DDI QUALIFICATION MATRIX

Background (1)

- The compound files within the Simcyp Simulator have been developed and added over 20 years.

- Substrates and inhibitors included as compound files within the Simcyp Simulator were selected for development based on the FDA and EMA recommendations for reference index substrates and inhibitors.

- These compounds are typically used in drug development to assess the DDI potential of substrates and inhibitors being developed.

- In addition to reference substrates and inhibitors, so-called “sensitive” substrates have also been included as well as weak, moderate and strong inhibitors (when possible).

Background (2)

- Throughout this 20-year period of development, clinical DDI studies for each compound were identified on an individual basis using UOW and literature searches.

- These clinical studies were reviewed to determine whether they should be included or excluded from the development and verification of the compound file.

- Clinical DDI studies were included if they were randomised controlled clinical DDI studies

- Clinical DDI studies were excluded if they were:
  - Conducted in patients
  - Case studies
  - Cocktail studies
  - Micro-dosing studies

Background (3)

- A set of clinical DDI studies was derived for each compound based on the inclusion/exclusion criteria.

- Typically, when developing PBPK models for compounds, some clinical studies are used to help develop and optimise the compound files (training sets) and other independent clinical studies are then used to verify the model (verification set).

- If clinical studies were used to optimise parameters relevant to prediction of DDIs, including fmCYP and inhibitory parameters, they were not used for verification.

- Compound file summaries describing the development and verification of each substrate and inhibitor have been provided in Appendix 2 of the briefing document.

- In summary, a carefully curated database of clinical DDI studies for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 involving key substrates and inhibitors was collated over 20 years and was used as a source for the DDI qualification matrix.

Search Strategy (1)

- One of the initial steps of the qualification process was to identify a DDI matrix that could be used for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 interactions to qualify the platform for CYP-mediated competitive inhibition and mechanism-based inhibition (MBI) via these enzymes.

- In addition to the curated DDI database, the University of Washington Drug Interaction Database (DIDB) was used to identify substrates and inhibitors used in clinical DDI studies involving CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 where observed increases in plasma exposure of substrates > 20% were reported.

Search Strategy (2)

- Substrate/inhibitor combinations were reviewed to determine whether additional substrates or inhibitors should be developed.

- Additional DIDB searches were performed for specific combinations of substrates and inhibitors when both were available within the Simcyp Simulator (V19 R1).

- Comparisons were made against the curated database collated for the compound file summaries.

CYP1A2

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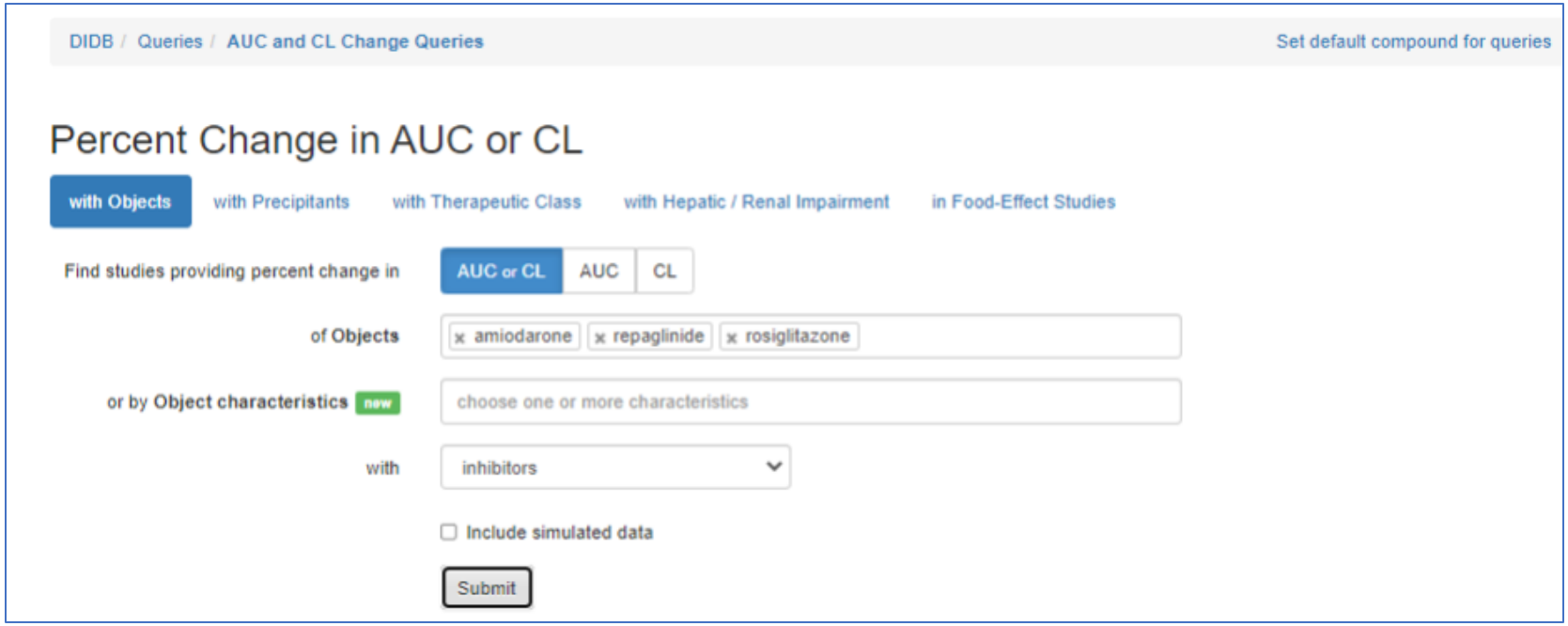
CYP2C8



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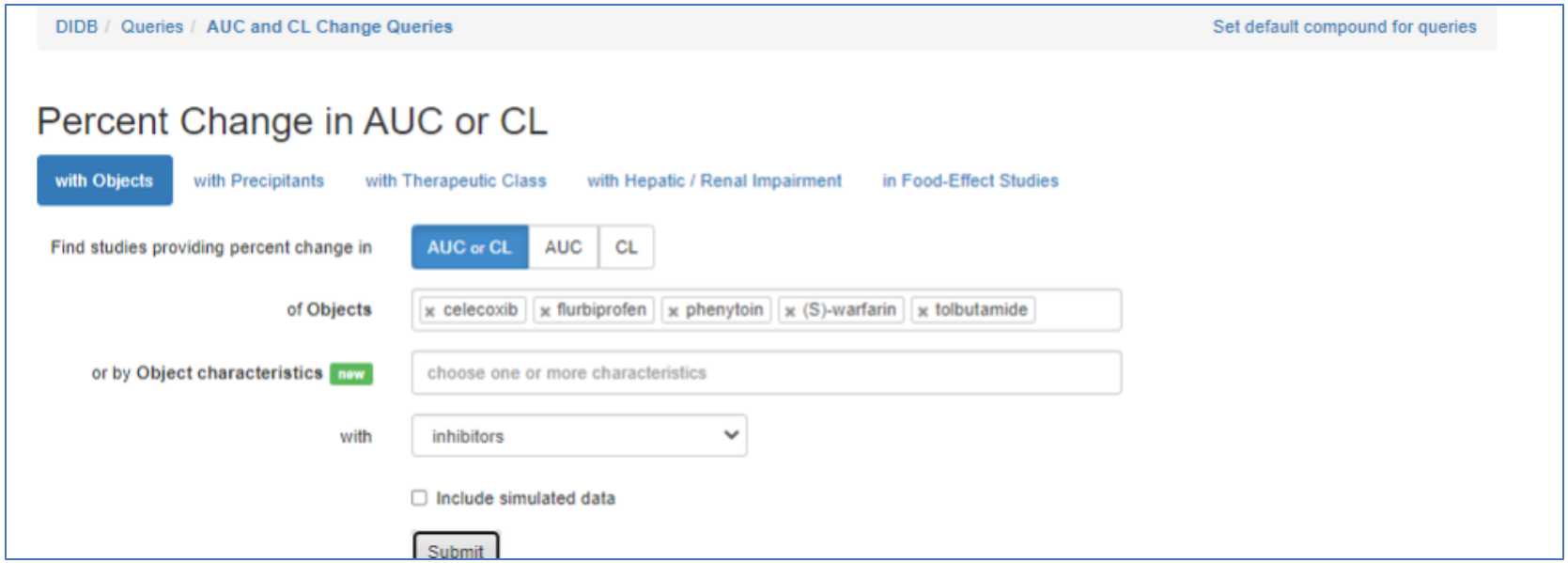
CYP2C9



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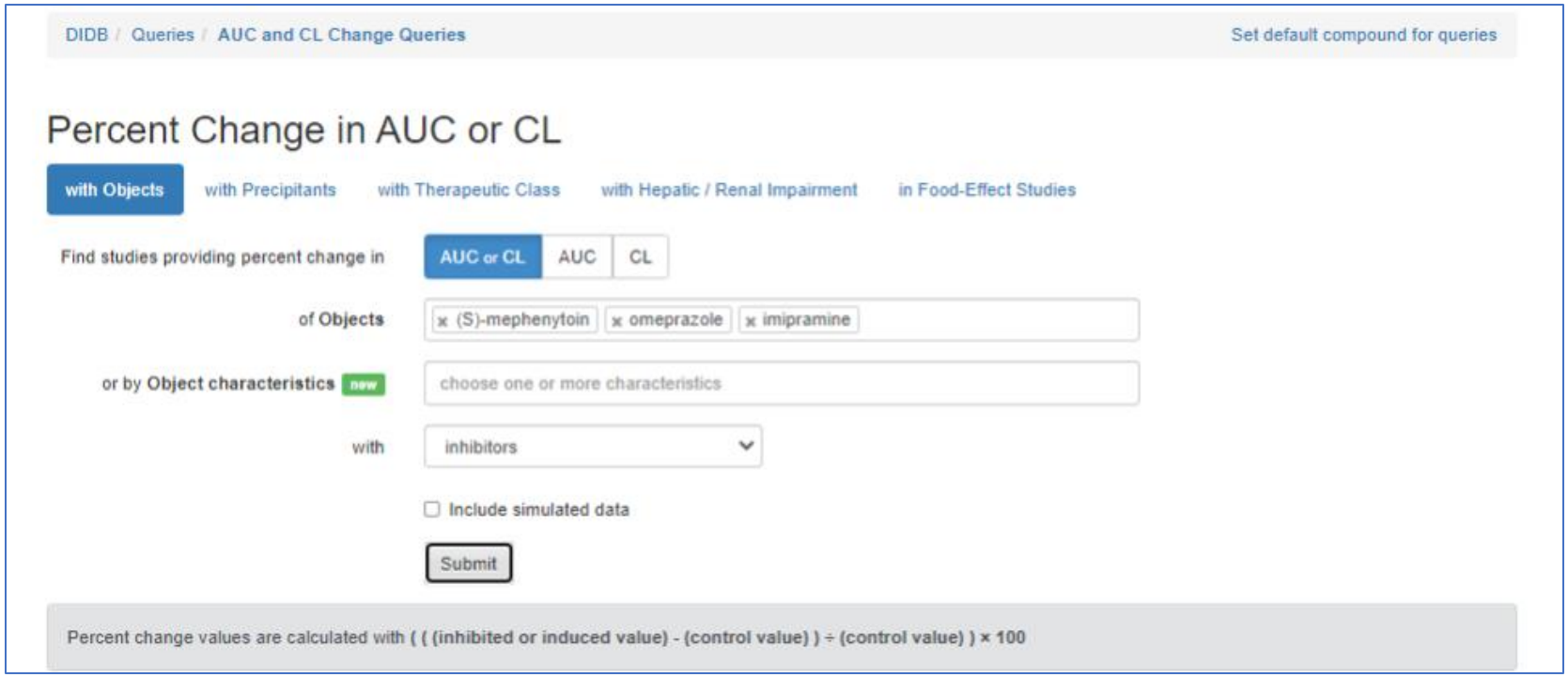
CYP2C19



