MetaDrug 教育訓練

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Outline

- How does MetaDrug help us?
  - MetaDrug 可輔助解決的問題
  - 挖掘化合物的ADMETox, 反應作用及生物活性等相關知識
  - 了解抗發炎天然化合物的藥物知識
  - 如何預測藥物的毒性、代謝、吸收等活性
  - 藥物標靶的預測與分析
  - 以化合物建構代謝網絡及分子路徑
- Summary

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How does MetaDrug help us ?

Chemical information
- Compound detail
- Therapeutic properties
- ADMETox properties
- Reactions
- Biologic activities

Drug/compound activity
- Metabolites
- CYP450 inhibition/metabolization
- Protein binding /side effects
- ADME activity
- Therapeutic activity
- Toxic effects

Drug /compound biologic activity
- Possible targets
- Metabolic nteworks
- Disease networks
- Interactions/Mechanisms

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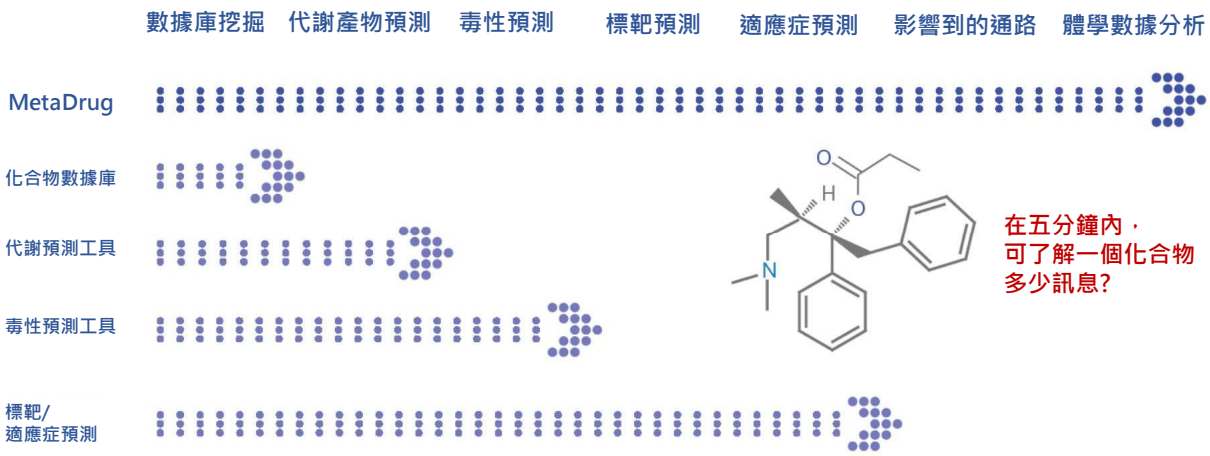
Metadrug 可輔助解決:



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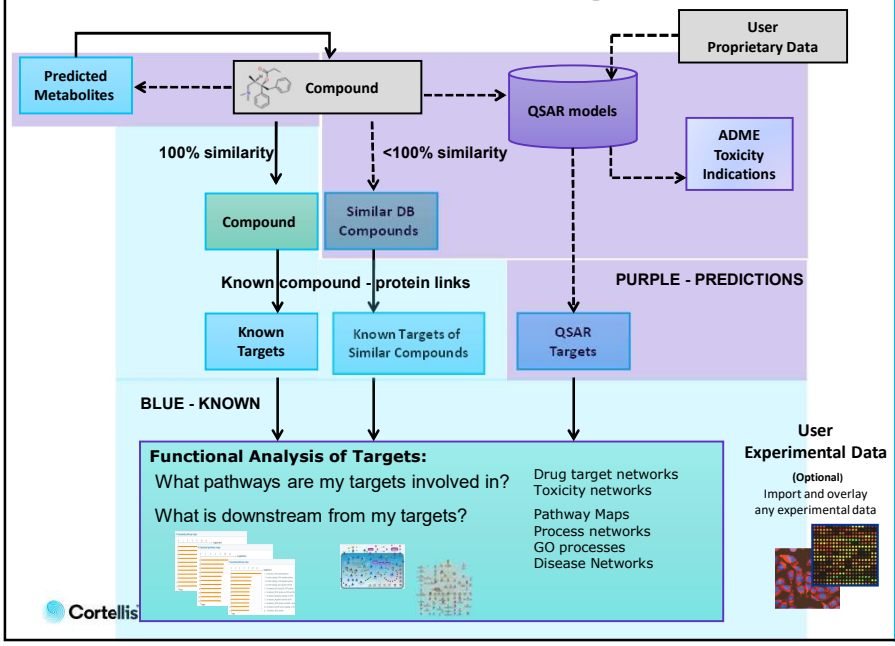
How does MetaDrug work?



- **A systems pharmacology platform for predicting bioactivity of small molecules.**
- Provides structure-based assessment of compound activity and liability.
- Predict metabolites, ADME Tox, targets and **affected pathways and processes**.

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Published: 24 April 2015

Predicting drug metabolism: experiment and/or computation?

Johannes Kirchmair, Andreas H. Göller, Dieter Lang, Jens Kunze, [illegible] Glen & Gisbert Schneider

Nature Reviews Drug Discovery **14**, 387–404(2015) | Cite this article
2329 Accesses | **197** Citations | **25** Altmetric | Metrics

Abstract

Drug metabolism can produce metabolites with physicoch
properties that differ substantially from those of the parer
important implications for both drug safety and efficacy. T
clinical-stage attrition due to the metabolic characteristics
need for efficient and reliable ways to predict drug metabo
In this Perspective, we provide an overview of the state of t
computational approaches for investigating drug metabol
limitations of these methods, and indicate strategies to ha
from combining measurement and prediction of drug metabolism.

receptor)[37,43,44]. On a broader scale, statistical and machine learning methods are used to predict comprehensive bioactivity spectra of small molecules. However, current mechanistic models generally do not take into account information beyond target annotation, and hence are limited in their ability to predict phenotypes[45]. Linking pathway information to targets can hence improve model accuracy. MetaCore and MetaDrug46,47, two pharmacology platforms that use comprehensive biological networks for estimating the pharmacological effects and risk of small molecules, harness this approach. However, the coverage and accuracy of annotated pathways is still a work in progress and there is often significantly less overlap between different databases of annotated pathways than one would expect. This is often compounded by lack of information on tissue expression levels and rate constants for metabolising enzymes. There clearly is an opportunity to invest additional effort in this area to further increase the reliability of computation models.

