gene2drug: a Computational Tool for Pathway-based Rational Drug Repositioning
Supplementary Information

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Fig. S1: Relation between PPI network-based and pathway based approaches. Given a therapeutic gene and the set of pathways it is annotated to according to the different databases, the other genes in the same pathways are topologically closer to it in the PPI network as compared to randomly chosen genes. The average shortest path from the selected gene to other pathway members is reported on the y axis for each database.
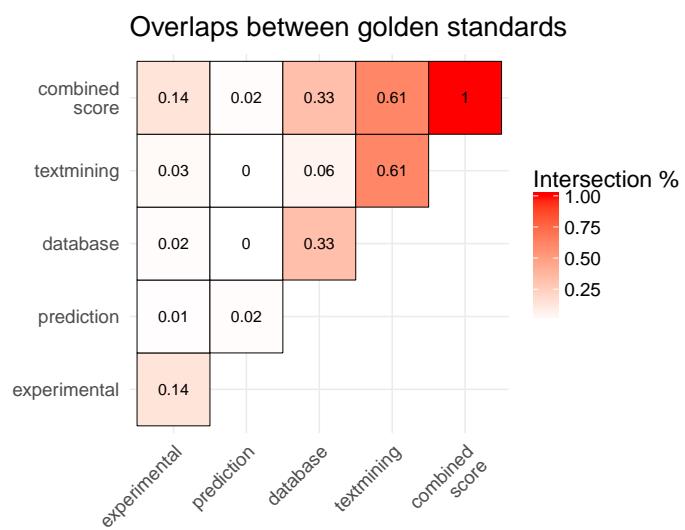
Fig. S2: Size of intersection between existent evidence scores in the STITCH database (subset matched against the Cmap database) as a percentage of the total number of evidences. Numbers on the diagonal represent how many times a drug-target evidence exists divided by the total number of reported pairs. A "combined score" always exist if one of the other evidences exist, thus "combined score" covers 100% of the pairs. Conversely, an "experimental" score is only present for 14% of the pairs. The "Text mining" evidence strongly drives the "combined score" covering 61% of all the known protein-target interactions in STITCH.
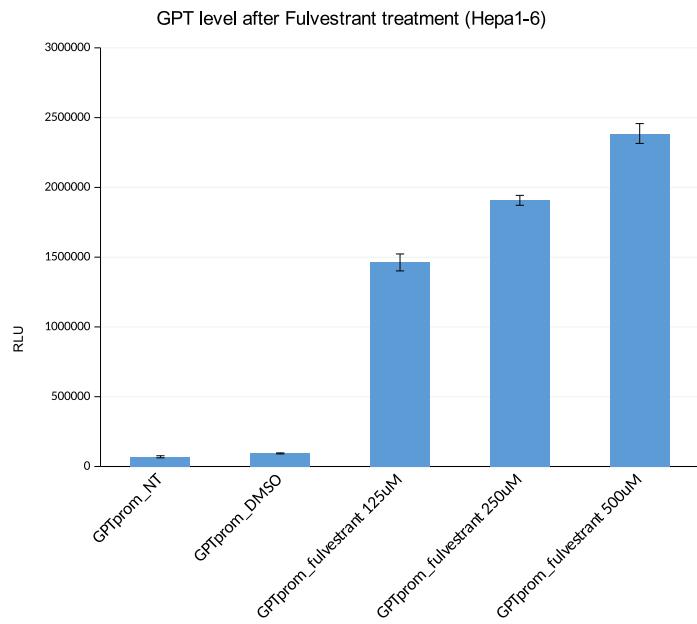
Fig. S3: Relative luminescence units (RLU) in Hepa1-6 cells transfected with a plasmid express-
ing the luciferase gene under the control of the GPT promoter and incubated with
various concentrations of fulvestrant.
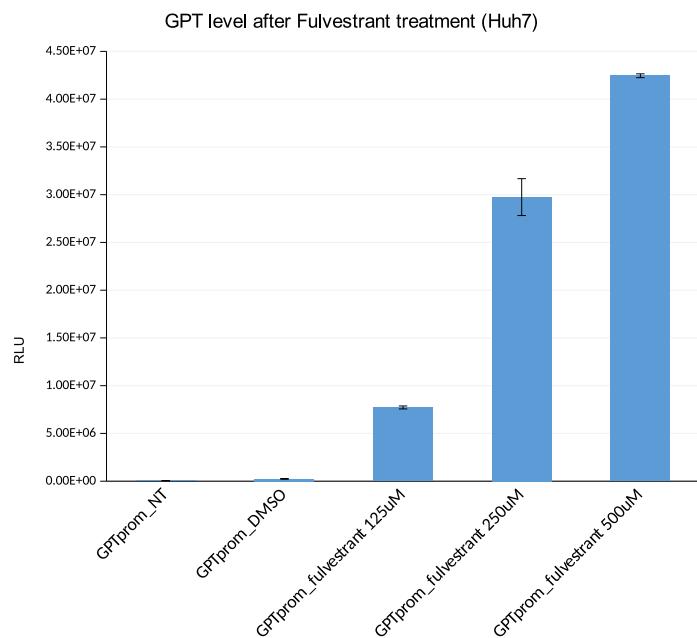
Fig. S4: Relative luminescence units (RLU) in Huh7 cells transfected with a plasmid expressing
the luciferase gene under the control of the GPT promoter and incubated with various
concentrations of fulvestrant.
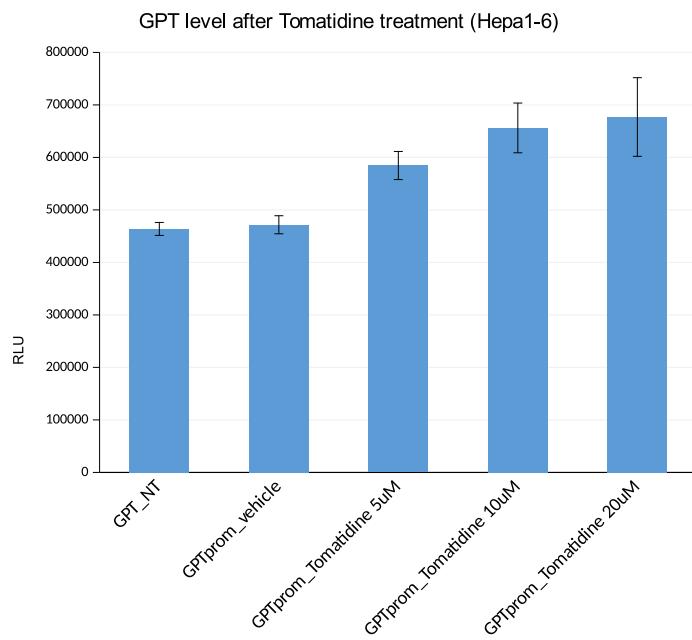
Fig. S5: Relative luminescence units (RLU) in Hepa1-6 cells transfected with a plasmid express-
