Volgograd State Medical University

Research Center of Innovative Medicines

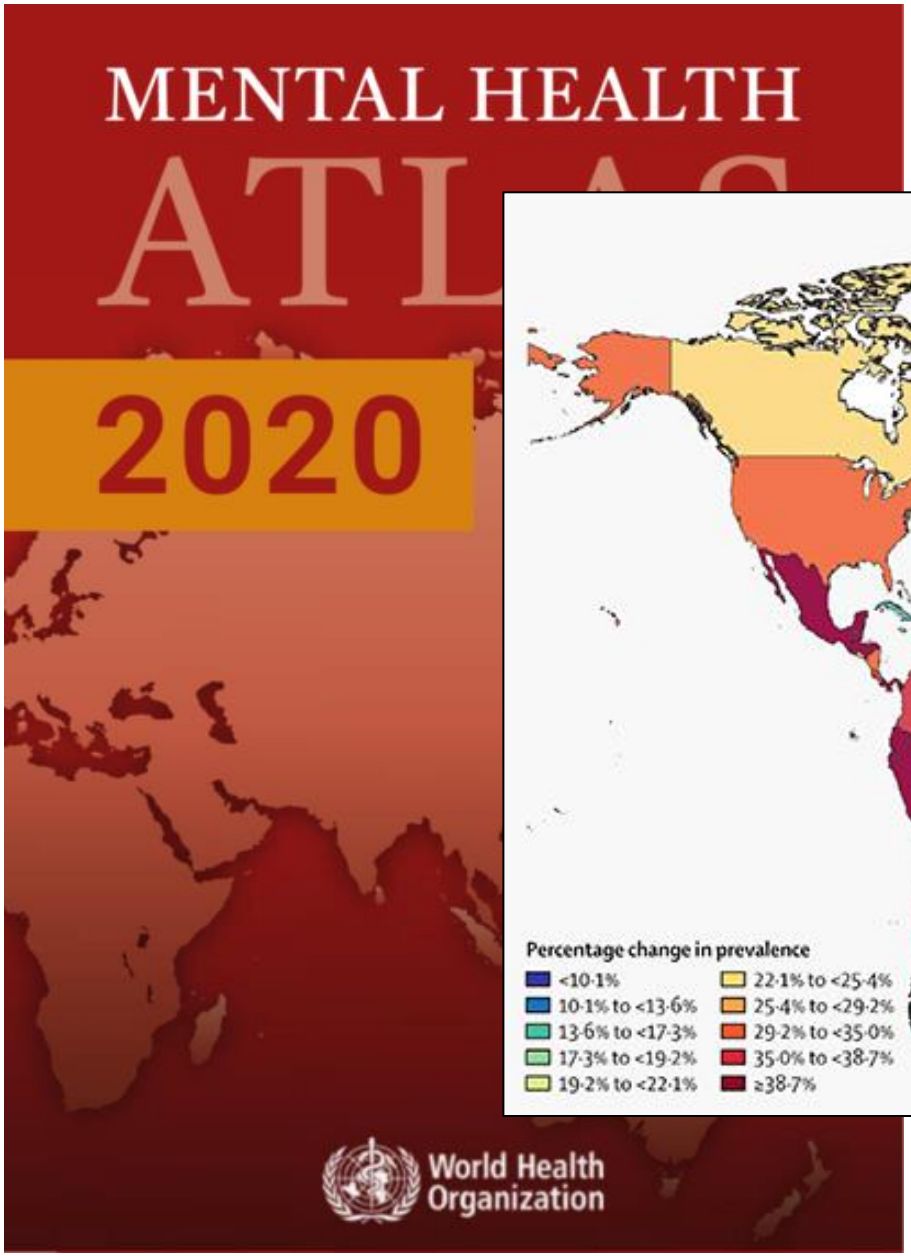
Laboratory for Information Technology in Pharmacology and Computer Modeling of Drugs