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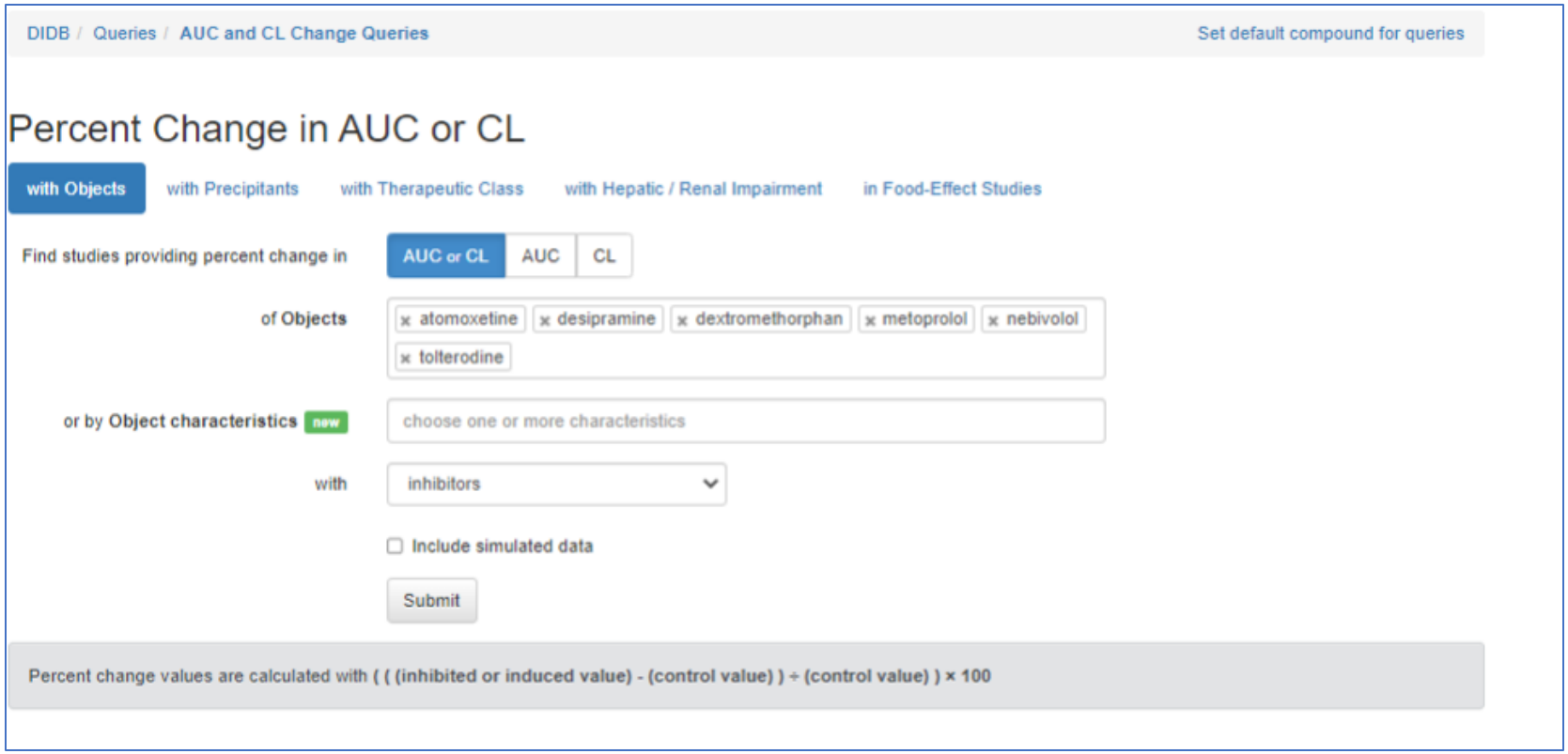
CYP2D6



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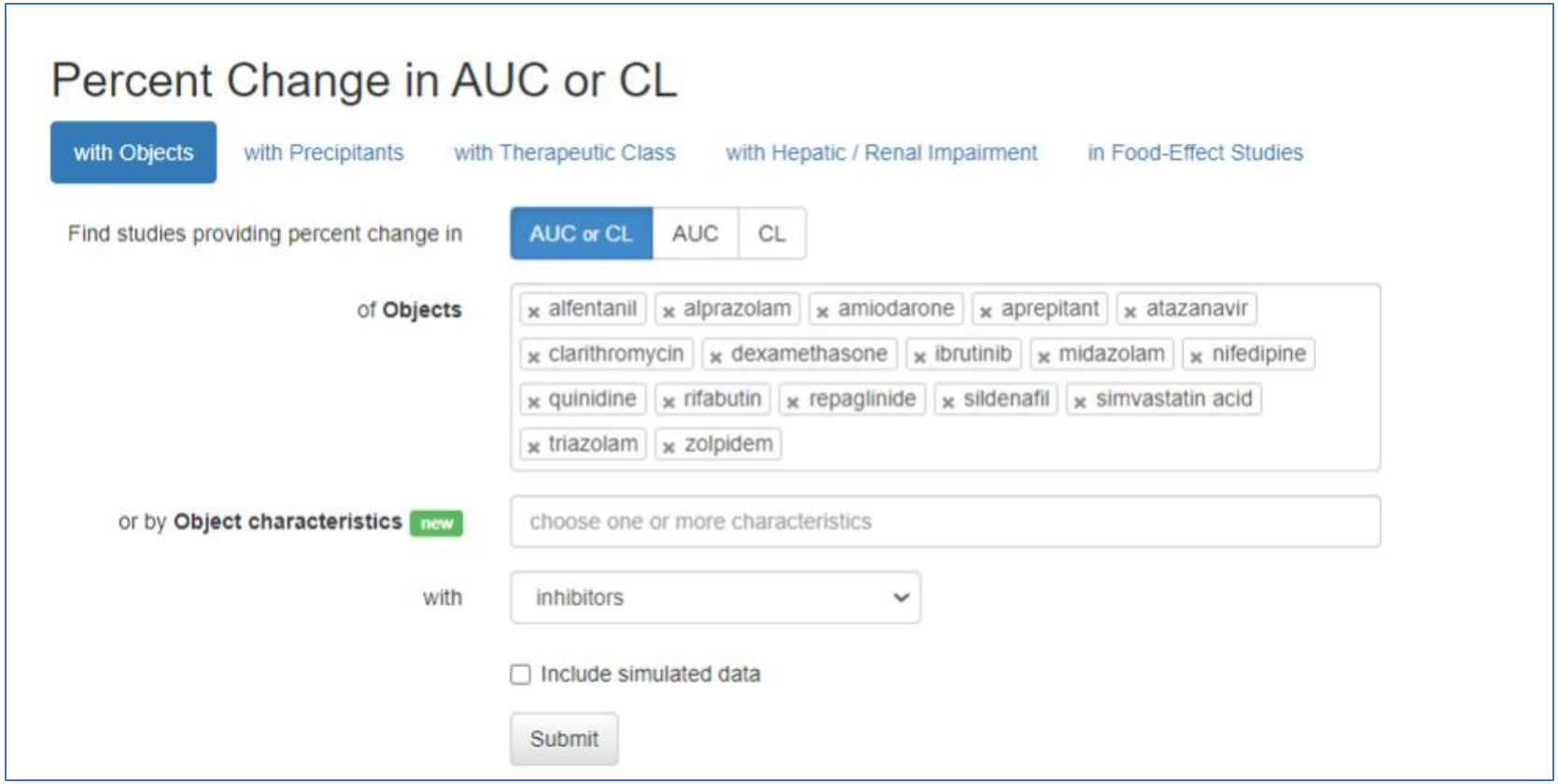
CYP3A4



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Studies in DIDB versus studies used in DDI matrix

	Identified in DIDB search	Used in DDI MATRIX
CYP1A2	39	20
CYP2C8	27	16
CYP2C9	30	24
CYP2C19	21	11
CYP2D6	33	28
CYP3A4	119	114

Fewer studies appeared in the DDI matrix than were identified in the DIDB searches mainly because of the exclusion criteria assigned previously.

See next slide for example for CYP1A2.

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CYP1A2 – DIDB search versus DDI matrix

The following notes were observed for why studies were excluded for the DDI matrix.

- 39 studies were identified in the DIDB
- 29 publications
- 15 of the 29 publications were included in the DDI qualification matrix
- Of the remaining 14
  - 4 were excluded because they were repeated using the same data
  - 2 involved patients
  - 3 reported clearance values without citing exposure data
  - 5 additional studies could have been included

Updated CYP1A2 Analysis – Including Additional Studies

CYP1A2	V19R1 Built 96	
	Cmax Ratio	AUC Ratio
AFE (bias)	0.91	1.03
AAFE (precision)	1.21	1.21
Number Studies	15	20
Number Studies	15	20

CYP1A2	V19R1 Built 96	
	Cmax Ratio	AUC Ratio
AFE (bias)	0.88	0.99
AAFE (precision)	1.23	1.28
Number Studies	18	29
Number Studies	18	29

Addition of the other studies does not markedly change the results.

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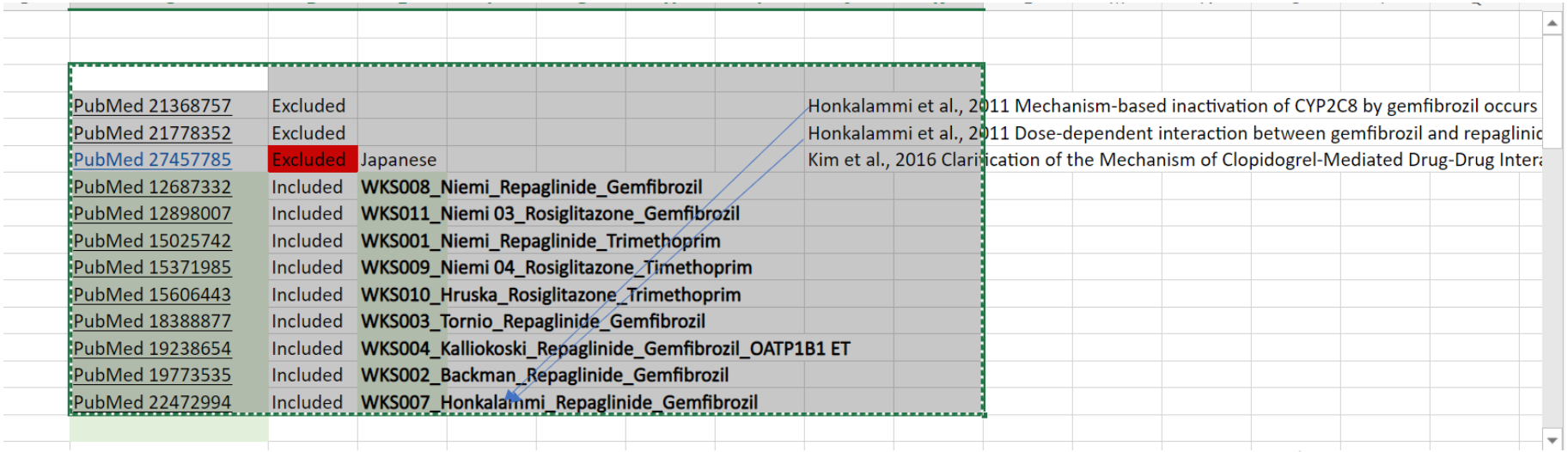
CYP2C8 – DIDB search versus DDI matrix

The following notes were observed for why studies were excluded for the DDI matrix.

