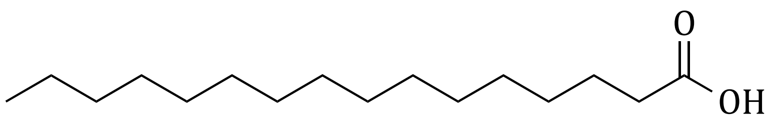
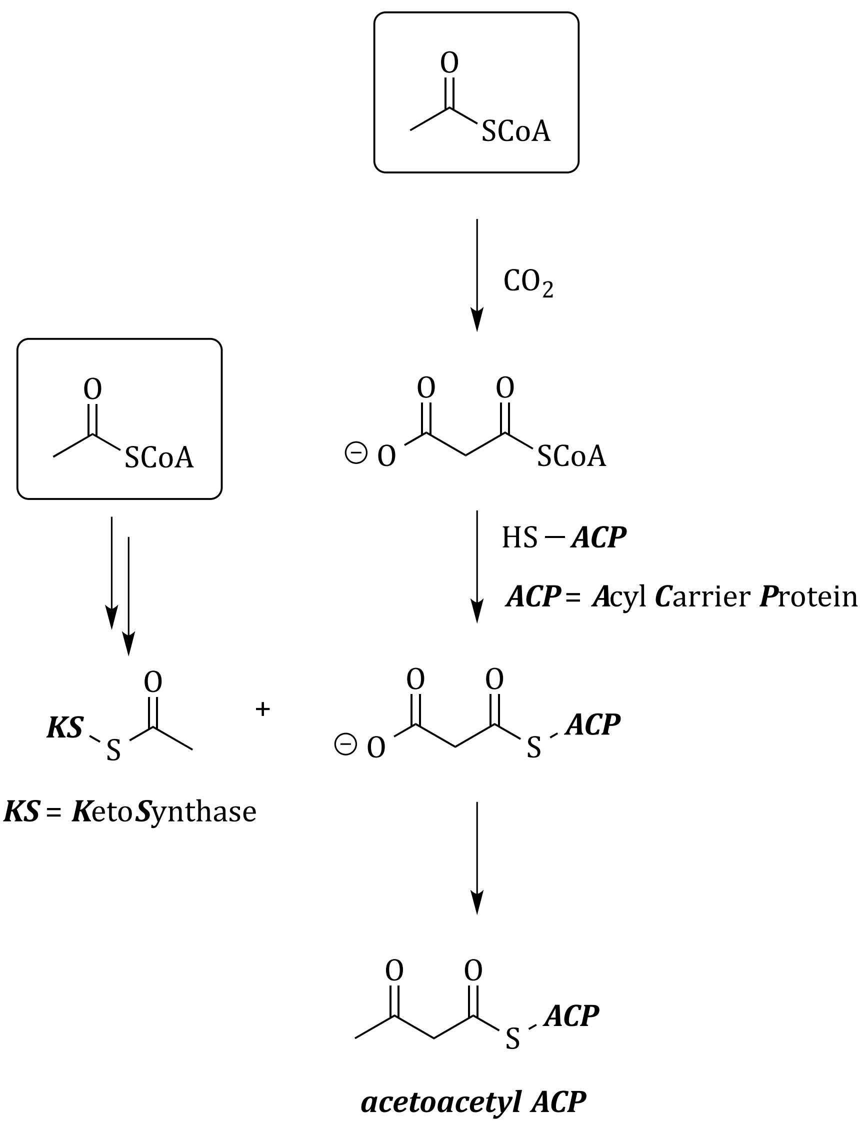
Fatty-Acid Biosynthesis:
1) C-C Bond Formation

