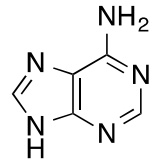
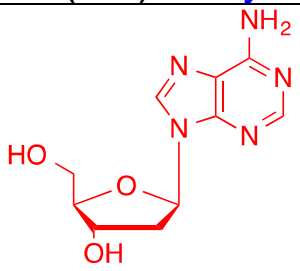
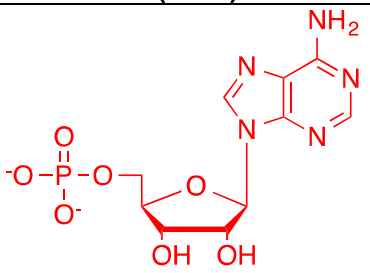
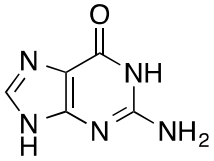
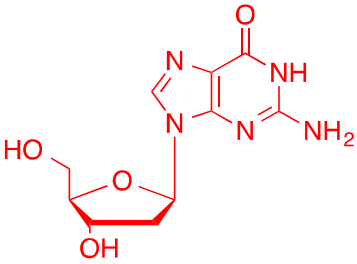
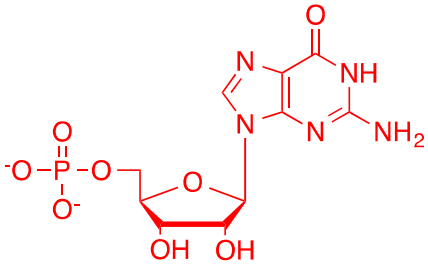
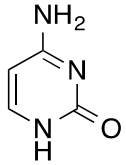
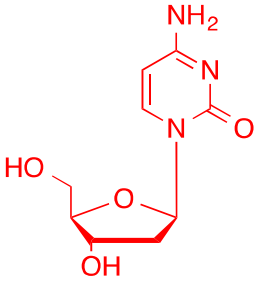
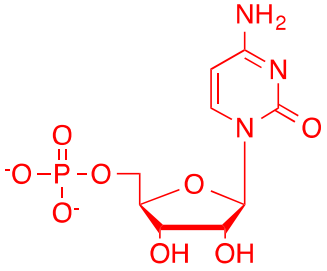
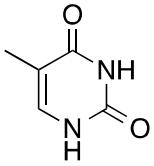
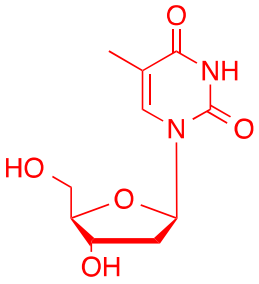
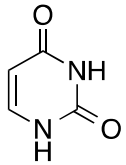
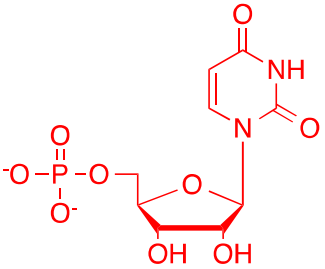
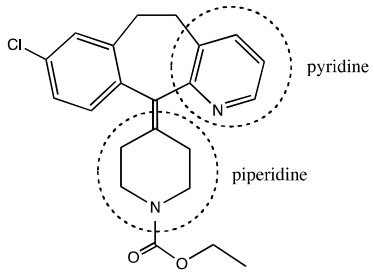
1.Build the nucleosides (sugar and base) & nucleotides (sugar, base, and 5' phosphate).

Nucleobase	Nucleoside (DNA) - deoxyribose	Nucleotide (RNA) - ribose
 Adenine		
 Guanine		
 Cytosine		
 Thymine		X
 Uracil	X	

