Library of MEF2-HDAC (class II) modulators.

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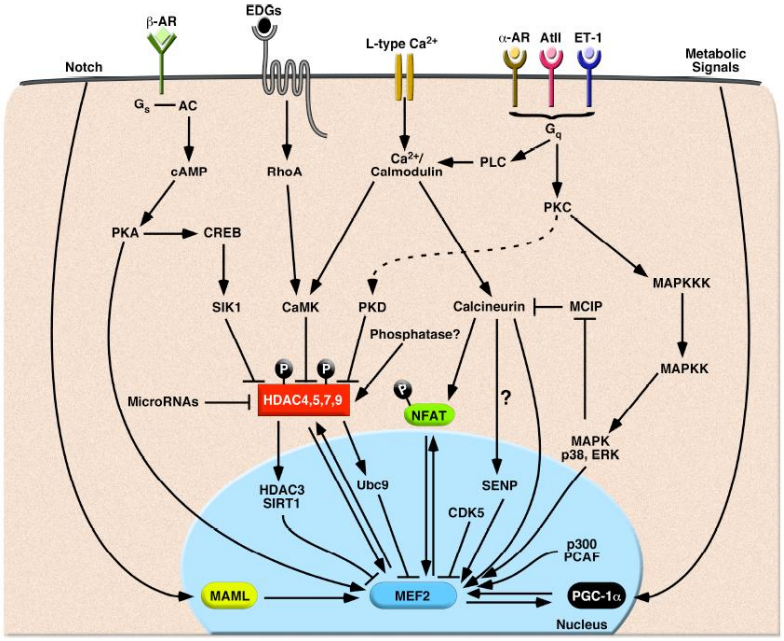
Description

The myocyte enhancer factor 2 (MEF2) transcription factor acts as a lynchpin in the transcriptional circuits that control differentiation of diverse cell types including skeletal, cardiac and smooth muscle cells, neurons, chondrocytes, lymphocytes, endothelial cells and neural crest cells. Class II histone deacetylase (HDAC) proteins bind to MEF2 and regulate MEF2 activity in a calcium-dependent manner in response to various signaling cascades.

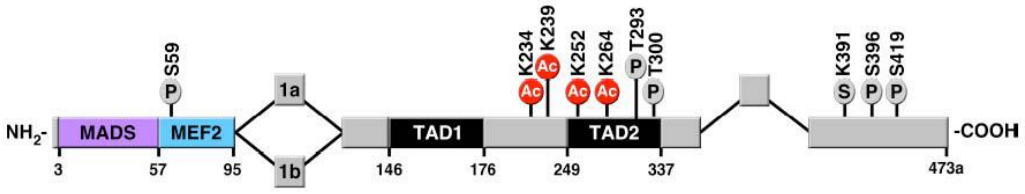
The crystal structure of a HDAC9/MEF2/DNA complex reveals that HDAC9 binds to a hydrophobic groove of the MEF2 dimer.

ChemDiv proposes the new library of MEF2-HDAC (class II) inhibitors/modulators. This library represents a selection of drug-like compounds aimed at modulating protein-protein interaction (PPI) of MEF2 with HDAC 4, 5, 7 or 9 involved in significant physiological processes. Library has been assembled using in house structural biology insight, molecular stimulation-modeling, virtual screening of ChemDiv's novel chemistries and medicinal chemistry filtering/ranking of the resulting hits. A representative example of a 'druggable' 'hot spots' included specific topological features of the MEF2-HDAC interaction (e.g. helix- or beta-sheet mimetics).

Important information inspired the library design

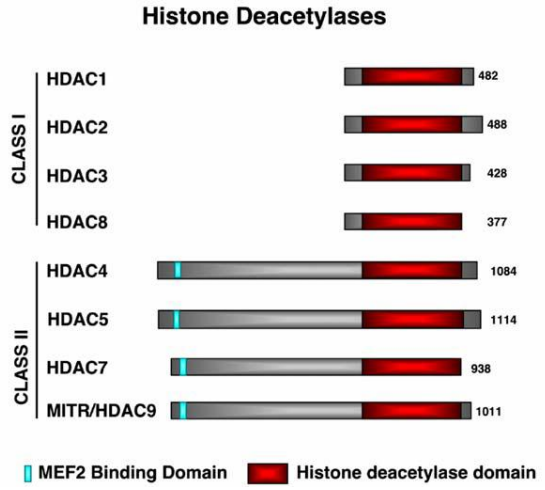


Signaling pathways regulating MEF2 activity.
Schematic diagram of signaling pathways that positively (arrows) or negatively (perpendicular lines) regulate MEF2 activity.



