1521-009X/46/6/835–845$35.00
Drug Metabolism and Disposition

https://doi.org/10.1124/dmd.117.078691
Drug Metab Dispos 46:835–845, June 2018

Minireview

Risk of Clinically Relevant Pharmacokinetic-Based Drug-Drug Interactions with Drugs Approved by the U.S. Food and Drug Administration Between 2013 and 2016[S]

Jingjing Yu, Zhu Zhou, Jessica Tay-Sontheimer, René H. Levy, and Isabelle Ragueneau-Majlessi

Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, Washington (J.Y., J.T.-S., R.H.L., I.R.-M.); and Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, California (Z.Z.)

Received September 29, 2017; accepted March 16, 2018

ABSTRACT

A total of 103 drugs (including 14 combination drugs) were approved by the U.S. Food and Drug Administration from 2013 to 2016. Pharmacokinetic-based drug interaction profiles were analyzed using the University of Washington Drug Interaction Database, and the clinical relevance of these observations was characterized based on information from new drug application reviews. CYP3A was involved in approximately two-thirds of all drug-drug interactions (DDIs). Transporters (alone or with enzymes) participated in about half of all interactions, but most of these were weak-to-moderate interactions. When considered as victims, eight new molecular entities (NMEs; cobimetinib, ibrutinib, isavuconazole, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax) were identified as sensitive substrates of CYP3A, two NMEs (pirfenidone and tasimelteon) were sensitive substrates of CYP1A2, one NME (dasabuvir) was a sensitive substrate of CYP2C8, one NME (eliglustat) was a sensitive substrate of CYP2D6, and one NME (grazoprevir) was a sensitive substrate of OATP1B1/3 (with changes in exposure greater than 5-fold when coadministered with a strong inhibitor). Approximately 75% of identified CYP3A substrates were also substrates of P-glycoprotein. As perpetrators, most clinical DDIs involved weak-to-moderate inhibition or induction. Only idelalisib showed strong inhibition of CYP3A, and lumacaftor behaved as a strong CYP3A inducer. Among drugs with large changes in exposure (≥5-fold), whether as victim or perpetrator, the most-represented therapeutic classes were antivirals and oncology drugs, suggesting a significant risk of clinical DDIs in these patient populations.

Introduction

Pharmacokinetic (PK)-based drug-drug interactions (DDIs) constitute one of the major causes of drug withdrawal from the market in recent decades (Huang et al., 2008). Mechanistic methodologies have been used by the pharmaceutical industry to assess DDI risk during the drug-development process. Currently, these methodologies include evaluation of the potential of a new molecular entity (NME) to affect the metabolism or transport of other drugs and the potential for the new drug's metabolism or transport to be affected by other drugs, with recommended clinical index substrates and specific inhibitors/inducers of drug-metabolizing enzymes (DMEs) or transporters (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; Food and Drug Administration, 2012a). Additionally, if an NME is commonly used with another drug in a designated patient population, it is recommended that the DDI risk between the two drugs be evaluated. This review encompasses a detailed analysis of clinical DDIs mediated by DMEs and transporters based on new drug applications (NDAs) approved by the U.S. Food and Drug Administration (FDA) from 2013 to 2016. It highlights the main mechanistic findings and discusses their clinical relevance, identifying substrates with varying degrees of sensitivity and inhibitors/inducers with varying potency of DMEs and transporters, and how these findings are reflected in the labeling. These findings will aid in the understanding, predict, and reduce DDI risk and associated adverse reactions in certain patient populations, in which polytherapy is common. Through systematic analysis, this review aimed to provide communications on DDI risk evaluation and management as well as clinical implications to pharmaceutical researchers and health care providers.

https://doi.org/10.1124/dmd.117.078691.
[S] This article has supplemental material available at dmd.aspetjournals.org.

Materials and Methods

This analysis was performed using the University of Washington Drug Interaction Database, a drug interaction and pharmacogenetic (PGx) database (http://www.druginteractioninfo.org). Clinical DDI study results included in this analysis were generated from dedicated DDI clinical trials, PGx studies, as well as physiologically based pharmacokinetics (PBPK) simulations that are used as alternatives to dedicated clinical studies. As in previous publications, mean area under the drug plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) ratios that are systematically presented by the Drug Interaction Database are the metrics used

ABBREVIATIONS: AUC, area under the drug plasma concentration-time curve; BCRP, breast cancer resistance protein; CNS, central nervous system; DDI, drug-drug interaction; DME, drug-metabolizing enzyme; FDA, Food and Drug Administration; FDC, fixed-dose combination; MRP, multidrug resistance-associated protein; NDA, new drug application; NME, new molecular entity; NTR, narrow therapeutic range; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P450, cytochrome P450; PBPK, physiologically based pharmacokinetics; P-gp, P-glycoprotein; PGx, pharmacogenetics; PK, pharmacokinetics; UM, ultrarapid metabolizer.

to evaluate clinical studies. In the present analysis, all positive clinical studies (defined as AUC ratios ≥1.25 for inhibition and ≤0.8 for induction) were analyzed. Because a 2-fold change in drug exposure often triggers dose recommendations, all DDI studies with exposure changes ≥2-fold were highlighted regardless of labeling effects. Also, studies with drug exposure changes of 1.25- to 2-fold and still triggering dose recommendations are presented. In accordance with the FDA classification (FDA, 2012a), NMEs were considered as sensitive or moderate sensitive clinical substrates if they demonstrated maximum AUC ratios of ≥5 or 2–5, respectively, with strong inhibitors of a given metabolic pathway. Therefore, in this review, the DDI results were presented based on inhibition studies when NMEs were evaluated as substrates, with additional evidence from drug interaction studies using strong inducers. On the other hand, an NME was considered as a strong, moderate, or weak clinical inhibitor or inducer (of a given disposition pathway) when the observed maximum AUC ratio was ≥5, 2–5, and 1.25–2, respectively, for inhibitors, and ≤0.2, 0.2–0.5, and 0.5–0.8, respectively, for inducers, with coadministration of a sensitive clinical substrate.

Results

From 2013 to 2016, a total of 103 NDAs [including 14 combination drugs, total NMEs = 107; Supplemental Table 1, with chemical structures presented in Supplemental Table 2 for drugs approved in 2016 and previous publications (Yu et al., 2014, 2016, 2017) for drugs approved from 2013 to 2015] and 32 biologics license applications were approved by the FDA. Because of the different disposition and elimination mechanisms of biologics compared with small molecules and their low risk for PK-based drug interactions, biologics license applications contain few studies relevant to the present analysis and were not included in this review. Among all the NDAs included in the analysis, the most represented therapeutic areas were oncology (21%) and anti-infective drugs (20%), followed by central nervous system (CNS) agents (13%), metabolism disorder/endocrinology drugs (11%), and cardiovascular drugs (10%). Among the anti-infective drugs ($N = 21$), there are 10 antivirals, six antibacterials, four antifungals, and one antiparasitic. Ninety-eight of the 103 NDAs had drug metabolism data and 81 had transporter data available, including in vitro and/or clinical evaluations. NDAs for all years analyzed included extensive in vitro evaluations of drug metabolism profiles ranging from 88% (in 2013) to 100% of the NDAs (in 2014). There was an increase in the percentage of NDAs that included assessment of in vitro transport from 73% to 80% evaluated between 2013 and 2015 to 93% evaluated in 2016. In particular, the number of transporter experiments per drug increased dramatically in the past 4 years, from 6 in 2013 to 22 in 2016. The types of transporters evaluated also expanded from 16 (in 2013) to 21 (in 2016). In addition to the nine transporters recommended by the FDA draft guidance (FDA, 2012a) and the International Transporter Consortium white paper (Hillgren et al., 2013), 18 other transporters were assessed in the NDAs. Transporters evaluated in these NDAs included apical sodium-dependent bile acid transporter; bile salt export pump; breast cancer resistance protein (BCRP); multidrug and toxin extrusion proteins 1 and 2-K (MATE1 and MATE2-K); multidrug resistance-associated proteins 1, 2, 3, 4, 5, and 8 (MRP1, MRP2, MRP3, MRP4, MRP5, and MRP8); organic anion transporters 1, 2, 3, and 4 (OAT1, OAT2, OAT3, and OAT4); organic anion transporting polypeptides 1A2, 1B1, 1B3, and 2B1 (OATP1A2, OATP1B1, OATP1B3, and OATP2B1); organic cation transporters 1, 2, and 3 (OCT1, OCT2, OCT3); organic cation/carnitine transporters 1 and 2 (OCTN1 and OCTN2); P-glycoprotein (P-gp); sodium-taurocholate cotransporting polypeptide; and urate transporter 1 (URAT1). Finally, in addition to clinical DDI studies, 16 NDAs presented PGx information, and 16 had PBPK simulation data that directly supported dosing recommendations. An analysis of clinically relevant DDI findings and related in vitro investigations is presented in the following sections. Key DDI findings are summarized in Tables 1–4,

TABLE 1

Inhibition DDIs with AUC ratios ≥5, NME as substrate

Drugs were orally administered unless specified.

Victim Drug	Inhibitor	Main Enzymes/Transporters Possibly Involved	AUC Ratio	Reference
Paritaprevir	Ritonavir	CYP3A, P-gp, BCRP, OATP1B1/3	47.43	FDA (2014m)
Eliglustat	Ketoconazole/paroxetine	CYP3A, CYP2D6[a]	37.85 (PBPK in EMs)	FDA (2014c)
Eliglustat	Paroxetine	CYP2D6	28.40 (UMs)	FDA (2014c)
Ibrutinib	Ketoconazole	CYP3A	23.90	FDA (2013g)
Eliglustat	Fluconazole/terbinafine	CYP3A, CYP2D6	19.31 ($AUC_{0-24\ h}$, PBPK in EMs)	FDA (2014c)
Grazoprevir	Cyclosporine	OATP1B1/3[b]	15.25 ($AUC_{0-24\ h}$)	FDA (2016d)
Grazoprevir	Lopinavir/ritonavir	CYP3A, OATP1B1/3[b]	12.87	FDA (2016d)
Naloxegol	Ketoconazole	CYP3A[a]	12.42	FDA (2014h)
Grazoprevir	Atazanavir/ritonavir	CYP3A, OATP1B1/3[b]	10.56	FDA (2016d)
Grazoprevir	Rifampin (i.v.)	OATP1B1/3	10.22	FDA (2016d)
Eliglustat	Paroxetine	CYP2D6	10.00 (EMs)	FDA (2014c)
Dasabuvir	Gemfibrozil	CYP2C8	9.90	FDA (2014m)
Eliglustat	Ketoconazole/paroxetine	CYP3A, CYP2D6[a]	9.81 (PBPK in IMs)	FDA (2014c)
Ibrutinib	Erythromycin	CYP3A	8.60 (PBPK)	FDA (2013g)
Grazoprevir	Rifampin	OATP1B1/3[b]	8.37	FDA (2016d)
Ivabradine	Josamycin	CYP3A[a]	7.70	FDA (2015c)
Ivabradine	Ketoconazole	CYP3A[a]	7.70	FDA (2015c)
Eliglustat	Fluconazole	CYP3A	7.54 (PBPK in PMs)	FDA (2014c)
Grazoprevir	Darunavir/ritonavir	CYP3A, OATP1B1/3[b]	7.49	FDA (2016d)
Simeprevir	Ritonavir	CYP3A[a]	7.18	FDA (2013i)
Tasimelteon	Fluvoxamine	CYP1A2[c]	6.87	FDA (2014f)
Pirfenidone	Fluvoxamine	CYP1A2	6.81 (smokers), 3.97 (nonsmokers)	FDA (2014d)
Cobimetinib	Itraconazole	CYP3A[a]	6.62	FDA (2015d)
Simeprevir	Erythromycin	CYP3A[a]	6.54	FDA (2013i)
Flibanserin	Fluconazole	CYP3A, CYP2C19	6.41	FDA (2015a)
Venetoclax	Ketoconazole	CYP3A, P-gp	6.40	FDA (2016e)
Eliglustat	Ketoconazole	CYP3A[a]	6.22 (PBPK in PMs)	FDA (2014c)
Ibrutinib	Diltiazem	CYP3A	5.50 (PBPK)	FDA (2013g)
Isavuconazonium sulfate (prodrug)	Ketoconazole	CYP3A, butyrylcholinesterase	5.22	FDA (2015e)
Eliglustat	Paroxetine	CYP2D6	5.20 (IMs)	FDA (2014c)

EM, CYP2D6 extensive metabolizer; IM, CYP2D6 intermediate metabolizer; PM, CYP2D6 poor metabolizer; UM, CYP2D6 ultrarapid metabolizer; i.v., intravenously.
[a]Also a substrate of P-gp based on in vitro results; inhibition of P-gp might contribute to the observed interaction.
[b]Also a substrate of P-gp and BCRP based on in vitro results.
[c]Also metabolized by CYP3A, CYP2C9, and CYP2C19; fluvoxamine inhibits these P450s.

TABLE 2

Induction DDIs with AUC ratios ≤0.2, NME as substrate

Drugs were orally administered; in all DDIs, rifampin was used as the inducer except for grazoprevir, where efavirenz was the inducer.

Victim Drug	Main Enzymes/Transporters Possibly Involved	AUC Ratio	Reference
Isavuconazonium sulfate	CYP3A, butyrylcholinesterase	0.03	FDA (2015e)
Eliglustat	CYP3A[a]	0.04 (PMs)	FDA (2014c)
Flibanserin	CYP3A, CYP2C19	0.04	FDA (2015a)
Ibrutinib	CYP3A[a]	0.08 (PBPK)	FDA (2013g)
Eliglustat	CYP3A[a]	0.09 (IMs)	FDA (2014c)
Eliglustat	CYP3A[a]	0.10 (EMs)	FDA (2014c)
Naloxegol	CYP3A[a]	0.11	FDA (2014h)
Olaparib	CYP3A[a]	0.11	FDA (2014g)
Rolapitant	CYP3A	0.12	FDA (2015o)
Suvorexant	CYP3A	0.12	FDA (2014b)
Tasimelteon	CYP3A[a,b]	0.14	FDA (2014f)
Palbociclib	CYP3A[a]	0.15	FDA (2015h)
Cobimetinib	CYP3A[a]	0.17 (PBPK)	FDA (2015d)
Grazoprevir	CYP3A[c]	0.17	FDA (2016d)
Velpatasvir	CYP2B6, CYP2C8, CYP3A, P-gp, BCRP	0.19	FDA (2016b)
Netupitant	CYP3A	0.20	FDA (2014a)

EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.
[a]Also a substrate of P-gp based on in vitro results; induction of P-gp might contribute to the observed interaction.
[b]Also metabolized by CYP1A2, CYP2C9, and CYP2C19; rifampin is an inducer of multiple P450s.
[c]Also a substrate of P-gp and BCRP based on in vitro results; induction of P-gp and BCRP might contribute to the observed interaction.

including maximum AUC ratios, enzymes and transporters possibly involved, and overall labeling impact. For each interaction, more detailed information, such as dosing regimen for victim and precipitant drugs, study design, study population, and specific labeling impact, is presented in Supplemental Tables 3–6.

NMEs as Substrates

Overall, for drugs evaluated as substrates, there were approximately 100 inhibition studies with AUC ratios ≥2 and 50 induction studies with AUC ratios ≤0.5 with concomitant administration of inhibitors and inducers, respectively. Additionally, approximately 30 inhibition studies with AUC ratios of 1.25–2 and 10 induction studies with AUC ratios of 0.5–0.8 were associated with dose recommendations included in the drug label. A total of 53 NMEs served as victim drugs in these interaction studies. Of these drugs, cancer treatments and antivirals are the dominant therapeutic areas (Figs. 1A and 2A).

DDIs with AUC Changes ≥5-fold: Sensitive Clinical Substrates. When NMEs served as victims, 14 drugs were found to have AUC ratios ≥5 when coadministered with strong inhibitors (Supplemental Table 3; Table 1). In terms of therapeutic classes, the most represented area is anti-infective agents (36%), including four antivirals and one antifungal, followed by cancer treatments ($N = 3$, 21%) and CNS agents ($N = 2$, 14%) (Supplemental Fig. 1A). This pattern of prevalence is consistent among drugs approved from 2013 to 2016.

The highest AUC change was observed with the antiviral paritaprevir, which exhibited a 47.43-fold increase in the presence of ritonavir (100-mg single dose, not an NME), a strong inhibitor of CYP3A (also an inhibitor of multiple transporters). This DDI effect was observed in a fixed-dose combination (FDC) drug (ombitasvir/paritaprevir/ritonavir copackaged with dasabuvir), where paritaprevir is administered at low dose (100 mg) and the role of ritonavir is to increase paritaprevir peak and trough concentrations as well as its overall drug exposure.

Eliglustat, a glucosylceramide synthase inhibitor indicated for the treatment of Gaucher disease, exhibited the second-largest DDI effect, wherein the strong CYP2D6 inhibitor paroxetine (30 mg once daily for 10 days) significantly increased eliglustat AUC 28.40-fold in CYP2D6 ultrarapid metabolizer subjects. Increases of 10.00- and 5.20-fold were observed in CYP2D6 extensive metabolizers and intermediate metabolizers, respectively, when eliglustat was coadministered with paroxetine. Consistent with these findings, the exposure to eliglustat (100 mg twice daily) was 2.60-fold higher in intermediate metabolizers, 7.80-fold higher in poor metabolizers, and 85.6% lower in ultrarapid metabolizers compared with CYP2D6 extensive metabolizer subjects. Based on these observations, genetic testing is considered necessary before administering eliglustat, and dose adjustment is needed depending on CYP2D6 polymorphism and/or coadministration with a strong or moderate CYP2D6 inhibitor (FDA, 2014c).

Regarding possible mechanism(s) of these large interactions, significant changes in victim drug exposure could be attributed to one or more of the following DMEs and transporters: CYP1A2, CYP2C8, CYP2D6, CYP3A, BCRP, OATP1B1/3, and P-gp (Supplemental Fig. 1B). CYP3A was involved in two-thirds of the drug interactions, either as a

TABLE 3

Inhibition DDIs with AUC ratios ≥5, NME as inhibitor

Drugs were orally administered.

Victim Drug	Inhibitor	Main Enzymes/Transporters Possibly Involved	AUC Ratio	Reference
Tacrolimus	Ombitasvir, paritaprevir, and ritonavir	CYP3A, P-gp	85.92	FDA (2014m)
Tacrolimus	Paritaprevir, dasabuvir, and ritonavir	CYP3A, P-gp	78.68	FDA (2014m)
Tacrolimus	Ombitasvir, paritaprevir, dasabuvir, and ritonavir	CYP3A, P-gp	57.07	FDA (2014m)
Cyclosporine	Ombitasvir, paritaprevir, dasabuvir, and ritonavir	CYP3A, P-gp	5.78	FDA (2014m)
Midazolam	Idelalisib	CYP3A	5.15	FDA (2014o)

TABLE 4

Induction DDIs with AUC ratios ≤0.5, NME as inducer

Drugs were orally administered.

Victim Drug	Inducer	Main Enzymes/Transporters Possibly Involved	AUC Ratio	Reference
Itraconazole	Ivacaftor and lumacaftor	CYP3A	0.18	FDA (2015k)
Ivacaftor	Lumacaftor	CYP3A	0.20	FDA (2015k)
Midazolam	Dabrafenib	CYP3A	0.26	FDA

main contributor or together with other cytochrome P450s (P450s) or transporters. Eight drugs in this group [cobimetinib, ibrutinib, isavuconazole (the active metabolite of prodrug isavuconazonium sulfate), ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax] were identified as sensitive clinical substrates of CYP3A, with AUC ratios of 6.62, 23.90, 5.22, 7.70, 12.42, 47.43, 7.18, and 6.40, respectively, when coadministered with strong CYP3A inhibitors such as itraconazole, ketoconazole, or ritonavir. For cobimetinib, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax, contributions of P-gp are possible, as in vitro studies showed that they are all substrates of P-gp (FDA, 2014c,h, 2015c,d), and itraconazole, ketoconazole, and ritonavir are known inhibitors of P-gp (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; FDA, 1996). Further, OATP1B1/3 (and possibly BCRP) may also be a factor in the interaction between paritaprevir and ritonavir. Due to a lack of specific inhibitors, it remains challenging to identify the exact contribution of each enzyme or transporter to drug disposition. On the other hand, these eight drugs are also sensitive to induction. Coadministration of the strong CYP3A inducers carbamazepine (for paritaprevir), rifampin (for cobimetinib, ibrutinib, isavuconazole, naloxegol, and venetoclax), or St. John's wort (for ivabradine PBPK simulations) or the moderate inducer efavirenz (for simeprevir) significantly reduced drug exposure by 70%–97%, suggesting a reduction in therapeutic efficacy (FDA, 2013i, 2014m, 2015c) (Supplemental Table 4; Table 2). In addition to being substrates of CYP3A, four of these drugs were identified as sensitive clinical substrates of other P450s—pirfenidone and tasimelteon of CYP1A2, dasabuvir of CYP2C8, and eliglustat of CYP2D6. The plasma exposure of pirfenidone, tasimelteon, dasabuvir, and eliglustat increased 6.81-, 6.87-, 9.90-, and 28.40-fold, respectively, when coadministered with the strong clinical inhibitors fluvoxamine, gemfibrozil, and paroxetine (FDA, 2014c,d,f,m). In vitro studies showed that tasimelteon is also metabolized by CYP3A (FDA, 2014f), and fluvoxamine is a weak inhibitor of CYP3A (Lam et al., 2003). However, coadministration of ketoconazole (strong CYP3A inhibitor) only slightly increased tasimelteon AUC (by 45%), suggesting that inhibition of CYP3A-mediated metabolism of tasimelteon by fluvoxamine is negligible (FDA, 2014f). A 6.41-fold increase in flibanserin exposure was observed when coadministered with fluconazole, a strong CYP2C19 inhibitor and a moderate CYP3A inhibitor, whereas a smaller change (4.61-fold) was observed with coadministration of the strong CYP3A inhibitor ketoconazole, suggesting that CYP3A plays a primary role in the disposition of flibanserin with partial contribution from CYP2C19, but flibanserin is not a sensitive substrate of CYP3A (FDA, 2015a).

In addition to metabolism, transporters seem to play an important role in some cases. For example, in vitro studies suggest that grazoprevir is a substrate of OATP1B1/3, BCRP, and P-gp (FDA, 2016f). Grazoprevir exposure was increased 10.22-fold with concomitant administration of intravenous rifampin, a clinical inhibitor of OATP1B1/3, suggesting that grazoprevir is a sensitive clinical substrate of OATP1B1/3. A 15.25-fold increase in grazoprevir AUC was observed when coadministered with the multitransporter inhibitor cyclosporine, suggesting an involvement of BCRP and P-gp in addition to OATP (FDA, 2016f).

Consistent with the large changes in drug exposure observed with these 14 drugs (13 identified as sensitive substrates), their product labels included clinical recommendations (contraindicate, avoid, not recommend, or reduce the dose).

DDIs with 2 ≤ AUC Ratios < 5: Moderate Sensitive Clinical Substrates. A total of 28 drugs (including eight drugs overlapping with the group of AUC ratios ≥5) demonstrated AUC increases of 2- to 5-fold when coadministered with inhibitors of enzymes and/or transporters. Detailed DDI data are presented in Supplemental Table 3. The majority of these DDIs were addressed in the product labeling, mostly with a recommendation to avoid coadministration or to reduce the dose. The largest number of drugs in this group are antivirals ($N = 8$), followed by cardiovascular drugs ($N = 5$), CNS agents ($N = 5$), cancer treatments ($N = 4$), and gastrointestinal agents ($N = 3$) (Supplemental Fig. 1C). In brief, among the 32 drug interactions identified in this group, the majority are attributable to inhibition of one enzyme or transporter by strong inhibitors (Supplemental Fig. 1D); therefore, the NMEs are considered moderate sensitive substrates in accordance with the FDA classification and terminology (FDA, 2012a). CYP3A plays a dominant role by mediating two-thirds of the drug interactions. Interestingly, P-gp, BCRP, and OATP1B1/3 are involved in approximately one-third of these interactions either as an individual contributor or together with other transporters or CYP3A (Supplemental Fig. 1D). Changes in victim exposure appeared to be no larger than 3-fold for most interactions.

