

Medicinal Chemistry (MDCH) 5220
Organic Medicinal Chemistry II
Spring Semester 2001, Second Professional Year
9:40-10:30 MW, Skaggs Hall 316

Exam 1 (31 January 2001) Study Guide:

Helpful readings:

- (1) Class notes!
- (2) <http://hnu.pharm.utah.edu/medchem/cheatham/courses.html>
- (3) Foye; Principles of Medicinal Chemistry
 - a. Chapter 21, diuretics
 - b. Chapter 25, NSAIDS
 - c. Chapter 23, Cholesterol, etc.
- (4) Goodman and Gilman; The Pharmacological Basis of Therapeutics
 - a. Chapter 29, diuretics
 - b. Chapter 27, NSAIDS
 - c. [Chapter 26 autocooids]
 - d. Chapter 59, adrenocortical hormones

Exam #1 will cover the first six lectures:

- diuretics (2 lectures)
- NSAIDS (2+ lectures)
- introduction to steroids (1 lecture)
- anti-inflammatory properties of steroids (1 lecture)

Emphasis will be on basic principles, common/obvious structure-activity relationships, MOA (mechanism of action) where known, and well-known, well used, and important drugs in each class. Don't panic!!!

Diuretics:

- (1) What are the major drug classes for the diuretics? For each class, in what part of the kidney/nephron do they act?
- (2) Why is it important to distinguish *efficacy* and *potency* with the diuretics?
- (3) What is an indirect diuretic (know the shown examples by name) and what, generally, are their mechanism of action?
- (4) The osmotic diuretics have a clear mechanism of action; understand this in general principles (*i.e.* osmosis or locally high concentrations of solute in the nephron which drags in water and associated electrolytes). Remember that various polyols, such as mannitol, sorbital and its bicyclic form (isosorbide) are osmotic diuretics. Be able to recognize these.
- (5) The carbonic anhydrase inhibitors also have a clear mechanism of action, specifically the inhibition of the enzyme carbonic anhydrase. Why is this important (generally)? Are these “good” diuretics (*i.e.* consider efficacy/potency/site of action vs. side effect of acidosis)? Why would we possibly use these inhibitors in Utah or if we were heading to Nepal to climb Mt. Everest?
 - a. What is the major structure activity relationship of these inhibitors?
[hint: the sulfonamide; why is this a SAR?]
 - b. Be able to recognize the prototype of this class: acetazolamide (diamox)
 - c. What happens if we make acetazolamide less polar via a substitution of methyl group on the ring (but not too close to the sulfonamide since this may inhibit binding): methazolamide (neptazane). What happens in general if we make the drugs less polar?
- (6) The thiazides have a less clear mechanism of action (via inhibition of $\text{Na}^+\text{-Cl}^-$ symport), however they do tend to act in a specific area. Are they effective (consider site of action)? What are the major adverse effects of this and most of the diuretics (fluid/electrolyte imbalance)? Remember that these drugs do not seem to inhibit carbonic anhydrase effectively (despite the presence of a sulfonamide on many of these!).
 - a. Practice writing down the structure of HCTZ (hydrochlorothiazide). This is an important drug in the top200 alone and in combination with other drugs such as triamterene (triamterene/HCTZ = Dyazide) (a K^+ sparing diuretic). HCTZ would be a wise drug to be able to easily recognize.
 - b. Know the important SAR for this class. For example, why is HCTZ more potent than flumethiazide (does saturation, *i.e.* removal of the 3,4 double bond and addition of a hydrogen ring a bell?)? Why, *in general*, and in

terms of delivery, is it important sometimes to have a weakly acidic group or in the case of the thiazides, an acidic proton at N2? What kind of group at C3 increases potency and duration? Be able to recognize, where it is obvious, the difference between a *polar* and *lipophilic* group. Also note that all of the thiazides presented have a sulfonamide at position 7 and an electron withdrawing group at 6. Remember that this electron withdrawing group at position 6 is necessary (and that all the drugs presented have either Cl or CF₃ at this position). Remember that the SO₂ at position 1 is not necessary (quinethazone (hydromox) a quinazolinone derivative).

