Library of small molecule modulators/inhibitors of Bromodomains

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

Description

Acetylation of lysine residues is a post-translational modification with broad relevance to cellular signaling and disease biology. Enzymes that 'write' histone acetyltransferases (HATs) and 'erase' (histone deacetylases, HDACs) acetylation sites are an area of extensive research in current drug development, but very few selective and potent modulators of the 'reading process have been described. Bromodomains (BRDs) are evolutionary conserved protein interaction modules that specifically recognize ε-N-lysine (KAc) acetylation motifs, a key event in the 'reading' process of epigenetic marks.

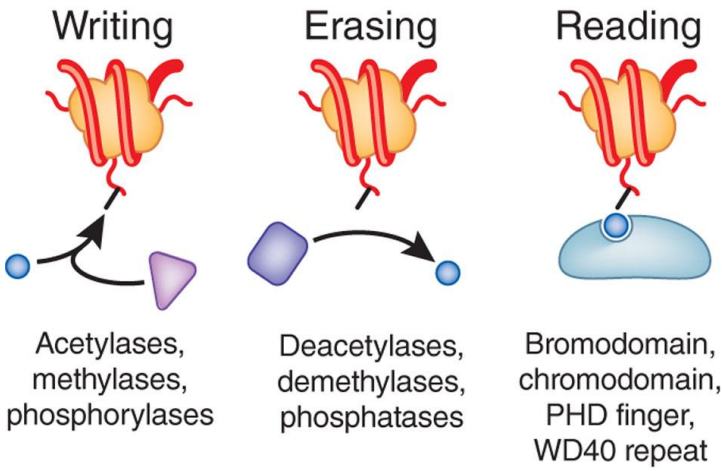
Bromodomains are named after the *Drosophila* gene *brahma* where they were first identified. These domains have been observed as part of numerous larger protein architectures, many of which are involved in regulating gene transcription, including HATs, ATP-dependent chromatin-remodeling complexes, methyltransferases, and transcriptional coactivators. There have been 61 bromodomains identified in the human proteome, which are found within 46 separate proteins, and that can be phylogenetically divided into eight distinct families [Cell 2012; 149: 214].

The precise cellular role of most bromodomain containing proteins (BCPs) is still unknown. However, those BCPs that have been studied in detail have been linked to certain diseases, and this work has been extensively reviewed [J Med Chem. 2012; 55: 9393]. As bromodomains are invariably components of large multidomain proteins, removal of the whole BCP does not provide information on the specific function of the bromodomain itself. Consequently, an important strategy in the study of bromodomain function is the development of small molecule effectors that selectively prevent the interaction of a given bromodomain with KAc, without affecting other functions of the BCP.

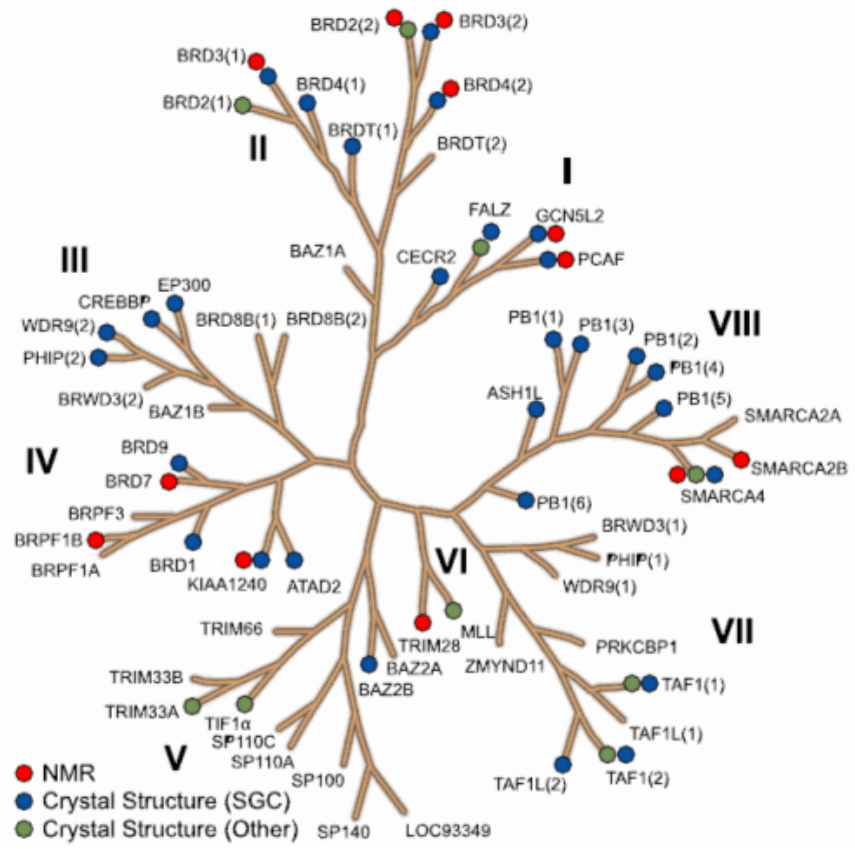
The large number of diseases that have been linked to BRD-containing proteins and the success of particular HDAC inhibitors indicate that BRD inhibitors will find a large number of applications in drug discovery and academic research. The relatively weak interaction of BRDs with their substrates, the diversity and physicochemical properties of the acetyl lysine binding site, and the large number of available crystal structures will facilitate the rational design of such inhibitors.

