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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

Calixarene Methylenebisphosphonic Acids: Alkaline Phosphatase Inhibition and Docking Studies

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To cite this Article Vovk, A. , Kalchenko, V. , Muzychka, O. , Tanchuk, V. , Muravyova, I. , Shivanyuk, A. , Cherenok, S. and Kukhar, V.(2008) 'Calixarene Methylenebisphosphonic Acids: Alkaline Phosphatase Inhibition and Docking Studies', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 183: 2, 625 — 626

To link to this Article: DOI: 10.1080/10426500701793311

URL: <http://dx.doi.org/10.1080/10426500701793311>

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Calixarene Methylenebisphosphonic Acids: Alkaline Phosphatase Inhibition and Docking Studies

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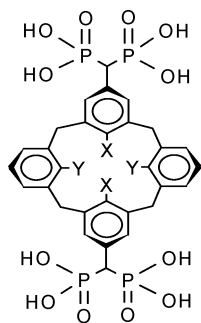
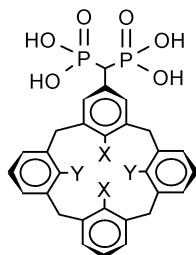
The inhibition of alkaline phosphatase from bovine intestine mucosa and bovine kidney by calix[4]arenes functionalized at the macrocyclic upper rim by one or two methylene bisphosphonic acid fragments have been investigated. The mechanisms of enzyme inhibition have been discussed using a molecular docking approach by computational modeling of inhibitors into active centers of E. coli alkaline phosphatase.

Keywords Calixarene; methylenebisphosphonic acid; alkaline phosphatase; inhibition; docking

Calix[4]arenes bearing one or two methylenebisphosphonic acid fragments were characterized as efficient calf intestine alkaline phosphatase inhibitors.¹ In this article, kinetics of interaction of these compounds with alkaline phosphatase isoenzymes are analyzed.

Calix[4]arene bis-methylenebisphosphonic acid **1** displayed stronger inhibition of alkaline phosphatase from bovine intestine mucosa than calix[4]arene methylenebisphosphonic acid **2**. At the same time these macrocyclic compounds showed almost identical affinities to bovine kidney isoenzyme. For elucidation of the molecular mechanism of inhibition the tested compounds **1** and **2**, as well as methylenebisphosphonate and 4-hydroxyphenyl methylenebisphosphonate were docked computationally to the active site of *E. Coli* alkaline phosphatase. On the basis of experimental and theoretical results obtained, the possible role of functionally important amino acid residues in formation of enzyme-inhibitor complex at the active centre of alkaline phosphatase is discussed.

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**1****2**

X=OH,

Y=OPr

REFERENCE

- [1] A. I. Vovk, V. I. Kalchenko, S. A. Cherenok, V. P. Kukhar, O. V. Muzychka, and M. O. Lozynsky, *Org. Biomol. Chem.*, **2**, 3162 (2004).