DEEP NEURAL NETWORK MODELING IDENTIFIES DIPHENYLAMINE NSAIDS AS HIGHLY BIOACTIVATED HEPATOTOXIC METABOLITES

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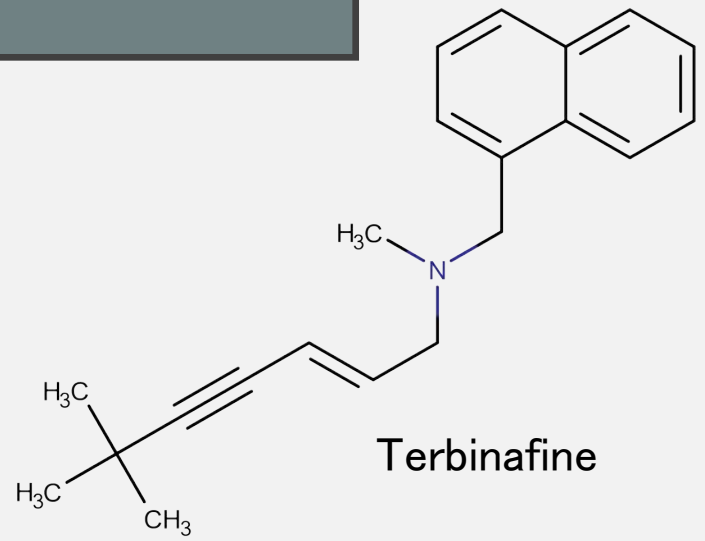
University of Arkansas for Medical Sciences

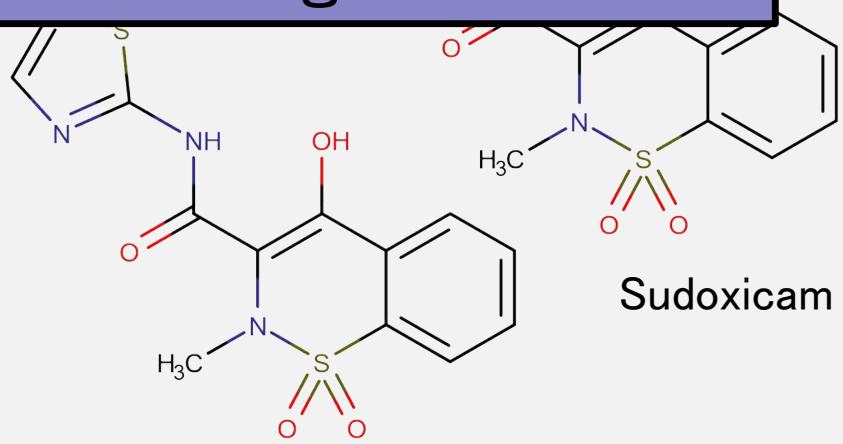
THE MILLER LABORATORY

- Identify and characterize drug metabolic bioactivation and subsequent hepatotoxicity
- Current standard: choose a compound of interest based upon literature searches and
- Employ computational modeling to isolate understudied compounds or structures, as well as those with greater risk



Terbinafine

What if we use bioinformatics to identify subsets of hepatotoxic molecules prior to computational modeling?



Sudoxicam

Meloxicam

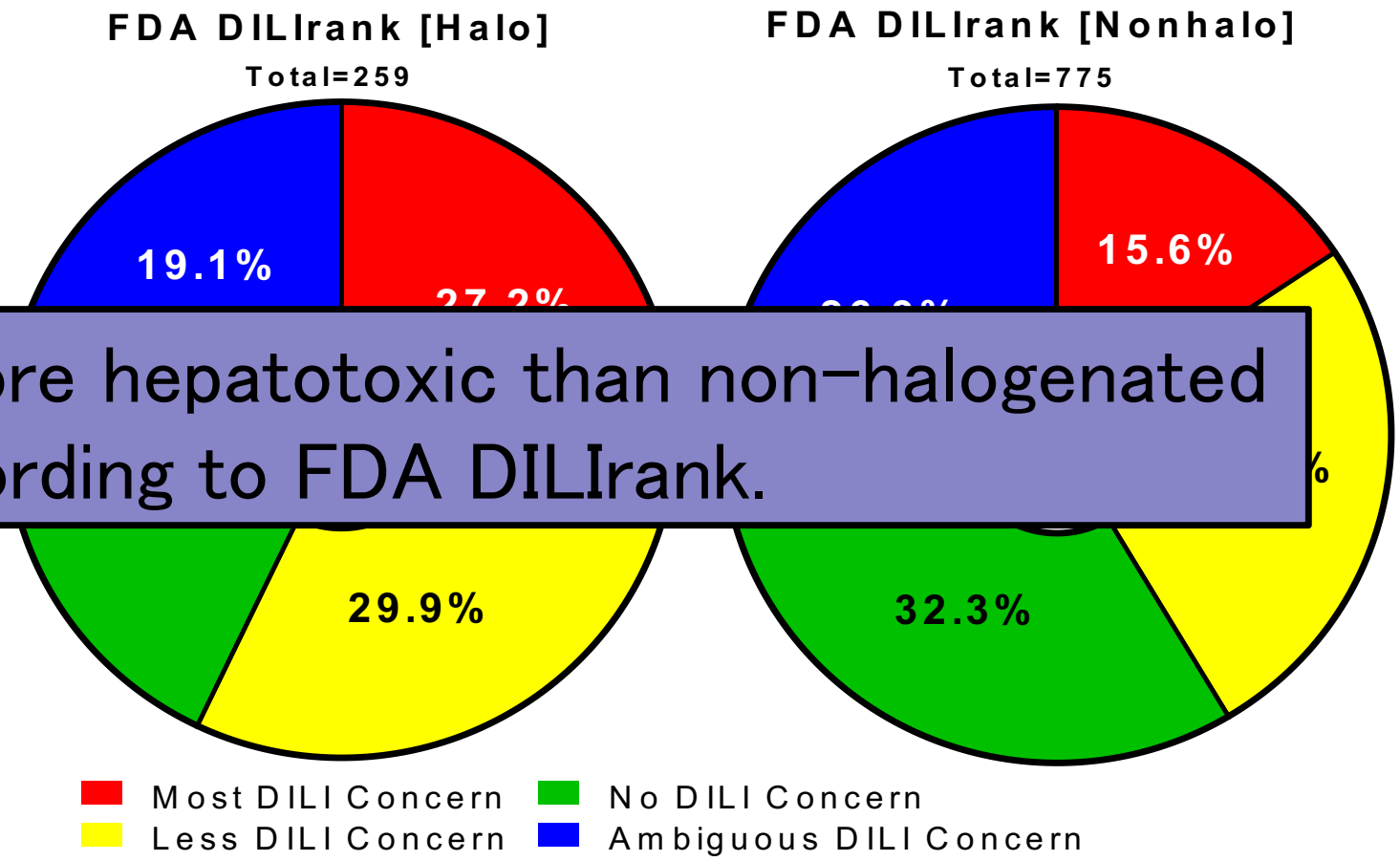
10.1016/j.bcp.2018.07.043; 10.1021/acs.chemrestox.9b00006; 10.1016/j.bcp.2019.113661; 10.1016/j.tox.2020.152478

