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Hepatic Clearance Predictions from In Vitro–In Vivo Extrapolation and the Biopharmaceutics Drug Disposition Classification System

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ABSTRACT

Predicting in vivo pharmacokinetic parameters such as clearance from in vitro data is a crucial part of the drug-development process. There is a commonly cited trend that drugs that are highly protein-bound and are substrates for hepatic uptake transporters often yield the worst predictions. Given this information, 11 different data sets using human microsomes and hepatocytes were evaluated to search for trends in accuracy, extent of protein binding, and drug classification based on the Biopharmaceutics Drug Disposition Classification System (BDDCS), which makes predictions about transporter effects. As previously reported, both in vitro systems (microsomes and hepatocytes) gave a large number of inaccurate results, defined as predictions falling more than 2-fold outside of in vivo values. The weighted average of the percentage of inaccuracy was 66.5%. BDDCS class 2 drugs, which are subject to transporter effects in vivo unlike class 1 compounds, had a higher percentage of inaccurate predictions and often had slightly larger bias. However, since the weighted average of the percentage of inaccuracy was still high in both classes (81.9% for class 2 and 62.3% for class 1), it may be currently hard to use BDDCS class to predict potential accuracy. The results of this study emphasize the need for improved in vitro to in vivo extrapolation experimental methods, as using physiologically based scaling is still not accurate, and BDDCS cannot currently help predict accurate results.

Introduction

The current drug-development process is expensive, time-consuming, and inefficient due to compound attrition (Pammolli et al., 2011). Although failures due to pharmacokinetic parameters have decreased in recent years (Waring et al., 2015), continued improvement in pharmacokinetic predictions is crucial.

Metabolic stability studies are some of the earliest in vitro studies conducted during drug development to determine the rate and extent to which a molecule is metabolized, and can be useful for rank ordering candidates. After measuring in vitro metabolic turnover, or intrinsic clearance (CL_{int}), in vivo hepatic clearance can be predicted using in vitro–in vivo extrapolation (IVIVE) methods. A common approach is to apply physiologically based scaling factors to the raw in vitro data, such as hepatocellularity for studies using hepatocytes or a factor to account for incomplete microsomal recovery for microsomes, and to then apply a model of hepatic disposition, such as the well stirred model (Houston, 1994). Although the results are often used in the drug-development process, there is perhaps an overemphasis placed on their reliability.

The first part of the present study examined the overall accuracy of hepatic clearance predictions in the field at this time. Many groups have attempted IVIVE, tried to create new models to improve predictions from old in vitro values, or investigated different experimental setups. A study published 10 years ago collected and examined results from 85 compounds, concluding there was a paucity of literature data (Nagilla et al., 2006); however, much work has been done since then.

When examining the accuracy of these values, a prediction bias has been found that is unresolved from human variability and experimental uncertainty (Hallifax and Houston, 2009). There is also a commonly cited trend that substrates for hepatic uptake transporters and highly protein-bound compounds yield the poorest predictions (Soars et al., 2007). The Biopharmaceutics Drug Disposition Classification System (BDDCS), which categorizes transporter effects on drug disposition, says class 1 compounds exhibit minimal clinically relevant transporter effects, whereas class 2 compounds may be governed by transporter effects in the gut and liver (Wu and Benet, 2005). BDDCS has become an important part of early drug discovery for predicting routes of elimination, food effects, and potential drug interactions (Wu and Benet, 2005). Given this trend, the main objective of this study was to determine if BDDCS classification could be a determinant of accurate IVIVE results.

Materials and Methods

A literature search was conducted for previously described compounds for which both in vitro and in vivo clearance data were available. Studies using human microsomes as well as human hepatocytes were considered, as both systems are routinely used in the pharmaceutical industry. The terms used as keywords to help in the search included "in vitro-in vivo extrapolation," "intrinsic clearance," "microsomes," "hepatocytes," or a combination of these.

All of the studies considered here used the well stirred model in their predictions, and predictions were made using physiologically based scaling factors, not empirical or regression-based factors. The data sets were examined separately, excluding re-examination of previously published data, as different experimental setups (such as the inclusion of serum in incubations) and scaling (such as the inclusion of fu_b and fu_{inc} versus no binding terms) were used in each.

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ABBREVIATIONS: AFE, average fold error; BDDCS, Biopharmaceutics Drug Disposition Classification System; CL_{int}, intrinsic clearance; IVIVE, in vitro to in vivo extrapolation; RMSE, root mean squared error.

Similarly, repeated drugs were not removed due to value differences among data sets. Overall evaluations were also tabulated. The data evaluated can be found in Supplemental Table 1.

The accuracy of predictions was determined based on whether the predictions fell within 2-fold of the true in vivo values, as has been a standard cutoff in previous studies (Zuegge et al., 2001; Blanchard et al., 2006; Fagerholm, 2007).

To measure bias, the average fold error (AFE) was calculated using the following equation (Obach et al., 1997):

$$\mathrm{AFE} = 10^{\frac{1}{N}\sum \log\left(\frac{\text{observed}}{\text{predicted}}\right)}$$

AFE was recorded as the whole number reciprocal if less than 1.

The precision was also calculated with the root mean squared error (RMSE) using the following (Sheiner and Beal, 1981):

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum(\text{predicted} - \text{observed})^2}$$

To divide the compounds based on their BDDCS classification, two publications categorizing over 900 drugs and over 175 drugs were consulted (Benet et al., 2011; Hosey et al., 2016). Five compounds were also classified here for the first time (class 1: amobarbital, bufuralol, levoprotiline, and triprolidine; class 2: tenidap). Trends in the accuracy of predictions compared with class 1 and class 2 drugs, where metabolism is the main route of elimination, were examined. Protein binding was also considered if the values used in the prediction calculations were available, as the interplay between protein binding, transporters, and enzymes is known to be important (Benet, 2009). Drugs with high protein binding were defined as having a free fraction less than or equal to 0.05.

