

SUPPLEMENTARY MATERIAL

Supplementary Table 1. MDDR Target Annotations Used in the Promiscuity Predictions

TARGET_KEY	EXTERNAL_ID
1001	prostaglandin-endoperoxide synthase
1002	cyclooxygenase 1
1003	cyclooxygenase 2
1046	ribonucleoside-diphosphate reductase
1112	thymidylate synthase
1209	phosphoribosylglycinamide formyltransferase
1609	purine-nucleoside phosphorylase
1611	uridine phosphorylase
1637	nad adp-ribosyltransferase
1657	transferring alkyl or aryl groups, other than methyl groups
1798	thymidine kinase
1814	protein kinase
1843	1-phosphatidylinositol 4-kinase
1883	protein-tyrosine kinase
1973	nucleotidyltransferase
2018	rna-directed dna polymerase
2121	phospholipase a2
2124	acetylcholinesterase
2282	phosphoric diester hydrolase
2283	phosphodiesterase i
2309	3',5'-cyclic-nucleotide phosphodiesterase
2310	3',5'-cyclic-gmp phosphodiesterase
2316	steryl-sulfatase
2414	alpha-glucosidase
2565	adenosylhomocysteinase
2576	peptidase
25	aldehyde reductase
2613	dipeptidyl-peptidase iv
2619	peptidyl-dipeptidase a
2624	serine-type d-ala-d-ala carboxypeptidase
2659	serine endopeptidase
2663	trypsin
2664	thrombin
2665	coagulation factor xa
2672	coagulation factor viia
2695	tryptase
2742	cathepsin b
2750	cathepsin l
2765	caspase-1
2784	hiv-1 retropepsin
2811	metalloendopeptidase
2822	stromelysin 1
286	xanthine oxidase
2978	beta-lactamase
3014	adenosine deaminase

3218	ornithine decarboxylase
3361	carbonate dehydratase
3552	adenylate cyclase
3553	guanylate cyclase
3703	lanosterol synthase
3813	tetrahydrofolylpolyglutamate synthase
3875	beta adrenoceptor
3876	beta adrenoceptor type 1
3880	histamine
3882	histamine type 2
38	hydroxymethylglutaryl-coa reductase (nadh2)
3970	endothelin
3971	eta
3976	interleukin-8
4045	adenosine type 1
4048	adenosine type 3
4059	platelet activating factor
4179	vitamin d3-like
4218	estrogen
4228	progesterone
4229	androgen
4270	glutamate receptor nmda subunit
4276	glutamate receptor kainate subunit
4285	gaba a alpha subunit
457	cholestenone 5alpha-reductase
568	monoamine oxidase a
597	dihydrofolate reductase
5	alcohol dehydrogenase
872	procollagen-proline dioxygenase
944	nitric-oxide synthase
974	unspecific monoxygenase

Supplementary Table 2. *In Silico* Predicted Promiscuous Targets with the Existing MDDR Activity Classes for their Ligands

#TARGET: procollagen.proline.dioxygenase

#ACT_CLASS: Liver Fibrosis, Agent for; Procollagen Prolyl Hydroxylase Inhibitor; Cystic Fibrosis;

#TARGET: cholestenone 5alpha-reductase

#ACT_CLASS: Prostate Disorders, Agent for; Antiacne; Steroid (5alpha) Reductase Inhibitor; Antidiabetic; Aldose Reductase Inhibitor; Ophthalmic Agent; Antiandrogen; Male Sexual Disorders, Agent for; Hair Growth Promoter; Chemopreventive;

#TARGET: gaba-a alpha subunit

#ACT_CLASS: Analgesic, Non-Opioid; GABA A/Benzodiazepine Receptor Complex-Related Drug; Sedative/Hypnotic; Anxiolytic; Benzodiazepine Agonist; Sleep Disorders, Agent for; Benzodiazepine Agonist; Alcohol Deterrent; Anticonvulsant; Agent for Premedication; Antimigraine; Anesthetic, Intravenous;

#TARGET: glutamate receptor kainate subunit

#ACT_CLASS: AMPA Receptor Antagonist; Kainic Acid Receptor Antagonist; Antiischemic, Cerebral; Neurogenic Pain, Agent for; Neuronal Injury Inhibitor;

#TARGET: androgen

#ACT_CLASS: Androgen; Aromatase Inhibitor; Antiandrogen; Steroid (5alpha) Reductase Inhibitor; Ophthalmic Agent; Prostate Disorders, Agent for; Antiandrogen; Male Sexual Disorders, Agent for; Hair Growth Promoter; Chemopreventive; Antineoplastic;

#TARGET: estrogen

#ACT_CLASS: Estrogen; Treatment for Osteoporosis; Estrogen Receptor Modulator; Antineoplastic; Antiestrogen; Postmenopausal Syndrome, Agent for; Antiinfertility, Female; Antineoplastic;

