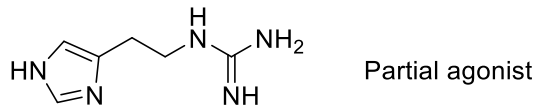
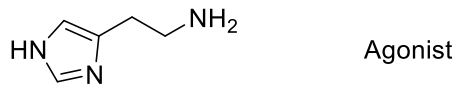


# BPS 2110

## Assignment 7 Answers

1. The initial treatment for an ulcer is often the use of antacids.
  - a. What general type of chemical is an antacid?  
**base**
  - b. What is the primary source of most antacids?  
**rocks**
  - c. Why is it not a good idea to use them for a long time?  
**The metal counterions build up in the body and cause problems (kidney is most common).**
2. During the development of Tagamet, the following observation was made:



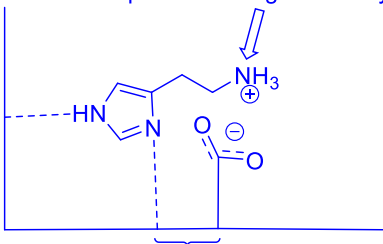
- a. What is a partial agonist and how does it produce the “partial” agonist effects?

**Agonist that produces a very weak “signal”. This can occur in 2 ways**

- Agonist binds to receptor and produces non-optimal shape change in the receptor. Weak or short duration signal is sent.
- Drug is capable of binding to receptor in more than one way. One binding mode changes the shape of the receptor to produce a biological signal (agonism). The other binding mode changes the shape of the receptor such that a biological signal cannot be sent (antagonism). The combo of these modes gives a weak signal

- b. How did the researchers explain the observation of partial agonism?

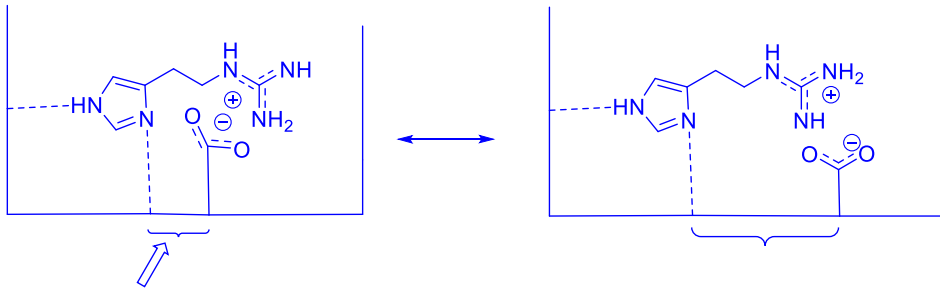
**positive charge can only be on one place in histamine**



**messenger binds and changes the conformation of the receptor such that the receptor sends a chemical message (agonist)**

**in this receptor conformation, the distance between the binding groups is relatively short**

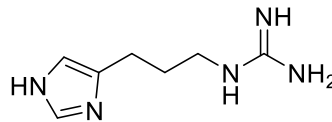
positive charge can be spread over several atoms in this drug



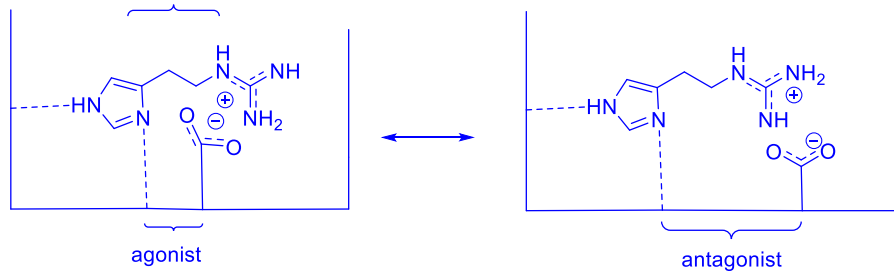
drug can bind such that the distance between the ring and + charge is relatively short  
the receptor changes conformation to the "active" shape such that the receptor sends a chemical message (agonist)

drug can bind such that the distance between the ring and + charge is relatively large  
the receptor changes conformation, but the conformation is not the same as the "active" conformation. In this shape, the receptor cannot a chemical message (antagonist)

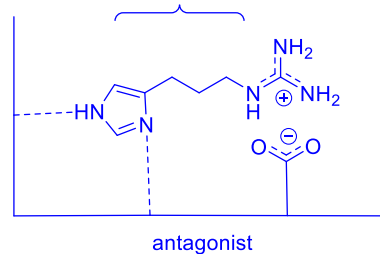
- c. Using the partial agonist as a guide, the following antagonist was prepared.  
Explain why this molecule is an antagonist and not a partial agonist.



