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Short communication

A phosphonamidate containing aromatic N-terminal amino group as inhibitor of leucine aminopeptidase—design, synthesis and stability

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Abstract

Fully deprotected phosphonamidate dipeptides, predicted as effective inhibitors of cytosolic leucine aminopeptidase, showed unexpected instability in water solution at pH below 12. Their hydrolysis rate was strictly correlated with basicity of the N-terminal amino group. To improve this feature a phosphonamidate analogue containing less basic, aromatic 2-aminophenylphosphonate residue in P1 position of the inhibitor was designed. The target compound was synthesised starting from diethyl 2-nitrophosphonate in several step procedure. The decrease in basicity of the terminal amino moiety of the modified analogue in fact resulted in satisfactory improvement of hydrolytic stability of the P–N bond. The developed phosphonamidate was proved to be fully resistant to hydrolysis above pH 7. Surprisingly, tested in enzymatic assays towards leucine aminopeptidase (optimum pH 8.5), it did not exhibit inhibition activity up to milimolar concentration. The explanation could be that diminishing the basic character of the terminal amino group may result in a change of its affinity towards the zinc ions.

Keywords: Phosphonamidate; LAP inhibitors; Hydrolytic stability

1. Introduction

Among pseudopeptides containing a phosphorus atom, phosphonamidates are considered to be the closest analogues of the high energy tetrahedral transition state of the amide bond hydrolysis [1–3]. This resemblance, together with metal complexing properties of the phosphonamidate moiety, makes them continuously attractive peptide isosteres for the design and construction of potent metalloprotease inhibitors [4–7]. The single disadvantage of their application is connected with limited hydrolytic stability of the phosphonamidate bond reported by numerous authors [4,8–14]. Recently, we have focused our interests on organophosphorus compounds [15,16], including P–N peptide mimetics [17], as potent inhibitors of cytosolic leucine aminopeptidase (LAP, E.C.3.4.11.1). LAP is a widespread bizinc hydrolaze whose function is to remove N-terminal amino acid residue, thus being involved in maturation, activation, modulation and degradation of bioactive peptide [18–21]. In mammals, it processes antigenic peptides for presentation by the major histocompatibility complex class I molecules [22]. Recently, it has been also identified as the key enzyme responsible for glutathione turnover [23,24]. Over-expression of LAP has been implicated in certain pathophysiological states including HIV infection, inflammation, cataracts and cancer [25–28].

Although fully deprotected P–N pseudodipeptides, exemplified by structure **1** (phosphonamidate analogue of leucylglycine, Fig. 1), represented the most promising LAP inhibitors, they revealed unexpected instability in aqueous solutions of pH below 12 [17,29]. Their *N*-protected derivatives remained significantly more stable, which indicates the vital role of N-terminal amino group in hydrolytic process and indeed such a dramatic enhancement of susceptibility of free analogues to hydrolysis was clearly correlated with the protonation state of the terminal α-amino group [29].

Therefore, although theoretically predicted as very potent (K_i ~ 45 nM) [17] phosphonamidate **1** was excluded from the

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enzymatic studies towards LAP. Two possible ways of its modification to increase the stability with simultaneous conservation of key functional and structural features crucial for efficient binding to the aminopeptidase could be envisaged. The first option accomplishes the replacement of amino group by other moieties. Indeed, the synthesised α-hydroxy analogue appeared to be satisfactory stable to be applied at pH 8.5 of the enzymatic assay nevertheless it exhibited only moderate potency (K_i = 4.88 μM) [17]. The second, not yet explored possibility relays on lowering the basicity of the terminal amino group and to evaluate influence of this change on inhibitor lability and its interactions with LAP. In this paper we report the design, synthesis, hydrolytic stability and activity of such modified analogues that may additionally represent new lead compounds for the development of aminopeptidase inhibitors.