CONSENSUS MODELING OF ANXIOLYTIC ACTIVITY OF CHEMICAL COMPOUNDS BY CONVOLUTIONAL NEURAL NETWORKS

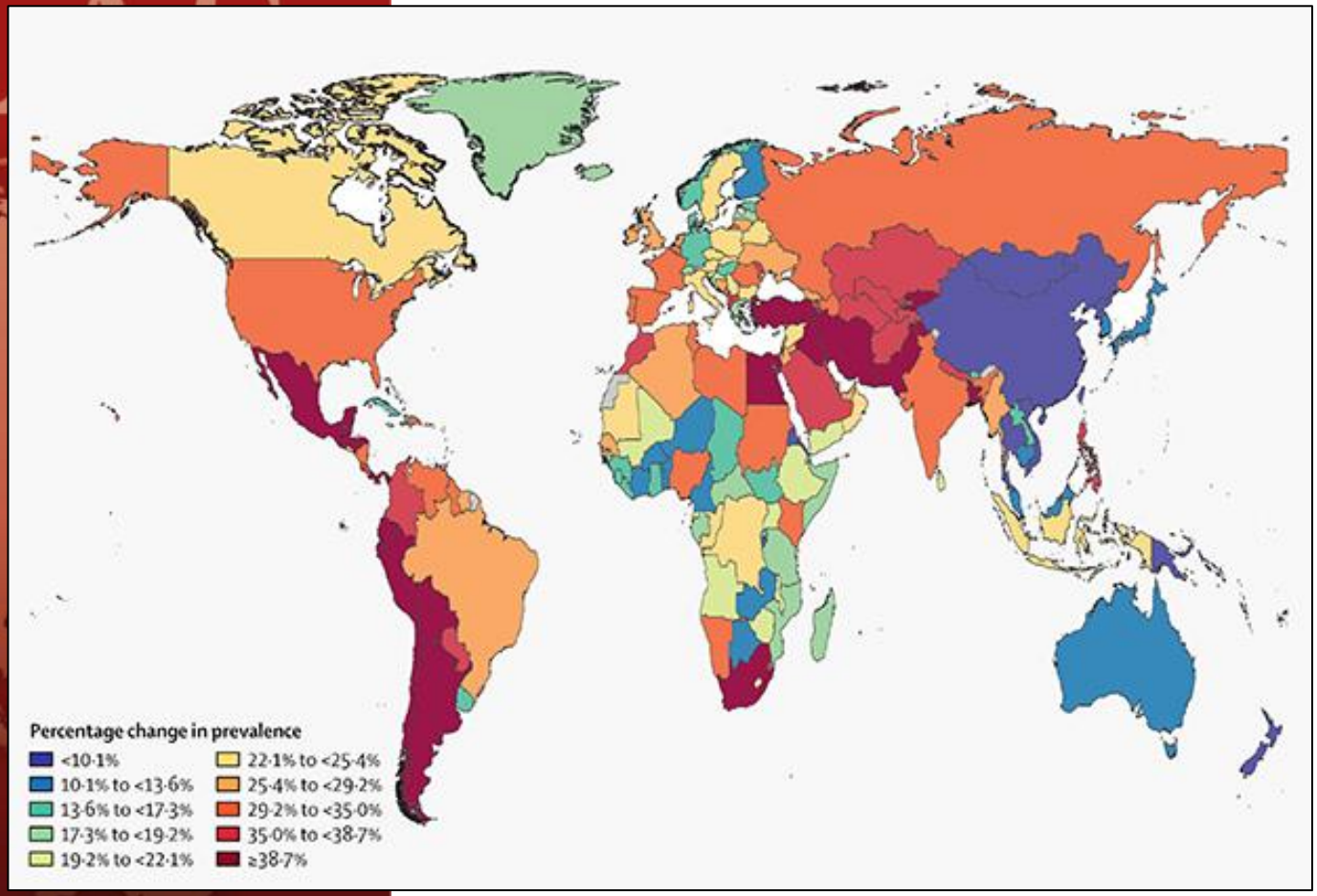
Vassiliev Pavel Mikhailovich

Research Center of Innovative Medicines

Depression and anxiety disorders



635 million people



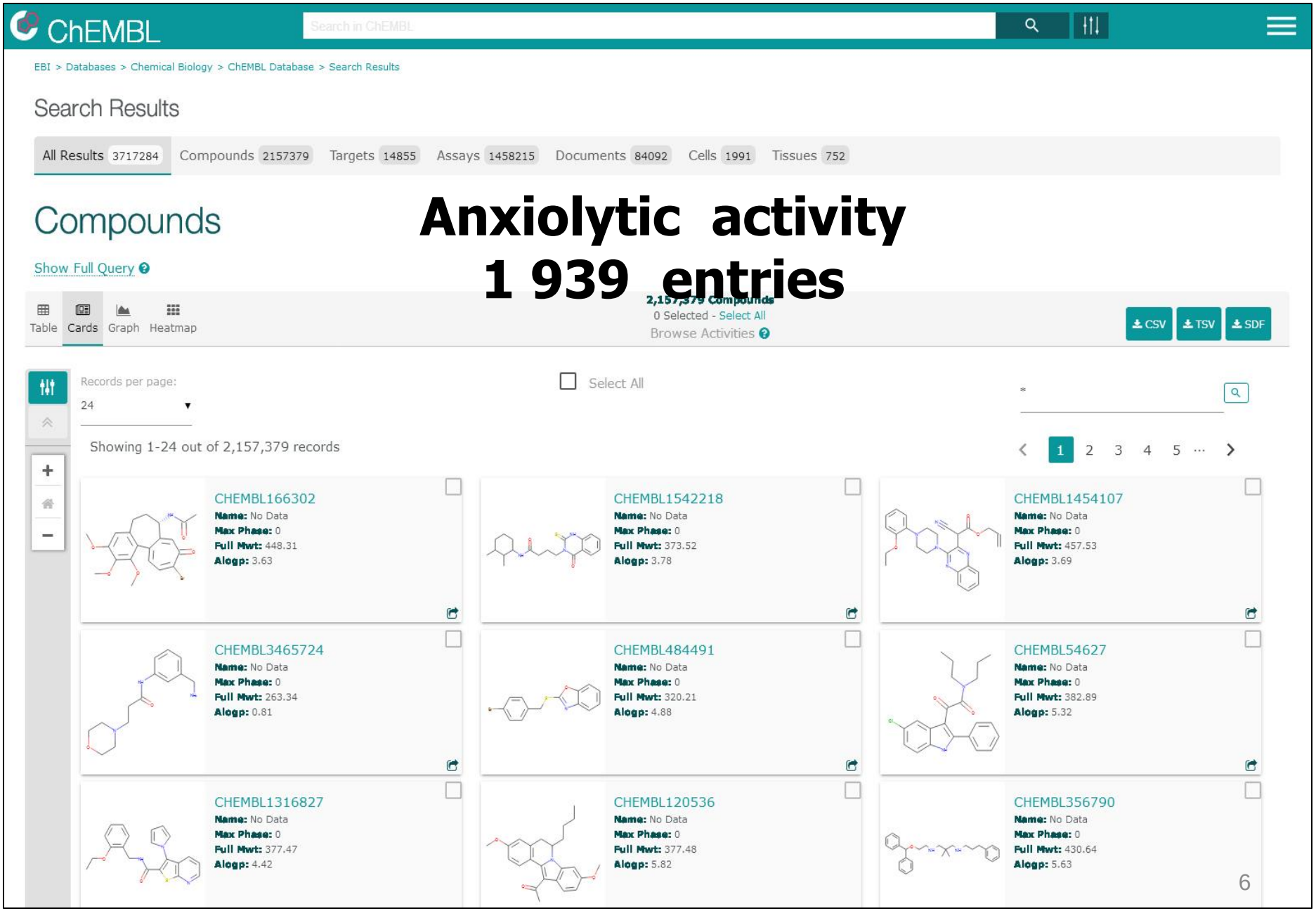
Goal

Build classification consensus ensemble model of dependence of anxiolytic activity of chemical compounds from their structural QL descriptors using method of convolution artificial neural networks

