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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Lomonosov Moscow State University,
Moscow, Russia

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

PhD

Dr.Habil.

Corr. member.

1981

Lomonosov Prize, MSU

1983

Academician RAS 1987

Council of ministers prize

1987

1935,

Yaroslavl,

September 13

Dr. Vlasov V.M.

Acad. RAS

Bachurin S.O.

Corr.member RAS

Martynov I.V.

IPAC RAS, Director 1989

State Prize, USSR 1989

Head of organic chemistry division 1994

Butlerov Prize 1994

State Prize of Russia 2000

Head of medicinal chemistry and advanced organic synthesis division,
Dept. of Chemistry, MSU

2015

2014

Head of medicinal chemistry and advanced organic synthesis division

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

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

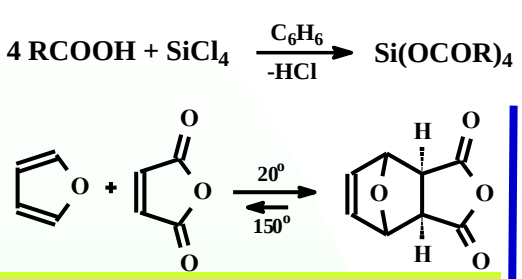
ИФАВ РАН

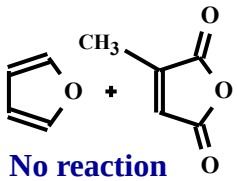
Chemical childhood and growing up

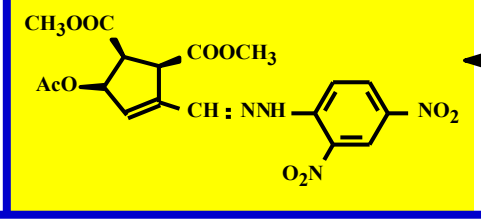
Prof. Yu.K.Yuriev

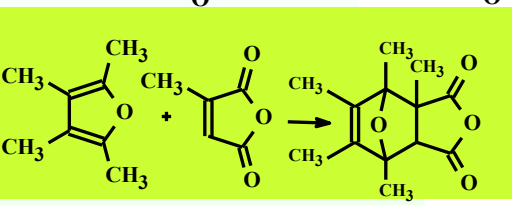
Acad. G.B.Elyakov

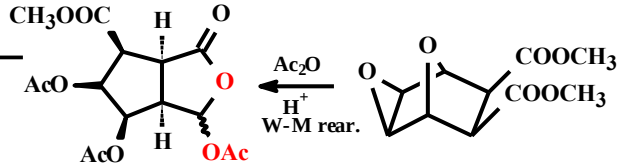
Yu.K.Yuriev, G.B.Elyakov, N.S.Zefirov, *Zh.Obsch.Khim*, 26, 3341 (1956); 27, 3264 (1957)

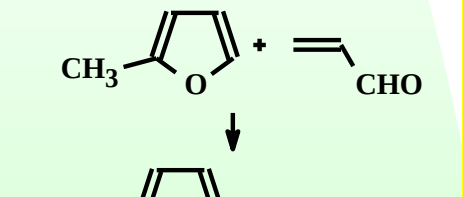




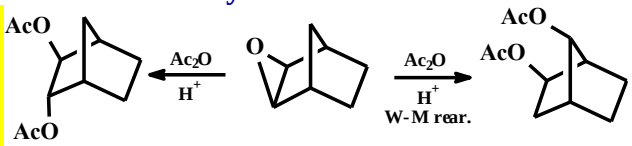


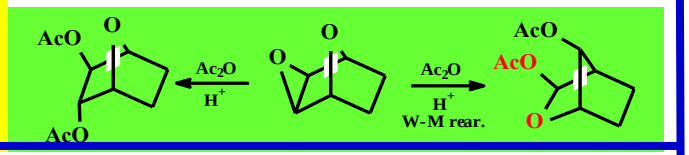


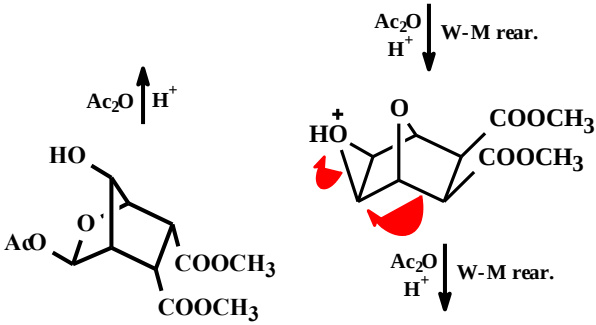


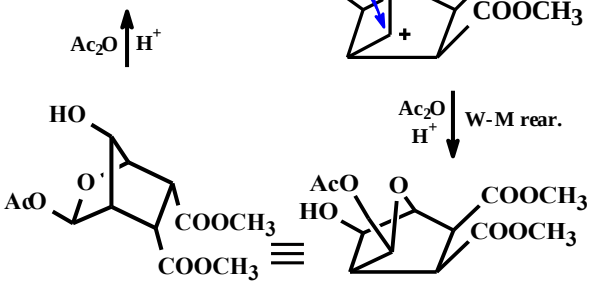


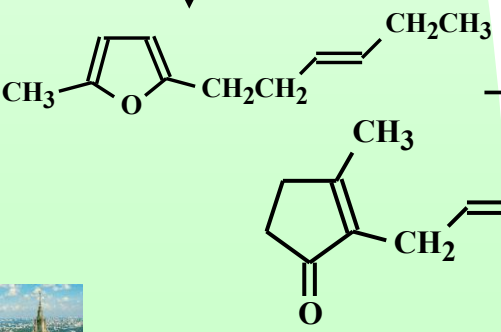
Chemistry without NMR!

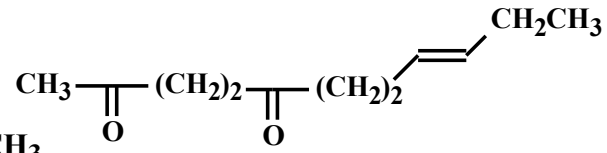












Synthesis of trans-jasmon:

Yu.K.Yuriev, N.S.Zefirov, 1961 – 1963; N.S.Zefirov, 1963 – 1966;

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Academician Nikolay S. Zefirov

MSU Honorable Professor

Member of International Academy of Mathematical Chemistry

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

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

More than 1900 papers and patents

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Synthetic organic chemistry

- New approaches in Ad_E reactions: (a) “doping addition”, (b) SO_3-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.

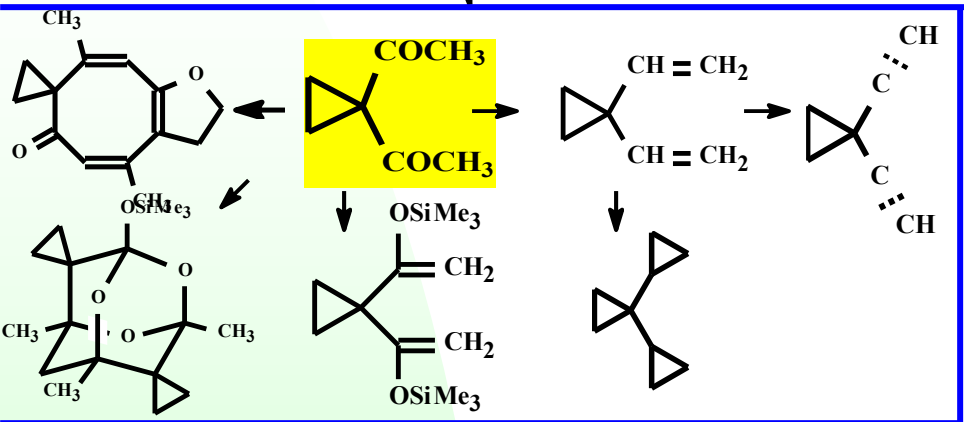
Discovery No. 293 (1984) USSR State Prize (1989)

- 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 $C(NO_2)_4$. Syntheses of heterocycles of various types.
- Photochemical reactions: [2+2]-cycloaddition, syntheses based on hexachlorocyclopentadiene, synthesis of oxazoles and λ^5-phosphinolines from phosphonium-iodonium ylides.

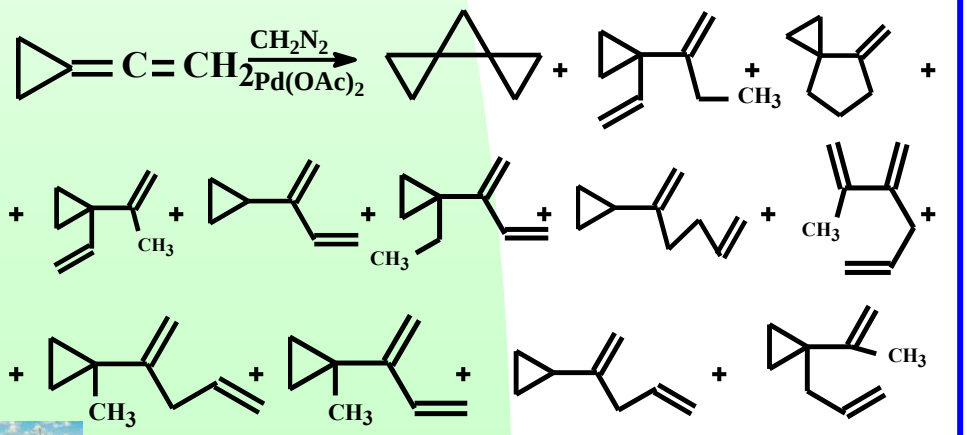
Synthetic organic chemistry: cycloprapanes

Dr. T.S.Kuznetsova

Synthesis of cage/polycyclic hydrocarbons containing a cyclopropane moiety



Oligomethyleneation of allenes



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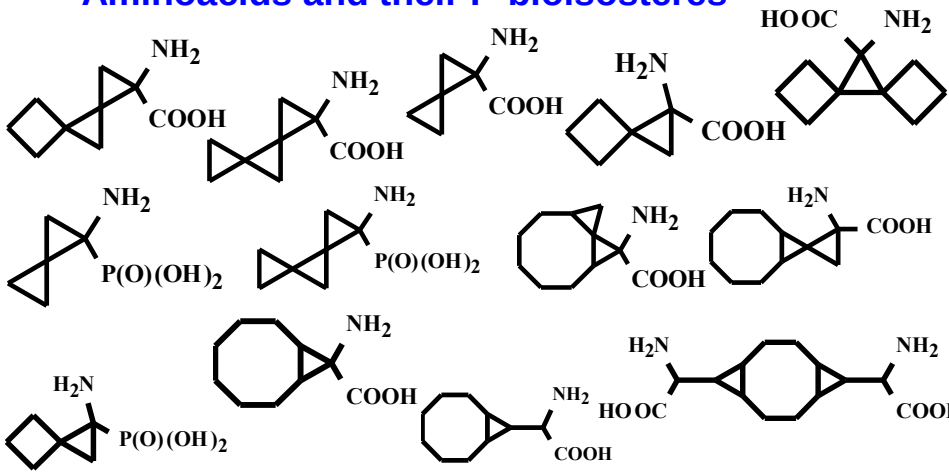
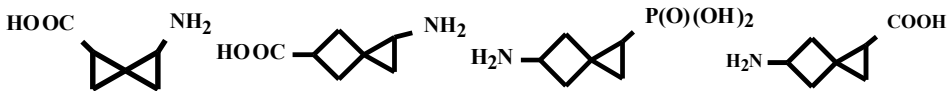
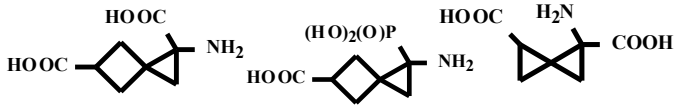
Aminoacids and their P-bioisosteres



Conformationally rigid analogues of GABA:

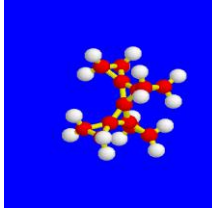


Conformationally rigid analogues of glutamic acid:



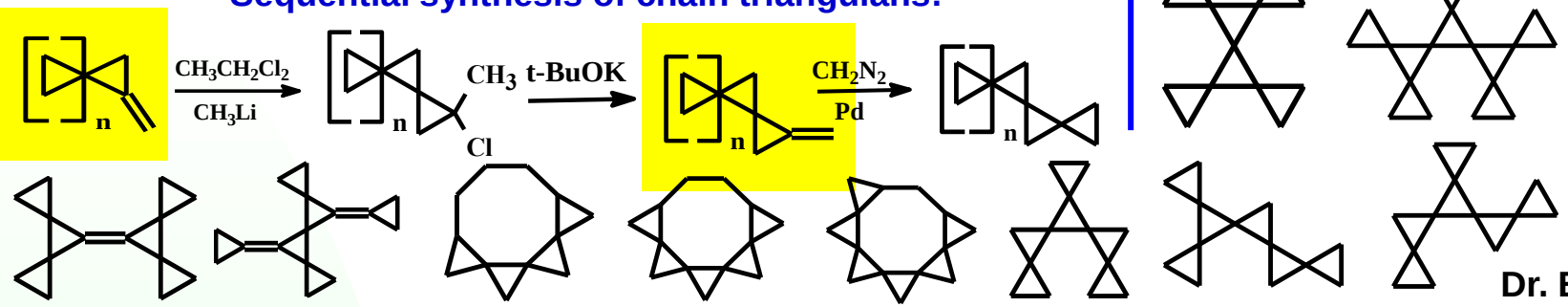
Dr. N.V.Yashin

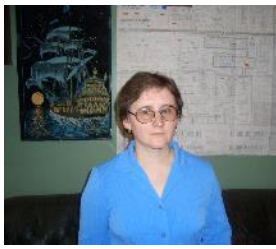
Synthetic organic chemistry: triangulanes



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).

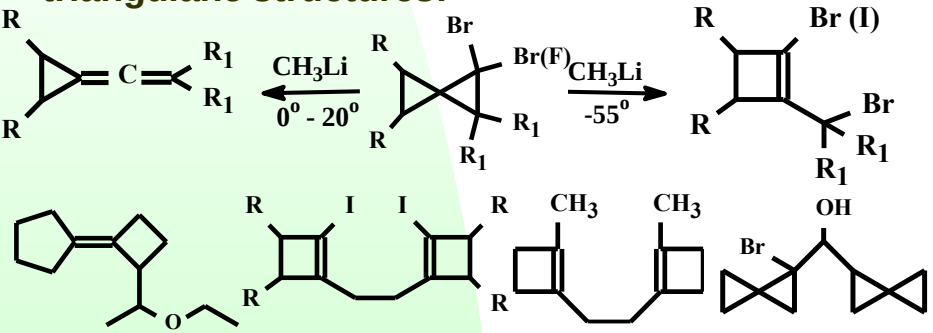
Sequential synthesis of chain triangulans:

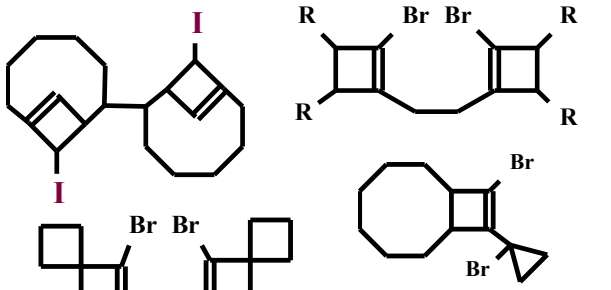




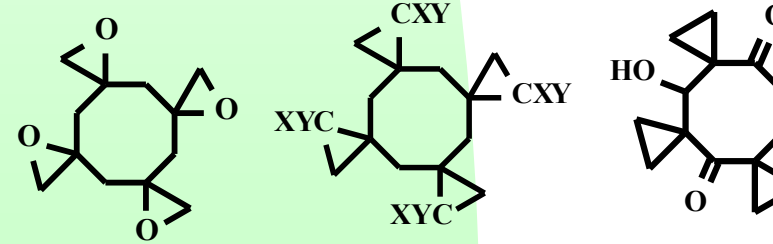
Dr. E.B.Averina

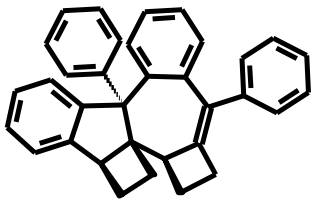
A new skeletal rearrangement in carbenoid triangulane structures:

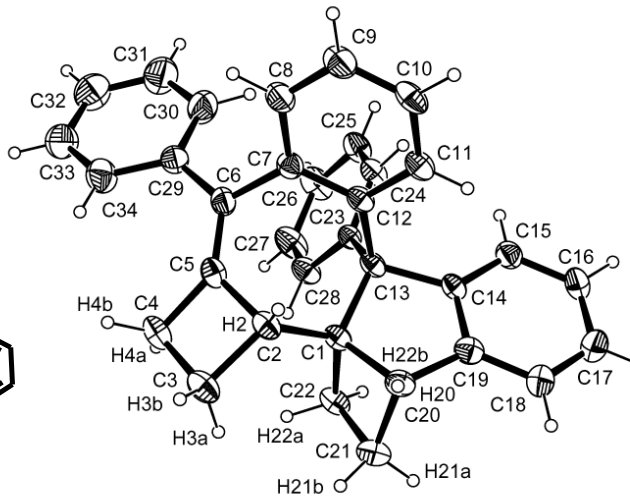




Dr. K.N.Sedenkova







Kuznetsova, Averina, Sedenkova

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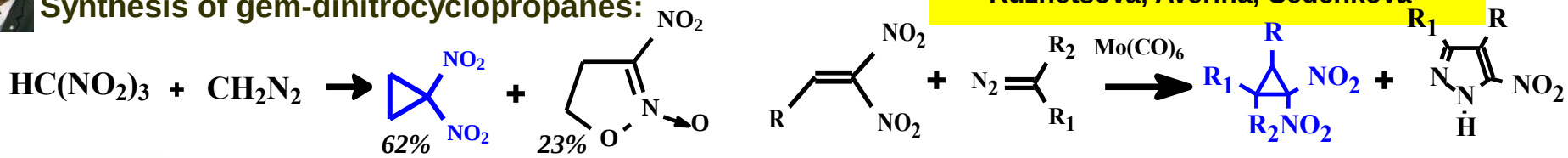
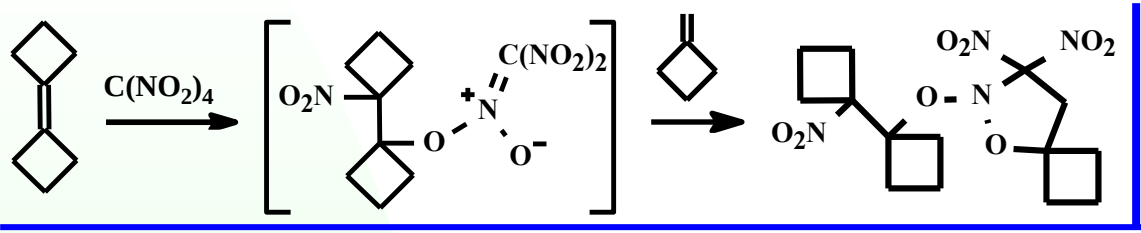
Synthetic organic chemistry:
synthetic studies in the field of nitro(poly-nitro) compounds

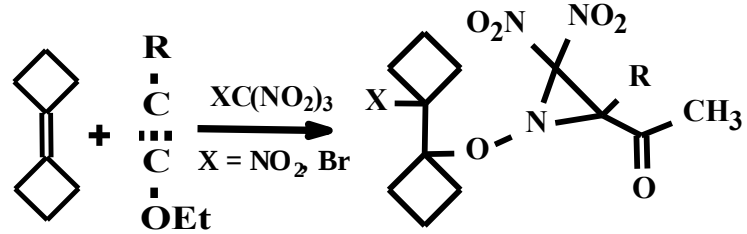
Kuznetsova, Averina, Sedenkova

Synthesis of gem-dinitrocyclopropanes:

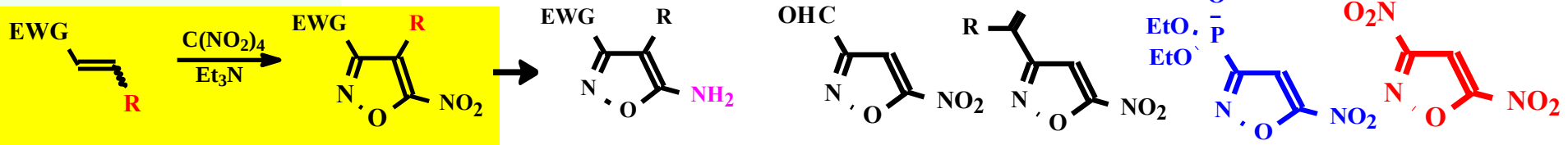


Tandem (two-step) reaction of $C(NO_2)_4$ with various olefins:

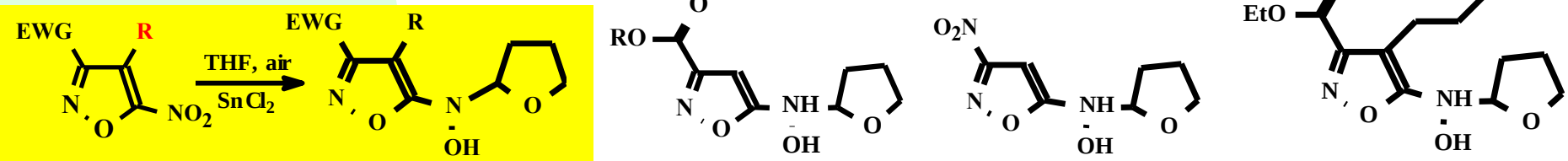




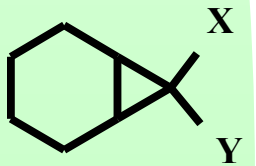
New reaction for the synthesis of isoxazoles. $C(NO_2)_4 \cdot Et_3N$ as a new reagent { $[Et_3N\text{-}NO_2]^+[C(NO_2)_3]^-$ }

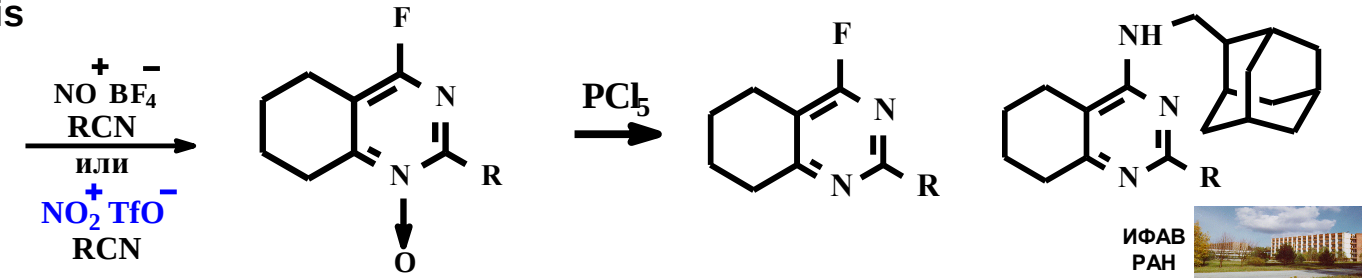


A new reaction for the synthesis of hydroxylamines (direct C-H functionalization):



New reaction for the synthesis of fluoropyrimidines(oxides):





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Synthetic organic chemistry:
nucleophilic properties of nucleofuge anions

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

TfO^- ClO_4^- FSO_3^- $ClSO_3^-$ H_2O — F^- AcO^- Cl^- Br^- I^- OH^- CN^- N_3^-

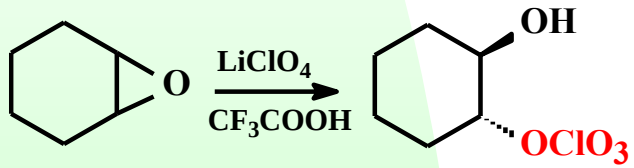
nucleofuge ⟷ nucleophile

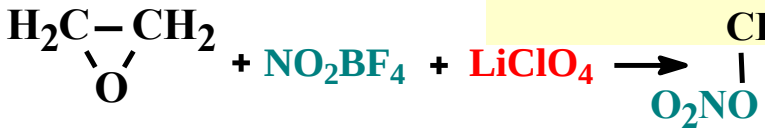
Competitive covalent binding of "nucleofuge" anions is a general phenomenon for a large series of carbocation-type reactions.

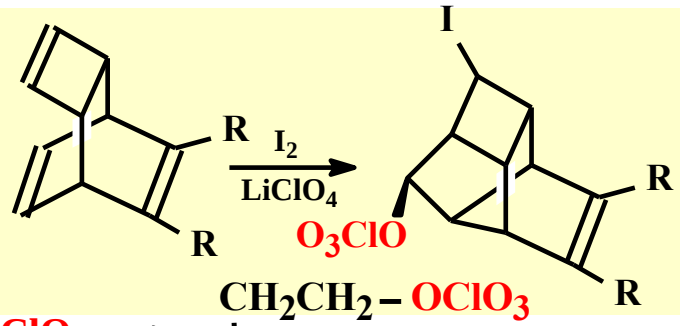
Discovery No. 293 (1984)

$H_2C(OSO_2CF_3)-CH_2Cl \xleftarrow[LiOSO_2CF_3]{Cl_2} H_2C=CH_2 \xrightarrow[LiOSO_2F]{Cl_2} H_2C(OSO_2F)-CH_2Cl$

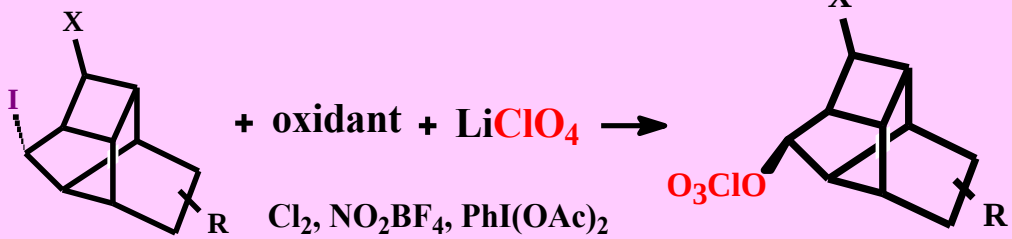
$CH_2=CH_2 + NO_2BF_4 + LiClO_4 \longrightarrow O_2N-CH_2CH_2-OClO_3$

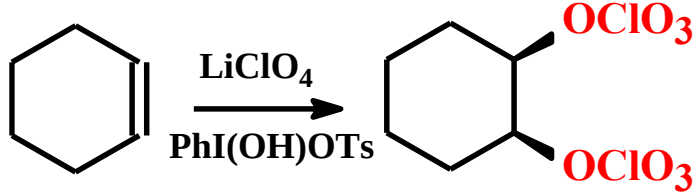


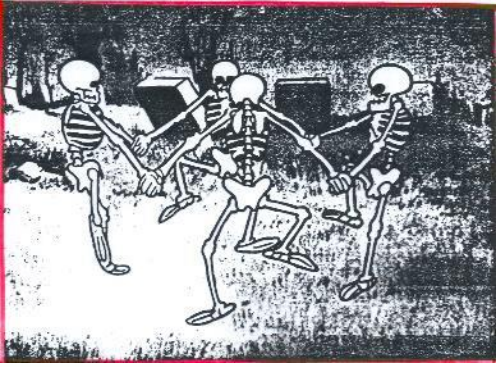




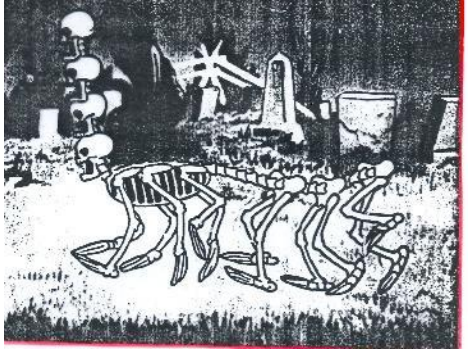
$CH_3I \xrightarrow[CF_3SO_3^- Bu_4N^+]{Cl_2} CH_3OSO_2CF_3$ $CH_2I_2 + LiClO_4 + NO_2BF_4 \longrightarrow O_3ClO-CH_2-OClO_3$



