Contribution of Metabolites to P450 Inhibition-Based Drug-Drug Interactions: Scholarship from the IQ DMLG Metabolite Group

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ABBREVIATIONS:

DMLG: Drug Metabolism Leadership Group; IQ: Innovation and Quality Consortium; EMA, European Medicines Agency; FDA, US Food and Drug Administration; DDI, drug-drug interactions; AUC, area under time-concentration curve; P450, cytochrome P450; NCE, new chemical entities; C_{max}, maximum concentration in human plasma; K_i, inhibition potency; MBI, mechanism-based inhibition; K_I, dissociation constant for the enzyme-inactivator complex; k_{inact}, maximum rate for the inactivation; QSAR, quantitative structure-activity relationships.

Abstract

Recent EMA (final) and FDA (draft) drug interaction guidances proposed that human circulating metabolites should be investigated in vitro for their drug-drug interaction (DDI) potential if present at ≥ 25% of parent AUC (FDA) or ≥25% parent and ≥10% of total drug-related AUC (EMA). To examine the application of these regulatory recommendations, a group of scientists, representing 18 pharmaceutical companies of the Drug Metabolism Leadership Group of the Innovation and Quality Consortium, conducted a scholarship to assess the risk of contributions by metabolites to cytochrome P450 inhibition-based DDI. The group assessed the risk of having a metabolite as the sole contributor to DDI based on literature data and analysis of 137 most frequently prescribed drugs, defined structural alerts associated with P450 inhibition/inactivation by metabolites, and analyzed current approaches to trigger in vitro DDI studies for metabolites. The group concluded that the risk of P450 inhibition caused by a metabolite alone is low. Only metabolites from 5 out of 137 drugs were likely the sole contributor to the in vivo P450 inhibition-based DDI. Two recommendations were provided when assessing the need to conduct in vitro P450 inhibition studies for metabolites: consider structural alerts that suggest P450 inhibition potential; and use multiple approaches, including approaches by Yu & Tweedie (2013, a metabolite cut-off value of 100% of parent AUC) and Callegari et al. (2013, the R_{met} strategy), to predict P450 inhibition-based DDI caused by metabolites in the clinic.

Introduction

The recent EMA Guideline on Investigation of Drug Interactions (European Medicines Agency, 2012) and the FDA Draft Guidance on Drug Interaction Studies (US FDA, 2012) have recommended that human metabolites which are present at ≥ 25% of parent AUC (FDA) or ≥25% parent AUC and ≥10% of total drug-related AUC (EMA), should trigger further in vitro inhibition/induction assessment of common drug metabolizing enzymes (mainly P450) to assess these metabolites as possible contributors to drug-drug interactions (DDI). There are a few examples of metabolites being the main contributor to clinically relevant DDI by inhibiting one or more major P450 enzymes. For example, bupropion metabolites, threohydrobupropion and erythrohydrobupropion, have 4- and 12-fold lower K_i values for CYP2D6, respectively, than the parent compound, and are also present at higher concentrations in human plasma than bupropion (Reese et al., 2008). Gemfibrozil glucuronide was identified as an unusual example of a conjugated metabolite which was a considerably more potent inhibitor of CYP2C8 than the parent molecule (Ogilvie et al., 2006). As drug safety (including DDI) is of paramount importance to both regulatory authorities and pharmaceutical companies, these examples clearly highlight the need to thoroughly examine the contribution of metabolites to DDI. To examine the application of these regulatory recommendations, a group of scientists, under the auspices of the Drug Metabolism Leadership Group (DMLG) of the Innovation and Quality (IQ) Consortium, formed the Metabolite-Mediated DDI Scholarship Group. The group, with representation from 18 pharmaceutical companies, conducted a thorough review and summary of the literature on the contribution of metabolites to DDI as well as an assessment of the current practices for in vitro P450 inhibition studies of metabolites in drug development. The Metabolite Scholarship Group focused on the contribution of metabolites to P450 inhibition-based DDI and tackled the issue

from four aspects. First, the group analyzed the risk of DDI caused solely (or mainly) by metabolites based on available literature. Second, the group collected data and analyzed the contribution of metabolites to DDI for the 137 most frequently prescribed drugs in 2012. Third, the group assessed the current literature approaches and common practices among member pharmaceutical companies to trigger in vitro P450 inhibition studies for metabolites to identify their DDI potential prospectively. Last, the group explored the possibility of using structural alerts of metabolites to predict their P450 inhibition/inactivation potential and to trigger in vitro studies. For the risk assessment of metabolites contributing to P450-based DDI, the group focused on identifying cases where a metabolite(s) is the sole contributor to the observed DDI. This manuscript summarizes the recommendations of the Metabolite Scholarship Group.

Risk assessment of contribution of metabolites to P450 inhibition-based DDI using literature data

Several recent publications have assessed the role of circulating metabolites as the perpetrator of DDI, specifically involving inhibition of P450 enzymes through either reversible or mechanism-based inhibition (MBI) (Isoherranen et al., 2009; Yeung et al., 2011). Subsequently, Yu & Tweedie (2013) and Callegari et al. (2013) published strategies that can be adopted by drug researchers in assessing risks of circulating metabolites as P450 enzyme inhibitors. It has been well known that metabolites can be the perpetrators of DDI via P450 inhibition. For example, the observed clinical DDI for verapamil and diltiazem are the combined effects of parent drug and metabolites (Wang et al., 2005; Rowland et al., 2010). A consistent theme from these recent publications was that there is a relatively low risk for clinical DDI (via P450 inhibition) that is

solely attributable to drug metabolites and not the drug itself. In fact, among the 1323 drugs on the US market evaluated by Isoherranen et al. (2009), only 129 drugs (~10% of all drugs) showed clinical DDI via P450 inhibition. The majority (~90%) of the 1323 marketed drugs (likely also including their metabolites) did not inhibit P450 in vivo. Yeung et al. (2011) further analyzed metabolite and parent data from 102 in vivo P450 inhibitors, which were all included in the 129 named drugs in the analysis by Isoherranen et al. (2009) with the exception of one drug. The exposure and K_i data for the parent and metabolites were available for only 24 of the 102 P450 inhibitors. When plasma concentrations and in vitro inhibition K_i values of metabolites were considered, only 3 drugs (amiodarone, bupropion, and sertraline) had clinical DDI via P450 inhibition attributable to metabolites alone (Figure 1). The results are largely consistent with the general understanding that metabolism of drugs usually results in metabolites with increased hydrophilicity relative to that of the parent drugs and decreased affinity for drug metabolizing enzymes. It is worth noting that metabolites may generally have lower plasma protein binding than the parent drug, which results in a higher free fraction. All points considered, metabolites are, in general, unlikely to be more potent P450 inhibitors than their respective parent drugs. Several published quantitative structure-activity relationship (QSAR) models evaluating reversible inhibition of CYP2C and CYP3A families also supported the positive correlation between lipophilicity (logP) and potency for enzyme inhibition (Lewis et al., 2006; Didziapetris et al., 2010). In addition, empirical observations indicate that metabolites are likely to have affinity for the same binding sites as parent (e.g. binding to the pharmacological target of the parent leading to “active metabolites”) and if a metabolite has any affinity for P450 binding sites, the binding pattern tends to be very similar to parent (Humphreys & Unger, 2006).

Recently, Callegari et al. (2013) evaluated 33 structurally diverse compounds with a total of 115 circulating metabolites from a Pfizer internal database. The authors noted that 94 out of the 115 human metabolites (82%) had circulating concentrations of less than 1 μM, which is below the concentrations that are typically associated with P450 inhibition in clinical studies (Callegari et al., 2013). In addition, for the 12 clinical candidates where concentrations and in vitro K_i values for P450 inhibition were available for both parent and metabolites, the DDI perpetrator risk due to metabolites was considered low for all metabolites based on the I/K_i values (all <0.1).

Collectively, recent publications on assessing perpetrator DDI via P450 inhibition by metabolites all point towards a low risk that DDI potential that is caused by metabolite alone. However, several notable exceptions have been published, including bupropion (Reese et al., 2008), gemfibrozil (Tornio et al., 2008), amiodarone (Nolan et al., 1989; McDonald et al., 2012), and sertraline (Masubuchi & Kawaguchi, 2013), where the perpetrator DDI results could not be sufficiently explained solely based on parent drug data.

In addition to the risk of inhibition of common drug metabolizing enzymes (mainly P450), metabolites may also have increased potential to interact with drug transporters as compared to corresponding parent drugs. DDI due to interactions with transporters or enzyme induction by metabolites are outside the scope of this scholarship. Readers may wish to refer to two recent International Transporter Consortium white papers (Zamek-Gliszczynski et al., 2013; 2014), where the concern of metabolites as both victims and perpetrators of transporter-based DDI was highlighted.

Contribution of metabolites to P450 inhibition-based DDI for the 137 most frequently prescribed drugs

A total of the 137 most frequently prescribed drugs (as of 2012) were selected to evaluate the contribution of their metabolites to in vivo DDI (based on P450 inhibition). These drugs were evaluated because of the high number of patients who use these drugs. The intention of the analysis of the 137 drugs is not to provide a comprehensive review of their DDI profiles. Instead, the authors focused on identifying compounds (within the 137 most prescribed drugs) that have metabolites that could cause DDI that was not predicted by the parent in vitro P450 inhibition properties. A total of 42 drugs out of these 137 drugs overlapped with the drugs analyzed by Isoherranen et al. (129 named drugs, 2009) and Yeung et al. (102 named drugs, 2011). The available data on in vitro P450 inhibition by parent drugs and their abundant metabolites (generally ≥25% of parent AUC and/or ≥10% of total AUC) and in vivo inhibition from clinical studies were collected as follows. These parameters were mainly obtained from the University of Washington Drug Interaction Database and the drug labels from the FDA website and the associated references.

1. *In vitro* inhibition parameters of parent drug towards major human P450 enzymes (IC_{50} and/or K_i (reversible inhibition); K_I and k_{inact} (MBI)).
2. Identification of abundant human metabolites in plasma (≥25% of parent AUC and/or ≥10% of AUC of total drug-related material).
3. *In vitro* inhibition parameters of abundant human metabolites towards major human P450 (IC_{50} and/or K_i values, K_I and k_{inact}).
4. AUC and C_{max} values of parent and abundant metabolites (when available) in human plasma.

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5. C_{max}/K_i values for the parent drug and abundant metabolites (when available).
6. Fold increase of AUC for victim drugs as a result of P450 inhibition by these 137 drugs (when DDI studies were performed). When drug interaction data were available from two or more clinical studies, data from the study with a sensitive P450 probe substrate were selected. Case reports in the University of Washington Drug Interaction Database were generally not used to obtain in vivo drug-interaction data.

The collected parameters (along with other pertinent information, e.g. dose) for all 137 drugs are shown in supplemental Table 1. Based on the in vitro and in vivo parent DDI data, the drugs were divided into five categories using the criteria described below (see Table 1 and Figure 2).

- Category 1 (in vitro inhibition negative and in vivo inhibition negative): parent compound shows no or low inhibition of a P450 isoform in vitro (IC_{50} >10 μM or $I_p/K_i \leq$ 0.1) and does not cause in vivo DDI for this P450 isoform (<1.25-fold change of AUC of the victim drug). If in vivo DDI data with the drug as a perpetrator are not reported, it is assumed that this drug is not an in vivo inhibitor for this P450 isoform due to its extensive use by patients and the lack of reported drug interaction data.
- Category 2 (in vitro inhibition positive, but in vivo inhibition negative): parent compound shows the inhibition of a P450 isoform in vitro (IC_{50} < 10 μM or $I_p/K_i \geq$0.1 or an inactivator) but does not cause in vivo DDI for this P450 isoform (<1.25-fold change of AUC of the victim drug). If in vivo DDI data with the drug as a perpetrator are not reported, it is assumed that this drug is not an in vivo inhibitor for this P450 isoform due to its extensive use by patients and the lack of reported drug interaction data.

- Category 3 (in vitro inhibition negative, but in vivo inhibition positive): parent compound shows no or low inhibition of a P450 isoform in vitro (IC_{50} >10 μM or $I_p/K_i \leq 0.1$) but causes unexpected in vivo DDI for this P450 isoform (>1.25-fold change of AUC of the victim drug).
- Category 4 (in vitro inhibition positive and in vivo inhibition positive): parent compound shows the inhibition of a P450 isoform in vitro (IC_{50} < 10 μM or $I_p/K_i \geq 0.1$ or an inactivator) and causes in vivo DDI for this P450 isoform (>1.25-fold change of AUC of the victim drug).
- Unassigned Category: There are no in vitro and/or in vivo DDI data for the parent drug and/or metabolites reported in the literature or described in the prescribing information.

As shown in Table 1, a total of 102 drugs belong to Categories 1-4 and 35 drugs are in the Unassigned Category. The predictability of the parent in vitro DDI data for in vivo DDI is depicted in Figure 2 for drugs belonging to Categories 1-4. There are 48 drugs in Category 1 (true negatives), 10 drugs in Category 3 (false negatives), 26 drugs in Category 4 (true positives), and 18 drugs in Category 2 (false positives). Therefore, based on the parent $[I]/K_i$ (in vitro) and in vivo DDI data, the true negatives are 83% (48 out of 58 drugs in Categories 1 &3); the false negatives are 17% (10 out of 58 drugs in Categories 1 &3); the true positives are 59% (26 out of 44 drugs in Categories 2 &4), and the false positives are 41% (18 out of 44 drugs in Categories 2 &4). A total of 66 drugs (65% of 102 drugs) in Category 1 and Category 2 did not show any clinical DDI with P450 substrates. This trend is consistent with the findings from Isoherranen et al. (2009) that the majority (~ 90%) of 1323 drugs on the US market did not show P450 inhibition in vivo. A total of 26 drugs (25% of 102 drugs) are in Category 4. These 26 drugs

showed P450 inhibition in vivo, which were predicted qualitatively by the in vitro P450 inhibition data of the parent drugs. Metabolites of clopidogrel (Tornio et al., 2014), diltiazem (Yeung et al., 1993; Zhao et al., 2007), fluoxetine (Yeung et al., 2011), imatinib (Yeung et al., 2011), and omeprazole (Shirasaka et al., 2013) likely have contributed to the observed in vivo P450 inhibition-based DDI based on their clinical concentrations and in vitro P450 inhibition potency. For all other drugs in Category 4, it is challenging to identify the contribution of metabolites to the observed P450 inhibition-based DDI due to the lack of data either on the metabolite concentrations or on their in vitro P450 inhibition potency.

The 10 drugs in Category 3 are the false negatives and of most concern to the prediction of clinical DDI potential. These 10 drugs showed in vivo P450 inhibition, which was not predicted by the in vitro P450 inhibition, inactivation, or IC_{50}/K_i values of the parent drug. Five of these 10 drugs showed ≤ 1.5-fold increase in AUC of the victim drugs, which is generally not considered clinically significant except for victim drugs with a narrow therapeutic window. These five drugs are atorvastatin (midazolam as the CYP3A substrate, McDonnell et al., 2003), venlafaxine (imipramine as the CYP2D6 substrate, Albers et al., 2000), sertraline (pimozide as the CYP3A substrate, Alderman, 2005; desipramine as the CYP2D6 substrate, Kurtz et al., 1997), amlodipine (simvastatin as the CYP3A substrate, Ma et al., 2000), and capecitabine (warfarin the CYP2C9 substrate, Camidge et al., 2005). The in vivo DDI of sertraline may be explained by the more potent inhibition of CYP3A4 by the N-desmethyl metabolite. It is important to note that the in vivo DDI observed with atorvastatin, venlafaxine, and amlodipine cannot be explained by inhibition due to their respective metabolites. The lactone metabolite of atorvastatin is a 100-fold more potent inhibitor of CYP3A4 than atorvastatin (Jacobson et al., 2000). However, the

lactone metabolite can't explain the observed in vivo inhibition of CYP3A4 when solely based on the $[I]/K_i$ ratio (<0.1). The major metabolite of venlafaxine (O-desmethylvenlafaxine) also had an I/K_i ratio less than 0.1. The AUC values of amlodipine metabolites were not available. Some of the metabolites were reported to have similar C_{max} values as amlodipine (Beresford et al, 1988). The P450 inhibition potency of amlodipine metabolites have not been reported in literature. Therefore it is not known whether amlodipine metabolites contributed to the observed weak drug interaction with simvastatin. The AUC values of the metabolites of capecitabine ranged from 0.4-fold to 23.6-fold of the AUC of capecitabine (Twelves et al., 1999). Although the inhibition potency of these metabolites towards CYP2C9 has not been reported, it is believed that the metabolites contributed to the observed drug interaction with warfarin (capecitabine drug label). Bupropion, gemfibrozil, and amiodarone, which are well documented (Reese et al., 2008; Tornio et al., 2008; Nolan et al.,1989; McDonald et al., 2012) to have caused "unexpected" in vivo P450 inhibition, all had metabolite(s) that were more potent inhibitors of P450 than the parent. In addition, the concentrations of their metabolites were approximately equal to or greater than concentrations of the parent drugs. Therefore, in the cases of bupropion, gemfibrozil, and amiodarone, the metabolites are considered the major/sole contributors to the observed clinical DDI. For ciprofloxacin and escitalopram, the "unexpected" inhibition of P450 in vivo is not completely explained in the available literature. Ciprofloxacin was not expected to inhibit CYP1A2 in vivo based on in vitro data (Karjalainen et al., 2008). However it is one of the most potent in vivo CYP1A2 inhibitors in clinical use (FDA DDI 2012 Draft DDI Guidance; Granfors et al., 2004). The most abundant circulating metabolite of ciprofloxacin is oxo-ciprofloxacin, which is present at only ~10% of the AUC of ciprofloxacin (Bergal et al., 1989). Since the in vitro inhibition parameter for this metabolite is not available, it is not known whether the

observed in vivo inhibition of CYP1A2 substrate is due to the oxo-ciprofloxacin metabolite. Pre-incubation of ciprofloxacin in human liver microsomes slightly increased the inhibition potency of CYP1A2, which suggests that ciprofloxacin could be a mechanism-based inhibitor (Karjalainen et al., 2008). In addition, ciprofloxacin may concentrate into hepatocytes due to its lipophilic and basic properties. It remains to be elucidated why ciprofloxacin is a potent in vivo CYP1A2 inhibitor. Similar to ciprofloxacin, escitalopram was not expected to inhibit CYP2D6 in vivo based on in vitro CYP2D6 inhibition data (Skjelbo and Brosen, 1992). Interestingly, it caused a modest 2-fold increase in the AUC of desipramine in humans (Forest Pharmaceuticals, 2005). The abundant human metabolite of escitalopram is N-desmethylcitalopram, which is present at ~36% of the AUC of escitalopram (Rao, 2007). It is worth noting that N-desmethylescitalopram is a 15-fold more potent inhibitor of CYP2D6 than the parent escitalopram (Skjelbo & Brosen, 1992). Therefore, N-desmethylescitalopram may be the major contributor to the modest DDI with desipramine in human. However, when solely based on its $[I]/K_i$ ratio (0.03), N-desmethylescitalopram cannot explain the observed CYP2D6 inhibition. In summary, metabolites were likely the sole contributors to the observed in vivo P450 inhibition for 5 of the 10 drugs in Category 3 (parent in vitro inhibition negative, in vivo inhibition positive). These 5 drugs are amiodarone, bupropion, sertraline, gemfibrozil, and capecitabine. The metabolites of atorvastatin and escitalopram may have also contributed to the observed in vivo DDI. It is not known whether the metabolites of amlodipine, venlafaxine and ciprofloxin contributed to the observed in vivo P450 inhibition.

Review of current literature approaches to trigger in vitro DDI studies for metabolites

Currently there are two approaches in the literature to trigger the in vitro assessment of P450 inhibition potential of metabolites (Callegari et al., 2013; Yu & Tweedie, 2013). These two approaches emphasize the importance of considering both the abundance (AUC or C_{max}) and inhibition potency of metabolites (K_i) in assessing their P450 inhibition potential. Yu and Tweedie (2013) proposed to conduct clinical DDI studies to assess the in vivo inhibition potential for both the parent and metabolites when the parent drug is an inhibitor of one or more P450 enzymes in vitro (i.e. $[I]/K_i > 0.1$, where [I] is the total concentration). When the parent drug is not expected to be an inhibitor of a P450, the proposed default cut-off value to trigger in vitro P450 inhibition studies for metabolites is that metabolite AUC is ≥ 100% of parent AUC. The rationale for the default cut-off value (100% of parent AUC) is based on the generally accepted assumption that metabolites tend to be less potent inhibitors of P450 due to the increased hydrophilicity. In addition to the default cut-off value, lower cut-off values were proposed for exceptions where metabolites are less hydrophilic or contain structural alerts for MBI. For metabolites which are less hydrophilic than the parent molecule, a lower cut-off value (25% of parent AUC) is recommended. For metabolites containing structural alerts for MBI, the cut-off value of metabolite level is considered on a case-by-case basis as it is challenging to ascribe a level of expected inhibition based simply on structure.

Callegari et al. (2013) recommended using an R_{met} strategy to trigger the study of the P450 inhibition by metabolites in vitro, where R_{met} is equal to $C_{max,\ metabolite}/K_{i,\ metabolite}$. When the K_i value of a metabolite is not available, the metabolite is considered a 4-fold more potent inhibitor than the parent, which is generally a conservative scenario. The $K_{i,\ metabolite}$ is therefore assumed to be 0.25 of $K_{i,\ parent}$. The R_{met} strategy was evaluated using metabolite C_{max} and parent K_i data

from Pfizer internal compounds and literature compounds, which successfully identified metabolites that were the main contributors to the in vivo P450 inhibition without introducing a high rate of false positives.

Drugs in Category 3 (parent in vitro inhibition negative, in vivo inhibition positive, see the 137 drugs section above) are of most importance in assessing the need to study P450 inhibition potential of metabolites in vitro. The 10 drugs in Category 3 were tested using the Yu & Tweedie and Callegari et al. approaches with the exception of amlodipine, for which the AUC values of the metabolites are not available. The objective was to evaluate the utility of these two approaches in triggering in vitro P450 inhibition studies for metabolites (Table 2). Using the default 100% of parent AUC cut-off value for metabolites strictly, the Yu & Tweedie approach would lead to the in vitro P450 inhibition studies for the metabolites of atorvastatin, venlafaxine, bupropion, amiodarone, sertraline, and capecitabine (at least one metabolite was predicted for each drug). In addition, since the abundant metabolite of escitalopram was formed via N-dealkylation from a tertiary amine to a secondary amine, which is a structural alert for MBI of P450 (see structural alert section below), the Yu and Tweedie approach would also lead to the study of the P450 inhibition and inactivation potential in vitro for the N-desmethylescitalopram metabolite.

Using the default R_{met} value of 0.1 strictly, the Callegari et al. approach would lead to the in vitro P450 inhibition studies for the metabolites of bupropion, amiodarone, gemfibrozil, sertraline and capecitabine (at least one metabolite was predicted for each drug). If both approaches are

combined, it would have covered 8 out of 10 drugs in Category 3 (only ciprofloxacin was not covered by either of these two approaches and these two approaches were not applied to amlodipine due to the lack of data). It is interesting to note that gemfibrozil glucuronide is not covered by the Yu & Tweedie approach if the 100% of AUC of parent cut-off value is strictly applied; however, it is covered by the Callegari et al. approach using the R_{met} strategy. The opposite is true for the venlafaxine o-desmethyl metabolite, which is not covered by the Callegari et al. approach but covered by the Yu & Tweedie approach. These two approaches appear to be complimentary in that the Yu & Tweedie approach triggers an examination of P450 inhibition by metabolites regardless of parent Ki values whereas Callegari et al. allows a more detailed examination of a particular P450 where there is a measurable parent K_i. Based on the discussion among scientists from the member pharmaceutical companies, it is a common practice to combine multiple approaches when assessing the need to study metabolite DDI potential in vitro. The key points to consider include: a) relative and absolute concentrations of the metabolites; b) potencies of the metabolites for P450 inhibition; c) the presence of structural alerts in metabolites; and d) contribution of metabolites to DDI when un-expected in vivo DDI are observed. Another important tool in predicting and understanding DDI is PBPK modeling. It is recommended to use PBPK modeling to integrate the contributions of parent and metabolites to DDI, especially in complex drug development programs. Investigations are currently underway to generate PBPK models for some drug/metabolite pairs to determine the usefulness of this approach.

Utility of structural alerts in assessing P450 inhibition and inactivation potential of metabolites

Alerts from chemical substructures frequently associated with the risk of P450 inhibition and inactivation are well-established (Halpert, 1995; Orr et al., 2012), especially for lipophilic and nitrogen-containing aromatic heterocyclic compounds and alkylamines. It is common practice to incorporate structural alerts contained in the parent compound in the initial assessment of P450 inhibition potential. Therefore, it is reasonable to also identify such structural alerts in the major circulating metabolites to prioritize in vitro testing for potential risk of P450 inhibition or inactivation. In practice, the chemical structures of major circulating metabolites (>10% of total drug related AUC) are generally elucidated and their plasma concentrations determined quantitatively or semi-quantitatively in early clinical development (e.g. Phase I) to satisfy the recommendation from the FDA MIST and ICH M3 (R2) Guidances (FDA, 2008 and EMA 2009). If the major metabolite retains the structural alert of the parent drug or contains a new structural alert for P450 inhibition as a result of biotransformation, then such information can be used to trigger determination of its P450 inhibition and inactivation in the overall process of assessment of DDI.