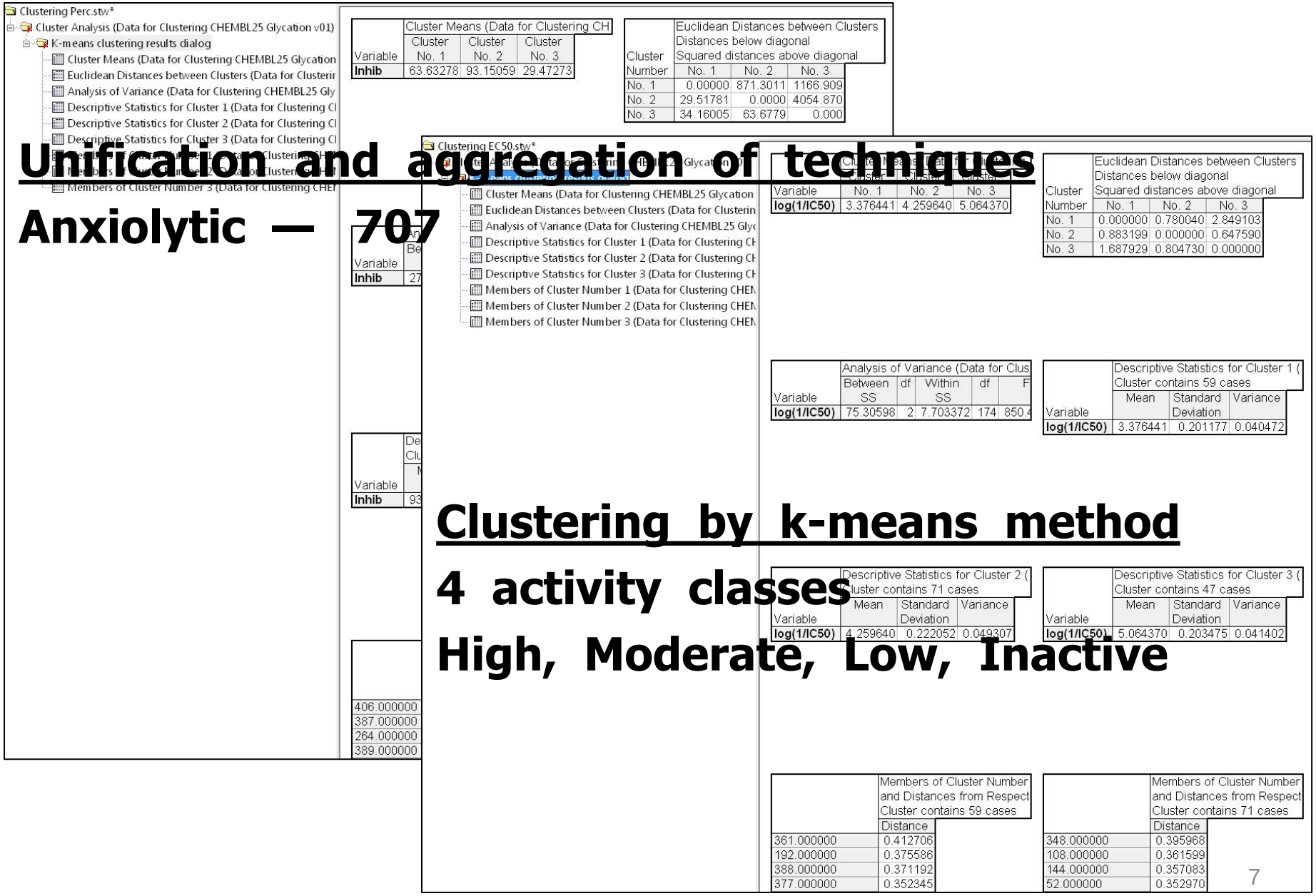
Tasks

- **Formation of verified training set for known anxiolytic substances**
- **Calculation of QL descriptor representation for training set compounds**
- **Line convolution of find structural parameters**
- **Training of neural networks and formation of consensus ensemble model**
- **Prediction of anxiolytic activity for new compounds**

Finding information about known compounds



Unification of techniques and activity clustering



Unification and aggregation of techniques

Anxiolytic — 707

Clustering by k-means method

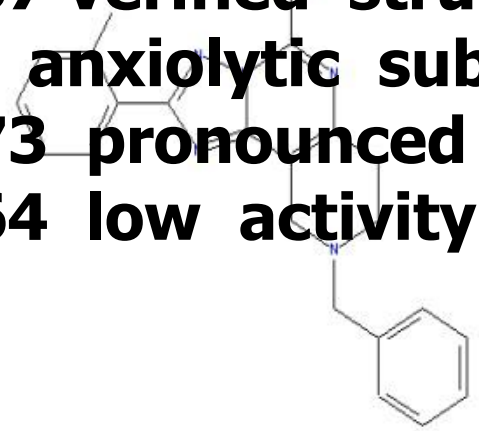
4 activity classes

High, Moderate, Low, Inactive

Formation of verified databases

Anxiolytic Substances v11 - Corrected — **24 January 2022**

Structure



537 verified structures of anxiolytic substances:
273 pronounced activity
264 low activity

Activity
Standard Type: ED50
pChEMBL Value:

Assay
Assay ChEMBL ID: CHEMBL779993
Assay Description: Anxiolytic response measure stimuli in rats.

Mol_ID	Brutto formula	Mol weight	Salt Component
1	$C_{21}H_{18}FN_5O$	375.3	

Activity Processing
Gen_Assay_IDs: Rat-07a
Gen_Assay_CHEMBLID: CHEMBL3256343 CHEMBL… CHEMBL784521 CHEMBL8…

Compound Codes & Names
MolFileName: CHEMBL99259
CODE - Molecule ChEMBL ID: CHEMBL99259
Molecule Name:
Compound Key: 8g

References

Document_ChEMBL_ID	Document Journal	Document_Year
CHEMBL1125833	J. Med. Chem.	1991

РОССИЙСКАЯ ФЕДЕРАЦИЯ

СВИДЕТЕЛЬСТВО

о государственной регистрации базы данных

№ 2022621744

Соединения с анксиолитической активностью

Правообладатель: ***Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации (RU)***

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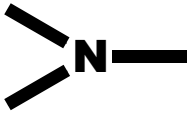
Руководитель Федеральной службы по интеллектуальной собственности