DDIs with 1.25 ≤ AUC Ratios < 2 and Triggering Dose Recommendations. As victims, 21 NMEs (five overlapping with the AUC ratio ≥5 group, three overlapping with the AUC ratios between 2 and 5 group, and one overlapping with both groups) were found to have slight increases of less than 2-fold in their exposure when coadministered with inhibitors; however, label recommendations were triggered due to safety concerns (Supplemental Table 3). In most of these cases, the labels included recommendations to monitor drug exposure and/or patients for increased drug exposure–associated adverse reactions and/or reduce dose. The most represented drug areas are cancer treatments ($N = 8$) and antivirals ($N = 4$) (Supplemental Fig. 1E).

CYP3A was again found to be a significant contributor, mediating more than 60% of the interactions, partially with contributions from other P450s or P-gp/OATP1B1/3 (Supplemental Fig. 1F). However, CYP3A did not seem to play a primary role in the drug disposition of the following NMEs: dabrafenib, dasabuvir, idelalisib, nintedanib, ospemifene, palbociclib, panobinastat, trabectedin, vilanterol, and vorapaxar.

Different label recommendations were triggered on the basis of different DDI scenarios. For example, as discussed earlier, venetoclax was identified as a sensitive CYP3A substrate through an interaction study with ketoconazole, a strong CYP3A inhibitor. Due to the large increase in venetoclax exposure, concomitant use of venetoclax with strong CYP3A inhibitors is contraindicated, or venetoclax dose reduction is recommended depending on different treatment phases (FDA, 2016e). When coadministered with moderate CYP3A inhibitors, such as ciprofloxacin, diltiazem, or fluconazole, a 40%–60% increase was observed in venetoclax exposure. Considering the risk of toxicities associated with increased exposure, concomitant use of venetoclax with moderate CYP3A inhibitors should also be avoided. If a moderate

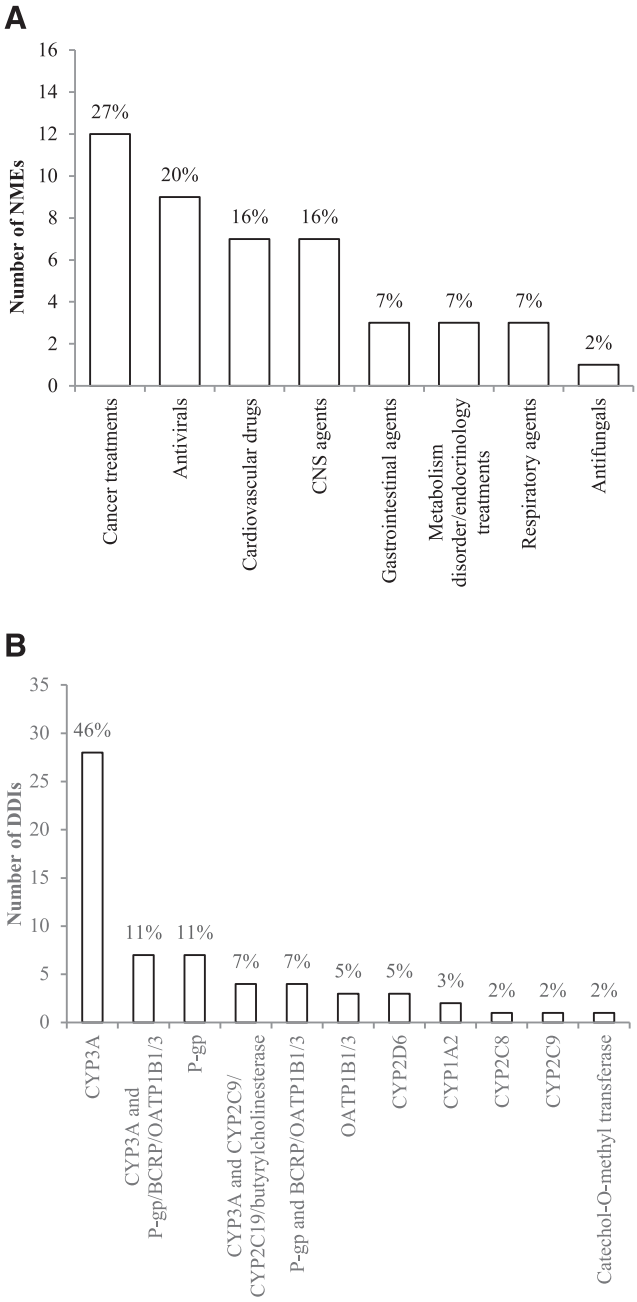

Fig. 1. Quantitation of NMEs acting as substrates in inhibition DDIs for drugs approved by the U.S. FDA between 2013 and 2016 and quantitation of those DDIs. (A) Therapeutic classes of NMEs acting as substrates in inhibition DDIs ($N = 45$ NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. (B) Mechanisms of inhibition DDIs with NMEs acting as the substrate ($N = 61$ DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

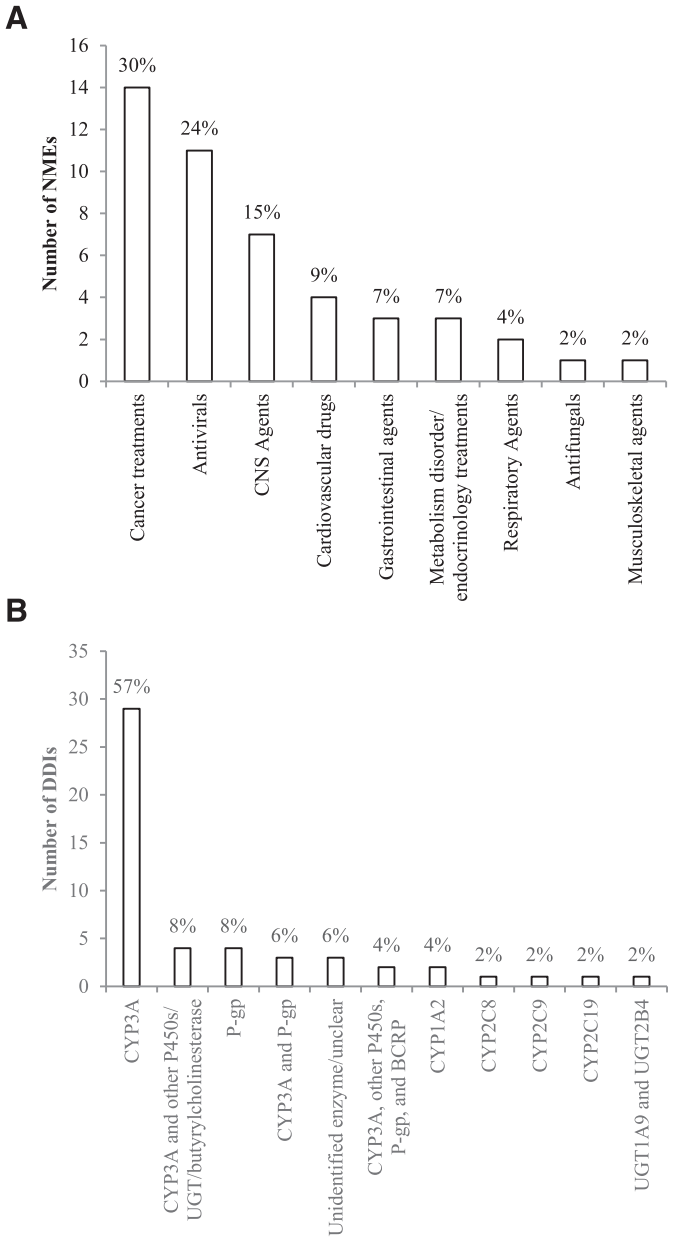

Fig. 2. Quantitation of NMEs acting as substrates in induction DDIs for drugs approved by the U.S. FDA between 2013 and 2016 and quantitation of those DDIs. (A) Therapeutic classes of NMEs acting as substrates in induction DDIs ($N = 46$ NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. (B) Mechanisms of induction DDIs with NMEs acting as the substrate ($N = 51$ DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

CYP3A inhibitor must be used, the dose of venetoclax should be reduced by at least 50%, and patients need to be monitored closely for signs of toxicities (FDA, 2016e). Exposure to venetoclax was not affected by coadministration of weak CYP3A inhibitors. Additionally, a 600-mg single dose of rifampin increased venetoclax AUC by 78% and C_{max} by 113%, likely by inhibiting P-gp–mediated efflux of ventoclax. Labeling recommendations similar to those with moderate CYP3A inhibitors were proposed for concomitant use of venetoclax with P-gp inhibitors (FDA, 2016e).

In Vitro–In Vivo Considerations for NMEs as Substrates. Overall, when all NMEs were evaluated as substrates, CYP3A and P-gp were involved to some degree in approximately 65% and 30% of all clinical interactions, respectively. When evaluated in vitro, CYP3A4/5 was shown to metabolize 64 NMEs (Fig. 3A). Of these, 39 NMEs were confirmed in vivo (systemic exposure increases ≥25%) when coadministered with strong or moderate CYP3A inhibitors. All the drugs with the exception of velpatasvir and netupitant included dosing recommendations in their labeling pertaining to inhibition and/or induction of CYP3A. With regard to P-gp, a total of 47 NMEs were shown to be substrates of P-gp in vitro (more than any other transporter) (Fig. 3B), and 74% of the clinical CYP3A substrates (29 out of 39 drugs) were shown to be substrates of P-gp in vitro. Twenty-six NMEs were further evaluated in vivo, and 21 showed positive results with AUC ratios of 1.25–7.70. However, among DDIs with large changes of ≥5-fold in victim exposure, the role of P-gp was unclear since the affected drugs were substrates of either CYP3A or OATP1B1/3.

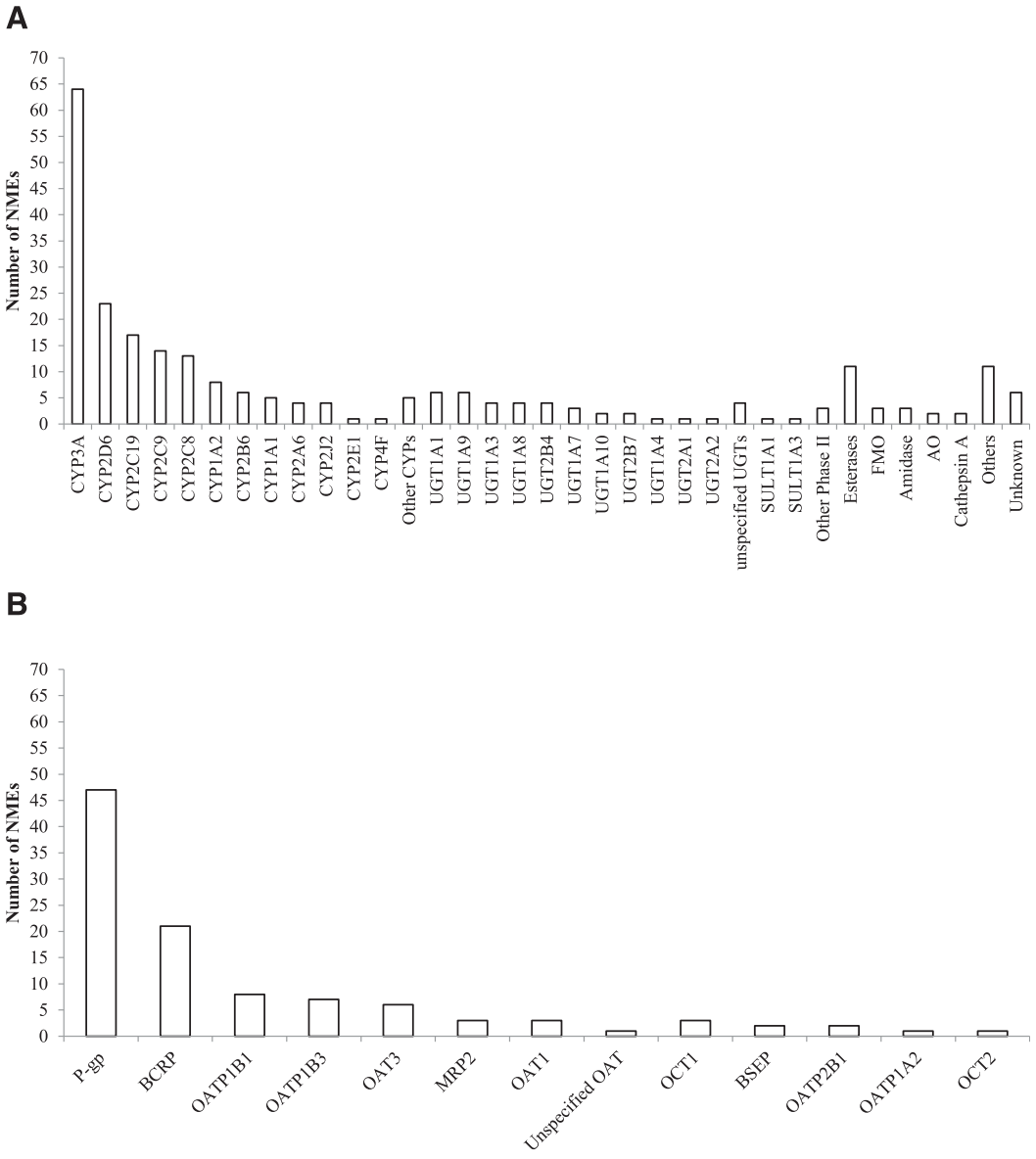

Fig. 3. Quantitation of NMEs acting as substrates of enzymes or transporters for drugs approved by the U.S. FDA between 2013 and 2016. (A) Drug-metabolizing enzymes contributing to NME metabolism. Only parent drugs as substrates of enzymes are shown. Other CYPs were not specified by the authors; other phase II enzymes include SULT2A1, other sulfotransferases, glutathione *S*-transferases, and unspecified conjugated enzymes; others include catecholamine pathway enzymes, epoxide hydrolase, hydrolases, phospholipidase, phosphatase, proteinase, nucleases, nucleotidase, thymidine phosphorylase, and unspecified biotransformation enzymes. AO, aldehyde oxidase; FMO, flavin-containing monooxygenase. (B) Transporters contributing to NME transport. Only parent drugs as substrates of transporters are shown. BSEP, bile salt export pump.

NMEs as Inhibitors

When NMEs were evaluated as inhibitors, 20 drugs were found to show clinically relevant inhibition, with approximately 40 DDIs presenting AUC ratios ≥2 and 50 DDIs presenting AUC ratios of 1.25–2 and triggering dose recommendations. Among these drugs, the most represented therapeutic areas are anti-infective agents (N = 8), including six antivirals, one antibacterial, and one antifungal, followed by cancer treatments (N = 4), CNS drugs (N = 3), gastrointestinal agents (N = 3), and metabolism disorder/endocrinology treatments (N = 2) (Fig. 4A).

DDIs with AUC Ratios ≥5: Strong Clinical Inhibitors. Only two drugs, the antiviral FDC drug Viekira Pak (paritaprevir, ritonavir, ombitasvir, and dasabuvir; manufactured by AbbVie Inc., North Chicago, IL) and the kinase inhibitor idelalisib, were found to cause strong inhibition, increasing exposure of victim drugs ≥5-fold (Supplemental Table 5; Table 3). CYP3A was the only enzyme affected, with partial contribution by P-gp. The largest change in exposure was observed with Viekira Pak (paritaprevir/ritonavir 150/100 mg once daily + ombitasvir 25 mg once daily + dasabuvir 400 mg twice daily for 28 days), showing a drastic increase in tacrolimus exposure with an AUC ratio of 57.07. Similarly, an approximately 5-fold increase in cyclosporine (a CYP3A and P-gp substrate) exposure was observed when coadministered with Viekira Pak. Considering the risks associated with large increases in exposure of tacrolimus and cyclosporine, significant dose adjustment and close monitoring of their blood concentrations are recommended for both immunosuppressants when coadministered with Viekira Pak (FDA, 2014m). Since the strong inhibition by Viekira Pak was caused by ritonavir, which is not an NME, this FDC drug was not counted as a strong inhibitor in this analysis. A larger increase in tacrolimus exposure, 80-fold AUC increase, was

observed when ritonavir was combined with paritaprevir/ombitasvir or paritaprevir/dasabuvir for 28 days. Idelalisib showed strong inhibition of CYP3A, increasing the AUC of midazolam 5.15-fold. Consequently, coadministration of idelalisib with CYP3A substrates should be avoided (FDA, 2014o), and idelalisib is considered a strong inhibitor of CYP3A.

DDIs with 2 ≤ AUC Ratios < 5: Moderate Clinical Inhibitors. When NMEs served as inhibitors, a total of 36 DDIs showed increases in exposure of victim drugs of 2- to 5-fold perpetrated by 12 drugs (including FDC drugs, so total NME = 15). Among these, five drugs (including eight NMEs) are antivirals (Supplemental Fig. 3A). Detailed DDI data are presented in Supplemental Table 5. In brief, transporters including BCRP, OATP1B1/3, and P-gp seem to play an important role, mediating half of the interactions (Supplemental Fig. 3B). However, due to a lack of substrate specificity, many interactions cannot be attributed to a specific transporter. CYP3A was involved in the drug interactions of four drugs, either as a single contributor or together with P-gp. In addition to P450 enzymes, UGT1A1 also participated in two drug interactions. It is worth noting that the three antiviral FDC drugs identified as moderate inhibitors (Harvoni (manufactured by Gilead Sciences, Inc., Foster City, CA), Viekira Pak, and Zepatier (manufactured by Merck Sharp & Dohme Corp., Whitehouse Station, NJ)) presented complex inhibition scenarios because each component itself is a clinical inhibitor of multiple enzymes and/or transporters.

DDIs with 1.25 ≤ AUC Ratios < 2 and Triggering Dose Recommendations: Weak Clinical Inhibitors. Compared with the number of drugs that showed strong and moderate inhibition, more drugs showed weak inhibition and triggered dose recommendations. Indeed, from approximately 50 DDI studies, a total of 20 NMEs (including three FDC drugs) showed less than 2-fold increases in exposure of victim drugs, and labeling recommendations were made based on these observations (Supplemental Table 5). The most represented drugs were anti-infective agents, including six antivirals, one antibacterial, and one antifungal (Supplemental Fig. 3C).

Transporters mediated half of these weak interactions, most of them attributable to inhibition of P-gp, followed by OATP1B1/3 (Supplemental Fig. 3D). Increases in plasma exposure of digoxin, a clinical substrate of P-gp and a narrow therapeutic range (NTR) drug, appear to be a major concern for DDIs relevant to inhibition of P-gp. Eight drugs, including daclatasvir, eliglustat, flibanserin, isavuconazonium sulfate (prodrug), rolapitant, simeprevir, suvorexant, and velpatasvir, increased the exposure of coadministered digoxin, with AUC and C_{max} ratios of 1.25–1.93. Consequently, it has been recommended to monitor digoxin (and other P-gp substrates with an NTR) concentrations and adverse reactions, and adjust digoxin doses if necessary, upon coadministration with any of these drugs (FDA, 2013i, 2014b,c, 2015a,e,f,o, 2016b). Regarding OATP1B1/3-mediated interactions, most involved the 3-hydroxy-3-methylglutaryl–CoA reductase inhibitors atorvastatin, pravastatin, rosuvastatin, and simvastatin as victims. Increased risk of myopathy associated with higher statin concentrations is the main reason triggering labeling recommendations. Dose reduction of statins and close monitoring for statin-associated adverse reactions are recommended for the following drugs: daclatasvir, elbasvir/grazoprevir, eluxadoline, grazoprevir, simeprevir, and Viekira Pak (FDA, 2013i, 2014m, 2015f,p, 2016f). The second-largest group of DDIs was mediated by CYP3A. For example, midazolam exposure was increased by 58%, 43%, and 47% when coadministered with palbociclib, simeprevir, or suvorexant, respectively. Consequently, a dose reduction is recommended for palbociclib, whereas caution and close monitoring of patients are warranted for simeprevir and suvorexant, when coadministered with sensitive CYP3A substrate with an NTR (FDA, 2013i, 2014b, 2015h). As discussed earlier, isavuconazonium sulfate (prodrug) was identified as a moderate inhibitor of CYP3A, with 103% and 125% increases observed in the exposure of coadministered midazolam or tacrolimus, respectively (both sensitive CYP3A substrates). A smaller increase (84%) was observed in sirolimus exposure (also a sensitive CYP3A substrate), whereas relatively weaker inhibition was observed when it was coadministered with atorvastatin (a moderate sensitive CYP3A substrate) or cyclosporine (a CYP3A substrate with an NTR), with 40% and 30% increases in victim drug exposure, respectively.

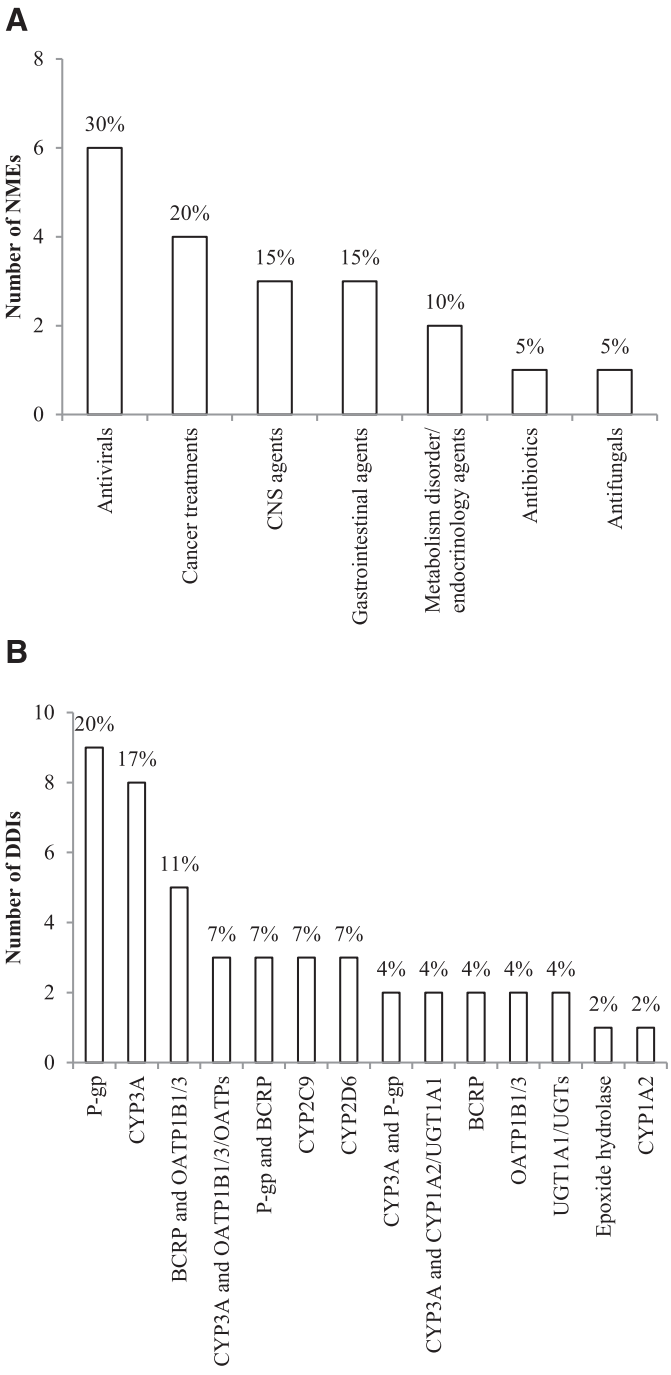

Fig. 4. Quantitation of NMEs acting as perpetrators in inhibition DDIs for drugs approved by the U.S. FDA between 2013 and 2016 and quantitation of those DDIs. (A) Therapeutic classes of NMEs acting as perpetrators in inhibition DDIs (N = 20 NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. (B) Mechanisms of inhibition DDIs with NMEs acting as the perpetrator (N = 46 DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

In Vitro–In Vivo Considerations for NMEs as Inhibitors. Overall, when all NMEs were evaluated as inhibitors, CYP3A and P-gp played a dominant role mediating approximately 60% (30% each) of all

