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="image1" alt="Adenine Nucleoside" /></td>
<td><img src="image2" alt="Adenine Nucleotide" /></td>
</tr>
<tr>
<td>Guanine</td>
<td><img src="image3" alt="Guanine Nucleoside" /></td>
<td><img src="image4" alt="Guanine Nucleotide" /></td>
</tr>
<tr>
<td>Cytosine</td>
<td><img src="image5" alt="Cytosine Nucleoside" /></td>
<td><img src="image6" alt="Cytosine Nucleotide" /></td>
</tr>
<tr>
<td>Thymine</td>
<td><img src="image7" alt="Thymine Nucleoside" /></td>
<td><img src="image8" alt="Thymine Nucleotide" /></td>
</tr>
<tr>
<td>Uracil</td>
<td><img src="image9" alt="Uracil Nucleoside" /></td>
<td><img src="image10" alt="Uracil Nucleotide" /></td>
</tr>
</tbody>
</table>
2. Heterocycles in drugs...

a) Loratadine

\[
\begin{align*}
\text{Cl} & \quad \text{pyridine} \\
& \quad \text{piperidine}
\end{align*}
\]

b) Rosuvastatin

\[
\begin{align*}
\text{pyrimidine} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} \\
& \quad \text{H}_3\text{C} & \quad \text{N} & \quad \text{S} & \quad \text{CH}_3 \\
& \quad \text{F}
\end{align*}
\]

c) Atorvastatin

\[
\begin{align*}
\text{pyrrole} & \quad \text{F} \\
& \quad \text{F}
\end{align*}
\]

d) Cimetidine

\[
\begin{align*}
imidazole
\end{align*}
\]

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.

\[
\begin{align*}
piperazine & \quad \text{piperazine} \\
& \quad \text{quinoline}
\end{align*}
\]

f) Tioconazole

\[
\begin{align*}
imidazole & \quad \text{thiophene}
\end{align*}
\]
3. Basicity in heterocycles...

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

\[
\text{Pyrrole} \quad \text{N} + H_2O \quad pK_a = 17.5 \quad \text{sp}^3
\]

\[
\text{Pyrrolidine} \quad \text{N} + H_2O \quad pK_a = 35 \quad \text{sp}^2
\]

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.

\[
\text{conjugate acid of pyrrole:} \quad \text{N} + H_2O \quad pK_a = 0.4
\]

\[
\text{conjugate acid of pyrrolidine:} \quad \text{N} + H_2O \quad pK_a = 11.3
\]

c) Pyrimidine ($pK_a \text{ conj. acid} = 1.3$; $pK_a = 12.7$) is less basic than pyridine ($pK_a \text{ conj. acid} = 5.25$; $pK_a = 8.75$) 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.

\[
\text{pyrimidine:} \quad \text{N} + H_2O \quad pK_a = 12.7
\]

\[
\text{pyridine:} \quad \text{N} + H_2O \quad pK_a = 8.75 \quad \text{less stable than}
\]
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 s-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)

- **Pyridine**: sp² hybridization, pKₐ = 8.75
- **Piperidine**: sp³ hybridization, 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)

- **Purine**
  - Less basic than imidazole
  - Electron density away from adjacent ring
- **Imidazole**
  - N3 is more electron-withdrawing than N1
  - Electron density away from adjacent ring

- **Purine anion**
  - Electron density away from adjacent ring
- **Imidazole anion**
  - Electron density away from adjacent ring

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)

- **Purine anion**
  - Electron density away from adjacent ring
- **Imidazole anion**
  - Electron density away from adjacent ring

- **Purine anion**
  - pKₐ conj. acid = 6.95; pKₐ = 7.05
- **Imidazole anion**
  - pKₐ conj. acid = 1.3
  - pKₐ = 12.7

- Both N atoms in purine are donor atoms.
- Both N atoms in imidazole are electron-withdrawing.

- **Pyrimidine**
  - Electron donor
  - pKₐ conj. acid = 1.3
  - pKₐ = 12.7

- Both N atoms are e-withdrawing.
4. Risperidone

less basic: sp² hybridized N

most basic: aliphatic amine (sp³ hybridized N)

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

I (major tautomer)  II  III  IV  V (minor tautomers)

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

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

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

9. 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).
10. Dinucleotide synthesis

![Diagram of dinucleotide synthesis]

11. Dinucleotide hydrolysis

![Diagram of dinucleotide hydrolysis]