Title: *In silico* and intuitive predictions of CYP46A1 inhibition by marketed drugs with subsequent enzyme crystallization in complex with fluvoxamine

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Supplemental Figure Legends

Supplemental Figure 1**.** Unbiased σ_A weighted 2|Fo|-|Fc| electron density for the FLV complex of CYP46A1 at 2.5 Å resolution contoured from 1σ to 5σ in intervals of 1σ. The primary amine of fluvoxamine (carbon atoms white, oxygen red, nitrogen blue, fluorine purple) is bonded to Fe of the heme.

Supplemental Figure 2. Photoisomerization of FLV in solution upon irradiation with UV light. Stock solution of FLV in water (5 mM) was left for 2 hrs at a 20 cm-distance from the UVC lamp (Philips TUV 30W T8 G30T8). The brown and gray traces show the spectrum of FLV solution before and after irradiation, respectively. These spectra are similar to those of the E and Z isomers in Miolo et al., 2002, Eur. J. Pharm.

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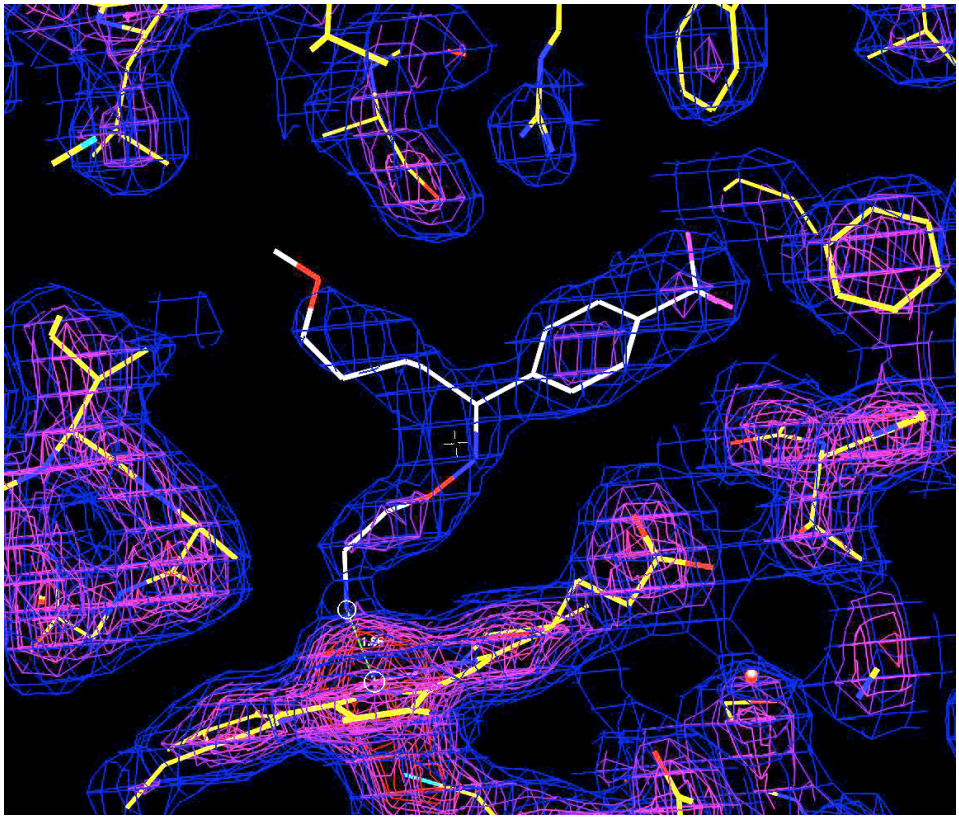
Supplemental Table 1. Crystallographic statistics for the FLV-CYP46A1 complex.

Supplemental Table 2. A summary of computational and intuitive predictions. The color code is the same as in Fig. 1.



