

Combinatorial Pharmacophore Modeling of Multidrug and Toxin Extrusion Transporter 1 Inhibitors: a Theoretical Perspective for Understanding Multiple Inhibitory Mechanisms

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Supplementary Table S1. Candidate pharmacophore hypotheses used for constructing CP model.

In.	Hypothesis	Survival score	Survival-inactive score	Selectivity score	Train_in	Train_non	Test_in	Test_non
1	HHR1*	2.88	2.68	1.10	10	47	12	58
2	HHR2*	2.95	2.89	0.97	8	15	7	21
3	HHR3	2.79	2.22	1.54	8	26	3	20
4	HHR4	3.01	2.89	1.01	11	31	9	28
5	HHH	2.00	1.91	0.88	9	42	7	50
6	DRR*	2.74	2.60	1.02	11	33	11	36
7	DHR1	2.71	2.52	1.12	9	51	9	43
8	DHR2	2.88	2.18	1.04	9	16	7	16
9	ARR	3.07	2.99	1.00	10	20	11	32
10	APR	2.87	2.74	1.25	11	31	14	26
11	AHP	2.92	2.85	1.11	7	15	5	13
12	AHH	2.96	2.78	1.09	6	42	8	54
13	ADR	2.92	2.80	1.04	12	35	13	24
14	ADH1	2.91	2.77	1.09	12	35	8	36
15	ADH2	2.89	2.80	1.07	10	25	5	23
16	AAR	2.81	2.68	0.94	11	35	12	36
17	AAP	2.99	2.91	1.31	8	15	5	16
18	HHHR	2.59	2.19	1.49	7	21	2	23
19	DHHR	2.33	1.72	1.55	6	22	6	35
20	DDHR	2.37	1.75	1.48	7	41	5	33
21	AHPR	3.00	2.74	1.65	7	8	5	8
22	AHHR1	2.71	1.99	1.49	7	33	6	35
23	AHHR2	2.63	1.97	1.50	7	32	6	36
24	AAHP	2.98	2.27	1.56	11	21	7	21
25	AAAP1*	3.06	2.42	1.62	11	22	7	24
26	AAAP2	3.07	2.41	1.59	9	23	7	21
27	AAHHR	2.43	1.41	1.74	8	37	7	31

Train_in: The number of matched inhibitors in training set.

Train_non: The number of matched noninhibitors in training set.

Test_in: The number of matched inhibitors in test set.

Test_non: The number of matched noninhibitors in test set.

*The hypotheses consist of the final CP model.

Supplementary Table S2. The site distances of single pharmacophore hypotheses comprising the obtained CP model.

Hypothesis	Site1	Site2	Distance(Å)
HHR1	H2	H1*	2.918
	H2	R1	3.789
	H1	R1	3.240
DRR	D1	R1	8.614
	D1	R2	3.241
	R1	R2	7.251
HHR2	H2	H1	6.348
	H2	R1	9.566
	H1	R1	13.153
AAAP	A1	A2	4.575
	A1	A3	4.228
	A1	P1	8.994
	A2	A3	5.347
	A2	P1	11.229
	A3	P1	7.517

*The feature numbers are used to distinguish the same type of features in the same hypothesis.

Supplementary Table S3. The site angles of single pharmacophore hypotheses comprising the obtained CP model.

Hypothesis	Site1	Site2	Site3	Angle(degree)
HHR1	H1*	H2	R1	56.0
	H2	H1	R1	75.7
	H2	R1	H1	48.3
DRR	R1	D1	R2	54.9
	D1	R1	R2	21.4
	D1	R2	R1	103.7
HHR2	H1	H2	R1	109.8
	H2	H1	R1	43.2
	H2	R1	H1	27.0
AAAP	A2	A1	A3	74.7
	A2	A1	P1	107.2
	A4	A1	P1	56.2
	A1	A2	A3	49.7
	A1	A2	P1	49.9
	A3	A2	P1	35.2
	A1	A3	A2	55.6
	A1	A3	P1	95.9
	A2	A3	P1	120.7
	A1	P1	A2	22.9
	A1	P1	A3	27.9
	A2	P1	A3	24.2

*The feature numbers are used to distinguish the same type of features in the same hypothesis.

Supplementary Table S4. The spatial arrangements of HHR4 in OCT2 CP model ¹.

Hypothesis	Site1	Site2	Distance (Å)
HHR4	H1*	H2	5.78
	H1	R	2.95
	H2	R	3.89

*The feature numbers are used to distinguish the same type of features in the same hypothesis.

