Library of small molecule inhibitors of beta-Catenin signaling

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Description

β-Catenin (Armadillo in Drosophila) is a fascinating protein with many important cellular and developmental functions. The roles of b-catenin are 'classically' defined: (i) as an adhesion protein and (ii) as a signaling protein, transducing extracellular signals to the nucleus to modify gene expression. b-catenin has many binding partners that mediate a diverse set of cellular functions, and the protein probably acts as a 'hub' on which many cellular signaling networks impinge.

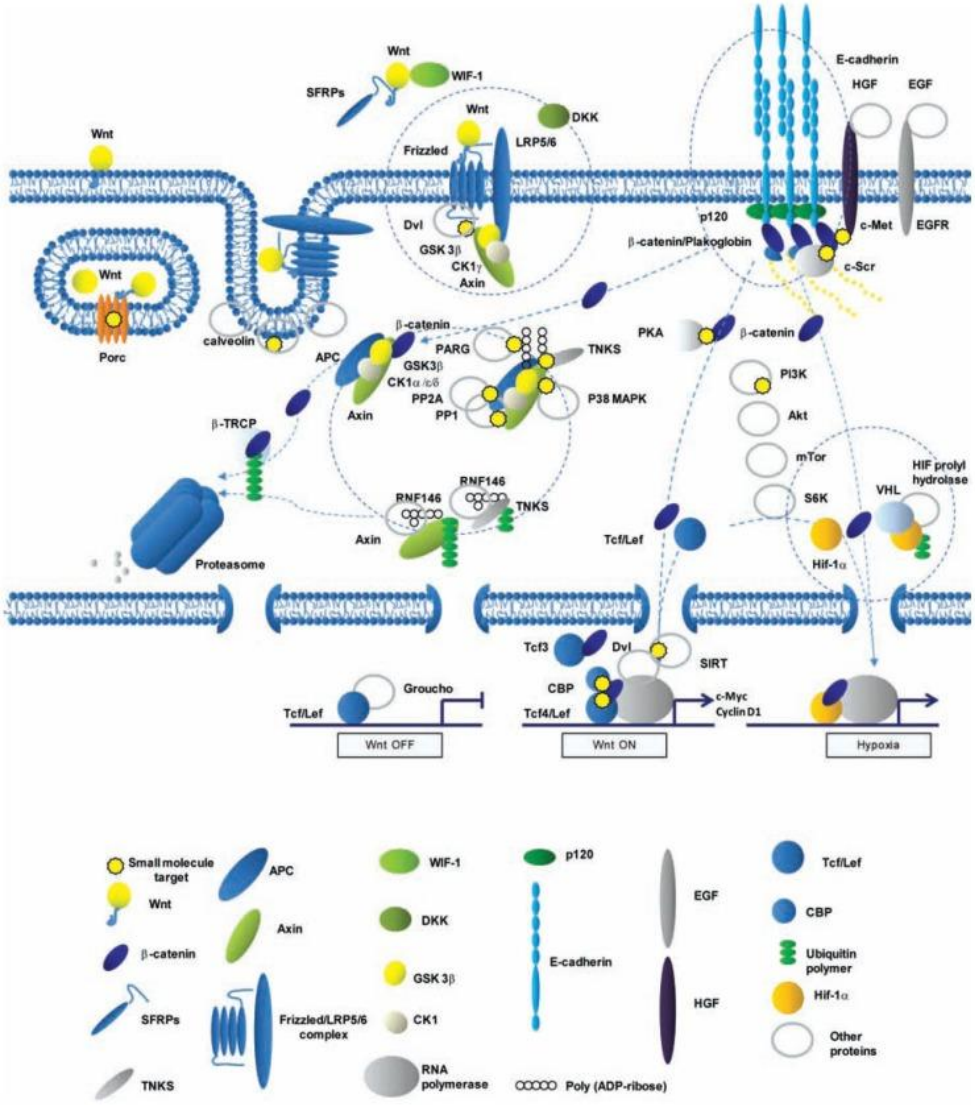
Wnt/β-catenin signaling is a branch of a functional network that is involved in a broad range of biological systems including stem cells, embryonic development and adult organs. Deregulation of components involved in Wnt/β-catenin signaling has been implicated in a wide spectrum of diseases including a number of cancers and degenerative diseases. The key mediator of Wnt signaling, β-catenin, serves several cellular functions. Central effectors of β-catenin levels are a family of cysteine-rich secreted glycoproteins, known as Wnt morphogens. Through the LRP5/6-Frizzled receptor complex, Wnt regulate the location and activity of the destruction complex and consequently intracellular β- catenin levels. However, β-catenin levels and their effects on transcriptional programs are also influenced by multiple other factors including hypoxia, inflammation, hepatocyte growth factor-mediated signaling, and the cell adhesion molecule E-cadherin. The broad implications of Wnt/β-catenin signaling in development, in the adult body and in disease render the pathway a prime target for pharmacological research and development.

The structure of b-catenin is a key to its regulation during Wnt signaling: many b-catenin interaction partners bind to a positively-charged groove in the Armadillo ARM-repeat protein region.

ChemDiv proposes the new library of beta-catenin inhibitors/modulators. This library represents a selection of drug-like compounds aimed at modulating protein-protein interaction (PPI) of b-catenin with different proteins 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 b-catenin interaction (e.g. positively-charged groove binders).