Kirchmair, J., Göller, A., Lang, D. et al. Predicting drug metabolism: experiment and/or computation?. Nat Rev Drug Discov 14, 387–404 (2015). https://doi.org/10.1038/nrd4581

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挖掘化合物的相關資訊

疾病治療、ADMETox、反應作用 及生物活性等相關知識

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紫錐花萃取物中具有充分的 Chicoric acid

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Live demo

資料查詢與檢索

以 Chicoric acid (辣椒酸) 為例。

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化合物的相關資訊分類

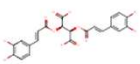
L-Chicoric acid

Compound | Build Network | Predict Compound Activity (MetaDrug) | Download structure

Table of Contents

- General
  - Compound Details
  - External Databases
- Therapeutic Properties
  - Therapeutic Information
- ADMETox Properties
  - ADMETox Information
  - Toxic Pathologies
  - ADMETox Samples
- Reactions
- Biologic Activity
  - Binding Sample
  - Functional Sample on a Cell Line (in vitro) or on Tissue/Organ but not on whole animal

Structure



ADMETox Properties

ADMETox Information

Biotransformation	L-Chicoric acid undergoes reductior glucuronide and trans-caffeic acid r acetoxy-desalkyl-chicoric acid, 4-ac dihydro-chicoric acid.

Toxic Pathologies

Toxic Agents for

#	Toxic Pathology	Drug
1	Pancreas-necrosis	L-Chicoric acid
		Streptozocin
2	Heart-relative weight gain ...	L-Chicoric acid
		Streptozocin
3	Pancreas lesions	L-Chicoric acid
		Streptozocin
4	Liver-relative weight gain (...	L-Chicoric acid
		Streptozocin

Therapeutic Properties

Therapeutic Information

L-Chicoric acid	
Pharmacology	HIV infection
Pharmacology	AIDS

External Databases

CAS registry	70831-56-0
ChEBI ID	CHEBI:3594
ChemIDplus	006537800, 070831560
ChemSpider	4445078
DTP/NCI	699173
KEGG	C10437
NIAID	029768
PubChem_Compound	5281764

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ADMETox Properties 化合物的ADMETox 性質及毒性致病性

ADMETox Information

Biotransformation	L-Chicoric acid undergoes reduction, methylation, glucuronidation and hydrolysis to form dihydro-chicoric acid, 4-methoxy-phenyl-chicoric acid, 4-carboxyl-methyl-chicoric acid, chicoric acid-3-O-glucuronide, chicoric acid-4-O-glucuronide and trans-caffeic acid respectively. trans-Caffeic acid further undergoes glucuronidation, acetylation, sulfation and reduction to form desalkyl-chicoric acid-3-O-glucuronide, desalkyl-chicoric acid-4-O-glucuronide, 3-acetoxy-desalkyl-chicoric acid, 4-acetoxy-desalkyl-chicoric acid, caffeic acid O3-sulfate, caffeic acid O4-sulfate and dihydro-desalkyl-chicoric acid respectively. Dihydro-chicoric acid further undergoes hydrolysis to form desacyl-dihydro-chicoric acid.

Toxic Pathologies

Toxic Agents for

#	Toxic Pathology	Drug	Dosage	Route&Delivery	Source
1	Pancreas-necrosis	L-Chicoric acid	60 mg/kg/day, 28 days	oral/in drinking water	PMID: 2
		Streptozocin	50 mg/kg bw, 5 days	intraperitoneal	
2	Heart-relative weight gain ...	L-Chicoric acid	60 mg/kg/day, 28 days	oral/in drinking water	PMID: 2
		Streptozocin	50 mg/kg bw, 5 days	intraperitoneal	
3	Pancreas lesions	L-Chicoric acid	60 mg/kg/day, 28 days	oral/in drinking water	PMID: 2
		Streptozocin	50 mg/kg bw, 5 days	intraperitoneal	
4	Liver-relative weight gain (...	L-Chicoric acid	60 mg/kg/day, 28 days	oral/in drinking water	PMID: 2
		Streptozocin	50 mg/kg bw, 5 days	intraperitoneal	

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化合物的ADMETox 的試驗及活性

ADMETox Samples

Toxicity

#	Cell line / Organ / Source	Enzyme / Cell Sample	Activity	PMID / Reference
1	MT-2 cell line/Human	Lethal dose (LD5) is the concentration of the compound that inhibits growth of MT-2 cells by 5% in 48 hrs	LD5 (uM) = 264	J. Med. Chem., 1999, 42 (3), 497-509, 9986720
2	MT-2 cell line/Human	Lethal dose of the compound against growth of human MT-2 cell line was determined (CT5 = 264 uM)	LD50 (uM) > 700	Curr. Med. Chem., 2005, 12 (15), 1811-1818, 16029149
3	MT-2 cell line	Cytotoxicity of the compound against MT-2 cell line viability upon incubation for 72h at 37 degree C	CT5 (uM) = 264	Bioorg. Med. Chem., 2006, 14 (13), 4552-4567, 16524737
4	MT-4 cell line/Human	Concentration of compound required to reduce MT-4 cell viability by 50%	IC50 (uM) = 45	J. Med. Chem., 1999, 42 (8), 1401-1414, 10212126

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Reactions 化合物的反應作用

Metabolic Reactions

Substrate of Reactions

#	Reaction	Reaction Type	Enzymes\EC number	Interaction info
1	L-Chicoric acid + S-Adenosyl-L-methionine = 4-Carboxyl-methyl-chicoric acid + S-Adenosyl-L-homocysteine	O-methyl transfer	2.1.1.-	
2	UDP-D-glucuronic acid + L-Chicoric acid = Chicoric acid-3-O-glucuronide + UDP	O-glucuronide transfer	2.4.1.17	
3	L-Chicoric acid + UDP-D-glucuronic acid = UDP + Chicoric acid-4-O-glucuronide	O-glucuronide transfer	2.4.1.17	
4	Electron donor + L-Chicoric acid = Dihydro-chicoric acid + Electron acceptor	Reduction	1.3.-.-	
5	L-Chicoric acid + H_2O = Caftaric acid + trans-Caffeic acid	ester hydrolysis	3.1.1.1	
6	S-Adenosyl-L-methionine + L-Chicoric acid = 4-Methoxy-phenyl-chicoric acid + S-Adenosyl-L-homocysteine	O-methyl transfer	2.1.1.-	

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Biologic Activity 化合物的生物活性

Binding Sample

#	Protein	Cell line / Organ / Source	Enzyme / Cell Sample	Activity	PMID / Reference
1	Integrase	Escherichia coli	Inhibitory concentration against HIV-1 integrase expressed in Escherichia coli after 90 min incubation at 33 degree C in pH 7.4 with the compound dissolved in DMSO	IC50 (uM) = 21	Arch. Pharm. Res., 2001, 24 (4), 286-291, 11534758
2	Integrase	HIV-1	Compound was evaluated for its inhibitory activity against HIV-1 integrase	IC50 (uM) = 24.9	Bioorg. Med. Chem. Lett., 2000, 10 (16), 1879-1882, 10969990
3	Integrase	HIV-1	Compound was tested for the inhibition of HIV-1 integrase	IC50 (ug/mL) = 11.8	Bioorg. Med. Chem., 2003, 11 (17), 3589-3593, 12901903
4	Integrase	HIV-1	Concentration at which inhibitory effect against HIV-1 integrase was observed; Range is 0.06-0.66ug/mL	Concentration (ug/mL) = 0.66	Med. Res. Rev., 2000, 20 (5), 323-349, 10934347
5	Integrase	HIV-1	Effective dose of the compound required to inhibit HIV-1 integrase	ED50 (uM) = 4.2	Bioorg. Med. Chem., 2006, 14 (13), 4552-4567, 16524737
6	Integrase	HIV-1	In vitro inhibitory concentration against 3'-strand processing activity by human immunodeficiency virus type 1 recombinant integrase	IC50 (uM) = 24.9	Curr. Top. Med. Chem., 2004, 4 (10), 1059-1077, 15193139
7	Integrase	HIV-1	Inhibition against Human Immunodeficiency Virus Type 1 Integrase (HIV-1 IN) upon incubation at 37 degree	Inhibition (%) = 96.9	J. Med. Chem., 1999, 42 (3), 497-509,

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化合物的體外試驗與活性

Functional Sample on a Cell Line (in vitro) or on Tissue/Organ but not on whole animal

#	Protein	Cell line / Organ / Source	Enzyme / Cell Sample	Activity	PMID / Reference
1		CEM / SS cell line/Virus	Anti viral effect of compound against virus in CEM-SS cells upon incubation at 37 degree C in a 5% CO2 atmosphere using XTT cytoprotection assay	EC50 (uM) NR	J. Med. Chem., 1999, 42 (8), 1401-1414, 10212126
2		CEM / SS cell line/Virus	Inhibitory concentration against virus in CEM-SS cells upon incubation at 37 degree C in a 5% CO2 atmosphere using XTT cytoprotection assay	IC50 (uM) = 20.1	J. Med. Chem., 1999, 42 (8), 1401-1414, 10212126
3		MT-2 cell line/HIV LAI	Effective dose of the compound required to protect MT-2 cell line from HIVLAI-induced cytopathic effect upon incubation for 72 h at 37 degree C	ED50 (uM) = 4	Antimicrob. Agents Chemother., 1998, 42 (1), 140-146, 9449274
4		MT-2 cell line/HIV-1	Concentration required to inhibit Human Immunodeficiency Virus Type 1 (HIV-1)-induced death of MT-2 cells upon incubation at 37 degree C for 72 hrs	ED50 (uM) = 4.2	J. Med. Chem., 1999, 42 (3), 497-509, 9986720
5		MT-2 cell line/Human	Effective Dose of the compound measured against human MT2 cell line	ED50 (uM) = 4.2	Curr. Med. Chem., 2003, 10 (18), 1795-1810, 12871105
6		MT-2 cell line/Human	Effective dose of the compound towards growth of human MT-2 cell line was determined	ED50 (uM) = 4.2	Curr. Med. Chem., 2005, 12 (15), 1811-1818, 16029149

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如何預測藥物的毒性、代謝、吸收等活性

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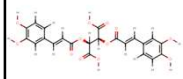
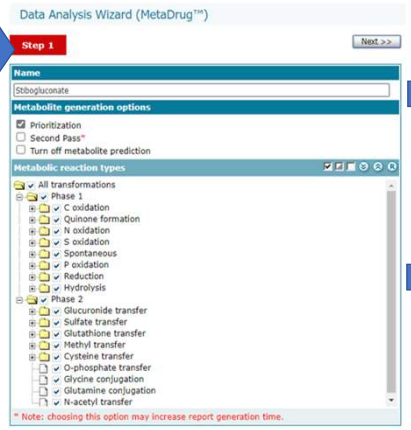
Chicoric acid 的藥物活性預測





