Supporting Information for

Structure Activity Relationship for FDA Approved Drugs as Inhibitors of the Human Sodium Taurocholate Co-transporting Polypeptide (NTCP)

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Table S1. List of forty-five retrieved compounds from a SCUT database search, using the qualitative common feature pharmacophore with ezetimibe shape restriction.

Compound	**Fit Value**	**Indication**
Irbesartan	2.4810	Angiotensin II receptor antagonist
Valsartan	2.3137	Angiotensin II receptor antagonist
Losartan	2.2480	Angiotensin II antagonist
Ropinirole	2.2391	Dopamine agonist
Sulfinpyrazone	2.1336	Inhibits renal tubular absorption of uric acid
Meperidine	2.0869	Narcotic analgesic
Bortezomib	1.9219	Proteasome inhibitor
Eletriptan	1.8245	Selective serotonin B1/D agonist
Haloperidol	1.8201	Antipsychotic, neuroleptic
Fenofibrate	1.8035	Inhibits triglyceride synthesis
Tolazamide	1.6502	Stimulates release of insulin from the pancreas, increases insulin sensitivity at peripheral sites, decreases hepatic glucose output
Cephradine	1.6286	Inhibits bacterial cell wall biosynthesis
Cefaclor	1.5905	Inhibits bacterial cell wall biosynthesis
Ramipril	1.5681	ACE inhibitor
Eprosartan	1.5642	Angiotensin II receptor antagonist
Cephalexin	1.5446	Inhibits bacterial cell wall biosynthesis
Loracarbef	1.4501	Antibacterial, inhibits cell wall

		synthesis
Indomethacin	1.3652	Inhibits prostaglandin synthesis
Loperamide	1.2300	Slows intestinal motility
Propafenone	1.0952	Class 1C antiarrhythmic
Paliperidone	1.0949	Antagonizes dopamine receptors
Ezetimibe	1.0896	HMG-CoA reductase inhibitor
Nafcillin	1.0087	Bactericidal, inhibits cell wall synthesis
Bumetanide	0.9628	Loop diuretic inhibits reabsorption of Na and Cl in the ascending loop of Henle and the distal renal tubule
Trandolapril	0.9525	ACE inhibitor
Tiagabine	0.8866	GABA inhibitor
Permethrin	0.8224	Pediculicide
Nateglinide	0.8063	Increases pancreatic release of insulin
Cocaine_metabolite_cocaethylene	0.7875	
Penicillin V	0.7691	Bactericidal
Quinapril	0.7147	ACE inhibitor
Cefadroxil	0.6845	Inhibits bacterial cell wall biosynthesis
Oseltamivir	0.6812	Inhibits viral neuroamidase
Raloxifene	0.5787	Partial antagonist of estrogen that behaves like estrogen
Benazepril	0.5356	Angiotensin converting enzyme inhibitor
Aztreonam	0.5148	Inhibits bacterial cell wall biosynthesis
Loratadine	0.4274	Antihistamine
Amoxicillin	0.0956	β-lactam antibiotic, inhibits

		bacterial cell wall synthesis
Thiethylperazine	0.0612	Antidopaminergic, antiemetic
Quinidine	0.0508	Class 1A antiarrhythmic
Alfuzosin	0.0267	A1-adrenoreceptor antagonist
Perindopril	0.0178	ACE inhibitor
Enalapril	0.0048	ACE inhibitor
Cefdinir	0.0020	Inhibits bacterial cell wall biosynthesis
Candesartan	0.0012	Angiotensin II antagonist

Table S2. List of eighty-five retrieved compounds from a CDD database search, using the qualitative common feature pharmacophore with ezetimibe shape restriction.

Compound	**Fit Value**	**Indication**
Phthalylsulfamethizole	2.7541	Antibiotic
Yohimbine	2.5767	Erectile dysfunction
Nateglinide	2.4916	Antidiabetic
Irbesartan	2.4810	Antihypertensive
Perindopril	2.3501	Antihypertensive
Losartan	2.2480	Antihypertensive
Ropinirole	2.2391	Antiparkinsonian
Haloperidol lactate	2.1229	Antipsychotic
Sulfinpyrazone	2.1049	Antiurolithic
Bortezomib	2.0127	Antineoplastic
Bensulide	1.9980	Antiinflammatory
TetradecylSulfate	1.9479	Antiseptic
Ezetimibe	1.9055	Antihyperlipidemic
Sodium dodecylbenzenesulfonate	1.8821	Antiseptic
Olmesartan	1.8402	Antihypertensive
Haloperidol	1.8201	Antispasmodic
Fenofibrate	1.8035	Antihyperlipidemic
Valsartan	1.7235	Antihypertensive
Tolazamide	1.6502	Antidiabetic
Cephradine	1.6286	Antibiotic
Cefaclor	1.5905	Antibiotic

Ramipril	1.5681	Antihypertensive
Tetrabenazine	1.5481	Antipsychotic
Cephalexin	1.5446	Antibiotic
Salicylic anhydride diacetate	1.5326	Antiinflammatory
Carbenicillin	1.5318	Antibiotic
Quinidine gluconate	1.5274	Antimalarial
Pipazethate	1.5217	Antitussive
Amprotropine	1.4779	Antihypertensive
Diphenoxylate	1.4643	Antispasmodic
Narceine	1.4581	Analgesic
Cyclomethycaine	1.4461	Analgesic
Piminodine	1.4187	Analgesic
Ticarcillin	1.3802	Antibiotic
Indomethacin	1.3652	Antiinflammatory
Loperamide	1.2279	Antidiarrheal
Temocillin	1.2096	Antibacterial
Almecillin	1.1761	Antibiotic
Anileridine	1.1586	Analgesic
Propafenone	1.0952	Antiarrhythmic
Eletriptan	1.0687	Antimigraine
Penicillin V	1.0495	Antibiotic
Pheneticillin	1.0376	Antibiotic
Ilomastat	1.0229	Opthalmic
Aztreonam	0.9810	Antibiotic
Bumetanide	0.9628	Diuretic
Triparanol	0.9571	Antihyperlipidemic

