Journal of Organic and Pharmaceutical Chemistry

Advanced Research

OPEN ACCESS

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UDC 547.6:546.18:547.261:615.281.8

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The Study of the Complexation of Calix[4]arene-Hydroxymethylphosphonic Acid and Calix[4]arene-Hydroxymethyldimethylphosphine Oxide with Antiviral Drugs

Abstract

The host-guest complexation of cone-shaped calix[4]arene-hydroxymethylphosphonic acid (**CPA**) and calix[4]arene-hydroxymethyldimethylphosphine oxide (**CPO**) with active pharmaceutical ingredients of antiviral drugs Remdesivir, Nevirapine, Vesatolimod, and Bictegravir in the aqueous-organic mobile phase on a Zorbax CN column has been studied using RP HPLC method. By analyzing the dependence of the drug capacity values on the concentration of calixarene in the mobile phase, the stability constants (K_A = 3672 – 6884 M^{-1}) of the complexes formed have been determined. Quantum-chemical calculations show that the drugs studied form supramolecular *exo*-complexes with **CPA** and **CPO** molecules. These complexes are stabilized by intermolecular hydrogen bonds of proton donor groups $P(O)(OH)_2$ **CPA** and proton acceptor groups $Me_2P{=}O$ **CPO** with the amino group of Remdesivir, the amide group of Nevirapine, the amino group and amide group of Vesatolimod, and the amide group of Bictegravir.

Keywords: calixarenes; antiviral drugs; supramolecular complexes; chromatography; molecular modeling

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Дослідження комплексоутворення калікс[4]арен-гідроксиметилфосфонової кислоти та калікс[4]арен-гідроксиметилдиметилфосфіноксиду з антивірусними препаратами

Анотація

Методами ОФ ВЕРХ у водно-органічній рухомій фазі на колонці Zorbax CN досліджено комплексоутворення конусоподібних калікс[4]арен-гідроксиметилфосфонової кислоти (**CPA**) та калікс[4]арен-гідроксиметилдиметилфосфіноксиду (**CPO**) з активними фармацевтичними інгредієнтами антивірусних препаратів Ремдесивір, Невірапін, Весатолімод та Біктегравір. Аналізом залежності значень ємності препаратів від концентрації каліксарену в рухомій фазі визначено константи стійкості утворених супрамолекулярних комплексів (K_A = 3672 – 6884 M^{-1}). Квантово-хімічні розрахунки доводять, що досліджені препарати утворюють з молекулами **CPA** та **CPO** супрамолекулярні екзокомплекси. Ці комплекси стабілізовані міжмолекулярними водневими зв'язками протонодонорних груп $P(O)(OH)_2$ **CPA** та протоноакцепторних груп $Me_2P{=}O$ **CPO** з аміногрупою Ремдесивіру, амідною групою Невірапіну, аміногрупою та амідною групою Весатилімоду, амідною групою Біктегравіру.

Ключові слова: каліксарени; антивірусні препарати; супрамолекулярні комплекси; хроматографія; молекулярне моделювання

Citation: Kalchenko, O. I.; Cherenok, S. O.; Selikhova, A. I.; López-Cornejo, P.; Drapailo, A. B.; Kalchenko V. I. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (3), 11–21.
https://doi.org/10.24959/ophcj.25.336375
Received: *4 July 2025*; **Revised:** *13 September 2025*; **Accepted:** *20 September 2025*

Funding: This work was supported by the National Academy of Sciences of Ukraine (grant No. 0120U104649), and by the Ministerio de Ciencia, Innovación y Universidades (PID2023-151642OB-I00) and the European Union (Feder Funds).
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

Cup-shaped calixarenes [1, 2] and their self-assembled supramolecular aggregates [3], forming host-guest supramolecular complexes with active pharmaceutical ingredients (APIs) of drugs are considered as promising objects in design of the drug delivery vectors [4–11]. Advantages of the calixarene vectors are low cytotoxicity [12–16] and the absence of immune reactions [17]. Among the variety of calixarenes, water-soluble calixarene sulfonic acids are the best studied vectors [18]. They are capable of forming supramolecular complexes with the known APIs – 3-phenyl-1*H*[1]benzofuro[3,2-*c*]pyrazole (tyrosine kinase III inhibitor) [19], Carvediol (treatment of hypertension) [20], Paclitaxel (ovarian, breast, lung and colon cancer treatment) [21], Tramadol (analgesic) [22], Irinotecan (colon cancer treatment) [23], Nifedipine (calcium channel blocker) [24], Tenofovir (antiretroviral drug) [25].

The water-soluble cup-shaped calixarenes functionalized on the upper or lower rim of the macrocycle with hydrophilic organophosphorus groups are also used in the creation of drug delivery systems. It should be noted that phosphorus is a biologically friendly element, and a number of drugs for medicine have been created on the basis of natural and synthetic organophosphorus compounds [26, 27].

Phosphorus-containing calixarenes are characterized by a high biological activity and low cytotoxicity [28–30]. The calixarene and thiacalixarene-phosphonic acids effectively and selectively inhibit ATP-hydrolase systems of smooth muscle cells [31] and therapeutically important phosphatases of various origins [32–36]. It has been shown that the lower-rim calixarene-diphosphoric acid, which forms supramolecular complexes with water-insoluble APIs in aqueous solutions, is appropriate for drug formulation and delivery [37]. This acid also activates the transfer of polyarginine cell-penetrating peptides through biological membranes [38].

The upper rim modification of the cup-shaped calix[4]arene with hydrophilic phosphine oxide groups and phosphonic or phosphinic acid groups yielded water-soluble derivatives that form supramolecular complexes with APIs of 5-Fluorouracil and 5-Methyluracil anticancer drugs [39] as well as with antiretroviral drugs Tenofovir and Emtricitabin [40]. Stability constants of the complexes were determined by the HPLC method in the aqueous-organic medium. The most favored structures of the calixarene complexes with the APIs were optimized at the DFT level of approximation. In the most favored structures, APIs coordinate *via* hydrogen bonding with the phosphorus groups at the upper rim of the calixarene ligands.

Micelles of amphiphilic alkoxycalixarene-methylphosphonic acid form three-component nanoparticles with the antitumor drugs Carboplatin and Taxol in the aqueous medium [41]. In such a three-component nanocomplex, Carboplatin enters the molecular cavity of calixarene, and Taxol is located among the alkyl substituents of the micellar structure. These nanocomposites showed higher cytotoxicity compared to a simple mixture of the two drugs on HT-29 and Caco-2 colon tumor cells.

Micellar alkoxycalixarene-hydroxymethylene-bisphosphonic acids form nanoscale supramolecular complexes with fluorescently labeled polylysine and HIV-1 nucleocapsid due to electrostatic interactions. Such nanocomplexes cross biological membranes and deliver the therapeutically important proteins into cells [42].