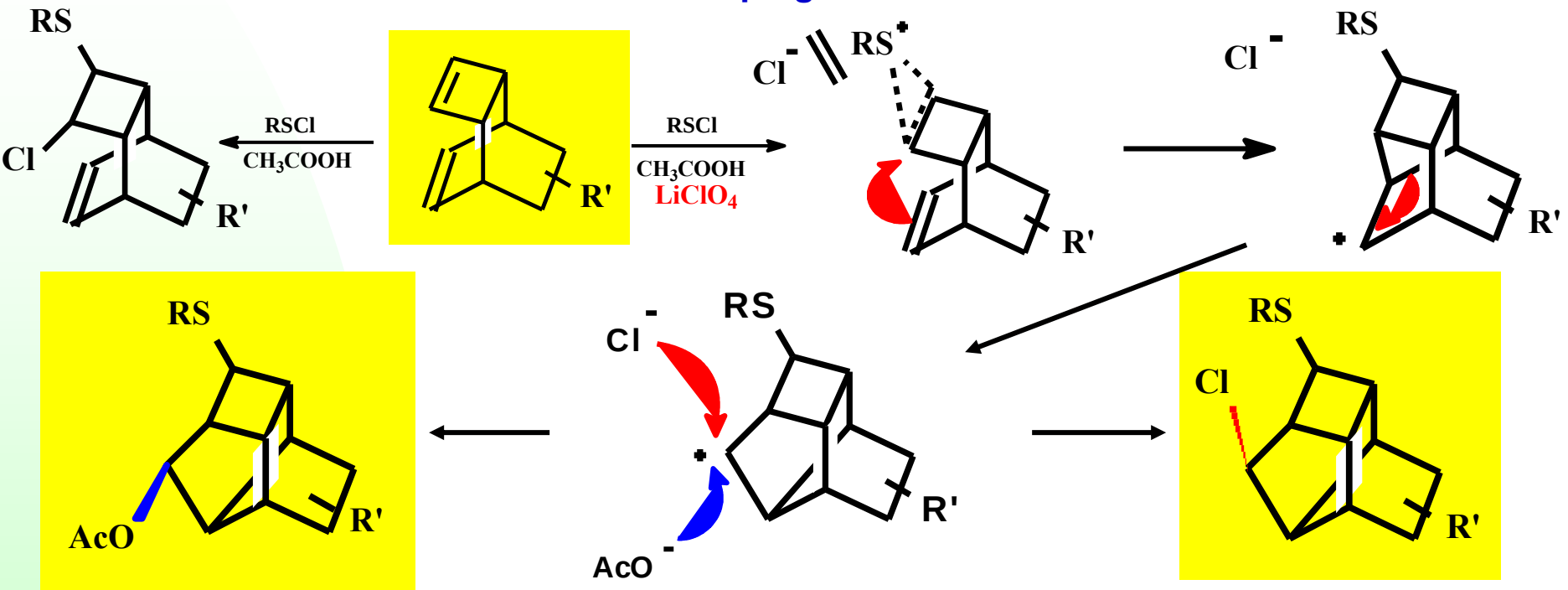


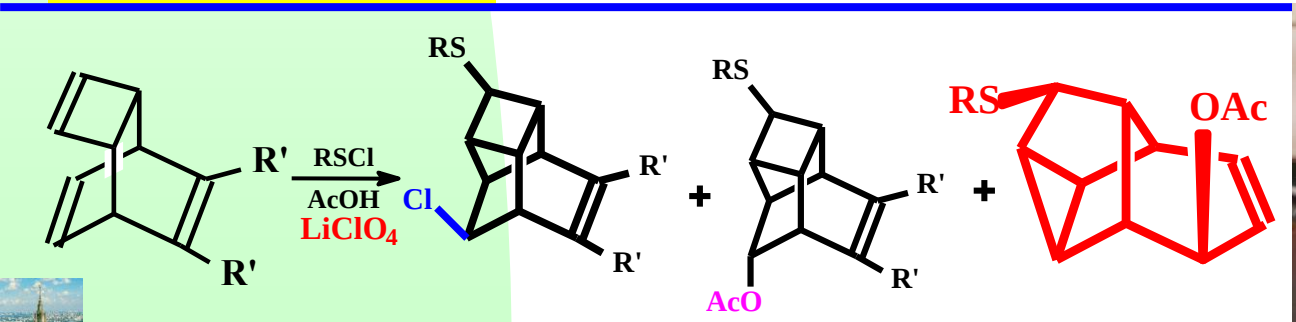


Physical organic chemistry: skeletal rearrangements



Ion-pair mechanism of Ad_E-reactions and "doping-addition"





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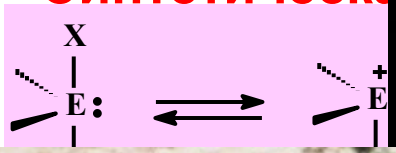
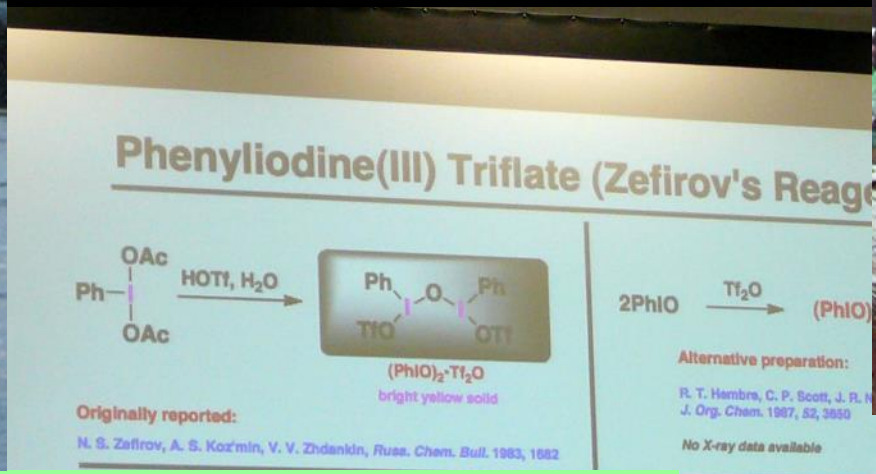
Синтетическая … валентные



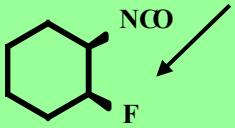


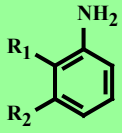
Dr. V.K. Brel

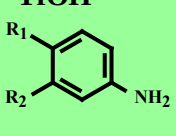
$RC{\equiv}CLi \xrightarrow[-LiBF_4]{BF_3} RC{\equiv}CBF_2 \xrightarrow{XeF_2} RC{\equiv}C{-}\overset{+}{Xe}\ BF_4^-$

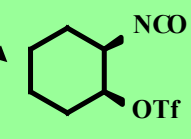
^{128}Xe NMR : δ -1898 ppm from XeF_2

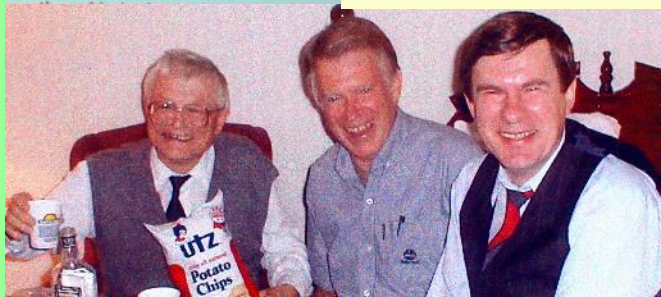
$FXeNCO \xleftarrow{Me_3SiN{=}C{=}O} XeF_2 \xrightarrow[TfOH]{Me_3SiN{=}C{=}O} TfOXeNCO$











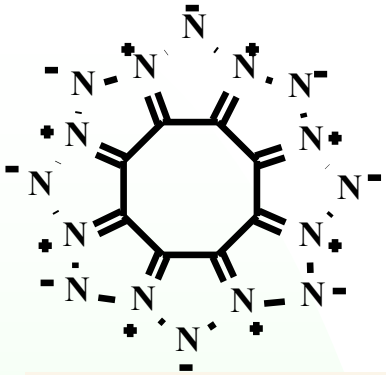
Physical organic chemistry, MO

- **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.

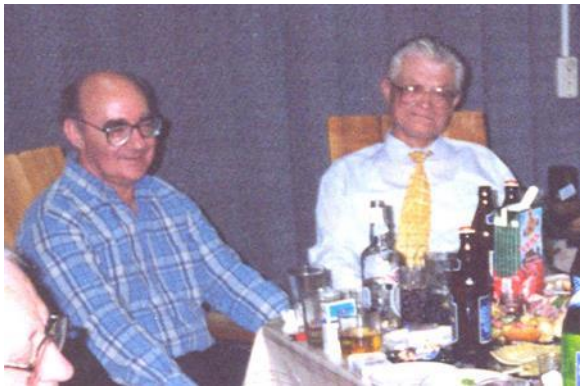


Results of DFT B3LYP/6-311G* :

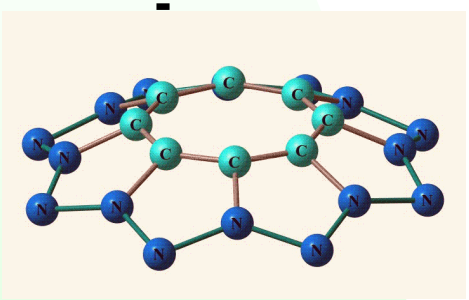
Bowl shape, flat C8 cycle, C_{8v},

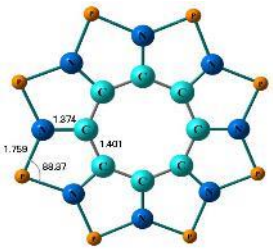
bowl ⇄ bowl >150 kcal/mol

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

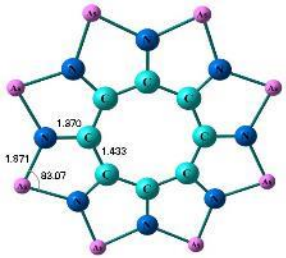


Academician V.I.Minkin





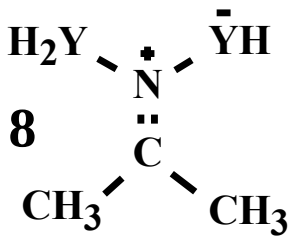
P

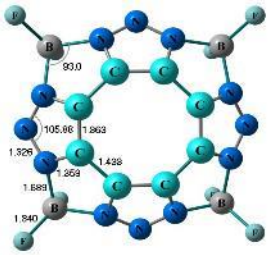


As

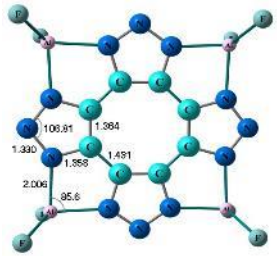
Homodesmotic reaction:

$C_8N_8Y_8 + 8\ YH_3 + 8\ CH_3\text{-}CH_3 \longleftrightarrow 8$





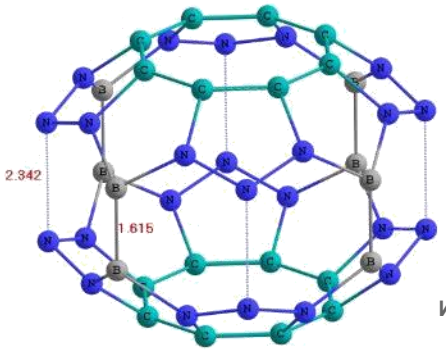
BF_2



AlF_2

ΔE_{arom} : Y = N 87.2 kcal/mol;

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



Cage derivatives

МГУ Химфак

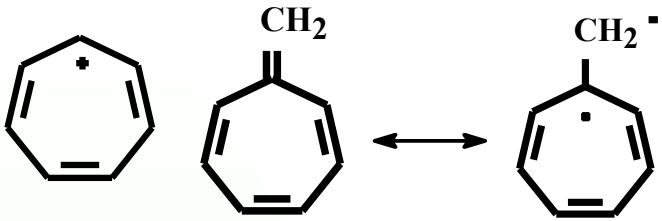
T.Gribanova, N.S.Zefirov, V.I.Minkin, *Dokl. Chem.*, 2009, *426*, 105; *Pure & Appl. Chem.*, 2010, *82*, 1011.

Physical organic chemistry, MO

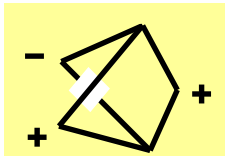
MO prediction of structures of new types.

