CALIXARENES
WITH BIO-MEDICAL POTENTIAL

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http://www.ioch.kiev.ua/calix

International Workshop
"Medical and Biological Aspects of Supramolecular Chemistry"
Katsiveli, 22 - 25 September 2009

Institute of Organic Chemistry
National Academy of Sciences of Ukraine

PERSONNEL

- Doctors of Scienses 20
- Candidates od Sciences 85
- Engineers 95
- Technicians and Workers 120

SCIENTIFIC DERARTMENTS

1. Organophosphorus Compounds
2. Heteroatom Chemistry
3. Colour and Structure of Organic Compounds
4. Mechanisms of Organic Reactions
5. Chemistry of Phosphoranes
6. Chemistry of Bio-active Compounds
7. Physico-chemical Investigations
8. Chemistry of Organo-fluorine Compounds
9. Chemistry of Organo-sulfur Compounds
10. Bio-medical Investigations

EXPERIMENTAL PLANT

Institute of Organic Chemistry
National Academy of Sciences of Ukraine

AREAS OF BASIC RESEARCH

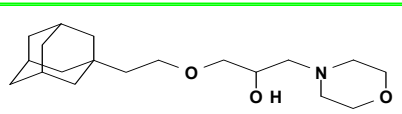
- fine organic synthesis
- organoelement chemistry (P, S, Si)
- heterocycle chemistry
- fluoroorganic chemistry
- polymethyne dyes, colour theory
- mechanisms of organic reactions
- chemistry of biologically active compounds
- supramolecular chemistry
- calixarene chemistry

MANUFACTURING

- organophosphorus extractants
- additives for polymers
- drug substances

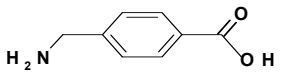
SUBSTANCES FOR MEDICINE AND VETERINARY

Produced by the Pilot Plant of the Institute of Organic Chemistry NAS, Ukraine



ADEMOL

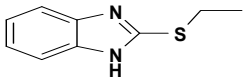
Original uterus stimulator



AMBENUM

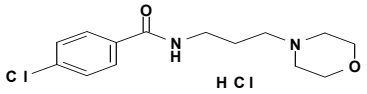
(pamba, gumbix, stuptopur)

Remedy for stop the blood



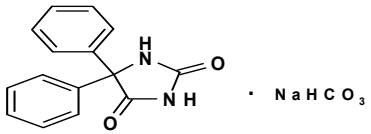
BEMITHILUM

Mental stimulator, Increases capacity for work



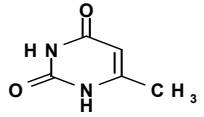
BEFOLUM

Anti-depression remedy



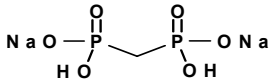
DIFENIUM

Is used for epilepsy treatment



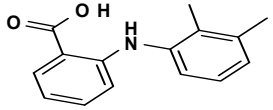
METHYLURACILUM

Anti-inflammation remedy. (accelerates the process of cells regeneration).



MEBIFON

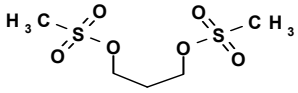
Anti-tumor remedy. Is used for treatment of malignant tumors of Mammae



ACIDUM MEPHENAMINUM

(Coslan, Lysalgo)

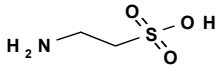
Analgesic, antipyretic,anti-phlogistic remedy.



MYELOSANUM

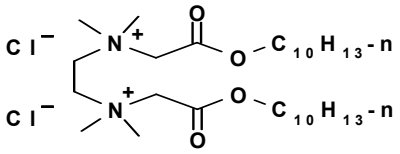
(busulphan, citosulfan)

Is applied for treatment of chronic granulocyte leukemia.



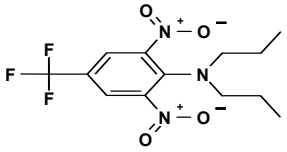
TAURINE (taufonum)

Obtains antispasmodic activity, is applied only in ophthalmology.



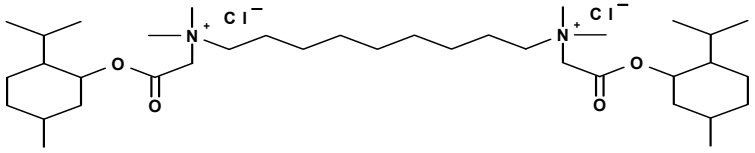
AETHONIUM

Efficient bactericide (for treatment of trophic ulcers, dermatitis, stomatitis, etc.).



TRIFLANE

herbicide

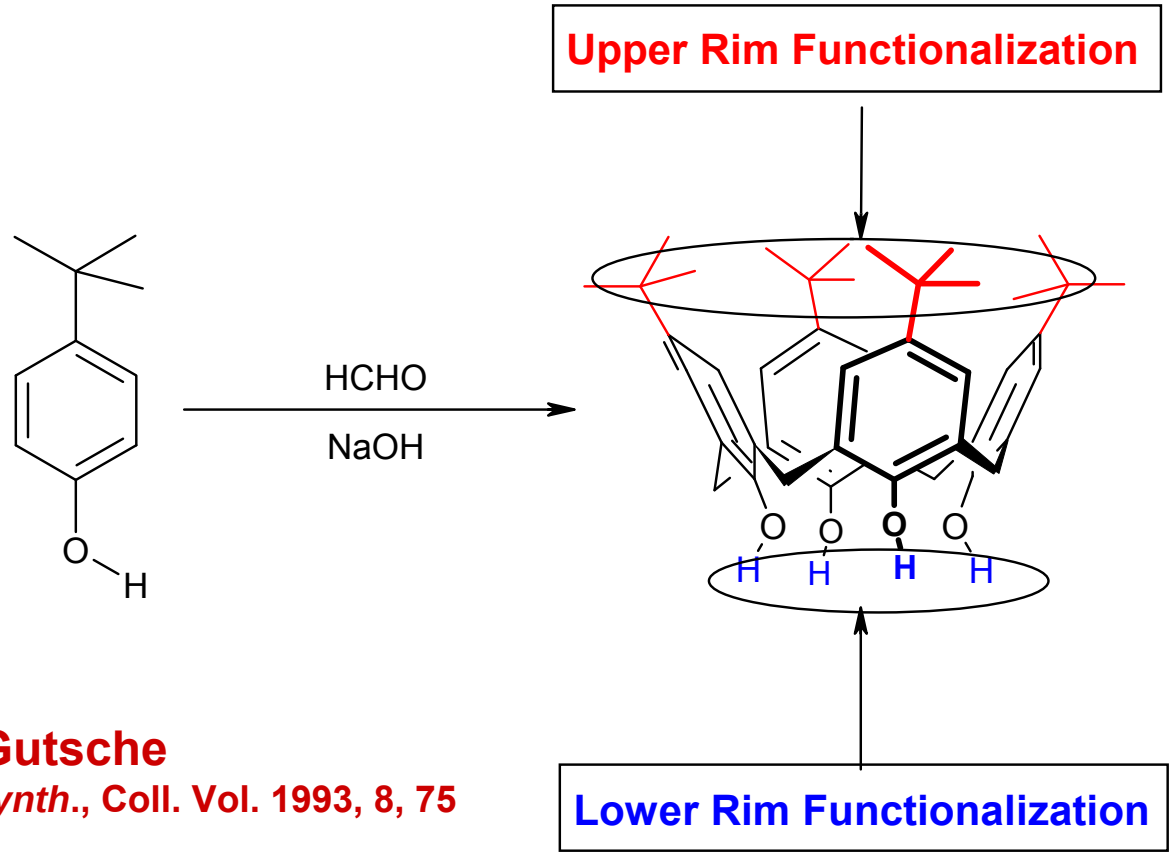


DECAMETHOXINUM

Anti-microbial, antiseptic remedy

CALIXARENES

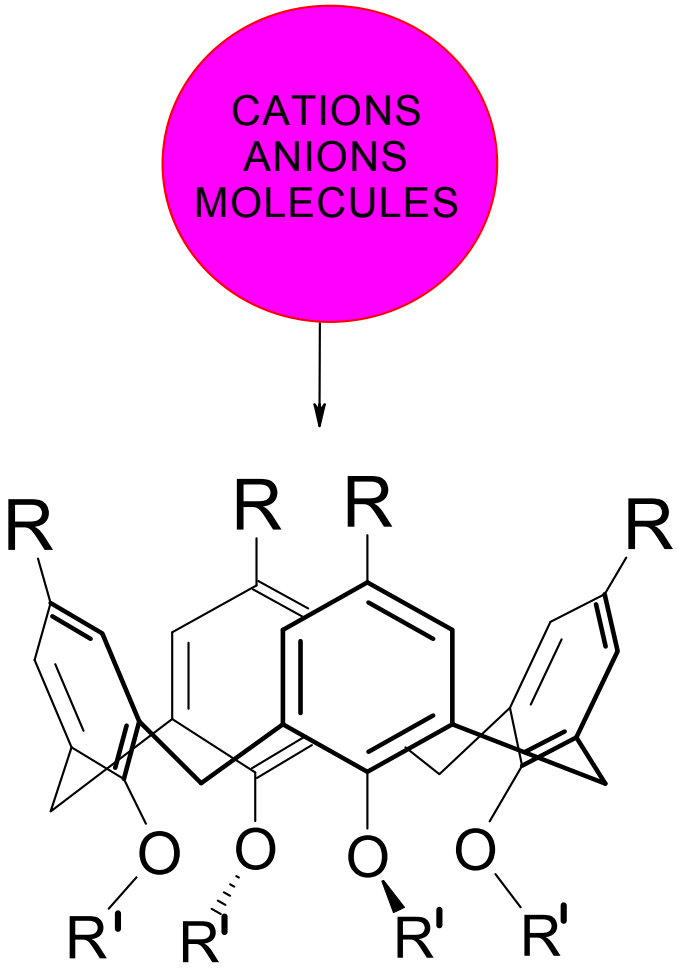
Cup Shaped Macrocyclic Compounds
Easily Synthesized in Simple One-pot Procedure



C.D.Gutsche
Org. Synth., Coll. Vol. 1993, 8, 75

Calixarenes are easily amenable to chemical modifications

CALIXARENE RECEPTORS



Calixarenes selectively bind and separate similar in properties species

CALIXARENES
Practical Application

- **Chemosensors:** *electronic nose and tongue*
- **Separation & Purification:** *chromatography, chiral technologies*
- **Catalysis:** *phase transfer, metallocomplexing, chiral*
- **Reprocessing of spent nuclear fuel:** *recovery cesium, americium*
- **Nanotechnologies:** *Langmuir-Blodgett films*, *nanoparticles*
- **Optoelectronics:** *Nonlinear optics materials, optodes*
- **Gases storage:** *H2, CH4, COx, NOx*
- **Pharmaceuticals & Nanomedicine:** *diagnostics, delivery systems, drug design*

Calixarenes 2001. ***Kluwer Academic Publishers (2001)***
Calixarenes for Separations. ***American Chemical Society (2000)***
Calixarenes in Action. ***Imperial College Press (2000)***
Calixarenes in the Nanoworld: ***Springer (2007)***

Institute of Organic Chemistry NAS Ukraine

Calixarene R&D

Research

Design of selective (chiral) receptors of cations, anions, molecules and bio-molecules

Development

Drug Design

Chemosensors

Radionuclide Extractants

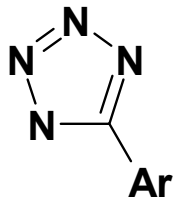
Sensors. 2006. 6. 962-977.
Current Organic Chemistry. 2006. 10. 2307-2331.
J. Am. Chem. Soc. 2007. 129. 1123-1131.
J. Org. Chem. 2007. 72. 3223-3231.
Pure Appl. Chem. 2008. 80. 1449-1458
J. Phys. Chem. C. 2009. 113. 1137-1142
Curr. Med. Chem. 2009. 2009. 16. 1630-1655

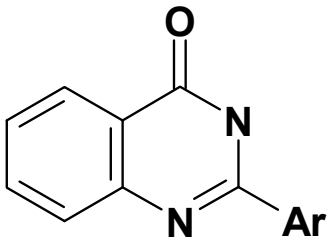
Diversity of Calixarene Functional Groups:

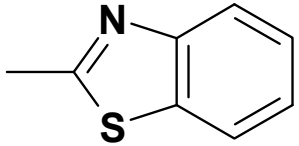
CH=O, CH_2OH, CH_2Cl, $OCH_2CF_2CHF_2$, C(O)Alk, C(O)OH, C(O)Cl, C(O)OAlk

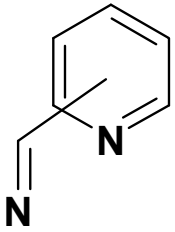
SH, SAlk, SAr, C(O)NCS, SO_2OH, SO_2Ar, $SCH_2CH_2P(O)R_2$

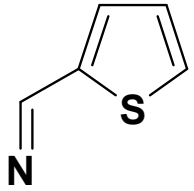
NO_2, NH_2, NHC(O)R, NHC(O)NHR, $N=C(R)NR_2$, $N=C(R)NSO_2Ph$, $NAlk_2$, N=C(Cl)Ar, $N^+(Me)_2CH_2CH_2OH$, N=C=N, $C(O)NR_2$, C(O)NCO, $C(O)NHNH_2$, $NHCH(Het)P(O)(OH)_2$



