

Supplementary Tables for**Selection of an optimal in vitro model to assess P-gp inhibition: comparison of vesicular and bi-directional transcellular transport inhibition assays**

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Supplemental Table 1. LC/MS/MS Parameters

Compound	MS Parameters^a			
	Q1	Q3	CE	DP
Alogliptin	340.2	116	38	105
Amiodarone	646.3	71.9	70	50
Apixaban	460.1	281.93	45	125
Asunaprevir	748.4	648.2	40	90
Atorvastatin	559.4	440.3	30	146
Azilsartan	569.3	233.1	55	90
Bosentan	552.3	202.1	60	115
Canagliflozin	445.3	267.2	25	65
Captopril	218.3	116	20	38
Carvedilol	407.5	224.1	30	100
Clarithromycin	748.6	158.2	50	53
Clopidogrel	322.1	155.1	45	45
Daclatasvir	739.5	565.2	55	200
Diltiazem	415	108.9	70	106
Dronedarone	646.3	58.1	70	50
Elagolix	632.3	529.3	65	160
Elbasvir	882.5	708.4	67	200
Eliglustat	405.3	149.1	15	135
Etravirine	435	303.8	52	200
Felodipine	384.2	338	24	65
Fidaxomicin	1055.7	231.1	-47	-100
Flibanserin	391.3	133.1	25	110
Isradipine	370.2	328.2	28	105
Itraconazole	705.5	392.2	50	56
Ivacaftor	393.3	115.9	100	64
Maraviroc	514.2	116.96	90	40
Mibepradil	496.4	202.1	65	89
Mirabegron	397.2	102.9	80	85
Nelfinavir	568.5	134.9	50	52
Nicardipine	480.3	315.1	50	90
Nifedipine	338.1	172.8	73	200

Nitrendipine	359.3	121.9	-20	-80
Paroxetine	329.8	70.1	110	45
Quinidine	325.2	307.1	70	30
Ranolazine	428.2	98.1	40	110
Ritonavir	721.5	296.2	25	85
Rolapitant	501.3	198.1	75	35
Rosuvastatin	482.4	270.19	52	120
Sertraline	306.1	158.9	90	35
Telaprevir	680.6	322.4	40	47
Telmisartan	515.6	305.2	30	131
Ticagrelor	523.3	153.1	55	120
Troglitazone	442.2	165.1	52	180
Valspodar	1215.7	425.3	59	90
Vandetanib	475.3	112.1	24	130
Velpatasvir	881.7	849.7	-30	-91
Vemurafenib	490.2	383.1	35	140
Verapamil	883.6	851.5	55	200

^aThe optimal MS parameters used for LC-MS/MS analysis

Supplemental Table 2: Clinical DDI data of test set compounds with orally administered digoxin

Inhibitor drugs	BCS ^a	Dose (mg)	I ₁ ^b (μM)	I ₂ (μM)	f _u ^{b, d}	AUC Ratio ^b	C _{max} Ratio ^b	Clinical DDI Y/N ^c
Cobicistat	II	150	2.34	773	0.03	1.09	1.47	Y
Dapagliflozin	III	10	0.35	98	0.09	1.00	0.99	N
Lapatinib	IV	1500	5.04	10326	0.01	1.63	2.09	Y
Linagliptin	III	5	0.01	42	0.11	1.01	0.94	N
Lurasidone	II	120	0.24	974	0.01	1.11	1.09	N
Neratanib	IV	240	0.13	1723	0.01	1.32	1.54	Y
Rifampin	II	600	8.00	2916	0.25	1.46	1.49	Y
Simeprevir	IV	150	10.88	800	0.001	1.39	1.31	Y
Tetrabenazine	III, IV	25	0.001	315	0.17	1.02	1.12	N
Tolvaptan	II, IV	60	0.96	535	0.02	1.18	1.27	Y
Valbenazine	I, III	80	2.19	765	0.01	1.33	1.87	Y
Vorapaxar	II	40	0.92	325	0.002	1.05	1.54	Y

AUC, area under the curve; BCS, biopharmaceutics classification; DDI, drug-drug interaction; I₁, maximum plasma concentration (C_{max}) of inhibitor drug following administration of clinical dose indicated; I₂, the concentration of inhibitor drug in the gastrointestinal tract at indicated dose dissolved in 250 ml; f_u, the fraction unbound in plasma.

