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# SEARCH FOR NEW ANXIOLYTIC SUBSTANCES BY NEURAL NETWORK MODELING USING MULTIPLE DOCKING

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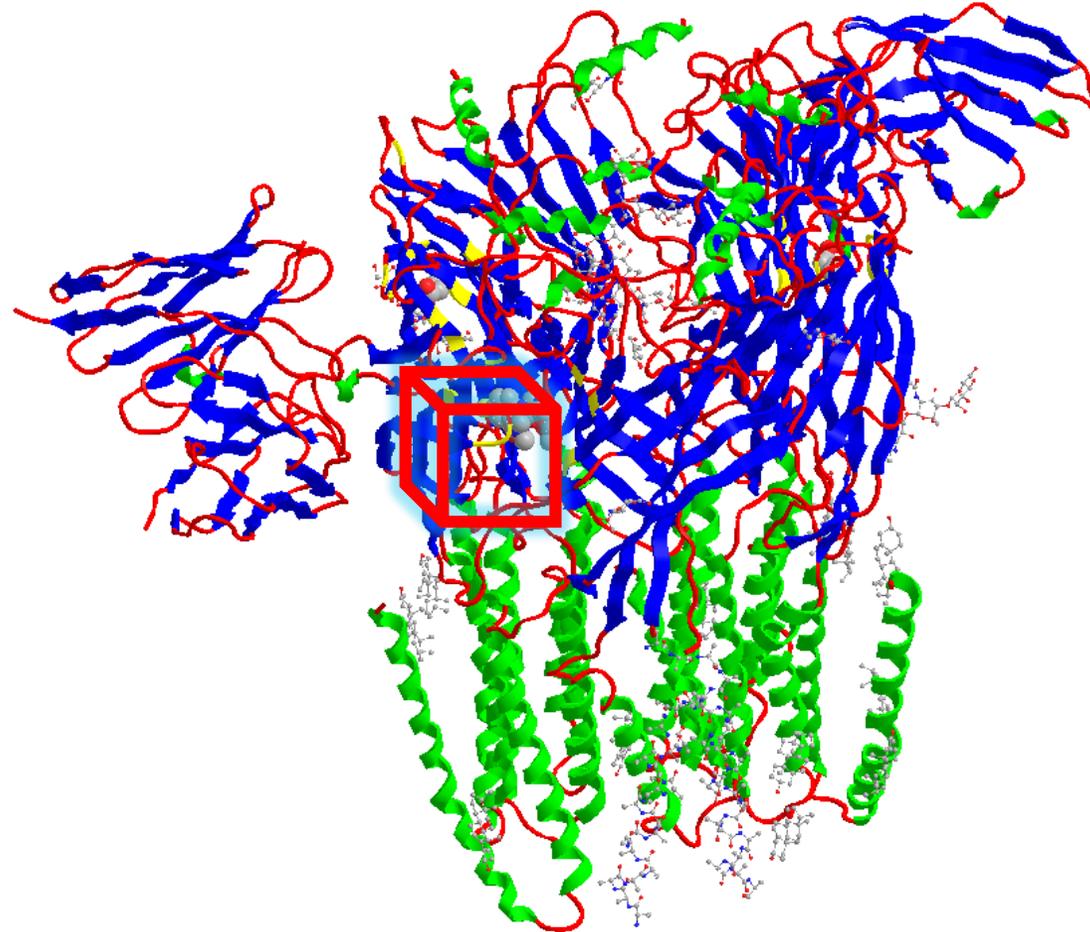
# The aim of the study

To provide high efficiency of drug discovery using neural network modeling based on multiple docking methodology.