FDA DILIRANK STRATIFICATION OF DRUG RISK

- 4 categories: Most, Less, Ambiguous, and No DILI Concern

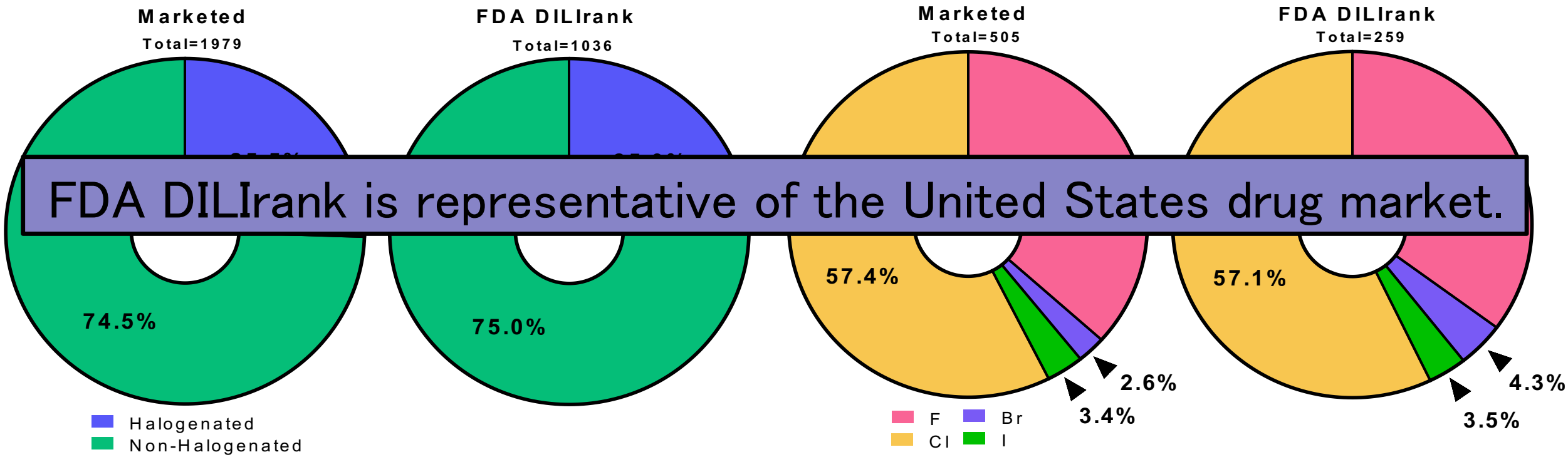
Halogenated drugs are more hepatotoxic than non-halogenated drugs, according to FDA DILIrank.

1. Severity of reactions
2. Frequency of reactions
3. Reaction causality



Manuscript in revision.

FDA DILIRANK COMPARED TO MARKETED DRUGS

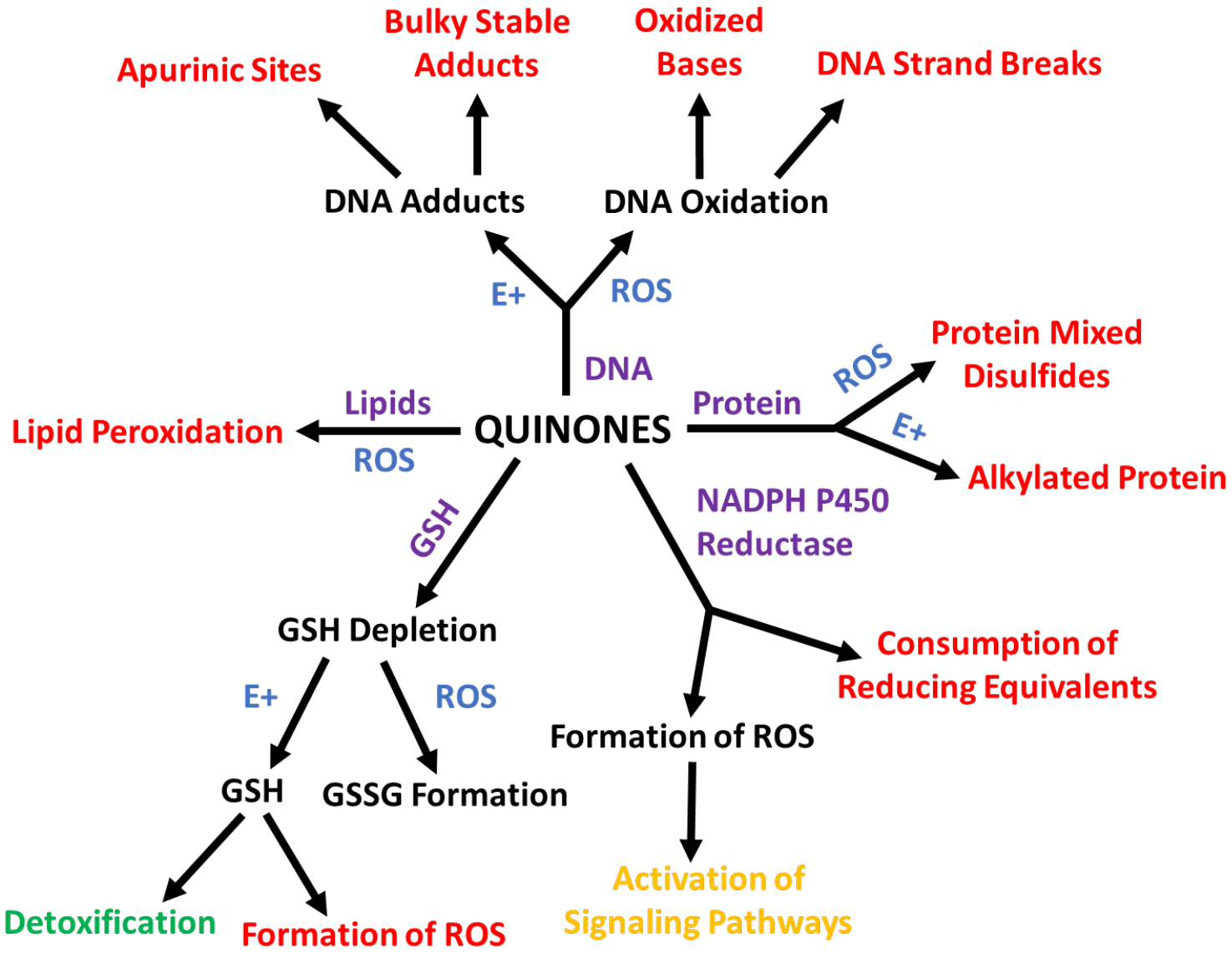


FDA DILIrank is representative of the United States drug market.

Manuscript in revision.