Ю.С. Зубов

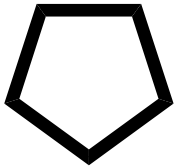
Elementary descriptors of QL language

Structural descriptors



-N< heteroatomic

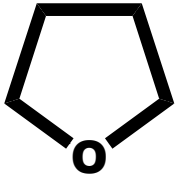
-CH3 carbonic



Cyc05 cyclic

Length descriptors

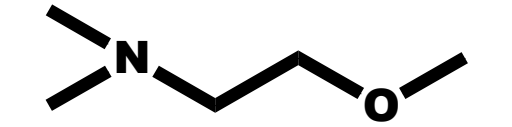
03 path length



-1 inclusion index

p..1 **Bond descriptors**

Composite descriptors of QL language



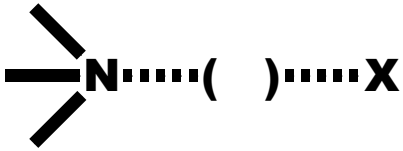
-N<	3	>O	...0

-NH2	3	-CH3	

-SH	4		

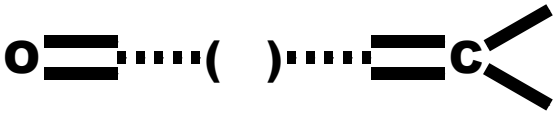
-OH		-Cl'	