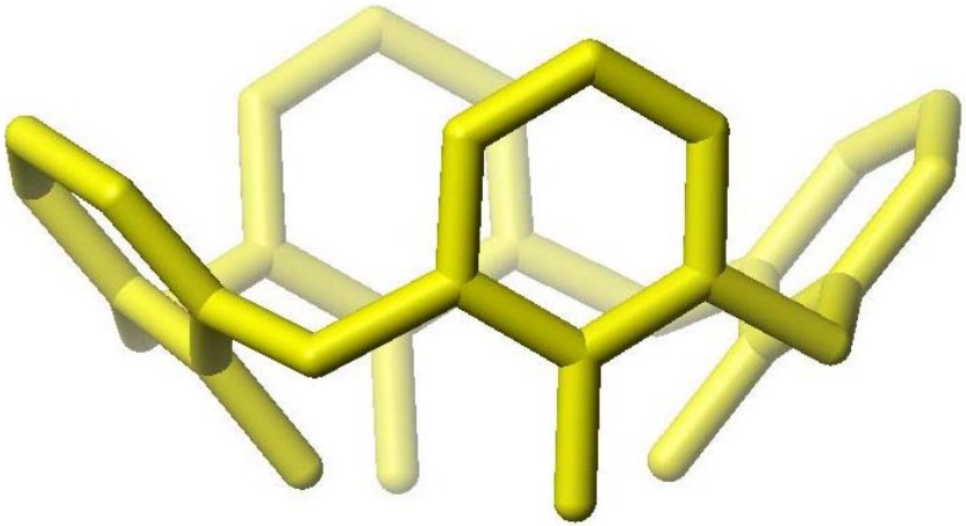


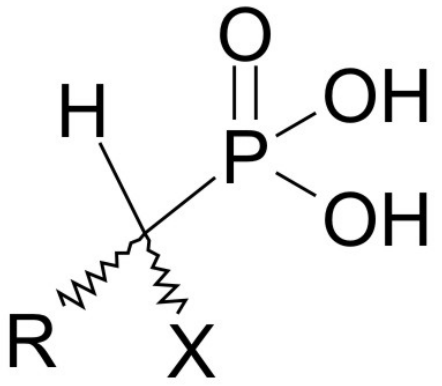






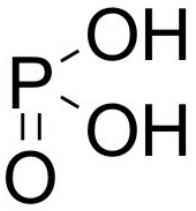
$PO(OH)_2$, P(O)(OH)R, $P(O)(OAlk)_2$, $P(O)Alk_2$, $P(O)Ar_2$, $CH(OH)P(O)(OR)_2$, $CH(NH_2)P(O)R_2$, $P(O)(R)CH_2C(O)NAlk_2$, $NHC(O)CH_2P(O)Ph_2$, $P(O)(R)CH_2P(O)R_2$, $P(O)(R)CH_2CH_2P(O)R_2$, $CH[P(O)R_2]_2$, $P(O)(R)CH_2OH$, $P(O)(R)CH_2Hlg$

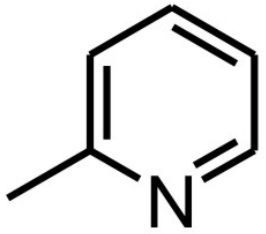




X= OH

NH_2





Institute of Organic Chemistry

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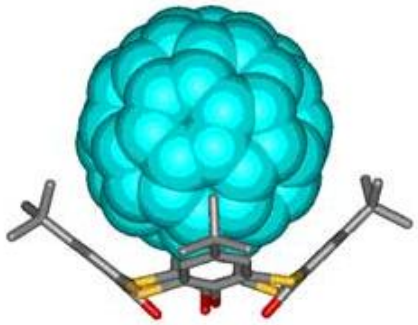
Home	Institute	Background	Prof.Kalchenko
Members	Publications	Compounds	Custom



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Calixarene + P + S + Amphiphility + Chirality + Recognition + Sensing + Binding + Bio + etc.

Last update 05/23/2005 15:48:18

http://www.ioch.kiev.ua/calix

Plan of presentation

1 Calixarene-based enzyme mimics

2 Calixarene-based mimetic of antibodies and enzyme inhibitors

3 Membranoactive calixarenes

4 Calixarenes in DNA transfection

5 Bioactive calixarenes

6 Calixarenes in magnetic resonance imaging

7 Toxicity of calixarenes

Literature

Sansone, F.; Segura, M.; Ungaro, R.
***Calixarenes in bioorganic and biomimetic chemistry*.**
In *Calixarenes 2001*. Asfari Z.; Boehmer V.; Harowfield J.; Vicens J. Ed.; Kluwer Academic Publishers: Dodrecht, *2001*; 496-512.

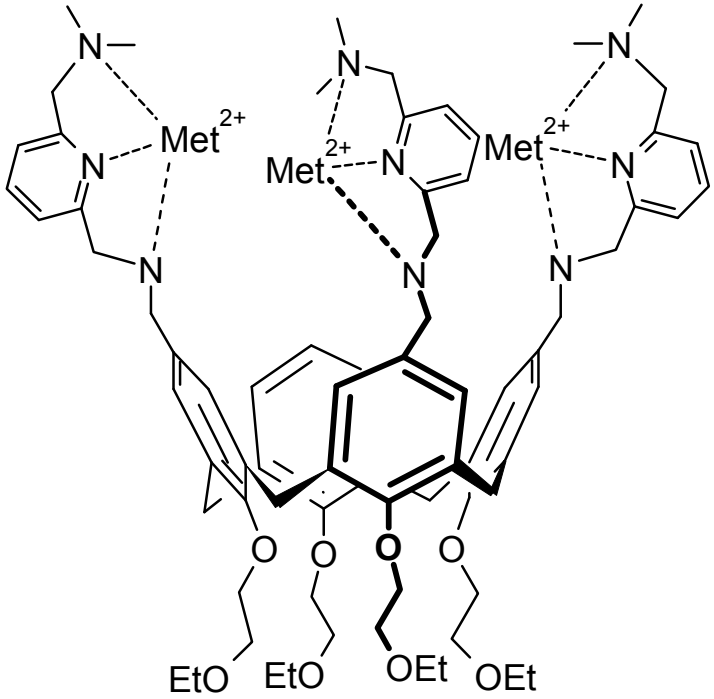
Casnati, A.; Sansone, F.; Ungaro, R.:
Peptido- and glycocalixarenes: playing with hydrogen bonds around hydrophobic cavities.
Acc. Chem. Res., *2003*, *36*, 246-254.

Da Silva, E.; Lazar, A.N.; Coleman, A.W.:
***Biopharmaceutical applications of calixarenes*.**
J. Drug. Sci. Tech., *2004*, *14.* 3-20.

Rodik R.V., Boyko V.I., Kalchenko V. I.
***Calixarenes in bio-medical researches*.**
Current Medicinal Chemistry. *2009*. 16. 1630-1655.

1. Enzyme mimics

Artificial esterase of phosphates

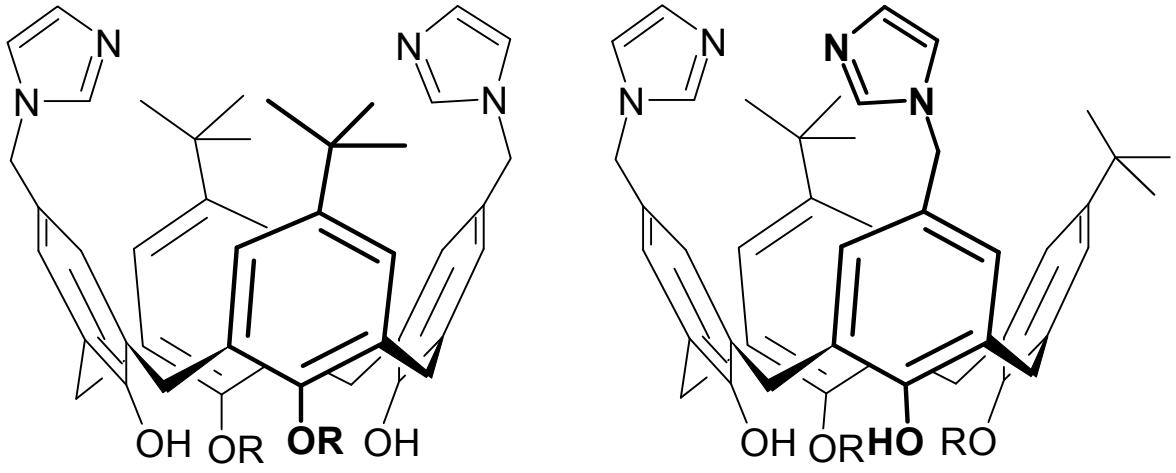


Met = 2Zn, Cu

More than 10^4-10^5 rate acceleration in the RNA dinucleotides cleavage

Molenveld, P., Engbersen, J.F.J., Reinhoudt, D.N. *Angew. Chem. Int. Ed.* **1999**, *38*, 3189-3192.

Carboxylate esterase activity

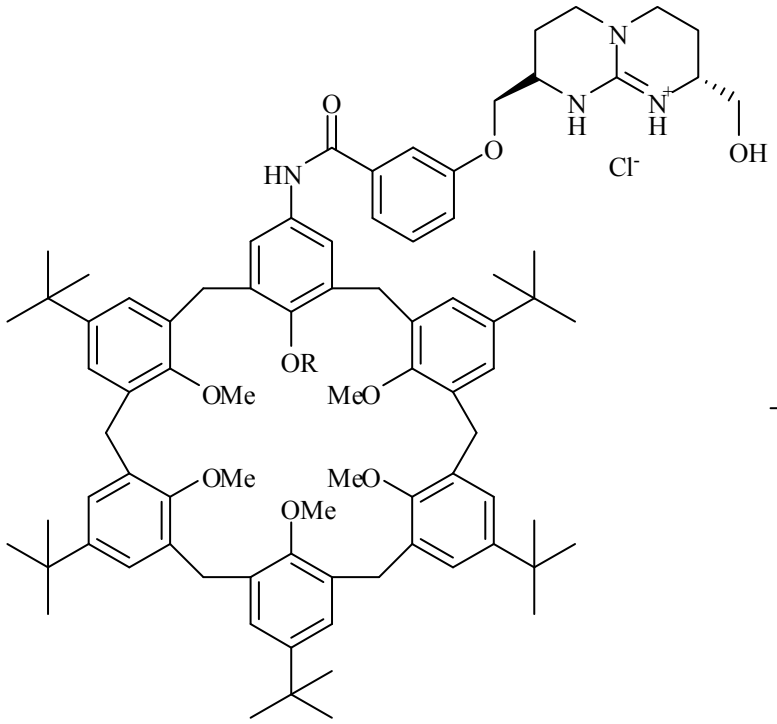


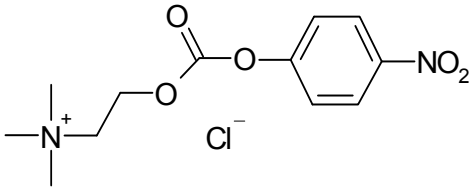
R = H, Bz

Rate enhancements of acyl groups displacement up to 10 times

Dospil G.; Schatz J. *Tetrahedron Lett.*, **2004**,. *42*, 7837-7840.

Carboxylcholine esterase mimic



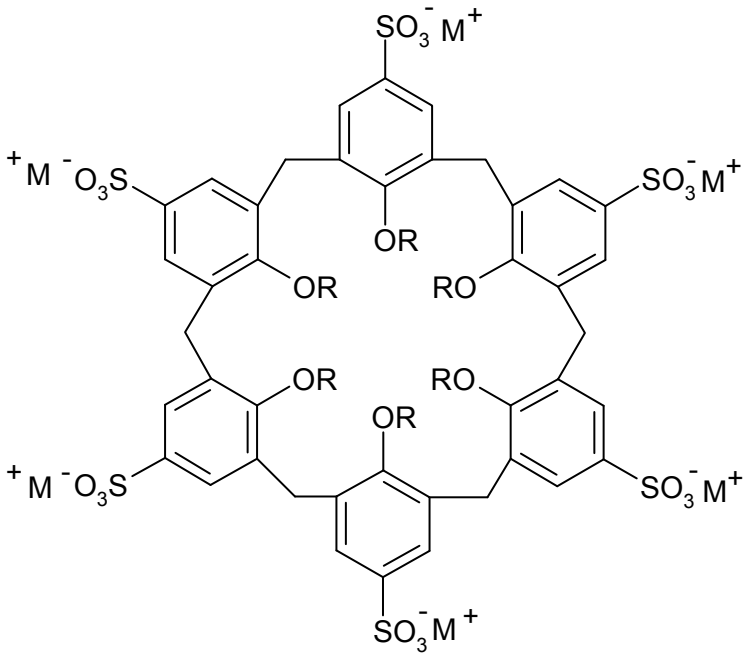


PNPCC

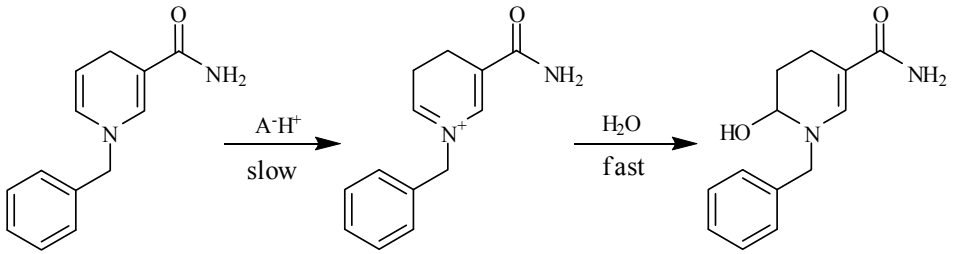
Acceleration of PNPCC hydrolysis (k_{cat}/k_0) is equal 1000

Cuevas, F.; Di Stefano, S.; Magrans, J.O.; Prados, P.; Mandolini, L.; de Mendoza, J. *Chem. Eur. J.*, **2000**, *6*, 3228-3234.