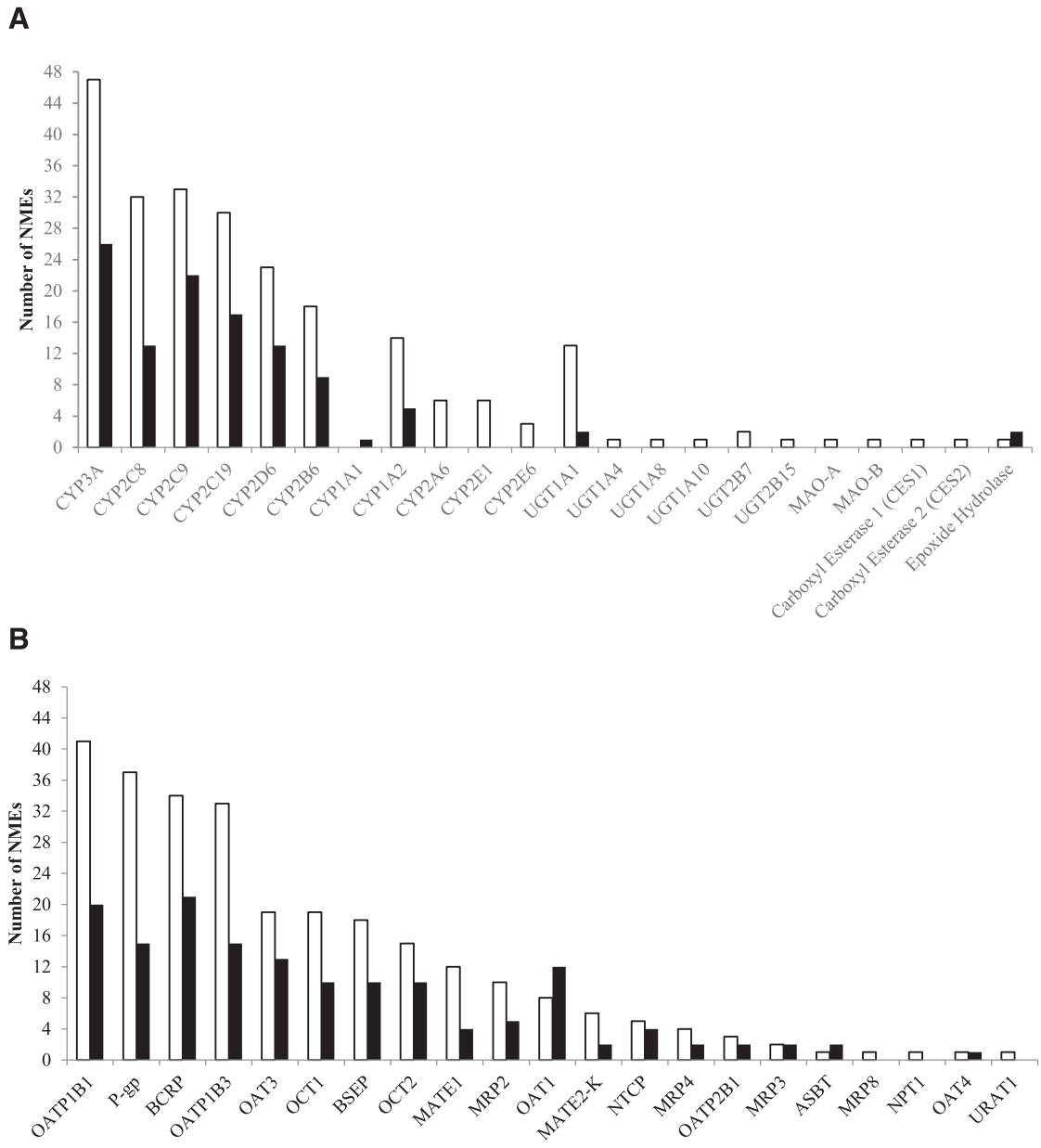

Fig. 5. Quantitation of NMEs acting as inhibitors of enzymes or transporters for drugs approved by the U.S. FDA between 2013 and 2016. (A) Drug-metabolizing enzymes inhibited by NMEs (open bars) and metabolites (closed bars). (B) Transporters inhibited by NMEs (open bars) and metabolites (closed bars). ASBT, apical sodium dependent bile acid transporter; BSEP, bile salt export pump; NTCP, sodium-taurocholate cotransporting polypeptide.

the interactions, followed by OATP1B1/3. As observed in previous years (Yu et al., 2014, 2016, 2017), the majority of the NMEs were extensively evaluated in vitro for their inhibition potential of DMEs and transporters. If an inhibitory effect was observed within the tested concentration range as provided in the NDA reviews, the NME was considered to show positive inhibition in vitro. Following regulatory recommendations described in the FDA draft guidance (FDA, 2012a), an in vitro to in vivo prediction estimate was calculated for major DMEs and transporters. Most drugs with higher $[I]/IC_{50}$, $[I]/K_i$, or R values than the cutoff were moved forward for clinical evaluations or alternative PBPK simulations. Not surprisingly, CYP3A was the most-often inhibited enzyme in vitro. However, whereas 47 NMEs showed positive inhibition of CYP3A in vitro (Fig. 5A), only 15 drugs (32%) presented clinical inhibition with ≥1.25-fold increase in the exposure of coadministered CYP3A substrate. With regard to transporters, 41 were in vitro inhibitors of OATP1B1 and 34 were inhibitors of OATP1B3 in vitro (Fig. 5B). When evaluated in vivo, only 10 of these drugs were identified as clinical inhibitors of OATP1B1/3, increasing the exposure of OATP1B1/3 substrate by ≥25%. In terms of P-gp, 37 NMEs were found to inhibit P-gp in vitro (Fig. 5B), and 23 drugs were further evaluated in vivo (including one that was evaluated using PBPK simulations). Only 14 drugs showed positive inhibition in vivo, with ≥1.25-fold increase in the exposure of coadministered P-gp substrate. Likewise, for BCRP, a total of 34 NMEs were found to be inhibitors of BCRP in vitro (Fig. 5B), whereas only 10 were confirmed to inhibit this transporter to a clinically relevant extent, with an AUC ratio ≥1.25 when coadministered with a BCRP substrate. These observations highlight the gap between in vitro–based predictions and clinical evaluation results, since quite a few drugs with a predicted potential risk were not clinically relevant inhibitors, suggesting a need to improve the current prediction models.

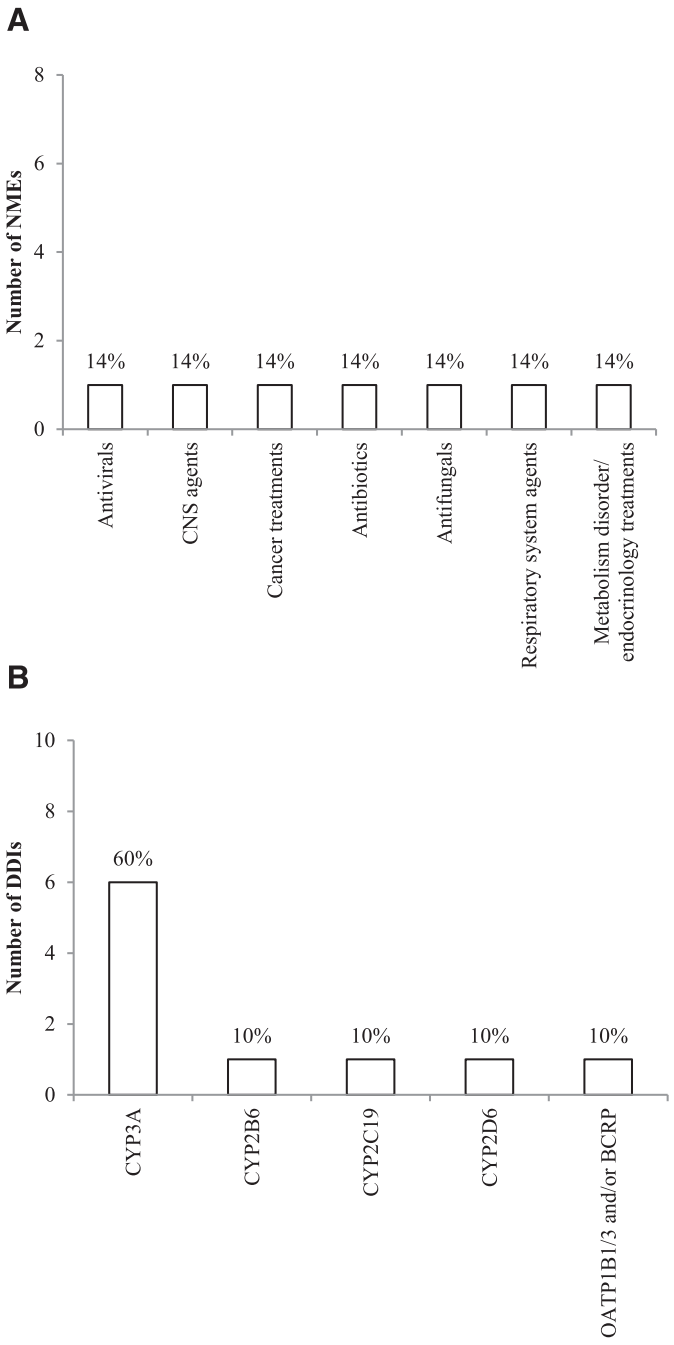

Fig. 6. Quantitation of NMEs acting as perpetrators in induction DDIs for drugs approved by the U.S. FDA between 2013 and 2016 and quantitation of those DDIs. (A) Therapeutic classes of NMEs acting as perpetrators in induction DDIs ($N = 7$ NMEs). The percentage of the total number of NMEs represented in each therapeutic class is shown. (B) Mechanisms of induction DDIs with NMEs acting as the perpetrator ($N = 10$ DDIs). The percentage of the total number of DDIs mediated by each mechanism is shown.

NMEs as Inducers

As perpetrators, only seven NMEs (including one FDC drug) showed clinically relevant induction (Supplemental Table 6; Table 4). Among them, three drugs are anti-infectives, including one antibacterial (oritavancin), one antifungal (isavuconazonium sulfate), and one antiviral (Viekira Pak) (Fig. 6A). The largest change in victim drug exposure was observed with lumacaftor, which significantly decreased the AUC of ivacaftor, a sensitive CYP3A substrate (FDA, 2012b), by 80% (lumacaftor and ivacaftor are two components of a combination drug for the treatment of cystic fibrosis). Interestingly, a similar exposure change was observed in itraconazole when it was coadministered with ivacaftor/lumacaftor (250/200 mg twice daily for 7 days). Based on this observation, coadministration of this combination drug with sensitive CYP3A substrates or CYP3A substrates with an NTR is not recommended. Additionally, hormonal contraceptives (CYP3A substrates) should not be relied upon as an effective method of contraception (FDA, 2015k). The second-largest induction was presented by dabrafenib, reducing the AUC of midazolam by 74%. Consequently, it was noted in the label that concomitant use of dabrafenib with drugs that are sensitive substrates of CYP3A may result in loss of efficacy (FDA, 2013m). In accordance with the FDA guidance (FDA, 2012a), lumacaftor and dabrafenib were identified as strong and moderate CYP3A inducers, respectively. Five drugs, eslicarbazepine acetate, isavuconazonium sulfate, lesinurad, oritavancin, and Viekira Pak (induction mainly caused by ritonavir, which is not an NME), were found to show weak induction (AUC ratios of 0.5–0.8) but still triggered labeling recommendations. Not surprisingly, most of the interactions were mediated by CYP3A. However, induction of other P450s was also observed with the three anti-infective drugs, isavuconazonium sulfate (200 mg once daily), Viekira Pak (paritaprevir/ritonavir 150/100 mg once daily + ombitasvir 25 mg once daily + dasabuvir 250 mg twice daily for 19 days), and oritavancin (1200 mg intravenously), which decreased the AUC of coadministered bupropion (CYP2B6 sensitive substrate), omeprazole (CYP2C19 sensitive substrate), and dextromethorphan (CYP2D6 sensitive substrate) by 42%, 38%, and 31%, respectively (concentration ratio of dextromethorphan to dextrorphan in urine). Interestingly, eslicarbazepine acetate caused a 35% reduction in rosuvastatin AUC and C_{max}, which maybe attributable to induction of OATP1B1/3 and/or BCRP. However, there is no in vitro evidence available to fully understand the mechanism.

In vitro evaluation showed that 24 NMEs induced CYP3A, whereas 15 and eight NMEs induced CYP2B6 and CYP1A2, respectively. Activation of the pregnane X receptor was evaluated for some drugs, and eight NMEs were found to activate this nuclear receptor to some extent (Fig. 7). Dabrafenib, lesinurab, and paritaprevir all showed induction of CYP3A, whereas isavuconazole (the active metabolite of isavuconazonium sulfate) induced both CYP2B6 and CYP3A at clinically relevant concentrations. However, the in vitro enzyme induction potential of eslicarbazepine was not conclusive based on the available data (Bialer et al., 2007; Bialer and Soares-da-Silva, 2012; FDA, 2013c; Zaccara et al., 2015).

Discussion and Conclusion

A detailed analysis of PK-based DDI data contained in the NDAs approved by the U.S. FDA in the past 4 years (from 2013 to 2016) was performed. Drug interaction profiles and clinical relevance of the outcomes were characterized. CYP3A was confirmed to be a major contributor to clinical DDIs involving NMEs as victims and/or perpetrators, which is consistent with what was found with all the drugs marketed in the past decades. Interestingly, it was found that transporter-based DDIs represented a significant number of all observed drug interactions (about 50%, with NMEs as either victims or inhibitors), although most of these were weak-to-moderate interactions. This also reflects the degree of involvement of transporters in DDI evaluations in the past few years.

Overall, when considered as victims, 13 NMEs were identified as sensitive substrates of CYP1A2 (pirfenidone and tasimelteon), CYP2C8 (dasabuvir), CYP2D6 (eliglustat), CYP3A (cobimetinib, ibrutinib, isavuconazole, ivabradine, naloxegol, paritaprevir, simeprevir, and venetoclax), or OATP1B1/3 (grazoprevir), with changes in exposure equal to or greater than 5-fold when coadministered with a strong inhibitor. Among these sensitive substrates, approximately 40% are anti-infective agents and 22% are cancer treatment drugs, suggesting a significant risk of clinically relevant DDIs in these patient populations in which therapeutic management is already complex due to

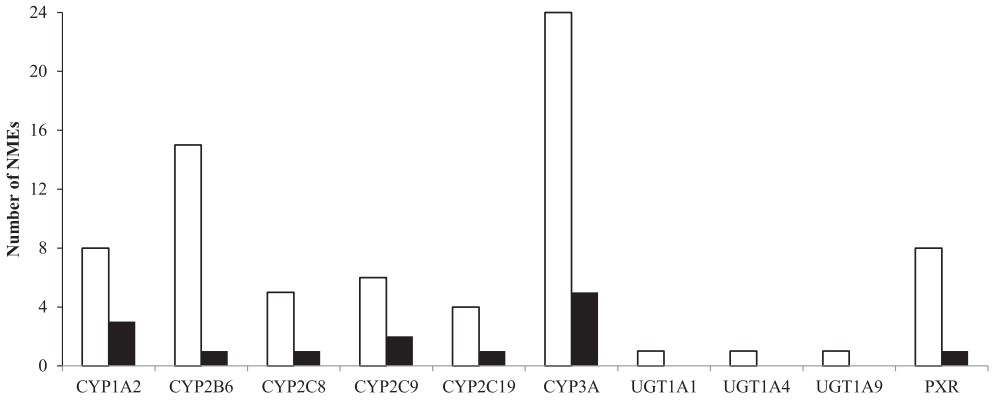

Fig. 7. Quantitation of NMEs acting as inducers of enzymes for drugs approved by the U.S. FDA between 2013 and 2016. Drug-metabolizing enzymes induced by NMEs (open bars) and metabolites (closed bars) are shown. PXR: pregnane X receptor.

polytherapy. These two classes of drugs are also the most represented therapeutics approved in the past 4 years, comprising approximately 40% of all the approved drugs. As expected, approximately 75% of drugs identified as CYP3A substrates were also substrates of P-gp, consistent with previous findings (Christians et al., 2005; Zhou, 2008). As perpetrators, most clinical DDIs involved weak-to-moderate inhibition or induction, with only one drug (idelalisib) showing strong inhibition of CYP3A, and one NME (lumacaftor) behaving as a strong clinical CYP3A inducer.

Not surprisingly, all the DDIs with exposure changes ≥5-fold in the victim drug were clearly addressed in their labels, mostly as contraindications and coadministration avoidance. There were approximately 125 DDIs with exposure changes (increases or decreases) of 2- to 5-fold with NMEs either as substrates or perpetrators, and over 80% of these effects triggered dose recommendations in the labels. Interestingly, most of the DDIs that were not reflected in the label pertained to antiviral comedications and were mediated by transporters, such as P-gp and BCRP, functioning as a main or partial factor. For example, coadministration of sofosbuvir with simeprevir, valtapasvir, darunavir/ritonavir + emtricitabine + tenofovir DF, raltegravir + emtricitabine + tenofovir DF, or atazanavir/ritonavir + emtricitabine + tenofovir DF increased the AUC of sofosbuvir 2- to 4-fold. However, considering the safety margins of sofosbuvir, the increase in sofosbuvir exposure was not considered clinically relevant by the sponsor; therefore, no dose adjustment is needed. It is worth noting that approximately 100 DDIs with AUC ratios of 1.25–2 (for inhibition) or 0.5–0.8 (for induction) resulted in labeling impact, with 52% related to drugs as substrates, 36% as inhibitors, and 12% as inducers. This is understandable because the majority of these interactions were NTR drugs for which small changes in drug exposure may increase the risk of adverse reactions or result in loss of efficacy. The number of DDIs of this group is comparable to that with AUC changes 2- to 5-fold that triggered dose recommendations. Given that a significant number of DDIs with smaller exposure changes triggered label recommendations, special attention should be given to DDIs for NTR drugs. Finally, 14 of the 103 recently approved drugs were combination drugs with highly complex drug interaction profiles in some cases, highlighting the continuous challenge of managing DDIs in clinical practice.

Acknowledgments

We thank Dr. Sophie Argon, Dr. Katie H. Owens, Dr. Ichiko Petri, Dr. Catherine K. Yeung, and Marjorie Imperial for their contributions to the NDA data curation.

Authorship Contributions

Participated in research design: Yu, Levy, Ragueneau-Majlessi.

Performed data analysis: Yu, Zhou, Tay-Sontheimer, Levy, Ragueneau-Majlessi.

Wrote or contributed to the writing of the manuscript: Yu, Zhou, Tay-Sontheimer, Levy, Ragueneau-Majlessi.

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FDA (2013c) *Drug Approval Package: Aptiom (Eslicarbazepine Acetate) FDA Application NDA 022416*, Food and Drug Administration, Silver Spring, MD.

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FDA (2015n) *Drug Approval Package: Uptravi (Selexipag). FDA Application NDA 207947*, Food and Drug Administration, Silver Spring, MD.
FDA (2015o) *Drug Approval Package: Varubi (Rolapitant). FDA Application NDA 206500*, Food and Drug Administration, Silver Spring, MD.
FDA (2015p) *Drug Approval Package: Viberzi (Eluxadoline). FDA Application NDA 206940*, Food and Drug Administration, Silver Spring, MD.
FDA (2015q) *Drug Approval Package: Vraylar (Cariprazine). FDA Application NDA 204370*, Food and Drug Administration, Silver Spring, MD.
FDA (2015r) *Drug Approval Package: Yondelis (Trabectedin). FDA Application NDA 207953*, Food and Drug Administration, Silver Spring, MD.
FDA (2015s) *Drug Approval Package: Zurampic (Lesinurad). FDA Application NDA 207988*, Food and Drug Administration, Silver Spring, MD.
FDA (2016a) *Drug Approval Package: Briviact (Brivaracetam). FDA Application NDA 205836*, Food and Drug Administration, Silver Spring, MD.
FDA (2016b) *Drug Approval Package: Epclusa (Aofosbuvir and Velpatasvir). FDA Application NDA 208341*, Food and Drug Administration, Silver Spring, MD.
FDA (2016c) *Drug Approval Package: Nuplazid (Pimavanserin). FDA Application NDA 207318*, Food and Drug Administration, Silver Spring, MD.
FDA (2016d) *Drug Approval Package: Ocaliva (Obeticholic Acid). FDA Application NDA 207999*, Food and Drug Administration, Silver Spring, MD.
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FDA (2016f) *Drug Approval Package: Zepatier (Elbasvir and Grazoprevir). FDA Application NDA 208261*, Food and Drug Administration, Silver Spring, MD.
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Address correspondence to: Isabelle Ragueneau-Majlessi, Drug Interaction Database Program, Department of Pharmaceutics, University of Washington, Box 357610, Seattle, WA 98195. E-mail: imaj@uw.edu

Title

Risk of Clinically Relevant Pharmacokinetic-based Drug-drug Interactions with Drugs Approved by the U.S. Food and Drug Administration Between 2013 and 2016

Jingjing Yu, Zhu Zhou, Jessica Tay-Sontheimer, René H. Levy, and Isabelle Ragueneau-Majlessi

Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA, USA (J.Y., J.T-S., R.H.L., I.R-M.); Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA 95211 (Z.Z.)