Results

Seven different papers were examined that fit the criteria mentioned earlier (Obach, 1999; McGinnity et al., 2004; Ito and Houston, 2005; Riley et al., 2005; Brown et al., 2007; Hallifax et al., 2010; Sohlenius-Sternbeck et al., 2010). Hallifax et al. (2010) compiled a large database of predictions from many of the papers also examined here; however, not all drugs from the original papers were included, and different values of $CL_{in\ vivo}$ were often compared, causing the same drugs to be accurately or inaccurately predicted based on the value choices. Furthermore, although it could be argued that the more recent Hallifax et al. (2010) paper provides refined values from the original papers, looking at the percentage of inaccuracy and AFE both overall and for class 1 and class 2 drugs reveals that the Hallifax et al. (2010) data often actually have a comparable or higher percentage of inaccuracy and AFE values compared with the original papers. All papers were therefore examined to try to obtain a fuller picture of the relationship to BDDCS. Five human microsome data sets, some with multiple scaling options, were included in this evaluation for a total of 332 values, and six human hepatocyte data sets were also included for a total of 332 values. The percentage of inaccurate predictions (more than 2-fold difference) for each data set as well as the AFE and RMSE are shown in Table 1. Every data set examined has 41.0% or greater inaccuracy, and AFE values are as high as 21.7. The paper by Sohlenius-Sternbeck et al. (2010) only provided individual prediction values using a regression model, so further analysis could not be conducted. However, since it is the most recent paper examined, the summary statistics using the well stirred model with protein binding that were given were still included in the table for comparison. The weighted average for the percentage of inaccurate results for microsomes is 66.8%, for hepatocytes is 66.2%, and overall is 66.5%.

The same papers and data sets were used to examine BDDCS trends. Class 1 and class 2 drugs were compiled from each set, and the inaccuracy of the predictions, AFE, and RMSE for each class was determined (Table 2). As expected, class 2 drugs have a higher percentage of inaccurate predictions than class 1 drugs in every case except one, where all predictions were inaccurate. The AFE was either slightly higher or almost identical for class 2 drugs compared with class 1 drugs. Considering a total of 305 class 1 drug values, the weighted average of the percentage of inaccurate predictions is 62.3%. For a total of 155 class 2 drug values, the weighted average of the percentage of inaccuracy is 81.9%. [The total number of class 1 and class 2 drugs is

TABLE 1

Percentage of inaccuracy, AFE, and RMSE of IVIVE predictions for 11 data sets

System	Number of Compounds Evaluated	Number of Inaccurate Predictions	AFE	RMSE
		(%)		
Brown et al. (2007)				
Hepatocytes	37	26 (70.3)	4.5	6460.2
Hallifax et al. (2010)				
Microsomes	68	53 (77.9)	5.2	3708.6
Hepatocytes	89	60 (67.4)	3.9	3137.7
Ito and Houston, (2005)				
Microsomes	52	45 (86.5)	7.9	1337.0
McGinnity et al. (2004)[a]				
Hepatocytes	44	22 (50.0)	1.4	94.1
Obach (1999)				
Microsomes (fu_b and fu_{inc})	29	13 (44.8)	2.3	4.9
Microsomes (fu_b)	29	22 (75.9)	4.3	6.8
Microsomes (no binding)	29	13 (44.8)	1.5	4.3
Riley et al. (2005)[b]				
Microsomes	37	27 (73.0)	3.3	2314.2
Hepatocytes	56	38 (67.9)	3.1	1356.5
Hepatocytes (with serum)	14	14 (100.0)	21.7	2124.3
Sohlenius-Sternbeck et al. (2010)[c]				
Microsomes (fu_b and fu_{inc})	44	70.0	3.8	5.8
Hepatocytes (fu_b and fu_{inc})	46	89.0	5.9	8.0
Microsomes (no binding)	44	41.0	0.5	6.1
Hepatocytes (no binding)	46	41.0	0.8	5.4

[a] CL_{int} data were evaluated.
[b] $CL_{int,\ ub,\ in\ vivo}$ data were evaluated.
[c] Individual values for predictions with well stirred model were not presented, only summary statistics.

TABLE 2

Percentage of inaccuracy, AFE, and RMSE of IVIVE predictions for BDDCS class 1 and class 2 drugs

System	Number of Class 1 Drugs	Number of Inaccurate Class 1 Predictions	AFE	RMSE	Number of Class 2 Drugs	Number of Inaccurate Class 2 Predictions	AFE	RMSE
		%				(%)		
Brown et al. (2007)								
Hepatocytes	24	14 (58.3)	3.0	294.5	12	11 (91.7)	7.4	11,335.9
Hallifax et al. (2010)								
Microsomes	42	30 (71.4)	5.2	4521.7	22	20 (91.0)	4.7	1834.4
Hepatocytes	55	36 (65.5)	4.0	3976.5	30	22 (73.3)	3.7	466.1
Ito and Houston (2005)								
Microsomes	32	27 (84.4)	6.8	390.8	16	15 (93.8)	11.2	2312.3
McGinnity et al. (2004)								
Hepatocytes	32	16 (50.0)	1.1	99.3	9	5 (55.6)	3.0	90.9
Obach (1999)								
Microsomes (fu_b and fu_{inc})	20	7 (35.0)	1.9	4.6	9	6 (66.6)	3.2	5.4
Microsomes (fu_b)	20	13 (65.0)	3.7	6.9	9	9 (100.0)	6.0	6.7
Microsomes (no binding)	20	7 (35.0)	1.2	4.0	9	6 (66.7)	2.5	4.8
Riley et al. (2005)								
Microsomes	24	16 (66.7)	2.7	2399.1	11	9 (81.8)	6.0	2298.5
Hepatocytes	28	16 (57.1)	2.4	175.7	22	18 (81.8)	3.8	2125.8
Hepatocytes (serum)	8	8 (100.0)	9.6	251.0	6	6 (100.0)	64.2	3232.0

less than 644, since individual drugs are not enumerated in Sohlenius-Sternbeck et al. (2010) and some unapproved proprietary compounds are included in other data sets.] For class 1 drugs, studies done in microsomes have a weighted average of 63.3% inaccuracy, whereas studies in hepatocytes are 66.2% inaccurate. For class 2 drugs, studies in microsomes have a weighted average of prediction inaccuracy of 85.6%, whereas studies in hepatocytes have a 78.4% average.

Finally, given that substrates of transporters and highly bound drugs often have the poorest clearance predictions (Soars et al., 2007), protein-binding differences were examined between the two BDDCS classes. First, the percentage of drugs with inaccurate predictions that are also highly protein-bound in both classes was determined (Table 3). There are more inaccurate class 2 drugs that are highly protein-bound than class 1 drugs in every case examined. The weighted average of inaccurate class 1 drugs with high protein binding is 19.8%, whereas the weighted average for class 2 is 67.3%. Since class 2 drugs in general are often highly protein-bound (Broccatelli et al., 2012), the numbers of highly bound drugs in both classes that have inaccurate predictions were also determined (Table 4). These results agree with several other conclusions that highly protein-bound compounds are often poorly predicted. Class 1 highly protein-bound drugs were inaccurately predicted 81.3% of the time, and class 2 highly bound drugs had an 85.7% average inaccuracy rate. In four data sets, highly bound class 2 drugs had a higher percentage of inaccuracy than class 1 drugs; in one data set, the opposite was true; and in the last set, all highly bound drugs were inaccurate.

