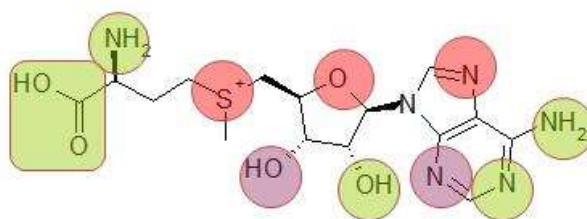


Nucleoside (SAM/SAH) Mimetics

The enzyme co-factor SAM/SAH is thought to be the second most common after ATP, exploited by protein methyltransferases for the transfer of a methyl group. A number of these enzymes have come to the fore as drug targets though strong interest in the field of epigenetics. This includes histone methyltransferases that have been implicated in various human diseases including liver cancer, leukemia, prostate cancer, drug addiction, lung cancer, mental retardation and maintenance of HIV. However, there is wide-ranging interest in SAM/SAH-dependent enzymes beyond epigenetics, including in the fields of anti-bacterials, anti-virals, anti-parasitics, crop-protection and industrial chemical processing. Compounds targeting the SAM/SAH site of these enzymes offer great potential, yet very few such molecules are readily available for the inclusion in screening collections.

A modular approach has been used by ASINEX to synthesize a library of SAM-SAH mimetics. We have developed a number of stereo- and enantio-selective methods for the synthesis of nucleoside-like core intermediates (e. g. mimics of adenosine). These unique intermediates have been extensively decorated by various long chain amines, acids and amino acids to yield the array of >3000 final compounds.

SAM-directed Designs



Key binding motifs:

Amino acid, one sugar OH, N of 6-member ring, and exo-NH₂; (green)

Occasional binding motifs:

Second sugar OH and N of 6-member ring; (purple)

Rare binding motifs:

S⁺, sugar OH or N of 5-member ring; (red)