



SIXTY YEARS IN SCIENCE OF PROFESSOR NIKOLAY S. ZEFIROV: FROM ORGANIC SYNTHESIS, CONFORMATIONAL ANALYSIS AND REACTION DESIGN – TO MEDICINAL CHEMISTRY AND CADD

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*The slides in this presentation are
based on the slides prepared by
Professor Nikolay Serafimovich Zefirov himself
for the celebration of his 80th birthday in 2015
and translated into English.*



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Academician Nikolay S. Zefirov

MSU Honorable Professor

Member of International Academy of Mathematical Chemistry



1953



1961

1966



Corr. member.

1981

Lomonosov
Prize, MSU
1983



1987

Academician RAS
1987
Council of ministers prize
1987



IPAC RAS, Director 1989

State Prize, USSR 1989
1994

Butlerov Prize 1994

State Prize of Russia 2000

Head of medicinal chemistry and advanced
organic synthesis division



1935,
Yaroslavl,
September 13



Dr. Vlasov V.M.
Head of medicinal chemistry and
advanced organic synthesis division,
Dept. of Chemistry, MSU



Scientific supervisor,
Institute of Physiologically Active
Compounds of Russian Academy of
Sciences

2015



“For the contribution in development
of education in Russia” 2015 г

2014

State Prize of Russia 2000

Head of medicinal chemistry and advanced
organic synthesis division



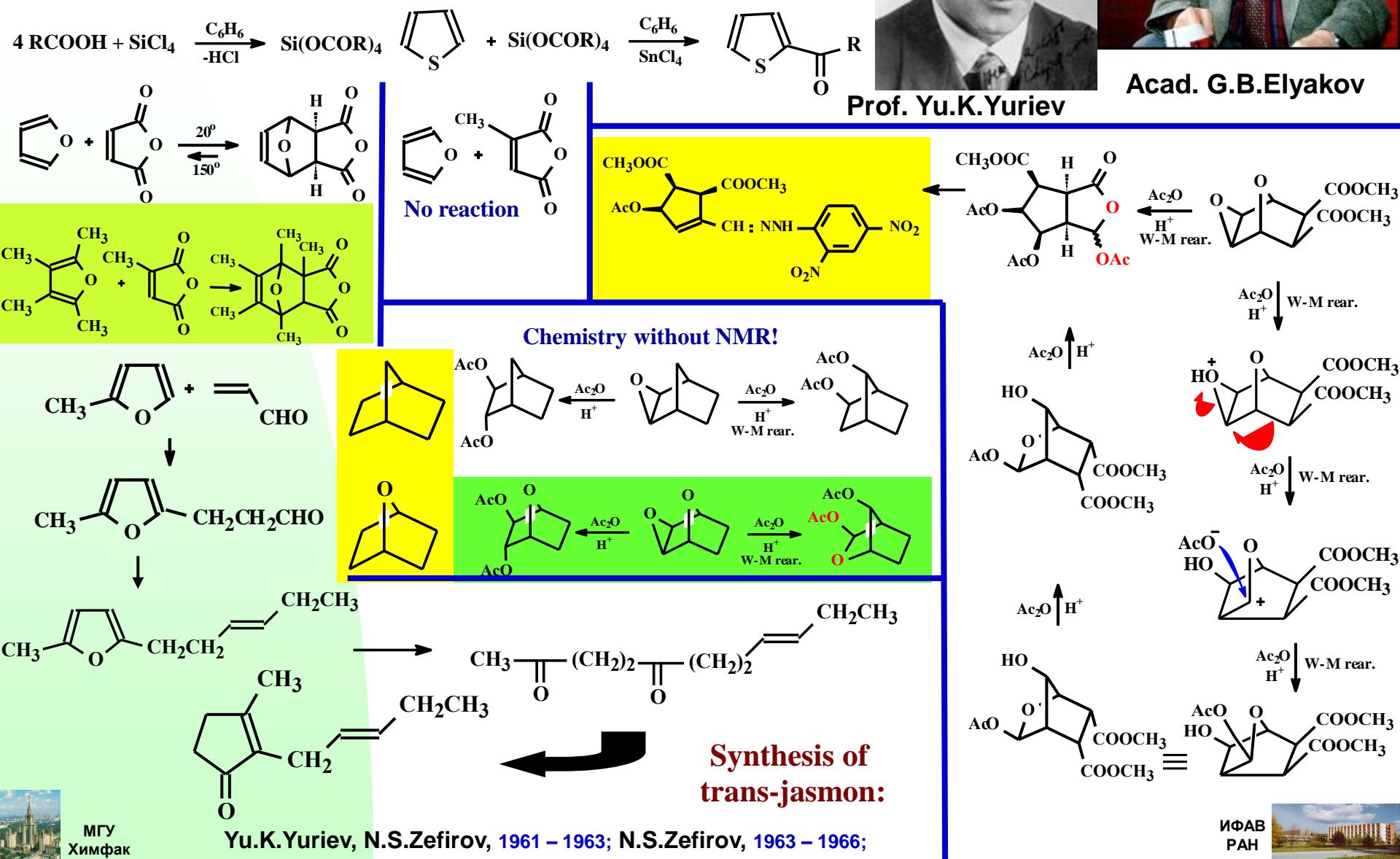
Chemical childhood and growing up



Yu.K.Yuriev, G.B.Elyakov, N.S.Zefirov, Zh.Obsch.Khim, 26, 3341 (1956); 27, 3264 (1957)



Acad. G.B.Elyakov

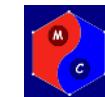




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Scientific supervisor, Institute of Physiologically Active Compounds of Russian Academy of Sciences



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- **Synthetic organic chemistry**
- **Physical organic chemistry, MO**
- **Stereochemistry and conformational analysis**
- **Mathematical and computational chemistry**
- **Medicinal chemistry**

More than 1900 papers and patents

ИФАВ
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Synthetic organic chemistry

- ◆ New approaches in Ad_E reactions: (a) “doping addition”, (b) SO₃-mediated addition.
- ◆ Nucleophilic properties of nucleofugal anions. Synthesis of organic perchlorates, triflates, fluorosulfates, etc. New reactions and reagents. New hypervalent I⁺³, Xe⁺², Se⁺⁴, Te⁺⁴ reagents.

Discovery No. 293 (1984)

USSR State Prize (1989)

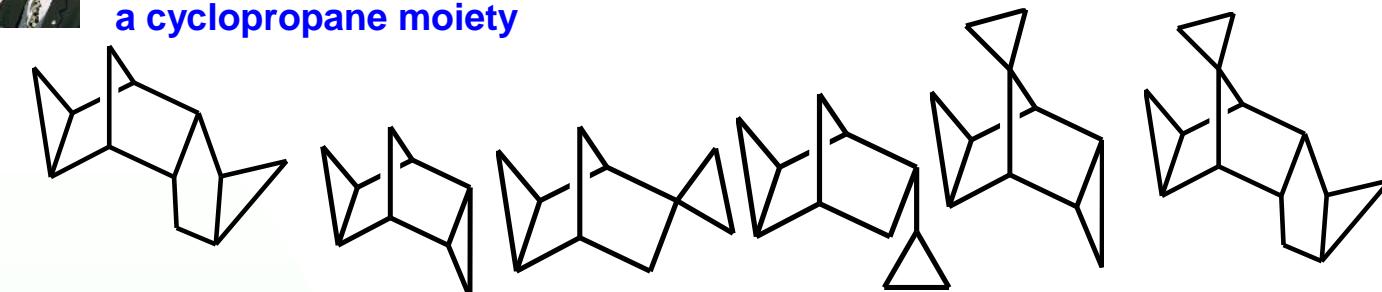
- ◆ Cage structures: (a) heteroadamantanes, (b) bicyclo[3.3.1]nonanes, (c) skeletal rearrangements.
- ◆ Cyclopropanes, triangulanes and related polycycles. High-energy compounds.
- ◆ Polynitro compounds. Syntheses based on C(NO₂)₄. Syntheses of heterocycles of various types.
- ◆ Photochemical reactions: [2+2]-cycloaddition, syntheses based on hexachlorocyclopentadiene, synthesis of oxazoles and λ⁵-phosphinolines from phosphonium-iodonium ylides.



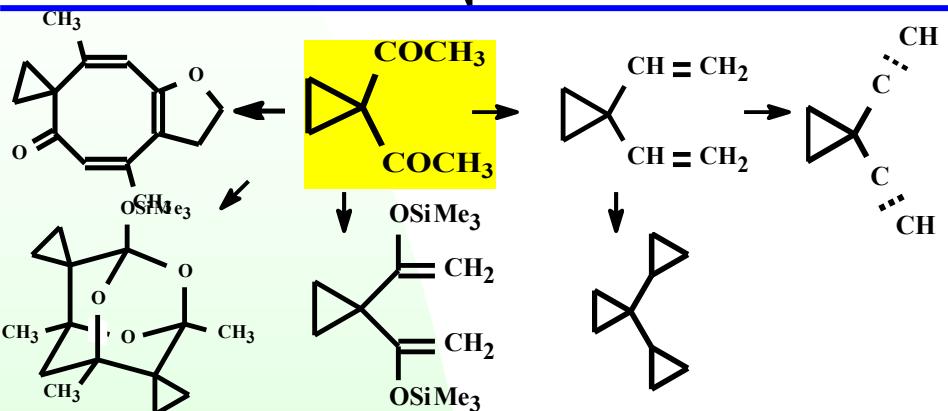
Synthetic organic chemistry: cyclopropanes



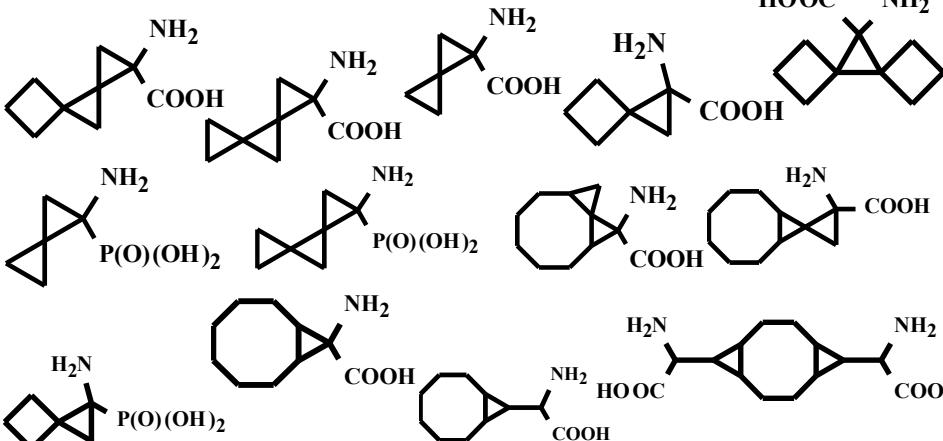
Synthesis of cage/polycyclic hydrocarbons containing a cyclopropane moiety



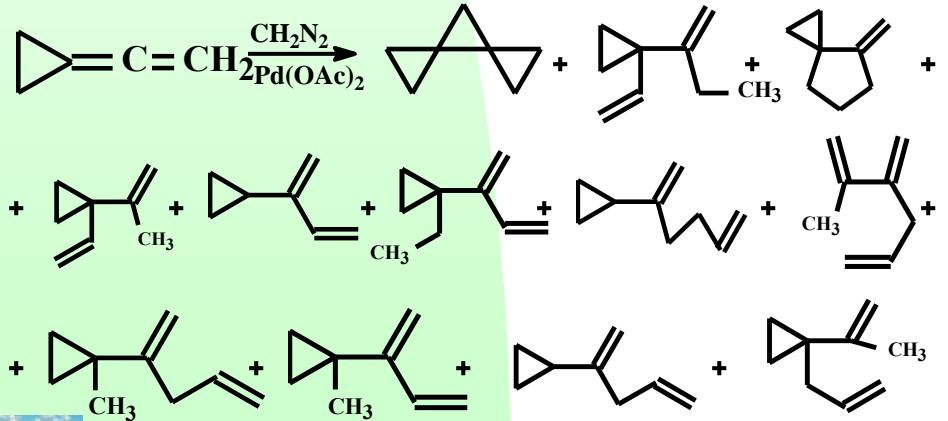
Dr. T.S.Kuznetsova



Aminoacids and their P-bioisosteres

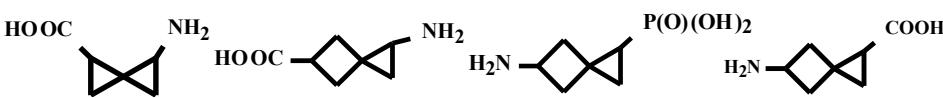


Oligomethyleneation of allenes

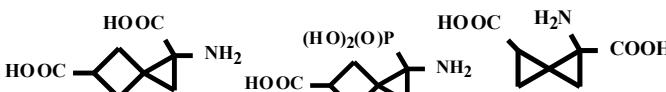


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Conformationally rigid analogues of GABA:



Conformationally rigid analogues of glutamic acid:



Dr. N.V.Yashin



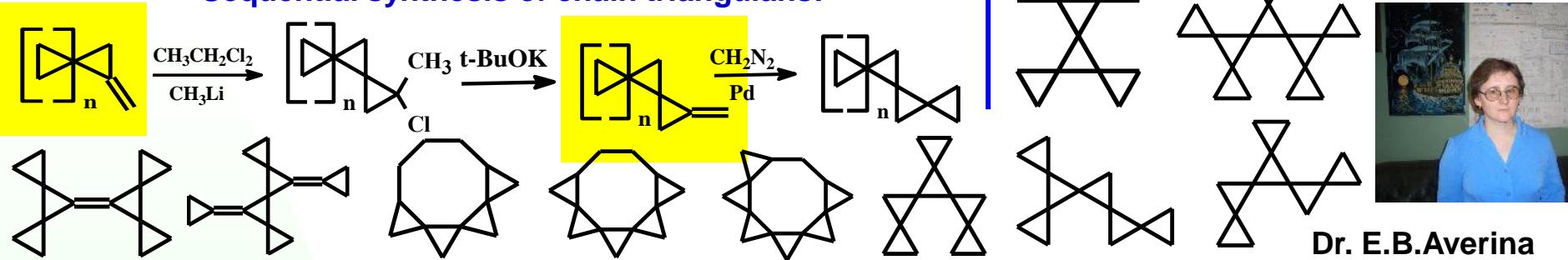


Synthetic organic chemistry: triangulanes



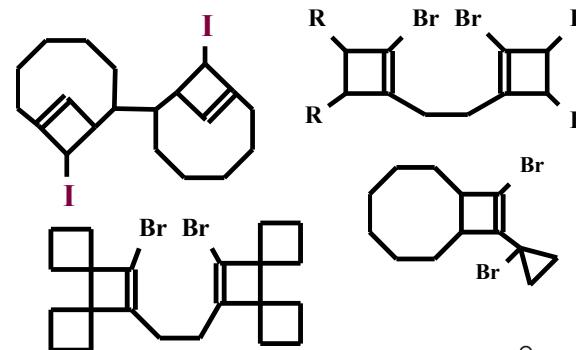
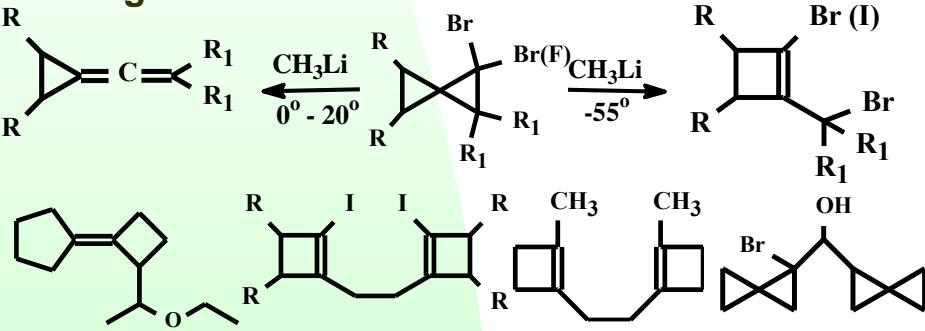
Triangulans are a class of hydrocarbons whose skeleton is constructed from spiro-linked cyclopropane rings. (Zefirov, Kuznetsova, Lukin et al., *J.Am.Chem.Soc.*, 1990, 112, 7702).