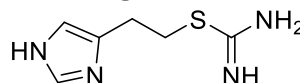
length of the spacer allows the ring and + charge to be close. this causes the receptor to bind such that it adopts the "active" conformation and sends a signal. in this binding mode the drug has agonist effects. however, the right-hand group can also place the + charge farther away from the ring. in this binding mode the receptor will adopt a conformation that cannot send a chemical signal and so the drug can also act as an antagonist



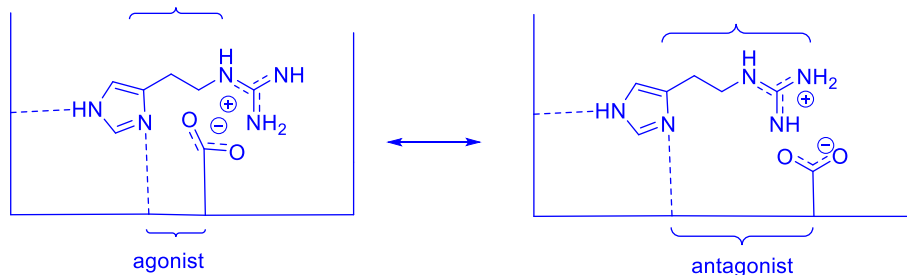
longer spacer does not allow the binding groups to be close enough to cause the receptor to adopt the "active" (agonist) conformation. drug binding induces only the receptor conformation that results in antagonism



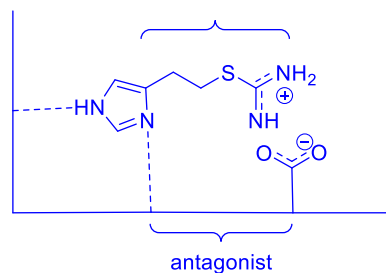
- d. Using the partial agonist as a guide, the following antagonist was prepared.  
Explain why this molecule is an antagonist and not a partial agonist.



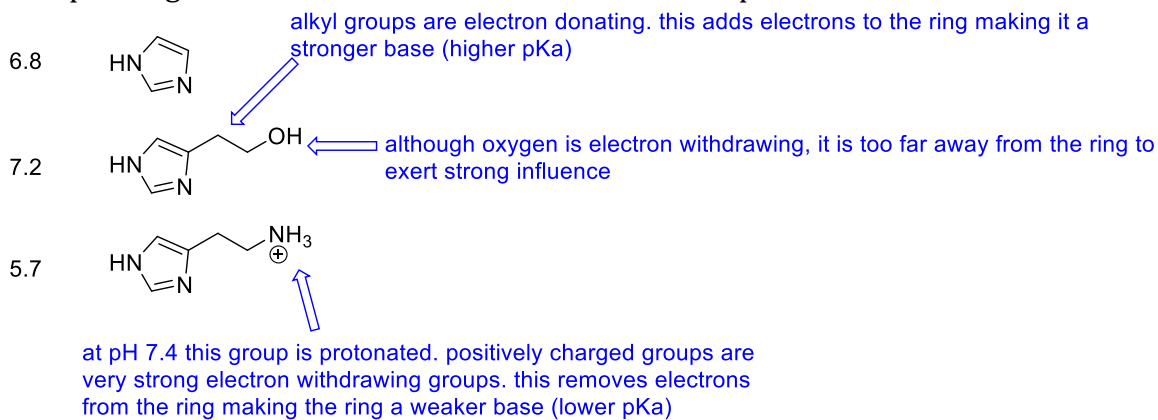
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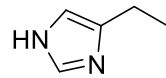
very little positive charge on sulfur (does not participate a lot in resonance), only the binding mode in which the receptor is in the "antagonist" conformation is possible  
molecule is an antagonist



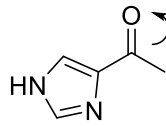
3. Imidazole is a weak biological base (pKa 6.8). This functional group is present on histamine, and also on other small molecules. The pKa values for this group vary depending on what is attached on the side chain. Explain this observation.