Although the intention of this manuscript is not to provide a detailed discussion on different types of P450 inhibition, it is necessary to highlight the mechanisms through which the moieties identified as structural alerts exert their inhibitory effects, as this is essential to understanding and assessing the potential risk of inhibition mediated by drug metabolites. There are three broad categories of P450 inhibition, reversible, quasi-irreversible and irreversible inhibition. There are examples in the literature of metabolites that fit into each of these categories. Reversible inhibition often involves competition for binding to the prosthetic heme iron and lipophilic region of protein within the active site. In general, potent P450 inhibitors are lipophilic

compounds which contain aromatic nitrogen-containing heterocycles such as pyridines, imidazoles, and quinolones. These compounds inhibit P450 through the interaction of the lone pair of electrons with the ferric heme iron of the P450 (Halpert, 1995). A notable example of reversible CYP450 inhibition by compounds is illustrated by itraconazole and its oxidative metabolites, which are as potent as or significantly more potent reversible inhibitors of CYP3A4 than parent (Isoherranen et al., 2004). Both itraconazole and its metabolites are nitrogen-containing aromatic heterocycles. The strong inhibition potencies of itraconazole and its metabolites together provide a reasonable prediction of the clinical DDI (Isoherranen et al., 2004). In addition to reversible P450 inhibition by metabolites, clinically relevant DDI have also been observed with metabolites causing mechanism-based P450 inhibition via irreversible inhibition (interaction with heme or the aproprotein) and quasi-irreversible inhibition. Perhaps the best-understood structural alerts for P450 inhibition are associated with quasi-irreversible inhibition by formation of metabolic-intermediate (MI) complexes, which have a diagnostic Soret peak in the visible spectrum at ~455 nm (Franklin, 1974). Although alkylamine-, arylamine-, and methylenedioxyphenyl- groups are well-known structural alerts for formation of stable MI complexes, the majority of clinical DDI caused by quasi-irreversible inhibitory metabolites are alkylamines (Figure 3). Interestingly, 3 of the 8 drugs in Category 3 (escitalopram, amiodarone, and sertraline) have abundant secondary or primary amine metabolites. More importantly, two of these amine metabolites (from escitalopram and amiodarone) are confirmed to be more potent P450 inhibitors than the respective parent drug. Alkylamine metabolites that inactivate P450 are predominantly secondary alkylamines except for norfluoxetine (a primary alkylamine, Hanson et al., 2010) which was shown to inactivate multiple P450 isoforms (Lutz et al., 2013). Historically, the quasi-irreversible inhibition of

CYP450 by secondary alkylamines is thought to occur via a reaction sequence involving *N*-dealkylation to primary alkylamines, which can be further N-hydroxylated to hydroxylamines, followed by further oxidation and dehydrogenation to nitroso derivatives (Figure 3). Recently, an alternative pathway has been reported in the formation of nitroso metabolites involving exclusively *N*-hydroxylation instead of *N*-dealkylation of secondary alkylamine drugs (Hanson et al., 2010). Regardless of the reaction sequence, it is the nitroso metabolites that bind to the ferrous form of the prosthetic heme iron of P450 with high affinity via coordinate bonds and cause quasi-irreversible inactivation of the enzyme (Franklin, 1991; Kalgutkar et al., 2007). The other well-known structural alert for causing quasi-irreversible inhibition of P450 is the arylamine moiety, which follows a similar mechanism as alkylamines (Figure 3, Kalgutkar et al., 2007; Hollenberg et al., 2008). Finally, the methylenedioxyphenyl groups (as seen in tadalafil and paroxetine), are metabolized to produce carbene intermediates (Figure 3). These carbene intermediates bind to both ferrous and ferric heme iron and cause quasi-irreversible inactivation of P450 enzymes. However, mechanism-based inhibition of P450 by methylenedioxyphenyl-containing compounds is generally covered by assessing the inactivation potential of the parent molecules, because biotransformation leading to retention of the methylenedioxyphenyl group in metabolites is rare.

Additional structural alerts for P450 inactivation are included in Table 3. Although they are not expected to be as important as the structural alerts outlined in Figure 3 in terms of P450 inactivation potential, it is important to consider assessing the P450 inactivation potential of these structural alerts proactively, if an abundant metabolite contains one or more of these structural alerts. It is also noteworthy to point out that many structural alerts are potentially

"masked" in the parent molecule, for example, substituted alkylamines, arylamines and aminophenols, and metabolism of these parent molecules may lead to "unmasking" of such structural alert in the metabolites thereby leading to enhanced potential for P450 inhibition.

The interesting results from mechanistic studies of the gemfibrozil and cerivastatin DDI (Backman et al., 2002), where the DDI was attributable in part to gemfibrozil acyl-β-glucuronide but not gemfibrozil, has raised the concern of acyl glucuronides being P450 inhibitors. Jenkins et al. (2011) evaluated acyl glucuronides of 11 compounds as direct-acting and metabolism-dependent inhibitors of CYP2C8. Lai et al. of Eisai Pharmaceuticals (personal communication) also assessed the P450 inhibition potential for the glucuronide metabolites (ether and acyl glucuronides) of several structurally-diverse drugs. The results from both studies show that MBI of CYP2C8 by gemfibrozil acyl-β-glucuronide appears to be specific to gemfibrozil and not likely generalizable to other glucuronide conjugates. However, a recent case of clinical DDI between cerivastatin and clopidogrel led to the identification of clopidogrel acyl-β-glucuronide as a potent time-dependent inhibitor of CYP2C8 (Tornio et al., 2014). Further investigation may be needed to address the potential risk of P450 inactivation (especially CYP2C8) by acyl glucuronides as a class of reactive metabolites and whether these conjugates should be added to the list of structure alerts for metabolite mediated DDI.

Discussion

The EMA (final) and FDA (draft) drug interaction guidances proposed that human circulating metabolites should be investigated in vitro for their drug-drug interaction (DDI) potential if present at ≥ 25% of parent AUC (FDA) or ≥25% parent and ≥10% of total drug-related AUC

(EMA). Based on the data from Callegari et al. (2013), it is estimated that approximately 2 metabolite per development compound (60 metabolites from 25 drugs were present at ≥ 25% of parent AUC) would meet the FDA criterion, which is more stringent than the EMA criterion. Besides the metabolite abundance requirement (≥ 25% of parent AUC and ≥ 10% of total AUC), the EMA guidance focuses on studying the DDI potential of Phase I metabolites, which can decrease the number of metabolites that need to be evaluated for DDI potential. For example, in the Callegari et al. paper (2013), only 26 out of a total of 115 circulating metabolites for 33 drugs were Phase I metabolites. Despite the difference in the cut-off criteria for metabolites, the FDA and EMA guidances highlighted the importance of including metabolites in the overall assessment of P450 inhibition-based DDI for development drugs. Early work by Isoherranen et al. (2009) and Yeung et al. demonstrated that circulating metabolites are often present with inhibitors of P450 enzymes and in vivo P450 inhibition-based DDI may only be explained by considering the metabolite in vitro P450 inhibition data for 3 drugs.

The Metabolite Scholarship Group performed a comprehensive risk analysis of P450 inhibition-based DDI that are caused solely by metabolites based on work by Isoherranen et al. (2009) and Yeung et al. (2011) and our own analysis of 137 most-frequently prescribed drugs, assessed the utility of current approaches in the literature as well as common practice within the pharmaceutical industry to trigger in vitro drug-metabolism studies for metabolites, and identified structural alerts of metabolites that may suggest their P450 inhibition/inactivation potential. Overall, the risk of metabolites as the sole contributor to P450 inhibition-based clinical DDI appears to be relatively low. Metabolites of 3 drugs (amiodarone, bupropion, and sertraline out of 102 drugs, which are the in vivo P450 inhibitors identified from 1323 drugs on

the US market) were identified as the sole contributor to the observed clinical DDI by Isoherranen et al. (2009) and Yeung et al. (2011). Metabolites of 5 drugs (amiodarone, bupropion, sertraline, gemfibrozil, and capecitabine, out of 137 most frequently prescribed drugs) were identified as the sole contributor to the observed clinical DDI by the Metabolite Scholarship Group. The difference between these two sets of analysis is that the metabolites of gemfibrozil and capecitabine were also identified as the sole contributor to the observed DDI by the Metabolite Scholarship Group. Gemfribrozil glucuronide is an MBI of CYP2C8 (Ogilvie et al., 2006). Several metabolites of capecitabine are highly abundant and believed to inhibit CYP2C9 (capecitabine drug label). Since DDI potential is an important part of drug safety, it is highly important to proactively manage the DDI risk of metabolites. The combination of the two literature approaches (Callegari et al., 2013; Yu & Tweedie, 2013), which involved a metabolite cut-off value of approximately 100% of AUC of parent, and consideration of metabolite C_{max}/K_i, was able to flag the metabolites of 8 of 10 drugs in Category 3 for investigating metabolite P450 inhibition potential in vitro. Structural alerts of metabolites can also be used proactively in planning and prioritizing in vitro DDI studies for metabolites, as in the case of escitalopram and amiodarone.

Similar to the literature analyses (Isoherranen et al., 2009; Yeung et al., 2011), our analysis of the 137 most-frequently prescribed drugs has also been limited by the lack of P450 inhibition data for some of the parent drugs and the lack of P450 inhibition and exposure data for most of the circulating metabolites. Due to these limitations, our approach focused on identifying compounds for which the parent drug did not show in vitro P450 inhibition, but caused P450 inhibition in vivo. Our analysis did not consider transporter mediated DDIs, which may

complicate the parent and metabolite in vitro-in vivo correlation of P450 inhibition. Additionally, our analysis did not account for the fact that metabolites can be enriched in the liver, resulting in higher intracellular free metabolite concentrations that are not reflected by the plasma concentration.

To summarize the considerations in addressing DDI risks of metabolite, a decision tree is proposed in Figure 4. The key intention of the decision tree is to propose the criteria to initiate in vitro inhibition assessment of metabolites based on the exposure of parent and metabolites in Phase I studies (very early in clinical development). The objective is to provide an early alert for "surprise" DDIs as a result of the formation of potential inhibitory metabolites. Briefly, if the parent compound is likely to inhibit P450 in vivo based on in vitro inhibition data and therapeutic exposure, conduct clinical DDI studies to assess the inhibition potential of both the parent and the metabolites. It is important to consider the pharmacokinetic properties of parent and metabolites to ensure steady state concentrations are achieved for the parent and metabolites in the clinical DDI studies. On the other hand, if the parent compound is not likely to inhibit P450 in vivo, consider in vitro P450 inhibition studies for abundant metabolites. If a metabolite does not contain a structural alert for P450 inhibition/inactivation, calculate R_{met} (using $C_{max,\ metabolite}$ and 0.25 of $K_{i,\ parent}$) and determine the abundance of the metabolite. If R_{met} is less than 0.1 and the abundance of the metabolite is less than 100% of parent AUC, the metabolite is probably not going to inhibit P450 in vivo (based on the amiodarone, gemfibrozil, sertraline, and bupropion examples) . Therefore in vitro P450 inhibition/inactivation studies are generally not needed. On the other hand, if R_{met} is > 0.1 or the abundance of the metabolite is above 100% of parent AUC, conduct in vitro P450 inhibition/inactivation studies for the metabolite. For

metabolites containing structural alerts for P450 inhibition/inactivation (e.g. alkylamine), extra caution should be exercised in assessing the need to conduct in vitro P450 inhibition/inactivation studies. However, given that a structural alert is not necessarily predictive of the extent of P450 inactivation, the in vivo abundance (C_{max} and AUC) of the metabolite may be a more important determinant of the need for in vitro P450 inhibition and inactivation studies. A reasonable starting point may be that when a metabolite with a structural alert is present at ≥25% of parent AUC and ≥10% of total AUC, consider in vitro P450 inhibition/inactivation studies for this metabolite. Once the in vitro P450 inhibition parameters are determined for the metabolite, similar approaches used to predict the parent in vivo DDI potential can be used to predict the in vivo DDI potential for the metabolite. If the metabolite is predicted to cause in vivo inhibition, a clinical DDI study is warranted to confirm the prediction.

The chemical synthesis of metabolites can present challenges. A semi-quantitative and resource-sparing approach (without the need to synthesize a metabolite standard) can be considered for cases where a metabolite is the major component of the mixture (e.g. ≥ 80%) after the incubation of the parent with either liver microsomes or hepatocytes. If CYP inhibition by the mixture is weak, the metabolite is unlikely to be a potent inhibitor of P450s.

The scholarship presented in this manuscript is intended to provide a useful framework for rational risk assessment during drug development and enable productive scientific exchanges with regulators. It should be pointed out that this and other analyses have focused on P450 inhibition-based DDI where data are relatively abundant. However, there are insufficient data on the evaluation of metabolites in P450 mediated induction, other enzyme systems (e.g. UGT's) or

transporter-mediated DDI. Additional data on metabolite contribution to DDI, when applicable, will need to be collected over the next few years to help drug metabolism scientists and clinicians to better understand the contribution of metabolites to DDI. The Metabolite Scholarship Group encourages collecting and sharing experiences with clinicians and regulators with metabolites as contributors to DDI to help gain a better understanding of this topic.

In conclusion, the in vivo P450 inhibition potential can be generally predicted by the in vitro P450 inhibition parameters of the parent drug. The risk for an unexpected in vivo DDI as a result of not assessing in vitro P450 inhibition by metabolites is considered low. However, the contribution of metabolites to DDI should be considered in light of the totality of data (in vitro K_i values and systemic concentrations) of both the parent drug and the metabolites, and strategies for evaluating metabolites in DDI after obtaining the exposure of parent and metabolite in Phase I studies have been proposed in this manuscript.

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Authorship Contributions

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Footnotes:

1. Robert L. Walsky also represented AstraZeneca.

2. Bo Wen also represented Roche.

Figure legends:

Figure 1. Role of metabolites as perpetrators of DDI via P450 inhibition based on literature data (Isoherranen et al., 2009 and Yeung et al. 2011)

Figure 2. Distribution of the 137 drugs in Categories 1-4

Figure 3. Main structural alerts for metabolites associated with inactivation of P450 enzymes (alkyl amine, aryl amine and methylenedioxyphenyl)

Figure 4. A proposed decision tree to investigate the P450 inhibition potential of metabolites

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Table 1 Summary of the 137 drugs in 5 different categories

Category 1 (in vitro -/ in vivo -) (48 drugs)		**Category 2 (18 drugs) In vitro +/ in vivo -**	**Category 3 (10 drugs) In vitro -/ in vivo +**	**Category 4 (26 drugs) In vitro +/ In vivo +**	**Unassigned (35 drugs) No in vitro and/or in vivo inhibition data**	
Amphetamine (2D6)	Metoprolol (2D6)	[3]Atomoxetine (2D6)	Amiodarone (2C9)	Atazanavir (2C8, 3A)	Alendronate	Lamotrigine
Amitriptyline (2C19 and 2D6)	Mometasone (2B6, 2C8)	Budesonide (3A)	Amlodipine (3A)	Azithromycin (3A)	Alfuzosin	Latanoprost
Anastrozole (2C9)	Moxifloxacin (2B6)	Diclofenac (3A)	Atorvastatin (3A)	Bicalutamide (3A)	Bisoprolol	Levalbuterol
Aripiprazole (2D6)	Olanzapine (1A2)	Ezetimibe (3A)	Bupropion (2D6)	Celecoxib (2D6)	Darbepoetin alfa	Meropenem
Bosentan ([1]major P450s)	Olmesartan (2C9)	Fenofibrate (2C8)	Capecitabine (2C9)	Clopidogrel (2B6)	Desloratadine	Metformin
Candesartan (3A)	Pemetrexed (1A2, 2C9, 2D6, 3A)	Fluticasone (3A)	Ciprofloxacin (1A2)	Cyclosporin (3A)	Donepezil	Oseltamivir
Carvedilol (2B6, 2C8)	Pioglitazone (2C8)	Irbesartan (2C9)	Escitalopram (2D6)	Diltiazem (3A)	Dorzolamide	Ramipril
Cefdinir (1A2, 2C19, 2D6, 3A)	Pramipexole (2D6)	Lansoprazole (2C19)	Gemfibrozil (2C8)	Duloxetine (2D6)	Doxazosin	Risedronate
Cetirizine (3A)	Pravastatin (2C9)	Levofloxacin (2C9)	Sertraline (2D6, 3A)	[2]Efavirenz (3A)	Enalapril	Rivastigmine
Docetaxel (3A)	Pregabalin (major P450s)	Montelukast (2C8)	Venlafaxine (2D6)	Erlotinib (3A)	Enoxaparin	Sevoflurane
Famotidine (2C19, 2D6, 3A4)	[1]Quetiapine (major P450s)	Ondansetron (3A)		Esomeprazole (2C19)	Erythropoietin	Somatostatin
Fentanyl (3A)	Ranitidine (1A2, 2C8, 2C9, 2D6, 3A)	Pantoprazole (2C19)		Fluconazole (2C9, 2C19, 3A)	Estrogen	Somatropin
Gabapentin (2B6, 2C9, 2D6, 3A)	Risperidone (2D6)	Rabeprazole (2C9, 2C19)		Fluoxetine (2C19, 2D6)	Eszopiclone	Sumatriptan
Glimepiride (2C9)	Ropinirole (1A2)	Raloxifene (2C9)		Fluvastatin (2C9)	Fexofenadine	Temozolomide
Irinotecan (3A)	Rosuvastatin (2C8)	Rosiglitazone (2C8)		Imatinib (3A)	Filgrastim	Teriparatide
Letrozole (3A)	Salmeterol (2C8)	Sildenafil (3A)		Lopinavir (3A)	Finasteride	Tiotropium
Levetiracetam (3A, 2C9)	Simvastatin (3A)	Tadalafil (3A)		Modafinil (2C19)	Goserelin	Valacyclovir

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Levothyroxine (2C8)	Telmisartan (2C9)	Tamoxifen (2D6)		Nefazodone (3A)		Zoledronate
Lidocaine (2D6, 3A)	Thalidomide (3A)			Nifedipine (3A)		
[1]Linezolid (major P450s)	Topiramate (2C9)			Omeprazole (2C19)		
Losartan (2C9)	Valsartan (2C9)			Oxcarbazepine (2C19)		
Meloxicam (2C9)	Vardenafil (3A)			Paroxetine (2D6)		
Memantine (2D6)	Ziprasidone (2D6)			Terbinafine (2D6)		
Mofetil (3A)	Zolpidem (1A2, 2D6, 3A)			Valproate (2C9)		
				Voriconazole (2B6, 2C8, 2C9, 3A)		
				Zileuton (1A2)		

1 Major P450s: major drug metabolizing P450s (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and CYP3A4)

2 Efavirenz induction masks in vivo inhibition

3 Atomoxetine: category 1 for 3A substrates

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Table 2 Application of the Yu & Tweedie and Callegari et al. approaches to trigger in vitro studies for metabolites from 9 drugs in Category 3

Drug	Metabolites	Inhibited P450	$AUC_{metabolite}$ /AUC_{parent}* 100%	R_{met}: $C_{max,met}$/ ($K_{i,parent}$/4)	Tweedie & Yu Predict	Callegari et al. Predict
Atorvastatin	Atorvastatin lactone	CYP3A4	89	0.004	No	No
	2-OH-atorvastatin	CYP3A4	123	0.007	Yes	No
	2-OH-atorvastatin lactone	CYP3A4	261	0.01	Yes	No
Venlafaxine	O-desmethyl-venlafaxine	CYP2D6	286	0.06	Yes	No
Bupropion	Hydroxybupropion	CYP2D6	10600	0.76	Yes	Yes
	Threohydro-bupropion	CYP2D6	413	0.44	Yes	Yes
	Erythrohydro-bupropion	CYP2D6	72	0.08	No	No
Amiodarone	N-desethyl-amiodarone	CYP2C9	150	0.12	Yes	Yes
Gemfibrozil	Gemfibrozil glucuronide	CYP2C8	65	4.7	No	Yes
Escitalopram	N-Desmethyl-citalopram	CYP2D6	36	0.007	[1]Yes	No
Sertraline	N-Desmethyl-sertraline	CYP3A4, CYP2D6	259	0.3	Yes	Yes
Ciprofloxacin	Oxociprofloxacin	CYP1A2	10	0.02	No	No
Capecitabine	5-deoxy-5-fluorocytidine	CYP2C9	284	0.41	Yes	Yes

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	5-deoxy-5-fluorouridine		235	0.376	Yes	Yes
	Dihydro-5-fluorouracil		40	0.16	No	Yes
	α-fluoro-β-analine		2360	1.164	Yes	Yes

Yes: in vitro P450 inhibition studies triggered by the Yu & Tweedie approach or the Callegari et al. approach.

No: in vitro P450 inhibition studies not triggered by the Yu & Tweedie approach or the Callegari et al. approach.

1: Covered due to the N-dealkylated metabolite (structural alert)

Table 3 Additional structural alert for P450 inactivation

Structural alert	Example	Reference
Alkene	secobarbital	He et al., 1996a; He et al., 1996b
Alkyne	17α-ethynylestradiol and erlotinib	Lin et al., 2002; Li et al., 2010
Hydrazine	1-aminobenzotriazole	Ortiz de Montellano and Watanabe 1987
Cyclopropylamine	*N*-(2-phenylcyclopropyl)amine	Bondon et al., 1989; Cerny and Hanzlik 2005; Shaffer et al., 2002; Kalgutkar et al., 2007
Dihaloalkane	chloramphenicol and halothane	Pohl et al., 1978; Orr et al., 2012
Furan	methoxsalen, bergamottin, 4-lpomeanol	Koenigs and Trager 1998; Lin et al., 2012; Orr et al., 2012
Thiophene	tienilic acid, ticlopidine, suprofen	Koenigs et al., 1999; Orr et al., 2012
Phenol and aminophenol	trazodone, dasatinib, tacrine	Baer et al., 2007; Hollenberg et al., 2008; Wen et al., 2009

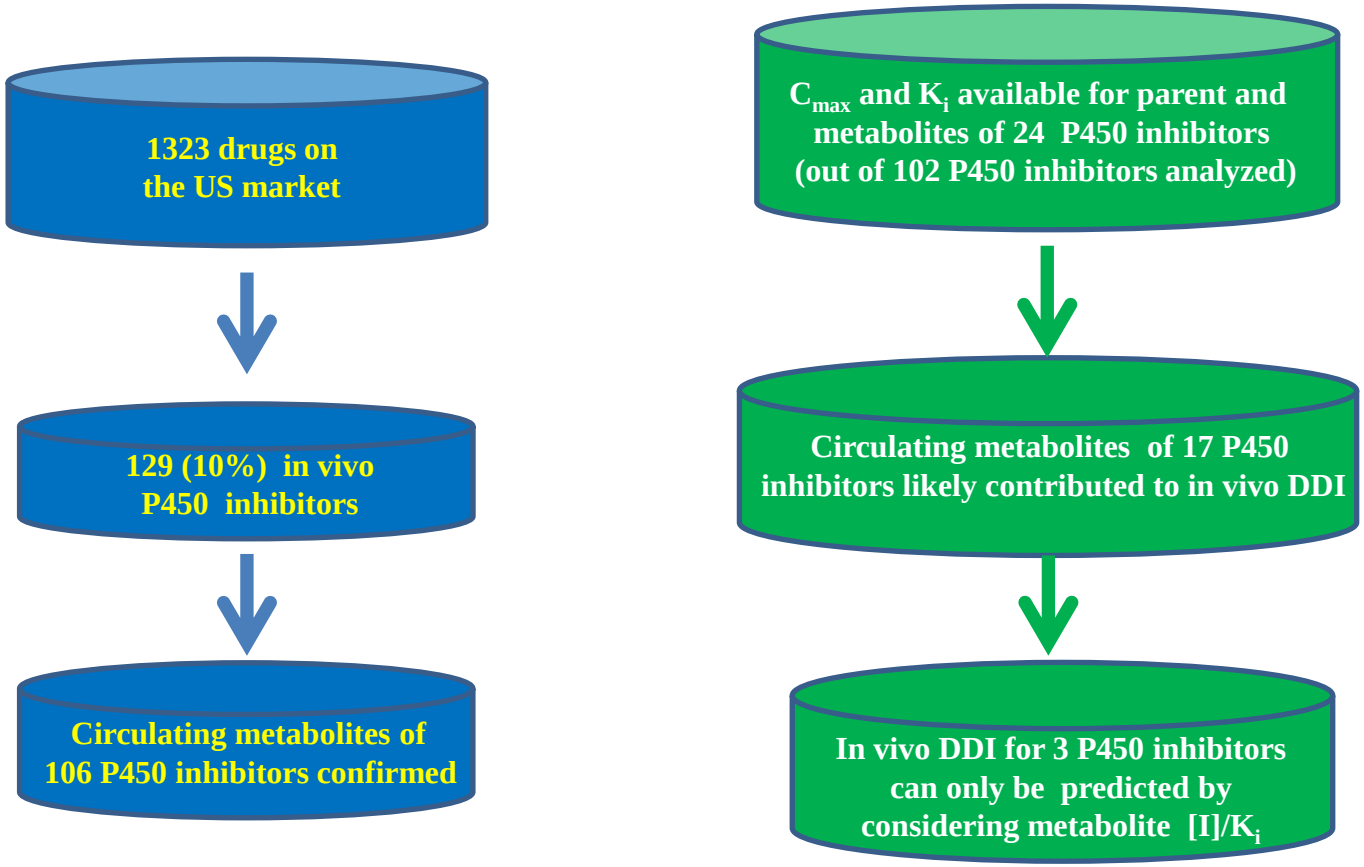
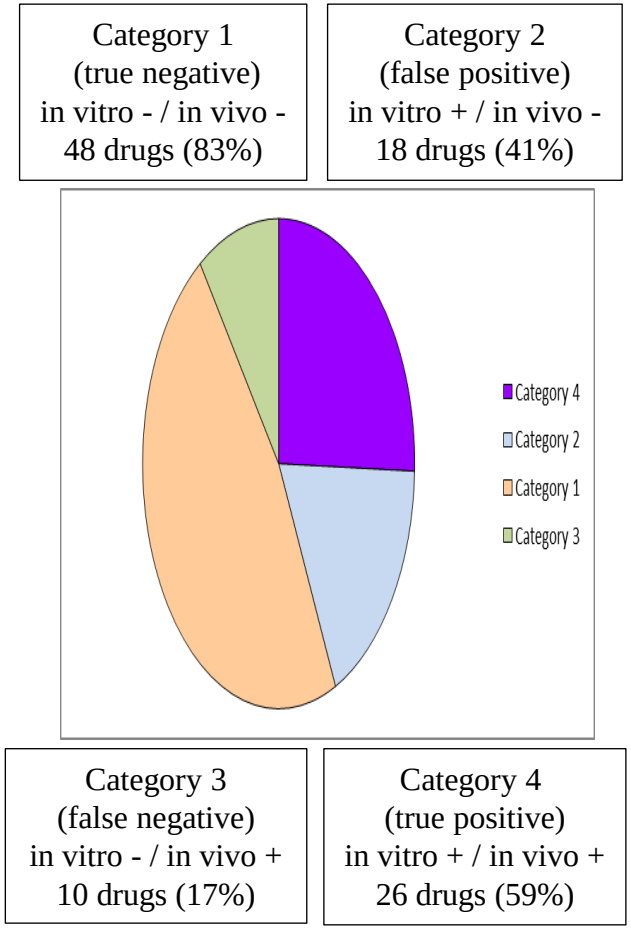