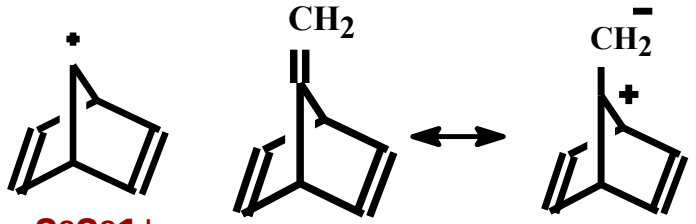
Definition of different types of conjugation

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

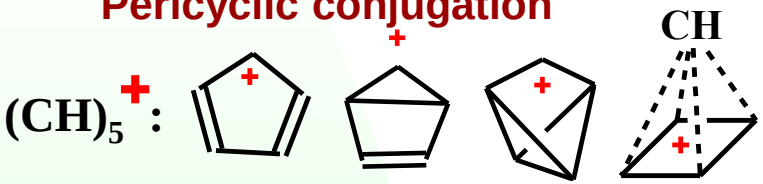


Pericyclic conjugation



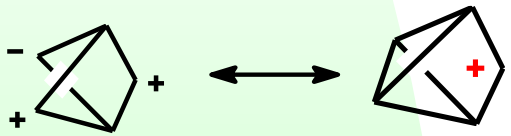


Longicyclic conjugation

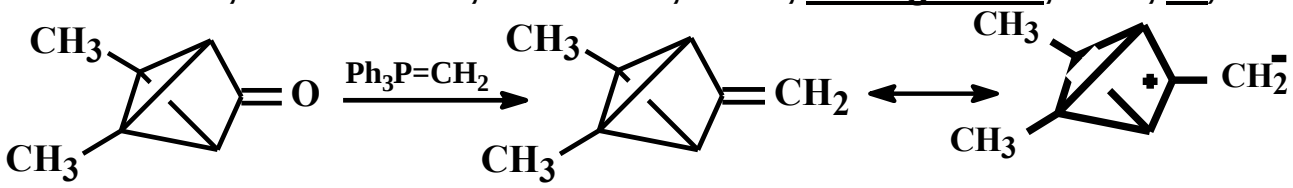


W. Stohrer, R. Hoffmann, *J. Am. Chem. Soc.*, 1972, *94*, 1661

Longicyclic conjugation in methylenehomotetrahedrane

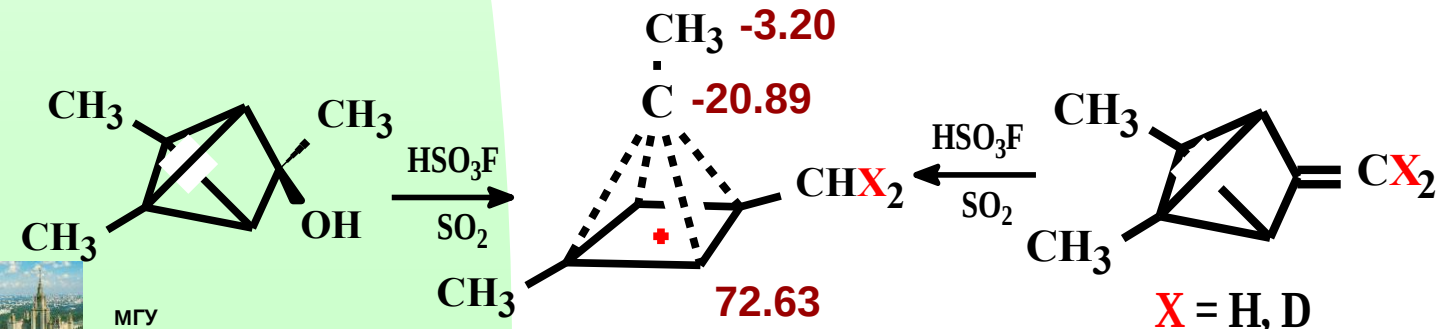


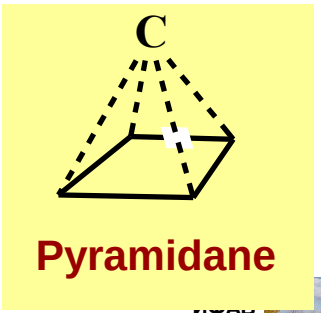
N.S. Zefirov, R. Hoffmann, V.I. Minkin, et. al., Zh.Org.Khim., 1980, *16*, 241



Tri-Me-C_5H_2 pyramidal cation

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





Stereochemistry and conformational analysis

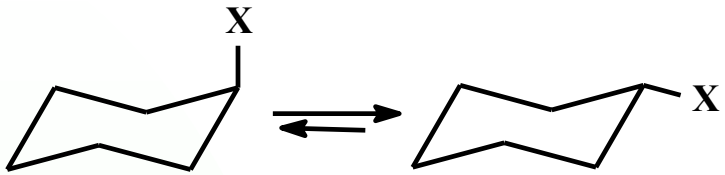
- Stereochemistry of some AdE reactions (e.g. oxymercuration, sulfenylation, nitrosochlorination, etc.).
- The problem of conformational effects. Anomeric effect. “Gauche” and “hockey stick” effects. Search for new conformational effects and anomalies (e.g. in bicyclo[3.3.1]nonanes).
- Description of 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)

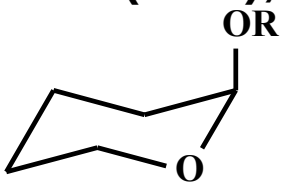
State Prize of Russia (2000)

Stereochemistry and conformational analysis:
problem of conformational effects

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



$A = -\Delta G_{eq}$ F, OR, Cl, Br , NR_2, CH_3, $C(CH_3)_3$

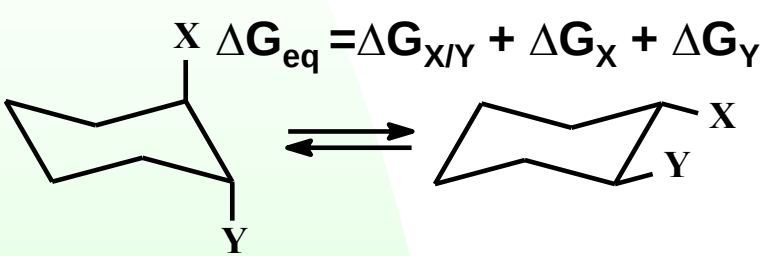


Anomeric effect

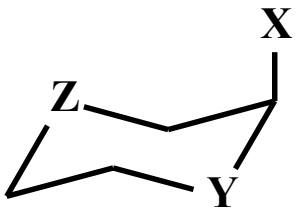
"Rabbit ears" effect

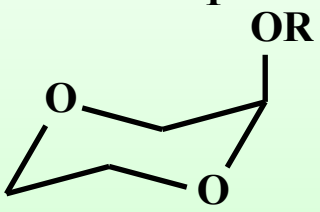
"Gosh effect"

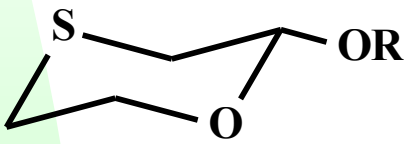
"Δ^2 instability factor"

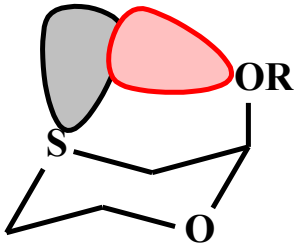


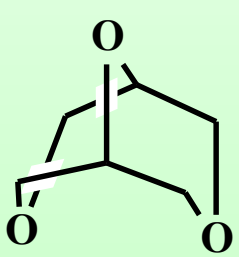
$\Delta G_{eq} = \Delta G_{X/Y} + \Delta G_X + \Delta G_Y$

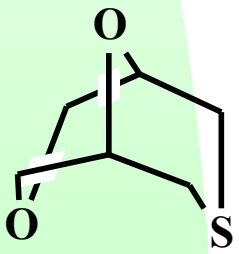


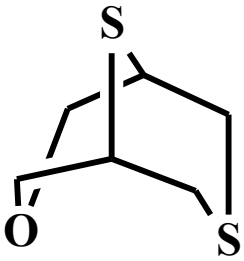


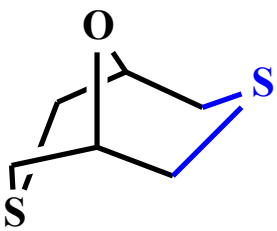


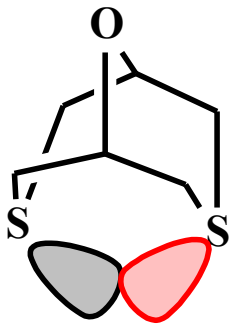


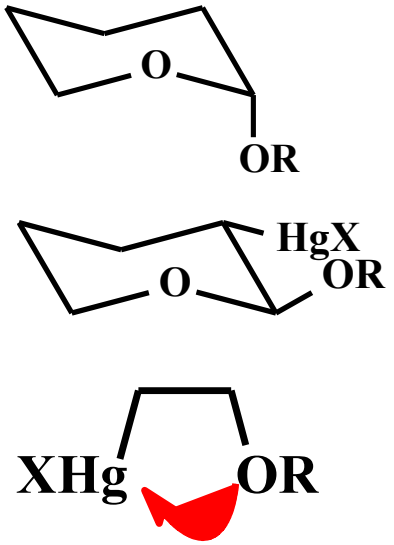










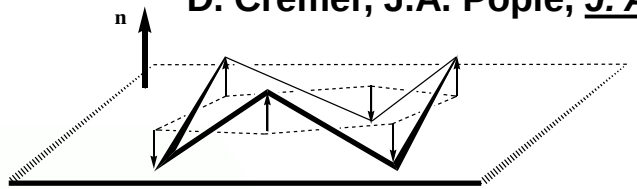


"Hockey sticks" effect

Zefirov et al., *Usp.Khim.*, 1973, *42*, 423; 1975, 44, 413; *Tetr.*, 1976, *32*, 1211; Zefirov, Palyulin, *Topics in Stereoch.*, 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

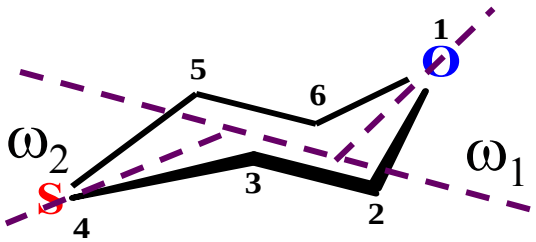
D. Cremer, J.A. Pople, *J. Am. Chem. Soc.*, 1975, *97*, 1354

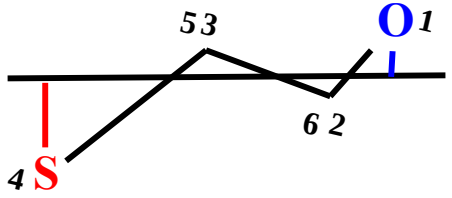


Cremer-Pople approach is based on the deviations from mean plane:

(1) two puckering amplitudes q_2 , q_3

(2) phase angle φ_2



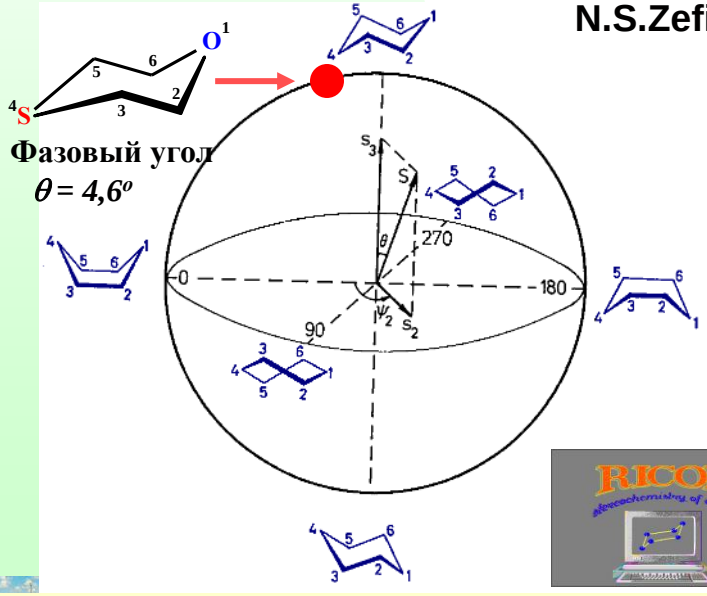


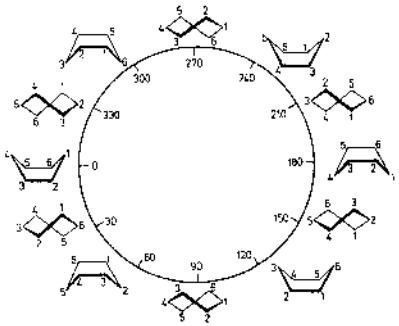
$\omega_2 = 47^o$ $\omega_1 = 56^o$ $C_3S_4C_5$ - flattened

Cremer-Pople approach: $C_6O_1C_2$ - flattened

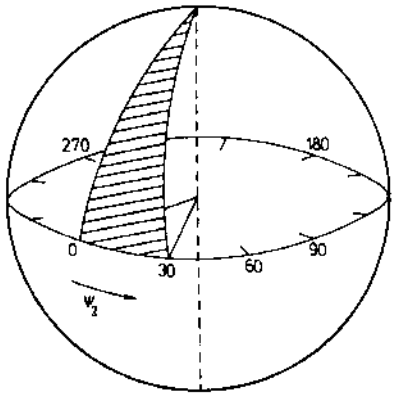
Zefirov-Palyulin approach – puckering parameters are based on (Sin φ/2)

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.