Glyceraldehyde-3-phosphate dehydrogenase mimic



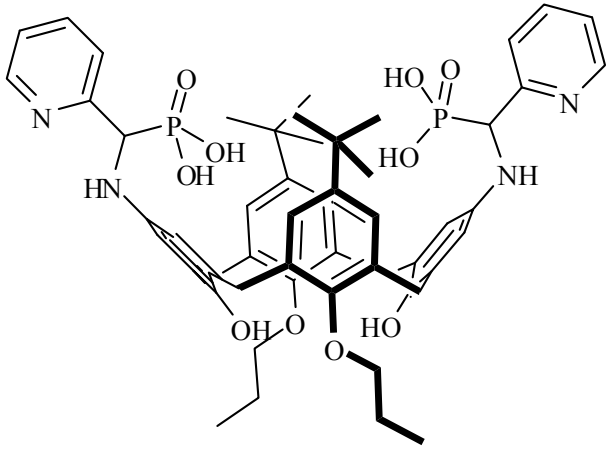
K **of catalytic hydration of NADH-model compound is 426-1220 time more than for noncyclic analogues**

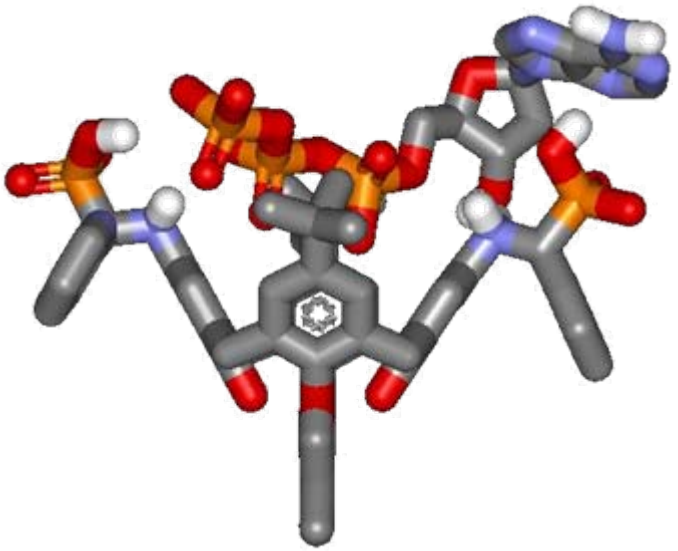


Scheme of catalytic hydration of NADH-model compound

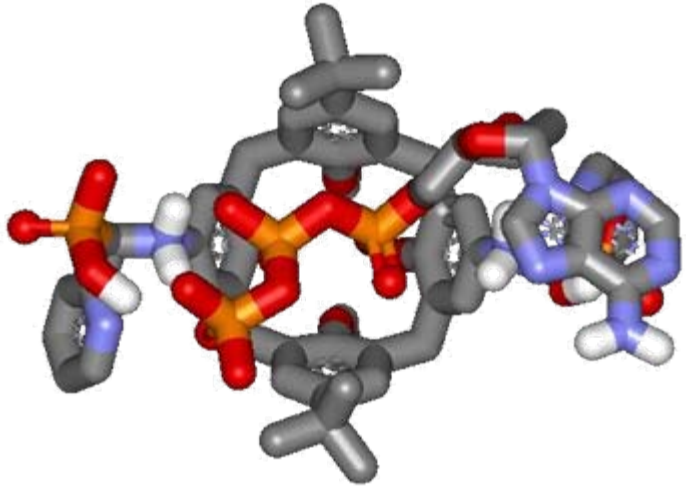
Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.*, **1986**, *108*, 2409-24

ATP-ase mimetic compounds





K_{dis} of the calixarene–ATP complex = $2 \cdot 10^{-4}$ M (*determined by reversed phase HPLC method in water solution*)

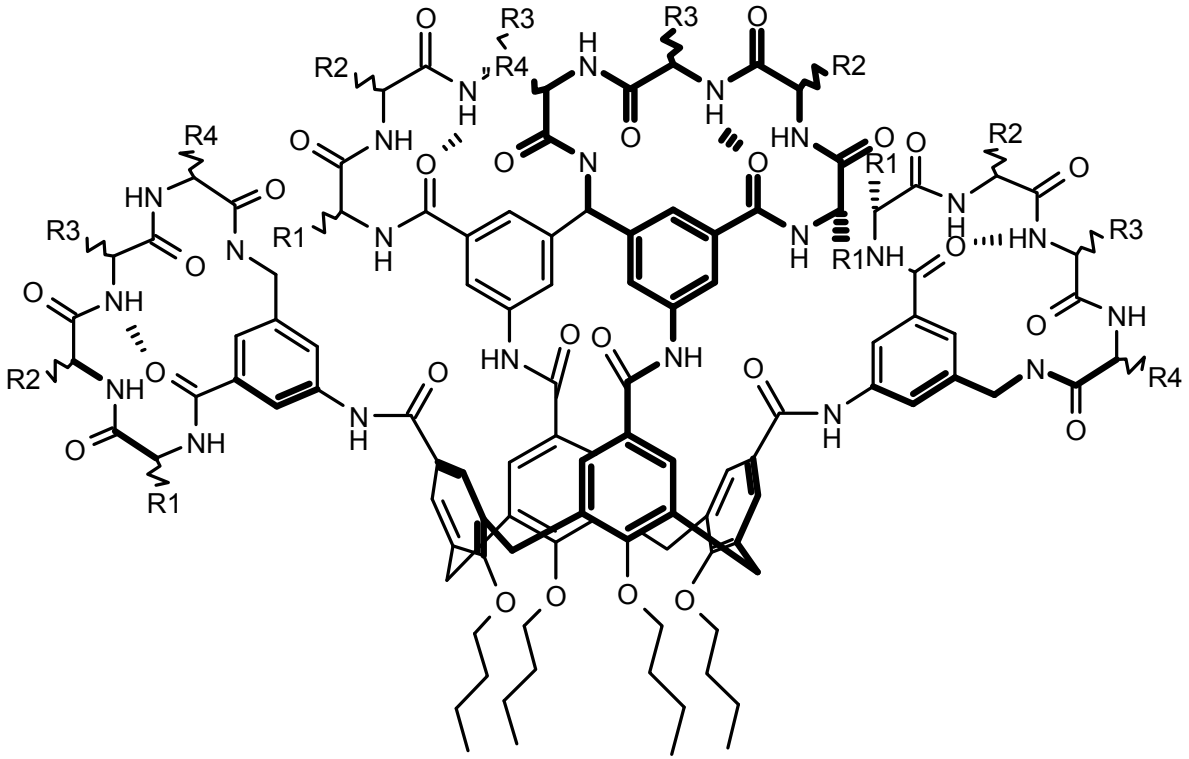


The velocity of calixarene-dependent hydrolysis of ATP exceeds the velocity of spontaneous hydrolysis of ATP at 15 times.

Shkrabak, O.A.; Kalchenko, O.I.; Rodik, R.V.; Veklich, T.O.; Kalchenko, V.I.; Kosterin, S.O. *Ukr. Biochem. J.,* **2008**, *80(2),* 90-100.

2. Calixarene-based mimetic of antibodies and enzyme inhibitors

Cytochrome c inhibitor

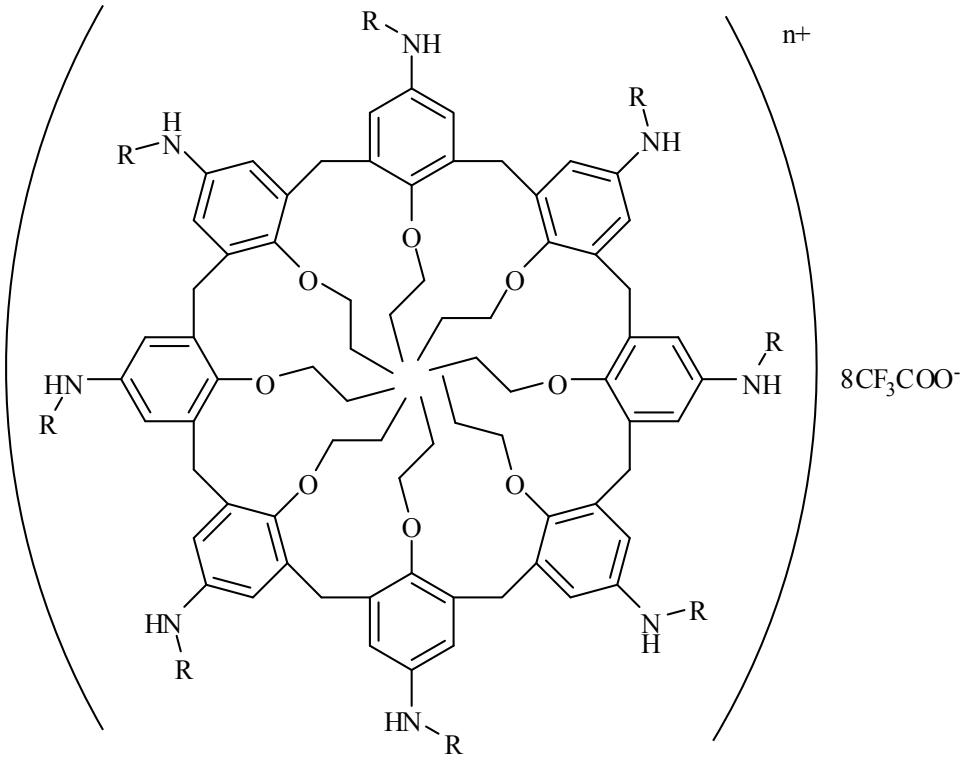


cyt c $K_{ass} = 3 \cdot 10^8\ M^{-1}$

In the presence of the calixarene (10 μM) the cyt c reduction rate is diminished ten fold

Hamilton, A.D., Hamuro, Y. *Patent US5770380*, **1998** (CA.129: 95721e)
Wei, Y., McLendon, G.L., Hamilton, A.D., Park, H.S., Lee. C.-S. *Chem. Commun.* **2001**, 1580-1581.

Heparin binder



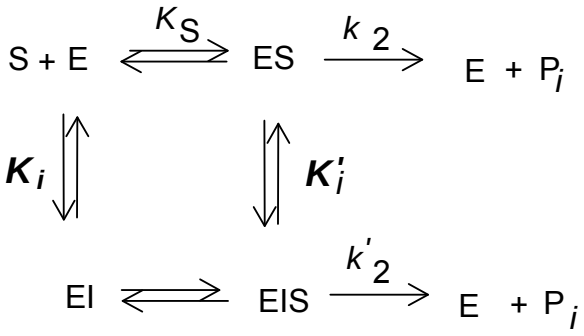
R = L-lys, $CO(CH_2)_6NH_3^+$

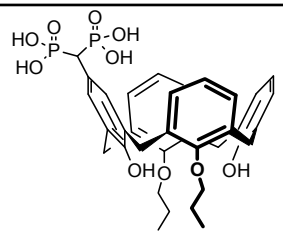
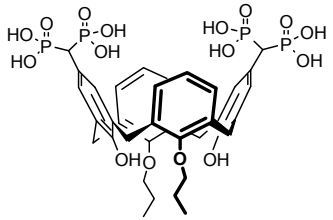
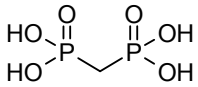
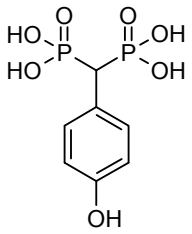
Polycationic calix[8]arenes are able to neutralize UF and LMW heparin faster and 10-35 times more efficiently than protamine and polylysine.

Mecca, T.; Consoli, G.M.L.; Geraci, C.; La Spina, R.; Cunsolo, F.
Org. Biomol. Chem., **2006**, *4*, 3763–3768.

Alkaline phosphatase inhibitors

Inhibition constants of calf intestine alkaline phosphatase

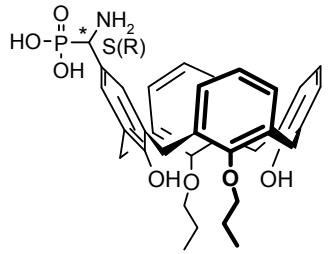
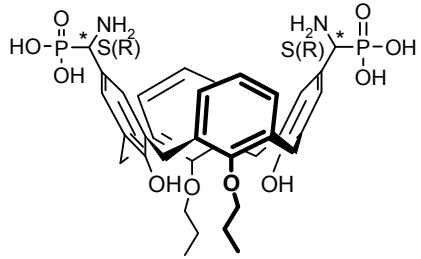
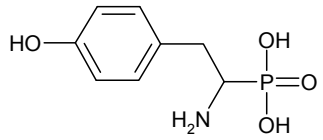


Inhibitor	K_i μM	K_i' μM
	2,5	46
	**0,38**	**2.8**
	67±5	750±100
	22±4	290±110

Vovk, A.I.; Kalchenko, V.I.; Cherenok, S.A.; Kukhar, V.P.; Muzychka, O.V.; Lozynsky, M.O.: *Org. Biomol. Chem*., **2004**, *2*, 3162-3166.

