20.201 Mechanisms of Drug Action

Lecture #1 9/7/05

Instructors

Prof. Peter Dedon

Prof. Steven Tannenbaum

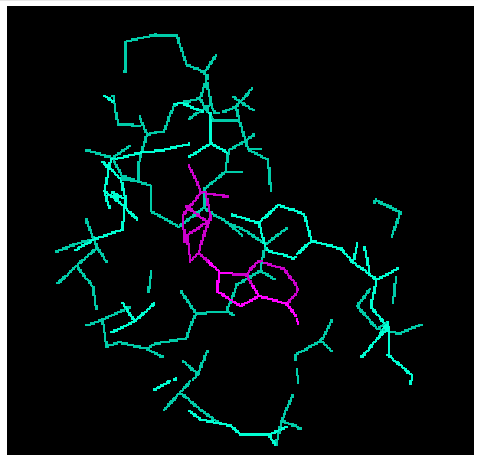
Monday and Wednesday 1:30-3:00 pm

Recitations on Friday 1:30-2:30 pm

Course Objectives

- Develop an understanding of the scientific basis for drug development and drug mechanisms
- Develop an appreciation for the role of pharmacokinetics, drug metabolism and drug interactions in the mechanisms of action of drugs
- Understand the balance between pharmacogenetics, toxicity and therapeutic outcome associated with any drug

What is the "mechanism of action of a drug?"



- Popular misconception: the mechanism of action of a drug is its interaction with a specific receptor
- This is termed, "pharmacodynamics"
- A drug, by definition, is a chemical agent that is both safe and efficacious in the treatment of a human disease
- If a chemical agent never reaches its receptor target, then it is not a drug and it has no "mechanism of action"

The mechanism of action of a drug involves every aspect of its fate

- The less appreciated facet of a drug's mechanism of action is its "pharmacokinetics"
- "Pharmacokinetics" and "pharmacodynamics" are the two foundations of a drug's mechanism of action
- Pharmacokinetics, in its broadest definition, involves:
  - **A** ~ Uptake = absorption
  - **D** ~ Distribution
  - **M** ~ Metabolism
  - **E** ~ Elimination
  - **T** ~ Toxicology (politically correct: "Drug Safety")

Topics Covered

First half of term:

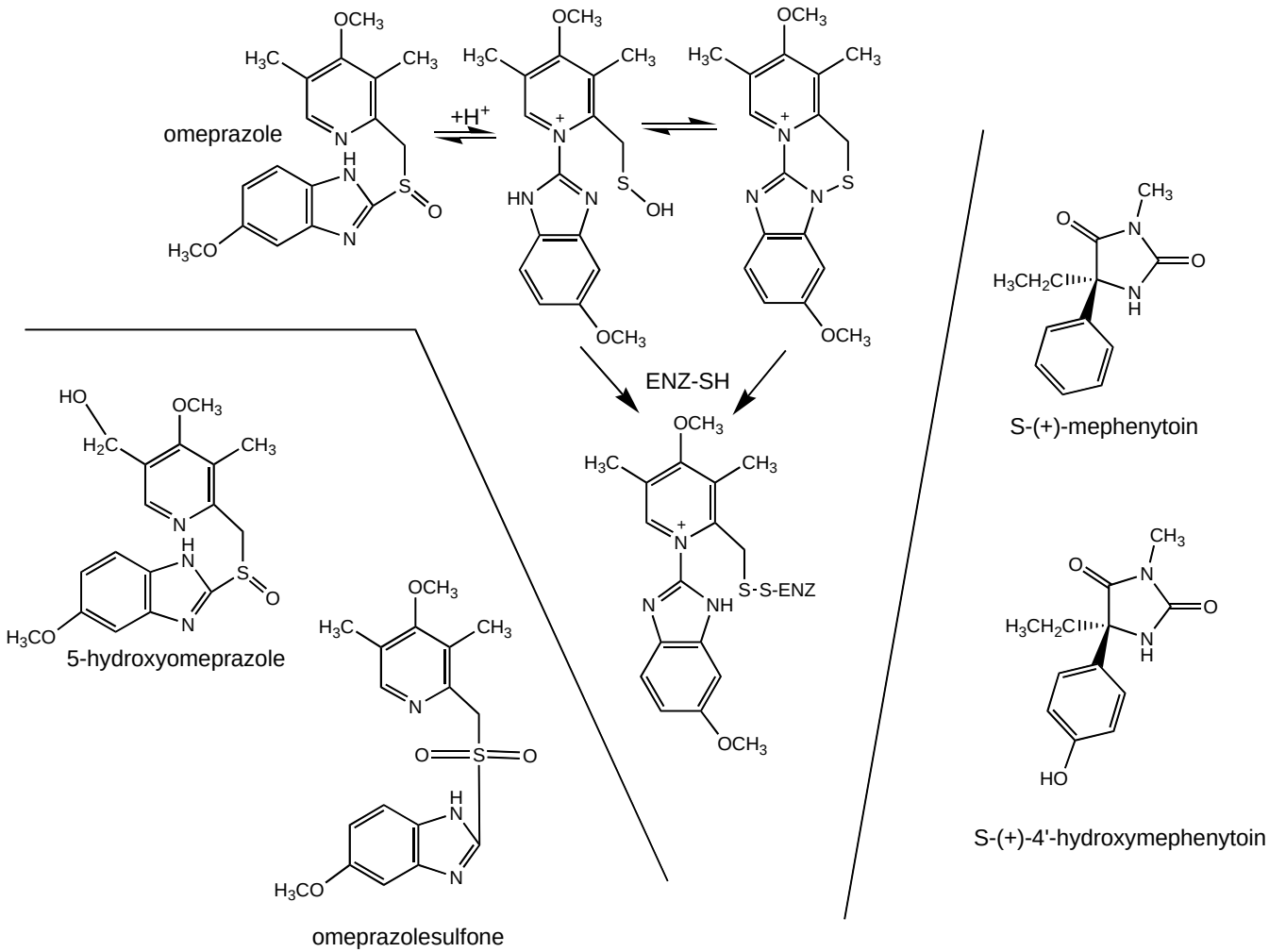
- Role of drug structure and drug transport proteins in uptake and distribution
- Kinetics of drug behavior in the human body
- Metabolism:
  - ~ chemical alterations of drugs
  - ~ generation of toxic metabolites
  - ~ metabolic activation of drugs
- Drug interactions leading to toxicity
- Drug-receptor interactions