Sequential synthesis of chain triangulans:

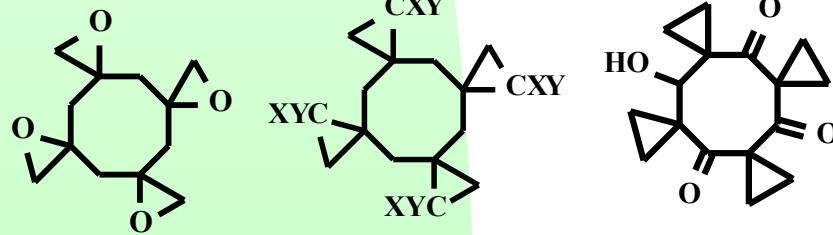


Dr. E.B. Averina

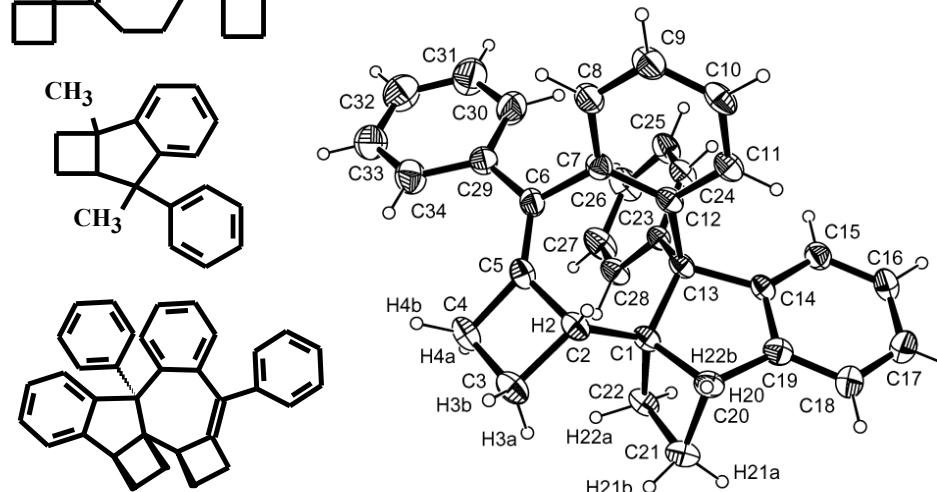
A new skeletal rearrangement in carbenoid triangulane structures:



Dr. K.N. Sedenkova



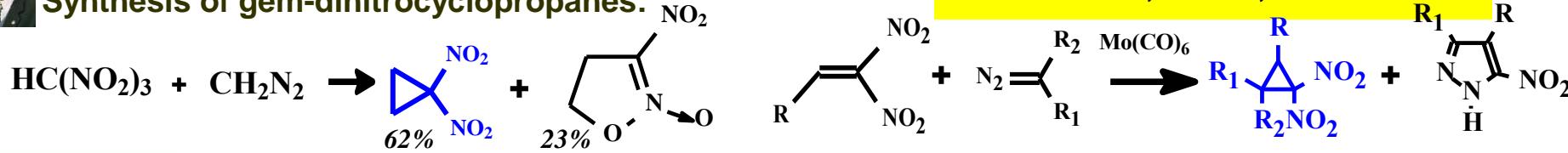
Kuznetsova, Averina, Sedenkova



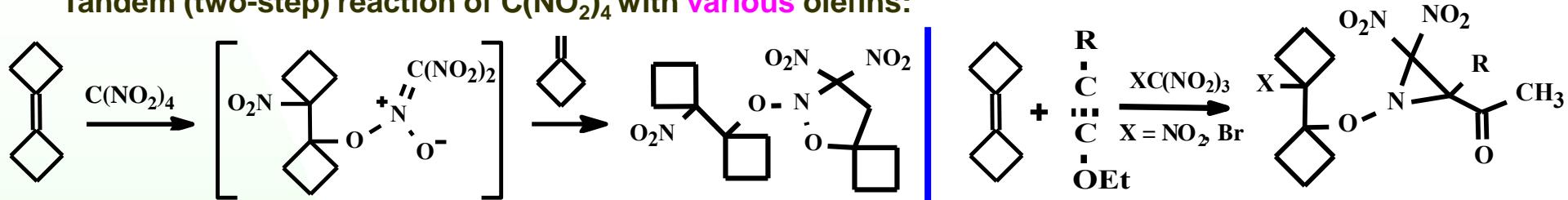


Synthetic organic chemistry: synthetic studies in the field of nitro(poly-nitro) compounds

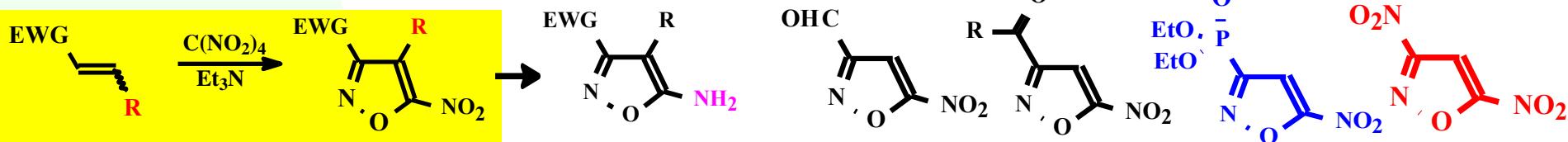
Synthesis of gem-dinitrocyclopropanes:



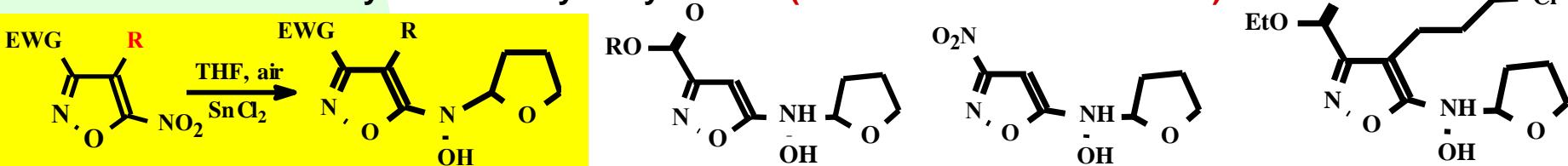
Tandem (two-step) reaction of $\text{C}(\text{NO}_2)_4$ with various olefins:



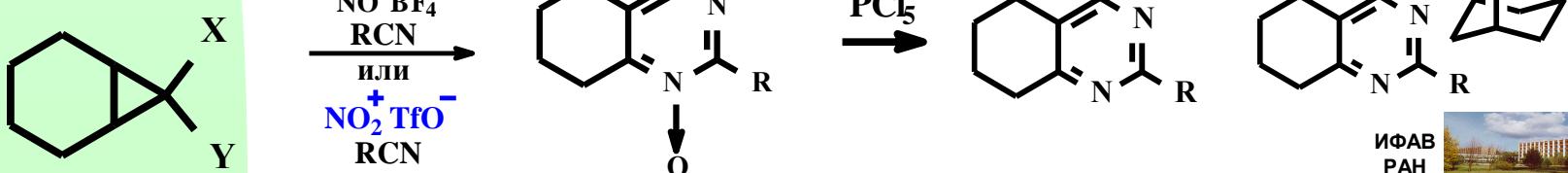
New reaction for the synthesis of isoxazoles. $\text{C}(\text{NO}_2)_4 \cdot \text{Et}_3\text{N}$ as a new reagent { $[\text{Et}_3\text{N}-\text{NO}_2]^+[\text{C}(\text{NO}_2)_3]^-$ }



A new reaction for the synthesis of hydroxylamines (direct C-H functionalization):



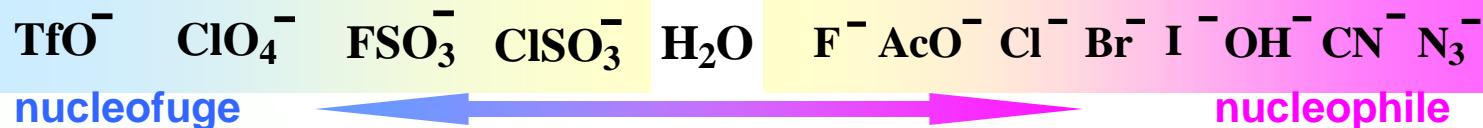
New reaction for the synthesis of fluoropyrimidines(oxides):





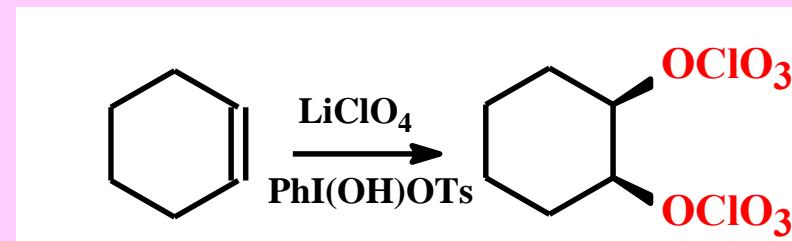
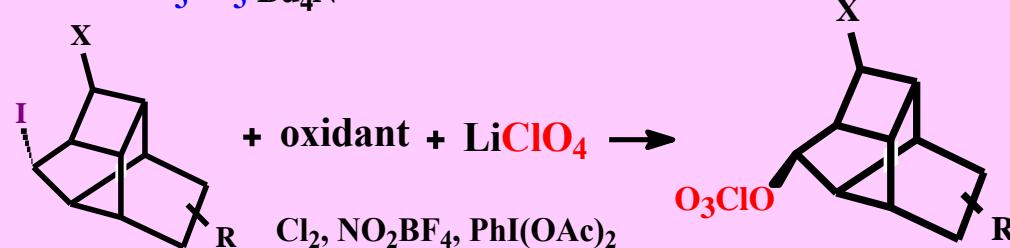
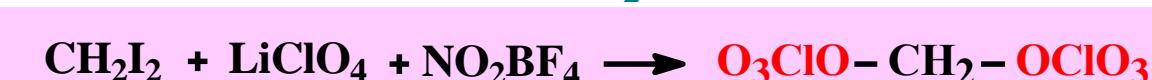
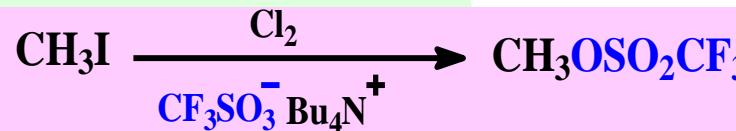
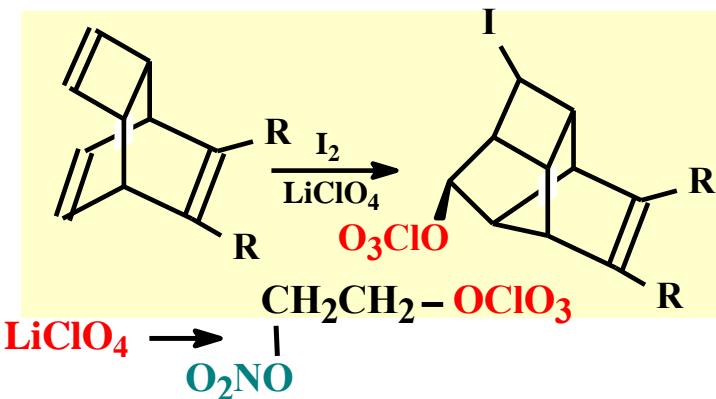
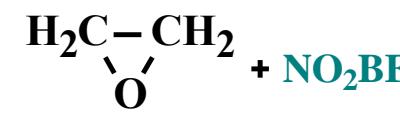
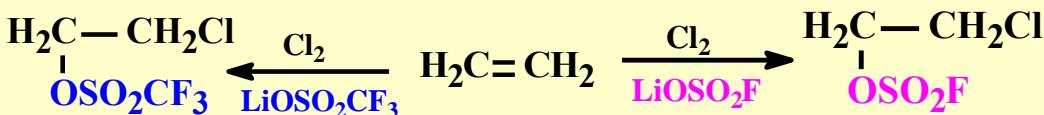
Synthetic organic chemistry: nucleophilic properties of nucleofuge anions

General scheme of nucleophilic substitution: $R - X \xrightarrow{Y^-} R - Y$ $R - Y / R - Z = ?$



Competitive covalent binding of “nucleofuge” anions is a general phenomenon for a large series of carbocation-type reactions.

Discovery No. 293 (1984)

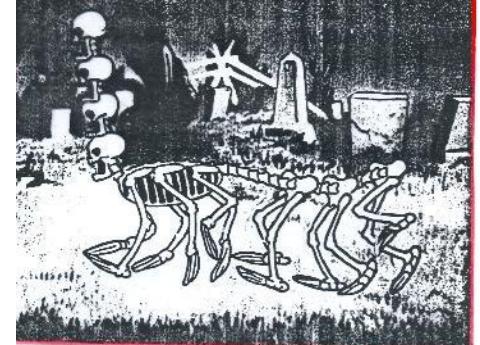
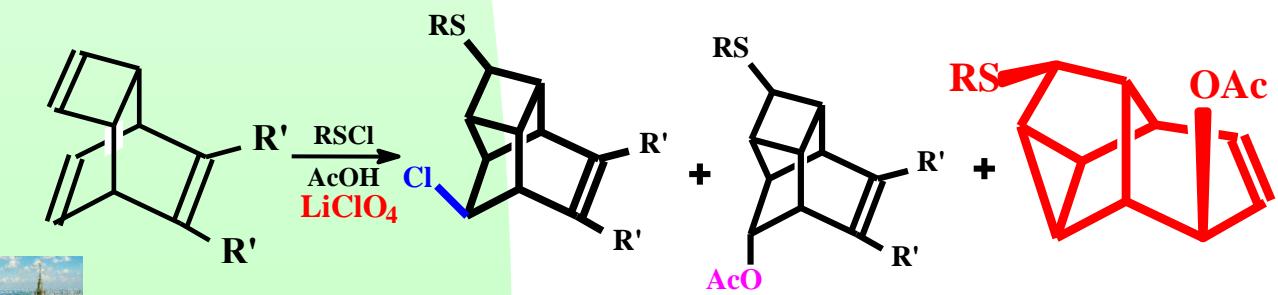
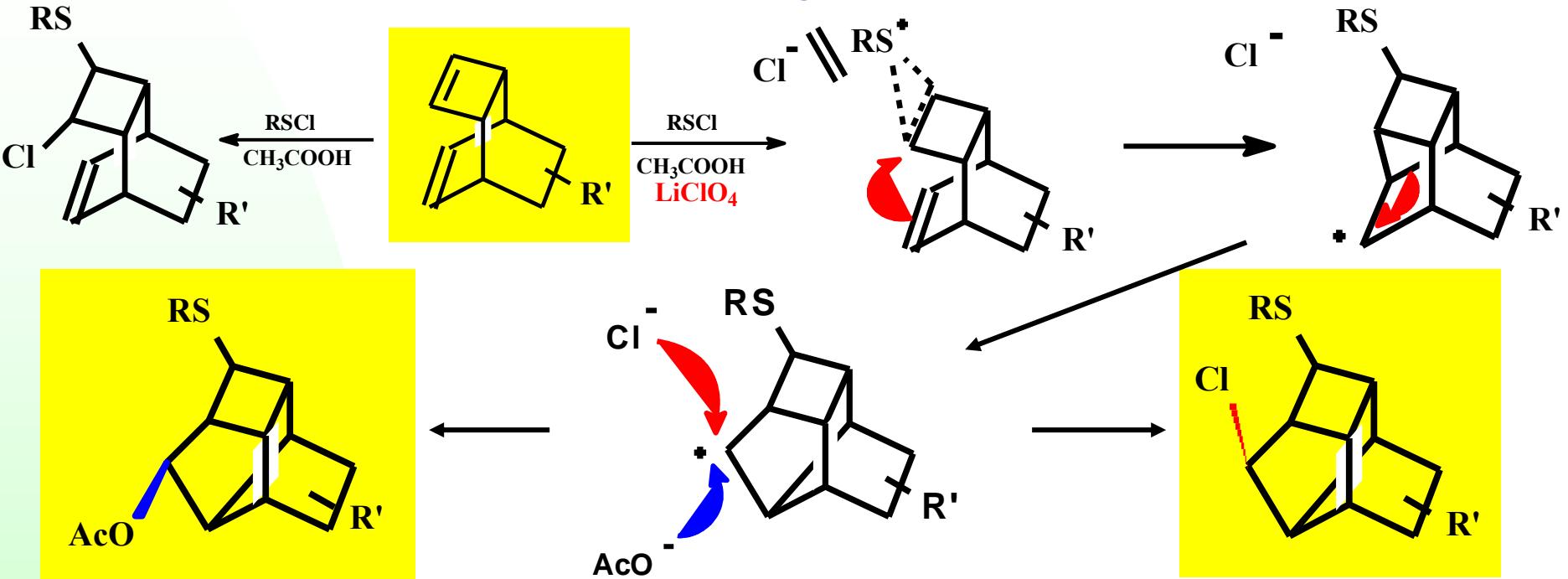


USSR State Prize (1989)



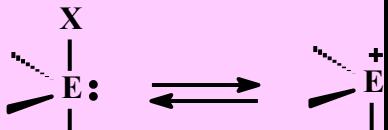
Physical organic chemistry: skeletal rearrangements

Ion-pair mechanism of Ad_E-reactions and
“doping-addition”



