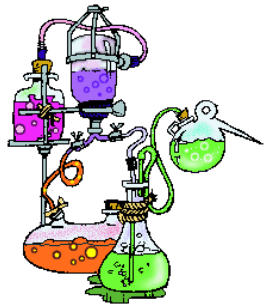
COMPUTER PREDICTION AND IN VITRO STUDY OF ANTIVIRAL ACTIVITY OF HETEROCYCLIC SYSTEMS CONTAINING THIOPYRANO[2,3-*b*]QUINOLINE AND TETRAZOLE MOIETIES

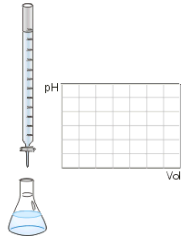
Vladimir A. Ostrovskii

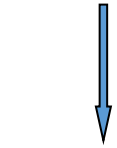
XXIX Symposium on Bioinformatics and
Computer-Aided Drug Discovery (BCADD-2023)

18-20 September 2023

Stages of development of an original drug





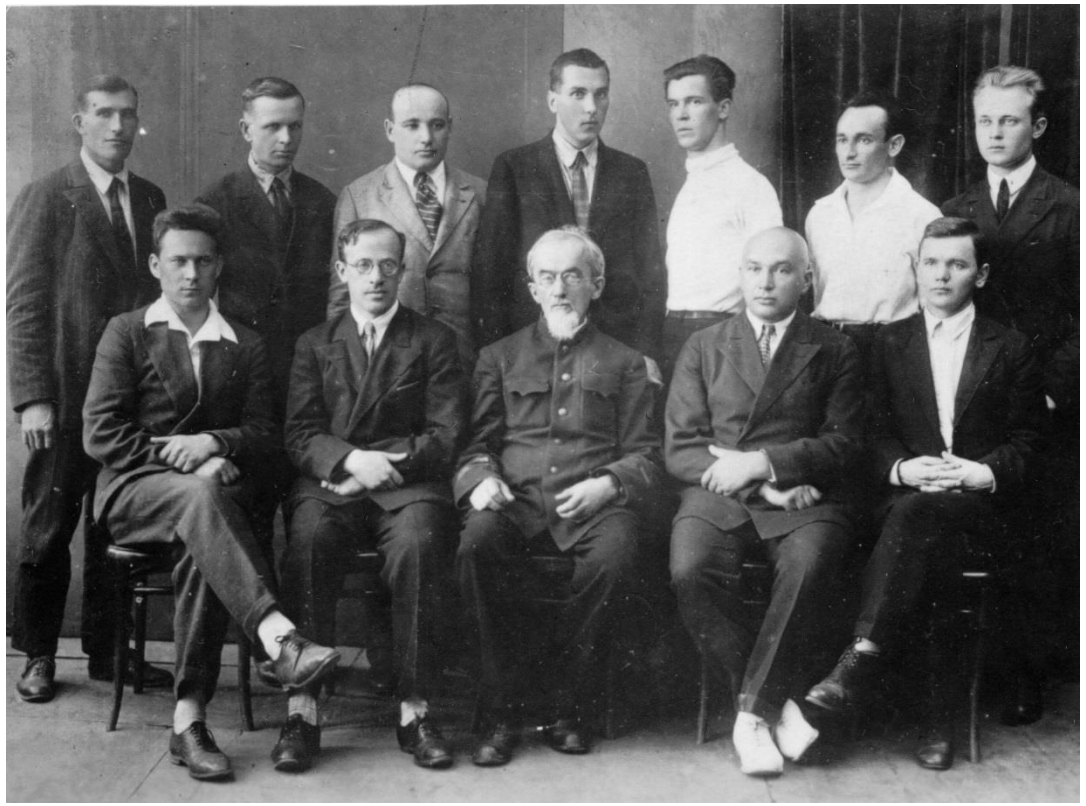


Founded on November 28 (December 10), 1828 by order of Nicholas I. “The purpose of the Practical Technological Institute is to prepare people with sufficient theoretical and practical knowledge to manage factories or individual parts thereof.”

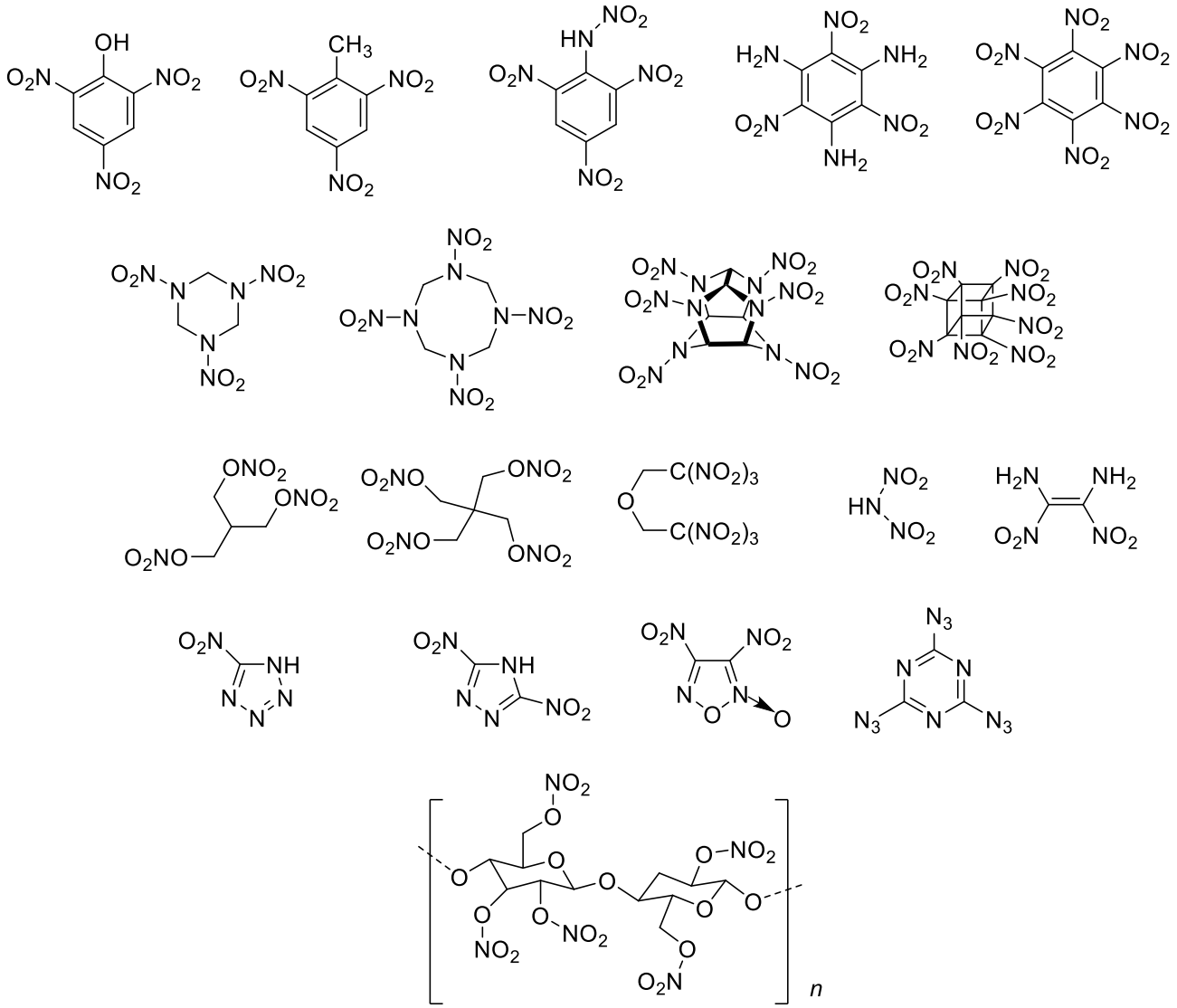
Professor Dmitry Mendeleev (1834 – 1907)

“If without science there cannot be modern industry, then without it there cannot be modern science”

Founder of the department, student of D.I. Mendeleev prof. S.P. Vukolov (in the center).
On the left – ac. RAS V.S. Shpak and prof. L.I. Bagal (Photo 1934)

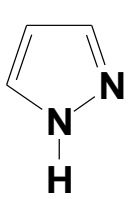


Nitro compounds as components of energy systems and materials

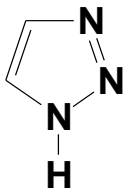


Some properties of Azoles
N,% (ΔH_f кДж/кг)

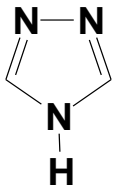
Tetrazole was first synthesized in 1885 by J. Bladin, Uppsala University,



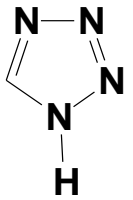
41.2 (1733)



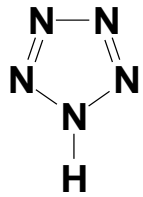
61.0 (2690)



61.0 (1593)



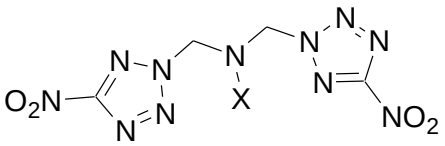
80(3370)

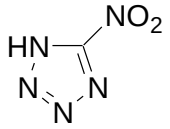


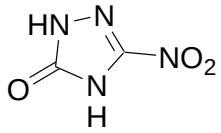
98.5(>6000)

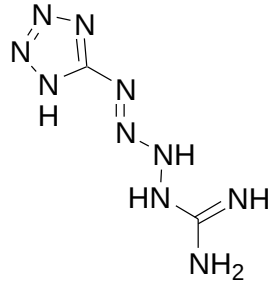
Ostrovskii V.A., Pevzner M.S., Kofman T.G. et al. Energetic 1,2,4-triazoles and tetrazoles. Synthesis, structure and properties. In :*Targets in Heterocyclic`Systems. Chemistry and Properties/Eds.O.Attanasi*, D.Spinelli. Ital.Soc.Chim.1999, *3*, 467-526.

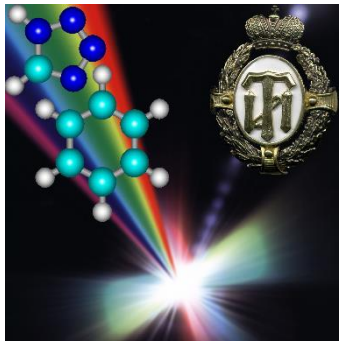
Ostrovskii V. A., Pevzner M. S., Kofman T. P., Shcherbinin M. B., Tselinskii I. V. Energetic 1,2,4-triazoles and tetrazoles. Synthesis, structure and properties. In: Targets in Heterocyclic Systems. Chemistry and Properties/Eds.:O.A. Attanasi, D. Spinelly. Ital.Soc.Chem. 1999.Vol.3. P.467-526.

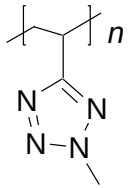


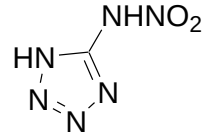


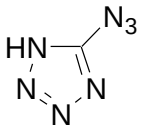


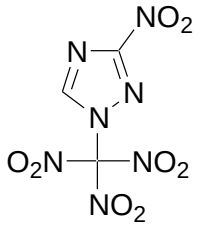


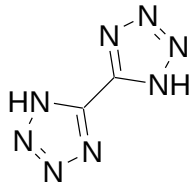


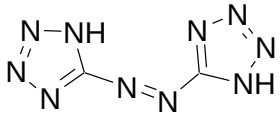








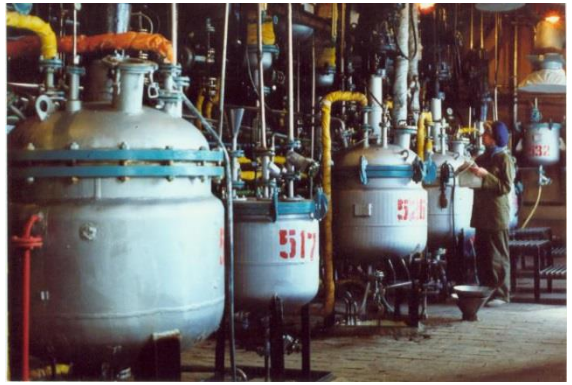




The history of organic chemistry in Russian universities. From the beginnings to the present day. Eds: E.K. Beloglazkina, I.P. Beletskaya, V.G. Nenaydenko. – M.: Technosphere, **2018.**

Professor Lev Bagal taught to his students:
“Didn’t you get a good explosive?
Check it out!
It's possible that you
synthesized a good medicine"

Production of active pharmaceutical ingredients of medicinal products at the pilot production of the Technological Institute and the «Pharmsintez» plant (St. Petersburg), (1992-2002.



Medicines introduced into clinical practice with the participation of some of the authors of this presentation

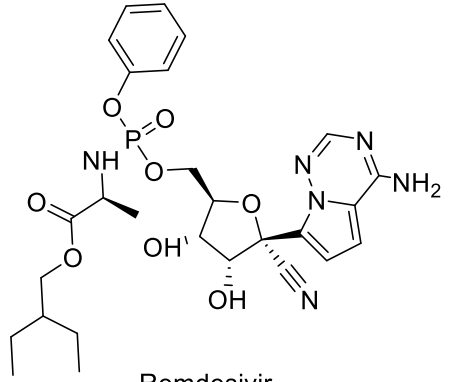
The purpose of this study: Computer prediction and in vitro study of antiviral activity of heterocyclic systems containing thiopyrano[2,3-*b*]quinoline and tetrazole moieties

Life cycle of Influenza virus

Kiselev, O. *Chemo Drugs and Influenza Chemotherapy*; Rostok: St. Petersburg, Russia, 2012.

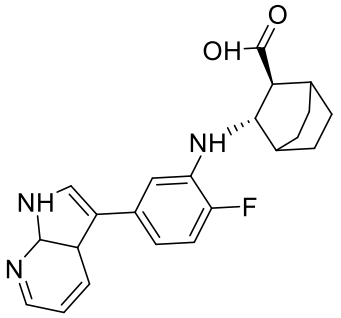
The following stages can be distinguished: - attachment (adsorption) of the virus to the cell; - penetration of the virus into the cell and deproteinization; - protein synthesis and genome replication; - formation of daughter viral particles; - release of daughter viral particles.

Active ingredients of some antiviral drug against influenza virus



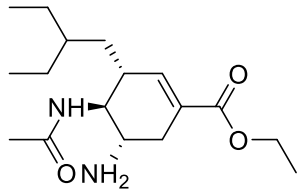
Remdesivir

(polymerase complex inhibitor)



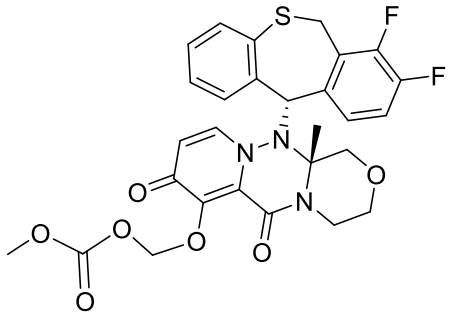
Pimodivir (VX-787)

(polymerase basic protein 2 (PB2) inhibitor).



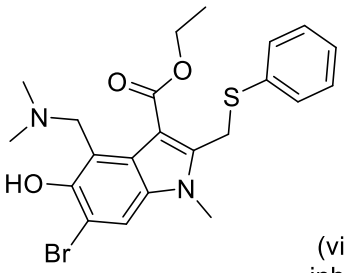
Oseltamivir (Tamiflu)

(neuraminidase inhybitor)



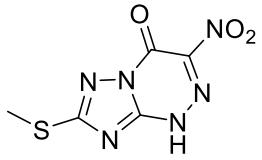
Baloxavir marboxil

(viral mRNA polymerase inhibitor)



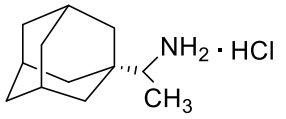
Umifenovir

(inhibitor of lipid virus membranes and cell membranes fusion)



Triazavirine

(viral RNA polymeraze inhibitor)



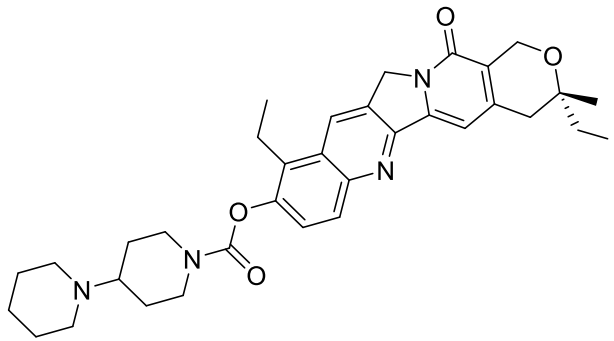
Rimantadine

(ion channel M2 inhibitor)

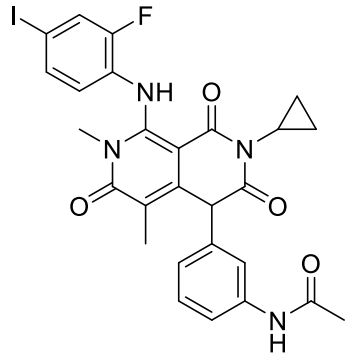
Some quinoline based anticancer drug molecules.

Kiran B.M., Nandeshwarappa B.P., Vaidya V.P., Mahadevan K.M. Thieno[2,3- *b*] and Thiopyrano[2,3- *b*]quinolones. *Phosphorus, Sulfur, and Silicon and the Related Elements*, **2007**, vol. 182, N5, p.969-980. https://doi.org/10.1080/10426500601088846.

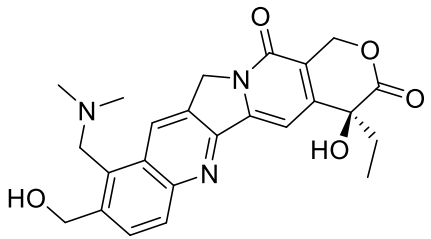
Sharma Sh., Singh Sh., "Molecular Docking Study for Binding Affinity of 2*H*-thiopyrano[2,3-*b*]quinoline Derivatives against CB1a", *Interdisciplinary Perspectives on Infectious Diseases*, vol. 2023, Article ID 1618082, 10 pages, 2023. https://doi.org/10.1155/2023/1618082



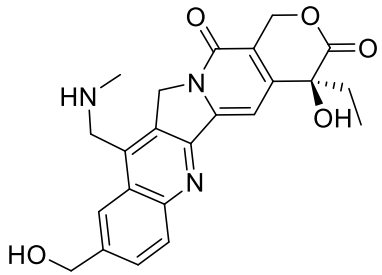
Irinotecean



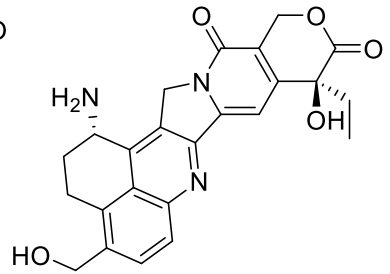
Trametinib



Camptothecin



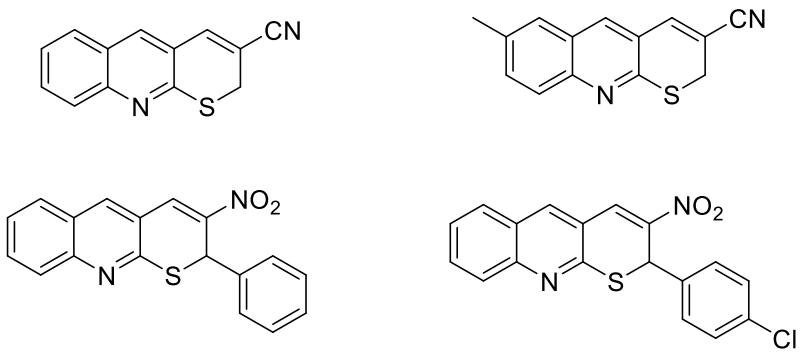
Topotecan



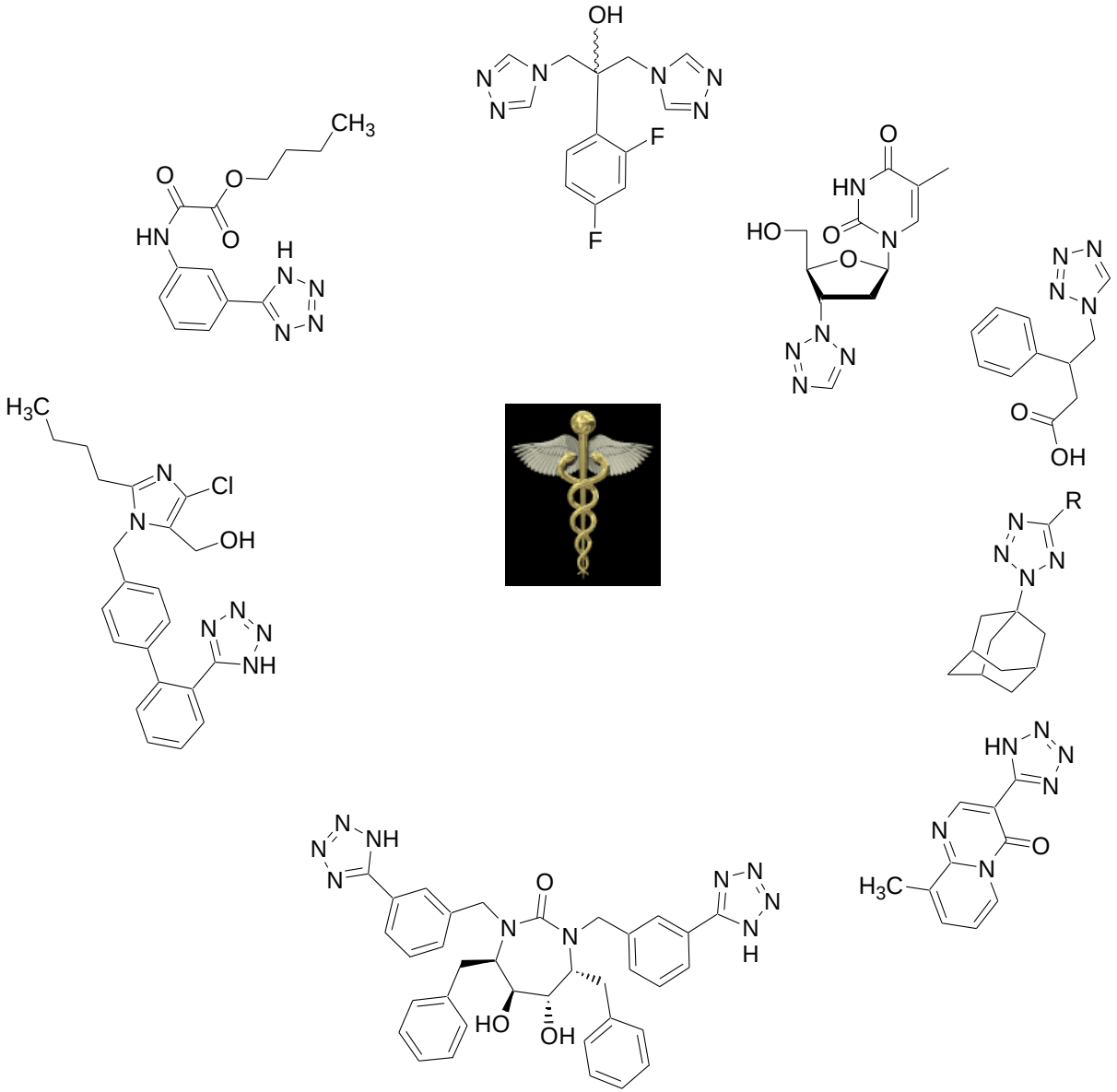
Exatecan

Structure of some compounds having 2*H*-thiopyrano[2,3-b]quinoline cores

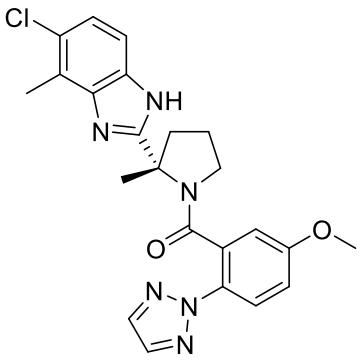
Sharma Sh., Singh Sh., "Molecular Docking Study for Binding Affinity of 2*H*-thiopyrano[2,3-*b*]quinoline Derivatives against CB1a", *Interdisciplinary Perspectives on Infectious Diseases*, vol. 2023, Article ID 1618082, 10 pages, 2023. https://doi.org/10.1155/2023/1618082



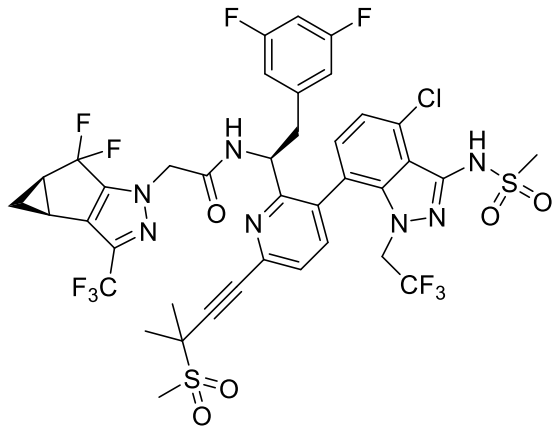
Popova E.A., Trifonov R.E., Ostrovskii V.A. Tetrazoles for biomedicine. *Russ. Chem. Rev.*, **2019**, vol.88. N6. P. 644-676;



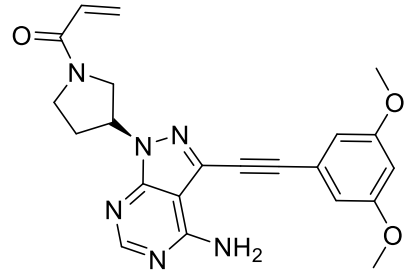
Some highly effective "small molecule" drugs approved by the FDA in **2022**



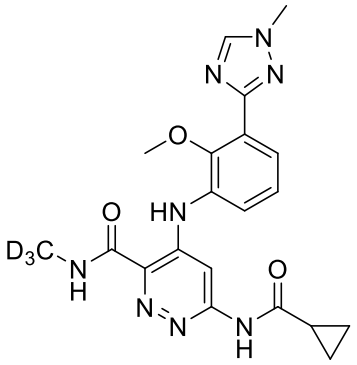
Quiviviq,
OX1/2 dual antagonist
(daridorexant)
for insomnia



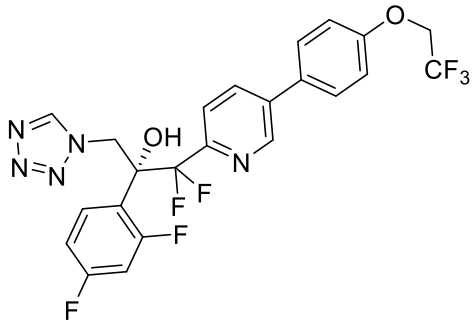
Sunlenca,
HIV-1 capsid inhibitor
(lenacapavir)
for multidrug resistant HIV-1 infection



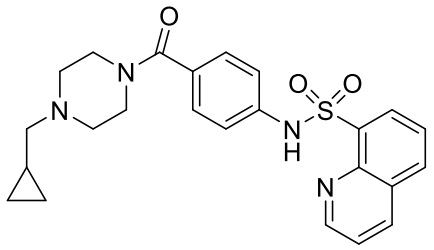
Lytgobi, irreversible
FGFR1-4 inhibitor
(futibatinib)
for iCCA with FGFR2 rearrangements



Sotyktu, TYK2
allosteric inhibitor
(deucravacitinib)
for moderate-to-severe plaque psoriasis



Vivjoa, antifungal
(CYP51 inhibitor)
(oteseconazole)
for RVVC in non-reproductive females



Pyrukynd, PK activator
(mitapivat)
for hemolytic anemia in PK deficiency hematology

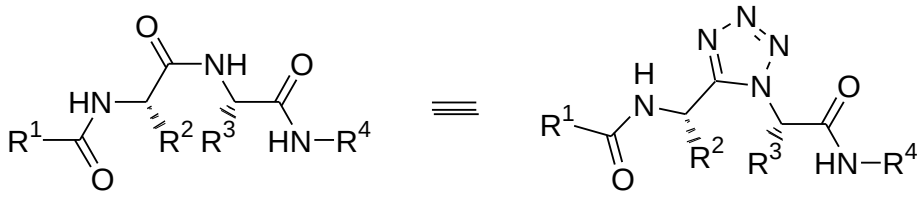
Herr R.J. Tetrazol-1-yl as bioisostere analogs of *cis*-amide group . *Bioorganic & Medicinal Chemistry*. **2002**, vol.10, p. 3379-3393.

Abell A.D. *Letter in Peptide Science*, **2002,** vol.8, p.267-272.


R. Jason Herr


Andrew Abell

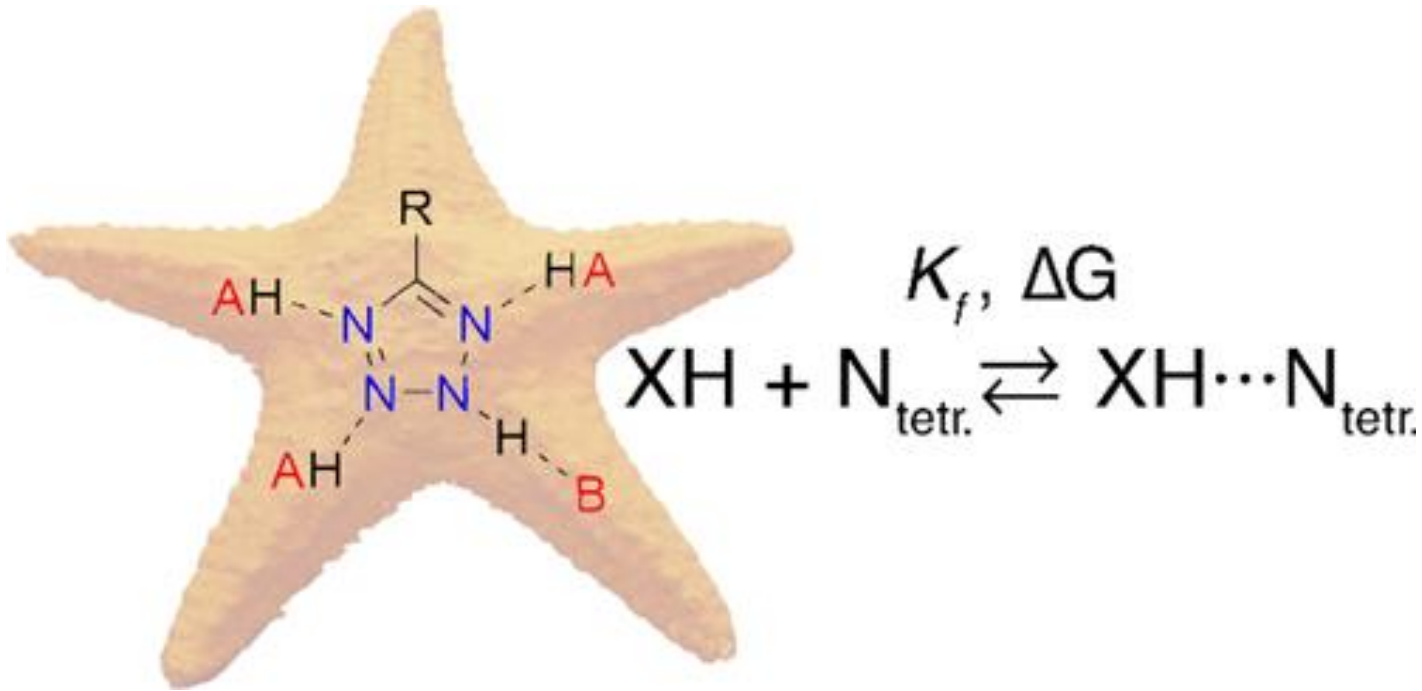
Popova E.A., Trifonov R.E., Ostrovskii V.A. Тетразолы для биомедицины. *Успехи химии*. **2019**. Т.88. №6, с.644-676. *Russ. Chem. Rev.*, **2019**, Vol.88. N6. P. 644-676.



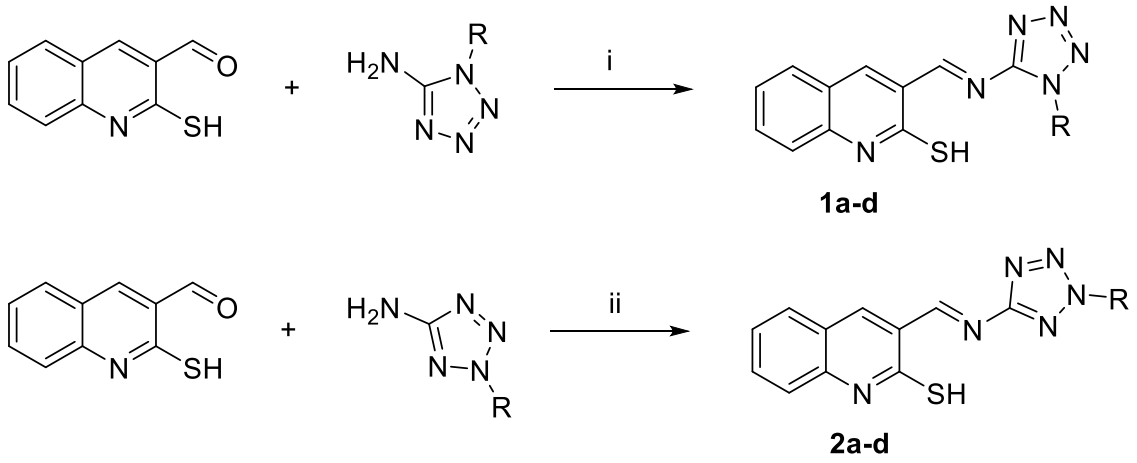
cis-amide **1** tetrazole isostere **2**

R^1, R^2 ,R^3, R^4 – amino acid side chains

Trifonov R. et al. J.Phys.Chem. A. 2023



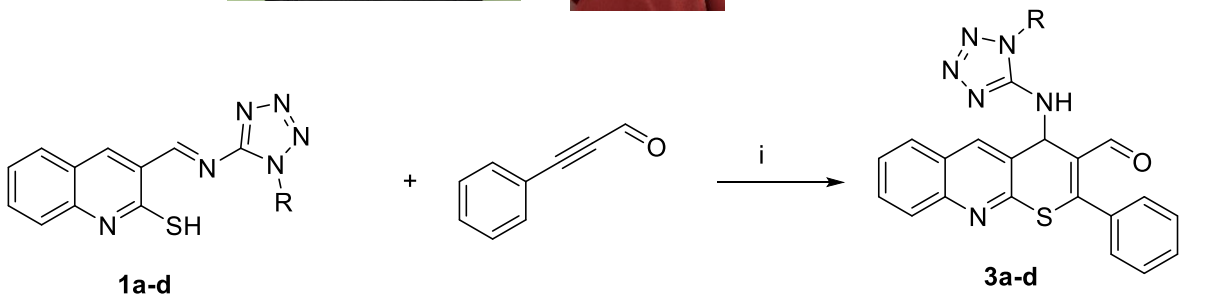
Synthesis of azomethines **1** and **2** which containing of tetrazole's ring by action of regioisomeric *N*-alkyl-5-aminotetrazoles on 2-mercaptoquinolin-3-carbaldehyde



i: piperidine, o-xylene, 2h, 73% (**a**); piperidine, toluene, 4–6h, 75% (**b**), 72% (**c**), 78% (**d**)
ii: piperidine, o-xylene, 0.5h, 77% (**a**); piperidine, toluene, 4–6h, 80% (**b**), 75% (**c**), 76% (**d**)
R = Me (**a**), Et (**b**), Pr (**c**), Bu (**d**)

Synthesis of thiopyrano[2,3-*b*]quinolones **3** and **4** containing regioisomeric N-alkyl-5-aminotetrazole moieties by the *thio-Michael/aza-Morita-Baylis-Hillman* tandem reaction* using azomethines **1** and **2** and 3-phenyl-2-propynal

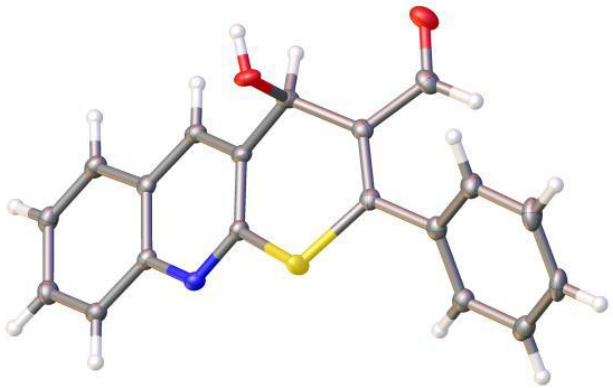
*Jie Jack Li. *Name Reactions*. Springer, 2003.

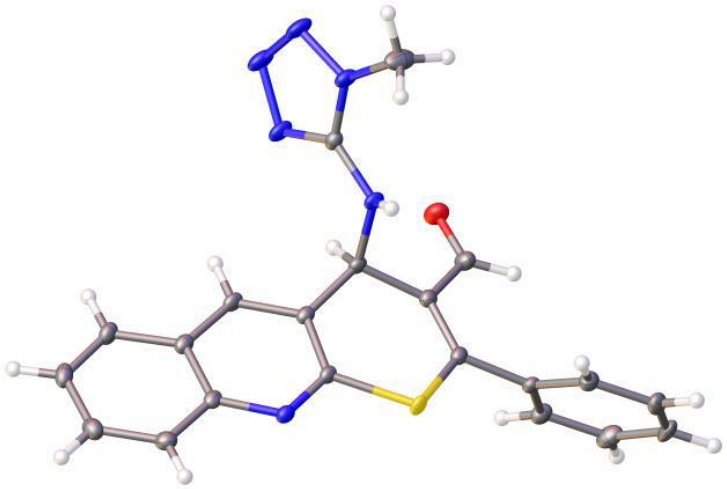


R = Me (**a**), Et (**b**), Pr (**c**), Bu (**d**)

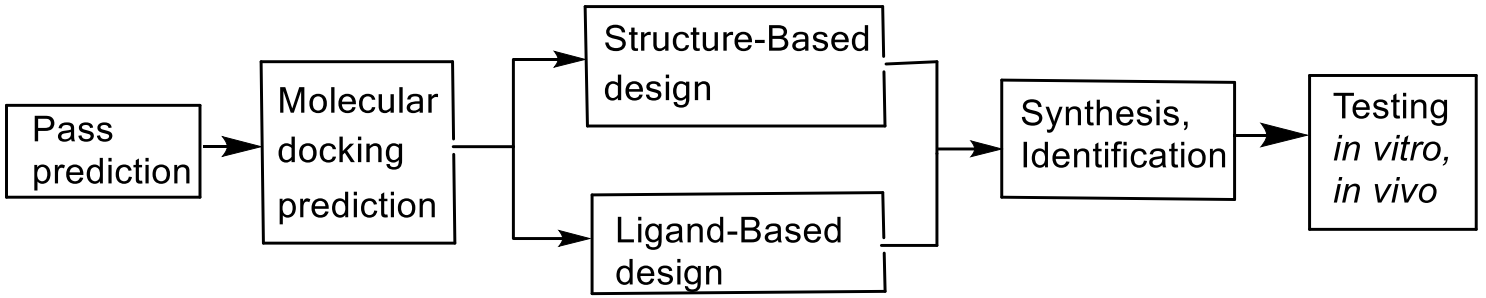
i: Et_3N, DMF, rt, near 20 min. Yields, 82-90%.

X-Ray crystallography data of 4-hydroxy-7-methyl-2-phenyl-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbaldehyde and its regioisomeric 1(2)-methyl-5-aminotetrazolyl analogists **3a** (**4a**)

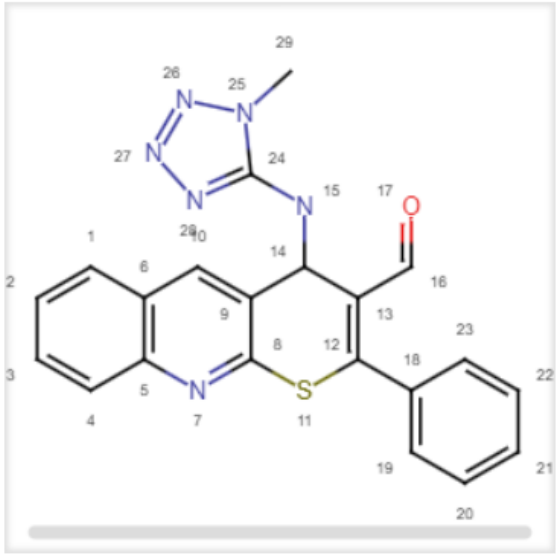




One of the algorithms for searching drug candidates using PASS and molecular docking



PASSonline testing for biological activity of compound **3a**



Powered by ChemAxon

AntiFun-Pred | AntiBac-Pred | AntiVir-Pred | DIGEP-Pred | CLC-Pred | PASSOnline (classic) | PASSOnline (2022)

KinScreen | Rosc-Pred | hERG-Pred | ADVER-Pred | SOMP

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Pa	Pi	Virus	Protein target
0.454	0.024	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab
0.180	0.019	Infectious bronchitis virus	3C-like protease
0.173	0.123	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase
0.101	0.071	SARS coronavirus	SARS coronavirus 3C-like proteinase

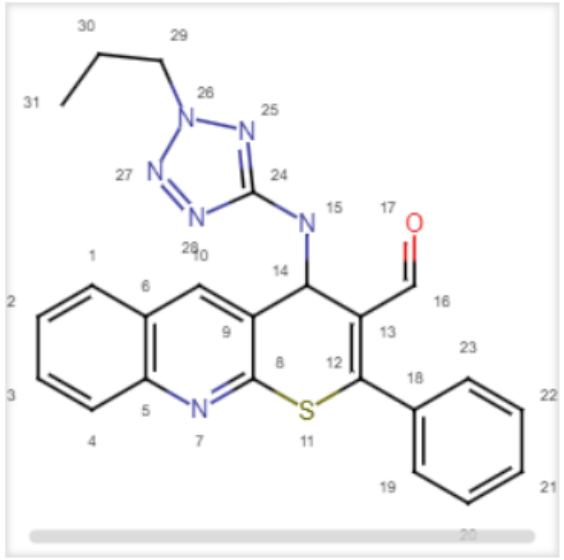
Pi

Show 10 entries

Showing 1 to 4 of 4 entries

Previous 1 Next

PASSonline-22 testing for biological activity of compound **4c**



AntiFun-Pred | AntiBac-Pred | AntiVir-Pred | DIGEP-Pred | CLC-Pred | PASSOnline (classic) | PASSOnline (2022)

KinScreen | Rosc-Pred | hERG-Pred | ADVER-Pred | SOMP

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Pa	Pi	Virus	Protein target
0.370	0.033	Severe acute respiratory syndrome coronavirus 2	Replicase polyprotein 1ab
0.179	0.019	Infectious bronchitis virus	3C-like protease
0.171	0.125	Vaccinia virus (strain Western Reserve) (VACV) (Vaccinia virus (strainWR))	DNA polymerase

