Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 41 (2006) 1385–1397
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Arylmethyl substituted derivatives of Fosmidomycin: Synthesis and antimalarial activity

Katrin Schlüter [a], Rolf D. Walter [b], Bärbel Bergmann [b], Thomas Kurz [a,*]

[a] *Institute of Pharmacy, University of Hamburg, Bundesstraße 45, D-20146 Hamburg, Germany*
[b] *Bernhard Nocht Institute for Tropical Medicine, Bernhard-Nocht-Straße 74, D-20359 Hamburg, Germany*

Received 19 April 2006; received in revised form 19 June 2006; accepted 22 June 2006
Available online 18 October 2006

Abstract

The phosphonohydroxamic acid Fosmidomycin is a drug candidate for the treatment of Malaria, currently in phase II trials in combination with Clindamycin. In order to obtain compounds of higher lipophilicity, we recently synthesized α-phenyl substituted Fosmidomycin derivatives which display high antimalarial activity. We now report the synthesis and in vitro antimalarial activity of arylmethyl substituted bis(pivaloyloxymethyl) ester prodrugs of Fosmidomycin and its acetyl analogue FR900098. The 3,4-dichlorobenzyl substituted derivative of Fosmidomycin proved to be about twice as active as the respective Fosmidomycin prodrug, however, less active than the corresponding FR900098 prodrug. Electron donating substituents as well as voluminous substituents led to a significant reduction of activity.

Keywords: Fosmidomycin; Chain-substituted analogues; Prodrugs; *Plasmodium falciparum*; DOXP-pathway

1. Introduction

Every year up to 3 million people die of Malaria worldwide. According to estimations by the World Health Organisation, more than 90% of these deaths occur in sub-Saharan Africa. *Plasmodium falciparum*, the causative agent of Malaria tropica, is responsible for most of the fatal malaria cases. Excessive use of established drugs such as Chloroquine and Sulphadoxine/Pyrimethamine resulted in high rates of resistance [1]. To overcome these problems, new antimalarial drugs based on novel modes of action have to be developed. Fosmidomycin (**I**) was found to repress *P. falciparum* growth by inhibiting the 1-desoxy-D-xylulose-5-phosphate (DOXP) reductoisomerase, a key enzyme of the DOXP/MEP pathway of isoprenoid biosynthesis [2,3]. This pathway is for instance present in algae, higher plants, several bacteria and protozoans, but not in humans. Therefore it represents an interesting target for the treatment of malaria and bacterial infectious diseases [3,4]. Clinical trials conducted with Fosmidomycin in combination with Clindamycin or Artesunate have shown high efficiency in the treatment of acute, uncomplicated Malaria tropica [5]. However, due to its short plasma half time of approximately 2.5 h and its low oral bioavailability of 30%, Fosmidomycin needs to be administered repeatedly in relatively high dosages [6].

Several research groups have contributed to the structural modification of Fosmidomycin **I** (Fig. 1) and its more active acetyl analogue (**II**) [7–11]. Among these modifications, the insertion of substituents in the α-position of the propyl chain seems to be most promising, whereas both the phosphonic acid and the hydroxamic acid moiety are essential for antimalarial activity [7,9–11]. Furthermore, various publications relate to ester prodrugs of FR900098 with improved in vivo antimalarial activity in the mouse model [8]. The hygroscopicity of Fosmidomycin and its analogues represents a general disadvantage of phosphonohydroxamic acids. In previous studies we have found that this drawback can be overcome

Abbreviations: DOXP, 1-desoxy-D-xylulose-5-phosphate; MEP, 1-*C*-methyl-D-erythritol-4-phosphate.

* Corresponding author. Tel.: +49 40 42838 3467; fax: +49 40 42838 6573.
E-mail address: kurz@chemie.uni-hamburg.de (T. Kurz).

0223-5234/$ - see front matter © 2006 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2006.06.015

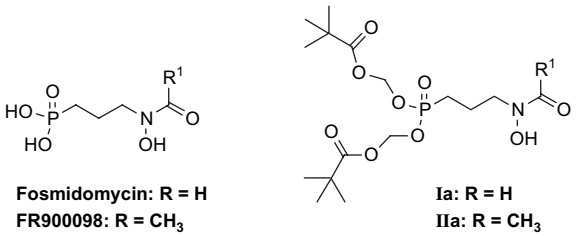


Fig. 1. Structures of Fosmidomycin, FR900098 and their bis(pivaloyloxymethyl) esters.

by masking the phosphonic acid moiety as bis(pivaloyloxymethyl) esters [11]. We reported the synthesis of α-phenyl substituted Fosmidomycin analogs and bis(pivaloyloxymethyl) ester prodrugs of **I** and **II**, which possess biological activity comparable to FR900098 [9,11]. Recently, these results were confirmed by Van Calenbergh et al. [10]. In this paper, we describe the synthesis and antimalarial activity of arylmethyl substituted bis(pivaloyloxymethyl) esters of Fosmidomycin and FR900098.

2. Chemistry

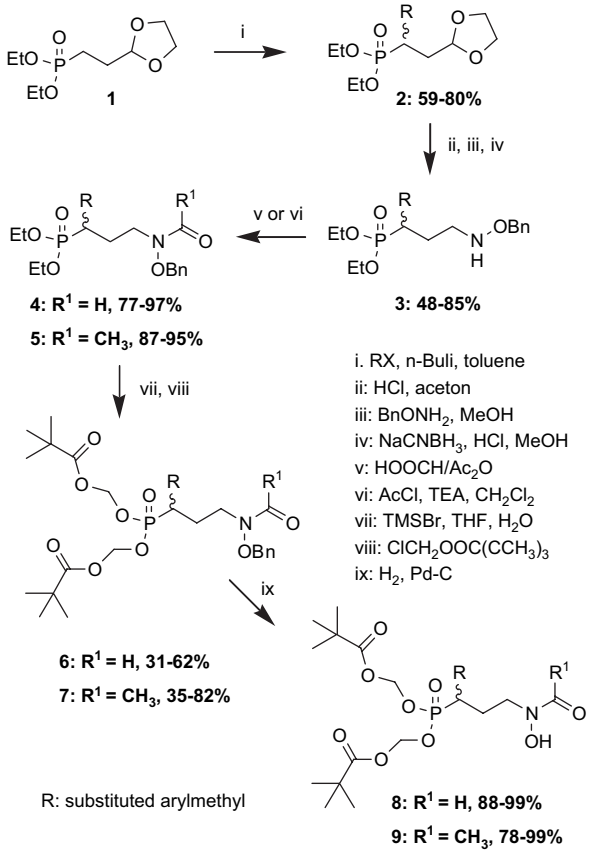
Synthesis of the target compounds (**8**, **9**) started with the alkylation of dioxolane **1** with the appropriate arylmethyl halides (Ar−CH_2−X) in the presence of *n*-BuLi in dry toluene. Acidic hydrolysis of **2**, oximation and subsequent reduction with sodium cyanoborohydride in acidic medium led to *O*-protected hydroxylamines **3** [7a]. Reactions of **3** with acetic−formic anhydride or acetyl chloride furnished hydroxamic acids **4** and **5** in 77−97% and 79−95% yield, respectively. Cleavage of the phosphonic acid ester functions of **4** and **5** was performed by treatment with bromotrimethyl silane and water [12]. All phosphonic acids were directly transformed into their corresponding bis(pivaloyloxymethyl) esters **6** and **7** by alkylation with chloromethyl pivalate in dry DMF [8,11,13]. In the final step, the *O*-benzyl group was cleaved by catalytic hydrogenation to give the final products **8** and **9** (Scheme 1). Under these reaction conditions, compounds **6e**,**f** and **7e**,**f** formed the respective tetrahydronaphthyl derivatives (**8**, **9**,**e**,**f**).

3. Biological activity

The in vitro antimalarial activity of all novel analogues was evaluated by 8-[^{3}H]hypoxanthine incorporation assay according to the method of Desjardins using the chloroquine sensitive strain 3D7 of *P. falciparum* [14a]. The inhibition of parasite growth at 100, 10 and 1 μM has been determined and compared to the bis(pivaloyloxymethyl) esters (**Ia**, **IIa**) of Fosmidomycin (**I**) and FR900098 (**II**) (Table 1).

4. Results and discussion

Among the novel Fosmidomycin derivatives, the 3,4-dichlorobenzyl substituted analogue **8c** was the most active compound with an inhibition rate of 59% at 1 μM (Table 1).



Scheme 1. Synthesis of α-substituted bis(pivaloyloxymethyl) ester analogues of Fosmidomycin and FR900098.

In the course of further investigations, an IC_{50} value of 0.9 μM was determined for **8c** (Table 2). The corresponding IC_{50} values obtained for the bis(pivaloyloxymethyl) esters of the lead structures are 2.1 μM for **Ia** and 0.4 μM for **IIa**. Consequently, in this assay **8c** is about twice as active as **Ia**, however, less active than **IIa**. The positive influence of the 3,4-dihaloaryl moiety on the biological activity of **8c** was also determined by our group and by Van Calenbergh and co-workers for phenyl substituted derivatives of Fosmidomycin [10,11]. The inhibition of parasite growth at 1 μM of the benzyl derivative **8a** is comparable to **Ia**, whereas electron donating substituents lead to a significant reduction of activity (**8b**,**d**, **9b**,**d**). A considerable loss of activity was also observed for derivatives which contain voluminous substituents such as tetrahydronaphthyl (**8e**, **9e**,**f**). In accordance with previous results, the formyl derivatives are more active than the corresponding acetyl derivatives.

5. Conclusion

The introduction of arylmethyl substituents into the α-position to the phosphonic acid moiety of Fosmidomycin and FR900098 as well as masking the phosphonic acid functionality as pivaloyloxymethyl esters led to a series of stable, non-hygroscopic Fosmidomycin analogues. The most active compound **8c** bears a 3,4-dichlorobenzyl substituent in the

Table 1
Inhibition of *P. falciparum* growth (%) at 100, 10 and 1 μM

Compound	R	100 μM	10 μM	1 μM
		Inhibition of *P. falciparum* growth (%)[a]		
8a	$C_6H_5-CH_2-$	100	58	38
8b	2,5-di$CH_3-C_6H_5-CH_2-$	85	37	6
8c	3,4-diCl$-C_6H_5-CH_2-$	99	76	59
8d	4-MeO$-C_6H_4-CH_2-$	86	38	6
8e	(5,6,7,8)-Tetrahydronaphthalene-2-ylmethyl	73	21	3
8f	(5,6,7,8)-Tetrahydronaphthalene-1-ylmethyl	99	67	19
9a	$C_6H_5-CH_2-$	100	14	10
9b	2,5-di$CH_3-C_6H_5-CH_2-$	72	20	3
9c	3,4-diCl$-C_6H_5-CH_2-$	98	23	12
9d	4-MeO$-C_6H_4-CH_2-$	76	24	3
9e	(5,6,7,8)-Tetrahydronaphthalene-2-ylmethyl	72	21	3
9f	(5,6,7,8)-Tetrahydronaphthalene-1-ylmethyl	99	7	0
Ia	H	98	83	32
IIa	H	100	96	71

[a] Mean values of two independent determinations.

α-position and is approximately twice as active as the bis(pivaloyloxymethyl) ester of Fosmidomycin (**Ia**), however, less active than the corresponding FR900098 prodrug. It should be noted that all arylmethyl substituted analogues were tested as racemates. Therefore, the resolution of the racemates should lead to improved antimalarial activity. Since the pivaloyloxymethyl ester prodrugs are converted into the corresponding free phosphonic acids by non-specific esterases, no animal experiments were necessary so far. Further investigations regarding the bioavailability of compound **8c** are intended.

6. Experimental

Elemental analyses were carried out with a Heraeus CHN–O–Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Melting points were determined on a Mettler FP 62. High resolution mass spectra were recorded on a VG 70-250S mass spectrometer.