QUINONES – DANGEROUS AND COMMON

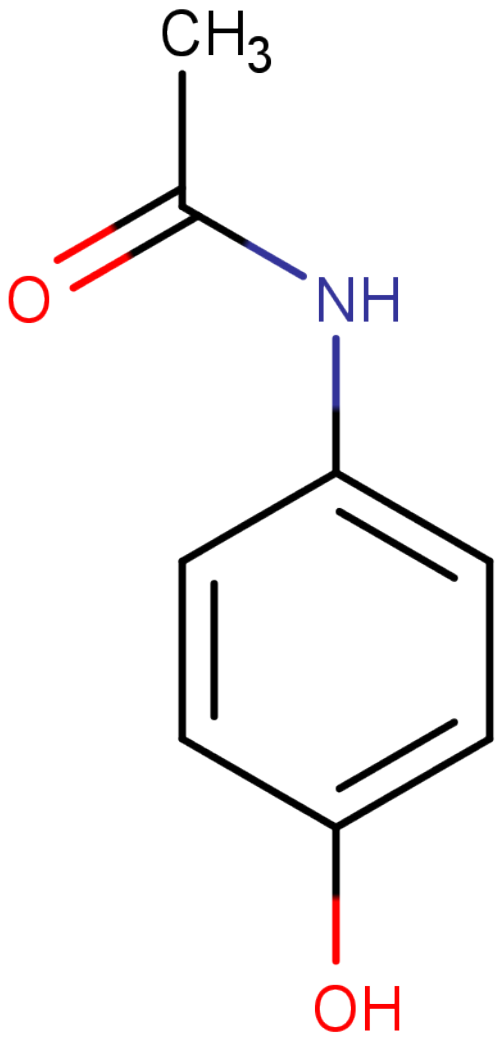
- Electrophilic metabolites capable of interacting with biomolecules



Adapted from Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J. Role of Quinones in Toxicology. Chem. Res. Toxicol. ***2000****, 13 (3), 135–160.*

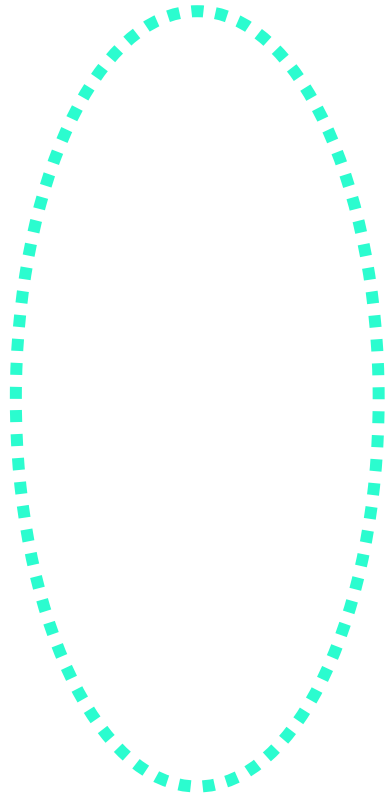
QUINONES – DANGEROUS AND COMMON

- Electrophilic metabolites capable of interacting with biomolecules
- Comprise over 40% of reactive metabolites



Acetaminophen

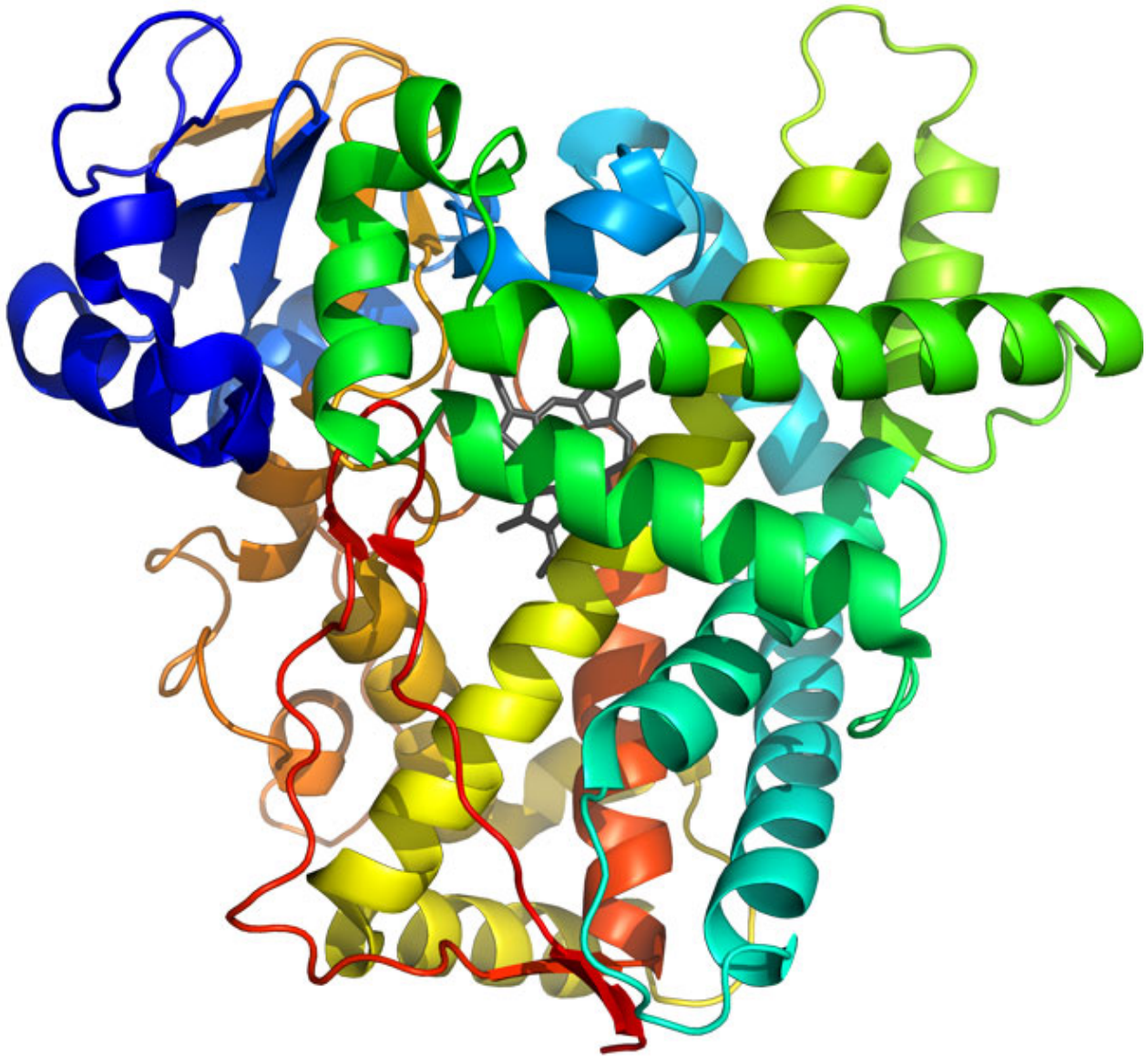
P450s



NAPQI

QUINONES – DANGEROUS AND COMMON

- Electrophilic metabolites capable of interacting with biomolecules
- Comprise over 40% of reactive metabolites
- Formed by cytochrome P450 and peroxidase metabolism

