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

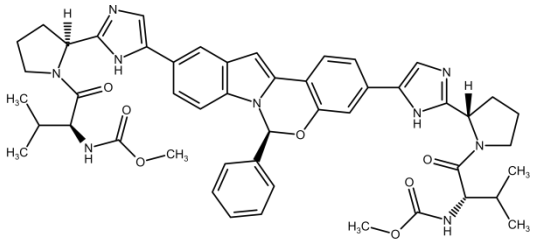
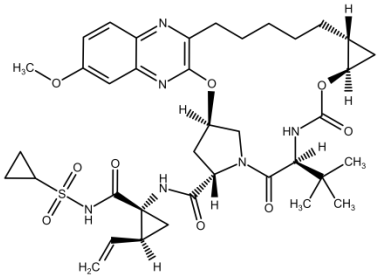
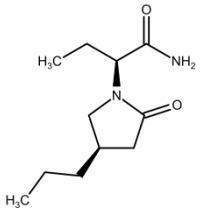
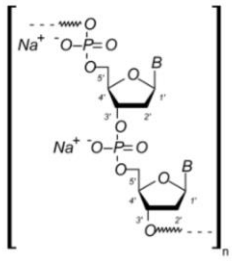
	agents			
Cangrelor	Cardiovascular drugs	KENGREAL	204958	06/22
Cariprazine	Central nervous system agents	VRAYLAR	204370	09/17
(Ceftazidime and) avibactam	Antibiotics	AVYCAZ	206494	02/25
Cholic acid	Metabolism disorder/endocrinology treatments	CHOLBAM	205750	03/17
Cobimetinib	Cancer treatments	COTELLIC	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

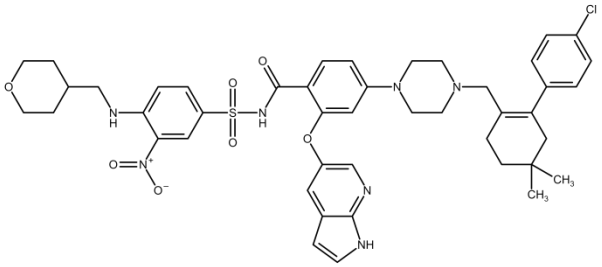
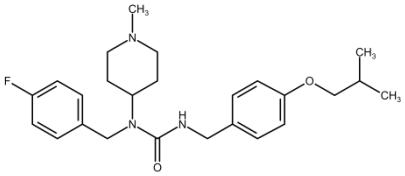
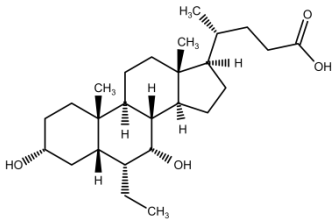
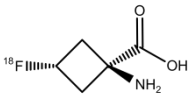
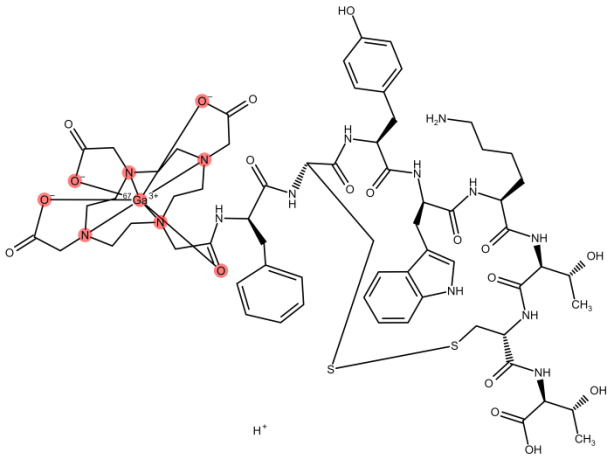
Flibanserin	Central nervous system agents	ADDYI	022526	08/18
Insulin degludec	Metabolism disorder agent	TRESIBA	203314	09/25
Isavuconazonium sulfate	Antifungals	CRESEMBA	207500/207501	03/06
Ivabradine	Cardiovascular drugs	CORLANOR	206143	04/15
Ixazomib citrate	Cancer treatments	NINLARO	208462	11/20
Lenvatinib	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

