Design of Libraries towards epigenetic targets

Intended for high probability initial hit discovery for each epigenetic target

Epigentic targets:

DNA -methyltransferases (DNMT)

Histone methyltransferases (HMT)

Histone deacetylase (HDACs)

domain–containing protein histone demethylases (JMJDs)

Bromodomain

Bromo Domain

500 conformations from 28 domains

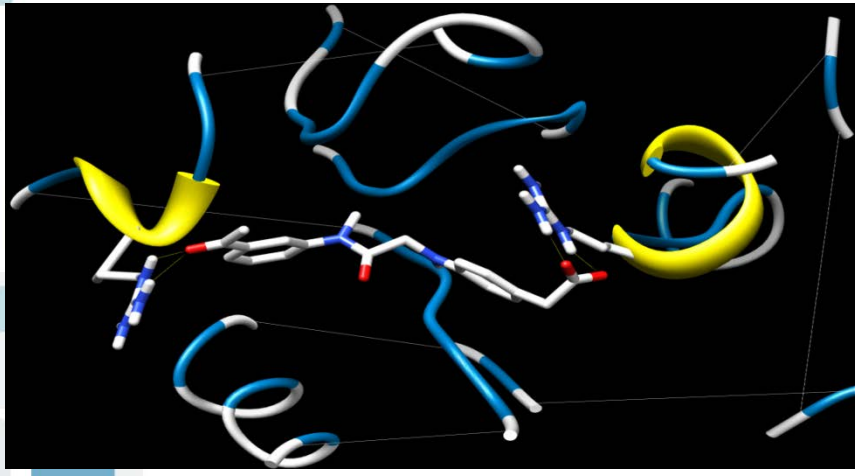
Comparing shapes of binding sites clastering