#TARGET: vitamin d3-like

#ACT_CLASS: Vitamin D Analog;

#TARGET: hydroxymethylglutaryl coa reductase

#ACT_CLASS: Hypolipidemic; HMG-CoA Reductase (beta) Inhibitor;

#TARGET: lanosterol synthase

#ACT_CLASS: Hypolipidemic; 2,3-Oxidosqualene-Lanosterol Cyclase Inhibitor; Antifungal;

#TARGET: adenosylhomocysteinase

#ACT_CLASS: Antiviral; S-Adenosyl-L-Homocysteine Hydrolase Inhibitor;

#TARGET: acetylcholinesterase

#ACT_CLASS: Cognition Disorders, Agent for; Acetylcholinesterase Inhibitor; Nootropic Agent; Nitric Oxide Synthase Inhibitor;

#TARGET: rna-directed dna polymerase

#ACT_CLASS: Antiviral (AIDS); Reverse Transcriptase Inhibitor;

#TARGET: thymidine kinase

#ACT_CLASS: Thymidine Kinase Inhibitor;

#TARGET: purine-nucleoside phosphorylase

#ACT_CLASS: Antibacterial; Antineoplastic; Purine Nucleoside Phosphorylase Inhibitor; Immunosuppressant; Antiprotozoal; Antiarthritic; Multiple Sclerosis, Agent for; Inflammatory Bowel Disease, Agent for; Antipsoriatic; Antiviral (AIDS);

#TARGET: ribonucleoside-diphosphate reductase

#ACT_CLASS: Neurologic Agent; Nitric Oxide Donor; Antiviral (AIDS); Antineoplastic; Antimetabolite; Ribonucleotide Reductase Inhibitor; Multiple Sclerosis, Agent for; Antipsoriatic;

Supplementary Table 3. In Vitro Predicted Promiscuous Targets with the Existing MDDR Activity Classes for their Ligands

#TARGET: Cyclooxygenase 1

#ACT_CLASS: Xanthine Oxidase Inhibitor; MAO A Inhibitor; Lipid Peroxidation Inhibitor; Antiobesity; Antipsoriatic; Antineoplastic; Chemopreventive; Chemoprotective; Cyclooxygenase-1 Inhibitor; Cyclooxygenase-2 Inhibitor; Analgesic, Non-Opioid; Antiinflammatory; Antiarthritic; Antimigraine; Antipyretic; Neuronal Injury Inhibitor; Antianginal; Nitric Oxide Donor; Platelet Antiaggregatory; Hematologic Agent; Chemopreventive; Cyclooxygenase-1 Inhibitor;

#TARGET: Cyclooxygenase 2

#ACT_CLASS: Antiarthritic; Nitric Oxide Synthase Inhibitor; Antiallergic/Antiasthmatic; Antiinflammatory, Topical; Chemopreventive; Tyrosine-Specific Protein Kinase Inhibitor; Cyclooxygenase-2 Inhibitor; Cyclooxygenase-1 Inhibitor; Cyclooxygenase-2 Inhibitor; Analgesic, Non-Opioid; Antimigraine; Treatment of Gout; Actinic Keratoses, Agent for; Antiangiogenic; Chemopreventive;

#TARGET: transferring alkyl or aryl groups, other than methyl groups

#ACT_CLASS: Antineoplastic; Farnesyl Protein Transferase Inhibitor; Signal Transduction Inhibitor; Farnesyl Protein Transferase Inhibitor; Geranylgeranyl Protein Transferase Inhibitor; Antimalarial;

#TARGET: rna-directed dna polymerase

#ACT_CLASS: Antiviral (AIDS); Reverse Transcriptase Inhibitor;

#TARGET: acetylcholinesterase

#ACT_CLASS: Cognition Disorders, Agent for; Acetylcholinesterase Inhibitor; Nootropic Agent; Nitric Oxide Synthase Inhibitor;

#TARGET: steryl-sulfatase

#ACT_CLASS: Antineoplastic; Estrone Sulfatase Inhibitor; Antiangiogenic; Aromatase Inhibitor; #LIG: 4TR

#TARGET: peptidase

#ACT_CLASS: Prolylendopeptidase Inhibitor; Antiviral (AIDS); Protease Inhibitor; Antihypertensive; ACE Inhibitor; Neutral Endopeptidase Inhibitor; HIV-1 Protease Inhibitor; Anticoagulant; Thrombin Inhibitor; Neuronal Injury Inhibitor; Antianginal; Analgesic, Opioid;

#TARGET: aldehyde reductase

#ACT_CLASS: Aldose Reductase Inhibitor; Antidiabetic, Symptomatic; Xanthine Oxidase Inhibitor; MAO A Inhibitor; Antioxidant; Antidiabetic; Glucosidase (alpha) Inhibitor; Antiinflammatory, Topical; Chemopreventive; Anticataract; Antiallergic/Antiasthmatic; H2 Antagonist; Antiulcerative; Hepatoprotectant; Antineoplastic; Antiangiogenic; Guanylate Cyclase Activator; Prostate Disorders, Agent for; Antiacne; Steroid (5alpha) Reductase Inhibitor;