^aBCS classification of inhibitor drugs was obtained from the University of Washington DDI database,

<https://www.druginteractionsolutions.org>, <https://www.pharmapendium.com> and the literature (Wu and Benet, 2005; Benet, 2013; Papich and Martinez, 2015). ^bClinical DDI data, I₁, and f_u values were collected from the University of Washington DDI database (<https://www.druginteractionsolutions.org>). I₁ reported from clinical DDI studies was used. Otherwise, I₁ at same or similar inhibitor dose regimen was collected. In the cases that I₁ at indicated inhibitor doses was not reported, extrapolated I₁ was used, assuming the linear PK. ^cEither AUC and/or C_{max} ratios (pharmacokinetic (PK) ratios) greater or equal to 1.25 was considered a positive clinical DDI. Yes (Y) indicates AUC or C_{max} Ratio ≥ 1.25 ; No (N) indicates AUC and C_{max} Ratio < 1.25 ; ^dIf f_u measured < 0.01, f_u value of 0.01 was used for DDI prediction.

Supplemental Table 3: In vitro P-gp IC₅₀ variability for verapamil and quinidine measured in MDR1 vesicles and bidirectional transport (BDT) inhibition assays

Inhibitor drugs	Vesicular assay (MDR1 vesicles)					BDT assay (LLC-MDR1 cells)				
		IC ₅₀ (V) (μ M) ^a	IC ₅₀ (μ M) (Mean \pm SD)	CV %	IC ₅₀ (μ M) reported in the literature ^b		IC ₅₀ (NSF) (μ M) ^c	IC ₅₀ (μ M) (Mean \pm SD)	CV %	IC ₅₀ (μ M) reported in the literature ^d
Verapamil	Study 1	3.2 \pm 0.42	3.9 \pm 0.7	18.2	1.2-3.3	Study 1	36.5 \pm 5.0	45.5 \pm 12.2	26.9	8.5-57
	Study 2	3.8 \pm 0.17				Study 2	40.5 \pm 3.5			
	Study 3	4.6 \pm 0.48				Study 3	59.4 \pm 7.7			
Quinidine	Study 1	6.4 \pm 0.42	7.1 \pm 0.6	8.9	1.0-9.8	Study 1	53.6 \pm 3.5	48.0 \pm 6.5	13.5	1.0-56
	Study 2	7.5 \pm 0.62				Study 2	40.9 \pm 4.4			
	Study 3	7.5 \pm 0.15				Study 3	49.5 \pm 3.0			

^a: IC₅₀(V) was measured in MDR1 vesicles using [³H]NMQ as an in vitro probe as described in the *Materials and Methods*.

^b: IC₅₀ values measured in MDR1 vesicles were collected from Ellens et al. (2013) using NMQ and /or vinblastine as in vitro probes and the University of Washington DDI database (<https://www.druginteractionsolutions.org>) using NMQ as an in vitro probe.

^c: IC₅₀(NSF) was measured in LLCPK1-MDR1 cells using [³H] digoxin as an in vitro probe as described in the *Materials and Methods*.

^d: IC₅₀ values measured in LLC-MDR1 cells were collected from Ellens et al. (2013) and the University of Washington DDI database (<https://www.druginteractionsolutions.org>) using digoxin as an in vitro probe.