6.1. Chemistry

6.1.1. General procedure for the preparation of (1-arylmethyl-2-[1,3]dioxolan-2-yl-ethyl)-phosphonic acid diethyl esters *2a–f*

Dioxolane **1** (50 mmol) was dissolved in dry toluene (50 mL), cooled down to −78 °C and treated with a stoichiometric amount of *n*-butyllithium (2.5 M in toluene). After stirring for 1 h under nitrogen atmosphere, the appropriate arylmethyl halide (50 mmol) was added in one portion. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. A solution of NH_4Cl (10%, 50 mL) was added and the product was extracted with diethyl ether. The organic layer was dried over Na_2SO_4, evaporated and the resulting residue (**2a–f**) was purified by column chromatography on silica gel with EtOAc and *n*-hexane (8:2) as eluents.

*6.1.1.1. (1-Benzyl-2-[1,3]dioxolan-2-yl-ethyl)-phosphonic acid diethyl ester (**2a**).* Yield: 80%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.18, 1.19 (2t, $J = 7.10$ Hz, 6H, $POCH_2CH_3$), 1.52–1.64 (m, 1H, CH_2), 1.77–1.88 (m, 1H, CH_2), 2.18–2.29 (m, 1H, PC*H*), 2.64–2.73 (m, 1H, CH_2), 2.94–3.03 (m, 1H, CH_2), 3.66–3.80 (m, 4H, OCH_2CH_2O), 3.91–4.01 (m, 4H, $POCH_2CH_3$), 4.84 (t, $J = 5.11$ Hz, 1H, OC*H*O), 7.18–7.31 (m, 5H, aromat.).^{13}C NMR (DMSO-d_6), δ (ppm): 16.6 (2d, $J_{C,P} = 5.6$ Hz, $POCH_2CH_3$), 32.7 (d, $J_{C,P} = 3.1$ Hz, CH_2), 34.1 (d, $J_{C,P} = 139.4$ Hz, PCH), 34.8 (d, $J_{C,P} = 3.1$ Hz, CH_2), 61.5, 61.6 (2d, $J_{C,P} = 6.6$ Hz, $POCH_2CH_3$), 64.4, 64.5 (OCH_2CH_2O), 102.3 (d, $J_{C,P} = 9.2$ Hz, OCHO), 126.6, 128.6, 129.4 (tert., aromat.), 139.6 (CH_2C quart., aromat.). IR: 1238 cm^{-1} (P=O). Anal. Calcd for $C_{16}H_{25}O_5P$: calculated C 58.53%, H 7.67%; found C 58.30%, H 7.54%.

*6.1.1.2. [1-(2,5-Dimethyl-benzyl)-2-[1,3]dioxolan-2-yl-ethyl]-phosphonic acid diethyl ester (**2b**).* Yield: 77%. MP: 46.0 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.29 (t, $J = 6.95$ Hz, 6H, $POCH_2CH_3$), 1.64–1.79 (m, 1H, CH_2), 1.95–2.15 (m, 1H, CH_2), 2.28 (s, 6H, PhCH_3), 2.31–2.46 (m, 1H, PC*H*), 2.60–2.77 (m, 1H, CH_2), 3.07–3.20 (m, 1H, CH_2), 3.68–3.93 (m, 4H, OCH_2CH_2O), 4.01–4.20 (m, 4H, $POCH_2CH_3$), 5.32 (t, $J = 5.32$ Hz, 1H, OC*H*O), 6.89–6.95 (m, 2H, aromat.),

Table 2
IC_{50} values of **8c** and pivaloyloxymethyl esters of Fosmidomycin and FR900098 against *P. falciparum*

Compound	Activity against *P. falciparum*		
	IC_{50} (μM)[a]	*n*	SEM[b]
8c	0.9	4	0.1
Ia	2.1	6	1.1
Iia	0.4	6	0.1

[a] Mean values of four or six independent determinations.
[b] Standard errors of the means.

6.96–7.07 (m, 1H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (d, $J_{C,P} = 6.1$ Hz, $POCH_2CH_3$), 19.4, 21.4 ($PhCH_3$), 32.7 (d, $J_{C,P} = 141.3$ Hz, PCH), 33.1 (d, $J_{C,P} = 3.0$ Hz, CH_2), 33.2 (d, $J_{C,P} = 3.0$ Hz, CH_2), 62.1 (2d, $J_{C,P} = 4.6$ Hz, $POCH_2CH_3$), 64.9, 65.0 (OCH_2CH_2O), 103.1 (d, $J_{C,P} = 8.1$ Hz, OCHO), 127.6, 130.7, 131.2 (tert., aromat.), 133.7, 135.5 (quart., aromat.), 137.5 (d, $J_{C,P} = 13.4$ Hz, CH_2C quart., aromat.). IR: 1234 cm^{-1} (P═O). Anal. Calcd for $C_{18}H_{29}O_5P$: calculated C 60.66%, H 8.20%; found C 60.52%, H 8.40%.

*6.1.1.3. [1-(3,4-Dichloro-benzyl)-2-[1,3]dioxolan-2-yl-ethyl]-phosphonic acid diethyl ester (**2c**).* Yield: 72%. MP: 51.0 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.21–1.31 (m, 6H, $POCH_2CH_3$), 1.63–1.78 (m, 1H, CH_2), 1.95–2.15 (m, 1H, CH_2), 2.23–2.40 (m, 1H, PCH), 2.72–2.86 (m, 1H, CH_2), 3.02–3.15 (m, 1H, CH_2), 3.75–3.96 (m, 4H, OCH_2CH_2O), 3.98–4.19 (m, 4H, $POCH_2CH_3$), 5.01 (t, $J = 4.87$ Hz, 1H, OCHO), 7.05–7.15 (m, 1H, aromat.), 7.30–7.42 (m, 2H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (2d, $J_{C,P} = 5.8$ Hz, $POCH_2CH_3$), 32.9 (d, $J_{C,P} = 3.5$ Hz, CH_2), 34.0 (d, $J_{C,P} = 141.3$ Hz, PCH), 34.7 (d, $J_{C,P} = 3.1$ Hz, CH_2), 62.2 (2d, $J_{C,P} = 5.9$ Hz, $POCH_2CH_3$), 65.2 (OCH_2CH_2O), 103.1 (d, $J_{C,P} = 9.2$ Hz, OCHO), 129.2, 130.5, 131.7 (tert., aromat.), 130.7, 132.5 (quart., aromat.), 140.1 (d, $J_{C,P} = 11.5$ Hz, CH_2C quart., aromat.). IR: 1240 cm^{-1} (P═O). Anal. Calcd for $C_{16}H_{23}Cl_2O_5P$: calculated C 48.38%, H 5.84%; found C 48.17%, H 5.98%.

*6.1.1.4. [2-[1,3]Dioxolan-2-yl-ethyl-1-(4-methoxy-benzyl)]-phosphonic acid diethyl ester (**2d**).* Yield: 80%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.28, 1.29 (2t, $J = 6.99$ Hz, $J = 7.14$ Hz, 6H, $POCH_2CH_3$), 1.64–1.80 (m, 1H, CH_2), 1.93–2.06 (m, 1H, CH_2), 2.24–2.37 (m, 1H, PCH), 2.62–2.76 (m, 1H, CH_2), 3.06–3.19 (m, 1H, CH_2), 3.68–3.91 (m, 7H, OCH_2CH_2O overlapping OCH_3), 3.99–4.16 (m, 4H, $POCH_2CH_3$), 4.93 (t, $J = 5.37$ Hz, 1H, OCHO), 6.76–6.89 (m, 2H, aromat.), 7.08–7.21 (m, 2H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (2d, $J_{C,P} = 5.6$ Hz, $J_{C,P} = 6.1$ Hz, $POCH_2CH_3$), 33.0 (d, $J_{C,P} = 3.7$ Hz, CH_2), 34.4 (d, $J_{C,P} = 139.9$ Hz, PCH), 34.6 (d, $J_{C,P} = 3.2$ Hz, CH_2), 55.7 (OCH_3), 62.1, 62.2 (2d, $J_{C,P} = 6.7$ Hz, $POCH_2CH_3$), 65.0 (OCH_2CH_2O), 103.2 (d, $J_{C,P} = 9.0$ Hz, OCHO), 114.1 (OCCH tert., aromat.), 130.6 (tert., aromat.), 131.7 (d, $J_{C,P} = 12.4$ Hz, CH_2C quart., aromat.), 158.6 (CH_3OC quart., aromat.). IR: 1246 cm^{-1} (P═O). Anal. Calcd for $C_{17}H_{27}O_6P$: calculated C 56.98%, H 7.59%; found C 56.58%, H 7.92%.

*6.1.1.5. [2-[1,3]Dioxolan-2-yl-ethyl-1-(naphthalene-2-yl-methyl)]-phosphonic acid diethyl ester (**2e**).* Yield: 68%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.18–1.31 (m, 6H, $POCH_2CH_3$), 1.70–1.85 (m, 1H, CH_2), 1.98–2.12 (m, 1H, CH_2), 2.41–2.56 (m, 1H, PCH), 2.85–2.98 (m, 1H, CH_2), 3.28–3.41 (m, 1H, CH_2), 3.66–3.85 (m, 4H, OCH_2CH_2O), 3.97–4.22 (m, 4H, $POCH_2CH_3$), 4.99 (t, $J = 5.46$ Hz, 1H, OCHO), 7.34–7.68 (m, 4H, aromat.), 7.76–7.84 (m, 3H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 ($POCH_2CH_3$), 33.2 (CH_2), 34.2 (d, $J_{C,P} = 141.4$ Hz, PCH), 35.8 (CH_2), 62.2 (2d, $J_{C,P} = 5.5$ Hz, $POCH_2CH_3$), 65.0 (OCH_2CH_2O), 103.1 (d, $J_{C,P} = 7.6$ Hz, OCHO), 125.8, 126.4, 128.0, 128.2, 128.4 (tert., aromat.), 132.6, 133.9 (quart., aromat.), 137.2 (d, $J_{C,P} = 11.3$ Hz, CH_2C quart., aromat.). IR: 1240 cm^{-1} (P═O). Anal. Calcd for $C_{20}H_{27}O_5P$: calculated C 63.48%, H 7.19%; found C 63.09%, H 7.28%.

*6.1.1.6. [2-[1,3]Dioxolan-2-yl-ethyl-1-(naphthalene-1-yl-methyl)]-phosphonic acid diethyl ester (**2f**).* Yield: 59%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.27 (t, $J = 6.93$ Hz, 6H, $POCH_2CH_3$), 1.73–1.92 (m, 1H, CH_2), 2.04–2.18 (m, 1H, CH_2), 2.43–2.65 (m, 1H, PCH), 3.04–3.27 (m, 1H, CH_2), 3.61–3.88 (m, 5H, OCH_2CH_2O overlapping CH_2), 3.98–4.23 (m, 4H, $POCH_2CH_3$), 4.91 (t, $J = 5.27$ Hz, 1H, OCHO), 7.34–7.60 (m, 4H, aromat.), 7.67–7.87 (m, 2H, aromat.), 8.07–8.13 (m, 1H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (d, $J_{C,P} = 5.9$ Hz, $POCH_2CH_3$), 33.2 (d, $J_{C,P} = 3.0$ Hz, CH_2), 33.3 (d, $J_{C,P} = 140.5$ Hz, PCH), 33.4 (d, $J_{C,P} = 3.2$ Hz, CH_2), 62.2 (d, $J_{C,P} = 6.5$ Hz, $POCH_2CH_3$), 64.9, 65.0 (OCH_2CH_2O), 103.1 (d, $J_{C,P} = 7.8$ Hz, OCHO), 124.2, 125.7, 125.9, 126.5, 127.7, 128.1, 129.2 (tert., aromat.), 132.4, 134.4 (quart., aromat.), 135.6 (d, $J_{C,P} = 12.9$ Hz, CH_2C quart., aromat.). IR: 1240 cm^{-1} (P═O). Anal. Calcd for $C_{20}H_{27}O_5P$: calculated C 63.48%, H 7.19%; found C 63.33%, H 7.28%.