In this article, within the context of further research on the drug formulation and delivery, the host-guest complexation of the cup-shaped calix[4]arene-*bis*-hydroxymethylphosphonic acid **CPA** and calix[4]arene-*bis*-hydroxymethyl-dimethylphosphine oxide **CPO** with the antiviral drugs Nevirapine, Remdesivir, Vesatolimod, and Bictegravir (**Figure 1**) in the aqueous-organic medium was studied using RP HPLC and molecular modeling methods.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

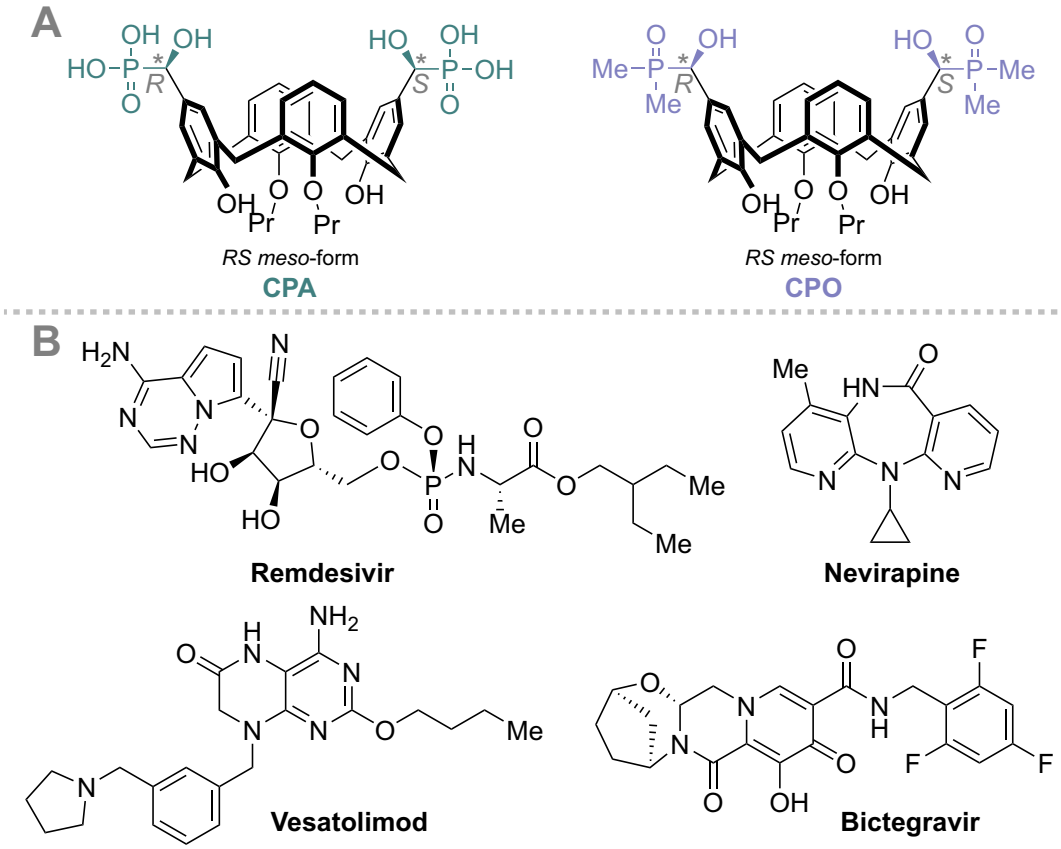

Figure 1. Calixarene-hydroxymethylphosphonic acid **CPA** (*RS meso*-form) and calixarene-hydroxymethyldimethylphosphine oxide **CPO** (*RS meso*-form) (hosts, *A*); and antiviral drugs Remdesivir, Nevirapine, Vesatolimod, Bictegravir (guests, *B*)

■ Materials and methods

Reagents and Materials

Calixarenes **CPA** and **CPO** were synthesized according to the methods [43, 44], respectively. Nevirapine, Vesatolimod and Bictegravir were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Abcam (Cambridge, UK). Remdesivir was obtained from UOSLAB (Kyiv, Ukraine).

HPLC analysis

The RP HPLC analysis of **CPA**, **CPO**, and antiviral drugs was performed on a Hitachi high-pressure liquid chromatography equipment (Hitachi, Ltd., Tokyo, Japan) under isocratic conditions using a Zorbax CN chromatographic column (250 × 4.6 mm) (supplier – Agilent) and the mobile phase of MeCN/H_2O/MeOH (79:20:1 by volume). The choice of a three-component mobile phase was driven by the need to solubilize calixarenes and antiretroviral drugs of different natures simultaneously. The concentration of **CPA** and **CPO** in the mobile phase varied within the range of 0.1×10^{-4}–1.4×10^{-4} M. Samples of the antiviral drugs for analysis were prepared in a solvent identical to the mobile phase (C = 1×10^{-5} M) and injected in amounts of 20 µL. All chromatograms were obtained at 28 °C. The UV detector wavelength was 254 nm. Each sample was analyzed in triplicate.

Molecular modeling

CPA and **CPO**, as well as their complexes with antiviral drugs, were simulated in vacuum (PM3, software package – evaluation version 8.0.10 of Hyper Chem program) [45]. The RMS gradient was 0.01 kcal mol^{-1}.

■ Results and discussion

Antiviral drugs are widely used to prevent and treat many infectious diseases [46, 47]. However, such drugs may have low bioavailability and cause side effects [48, 49]. Therefore, in some cases they are used in the form of prodrugs or supramolecular complexes with cyclodextrins. To search supramolecular complexing agents for Remdesivir, Nevirapine, Vesatolimod, and Bictegravir, we studied water-soluble calixarenes **CPA** possessing anionic $P(O)(OH)_2$ groups and calixarene **CPO** possessing neutral $Me_2P{=}O$ groups.

It is known that the highly polar $Me_2P{=}O$ group [50] is currently used in medicinal chemistry to improve the water solubility of drug molecules and optimize their pharmacokinetic profile [27, 51]. It was taken into account that the proton-accepting property of the oxygen atom of dimethylphosphine oxide derivatives exceeded the proton-accepting property of the oxygen atoms

of phosphates, phosphonates, sulfones, and carbonyl compounds [52]. A clear example of the effective use of the dimethylphosphine oxide group in medicinal chemistry is the recent creation of the drug Brigatinib [53, 54] and a number of clinical candidates [55]. The proton acceptor group $Me_2P(O)$ determines water solubility and ensures an effective interaction of Brigatinib with the biological target through the formation of strong hydrogen bonds. As a result, the medicinal efficacy of Brigatinib increases by 70 times compared to the corresponding non-phosphorylated analog.

The presence of hydrophilic proton-donating $P(O)(OH)_2$ or proton-accepting $Me_2P{=}O$ groups on the upper rim of **CPA** and **CPO** determines the water solubility of calixarenes. On the other hand, these groups stabilize supramolecular host-guest complexes by forming intermolecular hydrogen bonds P-OH···X or P=O···H-X (X = O, N) with amine, amide, hydroxyl, and other groups of the antiviral drugs.

The main criterion for assessing the complexing properties of a host molecule is the value of the stability constant of the supramolecular complex with a guest molecule. To determine the stability constants of the calixarene complexes, various physical methods are used: microcalorimetry [56], nuclear magnetic resonance [57], UV and fluorescence spectroscopy [58–60], selective transport through liquid membranes [61], mass spectrometry [62, 63], surface plasmon resonance [64], etc. However, the application of these methods may be limited by the unsatisfactory solubility of calixarene receptors or substrate molecules, or the high cost of the methods.

A convenient and rapid method for determining the stability constants of complexes is reversed-phase high-performance liquid chromatography [65, 66]. This method has been used to determine the stability constants of calixarene complexes with organic substrates of various natures in aqueous or aqueous-organic solutions [67–70]. According to this method, stability constants are determined from the dependence of the substrate's retention time or capacity factor on the calixarene concentration in the mobile phase. The addition of calixarenes to the mobile phase reduces the retention time of analytes due to the formation of supramolecular host-guest complexes and the increased polarity of the chromatographic column surface upon calixarene sorption. The inverse sorption of calixarenes by the column surface and the linear dependence of the capacity value $1/k'$ of the analyte on the calixarene concentration indicate 1:1 stoichiometry complexes in the mobile phase flow. This allows to use equation (1) [68, 69] to calculate the stability constants of the host-guest complexes:

$$1 / k' = 1 / k_0' + K_A \times [CA] / k_0' \qquad (1)$$

where k_0' and k' are the capacity factors of the analyte determined before and after the addition of calixarene to the mobile phase; [*CA*] is the concentration of calixarene in the mobile phase.