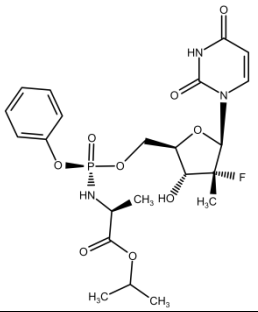
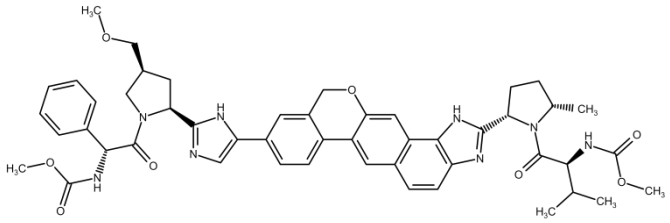
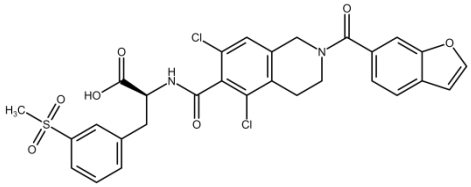
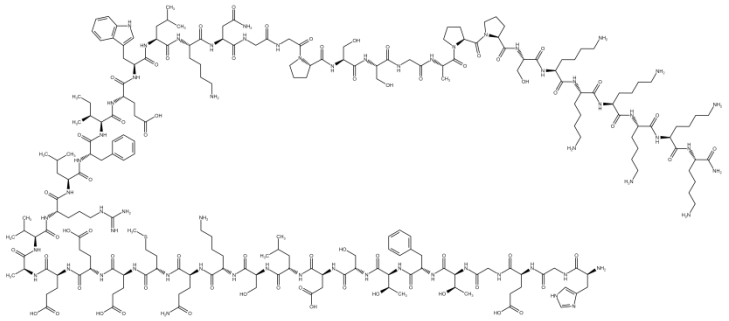
Selexipag	Cardiovascular drugs	UPTRAVI	207947	12/21
Sonidegib	Cancer treatments	ODOMZO	205266	07/24
Sugammadex	Antidotes	BRIDION	022225	12/15
Trabectedin	Cancer treatments	YONDELIS	207953	10/23
(Trifluridine and) tipiracil	Cancer treatments	LONSURF	207981	09/22
Uridine triacetate	Metabolism disorder/endocrinology 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

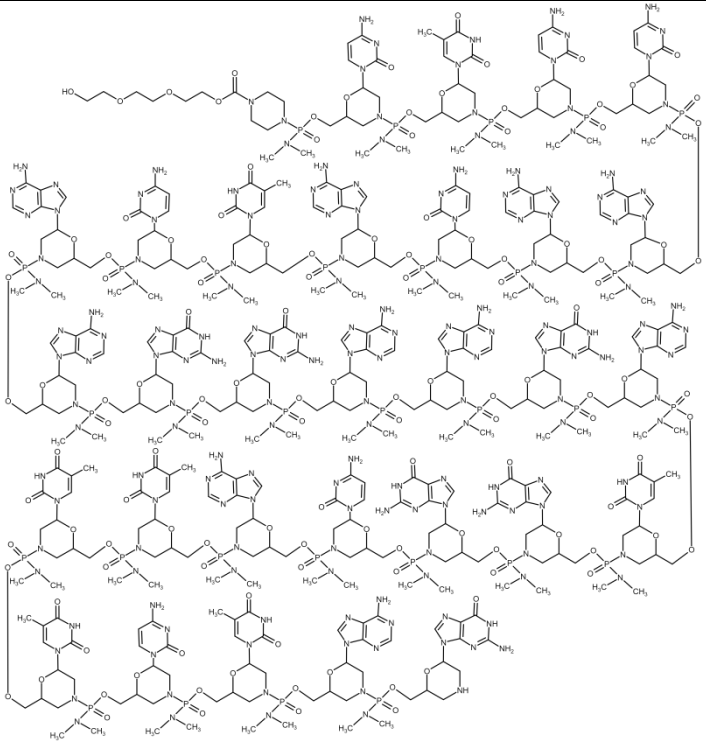
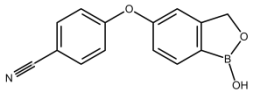
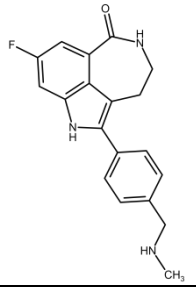
dotatate				
Lifitegrast	Ophthalmic agents	XIIDRA	208073	07/11
Lixisenatide	Metabolism disorder/endocrinology treatments	ADLYXIN	208471	07/27
Nusinersen	Central nervous system agents	SPINRAZA	209531	12/23
Obeticholic acid	Metabolism disorder/endocrinology treatments	OCALIVA	207999	05/27
Pimavanserin	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