代謝物活性預測

CYP450 代謝預測

蛋白質結合活性預測

身體代謝吸收活性預測

適應症治療活性預測

毒性影響預測

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Live demo

以化合物進行小分子藥物活性預測

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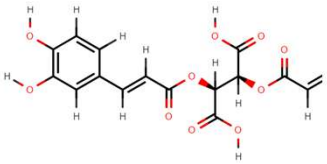
查看化合物基本資料及代謝物預測

Report: Chicoric acid

Export



Similar Compounds

Similar compounds for input molecule

#	Check	Database compound	Drug	Input molecule	Similarity %
	Check all / Uncheck all / Invert all				
1	☑	meso-Chicoric acid		5281764	100.00
2	☑	L-Chicoric acid		5281764	100.00
3	☑	Caftaric acid		5281764	98.52
4	☑	Dihydro-meso-chicoric acid		5281764	84.38
5	☑	Dihydro-chicoric acid		5281764	84.38
6	☑	1,3-Bis[[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]-2,5-dihydroxy-cyclohexanecarboxylic acid		5281764	79.63
7	☑	1,4-Dicaffeoylquinic acid		5281764	78.88

First pass major metabolites

2	☑	5281764_Ester_hydrolysis1B		C13H12O9	312.2300	7	-1.83
3	☑	5281764_o-Quinone_formation1		C22H18O12	474.3740	11	-2.57

Show first pass minor metabolites

Show first pass conjugated metabolites

12	☐	5281764_Cysteine_S-transfer_to_alkenes1		C25H25NO14S	595.5300	16	-2.70
13	☐	5281764_Cysteine_S-transfer_to_alkenes3		C25H25NO14S	595.5300	16	-2.70
14	☐	5281764_Glutathione_S-transfer_to_alkenes1		C32H37N3O17S	767.7100	25	-3.70

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以QSAR model 進行CYP450代謝預測

CYP450 QSAR models

#	Property	Model description	Value/(TP)
4	CYP2C19-inh, prob	Potential to inhibit CYP2C19 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9392, Test set N=3149, Sensitivity= 0.80, Specificity=0.79, Accuracy=0.79, MCC=0.59.	0.06 (74.85)
5	CYP2C9-inh, prob	Potential to inhibit CYP2C9 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=8977, Test set N=2993, Sensitivity=0.64, Specificity=0.88, Accuracy=0.80, MCC=0.54.	0.12 (70.30)
6	CYP2D6-inh, prob	Potential to inhibit CYP2D6 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9759, Test set N=3254, Sensitivity=0.62, Specificity=0.92, Accuracy=0.82, MCC=0.59.	0.04 (74.85)
7	CYP2D6-sub, prob	Potential to be metabolized by CYP2D6, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate that the compound is a substrate for CYP2D6. Model description: Training set N=375, Test set N=69, Sensitivity=0.77, Specificity=0.84, Accuracy=0.81, MCC=0.62. Reference: Clarivate Analytics.	0.10 (31.76)
8	CYP3A4-inh, prob	Potential to inhibit CYP3A4 at 10 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential inhibitors. Data taken from PubChem Bioassay 1851. Model description: Training set N=9145, Test set N=3049, Sensitivity=0.74, Specificity=0.83, Accuracy=0.79, MCC=0.57.	0.17 (74.85)

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以QSAR model 進行蛋白質結合預測

▼ **Protein binding QSAR models**

#	Property	Model description	Value/(TP)
1	5HT2B-act, prob	Potential to activate 5-hydroxytryptamine (serotonin) receptor 2B at 1 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate active compounds. Training set consists of chemicals and drugs that activate 5HT2B receptor resulting in valvular heart disease. Reference: Chekmarev et al., Chem Res Tox, 2008 (PMID: 18415049). Model description: Training set N=194, Test set N=38, Sensitivity=1.0, Specificity=0.96, Accuracy=0.97, MCC=0.94.	0.01 (28.97)
2	ADR-lig, prob	Potential to bind to Androgen receptor, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential Androgen receptor ligands. Reference: Fang H, Tong W, et al Chem Res Tox 2003 (PMID: 14565775). Model description: Training set N=165, Test set N=32, Sensitivity=1.0, Specificity=1.0, Accuracy=1.0, MCC=1.0.	0.39 (38.73)
3	ESR-lig, prob	Potential to bind to Estrogen receptor at 100 uM or less, range from 0 to 1. Cutoff is 0.5. Values higher than 0.5 indicate potential Estrogen receptor ligands. Training set is based on DSSTox KIERBL data (EPA). Model description: Training set N=164, Test set N=55, Sensitivity=1.0, Specificity=0.87, Accuracy=0.93, MCC=0.86.	0.50 (45.93)
4	PXR-act, prob	Pregnane X receptor activation binary model, range from 0 to 1. Values higher than 0.5 indicate potential PXR activators, values lower than 0.5 are preferable. Reference: Clarivate Analytics. Model description: N=95, R2=0.64, RMSE=0.29.	0.54 (30.65)
5	Pgp-inh, pIC50	Human P-glycoprotein transporter inhibition, pIC50 (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity. Clarivate Analytics. Model description: N=274, R2=0.85, RMSE=0.4.	-1.13 (34.50)
6	Pgp-sub, prob	Potential to be a substrate of human P-glycoprotein transporter, range from 0 to 1. Cutoff is 0.5. Values closer to 1 indicate potential ligands. Reference: Penzotti, Lamb, et al., 2002 (PMID: 11960484). Model description: N=192, R2=0.65, RMSE=0.3.	0.77 (38.94)
7	SERT-inh, pKi	Human serotonin transporter inhibition, pKi (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity of the metabolite. Clarivate Analytics. Model description: N=256, R2=0.91, RMSE=0.36.	0.28 (37.05)
8	hERG-inh, pKi	Human hERG (human ether a-go-go-related gene) channel inhibition, pKi (uM). Cutoff is -1.7. The higher the value, the higher the inhibition activity. Lower values are preferable. Reference: Clarivate Analytics. Model description: N=196, R2=0.93, RMSE=0.23.	-0.13 (31.43)