Синтетическая

валентные



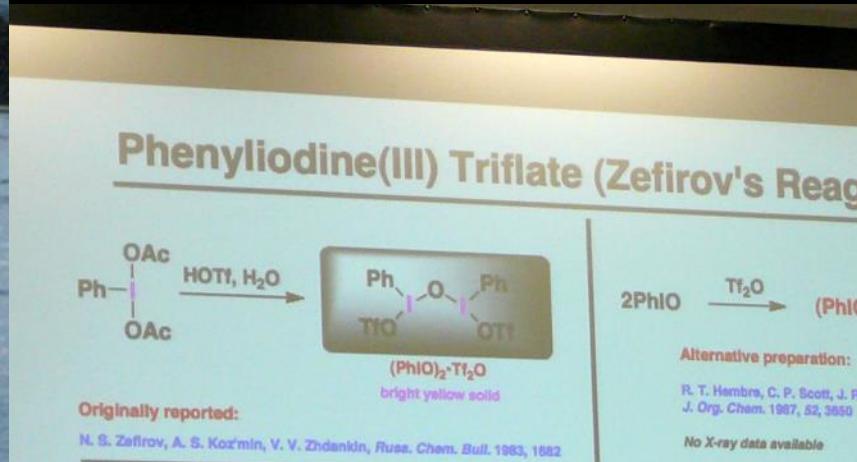
Prof. P. Stang



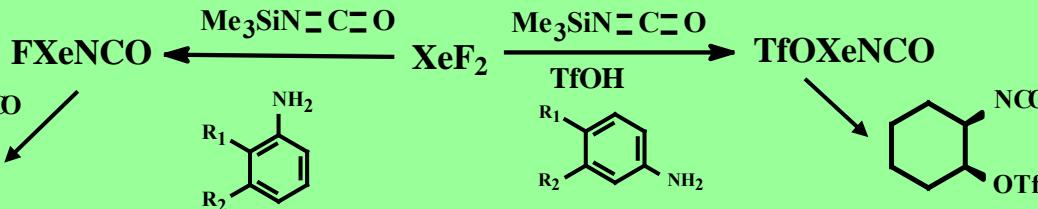
Prof. V.V. Zhdankin



Prof. R. Caple



Dr. V.K. Brel





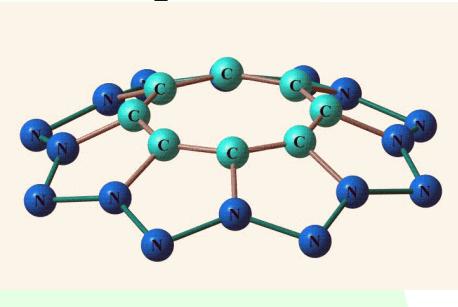
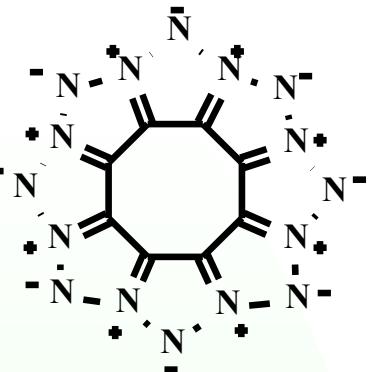
Physical organic chemistry, MO

- Kinetics and mechanism of some Ad_E reactions (e.g. oxymercuration, sulfenylation, nitrosochlorination, etc.).
Skeletal rearrangements in Ad_E reactions.
- Mechanism and skeletal rearrangements in carbenoid transformations.
- MO prediction of new types of structures.
- Calculation of atomic charges – calculation schemes taking into account the equilibration of atomic electronegativities (“Zefirov charges”: Zefirov N.S., et. al., *Dokl. Akad. Sci. USSR*, 1987, 296, 883; 1989, 304, 887. **New charge scheme:** Oliferenko A.A., Palyulin V.V., Zefirov N.S., *J.Phys. Org. Chem.*, 2001, 14, 355 ; *SAR QSAR Env. Res.*, 2002, 13, 297.)

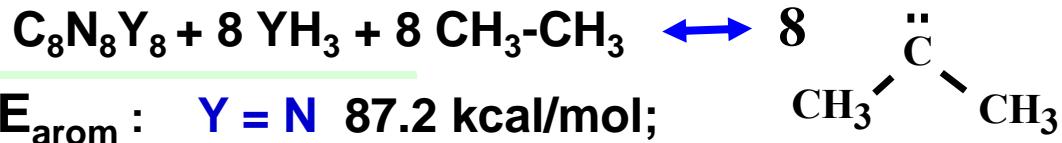


 C_8N_{16}

Physical organic chemistry, MO MO prediction of structures of new types.



Homodesmotic reaction:



ΔE_{arom} : $Y = N$ 87.2 kcal/mol;

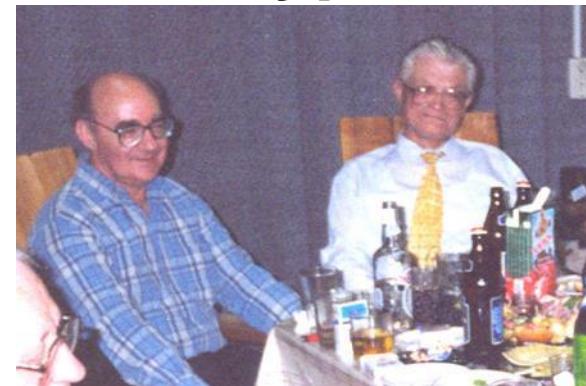
$Y = P$ 268.9 kcal/mol; $Y = As$ 246.4 kcal/mol

Cage derivatives

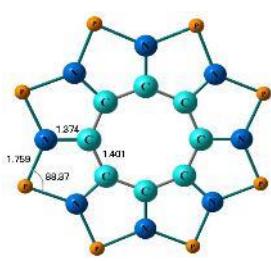
Results of DFT B3LYP/6-311G* :

Bowl shape, flat C_8 cycle, C_{8v} ,
 $\text{bowl} \rightleftharpoons \text{bowl}$ >150 kcal/mol

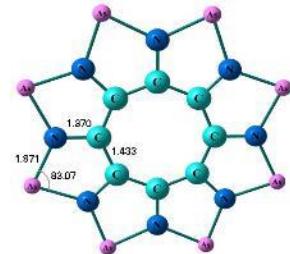
NICS(0) index in the center of
8-membered cycle – 3.3



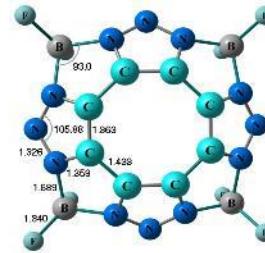
Academician V.I.Minkin



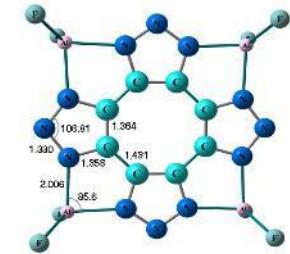
P



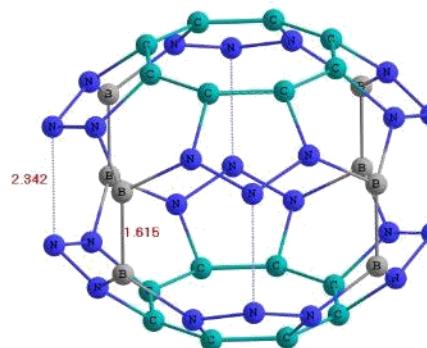
As



BF₂



AlF₂



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T.Gribanova, N.S.Zefirov, V.I.Minkin, *Dokl. Chem.*,
2009, 426, 105; *Pure & Appl. Chem.*, 2010, 82, 1011.

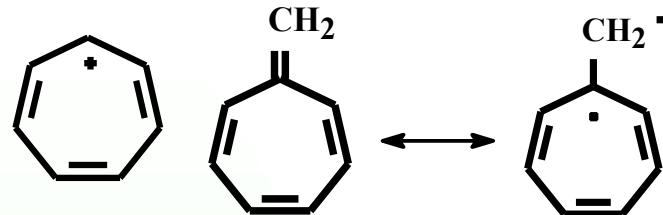




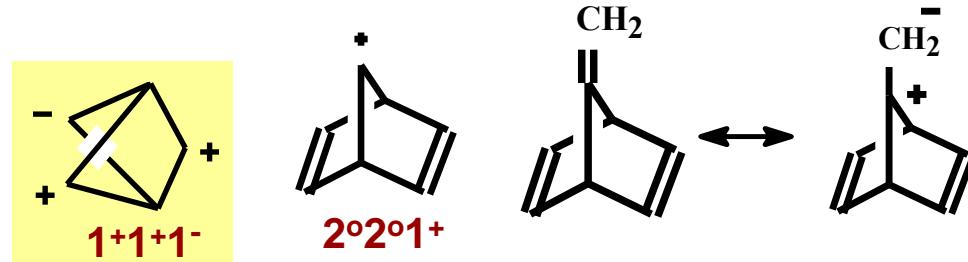
Physical organic chemistry, MO MO prediction of structures of new types.

Definition of different types of conjugation

M. Goldstein, R. Hoffmann, *J. A. C. S.*, 1971, **93**, 6193



Pericyclic conjugation

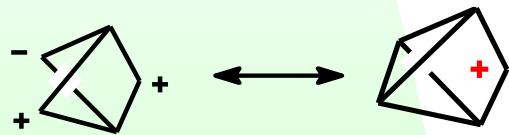


Longicyclic conjugation

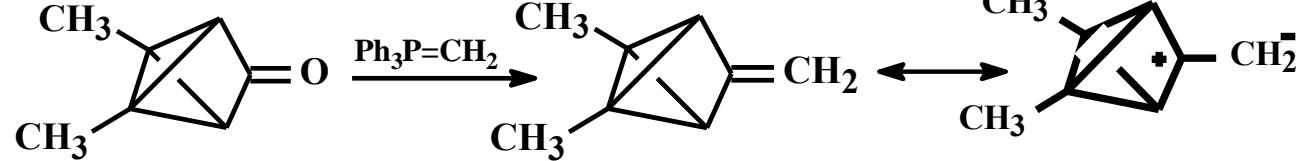


W. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.*, 1972, **94**, 1661

Longicyclic conjugation in methylenehomotetrahedrane

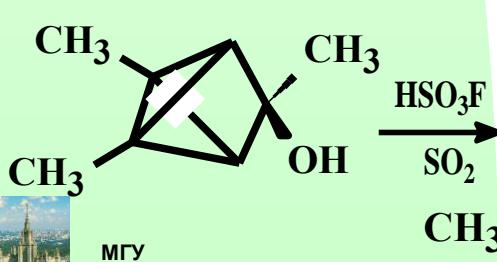


N.S. Zefirov, R. Hoffmann, V.I. Minkin, et. al., *Zh.Org.Khim.*, 1980, **16**, 241



Tri-Me-C₅H₂ pyramidal cation

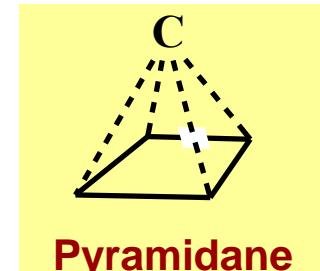
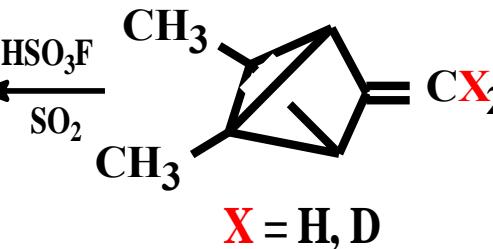
V.I. Minkin, N.S. Zefirov, et. al., *Zh.Org.Khim.*, 1981, **17**, 2616



CH₃ -3.20

C -20.89

72.63





Stereochemistry and conformational analysis

- Stereochemistry of some AdE reactions (e.g. oxymercuration, sulfenylation, nitrosochlorination, etc.).
- The problem of conformational effects. Anomeric effect. “Gauche” and “hockey stick” effects. Search for new conformational effects and anomalies (e.g. in bicyclo[3.3.1]nonanes).
- Description of the shape of cycles. “Puckering” coordinates. Computer algorithms, programs, complexes for solving stereochemical problems.
- Reactivity of conformationally mobile systems.
- Conformationally controlled crown ethers.
- Abstract configurations and chirality - an algebraic approach.

Butlerov prize of Russian Academy of Sciences (1994)

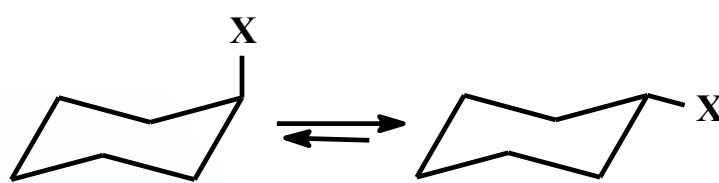
State Prize of Russia (2000)





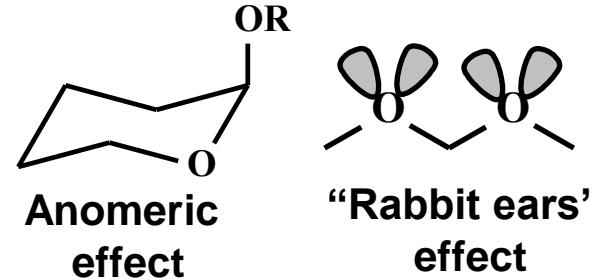
Stereochemistry and conformational analysis: problem of conformational effects

Conformational analysis: Hassel, Barton (1969); E. Eliel

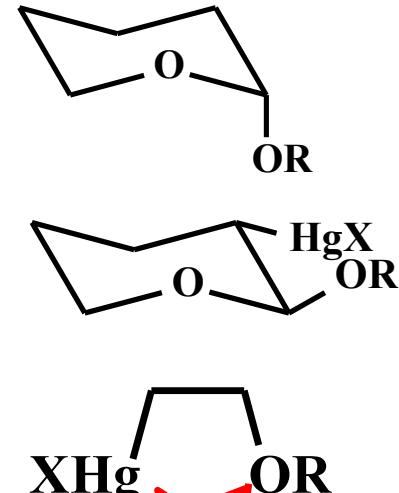
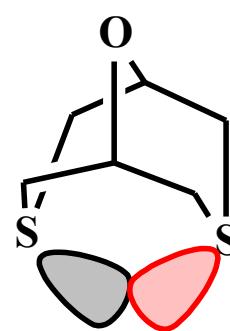
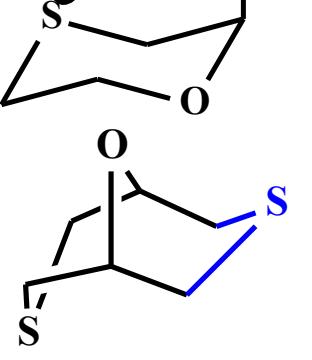
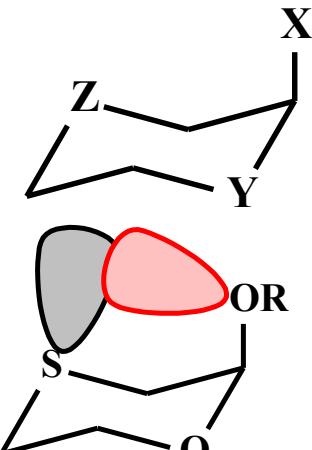
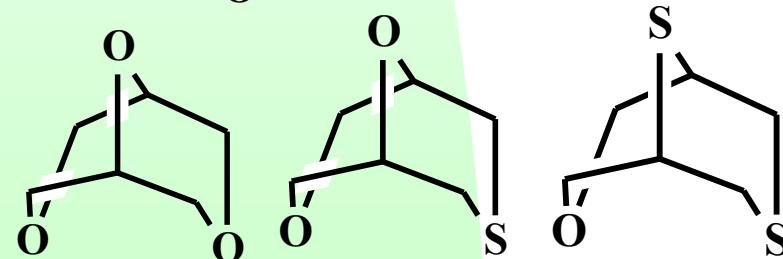
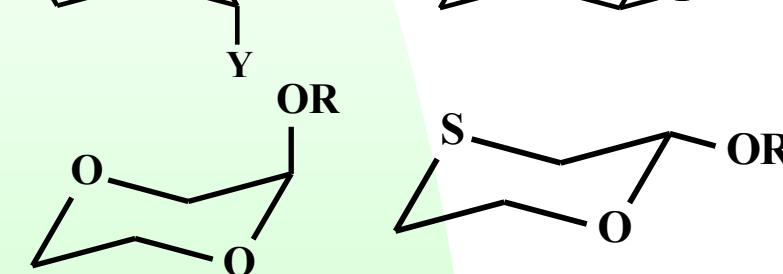
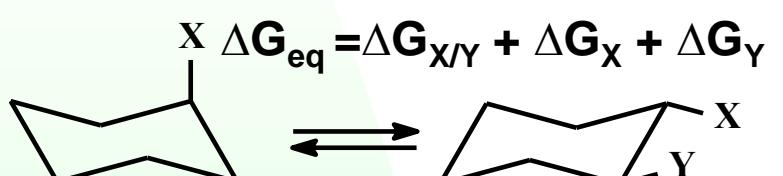


$$A = -\Delta G_{eq}$$

F, OR, Cl, Br, NR₂, CH₃, C(CH₃)₃



"Gosh effect"
"Δ² instability factor"



"Hockey sticks" effect

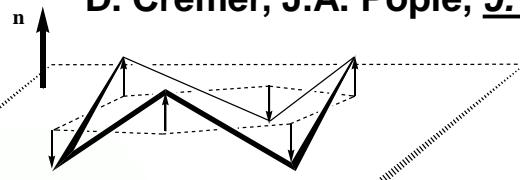
Zefirov et al., *Usp.Khim.*, 1973, 42, 423; 1975, 44, 413; *Tetr.*, 1976, 32, 1211; Zefirov, Palyulin, *Topics in Stereochem.*, 1991, 30, 171; Lyssenko, Pisarev, Palyulin, Zefirov, Antipin et al., *J.Phys.Chem.*, 2011, 115, 12738.