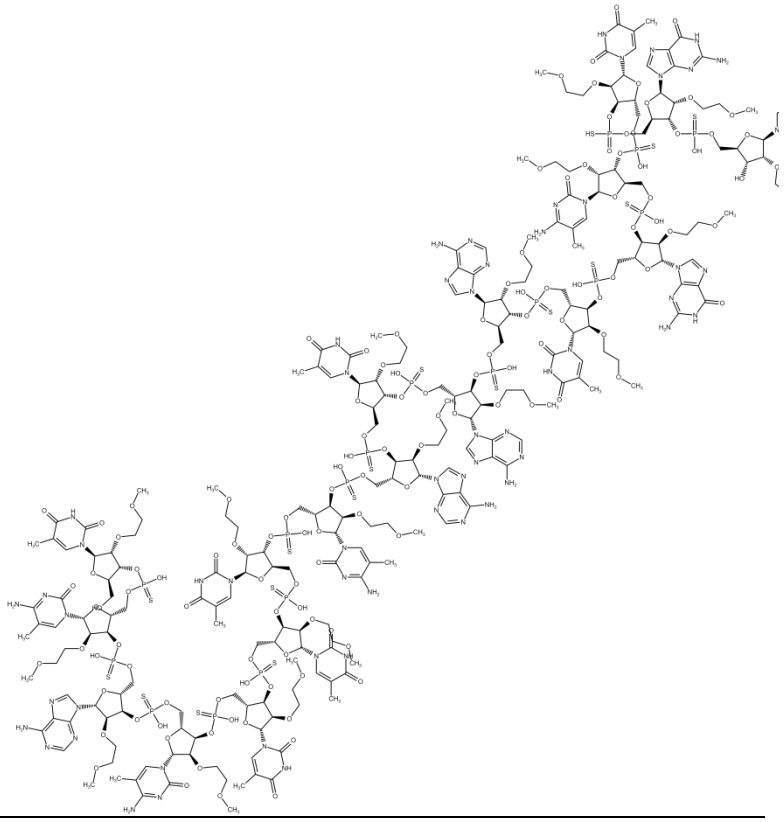
Supplemental Table 2. Chemical structures of compounds within the NDAs approved in 2016 (ordered by approval date)

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)

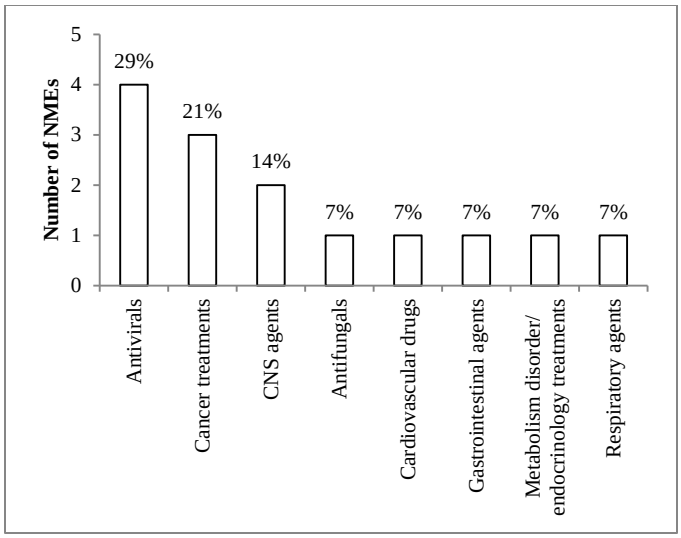
days)	ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg QD + dasabuvir 400 mg BID 14 days)						
Darunavir (with ritonavir, 600 mg QD 28 days)	Ombitasvir, paritaprevir, dasabuvir, and ritonavir (paritaprevir/ritonavir 150/100 QD + ombitasvir 25 mg QD + dasabuvir 250 mg BID 14 days)	CYP3A	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.

