

# OLEG A. RAEVSKY - SCIENTIST, TEACHER, PERSON



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Moscow, 2024

## The activity of a scientist



**Meeting of the International QSAR and Molecular Modeling Society Board, Boston (USA), August 1995.**

Left to right: Prof. King (USA), Prof. Charton (USA), Dr. Magi (USA), Prof. Raevsky (Russia), Prof. Block (USA).

# The activity of a scientist



## Meeting on the Rhine (July 1993).

Seminar on Hydrogen Bonding. Left to right: Prof. Lawrence (France), Prof. Kerry (USA), Prof. Schneider (Germany), Prof. Abraham (UK), Prof. Raevsky (Russia).

# The activity of a scientist



**Final meeting of project leaders and collaborators of the International Science and Technology Center project, Liverpool, England, August 2010.**

Standing left to right: Dr. A. Worth (Joint Research Center of the European Union, Italy), Prof. J.C. Dearden (John Moores University, Liverpool), and Prof. V.V. Poroikov (Institute of Biomedical Chemistry, Moscow).

## Foreign colleagues/co-authors

- Prof. Dr. H.-J. Schneider, University of Saarbrucken, Germany
- Dr. K.-J. Shaper, Research Center Borstel, Germany
- Prof. Dr. J.R. Chretien, University of Orleans, France
- Dr. H. Van de Waterbeemd, F. Hoffmann-La Roche Ltd, Switzerland
- Prof. Dr. J.C. Dearden, University John Moore, Liverpool, England
- Dr. J. McFarland, Pfizer, Groton, USA
- Dr. E.E. Weber Environmental Protection Agency (EPA), USA
- Prof. Dr. R. Mannhold, University of Dussedorf, Germany
- Dr. A. Worth, EU Joint Research Centre, Ispra, Italy

