Medicinal Chemistry

1. General terms and concepts

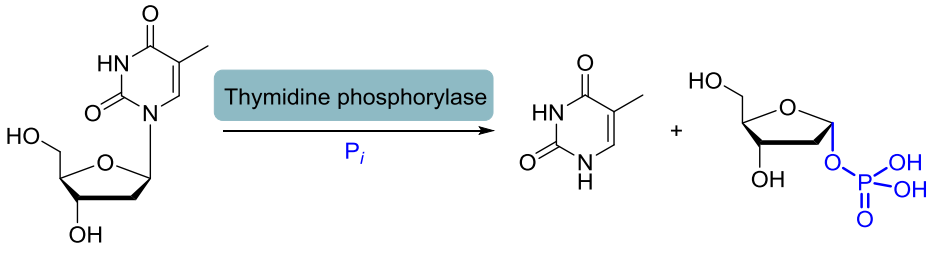
   a. Define the following terms and explain their relevance to "druglikeness":

      i. IC_{50}
      ii. log *P* and clog *P*
      iii. bioisostere
      iv. Fsp^3
      v. CYPinh
      vi. NOEL
      vii. MTD or DRF

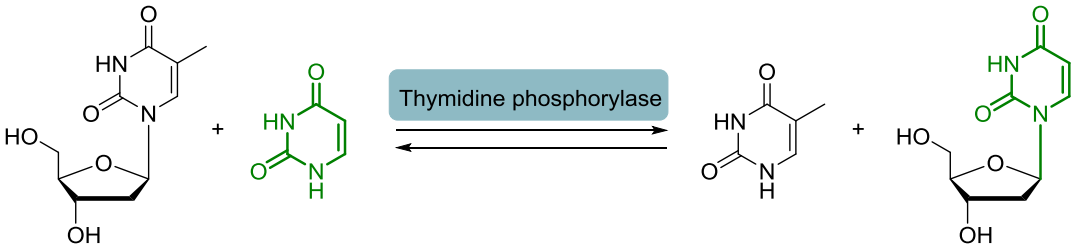
   b. What is the "Rule of Five" (Ro5)? Suggest ways in which the Ro5 may be deficient.

2. Enzymes in medicinal chemistry

   a. Thymidine phosphorylase catalyses the conversion of thymidine (dThd) to thymine, using either inorganic phosphate (P_i) or another pyrimidine (e.g. uracil). Explain why this enzyme is overexpressed in many cancer cells.

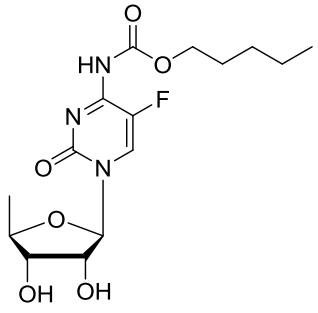


dThd



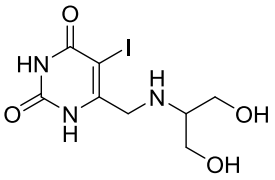
dThd **uracil**

   b. Explain how thymidine phosphorylase is key to the action of capecitabine, a chemotherapeutic agent.

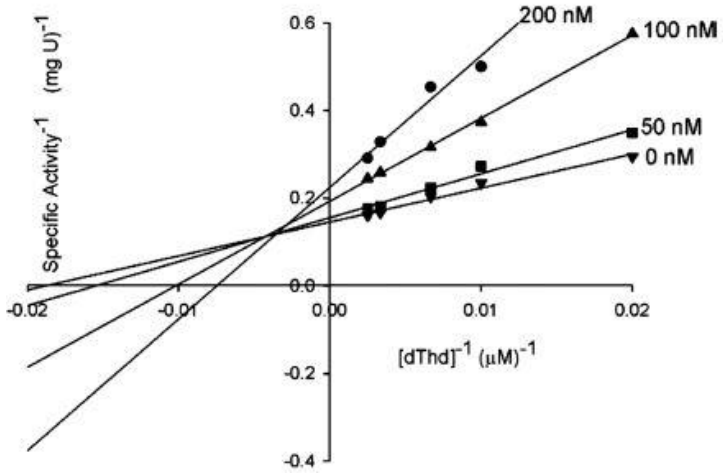


capecitabine

c. Thymidine phosphorylase can be inhibited by pyrimidine-2,4-diones. Consider the inhibitor shown below. What type of inhibitor would you expect it to be? What type of inhibition does it actually display, as evidenced by its Lineweaver-Burk plot (right)?