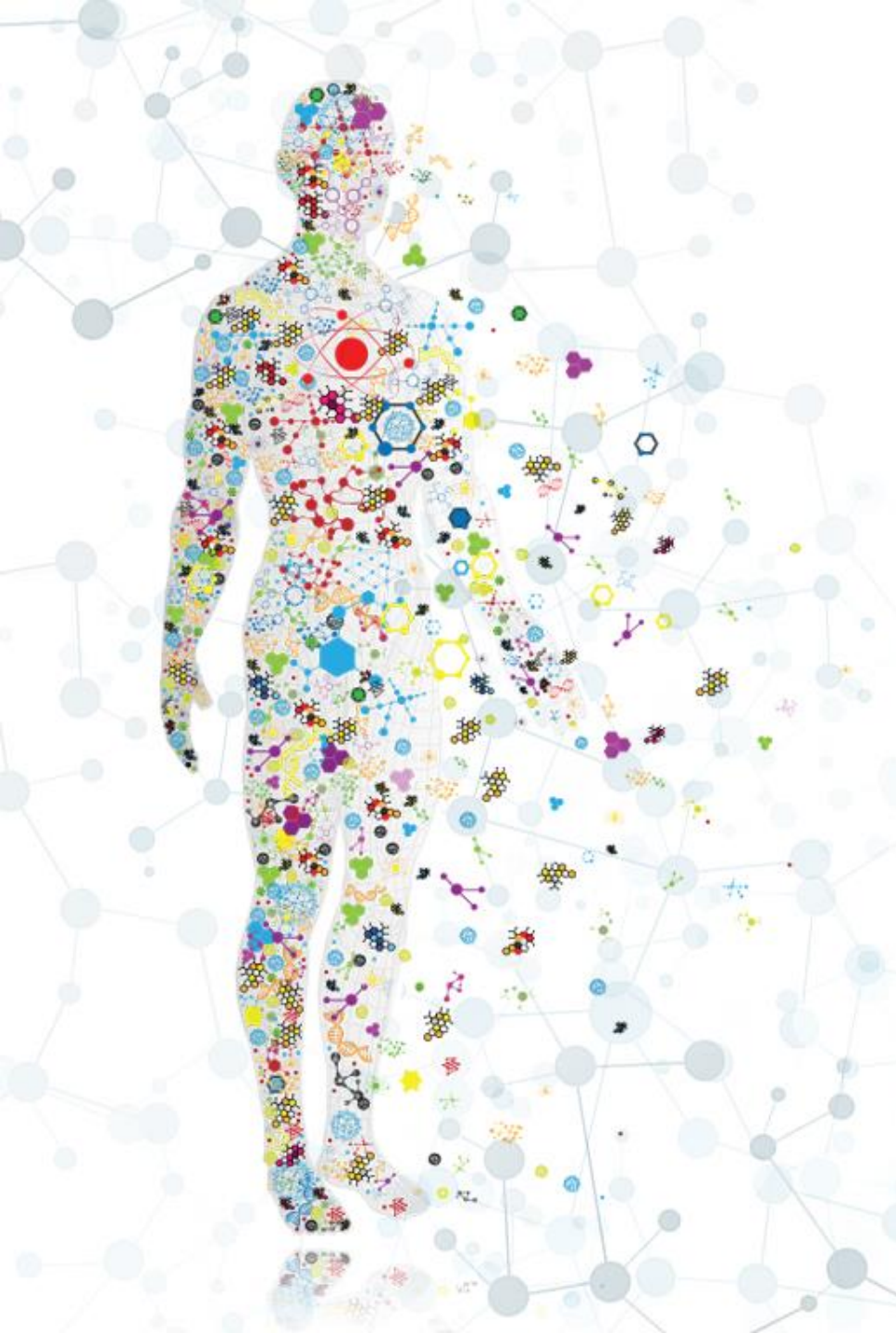
- 27 studies were identified in the DIDB
- 12 publications
- 9 of the 12 publications were included in the DDI qualification matrix
- 2 of the remaining 3 were excluded because they appeared to be repeated study designs



PubMed 21368757	Excluded		Honkalammi et al., 2011 Mechanism-based inactivation of CYP2C8 by gemfibrozil occurs
PubMed 21778352	Excluded		Honkalammi et al., 2011 Dose-dependent interaction between gemfibrozil and repaglinic
PubMed 27457785	Excluded	Japanese	Kim et al., 2016 Clarification of the Mechanism of Clopidogrel-Mediated Drug-Drug Intera
PubMed 12687332	Included	WKS008_Niemi_Repaglinide_Gemfibrozil	
PubMed 12898007	Included	WKS011_Niemi 03_Rosiglitazone_Gemfibrozil	
PubMed 15025742	Included	WKS001_Niemi_Repaglinide_Trimethoprim	
PubMed 15371985	Included	WKS009_Niemi 04_Rosiglitazone_Timethoprim	
PubMed 15606443	Included	WKS010_Hruska_Rosiglitazone_Trimethoprim	
PubMed 18388877	Included	WKS003_Tornio_Repaglinide_Gemfibrozil	
PubMed 19238654	Included	WKS004_Kalliokoski_Repaglinide_Gemfibrozil_OATP1B1 ET	
PubMed 19773535	Included	WKS002_Backman_Repaglinide_Gemfibrozil	
PubMed 22472994	Included	WKS007_Honkalammi_Repaglinide_Gemfibrozil	

Conclusions

- On occasion, we have found repeated studies in the DIDB or inaccurate study designs.
- **Thus, we also used our curated DDI database as a key source of clinical DDI studies.**
- Searches in DIDB were used to identify additional studies.
- A small number of relevant studies were not captured in the DDI qualification matrix but when included, they did not appear to have a significant impact on the results of the analysis e.g. CYP1A2.



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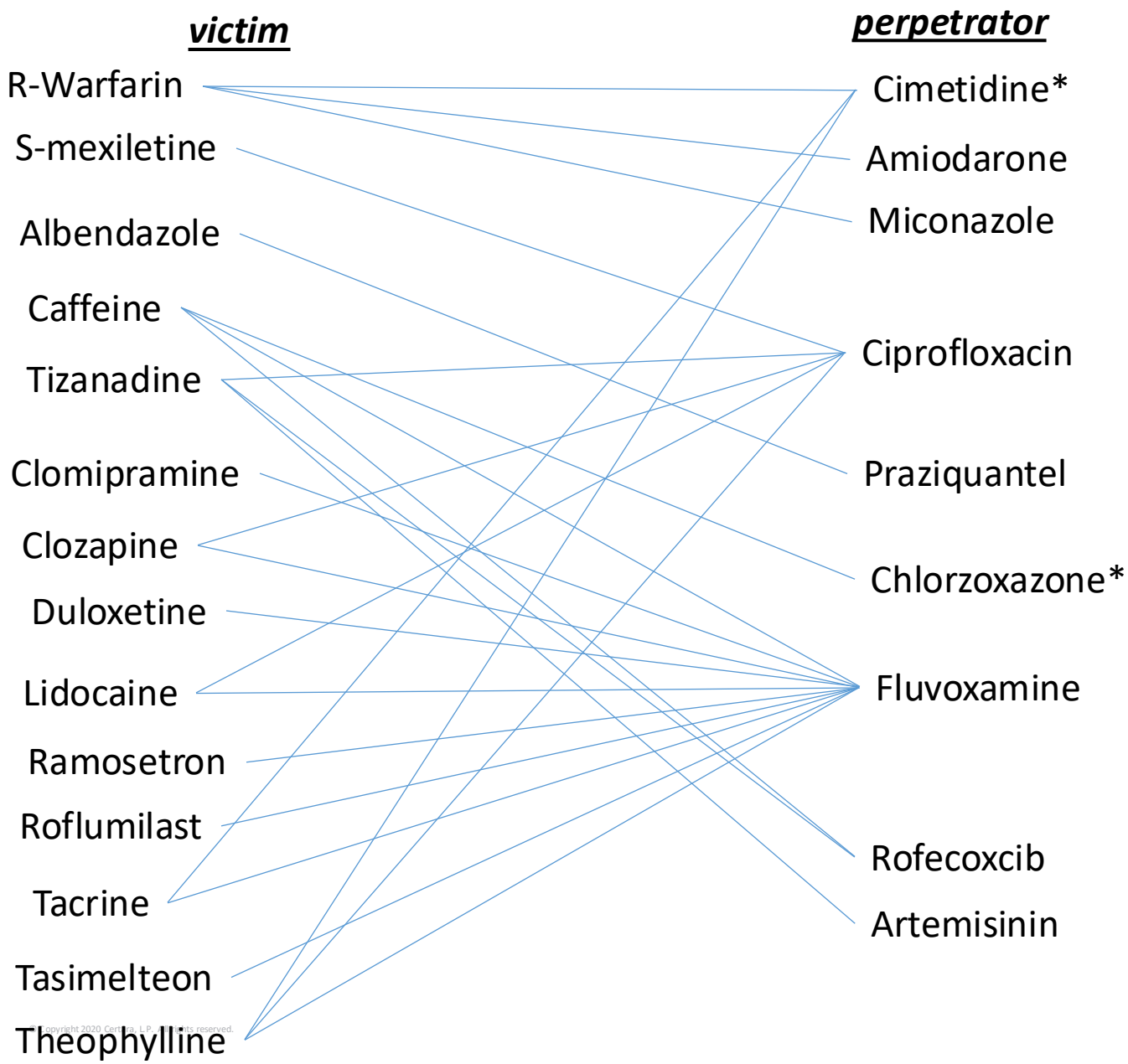
CYP1A2 Matrix

July 2020

UOW – CYP1A2 studies involving inhibition and induction

Row Labels	In Vivo Induction >20% Effect	In Vivo Inhibition >20% Effect
caffeine (1,3,7-TMX)	30	49
theophylline (1,3-DMX)		23
clozapine	8	19
tacrine		10
(R)-warfarin		9
imipramine		8
tasimelteon	8	8
lidocaine		7
roflumilast	2	7
clomipramine	1	6
amitriptyline		3
asenapine		3
ramosetron		3
ropivacaine	1	3
(S)-mexiletine	1	2
albendazole		2
deutetrabenazine		2
melatonin		2
olanzapine	1	2
tizanidine	2	2
R-MDMA		1
(R)-mexiletine	1	1
(R)-praziquantel		1
(R)-verapamil		1

CYP1A2 Matrix - Inhibition



*mixed effect on 1A1, 3A4…?