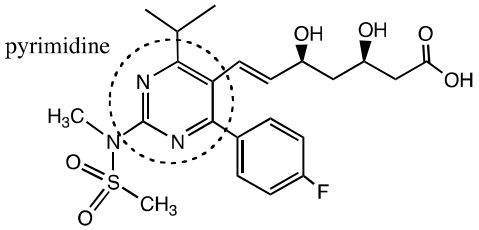
3. Heterocycles in drugs

– refer to Heterocycles Table on the 109 acrochem site under HW document

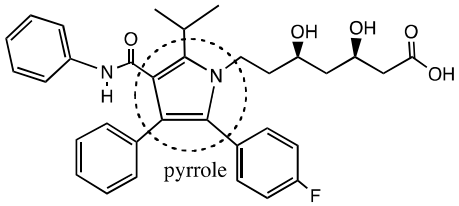
a) Loratadine



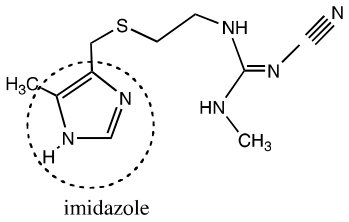
b) Rosuvastatin



c) Atorvastatin

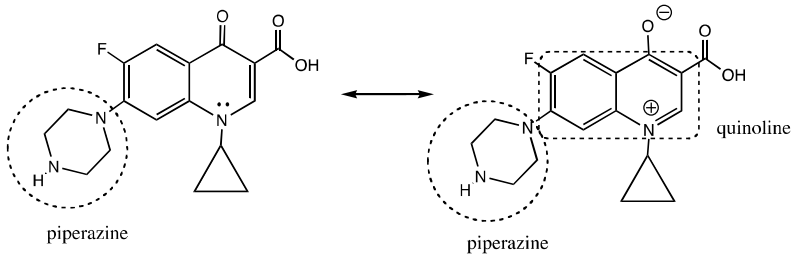


d) Cimetidine

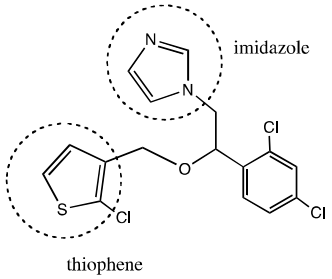


e) Ciprofloxacin

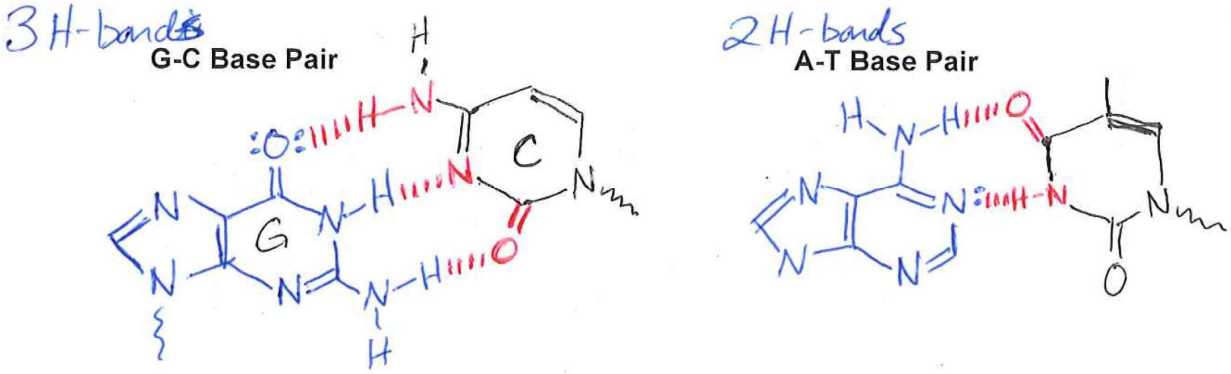
You may not recognize the quinoline ring system in the structure on the left, but it's easier to see it in the resonance structure on the right.



f) Tioconazole



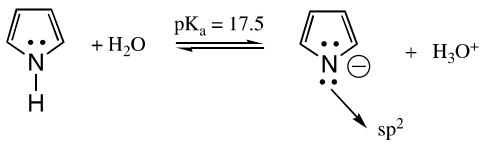
2. Draw the H-Bonding patterns for both A-T and G-C. Practice this a few times on your own without looking at the key (structures of bases will be given on the final).



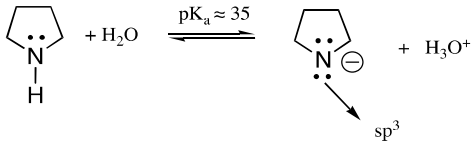
4. Basicity in heterocycles…

a) Pyrrole ($pK_a = 17.5$) is more acidic than pyrrolidine ($pK_a \approx 35$) because the anion of pyrrole is more stable than the anion of pyrrolidine. The higher acidity of pyrrole is due to the sp^2 hybridization of the N; sp^2 hybridized atoms have more *s*-character, hold electrons tighter and, in general, are more electronegative and more tolerant of negative charges than sp^3 hybridized atoms and, thus, yield more stable anions.