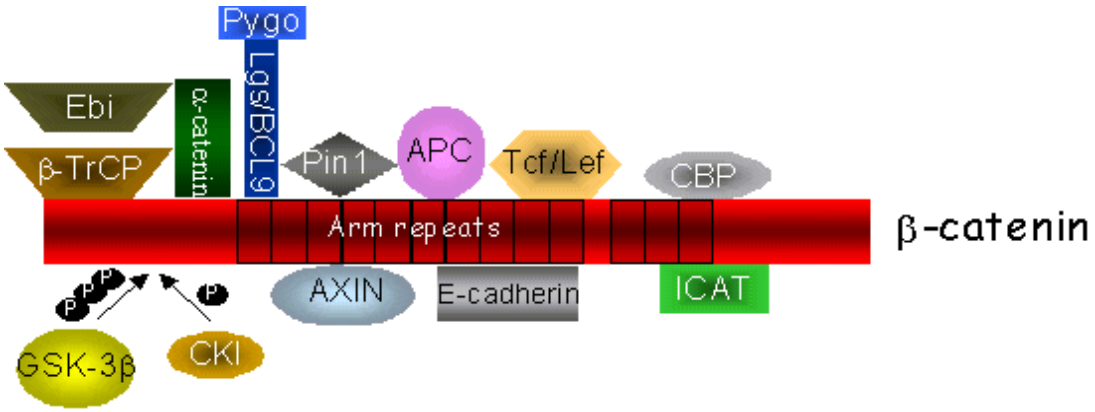
Important information inspired the library design



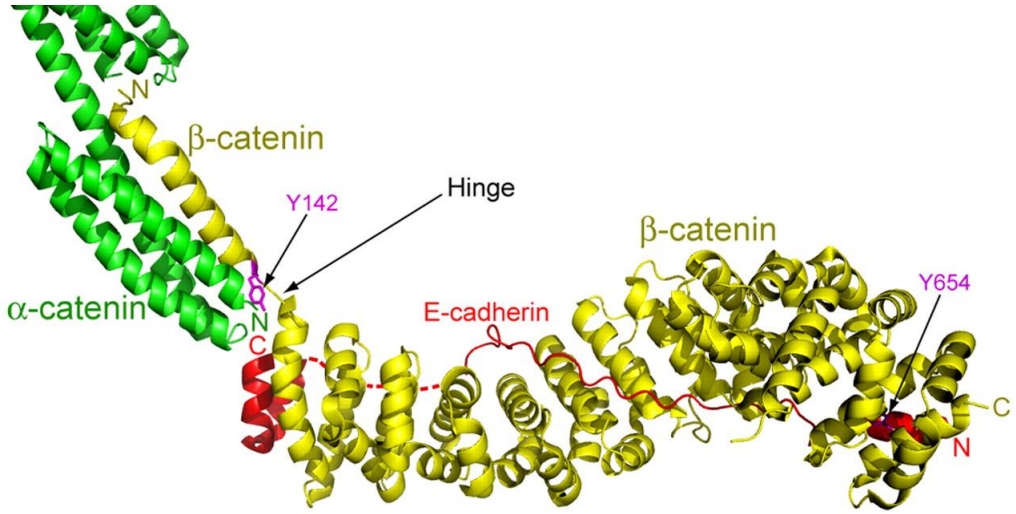
Simplified schematic representation of drug targets (yellow stars) in Wnt/β-catenin-mediated signaling.

Four key aspects that regulate β-catenin-mediated signaling are highlighted: the destruction complex, the Wnt/β-catenin signalosome, cadherin junctions, and the hypoxia sensing system Hif-1α (hipoxia induced factor 1β). Proteins that directly interact with Wnt/β-catenin are marked as colored structures, other proteins are marked as circles.

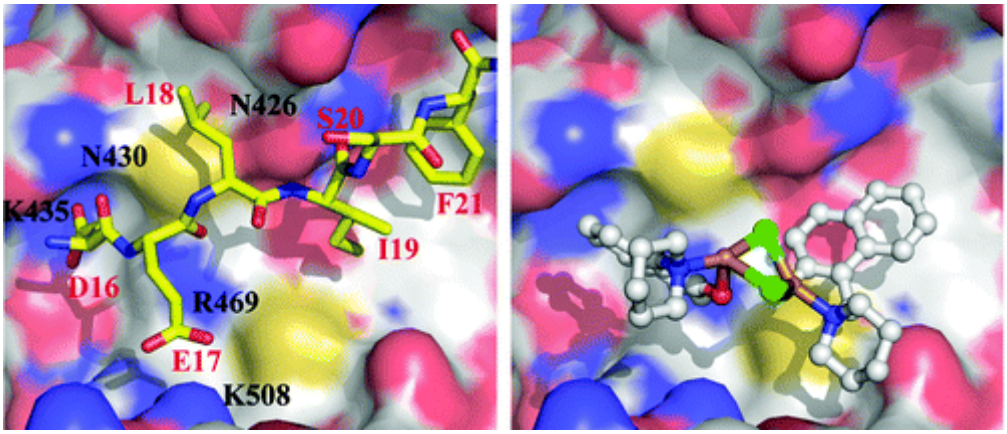
[Curr Phar Des. 2013; 19(4): 634]



beta-Catenin activity is controlled by a large number of binding partners that affect the stability and localization of b-catenin [http://atlasgeneticsoncology.org]



β-catenin complexes in cell adhesion. Crystal structures of the β-catenin armadillo repeat domain (yellow) in complex with the E-cadherin cytoplasmic domain (red) and the dimerization and β-catenin-binding domain of α-catenin (green) were superimposed on the basis of shared β-catenin residues 145-148. Note the disruption of the first helix in the armadillo repeat domain upon α-catenin binding, which potentially produces a hinge, allowing structural flexibility between α-catenin and β-catenin. β-catenin Y142, which disrupts α-catenin binding upon phosphorylation, and Y654, which modulates the interaction between β-catenin and E-cadherin upon phosphorylation, are shown in purple. Red dashes indicate flexible regions of E-cadherin.
[J Cell Sci. 2007; 120(19): 3337]



Interaction of β-catenin with T-cell factor (Tcf) DNA binding proteins is a key step in the activation of the proliferative genes in response to upstream signals of this Wnt/β-catenin pathway. A new small molecule inhibitor, named BC21, effectively inhibits the binding of β-catenin with Tcf4-derived peptide and suppresses β-catenin/Tcf4 driven reporter gene activity.