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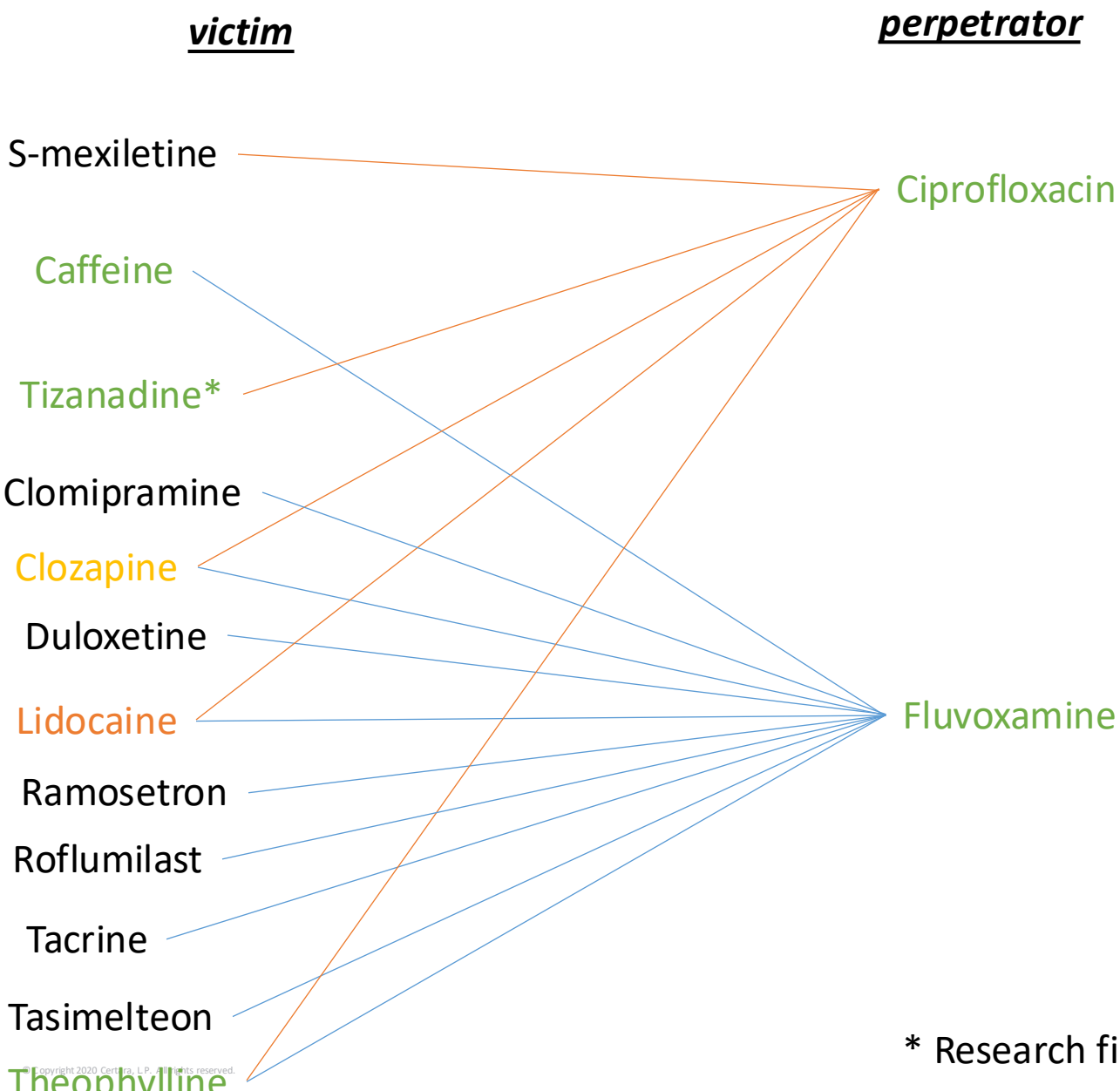
CYP1A2 Matrix – Inhibition with key inhibitors



* Research file

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Clomipramine (CYP1A2 Substrate)

- At best only 1 clinical study to use to verify CYP1A2 with Fluvoxamine

Clinical studies:

Clomipramine-Fluvoxamine: PubMed 8685072

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Clozapine (CYP1A2 Substrate)

- Reasonable amount of Clinical data available on DIDB
- **Many of these studies are in smokers and schizophrenics**

Object	Precipitant	Accession # or NDA/BLA #	Published
clozapine	phenobarbital	PubMed 9853978	1998 Dec
clozapine	valproic acid	PubMed 29620699	2018 Jun
clozapine	valproic acid	PubMed 7694927	1995 Apr
clozapine	caffeine (1,3,7-TMX)	PubMed 14725610	2004 Jan
clozapine	caffeine (1,3,7-TMX)	PubMed 9690697	1998 Aug
clozapine	ciprofloxacin	PubMed 11151749	2000 Nov
clozapine	fluoxetine	PubMed 8267110	1994 Jan
clozapine	fluoxetine	PubMed 8633698	1996 Jun
clozapine	fluoxetine	PubMed 9690983	1998 May
clozapine	fluvoxamine	PubMed 10445377	1999 Jul
clozapine	fluvoxamine	PubMed 10505485	1999 Jul
clozapine	fluvoxamine	PubMed 10982203	2000 Aug
clozapine	fluvoxamine	PubMed 11106150	2000 Dec
clozapine	fluvoxamine	PubMed 11763009	2001 Dec
clozapine	fluvoxamine	PubMed 12454566	2002 Dec
clozapine	fluvoxamine	PubMed 15199083	2004 Jul
clozapine	fluvoxamine	PubMed 15291653	2004 Jun
clozapine	fluvoxamine	PubMed 9472836	1998 Feb
clozapine	minocycline	PubMed 28466366	2018 03
clozapine	paroxetine	PubMed 11147928	2000 Nov
clozapine	paroxetine	PubMed 8633698	1996 Jun
clozapine	sertraline	PubMed 8633698	1996 Jun
clozapine	valproic acid	PubMed 10365650	1999 Jun
clozapine	valproic acid	PubMed 8267110	1994 Jan

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Lidocaine (CYP1A2 Substrate)

Would require development of a PBPK model

Object	Precipitant	Accession # or NDA/BLA #	Published
lidocaine	amiodarone	PubMed 8891878	1996 Oct
lidocaine	anticonvulsants	PubMed 7756103	1995 Jan
lidocaine	cimetidine	PubMed 3804509	1987 Jan
lidocaine	cimetidine	PubMed 4028631	1985 Sep
lidocaine	cimetidine	PubMed 6464978	1984 Aug
lidocaine	cimetidine	PubMed 6713782	1984 May
lidocaine	cimetidine	PubMed 7073151	1982 May
lidocaine	ciprofloxacin	PubMed 16211753	2005 Oct
lidocaine	erythromycin	PubMed 10193676	1999 Mar
lidocaine	erythromycin	PubMed 12534644	2003 Jan
lidocaine	erythromycin and fluvoxamine	PubMed 15845683	2005 May
lidocaine	erythromycin and fluvoxamine	PubMed 16918719	2006 Aug
lidocaine	fluvoxamine	PubMed 14749694	2004 Jan
lidocaine	fluvoxamine	PubMed 15845683	2005 May
lidocaine	fluvoxamine	PubMed 16918719	2006 Aug
lidocaine	itraconazole	PubMed 10193676	1999 Mar
lidocaine	metoprolol	PubMed 6822025	1983 Feb
lidocaine	propranolol	PubMed 2860914	1985 May
lidocaine	propranolol	PubMed 6822025	1983 Feb
lidocaine	propranolol	PubMed 7393249	1980 Aug 14

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Summary

- Two additional substrates could be added (clozapine and lidocaine) but they did not offer additional scope for CYP1A2 interactions above the options offered by current combinations.
- PBPK models would have to be developed for both compounds.
- Also note, many of the clozapine studies are in smokers or patients with schizophrenia

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CYP2D6 Matrix

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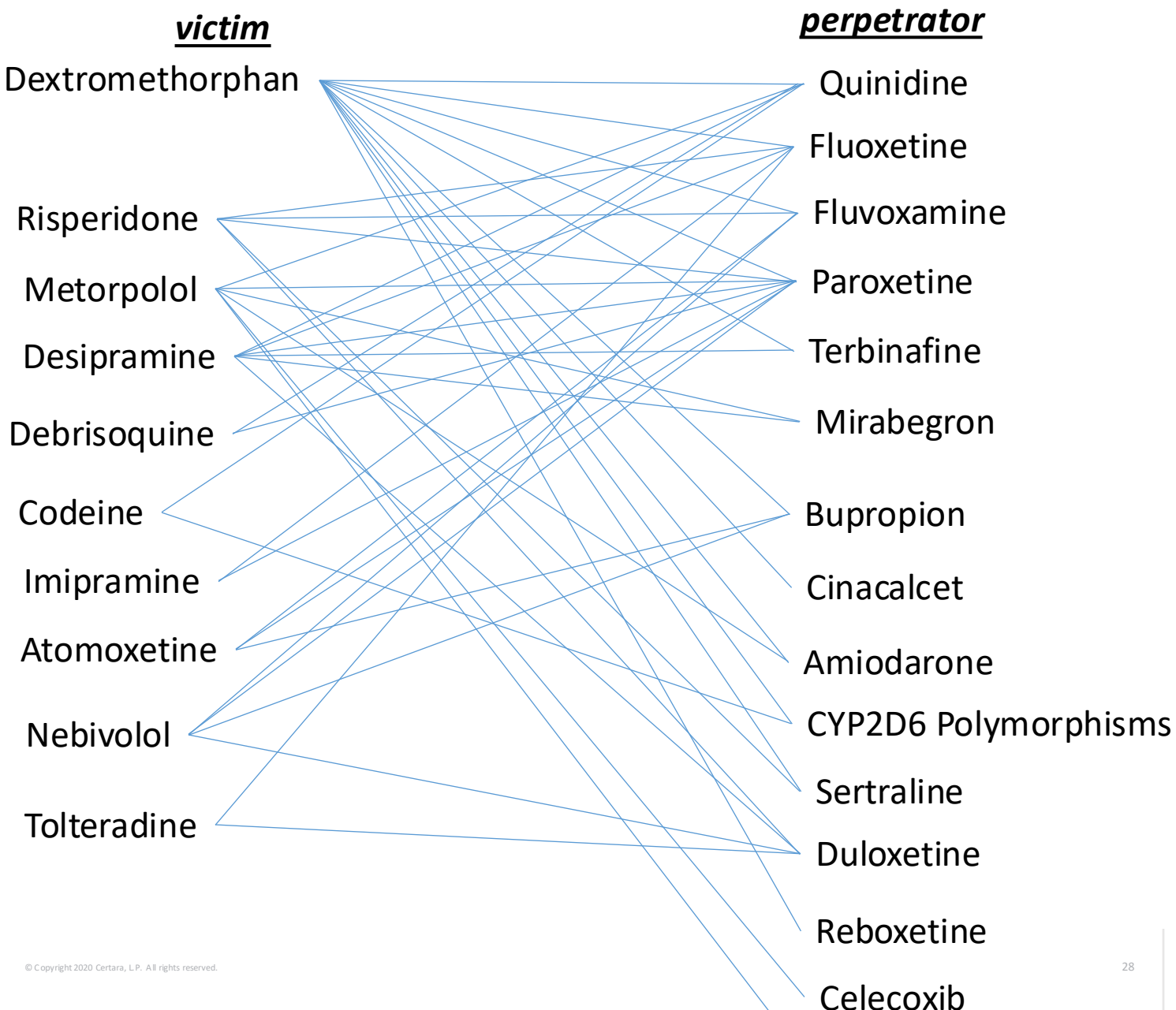
UOW – CYP2D6 studies involving inhibition and induction