2. Results and discussion

2.1. Design

To achieve the discussed effect of N-termini basicity decrease, a phosphonamidate containing 2-aminophenylphosphonic acid at P1 position of the inhibitor was designed (**2**, Fig. 1). Conjunction of nitrogen electron pair with the aromatic ring significantly lowers the pK_a of the amino group (roughly by five orders of magnitude). In order to evaluate theoretically possible interactions with LAP, this structure was docked [30] to the enzyme binding site obtained from the X-ray structure of bovine lens leucine aminopeptidase complexed with phosphonic analogue of leucine (LeuP) [31] similarly as described for previously studied compounds [17]. The results have been found promising. The relative orientation of the amino and the phosphonate groups as well as the overall size of 2-aminophenylphosphonate appears to be similar to LeuP fragment (Fig. 1). These analogies enable the favourable interactions with Zn489 and Asp273 (Fig. 2). Moreover, the aromatic ring of **2** can be involved in the hydrophobic interactions with the S1 pocket of LAP. Thus, the designed compound aroused as a new promising lead for the development of stable phosphonamidates containing free terminal amino group indispensable for good inhibitors of leucine aminopeptidase.

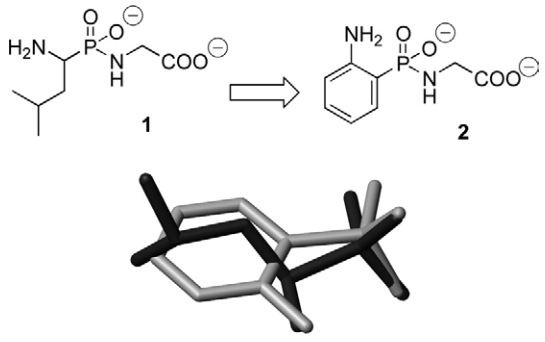


Fig. 1. The designed phosphonamidate inhibitors of leucine aminopeptidase: leucylglycine analogue of limited hydrolytic stability **1** [17,29], the analogue containing 2-aminophenylphosphonic acid in P1 position **2** potentially less labile due to decrease of basicity of the neighbouring group. Below, superimposition of 2-aminophenylophosphonic structure (grey) on phosphonic analogue of leucine (black), the latter originating from LAP-LeuP complex (1lcp in PDB) [31].

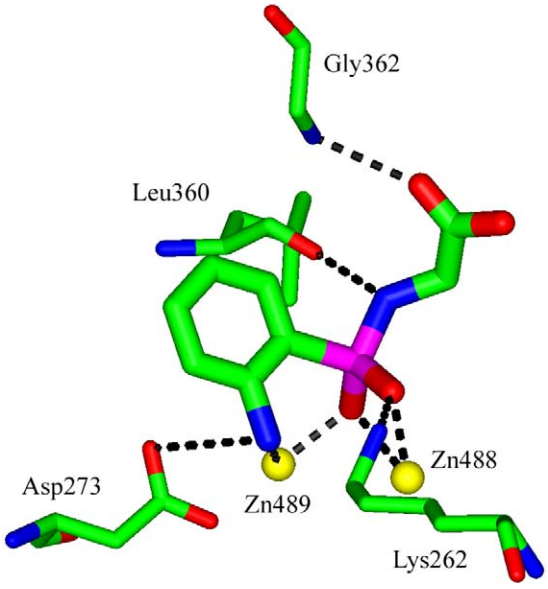
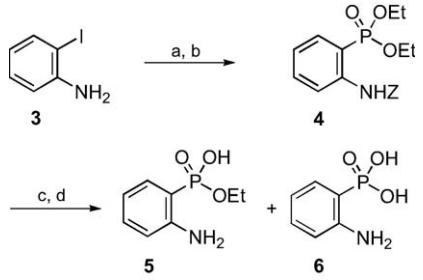


Fig. 2. The modelled binding mode of *N*-[(2-aminophenyl)hydroxyphosphinyl] glycinate **2** by leucine aminopeptidase obtained using the LAP crystal structure [31] and the Ludi computer programme [17,30]. The selected S1 pocket and the active site residues of LAP, interacting with dipeptide analogue, are presented. Hydrogen bonds and interactions of the inhibitor with zinc ions are shown as black dashed lines.