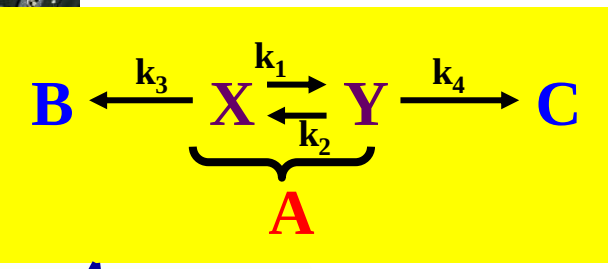
Equator of the sphere



Sphere in puckering coordinates

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

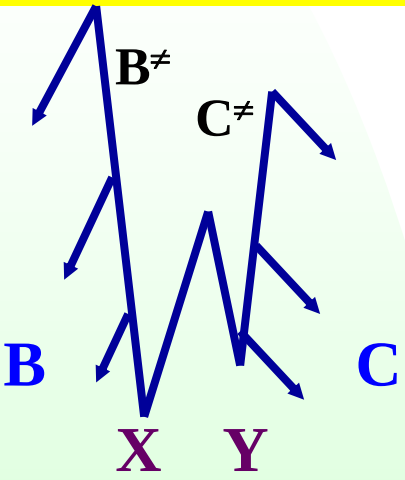
Stereochemistry and conformational analysis: reactions in conformationally mobile systems



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

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

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



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: $k_4, k_3 << k_1, k_2$ $\quad P_\infty = K_{eq}$

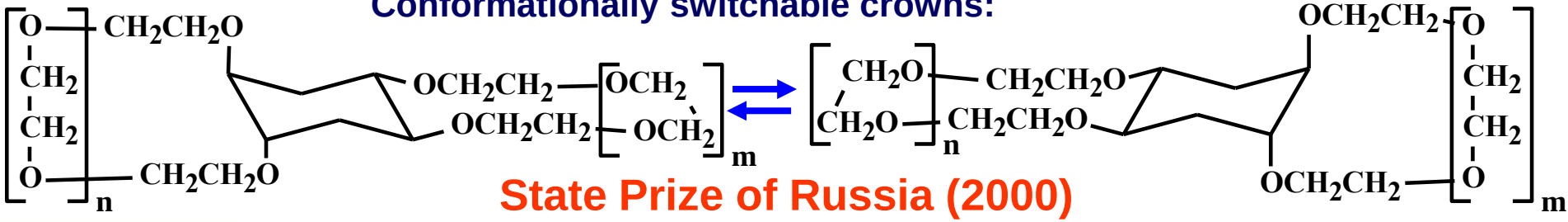
3. General case: any k_4, k_3, k_2, k_1 :

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

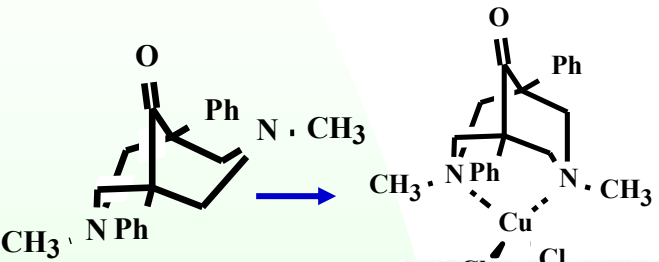
N.S.Zefirov, *Tetrahedron*, 1977, *33*, 2719; *Zh. Org. Chem.*, 1979, *15*, 1098;
J. Seeman, *Chem. Rev.*, 1983, *83*, 83.

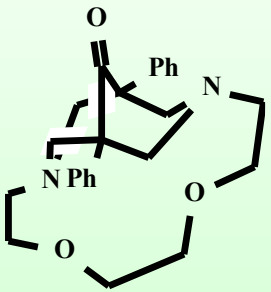
Stereochemistry and conformational analysis: crown-ethers and other ligands

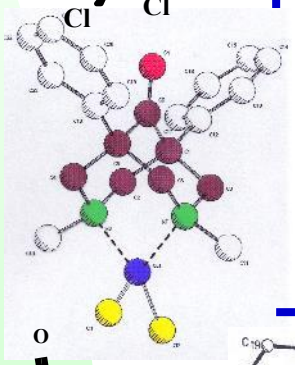
Conformationally switchable crowns:

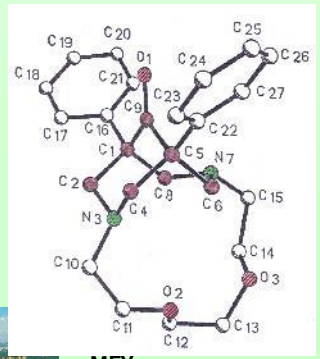


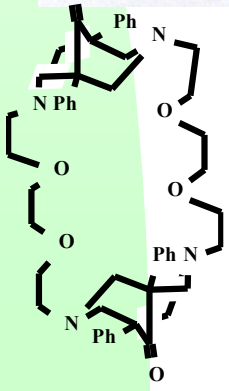
State Prize of Russia (2000)

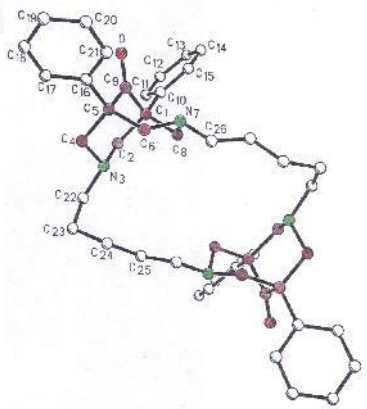






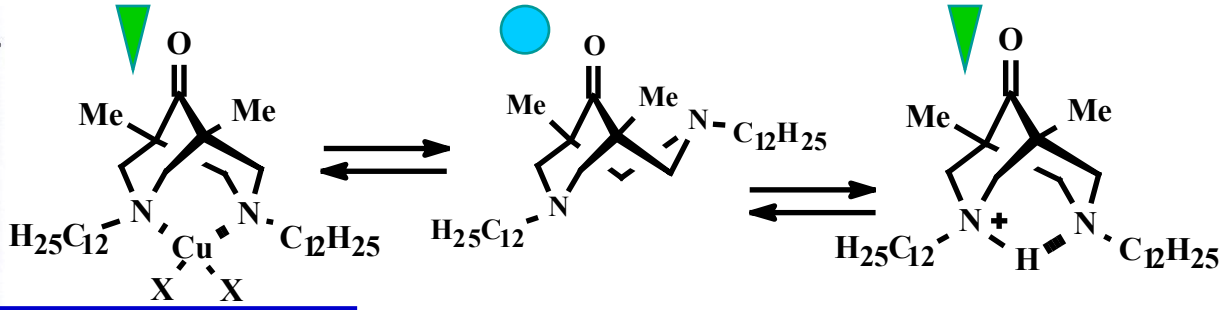


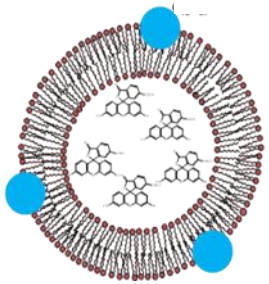


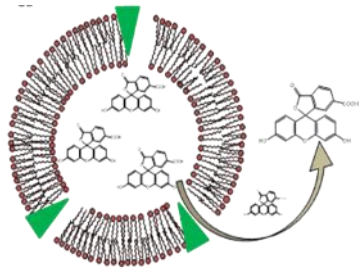


Creation of stimulus-sensitive liposomes based on substituted bispidinones for targeted delivery of biologically active substances

Veremeeva, Lapteva, Palyulin, Davydov, Sybachin, Yaroslavov







МГУ Химфак

ИФАВ РАН

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

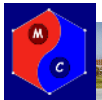
- **Creation of a "formal-logical approach" as a basis for (a) classification of organic reactions, (b) search for new reactions and reaction design, (c) non-empirical computer synthesis.**

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.**

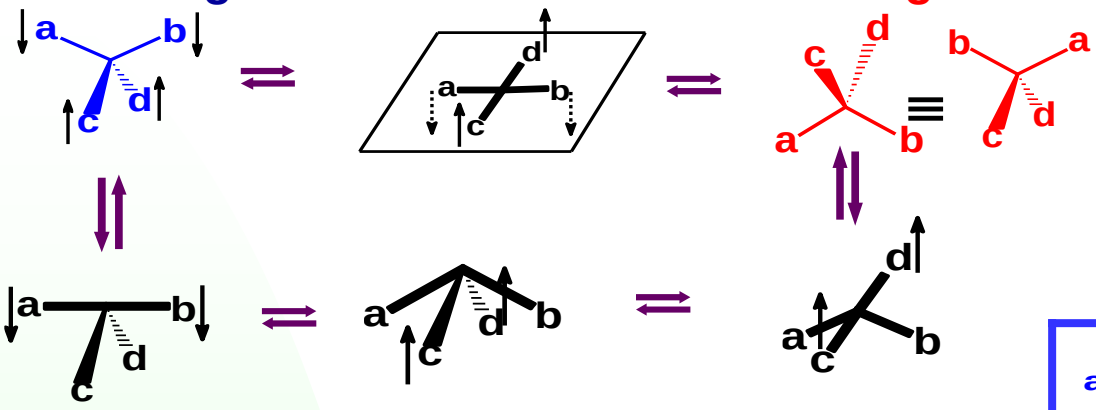
МГУ
Химфак

Member of International Academy of Mathematical Chemistry (IAMC).



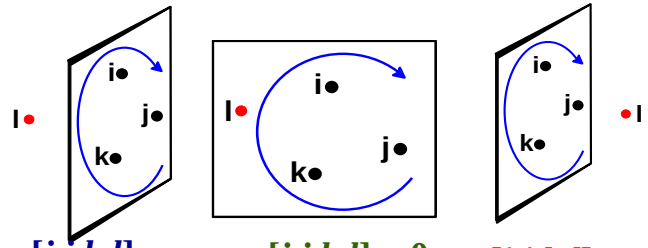
Mathematical Chemistry: An Algebraic Approach to the Concept of Configuration

R-configuration



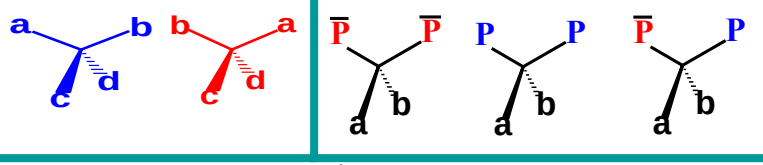
S-configuration

Point 3D configurations



$\psi[i,j,k,l] = -1$ $\psi[i,j,k,l] = 0$ $\psi[i,j,k,l] = +1$

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



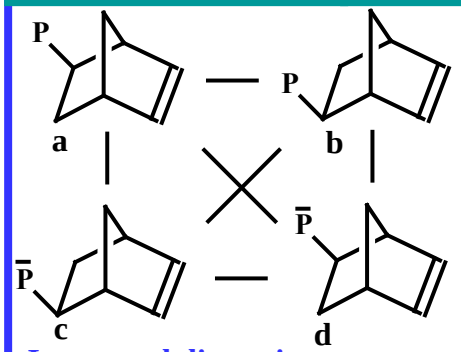
Algebraic criterion of chirality

For any function $\psi[i,j,k,l]$ there is a unique antipodal function ψ: $\psi[i,j,k,l] = -\psi[i,k,j,l]$. 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 ψ.

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



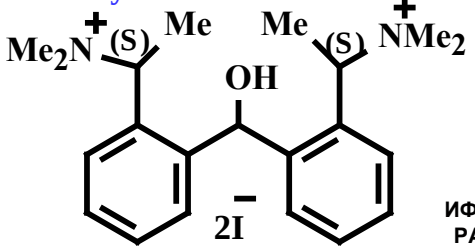
ab – enantiomers
cd – enantiomers

ad – holantiomers
bc – holantiomers

ac – nulantiomers
bd – nulantiomers

Integrated discussion on stereogenicity and chirality for restructuring stereochemistry

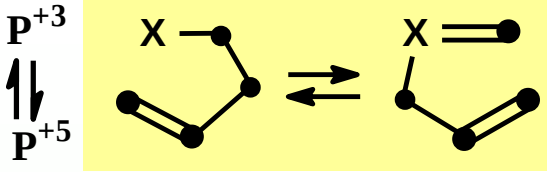
Holantio- and nulantio-RACEMATES: myth or reality?

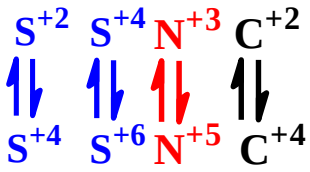


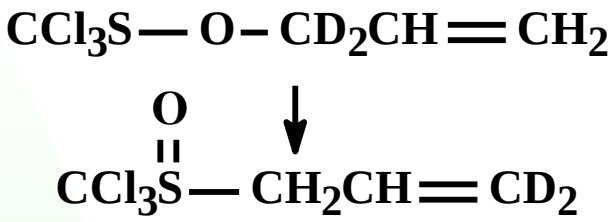
Mathematical and computational chemistry:

Formal-logical approach

Symbolic equation:

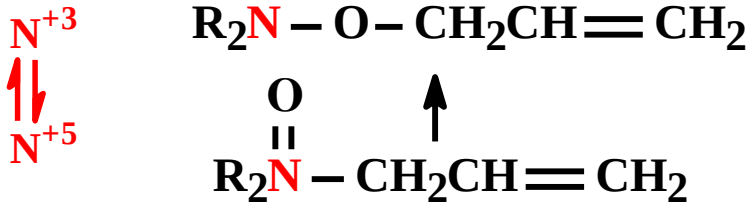


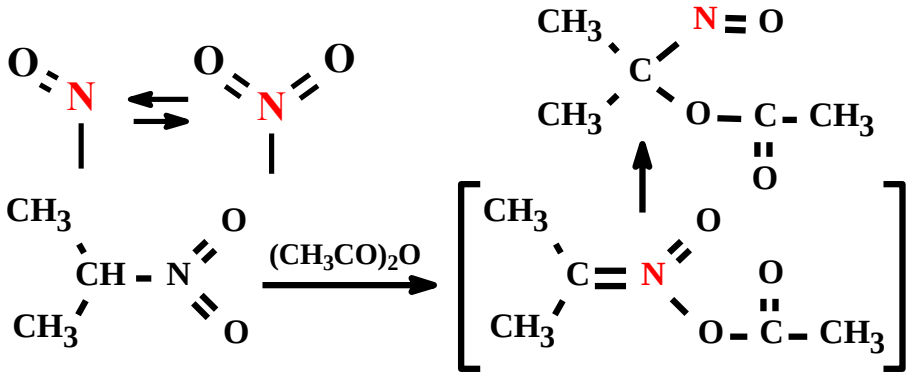




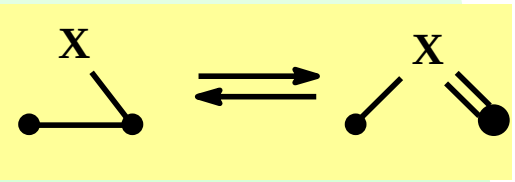
Mislow K. *JACS*, 90, 4861 (1968)
Braverman S. *Israel J.Chem.* 5,125(1967)
Zefirov N.S. et al. Vestn. MSU, 135 (1969);
Zh. Org.Chim., 7, 947 (1971).