Row Labels	In Vivo Induction > 20% Effect	In Vivo Inhibition > 20% Effect
dextromethorphan	8	73
risperidone	6	22
metoprolol		22
oxycodone	5	21
venlafaxine		18
debrisoquine	2	16
desipramine	2	13
codeine	2	11
imipramine		8
sparteine		7
(R)-mexiletine		6
(S)-mexiletine		6
mexiletine		5
aripiprazole	2	4
tramadol	1	4
(R)-3,4-methylenedioxymethamphetamine (R-MDMA)		4
(S)-3,4-methylenedioxymethamphetamine (S-MDMA)		4
atomoxetine		4
encainide		4
loratadine		4
nebivolol		4
tolterodine		4
(S)-citalopram (escitalopram)		3
3,4-methylenedioxymethamphetamine (MDMA, ecstasy)		3
ramosetron		3
tamoxifen	6	2
apatinib	2	2
propafenone	2	2
reduced dolasetron (hydrodolasetron)	2	2
clomipramine	1	2
clozapine	1	2
haloperidol	1	2
nortriptyline	1	2
propranolol	1	2

CYP2D6 Matrix - Inhibition



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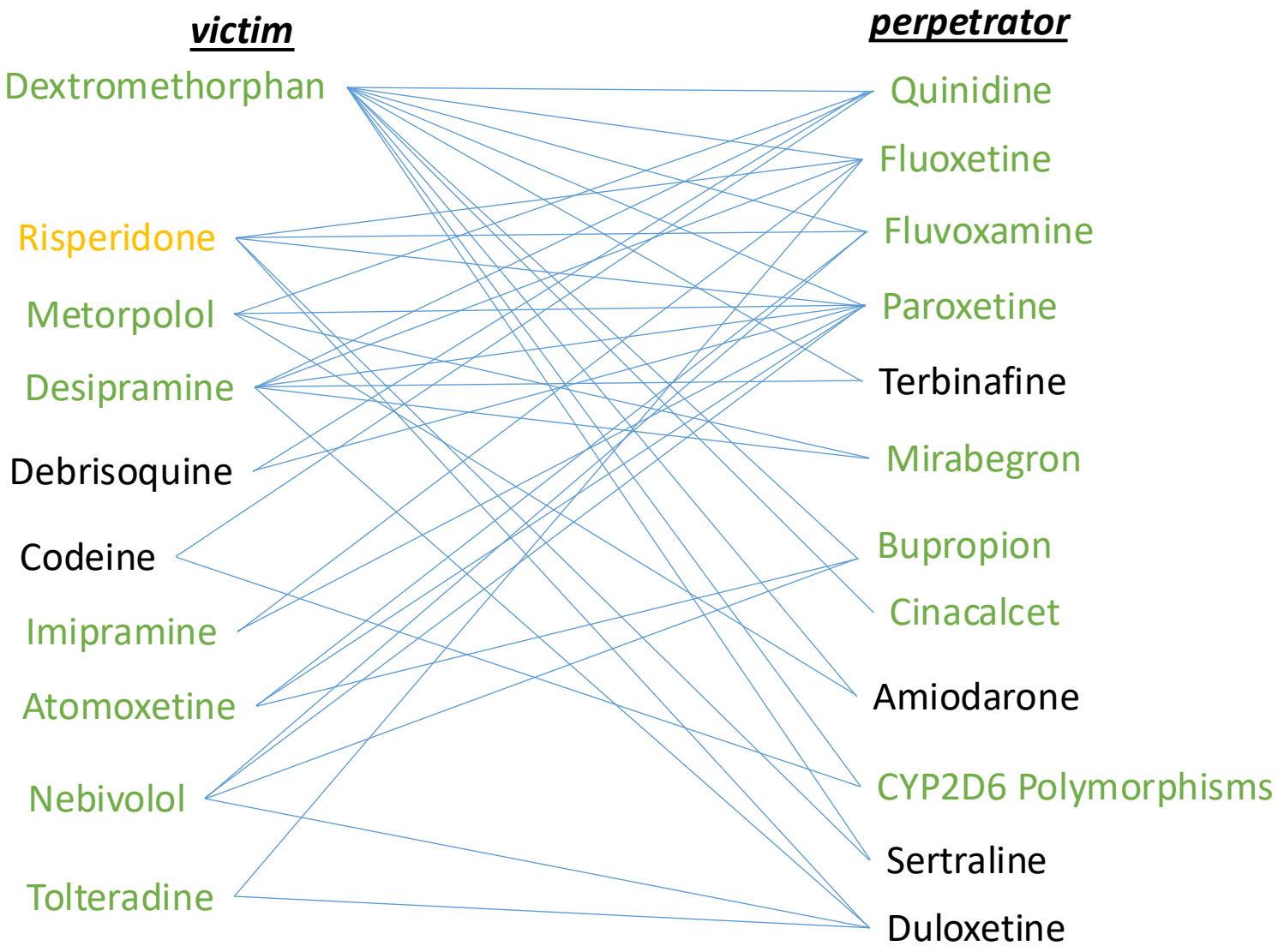
CYP2D6 Matrix – Inhibition edited for perpetrator



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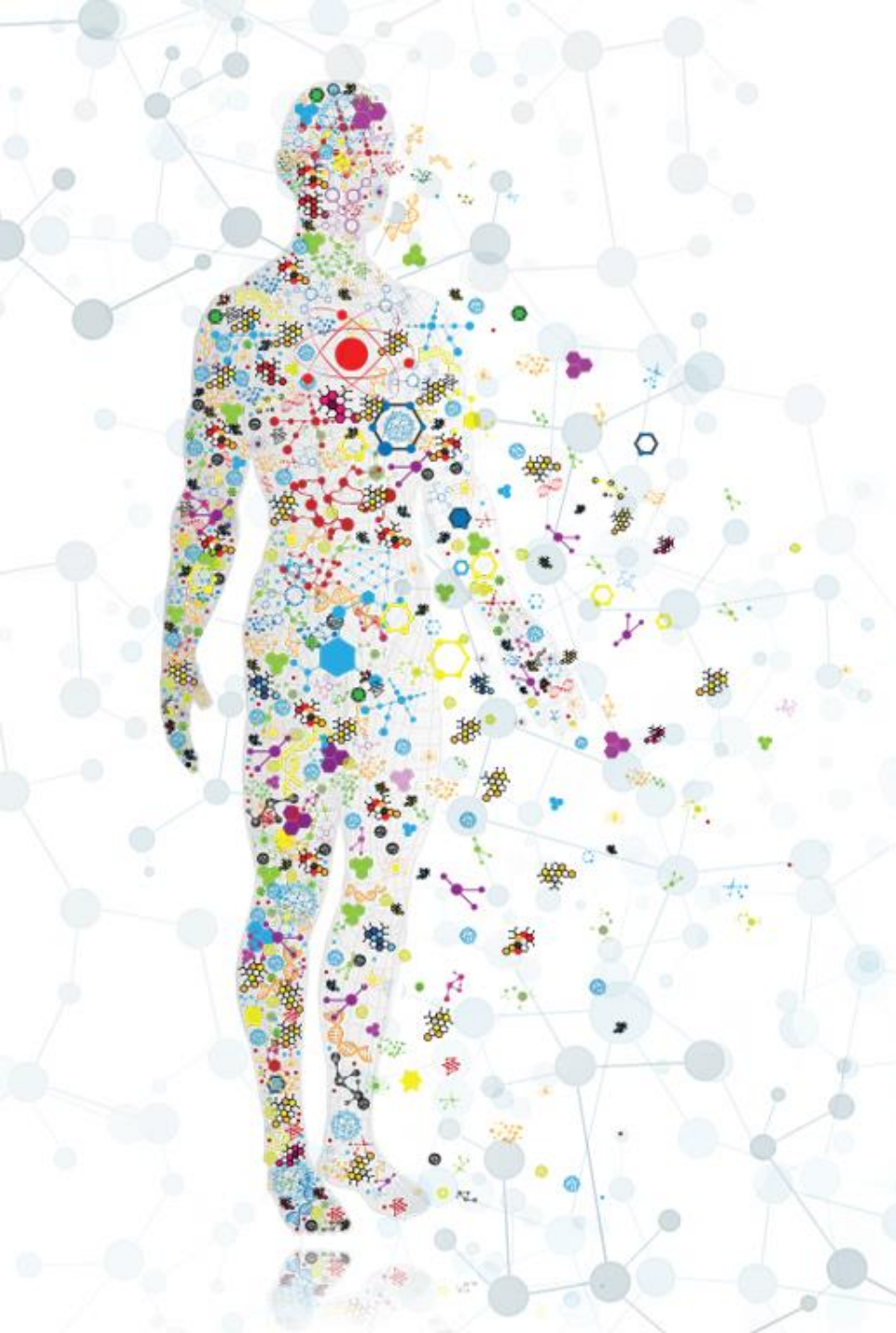
Summary

- Currently have
  - 7 substrates in simulator (or being added in V20, so files could be used in V19)
  - 7 inhibitors in simulator



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CYP2C8 Matrix

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UOW – CYP2C8 studies involving inhibition

compound	Number of studies
pioglitazone	44
repaglinide	**37**
rosiglitazone	**18**
daprodustat	18
cerivastatin (acid)	13
dasabuvir	12
montelukast	11
paclitaxel	11
buprenorphine	9

BOLD: Compounds in Simcyp

Inhibitors

Gemfibrozil	CYP2C8	Strong	24.1	-	-	MBI	In Vitro	(2-4)
Gemfibrozil 1-O-β Glucuronide	CYP2C8	-	4.88	27.1*	6.5*	-	-	(2-6)
Trimethoprim	CYP2C8	Weak	8.47	-	-	Competitive	In Vitro	(4)

Two reliable CYP2C8 substrates

Two CYP2C8 inhibitors (1 MBI and 1 competitive inhibitor)

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Summary

Evaluation of CYP2C8 Inhibition In Vitro: Utility of Montelukast as a Selective CYP2C8 Probe Substrate
DOI: https://doi.org/10.1124/dmd.111.039065

Table 3. AUC_I/AUC values obtained from the literature

	AUC_I/AUC[a]						
Inhibitor (mg/day)	CER	FLV	MTK	PIO	REP	ROS	references
Cimetidine (1000-1200 mg)	1.0				1.2		[c]
Gemfibrozil (1200 mg)[b]	5.6	1.1	4.5	3.3	7.7	2.3	[d]
Itraconazole (100-200 mg)	1.3	0.9		1.1	1.4		[e]
Montelukast (10 mg)				1.0	1.0	1.0	[f]
Telithromycin (800 mg)			1.0		1.8		[g]
Trimethoprim (320-400 mg)				1.4	1.6	1.4	[h]

[a]Abbreviations: Cerivastatin (CER); Fluvastatin (FLV); Montelukast (MTK); Pioglitazone (PIO); Repaglinide (REP); Rosiglitazone (ROS)
[b] Gemfibrozil glucuronide is a time-dependent inactivator of CYP2C8
[c] (Muck et al., 1997; Hatorp and Thomsen, 2000)
[d] (Spence et al., 1995; Backman et al., 2002; Niemi et al., 2003a; Niemi et al., 2003b; Niemi et al., 2004a; Deng et al., 2005; Jaakkola et al., 2005; Tornio et al., 2008a; Karonen et al., 2010)
[e] (Kivisto et al., 1998; Mazzu et al., 2000; Niemi et al., 2003b; Jaakkola et al., 2005)
[f] (Jaakkola et al., 2006; Kajosaari et al., 2006; Kim et al., 2007)
[g] (Kajosaari et al., 2006)
[h] (Niemi et al., 2004a; Niemi et al., 2004b; Hruska et al., 2005; Tornio et al., 2008b)

