Bayer HealthCare
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CypScore

A Quantum Chemistry based Approach for the Prediction of Likely Sites of P450-Mediated Metabolism

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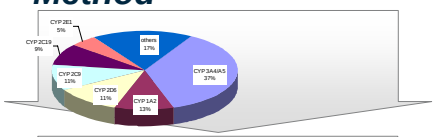
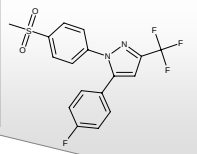
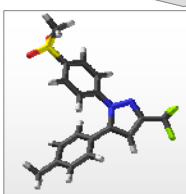
Method



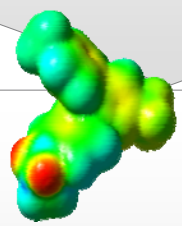
Database
2400 reaction
850 compounds



Corina
2D to 3D conversion



VAMP
AM1 optimization
wave function properties



Parasurf

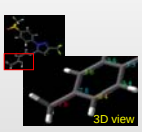
Parasurf
atom-based
reactivity descriptors

specific models
for each reaction type

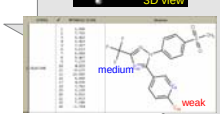
286 labile positions for aromatic hydroxylations in 7377 aromatic C_{sp}^2

Score = -0.58 SASA(C) + 0.0083 $|E|_{max}$(C) - 21.3 σ(C) + 7.54 Qπ (C) + 16.2

aliphatic hydroxylation
N-dealkylation
O-dealkylation
aromatic / arene oxidation
N-oxidation
S-oxidation



Prediction
CypScores are weighted reaction vs. reaction type intra- and intermolecular



metabolic optimization

Introduction

In silico methods for ADMET prediction can help to diminish attrition rates in drug discovery projects. They are especially helpful whenever the experimental setup is costly and time-consuming and whenever they guide the chemical modifications necessary to overcome ADMET problems.

Excessive **Metabolism** (the M in ADMET) frequently leads to low bioavailability of compounds. Additionally, toxic metabolites and metabolites altering the overall metabolism via inhibition or induction of CYP enzymes might cause severe side effects. Rational guidance for stabilizing labile atomic positions is therefore highly desirable.

CypScore predicts the labilities of specific atomic positions in drug molecules to cytochrome P450 mediated oxidation reactions. This is important since

- experimental metabolite determination can often not be performed for each interesting project compound
- even state-of-the-art experimental set-up often provides only larger molecular fragments but not the exact atomic position metabolized

CypScore is used for

- Metabolic stability optimization
- Metabolic pathway modelling
- Synthesis priorization
- Compound selection for experimental testing

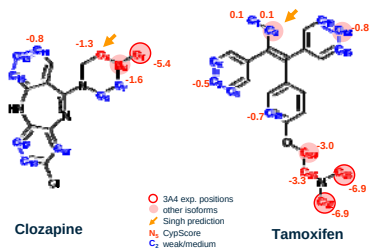
CypScore design

- specific models for all important P450 mediated oxidative reactions
- based on Parasurf-derived atomic reactivity descriptors from VAMP AM1 quantum chemistry calculated electron density distributions
- weighted reaction models allow for direct (semi-)quantitative comparison of the labile positions in one molecule (e.g. aliphatic hydroxylation vs. N-oxidation), in a congeneric series from a dataset, and in heterogenous datasets.
- not just a learned QSAR or a knowledge base approach but predicts under explicit consideration of 3D neighborhood effects

Application Examples

Metabolic Site Prediction

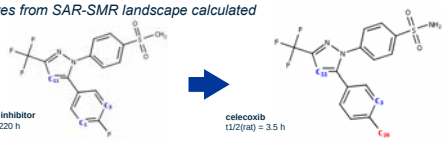
CypScore predicts more than 75 % of the metabolic positions in Singh dataset [4]
Singh approach yields 42% of CYP 3A4 and 26% of all labile positions in dataset

