

### Phase 1: Functionalization reactions

Oxidative pathways	Reduction	Hydrolytic reactions
<b>1. Alcohols &amp; Aldehydes</b>	<b>1. Aldehydes</b>	<b>1. Esters</b>
Ex: pyridoxine becoming pyridoxal	Become alcohols from H addition.	Ex: Cocaine, Aspirin, Mepiridine, Procaine
Aliphatic hydroxylation: addition of OH.	<b>2. Azo-reduction</b>	The ester (COO) gp becomes an acid.
<b>2. Oxidative N-demethylation</b>	Ex: Sulfasalazine--> Sulfapyridine	<b>2. Amides</b>
Ex: Methamphetamine, Lidocaine, Epinephrine	<b>3. Nitroreduction</b>	Ex: Procainamide
N with a CH <sub>3</sub> (or other) get replaced by =O	Ex: Nitrazepam, Chloramphenicol	<b>3. Glycosides</b>
<b>3. Oxidative deamination</b>	NO <sub>2</sub> becomes NH <sub>2</sub> .	Ex: Digoxin --> Digoxin aglycone
Ex: Norepinephrine, Histamine, Mescaline	<b>4. Dehalogenation</b>	<b>4. Epoxides</b>
Removal of NH <sub>2</sub> and its release as ammonia gas. Gets replaced by =O.	Ex: Halothane, Ethchlorvynol	Ex: DES metabolite--> DES
<b>4. Oxidative O-dealkylation</b>		
Ex: Phenacetin, Codeine, Mescaline, Papaverine		
O-alkyl becomes -OH.		
<b>5. N-Oxidation</b>		
Ex: Imipramine.		
Coordinate bond between tert-N and O.		
<b>6. S-Oxidation</b>		
Ex: Chlorpromazine; S-O (sulfoxide) then becomes (S=O) Sulfone.		
<b>7. Desulfuration</b>		
Ex: Thiobarbital, Parathion		
=S is replaced by =O		
<b>8. Epoxidation</b>		
Ex: DES; O in a strained tricyclic structure.		

### Phase 1: Functionalisation cont.

Decarboxylation	Oxidative pathways catalysed by other oxidoreductases	Reductive pathways by oxidoreductases
Ex: Histidine, a-methyl dopa, L-Dopa.	<b>Alcohol dehydrogenases</b>	Less significant
Removal of carboxylic acid.	1ry alcohol (benzylalcohol, phenethanol, retinol)--> Aldehydes	Include reactions on:
Histidine--> Histamine; L-Dopa--> dopamine.	2ry alcohols--> Ketones	1) C=O compounds 2) Olefins 3) Dehalogenation 4) other atoms
	3ry alcohols do not react.	Hydrolytic pathways
	<b>Aldehyde dehydrogenases</b>	include hydrolyses enzymes



### Phase 1: Functionalisation cont. (cont)

Aldehydes--> Acid They add a water to functional groups.

#### Monoamine oxidase (MAO)

Has 2 forms/isozymes A & B, that deaminate catecholamines.

Treats Parkinson's (esp MAO B).

### Phase 2: conjugation reaction

#### Methylation

A methyl group on carrier (SAM) adds the methyl to O/N/S on the drug or phase 1 metabolite.

O-methylation by COMT.

N-methylation by N-methyltransferase.

S-methylation by thiol or thiopurine methyltransferases.

Thiol containing drugs (captopril, mercaptopurine, propylthiouracil) are subjected to S-methylation.

Captopril is unique in that phase 2 S-methylation occurs first, then phase 1.

#### Acetylation & Acylation

Acyl-coenzyme A is required

Ex: Sulfamethoxazole where COCH<sub>3</sub> gp is added.

Some people are fast or slow acetylators and thus drug dose metabolized here should be adjusted.

#### Amino acid conjugation reactions

Glycine is used to conjugate COOH gp in xenobiotics.

Carrier is glycine N-acyltransferase.

### Phase 2: conjugation reaction cont.

#### Glucuronidation

Conjugation with glucuronic acid with carrier UDPG.

The enzyme, UDP-glucuronosyl transferase, acts on O, N, S in the compound.

#### Sulfate conjugation

A sulfate molecule is transferred from carrier, PAPS, to the substrate/drug by enzyme cytosolic sulfotransferases.

#### Glutathione (GSH) conjugation

In its reduced form, its the tripeptide GSH. But it becomes in the oxidized form GS-SG and the SG attaches to drug

#### Miscellaneous conjugation reactions

1) Phosphorylation via phosphotransferase

Ex: Zidovudine.

2) Endogenous carbonyl + Exogenous drug with hydrazines or hydrazides--> Hydrazones.