-OH	4		.A.1



-N<			...1

-OH	2	=O	...1



=O		>C=	...1

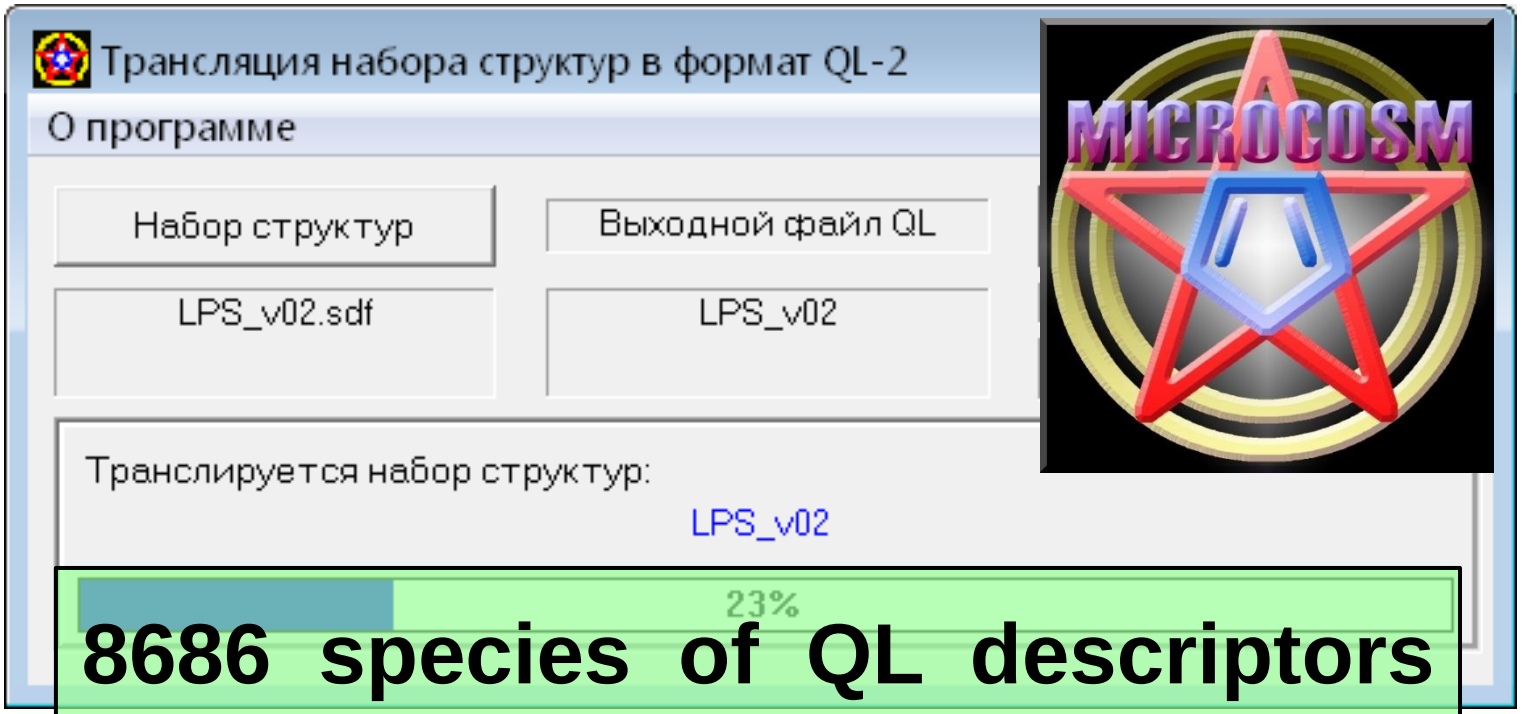
	4		p..1

4 rank Basic

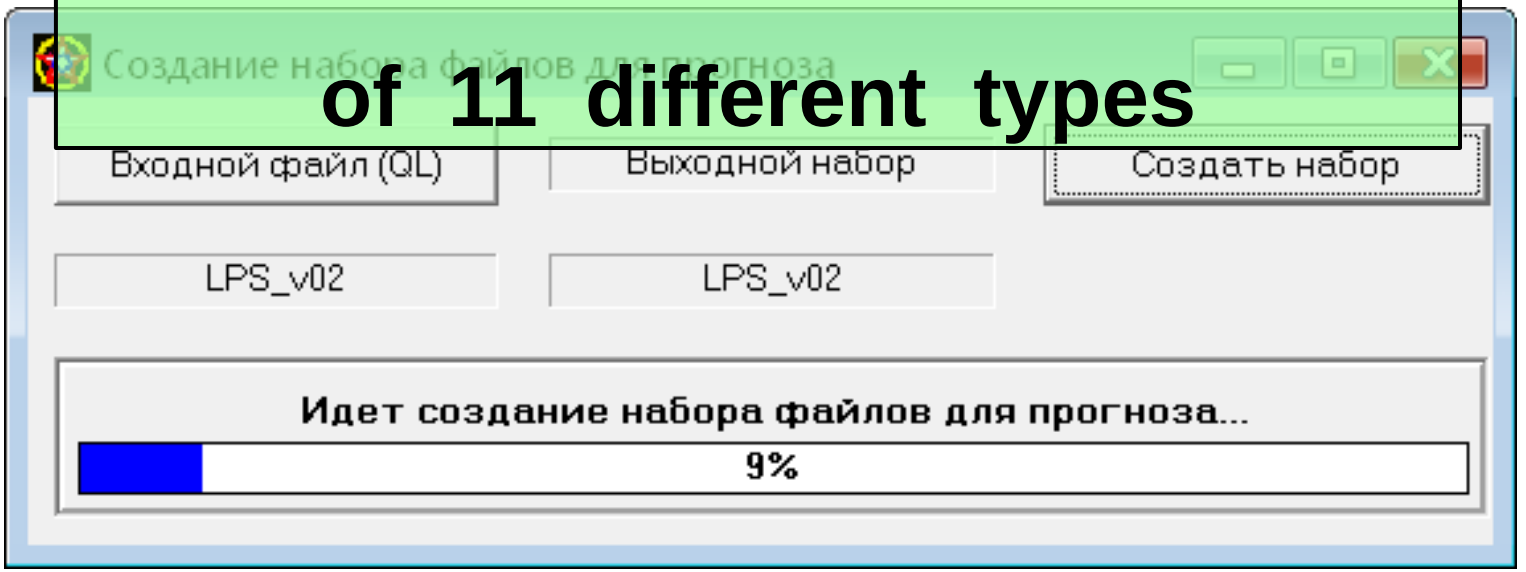
3 rank

2 rank

Calculation of QL descriptors



8686 species of QL descriptors of 11 different types



Linear convolution

Correlation of one sequence with the reversed second

$$y(n) = \sum_{m=0}^{n} h(n-m)x(m)$$

8686 QL descriptors ⟶ 66 convolution variables

Example of QL descriptor convolution

SD	-NH2	>NH	-N<	-N=	#N	>N+=	-OH	>O	=O
	0	0	2	3	0	0	1	0	0
BD	**...0**	**...1**	**..n1**	**.a.0**	**.a.1**	**.A.0**	**.A.1**	**p..0**	**p..1**
	12	30	0	10	23	15	30	0	0

Initial data

SD	-NH2	>NH	-N<	-N=	#N	>N+=	-OH	>O	=O
	0	0	2	3	0	0	1	0	0
BD	**p..1**	**p..0**	**.A.1**	**.A.0**	**.a.1**	**.a.0**	**..n1**	**...1**	**...0**
	0	0	30	15	23	10	0	30	12

Data for convolution

SD•BD = (0*0) + (0*0) + (2*30) + (3*15) + (0*23) + (0*10) + (1*0) + (0*30) + (0*12) = 0 + 0 + 60 + 45 + 0 + 0 + 0 + 0 + 0

= **105**

Formation of training set

Mol_ID	Code	LevHM	SD_1-1	SD_1-2	SD_1-3	SD_1-4	SD_1-5	SD_1-6	SD_1-7	SD_1-8	SD_1-9	SD_1-10	SD_1-11	SD_2-2	SD_2-3	SD_2-4
1	CHEMBL101045	hm	1089	3003	3003	6006	3003	6006	3003	3003	6006	3003	3003	8281	8281	16562
2	CHEMBL101304	hm	676	2418	2418	4836	2418	4836	2418	2418	4836	2418	2418	8649	8649	17298
3	CHEMBL13662	hm	529	3266	3266	6532	3266	6532	3266	3266	6532	3266	3266	20164	20164	40328
4	CHEMBL153823	hm	361	1615	1615	3230	1615	3230	1615	1615	3230	1615	1615	7225	7225	14450
5	CHEMBL154328	hm	2601	10455	10455	20910	10455	20910	10455	10455	20910	10455	10455	42025	42025	84050
6	CHEMBL154380	hm	2601	10455	10455	20910	10455	20910	10455	10455	20910	10455	10455	42025	42025	84050
7	CHEMBL155270	hm	361	1843	1843	3686	1843	3686	1843	1843	3686	1843	1843	9409	9409	18818
8	CHEMBL157522	hm	484	3036	3036	6072	3036	6072	3036	3036	6072	3036	3036	19044	19044	38088
9	CHEMBL187827	hm	529	3714	3714	7428	3714	7428	3714	3714	7428	3714	3714	13924	13924	27848
10	CHEMBL188332	hm	625	4500	4500	9000	4500	9000	4500	4500	9000	4500	4500	32400	32400	64800
11	CHEMBL189061	hm	784	7056	7056	14112	7056	14112	7056	7056	14112	7056	7056	63504	63504	127008
