Improving the decision-making process in the structural modification of drug candidates

Part I: Enhancing Metabolic Stability

Amin Kamel

Novartis Institutes for BioMedical Research
Metabolism and Pharmacokinetics
Cambridge, MA

THE NEW ENGLAND DRUG METABOLISM DISCUSSION GROUP SUMMER SYMPOSIUM

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Worcester Foundation Campus
Hoagland-Pincus Conference Center

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OUTLINE

- Significance of metabolite characterization and structure modification.
- Considerations to Enhance Metabolic Stability
- Approaches to assess the metabolism of a compound
- Advantages of Enhancing Metabolic Stability
- Strategies to Enhance Metabolic Stability
- Examples from literature
- Conclusions

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Significance of metabolite characterization and structure modification.

- Metabolite characterization has become one of the main drivers of the drug discovery process to help optimize ADME properties and to increase the success rate for drugs

- Metabolite identification helps identify potential metabolic liabilities or issues

- It provides a metabolism perspective to
  - *guide synthesis efforts with the aim of either blocking or enhancing metabolism*
  - *optimize the pharmacokinetic and safety profiles of newly synthesized drug candidates*

- It assists the prediction of the metabolic pathways of potential drug candidates

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Considerations to Enhance Metabolic Stability.

❑ One of the most important keys to successful drug design and development is a process of finding the right combination of multiple properties such as activity, toxicity and exposure.

❑ It is very important to first determine, and then optimize, the exposure-activity-toxicity relationships or the rule of three for drug candidates, and thus their suitability for advancement to development.

❑ The responsibility of the drug metabolism scientist is to optimize plasma $T_{1/2}$ (clearance compound), drug/metabolic clearance, metabolic stability, and the ratio of metabolic to renal clearance.

❑ Another concern is to minimize or eliminate the following:

- *gut/hepatic-first-pass metabolism*
- *inhibition/induction of drug-metabolizing enzymes by metabolites*
- *biologically active metabolites*
- *metabolism by polymorphically expressed drug-metabolizing enzymes*
- *formation of reactive metabolites.*

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Approaches to assess the metabolism of a compound

❑ There are two approaches to assess the metabolism of a compound: *in vitro* and *in vivo*. Which of these techniques is used depends on a variety of factors such as the nature of the program, the mindset of the company involved, and the resources available.

❑ Some companies may favor high-throughput *in vitro* studies to develop Structure Activity Relationship (SAR) around metabolic stability or even enzyme specificity for a series of compounds

❑ Whereas others may place value on *in vivo* dosing of promising leads at the early stages, which although of lower throughput provides much more information on the likely fate of a particular compound than the in vitro methods.

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Advantages of Enhancing Metabolic Stability

- Increased bioavailability and longer half-life, which in turn should allow lower and less frequent dosing thus promoting better patient compliance.

- Better congruence between dose and plasma concentration, thus reducing or even eliminating the need for expensive therapeutic monitoring.

- Reduction in metabolic turnover rates from different species which, in turn, may permit better extrapolation of animal data to humans.

- Lower patient-to-patient and intra-patient variability in drug levels, since this is largely based on differences in drug metabolic capacity.

- Diminishing the number and significance of active metabolites and thus lessening the need for further studies on drug metabolites in both animals and man.

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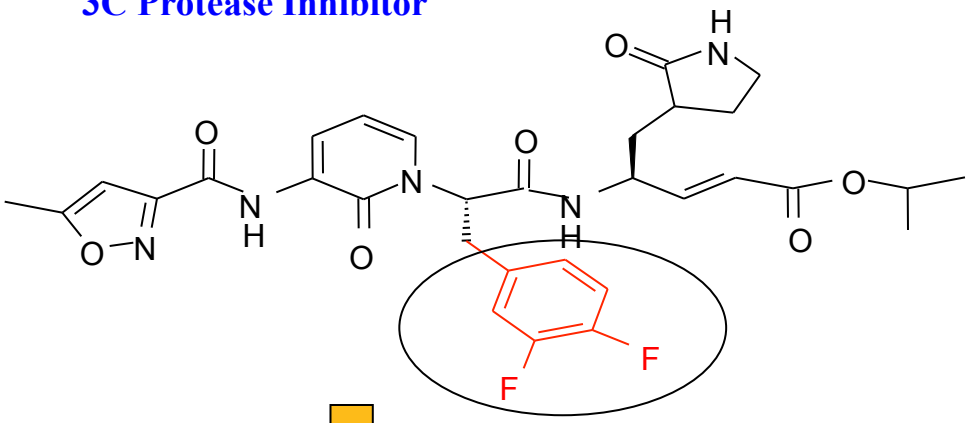
Strategies to Enhance Metabolic Stability

- The following strategies have been used:
  - *Deactivating aromatic rings towards oxidation by substituting them with strongly electron withdrawing groups (e.g., CF_3, SO_2NH_2, SO_3-).*
  - *Reduce size and lipophilicity*
  - *Replace H with CH_3 (do enough times to avoid stereocenter)*
  - *Block α-catbon hydrogens with CH_3*
  - *Introducing an N-t-butyl group to prevent N-dealkylation.*
  - *Replacing a labile ester linkage with an amide group.*
  - *Deuterated drug approach*
  - *Constraining the molecule in a conformation which is unfavorable to the metabolic pathway*
  - *Avoidance of the phenolic function which has consistently been shown to be rapidly glucuronidated.*
  - *Avoidance of other conjugation reactions as primary clearance pathways, would also be advised in the design stage in any drug destined for oral usage.*
  - *Anticipate a likely route of metabolism and prepare the expected metabolite if it has adequate intrinsic activity. For example, often N-oxides are just as active as the parent amine, but won't undergo further N-oxidation.*

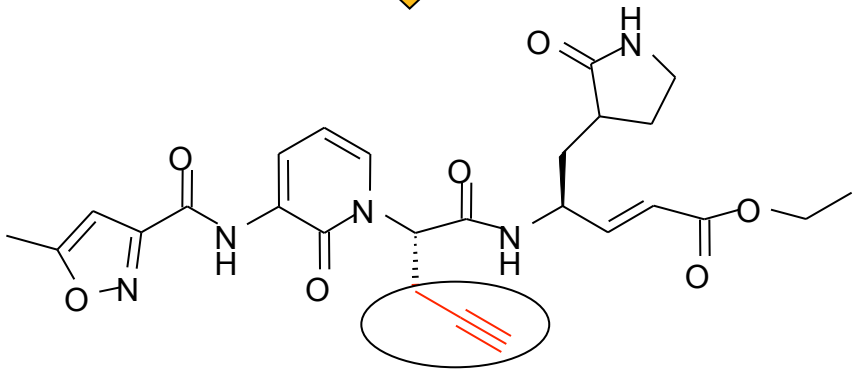
Examples from literature to enhance metabolic stability in the molecular design

Reduce the overall lipophilicity (logP, logD) of the structure

3C Protease Inhibitor



EC50 = 0.078 μM, clogP = 2.07
C7hr (monkey) = 0.012 μM



EC50 = 0.058 μM, clogP = 0.18
C7hr (monkey) = 0.057 μM

Dragovich, P. et al (2003). *Journal of Medicinal Chemistry*, 46(21), 4572-4585.

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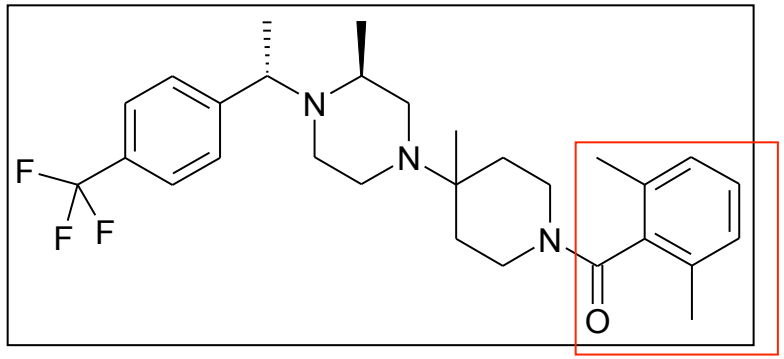
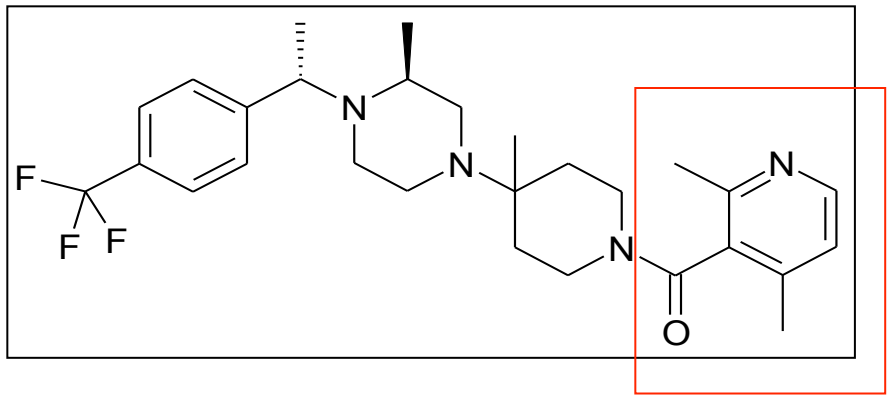
Introduce isosteric atoms or polar functional group

CCR5 antagonist



Ki = 1 nM, AUC 0-6h = 922 ng/ml hr



Ki = 2.3 nM, AUC 0-6h = 3905 ng/ml hr

Tagat J R et al (2001). Journal of medicinal chemistry, 44(21), 3343-6.