Supplemental Table 4. Comparison of In vitro IC₅₀(V) values with those reported in the literature using MDR1 vesicular inhibition assays

Inhibitor	Reported in Literature			
	IC ₅₀ (V) (μM) ^a	IC ₅₀ (V) (μM) ^b	In Vitro Probe	Source
Alogliptin	>1000	NR		
Amiodarone	14.8 ± 0.7	1.6-9.3	NMQ/VB	UWDIDB; Ellens et al., 2013; Fekete et al., 2015
Apixaban	>150	NR		
Asunaprevir	3.2 ± 0.2	NR		
Atorvastatin	17.0 ± 1.7	23.7	NMQ	UWDIDB; Safar et al., 2018
Azilsartan	8.2 ± 0.7	NR		
Bosentan	>15	NR		
Canagliflozin	>100	NR		
Captopril	>1000	>1000	NMQ/VB	Bentz et al., 2013
Carvedilol	4.1 ± 0.3	0.6-3.4	NMQ/VB	UWDIDB; Ellens et al., 2013
Clarithromycin	10.9 ± 2.4	8.9	NMQ	UWDIDB; Vermeer et al., 2016
Clopidogrel	157.4 ± 15.1	NR		
Daclatasvir	1.6 ± 0.1	NR		
Diltiazem	30.5 ± 2.8	12.0-53.8	NMQ/VB	UWDIDB; Ellens et al., 2013
Dronedarone	4.9 ± 0.5	NR		
Elagolix	24.8 ± 0.8	NR		
Elbasvir	0.3 ± 0.02	0.32	NMQ	UWDIDB; NDA 208261
Eliglustat	65.4 ± 2.1	NR		
Etravirine	>30	NR		
Felodipine	81.8 ± 5.1	5.4-24.1	NMQ/VB	UWDIDB; Ellens et al., 2013
Fidaxomicin	0.4 ± 0.05	NR		
Flibanserin	>120	NR		
Isradipine	53.7 ± 2.4	4.6-16.4	NMQ/VB	UWDIDB; Ellens et al., 2013

Itraconazole	0.34 ± 0.13	0.048-2	NMQ	UWDIDB; Vermeer et al., 2016; Lempers et al., 2016
Ivacaftor	> 1.0	NR		
Maraviroc	162.6 ± 8.5	NR		
Mibepradil	10.0 ± 1.6	3.2-9.5	NMQ/VB	UWDIDB; Ellens et al., 2013
Mirabegron	148.9 ± 21.8	NR		
Nelfinavir	20.3 ± 1.6	2.72	NMQ	UWDIDB; Heredi-Szabo et al., 2013
Nicardipine	6.4 ± 1.7	0.7-3.7	NMQ/VB	UWDIDB; Ellens et al., 2013
Nifedipine	115.6 ± 6.4	10.7-54.7	NMQ/VB	UWDIDB; Ellens et al., 2013
Nitrendipine	76.0 ± 1.4	6.5-28.1	NMQ/VB	UWDIDB; Ellens et al., 2013
Paroxetine	122.2 ± 15.3	NR		
Quinidine	14.5 ± 1.9	1.0-9.8	NMQ/VB	UWDIDB; Ellens et al., 2013; Horio et al., 1988; Fekete et al., 2015
Ranolazine	64.1 ± 4.1	2.9-85.5	NMQ/VB	UWDIDB; Ellens et al., 2013
Ritonavir	0.3 ± 0.03	0.24-0.33	NMQ	UWDIDB; Heredi-Szabo et al., 2013; Vermeer et al., 2016
Rolapitant	>30	NR		
Rosuvastatin	>300	>300	NMQ	UWDIDB; Safar et al., 2018
Sertraline	39.4 ± 2.8	6.0-50.9	NMQ/VB	UWDIDB; Ellens et al., 2013
Telaprevir	4.1 ± 0.5	7	VC	UWDIDB; Fujita et al., 2013
Telmisartan	0.8 ± 0.1	0.1-3.6	NMQ/VB	UWDIDB; Ellens et al., 2013
Ticagrelor	>30	NR		
Troglitazone	19.4 ± 1.3	5.4-12.4	NMQ/VB	UWDIDB; Ellens et al., 2013
Valspodar	0.2 ± 0.01	0.031	NMQ	UWDIDB; Heredi-Szabo et al., 2013
Vandetanib	96.1 ± 9.1	NR		
Velpatasvir	4.9 ± 0.7	NR		
Vemurafenib	>30	NR		
Verapamil	2.8 ± 0.3	1.2-59	NMQ/VB/VC	UWDIDB; Ellens et al., 2013; Horio et al., 1988; Schaefer et al., 2006

UWDIDB: University of Washington DDI database (<https://www.druginteractionsolutions.org>); NR, not reported; NMQ, N-methyl-quinidine; VB, vinblastine; VC, vincristine.