12	CHEMBL190772	hm	729	7101	7101	14202	7101	14202	7101	7101	14202	7101	7101	69169	69169	138338
13	CHEMBL20042	hm	625	3000	3000	6000	3000	6000	3000	3000	6000	3000	3000	14400	14400	28800
14	CHEMBL204240	hm	484	2276	2276	4552	2276	4552	2276	2276	4552	2276	1276	3364	3364	6728
15	CHEMBL2263292	hm	784	2044	2044	4088	2044	4088	2044	2044	4088	2044	2044	5329	5329	10658
16	CHEMBL2263293	hm	784	2044	2044	4088	2044	4088	2044	2044	4088	2044	2044	5329	5329	10658
17	CHEMBL2263296	hm	784	2604	2604	5208	2604	5208	2604	2604	5208	2604	2604	8649	8649	17298
18	CHEMBL239259	hm	1089	3960	3960	7920	3960	7920	3960	3960	7920	3960	3960	14400	14400	28800
19	CHEMBL260870	hm	1225	5845	5845	11690	5845	11690	5845	5845	11690	5845	5845	27889	27889	55778
20	CHEMBL260872	hm	1089	4224	4224	8448	4224	8448	4224	4224	8448	4224	4224	16384	16384	32768
21	CHEMBL260994	hm	961	3255	3255	6510	3255	6510	3255	3255	6510	3255	3255	11025	11025	22050
22	CHEMBL289742	hm	784	5348	5348	10696	5348	10696	5348	5348	10696	5348	5348	36481	36481	72962
23	CHEMBL290906	hm	784	5264	5264	10528	5264	10528	5264	5264	10528	5264	5264	35344	35344	70688
24	CHEMBL307116	hm	576	3552	3552	7104	3552	7104	3552	3552	7104	3552	3552	21904	21904	43808
25	CHEMBL3084529	hm	1444	7562	7562	15124	7562	15124	7562	7562	15124	7562	7562	39601	39601	79202
26	CHEMBL314608	hm	729	3186	3186	6372	3186	6372	3186	3186	6372	3186	3186	13924	13924	27848
27	CHEMBL319178	hm	1024	3488	3488	6976	3488	6976	3488	3488	6976	3488	3488	11881	11881	23762
28	CHEMBL319966	hm	625	2450	2450	4900	2450	4900	2450	2450	4900	2450	2450	9604	9604	19208
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30	CHEMBL3246317	hm	729	3213	3213	6426	3213	6426	3213	3213	6426	3213	3213	14161	14161	28322
31	CHEMBL3251778	hm	841	3712	3712	7424	3712	7424	3712	3712	7424	3712	3712	16384	16384	32768
32	CHEMBL3277537	hm	784	3080	3080	6160	3080	6160	3080	3080	6160	3080	3080	12100	12100	24200
33	CHEMBL3277538	hm	961	3627	3627	7254	3627	7254	3627	3627	7254	3627	3627	13689	13689	27378
34	CHEMBL3277539	hm	1024	4320	4320	8640	4320	8640	4320	4320	8640	4320	4320	18225	18225	36450
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37	CHEMBL3277544	hm	784	3108	3108	6216	3108	6216	3108	3108	6216	3108	3108	12321	12321	24642

