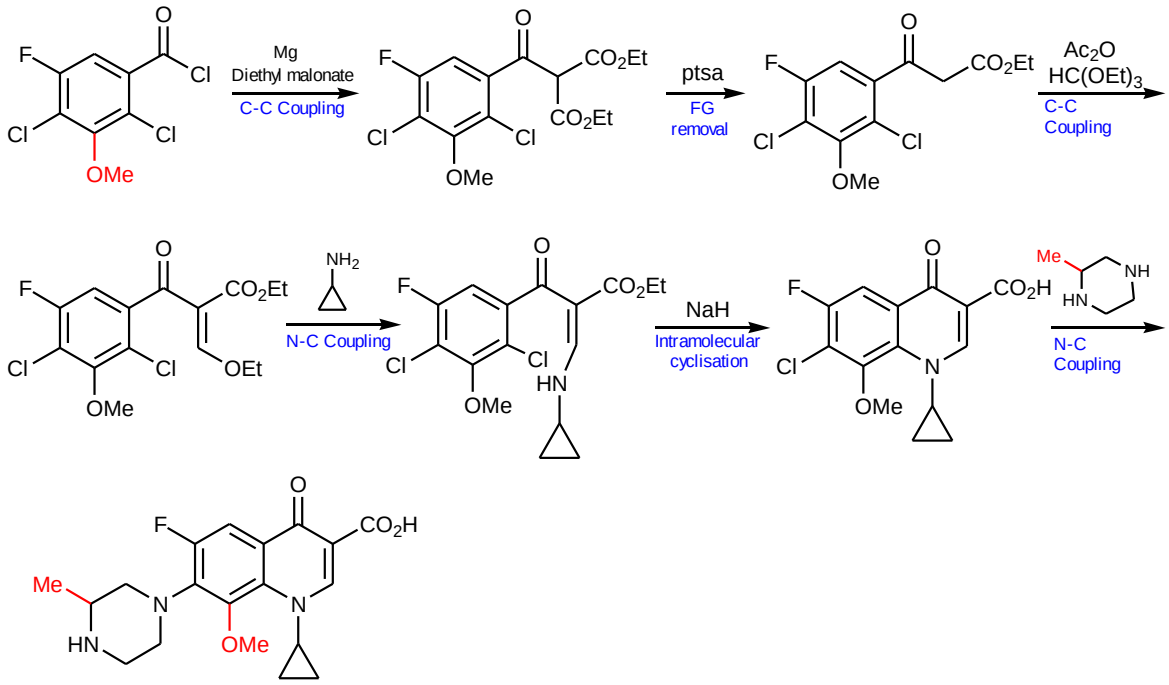
Chapter 14: Quinolones and fluoroquinolones

Question 14.1

Show how the synthesis used to produce **enrofloxacin** can be modified to produce **gatifloxacin** instead. What is the added complication in this synthesis and how significant it is likely to be?

Answer

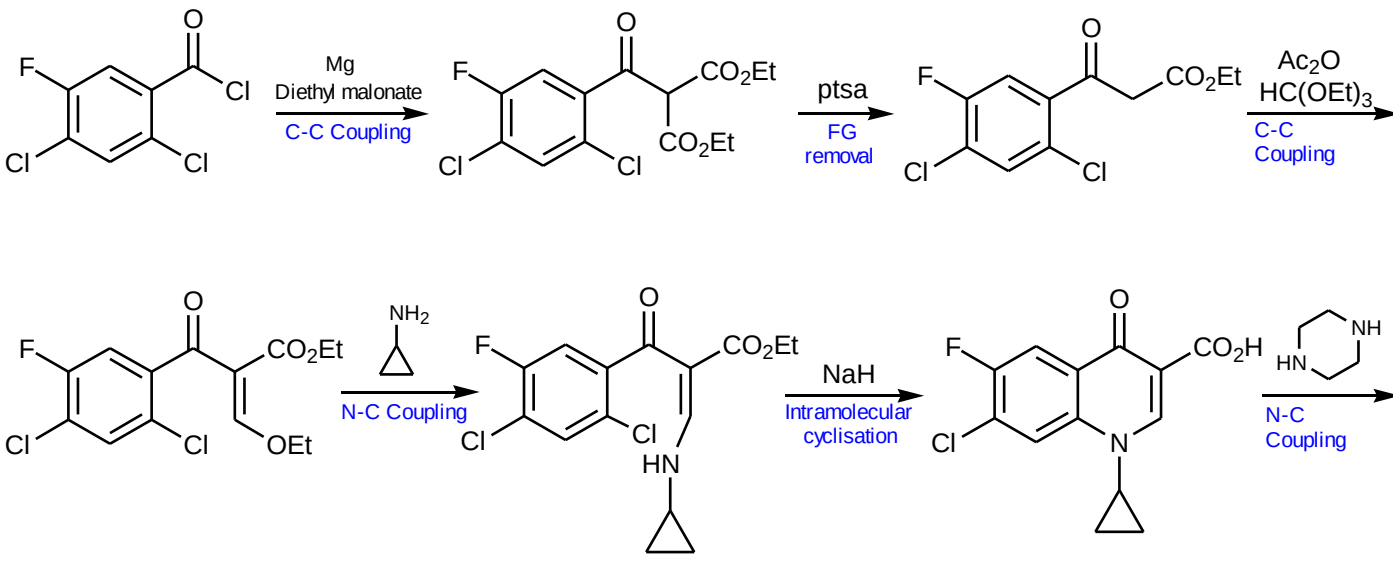
The synthesis for gatifloxacin requires a different acid chloride and a different piperazine (differences indicated in red).