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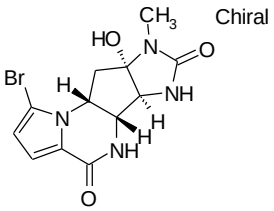
[Biochemistry. 2012; 51(2): 724]

Examples of known beta-catenin inhibitor



ID #	271674
Formula	$C_{12}H_{13}BrN_4O_3$
MW	341.166
PSA	
Highest_Phase	Preclinica
Under_Active_Development	NO
Company_Code	
Name	Agelastatin A

Condition

Antineoplastic agents 470. Absolut
configuration of the marine spong
bromopyrrole agelastatin
Oncol Res 2005, 15(1): 1

Natural_Source

marine sponge Agelas dendromorph

Therapeutic_Group

Oncolytic Drug

Reference

WO 2004106341
WO 2006055575
WO 2008078109

Mechanism_of_action

Agelastatin A (AgA), a marine sponge derive
alkaloid, inhibits Wnt/beta-catenin signaling ar
selectively induces apoptosis in chroni
lymphocytic leukemia independently of p
Blood 2011, 118(21): Abst 178

Organization

Penn State Research Foundation (Originat

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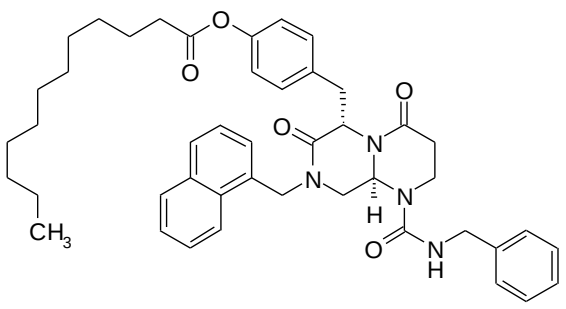

ID #	810060
Formula	$C_{45}H_{54}N_4O_5$
MW	730.956
