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

<table>
<thead>
<tr>
<th>Nucleobase</th>
<th>Nucleoside (DNA) - deoxyribose</th>
<th>Nucleotide (RNA) - ribose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine</td>
<td><img src="image" alt="Adenine Structure" /></td>
<td><img src="image" alt="Adenine Structure" /></td>
</tr>
<tr>
<td>Guanine</td>
<td><img src="image" alt="Guanine Structure" /></td>
<td><img src="image" alt="Guanine Structure" /></td>
</tr>
<tr>
<td>Cytosine</td>
<td><img src="image" alt="Cytosine Structure" /></td>
<td><img src="image" alt="Cytosine Structure" /></td>
</tr>
<tr>
<td>Thymine</td>
<td><img src="image" alt="Thymine Structure" /></td>
<td><img src="image" alt="Thymine Structure" /></td>
</tr>
<tr>
<td>Uracil</td>
<td><img src="image" alt="Uracil Structure" /></td>
<td><img src="image" alt="Uracil Structure" /></td>
</tr>
</tbody>
</table>

Note: X indicates that the nucleotide is not found in RNA.
2. Heterocycles in drugs (refer to table in Lecture 13 notes)

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
3. Basicity in heterocycles...

a) Pyrrole (pKₐ = 17.5) is more acidic than pyrrolidine (pKₐ = 35) because the anion of pyrrole is more stable than the anion of pyrrolidine. The higher acidity of pyrrole is due to the sp³ hybridization of the N; sp³ hybridized atoms have more s-character, hold electrons tighter and, in general, are more electronegative and more tolerant of negative charges than sp² hybridized atoms and, thus, yield more stable anions.

\[
\text{Pyrrole} \quad \text{H}_2\text{O} \xrightarrow{pK_a = 17.5} \text{sp}^3
\]

\[
\text{Pyrrolidine} \quad \text{H}_2\text{O} \xrightarrow{pK_a = 35} \text{sp}^2
\]

b) The conjugate acid of pyrrole (pKₐ = 0.4) is more acidic than the conjugate acid of pyrrolidine (pKₐ = 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.

\[
\text{Conjugate acid of pyrrole:} \quad \text{pK}_a = 0.4
\]

\[
\text{Conjugate acid of pyrrolidine:} \quad \text{pK}_a = 11.3
\]

c) Pyrimidine (pKₐ conj. acid = 1.3; pKₐ = 12.7) is less basic than pyridine (pKₐ conj. acid = 5.25; pKₐ = 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.

\[
\text{Pyrimidine:} \quad \text{pK}_a = 12.7
\]

\[
\text{Pyridine:} \quad \text{pK}_a = 8.75
\]
3 con'td...

d) Pyridine is less basic than piperidine because in pyridine the lone electron pair is on an sp² hybridized orbital which, having more σ-character, is more electronegative and more difficult to get protonated than the electron pair in piperidine which is located on an sp³ orbital.

![Pyridine and Piperidine](image)

pKₐ = 8.75
pKₐ = 2.8

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.

![Purine and Imidazole](image)

f) The H on purine’s N9 is more acidic (pKₐ = 8.9) than the H on imidazole’s N1 (pKₐ = 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.

![Purine Anion and Imidazole Anion](image)

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.

![Imidazole and Pyrimidine](image)

pKₐ conj. acid = 6.95; pKₐ = 7.05

pKₐ conj. acid = 1.3
pKₐ = 12.7

both N are e-withdrawing
4. Risperidone

Lecture 14 HW Key

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

   ![Diagram of uracil enol forms]

   **Two arrows missing in key above (arrows moving e- back to O in 1st and last steps)**
3. Mutation of methyl cytosine...

4. At pH 7.4, the main species in equilibrium are $\text{HPO}_4^{2-}$ (major) and $\text{H}_2\text{PO}_4^-$ (minor). The dibasic anion is the more dominant species because pH 7.4 is closer to its $pK_a$ (7.21).

5. 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).
6. Dinucleotide synthesis

**It is still OK to use the lazy NAS mechanism on phosphorus, I just didn’t want you to forget that it is an abbreviation!**

7. Dinucleotide hydrolysis