*6.1.2. General procedure for the preparation of (1-arylmethyl-3-benzyloxyamino-propyl)-phosphonic acid diethyl esters **3a–f***

Dioxolanes **2** (30 mmol) were treated with 2 M HCl (100 mL) and aceton (10 mL) and heated to 50 °C for 3 h. Aceton was removed and the aqueous layer was extracted with dichloromethane (3 × 30 mL). Afterwards, the organic layer was dried over $MgSO_4$ and the solvent was evaporated. Without further purification, the resulting crude aldehydes were dissolved in MeOH (20 mL), treated with *O*-benzylhydroxylamine (30 mmol) and stirred for 1 h. After addition of further 430 mL of MeOH, the mixture was treated portionwise with $NaBH_3CN$ (90 mmol). Over a period of 30 min, HCl (37%, 30 mL) was added dropwise under ice cooling. The mixture was allowed to warm up to room temperature and another 20 mmol of $NaBH_3CN$ were added. After an overall time of 2 h, the solution was concentrated and treated with aqueous KOH (10%) under ice cooling until alkaline reaction of the mixture. The product was extracted three times with CH_2Cl_2 (50 mL), the organic layers were combined, dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane 8:2) to give (1-arylmethyl-3-benzyloxy-amino-propyl)-phosphonic acid diethyl esters **3** as colourless oils.

*6.1.2.1. [3-Benzyloxyamino-1-benzyl-propyl]-phosphonic acid diethyl ester (**3a**).* Yield: 85%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19 (t, 6H, $J = 7.09$ Hz), 1.50–1.78 (m, 2H, CH_2), 2.16–2.28 (m, 1H, PCH), 2.52–2.61 (m, 1H, CH_2), 2.73–2.87 (m, 2H, CH_2), 2.95–3.02 (m, 1H, CH_2), 3.93–4.03 (m, 4H, $POCH_2CH_3$), 4.42 (s, 2H, $PhCH_2O$), 6.55 (t, $J = 5.58$ Hz, 1H, NH), 7.09–7.33 (m, 10H, aromat.). ^{13}C NMR (DMSO-d_6), δ (ppm): 16.2 (2d,

$J = 5.6$ Hz, $POCH_2CH_3$), 25.4 (d, $J_{C,P} = 3.6$ Hz, CH_2), 34.3 (d, $J_{C,P} = 2.6$ Hz, CH_2), 34.5 (d, $J_{C,P} = 137.8$ Hz, PCH), 49.1 (d, $J_{C,P} = 6.6$ Hz, NCH_2), 60.8, 60.9 (2d, $J_{C,P} = 5.9$ Hz, $POCH_2CH_3$), 74.9 ($PhCH_2O$), 126.1, 127.2, 127.8, 127.9, 128.1, 128.3, 128.9 (tert., aromat.), 138.3 (quart., aromat.), 139.4 (d, $J_{C,P} = 13.2$ Hz, CH_2C quart., aromat.). IR: 3249 cm^{-1} (N–H), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{21}H_{30}NO_4P$: calculated C 64.44%, H 7.72%, N 3.58%; found C 64.28%, H 7.82%, N 3.66%.

*6.1.2.2. [3-Benzyloxyamino-1-(2,5-dimethyl-benzyl)-propyl]-phosphonic acid diethyl ester (**3b**).* Yield: 56%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.29–1.32 (m, 6H, $POCH_2CH_3$) 1.64–1.94 (m, 2H, CH_2), 2.13–2.32 (m, 7H, $PhCH_3$ overlapping PCH), 2.51–2.61 (m, 1H, CH_2), 2.88–3.03 (m, 2H, CH_2), 3.10–3.19 (m, 1H, CH_2), 4.05–4.18 (m, 4H, $POCH_2CH_3$), 4.45 (s, 2H, $PhCH_2O$), 5.51 (bs, 1H, NH), 6.85–7.06 (m, 3H, aromat.), 7.16–7.40 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.7 ($POCH_2CH_3$), 19.4, 21.3 ($PhCH_3$), 26.1 (d, $J_{C,P} = 2.4$ Hz, CH_2), 32.9 (d, $J_{C,P} = 3.2$ Hz, CH_2), 34.8 (d, $J_{C,P} = 138.0$ Hz, PCH), 50.5 (d, $J_{C,P} = 5.7$ Hz, NCH_2), 62.1 (m, $POCH_2CH_3$), 76.5 ($PhCH_2O$), 127.1, 128.2, 128.7, 130.8, 131.3 (tert., aromat.), 133.6, 135.6 (quart., aromat.), 137.6 (d, $J_{C,P} = 14.3$ Hz, CH_2C quart., aromat.), 137.9 (quart., aromat.). IR: 3253 cm^{-1} (N–H), 1230 cm^{-1} (P=O). Anal. Calcd for $C_{23}H_{34}NO_4P$: calculated C 65.85%, H 8.17%, N 3.35%; found C 65.46%, H 8.14%, N 3.42%.

*6.1.2.3. [3-Benzyloxyamino-1-(3,4-dichloro-benzyl)-propyl]-phosphonic acid diethyl ester (**3c**).* Yield: 62%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.23–1.33 (m, 6H, $POCH_2CH_3$), 1.67–2.02 (m, 2H, CH_2), 2.16–2.29 (m, 1H, PCH), 2.55–2.67 (m, 1H, CH_2), 3.01–3.18 (m, 3H, CH_2), 4.00–4.16 (m, 4H, $POCH_2CH_3$), 4.74 (s, 2H, $PhCH_2O$), 5.66 (bs, 1H, NH), 7.01–7.08 (m, 1H, aromat.), 7.25–7.39 (m, 7H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (m, $POCH_2CH_3$), 26.4 (d, $J_{C,P} = 3.4$ Hz, CH_2), 34.6 (d, $J_{C,P} = 2.7$ Hz, CH_2), 35.9 (d, $J_{C,P} = 140.0$ Hz, PCH), 50.1 (d, $J_{C,P} = 6.2$ Hz, NCH_2), 62.2 (m, $POCH_2CH_3$), 76.6 ($PhCH_2O$), 128.2, 128.7, 128.8, 129.0, 130.7, 131.5 (tert., aromat.), 132.6, 138.1, 140.3 (quart., aromat.). IR: 3249 cm^{-1} (N–H), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{21}H_{28}Cl_2NO_4P$: calculated C 54.79%, H 6.13%, N 3.04%; found C 54.81%, H 6.30%, N 3.07%.

*6.1.2.4. [3-Benzyloxyamino-1-(4-methoxy-benzyl)-propyl]-phosphonic acid diethyl ester (**3d**).* Yield: 48%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.27–1.34 (m, 6H, $POCH_2CH_3$), 1.67–1.94 (m, 2H, CH_2), 2.08–2.24 (m, 1H, PCH), 2.46–2.60 (m, 1H, CH_2), 2.92–3.18 (m, 3H, CH_2), 3.76 (s, 3H, OCH_3), 4.03–4.15 (m, 4H, $POCH_2CH_3$), 4.59 (s, 2H, $PhCH_2O$), 6.75–6.87 (m, 2H, aromat.), 7.04–7.14 (m, 2H, aromat.), 7.22–7.39 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 6.1$ Hz, $POCH_2CH_3$), 26.0 (CH_2), 34.5 (d, $J_{C,P} = 2.9$ Hz, CH_2), 36.4 (d, $J_{C,P} = 138.6$ Hz, PCH), 50.3 (d, $J_{C,P} = 6.2$ Hz, NCH_2), 55.6 (OCH_3), 62.1 (2d, $J_{C,P} = 6.8$ Hz, $POCH_2CH_3$), 76.6 ($PhCH_2O$), 114.3 (OCCH tert., aromat.), 128.2, 128.7, 128.8, 130.5 (tert., aromat.), 131.7 (d, $J_{C,P} = 13.4$ Hz, CH_2C quart., aromat.), 158.6 (CH_3OC quart., aromat.). IR: 3250 cm^{-1} (N–H), 1244 cm^{-1} (P=O). Anal. Calcd for $C_{22}H_{32}NO_5P$: calculated C 62.69%, H 7.65%, N 3.32%; found C 62.46%, H 7.60%, N 3.17%.

*6.1.2.5. [3-Benzyloxyamino-1-(naphthalene-2-yl-methyl)-propyl]-phosphonic acid diethyl ester (**3e**).* Yield: 48%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.22–1.35 (m, 6H, $POCH_2CH_3$), 1.69–1.97 (m, 2H, CH_2), 2.25–2.40 (m, 1H, PCH), 2.67–3.13 (m, 3H, CH_2), 3.27–3.43 (m, 1H, CH_2), 3.98–4.19 (m, 4H, $POCH_2CH_3$), 4.47 (dd, $J_{AB} = 11.67$ Hz, 2H, $PhCH_2O$), 6.97–7.91 (m, 12H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 6.1$ Hz, $J_{C,P} = 6.9$ Hz, $POCH_2CH_3$), 26.4 (d, $J_{C,P} = 3.2$ Hz, CH_2), 35.6 (d, $J_{C,P} = 2.1$ Hz, CH_2), 36.0 (d, $J_{C,P} = 140.0$ Hz, PCH), 50.4 (d, $J_{C,P} = 6.0$ Hz, NCH_2), 62.1 (2d, $J_{C,P} = 7.0$ Hz, $POCH_2CH_3$), 76.5 ($PhCH_2O$), 125.9, 126.5, 127.7, 127.9, 128.0, 128.1, 128.5, 128.6, 128.7 (tert., aromat.), 132.7, 133.9 (quart., aromat.), 137.3 (d, $J_{C,P} = 15.3$ Hz, CH_2C quart., aromat.), 138.2 (quart., aromat.). IR: 3269 cm^{-1} (N–H), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{25}H_{32}NO_4P$: calculated C 68.01%, H 7.31%, N 3.17; found C 67.75%, H 7.56%, N 2.85%.

*6.1.2.6. [3-Benzyloxyamino-1-(naphthalene-1-yl-methyl)-propyl]-phosphonic acid diethyl ester (**3f**).* Yield: 59%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19–1.27 (m, 6H, $POCH_2CH_3$) 1.53–1.89 (m, 2H, CH_2), 2.23–2.43 (m, 1H, PCH), 2.64–2.99 (m, 3H, CH_2), 3.52–3.66 (m, 1H, CH_2), 3.96–4.19 (m, 6H, $POCH_2CH_3$ overlapping $PhCH_2O$), 6.49 (t, $J = 5.09$ Hz, 1H, NH), 6.96–7.06 (m, 2H, aromat.), 7.18–7.30 (m, 3H, aromat.), 7.38–7.48 (m, 2H, aromat.), 7.50–7.63 (m, 2H, aromat.), 7.78–7.86 (m, 1H, aromat.), 7.91–7.98 (m, 1H, aromat.), 8.01–8.11 (m, 1H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (m, $POCH_2CH_3$), 25.9 (d, $J_{C,P} = 4.2$ Hz, CH_2), 33.2 (d, $J_{C,P} = 3.0$ Hz, CH_2), 35.4 (d, $J_{C,P} = 140.1$ Hz, PCH), 50.2 (d, $J_{C,P} = 5.1$ Hz, NCH_2), 62.4 (m, $POCH_2CH_3$), 76.4 ($PhCH_2O$), 124.1, 125.7, 126.1, 126.6, 127.9, 128.2, 128.7, 128.8, 129.4 (tert., aromat.), 132.2, 134.5 (quart., aromat.), 135.4 (d, $J_{C,P} = 15.1$ Hz, CH_2C quart., aromat.). IR: 3252 cm^{-1} (N–H), 1234 cm^{-1} (P=O). Anal. Calcd for $C_{25}H_{32}NO_4P$: calculated C 68.01%, H 7.31%, N 3.17%; found C 67.83%, H 7.55%, N 2.75%.

