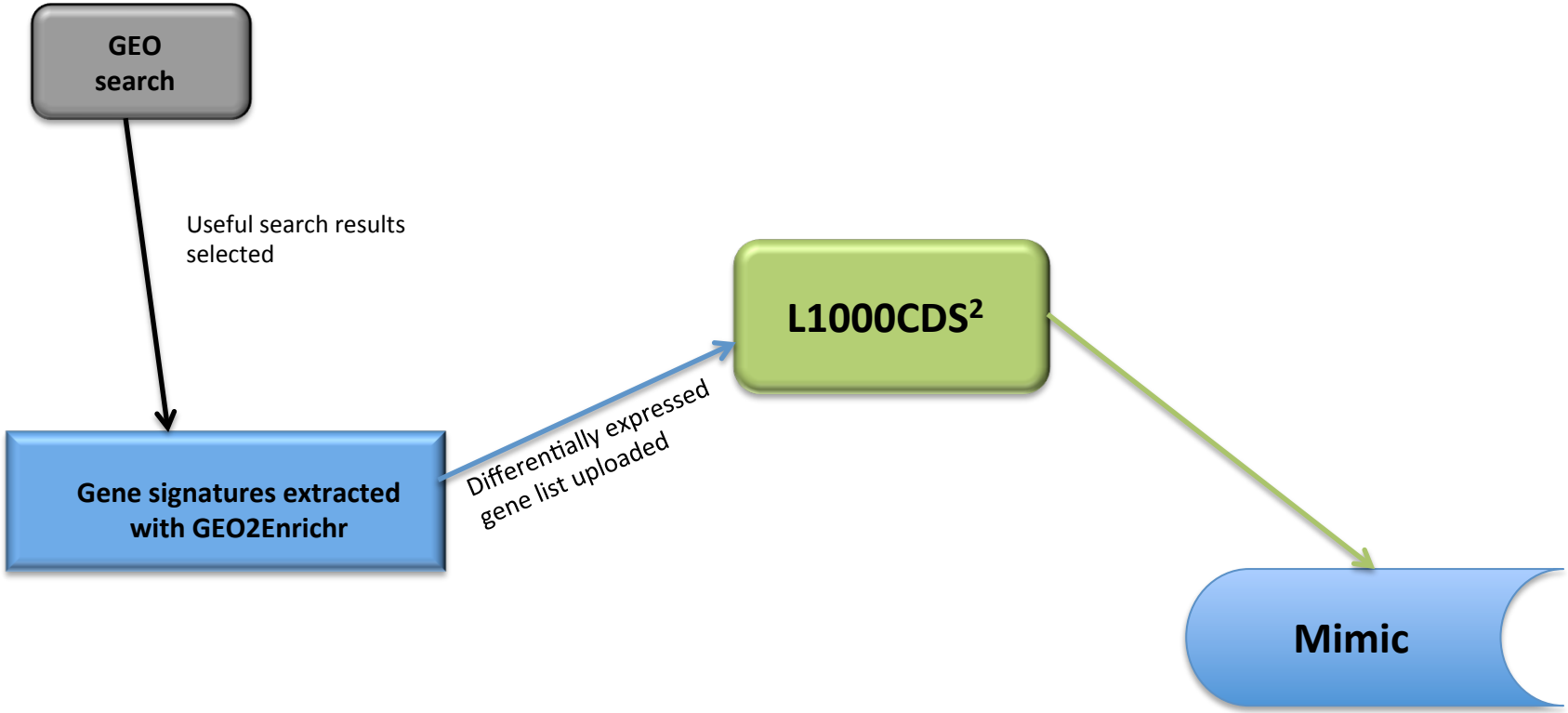
Icahn School of Medicine at Mount Sinai

Ma'ayan lab

Fibroblast to Dermal papilla



Rank	1-cos(α)	Perturbation	Perturbation LIFE URL	Perturbation PubChem URL	Perturbation DrugBank URL	Cell-line	Dose	Time	Signature URL
1	0.817	BRD-K68548958	http://life.ccs.miami.edu/life/summary?mode=SmallMolecule&source=BROAD&input=BRD-K68548958	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1285940	None	MCF7	20.0um	24.0h	http://amp.pharm.mssm.edu/L1000CDS2/meta?sig_id=CPC006_MCF7_24H:BRD-K68548958:20.0
2	0.8208	BRD-K67439147	http://life.ccs.miami.edu/life/summary?mode=SmallMolecule&source=BROAD&input=BRD-K67439147	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5311432	None	MCF7	10.0um	24.0h	http://amp.pharm.mssm.edu/L1000CDS2/meta?sig_id=CPC018_MCF7_24H:BRD-K67439147:10.0
3	0.8252	Trifluridine	http://life.ccs.miami.edu/life/summary?mode=SmallMolecule&source=BROAD&input=BRD-K03243820	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6256	http://www.drugbank.ca/drugs/DB00432	MCF7	10.0um	24.0h	http://amp.pharm.mssm.edu/L1000CDS2/meta?sig_id=CPD003_MCF7_24H:BRD-K03243820:10.0

Drug perturbations predicted to mimic the different expression from the uploaded gene lists.

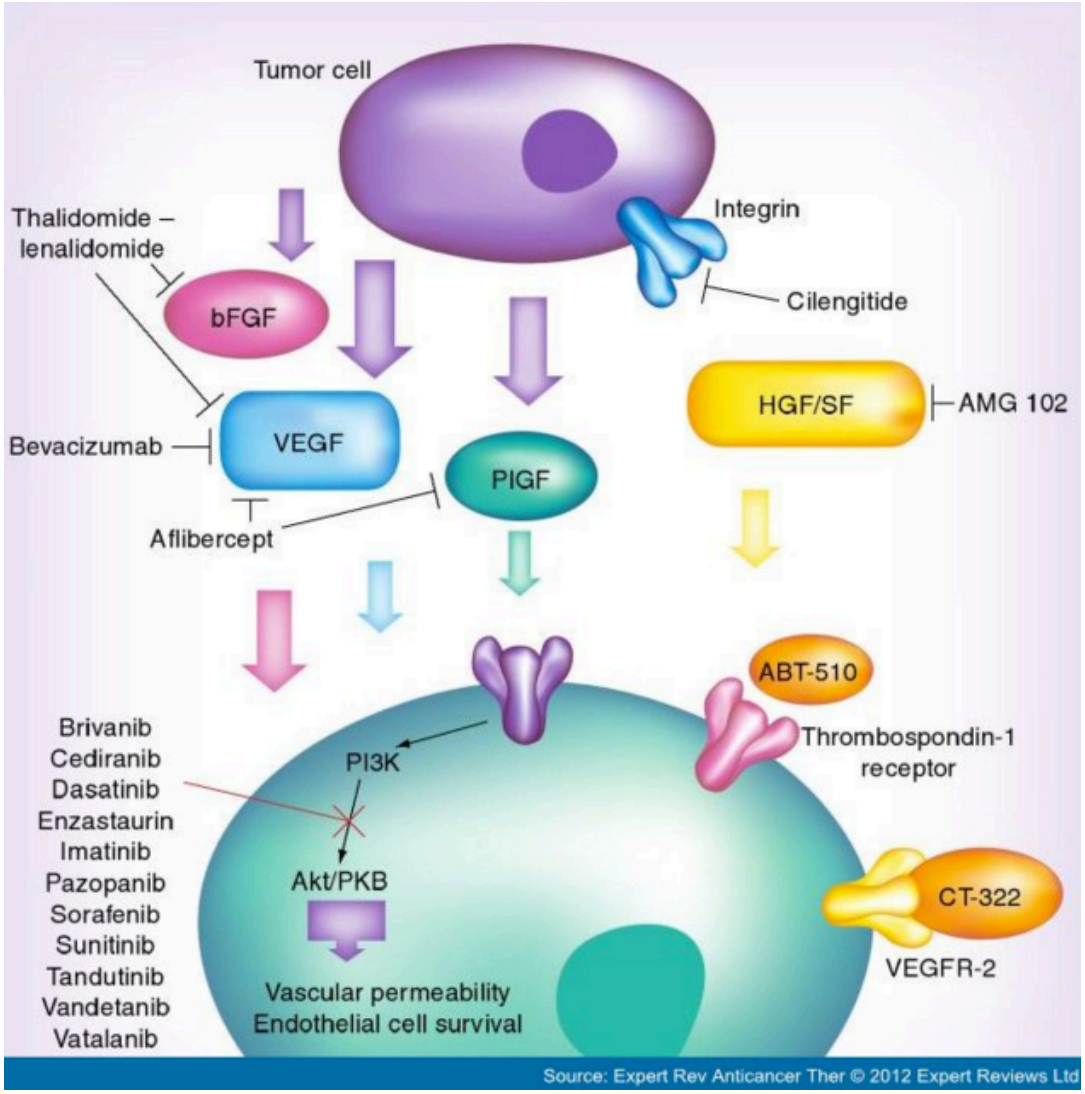
Perturbation	Total Hits in all conditions and organisms	Have hits in same study and organism	Multiple hits in same condition	Organism			Number of hits found in multiple conditions		Number of conditions across all studies with hits	Number of different studies
				Mouse	Human	Human and Mouse	In Human Study	In Mouse Study		
3544	1	Y	N		X		N	N	1	1
7061815	1	Y	N	X			N	N	1	1
4-Demethoxydaunorubicin hydrochloride (65)	3	Y	Y		X		N	N	1	1
5-fluorouracil	1	Y	N		X		N	N	1	1
A443654	6	N	Y			X	1	5	2	2
afatinib	1	Y	N		X		N	N	1	1
AMIODARONE HYDROCHLORIDE	1	Y	N		X		N	N	1	1
Angiogenesis Inhibitor	1	Y	N		X		N	N	1	1
AZD-5438	2	N	N			X	N	N	1	2
AZD-8330	1	Y	N	X			N	N	1	1
BI-2536	1	Y	N	X			N	N	1	1
BJM-ctd2-9	1	Y	N		X		N	N	1	1
BRD-A10715913	1	Y	N	X			N	N	1	1
BRD-A30655177	1	Y	N	X			N	N	1	1
BRD-A35588707	1	Y	N		X		N	N	1	1
BRD-A36630025	3	Y	Y		X		3	N	1	1
BRD-A43155244	1	Y	N	X			N	N	1	1

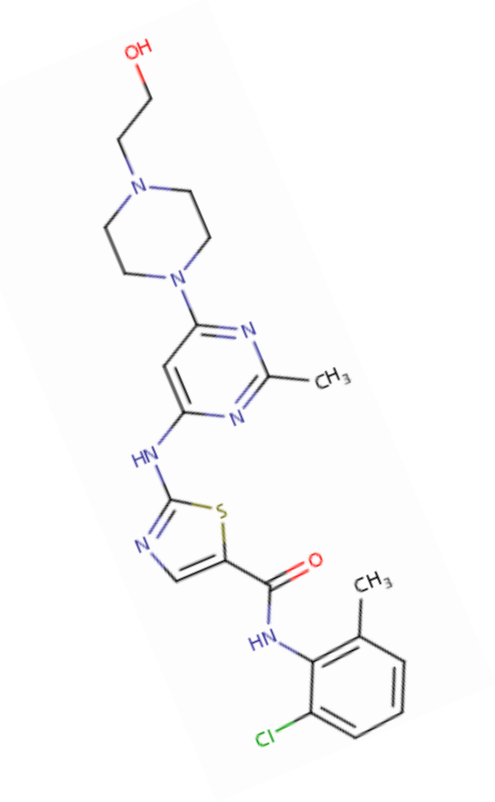
Accession	GSE31324	GSE31324	GSE31324	GDS1323	GSE70288
G2E link	142430a1f1	ec6e63c2a5	163035b609	d6679a5205	2ef250339b
Organism	human	human	human	mouse	mouse

3 unique GEO studies generated 5 gene signature entries to GEO2Enrichr.

Most commonly found drug perturbations

Dasatinib


Tumor cell
Integrin
Thalidomide –
lenalidomide
bFGF
Cilengitide
HGF/SF
AMG 102
Bevacizumab
VEGF
PIGF
Aflibercept
ABT-510
Thrombospondin-1
receptor
Brivanib
Cediranib
Dasatinib
Enzastaurin
Imatinib
Pazopanib
Sorafenib
Sunitinib
Tandutinib
Vandetanib
Vatalanib
PI3K
Akt/PKB
CT-322
VEGFR-2
Vascular permeability
Endothelial cell survival
Source: Expert Rev Anticancer Ther © 2012 Expert Reviews Ltd



Mechanism of action	<u>Inhibits kinases:</u> BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, is predicted to bind to multiple conformations of the ABL kinase. Was active (in vitro) in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease.
Protein binding	96%
Metabolism	Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4
Elimination	Primarily via the feces.
Half life	The overall mean terminal half-life is 3-5 hours.

http://www.drugbank.ca/drugs/DB01254

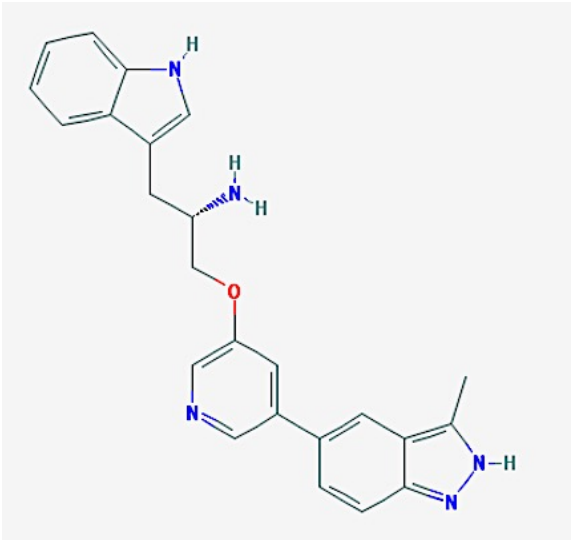
A443654

Experimental

Experimental Properties NA

Predicted Properties

Property	Value	Source
Water Solubility	0.00172 mg/mL	ALOGPS
logP	3.72	ALOGPS
logP	3.07	ChemAxon
logS	-5.4	ALOGPS
pKa (Strongest Acidic)	14.17	ChemAxon
pKa (Strongest Basic)	9.24	ChemAxon
Physiological Charge	1	ChemAxon
Hydrogen Acceptor Count	4	ChemAxon
Hydrogen Donor Count	3	ChemAxon
Polar Surface Area	92.61 $Å_2$	ChemAxon
Rotatable Bond Count	6	ChemAxon
Refractivity	118.18 $m_3 \cdot mol_{-1}$	ChemAxon
Polarizability	44.51 $Å_3$	ChemAxon
Number of Rings	5	ChemAxon
Bioavailability	1	ChemAxon
Rule of Five	Yes	ChemAxon
Ghose Filter	Yes	ChemAxon
Veber's Rule	Yes	ChemAxon
MDDR-like Rule	Yes	ChemAxon



(2S)-1-(1H-INDOL-3-YL)-3-{[5-(3-METHYL-1H-INDAZOL-5-YL)PYRIDIN-3-YL]OXY}PROPAN-2-AMINE

http://www.drugbank.ca/drugs/DB08073

Vorinostat

Inhibits the enzymatic activity of histone deacetylases:
HDAC1,
HDAC2 and
HDAC3 (Class I) and
HDAC6 (Class II) at nanomolar concentrations (IC_{50}< 86 nM).

Mechanism of action

These enzymes catalyze the removal of acetyl groups from the lysine residues of histones proteins. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. By inhibiting histone deacetylase, causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells.

The antineoplastic mechanism of vorinostat has not been fully characterized.

Protein binding

71%

Metabolism

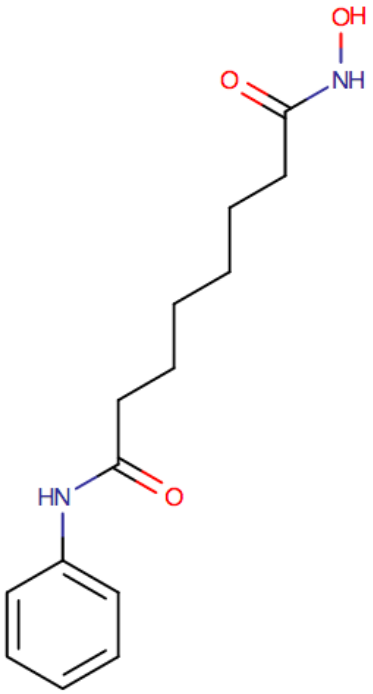
Involves glucuronidation and hydrolysis followed by β-oxidation.

Route of elimination

Predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine

Half life

2 hours



http://www.drugbank.ca/drugs/DB02546