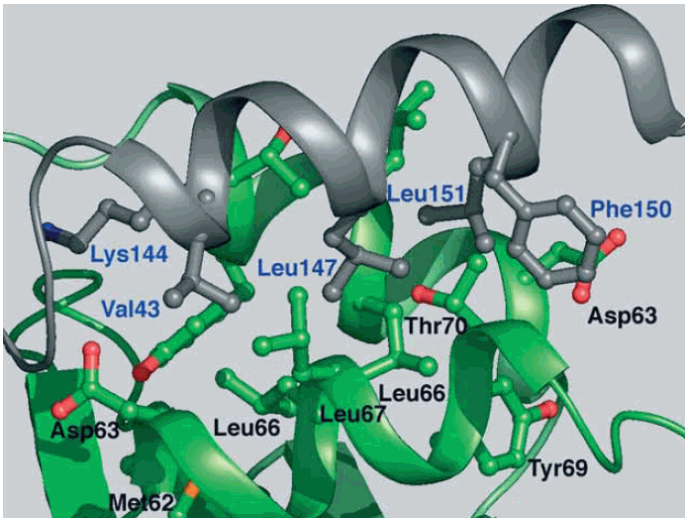
Domain structure of human MEF2C.

MEF2C contains an N-terminal MADS-box and MEF2 domain, which together mediate DNA-binding and co-factor interactions. The C-terminal region of MEF2C contains the transactivation domains (TAD) and this region is subject to alternative splicing. Ac, Acetyl; P, phosphate; S, sumo.



Class I and II HDAC family domain structure.

Class I HDACs are almost completely comprised of a deacetylase domain (red), while class II HDACs possess an N-terminal extension containing a MEF2 binding domain (blue)



Structural and biochemical analyses of the HDAC9/MEF2/DNA complex
[J. Mol. Biol. (2005) 345, 91–102]

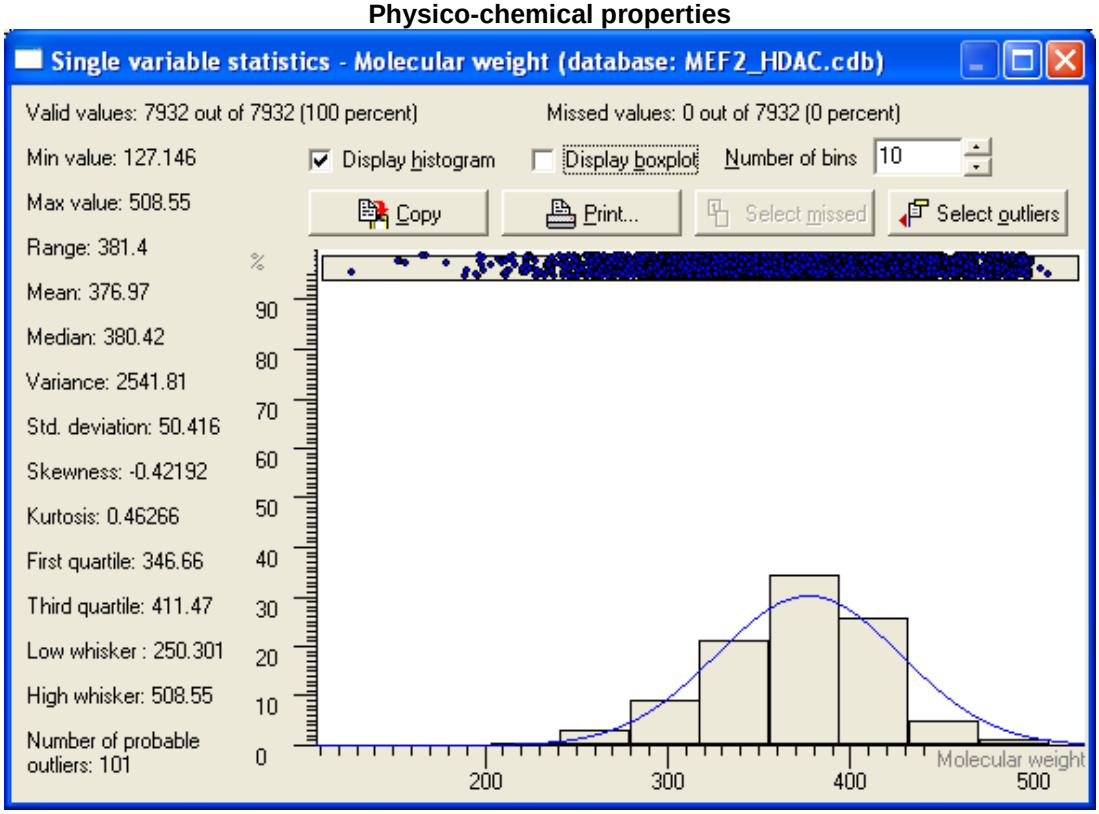
The MEF2-binding motif of HDAC9 binds MEF2 as an amphipathic helix (gray). The hydrophobic face of the helix, composed of ***Val143***, ***Leu147***, ***Phe150***, and ***Leu151***, fits snugly into a hydrophobic groove formed by helix H2 and the central β sheet. At the center of the HDAC9/MEF2 interface, the side-chain of ***Leu147*** inserts into a hydrophobic pocket formed by ***Leu66***, ***Tyr69*** and ***Thr70*** of each MEF2 monomer. The long aliphatic side-chains of polar resides surrounding ***Leu147***, including ***Lys144***, ***Lys146*** and ***Gln148***, also make extensive van der Waals contacts to MEF2. The interface is largely hydrophobic and the intimate surface complementarity is likely the main source of binding specificity