Under the analysis conditions, antiviral drugs and calixarenes have retention times t_R: 6.735 min (Remdesivir), 6.915 min (Nevirapine), 7.327 min (Vesatolimod), 5.873 (Bictegravir), 7.382 min (**CPA**), and 6.958 min (**CPO**) (**Figure 2**).

Calixarenes **CPA** and **CPO** were characterized by linear adsorption isotherms (**Figures 3** and **4**), which indicated their reverse adsorption on the surface of the Zorbax CN column.

The addition of calixarenes to the mobile phase reduces the retention time t_R of antiviral drugs. The linear nature of the dependences of their parameters $1/k'$ on the concentration of calixarenes in the mobile phase (**Figures 5** and **6**) indicates the formation of supramolecular host-guest complexes with a stoichiometry of 1:1.

The stability constants of the complexes K_A (3672–6884 M^{-1}) calculated by formula (1), and the values of the Gibbs free energies $-\Delta G$ (4.852–5.224 $kJ \cdot mol^{-1}$) calculated by the equation $\Delta G = -RT \times \ln K_A$ are given in **Table 1**. The stability constants K_A are rather close to the stability constant of the 1:1 complex of the calix[4]arene-sulfonic acid with the antiretroviral drug Tenofovir disoproxil fumarate determined by UV/Vis spectroscopy in the DMSO solution [42]. This calix[4]-arene-sulfonic acid complex was further studied for antimicrobial applications against methicillin resistant *Staphylococcus aureus* (MRSA).

The values of the stability constants K_A and Gibbs free energies ΔG depend on the structure of the calixarene host and the antiviral drug guest and increase in the following order

Bictegravir < Vesatolimod <
< Nevirapine < Remdesivir

for complexes with CPA, and

Nevirapine < Vesatolimod <
< Remdesivir < Bictegravir

for complexes with CPO.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

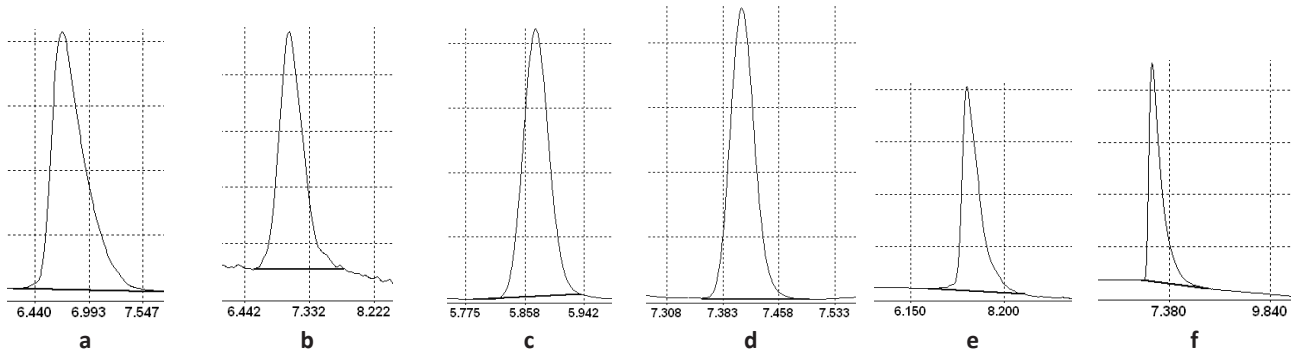

Figure 2. Chromatograms of Remdesivir (a), Nevirapine (b), Bictegravir (c), Vesatolimod (d), **CPA** (e), **CPO** (f)