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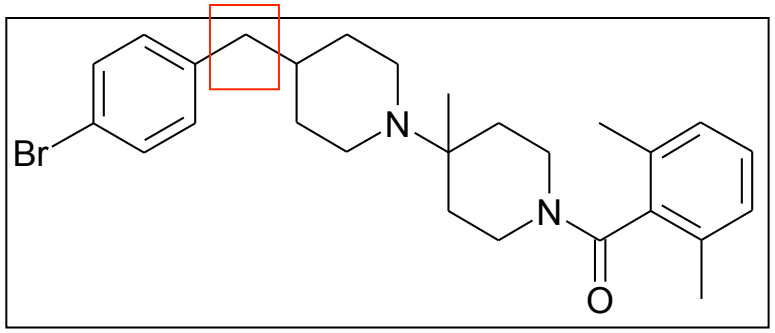
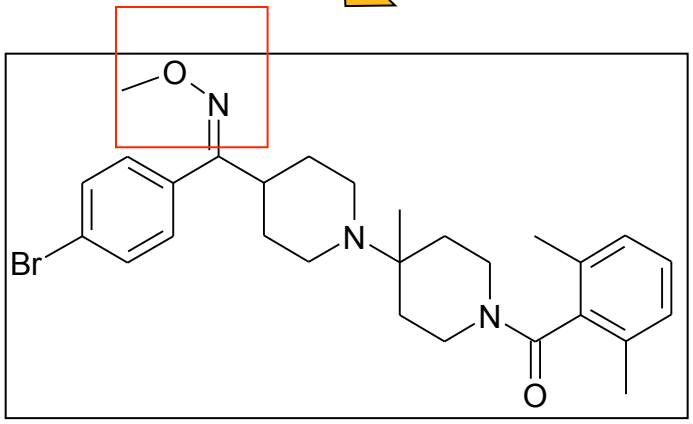
Remove or block the vulnerable site of metabolism (Benzylic oxidation)

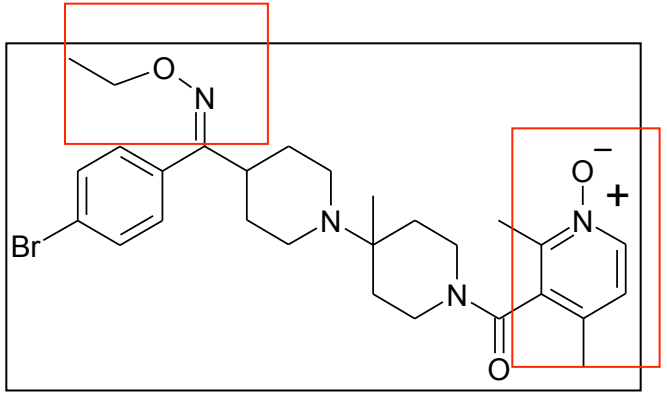
CCR5 antagonist



Ki = 66 nM, AUC 0-6h = 40 ng/ml hr



Ki = 2 nM, AUC 0-6h = 1400 ng/ml hr



Ki = 2.1 nM, AUC 0-6h = 6500 ng/ml hr

Palani, A. et al (2002) Journal of Medicinal Chemistry, 45(14), 3143-3160.

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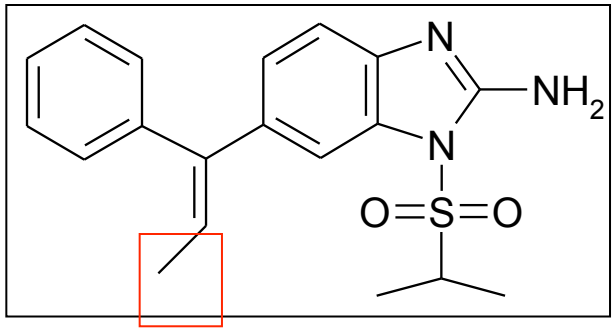
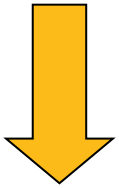
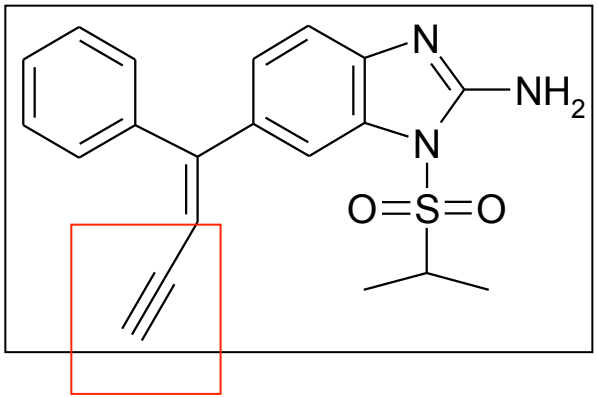
Remove or block the vulnerable site of metabolism (Allylic oxidation)

Vinyl acetylene antiviral



IC50 = 0.06 μg/ml
Cmax = 14-140 ng/ml





IC50 = 0.02 μg/ml
Cmax = 70-300 ng/ml

Victor F et al (1997). Journal of medicinal chemistry, 40(10), 1511-8.

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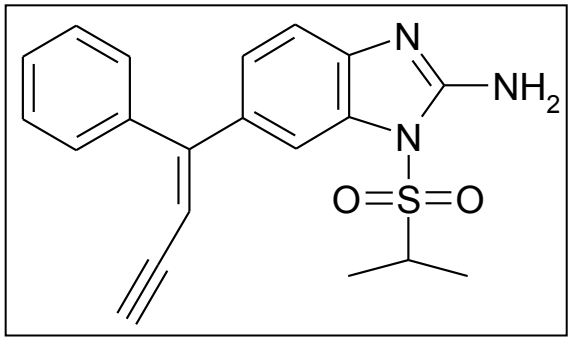
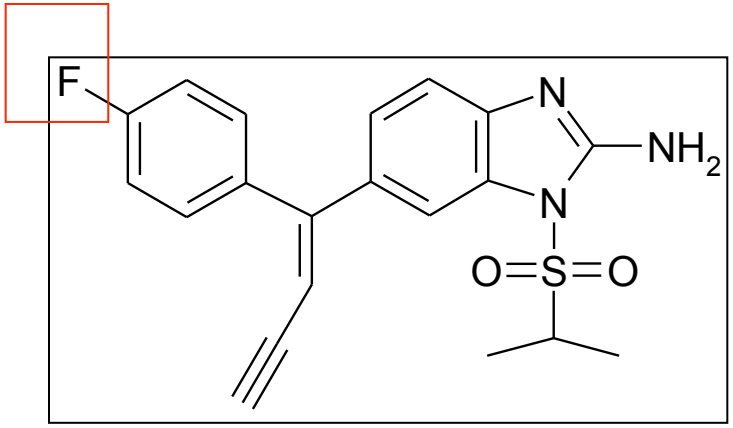
Remove or block the vulnerable site of metabolism (Phenyl oxidation)

Vinyl acetylene antiviral



IC50 = 0.02 μg/ml, % F = 9



IC50 = 0.04 μg/ml, % F = 23

Victor F et al (1997). Journal of medicinal chemistry, 40(10), 1511-8.

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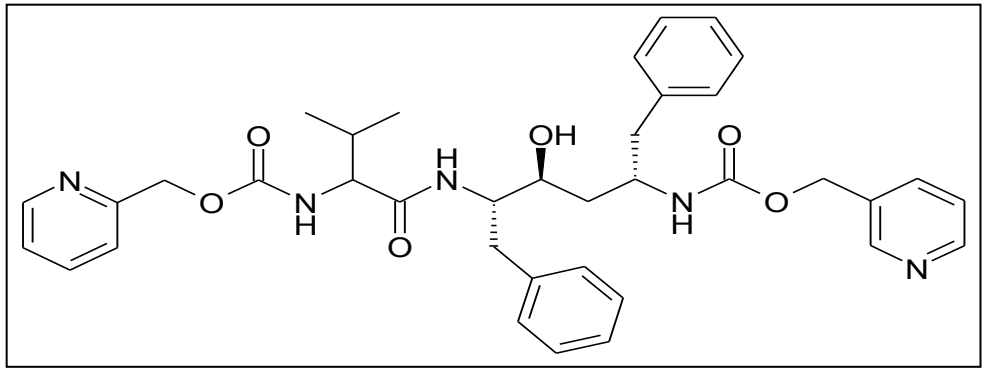
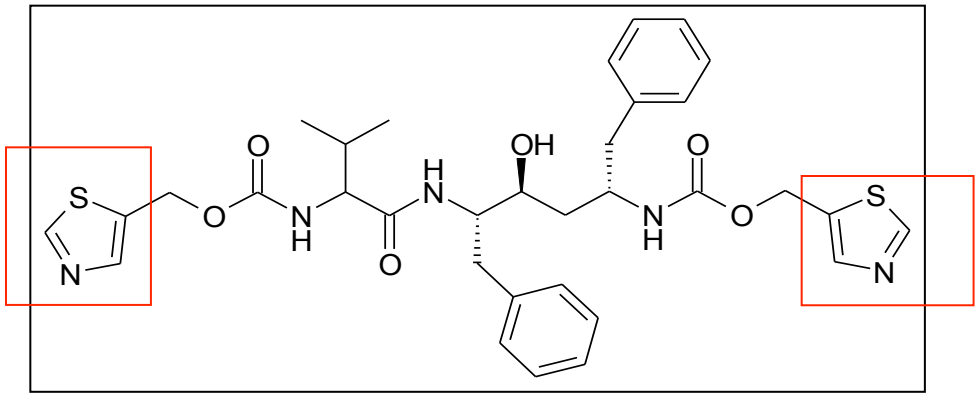
Remove or block the vulnerable site of metabolism (N-oxidation)



AUC = 1.98 μg.h/ml
% F = 26

HIV Protease Inhibitor



AUC = 4.24 μg.h/ml
% F = 47

Kempf, D. et al (1998). Journal of Medicinal Chemistry, 41(4), 602-617

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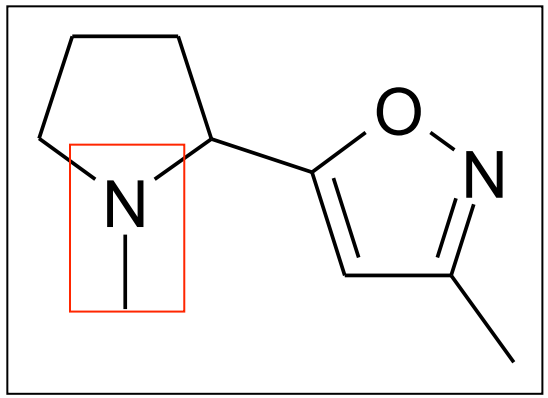
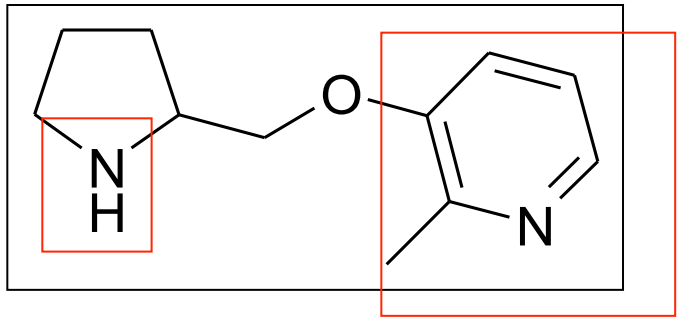
Remove or block the vulnerable site of metabolism (N-demethylation)

nAChR



t1/2 (dog liver slices) = 3 hr
%F = 1.2



t1/2 (dog liver slices) = 24 hr
%F = 61.5

Lin N. H. et al (1997) Journal of medicinal chemistry, 40(3), 385-90.