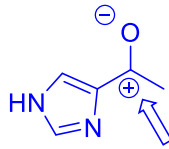
4. 3-Ethyl imidazole is a weak base with a pKa of 7.1. Predict the relative pKa (higher/lower) of the molecule shown and justify your answer.



pKa = 7.1



pKa < 7.1



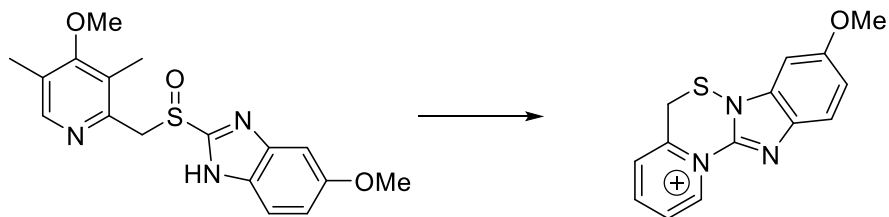
in this resonance form there is a + charge adjacent to the ring. the + charge is strongly electron withdrawing. this will reduce the electron donating ability of the ring making it a weaker base. pKa will be lower than 7.1

5. What is the main advantage of controlling stomach acid with a proton pump inhibitor rather than with an H2 antagonist?

There are 3 hormones that activate the proton pump. Histamine, acetylcholine and gastrin. H2 antagonists only block the signaling of histamine. H2 antagonists give partial relief because acid production can also be stimulated by gastrin or acetylcholine.

Blocking the proton pump directly has the same effect as blocking all three pathways. You get a greater reduction in stomach acid production because there is no "bypass" signal.

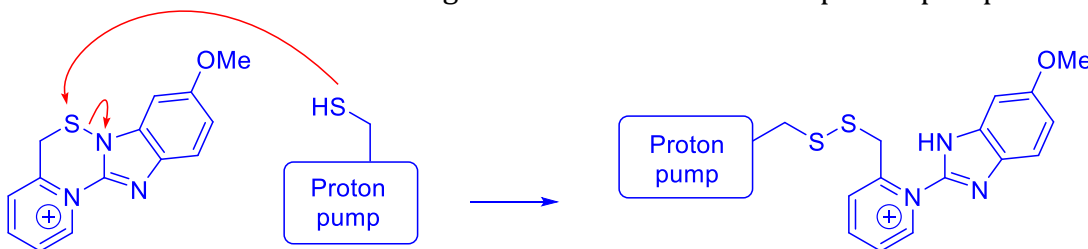
6. Omeprazole has a unique mechanism of action that transforms it into a different molecule in the body.



- a. What conditions are required in order to achieve this transformation?

pH < 2

- b. How does this drug inhibit the function of the proton pump?



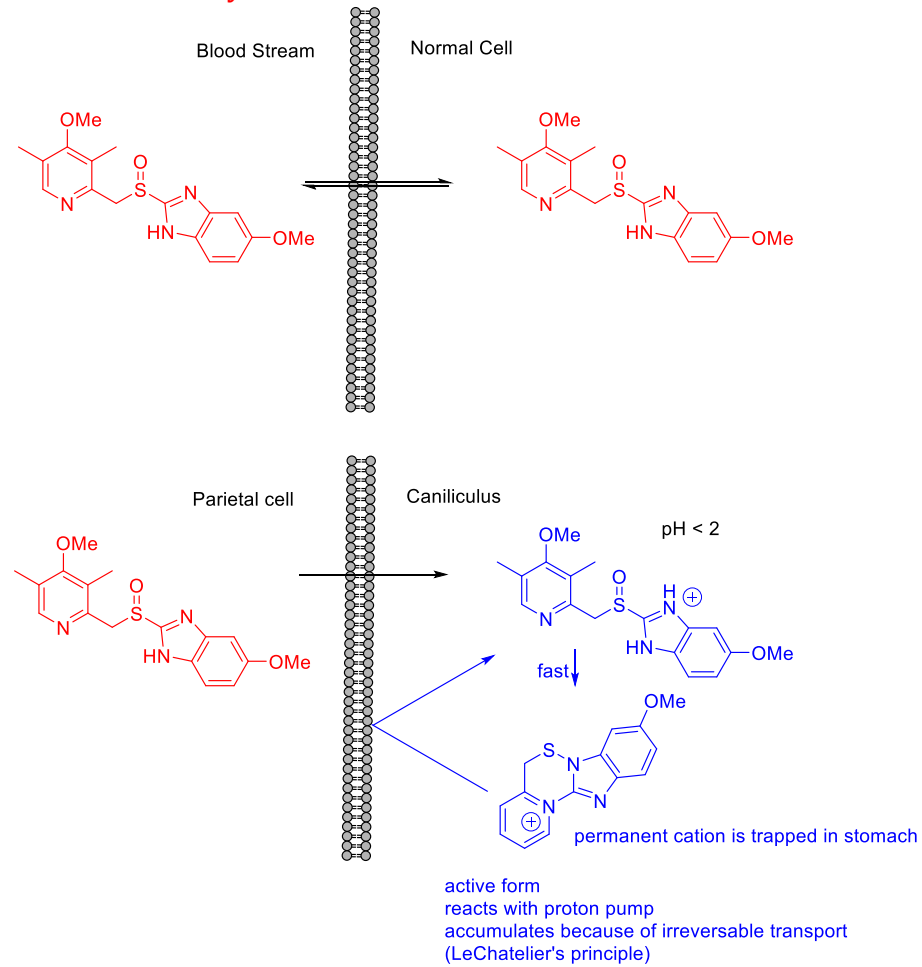
covalent attachment alters conformation of protein and inactivates it