Looking at the bias between the high and low protein-binding drugs in the two classes (Table 5), it is difficult to see trends between the two classes; however, the bias is always higher for the high protein-binding drugs, except in the case of the data from Obach (1999), using fu_b and fu_{inc}, and Brown et al. (2007), where there are only two class 1 high protein-binding drugs and four class 2 low protein-binding drugs, perhaps skewing the results.

Discussion

Being able to accurately predict pharmacokinetic parameters, especially clearance, early in the drug-development process is a key part of lead optimization. However, although some studies have claimed to find success in predicting in vivo clearance from in vitro data, others have questioned the reliability (Masimirembwa et al., 2003). Underpredicting in vivo clearance may result in inefficiency in the drug-discovery pipeline or an ineffective therapeutic dosing regimen, whereas overpredicting in vivo clearance may lead to missed opportunities that were rejected early in the development process (Clarke and Jeffrey, 2001).

TABLE 3

Percentage inaccuracy of BDDCS class 1 and class 2 drugs that are highly protein-bound

System	Number of Inaccurate Class 1 Predictions	Number of Inaccurate Highly Protein-Bound Class 1 Predictions	Number of Inaccurate Class 2 Predictions	Number of Inaccurate Highly Protein-Bound Class 2 Predictions
		(%)		(%)
Brown et al. (2007)				
Hepatocytes	14	1 (7.1)	11	7 (63.6)
Hallifax et al. (2010)				
Microsomes	30	6 (20.0)	20	9 (45.0)
Hepatocytes	36	9 (25.0)	22	15 (68.2)
Obach (1999)				
Microsomes (fu_b and fu_{inc})	7	1 (14.3)	6	4 (66.6)
Microsomes (fu_b)	13	1 (7.7)	9	4 (44.4)
Microsomes (no binding)	7	2 (28.6)	6	4 (66.7)
Riley et al. (2005)				
Hepatocytes	16	4 (25.0)	18	17 (94.4)
Hepatocytes (serum)	8	2 (25.0)	6	6 (100.0)

TABLE 4

Percentage of highly protein-bound BDDCS class 1 and class 2 drugs that are inaccurate

System	Number of Highly Protein-Bound Class 1 Drugs	Number of Inaccurate Highly Protein-Bound Class 1 Predictions	Number of Highly Protein-Bound Class 2 Drugs	Number of Inaccurate Highly Protein-Bound Class 2 Predictions
		(%)		(%)
Brown et al. (2007)				
Hepatocytes	2	1 (50.0)	8	7 (87.5)
Hallifax et al. (2010)				
Microsomes	8	6 (75.0)	10	9 (90.0)
Hepatocytes	9	9 (100.0)	20	15 (75.0)
Obach (1999)				
Microsomes (fu_b and fu_{inc})	2	1 (50.0)	4	4 (100.0)
Microsomes (fu_b)	2	1 (50.0)	4	4 (100.0)
Microsomes (no binding)	2	2 (100.0)	4	4 (100.0)
Riley et al. (2005)				
Hepatocytes	5	4 (80.0)	21	17 (81.0)
Hepatocytes (serum)	2	2 (100.0)	6	6 (100.0)

The goal of this study was to compile data to examine the accuracy of the prediction methods for in vivo clearance and relate this accuracy to BDDCS classification. For the 11 data sets considered, there is a large percentage of inaccuracy. To have a true understanding of the accuracy of in vitro methods, physiologically scaled in vitro estimations and observed in vivo clearance were directly compared, since incorporating established physiologic scaling factors as well as unbound fractions in the blood and possibly in vitro matrix should, in theory, give accurate predictions. This is in contrast to some groups creating linear regression equations from reference compound data and then applying an empirical scaling factor to try to further improve predictions (Sohlenius-Sternbeck et al., 2012). The fact that 66.5% of predictions overall are inaccurate emphasizes the idea that a mechanistic understanding of this inaccuracy still needs to be determined before IVIVE predictions can be completely trusted.

BDDCS classification and protein binding were then examined to evaluate if accurate results could be separated from inaccurate results to help determine whether predictions can be trusted in the future or not. Class 1 drugs, or those that are extensively metabolized and highly soluble, appear to overwhelm transporter effects, whereas class 2 drugs, also extensively metabolized but poorly soluble, can be affected by efflux transporters in the gut and both uptake and efflux transporters in the liver (Shugarts and Benet, 2009). Given the trend that poorly predicted compounds are often substrates for transporters (Soars et al., 2007), it was expected that class 1 drugs that have no clinically relevant transporter effects would yield better predictions than class 2 drugs. The other part of the trend is that poorly predicted compounds are also often highly protein-bound, which is why protein binding was considered when data were available (Ring et al., 2011). Overall, the hypothesis was that class 2 drugs would be more poorly predicted due to the fact that they are substrates for transporters, and these poorly predicted class 2 drugs would also be highly protein-bound.

As expected, class 2 drugs yielded poorer predictions in every case examined; however, there was still large inaccuracy for both class 1 and class 2 drugs. Class 2 drugs also often had a higher AFE, but the difference was not enough (or sometimes did not exist at all) to indicate bias. However, AFE provides a better measure of bias than RMSE, which is highly influenced by the marked differences in CL_{int} values from study to study. For example, the values reported by Brown et al. (2007) for predicted and measured CL_{int} for propofol were 2773 and 5052 ml/min/kg, respectively, whereas for the same drug McGinnity et al. (2004) reported 283 and 24 ml/min/kg. At this point in time, with the current methodology, relying on BDDCS class cannot confidently provide information about whether predictions will be accurate or not. This agrees with previous findings from Poulin et al. (2012), who found that predictivity was similar between classes for a human microsome data set of 42 drugs. It is interesting to note that microsomes and hepatocytes gave similar prediction accuracies in both class 1 and class 2 drugs. A bigger difference between the two systems would have been expected for class 2 drugs where transporters play a role, since necessary uptake transporters are not present in microsomes. This again emphasizes that there are likely major missing determinants when trying to mimic the interplay between protein binding, uptake, and metabolism in vitro.

