# *Medicinal Chemistry Strategies to Address Bioactivation Liabilities in Drug Discovery*

*Designing Safer Medicines in Discovery:*
*Current and Emerging Opportunities to Reduce Attrition*

*SCI, London, UK, 17 March 2011*

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# *Drug-Induced Toxicity*

*Susceptibility to adverse drug reactions is a function of:*

***(a) Chemistry of drug and its interaction with biological systems***

On- and off-target pharmacology (normally dose-dependent, predictable, reproducible in animals)

***(b) Phenotype and genotype of patient***

Not related to pharmacology of drug (no clear dose-response relationship, unpredictable, may not be reproduced in animals)

***"Idiosyncratic" drug reactions can result from the sequence:***

metabolic activation of parent

covalent modification of proteins

presentation of adducted proteins to T cells via HLA class II proteins

immune-mediated organ damage (often liver)

G. P. Aithal and A. K. Daly, *Nature Genetics* **42**: 650-651 (2010)

# *Assessing Formation of / Exposure to Reactive Drug Metabolites*

(A) *In vitro* “trapping” experiments (eg with GSH, $CN^-$), or *in vivo* metabolic profiling studies:

- Invaluable in enabling rational structural re-design

(B) Observation of time-dependent P450 inhibition:

- Implications for drug-drug interactions

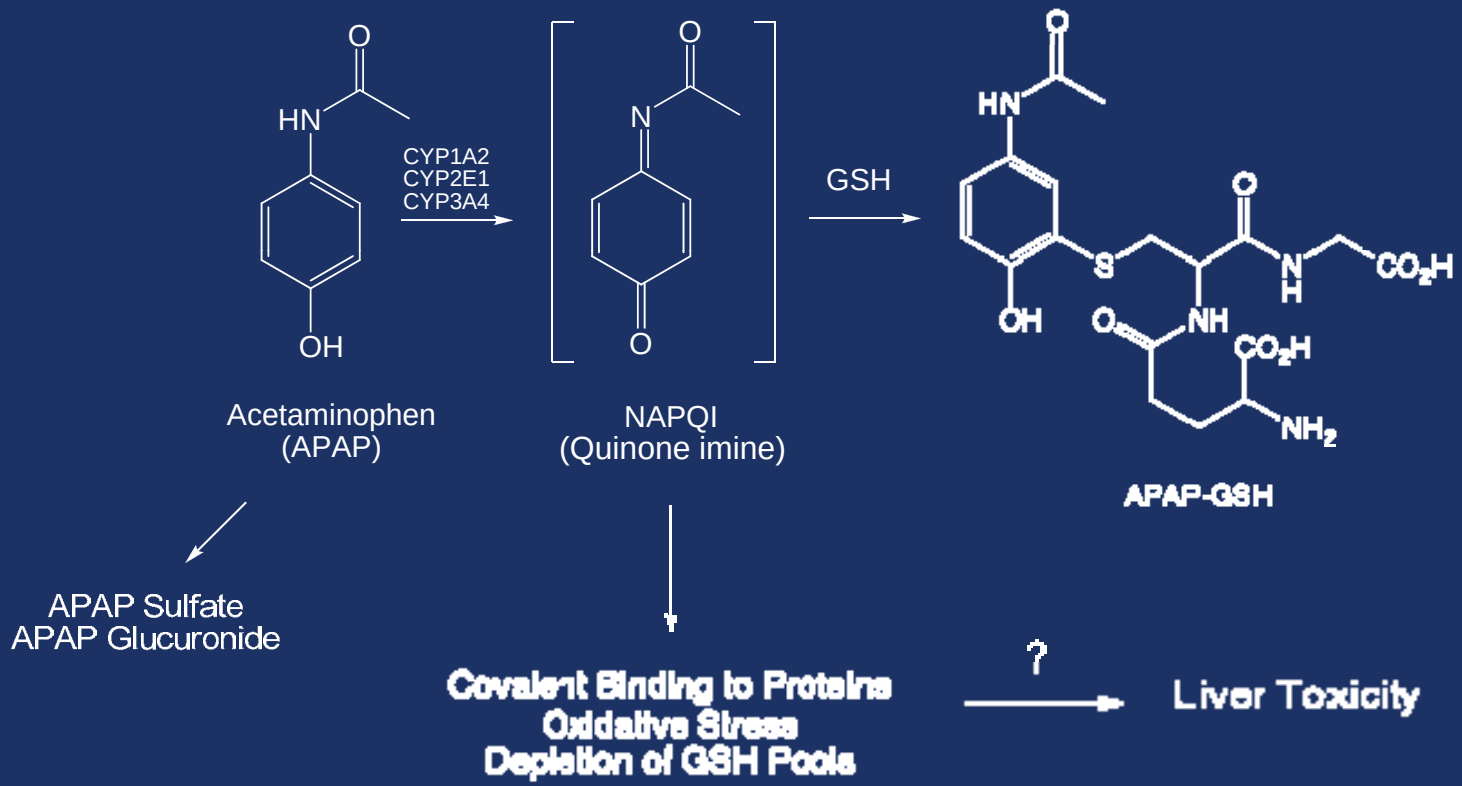
(C) Covalent binding studies:

- Measures “total” burden of protein-bound drug residue
- Helpful complement to trapping studies

***These approaches employ different end-points and serve different purposes!***

In the absence of a more complete mechanistic understanding of reactive metabolite-induced toxicities, “avoidance strategies” seem most prudent

# Bioactivation and Liver Toxicity
## Acetaminophen




J. R. Mitchell *et al., J. Pharmacol. Exp. Ther.,* **187**, 185-194 (1973)
I. M. Copple *et al., Hepatology,* **48**, 1292-1301 (2008)