Supplementary Table S5. The list of all compounds used in this study

No	Name	Inhibitor (Yes/No)	PubChem ID
1	1-(2-Chlorobenzoyl)-4-(Phenylmethyl)-Piperidine	Y	667590
2	Alpha-ERGOCRYPTINE	Y	99049
3	Amiloride	Y	16231
4	Amlodipine	Y	2162
5	Antimycin A	Y	12550
6	Azelastine	Y	2267
7	Bazedoxifene	Y	154257
8	Benzethonium Chloride	Y	8478
9	Bexarotene	Y	82146
10	Bithionol	Y	2406
11	Buspirone	Y	2477
12	Caffeic Acid Phenethyl Ester	Y	108042
13	Camostat	Y	2536
14	Cetylpyridinium Bromide	Y	8816
15	Chlorhexidine	Y	62517
16	Ciclopirox	Y	2749
17	Cimetidine	Y	2756
18	Closantel	Y	42574
19	Danazol	Y	28417
20	Dihydroergocristine Mesylate	Y	444034
21	Dihydroergotamine	Y	3066
22	Domperidone	Y	3151
23	Doxazosin	Y	3157
24	Droperidol	Y	3168
25	D-Tubocurarine Chloride	Y	6000
26	Epinastine	Y	3241
27	Ergocornine	Y	3067
28	Ergonovine	Y	443884
29	Ergotamine	Y	3251
30	Ethinylestradiol	Y	5991
31	Famotidine	Y	3325
32	Fenbendazole	Y	3334
33	Gabexate	Y	3447
34	Genistein	Y	5280961
35	Gentian Violet	Y	3468
36	Granisetron	Y	3510
37	Guanfacine	Y	3519
38	Hexachlorophene	Y	3598
39	Idebenone	Y	3686
40	Imatinib	Y	5291
41	Indinavir	Y	60944
42	Kitasamycin	Y	5282189
43	L-744832	Y	6451153
44	Lamotrigine	Y	3878
45	Loperamide	Y	3955
46	Maprotiline	Y	4011
47	Mechlorethamine	Y	4033

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48	Medroxyprogesterone Acetate	Y	6279
49	Megestrol Acetate	Y	11683
50	Mestranol	Y	6291
51	Metergoline	Y	28693
52	Methylene Blue	Y	4139
53	Mitoxantrone	Y	4212
54	Mosapride	Y	119584
55	Niacin	Y	938
56	Nifekalant	Y	4486
57	Norethindrone Acetate	Y	5832
58	Norgestrel	Y	13109
59	Ondansetron	Y	4595
60	Oxymetazoline	Y	4636
61	Oxytocin	Y	439302
62	Pantoprazole	Y	4679
63	Pentamidine	Y	4735
64	Perospirone	Y	115368
65	Phenacetin	Y	4754
66	Podophyllotoxin	Y	10607
67	Prazosin	Y	4893
68	Propoxyphene	Y	10100
69	Rimantadine	Y	5071
70	Ritonavir	Y	392622
71	Rwj-68354	Y	9819053
72	Salicylic Acid	Y	338
73	Selegiline	Y	5195
74	Sildenafil	Y	5212
75	Sulfacetamide	Y	5320
76	Sulindac Sulfide	Y	5352624
77	Tannic Acid	Y	250395
78	Terconazole	Y	441383
79	Thiabendazole	Y	5430
80	Topotecan	Y	60700
81	Trazodone	Y	5533
82	Tropisetron	Y	656665
83	Vecuronium Bromide	Y	39764
84	Zafirlukast	Y	5717
85	(-)-Thalidomide	N	92142
86	(+)-Thalidomide	N	75792
87	(R)-Bicalutamide	N	2375
88	(S)-(-)-Pindolol	N	688095
89	1-(2-Fluorobenzoyl)-4-(Phenylmethyl)-Piperidine	N	667749
90	1-(2-Methoxybenzoyl)-4-(Phenylmethyl)-Piperidine	N	667750
91	1-(2-Methylbenzoyl)-4-(Phenylmethyl)-Piperidine	N	1379258
92	1,3-Diphenylguanidine	N	7594
93	10,11-Dihydro-Carbamazepine	N	19099
94	17-Methyltestosterone	N	6010
95	1-Aminobenzotriazole	N	1367
96	1-Benzylimidazole	N	77918

