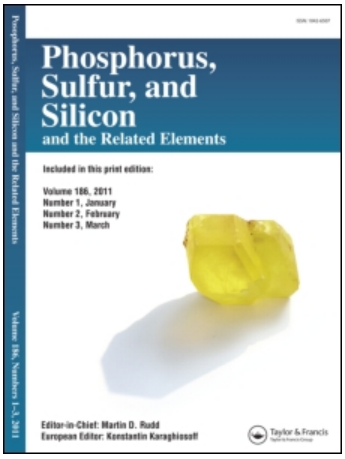

Phosphorus, Sulfur, and Silicon and the Related Elements

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Novel Bioreversible Prodrugs of Clodronate

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Novel Bioreversible Prodrugs of Clodronate

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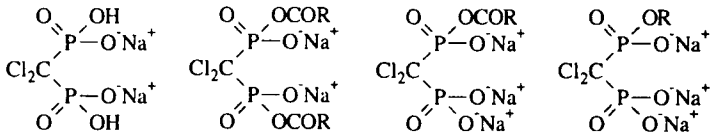
Clodronate (**1**) belongs to family of bisphosphonates which are used to inhibit mineralization of soft tissues as well as bone formation and resorption disorders.[1] The clinical use of bisphosphonates is limited due to their poor bioavailability which is mostly attributed to their hydrophilic structure. More lipophilic molecules are obtained if some or all of the anionic sites are converted to covalent bonds. We herein report a new prodrug serie for clodronate: the anhydrides **2** and **3**. Previously we have reported that the simple alkyl esters **4** do not release clodronate via chemical or enzymatic hydrolysis.[2] The prepared new derivatives are stable in water (pH 5-7.5) but clodronate is relased rapidly with enzymatic hydrolysis.



1 **2** **3** **4**

The target clodronate dianhydrides were prepared with high selectivity and reasonable yields (34-74%) from tetrasodium clodronate by using a large excess of corresponding acid anhydride at elevated temperature.

The synthesized Cl_2MBP dianhydride derivatives fullfill the criteria of prodrug: 1) compounds were rather stable against chemical hydrolysis, 2) enzymatic hydrolyses were very fast and 3) all the compounds showed to be more lipophilic than clodronate.

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[2] R. Niemi, H. Taipale, M. Ahlmark, J. Vepsäläinen, T. Järvinen, *J. Chromatography B* **701**, 97, (1997).