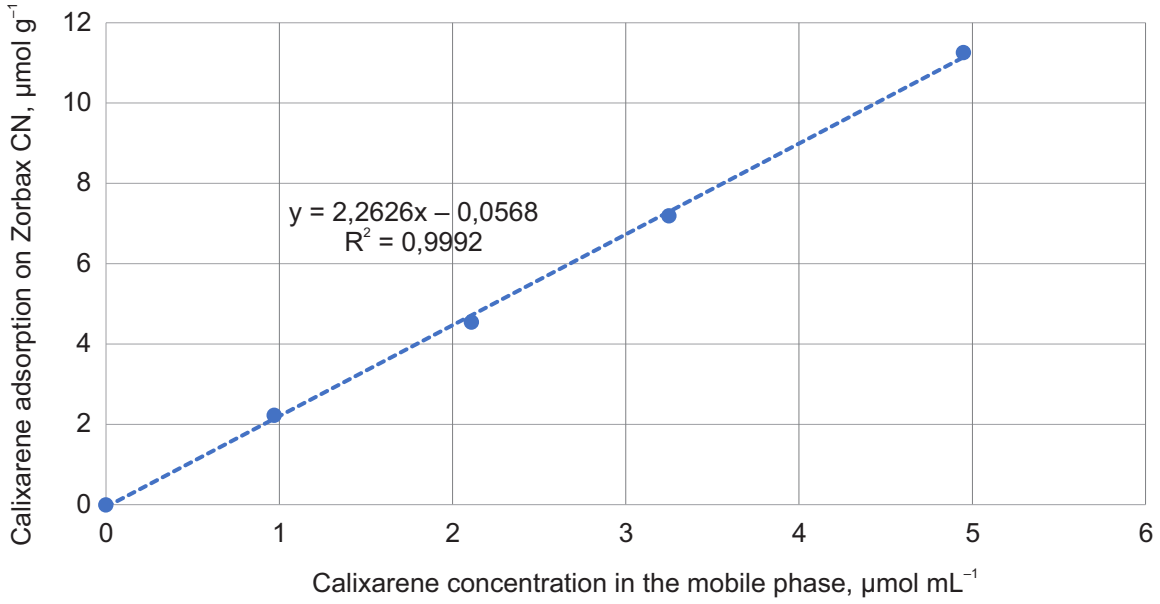

Figure 3. The adsorption isotherm of calixarene **CPA**

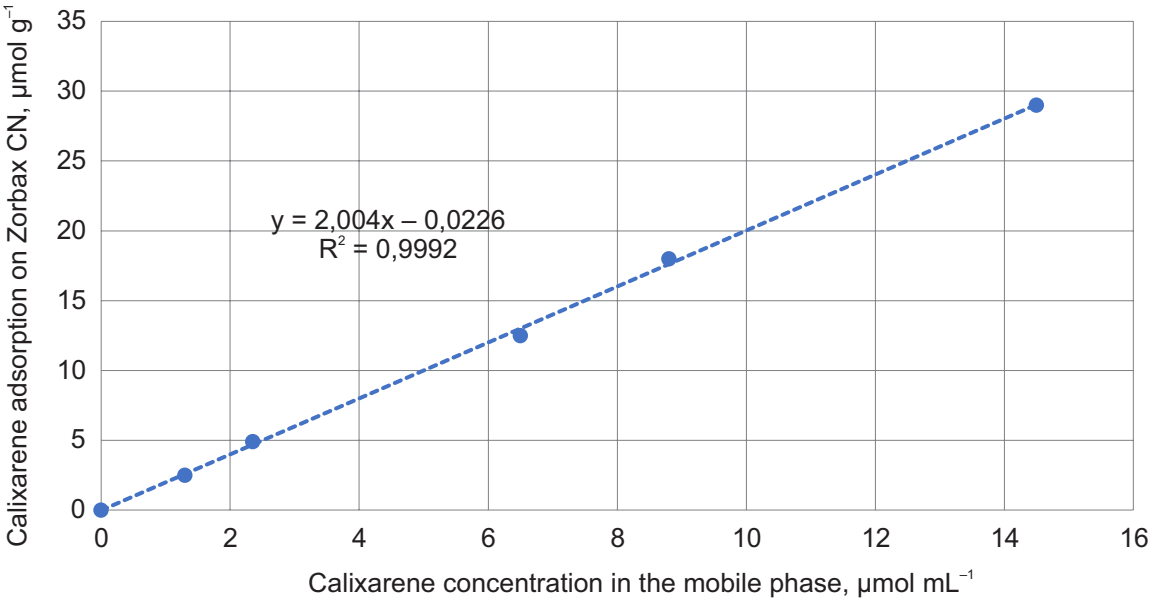

Figure 4. The adsorption isotherm of calixarene **CPO**

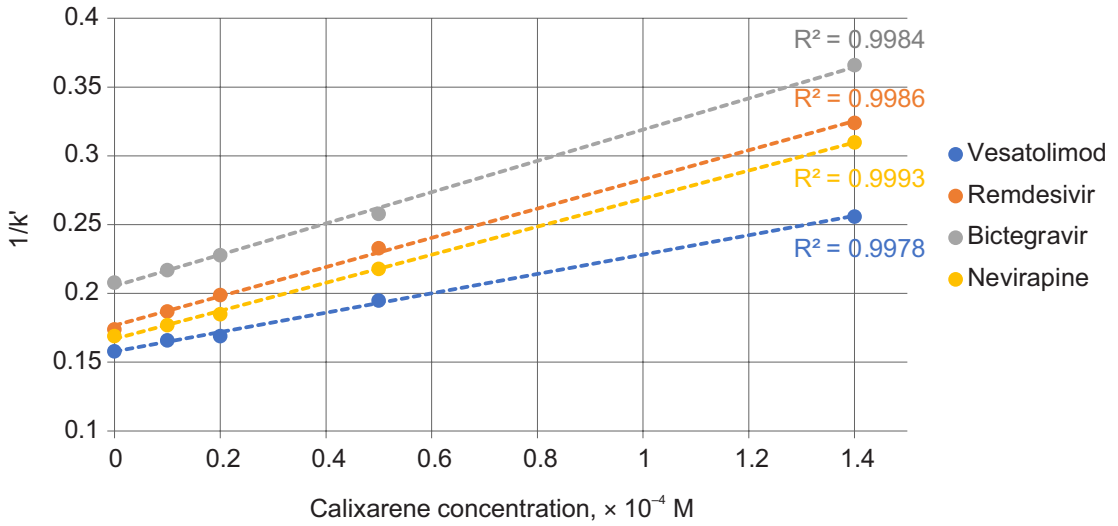

Figure 5. The dependence of 1/*k'* values of the antiviral drugs on the concentration of **CPA** in the mobile phase

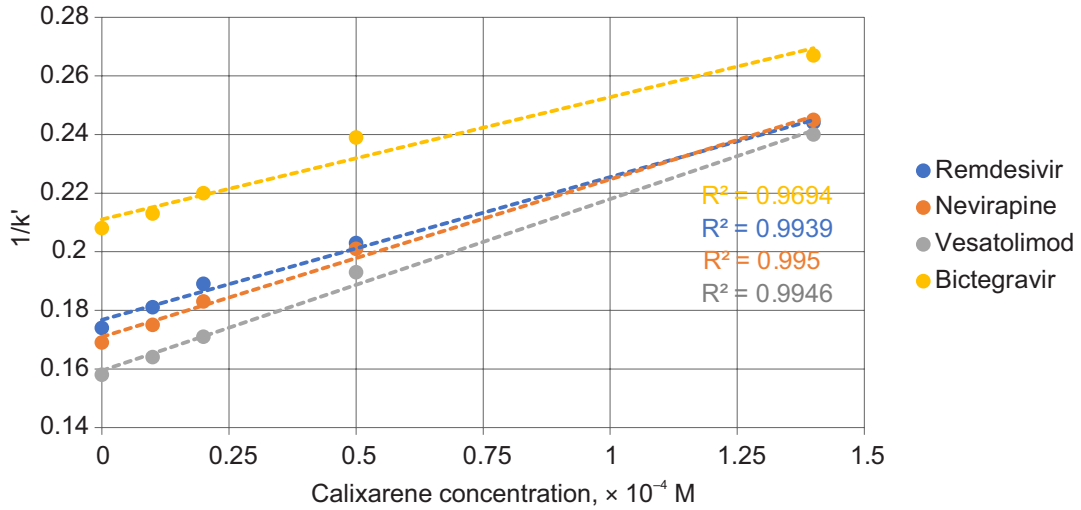

Figure 6. The dependence of 1/*k'* values of the antiviral drugs on the concentration of **CPO** in the mobile phase (R^2=0.99)

Table 1. Stability constants K_A and Gibbs free energies ΔG of the complexes of **CPA** and **CPO** with antiviral drugs

Antiviral drug	CPA		CPO	
	K_A, M^{-1} (RSD, %)	ΔG, kJ·mol^{-1}	K_A, M^{-1} (RSD, %)	ΔG, kJ·mol^{-1}
Remdesivir	6884 (19)	5.224	4695 (15)	4.998
Nevirapine	5305 (27)	5.070	3672 (25)	4.852
Vesatolimod	4875 (21)	5.020	4015 (18)	4.905
Bictegravir	4850 (20)	5.017	5328 (27)	5.072

The dependence of the stability constants on the structure of the calixarene and the antiviral agent is complicated and can be determined by hydrogen bonds, van der Waals forces, solvatophobic and other non-covalent interactions.

To understand the nature of complex formation, the structures of calixarenes and their complexes with molecules of antiviral agents were energetically minimized. According to energy minimization data, **CPA** and **CPO** molecules exist in a *flattened cone* conformation, in which the phosphorylated benzene rings are oriented "coplanarly" and the unsubstituted rings are oriented "perpendicularly" to the main plane of the molecule formed by the methylene groups of the macrocyclic backbone. This conformation is stabilized by two intramolecular hydrogen bonds Ar-OH···O-Alk on the lower rim of the macrocycle (**Figure 7**).

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Figure 7. Energy-minimized molecular structures of **CPA** (a) and **CPO** (b)