ing the luciferase gene under the control of the GPT promoter and incubated with
various concentrations of tomatidine.
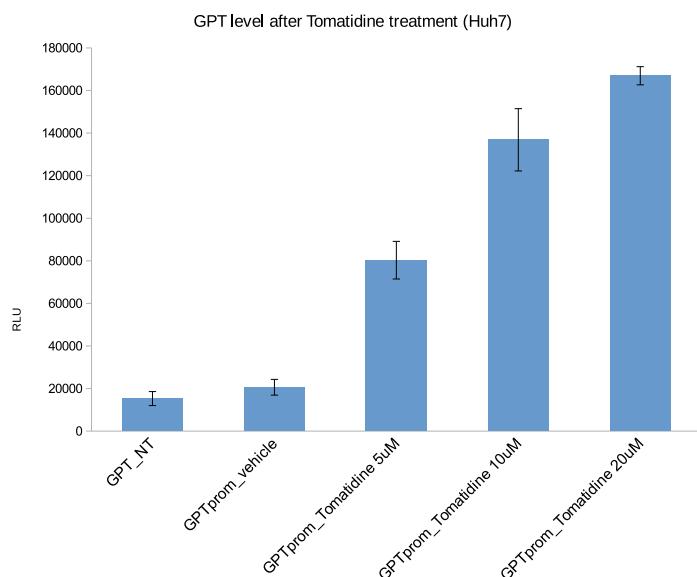
Fig. S6: Relative luminescence units (RLU) in Huh7 cells transfected with a plasmid expressing
the luciferase gene under the control of the GPT promoter and incubated with various
concentrations of tomatidine.
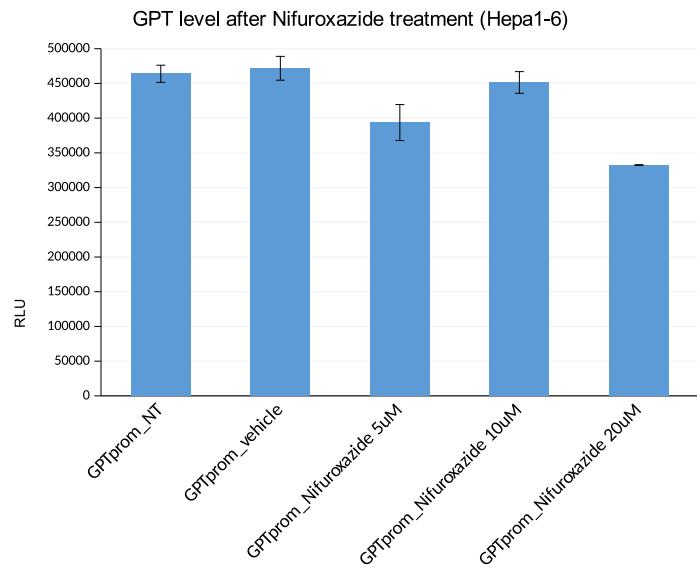
Fig. S7: Relative luminescence units (RLU) in Hepa1-6 cells transfected with a plasmid express-
ing the luciferase gene under the control of the GPT promoter and incubated with
various concentrations of nifuroxazide.
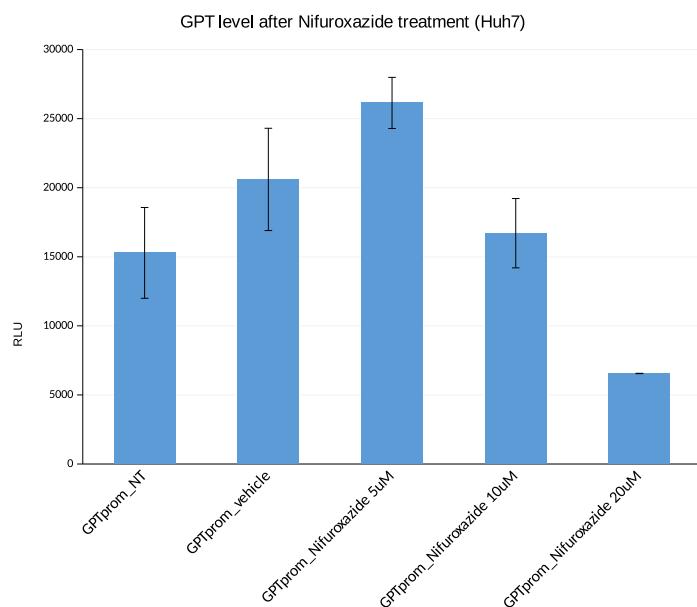
Fig. S8: Relative luminescence units (RLU) in Huh7 cells transfected with a plasmid expressing
the luciferase gene under the control of the GPT promoter and incubated with various
concentrations of nifuroxazide.

