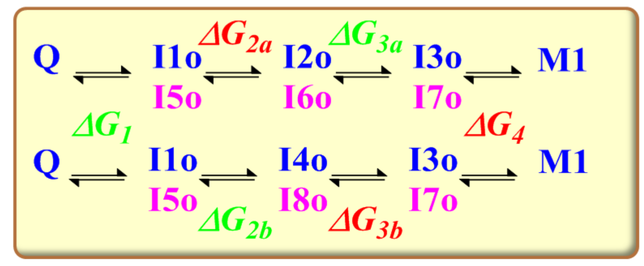
A = bits set to "1" in object "a"
B = bits set to "1" in object "b"
C = number of "1" bits common to both

$$\textit{Tanimoto Similarity (continuous data)} = \frac{\sum_{j=1}^{n} x_j A . x_j B}{\sum_{j=1}^{n} (x_j A)^2 + \sum_{j=1}^{n} (x_j B)^2 - \sum_{j=1}^{n} x_j A . x_j B}$$

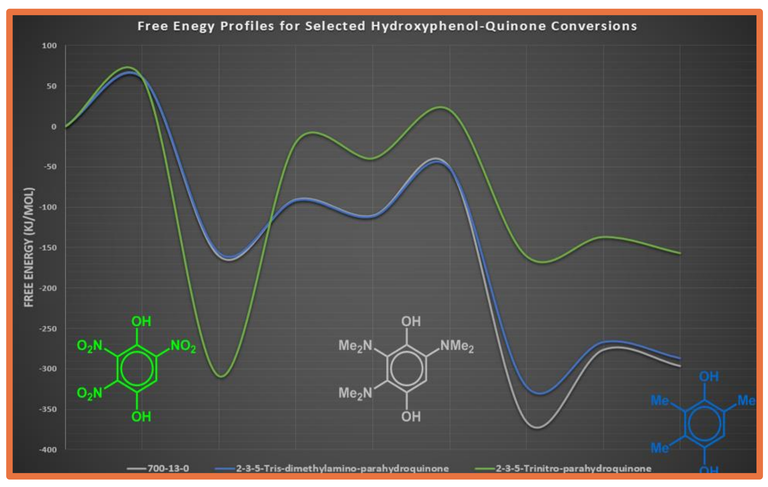
METHOD 3.

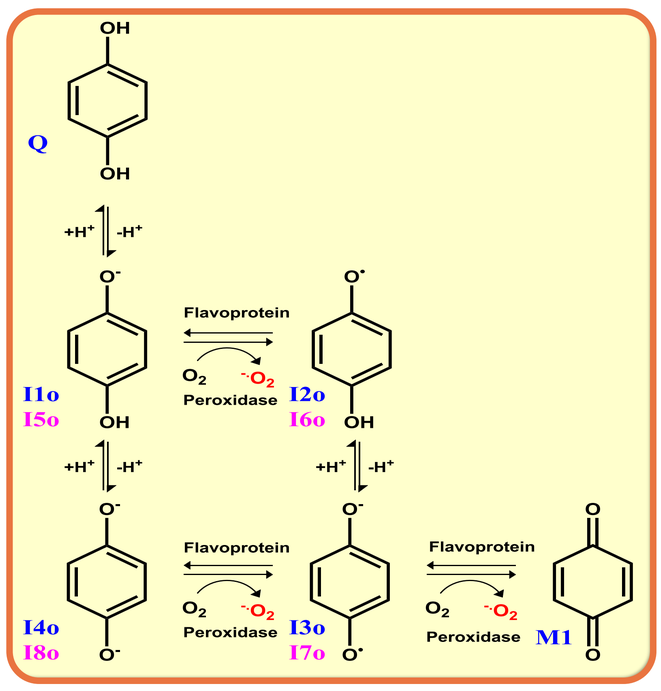
Redox Cycling of Dihydroquinone Analogues - Using Quantum Chemistry to Construct Free Energy Profile Similarities.

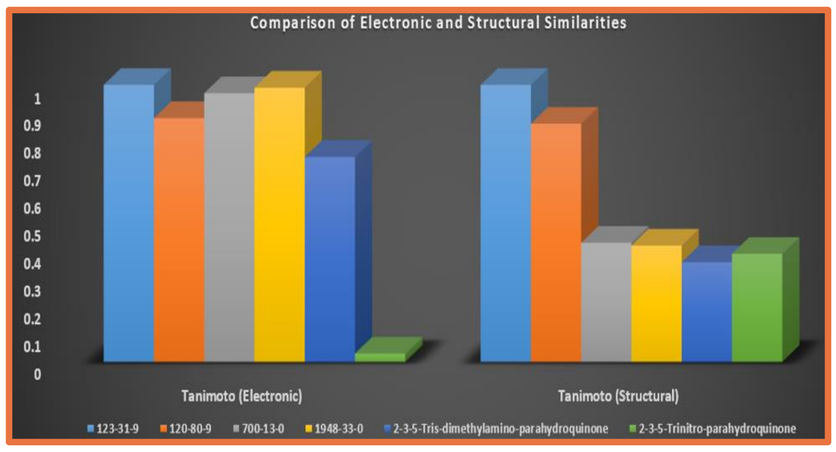
In this specific method, we have used a quantum mechanical technique, density functional theory (DFT), to compute the free energy changes for each component reaction in the multistep oxidation of dihydroquinones to quinones. These free energy values are normalised across all members of the analogue group and, again, similarities in the overall reaction profile can be compared using the continuous data Tanimoto method. This method has the potential to be extended into larger electronic holograms using other DFT-computed parameters such as highest occupied and lowest unoccupied molecular orbitals, ionisation potentials and electron affinities.



(De)Protonation
Single Electron Transfer







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http://www.eu-toxrisk.eu/