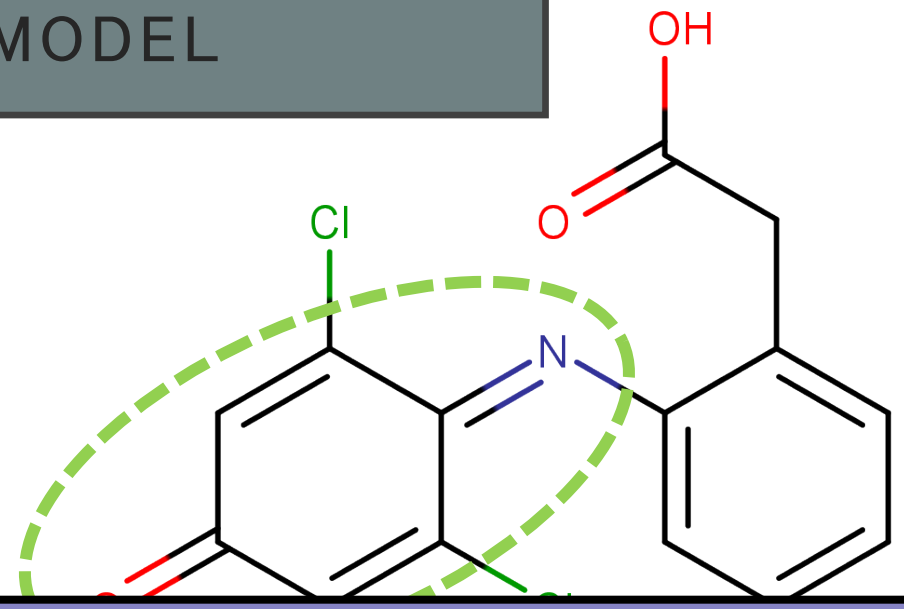


Courtesy of Dr. Emily Scott, http://scottlab.info/

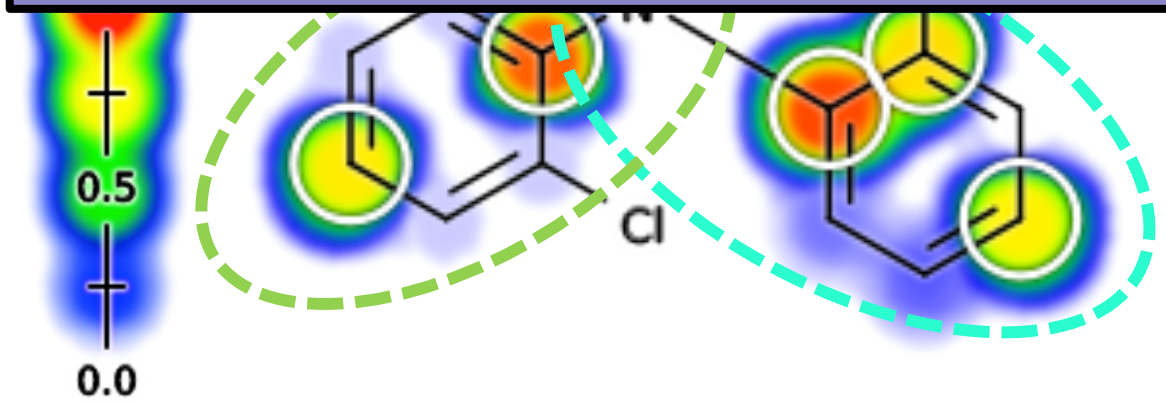
All computational models shown can be found at:
https://swami.wustl.edu/xenosite/

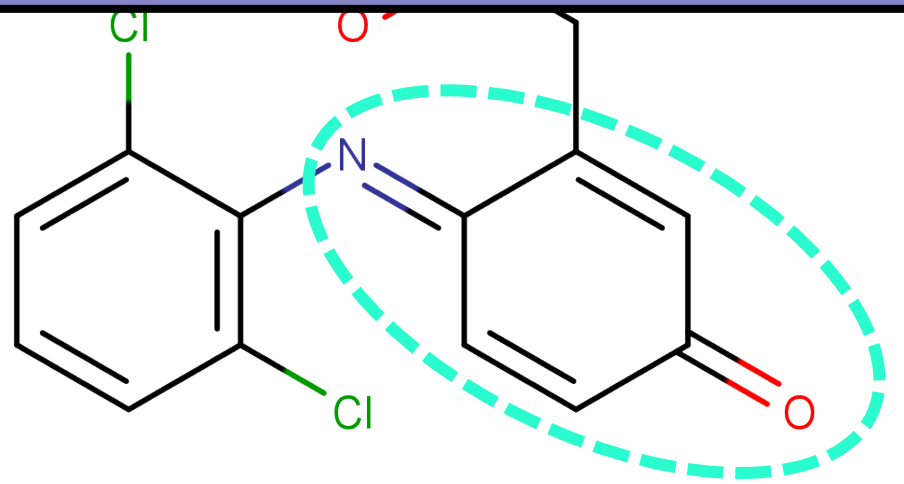
USING THE QUINONE MODEL

- Trained on ~600 *in vitro* and *in vivo* metabolic reactions
- Quinone–forming molecule accuracy of 88.2% ROC AUC