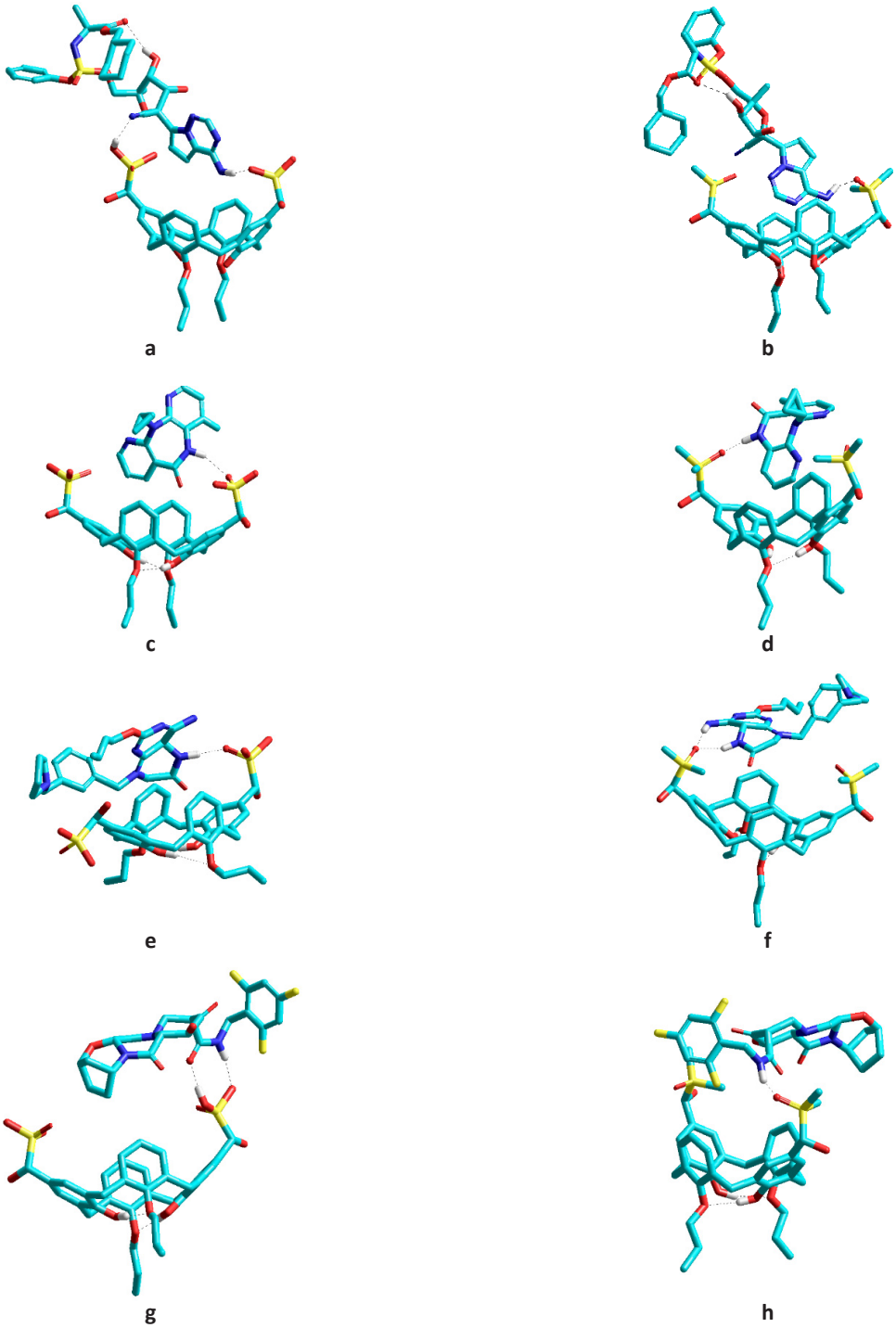

Figure 8. Energy-minimized molecular structures of supramolecular exo-complexes CPA@Remdesivir (a), CPO@Remdesivir (b), CPA@Nevirapine (c), CPO@Nevirapine (d), CPA@Vesatolimod (e), CPO@Vesatolimod (f) CPA@Bictegravir (g), CPO@Bictegravir (h)

According to the calculations, calixarenes form *exo*-complexes with large and branched molecules Remdesivir, Nevirapine, Vesatolimod, and Bictegravir, which "hang" over the upper rim of the macrocycle (**Figure 8**). The complexes are stabilized by intermolecular hydrogen bonds of proton donor groups $P(O)(OH)_2$ of **CPA** and proton acceptor groups $Me_2P{=}O$ of **CPO** with the amino group and nitrile group of Remdesivir, the amide group of Nevirapine, the amino group and amide group of Vesatilimod, and the amide group of Bictegravir.

It should be noted that among the drugs studied, the most compact Nevirapine molecule is directed by a nonmethylated pyridine fragment into the lipophilic macrocyclic cavity of calixarenes (**Figures 8**c,d). In this case, the complexes, in addition to hydrogen bonds of the amide group of Nevirapine with the phosphorus groups of **CPA** and **CPO**, can also be stabilized by van der Waals forces, or solvatophobic interactions.

■ Conclusions

The value of stability constants K_A (3672–6884 M^{-1}) of supramolecular host-guest complexes between water-soluble calix[4]arenehydroxymethylphosphonic acid **CPA** and calix[4]arenehydroxymethyldimethylphosphine oxide **CPO** with active pharmaceutical ingredients of antiviral drugs Remdesivir, Nevirapine, Vesatolimod and Bictegravir depends on the structures of the calixarene and the antiviral drug and increases in the following order

Bictegravir < Vesatolimod <
< Nevirapine < Remdesivir

for complexes with CPA and

Nevirapine < Vesatolimod <
< Remdesivir < Bictegravir

for complexes with CPO.

According to energy minimized data, the **CPA** and **CPO** molecules exist in a *flattened cone* conformation, which is suitable for the host-guest complexation and in which the phosphorylated benzene rings are oriented "coplanarly", while the unsubstituted rings are oriented "perpendicularly" to the main plane of the molecule formed by the methylene groups of the macrocyclic backbone. According to the molecular modeling, calixarenes form *exo*-complexes with large and branched molecules of antiviral drugs, which "hang" over the upper rim of the macrocycle. The complexes are stabilized by intermolecular hydrogen bonds of proton donor groups $P(O)(OH)_2$ of **CPA** and proton acceptor groups $Me_2P{=}O$ of **CPO** with the amino group of Remdesivir, the amide group of Nevirapine, the amino group and amide group of Vesatilimod, and the amide group of Bictegravir.

Thus, the synthetically available water-soluble anionic or neutral calixarenes **CPA** and **CPO** possessing wide possibilities of chemical modification have the prospect of application in formulations of the antiviral drugs and the creation of vectors for their delivery systems.

■ Acknowledgements

Anna I. Selikhova thanks for the scholarship for this work received in the framework of the Erasmus+ Program funded by the University of Seville within the Agreement on Academic, Scientific and Cultural Cooperation signed by the University of Seville (Spain) and the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine (Ukraine).

■ References

1. *Calixarenes and Beyond*; Neri, P.; Sessler, J. L.; Wang, M.-X., Eds.; Springer International Publishing: Cham, 2016. https://doi.org/10.1007/978-3-319-31867-7.
2. *Calixarenes in the Nanoworld*; Vicens, J.; Harrowfield, J.; Baklouti, L., Eds.; Springer Netherlands, 2007. https://doi.org/10.1007/978-1-4020-5022-4.
3. Liu, Z.; Dai, X.; Sun, Y.; Liu, Y. Organic Supramolecular Aggregates Based on Water-soluble Cyclodextrins and Calixarenes. *Aggregate* **2020**, *1* (1), 31–44. https://doi.org/10.1002/agt2.3.
4. Español, E. S.; Villamil, M. M. Calixarenes: Generalities and Their Role in Improving the Solubility, Biocompatibility, Stability, Bioavailability, Detection, and Transport of Biomolecules. *Biomolecules* **2019**, *9* (3), 90. https://doi.org/10.3390/biom9030090.
5. Rodik, R. V.; Boyko, V. I.; Kalchenko, V. I. Calixarenes in Biotechnology and Bio-Medical Research. In *Frontiers in Medicinal Chemistry*; Atta-ur-Rahman; Choudhary, M. I.; Reitz, A. B., Eds.; Bentham Science Publishers, 2016; pp 206–301. https://doi.org/10.2174/9781681081755116080008.
6. Pan, Y.; Hu, X.; Guo, D. Biomedical Applications of Calixarenes: State of the Art and Perspectives. *Angew. Chem. Int. Ed.* **2021**, *60* (6), 2768–2794. https://doi.org/10.1002/anie.201916380.
7. Fan, X.; Guo, X. Development of Calixarene-Based Drug Nanocarriers. *Journal of Molecular Liquids* **2021**, *325*, 115246. https://doi.org/10.1016/j.molliq.2020.115246.
8. Bai, H.; Wang, J.; Li, Z.; Tang, G. Macrocyclic Compounds for Drug and Gene Delivery in Immune-Modulating Therapy. *IJMS* **2019**, *20* (9), 2097. https://doi.org/10.3390/ijms20092097.
9. Baldini, L.; Casnati, A.; Sansone, F. Multivalent and Multifunctional Calixarenes in Bionanotechnology. *Eur. J. Org. Chem.* **2020**, *2020* (32), 5056–5069. https://doi.org/10.1002/ejoc.202000255.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