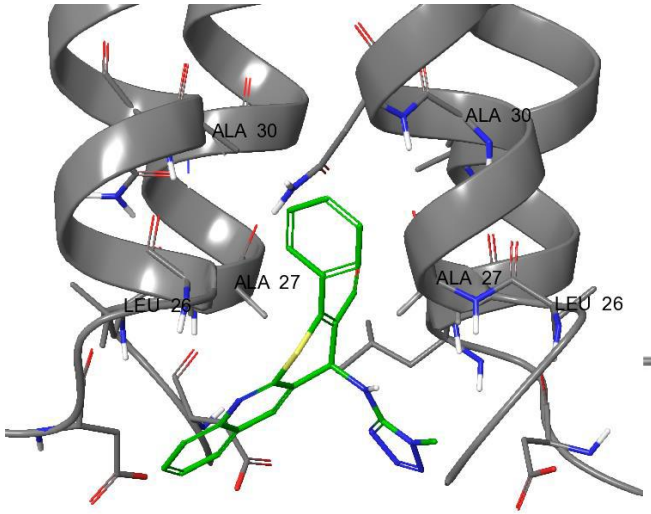
Pi

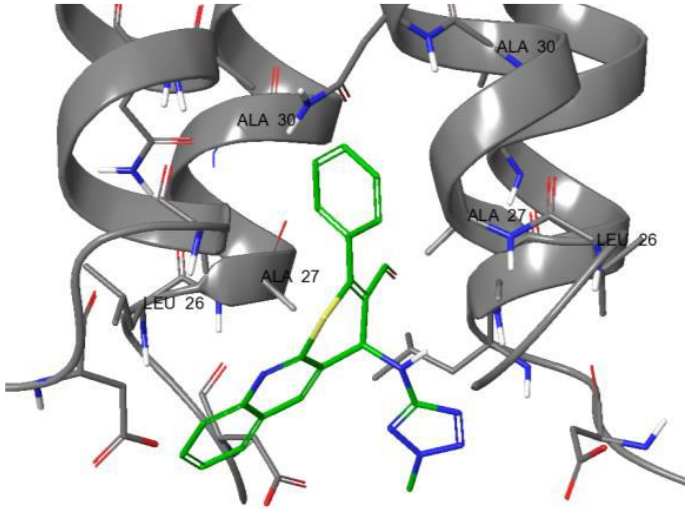
Show 10 entries

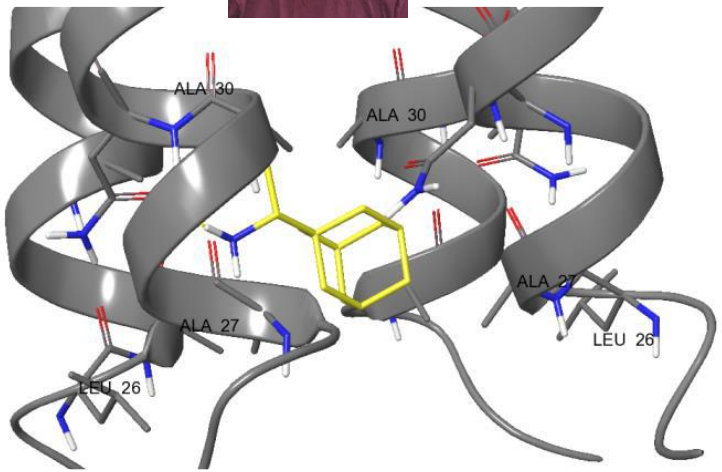
Showing 1 to 3 of 3 entries

Previous 1 Next

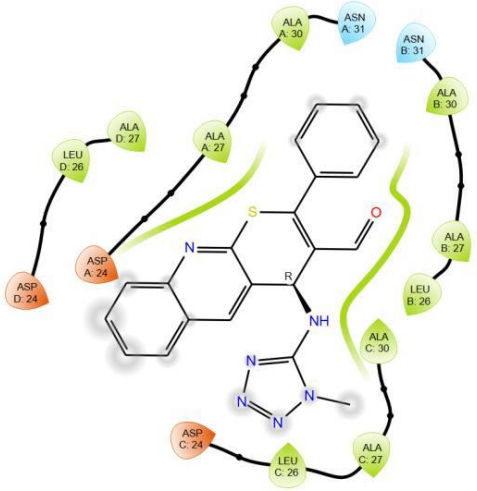
Protein-ligand complexes of compounds **3a**, **4a** and rimantadine with M2 channel. Computer modeling using the Schrödinger Suite 2022-4 software package.

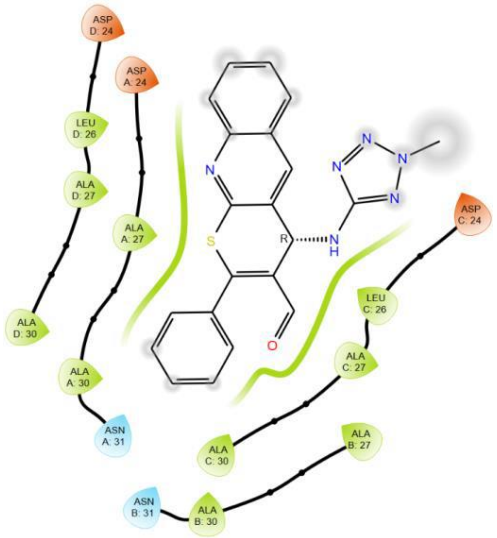


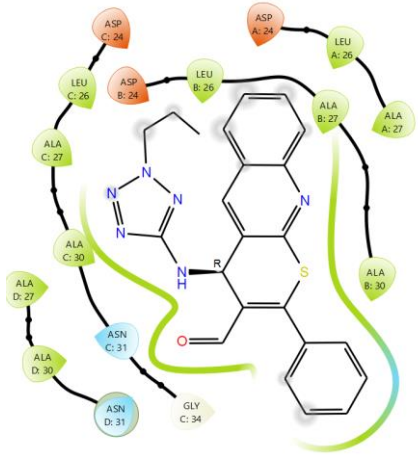


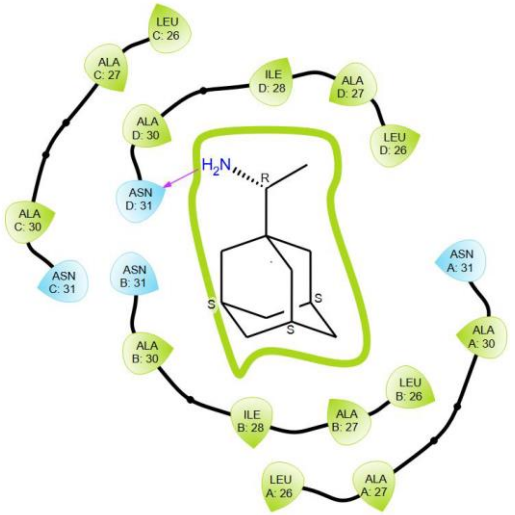


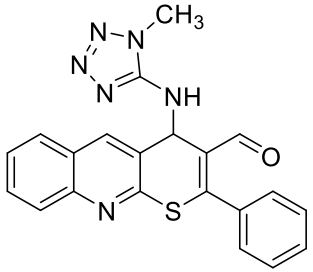
Ligand interactions diagrams for compounds **3a, 4**a, **4c** and rimantadine with M2 channe



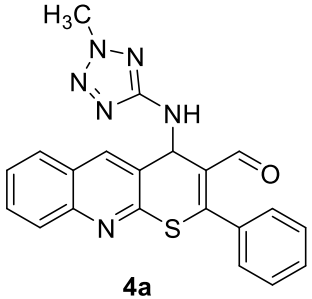




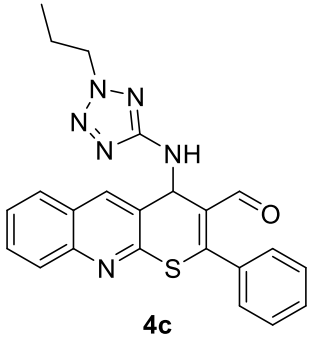




3a



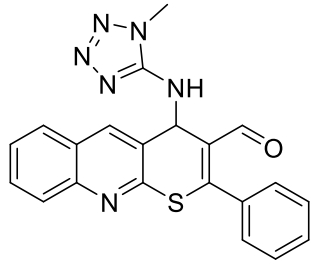
4a

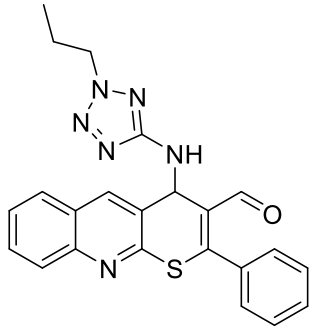


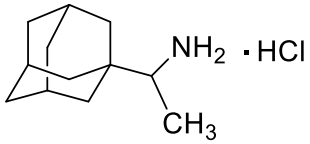
4c

GlideScore, kcal/mol	**-8.34**	**-3.99**	**-5.08**	**-6.6**

The cytotoxic and antiviral properties of the synthesized compounds were tested *in vitro* against influenza A/Puerto Rico/8/34 virus in MDCK cells.







Compound No	3a	4c	Rimantadine
CC_{50}, µM	>750	>700	312.3±22.8
IC_{50}, µM	46±5	18.4±2.7	64.1±7.2
SI	>16	>38	5

Conclusion and recommendation :

1. In accordance with the computer prediction, the synthesized thiopyrano[2,3-b]quinolines with tetrazole moieties exhibit moderate in vitro activity against influenza A/Puerto Rico/8/34 virus in MDCK cells.

2. Research in this direction confirm of perspective and should be continued in the direction of computer prediction, synthesis and testing of the antiviral activity of a few analogues of previously obtained compounds containing a larger substituents on the nitrogen atoms of the regioisomeric tetrazole rings. For example – *n*Bu. *i*Pr, *t*Bu, etc

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[2]St. Petersburg State Institute of Technology (Technical University), St. Petersburg, Russia;
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[4]St. Petersburg Pasteur Research Institute of Epidemiology and Microbiology, St. Petersburg, Russia







Thank you for attention!

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