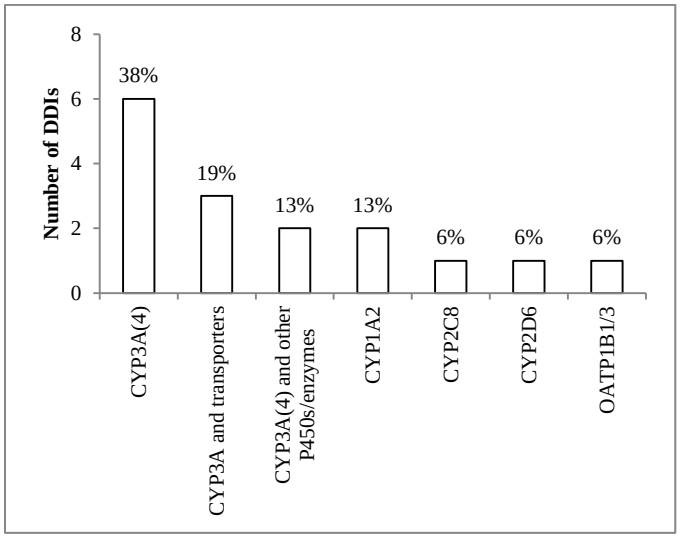
BID, twice daily; IV, intravenously; N/P – not provided; NTR, narrow therapeutic range; QD, once daily; SD, single dose

[a] – Activation of UGT1A1 might also contribute

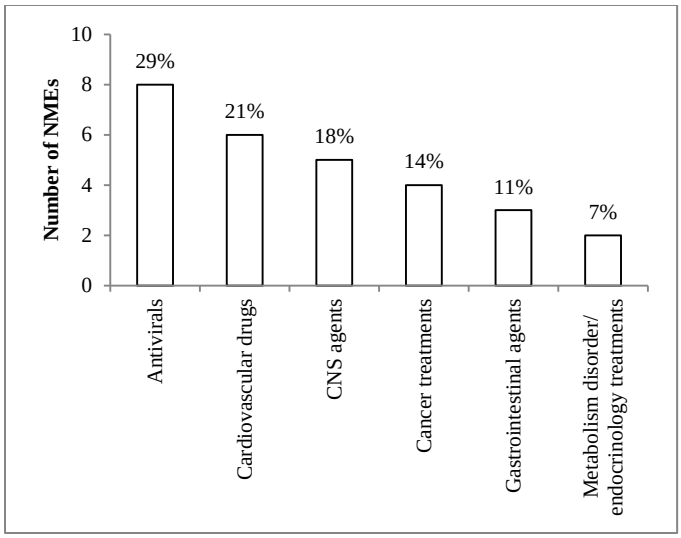
[b] – Changes in the concentration ratio of dextromethorphan to dextrorphan in urine



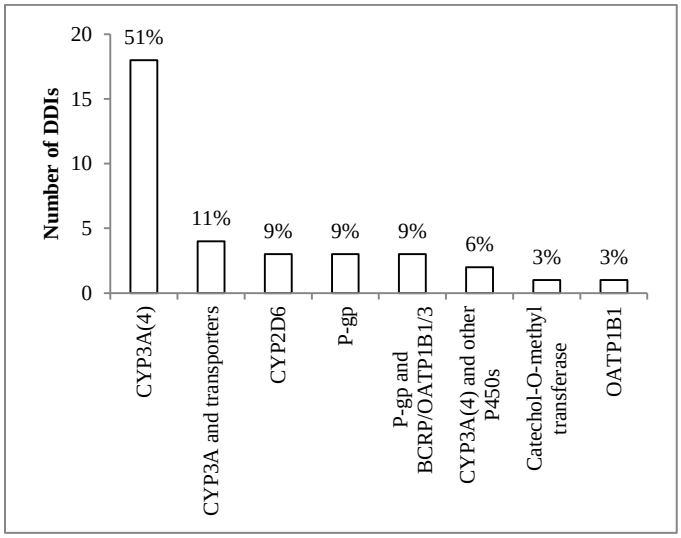
Supplemental Figure 1A. Therapeutic classes for inhibition DDIs with AUC ratios ≥ 5, NME as substrate (N = 14)