Pyrrole

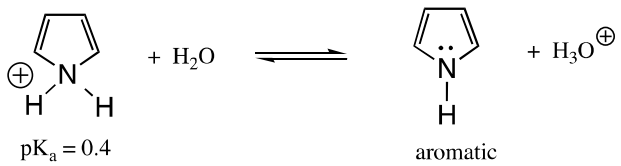


Pyrrolidine

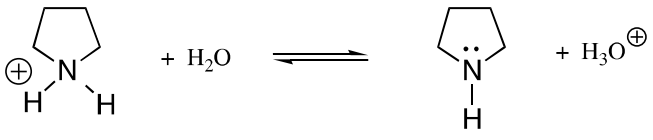


b) The conjugate acid of pyrrole ($pK_a = 0.4$) is more acidic than the conjugate acid of pyrrolidine ($pK_a = 11.3$) because pyrrole is an aromatic compound while its conjugate acid is not. Deprotonation of the conjugate acid of pyrrole restores the aromaticity to the pyrrole ring with a significant increase in stability. Such gain in stability does not occur in the deprotonation of pyrrolidine, an aliphatic amine.

conjugate acid of pyrrole:

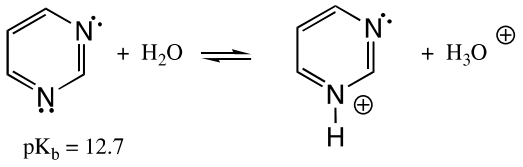


conjugate acid of pyrrolidine:

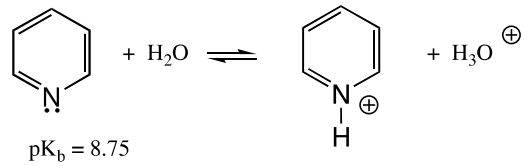


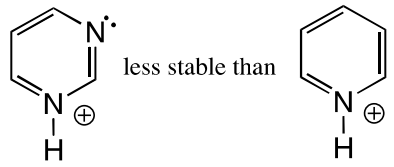
c) Pyrimidine (pK_a conj. acid = 1.3; pK_b = 12.7) is less basic than pyridine (pK_a conj. acid = 5.25; pK_b = 8.75) because the second N atom in pyrimidine is electron-withdrawing and destabilizes the positively charged conjugate acid. It can also be explained by saying that the electron-withdrawing effect of the second N makes the electron pair less prone to protonation.

pyrimidine:

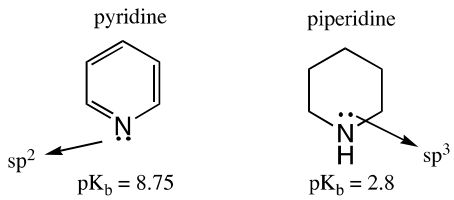


pyridine:

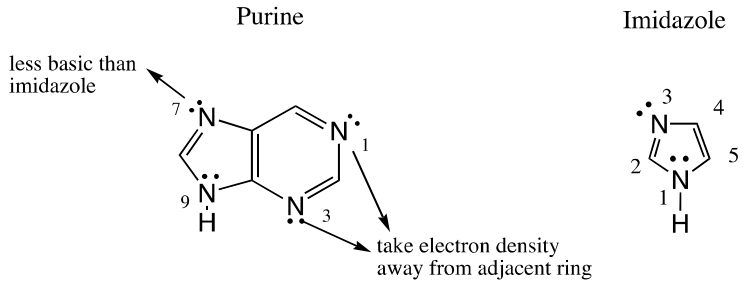




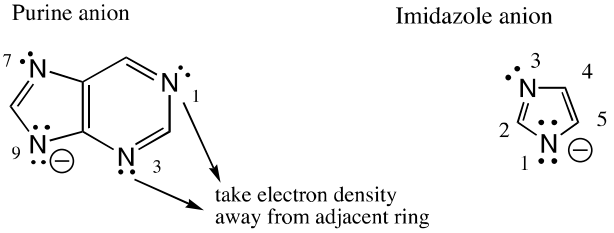
d) Pyridine is less basic than piperidine because in pyridine the lone electron pair is on an sp^2 hybridized orbital which, having more *s*-character, is more electronegative and more difficult to get protonated than the electron pair in piperidine which is located on an sp^3 orbital.



