CYP Inhibition in Drug-Drug Interaction: Preclinical Assessment

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Drug-Drug Interactions

Definition

- Pharmacokinetic drug-drug interaction:
  - Broadly defined as the effects of one drug on the ADME of another, which may increase or decrease plasma/tissue drug concentrations to which with significant toxic consequences or therapeutic incompetence.

Consequences

- Exaggerated pharmacology and adverse effects including toxicity
- Decreased therapeutic effect and lack of efficacy
- Major concern for pharmaceutical industry and regulatory authorities
Pharmacokinetic Drug Interaction

- Another Drug
- Toxicity
- Therapeutic Window
- Lack of Therapeutic Effect

- Drug Concentration
- Alone at SS
- DDI
- Time
Why Care about DDI

• Rising rates of polypharmacy increase the risk of potential serious DDIs (Guthrie 2015)
  – In > 300,000 subjects surveyed in the Tayside region of Scotland between 1995 and 2010, proportion of adults dispensed ≥ 5 drugs doubled to 20.8%, and ≥10 drugs tripled to 5.8%
    ✓ Largest absolute rises were for cardiovascular, central nervous system and gastrointestinal drugs
  – Serious DDIs were over twice as common in 2010 than 1995
    ✓ Drug groups most commonly implicated in potentially serious DDIs in 1995 were cardiovascular, central nervous system and musculoskeletal drug, which remained in 2010 but with significantly increased prevalence
• Drug-drug interactions have been implicated in approximately 20% of adverse drug reactions (ADR) (Wrighton 2003)
• Five of 12 drugs withdrawn from the US market from 1997 to 2002 were prone to metabolic drug-drug interactions (Huang 2004)
Impact on Medical Community

- Patients – Adverse drug effect, such as morbidity and mortality or lack of efficacy
- Physicians – Medical-legal liability
- Healthcare systems – Increased cost due to increased incidents
- Pharmaceutical companies – Medical-legal liability, drug attrition or restriction, increased cost in drug R&D
Mechanisms of DDI

Role

- **Victim**: susceptible to effects of enzyme/transporter inhibitors or inducers
  - Substrate
- **Perpetrator**: alter the elimination or bioavailability of existing drugs
  - Inhibitor
  - Inducer

Mechanism

- CYP mediated
- Transporter mediated
- Gastric acid reducing agents (ARA)
- Therapeutic proteins
- Others: other enzymes, food, herbs, etc.
Major Sites of DDI Concern

- Absorption
- ARA
- Metabolism, distribution, clearance
- CYP, transporter, other enzymes
- Clearance, distribution, metabolism
- Transporter, enzymes
- Distribution
- Transporter
- Absorption, metabolism
- Transporter, CYP3A

http://baike.sogou.com/v9376738.htm
Cytochrome P450 (CYP or P450)

- A diverse super family of hemoproteins found in a variety of animals, plants, and microorganisms
- In mammals, present predominantly in liver, also found in intestine, kidney, lung, brain, adrenal cortex and other tissues
- In hepatocytes, P450s mainly localize in the endoplasmic reticulum (ER)
Elimination of Top 200 Most Prescribed Drugs in 2002: Role of CYPs

Weinkers and Heath, Nat. Rev. Drug Disc., 2005
## CYP Inhibition on PK of Antidiabetic Drugs

<table>
<thead>
<tr>
<th>Victim drug</th>
<th>Perpetrator drug (daily dose, mg)</th>
<th>Changes in pharmacokinetic parameters</th>
<th>Enzyme or transporter involved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC</td>
<td>C_{max}</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil (1200)</td>
<td>+239%</td>
<td>NS</td>
<td>+124%</td>
</tr>
<tr>
<td>Gemfibrozil (1200)</td>
<td>+222%</td>
<td>NS</td>
<td>+174%</td>
</tr>
<tr>
<td>Gemfibrozil (1200) + Itraconazole (100)</td>
<td>+291%</td>
<td>NS</td>
<td>+383%</td>
</tr>
<tr>
<td>Trimethoprim (320)</td>
<td>+42%</td>
<td>NS</td>
<td>+32%</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (100)</td>
<td>+21%</td>
<td>NS</td>
<td>+38%</td>
</tr>
<tr>
<td>Gemfibrozil (1200)</td>
<td>+129%</td>
<td>+22%</td>
<td>+112%</td>
</tr>
<tr>
<td>Ketoconazole (400)</td>
<td>+47%</td>
<td>+17%</td>
<td>+53%</td>
</tr>
<tr>
<td>Trimethoprim (320)</td>
<td>+37%</td>
<td>+14%</td>
<td>+24%</td>
</tr>
<tr>
<td>Trimethoprim (400)</td>
<td>+31%</td>
<td>NS</td>
<td>+27%</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (400)</td>
<td>+101%</td>
<td>+196%</td>
<td>NA</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem (350)</td>
<td>+109%</td>
<td>+63%</td>
<td>NA</td>
</tr>
<tr>
<td>Ketoconazole (400)</td>
<td>+145%</td>
<td>+62%</td>
<td>NA</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (600 single dose)</td>
<td>+29%</td>
<td>+68%</td>
<td>−9%</td>
</tr>
</tbody>
</table>

