Annotated library of MDM2-p53 interaction inhibitors

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Description

The p53 tumor suppressor protein is a transcriptional factor that plays a key role in regulation of several cellular processes, including the cell cycle, apoptosis, DNA repair, and angiogenesis. Activation of the p53 protein protects the organism against the propagation of cells that carry damaged DNA with potentially oncogenic mutations.

The MDM2 (murine double minute 2) oncogene is the primary cellular negative regulator of p53. In unstressed cells, a negative feedback loop maintains both p53 and MDM2 at very low levels. MDM2 is transcriptionally activated by p53, and the activity of p53 is regulated by MDM2 through three main mechanisms. First, MDM2 represses p53 transcriptional activity by binding to the p53 transactivation domain. Second, MDM2 transports p53 from the nucleus to the cytosol. Finally, MDM2 functions as an E3 ubiquitin ligase and facilitates the degradation of both p53 and itself in the cellular 26S proteasome.

The interaction between p53 and MDM2 is conformation-based and is tightly regulated on multiple levels. Disruption of the p53-MDM2 complex by multiple routes is the pivotal event for p53 activation, leading to p53 induction and its biological response. Because the p53-MDM2 interaction is structurally and biologically fairly understood, the design of small peptidomimetic molecules that disrupt or prevent it has become an important target for the treatment of cancer and other human diseases.

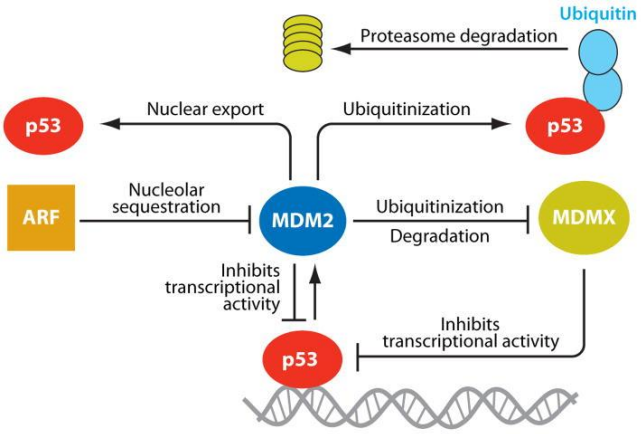
Major advances have been made in the design of small-molecule inhibitors of the MDM2-p53 interaction in recent years, and several compounds have moved into preclinical and Phase I development.

Unfortunately, most of the known modulators of MDM2 have non-optimal physico-chemical properties, and do not seem drug-like.

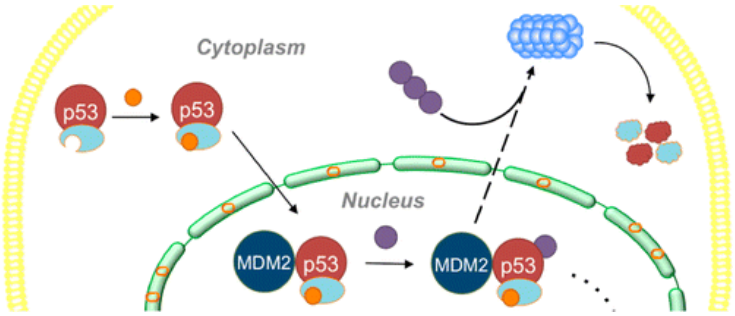
ChemDiv proposes the new library of drug-like MDM2-p53 interaction inhibitors: This library represents a selection of drug-like compounds aimed at modulating protein-protein interaction (PPI) of MDM2 with protein p53 involved in tumorogenesis. Library has been assembled using ChemDiv's in house structural 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 MDM2-p53 interaction. For example, the cocrystal structure reveals that three amino acid residues of p53 (Trp23, Leu26, and Phe19) are responsible for key hydrophobic contacts with the MDM2 protein. Furthermore, the cocrystal structures of known small molecules bound to MDM2 support the importance of targeting these three hydrophobic regions when attempting to disrupt the MDM2−p53 PPI.

ChemDiv combined a number of *in silico* screening approaches and specific spatial PPI information to design sub-libraries centered on a scaffolds that project side chain functionalities with distance and angular properties similar to those seen in the MDM2 interacting motif of p53.

Important information inspired the library design

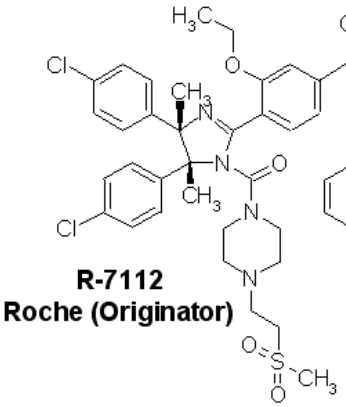


Autoregulatory feedback loop of inhibition of p53 by MDM2. MDM2 directly binds to p53 and inhibits its transcriptional activity, causes ubiquitinization and proteasomal degradation of p53, and exports p53 out of the nucleus. MDMX, a homolog of MDM2, also directly binds to the transactivation domain of p53 and inhibits p53 activity, but does not cause degradation of p53. Tumor suppressor ARF binds to MDM2 and sequesters MDM2 into the nucleolus, leading to stabilization of p53. [**Annu Rev Pharmacol Toxicol. 2009; 49: 223-41**].

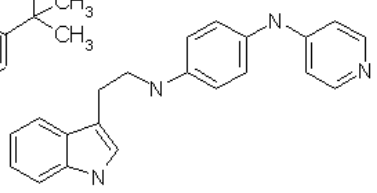


Controlled Access of p53 to the Nucleus Regulates Its Proteasomal Degradation by MDM2.
[Mol. Pharmaceutics, 2013, 10 (4), pp 1340]

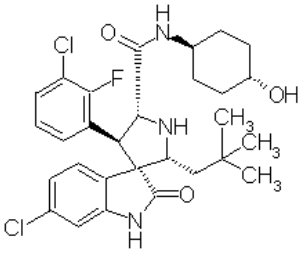
Phase I MDM2 Inhibitors



R-7112
Roche (Originator)



Serdemetan (Prop INN)
Johnson & Johnson (Originator)

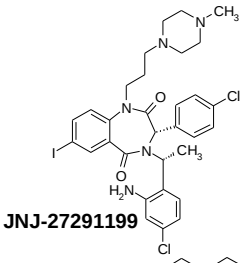


MI-773
SAR-405838
Sanofi

Structure is not disclosed
RO-5503781
Roche (Originator)

Structure is not disclosed
RG-7388
Roche (Originator)

Preclinical MDM2 Inhibitors



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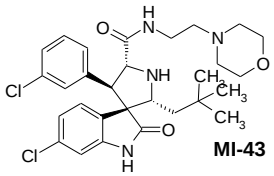
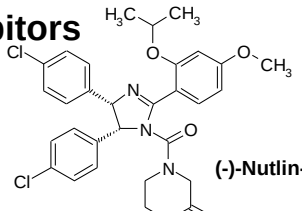
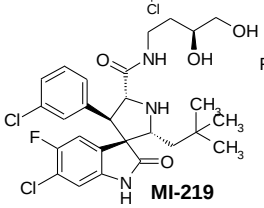