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以QSAR model 進行吸收、擴散、代謝及排泄等預測

▼ **ADME QSAR models**

#	Property	Model description	Value/(TP)
1	BBB, log ratio	Blood brain barrier penetration model. The data is expressed as log values of the ratio of the metabolite concentrations in brain and plasma. Cutoff is -0.3. Larger values indicate that the metabolite is more likely to enter the brain. Reference: Clarivate Analytics. Model description: N=107, R2=0.89, RMSE=0.26.	-1.20 (30.41)
2	G-LogP	Lipophilicity, log of compound octanol-water distribution. Cutoffs are -0.4 to 5.6. Values greater than 5.6 correspond to overly hydrophobic compounds. Reference: Syracuse Research, PHYSPROP database. Model description: N=13474, R2=0.95, RMSE=0.21.	3.09
3	Prot-bind, %	Human serum protein binding, %. Cutoff is 50%. A value of more than 95% is highly bound, less than 50% is a low binding metabolite. Reference: Thummel and Shen, 2001 in Goodman & Gilman's The Pharmacological Basis of Therapeutics. Model description: N=265, R2=0.909, RMSE=10.11.	64.11 (31.43)
4	Prot-bind, log t	Affinity to human serum albumin, log value of the retention time. Cutoff is 0. Positive values correspond to higher protein binding, negative values to lower protein binding. An acceptable level of binding is project dependent. The model is based on retention times of compounds assayed by HPLC using an immobilized HSA column. Values are expressed as log values of the retention time. Reference: Colmenarejo, Alvarez-Pedraglio, et al., 2001 (PMID: 11728183). Model description: N=95, R2=0.904, RMSE=0.2.	-0.15 (30.41)
5	WSol, log mg/L	Water solubility at 25??C, log mg/L. Cutoffs are from 2 to 4. An acceptable level of solubility is project dependent. Reference: Syracuse Research, PHYSPROP database. Model description: N=2871, 2=0.91, RMSE=0.54.	1.61

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以QSAR model 進行20+種適應症治療活性預測

▼ **Prediction of therapeutic activity**

#	Property	Model description	Value/(TP)
16	Mycosis	Potential antifungal activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=172, Test set N=47, Sensitivity= 0.90, Specificity=0.88, Accuracy=0.89, MCC=0.79. Reference: Clarivate Analytics.	0.60 (39.56)
17	Obesity	Potential activity against obesty. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=472, Test set N=75, Sensitivity= 0.89, Specificity=0.97, Accuracy=0.93, MCC=0.87. Reference: Clarivate Analytics.	0.93 (31.64)
18	Osteoporosis	Potential anti-osteoporosis activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=595, Test set N=86, Sensitivity= 0.84, Specificity=0.85, Accuracy=0.85, MCC=0.70. Reference: Clarivate Analytics.	0.67 (39.66)
19	Pain	Potential analgetic activity. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=525, Test set N=84, Sensitivity= 0.92, Specificity=0.67, Accuracy=0.79, MCC=0.60. Reference: Clarivate Analytics.	0.10 (38.89)
20	Parkinson	Potential activity against Parkinson's disease. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=298, Test set N=49, Sensitivity= 0.96, Specificity=0.96, Accuracy=0.96, MCC=0.92. Reference: Clarivate Analytics.	0.08 (35.89)
21	Psoriasis	Potential activity against psoriasis. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=199, Test set N=32, Sensitivity= 0.93, Specificity=0.82, Accuracy=0.89, MCC=0.74. Reference: Clarivate Analytics.	0.14 (50.63)
22	Schizophrenia	Potential activity against schizophrenia. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs, drug candidates in clinical trials and preclinical compounds with in vivo activity. Model description: Training set N=616, Test set N=93, Sensitivity= 0.89, Specificity=0.91, Accuracy=0.90, MCC=0.80. Reference: Clarivate Analytics.	0.71 (53.33)
23	Skin Diseases	Potential activity against skin diseases. Cutoff is 0.5. Values higher than 0.5 indicate potentially active compounds. Training set consists of approved drugs. Model description: Training set N=255, Test set N=36, Sensitivity= 1.00, Specificity=0.76, Accuracy=0.86, MCC=0.76. Reference: Clarivate Analytics.	0.64 (41.76)

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以QSAR model 進行20+種毒性預測

▼ **Prediction of toxic effects**

#	Property	Model description	Value/(TP)
1	AMES	Potential to be mutagenic (AMES positive), range from 0 to 1. A value of 1 is AMES positive (mutagenic), and a value of 0 is AMES negative (non-mutagenic). Cutoff is 0.5. Values close to zero are preferable. The AMES assay is based upon the reversion of mutations in the histidine operon in the bacterium Salmonella enterica sv Typhimurium. Reference: Young, Gombar, et al., 2002 (DOI: 10.1016/S0169-7439(01)00181-2). Model description: N=1780, R2=0.69, RMSE=0.29.	0.22 (74.85)
2	Anemia	Potential for causing anemia. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing anemia in vivo. Model organisms: human. Model description: Training set N=324, Test set N=51, Sensitivity= 0.82, Specificity=0.90, Accuracy=0.86, MCC=0.72. Reference: Clarivate Analytics.	0.22 (36.32)
3	Carcinogenicity	Potential for inducing carcinogenicity in rats and mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse, rat. Reference: ISSCAN data. Model description: Training set N=1210, Test set N=185, Sensitivity= 0.96, Specificity=0.90, Accuracy=0.93, MCC=0.86.	0.10 (53.33)
4	Carcinogenicity Mouse Female	Potential for inducing carcinogenicity in female mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female mice. Reference: ISSCAN data. Model description: Training set N=640, Test set N=94, Sensitivity= 0.90, Specificity=0.93, Accuracy=0.92, MCC=0.83.	0.16 (53.33)
5	Carcinogenicity Mouse Male	Potential for inducing carcinogenicity in male mice. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: mouse male. Reference: ISSCAN data. Model description: Training set N=584, Test set N=93, Sensitivity= 0.91, Specificity=0.88, Accuracy=0.89, MCC=0.78.	0.20 (53.33)
6	Carcinogenicity Rat Female	Potential for inducing carcinogenicity in female rats. Cutoff is 0.5. Values higher than 0.5 indicate potentially toxic compounds. Training set consists of chemicals and drugs causing carcinogenicity in vivo. Model organisms: female rat. Reference: ISSCAN data. Model description: Training set N=667, Test set N=120, Sensitivity= 0.90, Specificity=0.96, Accuracy=0.93, MCC=0.86.	0.07 (39.56)