2.2. Chemistry

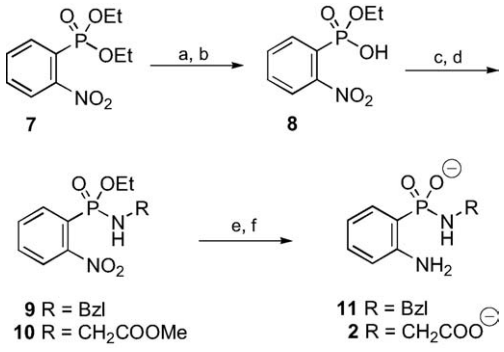
The synthetic strategy of P–N bond formation usually involves aminolysis of the appropriate phosphonochloridate monoesters [32–36]. In this work the target phosphonamidate **2** was planned to be synthesised in such manner starting from *o*-iodoaniline **3** (Scheme 1). After *N*-protection of the latter by means of benzyl chloroformate [37] the product was coupled with diethyl phosphite in presence of triethylamine and tetrakis (triphenylphosphine)palladium catalyst according to the reported procedure [38]. After purification on column chromatography the phosphonate **4** was obtained in low yield (~20%) as colourless, dense oil. Unfortunately, it underwent deprotection in conditions standardly used for the removal of the single phosphonate ester group. Thus, its treatment with aqueous 2 M NaOH/methanol solution followed by acidification yielded



Scheme 1. Reagents and conditions: (a) ZCl, 1 M NaOH, rt, 5 h, 90%; (b) $HP(O)(OEt)_2$, NEt_3, $(Ph_3)_4Pd$, N_2, anhydrous toluene, reflux, 8 h, 20%; (c) 1 M NaOH/MeOH, reflux, 2 h then evaporation; (d) pH 1.

a mixture that constituted products lacking benzyloxycarbonyl protection group (**5** and **6**). Without participation of the neighbouring phosphonate groups, this fact can be explained by carbamate cleavage in alkaline conditions as described previously or for Z-aniline derivatives [39] as well as for the cyclic carbamate analogues [40].

To avoid the observed inconveniences a derivative **7** [41] with nitro moiety as the amino masking group was selected to use instead of **4** (Scheme 2). Its basic hydrolysis under conditions mentioned above proceeded gently and, after removal of alcohol, acidification of the water phase and extraction of the product to ethyl acetate, yielded the expected monoester **8** [42]. Then, thionyl chloride was applied for the preparation of the corresponding phosphonochloridate similarly as described in [17,36,43]. Removal of volatile components under reduced pressure gave crude chloridate which was used to treat glycine methyl ester or benzylamine. Although the C-terminal carboxy residue was evidenced not to influence the stability of the phosphonamidate moiety [29], the benzylamine analogue missing such function was also synthesised as a simpler model compound to study the P–N lability. After standard work up the protected compounds (**9** and **10**) were purified chromatographically giving yellowish oils. The overall yields of the phosphonamidate synthesis procedure varied between 35% and 40%, which is of good accordance with the literature since they are lowered by contaminating formation of pyrophosphonates [33]. In the next step the nitro group was reduced quantitatively to the amino one in mild conditions of hydrogenolysis on Pd catalyst. Finally, the hydrolysis of the ester groups was achieved in basic conditions of aqueous 1.5 M LiOH/methanol. Similarly to reduction the ester deprotection step proceeded with yields exceeding 95%. After evaporation to dryness the target compounds (**2** and **11**) were obtained as the appropriate lithium salts. They were stored at –20 °C in presence of excess of LiOH. The demanded pH used for stability or enzymatic studies was adjusted before the tests. It is worth to mention that, in pH non-dependent process, samples underwent slow oxidation getting dark after prolonged storage (more than 1 month) what could be also visible by spectroscopic methods as appearance of impurities.



Scheme 2. Reagents and conditions: (a) 1 M NaOH/MeOH, reflux, 2 h then evaporation (b) pH 1 then extraction to ethyl acetate (three times), 75% starting from **7**; (c) $SOCl_2$, anhydrous CH_2Cl_2, reflux, 2 h then evaporation to dryness; (d) $BzlNH_2$ or HCl·GlyOMe, NEt_3, anhydrous CH_2Cl_2, 0 °C → rt, overnight, 35–40% starting from **8**; (e) H_2, 10% Pd/C, MeOH, 2 h, > 95%; (f) 1.5 M LiOH/MeOH, reflux, 2 h, > 95%.