Figure 1



35 unassigned drugs not included in the calculation
no DDI data reported

Figure 2

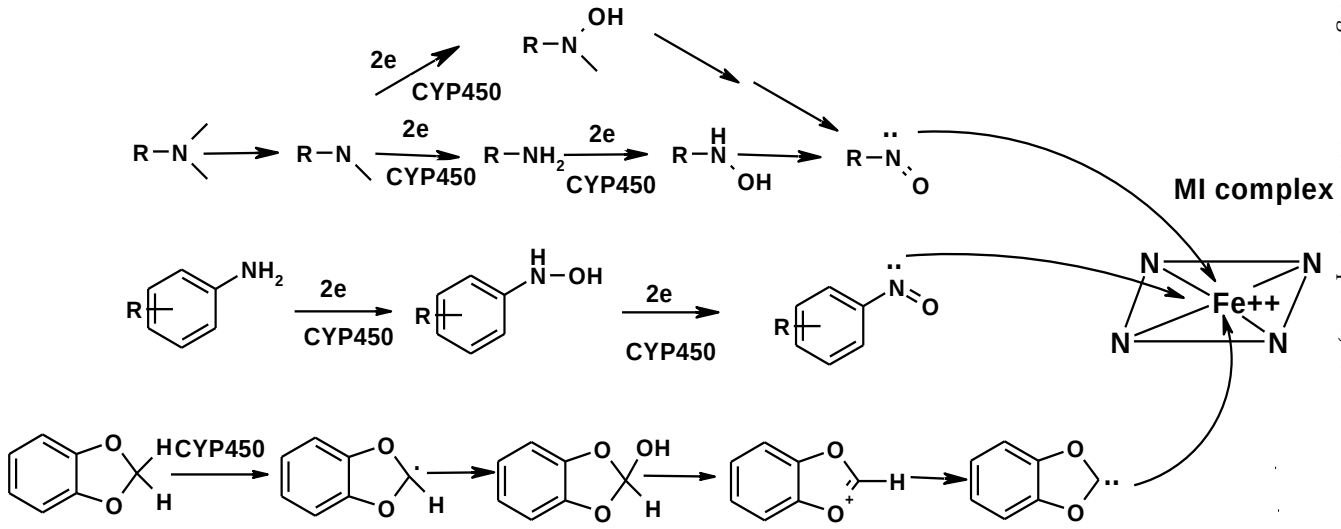


Figure 3

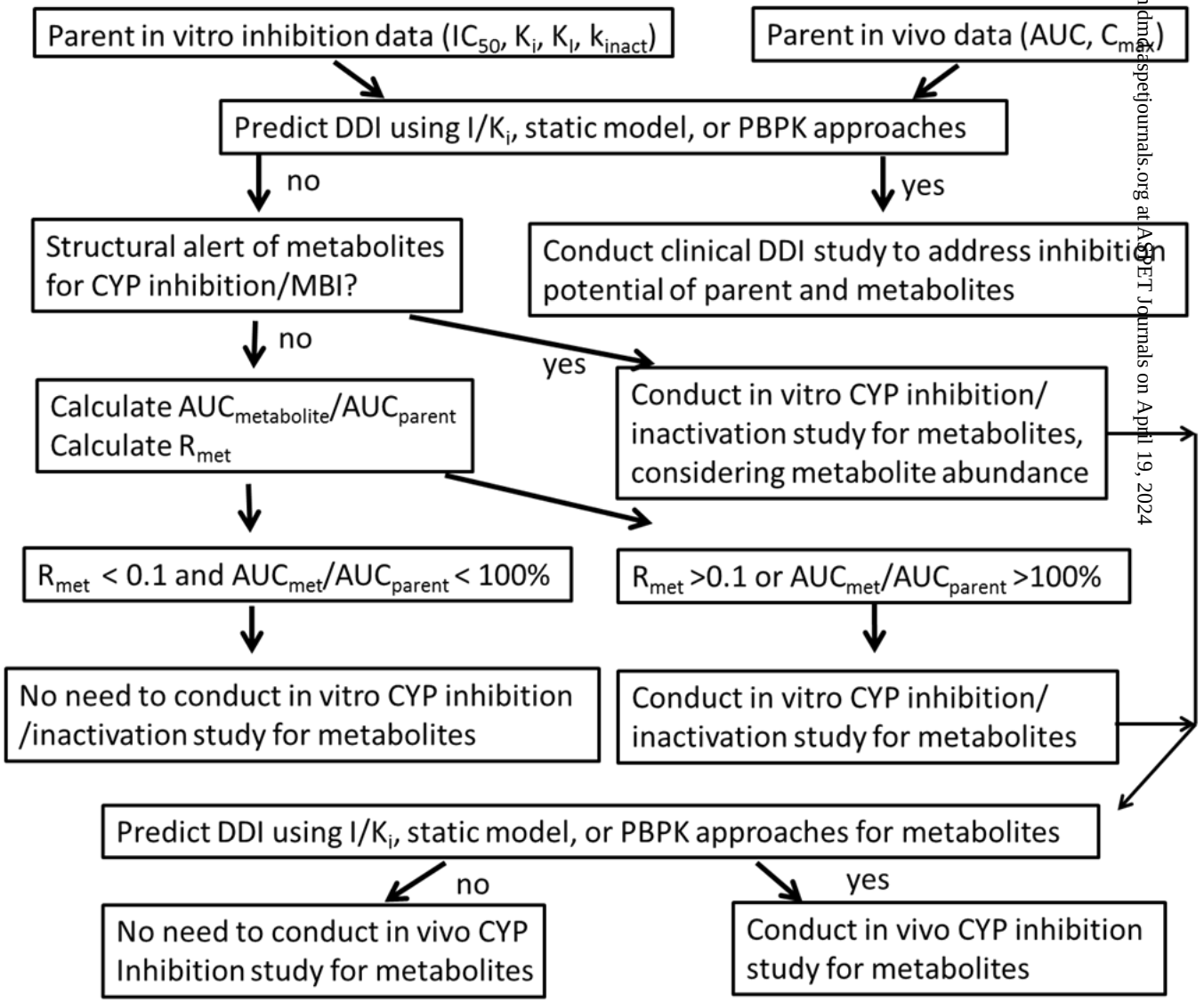


Figure 4

Drug Metabolism and Disposition, Manuscript # 59345 Yu, H. et al.
Contribution of Metabolites to P450 Inhibition-Based Drug-Drug Interactions: Scholarship from the IQ DMLG Metabolite Group

				Parent Dose	CYP450 In Vitro Ki or IC50/2	In Vitro Ki or IC50/2	Probe Substrate	AUC Increase of Victim Drug	Parent Drug AUC	Parent Drug Cmax	Metabolite AUC	Metabolite Cmax	Metabolite /Parent	Metabolite CYP450	Metabolite Ki or IC50/2	Parent Cmax/Ki	Metabolite Cmax/Ki	Parent K_I/k_{inact}	Metabolite K_I/k_{inact}	References
Category	Parent Drug	Metabolite(s)	MW	mg (interval)	CYPs determined	(µM)	(In Vivo Inhibition)	(fold increase w/wo Innhibitor)	(µM*h)	(µM)	(µM*h)	(µM)	(ratio)	in vitro inhibition	(µM)	ratio	ratio			
Unassigned	Alendronate	no data	249.1	70mg weekly	no data	no data	no data	no data	0.44	0.15	no data	no data	no data	no data	no data	no data	no data	no data	no data	Porras AG, Holland SD, and Gertz BJ (1999) Pharmacokinetics of alendronate. Clinical pharmacokinetics 36:315-328.
																				Yun MH, Woo JS, and Kwon KI (2006) Bioequivalence and pharmacokinetics of 70 mg alendronate sodium tablets by measuring alendronate in plasma. Archives of pharmacal research 29:328-332.
																				Peters ML, Leonard M, and Licata AA (2001) Role of alendronate and risedronate in preventing and treating osteoporosis. Cleveland Clinic journal of medicine 68:945-951.
Unassigned	Alfuzosin	no data	389.5	5mg single	no data	no data	no data	no data	0.254	0.03	no data	no data	not calculated	no data	no data	no data	no data	no data	no data	Salva P, Bianchetti G, Morselli P, Garcia-Teresa G, and Costa J (1992) Pharmacokinetics of alfuzosin after single oral administration to healthy volunteers, of three different doses. Biopharmaceutics & drug disposition 13:583-590.
3	Amiodarone		645.3	400mg qd	CYP2C8, 2C9, 2D6, 3A	1.2, 95, 45, 272	Warfarin (2C9)	2.1		1.0		1.2	0.78	CYP2C9	2.3	0.01	0.52	CYP2C8 KI = 1.5 uM, kinact = 0.079 min-1	CYP1A2 KI = 12 µM, kinact = 0.03 min-1	Ohyama K, Nakajima M, Suzuki M, Shimada N, Yamazaki H, and Yokoi T (2000) Inhibitory effects of amiodarone and its N-deethylated metabolite on human cytochrome P450 activities: prediction of in vivo drug interactions. British journal of clinical pharmacology 49:244-253.
				200mg sd					32	1.8										
		Desethylamiodarone	617.3				Metoprolol (2D6)	2.0						CYP2D6	4.5	0.02	0.27		CYP2B6 KI = 0.6 µM, kinact = 0.02 min-1	Polasek TM, Elliot DJ, Lewis BC, and Miners JO (2004) Mechanism-based inactivation of human cytochrome P4502C8 by drugs in vitro. The Journal of pharmacology and experimental therapeutics 311:996-1007.
							Simvastatin (3A)	1.8						CYP3A	12.1	0.003	0.1	CYP3A KI = 13 µM, kinact = 0.06 min-1	CYP2D6 KI = 1.3 µM, kinact = 0.12 min-1	Shoaf SE, Elizari MV, Wang Z, Sekar K, Grinfeld LR, Barbagelata NA, Lerman J, Bramer SL, Tronge J, and Orlandi C (2005) Tolvaptan administration does not affect steady state amiodarone concentrations in patients with cardiac arrhythmias. Journal of cardiovascular pharmacology and therapeutics 10:165-171.
																				Heimark LD, Wienkers L, Kunze K, Gibaldi M, Eddy AC, Trager WF, O'Reilly RA, and Goulart DA (1992) The mechanism of the interaction between amiodarone and warfarin in humans. Clinical pharmacology and therapeutics 51:398-407.

																				Funck-Brentano C, Becquemont L, Kroemer HK, Buhl K, Knebel NG, Eichelbaum M, and Jaillon P (1994) Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. Clinical pharmacology and therapeutics 55:256-269.
1	Amitriptyline		277.4	25mg tid	CYP1A2, 2C19, 2D6	57, 1.1, 31	Risperidone (2D6)	1.2	2.2	0.07	no data	0.16	not calculated	CYP2D6	Ki = 0.85 uM, 2.5 uM	0.001 (1A2); 0.005-0.066 (2C19)	no data	no data	no data	Baumann P, Meyer JW, Amey M, Baettig D, Bryois C, Jonzier-Perey M, Koeb L, Monney C, and Woggon B (1992) Dextromethorphan and mephenytoin phenotyping of patients treated with thioridazine or amitriptyline. Therapeutic drug monitoring 14:1-8.
		Nortriptyline	263.4				Mephenytoin	no interaction						CYP2D6	7.9					Foti RS and Wahlstrom JL (2008) CYP2C19 inhibition: the impact of substrate probe selection on in vitro inhibition profiles. Drug metabolism and disposition: the biological fate of chemicals 36:523-528.
																				Gupta SK, Shah JC, and Hwang SS (1999) Pharmacokinetic and pharmacodynamic characterization of OROS and immediate-release amitriptyline. British journal of clinical pharmacology 48:71-78.
																				Isoherranen N, Hachad H, Yeung CK, and Levy RH (2009) Qualitative analysis of the role of metabolites in inhibitory drug-drug interactions: literature evaluation based on the metabolism and transport drug interaction database. Chemical research in toxicology 22:294-298.
																				Daniel WA, Syrek M, Rylko Z, and Kot M (2001) Effects of phenothiazine neuroleptics on the rate of caffeine demethylation and hydroxylation in the rat liver. Polish journal of pharmacology 53:615-621.
																				Shin JG, Park JY, Kim MJ, Shon JH, Yoon YR, Cha IJ, Lee SS, Oh SW, Kim SW, and Flockhart DA (2002) Inhibitory effects of tricyclic antidepressants (TCAs) on human cytochrome P450 enzymes in vitro: mechanism of drug interaction between TCAs and phenytoin. Drug metabolism and disposition: the biological fate of chemicals 30:1102-1107.
3	Amlodipine		408.9	10mg qd	CYP2B6, 3A	0.68,2	Simvastatin (3A)	1.3	0.58	0.014	no data	no data	no data	no data	no data	0.021 (2B6), 0.007 (3A)	no data	no data	no data	Ma B, Prueksaritanont T, and Lin JH (2000) Drug interactions with calcium channel blockers: possible involvement of metabolite-intermediate complexation with CYP3A. Drug metabolism and disposition: the biological fate of chemicals 28:125-130.
																				Katoh M, Nakajima M, Shimada N, Yamazaki H, and Yokoi T (2000) Inhibition of human cytochrome P450 enzymes by 1,4-dihydropyridine calcium antagonists: prediction of in vivo drug-drug interactions. European journal of clinical pharmacology 55:843-852.
																				Meredith PA and Elliott HL (1992) Clinical pharmacokinetics of amlodipine. Clinical pharmacokinetics 22:22-31.

																				Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, and Ohashi K (2005) Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertension research : official journal of the Japanese Society of Hypertension 28:223-227.
																				Beresford AP, McGibney D, Humphrey MJ, Macrae PV, and Stopher DA (1988) Metabolism and kinetics of amlodipine in man. Xenobiotica; the fate of foreign compounds in biological systems 18:245-254.
1	Amphetamine	no data	135.2	30mg	CYP2D6	27	no data	no data	13	0.66	no data	no data	no data	no data	no data	0.02	no data	no data	no data	http://www.pharmacologyweekly.com/content/pages/drug-reference-table-cyp-p450-ugt-enzymes-transporters-ab
																				Wu D, Otton SV, Inaba T, Kalow W, and Sellers EM (1997) Interactions of amphetamine analogs with human liver CYP2D6. Biochemical pharmacology 53:1605-1612.
																				Clausen SB, Read SC, and Tulloch SJ (2005) Single- and multiple-dose pharmacokinetics of an oral mixed amphetamine salts extended-release formulation in adults. CNS spectrums 10:6-15.
1	Anastrozole	no data	293.4	1mg qd	CYP1A2, 2C9, 3A4	8, 10, 10	Warfarin (2C9)	1	1.9	0.12	no data	no data	not calculated	no data	no data	0.015	no data	no data	no data	Grimm SW and Dyroff MC (1997) Inhibition of human drug metabolizing cytochromes P450 by anastrozole, a potent and selective inhibitor of aromatase. Drug metabolism and disposition: the biological fate of chemicals 25:598-602.
																				Yates RA, Wong J, Seiberling M, Merz M, Marz W, and Nauck M (2001) The effect of anastrozole on the single-dose pharmacokinetics and anticoagulant activity of warfarin in healthy volunteers. British journal of clinical pharmacology 51:429-435.
																				Dowsett M, Cuzick J, Howell A, Jackson I, and Group AT (2001) Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. British journal of cancer 85:317-324.
1	Aripiprazole		448.4	15mg qd	CYP2D6, CYP3A	3.2, 8	Venlafaxine (2D6)	no interaction	9.2	0.14			0.6	no data	no data	0.04 (2D6) and 0.02 (3A4)	Not calculated	no data	no data	Bauman JN, Frederick KS, Sawant A, Walsky RL, Cox LM, Obach RS, and Kalgutkar AS (2008) Comparison of the bioactivation potential of the antidepressant and hepatotoxin nefazodone with aripiprazole, a structural analog and marketed drug. Drug metabolism and disposition: the biological fate of chemicals 36:1016-1029.
		Dehydroaripiprazole	446.4				Dextromethorphan (2D6)	no interaction		(15mg single dose)	5.5	0.02								Boulton DW, Balch AH, Royzman K, Patel CG, Berman RM, Mallikaarjun S, and Reeves RA (2010) The pharmacokinetics of standard antidepressants with aripiprazole as adjunctive therapy: studies in healthy subjects and in patients with major depressive disorder. Journal of psychopharmacology (Oxford, England) 24:537-546.

																				Boulton DW, Kollia G, Mallikaarjun S, Komoroski B, Sharma A, Kovalick LJ, and Reeves RA (2008) Pharmacokinetics and tolerability of intramuscular, oral and intravenous aripiprazole in healthy subjects and in patients with schizophrenia. Clinical pharmacokinetics 47:475-485. Mallikaarjun S, Shoaf SE, Boulton DW, Bramer SL Effect of hepatic or renal impairment on the pharmacokinetics of Aripiprazole Clin Pharmacokinetics 2008 47: 533-542.
4	Atazanavir		704.9	400mg qd	CYP1A2, 2C8, 2C9, 3A	12, 2.1, 12, 2.4	Maraviroc (3A)	3.6	42	6.3	no data	no data		no data	no data	2.6	no data	CYP3A KI = 0.84 µM, kinact = 0.07 min-1	no data	ter Heine R, Hillebrand MJ, Rosing H, van Gorp EC, Mulder JW, Beijnen JH, and Huitema AD (2009) Identification and profiling of circulating metabolites of atazanavir, a HIV protease inhibitor. Drug metabolism and disposition: the biological fate of chemicals 37:1826-1840.
							Rosiglitazone (2C8)	1.4												Perloff ES, Duan SX, Skolnik PR, Greenblatt DJ, and von Moltke LL (2005) Atazanavir: effects on P-glycoprotein transport and CYP3A metabolism in vitro. Drug metabolism and disposition: the biological fate of chemicals 33:764-770.
		M1 - M5											<0.1							http://www.hiv-druginteractions.org/data/NewsItem/62_9PK_NewOrleans.pdf
																				Abel S, Russell D, Taylor-Worth RJ, Ridgway CE, and Muirhead GJ (2008) Effects of CYP3A4 inhibitors on the pharmacokinetics of maraviroc in healthy volunteers. British journal of clinical pharmacology 65 Suppl 1:27-37.
																				http://www.medicines.org.uk/emc/medicine/14145
																				Busti AJ, Hall RG, and Margolis DM (2004) Atazanavir for the treatment of human immunodeficiency virus infection. Pharmacotherapy 24:1732-1747.
2	Atomoxetine		255.4	40mg qd	CYP2D6, 3A	3.6, 34	Desipramine (2D6)	no interaction	14	1.8						0.5 (2D6), 0.05 (3A)		no data	no data	Sauer JM, Long AJ, Ring B, Gillespie JS, Sanburn NP, DeSante KA, Petullo D, VandenBranden MR, Jensen CB, Wrighton SA, Smith BP, Read HA, and Witcher JW (2004) Atomoxetine hydrochloride: clinical drug-drug interaction prediction and outcome. The Journal of pharmacology and experimental therapeutics 308:410-418.
		4-Hydroxyatomoxetine	271.0				Midazolam (3A)	1.15			no data	0.01 to 0.03 µM	not Calculated	CYP2D6, 3A	17, 461		0.00176 (2D6)			Cui YM, Teng CH, Pan AX, Yuen E, Yeo KP, Zhou Y, Zhao X, Long AJ, Bangs ME, and Wise SD (2007) Atomoxetine pharmacokinetics in healthy Chinese subjects and effect of the CYP2D6*10 allele. British journal of clinical pharmacology 64:445-449.
		N-Desmethylatomoxetine	241.0								no data	0.2 to 6.3 µM	not Calculated	CYP1A2, 2C9, 2D6, 3A	271, 53, 5.3, 16		1.188 (2D6)			
3	Atorvastatin		558.6	40mg qd	CYP3A	8	Midazolam (3A)	1.4 (IV)	0.11	0.023						0.0028		no data	no data	Mc Donnell CG, Harte S, O'Driscoll J, O'Loughlin C, Van Pelt FN, and Shorten GD (2003) The effects of concurrent atorvastatin therapy on the pharmacokinetics of intravenous midazolam. Anaesthesia 58:899-904.
		Atorvastatin lactone	540.6								0.098	0.0078			0.9		0.01			Lilja JJ, Kivisto KT, and Neuvonen PJ (1999) Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. Clinical pharmacology and therapeutics 66:118-127.
		2-Hydroxyatorvastatin	574.6								0.14	0.013								
		2-Hydroxyatorvastatin lactone	556.6								0.29	0.022								

4	Azithromycin	no data	749.0	500mg sd	CYP3A	MBI	Midazolam (3A)	1.3	7.1	0.76	no data	no data	no data	no data	no data	not calculated	no data	CYP3A KI = 623 µM, kinact = 0.016 min-1	no data	Westphal JF (2000) Macrolide - induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. British journal of clinical pharmacology 50:285-295.
																				Harahap, Y, Prasaja, B, Lustholm, W, Hardiyanti, Ginting, MB, and Lipin (2012) A bioequivalence study of two azithromycin formulations in indonesian healthy subjects. Journal of Bioequivalence & Bioavailability 4:48-51.
																				Ito K, Ogihara K, Kanamitsu S, and Itoh T (2003) Prediction of the in vivo interaction between midazolam and macrolides based on in vitro studies using human liver microsomes. Drug metabolism and disposition: the biological fate of chemicals 31:945-954.
4	Bicalutamide	no data	430.4	50mg, qd	CYP2C9, 2C19, 2D6, 3A (R-bicalutamide)	65, 16, 70, 2.3 (R-bicalutamide)	Midazolam (3A)	1.3 (midazolam with 150 mg dose)	536 (R-bicalutamide)	1.97 (R-bicalutamide)	no data	no data	no data	no data	no data	0.86 (CYP3A4; R-bicalutamide)	no data	no data	no data	Cockshott ID (2004) Bicalutamide: clinical pharmacokinetics and metabolism. Clinical pharmacokinetics 43:855-878.
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/079089s000lbl.pdf
																				Lee S, Chung YJ, Kim BH, Shim JH, Yoon SH, Shin SG, Jang IJ, and Yu KS (2009) Comparative pharmacokinetic evaluation of two formulations of bicalutamide 50-mg tablets: an open-label, randomized-sequence, single-dose, two-period crossover study in healthy Korean male volunteers. Clinical therapeutics 31:3000-3008.
Unassigned	Bisoprolol		325.4	5-20mg qd	no data	no data	Imidapril	no interaction	3.1 (20mg)	0.215 (20mg)										http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019982s016lbl.pdf
		M1 (Odealkylation/oxidation)	313.4								no Data	no Data	no Data	no Data	no Data	no Data	No Data	No Data	No Data	Leopold G (1986) Balanced pharmacokinetics and metabolism of bisoprolol. Journal of cardiovascular pharmacology 8 Suppl 11:S16-20.
																				Buhring KU, Sailer H, Faro HP, Leopold G, Pabst J, and Garbe A (1986) Pharmacokinetics and metabolism of bisoprolol-14C in three animal species and in humans. Journal of cardiovascular pharmacology 8 Suppl 11:S21-28.
																				Breithaupt-Grogler K, Ungethum W, Meurer-Witt B, and Belz GG (2001) Pharmacokinetic and dynamic interactions of the angiotensin-converting enzyme inhibitor imidapril with hydrochlorothiazide, bisoprolol and nilvadipine. European journal of clinical pharmacology 57:275-284.
1	Bosentan	no data	551.6	62.5mg sd	no inhibition of major CYP450s	values not reported	none reported	no data	7.7	1.1	no data	no data	not calculated	no data	no data	not calculated	not calculated	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021290s019lbl.pdf
																				van Giersbergen PL, Halabi A, and Dingemanse J (2002) Single- and multiple-dose pharmacokinetics of bosentan and its interaction with ketoconazole. British journal of clinical pharmacology 53:589-595.
2	Budesonide	no data	430.5	inhalation	3A	0.038 (0.1 um for midazolam)	no CYP3A probe substrate study	no data on CYP3A probe substrate interaction	0.015	0.006	no data	no data	not calculated	no data	no data	0.004-0.16 (3A); 0.15 for midazolam	no data	no data	no data	Harrison TW and Tattersfield AE (2003) Plasma concentrations of fluticasone propionate and budesonide following inhalation from dry powder inhalers by healthy and asthmatic subjects. Thorax 58:258-260.