Drug Metabolism and Disposition

Supplemental Data

Contents:

Supplemental Table 1. NDAs approved by the U.S. FDA from 2013 to 2016

Drug Name	Therapeutic Class	Brand Name	NDA #	Approval Date
2013 (N = 25)				
Afatinib	Cancer treatments	GILOTRIF	201192	07/12
Alogliptin	Metabolism disorder/endocrinology treatments	NESINA	022271	01/25
Canagliflozin	Metabolism disorder/endocrinology treatments	INVOKANA	204042	03/29
(Conjugated estrogens and) bazedoxifene	Metabolism disorder/endocrinology treatments	DUAVEE	022247	10/03
Dabrafenib	Cancer treatments	TAFINLAR	202806	05/29
Dimethyl fumarate	Central nervous system agents	TECFIDERA	204063	03/27
Dolutegravir	Antivirals	TIVICAY	204790	08/12
Eslicarbazepine acetate	Central nervous system agents	APTIOM	022416	11/08
Flutemetamol F-18	Diagnostic agents	VIZAMYL	203137	10/25

(Fluticasone and) vilanterol	Respiratory system agents	BREO ELLIPTA	204275	05/10
Gadoterate meglumine	Diagnostic agents	DOTAREM	204781	03/20
Ibrutinib	Cancer treatments	IMBRUVICA	205552	11/13
Luliconazole	Antifungals	LUZU	204153	11/14
Macitentan	Cardiovascular drugs	OPSUMIT	204410	10/18
Mipomersen	Metabolism disorder/endocrinology treatments	KYNAMRO	203568	01/29
Ospemifene	Metabolism disorder/endocrinology treatments	OSPHENA	203505	02/26
Pomalidomide	Cancer treatments	POMALYST	204026	02/08
Radium Ra 223 dichloride	Cancer treatments	XOFIGO	203971	05/15
Riociguat	Cardiovascular drugs	ADEMPAS	204819	10/08
Simeprevir	Antivirals	OLYSIO	205123	11/22
Sofosbuvir	Antivirals	SOVALDI	204671	12/06
Technetium Tc-99M tilmanocept	Diagnostic agents	LYMPHOSEEK	202207	03/13

Trametinib	Cancer treatments	MEKINIST	204114	05/29
Umeclidinium (and vilanterol)	Respiratory system agents	ANORO ELLIPTA	203975	12/08
Vortioxetine	Central nervous system agents	BRINTELLIX	204447	09/30
2014 (N = 30)				
Apremilast	Musculoskeletal Agent	OTEZLA	205437	03/21
Belinostat	Cancer treatments	BELEODAQ	206256	07/03
Ceftolozane and Tazobactam	Antibiotics	ZERBAXA	206829	12/19
Ceritinib	Cancer treatments	ZYKADIA	205755	04/29
Dalbavancin	Antibiotics	DALVANCE	021883	05/23
Dapagliflozin	Metabolism disorder/endocrinology treatments	FARXIGA	202293	01/08
Droxidopa	Cardiovascular drugs	NORTHERA	203202	02/18
Efinaconazole	Antifungals	JUBLIA	203567	06/06
Eliglustat	Metabolism disorder/endocrinology treatments	CERDELGA	205494	08/19
Empagliflozin	Metabolism	JARDIANCE	204629	08/01

	disorder/endocrinology treatments			
Finafloxacin	Antibiotics	XTORO	206307	12/17
Florbetaben	Diagnostic agents	NEURACEQ	204677	03/19
Idelalisib	Cancer treatments	ZYDELIG	206545	07/23
Ledipasvir (and sofosbuvir)	Antivirals	HARVONI	205834	10/10
Miltefosine	Antiparasitics	IMPAVIDO	204684	03/19
Naloxegol	Gastrointestinal agents	MOVANTIK	204760	09/06
Netupitant (and Palonosetron)	Gastrointestinal agents	AKYNZEO	205718	10/10
Nintedanib	Respiratory system agents	OFEV	205832	10/15
Olaparib	Cancer treatments	LYNPARZA	206162	12/19
Olodaterol	Respiratory system agents	STRIVERDI RESPIMAT	203108	07/31
Ombitasvir, Paritaprevir, and (Ritonavir) co-packaged with Dasabuvir	Antivirals	VIEKIRA PAK	206619	12/19

Oritavancin	Antibiotics	ORBACTIV	206334	08/06
Peramivir	Antivirals	RAPIVAB	206426	12/19
Pirfenidone	Respiratory system agents	ESBRIET	022535	10/15
Sulfur hexafluoride lipid-type A microspheres	Diagnostic agents	LUMASON	203684	10/10
Suvorexant	Central nervous system agents	BELSOMRA	204569	08/13
Tasimelteon	Central nervous system agents	HETLIOZ	205677	01/31
Tavaborole	Antifungals	KERYDIN	204427	07/07
Tedizolid phosphate	Antibiotics	SIVEXTRO	205435	06/20
Vorapaxar	Cardiovascular drugs	ZONTIVITY	204886	05/08
2015 (N = 33)				
Alectinib	Cancer treatments	ALECENSA	208434	12/11
Aripiprazole lauroxil	Central nervous system agents	ARISTADA	207533	10/05
Brexpiprazole	Central nervous system	REXULTI	205422	7/10

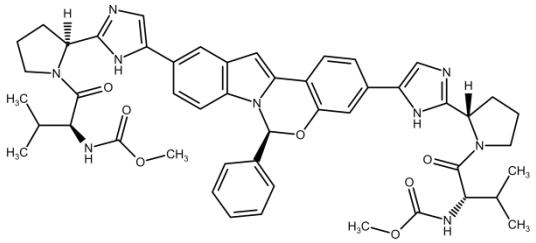
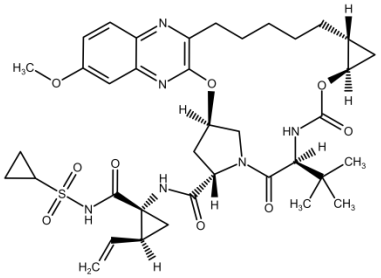
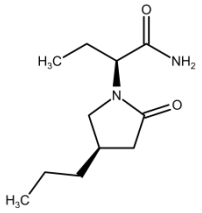
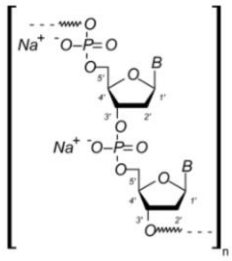
	agents			
Cangrelor	Cardiovascular drugs	KENGREAL	204958	06/22
Cariprazine	Central nervous system agents	VRAYLAR	204370	09/17
(Ceftazidime and) avibactam	Antibiotics	AVYCAZ	206494	02/25
Cholic acid	Metabolism disorder/endocrinology treatments	CHOLBAM	205750	03/17
Cobimetinib	Cancer treatments	COTELLIC	206192	11/10
Daclatasvir	Antivirals	DAKLINZA	206843	07/24
Deoxycholic acid	Metabolism disorder/endocrinology treatments	KYBELLA	206333	04/29
Edoxaban	Cardiovascular drugs	SAVAYSA	206316	01/08
Eluxadoline	Gastrointestinal agents	VIBERZI	206940	05/27
(Elvitegravir, cobicistat, emtricitabine, and) tenofovir alafenamide fumarate sulfate	Antivirals	GENVOYA	207561	11/05

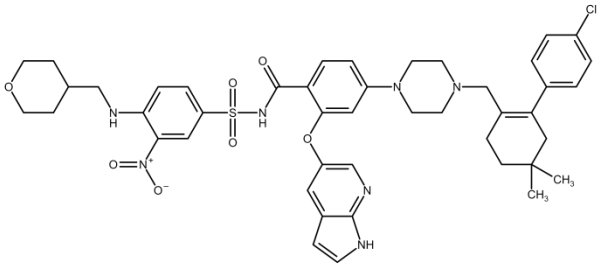
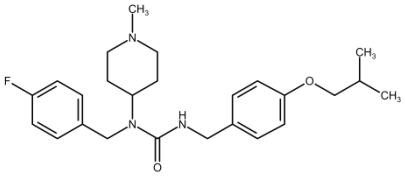
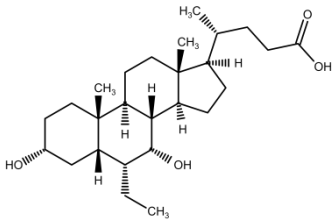
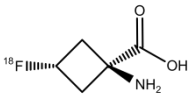
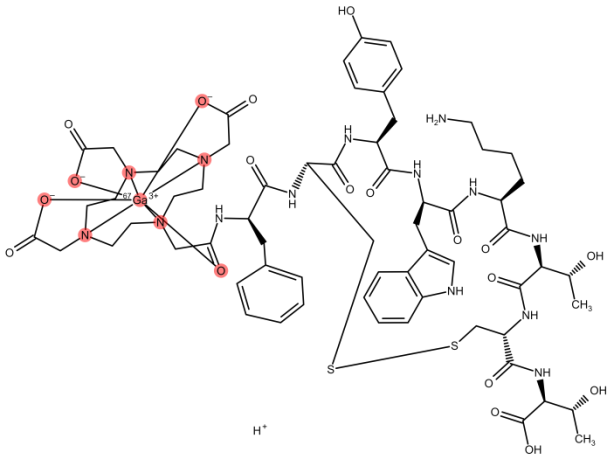
Flibanserin	Central nervous system agents	ADDYI	022526	08/18
Insulin degludec	Metabolism disorder agent	TRESIBA	203314	09/25
Isavuconazonium sulfate	Antifungals	CRESEMBA	207500/207501	03/06
Ivabradine	Cardiovascular drugs	CORLANOR	206143	04/15
Ixazomib citrate	Cancer treatments	NINLARO	208462	11/20
Lenvatinib	Cancer treatments	LENVIMA	206947	02/13
Lesinurad	Antigout and uricosuric agents	ZURAMPIC	207988	12/22
Lumacaftor (and ivacaftor)	Respiratory system agents	ORKAMBI	206038	07/02
Osimertinib	Cancer treatments	TAGRISSO	208065	11/13
Palbociclib	Cancer treatments	IBRANCE	207103	02/03
Panobinostat	Cancer treatments	FARYDAK	205353	02/23
Patiromer	Antidotes	VELTASSA	205739	10/21
Rolapitant	Antiemetics	VARUBI	206500	09/01
Sacubitril (and valsartan)	Cardiovascular drugs	ENTRESTO	207620	07/07

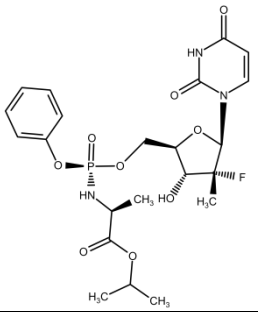
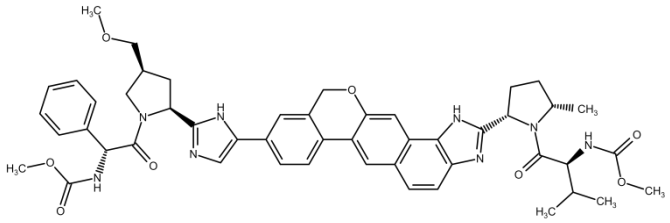
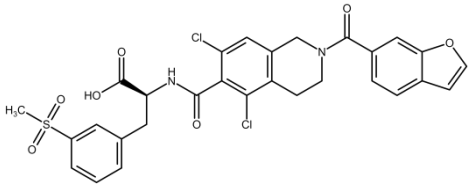
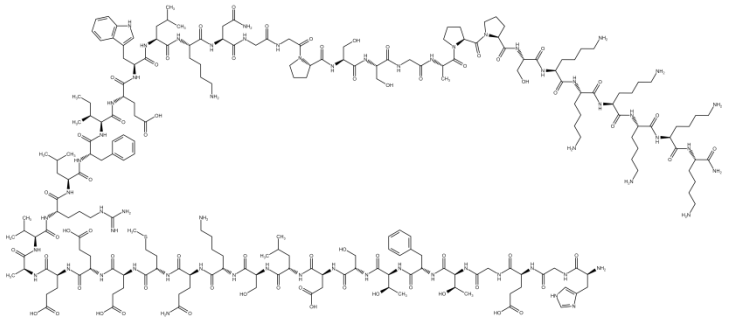
Selexipag	Cardiovascular drugs	UPTRAVI	207947	12/21
Sonidegib	Cancer treatments	ODOMZO	205266	07/24
Sugammadex	Antidotes	BRIDION	022225	12/15
Trabectedin	Cancer treatments	YONDELIS	207953	10/23
(Trifluridine and) tipiracil	Cancer treatments	LONSURF	207981	09/22
Uridine triacetate	Metabolism disorder/endocrinology treatments	XURIDEN	208169	09/04
2016 (N = 15)				
Brivaracetam	Central nervous system agents	BRIVIACT	205836	02/18
Crisaborole	Skin agents	EUCRISA	207695	12/14
Defibrotide sodium	Cardiovascular drugs	DEFITELIO	208114	03/30
Elbasvir and grazoprevir	Antivirals	ZEPATIER	208261	01/28
Eteplirsen	Central nervous system agents	EXONDYS 51	206488	09/19
Fluciclovine F 18	Diagnostic agents	AXUMIN	208054	05/27
Gallium Ga 68	Diagnostic agents	NETSPOT	208547	06/01

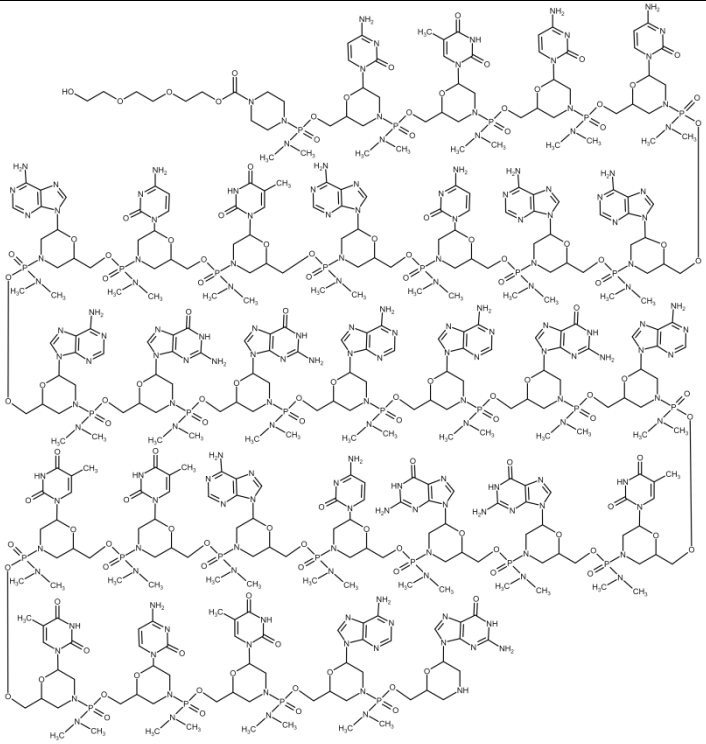
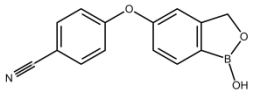
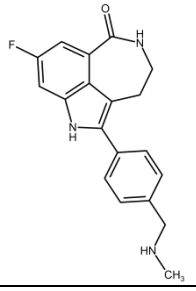
dotatate				
Lifitegrast	Ophthalmic agents	XIIDRA	208073	07/11
Lixisenatide	Metabolism disorder/endocrinology treatments	ADLYXIN	208471	07/27
Nusinersen	Central nervous system agents	SPINRAZA	209531	12/23
Obeticholic acid	Metabolism disorder/endocrinology treatments	OCALIVA	207999	05/27
Pimavanserin	Central nervous system agents	NUPLAZID	207318	04/29
Rucaparib	Cancer treatments	RUBRACA	209115	12/19
(Sofosbuvir and) velpatasvir	Antivirals	EPCLUSA	208341	06/28
Venetoclax	Cancer treatments	VENCLEXTA	208573	04/11

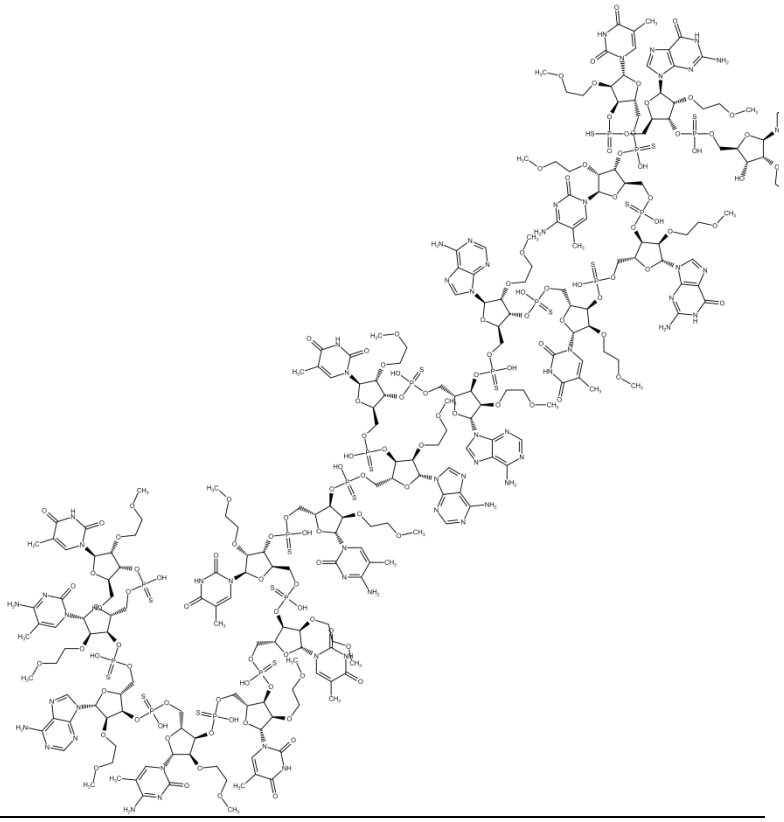
Supplemental Table 2. Chemical structures of compounds within the NDAs approved in 2016 (ordered by approval date)

NDA	Compound (CAS Registry Number)	Structure[b]
208261 (01/28)	Elbasvir (1370468-36-2)	
	Grazoprevir (1350514-68-9)	
205836 (02/18)	Brivaracetam (357336-20-0)	
208114 (03/30)	Defibrotide sodium (83712-60-1)	

208573 (04/11)	Venetoclax (1257044-40-8)	
207318 (04/29)	Pimavanserin (706779-91-1)	
207999 (05/27)	Obeticholic acid (459789-99-2)	
208054 (05/27)	Fluciclovine F-18 (222727-39-1)	
208547 (06/01)	Gallium Ga 68 dotatate	

208341 (06/28)	Sofosbuvir[a] (1190307-88-0)	
	Velpatasvir (1377049-84-7)	
208073 (07/11)	Lifitegrast (1025967-78-5)	
208471 (07/27)	Lixisenatide (320367-13-3)	

206488 (09/19)	Eteplirsen (1173755-55-9)	
207695 (12/14)	Crisaborole (906673-24-3)	
209115 (12/19)	Rucaparib	

209531 (12/23)	Nusinersen (1258984-36-9)	

[a] Approved in 2013

[b] Chemical structure was obtained from https://chem.sis.nlm.nih.gov/chemidplus/, accessed January 2017, except for defibrotide sodium whose structure was obtained from the DEFITELIO Product Label.

Supplemental Table 3. Inhibition DDIs, NME as substrate

Victim Drug (Dose)	Inhibitor (Dose)	Main Enzymes / Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population	Labeling Impact	Reference
AUC ratios $\geqslant 5$							
Paritaprevir (300 mg SD)	Ritonavir (100 mg SD)	CYP3A, P-gp, BCRP, OATP1B1/3	47.43	28.07	Parallel / 6 healthy subjects per group	Combination drug; risk of increased plasma concentrations of paritaprevir with strong CYP3A inhibitors and inhibitors of P-gp, BCRP, and OATPP1B1/3	(FDA, 2014m)
Eliglustat (100 mg QD 18 days)	Ketoconazole/paroxetine (400 mg/30 mg QD 10 days)	CYP3A[a], CYP2D6	37.85 (PBPK)	18.25 (PBPK)	One-sequence / 36 healthy subjects (CYP2D6 EMs)	Contraindicate with strong CYP2D6 inhibitors concomitantly with strong CYP3A4 inhibitors in CYP2D6 EMs	(FDA, 2014c)

Eliglustat (100 mg BID 17 days)	Paroxetine (30 mg QD 10 days)	CYP2D6	28.40	22.00	One-sequence / 1 healthy subject (CYP2D6 UM)	Reduce dose of eliglustat with strong CYP2D6 inhibitors in CYP2D6 EMs	(FDA, 2014c)
Eliglustat (100 mg BID 18 days)	Ketoconazole/paroxetine (400 mg/30 mg QD 10 days)	CYP3A[a], CYP2D6	24.16 (PBPK)	16.68 (PBPK)	One-sequence / 36 healthy subjects (CYP2D6 EMs)	Contraindicate with strong CYP2D6 inhibitors concomitantly with strong CYP3A4 inhibitors in CYP2D6 EMs	(FDA, 2014c)
Ibrutinib (120 mg (alone), 40 mg with ketoconazole SD)	Ketoconazole (400 mg QD 6 days)	CYP3A	23.90	28.60	One-sequence / 18 healthy males	Avoid strong CYP3A inhibitors	(FDA, 2013g)
Eliglustat (100 mg QD 18 days)	Fluconazole/terbinafine (400 mg loading dose then	CYP3A, CYP2D6	19.31 (AUC_{0-24h},	10.71 (AUC_{0-24h},	One-sequence / 10 healthy subjects	Contraindicate with moderate CYP2D6 inhibitors concomitantly with moderate CYP3A4 inhibitors in CYP2D6 EMs	(FDA, 2014c)

	200 mg/250 mg QD 10 days)		PBPK)	PBPK)	(CYP2D6 EMs)		
Grazoprevir (200 mg QD 13 days)	Cyclosporine (400 mg SD)	OATP1B1/3[b]	15.25 (AUC_{0-24h})	17.03	One-sequence / 13 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors	(FDA, 2016d)
Eliglustat (100 mg BID 18 days)	Fluconazole/terbinafine (400 mg loading dose then 200 mg/250 mg QD 10 days)	CYP3A, CYP2D6	13.58 (AUC_{0-12h}, PBPK)	10.16 (AUC_{0-12h}, PBPK)	One-sequence / 10 healthy subjects (CYP2D6 EMs)	Contraindicate with moderate CYP2D6 inhibitors concomitantly with moderate CYP3A4 inhibitors in CYP2D6 EMs	(FDA, 2014c)
Grazoprevir (200 mg QD 7 days)	Lopinavir/ritonavir (400 mg/100 mg BID 7 days)	CYP3A4, OATP1B1/3[b]	12.87	7.31	One-sequence / 13 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors and not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Naloxegol (25 mg SD)	Ketoconazole (400 mg QD 5 days)	CYP3A4[a]	12.42	9.12	One-sequence / 22 healthy subjects	Contraindicate with strong CYP3A4	(FDA, 2014h)

Grazoprevir (200 mg QD 7 days)	Atazanavir/ritonavir (300 mg/100 mg QD 7 days)	CYP3A, OATP1B1/3[b]	10.56	6.24	One-sequence / 11 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors and not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Grazoprevir (200 mg SD)	Rifampin (600 mg single IV)	OATP1B1/3	10.22	10.96	One-sequence / 12 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors	(FDA, 2016d)
Eliglustat (100 mg BID 17 days)	Paroxetine (30 mg QD 10 days)	CYP2D6	10.00	8.20	One-sequence / 24 healthy subjects (CYP2D6 EMs)	Reduce dose of eliglustat with strong CYP2D6 inhibitors in CYP2D6 EMs	(FDA, 2014c)
Dasabuvir (400 mg SD)	Gemfibrozil (600 mg BID 5 days)	CYP2C8	9.90	1.91	One-sequence / 11 healthy subjects	Contraindicate with strong CYP2C8 inhibitors	(FDA, 2014m)
Eliglustat (100 mg BID 18 days)	Ketoconazole/paroxetine (400 mg/30 mg QD 10	CYP3A[a], CYP2D6	9.81 (PBPK)	7.48 (PBPK)	One-sequence / 36 healthy subjects	Contraindicate with strong CYP2D6 inhibitors concomitantly with strong CYP3A4 inhibitors in	(FDA, 2014c)

	days)				(CYP2D6 IMs)	CYP2D6 IMs	
Ibrutinib (dosing regimen N/P)	Erythromycin (dosing regimen N/P)	CYP3A	8.60 (PBPK)	N/P	N/P	Avoid moderate CYP3A inhibitors; if not, reduce dose of ibrutinib	(FDA, 2013g)
Grazoprevir (200 mg SD)	Rifampin (600 mg SD)	OATP1B1/3[b]	8.37	6.52	One-sequence / 12 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors	(FDA, 2016d)
Ivabradine (dosing regimen N/P)	Josamycin (dosing regimen N/P)	CYP3A4[a]	7.70	3.60	N/P	Contraindicate with strong CYP3A4 inhibitors	(FDA, 2015c)
Ivabradine (dosing regimen N/P)	Ketoconazole (200 mg QD)	CYP3A4[a]	7.70	3.60	N/P	Contraindicate with strong CYP3A4 inhibitors	(FDA, 2015c)
Eliglustat (100 mg BID 18 days)	Fluconazole (200 mg QD 11 days)	CYP3A	7.54 (PBPK)	3.76 (PBPK)	One-sequence / 10 healthy	Not recommend with moderate CYP3A inhibitors in CYP2D6 PMs	(FDA, 2014c)

					subjects (CYP2D6 PMs)		
Grazoprevir (200 mg QD 7 days)	Darunavir/ritonavir (600 mg/100 mg BID 7 days)	CYP3A, OATP1B1/3[b]	7.49	5.27	One-sequence / 11 healthy nonsmokers	Contraindicate with OATP1B1/3 inhibitors and not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Simeprevir (200 mg QD 7 days)	Ritonavir (100 mg BID 15 days)	CYP3A[a]	7.18	4.70	N/P /12 subjects	Not recommend with ritonavir	(FDA, 2013i)
Tasimelteon (5 mg SD)	Fluvoxamine (50 mg QD 7 days)	CYP1A2[c]	6.87	2.28	One-sequence / 24 healthy subjects	Avoid strong CYP1A2 inhibitors	(FDA, 2014f)
Pirfenidone (801 mg SD)	Fluvoxamine (50-100 mg QD or BID 10 days)	CYP1A2	6.81 (smokers), 3.97 (nonsmokers)	2.24 (smokers), 1.69 (nonsmokers)	One-sequence / healthy subjects (26 smokers and 25	Reduce dose of pirfenidone with strong or moderate CYP1A2 inhibitors	(FDA, 2014d)

					nonsmokers)		
Cobimetinib (10 mg SD)	Itraconazole (200 mg QD 14 days)	CYP3A[a]	6.62	3.17	One-sequence / 15 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015d)
Simeprevir (150 mg QD 7 days)	Erythromycin (500 mg TID 6.5 days)	CYP3A[a]	6.54	4.02	Random crossover / 24 healthy subjects	Not recommend with erythromycin; caution for potential increased plasma concentrations of simeprevir with moderate or strong inhibitors of CYP3A	(FDA, 2013i)
Flibanserin (100 mg SD)	Fluconazole (200 mg QD 6 days)	CYP3A4, CYP2C19	6.41	2.11	One-sequence / 15 healthy females	Contraindicate with CYP3A4 moderate inhibitors	(FDA, 2015a)
Venetoclax (50 mg SD)	Ketoconazole (400 mg QD 7 days)	CYP3A, P-gp	6.40	2.33	One-sequence / 11 patients	Contraindicate with strong CYP3A inhibitors at initiation and during ramp-up phase; if strong CYP3A inhibitors must be used after the ramp-up phase, reduce dose of venetoclax; avoid P-gp inhibitors, if not, reduce dose of venetoclax and	(FDA, 2016e)

						monitor for signs of venetoclax toxicities	
Eliglustat (100 mg QD 14 days)	Ketoconazole (400 mg QD 7 days)	CYP3A[a]	6.22 (PBPK)	4.27 (PBPK)	One-sequence / 36 healthy subjects (CYP2D6 PMs)	Contraindicate with strong CYP3A inhibitors in CYP2D6 PMs	(FDA, 2014c)
Eliglustat (100 mg BID 14 days)	Ketoconazole (400 mg QD 7 days)	CYP3A[a]	5.54 (PBPK)	4.55 (PBPK)	One-sequence / 36 healthy subjects (CYP2D6 PMs)	Contraindicate with strong CYP3A inhibitors in CYP2D6 PMs	(FDA, 2014c)
Ibrutinib (dosing regimen N/P)	Diltiazem (dosing regimen N/P)	CYP3A	5.50 (PBPK)	N/P	N/P	Avoid moderate CYP3A inhibitors; if not, reduce dose of ibrutinib	(FDA, 2013g)
Isavuconazonium sulfate (prodrug) (200 mg SD)	Ketoconazole (200 mg BID 24 days)	CYP3A, butyrylcholinesterase	5.22	1.09	N/P	Contraindicate with strong CYP3A4 inhibitors	(FDA, 2015e)

