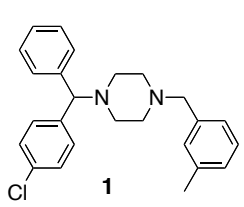
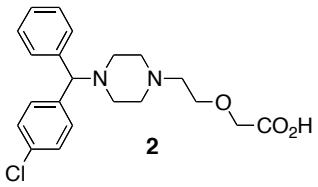
Exercise 1, KJ 5230: November 9th – 2010

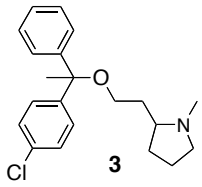
1. The structure of 3 antihistamines **1**, **2** and **3** are shown below.



1



2



3

(a) 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 (activity in the central nervous system)?

(b) Where are the compounds best absorbed, stomach or intestine?

(c) Predict ca % ionization of compound **3** at physiolog. pH.

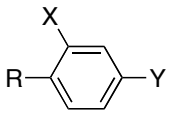
(d) Use table 2.5 (p 36) in Foye's to predict water solubility of the neutral forms of compounds **1** and **2**.

(e) 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 hypothetic bioactive compounds **5** is summarized in the table below.

(a) What information regarding SAR can be extracted from the table?

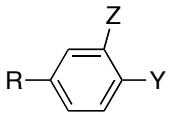
(b) The compound **5b** (X=H, Y=F) is equally active to **5a** (X=Y=H). However there are advantages with the use of **5b**, compared to **5a**, as a drug. Explain



5

X	Y	% Antibacterial activity *in vitro*
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:

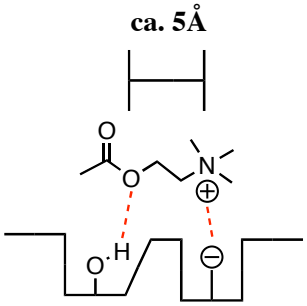


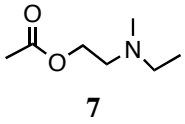
6

Z	Y	% Antibacterial activity *in vitro*
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.





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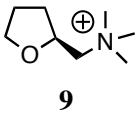

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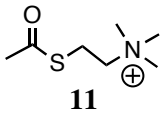
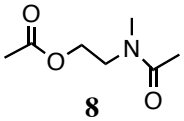


11



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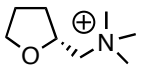
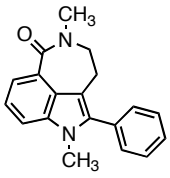
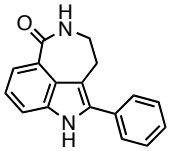


10

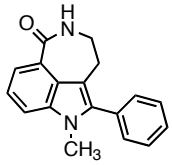
5. Compound **12** is a lead compound (enhanced cytotox. of anticancer drugs). How would you interpret the activity of compounds**13**-**17**? What do you know about the pharmacophoric groups in **12**?



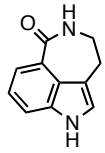
12



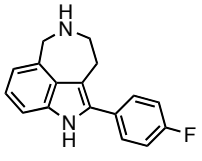
13
>10^3 increase in activity



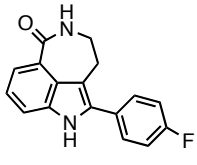
14
>10^3 increase in activity



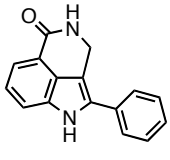
15
1/6 of the activity of **13**



16
>10^3 decrease in activity over **13**



16
slightly more potent than **13**



17
slightly more potent than **13**

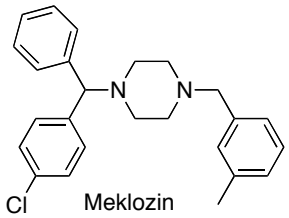
6.

(a) Lipinski has formulated :

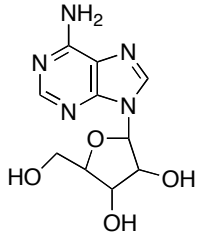
A drug canditate is more likely to have poor absorbtion or permeability if:

1. Mw>500
2. logP>5
3. Σ H-bond donors (NH, OH) >5
4. Σ H-bond acceptors (N, O) >10

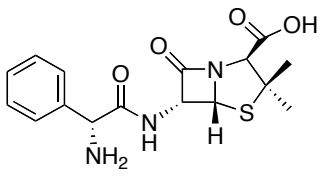
How does the compounds below apply with "Lipinski rule of five"? (Hint: You can find logP from SciFinder)



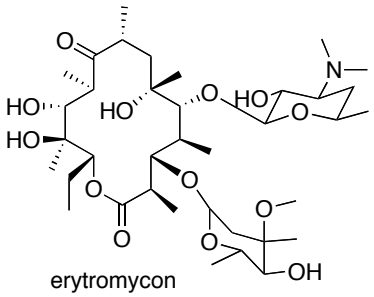
Meklozin



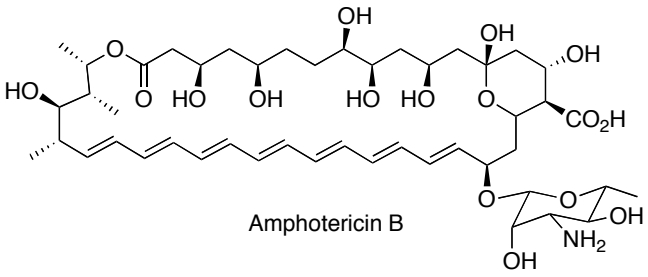
Adenosin



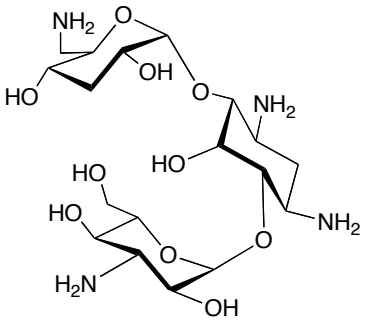
Ampicillin



erytromycon



Amphotericin B



kanamycin A