Variable statistics for 7,932 compounds from MEF2_HDAC library.

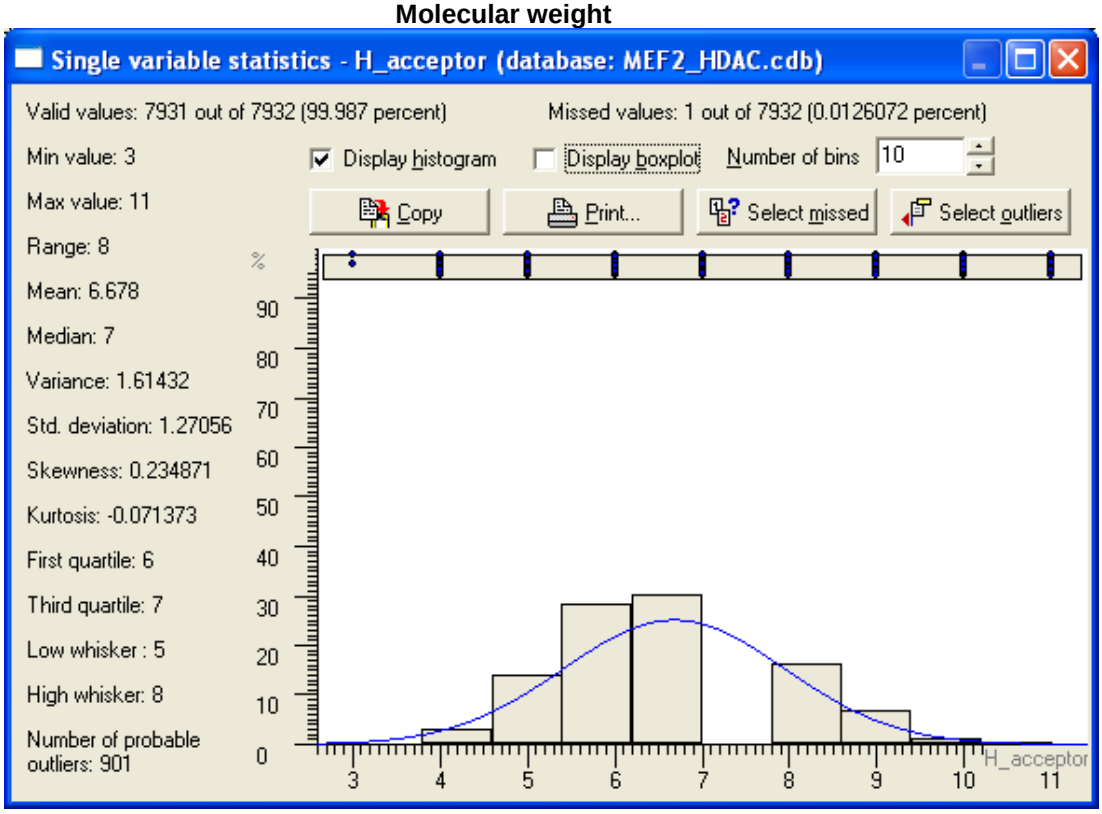
Diversity **0,7397**
The number of screens in dataset **2085**
Number of unique heterocycles **82**
The number of Scaffolds **83**
Singletons **0**
Novelty: The number of compounds synthesized (%) per year