Meisenheimer (1919)

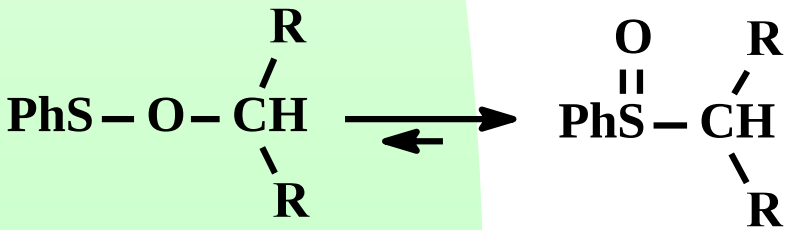




Zefirov N.S., et. al. Zh.Org.Khim., 38,1484 (2002)

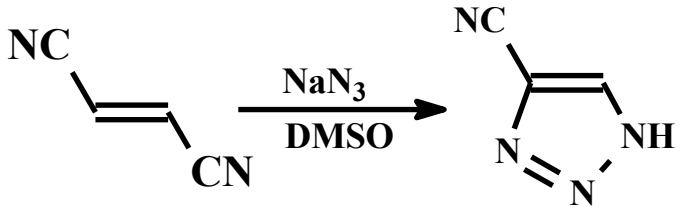


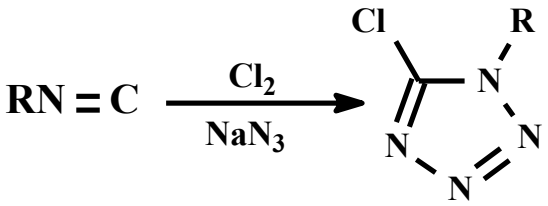
N.S. Zefirov et al.,
Zh.Org.Chim.,
8, 433 (1972)



R = Ph, cyclo-C_3H_5

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

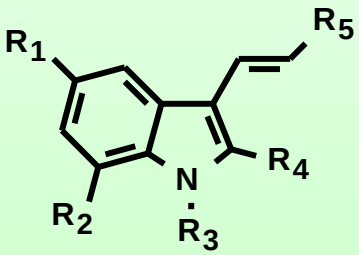
N.S.Zefirov, V.A.Palyulin et al., *J. Chem. Inf. Comput. Sci.*, 2002, *41*, 1112; Proc. RAS, 2003, 1005

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").

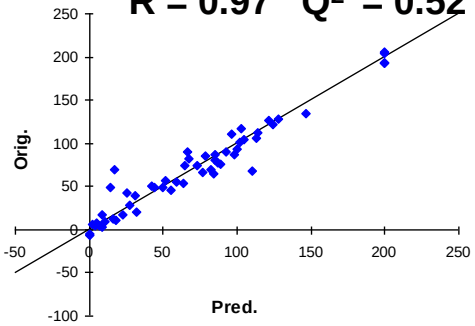
3. Neural networks and "support vector machines".

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

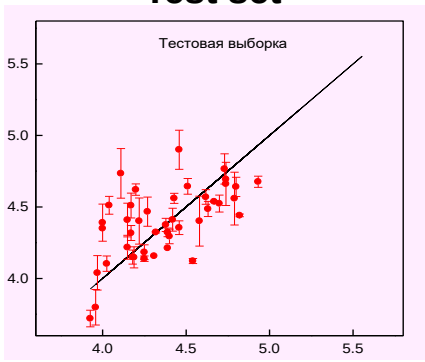


R = CH_3, Et
R_1 = Hal, CH_3, OCH_3
R_2 = CH_3, Et

Training set : 57 structures
R = 0.97 Q^2 = 0.52



Test set



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

K_1 – Ca^{2+} K_2 – Glu + Ca^{2+}
K_3 – test compound + Ca^{2+}
K_4 – test compound + Glu + Ca^{2+}

NT-1515

Bachurin, Tkachenko, Zefirov, Palyulin

МГУ Химфак

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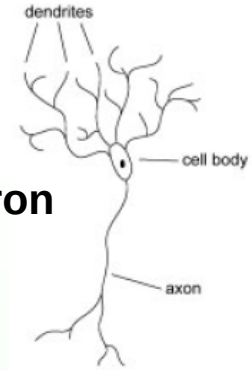
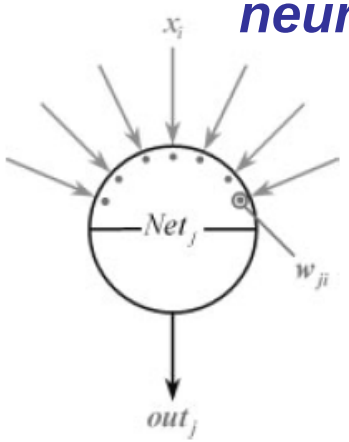
Mathematical and computational chemistry:
neural networks in chemistry

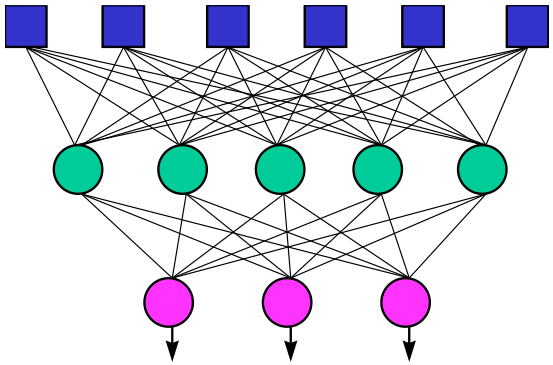
Neuron





Artificial neuron

Neural network with two layers of active neurons

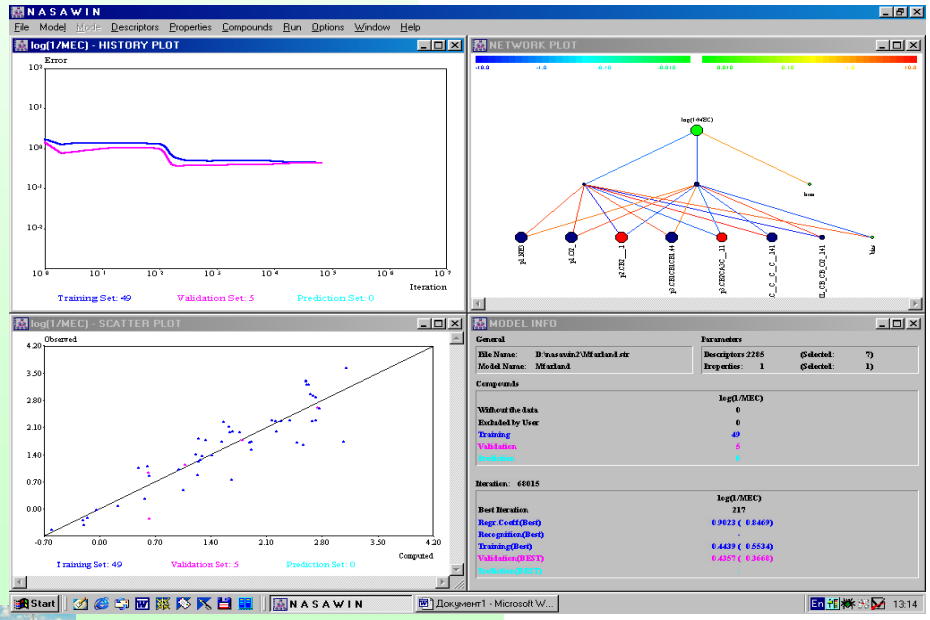


Input layer

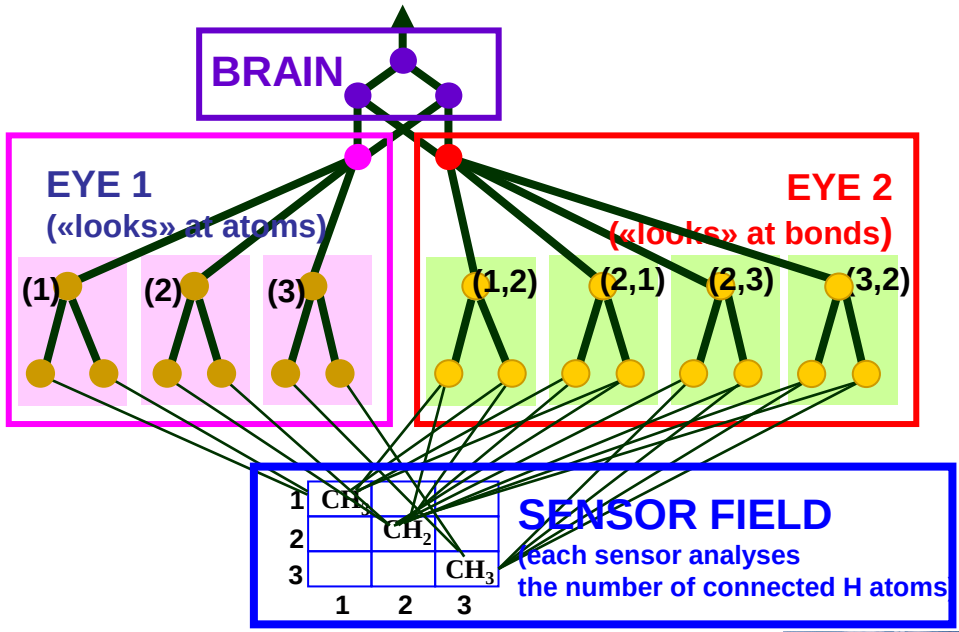
Hidden layer

Output layer

Software package NASAWIN:
anticoccidial activity of triazinediones



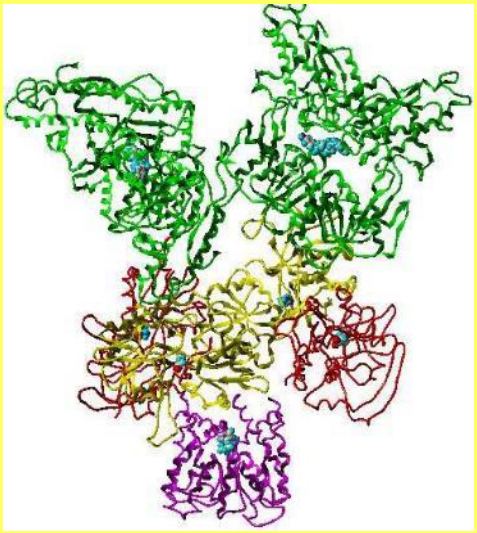
Architecture of neural device for direct QSAR (propane molecule is shown) :



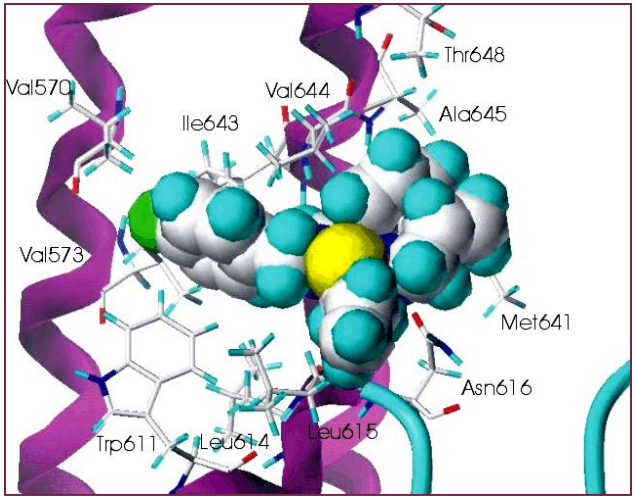
Baskin, I. I.; Palyulin, V. A.; Zefirov, N. S. et al., *J. Chem. Inf. Comput. Sci.*, 1997, *37*, 715; *SAR QSAR Env. Res.*, 2001, *12*, 401; 2002, *13*, 35; *Usp.Khim.*, 2003, *72*, 706.

Medicinal chemistry

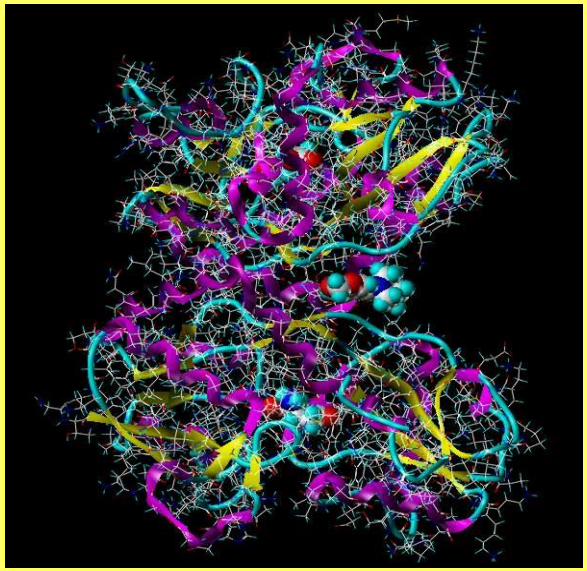
Hyperactivation of NMDA receptors leads to the development of neurotoxicity. Simultaneous blockade of NMDA receptors and activation of AMPA receptors. Molecular models of NMDA and AMPA receptors. Docking of NMDA receptor ion channel blockers and antagonists. Design of multitarget glutamatergic drugs.