6 conformations chosen for virtual screening

Virtual screening (Enamine's 1.5 M cmpds) Processing

Library of ~5000 drug-lke cmpds
Validated activity

DNMT



Analysis of all accessible X-ray photographs

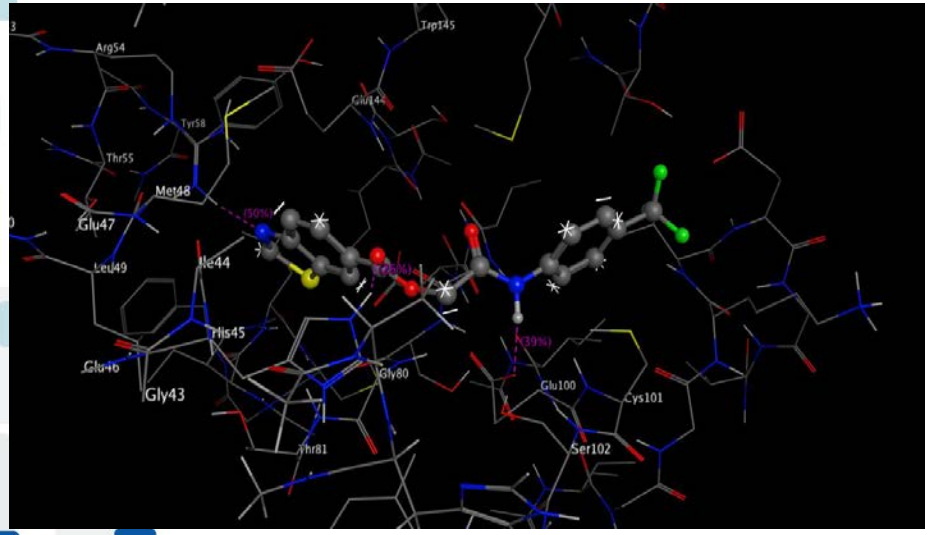
7 centroids were chosen

13K cmpds are selected for docking

Docking, processing, manual filtering

~1.5 K drug-like cmpds

HMT



Analysis of all accessible X-ray photographs

7 centroids were chosen

50K cmpds are selected for docking

Docking, processing, manual filtering

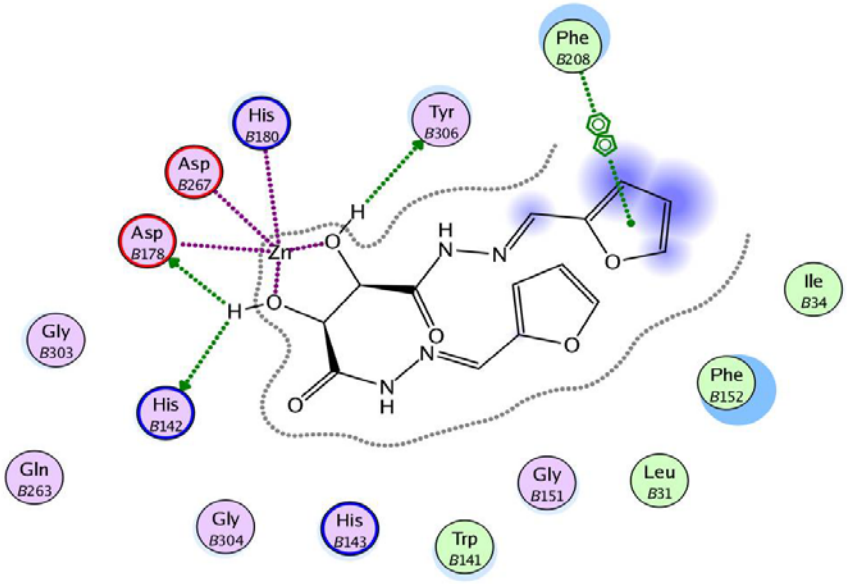
~4.4 K drug-like cmpds

HDACs

Criteria for receptor selection:
the spatial arrangement of AA-residues
of Hys and Asp at the zinc binding site

the size and structure of the catalytic pocket

binding mode of co-crystallized inhibitors
and their location in the catalytic pocket