^a: IC₅₀(V) was measured in MDR1 vesicles using [³H] NMQ as an in vitro probe as described in the *Materials and Methods*.

^b: IC₅₀(V) values measured in MDR1 vesicles were collected from the University of Washington DDI database

(<https://www.druginteractionsolutions.org>) and selected references using in vitro probe substrate(s) as indicated.

Supplemental Table 5. List of false negative and false positive prediction of digoxin clinical DDIs for training set compounds

	Verapamil 120mg, BCS I							✓										✓					
	Verapamil 80mg, BCS I								✓										✓				
^a False positive	Alogliptin, BCS III																			✓		✓	
	Apixaban, BCS III																					✓	
	Atorvastatin 80mg, BCS II	✓	✓												✓					✓			
	Azilsartan kamedoxomil, BCS IV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Bosentan, BCS II	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Carvedilol, male, BCS II		✓		✓	✓					✓	✓	✓	✓	✓					✓	✓	✓	✓
	Etravirine, BCS IV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Fidaxomicin, BCS IV	✓	✓	✓							✓	✓	✓							✓			
	Maraviroc, BCS III		✓								✓									✓			
	Mibepradil 50mg, BCS II	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Nicardipine 20mg, BCS I	✓	✓		✓	✓	✓	✓	✓			✓		✓	✓	✓	✓	✓		✓	✓	✓	✓
	Nicardipine 30mg, BCS I	✓	✓		✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Nifedipine 20mg, BCS I, II					✓									✓							✓	
	Nitrendipine 10mg, BCS II					✓	✓								✓	✓						✓	
	Paroxetine, BCS I					✓	✓								✓	✓						✓	
	Sertraline, BCS I, II	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Troglitazone, BCS II	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

^a: IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) were used in the static models for DDI prediction, respectively. IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) was determined as described in the *Materials and Methods*.

^b: The cut-off value was obtained from FDA final DDI guidance (FDA, 2020)

^c: The cut-off value was obtained from Ellens et al (2013).

^d: The cut-off value was obtained from (Agarwal et al., 2013)

^e: The cut-off value was obtained from EMA DDI guidance (EMA, 2012)

Supplemental Table 6: In vitro IC₅₀ values of test set compounds measured in bidirectional and vesicular transport inhibition assays

Inhibitor drugs	IC ₅₀ (NSF) ^a (μM)	IC ₅₀ (ER) ^a (μM)	IC ₅₀ (V) ^b (μM)
Cobicistat	47.0 ± 11.1	>100	0.3±0.01
Dapagliflozin	>100	>100	>100
Lapatinib	41.5 ± 8.5	17.2±4.7	>3
Linagliptin	>100	>100	62.7±7.6
Lurasidone	3.7 ± 0.5	1.9±0.6	3.2±0.6
Neratanib	31.1 ± 14.0	1.4±0.2	3.1±0.2
Rifampin	>30	>30	27.8±2.3
Simeprevir	5.6±0.4	5.1±0.4	5.9±0.5
Tetrabenazine	>100	37.0±15.2	>100
Tolvaptan	38.9 ± 2.2	17±5.2	18.8±1.3
Valbenazine	14.3± 1.7	3.7±0.3	8.4±0.6
Vorapaxar	5.9 ±0.8	2.7±0.3	7.6±0.6

^aIC₅₀(NSF) and IC₅₀(ER) represent IC₅₀ values estimated by calculating digoxin net transport using net secretory flux and efflux ratio, respectively. ^bIC₅₀(V) represent IC₅₀ values measured for inhibition of ATP-dependent NMQ vesicular uptake. Data were reported as mean ± SD (n=3).