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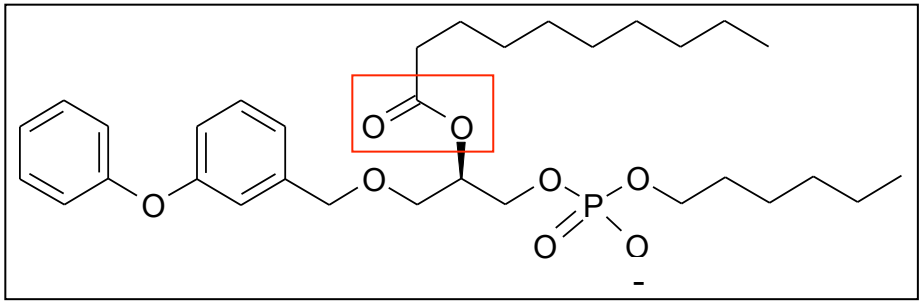
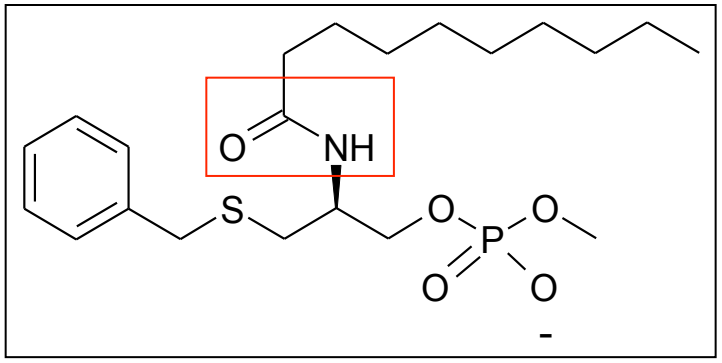
Remove or block the vulnerable site of metabolism (Ester hydrolysis)



t1/2 = 33 min, Cmax = 465 ng/ml,
% F = 4

Phospholipase A Inhibitor



t1/2 = 39 min, Cmax = 3261 ng/ml,
% F = 90

Blanchard S G et al (1998). Pharmaceutical biotechnology, 11, 445-63.

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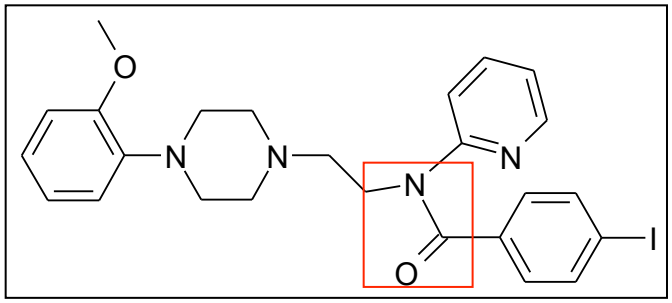
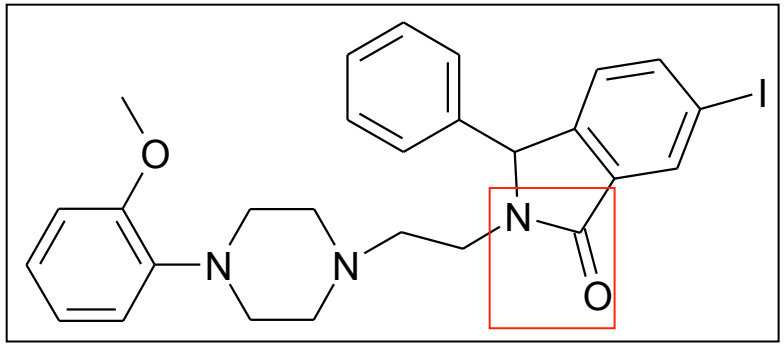
Remove or block the vulnerable site of metabolism (amide hydrolysis)

5-HT$_{1A}$



ki = 0.2 nM, 40% and > 60 % degradation in human liver cytosole and microsomes, respectively



ki = 0.069 nM, 10% and < 5 % degradation in human liver cytosole and microsomes, respectively

Zhuang Z P. et al (1998). Journal of medicinal chemistry (1998 Jan 15), 41(2), 157-66.

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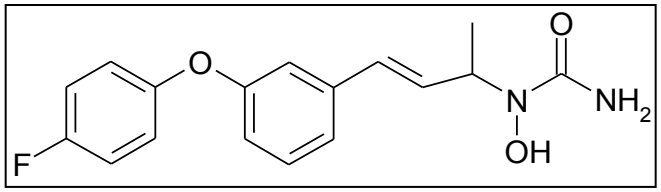
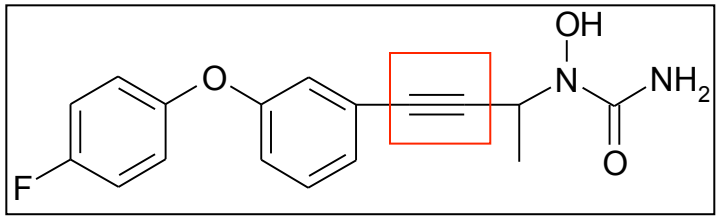
Remove or block the vulnerable site of metabolism (Glucuronidation)

Effect of linker

5-LO Inhibitor

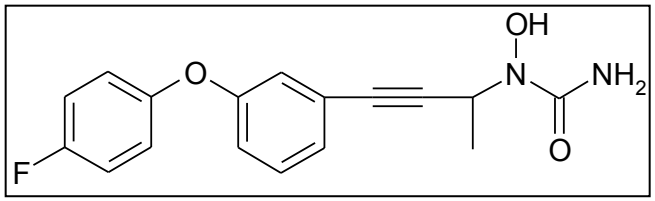


UDPGA rate (nmol/min/mg protein) = 0.19, t1/2 = 4.7 hr

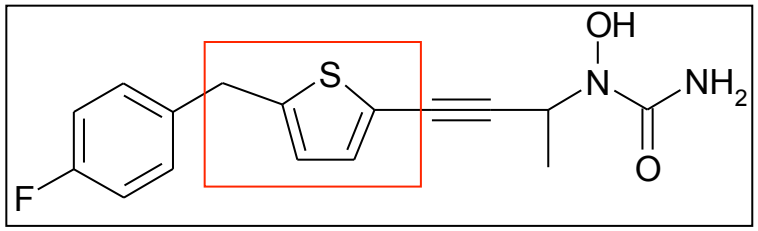


UDPGA rate (nmol/min/mg protein) = 0.05, t1/2 = 5.5 hr

Effect of template

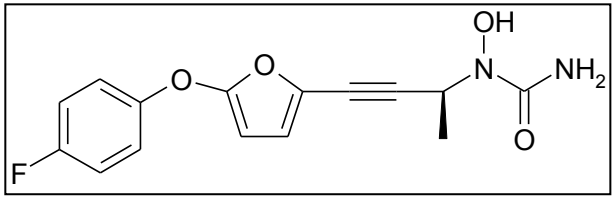


UDPGA rate (nmol/min/mg protein) = 0.05, t1/2 = 5.5 hr

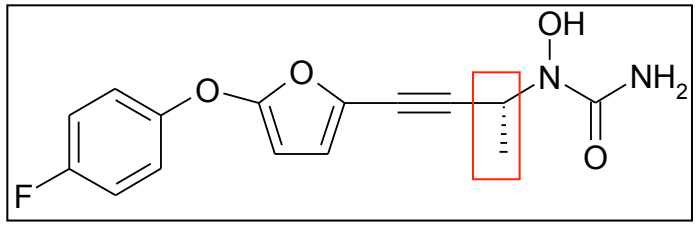


UDPGA rate (nmol/min/mg protein) = 0.012, t1/2 = 14.5 hr

Effect of stereochemistry



UDPGA rate (nmol/min/mg protein) = 0.02, t1/2 = 7.7 hr



UDPGA rate (nmol/min/mg protein) = 0.01, t1/2 = 8.7 hr

Bouska J J. et al (1997) Drug metabolism and disposition: biological fate of chemicals, 25(9), 1032-8.

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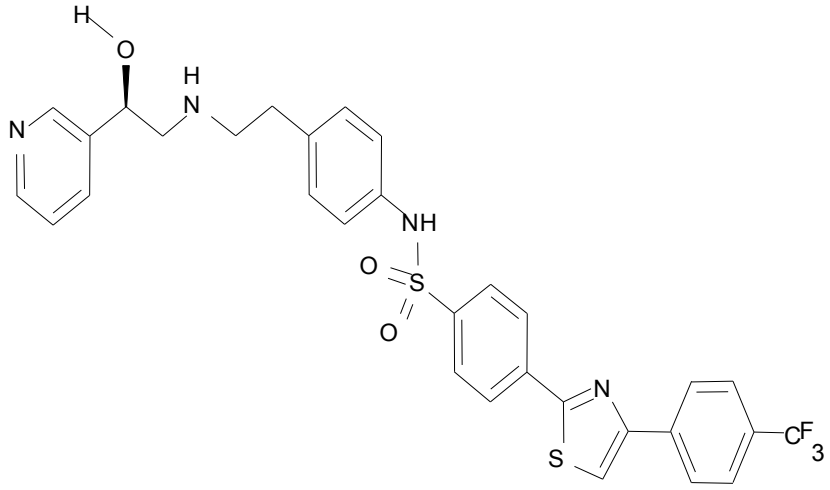
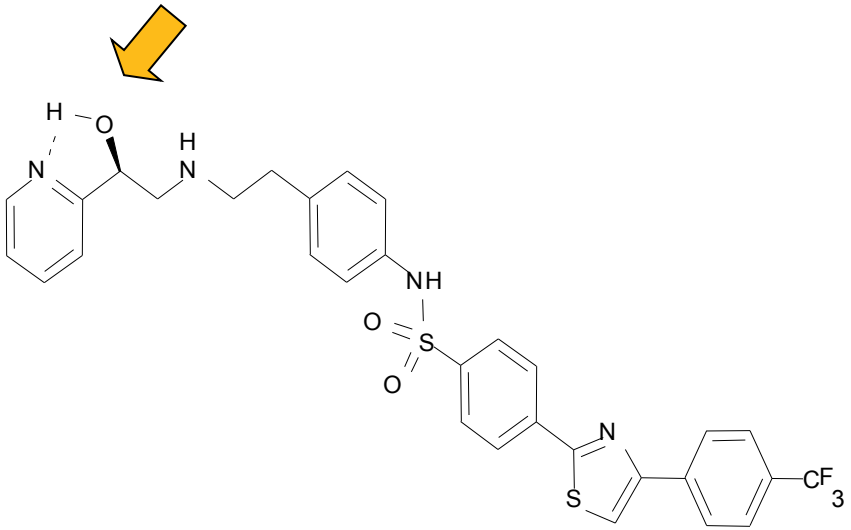
Remove or block intermolecular interaction

Improve oral bioavailability of a 3-pyridyl thiazole benzenesulfonamide adrenergic receptor agonist

•The linkage to the pyridine moiety was changed from the 3- to the 2-position so that the pyridyl-nitrogen atom was positioned to the hydrogen bond with the ethanolamine hydroxyl group; this minimized intermolecular interactions that may limit the oral absorption of this compound class.