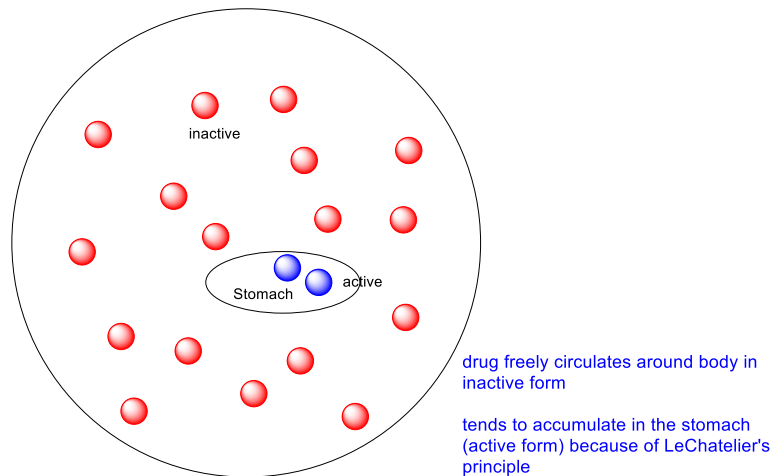
- c. This drug shows a very low incidence of side effects, due to the way it is distributed in the body. Describe how this drug is distributed and (a diagram may be helpful) how this leads to a “clean” side effect profile.

Drug is administered as the inactive form, which is also a neutral molecule. It is able to freely diffuse into and out of cells in the body, and when inside cells it is inactive. – low side effects

When secreted into the stomach, the low pH triggers the formation of a permanent cation, which is now the active form of the drug. The permanent cation cannot cross biological membranes and so is trapped in the location in the stomach where it inhibits the proton pump. The active form of the drug therefore builds up in the canaliculi (stomach pores)

Inhibition is very selective and so side effects are low.





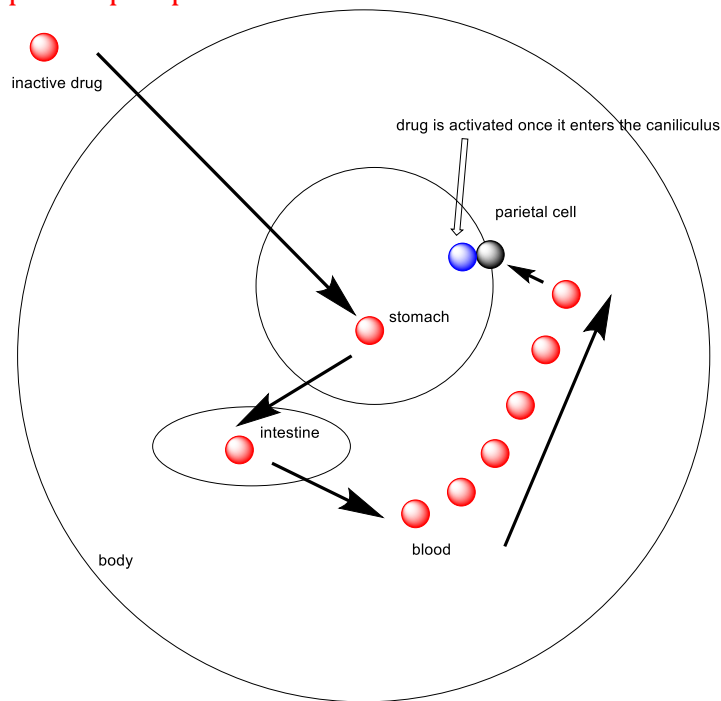
- d. Pills containing omeprazole have a special enteric coating. Why is it necessary to cover the pills with this coating?