10. Ostos, F. J.; Lebrón, J. A.; López-Cornejo, P.; López-López, M.; García-Calderón, M.; García-Calderón, C. B.; Rosado, I. V.; Kalchenko, V. I.; Rodik, R. V.; Moyá, M. L. Self-Aggregation in Aqueous Solution of Amphiphilic Cationic Calix[4]Arenes. Potential Use as Vectors and Nanocarriers. *Journal of Molecular Liquids* **2020**, *304*, 112724. https://doi.org/10.1016/j.molliq.2020.112724.
11. Lebrón, J. A.; López-López, M.; García-Calderón, C. B.; V. Rosado, I.; Balestra, F. R.; Huertas, P.; Rodik, R. V.; Kalchenko, V. I.; Bernal, E.; Moyá, M. L.; López-Cornejo, P.; Ostos, F. J. Multivalent Calixarene-Based Liposomes as Platforms for Gene and Drug Delivery. *Pharmaceutics* **2021**, *13* (8), 1250. https://doi.org/10.3390/pharmaceutics13081250.
12. Perret, F.; Mazzorana, M.; Shahgaldian, P.; Coleman, A. W. First step in the study of the cellular toxicity of the calixarene. International Symposium on Supramolecular Chemistry XI, Fukuoka, 2000; PB-26, 387.
13. Da Silva, E.; Shahgaldian, P.; Coleman, A. W. Haemolytic Properties of Some Water-Soluble Para-Sulphonato-Calix-[n]-Arenes. *International Journal of Pharmaceutics* **2004**, *273* (1–2), 57–62. https://doi.org/10.1016/j.ijpharm.2003.12.008.
14. Coleman, A. W.; Jebors, S.; Cecillon, S.; Perret, P.; Garin, D.; Marti-Battle, D.; Moulin, M. Toxicity and Biodistribution of Para-Sulfonato-Calix[4]Arene in Mice. *New J. Chem.* **2008**, *32* (5), 780. https://doi.org/10.1039/b718962a.
15. Chernyshenko, V. O.; Korolova, D. S.; Nikolaienko, T. V.; Dosenko, V. E.; Pashevin, D. O.; Kalchenko, V. I.; Cherenok, S. O.; Khranovska, N. N.; Garmanchuk, L. V.; Lugovskoy, E. V.; Komisarenko, S. V. Calix[4]arene C-145 Effects on Cellular Haemostasis. *Biotechnologia acta* **2016**, *9* (3), 37–43. https://doi.org/10.15407/biotech9.03.037.
16. Shahgaldian, P.; Da Silva, E.; Coleman, A. W. A First Approach to the Study of Calixarene Solid Lipid Nanoparticle (SLN) Toxicity. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **2003**, *46* (3/4), 175–177. https://doi.org/10.1023/A:1026301906487.
17. 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. Design of Nonpeptidic Topomimetics of Antiangiogenic Proteins with Antitumor Activities. *JNCI: Journal of the National Cancer Institute* **2006**, *98* (13), 932–936. https://doi.org/10.1093/jnci/djj247.
18. Perret, F.; Lazar, A. N.; Coleman, A. W. Biochemistry of the Para-Sulfonato-Calix[n]Arenes. *Chem. Commun.* **2006**, *2006* (23), 2425–2438. https://doi.org/10.1039/b600720c.
19. Galindo-Murillo, R.; Olmedo-Romero, A.; Cruz-Flores, E.; Petrar, P. M.; Kunsagi-Mate, S.; Barroso-Flores, J. Calix[n]Arene-Based Drug Carriers: A DFT Study of Their Electronic Interactions with a Chemotherapeutic Agent Used against Leukemia. *Computational and Theoretical Chemistry* **2014**, *1035*, 84–91. https://doi.org/10.1016/j.comptc.2014.03.001.
20. Menon, S. K.; Mistry, B. R.; Joshi, K. V.; Modi, N. R.; Shashtri, D. Evaluation and Solubility Improvement of Carvedilol: PSC[n]Arene Inclusion Complexes with Acute Oral Toxicity Studies. *J. Incl. Phenom. Macrocycl. Chem.* **2012**, *73* (1–4), 295–303. https://doi.org/10.1007/s10847-011-0056-x.
21. Chen, M.-X.; Li, T.; Peng, S.; Tao, D. Supramolecular Nanocapsules from the Self-Assembly of Amphiphilic Calixarene as a Carrier for Paclitaxel. *New J. Chem.* **2016**, *40* (12), 9923–9929. https://doi.org/10.1039/C6NJ01986B.
22. Zhao, Q.-H.; Chen, C.-P.; Pang, T.-T.; Du, L.-M.; Li, Y.; Xie, J.-H.; Fu, Y.-L. Investigated the Supramolecular Interaction of Tramadol Hydrochloride with P-Sulfonated Calix[4,6,8]Arene. *J. Chil. Chem. Soc.* **2015**, *60* (4), 2659–2663. https://doi.org/10.4067/S0717-97072015000400007.
23. Wang, Y.-X.; Guo, D.-S.; Duan, Y.-C.; Wang, Y.-J.; Liu, Y. Amphiphilic P-Sulfonatocalix[4]Arene as "Drug Chaperone" for Escorting Anticancer Drugs. *Sci. Rep.* **2015**, *5* (1), 9019. https://doi.org/10.1038/srep09019.
24. Yang, W.; De Villiers, M. M. The Solubilization of the Poorly Water Soluble Drug Nifedipine by Water Soluble 4-Sulphonic Calix[n]Arenes. *European Journal of Pharmaceutics and Biopharmaceutics* **2004**, *58* (3), 629–636. https://doi.org/10.1016/j.ejpb.2004.04.010.
25. Jarange, A. B.; Patil, S. V.; Malkhede, D. D.; Deodhar, S. M.; Nandre, V. S.; Athare, S. V.; Kodam, K. M.; Gejji, S. P. P-Sulfonatocalixarene versus p-Thiasulfonatocalixarene: Encapsulation of Tenofovir Disoproxil Fumarate and Implications to ESI-MS, HPLC, NMR, DFT and Anti-MRSA Activities. *J. Incl. Phenom. Macrocycl. Chem.* **2021**, *99* (1-2), 43-59. https://doi.org/10.1007/s10847-020-01022-w.
26. *Organophosphorus Chemistry: Novel Developments*; Keglevich, G., Ed.; De Gruyter, 2018. https://doi.org/10.1515/9783110535839.
27. Finkbeiner, P.; Hehn, J. P.; Gnamm, C. Phosphine Oxides from a Medicinal Chemist's Perspective: Physicochemical and *in Vitro* Parameters Relevant for Drug Discovery. *J. Med. Chem.* **2020**, *63* (13), 7081–7107. https://doi.org/10.1021/acs.jmedchem.0c00407.
28. Komisarenko, S. V.; Kosterin, S. O.; Lugovskoy, E. V.; Cherenok, S. O.; Tanchuk, V. Yu.; Vovk, A. I.; Kalchenko, V. I. Synthesis and characterization of calixarene methylene bisphosphonic acids as effectors of biochemical processes. In *Ligands: synthesis, characterization and role in biotechnology*; Gawryszewska, P.; Smolenski, P., Eds.; Nova Science Publishers, Inc: New York, 2014; Chapter 3, 67-116.
29. Labyntseva, R. D.; Yavorovska, V. I.; Bevza, O. V.; Kalchenko, V. I.; Kosterin, S. O. Calix[4]arenes as the effectors of smooth muscle myosin ATPase. In *Myosin: biosynthesis, classes and function*; Broadbent, D., Ed. Nova Science Publishers, Inc.: New York, 2018; Chapter 2, 89-135.
30. Tauran, Y.; Coleman, A.; Perret, F.; Kim, B. Cellular and in Vivo Biological Activities of the Calix[n]Arenes. *Current Organic Chemistry* **2015**, *19* (23), 2250–2270. https://doi.org/10.2174/1385272819666150608222114.
31. Kosterin, S. O.; Kalchenko, V. I.; Veklich, T. O.; Babich, L. G.; Shlikov, S. G. *Calix[4]arenes as modulators of ATP-hydrolase systems of smooth muscle cells*. Naukova Dumka: Kyiv, 2019.
32. Trush, V. V.; Cherenok, S. O.; Tanchuk, V. Yu.; Kukhar, V. P.; Kalchenko, V. I.; Vovk, A. I. Calix[4]Arene Methylenebisphosphonic Acids as Inhibitors of Protein Tyrosine Phosphatase 1B. *Bioorganic & Medicinal Chemistry Letters* **2013**, *23* (20), 5619–5623. https://doi.org/10.1016/j.bmcl.2013.08.040.
33. Vovk, A. I.; Tanchuk, V. Yu.; Kononets, L. A.; Cherenok, S. O.; Drapailo, A. B.; Kalchenko, V. I.; Kukhar, V. P. A Novel Approach to the Design of Phosphonate Inhibitors of Protein Tyrosine Phosphatase. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2011**, *186* (4), 958–960. https://doi.org/10.1080/10426507.2010.521213.
34. Vovk, A. I.; Kononets, L. A.; Tanchuk, V. Yu.; Cherenok, S. O.; Drapailo, A. B.; Kalchenko, V. I.; Kukhar, V. P. Inhibition of Yersinia Protein Tyrosine Phosphatase by Phosphonate Derivatives of Calixarenes. *Bioorganic & Medicinal Chemistry Letters* **2010**, *20* (2), 483–487. https://doi.org/10.1016/j.bmcl.2009.11.126.
35. Vovk, A. I.; Mischenko, I. M.; Cherenok, S. O.; Tanchuk, V. Yu.; Kalchenko, V. I.; Kukhar, V. P. Phosphorylated Calix[4]Arenes as Inhibitors of Glutathione S-Transferase. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2011**, *186* (4), 961–963. https://doi.org/10.1080/10426507.2010.514313.
36. Trush, V. V.; Kharchenko, S. G.; Tanchuk, V. Yu.; Kalchenko, V. I.; Vovk, A. I. Phosphonate Monoesters on a Thiacalix[4]Arene Framework as Potential Inhibitors of Protein Tyrosine Phosphatase 1B. *Org. Biomol. Chem.* **2015**, *13* (33), 8803–8806. https://doi.org/10.1039/C5OB01247C.
37. Bayrakci, M.; Ertul, Ş.; Yilmaz, M. Phase Solubility Studies of Poorly Soluble Drug Molecules by Using *O*-Phosphorylated Calixarenes as Drug-Solubilizing Agents. *J. Chem. Eng. Data* **2012**, *57* (1), 233–239. https://doi.org/10.1021/je200992c.
38. Perret, F.; Nishihara, M.; Takeuchi, T.; Futaki, S.; Lazar, A. N.; Coleman, A. W.; Sakai, N.; Matile, S. Anionic Fullerenes, Calixarenes, Coronenes, and Pyrenes as Activators of Oligo/Polyarginines in Model Membranes and Live Cells. *JACS* **2005**, *127* (4), 1114–1115. https://doi.org/10.1021/ja043633c.