%F = 17 (rats), %F = 4 (monkeys)



%F = 30 (rats), %F = 23 (monkeys)

Stearns *et al.* DMD, 30(7), 771-777, 2002

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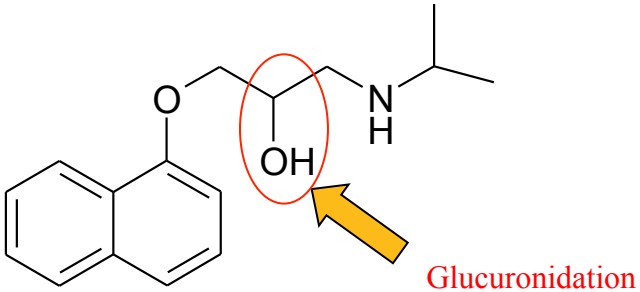
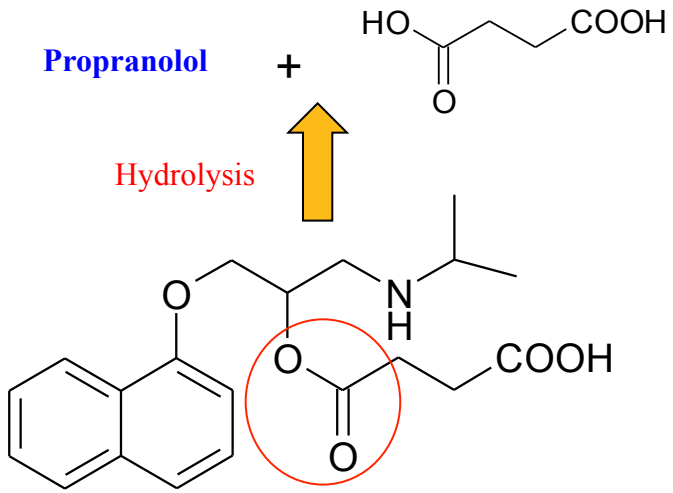
Apply prodrug approach to minimize first-pass effect

•Oral dosage of propranolol (Hasegawa *et al* 1978) produces a low bioavailability and a wide variation from patient to patient when compared to intravenous administration; this difference is attributed to first-pass elimination of the drug.

•Hemisuccinate ester of propranolol was selected as a potential prodrug with the hypothesis that propranolol hemisuccinate ester administration would avoid glucuronide formation during absorption and subsequently be released in the blood by hydrolysis.



Propranolol **AUC 0-6 = 132 ng/ml.h**



Hemisuccinate ester of propranolol **AUC 0-6 = 1075 ng/ml.h**

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Conclusions

❑ Structural information on metabolites is a great help in enhancing as well as streamlining the process of developing new drug candidates.

❑ By improving our ability to identify both helpful and harmful metabolites, suggestions for structural modifications will optimize the likelihood that other compounds in the series are more successful.

❑ In-silico and in vitro techniques are available to screen compounds for key ADME characteristics.

❑ Structural modifications to solve a metabolic stability problem may not necessarily lead to a compound with an overall improvement in PK properties.

❑ Solving metabolic stability problems at one site could result in the increase in the rate of metabolism at another site, a phenomenon known as metabolic switching. Further, reduction in hepatic clearance may lead to increased renal or biliary clearance of a parent drug or inhibition of one or more drug-metabolizing enzymes. Therefore, it is advisable that in vitro metabolic stability data be integrated with other ADME screening.

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Improving the decision-making process in the structural modification of drug candidates

Part II: The Use of Deuterium Isotope Effects to Probe Metabolic liabilities and mechanisms of the formation of reactive metabolites that can cause toxicity

Amin Kamel

Novartis Institutes for BioMedical Research
Metabolism and Pharmacokinetics
Cambridge, MA

Wednesday, June 9, 2010
University of Massachusetts Medical School
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Hoagland-Pincus Conference Center

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OUTLINE

- ❑ Deuterium Isotope Effects: general aspects and background
- ❑ Understanding how the deuterium isotope concept affects the rate of reaction from a mechanistic perspective (HAT vs SET)
- ❑ Uses of deuterated drug approach to probe metabolic liabilities and improve PK parameters
- ❑ Uses of deuterated drug approach to probe metabolism-related toxicity
  - *Mechanism of drug-induced toxicities*
  - *Key factors in drug-induced toxicities*
- ❑ Conclusions

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Deuterium Kinetic Isotope Effects (KIE)
General aspects and background

Heavy Drugs
Ted Agres, Contributing Editor
Drug Discovery & Development - May 01, 2009

- KIE became an attractive concept → replacement of one or more hydrogens in a drug molecule with deuterium would have negligible effects on the physico-chemical properties.
- The more stable deuterium bond requires a greater energy of activation→ a C-H bond cleavage is typically 6-10 times faster than the corresponding C-D bond (k_H/k_D values are in the range of 2-5)
- KIE studies are sometimes accompanied by Metabolic Switching → could be deployed deliberately as a parameter in drug design to generate active metabolites and/or deflect metabolism away from pathways leading to metabolites with toxic properties

- Although no deuterated compound has been approved as a human medicine, the early clinical evaluation of several candidate compounds has been encouraging and has the potential to provide a unique approach to creating new medicines that can address important unmet medical needs.

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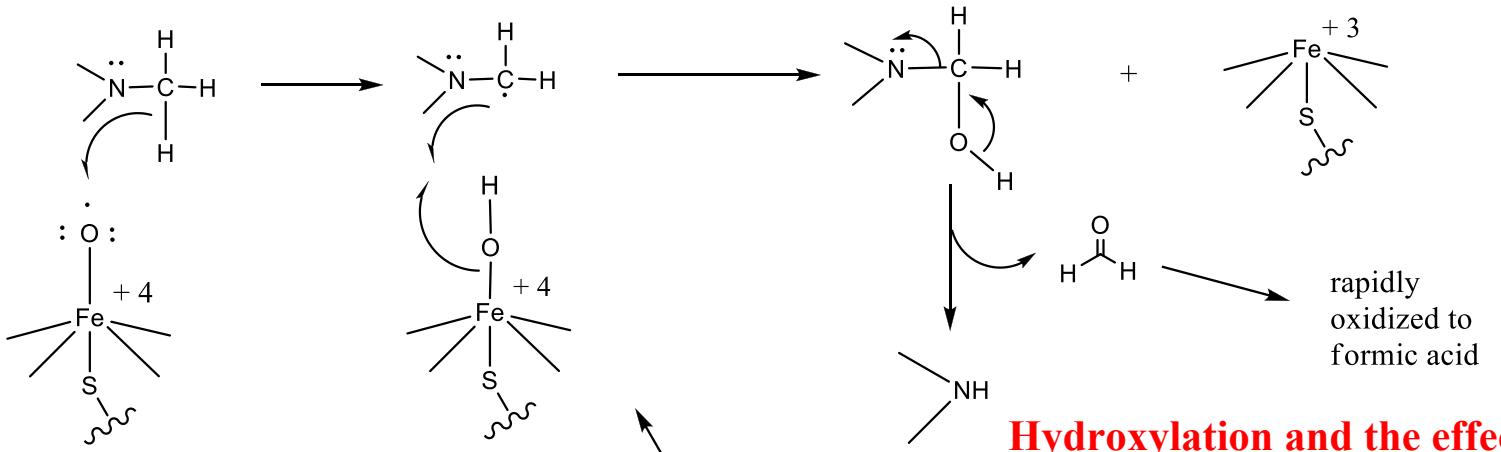
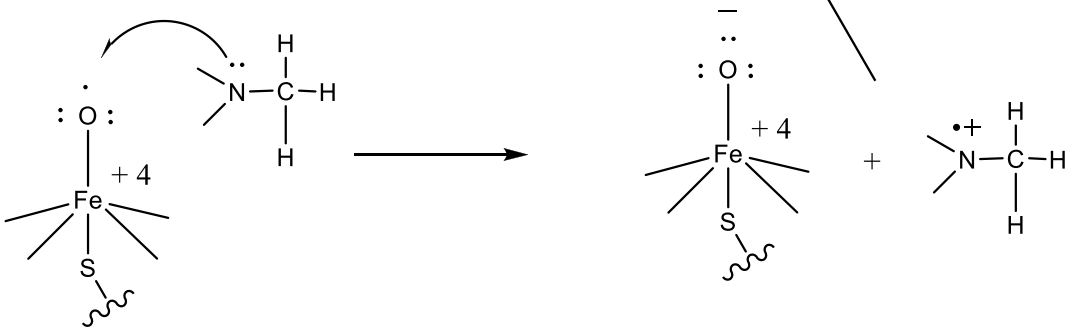
Proposed mechanisms for P-450 Oxidations involving carbon-heteroatom bond cleavage (N-, O- and S-dealkylations) showing N-dealkylation as an example

Direct Hydrogen Atom Transfer (HAT)



Single Electron Transfer (SET)



Hydroxylation and the effect of deuteration

For aromatic compounds the reaction usually involves the initial formation of an arene oxide and subsequent rearrangement into a phenol. However, for aliphatic compounds and moieties, direct hydrogen abstraction occurs first to give a carbon radical which is then hydroxylated and thus deuterium isotope effect would be expected

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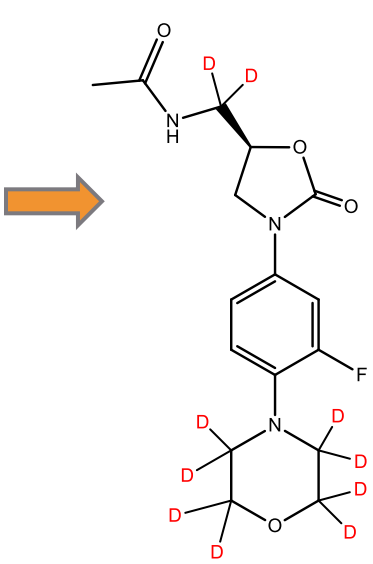
Uses of deuterated drug approach to probe metabolic liabilities and improve PK parameters

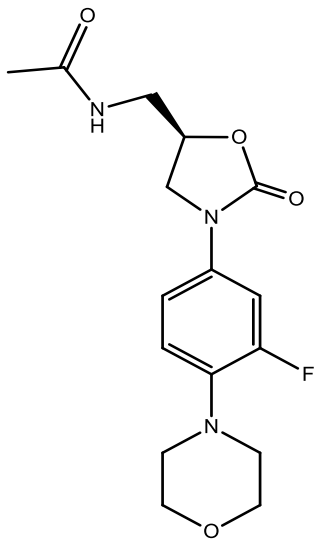
Effect of deuteration of Linezolid on efficacy, exposure and half-life

- In August 2008, **Concert Pharmaceuticals Inc.** has presented pre-clinical results for the deuterated analog of the antibiotic linezolid (C-20081), for possible once-daily oral and intravenous dosing.