ChemDiv proposes the new library of BRDs inhibitors/modulators. This library represents a selection of drug-like compounds aimed at modulating protein-protein interaction of BCPs 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. Evaluation of the rich body of structural information on bromodomains enabled detailed family-wide structural analysis of the human BRD family and its "druggability". ChemDiv combined a number of *in silico* screening approaches and spatial information of putative acetyl-lysine mimetics to identify chemical starting points for the development of BRDs inhibitor library.

Important information inspired the library design



'Writers' introduce histone marks (circles), 'erasers' take them out and 'readers' can recognize a particular form of histone modification



Phylogenetic tree of the human BRD family. The different families are named by Roman numbers (I–VIII). Structures determined in this study, by NMR, or by other groups are indicated by blue, red, and green dots, respectively.
[Cell 2012; 149: 214]

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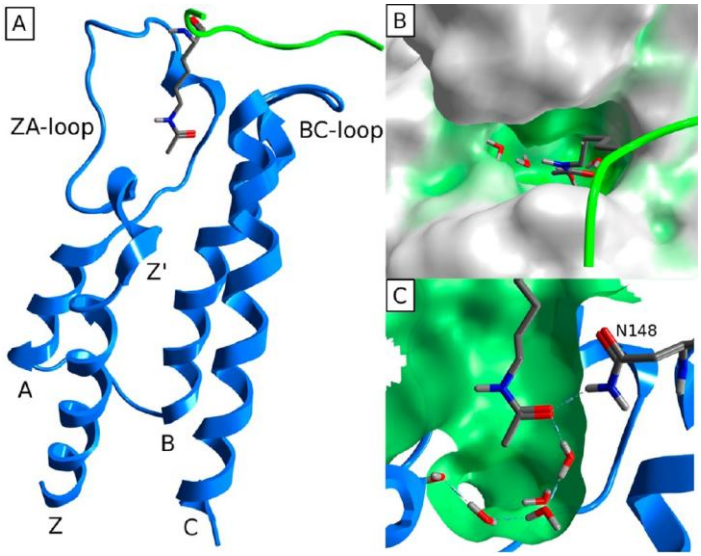
EMAIL: chemdiv@chemdiv.com, www.chemdiv.com