The *fatty acids* are long-chain carboxylic acids, like palmitic acid (a saturated fatty acid found in palm oil, among other foods):



palmitic acid

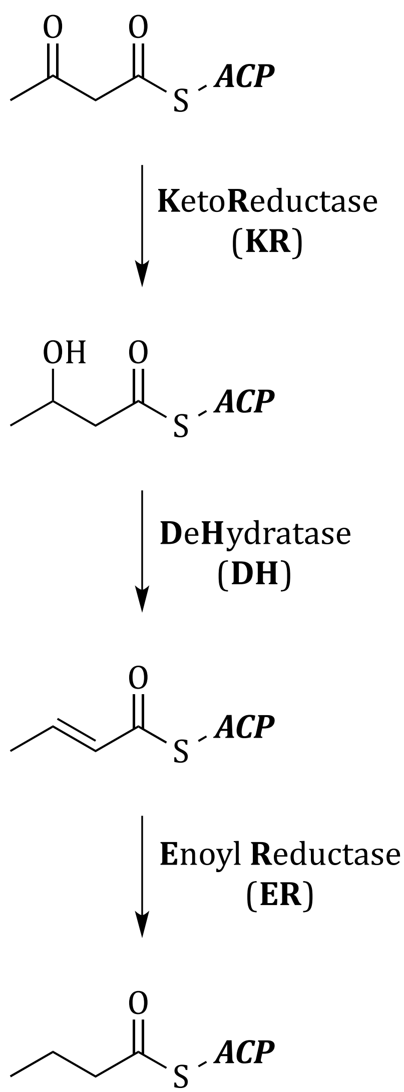
Fatty acids are *also* synthesized from acetyl CoA. The **first steps** in fatty-acid synthesis involve the **formation of a carbon-carbon bond**. Propose a mechanism:



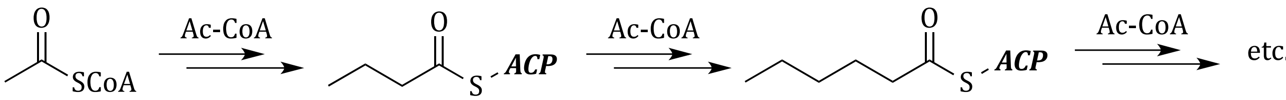
Reading: Section 22.6

Fatty-Acid Biosynthesis:
2) Changing Functional Groups

Now that the new C-C bond has been formed, we must reduce the ketone to the alkane chain we desire. Propose mechanisms for the following steps; note that some *cofactors* will be required:

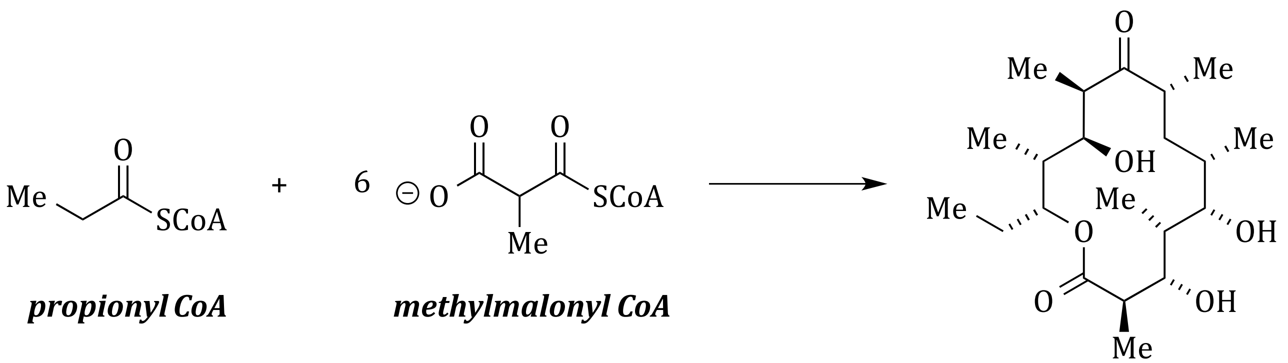


The whole process added 2 carbons to acetyl CoA. The process can be repeated:



Polyketide Biosynthesis

The pathway for synthesizing fatty acids can be modified by *removing* some of the functional-group transformation steps. The resulting products are highly-functionalized natural products known as *polyketides*. One of the best-known polyketides is the antibiotic *erythromycin*. The key intermediate in the synthesis of erythromycin is the macrolactone 6-deoxyerythronolide B, which is synthesized from some very simple molecules:

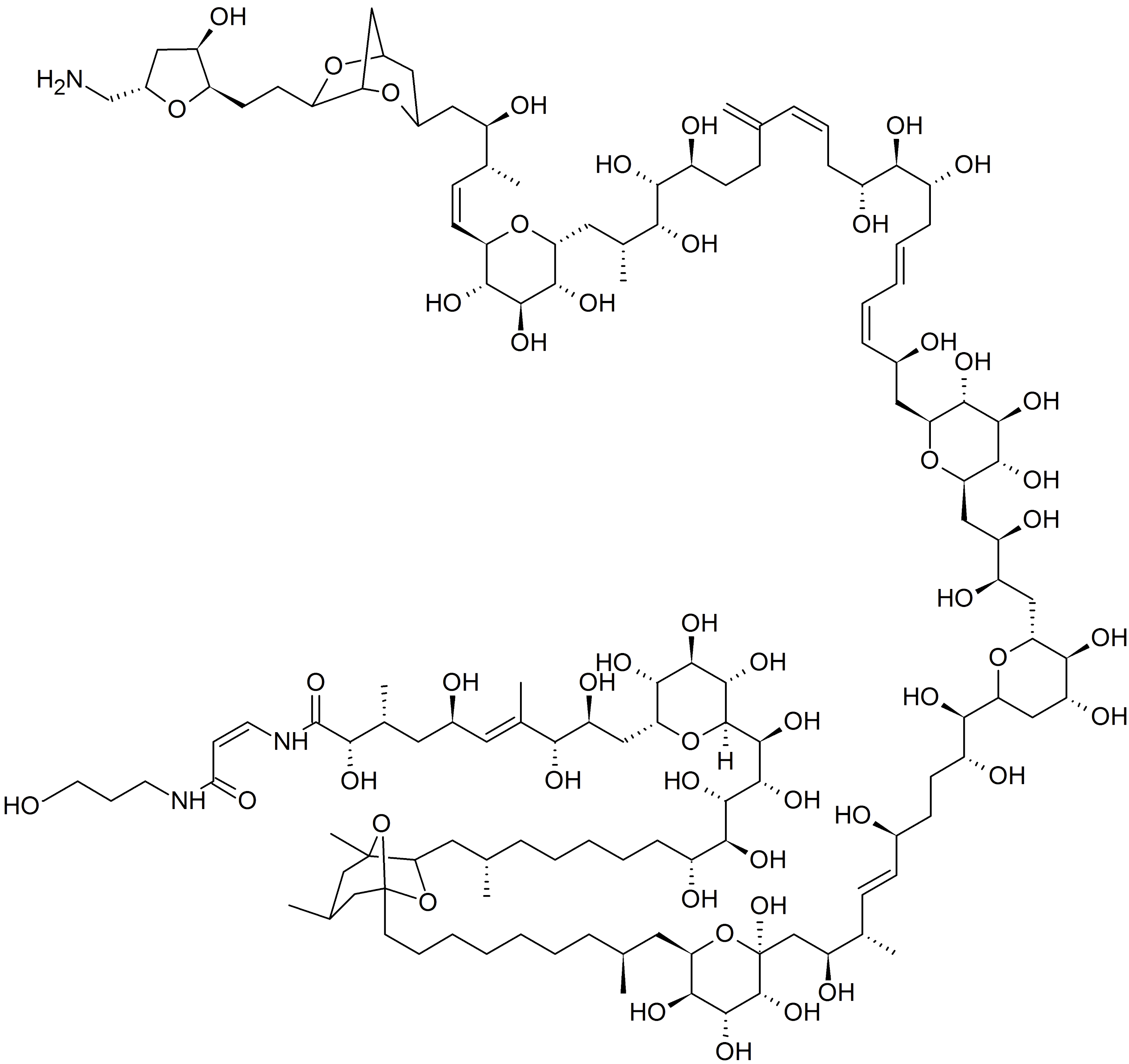


propionyl CoA ***methylmalonyl CoA*** ***6-deoxyerythronolide B***

Can you find which carbons in the starting materials end up as the various carbons in product?

Methylmalonyl CoA is synthesized from propionyl CoA. Propose a mechanism.