MI-43



(-)-Nutlin-3



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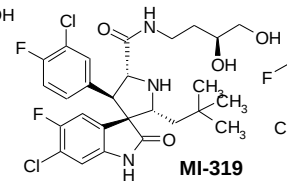

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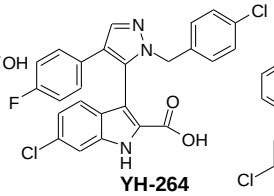
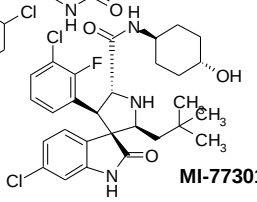


YH-264



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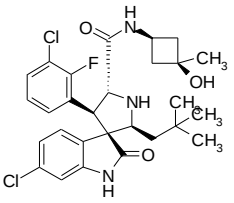

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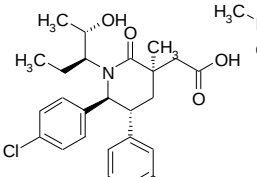
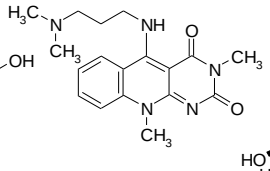
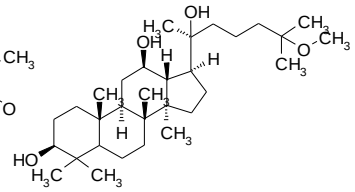


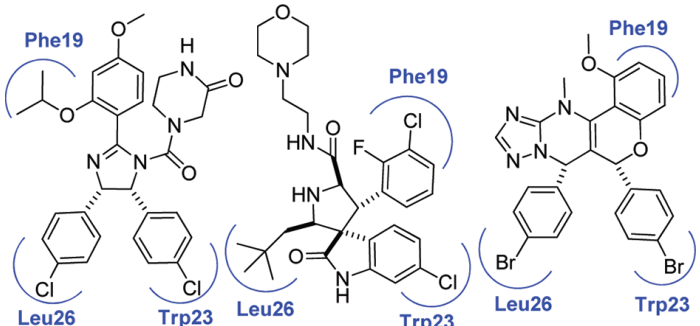
AM-8553



HLI-373



25-OCH3-PPD



Nutlin-3a[14]
0.018 ± 0.004 μM[a]
0.089 ± 0.012 μM[b]

MI-63[15,19]
0.009 ± 0.003 μM[a]
0.021 ± 0.015 μM[b]

Amgen, HTS Lead[12]
0.070 ± 0.010 μM[a]
0.96 ± 0.09 μM[b]

Binding mode of three known MDM2 inhibitors. Blue labels indicate the positions normally occupied by key p53 residues. [a]IC50 in biochemical assay (HTRF, serum free). [b]IC50 in biochemical assay (HTRF, 15% human serum) [**J Med Chem. 2012; 55: 4936**].

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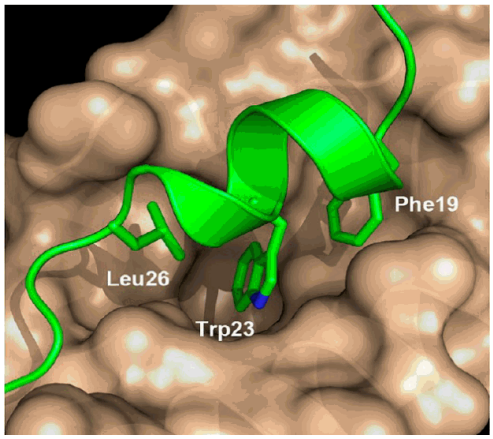
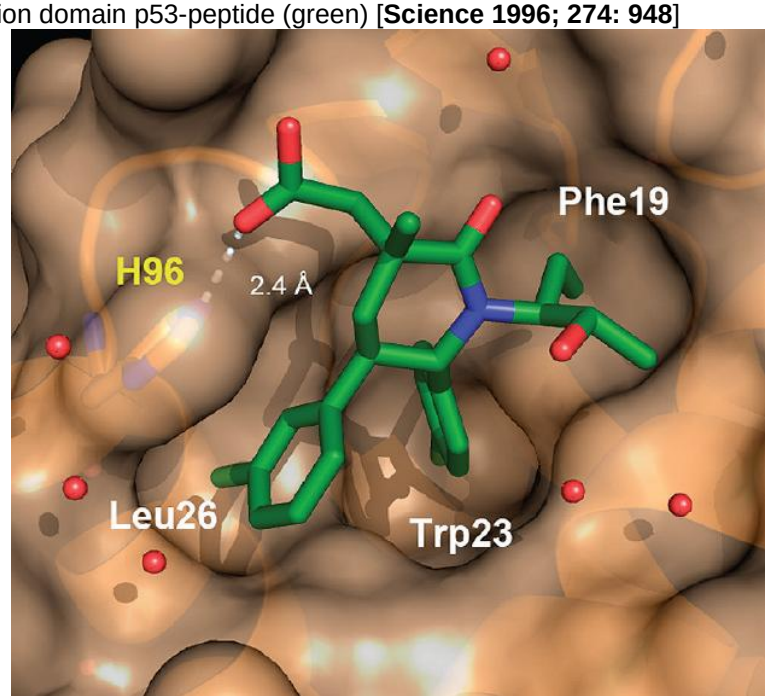


The X-ray cocrystal structure of the 109-residue amino-terminal domain of MDM2 (tan) bound to a 15-residue transactivation domain p53-peptide (green) [**Science 1996; 274: 948**]



Cocrystal structure of preclinical inhibitor **AM-8553** bound to human MDM2 (17−111) at 2.0 Å resolution. White labels indicate the positions normally occupied by key p53 residues. H96 is labeled in yellow. Cocrystallized water molecules are shown in red [**J Med Chem. 2012; 55: 4936**]

Variable statistics for 8,838 compounds from MDM2 library.