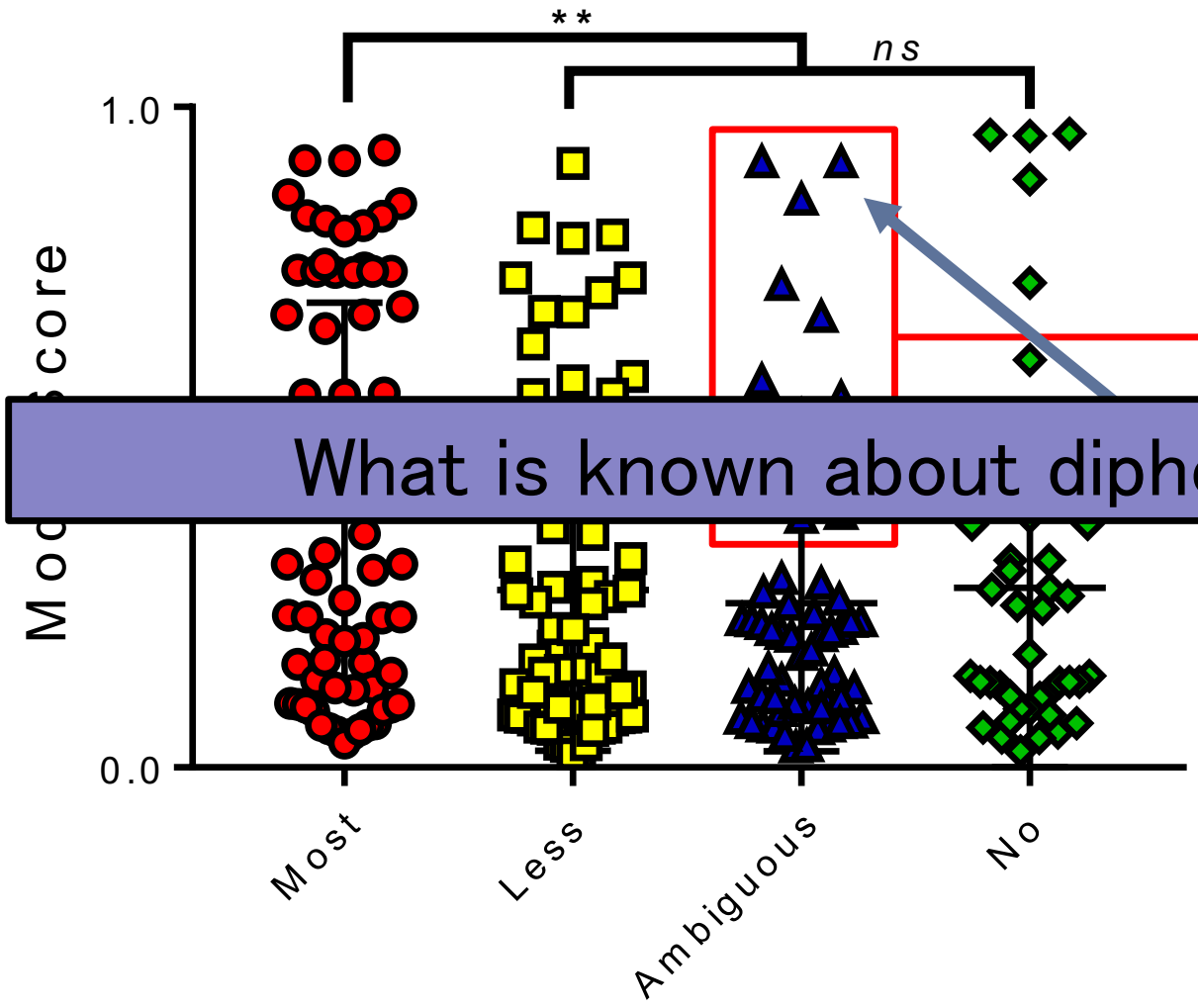
Can we identify a subset of halogenated drugs which may form quinone metabolites?





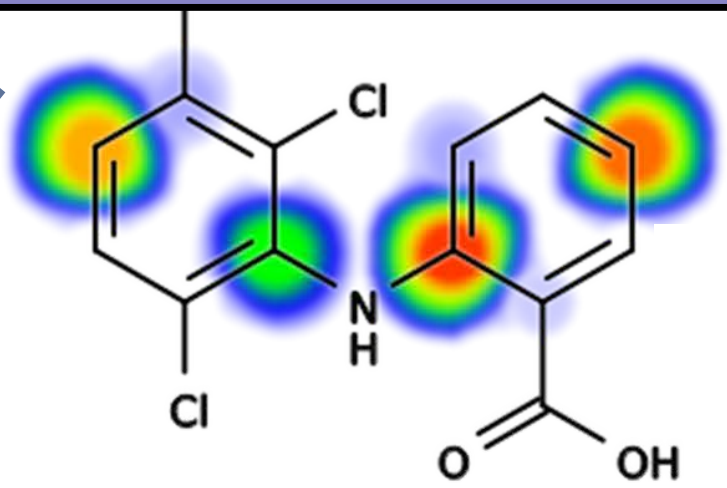
*Hughes, T. B., and Swamidass, S. J. (2017) Deep Learning to Predict the Formation of Quinone Species in Drug Metabolism. Chemical Research in Toxicology. **30**, 642–656*

STRATIFICATION OF DRUG RISK



Potential Test Compounds

What is known about diphenylamine hepatotoxicity?



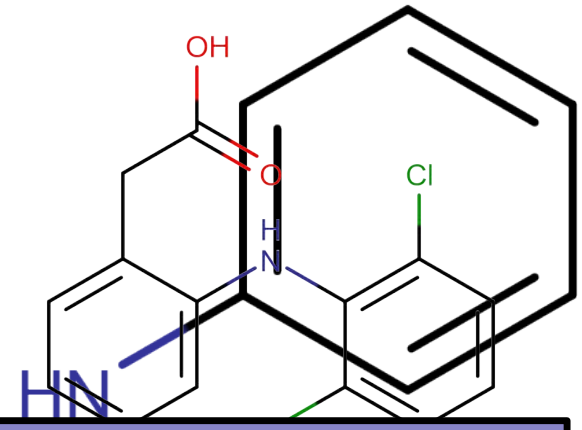
Meclofenamate

Manuscript in revision.

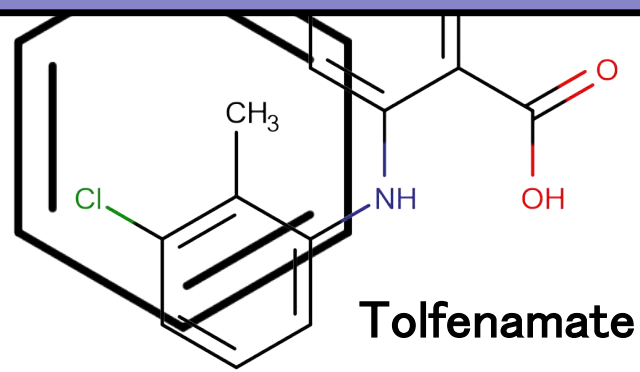
DIPHENYLAMINE HEPATOTOXICITY

- Diphenylamine structure shown to cause hepatotoxicity by uncoupling mitochondrial respiration
  - The potency of uncoupling varies between NSAIDs
- Lipophilicity, acidity, and substituted groups on the
- a general cytochromes P450 inhibitor
- Diphenylamine structure does not lead to changes in the mitochondrial permeability transition but tolfenamate and diclofenac do

Can we experimentally assess metabolic bioactivation of multiple structurally similar diphenylamine drugs?