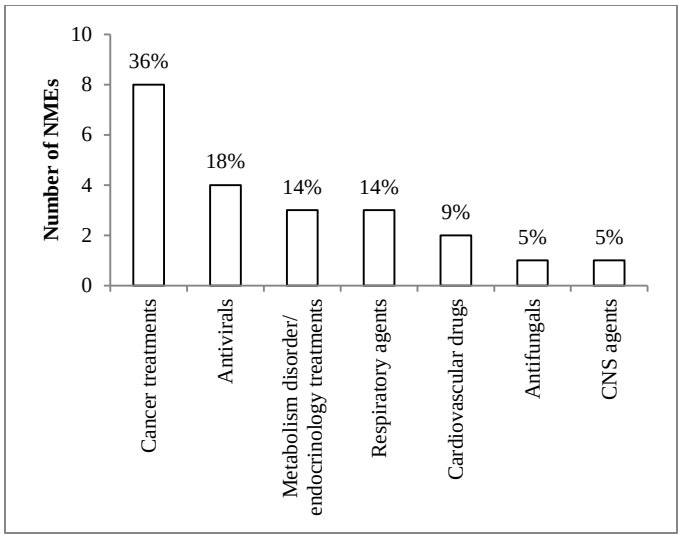
Supplemental Figure 1B. Mechanisms for inhibition DDIs with AUC ratios ≥ 5, NME as substrate (N = 16)



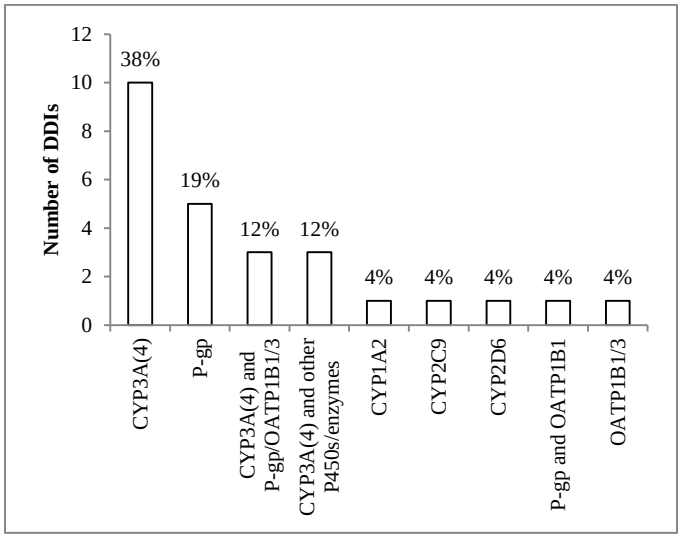
Supplemental Figure 1C. Therapeutic classes for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as substrate (N = 28)



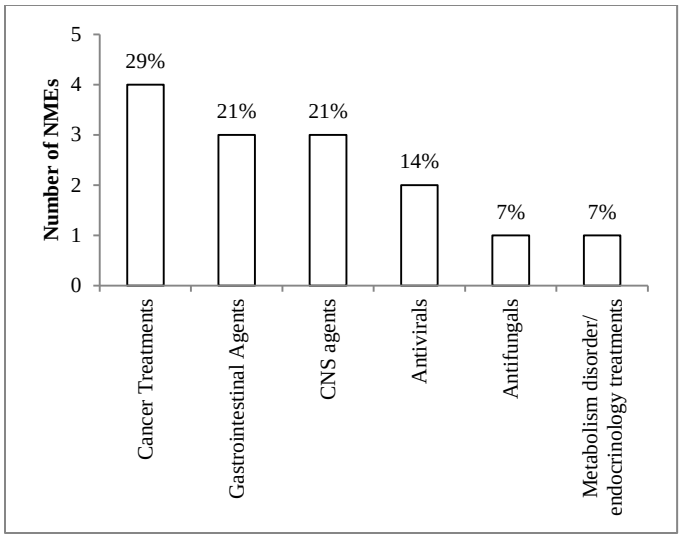
Supplemental Figure 1D. Mechanisms for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as substrate (N = 35)