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化合物活性預測數據註解

Abbreviations	
CL	The Intrinsic Clearance (CL) of a drug is the volume of plasma from which the drug is completely removed per unit of time. The amount eliminated is proportional to the concentration of the drug in the blood.
IC50	IC50 is a parameter used in pharmacological research. IC50, the half maximal inhibitory concentration, represents the concentration of an inhibitor that is required for 50% inhibition of its target or a process (i.e. an enzyme, receptor, cell proliferation).
Km	Km represents the dissociation constant (affinity for substrate) of the enzyme-substrate (ES) complex. Low values indicate that the ES complex is held together very tightly and rarely dissociates without the substrate first reacting to form a product.
Ki	The inhibitor constant (Ki) is the dissociation constant of an enzyme-inhibitor complex. A large value of Ki indicates a low affinity and vice versa.
N	Number of compounds used to build the model.
R2	Correlation coefficient between actual and predicted values, the higher the coefficient, the better the prediction of the model.
RMSE	Root mean squared error, the less the value, the better the prediction of the model.
Vmax	The speed V means the number of reactions per second that are catalyzed by an enzyme. With increasing substrate concentration [S], the enzyme asymptotically approaches its maximum speed Vmax, but never actually reaches it. Because of that, no [S] for Vmax can be given. Instead, the characteristic value for the enzyme is defined by the substrate concentration at its half-maximum speed (Vmax/2).
TP	Tanimoto Prioritization (TP) is a maximal Tanimoto coefficient calculated for all of the molecules of the training set. TP is a similarity to the most-similar hit of the QSAR training set.

Colors
Green color is used for values within thresholds. **Red** - for values beyond thresholds. **Blue** - for physicochemical properties. In the case of binary models and bioactivity-toxicity QSAR models, coloring depends on the model. Users should carefully read the description of the model before use.

Cutoffs
Cutoff for QSAR models is log Km (IC50,EC50) = 1.7 (-1.7 in case of log 1/Km (1/IC50, 1/EC50)). This value corresponds to the cutoff for active/non-active metabolites and is equal to 50 mkM. Values lower than 1.7 are marked green and the correspondent protein appears in the Possible targets list.

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Mol. Nutr. Food Res. 2008, 52, 789–798 DOI 10.1002/mnfr.200700113

Review

A critical evaluation of drug interactions with *Echinacea* spp.

Camille Freeman [1,3] **and Kevin Spelman** [2,3]

[1] Department of Physiology and Biophysics (MS candidate), Georgetown University, Washington, DC, USA
[2] Department of Chemistry and Biochemistry, University of North Carolina, Greensboro, NC, USA
[3] Department of Herbal Medicine, Tai Sophia Institute, Laurel, MD, USA

Another isoform of the CYP 450 system, CYP2D6, is known to play a primary role in the metabolism of pharmaceuticals used to treat psychiatric disorders (attention deficit/hyperactivity disorders, bipolar disorder, depression, schizophrenia) as well as cardiovascular disorders (β-block-

紫錐花萃取物可能透過 cytochrome P450 活性抑制，影響精神失調相關的治療。

Analysis of the inhibitory potential of Ginkgo biloba, Echinacea purpurea, and Serenoa repens on the metabolic activity of cytochrome P450 3A4, 2D6, and 2C9

Steven H Yale [1], Ingrid Glurich

Affiliations + expand

PMID: 15992226 DOI: 10.1089/acm.2005.11.433

Results: S. repens showed potent inhibition of the metabolic activity of all three CYPs tested. The effects of G. biloba and E. purpurea varied. E. purpurea demonstrated mild inhibition of CYP3A4 activity with 7- benzyloxy-4-trifluoromethylcoumarin (BFC) as the model substrate, but mild inducing effects in the presence of the model substrate resorufin benzyl ether (BzRes). Little effect on CYP2D6 and moderate inhibition of CYP2C9 was seen with both E. purpurea and G. biloba. G. biloba also showed mild-to-moderate inhibition of CYP3A4 depending on the model substrate.