Table 1. Bromodomain-containing proteins and their functions

Protein	Name	Function	BRDs
ASH1L	Absent, small or homeotic-like	Methyltransferase	1
ATAD2A/B	AAA domain-containing protein 2	ATPase, coactivator	1
BAZ1A/B	BRD adjacent to zinc finger domain protein 1A	Chromatin assembly and remodelling	1
BAZ2A/B	BRD adjacent to zinc finger domain protein 2A/B	Unknown	1
BRD1	BRD-containing 1	Transcription factor	1
BRD2	BRD-containing 2	Transcription factor	2
BRD3	BRD-containing 3	Transcription factor	2
BRD4	BRD-containing 4	Transcription factor	2
BRDT	BRD-containing protein testis specific	Transcription factor	2
BRD7	BRD-containing 7	Transcriptional repressor	1
BRD8A/B	BRD-containing 8A/B	TRRAP/TIP60 complex	2
BRD9	BRD-containing 9	Unknown	1
BRPF1A/B	Peregrin	MOZ complex subunit	1
BRPF3A	BRD and PHD-finger-containing protein 3	Unknown	1
BRWD3	BRD and WD-repeat-containing protein 3	JAK/STAT signalling	2
CECR2	Cat eye syndrome critical region 2	Chromatin remodelling	1
CREBBP	CREB-binding protein	HAT	1
EP300	HAT p300	HAT	1
FALZ	Fetal Alzheimer antigene	Chromatin remodelling	1
GCN5L2	General control of amino acid synthesis protein 5-like 2	HAT	1
MLL	Mixed lineage leukaemia	Histone methyltransferase	1
PB1	Polybromo	SWI/SNF PBAF subunit	6
PCAF	P300/CBP-associated factor	HAT	1
PHIP	PH-interacting protein	Insulin signalling	2
PRKCBP1	Protein kinase C-binding protein 1	Transcriptional regulator	1
SMARCA2A/B	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin	SWI/SNF ATPase	1
SMARCA4	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin	SWI/SNF ATPase	1
SP100/SP110/SP140	Nuclear body protein	Transcriptional regulator	
TAF1/TAF1L	Transcription initiation TFIID-associated factor	Transcription initiation	2
TRIM24/TRIM28/TRIM33/TRIM66	Transcription intermediary factor	Transcriptional silencer	1
WDR9	BRD and WD-repeat-containing protein 1	Chromatin remodelling	2
ZMYND11	Zinc finger MYND-domain-containing protein 11	Corepressor	1

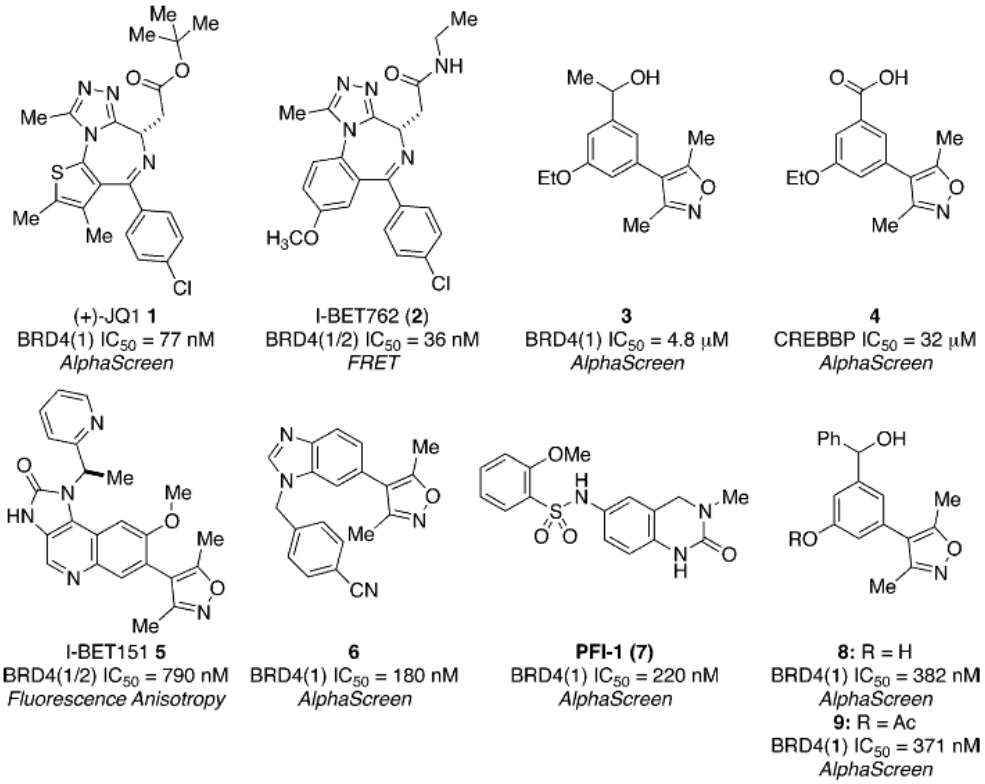
BRD, bromodomain; HAT, histone acetyltransferase; MOZ, monocytic leukaemia zinc finger protein; PHD, plant homology domain; SNF, sucrose nonfermenting.