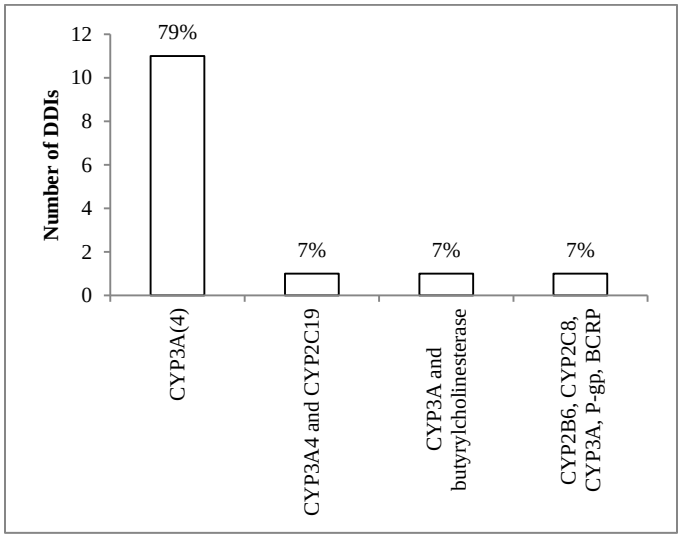
Supplemental Figure 1E. Therapeutic classes for inhibition DDIs with AUC ratios < 2, NME as substrate (N = 22)



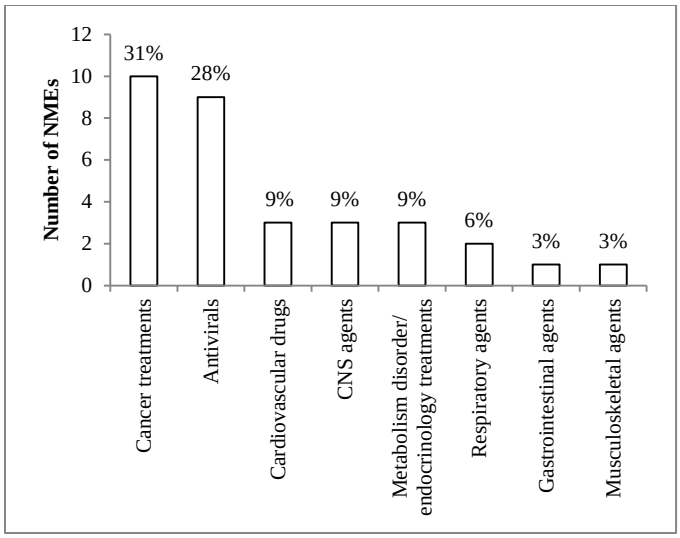
Supplemental Figure 1F. Mechanisms for inhibition DDIs with AUC ratios < 2, NME as substrate (N = 26)



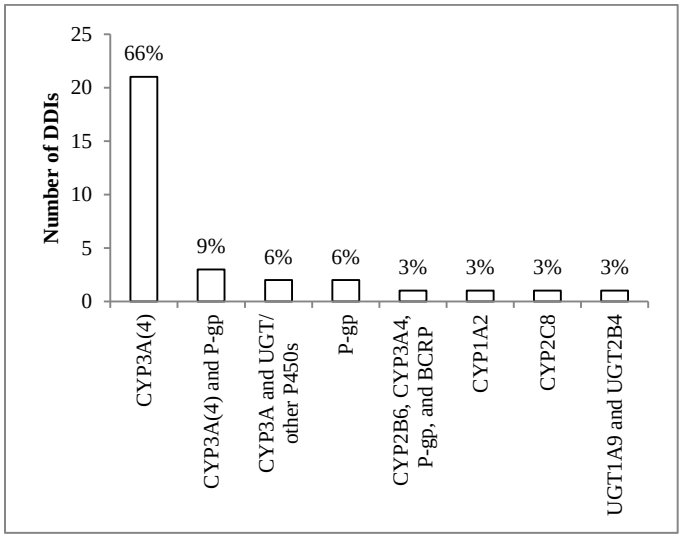
Supplemental Figure 2A. Therapeutic classes for induction DDIs with AUC ratios ≤ 0.2, NME as substrate (N = 14)



