

Drug Metabolism

Prof. Patrick Davis
Basic Medicinal Chemical Principles
PHR 143M Fall-08

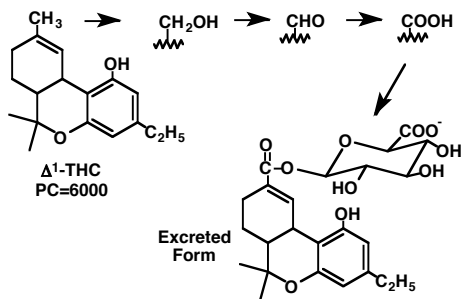
Importance of Drug Metabolism

- *The basic premise:*

Lipophilic Drugs --> Hydrophilic Metabolites
(Not Excreted) (Excreted)

- Water soluble => increased renal excretion
-and-
decreased tubular re-absorption of lipophilics.

Importance of Drug Metabolism

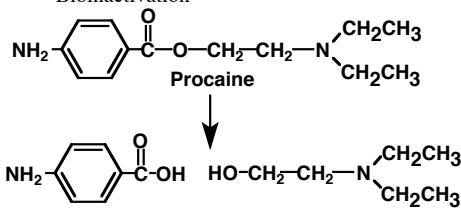


Importance of Drug Metabolism

- Metabolism => Termination of Drug Action
 - Bioinactivation -and/or-
 - Detoxification -and/or-
 - Elimination -and/or-

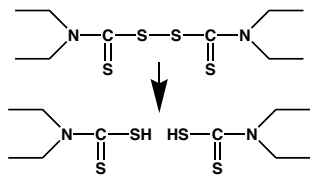
Importance of Drug Metabolism

- Metabolism => Termination of Drug Action
 - Bioinactivation



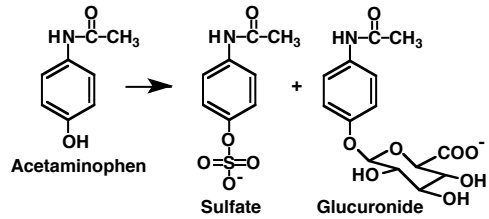
Importance of Drug Metabolism

- Metabolism => Termination of Drug Action
 - Detoxification
 - Disulfiram (Atabuse®)



Importance of Drug Metabolism

- Metabolism => Termination of Drug Action
 - Elimination (water soluble).



Importance of Drug Metabolism

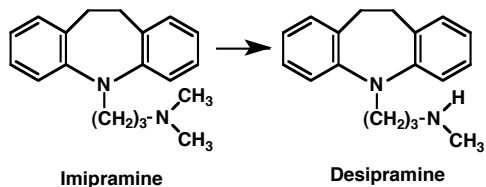
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Importance of Drug Metabolism

- Metabolism => Bioactivation
 - Active Metabolites
 - Prodrugs
 - Toxication

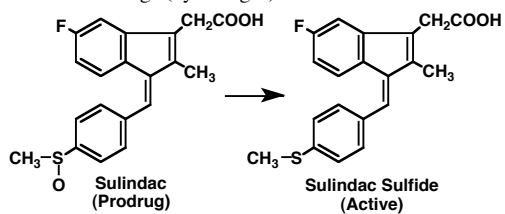
Importance of Drug Metabolism

- Metabolism => Bioactivation
 - Active Metabolites (Surprise! :)



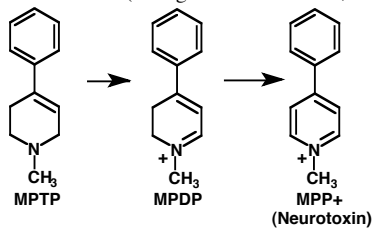
Importance of Drug Metabolism

- Metabolism => Bioactivation
 - Prodrugs (by Design!)



Importance of Drug Metabolism

- Metabolism => Bioactivation
 - Toxicification ("toxigenic" metabolism; Oops!)

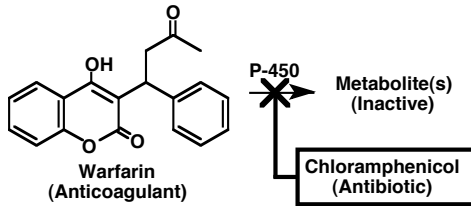


Importance of Drug Metabolism

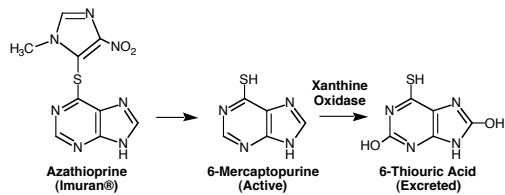
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 - Prodrugs
 - Toxicification

Importance of Drug Metabolism

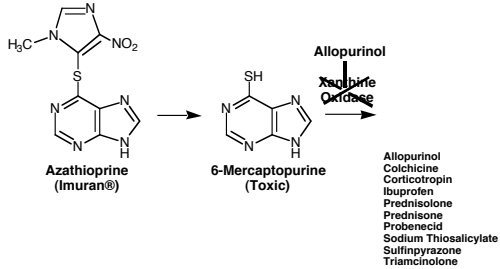
- Metabolism => Drug Interactions



Is This Just Hype?

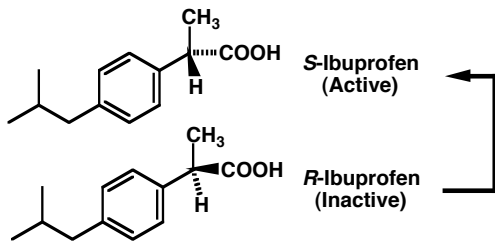


How Real Is This?



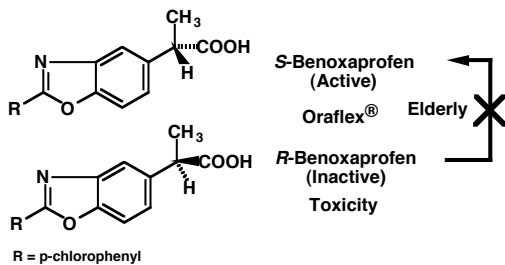
Importance of Drug Metabolism

- Stereochemical Implications of Metabolism



Importance of Drug Metabolism

- Stereochemical Implications of Metabolism



Importance of Drug Metabolism

- Control of Metabolism Through Drug Design
If you can predict metabolic pathways =>
 - Avoid toxigenic pathways.
 - cytotoxicity, carcinogenicity, mutagenicity
 - risk assessment (drug development)
 - acute vs long-term therapy
 - Speed up metabolism?? Why??
 - Slow down metabolism?? Why??

Importance of Drug Metabolism Review

- Termination of Drug Action
- Bioactivation
- Drug Interactions
- Stereochemical Implications
- Control of Metabolism
- Absolutely Required by FDA
 - Clearly affects 'efficacy'
 - Clearly affects 'toxicity'

Importance of Drug Metabolism Understanding It

- Practice problems: Foye's "Med. Chem."
 - Liver Game (class exercise).
 - Online Practice Quizzes.* [Do Pre-Test Now]
 - Previous Exams (view as practice problems).*
 - Flash Metabolism Tutorials*
 - Blackboard Discussion Board; Office Hours; eOffice Hours*
 - Concept Map Lab
- *[<http://courses.utexas.edu> or UTDirect]

Drug Metabolism References

- Foye's "Principles of Medicinal Chemistry", 6th Edition (2007), Chapter 10 (Drug Metabolism) [your required text].
- Goodman & Gilman "Pharmacological Basis of Therapeutics, 11th Edition (2005), Chap 3 (Drug Metabolism) [your required text].
- Online references [Blackboard website]
- PRACTICE DRAWING PATHWAYS!

Phase-1 vs. Phase-2 Metabolism

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Phase-1 Metabolism Description

- Phase 1 = "Functionalization" Reactions
 - New polar functional groups.
 - Interchange existing functional groups
 - Unmask existing polar groups.

Phase-1 Metabolism Description

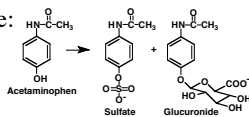
- Reactions include:
 - Oxidations (hydroxylations) = “new”
 $RH \rightarrow ROH$
 - Reductions = “interconversion”
 $C=O \rightarrow CH-OH$
 - Hydrolyses = “unmasking”
 $R-CO_2CH_3 \rightarrow RCOOH + CH_3OH$

Phase-1 Metabolism Description

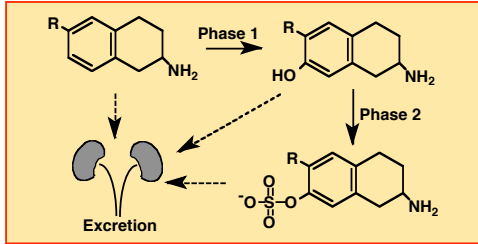
- Purpose:
 - enhance excretion
 $RH \rightarrow ROH$ (more water soluble)
 - prepare for phase 2
 $RH \rightarrow ROH$ (functional handle)

Phase-2 Metabolism Description

- Phase 2 = "Conjugation" Reactions
 - Acts on parent drug or
 - Acts on phase 1 metabolite.
- Links to endogenous, polar, ionizable cpd.
- Purpose: enhance excretion.
- Reaction types include:
 - Glucuronidation
 - Sulfate formation

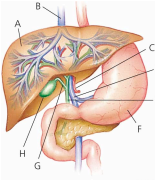


Phase-1 & Phase-2 Complimentary NOT Mutually Exclusive

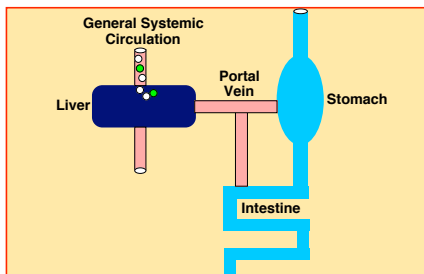


Principle Sites of Drug Metabolism

- Liver
 - Major xenobiotic metabolism
"nonessential exogenous (foreign) compounds"
 - Major endobiotic metabolism
"endogenous compounds"
 - The Presystemic "First pass effect"



Principle Sites of Drug Metabolism

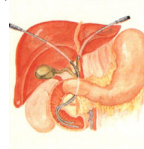


Presystemic “First Pass Effect”

- Source:
 - Hepatic first pass metabolism.
 - Metabolism by GI mucosa during absorption.
- Significance?
 - “regular” drugs
 - “prodrugs”
 - See Foye’s Table 8.13
- How Overcome?

Principle Sites of Drug Metabolism

- GI Tract
 - Epithelium very rich in drug-metabolizing enzymes; phase-1 and phase-2 (significant contribution oral bioavail)
 - Gut flora
 - Reduction (e.g. azulfidine)
 - deconjugation (e.g. premarin)
 - enterohepatic recycling (EHC)
 - Endobiotic = bile salt recycling
 - Xenobiotic = conjugates >500 MW excreted by p-glycoprotein and MDR-2 transport systems into bile.



Principle Sites of Drug Metabolism

- Liver
- GI Tract
- Kidneys, Lungs, Brain, etc
 - localized bioactivation (e.g. PAH’s in cigarette smoke)
 - localized toxicity (e.g. MPTP)

Phase-1 vs. Phase-2 Metabolism

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