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A novel method for predicting ligand regioselectivity to metabolism by the CYP3A4 enzyme

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The CYP-P450 3A4 enzyme is responsible for metabolizing 50% of marketed drugs, covering a wide space of structural diversity [1]. From a drug discovery standpoint, knowledge of ligand regional propensity to metabolism is essential.

Experimental metabolite characterization is done using liquid chromatography/tandem mass spectrometry [2]. While accurate, this technique is time consuming and labor intensive. This is unfeasible for high throughput testing of molecules under development early in the drug discovery process. What is needed is a quick, accurate, interpretable technique for identifying ligand regioselectivity to metabolism by the 3A4 isozyme. A number of *in silico* methods have been reported upon CYP 3A4 site of metabolism prediction. These methods revolve around one of two metrics: a ligand based QSAR analysis [3], or fingerprint based molecular docking and scoring [4].

In the present method, topologically distinct regions of a ligand are identified and ranked as putative metabolic sites. Ranking is performed on the basis of 1) easily calculable electronic properties of each unique region and 2) spacial and steric scoring based upon a constrained rapid dynamics simulation. The electronic property based component of this methodology has already been reported and was found to be 71% accurate in the absence of the rapid simulation component [5]. The final combined method can be used as a reliable metric for evaluating metabolic liability of lead compounds.

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