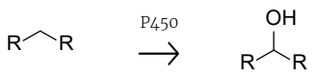
Phase I Metabolism

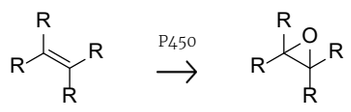
Oxidation

Aliphatic Hydroxylation



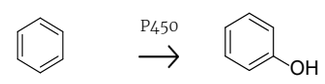
Aliphatic Hydroxylation: Norketamine
Ketamine, a dissociative anesthetic, has recently emerged as a novel antidepressant. Norketamine is the *N*-demethylated major metabolite of ketamine. Aliphatic hydroxylation of norketamine at the six position results in hydroxynorketamine (HNK). Ketamine is racemic and forms several HNK stereoisomer metabolites. The HNK metabolites of ketamine do not produce anesthetic effects and were long thought to be inactive; however, recently, it was demonstrated that these hydroxylated metabolites of ketamine exert antidepressant behavioral-relevant responses in rodent models.

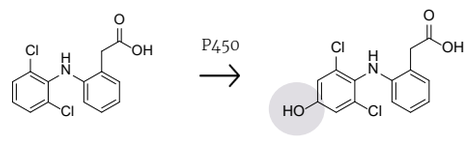
Epoxidation



Epoxidation: Carbamazepine
Carbamazepine is a commonly prescribed antiepileptic drug and is on the World Health Organization's most recent list of essential medicines. Carbamazepine is a prodrug which is activated by the epoxidation of the stilbene to carbamazepine-10,11-epoxide.

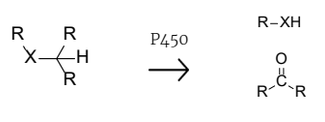
Aromatic Hydroxylation

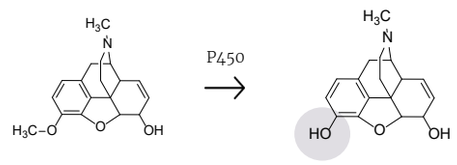




Aromatic Hydroxylation: Diclofenac
Diclofenac is a commonly prescribed non-steroidal anti-inflammatory drug (NSAID). Its use can lead to idiosyncratic drug-induced liver injury (IDILI). IDILI, a rare but severe side effect of diclofenac, is thought to be caused by the formation of diclofenac-1',4'-quinone imine. The first metabolic step towards forming this toxic reactive metabolite is 4'-aromatic hydroxylation of the chlorobenzene.

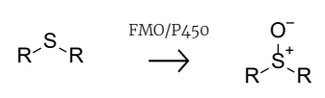
Dealkylation

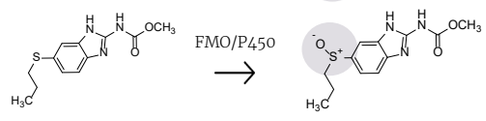




Dealkylation: Codeine
Codeine acts as a central analgesic prescribed for pain management. Codeine is a weaker agonist at μ-opioid receptors than morphine, its *O*-dealkylated metabolite. The enzyme responsible for codeine's metabolism to morphine, CYP2D6, is highly polymorphic with poor, intermediate, and ultrarapid metabolizer phenotypes existing across the population. Codeine has been shown to be devoid of analgesic effects in poor metabolizers, indicating that morphine is predominantly responsible for the analgesic effects of codeine.

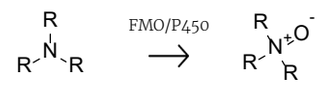
S-Oxidation

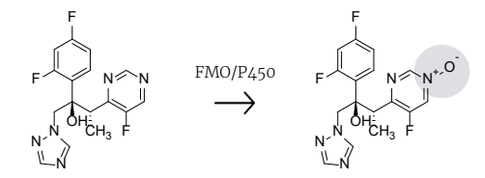




S-Oxidation: Albendazole
Albendazole, listed on the WHO's current List of Essential Medicines, is an oral, broad-spectrum anthelmintic drug used to treat a broad spectrum of parasitic infections. Albendazole is activated by P450 and FMO3-mediated sulfur oxidation to sulfoxide enantiomers which possess different pharmacological properties (most activity is attributable to the *R*-enantiomer). The active metabolite of albendazole, albendazole sulfoxide, acts by preferentially binding parasitic β-tubulin, preventing polymerization or assembly into microtubules.

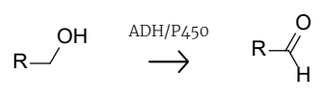
N-Oxidation

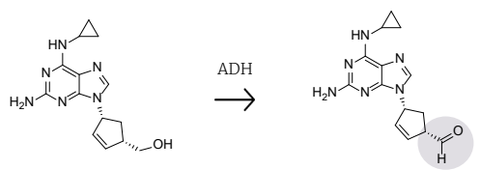




N-Oxidation: Voriconazole
Voriconazole is a triazole antifungal agent. It is commonly used to treat invasive aspergillosis, a common mold infection in immunocompromised patients. *N*-oxidation is a major metabolic route for voriconazole. P450s catalyze approximately 70% of voriconazole *N*-oxidation, while FMOs catalyze the remaining 30%. The *N*-oxide metabolite has minimal antifungal activity, while it has been demonstrated to potentiate phototoxicity, generate reactive oxidative species, and is considered a potential skin cancer-inducing substance. Polymorphisms in various P450s and FMOs can alter exposure to the N-oxide metabolite.

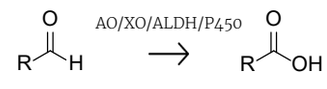
Alcohol Oxidation

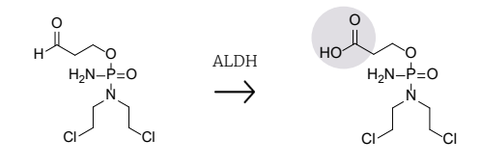




Alcohol Oxidation: Abacavir
Abacavir is a prodrug that is converted to the active metabolite carbovir triphosphate, an analog of dGTP. Abacavir is prescribed to treat the retrovirus HIV. It acts by inhibiting HIV reverse transcriptase and incorporating into viral DNA. Long-term exposure to abacavir is associated with an increased risk of myocardial infarction, which is thought to be caused by the intermediate aldehyde metabolite produced by ADH-mediated alcohol oxidation. The aldehyde metabolite is a great electrophile and allows for the adduction of the compound to proteins, a significant contributor to cell toxicity.

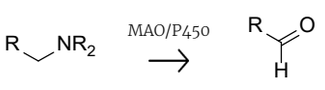
Aldehyde Oxidation





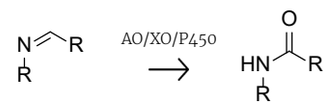
Aldehyde Oxidation: Cyclophosphamide
Cyclophosphamide is a chemotherapeutic and immunosuppressive drug that is activated by 4' hydroxylation. Ring-opening reveals the aldophosphamide, which can either decompose to reactive acrolein and phosphoramide mustard which can adduct to DNA, or the aldehyde can be oxidized by ALDH to produce the less reactive carboxyphosphamide. It is because of this detoxification pathway that high ALDH levels are cytoprotective. Induction or overexpression of ALDH in target cells is thought to be responsible for cyclophosphamide-specific acquired resistance exhibited by many cancerous cells.

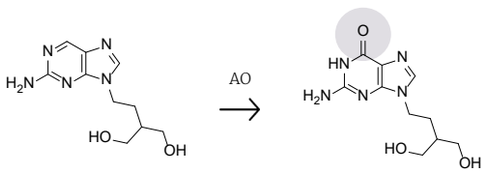
Amine Oxidation



Amine Oxidation: Tyramine
When individuals are on MAO inhibitors, they should not consume large amounts of tyramine. If tyramine is not oxidized to inactive p-Hydroxyphenylacetic acid by MAO, high levels of tyramine can build up and displace stored monoamine neurotransmitters in synaptic vesicles and cause a hypertensive crisis. Severe headaches have been associated with eating aged cheeses while on MAO inhibitors. Stinky-aged cheeses like blue cheese are often high in tyramine.