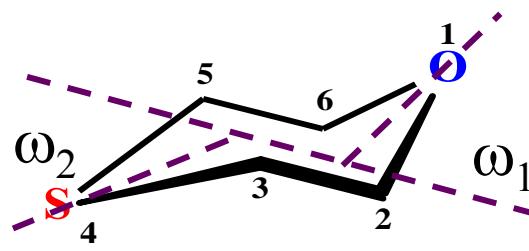
Stereochemistry and conformational analysis: description of ring shapes and puckering coordinates

D. Cremer, J.A. Pople, *J. Am. Chem. Soc.*, 1975, 97, 1354



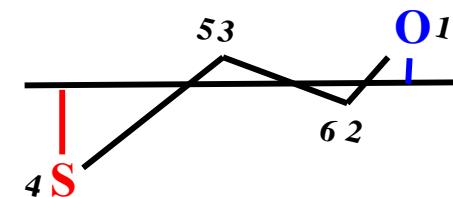
Cremer-Pople approach is based on the deviations from mean plane:

- (1) two puckering amplitudes q_2, q_3
- (2) phase angle ϕ_2



$$\omega_2 = 47^\circ$$

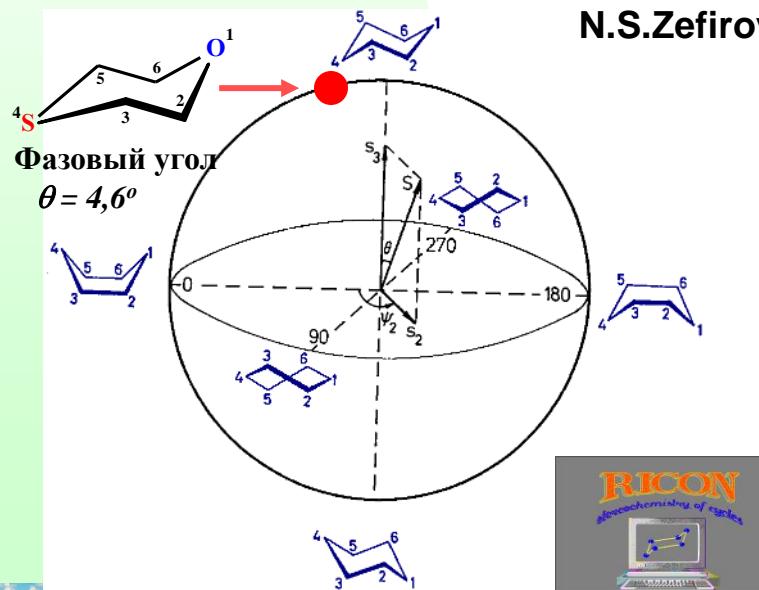
$$\omega_1 = 56^\circ$$



$C_3S_4C_5$ - flattened

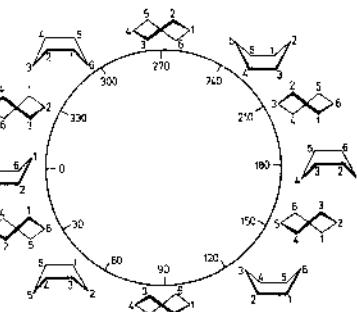
Cremer-Pople approach: $C_6O_1C_2$ - flattened

Zefirov-Palyulin approach – puckering parameters are based on $(\sin \phi/2)$

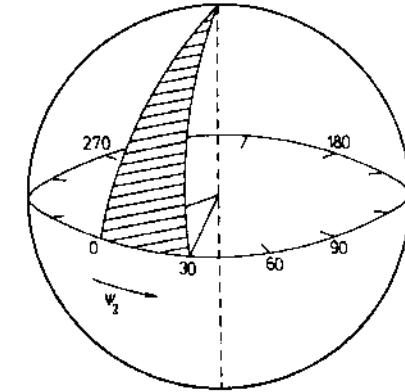


Sphere in puckering coordinates

N.S.Zefirov, V.A. Palyulin, et al., *Dokl. Chem.*, 1980, 252, 111; *Dokl. Chem.*, 1987, 292, 1380; *J.Phys.Org.Chem.*, 1990, 3, 147.



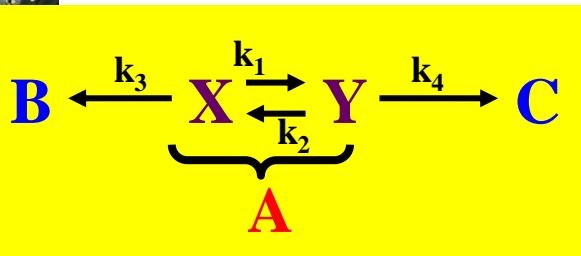
Equator of the sphere



Minimum area of variation of puckering parameters.
Accounting for renumbering and selection of enantiomer – reduction to the narrow sector.



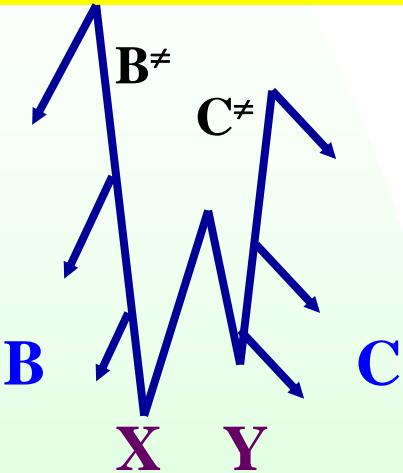
Stereochemistry and conformational analysis: reactions in conformationally mobile systems



$$K_{eq} = k_1/k_2 = [Y]_0/[X]_0 \quad P_\infty = [C]_\infty/[B]_\infty \quad ?$$

1. The case $k_4, k_3 \gg k_1, k_2$ (Kurtin-Hammett)

$$P_\infty = [C]_\infty/[B]_\infty = e^{(G_{B^\neq} - G_{C^\neq})/RT} = K_{eq} \cdot k_4/k_3$$



Curtin-Hammett principle:

“the relative progress of the reaction through the transition states B^\neq and C^\neq **DOES NOT DEPEND** on the relative proportion of conformations X and Y in the ground state; the amounts of products depend only on the difference in free energies of transition states B^\neq and C^\neq “

2. Conformational control: $k_4, k_3 \ll k_1, k_2$ $P_\infty = K_{eq}$

3. General case: any k_4, k_3, k_2, k_1 :

$$P_\infty = [C]_\infty/[B]_\infty = K_{eq} \cdot k_4(k_1+k_2+k_3)/k_3(k_1+k_2+k_4)$$

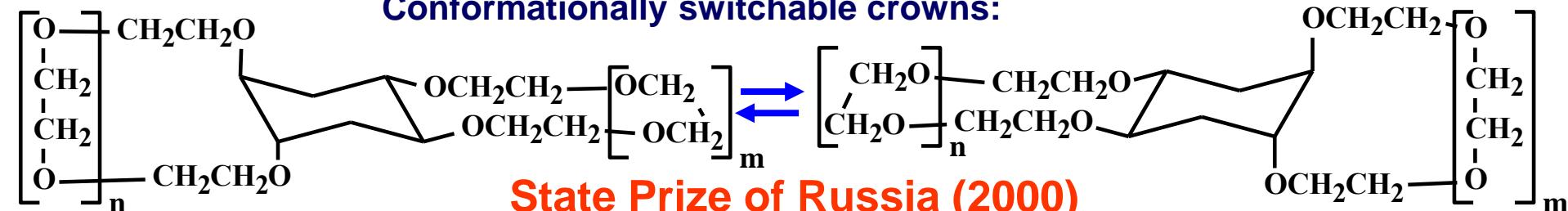
N.S.Zefirov, *Tetrahedron*, 1977, 33, 2719; *Zh. Org. Chem.*, 1979, 15, 1098;
J. Seeman, *Chem. Rev.*, 1983, 83, 83.



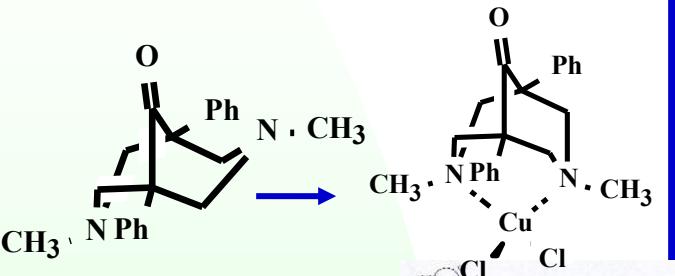


Stereochemistry and conformational analysis: crown-ethers and other ligands

Conformationally switchable crowns:

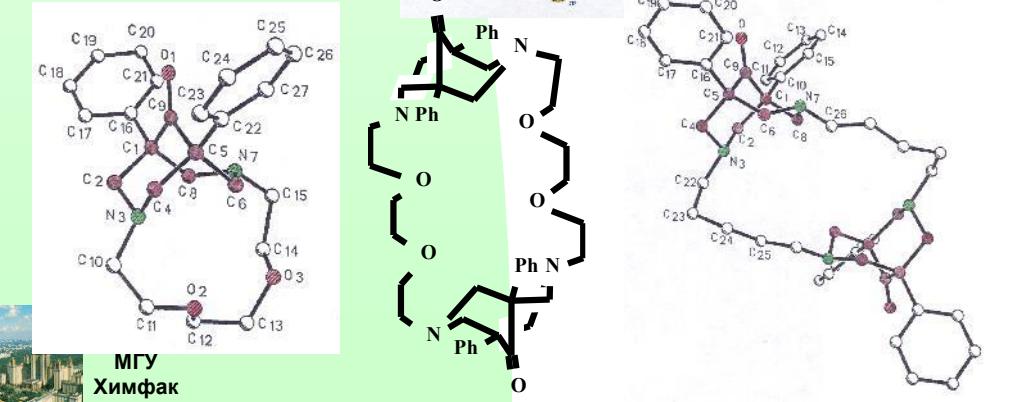
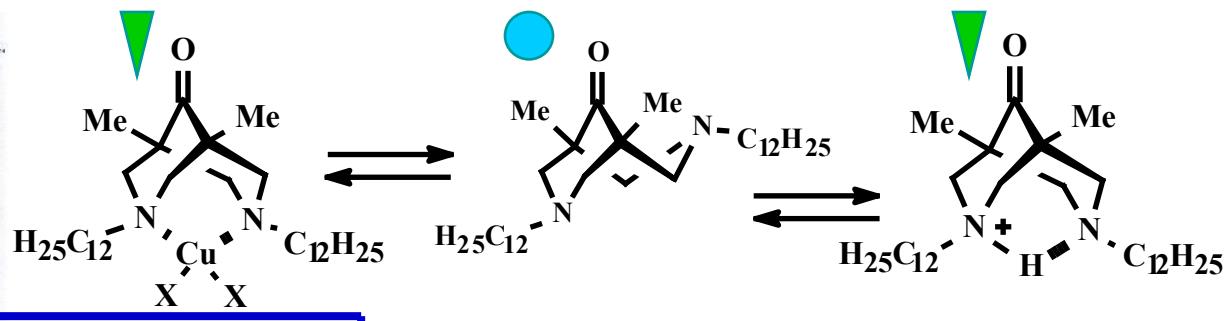


State Prize of Russia (2000)



Creation of stimulus-sensitive liposomes based on substituted bispidinones for targeted delivery of biologically active substances

Veremeeva, Lapteva, Palyulin, Davydov, Sybachin, Yaroslavov





Mathematical and computational chemistry

Academician V.A.Koptyug

“... Any attempt to apply mathematical methods to the study of chemical problems must be regarded as purely irrational and contrary to the very spirit of chemical science.”

Auguste Comte, 1830



Dr.
S.S.Trach
Acad. IAMC

Prof.
Gasteiger
Acad. IAMC

Dr. Nekrasov

- Creation of a "formal-logical approach" as a basis for (a) classification of organic reactions, (b) search for new reactions and reaction design, (c) non-empirical computer synthesis.

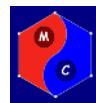
MSU Lomonosov Prize (1983)

- QSAR. Inverse problem in QSAR. Problems of topological description of molecules. Topological and fragment indices. Graph theory applied to chemical problems. Structural design, structural generators. Neural networks.
- Creation of new computer algorithms and software packages for solving chemical problems.



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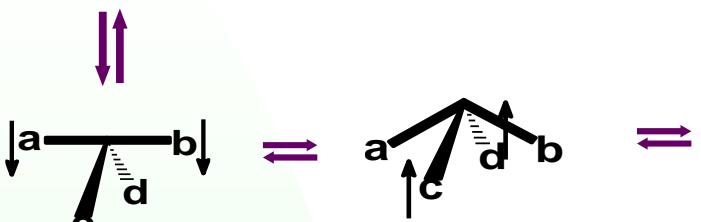
Member of International Academy of Mathematical Chemistry (IAMC).



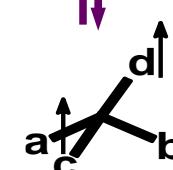
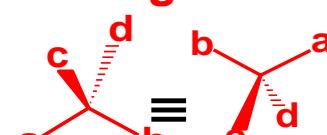


Mathematical Chemistry: An Algebraic Approach to the Concept of Configuration

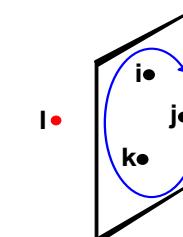
R-configuration



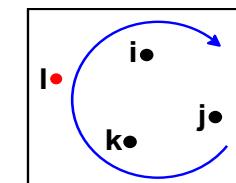
S-configuration



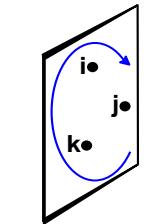
Point 3D configurations



$$\psi[i,j,k,l] = +1$$



$$\psi[i,j,k,l] = 0$$



$$\psi[i,j,k,l] = +1$$

$$\psi[i,j,k,l] = -\psi[i,k,j,l]$$

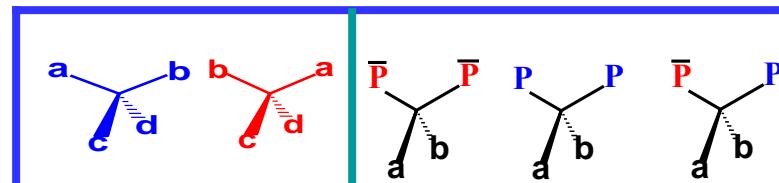
Algebraic criterion of chirality

■ For any function $\psi[i,j,k,l]$ there is a unique antipodal function $\bar{\psi}$: $\bar{\psi}[i,j,k,l] = -\psi[i,k,j,l]$. They may belong either to the same or to different equivalence classes.

■ There exist TWO groups of automorphisms:

(a) “Normal group” $Aut(\psi)$ consisting of (+)-automorphisms that transform the function into itself and (b) the extended group $Aut[\psi]$, which also contains (-)-automorphisms that transform the function ψ into the antipodal function $\bar{\psi}$.