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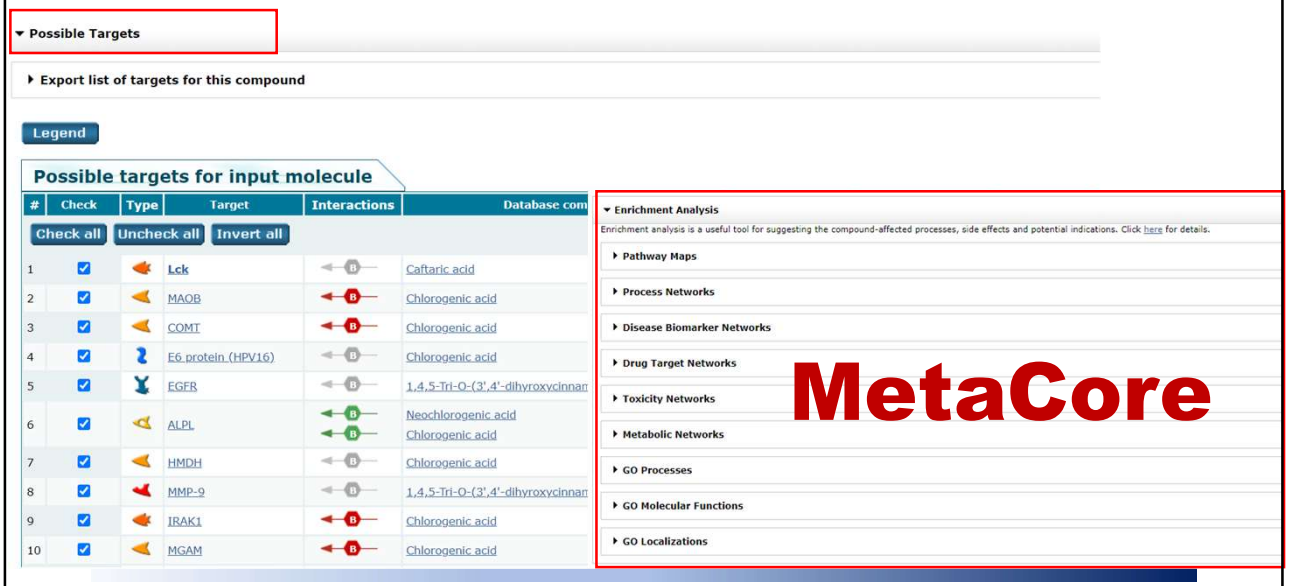
預測化合物相對應的可能標靶，亦可分子及路徑機制分析



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以化合物建構代謝網絡或分子路徑

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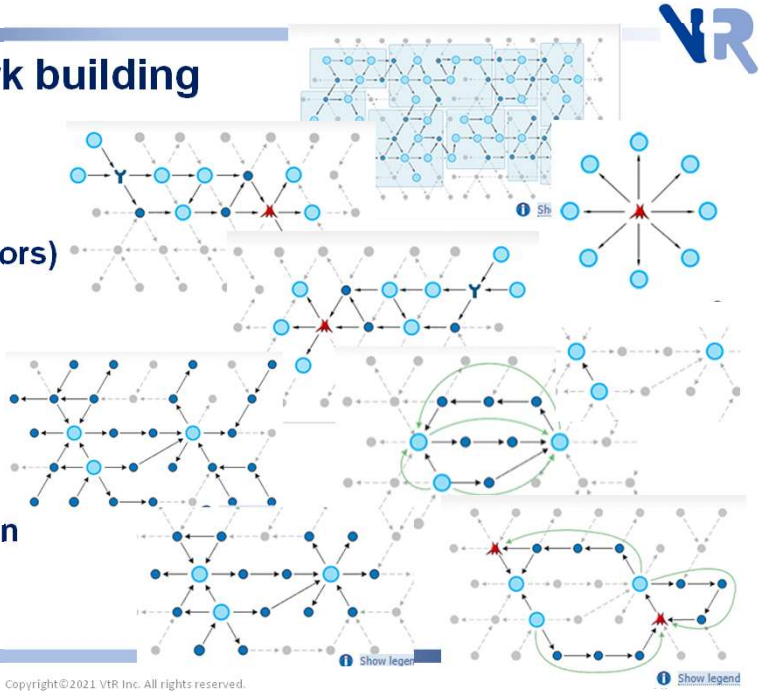
Algorithms of network building

- Analyze network
- Analyze network (TF)
- Analyze network (Receptors)
- Transcription regulation
- Shortest paths
- Direct interactions
- Self regulation
- Auto expand
- Expand by one interaction
- Manual expand



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Live demo

以化合物建構代謝網絡或分子路徑

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以化合物建構代謝網絡

#	Name	GO processes	# Nodes Total	# Nodes Seed	Pathways	p-Value	zScore	gScore	Edit
1	L-Chicoric acid intracellular, trans-Caffeic acid intracellular, H(,2)O + Neochlorogenic acid = trans-Caffeic acid + Quinic acid, Isoacteoside + H(,2)O = trans-Caffeic acid + Decaffeoyl acteoside, L-Chicoric acid + H(,2)O = Caftaric acid + trans-Caffeic acid		28	1	0	2.25e-05	210.65	210.65	

Choose building algorithm

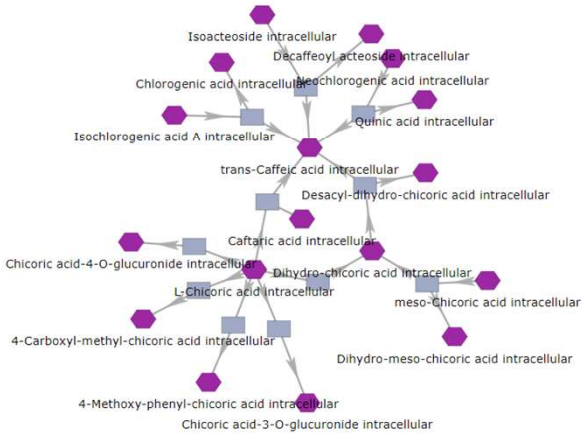
Analyze network

Number of nodes in a network 50

Use canonical pathways (processing takes longer for large datasets)

Build network

Show additional options



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以 Auto expand 尋找與化合物相關的分子及作用機制

Choose building algorithm

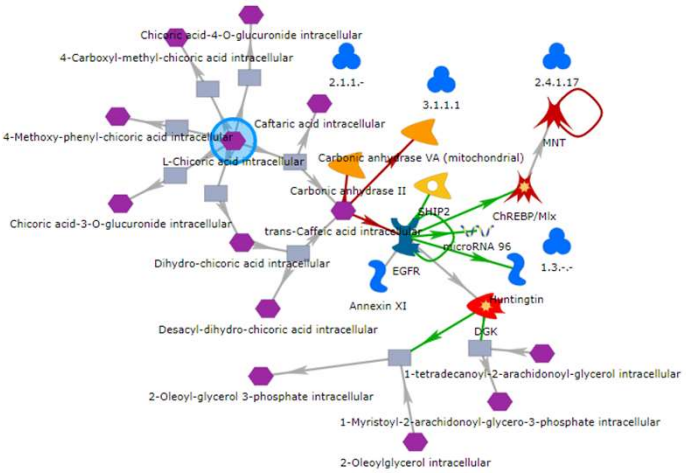
Auto expand

Number of nodes in a network 50

Use canonical pathways (processing takes longer for large datasets)