Diversity 0,8064
The number of screens in dataset 2,197
Number of unique heterocycles 85
The number of Scaffolds 88
Singletons 8
Novelty: the number of compounds (%) per year

date	numbers	%
2013	3556	**40.24**
2012	4085	**46.22**
2011	1194	**13.51**
2006	1	0.01
2004	1	0.01
2002	1	0.01

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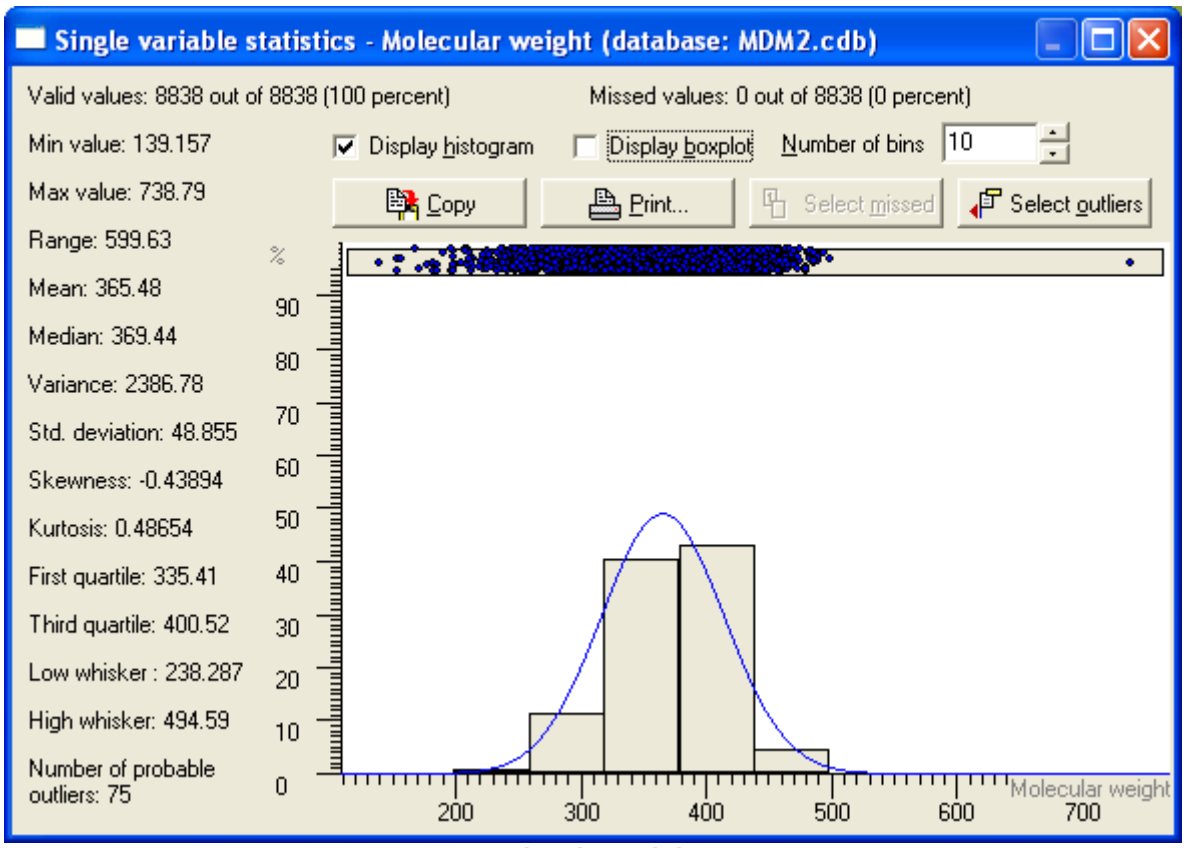
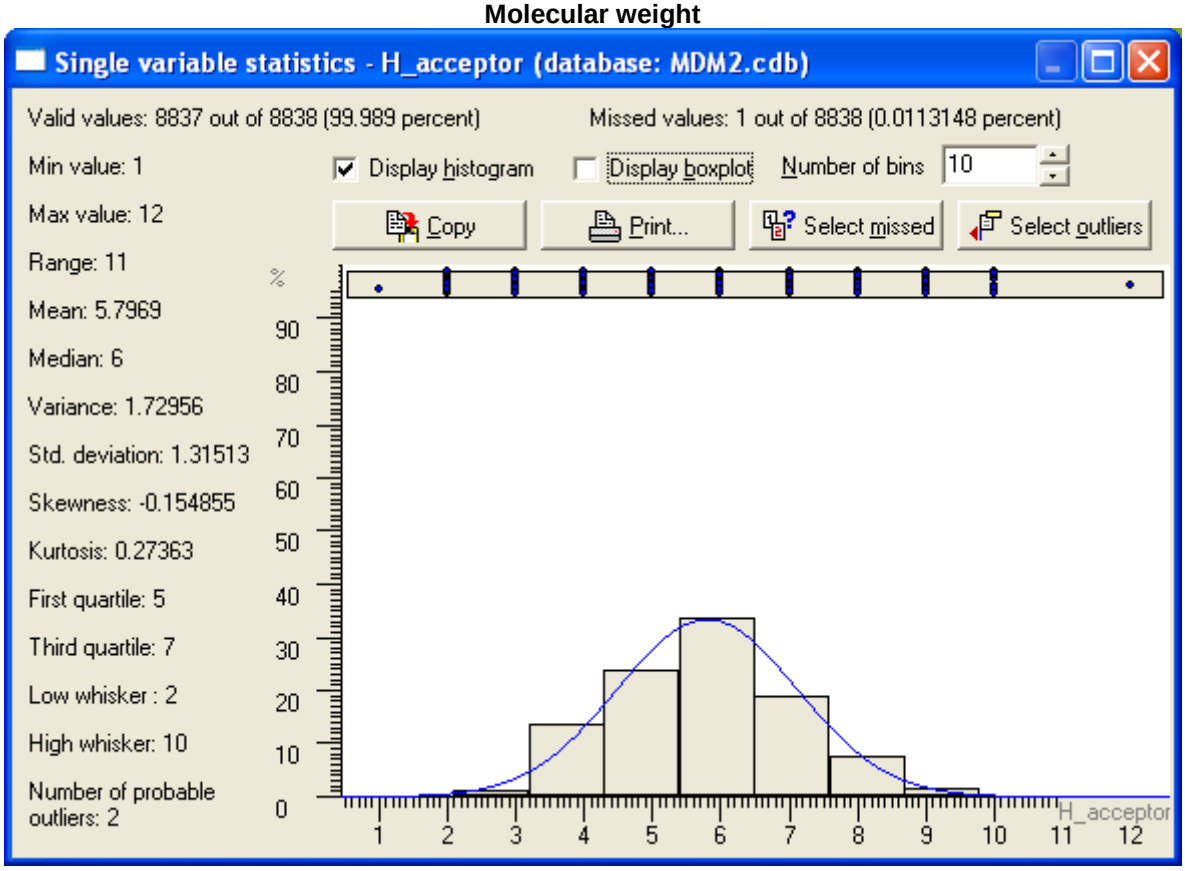
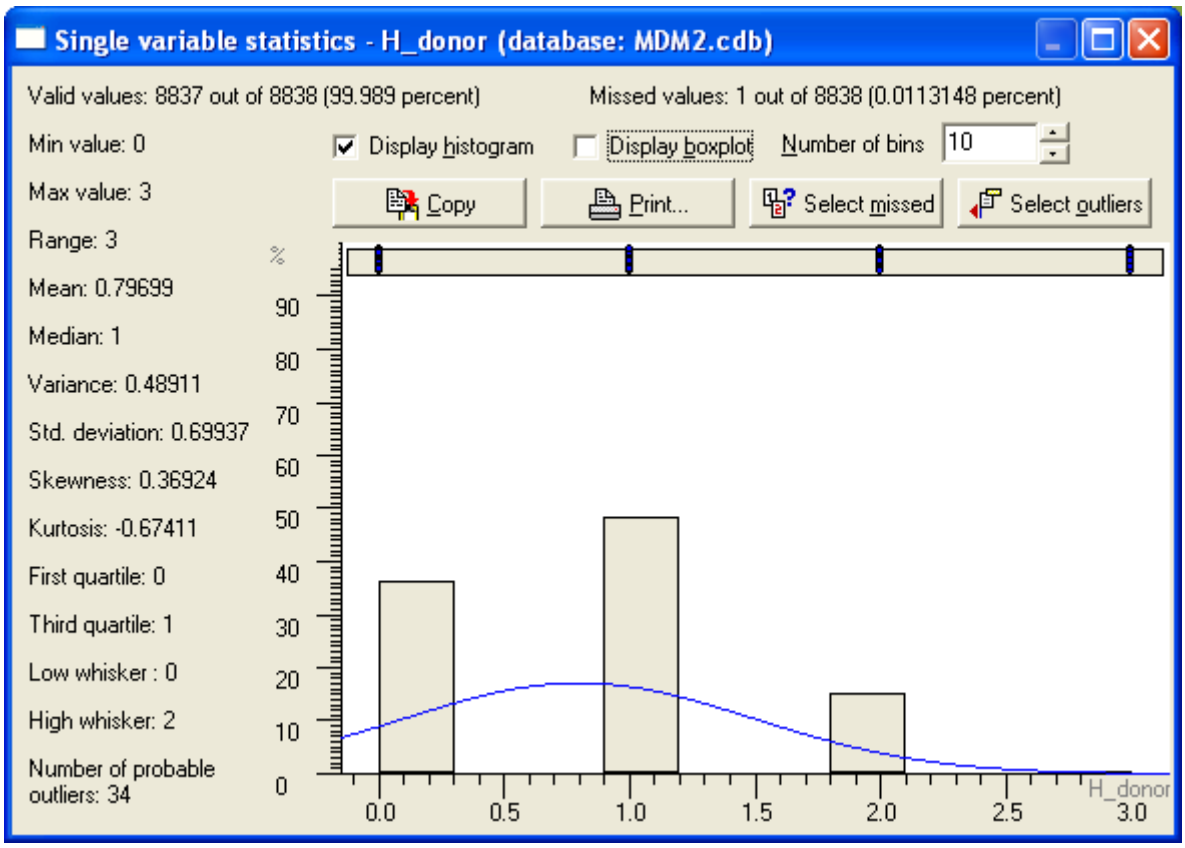