# Tasks

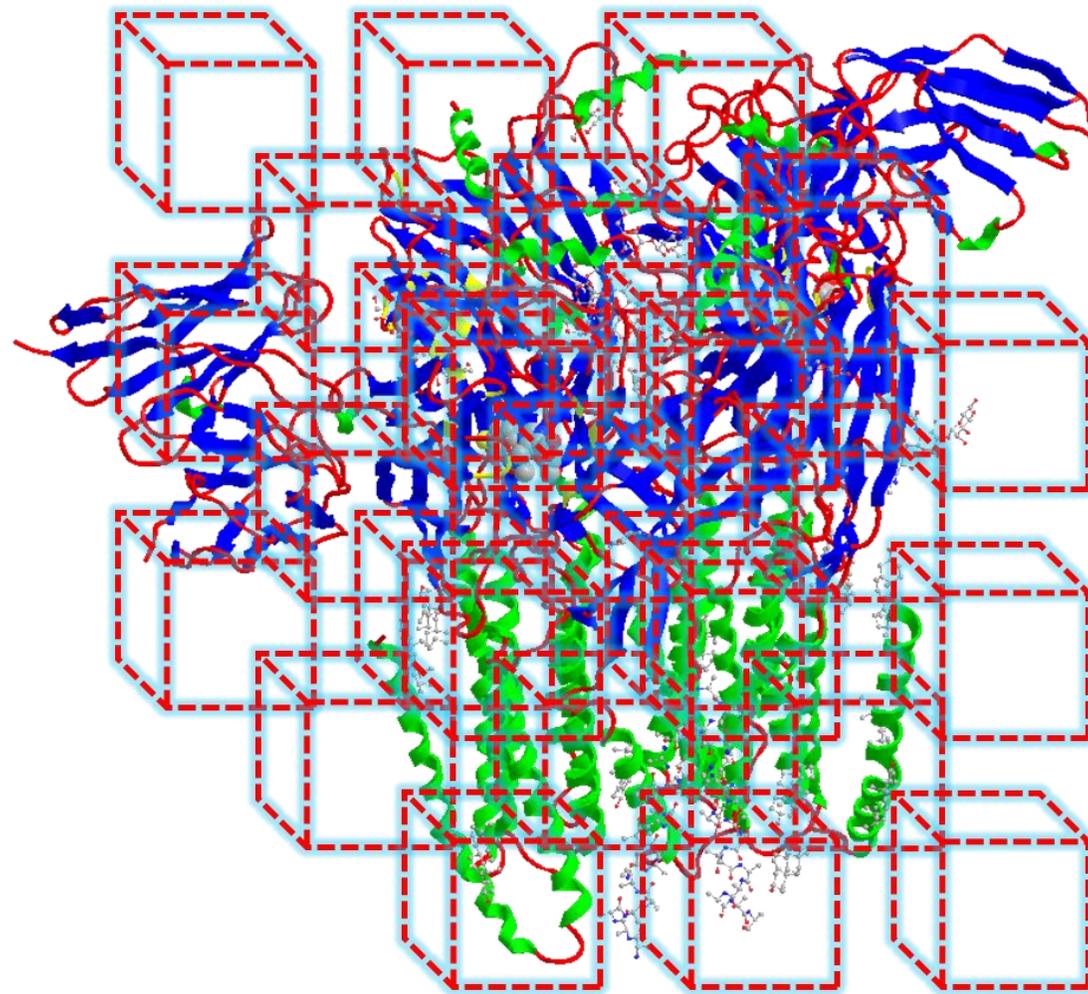
1. Perform multiple docking of new quinazoline-2,4(1*H*,3*H*)-dione derivatives.
2. Predict the activity level of new compounds using a previously built neural network model.
3. Conduct an experiment in behavioral tests to confirm the prediction.
4. Prepare new compounds for future research.

# Simple docking



A 3D molecular docking simulation showing a protein structure (blue and red ribbons) and a ligand (green and red spheres) bound to a specific site. The protein is composed of several alpha-helices and beta-sheets. The ligand is a small molecule with a complex structure, including a central ring system and several side chains. A red box highlights the binding site, which is a pocket formed by the protein's structure. The ligand is shown in a stick representation, with atoms colored by element (carbon in grey, oxygen in red, nitrogen in blue). The protein backbone is shown as a ribbon, with different colors (blue, red, green) representing different parts of the structure. The overall structure is complex and multi-domain.

# Multiple docking



# Comparison of simple and multiple docking

Prediction accuracy indicator	Value for model using	
	$\Delta E_0$	$\Delta E_1 \dots \Delta E_{27}$
$F_0, \%$	51,3	94,8
$F_a, \%$	66,7	83,3
$F_n, \%$	49,1	96,4
$z_0$	0,58	8,73
$z_a$	1,08	2,23
$z_n$	0,14	8,45
$p_0$	0,281	$<1 \cdot 10^{-15}$
$p_a$	0,139	0,0127
$p_n$	0,555	$<1 \cdot 10^{-15}$

Примечание.