# Education. The beginning of scientific work.



School, 1947-1957

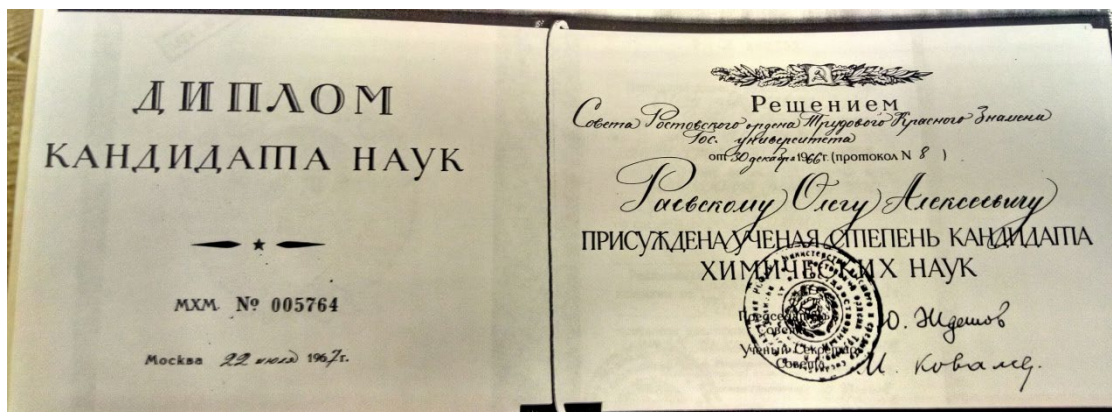


Rostov State  
University,  
1957-1962

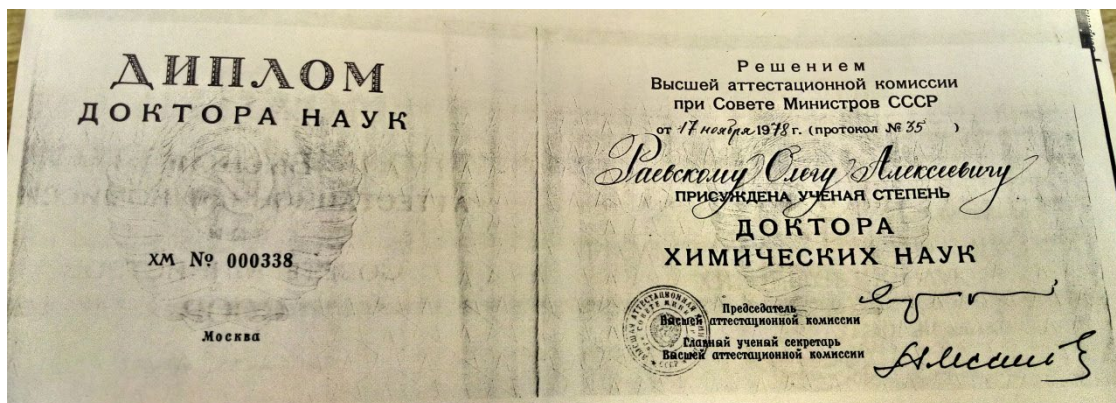


Institute of Organic and Physical Chemistry, 1962-1979

# Education



PhD thesis (1966): "Physicochemical properties and structure of semithiosemicarbazones"



Doctoral dissertation (1978): "Spatial structure and intramolecular interactions in a series of acyclic organophosphorus compounds".

# Work



Laboratory of Physico-Chemical Research (1983)



Department of Computer Aided Molecular Design (1991)



Department of Computer Aided Molecular Design (2015)



Deputy Director of the IPAS RAS for research(2006)



# Work

Research interests:

- Physical chemistry
- Spectroscopy
- Molecular modeling
- Study of the structure-property relationship
- Design and computer search for new physiologically active compounds
- Development of computer programs and creation of databases

# Parameterization of H-bond (database)

File Edit Search View Tools Combinatorial libraries Diversity Drug-likeness Process structures Spectra Window Help

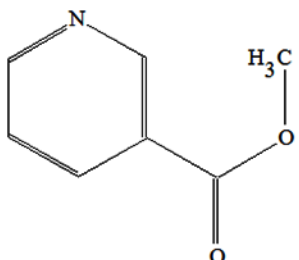
Hydrogen Bond thermodynamic  
E-mail: raevsky@ipac.ac.ru

1 Update Form SingleP Table Default Zoom 100 200

Logical No.	Mar	Solvent	Name H-bond d	CAS ID H-bond	Name H-bond
0000001		CCl4	PHENOL	93-60-7	METHYL EST

All data |

**Acceptor**



Molecular weight acceptor: 137.14

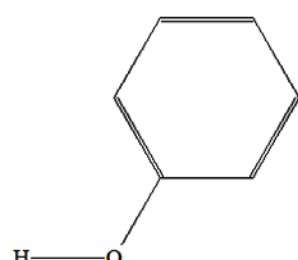
Brutto-formula acceptor: C<sub>7</sub>H<sub>7</sub>NO<sub>2</sub>

CAS ID H-bond acceptor: 93-60-7

ID: 1

Name H-bond acceptor: METHYL ESTER 3-PYRIDINECARBOXYLIC ACID

**Donor**



Molecular weight donor: 94.11

Brutto-Formula donor: C<sub>6</sub>H<sub>6</sub>O

CAS ID H-bond donor: 108-95-2

Solvent: CCl<sub>4</sub>

Name H-bond donor: PHENOL

-Delta G	Method G	-Delta H	Method H	Complex D/A	Shift IR	Shift NMR	H-bond	Temperature	TYPE
7.92	IR	19.10	IR	1:1			1	298.15	OH...N

Authors	Source	Volume	Number	Year	Page
Szemik A., Zeegers-Huyskens Th.	J. Mol. Struct.	117		1984	265-273

Assignment	Comment
1	

# Parameterization of H-bond (model/scale)

Database : (CCl<sub>4</sub>; 1:1; 163 H-donor; 195 H-acceptors; N=936)

Additive-multiplicative model:

$E_a$  – enthalpy H-acceptor descriptor

$E_d$  – enthalpy H-donor descriptor

$C_a$  – free energy H-acceptor descriptor

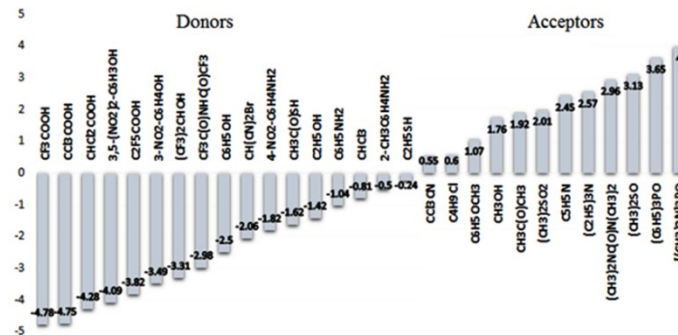
$C_d$  – free energy H-donor descriptor

Standard H-donor: phenol ( $E_d=-2.50$ ;  $C_d=-2.50$ )