In Vitro Assessment

FDA Draft Guidance 2012

- Use of in vitro tools to determine whether a drug is a substrate, inhibitor, or inducer of metabolizing enzymes, followed by in vivo interaction studies to assess potential interactions, has become an integral part of drug development and regulatory review.

- Findings from in vitro metabolism, transport, and drug interaction studies are valuable in quantitatively assessing the drug-drug interaction potential of an investigational drug.

- Along with clinical pharmacokinetic data, results from in vitro studies can serve as a screening mechanism to rule out the need for additional in vivo studies, or provide a mechanistic basis for proper design of clinical studies using a modeling and simulation approach.

- Considerations critical for conducting in vitro studies include, but are not limited to, appropriately validated experimental methods, choice of test systems, and rational selection of substrate/interacting drug and their concentrations.
CYP Inhibition Study in Drug Discovery and Development

Wienkers and Heath, Nat Rev Drug Disc, 2005, 4: 825-833
CYP Inhibition Assays/Methods

From Discovery to Development

- **In vitro screening**
  - Single concentration of test compound with single concentration of probe substrate
  - Discovery phase

- **IC50 estimation**
  - Co-incubation of series of test compound concentration with single concentration of probe substrate
  - Early development phase

- **Ki determination**
  - Multiple concentration of test compound with multiple concentration of probe substrate
  - Development phase

- **Time-dependent inhibition**
  - $k_{obs}$
  - $K_I$ and $k_{inact}$

- **Modeling & Simulation**
  - Mathematical calculations and M&S (e.g., Simcyp DDI)

- **Clinical DDI study**
  - At present, no in vivo animal models can replace human clinical DDI studies
## Recommended Substrates and Inhibitors for in vitro CYP Inhibition Studies

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
<td>α-Naphthoflavone, furafylline</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin, nicotine</td>
<td>Tryptamine, tranylcypromine, methoxsalen</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion, efavirenz</td>
<td>Ticlopidine, clopidogrel</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Paclitaxel</td>
<td>Trimethoprin, montelukast, quercetin</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Tolbutamide, diclofenac, S-warfarin</td>
<td>Sulfaphenazole</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-Mephenytoin, omeprazole</td>
<td>Ticlopidine, nootkatone</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Bufuralol, dextromethorphan</td>
<td>Quinidine</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chloroxoxazone</td>
<td>Clomethiazole</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Midazolam, testosterone, nifedipine</td>
<td>Ketoconazole, itraconazole, troleandomycin</td>
</tr>
</tbody>
</table>
Enzyme Kinetics for Probe Substrates

*Km and Vmax*

- Linear with respect to time and protein concentration
- Test a series of concentrations
- Fit rate of metabolite formation to kinetic models (e.g., Michaelis–Menten, Allosteric sigmoidal)

Michaelis–Menten model:

\[ v = \frac{V_{max} \times [S]}{K_m + [S]}, \]

Allosteric sigmoidal model:

\[ v = \frac{V_{max} \times [S]^h}{K_{prime} + [S]^h}, \]
Reversible Inhibition

- Responsible for the majority (62%) of strong in vivo drug drug interactions
  - 33% of irreversible inhibitors cause strong DDIs [Chem Res Toxicol, 2009, 22(2):294-8]

- Mechanisms
  - Competitive: inhibitor and substrate compete for binding
  - Uncompetitive: inhibitor binds only to the substrate-enzyme complex
  - Noncompetitive: binding of the inhibitor to the enzyme reduces its activity but does not affect the binding of substrate
  - Mixed-type: hybrid combination of the above three mechanisms
Reversible CYP Inhibition Assays

- Test compound co-incubated with a CYP probe substrate,
  - Evaluate DDI potential in co-administration

- Fluorescence CYP inhibition screening assay for prioritization and SAR at LI/LO stage
  - Utilize fluorescent CYP probes and cDNA engineered CYP isoforms
  - CYP enzymes tested: CYP1A2, 2C9, 2C19, 2D6 and 3A4
  - IC50 generated