2 Tables

Tab. S1: Drugs UP-regulating the GPT gene according to Gene2Drug. The database used was Reactome, using all the pathways that GPT is annotated to, i.e.: *positive regulation of transcription, DNA-dependent*; *embryonic placenta development*; *lysosome organization*; *positive regulation of autophagy*; *autophagy*; *humoral immune response.*

Drug	Rank	ES	p
fulvestrant	1	0.979	0.001
tomatidine	2	0.972	0.002
nifuroxazide	3	0.967	0.002
terguride	4	0.963	0.003
monastrol	5	0.958	0.004
triflusal	6	0.957	0.004
5707885	7	0.955	0.004
enilconazole	8	0.954	0.005
5666823	9	0.951	0.005
SC-19220	10	0.949	0.006
mycophenolic_acid	11	0.949	0.006
ciclosporin	12	0.948	0.006
cefotiam	13	0.945	0.007
erastin	14	0.945	0.007
epitiostanol	15	0.940	0.008
benperidol	16	0.937	0.008
cefapirin	17	0.933	0.010
betulinic_acid	18	0.931	0.010
nitrofural	19	0.931	0.010
phenoxybenzamine	20	0.931	0.010
apomorphine	21	0.925	0.012
riluzole	22	0.922	0.013
vanoxerine	23	0.919	0.014
oxybenzone	24	0.918	0.014
fasudil	25	0.913	0.016
16-phenyltetranorprostaglandin_E2	26	0.910	0.017
oxybuprocaine	27	0.909	0.017
spaglumic_acid	28	0.909	0.017
AG-013608	29	0.907	0.018
glycopyrronium_bromide	30	0.907	0.018

Tab. S2: Drugs UP-regulating the GPT gene according to its fold-change as obtained through microarray analysis (Single Gene Expression method). For each drug, its rank according to how much GPT is UP-regulated is reported in the second column. Moreover, the rank of the gene in the profile of each drug is reported in column 2. Tomatidine, which was shown to be strongly effective (see Main Text), is ranked only 247 by the Single Gene Expression method.

Drug	Drug Rank for GPT	GPT Rank for Drug
PF-00562151-00	1	273
hydroxyzine	2	323
amiloride	3	378

piperine	4	384
theophylline	5	407
chlorphenesin	6	416
etidronic_acid	7	468
ambroxol	8	483
ginkgolide_A	9	518
debrisoquine	10	529
tolazoline	11	532
ascorbic_acid	12	554
lumicolchicine	13	562
metanephrine	14	570
cefotiam	15	578
oxetacaine	16	594
conessine	17	605
serotonin	18	608
fenoprofen	19	622
delsoline	20	632
colforsin	21	639
quinethazone	22	652
colecalciferol	23	653
tiabendazole	24	658
betamethasone	25	670
orlistat	26	674
tetracaine	27	679
ergocalciferol	28	695
prochlorperazine	29	714
terconazole	30	716
oxybuprocaine	31	721
PF-00539758-00	32	726
chlortetracycline	33	730
metixene	34	735
acetazolamide	35	736
probenecid	36	748
rifampicin	37	753
ioxaglic_acid	38	757
zoxazolamine	39	763
metrizamide	40	765
zidovudine	41	769
fludroxycortide	42	788
methapyrilene	43	801
N-acetyl-L-aspartic_acid	44	815
ciclosporin	45	829
chloropyrazine	46	830
iopromide	47	838
Prestwick-1084	48	853
ciprofloxacin	49	868
dihydrostreptomycin	50	868
nafcillin	51	882
cefotetan	52	904

flufenamic_acid	53	912
tretinoin	54	923
tetracycline	55	924
cyclobenzaprine	56	929
risperidone	57	961
ciprofibrate	58	977
budesonide	59	989
ethaverine	60	992
fursultiamine	61	994
isoxsuprine	62	994
trimetazidine	63	994
etomidate	64	1004
indoprofen	65	1014
clidinium_bromide	66	1028
rolitetracycline	67	1033
xamoterol	68	1050
acetylsalicylsalicylic_acid	69	1065
quercetin	70	1072
colchicine	71	1074
cefixime	72	1077
alpha-yohimbine	73	1081
sertaconazole	74	1089
monastrol	75	1096
bromopride	76	1110
securinine	77	1116
pyrazinamide	78	1121
raloxifene	79	1137
sulmazole	80	1147
calcium_pantothenate	81	1148
neostigmine_bromide	82	1148
buspirone	83	1155
karakoline	84	1163
Prestwick-675	85	1171
hydrocotarnine	86	1177
primidone	87	1187
lactobionic_acid	88	1188
STOCK1N-35215	89	1233
sulconazole	90	1233
(-)-atenolol	91	1236
clofilium_tosylate	92	1248
azlocillin	93	1250
ethambutol	94	1252
mephenytoin	95	1269
thiamine	96	1271
nilutamide	97	1285
proadifen	98	1304
moxonidine	99	1313
sulfaquinoxaline	100	1313
naringenin	101	1315