Highest_Phase	Biological Testin
Under_Active_Development	NO
Natural_Source	
Company_Code	Laura-8
Generic_Name	Laura-8

Condition	Therapeutic_Group
Aging Alopecia	Age-Related Disorders, Treatment Hair Growth Stimulant
Related_Basic_Patent	**Mechanism_of_action**
WO 201305216	CBP/beta-Catenin Complex Inhibito
Organization	
University of Southern California (USC (Originator	

Variable statistics for 11,149 compounds from betaCatenin library.

Diversity **0,7768**
The number of screens in dataset **2658**
The number of unique heterocycles **116**
The number of scaffolds **107**
Singletons **43**

Novelty: The number of compounds synthesized (%) per year

date	number	%
2013	3593	**32.23**
2012	6463	**57.97**
2011	429	**3.85**
2010	72	0.65
2009	60	0.54
2008	9	0.08
2007	222	1.99
2006	133	1.19
2005	9	0.08

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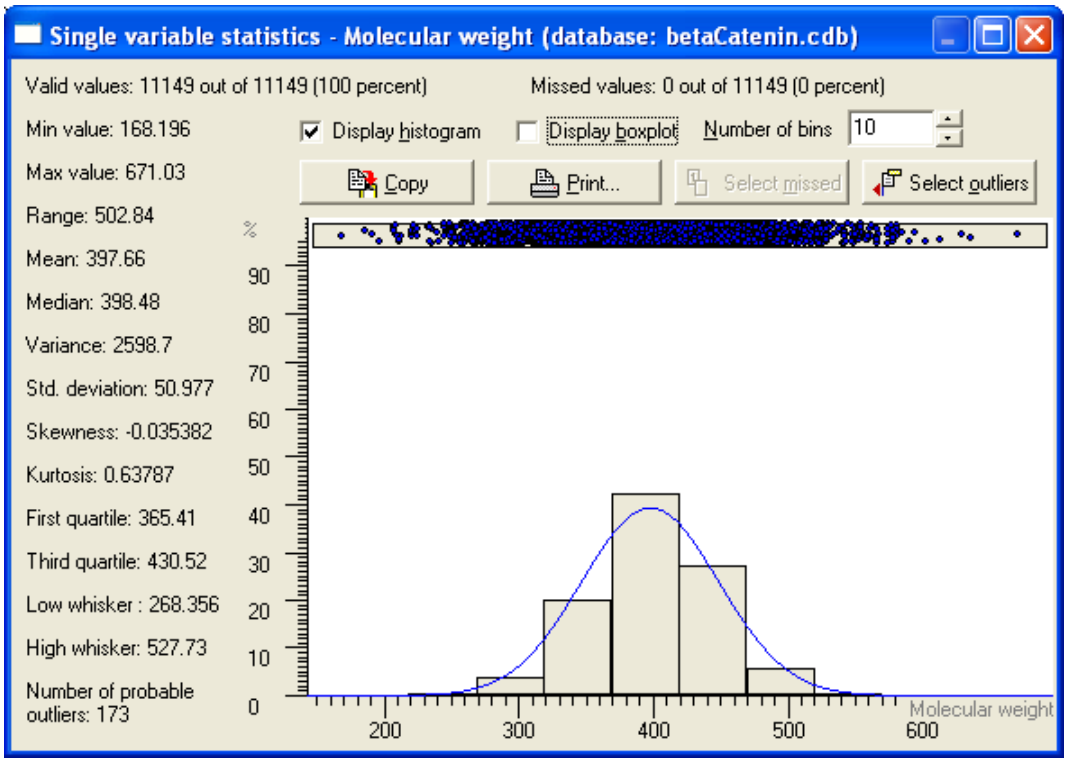
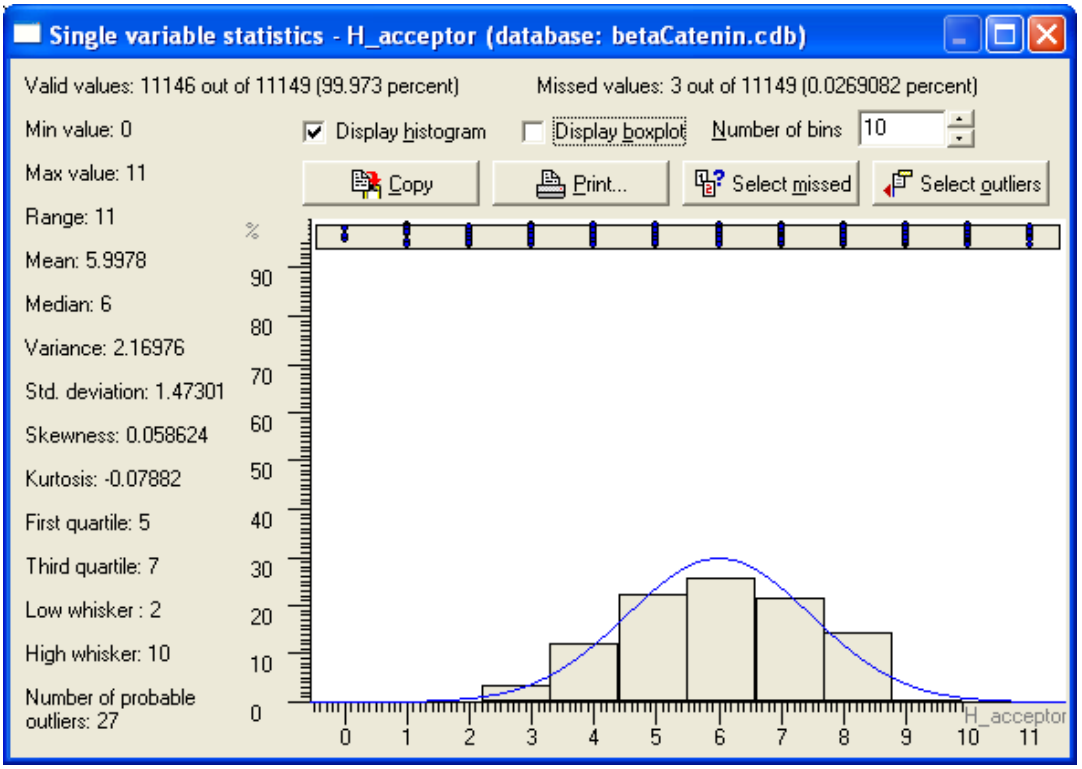
2004	14	0.13
2003	101	0.91
2002	2	0.02
2001	9	0.08
2000	33	0.30