Gimatecan	0.9274	Antineoplastic
Tiagabine	0.8866	Anticonvulsant
Permethrin	0.8224	Dermatologic
Nafcillin	0.8223	Antibiotic
Arbutamine	0.7915	Antihypotensive
Penicillin G	0.7781	Antibacterial
Penicillin V	0.7691	Antibiotic
Azlocillin	0.7484	Antibiotic
Pyrethrins	0.7174	Insecticide
Quinapril	0.7147	Antihypertensive
Nylidrin	0.7012	Vasodilator
Cefadroxil	0.6845	Antibiotic
Clomiphene Citrate	0.6720	Selective estrogen receptor modulators
Hetacillin	0.6530	Antibacterial
Penicillin G sodium	0.6105	Antibiotic
Oseltamivir	0.6046	Antiviral
Raloxifene	0.5787	Bone resorption inhibitor
Omalizumab	0.5649	Antihistaminic, antihypertensive
Benazepril	0.5356	Antihypertensive
Loratadine	0.4274	Antihistaminic
Penicillin G benzathine	0.3545	Antibiotic
Cefamandole	0.2818	Antibiotic
Oxacillin	0.2225	Antibiotic
Enazepril	0.2036	Antihypertensive
Piperacetazine	0.1774	Antipsychotic
Eprosartan	0.1724	Antihypertensive

Methicillin	0.1237	Antibiotic
Estradiol cypionate	0.1118	Estrogen
Colchicine	0.0932	Antigout agent
Thiethylperazine	0.0612	Antiemetic
Trandolapril	0.0608	Antihypertensive
Alfuzosin	0.0267	Antihypertensive
Perindopril	0.0178	Antihypertensive
Enalapril	0.0048	Antihypertensive
Chlordantoin	0.0034	Antifungal
Candesartan	0.0012	Antihypertensive
Indigosol	0.0008	Unclassified
Finasteride	0.0003	Urologic

Table S3. Bayesian model leave-one-out cross-validation results. This model was built using 50 samples, and validated using a leave-one-out cross-validation. A ROC plot was generated, and the area under the curve (XV ROC AUC) calculated. Best Split was calculated by picking the split that minimized the sum of the percent misclassified for category members and for category nonmembers, using the cross-validated score for each sample. Using that split, a contingency table was constructed, containing the number of true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN).

Output	**XV ROC AUC**	**Best Split**	**TP/FN FP/TN**	**# in Category**
NTCP N50 with sig cutoff Bayesian	0.769	-0.956	23/5 6/16	28

Table S4. Bayesian model enrichment results. This table shows the output name, the percentage of samples that are in that particular category, the number of category members, and the percentage of true members found. Percentages that are less than 100% are in bold.

Output	**Category %**	**1%**	**5%**	**10%**	**25%**	**50%**	**75%**	**90%**	**95%**	**99%**
NTCP N50 with sig cutoff Bayesian	56%	0%	7.1%	14.3%	35.7%	71.4%	89.3%	92.9%	100%	100%

Table S5. Bayesian model percentile results. This table shows, for each model, the cutoff needed to capture a particular percentage of the good samples. For each cutoff, it shows below the estimated percentages of false positives and true negatives for the non-good samples. This table is designed to help you pick the cutoff value that best balances your desire to capture as many good samples as possible, while keeping the number of false positives at a minimum. Cutoff which lead to 10% or greater false positives are displayed in bold for ease of identification.

Model Name	**99%**	**95%**	**90%**	**70%**	**50%**	**30%**	**10%**	**5%**	**1%**
NTCP N50 with sig cutoff Bayesian	-7.410 90%/10%	-4.709 74%/26%	-3.242 63%/37%	-1.622 48%/52%	-1.622 22%/78%	4.938 7%/93%	6.558 3%/97%	8.025 2%/98%	10.726 1%/99%

Table S6. Bayesian model category statistics results. This table shows, for each category, statistics derived from the cross-validated predictions of the model built for that category as applied to members of that category and non-members of that category. For each group, the number of members/nonmembers (N) is given; the mean prediction for each subset (Mean); and the estimate standard deviation of the predictions for each subset (StdDev).

Output	**Category N**	**Category Mean (±StdDev)**	**Noncategory N**	**Noncategory Mean (±StdDev)**
NTCP N50 with sig cutoff Bayesian	28	1.66 (±3.86)	22	-1.89 (±4.43)

Table S7. External testing of Bayesian Model using different sized leave out groups.

Leave out 10% 100 x					
	External_ROC	Internal_ROC	Concordance	Specificity	Sensitivity
Mean	0.71	0.73	60.36	59.65	56.15
STDEV	0.19	0.059	26.27	37.99	34.37
Leave out 30% 100x					
	External_ROC	Internal_ROC	Concordance	Specificity	Sensitivity
Mean	0.66	0.70	58.09	67.15	50.19
STDEV	0.11	0.10	10.21	23.73	23.12
Leave out 50% 100x					
	External_ROC	Internal_ROC	Concordance	Specificity	Sensitivity
Mean	0.60	0.69	54.18	64.40	45.81
STDEV	0.08	0.14	8.54	23.52	22.80

Table S8. Comparison of 72 drugs in terms of NTCP and ASBT inhibition, from screening studies (i.e. single concentration studies). For each NTCP and ASBT, the percent taurocholate uptake compared to no-drug control was listed. Compounds are listed in alphabetical order.