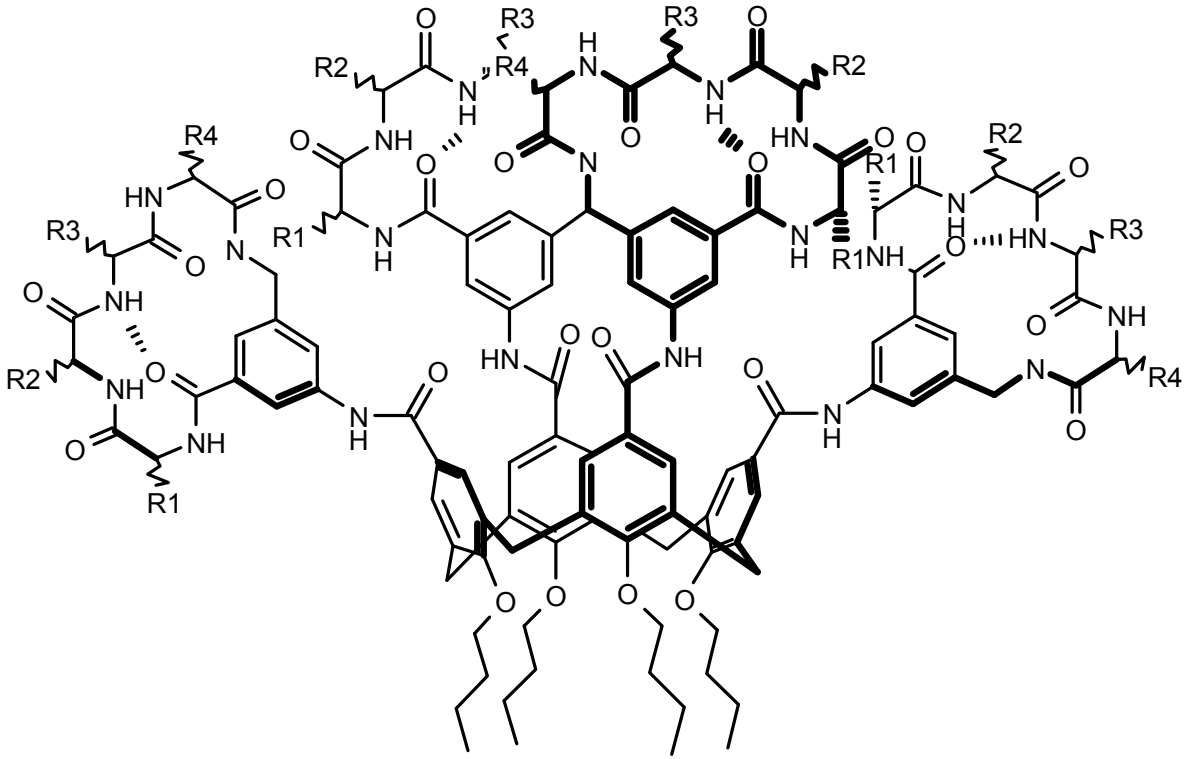
Alkaline phosphatase inhibitors

Inhibition constants of calf intestine alkaline phosphatase

Inhibitor		K_I	K_I'	ΔG_1
	**R**	73± 13	540± 90	-5.6
	S	**32± 5**	780± 100	-6.1
	**RR**	**1.7± 3**	130± 30	-7.8
	SS	86± 11	610± 210	-5.5
	**S**	580± 110	6800± 840	-4.4

Cherenok S.; Vovk A.; Muravyova I.; Shivanyuk A.; Kukhar V.; Lipkowski J.; Kalchenko V.
Organic Lett., **2006**, *8,* 549

Chymotrypsin inhibitor

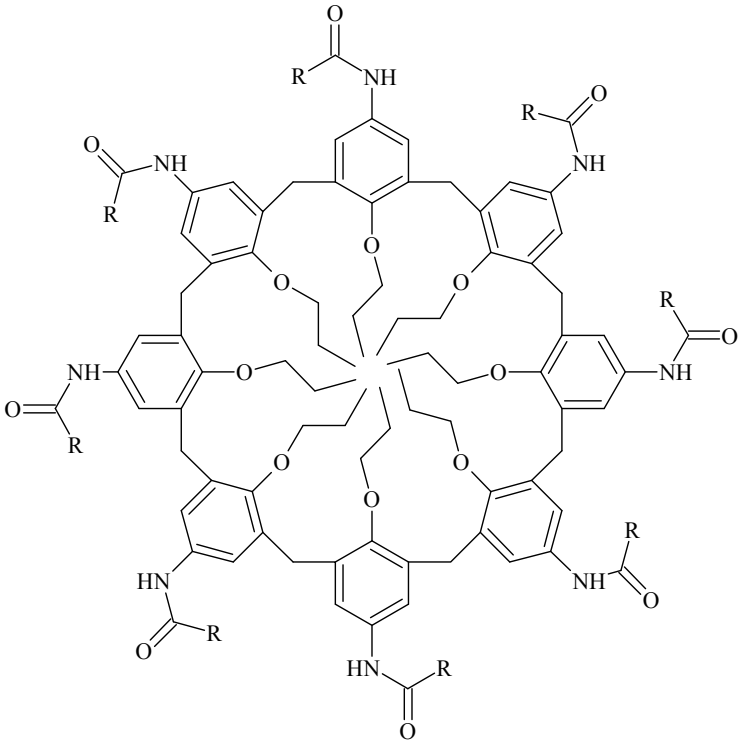


K_i = 0.81 μM, K_i' = 0.11 μM

Peptide bonds of inhibitor are stable to protolytic action of chymotrypsin!

Park, H.S.; Lin, Q.; Hamilton, A.D. *J. Am. Chem. Soc.,* **1999**, *121*, 8-13.

Tryptase inhibitor



a: R = $(CH_2)_2NH_2$
b: R = $CH(NH_2)(CH_2)_4NH_2$
c: R = $(CH_2)_5NH_2$
d: R = $(CH_2)_7NH_2$

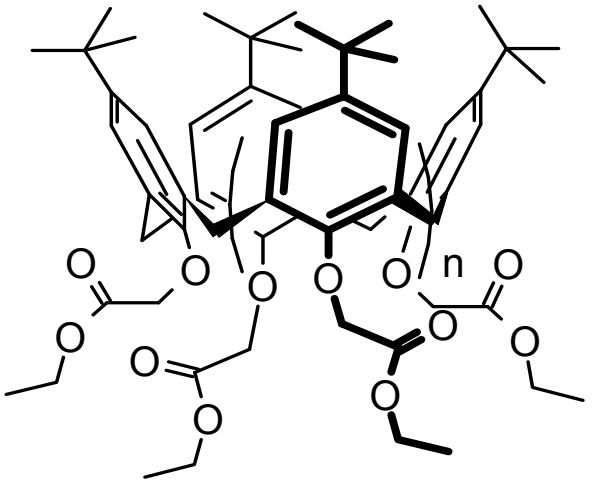
Initial and steady-state rate constants of human lungs tryptase inhibition are in the nanomolar range.

Mecca, T.; Consoli, G.M.L.; Geraci, C.; Cunsolo, F. *Bioorg. Med. Chem.,* **2004**, *12*, 5057–5062.

3. Membranoactive calixarenes

Alkali metal cation transporters

(across phospholipid bilayer membrane)



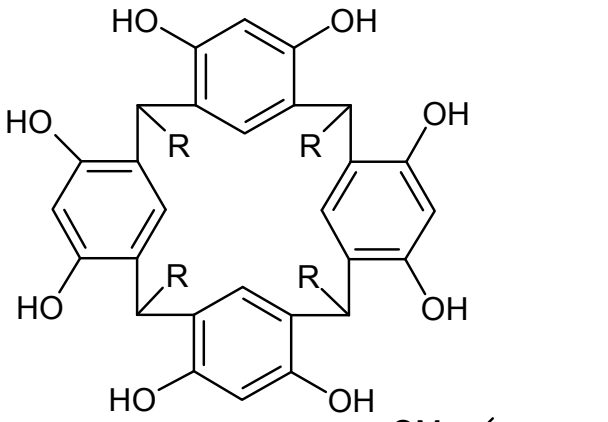
n = 1-5

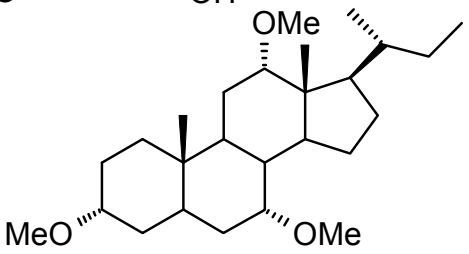
Selectivity:

n = 1 for Na^+;
n = 2 for K^+;
n = 3 for Cs^+;
n = 4 for Cs^+;
n = 5 no transport activity

Jin, T.; Kinjo, M.; Koyama, Y.; Kobayashi, Y.; Hirata, H. *Langmuir,* **1996**, *12*, 2684-2689.
Jin, T.; Kinjo, M.; Kobayashi, Y.; Hirata, H. *J. Chem. Soc. Faraday Trans*., **1998**, *94*, 3135-3140.

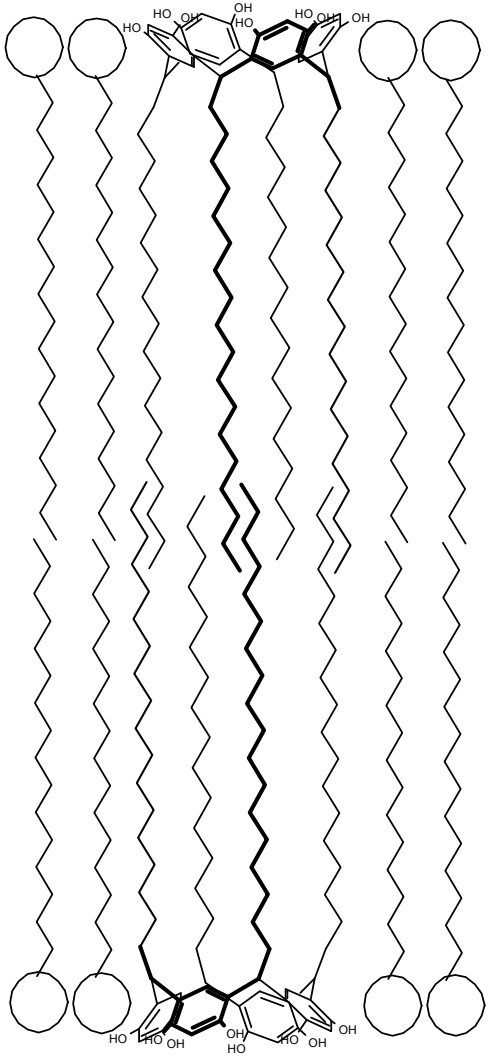
Membrane cation channels





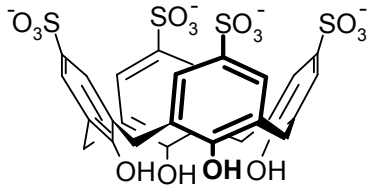
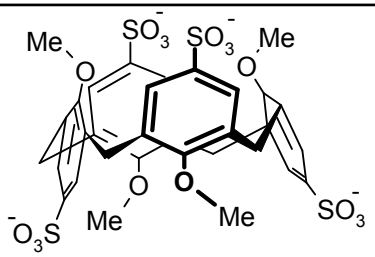
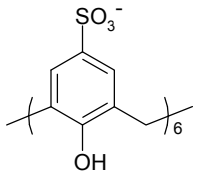
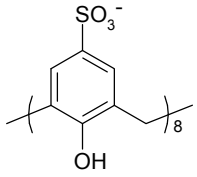
R = $C_{17}H_{35}$,

P_{K+}/P_{Na+} = 2.8-3.0, P_{K+}/P_{Cl-} = 20



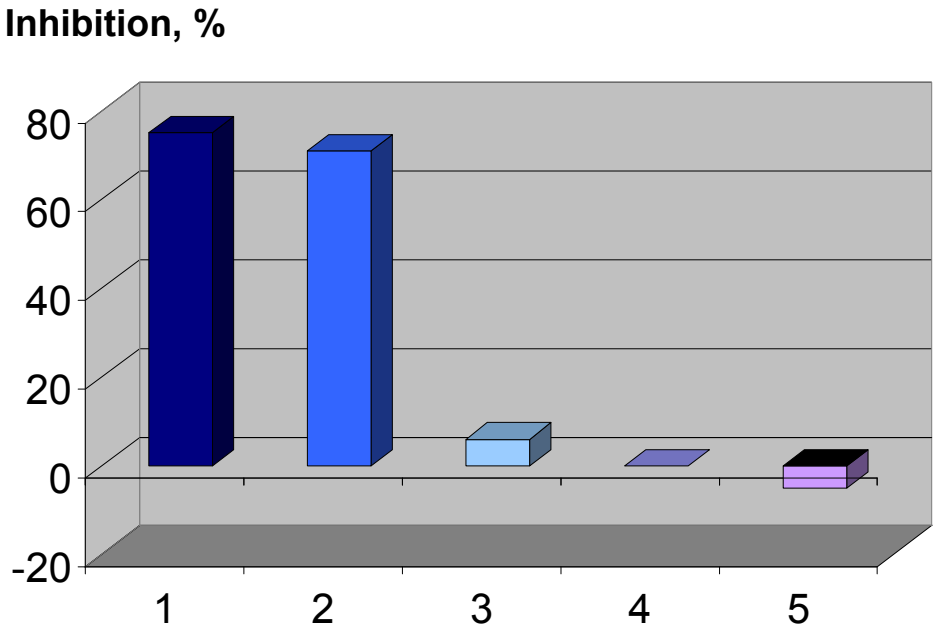
Tanaka, Y.; Kobuke, Y.; Sokabe, M. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 693-694.
Kobuke, Y.; Nagatani, T. *Chem. Lett.*, **2000**, 298-306.