Topics Covered

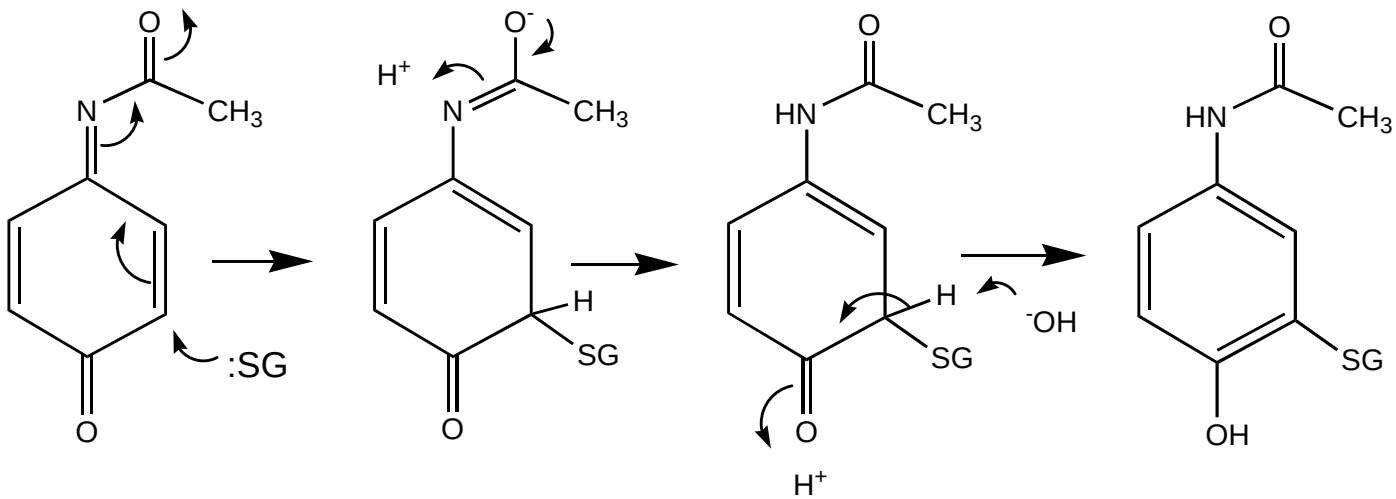
Second half of term:

- Apply basic concepts to case studies of specific drugs
- Pharmacogenetics and biological variability in drug action
- The science of clinical trials for drug candidates