- Definitive HLM-LC/MS assay for advanced compounds
  - Utilize drugs as probe substrates and human liver microsomes
  - CYP enzymes tested: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5
  - Data (IC50 or Ki) required for DDI prediction and assessment
Enzyme Kinetics for Reversible Inhibitors

- Test a series of concentrations of inhibitors and substrates
  - e.g., 0.25- to 5-fold of IC50; 0.3- to 10-fold of Km
- Explore type of inhibition
- Estimate Ki

<table>
<thead>
<tr>
<th>Inhibition type</th>
<th>Rate equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitive</td>
<td>$v = \frac{V_{max}[S]}{[S] + K_m \left(1 + \frac{[I]}{K_i}\right)}$</td>
</tr>
<tr>
<td>Non-competitive</td>
<td>$v = \frac{V_{max}[S]}{K_m \left(1 + \frac{[I]}{K_i}\right) + [S] \left(1 + \frac{[I]}{K_i}\right)}$</td>
</tr>
<tr>
<td>Uncompetitive</td>
<td>$v = \frac{V_{max}[S]}{K_m + [S] \left(1 + \frac{[I]}{K_i}\right)}$</td>
</tr>
<tr>
<td>Mixed</td>
<td>$v = \frac{V_{max}[S]}{K_m \left(1 + \frac{[I]}{K_i}\right) + [S] \left(1 + \frac{[I]}{\alpha K_i}\right)}$</td>
</tr>
</tbody>
</table>
Time-Dependent Inhibition (TDI)

**Mechanism**

- Irreversible covalent binding or quasi-irreversible non-covalent tight binding of a chemically reactive intermediate to the enzyme, also known as mechanism-based inhibition (MBI)

- **Inactivation pathways**
  - Reaction with nucleophilic amino acids in the active site of the enzyme
  - Reaction with the heme nitrogen atoms
  - Coordination of the heme iron ion to form a metabolic intermediate complex

- **Differentiation of metabolism-dependent reversible, quasi-irreversible, and irreversible CYP inhibition (MDI, Lee 2012)**
  - All exhibit TDI character
  - Ultracentrifugation to separate reversible MDI
  - Potassium ferricyanide to resolve quasi-irreversible inhibition
Time-Dependent Inhibition (TDI)

Consequences

- Complicate PK profile if the inactivated enzyme is the primary enzyme of metabolism
  - Auto-inhibition of own metabolism, non-linear PK, unpredictable drug accumulation
  - More problematic for drugs having narrow safety margin

- Substantially increase DDI potency
  - Irreversibly decrease enzyme activity
  - Inhibitory effect increases over time following multiple dosing and is not promptly reversible (unlike reversible enzyme inhibition)

- Difficult to overcome and predict
  - Quantitative in vitro/in vivo correlation needs to be established
  - DDI simulations (e.g., Simcyp) can be used for MBI
Enzyme Kinetics for TDI

- **IC50-shift approach**
  - IC50s obtained by secondary incubation without pre-incubation step depict direct inhibition (DI)
  - Shifted IC50s obtained by pre-incubation and subsequent secondary incubation (TDI)
  - Fold-shift value reflects TDI potency
    \[
    IC_{50}^{\text{fold-shift}} = \frac{\text{shifted IC}_{50}}{IC_{50}}
    \]

- **TDI kinetic parameters** (\(k_{\text{obs}}, K_I, \text{ and } k_{\text{inact}}\))
  - \(k_{\text{obs}}\): slope of the initial linear phase of the plot of natural logarithm of remaining CYP activity vs. incubation time
  - \(K_I\) and \(k_{\text{inact}}\): nonlinear least-squares method
    \[
    k_{\text{obs}} = k_{\text{inact}} \times \frac{[I]}{(K_I + [I])}
    \]
Factors Considered in in vitro Incubations

- **Buffer composition**
  - Phosphate buffer: CYP2E1
  - Tris-HCl buffer: CYP2A6, CYP2B6, CYP2C9, CYP2C19
Organic solvents:
- Generally ≤ 1%
- Methanol: 34% of CYP2E1 activity decrease at 1%
- Acetonitrile: 40% of CYP2A6 activity decrease at 1%
- DMSO: Strong inhibitory effects (32–61%) to CYP2B6, CYP2C19, CYP2D6, CYP3A4 and CYP2E1 even at 0.5%

Bovine serum albumin
- Effect on Km: sequestration of inhibitory long-chain unsaturated fatty acids