Models of all domains of NMDA receptor



Virtual screening of databases (NMDA-receptor)

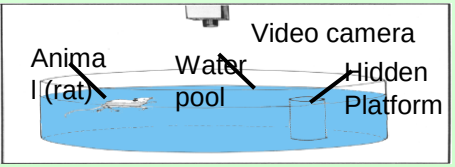


Model of the dimer of ligand-binding domain of AMPA receptor

Virtual screening of databases (AMPA-receptor)

Selected for synthesis and synthesized: 600

Preclinical trials - 6



Biotest

Dimebon - a new promising drug for the treatment of neurodegenerative diseases

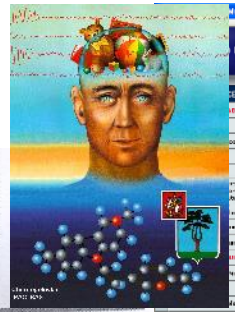
SF BUSINESS TIMES | JUNE 17-23, 2005 sanfrancisco.

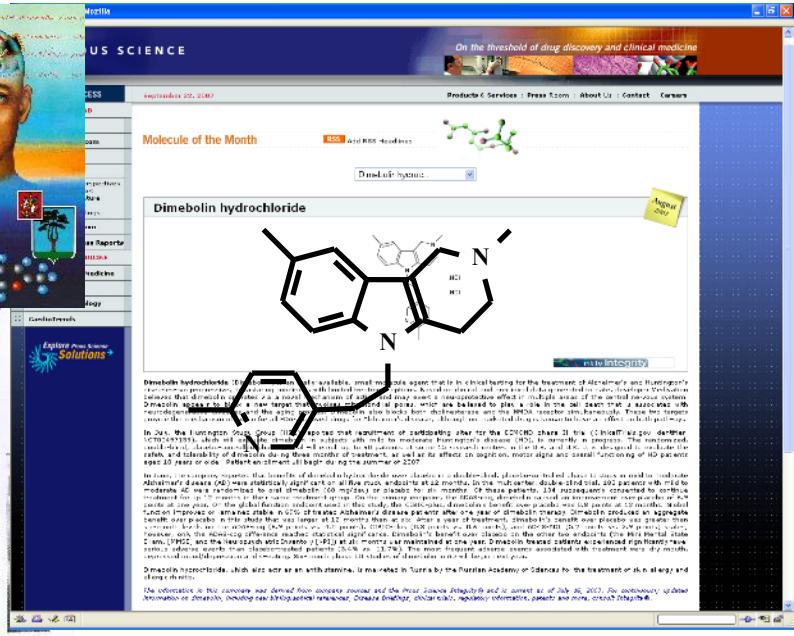
S.F. firm thinks Russian drug nothing to sneeze at

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 tha history in Russia as an antihista has indications that it might be tive new treatment for Alzheir ease. The company is launchi stage clinical trial in Russia to human proof-of-concept of Di





BC TV / FILM

The New York Times
nytimes.com
June 11, 2007
Antihistamine Shows Promis

OPINION
Boston Legal, Alzheimer's, and Dimebon

Russia in 1983, but a scientist
Dr. David T. Hung, an
and started Medivation in
led after the results from the
ptember.
mer's disease center at the
effect of Dimebon was "larger
medications and it persists

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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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BusinessWire
Medivation Provides Business Update; Alzheimer's Program on

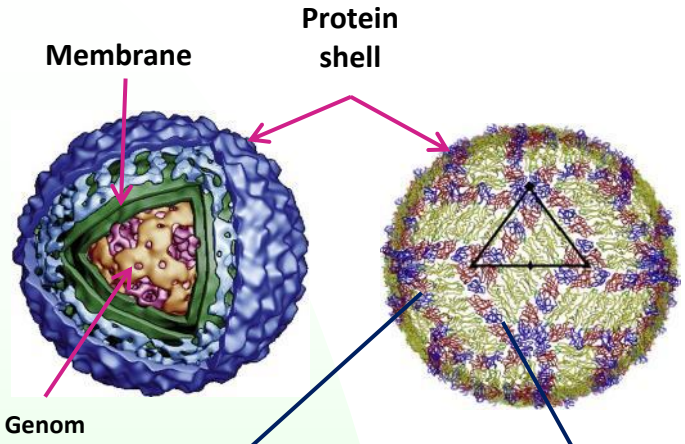
Medivation receives FDA clearance to begin trials of Dimebon against Huntington's disease.

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

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

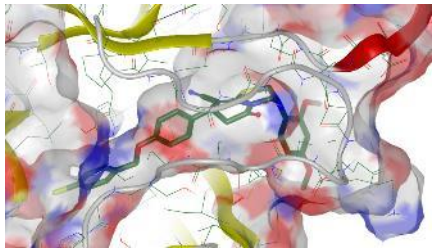
Palyulin, Osolodkin

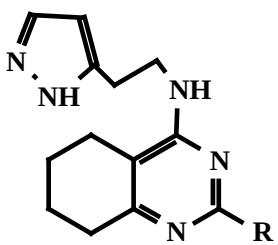
Kuznetsova, Averina, Sedenkova



Modeling (supercomputer) of spike formation blockers

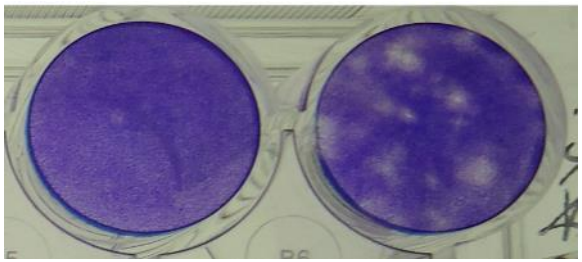
Virtual screening: 5886 compounds
Tested *in vitro:* 100 соединений
Active: 12 compounds

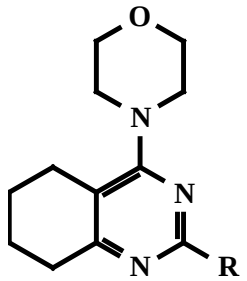


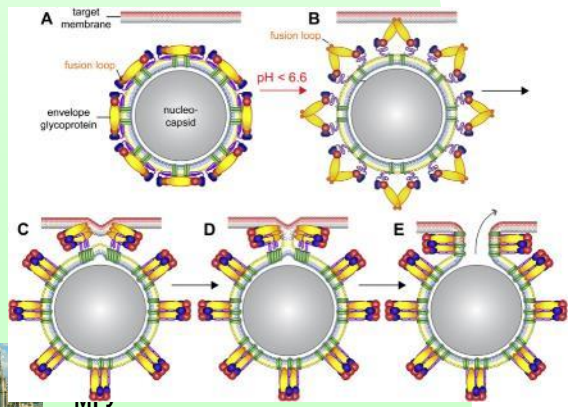


Inhibitor: cells are protected

Without inhibitor: no protection







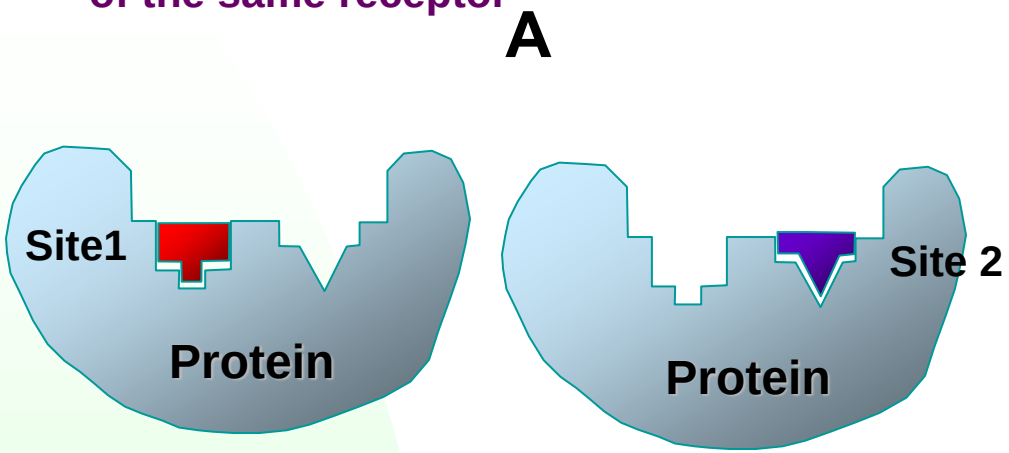
As a result of modeling and screening, inhibitors of tick-borne encephalitis virus fusion with cells with low cytotoxicity were found

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

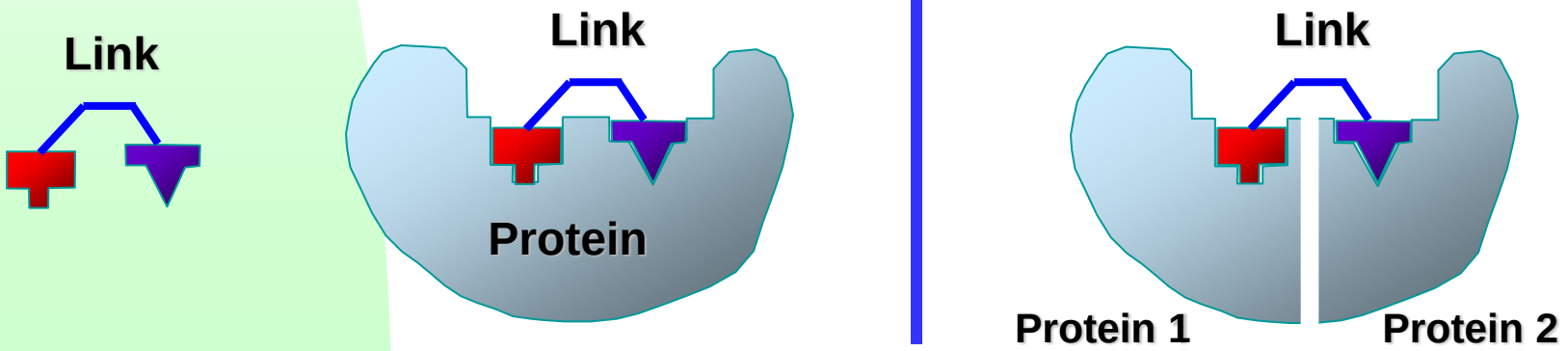
Bivalent drugs
(twin-drug)

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

(B) by different receptors

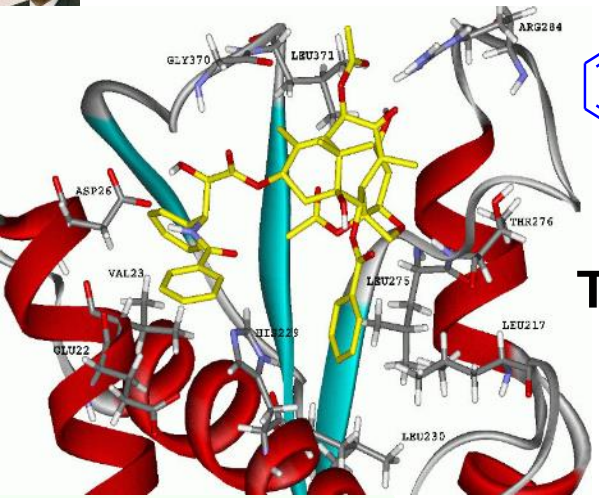


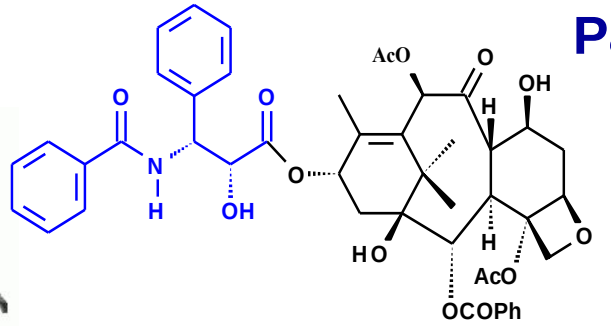
2. Connecting the fragments with a “linker”



Drug discovery, 3, 666 (2004); *Eur. J. Med. Chem*, 77, 422, (2014)

Tubulin – the target of taxol





Palitaxel (TAXOL)

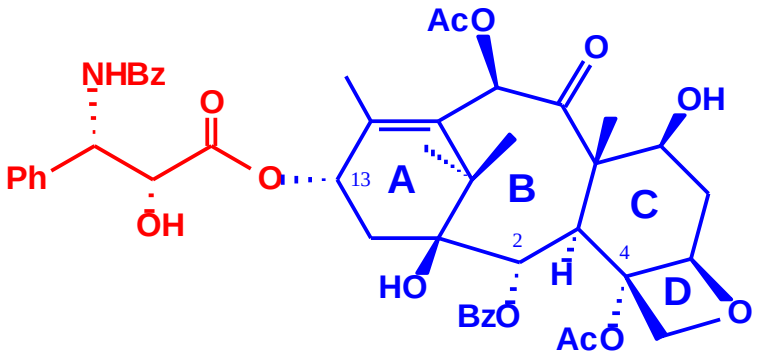
Anticancer drug

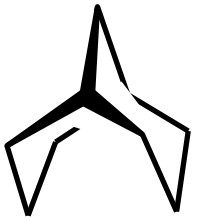
Annual sells: $ 1.6 billion

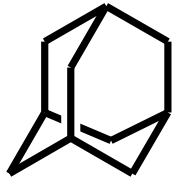
Taxol causes uncontrolled polymerization of tubulin and thus blocks mitosis.