Poulin et al. (2012) also suggested that an approach involving determination of effective fraction unbound in plasma based on albumin-facilitated hepatic uptake of acidic/neutral drugs improved the prediction accuracy and precision for 25 high protein-binding drugs. Hallifax and Houston (2012) examined this approach for 107 drugs studied in hepatocytes and microsomes, also finding an increase in prediction accuracy but no change

TABLE 5

AFE and RMSE of high and low protein-binding BDDCS class 1 and class 2 drugs

Protein Binding	Class 1		Class 2	
	AFE	RMSE	AFE	RMSE
Brown et al. (2007)				
Hepatocytes				
High	2.0	56.4	6.3	13,882.7
Low	3.1	307.1	10.3	229.6
Hallifax et al. (2010)				
Microsomes				
High	7.8	10,335.3	5.3	2671.0
Low	4.8	349.9	4.2	473.3
Hepatocytes				
High	12.1	9814.8	4.2	479.9
Low	3.3	242.7	2.9	437.0
Obach (1999)				
Microsomes (fu_b and fu_{inc})				
High	1.7	0.3	4.7	3.1
Low	2.0	4.9	2.3	6.7
Microsomes (fu_b)				
High	4.7	0.4	7.3	3.1
Low	3.6	7.3	5.2	8.6
Microsomes (no binding)				
High	13.7	1.5	7.7	6.8
Low	1.1	17.7	1.0	2.2
Riley et al. (2005)				
Hepatocytes				
High	3.1	175.2	3.9	2175.6
Low	2.2	173.3	2.8	136.5
Hepatocytes (serum)				
High	17.0	406.3	64.2	3232.0
Low	8.0	170.2	—	—

in precision, and reported that there was no evidence that prediction bias was associated with measured fraction unbound in plasma. These latter authors emphasized the need for further "mechanistic elucidation to improve prediction methodology rather than empirical correction of bias" (Hallifax and Houston, 2012).

Last, protein binding was considered along with BDDCS. Given current trends, class 2 drugs with high protein binding would have been expected to yield the poorest results. There were more inaccurate class 2 drugs that had higher protein binding than class 1, but this may be because class 2 drugs generally have higher protein binding than class 1 (Broccatelli et al., 2012). This coupled to the fact that there may be a slight dependency of bias on protein binding, both here and as found previously with hepatocytes by Hallifax et al. (2010), could explain some of the difference seen between the inaccuracies in class 1 and class 2 drugs. However, on average, highly bound drugs in both classes had similar high percentages of inaccuracy, and there were no clear trends in the bias or precision of highly bound drugs between classes.

This study emphasizes the fact that the in vitro to in vivo extrapolation of hepatic clearance needs to be improved through a better understanding of clearance mechanisms, as in vitro methods on their own are often not accurate, and looking at BDDCS class cannot separate out which compounds will have accurate predictions.

Authorship Contributions

Participated in research design: Bowman, Benet.

Conducted experiments: Bowman.

Performed data analysis: Bowman.

Wrote or contributed to the writing of the manuscript: Bowman, Benet.

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Hepatic clearance predictions from *in vitro-in vivo* extrapolation and BDDCS

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Drug Metabolism and Disposition

Supplementary Table 1: Compiled IVIVE predictions and BDDCS classifications

Author	System	Drug	CL Predicted	CL Observed	Fold Difference	BDDCS Class	f_{ub}
Brown et al.	Hepatocytes	Furosemide	0.91	162	178.02	4	0.022
(2007)		Ketoprofen	4.7	129	27.45	2	0.018
		Mephenytoin	3.6	64	17.78	2	0.714
		Timolol	4.4	77	17.50	1	0.476
		Metoprolol	4.3	75	17.44	1	0.788
		Lorazepam	0.95	14	14.74	1	0.090
		Tolbutamide	0.38	4.9	12.89	2	0.067
		Gemfibrozil	5.5	67	12.18	2	0.055
		Propranolol	39	454	11.64	1	0.157
		Terfenadine	4136	43333	10.48	2	0.030
		Dextromethorphan	172	1482	8.62	1	0.284
		Naproxen	1.4	11	7.86	2	0.018
		Imipramine	49	380	7.76	1	0.094
		Lidocaine	21	157	7.48	1	0.337
		Ibuprofen	12	80	6.67	2	0.018
		Diltiazem	19	125	6.58	1	0.220
		Triazolam	11	66	6.00	1	0.132
		Diclofenac	98	561	5.72	2	0.018
		Oxazepam	6.9	34	4.93	2	0.045

		Flunitrazepam	4.5	20	4.44	1	0.282
		Nifedipine	146	597	4.09	2	0.068
		Quinidine	18	61	3.39	1	0.149
		S-Warfarin	1.9	6.1	3.21	2	0.018
		Diazepam	6.6	18	2.73	1	0.040
		Desipramine	74	167	2.26	1	0.188
		Bufuralol	45	99	2.20	1	0.238
		Propofol	2773	5052	1.82	2	0.016
		Alprazolam	2.1	3.7	1.76	1	1.000
		Midazolam	200	314	1.57	1	0.076
		Chlorpromazine	188	267	1.42	1	0.043
		Methylprednisolone	33	45	1.36	1	0.220
		Antipyrine	0.67	0.69	1.03	1	0.970
		Caffeine	2.1	2	0.95	1	0.651
		Prednisolone	30	27	0.90	1	0.100
		Theophylline	2.6	2.1	0.81	1	0.530
		Naloxone	284	200	0.70	1	0.459
		Codeine	35	19	0.54	1	0.930
Hallifax et al.	Microsomes	Prochlorperazine	199	29240	146.93	1	0.003
(2010)		Theophylline	0.03	2.61	87.00	1	0.53
		Felodipine	98	4300	43.88	2	0.003
		Mianserin	34.6	1463	42.28	1	0.14
		FK1052	40	1600	40.00	-	0.021
		Amitriptyline	13	490	37.69	1	0.058
		Clozapine	4.4	160	36.36	2	0.051
		Propranolol	7.8	267	34.23	1	0.14
		Mexiletine	0.77	26	33.77	1	0.39
		Lidocaine	3.1	82.1	26.48	1	0.33
		Methoxsalen	38	1000	26.32	2	0.13