date	number	%
2013	4692	59.15
2012	3240	40.85

Physico-chemical properties



Molecular weight



HBA

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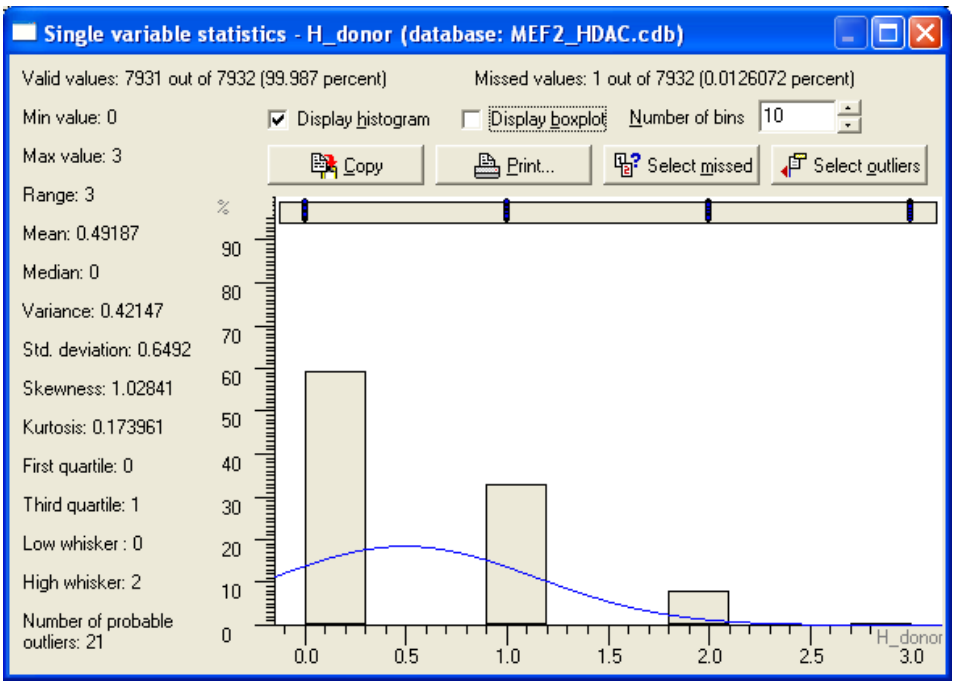
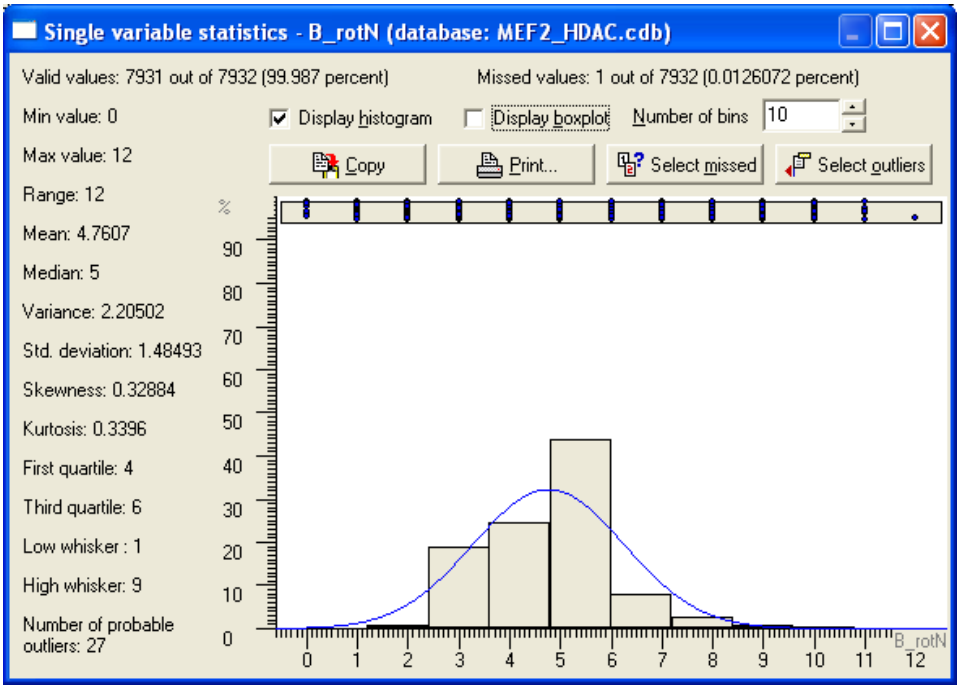