Eliglustat (100 mg BID 17 days)	Paroxetine (30 mg QD 10 days)	CYP2D6	5.20	4.10	One-sequence / 8 healthy subjects (CYP2D6 IMs)	Reduce dose of eliglustat with strong CYP2D6 inhibitors in CYP2D6 IMs	(FDA, 2014c)
2 ⩽ AUC ratios < 5							
Eliglustat (100 mg BID 18 days)	Fluconazole/terbinafine (400 mg loading dose then 200 mg/250 mg QD 10 days)	CYP3A, CYP2D6	4.99 (PBPK)	4.16 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 IMs)	Contraindicate with moderate CYP2D6 inhibitors concomitantly with moderate CYP3A4 inhibitors in CYP2D6 IMs	(FDA, 2014c)
Elbasvir (50 mg QD 7 days)	Atazanavir/ritonavir (300 mg/100 mg QD 7 days)	CYP3A[a]	4.77	4.15	One-sequence / 8 healthy nonsmokers	Not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Flibanserin (50 mg SD)	Ketoconazole (400 mg QD 5 days)	CYP3A4	4.61	1.84	Random crossover / 20 healthy	Contraindicate with CYP3A4 strong inhibitors	(FDA, 2015a)

					females		
Naloxegol (25 mg SD)	Erythromycin (dosing regimen N/P)	CYP3A4[a]	4.60 (PBPK)	N/P	N/P	Avoid moderate CYP3A4 inhibitors, if not, reduce dose of naloxegol and monitor for adverse reactions	(FDA, 2014h)
Sofosbuvir (400 mg SD)	Cyclosporine (600 mg SD)	P-gp, BCRP	4.53	2.54	N/P / 19 healthy subjects	None	(FDA, 2016b)
Eliglustat (100 mg BID 18 days)	Terbinafine (250 mg QD 10 days)	CYP2D6	4.49 (PBPK)	280.2 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 EMs)	Reduce dose of eliglustat with moderate CYP2D6 inhibitors in CYP2D6 EMs	(FDA, 2014c)
Eliglustat (100 mg BID 14 days)	Ketoconazole (400 mg QD 7 days)	CYP3A[a]	4.40	4.25	One-sequence / 24 healthy subjects (CYP2D6	Reduce dose of eliglustat with strong CYP3A inhibitors in CYP2D6 EMs	(FDA, 2014c)

					EMs)		
Cobimetinib (60 mg QD 35 days)	Erythromycin (500 mg TID 35 days)	CYP3A[a]	4.27 (PBPK)	3.76 (PBPK)	PBPK modeling/ simuations of healthy subjects	Avoid CYP3A moderate inhibitors	(FDA, 2015d)
Sofosbuvir (400 mg QD 7 days)	Atazanavir/ritonavir/emtricitabine/tenofovir DF (atazavanir/ritonavir 400/100 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg QD at least 4 weeks)	P-gp	4.22	2.04	Parallel / 16 patients	None	(FDA, 2013l)

Eluxadoline (100 mg SD)	Cyclosporine (600 mg SD)	OATP1B1	4.20	6.81	Random crossover / 30 healthy subjects	Avoid OATP1B1 inhibitors; if not, reduce dose of eluxadaline and monitor for adverse reactions	(FDA, 2015p)
Eliglustat (100 mg BID 14 days)	Ketoconazole (400 mg QD 7 days)	CYP3A[a]	4.10	3.05	One-sequence / 8 healthy subjects (CYP2D6 IMs)	Contraindicate with strong CYP3A inhibitors in CYP2D6 IMs	(FDA, 2014c)
Macitentan (10 mg SD)	Ritonavir (100 mg BID 15 days)	CYP3A4	3.00-4.00 (PBPK)	N/P	N/P / 100 healthy subjects	Avoid strong CYP3A4 inhibitors	(FDA, 2013j)
Cariprazine (0.5 mg QD 14 days)	Ketoconazole (400 mg QD)	CYP3A4	3.78	3.27	N/P / 16 patients	Reduce dose of cariprazine with CYP3A4 strong inhibitors	(FDA, 2015q)
Elbasvir (50 mg QD 7 days)	Lopinavir/ritonavir (400 mg/100 mg	CYP3A[a]	3.70	2.87	One-sequence / 9 healthy	Not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)

	BID 7 days)				nonsmokers		
Sofosbuvir (400 mg SD)	Cyclosporine (600 mg SD)	P-gp, BCRP	3.57	2.22	Random crossover / 19 healthy subjects	None	(FDA, 2013l)
Paritaprevir (150 mg QD 28 days)	Lopinavir/ritonanir (800 mg/200 mg QD 14 days)	CYP3A, P-gp, BCRP, OATP1B1/3	3.55	1.78	One-sequence / 11 healthy subjects	Not recommend with lopinavr/ritonavir	(FDA, 2014m)
Sofosbuvir (400 mg QD 7 days)	Raltegravir/emtricitabine/tenofovir DF (raltegravir 400 mg BID + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg QD at least 4	P-gp	3.32 (AUC_{tau})	2.17	Parallel / 13 patients	None	(FDA, 2013l)

	weeks)						
Cobimetinib (60 mg SD)	diltiazem (1200 mg BID)	CYP3A[a]	3.26 (PBPK)	1.85 (PBPK)	PBPK modeling /simuations of healthy subjects	Avoid CYP3A moderate inhibitors	(FDA, 2015d)
Naloxegol (25 mg SD)	Diltiazem (240 mg QD 5 days)	CYP3A4[a]	3.24	2.78	One-sequence / 43 healthy subjects	Avoid moderate CYP3A inhibitors; if not, reduce dose of naloxegol and monitor for adverse reactions	(FDA, 2014h)
Eliglustat (100 mg BID 18 days)	Fluconazole (200 mg QD 10 days)	CYP3A	3.21 (PBPK)	3.04 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 EMs)	Reduce dose of eliglustat with moderate CYP3A inhibitors in CYP2D6 EMs	(FDA, 2014c)
Sofosbuvir (400 mg QD 12 or 24	Simeprivir (150 mg QD 12 or 24	P-gp	3.16	1.91	N/P / 22 subjects	None	(FDA, 2013i)

weeks)	weeks)						
Grazoprevir (100 mg SD)	Ketoconazole (400 mg QD)	CYP3A[b]	3.02	2.01	N/P / 8 healthy subjects	Not recommend with ketoconazole and certain strong CYP3A inhibitors	(FDA, 2016d)
Daclatasvir (10 mg SD)	Ketoconazole (400 mg QD 9 days)	CYP3A[a]	3.01	1.57	One-sequence / 13 healthy subjects	Reduce dose of daclatasvir with CYP3A strong inhibitors	(FDA, 2015f)
Pimavanserin (40 mg SD)	Ketoconazole (400 mg QD 14 days)	CYP3A4	3.01	1.47	One-sequence / 19 subjects	Reduce dose of pimavanserin with strong CYP3A inhibitors	(FDA, 2016c)
Eliglustat (100 mg BID 17 days)	Ketoconazole (30 mg QD 10 days)	CYP3A[a]	3.00	2.20	One-sequence / 1 healthy subject (CYP2D6 UM)	Reduce dose of eliglusat with strong CYP3A inhibitors in CYP2D6 EMs	(FDA, 2014c)
Ivabradine (dosing regimen	Diltiazem (120 mg BID)	CYP3A4[a]	3.00	2.50	N/P	Avoid strong CYP3A4 inhibitors	(FDA, 2015c)

N/P)							
Eliglustat (100 mg QD 18 days)	Fluconazole (200 mg QD 11 days)	CYP3A	2.95 (PBPK)	2.38 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 PMs)	Contraindicate with strong CYP3A4 inhibitors in CYP2D6 PMs	(FDA, 2014c)
Ceritinib (450 mg SD)	Ketoconazole (200 mg BID 14 days)	CYP3A[a]	2.88	1.23	One-sequence / 19 healthy subjects	Avoid strong CYP3A inhibitors; if not, adjust dose of ceritinib	(FDA, 2014p)
Eliglustat (100 mg BID 18 days)	Fluconazole (400 mg loading dose then 200 mg QD 11 days)	CYP3A	2.85 (PBPK)	2.85 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 IMs)	Not recommend with moderate CYP3A inhibitors in CYP2D6 IMs	(FDA, 2014c)
Paritaprevir (paritaprevir/ritonavir 150 mg/100	Atazanavir/ritonavir (300 mg /100 mg QD in the	CYP3A, P-gp, BCRP,	2.81	1.79	One-sequence / 10 healthy	When co-administered with VIEKIRA PAK, atazanvir 300 mg (without ritonavir) should only	(FDA, 2014m)

mg QD + ombitasvir 25 mg QD in the morning + dasabuvir 400 mg BID 28 days)	evening 14 days)	OATP1B1/3			subjects	be given in the morning	
Naloxegol (25 mg SD)	Fluconazole (dosing regimen N/P)	CYP3A4	2.80 (PBPK)	N/P	N/P	Avoid moderate CYP3A4 inhibitors, if not, reduce dose of naloxegol and monitor for adverse reactions	(FDA, 2014h)
Sonidegib (200 mg QD for steady state)	Erythromycin (500 mg QD 120 days)	CYP3A	2.80 (PBPK)	2.40 (PBPK)	PBPK modeling / simuations of patients	Avoid long term use of CYP3A moderate inhibitors	(FDA, 2015j)
Suvorexant (4 mg SD)	Ketoconazole (400 mg QD 11 days)	CYP3A	2.79	1.23	One-sequence / 11 healthy males	Not recommend with strong CYP3A inhibitors	(FDA, 2014b)

Ospemifene (60 mg SD)	Fluconazole (200 mg QD 8 days)	CYP3A, CYP2C9, CYP2C19	2.78	1.58	Random crossover / 14 post-menopausal healthy females	Not recommend with fluconazole	(FDA, 2013k)
Simeprevir (150 mg QD 20 days)	Ledipasvir (30 mg QD 10 days)	P-gp	2.69	2.61	N/P / 28 subjects	None	(FDA, 2013i)
Olaparib (100 mg SD)	Itraconazole (200 mg QD 8 days)	CYP3A[a]	2.59	1.36	One-sequence / 56 patients	Avoid strong CYP3A inhibitors; if not, adjust dose of olaparib	(FDA, 2014g)
Simeprevir (150 mg (alone), 50 mg with darunavir/ritonavir QD 7 days)	Darunavir/ritonavir (800 mg/100 mg QD 7 days)	CYP3A[a]	2.59	1.79	Random crossover / 21 healthy subjects	Not recommend with darunavir/ritonavir	(FDA, 2013i)
Flibanserin (50	Itraconazole (200	CYP3A4,	2.58	1.70	Random crossover /12	Contraindicate with CYP3A4 strong inhibitors	(FDA,

mg SD)	mg QD 7 days)	CYP2C19			healthy subjects		2015a)
Riociguat (single dose)	Ketoconazole (400 mg QD repeated doses)	CYP3A, P-gp, BCRP	2.50	N/P	N/P / healthy subjects	Adjust starting dose of riociguat with strong P450 and P-gp/BCRP inhibitors and monitor for hypotension	(FDA, 2013a)
Sofosbuvir (400 mg QD 7 days)	Darunavir/ritonavir/emtricitabine/tenofovir DF (darunavir/ritonavir 800/100 mg + emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg QD at least 4 weeks)	P-gp	2.49	1.12	Parallel / 13 patients	None	(FDA, 2013l)
Velpatasvir (100	Atazanavir/ritonav	CYP3A, P-gp,	2.43	1.55	Random	None	(FDA,

mg QD 10 days)	ir/emtricitabine/tenofovir DF (atazanavir: 300 mg; ritonavir 100 mg; emtricitabine/tenofovir DF: 200/300 mg QD 10 days)	BCRP			crossover / 24 healthy subjects		2016b)
Netupitant (300 mg SD)	Ketoconazole (400 mg QD 12 days)	CYP3A4[a]	2.42	1.19	Random crossover / 18 healthy subjects	None	(FDA, 2014m)
Macitentan (10 mg SD)	Ketoconazole (400 mg QD 24 days)	CYP3A4	2.32 (AUC_{tau})	1.28	Random crossover / 10 healthy subjects	Avoid strong CYP3A4 inhibitors	(FDA, 2013j)
Sofosbuvir (400	Velpatasvir (150	P-gp, BCRP	2.38	1.81	One-sequence	None (combination drug)	(FDA,

mg SD)	mg QD 10 days)				/ 18 healthy subjects		2016b)
Vortioxetine (10 mg QD 28 days)	Bupropion (75 mg BID 3 days then 150 mg BID 11 days)	CYP2D6	2.28	2.14	One-sequence / 24 healthy subjects	Reduce dose of vortioxetine with strong CYP2D6 inhibitors	(FDA, 2013e; Mogalian et al., 2016)
Sonidegib (800 mg SD)	Ketoconazole (200 mg BID 14 days)	CYP3A	2.26	1.50	Parallel / 15 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015j)
Daclatasvir (60 mg QD 7 days)	Simepravir (150 mg QD 7 days)	CYP3A[a]	2.20	1.60	Random crossover /15 healthy nonsmokers	Reduce dose of daclatasvir with simeprevir	(FDA, 2015f)
Naloxegol (25 mg SD)	Verapamil (dosing regimen N/P)	CYP3A4[a]	2.20 (PBPK)	N/P	N/P	Avoid moderate CYP3A4 inhibitors, if not, reduce dose of naloxegol and monitor for adverse	(FDA, 2014h)

						reactions	
Ivabradine (dosing regimen N/P)	Grapefruit juice (doing regimen N/P)	CYP3A4[a]	2.20	1.60	N/P	Avoid moderate CYP3A4 inhibitors	(FDA, 2015c)
Brexpiprazole (2 mg SD)	Ketoconazole (200 mg BID 7 days)	CYP3A[a]	2.17	1.18	One-sequence /12 healthy subjects (CYP2D6 EMs and IMs)	Reduce dose of brexpiprazole with CYP3A strong inhibitors	(FDA, 2015l)
Daclatasvir (60 mg QD 4 days + 20 mg QD 10 days)	Atazanavir/ritonavir (300 mg/100 mg QD 10 days)	CYP3A[a]	2.10	1.35	One-sequence / 14 healthy subjects	Reduce dose of daclatasvir with stong CYP3A inhibitors	(FDA, 2015f)
Ledipasvir (90 mg QD 10 days)	Atazanavir/ritonavir (atazanavir/ritonavir 300 mg/100 mg	P-gp	2.05	1.93	Random crossover / 30 healthy	None	(FDA, 2014e)

	QD 10 days)				subjects		
Suvorexant (20 mg SD)	Diltiazem (240 mg QD 6 days)	CYP3A	2.05	1.22	One-sequence / 18 healthy subjects	Adjust dose with moderate CYP3A inhibitors	(FDA, 2014b)
Brexpiprazole (2 mg SD)	Quinidine (324 mg QD 7 days)	CYP2D6	2.03 (EMs)	1.12 (EMs)	One-sequence / 11 healthy subjects (CYP2D6 EMs and IMs)	Reduce dose of brexpiprazole with strong CYP2D6 inhibitors	(FDA, 2015l)
Grazoprevir (200 mg SD)	Ritonavir (100 mg BID 21 days)	CYP3A, OATP1B1/3[b]	2.03	1.15	One-sequence / 10 healthy subjects	Not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Velpatasvir (100 mg SD)	Cyclosporine (600 mg SD)	P-gp, BCRP	2.03	1.56	Random crossover / 12 healthy subjects	None	(FDA, 2016b)

Droxidopa (dosing regimen N/P)	DOPA Decarboxylase Inhibitors (not specified)	Catechol-O-methyl transferase	2.00	N/P	N/P	Adjust dose of droxidopa with DOPA decarboxylase inhibitors	(FDA, 2014i)
Ivabradine (dosing regimen N/P)	Verapamil (120 mg BID)	CYP3A4[a]	2.00	1.90	N/P	Avoid moderate CYP3A4 inhibitors	(FDA, 2015c)
Olaparib (100 mg SD)	Fluconazole (200 mg QD 7 days)	CYP3A	2.00 (PBPK)	N/P	Crossover / 100 subjects	Avoid moderate CYP3A inhibitors; if not, adjust dose of olaparib	(FDA, 2014g)
Selexipag (dosing regimen N/P)	Lopinavir/ritonavir (dosing regimen N/P)	P-gp, OATP1B1/3	2.00	2.00	N/P	None	(FDA, 2015n)
1.25 ⩽ AUC ratios < 2 with dose recommendation							
Isavuconazonium sulfate (prodrug)	Lopinavir/ritonavir (400 mg/100 mg BID)	CYP3A, butyrylcholinesterase	1.96	1.74	N/P	Contraindicate with strong CYP3A4 inhibitors	(FDA, 2015e)

Vorapaxar (20 mg loading dose then 2.5 mg QD 22 days)	Ketoconazole (400 mg QD 28 days)	CYP3A[d]	1.96	1.93	Parallel, placebo-controlled / 12 healthy subjects	Avoid strong inhibitors of CYP3A	(FDA, 2014n)
Vilanterol (25 µg SD inhalation)	Ketoconazole (400 mg QD 6 days)	CYP3A4[a]	1.90	0.89	Random crossover, placebo-controlled / 18-20 healthy subjects	Caution with strong CYP3A4 inhibitors for cardiovascular effects	(FDA, 2013b)
Ledipasvir (30 mg QD 10 days)	Simeprevir (150 mg QD 10 days)	P-gp	1.88	1.78	Random crossover / 22 healthy subjects	Not recommend with simeprevir	(FDA, 2014e)
Edoxaban (60 mg SD)	Ketoconazole (400 mg QD 7 days)	P-gp	1.87	1.89	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)

Edoxaban (60 mg SD)	Erythromycin (500 mg QID 8 days)	P-gp	1.85	1.68	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Palbociclib (dosing regimen N/P)	Itraconazole (dosing regimen N/P)	CYP3A[a]	1.85	1.35	One-sequence / 12 healthy subjects	Avoid CYP3A strong inhibitors	(FDA, 2015h)
Edoxaban (60 mg SD)	Dronedarone (400 mg BID repeated dosing)	P-gp	1.84	1.45	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Paritaprevir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD in the morning + dasabuvir 400 mg	Atazanavir (300 mg QD in the morning 14 days)	CYP3A, OATP1B1/3	1.81	1.28	One-sequence / 10 healthy subjects	When co-administered with VIEKIRA PAK, atazanvir 300 mg (without ritonavir) should only be given in the morning	(FDA, 2014m)

BID 28 days)							
Elbasvir (50 mg SD)	Ketoconazole (400 mg QD)	CYP3A[a]	1.80	1.89	N/P / 7 healthy subjects	Not recommend with certain strong CYP3A inhibitors	(FDA, 2016d)
Pirfenidone (801 mg SD)	Ciprofloxacin (750 mg BID 5 days)	CYP1A2	1.80	1.22	One-sequence / 27 healthy nonsmoker subjects	Reduce dose of pirfenidone with moderate inhibitors of CYP1A2	(FDA, 2014d)
Sonidegib (200 mg QD for steady state)	Erythromycin (500 mg QID 14 days)	CYP3A	1.80 (PBPK)	1.60 (PBPK)	PBPK modeling / simuations of patients	Monitor for adverse reactions when co-administered with moderate CYP3A inhibitors for less than 14 days	(FDA, 2015j)
Idelalisib (400 mg SD)	Ketoconazole (400 mg QD 4 days)	CYP3A[a]	1.79	1.25	Random crossover / 11 healthy male subjects	Monitor for signs of idelalisib toxicities with CYP3A inhibitors	(FDA, 2014o)

Venetoclax (200 mg SD)	Rifampin (600 mg SD)	P-gp	1.78	2.13	One-sequence / 12 healthy female subjects	Avoid P-gp inhibitors; if not, reduce dose of venetoclax and monitor for signs of venetoclax toxicities	(FDA, 2016e)
Edoxaban (60 mg SD)	Quinidine (300 mg TID)	P-gp	1.75 (AUC_{0-24h})	1.75	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Edoxaban (60 mg SD)	Cyclosporine (500 mg SD)	P-gp, OATP1B1	1.73; 6.87 (M4)	1.74; 8.71 (M4)	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Trabectedin (1.3 mg/m2 SD (alone); 0.58 mg/m2 (co-administration))	Ketoconazole (200 mg BID 15 doses)	CYP3A[a]	1.69	1.21	Random crossover / 8 patients	Avoid CYP3A strong inhibitors	(FDA, 2015r)
Elbasvir (50 mg	Darunavir/ritonavir (600 mg/100 mg	CYP3A[a]	1.66	1.67	One-sequence / 8 healthy	Not recommend with certain strong CYP3A	(FDA,

QD 7 days)	BID 7 days)				nonsmokers	inhibitors	2016d)
Panobinostat (20 mg SD)	Ketoconazole (400 mg QD 5 days)	CYP3A[a]	1.66	1.62	One-sequence / 14 patients	Reduce dose of panobinostat with strong CYP3A inhibitors	(FDA, 2015g)
Vilanterol (25 µg QD 7 days inhalation administered with 200 µg fluticasone furoate)	Ketoconazole (400 mg QD 11 days)	CYP3A4[a]	1.65	1.22	Random crossover, double-blind, placebo-controlled / 18 healthy subjects	Caution with strong CYP3A4 inhibitors which may cause systemic corticosteroid and cardiovascular effects	(FDA, 2013b); (FDA, 2013d)
Eliglustat (100 mg BID 18 days)	Terbinafine (250 mg QD 10 days)	CYP2D6	1.64 (PBPK)	54.5 (PBPK)	One-sequence / 10 healthy subjects (CYP2D6 IMs)	Reduce dose of eliglustat with moderate CYP2D6 inhibitors in CYP2D6 IMs	(FDA, 2014c)
Nintedanib (50	Ketoconazole (400	CYP3A4, P-	1.61	1.79	Random crossover / 29	Risk of increased nintedanib exposure; monitor	(FDA,

mg SD)	mg QD 3 days)	gp			healthy male subjects	for tolerability of nintedanib	2014j)
Venetoclax (dosing regimen N/P)	Ciprofloxacin (dosing regimen N/P)	CYP3A, P-gp	1.40-1.60 (AUC_{0-24h})	N/P	N/P	Avoid moderate CYP3A inhibitors and P-gp inhibitors; if not, reduce dose of venetoclax and monitor for signs of venetoclax toxicities	(FDA, 2016e)
Venetoclax (dosing regimen N/P)	Diltiazem (dosing regimen N/P)	CYP3A, P-gp	1.40-1.60 (AUC_{0-24h})	N/P	N/P	Avoid moderate CYP3A inhibitors and P-gp inhibitors; if not, reduce dose of venetoclax and monitor for signs of venetoclax toxicities	(FDA, 2016e)
Venetoclax (dosing regimen N/P)	Fluconazole (dosing regimen N/P)	CYP3A	1.40-1.60 (AUC_{0-24h})	N/P	N/P	Avoid moderate CYP3A inhibitors; if not, reduce dose of venetoclax and monitor for signs of venetoclax toxicities	(FDA, 2016e)
Dabrafenib (75 mg BID 22 days)	Ketoconazole (400 mg QD 4 days)	CYP3A4[a,e]	1.57	1.26	N/P / 7 patients	Not recommend with strong inhibitors of CYP3A4 ; if not, monitor for adverse reactions	(FDA, 2013m)