colistin	102	1316
promethazine	103	1324
exemestane	104	1326
mepacrine	105	1329
carisoprodol	106	1335
tolazamide	107	1345
iobenguane	108	1359
trapidil	109	1360
carbarsone	110	1364
danazol	111	1364
tolmetin	112	1392
palmatine	113	1397
clioquinol	114	1400
altretamine	115	1409
procyclidine	116	1416
mesalazine	117	1421
bretylium_tosilate	118	1425
sparteine	119	1431
methazolamide	120	1439
orciprenaline	121	1455
xylazine	122	1468
epiandrosterone	123	1471
benzonatate	124	1492
vitexin	125	1493
etilefrine	126	1496
piperidolate	127	1508
myricetin	128	1511
fasudil	129	1526
diphenhydramine	130	1541
piracetam	131	1543
pentolonium	132	1546
3-nitropropionic_acid	133	1553
hexetidine	134	1553
probucol	135	1559
rotenone	136	1566
Prestwick-559	137	1592
trimipramine	138	1597
propranolol	139	1601
octopamine	140	1603
ciclacillin	141	1606
apigenin	142	1615
alprenolol	143	1632
pyrantel	144	1632
brinzolamide	145	1635
lovastatin	146	1637
zalcitabine	147	1637
eldeline	148	1640
aminophenazone	149	1648
saquinavir	150	1656

clopamide	151	1658
ondansetron	152	1663
corbadrine	153	1665
0225151-0000	154	1668
Prestwick-1103	155	1669
cefoxitin	156	1674
salsolinol	157	1692
spironolactone	158	1693
buflomedil	159	1704
sulfadoxine	160	1707
tonzonium_bromide	161	1722
procaine	162	1753
iopanoic_acid	163	1756
dipivefrine	164	1760
R-atenolol	165	1765
puromycin	166	1776
rottlerin	167	1781
dipyridamole	168	1782
raubasine	169	1783
sulfachlorpyridazine	170	1784
mefloquine	171	1791
metronidazole	172	1793
tacrine	173	1794
bromperidol	174	1811
dexibuprofen	175	1811
piperlongumine	176	1816
gemfibrozil	177	1823
scoulerine	178	1826
piromidic_acid	179	1836
melatonin	180	1839
tobramycin	181	1860
7-aminocephalosporanic_acid	182	1870
MG-262	183	1870
alcuronium_chloride	184	1875
oxolamine	185	1877
molindone	186	1880
chloramphenicol	187	1897
brompheniramine	188	1916
cytochalasin_B	189	1933
flavoxate	190	1938
amantadine	191	1949
metampicillin	192	1958
ciclopirox	193	1959
gliquidone	194	1962
quinidine	195	1968
molsidomine	196	1969
reserpine	197	1975
meclozine	198	1981
norcyclobenzaprine	199	1984

cefamandole	200	2007
apramycin	201	2009
diclofenamide	202	2009
pronetalol	203	2013
6-azathymine	204	2019
cefotaxime	205	2020
(+/-)-catechin	206	2022
10-methoxyharmalan	207	2022
lasalocid	208	2054
gramine	209	2057
esculetin	210	2061
vinpocetine	211	2064
santonin	212	2092
benzthiazide	213	2100
bacampicillin	214	2101
imidurea	215	2118
hydrastine_hydrochloride	216	2133
liothyronine	217	2133
dioxybenzone	218	2147
mephentermine	219	2154
amiodarone	220	2174
nomifensine	221	2177
resveratrol	222	2177
ofloxacin	223	2188
etynodiol	224	2203
riluzole	225	2203
piperacetazine	226	2209
leflunomide	227	2221
lanatoside_C	228	2224
oxybutynin	229	2229
12,13-EODE	230	2245
PF-00539745-00	231	2276
azacitidine	232	2278
myosmine	233	2279
gentamicin	234	2280
spiperone	235	2285
bendroflumethiazide	236	2299
clindamycin	237	2336
prazosin	238	2346
meropenem	239	2355
trimethoprim	240	2360
butirosin	241	2367
depudecin	242	2373
DL-thiorphan	243	2378
crotamiton	244	2379
tolfenamic_acid	245	2380
sulfamonomethoxine	246	2387
tomatidine	247	2391
alexidine	248	2396