Palytoxin

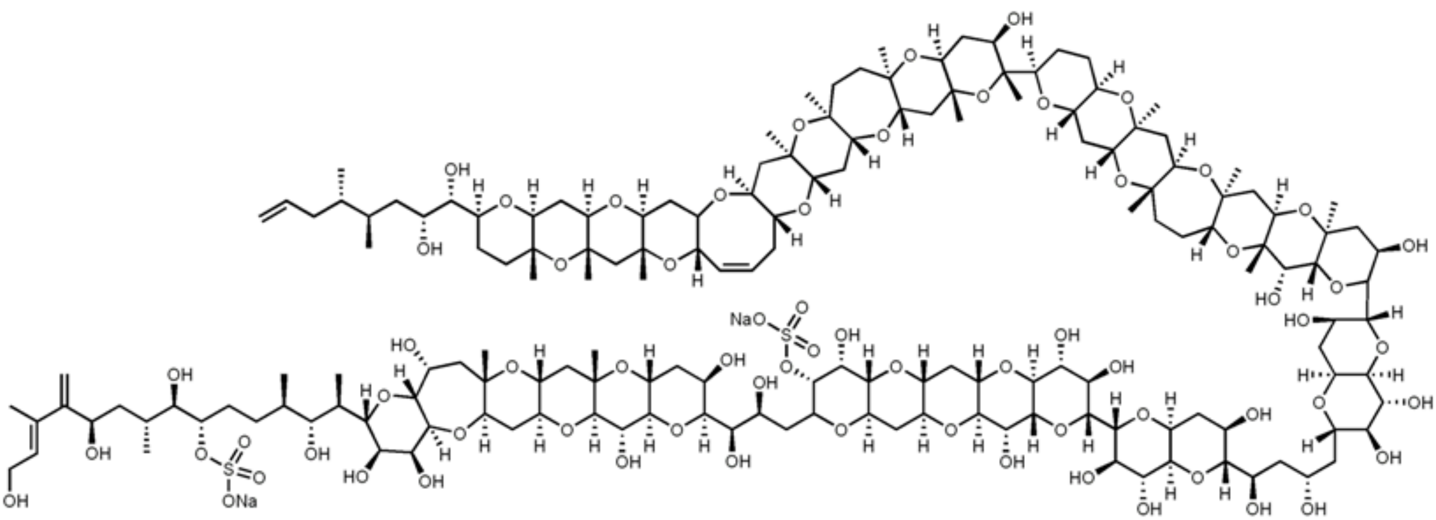


Biosynthesis: ~60 malonate units; synthase complex probably ~100,000 amino acids. Synthesized by a marine coral.

Laboratory synthesis (Kishi): ~65 steps, involved 42 total protecting groups (8 different kinds!). Synthesized by 21 researchers of a period of several years. Probably the most complicated laboratory organic synthesis ever.

This is the apex of laboratory organic synthesis, *not* the apex of biosynthesis!

Maitotoxin



The largest and most complex non-polymeric natural product known ($C_{164}H_{256}O_{68}S_2Na_2$, with 108 stereocenters!)

Isolated from marine plankton (the same species responsible for “red tide”)

Extremely toxic (LD_{50} = 50 ng/kg)!

It’s a *polyketide*! Can you find the carbon chain that threads through the structure?

Why would the organism make such a molecule?

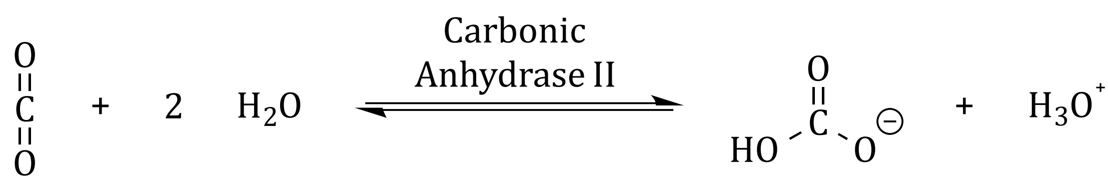
Nature uses organic chemistry to build virtually everything we are… and we can mimic it, to a point.