Omeprazole

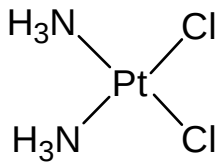

omeprazole
+H+
ENZ-SH
S-S-ENZ
5-hydroxyomeprazole
omeprazolesulfone
S-(+)-mephenytoin
S-(+)-4'-hydroxymephenytoin

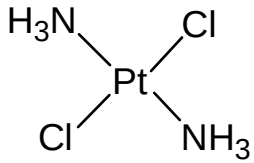
Acetominophen



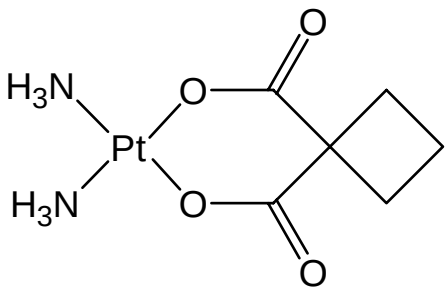
Cisplatin

Cisplatin
cis-diamminedichloroplatinum(II)

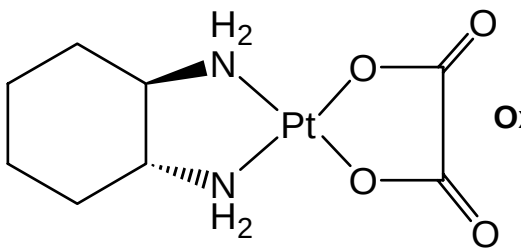




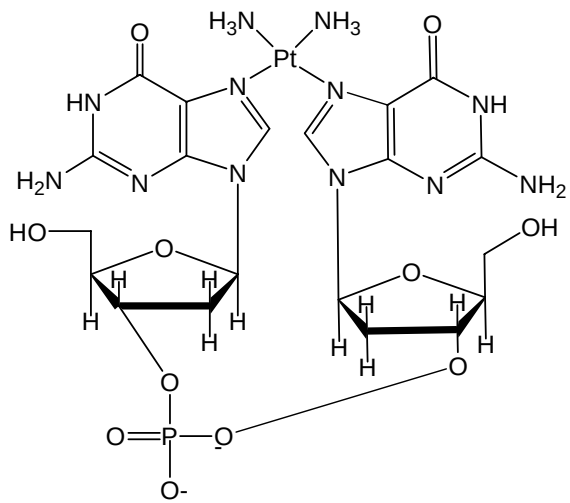
Transplatin
trans-diamminedichloroplatinum(II)



Carboplatin
cis-diammine(1,1-cyclobutane dicarboxylato)platinum(II)



Oxaliplatin



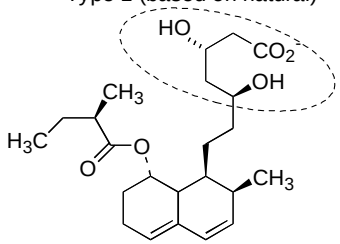
Adapted from: Zipes, D.P., et al. "Rosuvastatin: An independent analysis of risks and benefits." *MedGenMed* 8: 73 (2006); available at: http://medgenmed.medscape.com/viewarticle/533930.

Statins

Parameter		Crestor (rosuvastatin)	Pravacol (pravastatin)	Zocor (atorvastatin)	Lipitor (simvastatin)	Baycol (cerivastatin)
F[a]		20%[b]	18%[d]	12%[d]	<5%[d]	60%[d]
Absorption		50%[b]	32%[d]	30%[d]	60-80%[d]	80-98%[d]
E_H[a]		0.63[b]	0.47[e]		0.4[d]	
V_{ss}[a], L		134[b]	32[d,f]	381		23[d,f]
Protein Binding		88%[c]	50%[d]	98%[d]	>95%[d]	>99%[d]
C_{max} ng/mL	10 mg	5[g]	9[d]	7[d]		5 (0.3 mg)[d]
	20 mg	8[g]	19[d]	15[d]	18[d]	6 (0.4 mg)
	40 mg	26[g]	43[d]	67[d]	57[d], 35[d]	14 (0.8 mg)
	80 mg	44[g]	138[d]	252[d]		
t_{max} hr	10 mg	4[g]	1[d]	2[d]		2 (0.3 mg)[d]
	20 mg	4[g]	1[d]	2[d]	2[d]	2 (0.4 mg)[d]
	40 mg	4[g]	1[d]	2[d]	1.4[d], 2.5[d]	2 (0.8 mg)[d]
	80 mg	4[g]	1[d]	2[d]		
$t_{1/2}$ hr	10 mg	31[g]	2[d]	24[d]		4 (0.3 mg)[d]
	20 mg	15[g]	2[d]	20[d]	2-16[d,h]	4 (0.4 mg)[d]
	40 mg	21[g]	2[d], 5[d]	21[d]		4 (0.8 mg)[d]
	80 mg	16[g]	8[d]	19[d]		
Active metabs?		No	No	Yes	Yes	Yes
Lipophilicity LogP[j]		0.16	-0.23	4	4.7	1.5
Lipophilicity LogD[j]		-0.3	-0.8	1-2	1-2	1-2
P-glycoprotein substrate?[k]		No	Possible[l]	Yes	Yes	Yes
OATP-B/C substrate?[m]		Yes	Yes	Yes	Yes	Yes
Active Renal Secretion		Yes[b]	Yes[n]	?	?	?

