ADMET=Absorption, Distribution, Metabolism, Excretion and Toxicity

-ADMET is a part of _____

*Pharmacokinetics = journey of drug from _____

-pharmacokinetics is part of _____

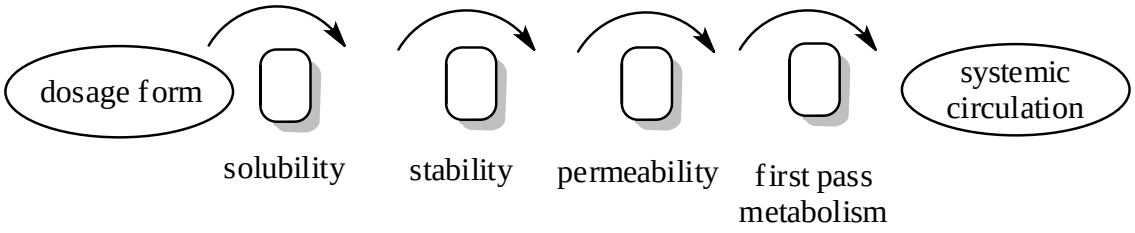
-in practice, pharmacologists are more on the _____ of drug development

- pharmacodynamics (PD) = _____

One of the most important hurdles in the drug development process is_____

_____.

VP of research at BMS recently related the company's perspective on drug delivery as follows)



_____ are recognized for a drug to get to into a person's body and to the target

Why compounds fail in drug development?