Gemfibrozil is the only strong CYP2C9 inhibitor

Although a number of CYP2C8 substrates are available, not really possible to develop a CYP2C8 matrix based on available substrates and inhibitors

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CYP2C9 Matrix

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"Sensitive" CYP2C9 substrates

DRUG INTERACTION SOLUTIONS

In Vivo CYP2C9 Sensitive Substrates

Based on Drug-Drug Interaction Studies

Substrate (oral)	Therapeutic Class	Max AUCR or CL Ratio	Precipitant	Precipitant Dose (oral)	PMID #	Published
tolbutamide	Sulfonylureas	**5.76**	tasisulam	individualized dose single infusion (IV)	29119333	2018 Jun
(S)-warfarin	Anticoagulants and Antiplatelets	**0.19 (CL Ratio)**	miconazole	125 mg QD (18 days)	1611805	1992 Jun

Based on Pharmacogenetic Studies

Substrate (oral)	Therapeutic Class	Max AUCR or CL Ratio	Genotype/Phenotype	Substrate Dose (oral)	PMID #	Published
benzbromarone	Anticoagulants and Antiplatelets	**0.15 (CL Ratio)**	*3/*3 (PM) vs *1/*1 (NM) (n = 1)	100 mg SD	20962433	2011
celecoxib	NSAIDS	**6.94**	*3/*3 (PM) vs *1/*1 (NM) (n = 3)	200 mg QD (7 days)	16513453	2006
ibuprofen		**8.71**				
(R)-ibuprofen	NSAIDS	**8.71**	*2/*2 (IM) vs *1/*1 (NM) (n = 2)	400 mg SD (racemic)	15289789	2004
(S)-ibuprofen		**7.75**				
glimepiride	Sulfonylureas	**0.18 (CL Ratio)**	*3/*3 (PM) vs *1/*1 (NM) (n = 1)	2 mg SD	21208246	2012
glipizide	Sulfonylureas	**5.45**	*3/*3 (PM) vs NM (n = 1)	10 mg SD	10208645	1999
lornoxicam	NSAIDS	**39.49**	*3/*13 (PM) vs *1/*1 (NM) (n = 1)	8 mg SD	15606435	2005
meloxicam	NSAIDS	**8.22**	*3/*3 (PM) vs *1/*1 (NM) (n = 3)	15 mg SD	24322170	2014
piroxicam	NSAIDS	**5.31**	*3/*3 (PM) vs *1/*1 (NM) (n = 1)	20 mg SD	17112811	2006
(S)-warfarin	Anticoagulants and Antiplatelets	**0.09 (CL Ratio)**	*3/*3 (PM) vs *1/*1 (NM) (n = 2)	chronic treatment 6.25-70 mg/week	12496751	2002
tolbutamide	Sulfonylureas	**0.15 (CL Ratio)**	*3/*3 (PM) vs *1/*1 (NM) (n = 3)	500 mg SD	11875364	2002

NOTE: The present list includes CYP2C9 substrates with AUCR ≥ 5 or CL Ratio ≤ 0.20
Some known substrates of the enzyme may not be listed because they do not have changes in exposure reaching that level, or may not have DDI studies with AUC/CL changes available.
NM, CYP2C9 normal metabolizer; IM, CYP2C9 intermediate metabolizer; PM, CYP2C9 poor metabolizer

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Inhibitors

Inhibitor	Therapeutic class	Inhibitor Dose (oral)	Substrate (oral, unless otherwise specified)	Max AUCR or CL Ratio	PMID or NDA #	Published
Strong Inhibitors (AUCR ≥ 5 or CL Ratio ≤ 0.20)						
tasisulam	Cancer Treatment	individualized dose single infusion (i.v.)	tolbutamide	**5.76**	29119333	2018 Jun
sulfaphenazole	Antibiotics	500 mg BID (4 days)	tolbutamide	**5.28**	2311340	1990 Mar
miconazole	Antifungals	125 mg QD (18 days)	(S)-warfarin	**81.0% ↓ CL**	1611805	1992 Jun
Moderate Inhibitors (2 ≤ AUCR < 5 or 0.20 < CL Ratio ≤ 0.50)						
ataciguat	Cardiovascular Drugs	100 mg QD (16 days)	(S)-warfarin	**3.21**	17192504	2007 Jan
tienilic acid	Diuretics	250 mg/day (19 days)	(S)-warfarin	**2.92**	7105625	1982 Sep
fluconazole	Antifungals	400 mg QD (14 days)	(S)-warfarin	**2.85**	8801057	1996 Apr
oxandrolone	Miscellaneous Agents	5-10 mg BID (21 days)	(S)-warfarin	**2.65**	NDA # 013718	2002
AZD1981	Antiasthmatics	400 mg BID (14 days)	(S)-warfarin	**2.40**	27558866	2017 Feb
piperine[1]	Food Products	44 mg SD in 200 mL soup	phenytoin	**2.33**	11808866	2001 Oct-Dec
nitisinone	Other	80 mg QD (16 days)	tolbutamide	**2.22**	30443705	2019 Mar
amiodarone	Antiarrhythmics	200 mg BID (10 days)	(S)-warfarin	**2.11**	3621782	1987 Sep
milk thistle (Silybum marianum)	Herbal Medications	140 mg TID (14.5 days)	losartan[2]	**2.09**	19221727	2009 Jun
phenylbutazone	NSAIDS	100 mg TID (12 days)	(S)-warfarin	**0.22 (CL Ratio)**	6661352	1986 Jan
azapropazone	NSAIDS	900 mg/day (4 days)	tolbutamide (IV)	**0.30 (CL Ratio)**	7295492	1981 Oct
bucolome	NSAIDS	300 mg/day (chronically)	(S)-warfarin	**0.30 (CL Ratio)**	10497145	1999 Oct
benzbromarone	Antigout & Uricosuric Agents	50 mg QD (chronically)	(S)-warfarin	**0.46 (CL Ratio)**	10613612	1999 Dec

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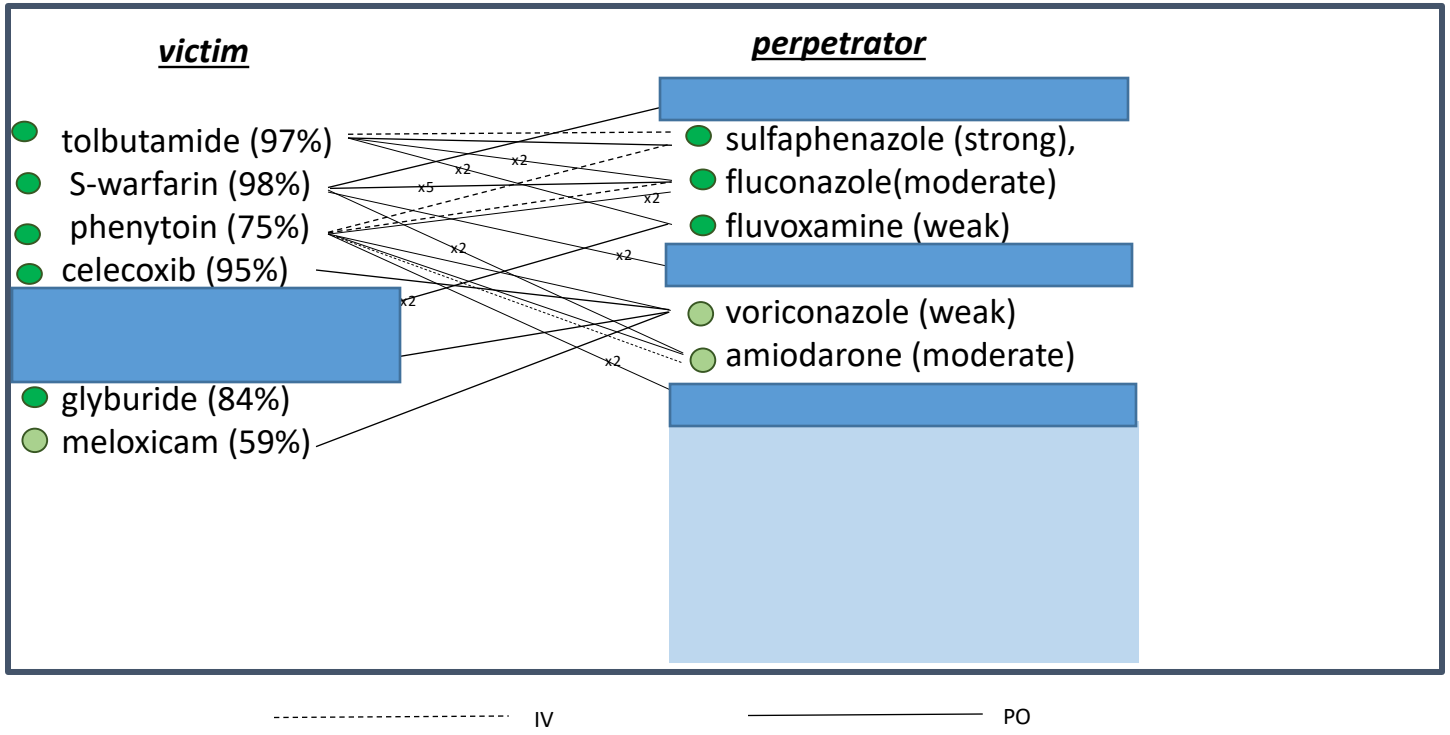
CYP2C9



DDI studies: Tolbutamide

Study	2C9 inhibitor	Inhibitor dose	Observed AUC ratio
Lazar et al 1990	Fluconazole	150mg SD	1.90
Lazar et al 1990	Fluconazole	100mg QD	2.09
Veronese et al 1990	*Sulphaphenazole*	*500mg BID*	*5.28*
Back et al 1998	Sulphaphenazole	500mg BID	0.32 (CL ratio)
Pond et al 1977	Sulphaphenazole	1000mg SD	Change in half life reported. 2 subjects with c-t profiles
Madsen et al 2001	Fluvoxamine	75mg QD	1.25
Madsen et al 2001	Fluvoxamine	150mg QD	1.93

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DDI studies: S-warfarin

Study	2C9 inhibitor	Inhibitor dose	Observed AUC ratio
Black et al 1996	Fluconazole	400mg QD	2.92
Neal et al 2003	*Fluconazole*	*100mg QD*	*1.35*
Neal et al 2003	*Fluconazole*	*200mg QD*	*1.86*
Neal et al 2003	*Fluconazole*	*300mg QD*	*2.00*
Bavisotto et al 2011	Fluconazole	400mg QD	2.54

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DDI studies: Phenytoin; Celecoxib

Phenytoin

Study	2C9 inhibitor	Inhibitor dose	Observed AUC ratio
Touchette *et al* 1992	Fluconazole	400mg QD	1.33
Blum *et al* 1991	Fluconazole	200mg QD	1.88
Lazar et al 1990	Fluconazole	200mg QD	1.75
Hansen et al 1979	Sulphaphenazole	2000mg QD	0.33 (CL ratio)

Celecoxib

Study	2C9 inhibitor	Inhibitor dose	Observed AUC ratio
FDA CDER 20998	Fluconazole	200mg QD	2.3

Voriconazole study in Chinese

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Additional DDIs?