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97	1-Naphthyl Isothiocyanate	N	11080
98	2-Acetylaminofluorene	N	5897
99	2-HYDROXYPROPYL-Beta-CYCLODEXTRIN	N	44134771
100	2-Mercaptobenzothiazole	N	697993
101	3,3',4',5-Tetrachlorosalicylanilide	N	14385
102	3-Acetamidophenol	N	12124
103	3-Aminobenzamide	N	1645
104	4-(Phenylmethyl)-1-[2-(Trifluoromethyl)Benzoyl]-Piperidine	N	17683252
105	4,4'-Diethylaminoethoxyhexestrol	N	66143
106	4-Amino-1,8-Naphthalimide	N	1720
107	4-Methylpyrazole	N	3406
108	4-Nitrobenzoic Acid	N	6108
109	4-Nonylphenol	N	1752
110	4-Octylphenol	N	15730
111	5-Fluoro-2'-Deoxyuridine	N	5790
112	6(5h)-Phenanthridinone	N	1853
113	6-Mercaptopurine	N	667490
114	6-Methoxy-2-Naphthylacetic Acid	N	32176
115	8-Azaguanine	N	8646
116	Acarbose	N	41774
117	Aceclofenac	N	71771
118	Acemetacin	N	1981
119	Acetaminophen	N	1983
120	Acetazolamide	N	1986
121	Acetylcholine Chloride	N	6060
122	Acetylcysteine	N	12035
123	Aclarubicin	N	2008
124	Aconitine	N	2012
125	Actarit	N	2018
126	Acyclovir	N	2022
127	Adapalene	N	60164
128	Adrenosterone	N	223997
129	Albendazole	N	2082
130	Alfacalcidol	N	2091
131	Allopurinol	N	2094
132	Alpha-CYCLODEXTRIN	N	24796
133	Alpha-CYPERMETHRIN	N	49833
134	Alpha-NAPHTHOFLAVONE	N	11790
135	Alprazolam	N	2118
136	Alprenolol	N	2119
137	Alprostadi	N	5280723
138	Aluminum Lactate	N	92422
139	Amantadine	N	2130
140	Ambroxol	N	2132
141	Aminacrine	N	7019
142	Amineptine	N	34870
143	Aminoglutethimide	N	2145
144	Aminopterin	N	169371
145	Aminosalicylic Acid	N	4649

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146	Amiodarone	N	2157
147	Amitraz	N	36324
148	Amitriptyline	N	2160
149	Amorolfine	N	2168
150	Amphotericin B	N	14956
151	Ampiroxicam	N	2176
152	Amprenavir	N	44342222
153	Amrinone	N	3698
154	Amsulosin	N	121829
155	Amygdalin(D)	N	2180
156	Anastrozole	N	2187
157	Androsterone	N	5879
158	Aniracetam	N	2196
159	Anisindione	N	2197
160	Antazoline	N	2200
161	Antipyrine	N	2206
162	Artemether	N	68911
163	Artemisinin	N	68827
164	Ascorbic Acid	N	54670067
165	Aspirin	N	2244
166	Astemizole	N	2247
167	Atenolol	N	2249
168	Atractyloside	N	2255
169	Atropine	N	3661
170	Auranofin	N	6918453
171	Azacitidine	N	9444
172	Azaribine	N	16574
173	Azaserine	N	830
174	Azathioprine	N	2265
175	Azauridine	N	5901
176	Azelaic Acid	N	2266
177	Azithromycin	N	55185
178	Azlocillin	N	2271
179	Aztreonam	N	2274
180	Bacitracin	N	2283
181	Balsalazide	N	5362070
182	Bay 11-7085	N	6603741
183	Beclomethasone	N	20469
184	Beclomethasone Dipropionate	N	21700
185	Bemegride	N	2310
186	Benazepril	N	5362124
187	Bendazac	N	2313
188	Bendroflumethiazide	N	2315
189	Benoxaprofen	N	39941
190	Benoxinate	N	4633
191	Benserazide	N	2327
192	Benzo[A]Pyrene	N	2336
193	Benzo[E]Pyrene	N	9128
194	Benzoic Acid	N	243

(Continued)