																				Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2010) Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. Drug metabolism and disposition: the biological fate of chemicals 38:981-987.
3	Bupropion		239.7	300mg/day, 100 mg tid	CYP2D6	21	Desipramine (2D6)	5.2	7.3	0.67						0.032		no data		http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020711s032s033lbl.pdf
		Hydroxybupropion	255.0								54	4		CYP2D6	39		0.103		no data	Hesse LM, Venkatakrishnan K, Court MH, von Moltke LL, Duan SX, Shader RI, and Greenblatt DJ (2000) CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants. Drug metabolism and disposition: the biological fate of chemicals 28:1176-1183.
		Threohydrobupropion	241.0								22	2.34		CYP2D6	5.4		0.43		no data	Reese MJ, Wurm RM, Muir KT, Generaux GT, St John-Williams L, and McConn DJ (2008) An in vitro mechanistic study to elucidate the desipramine/bupropion clinical drug-drug interaction. Drug metabolism and disposition: the biological fate of chemicals 36:1198-1201.
		Erythrohydrobupropion	241.0									0.43		CYP2D6	1.7		0.25		no data	Jefferson JW, Pradko JF, and Muir KT (2005) Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. Clinical therapeutics 27:1685-1695.
1	Candesartan cilexetil		440.5	4-32mg qd	CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4	all > 500	Nifedipine (3A)	no interaction	1.46	0.19	no data	no data	not calculated	no data	no data	<0.00076	Not calculated	no data	no data	van Lier JJ, van Heiningen PN, and Sunzel M (1997) Absorption, metabolism and excretion of 14C-candesartan and 14C-candesartan cilexetil in healthy volunteers. Journal of human hypertension 11 Suppl 2:S27-28.
		minor metabolism via O-Deethylation	412.5																	Taavitsainen P, Kiukaanniemi K, and Pelkonen O (2000) In vitro inhibition screening of human hepatic P450 enzymes by five angiotensin-II receptor antagonists. European journal of clinical pharmacology 56:135-140.
																				Brendel E, Weimann B, Dietrich H, Froede C, and Thomas D (2013) Investigation of bioequivalence of a new fixed-dose combination of nifedipine and candesartan with the corresponding loose combination as well as the drug-drug interaction potential between both drugs under fasting conditions. International journal of clinical pharmacology and therapeutics 51:753-762.
3	Capecitabine	5'-deoxy-5-fluorocytidine, 5'-deoxy-5-fluorouridine, dihyro-5-fluorouracil, alpha-fluoro-beta-analine	359.4	1250mg/m2 bid	the hydrolysis product of capecitabine (5-fluorouracil) does not inhibit major CYP450s (1A2, 2C8, 2C19, 2D6, 3A4)	>200	S-Warfarin (2C9)	1.5	20.2	11					no data	<0.055		no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020896s026lbl.pdf
		5'-deoxy-5-fluorocytidine	245.2								57.5	20.5	2.84 (or 284%)	the four major metabolites did not inhibit major CYP450s (1A2, 2A6, 3A4, 2C19, 2D6 and 2E1)	no data		not calculated	no data	no data	XELODA® [package insert]. Genentech, Inc. 2010

		5'-deoxy-5-fluorouridine	246.2								47.5	18.8	2.35(or 235%)		no data		not calculated	no data	no data	Camidge R, Reigner B, Cassidy J, Grange S, Abt M, Weidekamm E, and Jodrell D (2005) Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23:4719-4725.
		Dihydro-5-fluorouracil	132.1								30.6	8	0.40 (or 40%)		no data		not calculated	no data	no data	Twelves C, Glynne-Jones R, Cassidy J, Schuller J, Goggin T, Roos B, Banken L, Utoh M, Weidekamm E, and Reigner B (1999) Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. Clinical cancer research : an official journal of the American Association for Cancer Research 5:1696-1702.
		Alpha-fluoro-beta-analine	107.1								477	58.2	23.6 (or 2360%)		no data		not calculated	no data	no data	
1	Carvedilol		406.5	25mg qd	CYP2B6, 2C8	6.0, 8.4	Cyclosporin (P-gp)	1.4	1.0	0.26	no data	no data	not calculated	no data	no data	0.022	no data	no data	no data	Walsky RL, Astuccio AV, and Obach RS (2006) Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. Journal of clinical pharmacology 46:1426-1438.
																				Gehr TW, Tenero DM, Boyle DA, Qian Y, Sica DA, and Shusterman NH (1999) The pharmacokinetics of carvedilol and its metabolites after single and multiple dose oral administration in patients with hypertension and renal insufficiency. European journal of clinical pharmacology 55:269-277.
																				Kaijser M, Johnsson C, Zezina L, Backman U, Dimeny E, and Fellstrom B (1997) Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients. Clinical transplantation 11:577-581.
1	Cefdinir		395.4	200mg qd	CYP1A2, 2C19, 2D6, 3A	no inhibition	no 1A2, 2C19, 2D6, 3A substrate	no data	19	3.6	no data	no data	no data	no data	no data	no data	no data	no data	no data	Niwa T, Shiraga T, Hashimoto T, and Kagayama A (2004) Effect of cefixime and cefdinir, oral cephalosporins, on cytochrome P450 activities in human hepatic microsomes. Biological & pharmaceutical bulletin 27:97-99.
																				Zhang, C-L, Jiao, J-J, Wu, Y-N, Song, J-Q, Gao, W-Z, Ma, D-L, and Lou, J-S (2011) Study on pharmacokinetics and bioequivalence of cefdinir dispersible tablet in healthy chinese volunteers. Journal of Bioequivalence & Bioavailability 3:114-117.
4	Celecoxib		381.4	200mg sd	CYP2D6	4.2	Metoprolol (2D6)	1.6	21	1.9	no data	no data	no data	no data	no data	0.44	no data	no data	no data	Davies NM, McLachlan AJ, Day RO, and Williams KM (2000) Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. Clinical pharmacokinetics 38:225-242.
		Hydroxycelecoxib	397.4																	http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20998AP_clinphrmr_P1.pdf
		Carboxycelecoxib	411.4																	Werner U, Werner D, Rau T, Fromm MF, Hinz B, and Brune K (2003) Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. Clinical pharmacology and therapeutics 74:130-137.
		Celecoxib-1-glucuronide	587.5																	
1	Cetirizine		388.9	10mg qd	CYP1A2, 2C9, 2C19, 2D6, 3A	no inhibition	Ritonavir (3A)	no interaction	6.9	0.8	no data	no data	no data	no data	no data	no data	no data	no data	no data	Wood SG, John BA, Chasseaud LF, Yeh J, and Chung M (1987) The metabolism and pharmacokinetics of 14C-cetirizine in humans. Annals of allergy 59:31-34.
																				http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022429s000_SumR.pdf

3	Ciprofloxacin	Oxo-ciprofloxacin (only 10% of parent AUC)	331.4	500mg bid	CYP1A2, 2C9, 3A4	145, 180, >200	Tizanidine (1A2)	10	61	13.1	5.8	0.8	9.50%	no data	no data	#VALUE!	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019537s074,020780s032lbl.pdf
																				Granfors MT, Backman JT, Neuvonen M, and Neuvonen PJ (2004) Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. Clinical pharmacology and therapeutics 76:598-606.
																				Karjalainen MJ, Neuvonen PJ, and Backman JT (2008) In vitro inhibition of CYP1A2 by model inhibitors, anti-inflammatory analgesics and female sex steroids: predictability of in vivo interactions. Basic & clinical pharmacology & toxicology 103:157-165.
																				Zhang L, Wei MJ, Zhao CY, and Qi HM (2008) Determination of the inhibitory potential of 6 fluoroquinolones on CYP1A2 and CYP2C9 in human liver microsomes. Acta pharmacologica Sinica 29:1507-1514.
							Warfarin	1.2												Israel DS, Stotka J, Rock W, Sintek CD, Kamada AK, Klein C, Swaim WR, Pluhar RE, Toscano JP, Lettieri JT, Heller AH, and Polk RE (1996) Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 22:251-256.
							Sildenafil (3A)	2.1												Hedaya MA, El-Afify DR, and El-Maghraby GM (2006) The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. Biopharmaceutics & drug disposition 27:103-110.
																				Bergan T, Thorsteinsson SB, Rohwedder R, and Scholl H (1989) Elimination of ciprofloxacin and three major metabolites and consequences of reduced renal function. Chemotherapy 35:393-405.
4	Clopidogrel		321.8	150mg sd	CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19	2.2, 0.023, 0.023, 9, 10.5, 1.9	Bupropion (2B6)	1.6	0.093	0.023						1.0		CYP2B6 KI = 1.4 µM, kinact = 1.9 min-1 (est)	no data	Walsky RL and Obach RS (2007) A comparison of 2-phenyl-2-(1-piperidinyl)propane (ppp), 1,1',1''-phosphinothioylidynetrisaziridine (thioTEPA), clopidogrel, and ticlopidine as selective inactivators of human cytochrome P450 2B6. Drug metabolism and disposition: the biological fate of chemicals 35:2053-2059.
		Clopidogrel active metabolte	355.8	300mg sd EM			Sibutramine (3A)	2.3			0.16	0.11	1.7	All >30 µM						Turpeinen M, Tolonen A, Uusitalo J, Jalonen J, Pelkonen O, and Laine K (2005) Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. Clinical pharmacology and therapeutics 77:553-559.
		2-Oxo-clopidogrel	337.8											CYP2B6, 2C19	0.65, 0.5					Bae JW, Jang CG, and Lee SY (2011) Effects of clopidogrel on the pharmacokinetics of sibutramine and its active metabolites. Journal of clinical pharmacology 51:1704-1711.
		Clopidogrel acid metabolite	307.8	75mg sd							26	10	280	All >50 µM						Lainesse A, Ozalp Y, Wong H, and Alpan RS (2004) Bioequivalence study of clopidogrel bisulfate film-coated tablets. Arzneimittel-Forschung 54:600-604.

																				Takahashi M, Pang H, Kawabata K, Farid NA, and Kurihara A (2008) Quantitative determination of clopidogrel active metabolite in human plasma by LC-MS/MS. Journal of pharmaceutical and biomedical analysis 48:1219-1224.
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																				Ksycinska H, Rudzki P, and Bukowska-Kiliszek M (2006) Determination of clopidogrel metabolite (SR26334) in human plasma by LC-MS. Journal of pharmaceutical and biomedical analysis 41:533-539.
4	Cyclosporine		1203	344mg qd	CYP2C19, 2D6, 3A	>20, >20, 0.98	Midazolam (3A)	1.3	7.3	1.5	no data	no data		no data	no data	1.5	no data	CYP3A KI = 3.3 µM, kinact = 0.033 min-1	no data	Niwa T, Yamamoto S, Saito M, Shiraga T, and Takagi A (2007) Effect of cyclosporine and tacrolimus on cytochrome p450 activities in human liver microsomes. Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan 127:209-216.
		Oxidated cyclosporine											0.7							Zimmerlin A, Trunzer M, and Faller B (2011) CYP3A time-dependent inhibition risk assessment validated with 400 reference drugs. Drug metabolism and disposition: the biological fate of chemicals 39:1039-1046.
																				de Jonge H, de Loor H, Verbeke K, Vanrenterghem Y, and Kuypers DR (2011) In vivo CYP3A activity is significantly lower in cyclosporine-treated as compared with tacrolimus-treated renal allograft recipients. Clinical pharmacology and therapeutics 90:414-422.
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050715s027,050716s028lbl.pdf
																				Amundsen R, Asberg A, Ohm IK, and Christensen H (2012) Cyclosporine A- and tacrolimus-mediated inhibition of CYP3A4 and CYP3A5 in vitro. Drug metabolism and disposition: the biological fate of chemicals 40:655-661.
																				Wang CP, Hartman NR, Venkataramanan R, Jardine I, Lin FT, Knapp JE, Starzl TE, and Burckart GJ (1989) Isolation of 10 cyclosporine metabolites from human bile. Drug metabolism and disposition: the biological fate of chemicals 17:292-296.
Unassigned	Darbepoetin alfa		37 Kd		not applicable (protein)															Protein drug-no CYP interaction or metabolism data available; systemic PK differs between patient populations and routes of administration (IV or SC)
unassigned	Desloratadine		310.8	5mg sd	no data	no data	Azithromycin	no interaction	0.14	0.0078			0.86	no data	no data	no data	no data	no data	no data	Barecki ME, Casciano CN, Johnson WW, and Clement RP (2001) In vitro characterization of the inhibition profile of loratadine, desloratadine, and 3-OH-desloratadine for five human cytochrome P-450 enzymes. Drug metabolism and disposition: the biological fate of chemicals 29:1173-1175.
		3-Hydroxydesloratadine	326.8	5mg sd			Fluoxetine	no interaction			0.12	0.0041								Xu HR, Li XN, Chen WL, and Chu NN (2007) Simultaneous determination of desloratadine and its active metabolite 3-hydroxydesloratadine in human plasma by LC/MS/MS and its application to pharmacokinetics and bioequivalence. Journal of pharmaceutical and biomedical analysis 45:659-666.

							Montelukast	no interaction											Hakooz N and Salem, II (2012) Prevalence of desloratadine poor metabolizer phenotype in healthy Jordanian males. Biopharmaceutics & drug disposition 33:15-21.
																			Gupta S, Banfield C, Affrime M, Marco A, Cayen M, Herron J, and Padhi D (2002) Desloratadine demonstrates dose proportionality in healthy adults after single doses. Clinical pharmacokinetics 41 Suppl 1:1-6.
2	Diclofenac		296.2	100 to 150mg qd	CYP3A (does not inhibit other major CYP450s)	inactivator	Quinidine	no change	5.2	4.2	5.7	1.5	1.1 or 110%	no data	no data	not calculated	not calculated	CYP3A KI = 1640 µM, kinact = 0.246 min-1	no data	Silva LC, Simoes IG, Lerner FE, Belem GR, de Moraes ME, and De Nucci G (1999) Comparative bioavailability of two different diclofenac formulations in healthy volunteers. Arzneimittel-Forschung 49:920-924.
		4-Hydroxydiclofenac	312.2								2.1	0.22	1.1							Yasar U, Eliasson E, Forslund-Bergengren C, Tybring G, Gadd M, Sjoqvist F, and Dahl ML (2001) The role of CYP2C9 genotype in the metabolism of diclofenac in vivo and in vitro. European journal of clinical pharmacology 57:729-735.
																			Masubuchi Y, Ose A, and Horie T (2002) Diclofenac-induced inactivation of CYP3A4 and its stimulation by quinidine. Drug metabolism and disposition: the biological fate of chemicals 30:1143-1148.
4	Diltiazem		414.5	120mg bid	CYP3A	120			4.3	0.60			0.5			0.005		CYP3A KI = 4.8 µM, kinact = 0.012 min-1	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018602s063lbl.pdf
				180mg qd			Triazolam (3A)	4.0											Jones DR, Gorski JC, Hamman MA, Mayhew BS, Rider S, and Hall SD (1999) Diltiazem inhibition of cytochrome P-450 3A activity is due to metabolite intermediate complex formation. The Journal of pharmacology and experimental therapeutics 290:1116-1125.
		N-Desmethyldiltiazem	400.5	240mg qd			Simvastatin (3A)	5.0			2.1	0.22		CYP3A	11		0.02			Kosuge K, Nishimoto M, Kimura M, Umemura K, Nakashima M, and Ohashi K (1997) Enhanced effect of triazolam with diltiazem. British journal of clinical pharmacology 43:367-372.
		N,N-didesmethyldiltiazem	386.5	180mg qd			Buspirone (3A)	5.5						CYP3A	0.6					Mousa O, Brater DC, Sunblad KJ, and Hall SD (2000) The interaction of diltiazem with simvastatin. Clinical pharmacology and therapeutics 67:267-274.
				180mg qd			Midazolam (3A)	3.8												Montamat SC and Abernethy DR (1987) N-monodesmethyldiltiazem is the predominant metabolite of diltiazem in the plasma of young and elderly hypertensives. British journal of clinical pharmacology 24:185-189.
				270mg qd			Nifedipine (3A)	3.1												Lamberg TS, Kivisto KT, and Neuvonen PJ (1998) Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. Clinical pharmacology and therapeutics 63:640-645.
																				Backman JT, Olkkola KT, Aranko K, Himberg JJ, and Neuvonen PJ (1994) Dose of midazolam should be reduced during diltiazem and verapamil treatments. British journal of clinical pharmacology 37:221-225.
																				Rowland Yeo K, Walsky RL, Jamei M, Rostami-Hodjegan A, and Tucker GT (2011) Prediction of time-dependent CYP3A4 drug-drug interactions by physiologically based pharmacokinetic modelling: impact of inactivation parameters and enzyme turnover. Eur J Pharm Sci 43:160-173.

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1	Docetaxel		807.9	100mg/m2 sd	no inhibition of major CYP450s	no data	lapatinib	no interaction	3.5	5.14	no data	no data	no data	no data	no data	no data	no data	no data	no data	Bun SS, Ciccolini J, Bun H, Aubert C, and Catalin J (2003) Drug interactions of paclitaxel metabolism in human liver microsomes. Journal of chemotherapy (Florence, Italy) 15:266-274.
																				Dumez H, Louwerens M, Pawinsky A, Planting AS, de Jonge MJ, Van Oosterom AT, Highley M, Guetens G, Mantel M, de Boeck G, de Bruijn E, and Verweij J (2002) The impact of drug administration sequence and pharmacokinetic interaction in a phase I study of the combination of docetaxel and gemcitabine in patients with advanced solid tumors. Anti-cancer drugs 13:583-593.
		Hydroxy-t-butylpropionate	823.9																	Clarke SJ and Rivory LP (1999) Clinical pharmacokinetics of docetaxel. Clinical pharmacokinetics 36:99-114.
Unassigned	Donepezil		379.5	2mg sd	no data	no data	no data	no data	0.53	0.0084	no data	no data	no data	no data	no data	no data	no data	no data	no data	Ohnishi A, Mihara M, Kamakura H, Tomono Y, Hasegawa J, Yamazaki K, Morishita N, and Tanaka T (1993) Comparison of the pharmacokinetics of E2020, a new compound for Alzheimer's disease, in healthy young and elderly subjects. Journal of clinical pharmacology 33:1086-1091.
			379.5	5mg qd			Levadopa/Carbadopa (non-CYP)	1.2	0.71	0.073										Okereke CS, Kirby L, Kumar D, Cullen EI, Pratt RD, and Hahne WA (2004) Concurrent administration of donepezil HCl and levodopa/carbidopa in patients with Parkinson's disease: assessment of pharmacokinetic changes and safety following multiple oral doses. British journal of clinical pharmacology 58 Suppl 1:41-49.
			379.5	10mg sd					2.5	0.045										Pilli NR, Inamadugu JK, Kondreddy N, Karra VK, Damaramadugu R, and Rao JV (2011) A rapid and sensitive LC-MS/MS method for quantification of donepezil and its active metabolite, 6-o-desmethyl donepezil in human plasma and its pharmacokinetic application. Biomedical chromatography : BMC 25:943-951.
		6-O-Desmethyldonepezil	365.5	10mg sd							0.019	0.00060								
Unassigned	Dorzolamide		324.4	one drop of 20mg/ml solution tid	no reported data	no reported data	no reported data	no reported data	drug below limit of quantitation in plasma	drug below limit of quantitation in plasma	metabolite below limit of quantitation	metabolite below limit of quantitation	not calculated	no reported data	no reported data	not calculated	not calculated	no reported data	no reported data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020408s047lbl.pdf
Unassigned	Doxazosin	no data	451.5	2mg qdx7days	no data		Tacrolimus	no inhibition	0.50	0.038	no data	no data	not calculated	no data	no data	not calculated	not calculated	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019668s021lbl.pdf
																				Vashi V, Chung M, Dias N, and Phillips K (1996) Effect of time of administration on the pharmacokinetics and tolerance of doxazosin in healthy male volunteers. Journal of clinical pharmacology 36:325-331.
																				Zhang Y, Wang Y, Zhang P, Zhang XD, and Yang Y (2009) Extended-release doxazosin for treatment of renal transplant recipients with benign prostatic hyperplasia. Transplantation proceedings 41:3747-3751.

4	Duloxetine	no data	297.4	60mg bid	CYP1A2, 2C19, 2D6	18, 7.1, 2.4	Desipramine (2D6)	2.9	2.0	0.13	no data	no data	not calculated	no data	no data	0.054 (2D6)	no data	no data	no data	Skinner MH, Kuan HY, Pan A, Sathirakul K, Knadler MP, Gonzales CR, Yeo KP, Reddy S, Lim M, Ayan-Oshodi M, and Wise SD (2003) Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clinical pharmacology and therapeutics 73:170-177.
				60mg qd			Metoprolol (2D6)	2.0	11	0.86	no data	no data		no data	no data	0.36 (2D6)	no data			Preskorn SH, Greenblatt DJ, Flockhart D, Luo Y, Perloff ES, Harmatz JS, Baker B, Klick-Davis A, Desta Z, and Burt T (2007) Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. Journal of clinical psychopharmacology 27:28-34.
																				Knadler MP, Lobo E, Chappell J, and Bergstrom R (2011) Duloxetine: clinical pharmacokinetics and drug interactions. Clinical pharmacokinetics 50:281-294.
4	Efavirenz	8-Hydroxyefavirenz	315.7	600mg qd	1A2 (no inhibition), CYP2B6, 2C8, 2C9, 2C19, 2D6 (no inhition), 3A (weak inhibition)	1.7, 4.8, 20, 21, 40	induction masks inhibition	no data	184	13	no data	no data		no data	no data	7.6	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020972s042,021360s030lbl.pdf
																				Sustiva (efavirenz) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2012.
					CYP2C8	4.8	Amodiaquine (2C8)	4.0												German P, Greenhouse B, Coates C, Dorsey G, Rosenthal PJ, Charlebois E, Lindegardh N, Havlir D, and Aweeka FT (2007) Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 44:889-891.
					CYP2C9	19.5	Phenytoin (2C9)	2.1												Robertson SM, Penzak SR, Lane J, Pau AK, and Mican JM (2005) A potentially significant interaction between efavirenz and phenytoin: a case report and review of the literature. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 41:e15-18.
					CYP2C19	21.3	induction masks inhibition	no data												Xu C and Desta Z (2013) In vitro analysis and quantitative prediction of efavirenz inhibition of eight cytochrome P450 (CYP) enzymes: major effects on CYPs 2B6, 2C8, 2C9 and 2C19. Drug metabolism and pharmacokinetics 28:362-371.
					CYP3A	40.3	induction masks inhibition	no data												Robertson SM, Maldarelli F, Natarajan V, Formentini E, Alfaro RM, and Penzak SR (2008) Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects. Journal of acquired immune deficiency syndromes (1999) 49:513-519.
																				Ogburn ET, Jones DR, Masters AR, Xu C, Guo Y, and Desta Z (2010) Efavirenz primary and secondary metabolism in vitro and in vivo: identification of novel metabolic pathways and cytochrome P450 2A6 as the principal catalyst of efavirenz 7-hydroxylation. Drug metabolism and disposition: the biological fate of chemicals 38:1218-1229.
Unassigned	Enalapril		376.4	10-40mg qd	no data available	no data	no DDI study reported	no data	0.35 (ss value after 10 mg qd for 7 days)	0.24 (ss value after 10 mg qd for 7 days)				no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/018998s076lbl.pdf
		Enalaprilat	384.4								0.83 (ss value, Day 7)	0.11 (ss value, Day 7)	M/P ratio: 2.4; M/total: ~0.7							Tian L, Liu H, Xie S, Jiang J, Han L, Huang Y, and Li Y (2011) Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single - and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men. Clinical Therapeutics 33: 655-663.
Unassigned	Enoxaparin	no data	5 Kd	30-150mg	no metabolism or DDI data	no data	no DDI study conducted	no data	Plasma PK expressed as IU/mL	Plasma PK expressed as IU/mL	no data	no data	no data	no data	no data	no data	no data	no data	no data	No perpetrator DDI info available based on ref 1