		Promazine	62.8	1595	25.40	1	0.029
		Phenytoin	0.16	4	25.00	2	0.12
		Labetalol	18.4	450	24.46	1	0.32
		Ondansetron	1.7	31.8	18.71	1	0.27
		Imipramine	18	318	17.67	1	0.13
		Promethazine	76.3	1318	17.27	1	0.023
		Lorcainide	48	710	14.79	1	0.30
		Phenacetin	42.3	615	14.54	2	0.60
		Dofetilide	0.4	4.5	11.25	3	0.36
		Quinidine	3.2	34.2	10.69	1	0.15
		Warfarin	0.49	4.5	9.18	2	0.005
		Indinavir	16	130	8.13	2	0.39
		Prednisone	2.6	21	8.08	2	0.10
		Omeprazole	67	520	7.76	1	0.068
		Desipramine	16	118	7.38	1	0.25
		Ibuprofen	8.2	59.1	7.21	2	0.015
		Nilvadipine	1200	8400	7.00	2	0.016
		FK480	51	340	6.67	-	0.008
		Glyburide	57.9	385	6.65	2	0.004
		Caffeine	0.43	2.82	6.56	1	0.65
		Trimipramine	205	1344	6.56	2	0.051
		Buprenorphine	449	2938	6.54	1	0.040
		Clomipramine	192	1047	5.45	1	0.022
		Fluphenazine	302	1581	5.24	2	0.012
		Dexamethasone	2.9	14	4.83	1	0.34
		Ketamine	28.6	138	4.83	1	0.59
		Antipyrine	0.14	0.6	4.29	1	0.97
		Diclofenac	108	418	3.87	2	0.014
		Methohexital	47	180	3.83	1	0.39
		Diltiazem	40.6	143	3.52	1	0.20

		Metoprolol	18	62.2	3.46	1	0.80
		Fenoprofen	13.5	34.3	2.54	2	0.018
		Flunitrazepam	5	12.7	2.54	1	0.28
		Propafenone	133	328	2.47	2	0.059
		Alprenolol	48.5	117	2.41	1	0.27
		Tolbutamide	1.2	2.82	2.35	2	0.16
		Chlorpheniramine	2	4.62	2.31	1	0.30
		Gemfibrosil	30.1	68.4	2.27	2	0.036
		Tenoxicam	1.6	3.33	2.08	1	0.013
		Verapamil	193	310	1.61	1	0.12
		Bepridil	992	1583	1.60	1	0.005
		Nicardipine	1200	1900	1.58	1	0.068
		Amobarbital	0.89	1.4	1.57	1	0.26
		Diazepam	10	15.3	1.53	1	0.036
		Zolpidem	23.1	31.9	1.38	1	0.17
		Chlorpromazine	208	287	1.38	1	0.053
		Bupivacaine	83	110	1.33	1	0.068
		Tenidap	7.9	8.3	1.05	2	0.001
		Alprazolam	2	2.08	1.04	1	0.64
		Risperidone	43.3	43	0.99	1	0.17
		YW796	15	14	0.93	-	0.63
		Sildenafil	121	89.8	0.74	1	0.094
		Triazolam	43.5	30.6	0.70	1	0.17
		Domperidone	520	275	0.53	2	0.060
		Trazodone	65.4	32.3	0.49	2	0.061
		Midazolam	708	134	0.19	1	0.072
		Glimepiride	35.4	5.1	0.14	2	0.14
Hallifax et al.	Hepatocytes	Prochlorperazine	45.6	29240	641.23	1	0.003
(2010)		Furosemide	0.91	84.9	93.30	4	0.022

		Buprenorphine	40	2938	73.45	1	0.040
		Mianserin	22.3	1463	65.61	1	0.14
		Fluoxetine	5.3	228	43.02	1	0.060
		Levoprotiline	8.1	261	32.22	1	0.19
		Labetalol	16.4	450	27.44	1	0.32
		Promazine	64.6	1595	24.69	1	0.029
		Fluphenazine	69.9	1581	22.62	2	0.012
		Glyburide	17.2	385	22.38	2	0.004
		Phenacetin	36.2	615	16.99	2	0.60
		Montelukast	96.3	1503	15.61	2	0.001
		Lorazepam	1	14.2	14.20	1	0.090
		Promethazine	101	1318	13.05	1	0.023
		Metoprolol	5.3	62.2	11.74	1	0.80
		Cyclosporin A	13.5	152	11.26	2	0.040
		Flumazenil	16.3	183	11.23	1	0.52
		Timolol	4.4	49.3	11.20	1	0.48
		Trimipramine	138	1344	9.74	2	0.051
		Clomipramine	109	1047	9.61	1	0.022
		Verapamil	33.4	310	9.28	1	0.12
		Propranolol	29.2	267	9.14	1	0.14
		Temazepam	5.7	51.4	9.02	1	0.027
		Diltiazem	16	143	8.94	1	0.20
		Ondansetron	3.9	31.8	8.15	1	0.27
		Clozapine	20.8	160	7.69	2	0.051
		Imipramine	42.8	318	7.43	1	0.13
		Tolbutamide	0.38	2.82	7.42	2	0.16
		Glipizide	7.1	50.3	7.08	2	0.020
		Ketoprofen	11	77.5	7.05	2	0.017
		Prazosin	6.2	39.7	6.40	1	0.085
		Diphenhydramine	16	94.2	5.89	1	0.19

		Oxazepam	6.9	38.5	5.58	2	0.045
		Lidocaine	15.3	82.1	5.37	1	0.33
		Diclofenac	86.8	418	4.82	2	0.014
		Bepridil	337	1583	4.70	1	0.005
		Indomethacin	27.1	126	4.65	2	0.020
		Propafenone	76.4	328	4.29	2	0.059
		Naproxen	1.4	5.86	4.19	2	0.018
		Oxaprozin	24.4	100	4.10	2	0.001
		Zolpidem	8	31.9	3.99	1	0.17
		Sildenafil	24.4	89.8	3.68	1	0.094
		Diflunisal	9.9	34.3	3.46	2	0.005
		Ketamine	40.5	138	3.41	1	0.59
		Bupivacaine	32.6	110	3.37	1	0.068
		Triprolidine	39.6	130	3.28	1	0.10
		Domperidone	88.1	275	3.12	2	0.060
		Ritonavir	30.5	86.1	2.82	2	0.015
		Flunitrazepam	4.5	12.7	2.82	1	0.28
		Morphine	64.6	179	2.77	1	0.77
		Gemfibrosil	24.9	68.4	2.75	2	0.036
		Desipramine	45.3	118	2.60	1	0.25
		Acetaminophen	2.5	6.28	2.51	1	0.79
		Triazolam	12.3	30.6	2.49	1	0.17
		Diazepam	6.6	15.3	2.32	1	0.036
		Irbesartan	58.8	118	2.01	2	0.040
		Quinidine	18	34.2	1.90	1	0.15
		Trazodone	17.4	32.3	1.86	2	0.061
		Alprenolol	64.5	117	1.81	1	0.27
		Ibuprofen	32.6	59.1	1.81	2	0.015
		Carvedilol	282	500	1.77	2	0.030