*6.1.3. General procedure for the preparation of [1-aryl-methyl-3-(benzyloxy-formyl-amino)-propyl]-phosphonic acid diethyl esters **4a–f***

Formic acid (500 mmol) was treated with acetic acid anhydride (50 mmol) and the reaction mixture was stirred under exclusion of humidity. After 20 min the solution was cooled to 0 °C, and the respective hydroxylamine **3** (10 mmol), dissolved in dry THF (20 mL), was added dropwise. After 10 min, the mixture was allowed to warm up to room temperature and stirred for another 2 h. The solution was treated with 200 mL of EtOAc and successively washed with water (3 × 50 mL), aqueous KOH (0.1 M, 3 × 25 mL) and once again with water. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc to give

[1-arylmethyl-3-(benzyloxy-formyl-amino)-propyl]-phosphonic acid diethyl esters **4** as colourless oils.

*6.1.3.1. [3-(Benzyloxy-formyl-amino)-1-benzyl-propyl]-phosphonic acid diethyl ester (**4a**).* Yield: 91%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19 (t, $J = 7.1$ Hz, 6H, $POCH_2CH_3$), 1.57–1.87 (m, 2H, CH_2), 2.09–2.24 (m, 1H, CH), 2.57–2.68 (m, 1H, CH_2), 2.94–3.02 (m, 1H, CH_2), 3.45–3.78 (m, 2H, CH_2), 3.94–4.02 (m, 4H, $POCH_2CH_3$), 4.77 (s, 2H, $PhCH_2O$), 7.19–7.40 (m, 10H, aromat.), 7.76–8.25 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.4, 16.5 (2d, $J_{C,P} = 5.6$ Hz, $POCH_2CH_3$), 25.4 (CH_2), 34.8 (CH_2), 35.8 (d, $J_{C,P} = 139.9$ Hz, PCH), 42.5 (NCH_2), 61.8, 61.9 (2d, $J_{C,P} = 7.1$ Hz, $J_{C,P} = 7.6$ Hz, $POCH_2CH_3$), 77.6 ($PhCH_2O$), 126.6, 128.6, 129.1, 129.3 (tert., aromat.), 134.3 (quart., aromat.), 138.9 (d, $J_{C,P} = 14.2$ Hz, CH_2C quart., aromat.), 162.8 (C=O). IR: 1680 cm^{-1} (C=O), 1233 cm^{-1} (P=O). Anal. Calcd for $C_{22}H_{30}NO_5P$: calculated C 63.00%, H 7.21%, N 3.34%; found C 62.55%, H 7.20%, N 3.66%.

*6.1.3.2. [3-(Benzyloxy-formyl-amino)-1-(2,5-dimethyl-benzyl)-propyl]-phosphonic acid diethyl ester (**4b**).* Yield: 89%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.32, 1.33 (2t, $J = 7.01$ Hz, $J = 7.03$ Hz, 6H, $POCH_2CH_3$), 1.77–2.17 (m, 3H, CH_2, CH), 2.25, 2.26 (2s, 6H, $PhCH_3$), 2.43–2.69 (m, 1H, CH_2), 3.01–3.81 (m, 3H, CH_2), 3.94–4.28 (m, 4H, $POCH_2CH_3$), 4.48–4.95 (m, 2H, $PhCH_2O$), 6.75–7.47 (m, 8H, aromat.), 7.61–8.24 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 5.5$ Hz, $J_{C,P} = 5.8$ Hz, $POCH_2CH_3$), 19.4, 21.3 ($PhCH_3$), 25.8 (d, $J_{C,P} = 4.9$ Hz, CH_2), 32.7 (d, $J_{C,P} = 3.7$ Hz, CH_2), 34.7 (d, $J_{C,P} = 135.4$ Hz, PCH), 43.1 (NCH_2), 62.3 (m, $POCH_2CH_3$), 77.1 ($PhCH_2O$), 127.9, 129.1, 129.4, 129.7, 131.0, 131.2 (tert., aromat.), 133.6, 135.8, 135.9 (quart., aromat.), 137.2 (d, $J_{C,P} = 15.7$ Hz, CH_2C quart., aromat.), 163.2 (C=O). IR: 1676 cm^{-1} (C=O), 1234 cm^{-1} (P=O). Anal. Calcd for $C_{24}H_{34}NO_5P$: calculated C 64.42%, H 7.66%, N 3.13%; found C 64.29%, H 7.68%, N 3.20%.

*6.1.3.3. [3-(Benzyloxy-formyl-amino)-1-(3,4-dichloro-benzyl)-propyl]-phosphonic acid diethyl ester (**4c**).* Yield: 97%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.17, 1.18 (2t, $J = 7.09$ Hz, $J = 7.11$ Hz, 6H, $POCH_2CH_3$), 1.47–1.90 (m, 2H, CH_2), 2.09–2.34 (m, 1H, PCH), 2.60–3.00 (m, 2H, CH_2), 3.50–3.83 (m, 2H, CH_2), 3.88–4.11 (m, 4H, $POCH_2CH_3$), 4.81 (s, 2H, $PhCH_2O$), 7.16–7.63 (m, 8H, aromat.), 7.84–8.33 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (m, $POCH_2CH_3$), 25.8 (d, $J_{C,P} = 5.6$ Hz, CH_2), 34.3 (CH_2), 35.7 (d, $J_{C,P} = 141.5$ Hz, PCH), 42.6 (NCH_2), 62.5 (m, $POCH_2CH_3$), 78.1 ($PhCH_2O$), 129.1, 129.2, 129.6, 129.8, 130.8, 131.5 (tert., aromat.), 132.7, 134.5, 139.6 (quart., aromat.), 163.4 (C=O). IR: 1677 cm^{-1} (C=O), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{22}H_{28}Cl_2NO_5P$: calculated C 54.11%, H 5.78%, N 2.87%; found C 53.98%, H 5.95%, N 2.79%.

*6.1.3.4. [3-(Benzyloxy-formyl-amino)-1-(4-methoxy-benzyl)-propyl]-phosphonic acid diethyl ester (**4d**).* Yield: 77%. MP: 43.4 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.30, 1.31 (2t, $J = 7.02$ Hz, $J = 7.04$ Hz, 6H, $POCH_2CH_3$), 1.72–2.20 (m, 3H, CH_2, CH), 2.37–2.73 (m, 1H, CH_2), 3.02–3.22 (m, 1H, CH_2), 3.25–3.85 (m, 5H, CH_2 overlapping OCH_3), 3.96–4.26 (m, 4H, $POCH_2CH_3$), 4.60–4.94 (m, 2H, $PhCH_2O$), 6.73–7.44 (m, 9H, aromat.), 7.65–8.23 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 2.9$ Hz, $POCH_2CH_3$), 25.7 (CH_2), 34.2 (CH_2), 36.3 (d, $J_{C,P} = 142.9$ Hz, PCH), 42.8 (NCH_2), 55.6 (OCH_3), 62.2 (m, $POCH_2CH_3$), 76.5 ($PhCH_2O$), 114.4 (OCCH tert., aromat.), 129.1, 129.4, 129.7, 130.4 (tert., aromat.), 131.3, 134.6 (quart., aromat.), 158.7 (CH_3OC quart., aromat.), 163.2 (C=O). IR: 1682 cm^{-1} (C=O), 1250 cm^{-1} (P=O). Anal. Calcd for $C_{23}H_{32}NO_6$Pmiddot;0.5H_2O: calculated C 60.25%, H 7.25%, N 3.05%; found C 60.02%, H 6.91%, N 2.91%.

*6.1.3.5. [3-(Benzyloxy-formyl-amino)-1-(naphthalene-2-yl-methyl)-propyl]-phosphonic acid diethyl ester (**4e**).* Yield: 89%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.44–1.60 (m, 6H, $POCH_2CH_3$), 1.97–2.60 (m, 3H, CH_2, CH), 2.84–3.14 (m, 1H, CH_2), 3.43–4.06 (m, 3H, CH_2), 4.20–4.49 (m, 4H, $POCH_2CH_3$), 4.69–5.12 (m, 2H, $PhCH_2O$), 7.15–8.40 (m, 13H, aromat. overlapping formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (m, $POCH_2CH_3$), 25.8 (CH_2), 35.0 (d, $J_{C,P} = 135.9$ Hz, PCH), 35.3 (CH_2), 42.8 (NCH_2), 62.4 (m, $POCH_2CH_3$), 76.7 ($PhCH_2O$), 126.0, 126.6, 127.6, 127.9, 128.1, 128.7, 129.1, 129.6, 130.4 (tert., aromat.), 132.7, 133.9, 134.5, 137.0 (quart., aromat.), 163.3 (C=O). IR: 1681 cm^{-1} (C=O), 1236 cm^{-1} (P=O). Anal. Calcd for $C_{26}H_{32}NO_5P$: calculated C 66.51%, H 6.87%, N 2.98%; found C 66.11%, H 6.97%, N 2.85%.

*6.1.3.6. [3-(Benzyloxy-formyl-amino)-1-(naphthalene-1-yl-methyl)-propyl]-phosphonic acid diethyl ester (**4f**).* Yield: 96%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.18–1.27 (m, 6H, $POCH_2CH_3$), 1.67–1.95 (m, 2H, CH_2), 2.12–2.36 (m, 1H, PCH), 2.89–3.03 (m, 1H, CH_2), 3.36–3.77 (m, 3H, CH_2), 3.95–4.12 (m, 4H, $POCH_2CH_3$), 4.48–4.72 (m, 2H, $PhCH_2O$), 7.13–8.16 (m, 13H, aromat. overlapping formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9, 17.0 (2d, $J_{C,P} = 5.5$ Hz, $J_{C,P} = 5.8$ Hz, $POCH_2CH_3$), 26.0 (CH_2), 32.9 (CH_2), 35.2 (d, $J_{C,P} = 137.1$ Hz, PCH), 43.0 (NCH_2), 62.4 (m, $POCH_2CH_3$), 77.7 ($PhCH_2O$), 124.0, 125.8, 126.2, 126.7, 128.1, 129.0, 129.4, 129.7 (tert., aromat.), 132.1, 134.5 (quart., aromat.), 135.2 (d, $J_{C,P} = 15.8$ Hz, CH_2C quart., aromat.), 163.3 (C=O). IR: 1679 cm^{-1} (C=O), 1240 cm^{-1} (P=O). Anal. Calcd for $C_{26}H_{32}NO_5P$: calculated C 66.51%, H 6.87%, N 2.98%; found C 66.40%, H 7.06%, N 2.86%.

*6.1.4. General procedure for the preparation of [3-(acetyl-benzyloxy-amino)-1-arylmethyl-propyl]-phosphonic acid diethyl esters **5a–f***

A solution of the respective hydroxylamine (**3**; 10 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and treated successively with triethylamine (12 mmol) and with acetyl chloride (12 mmol). The ice bath was removed, and the mixture was stirred at room temperature for 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in

EtOAc (100 mL) and washed with 10% K_2CO_3 solution (2 × 50 mL) and 1 M HCl (2 × 50 mL). The organic layer was dried over $MgSO_4$, evaporated, and the residue was purified by column chromatography on silica gel with EtOAc as an eluent to give [3-(acetyl-benzyloxy-amino)-1-aryl-methyl-propyl]-phosphonic acid diethyl esters **5** as colourless oils.