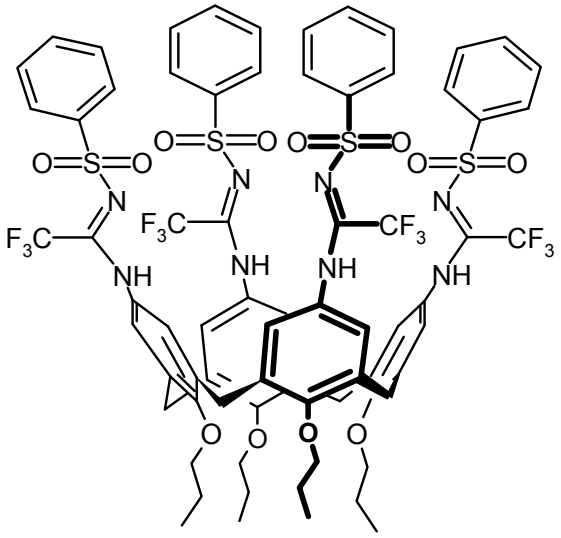
Chloride channel blockers

Compound	Maximum block period, s	K_i, nM
	3-4	800-900
Tetrahydroxycalix[4]arene	No block up to 0.1 mM	–
Tetramethoxycalix[4]arene	No block up to 0.1 mM	–
	>> 100	< 3
	30-40	400-500
	>> 100	< 50

Atwood, J.L.; Bridges, R.J.; Juneja, R.K.; Singh, A.K.: *Patent US 5489612*, **1996**.
Droogmans, G.; Prenen, J.; Eggermont, J.; Voets, T.; Nilius, V. *Am. J. Physiol.*, **1998**, *275*, c646-c652.

Calcium pumps modulator

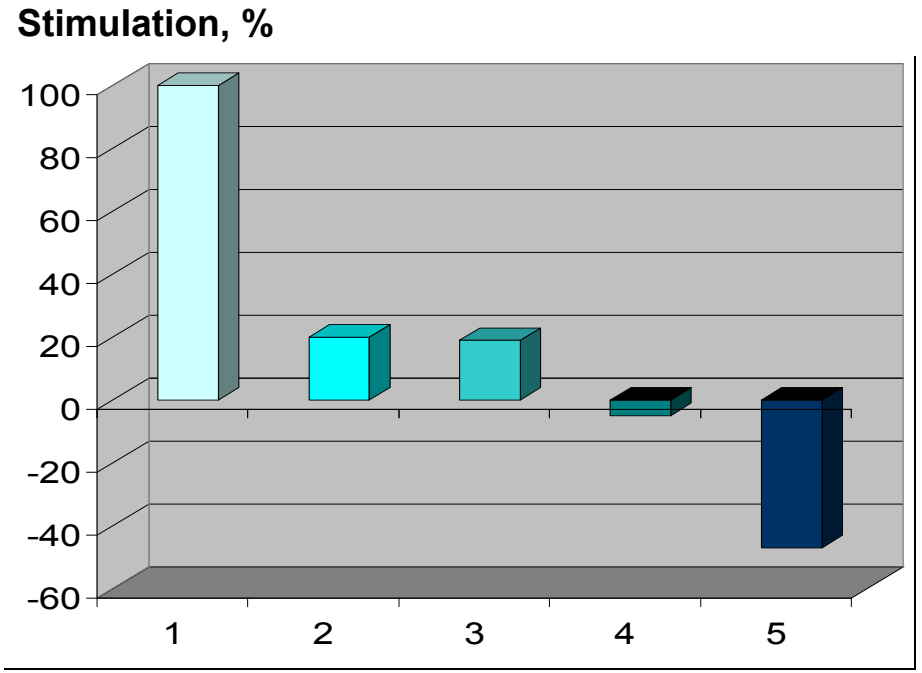


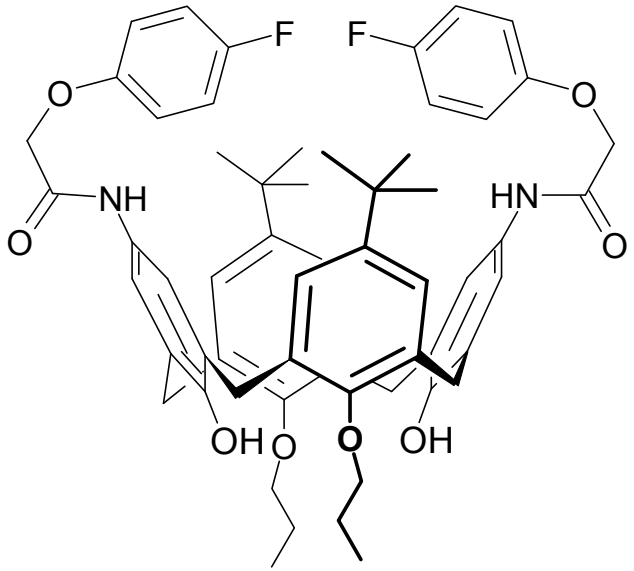


1. **Mg^{2+},ATP-dependent Ca^{2+} accumulation in the miometrial sarcoplasmic reticulum.**
2. **Mg^{2+}, ATP-dependent calcium pump of the plasma membrane.**
3. **Ouabaine-suppressed Na^{+},K^{+}-ATPase.**
4. **Mg^{2+},ATP-dependent Ca^{2}+ accumulation in the mitochondria.**
5. **Ca^{2+}-independent Mg^{2+}-ATPase ("basal" Mg^{2+}-ATPase).**

Rodik, R.V.; Boyko, V.I.; Danylyuk, O.B.; Suwinska, K.; Tsymbal, I.F.; Slinchenko, N.V.; Babich, L.G.; Shlykov, S.O.; Kosterin, S.O.; Lipkowski, J.; Kalchenko, V.I.: *Tetrahedron Lett.*, **2005**, *46*, 7459.
Labyntseva, R.D.; Slinshenko, N.M.; Veklich, T.O.; Rodik, R.V.; Cherenok, S.O.; Boyko, V.I.; Kalchenko, V.I.; Kosterin, S.O.: *Ukr. Biochem. J.,* **2007**, *79(3),* 44-54.

Calcium pumps modulator





1. **Mg^{2+}, ATP-dependent Ca^{2+} accumulation in the mitochondria.**
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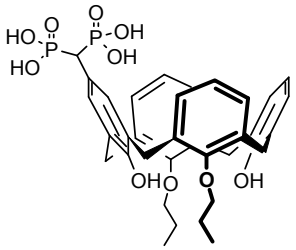
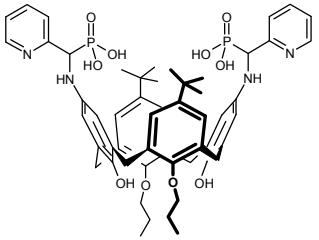
4. **Mg^{2+}, ATP-dependent calcium pump of the plasma membrane.**
5. **Ca^{2+}-independent Mg^{2+}-ATPase ("basal" Mg^{2+}-ATPase).**

Labyntseva, R.D.; Slinshenko, N.M.; Veklich, T.O.; Rodik, R.V.; Cherenok, S.O.; Boyko, V.I.; Kalchenko, V.I.; Kostenin, S.O.: *Ukr. Biochem. J.,* **2007**, *79(3),* 44-54.

Sodium-Potassium pump modulator

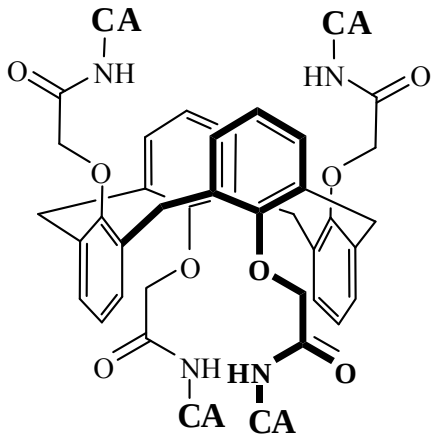
Inhibitors	Full inhibition concentration, μM	Pseudo constant of inhibition, $I_{0,5}$, nM
	~ 10	33±4
	~ 10	54±6
ouabaine	1000	21000±5000

Veklich, T.O.; Kosterin, S.O.; Rodik, R.V.; Cherenok, S.O.; Boyko, V.I.; Kalchenko, V.I.: *Ukr. Biochem. J.,* **2006**, *78(1),* 70-86.

Veklich, T.O.; Shkrabak, O.A.; Kosterin, S.O.; Rodik, R.V.; Cherenok, S.O.; Boyko, V.I.; Kalchenko, V.I.: *Ukr. Biochem. J.,* **2006**, *78(6)*, 53-63.

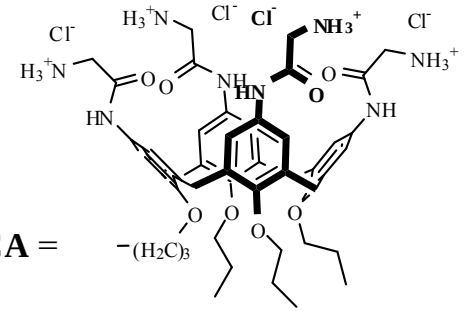
4. Calixarenes in DNA transfection

Polycationic multicalixarenes in DNA transfection

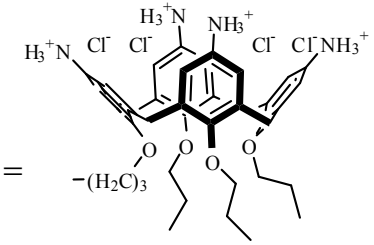


a, b

a: CA =



b: CA =

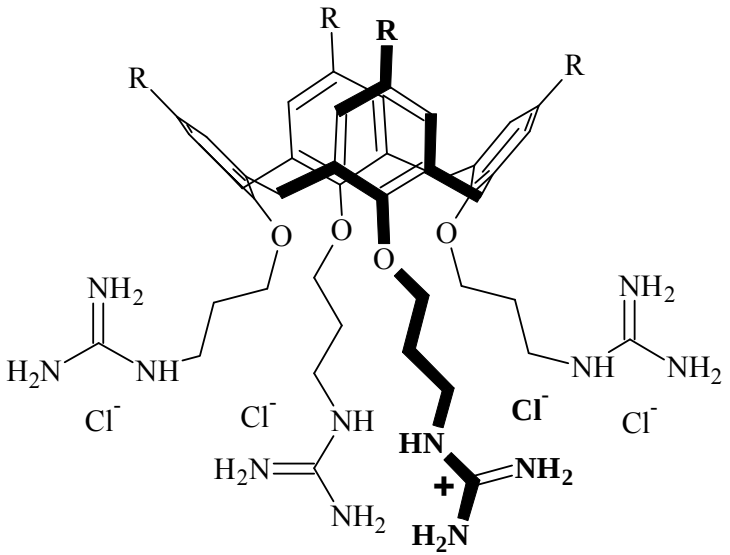


Effectively bind DNA plasmid at concentration 200 μM

Derivative **a** shows significant transfection

Lalor, R.; DiGesso, J.L.; Mueller, A.; Matthews, S.E. *Chem. Commun*., **2007**, 4907 – 4909.

Polycationic calixarenes in DNA transfection



a: R = *t*-Bu
b: R = H
c: R = *n*-Hex

Effectively bind DNA plasmid at concentration 0.6 – 2.5 μM

Derivative **b** shows 48% transfection of human rhabdomiosarcoma cells in the presence of DOPE. Lipofectamine® shows only 30%.

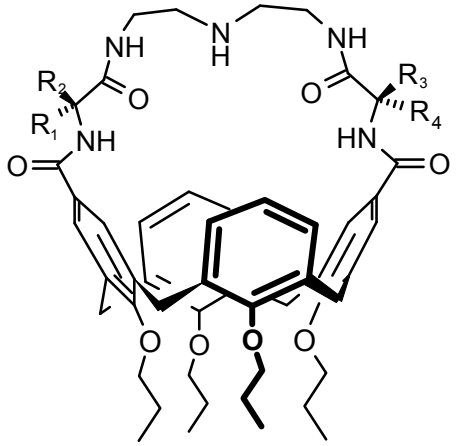
Bagnacani, V.; Sansone, F.; Donofrio, G.; Baldini, L.; Casnati, A.; Ungaro, R.
Org. Lett., **2008**, *10*, 3953-3956.

5. Bioactive calixarenes

Bactericidal properties

In vitro activities of peptide calixarenes and Vancomycin against selected Gram-positives and strains.