# *Acetaminophen-Induced Liver Toxicity*

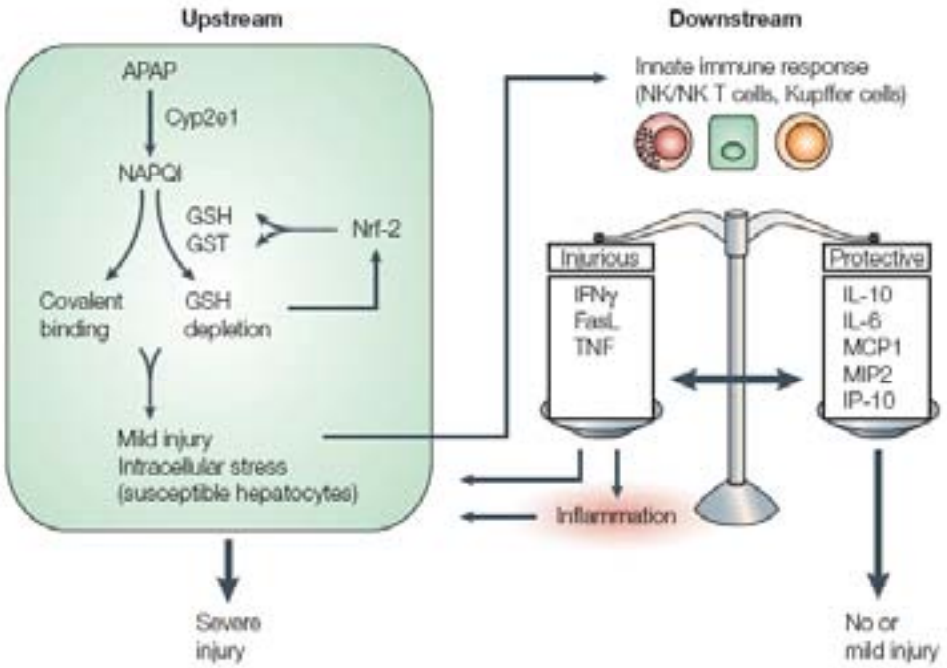



Figure 2 | **Current concepts of experimental acetaminophen (APAP) hepatotoxicity.** Upstream events in hepatocytes lead to exposure to NAPQI which undergoes covalent binding after preferential depletion of glutathione (GSH). A protective response mediated by the transcription factor NRF2 modulates the toxic threshold. Upstream events promote intracellular stress and mild injury activates the downstream innate immune system, which represents a balance of pro- and anti-inflammatory responses, the interplay of which determines progression to severe injury or no injury. APAP, acetaminophen; FasL, Fas ligand; GSH, glutathione; GST, GSH S-transferase; IFN, interferon; MCP1, monocyte chemoattractant protein 1; MIP2, macrophage inflammatory protein 2; NK, natural killer; TNF, tumour-necrosis factor.

N. Kaplowitz, *Nat. Rev. Drug Discov.,* **4**, 489-499 (2005)
D. P. Williams, *Toxicology* **226**, 1-11 (2006)

Los Angeles Times | Health

A CLOSER LOOK: Acetaminophen

## Acetaminophen: The dark side of pain relief

By Jill U. Adams | Fri, 17 Jul 2009 6:13:13 PM

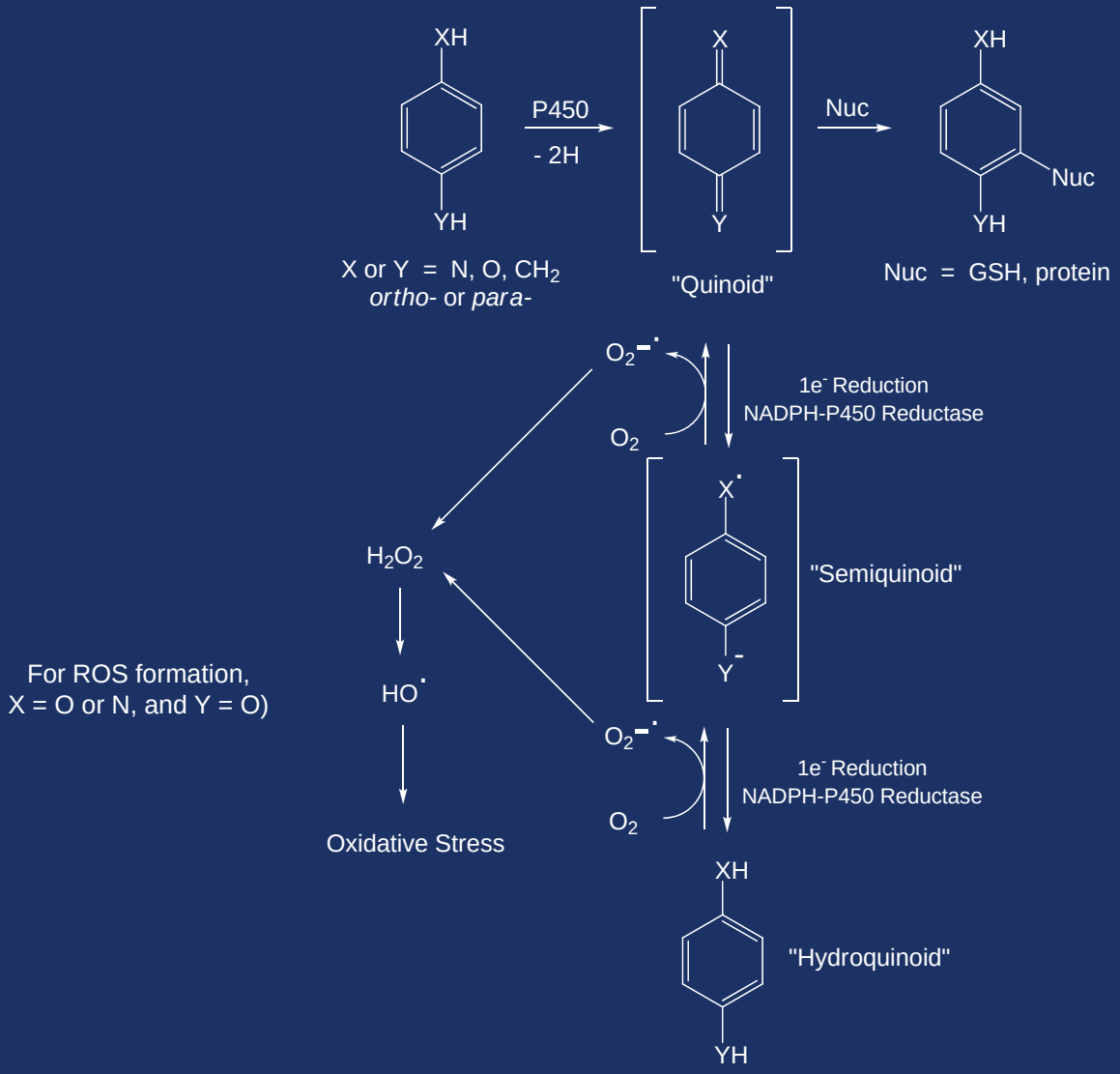
Tylenol and other drugs are safe when taken as directed. But treating them...