4	Erlotinib		394.4	100md qd	CYP2C8, 3A	3.1, 10	OSI-930 (a CYP3A substrate)	2	36	3.5	1.8	0.19	no data	no data	no data	1.1 (2C8)	no data	no data	no data	Ling J, Johnson KA, Miao Z, Rakhit A, Pantze MP, Hamilton M, Lum BL, and Prakash C (2006) Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. Drug metabolism and disposition: the biological fate of chemicals 34:420-426. Interaction between OSI-930 and erlotinib (inhibition of CYP3A): Eur J of Cancer (2013): 49: 782-789
		O-Desmethylerlotinib	379.4	150mg qdx24					27	5.4										Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, Eckhardt SG, Tolcher A, Britten CD, Denis L, Ferrante K, Von Hoff DD, Silberman S, and Rowinsky EK (2001) Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 19:3267-3279.
Unassigned	Erythropoietin	no data	36 Kd	40000 units /week	not applicable (protein)															Protein drug-no CYP interaction or metabolism data available
3	Escitalopram		324.4	30mg qd	no inhibtion of major CYP450s	35	Desipramine (2D6)	2.0	3.4	0.2	1.2	0.06	0.35			0.006		no data	no data	von Moltke LL, Greenblatt DJ, Giancarlo GM, Granda BW, Harmatz JS, and Shader RI (2001) Escitalopram (S-citalopram) and its metabolites in vitro: cytochromes mediating biotransformation, inhibitory effects, and comparison to R-citalopram. Drug metabolism and disposition: the biological fate of chemicals 29:1102-1109.
		N-Desmethylcitalopram	310.2											15-fold more potent inhibitor of CYP2D6 (2.3 μM)	2.3 μM for 2D6		0.03			
4	Esomeprazole		345.4	40mg qd	CYP2C19	8, 0.75 (after incubation)	Diazepam	1.8 (with 30 mg esomeprazole)	11.2	4.64						0.67 (EM), 3.2 (PM)		CYP2C19 K_I=0.87,K $_{inact}$=0.049		Ogilvie BW, Yerino P, Kazmi F, Buckley DB, Rostami-Hodjegan A, Paris BL, Toren P, and Parkinson A (2011) The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel. Drug metabolism and disposition: the biological fate of chemicals 39:2020-2033.
																				Andersson T, Hassan-Alin M, Hasselgren G and Röhss K (2001) Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. Clinical Pharmacokinetics 40: 523-537.
		Omeprazole sufone	361.4								16.2	1.71	M/P: 1.5, M/total: ~0.57	CYP2C19 (rev and TDI)	6,2.8 (post incubation)		0.2		CYP2C19 K_I = 5.7 μM, K_{inact} = 0.015 min-1	Hassan-Alin M, Andersson T, Bredberg E and Röhss K (2000) Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. European Journal of Clinical Pharmacology 56:665-670.
		5'-Hydroxyomeprazole	361.4								0.97	0.28	M/P: 0.09, M/total: ~0.03	CYP2C19	>100 (IC50)		NC (not calculated)			Shirasaka Y, Sager JE, Lutz JD, Davis C, and Isoherranen N (2013) Inhibition of CYP2C19 and CYP3A4 by omeprazole metabolites and their contribution to drug-drug interactions. Drug metabolism and disposition: the biological fate of chemicals 41:1414-1424.
Unassigned	Estrogen	no data		2*0.625mg	no data	no data	no data	no data	46.46ng.h/ml	3.27ng/ml	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203752lbl.pdf
Unassigned	Eszopiclone	no data	388.8	3mg qd	no data	no data	NO interaction with warfarin and digoxin and minimal effect on lorazepam	no interaction	0.72	0.10	no data	no data	no data	no data	no data	no data	no data	no data	no data	Greenblatt DJ and Zammit GK (2012) Pharmacokinetic evaluation of eszopiclone: clinical and therapeutic implications. Expert opinion on drug metabolism & toxicology 8:1609-1618.
		Desmethyleszopiclone	374.0								0.07	0.034	0.1	no data	no data	no data	no data	no data	no data	
2	Ezetimibe		409.4	10mg qd	CYP2B6, 3A	5.1, 0.12	Efavirenz (2B6)	no interaction	0.13	0.12	0.8	0.13	6.15	no data	no data	1 (CYP3A)	not calculated	no data	no data	Oswald S, Meyer zu Schwabedissen HE, Nassif A, Modess C, Desta Z, Ogburn ET, Mostertz J, Keiser M, Jia J, Hubeny A, Ulrich A, Runge D, Marinova M, Lutjohann D, Kroemer HK, and Siegmund W (2012) Impact of efavirenz on intestinal metabolism and transport: insights from an interaction study with ezetimibe in healthy volunteers. Clinical pharmacology and therapeutics 91:506-513.

							Simvastatin (3A)	no interaction												Kosoglou T, Meyer I, Veltri EP, Statkevich P, Yang B, Zhu Y, Mellars L, Maxwell SE, Patrick JE, Cutler DL, Batra VK, and Affrime MB (2002) Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. British journal of clinical pharmacology 54:309-319.
		Ezetimibe glucuronide	585.4																	Parkinson A, Kazmi F, Buckley DB, Yerino P, Ogilvie BW, and Paris BL (2010) System-dependent outcomes during the evaluation of drug candidates as inhibitors of cytochrome P450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes: human hepatocytes versus liver microsomes versus recombinant enzymes. Drug metabolism and pharmacokinetics 25:16-27.
1	Famotidine		337.5	40mg qd	CYP2B6, 2C19, 2D6, 3A	82, >100, 189, 365	Aminopyrine	no interaction	2.2	0.31						0.002				http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022310s000_ClinPharmR.pdf
							Antipyrine	no interaction												Ohbuchi M, Noguchi K, Kawamura A, and Usui T (2012) Different effects of proton pump inhibitors and famotidine on the clopidogrel metabolic activation by recombinant CYP2B6, CYP2C19 and CYP3A4. Xenobiotica; the fate of foreign compounds in biological systems 42:633-640.
							Diazepam (3A)	no interaction												Humphries TJ (1987) Famotidine: a notable lack of drug interactions. Scandinavian journal of gastroenterology Supplement 134:55-60.
							Theophyline (1A2)	no interaction												Moody DE, Liu F, and Fang WB (2013) In vitro inhibition of methadone and oxycodone cytochrome P450-dependent metabolism: reversible inhibition by H2-receptor agonists and proton-pump inhibitors. Journal of analytical toxicology 37:476-485.
							Phenytoin (2C9)	no interaction												Echizen H and Ishizaki T (1991) Clinical pharmacokinetics of famotidine. Clinical pharmacokinetics 21:178-194.
							Warfarin (2C9)	no interaction												
2	Fenofibrate		360.8	50-150mg qd	CYP2C8, 3A	82, > 75	Repaglinide (2C8)	no interaction	268 (200mg)	14.7 (200 mg)	no data	no data	not calculated	no data	no data	0.18 (CYP2C8), <0.2 (CYP3A)	not calculated	no data	no data	Weil A, Caldwell J, and Strolin-Benedetti M (1990) The metabolism and disposition of 14C-fenofibrate in human volunteers. Drug metabolism and disposition: the biological fate of chemicals 18:115-120.
		Fenofibric acid	318.8				Simvastatin (3A)	no interaction												Kajosaari LI, Laitila J, Neuvonen PJ, and Backman JT (2005) Metabolism of repaglinide by CYP2C8 and CYP3A4 in vitro: effect of fibrates and rifampicin. Basic & clinical pharmacology & toxicology 97:249-256.
		Fenofibric acid glucuronide	494.9																	Kajosaari LI, Backman JT, Neuvonen M, Laitila J, and Neuvonen PJ (2004) Lack of effect of bezafibrate and fenofibrate on the pharmacokinetics and pharmacodynamics of repaglinide. British journal of clinical pharmacology 58:390-396.
																				Kosoglou T, Statkevich P, Fruchart JC, Pember LJ, Reyderman L, Cutler DL, Guillaume M, Maxwell SE, and Veltri EP (2004) Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. Current medical research and opinion 20:1197-1207.
																				Bergman AJ, Murphy G, Burke J, Zhao JJ, Valesky R, Liu L, Lasseter KC, He W, Prueksaritanont T, Qiu Y, Hartford A, Vega JM, and Paolini JF (2004) Simvastatin does not have a clinically significant pharmacokinetic interaction with fenofibrate in humans. Journal of clinical pharmacology 44:1054-1062.
1*	Fentanyl		336.5	200 ug IV	CYP3A	24	Midazolam (3A)	no interaction	0.011	0.01			1.2	no data	no data	0.0004 (3A)	no data	no data	no data	Oda Y, Mizutani K, Hase I, Nakamoto T, Hamaoka N, and Asada A (1999) Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 in vitro. British journal of anaesthesia 82:900-903.

		Norfentanyl	332.0								0.0130	0.00078								Hase I, Oda Y, Tanaka K, Mizutani K, Nakamoto T, and Asada A (1997) I.v. fentanyl decreases the clearance of midazolam. British journal of anaesthesia 79:740-743.
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019813s044lblnew.pdf
																				Ziesenitz, VC, Skopp, G, Konig, SK, Burhenne, J, Mahlke, N, and Mikas, G, (2011, September) Pharmacokinetic interaction between the opiod-analgesic fentanyl and the CYP3A inhibitor ketoconazole. Poster session presented at Painweek 2011, Las Vegas, Nevada, USA
																				http://www.klinikum.uni-heidelberg.de/fileadmin/medizinische_klinik/Abteilung_6/pdf/Poster_Painweek2011_K292_V7_final.pdf
Unassigned	Fexofenadine	no data	501.7	60mg sd	no data	no data	Omeprazole (2C19)	no interaction	R: 1.6; S: 1.0	R: 0.3; S: 0.2	no data	no data	no data	no data	no data	no data	no data	no data	no data	Miura M, Uno T, Tateishi T, and Suzuki T (2007) Pharmacokinetics of fexofenadine enantiomers in healthy subjects. Chirality 19:223-227.
																				Takahata T, Yasui-Furukori N, Yoshiya G, Uno T, Sugawara K, Tateishi T. (2013) Fexofenadine does not affect omeprazole pharmacokinetics: both are putative P-glycoprotein substrates. Drug Metabolism and disposition: the biological fate of chemicals 41:60-71.
Unassigned	Filgrastim	no data	19 Kd	5-10 µg/kg/day (IV or SC)	no data	no data	no data	no data	0.0528 (10 µg/kg single IV dose)	0.0230 (10 µg/kg single IV dose)	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/1998/filgamg040298lb.pdf
																				Lubenau H, Bias P, Maly AK, Siegler KE, and Mehltretter K (2009) Pharmacokinetic and pharmacodynamic profile of new biosimilar filgrastim XM02 equivalent to marketed filgrastim Neupogen: single-blind, randomized, crossover trial. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy 23:43-51.
Unassigned	Finasteride		372.6	5mg qd	no data on in vitro inhibition	no data	Digoxin	no interaction	1.0	0.10	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020180s037lbl.pdf
		omega-Hydroxyfinasteride	388.0				Propranalol	no interaction												Carlin JR, Hoglund P, Eriksson LO, Christofalo P, Gregoire SL, Taylor AM, and Andersson KE (1992) Disposition and pharmacokinetics of [14C]finasteride after oral administration in humans. Drug metabolism and disposition: the biological fate of chemicals 20:148-155.
		Finasteride-omega-oic acid	402.0				Theofylline (1A2)	no interaction												
4	Fluconazole	no data	306.3	400mg single	CYP2C9, 2C19, 3A	15.2, 6.2, 6.6	Midazolam (3A)	4.9	no data	16.6	no data	no data	not calculated	no data	no data	2.5	no data	no data	no data	Niwa T, Shiraga T, and Takagi A (2005) Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. Biological & pharmaceutical bulletin 28:1805-1808.
				400mg qd			S-Warfarin (2C9)	2.8	no data	70.4	no data	no data	not calculated	no data	no data	4.6	no data			Brammer KW, Coakley AJ, Jezequel SG, and Tarbit MH (1991) The disposition and metabolism of [14C]fluconazole in humans. Drug metabolism and disposition: the biological fate of chemicals 19:764-767.
				100mg qd			Omeprazole (2C19)	6.3	no data	14.4	no data	no data	not calculated	no data	no data	2.3	no data			Kharasch ED, Walker A, Hoffer C, and Sheffels P (2005) Evaluation of first-pass cytochrome P4503A (CYP3A) and P-glycoprotein activities using alfentanil and fexofenadine in combination. Journal of clinical pharmacology 45:79-88.
				150mg single			PK only	PK only	34	14	no data	no data	not calculated	no data	no data	2.3	no data			Sakaeda T, Iwaki K, Kakumoto M, Nishikawa M, Niwa T, Jin JS, Nakamura T, Nishiguchi K, Okamura N, and Okumura K (2005) Effect of micafungin on cytochrome P450 3A4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. The Journal of pharmacy and pharmacology 57:759-764.

																				Black DJ, Kunze KL, Wienkers LC, Gidal BE, Seaton TL, McDonnell ND, Evans JS, Bauwens JE, and Trager WF (1996) Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. Drug metabolism and disposition: the biological fate of chemicals 24:422-428.
																				Kang BC, Yang CQ, Cho HK, Suh OK, and Shin WG (2002) Influence of fluconazole on the pharmacokinetics of omeprazole in healthy volunteers. Biopharmaceutics & drug disposition 23:77-81.
																				Palma-Aguirre, JA, Lopez-Gamboa, M, Castro-Sandoval, TdJ, Henandez-Gonzalez, R, Mejia-Callejas, J, Melchor-Baltazar, MdlA, and Canales-Gomez, JS (2010) Bioequivalence of two oral fluconazole formulations in healthy subjects: a single dose, open label, randomized, two-period crossover study. Journal of Bioequivalence & Bioavailability 2:23-27.
4	Fluoxetine		309.3	60mg qd 1 week	[R] CYP2C9, 2C19, 2D6, 3A	31, 2.3, 0.86, 80	Desipramine (2D6)	7.4		0.42				no data	no data	7.5	no data	CYP2C19 KI = 2 µM, kinact = 0.017 min-1	no data	VandenBrink BM, Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2012) Prediction of CYP2D6 drug interactions from in vitro data: evidence for substrate-dependent inhibition. Drug metabolism and disposition: the biological fate of chemicals 40:47-53.
				20mg sd	[S] CYP2C9, 2C19, 2D6, 3A	31, 34, 0.068, 47	Dextromethorphan (2D6)	27	2.6	0.046	9.5	0.036				0.82				Preskorn SH, Alderman J, Chung M, Harrison W, Messig M, and Harris S (1994) Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. Journal of clinical psychopharmacology 14:90-98.
							Omeprazole (2C19)	7.1										CYP3A KI = 21 µM, kinact = 0.055 min-1		Nelson MH, Birnbaum AK, and Remmel RP (2001) Inhibition of phenytoin hydroxylation in human liver microsomes by several selective serotonin re-uptake inhibitors. Epilepsy research 44:71-82.
							Lansoprazole (2C19)	2.6												Bergstrom RF, Peyton AL, and Lemberger L (1992) Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. Clinical pharmacology and therapeutics 51:239-248.
							Alprazolam (3A)	1.3												Vlase L, Popa A, Neag M, Muntean D, and Leucuta SE (2011) Effect of fluoxetine on the pharmacokinetics of lansoprazole: a two-treatment period study in healthy male subjects. Clinical drug investigation 31:727-733.
																				Hall J, Naranjo CA, Sproule BA, and Herrmann N (2003) Pharmacokinetic and pharmacodynamic evaluation of the inhibition of alprazolam by citalopram and fluoxetine. Journal of clinical psychopharmacology 23:349-357.
																				Sager JE, Lutz JD, Foti RS, Davis C, Kunze KL, and Isoherranen N (2014) Fluoxetine- and norfluoxetine-mediated complex drug-drug interactions: in vitro to in vivo correlation of effects on CYP2D6, CYP2C19, and CYP3A4. Clinical pharmacology and therapeutics 95:653-662.
							Midazolam (3A)	0.8												Alfaro CL, Lam YW, Simpson J, and Ereshefsky L (2000) CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. Journal of clinical pharmacology 40:58-66.
							Lovastatin (3A)	0.94												Brunswick DJ, Amsterdam JD, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, and Beasley CM, Jr. (2002) Fluoxetine and norfluoxetine plasma concentrations during relapse-prevention treatment. Journal of affective disorders 68:243-249.
																				Stevens JC and Wrighton SA (1993) Interaction of the enantiomers of fluoxetine and norfluoxetine with human liver cytochromes P450. The Journal of pharmacology and experimental therapeutics 266:964-971.

		Norfluoxetine	295.3	20mg qd										[R] CYP2C9, 2C19, 2D6, 3A	51, 15, 0.5, 5.1					Otton SV, Wu D, Joffe RT, Cheung SW, and Sellers EM (1993) Inhibition by fluoxetine of cytochrome P450 2D6 activity. Clinical pharmacology and therapeutics 53:401-409.
														[S] CYP2C9, 2C19, 2D6, 3A	51, 4.1, 0.035, 11					Chauret N, Dobbs B, Lackman RL, Bateman K, Nicoll-Griffith DA, Stresser DM, Ackermann JM, Turner SD, Miller VP, and Crespi CL (2001) The use of 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin (AMMC) as a specific CYP2D6 probe in human liver microsomes. Drug metabolism and disposition: the biological fate of chemicals 29:1196-1200.
																				Keller T, Cambon N, Genevray M, Crivelli F, Crivelli M, Dal BL, Mazzucchelli P, Ismaili S, and Marzo A (2005) Bioequivalence study of fluoxetine hydrochloride in healthy volunteers. Arzneimittel-Forschung 55:491-497.
2	Fluticasone		444.5	110µg qd (as furoate)	CYP3A TDI		probe substrate of CYP3A not tested	no data	NA	BDL	no data		not Calculated	no data	no data	no data	no data	CYP3A4 KI = 3.5 µM, kinact = 0.006 min-1	no data	Falcoz C, Oliver R, McDowall JE, Ventresca P, Bye A, and Daley-Yates PT (2000) Bioavailability of orally administered micronised fluticasone propionate. Clinical pharmacokinetics 39 Suppl 1:9-15.
			396.4	220µg qd (as propionate)														CYP3A5 KI = 16 µM, kinact = 0.027 min-1		Murai T, Reilly CA, Ward RM, and Yost GS (2010) The inhaled glucocorticoid fluticasone propionate efficiently inactivates cytochrome P450 3A5, a predominant lung P450 enzyme. Chemical research in toxicology 23:1356-1364.
		17b-Carboxylic acid									NA	BDL								Hughes SC, Shardlow PC, Hollis FJ, Scott RJ, Motivaras DS, Allen A, and Rousell VM (2008) Metabolism and disposition of fluticasone furoate, an enhanced-affinity glucocorticoid, in humans. Drug metabolism and disposition: the biological fate of chemicals 36:2337-2344.
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022051s007lbl.pdf
4	Fluvastatin	no data	411.5	40mg sd	CYP2C9	0.28	Diclofenac (2C9)	1.3	0.79	0.48	no data	no data	not calculated	no data	no data	1.7	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021192s019lbl.pdf
																				Appel S, Rufenacht T, Kalafsky G, Tetzloff W, Kallay Z, Hitzenberger G, and Kutz K (1995) Lack of interaction between fluvastatin and oral hypoglycemic agents in healthy subjects and in patients with non-insulin-dependent diabetes mellitus. The American journal of cardiology 76:29A-32A.
																				Transon C, Leemann T, Vogt N, and Dayer P (1995) In vivo inhibition profile of cytochrome P450TB (CYP2C9) by (+/-)-fluvastatin. Clinical pharmacology and therapeutics 58:412-417.
																				Transon C, Leemann T, and Dayer P (1996) In vitro comparative inhibition profiles of major human drug metabolising cytochrome P450 isozymes (CYP2C9, CYP2D6 and CYP3A4) by HMG-CoA reductase inhibitors. European journal of clinical pharmacology 50:209-215.
																				Kivisto KT, Kantola T, and Neuvonen PJ (1998) Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. British journal of clinical pharmacology 46:49-53.
							S-Warfarin	1.4												Kim MJ, Nafziger AN, Kashuba AD, Kirchheiner J, Bauer S, Gaedigk A, and Bertino JS, Jr. (2006) Effects of fluvastatin and cigarette smoking on CYP2C9 activity measured using the probe S-warfarin. European journal of clinical pharmacology 62:431-436.
1	Gabapentin	no data	171.2	1200mg qd	no inhibition of major P450s	no data	Phenytoin (2C9)	no interaction	647	52	no data	no data	no data	no data	no data	no data	no data	no data	no data	McLean MJ (1994) Clinical pharmacokinetics of gabapentin. Neurology 44:S17-22; discussion S31-12.

							Carbamazepine	no interaction												Cowles VE, Gordi T, and Hou SY (2012) Steady-state pharmacokinetics of gabapentin after administration of a novel gastroretentive extended-release formulation in postmenopausal women with vasomotor symptoms. Clinical drug investigation 32:593-601.
							Valproic acid	no interaction												
							Phenobarbital	no interaction												
							Naproxin	no interaction												
							Morphine	no interaction												
							Ethynylestradiol	no interaction												
3	Gemfibrozil		250.3	600mg BID	CYP2C8, 2C9, 3A	30, 5.8, >150	Warfarin (2C9)	<1.0 (after 600 mg BID)												Niemi M, Backman JT, Neuvonen M and Neuvonen PJ (2003) Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of rapaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. Diabetologia 46: 347-351.
							Simvastatin (CYP3A, OATP)	1.4 (after 600 mg BID)						CYP3A4/5	>150	NA	NA	NA		Ogilvie BW, Zhang D, Li W, Rodrigues D, Gipson AE, Holsapple J, Toren P, and Parkinson (2006) Glucuronidation converts gemfibrozil to a potent, metabolism-dependent inhibitor of CYP2C8: implications for drug-drug interactions. Drug Metabolism and Disposition: the biological fate of chemicals 34: 191-197.
							Repaglinide (2C8)	1.8 (after 30 mg single dose)	8.4	5.6	2.2	1.2	M/P: 0.26	CYP2C8	0.9 (after incubation)	0.186667	1.3		CYP2C8 K_I = 20, kinact: 0.21 min^{-1}	Wen X, Wang, J-S, Backman JT, Kivistö KT, and Neuvonen PJ (2001) Gemfibrozil is a potent inhibitor of human cytochrome P450 2C9. Drug Metabolism and Disposition: the biological fate of chemicals 29: 1359-1361.
		Gemfibrozil glucuronide	426.5				Repaglinide (2C8)	8.1 (after 600 mg BID)												Kojosaari LI, Laitila J, Neuonen PJ, and Backman JT (2005) Metabolism of repaglinide by CYP2C8 and CYP3A4 in vitro: effect of fibrates and rifampin. Basic and Clinical Pharmacology and Toxicology 97: 249-256.
																				Backman JT, Kryklund C, Kivistö KT, Wang J-S, and Neuvonen PJ (2000) Plasma concentrations of active simvastatin acid are increased by gemfibrozil. Clinical Pharmacology and Therapeutics 68: 122-129.
																				Hokalammi J, Niemi M, Neuvonen PJ, and Backman JT (2011) Dose-dependent interaction between gemfibrozil and repaglinide in humans: strong inhibition of CYP2C8 with subtherapeutic gemfibrozil doses. Drug Metabolism and Disposition: the biological fate of chemicals 39: 1977-1986.
																				Lilja JJ, Backman JT, and Neuvonen PJ (2004) Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. British Journal of Clinical Pharmacology 59: 433-439.
1	Glimepiride		490.6	1mg	CYP2C9	2	no CYP2C9 substrate tested	no data	6.5	1.1	no data	no data	no data	no data	no data	0.55	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020496s015lbl.pdf
		Cyclohexyl hydroxymethyl metabolite (M1)	506.0																	
		Carboxyl derivative (M2)	520.0																	
Unassigned	Goserelin	no data	1269.4	10.8mg q12wk	no data (synthetic polypeptide)	no data	no DDI study reported	no data	0.0082	0.002	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020578s028s029s030lbl.pdf
																				Cockshott ID (2000) Clinical pharmacokinetics of goserelin. Clinical pharmacokinetics 39:27-48.
4	Imatinib		493.6	400mg qd	CYP2C8, 2D6, 3A	8.4, 7.5, 23	Simvastatin (3A)	3.5	52	3.3	no data	no data	no data	no data	no data	0.39 (2C8), 0.44 (2D6), 0.14 (3A)	no data	no data	no data	Filppula AM, Laitila J, Neuvonen PJ, and Backman JT (2012) Potent mechanism-based inhibition of CYP3A4 by imatinib explains its liability to interact with CYP3A4 substrates. British journal of pharmacology 165:2787-2798.
			493.6				Irinotecan	1.6												Johnson FM, Krug LM, Tran HT, Shoaf S, Prieto VG, Tamboli P, Peeples B, Patel J, and Glisson BS (2006) Phase I studies of imatinib mesylate combined with cisplatin and irinotecan in patients with small cell lung carcinoma. Cancer 106:366-374.