Organism	Minimum inhibitory concentration, MIC, mg/l.		
	Vancomycin	**a**	**b**
S. aureus 663	2	8	8
S. aureus 853	2	16	8
S. aureus 1131	**2**	**4**	**4**
S. epidermidis	2	4	8
B. cereus	2	16	NT
S. cerevisae	>128	>128	>128
C. albicans	>128	>128	>128
A.laidlawii	>128	>128	>128

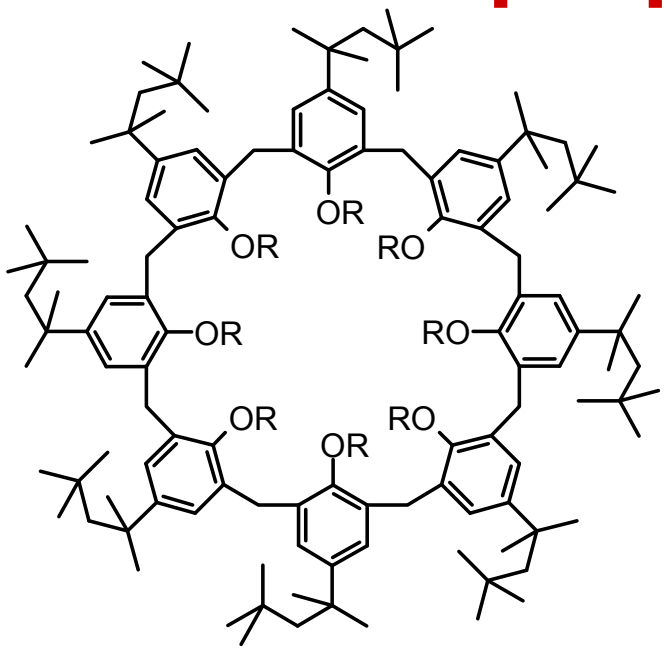


a: $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$;
b: $R_2 = R_4 = H$, $R_1 = R_3 = CH_3$

Log K_a = **3.4**
for N-acetyl-L-ala-L-alanine (**b**) complex

Casnati, A.; Fabbi, M.; Pelizzi, N.; Pochini, A.; Francgesco, S.; Ungaro, R.; di Modugno, E.; Tarzia, G.: *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 2699-2704.

Antituberculosis properties



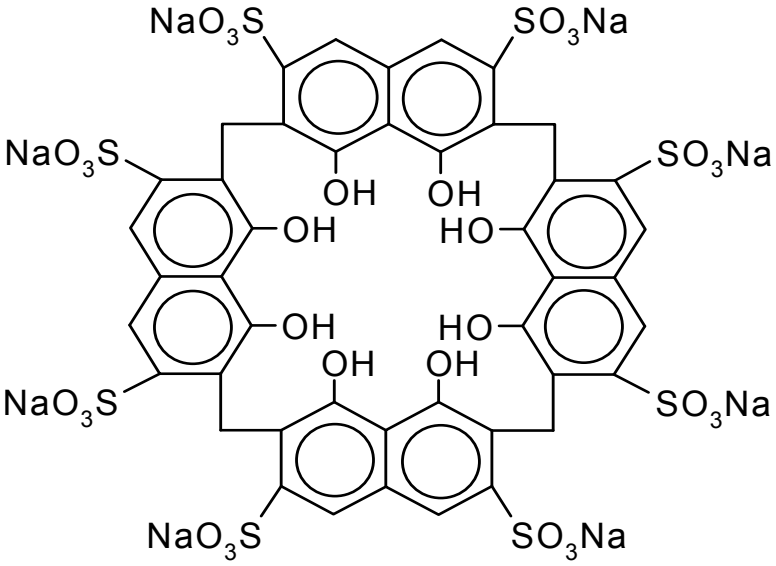
R = $O(CH_2CH_2O)_nC_2H_5$

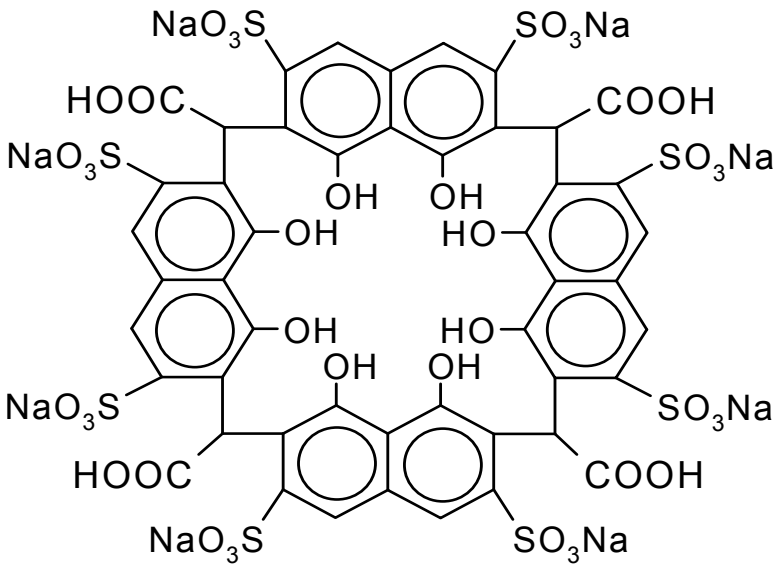
a: n = 12.5
b: n = 60.0

Compound **a** inhibits growth of *Mycobacterium tuberculosis* inside macrophages, but compound **b** stimulate it!

Hart, P.D.; Armstrong, J.A.; Brodaty, E. *Infect. and Immun*., **1996**, *64*, 1491-1493.

Antiviral activity





***in vitro* test the macrocycles superior the well-known drugs: acyclovir, ganciclovir, phosphonoformate and phosphomethoxyethyladenine**

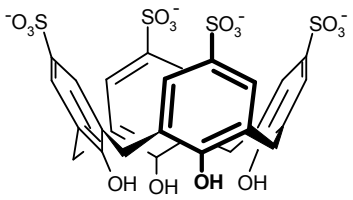
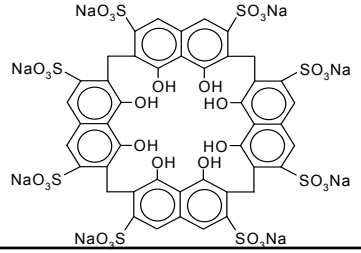
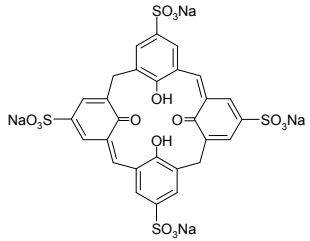
ED_{50} against HSV-1 virus is **0.7-2.7 mg/l**, HSV-2 – **1.2-2.7** mg/l.
HIV (HTLV-IIIB and RF-II strains) **0.07-0.50** mg/l
RSV – **0.19-4.00** mg/l
Influenza A – **5.0-7.9** mg/l

ED_{50} – effective dose with a 50% survival rate;

Hwang, K.M.; Qi, Y.M.; Liu, S.-Y. *Patent US5312837,* **1994**.

Anticoagulant and antithrombotic properties

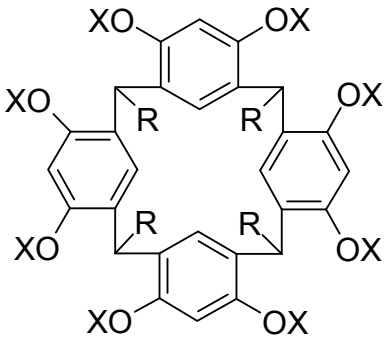
Effect of *in vivo* administration of calixarenes on PT, APTT, and Fibrinogen assay.

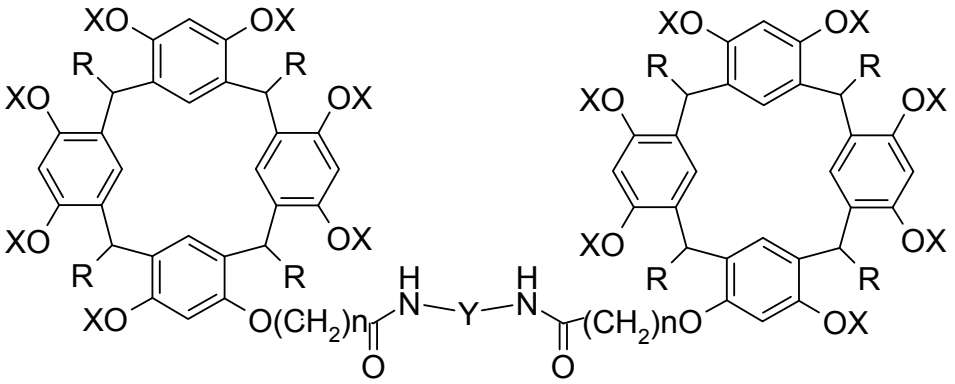
Calixarene	Dose, mg/kg	PT, %	APTT, %	Fibrinogen, Δ mg/l
	5	112	167	7
	10	128	167	no effect
	5	120	**>600**	-21
	10	**188**	**>600**	-59
	5	125	193	no effect
	10	130	**>600**	-26

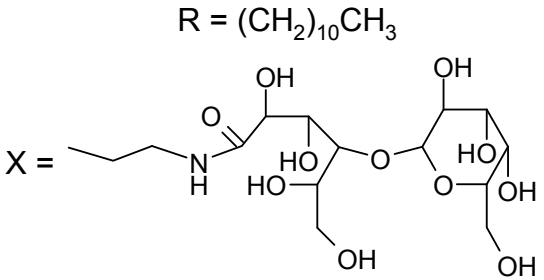
PT- prothrombin time assay, APTT – activated partial thromboplastin time.

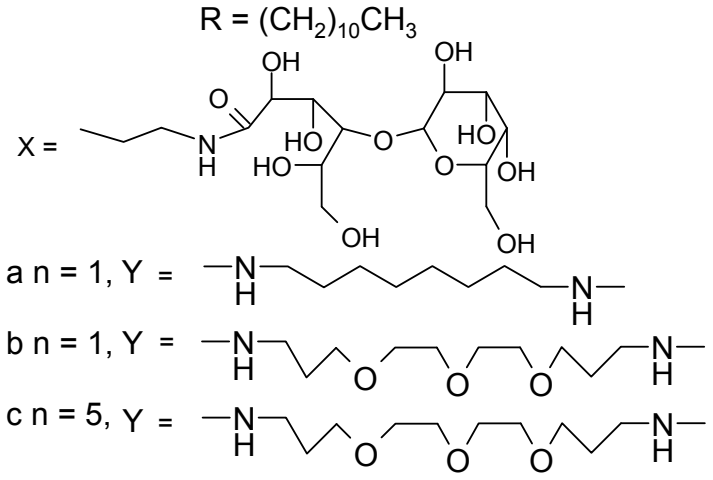
Hwang, K.M.; Qi, Y.M.; Liu, S.-Y.; Thomas, B.; Lee, C.; Bruno, S.; Choy W.; Chen, J.
Patent US5409959, **1995**.

Anticancer properties of galactosocalixarenes









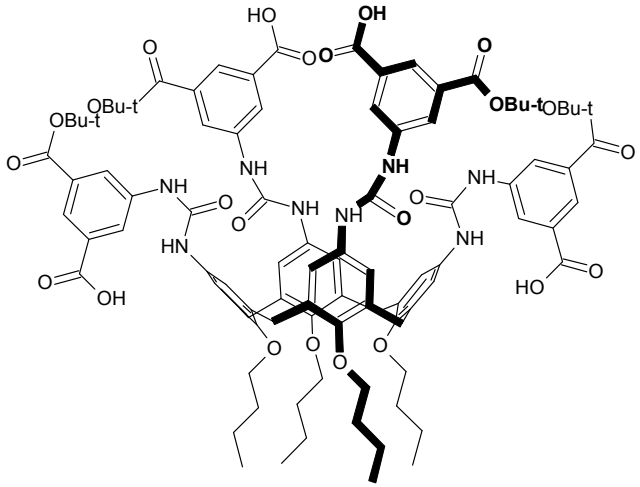
The calixarenes form “cancer-net” on the surface of rat hepatoma cells (RLC-16)

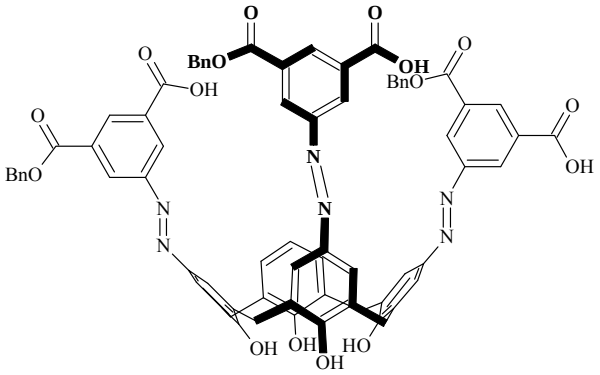
Fujimoto, K., Miyata, T., Aoyama, Y. J. Am. Chem. Soc. 2000. Vol. 122. P. 3558-3559.

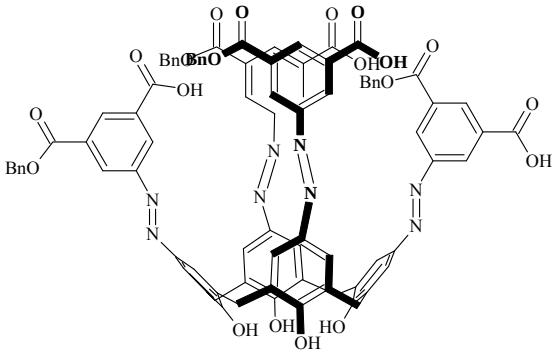
Menger, F.M., Bian, J., Sizova, E., Martinson, D.E., Seredyuk, V.A. Org. Lett. 2004. Vol. 6. P. 261-264.