537 Anxiolytics

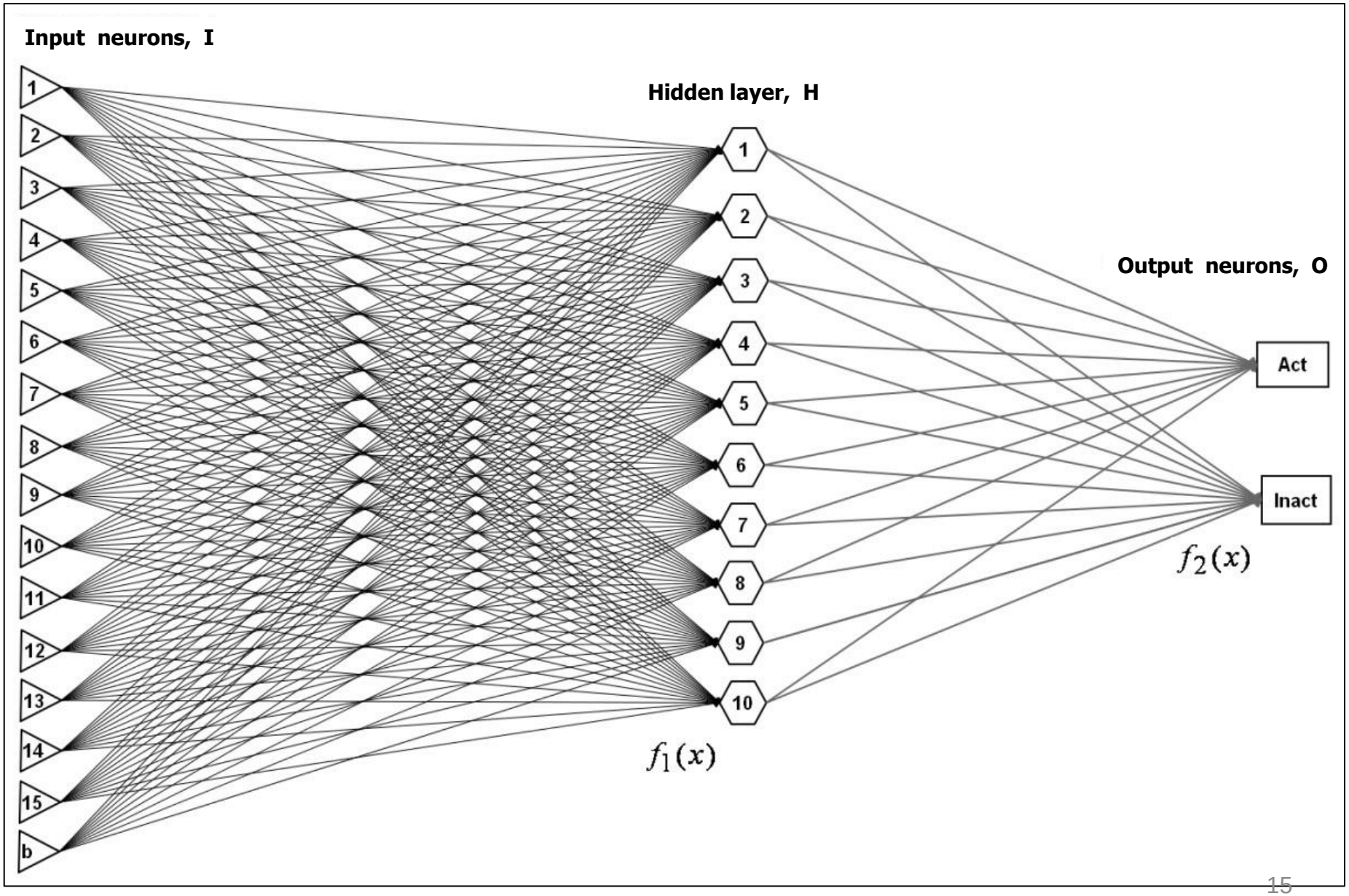
273 with pronounced activity

264 with low activity

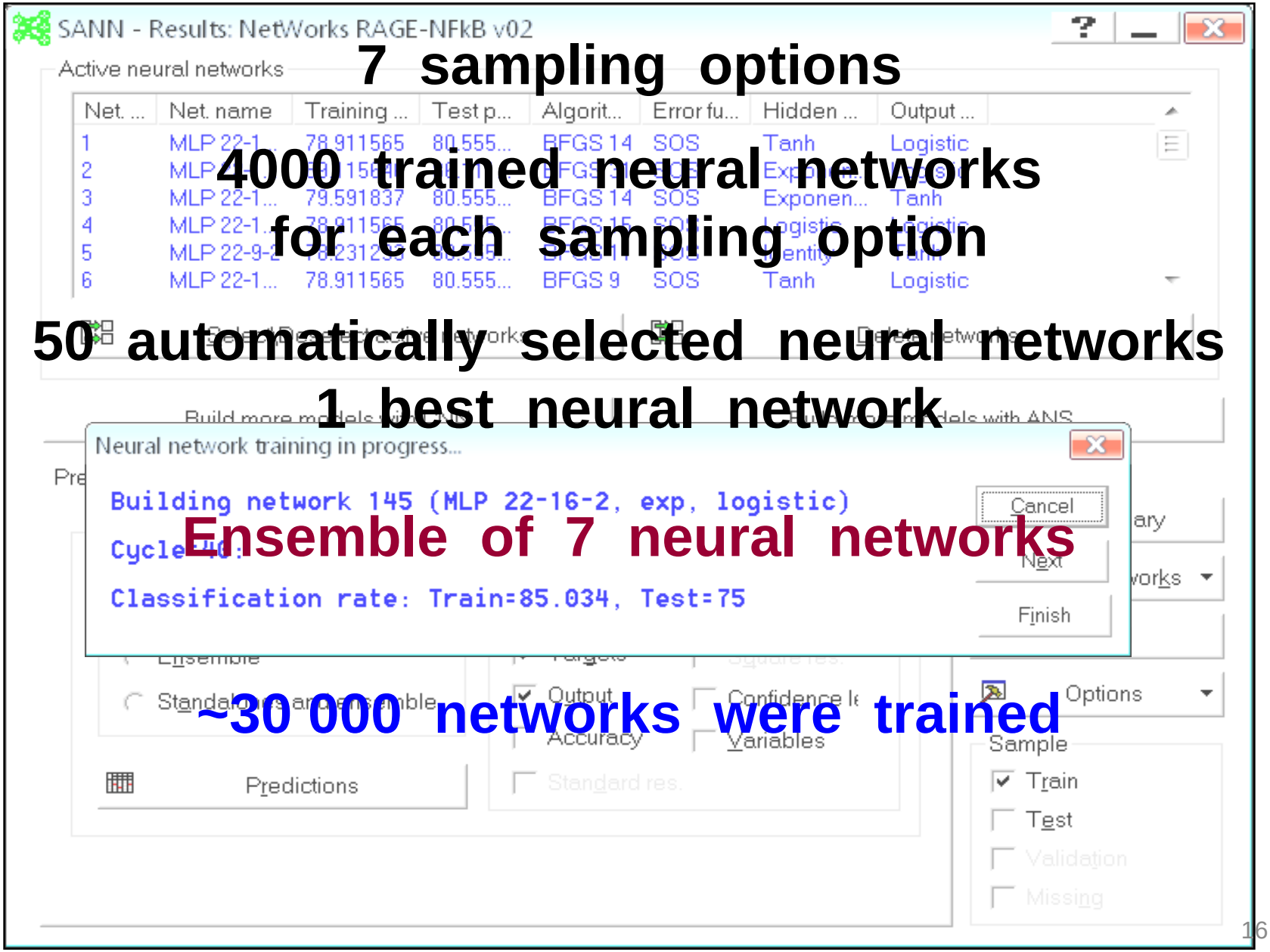
66 neurons

7 samplings

Neural network with bottle-neck



Training of neural networks and formation of ensemble



7 sampling options

4000 trained neural networks for each sampling option

50 automatically selected neural networks

1 best neural network

Ensemble of 7 neural networks

~30 000 networks were trained

Accuracy of neural network ensemble

Accuracy F_0 = 78%

Sensitivity F_a = 85%

Specificity F_n = 70%

	Code	Метка	Sampl1	Sampl2	Sampl3	Sampl4	Sampl5	Sampl6	Sampl7	Ind1	Ind2	Ind3	Ind4	Ind5	Ind6	Ind7	Cons>=4	Cons>=5	Cons>=6	Cons=7	GenCons	Correct
2	CHEMBL100144	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
3	CHEMBL101045	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
4	CHEMBL101304	hm	hm	hm	hm	nhm	hm	hm	hm	1	1	1		1	1	1	hm	hm	hm		hm	1
5	CHEMBL1059	hm	hm	hm	hm	nhm	nhm	hm	hm	1	1	1			1	1	hm	hm			hm	1
6	CHEMBL1112	hm	hm	hm	nhm	hm	hm	hm	hm	1	1		1	1	1	1	hm	hm	hm		hm	1
7	CHEMBL13662	hm	hm	hm	nhm	nhm	hm	hm	hm	1	1			1	1	1	hm	hm			hm	1
8	CHEMBL153823	hm	hm	hm	hm	nhm	nhm	hm	hm	1	1	1			1	1	hm	hm			hm	1
9	CHEMBL153953	hm	nhm	hm	hm	nhm	nhm	hm	hm	1	1	1			1	1	hm	hm			hm	1
10	CHEMBL154043	hm	hm	hm	hm	nhm	hm	hm	hm	1	1	1			1	1	hm	hm	hm		hm	1
11	CHEMBL154328	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
12	CHEMBL154380	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
13	CHEMBL154754	hm	hm	hm	hm	nhm	hm	hm	hm	1	1	1		1	1	1	hm	hm	hm		hm	1
14	CHEMBL155270	hm	nhm	hm	hm	nhm	nhm	nhm	nhm		1	1			1	1	hm	hm			hm	1
15	CHEMBL157522	hm	hm	hm	nhm	nhm	nhm	hm	hm		1				1	1	hm				hm	1
16	CHEMBL1836783	hm	hm	hm	hm	hm	hm	nhm	hm	1	1	1	1	1		1	hm	hm	hm		hm	1
17	CHEMBL187827	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
18	CHEMBL188138	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
19	CHEMBL188280	hm	nhm	hm	nhm	nhm	nhm	nhm	nhm												nhm	
20	CHEMBL188335	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
21	CHEMBL189061	hm	hm	hm	hm	hm	nhm	hm	hm	1	1	1	1		1	1	hm	hm	hm		hm	1
22	CHEMBL190772	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
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24	CHEMBL20042	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
25	CHEMBL204040	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
26	CHEMBL204091	hm	nhm	nhm	nhm	nhm	hm	nhm	nhm					1							nhm	
27	CHEMBL204240	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
28	CHEMBL204755	hm	nhm	nhm	nhm	nhm	nhm	nhm	nhm												nhm	
29	CHEMBL207493	hm	hm	hm	hm	nhm	nhm	hm	hm	1	1	1			1	1	hm	hm			hm	1
30	CHEMBL207517	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
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32	CHEMBL2263292	hm	nhm	hm	hm	hm	hm	hm	nhm		1	1	1	1	1		hm	hm			hm	1
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35	CHEMBL2263295	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
36	CHEMBL2263296	hm	hm	hm	hm	hm	hm	hm	hm	1	1	1	1	1	1	1	hm	hm	hm	hm	hm	1
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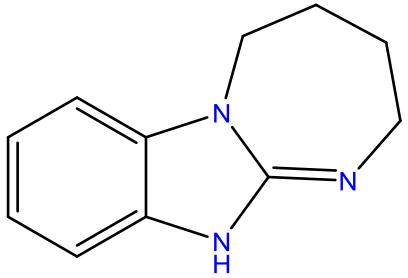
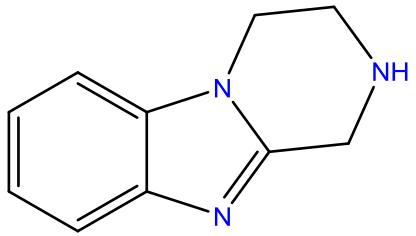
39	CHEMBL231825	hm	hm	hm	nhm	hm	hm	nhm	hm	1	1		1	1		1	hm	hm			hm	1
40	CHEMBL232188	hm	hm	hm	nhm	nhm	hm	hm	hm	1	1			1	1	1	hm	hm			hm	1

