

CypScore - *in silico* Case Studies on Metabolic Stability Optimization

A. H. Göller¹

M. Hennemann², T. Clark²

¹ Bayer Healthcare AG, Bayer Schering Pharma Global Drug Discovery, Wuppertal, Germany

² Computer Chemie Centrum, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany.

Metabolism (the M in ADMET) via first-pass clearance leads to low bioavailabilities and is one of the unfavorable ADMET properties leading to the termination of lead optimization and development projects. Additionally, toxic metabolites and metabolites altering the overall metabolism via inhibition or induction of CYP enzymes cause severe side effects.

It is therefore highly desirable to have a tool to predict the lability of specific atomic positions and the metabolites of any compound *in silico*, since (i) experimental metabolite determinations can often not be done for each interesting project compound due to resource limitations, (ii) even state-of-the-art experiments often provide only larger fragments but not the exact atomic position metabolized, (iii) an *in silico* method allows to calculate labilities for compounds not yet synthesized and the metabolism of the metabolites, i.e. to simulate multi-step reactions.

CypScore is an *in silico* prediction software for small molecule metabolic oxidations [1] mediated by cytochrome P450s by applying distinct models for the most important types of oxidation reactions. The models were established based on an in-house created literature compound database comprised of about 850 compounds with about 20000 non-hydrogen atoms labile to about 2400 metabolic transformations. The models were created by a combination of data-mining and linear regression techniques to yield optimized predictions of the labilities of the compounds. The models are based on Paracore atomic reactivity descriptors [2] from VAMP AM1 quantum chemistry [3] calculated electron density distributions fitted against positionally defined labile molecular positions. The different reaction models in CypScore are appropriately weighted and allow for direct semi-quantitative comparison of the labile positions in one molecule (e.g. aliphatic oxidation vs. hydroxylation), in congeneric series, and in heterogeneous datasets. Due to the quantum-chemistry base of the reactivity descriptors, CypScore does predictions *ab initio* and is not just a learned method. Thus, it is able to extrapolate outside the dataset used for calibrating the models.

CypScore was carefully validated against literature and in-house data sets where the software was able to find the major metabolite(s) for about 90 % of the compounds if considering the 3 weakest positions in each molecule. It is regularly applied to in-house projects for parallel SAR and metabolism optimization.

In this paper we present several literature examples of optimization strategies to reduce first-pass metabolism in CCR5 antagonists, endothelin antagonists, farnesyltransferase inhibitors, Cox-2 inhibitors, thrombin inhibitors and mGlu5 allosteric antagonists and one generic in-house example which illustrate the capabilities of the CypScore approach.

1. (a) GRC Computational Chemistry, 2006, Les Diablerets, Switzerland, Talk; (b) SMI *in silico* ADMET conference, 2007, London, UK, Talk; (c) 4th Joint Sheffield Conference on Chemoinformatics, 2007, Sheffield, UK, Poster; (d) publication in preparation.
2. Paracore, CEPOS InSilico Ltd., 26 Brookfield Gardens Ryde, Isle of Wight PO33 3NP.
3. VAMP 10.0, Clark, T.; et al., Erlangen 2007.