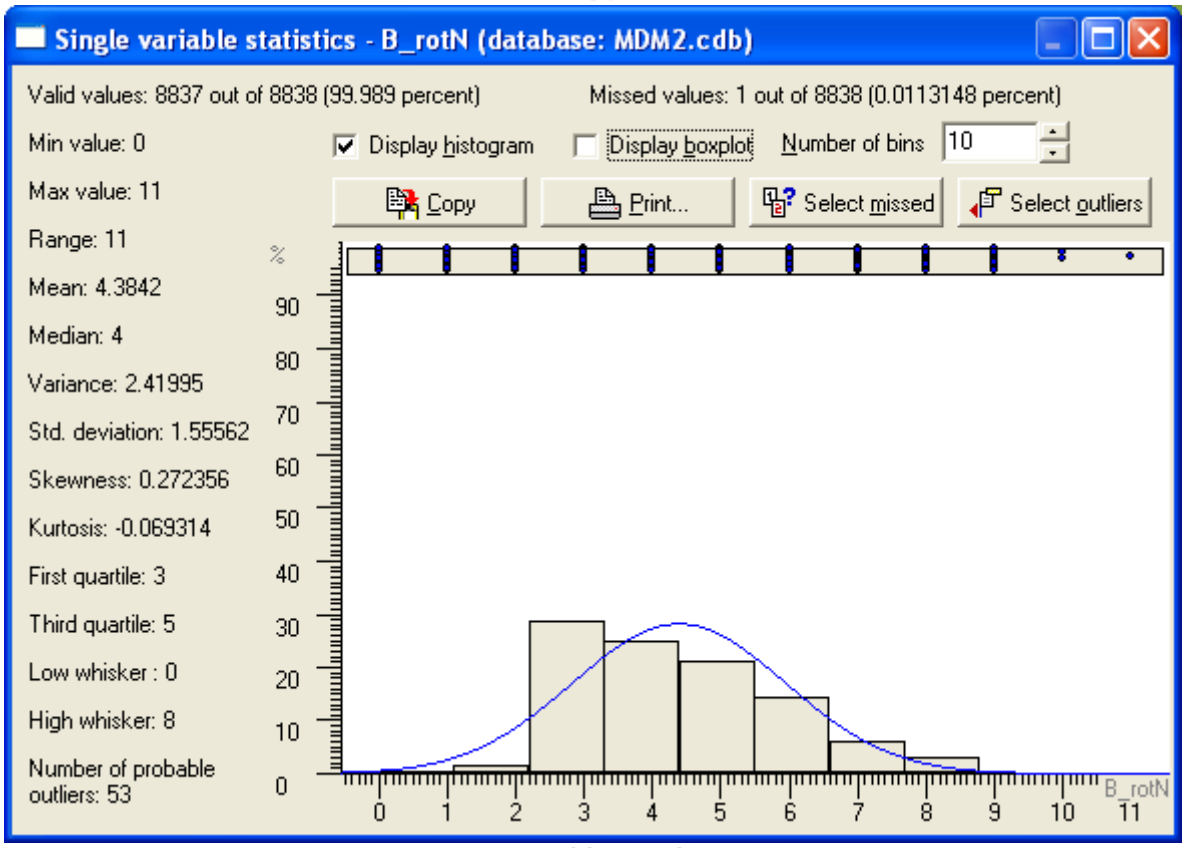
Molecular weight



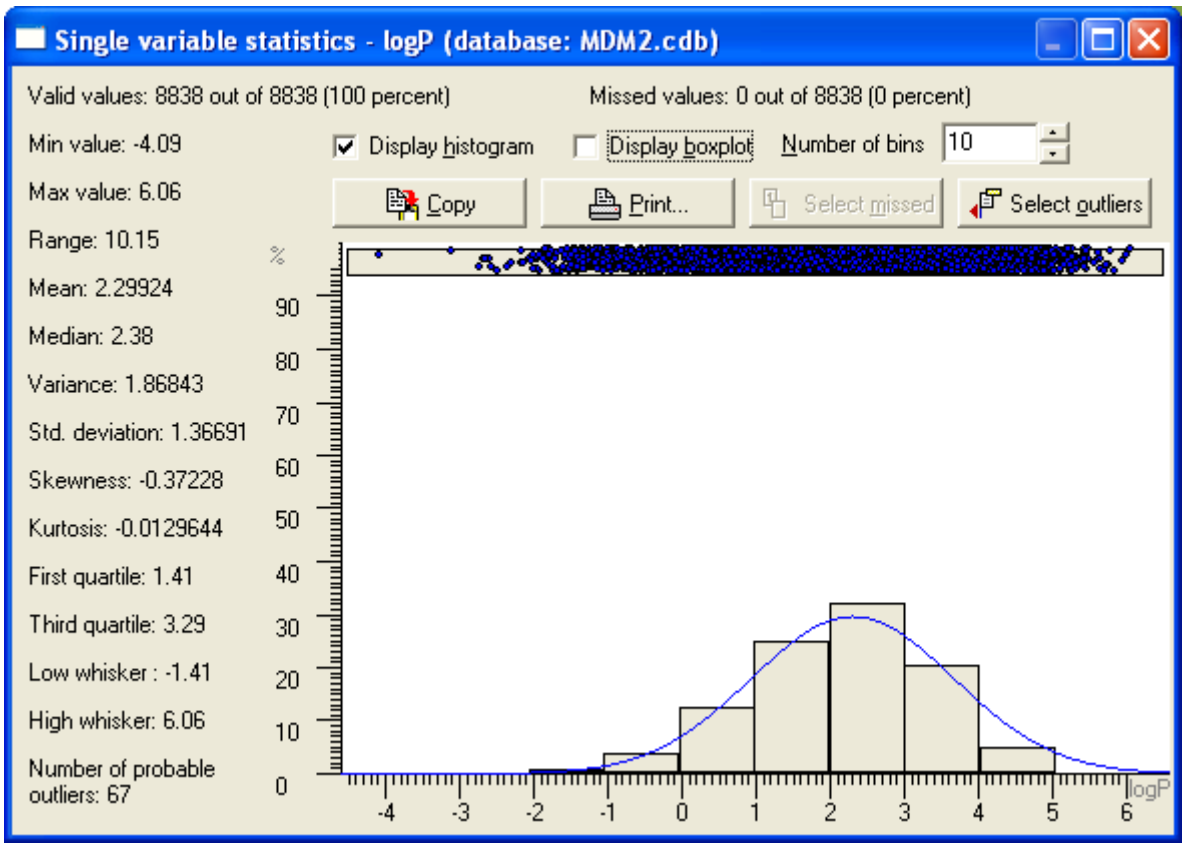
HBA



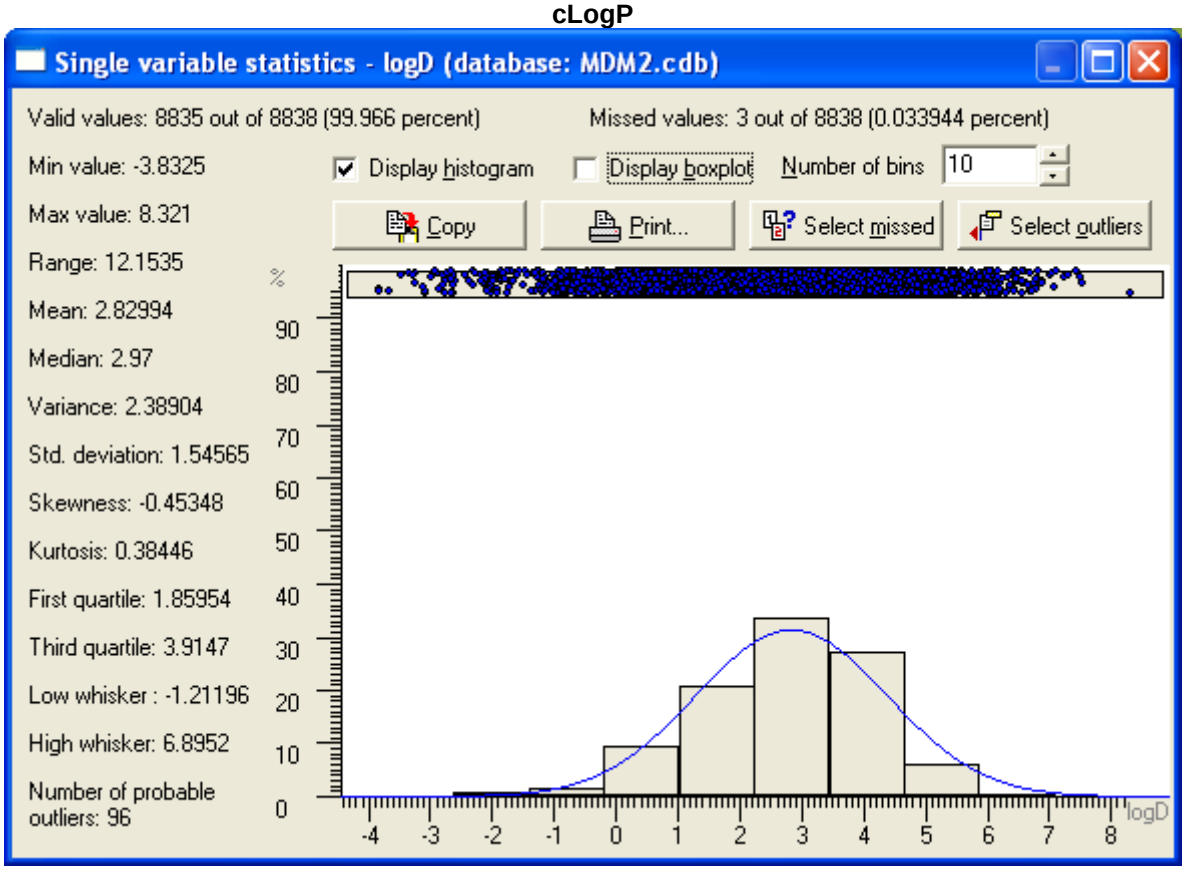
HBD



Rotatable Bonds


Single variable statistics - logP (database: MDM2.cdb)
Valid values: 8838 out of 8838 (100 percent)
Missed values: 0 out of 8838 (0 percent)
Min value: -4.09
Max value: 6.06
Range: 10.15
Mean: 2.29924
Median: 2.38
Variance: 1.86843
Std. deviation: 1.36691
Skewness: -0.37228
Kurtosis: -0.0129644
First quartile: 1.41
Third quartile: 3.29
Low whisker : -1.41
High whisker: 6.06
Number of probable outliers: 67
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
%
90
80
70
60
50
40
30
20
10
0
-4
-3
-2
-1
0
1
2
3
4
5
6
logP