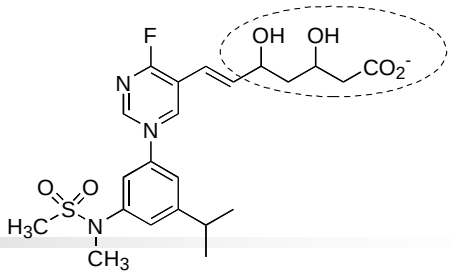
[a] F, bioavailability (%); E_H, hepatic extraction (%); V_{ss}, steady-state volume of distribution (L)
[b] (Martin *et al.*, 2003b)
[c] (Anonymous, 2003a)
[d] (Garcia *et al.*, 2003); dose in parentheses
[e] (Hatanaka, 2000)
[f] Based on 70 kg
[g] From Table III.1
[h] Major active form has $t_{1/2}$ ~ 2 hours
[i] (Serajuddin *et al.*, 1991; Nezasa *et al.*, 2002a)
[j] (Smith *et al.*, 2000)
[k] (Wacher *et al.*, 1995; Christians *et al.*, 1998; Bogman *et al.*, 2001; Huang *et al.*, 2003; Kivisto *et al.*, 2004)
[l] (Hooiveld *et al.*, 1999; Sakaeda *et al.*, 2002; Chen *et al.*, 2004)
[m] (Hsiang *et al.*, 1999; Brown *et al.*, 2001; Nakai *et al.*, 2001; Simonson *et al.*, 2004b)
[n] (Singhvi *et al.*, 1990)

Type 1 (based on natural)

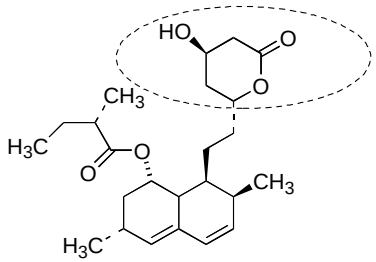


Compactin (mevastatin)

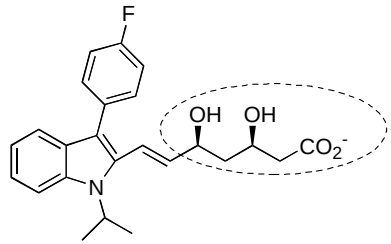
Type 2 (synthetic)



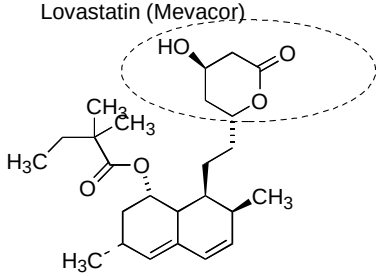
Rosuvastatin (Crestor)



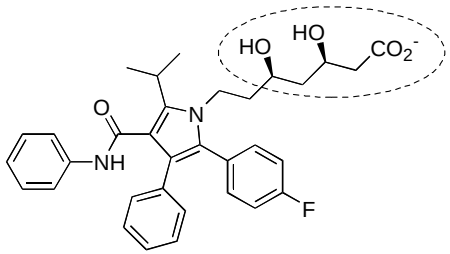
Lovastatin (Mevacor)



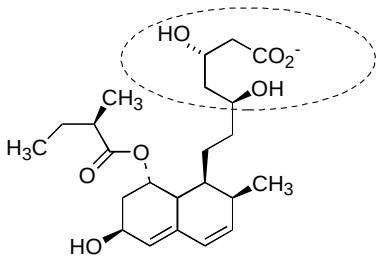
Fluvastatin (Lescol)



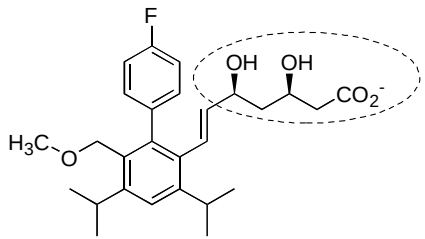
Simvastatin (Zocor)



Atorvastatin (Lipitor)



Pravastatin (Pravachol)



Cerivustatin (Baycol)

Grading Policy

Percentage contributions to the final grade:

60%	Quizzes (30% each)
20%	Project presentation/paper
	~ 10% Paper
	~ 10 % Final team presentation of project
10%	Homework assignments
10%	Class participation

Recitations

- Recitations offered Fridays from 1:30-2:30.

