

Phase 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 CH ₃ (or other) get replaced by =O	Ex: Nitrazepam, Chloramphenicol	3. Glycosides
3. Oxidative deamination	NO ₂ becomes NH ₂ .	Ex: Digoxin --> Digoxin aglycone
Ex: Norepinephrine, Histamine, Mescaline	4. Dehalogenation	4. Epoxides
Removal of NH ₂ and its release as ammonia gas. Gets replaced by =O.	Ex: Halothane, Ethchlorvynol	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-methyl dopa, 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

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 COCH₃ 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.