cLogP


Single variable statistics - logD (database: MDM2.cdb)
Valid values: 8835 out of 8838 (99.966 percent)
Missed values: 3 out of 8838 (0.033944 percent)
Min value: -3.8325
Max value: 8.321
Range: 12.1535
Mean: 2.82994
Median: 2.97
Variance: 2.38904
Std. deviation: 1.54565
Skewness: -0.45348
Kurtosis: 0.38446
First quartile: 1.85954
Third quartile: 3.9147
Low whisker : -1.21196
High whisker: 6.8952
Number of probable outliers: 96
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
%
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80
70
60
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40
30
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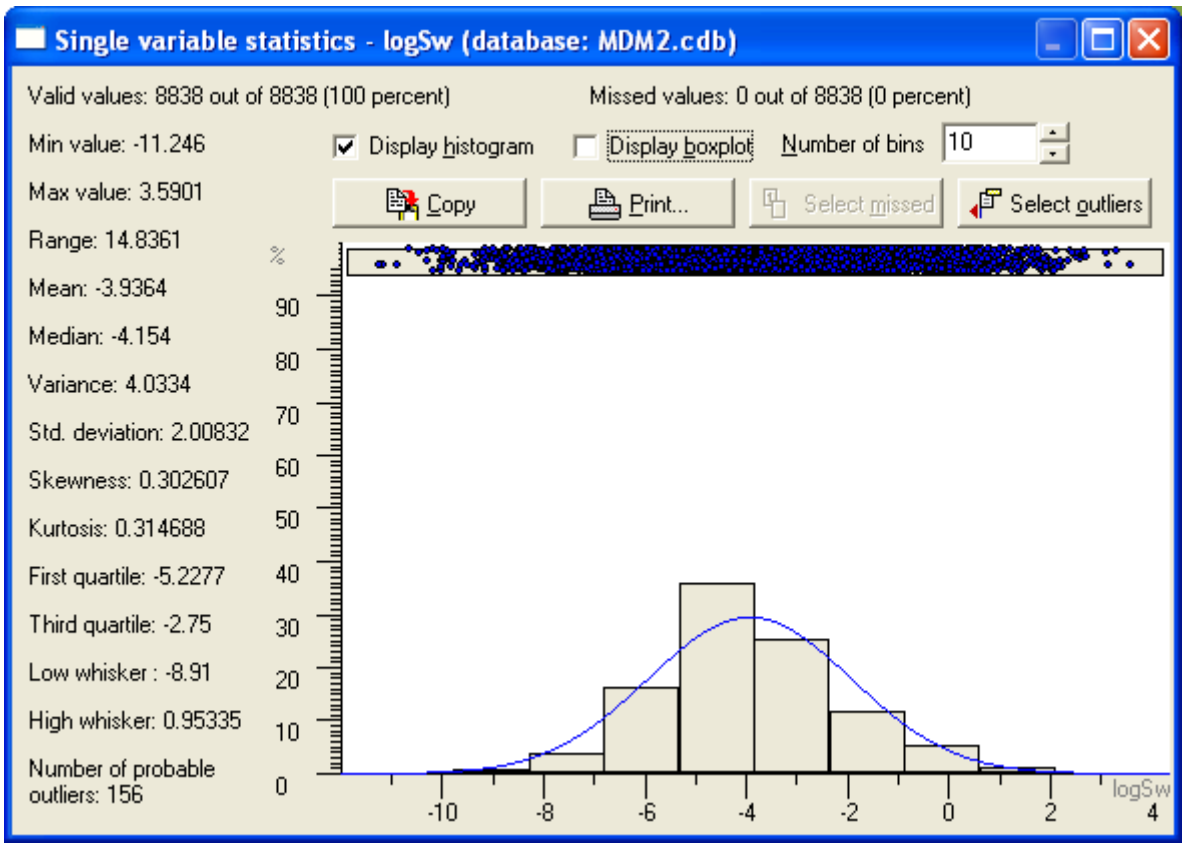
7
8
logD

cLogD


Single variable statistics - logSw (database: MDM2.cdb)
Valid values: 8838 out of 8838 (100 percent)
Missed values: 0 out of 8838 (0 percent)
Min value: -11.246
Max value: 3.5901
Range: 14.8361
Mean: -3.9364
Median: -4.154
Variance: 4.0334
Std. deviation: 2.00832
Skewness: 0.302607
Kurtosis: 0.314688
First quartile: -5.2277
Third quartile: -2.75
Low whisker : -8.91
High whisker: 0.95335
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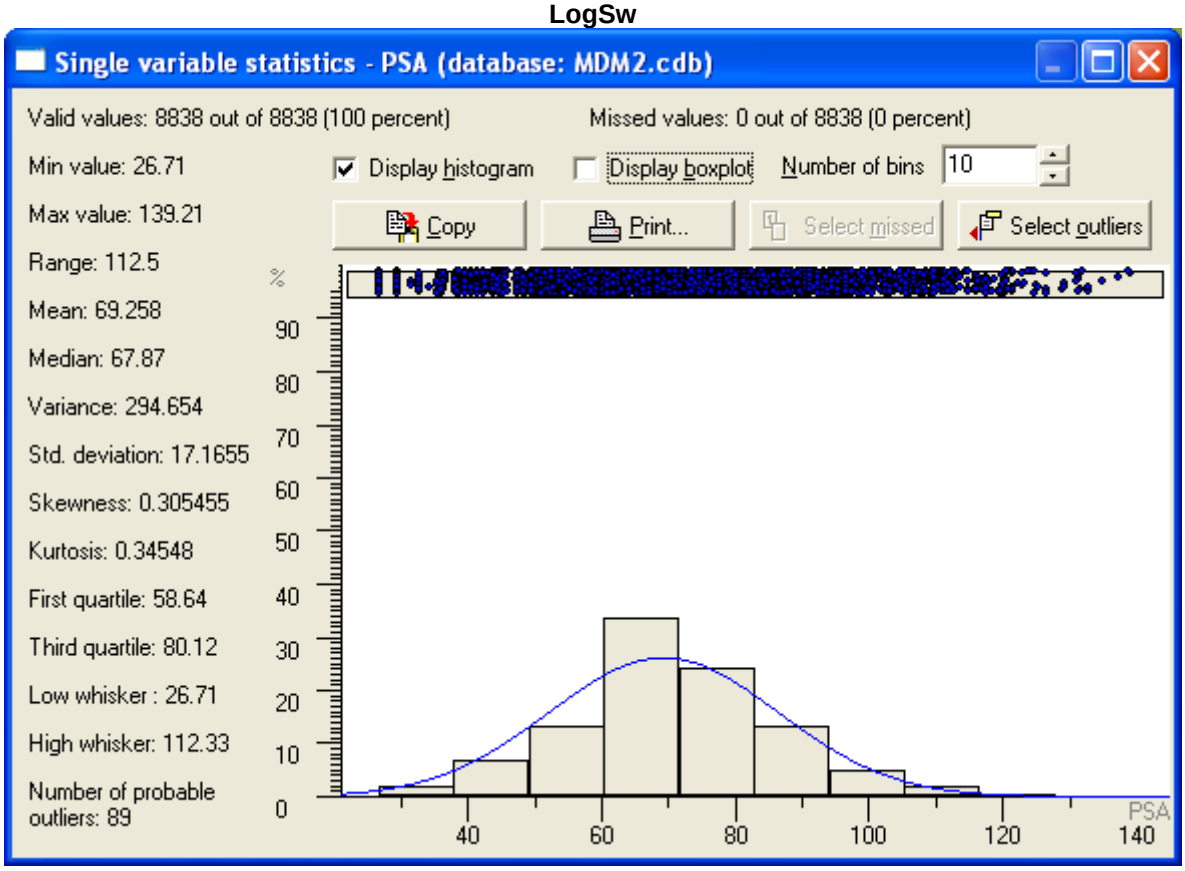
4
logSw