[Exp Rev Mol Med. 2011; 13: e29]



(A) Conserved protein fold of bromodomains comprising the four canonical helices αZ, αA, αB, and αC. (B) Surface representation of a typical KAc binding site. (C) Typical binding of KAc to bromodomain.
[J Med Chem. 2012; 55: 7346]

The conserved BRD fold contains a deep, largely hydrophobic acetyl lysine binding site, which represents an attractive pocket for the development of small, pharmaceutically active molecules.



(+)-JQ1 **1**
BRD4(1) IC_{50} = 77 nM
AlphaScreen

I-BET762 (**2**)
BRD4(1/2) IC_{50} = 36 nM
FRET

3
BRD4(1) IC_{50} = 4.8 μM
AlphaScreen

4
CREBBP IC_{50} = 32 μM
AlphaScreen

I-BET151 **5**
BRD4(1/2) IC_{50} = 790 nM
Fluorescence Anisotropy

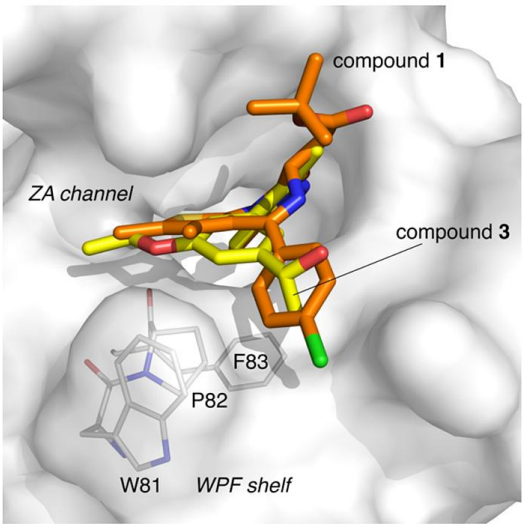
6
BRD4(1) IC_{50} = 180 nM
AlphaScreen

PFI-1 (7)
BRD4(1) IC_{50} = 220 nM
AlphaScreen

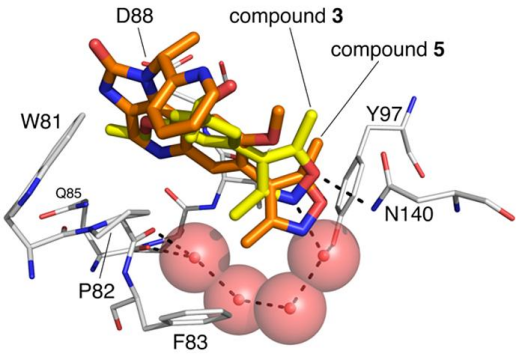
8: R = H
BRD4(1) IC_{50} = 382 nM
AlphaScreen
9: R = Ac
BRD4(1) IC_{50} = 371 nM
AlphaScreen