But can we use organic chemistry to fix biological systems when they fail?

Medicinal Chemistry: An Introduction

One of the most prominent intersections of medicine and organic synthesis is in *drug development.* How do chemists use biological research to design new molecules?

Let's examine a case study.



Malfunctions (overactivity or overexpression, in this case) of enzymes cause problems!

Glaucoma

Epilepsy

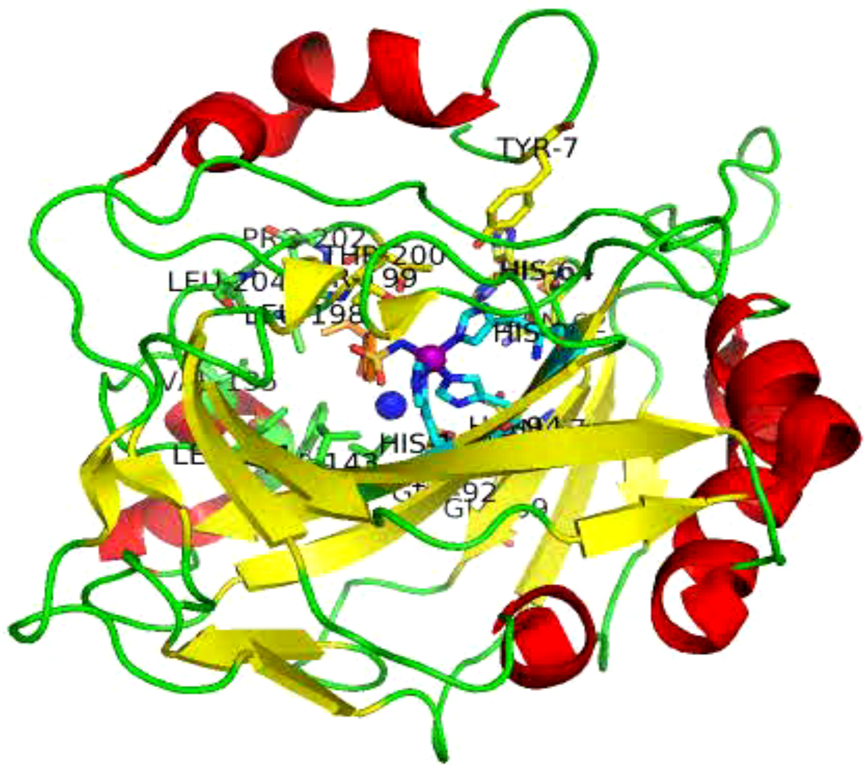
Obesity

Altitude Sickness

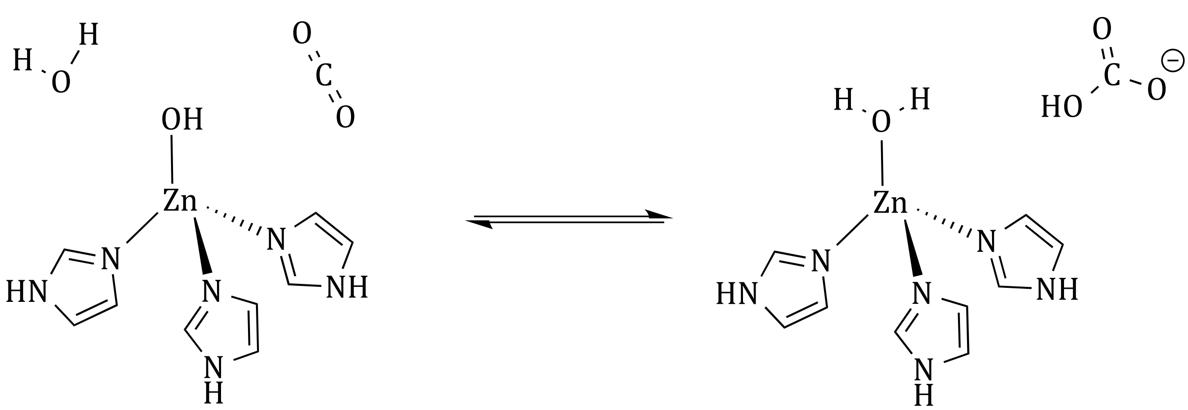
Cancer?