*"Current recommendations say that the maximum single dose is 1,000 milligrams -- the amount in two Extra Strength Tylenol tablets; the advisory panel recommended lowering that amount to 625 milligrams. The current maximum total daily dose is 4 grams; the panel recommended reducing that as well, to 3.25 grams or less."*

*"People vary in their responses, so it's hard to say what an overdose is for any particular individual. Poison control experts generally consider 10 to 12 grams at one time an overdose, but even 8 grams can be dangerous in someone who weighs 120 pounds, and 3 grams can be risky for a 40-pound child. In addition, people who regularly consume three or more alcoholic drinks per day tend to be more sensitive to the toxic effects of acetaminophen, which means they should be more careful in limiting dose."*

**Acetaminophen *"is the most common cause of acute liver failure in the US"***

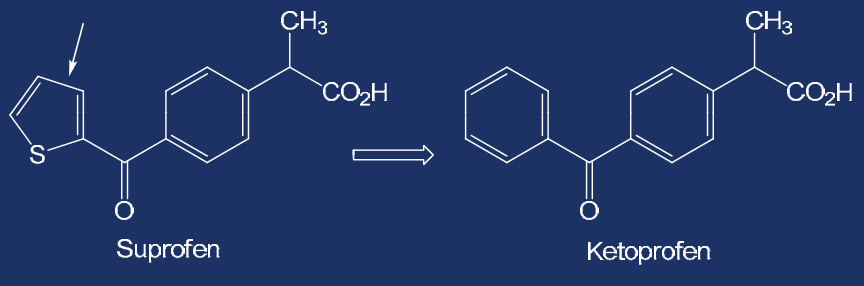
# *Quinoid Precursors as Structural Alerts*



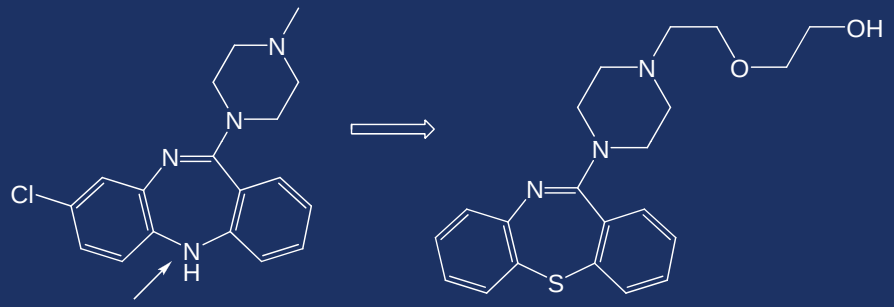

T. A. Baillie and A. E. Rettie, *Drug Metab. Pharmacokinet.*, **26**: 1-15 (2011)

# *Structural Alerts for Metabolic Activation*

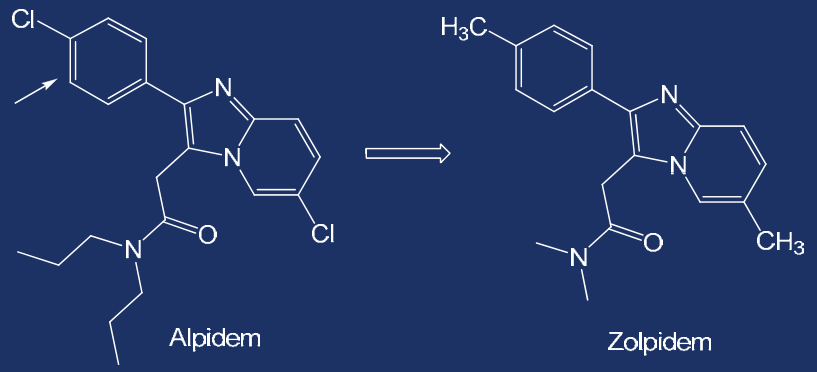
- Evolved from consideration of genotoxic carcinogens (“hard” electrophiles)
- Do not translate as readily to “soft” electrophilic drug metabolites which usually demonstrate a “threshold” for toxicity



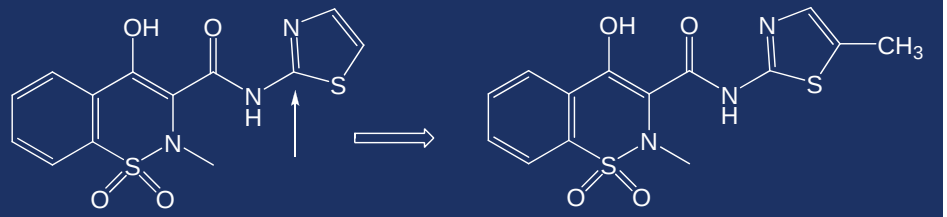

Suprofen Ketoprofen




Clozapine Quetiapine



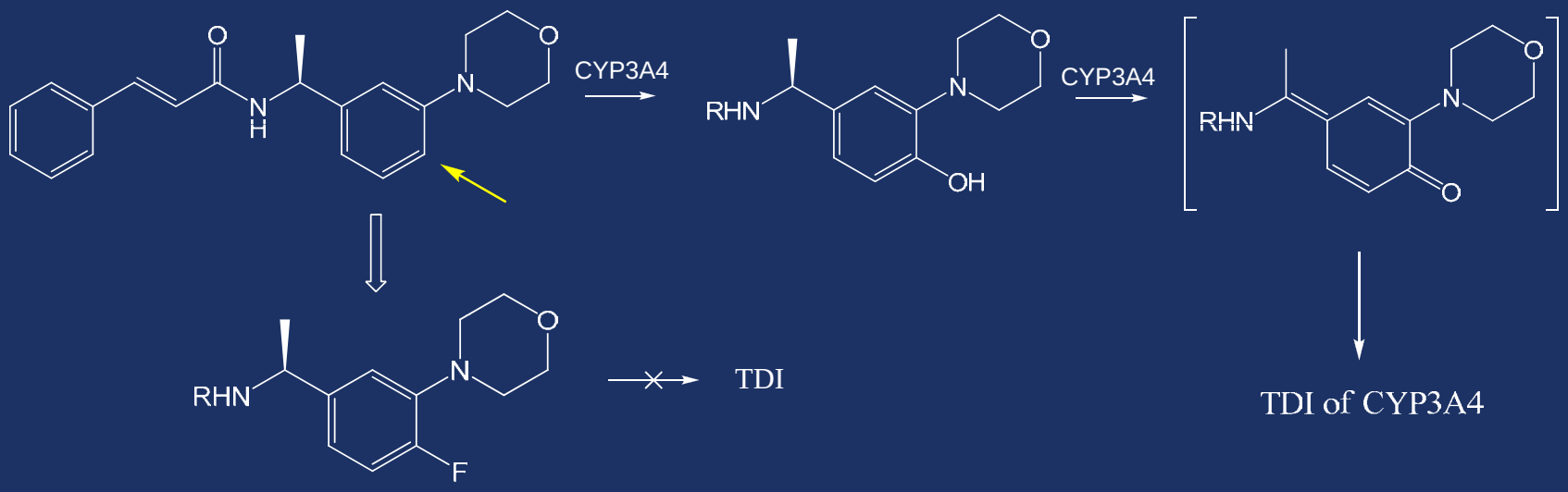

Alpidem Zolpidem



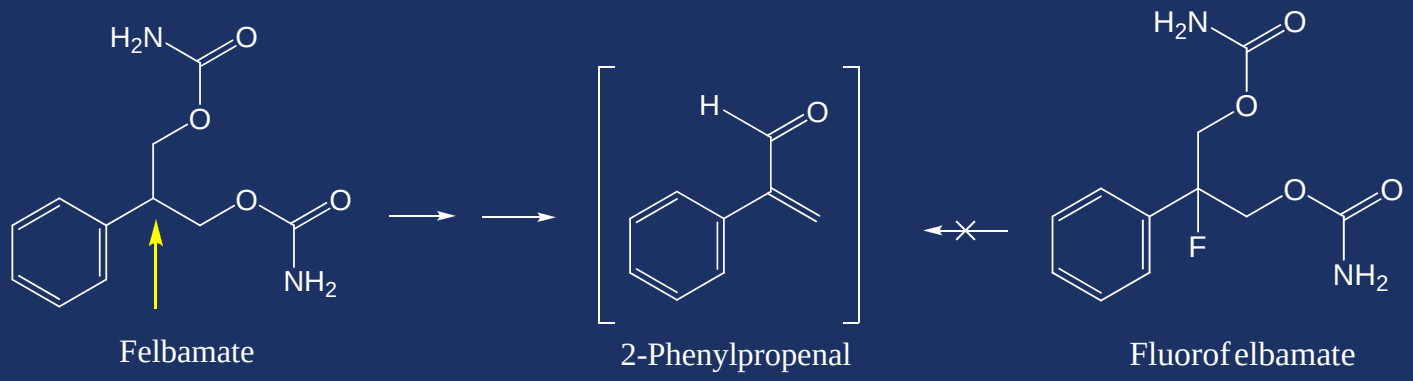

Sudoxicam Meloxicam

***Structural alerts must be supplemented by experimental data!***

# *Minimizing Metabolic Activation: (1) Block Site of Metabolism*

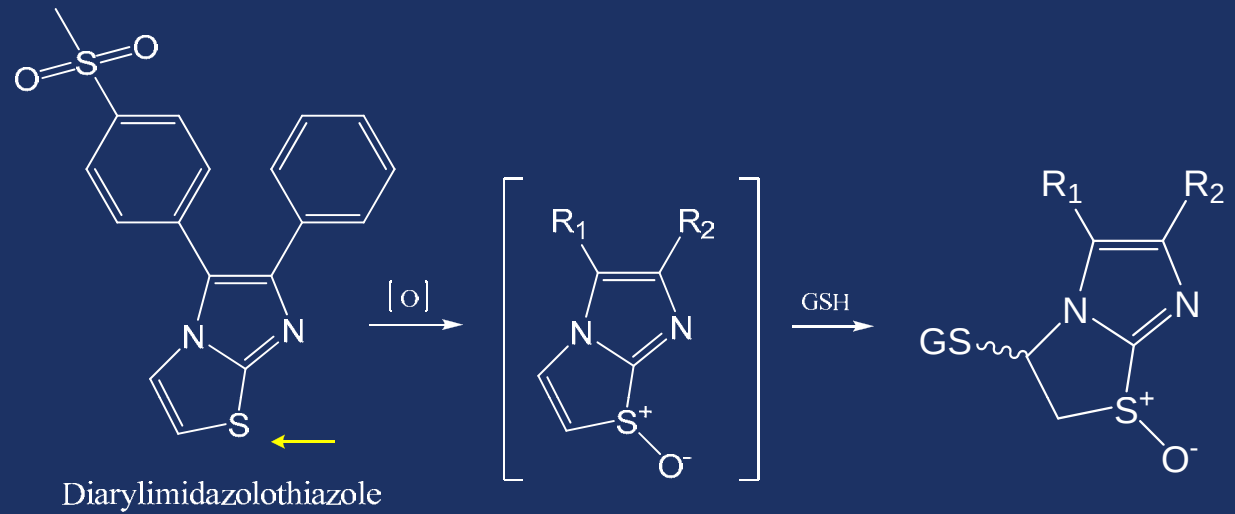



Y.-J. Wu *et al., J. Med. Chem.*, **46**, 3778-3781 (2003)

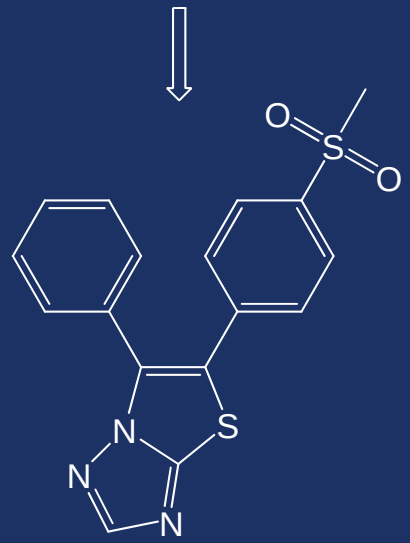



C. M. Diekhaus *et al., Chem.-Biol. Interact.*, **142**, 99-117 (2002)

# *Minimizing Metabolic Activation: (2) Introduce Steric Hindrance*




Diarylimidazolothiazole

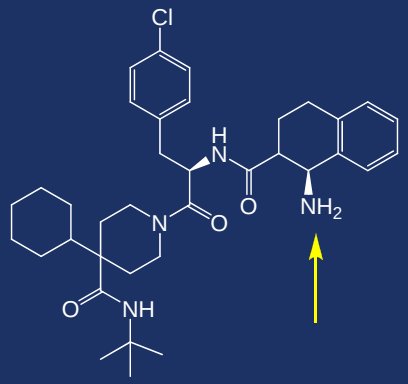


Diarylthiazolotriazole

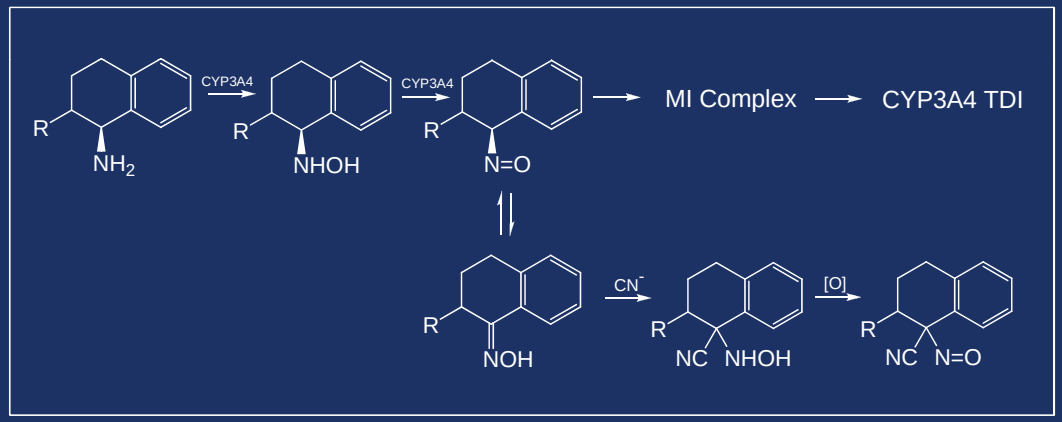
Steric hindrance from the phenylsulfone reduces oxidative metabolism on the thiazole S atom