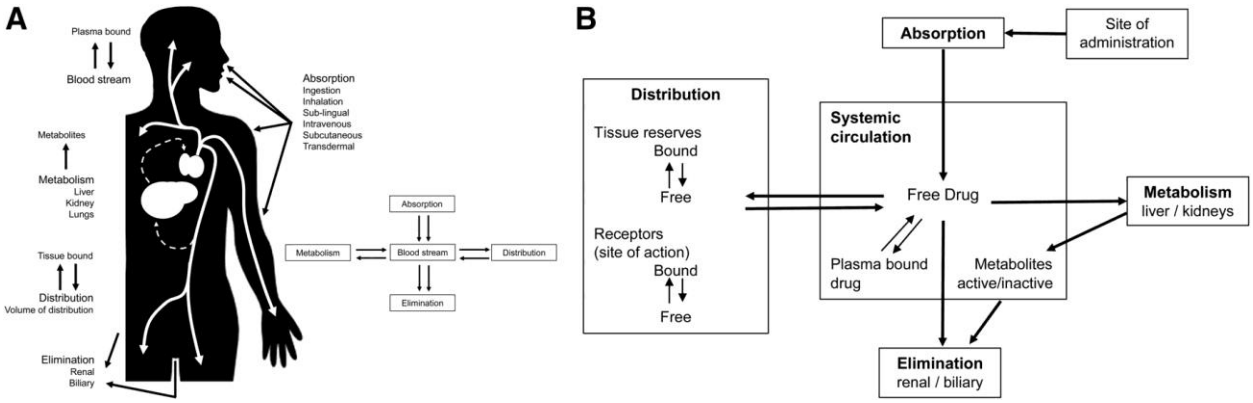
1. _____ properties (_____)…41%

2. lack of _____…31%

3. _____…22%

4. _____ (_____)…6%

*Modern Drug Discovery, Feb. 1999, p. 55



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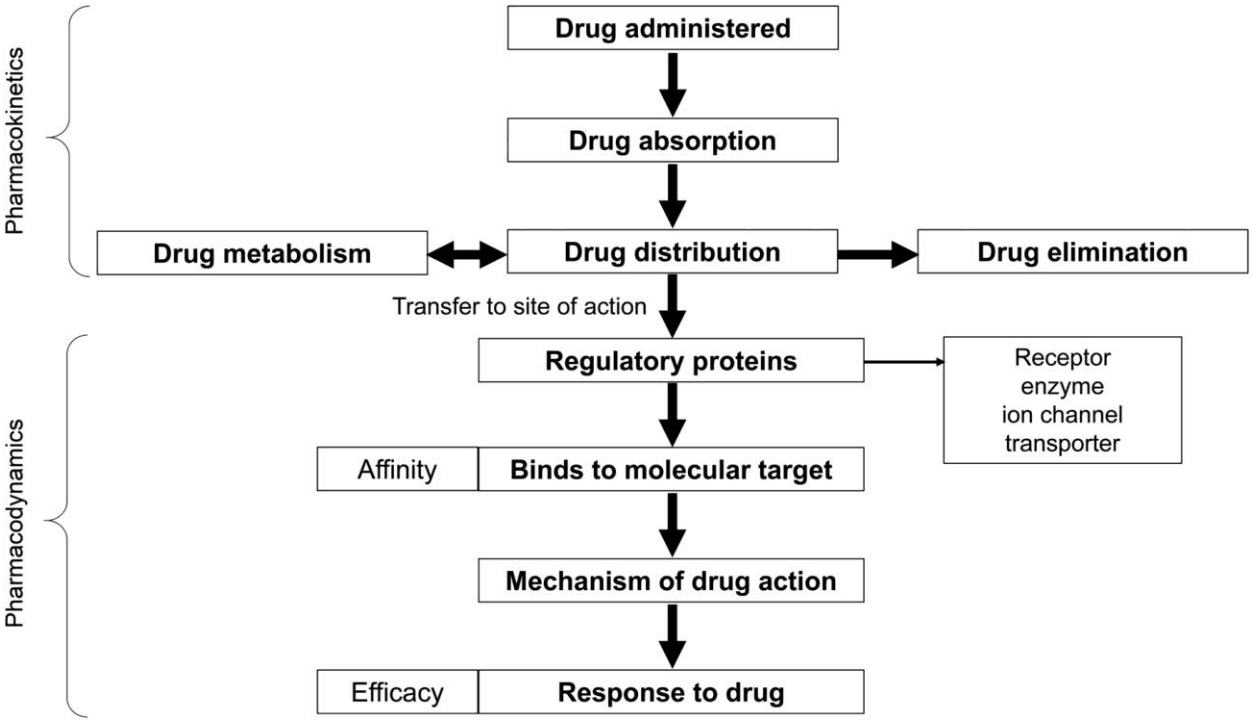

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PK

-_____→ _____ → _____

A. Drug _____

-two basic categories

1. **_____** (_____=administration through _____),

Latin abbreviation: p.o. (_____)

-leads to _____ drug administration

two modes of GI absorption:

a) **_____**=passes through cell membrane to equalize a _____

_____

b) **_____**=molecules carried against a _____

-a _____ assists in transporting the drug across the _____

_____. In addition, _____ is expended by the cell to perform the transport.

2. non-oral (_____=not through the intestines)

-several variations

a) **_____** – good, quick, efficient, common

b) **_____** – lumbar puncture to administer to the central nervous system.

-necessary for drugs that do not penetrate the _____

c) **_____** – less reliable than i.v. in terms of bioavailability, rate of absorption, and local effects

-useful in _____ medicines

d) **_____** - suffers from similar problems as intramuscular injections (but rate of absorption more easily regulated)

-e.g. insulin, rate of absorption regulated by using preparations of different solubility (amorphous or crystalline Zn complexes)

e) <u>miscellaneous</u>

-sublingual (_____)→ _____ tablets for angina pectoris attacks

-intra_____→ decongestants

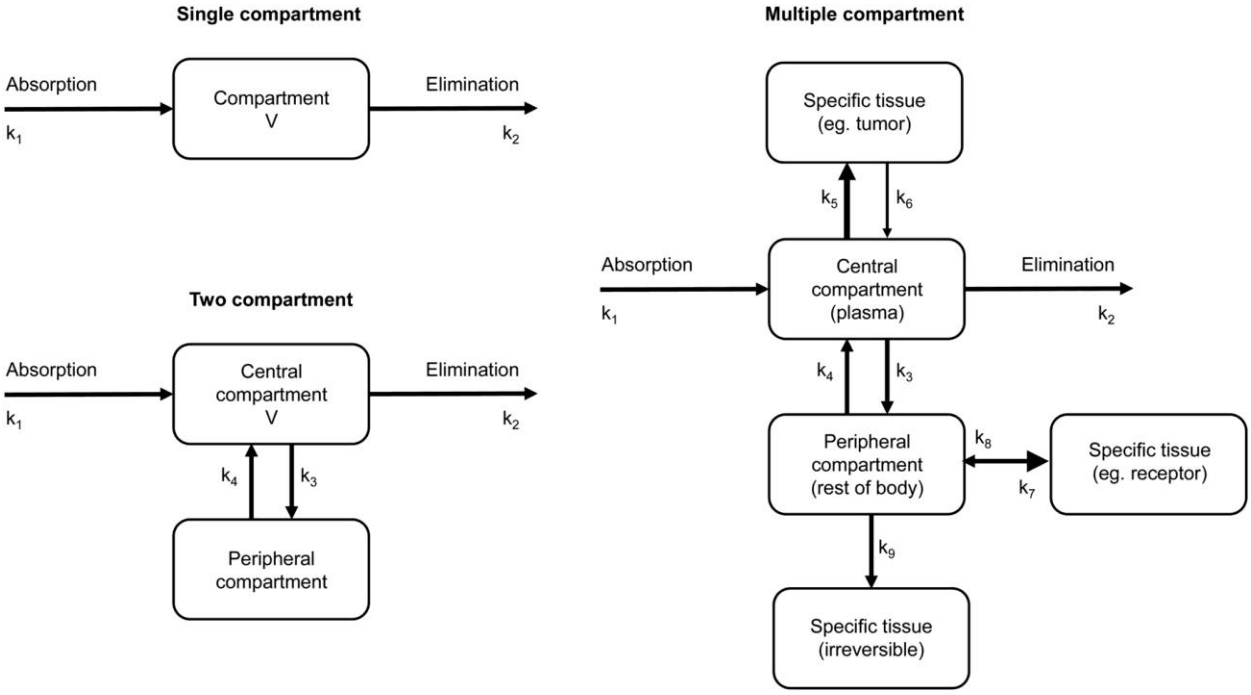
-_____→ skin cancer anti-neoplastics, _____