Prestwick-860	249	2398
fenbendazole	250	2400
tracazolate	251	2407
drofenine	252	2411
metaraminol	253	2416
fluoxetine	254	2417
yohimbic_acid	255	2457
trimethylcolchicinic_acid	256	2459
desipramine	257	2463
cycloserine	258	2473
canadine	259	2483
pentetic_acid	260	2483
dantrolene	261	2494
tyrphostin_AG-1478	262	2502
phenoxybenzamine	263	2509
paclitaxel	264	2528
IC-86621	265	2529
morantel	266	2537
Trolox_C	267	2540
levodopa	268	2548
tetroquinone	269	2550
memantine	270	2566
desoxycortone	271	2567
levobunolol	272	2580
doxylamine	273	2597
DL-PPMP	274	2620
azaperone	275	2624
hexamethonium_bromide	276	2624
iloprost	277	2629
urapidil	278	2644
diltiazem	279	2651
alprostadil	280	2663
alsterpaullone	281	2675
retrorsine	282	2684
fosfosal	283	2686
thioguanosine	284	2693
naltrexone	285	2702
torasemide	286	2703
bephenium_hydroxynaphthoate	287	2706
nicardipine	288	2707
ganciclovir	289	2709
digitoxigenin	290	2710
dexpanthenol	291	2717
amphotericin_B	292	2736
oxprenolol	293	2742
sulfametoxydiazine	294	2743
Prestwick-983	295	2744
nicergoline	296	2752
alvespimycin	297	2776

sulfadimethoxine	298	2790
novobiocin	299	2813
nadolol	300	2817

Tab. S3: Drugs UP-regulating the TFEB gene according to Gene2Drug. The database used was GO-BP, using all the pathways that GPT is annotated to, i.e.: *metabolism of amino acids and derivatives*; *amino acid synthesis and interconversion transamination*.

Drug	Rank	ES	p
pimozide	1	0.792	0.001
deptropine	2	0.780	0.001
maprotiline	3	0.765	0.002
nifurtimox	4	0.752	0.002
benzethonium_chloride	5	0.747	0.003
alprenolol	6	0.746	0.003
0297417-0002B	7	0.744	0.003
miconazole	8	0.743	0.003
loperamide	9	0.732	0.003
etoposide	10	0.729	0.003
cytochalasin_B	11	0.713	0.005
astemizole	12	0.712	0.005
valinomycin	13	0.712	0.005
oxyphenbutazone	14	0.710	0.005
methylbenzethonium_chloride	15	0.706	0.005
emetine	16	0.696	0.006
pyrvinium	17	0.696	0.006
oligomycin	18	0.695	0.006
oxybuprocaine	19	0.694	0.006
homochlorcyclizine	20	0.692	0.006
cyclic_adenosine_monophosphate	21	0.688	0.007
fenoterol	22	0.675	0.009
proadifen	23	0.671	0.009
rottlerin	24	0.670	0.009
pimethixene	25	0.663	0.010
tamoxifen	26	0.657	0.011
protriptyline	27	0.656	0.012
clonidine	28	0.653	0.012
carbenoxolone	29	0.651	0.012
quinostatin	30	0.650	0.013

Tab. S4: Drugs UP-regulating the TFEB gene according to its fold-change as obtained through microarray analysis (Single Gene Expression method). For each drug, its rank according to how much TFEB is UP-regulated is reported in the second column. Moreover, the rank of the gene in the profile of each drug is reported in column 2. Loperamide, which was shown to be effective at low concentration (see Main Text), is ranked only 242 by the Single Gene Expression method.