		Oxprenolol	14.9	26.2	1.76	1	0.30
		S-Warfarin	1.9	3.31	1.74	2	0.018
		Chlorpromazine	182	287	1.58	1	0.053
		Ranitidine	3	4.38	1.46	3	0.77
		Bufuralol	45	64.5	1.43	1	0.24
		Methylprednisolone	33	45	1.36	1	0.22
		Scopolamine	19.6	26.7	1.36	1	0.88
		Caffeine	2.1	2.82	1.34	1	0.65
		Nifedipine	146	196	1.34	2	0.068
		Fenoprofen	27.4	34.3	1.25	2	0.018
		Cimetidine	3.4	4.21	1.24	3	0.90
		Pindolol	7.8	9.58	1.23	1	0.55
		Metoclopramide	10	11.6	1.16	1	0.76
		Betaxolol	7.4	8.58	1.16	1	0.56
		Granisetron	29.7	33.5	1.13	1	0.70
		Acebutolol	5.1	5.33	1.05	1	0.96
		Theophylline	2.6	2.61	1.00	1	0.53
		Alprazolam	2.1	2.08	0.99	1	0.64
		Midazolam	138	134	0.97	1	0.072
		Prednisolone	30	27.1	0.90	1	0.10
		Antipyrine	0.67	0.6	0.90	1	0.97
		Etodolac	81.2	69.9	0.86	2	0.020
		Glimepiride	9.4	5.1	0.54	2	0.14
		Codeine	35	18.9	0.54	1	0.93
		Chlorpheniramine	9.4	4.62	0.49	1	0.30
		Nadolol	7.7	3.48	0.45	3	0.97
		Tenoxicam	8.8	3.33	0.38	1	0.013
		Carbamazepine	5.9	1.32	0.22	2	0.31
Ito et al.	Microsomes	Theophylline	0.033	3.5	106.06	1	

(2005)		Felodipine	98	4300	43.88	2	
		FK1052	40	1600	40.00	-	
		Amitriptyline	13	490	37.69	1	
		r-Warfarin	0.15	5.4	36.00	2	
		Mexiletine	0.77	26	33.77	1	
		Methoxsalen	38	1000	26.32	2	
		Diphenhydramine	2	52	26.00	1	
		Phenytoin	0.16	4	25.00	2	
		Propafenone	160	4000	25.00	2	
		Ketamine	26	550	21.15	1	
		Ondansetron	1.7	33	19.41	1	
		Diclofenac	35	630	18.00	2	
		Lidocaine	3.1	55	17.74	1	
		Imipramine	18	310	17.22	1	
		Chlorpromazine	24	370	15.42	1	
		Verapamil	120	1800	15.00	1	
		Lorcainide	48	710	14.79	1	
		Clozapine	4.4	59	13.41	2	
		Dofetilide	0.4	4.5	11.25	3	
		Tenidap	7.9	80	10.13	2	
		Ibuprofen	8.2	83	10.12	2	
		Desipramine	16	150	9.38	1	
		Warfarin	0.49	4.5	9.18	2	
		Caffeine	0.43	3.5	8.14	1	
		Indinavir	16	130	8.13	2	
		Prednisone	2.6	21	8.08	2	
		Zolpidem	20	160	8.00	1	
		Omeprazole	67	520	7.76	1	
		Nilvadipine	1200	8400	7.00	2	
		Quinidine	3.2	22	6.88	1	

		FK480	51	340	6.67	-	
		Midazolam	44	270	6.14	1	
		s-Warfarin	1	5.7	5.70	2	
		Dexamethasone	2.9	14	4.83	1	
		Methohexital	47	180	3.83	1	
		Propranolol	90	340	3.78	1	
		Hexobarbital	2.2	8.2	3.73	1	
		Diltiazem	81	300	3.70	1	
		Antipyrine	0.14	0.51	3.64	1	
		Diazepam	4.1	13	3.17	1	
		Triazolam	13	38	2.92	1	
		Phenacetin	19	46	2.42	2	
		Flunitrazepam	5	11	2.20	1	
		Diazepam	10	21	2.10	1	
		Tolbutamide	1.2	2	1.67	2	
		Nicardipine	1200	1900	1.58	1	
		Amobarbital	0.89	1.4	1.57	1	
		Alprazolam	2	3.1	1.55	1	
		Metoprolol	18	26	1.44	1	
		Tenoxicam	1.6	2.2	1.38	1	
		YW796	15	14	0.93	-	
McGinnity et al.	Hepatocytes	Imipramine	21	113	5.38	1	
(2004)		Fluoxetine	2.6	13	5.00	1	
		Desipramine	7.9	30	3.80	1	
		Propranolol	26	80	3.08	1	
		Morphine	63	180	2.86	1	
		Omeprazole	4.5	12	2.67	1	
		Ondansetron	3.7	8.4	2.27	1	
		Metoprolol	19	37	1.95	1	

		Zileuton	5.5	8.6	1.56	2	
		Doxepin	34	47	1.38	1	
		Bepridil	5.3	7.2	1.36	1	
		Ranitidine	2.6	3.4	1.31	3	
		Verapamil	46	60	1.30	1	
		Scopolamine	19	24	1.26	1	
		Diltiazem	24	30	1.25	1	
		Diphenhydramine	16	19	1.19	1	
		Cimetidine	3.2	3.8	1.19	3	
		Triprolidine	11	13	1.18	1	
		Triazolam	2.6	2.9	1.12	1	
		Acebutolol	4.8	5.2	1.08	1	
		Granisetron	24	24	1.00	1	
		Nifedipine	15	15	1.00	2	
		Clozapine	16	12	0.75	2	
		Betaxolol	6.6	4.8	0.73	1	
		Pindolol	7.4	5.3	0.72	1	
		Cyclosporin A	9.2	6.1	0.66	2	
		Bromocriptine	98	60	0.61	1	
		Prazosin	6.1	3.1	0.51	1	
		Diazepam	0.8	0.4	0.50	1	
		Dextromethorphan	20	8.6	0.43	1	
		Lorazepam	2.6	1.1	0.42	1	
		Ethinylestradiol	19	7.4	0.39	1	
		Bisoprolol	4.2	1.4	0.33	3	
		Isradipine	47	13	0.28	2	
		Midazolam	37	9.9	0.27	1	
		Caffeine	8.7	2.3	0.26	1	
		Temazepam	5.3	1.4	0.26	1	
		Ritonavir	5.5	1.3	0.24	2	