Build network

Show additional options



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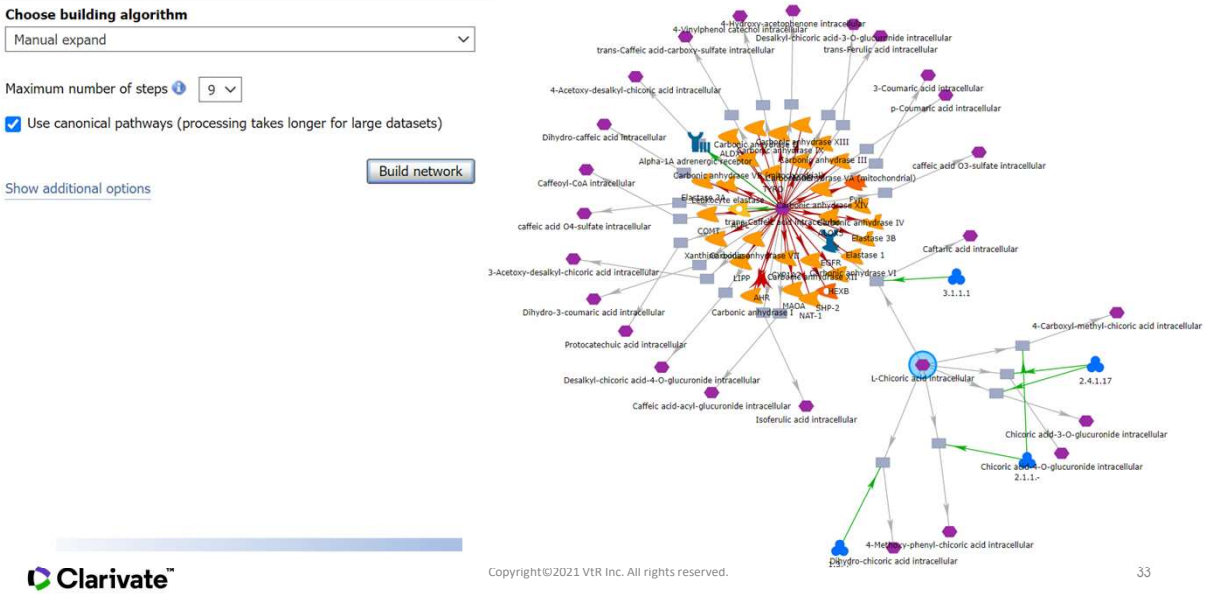
以 Manual expand 尋找更多相關的分子作用與機制



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MetaDrug的底層資料

- >70 QSAR 模型，用於預測化合物毒性、藥代動力學特徵、治療活性
- > 160 種代謝規則，用於代謝產物預測
- > 1,600 個經典範式通路圖，涵蓋近200,000 個人類、小鼠、大鼠代謝和信號通路（基於文獻報導的一致性）
- >1,800,000 個蛋白與蛋白、DNA、RNA、代謝物、外源物相互作用
- 數千種疾病生物標記物（Biomarker）
- >800,000 個化合物及其靶標與生物活性資料
- > 5,000 個代謝反應
- > 9,100 個藥物
- >30,000 個內源代謝產物
- 上百萬個基因、蛋白和化合物的別稱（同種異名）
- 人、小鼠、大鼠的蛋白複合物和蛋白家族

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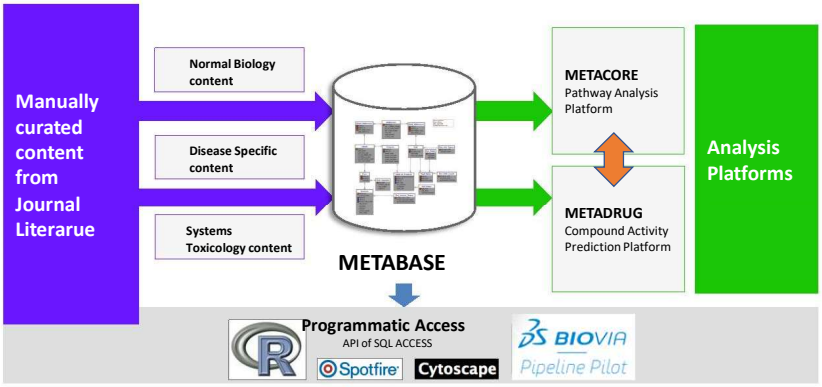
科學研究及再發現



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Summary

- 預測小分子化合物的潛在靶點
- 找出小分子化合物影響的生物學路徑
- 預測藥物的適應症
- 發現藥效的生物標記物
- 預測化合物的代謝產物、藥代動力學特徵和副作用

- 藥物研發
- 先導化合物的確認及優化
- 靶標發現
- 疾病領域研究
- 化合物篩選
- 化學資訊學和藥物化學
- 藥代動力學研究
- 毒性評估

(1)針對每個已知化合物，整合其已有資訊，並預測其未知特性，如：標靶，作用機制、代謝產物、毒性等。
(2)針對新合成或分離出來的化合物，根據結構預測其未知的特性，如：標靶、作用機制、代謝產物、毒性等。
(3)從化合物庫中篩選已知資訊並預測未知的特性，對其進行比較與評估重要性。

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研究者以
MetaDrug
進行分析後發表，
受知名期刊重視。

Science Translational Medicine AAAS
nature reviews drug disc
Science Advances AAAS
bioRxiv THE PREPRINT SERVER FOR BIOLOGY
Cell Metabolism
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nature
SCIENTIFIC REPORTS

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From Virtual to Real… and back

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