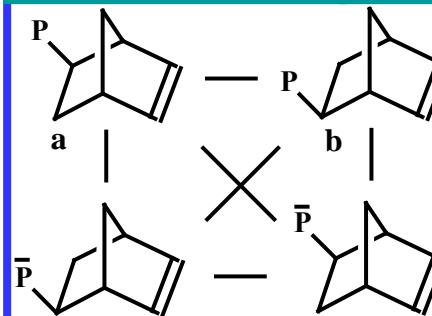
■ If $Aut(\psi) = Aut[\psi]$, functions ψ and $\bar{\psi}$ belong to different equivalence classes and these configurations are chiral.



ab – enantiomers
cd – enantiomers

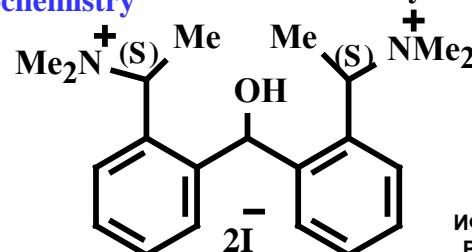
ad – holantiomers
bc – holantiomers

ac – nulantiomers
bd – nulantiomers



Integrated discussion on stereogenicity and chirality for restructuring stereochemistry

Holantio- and nulantio-RACEMATES: myth or reality?

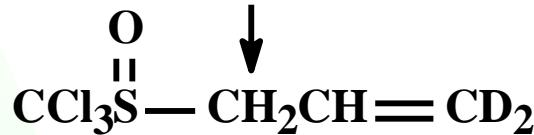
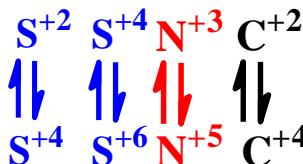
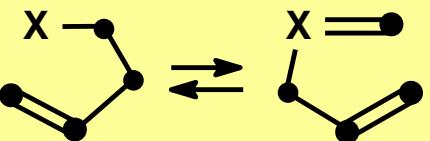




Mathematical and computational chemistry:

Formal-logical approach

**Symbolic
equation:**

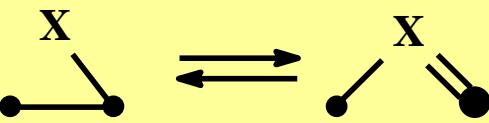


Mislow K. *JACS*, 90, 4861 (1968)

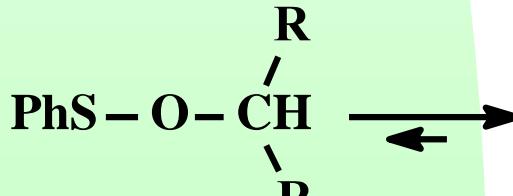
Braverman S. *Israel J.Chem.* 5, 125(1967)

Zefirov N.S. et al. *Vestn. MSU*, 135 (1969);

Zh. Org.Chim., 7, 947 (1971).

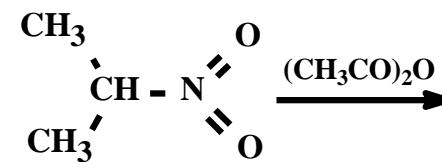
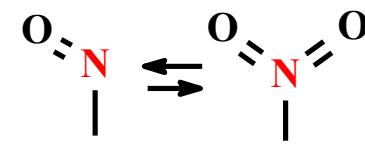


N.S. Zefirov et al.,
Zh.Org.Chim.,
8, 433 (1972)



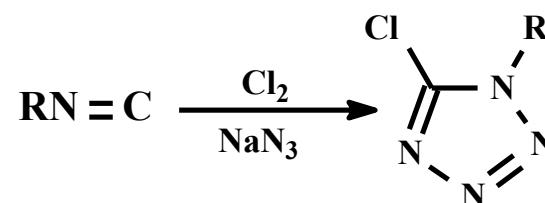
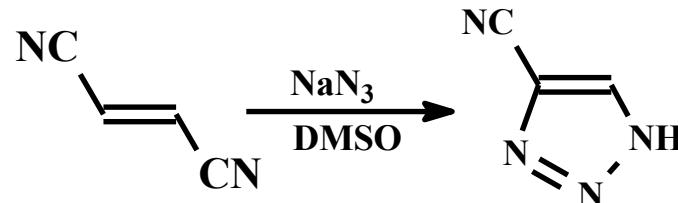
R = Ph, cyclo-C₃H₅

Meisenheimer (1919)



Zefirov N.S., et. al. *Zh.Org.Khim.*, 38, 1484 (2002)

Zh.Org.Chim., 4, 722, 1300 (1968); 6, 2596 (1970);
8, 1335, (1972); *J.C.S., Chem. Comm.*, (1971), 1001.





Mathematical and computational chemistry: QSAR (*Quantitative Structure-Activity Relationships*) and QSPR

1. A set of compounds with known activity is divided into **training** and **test** sets.
2. Selection of a set of **descriptors** adequate to the characterized property.
3. Correlation of the **property** with the selected **descriptors** for the **training** set is constructed using statistical methods.
4. **The predictive ability** of the QSAR model is evaluated on a **test** set of compounds with known property.

Topological indices:

Stankevich I.V., Stankevich M.I., Zefirov N.S. *Usp.Khim.*, 1988, 57, 337

Connectivity indices [Randic, c; Kier-Hall, k], Wiener index [W], Balaban and Gutman indices, Hosoya index, Merifield index, solvation index (Zefirov-Palyulin), information indices.

Physico-chemical:

Oliferenko A.A., Palyulin V.V., Zefirov N.S., *J.Phys. Org. Chem.*, 2001, 14, 355 ;
SAR, QSAR Env. Res., 2002, 13, 297

Electronegativity-based indices, electrotopology, atomic charges (e.g. Gasteiger charges and Zefirov charges), van der Waals volumes and surfaces, hydrogen bond descriptors, lipophilicity

Quantum-chemical

A.R.Katritzky et al., *Chem. Rev.*, 1996, 96, 1027

Charges, HOMO-LUMO energies, superdelocalizability, atom-atom and molecular potentials, orbital and electron densities, dipole moments and polarizability indices

Fragmental (substructural) descriptors

N.S.Zefirov, V.A.Palyulin et al., *J. Chem. Inf. Comput. Sci.*, 2002, 41, 1112; *Proc. RAS*, 2003, 1005

ИФАВ
РАН



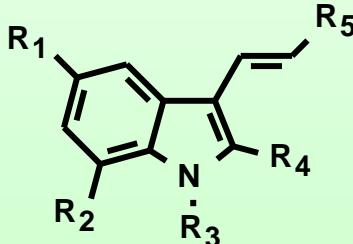


1. **QSAR models:** (1) boiling point; (2) flash point; (3) mp; (4) retention indices; (5) pKa; (6) solubility; (7) heats of solvation; (8) heats of formation; (9) enthalpies of sublimation; (10) magnetic susceptibility; (11) polarizability; (12) lipophilicity; (13) rate constants of homolysis of nitro compounds; (14) affinity of dyes for fabric; (15) mutagenicity; (16) toxicity; (17) diffusion in rubber; (18) molar refraction (19) neural network models for calculating Hammett and Taft constants; (20) inhibition of serine esterases; (21) octane number, etc.

2. **Schemes for calculating partial atomic charges** for reproducing molecular electrostatic potential. (“Zefirov charges”).

3. Neural networks and “support vector machines”.

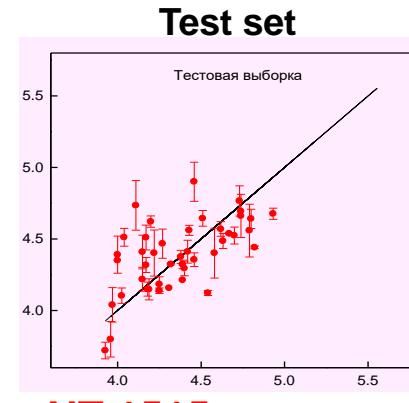
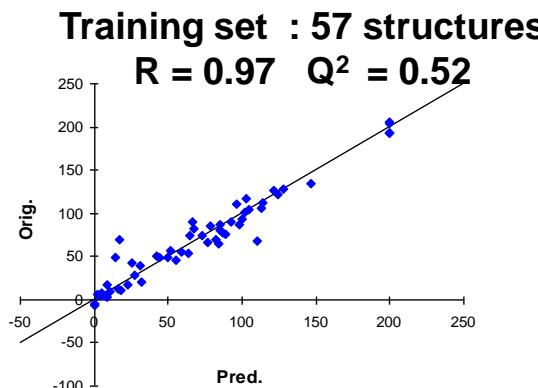
QSAR: Inhibition of Ca^{2+} influx by indoles



$R = \text{CH}_3, \text{Et}$
 $R_1 = \text{Hal}, \text{CH}_3, \text{OCH}_3$
 $R_2 = \text{CH}_3, \text{Et}$

Modeled activity - $(K_4 - K_3) / (K_2 - K_1)$
 $^{45}\text{Ca}^{2+}$ uptake inhibition in synaptosomes:

$K_1 - \text{Ca}^{2+}$ $K_2 - \text{Glu} + \text{Ca}^{2+}$
 $K_3 - \text{test compound} + \text{Ca}^{2+}$
 $K_4 - \text{test compound} + \text{Glu} + \text{Ca}^{2+}$



NT-1515

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Bachurin, Tkachenko, Zefirov, Palyulin

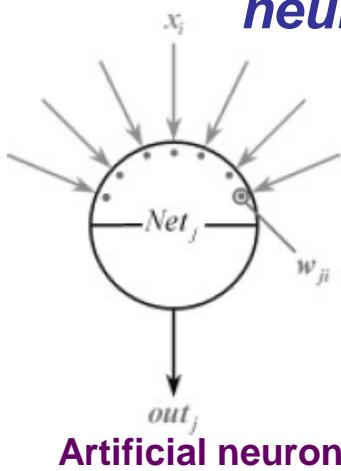
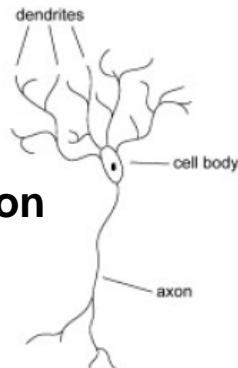


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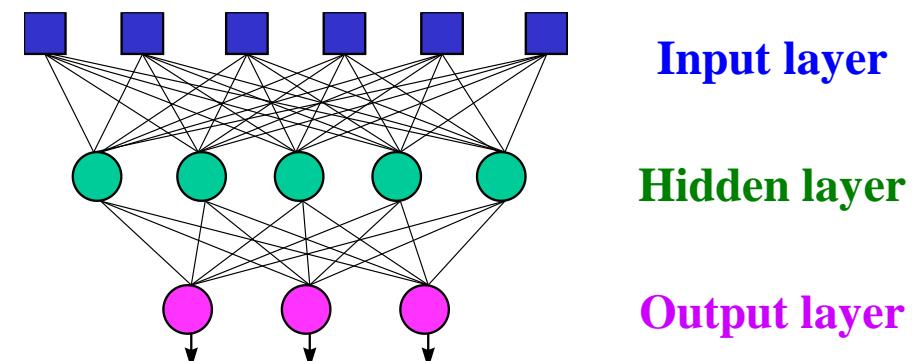




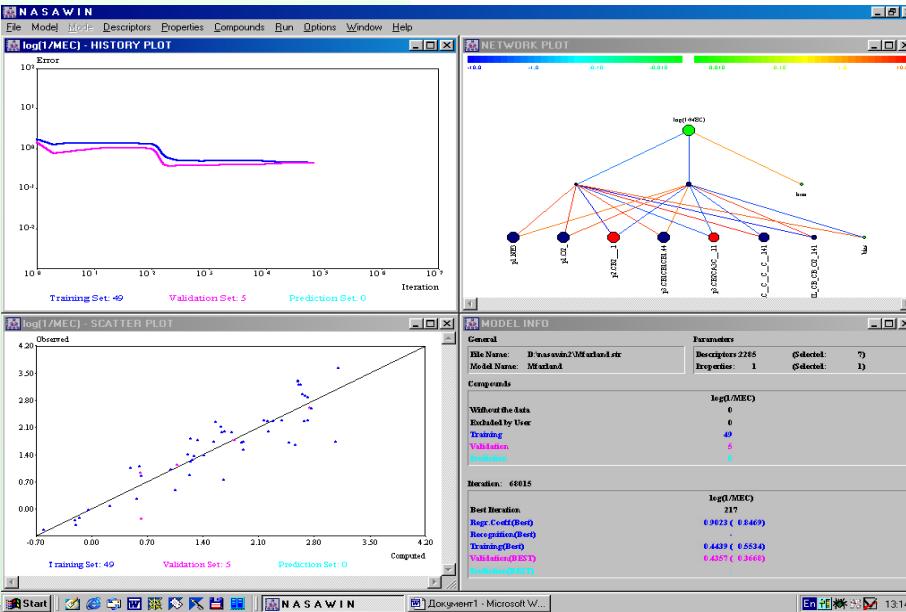
Mathematical and computational chemistry: neural networks in chemistry



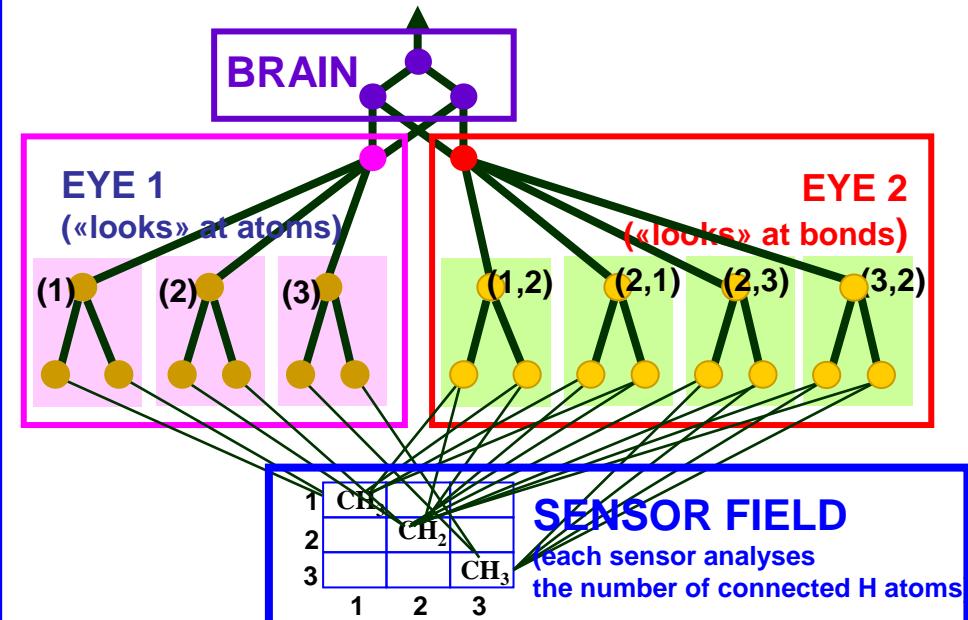
Neural network with two layers of active neurons



Software package NASAWIN:
anticoccidial activity of triazinediones



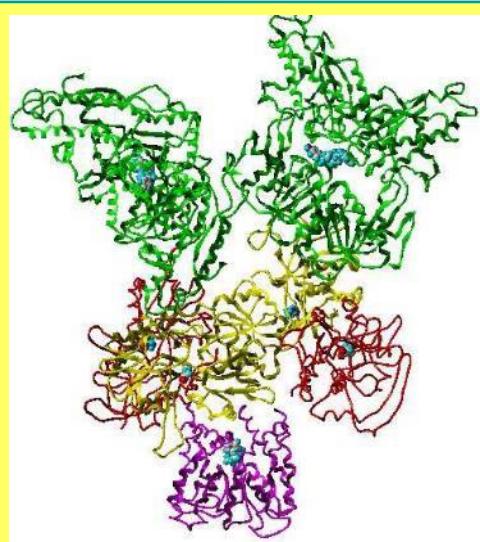
Architecture of neural device for direct QSAR (propane molecule is shown) :



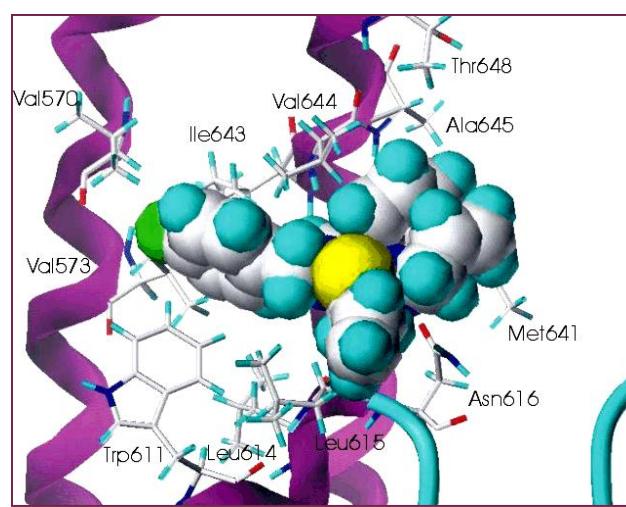


Medicinal chemistry

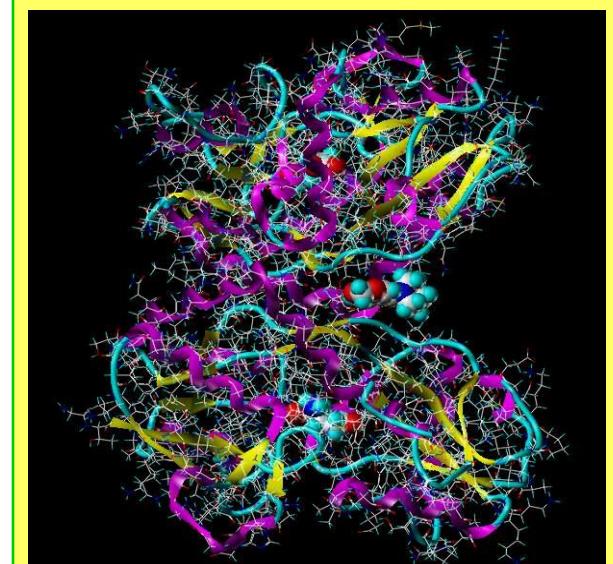
Hyperactivation of NMDA receptors leads to the development of neurotoxicity.
Simultaneous blockade of NMDA receptors and activation of AMPA receptors.
Molecular models of NMDA and AMPA receptors. Docking of NMDA receptor ion channel blockers and antagonists. Design of multitarget glutamatergic drugs.



