

Homework #2 Answer Key

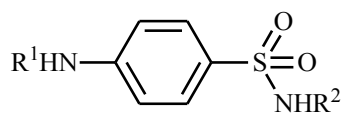
Chapter 13

3) The results can be explained by proposing that the ester is acting as a prodrug. In the *in vivo* bioassays, the ester will be less polar than the carboxylic acid and so the prodrug will be able to cross fatty cell membranes such as those of the cells lining the gut wall. Once absorbed, esterases in the blood supply will hydrolyse the ester to reveal the carboxylic acid and generate the active drug. If the active drug is administered orally, the polar carboxylic acid hinders the drug crossing cell membranes and the drug fails to reach its target, accounting for the lack of activity.

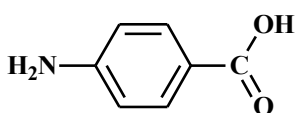
In the *in vitro* bioassay, the drug interacts directly with its target and is active, whereas the ester prodrug is inactive since the ester masks the important carboxylic acid group. There are no esterases present in the *in vitro* bioassay to hydrolyse the ester.

Chapter 19

4) The sulfonamides act as competitive inhibitors of the enzyme, dihydropteroate synthetase. They do this by mimicking one of the natural substrates for the enzyme, mainly *para*-aminobenzoic acid.

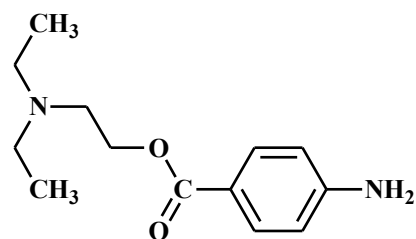


Sulfonamides



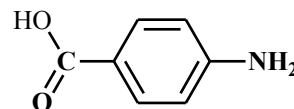
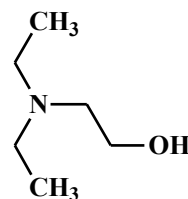
para-Aminobenzoic acid

Procaine is a local anaesthetic containing an ester group which can be hydrolysed by esterases in the blood supply. This generates *para*-aminobenzoic acid. The levels of *para*-aminobenzoic acid produced in the body now rise and can compete more effectively against sulfonamide for the enzyme's active site. Thus, the effectiveness of sulfonamide decreases.



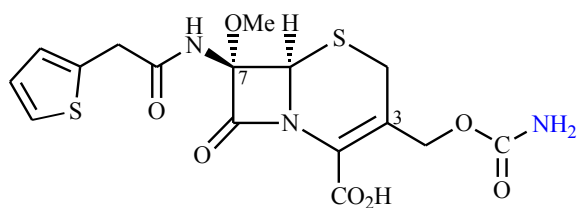
Procaine

Esterases

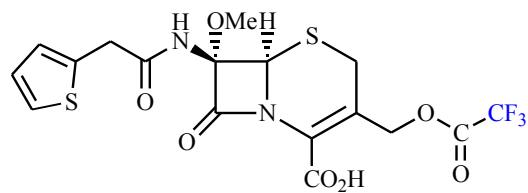


para-Aminobenzoic acid

7)

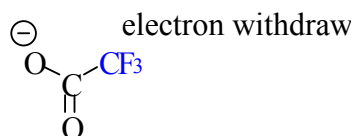


Cefoxitin



Cefoxitin analogue

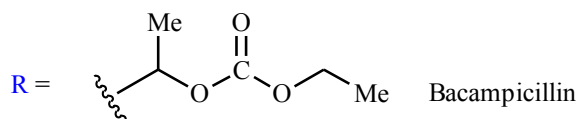
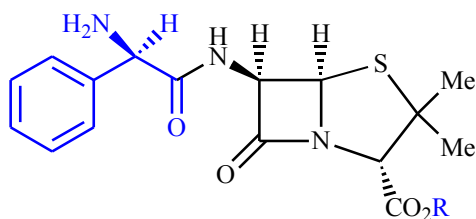
The analogue contains a trifluoromethyl group in place of an amino group. The trifluoromethyl group is a good electron withdrawing group and would make the trifluoroacetate moiety a good leaving group.



