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Human *In vitro* Drug Metabolism Dataset

Transforming scientific data into clinical knowledge

The Drug Metabolism Dataset contains results from *in vitro* metabolism studies, where a drug is tested as an inhibitor/activator/inducer (precipitant) or a substrate (object) for a given human drug metabolizing enzyme (including variants).

- **Metabolism parameters** (IC_{50}, K_i, K_I, k_{inact}, % inhibition, % activation, % or fold increase, EC_{50}, E_{max}, K_m, V_{max}, and CL_{int}), along with detailed experimental conditions, are extracted from published articles (citations) and NDA/BLA reviews.

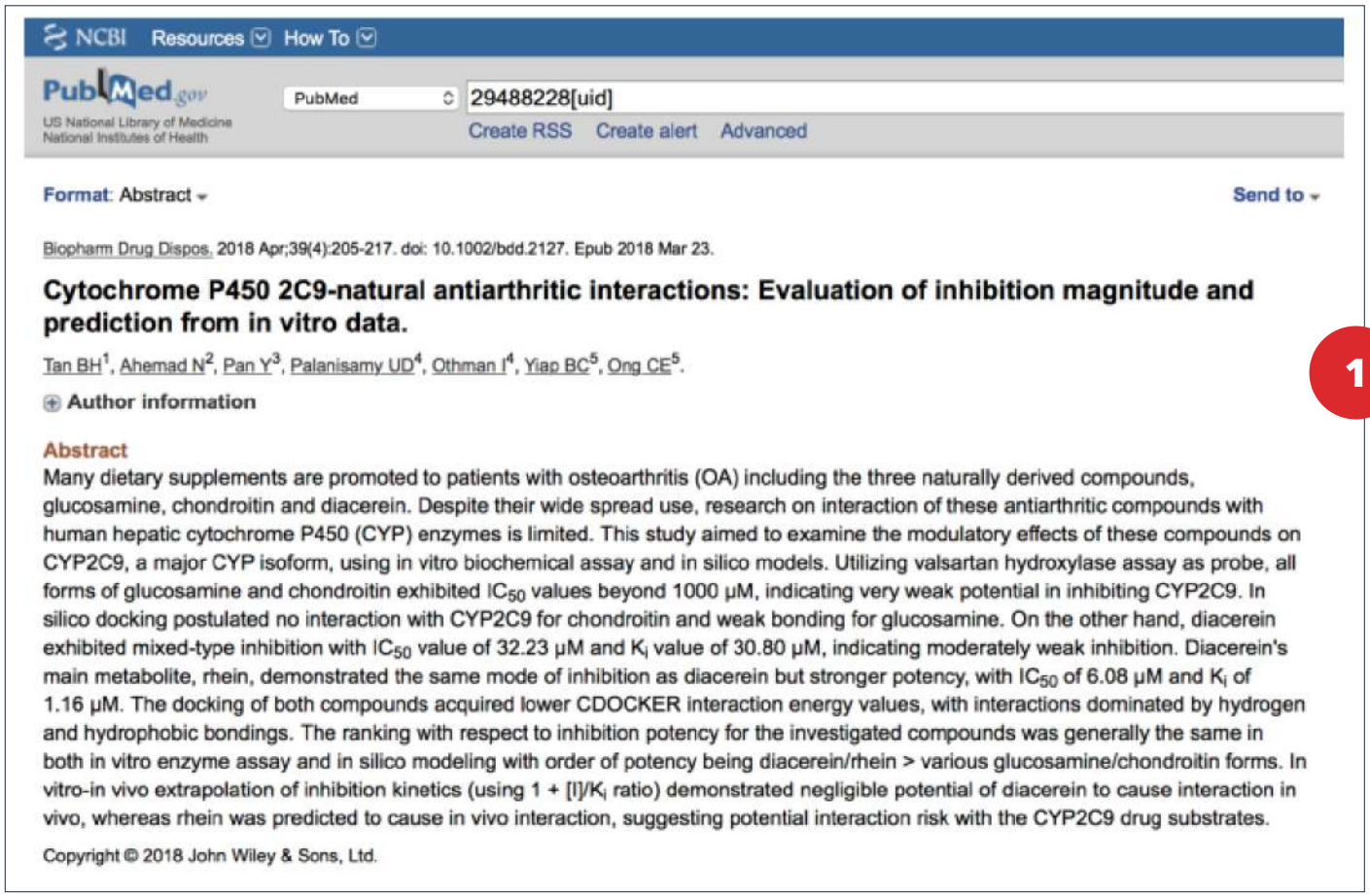
- **Study results** are organized according to the overall effect and mechanism of the interaction:
  → Enzyme inhibition entry: drug as inhibitor or non-inhibitor
  → Enzyme activation entry: drug as activator or non-activator
  → Enzyme induction entry: drug as inducer, down-regulator, or non-inducer
  → Enzyme substrate entry: drug as substrate