In order to *inhibit* CA II, we should know how it works...

Medicinal Chemistry: Carbonic Anhydrase II

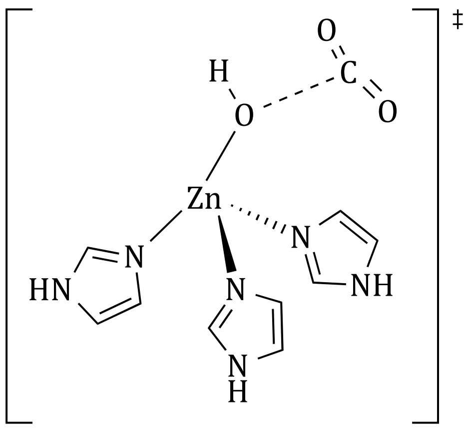


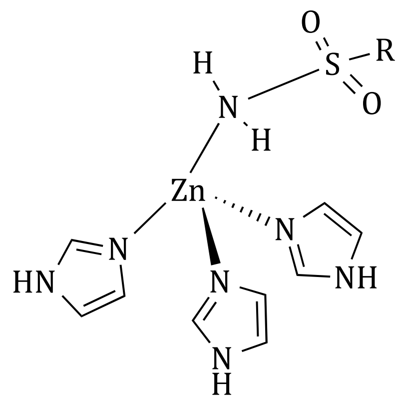
The enzyme active site:



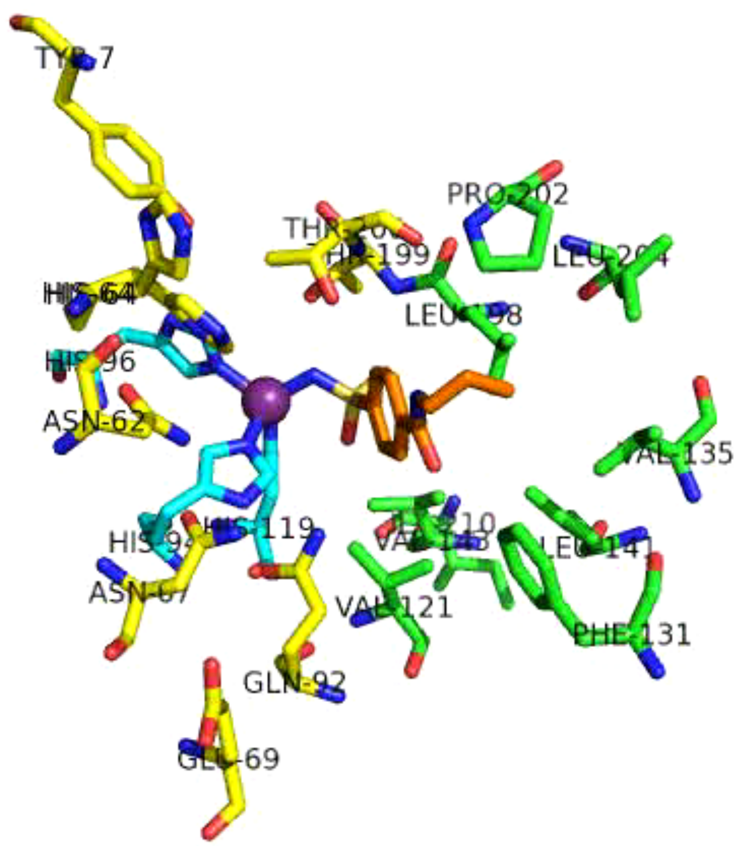
Medicinal Chemistry: Carbonic Anhydrase II

The strategy: Design a molecule that will bind in the active site and prevent CO_2 from entering.