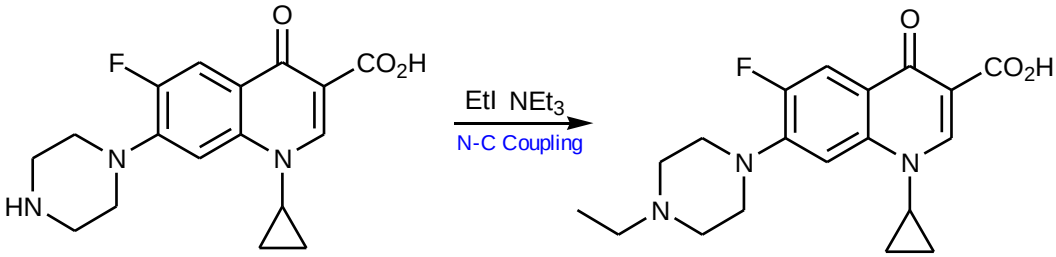


Gatifloxacin

The added complication is the methyl substituent on the piperazine ring. This introduces a chiral centre into the final structure and so this synthesis will produce a racemic mixture of the two enantiomers. Both enantiomers would have to be tested separately to see whether they had similar biological properties. If both enantiomers proved non toxic, the product could be marketed as the racemate. if it was necessary to use a single enantiomer, a resolution of the final product would have to be carried out. This would add significant expense and marketig the racemate would be preferable.

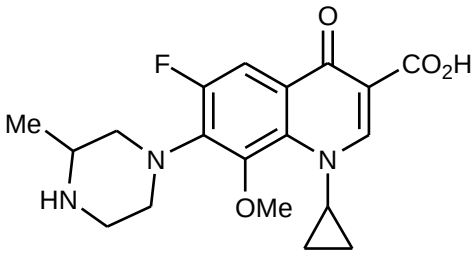
Another complication is the additional substituent present in the acid chloride. This may require a separate synthesis.





Ciprofloxacin

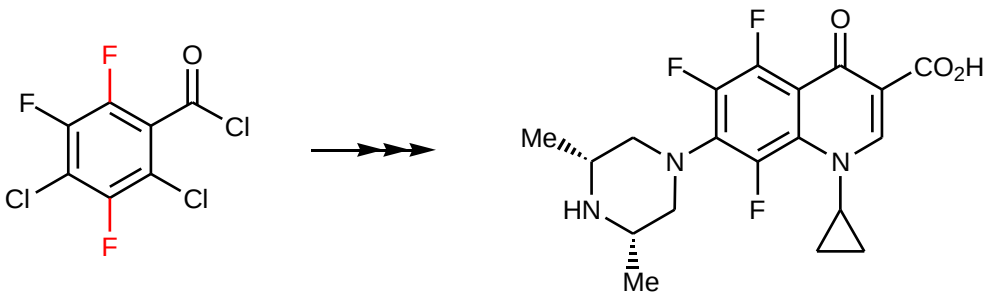
Enrofloxacin



Gatifloxacin

Question 14.2
What starting material would be needed in order to synthesise **orbifloxacin** if you wished to use the same strategy involved in synthesising **enrofloxacin?**

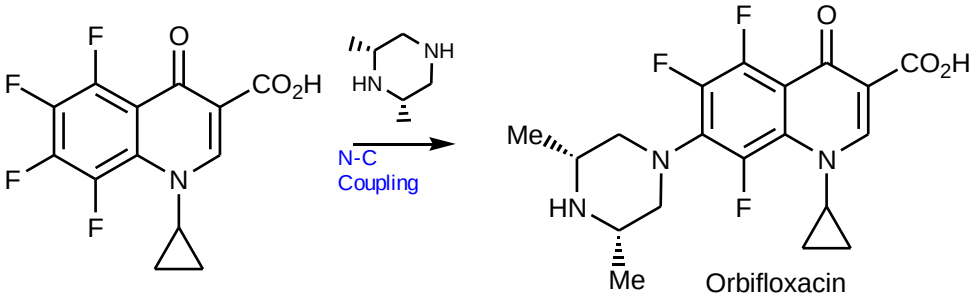
Answer



Orbifloxacin

Question 14.3

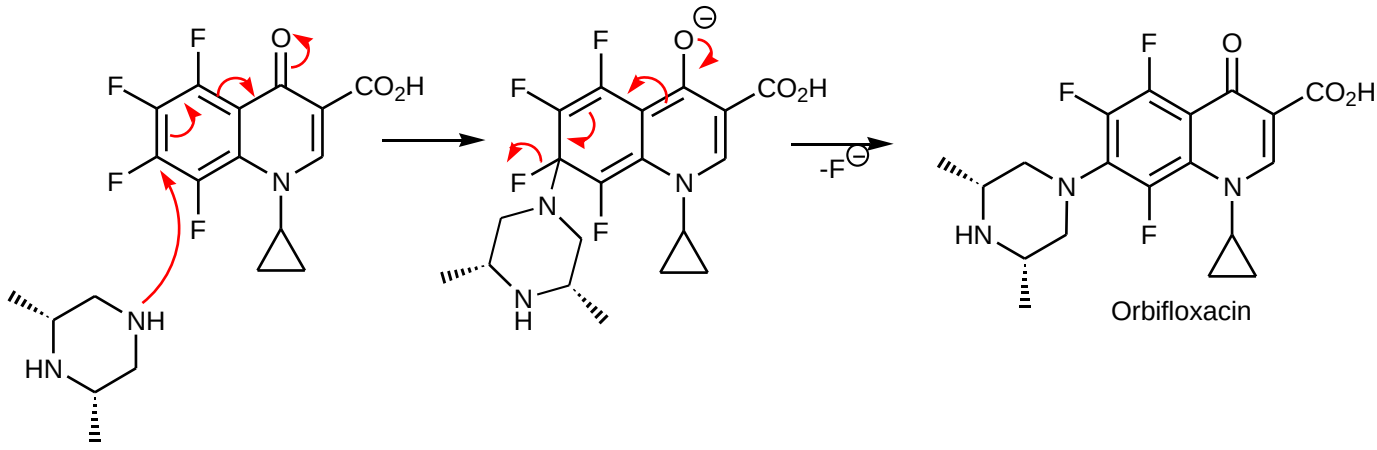
The final step of the synthesis leading to orbifloxacin involves an N-C coupling where a fluoro substituent is replaced at position 7. Why does the nucleophilic substitution occur selectively at this position and not at any of the other 3 positions bearing fluoro substituents?



Orbifloxacin

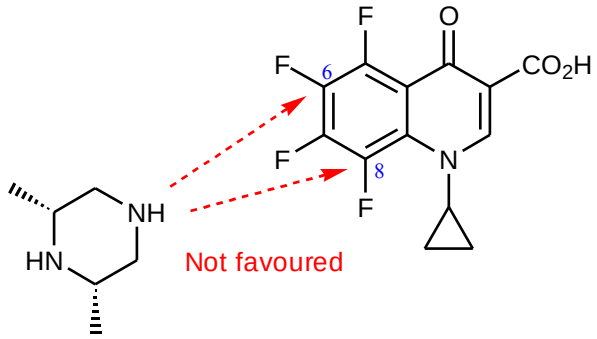
Answer

A mechanism can be drawn that involves the participation of the ketone group. This would assist the reaction by stabilising the negative charge in the intermediate.

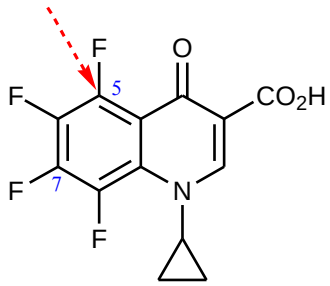


Orbifloxacin

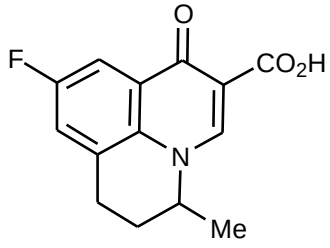
If the piperazine reacted at position 6 or 8, it would not be possible for the negative charge to end up on the oxygen atom, and so the negative charge is less stabilised.



Reaction at position 5 could result in an intermediate where the negative charge could be stabilised by being moved onto the oxygen atom. However, there are likely to be unfavourable steric interactions in the piperazine accessing that position compared to the more accessible 7-position.

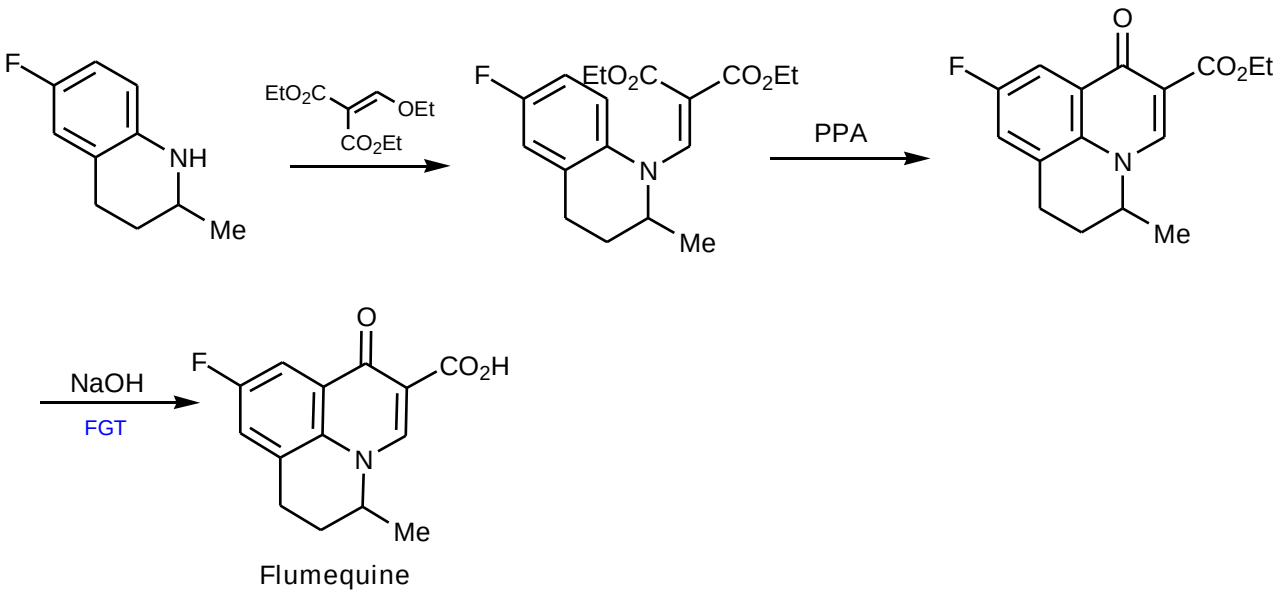


Question 14.4
Flumequine is a first-generation fluoroquinolone which has now been discontinued, although it is still used in veterinary medicine. Propose a possible synthesis.



Flumequine

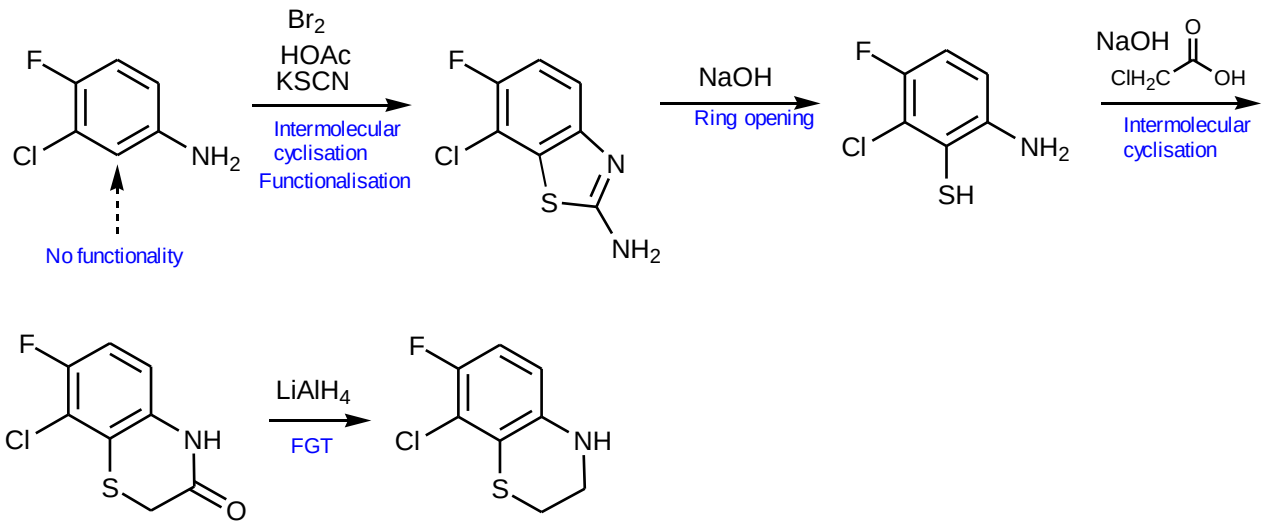
Answer
A possible synthesis is the following.



Flumequine

Question 14.5

Propose mechanisms for the two cyclisations shown in figure 14.21.



Answer

The key intermediates in the mechanism are likely to be the following structures (shown in brackets).