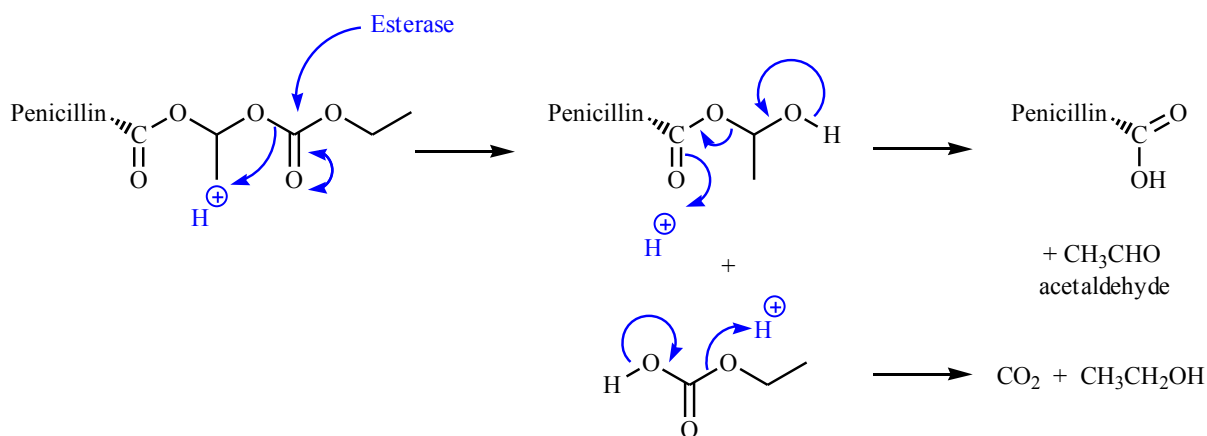
Good leaving group

This is good for the mechanism of action of cephalosporins (see Fig. 19.36). However, it also makes the group a good leaving group when it comes to ester hydrolysis, either chemically or enzymatically. Therefore, the compound is likely to have too short a lifetime in the body to be useful.

8) The structure of bacampicillin is as follows:



The mechanism by which it is transformed to ampicillin is as follows:

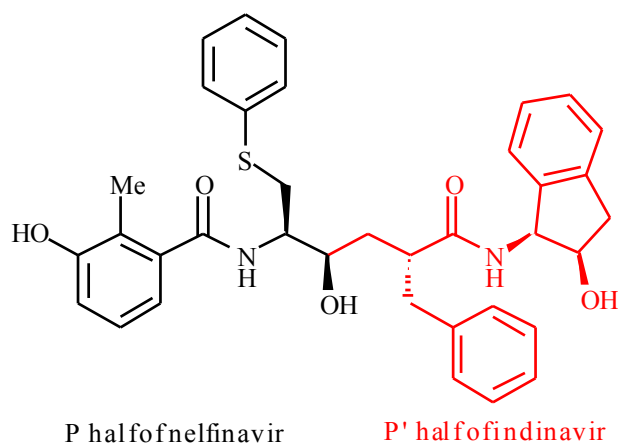


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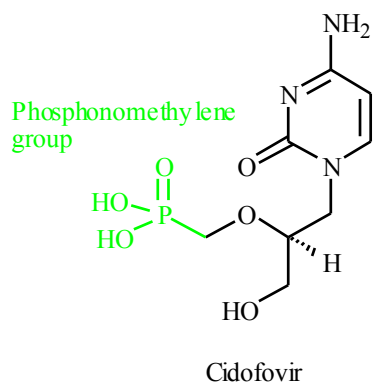
1) There are various possibilities where one could link one half of a protease inhibitor with one half of a different one.

There is no guarantee that they would be active, but they would be worth testing.

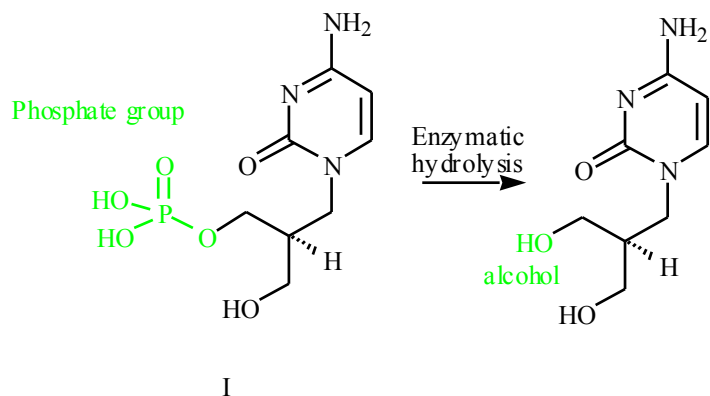
For example, the P half of nelfinavir could be linked to the P' half of indinavir.