Physico-chemical properties



Molecular weight



HBA

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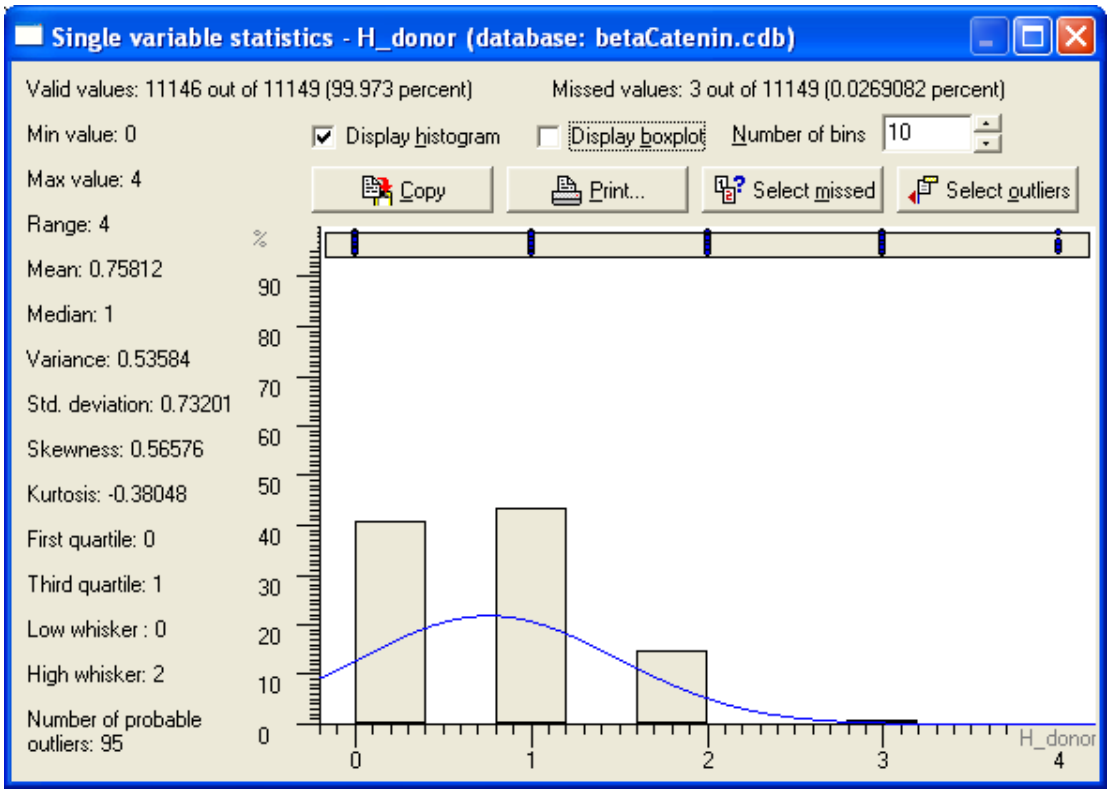
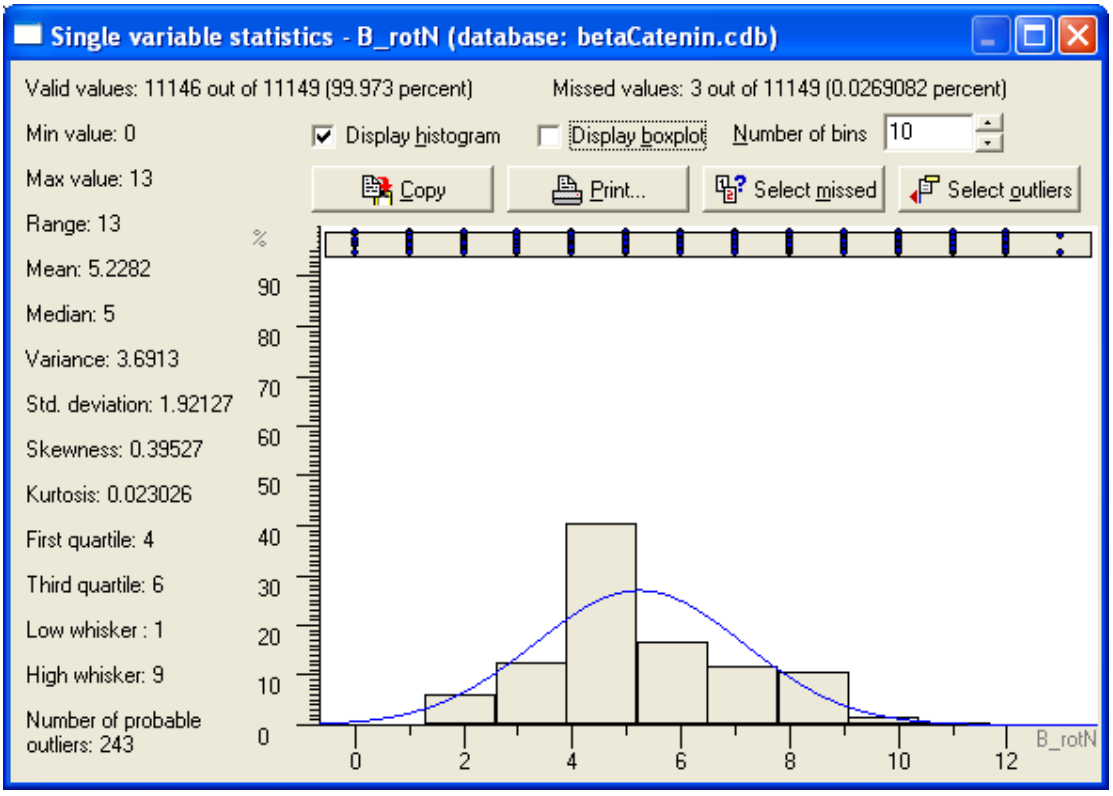