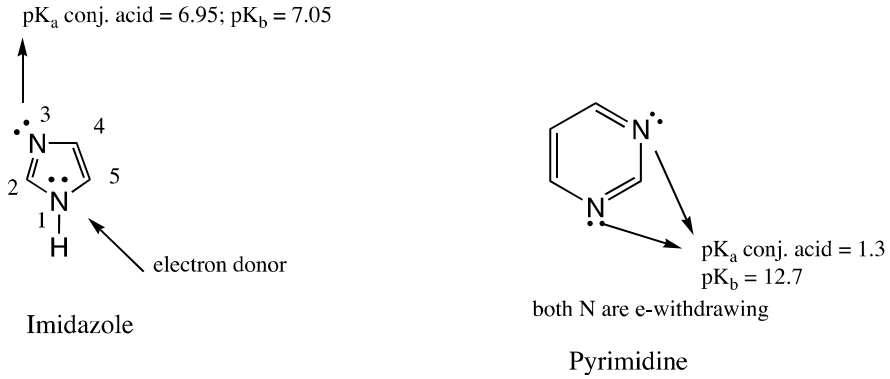
e) N7 in purine is less basic than N3 in imidazole because the pyrimidine ring, present in purine but not in imidazole, due to its two electron-withdrawing N atoms takes electron density away from the adjacent ring, making it less prone to protonation.



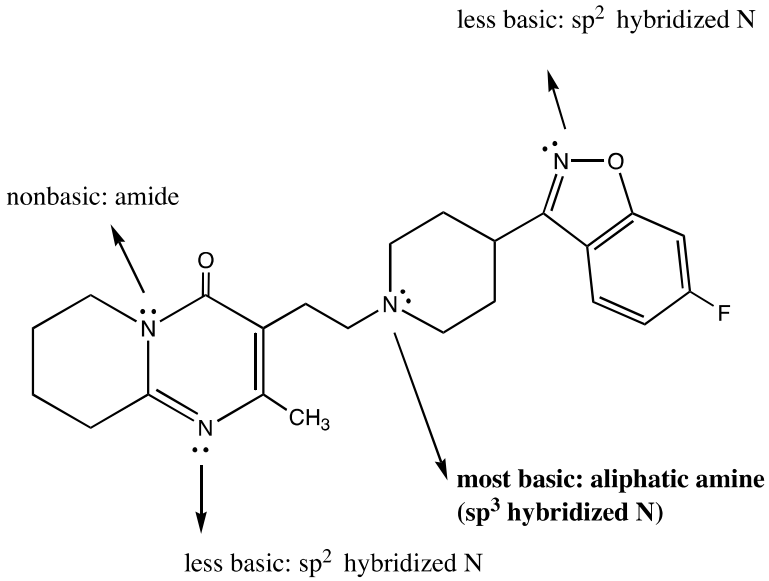
f) The H on purine's N9 is more acidic (pK_a = 8.9) than the H on imidazole's N1 (pK_a = 14.2), because the conjugate base of purine (anion on N9) is more stabilized than the conjugate base of imidazole (anion on N1) due to the presence of the electron-withdrawing pyrimidine ring.



g) Both heterocycles have two N atoms. In pyrimidine, a π-deficient ring, both N atoms with their electron pairs outside the ring, are electron withdrawing and they mutually decrease their electron densities, making themselves less basic. In imidazole, on the other hand, N1 with an electron pair inside the ring, donates electron density and increases the electron density on the other nitrogen, N3, making it more basic.