L. A. Trimble *et al., Bioorg. Med. Chem. Lett.,* **7**, 53-56 (1997)
P. Roy *et al., Bioorg. Med. Chem. Lett.,* **7**, 57-62 (1997)

# *Minimizing Metabolic Activation: (2) Introduce Steric Hindrance*




MC-4R Agonist Lead



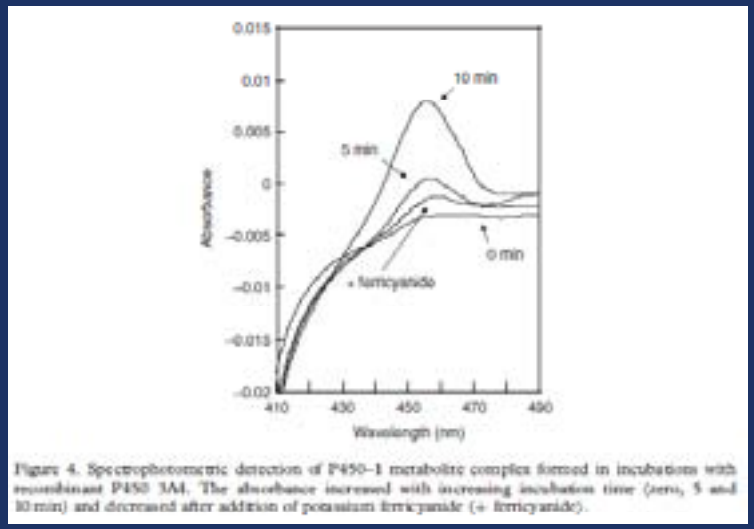
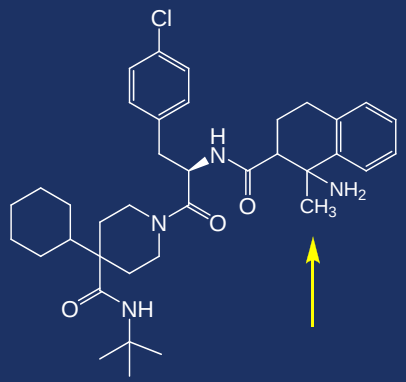



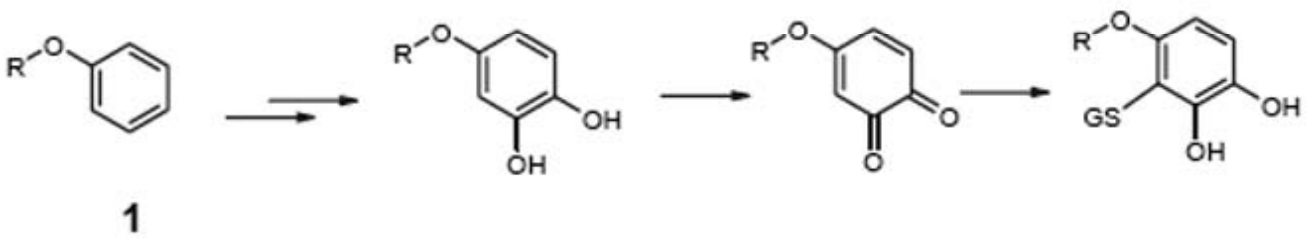

Figure 4. Spectrophotometric detection of P450–1 metabolite complex formed in incubations with recombinant P450 3A4. The absorbance increased with increasing incubation time (zero, 5 and 10 min) and decreased after addition of potassium ferricyanide (+ ferricyanide).

W. Tang *et al.*, *Xenobiotica* **38**, 1437-1451 (2008)



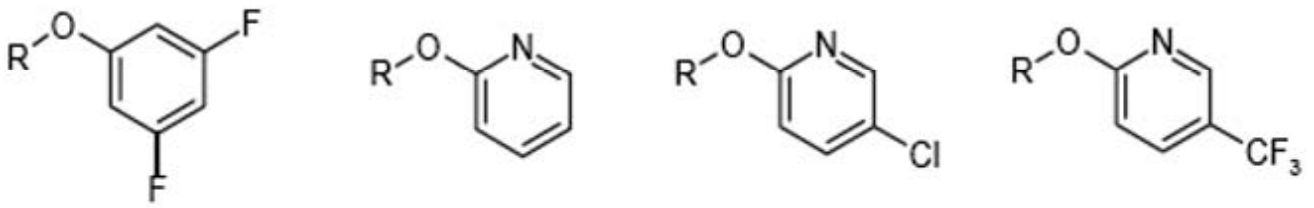
# *Minimizing Metabolic Activation: (3) Introduce Electronic Changes*






1

**Figure 1** Metabolic activation of an aryloxy-substituted drug candidate (**1**).

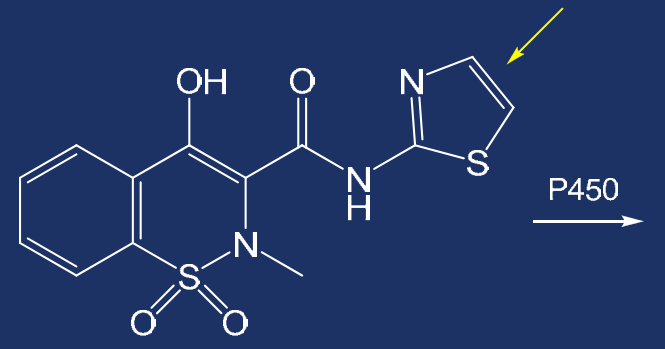



(1690) (911) (303) (88)

**Figure 2** Improved analogs of the lead compound **1** showing reduced levels of covalent binding (pmol-equiv/mg protein, shown in parentheses).