Precipitant	Precipitant Administration	Object	Object Administration	Percent Change AUC	Precipitant Dose
voriconazole	Oral	phenytoin	Oral	49.8	400 mg (10 days)
Precipitant	**Precipitant Administration**	**Object**	**Object Administration**	**Percent Change AUC**	**Precipitant Dose**
amiodarone	Oral	phenytoin	IV	39.6	200 mg (3 weeks)
amiodarone	Oral	phenytoin	Oral	40.4	200 mg (6.5 weeks)
Precipitant	**Precipitant Administration**	**Object**	**Object Administration**	**Percent Change AUC**	**Precipitant Dose**
amiodarone	Oral	(S)-warfarin CYP2C9 in vivo Probe	Oral	26.9	300 mg (3 days)
amiodarone	Oral	(S)-warfarin CYP2C9 in vivo Probe	Oral	110.9	200 mg (10 days)
Object	**Object Administration**	**Precipitant**	**Precipitant Administration**	**Percent Change AUC**	**Object Dose**
flurbiprofen	Oral	fluconazole	Oral	25.3	50 mg
flurbiprofen	Oral	fluconazole	Oral	33	50 mg
flurbiprofen	Oral	fluconazole	Oral	43.1	50 mg
flurbiprofen	Oral	fluconazole	Oral	62.2	100 mg
flurbiprofen	Oral	fluconazole	Oral	79	50 mg
flurbiprofen	Oral	fluconazole	Oral	81.4	100 mg
flurbiprofen	Oral	fluconazole	Oral	91.9	100 mg
flurbiprofen	Oral	fluconazole	Oral	102.3	50 mg
flurbiprofen	Oral	fluconazole	Oral	116	50 mg
flurbiprofen	Oral	fluconazole	Oral	147.7	50 mg
flurbiprofen	Oral	fluconazole	Oral	180.4	50 mg
flurbiprofen	Oral	fluconazole	Oral	202.6	50 mg
flurbiprofen	Oral	fluvoxamine and voriconazole	Oral	36.6	25 mg
Object	**Object Administration**	**Precipitant**	**Precipitant Administration**	**Percent Change AUC**	**Object Dose**
ibuprofen	Oral	diazepam	Oral	31.7	400 mg
ibuprofen	Oral	diazepam	Oral	46.6	400 mg

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Summary

- Currently have
  - 4 substrates in simulator – now adding flurbiprofen

CERTARA | SIMCYP

CYP2C19 Matrix

July 2020

CYP2C19 DIDB Summary

#	Enzyme/transporter	Responsible OH	Number studies	Number in vivo compounds	Total Number clinical studies	# Case Report	# Renal Impairment Study	# Hepatic Impairment Study	# Food-Effect Study	# Cocktail Study	References
6	CYP2C19	OH	2409	72	475	17	17	17	17	17	347

- **Green – Compound file with this function available in V19R1**
- **Blue – Compound file with this function in development for V20R1**
- **Yellow – Compound file had been looked at/is feasible or currently missing functionality**
- **Red – not available, not feasible**
- **This colour - not looked yet**

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DIDB Summary

Substrate	In Vivo Induction > 20% Effect	In Vivo Inhibition > 20% Effect	In Vivo No Induction	In Vivo No Inhibition	In Vivo Pharmacokinetics	Grand Total
omeprazole	20	30	5	51	17	127
proguanil		10		8	1	19
imipramine		9		1		10
mephenytoin	6	9	6	18	1	40
clopidogrel	2	8	1	3	2	16
clobazam	1	7			2	10
diazepam	1	6	1	6		14
(S)-citalopram (escitalopram)	2	5	1	2	2	12
amitriptyline	2	5		1	1	9
clomipramine	1	5		1	1	8
cannabidiol		4		4	9	17
lansoprazole		4		2	3	9
nelfinavir	3	4	3	4	2	16
sibutramine		4				4
(R)-warfarin		3				3
clozapine	2	3				5
ospemifene (deamino-hydroxytoremifene)	2	3		3	2	10
tilidine		3				3
venlafaxine		3	1	1		5

Multiple enzymes

Mainly 3A4

Mainly 3A4

Mainly 1A2 &3A4

Mainly 1A2

Multiple enzymes

CYP2D6

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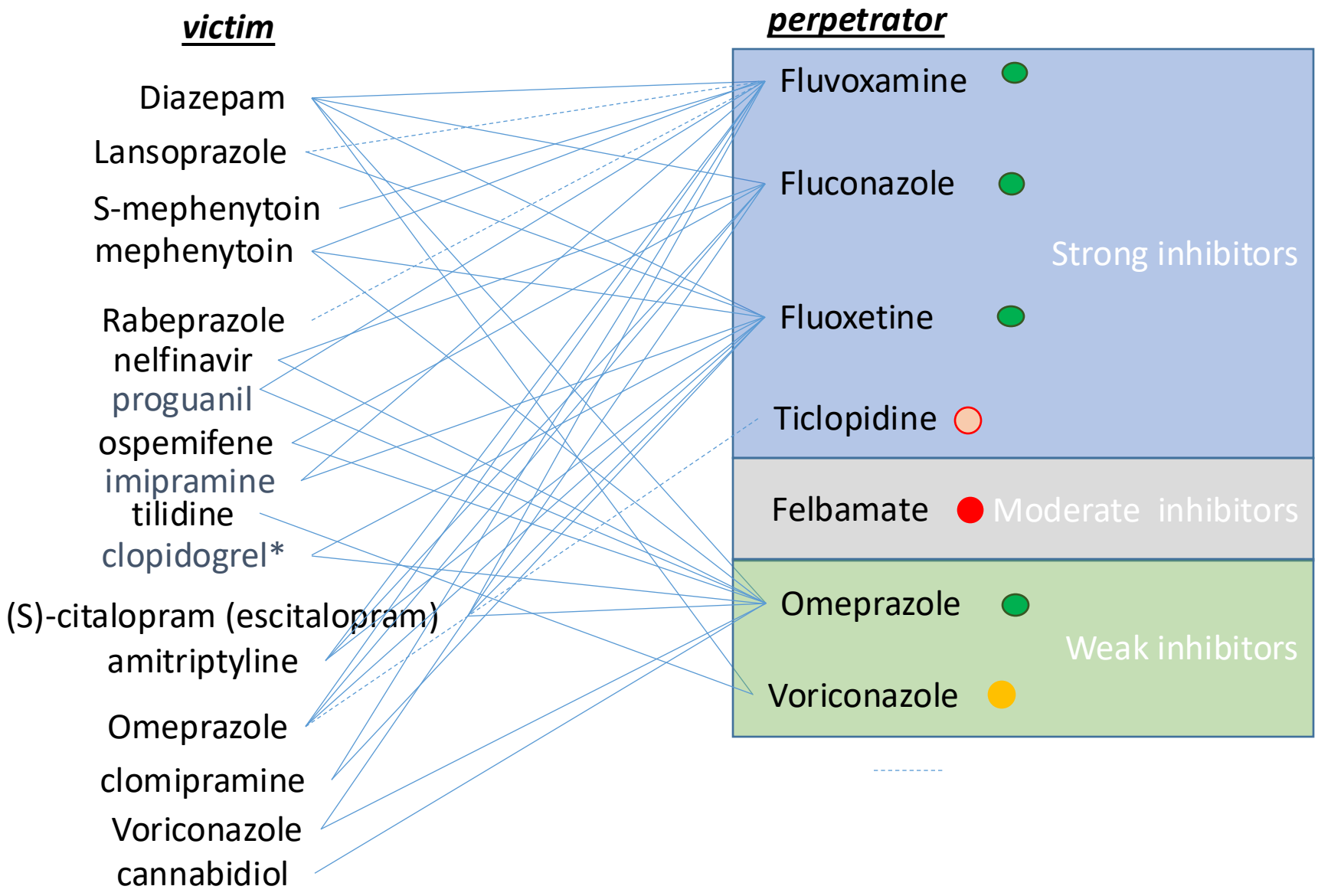
CYP2C19 Matrix - inhibitors



*multiple enzymes

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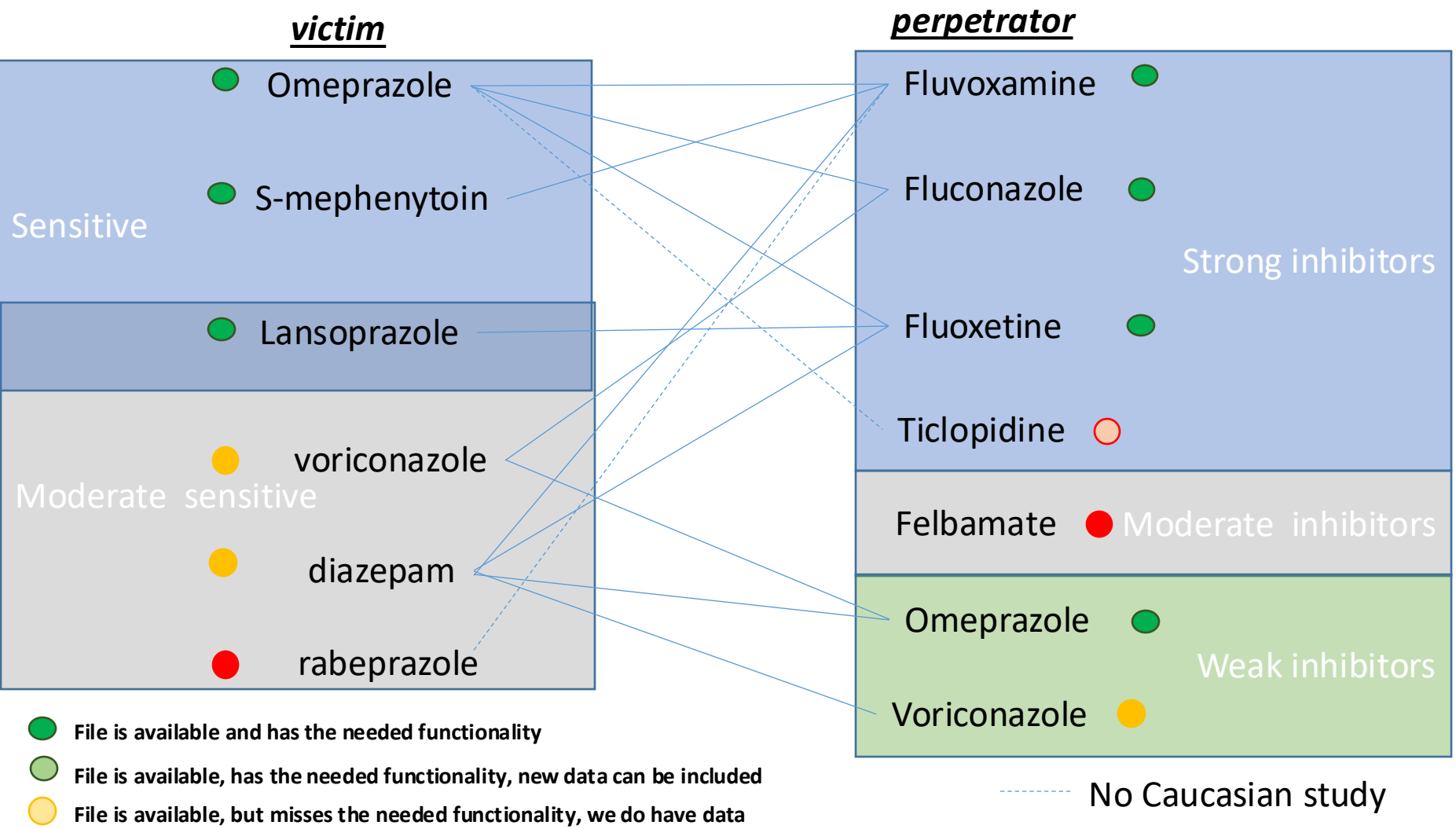
CYP2C19 Matrix - inhibitors