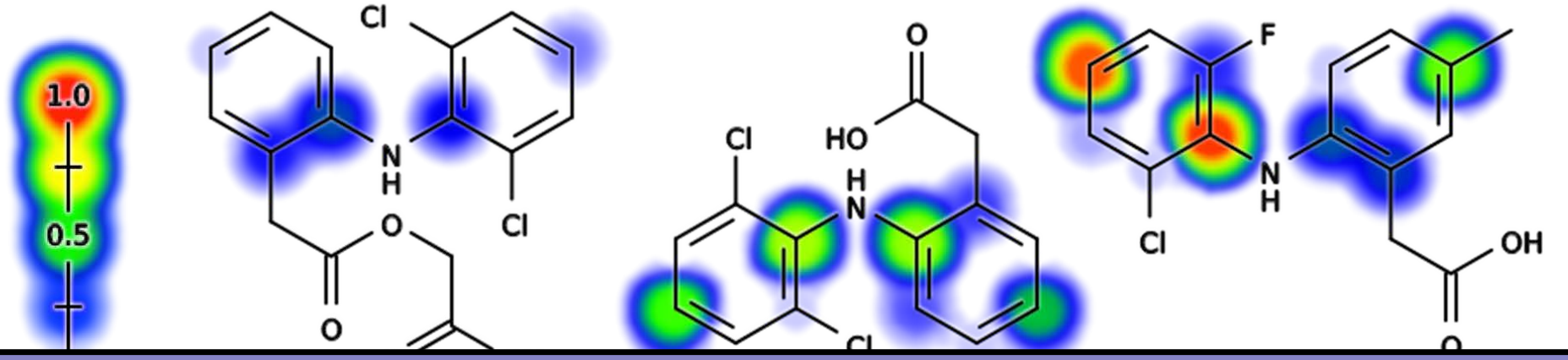


Diphenylamine

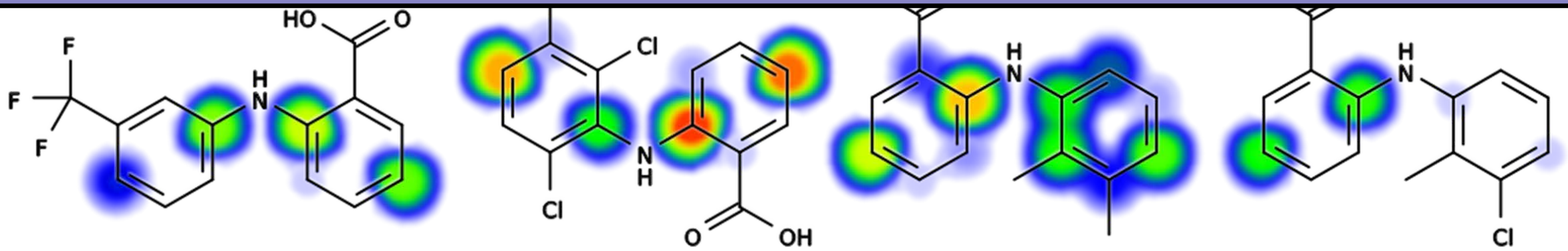


Tolfenamate

PROPAGATION OF THE DIPHENYLAMINE FAMILY



Can we computationally predict metabolite structures and downstream reactivity with macromolecules?



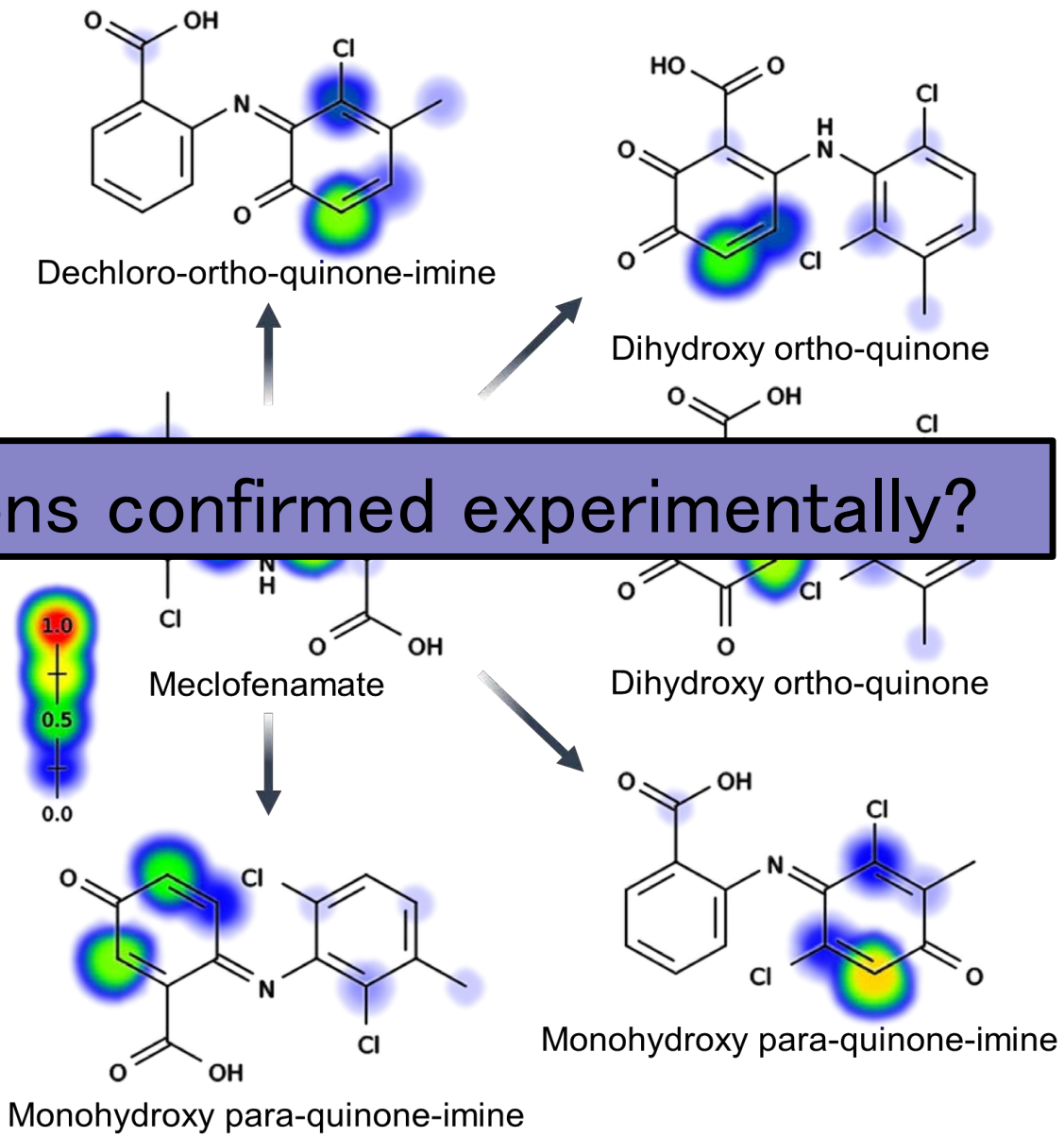
Flufenamate **Meclofenamate** **Mefenamate** **Tolfenamate**

Manuscript in revision.