- (7) High ceiling or loop diuretics: why are they so named? Why are these more dangerous than the other diuretics?
- Furosemide (Lasix) is a top200 drug. It would be wise to be able to recognize this. Based simply on the structure, what other class(es) of diuretic might this drug fall into?
 - Remember that the structure-activity relationships for the drugs in this class are not obvious, however with a strongly electron withdrawing group next to the sulfonamide, as in bumetanide, you get greater potency...
 - Why does ethacrynic acid (Edecrin) stand out in this class? No sulfonamide, irreversible inhibitor (via protein S-H binding to the ethylene group). Also, if you had to make a guess as to a SAR for why this drug leads to gastric problems, what would you guess (think NSAIDs)?
- (8) Among the K⁺ sparing diuretics, there are two major mechanisms of action, what are these? What is the big side effect of this class of drugs?
- Remember the example of a K⁺ sparing diuretic that acts not via mineralocorticoid antagonism but via inhibiting Na⁺ channels in the renal epithelium that happens to be in the top200 in combination with HCTZ
 - Aldosterone antagonists: spironolactone (aldactone). How does this differ from aldosterone? Can you draw and number the core structure? Remember that spironolactone is converted to canrenonic acid anion. A big difference to aldosterone is the double bond at Δ⁶ and the hydroxyl group at 17 instead of 18.

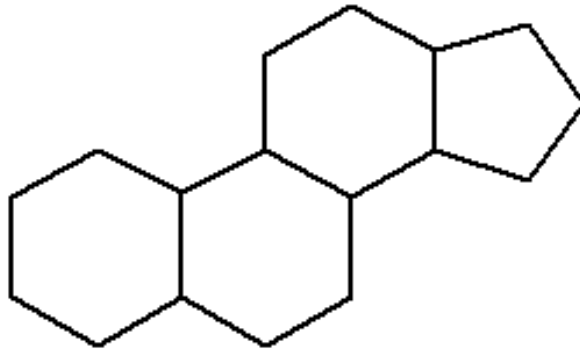
NSAIDS:

- (1) NSAID: what does this stand for? What are the primary actions of NSAIDs? Do all drugs in this class share all the activities?
- (2) A common MOA of drugs of this class is inhibition of prostaglandin synthesis. How is this pathway disrupted? (How does this differ from the steroid anti-inflammatory drugs?). Where do the prostaglandins come from (lipid derived arachidonic acid) and what are they (eicosanoids, i.e. 20 carbon molecules with double bonds; all the prostaglandins are variously substituted with oxygens (keto- and hydroxyl- groups)? What also comes from this arachidonic acid cascade? If we block synthesis of prostaglandins, what else do we block the formation of? What implications does this have in terms of side effects? Remember that cyclooxygenase acts early in the cascade to produce PGG₂ (a peroxide) that converts to PGH₂. Remember that the PGE series have a protective effect on the gastric mucosa by...
- (3) Regarding the major side effect, what is the dual insult? Why might we want to target COX-2 over COX-1 cyclooxygenases? Why not just give oral PGE₁? How about an analogue? What is an approved analogue?
- (4) Why might NSAIDS, and particularly aspirin, be useful for stroke prevention or prevention of heart attacks?
- (5) What is the structure of aspirin. Why is aspirin a special salicylic acid? What is the structure of salicylic acid?
 - a. What part of the molecule is responsible for the adverse GI effects? If we reduce the acidity (say by substitution with an amide COOH to CONH₂), what happens (less GI but no anti-inflammatory activity)?
 - b. In salicylic acid, there is a hydroxyl group ortho to the carboxylic acid. What happens if we move this meta or para? What happens if we substitute this hydroxyl with NH-R substituents (remember fenamates).
 - c. How can we increase potency? (substitution of halogens or aryl groups on ring). Example: diflunisal
- (6) Why does phenylbutazone have anti-inflammatory activity but antipyrine not even though they have similar structures?
- (7) What is the basis SAR of the arylalkanoic acids?
 - a. Is there an issue with additions of the methyl groups on the single carbon separating the acidic (carboxylic acid) and aryl or heteroaryl ring? Does it matter *in vivo*?