$F_0, F_a, F_n$  – overall predictive accuracy, sensitivity, specificity

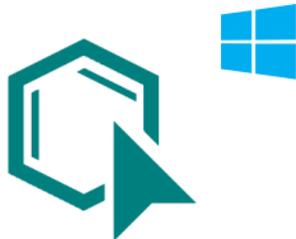
$z_0, z_a, z_n$  – binomial test for  $F_0, F_a, F_n$ .

$p_0, p_a, p_n$  – significance  $F_0, F_a, F_n$ .

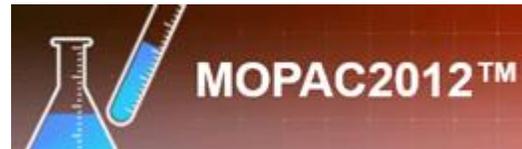
# Databases and software



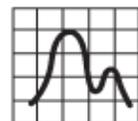
ChemAxon



MarvinSketch



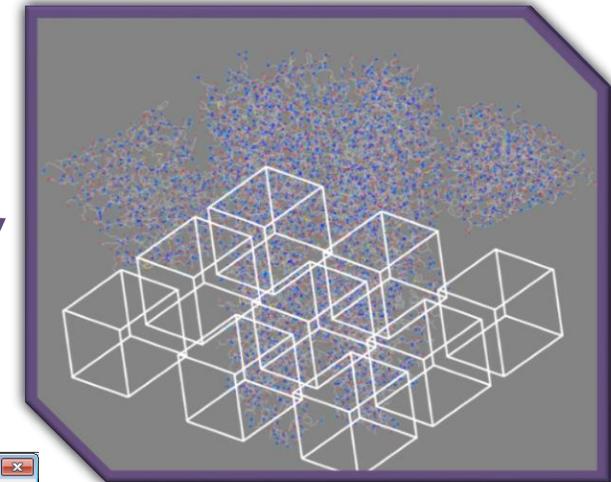
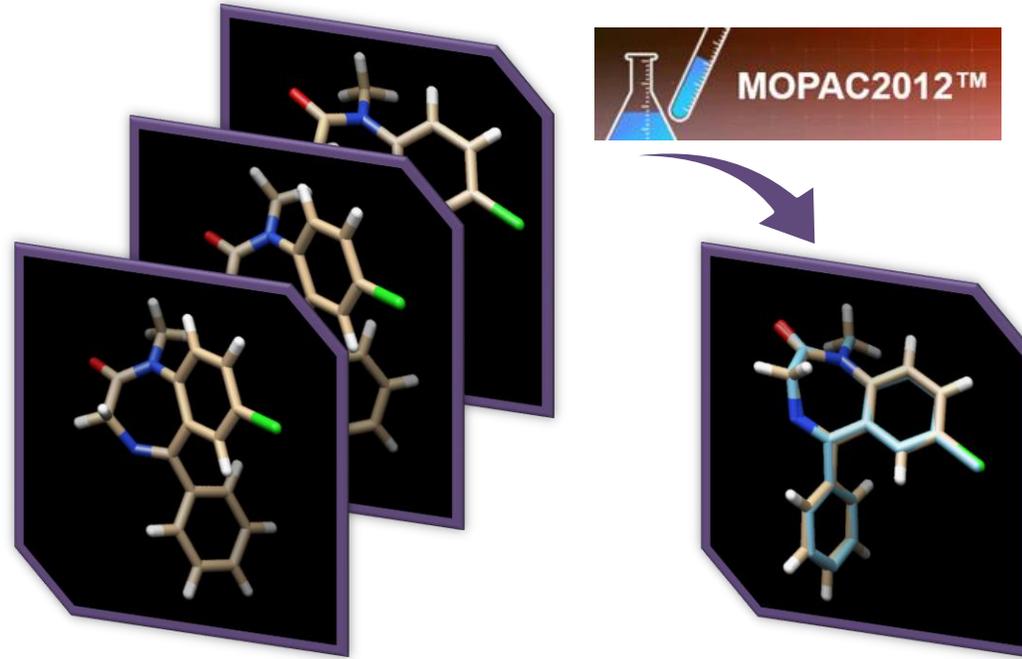
AutoDock Vina



StatSoft®

STATISTICA

# General scheme



Data: VMA\_GABAR-27\_Pre1\* (30v by 6c)

Data4_3Class						
	1	2	3	4	5	6
	Level_IC50	LevH	LevHM	E-01	E-02	E-03
1	high	h	hm	-4.9	-6.2	-5.9
2	high	h	hm	-5.0	-6.6	-6.7
3	high	h	hm	-6.3	-7.8	-7.8
4	high	h	hm	-5.4	-7.0	-7.0
5	high	h	hm	-5.7	-7.3	-7.3
6	high	h	hm	-5.3	-6.3	-6.6

