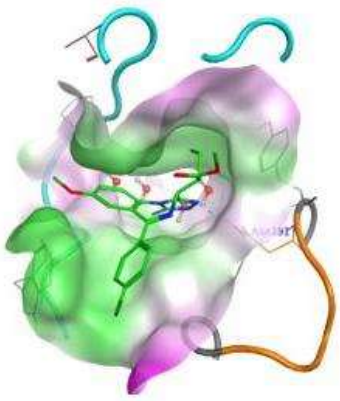
Epigenetic Library

ASINEX

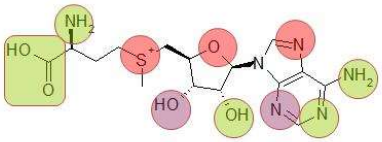
Bromodomain containing proteins

The bromodomain containing proteins represent an important class of histone modification reader proteins that recognize acetylated lysine residues. Structures of 23 of the 61 human bromodomains have been experimentally determined allowing for Structure Based targeted library design.

The orthosteric binding groove that recognizes the acetylated Lys is hydrophobic in character with a conserved Asp residue. ASINEX Bromodomain targeted library is based on molecules that are able to mimic the key interaction with Asp. In turn, scaffold-based selection of analog molecules provide a platform for SAR exploration and early start to selectivity design. Our models are based on the latest available co-crystal structures from the PDB. This is paralleled with 20+ years of medicinal chemistry expertise, delivering designs with outstanding ADMET and PK properties, optimizing chances in hit to candidate development.



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)

Histone Methyltransferases

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. 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 uniquie final compounds.