195	Benztropine	N	441353
196	Benzyl Alcohol	N	244
197	Beta Cyclodextrin	N	444294
198	Beta-ESTRADIOL	N	5757
199	Beta-ESTRADIOL 3-BENZOATE	N	222757
200	Betahistine	N	2366
201	Betaine	N	247
202	Betamethasone	N	9782
203	Betamipron	N	71651
204	Beta-NAPHTHOFLAVONE	N	2361
205	Bezafibrate	N	39042
206	Bifonazole	N	2378
207	Bisacodyl	N	2391
208	Bisphenol A	N	6623
209	Bopindolol	N	44112
210	Boric Acid	N	7628
211	Bretylum Tosylate	N	2431
212	Brilliant Green	N	12450
213	Brimonidine	N	2435
214	Bromfenac	N	60726
215	Bromhexine	N	2442
216	Bromisovalum	N	1176
217	Brompheniramine	N	6834
218	Budesonide	N	5281004
219	Bufexamac	N	2466
220	Buflomedil	N	2467
221	Buformin	N	2468
222	Bupivacaine Hydrochloride	N	64737
223	Bupropion	N	444
224	Busulfan	N	2478
225	Butamben	N	2482
226	Butenafine	N	2484
227	Butylparaben	N	7184
228	C8 Ceramide	N	5702614
229	Cadmium Acetate	N	10986
230	Caffeine	N	2519
231	Calcitriol	N	2524
232	Candesartan	N	2541
233	Cantharidin	N	2545
234	Capsaicin	N	2548
235	Captopril	N	2550
236	Carbachol	N	2551
237	Carbamazepine	N	2554
238	Carbimazole	N	31072
239	Carbinoxamine	N	2564
240	Carisoprodol	N	2576
241	Carmofur	N	2577
242	Carmustine	N	2578
243	Carvedilol	N	2585

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244	Cefdinir	N	6398970
245	Cefixime	N	2675
246	Cefmetazole	N	2626
247	Cefotaxime	N	2632
248	Cefpodoxime Proxetil	N	441393
249	Cefuroxime	N	2659
250	Celecoxib	N	2662
251	Cerivastatin	N	2676
252	Cetirizine	N	2678
253	Cetraxate	N	2680
254	Chlordiazepoxide	N	2712
255	Chlormadinone Acetate	N	9324
256	Chlorobutanol	N	5977
257	Chlorothiazide	N	2720
258	Chloroxylenol	N	2723
259	Chlorphenesin Carbamate	N	2724
260	Chlorpheniramine	N	2725
261	Chlorpromazine	N	2726
262	Chlorpropamide	N	2727
263	Chlorprothixene	N	2729
264	Chlorquinaldol	N	6301
265	Chlorzoxazone	N	2733
266	Cholecalciferol	N	5283711
267	Cholic Acid	N	221493
268	Choline Chloride	N	6209
269	Cilostazol	N	2754
270	Cinnamaldehyde	N	307
271	Cinnarizine	N	2761
272	Cisapride	N	2769
273	Citalopram	N	2771
274	Citric Acid	N	311
275	Cladribine	N	1546
276	Clarithromycin	N	54688
277	Clebopride	N	2780
278	Clenbuterol	N	2783
279	Clidinium Bromide	N	19004
280	Clioquinol	N	2788
281	Clobetasol Propionate	N	32798
282	Clofibric Acid	N	2797
283	Clomacran	N	21382
284	Clomiphene	N	60974
285	Clomipramine	N	2801
286	Clonazepam	N	2802
287	Clonidine	N	2803
288	Clopidogrel	N	2806
289	Clorprenaline	N	2810
290	Clotrimazole	N	2812
291	Cloxacillin	N	6098
292	Clozapine	N	2818

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293	Cobalt(Ii) Acetylacetonate	N	407383
294	Cocculin	N	5311359
295	Colchicine	N	6167
296	Colistin	N	73091
297	Cortisone	N	5753
298	Coumarin	N	323
299	Cromolyn	N	2882
300	Crotamiton	N	6604255
301	Cyclandelate	N	2893
302	Cyclobenzaprine	N	2895
303	Cycloheximide	N	6197
304	Cyclophosphamide	N	2907
305	Cyproheptadine	N	2913
306	Cyproterone Acetate	N	9880
307	Cyromazine	N	47866
308	Cytarabine	N	6253
309	Dacarbazine	N	5281007
310	Dactinomycin	N	2019
311	Dapiprazole	N	3033538
312	Dapsone	N	2955
313	Daunorubicin	N	30323
314	D-Camphor	N	159055
315	Deferoxamine	N	2973
316	Dehydrocholic Acid	N	6674
317	Dequalinium Chloride	N	2993
318	Desipramine	N	2995
319	Deslanoside	N	2996
320	Desloratadine	N	124087
321	Desoximetasone	N	5311067
322	Dexamethasone	N	5743
323	Dexamethasone Phosphate	N	9400
324	Dexbrompheniramine	N	16960
325	Dexchlorpheniramine	N	33036
326	Dexfenfluramine	N	65801
327	Dexibuprofen	N	39912
328	Dexketoprofen	N	667550
329	Dexpanthenol	N	131204
330	Dextromethorphan	N	5362449
331	D-Galactosamine	N	2794221
332	Diazepam	N	3016
333	Diazoxide	N	3019
334	Dibucaine	N	3025
335	Dichlorvos	N	3039
336	Diclofenac	N	3033
337	Dicyclomine	N	3042
338	Didanosine	N	3043
339	Dideoxycytidine	N	24066
340	Dieldrin	N	969491
341	Diethylcarbamazine	N	3052