Lesinurad (400 mg SD)	Fluconazole (400 mg loading dose then 200 mg QD 2 days)	CYP2C9	1.54	1.34	One-sequence / 12 healthy males	Caution with moderate CYP2C9 inhibitors	**(FDA, 2015s)**
Edoxaban (60 mg SD)	Verapamil (240 mg QD 11 days)	P-gp	1.53 (AUC_{0-24h})	1.53	N/P / healthy subjects	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Afatinib (20 mg SD)	Ritonavir (200 mg BID 3 days)	P-gp	1.48	1.39	One-sequence / 24 healthy subjects	Reduce dose of afatinib with P-gp inhibitors	(FDA, 2013f)
Flibanserin (25-100 mg SD)	Oral contraceptives (dosing regimen N/P)	CYP3A4, CYP2C19	1.42	1.12	N/P / 39 healthy female subjects and patients	Caution for increased flibanserin exposures and incidence of adverse reaction with oral contraceptives and other weak CYP3A4 Inhibitors	(FDA, 2015a)
Panobinostat (25 mg TIW for 3	Bortezomib (1.3 mg/m2 IV injection BIW 2	CYP3A[a]	1.42	1.50	One-sequence / 7 patients	Reduce dose of panobinostat with strong CYP3A inhibitors	(FDA, 2015g)

weeks)	weeks)						
Ospemifene (60 mg SD)	Ketoconazole (400 mg QD 8 days)	CYP3A, CYP2C9	1.41	1.35	Random crossover / 12 post-menopausal females	Caution for increased risk of ospemifen-related adverse reactions with ketoconazole	(FDA, 2013k)
Edoxaban (60 mg SD)	Amiodarone (400 mg QD 4 days)	P-gp	1.40	1.60	N/P	Reduce dose of edoxaban if necessary	(FDA, 2015m)
Dasabuvir (250 mg SD)	Ketoconazole (400 mg QD 6 days)	P-gp[f]	1.40	1.16	One-sequence / 12 healthy subjects	Caution for increased plasma concentrations of dasabuvir with P-gp inhibitors	(FDA, 2014m)
Paritaprevir (150 mg SD)	Gemfibrozil (600 mg BID 5 days)	OATP1B1/3	1.35	1.29	One-sequence / 11 healthy subjects	Risk of increased plasma concentrations of paritaprevir with OATP1B1/3 inhibitors	(FDA, 2014m)
Flibanserin (100 mg SD)	Grapefruit juice (240 mL regular	CYP3A4, CYP2C19	1.34	1.07	One-sequence / 26 healthy	Contraindicate with CYP3A4 moderate inhibitors	(FDA, 2015a)

strength SD)		females

Drugs were orally administered unless specified; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

BID, twice daily; EM, extensive metabolizer; IM, intermediate metabolizer; IV, intravenously; N/P – not provided; PM, poor metabolizer; QD, once daily; QID, four times daily; SD, single dose; TID, three times daily; TIW, three times a week; UM, ultrarapid metabolizer

[a] – Also a substrate of P-gp based on in vitro results; inhibition of P-gp might contribute to the observed interaction

[b] – Also a substrate of P-gp and BCRP based on in vitro results

[c] – Also metabolized by CYP3A4, CYP2C9, and CYP2C19; fluvoxamine inhibits these P450s

[d] – Also metabolized by CYP2J2; ketoconazole inhibits CYP2J2 in vitro

[e] – Mainly metabolized by CYP2C8, with contributions from CYP3A4 and other P450s; ketoconazole is a weak inhibitor of CYP2C8 in vivo

[f] – Dasabuvir is a sensitive substrate of CYP2C8; ketoconazole weakly inhibits CYP2C8 in vivo

Supplemental Table 4. Induction DDIs, NME as substrate

Victim Drug (Dose)	Inducer (Dose)	Main Enzymes /Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population	Labeling Impact	Reference
AUC ratios ⩽0.2							
Isavuconazonium sulfate (200 mg QD)	Rifampin (600 mg QD)	CYP3A, butyrylcholine sterase	0.03	0.25	N/P	Contraindicate with strong CYP3A4 inducers	(FDA, 2015e)
Eliglustat (100 mg BID 6 days)	Rifampin (600 mg QD IV dose 6 days)	CYP3A[a]	0.04	0.05	One-sequence / 6 healthy subjects (CYP2D6 PMs)	Not recommend with strong CYP3A inducers	(FDA, 2014c)
Flibanserin (100 mg SD)	Rifampin (600 mg QD 9 days)	CYP3A4, CYP2C19	0.04	0.10	Random crossover / 23 healthy	Not recommend with CYP3A4 inducers	(FDA, 2015a)

					females		
Ibrutinib (dosing regimen N/P)	Rifampin (dosing regimen N/P)	CYP3A[a]	0.08 (PBPK)	0.07 (PBPK)	N/P	Avoid strong CYP3A inducers	(FDA, 2013g)
Eliglustat (150 mg BID 6 days)	Rifampin (600 mg QD IV dose 6 days)	CYP3A[a]	0.09	0.09	One-sequence / 2 healthy subjects (CYP2D6 IMs)	Not recommend with strong CYP3A inducers	(FDA, 2014c)
Eliglustat (150 mg BID 6 days)	Rifampin (600 mg QD IV dose 6 days)	CYP3A[a]	0.10	0.11	One-sequence / 12 healthy subjects (CYP2D6 EMs)	Not recommend with strong CYP3A inducers	(FDA, 2014c)
Naloxegol (25 mg SD)	Rifampin (600 mg QD 10 days)	CYP3A4[a]	0.11	0.26	One-sequence / 22 healthy subjects	Not recommend with strong CYP3A4 inducers	(FDA, 2014h)

Olaparib (300 mg SD)	Rifampin (600 mg QD 13 days)	CYP3A[a]	0.11	0.3	One-sequence / 17 patients with advanced solid tumors	Avoid strong and moderate CYP3A inducers; if not, caution for decreased efficacy	(FDA, 2014g)
Rolapitant (200 mg SD)	Rifampin (600 mg QD14 days)	CYP3A4	0.12	0.68	One-sequence / 20 healthy subjects	Avoid CYP3A4 strong inducers	(FDA, 2015o)
Suvorexant (40 mg SD)	Rifampin (600 mg QD 17 days)	CYP3A	0.12	0.36	One-sequence / 10 healthy subjects	Caution for reduced efficacy with strong CYP3A inducers	(FDA, 2014b)
Tasimelteon (20 mg SD)	Rifampin (600 mg QD 11 days)	CYP3A4[a,b]	0.14	0.23	One-sequence / 24 healthy subjects	Avoid strong CYP3A4 inducers	(FDA, 2014f)
Palbociclib (125 mg SD)	Rifampin (600 mg QD 12 days)	CYP3A[a]	0.15	0.28	One-sequence / 14 healthy subjects	Avoid moderate and strong CYP3A inducers	(FDA, 2015h)

Cobimetinib (60 mg SD)	Rifampin (600 mg QD)	CYP3A[a]	0.17 (PBPK)	0.37 (PBPK)	PBPK modeling/simuations of healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015d)
Grazoprevir (200 mg QD 7 days)	Efavirenz (600 mg QD 21 days)	CYP3A[c]	0.17	0.13	One-sequence / 11 healthy nonsmokers	Contraindicate with strong CYP3A inducers and efavirenz; not recommend with moderate CYP3A inducers	(FDA, 2016d)
Velpatasvir (100 mg SD)	Rifampin (600 mg QD 8 days)	CYP2B6, CYP2C8, CYP3A, P-gp, BCRP	0.19	0.29	Random crossover / 12 healthy subjects	Not recommend with P-gp inducers and/or moderate to strong CYP inducers	(FDA, 2016b)
Netupitant (300 mg SD)	Rifampin (600 mg QD 17 days)	CYP3A4	0.20	0.45	Random crossover / 18 healthy subjects	Avoid strong CYP3A4 inducers	(FDA, 2014a)

0.2 < AUC ratios ⩽ 0.5							
Daclatasvir (60 mg SD)	Rifampin (600 mg QD 9 days)	CYP3A[a]	0.21	0.44	One-sequence / 14 healthy Asian Males	Contraindicate with strong CYP3A inducers	(FDA, 2015f)
Macitentan (30 mg SD on day 1, 10 mg QD 12 days)	Rifampin (600 mg QD 7 days)	CYP3A4	0.21	0.07 (C_{min})	One sequence / healthy male subjects	Avoid strong CYP3A4 inducers	(FDA, 2013j)
Brexpiprazole (4 mg SD)	Rifampin (600 mg QD 13 days)	CYP3A[a]	0.24	0.69	One-sequence / 16 healthy subjects	Increase dose of brexpiprazole with CYP3A strong inducers	(FDA, 2015l)
Idelalisib (150 mg SD)	Rifampin (600 mg QD 8 days)	CYP3A, P-gp	0.24	0.43	One-sequence / 11 healthy subjects	Avoid strong CYP3A and P-gp inducers	(FDA, 2014o)
Ixazomib citrate (4 mg SD)	Rifampin (600 mg QD14 days)	CYP3A[a]	0.26	0.46	Parallel / 16 patients	Avoid CYP3A strong inducers	(FDA, 2015i)

Alectinib (600 mg SD)	Rifampin (600 mg QD 13 days)	CYP3A4[a]	0.27; 1.79 (M4)	0.49; 2.20 (M4)	One-sequence / 24 healthy subjects	None	(FDA, 2015b)
Cobimetinib (60 mg QD 21 days)	Efavirenz (600 mg QD 21 days)	CYP3A4[a]	0.27 (PBPK)	0.29 (PBPK)	PBPK modeling/simuations of healthy subjects	Avoid CYP3A moderate inducers	(FDA, 2015d)
Vortioxetine (20 mg SD)	Rifampin (600 mg QD 11 days)	CYP3A[d]	0.27	0.49	One-sequence / 14 healthy subjects	Increase dose of vortioxetine with a strong CYP inducer for more than 14 days	(FDA, 2013e)
Apremilast (30 mg SD)	Rifampin (600 mg QD 15 days)	CYP3A4[e]	0.28	0.57	One-sequence / 21 healthy subjects	Not recommend with strong CYP inducers	(FDA, 2014l)
Sofosbuvir (400 mg SD)	Rifampin (600 mg QD duration N/P)	P-gp	0.28	0.23	N/P / 17 healthy	Not recommend with P-gp inducers	(FDA, 2016b)

					subjects		
Sonidegib (800 mg SD)	Rifampin (600 mg QD 14 days)	CYP3A	0.28	0.46	Parallel / 16 healthy subjects	Avoid CYP3A strong inducers	(FDA, 2015j)
Simeprevir (150 mg QD 14 days)	Efavirenz (600 mg QD 14 days)	CYP3A[a]	0.29	0.48	Random crossover / 23 healthy subjects	Not recommend with moderate inducers of CYP3A	(FDA, 2013i)
Venetoclax (200 mg SD)	Rifampin (600 mg QD 13 days)	CYP3A, P-gp	0.29	0.60	One-sequence / 12 healthy female subjects	Avoid with strong and moderate CYP3A inducers, and consider alternatives with less CYP3A induction	(FDA, 2016e)
Ceritinib (750 mg SD)	Rifampin (600 mg QD 14 days)	CYP3A	0.30	0.56	One-sequence / 19 healthy subjects	Avoid strong CYP3A inducers; if not, adjust dose of ceritinib	(FDA, 2014p)
Dasabuvir (250	Carbamazepine	CYP2C8[a]	0.30	0.46	One-sequence	Contraindicate with strong inducers of CYP2C8	(FDA,

mg SD)	(200 mg QD 3 days, then BID 21 days)				/ 12 healthy subjects		2014m)
Dolutegravir (50 mg QD 19 days)	Etravirine (200 mg BID 14 days)	CYP3A, UGT	0.30	0.48	One-sequence / 15 healthy male subjects	Should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir	(FDA, 2013n)
Paritaprevir (150 mg SD)	Carbamazepine (200 mg QD 3 days, then BID 21 days)	CYP3A[a]	0.30	0.44	One-sequence / 12 healthy subjects	Contraindicate with strong inducers of CYP3A	(FDA, 2014m)
Sonidegib (200 mg QD for steady state)	Efavirenz (600 mg QD 120 days)	CYP3A	0.31 (PBPK)	0.4 (PBPK)	PBPK modeling/simuations of patients	Avoid CYP3A moderate inducers	(FDA, 2015j)
Panobinostat (20 mg SD)	Rifampin (600 mg QD 14 days)	CYP3A[a]	0.35 (PBPK)	0.43 (PBPK)	PBPK modeling/simuations of 10	Avoid strong CYP3A inducers	(FDA, 2015g)

					trials of 10 healthysubjects		
Dabrafenib (150 mg BID 21 days)	Phenytoin (300 mg BID duration N/P)	CYP3A[a]	0.38	0.23	One-sequence / 8 pateints alone, 1 patient with pheyntoin	Not recommend with strong inducers of CYP3A4; if not, monitor patients closely for loss of efficacy	(FDA, 2013m)
Eliglustat (150 mg BID 6 days)	Rifampin (600 mg QD IV dose 6 days)	CYP3A[a]	0.38	0.40	One-sequence / 5 healthy subjects (CYP2D6 UMs)	Not recommend with strong inducers of CYP3A	(FDA, 2014c)
Ibrutinib (dosing regimen N/P)	Efavirenz (dosing regimen N/P)	CYP3A	0.38 (PBPK)	N/P	N/P	None	(FDA, 2013g)
Ivabradine (dosing regimen	St. John's Wort extract (dosing	CYP3A4[a]	0.40	0.50	N/P	Avoid CYP3A4 inducers	(FDA,

N/P)	regimen N/P)						2015c)
Ledipasvir (90 mg SD)	Rifampin (600 mg QD 7 days)	P-gp	0.40	0.69	One-sequence / 31 healthy subjects	Not recommend with P-gp inducers	(FDA, 2014e)
Olaparib (300 mg SD)	Efavirenz (400 mg QD 13 days)	CYP3A[a]	0.40-0.50 (PBPK)	0.69-0.78 (PBPK)	Crossover / 100 subjects	Avoid moderate CYP3A inducers; if not, caution for decreased efficacy	(FDA, 2014g)
Dolutegravir (50 mg QD 10 days)	Tipranavir and ritonavir (500 mg /200 mg BID 5 days)	CYP3A, UGT	0.41	0.53	One-sequence / 14 healthy subjects	Increase dosing interval of dolutegravir	(FDA, 2013n)
Ospemifene (60 mg SD)	Rifampin (600 mg QD 5 days)	CYP3A, CYP2C9, CYP2C19	0.41	0.47	Random crossover / 12 post-menopausal female	Caution for decreased clinical effect of ospemifene with drugs that induce CYP3A4, CYP2C9 and/or CYP2C19	(FDA, 2013k)

					subjects		
Dolutegravir (50 mg QD 19 days)	Efavirenz (600 mg QD 14 days)	CYP3A, UGT	0.43	0.61	One-sequence / 12 healthy male subjects	Increase dosing interval of dolutegravir	(FDA, 2013n)
Sonidegib (200 mg QD for steady state)	Efavirenz (600 mg QD 14 days)	CYP3A	0.44 (PBPK)	0.51 (PBPK)	PBPK modeling/simuations of patients	Avoid moderate CYP3A inducers	(FDA, 2015j)
Dolutegravir (50 mg BID 21 days)	Rifampin (600 mg QD 14 days)	CYP3A, UGT	0.46	0.56	One-sequence / 12 healthy subjects	Increase dosing interval of dolutegravir	(FDA, 2013n)
Elbasvir (50 mg QD 8 days)	Efavirenz (600 mg QD 22 days)	CYP3A[a]	0.46	0.55	One-sequence / 7 healthy nonsmokers	Contraindicate with strong CYP3A inducers and efavirenz; not recommend with moderate CYP3A inducers	(FDA, 2016f)
Vorapaxar (20 mg loading dose,	Rifampin (600 mg QD 28 days)	CYP3A	0.46	0.61	Parallel, placebo-	Not recommend with strong inducers of CYP3A	(FDA, 2014n)

2.5 mg QD 22 days)					controlled / 12 healthy subjects		
Velpatasvir (100 mg QD 28 days)	Efavirenz and emtricitabine and tenofovir DF (600/200/300 mg QD 14 days)	CYP2B6, CYP3A4, P-gp, BCRP	0.47	0.53	One-sequence / 14 healthy volunteers	Not recommend with moderate to potent CYP inducers and P-gp inducers	(FDA, 2016b)
Canagliflozin (300 mg SD)	Rifampin (600 mg QD 8 days)	UGT2B4, UGT1A9	0.49	0.72	Not provided / healthy subjects	Increase dose of canaligflozin with UGT inducers	(FDA, 2013h)
Pirfenidone (801 mg SD)	Cigarette smoking (dosing regimen N/P)	CYP1A2	0.49	0.71	Parallel / healthy subjects (26 smokers and 25 nonsmokers)	Reduce dose of pirfenidone with strong or moderate CYP1A2 inhibitors	(FDA, 2014d)

Naloxegol (25 mg SD)	Efavirenz (dosing regimen N/P)	CYP3A4[a]	0.50 (PBPK)	N/P	PBPK modeling/simuations of patients	None	(FDA, 2014h)
Nintedanib (150 mg SD)	Rifampin (600 mg QD 7 days)	CYP3A4, P-gp	0.50	0.60	One-sequence / 25 healthy males	Avoid CYP3A4 and P-gp inducers	(FDA, 2014j)
0.5 < AUC ratios ⩽ 0.8 with dose recommendation							
Simeprevir (200 mg QD 7 days)	Rifampin (600 mg QD 7 days)	CYP3A[a], OATP (inhibition)	0.52	0.08 (C_{min})	Random crossover / 17 healthy subjects	Not recommend with strong inducers of CYP3A	(FDA, 2013i)
Tasimelteon (20 mg SD)	Cigarette smoking (minimum of 10 tobacco cigarettes/day 6	CYP1A2	0.53	0.57	Parallel / healthy subjects (24 smokers and 24	Caution for reduced efficacy of tasimelteon in smokers	(FDA, 2014f)

	months)				nonsmokers)		
Brivaracetam (150 mg SD)	Rifampin (600 mg QD 8 days)	CYP2C19	0.55	0.89	Random crossover / 26 healthy male nonsmokers	Increase dose of brivaracetam with rifampin	(FDA, 2016a)
Trabectedin (1.3 mg/m2 SD)	Rifampin (600 mg QD 6 days)	CYP3A [a]	0.55	0.77	Random crossover / 8 patients	Avoid CYP3A strong inducers	(FDA, 2015r)
Edoxaban (60 mg SD)	Rifampin (600 mg QD 7 days)	P-gp	0.60	1.00	N/P	Avoid rifampin	(FDA, 2015m)
Lesinurad (400 mg SD)	Rifampin (600 mg QD 14 days)	CYP2C9	0.62	0.76	One-sequence / 14 healthy males	Monitor for potential reduction in efficacy with moderate CYP2C9 inducer	(FDA, 2015s)
Daclatasvir (60 mg QD 14 days and 120 mg QD 5	Efavirenz (600 mg QD 14 days)	CYP3A [a]	0.68	0.83	One-sequence/17 healthy	Increase dose of daclatasvir with CYP3A moderate inducers	(FDA, 2015f)

days)					subjects		
Afatinib (40 mg SD)	Rifampin (600 mg BID 7 days)	P-gp	0.66	0.78	One-sequence / 22 healthy subjects	Increase dose of afatinib with chronic P-gp inducers	(FDA, 2013f)
Eslicarbazepine (800 mg as eslicarbazepine acetate QD 35 days)	Carbamazepine (200 mg QD 7 days, 400 mg QD 7 days, then 400 mg BID 14 days)	Unidentified enzyme	0.68	0.78	One-sequence / 18 healthy subjects	Adjust dose for eslicarbazepine or carbamazepine as needed	(FDA, 2013c)
Eslicarbazepine (600 mg QD first 2 days, 1200 mg QD 27 days)	Phenytoin (100 mg QD first 2 days, 300 mg QD 19 days)	Unidentified enzyme	0.68	0.69	One-sequence / 15 healthy male subjects	Increase dose of eslicarbazepine if necessary and adjust dose for phenytoin as needed	(FDA, 2013c)
Nintedanib (150 mg BID 28 days)	Pirfenidone (600 mg TID 28 days)	CYP3A4 [a]	0.69	0.59	Double-Blind, parallel, placebo-controlled / 9	Avoid CYP3A4 inducers	(FDA, 2014j)

					patients)		
Flibanserin (100 mg SD)	Etravirine (200 mg BID 15 days)	CYP3A4, CYP2C19	0.75	0.97	One-sequence/24 healthy females	Not recommend with CYP3A4 inducers	(FDA, 2015a)
Nintedanib (dosing regimen N/P)	Cigarette smoke (dosing regimen N/P)	Unclear	0.79 (smokers, PopPK)	N/P	N/P	Recommend patients to stop smoking prior to treatment and to avoid smoking when using nintedanib	(FDA, 2014j)

Drugs were orally administered unless specified; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

BID, twice daily; EM, extensive metabolizer; IM, intermediate metabolizer; IV, intravenously; N/P – not provided; PM, poor metabolizer; QD, once daily; SD, single dose; TID, three times daily; UM, ultrarapid metabolizer

[a] – Also a substrate of P-gp based on in vitro results; induction of P-gp might contribute to the observed interaction

[b] – Also metabolized by CYP1A2, CYP2C9, and CYP2C19; rifampin in an inducer of multiple P450s

[c] – Also a substrate of P-gp and BCRP based on in vitro results; induction of P-gp and BCRP might contribute to the observed interaction

[d] – Also metabolized by CYP2D6, CYP2C9, CYP2C19, and CYP2A6

[e] – Also metabolized by CYP1A2 and CYP2A6

[f] – Also metabolized by CYP2C9 and CYP3A

Supplemental Table 5. Inhibition DDIs, NME as inhibitor

Victim Drug (Dose)	Inhibitor (Dose)	Main Enzymes / Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population	Labeling Impact	Reference
AUC ratios ⩾ 5							
Tacrolimus (2 mg-0.5 mg SD)	Ombitasvir, paritaprevir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD 28 days)	CYP3A, P-gp	85.92	24.54 (C_{min})	One-sequence / 12 healthy subjects	Contraindicate with drugs that are highly dependent on CYP3A for clearance	(FDA, 2014m)
Tacrolimus (2 mg-0.5 mg SD)	paritaprevir, dasabuvir, and	CYP3A, P-gp	78.68	24.88 (C_{min})	One-sequence / 12 healthy	Contraindicate with drugs that are highly dependent on CYP3A for clearance	(FDA, 2014m)

	ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + dasabuvir 400 mg BID 28 days)				subjects		
Tacrolimus (2 mg-0.5 mg SD)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 28 days)	CYP3A, P-gp	57.07	16.48 (C_{min})	One-sequence / 12 healthy subjects	Contraindicate with drugs that are highly dependent on CYP3A for clearance	(FDA, 2014m)

Cyclosporine (100 mg SD alone, 10 mg SD with inhibitors)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 21 days)	CYP3A, P-gp	5.78	15.73 (C_{min})	One-sequence / 12 healthy subjects	Reduce dose of cyclosporine and frequently assess renal function and cyclosporine-related side effects	(FDA, 2014m)
Midazolam (5 mg SD)	Idelalisib (150 mg BID 8 days)	CYP3A	5.15	2.31	One-sequence / 11 healthy subjects	Avoid with CYP3A substrates	(FDA, 2014o)
2 ⩽AUC ratios < 5							
Cyclosporine	Paritaprevir,	CYP3A, P-gp	4.48	13.33	One-sequence	Reduce dose of cyclosporine; assess renal	(FDA,