HBD



Rotatable Bonds

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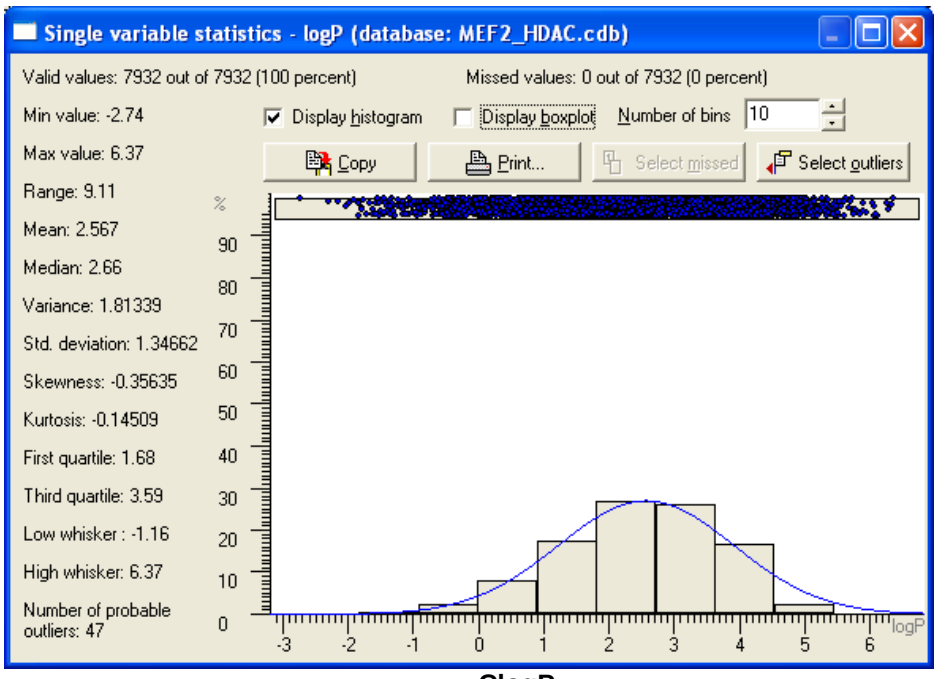
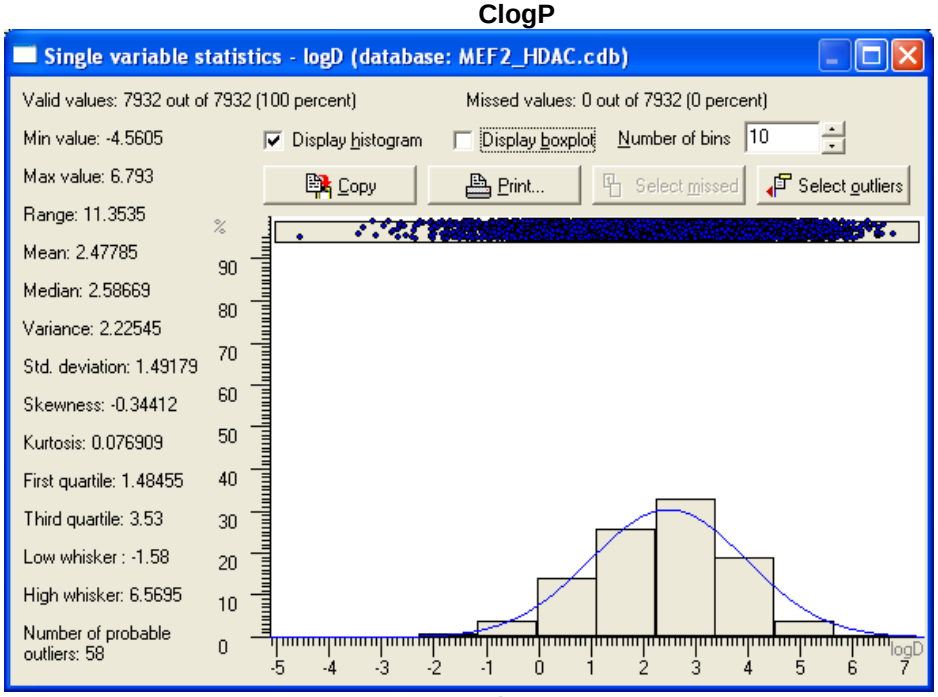

Single variable statistics - logP (database: MEF2_HDAC.cdb)
Valid values: 7932 out of 7932 (100 percent)
Missed values: 0 out of 7932 (0 percent)
Min value: -2.74
Max value: 6.37
Range: 9.11
Mean: 2.567
Median: 2.66
Variance: 1.81339
Std. deviation: 1.34662
Skewness: -0.35635
Kurtosis: -0.14509
First quartile: 1.68
Third quartile: 3.59
Low whisker : -1.16
High whisker: 6.37
Number of probable outliers: 47
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
%
90
80
70
60
50
40
30
20
10
0
-3
-2
-1
0
1
2
3
4
5
6
logP