THE XENONET/METABOLIC FOREST MODEL

- Literature-derived database of ~21k metabolic reactions
- Employs Metabolic Forest algorithm to generate a tree of pathways which span multiple metabolic transformations and
- Top-one pathway accuracy of 93.6% and intermediate metabolite accuracy of 51.9%
- Coupling with reactivity model yields important biological information such as glutathione or protein adduction propensity

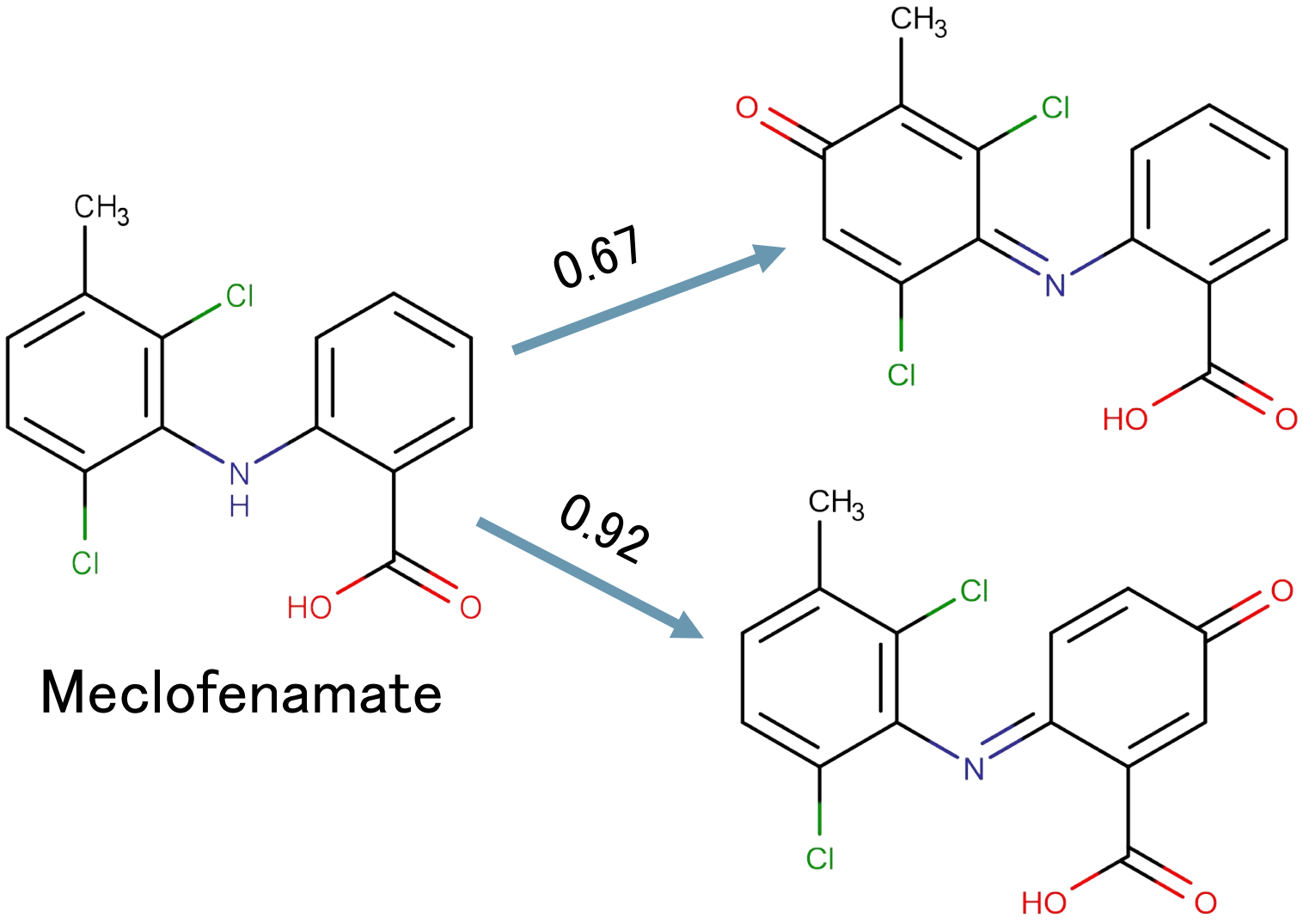
Are these computational predictions confirmed experimentally?



M.A. Schleiff et al. Significance of Multiple Bioactivation Pathways for Meclofenamate as Revealed through Modeling and Reaction Kinetics, Drug Metab Dispos. (2020). https://doi.org/10.1124/dmd.120.000254.

EXPERIMENTAL RESULTS

Monohydroxy–para–quinone–imine

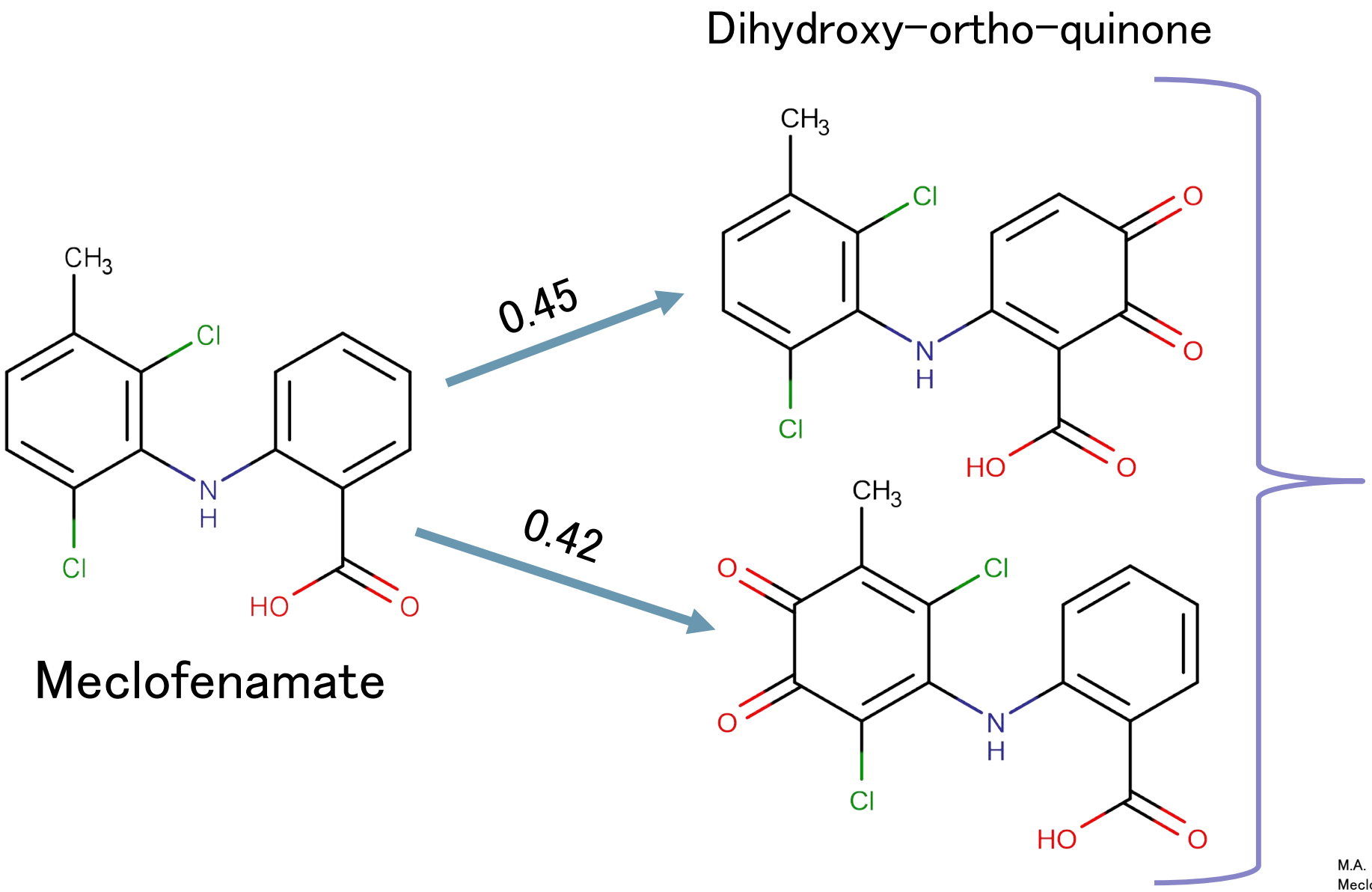


Meclofenamate

Comprises **7.0%** of all meclofenamate metabolism

M.A. Schleiff et al. Significance of Multiple Bioactivation Pathways for Meclofenamate as Revealed through Modeling and Reaction Kinetics, Drug Metab Dispos. (2020). https://doi.org/10.1124/dmd.120.000254.