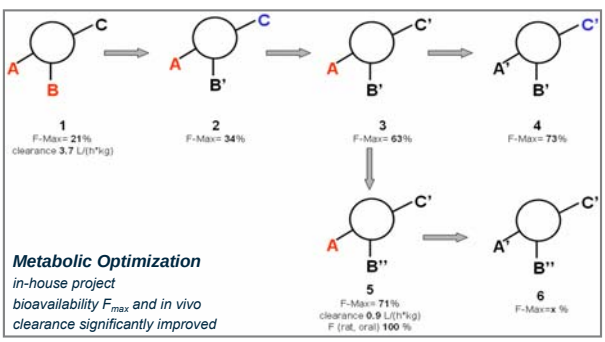


Clozapine Tamoxifen

Optimization of Metabolic Stability [5]

half-life reduction from 220h to acceptable time frame of 3.5 h
many derivatives from SAR-SMR landscape calculated

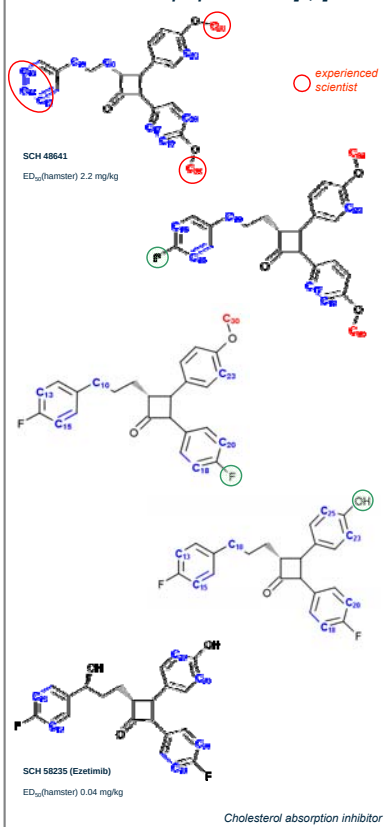




Metabolic Optimization

in-house project
bioavailability F_{max} and in vivo
clearance significantly improved

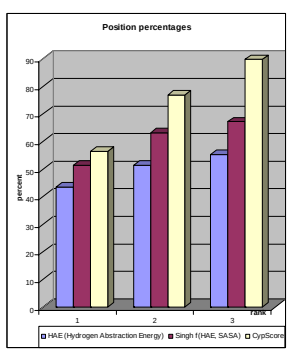
Ezetimib: a multistep optimization [6,7]



Cholesterol absorption inhibitor
in bile rapid appearance of metabolite mixture
alcohol derivative better inhibitor, modifications increas ED_{50}

Validation

- **Set 1: 70 compounds, 41 of Singh, plus 29 additional challenging ones**
  - 187 weak positions in 1797 heavy atoms (1 to 5 per molecule)
  - all types of reactions
  - 124 aliphatic hydroxylations, 50 double bond oxidations, 12 N-oxidations
  - 73% of metabolic positions found
- **Set 2: 39 compounds from 12 in-house projects**
  - for these compounds the positions are clearly identified experimentally
  - all types of reactions
  - 90 % of metabolic positions found



Citations

[1] Corina, Molecular Networks GmbH, Henkestraße 91, 91052 Erlangen, Germany.
[2] T. Clark, A. Alex, B. Beck, F. Burkhardt, J. Chandrasekhar, P. Gedeck, A. H. C. Horn, M. Hutter, B. Martin, G. Rauhut, W. Sauer, T. Schindler, and T.Steinke, **VAMP** 8.2, Erlangen **2002**,[3] **Parasurf**, CePos InSilico Ltd., 26 Brookfield Gardens, Isle of Wight, PO33 3NP.
[4] Singh, B. S. et al., *J. Med. Chem.* **2003**, *46*, 1330-1336
[5] Penning, T.D. *J. Med. Chem.* **1997**, *40*, 1347-1365
[6] van de Waterbeemd, H., Walker, D.K. Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, **2001**, p. 85
[7] van Heek, M.; et al., *J. Pharmacol. Exp. Ther.* **1997**, *283*, 157-163.