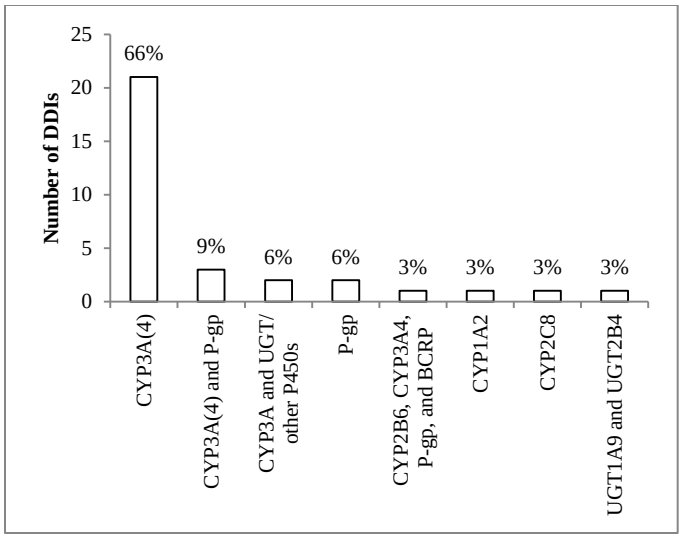
Supplemental Figure 2B. Mechanisms for induction DDIs (AUC ratios ≤ 0.2), NME as substrate (N = 14)



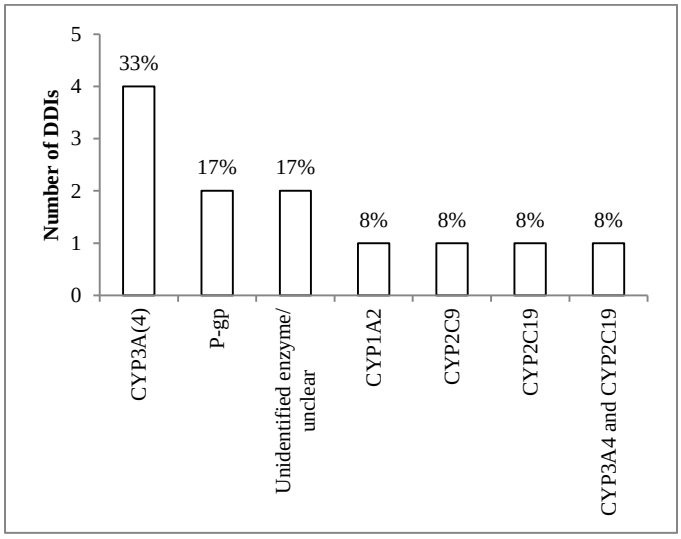
Supplemental Figure 2C. Therapeutic classes for induction DDIs with 0.2 < AUC ratios ≤ 0.5, NME as substrate (N = 32)



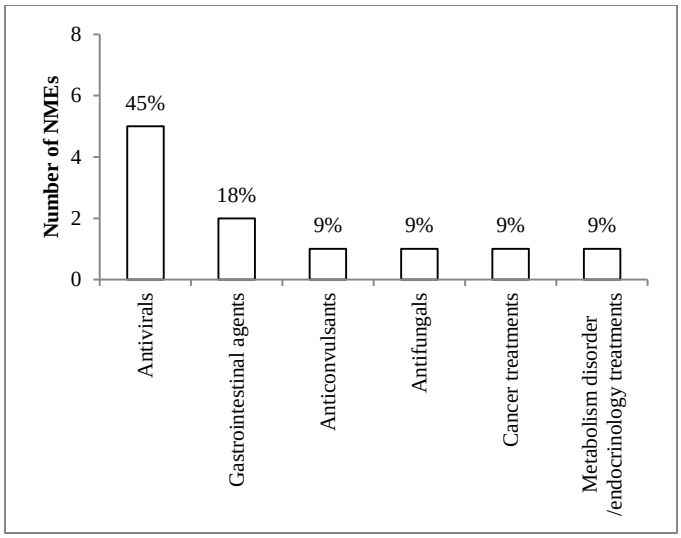
Supplemental Figure 2D. Mechanisms for induction DDIs (0.2 < AUC ratios ≤ 0.5), NME as substrate (N = 32)