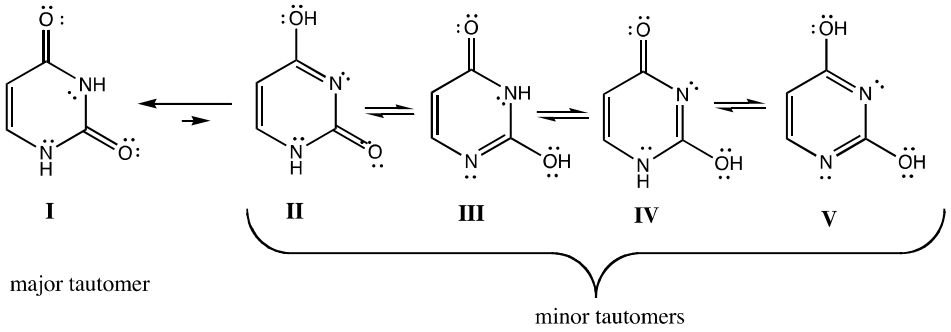


5. Risperidone

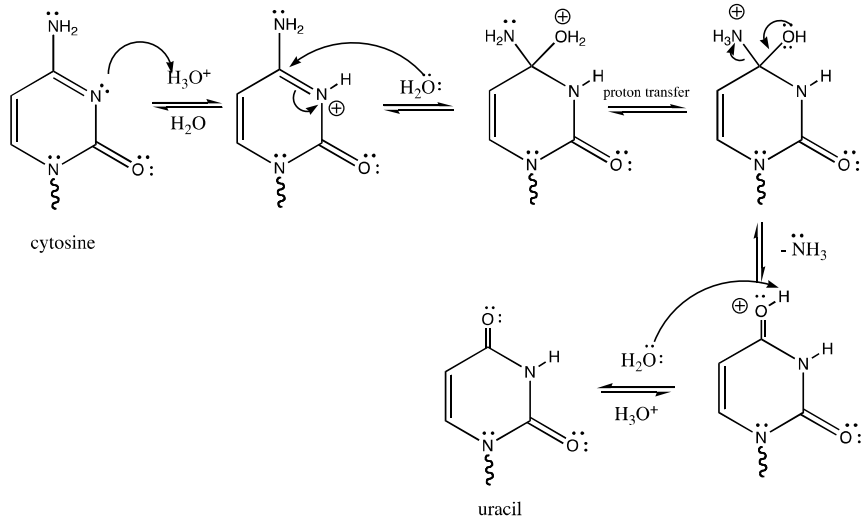


LECTURE 14 HW KEY

1. Draw structures for four different enol forms of uracil.

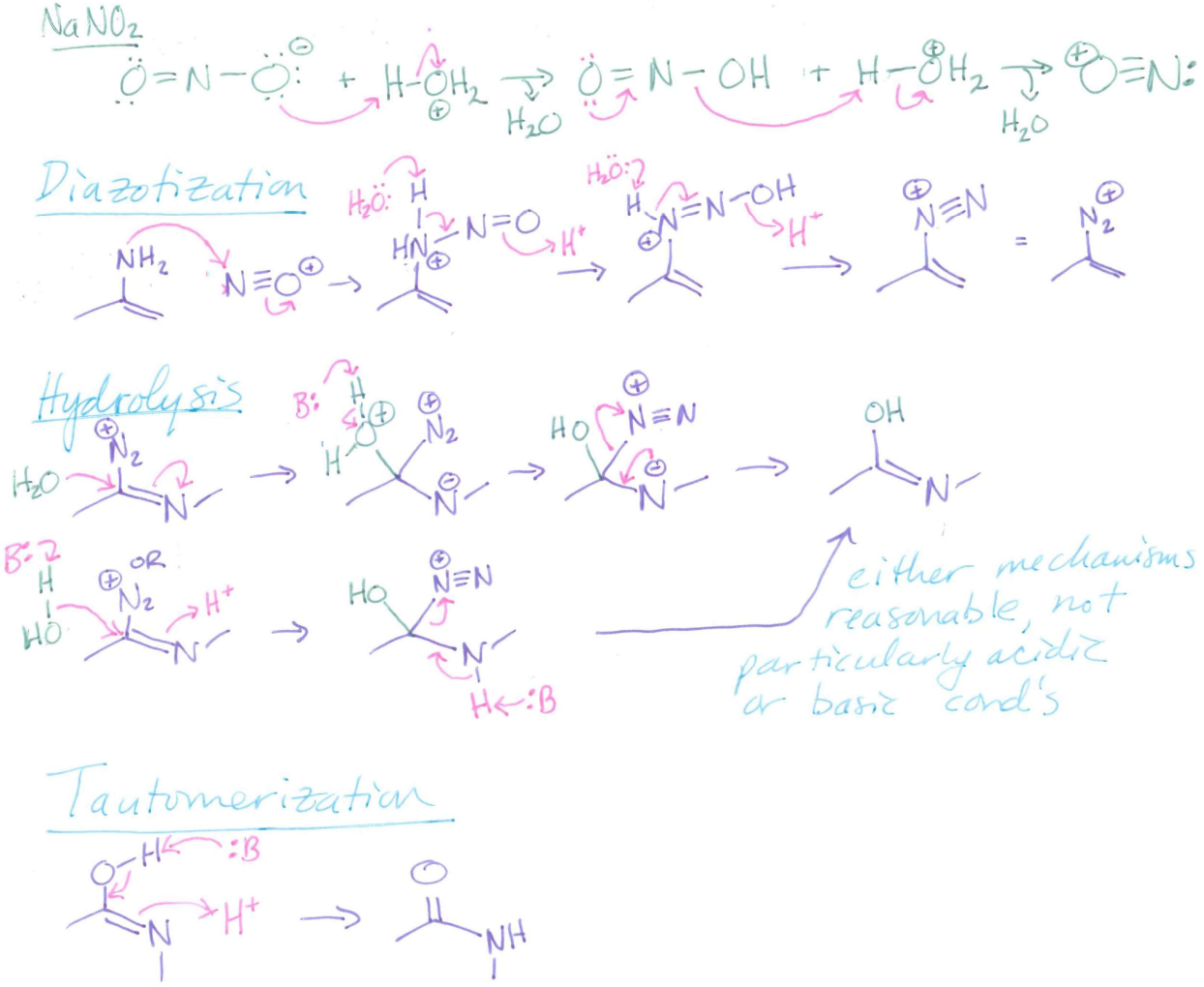


1. Propose a mechanism for the deamination of cytosine catalyzed by acid (+ charges):

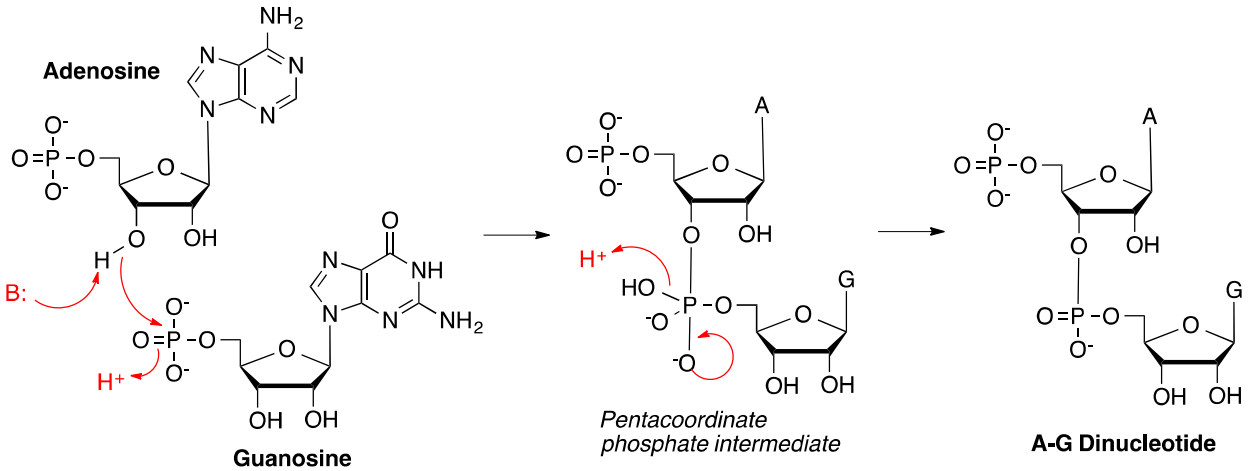


**Two arrows missing in key above (arrows moving e- back to O in 1st and last steps)

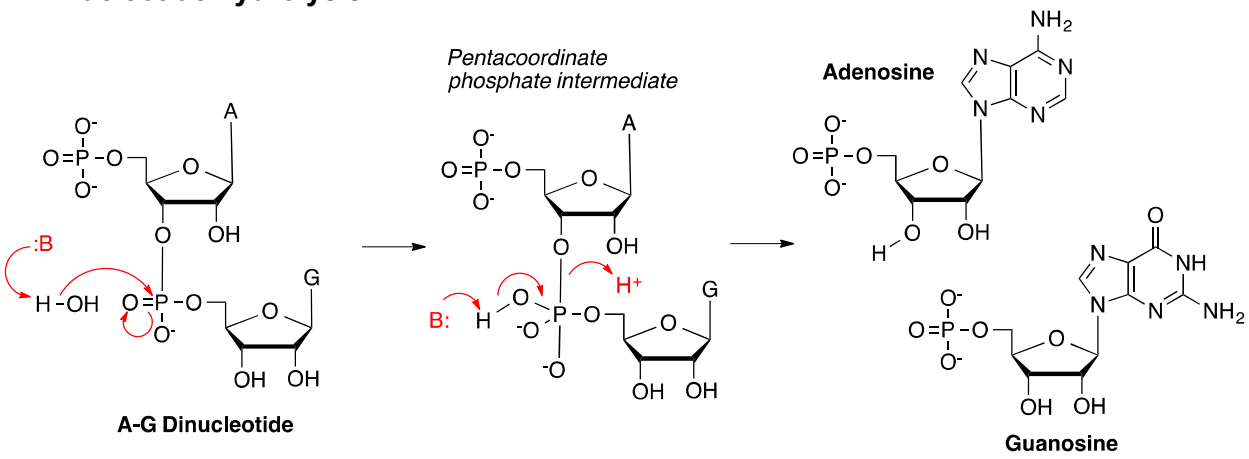
2. Mutation of methyl cytosine…



3. Dinucleotide synthesis – Lazy NAS on P isn't adequate for this mechanism – 2 H's need to be added to make water, mechanism requires two steps



4. Dinucleotide hydrolysis



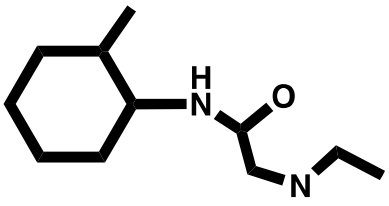