2.3. Stability

Studies on the dependence of the phosphonamidate hydrolysis rate on pH were performed using ^{31}P NMR spectroscopy similarly as described before [29]. A dry sample was dissolved in D_2O to reach concentration of 50 mM and the appropriate starting pH (the range 5–11) was adjusted with diluted HCl. The decrease of a non-hydrolysed phosphonamidate concentration was monitored by integration of a set of performed ^{31}P NMR spectra at time intervals. Time dependent hydrolysis rate of phosphonamidate bond of compound **11** at selected pH is presented in Fig. 3 (continuous lines).

Phosphonamidate **11** appeared to be fully stable approximately up to pH 7 with significant hydrolysis (more than 20% within several hours) evidenced at pH far below 6. If compared with reported hydrolysis of our lead compound **1** (dashed curves) [29] it is clearly visible that similar hydrolysis rate was achieved in solutions of acidity differing by five orders of magnitude. This observation can be related to the pK_a differences between amino groups of both analogues. There is also additional key disparity in hydrolytic behaviour of compounds **1** and **11**. Phosphonamidate cleavage of aliphatic compound **1** is autocatalytic, since it is accompanied by pH lowering (if not buffered), whereas decomposition of **11** slightly alkalises the solution. Certainly, this observation is connected with differences of pK_a of basic (free amino groups) and acidic (free phoshonate groups) moieties appearing in the course of hydrolysis of P–N bond. There was no significant difference in hydrolytic behaviour between model compound **11** and target inhibitor **2** bearing the additional carboxy func-

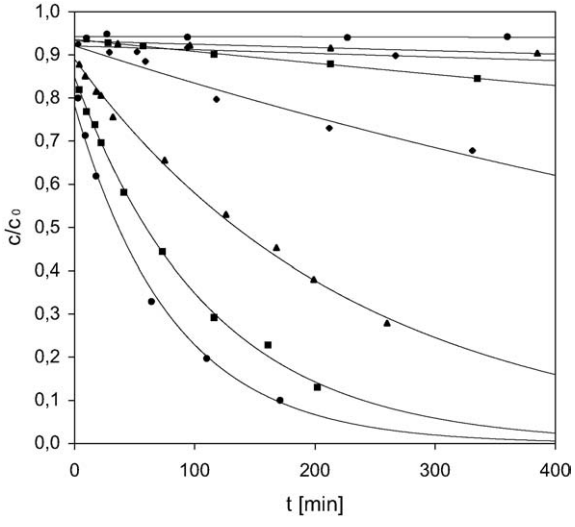


Fig. 3. Time dependent hydrolysis of phosphonamidate bond of *N*-[(2-aminophenyl)-hydroxyphosphinyl]benzylamine **11** (continuous curves, ● - pH 8.5, ▲ - pH 7.5, ■ - pH 6.5, ♦ - pH 5.8) compared to leucylglycine analogue **1** (dashed curves, ♦ - pH 11.7, ▲ - pH 11.1, ■ - pH 10.9, ● - pH 10.7) [29]. Decreasing of substrate concentration assisted by ^{31}P NMR monitoring and calculated basing on signal integration.

tion (data not included as phosphonamidate **2** was not studied in details covering broad pH range). This observation is also consistent with the data obtained for aliphatic analogues [29].

2.4. Conclusions

Encouraged by promising results of stability of modified phosphonamidates we tested the activity of derivative **2** towards leucine aminopeptidase. To our surprise it did not exhibit any inhibition up to concentration of 1.15 mM. Although the result is negative, this observation seems to have some significant meaning. Phosphorus containing peptide analogues are generally considered as excellent mimics of tetrahedral transition state of the amide bond hydrolysis. However, except for the metalloprotease superfamily, they do not effectively serve for construction of satisfactory potent inhibitors of other classes of proteases. This might suggest that the metal complexing property represents the essential factor responsible for their efficient binding. This statement is of particular importance for leucine aminopeptidase since it contains two zinc ions in the active site. Consequently, diminishing the basic character of the terminal amino group in compound **2** in relation to compound **1** may result in dramatic change of its affinity towards the zinc ions [44] and therefore reduction of inhibitory potency of such a modified analogue.

