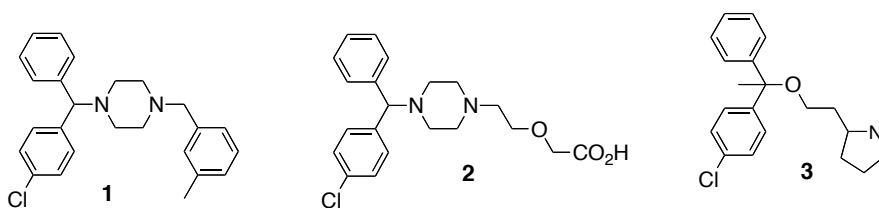


Exercises KJ 5230: October 20th – 2004

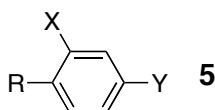
1. The structure of 3 antihistamines **1**, **2** and **3** are shown below.



- Identify functional groups in both compounds and discuss how each functional group will affect the compounds ability to cross lipophilic membranes. Which compound do you believe will cause less drowsiness?
- Where are the compounds best absorbed, stomach or intestine?
- Predict ca % ionization of compound **3** at physiolog. pH.
- Use table 2.5 (p 46) in Foye's to predict water solubility of the neutral forms of compounds **1** and **2**.
- Compound **2** is also a metabolite formed by oxidation of another antihistamine **4**. Suggest a structure for compound **4**.

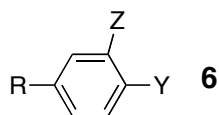
2. The results of a SAR study of hypothetical bioactive compounds **5** is summarized in the table below.

- What information regarding SAR can be extracted from the table?
- The compound **5b** (X=H, Z=F) is equally active to **5a** (X=Z=H). However there are advantages with the use of **5b**, compared to **5a**, as a drug. Explain



X	Z	% Antibacterial activity <i>in vitro</i>
H	H	50
H	Cl	80
H	CH ₃	45
H	OCH ₃	25
H	OH	10
Cl	Cl	20
F	Cl	70
CH ₃	Cl	40
H	CF ₃	85
H	NO ₂	55

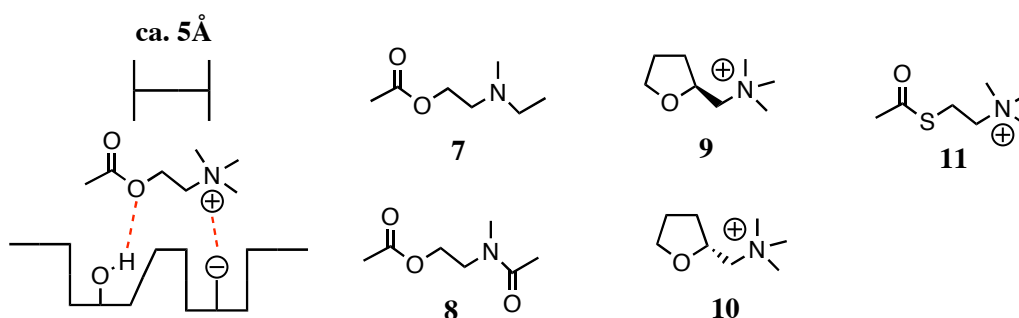
3. For a series of antibacterial compounds, you have the following information:



Z	Y	% Antibacterial activity <i>in vitro</i>
H	H	35
H	Cl	38
H	CH ₃	32
H	OCH ₃	5
Cl	Cl	0
Cl	H	55

Use the “Topliss Tree”, see *J. Med. Chem.* **1972**, *15*, 1006, to suggest improved structure(s).

4. Consider the simple model of acetylcholine bond to receptor, shown below. Discuss compound 7-11's potential as acetylcholine agonists.



5. Compound **12** is a lead compound (enhanced cytotox. of anticancer drugs). How would you interpret the activity of compounds **13-17**? What do you know about the pharmacophoric groups in **12**?