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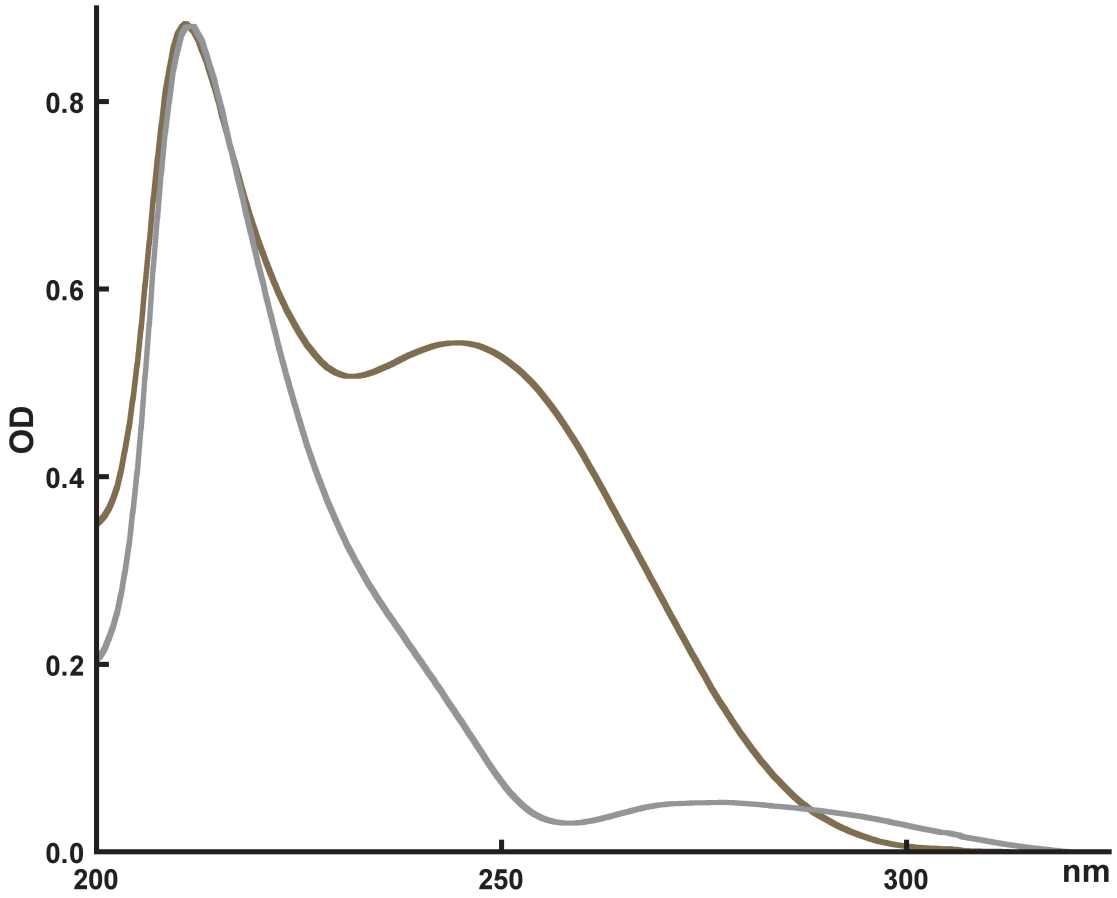

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Supplemental Table 1

Crystallographic statistics for the FLV-CYP46A1 complex

CYP46A1 complex	**Fluvoxamine**
PDB code	4ENH
Space group	$I4_122$
Unit cell dimensions (Å)	121.1 121.1 141.9
Molecules per asymmetric unit	1
Solvent content	50.7%
Data	
Total observations > $0\sigma_F$	131,207
Unique reflections > $0\sigma_F$	18,625
Redundancy	7.0
Completeness	100.0%
Resolution (last shell) (Å)	2.64 – 2.50
$\langle I/\sigma_I \rangle$ all data (last shell)	6.2 (1.3)
Rmerge all data (last shell)	0.101 (0.600)
Refinement	
R-factor	0.210
Rfree	0.272
Reflections used	17,630
Test set	950 (5.1%)
RMSD from ideality	
Bond lengths (Å)	0.010
Bond angles (deg.)	1.19
Ramachandran plot	
Favored regions	96.7%
Allowed regions	99.3%
Model	Residues / Avg. B ($Å^2$)
Protein	426 (44.2)
Heme	1 (25.8)
FLV	1 (77.2)
H_2O molecules	132 (53.2)

Supplemental Table 2. A summary of computational and intuitive predictions. The color code is the same as in Fig. 1.