*6.1.4.1. [3-(Acetyl-benzyloxy-amino)-1-benzyl-propyl]-phosphonic acid diethyl ester (**5a**).* Yield: 92%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19 (t, $J = 7.1$ Hz, 6H, POCH$_2$CH_3), 1.56–1.70 (m, 4H, CH_2 overlapping acetyl. CH_3), 1.72–1.86 (m, 1H, CH_2), 2.12–2.24 (m, 1H, PCH), 2.55–2.68 (m, 1H, CH_2), 2.93–3.01 (m, 1H, CH_2), 3.51–3.58 (m, 1H, CH_2), 3.71–3.81 (m, 1H, CH_2), 3.94–4.02 (m, 4H, POCH_2CH$_3$), 4.74 (s, 2H, PhCH_2O), 7.18–7.40 (m, 10H, aromat.), ^{13}C NMR ($CDCl_3$), δ (ppm): 16.4, 16.5 (2d, $J_{C,P} = 6.1$ Hz, POCH$_2$CH_3), 20.5 (acetyl. CH_3), 25.4 (d, $J_{C,P} = 3.1$ Hz, CH_2), 34.8 (d, $J_{C,P} = 2.5$ Hz, CH_2), 35.8 (d, $J_{C,P} = 139.9$ Hz, PCH), 43.7 (NCH_2), 61.8 (2d, $J_{C,P} = 6.6$ Hz, $J_{C,P} = 7.1$ Hz, POCH_2CH$_3$), 76.1 (PhCH_2O), 126.5, 128.5, 128.6, 128.9, 129.1, 129.2 (tert., aromat.), 134.4 (quart., aromat.), 139.2 (d, $J_{C,P} = 14.3$ Hz, CH$_2$C quart., aromat.), 172.0 (C=O). IR: 1662 cm^{-1} (C=O), 1234 cm^{-1} (P=O). HRFAB-MS $C_{23}H_{32}NO_5P$ $[M + H]^+$: calculated 434.2096; found 434.2122.

*6.1.4.2. [3-(Acetyl-benzyloxy-amino)-1-(2,5-dimethyl-benzyl)-propyl]-phosphonic acid diethyl ester (**5b**).* Yield: 91%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.23–1.37 (m, 6H, POCH$_2$CH_3), 1.79–1.93 (m, 2H, CH_2), 1.97 (s, 3H, acetyl. CH_3), 2.06–2.18 (m, 1H, PCH), 2.24 (s, 3H, PhCH_3), 2.25 (s, 3H, PhCH_3), 2.50–2.64 (m, 1H, CH_2), 3.07–3.21 (m, 1H, CH_2), 3.50–3.83 (m, 2H, CH_2), 4.01–4.21 (m, 4H, POCH_2CH$_3$), 4.65 (s, 2H, PhCH_2O), 6.88–7.06 (m, 3H, aromat.), 7.21–7.41 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.5 (2d, $J_{C,P} = 6.1$ Hz, POCH$_2$CH_3), 19.0, 20.9 (PhCH_3), 20.5 (acetyl. CH_3), 25.4 (d, $J_{C,P} = 3.4$ Hz, CH_2), 32.3 (d, $J_{C,P} = 2.5$ Hz, CH_2), 34.4 (d, $J_{C,P} = 139.4$ Hz, PCH), 43.8 (NCH_2), 62.1 (2d, $J_{C,P} = 6.8$ Hz, $J_{C,P} = 6.6$ Hz, POCH_2CH$_3$), 76.0 (PhCH_2O), 127.2, 128.6, 128.8, 129.1, 130.5, 130.8 (tert., aromat.), 133.1, 135.3, 137.0 (quart., aromat.), 137.6 (d, $J_{C,P} = 14.3$ Hz, CH$_2$C quart., aromat.), 175.5 (C=O). IR: 1664 cm^{-1} (C=O), 1232 cm^{-1} (P=O). HRFAB-MS $C_{25}H_{36}NO_5P$ $[M + H]^+$: calculated 462.2409; found 462.2425.

*6.1.4.3. [3-(Acetyl-benzyloxy-amino)-1-(3,4-dichlor-benzyl)-propyl]-phosphonic acid diethyl ester (**5c**).* Yield: 95%. MP: 66.8 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.24–1.33 (m, 6H, POCH$_2$CH_3), 1.68–1.85 (m, 1H, CH_2), 1.90–2.19 (m, 5H, acetyl. CH_3 overlapping PCH, CH_2), 2.56–2.72 (m, 1H, CH_2), 2.98–3.10 (m, 1H, CH_2), 3.59–3.89 (m, 2H, CH_2), 3.97–4.16 (m, 4H, POCH_2CH$_3$), 4.74 (s, 2H, PhCH_2O), 7.00–7.10 (m, 1H, aromat.), 7.23–7.46 (m, 7H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8 (2d, $J_{C,P} = 6.1$ Hz, $J_{C,P} = 6.0$ Hz, POCH$_2$CH_3), 20.9 (acetyl. CH_3), 25.8 (d, $J_{C,P} = 2.8$ Hz, CH_2), 34.4 (d, $J_{C,P} = 2.8$ Hz, CH_2), 35.9 (d, $J_{C,P} = 140.7$ Hz, PCH), 43.8 (NCH_2), 62.3 (2d, $J_{C,P} = 7.2$ Hz, $J_{C,P} = 7.1$ Hz, POCH_2CH$_3$), 76.7 (PhCH_2O), 129.0, 129.1, 129.4, 129.6, 130.7, 131.5 (tert., aromat.), 130.9, 132.7, 134.7 (quart., aromat.), 139.9 (d, $J_{C,P} = 14.5$ Hz, CH$_2$C quart., aromat.), 172.1 (C=O). IR: 1655 cm^{-1} (C=O), 1227 cm^{-1} (P=O). Anal. Calcd for $C_{23}H_{30}Cl_2NO_5P$: calculated C 54.99%, H 6.02%, N 2.79%; found C 55.01%, H 6.24%, N 3.14%.

*6.1.4.4. [3-(Acetyl-benzyloxy-amino)-1-(4-methoxy-benzyl)-propyl]-phosphonic acid diethyl ester (**5d**).* Yield: 87%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20 (t, $J = 6.98$ Hz, 6H, POCH$_2$CH_3), 1.55–1.84 (m, 2H, CH_2), 1.95 (s, 3H, acetyl. CH_3), 2.05–2.22 (m, 1H, PCH), 2.85–2.97 (m, 1H, CH_2), 3.48–3.64 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.73–3.84 (m, 1H, CH_2), 3.93–4.05 (m, 4H, POCH_2CH$_3$), 4.73 (s, 2H, PhCH_2O), 6.80–6.85 (m, 2H, aromat.), 7.13–7.18 (m, 2H, aromat.), 7.29–7.40 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 6.1$ Hz, $J_{C,P} = 5.8$ Hz, POCH$_2$CH_3), 20.9 (acetyl. CH_3), 25.6 ($J_{C,P} = 3.0$ Hz, CH_2), 34.2 (d, $J_{C,P} = 2.6$ Hz, CH_2), 36.3 (d, $J_{C,P} = 139.6$ Hz, PCH), 44.2 (NCH_2), 55.6 (OCH_3), 62.3 (m, POCH_2CH$_3$), 76.5 (PhCH_2O), 114.3 (OCCH tert., aromat.), 129.1, 129.3, 129.5, 130.5 (tert., aromat.), 131.5 (d, $J_{C,P} = 15.0$ Hz, CH$_2$C quart., aromat.), 134.8 (quart., aromat.), 158.7 (CH$_3$OC quart., aromat.), 172.4 (C=O). IR: 1664 cm^{-1} (C=O), 1250 cm^{-1} (P=O). Anal. Calcd for $C_{24}H_{34}NO_6P$: calculated C 62.19%, H 7.39%, N 3.02%; found C 62.64%, H 7.45%, N 2.77%.

*6.1.4.5. [3-(Acetyl-benzyloxy-amino)-1-(naphthalene-2-yl-methyl)-propyl]-phosphonic acid diethyl ester (**5e**).* Yield: 95%. MP: 78.5 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20–1.36 (m, 6H, POCH$_2$CH_3), 1.78–2.10 (m, 5H, acetyl. CH_3 overlapping CH_2), 2.17–1.32 (m, 1H, PCH), 2.74–2.90 (m, 1H, CH_2), 3.26–3.41 (m, 1H, CH_2), 3.53–3.91 (m, 2H, CH_2), 4.04–4.19 (m, 4H, POCH_2CH$_3$), 4.95 (s, 2H, PhCH_2O), 7.09–7.50 (m, 8H, aromat.), 7.63–7.84 (m, 4H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9 (2d, $J_{C,P} = 5.7$ Hz, POCH$_2$CH_3), 20.9 (acetyl. CH_3), 25.8 (CH_2), 35.4 (d, $J_{C,P} = 2.7$ Hz, CH_2), 35.8 (PCH), 44.2 (NCH_2), 62.3 (m, POCH_2CH$_3$), 76.5 (PhCH_2O), 125.9, 126.5, 127.7, 128.0, 128.1, 128.6, 129.0, 129.2, 129.4 (tert., aromat.), 132.7, 133.9, 134.7 (quart., aromat.), 137.0 (d, $J_{C,P} = 15.0$ Hz, CH$_2$C quart., aromat.), 175.5 (C=O). IR: 1651 cm^{-1} (C=O), 1227 cm^{-1} (P=O). Anal. Calcd for $C_{27}H_{34}NO_5P$: calculated C 67.07%, H 7.09%, N 3.20%; found C 67.16%, H 7.14%, N 2.99%.

*6.1.4.6. [3-(Acetyl-benzyloxy-amino)-1-(naphthalene-1-yl-methyl)-propyl]-phosphonic acid diethyl ester (**5f**).* Yield: 94%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.29–1.37 (m, 6H, POCH$_2$CH_3), 1.81 (s, 3H, acetyl. CH_3), 1.84–2.03 (m, 2H, CH_2), 2.20–2.40 (m, 1H, PCH), 2.83–2.98 (m, 1H, CH_2), 3.37–3.84 (m, 3H, CH_2), 4.04–4.23 (m, 4H, POCH_2CH$_3$), 4.50 (s, 2H, PhCH_2O), 7.10–7.20 (m, 2H, aromat.), 7.28–7.39 (m, 5H, aromat.), 7.44–7.55 (m, 2H, aromat.), 7.68–7.76 (m, 1H, aromat.), 7.81–7.88 (m, 1H, aromat.), 8.01–8.07 (m, 1H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9, 17.0

(2d, $J_{C,P} = 5.6$ Hz, $J_{C,P} = 6.0$ Hz, $POCH_2CH_3$), 20.7 (acetyl. CH_3), 26.0 (d, $J_{C,P} = 3.0$ Hz, CH_2), 33.2 (d, $J_{C,P} = 2.6$ Hz, CH_2), 35.1 (d, $J_{C,P} = 139.4$ Hz, PCH), 44.2 (NCH_2), 62.4 (d, $J_{C,P} = 6.2$ Hz, $POCH_2CH_3$), 76.3 ($PhCH_2O$), 124.1, 125.8, 126.0, 126.6, 127.9, 128.2, 129.0, 129.2, 129.4, 129.5 (tert., aromat.), 132.1, 134.5 (quart., aromat.), 135.4 (d, $J_{C,P} =$ 15.7 Hz, CH_2C quart., aromat.), 172.8 (C=O). IR: 1666 cm^{-1} (C=O), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{27}H_{34}NO_5P$: calculated C 67.07%, H 7.09%, N 3.20%; found C 66.68%, H 7.30%, N 2.90%.

*6.1.5. General procedure for the preparation of [3-(acyl-benzyloxy-amino)-1-arylmethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **6a–f**, **7a–f***

Trimethylsilylbromide (15 mmol) was added to a stirred solution of the phosphonic acid diethyl esters **4a–f**, **5a–f** (3 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After 1 h, the solution was allowed to warm up to room temperature and was stirred overnight. The solvent was removed under reduced pressure and the residue was dissolved in dry THF (10 mL) and treated with water (0.1 mL) for 5 min. The solvent was evaporated and the residue was dried at the vacuum pump in order to remove remaining traces of water. For the alkylation step, the resulting oil was dissolved in anhydrous DMF (20 mL), treated with triethylamine (9 mmol) and stirred for 5 min at room temperature. Chloromethyl pivalate (30 mmol) was added and the mixture was stirred at 70 °C for 5 h. After cooling to room temperature, another 3 mmol of triethylamine and 5 mmol of chloromethyl pivalate were added and the mixture was stirred at room temperature overnight. Diethyl ether (100 mL) was added and the solution was successively washed with water (50 mL), saturated $NaHCO_3$ solution (2×50 mL) and again with water (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting pale yellow oils were purified by column chromatography on silica gel with Et_2O as an eluent to give [3-(acyl-benzyloxy-amino)-1-arylmethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **6**, **7**.

