Prediction of Cytochrome P450 Mediated Metabolism

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90% of Drugs are metabolized by P450s
Creates toxicity
Semi-empirical data is unreliable.
200+ Transition States

All major reaction types
\[ 40 \text{ kJ/mol} \]
Maxbonds_{i} = 5  \quad \text{Maxbonds}_{\text{all}} = 7

\text{Accessibility} = \frac{5}{7} = 0.7
SMARTCyp

Score = Energy – 8*Accessibility
SMARTCyp

1. Assign Energies By SMARTS matching

\[
\begin{array}{|c|c|c|}
\hline
\text{Atom} & \text{SMARTS} & \text{Energy} \\
\hline
1 & [CX3H1](=O)[#6] & 40.2 \\
2 & [CX4][N] & 39.8 \\
3 & [N^3][H1,H2] & 54.1 \\
\hline
\end{array}
\]

2. Compute Accessibility Descriptor

\[ A_i = \frac{\text{Maxbonds}_i}{\text{Maxbonds}_{all}} \]

\[
\begin{align*}
A_1 &= \frac{2}{3} = 0.67 \\
A_2 &= \frac{2}{3} = 0.67 \\
A_3 &= \frac{3}{3} = 1.00
\end{align*}
\]

3. Compute Score and Rank Atoms

Score, \( S = E - 8A \)

Lowest score gets rank 1

\[
\begin{align*}
S_1 &= 40.2 - 8 \times 0.67 = 34.84 & \text{Atom 1 - Rank 2} \\
S_2 &= 39.8 - 8 \times 0.67 = 34.44 & \text{Atom 2 - Rank 1} \\
S_3 &= 54.1 - 8 \times 1.00 = 46.10 & \text{Atom 3 - Rank 3}
\end{align*}
\]
Isoform Unspecific Metabolism

![Bar chart showing SMARTCyp and CypScore rankings.]

- Rank 1: SMARTCyp 67, CypScore 60
- Rank 1-2: SMARTCyp 85, CypScore 85
- Rank 1-3: SMARTCyp 94, CypScore 94
Database Problems

![Chemical Structures]
False negatives

Image from: M. Hennemann et al., ChemMedChem, 2009, 4, 657-669
False negatives – N-dealkylation

Clomipramine

Chlorpromazine
False negatives – N-dealkylation

Clomipramine

Chlorpromazine
SMARTCyp Accuracy for Nine Isoforms

- 1A2: 79
- 2A6: 83
- 2B6: 74
- 2C19: 74
- 2C8: 73
- 2C9: 67
- 2D6: 58
- 2E1: 81
- 3A4: 74
- Any: 75
SMARTCyp Accuracy for Nine Isoforms

1A2: 79
2A6: 83
2B6: 74
2C19: 74
2C8: 73
2C9: 67
2D6: 58
2E1: 81
3A4: 74
Any: 75
Enrichment

1A2: 53
2A6: 51
2B6: 49
2C19: 54
2C8: 51
2C9: 45
2D6: 37
2E1: 45
3A4: 53
Any: 49

Any
SMARTCyp Web Service

SMARTCyp predicts the sites in molecules that are most liable to cytochrome P450 mediated metabolism.

You have 3 options for creating/importing molecules:

- Draw your molecule
- Upload a file
- Enter SMILES strings
SMARTCyp is Flexible
SMARTCyp Extended with RS-Predictor

- 1A2: 82%
- 2A6: 86%
- 2B6: 77%
- 2C19: 86%
- 2C8: 84%
- 2C9: 84%
- 2D6: 84%
- 2E1: 81%
- 3A4: 82%
- Any: 86%
The Next Step: Sensible Atomic Descriptors

15 vs. 150 descriptors
Metabolite prediction in ToxTree 2.5

http://toxtree.sourceforge.net/
Usage and Availability

www.farma.ku.dk/smartcyp
ToxTree

MOE
Pipeline Pilot

Bioclipse
METEOR
What do we need?
What does the future hold?

Better and more understandable models
More knowledge of P450 metabolism

for references

google "smartcyp"
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