LogSw


Single variable statistics - PSA (database: MDM2.cdb)
Valid values: 8838 out of 8838 (100 percent)
Missed values: 0 out of 8838 (0 percent)
Min value: 26.71
Max value: 139.21
Range: 112.5
Mean: 69.258
Median: 67.87
Variance: 294.654
Std. deviation: 17.1655
Skewness: 0.305455
Kurtosis: 0.34548
First quartile: 58.64
Third quartile: 80.12
Low whisker : 26.71
High whisker: 112.33
Number of probable outliers: 89
Display histogram
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Select missed
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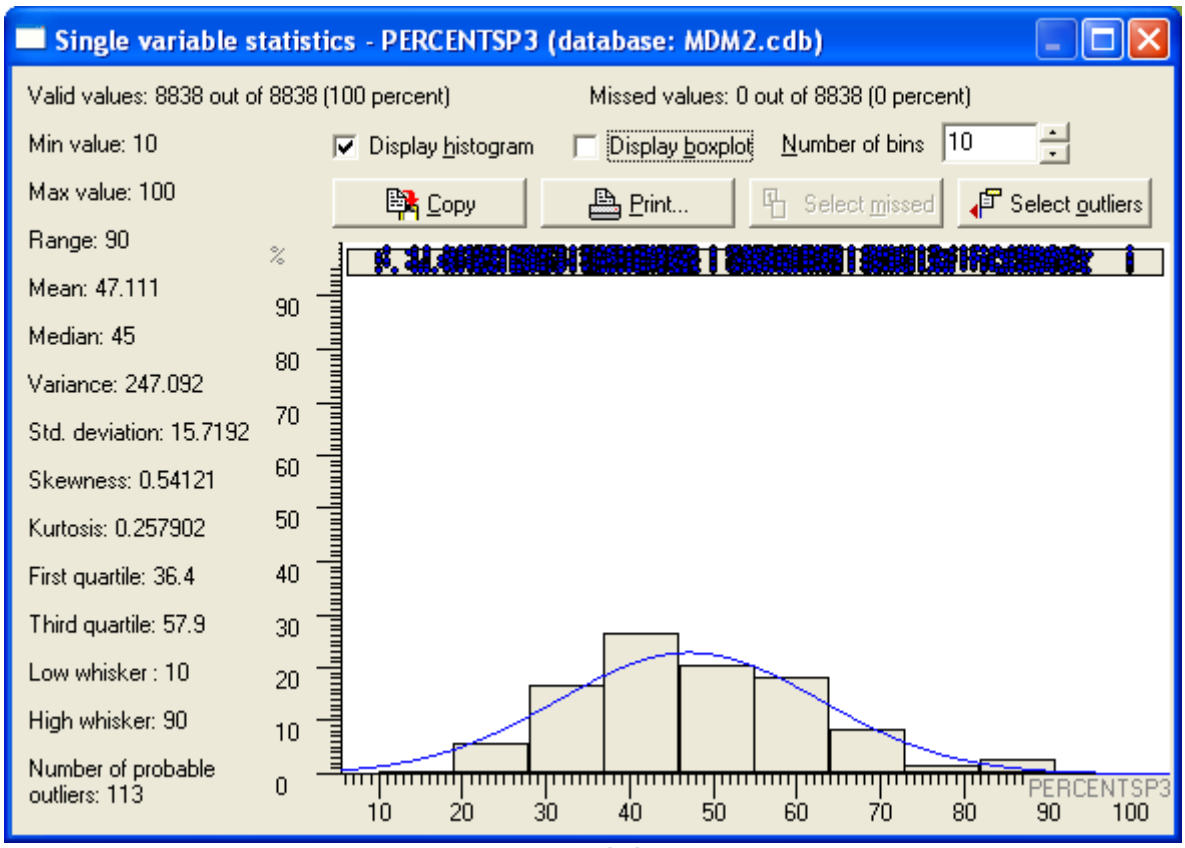
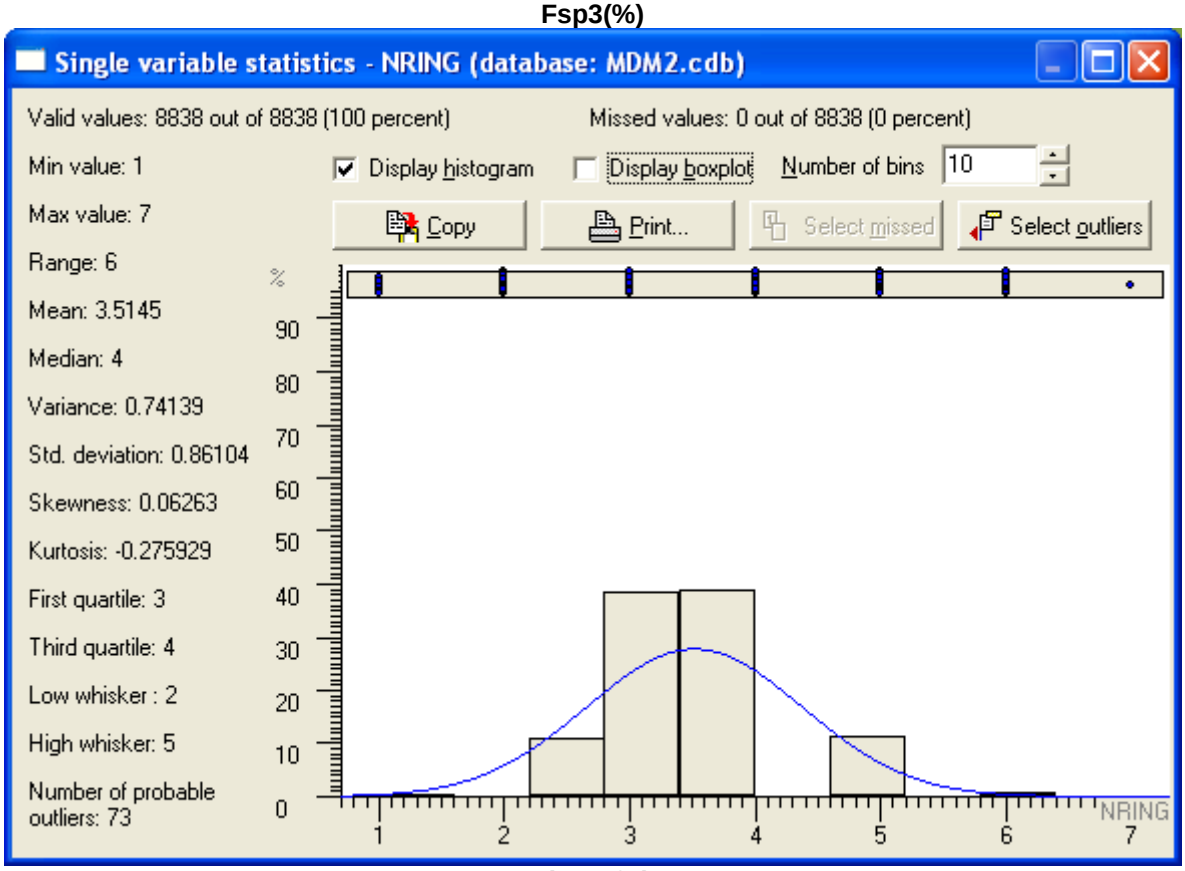
PSA