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342	Diethylstilbestrol	N	448537
343	Diflorasone Diacetate	N	71414
344	Diflunisal	N	3059
345	Digitonin	N	25444
346	Digitoxin	N	3061
347	Digoxin	N	3062
348	Diltiazem	N	39186
349	Dimenhydrinate	N	10660
350	Diphenhydramine	N	3100
351	Diphenidol	N	3055
352	Dipyridamole	N	3108
353	Disopyramide	N	3114
354	Disulfiram	N	3117
355	Dobutamine	N	36811
356	Docetaxel	N	64780
357	Donepezil	N	3152
358	Doxapram	N	3156
359	Doxepin	N	667477
360	Doxifluridine	N	3159
361	Doxofylline	N	50942
362	Doxorubicin	N	31703
363	Doxycycline	N	373075
364	Dyclonine Hydrochloride	N	3180
365	Dyphylline	N	3182
366	Ebastine	N	3191
367	Econazole	N	3198
368	Edaravone	N	4021
369	Edrophonium Chloride	N	8307
370	Efavirenz	N	3203
371	Emetine	N	10219
372	Enalapril	N	5362032
373	Enrofloxacin	N	71188
374	Epalrestat	N	1549120
375	Eperisone	N	3236
376	Epirubicin	N	41867
377	Erythromycin	N	3255
378	Erythromycin Propionate	N	3258
379	Esmolol	N	59768
380	Estriol	N	5756
381	Estrone	N	5870
382	Ethacrynic Acid	N	3278
383	Ethambutol	N	3279
384	Ethionamide	N	3284
385	Ethisterone	N	5284557
386	Ethosuximide	N	3291
387	Ethylenediamine	N	3301
388	Ethylestrenol	N	13765
389	Ethylparaben	N	8434
390	Ethynodiol Diacetate	N	9270

(Continued)

391	Etodolac	N	3308
392	Etoposide	N	3310
393	Eucalyptol (Cineole)	N	2758
394	Exemestane	N	60198
395	Felbinac	N	3332
396	Felodipine	N	3333
397	Fenbufen	N	3335
398	Fenofibrate	N	3339
399	Fenoprofen	N	3342
400	Ferulic Acid	N	709
401	Fexofenadine	N	3348
402	Finasteride	N	57363
403	Fluconazole	N	3365
404	Flucytosine	N	3366
405	Fludarabine	N	30751
406	Fludrocortisone Acetate	N	225609
407	Flufenamic Acid	N	3371
408	Flumazenil	N	3373
409	Flunarizine	N	941361
410	Flunisolide	N	82153
411	Flunoxaprofen	N	39940
412	Fluocinolone Acetonide	N	6215
413	Fluocinonide	N	9642
414	Fluorometholone	N	9878
415	Fluorouracil	N	3385
416	Fluoxetine	N	3386
417	Fluphenazine	N	3372
418	Flurandrenolide	N	15209
419	Flurbiprofen	N	3394
420	Folic Acid	N	3405
421	Formoterol	N	3410
422	Furazolidone	N	5323714
423	Furosemide	N	3440
424	Galantamine	N	3449
425	Gallamine Triethiodide	N	3450
426	Gamma-Cyclodextrin	N	86575
427	Ganciclovir	N	3454
428	Gemcitabine	N	3461
429	Gemfibrozil	N	3463
430	Genaconazole (RR(+)) Isomer	N	60741
431	Geraniol	N	637566
432	Gliclazide	N	3475
433	Glimepiride	N	3476
434	Glipizide	N	3478
435	Glyburide	N	3488
436	Glycolic Acid	N	757
437	Glycyrrhizin	N	14982
438	Goserelin	N	47725
439	Gramicidin	N	73357

