Focused Epigenetics Set

30,431 Compounds

Medicinal and Computational Chemistry Dept., ChemDiv, Inc., 6605 Nancy Ridge Drive, San Diego, CA 92121 USA, Service: +1 877 ChemDiv, Tel: +1 858-794-4860, Fax: +1 858-794-4931, Email: ChemDiv@chemdiv.com

In designing our 'epigenetics' focused set, we aimed at several specific families of epigenetic proteins, namely:

- Writers (Lys, Arg or DNA methyltransferases)
- Erasers (HDACs and SirTs) and
- Readers (proteins/domains binding PTMs, ex. Bromodomains)

Specifically, three key strategies went into consideration while assembling small molecule modulators of these target families, namely:

- Known/'suspected' ligands (ligand-based selection)
- 'Vicarious' structure-function information (mutagenesis, homology/isoform-based structural modeling, etc.) and
- 'Wet' structural biology (crystallography or NMR) yielding more 'accurate' modeling environment for the identification of pharmacophore models and 'hot spots'

In addition, we did consider drug-/lead-like character of a ligand (MW, lipophilicity, cell permeability potential) including potential liabilities (RedOx, covalent bond formation, 'active reactive' species, etc).

A representative selection of targets analyzed and populated with focused small molecule ligands and their analogues is as follows:

- HDACs class I-IV: the most studied family of epigenetic proteins to-date; importantly, we did include both pan- as well as 'preferential'- (ex., class IIa) inhibitors; depending on your screening and ultimately therapeutic needs, these could be of utility;
- Notably, whereas there are several well characterized Class III HDAC (SirT) inhibitors, the respective direct activators are still lacking; in order to compensate for this 'deficiency', we included a subset of small molecules that were modeled into our internal

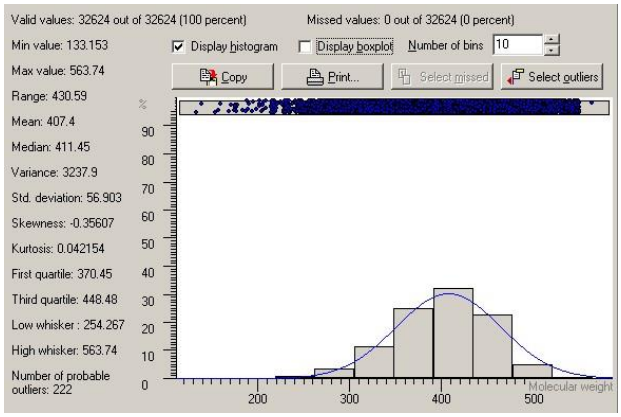
model of SirT1 reflective of a multitude of pharmacological ideas including allosteric modulation;

- HAT (Histone N-Acetyl Transferases), ex. p300, Gcn5, EZH2, EHMT2, DOT1L, SU(VAR)3-9
- Histon Demethylases, ex. KDM1A, KDM5B, JMJD2, H3K27
- PARP1
- PRMTs (protein arginine methyltransferases), ex. CARM1, PRMT4, PRMT5; multiple series were modeled into the key protein-protein interaction PRMT5:MeP50 to yield a subset of compounds for this specific interface

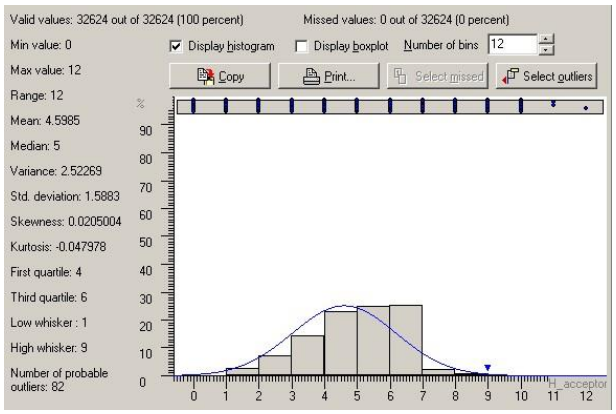
Bromodomains, ex. BRD2-4, BRDT, PHIP, WDR9, TAF1, TIF1

The drug-like properties of the 'epigenetics' focused set confirm following figures illustrating the physico-chemical properties of compound selected.