Drug	Drug rank for TFEB	TFEB rank for drug
foliosidine	1	344

azathioprine	2	410
trimetazidine	3	427
calcium_pantothenate	4	450
nomifensine	5	456
fenspiride	6	464
diazoxide	7	468
naringin	8	490
cefadroxil	9	491
ivermectin	10	513
pioglitazone	11	591
acenocoumarol	12	604
natamycin	13	611
hemicholinium	14	618
mefloquine	15	627
butacaine	16	651
hydralazine	17	652
hycanthone	18	686
minaprine	19	699
ramifenazone	20	721
(-)-atenolol	21	733
apomorphine	22	734
ketoprofen	23	734
nicergoline	24	738
tamoxifen	25	740
guanethidine	26	746
meptazinol	27	753
CP-863187	28	757
fursultiamine	29	762
flupentixol	30	788
terfenadine	31	791
lidoflazine	32	803
riluzole	33	822
valproic_acid	34	828
dosulepin	35	832
etiocholanolone	36	835
carbinoxamine	37	838
etodolac	38	842
ginkgolide_A	39	842
pyrithyldione	40	853
bisoprolol	41	856
bacampicillin	42	874
streptozocin	43	877
repaglinide	44	886
chlorprothixene	45	918
edrophonium_chloride	46	922
cinnarizine	47	930
myricetin	48	940
practolol	49	943
thioproperazine	50	955

dihydrostreptomycin	51	983
pepstatin	52	987
oxybuprocaine	53	998
harmine	54	1011
tocainide	55	1043
ketotifen	56	1052
Chicago_Sky_Blue_6B	57	1053
ascorbic_acid	58	1059
nifurtimox	59	1059
aztreonam	60	1063
dizocilpine	61	1075
debrisoquine	62	1081
tetrahydroalstonine	63	1081
pentolonium	64	1084
benzbromarone	65	1096
trifluridine	66	1098
bupivacaine	67	1105
BCB000040	68	1113
tranylcypromine	69	1121
cyanocobalamin	70	1127
mepyramine	71	1127
tolazoline	72	1135
alfuzosin	73	1147
molindone	74	1148
probucol	75	1151
lisuride	76	1155
pempidine	77	1159
neomycin	78	1163
testosterone	79	1165
BCB000039	80	1167
cefalexin	81	1167
sulfacetamide	82	1177
picotamide	83	1181
aminophylline	84	1195
pimethixene	85	1205
hydrochlorothiazide	86	1227
lynestrenol	87	1240
prasterone	88	1253
proadifen	89	1270
prednisone	90	1271
chlorambucil	91	1305
chloroquine	92	1313
desipramine	93	1321
econazole	94	1360
mebendazole	95	1363
rolitetracycline	96	1364
ursolic_acid	97	1377
sulfamethoxypyridazine	98	1399
miconazole	99	1400

PF-00875133-00	100	1406
lomustine	101	1407
fluvastatin	102	1419
sulfaguanidine	103	1434
clorgiline	104	1450
metanephrine	105	1455
tolfenamic_acid	106	1456
nalbuphine	107	1466
serotonin	108	1476
colecalciferol	109	1485
chlorphenamine	110	1492
trimethobenzamide	111	1493
cefixime	112	1497
coralyne	113	1526
daunorubicin	114	1562
diloxanide	115	1571
thioperamide	116	1572
flucytosine	117	1577
mimosine	118	1581
retrorsine	119	1594
chlorogenic_acid	120	1596
napelline	121	1611
guanadrel	122	1646
prednisolone	123	1649
dydrogesterone	124	1650
piretanide	125	1660
ranitidine	126	1661
amitriptyline	127	1664
ciclosporin	128	1677
scoulerine	129	1677
tremorine	130	1680
cyclopenthiazide	131	1681
piracetam	132	1690
withaferin_A	133	1707
piperine	134	1713
propantheline_bromide	135	1716
stachydrine	136	1729
harmaline	137	1745
perhexiline	138	1746
labetalol	139	1750
PF-01378883-00	140	1753
hexamethonium_bromide	141	1755
naftifine	142	1788
lactobionic_acid	143	1806
doxycycline	144	1814
amylocaine	145	1822
naftopidil	146	1825
oleandomycin	147	1834
6-benzylaminopurine	148	1838

azaperone	149	1839
probenecid	150	1843
5155877	151	1850
vinblastine	152	1852
dapsone	153	1856
mecamylamine	154	1856
acebutolol	155	1865
dipivefrine	156	1874
aminoglutethimide	157	1888
bambuterol	158	1895
primidone	159	1895
bromopride	160	1900
dyclonine	161	1933
mepacrine	162	1935
5248896	163	1936
propoxycaine	164	1965
meclofenoxate	165	1986
pyrimethamine	166	1986
torasemide	167	1991
phenindione	168	1998
scriptaid	169	2002
amprolium	170	2006
emetine	171	2017
brompheniramine	172	2018
carteolol	173	2026
isotretinoin	174	2026
fusaric_acid	175	2033
salsolinol	176	2036
celastrol	177	2041
cloxacillin	178	2043
mevalolactone	179	2059
rifabutin	180	2061
nifenazone	181	2063
Prestwick-559	182	2070
6-bromoindirubin-3'-oxime	183	2071
rilmenidine	184	2075
flufenamic_acid	185	2083
tranexamic_acid	186	2083
tretinoin	187	2093
benzamil	188	2102
Prestwick-1103	189	2105
ioxaglic_acid	190	2107
bufexamac	191	2110
chenodeoxycholic_acid	192	2115
propidium_iodide	193	2119
isoconazole	194	2127
pridinol	195	2132
flunixin	196	2135
phenoxybenzamine	197	2136

caffeic_acid	198	2145
astemizole	199	2150
lorglumide	200	2151
pheniramine	201	2152
tacrine	202	2164
dimethadione	203	2171
Prestwick-967	204	2174
flumetasone	205	2200
norethisterone	206	2200
alprenolol	207	2201
cefazolin	208	2210
carcinine	209	2213
aminophenazone	210	2223
ceforanide	211	2224
atovaquone	212	2233
diclofenamide	213	2255
isoetarine	214	2257
5152487	215	2261
dl-alpha_tocopherol	216	2273
mesalazine	217	2276
chlortetracycline	218	2301
phenacetin	219	2313
ethambutol	220	2319
nocodazole	221	2329
phenformin	222	2355
sertaconazole	223	2362
sulfamethoxazole	224	2366
homochlorcyclizine	225	2380
triamcinolone	226	2386
N6-methyladenosine	227	2392
cefoxitin	228	2406
zuclopenthixol	229	2416
Prestwick-682	230	2418
thioguanosine	231	2428
sulfinpyrazone	232	2437
dihydroergotamine	233	2452
cyclizine	234	2466
protoveratrine_A	235	2482
(+)-chelidonine	236	2497
simvastatin	237	2498
carmustine	238	2524
corbadrine	239	2524
finasteride	240	2528
loperamide	241	2528
hesperetin	242	2538
vinpocetine	243	2541
amantadine	244	2549
imipenem	245	2552
3-acetylcoumarin	246	2553

hydroxyzine	247	2558
cephaeline	248	2563
xamoterol	249	2588
rolipram	250	2597
buspirone	251	2601
Prestwick-984	252	2614
monobenzone	253	2616
troglitazone	254	2617
diclofenac	255	2624
glycopyrronium_bromide	256	2633
nabumetone	257	2639
timolol	258	2646
fendiline	259	2660
2-aminobenzenesulfonamide	260	2662
kawain	261	2664
nadolol	262	2667
epivincamine	263	2670
dexverapamil	264	2671
doxazosin	265	2684
SB-203580	266	2709
bergenin	267	2712
PNU-0230031	268	2714
niridazole	269	2724
pirenzepine	270	2746
sulfametoxydiazine	271	2752
lysergol	272	2761
chlorcyclizine	273	2785
5194442	274	2788
aciclovir	275	2798
cotinine	276	2808
picrotoxinin	277	2808
HC_toxin	278	2829
xylometazoline	279	2838
AG-012559	280	2840
5224221	281	2851
loxapine	282	2883
sulconazole	283	2894
thapsigargin	284	2895
4,5-dianilinophthalimide	285	2920
MS-275	286	2927
meteneprost	287	2936
cefotiam	288	2941
oxybutynin	289	2949
disulfiram	290	2952
flucloxacillin	291	2961
procaine	292	2966
bretylium_tosilate	293	2979
erastin	294	2979
methylprednisolone	295	2982

carbamazepine	296	2991
decamethonium_bromide	297	3004
celecoxib	298	3010
primaquine	299	3034
NS-398	300	3036