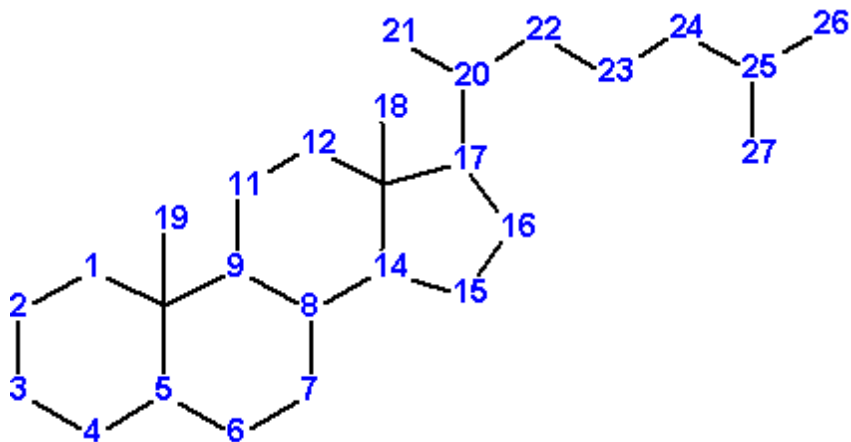
- b. Indomethacin is a prototype drug of this class that would be good to recognize.
 - c. Why does sulindac have less GI irritation?
 - d. Tolmetin and zomepiriac: such subtle changes in structure can have drastic effects...
 - e. Lipophilic groups off the aryl group increase activity as long as the group is out of plane; diclofenac (a drug that is in wide use) manages this through substitution of what on the lipophilic aryl group attached...
 - f. Why is nabumetone classified as an arylacetic acid? Why is this a good drug for someone who needs an anti-inflammatory yet has serious GI disturbances?
- (8) Aryl and heteroaryl propionic acids. Ibuprofen, naproxen and oxaprozin are rather widely used NSAIDS. Which ones are over the counter? How is oxaprozin different? What's the basic SAR of this whole series (question 7)? What happens if we remove the methyl group α to the carboxylic acid?
- (9) The anilines and *p*-aminophenols: Tylenol or acetaminophen. It would be wise to be able to recognize acetaminophen. Why do these drugs not have anti-inflammatory activity? What is the major side effect? Why are phenacetin and acetanilide no available in the US as drugs?
- (10) COX-1 vs. COX-2: which drugs are primarily COX-2 specific? Why is this important. Which of the common drugs are the least COX-2 specific and likely to cause GI disturbance? (ibuprofen, aspirin, indomethacin, tolmetin, naproxen). Ketorolac is in this series but a little different; what sets it apart in terms of its activity/delivery? It would be wise to be able to recognize rofecoxib (vioxx) and celecoxib (celebrex)
- (11) The leukotrienes are involved in inflammation and specifically in asthma. What are two means one might block the activity (block production vs. antagonize receptor)
- (12) What are mechanisms to prevent or alleviate gout? Remember allopurinol and probenecid

Steroids: nomenclature, recognizing the common elements and anti-inflammation

(1) Know how to name the rings (A, B, C, D):



(2) Know how to number cholestane



(3) Remember the cis/trans and syn/anti relationship. Are all naturally occurring corticosteroids syn or anti?

(4) Remember the important positions (3-keto, 5 α or β , 17 hydroxyl, hydroxyl at 21, where the double bonds are active...)

(5) Recognize cholesterol, cortisol, aldosterone, cortisone. What are the classes of steroids? What are the differences between the glucocorticoids and the mineralocorticoids (in structure and activity)?

(6) Know the important glucocorticoids used as anti-inflammatories as discussed in Monday's lecture...