		Codeine	61	12	0.20	1	
		Chlorpheniramine	7.4	1.4	0.19	1	
		Carvedilol	93	15	0.16	2	
		Propofol	283	24	0.08	2	
		Carbamazepine	5.3	0.4	0.08	2	
		Naloxone	570	37	0.06	1	
Obach et al.	Microsomes	Zolpidem	0.5	5.7	11.40	1	0.105
(1999)	(fu_b and fu_{inc})	Ibuprofen	0.2	1.5	7.50	2	0.018
		Tolbutamide	0.07	0.36	5.14	2	0.073
		Diclofenac	1.6	7.6	4.75	2	0.009
		Diphenhydramine	2.2	9.5	4.32	1	0.338
		Warfarin	0.02	0.08	4.00	2	0.018
		Methoxsalen	4.5	18	4.00	2	0.134
		Dexamethasone	1	3.8	3.80	1	0.344
		Tenidap	0.03	0.1	3.33	2	0.001
		Diltiazem	3.6	12	3.33	1	0.220
		Diazepam	0.2	0.6	3.00	1	0.018
		Amitriptyline	4.2	12	2.86	1	0.058
		Hexobarbital	1.4	3.6	2.57	1	0.530
		Quinidine	1.4	2.7	1.93	1	0.141
		Imipramine	6.6	12	1.82	1	0.091
		Lorcainide	9.9	18	1.82	1	0.195
		Clozapine	1.9	2.9	1.53	2	0.057
		Propafenone	13	19	1.46	2	0.057
		Verapamil	13	19	1.46	1	0.130
		Methohexital	11	16	1.45	1	0.386
		Prednisone	3.4	4.9	1.44	2	0.301
		Triazolam	3.3	4.7	1.42	1	0.161
		Desipramine	8.8	12	1.36	1	0.188

		Ketamine	15	20	1.33	1	1.073
		Chlorpromazine	8.6	11	1.28	1	0.064
		Amobarbital	0.32	0.35	1.09	1	0.260
		Tenoxicam	0.03	0.03	1.00	1	0.013
		Midazolam	9.4	8.7	0.93	1	0.094
		Alprazolam	0.95	0.76	0.80	1	0.410
Obach et al.	Microsomes	Zolpidem	0.3	5.7	19.00	1	0.105
(1999)	(fu_b)	Amitriptyline	0.8	12	15.00	1	0.058
		Diazepam	0.04	0.6	15.00	1	0.018
		Diphenhydramine	0.7	9.5	13.57	1	0.338
		Tenidap	0.01	0.1	10.00	2	0.001
		Clozapine	0.3	2.9	9.67	2	0.057
		Warfarin	0.01	0.08	8.00	2	0.018
		Ibuprofen	0.2	1.5	7.50	2	0.018
		Imipramine	1.6	12	7.50	1	0.091
		Chlorpromazine	1.5	11	7.33	1	0.064
		Prednisone	0.8	4.9	6.13	2	0.301
		Quinidine	0.5	2.7	5.40	1	0.141
		Tolbutamide	0.07	0.36	5.14	2	0.073
		Diclofenac	1.6	7.6	4.75	2	0.009
		Desipramine	2.8	12	4.29	1	0.188
		Methoxsalen	4.3	18	4.19	2	0.134
		Diltiazem	2.9	12	4.14	1	0.220
		Dexamethasone	1	3.8	3.80	1	0.344
		Hexobarbital	1.2	3.6	3.00	1	0.530
		Propafenone	6.5	19	2.92	2	0.057
		Lorcainide	6.7	18	2.69	1	0.195
		Verapamil	9	19	2.11	1	0.130
		Triazolam	2.7	4.7	1.74	1	0.161

		Ketamine	12	20	1.67	1	1.073
		Methohexital	9.9	16	1.62	1	0.386
		Tenoxicam	0.02	0.03	1.50	1	0.013
		Amobarbital	0.24	0.35	1.46	1	0.260
		Alprazolam	0.64	0.76	1.19	1	0.410
		Midazolam	8.8	8.7	0.99	1	0.094
Obach et al.	Microsomes	Diphenhydramine	1.9	9.5	5.00	1	0.338
(1999)	(no binding)	Zolpidem	2.5	5.7	2.28	1	0.105
		Prednisone	2.4	4.9	2.04	2	0.301
		Hexobarbital	2.1	3.6	1.71	1	0.530
		Ketamine	12	20	1.67	1	1.073
		Amitriptyline	8.2	12	1.46	1	0.058
		Dexamethasone	2.6	3.8	1.46	1	0.344
		Diltiazem	8.7	12	1.38	1	0.220
		Methoxsalen	14	18	1.29	2	0.134
		Desipramine	9.4	12	1.28	1	0.188
		Imipramine	10	12	1.20	1	0.091
		Lorcainide	15	18	1.20	1	0.195
		Methohexital	15	16	1.07	1	0.386
		Verapamil	18	19	1.06	1	0.130
		Propafenone	19	19	1.00	2	0.057
		Chlorpromazine	11	11	1.00	1	0.064
		Quinidine	2.9	2.7	0.93	1	0.141
		Clozapine	3.8	2.9	0.76	2	0.057
		Alprazolam	1.5	0.76	0.51	1	0.410
		Triazolam	10	4.7	0.47	1	0.161
		Midazolam	19	8.7	0.46	1	0.094
		Tolbutamide	0.86	0.36	0.42	2	0.073
		Diclofenac	19	7.6	0.40	2	0.009

