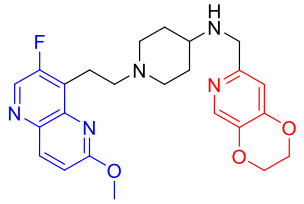
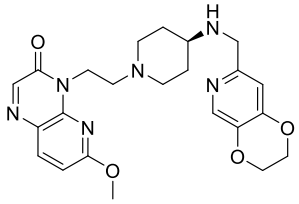
Bacterial Topoisomerase Inhibitors



1



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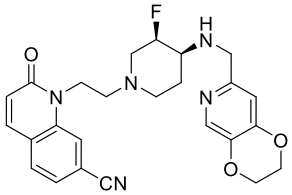
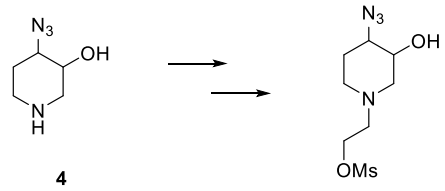


3

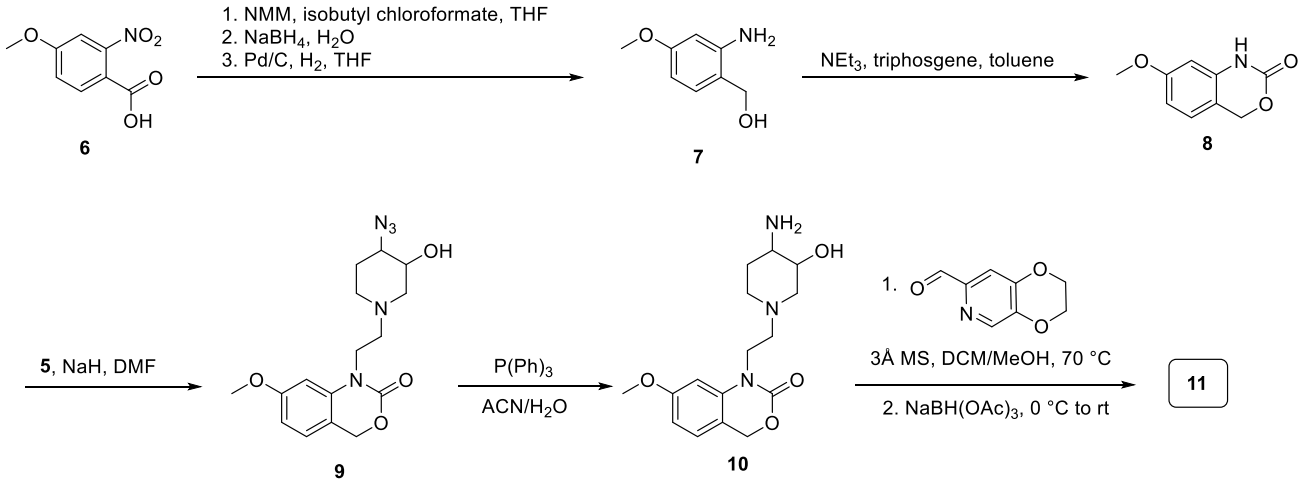
Compounds **1-3** were synthesized as potential antibacterial agents targeting bacterial topoisomerase. The established pharmacophore shows that the left-hand side (blue) intercalates bacterial DNA and the right-hand side (red) interacts with the topoisomerase enzyme. Despite their good antibacterial activity and physicochemical properties, compounds **1** and **2** were not progressed because they were also potent hERG inhibitors.

1. a) Why is hERG inhibition a potential problem in drug development? In targeting the hERG liability, what is the advantage of **2** over **1**? **3** over **2**?
   b) From an SAR perspective, what are the key disconnections of the compound **3** chemotype?

Refer to the scheme below to answer questions 2-7.



4 **5**



6 **7** **8** **9** **10**

2. Propose a synthetic route to get to compound **5** from starting material **4**.

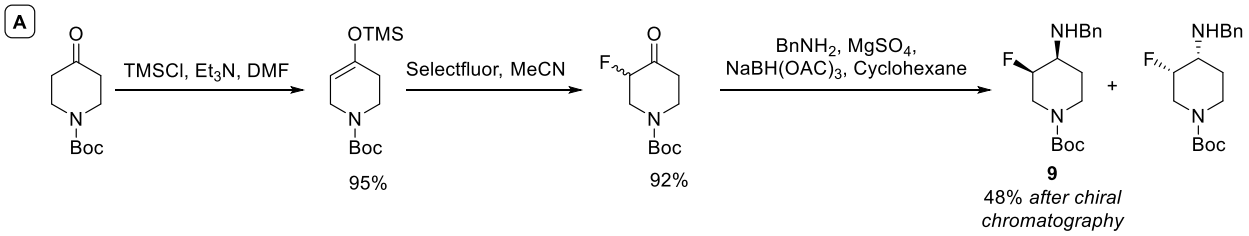
3. Give the mechanism for all steps to form compound **7**.

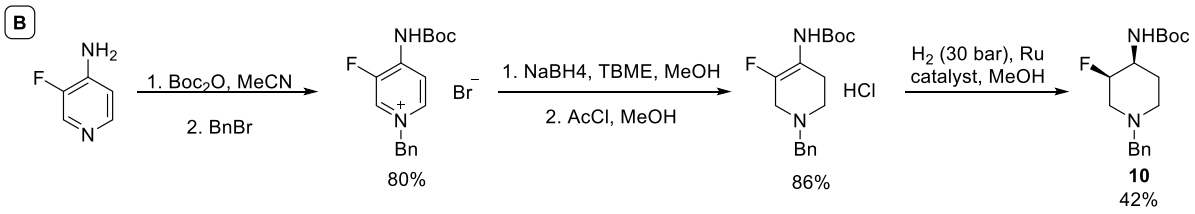
4. a) Give the mechanism for the formation of compound **8**.
   b) Give the mechanism for the decomposition of triphosgene to phosgene.

5. Name and give the mechanism for the transformation from **9** to **10**.

6. a) Provide the structure of **11** and give the mechanism of its formation from **10**.
   b) When **11** was prepared on a process scale, the reaction did not go to completion without the addition of 5 mol % AcOH. Propose a mechanistic reason that the addition of AcOH improved the reaction and a reason why it was required with scale-up.

7. Shown below are A) the medicinal chemistry route and B) the process chemistry route to the fluorinated intermediates **9** and **10**. Give at least two advantages of the process route.





References

10.1021/jm2008826 (Initial SAR/N-linked cores)
10.1021/jm300690s (pK_a Modulation)
10.1021/acs.oprd.0c00029 (Process chemistry)