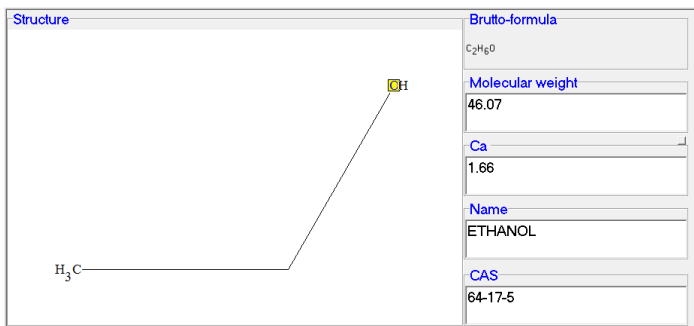
Standard H-acceptor : HMPA ( $E_a=2.50$ ;  $C_a=4.00$ )

$$\Delta H(\text{kJ/mol}) = k_1 * E_a E_d + k_2; \quad k_1=4.96; k_2=0.00$$

$$\Delta G(\text{kJ/mol}) = k_3 * E_a E_d + k_4; \quad k_3=2.43; k_4=5.70$$



# Parameterization of H-bond (HBPLUS)



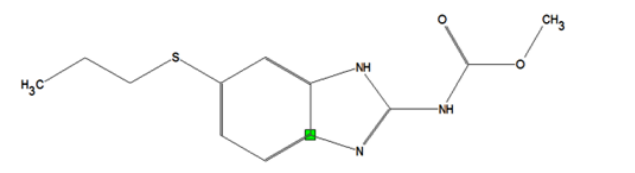
HBPlus

Stay on top

New...

	Alpha	28.77	maxEa	1.77	Sum(Ead)	10.63	Sum(Cd)JA	-0.141
	max(Q-)	-0.30	maxCa	1.80	Sum(Ca)	4.93	Sum(Cad)JA	0.313
	max(Q+)	0.34	maxEd	-1.83	Sum(Cd)	-4.06		
	Sum(Q-)	-1.33	maxCd	-2.06	Sum(Cad)	9.00		
	Sum(Q+)	1.33	maxEa*maxEd	-3.23	Sum(Ea)JA	0.251		
	Sum(QI)	2.67	maxCa*maxCd	-3.71	Sum(Ed)JA	-0.118		
	Sum(Q-)JA	-0.046	Sum(Ea)	7.23	Sum(Ead)JA	0.369		
	Sum(Q+)JA	0.046	Sum(Ed)	-3.40	Sum(Ca)JA	0.171		

Polarizability	Char...	E	C
1.90	0.02	0.09	0.06
1.95	-0.08	0.09	0.06
1.90	0.02	0.09	0.06
1.95	0.00	0.06	0.05
1.95	-0.07	0.06	0.05
1.95	-0.00	0.09	0.06
1.09	-0.15	1.69	0.70
1.95	0.29		
1.05	-0.10	1.75	1.30
1.09	-0.26	0.21	0.22
1.95	0.34		
0.27	-0.30	0.18	0.18
0.64	-0.16	1.77	1.80
1.06	0.03		
2.70	-0.01	1.10	0.41
1.06	-0.06		
1.06	-0.07		
1.06	-0.07		
0.99	0.04		
0.99	0.04		
0.99	0.05		
0.99	0.05		
0.99	0.09	-1.57	-2.06
0.99	0.10	-1.88	-2.00
0.99	0.05		
0.99	0.04		
0.99	0.03		
0.99	0.03		
0.99	0.08		