G. A. Doss and T. A. Baillie, *Drug Metab. Rev.,* **38**, 641-649 (2006)
K. Samuel *et al., J. Mass Spectrom.,* **38**, 211-221 (2003)

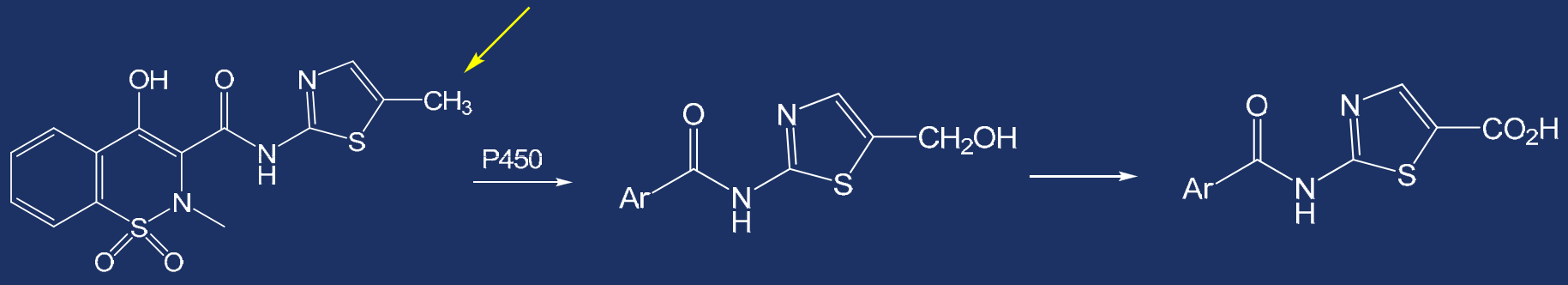
# *Minimizing Metabolic Activation: (4) Redirect Metabolism to "Soft Spot"*




Sudoxicam
(Withdrawn during Phase III trials)

P450

Reactive metabolites of thiazole ring oxidation, thiourea formation

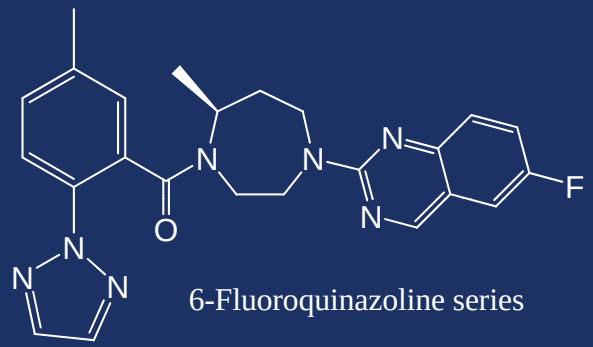



Meloxicam
(Non-hepatotoxic)

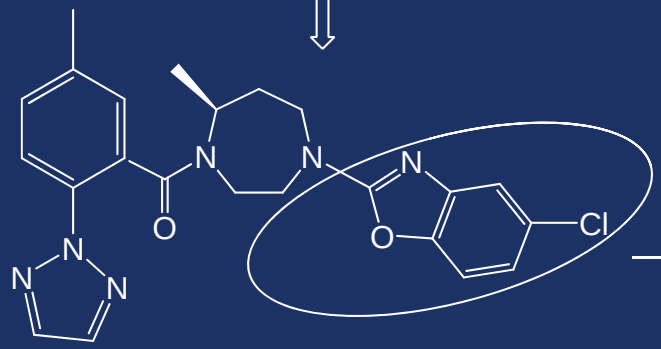
R. S. Obach *et al., Chem. Res. Toxicol.*, **21**, 1890-1899 (2008)