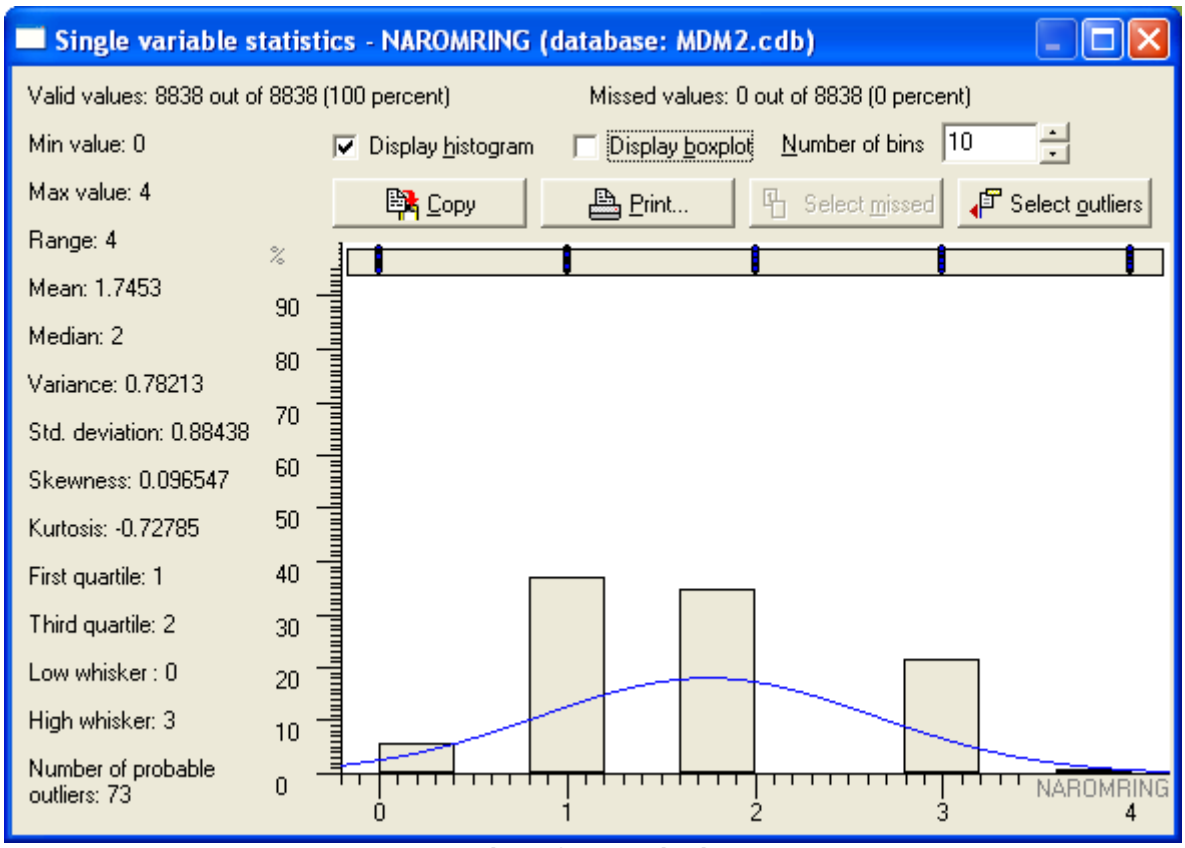
PSA



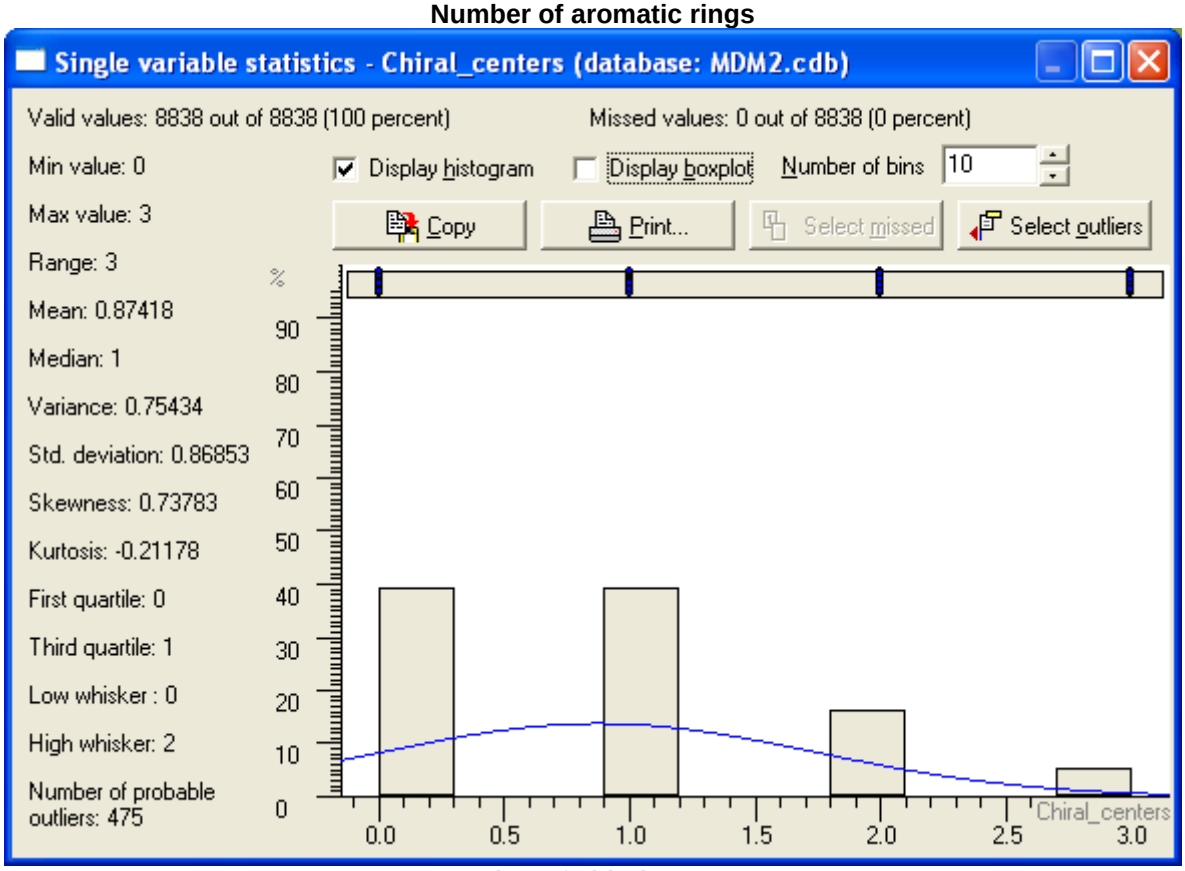
Fsp3(%)



Number of rings



Number of aromatic rings



Number of chiral centers