HBD



Rotatable Bonds

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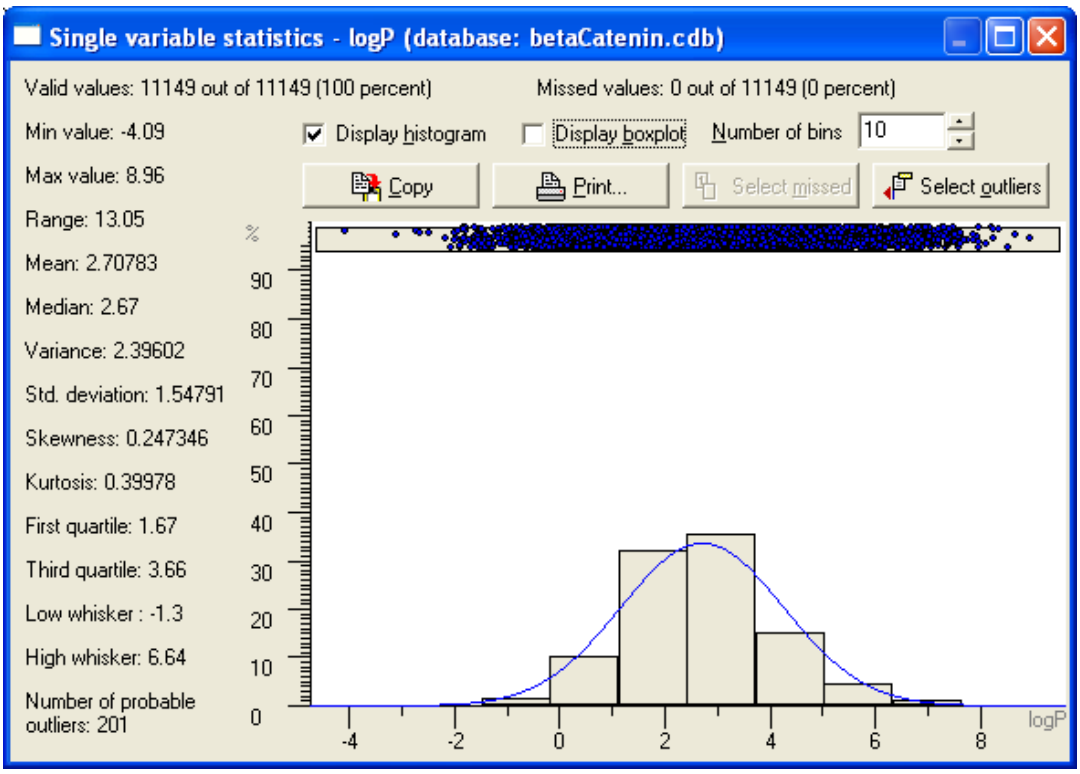
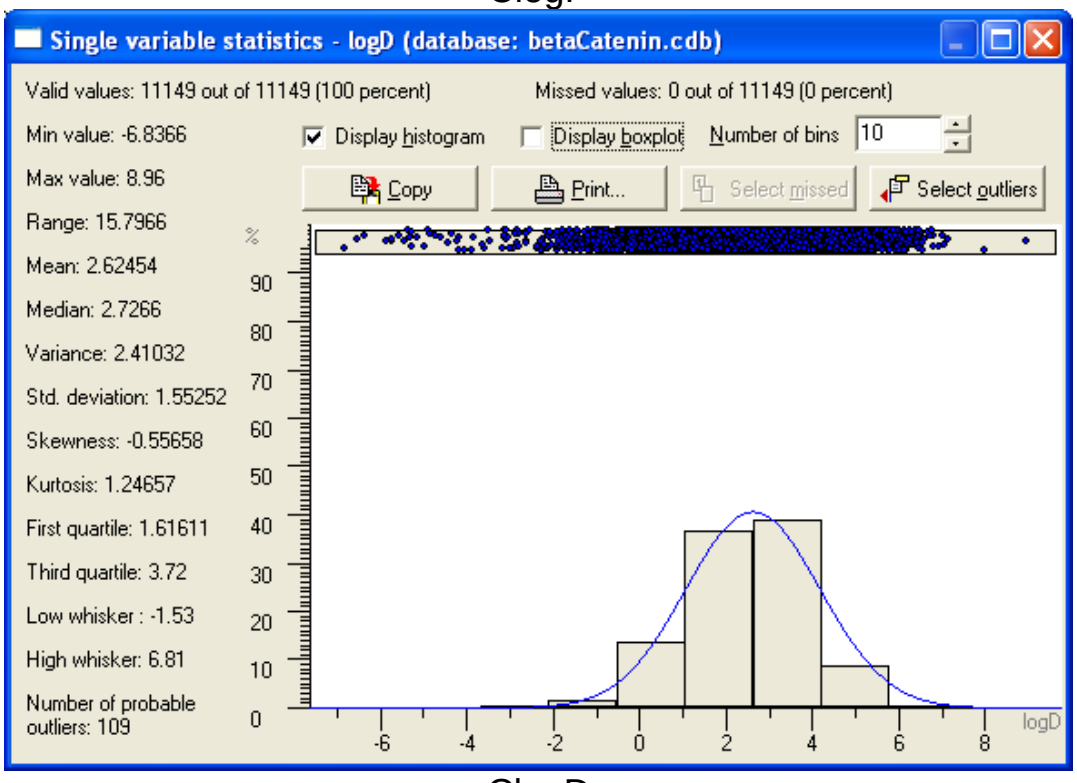
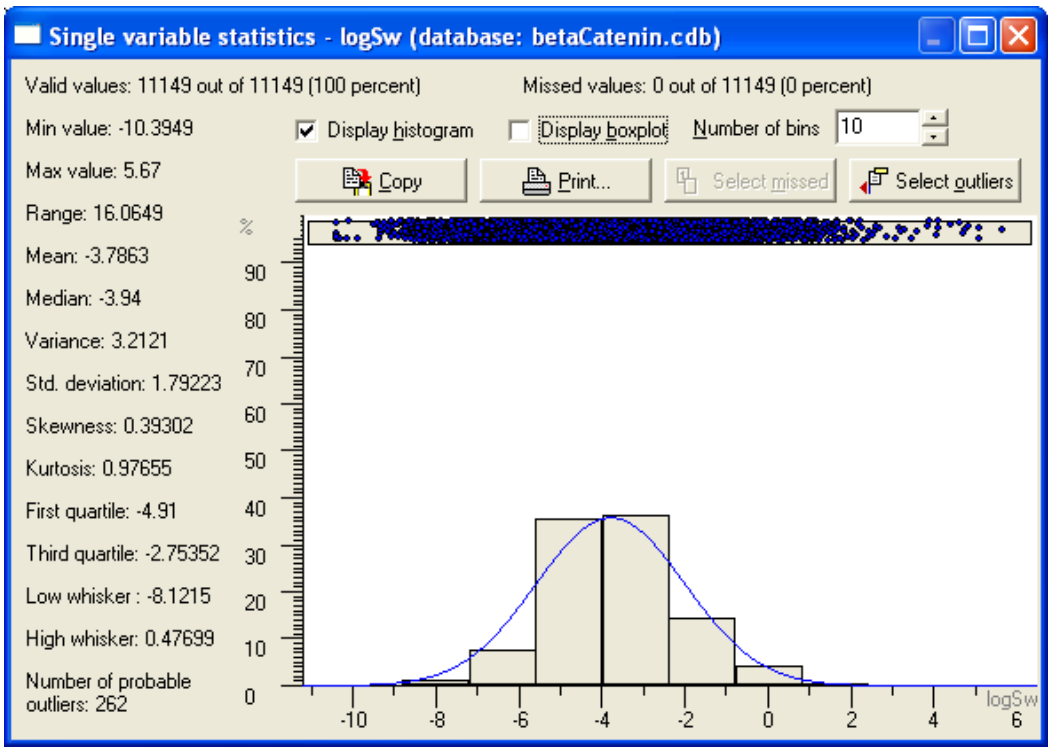

Single variable statistics - logP (database: betaCatenin.cdb)
Valid values: 11149 out of 11149 (100 percent)
Missed values: 0 out of 11149 (0 percent)
Min value: -4.09
Max value: 8.96
Range: 13.05
Mean: 2.70783
Median: 2.67
Variance: 2.39602
Std. deviation: 1.54791
Skewness: 0.247346
Kurtosis: 0.39978
First quartile: 1.67
Third quartile: 3.66
Low whisker : -1.3
High whisker: 6.64
Number of probable outliers: 201
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
-2
0
2
4
6
8
logP

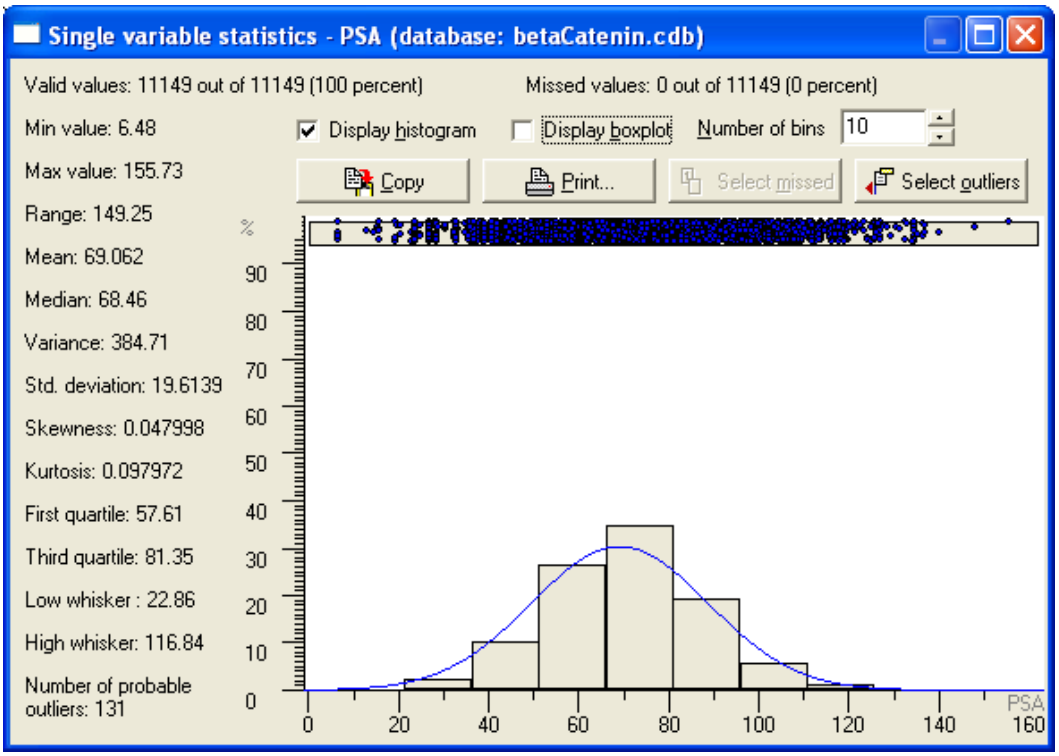
ClogP


Single variable statistics - logD (database: betaCatenin.cdb)
Valid values: 11149 out of 11149 (100 percent)
Missed values: 0 out of 11149 (0 percent)
Min value: -6.8366
Max value: 8.96
Range: 15.7966
Mean: 2.62454
Median: 2.7266
Variance: 2.41032
Std. deviation: 1.55252
Skewness: -0.55658
Kurtosis: 1.24657
First quartile: 1.61611
Third quartile: 3.72
Low whisker : -1.53
High whisker: 6.81
Number of probable outliers: 109
Display histogram
Display boxplot
Number of bins
10
Copy
Print...
Select missed
Select outliers
%
90
80
70
60
50
40
30
20
10
0
-6
-4
-2
0
2
4
6
8
logD

ClogD



LogSW



PSA

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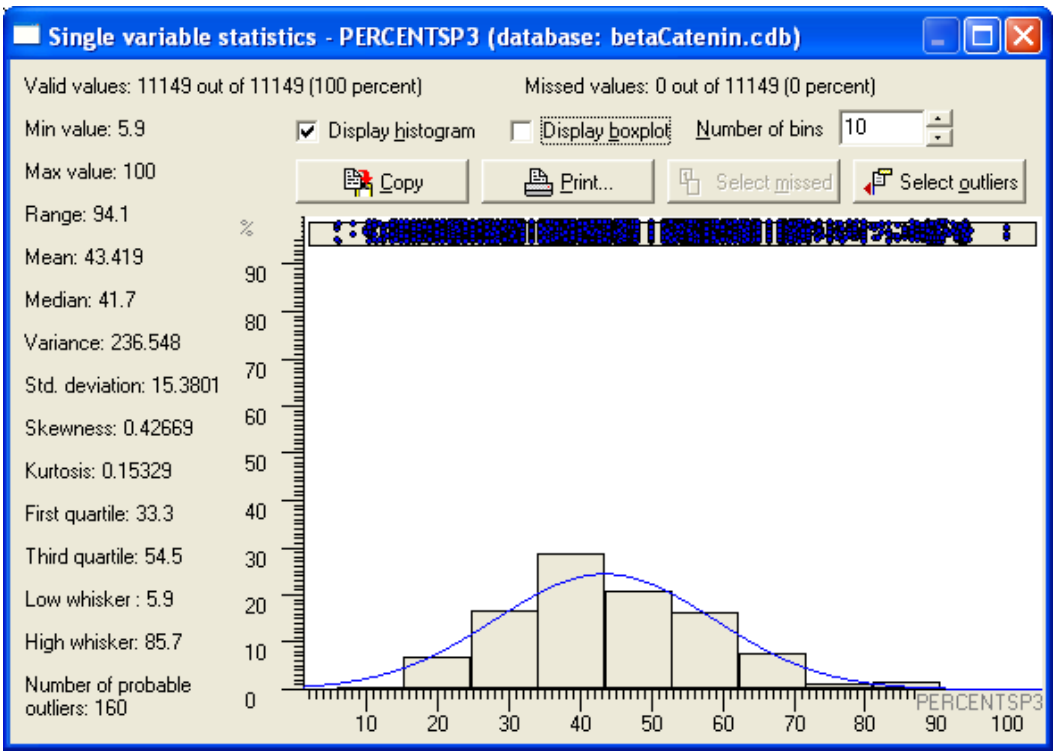

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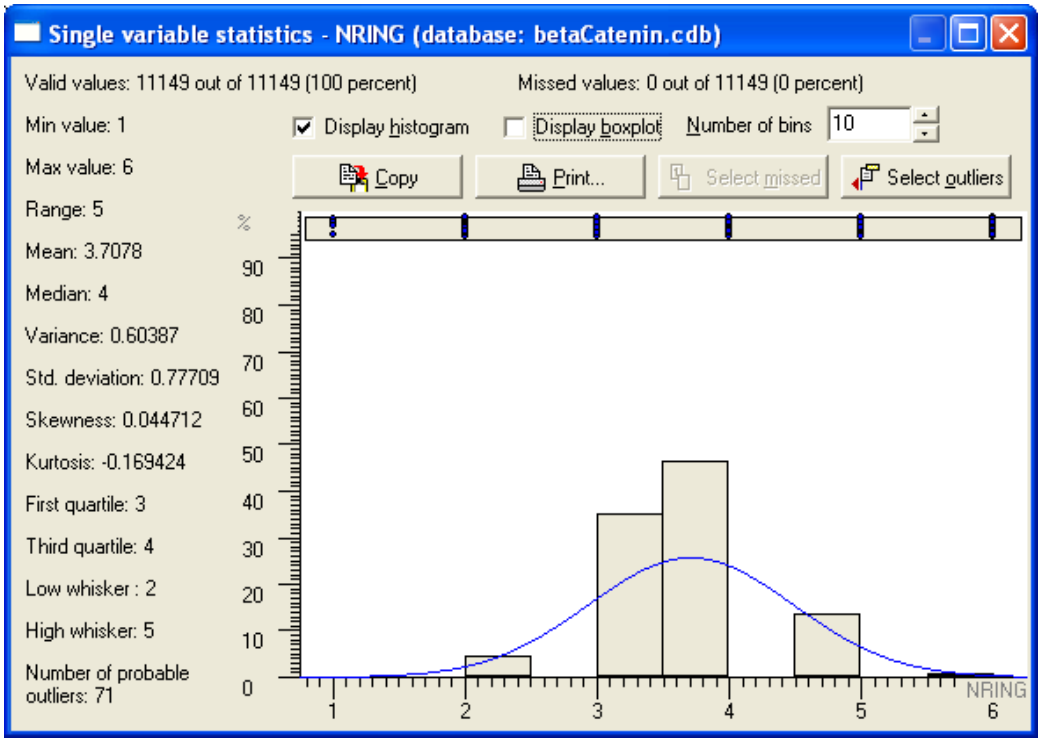
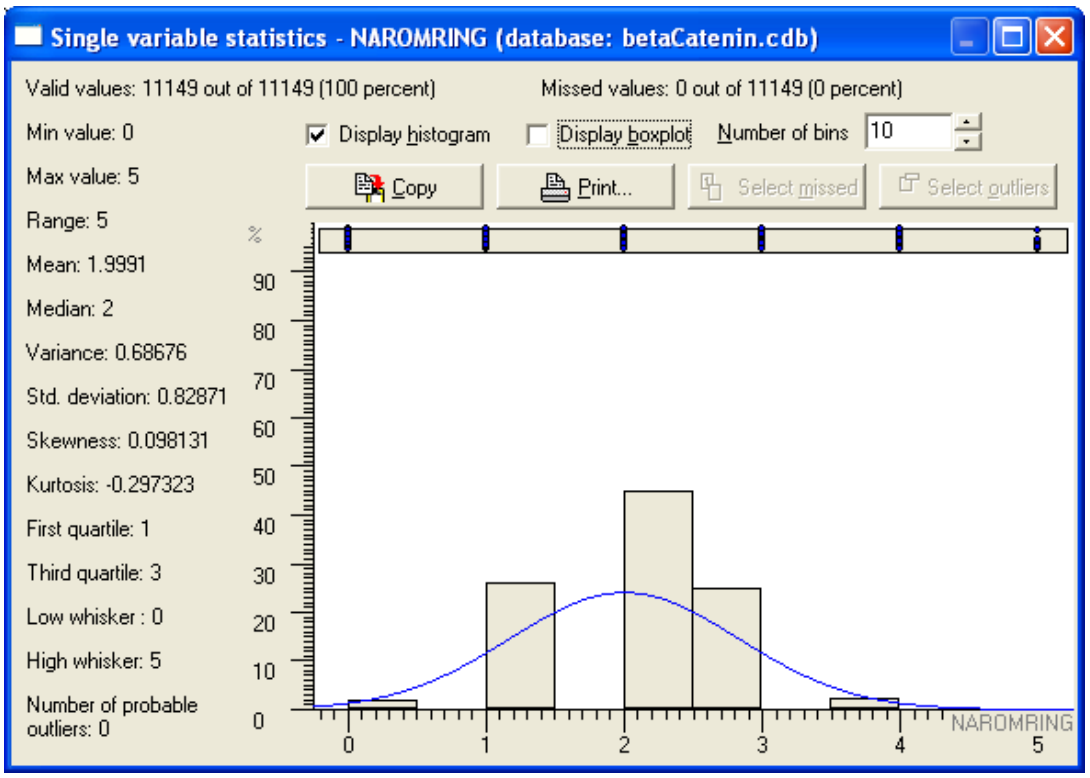
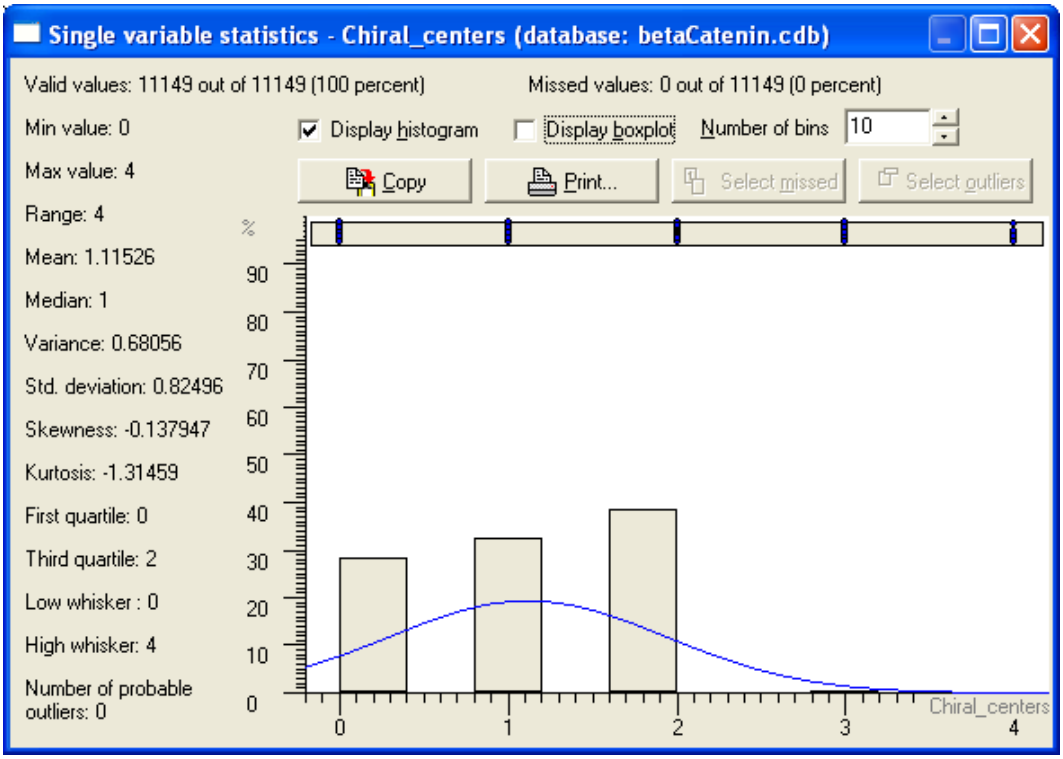


Number of rings



Number of aromatic rings



Number of chiral centers

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