Peng et al, Xenobiotica, 2015
Factors Considered in Incubation (cont)

- **Multiple binding regions at enzyme active site**
  - Three possible binding regions for CYP3A4 depending on three distinct groups of probe substrates (benzodiazepines, steroids, dihydropyridines, Kenworthy 1999)
  - More than one binding regions for CYP2C9 (Mo 2009, Williams 2003)
  - CYP2D6 and CYP2C19 also substrate-dependent inhibition
DDI Involve Multiple Inhibitor Systems

- **Inhibitory metabolites**
  - Itraconazole has three metabolites: hydroxy-, keto- and N-desalkyl-
    - Ki for CYP3A4 of nM
    - Increase in midazolam exposure can not be predicted by itraconazole alone but all four inhibitors

- **Racemic mixture of steoroisomers**
  - Omeprazole
    - (S)-isomer has 1.8~2.5-fold higher exposure than (R)-isomer
    - (R)-isomer is 15.4/1.5-fold more potent CYP2C9 and CYP2C19 inhibitor, respectively, than (S)-isomer

- **Co-administration of inhibitors of the same enzyme**
  - HIV Protease inhibitors that are CYP3A inhibitors are administered together during HIV antiretroviral therapy
    - Ritonavir to metabolically ‘boost’ saquinavir, indinavir or lopinavir concentrations via CYP3A4 inactivation
Application of in vitro Data

**Basic Model**

<table>
<thead>
<tr>
<th>Is the calculated R value &gt;1.1 (also, for CYP3A inhibitors given orally, is alternate R value &gt;11)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible inhibitor, $R_1 = I + [I]/K_i$</td>
</tr>
<tr>
<td>TDI, $R_2 = (K_{obs} + K_{deg})/K_{deg}$ and $K_{obs} = k_{inact} \times [I]/(K_i + [I])$</td>
</tr>
</tbody>
</table>

- $[I]$  
  - maximal total systemic inhibitor concentration in plasma  
  - For CYP3A oral inhibitor, $[I]$ should also be estimated by $[I] = I_{gut} = \text{Molar Dose}/250 \text{ mL}$

- Simple, practical and conservative  
  - Eliminates unnecessary clinical studies  
  - Rank ordering of inhibition potential across different CYP enzymes for the same drug.

FDA Draft Guidance 2012
Application of in vitro Data

Mechanistic Model

- Static model

\[
\text{Is AUCR} > 1.25 \text{ (inhibition)} \text{ or } \text{AUCR} < 0.8 \text{ (induction)}? \quad [d]
\]

Estimate AUCR of a sensitive probe substrate using
- a mechanistic static model\([a]\)

\[
\text{AUCR} = \left( \frac{1}{A_g \times B_g \times C_g \times (1 - F_g) + F_g} \right) \times \left( \frac{1}{A_h \times B_h \times C_h \times f_m + (1 - f_m)} \right)
\]
- or a dynamic model, including PBPK\([f]\)

<table>
<thead>
<tr>
<th></th>
<th>Gut</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible inhibition</td>
<td>(A_g = \frac{1}{1 + \frac{[I]_g}{K_i}})</td>
<td>(A_h = \frac{1}{1 + \frac{[I]_h}{K_i}})</td>
</tr>
<tr>
<td>Time-dependent inhibition</td>
<td>(B_g = \frac{k_{\text{deg},g}}{k_{\text{deg},g} + \frac{[I]<em>g \times k</em>{\text{inact}}}{[I]_g + K_I}})</td>
<td>(B_h = \frac{k_{\text{deg},h}}{k_{\text{deg},h} + \frac{[I]<em>h \times k</em>{\text{inact}}}{[I]_h + K_I}})</td>
</tr>
</tbody>
</table>

- Dynamic model: PBPK

FDA Draft Guidance 2012
Case Study – LCL161 DDI Assessment

- LCL161 is an orally bioavailable small molecule oral inhibitor of apoptosis proteins (IAP) antagonist in development for use in combination with cytotoxic agents

- Once-weekly dosing resulted in rapid and sustained degradation of cIAP1 in tumor, skin, and peripheral blood mononuclear cells, as well as induction of circulating cytokines

- Potential for clinically relevant DDI could critically influence the selection of combination partners and other co-medications

LCL161 inhibited CYP3A in a concentration- and time-dependent manner ($K_i$ of 0.797 μM and $k_{inact}$ of 0.0803 min$^{-1}$)

LCL161 activated human PXR in a reporter gene assay and induced CYP3A4 mRNA up to ~5-fold in human hepatocytes.
LCL161 CYP3A DDI Prediction