Models of all domains
of NMDA receptor

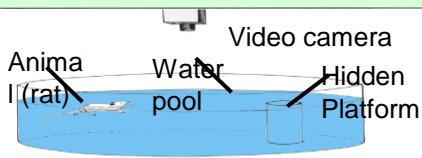


Virtual screening of
databases (NMDA-receptor)



Model of the dimer of ligand-
binding domain of AMPA receptor

Preclinical trials - 6



Biotest

Selected for synthesis
and synthesized: 600



Virtual screening of
databases (AMPA-receptor)

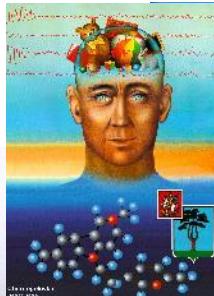


S.F. firm thinks Russian drug nothing to sneeze at

BY DANIEL S. LEVINE
dlevine@bizjournals.com

A fledgling San Francisco biopharmaceutical believes a Russian antihistamine may not only help runny noses, but halt the progression of Alzheimer's disease.

Medivation obtained the rights to Dimebon, which has a more than history in Russia as an antibiotic; has indications that it might be a new treatment for Alzheimer's disease. The company is launching a stage clinical trial in Russia to human proof-of-concept of Dimebon.



S SCIENCE

On the threshold of drug discovery and clinical medicine

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Molecule of the Month

BBS Grid BBS-Headlines

Dimebolin hydrochloride

August 2007

Dimebolin hydrochloride (CN1C=CC=C2=C1C(=N)C(=N)C=C2C3=C(C=C3)C=C4=C3C=C(N)C=C4C(=O)N5C=C(C=C5)C=C6=C5C=C(N)C=C6C(=O)N7C=C(C=C7)C=C8=C7C=C(N)C=C8C(=O)N9C=C(C=C9)C=C10=C9C=C(N)C=C10C(=O)N11C=C(C=C11)C=C12=C11C=C(N)C=C12C(=O)N13C=C(C=C13)C=C14=C13C=C(N)C=C14C(=O)N15C=C(C=C15)C=C16=C15C=C(N)C=C16C(=O)N17C=C(C=C17)C=C18=C17C=C(N)C=C18C(=O)N19C=C(C=C19)C=C20=C19C=C(N)C=C20C(=O)N21C=C(C=C21)C=C22=C21C=C(N)C=C22C(=O)N23C=C(C=C23)C=C24=C23C=C(N)C=C24C(=O)N25C=C(C=C25)C=C26=C25C=C(N)C=C26C(=O)N27C=C(C=C27)C=C28=C27C=C(N)C=C28C(=O)N29C=C(C=C29)C=C30=C29C=C(N)C=C30C(=O)N31C=C(C=C31)C=C32=C31C=C(N)C=C32C(=O)N33C=C(C=C33)C=C34=C33C=C(N)C=C34C(=O)N35C=C(C=C35)C=C36=C35C=C(N)C=C36C(=O)N37C=C(C=C37)C=C38=C37C=C(N)C=C38C(=O)N39C=C(C=C39)C=C40=C39C=C(N)C=C40C(=O)N41C=C(C=C41)C=C42=C41C=C(N)C=C42C(=O)N43C=C(C=C43)C=C44=C43C=C(N)C=C44C(=O)N45C=C(C=C45)C=C46=C45C=C(N)C=C46C(=O)N47C=C(C=C47)C=C48=C47C=C(N)C=C48C(=O)N49C=C(C=C49)C=C50=C49C=C(N)C=C50C(=O)N51C=C(C=C51)C=C52=C51C=C(N)C=C52C(=O)N53C=C(C=C53)C=C54=C53C=C(N)C=C54C(=O)N55C=C(C=C55)C=C56=C55C=C(N)C=C56C(=O)N57C=C(C=C57)C=C58=C57C=C(N)C=C58C(=O)N59C=C(C=C59)C=C60=C59C=C(N)C=C60C(=O)N61C=C(C=C61)C=C62=C61C=C(N)C=C62C(=O)N63C=C(C=C63)C=C64=C63C=C(N)C=C64C(=O)N65C=C(C=C65)C=C66=C65C=C(N)C=C66C(=O)N67C=C(C=C67)C=C68=C67C=C(N)C=C68C(=O)N69C=C(C=C69)C=C70=C69C=C(N)C=C70C(=O)N71C=C(C=C71)C=C72=C71C=C(N)C=C72C(=O)N73C=C(C=C73)C=C74=C73C=C(N)C=C74C(=O)N75C=C(C=C75)C=C76=C75C=C(N)C=C76C(=O)N77C=C(C=C77)C=C78=C77C=C(N)C=C78C(=O)N79C=C(C=C79)C=C80=C79C=C(N)C=C80C(=O)N81C=C(C=C81)C=C82=C81C=C(N)C=C82C(=O)N83C=C(C=C83)C=C84=C83C=C(N)C=C84C(=O)N85C=C(C=C85)C=C86=C85C=C(N)C=C86C(=O)N87C=C(C=C87)C=C88=C87C=C(N)C=C88C(=O)N89C=C(C=C89)C=C90=C89C=C(N)C=C90C(=O)N91C=C(C=C91)C=C92=C91C=C(N)C=C92C(=O)N93C=C(C=C93)C=C94=C93C=C(N)C=C94C(=O)N95C=C(C=C95)C=C96=C95C=C(N)C=C96C(=O)N97C=C(C=C97)C=C98=C97C=C(N)C=C98C(=O)N99C=C(C=C99)C=C100=C99C=C(N)C=C100C(=O)N101C=C(C=C101)C=C102=C101C=C(N)C=C102C(=O)N103C=C(C=C103)C=C104=C103C=C(N)C=C104C(=O)N105C=C(C=C105)C=C106=C105C=C(N)C=C106C(=O)N107C=C(C=C107)C=C108=C107C=C(N)C=C108C(=O)N109C=C(C=C109)C=C110=C109C=C(N)C=C110C(=O)N111C=C(C=C111)C=C112=C111C=C(N)C=C112C(=O)N113C=C(C=C113)C=C114=C113C=C(N)C=C114C(=O)N115C=C(C=C115)C=C116=C115C=C(N)C=C116C(=O)N117C=C(C=C117)C=C118=C117C=C(N)C=C118C(=O)N119C=C(C=C119)C=C120=C119C=C(N)C=C120C(=O)N121C=C(C=C121)C=C122=C121C=C(N)C=C122C(=O)N123C=C(C=C123)C=C124=C123C=C(N)C=C124C(=O)N125C=C(C=C125)C=C126=C125C=C(N)C=C126C(=O)N127C=C(C=C127)C=C128=C127C=C(N)C=C128C(=O)N129C=C(C=C129)C=C130=C129C=C(N)C=C130C(=O)N131C=C(C=C131)C=C132=C131C=C(N)C=C132C(=O)N133C=C(C=C133)C=C134=C133C=C(N)C=C134C(=O)N135C=C(C=C135)C=C136=C135C=C(N)C=C136C(=O)N137C=C(C=C137)C=C138=C137C=C(N)C=C138C(=O)N139C=C(C=C139)C=C140=C139C=C(N)C=C140C(=O)N141C=C(C=C141)C=C142=C141C=C(N)C=C142C(=O)N143C=C(C=C143)C=C144=C143C=C(N)C=C144C(=O)N145C=C(C=C145)C=C146=C145C=C(N)C=C146C(=O)N147C=C(C=C147)C=C148=C147C=C(N)C=C148C(=O)N149C=C(C=C149)C=C150=C149C=C(N)C=C150C(=O)N151C=C(C=C151)C=C152=C151C=C(N)C=C152C(=O)N153C=C(C=C153)C=C154=C153C=C(N)C=C154C(=O)N155C=C(C=C155)C=C156=C155C=C(N)C=C156C(=O)N157C=C(C=C157)C=C158=C157C=C(N)C=C158C(=O)N159C=C(C=C159)C=C160=C159C=C(N)C=C160C(=O)N161C=C(C=C161)C=C162=C161C=C(N)C=C162C(=O)N163C=C(C=C163)C=C164=C163C=C(N)C=C164C(=O)N165C=C(C=C165)C=C166=C165C=C(N)C=C166C(=O)N167C=C(C=C167)C=C168=C167C=C(N)C=C168C(=O)N169C=C(C=C169)C=C170=C169C=C(N)C=C170C(=O)N171C=C(C=C171)C=C172=C171C=C(N)C=C172C(=O)N173C=C(C=C173)C=C174=C173C=C(N)C=C174C(=O)N175C=C(C=C175)C=C176=C175C=C(N)C=C176C(=O)N177C=C(C=C177)C=C178=C177C=C(N)C=C178C(=O)N179C=C(C=C179)C=C180=C179C=C(N)C=C180C(=O)N181C=C(C=C181)C=C182=C181C=C(N)C=C182C(=O)N183C=C(C=C183)C=C184=C183C=C(N)C=C184C(=O)N185C=C(C=C185)C=C186=C185C=C(N)C=C186C(=O)N187C=C(C=C187)C=C188=C187C=C(N)C=C188C(=O)N189C=C(C=C189)C=C190=C189C=C(N)C=C190C(=O)N191C=C(C=C191)C=C192=C191C=C(N)C=C192C(=O)N193C=C(C=C193)C=C194=C193C=C(N)C=C194C(=O)N195C=C(C=C195)C=C196=C195C=C(N)C=C196C(=O)N197C=C(C=C197)C=C198=C197C=C(N)C=C198C(=O)N199C=C(C=C199)C=C200=C199C=C(N)C=C200C(=O)N201C=C(C=C201)C=C202=C201C=C(N)C=C202C(=O)N203C=C(C=C203)C=C204=C203C=C(N)C=C204C(=O)N205C=C(C=C205)C=C206=C205C=C(N)C=C206C(=O)N207C=C(C=C207)C=C208=C207C=C(N)C=C208C(=O)N209C=C(C=C209)C=C210=C209C=C(N)C=C210C(=O)N211C=C(C=C211)C=C212=C211C=C(N)C=C212C(=O)N213C=C(C=C213)C=C214=C213C=C(N)C=C214C(=O)N215C=C(C=C215)C=C216=C215C=C(N)C=C216C(=O)N217C=C(C=C217)C=C218=C217C=C(N)C=C218C(=O)N219C=C(C=C219)C=C220=C219C=C(N)C=C220C(=O)N221C=C(C=C221)C=C222=C221C=C(N)C=C222C(=O)N223C=C(C=C223)C=C224=C223C=C(N)C=C224C(=O)N225C=C(C=C225)C=C226=C225C=C(N)C=C226C(=O)N227C=C(C=C227)C=C228=C227C=C(N)C=C228C(=O)N229C=C(C=C229)C=C230=C229C=C(N)C=C230C(=O)N231C=C(C=C231)C=C232=C231C=C(N)C=C232C(=O)N233C=C(C=C233)C=C234=C233C=C(N)C=C234C(=O)N235C=C(C=C235)C=C236=C235C=C(N)C=C236C(=O)N237C=C(C=C237)C=C238=C237C=C(N)C=C238C(=O)N239C=C(C=C239)C=C240=C239C=C(N)C=C240C(=O)N241C=C(C=C241)C=C242=C241C=C(N)C=C242C(=O)N243C=C(C=C243)C=C244=C243C=C(N)C=C244C(=O)N245C=C(C=C245)C=C246=C245C=C(N)C=C246C(=O)N247C=C(C=C247)C=C248=C247C=C(N)C=C248C(=O)N249C=C(C=C249)C=C250=C249C=C(N)C=C250C(=O)N251C=C(C=C251)C=C252=C251C=C(N)C=C252C(=O)N253C=C(C=C253)C=C254=C253C=C(N)C=C254C(=O)N255C=C(C=C255)C=C256=C255C=C(N)C=C256C(=O)N257C=C(C=C257)C=C258=C257C=C(N)C=C258C(=O)N259C=C(C=C259)C=C260=C259C=C(N)C=C260C(=O)N261C=C(C=C261)C=C262=C261C=C(N)C=C262C(=O)N263C=C(C=C263)C=C264=C263C=C(N)C=C264C(=O)N265C=C(C=C265)C=C266=C265C=C(N)C=C266C(=O)N267C=C(C=C267)C=C268=C267C=C(N)C=C268C(=O)N269C=C(C=C269)C=C270=C269C=C(N)C=C270C(=O)N271C=C(C=C271)C=C272=C271C=C(N)C=C272C(=O)N273C=C(C=C273)C=C274=C273C=C(N)C=C274C(=O)N275C=C(C=C275)C=C276=C275C=C(N)C=C276C(=O)N277C=C(C=C277)C=C278=C277C=C(N)C=C278C(=O)N279C=C(C=C279)C=C280=C279C=C(N)C=C280C(=O)N281C=C(C=C281)C=C282=C281C=C(N)C=C282C(=O)N283C=C(C=C283)C=C284=C283C=C(N)C=C284C(=O)N285C=C(C=C285)C=C286=C285C=C(N)C=C286C(=O)N287C=C(C=C287)C=C288=C287C=C(N)C=C288C(=O)N289C=C(C=C289)C=C290=C289C=C(N)C=C290C(=O)N291C=C(C=C291)C=C292=C291C=C(N)C=C292C(=O)N293C=C(C=C293)C=C294=C293C=C(N)C=C294C(=O)N295C=C(C=C295)C=C296=C295C=C(N)C=C296C(=O)N297C=C(C=C297)C=C298=C297C=C(N)C=C298C(=O)N299C=C(C=C299)C=C300=C299C=C(N)C=C300C(=O)N301C=C(C=C301)C=C302=C301C=C(N)C=C302C(=O)N303C=C(C=C303)C=C304=C303C=C(N)C=C304C(=O)N305C=C(C=C305)C=C306=C305C=C(N)C=C306C(=O)N307C=C(C=C307)C=C308=C307C=C(N)C=C308C(=O)N309C=C(C=C309)C=C310=C309C=C(N)C=C310C(=O)N311C=C(C=C311)C=C312=C311C=C(N)C=C312C(=O)N313C=C(C=C313)C=C314=C313C=C(N)C=C314C(=O)N315C=C(C=C315)C=C316=C315C=C(N)C=C316C(=O)N317C=C(C=C317)C=C318=C317C=C(N)C=C318C(=O)N319C=C(C=C319)C=C320=C319C=C(N)C=C320C(=O)N321C=C(C=C321)C=C322=C321C=C(N)C=C322C(=O)N323C=C(C=C323)C=C324=C323C=C(N)C=C324C(=O)N325C=C(C=C325)C=C326=C325C=C(N)C=C326C(=O)N327C=C(C=C327)C=C328=C327C=C(N)C=C328C(=O)N329C=C(C=C329)C=C330=C329C=C(N)C=C330C(=O)N331C=C(C=C331)C=C332=C331C=C(N)C=C332C(=O)N333C=C(C=C333)C=C334=C333C=C(N)C=C334C(=O)N335C=C(C=C335)C=C336=C335C=C(N)C=C336C(=O)N337C=C(C=C337)C=C338=C337C=C(N)C=C338C(=O)N339C=C(C=C339)C=C340=C339C=C(N)C=C340C(=O)N341C=C(C=C341)C=C342=C341C=C(N)C=C342C(=O)N343C=C(C=C343)C=C344=C343C=C(N)C=C344C(=O)N345C=C(C=C345)C=C346=C345C=C(N)C=C346C(=O)N347C=C(C=C347)C=C348=C347C=C(N)C=C348C(=O)N349C=C(C=C349)C=C350=C349C=C(N)C=C350C(=O)N351C=C(C=C351)C=C352=C351C=C(N)C=C352C(=O)N353C=C(C=C353)C=C354=C353C=C(N)C=C354C(=O)N355C=C(C=C355)C=C356=C355C=C(N)C=C356C(=O)N357C=C(C=C357)C=C358=C357C=C(N)C=C358C(=O)N359C=C(C=C359)C=C360=C359C=C(N)C=C360C(=O)N361C=C(C=C361)C=C362=C361C=C(N)C=C362C(=O)N363C=C(C=C363)C=C364=C363C=C(N)C=C364C(=O)N365C=C(C=C365)C=C366=C365C=C(N)C=C366C(=O)N367C=C(C=C367)C=C368=C367C=C(N)C=C368C(=O)N369C=C(C=C369)C=C370=C369C=C(N)C=C370C(=O)N371C=C(C=C371)C=C372=C371C=C(N)C=C372C(=O)N373C=C(C=C373)C=C374=C373C=C(N)C=C374C(=O)N375C=C(C=C375)C=C376=C375C=C(N)C=C376C(=O)N377C=C(C=C377)C=C378=C377C=C(N)C=C378C(=O)N379C=C(C=C379)C=C380=C379C=C(N)C=C380C(=O)N381C=C(C=C381)C=C382=C381C=C(N)C=C382C(=O)N383C=C(C=C383)C=C384=C383C=C(N)C=C384C(=O)N385C=C(C=C385)C=C386=C385C=C(N)C=C386C(=O)N387C=C(C=C387)C=C388=C387C=C(N)C=C388C(=O)N389C=C(C=C389)C=C390=C389C=C(N)C=C390C(=O)N391C=C(C=C391)C=C392=C391C=C(N)C=C392C(=O)N393C=C(C=C393)C=C394=C393C=C(N)C=C394C(=O)N395C=C(C=C395)C=C396=C395C=C(N)C=C396C(=O)N397C=C(C=C397)C=C398=C397C=C(N)C=C398C(=O)N399C=C(C=C399)C=C400=C399C=C(N)C=C400C(=O)N401C=C(C=C401)C=C402=C401C=C(N)C=C402C(=O)N403C=C(C=C403)C=C404=C403C=C(N)C=C404C(=O)N405C=C(C=C405)C=C406=C405C=C(N)C=C406C(=O)N407C=C(C=C407)C=C408=C407C=C(N)C=C408C(=O)N409C=C(C=C409)C=C410=C409C=C(N)C=C410C(=O)N411C=C(C=C411)C=C412=C411C=C(N)C=C412C(=O)N413C=C(C=C413)C=C414=C413C=C(N)C=C414C(=O)N415C=C(C=C415)C=C416=C415C=C(N)C=C416C(=O)N417C=C(C=C417)C=C418=C417C=C(N)C=C418C(=O)N419C=C(C=C419)C=C420=C419C=C(N)C=C420C(=O)N421C=C(C=C421)C=C422=C421C=C(N)C=C422C(=O)N423C=C(C=C423)C=C424=C423C=C(N)C=C424C(=O)N425C=C(C=C425)C=C426=C425C=C(N)C=C426C(=O)N427C=C(C=C427)C=C428=C427C=C(N)C=C428C(=O)N429C=C(C=C429)C=C430=C429C=C(N)C=C430C(=O)N431C=C(C=C431)C=C432=C431C=C(N)C=C432C(=O)N433C=C(C=C433)C=C434=C433C=C(N)C=C434C(=O)N435C=C(C=C435)C=C436=C435C=C(N)C=C436C(=O)N437C=C(C=C437)C=C438=C437C=C(N)C=C438C(=O)N439C=C(C=C439)C=C440=C439C=C(N)C=C440C(=O)N441C=C(C=C441)C=C442=C441C=C(N)C=C442C(=O)N443C=C(C=C443)C=C444=C443C=C(N)C=C444C(=O)N445C=C(C=C445)C=C446=C445C=C(N)C=C446C(=O)N447C=C(C=C447)C=C448=C447C=C(N)C=C448C(=O)N449C=C(C=C449)C=C450=C449C=C(N)C=C450C(=O)N451C=C(C=C451)C=C452=C451C=C(N)C=C452C(=O)N453C=C(C=C453)C=C454=C453C=C(N)C=C454C(=O)N455C=C(C=C455)C=C456=C455C=C(N)C=C456C(=O)N457C=C(C=C457)C=C458=C457C=C(N)C=C458C(=O)N459C=C(C=C459)C=C460=C459C=C(N)C=C460C(=O)N461C=C(C=C461)C=C462=C461C=C(N)C=C462C(=O)N463C=C(C=C463)C=C464=C463C=C(N)C=C464C(=O)N465C=C(C=C465)C=C466=C465C=C(N)C=C466C(=O)N467C=C(C=C467)C=C468=C467C=C(N)C=C468C(=O)N469C=C(C=C469)C=C470=C469C=C(N)C=C470C(=O)N471C=C(C=C471)C=C472=C471C=C(N)C=C472C(=O)N473C=C(C=C473)C=C474=C473C=C(N)C=C474C(=O)N475C=C(C=C475)C=C476=C475C=C(N)C=C476C(=O)N477C=C(C=C477)C=C478=C477C=C(N)C=C478C(=O)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Friday, September 19, 2008