Local Descriptors

$$C_D^{\max}$$

$$E_D^{\max}$$

$$C_A^{\max}$$

$$C_D^i E_D^i C_A^i E_A^i$$

Molecular Descriptors

$$\sum C_D$$

$$\sum E_D$$

$$\sum C_A$$

$$\sum C_A + \sum C_D$$

Composed Descriptors

$$\sum C_D / MW$$

$$\sum E_D / MW$$

$$\sum C_A / MW$$

$$(\sum C_A + \sum C_D) / MW$$

# Parameterization of H-bond (QSAR)

## Water solubility:

$$\log S = 0.43(\pm 0.12) - 0.298(\pm 0.009)\alpha + 1.09(\pm 0.05)\Sigma C_a - 0.30(\pm 0.05)\Sigma C_d$$

$n=630; r^2=0.90; s=0.54$

## Acute toxicity (*Guppy*):

$$\log LC_{50} = 5.14(\pm 0.12) - 0.259(\pm 0.008)\alpha + 0.79(\pm 0.03)\Sigma C_a$$

$n=90; r^2=0.95; s=0.32$

## Blood-brain barrier penetration:

RF\_cv:  $n=1000; SN=0.824; SP=0.756; ACC=0.790$

RF\_test:  $n=100; SN=0.940; SP=0.700; ACC=0.820$

# Computer programs

**HBPLUS** (Hydrogen Bond PLUS): 2D H-bond descriptors

**DNESTR** (Design New Effective STRuctures): 2D molecular descriptors

**MOLTRA** (MOLEcular TRansform Analysis): 3D H-bond descriptors

**SLIPPER** (Solubility LIPOphilicity, PERmeability): solubility, lipophilicity, permeability

**MOLDIVS** (MOLEcular DIVersity and Similarity): molecular similarity and diversity

**DISCON** (DISsociation CONstants): pKa

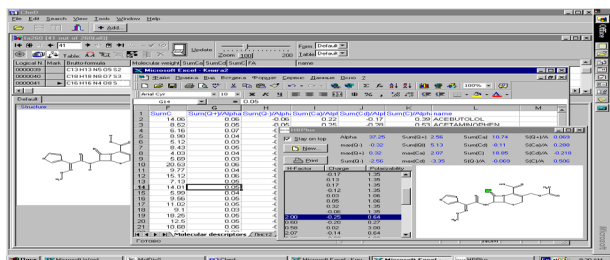
**AMP** (Arithmetic Mean Property)

**LOREP** (LOcal REgression Property)

**SOCR** (Super Overlapping Cluster Regression)

# HYBOT (HYdrogen BOND Thermodynamics)

*Complete description of hydrogen bonding for QSAR, Molecular Modelling and Drug Design on your desk!*

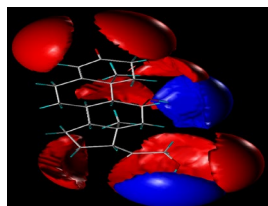
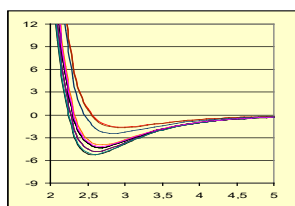


Program package HYBOT under Windows, UNIX, LINUX contains vast databases of thermodynamics parameters of H-bonding (15000 complexes), enthalpy and free energy factors (34000), the program for calculation of enthalpy and free energy of H-bonding as well as 16 two and 10 three dimensional original descriptor.

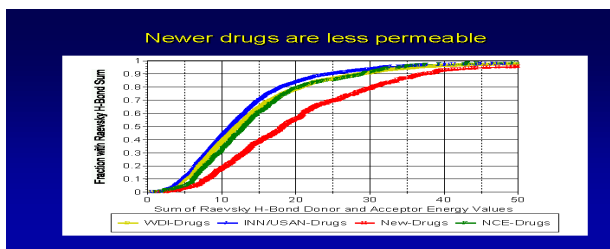
The screenshot shows the output window of the HYBOT program. It displays a table with 11 rows of data. The columns are labeled with various descriptors and their corresponding values.