Compounds	**Percent taurocholate Uptake by NTCP**	**Percent taurocholate Uptake by ASBT**
Abacavir	94.9±4.4	95.8±5.9
Acarbose	99.7±4.9	106±7
Aztreonam	104±4	95.7±7.5
Bendroflumethiazide	27.6±0.7	71.8±1.2
Bortezomib	107±4	92.7±1.7
Budesonide	79.3±6.4	48.9±6.2
Candesartan	68.0±7.2	50.8±9.9
Cefaclor	99.1±6.2	96.7±0.4
Cerivastatin	68.6±7.4	77.0±8.9
Chloroquine	83.0±4.5	105±3
Chlorpromazine	91.8±3.0	43.9±2.8
Cimetidine	82.9±2.9	76.0±4.4
Cyclosporine A	24.0±1.9	55.5±4.3
Daunorubicin	107±3	153±9
Dibucaine	100±1	56.6±0.6
Diltiazem	87.5±5.9	78.3±1.5
Doxazosin	70.8±3.7	57.2±7.5
Econazole	92.3±4.5	36.3±4.8

Eletriptan	104±8	68.3±8.2
Enalapril	111±4	71.1±8.4
Eprosartan	99.9±0.7	78.9±9.0
Ethosuximide	88.2±3.8	82.6±2.4
Ezetimibe	62.5±1.4	15.3±2.0
Famotidine	84.9±3.6	97.2±15
Fenofibrate	76.3±6.0	64.7±6.1
Formoterol	111±2	73.4±8.1
Furosemide	81.6±6.9	113±9
Imatinib	90.7±1.6	73.0±3.5
Indomethacin	68.4±2.5	32.5±5.5
Irbesartan	15.9±1.6	67.0±6.2
Isradipine	59.3±3.2	22.1±2.1
Itraconazole	81.8±5.6	77.6±8.6
Ketoconazole	59.1±3.0	48.8±10
Ketoprofen	84.6±6.1	88.2±8.6
Losartan	60.7±2.0	67.9±9.5
Lovastatin	74.7±3.2	25.4±1.7
Methylprednisolone	79.5±3.5	101±9
Metronidazole	84.3±2.7	77.3±7.7
Miconazole	94.6±2.6	65.1±6.4
Nafcillin	96.7±5.6	113±9
Naproxen	76.0±5.2	67.5±2.1
Nateglinide	62.0±1.4	55.2±4.8
Nefazodone	60.8±1.9	34.0±2.4
Nicardipine	81.8±6.5	68.4±0.5

Nifedipine	67.7±5.8	57.8±8.4
Nimodipine	55.9±1.6	32.5±1.1
Nitrendipine	67.7±1.6	50.5±4.9
Olmesartan	86.0±5.5	94.2±2.0
Omeprazole	105±6	61±5
Oseltamivir	102±9	94.1±0.3
Oxiconazole	99.5±2.6	74.2±7.3
Prednisolone	83.0±8.4	57.7±7.5
Probenecid	86.8±3.3	86.7±4.3
Procainamide HCl	84.8±6.7	124.2±13
Prochlorperazine	81.0±2.5	31.6±3.2
Propafenone HCl	85.4±3.8	43.5±9.1
Quinine	95.6±1.8	78.3±8.6
Raloxifene HCl	90.5±4.6	66.7±2.9
Reserpine	83.8±8.3	57.0±3.2
Ritonavir	27.0±1.2	42.1±5.2
Ropinirole	133±4	33.7±7.8
Rosuvastatin	59.1±3.0	71.3±4.2
Simvastatin	47.6±4.2	60.1±4.2
Sulconazole	86.7±7.2	64.2±0.4
Sulfanilamide	78.4±3.4	74.7±2.3
Sulfinpyrazone	96.1±3.2	89.2±7.0
Thiothixene	99.2±1.0	99.4±7.9
Tioconazole	84.3±5.1	27.0±4.4
Triamterene	85.7±4.3	62.8±0.6
Valsartan	101±3	95.0±6.1

Warfarin	102±2	59.7±6.8
Yohimbine	108±4	85.5±11

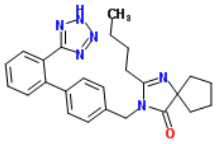
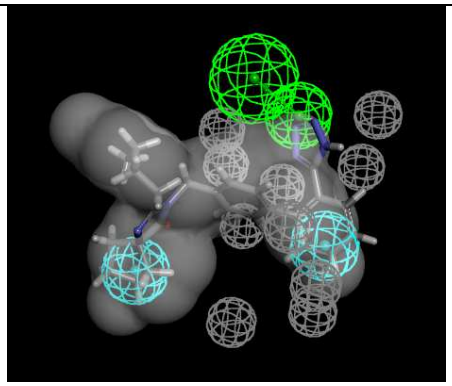
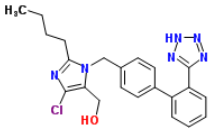
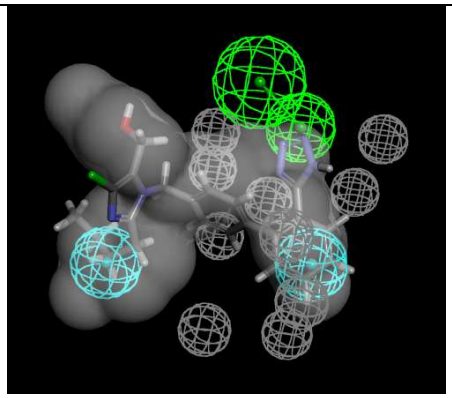
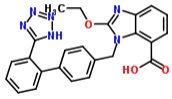
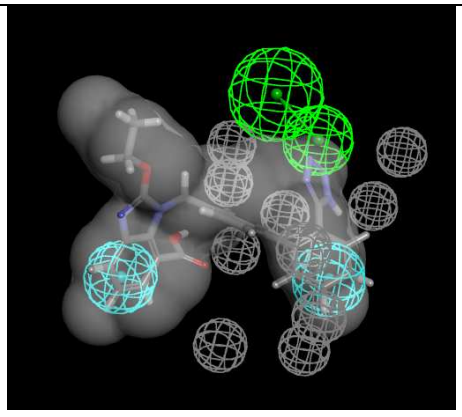
Table S9. Results from drug cytotoxicity testing. Cytotoxicity is shown in terms of percent cell viability. Drug is considered cytotoxic when cell viability in the presence of drug was less than 80% of cell viability in the absence of drug.