# *Minimizing Metabolic Activation: (5) Replacement of Structural Element*

Orexin receptor antagonist lead



6-Fluoroquinazoline series

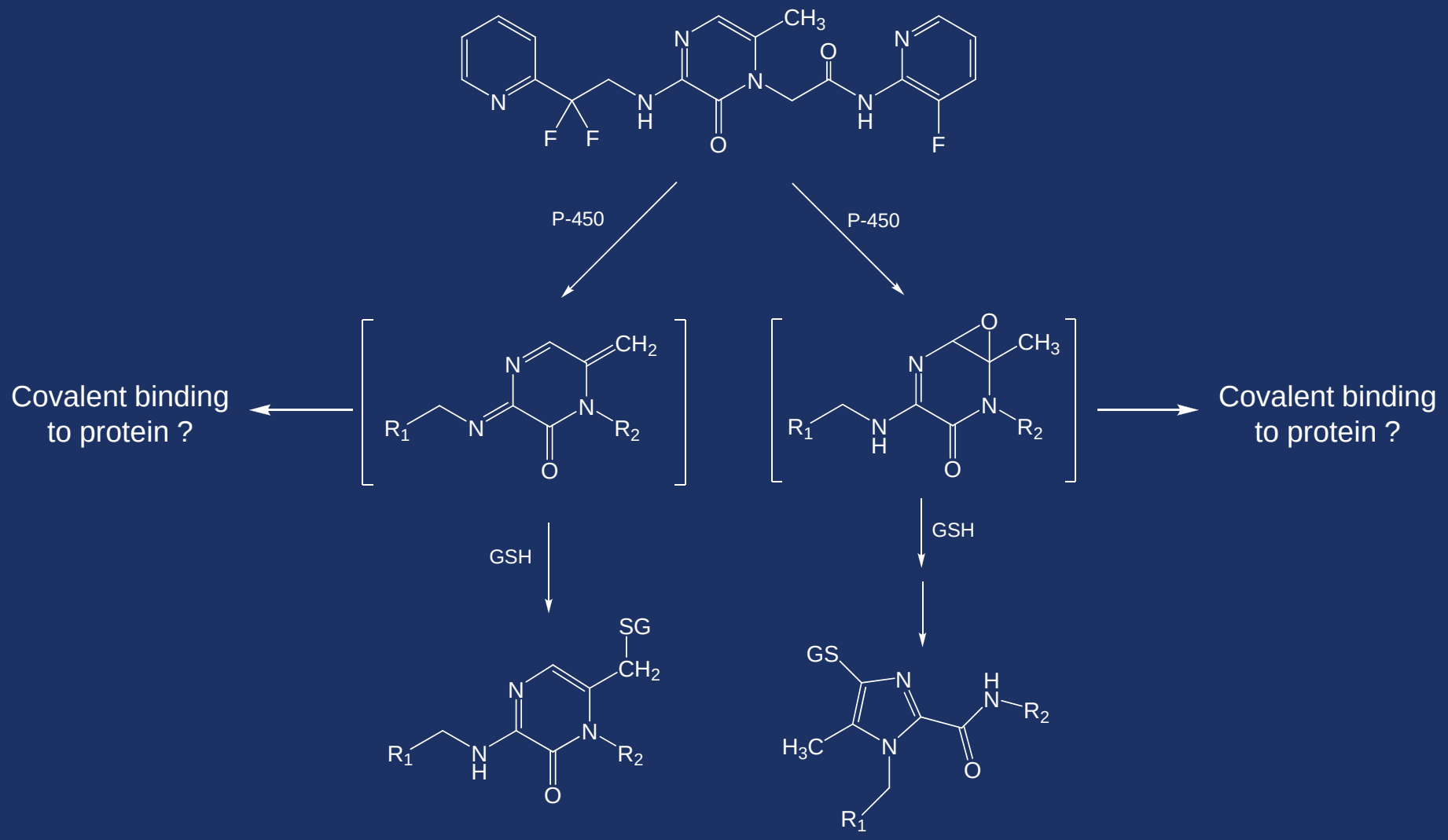



6-Chlorobenzoxazole series
MK-4305

No evidence of metabolic activation

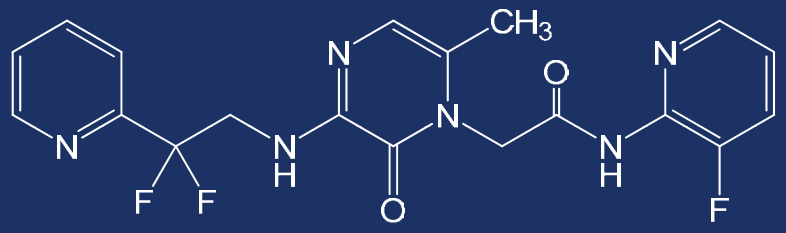
C. Boss *et al., ChemMedChem,* **5**: 1197-1214 (2010)

# *Minimizing Metabolic Activation: (6) Combination of Steric and Electronic Changes*




R. Singh *et al., Chem. Res. Toxicol.,* **16**, 198-207 (2003)

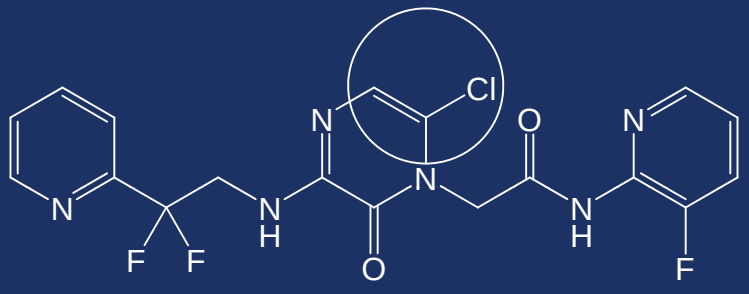
# *Minimizing Metabolic Activation: (6) Combination of Steric and Electronic Changes*




Original Lead

Potent, selective, good PK

High degree of metabolic activation



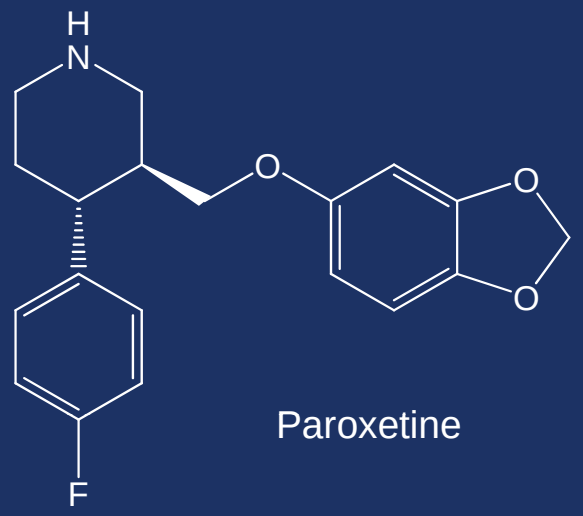

Chloro analog

Potent, selective, good PK

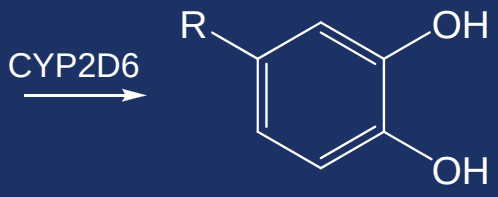
Low degree of metabolic activation

R. Singh *et al., Chem. Res. Toxicol.,* **16**, 198-207 (2003)

# *Minimizing Metabolic Activation: (7) Selective Deuteration*




Paroxetine

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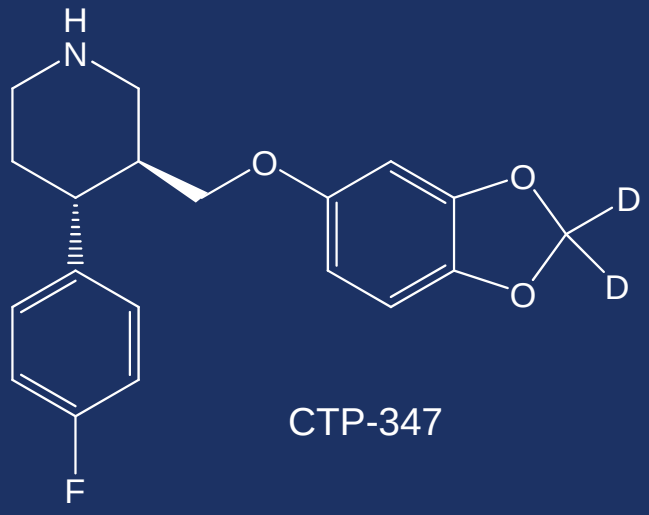
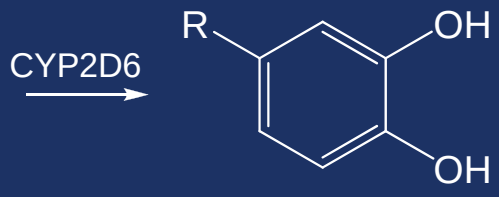
TDI of CYP2D6 (MI complex formation)
Drug-drug interactions (eg tamoxifen)