File	ESR	View	Info	Graph	Options	QSAR
1. Cd-00000001	3. Alpha	10.71	4. maxCd*	0.92	5. maxCd*	6. maxCd*
2. Cd-00000002		12.54		1.09		
3. Cd-00000003		12.64		0.85		
4. Cd-00000004		12.92		0.95		
5. Cd-00000005		12.54		1.02		
6. Cd-00000006		10.62		0.79		
7. Cd-00000007		12.94		0.94		
8. Cd-00000008		13.33		0.70		
9. Cd-00000009		10.96		0.93		
10. Cd-00000010		12.26		0.69		
11. Cd-00000011		12.64		1.10		

«Calculation of many different descriptors is possible using a range of commercially available software packages, such as Sybyl, Cerius2, Tsar, Malconn-Z, HYBOT etc.» (H. Waterbeemd, D.S. Smith, K. Beaumont, D.K. Walker. *J. Med. Chem.*, 44, 1313-1333 (2001)).



«We have used ABSOLV and three other commercial software packages (HYBOT-PLUS, Molecular modeling Pro and QsarIS) that calculate descriptors of similar classes, to model partitioning in the four solvent-water systems. Overall, HYBOT-PLUS gave the best results.» (J.C. Dearden, D. Bentley. *SAR QSAR Environ Res.*, 13, 185–197 (2002)).



C.A. Lipinski (Pfizer, Groton, USA) used the HYBOT descriptor  $\Sigma C_{ad}$  as global measure of permeability for analysis of four data bases (WDI, INN/USAN0DRUGS, NSE DRUGS and New Drugs) and estimated that the “newer drugs are less permeable”. This declaration had essential influence on Drug Development projects of not only this company but also many others.

# Database of the Institute of Physiologically Active Compounds (IPAC) of the Russian Academy of Sciences

File Edit Search View Tools Window Help

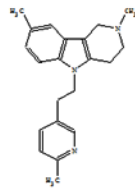
+ Add... WEB

235 Update Form 43 Table 43 Zoom 100 200

Logical No.	Mat	Code
0000235		dimebon
0000236		CA-7502 TT-2128
0000237		FC-2974

Common | AChE BChE CE | NMDAR MK-801 Ifenprodil | Mitochondrial membrane | Mitochondrial pore | Tubuline | SH-SY5Y | PI displacement | ABTS activity | ORAC

Structure



Brutto-f. Molecul. Code Chemist

Soluble Melting I

Comments

IC50(1)n IC50(2)n IC50(3)n IC50(4)n

IC50(5)n Tubuline

IC50(10) IC50(11)

Ligand\_Name

Test(1)	Target(1)	Source	Organism(1)	IC50 mkM(1)	Inhibition percentage(1)
Test(2)	Target(2)	Source	Organism(2)	IC50 mkM(2)	Inhibition percentage(2)
Test(3)	Target(3)	Source	Organism(3)	IC50 mkM(3)	Inhibition percentage(3)
Test(4)	Target(4)	Source	Organism(4)	IC50 mkM(4)	Blockage percentage(4)
Test(5)	Target(5)	Source	Organism(5)	IC50 mkM(5)	Blockage percentage(5)
Test(6)	Target(6)	Source	Organism(6)		Denolization
Test(7)	Target(7)	Source	Organism(7)		lnMPT
Test(8)	Target(8)	Source	Organism(8)		Tubuline Polymerization
Test(9)	Target(9)	Source	Organism(9)	IC100 mkM(9)	Concentration mkM(9)   Glutam
Test(10)	Target(10)	Source	Organism(10)	IC50 mkM(10)	Displacement(1) percentage   Concentration(1) mkM
Test(11)	Target(11)	IC50 mkM(11)	Quench(1) percentage(1)	Concentration(1) mkM(11)	Quench(2) perc
Test(12)	Target(12)				Trolox equivalent(12)