Examples of known BRDs inhibitor

A



B

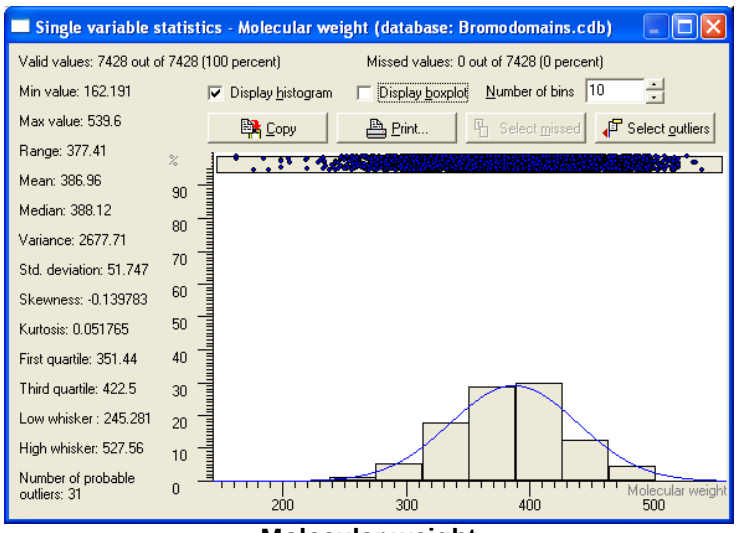


(A) Overlaid X-ray crystal structures of compound **3** (PDB code 3SVG, carbon = yellow) and compound **1** (PDB code 3MXF, carbon = orange), both bound to human BRD4(1). The methyl group of **3** does not occupy the WFP shelf as effectively as the chlorophenyl moiety of **1**.
(B) Overlaid X-ray crystal structures of compound **3** (PDB code 3SVG, carbon = yellow) and compound **5** (PDB code 3ZYU, carbon = orange), both bound to human BRD4(1).
[J Med Chem. 2013; 56: 3217]

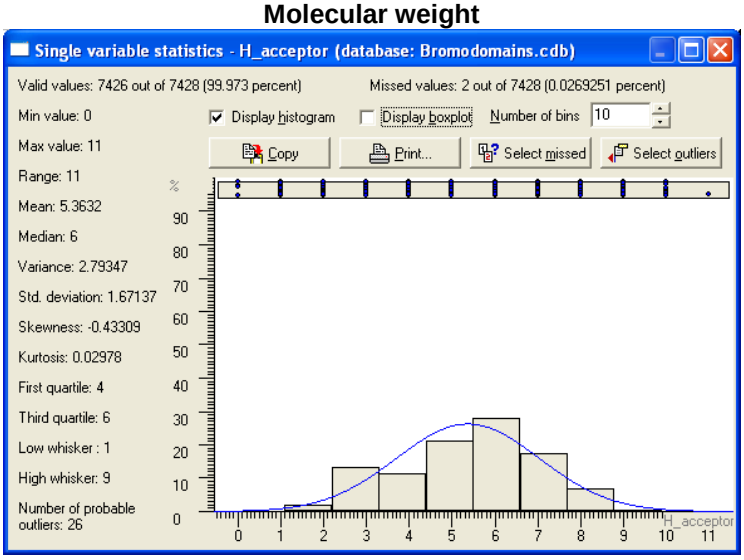
Variable statistics for 7,428 compounds from Bromodomains library.

Diversity **0,7776**
The number of screens in dataset **2671**
Number of unique heterocycles **116**
The number of Scaffolds **143**
Singletons **22**
Novelty: The number of compounds (%) per year

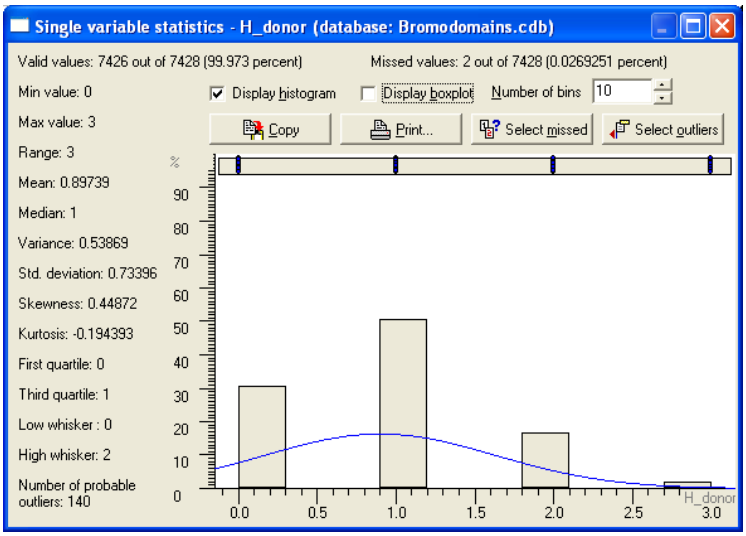
date	numbers	%
2013	1638	**22.05**
2012	3469	**46.70**
2011	342	**4.60**
2010	551	7.42
2009	704	9.48
2008	106	1.43
2007	49	0.66
2006	265	3.57
2005	139	1.87
2004	5	0.07
2003	57	0.77
2002	99	1.33
2001	2	0.03
2000	1	0.01
1999	1	0.01