-_____→ eye drops to decrease pressure caused by _____

-_____→ used where oral administration is difficult (_____

_____); reasonable absorption, but less than small intestines.

Distribution



from: Pharmacology, Part 2: Introduction to Pharmacokinetics, Geoffrey M. Currie, Journal of Nuclear Medicine Technology September 2018, 46 (3) 221-230.

B. Drug _____

*very important consideration in drug action

Basic tenet: _____

_____.

Two basic modes of drug metabolism:

1. Phase I=_____; i.e. polar functional groups are introduced or revealed by oxidation (most common), reduction or hydrolysis.

2. Phase II=_____; i.e. drug or drug metabolite (from Phase I) is _____ glucuronic acid, sulfate, glutathione, acetate, methyl, or an amino acid (Gly, Gln) to become even more polar or eliminate the molecule's bioactivity.

Details…

1. Phase I reactions

a) _____ reactions

*by far the most important path for drug metabolism!

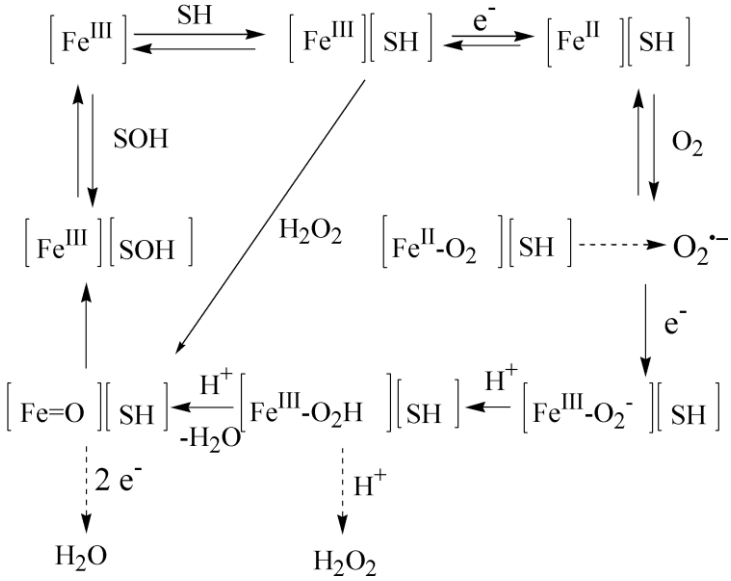
*_____ is a superfamily of enzymes that catalyze these rxns.

-450 for the visible spectrum absorption of the heme present in CYP's when exposed to C=O

-as a superfamily there are many different CYP _____:

-most important for drug metabolism: CYP_____, ~46%; CYP_____, ~16%; CYP_____, ~12%; CYP_____ ~12%; and CYP_____, ~10%. These five account for _____. (W. W. Jonson, Drug Metabolism Reviews 2008, 40, 101-147.)

-CYP mechanism: (from Montellano review in *Nat. Prod. Rep.* **2002**, *19*, 477-493 *excellent review for info on CYP's!)



-CYP rxns. _____; therefore functional groups

that easily form _____ will be most susceptible to oxidation.

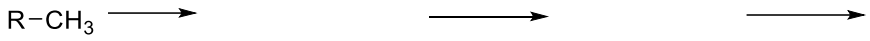
-O_2 and NADH used by CYP's to oxidize molecules

-CYP's found in _____ microsomes

*flavin-containing monooxygenases catalyze many related rxns.

Rxns. catalyzed by CYP's

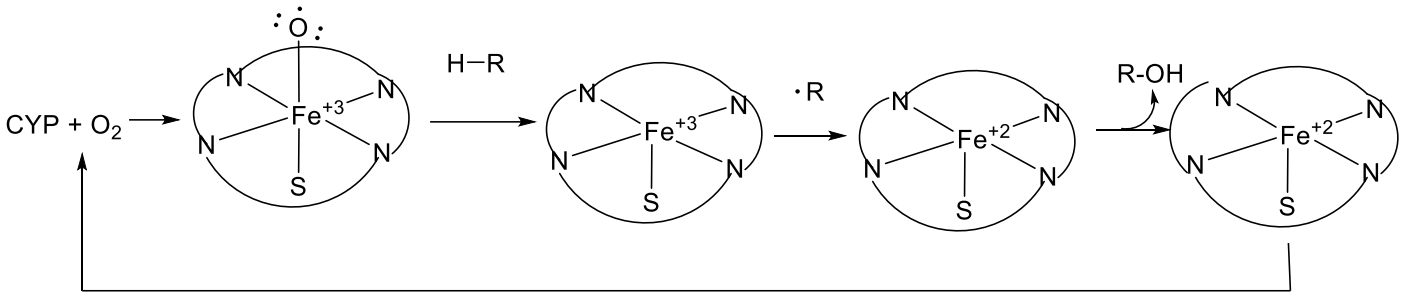
(i) alkane/alcohol/aldehyde oxidation



(1) Mechanism of alkane (R-H) oxidation reaction

{-mechanism: (Bruice 7th ed. 13.11)]

recent authoritative review: "Mechanisms of Cytochrome P450-Catalyzed Oxidations" F. Peter Guengerich, *ACS Catal.* **2018**, *8*, 12, 10964–10976. https://pubs.acs.org/doi/10.1021/acscatal.8b03401

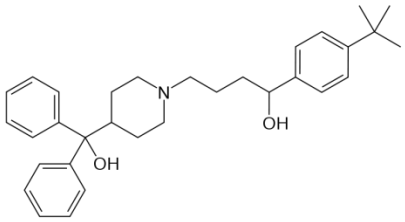


-this process is called the "_____" mechanism (J. T. Groves, P. R. Ortiz de Montellano et al. *JACS* 2002, *124*, 6020.)

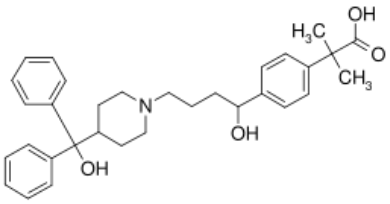
-sites that can form stable _____, i.e.

_____, although sterics

become a consideration as well and _____ are often less accessible.

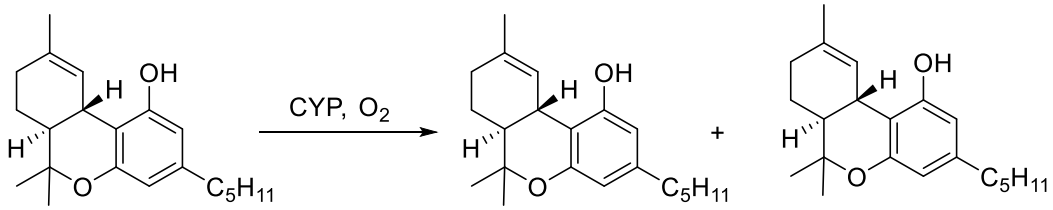


terfenadine (Seldane)

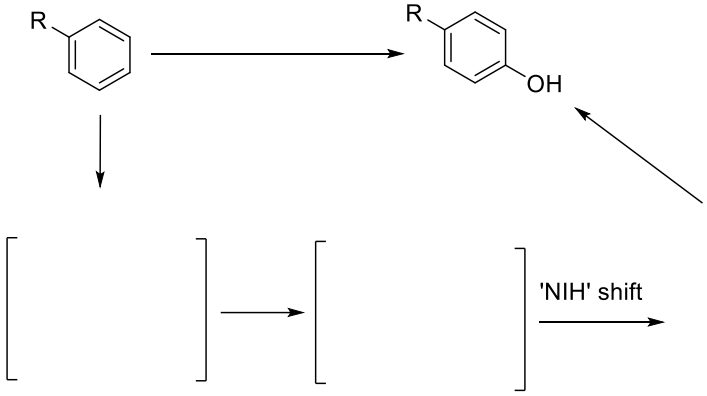


fexofenadine (Allegra)