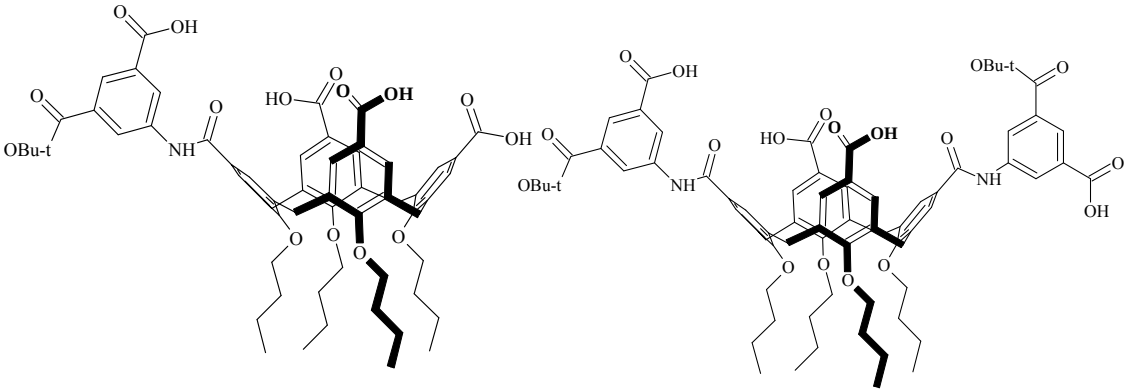
Anticancer agents

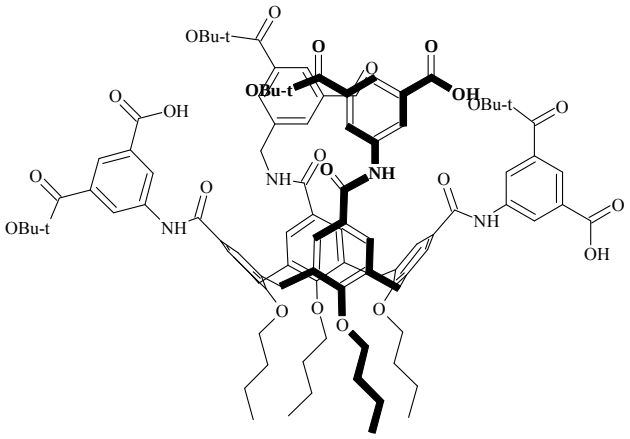
PDGF antagonists (binders)





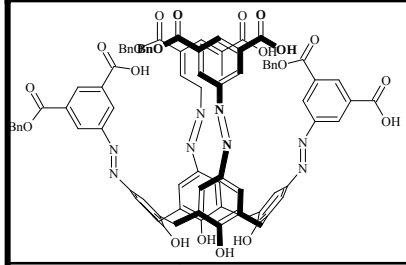
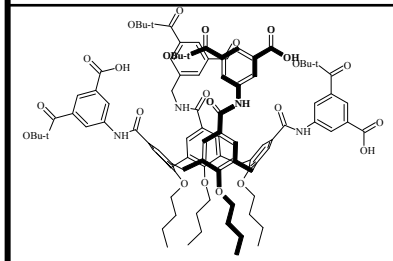
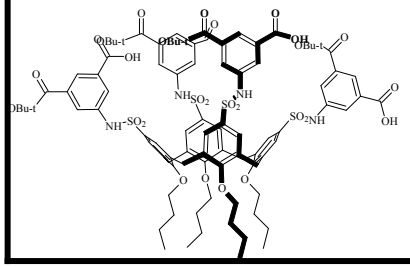


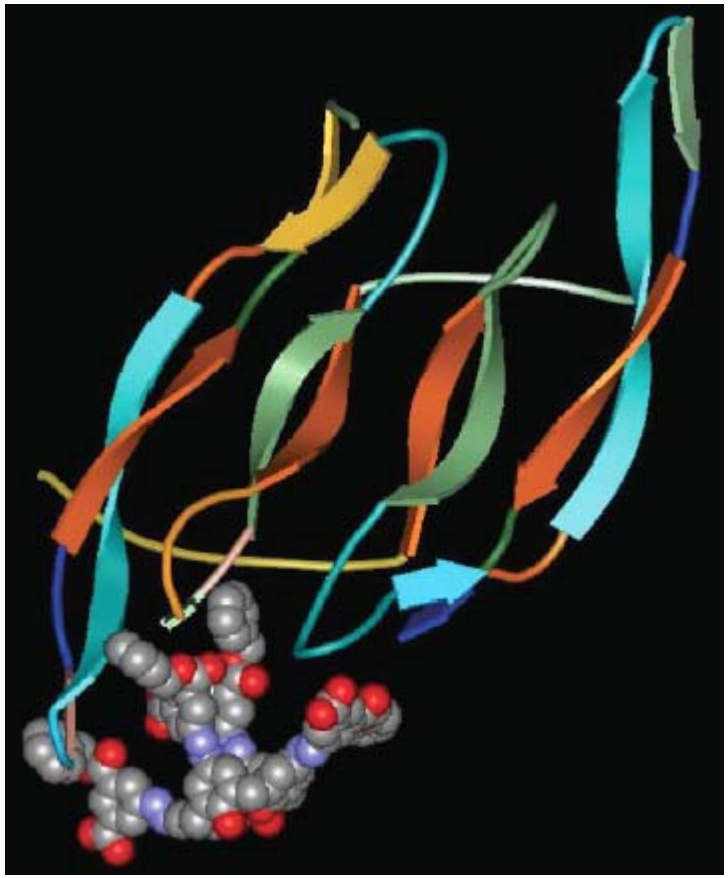




Anticancer agents

The dissociation constants K_d of PDGF-BB subunit with calixarenes and the corresponding IC_{50} values for the inhibition of PDGFR autophosphorylation

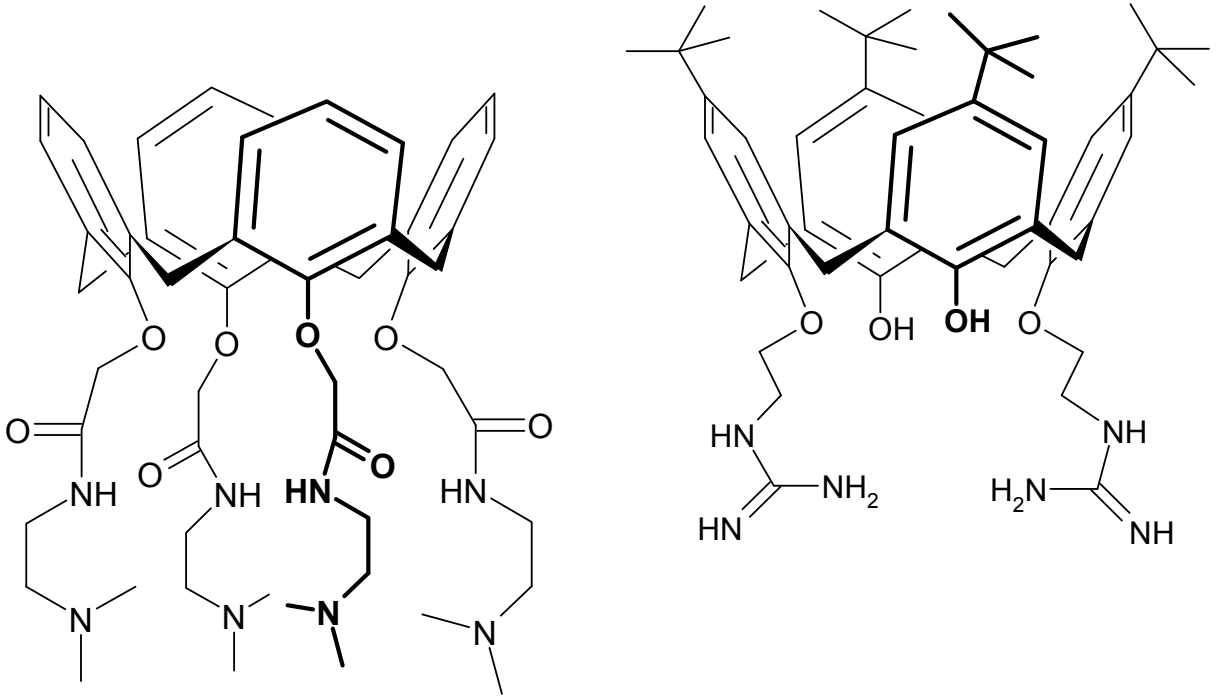
Calixarene	K_d nM^{-1}	IC_{50}, μM
	22.60	**0.11±0.04**
	**9.26**	0.35±0.31
	13.70	>10



The docking between PDGF-BB and diazo-calixarene

Zhou, H.; Wang, D.; Baldini, L.; Ennis, E.; Jain, R.; Carie, A.; Sebti, S.M.; Hamilton, A.D.:
Org. Biomol. Chem., **2006**, *4*, 2376-2386.

Anticancer agents



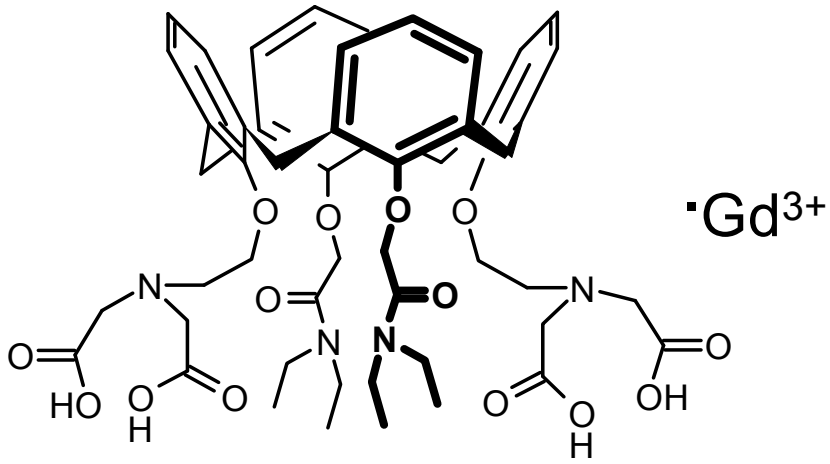
Inhibition of tumor growth by 58-79% (doses <10 mg/kg). MA148 human ovarian carcinoma and B16 murine melanoma were engrafted to mice.

angiogenesis inhibitors

Dings, R.P.M.; Chen, X.; Hellebrekers, D.M.E.I.; van Eijk, L.I.; Zhang, Y.; Hoye, T.R.; Griffioen, A.W.; Mayo, K.H. *J. Natl. Cancer Inst.*, **2006**, *98*, 932-936.

6 Calixarenes in magnetic resonance imaging

Calixarene lanthanide complexes for MRI



K_d $1 \cdot 10^{-13}$ M

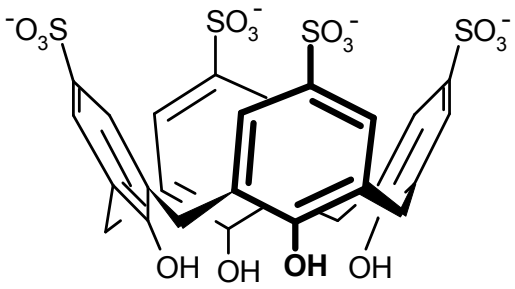
Affinity constant with HSA was calculated as $2.4 \cdot 10^4$ M^{-1}

Aime, S.; Barge, A.; Botta, M.; Casnati, A.; Fragai, M.; Luchinat, C.; Ungaro, R. *Angew. Chem. Int. Ed. Engl.,* **2001**, *40*, 4737-4739.

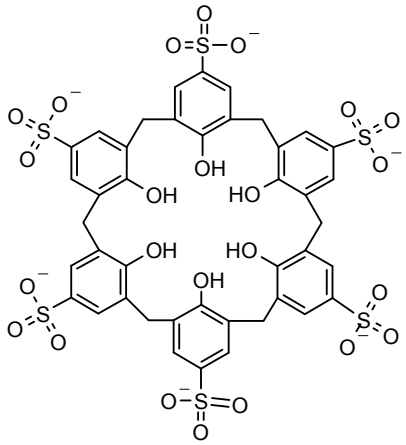
7 Toxicity of calixarenes

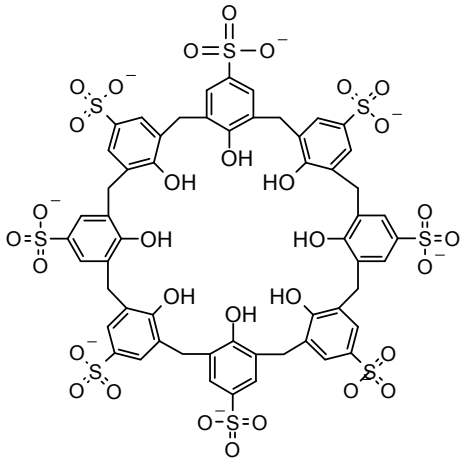
Inhibition of cell growth

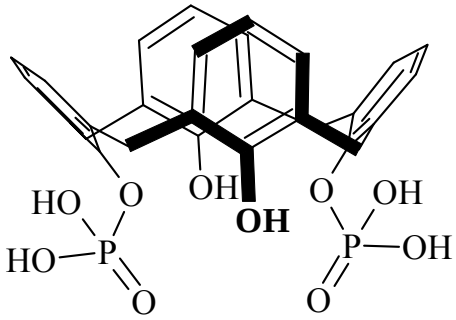
Tests on human fibroblasts



Shows medium toxicity







TOXIC AS GLUCOSE!!!