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440	Griseofulvin	N	3512
441	Guaifenesin	N	3516
442	Guanabenz	N	3517
443	GW-1929	N	6518171
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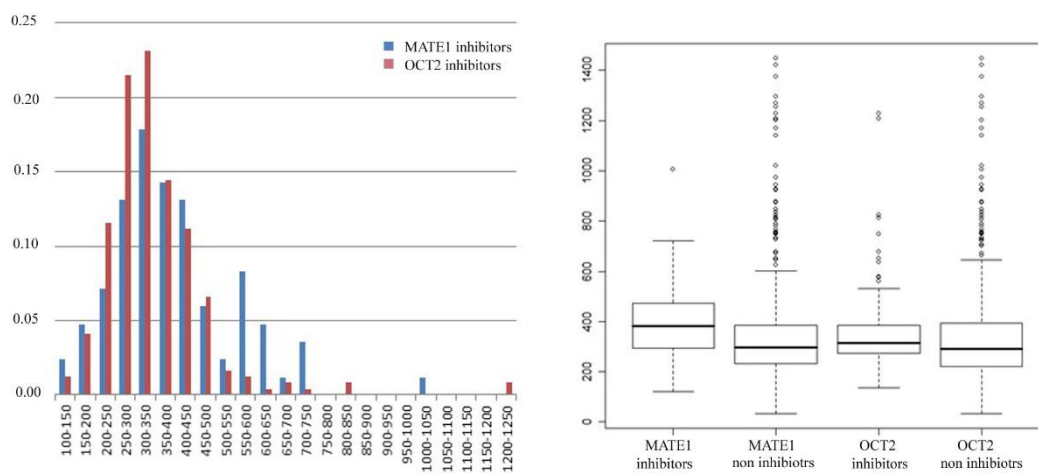
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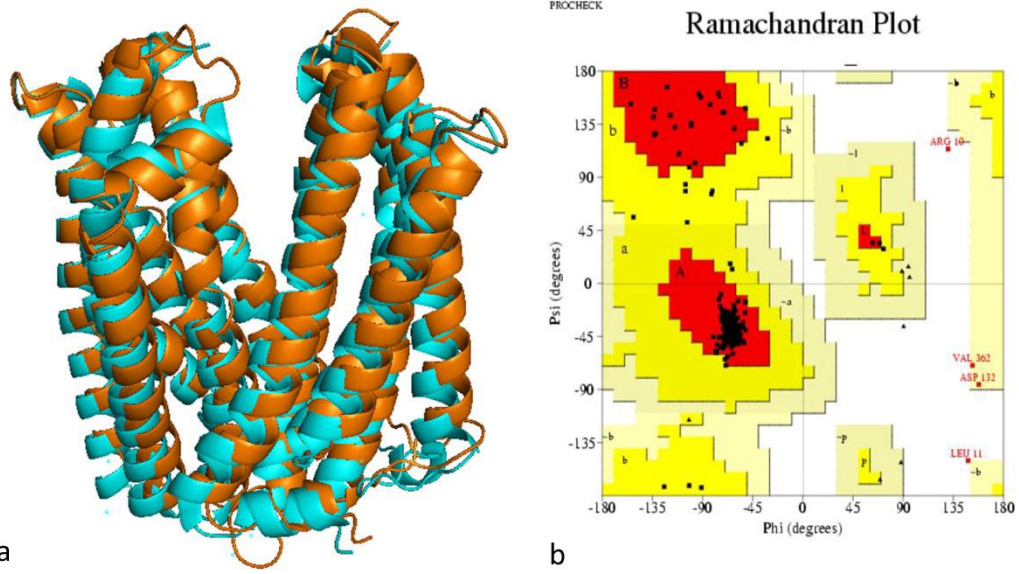
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Supplementary Figure S1. The molecular weight distribution of MATE1 and OCT2 inhibitors.



Supplementary Figure S3. The homology model of hMATE1. **a.** The structural alignment of homology model and pfMATE, where hMATE1 is in orange color, and the crystal structure of pfMATE in cyan. **b.** Ramachandran plot of homology model, where 95% residuals are in the core region.

References

- 1 Xu, Y. *et al.* Combinatorial Pharmacophore Modeling of Organic Cation Transporter 2 (OCT2) Inhibitors: Insights into Multiple Inhibitory Mechanisms. *Mol. Pharm.* **10**, 4611-4619 (2013).