- Results indicated that C-20081 with efficacy identical to that of linezolid had a 43% increase in plasma half-life compared to linezolid and showed improved tolerability for such serious bacterial infections as methicillin-resistant staphylococcus aureus (MRSA) and drug-resistant tuberculosis (improved i.v. and oral pharmacokinetics, including increased exposure and half-life were exhibited in chimpanzees)

Deuterated analog
(C-20081)



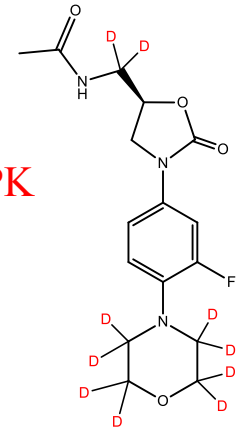


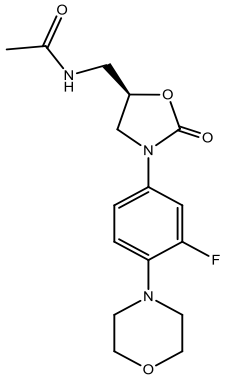
linezolid

Major metabolic pathways of Linezolid

Deuterated analog
(C-20081)

Improved i.v. and oral PK
↑ exposure and half-life

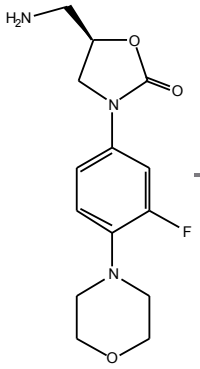


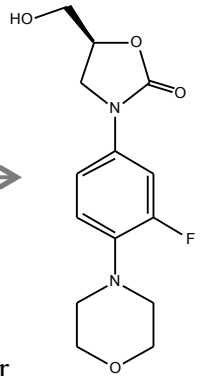


linezolid

amidase

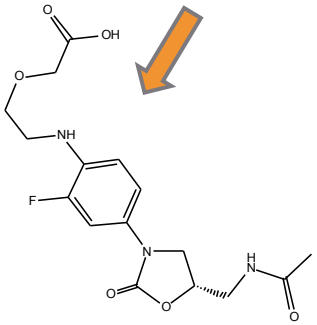
NAT

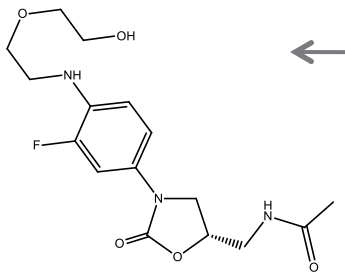




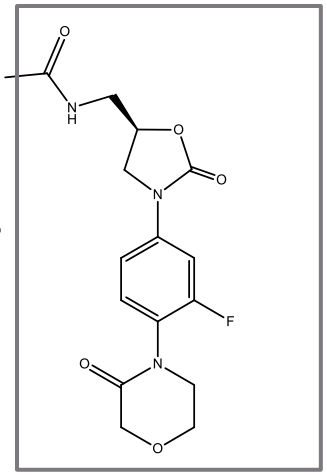
Minor

Major in urine & feces

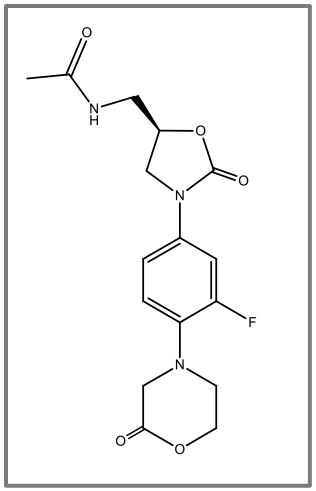




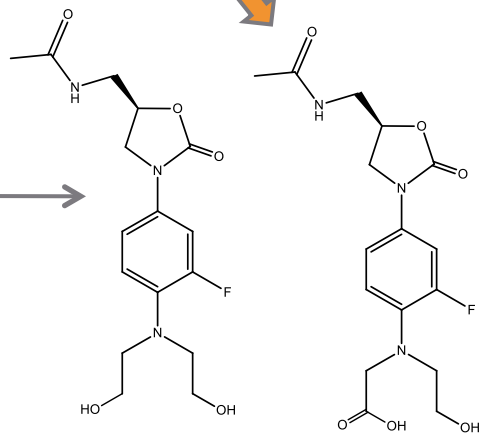
Lactam pathway



Lactone pathway



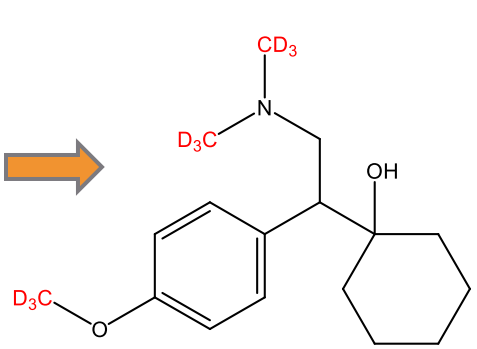
Major in urine & feces
Rate-limiting step in linezolid clearance

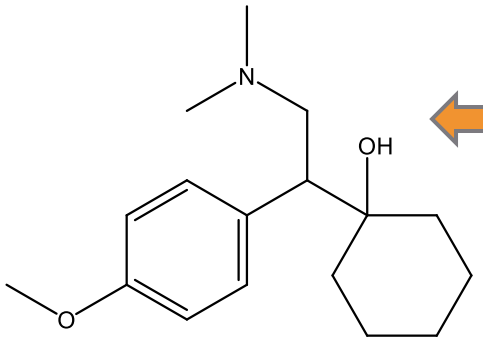


Effect of deuteration of N- and O-CH_3 groups of venlafaxine on its metabolism and duration of effect

- The anti-depression drug venlafaxine is one case in which deuteration approach has been successful. Venlafaxine is the blockbuster selective serotonin-norepinephrine reuptake inhibitor (SNRI) drug for major depressive disorder, originally marketed by **Wyeth** as Effexor in 1993.
- Venlafaxine has a methoxy group that is rapidly converted to a hydroxyl group in the liver and it also has a dimethylamine group that is quickly metabolized to a primary amine.
- In October 2008, Auspex announced initial Phase I clinical trial results for its deuterated version of venlafaxine in 16 healthy volunteers. The data showed that the compound, designated as SD-254, was metabolized half as fast as venlafaxine and persisted at effective levels in the body far longer. Auspex has received a patent on SD-254

deuterated venlafaxine (SD-254)





venlafaxine

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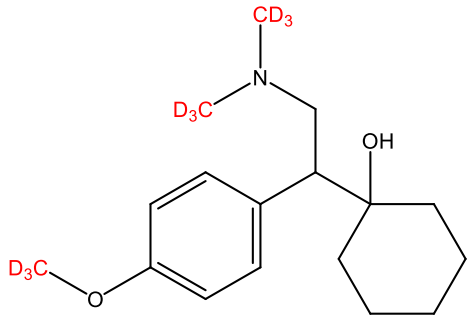
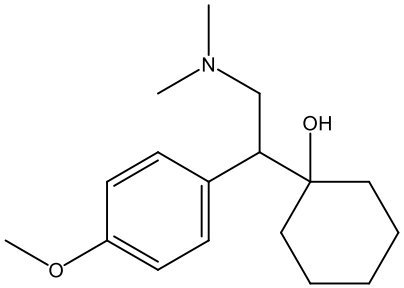
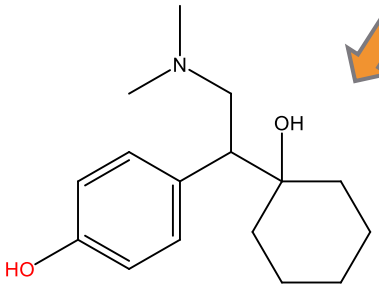
Major metabolic pathways of venlafaxine

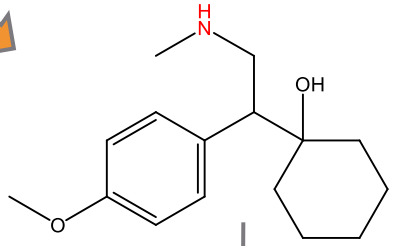


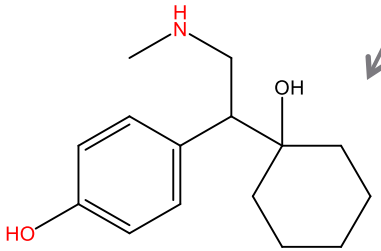
Deuterated venlafaxine (SD-254)