- **Multiple queries** allow users to retrieve an *in vitro* dataset by drug name, enzyme name, or mechanism of the interaction (drug as precipitant or as object).

- **Results** can be viewed, customized, and downloaded in multiple formats, allowing users to compile and organize the large body of information available.

FROM A **CITATION** OR **NDA/BLA REVIEW**

The latest, most relevant, peer-reviewed publications and regulatory documents are identified and fully analyzed. Study protocol and results are manually curated to update the knowledgebase on a daily basis.



NCBI Resources How To

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Biopharm Drug Dispos. 2018 Apr;39(4):205-217. doi: 10.1002/bdd.2127. Epub 2018 Mar 23.

Cytochrome P450 2C9-natural antiarthritic interactions: Evaluation of inhibition magnitude and prediction from in vitro data.

Tan BH[1], Ahemad N[2], Pan Y[3], Palanisamy UD[4], Othman I[4], Yiap BC[5], Ong CE[5].

Author information

Abstract

Many dietary supplements are promoted to patients with osteoarthritis (OA) including the three naturally derived compounds, glucosamine, chondroitin and diacerein. Despite their wide spread use, research on interaction of these antiarthritic compounds with human hepatic cytochrome P450 (CYP) enzymes is limited. This study aimed to examine the modulatory effects of these compounds on CYP2C9, a major CYP isoform, using in vitro biochemical assay and in silico models. Utilizing valsartan hydroxylase assay as probe, all forms of glucosamine and chondroitin exhibited IC_{50} values beyond 1000 μM, indicating very weak potential in inhibiting CYP2C9. In silico docking postulated no interaction with CYP2C9 for chondroitin and weak bonding for glucosamine. On the other hand, diacerein exhibited mixed-type inhibition with IC_{50} value of 32.23 μM and K_i value of 30.80 μM, indicating moderately weak inhibition. Diacerein's main metabolite, rhein, demonstrated the same mode of inhibition as diacerein but stronger potency, with IC_{50} of 6.08 μM and K_i of 1.16 μM. The docking of both compounds acquired lower CDOCKER interaction energy values, with interactions dominated by hydrogen and hydrophobic bondings. The ranking with respect to inhibition potency for the investigated compounds was generally the same in both in vitro enzyme assay and in silico modeling with order of potency being diacerein/rhein > various glucosamine/chondroitin forms. In vitro-in vivo extrapolation of inhibition kinetics (using 1 + [I]/K_i ratio) demonstrated negligible potential of diacerein to cause interaction in vivo, whereas rhein was predicted to cause in vivo interaction, suggesting potential interaction risk with the CYP2C9 drug substrates.

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TO A FULLY **CURATED DATASET**

Prior to integration, all data are carefully and critically evaluated. The richness of each citation, including relevant insights, is exploited, generating a highly detailed dataset.