- File is available and has the needed functionality
- File is available, has the needed functionality, new data can be included
- File is available, but misses the needed functionality, we do have data
- File is not available, but can be build
- File is available, but misses the needed functionality & we miss data
- File is not available, and cannot be build based on the available data

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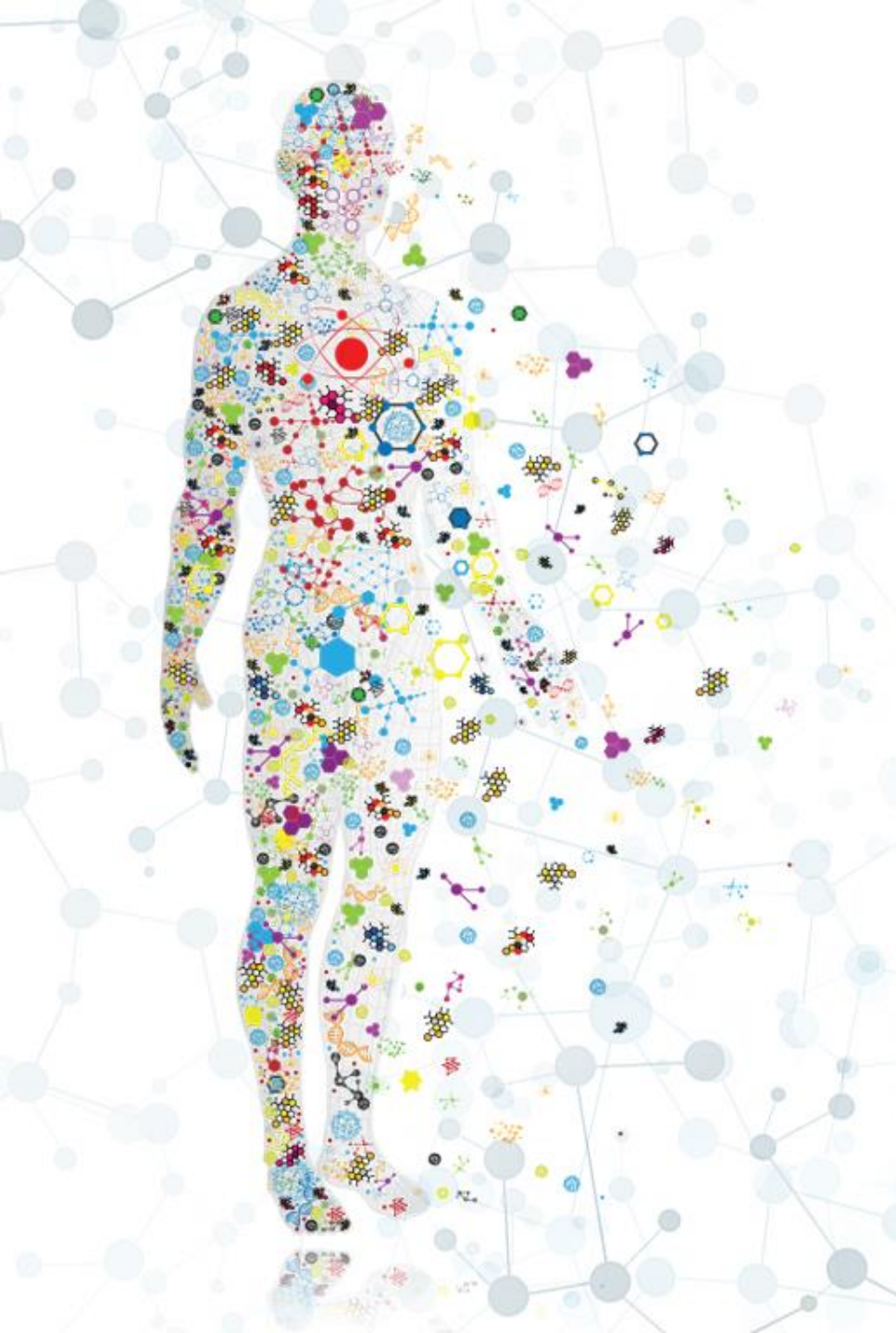
Summary

- Currently have
  - 3 substrates in simulator
  - A range of inhibitors with differing potency



CERTARA | SIMCYP

CYP3A4 Matrix

July 2020

CYP3A4 verification dataset

- 280 compounds returned from DIDB
- 223 compounds from DIDB have at least 1 positive DDI mediated by CYP3A4
  - ✓ 22 library compounds
  - ✓ 9 compounds with PBPK model available from Xian's work on Rifampicin CYP3A4 Induction
- In addition, there are 21 compounds from the Rifampicin CYP3A4 Induction work that are not within the DIDB database
  - ✓ These compounds at least have 2 DDI studies (1 with rifampicin)
- In total 52 compounds

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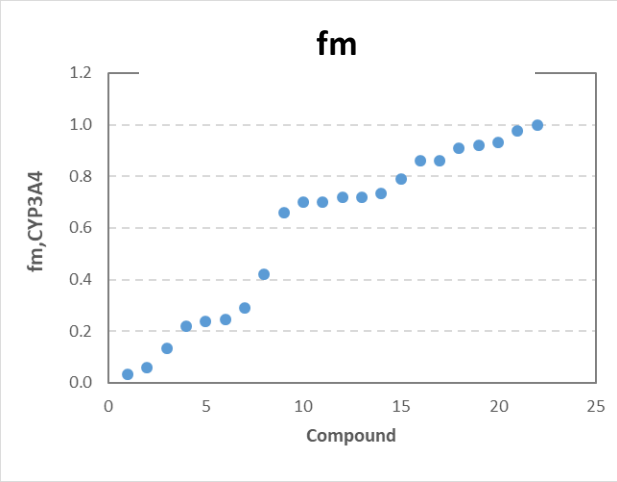
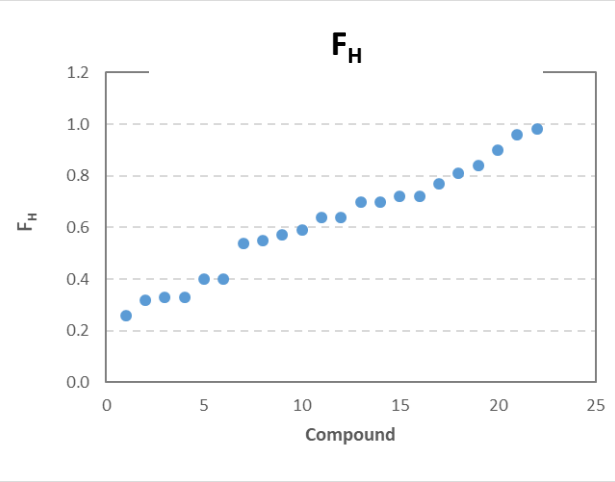
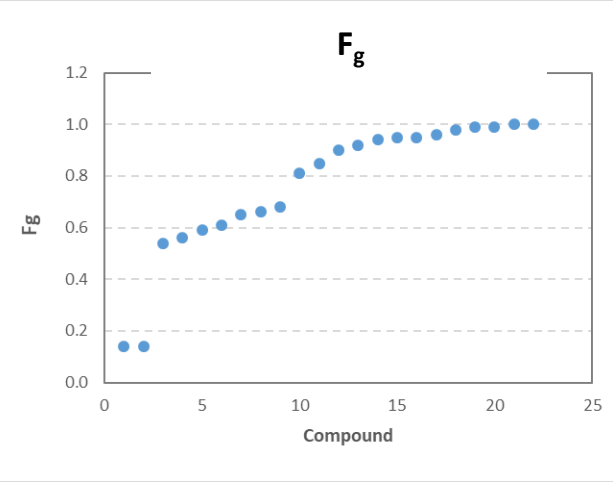
Distribution profiles of metabolic properties for library compounds

fm, FH and Fg from static calculation using Simcyp library compounds (N = 22) within the DIDB database







fm_{CYP3A4}: 0.03 – 1.00

F_H: 0.26 – 0.98

F_g: 0.14 – 1.00

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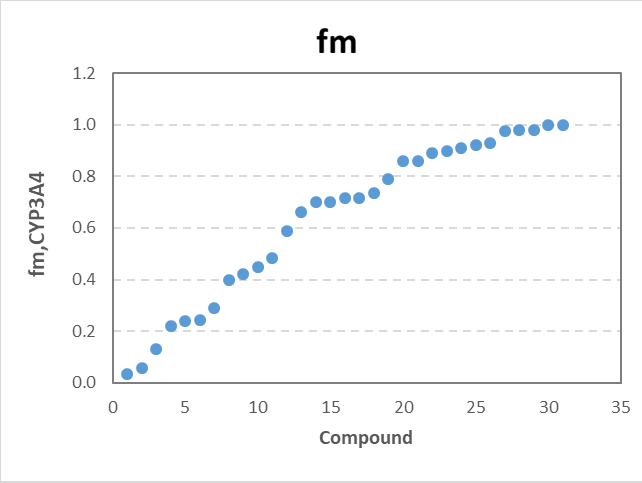
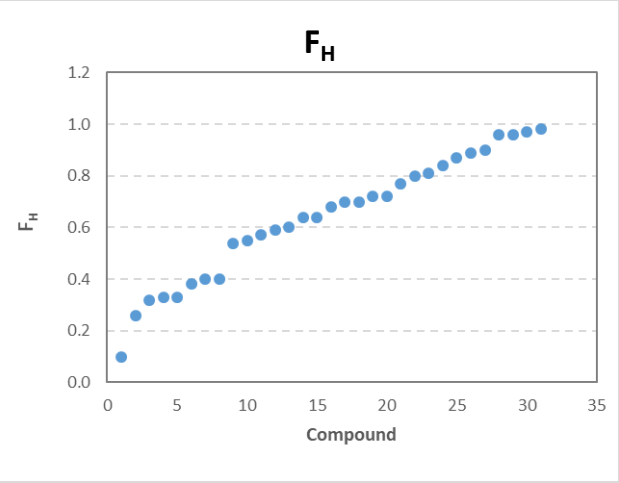
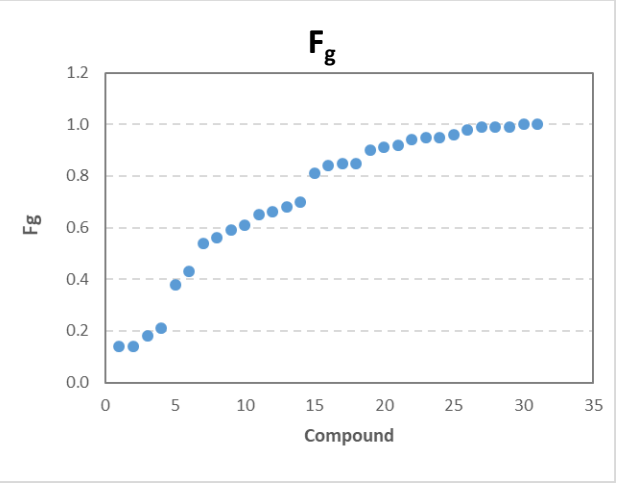
Distribution profiles of metabolic properties for library and extra compounds

fm, FH and Fg from static calculation using Simcyp library compounds (N = 22) and extra compounds (N = 9) within the DIDB database







fm_{CYP3A4}: 0.03 – 1.00

F_H: 0.10 – 0.98

F_g: 0.14 – 1.00

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Conclusion

- Sufficient compounds for CYP3A4 verification
- The compounds with PBPK models available cover the full range of metabolic properties

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