Compound	**NTCP cell viability (%)**	**ASBT cell viability (%)**
Irbesartan	97.8±4.1	99.0±7.4
Cyclosporine A	92.1±8.8	100±1.9
Ritonavir	101±1	100±2.9
Bendroflumethiazide	99.2±6.3	115±3
Doxazosin	85.3±31	113±5
Ezetimibe	87.8±3.5	110±6
Simvastatin	93.3±2.2	123±4
Nitrendipine	97.8±3.6	107±6
Itraconazole	127±10	122±9
Nimodipine	84.8±7.1	104±32
Reserpine	135±16	141±0
Ketoconazole	86.8±12	126±6
Isradipine	85.8±5.4	133±0.4
Rosuvastatin	106±10	117±3
Nefazodone	93.5±1.2	129±9
Losartan	95.4±36	106±2
Nateglinide	100±4	108±8
Sulconazole	123±6	169±0
Indomethacin	98.8±7.0	131±1
Nifedipine	97.9±3.6	84.5±1.4

Candesartan	96.3±5.8	88.9±3.8
Cerivastatin	112±11	126±7
Tioconazole	122±7	107±21
Lovastatin	96.9±5.5	144±3
Fenofibrate	131±19	79.2±5.4
Naproxen	89.8±2.1	137±7
Sulfanilamide	80.6±6.8	143±1
Methylprednisolone	97.0±5.1	104±7
Budesonide	86.1±30	126±5
Prochlorperazine	83.3±2.6	91.6±1.3
Furosemide	87.2±9.3	111±7
Nicardipine	89.9±6.7	140±1
Raloxifene HCl	166±31	80.4±8.0
Cimetidine	97.0±24	117±3
Prednisolone	89.2±8.3	153±5
Chloroquine	95.1±3.3	120±8
Ketoprofen	91.9±1.2	104±5
Metronidazole	87.3±13	115±5
Procainamide HCl	175±25	144±5
Famotidine	97.8±9.6	120±3
Propafenone HCl	85.8±3.9	129±6
Triamterene	147±34	175±2
Econazole	101±4	106±4
Olmesartan	99.2±3.1	136±5
Probenecid	91.0±2.8	130±2
Diltiazem	92.4±4.2	120±6

Ethosuximide	98.2±5.5	106±1
Miconazole	92.0±31	113±6
Imatinib	165±15	119±1
Chlorpromazine	94.3±5.3	102±8
Abacavir	97.9±1.3	123±10
Quinine	86.0±4.8	136±4
Sulfinpyrazone	104±9	83.3±1.5
Nafcillin	80.6±6.3	91.1±11
Acarbose	96.5±3.7	127±11
Aztreonam	85.5±3.1	107±12
Bortezomib	105±1	102±5
Cefaclor	97.9±3.9	95.4±8.7
Daunorubicin	108±10	124±3
Dibucaine	101±10	130±1
Eletriptan	96.3±2.0	83.9±0.3
Enalapril	100±6	84.0±7.8
Eprosartan	83.8±11	107±0
Formoterol	95.6±9.6	102±14
Omeprazole	101±4	131±8
Oseltamivir	96.6±1.6	95.3±8.9
Oxiconazole	90.5±0.2	140±9
Ropinirole	102±8	92.2±16
Thiothixene	103±8	136±8
Valsartan	111±38	77.9±5.7
Warfarin	105±4	135±6

Table S10. SAR of angiotensin II antagonists and mapping to pharmacophore.

Compounds	**Est K_i (µM)**	**Chemical structure**	**Pharmacophore mapping**
Irbesartan	12.0±1.6		
Losartan	105±9		
Candesartan	145±44		