			493.6	239mg sd					22	1.9										Peng B, Lloyd P, and Schran H (2005) Clinical pharmacokinetics of imatinib. Clinical pharmacokinetics 44:879-894.
		N-Desmethylimatinib	479.6	239mg sd							3.5	0.24	0.160	CYP2C8, 2D6, 3A	12.8, 13.5, 18.1					Gschwind HP, Pfaar U, Waldmeier F, Zollinger M, Sayer C, Zbinden P, Hayes M, Pokorny R, Seiberling M, Ben-Am M, Peng B, and Gross G (2005) Metabolism and disposition of imatinib mesylate in healthy volunteers. Drug metabolism and disposition: the biological fate of chemicals 33:1503-1512.
																				Frye RF, Fitzgerald SM, Lagattuta TF, Hruska MW, and Egorin MJ (2004) Effect of St John's wort on imatinib mesylate pharmacokinetics. Clinical pharmacology and therapeutics 76:323-329.
2	Irbesartan		428.5	300mg qd	weak 2C9	24	Warfarin (2C9)	no interaction	46	7.7	no data	no data	no data	no data	no data	0.32	no data	no data	no data	Taavitsainen P, Kiukaanniemi K, and Pelkonen O (2000) In vitro inhibition screening of human hepatic P450 enzymes by five angiotensin-II receptor antagonists. European journal of clinical pharmacology 56:135-140.
		Glucuronide (minor, 6% in Plasma)	604.7				Digoxin	no interaction												
							Nifedipine (3A)	no interaction												
1	Irinotecan		586.7	340mg/m2 infusion	CYP3A	129	no data	no data	35	5.8				no data	no data	0.05		CYP3A KI = 24 µM, kinact = 0.06 min-1		http://www.drugbank.ca/drugs/DB00762#enzymes, http://labeling.pfizer.com/ShowLabeling.aspx?id=533
		SN-38	392.4		CYP2A6, 2C9, 3A	181, 156, 121					1.2	0.14	0.034				0.001		CYP3A KI = 26 µM, kinact = 0.10 min-1	Hanioka N, Ozawa S, Jinno H, Tanaka-Kagawa T, Nishimura T, Ando M, and Sawada Ji J (2002) Interaction of irinotecan (CPT-11) and its active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) with human cytochrome P450 enzymes. Drug metabolism and disposition: the biological fate of chemicals 30:391-396.
Unassigned	Lamotrigine		256.1	25-250mg bid	no data	no data	no data	no data	117−824	2.3-18.0	not reported	not reported	not calculated	no data	no data	not calculated	Not calculated	No data	no data	Warner T, Patsalos PN, Prevett M, Elyas AA, and Duncan JS (1992) Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. Epilepsy research 11:147-150.
		2-N-lamotrigine glucuronide	432.1																	http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022251,020764s029,020241s036lbl.pdf
2	Lansoprazole		369.4	30mg qd	CYP2C19	0.6	Clopidogrel	0.99	7.2	2.8					no data	4.7	Not calculated	No data	no data	Landes BD, Petite JP, and Flouvat B (1995) Clinical pharmacokinetics of lansoprazole. Clinical pharmacokinetics 28:458-470.
		Sulfone	385.4								1.19	0.23	M/P 0.17	Data not available						Small DS, Farid NA, Payne CD, Weerakkody GJ, Li YG, Brandt JT, Salazar DE, and Winters KJ (2008) Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. Journal of clinical pharmacology 48:475-484.
		Hydroxylansoprazole	385.4								0.29	0.18	M/P <0.1	Data not available						Itagaki M, Homma M, Yuzawa K, Nishimura M, Naito S, Ueda N, Ohkohchi N and Kohda Y (2004) Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. Journal of Pharmacy and Pharmacology 56: 1055-1059.
Unassigned	Latanoprost	no data	432.6	ophthalmic solution	no data	no data	no data	no data	no data	no data (ophthalmic solution)	no data	no data	not calculated	no data	no data	no data	no data	no data	no data	
1	Letrozole		285.3	2.5mg qd	CYP2A6, 2C19, no effects on other CYP450s	4.6, 42.2	Everolimus	no interaction	8.9	0.47						0.1 for CYP2A6 and 0.01 for CYP2C19		no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020726s024lbl.pdf
		4,4'-Methanol-bisbenzonitrile	234.3		CYP2B6, 2C19	17, 10	Lapatinib	no interaction			no data	no data	not calculated	CYP2B6, 2C19	IC50 for CYP2C19: 19.5 uM, CYP2B6: 33.1 uM		no data			Jeong S, Woo MM, Flockhart DA, and Desta Z (2009) Inhibition of drug metabolizing cytochrome P450s by the aromatase inhibitor drug letrozole and its major oxidative metabolite 4,4'-methanol-bisbenzonitrile in vitro. Cancer chemotherapy and pharmacology 64:867-875.

							Methadone	1.2												Lu WJ, Thong N, Flockhart DA. (2012) Reduced methadone clearance during aromatase inhibition. J Clin Psychopharmacol. 2012 32:511-7.
																				Chu QS, Cianfrocca ME, Goldstein LJ, Gale M, Murray N, Loftiss J, Arya N, Koch KM, Pandite L, Fleming RA, Paul E, and Rowinsky EK (2008) A phase I and pharmacokinetic study of lapatinib in combination with letrozole in patients with advanced cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 14:4484-4490.
																				Pfister CU, Martoni A, Zamagni C, Lelli G, De Braud F, Souppart C, Duval M, and Hornberger U (2001) Effect of age and single versus multiple dose pharmacokinetics of letrozole (Femara) in breast cancer patients. Biopharmaceutics & drug disposition 22:191-197.
																				Awada A, Cardoso F, Fontaine C, Dirix L, De Greve J, Sotiriou C, Steinseifer J, Wouters C, Tanaka C, Zoellner U, Tang P, and Piccart M (2008) The oral mTOR inhibitor RAD001 (everolimus) in combination with letrozole in patients with advanced breast cancer: results of a phase I study with pharmacokinetics. European journal of cancer 44:84-91.
Unassigned	Levalbuterol		239.3	90 µg q4-6h (aerosol)	no data	no data	no data	no data	0.013 (after 1.25 mg nebulizer dose)	0.005 (after 1.25 mg nebulizer dose)	no data	no data	no data	no data	no data	no data	no data	no data	no data	Gumbhir-Shah K, Kellerman DJ, DeGraw S, Koch P, and Jusko WJ (1998) Pharmacokinetic and pharmacodynamic characteristics and safety of inhaled albuterol enantiomers in healthy volunteers. Journal of clinical pharmacology 38:1096-1106.
				0.63-1.25 mg q6-8h (nebulizer)																Boulton DW and Fawcett JP (2001) The pharmacokinetics of levosalbutamol: what are the clinical implications? Clinical pharmacokinetics 40:23-40.
1	Levetiracetam		170.2	1500mg sd	CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A	>1000	Carbamazepam (3A)	no interaction	2000	277						<0.28				Patsalos PN (2004) Clinical pharmacokinetics of levetiracetam. Clinical pharmacokinetics 43:707-724.
		Carboxylic acid	171.0		None		Valproic Acid (2C9)	no interaction			no data	no data	no data	no data	no data		no data	no data	no data	Strolin Benedetti M, Whomsley R, Nicolas JM, Young C, and Baltes E (2003) Pharmacokinetics and metabolism of 14C-levetiracetam, a new antiepileptic agent, in healthy volunteers. European journal of clinical pharmacology 59:621-630.
																				Otoul C, De Smedt H, and Stockis A (2007) Lack of pharmacokinetic interaction of levetiracetam on carbamazepine, valproic acid, topiramate, and lamotrigine in children with epilepsy. Epilepsia 48:2111-2115.
																				Nicolas JM, Collart P, Gerin B, Mather G, Trager W, Levy R, and Roba J (1999) In vitro evaluation of potential drug interactions with levetiracetam, a new antiepileptic agent. Drug metabolism and disposition: the biological fate of chemicals 27:250-254.
																				Zhao Q, Jiang J, Li X, Lu ZS, and Hu P (2007) Single-dose pharmacokinetics of levetiracetam in healthy Chinese male subjects. British journal of clinical pharmacology 63:614-617.
2	Levofloxacin	no data	361.4	250-750mg qd	CYP2C9	105	Warfarin (2C9)	no interaction	252 (ss value 750 mg qd)	23.8 (ss value 750 mg qd)	no data	no data	no data	no data	no data	0.23	no data	no data	no data	Zhang L, Wei MJ, Zhao CY, and Qi HM (2008) Determination of the inhibitory potential of 6 fluoroquinolones on CYP1A2 and CYP2C9 in human liver microsomes. Acta pharmacologica Sinica 29:1507-1514.

							Cyclosporine (3A)	1.3											http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021721s020_020635s57_020634s52_lbl.pdf
							Tacrolimus (3A)	1.3											Fish DN and Chow AT (1997) The clinical pharmacokinetics of levofloxacin. Clinical Pharmacokinetics 32:101-119.
							Theophylline (1A2)	no interaction											Federico S, Carrano R, Capone D, Gentile A, Palmiero G, and Basile V (2006) Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients: ciclosporin, tacrolimus and levofloxacin in renal transplantation. Clinical pharmacokinetics 45:169-175.
1	Levothyroxine	no data	776.9	600 µg qd	CYP2C8	1.7	no data	no data	3.4	0.091	no data	no data	no data	no data	no data	0.053	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021402s017lbl.pdf
																				Walsky RL, Gaman EA, and Obach RS (2005) Examination of 209 drugs for inhibition of cytochrome P450 2C8. Journal of clinical pharmacology 45:68-78.
																				Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, and Braverman LE (2004) Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? Thyroid : official journal of the American Thyroid Association 14:191-200.
1	Lidocaine		234.3		does not inhibit tacrolimus and imipramine	no data	no data	no data	no data	0.55	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/010417s027lbl.pdf; Am J. Health Syst Pharm 2003 59: 1258-66.
1	Linezolid		337.4	600mg qd	does not inhibit major CYP450s	not calculated	no data	no data	409	63	no data	no data	not calculated	no data	no data	not calculated	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021130s028lbl.pdf
																				Wynalda MA, Hauer MJ, and Wienkers LC (2000) Oxidation of the novel oxazolidinone antibiotic linezolid in human liver microsomes. Drug metabolism and disposition: the biological fate of chemicals 28:1014-1017.
																				Slatter JG, Stalker DJ, Feenstra KL, Welshman IR, Bruss JB, Sams JP, Johnson MG, Sanders PE, Hauer MJ, Fagerness PE, Stryd RP, Peng GW, and Shobe EM (2001) Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of [(14)C]linezolid to healthy human subjects. Drug metabolism and disposition: the biological fate of chemicals 29:1136-1145.
4	Lopinavir		628.8	400/100mg bid	CYP2C9, 2C19, 2D6, 3A	6.9, 14, 6.8, 0.76	Atorvastatin (3A)	5.9	132	16	no data	no data	no data	no data	no data	21	no data	CYP3A KI = 1.0 µM, kinact = 0.11 min-1	no data	Ernest CS, 2nd, Hall SD, and Jones DR (2005) Mechanism-based inactivation of CYP3A by HIV protease inhibitors. The Journal of pharmacology and experimental therapeutics 312:583-591.
			628.8	400/100mg bid			Aplaviroc (3A)	7.7	9.4	1.7										Adkison KK, Shachoy-Clark A, Fang L, Lou Y, Otto VR, Berrey MM, and Piscitelli SC (2006) The effects of ritonavir and lopinavir/ritonavir on the pharmacokinetics of a novel CCR5 antagonist, aplaviroc, in healthy subjects. British journal of clinical pharmacology 62:336-344.
		M1, M2, M3																		Hurst M and Faulds D (2000) Lopinavir. Drugs 60:1371-1379; discussion 1380-1371.
	Ritonavir (combo)		721.0	400mg/100mg bid					13	0.97								CYP3A KI = 0.17 µM, kinact = 0.40 min-1		Carr, RA, Andre, AK, Bertz, RJ, Hsu, A, Lam, W, Chang, M, et al., (2000) Concominant administration of ABT-378/ritonavir (ABT-378/r) results in a clinically important pharmacokinetic (PK) interaction with atorvastatin. 40th Conf Antimicrob Agent Chemotherap (ICAAC) Abstract 1644.
1	Losartan		422.9	50mg	CYP2C9, 2C19	40.5, 69	Warfarin (2C9)	no interaction	1.0	0.6						0.02 (CYP2C9)		no data	no data	Lo MW, Goldberg MR, McCrea JB, Lu H, Furtek CI, and Bjornsson TD (1995) Pharmacokinetics of losartan, an angiotensin II receptor antagonist, and its active metabolite EXP3174 in humans. Clinical pharmacology and therapeutics 58:641-649.

		EXP3174 (Losartan carboxylic acid)	436.9								3.0	0.5	M/P 3.2; M/total: >0.1	CYP2C9	24.5		0.02 (CYP2C9)			Kong AN, Tomasko L, Waldman SA, Osborne B, Deutsch PJ, Goldberg MR, and Bjornsson TD (1995) Losartan does not affect the pharmacokinetics and pharmacodynamics of warfarin. Journal of clinical pharmacology 35:1008-1015.
																				Kamiyama E, Yoshigae Y, Kasuya A, Takei M, Kurihara A and Ikeda T (2007) Inhibitory effects of angiotensin receptor blockers on CYP2C9 activity in human liver microsomes. Drug Metabolism and Pharmacokinetics 22:267-275.
1	Meloxicam		351.4	15mg qd	CYP1A2, 2C9, 2C19, 2D6, 3A	>50	Warfarin (2C9)	no interaction	85	5.4	no data	no data	no data	no data	no data	<0.1	no data	no data	no data	Turck D, Roth W, and Busch U (1996) A review of the clinical pharmacokinetics of meloxicam. British journal of rheumatology 35 Suppl 1:13-16.
		5-Hydroxymethylmeloxicam	367.4																	Chesne C, Guyomard C, Guillouzo A, Schmid J, Ludwig E, and Sauter T (1998) Metabolism of Meloxicam in human liver involves cytochromes P4502C9 and 3A4. Xenobiotica; the fate of foreign compounds in biological systems 28:1-13.
																				Turck D, Su CA, Heinzel G, Busch U, Bluhmki E, and Hoffmann J (1997) Lack of interaction between meloxicam and warfarin in healthy volunteers. European journal of clinical pharmacology 51:421-425.
1	Memantine		179.3	20mg sd	CYP2B6, 2D6	77, 95	Dextromethorphan (2D6)	no interaction	10.0	0.15	no data	no data	no data	no data	no data	0.0019	no data	no data	no data	Micuda S, Mundlova L, Anzenbacherova E, Anzenbacher P, Chladek J, Fuksa L, and Martinkova J (2004) Inhibitory effects of memantine on human cytochrome P450 activities: prediction of in vivo drug interactions. European journal of clinical pharmacology 60:583-589.
					CYP1A2, 2A6, 2C9, 2C19, 2E1, 3A	All >1000														
		4-Hydroxymemantine	195.0		No data															Liu MY, Meng SN, Wu HZ, Wang S, and Wei MJ (2008) Pharmacokinetics of single-dose and multiple-dose memantine in healthy chinese volunteers using an analytic method of liquid chromatography-tandem mass spectrometry. Clinical therapeutics 30:641-653.
		6-Hydroxymemantine	195.0		No data															http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000378/WC500029678.pdf
Unassigned	Meropenem		383.5	1000mg tid	no in vitro inhibition data	no data	no data	no data	175	143	no data	no data	no data	no data	no data	no data	no data	no data	no data	Lowe MN and Lamb HM (2000) Meropenem: an updated review of its use in the management of intra-abdominal infections. Drugs 60:619-646.
		Ring opened metabolite ICI21389	401.0		No data															
Unassigned	Metformin	no data	129.2	500 - 2000mg qd	no inhibition data	no data	no data	no data	66	11	no data	no data	no data	no data	no data	no data	no data	no data	no data	Scheen AJ (1996) Clinical pharmacokinetics of metformin. Clinical pharmacokinetics 30:359-371.
									(500mg)	(500mg)										Santos-Caballero, N, and Flores-Murrieta, FJ (2012) Comparative Pharmacokinetic study between metformin alone and combined with orlistat in healthy mexican volunteers. Pharmacology & Pharmacy 3:300-306.
1	Metoprolol		267.4	25-400mg qd	CYP2D6	10.3	Propafenone (2D6)	no interaction	3.0	0.43	1.72	0.244	0.6	no data	no data	0.04	Not calculated	No data	no data	Bauer LA, Horn JR, Maxon MS, Easterling TR, Shen DD, and Strandness DE, Jr. (2000) Effect of metoprolol and verapamil administered separately and concurrently after single doses on liver blood flow and drug disposition. Journal of clinical pharmacology 40:533-543.

		alpha-Hydroxymetoprolol	283.4						(100mg)	(100mg)	(100mg)	(100mg)								VandenBrink BM, Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2012) Prediction of CYP2D6 drug interactions from in vitro data: evidence for substrate-dependent inhibition. Drug metabolism and disposition: the biological fate of chemicals 40:47-53.
																				Conrad KA, Byers JM, 3rd, Finley PR, and Burnham L (1983) Lidocaine elimination: effects of metoprolol and of propranolol. Clinical pharmacology and therapeutics 33:133-138.
																				Wagner F, Kalusche D, Trenk D, Jahnchen E, and Roskamm H (1987) Drug interaction between propafenone and metoprolol. British journal of clinical pharmacology 24:213-220.
4	Modafinil		273.4	200mg qd	CYP2C19	39	Clomipramine	In one case report, co-adminitration of modafinil and clomipramine increased the concentration of clomipramine in a dose-depedent manner.	220	18	no data	no data	not calculated	CYP2C19	no data	0.45	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020717s030s034s036lbl.pdf
		Modafinil sulfone	289.4		(did not inhibit other major CYP450s)			(warning against co-administration with diazepam, propranolol, phenytoin, S-mephenytoin)			181	9	M/P 0.8	CYP2C19	comparable as parent		0.23			Robertson P, DeCory HH, Madan A, and Parkinson A (2000) In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. Drug metabolism and disposition: the biological fate of chemicals 28:664-671.
		Modafinil acid	274.3								93	11	M/P 0.4							Grozinger M, Hartter S, Hiemke C, Griese EU, and Roschke J (1998) Interaction of modafinil and clomipramine as comedication in a narcoleptic patient. Clinical neuropharmacology 21:127-129.
																				Robertson P, Jr., Hellriegel ET, Arora S, and Nelson M (2002) Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. Clinical pharmacology and therapeutics 71:46-56.
1	Mofetil	Mycophenolic acid (prodrug)	433.5	1000mg bid	no CYP inhibition (UGT inhibitor)	no CYP inhibition	Tacrolimus (3A)	statistically not significant	no data (prodrug)	no data (prodrug)	37.4	13	not calculated	no data	no data	no inhibition	no data	no data	no data	Jain A, Venkataramanan R, Kwong T, Mohanka R, Orloff M, Abt P, Kashyap R, Tsoulfas G, Mack C, Williamson M, Batzold P, and Bozorgzadeh A (2007) Pharmacokinetics of mycophenolic acid in liver transplant patients after intravenous and oral administration of mycophenolate mofetil. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 13:791-796.
		Mycophenolic acid	320.3								37	13								
1	Mometasone	no data	427.4	800 ug tid inhaled	CYP2B6, 2C8	2.9, 0.16	no data	no data	0.0001	0.00005	no data	no data	not calculated	no data	no data	<0.00013	not calculated	no data	no data	Daley-Yates PT, Kunka RL, Yin Y, Andrews SM, Callejas S, and Ng C (2004) Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. European journal of clinical pharmacology 60:265-268.
																				Walsky RL, Gaman EA, and Obach RS (2005) Examination of 209 drugs for inhibition of cytochrome P450 2C8. Journal of clinical pharmacology 45:68-78.
																				Walsky RL, Astuccio AV, and Obach RS (2006) Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. Journal of clinical pharmacology 46:1426-1438.
2	Montelukast	no data	586.2	10mg QD	CYP2C8	0.01	Pioglitazone	1.0	6.8	1.0	no data	no data	no data	no data	no data	103	no data	no data	no data	Walsky RL, Obach RS, Gaman EA, Gleeson JP, and Proctor WR (2005) Selective inhibition of human cytochrome P4502C8 by montelukast. Drug metabolism and disposition: the biological fate of chemicals 33:413-418.

							Rosiglitazone	1.0												Kim KA, Park PW, Kim KR, and Park JY (2007) Effect of multiple doses of montelukast on the pharmacokinetics of rosiglitazone, a CYP2C8 substrate, in humans. British journal of clinical pharmacology 63:339-345.
																				Jaalloja T, Backman JT, Neuvonen M, Niemi M and Neuvonen PJ (2006) Montelukast and zafirlukast do not affect the pharmacokinetics of the CYP2C8 substrate pioglitazone. Euuropean Journal of Clinical Pharmacology 62:503-509.
																				Zhao JJ, Rogers D, Holland SD, Larson P, Amin RD, Haesen R, Freeman A, Seiberling M, Merz M and Cheng H (1997) Pharmacokinetics and bioavailability of montelukast sodium (MK-0476) in healthy young and elderly volunteers. Biopharmaceutics and Drug Disposition 18: 769-777.
																				Markham A and Faulds D (1998) Montelukast. Drugs 56:251-256; discussion 257.
1	Moxifloxacin	no data	401.4	400mg sd	CYP1A2, 2B6, 2C9, 3A	>400, >30, >400, >100	no data	no data	74	6.2	no data	no data	no data	no data	no data	<0.21	no data	no data	no data	Moise PA, Birmingham MC, and Schentag JJ (2000) Pharmacokinetics and metabolism of moxifloxacin. Drugs of today 36:229-244.
																				Zhang L, Wei MJ, Zhao CY, and Qi HM (2008) Determination of the inhibitory potential of 6 fluoroquinolones on CYP1A2 and CYP2C9 in human liver microsomes. Acta pharmacologica Sinica 29:1507-1514.
																				Horita Y and Doi N (2014) Comparative Study of the Effects of Antituberculosis Drugs and Antiretroviral Drugs on Cytochrome P450 3A4 and P-Glycoprotein. Antimicrobial agents and chemotherapy 58:3168-3176.
																				Walsky RL, Astuccio AV, and Obach RS (2006) Evaluation of 227 drugs for in vitro inhibition of cytochrome P450 2B6. Journal of clinical pharmacology 46:1426-1438.
																				http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-085_Avelox_biopharmr.pdf
																				http://www.drugs.com/dosage/moxifloxacin.html
																				http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=9399
4	Nefazodone		470.0	200mg sd	CYP3A	0.6	Triazolam (3A)	3.9	2.3	0.83	no data	no data	no data	no data	no data	1.4	no data	CYP3A KI = 9.9 µM, kinact = 0.16 min-1	no data	von Moltke LL, Greenblatt DJ, Granda BW, Grassi JM, Schmider J, Harmatz JS, and Shader RI (1999) Nefazodone, meta-chlorophenylpiperazine, and their metabolites in vitro: cytochromes mediating transformation, and P450-3A4 inhibitory actions. Psychopharmacology 145:113-122.
				200mg bid X7d			Alprazolam (3A)	2.0	16	3.7						6.1				Barbhaiya RH, Shukla UA, Kroboth PD, and Greene DS (1995) Coadministration of nefazodone and benzodiazepines: II. A pharmacokinetic interaction study with triazolam. Journal of clinical psychopharmacology 15:320-326.
			470.0	200mg bid X7d			Terfenadine (3A)	5.6												Abernethy DR, Barbey JT, Franc J, Brown KS, Feirrera I, Ford N, and Salazar DE (2001) Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QTc prolongation. Clinical pharmacology and therapeutics 69:96-103.

		Hydroxynefazodone	486.0								5.6	0.85								Greene DS, Salazar DE, Dockens RC, Kroboth P, and Barbhaiya RH (1995) Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. Journal of clinical psychopharmacology 15:399-408.
		Triazoledione	458.0								22	2.0								Barbhaiya RH, Dandekar KA, and Greene DS (1996) Pharmacokinetics, absolute bioavailability, and disposition of [14C]nefazodone in humans. Drug metabolism and disposition: the biological fate of chemicals 24:91-95.
		MCPP	196.7								1.3	0.17								
		para-Hydroxynefazodone	486.0																	
4	Nifedipine		346.3	20mg sd	CYP2C8, 2C9, 2C19, 3A	1.5, 0.34, 0.55, 1.8			2.7	0.61					no data	1.8	no data	no data	no data	Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2010) Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. Drug metabolism and disposition: the biological fate of chemicals 38:981-987.
				10mg tid			Diltiazem (3A)	1.5												VandenBrink BM, Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2011) Evaluation of CYP2C8 inhibition in vitro: utility of montelukast as a selective CYP2C8 probe substrate. Drug metabolism and disposition: the biological fate of chemicals 39:1546-1554.
		Hydroxycarboxylic acid		10mg tid			Vincristine (3A)	2.5					>1	no data						Racha JK, Zhao ZS, Olejnik N, Warner N, Chan R, Moore D, and Satoh H (2003) Substrate dependent inhibition profiles of fourteen drugs on CYP3A4 activity measured by a high throughput LCMS/MS method with four probe drugs, midazolam, testosterone, nifedipine and terfenadine. Drug metabolism and pharmacokinetics 18:128-138.
		Pyridine derivative		10mg sd			Repaglinide (2C8)	0.9	0.4	0.29			0.2-0.9	no data						Tateishi T, Ohashi K, Sudo T, Sakamoto K, Fujimura A, and Ebihara A (1993) The effect of nifedipine on the pharmacokinetics and dynamics of diltiazem: the preliminary study in normal volunteers. Journal of clinical pharmacology 33:738-740.
																				Fedeli L, Colozza M, Boschetti E, Sabalich I, Aristei C, Guerciolini R, Del Favero A, Rossetti R, Tonato M, Rambotti P, and et al. (1989) Pharmacokinetics of vincristine in cancer patients treated with nifedipine. Cancer 64:1805-1811.
																				Raemsch KD and Sommer J (1983) Pharmacokinetics and metabolism of nifedipine. Hypertension 5:II18-24.
																				Ahmad, M, Ahmad, T, Sultan, RA, and Murtaza, G (2009) Pharmacokinetic study of nifedipine in healthy adult male human volunteers. Tropical Journal of Pharmaceutical Research 8:385-391.
																				Kumar V, Wahlstrom JL, Rock DA, Warren CJ, Gorman LA, and Tracy TS (2006) CYP2C9 inhibition: impact of probe selection and pharmacogenetics on in vitro inhibition profiles. Drug metabolism and disposition: the biological fate of chemicals 34:1966-1975.
																				Foti RS and Wahlstrom JL (2008) CYP2C19 inhibition: the impact of substrate probe selection on in vitro inhibition profiles. Drug metabolism and disposition: the biological fate of chemicals 36:523-528.
1	Olanzapine		312.4	10mg sd	CYP1A2, 2D6	36, 89	no data	no data	1.9	0.049	no data	no data	no data	no data	no data	0.0014	no data	no data	no data	Ring BJ, Binkley SN, Vandenbranden M, and Wrighton SA (1996) In vitro interaction of the antipsychotic agent olanzapine with human cytochromes P450 CYP2C9, CYP2C19, CYP2D6 and CYP3A. British journal of clinical pharmacology 41:181-186.