- Initial risk assessment (Contour Plot) suggested a high risk for a strong clinical DDI effect

- Simcyp simulated a 12- and 2.6-fold increase in midazolam AUC and Cmax, respectively, on Day 3; a 2.1- and 1.5-fold increase in AUC and Cmax, respectively, on Day 6; and recovery on Day 10

LCL161 CYP3A DDI in Clinical

- Open-label, fixed sequence, 18 HV study
- MDZ given 2-days before (day 1), 4 hours after, 3-days after, and 7-days after a single oral dose of LCL161 at 600 mg
  - Initial modeling suggested a similar magnitude of DDI for 500 and 1800 mg (clinical dose)
- Midazolam AUC and Cmax increased by 9.3- and 3.2-fold on Day 3, respectively; but AUC and Cmax decreased by 30% and 27%, respectively, on Day 6; and no significant change on Day 10

LCL161 CYP3A DDI - Summary

- LCL161 demonstrated dual inhibition and induction effects of CYP3A in vitro and in a clinical study with midazolam in healthy subjects.

- Clinical observations of strong time-dependent inhibition of CYP3A on the same day of LCL161 dosing were accurately predicted by dynamic PBPK modeling in Simcyp.

- Changes in midazolam pharmacokinetics at 3 days after the single dose of LCL161 was not predicted using Simcyp.
  - Mean maximum concentration of LCL161 was well below the concentrations resulting in PXR activation in vitro and induction of CYP3A by LCL161 in hepatocytes.
  - Mechanism underlying the induction effect was not investigated in this study. It is suspected to be related to the pharmacology of LCL161.

High prevalence of co-medication and polypharmacy increases risk of drug interactions that may alter the pharmacokinetic properties of the drug, and lead to unwanted/unexpected AEs or lack of efficacy.

Pharmacokinetic drug interactions should be defined during drug discovery and development, as part of an adequate assessment of drug safety and effectiveness.

- Early screening to identify liable pharmacophores and to minimize late attritions
- Preclinical assessment to define DDI characteristics and to predict clinical DDI potencies

In vitro data coupled with IVIVE have become integral to DDI risk assessment, clinical decision making and clinical DDI study design.

Interplay of complex DDI mechanisms (CYPs and transporters) shall be considered and assessed.
Complex Drug Interaction

- Concurrent inhibition and induction of one enzyme or concurrent inhibition of enzyme and transporter by a drug
- Increased inhibition of drug elimination by the use of more than one inhibitor of the same enzyme that metabolizes the drug
- Increased inhibition of drug elimination by use of inhibitors of more than one enzyme that metabolizes the drug
- Inhibition by a drug and its metabolite or metabolites, both of which inhibit the enzyme that metabolizes the substrate drug
- Inhibition of an enzyme other than the genetic polymorphic enzyme in poor metabolizers taking substrate that is metabolized by both enzymes
- Use of enzyme/transporter inhibitors in subjects with varying degrees of impairment of drug eliminating organs (e.g., liver or kidney)
**Sensitive in vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range**

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine</td>
<td>Theophylline, tizanidine</td>
</tr>
<tr>
<td>CYP2B6[^4]</td>
<td>Bupropion, efavirenz</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Celecoxib</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clobazam, lansoprazole, omeprazole, S-mephenytoin</td>
<td>S-mephenytoin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine</td>
<td>Thioridazine, pimozide</td>
</tr>
</tbody>
</table>

[^2]: Literature references and specific details on sensitive substrates are provided in the original document.

[^3]: Specific notes on substrates within the narrow therapeutic range are referenced from FDA Draft Guidance 2012.

[^4]: Additional details on CYP2B6 substrates are noted, highlighting the importance in clinical contexts.

[^5]: Repaglinide is highlighted as a significant substrate for CYP2C8, indicating potential pharmacokinetic interactions.

[^6]: CYP3A enzymes are noted for their role in metabolism, with midazolam highlighted as a key substrate.

[^7]: Specific references to substrates within CYP3A, emphasizing their clinical relevance.
Example of TDI IC50-Shift Method

Kozakai, Drug Metab. Pharmacokinetc., 2014, 29:198-207
TDI Prediction using Shifted $IC_{50}$ or Single Concentration $k_{\text{obs}}$

Kozakai, Drug Metab. Pharmacokinetc., 2014, 29:198-207
MBI Interaction Contour Map

Venkatakrishnan and Obach, *Current Drug Metabolism*, 2007, 8, 449-462

\[
Y = \left(1 + \frac{1}{X}\right) \times (R - 1)
\]