#TARGET: dipeptidyl-peptidase iv

#ACT_CLASS: Dipeptidyl Aminopeptidase IV Inhibitor; Antiarthritic; Immunomodulator; Immunosuppressant; Antidiabetic; Insulin Promoter;

#TARGET: thrombin

#ACT_CLASS: Anticoagulant; Thrombin Inhibitor; Factor Xa Inhibitor; Trypsin Inhibitor; Protease Inhibitor; Factor Xa Inhibitor;

#TARGET: coagulation factor xa

#ACT_CLASS: Anticoagulant; Factor Xa Inhibitor; Factor VIIa Inhibitor; Thrombin Inhibitor; Trypsin Inhibitor; Antineoplastic; Neuronal Injury Inhibitor; Antianginal; Agent for Cardiovascular Disorders; #PDB:

#TARGET: hiv-1 retropepsin

#ACT_CLASS: Antiviral (AIDS); HIV-1 Protease Inhibitor; Antifungal; Protease Inhibitor;

#TARGET: metalloendopeptidase

#ACT_CLASS: Antineoplastic; Antiangiogenic; Signal Transduction Inhibitor; Matrix Metalloproteinase Inhibitor; Antiarthritic; Collagenase Inhibitor; Matrix Metalloproteinase Inhibitor; Bone Resorption Inhibitor; Corneal Wound Healing Stimulator; Chronic Obstructive Pulmonary Disease, Agent for; Restenosis, Agent for; Inflammatory Bowel Disease, Agent for; Antineurotoxic; Neuronal Injury Inhibitor; Ophthalmic Agent; Restenosis, Agent for; Agent for Cardiovascular Disorders;

#TARGET: adenosine deaminase

#ACT_CLASS: Antimalarial; Adenosine Deaminase Inhibitor; Antiarthritic; Agent for Autoimmune Diseases; Antianginal; Antineoplastic Enhancer; Antiarthritic; Septic Shock, Treatment for; Immunosuppressant; Transplant Rejection, Agent for; Antineoplastic; Antimetabolite; Multiple Sclerosis, Agent for;

#TARGET: estrogen

#ACT_CLASS: Estrogen; Treatment for Osteoporosis; Estrogen Receptor Modulator; Antineoplastic; Antiestrogen; Postmenopausal Syndrome, Agent for; Antiinfertility, Female; Antineoplastic;

#TARGET: androgen

#ACT_CLASS: Androgen; Aromatase Inhibitor; Antiandrogen; Steroid (5alpha) Reductase Inhibitor; Ophthalmic Agent; Prostate Disorders, Agent for; Antiandrogen; Male Sexual Disorders, Agent for; Hair Growth Promoter; Chemopreventive; Antineoplastic;

#TARGET: gaba-a alpha subunit

#ACT_CLASS: Analgesic, Non-Opioid; GABA A/Benzodiazepine Receptor Complex-Related Drug; Sedative/Hypnotic; Anxiolytic; Benzodiazepine Agonist; Sleep Disorders, Agent for; Benzodiazepine Agonist; Alcohol Deterrent; Anticonvulsant; Agent for Premedication; Antimigraine; Anesthetic, Intravenous;

#TARGET: dihydrofolate reductase

#ACT_CLASS: Antibacterial; Dihydrofolate Reductase Inhibitor; Antiinfective (AIDS); Antiprotozoal; Dihydrofolate Reductase Inhibitor; Antifungal; Myasthenia Gravis, Agent for; Antipsoriatic; Immunosuppressant; Antimalarial; Antineoplastic; Antimetabolite; Antitrypanosomal; Antiinfective (AIDS); Metabolic Diseases, Agent for; Folylpolyglutamate Synthetase Inhibitor;

#TARGET: nitric-oxide synthase

#ACT_CLASS: Nitric Oxide Synthase Inhibitor; Septic Shock, Treatment for; Antiarthritic; Antiallergic/Antiasthmatic; Antiinflammatory, Topical; Chemopreventive; Tyrosine-Specific Protein Kinase Inhibitor; Cyclooxygenase-2 Inhibitor; Agent for Cardiovascular Disorders; Antiischemic, Cerebral; Cognition Disorders, Agent for; Acetylcholinesterase Inhibitor;

#TARGET: unspecific monooxygenase

#ACT_CLASS: Androgen; Aromatase Inhibitor; Antiinfertility, Male; Antineoplastic; Aromatase Inhibitor; Dermatological Agent; Antifungal; Prostate Disorders, Agent for; Estrone Sulfatase Inhibitor; Cytochrome P450 Oxidase Inhibitor;