Drug generic name	Residual CYP46A1 activity, %	Round of *in-silico* screening		Intuitive predictions
		Round 1, free energy	Round 2, free energy	
acebutolol	99±2			+
acenocoumarol	89±4			+
acepromazine	108±3	-18.31		
acetaminophen	132±3	-17.97	-34.1915	
acetazolamide	100±3	-51.93		
acetohexamide	97±3			+
acetylsalicylic acid	79±2	-22.39		
agomelatine	110±3			+
albaconazole	34±7			+
alendronate	99±1	-51.4		
alosetron	113±3	-19.33		
altretamine	83±2	-15.61		
amiloride	90±9	-27.76	-57.3359	
aminoglutethimide	98±3	-23.01	-41.7141	
aminolevulinic acid	93±8	-18.79	-46.5299	
amisulpride	101±5	-24.3		
amitriptyline	99±3	-14.66		
amoxapine	107±9	-22.97		
amrinone	63±1			+
anastrozole	97±2	-19.43		
apraclonidine	95±3	-22.78		
aprepitant	113±3			+
aspartam	99±3			+
atenolol	95±5	-20.19		
atropine	100±3	-22.65		
azacitidine	96±1	-30.54	-55.8407	
azathioprine	53±1	-22.47	-36.9867	
benoxinate	99±2			+
benserazide	77±4	-32.43	-62.8826	
benzocaine	93±8	-20.06	-47.0995	
benzthiazide	100±5	-73.65		
betaxolol	101±3			+
bethanechol	91±7	-20.36	-39.6212	
bicalutamide	35±4	-40.91		
brimonidine	91±1	-21.65		
brinzolamide	104±3	-60.81		
bupropion	101±3	-19.51		
cabergoline	86±3			
caffeine	103±3	-17.51		
candesartan	85±6	-32.82		
captopril	95±6	-20.07		
carbachol	91±1		-45.3308	
carbenoxolone	52±1			+
carbidopa	78±1	-26.14		
carisoprodol	90±5	-20.69		
cefoxitin	92±5	-35.95		

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cidofovir	107±1	-33.77		
cimetidine	8±2	-21.64	-28.9885	
ciprofloxacin	99±3	-32.62		
citalopram	91±7	-20.6		
clobazam	88±3			+
clofibrate	109±3	-26.52		
clonidine	80±2	-17.13		
clotrimazole	16±1	-19.89		
clozapine	96±3	-22.87		
colistin	107±4			+
cyclobenzaprine	111±3	-16.09		
cycloserine	93±6	-15.98	-34.3689	
dacarbazine	82±5	-22.77		
dapsone	89±6	-36.6		
debrisoquine	90±3			+
demeclocycline	103±1	-44.49		
desipramine	104±4	-14.33		
desloratadine	86±7	-21.69		
desogestrel	101±3	-15.24		
dexmedetomidine	8±2	-14.66	-30.097	
dextromethorphan	79±4	-18.7		
dehydroepiandrosterone	58±3			+
diclofenac	84±4	-22.69		
diflunisal	78±3	-23.61		
dimenhydrinate	106±3			+
disulfiram	84±4	-16.07		
dopamine	83±2	-24.7	-40.3644	
dorzolamide	77±3	-71.81		
droperidol	78±7	-28.44		
droxidopa	61±2			+
duloxetine	107±5	-15.37		
edrophonium	85±3	-15.6		
entacapone	84±6	-23.26		
entecavir	102±7	-28.8		
ephedrine	49±2			+
epinastine	106±4	-17.13	-21.28	
epinephrine	25±1	-22.26	-47.8781	
equilenin	89±3			+
ergonovine	110±1			+
estradiol	32±2.4	-20.31		
estrone	95±3	-19.56		
estropipate	97±7	-31.49		
ethinamate	107±6	-20.64	-48.578	
ethinyl estradiol	107±8	-23.54		
ethotoin	98±3	-19.77		
exemestane	85±4	-17.64		
famotidine	60±3	-41.07	-115.6139	
felbamate	98±8	-29.4	-43.6726	
fenofibrate	104±3			+