Imine Oxidation

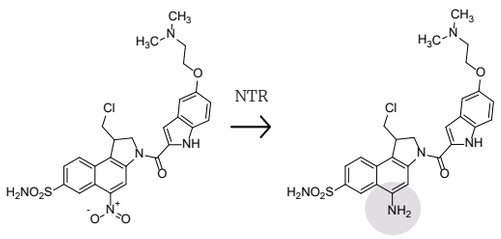




Imine Oxidation: Famciclovir
Famciclovir is a prodrug used to treat herpes virus infections. The prodrug is rapidly hydrolyzed to 6-deoxypenciclovir (shown in the graphic) and subsequently oxidized by AO to form penciclovir. Penciclovir is then phosphorylated to penciclovir triphosphate, which inhibits viral DNA polymerases in HSV-1-, HSV-2-, and VZV-infected cells.

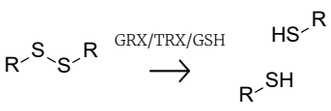
Reduction

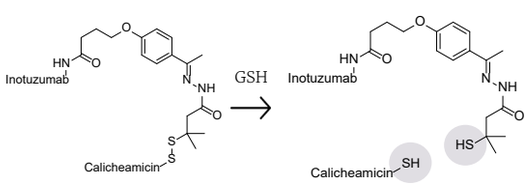
Nitro Reduction



Nitro Reduction: Nitrochloromethylbenzindoline (NitroCBI)
The only experimental drug in this graphic, nitroCBI, is a prodrug activated in hypoxic conditions to reveal a potent DNA minor groove alkylating agent. Since severe hypoxia is rarely found in normal tissues, hypoxia-activated prodrugs like nitroCBI are an interesting approach to target solid tumors selectively. The nitro group is reduced to an amine by an undetermined nitroreductase. The amine can donate an electron pair to resonate with the aromatic ring system, which allows the rearrangement of double bonds and the formation of the reactive cyclopropane through the elimination of chlorine. This reactive cyclopropane then acts as an electrophile to form adducts with DNA.

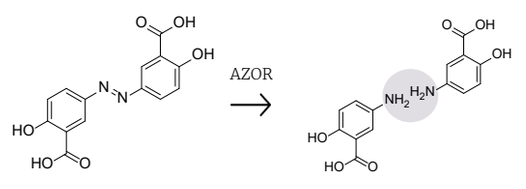
Disulfide Reduction





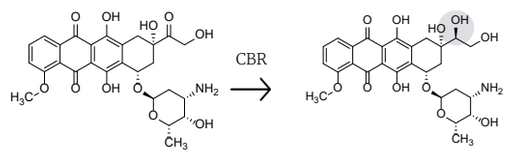
Disulfide Reduction: Inotuzumab ozogamicin
This drug is unique as the only example of biologics discussed here. Inotuzumab-ozogamicin is used to treat CD22+ B-cell lymphoma. The drug consists of a monoclonal antibody that targets the CD22 receptor on the surface of B cells. This antibody is conjugated to the cytotoxic antibiotic N-acetyl-gamma-calicheamicin dimethylhydrazide through acetyl butyrate linker via a disulfide linkage. To be pharmacologically active, the cytotoxic payload calcheamicin must be released from the antibody via the disulfide reduction. The reduction of the disulfide is thought to be carried out through chemical reduction by glutathione (GSH). This triggers a further intramolecular cyclization on calicheamicin to generate reactive radicals.

Azo Reduction



Azo Reduction: Olsalazine
Olsalazine is an anti-inflammatory drug taken to treat inflammatory bowel disease. It is a prodrug consisting of two diazo-linked molecules of the anti-inflammatory compound mesalazine. Olsalazine is bioactivated in the gut by bacterial azoreductases, which cleave and reduce the azo-bond linking the two mesalazine molecules. The active metabolite of olsalazine, free amine mesalazine, is thought to exert its anti-inflammatory activity by reducing prostaglandin synthesis in the colon through COX inhibition. Olsalazine is thus an interesting prodrug, which is activated by bacterial enzymes. It is minimally absorbed and acts locally along the colon.