CTP-347

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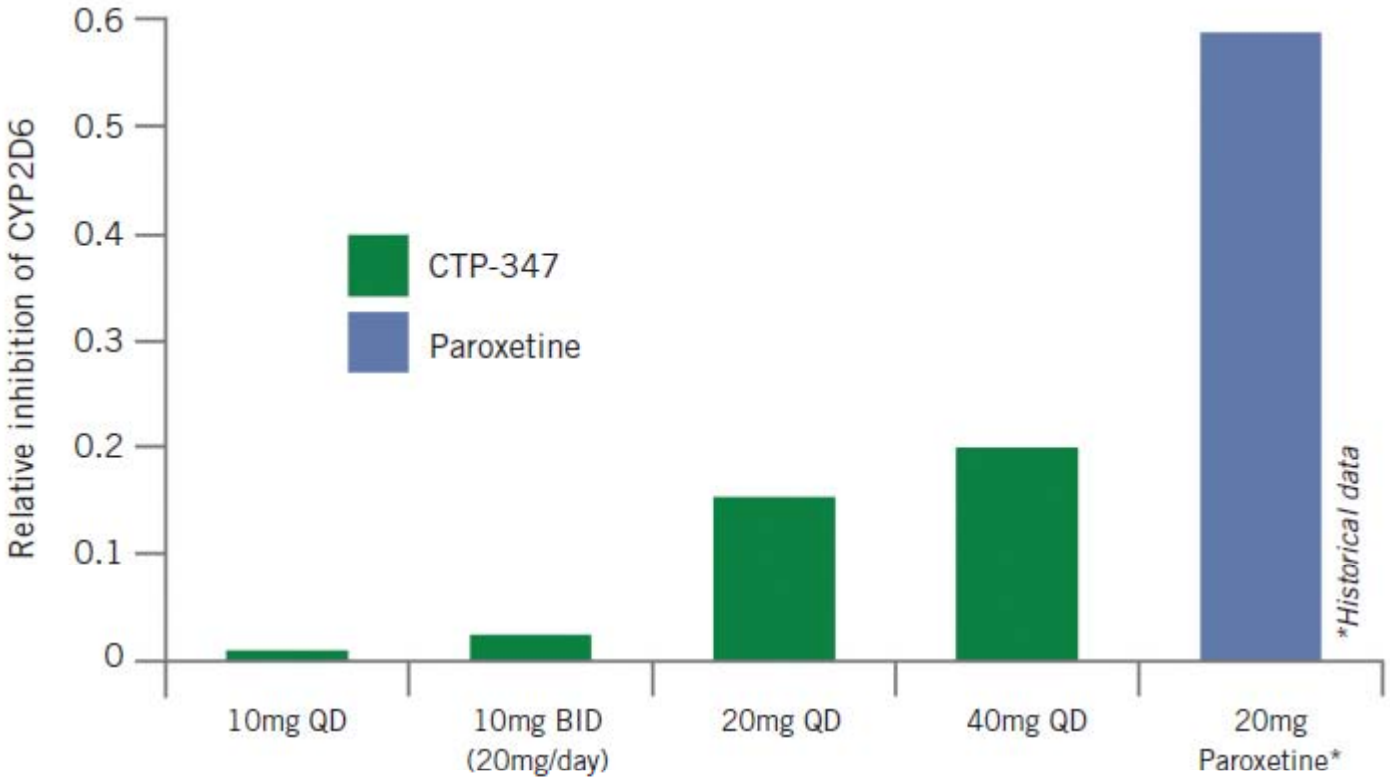
<u>NO</u> TDI of CYP2D6 *in vitro*

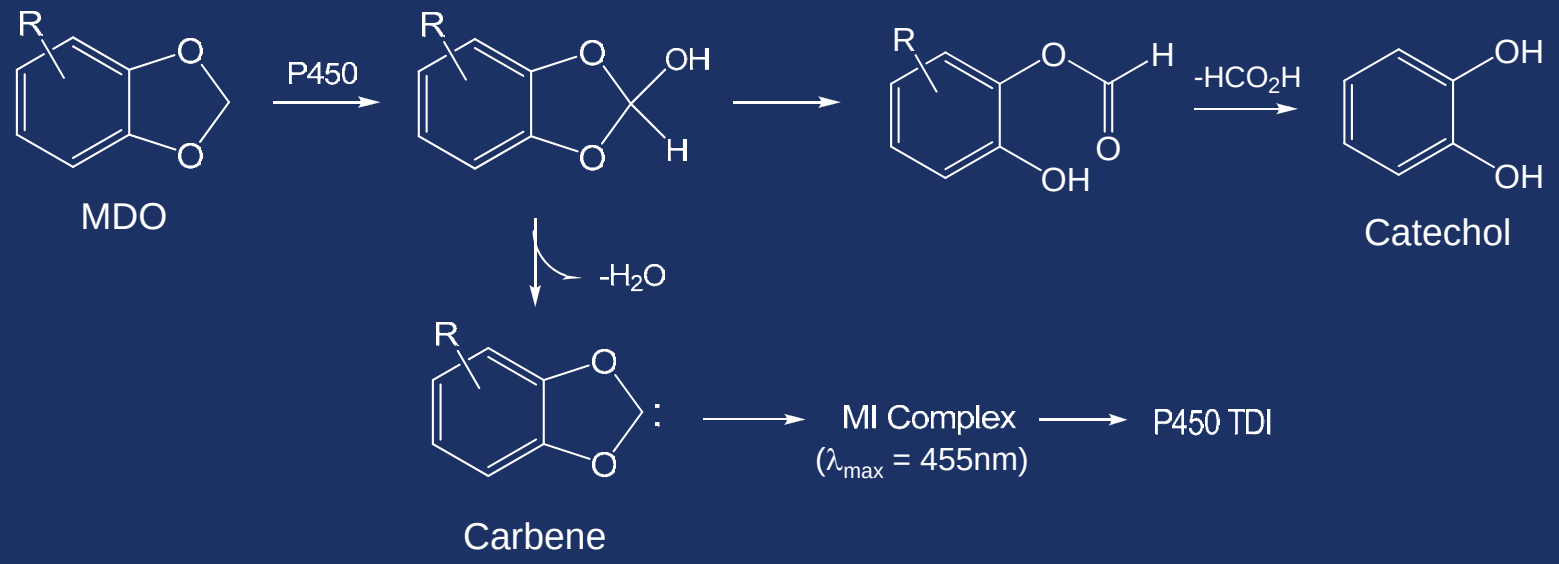
A. T. Yarnell, *Chem. Eng. News* **87**, 36-39 (2009)

**Figure 3:** Drug-drug interaction between CTP-347 and dextromethorphan from Phase Ib study. Y-axis shows the ratio of intact excreted dextromethorphan versus dextrorphan metabolite (9)




http://www.concertpharma.com/news/documents/IPT32ConcertPharma.pdf

# *MI Complex Formation from Methylenedioxyphenyl Compounds*




M. Murray, *Curr. Drug Metab.*, 1, 67-84 (2000)

- Deuterium substitution at the methylene bridge appears to alter the partition between ring scission and MI complex formation
- Deuterium isotope effects can be unpredictable !

# *Conclusions*

- While not all reactive drug metabolites are toxic, metabolic activation generally is perceived as a risk factor in drug development
- Strategies for the detection and identification of reactive drug metabolites should be incorporated as a routine element in the lead optimization stage of drug discovery
- Based on an understanding of metabolic activation pathways, a number of practical medicinal chemistry strategies are available to minimize the formation of reactive metabolites and the associated toxicological risk