*6.1.5.1. 2,2-Dimethyl-propionic acid [1-benzyl-3-(benzyloxy-formyl-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6a**).* Yield: 62%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16 (s, 18H, $C(CH_3)_3$), 1.55–1.87 (m, 2H, CH_2), 2.25–2.42 (m, 1H, CH), 2.56–2.67 (m, 1H, CH_2), 2.94–3.06 (m, 1H, CH_2), 3.41–3.74 (m, 2H, CH_2), 4.74 (s, 2H, $PhCH_2O$), 5.55–5.66 (m, 4H, OCH_2O), 7.18–7.40 (m, 10H, aromat.), 7.71–8.20 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 25.0 (d, $J_{C,P} = 4.1$ Hz, CH_2), 26.9 ($C(CH_3)_3$), 34.3 (d, $J_{C,P} = 3.1$ Hz, CH_2), 36.1 (d, $J_{C,P} = 139.4$ Hz, PCH), 38.8 ($C(CH_3)_3$), 42.2 (NCH_2), 76.2 ($PhCH_2O$), 81.5, 81.6 (2d, $J_{C,P} = 8.1$ Hz, $J_{C,P} = 7.1$ Hz, OCH_2O), 126.9, 128.7, 129.1, 129.4 (tert., aromat.), 134.2 (quart., aromat.), 138.1 (d, $J_{C,P} = 17.3$ Hz, CH_2C quart., aromat.), 162.8 (C=O, hydroxamate), 176.9 (C=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1680 cm^{-1} (C=O, hydroxamate), 1260 cm^{-1} (P=O). Anal. Calcd for $C_{30}H_{42}NO_9P$: calculated C 60.90%, H 7.16%, N 2.37%; found C 60.79%, H 7.07%, N 2.46%.

*6.1.5.2. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(2,5-dimethyl-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6b**).* Yield: 44%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16, 1.17 (2s, 18H, $C(CH_3)_3$), 1.62–1.91 (m, 2H, CH_2), 2.18 (s, 6H, $PhCH_3$), 2.22–2.35 (m, 1H, CH), 2.89–3.01 (m, 1H, CH_2), 3.22–3.33 (m, 1H, CH_2), 3.41–3.68 (m, 2H, CH_2), 4.56–4.78 (m, 2H, $PhCH_2O$), 5.55–5.75 (m, 4H, OCH_2O), 6.87–7.11 (m, 3H, aromat.), 7.18–7.43 (m, 5H, aromat.), 7.73–8.18 (m, 1H, formyl.). ^{13}C NMR (DMSO-d_6), δ (ppm): 18.8, 20.8 (2s, $PhCH_3$), 24.8 (CH_2), 26.8 ($C(CH_3)_3$), 31.4 (d, $J_{C,P} = 1.8$ Hz, CH_2), 34.4 (d, $J_{C,P} = 138.9$ Hz, PCH), 38.6 ($C(CH_3)_3$), 41.8 (NCH_2), 76.9 ($PhCH_2O$), 81.8 (OCH_2O), 127.7, 128.7, 129.1, 129.8, 130.7 (tert., aromat.), 133.2, 135.1 (quart., aromat.), 136.4 (d, $J_{C,P} = 15.0$ Hz, CH_2C quart., aromat.), 162.9 (C=O, hydroxamate), 176.6 (C=O, ester). IR: 1755 cm^{-1} (C=O, ester), 1675 cm^{-1} (C=O, hydroxamate), 1255 cm^{-1} (P=O). Anal. Calcd for $C_{32}H_{46}NO_9P$: calculated C 62.02%, H 7.48%, N 2.26%; found C 61.64%, H 7.57%, N 2.31%.

*6.1.5.3. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(3,4-dichloro-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6c**).* Yield: 48%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.15, 1.16 (2s, 18H, $C(CH_3)_3$), 1.53–1.91 (m, 2H, CH_2), 2.31–2.43 (m, 1H, CH), 2.58–3.08 (m, 2H, CH_2), 3.47–3.81 (m, 2H, CH_2), 4.58–4.88 (m, 2H, $PhCH_2O$), 5.52–5.68 (m, 4H, OCH_2O), 7.17–7.61 (m, 8H, aromat.), 7.79–8.25 (m, 1H, formyl.). ^{13}C NMR (DMSO-d_6), δ (ppm): 25.0 (CH_2), 26.9 ($C(CH_3)_3$), 33.4 (CH_2), 35.8 (d, $J = 138.4$ Hz, PCH), 38.8 ($C(CH_3)_3$), 42.0 (NCH_2), 77.6 ($PhCH_2O$), 81.6 (m, OCH_2O), 128.5, 128.8, 129.1, 129.4, 130.5, 131.0 (tert., aromat.), 132.6, 134.1, 138.3 (quart., aromat.), 162.9 (C=O, hydroxamate), 176.9 (C=O, ester). IR: 1747 cm^{-1} (C=O, ester), 1676 cm^{-1} (C=O, hydroxamate), 1259 cm^{-1} (P=O). Anal. Calcd for $C_{30}H_{40}Cl_2NO_9P$: calculated C 54.55%, H 6.10%, N 2.12%; found C 54.61%, H 6.25%, N 1.95%.

*6.1.5.4. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(4-methoxy-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6d**).* Yield: 34%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.15, 1.16 (2s, 18H, $C(CH_3)_3$), 1.50–1.88 (m, 2H, CH_2), 2.19–2.36 (m, 1H, CH), 2.52–2.63 (m, 1H, CH_2), 2.83–3.07 (m, 1H, CH_2), 3.39–3.61 (m, 5H, OCH_3 overlapping CH_2), 4.54–4.80 (m, 2H, $PhCH_2O$), 5.49–5.73 (m, 4H, OCH_2O), 6.79–6.86 (m, 2H, aromat.), 7.04–7.45 (m, 7H, aromat.), 7.73–8.23 (m, 1H, formyl.). ^{13}C NMR (DMSO-d_6), δ (ppm): 24.5 (CH_2), 26.8 ($C(CH_3)_3$), 32.7 (d, $J_{C,P} = 1.8$ Hz, CH_2), 34.0 (d, $J_{C,P} = 137.1$ Hz, PCH), 38.6 ($C(CH_3)_3$), 41.6 (NCH_2), 55.3 (OCH_3), 77.2 ($PhCH_2O$), 81.7 (OCH_2O), 114.2 (OCCH tert., aromat.), 128.7, 129.1, 129.9, 130.3 (tert., aromat.), 130.2, 130.4 (quart., aromat.), 158.3 (CH_3OC quart., aromat.), 162.1 (C=O, hydroxamate), 176.6 (C=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1668 cm^{-1}

(C=O, hydroxamate), 1242 cm^{-1} (P=O). Anal. Calcd for $C_{31}H_{44}NO_{10}P$: calculated C 59.89%, H 7.13%, N 2.25%; found C 59.53%, H 7.27%, N 2.19%.

*6.1.5.5. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(naphthalene-2-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6e**).* Yield: 35%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16 (2d, 18H, C(CH_3)$_3$), 1.63–1.93 (m, 2H, CH_2), 2.40–2.49 (m, 1H, CH), 2.72–2.91 (m, 1H, CH_2), 3.07–3.26 (m, 1H, CH_2), 3.51–3.79 (m, 2H, CH_2), 4.54–4.73 (m, 2H, PhCH_2O), 5.52–5.76 (m, 4H, OCH_2O), 7.00–7.54 (m, 8H, aromat.), 7.74–7.91 (m, 4H, aromat.), 7.93–8.29 (m, 1H, formyl.). ^{13}C NMR (DMSO-d_6), δ (ppm): 24.3 (*C*H_2), 26.8 (C(*C*H_3)$_3$), 33.8 (*C*H_2), 34.6 (d, $J_{C,P}$ = 140.0 Hz, P*C*H), 38.8 (*C*(CH$_3$)$_3$), 41.1 (N*C*H$_2$), 76.4 (Ph*C*H$_2$O), 81.4 (O*C*H$_2$O), 125.5, 126.1, 127.1, 127.3, 127.5, 127.9, 128.2, 128.6, 129.2 (tert., aromat.), 131.8, 132.9, 134.3 (quart., aromat.), 135.7 (d, $J_{C,P}$ = 14.1 Hz, CH$_2$*C* quart., aromat.), 162.5 (*C*=O, hydroxamate), 176.1 (*C*=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1679 cm^{-1} (C=O, hydroxamate), 1263 cm^{-1} (P=O). Anal. Calcd for $C_{34}H_{44}NO_9P$: calculated C 63.64%, H 6.91%, N 2.18%; found C 63.98%, H 7.24%, N 2.03%.

*6.1.5.6. 2,2-Dimethyl-propionic acid [3-(benzyloxy-formyl-amino)-1-(naphthalene-1-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**6f**).* Yield: 31%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.15, 1.17 (2s, 18H, C(CH_3)$_3$), 1.85–1.95 (m, 2H, CH_2), 2.25–2.44 (m, 1H, CH), 2.83–3.00 (m, 1H, CH_2), 3.34–3.69 (m, 3H, CH_2), 4.39–4.72 (m, 2H, PhCH_2O), 5.53–5.81 (m, 4H, OCH_2O), 7.04–7.59 (m, 9H, aromat.), 7.73–8.17 (m, 4H, aromat. overlapping formyl.). ^{13}C NMR (DMSO-d_6), δ (ppm): 25.6 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 31.4 (*C*H$_2$), 34.7 (d, $J_{C,P}$ = 138.1 Hz, P*C*H), 38.6 (*C*(CH$_3$)$_3$), 41.8 (N*C*H$_2$), 75.2 (Ph*C*H$_2$O), 81.9 (O*C*H$_2$O), 123.5, 125.3, 125.7, 126.2, 126.8, 127.9, 128.1, 128.7, 129.3 (tert., aromat.), 131.5, 133.9, 134.3 (quart., aromat.), 162.7 (*C*=O, hydroxamate), 176.6 (*C*=O, ester). IR: 1757 cm^{-1} (C=O, ester), 1683 cm^{-1} (C=O, hydroxamate), 1256 cm^{-1} (P=O). Anal. Calcd for $C_{34}H_{44}NO_9P$: calculated C 63.64%, H 6.91%, N 2.18%; found C 63.70%, H 7.12%, N 2.21%.

*6.1.5.7. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-benzyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7a**).* Yield: 82%. MP: 50.2 °C. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.15, 1.16 (2s, 18H, C(CH_3)$_3$), 1.58–1.86 (m, 2H, CH_2), 1.92 (s, 3H, acetyl. CH_3), 2.27–2.41 (m, 1H, CH), 2.56–2.64 (m, 1H, CH_2), 2.95–3.03 (m, 1H, CH_2), 3.47–3.55 (m, 1H, CH_2), 3.65–3.76 (m, 1H, CH_2), 4.72 (s, 2H, PhCH_2O), 5.54–5.65 (m, 4H, OCH_2O), 7.19–7.34 (m, 7H, aromat.), 7.36–7.41 (m, 3H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.4 (acetyl. *C*H$_3$), 24.9 (d, $J_{C,P}$ = 3.1 Hz *C*H$_2$), 26.9 (C(*C*H$_3$)$_3$), 34.2 (d, $J_{C,P}$ = 3.1 Hz, *C*H$_2$), 36.1 (d, $J_{C,P}$ = 139.4 Hz, P*C*H), 38.7 (*C*(CH$_3$)$_3$), 43.5 (N*C*H$_2$), 76.1 (Ph*C*H$_2$O), 81.5, 81.6 (2d, $J_{C,P}$ = 6.1 Hz, O*C*H$_2$O), 126.7, 128.6, 128.7, 128.9, 129.1, 129.2 (tert., aromat.), 134.4 (quart., aromat.), 138.3 (d, $J_{C,P}$ = 14.2 Hz, CH$_2$*C* quart., aromat.), 172.1 (*C*=O, hydroxamate), 176.9 (*C*=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1667 cm^{-1} (C=O, hydroxamate), 1260 cm^{-1} (P=O). Anal. Calcd for $C_{31}H_{44}NO_9P$: calculated C 61.48%, H 7.32%, N 2.31%; found C 61.42%, H 7.39%, N 2.52%.