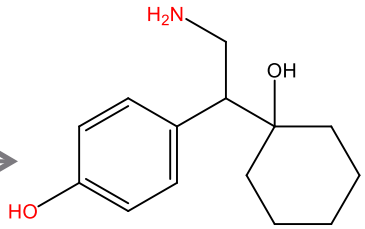


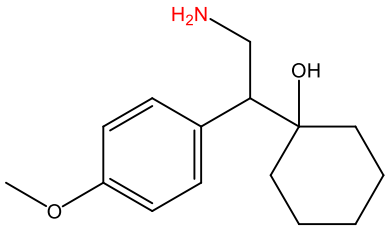
venlafaxine











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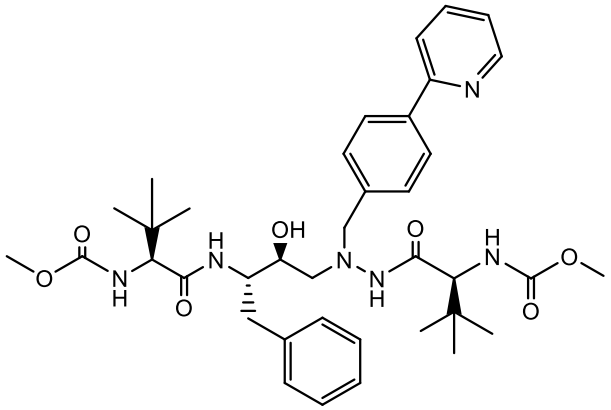
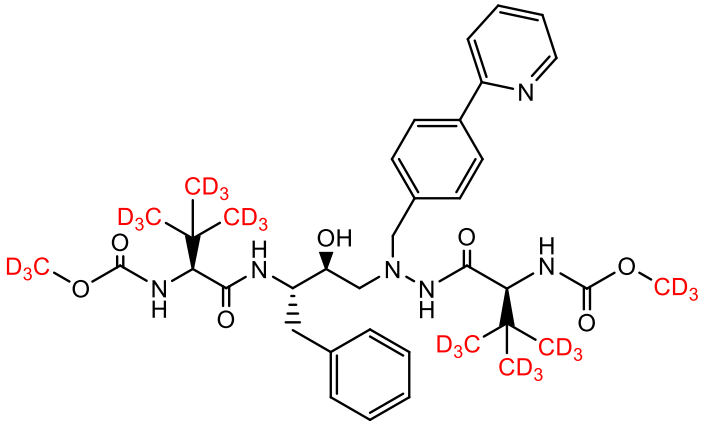
Effect of deuteration of atazanavir on half-life, Cmax and AUC

- In human liver microsomes, the deuterated analog of the antiviral atazanavir (CTP-518) showed an approximately 50% increase in half life compared with atazanavir.
- Following oral co-dosing in rats, CTP-518 showed a 43% increase in half life, a 67% increase in Cmax and an 81% increase in AUC compared with atazanavir.
- When administered to chimps, CTP-518 showed around 50% increases in half life compared with atazanavir.
- The deuteration of atazanavir slows the rate at which the HIV drug is eliminated from the body, potentially abolishing the current need to coadminister the drug with ritonavir or another anti-HIV booster agent. CTP-518 is scheduled to enter Phase I clinical trials later last year (2009)



atazanavir (Reyataz™)
HIV protease inhibitor



Deuterated atazanavir (CTP-518)

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Uses of deuterated drug approach to probe metabolism-related toxicities

Mechanism of drug-induced toxicities

❑Type A (predictable)

• Reactions are dose-dependent and predictable based on the pharmacology of the drug.

•Type A reactions can be reversed by reducing the dosage or, if necessary, discontinuing the drug altogether.

❑ Type B (unpredictable or idiosyncratic)

• Reactions are dose-independent and cannot be predicted on the basis of the pharmacology of the drug.

•Type B reactions are typically caused by formation of electrophilic reactive metabolites which bind to nucleophilic groups present in vital cellular proteins and nucleic acids.

• Reactive metabolites can cause carcinogenicity, teratogenicity, and immune-mediated toxicity.

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Uses of deuterated drug approach to probe metabolism-related toxicities

Key factors in drug-induced toxicities

- Potency → low potency translates to high dose
- Selectivity → poor selectivity is problematic, e.g inhibition of Ikr channel via drug binding to hERG
- Duration of therapy and Dose → high dose is often problematic
- Drug-Drug Interaction (DDI)
  - "victim" or "perpetrator"
  - Mechanism: enzyme induction or enzyme inhibition (most serious, potential toxicity)
- Bioactivation → Risk factor via reactive intermediate

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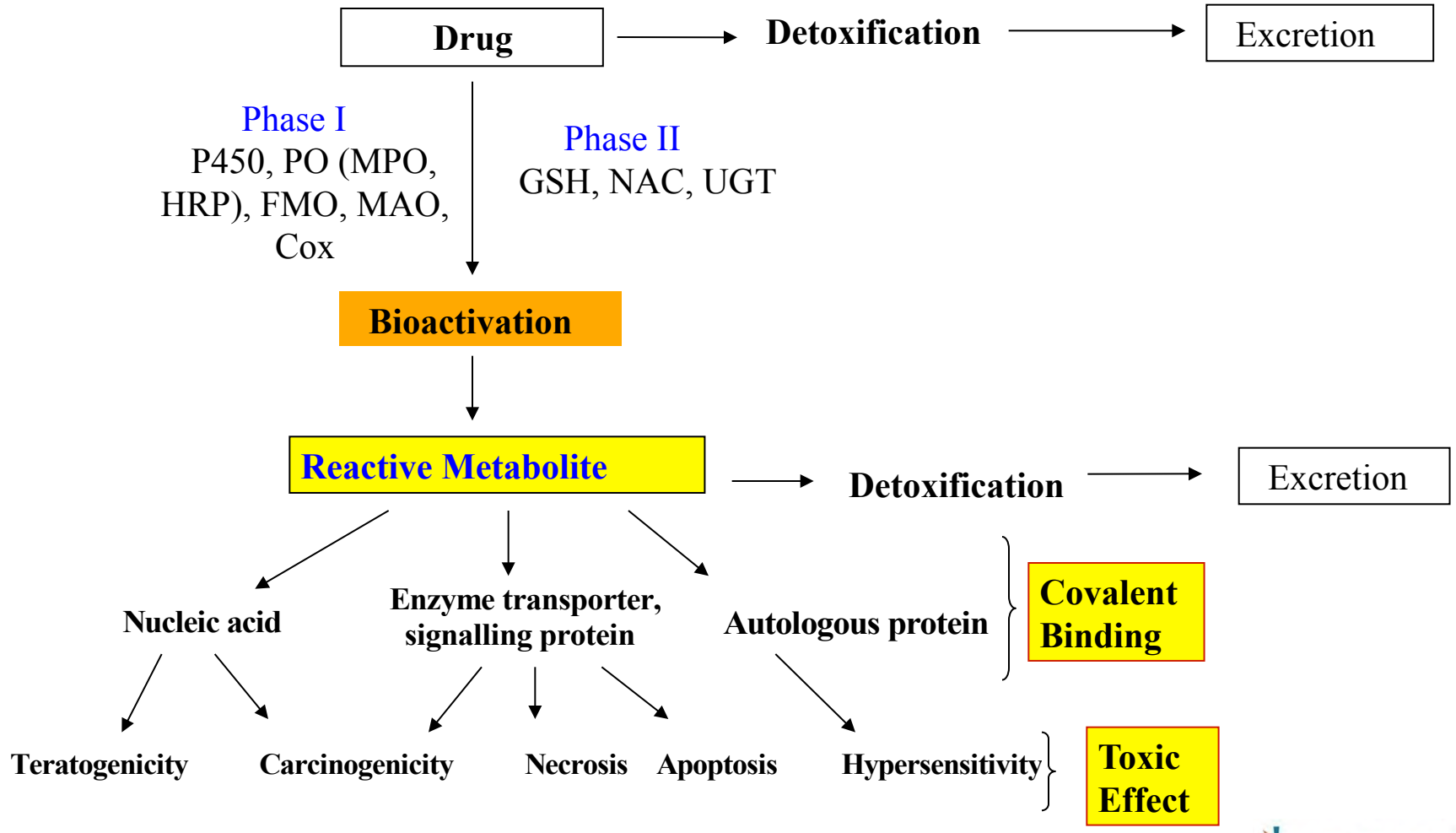
Reactive intermediate paradigm and idiosyncratic reactions



Examples of chemical structures activating to produce toxic metabolites (cont'd)

Aryl nitro	Reduction	Nitroso	Tolcapone	Parkinson's disease	Liver toxicity
			Chloramphenicol	Antibiotic	Aplastic anemia Bone marrow toxicity
			Dantrolene	Muscle relaxant	Liver toxicity
			Nimesulide	COX 2 inhibitors	Liver toxicity
Nitrogen-containing aromatic	Oxidation	Nitrenium ion Free radical	Clozapine	Antipsychotic agent	Agranulocytosis Liver toxicity Myocarditis
			Aminopyrine	Painkiller	Agranulocytosis CNS toxicity
			Dipyrone	Painkiller	Agranulocytosis
Aryl amines	Oxidation to hydroxylamine	Nitroso	Sulfamethoxazole	Antibacterial agent	Hepatotoxicity Agranulocytosis Lupus-like syndrome Skin rashes
			Dapsone	Antiparasitic	Agranulocytosis Flu-like syndrome Hemolytic anemia Methemoglobinemia
			Procainamide	Cardiac antiarrhythmic	Lupus-erythematosis Agranulocytosis Fever
			Nomifensine	Antidepressant	Hemolytic anemia Allergic reactions
			Sulfasalazine	Ulcerative colitis	Abnormal liver function Decreased blood counts Allergic reactions
			Aminoglutethimide	Breast cancer	Skin rashes Fever Agranulocytosis Thrombocytopenia Liver toxicity

Examples of chemical structures activating to produce toxic metabolites

Chemical class	Biotransformation	Toxic metabolite	Compound		Biological effects
			Name	Clinical use	
Quinone	Oxidation	Quinone-type	Tacrine	Alzheimer's disease	Hepatic toxicity
			Troglitazone	Treat Type II diabetes	Hepatic toxicity
			Minocycline	Antibiotics	Hepatic toxicity Lupus-like syndrome
			Acetaminophen	Analgesic agent	Hepatic toxicity
			Aminosalicylic acid	Inflammatory bowel disease	Lupus-like syndrome Pancreatic toxicity Hepatic toxicity Renal toxicity
			Amodiaquine	Treat malaria	Hepatic toxicity Agranulocytosis
			Phenytoin	Anticonvulsant	Drug-induced hypersensitivity Teratogenicity
			Carbamazepine	Anticonvulsant	Teratogenicity
			Vesnarinone	Phosphodiesterase inhibitor	Agranulocytosis
			Prinomide	Antiinflammatory	Agranulocytosis
			Estrogens	NSAID	Breast cancer Uterine cancer
			Tamoxifen	NSAID	Endometrial cancer
			Fluperlapine	Antipsychotic agent	Agranulocytosis