(100 mg (tablet) - 10 mg (suspension) SD)	dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + dasabuvir 400 mg BID 21 days)			(C_{min})	/ 12 healthy subjects	function and cyclosporine-related side effects	2014m)
Cyclosporine (100 mg (tablet) - 10 mg (suspension) SD)	Ombitasvir, paritaprevir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD 21 days)	CYP3A, P-gp	4.28	12.5 (C_{min})	One-sequence / 12 healthy subjects	Reduce dose of cyclosporine; assess renal function and cyclosporine-related side effects	(FDA, 2014m)
Rilpivirine (25 mg QD 28	Ombitasvir, paritaprevir,	CYP3A	3.40	1.00	One-sequence / 10 healthy	Not recommend for co-administration	(FDA, 2014m)

days)	dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)				subjects		
Dextromethorphan (30 mg SD)	Rolapitant (200 mg SD)	CYP2D6	3.33	2.77	One-sequence / 26 subjects (CYP2D6 EMs and IMs)	Monitor for adverse reactions with NTR CYP2D6 substrates	(FDA, 2015o)
Rilpivirine (25 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir	CYP3A	3.27	2.55	One-sequence / 8 healthy subjects	Not recommend for co-administration	(FDA, 2014m)

	(paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
Sofosbuvir (10 mg SD)	Simeprevir (150 mg QD 12 or 24 weeks)	P-gp	3.16	1.91	N/P / 22	None	(FDA, 2013i)
Atorvastatin (20 mg SD)	Grazoprevir (200 mg QD 8 days)	BCRP, OATP1B1/3	3.00	5.67	One-sequence / 9 healthy caucasian nonsmokers	Reduce dose of atorvastatin	(FDA, 2016d)
Simeprevir (150 mg QD 10 days)	Ledipasvir (30 mg QD 10 days)	P-gp	2.84 (AUC_{tau})	2.56	Random crossover / 28 healthy	Not recommend for co-administration	(FDA, 2014e)

					subjects		
Rosuvastatin (10 mg SD)	Simeprevir (150 mg QD 7 days)	OATP1B1/3	2.81	3.17	N/P/ 16	Reduce and titrate the statin dose; monitor for adverse reactions	(FDA, 2013i)
Ritonavir (100 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg /100 mg QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 14 days)	CYP3A, P-gp	2.78	2.54	One-sequence / 12 healthy subjects	None	(FDA, 2014m)
Dexamethasone (20 mg on Day	Netupitant (450	CYP3A	2.76 (AUC_{84-}	1.89 (C_{max8}	Random crossover / 30	Reduce dose of dexamethansone	(FDA,

1 followed by 8 mg BID on Day 2-4)	mg SD)		$_{108h}$)	$_{4\text{-}108h}$)	healthy subjects		2014a)
Norgestimate (250 µg QD 21 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 19 days)	CYP3A, UGT1A1	2.75 (norelgestromin), 2.64 (norgestgrel)	2.30 (norelgestromin); 2.46 (norgestrel)	One-sequence / 3 healthy females	None [a]	(FDA, 2014m)
Rosuvastatin (10 mg SD)	Velpatasvir (100 mg QD 11 days)	BCRP, OATP1B1/3	2.69	2.61	Random crossover / 18 healthy	Reduce dose of rosuvastatin	(FDA, 2016b)

					subjects		
Ritonavir (100 mg BID 28 days)	Paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + dasabuvir 400 mg BID 14 days)	CYP3A, P-gp	2.66	2.34	One-sequence / 12 healthy subjects	None	(FDA, 2014m)
dexamethasone (20 mg on Day 1 followed by 8 mg BID on Day 2)	Netupitant (450 mg SD)	CYP3A	2.64 (AUC_{24-36h})	1.89 ($C_{max2\ 4-36h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)
Rosuvastatin (5 mg QD 21 days)	Ombitasvir, paritaprevir, dasabuvir, and	OATP1B1/ 1B3, BCRP	2.59	7.15	One-sequence / 12 healthy subjects	Reduce dose of rosuvastatin	(FDA, 2014m)

	ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
Rilpivirine (25 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14	CYP3A	2.59	2.20	One-sequence / 9 healthy subjects	Not recommend for co-administration	(FDA, 2014m)

	days)						
Carbamazepine (300 mg BID 31 days)	Brivaracetam (200 mg BID 13 days)	Epoxide hydrolase	2.57 (carbamazepine-10,11-epoxide), carbamazepine no change	2.64 (carbamazepine-10,11-epoxide), carbamazepine no change	One-sequence / 13 healthy male nonsmokers	Reduce dose of carbamazepine	(FDA, 2016a)
Amlodipine (5 mg SD)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir	CYP3A	2.57	1.26	One-sequence / 14 healthy subjects	Reduce dose of amlodipine; monitor for adverse reactions	(FDA, 2014m)

	(paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 24 days)						
Midazolam (7.5 mg SD)	Netupitant (300 mg SD)	CYP3A	2.44	1.40	Random Crossover / 20 healthy subjects	Caution with CYP3A substrates	(FDA, 2014a)
Sofosbuvir (400 mg SD)	Elbasvir and grazoprevir (50 mg/200 mg QD 15 days)	BCRP	2.44	2.27	One-sequence / 16 healthy nonsmokers	None	(FDA, 2016f)
Sofosbuvir (400 mg SD)	Velpatasvir (150 mg QD 10 days)	P-gp, BCRP	2.38	1.81	One-sequence / 186 healthy	None (combination drug)	(FDA, 2016b)

					subjects		
Metoprolol (50 mg SD)	Eliglustat (150 mg BID 5 days)	CYP2D6	2.33 (EM), 1.63 (IM)	1.72 (EM), 1.19 (IM)	One-sequence / 8 healthy subjects (CYP2D6 EMs)	Caution; reduce dose of sensitive CYP2D6 substrates	(FDA, 2014c)
Dextromethorphan (60 mg SD)	Panobinostat (20 mg QD 3 days)	CYP2D6	2.30	3.00	One-sequence / 14 patients (CYP2D6 EMs)	Avoid sensitive or NTR CYP2D6 substrates	(FDA, 2015g)
Dexamethasone (20 mg on Day 1 followed by 8 mg BID on Day 2-4)	Netupitant (300 mg SD)	CYP3A	2.30 ($AUC_{84-108h}$)	1.65 ($C_{max84-108h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)
Dexamethasone (20 mg on Day	Netupitant (300	CYP3A	2.30 (AUC_{24-}	1.60 (C_{max2}	Random crossover / 30	Reduce dose of dexamethansone	(FDA,

1 followed by 8 mg BID on Day 2)	mg SD)		$_{36h}$)	$_{4\text{-}36h}$)	healthy subjects		2014a)
Ritonavir (100 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)	CYP3A, P-gp	2.27	1.36	One-sequence / 12 healthy subjects	None	(FDA, 2014m)
Raltegravir (400 mg BID 17 days)	Ombitasvir, paritaprevir, dasabuvir, and	UGT1A1	2.26	2.27	One-sequence / 12 healthy subjects	None	(FDA, 2014m)

	ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
Rosuvastatin (10 mg SD)	Elbasvir and grazoprevir (50 mg/200 mg QD 11 days)	BCRP, OATP1B1/3	2.25	5.51	One-sequence / 11 healthy white/latino nonsmokers	Reduce dose of rosuvastatin	(FDA, 2016d)
Tacrolimus (5 mg SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole TID 13 days)	CYP3A4	2.25	1.42	N/P	Monitor tacrolimus concentrations; adjust dose as needed	(FDA, 2015e)

Sofosbuvir (400 mg SD)	Ledipasvir (90 mg QD 11 days）	P-gp, BCRP	2.21	2.02	One-sequence / 17 healthy subjects	None (combination drug)	(FDA, 2014e)
Atorvastatin (400 mg QD 12 or 24 weeks)	Simeprevir (150 mg QD 12 days)	OATP1B1/3, CYP3A4	2.19	1.66	One-sequence / 36 healthy subjects	Reduce and titrate the statin dose; monitor for adverse reactions	(FDA, 2013i)
Sulfasalazine (500 mg SD)	Rolapitant (200 mg SD)	BCRP	2.18	2.38	One-sequence / 20	Monitor for adverse reactions	(FDA, 2015o)
Ketoconazole (400 mg QD 6 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir/ombitasvir 150 mg/100 mg /25 mg + dasabuvir	CYP3A	2.15	1.13	One-sequence / 12 healthy subjects	Reduce dose of ketoconazole	(FDA, 2014m)

	250 mg SD)						
Buprenorphine (median 16 (4-24) mg QD 25 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)	CYP3A	2.05	2.00	One-sequence / 10 patients	Monitor for adverse reactions	(FDA, 2014m)
Midazolam (3 mg SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole three time daily 11	CYP3A4	2.03	1.72	N/P	Reduce dose of midazolam	(FDA, 2015e)

	days)						
1.25 ⩽AUC ratios < 2 with dose recommendation							
Atorvastatin (10 mg SD)	Elbasvir and grazoprevir (50 mg/200 mg QD 9-13 days)	BCRP, OATP1B1/3	1.95	4.33	One-sequence / 16 healthy nonsmokers	Reduce dose of atorvastatin	(FDA, 2016d)
Tenofovir (tenofovir DF 300 mg QD 28 days, administered with efavirenz and emtricitabine as ATRIPLA)	Ledispavir and Sofosbuvir (90 mg/400 mg QD 14 days)	P-gp	1.94	1.72	One-sequence / 14 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2014e)
Digoxin (0.5	Flibanserin (100	P-gp	1.93	1.46	Random crossover / 23	Monitor digoxin concentrations	(FDA,

mg SD)	mg QD 8 days)				healthy subjects		2015a)
ledipasvir (30 mg QD 10 days)	Simeprevir (150 mg QD 10 days)	P-gp	1.88 (AUC_{tau})	1.78	Random crossover/ 22 healthy subjects	Not recommend for co-administration	(FDA, 2014e)
Sirolimus (2 mg SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole three time daily 13 days)	CYP3A4	1.84	1.65	N/P	Monitor sirolimus concentrations; adjust dose as needed	(FDA, 2015e)
Pravastatin (10 mg QD 17 days)	Ombitasvir, Paritaprevir, Dasabuvir, and Ritonavir (paritaprevir/ritona	CYP3A, OATPs	1.82	1.36	One-sequence/ 12 healthy subjects	Reduce dose of pravastatin	(FDA, 2014m)

	vir/ombitasvir 150 mg/100 mg/25 mg QD + dasabuvir 400 mg BID 14 days)						
Dexamethasone (20 mg SD)	Netupitant (450 mg SD)	CYP3A	1.82 (AUC_{0-24h})	1.22 ($C_{max0-24h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)
Tenofovir (tenofovir DF 300 mg (administered with efavirenz/emtricitabine as ATRIPLA) QD	Sofosbuvir and velpatasvir (400 mg/100 mg QD 14 days)	P-gp, BCRP	1.81 (AUC_{tau})	1.77	One-sequence / 15 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian et al., 2016)

28 days)							
Dexamethasone (20 mg on Day 1 followed by 8 mg BID on Day 2)	Netupitant (450 mg SD)	CYP3A	1.81 (AUC_{24-36h})	1.51 ($C_{max24-36h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)
Simvastatin (40 mg SD)	Simeprevir (150 mg QD 12 days)	CYP3A4, OATP1B1/3	1.71	1.82	One-sequence / 36 healthy subjects	Reduce and titrate the statin dose; monitor for adverse reactions	(FDA, 2013i)
Caffeine (200 mg SD)	Obeticholic acid (25 mg QD 14 days)	CYP1A2	1.65	1.10	One-sequence / 21 healthy subjects	Monitor drug concentrations of CYP1A2 substrates with a NTR	(FDA, 2016d)
Dexamethasone (20 mg SD)	Netupitant (300 mg SD)	CYP3A	1.64 (AUC_{0-24h})	1.09 ($C_{max0-24h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)

Rosuvastatin (10 mg SD)	grazoprevir (200 mg QD 9 days)	BCRP, OATP1B1/3	1.59	4.25	One-sequence / 11 healthy white/latino nonsmokers	Reduce dose of rosuvastatin	(FDA, 2016d)
Midazolam (2 mg SD)	Palbociclib (125 mg QD 8 days)	CYP3A	1.58	1.38	Random crossover / 26 healthy females	Reduce dose of sensitive CYP3A substrates with a NTR	(FDA, 2015h)
Buprenorphine (median 16 (8-24) mg QD 25 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir	CYP3A	1.58	1.26	One-sequence / 10 patients	Monitor for sedation and cognitive effects	(FDA, 2014m)

	400 mg BID 14 days)						
dexamethasone (20 mg on Day 1 followed by 8 mg BID on Day 2-4)	Netupitant (100 mg SD)	CYP3A	1.53 ($AUC_{84-108h}$)	1.39 ($C_{max84-108h}$)	Random crossover / 30 healthy subjects	Reduce dose of dexamethansone	(FDA, 2014a)
Simepravir (150 mg QD 7 days)	Daclatasvir (60 mg QD 7 days)	OATP1B1/3	1.51	1.43	Random crossover / 24 healthy nonsmokers	Reduce dose of daclatasvir[b]	(FDA, 2015f)
Digoxin (0.25 mg SD)	Eliglustat (150 mg in EMs, UMs, and IMs and 100 mg in PMs BID 7 days)	P-gp	1.49 (AUC_{last})	1.71	One-sequence / 27 healthy subjects (CYP2D6 EMs [n=19], UMs [n=4],	Reduce dose; monitor drug concentrations of digoxin and other P-gp substrates	(FDA, 2014c)

					IM [n=1], PMs [n=4]		
Midazolam (2 mg SD (syrup))	Suvorexant (80 mg QD 14 days)	CYP3A	1.47	1.23	One-sequence / 12 healthy subjects	Monitor patients on sensitive CYP3A substrates with a NTR	(FDA, 2014b)
Rosuvastatin (10 mg SD)	Daclatasvir (60 mg QD 9 days)	BCRP, OATP1B1/3	1.47	1.84	One-sequence / 21 healthy subjects	Monitor for adverse events	(FDA, 2015f)
Midazolam (0.075 mg/kg SD)	Simeprevir (150 mg QD 11 days)	CYP3A4	1.43 (AUC_{last})	1.31	Random crossover / 16 healthy subjects	Caution is warranted when midazolam is co-administered	(FDA, 2013i)
Caffeine (200 mg SD)	Obeticholic acid (10 mg QD 14 days)		1.42	1.06	One-sequence / 21 healthy subjects	Monitor drug concentrations of CYP1A2 substrates with a NTR	(FDA, 2016d)
Tacrolimus (2	Elbasvir and	CYP3A	1.42	1.7	One-sequence	Monitor for tacrolimus concentrations, renal	(FDA,

mg SD)	grazoprevir (50 mg/200 mg QD 16 days)			(C_{min})	/ 16 healthy nonsmokers	function, and tacrolimus-related side effects	2016f)
Docetaxel (75-100 mg/m^2 IV SD in combination with 0.5 mg palonosetron)	Netupitant (300 mg SD in combination with 0.5 mg palonosetron)	CYP3A	1.42	1.49	Random crossover / 6 patients	Caution; monitor for chemotherapeutic related adverse reactions	(FDA, 2014a)
Rosuvastatin (20 mg SD)	Eluxadoline (100 mg SD)	OATP1B1	1.41	1.18	Random crossover / 27 healthy subjects	Reduce dose of rosuvastatin; caution for statin-related toxicity	(FDA, 2015p)
Tenofovir (300 mg QD 8 days with a moderate fat meal (as	Sofosbuvir and velpatasvir (400 mg/100 mg QD 8 days)	P-gp, BCRP	1.40 (AUC_{tau})	1.44	Random crossover / 24 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian et al.,

emtricitabine/rilpivirine/tenofovir DF: 200/25/300 mg; COMPLERA))							2016)
Tenofovir (300 mg QD 7 days with breakfast (as emtricitabine/tenofovir DF 200/300 mg) co-administered with raltegravir 400 mg BID)	Sofosbuvir and velpatasvir (400 mg/100 mg QD 7 days)	P-gp, BCRP	1.40 (AUC_{tau})	1.46	Random crossover / 30 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian et al., 2016)
Atorvastatin (20 mg SD)	Isavuconazonium sulfate (equivalent	CYP3A4	1.40	1.05	N/P	Caution; monitor for adverse reactions	(FDA, 2015e)

	to 200 mg isavuconazole TID 8 days)						
Tenofovir (300 mg QD 10 days with breakfast (as emtricitabine/tenofovir DF 200/300 mg) co-administered with darunavir 800 mg and ritonavir 100 mg)	Sofosbuvir and velpatasvir (400 mg/100 mg QD 10 days)	P-gp, BCRP	1.39 (AUC_{tau})	1.55	Random crossover / 29 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian et al., 2016)
Digoxin (0.25 mg SD)	Simeprevir (150 mg QD 7 days)	P-gp	1.39	1.31	N/P / 16	Monitor digoxin concentrations	(FDA, 2013i)

Mycophenylate mofetil (1 g SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole TID 8 days)	UGTs	1.35 (mycophenolic acid)	0.89 (mycophenolic acid)	N/P	Monitor for mycophenolic acid-related toxicity	(FDA, 2015e)
Alprazolam (0.5 mg SD)	Ombitasvir, Paritaprevir, Dasabuvir, and Ritonavir (paritaprevir/ritonavir/ombitasvir 150 mg/100 mg/25 mg QD + dasabuvir 250 mg BID 18 days)	CYP3A	1.34	1.09	One-sequence / 12 healthy subjects	Monitor patients ; reduce dose of alprazolam as needed	(FDA, 2014m)
Digoxin (0.25 mg SD)	Velpatasvir (100 mg QD 4 days)	P-gp	1.34	1.88	Random crossover / 21	Monitor digoxin concentrations	(FDA, 2016b;

					healthy subjects		Mogalian et al., 2016)
Tenofovir (300 mg QD 10 days with a moderate fat meal (as elvitegravir/cobicistat/emtricitabine/tenofovir DF: 150/150/200/300 mg))	Sofosbuvir and velpatasvir (400 mg/100 mg QD 10 days)	P-gp, BCRP	1.34 (AUC_{tau})	1.36	Random crossover / 24 healthy subjects	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian et al., 2016)
Dexamethasone (20 mg SD)	Netupitant (100 mg SD)	CYP3A	1.33 (AUC_{0-24h})	1.03 ($C_{max0-24h}$)	Random crossover / 30 healthy	Reduce dose of dexamethansone	(FDA, 2014a)

					subjects		
Warfarin (25 mg SD)	Obeticholic acid (25 mg QD 13 days)	R-warfarin: CYP1A2, CYP3A4, S-warfarin: CYP2C9	1.32 (R-warfarin), 1.18 (S-warfarin)	1.05 (R-warfarin), 1.06 (S-warfarin)	One-sequence / 22 healthy subjects	Monitor International Normalized Ratio (INR); adjust dose of warfarin as needed	(FDA, 2016d)
(S)-warfarin (dose N/P, SD as part of the Cooperstown 5+1 cocktail)	Oritavancin (1200 mg single IV)	CYP2C9	1.32	N/P	Cocktail study, one-sequence/16 healthy subjects	Caution for potential risk of bleeding and frequently monitor for signs of bleeding	(FDA, 2014k)
Tenofovir (300 mg QD 10 days with breakfast	Sofosbuvir and velpatasvir (400 mg/100 mg QD 10	P-gp, BCRP	1.30 (AUC_{tau})	1.55	Random crossover / 24 healthy	Monitor for tenofovir-associated adverse reactions	(FDA, 2016b; Mogalian

(as emtricitabine/tenofovir DF 200/300 mg) co-administered with atazanavir 300 mg and ritonavir 100 mg)	days)				subjects		et al., 2016)
Cyclosporine (300 mg SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole TID 8 days)	CYP3A4	1.30	1.10	N/P	Monitor cyclosporine concentrations; adjust dose as needed	(FDA, 2015e)
Naloxone (median 4 (1-6) mg QD 25	Ombitasvir, paritaprevir, dasabuvir, and	UGT1A1	1.30	1.25	One-sequence / 12 patients	Monitor for sedation and cognitive effects	(FDA, 2014m)

days)	ritonavir (paritaprevir/ritonavir 150 mg/100 mg QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
(S)-warfarin (racemic warfarin 5 mg SD)	Venetoclax (400 mg SD)	CYP2C9	1.28	1.18	One-sequence / 3 healthy female subjects	Monitor for INR	(FDA, 2016e)
Digoxin (0.125 mg QD 20 days)	Daclatasvir (60 mg QD 10 days)	P-gp	1.27	1.65	One-sequence / 15 healthy subjects	Monitor digoxin concentrations; adjust digoxin doses if necessary	(FDA, 2015f)
Digoxin (0.5 mg SD)	Rolapitant (180 mg SD)	P-gp	1.27	1.67	One-sequence / 16	Monitor for adverse reactions associated with P-gp substrates with an NTR	(FDA, 2015o)

Digoxin (0.5 mg SD)	Suvorexant (40 mg QD 11 days)	P-gp	1.27	1.21	Random crossover / 19 healthy subjects	Monitor digoxin concentrations	(FDA, 2014b)
Digoxin (0.5 mg SD)	Isavuconazonium sulfate (equivalent to 200 mg isavuconazole TID 12 days)	P-gp	1.25	1.33	N/P	Adjust dose of P-gp substrates with a NTR; monitor digoxin concentrations	(FDA, 2015e)
Midazolam (2 mg SD (syrup))	Suvorexant (80 mg QD 4 days)	CYP3A	1.25	1.06	One-sequence / 12 healthy subjects	Monitor patients on sensitive CYP3A substrates with a NTR	(FDA, 2014b)

Drugs were orally administered unless specified; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

BID, twice daily; EM, extensive metabolizer; IM, intermediate metabolizer; INR, International normalized ratio; IV, intravenously; N/P – not provided; NTR, narrow therapeutic range; PM, poor metabolizer; QD, once daily; SD, single dose; TID, three times daily; UM, ultrarapid metabolizer

[a] – Because norgestimate is in combination with ethinyl estradiol, according to the product label, “Although there is no labeling recommendation specific to norgestimate, ethinyl estradiol-containing oral contraceptives are contraindicated with Viekira Pak due to potential alanine aminotransferase elevation"

[b] – Labeling recommendations are extracted from the NDA Clinical Pharmacology and Biopharmaceutics Review(s)

Supplemental Table 6. Induction DDIs, NMEs as inducers

Victim Drug (Dose)	Inducer (Dose)	Main Enzymes /Transporters Possibly Involved	AUC Ratio	C_{max} Ratio	Study Design / Population	Labeling Impact	Reference
AUC ratios ⩽0.2							
Itraconazole (200 mg QD 7 days)	Ivacaftor and lumacaftor (250 mg/200 mg BID 7 days)	CYP3A	0.18	0.10	One-sequence / 17 healthy subjects	Not recommend with sensitive or NTR CYP3A substrates	(FDA, 2015k)
Ivacaftor (200 mg QD 14 days)	Lumacaftor (150 mg BID 14 days)	CYP3A	0.20	0.19	One-sequence / 17 healthy subjects	Not recommend with sensitive or NTR CYP3A substrates	(FDA, 2015k)
0.2 < AUC ratios ⩽0.5							
Ivacaftor (200 mg QD 14	Lumacaftor (250 mg BID 14 days)	CYP3A	0.21	0.25	One-sequence / 16 healthy	Not recommend with sensitive or NTR CYP3A substrates	(FDA, 2015k)

days)					subjects		
Ivacaftor (400 mg QD 14 days)	Lumacaftor (150 mg BID 14 days)	CYP3A	0.26	0.43	One-sequence / 13 healthy subjects	Not recommend with sensitive or NTR CYP3A substrates	(FDA, 2015k)
Midazolam (3 mg SD)	Dabrafenib (150 mg BID repeated dosing)	CYP3A	0.26	0.39	N/P/ 12 patients	Caution for efficacy loss of drugs that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6	(FDA, 2013m)
0.5 < AUC ratios ⩽ 0.8 with dose recommendation							
Simvastatin (80 mg SD)	Eslicarbazepine acetate (800 mg QD 14 days)	CYP3A	0.51	0.39	Random crossover / 24 healthy subjects	Adjust dose of simvastatin if necessary	(FDA, 2013c)
Bupropion (dosing regimen N/P)	Isavuconazonium sulfate (200 mg QD)	CYP2B6	0.58	0.69	N/P	Increase dose of bupropion	(FDA, 2015e)
Amlodipine (5	Lesinurad (400 mg	CYP3A	0.58	0.61	One-sequence	Monitor for a potential reduction in efficacy of	(FDA,

mg QD 28 days)	QD 24 days)				/ 13 healthy males	sensitive CYP3A substrates	2015s)
Omeprazole (40 mg SD)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg once daily+ dasabuvir 250 mg BID 19 days)	CYP2C19	0.62	0.62	One-sequence / 11 healthy subjects	Monitor for decreased efficacy; increase dose of omeprazole dose if necessary	(FDA, 2014m)
Rosuvastatin (40 mg SD)	Eslicarbazepine acetate (400 mg QD for 7 days, then 800 mg QD for 7 days, then	OATP1B1/3 and/or BCRP	0.65	0.65	One-sequence / 30 healthy subjects	Adjust dose of rosuvastatin if necessary	(FDA, 2013c)