The main idea: bioisosteric replacement of cage fragment

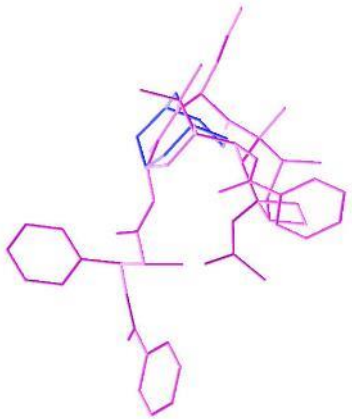
Retain amino acid — **Replace cage structure**

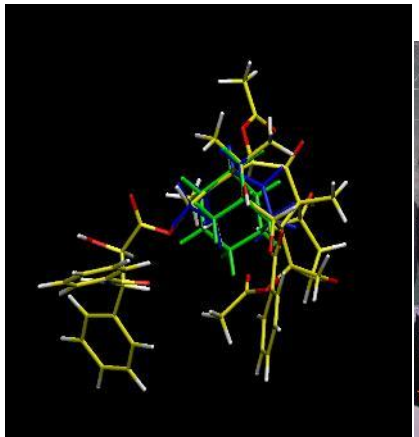






Prof. O.N. Zefirova



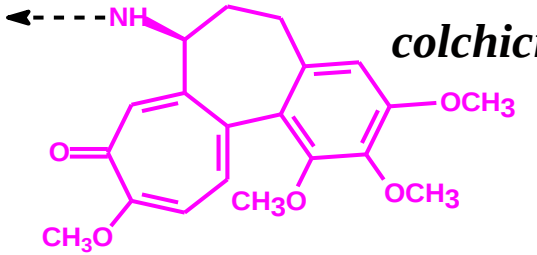


Dr. E.V.Nurieva

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

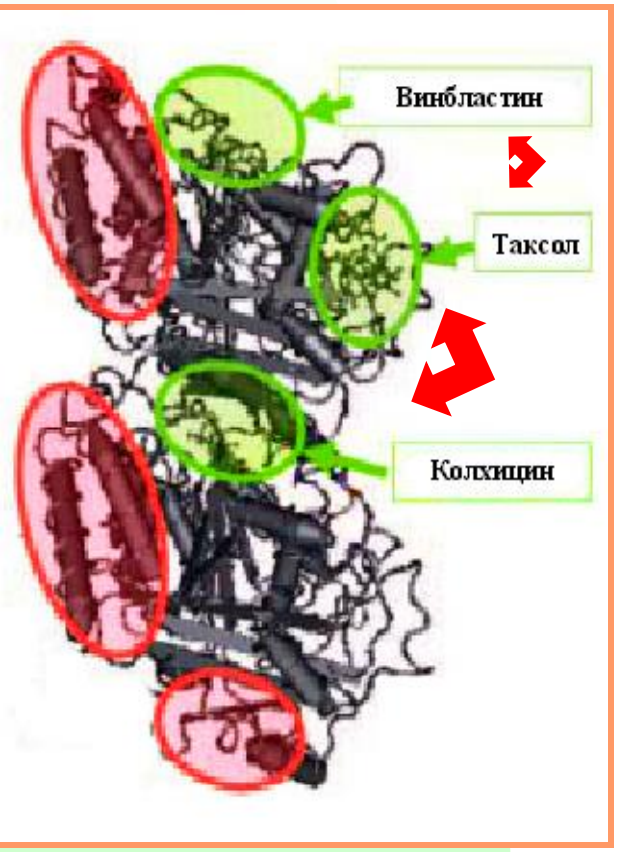
Development of “TUBULOCLASTINS” as “bivalent drugs” :

Simplified analog of taxol

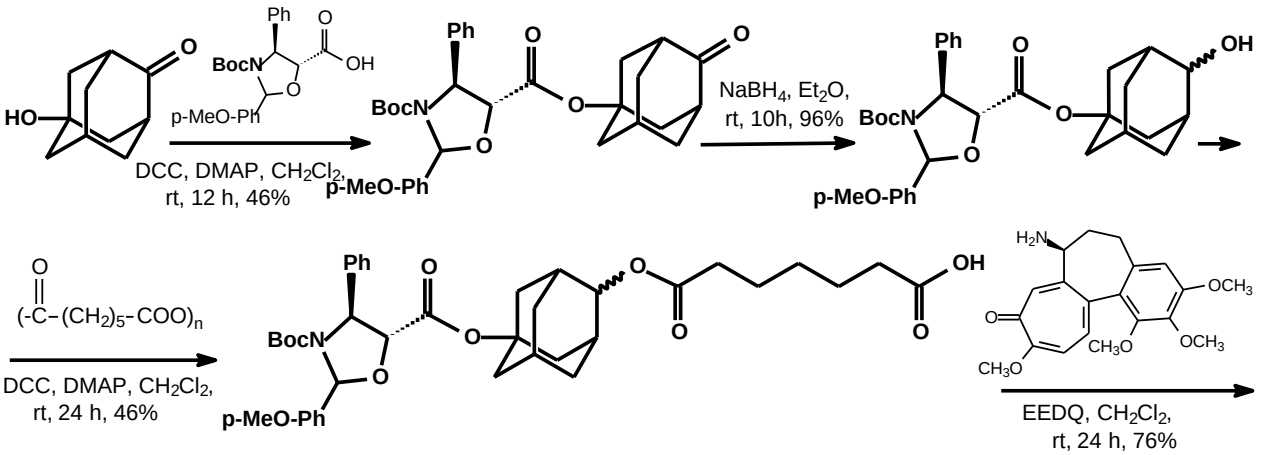


colchicine

Colchicum autumnale



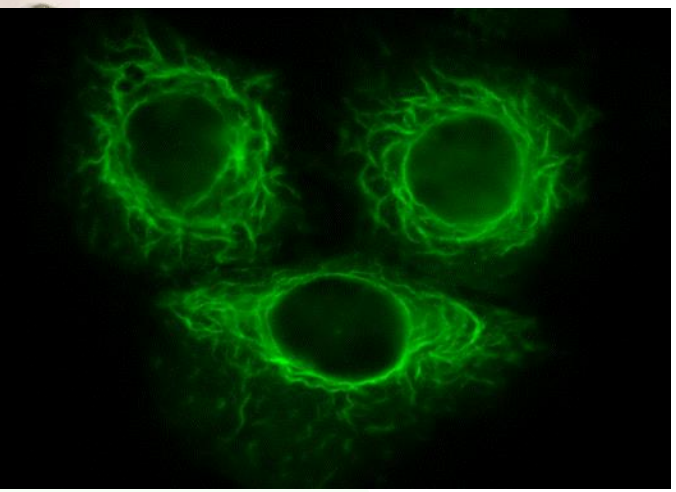
Scheme of synthesis:

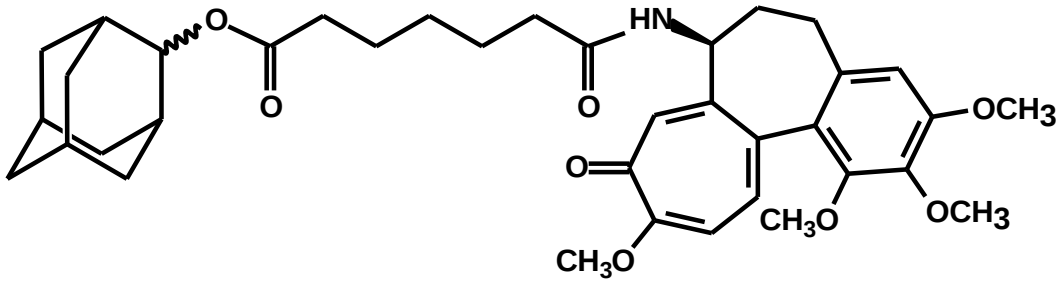


МГУ
Химфак

ИФАВ
РАН

“TUBULOCLASTIN “





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

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»).

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.*, *Biorg. Med. Chem.*, 2011, 19, 5529; *Chem. Biochem.*, 2013, 14, 1444.

OPTIMIZATION

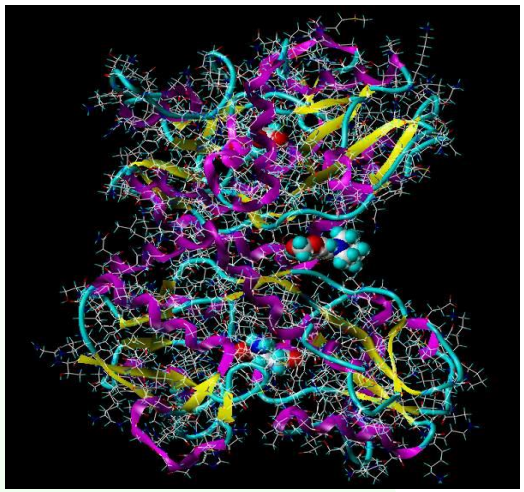
Replacement of colchicine with:
combretastatin
podophyllotoxin
methoxyestradiol
with variation of linker length.
Zefirova, Shishov, Zefirov N.A.

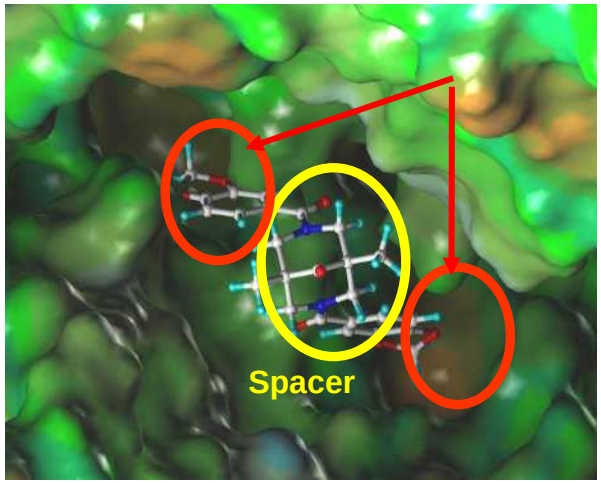
NEUROTROPIC ("MNEMOTROPIC") PROPERTIES OF BIVALENT LIGANDS OF AMPA RECEPTORS

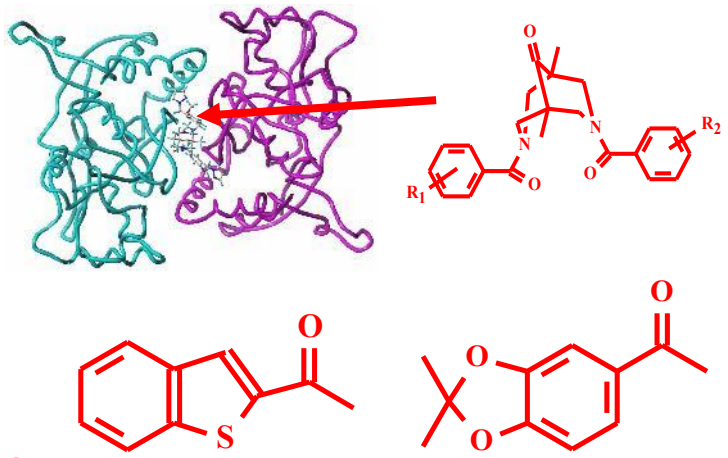
(MSU, IPAC RAS, Institute of normal physiology)

Palyulin, Lavrov

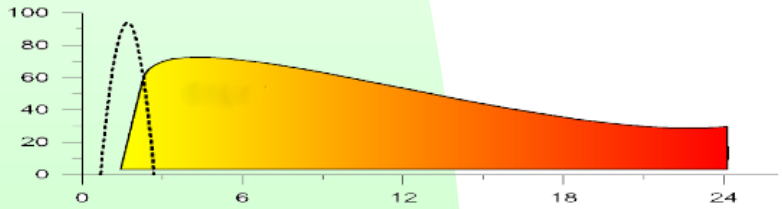
Novel positive AMPA receptor modulator OSPL-502 that improves cognitive functions and long-term memory is in preclinical trials

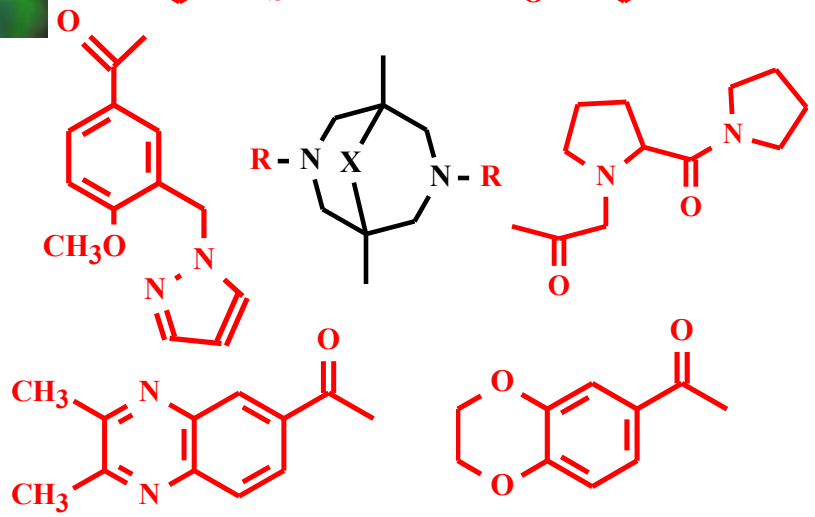






Using molecular modeling, large series of molecules that simultaneously bind to two AMPA receptor sites were designed and synthesized.





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.

Patents RU 2333211 and 2417082.

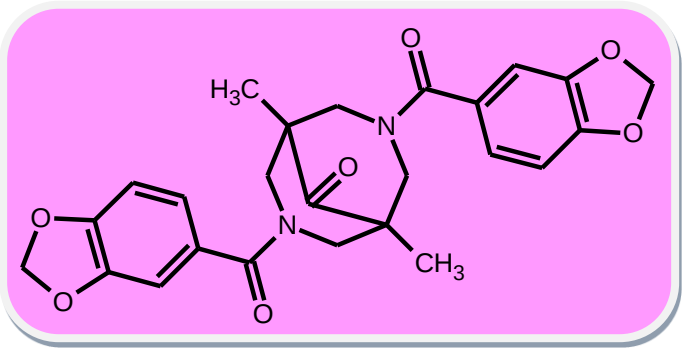
Preclinical studies of a drug for the treatment of Alzheimer's disease based on diazabicyclononane (“Cyclomemorin”)

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: 675 times the recommended human dose

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

Dosage form

Experiments on dogs

Scopolamine test: elimination of disturbances at a dose of 0.1 mg/kg

SINCERE GRATITUDE TO ALL CO-AUTHORS

THANK YOU
FOR YOUR ATTENTION

«...I like this work...»

Johann Joachim Becher, XVI century