SANN - Analysis/Deployment: VMA\_GABAR-27\_Pre1

New analysis/Deployment

Deployment

New analysis

- Regression
- Classification
- Time series (regression)
- Time series (classification)
- Cluster analysis

Select variables for analysis

1 - Level_IC50	11 - Level_IC50	1 - Level_IC50	11 - Level_IC50
2 - LevH	12 - LevH	2 - LevH	12 - LevH
3 - LevHM	13 - LevHM	3 - LevHM	13 - LevHM
4 - E-01	14 - E-01	4 - E-01	14 - E-01
5 - E-02	15 - E-02	5 - E-02	15 - E-02
6 - E-03	16 - E-03	6 - E-03	16 - E-03
7 - E-04	17 - E-04	7 - E-04	17 - E-04
8 - E-05	18 - E-05	8 - E-05	18 - E-05
9 - E-06	19 - E-06	9 - E-06	19 - E-06
10 - E-07	20 - E-07	10 - E-07	20 - E-07

Workbook1 - Predictions spreadsheet for LevHM (ZDM\_GABAR-27\_Pre1)

Predictions spreadsheet for LevHM (ZDM\_GABAR-27\_Pre1)

Case name	LevHM - Output	LevHM - Confidence levels
1	hm	0.999694
2	hm	0.993592
3	hm	0.987491
4	hm	0.999877
5	hm	0.999808
6	hm	0.998387

# Results

Predictions spreadsheet for LevHM (VMA_GABAR-27_Pre1)				
Samples: Test				
Case name	LevHM Target	LevHM - Output 1. MLP 27-7-2	LevHM - Residuals 1. MLP 27-7-2	LevHM - Confidence levels 1. MLP 27-7-2
1	hm	nhm	Incorrect	0.978494
2	hm	nhm	Incorrect	0.845162
3	hm	hm	Correct	0.997323
4	hm	nhm	Incorrect	0.999198
5	hm	nhm	Incorrect	0.994857
6	hm	hm	Correct	0.999218

Compound	Level of activity	Membership function $F_m$	Compound	Latent period	Line crossings	Rearing	Center square entries	Center square duration	Indicator of priming action
1	nhm	0.978	1	103±34	-26±25	0±0	-11±40	-25±4	0
2	nhm	0.999	2	-80±6 <sup>b</sup>	34±20	50±120 <sup>b</sup>	-22±0	-89±0	2
3	nhm	0.995	3	135±31	28±34	0±0	89±102 <sup>c</sup>	197±22 <sup>b</sup>	3
4	nhm	0.845	4	-74±5	70±21 <sup>b</sup>	250±582 <sup>c</sup>	111±162 <sup>d</sup>	-41±24 <sup>b</sup>	4
5	hm	<b>0.997</b>	5	<b>-75±10</b>	<b>101±30<sup>b</sup></b>	<b>217±465<sup>c</sup></b>	<b>200±242<sup>d</sup></b>	<b>9±29<sup>b</sup></b>	7
Diazepam	hm	<b>0.999</b>	Diazepam	<b>-97±0<sup>d</sup></b>	<b>135±42<sup>d</sup></b>	<b>0±0</b>	<b>167±194<sup>c</sup></b>	<b>13±31<sup>b</sup></b>	9

\* hm is the high or moderate level of activity; nhm is the low level of activity or its absence; the data for compounds assigned by the prediction to the class of compounds with pronounced activity are highlighted in bold.

<sup>a</sup> The values of the indicators are given in percent to the control. The indicators for compounds with very pronounced priming activity are highlighted in bold. Significance of changes according to the Mann–Whitney U-test:

<sup>b</sup> very weak,  $0.1 \leq p < 0.2$ ;

<sup>c</sup> weak, statistically insignificant,  $0.05 \leq p < 0.1$ ;

<sup>d</sup> statistically significant,  $0.01 \leq p < 0.05$ .

# Results

1. We have performed ensemble multiple docking of new acetamide derivatives of quinazolines.
2. We have performed an activity level prediction of new compounds based on a new methodology with consensus ensemble neural network classification model.
3. We tested these compounds in an experiment.
4. We have shown that the developed methodology is effective and can be used for other types of activities.

Thank you for listening