EXPERIMENTAL RESULTS

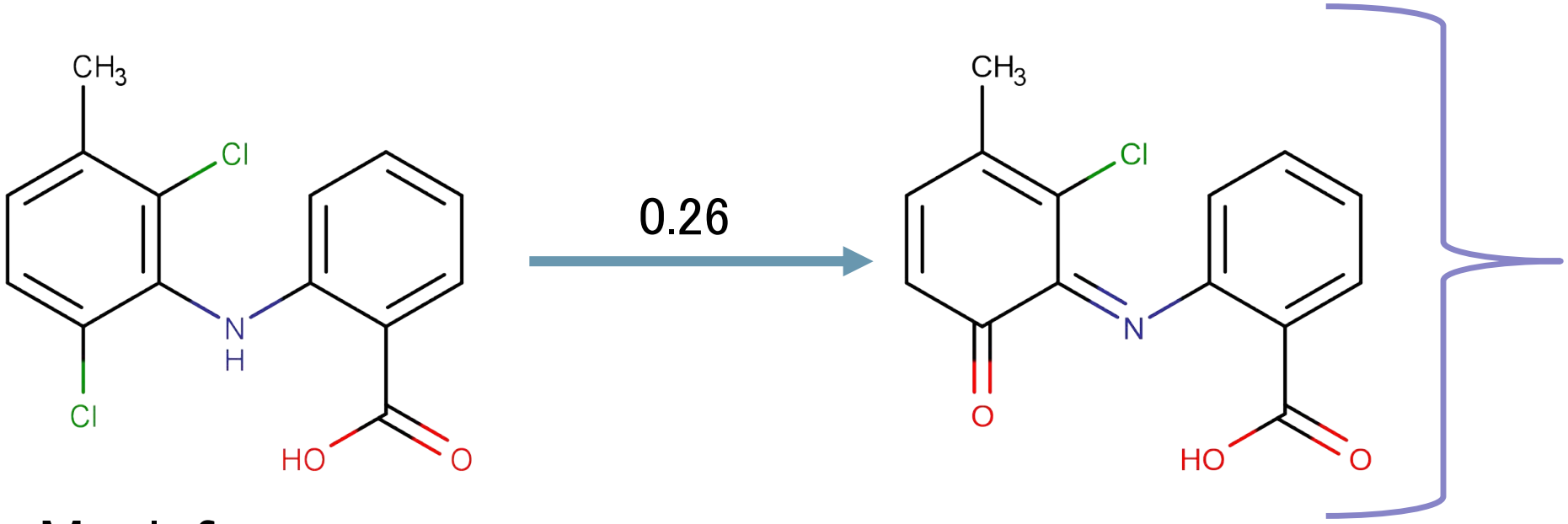


Comprises **0.2%** of all meclofenamate metabolism

M.A. Schleiff et al. Significance of Multiple Bioactivation Pathways for Meclofenamate as Revealed through Modeling and Reaction Kinetics, Drug Metab Dispos. (2020). https://doi.org/10.1124/dmd.120.000254.

EXPERIMENTAL RESULTS

Dechloro–ortho–quinone–imine



Meclofenamate

Comprises **5.3%** of all meclofenamate metabolism

M.A. Schleiff et al. Significance of Multiple Bioactivation Pathways for Meclofenamate as Revealed through Modeling and Reaction Kinetics, Drug Metab Dispos. (2020). https://doi.org/10.1124/dmd.120.000254.

Goals:

1. Improve computational model outputs for more accurate predictions of potentially toxic lead molecules.
2. Identify potential toxifying or detoxifying drug substituents.
3. Provide insights into enzymatic effects of halogens on reactive metabolite formation.
4. Promote more personalized patient care.

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Matt Matlock

Noah Flynn

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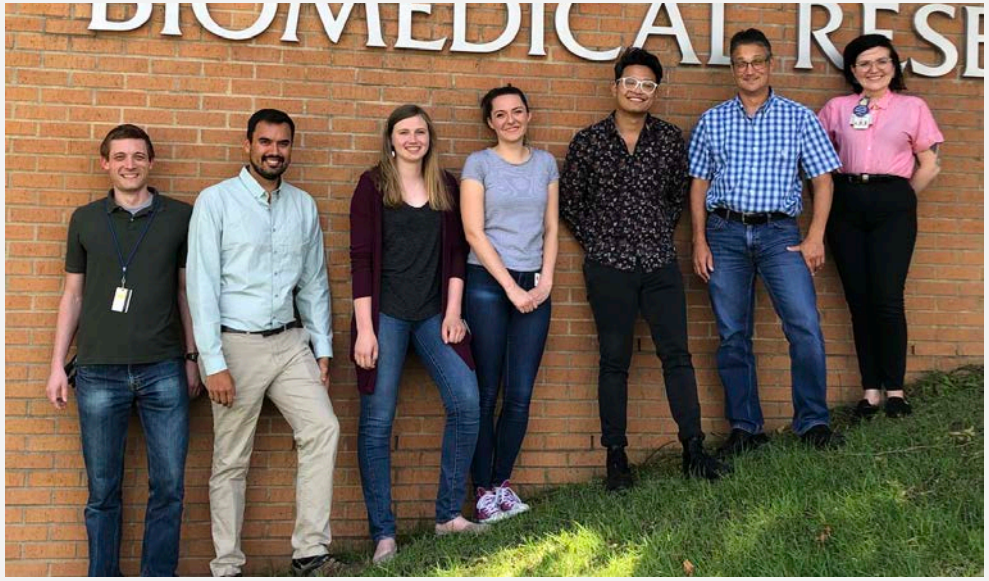
Laura Osborn

Anna Pinson



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NLM-R01-LM012222

THANK YOU FOR YOUR ATTENTION!

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RELEVANT PUBLICATIONS:

QUINONE MODEL – 10.1021/ACS.CHEMRESTOX.6B00385

XENONET – 10.1021/ACS.JCIM.0C00361

METABOLIC FOREST – 10.1021/ACS.JCIM.0C00360

MECLOFENAMATE – 10.1124/DMD.120.000254