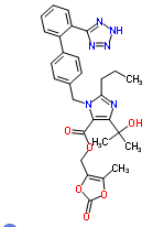
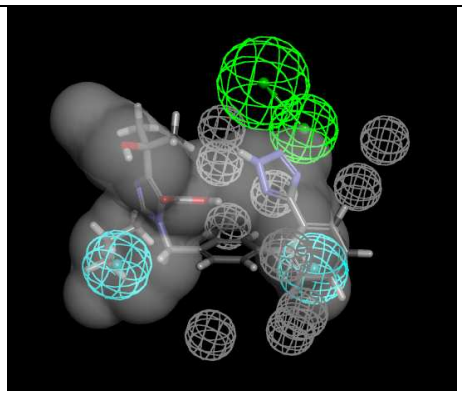
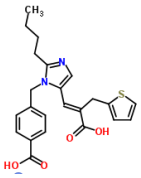
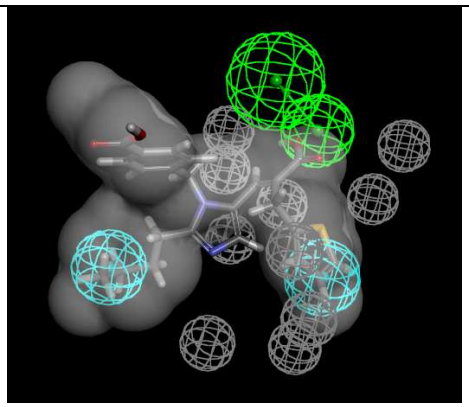
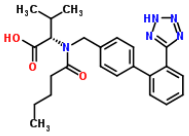
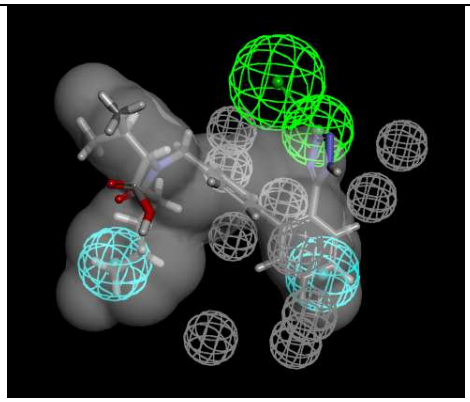
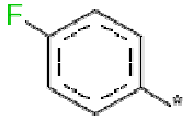
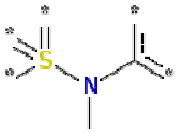
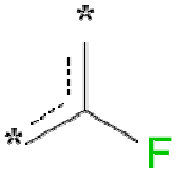
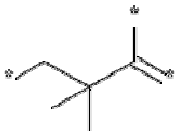
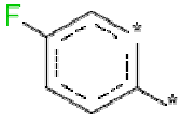
Olmesartan	422±204		
Eprosartan	3000		
Valsartan	3000		

Table S11. NTCP binding features from Bayesian analysis. Both good and bad features are identified.

Good features from FCFP_6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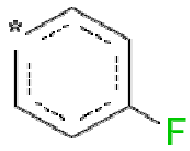	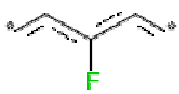	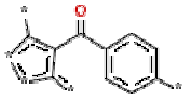	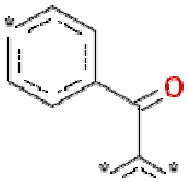	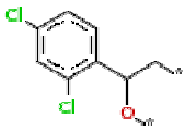
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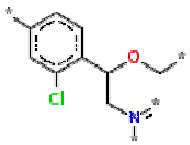	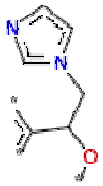	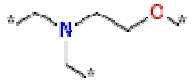	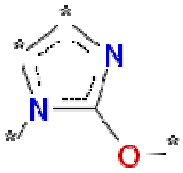	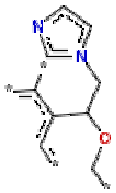
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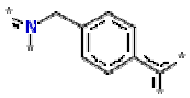	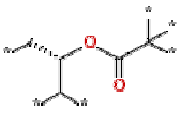	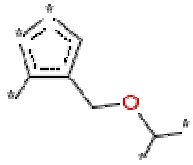	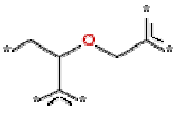	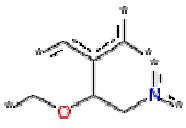
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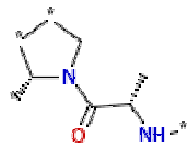
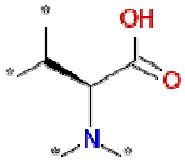
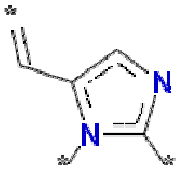
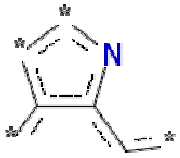
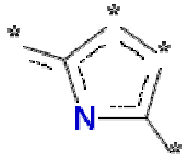
Bad features from FCFP_6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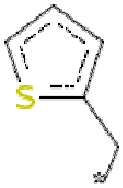	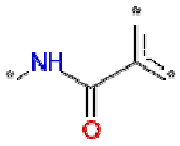	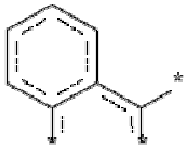	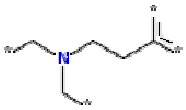	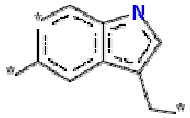
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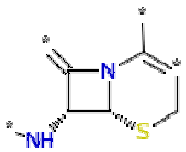	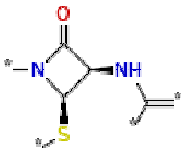	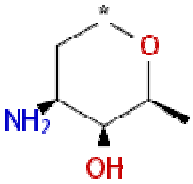	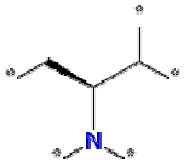	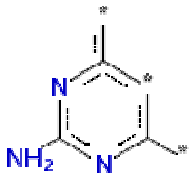
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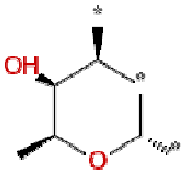	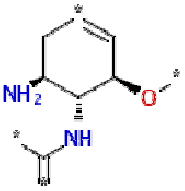	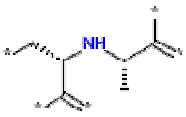	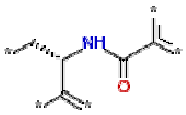	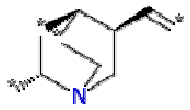
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Table S12. Percent taurocholate uptake at the highest drug concentration evaluated. Nine compounds reduced taurocholate uptake below 50%. Compounds are listed in same order at Table 5.