ClogP


Single variable statistics - logD (database: MEF2_HDAC.cdb)
Valid values: 7932 out of 7932 (100 percent)
Missed values: 0 out of 7932 (0 percent)
Min value: -4.5605
Max value: 6.793
Range: 11.3535
Mean: 2.47785
Median: 2.58669
Variance: 2.22545
Std. deviation: 1.49179
Skewness: -0.34412
Kurtosis: 0.076909
First quartile: 1.48455
Third quartile: 3.53
Low whisker : -1.58
High whisker: 6.5695
Number of probable outliers: 58
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
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90
80
70
60
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40
30
20
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-4
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-1
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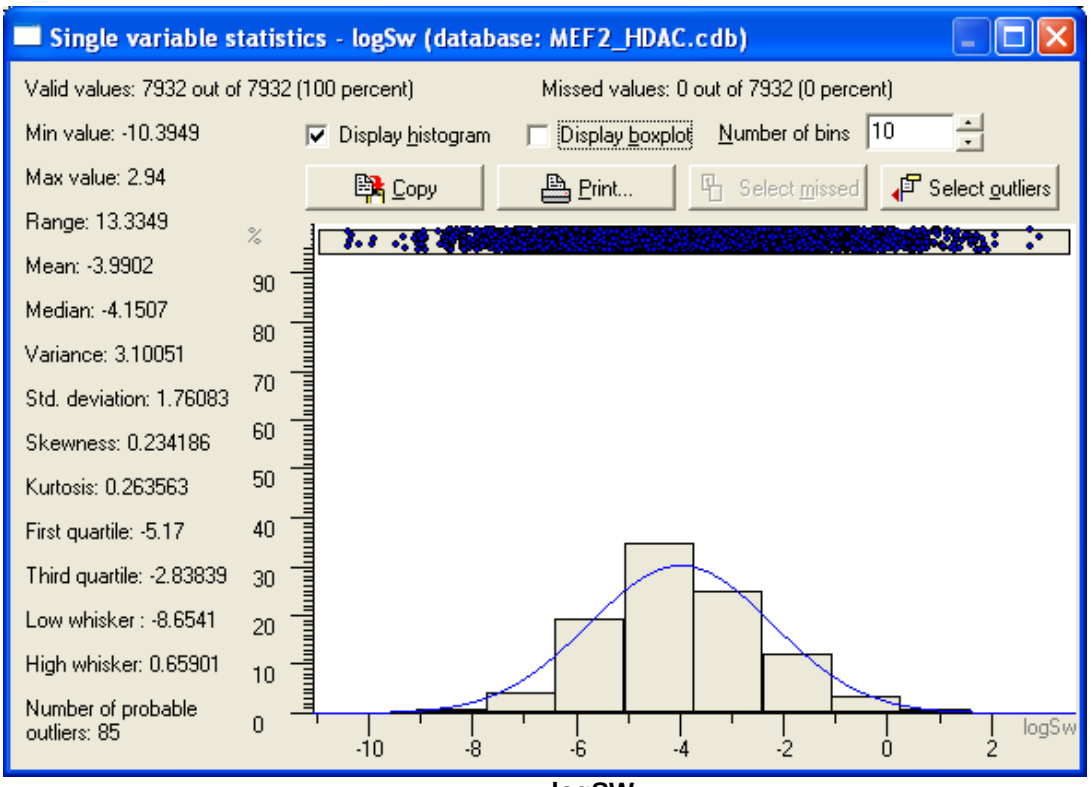
1
2
3
4
5
6
7
logD

ClogD


Single variable statistics - logSw (database: MEF2_HDAC.cdb)
Valid values: 7932 out of 7932 (100 percent)
Missed values: 0 out of 7932 (0 percent)
Min value: -10.3949
Max value: 2.94
Range: 13.3349
Mean: -3.9902
Median: -4.1507
Variance: 3.10051
Std. deviation: 1.76083
Skewness: 0.234186
Kurtosis: 0.263563
First quartile: -5.17
Third quartile: -2.83839
Low whisker : -8.6541
High whisker: 0.65901
Number of probable outliers: 85
Display histogram
Display boxplot
Number of bins
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Select missed
Select outliers
%
90
80
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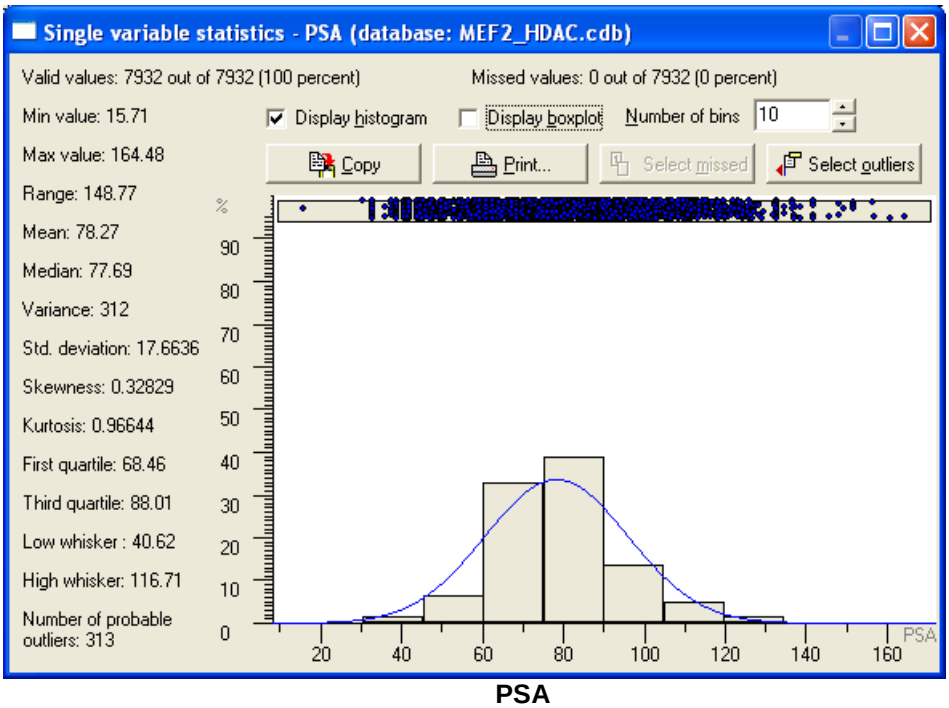
0
2
logSw