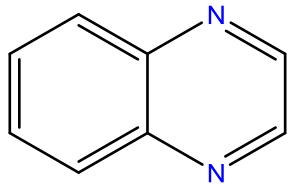
Prediction results



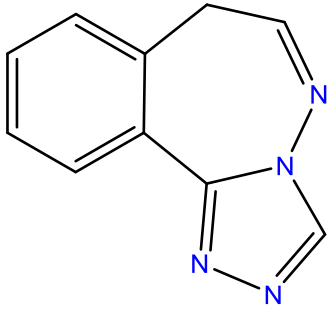
Diazepinobenzimidazole



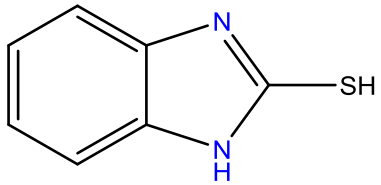
Benzoimidazopyrazine



Quinoxaline



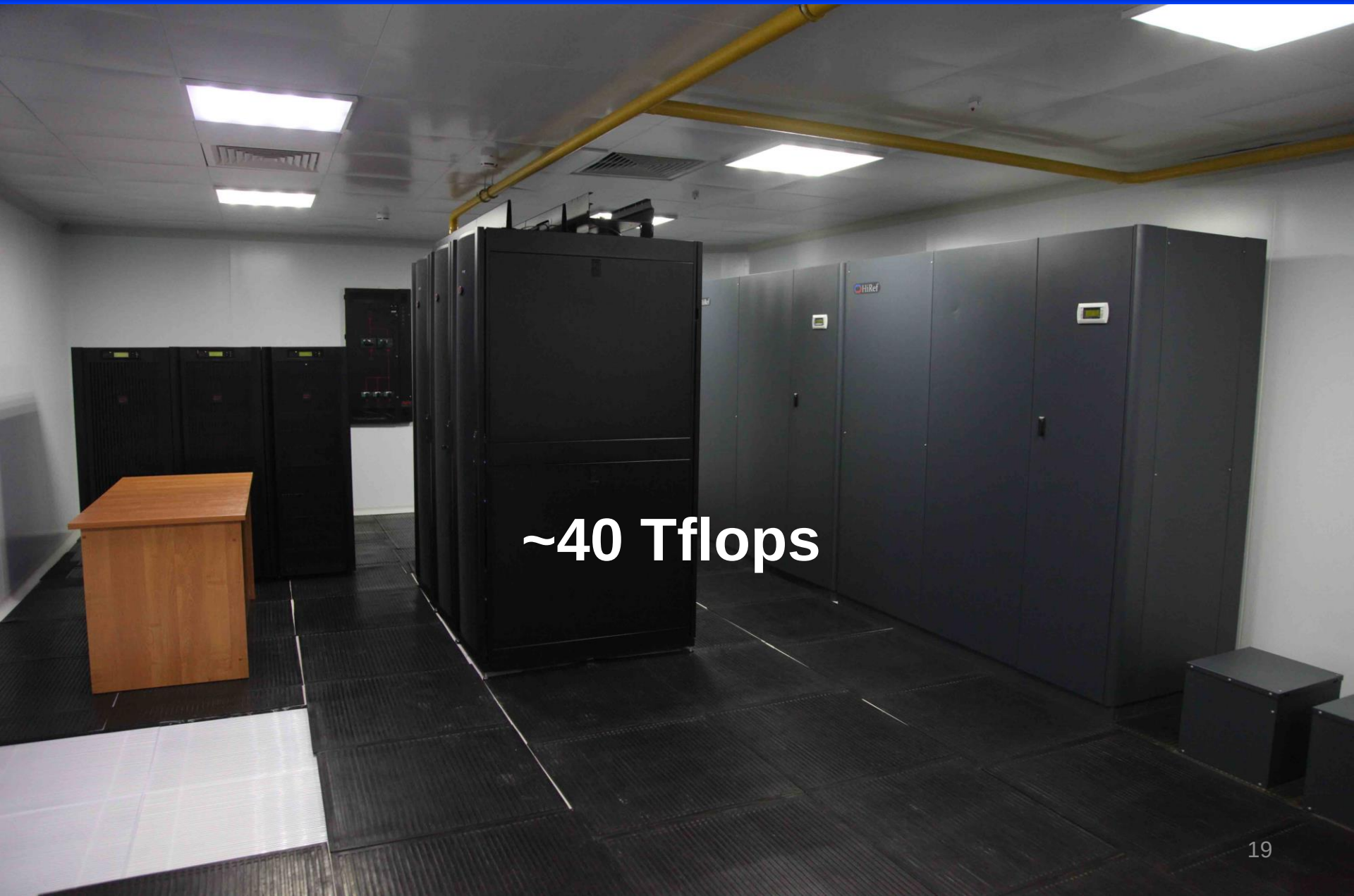
Triazolobenzodiazepine



Mercaptobenzimidazole

97 new compounds – 53 active

Laboratory for Information Technology in Pharmacology and Computer Modeling of Drugs




Thank You for Your attention!