3. Experimental protocols

3.1. Chemistry: general

Unless otherwise stated, materials were obtained from commercial suppliers (Sigma-Aldrich, Fluka, Merck, POCh) and used without further purification. Thionyl chloride and triethylamine were freshly distilled, NEt_3 was stored over KOH. Anhydrous methylene chloride and benzene were obtained by their distillation over P_2O_5, methylene chloride was prepared prior to use, benzene was stored over Na. Column chromatography was performed on silica gel 60 (70–230 mesh).

Proton and phosphorus NMR spectra were recorded on Bruker DRX spectrometer operating at 300.13 MHz for ^1H and 121.50 MHz for ^{31}P. Measurements were made in $CDCl_3$ or D_2O solutions. Proton chemical shifts were referenced to $CHCl_3$ (δ 7.27) and HDO (δ 4.70), respectively. ^{31}P NMR spectra were obtained with use of broad-band ^1H decoupling; chemical shifts are reported in relation to 85% H_3PO_4 (sealed capillary).

3.2. Phosphonamidate synthesis: the representative procedure

Ethyl 2-nitrophenylphosphonate **8** (0.46 g, 2 mmol) was dissolved in anhydrous methylene chloride (10 ml) and thionyl chloride was added (0.29 ml, 4 mmol). The solution was stirred for 2 h at room temperature and refluxed for additional 2 h. The volatile components were evaporated under reduced pressure, the residue was treated with anhydrous benzene (20 ml) and evaporated again. The resulting phosphonochloridate was dissolved in methylene chloride (10 ml) and added dropwise to benzylamine (0.55 ml, 5 mmol) or to the mixture of glycine methyl ester hydrochloride (0.25 g, 2 mmol) and triethylamine (0.70 ml, 5 mmol) in methylene chloride (10 ml) cooled in an ice bath. The resulting suspension was stirred overnight and then evaporated to dryness. The residue was taken up with ethyl acetate (30 ml) and water (10 ml), and washed successively with: 1 M NaOH, water, 5% HCl, water, 1 M Na_2CO_3 and brine (10 ml of each). The organic layer was dried over Na_2SO_4. The crude phosphonamidate was purified on column chromatography using the ethyl acetate/hexane mixture gradient (3:1 → 1:0). The pure product was obtained as yellowish oil slowly crystallising in the refrigerator.

3.2.1. N-[(2-Nitrophenyl)ethoxyphosphinyl]benzylamine (**9**)

Yield: 40%. ^{31}P NMR ($CDCl_3$): δ 18.25. ^1H NMR: δ 1.28 (t, $J = 7.4$ Hz, 3H, CH_3); 3.89 (bs, 1H, NH); 4.11 (m, 2H, OCH_2); 4.31 (m, 2H, NCH_2); 7.27 (m, 5H, Ph); 7.68 (m, 2H, $2 \times H_{ar}$); 7.90 (m, 1H, H_{ar}); 8.27 (m, 1H, H_{ar}).

3.2.2. Methyl N-[(2-nitrophenyl)ethoxyphosphinyl]glycinate (**10**)

Yield: 35%. ^{31}P NMR ($CDCl_3$): δ 17.91. ^1H NMR: δ 1.32 (t, $J = 7.1$ Hz, 3H, CH_3); 3.68 (s, 3H, OCH_3); 3.92–4.27 (m, 5H, $HNCH_2$ and OCH_2); 7.71 (m, 2H, $2 \times H_{ar}$); 7.99 (m, 1H, H_{ar}); 8.27 (m, 1H, H_{ar}).