Supplemental Table 7. Summary of predictive performance of test set compounds using the cut-off values derived from ROC analysis and the comparison with other recommended cut-off criteriaSup. Table 7-1: Model 1 (I_2/IC_{50})

Model 1 (I_2/IC_{50})	IC ₅₀ (V) ^a			IC ₅₀ (ER) ^a			IC ₅₀ (NSF) ^a		
	ROC Analysis	FDA 2020 ^d	Ellens et al. 2013 ^c	ROC Analysis	FDA 2020 ^d	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c
Cut-off values	25.9	10	45	13.7	10	45	9.3	10	45
TP % (sensitivity)	100 (8/8)	100 (8/8)	75 (6/8)	87.5 (7/8)	87.5 (7/8)	75 (6/8)	100 (8/8)	100 (8/8)	75 (6/8)
TN % (specificity)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)
FP %	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)
FN %	0 (0/8)	0 (0/8)	25 (2/8)	12.5 (1/8)	12.5 (1/8)	25 (2/8)	0 (0/8)	0 (0/8)	25 (2/8)
Average Accuracy	0.917	0.917	0.75	0.833	0.833	0.75	0.917	0.917	0.75
Overall Accuracy	0.875	0.875	0.75	0.812	0.812	0.75	0.875	0.875	0.75

Sup. Table 7-2: Model 2 (I_1/IC_{50} or I_2/IC_{50})

Model 2 (I_1/IC_{50} or I_2/IC_{50})	IC ₅₀ (V) ^a			IC ₅₀ (ER) ^a			IC ₅₀ (NSF) ^a		
	ROC Analysis	Agarwal et al. 2013 ^b	Ellens et al. 2013 ^c	ROC Analysis	Agarwal et al. 2013 ^b	Ellens et al. 2013 ^c	ROC Analysis	Agarwal et al. 2013 ^b	Ellens et al. 2013 ^c
Cut-off values	(0.032,40)	(0.1,10)	(0.03,45)	(0.081,26.7)	(0.1,10)	(0.03,45)	(0.026,10)	(0.1,10)	(0.03,45)
TP % (sensitivity)	100 (8/8)	100 (8/8)	100 (8/8)	87.5 (7/8)	87.5 (7/8)	87.5 (7/8)	100 (8/8)	100 (8/8)	87.5 (7/8)
TN % (specificity)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)
FP %	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)
FN %	0 (0/8)	0 (0/8)	0 (0/8)	12.5 (1/8)	12.5 (1/8)	12.5 (1/8)	0 (0/8)	0 (0/8)	12.5 (1/8)
Average Accuracy	0.917	0.917	0.917	0.833	0.833	0.833	0.917	0.917	0.833
Overall Accuracy	0.875	0.875	0.875	0.812	0.812	0.812	0.875	0.875	0.812

Sup. Table 7-3: Model 3 (I_{1u}/IC_{50} or I_2/IC_{50})

Model 3 (I_{1u}/IC_{50} or I_2/IC_{50})	IC ₅₀ (V) ^a		IC ₅₀ (ER) ^a		IC ₅₀ (NSF) ^a	
	ROC Analysis	EMA 2012 ^e	ROC Analysis	EMA 2012 ^e	ROC Analysis	EMA 2012 ^e
Cut-off values	(0.00141,3334)	(0.02,10)	(0.00177,62)	(0.02,10)	(0.00052,94)	(0.02,10)
TP % (sensitivity)	62.5 (5/8)	100 (8/8)	75 (6/8)	87.5 (7/8)	75 (6/8)	100 (8/8)
TN % (specificity)	100 (4/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)	75 (3/4)
FP %	0 (0/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)	25 (1/4)
FN %	37.5 (3/8)	0 (0/8)	25 (2/8)	12.5 (1/8)	25 (2/8)	0 (0/8)
Average Accuracy	0.75	0.917	0.75	0.833	0.75	0.917
Overall Accuracy	0.812	0.875	0.75	0.812	0.75	0.875

EMA, European Medicines Agency; FDA, US Food and Drug Administration; TN, true negative; TP, true positive; FN, false negative; FP, false positive; IC₅₀, half-maximal inhibitory concentration; I₁, the mean steady-state total (free and bound) maximum plasma concentration (C_{max}) of inhibitor following administration of the highest proposed clinical dose; I_{1,u}, unbound I₁; I₂, the concentration of inhibitor in the gastrointestinal tract based on highest approved dose dissolved in 250 ml.