39. Kalchenko, O. I.; Rozhenko, A. B.; Cherenok, S. O.; Selikhova, A. I.; Suikov, S. Yu.; Kyrylchuk, A. A.; Kalchenko, V. I. Complexation of Water-Soluble Phosphorylated Calixarenes with Uracils. Stability Constants and DFT Study of the Supramolecular Complexes. *J. Incl. Phenom. Macrocycl. Chem.* **2023**, *103* (9–10), 369–383. https://doi.org/10.1007/s10847-023-01198-x.
40. Kalchenko, O. I.; Rozhenko, A. B.; Cherenok, S. O.; Selikhova, A. I.; Drapailo, A. B.; López-Cornejo, P.; Kalchenko, V. I. Stability Constants and DFT Calculations of Anionic Calixarene Complexes with Antiretroviral Drugs Tenofovir and Emtricitabine. *J. Incl. Phenom. Macrocycl. Chem.* **2025**, *105* (5–6), 297–310. https://doi.org/10.1007/s10847-024-01273-x.
41. Li, M.; Mao, L.; Chen, M.; Li, M.; Wang, K.; Mo, J. Characterization of an Amphiphilic Phosphonated Calixarene Carrier Loaded with Carboplatin and Paclitaxel: A Preliminary Study to Treat Colon Cancer in Vitro and in Vivo. *Front. Bioeng. Biotechnol.* **2019**, *7*, 238. https://doi.org/10.3389/fbioe.2019.00238.
42. Rodik, R. V.; Cherenok, S. O.; Postupalenko, V. Y.; Oncul, S.; Brusianska, V.; Borysko, P.; Kalchenko, V. I.; Mely, Y.; Klymchenko, A. S. Anionic Amphiphilic Calixarenes for Peptide Assembly and Delivery. *Journal of Colloid and Interface Science* **2022**, *624*, 270–278. https://doi.org/10.1016/j.jcis.2022.05.124.
43. Cherenok, S. O.; Yushchenko, O. A.; Tanchuk, V. Yu.; Mischenko, I. M.; Samus, N. V.; Ruban, O. V.; Matvieiev, Y. I.; Karpenko, J. A.; Kukhar, V. P.; Vovk, A. I.; Kalchenko, V. I. Calix[4]Arene-α-Hydroxyphosphonic Acids. Synthesis, Stereochemistry, and Inhibition of Glutathione S-Transferase. *Arkivoc* **2012**, *2012* (4), 278–298. https://doi.org/10.3998/ark.5550190.0013.421.
44. Cherenok, S. O.; Shishkina, S. V.; Selikhova. A. I.; Drapailo, A. B.; Kalchenko, V. I. Synthesis and self-assembling of calix[4]arene-hydroxymethyl-dimethylphosphine oxides. Book of Abstracts, XXVI Ukrainian Conference on Organic and Bioorganic Chemistry, Uzhhorod, September 16–20, 2024, 41.
45. Hypercube Downloads http://www.hypercubeusa.com/Download/tabid/357/Default.aspx (accessed May 11, 2025).
46. Gupta, R. K.; Van De Vijver, D. A. M. C.; Manicklal, S.; Wainberg, M. A. Evolving Uses of Oral Reverse Transcriptase Inhibitors in the HIV-1 Epidemic: From Treatment to Prevention. *Retrovirology* **2013**, *10* (1), 82. https://doi.org/10.1186/1742-4690-10-82.
47. Arts, E. J.; Hazuda, D. J. HIV-1 Antiretroviral Drug Therapy. *Cold Spring Harbor Perspectives in Medicine* **2012**, *2* (4), a007161–a007161. https://doi.org/10.1101/cshperspect.a007161.
48. Margolis, A. M.; Heverling, H.; Pham, P. A.; Stolbach, A. A Review of the Toxicity of HIV Medications. *J. Med. Toxicol.* **2014**, *10* (1), 26–39. https://doi.org/10.1007/s13181-013-0325-8.
49. Paik, S. Fatal Nevirapine-Induced Toxic Epidermal Necrolysis in a HIV Infected Patient. *JCDR* **2016**. https://doi.org/10.7860/JCDR/2016/16360.7415.
50. Fedyk, A.; Slobodyanyuk, E. Y.; Stotska, O.; Vashchenko, B. V.; Volochnyuk, D. M.; Sibgatulin, D. A.; Tolmachev, A. A.; Grygorenko, O. O. Heteroaliphatic Dimethylphosphine Oxide Building Blocks: Synthesis and Physico-Chemical Properties. *Eur. J. Org. Chem.* **2021**, *2021* (47), 6591–6603. https://doi.org/10.1002/ejoc.202100581.
51. Fedyk, A. V.; Chalyk, B. A. Synthesis of Functionalized 4,5-Dihydroisoxazoles Decorated with the Dimethylphosphinoyl Group. *J. Org. Pharm. Chem.* **2023**, *21* (2), 41–52. https://doi.org/10.24959/ophcj.23.283988.
52. Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. The p K_{BHX} Database: Toward a Better Understanding of Hydrogen-Bond Basicity for Medicinal Chemists. *J. Med. Chem.* **2009**, *52* (14), 4073–4086. https://doi.org/10.1021/jm801331y.
53. National Cancer Institute. FDA grants Brigatinib accelerated approval for metastatic non-small cell lung cancer. https://www.cancer.gov/news-events/cancer-currents-blog/2017/brigatinib-fda-lung-cancer (accessed Jun 23, 2025).
54. Uchibori, K.; Inase, N.; Araki, M.; Kamada, M.; Sato, S.; Okuno, Y.; Fujita, N.; Katayama, R. Brigatinib Combined with Anti-EGFR Antibody Overcomes Osimertinib Resistance in EGFR-Mutated Non-Small-Cell Lung Cancer. *Nat. Commun.* **2017**, *8* (1), 14768. https://doi.org/10.1038/ncomms14768.
55. Yu, H.; Yang, H.; Shi, E.; Tang, W. Development and Clinical Application of Phosphorus-Containing Drugs. *Medicine in Drug Discovery* **2020**, *8*, 100063. https://doi.org/10.1016/j.medidd.2020.100063.
56. Zielenkiewicz, W.; Marcinowicz, A.; Poznański, J.; Cherenok, S.; Kalchenko, V. Complexation of Isoleucine by Phosphorylated Calix[4]Arene in Methanol Followed by Calorimetry, NMR and UV–VIS Spectroscopies, and Molecular Modeling Methods. *Journal of Molecular Liquids* **2005**, *121* (1), 8–14. https://doi.org/10.1016/j.molliq.2004.08.031.
57. Yakovenko, A. V.; Boyko, V. I.; Kalchenko, V. I.; Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *N*- Linked Peptidocalix[4]Arene Bisureas as Enantioselective Receptors for Amino Acid Derivatives. *J. Org. Chem.* **2007**, *72* (9), 3223–3231. https://doi.org/10.1021/jo062410x.
58. Sansone, F.; Barboso, S.; Casnati, A.; Sciotto, D.; Ungaro, R. A New Chiral Rigid Cone Water Soluble Peptidocalix[4]Arene and Its Inclusion Complexes with α-Amino Acids and Aromatic Ammonium Cations. *Tetrahedron Letters* **1999**, *40* (25), 4741–4744. https://doi.org/10.1016/S0040-4039(99)00838-2.
59. Acharya, A.; Ramanujam, B.; Chinta, J. P.; Rao, C. P. 1,3-Diamido-Calix[4]Arene Conjugates of Amino Acids: Recognition of −COOH Side Chain Present in Amino Acids, Peptides, and Proteins by Experimental and Computational Studies. *J. Org. Chem.* **2011**, *76* (1), 127–137. https://doi.org/10.1021/jo101759f.
60. Li, W. Y.; Li, H.; Zhang, G. M.; Chao, J. B.; Ling, L. X.; Shuang, S. M.; Dong, C. Interaction of Water-Soluble Calix[4]Arene with l-Tryptophan Studied by Fluorescence Spectroscopy. *Journal of Photochemistry and Photobiology A: Chemistry* **2008**, *197* (2–3), 389–393. https://doi.org/10.1016/j.jphotochem.2008.02.002.
61. Kim, L.; Hamdi, A.; Stancu, A. D.; Souane, R.; Mutihac, L.; Vicens, J. Selective Membrane Transport of Amino Acids by Functionalised Calix[4]Arenes. *J. Incl. Phenom. Macrocycl. Chem.* **2010**, *66* (1–2), 55–59. https://doi.org/10.1007/s10847-009-9622-x.
62. Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. Enantiomeric Recognition of Amino Acid Derivatives by Chiral Schiff Bases of Calix[4]Arene. *Tetrahedron: Asymmetry* **2007**, *18* (7), 900–905. https://doi.org/10.1016/j.tetasy.2007.04.001.
63. Stone, M. M.; Franz, A. H.; Lebrilla, C. B. Non-Covalent Calixarene-Amino Acid Complexes Formed by MALDI-MS. *J. Am. Soc. Mass Spectrom.* **2002**, *13* (8), 964–974. https://doi.org/10.1016/S1044-0305(02)00417-8.
64. Chen, H.; Gu, L.; Yin, Y.; Koh, K.; Lee, J. Molecular Recognition of Arginine by Supramolecular Complexation with Calixarene Crown Ether Based on Surface Plasmon Resonance. *IJMS* **2011**, *12* (4), 2315–2324. https://doi.org/10.3390/ijms12042315.
65. Lipkowski, J.; Kalchenko, O. I.; Slowikowska, J.; Kalchenko, V. I.; Lukin, O. V.; Markovsky, L. N.; Nowakowski, R. Host-Guest Interactions of Calix[4]Resorcinarenes with Benzene Derivatives in Conditions of Reversed-Phase High-Performance Liquid Chromatography. Determination of Stability Constants. *J. Phys. Org. Chem.* **1998**, *11* (6), 426–437. https://doi.org/10.1002/(SICI)1099-1395(199806)11:6%253C426::AID-POC963%253E3.0.CO;2-R.
66. Kalchenko, O. I.; Lipkowski, J.; Kalchenko, V. I.; Vysotsky, M. A.; Markovsky, L. N. Effect of Octakis(Diethoxyphosphoryloxy)-Tert-Butyl-Calix[8]Arene in Mobile Phase on the Reversed-Phase Retention Behavior of Aromatic Compounds: Host-Guest Complex Formation and Stability Constants Determination. *Journal of Chromatographic Science* **1998**, *36* (5), 269–273. https://doi.org/10.1093/chromsci/36.5.269.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