3.3. Deprotection—the representative procedure

To reduce the aromatic nitro group, a phosphonamidate (**9** or **10**) (0.5 mmol) was dissolved in methanol (5 ml) and hydrogenated in presence of 10% Pd/C catalyst (0.05 g). Hydrogen was passed through the solution by gentle bubbling. The reaction followed by TLC as well as by ^{31}P NMR proceeded nearly quantitatively (yield exceeding 95%) and it was completed within 2 h. The catalyst was filtered off and the solution was evaporated to dryness giving colourless oil. Removal of the ester groups was achieved by gentle reflux for 2 h in alkaline conditions of 1.5 M $LiOH_{aq}$/MeOH (1:1) solution. Double excess of LiOH was used (2 eq. for the benzylamine and 4 eq. for the glycine derivative). Evaporation of the solvents gave the final samples of satisfactory purity in the form of their lithium salt. The samples were stored at –20 °C was they used directly for tests.

3.3.1. Dilithium N-[(2-aminophenyl)oxyphosphinyl]glycinate (**2**)

^{31}P NMR (D_2O): δ 18.60. ^1H NMR: δ 3.13 (d, $J = 7.2$ Hz, 2H, CH_2); 6.70 (m, 2H, $2 \times H_{ar}$); 7.14 (dd, $J_1 \approx J_2 \approx 7.6$ Hz, 1H, H_{ar}); 7.39 (dd, $J_1 = 7.6$ Hz, $J_2 = 13.6$ Hz, 1H, H_{ar}).

3.3.2. Lithium N-[(2-aminophenyl)oxyphosphinyl]benzylamine (**11**)

^{31}P NMR (D_2O): δ 18.32. ^1H NMR: δ 3.71 (d, $J = 8.9$ Hz, 2H, CH_2); 6.65 (m, 2H, $2 \times H_{ar}$); 7.12 (m, 6H, Ph and H_{ar}); 7.40 (dd, $J_1 = 7.6$ Hz, $J_2 = 13.5$ Hz, 1H, H_{ar}).