Supplemental Table 2. A summary of computational and intuitive predictions. The color code is the same as in Fig. 1.

fluconazole	98±3	-23.31	-42.5044	
flucytosine	85±2	-17.64		
fludrocortisone	106±3	-30.85		
fluoxetine	105±4	-19.36		
fluphenazine	109±4.0			+
flurazepam	88±3	-8.26		
flurbiprofen	97±5	-24.68		
fluspirilene	107±6			+
fluvoxamine	11±0.2	-22.54		
folate	100±3	-35.92		
furosemide	111±3	-34.71		
gabapentin	100±8	-18.67		
galantamine	115±1	-25.35		
genistein	91±2			+
glucosamine	92±3	-27.03		
guanabenz	89±9	-23.46	-45.3602	
guanethidine	98±6	-20.4	-40.555	
guanfacine	98±5	-24.79	-52.3205	
hexaconazole	46±5			+
histamine phosphate	70±5	-16.16	-31.5727	
huperzine	113±4			+
hydralazine	59±2	-16.58	-36.7232	
hydroxyurea	91±6	-15.36	-47.0012	
Ibuprofen	93±3	-19.38		
imexon	99±3			+
irbesartan	89±8	-30.63		
isocarboxazid	88±7	-22.67		
isoniazid	88±9	-15.9	-38.4696	
isoproterenol	53±7	-23.59		
itraconazole	55±1			+
ketamine	110±3	-18.03		
ketoconazole	55±1			+
labetalol	105±9	-22.24		
lacosamide	97±7	-25.29		
lamivudine	94±5	-25.72	-52.0697	
lansoprazole	86±5	-23.75		
latanoprost	60±2			+
letrozole	97±3	-21.49	-33.2698	
levetiracetam	86±7	-19.11		
levodopa	100±5	-22.5		
levothyroxine	80±3			+
linezolid	117±5	-24.99		
mafenide	89±8	-40.69	-96.5939	
maprotiline	102±3	-17.8		
mebendazole	105±3	-22.24		
melphalan	107±3	-26.09		
mepivacaine	56±2	-17.48		
meprobamate	115±3	-23.14	-48.4217	
mesalamine	104±6	-21.84		

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mestranol	90±3	-27.52		
metaraminol	89±2	-21.88		
methamphetamine	98±3	-11.63		
methazolamide	100±6	-38.19		
methocarbamol	106±1	-25.09	-43.2215	
methoxamine	109±5	-20.98		
methyldopa	92±1	-26.78		
metipranolol	72±3	-17.15		
metolazone	53±1	-37.45		
metoprolol	96±4			+
mexiletine	107±3	-14.72		
mianserin	104±4	-18.37		
midodrine	94±1	-21.68	-45.8917	
milnacipran	52±1			+
minocycline	86±4	-20.31		
minoxidil	90±4	-23.94	-37.4552	
mirtazapine	130±5	-18.59		
mitomycin	41±1	-32.97		
mizoribine	100±9	-30.18		
moclobemide	94±2			+
modafinil	89±2	-30.88	-44.9537	
molindone	99±2			+
naproxen	102±5	-21.36		
nelarabine	103±10	-34.27		
nepafenac	92±4	-25.57	-30.446	
nicotinamide	92±6			+
nifedipine	101±3	-25.67		
nitrofurazone	74±4	-23.73	-53.4429	
nizatidine	40±5	-17.75		
norepinephrine	83±3	-23.02		
norgestimate	105±2			+
olanzapine	100±3	-17.48		
ondansetron	104±2	-21.05		
orphenadrine	106±2	-15.73		
oxazepam	106±3	-25		
paroxetine	98±3	-24.73		
pemirolast	112±1	-21.63	-51.7591	
pemoline	106±4	-21.16	-45.0975	
pentoxifylline	110±5	-18.73		
pergolide	109±3			+
phenacemide	100±3	-20.6	-39.8843	
phenazopyridine	99±2	-20.18	-37.2026	
phenformin	102±3			+
phentolamine	98±4	-19.59		
Phenylalanine	90±1			+
Phenylephrine	87±3	-20.53		
Phenytoin	84±5	-22.81		
picrotoxin	62±3			+
pilocarpine	79±2	-18.11	-29.6984	

