ASSISTS with DOSE SELECTION for clinical trials

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

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

Human In vitro Drug Metabolism DATASET

Transforming scientific data into clinical knowledge
Human *In vitro* Drug Metabolism Dataset

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** ($IC_{50}$, $K$, $K_r$, $k$, % 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 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.

druginteractionsolutions.org
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.

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

Tan Bi#1, Ahmed N2, Pan Y3, Pelinaram YU4, Ohman F4, Yao Bo5, Cong C25.

**Abstract**

Many dietary supplements are promoted to patients with osteoarthritis (OA) including the three naturally derived compounds, glucosamine, chondroitin and diacerein. Despite their widespread 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 IC50 values beyond 1000 μM, indicating very weak potential in inhibiting CYP2C9. In silico docking postulated no interaction with CYP2C9 for chondroitin and weak binding for glucosamine. On the other hand, diacerein exhibited mixed-type inhibition with IC50 value of 32.23 μM and Ki 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 IC50 of 6.08 μM and Ki of 1.16 μM. The docking of both compounds acquired lower DOCKING 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/Ki) 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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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.

**Mechanism:** valsartan as a substrate of CYP2C9

**Test system and test concentrations**

**Study results:** $K_m$, $V_{max}$, and $CL_{int}$ values

**Other experimental details**

**Mechanism:** diacerein as an inhibitor of CYP2C9-mediated valsartan 4-hydroxylation

**Study results:** $IC_{50}$ value and mode of inhibition

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?
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**

Filter

**Multiple formats for viewing and downloading**

Table View of Query Results

Obtain a complete list of *in vitro* inhibitors of CYP2C9
IN VITRO METABOLISM DATASET IN NUMBERS
(as of April 16, 2020)

- **5,213** citations
- **270** NDAs/BLAs
- **19,649** substrate entries
- **40,842** inhibition entries
- **636** activation entries
- **6,761** induction entries
- **55,678** positive entries
- **11,716** negative entries
- **2,125** compounds as substrates
- **4,433** compounds as inhibitors
- **225** compounds as activators
- **1,500** compounds as inducers
- **639** food products
- **1,555** herbal medications

APPLICATIONS OF THE IN VITRO METABOLISM DATASET

- PROVIDES CONTEXT for RESULTS OBTAINED with candidate compounds
- 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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