## Database of IPAC RAS (tests)

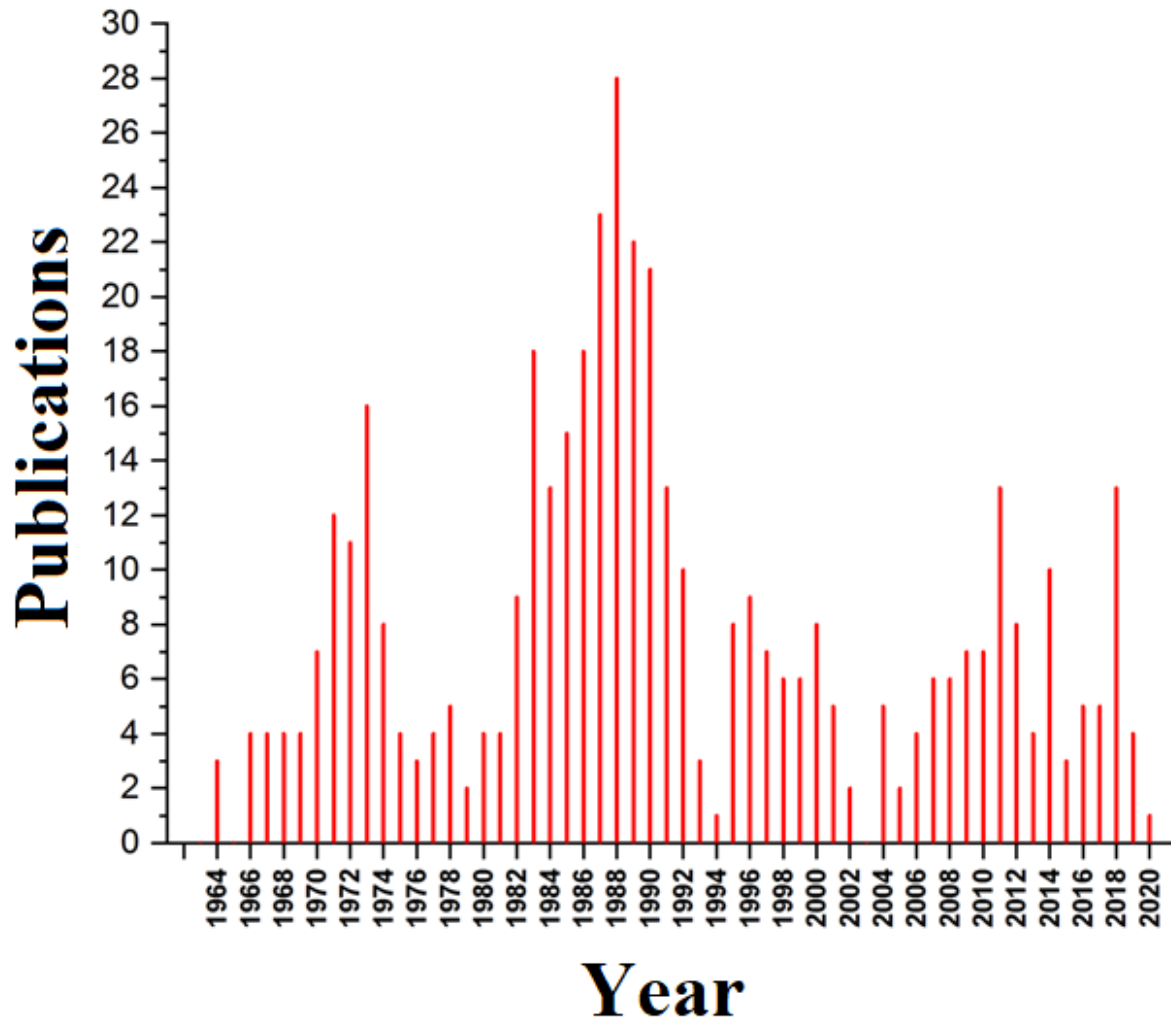
- acetylcholinesterase (AChE) inhibition
- butyrylcholinesterase (BChE) inhibition
- carboxylesterase (CE) inhibition
- N-methyl-D-aspartate (NMDA) receptor blockade, [3H]MK-801 binding site
- NMDA receptor blockade, [3H]ifenprodil binding site
- mitochondrial potential
- effect on opening of non-specific mitochondrial pore MPT (Mitochondrial permeability transition)
- tubulin polymerization
- cytotoxicity and protection from glutamate-induced toxicity
- inhibition of AChE-induced beta-amyloid aggregation
- antioxidant activity, ABTS test
- antioxidant activity, ORAC test

# Publication activity (Russian Science Citation Index)

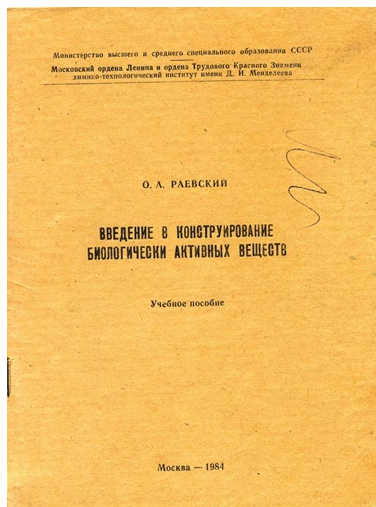
Number of publications : 454 (1964-2020)