Pills first enter lumen of stomach. If exposed to acid, the drug will activate, and will likely react with random molecules in food, rather than with the proton pump.

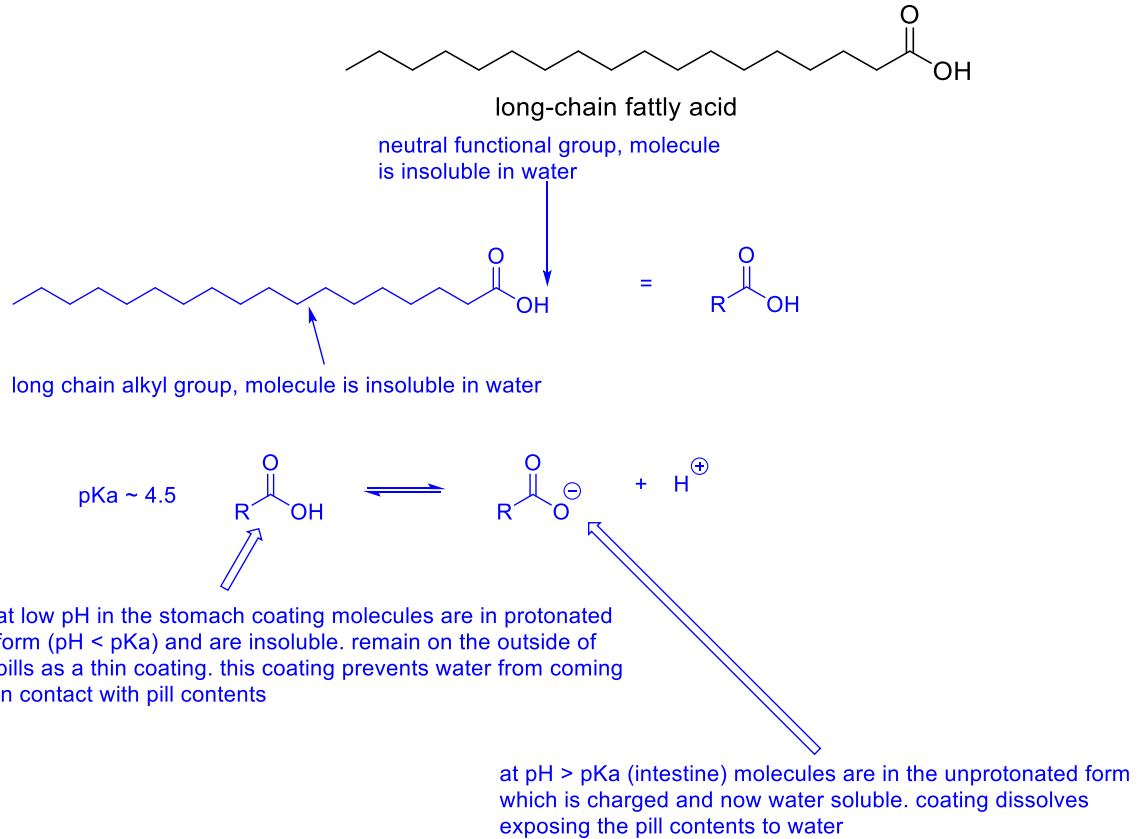
Enteric coating protects the pills from acid.

When the pills enter the intestine, the pH increase causes the coating to dissolve releasing the drug from the pills.

Drug enters the blood, circulates through the body and eventually is secreted into the canaliculi where low pH activates the drug in close proximity to the proton pumps.



- e. Enteric coatings sometimes consist of long-chain fatty acids. Explain how these coatings function in the body.



7. What is meant by a chiral switch and what is the advantage of using this strategy for a drug company?

- Strategy to protect and extend market share
- Make, patent and sell drug as a racemic mixture
- Just before patent expires, patent the single enantiomer form of the drug. (this patent is usually for the process to make it)
- Make and sell a single enantiomer version of the drug (the racemate is still sold)
- Generic companies can only sell the racemate. by selling both forms market share is protected for the original patenting company.