*6.1.5.8. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(2,5-dimethyl-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7b**).* Yield: 48%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16 (2s, 18H, C(CH_3)$_3$), 1.62–1.85 (m, 2H, CH_2), 1.89 (s, 3H, acetyl. CH_3), 2.17 (s, 6H, PhCH_3), 2.21–2.32 (m, 1H, CH), 2.41–2.48 (m, 1H, CH_2), 2.90–3.00 (m, 1H, CH_2), 3.44–3.54 (m, 1H, CH_2), 3.59–3.69 (m, 1H, CH_2), 4.69 (s, 2H, PhCH_2O), 5.55–5.67 (m, 4H, OCH_2O), 6.87–7.06 (m, 3H, aromat.), 7.24–7.43 (m, 5H, aromat.). ^{13}C NMR (DMSO-d_6), δ (ppm): 18.8, 20.9 (2s, Ph*C*H$_3$), 20.6 (acetyl. *C*H$_3$), 24.8 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 31.4 (d, $J_{C,P}$ = 3.0 Hz, *C*H$_2$), 34.1 (d, $J_{C,P}$ = 136.7 Hz, P*C*H), 38.6 (*C*(CH$_3$)$_3$), 43.0 (N*C*H$_2$), 75.5 (Ph*C*H$_2$O), 81.8 (O*C*H$_2$O), 127.6, 128.8, 129.0, 129.5, 130.6, 130.7 (tert., aromat.), 133.1, 135.0 (quart., aromat.), 136.5 (d, $J_{C,P}$ = 13.9 Hz, CH$_2$*C* quart., aromat.), 172.1 (*C*=O, hydroxamate), 176.5 (*C*=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1668 cm^{-1} (C=O, hydroxamate), 1257 cm^{-1} (P=O). Anal. Calcd for $C_{33}H_{48}NO_9P$: calculated C 62.55%, H 7.63%, N 2.21%; found C 62.40%, H 7.76%, N 2.11%.

*6.1.5.9. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(3,4-dichloro-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7c**).* Yield: 48%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.22 (s, 18H, C(CH_3)$_3$), 1.71–1.85 (m, 1H, CH_2), 1.88–1.99 (m, 1H, CH_2), 2.01 (s, 3H, acetyl. CH_3), 2.14–2.27 (m, 1H, CH), 2.56–2.64 (m, 1H, CH_2), 3.01–3.07 (m, 1H, CH_2), 3.62–3.82 (m, 2H, CH_2), 4.73 (s, 2H, PhCH_2O), 5.60–5.72 (m, 4H OCH_2O), 6.98–7.05 (m, 1H, aromat.), 7.27–7.40 (m, 7H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.8 (acetyl. *C*H$_3$), 25.4 (d, $J_{C,P}$ = 3.3 Hz, *C*H$_2$), 27.3 (C(*C*H$_3$)$_3$), 33.8 (d, $J_{C,P}$ = 2.3 Hz, *C*H$_2$), 36.2 (d, $J_{C,P}$ = 140.1 Hz, P*C*H), 39.2 (*C*(CH$_3$)$_3$), 43.6 (N*C*H$_2$), 76.7 (Ph*C*H$_2$O), 81.5, 81.6 (2d, $J_{C,P}$ = 10.0 Hz, $J_{C,P}$ = 9.2 Hz, O*C*H$_2$O), 129.0, 129.2, 129.4, 129.6, 130.9, 131.3 (tert., aromat.), 131.2, 132.9, 134.7 (quart., aromat.), 139.1 (d, $J_{C,P}$ = 14.7 Hz, CH$_2$*C* quart., aromat.), 172.2 (*C*=O, hydroxamate), 177.3 (*C*=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1666 cm^{-1} (C=O, hydroxamate), 1259 cm^{-1} (P=O). Anal. Calcd for $C_{31}H_{42}Cl_2NO_9P$: calculated C 55.20%, H 6.28%, N 2.08%; found C 55.36%, H 6.59%, N 2.01%.

*6.1.5.10. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(4-methoxy-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7d**).* Yield: 40%. MP: 42.9 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20, 1.21 (2s, 18H, C(CH_3)$_3$), 1.72–1.96 (m, 2H, CH_2), 1.98 (s, 3H, acetyl. CH_3), 2.13–2.30 (m, 1H, CH), 2.47–2.62 (m, 1H, CH_2), 2.99–3.13 (m, 1H, CH_2), 3.51–3.82 (m, 5H, OCH_3 overlapping CH_2), 4.67 (s, 2H, PhCH_2O), 5.56–5.73 (m, 4H, OCH_2O), 6.75–6.83

(m, 2H, aromat.), 7.03–7.14 (m, 2H, aromat.), 7.26–7.38 (m, 5H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.9 (acetyl. CH_3), 25.2 (d, $J_{C,P} = 3.1$ Hz, CH_2), 27.3 ($C(CH_3)_3$), 33.7 (d, $J_{C,P} = 2.5$ Hz, CH_2), 36.7 (d, $J_{C,P} = 136.3$ Hz, PCH), 39.2 ($C(CH_3)_3$), 43.8 (NCH_2), 55.6 (OCH_3), 76.6 ($PhCH_2O$), 81.4 (OCH_2O), 114.4 (OCCH tert., aromat.), 129.1, 129.3, 129.6, 130.5 (tert., aromat.), 130.7, 134.4 (quart., aromat.), 158.8 (CH_3OC quart., aromat.), 172.0 (C=O, hydroxamate), 177.3 (C=O, ester). IR: 1749 cm^{-1} (C=O, ester), 1664 cm^{-1} (C=O, hydroxamate), 1246 cm^{-1} (P=O). Anal. Calcd for $C_{32}H_{46}NO_{10}P$: calculated C 60.46%, H 7.29%, N 2.20%; found C 60.54%, H 7.43%, N 2.11%.

*6.1.5.11. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(naphthalene-2-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7e**).* Yield: 35%. MP: 60.6 °C. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.15, 1.16 (2s, 18H, $C(CH_3)_3$), 1.60–1.85 (m, 2H, CH_2), 1.88 (s, 3H, acetyl. CH_3), 2.41–2.48 (m, 1H, CH), 2.71–2.87 (m, 1H, CH_2), 3.10–3.25 (m, 1H, CH_2), 3.49–3.63 (m, 1H, CH_2), 3.68–3.81 (m, 1H, CH_2), 4.66 (s, 2H, $PhCH_2O$), 5.57–5.71 (m, 4H, OCH_2O), 7.07–7.54 (m, 8H, aromat.), 7.71–7.93 (m, 4H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH_3), 24.7 (d, $J_{C,P} = 3.9$ Hz, CH_2), 26.8 ($C(CH_3)_3$), 33.8 (d, $J_{C,P} = 1.9$ Hz, CH_2), 35.1 (d, $J_{C,P} = 136.7$ Hz, PCH), 38.6 ($C(CH_3)_3$), 43.0 (d, $J_{C,P} = 14.9$ Hz, NCH_2), 75.6 ($PhCH_2O$), 81.8 (OCH_2O), 126.0, 126.5, 127.5, 127.7, 127.8, 127.9, 128.3, 128.7, 128.9, 129.6 (tert., aromat.), 132.2, 133.4, 134.9 (quart., aromat.), 136.2 (d, $J_{C,P} = 15.4$ Hz, CH_2C quart., aromat.), 172.5 (C=O, hydroxamate), 176.5 (C=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1663 cm^{-1} (C=O, hydroxamate), 1258 cm^{-1} (P=O). Anal. Calcd for $C_{35}H_{46}NO_9P$: calculated C 64.11%, H 7.07%, N 2.14%; found C 64.48%, H 7.30%, N 2.04%.

*6.1.5.12. 2,2-Dimethyl-propionic acid [3-(acetyl-benzyloxy-amino)-1-(naphthalene-1-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**7f**).* Yield: 52%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.22, 1.24 (2s, 18H, $C(CH_3)_3$), 1.76 (s, 3H, acetyl. CH_3), 1.82–2.07 (m, 2H, CH_2), 2.35–2.49 (m, 1H, CH), 2.81–2.96 (m, 1H, CH_2), 3.42–3.84 (m, 3H, CH_2), 4.48 (s, 2H, $PhCH_2O$), 5.66–5.82 (m, 4H, OCH_2O), 7.10–7.21 (m, 2H, aromat.), 7.29–7.40 (m, 5H, aromat.), 7.44–7.57 (m, 2H, aromat.), 7.70–8.00 (m, 3H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH_3), 25.8 (d, $J_{C,P} = 2.8$ Hz, CH_2), 27.3 ($C(CH_3)_3$), 32.4 (d, $J_{C,P} = 2.2$ Hz, CH_2), 35.3 (d, $J_{C,P} = 139.3$ Hz, PCH), 39.2 ($C(CH_3)_3$), 44.0 (d, $J_{C,P} = 15.1$ Hz, NCH_2), 76.3 ($PhCH_2O$), 82.1 (OCH_2O), 123.9, 125.7, 126.2, 126.9, 128.2, 128.3, 129.0, 129.2, 129.4, 129.5 (tert., aromat.), 132.0, 134.4, 134.5, 134.6 (quart., aromat.), 172.0 (C=O, hydroxamate), 177.3 (C=O, ester). IR: 1753 cm^{-1} (C=O, ester), 1666 cm^{-1} (C=O, hydroxamate), 1255 cm^{-1} (P=O). Anal. Calcd for $C_{35}H_{46}NO_9P$: calculated C 64.11%, H 7.07%, N 2.14%; found C 63.92%, H 7.39%, N 2.15%.

*6.1.6. General procedure for the preparation of 2,2-dimethyl-propionic acid [3-(acyl-hydroxy-amino)-1-arylmethyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **8a–f**, **9a–f***

The appropriate *O*-protected hydroxamic acids **6a–f**, **7a–f** (1 mmol) were dissolved in freshly distilled methanol (50 mL). After addition of the Pd–C catalyst, hydrogen gas was added and the mixture was hydrogenated for 2 h, except for compounds **6e**,**f** and **7e**,**f** which required a reaction time of 14 h in order to obtain the pure tetrahydronaphthyl derivatives. In case of hydroxamic acids **8**,**9c** ethyl acetate was used as solvent. The suspension was filtrated through an SPE tube RP-18 purchased from Supelco. The filtrate was evaporated to give 2,2-dimethyl-propionic acid [3-(acyl-hydroxyamino)-1-arylmethylpropyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl esters **8a–f**, **9a–f** as pale yellow oils.