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pirenzepine	90±2			+
posaconazole	13±1			+
pramipexole	105±3	-19.36	-31.5771	
prazepam	71±6	-23.6		
pregabalin	93±10	-19.16		
primaquine	54±6	-19.7		
procainamide	101±2	-23.7		
procarbazine	88±2	-20.03		
propericiazine	96±3			+
propofol	105±3	-20.81		
propranolol	106±3	-18.04		
pseudoephedrine	113±3	-17.44		
pyrazinamide	101±4	-16.99	-32.1946	
pyrimethamine	93±2	-23.65	-41.3082	
quinestrol	70±3	-23.2		
quinethazone	101±3	-38.66		
quinidine	68±4	-22.58	-43.3095	
quinine	112±5	-27.94		
ranitidine	9±2	-23.34		
ravuconazole	50±2			+
ribavirin	109±1	-27.85	-64.4542	
riluzole	106±5	-19.77		
risedronate	101±1	-42.68		
ritodrine	101±2	-24.76		
rivastigmine	106±3	-16.46		
rofecoxib	89±3			+
rosiglitazone	93±5	-27.98		
rufinamide	88±5	-21.41	-37.9069	
salicylate-sodium	92±2			
salsalate	112±3			+
scopolamine	90±2	-29.76		
selegiline	18±1	-10.92		
sertindole	98±3			+
sodium phenylacetate	68±7	-19.52		
d-sorbitol	106±5	-30.37		
stanozolol	99±6	-23.88		
sulfadoxine	98±9	-41.47		
sulfamethazine	90±2			+
sulfanilamide	75±2	-38.05	-81.2577	
sumatriptan	99±8	-30.72		
suprofen	107±2	-21.05		
tacrine	99±2	-16.99		
tazobactam	114±1	-45.07	-88.9393	
telbivudine	93±2	-26.42	-55.0371	
temozolomide	89±8	-21.86	-40.6917	
terbutaline	80±2	-21.08		
testosterone	49±4	-15.41		
thiabendazole	95±2	-13.91		
thiamylal	80±2	-25.92		

Supplemental Table 2. A summary of computational and intuitive predictions. The color code is the same as in Fig. 1.

ticlopidine	117±2	-15.32		
tiludronate	99±1	-52.62		
timolol	96±1	-18.93		
tinidazole	83±2	-35.09		
tizanidine	117±2	-19.88		
topiramate	106±7	-33.37		
tramadol	98±2	-20.17		
tranylcypromine	0	-12.29	-25.0257	
travoprost	51±1			+
triamterene	94±3	-23.53		
trihexyphenidyl	97±8	-21.57		
trimetazidine hydrochloride	93±7	-19.19		
trimethoprim	112±2	-26.43		
tripelennamine	101±2	-15.74		
tropicamide	59±1	-22.81		
ttnpb	104±7			+
l-tyrosine	80±3	-23.3		
varenicline	96±2	-16.26		
voriconazole	12±3	-23	-16.0695	
vorinostat	96±2	-23.73		
zaleplon	84±2	-18.76		
zanamivir	112±1	-35.24		
zidovudine	92±3	-24.74	-50.466	
zileuton	107±5	-20.41	-40.2061	
zolmitriptan	97±2	-22.21		
zonisamide	93±1	-37.17		