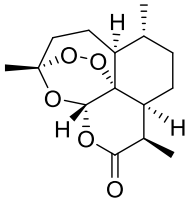


pyrimidine-2,4-dione inhibitor
IC_{50} = 0.12 μM



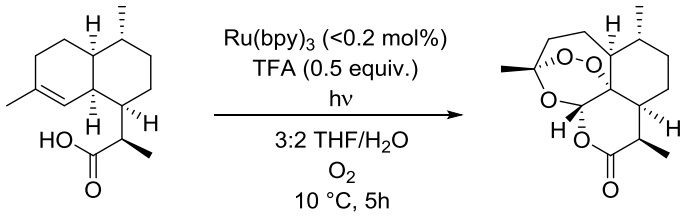
3. Antimalarials

a. What is the mode of action of artemisinin? Explain how this mode of action ensures that artemisinin is selective for parasite-infected red blood cells.



artemisinin

b. Give a mechanism for the photochemical conversion of dihydroartemisinic acid to artemisinin, as shown below.

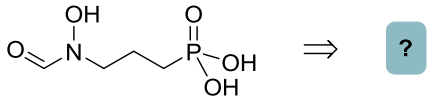


dihydroartemisinic acid

artemisinin
66 %

Nature Chem., **2015**, *7*, 489

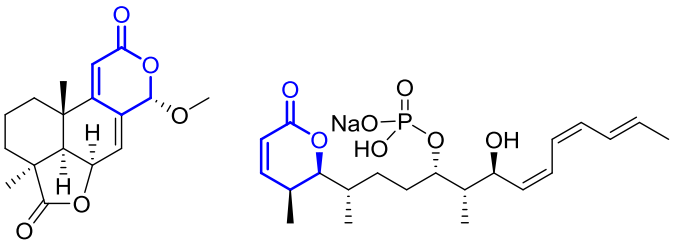
c. Suggest a route for the synthesis of fosmidomycin, an alternative antimalarial agent (shown below). What is the mode of action of fosmidomycin?



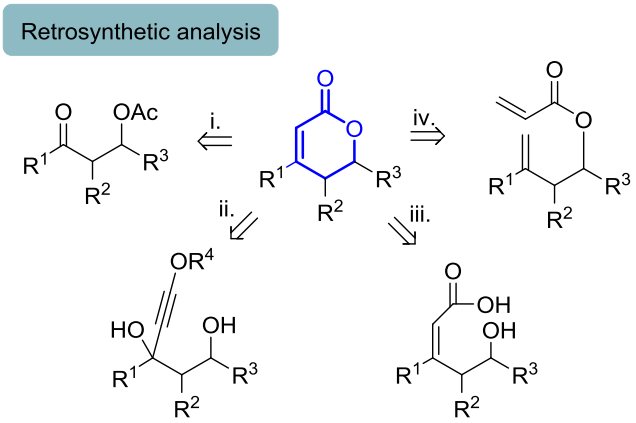
fosmidomycin

4. Drug scaffolds
   A number of medicinally active compounds contain the α,β-unsaturated δ-lactam motif (also known as the 'pentenolide' motif). Shown below are four different retrosynthetic approaches to this motif.

   a. For each retrosynthesis, suggest appropriate conditions for the corresponding forward synthesis.
   b. Which of these approaches would be the most useful in the preparation of LL-Z1271α and cytostatin, respectively?
   c. Comment on the toxicological implications of the four approaches – which possible impurities could present problems for biological testing?

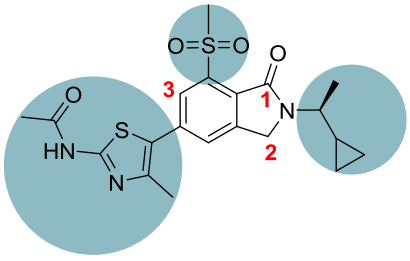


LL-Z1271α **cytostatin**



5. Combinatorial approaches to drug design
   PI3Kγ is an enzyme that plays a key regulatory role in leukocytes; as such it is an important target for the treatment of inflammation and autoimmune disorders. Isoindolones, including the compound below, have been identified as potent PI3Kγ inhibitors.

   a. Plan a short synthesis of the shown isoindolone which allows the highlighted regions to be quickly changed.
   b. How might you change the synthesis to introduce functionality at positions 1, 2, and 3?



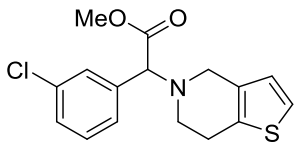
isoindolone scaffold

6. Late-stage functionalisation

   a. C-H activation is an increasingly useful tool for the late-stage functionalisation of bioactive fragments. Give an example of C-H activation with where selectivity is determined by:

      i. Directing groups
      ii. Bond strength
      iii. Steric guidance

   b. In addition to the three C-H functionalisation strategies mentioned above, C-H bonds can also be functionalised by deprotonation (at acidic positions) and both nucleophilic and electrophilic aromatic substitutions (S_NAr and S_EAr, respectively). Annotate all C-H bonds on clopidogrel (an anti-platelet agent) indicating to which of the 6 mentioned reaction pathways each bond is susceptible.



clopidogrel

-directed C-H functionalisation
-C-H functionalisation based on bond strength
-sterically guided C-H functionalisation
-deprotonation
-S_NAr
-S_EAr