Compound	**Percent taurocholate uptake** [a]
Cyclosporine A	24.0±1.9
Irbesartan	7.4±0.7
Ritonavir	27.0±1.2
Bendroflumethiazide	28.3±2.2
Doxazosin	58.1±1.9
Ezetimibe	43.1±1.7
Simvastatin	31.8±1.1
Nitrendipine	75.2±0.4
Nimodipine	63.2±1.9
Ketoconazole	59.1±3.0
Nefazodone	38.2±5.6
Rosuvastatin	51.8±2.8
Losartan	36.1±1.8
Nateglinide	72.9±4.5
Indomethacin	51.4±0.6
Nifedipine	43.3±2.1
Candesartan	67.3±3.5
Tioconazole	82.1±6.0
Fenofibrate	65.5±6.3
Methylprednisolone	67.3±1.1
Budesonide	61.4±3.1

Prochlorperazine	63.6±3.5
Raloxifene HCl	91.9±2.7
Ketoprofen	74.0±5.7
Olmesartan	70.9±0.3
Probenecid	75.2±3.4
Diltiazem	74.0±0.5

[a] Compound concentrations were 50μM (cyclosporine A, doxazosin, ezetimibe, nitrendipine, tioconazole, raloxifene HCl), 100μM(ritonavir, ketoconazole, nateglinide, Fenofibrate), 200μM (irbesartan, bendroflumethiazide, simvastatin, nimodipine, nefazodone, rosuvastatin, losartan, indomethacin, nifedipine, candesartan, methylprednisolone, budesonide, prochlorperazine, olmesartan), or 250μM (ketoprofen, probenecid, diltiazem).

Figure S1. Uptake of taurocholate into NTCP-HEK293 cells. In NTCP transfected cells with sodium, taurocholate uptake exhibited nonlinear kinetics. In the absence of sodium, uptake into NTCP transfected cells was low and linear. Curves are simultaneous fits to a) the Michaelis-Menten model with a passive uptake component and b) the passive uptake component only. Fitted kinetic parameters were: K_m = 22.7(±3.4) μM, V_{max} = 1.80(±0.03) pmol/sec/cm^2, and passive permeability Pp = 1.27(±0.03)x10^{-6} cm/sec. Also plotted are uptakes into mock-transfected HEK293 cells with and without sodium, which were low and similar to uptake into NTCP transfected cells without sodium.

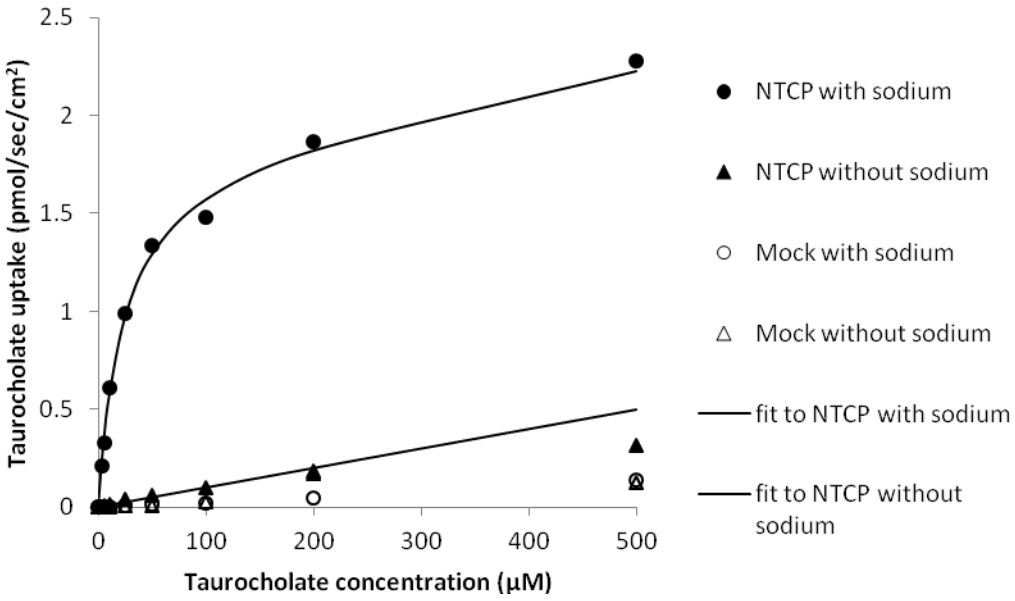
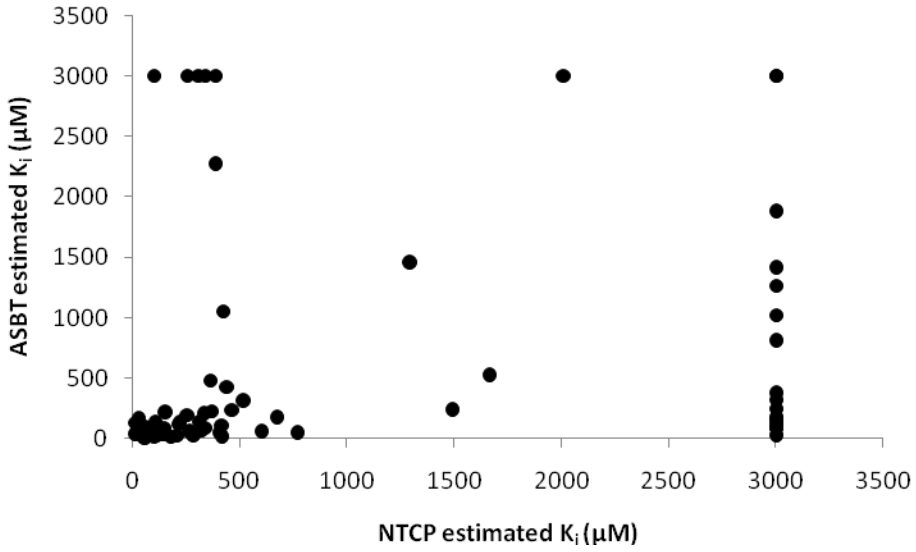
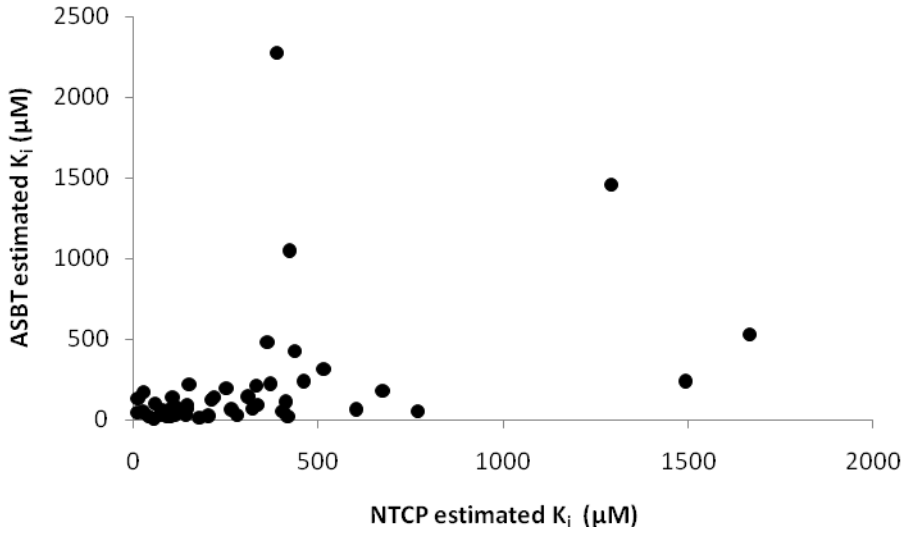