Molecular weight



HBA



HBD

ChemDiv, Inc. 6605 Nancy Ridge Drive, San Diego, CA 92121 USA
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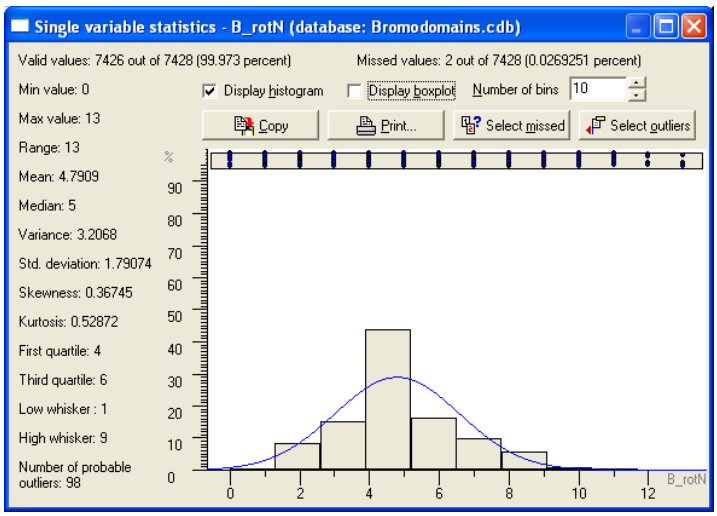
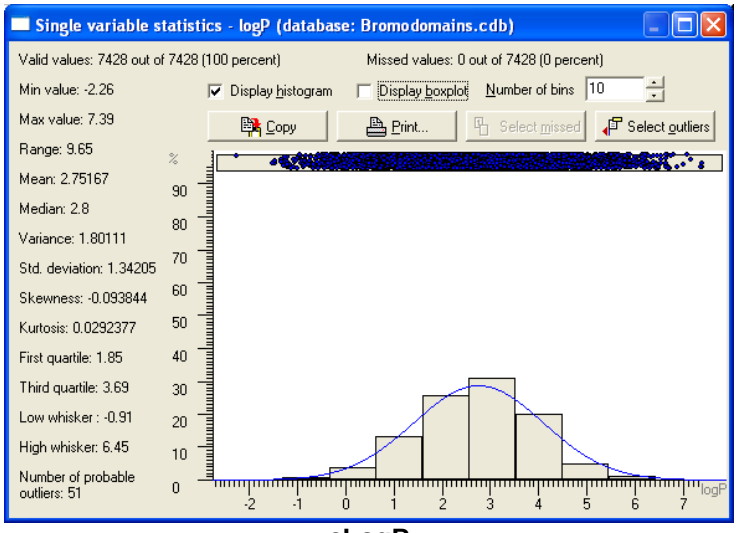
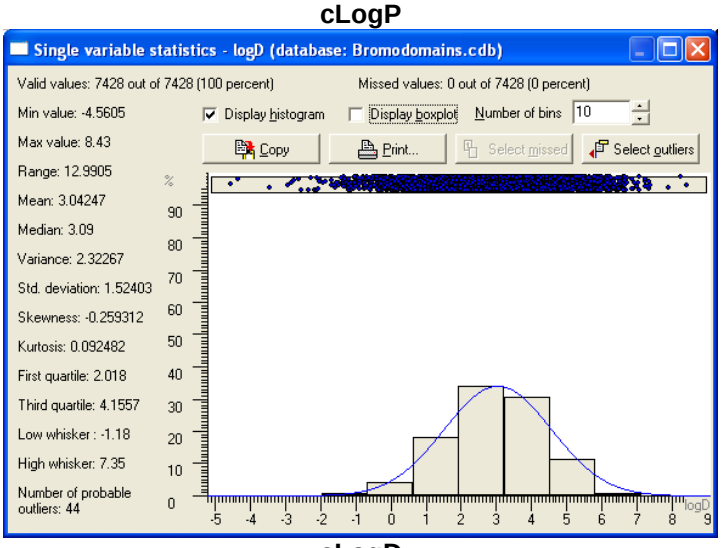