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References

[1] H.M. Holden, D.E. Tronrud, A.F. Monzingo, L.H. Weaver, B.W. Matthews, Biochemistry 26 (1987) 8542–8553.
[2] D.E. Tronrud, H.M. Holden, B.W. Matthews, Science 235 (1987) 571–574.
[3] J.L. Radkiewicz, M.A. McAllister, E. Goldstein, K.N. Houk, J. Org. Chem. 63 (1998) 1419–1428.
[4] N.E. Jacobsen, P.A. Bartlett, J. Am. Chem. Soc. 103 (1981) 654–657.
[5] P.A. Bartlett, C.K. Marlowe, P.E. Giannousis, J.E. Hanson, Cold Spring Harb. Symp. Quant. Biol. 52 (1987) 83–90.
[6] P.A. Bartlett, C.K. Marlowe, Science 235 (1987) 569–571.
[7] P. Kafarski, B. Lejczak, Aminophosphonic and Aminophosphinic Acids, in: V.P. Kukhar, H.H. Hudson (Eds.), Chemistry and Biological Activity, John Wiley & Sons, Chichester, 2000, pp. 407–442.
[8] M. Hariharan, R.J. Motekaites, A.E. Martell, J. Org. Chem. 40 (1975) 470–473.
[9] K. Yamauchi, S. Ohtsuki, M. Kinoshita, J. Org. Chem. 49 (1984) 1158–1163.
[10] K. Yamauchi, S. Ohtsuki, M. Kinoshita, Biochim. Biophys. Acta 827 (1985) 275–282.
[11] K.A. Mookthiar, C.K. Marlowe, P.A. Bartlett, H.E. Van Wart, Biochemistry 26 (1987) 1962–1965.
[12] D.W. Christianson, W.N. Lipscomb, J. Am. Chem. Soc. 108 (1986) 545–546.
[13] D.W. Christianson, W.N. Lipscomb, J. Am. Chem. Soc. 110 (1988) 5560–5565.
[14] A. Yiotakis, A. Lecoq, A. Nicolaou, J. Labadie, V. Dive, Biochem. J. 303 (1994) 323–327.
[15] J. Grembecka, P. Kafarski, Mini Rev. Med. Chem. 1 (2001) 133–144.
[16] M. Drąg, J. Grembecka, M. Pawełczak, P. Kafarski, Eur. J. Med. Chem. 40 (2005) 764–771.
[17] J. Grembecka, A. Mucha, T. Cierpicki, P. Kafarski, J. Med. Chem. 46 (2003) 2641–2655.
[18] A. Taylor, Trends Biochem. Sci. 18 (1993) 167–171.
[19] A. Taylor, FASEB J. 7 (1993) 290–298.
[20] W.T. Lowther, B.W. Matthews, Chem. Rev. 102 (2002) 4581–4607.
[21] N. Sträter, W.N. Lipscomb, in: A.J. Barrett, N.D. Rawlings, J.F. Woessner (Eds.), Handbook of Proteolytic Enzymes, Elsevier, London, 2004, pp. 896–901.
[22] I.A. York, A.L. Goldberg, X.Y. Mo, K.L. Rock, Immunol. Rev. 172 (1999) 49–66.
[23] C. Jösch, L.-O. Klotz, H. Sies, Biol. Chem. 384 (2003) 213–218.
[24] M. Cappiello, A. Lazzarotti, F. Buono, A. Scaloni, C. D'Ambrosio, P. Amodeo, B.L. Méndez, P. Pelosi, A. Del Corso, U. Mura, Biochem. J. 378 (2004) 35–44.
[25] G. Pulido-Cejudo, B. Conway, P. Proulx, R. Brown, C.A. Izaguirre, Antiviral Res. 36 (1997) 167–177.
[26] J. Beninga, K.L. Rock, A.L. Goldberg, J. Biol. Chem. 273 (1998) 18734–18742.
[27] A. Taylor, M. Daims, J. Lee, T. Surgenor, Curr. Eye Res. 2 (1982) 47–56.
[28] H. Umezawa, Recent Results Cancer Res. 75 (1980) 115–125.
[29] A. Mucha, J. Grembecka, T. Cierpicki, P. Kafarski, Eur. J. Org. Chem. 46 (2003) 4797–4803.
[30] Insight 2000 Molecular Modelling Program Package, Accelrys, 2000.
[31] N. Sträter, W.N. Lipscomb, Biochemistry 34 (1995) 9200–9210.
[32] P. Kafarski, B. Lejczak, Aminophosphonic and Aminophosphinic Acids, in: V.P. Kukhar, H.H. Hudson (Eds.), Chemistry and Biological Activity, John Wiley & Sons, Chichester, 2000, pp. 173–203.
[33] R. Hirschmann, K.M. Yager, C.M. Taylor, J. Witherington, P.A. Sprengeler, B.W. Phillips, W. Moore, A.B. Smith III, J. Am. Chem. Soc. 119 (1997) 8177–8190.
[34] W.P. Malachowski, J.K. Coward, J. Org. Chem. 59 (1994) 7616–7624.
[35] W.P. Malachowski, J.K. Coward, J. Org. Chem. 59 (1994) 7625–7634.
[36] A. Mucha, P. Kafarski, F. Plenat, H.-J. Cristau, Tetrahedron 50 (1994) 12743–12754.
[37] J.A. Nieman, M.D. Ennis, J. Org. Chem. 66 (2001) 2175–2177.
[38] M. Bayle-Lacoste, J. Moulines, N. Collignon, A. Boumekouez, E. de Tinguy-Moreaud, E. Neuzil, Tetrahedron 46 (1990) 7793–7802.
[39] A.E. Beguin, C.S. Hamilton, J. Am. Chem. Soc. 61 (1939) 355–357.
[40] A.B. Smith III, L. Ducry, M. Corbett, R. Hirschmann, Org. Lett. 2 (2000) 3887–3890.
[41] J.I.G. Cadogan, D.J. Sears, D.M. Smith, J. Chem. Soc. C (1969) 1314–1318.
[42] E.N. Dolzhnikova, E.N. Tsvetkov, G.S. Petrova, R.V. Poponova, B.V. Zhabanov, Zh. Obshch. Khim. 48 (1978) 525–531.
[43] A. Mucha, P. Kafarski, Tetrahedron 58 (2002) 12743–12754.
[44] T. Kiss, I. Lázár, Aminophosphonic and Aminophosphinic Acids, in: V.P. Kukhar, H.H. Hudson (Eds.), Chemistry and Biological Activity, John Wiley & Sons, Chichester, 2000, pp. 285–325.