5. Associate each one of the following terms with one of the three phases: pharmaceutical (PC), pharmacokinetic (PK), pharmacodynamics (PD)
PC refers to getting the drug into the patient; PK refers to getting the drug where it needs to go in the body, considering ADME (adsorption, distribution, metabolism, and elimination)

(a) Absorption - PK
(b) dosage form - PC
(c) receptor - PD
(d) metabolism - PK
(e) binding site - PD
(f) elimination - PK
(g) excipient (inactive ingredients like solvent) - PC
(h) oral administration – PC

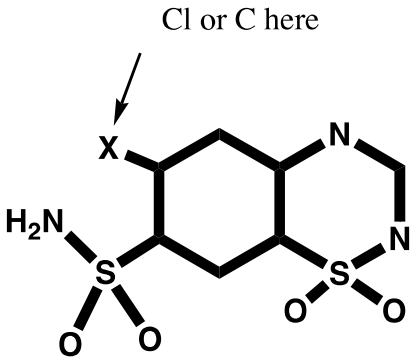
6. Classify each method of drug administration as enteral (E) or parenteral (P):

(a) Inhalation - P
(b) Subcutaneous - P
(c) Rectal - E
(d) Intravenous - P
(e) Oral - E
(f) Topical - P
(g) Intramuscular - P
(h) Sublingual – P

7. Consider the following local anesthetic agents and find the pharmacophore. Double bonds have been omitted for clarity.



8. Consider the following local anesthetic agents and find the pharmacophore. Double bonds have been omitted for clarity.



9. Calculate the therapeutic index of a drug that produces a toxic effect in 50% of the test population at a dose of 85 mg/kg and has a therapeutic effect in 50% of the test population at a dose of 100 μg/kg. Is this a better drug than a similar one with a therapeutic index of 100? Justify your answer.

100 μg/kg = 0.1 mg/kg. TI is unitless, provided the units in the numerator and denominator are the same.

$$TI = \frac{ToxicEffect_{50}}{TherapeuticEffect_{50}} = \frac{85 mg/kg}{0.1 mg/kg} = 850$$

This is a better drug than another with a TI of 100. The greater the TI, the larger the margin of safety.