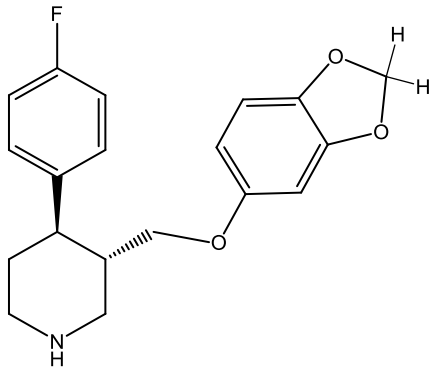
Examples of chemical structures activating to produce toxic metabolites (cont'd)

Michael Acceptors	Hydrolysis Oxidation	Aldehyde Co-A conjugate	Felbamate	Anticonvulsant	Aplastic anemia Liver toxicity
			Terbinafine	Antifungal agent	Bone marrow toxicity Liver toxicity Skin rashes
			Valproic acid	Anticonvulsant	Liver toxicity
			Mianserin	Antidepressant	Agranulocytosis
			Leflunomide	Inflammatory arthritis	Liver toxicity Agranulocytosis
Carboxylic acids	Glucuronidation	Acyl glucuronides	Diclofenac	NSAID	Liver toxicity Agranulocytosis
			Zomepirac	NSAID	Liver toxicity
			Ibufenac	NSAID	Liver toxicity
			Bromfenac	NSAID	Liver toxicity
			Benoxaprofen	NSAID	Liver toxicity
			Indomethacine	NSAID	Bone marrow toxicity

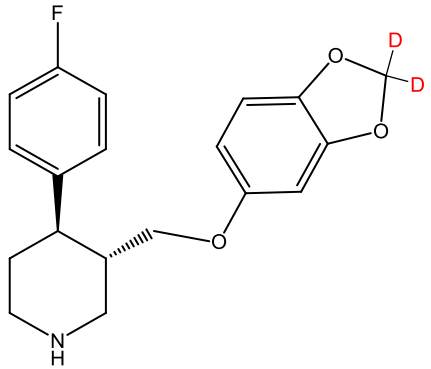
Uses of deuterated drug approach to probe DDI findings

Effect of deuteration of methylenedioxy bridge of Paroxetine on the activity of CYP2D6

- Paroxetine (Paxil) is an antidepressant selective serotonin reuptake inhibitor (SSRI) blockbuster drug and also reduces menopausal hot flashes.
- However, it irreversibly inactivates CYP2D6 → potential drug-drug interaction (DDI) with other medications mediated by CYP2D6
- A deuterated analog of paroxetine (CTP-347) was introduced by **Concert** as a potential nonhormonal treatment for menopausal hot flashes.
- Earlier last year (March 2009), Concert announced encouraging Phase I clinical trial results for CTP-347: in a trial of 94 women, the deuterated version CTP-347 showed less metabolic inhibition of CYP2D6 and potentially enabling its broader use with other drugs



paroxetine (Paxil)



CTP-347

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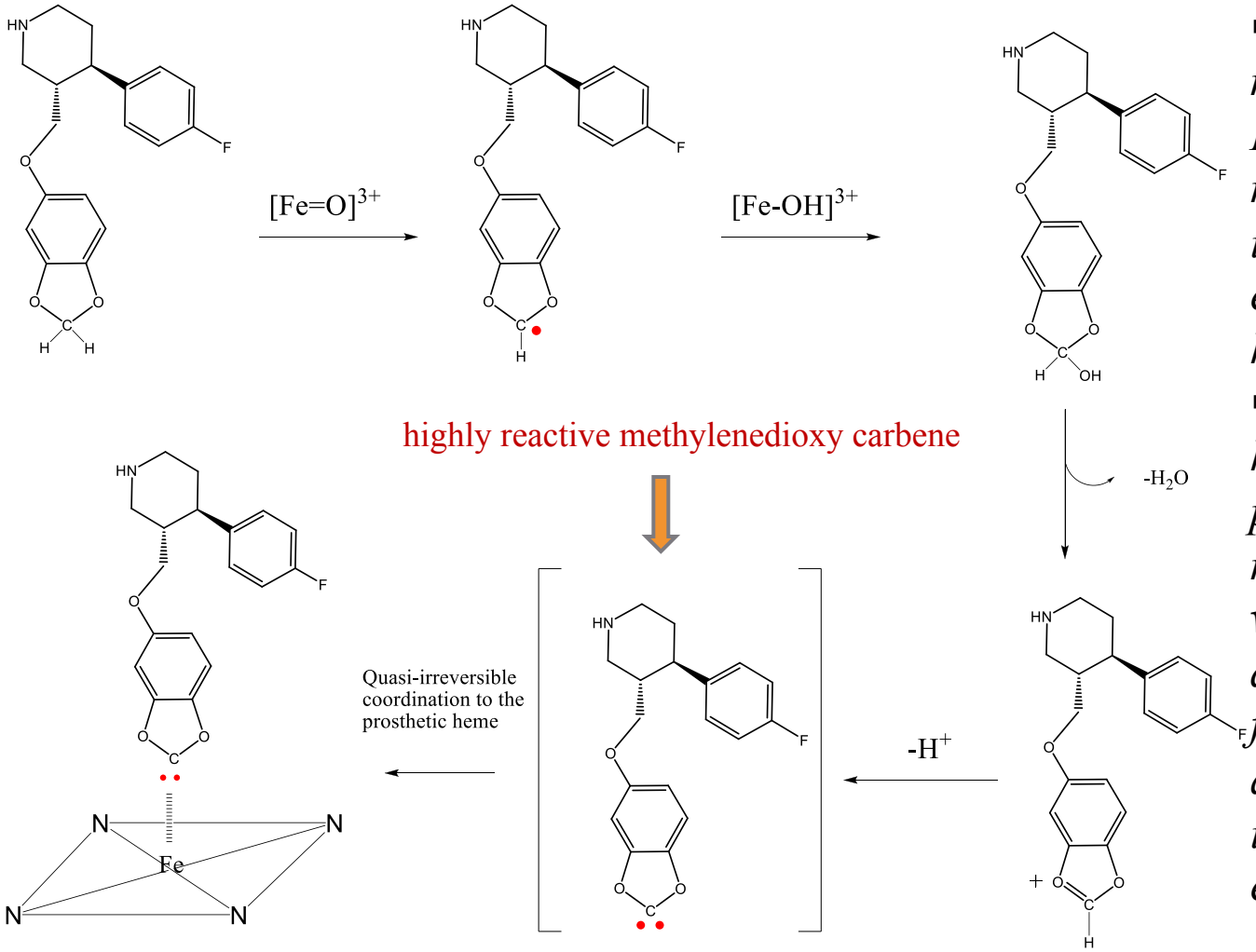
Proposed mechanism for the formation of the highly reactive methylenedioxy carbene function of paroxetine by CYP2D6 and subsequent quasi-irreversible inhibition to inactivate CYP2D6



metabolic intermediate (MI) complex

- *CYP2D6 metabolizes the methylenedioxy portion of Paxil to the highly reactive carbene that then irreversibly inhibits the enzyme by binding its heme iron active site.*
- *Replacing the pair of hydrogens on paroxetine's methylenedioxy bridge with a pair of deuteriums dramatically reduces the formation of the carbene and thus lessens the inactivation of the enzyme.*

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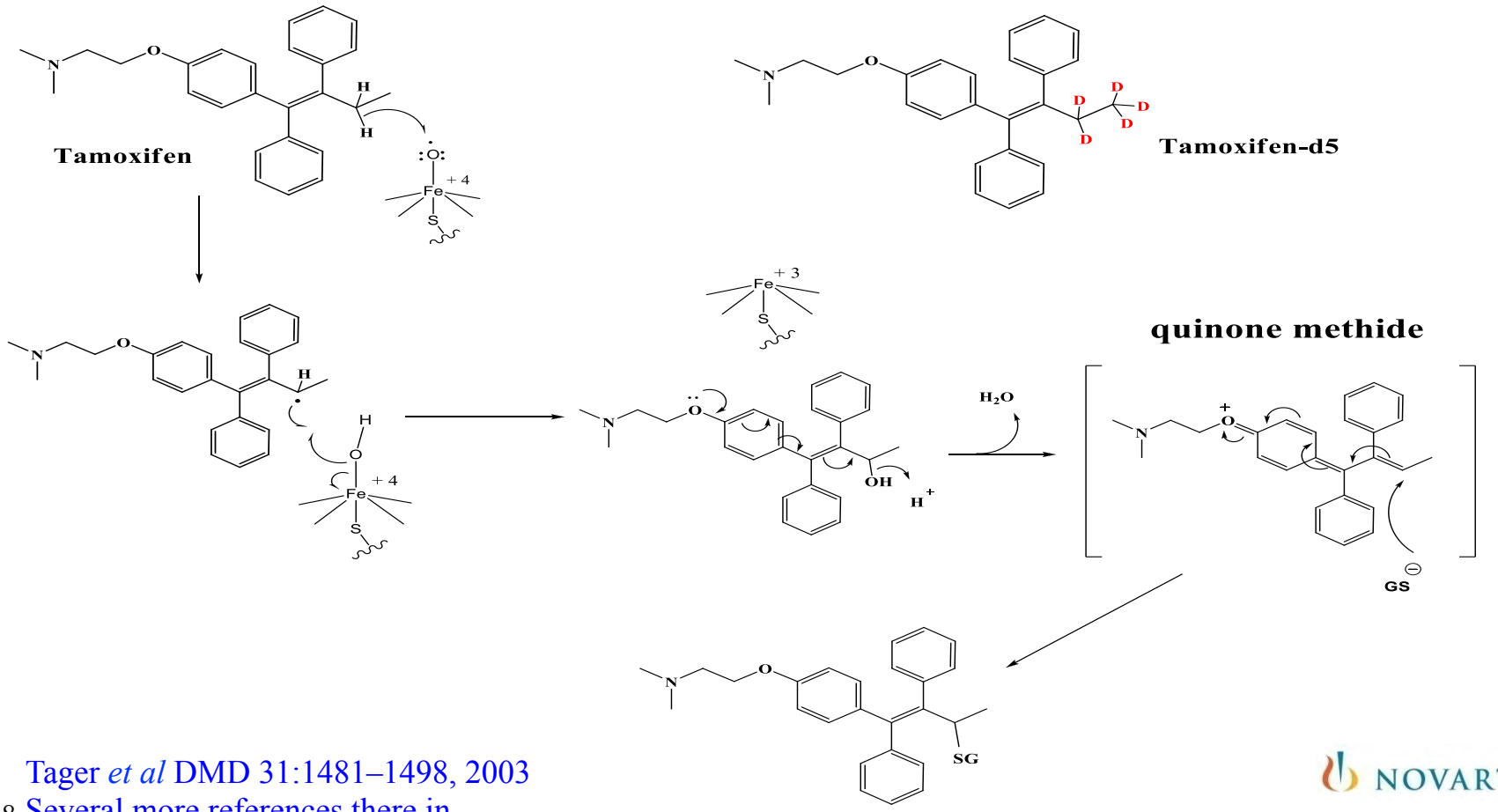
Uses of deuterated drug approach to probe mechanism of the formation of reactive metabolites that can cause toxicity

Effect of deuteration of Tamoxifen on the genotoxicity

❑ Genotoxicity of the antitumor drug, tamoxifen, was decreased 2- to 3-fold in vivo in rats by deuterium substitution for hydrogen in the allylic ethyl group suggesting that liver carcinogenicity involves allylic α-carbon oxidation that may generate a reactive quinone methide.