Example: *tetrahydrocannabinol (THC)*, active ingredient in marijuana



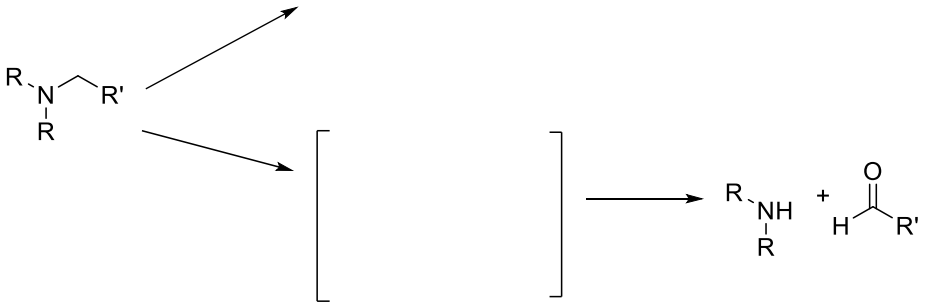
(ii) _____ oxidation



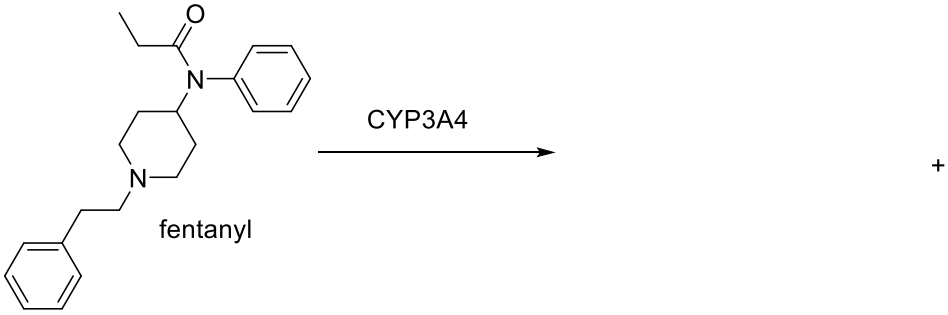
-note: this path can result in aromatic _____

-isolated alkenes are oxidized to _____ that are subsequently hydrolyzed to _____

(iii) _____



*Fentanyl's predominant metabolic pathway is _____



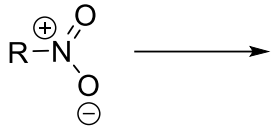
(iv) O-dealkylation/S-dealkylation

b) _____ reactions

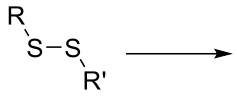
-since enzyme catalysis is reversible, some of these rxns. are also catalyzed by _____

-_____ used as co-factor

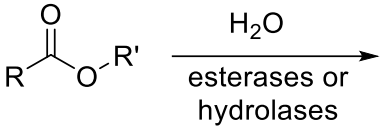
(i) nitro groups → _____

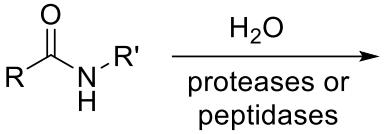


(ii) disulfide groups → _____



c) _____ reactions



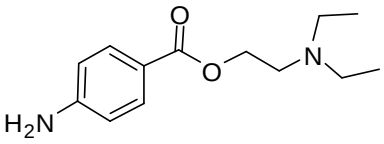


-amides are _____ to hydrolysis. Why? _____

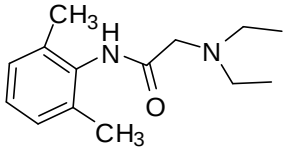
_____

-*example of refinement of drug activity to control bioavailability:

_____ (local anesthetic, a.k.a. Novocaine) is easily metabolized through hydrolysis and therefore deactivated.

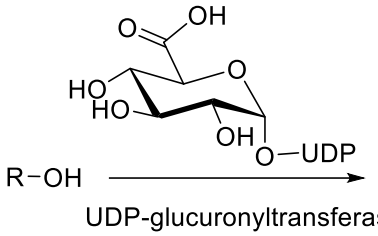


_____ (local anesthetic)-longer acting analogue:



2. Phase II reactions

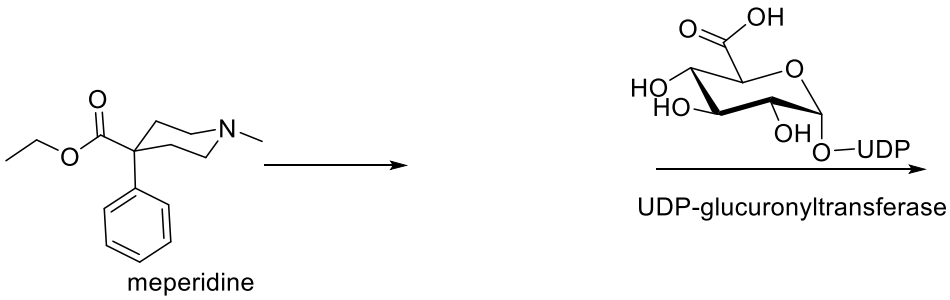
a) _____ formation



-UDP=uridine 5'-diphospho- (uridine=pyrimidine w/C-2 and C-4 carbonyl; see wiki)

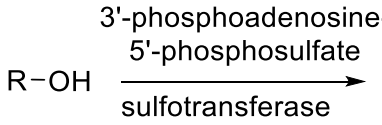
-can also form with _____

drug e.g.: Demerol or meperidine, a fast-acting opioid analgesic (related to morphine)



glucuronyl conjugate
of meperidine

b) Sulfate formation

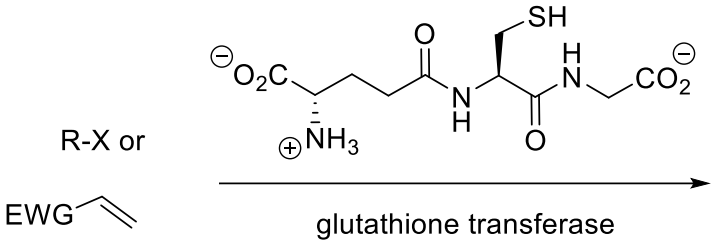


-amines also react to make _____

c) _____ conjugation

-glutathione= _____

-What's the most nucleophilic functionality at physiological pH?



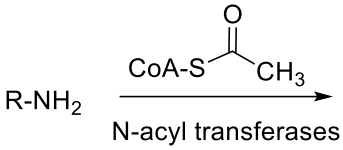
e.g. morphine after oxidation by morphine 6-dehydrogenase and then conjugate add'n of G-SH