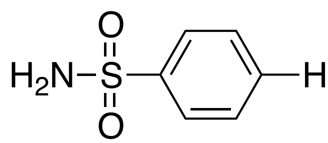


a "transition state mimic"

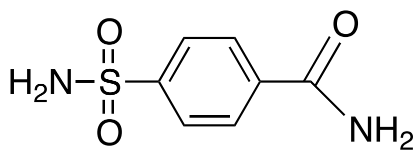


Medicinal Chemistry: Carbonic Anhydrase II

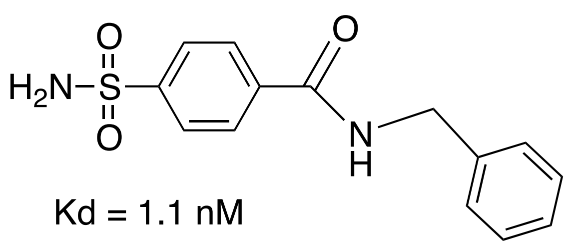
Test the idea….



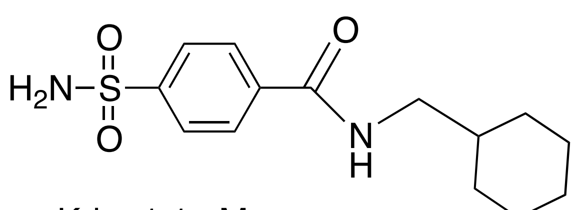
Kd = 200-1500 nM



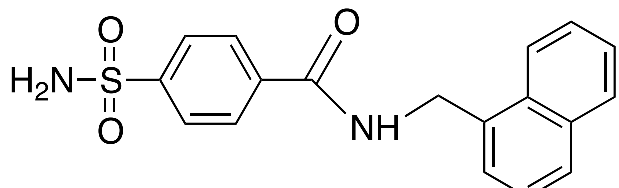
Kd = 120 nM



Kd = 1.1 nM



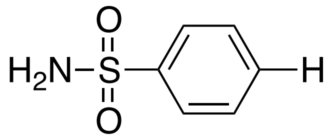
Kd = 1.1 nM



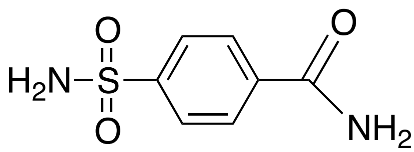
Kd = 0.6 nM

Medicinal Chemistry: Carbonic Anhydrase II

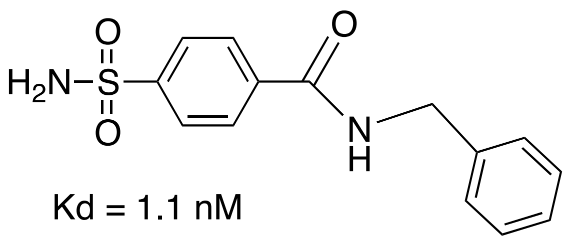
Identify patterns…



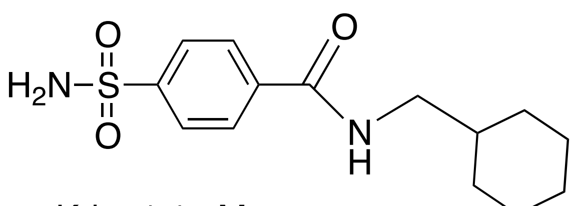