- Several sessions will consist of seminars presented by scientists from local pharmaceutical and biotechnology companies.

- Other sessions run by the T.A. to answer questions, plan projects and provide background help with chemistry and biochemistry

Homework Assignments and Readings

- Homework assignments cover:
  - ~ Specific papers and book chapters
  - ~ Problem sets associated with the reading
  - ~ Problem sets relevant to lecture material
- Assignments available as PDF files in the Assignments section.
- Homework due as noted in class, with 20% reduction in grade for each day late

Quizzes

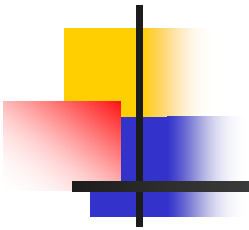
- There will be two quizzes during the term

- Both are non-comprehensive, in-class quizzes given during the regular lecture period

- There is no final examination

Projects

- Class divided into groups of 3-5 students to work as a team on a project to investigate a drug (teams assigned 9/21)
- Choose a topic based on selections provided by the instructors (topic choice due 10/05).
- Submit a one-page description of your project and definition of the roles played by each team member (proj summary due 10/24)
- Meet with T.A. at least twice during term to discuss the progress



Project Papers

- Each team writes a paper describing an in-depth analysis of their topic. Not a book report or survey paper. We expect critical evaluation.
- 20 double-spaced pages
- All team members will participate in writing
- References from the primary literature!!
- Papers due on 11/30

Final Project Presentation

- Each team makes a 15-20 minute presentation of their paper on 12/5, 12/7 or 12/12.

- Presentations involve ALL TEAM MEMBERS.

- Grading of the presentations and paper will consist of a group component for the overall quality as well as individual contributions by team members.

Required Text

- "Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy," by David E. Golan *et al.*, Lippincott Williams and Wilkins, 2005

Recommended Texts

- 6th edition of "Casarett and Doull's Toxicology, the Basic Science of Poisons, ed. Curtis Klassen, McGraw-Hill, NY, 2001

- *Other pharmacology text*: "The Pharmacologic Basis of Therapeutics" by Gilman, Rall, Nies and Taylor; Pergamon Press

- **Physiology texts:**
  - ~ "A Textbook of Medical Physiology" by Arthur Guyton (W.B. Saunders)
  - ~ "Human Physiology: The Mechanisms of Body Function" by Vander, Sherman, and Luciano

- **Histology texts:**
  - ~ "Basic Histology" by Junqueira, Carneiro, and Kelley; Appleton/Lange
  - ~ "A Textbook of Histology" by Bloom and Fawcet

The Chemistry/Biochemistry You Need to Know or Learn

Structures and Functional Groups

- carboxylic acids - aldehydes - ketones
- aromatic molecules/heterocycles - esters
- amides - thiols (sulfhydryls) - epoxides

Nucleophiles/electrophiles

Bonding

- covalent bonds - coordinate covalent bonds - ionic bonds
- hydrogen bonding - van der Waal's interactions

Reduction/oxidation

Thermodynamics and Equilibria

Acid/base chemistry

Reaction kinetics and mechanisms:

- zero-, first- and second-order reaction kinetics
- S_N1 and S_N2 nucleophilic substitution mechanisms
- Michael acceptors

The Chemistry/Biochemistry You Need to Know or Learn

Enzymes

- kinetics
- cofactors: NAD+/NADH; FAD/FADH; FMN; Coenzyme A/acetyl CoA; UDP-glucuronic acid; ATP; GTP; cAMP; cGMP; PAPS (3'-phosphoadenosine-5'-phosphosulfate); s-adenosylmethionine (SAM); glutathione

Lipids

- membrane structure
- types of lipid: fatty acids (arachadonic acid); triglycerides; cholesterol; phospholipids

Mitochondrial structure and function

Metabolism and ATP generation

DNA structure

- bases, nucleosides, nucleotides
- primary, secondary structure

Proteins/peptides

- amino acid structure and side chain chemistry
- peptide bonds - glutathione