VOLGOGRAD STATE MEDICAL UNIVERSITY

Laboratory for Information Technology in Pharmacology
and Computer Modeling of Drugs for
Research Center of Innovative Medicines

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Consensus Methodology For Directed Searching Compounds With Antimicrobial Activity Against S. aureus

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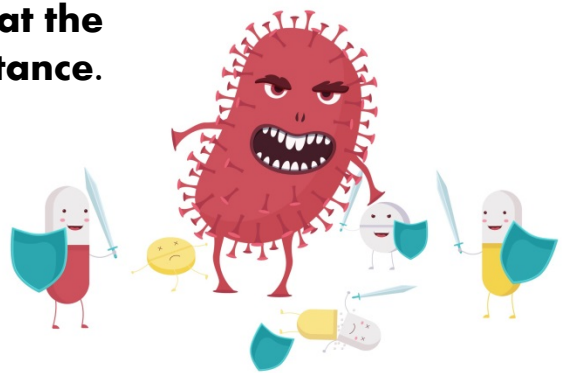
Background

- **Antimicrobial resistance is a global health threat, posing significant challenges to public health.**
- **Staphylococcus aureus is a major cause of infections, contributing to the urgency of finding new antimicrobial compounds.**
- **There is a critical need for new antimicrobial compounds to combat the rising threat of antimicrobial resistance.**



GLOBAL **A failure to address the problem of antibiotic resistance could result in:**

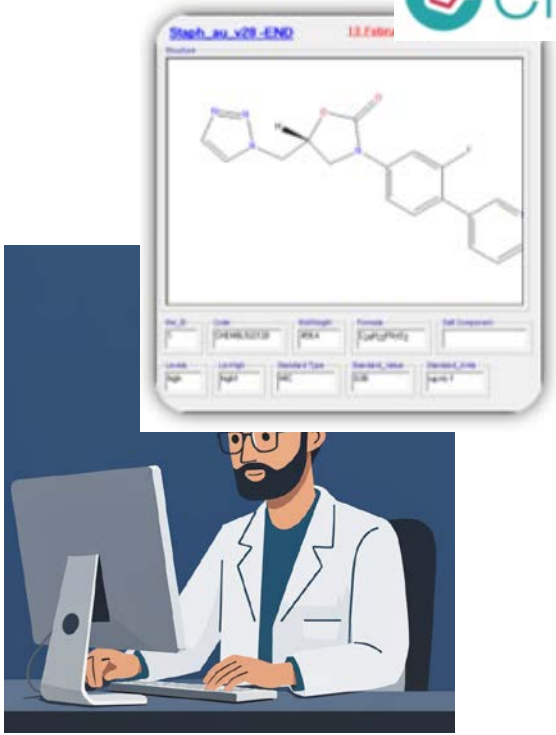
10m deaths by 2050

Guidance Health matters: antimicrobial resistance Published 10 December 2015 (Public Health England (PHE))
https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance

Objective

The objective of this study was to develop a consensus methodology for predicting antimicrobial activity against *Staphylococcus aureus* using 4 different predictive models.

Additionally, the study aimed to conduct a directed searching for promising compounds suitable for subsequent synthesis using this methodology.

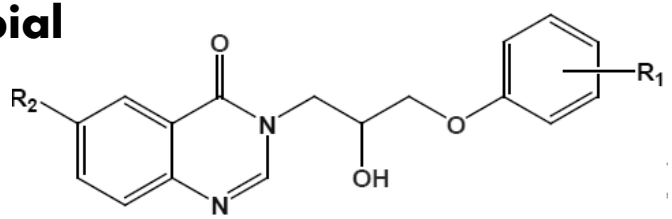


Training datasets

- 284 structural analogs of the studied scaffold 4(3H)-quinazolinone
- verified database of 3768 antimicrobial substances with experimentally established levels of antimicrobial activity

Predictive dataset

database of 71 new 4(3H)-quinazolinone derivatives with an assumed antimicrobial activity of S. aureus