		Olanzapine-N-glucuronide	488.6																Wrighton SA and Ring BJ (1999) Predicting drug interactions and pharmacokinetic variability with in vitro methods: the olanzapine experience. Drug metabolism reviews 31:15-28.
		2-Carboxyolanzapine																	Sathirakul, K, Chan, C, Teng, L, Bergstrom, RF, Yeo, KP, and Wise, SD (1999) Olanzapine pharmacokinetics are similar in chinese and caucasian subjects. Drug Metabol Rev 31:15-28.
1	Olmesartan	no data	446.5	20 mg qd	CYP2C9	> 300	Warfarin (2C9)	no interaction	6.6	1.1	no data	no data	not calculated	no data	no data	< 0.004	no data	no data	no data	Schwocho LR and Masonson HN (2001) Pharmacokinetics of CS-866, a new angiotensin II receptor blocker, in healthy subjects. Journal of clinical pharmacology 41:515-527.
4	Omeprazole		345.4		CYP2C19, 3A	3.1, 52	PK only	PK only	3.92	1.6	no data	no data		CYP2C19	Ki = 8.2 uM	0.8	0.046	KI = 9.1 uM kinact = 0.046 min-1		Chiba K, Kobayashi K, Manabe K, Tani M, Kamataki T, and Ishizaki T (1993) Oxidative metabolism of omeprazole in human liver microsomes: cosegregation with S-mephentytoin 4'-hydroxylation. The Journal of pharmacology and experimental therapeutics 266:52-59.
		5-Hydroxyomeprazole		20mg single			PK only	PK only	1.2	0.66	1.0	0.48	M/P (AUC) 0.83; M/total 0.27	2C19; 3A4	Ki = N.D.; N.D.	0.08 (2C19); 0.013 (3A4)	not available	283 (2C19); 1793 (3A4)	not available	Shirasaka Y, Sager JE, Lutz JD, Davis C, and Isoherranen N (2013) Inhibition of CYP2C19 and CYP3A4 by omeprazole metabolites and their contribution to drug-drug interactions. Drug metabolism and disposition: the biological fate of chemicals 41:1414-1424.
		5'-O-Desmethylomeprazole		20mg single			PK only	PK only	1.2	0.66	0.049	0.03	M/P (AUC) 0.041; M/total 0.013	2C19; 3A4	Ki = 8.7 (2C19); 61 (3A4)	0.08 (2C19); 0.013 (3A4)	0.003; 0.0005	283 (2C19); 1793 (3A4)	435 (2C19); 709 (3A4)	Ko JW, Sukhova N, Thacker D, Chen P, and Flockhart DA (1997) Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. Drug metabolism and disposition: the biological fate of chemicals 25:853-862.
		Omeprazole sulfone		20mg single			PK only	PK only	1.2	0.66	0.39	0.14	M/P (AUC) 0.33; M/total 0.10	2C19; 3A4	Ki = 5.7 (2C19); N.D.	0.08 (2C19); 0.013 (3A4)	0.025; not available	283 (2C19); 1793 (3A4)	380 (2C19); not available	Ogilvie BW, Yerino P, Kazmi F, Buckley DB, Rostami-Hodjegan A, Paris BL, Toren P, and Parkinson A (2011) The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel. Drug metabolism and disposition: the biological fate of chemicals 39:2020-2033.
		Carboxyomeprazole		20mg single			PK only	PK only	1.2	0.66	1.1	0.25	M/P (AUC) 0.92; M/total 0.29	2C19; 3A4	Ki = N.D.; N.D.	0.08 (2C19); 0.013 (3A4)	not available	283 (2C19); 1793 (3A4)	not available	Yeung CK, Fujioka Y, Hachad H, Levy RH, and Isoherranen N (2011) Are circulating metabolites important in drug-drug interactions?: Quantitative analysis of risk prediction and inhibitory potency. Clinical pharmacology and therapeutics 89:105-113.
				20mg qd			Citalopram (2C19)	1.9	1.2	0.66	no data	no data	no data	no data	no data	0.08 (2C19)	no data	no data	no data	Rocha A, Coelho EB, Sampaio SA, and Lanchote VL (2010) Omeprazole preferentially inhibits the metabolism of (+)-(S)-citalopram in healthy volunteers. British journal of clinical pharmacology 70:43-51.
				40mg qd			Moclobemide (2C19)	2.2	no data	4.1	no data	no data		no data	no data	0.5 (2C19)	no data	no data	no data	Yu KS, Yim DS, Cho JY, Park SS, Park JY, Lee KH, Jang IJ, Yi SY, Bae KS, and Shin SG (2001) Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clinical pharmacology and therapeutics 69:266-273.
				80mg qd			Clopidogrel (2C19)	1.4	no data	no data	no data	no data		no data	no data	no data	no data	no data	no data	Angiolillo DJ, Gibson CM, Cheng S, Ollier C, Nicolas O, Bergougnan L, Perrin L, LaCreta FP, Hurbin F, and Dubar M (2011) Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. Clinical pharmacology and therapeutics 89:65-74.

				20mg qd			Raltegravir	3.1	1.2	0.66	no data	no data		no data	no data	no data	no data	no data	no data	Iwamoto M, Wenning LA, Nguyen BY, Teppler H, Moreau AR, Rhodes RR, Hanley WD, Jin B, Harvey CM, Breidinger SA, Azrolan N, Farmer HF, Jr., Isaacs RD, Chodakewitz JA, Stone JA, and Wagner JA (2009) Effects of omeprazole on plasma levels of raltegravir. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 48:489-492.
				40mg qd			Saquinavir (3A)	1.8	no data	4.1	no data	no data		no data	no data	0.08 (3A)	no data	no data	no data	Winston A, Back D, Fletcher C, Robinson L, Unsworth J, Tolowinska I, Schutz M, Pozniak AL, Gazzard B, and Boffito M (2006) Effect of omeprazole on the pharmacokinetics of saquinavir-500 mg formulation with ritonavir in healthy male and female volunteers. Aids 20:1401-1406.
				20mg bid			Carbamazepine	1.9	no data	0.68	no data	no data		no data	no data	no data	no data	no data	no data	Dixit RK, Chawla AB, Kumar N, and Garg SK (2001) Effect of omeprazole on the pharmacokinetics of sustained-release carbamazepine in healthy male volunteers. Methods and findings in experimental and clinical pharmacology 23:37-39.
																				Zomorodi K and Houston JB (1996) Diazepam-omeprazole inhibition interaction: an in vitro investigation using human liver microsomes. British journal of clinical pharmacology 42:157-162.
2	Ondansetron		293.4	8mg tid 24mg qd	CYP2D6, 3A	21, 1.0	Casopitant (2D6)	no interactions	0.77	0.16 (3A4), 0.008 (2D6)	no data	no data	not calculated	no data	no data	0.16	Not calculated	CYP3A KI = 0.8 µM, kinact = 0.048 min-1	no data	Saynor DA and Dixon CM (1989) The metabolism of ondansetron. European journal of cancer & clinical oncology 25 Suppl 1:S75-77.
		8-Hydroxyondansetron	309.4				Temazepam (3A)	no interaction	(8mg)	(8mg)										Zimmerlin A, Trunzer M, and Faller B (2011) CYP3A time-dependent inhibition risk assessment validated with 400 reference drugs. Drug metabolism and disposition: the biological fate of chemicals 39:1039-1046.
																				Fischer V, Vickers AE, Heitz F, Mahadevan S, Baldeck JP, Minery P, and Tynes R (1994) The polymorphic cytochrome P-4502D6 is involved in the metabolism of both 5-hydroxytryptamine antagonists, tropisetron and ondansetron. Drug metabolism and disposition: the biological fate of chemicals 22:269-274.
																				Johnson B, Adams L, Lu E, Zhang K, Lebowitz P, Lates C, and Blum R (2009) Impact of casopitant, a novel NK-1 antagonist, on the pharmacokinetics of ondansetron and dexamethasone. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 17:1177-1185.
																				de Wit R, Beijnen JH, van Tellingen O, Schellens JH, de Boer-Dennert M, and Verweij J (1996) Pharmacokinetic profile and clinical efficacy of a once-daily ondansetron suppository in cyclophosphamide-induced emesis: a double blind comparative study with ondansetron tablets. British journal of cancer 74:323-326
Unassigned	Oseltamivir		312.4	150mg sd	no in vitro data	no data	Tacrolimus (3A)	no interaction	1.0	0.61	14	1.62	14	no data	no data	no data	no data	no data	no data	Mulla H, Peek GJ, Harvey C, Westrope C, Kidy Z, and Ramaiah R (2013) Oseltamivir pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation support. Anaesthesia and intensive care 41:66-73.
																				Hill G, Cihlar T, Oo C, Ho ES, Prior K, Wiltshire H, Barrett J, Liu B, and Ward P (2002) The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of in vivo and in vitro studies. Drug metabolism and disposition: the biological fate of chemicals 30:13-19.

		Carboxylate	284.4				Warfarin (2C9)	no interaction												Jittamala P, Pukrittayakamee S, Tarning J, Lindegardh N, Hanpithakpong W, Taylor WR, Lawpoolsri S, Charunwattana P, Panapipat S, White NJ, and Day NP (2014) Pharmacokinetics of orally administered oseltamivir in healthy obese and nonobese Thai subjects. Antimicrobial agents and chemotherapy 58:1615-1621.
4	Oxcarbazepine		252.3	600mg qd	CYP2C19	31.2	Phenytoin (2C9)	1.4	878	29							0.91	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021014s015s019s022s024s025s027s028,021285s009s013s015s018s019s020s022lbl.pdf
		10,11-Dihydro-10-hydrocarbamazepine	254.3								900	89		CYP2C19	32		2.8			Lakehal F, Wurden CJ, Kalhorn TF, and Levy RH (2002) Carbamazepine and oxcarbazepine decrease phenytoin metabolism through inhibition of CYP2C19. Epilepsy research 52:79-83.
																				van Heiningen PN, Eve MD, Oosterhuis B, Jonkman JH, de Bruin H, Hulsman JA, Richens A, and Jensen PK (1991) The influence of age on the pharmacokinetics of the antiepileptic agent oxcarbazepine. Clinical pharmacology and therapeutics 50:410-419.
																				Tartara A, Galimberti CA, Manni R, Morini R, Limido G, Gatti G, Bartoli A, Strada G, and Perucca E (1993) The pharmacokinetics of oxcarbazepine and its active metabolite 10-hydroxy-carbazepine in healthy subjects and in epileptic patients treated with phenobarbitone or valproic acid. British journal of clinical pharmacology 36:366-368.
2	Pantoprazole		383.4	40mg qd	CYP2C19	33	Clopidogrel	1.2	12.5	6.5	no data	no data	no data	no data	no data	0.2	no data	no data	no data	Radhofer-Welte S (1999) Pharmacokinetics and metabolism of the proton pump inhibitor pantoprazole in man. Drugs of today 35:765-772.
							co-administered with pentoprazole 80 mg													http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020987s045lbl.pdf
		Desmethylpantoprazole sulfate	449.4																	Angiolillo DJ, Gibson CM, Cheng S, Ollier C, Nicolas O, Bergougnan L, Perrin L, LaCreta FP, Hurbin F, and Dubar M (2011) Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. Clinical pharmacology and therapeutics 89:65-74.
4	Paroxetine		329.4	20mg qd	CYP2D6	0.15	(R) Metoprolol (2D6)	8.0	0.55 EM, 3.9 PM	0.19 (SS after 30 mg dose)						1.3		CYP2D6 KI = 4.8 μM, kinact = 0.17 min-1		Bertelsen KM, Venkatakrishnan K, Von Moltke LL, Obach RS, and Greenblatt DJ (2003) Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug metabolism and disposition: the biological fate of chemicals 31:289-293.
							(S) Metoprolol (2D6)	5.1											no data	Crewe HK, Lennard MS, Tucker GT, Woods FR, and Haddock RE (1992) The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. British journal of clinical pharmacology 34:262-265.
		M1 glucuronide	507.4								no data	no data	no data	CYP2D6	>200					Venkatakrishnan K and Obach RS (2005) In vitro-in vivo extrapolation of CYP2D6 inactivation by paroxetine: prediction of nonstationary pharmacokinetics and drug interaction magnitude. Drug metabolism and disposition: the biological fate of chemicals 33:845-852.

		M1 sulfate	411.4								no data	no data	no data	CYP2D6	120					Hemeryck A, Lefebvre RA, De Vriendt C, and Belpaire FM (2000) Paroxetine affects metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clinical pharmacology and therapeutics 67:283-291.
1	Pemetrexed	no data	427.4	500mg/m2 QW every cycle	CYP1A2, 2C9, 2D6, 3A	no inhibition	no probe substrate of 1A2, 2C9, 2D6, 3A	no interaction	454	313	no data	no data	no data	no data	no data	no data	no data	no data	no data	www.accessdata.fda.gov/drugsatfda_docs/label/2009/021462s021lbl.pdf
																				Hazarika M, White RM, Johnson JR, and Pazdur R (2004) FDA drug approval summaries: pemetrexed (Alimta). The oncologist 9:482-488.
																				Li KM, Rivory LP, and Clarke SJ (2007) Pemetrexed pharmacokinetics and pharmacodynamics in a phase I/II study of doublet chemotherapy with vinorelbine: implications for further optimisation of pemetrexed schedules. British journal of cancer 97:1071-1076.
1	Pioglitazone	no data	356.4	30mg qd	CYP2C8, 2C9, 2C19, 26A1, 3A	9.4, 32, 83, 8.6, 12	Repaglinide (2C8)	no interaction	8.3	0.60	no data	no data	no data	no data	no data	all below 0.1	no data	no data	no data	Kajosaari LI, Jaakkola T, Neuvonen PJ, and Backman JT (2006) Pioglitazone, an in vitro inhibitor of CYP2C8 and CYP3A4, does not increase the plasma concentrations of the CYP2C8 and CYP3A4 substrate repaglinide. European journal of clinical pharmacology 62:217-223.
																				Sahi J, Black CB, Hamilton GA, Zheng X, Jolley S, Rose KA, Gilbert D, LeCluyse EL, and Sinz MW (2003) Comparative effects of thiazolidinediones on in vitro P450 enzyme induction and inhibition. Drug metabolism and disposition: the biological fate of chemicals 31:439-446.
																				Thatcher JE, Buttrick B, Shaffer SA, Shimshoni JA, Goodlett DR, Nelson WL, and Isoherranen N (2011) Substrate specificity and ligand interactions of CYP26A1, the human liver retinoic acid hydroxylase. Molecular pharmacology 80:228-239.
																				Smulders RA, Zhang W, Veltkamp SA, van Dijk J, Krauwinkel WJ, Keirns J, and Kadokura T (2012) No pharmacokinetic interaction between ipragliflozin and sitagliptin, pioglitazone, or glimepiride in healthy subjects. Diabetes, obesity & metabolism 14:937-943.
1	Pramipexole	no data	211.3	0.125mg sd	CYP2D6 (does not inhibit other major CYP450s)	30	no interaction reports	no data	0.038	0.0029	no data	no data	no data	no data	no data	< 0.001	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020667s019s021s022s023s024lbl.pdf
																				http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Mirapex/Mirapex.pdf
																				Abib Jr, EA, Duarte, LF, and Pereira, R (2012) Comparative bioavailability: two pramipexole formulations in healthy volunteers after a single dose administration under fasting conditions. Bioequivalence & Bioavailability 4:56-59.
1	Pravastatin		424.5	40mg qd	CYP2C9, 2D6, 3A4	~70 (CYP2C9), >50/not determined (CYP2D6, CYP3A4)	Warfarin (2C9)	1.2	0.36 (ss 40 mg qd)	0.15 (ss 40 mg qd)				no data	no data	0.002	no data	no data	no data	Everett DW, Chando TJ, Didonato GC, Singhvi SM, Pan HY, and Weinstein SH (1991) Biotransformation of pravastatin sodium in humans. Drug Metabolism and disposition: the biological fate of chemicals 19: 740-748.
		3-α-Isopravastatin	424.5								Data not available	Data not available	M/P ratio ~ 1 at 1 h							Hatanaka T (2000) Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. Clinical pharmacokinetics 39:397-412.
																				Pan HY, DeVault AR, Wang-Iverson D, Ivaskhkiv E, Swanson BN, and Sugerman AA (1990) Comparative pharmacokinetics and pharmacodynamics of pravastatin and lovastatin. The Journal of Clinical Pharmacology 30: 1128-1135.
																				Transon C, Leemann T, and Dayer P (1996) In vitro comparative inhibition profiles of major human drug metabolising cytochrome P450 isozymes (CYP2C9, CYP2D6 and CYP3A4) by HMG-CoA reductase inhibitors. European Journal of Clinical Pharmacology 50: 209-215.
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019898s062lbl.pdf

																				Hatanaka T (2000) Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. Clinical pharmacokinetics 39:397-412.
1	Pregabalin	no data	159.2	150-600mg qd	CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A	no inhibition	Gabapentin	no interaction	371 (ss 300mg BID)	57 (SS 300mg BID)	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021446s026,022488s005lbl.pdf
							Norethidrone	no interaction												Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, Randinitis EJ, Corrigan BW, Haig GM, Boyd RA, and Wesche DL (2010) Clinical pharmacokinetics of pregabalin in healthy volunteers. Journal of clinical pharmacology 50:941-950.
							Ethinylestradiol	no interaction												
							Oxycodone	no interaction												
							Lorazepam	no interaction	87	14										
1	Quetiapine		383.5	400mg bid	None	>10 (CYP1A2, 2C8/9, 2C19, 2D6,3A4)	Antipyrine	no interaction	11.8	2.9						Data not available	no data	no data	no data	DeVane CL and Nemeroff CB (2001) Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clinical pharmacokinetics 40:509-522.
		Quetiapine sulfoxide	399.5								12.2	2.5	M/P ratio: 1.0, M/total >0.1	CYP1A2, 2C8/9, 2C19, 2D6, 3A	>10	Data not available				Winter HR, Earley WR, Hamer-Maansson JE, Davis PC and Smith MA (2008) Steady-state pharmacokinetic, safety, and tolerability profiles of quetiapine, and other quetiapine metabolites in pediatric and adult patients with psychotic disorders. Journal of Child and Adolescent Psychopharmacology 18: 81-98.
		N-Desalkylquetiapine	327.8								7.9	0.9	M/P ratio: 0.67, M/total >0.1	CYP1A2, 2C8/9, 2C19, 2D6, 3A	>10	Data not available				Bui K, Earley W, and Nyberg S (2013) Pharmacokinetic profile of the extended-release formulation of quetiapine fumarate (quetiapine XR): clinical implications. Current medical research and opinion 29:813-825.
2	Rabeprazole		359.4	20mg qd	CYP2C9, 2C19, 3A	5.8, 9, 51	Diazepam (2C19)	no interaction	6.8	1.7						0.29 (2C9), 0.2 (2C19), 0.03 (3A)	no data	no data	no data	Li XQ, Andersson TB, Ahlstrom M, and Weidolf L (2004) Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug metabolism and disposition: the biological fate of chemicals 32:821-827.
		Thioether	343.4				Tacrolimus (3A)	no interaction			no data	no data	no data	CYP2C9, 2C19, 2D6, 3A	5.8,8.3, 12.4, 15					Shin JM and Kim N (2013) Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. Journal of neurogastroenterology and motility 19:25-35.
2	Raloxifene		473.6	70mg sd	CYP2C9, 2C19, 2D6, 3A	0.37, 0.31, 1.2, 0.75	Warfarin	no interaction	4.0	0.074	no data	no data	no data	no data	no data	0.24	no data	CYP3A KI = 9.9 µM, kinact = 0.16 min-1	no data	Hochner-Celnikier D (1999) Pharmacokinetics of raloxifene and its clinical application. European journal of obstetrics, gynecology, and reproductive biology 85:23-29.
	normalized to 70 kg	Raloxifene-4-glucuronide																		Chen Q, Ngui JS, Doss GA, Wang RW, Cai X, DiNinno FP, Blizzard TA, Hammond ML, Stearns RA, Evans DC, Baillie TA, and Tang W (2002) Cytochrome P450 3A4-mediated bioactivation of raloxifene: irreversible enzyme inhibition and thiol adduct formation. Chemical research in toxicology 15:907-914.
		Raloxifene-6-glucuronide																		Miller JW, Skerjanec A, Knadler MP, Ghosh A, and Allerheiligen SR (2001) Divergent effects of raloxifene HCI on the pharmacokinetics and pharmacodynamics of warfarin. Pharmaceutical research 18:1024-1028.
Unassigned	Ramipril		416.5	10mg qd	No data	no data	Aliskerin	1.1	0.25	0.13						data not available		no data	no data	Meisel S, Shamiss A and Rosenthal T (1994) Clinical pharmacokinetics of ramipril. Clinical Pharmacokinetics 26: 7-15.
		Ramiprilat	388.4								0.56	0.086	M/P ratio: 2.24, M/total >0.1	data not available	data not available		data not available			Vaidyanathan S, Valencia J, Kemp C, Zhao C, Yeh C-M, Bizot M-N, Denouel J, Dieterich HA, and Dole WP (2006) Lack of pharmacokientic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. International Journal of Clinical Practice 60: 1343-1356.

																			Verho M, Luck C, Stelter WJ, Rangoonwala B, and Bender N (1995) Pharmacokinetics, metabolism and biliary and urinary excretion of oral ramipril in man. Current Medical Research and Opinion 13: 264-273.
																			Meyer BH, Müller O, Badian M, Eckert H-G, Hajdú, Irmisch R, and Schmidt D (1987) Pharmacokinetics of ramipril in the elderly. The Americal Journal of Cardiology 59: 33D-37D.
																			http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022021s007lbl.pdf
1	Ranitidine	no data	314.4	200mg sd	no inhibition of 1A2, 2C8, 2C9, 2D6, 3A,	no inhibition	Theophylline (1A2)	no interaction	3.5	17.0	no data	no data	not Calculated	no data	no data	no data	no data	no data	no data	Obach RS, Walsky RL, Venkatakrishnan K, Gaman EA, Houston JB, and Tremaine LM (2006) The utility of in vitro cytochrome P450 inhibition data in the prediction of drug-drug interactions. The Journal of pharmacology and experimental therapeutics 316:336-348.
							Rosiglitazone (2C9)	no interaction												http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/074467.pdf
							Warfarin (2C9)	no interaction												
							Midazolam (3A)	no interaction												Zhou Q, Ruan ZR, Yuan H, Jiang B, and Xu DH (2006) Pharmacokinetics and bioequivalence of ranitidine and bismuth derived from two compound preparations. World journal of gastroenterology : WJG 12:2742-2748.
Unassigned	Risedronate	no data	305.1	5mg qd	no data	no data	no data	no data	0.013	0.0030	no data	no data	not calculated	no data	no data	not calculated	Not calculated	No data	no data	Mitchell DY, Eusebio RA, Sacco-Gibson NA, Pallone KA, Kelly SC, Nesbitt JD, Brezovic CP, Thompson GA, and Powell JH (2000) Dose-proportional pharmacokinetics of risedronate on single-dose oral administration to healthy volunteers. Journal of clinical pharmacology 40:258-265.
1	Risperidone		410.5	0.5mg bid	CYP2D6	6.9	Donepezil	<1.0	0.048	0.0080						0.0012				Prakash C, Kamel A, Cui D, Whalen RD, Miceli JJ, and Tweedie D (2000) Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. British journal of clinical pharmacology 49 Suppl 1:35S-42S.
																				Zhao Q, Xie C, Pesco-Koplowitz L, Jia X, and Parier JL (2003) Pharmacokinetic and safety assessments of concurrent administration of risperidone and donepezil. Journal of clinical pharmacology 43:180-186.
		9-Hydroxyrisperidone	426.5		CYP2D6						0.155	0.016	M/P ratio 3.37; M/total <0.1 in PM, ~0.14 in IM, ~0.67 in EM	CYP2D6	16		0.001			Mannens G, Huang M-L, Meuldermans W, Hendrickx J, Woestenborghs R and Heykants J (1993) Absorption, metabolism, and excretion of risperidone in humans. Drug Metabolism and Disposition: the Biological Fate of Chemicals 21:1134-1141.
Unassigned	Rivastigmine		250.3	1.5-6mg bid	no data	no data	no data	no data	0.27	0.059	0.33	0.062	1.22	no data	no data	not calculated	not calculated	no data	no data	Shua-Haim J, Smith J, Picard F, Sedek G, Athalye S, Pommier F, and Lefevre G (2008) Steady-state pharmacokinetics of rivastigmine in patients with mild to moderate Alzheimer's disease not affected by co-administration of memantine: an open-label, crossover, single-centre study. Clinical drug investigation 28:361-374.
		NAP 226-90 (Decarbamylated rivastigmine)																		Tsurkan LG, Hatfield MJ, Edwards CC, Hyatt JL, and Potter PM (2013) Inhibition of human carboxylesterases hCE1 and hiCE by cholinesterase inhibitors. Chemico-biological interactions 203:226-230.
1	Ropinirole		260.4	2mg qd	CYP2D6	0.27	Theophilline (1A2)	no interaction	0.084	0.021						0.08	no data	no data	no data	Wynalda MA and Wienkers LC (1997) Assessment of potential interactions between dopamine receptor agonists and various human cytochrome P450 enzymes using a simple in vitro inhibition screen. Drug metabolism and disposition: the biological fate of chemicals 25:1211-1214.

