Phae 1: Functionalization reactions

Oxidative pathways	Reduction	Hydrolytic reactions
1. Alcohols & Aldehydes	**1. Aldehydes**	**1. Esters**
Ex: pyridoxine becoming pyridoxal	Become alcohols from H addition.	Ex: Cocaine, Aspirin, Mepiridine, Procaine
Aliphatic hydroxylation: addition of OH.	**2. Azo-reduction**	The ester (COO) gp becomes an acid.
2. Oxidative N-demethylation	Ex: Sulfasalazine--> Sulfapyridine	**2. Amides**
Ex: Methamphetamine, Lidocaine, Epinephrine	**3. Nitroreduction**	Ex: Procainamide
N with a CH3 (or other) get replaced by =O	Ex: Nitrazepam, Chloramphenicol	**3. Glycosides**
3. Oxidative deamination	NO2 becomes NH2.	Ex: Digoxin --> Digoxin aglycone
Ex: Norepinephrine, Histamine, Mescaline	**4. Dehalogenation**	**4. Epoxides**
Removal of NH2 and its release as ammonia gas. Gets replaced by =O.	Ex: Halothane, Ethchlovynol	Ex: DES metabolite--> DES
4. Oxidative O-dealkylation		
Ex: Phenacetin, Codeine, Mescaline, Papaverine		
O-alkyl becomes -OH.		
5. N-Oxidation		
Ex: Imipramine.		
Coordinate bond between tert-N and O.		
6. S-Oxidation		
Ex: Chlorpromazine; S-O (sulfoxide) then becomes (S=O) Sulfone.		
7. Desulfuration		
Ex: Thiobarbital, Parathion		
=S is replaced by =O		
8. Epoxidation		
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-methyldopa, L-Dopa.	**Alcohol dehydrogenases**	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
	Aldehyde dehydrogenases	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	Acetylation & Acylation	Amino acid conjugation reactions
A methyl group on carrier (SAM) adds the methyl to O/N/S on the drug or phase 1 metabolite.	Acyl-coenzyme A is required	Glycine is used to conjugate COOH gp in xenobiotics.
O-methylation by COMT.	Ex: Sulfamethoxazole where COCH3 gp is added.	Carrier is glycine N-acyltransferase.
N-methylation by N-methyltransferase.	Some people are fast or slow acetylators and thus drug dose metabolized here should be adjusted.	

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.

Phase 2: conjugation reaction cont.

Glucuronidation	Sulfate conjugation	Glutathione (GSH) conjugation	Miscellaneous conjugation reactions
Conjugation with glucuronic acid with carrier UDPG.	A sulfate molecule is transferred from carrier, PAPS, to the substrate/drug by enzyme cytosolic sulfotransferases.	In its reduced form, its the tripeptide GSH. But it becomes in the oxidized form GS-SG and the SG attachs to drug	1) Phosphorylation via phosph-otransferase
The enzyme, UDP-gluco-uronosyl transferase, acts on O, N, S in the compound.			Ex: Zidovudine.
			2) Endogenous carbonyl + Exogenous drug with hydrazines or hydrazides---> Hydrazones.