Tree View of Citation Data

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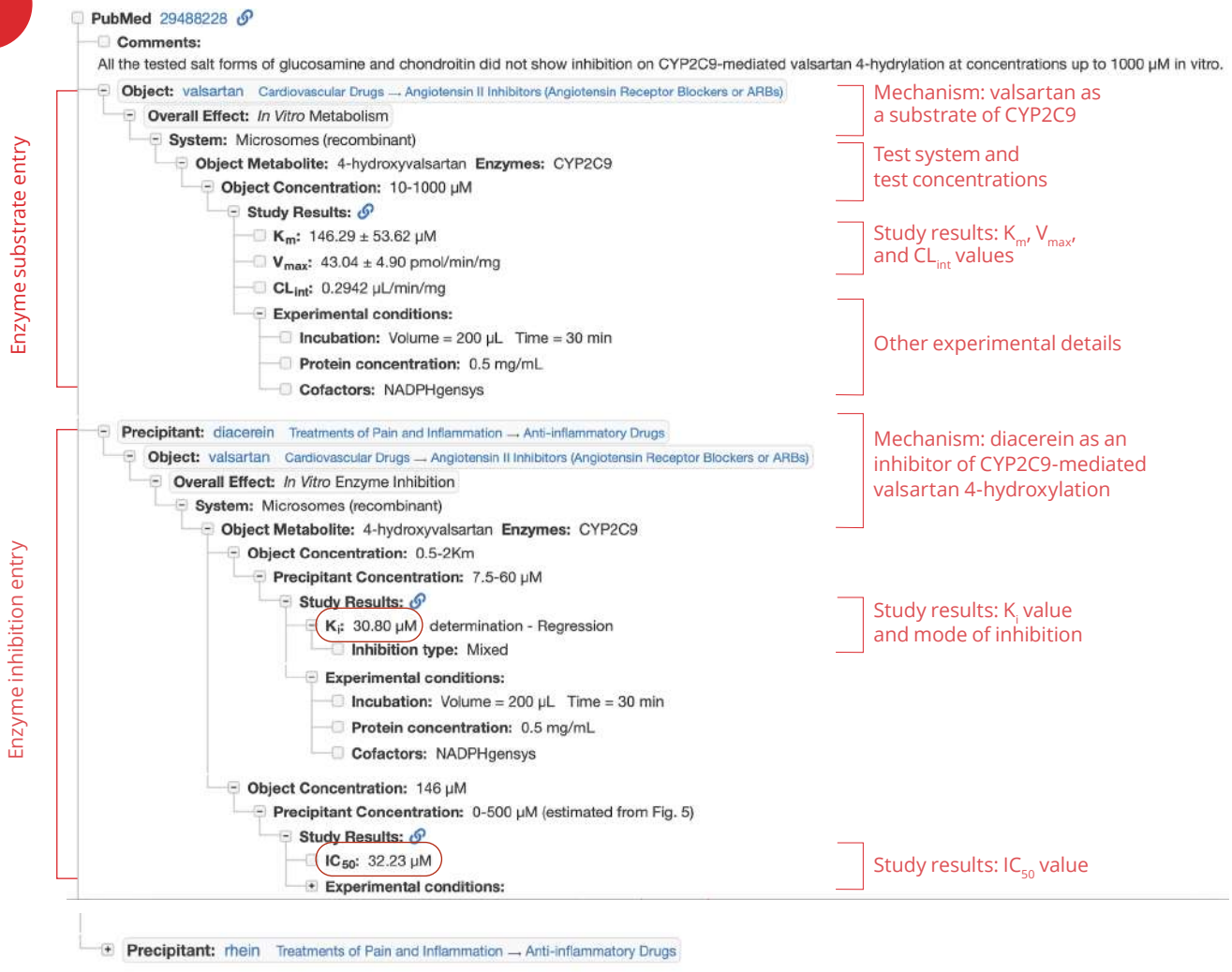

Diacerein inhibits CYP2C9 with an IC_{50} value of 32.23 µM and a K_i value of 30.80 µM.
What other drugs inhibit the CYP2C9 index substrate diclofenac?

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POWERFUL TOOL FOR **DATA INTEGRATION**: FROM ONE CITATION TO METADATA ANALYSIS

The data are formatted for immediate use and can be filtered and re-arranged to allow meta-analysis of multiple results.

Query all CYP2C9 inhibitors

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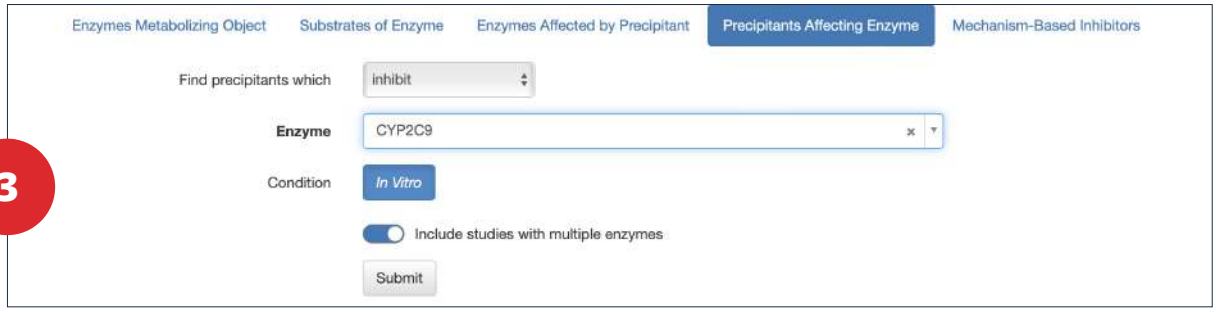

