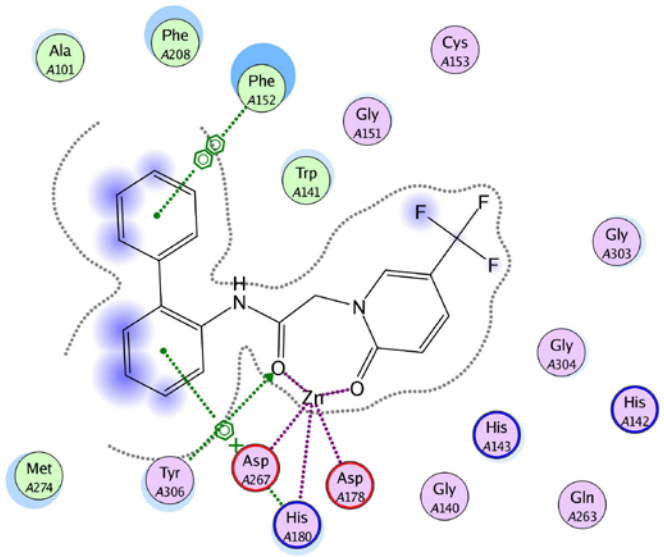
Epigenetics Targeted Libraries

A solid molecular basis for the ways in which heritable information other than DNA sequence can regulate organism function is provided by recent findings in the area of epigenetics. Enamine is proud to provide our customers with compounds libraries focusing on several classes of epigenetic targets: Histone deacetylases (HDACs), Jumonji C -domain-containing histone demethylases (JMJD), Histone methyltransferases (HMT), DNA methyltransferase (DNMT), Bromodomain.

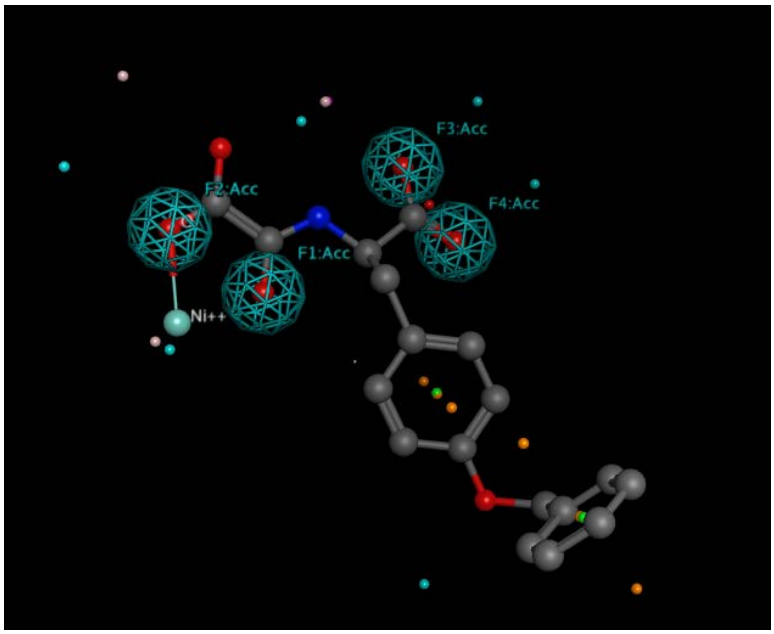
Due to the extremely wide variety among epigenetic target classes, different approaches were used to create Targeted libraries. Each class of epigenetic targets is represented with diverse families, which should be treated individually. When creating the libraries main idea was to make family-specific compound libraries, rather than particular molecular target oriented. Such an approach is based on dividing molecular targets from similar family into bunch of clusters according to the information of their binding sites, including site's spatial structure, amino-acid composition etc., thus allowing us to build a profile describing the family of targets and specificity of their interactions with ligands. This data provides a strong basis for selecting both: the most representative, centroid protein structure and allows building preliminary pharmacophore model to filter out those compounds not having sufficient structural features to show good binding. The next step includes advanced 3D pharmacophore model creation in order to further decrease the number of compounds to be subjected to docking procedure. Next comes docking with the final filtering and inspection of obtained results.
The library for each target class was created utilizing combined method, which includes both ligand-based as well as receptor-based approaches. Thus, generic flow chart may be represented as follows:

1. Analyzing all available structural data (PDB, literature sources etc.)
2. Preliminary pharcophore model creating
3. Advanced pharmacophore search, utilizing key points of interactions, forbidden volumes, molecule volume limits and spatial conformation requirements
4. Molecular docking
5. Precise tuning of obtained results with in-house software packages and visual inspection

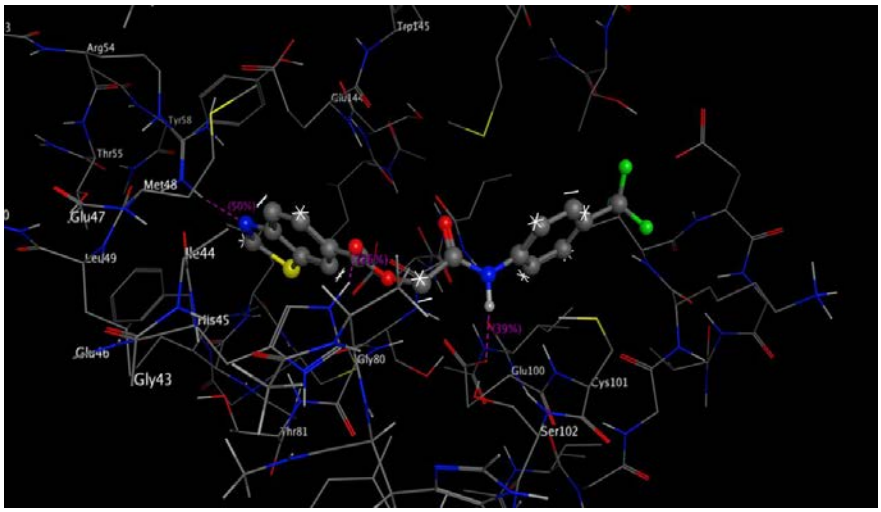
Such a method allows us to create libraries which may come as invaluable tool for early stages study of poorly explored targets, giving an opportunity to reveal compounds with high affinity to the target. Therefore providing solid basis for the further hit exploration step, during which the researcher may focus on increasing the specificity of obtained hit compounds towards other representatives of the targeted family.



HDACs pattern of the ligand-receptor interaction.



JMJD 4-point Pharmacophore model



HMT binding site with an inhibitor.

Targeted Library	Nb of compounds
Histone deacetylases (HDACs)	1 950
Jumonji C -domain-containing histone demethylases (JMJD)	329
Histone methyltransferases (HMT):	2 700
DNA methyltransferase (DNMT)	1 027
Bromodomains	5 546
Sirtuin (SIRT) proteins	592