logSW


Single variable statistics - PSA (database: MEF2_HDAC.cdb)
Valid values: 7932 out of 7932 (100 percent)
Missed values: 0 out of 7932 (0 percent)
Min value: 15.71
Max value: 164.48
Range: 148.77
Mean: 78.27
Median: 77.69
Variance: 312
Std. deviation: 17.6636
Skewness: 0.32829
Kurtosis: 0.96644
First quartile: 68.46
Third quartile: 88.01
Low whisker : 40.62
High whisker: 116.71
Number of probable outliers: 313
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
%
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100
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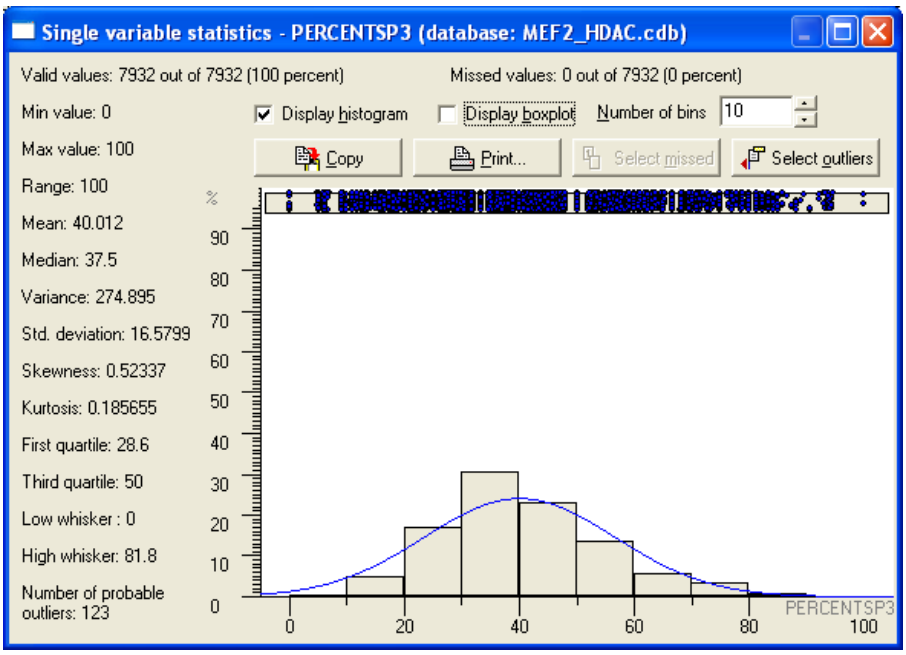
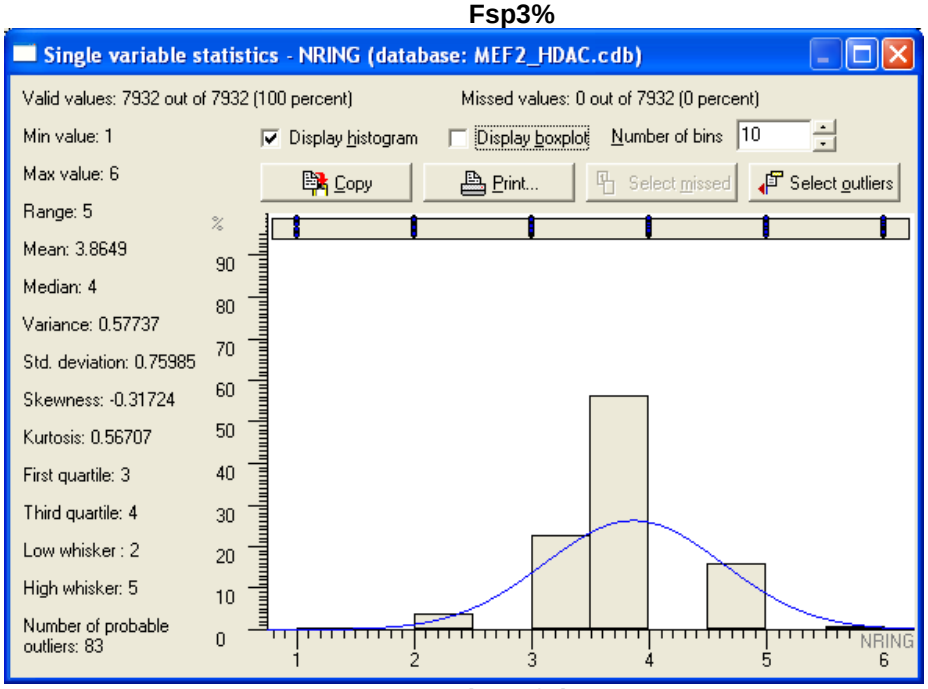
140
160
PSA