Analysis of X-ray data

Selection of receptors for docking

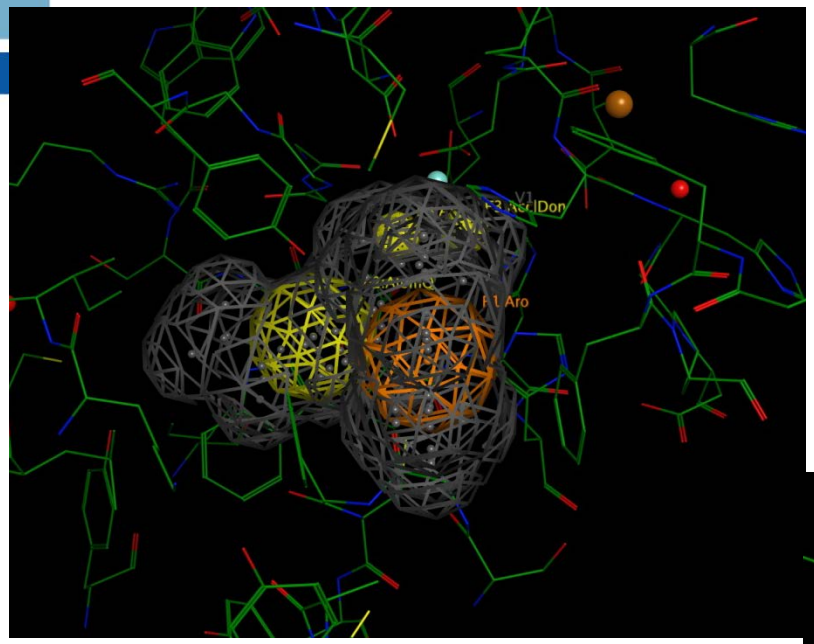
20K cmpds are selected for docking

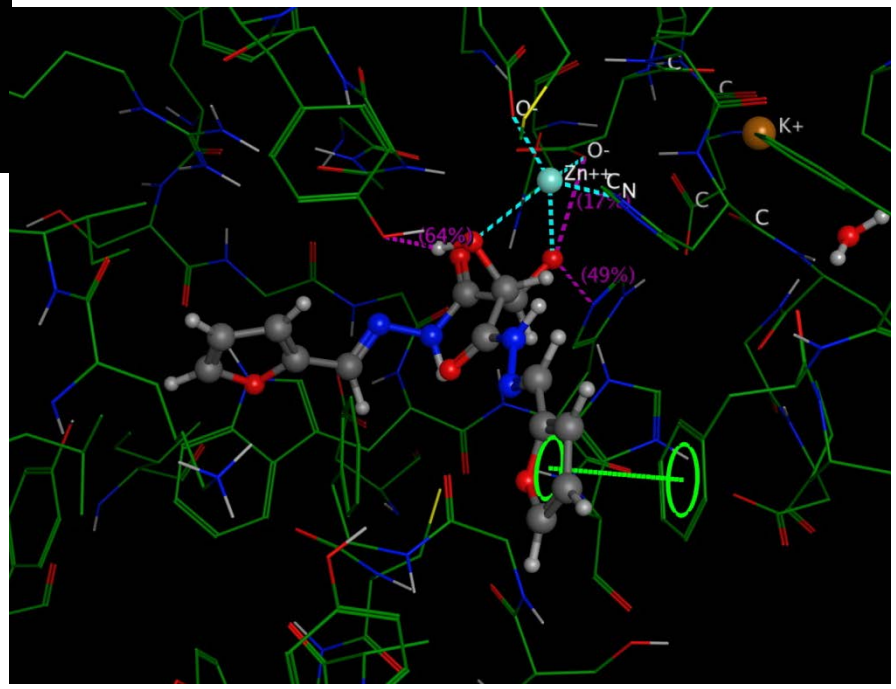
Docking, processing, manual filtering

~4.5 K drug-like cmpds

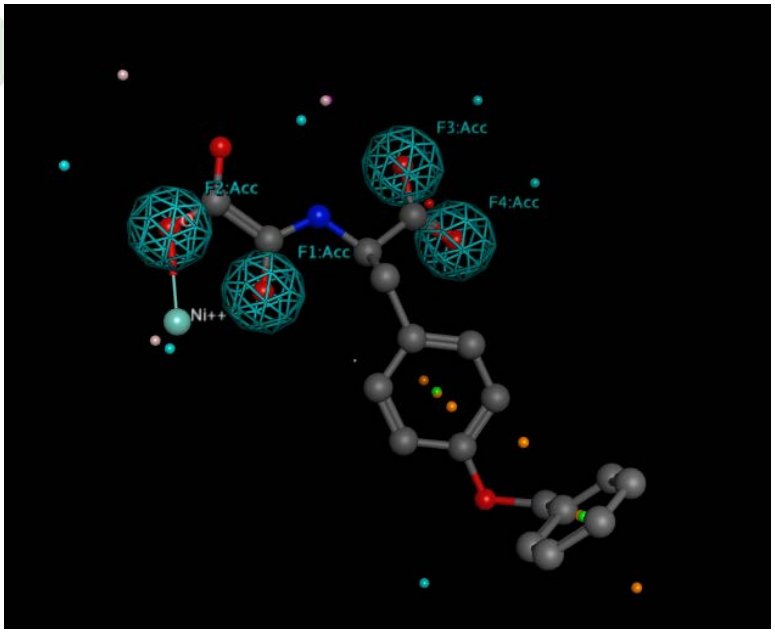
HDACs.

Example of 3-point pharmocophore model and docking result





JMJDs



Analysis of inhibitors with X-ray data

Creation of pharmocophore models

30K cmpds are selected for docking

Docking, processing, manual filtering

~3.2 K drug-like cmpds