Kd = 200-1500 nM



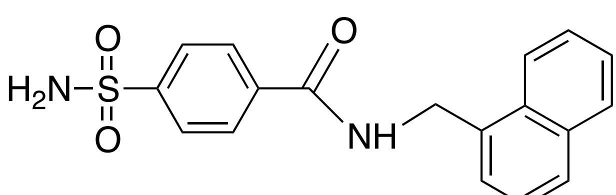
Kd = 120 nM



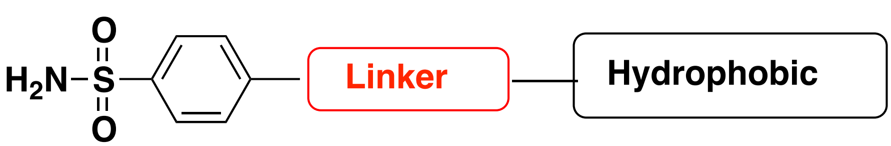
Kd = 1.1 nM



Kd = 1.1 nM

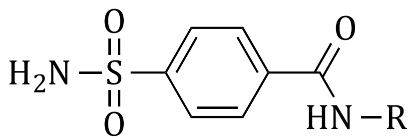


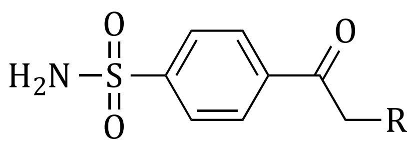
Kd = 0.6 nM

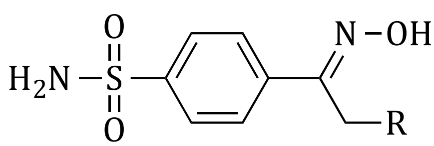


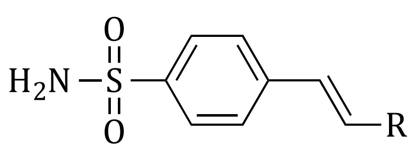
Medicinal Chemistry: Carbonic Anhydrase II

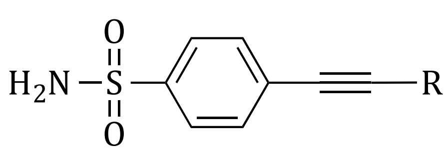
Conceive "isosteric" variations:

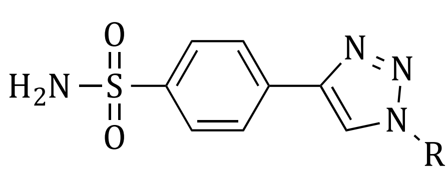






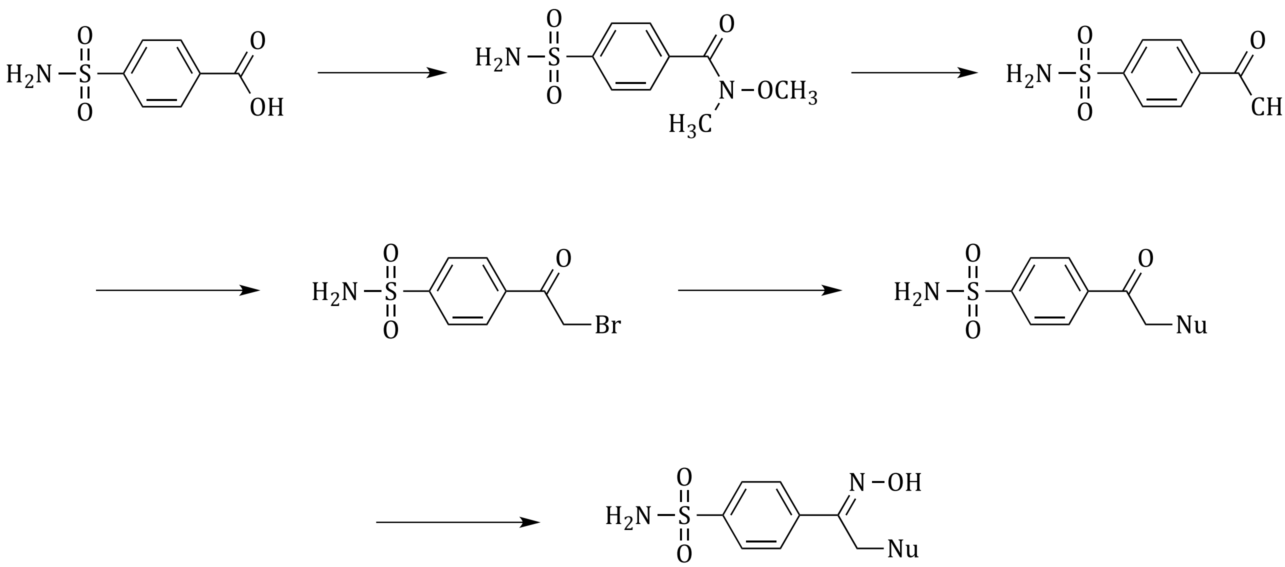






Medicinal Chemistry: Carbonic Anhydrase II

Synthesize and test!



Now it's your turn…