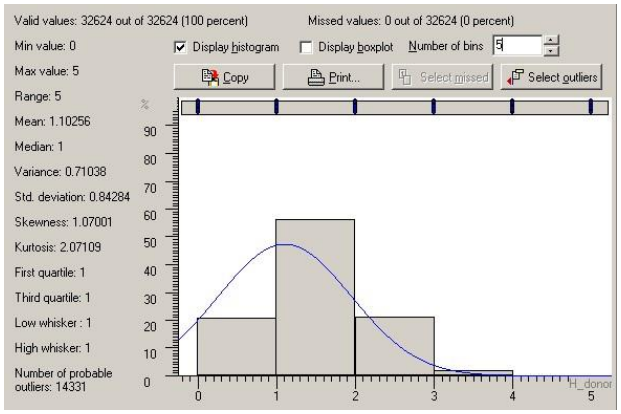
Molecular weight:



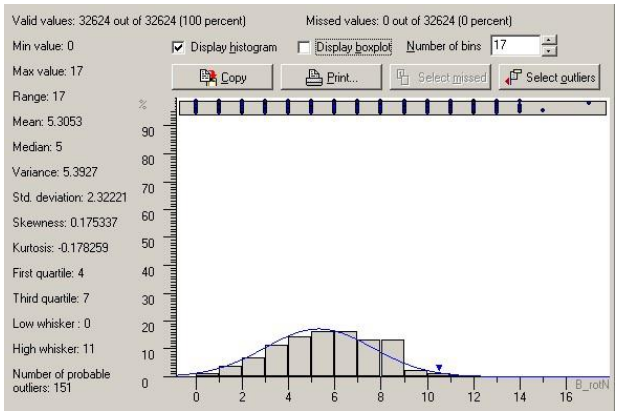
H_acceptors:



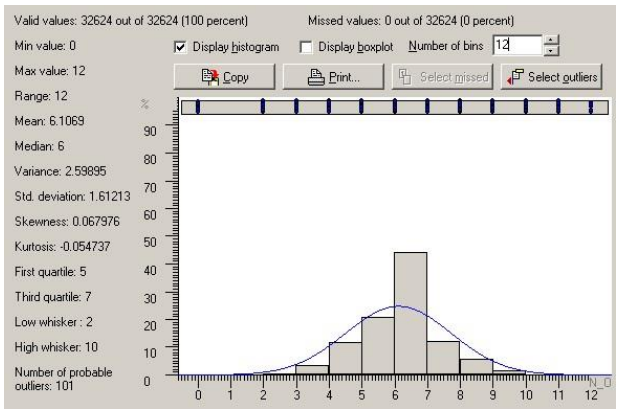
H_donors:



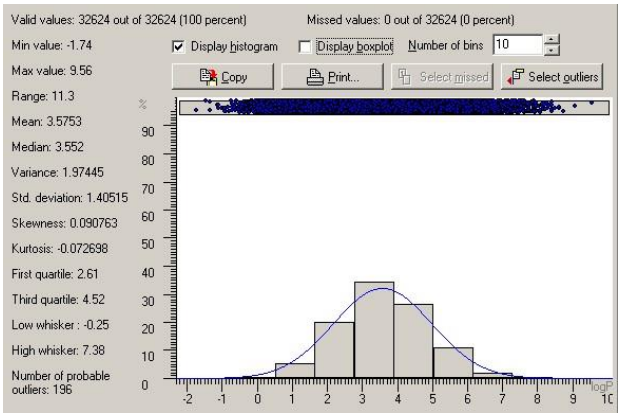
Rotatable bonds:



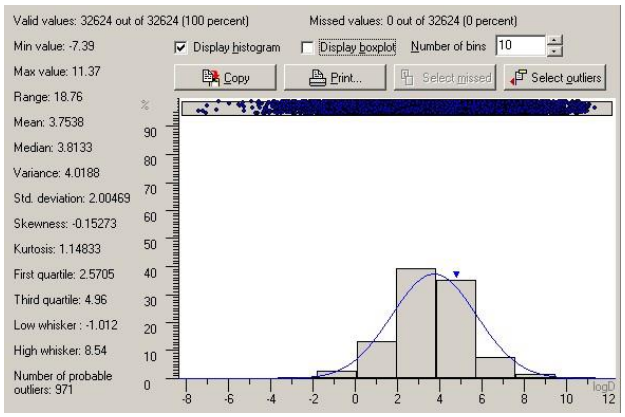
Sum of atoms N and O:



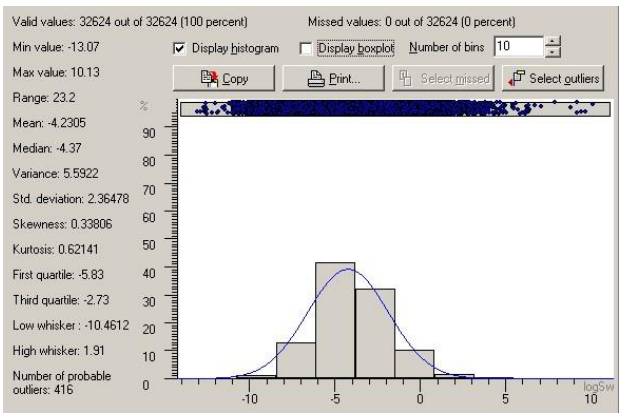
LogP:



LogD:



LogSw:



PSA: