

Library of small molecule inhibitors of beta-Catenin signaling

Description

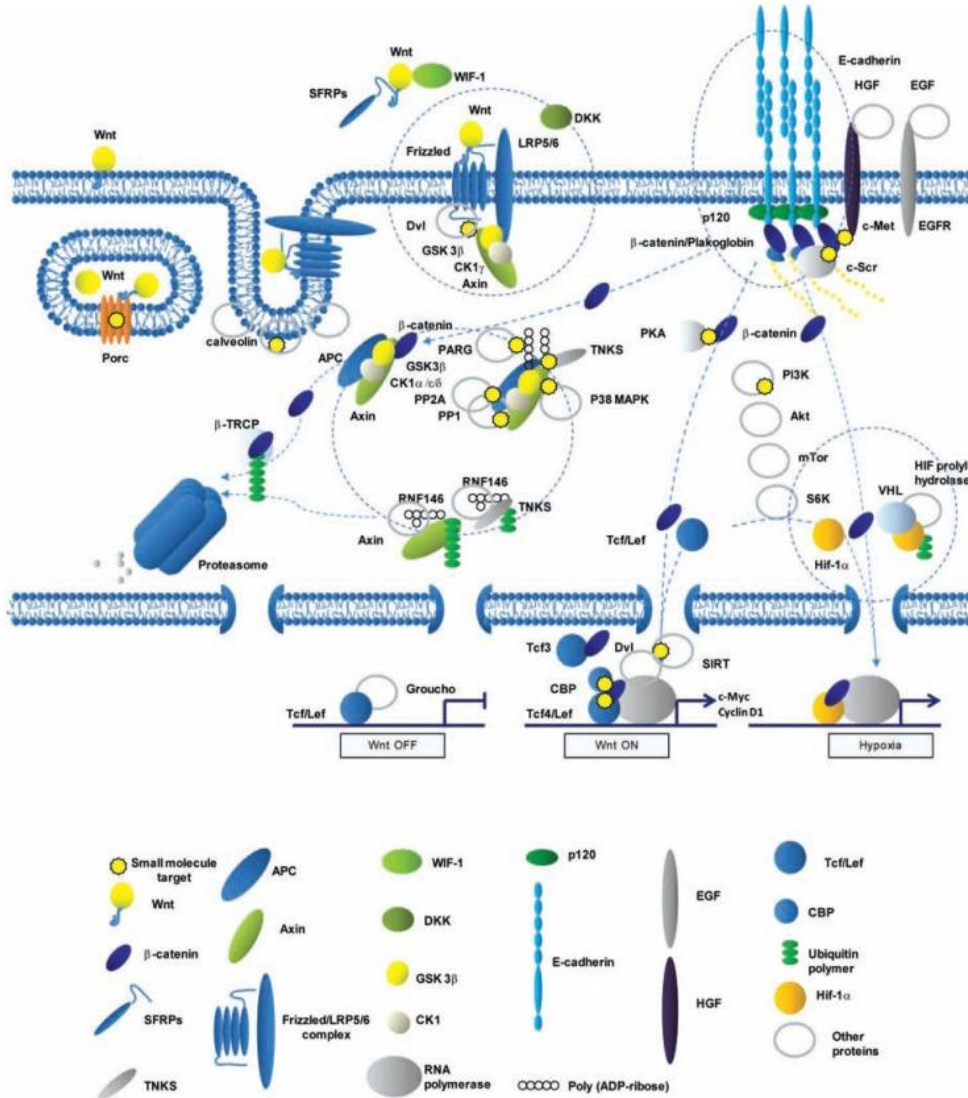
β -Catenin (Armadillo in *Drosophila*) is a fascinating protein with many important cellular and developmental functions. The roles of β -catenin are 'classically' defined: (i) as an adhesion protein and (ii) as a signaling protein, transducing extracellular signals to the nucleus to modify gene expression. β -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 β -catenin is a key to its regulation during Wnt signaling: many β -catenin interaction partners bind to a positively-charged groove in the Armadillo ARM-repeat protein region.

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

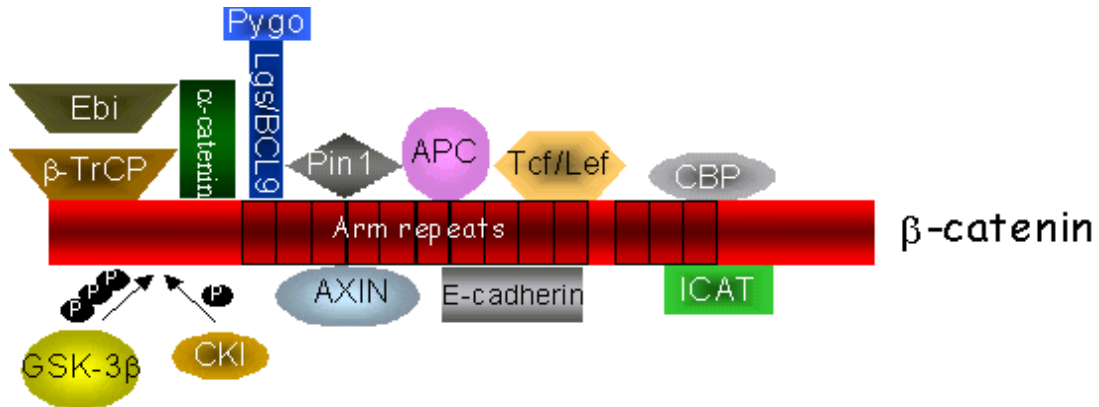
Important information inspired the library design



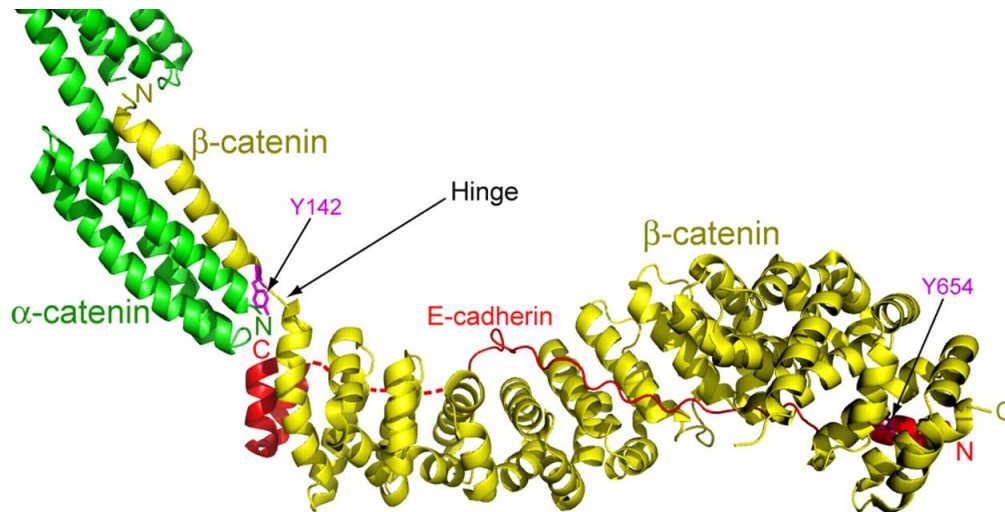
Simplified schematic representation of drug targets (yellow stars) in Wnt/β-catenin-mediated signaling.

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 (hypoxia 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
[\[http://atlasgeneticsoncology.org\]](http://atlasgeneticsoncology.org)

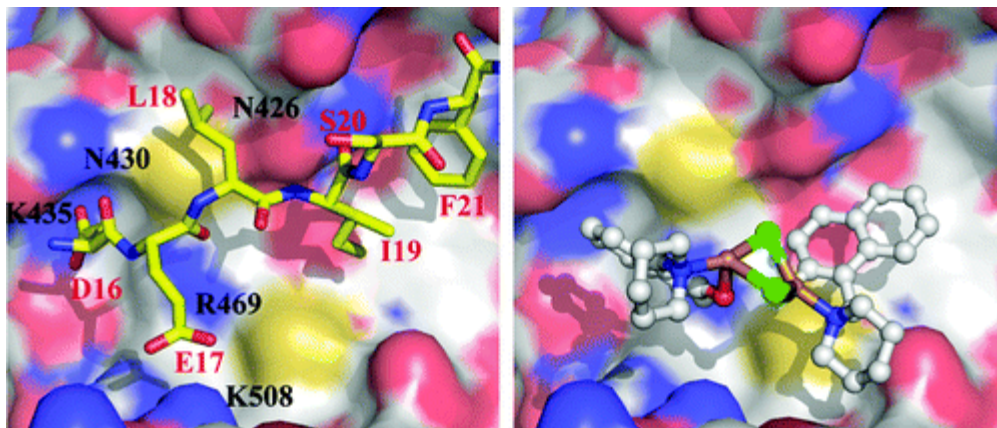


β-catenin complexes in cell adhesion. Crystal structures of the β-catenin armadillo repeat domain (yellow) in complex with the E-cadherin cytoplasmic domain (red) and the dimerization and β-catenin-binding domain of α-catenin (green) were superimposed on the basis of shared β-catenin residues 145-148.

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.

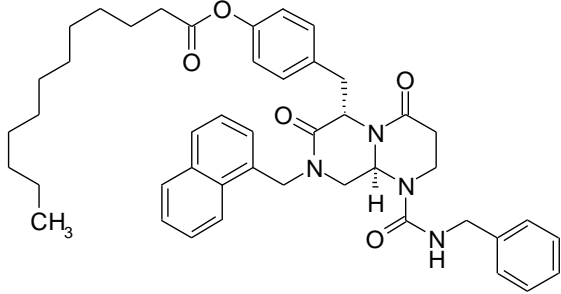
[J Cell Sci. 2007; 120(19): 3337]



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.
[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	Preclinical	
	Under_Active_Development	NO	
	Company_Code		
Name	Agelastatin A		
Condition	Antineoplastic agents 470. Absolute configuration of the marine sponge bromopyrrole agelastatin. <i>Oncol Res</i> 2005, 15(1): 1	Natural_Source	marine sponge <i>Agelas dendromorph</i>
Reference	WO 200410634 WO 200605557 WO 200807810	Therapeutic_Group	Oncolytic Drug
Organization	Penn State Research Foundation (Originator)	Mechanism_of_action	Agelastatin A (AgA), a marine sponge derived alkaloid, inhibits Wnt/ β -catenin signaling and selectively induces apoptosis in chronic lymphocytic leukemia independently of p53. <i>Blood</i> 2011, 118(21): Abstr 178

	ID #	810060
	Formula	C ₄₅ H ₅₄ N ₄ O ₅
	MW	730.956
	Highest_Phase	Biological Testing
	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 Inhibitor	
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**

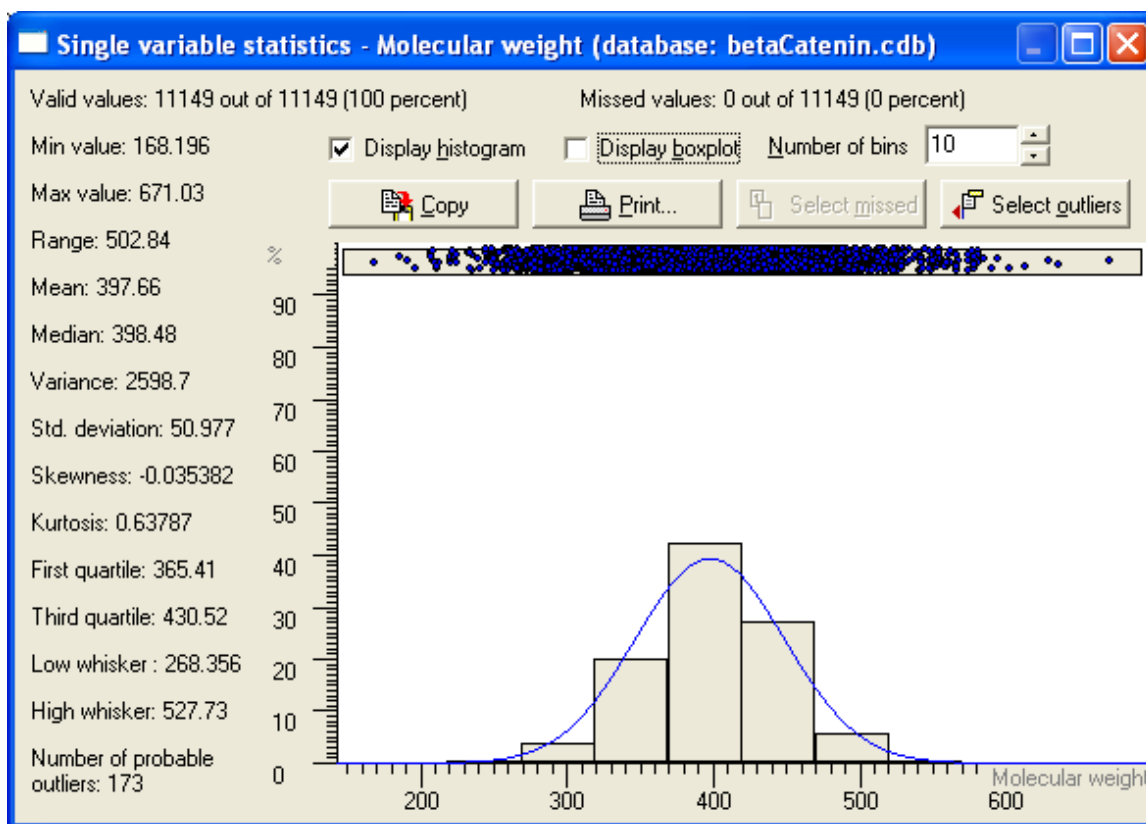
The number of scaffolds **107**

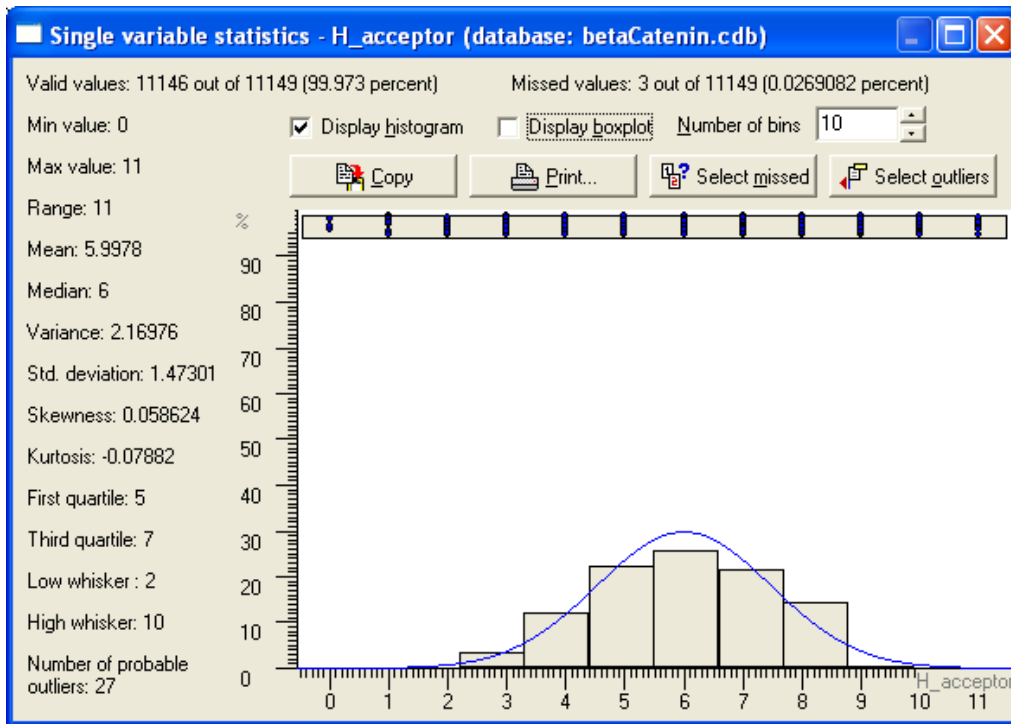
Singletons **43**

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

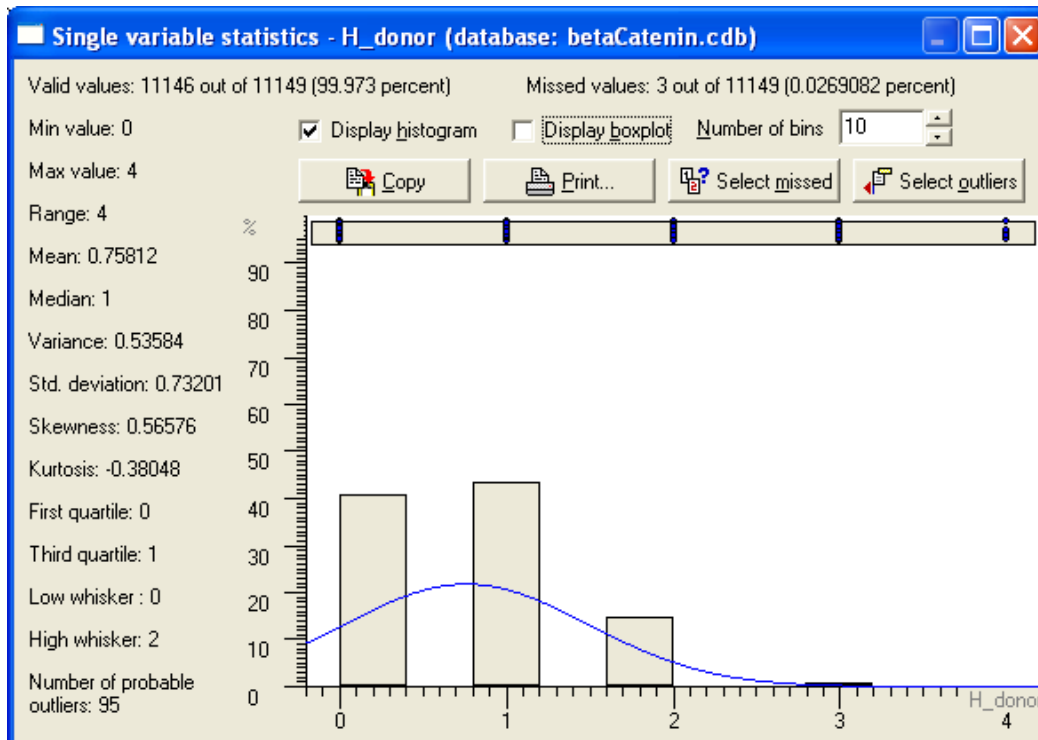
date	number	%
2013	3593	32.23
2012	6463	57.97
2011	429	3.85
2010	72	0.65
2009	60	0.54
2008	9	0.08
2007	222	1.99
2006	133	1.19
2005	9	0.08
2004	14	0.13
2003	101	0.91
2002	2	0.02
2001	9	0.08
2000	33	0.30

Physico-chemical properties

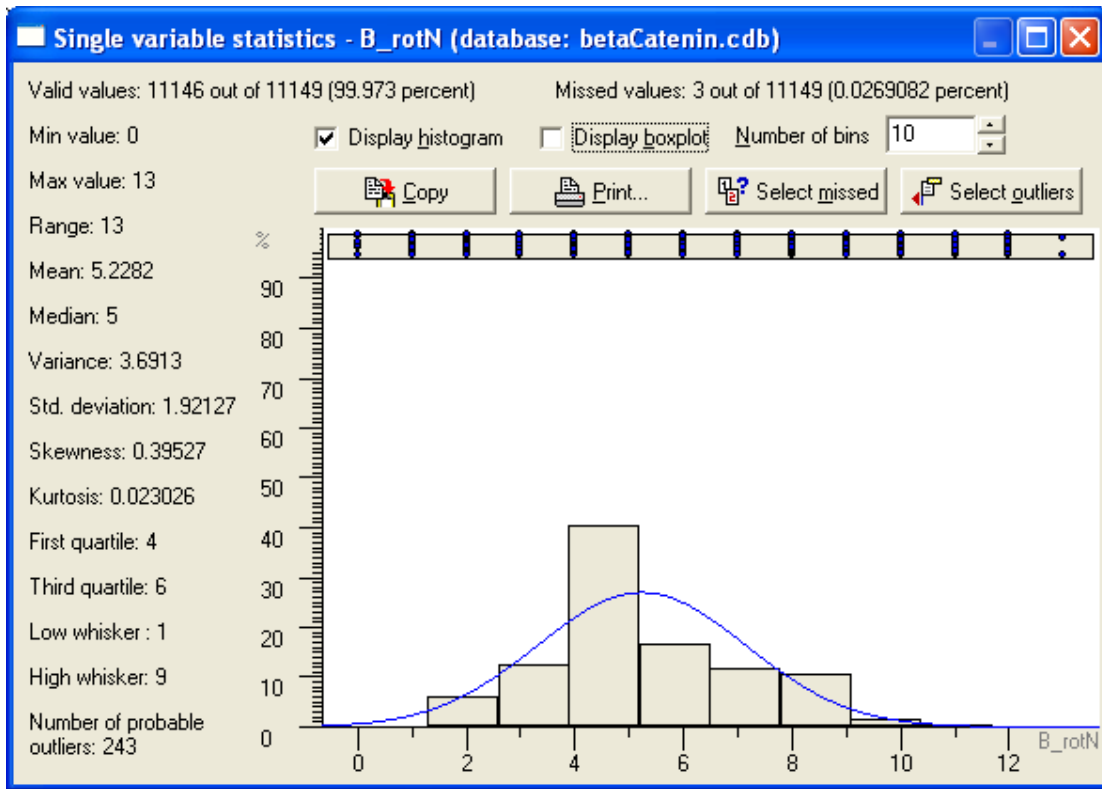




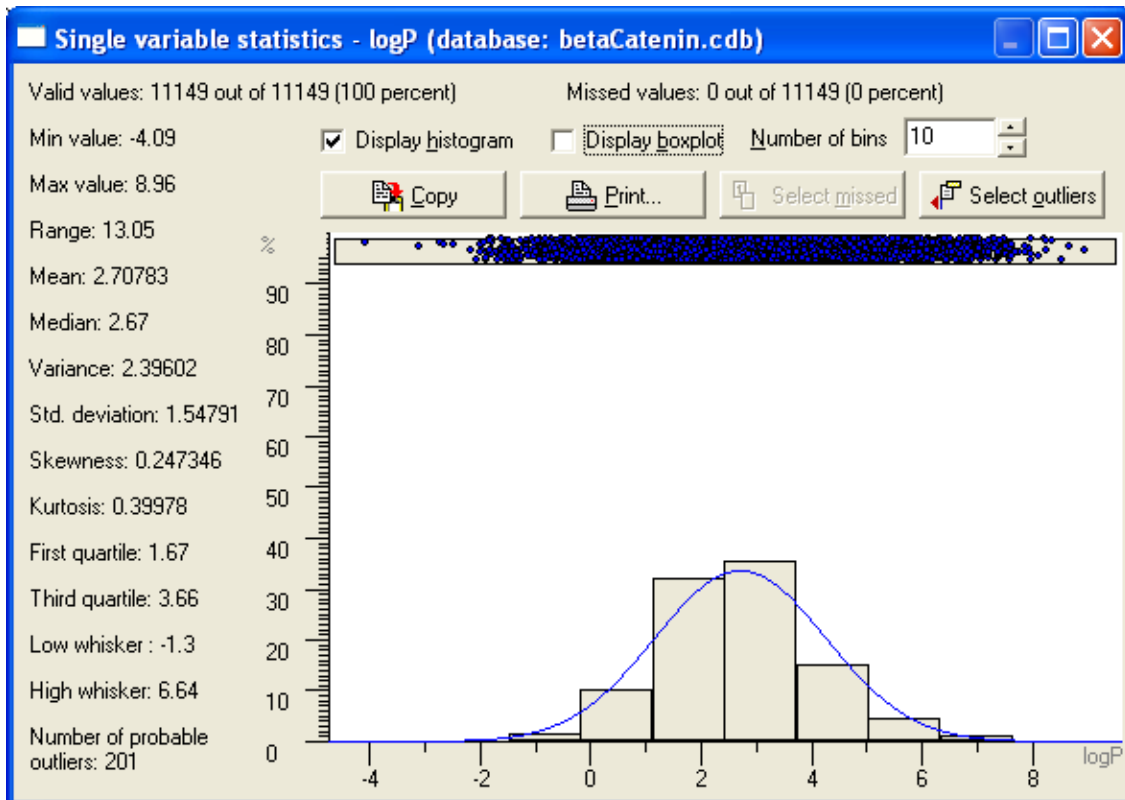
HBA



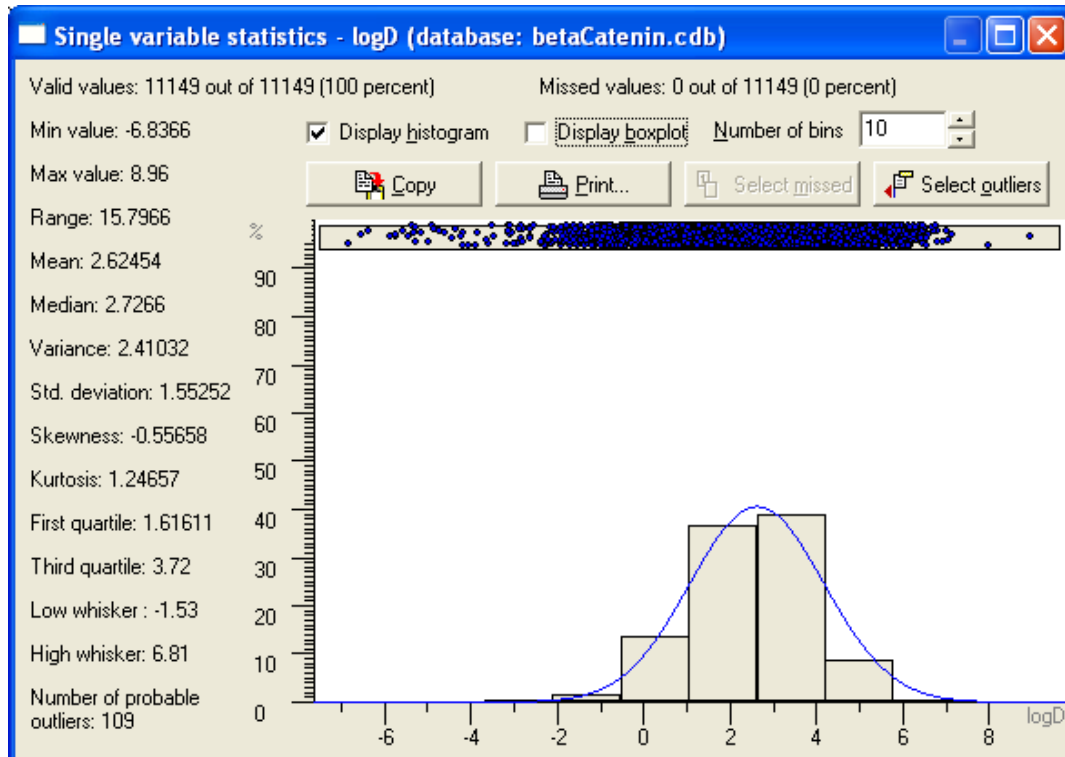
HBD



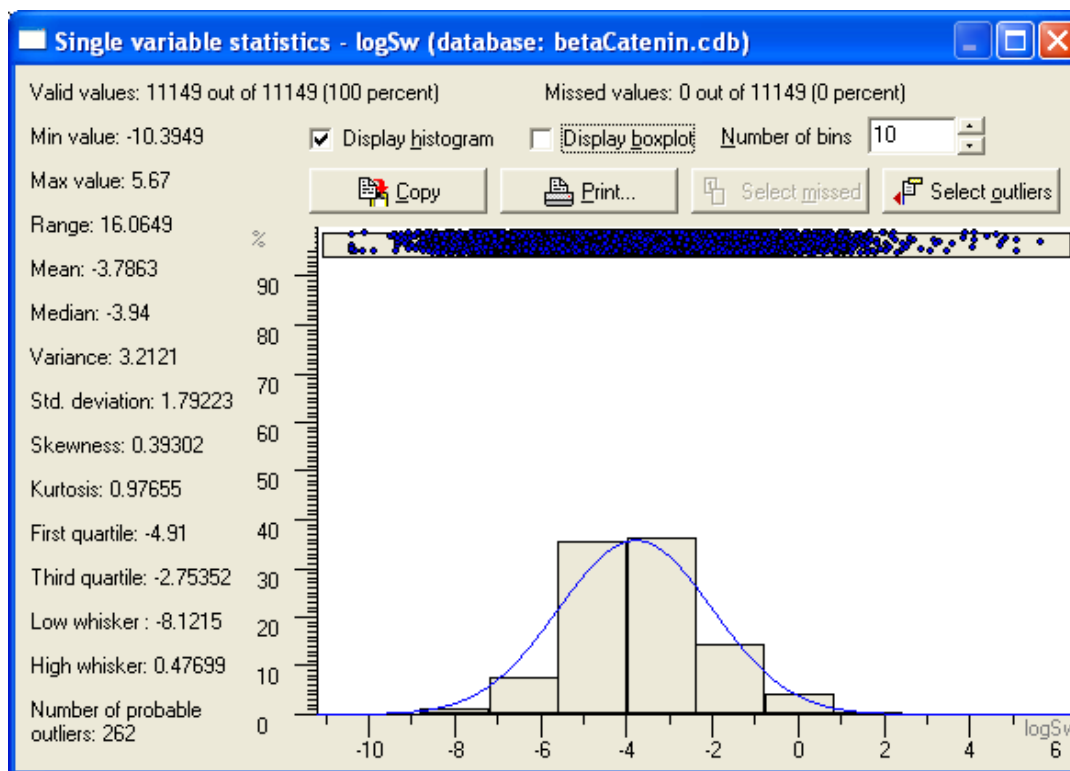
Rotatable Bonds



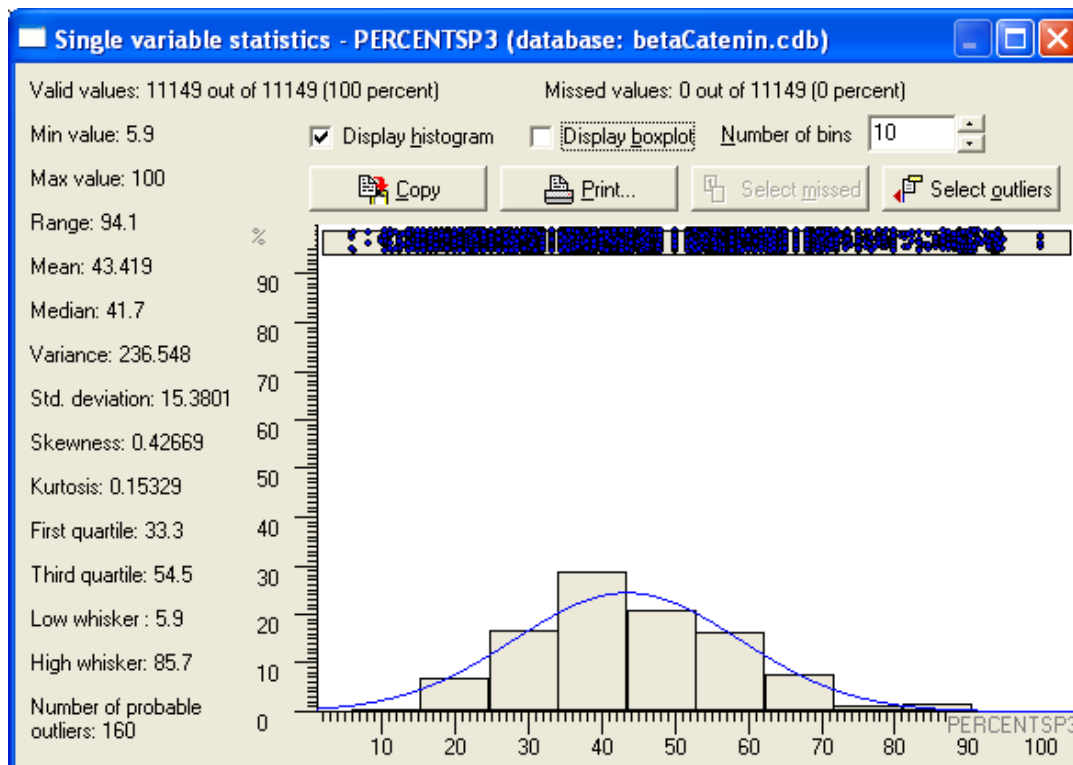
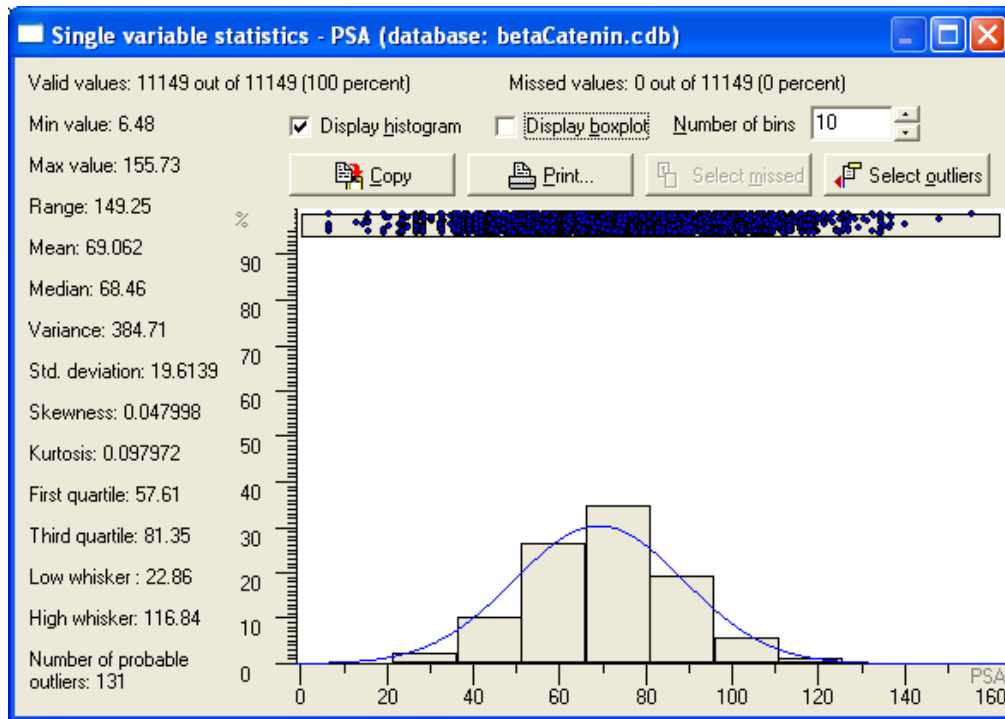
ClogP



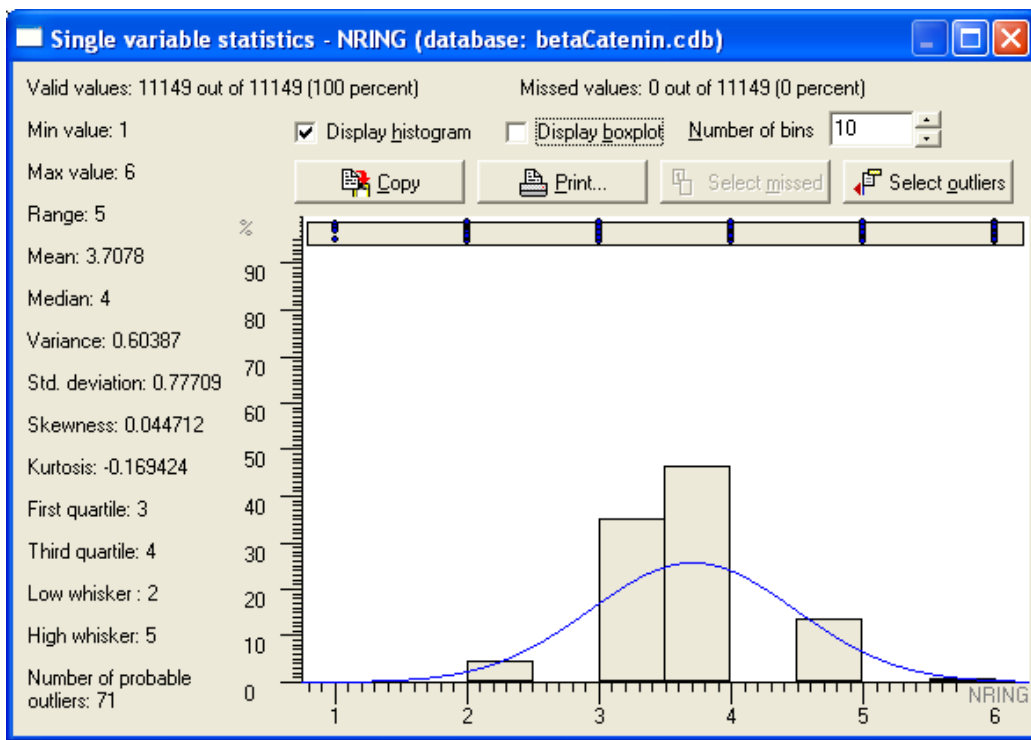
ClogD



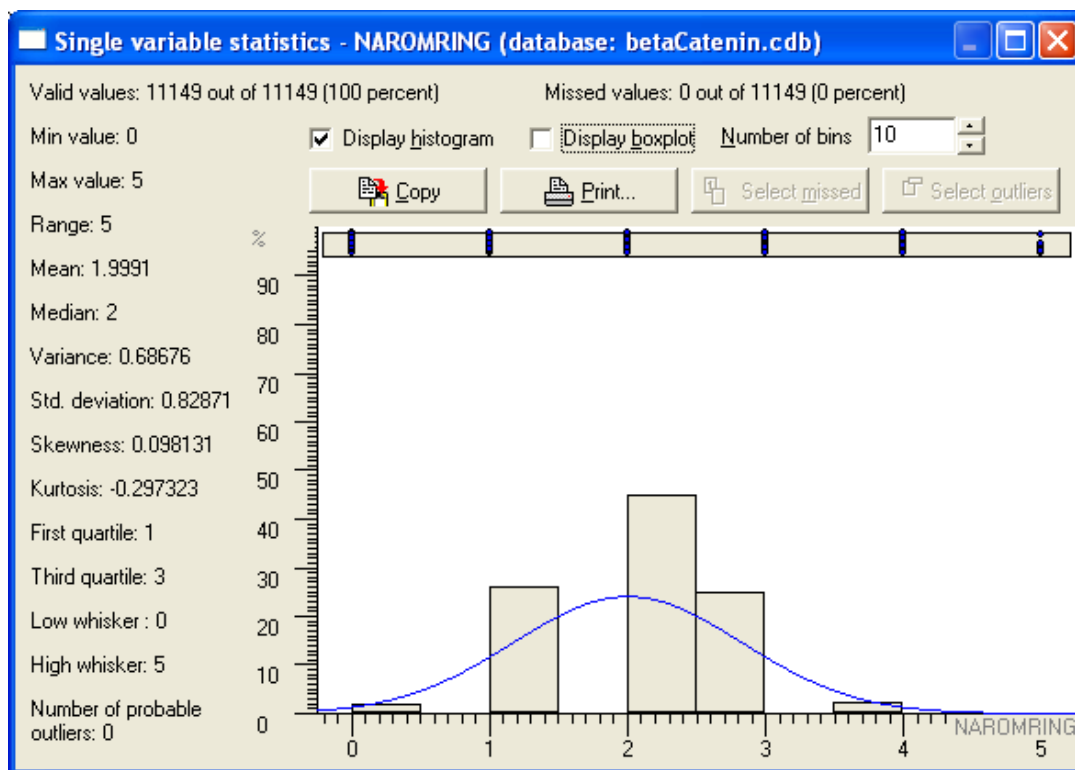
LogSW



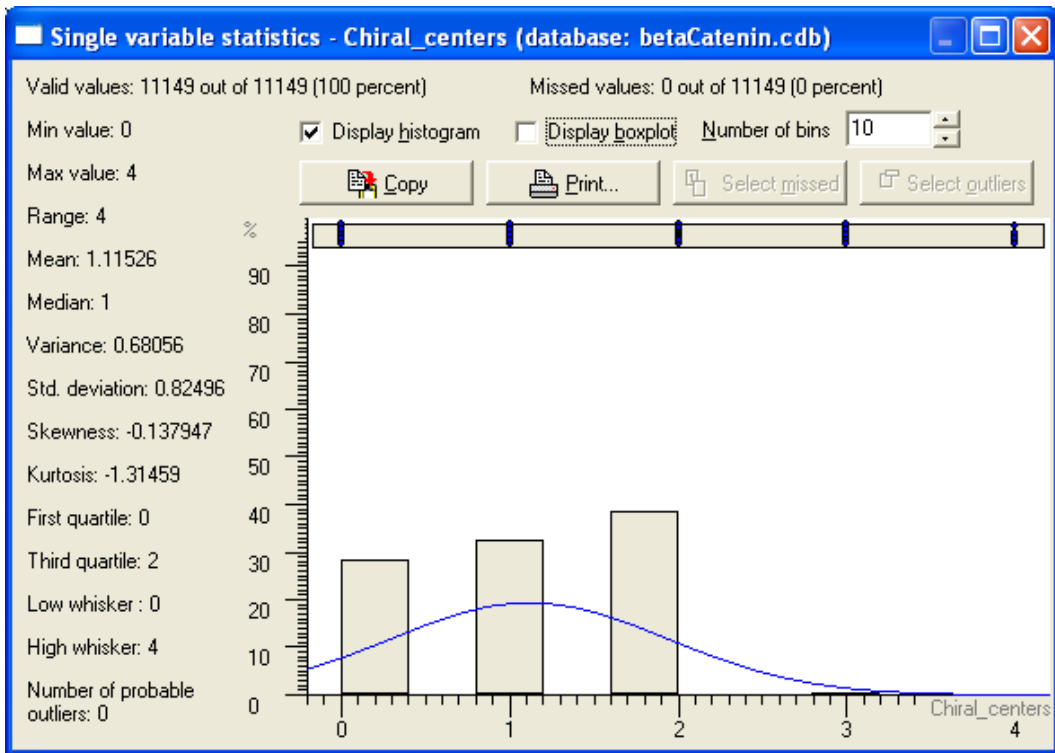
Fsp3%



Number of rings



Number of aromatic rings



Number of chiral centers