PSA



Fsp3%



Number of rings

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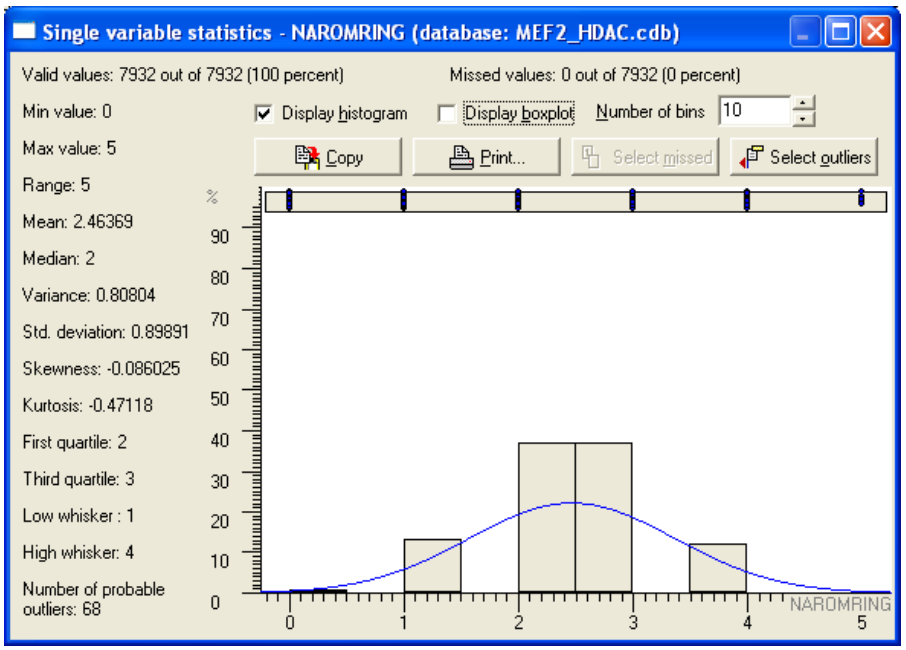
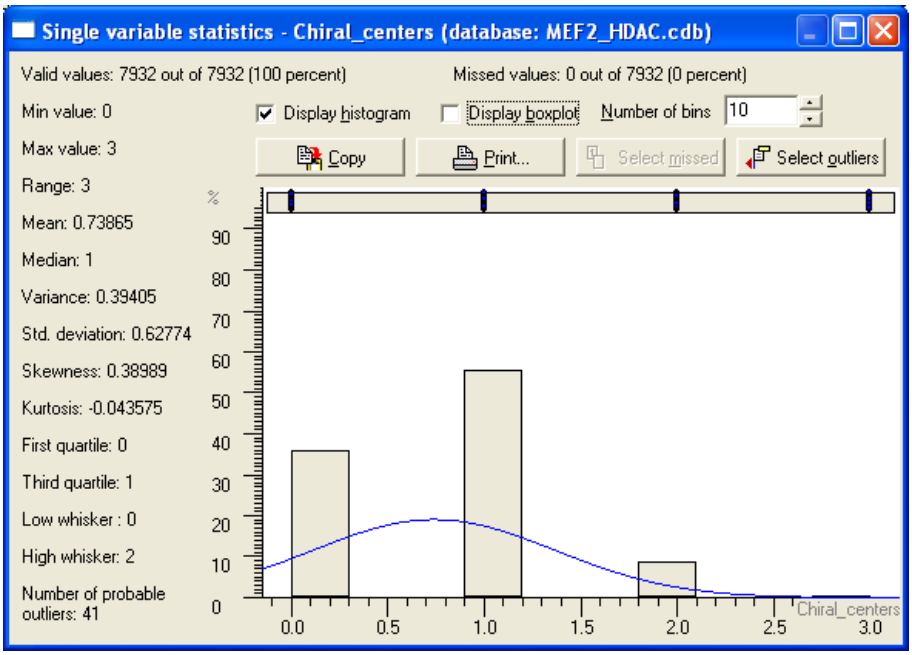


Number of aromatic rings



Number of chiral centers

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