-only part of morphine's structure is shown

d) _____

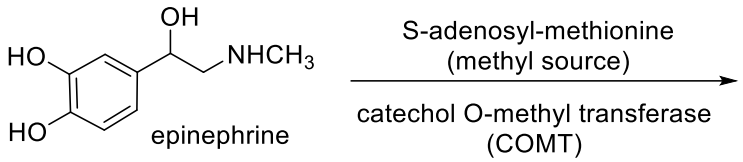
-does not make molecule more _____

-process causes _____ of bioactive amines



e) _____

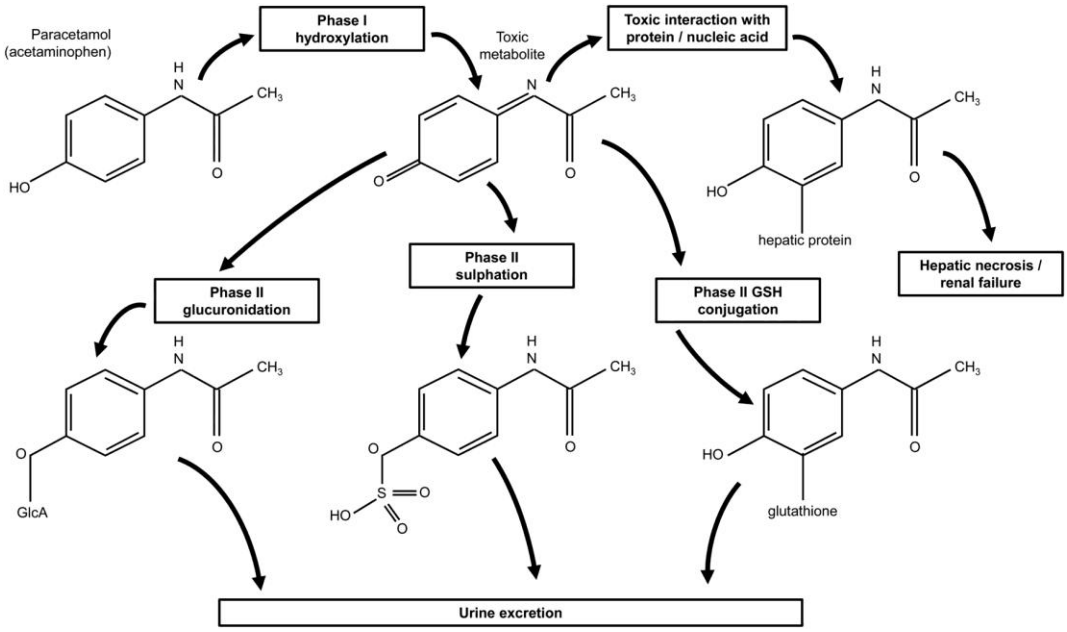
-like acetylation, methylation _____



f) _____ conjugation

3. Example of Drug Metabolism

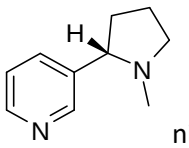
a) acetaminophen/paracetamol



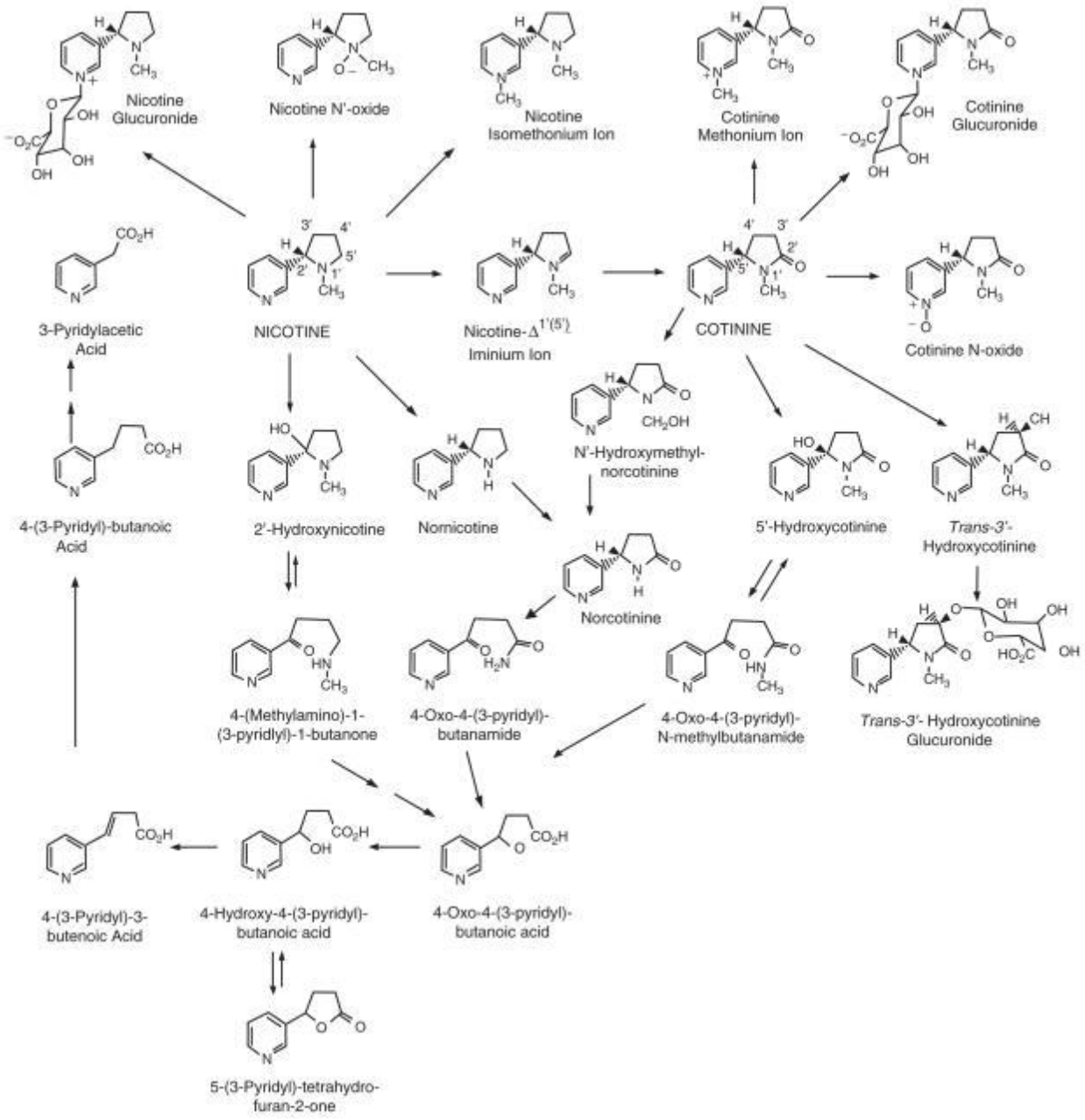
from: Pharmacology, Part 2: Introduction to Pharmacokinetics, Geoffrey M. Currie, Journal of Nuclear Medicine Technology September 2018, 46 (3) 221-230.