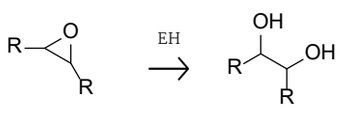
Carbonyl Reduction

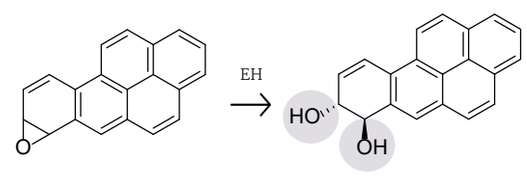


Carbonyl Reduction: Doxorubicin
Doxorubicin, an anthracycline anticancer drug, is known to cause irreversible cardiotoxicity. The 13-hydroxy anthracycline metabolite produced by carbonyl reductase is believed to induce congestive heart failure. CBR inhibitors might be used in combination with doxorubicin to decrease exposure to 13-hydroxy anthracycline and mitigate its deleterious effects on the heart.

Hydrolysis

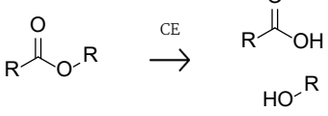
Epoxide Hydration

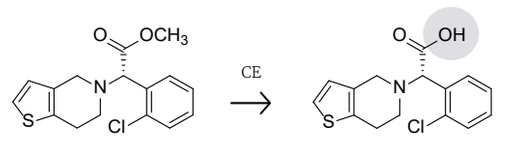




Epoxide Hydration: Benzo[a]pyrene
Benzo[a]pyrene is a polycyclic aromatic hydrocarbon that is an environmental toxin encountered in cigarette smoke. This compound is bioactivated by P450 mediated epoxidation followed by EH mediated hydrolysis to B[a]P-7,8-trans-dihydrodiol. A final P450 mediated epoxidation yields the reactive anti-B[a]P-7,8-diol-9,10-epoxide, a potent carcinogen.

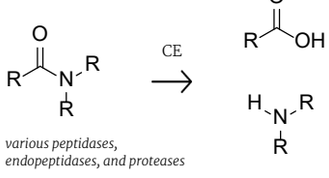
Ester Hydrolysis

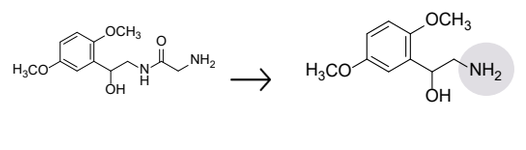




Ester Hydrolysis: Clopidogrel
Examples for ester hydrolysis often focus on prodrugs, designed with hydrolyzable esters, that are bioactivated upon ester hydrolysis, but ester hydrolysis can also lead to inactivation. Clopidogrel is a thienopyridine P2Y12 inhibitor taken to reduce the risk of myocardial infarction. Clopidogrel acts by forming a stable disulfide bond with P2Y12, a GPCR involved in platelet aggregation. Clopidogrel is a prodrug that undergoes a series of oxidation by P450s and produces a reactive thiol. The ester is required for activity. The bioactivation of clopidogrel is relatively inefficient and the major competitive reaction is CE-mediated ester hydrolysis resulting in an inactive carboxylic acid metabolite. Other iterations of thienopyridine platelet inhibitors are designed with a stable carbonyl group, instead of a hydrolyzable ester, to improve the stability and efficacy of this drug type.

Amide Hydrolysis





Amide Hydrolysis: Midodrine
Midodrine is a prodrug administered to treat postural orthostatic tachycardia syndrome (POTS). Patients with POTS suffer a severe drop in blood pressure when they stand because blood pools in their legs when vessels fail to constrict. The prodrug is hydrolyzed by peptidases, which cleave the amide bond linking the active compound desglycomidodrine to glycine. The released desglycomidodrine activates peripheral alpha1-adrenergic receptors, which leads to an increase in vascular tone and an elevation of blood pressure.

Abbreviations:

P450 cytochrome P450
FMO flavin-containing monooxygenase
ADH alcohol dehydrogenase
AO aldehyde oxidase
XO xanthine oxidase
ALDH aldehyde dehydrogenase
MAO monoamine oxidase
NTR nitroreductase *(Not a specific family of enzymes, overhead term for enzymes that can reduce nitro moieties.)*
GRX glutaredoxin
TRX thioredoxin
GSH glutathione *(Not an enzyme, the endogenous metabolite glutathione can chemically reduce disulfide bonds.)*
AZOR azoreductase *(Not a specific family of enzymes, overhead term for enzymes that can reduce azo moieties.)*
CBR carbonyl reductase
EH epoxide hydrolase
CE carboxylesterase

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