67. Kalchenko, O. I.; Da Silva, E.; Coleman, A. W. Determination of the Stability Constants of Inclusion Complexes of P-H-37-(Carboxy-Methyloxy)-Calix-[6]-Arene and p-Sulphonato-37-(2-Carboxy-Methyloxy)Calix[6]Arene with 15 Amino Acids by RP HPLC. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **2002**, *43* (3/4), 305–310. https://doi.org/10.1023/A:1021203505307.
68. Kalchenko, O.; Cherenok, S.; Suikov, S.; Kalchenko, V. Study of Calixarene Complexation with Biologically Active Carboxylic Acids by RP HPLC Method. *Fr. Ukr. J. Chem.* **2017**, *5* (2), 49–55. https://doi.org/10.17721/fujcV5I2P49-55.
69. Solovyov, A. V.; Cherenok, S. O.; Kalchenko, O. I.; Atamas, L. I.; Kazantseva, Z. I.; Koshets, I. A.; Tsymbal, I. F.; Kalchenko, V. I. Synthesis and Complexation of Amphiphilic Calix[4]Arene Phosphonates with Organic Molecules in Solutions and Langmuir-Blodgett Films. *Journal of Molecular Liquids* **2011**, *159* (2), 117–123. https://doi.org/10.1016/j.molliq.2010.12.007.
70. Kalchenko, O. I.; Cherenok, S. O.; Solovyov, A. V.; Kalchenko, V. I. Influence of Calixarenes on Chromatographic Separation of Benzene or Uracil Derivatives. *Chromatographia* **2009**, *70* (5–6), 717–721. https://doi.org/10.1365/s10337-009-1229-2.

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