		Amobarbital	0.9	0.35	0.39	1	0.260
		Diazepam	2.1	0.6	0.29	1	0.018
		Ibuprofen	6.2	1.5	0.24	2	0.018
		Warfarin	0.46	0.08	0.17	2	0.018
		Tenidap	5.9	0.1	0.02	2	0.001
		Tenoxicam	1.6	0.03	0.02	1	0.013
Riley et al.	Microsomes	Methoxsalen	43	1340	31.16	2	
(2005)		Phenacetin	9.9	212.5	21.46	2	
		Propranolol	16.3	284.5	17.45	1	
		Fluvastatin	75.4	1052	13.95	1	
		Propafenone	644.9	6650	10.31	2	
		Lorcainide	97.1	924	9.52	1	
		Diclofenac	183.8	1667.3	9.07	2	
		FK1052	182	1525	8.38	-	
		Ibuprofen	12.3	102.4	8.33	2	
		Phenytoin	0.5	4	8.00	2	
		Diphenhydramine	7.3	53.5	7.33	1	
		Zolpidem	17.9	115.5	6.45	1	
		Amitriptyline	94.3	516	5.47	1	
		Omeprazole	101	502.7	4.98	1	
		Tolbutamide	1.3	6.4	4.92	2	
		Dexamethasone	3	13.6	4.53	1	
		Methohexital	57.6	207.4	3.60	1	
		Imipramine	106.6	330	3.10	1	
		Tenidap	26.2	80.4	3.07	2	
		Diltiazem	77.7	232.6	2.99	1	
		Metoprolol	6.8	20.2	2.97	1	
		Hexobarbital	2.9	8.3	2.86	1	

		Diazepam	11.8	28	2.37	1	
		Nilvadipine	3867	8123.4	2.10	2	
		Quinidine	10.7	22.1	2.07	1	
		Desipramine	81.8	160	1.96	1	
		Verapamil	553.6	935.3	1.69	1	
		Chlorpromazine	229.6	381.3	1.66	1	
		Clozapine	35.7	59	1.65	2	
		Prednisone	13.6	21.5	1.58	2	
		Triazolam	24.6	38.1	1.55	1	
		Amobarbital	1.2	1.4	1.17	1	
		Tenoxicam	2.2	2.2	1.00	1	
		Midazolam	183.7	163.2	0.89	1	
		Alprazolam	2.4	1.9	0.79	1	
		FK480	662	327.3	0.49	-	
		Nicardipine	13460	1806.7	0.13	1	
Riley et al.	Hepatocytes	FK1052	32.38	1570	48.49	-	0.021
(2005)		Troglitazone	306.36	10000	32.64	2	0.0017
		Montelukast	96.27	1495.15	15.53	2	0.0009
		Cyclosporin A	13.46	155.27	11.54	2	0.04
		FK079	56.38	636	11.28	-	0.0288
		Lorazepam	1.16	12.38	10.67	1	0.094
		Sildenafil	24.35	214.29	8.80	1	0.04
		Glipizide	7.13	60.52	8.49	2	0.02
		Nifedipine	32.6	253.7	7.78	2	0.05
		Prazosin	6.16	42.23	6.86	1	0.07
		FK480	49.41	336	6.80	-	0.008
		Naloxone	150.28	924.35	6.15	1	0.56
		Midazolam	40.08	246.27	6.14	1	0.04
		Indomethacin	27.13	145.77	5.37	2	0.02

		Propranolol	59.2	291.87	4.93	1	0.12
		Diazepam	6.41	31.29	4.88	1	0.012
		Oxazepam	8.23	38.8	4.71	2	0.03
		Ketoprofen	22.44	103.95	4.63	2	0.02
		Zidovudine	9.87	42.1	4.27	1	0.8
		Oxaprozin	24.4	100.36	4.11	2	0.0007
		Lidocaine	24.61	100.68	4.09	1	0.3
		Furosemide	5.95	22.85	3.84	4	0.029
		Fenoprofen	56.52	216.15	3.82	2	0.01
		Quinidine	12.95	48.63	3.76	1	0.15
		Diflunisal	9.86	34.8	3.53	2	0.0053
		Timolol	6.55	22.75	3.47	1	0.4
		Diclofenac	618.36	2083.46	3.37	2	0.0055
		Triprolidine	39.61	133.33	3.37	-	0.1
		Metoprolol	13.87	40.62	2.93	1	0.747
		Ritonavir	30.51	86.26	2.83	2	0.0148
		Phenacetin	76.01	212.5	2.80	2	0.594
		Acetaminophen	2.53	6.71	2.65	1	0.79
		Buspirone	613.8	1582	2.58	2	0.05
		Gemfibrozil	325.82	773.37	2.37	2	0.005
		Ondansetron	5.23	12.4	2.37	1	0.68
		Irbesartan	58.75	131.31	2.24	2	0.04
		Warfarin	3.69	8.22	2.23	2	0.018
		Chlorpromazine	230.33	502.92	2.18	1	0.03
		Carvedilol	281.58	521.97	1.85	2	0.03
		Diltiazem	77.81	143.61	1.85	1	0.22
		Prednisolone	35.54	59.22	1.67	1	0.26
		Ranitidine	3	4.4	1.47	3	0.77
		Methylprednisolone	37.08	52.17	1.41	1	0.23
		Verapamil	278.92	388.33	1.39	1	0.115

		Imipramine	92.57	125.59	1.36	1	0.1
		Tolbutamide	6.91	8.99	1.30	2	0.04
		Cimetidine	3.35	4.23	1.26	3	0.9
		Granisetron	29.72	35.14	1.18	1	0.7
		Ibuprofen	71.34	82.7	1.16	2	0.0182
		Etodolac	81.2	82.84	1.02	2	0.02
		Theophylline	1.67	1.68	1.01	1	0.4
		Desipramine	127.16	124.92	0.98	1	0.17
		Antipyrine	0.82	0.69	0.84	1	0.94
		Caffeine	2.89	2.25	0.78	1	0.685
		Pindolol	9.28	5.91	0.64	1	0.9
		Tenoxicam	8.77	4.46	0.51	1	0.0164
Riley et al.	Hepatocytes	Tolcapone	6.41	1650.32	257.46	2	0.0018
(2005)	(serum)	Mibefradil	41.3	4888.9	118.38	2	0.005
		Felodipine	72.08	6111.11	84.78	2	0.004
		Bosentan	0.67	42.1	62.84	2	0.02
		Diltiazem	8.45	205.44	24.31	1	0.22
		Oxazepam	1.52	36.94	24.30	2	0.03
		Midazolam	25.74	599.04	23.27	1	0.04
		Propranolol	21.67	388.75	17.94	1	0.1
		Warfarin	0.34	6.02	17.71	2	0.018
		Lorazepam	1.24	16.71	13.48	1	0.094
		Diazepam	3.44	42.78	12.44	1	0.012
		Theophylline	0.35	1.55	4.43	1	0.4
		Caffeine	0.37	1.4	3.78	1	0.83
		Antipyrine	0.23	0.6	2.61	1	0.94