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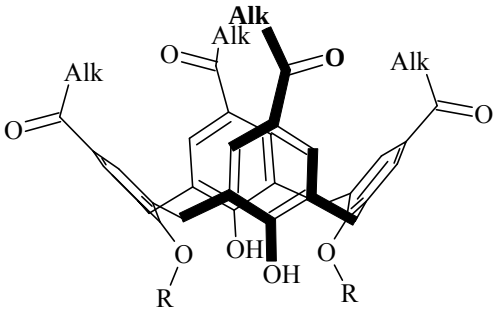
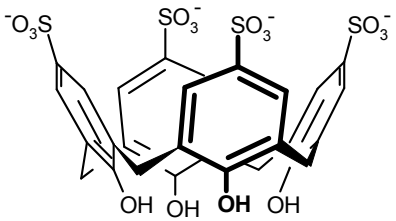
Hemolytic effect



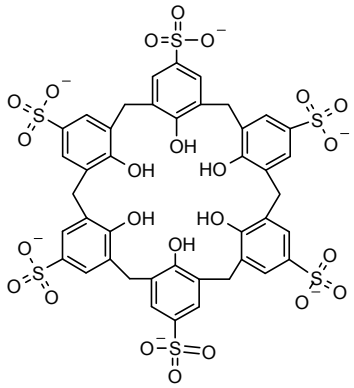
	Alk	R
a	C_7H_{15}	H
b	C_9H_{19}	H
c	$C_{11}H_{23}$	H
d	$C_{11}H_{23}$	$PO(OH)_2$

Solid lipid nanoparticles based on amphipihilic calix[4]arene derivatives **a-d** show zero haemolytic effects at concentrations ranging up to 300 mg/l

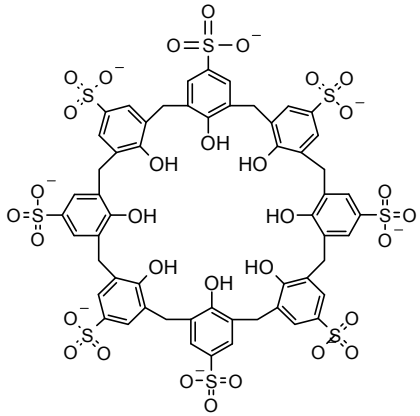
Concentration which causes 5% hemolysis



200mM



50mM



20mM

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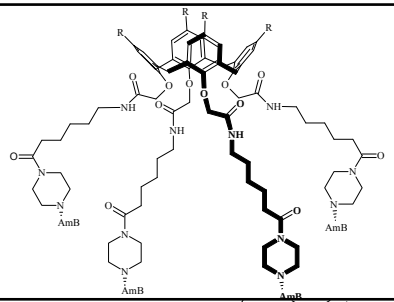
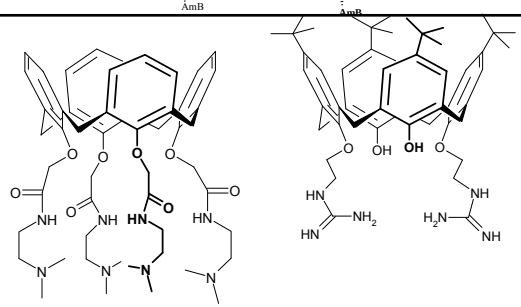
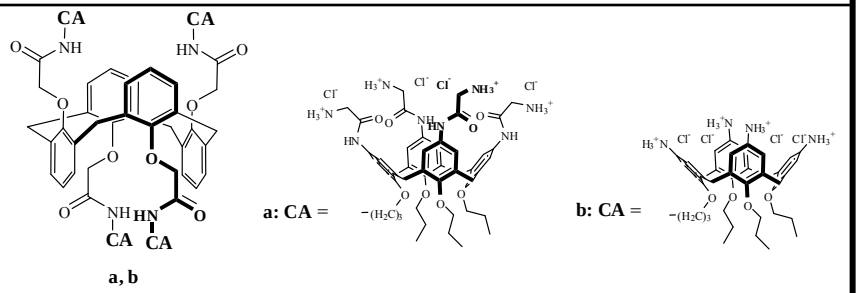
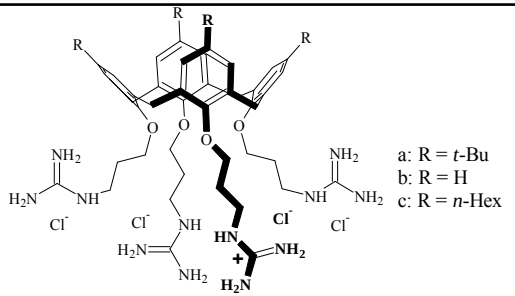
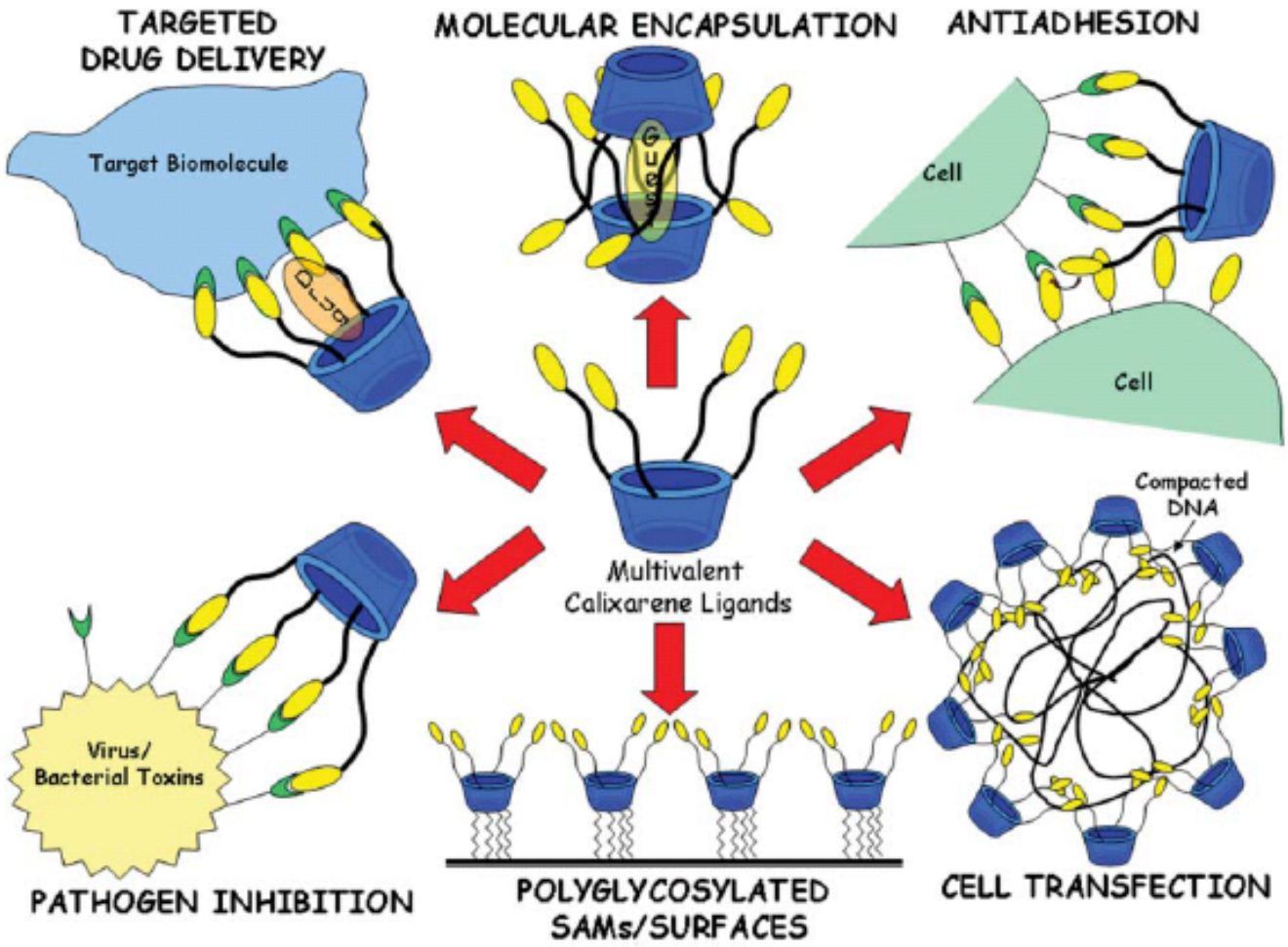
Toxicity data

The hemotoxicity of the calixarene-AmB conjugates was considerably lower (at least 10 times) than the hemotoxicity of AmB	
Treatment with calixarenes on the mice did not cause observable toxicity as assessed by behavior, body weight change, and hematocrit level	
DNA-tranfection calixarenes show lack of cell toxicity (in Chinese Hamster Ovary and Human Embryotic Kidney cell lines) over the full pharmaceutically relevant concentration range	
Calixarene **b** exhibits low toxicity showing 75-80% RD-4 cell viability at 48h from transfection, similar results were obtained for **a**	

Curr. Med. Chem. 2009. 16. 1630-1655



Cup-shaped nano-sized calixarenes due to unique ability to selective complexation with bio-polymers, such as enzymes, proteins and to formation of membrane channels show broad spectrum of bio-activity. High antiviral, antibacterial, anticancer, antitrombotic activities were patented and documented. At the same time, the calixarenes (as well their nanoparticles) have demonstrated neither toxicity nor immune responses, thus increasing the interest to them in the field of biopharmaceutical applications.

Kyiv Calixarene Team

Acknowledgements

Synthesis

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Dr R. Rodik
Dr S. Cherenok
Dr S. Miroshnichenko
PhD st M. Klyachina

HPLC
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Biochemical investigations

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Dr O. Muzychka
Dr V. Tanchuk
Dr I. Muravyova

Prof S. Kosterin — ***Institute of Biochemistry NASU, Kyiv***
Dr T. Veklich
Eng O. Shkrabak

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"New bio-medical problems and human environment"

"Sensors and sensor technologies"

Joint NASU-RFBR project

"Functionalised calixarenes for recognition, binding and transport of bio-molecules"

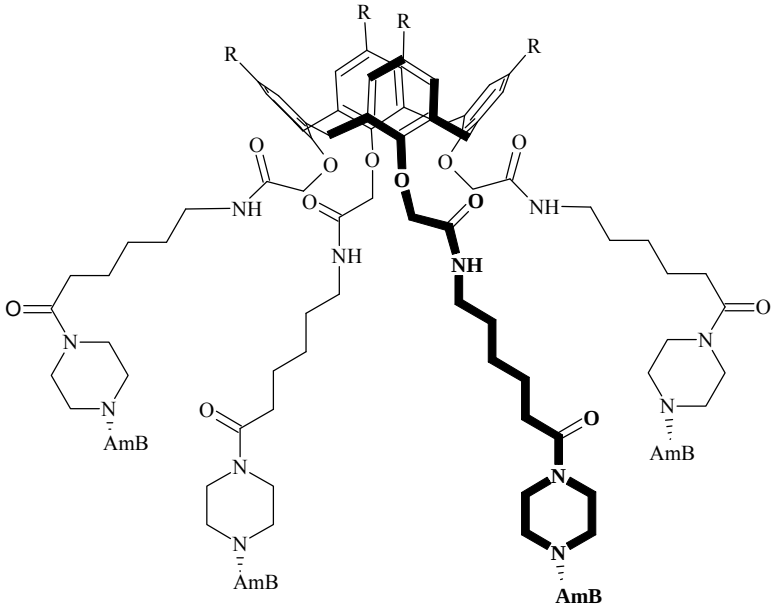
SupraChem

Young Scientists Grants for PhD student Masha Klyachina, Dr Roman Rodik and Dr Stanislav Miroshnichenko

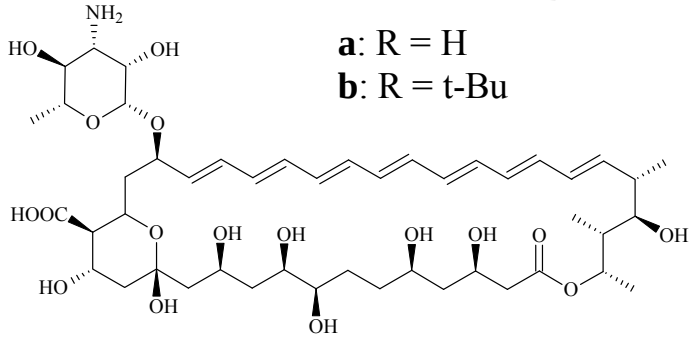
Thank you !

- APPENDIX

Antifungal activity



a: R = H
b: R = t-Bu



amphotericin B AmB

Compound	MIC BY4741, μM	EH_{50}, μM
AmB	0.30	4.0
a	0.10	**50**
b	0.25	**40**

MIC BY4741 : minimal, inhibitory concentration for *S. cerevisiae* cell line;
EH50: concentration, causing 50% hemoglobin release in human erythrocytes.

Paquet, V.; Zumbuehl, A.; Carreira, E. M. *Bioconjugate Chem.,* **2006,** *17*, 1460-1463.