^a: IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) were used in the static models for DDI prediction, respectively. IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) was determined as described in the *Materials and Methods*.

^b: The cut-off value was obtained from FDA final DDI guidance (FDA, 2020)

^c: The cut-off value was obtained from Ellens et al (2013).

^d: The cut-off value was obtained from (Agarwal et al., 2013)

^e: The cut-off value was obtained from EMA DDI guidance (EMA, 2012)

Supplemental Table 8. List of false negative and false positive prediction of digoxin clinical DDIs for test set compounds

False positive	False negative	Model 1 (I_2/IC_{50})										Model 2 (I_1/IC_{50} or I_2/IC_{50})						Model 3 (I_{1u}/IC_{50} or I_2/IC_{50})						
		IC ₅₀ (V) ^a			IC ₅₀ (ER) ^a			IC ₅₀ (NSF) ^a			IC ₅₀ (V) ^a			IC ₅₀ (ER) ^a			IC ₅₀ (NSF) ^a			IC ₅₀ (V) ^a		IC ₅₀ (ER) ^a		IC ₅₀ (NSF) ^a
		ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	EMA 2012 ^e	EMA 2012 ^e	EMA 2012 ^e	EMA 2012 ^e			
	cut-off values	25.9			10			45			13.7			10			45			9.3				
Cobicistat				✓	✓	✓														(0.032,40)				
Tolvaptan				✓				✓												(0.1,10)				
Vorapaxar				✓																(0.03,45)				
Neratinib																				(0.081,26.7)				
Lurasidone	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

^a: IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) were used in the static models for DDI prediction, respectively. IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) was determined as described in the *Materials and Methods*.

^b: The cut-off value was obtained from FDA final DDI guidance (FDA, 2020)

^c: The cut-off value was obtained from Ellens et al (2013).

^d: The cut-off value was obtained from (Agarwal et al., 2013)

^e: The cut-off value was obtained from EMA DDI guidance (EMA, 2012)

Supplemental Table 9. List of false negative and false positive prediction of clinical DDIs using dabigatran etexilate and fexofenadine as P-gp probe drugs

Model 1 (I_2/IC_{50})										
	cut-off	IC ₅₀ (V) ^a			IC ₅₀ (ER) ^a			IC ₅₀ (NSF) ^a		
		ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c	ROC Analysis	FDA 2000 ^b	Ellens et al. 2013 ^c
False negative	Clarithromycin 500mg, BCS III, Dabigatran 150mg	25.9			13.7					
	Clarithromycin 500mg, BCS III, Dabigatran 0.375mg							✓		✓
	Clopidogrel 300mg, BCS II, Dabigatran 150mg BID	✓		✓			✓			✓
	Cobicistat, BCS II, Dabigatran 150mg					✓	✓	✓		✓
	Dronedarone, BCS II, Dabigatran 150mg									✓
	Quinidine, BCS I, Dabigatran 150mg									✓
	ticagrelor 90mg, BCS IV, Dabigatran 150mg	✓		✓						
	Verapamil 120mg, BCSII, Dabigatran 150mg									✓
	Alogliptin, BCS III, fexofenadine 80mg	✓	✓	✓	✓		✓			✓
	Itraconazole, BCS II, Fexofenadine 180mg									✓
False positive	Paroxetine, BCS I, Fexofenadine 60mg				✓					✓
	Quinidine, BCS I, Fexofenadine 25mg									✓
	Atorvastatin, BCS II, Dabigatran 150mg BID	✓		✓						
	Clopidogrel 75mg, BCS II, Dabigatran 150mg							✓		
	Ritonavir, BCS IV, Dabigatran 150mg	✓	✓	✓	✓	✓		✓	✓	
	Sertraline, BCS I, Fexofenadine 50mg			✓	✓	✓	✓	✓	✓	

^a: IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) were used in the static models for DDI prediction, respectively. IC₅₀(V), IC₅₀(ER), and IC₅₀(NSF) was determined as described in the *Materials and Methods*.

^b: The cut-off value was obtained from FDA final DDI guidance (FDA, 2020)

^c: The cut-off value was obtained from Ellens et al (2013).

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