Figure S2. Correlation between ASBT inhibition and NTCP inhibition. The ASBT estimated K_i was plotted against NTCP estimated K_i. In panel A, all 72 drugs were plotted, including when K_i assigned a value of 3000 μM. In panel B, only drugs with both estimated K_i's less than 3000 μM were plotted (i.e. lowers taurocholate uptake to 95% or less for each transporter). In panel C, only drugs with both estimated K_i's less than 500 μM were plotted.

Panel A of Figure S2



Panel B of Figure S2



Panel C of Figure S2

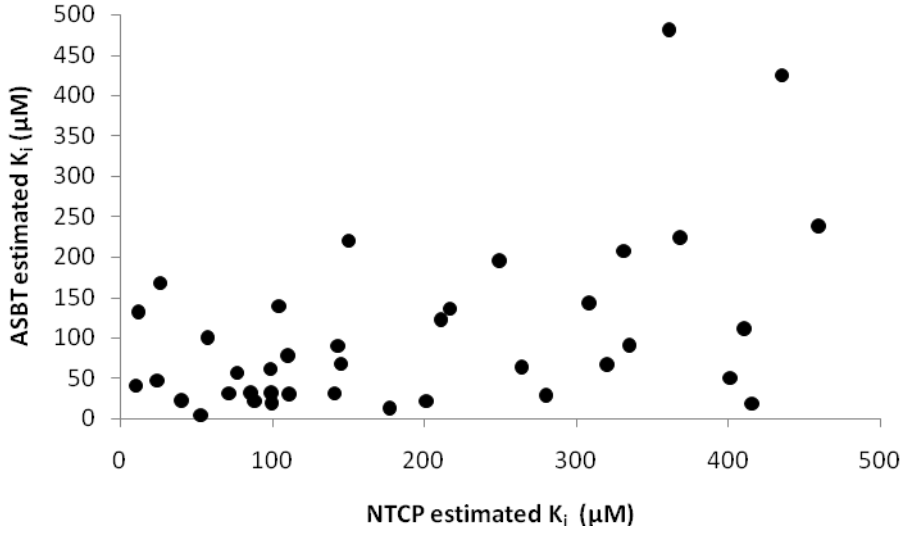


Figure S3. Correlation between NTCP observed K_i and estimated K_i for 27 drugs used in the common feature pharmacophore. Observed K_i employed data using seven drug concentrations that spanned 0-200 μM. Estimated K_i was calculated from screening data (i.e. only one drug concentration). Linear regression yielded a slope of 0.937 ($\pm$0.104) and r^2=0.763.