		N-Despropyl	218.3		Not significant for 1A2, 2C9/19, 2E, 3A, but 2D6						no data	no data	no data	no data	no data					Thalamas C, Taylor A, Brefel-Courbon C, Eagle S, Fitzpatrick K, and Rascol O (1999) Lack of pharmacokinetic interaction between ropinirole and theophylline in patients with Parkinson's disease. European journal of clinical pharmacology 55:299-303.
2	Rosiglitazone		357.4	8mg sd	CYP2C8, 2C9	9, 25	no interaction with 2C8 substrate	no data	6.7	1.0						0.11				Baldwin SJ, Clarke SE, and Chenery RJ (1999) Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. British journal of clinical pharmacology 48:424-432.
			357.4	4mg sd					5.3	0.95										Freed MI, Wilson DE, Thompson KA, Harris RZ, Ilson BE, and Jorkasky DK (1999) Pharmacokinetics and pharmacodynamics of SB 209670, an endothelin receptor antagonist: effects on the regulation of renal vascular tone. Clinical pharmacology and therapeutics 65:473-482.
		N-Desmethylrosiglitazone	343.4	4mg sd							5.9	0.33	1.1132075	no data	no data	no data	no data	no data	no data	Kim KB, Lee DJ, Yeo CW, Shin JG, and Bae SK (2009) Simultaneous quantification of rosiglitazone and its two major metabolites, N-desmethyl and p-hydroxy rosiglitazone in human plasma by liquid chromatography/tandem mass spectrometry: application to a pharmacokinetic study. Journal of chromatography 877:1951-1956.
		para-Hydroxyrosiglitazone	373.4	4mg sd							0.22	0.015	0.0415094	no data	no data	no data	no data	no data	no data	
		ortho-Hydroxyrosiglitazone	373.4																	
1	Rosuvastatin	no data	481.5	20mg sd	CYP2C8	no inhibition	no in vivo study with 2C8 substrate	no data	0.063	0.0061	Mets <25% of parent	no data	no data	no data	no data	no data	no data	no data	no data	Martin PD, Warwick MJ, Dane AL, Hill SJ, Giles PB, Phillips PJ, and Lenz E (2003) Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. Clinical therapeutics 25:2822-2835.
																				Martin PD, Warwick MJ, Dane AL, Brindley C, and Short T (2003) Absolute oral bioavailability of rosuvastatin in healthy white adult male volunteers. Clinical therapeutics 25:2553-2563.
																				Martin PD, Warwick MJ, Dane AL, and Cantarini MV (2003) A double-blind, randomized, incomplete crossover trial to assess the dose proportionality of rosuvastatin in healthy volunteers. Clinical therapeutics 25:2215-2224.
																				Martin PD, Dane AL, Schneck DW, and Warwick MJ (2003) An open-label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. Clinical therapeutics 25:459-471.
1	Salmeterol		415.6	300 µg	CYP2C8	0.94	no CYP2C8 substrate	no data	0.0000054	0.0000048	no data	no data	no data	no data	no data	5.11E-06	no data	no data	no data	Manchee GR, Barrow A, Kulkarni S, Palmer E, Oxford J, Colthup PV, Maconochie JG, and Tarbit MH (1993) Disposition of salmeterol xinafoate in laboratory animals and humans. Drug metabolism and disposition: the biological fate of chemicals 21:1022-1028.
		alpha-Hydroxysalmeterol	431.0																	
3	Sertraline		306.2	50mg sd	CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A	6.5, 1.7, 41, 2.1, 0.90, 8	Clozapine (1A2)	no interaction	1.9	0.086	5.0	0.32	2.63			0.01 (A2), 0.04 (2B6), 0.002 (2C9), 0.03 (2C19), 0.07 (2D6), 0.008 (3A)		No data	no data	Kristensen JH, Ilett KF, Dusci LJ, Hackett LP, Yapp P, Wojnar-Horton RE, Roberts MJ, and Paech M (1998) Distribution and excretion of sertraline and N-desmethylsertraline in human milk. British journal of clinical pharmacology 45:453-457.
		N-Desmethylsertraline	292.2				Tolbutamide (2C9)	no interaction						CYP2D6, 3A	16, 3.5		0.09			Obach RS, Walsky RL, Venkatakrishnan K, Gaman EA, Houston JB, and Tremaine LM (2006) The utility of in vitro cytochrome P450 inhibition data in the prediction of drug-drug interactions. The Journal of pharmacology and experimental therapeutics 316:336-348.

							Desipramine (2D6)	1.5												Kurtz DL, Bergstrom RF, Goldberg MJ, and Cerimele BJ (1997) The effect of sertraline on the pharmacokinetics of desipramine and imipramine. Clinical pharmacology and therapeutics 62:145-156.
							Alprazolam (3A)	no interaction												Park MK, Shin KH, Kim KP, Kim TE, Yoon SH, Cho JY, Shin SG, Jang IJ, and Yu KS (2011) Open label, three period, single sequence, study of 5, 25, 50 mg sertraline pharmacokinetics in healthy male Korean volunteers. International journal of clinical pharmacology and therapeutics 49:672-678.
							Pimozide	1.4												Yeung CK, Fujioka Y, Hachad H, Levy RH, and Isoherranen N (2011) Are circulating metabolites important in drug-drug interactions?: Quantitative analysis of risk prediction and inhibitory potency. Clinical pharmacology and therapeutics 89:105-113.
Unassigned	Sevoflurane	no data	200.1	1% Inhaled 30 min	No data (inhaled)	no data	no data	no data	no data	30	no data	no data	no data	no data	no data	no data	no data	no data	no data	Behne M, Wilke HJ, and Harder S (1999) Clinical pharmacokinetics of sevoflurane. Clinical pharmacokinetics 36:13-26.
2	Sildenafil		474.6	25-100mg tid	CYP3A	0.71	Tacrolimus (3A)	no interaction	1.55 (50 mg)	0.57 (50 mg)	0.69 (50 mg)	0.27 (50 mg)	0.45	no data	no data	0.33	not calculated	no data	no data	Foti RS, Rock DA, Wienkers LC, and Wahlstrom JL (2010) Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using in vitro data and in vivo simulation. Drug metabolism and disposition: the biological fate of chemicals 38:981-987.
		N-Desmethylsildenafil	460.6																	Christ B, Brockmeier D, Hauck EW, and Friemann S (2001) Interactions of sildenafil and tacrolimus in men with erectile dysfunction after kidney transplantation. Urology 58:589-593.
																				Burgess G, Hoogkamer H, Collings L, and Dingemanse J (2008) Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. European journal of clinical pharmacology 64:43-50.
1	Simvastatin		418.6	40md sd	CYP3A	10	Midazolam (3A)	no interaction	0.028	0.0077			0.61	no data	no data	0.00077	no data	no data	no data	Prueksaritanont T, Gorham LM, Ma B, Liu L, Yu X, Zhao JJ, Slaughter DE, Arison BH, and Vyas KP (1997) In vitro metabolism of simvastatin in humans [SBT]identification of metabolizing enzymes and effect of the drug on hepatic P450s. Drug metabolism and disposition: the biological fate of chemicals 25:1191-1199.
		6β-Hydroxy acid simvastatin	436.6	40md sd							0.017	0.0017								Najib NM, Idkaidek N, Adel A, Admour I, Astigarraga RE, Nucci GD, Alam SM, Dham R, and Qumaruzaman (2003) Pharmacokinetics and bioequivalence evaluation of two simvastatin 40 mg tablets (Simvast and Zocor) in healthy human volunteers. Biopharmaceutics & drug disposition 24:183-189.
		6β-Hydroxysimvastatin	434.6																	Kokudai M, Inui N, Takeuchi K, Sakaeda T, Kagawa Y, and Watanabe H (2009) Effects of statins on the pharmacokinetics of midazolam in healthy volunteers. Journal of clinical pharmacology 49:568-573.
		3'-Hydroxysimvastatin	434.6																	
		6'-Exomethylenesimvastatin	416.6																	
		3',5'-Dihydrodiolsimvastatin	452.6																	
Unassigned	Somatropin	no data	22.1 kD	5-8.8mg	no data	no data	no data	no data	0.018	0.0025	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/19764s020lbl.pdf
Unassigned	Sumatriptan	no data	295.4	25mg single	no data	no data	no data	no data	0.18	0.06	no data	no data	not calculated	no data	no data	no data	no data	no data	no data	Duquesnoy C, Mamet JP, Sumner D, and Fuseau E (1998) Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. Eur J Pharm Sci 6:99-104.
2	Tadalafil		389.4	20mg qd x 10d	CYP1A2, 2C9, 2C19, 2D6, 3A	14, 66, 73, >100, 41	Theophylline (1A2)	no interaction	19	1.2								CYP3A KI = 12 μM, kinact = 0.21 min-1	no data	Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE, and Mitchell MI (2006) Tadalafil pharmacokinetics in healthy subjects. British journal of clinical pharmacology 61:280-288.

		Catechol	373.0				Warfarin (2C9)	no interaction												Ring BJ, Patterson BE, Mitchell MI, Vandenbranden M, Gillespie J, Bedding AW, Jewell H, Payne CD, Forgue ST, Eckstein J, Wrighton SA, and Phillips DL (2005) Effect of tadalafil on cytochrome P450 3A4-mediated clearance: studies in vitro and in vivo. Clinical pharmacology and therapeutics 77:63-75.
		Methylcatechol	387.0				Lovastatin (3A)	no interaction							no data	all < 0.1				http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022332s000_ClinPharmR.pdf
		Methylcatechol glucuronide	565.0	20mg qd x 10d			Midazolam (3A)	no interaction			17	0.78	1.3	no data						
2	Tamoxifen		371.5	20mg qd	CYP2D6, 3A	1.7, 6	none reported	no data	7.3	0.40						0.24		CYP3A KI = 0.2 µM, kinact = 0.04 min-1		Zhao, X-J, Jones, DR, Wang, Y-H, Grimm, SW, and Hall, SD (2002) Reversible and irreversible inhibition of CYP3A enzymes by tamoxifen and metabolites. Xenobiotica 32:863-878.
		N-Desmethyltamoxifen	357.5	20mg qd							21	1.1	2.9	CYP3A	8	0.14	no data		CYP3A KI = 1.0, kinact = 0.11 min-1	Buzdar AU, Hortobagyi GN, Frye D, Ho D, Booser DJ, Valero V, Holmes FA, Birmingham BK, Bui K, Yeh C, and et al. (1994) Bioequivalence of 20-mg once-daily tamoxifen relative to 10-mg twice-daily tamoxifen regimens for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 12:50-54.
		4-Hydroxytamoxifen	387.5	20mg qd										CYP3A	<5		no data			
1	Telmisartan		514.6	20-80mg qd	CYP2C9	2.4	Warfarin (2C9)	no interaction	0.95 (40 mg)	0.087 (40 mg)	0.18 (40 mg)	0.013 (40 mg)	0.19	no data	no data	0.036	not calculated	no data	no data	Ren S, Zeng J, Mei Y, Zhang JZ, Yan SF, Fei J, and Chen L (2013) Discovery and characterization of novel, potent, and selective cytochrome P450 2J2 inhibitors. Drug metabolism and disposition: the biological fate of chemicals 41:60-71.
		Telmisatrten glucuronide	693.8																	Kamiyama E, Yoshigae Y, Kasuya A, Takei M, Kurihara A, and Ikeda T (2007) Inhibitory effects of angiotensin receptor blockers on CYP2C9 activity in human liver microsomes. Drug metabolism and pharmacokinetics 22:267-275.
																				Bajcetic M, Benndorf RA, Appel D, Schwedhelm E, Schulze F, Riekhof D, Maas R, and Boger RH (2007) Pharmacokinetics of oral doses of telmisartan and nisoldipine, given alone and in combination, in patients with essential hypertension. Journal of clinical pharmacology 47:295-304.
																				Stangier J, Su CA, Hendriks MG, van Lier JJ, Sollie FA, Oosterhuis B, and Jonkman JH (2000) Steady-state pharmacodynamics and pharmacokinetics of warfarin in the presence and absence of telmisartan in healthy male volunteers. Journal of clinical pharmacology 40:1331-1337.
Unassigned	Temozolomide	no data	194.2	200mg/m^2/d iv infustion	no reported data	no reported data	no reported data	no reported data	154	57	no data	no data	not calculated	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021029s021,022277s005lbl.pdf
																				Hammond LA, Eckardt JR, Baker SD, Eckhardt SG, Dugan M, Forral K, Reidenberg P, Statkevich P, Weiss GR, Rinaldi DA, Von Hoff DD, and Rowinsky EK (1999) Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 17:2604-2613.
4	Terbinafine		327.9	250mg qd	CYP2D6, 3A	0.0224, 204	Desipramine (2D6)	4.9	14	3.1						136				http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020539s021lbl.pdf
																				Abdel-Rahman SM, Marcucci K, Boge T, Gotschall RR, Kearns GL, and Leeder JS (1999) Potent inhibition of cytochrome P-450 2D6-mediated dextromethorphan O-demethylation by terbinafine. *Drug metabolism and disposition: the biological fate of chemicals* 27:770-775.

																				Kosugi Y, Hirabayashi H, Igari T, Fujioka Y, Hara Y, Okuda T, and Moriwaki T (2012) Evaluation of cytochrome P450-mediated drug-drug interactions based on the strategies recommended by regulatory authorities. Xenobiotica; the fate of foreign compounds in biological systems 42:127-138.
																				Madani S, Barilla D, Cramer J, Wang Y, and Paul C (2002) Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. Journal of clinical pharmacology 42:1211-1218.
Unassigned	Teriparatide	no data	4118	20 µg qd	No data	no data	Digoxin	no interaction	no data	65 pg/mL	no data	no data	no data	no data	no data	no data	no data	no data	no data	http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21318s004lbl.pdf
							Furosamide	no interaction												
1	Thalidomide	no data	258.2	50-300mg qd	CYP2C19, CYP3A4	135, no inhibition	Ethinyl estradiol (CYP3A)	No interaction	141	11	no data	no data	not calculated	No data	No data	0.08	Not calculated	No data	no data	Okada Y, Murayama N, Yanagida C, Shimizu M, Guengerich FP, and Yamazaki H (2009) Drug interactions of thalidomide with midazolam and cyclosporine A: heterotropic cooperativity of human cytochrome P450 3A5. Drug metabolism and disposition: the biological fate of chemicals 37:18-23.
																				Teo SK, Sabourin PJ, O'Brien K, Kook KA, and Thomas SD (2000) Metabolism of thalidomide in human microsomes, cloned human cytochrome P-450 isozymes, and Hansen's disease patients. Journal of biochemical and molecular toxicology 14:140-147.
Unassigned	Tiotropium	no data	472.4	0.018mg (1-3x inhaled)	no data	no data	no data	no data	0.0001	0.000030	no data	no data	not calculated	no data	no data	not calculated	not calculated	no data	no data	Durham MC (2004) Tiotropium (Spiriva): a once-daily inhaled anticholinergic medication for chronic obstructive pulmonary disease. Proceedings 17:366-373. Turck et al. Pharmacokinetics of intravenous, single-dose tiotropium in subjects with different degrees of renal impairment J. Clin Pharmacol. 2004 44: 163-72.
1	Topiramate	no data	339.4	15-200mg bid	2C19	> 200 µM	Phenytoin (2C9)	1.1	179	22	no data	no data	not applicable	no data	no data	< 0.1	Not calculated	No data	No data	Sachdeo RC, Sachdeo SK, Levy RH, Streeter AJ, Bishop FE, Kunze KL, Mather GG, Roskos LK, Shen DD, Thummel KE, Trager WF, Curtin CR, Doose DR, Gisclon LG, and Bialer M (2002) Topiramate and phenytoin pharmacokinetics during repetitive monotherapy and combination therapy to epileptic patients. Epilepsia 43:691-696.
																				Britzi M, Soback S, Isoherranen N, Levy RH, Perucca E, Doose DR, Maryanoff BE, and Bialer M (2003) Analysis of topiramate and its metabolites in plasma and urine of healthy subjects and patients with epilepsy by use of a novel liquid chromatography-mass spectrometry assay. Therapeutic drug monitoring 25:314-322.
Unassigned	Valacyclovir	Acyclovir (prodrug)	324.3	1000mg tid	no data	no data	no data	no data	no data	15.8 uM	76.3	26.6	not calculated	no data	no data	no inhibition	no data	no data	no data	Hoglund M, Ljungman P, and Weller S (2001) Comparable aciclovir exposures produced by oral valaciclovir and intravenous aciclovir in immunocompromised cancer patients. The Journal of antimicrobial chemotherapy 47:855-861.
4	Valproate		144.21	500mg tid	CYP2C9, 2C19, 3A	600, 8553, 7975	Losartan	increased the ratio between losartan to its CYP2C9 metabolite from 0.6 (no valproic acid to 1.1 (with valproic acid)	no data	416	no data	no data	not calculated	no data	no data	0.69 (2C9)	no data	CYP2A6 KI = 9150 µM, kinact = 0.048 min-1	no data	Gunes A, Bilir E, Zengil H, Babaoglu MO, Bozkurt A, and Yasar U (2007) Inhibitory effect of valproic acid on cytochrome P450 2C9 activity in epilepsy patients. Basic & clinical pharmacology & toxicology 100:383-386.
		2-(E)-ene-Valproate	142.2	250mg qid			PK only	PK only	11296	613	no data	no data		no data	no data	1.0 (2C9)	no data	no data	no data	Hussein Z, Mukherjee D, Lamm J, Cavanaugh JH, and Granneman GR (1994) Pharmacokinetics of valproate after multiple-dose oral and intravenous infusion administration: gastrointestinal-related diurnal variation. Journal of clinical pharmacology 34:754-759.

		3-oxo-Valproate,	142.2	500mg bid			Amitriptyline (2C19)	1.3	no data	564	no data	no data		no data	no data	0.066 (2C19)	no data			Dhillon S and Richens A (1982) Valproic acid and diazepam interaction in vivo. British journal of clinical pharmacology 13:553-560.
		4-ene-Valproate	142.2	1000-2000mg per day			Nimodipine	1.6	no data	549	no data	no data		no data	no data	0.92 (2C9)	no data			Wen X, Wang JS, Kivisto KT, Neuvonen PJ, and Backman JT (2001) In vitro evaluation of valproic acid as an inhibitor of human cytochrome P450 isoforms: preferential inhibition of cytochrome P450 2C9 (CYP2C9). British journal of clinical pharmacology 52:547-553.
1	Valsartan		435.5	80 mg qd	CYP2C9	170	no data for CYP2C9 substrate	no data	15	4.6	no data	no data	no data	no data	no data	0.027	no data	no data	no data	Taavitsainen P, Kiukaanniemi K, and Pelkonen O (2000) In vitro inhibition screening of human hepatic P450 enzymes by five angiotensin-II receptor antagonists. European journal of clinical pharmacology 56:135-140.
																				Israili ZH (2000) Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. Journal of human hypertension 14 Suppl 1:S73-86.
1	Vardenafil	Desethylpiperazine	488.6	20mg sd	no in vitro inhibition	no in vitro inhibition	Nifedipine (3A)	no interaction	0.067	0.017	0.031	0.017	0.46	no data	no data	not calculated	no data	no data	no data	Rajagopalan P, Mazzu A, Xia C, Dawkins R, and Sundaresan P (2003) Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. Journal of clinical pharmacology 43:260-267.
3	Venlafaxine		277.4	50mg tid	CYP2D6	33	Imipramine (2D6)	1.3	2.1	0.30						0.01				Ball SE, Ahern D, Scatina J, and Kao J (1997) Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. British journal of clinical pharmacology 43:619-626.
		O-Desmethylvenlafaxine	263.4		CYP2D6						5.91	0.46		CYP2D6	>100		<0.0046			Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, and Sellers EM (1996) Venlafaxine oxidation in vitro is catalysed by CYP2D6. British journal of clinical pharmacology 41:149-156.
		N-Desmethylvenlafaxine	263.4		CYP2D6						NA (data not available, generally low in CYP2D6 EM, higher in PM)	NA (data not available, generally low in CYP2D6 EM, higher in PM)		CYP2D6	20					Albers LJ, Reist C, Vu RL, Fujimoto K, Ozdemir V, Helmeste D, Poland R, and Tang SW (2000) Effect of venlafaxine on imipramine metabolism. Psychiatry research 96:235-243.
																				Olver JS, Burrows GD, and Norman TR (2004) The treatment of depression with different formulations of venlafaxine: a comparative analysis. Human psychopharmacology 19:9-16.
																				Klamerus KJ, Maloney K, Rudolph RL, Sisenwine SF, Jusko WJ, and Chiang ST (1992) Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active O-desmethyl metabolite. Journal of clinical pharmacology 32:716-724.
4	Voriconazole		349.3	400mg BIDx7	CYP2B6, 2C9, 2C19, 3A	0.40, 2.8, 5.1, 0.66	Efavirenz	1.4	108	15	no data	no data	no data	no data	no data	37.8	no data	no data	no data	Jeong S, Nguyen PD, and Desta Z (2009) Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. Antimicrobial agents and chemotherapy 53:541-551.
		N-Oxidation	365.3																	Hyland R, Jones BC, and Smith DA (2003) Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug metabolism and disposition: the biological fate of chemicals 31:540-547.
							Sirolimus (3A)	11												Jeu L, Piacenti FJ, Lyakhovetskiy AG, and Fung HB (2003) Voriconazole. Clinical therapeutics 25:1321-1381.
							Tacrolimus (2C8)	3.2												http://www.drugs.com/pro/vfend.html

							Omeprazole (2C9)	2.2												Liu P, Foster G, LaBadie RR, Gutierrez MJ, and Sharma A (2008) Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. Journal of clinical pharmacology 48:73-84.
							Cyclosporine (3A)	1.7												
4	Zileuton	no data	236.3	600mg sd	TDI of 1A2	IC50 > 50 uM for all other CYPs	Theophylline (1A2)	2.0	81	21	no data	no data	no data	no data	no data	no data	no data	CYP1A2 (S) KI = 98.2 µM, kinact = 0.037 min-1	no data	Lu P, Schrag ML, Slaughter DE, Raab CE, Shou M, and Rodrigues AD (2003) Mechanism-based inhibition of human liver microsomal cytochrome P450 1A2 by zileuton, a 5-lipoxygenase inhibitor. Drug metabolism and disposition: the biological fate of chemicals 31:1352-1360.
							Warfarin (2C9)	1.2												http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022052s005lbl.pdf
1	Ziprasidone		412.9	20mg sd	CYP2D6, 3A	16, 36	Dextromethorphan	no interaction	0.83	0.14	no data	no data	no data	no data	no data	0.0088	no data	no data	no data	Prakash C, Kamel A, Cui D, Whalen RD, Miceli JJ, and Tweedie D (2000) Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. British journal of clinical pharmacology 49 Suppl 1:35S-42S.
		M9																		Wilner KD, Tensfeldt TG, Baris B, Smolarek TA, Turncliff RZ, Colburn WA, and Hansen RA (2000) Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. British journal of clinical pharmacology 49 Suppl 1:15S-20S.
		M10																		
Unassigned	Zoledronate	no data	272.1	4mg q3-4wk (IV infusion) for oncology; 5 mg q1-2y (IV infusion) for osteoporosis	no CYP inhibition	NA	No DDI study/data reported	no data	1.48 after 4 mg (5 or 15 min infusion)	1.18 after 4 mg (5 or 15 min infusion)	Compound not metabolized		no data	no data	no data	no data	no data	no data	no data	Chen T, Berenson J, Vescio R, Swift R, Gilchick A, Goodin S, LoRusso P, Ma P, Ravera C, Deckert F, Schran H, Seaman J, and Skerjanec A (2002) Pharmacokinetics and pharmacodynamics of soledronic acid in cancer patients with bone metastasis. Journal of Clinical Pharmacology 42: 122801236,
																				http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21223lbl.pdf
																				https://www.pharma.us.novartis.com/product/pi/pdf/reclast.pdf
1	Zolpidem	no data	307.4	10mg qd	CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A	>100 uM	Caffeine	no interaction	1.2	0.27	no data	no data	no data	no data	no data	<0.0027	no data	no data	no data	Salva P and Costa J (1995) Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clinical pharmacokinetics 29:142-153.
							Fluoxetine	no interaction												Hojo Y, Echizenya M, Ohkubo T, and Shimizu T (2011) Drug interaction between St John's wort and zolpidem in healthy subjects. Journal of clinical pharmacy and therapeutics 36:711-715.
							Sertraline	no interaction												Bomsien S, Aderjan R, Mattern R, and Skopp G (2006) Effect of psychotropic medication on the in vitro metabolism of buprenorphine in human cDNA-expressed cytochrome P450 enzymes. European journal of clinical pharmacology 62:639-643.
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