Biotech

Diamond in the rough' at center of Pfizer-Medivation deal

San Francisco Business Times - by Ron Leuty



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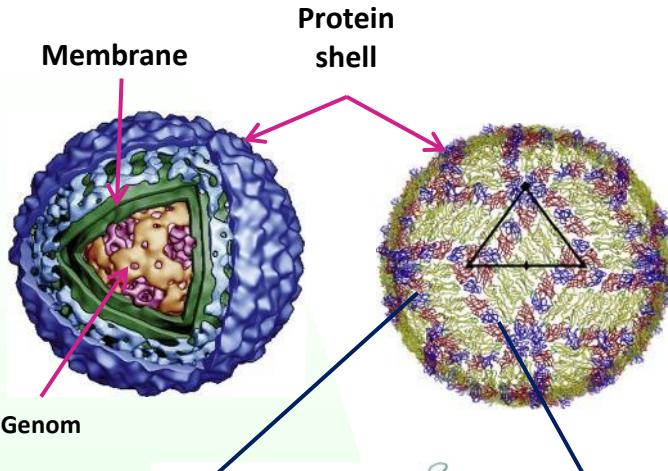
Medivation receives FDA clearance to begin trials of Dimebon against Huntington's disease.

Pfizer and Medivation have announced an agreement to jointly commercialize dimebon.

Development of medicinal substances for the treatment of tick-borne encephalitis

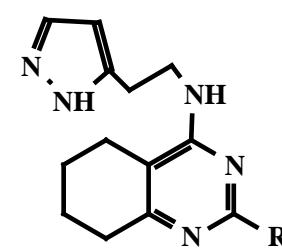
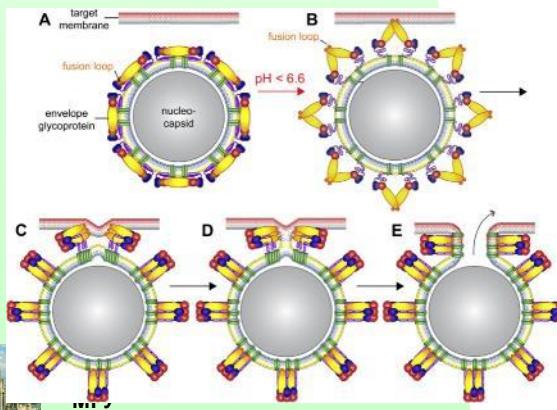
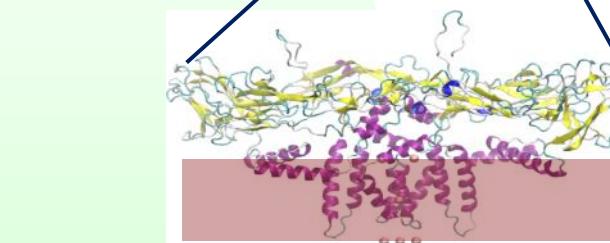
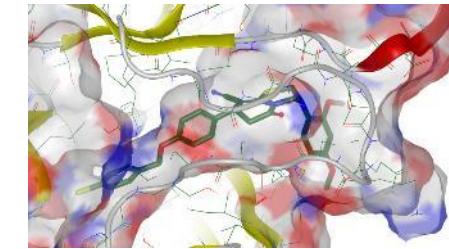


Palyulin, Osolodkin

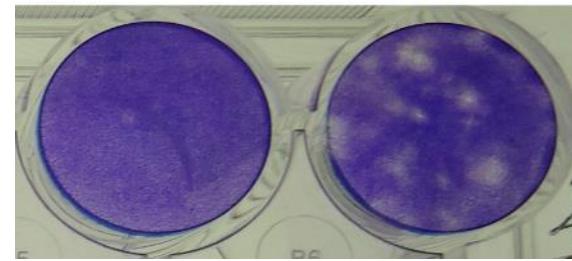


Modeling (supercomputer) of spike formation blockers

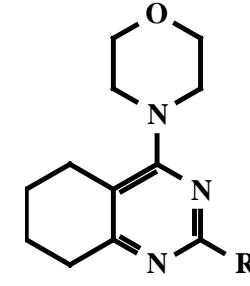
Virtual screening: 5886 compounds
Tested *in vitro*: 100 соединений
Active: 12 compounds



Inhibitor:
cells are protected



Without inhibitor:
no protection



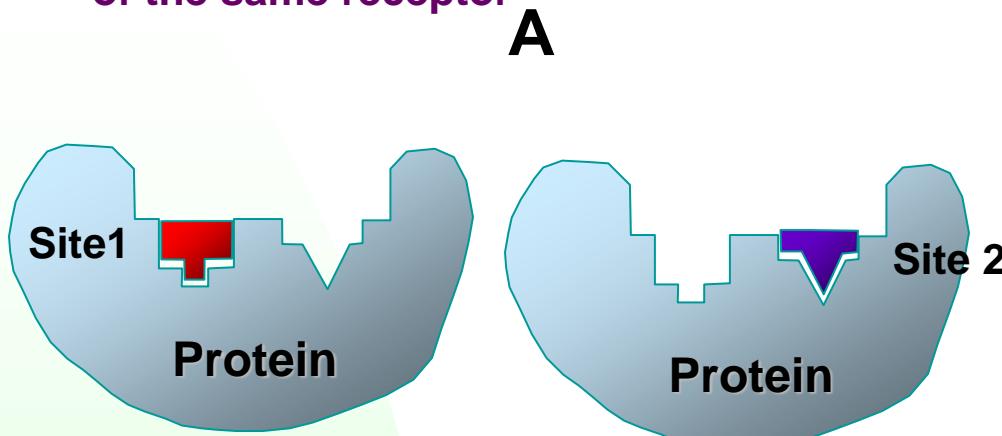
As a result of modeling and screening, inhibitors of tick-borne encephalitis virus fusion with cells with low cytotoxicity were found

D.I.Osolodkin, V.A.Palyulin, N.S.Zefirov, et al., *Biochem. Biophys. Res. Comm.*; *Curr.Pharm.Design*; *ACS Med.Chem.Lett.*

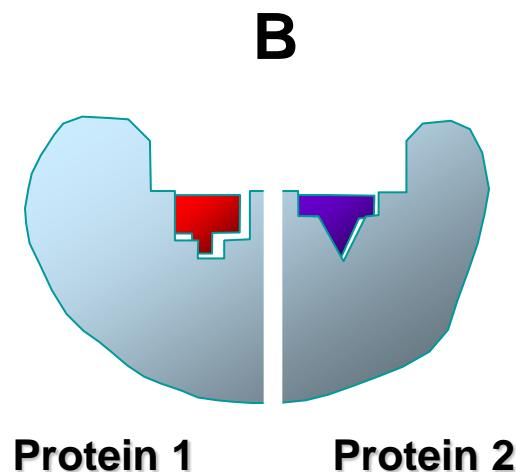


Bivalent drugs (twin-drug)

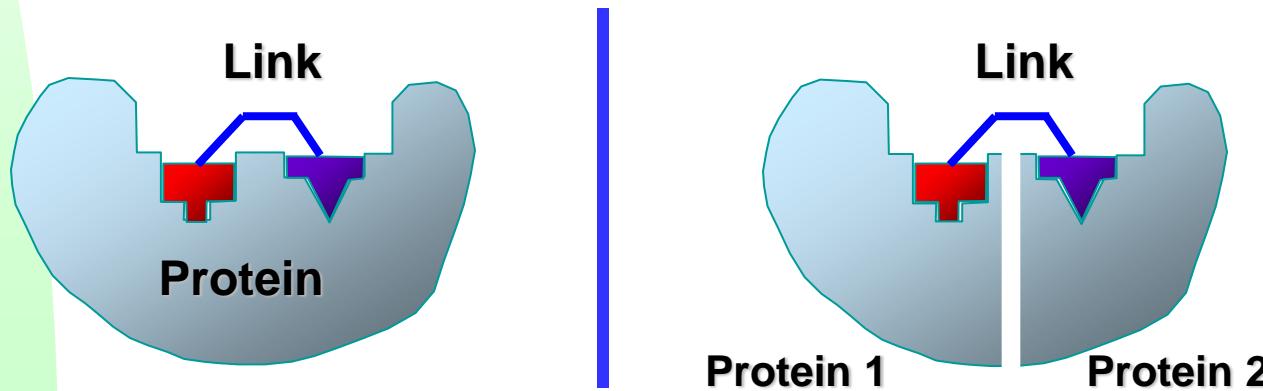
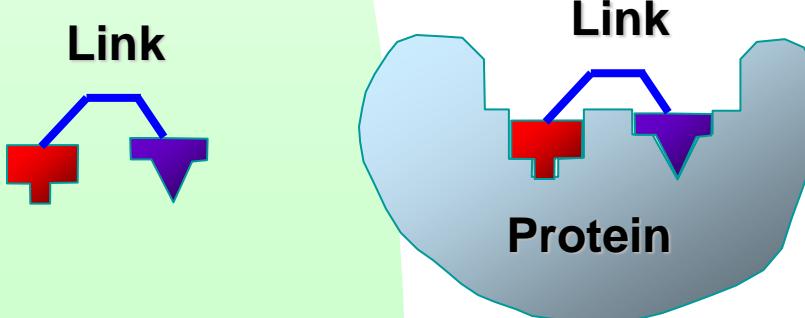
1. Binding of molecules (A) by different sites of the same receptor



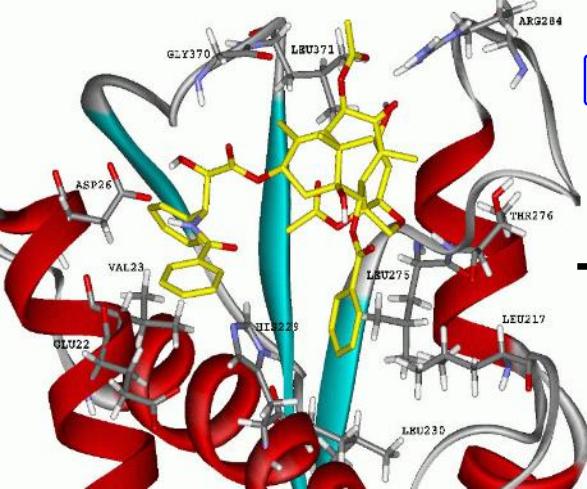
- (B) by different receptors



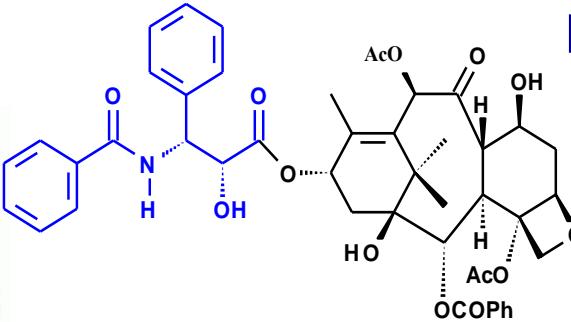
2. Connecting the fragments with a “linker”



Tubulin – the target of taxol



Taxol causes uncontrolled polymerization of tubulin and thus blocks mitosis.