Number of citations : 4687

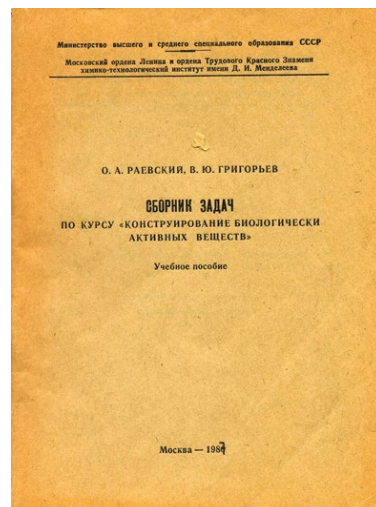
*h-index* : 27



# Publication activity



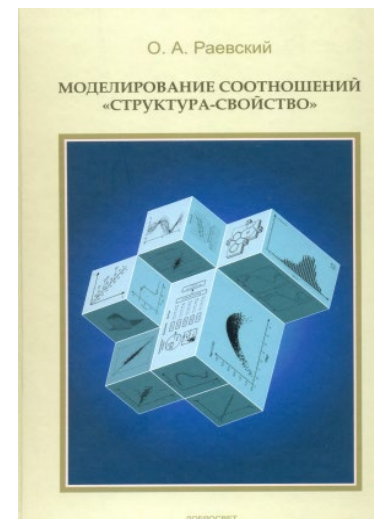
1984



1987



2013



2015

# Most cited works (Russian Science Citation Index)

1. Van De Waterbeemd H., Camenisch G., Folkers G., Chretien J.R., Raevsky O.A. ESTIMATION OF BLOOD-BRAIN BARRIER CROSSING OF DRUGS USING MOLECULAR SIZE AND SHAPE, AND H-BONDING DESCRIPTORS // J. Drug Target. 1998. Vol. 6. P. 151-165.
2. Van Waterbeemd H.D., Camenisch G., Folkers G., Raevsky O.A. ESTIMATION OF CACO-2 CELL PERMEABILITY USING CALCULATED MOLECULAR DESCRIPTORS // Quant. Struct.-Act. Relat. 1996. Vol. 15. P. 480-490.
3. Raevsky O.A., Grigor'ev V., Kireev D., Zefirov N. COMPLETE THERMODYNAMIC DESCRIPTION OF H-BONDING IN THE FRAMEWORK OF MULTIPLICATIVE APPROACH // Quant. Struct. –Act. Relat. 1992. Vol. 11. P. 49-63.
4. Raevsky O.A. MOLECULAR STRUCTURE DESCRIPTORS IN THE COMPUTER-AIDED DESIGN OF BIOLOGICALLY ACTIVE COMPOUNDS // Russ. Chem. Rev. 1999. Vol. 68. P. 505-524.
5. McFarland J.W., Avdeef A., Berger C.M., Raevsky O.A. ESTIMATING THE WATER SOLUBILITIES OF CRYSTALLINE COMPOUNDS FROM THEIR CHEMICAL STRUCTURES ALONE // J. Chem. Inf. Comput. Sci. 2001. Vol. 41. P. 1355-1359.

Selected works of O.A. Raevsky in the field of computer molecular design in Russian can be downloaded from the link :

<https://new.ras.ru/upload/iblock/e23/ss3xm4zb5kbnioockwj3z72smie071j0.pdf?ysclid=m0f1jizolk18528432>

# The Laboratory of Quantitative Structure-Activity Relationships (QSAR)

Main research areas:

- experimental study of the physicochemical properties of physiologically active compounds
- study of the relationship between the structure and biological activity of chemical compounds based on machine learning
- creation of new approaches to studying the “structure – property” relationship using fractal geometry and nonlinear dynamics methods

# Interests, hobbies, travels



Chernogolovka, 2007



New York, 1995



Venice, 2007



Chernogolovka, 1991

Uglich, 1997



**Thank you for your attention!**