Table View of Query Results

Filter

Multiple formats for viewing and downloading

Showing 201 to 300 of 1,078 entries (filtered from 3,910 total entries)

Advanced Table Search | Select columns | Copy | Excel | CSV | Print

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Precipitant	Precipitant Therapeutic Class	Object	Object Metabolite	System	K_i	Inhibition Type	IC_{50}	Accession # or NDA/BLA #	Published
		diclo							
nifedipine	Cardiovascular Drugs → Calcium Channel Blockers	diclofenac	4'-hydroxydiclofenac	Microsomes (recombinant)	0.57 µM	Competitive		PubMed 16963489	2006 Dec
triclabendazole sulfoxide	Anti-Infective Agents → Antiparasitics	diclofenac	4'-hydroxydiclofenac	Microsomes HL	Ki,u = 0.565 ± 0.03 µM; Ki = 1.33 ± 0.063 µM	Competitive		NDA 208711	2019
honokiol	Natural Products → Herbal Medications	diclofenac	4'-hydroxydiclofenac	Microsomes HL (pooled)	0.54 µM	Competitive		PubMed 24005963	2013 Sep 03
fluvastatin (acid)	Cardiovascular Drugs → HMG CoA Reductase Inhibitors (Statins)	diclofenac	4'-hydroxydiclofenac	Microsomes HL	0.5 ± 0.1 µM	Mixed		PubMed 10064574	1999 Mar
galangin	Natural Products → Herbal Medications	diclofenac	4'-hydroxydiclofenac	Recombinant enzyme	0.50 µM	Competitive		PubMed 19074529	2009 Mar
glycyrol	Natural Products → Herbal Medications	diclofenac	4'-hydroxydiclofenac	Microsomes HL (pooled)	0.50 µM	Competitive		PubMed 26750984	2016 Oct
sulfaphenazole	Anti-Infective Agents → Antibiotics	diclofenac	4'-hydroxydiclofenac	Microsomes (recombinant)	0.5 µM	Competitive		PubMed 11207028	2001 Feb
alpha-naphthoflavone	Miscellaneous Agents →	diclofenac	4'-hydroxydiclofenac	Microsomes (recombinant)	0.41 µM	Competitive		PubMed 16963489	2006 Dec

Obtain a complete list of *in vitro* inhibitors of CYP2C9

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IN VITRO METABOLISM DATASET IN NUMBERS

(as of October 16, 2023)

6,206 citations / **404** NDAs/BLAs

24,269 substrate entries / **51,831** inhibition entries

735 activation entries / **8,905** induction entries

69,926 positive entries / **14,517** negative entries

36 *in vitro* metabolism queries with **117** possible searches

186 drug metabolizing isozymes & **72** variants

2,764 compounds as substrates / **5,306** compounds as inhibitors

265 compounds as activators / **1,975** compounds as inducers

705 food products & **1,960** herbal medications

APPLICATIONS OF THE IN VITRO METABOLISM DATASET

PROVIDES CONTEXT for RESULTS OBTAINED for candidate compouds

ALLOWS ASSESSMENT of MEASUREMENT VARIABILITY
(inter-lab, substrate- and system-dependency, etc.)

SUPPORTS STATIC PREDICTIONS and PBPK MODELING
with input parameters

HELPS OPTIMIZE IN VITRO STUDY DESIGN
(cell system, incubation conditions, test concentrations, choice of substrate/inhibitor, etc.)

ASSISTS with DOSE SELECTION for clinical trials

PROVIDES *IN VITRO* EVIDENCE to EXPLAIN CLINICAL RESULTS and improve understanding of drug interaction mechanisms

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To learn more, visit www.druginteractionsolutions.org

or email DIDBase@Certara.com

About Certara

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