*Ethanol toxicity-alcohol induces CYP's which can oxidize acetaminophen making a strong Michael acceptor.

b) nicotine



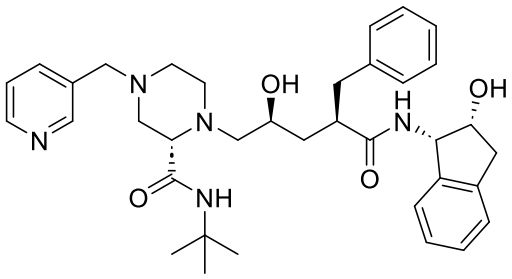
nicotine



[Nicotine Chemistry, Metabolism, Kinetics and Biomarkers - PMC]

c) indinavir (Crixivan) metabolism:

-see PS #4 for metabolism results



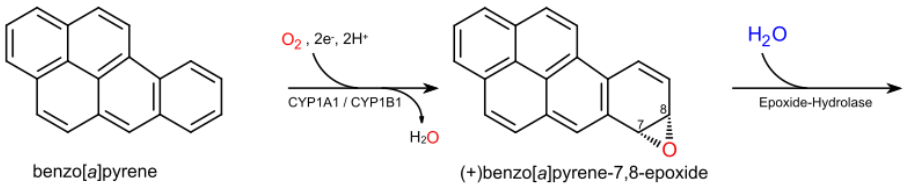
4. Important Perspective Comment:

-unlike for drug distribution, drug metabolism is extremely different in going from mouse to dog to human. Consequently, you can't extrapolate from mouse, dog studies easily. Although you can predict the types of metabolites, you can't predict the amounts!

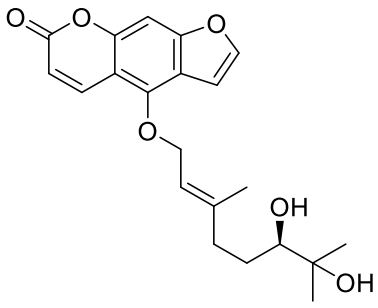
5. _____ resulting from metabolism

a) Benzapyrene toxicity: _____of arene system and DNA alkylation

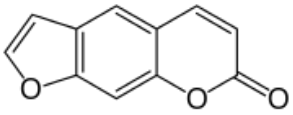
-Benzo[a]pyrene is found in coal tar, in automobile exhaust fumes (especially from diesel engines), in all smoke resulting from the combustion of organic material, and in charbroiled food. Metabolism of benzapyrene which results in toxicity (from wiki):



b) Grapefruit effect- drinking grapefruit juice _____ of many drugs as some component of grapefruit juice inhibits CYP's. This can have an effect on drug activity.

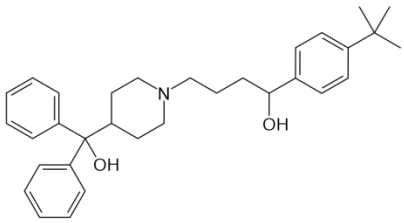


(6',7'-dihydroxybergamottin; dimerized it is paradisin A)

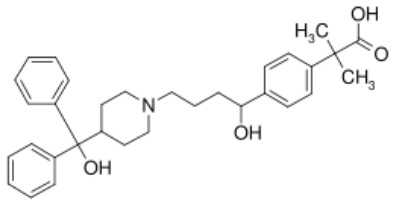


(psoralen; core structure)

- Dangerous grapefruit effects: Seldane showed _____!



terfenadine (Seldane)



fexofenadine (Allegra)

c) _____ (promotes CYP activity!) and, consequently, decreases the effectiveness of _____

d) _____ inhibits CYP3A4 and can therefore influence plasma levels of other HIV PI's, for example _____.