Tager *et al* DMD 31:1481–1498, 2003

Several more references there in

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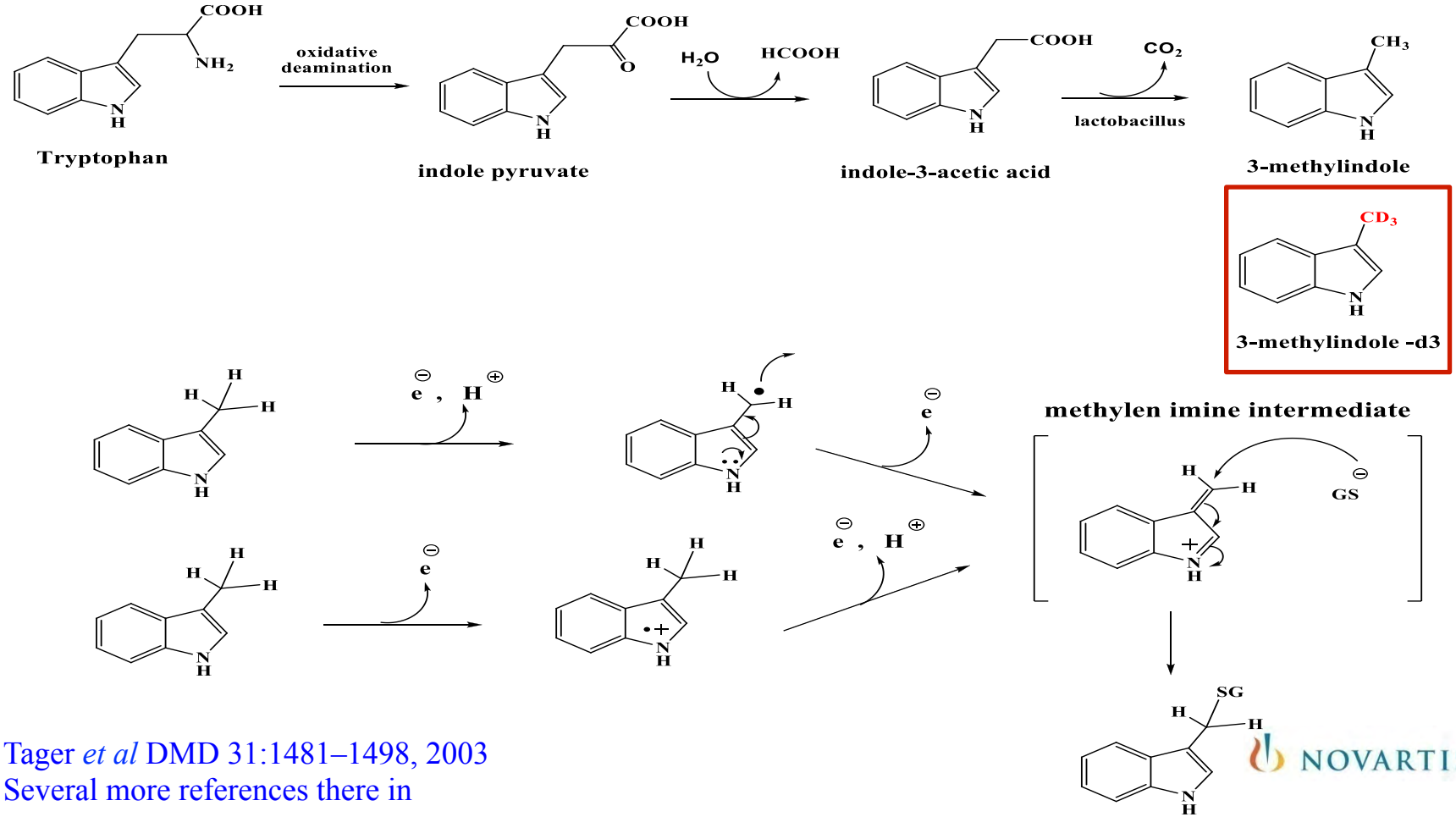
Uses of deuterated drug approach to probe mechanism of the formation of reactive metabolites that can cause toxicity

Effect of deuteration of the pneumotoxin 3-methylindole (3 MI)

- Damage to lungs in mice was found to be significantly decreased by deuteration of the methyl group, as was the rate of glutathione depletion (Huijzer et al.,1987; Yost, 1989).
- Mechanistic studies suggested that hydrogen abstraction from the methyl group was the rate-limiting step in the initiation of toxicity by 3MI via the formation of methylene imine intermediate.



Tager *et al* DMD 31:1481–1498, 2003

Several more references there in

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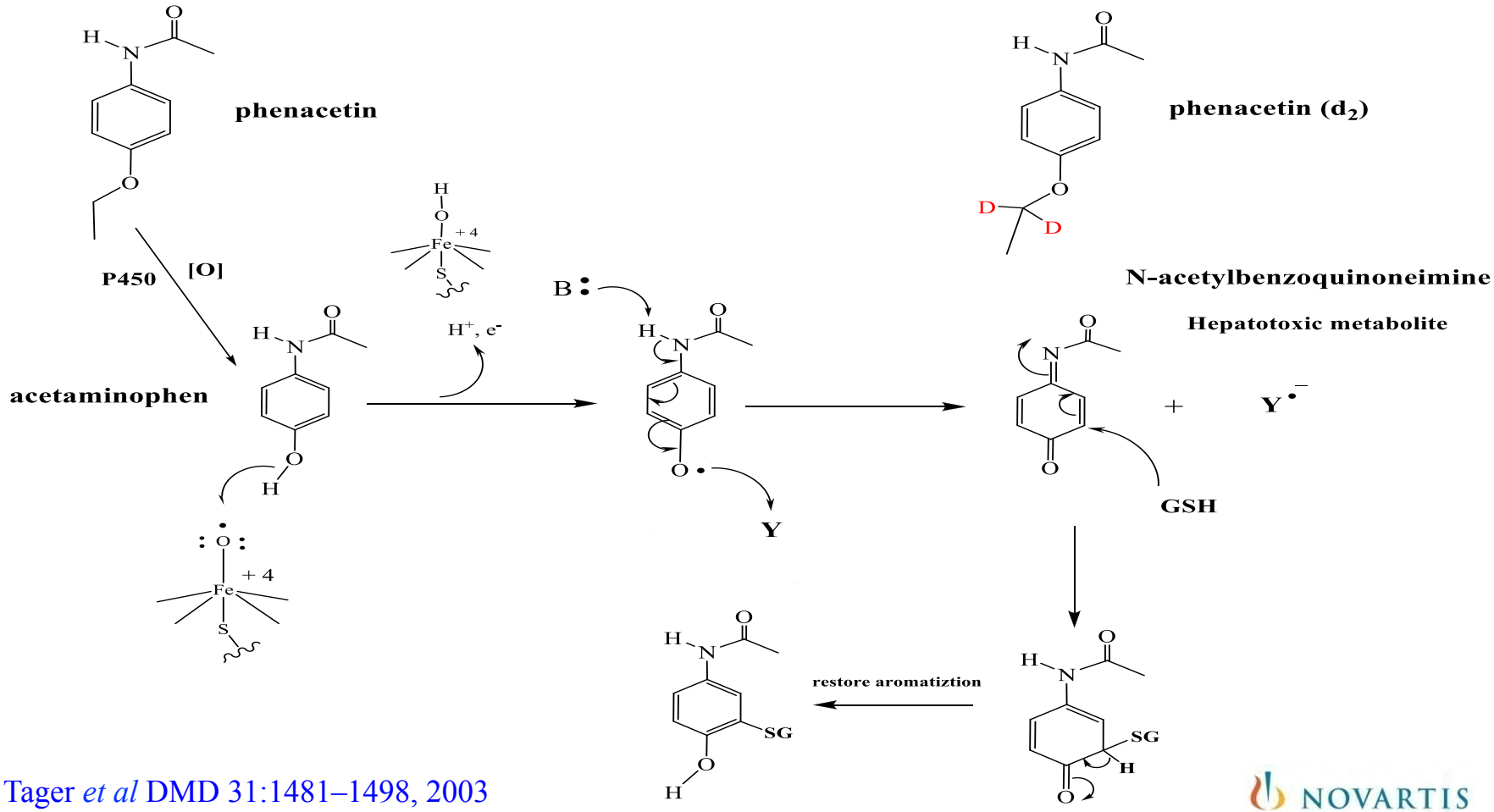
Uses of deuterated drug approach to probe mechanism of the formation of reactive metabolites that can cause toxicity

Effect of deuteration of Phenacetin on liver toxicity

❑ Deuterium substitution for hydrogen in the ethoxymethylene carbon of phenacetin significantly decreased the extent of hepatic necrosis (~ 3-fold) via decreasing the oxidative O-deethylation pathway to acetaminophen, which is further oxidized to its reactive toxic quinone imine



Tager *et al* DMD 31:1481–1498, 2003

Several more references there in

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Conclusions

- Deuterated drug approach would be most applicable with existing drugs (well-defined PK and metabolism data).
- Deuterated drugs approach can potentially lead to a variety of beneficial effects:
  - *longer duration of pharmacological action*
  - *reduced levels of toxic metabolites*
  - *metabolic switching to generate active metabolites from prodrugs*
  - improve existing drugs and reduce the risk of failure in drug design/development.
  - *have the same physico-chemical properties and thus requirements for toxicological data and clinical trials may be streamlined quicker by FDA*
- Reducing toxicity may be improved by
  - *Screening for reactive intermediates with the use of radiolabeled reagents*
  - *Introduce trapping agents, such as semicarbazide and potassium cyanide that are able to trap **hard** electrophiles*
  - *Focus on the mechanisms by which IDRs occur and continue dialogue among the disciplines involved in the entire process*
  - *Avoiding chemical functional groups that are well known to cause toxicity during drug design*

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