Rotatable Bonds



cLogP



cLogD

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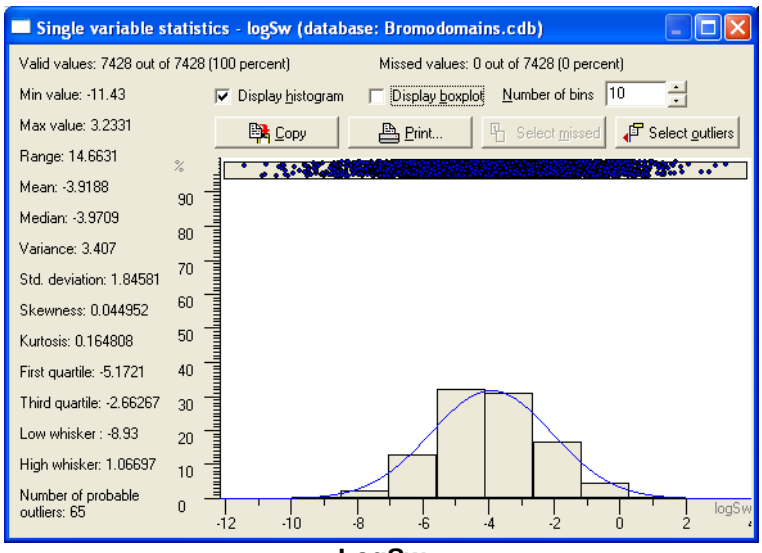
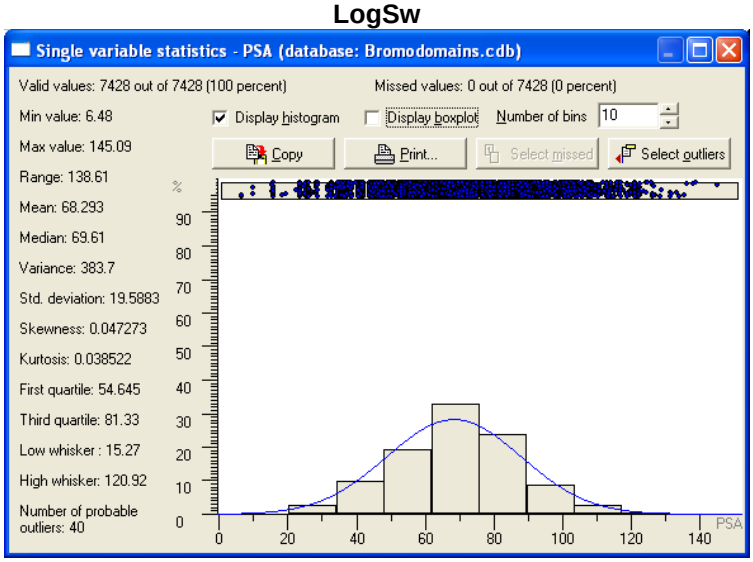
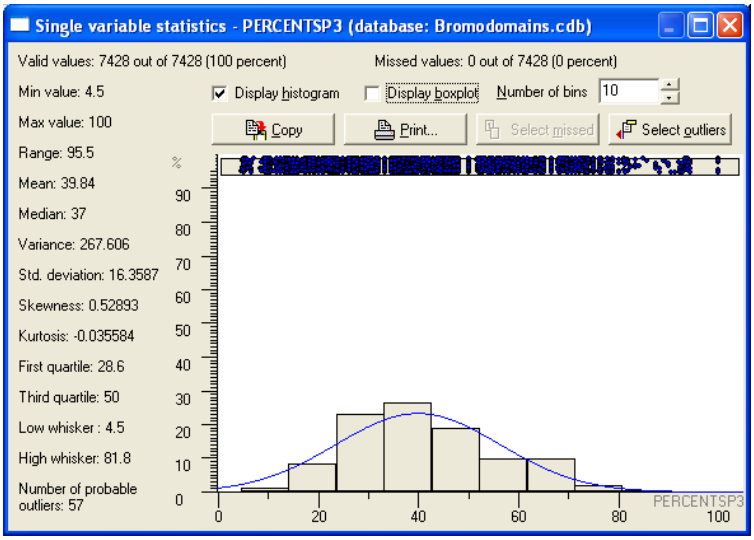