3) Cidofovir is an analogue of deoxycytidine 5-monophosphate where the sugar and phosphate groups have been replaced by an acyclic group and a phosphonomethylene group respectively. The latter group acts as a bio-isostere for the phosphate group and can be phosphorylated twice by cellular kinases to give the active compound. Since a phosphate bioisostere is present, the compound is active against viral strains lacking viral thymidine kinase. This enzyme normally catalyses the phosphorylation of antiviral drugs such as aciclovir to give a monophosphate which is then phosphorylated twice to the active triphosphate by cellular kinases. The phosphonomethylene group is also stable to phosphorylase enzymes which hydrolyse phosphate groups.

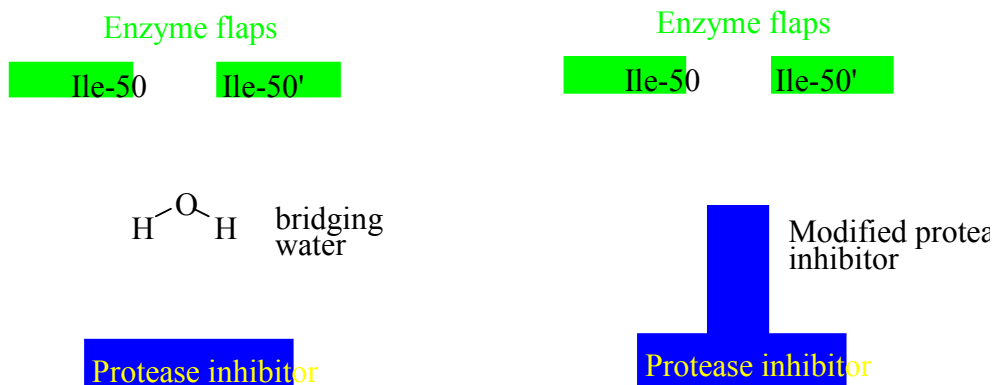


If a phosphate group is used as in structure 1, the molecule would be susceptible to enzymatic hydrolysis, resulting in formation of the alcohol shown.

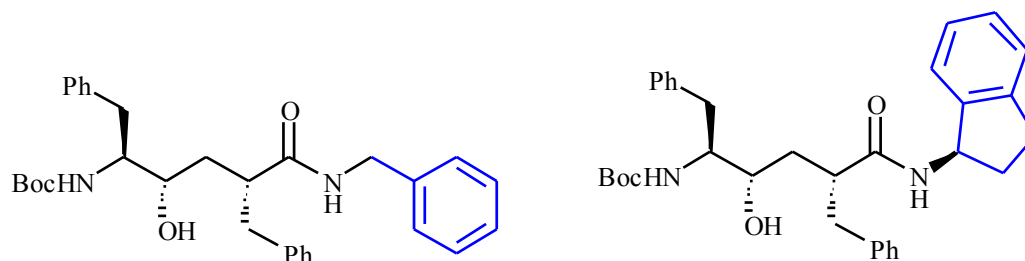


The latter would only be effective against viral strains containing viral thymidine kinase - the enzyme required to add the first of the three phosphate groups required for activity.

7) The fact that a bridging water molecule is required for hydrogen bonding interactions with the enzyme flaps indicates that this region of the enzyme active site is not occupied by conventional protease inhibitors. Novel protease inhibitors can be designed where this space is occupied with a group that can directly interact with the enzyme flaps by hydrogen bonding.

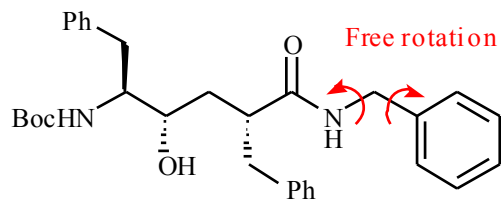


8) The two structures differ in the terminal group at the 'right hand' end. One contains a simple benzyl group while the other has a bicyclic system.



The latter structure has the higher activity which indicates that the bicyclic system is better for activity than the benzyl group. This is an example of a rigidification strategy. In the first structure, there is free

rotation round the bonds shown. This means that the aromatic ring can 'flop about' and there is less chance of the molecule being in the active conformation when it reaches the target binding site.



In the second structure, one of these rotatable bonds has been locked into a ring system and so the aromatic ring is more restricted in the number of possible conformations it can adopt relative to the rest of the molecule. As long as the active conformation is still allowed, activity should increase since there is more chance of the molecule being in the active conformation.