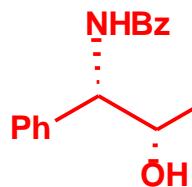
Palitaxel (TAXOL) Anticancer drug

Annual sells: \$ 1.6 billion

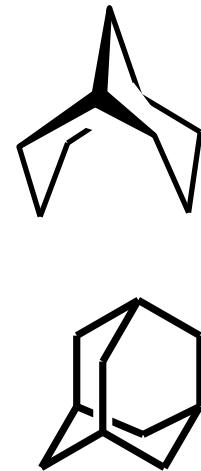
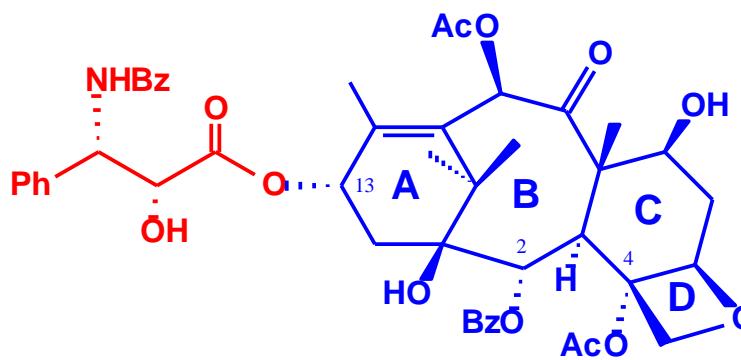


The main idea: bioisosteric replacement of cage fragment

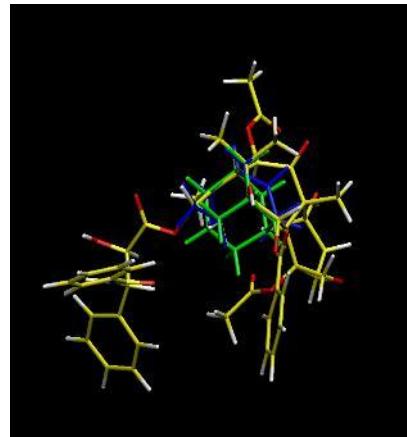
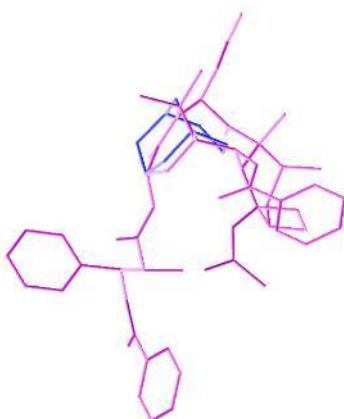
Retain amino acid



Replace cage structure



Prof. O.N. Zefirova



Dr. E.V. Nurieva

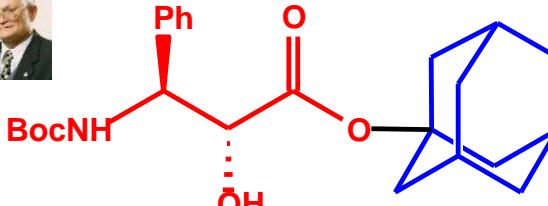


All synthesized compounds (>50) showed cytotoxicity towards A549 cell culture with IC50 in the micromolar concentration range.

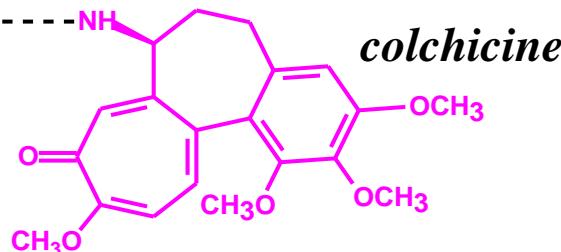
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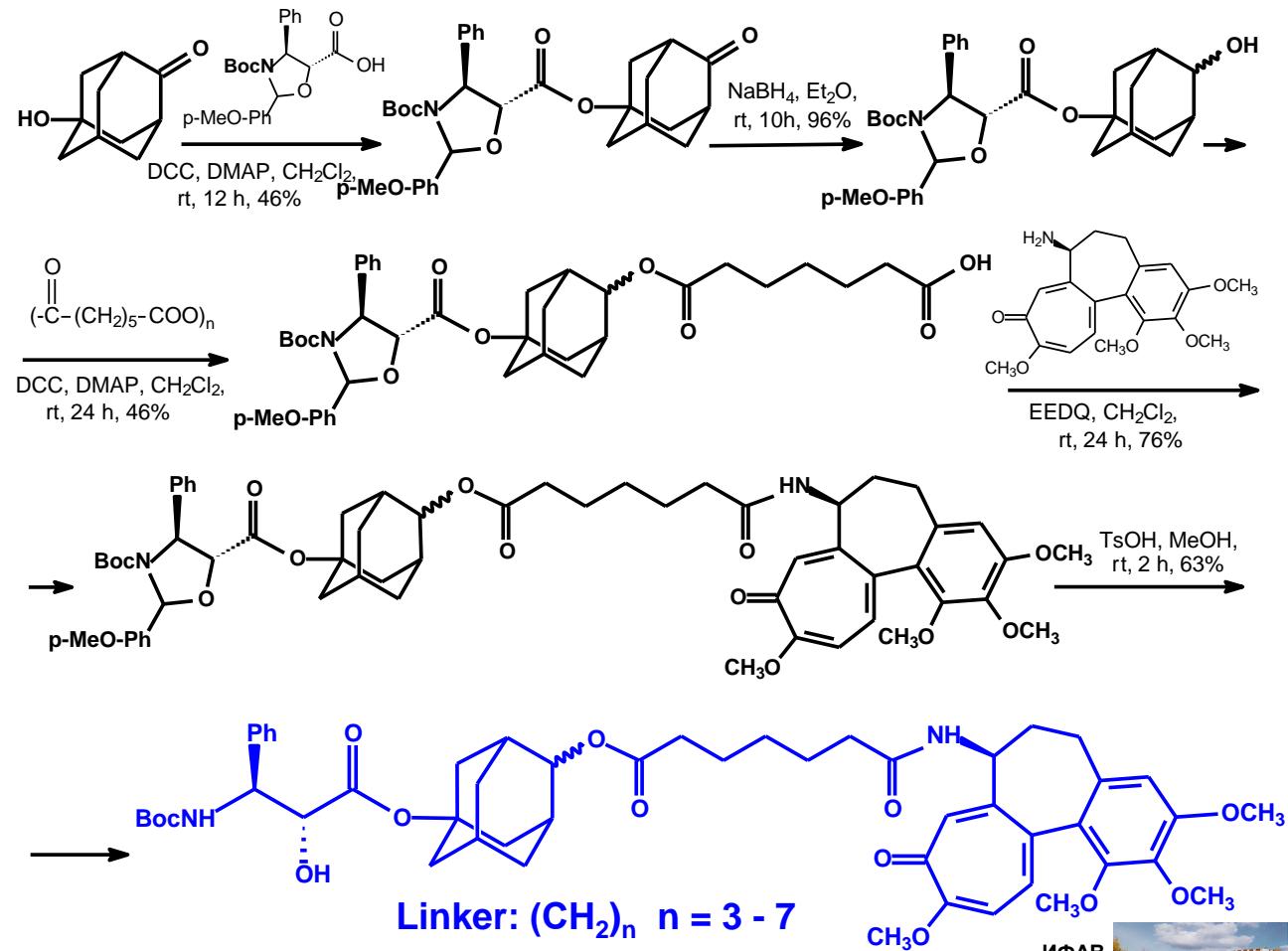
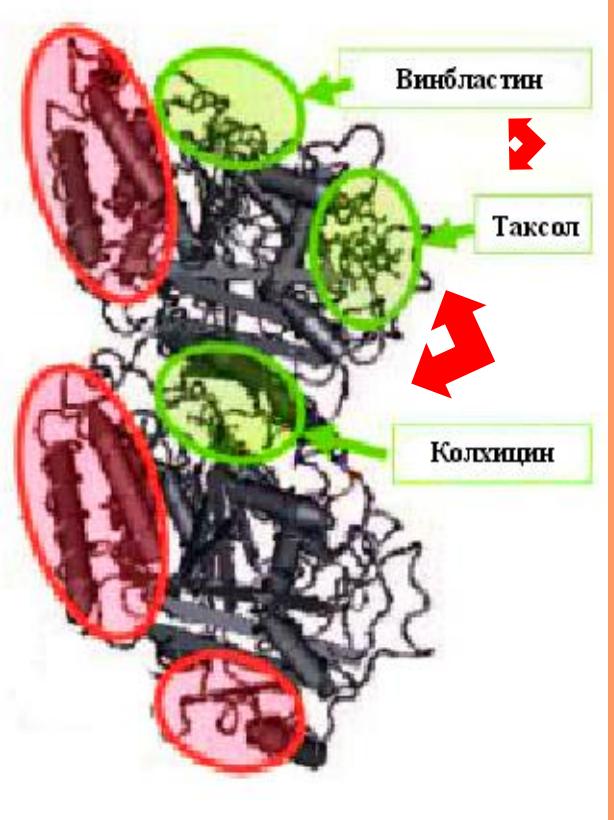
Development of “TUBULOCLASTINS” as “bivalent drugs” :



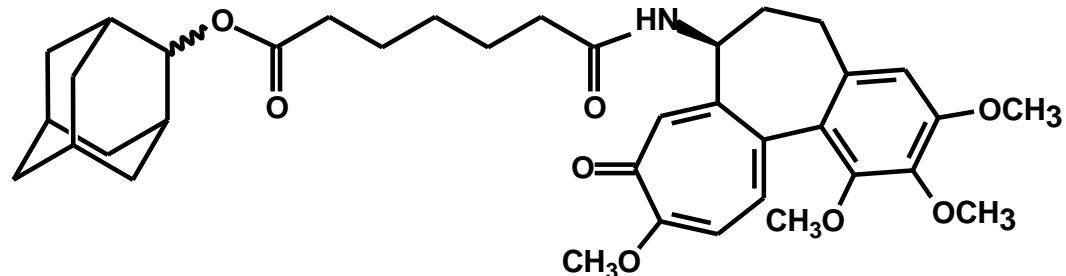
Simplified analog of taxol



*Colchicum
autumnale*



“TUBULOCLASTIN “



Using immunofluorescence microscopy, the dual activity of tubuloclastin was discovered. It causes both the depolymerization of microtubules and the formation of tubulin aggregates. Tubulin aggregates are collected in long clusters, which, concentrating near cell nuclei, form an unusual pattern, which we have called «solar eclipse-like pattern»).

Tubuloclastin activity was detected on human lung carcinoma A549 cells in the **nanomolar** concentration range.

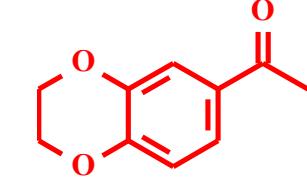
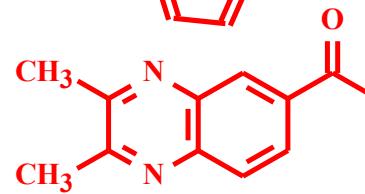
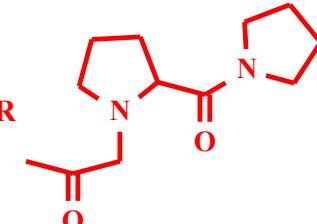
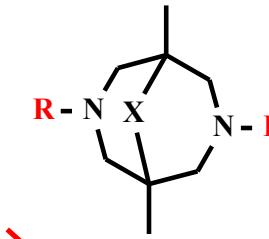
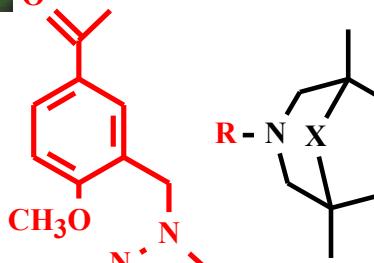
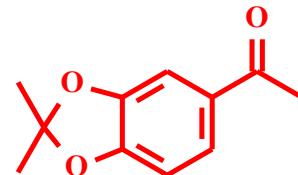
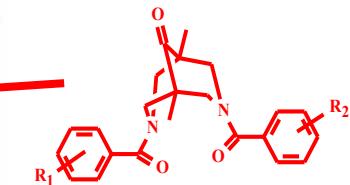
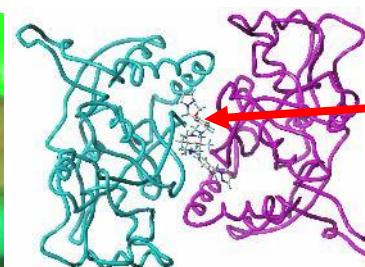
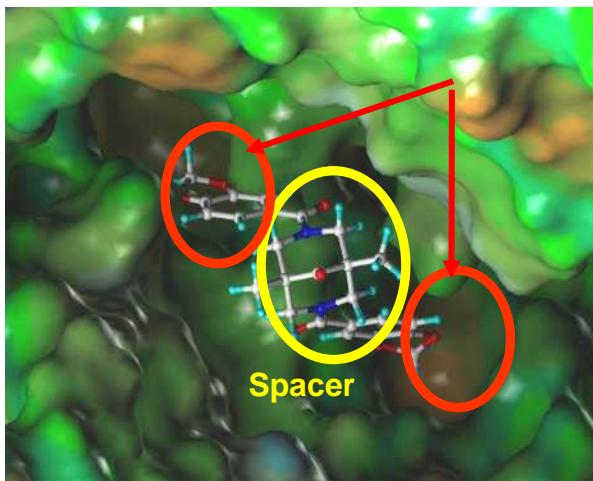
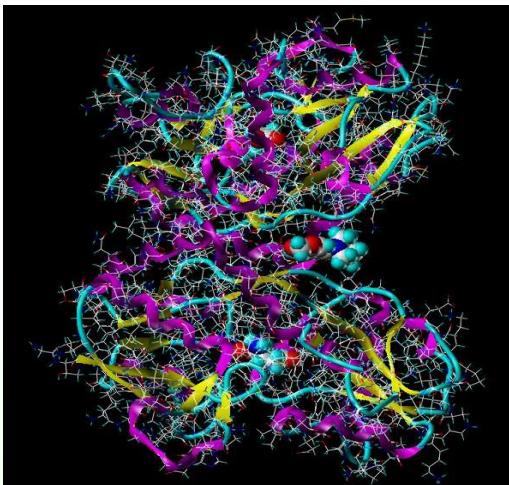
Compound	Cytotoxicity	Effect of 1 μM substance on microtubule network
Tubulo-clastin	6 ± 1.4	Depolymerization (+++) and cluster formation (+++)
Taxol	5 ± 0.7	“Bundles” of microtubules

Zefirova, O.A., Nurieva, E.V., Weiss, D.G., Zefirov N.S., Kuznetsov, S.A., et al., *Bior. Med. Chem.*, 2011, **19**, 5529; *Chem. Biochem.*, 2013, **14**, 1444.

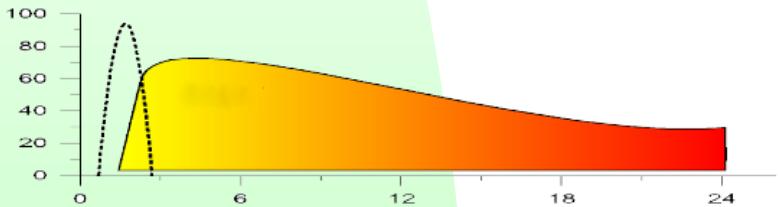
OPTIMIZATION
 Replacement of colchicine with:
 combretastatin
 podophyllotoxin
 methoxyestradiol
 with variation of linker length.
**Zefirova, Shishov,
 Zefirov N.A.**



Novel positive AMPA receptor modulator OSPL-502 that improves cognitive functions and long-term memory is in preclinical trials



Using molecular modeling, large series of molecules that simultaneously bind to two AMPA receptor sites were designed and synthesized.



Experimental animals restore (remember) lost skills 24 hours after training when the drug is administered.

The bivalent allosteric ligand of AMPA receptors OSPL-502 exhibits positive modulator properties at picomolar concentrations. A molecule with record activity and extremely low toxicity (!) was selected for preclinical studies.



Preclinical studies of a drug for the treatment of Alzheimer's disease based on diazabicyclononane (“Cyclomemorin”)



Bioavailability:
44,4 %

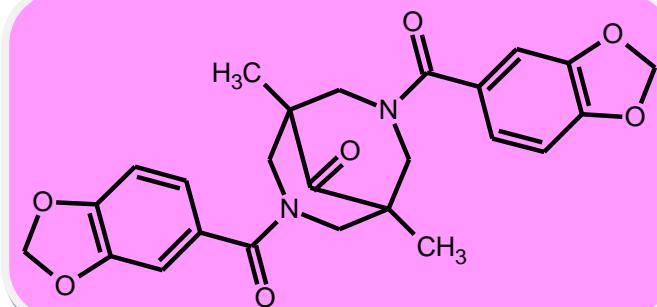
Synthesis from 50 mg to 400 g

Subchronic (1 month)
toxicity: 180 mg/kg

Acute toxicity: more
than 5000 mg/kg

Chronic toxicity (6 months) of
the dosage form: no violations
were identified

Chronic toxicity: 675 times
the recommended human
dose



Dosage form

Experiments on
dogs



SINCERE GRATITUDE TO ALL CO-AUTHORS

THANK YOU
FOR YOUR ATTENTION



«...I like this work...»

Johann Joachim Becher, XVI century