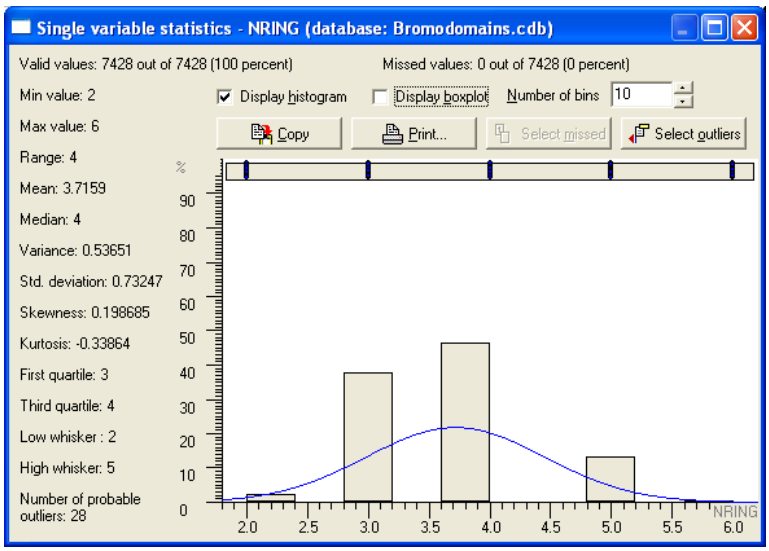
LogSw



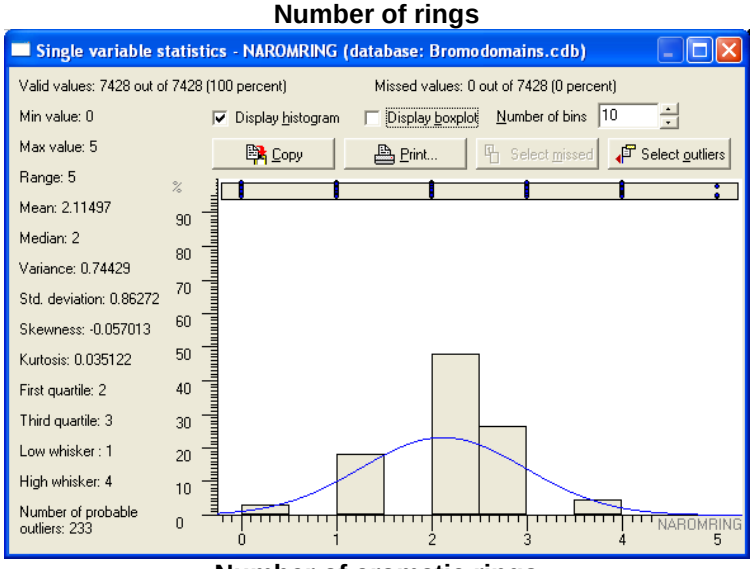
PSA



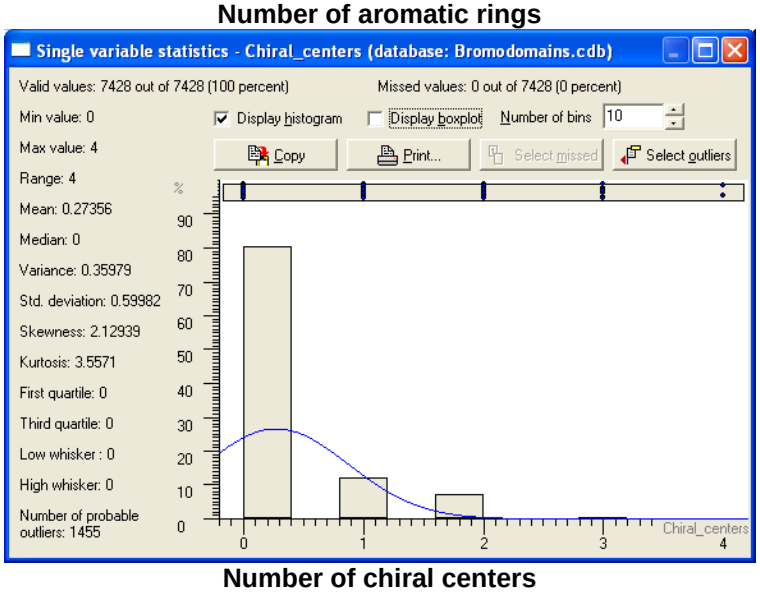
Fsp3(%)



Number of rings



Number of aromatic rings



Number of chiral centers

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