	1200 mg QD for 17 days						
Sildenafil (50 mg SD)	Lesinurad and allopurinol (300 mg/ 200 mg QD 10 days)	CYP3A	0.66	0.66	Random crossover / 12 healthy males	Monitor for a potential reduction in efficacy of sensitive CYP3A substrates	(FDA, 2015s)
Ritonavir (100 mg BID)	Isavuconazonium sulfate (multiple doses)	CYP3A	0.69	N/P	N/P	Caution for possible loss of antiviral efficacy	(FDA, 2015e)
Ethinyl estradiol (30 ug SD)	Eslicarbazepine acetate (800 mg QD 15 days)	CYP3A[a]	0.69	0.91	Random crossover / 19 healthy female subjects	Use additional or alternative non-hormonal birth control	(FDA, 2013c)
Dextromethorphan (dose N/P SD)	Oritavancin (1200 mg single IV)	CYP2D6	N/P	0.69[b]	Cocktail ctudy, One-sequence/13 healthy	Caution with NTR P450 substrates	(FDA, 2014k)

					subjects		
Lopinavir (400 mg BID)	Isavuconazonium sulfate (multiple doses)	CYP3A	0.73	N/P	N/P	Caution for possible loss of antiviral efficacy	(FDA, 2015e)
Darunavir (with ritonavir, 800 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 14 days)	CYP3A	0.74	0.78	One-sequence / 12 healthy subjects	Not recommend for co-administration	(FDA, 2014m)
Darunavir (with ritonavir, 800 mg QD 28	Ombitasvir, paritaprevir, dasabuvir, and	CYP3A	0.75	0.92	One-sequence / 12 healthy subjects	Not recommend for co-administration	(FDA, 2014m)

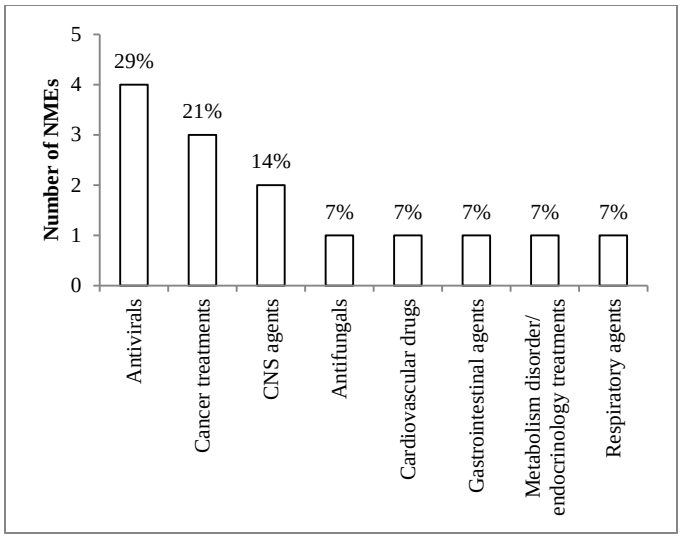
days)	ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
Darunavir (with ritonavir, 600 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 14 days)	CYP3A	0.79	0.86	One-sequence / 12 healthy subjects	Not recommend for co-administration	(FDA, 2014m)

Drugs were orally administered unless specified; either CYP3A or CYP3A4 depending on how the enzyme is presented in the NDA reviews.

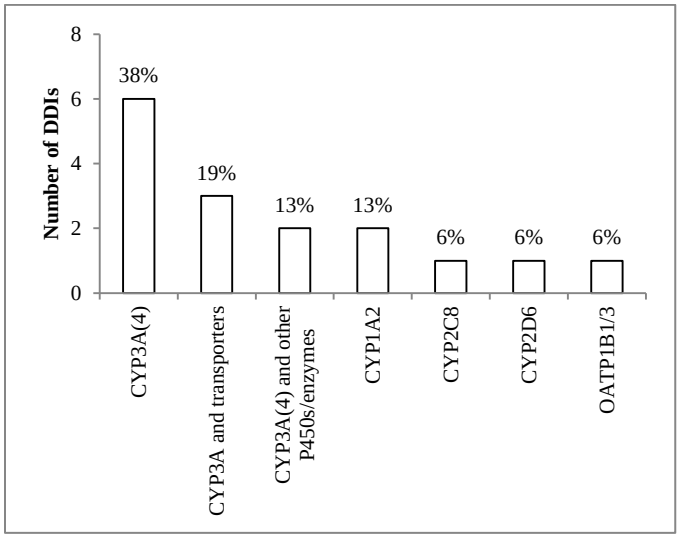
BID, twice daily; IV, intravenously; N/P – not provided; NTR, narrow therapeutic range; QD, once daily; SD, single dose

[a] – Activation of UGT1A1 might also contribute

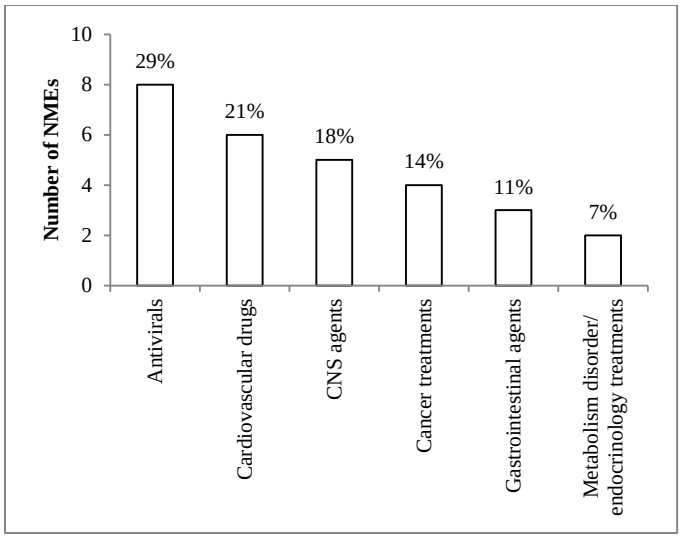
[b] – Changes in the concentration ratio of dextromethorphan to dextrorphan in urine



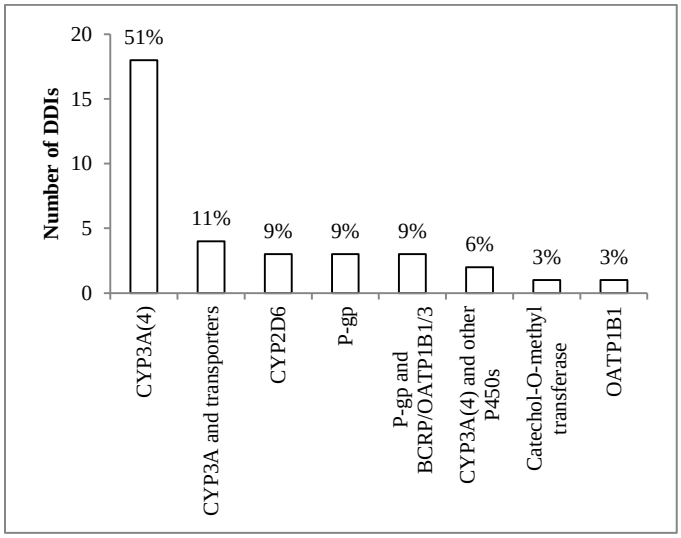
Supplemental Figure 1A. Therapeutic classes for inhibition DDIs with AUC ratios ≥ 5, NME as substrate (N = 14)



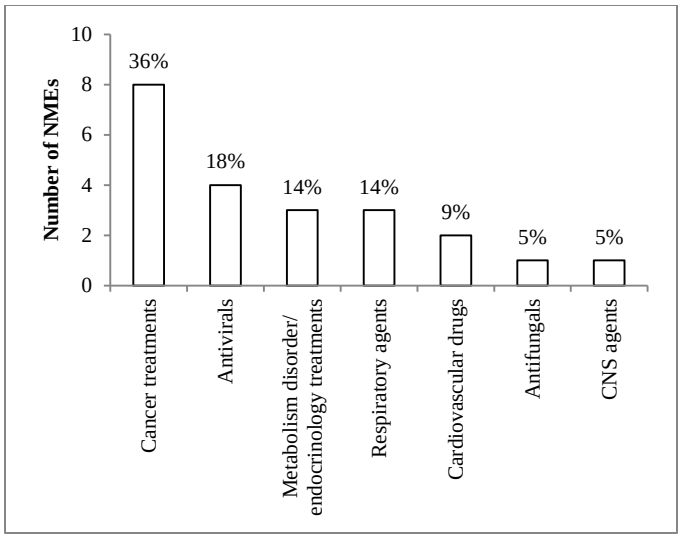
Supplemental Figure 1B. Mechanisms for inhibition DDIs with AUC ratios ≥ 5, NME as substrate (N = 16)



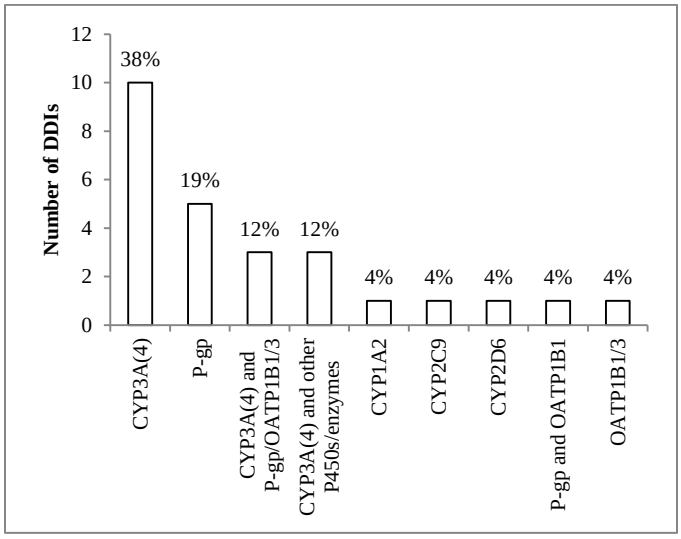
Supplemental Figure 1C. Therapeutic classes for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as substrate (N = 28)



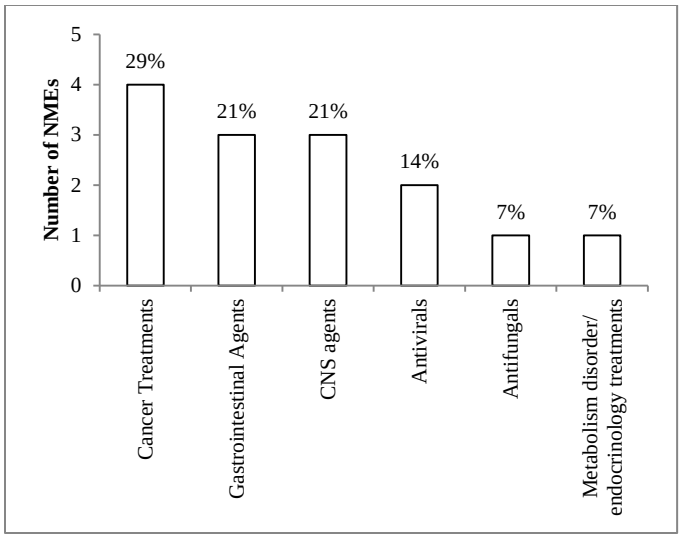
Supplemental Figure 1D. Mechanisms for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as substrate (N = 35)



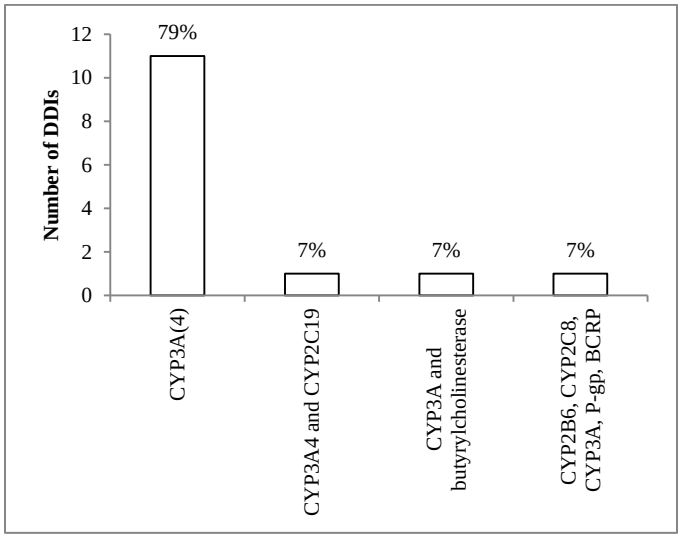
Supplemental Figure 1E. Therapeutic classes for inhibition DDIs with AUC ratios < 2, NME as substrate (N = 22)



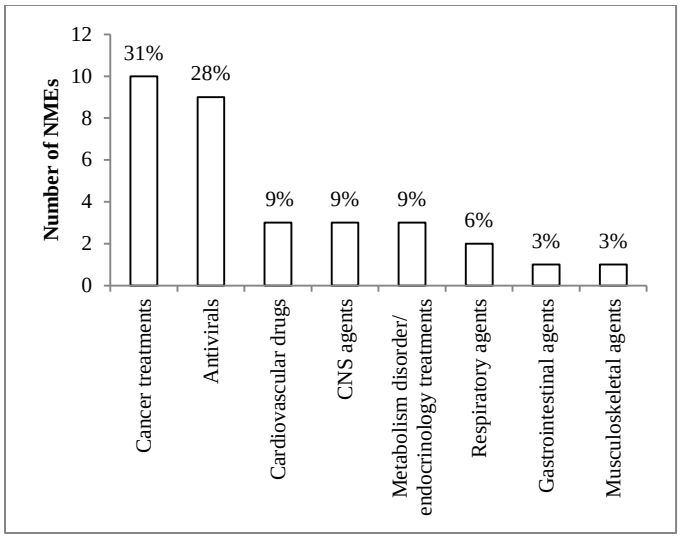
Supplemental Figure 1F. Mechanisms for inhibition DDIs with AUC ratios < 2, NME as substrate (N = 26)



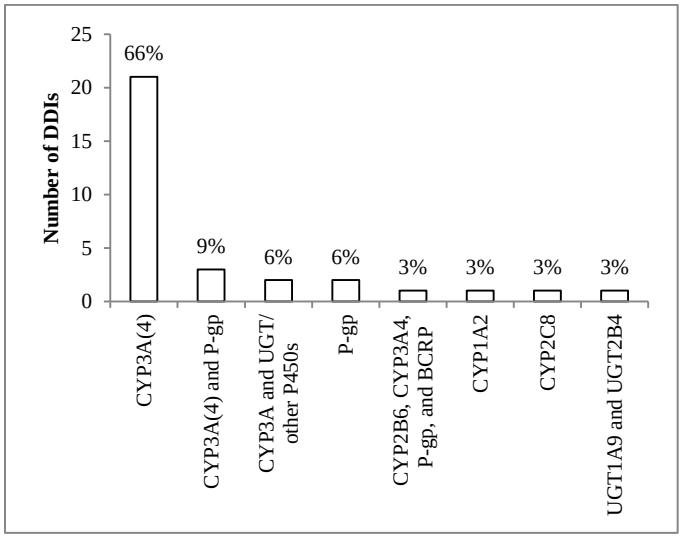
Supplemental Figure 2A. Therapeutic classes for induction DDIs with AUC ratios ≤ 0.2, NME as substrate (N = 14)



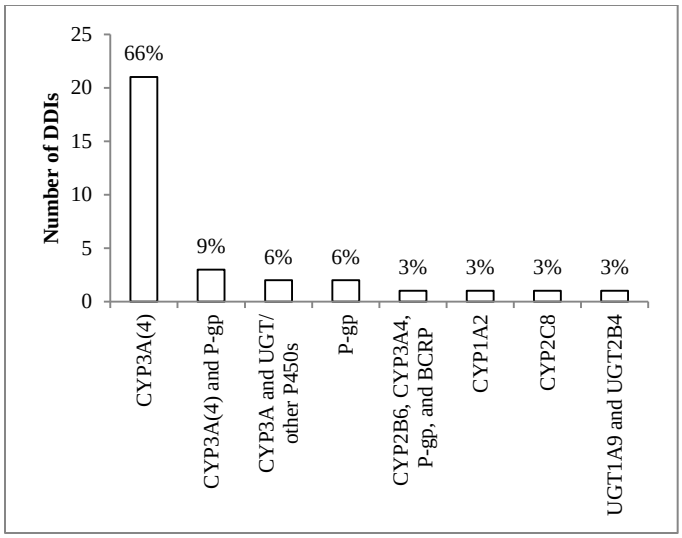
Supplemental Figure 2B. Mechanisms for induction DDIs (AUC ratios ≤ 0.2), NME as substrate (N = 14)



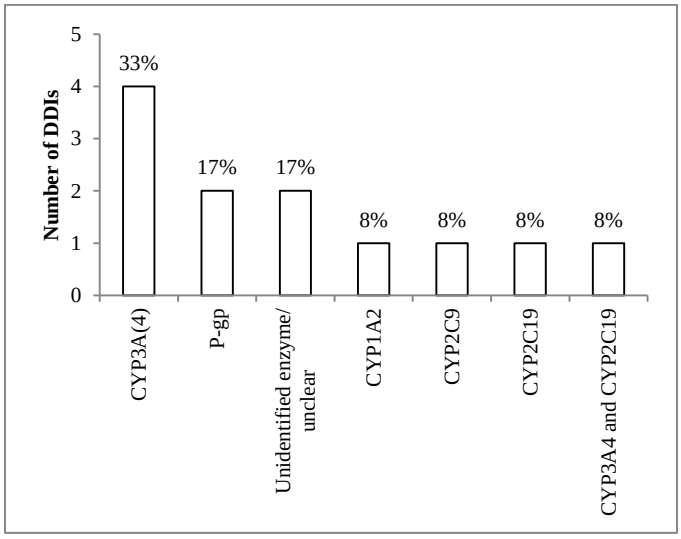
Supplemental Figure 2C. Therapeutic classes for induction DDIs with 0.2 < AUC ratios ≤ 0.5, NME as substrate (N = 32)



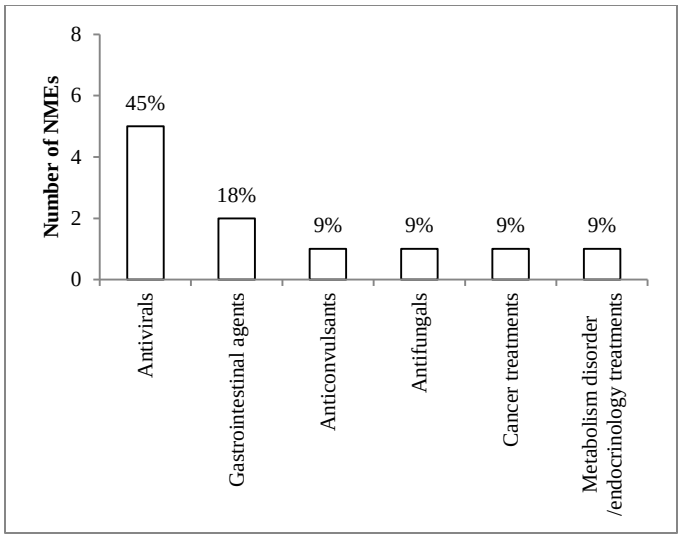
Supplemental Figure 2D. Mechanisms for induction DDIs (0.2 < AUC ratios ≤ 0.5), NME as substrate (N = 32)



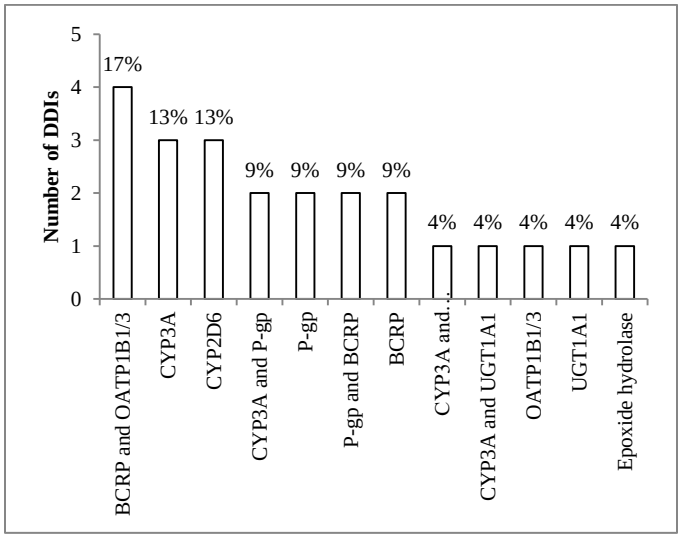
Supplemental Figure 2E. Therapeutic classes for induction DDIs with 0.5 < AUC ratios ≤ 0.8, NME as substrate (N = 11)



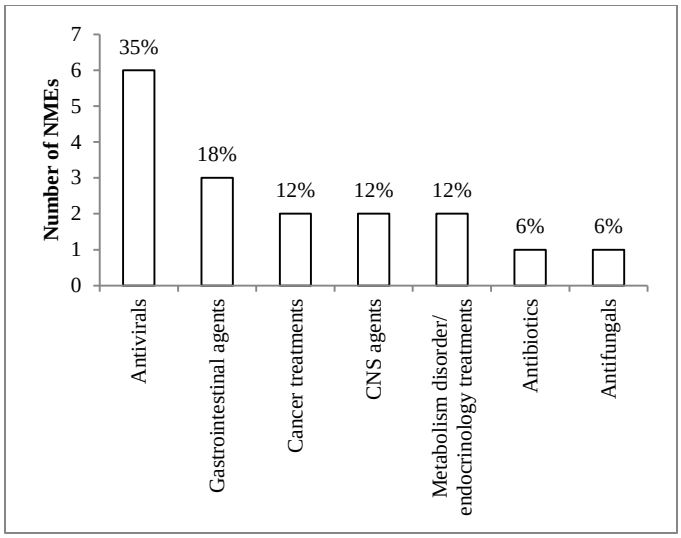
Supplemental Figure 2F. Mechanisms for induction DDIs (0.5 < AUC ratios ≤ 0.8), NME as substrate (N = 12)



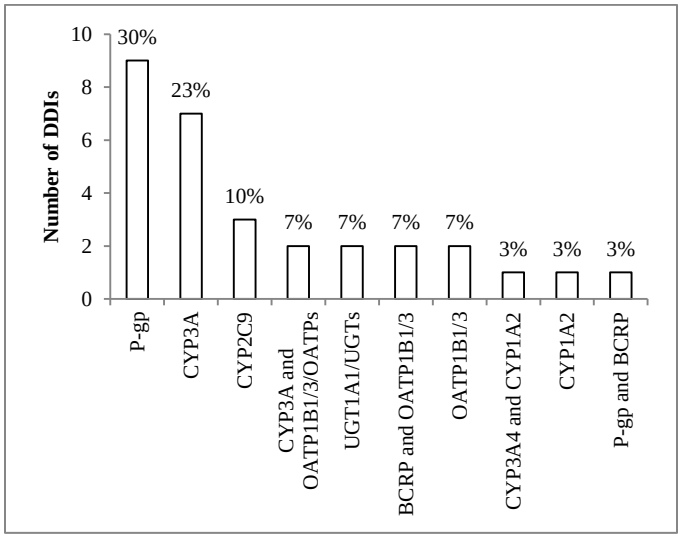
Supplemental Figure 3A. Therapeutic classes for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as inhibitor (N = 11)



Supplemental Figure 3B. Mechanisms for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as inhibitor (N = 23)



Supplemental Figure 3C. Therapeutic classes for inhibition DDIs with AUC ratios < 2, NME as inhibitor (N = 17)



Supplemental Figure 3D. Mechanisms for inhibition DDIs with AUC ratios < 2, NME as inhibitor (N = 30)