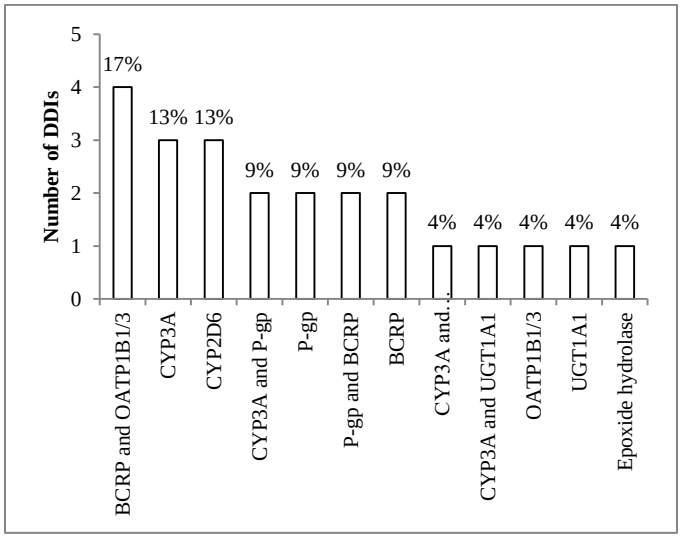
Supplemental Figure 2E. Therapeutic classes for induction DDIs with 0.5 < AUC ratios ≤ 0.8, NME as substrate (N = 11)



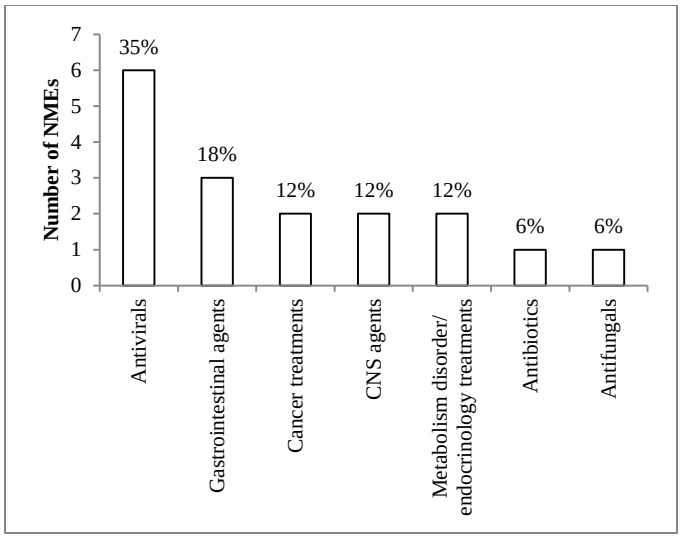
Supplemental Figure 2F. Mechanisms for induction DDIs (0.5 < AUC ratios ≤ 0.8), NME as substrate (N = 12)



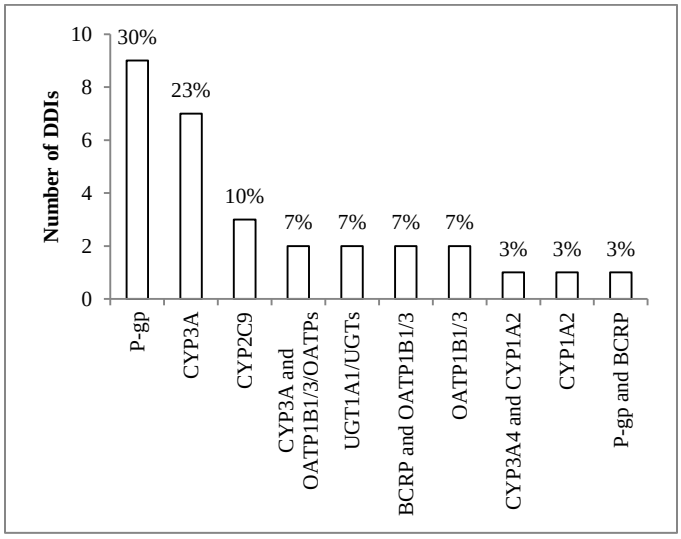
Supplemental Figure 3A. Therapeutic classes for inhibition DDIs with 2 ≤ AUC ratios < 5, NME as inhibitor (N = 11)



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)