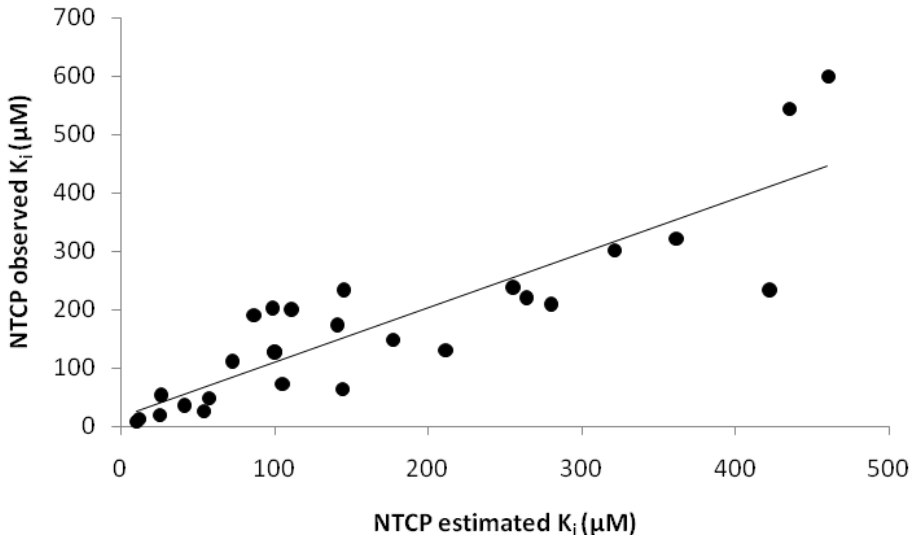


Figure S4. Principal component analysis of CDD FDA approved drug space (blue) and compounds tested against NTCP (yellow) using ALogP, molecular weight, number of H-bond donors, number of H-bond acceptors, number of rotatable bonds, number of rings, number of aromatic rings and molecular fractional polar surface area calculated with Discovery Studio 3.5. Three principal components explain 81.3% of the variance.

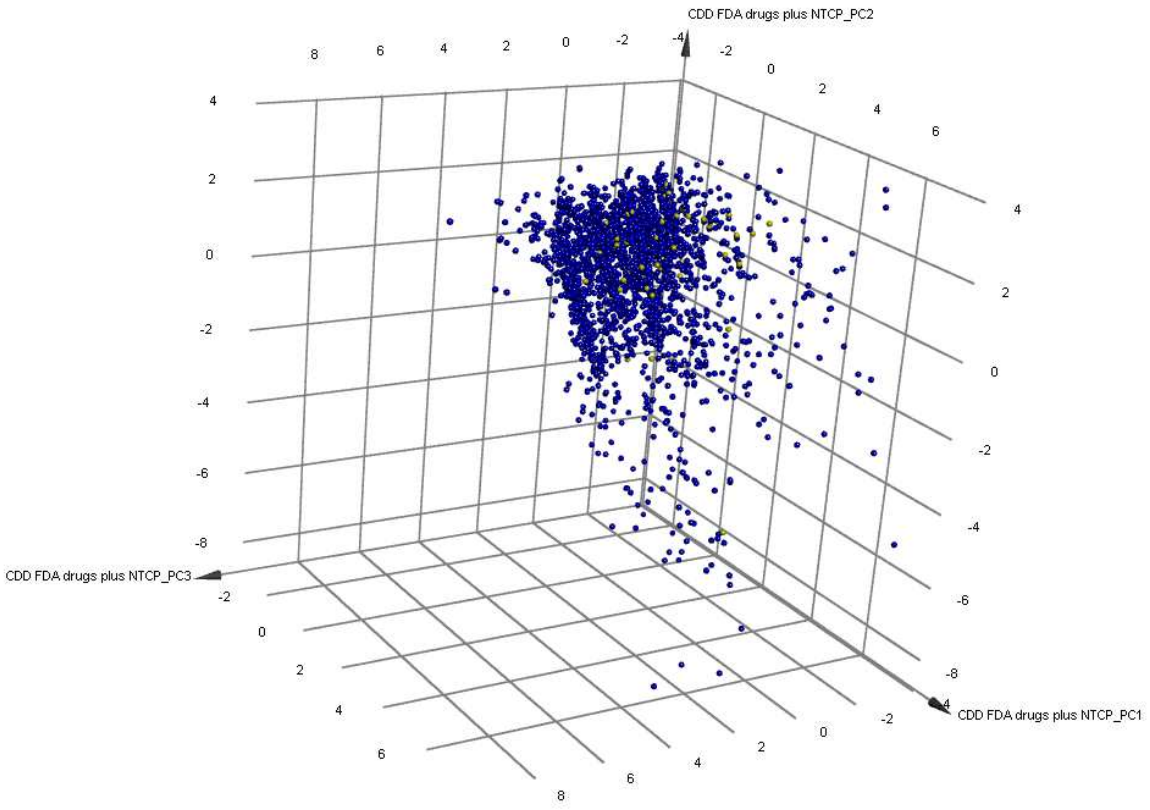
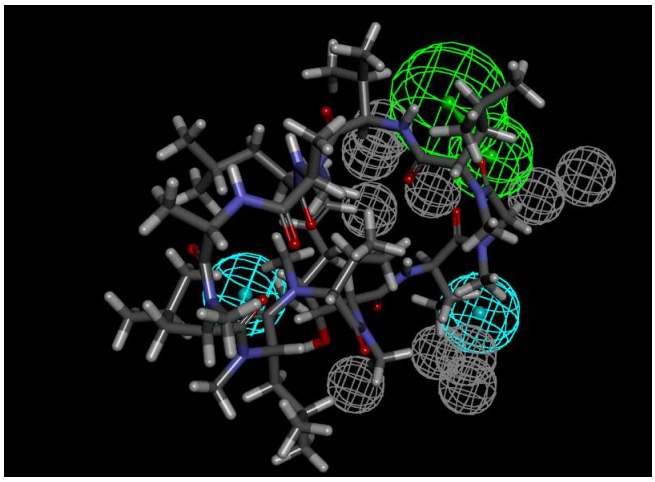


Figure S5. Cyclosporine A and ritonavir were mapped to common feature pharmacophore without ezetimibe shape. In panel A, cyclosporine A was mapped to the pharmacophore after the ezetimibe shape was removed. The fit value of the cyclosporine A was 0.45. In panel B, ritonavir was mapped to the pharmacophore after removing the ezetimibe shape. The fit value of the ritonavir was 2.08.

Panel A of Figure S5



Panel B of Figure S5