Methods for targeted discovery of promising compounds

novel architecture of fully connected convolutional neural network based on correlation convolution of multiple docking energy spectra

assessment Testing[73] of the Microcosm IT system

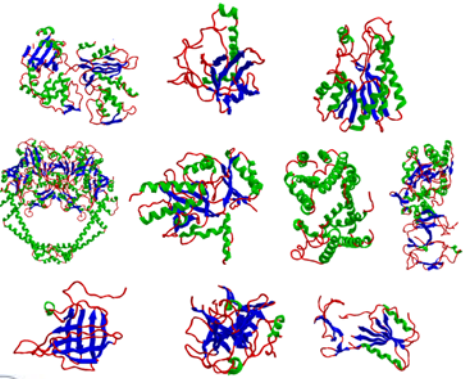
convolutional feedforward neural network correlation based on multiple docking energies

multidescriptor perceptron neural network model based on structural, physical and quantum chemical parameters

novel architecture of fully connected convolutional neural network based on correlation convolution of multiple docking energy spectra

experimental 3D models

ChEMBL UniProt RCSB PDB PROTEIN DATA BANK

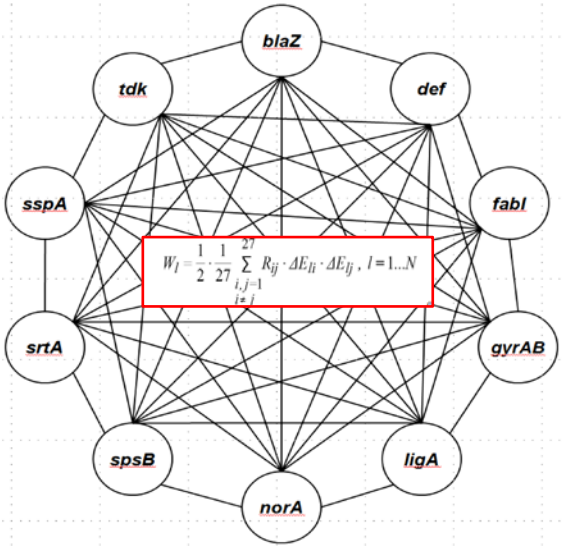


preparation software

MarvinSketch MOPAC2012™

27 spaces by Msite program

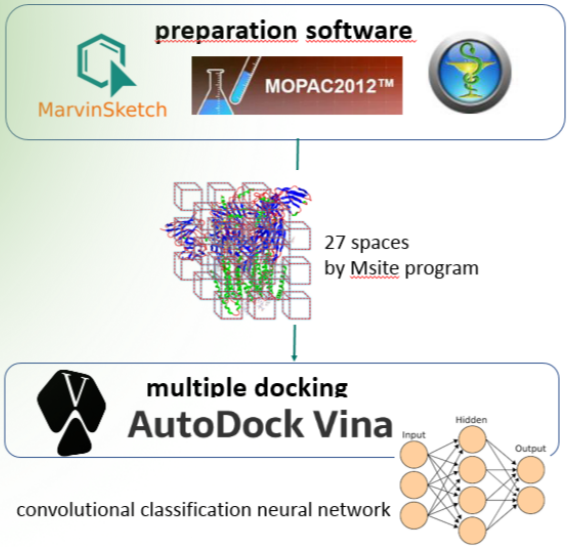
multiple docking AutoDock Vina

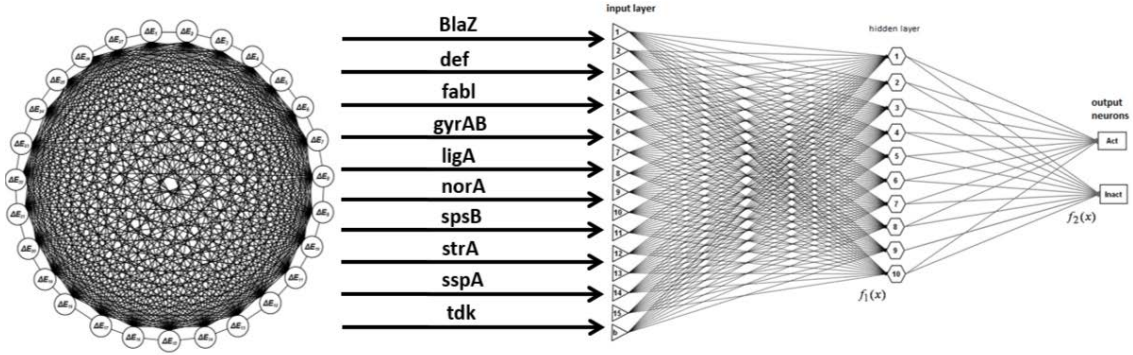


Acc, %	Sens, %	Spec, %	AUC ROC, %
79	81	68	75

Vassiliev, P.M., Golubeva, A.V., Perfilev, M.A., et al. (2025). The Journal of Ural Medical Academic Science, 22(3), 21.

convolutional feedforward neural network correlation based on multiple docking energies





Acc, %	Sens, %	Spec, %	AUC ROC, %
89	94	80	92

Golubeva, A.V., Vassiliev, P.M., Perfilev, M.A., et al. (2024). XXII Mendeleev Congress on General and Applied Chemistry, 5, 372.

multidescriptor perceptron neural network model based on structural, physical and quantum chemical parameters

124 QL-descriptors (IT Microcosm)

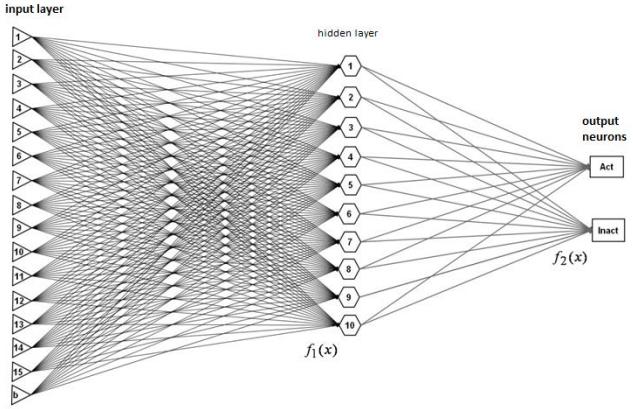
- structural
- bond
- lengths

20 quantum chemical parameters (HiperChem)

- HOMO
- LUMO

12 physico-chemical parameters (DruLiTo)

- logP
- AMR
- TPSA et al.

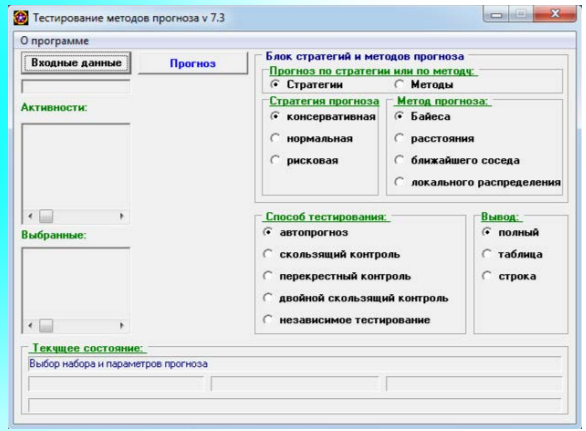


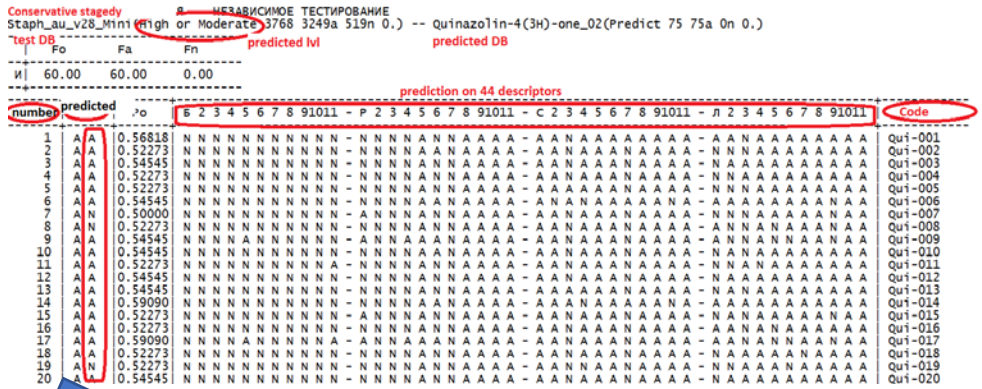
Model	Network architecture	Acc, %	Sens, %	Spec, %	AUC ROC, %
Sampl Random-2000-HM	MLP 156-24-2 (Tanh)	**93.5**	**64.3**	**98.2**	**89.2**
Sampl 1-2000-HM	MLP 156-15-2 (Logistic)	**93.6**	**74.1**	**96.8**	**91.3**
Sampl 1-4000-HM	MLP 156-19-2 (Logistic)	**93.3**	**70.0**	**97.1**	**93.1**

The results of training various sampling and selecting optimal accuracy neural networks for a high or moderate (**HM**) level of antimicrobial activity in Statistica.

*MLP- multilayer perceptron, k-m-2, k – input; m – hidden, 2 – output neurons. Tanh, Logistic - external activation functions. Acc – overall accuracy; Sens – sensitivity; Spec – specificity; AUC ROC – area under the ROC curve

assessment Testing73 of the Microcosm IT system





Vassiliev, P.M., Spasov, A.A., Kosolapov, V.A., et al. (2014). Application of Computational Techniques in Pharmacy and Medicine, 369-431.

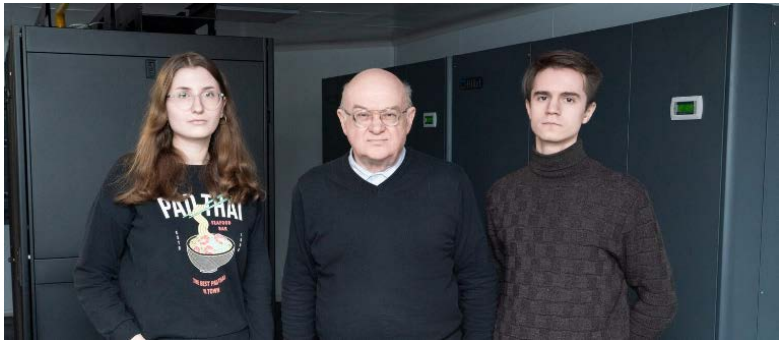
Compounds for synthesis were selected based on:

- **energy of a fully connected convolutional correlation neural network W_l (from 266.5 to 446.9)**
- **presence HM level by the other three methods**

- **Generalization of predictive estimates allowed to identify 14 promising structures among 71 new derivatives of 4(3H)-quinazolinone with moderate antimicrobial activity against S. aureus for further synthesis.**

Code	V VHM > 266.5 VH > 446.9	Cons-HM	HM Quin_v05_Mdesc Staph_au_v28_M Desc_Pre	Predict Saur_SimScaf FCCorNet_hm	
Qui-055	279.0	A	hm	hm	*Synthesize!
Qui-002	276.6	A	hm	hm	*Synthesize!
Qui-006	269.3	A	hm	hm	*Synthesize!
Qui-015	289.5	A	hm	hm	*Synthesize!
Qui-010	295.8	A	hm	hm	*Synthesize!
Qui-009	340.1	A	hm	hm	*Synthesize!
Qui-059	365.9	A	hm	hm	*Synthesize!
Qui-075	382.6	A	hm	hm	*Synthesize!
Qui-050	360.2	A	hm	hm	*Synthesize!
Qui-013	276.1	A	hm	hm	*Synthesize!
Qui-017	366.9	A	hm	hm	*Synthesize!
Qui-067	397.2	A	hm	hm	*Synthesize!
Qui-042	369.7	A	hm	hm	*Synthesize!
Qui-065	300.6	A	hm	hm	*Synthesize!
Qui-077	272.3	?	nhm	hm	
Qui-001	277.9	A	nhm	hm	
Qui-051	280.7	N	nhm	hm	

Consensus combination of several prediction methods enabled a directed searching promising derivatives of 4(3H)-quinazolinone with antimicrobial activity against S. aureus for further synthesis



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Thanks for your attention!

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