*6.1.6.1. 2,2-Dimethyl-propionic acid [1-benzyl-3-(formyl-hydroxyamino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8a**).* Yield: 99%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16, 1.17 (2s, 18H, $C(CH_3)_3$), 1.54–1.87 (m, 2H, CH_2), 2.25–2.42 (m, 1H, CH_2), 2.57–2.69 (m, 1H, CH_2), 2.92–3.04 (m, 1H, CH_2), 3.38–3.63 (m, 2H, CH_2), 5.51–5.65 (m, 4H, OCH_2O), 7.20–7.33 (m, 5H, aromat.), 7.73 (s, 0.5H, formyl.), 8.15 (s, 0.5H, formyl.), 9.48 (s, 0.5H, OH), 9.92 (s, 0.5H, OH). ^{13}C NMR ($CDCl_3$), δ (ppm): 23.3, 25.1 (2d, $J_{C,P} = 3.1$ Hz, CH_2), 26.9 ($C(CH_3)_3$), 34.5, 34.6 (2d, $J_{C,P} = 4.1$ Hz, $J_{C,P} = 3.1$ Hz, CH_2), 35.5 (d, $J_{C,P} = 137.3$ Hz, PCH), 38.8 ($C(CH_3)_3$), 45.1, 47.2 (2d, $J_{C,P} = 4.1$ Hz, $J_{C,P} = 5.1$ Hz, NCH_2), 81.5, 81.9 (2d, $J_{C,P} = 7.1$ Hz, OCH_2O), 127.0, 128.8, 128.9 (tert., aromat.), 137.4, 138.0 (2d, $J_{C,P} = 16.3$ Hz, CH_2C quart., aromat.), 156.2, 163.6 (C=O, hydroxamate), 176.8, 177.0 (C=O, ester). IR: 3205 cm^{-1} (O–H), 1753 cm^{-1} (C=O, ester), 1673 cm^{-1} (C=O, hydroxamate), 1256 cm^{-1} (P=O). Anal. Calcd for $C_{23}H_{36}NO_9P$: calculated C 55.08%, H 7.24%, N 2.79%; found C 54.52%, H 6.96%, N 2.72%.

*6.1.6.2. 2,2-Dimethyl-propionic acid [1-(2,5-dimethyl-benzyl)-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8b**).* Yield: 92%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.19, 1.20 (2s, 18H, $C(CH_3)_3$), 1.57–1.93 (m, 2H, CH_2), 2.14–2.35 (m, 7H, $PhCH_3$ overlapping CH), 2.90–3.04 (m, 1H, CH_2), 3.26–3.63 (m, 3H, CH_2), 5.51–5.70 (m, 4H, OCH_2O), 6.88–7.13 (m, 3H, aromat.), 7.66–8.18 (m, 1H, formyl.), 9.45–9.99 (m, 1H, OH). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.9, 20.9 ($PhCH_3$), 26.1, 27.8 (2d, $J_{C,P} = 3.5$ Hz, $J_{C,P} = 4.1$ Hz, CH_2), 26.8 ($C(CH_3)_3$), 31.4, 31.5 (2d, $J_{C,P} = 2.4$ Hz, $J_{C,P} = 2.9$ Hz, CH_2), 33.3, 33.4 (2d, $J_{C,P} = 136.2$ Hz, $J_{C,P} = 137.1$ Hz, PCH), 38.6 ($C(CH_3)_3$), 44.4, 47.5 (2d, $J_{C,P} = 6.9$ Hz, NCH_2), 81.8 (OCH_2O), 127.6, 130.6, 130.7 (tert., aromat.), 133.1, 135.0 (quart., aromat.), 136.7 (d, $J_{C,P} = 14.5$ Hz, CH_2C quart., aromat.), 157.2, 161.1, 161.9 (C=O, hydroxamate), 176.5 (C=O, ester). IR: 3205 cm^{-1} (O–H), 1752 cm^{-1} (C=O, ester), 1674 cm^{-1} (C=O, hydroxamate), 1246 cm^{-1} (P=O). Anal. Calcd for

$C_{25}H_{40}NO_9P$: calculated C 56.70%, H 7.61%, N 2.64%; found C 56.46%, H 7.51%, N 2.57%.

*6.1.6.3. 2,2-Dimethyl-propionic acid [1-(3,4-dichloro-benzyl)-3-(formyl-hydroxy-amino)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8c**).* Yield: 88%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.23–1.26 (m, 18H, C(CH_3)$_3$), 1.84–2.34 (m, 3H, CH, CH_2), 2.49–2.66 (m, 1H, CH_2), 2.95–3.14 (m, 1H, CH_2), 3.30–3.76 (m, 2H, CH_2), 5.54–5.76 (m, 4H, OCH_2O), 6.98–7.42 (m, 3H, aromat.), 7.81–8.46 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 23.6, 25.0 (2s, CH_2), 26.9 (C(CH_3)$_3$), 33.7 (CH_2), 35.2 (d, $J_{C,P} = 138.8$ Hz, PCH), 38.8 (C(CH$_3$)$_3$), 44.8, 46.9 (NCH_2), 127.5, 130.8, 131.0 (tert., aromat.), 132.7, 137.9, 142.9 (quart., aromat.), 156.5, 163.7 (C=O, hydroxamate), 163.7, 176.9, 177.1 (C=O, ester). IR: 3207 cm^{-1} (O–H), 1749 cm^{-1} (C=O, ester), 1670 cm^{-1} (C=O, hydroxamate), 1256 cm^{-1} (P=O). HRFAB-MS $C_{23}H_{34}Cl_2NO_9P$ $[M+H]^+$: calculated 570.1428; found 570.1444.

*6.1.6.4. 2,2-Dimethyl-propionic acid [3-(formyl-hydroxy-amino)-1-(4-methoxy-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8d**).* Yield: 92%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20–1.28 (m, 18H, C(CH_3)$_3$), 1.60–2.32 (m, 3H, CH_2, CH), 2.43–2.63 (m, 1H, CH_2), 2.97–3.71 (m, 3H, CH_2), 3.79 (s, 3H, OCH_3), 5.56–5.78 (m, 4H, OCH_2O), 6.78–6.90 (m, 2H, aromat.), 7.01–7.16 (m, 2H, aromat.), 7.64–8.49 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 23.6, 25.3 (2d, $J_{C,P} = 2.3$ Hz), 27.3 (C(CH_3)$_3$), 34.0, 34.1 (2d, $J_{C,P} = 3.9$ Hz, $J_{C,P} = 2.3$ Hz, CH_2), 35.6, 36.0 (2d, $J_{C,P} = 137.6$ Hz, $J_{C,P} = 136.4$ Hz, PCH), 39.2 (C(CH$_3$)$_3$), 45.5, 47.6 (2d, $J_{C,P} = 3.6$ Hz, $J_{C,P} = 6.0$ Hz, NCH_2), 55.7 (OCH_3), 81.9 (OCH_2O), 114.6 (OCCH tert., aromat.), 130.3 (tert., aromat.), 129.6 (d, $J_{C,P} = 17.7$ Hz, CH_2C quart., aromat.), 158.9 (CH_3OC quart., aromat.), 156.5, 161.7, 164.0 (C=O, hydroxamate), 177.4 (C=O, ester). IR: 3219 cm^{-1} (O–H), 1753 cm^{-1} (C=O, ester), 1666 cm^{-1} (C=O, hydroxamate), 1247 cm^{-1} (P=O). Anal. Calcd for $C_{24}H_{38}NO_{10}P$: calculated C 54.23%, H 7.21%, N 2.64%; found C 54.37%, H 7.08%, N 2.74%.

*6.1.6.5. 2,2-Dimethyl-propionic acid [3-(formyl-hydroxy-amino)-1-(5,6,7,8-tetrahydronaphthalene-2-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8e**).* Yield: 92%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.24, 1.25 (2s, 18H, C(CH_3)$_3$, 1.40–2.54 (m, 8H, CH_2, CH), 2.59–2.92 (m, 4H, CH_2), 2.99–3.55 (m, 3H, CH_2), 5.59–5.82 (m, 4H, OCH_2O), 6.73–7.13 (m, 3H, aromat.), 7.90–8.24 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 23.1 (d, $J_{C,P} = 4.3$ Hz, CH_2), 26.9 (C(CH_3)$_3$), 27.1, 27.2 (CH_2), 29.0, 29.4 (CH_2), 31.3 (d, $J_{C,P} = 143.8$ Hz, PCH), 36.1 (CH_2), 38.8 (C(CH$_3$)$_3$), 81.5 (OCH_2O), 129.4, 129.6 (tert., aromat.), 133.9, 135.7, 138.7 (quart., aromat.), 161.2 (C=O, hydroxamate), 177.9 (C=O, ester). IR: 3292 cm^{-1} (O–H), 1753 cm^{-1} (C=O, ester), 1679 cm^{-1} (C=O, hydroxamate), 1263 cm^{-1} (P=O). Anal. Calcd for $C_{27}H_{42}NO_9P$: calculated C 58.37%, H 7.62%, N 2.52%; found C 58.73%, H 7.96%, N 2.53%.

*6.1.6.6. 2,2-Dimethyl-propionic acid [3-(formyl-hydroxy-amino)-1-(5,6,7,8-tetrahydronaphthalene-1-yl-methyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**8f**).* Yield: 91%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.17–1.28 (m, 18H, C(CH_3)$_3$), 1.53–2.40 (m, 8H, CH, CH_2), 2.50–2.85 (m, 4H, CH_2), 3.00–3.65 (m, 3H, CH_2), 5.57–5.78 (m, 4H, OCH_2O), 6.84–7.15 (m, 3H, aromat.), 7.54–8.46 (m, 1H, formyl.). ^{13}C NMR ($CDCl_3$), δ (ppm): 22.7, 23.3 (CH_2), 25.6 ($J_{C,P} = 4.2$ Hz, CH_2), 26.9 (C(CH_3)$_3$), 30.0, 31.4, 36.4 (CH_2), 33.3 (d, $J_{C,P} = 136.2$ Hz, PCH), 38.8 (C(CH$_3$)$_3$), 45.3 (NCH_2), 80.0 (m, OCH_2O), 125.4, 127.3, 128.4 (tert., aromat.), 135.5 (quart., aromat.), 138.1 (d, $J_{C,P} = 12.4$ Hz, CH_2C quart., aromat.), 156.0, 161.2, 163.5 (C=O, hydroxamate), 176.9 (C=O, ester). IR: 3199 cm^{-1} (O–H), 1755 cm^{-1} (C=O, ester), 1670 cm^{-1} (C=O, hydroxamate), 1240 cm^{-1} (P=O). Anal. Calcd for $C_{27}H_{42}NO_9P$: calculated C 58.37%, H 7.62%, N 2.52%; found C 58.41%, H 7.74%, N 2.50%.

*6.1.6.7. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-benzyl-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9a**).* Yield: 99%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16, 1.17 (2s, 18H, C(CH_3)$_3$), 1.53–1.67 (m, 1H, CH_2), 1.72–1.93 (m, 4H, acetyl. CH_3 overlapping CH_2), 2.26–2.40 (m, 1H, CH), 2.56–2.68 (m, 1H, CH_2), 2.91–3.02 (m, 1H, CH_2), 3.36–3.43 (m, 1H, CH_2), 3.55–3.65 (m, 1H, CH_2), 5.50–5.63 (m, 4H, OCH_2O), 7.19–7.33 (m, 5H, aromat.), 9.66 (s, 1H, OH). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH_3), 23.6 ($J_{C,P} = 2.0$ Hz, CH_2), 26.9 (C(CH_3)$_3$), 34.5 (d, $J_{C,P} = 4.1$ Hz, CH_2), 35.4 (d, $J_{C,P} = 137.3$ Hz, PCH), 38.8 (C(CH$_3$)$_3$), 46.0 (NCH_2), 81.6, 81.8 (2d, $J_{C,P} = 8.1$ Hz, $J_{C,P} = 6.1$ Hz, OCH_2O), 126.9, 128.8, 128.9 (tert., aromat.), 137.5 (d, $J_{C,P} = 17.3$ Hz, CH_2C quart., aromat.), 172.8 (C=O, hydroxamate), 176.8, 176.9 (C=O, ester). IR: 3195 cm^{-1} (O–H), 1754 cm^{-1} (C=O, ester), 1622 cm^{-1} (C=O, hydroxamate), 1233 cm^{-1} (P=O). Anal. Calcd for $C_{24}H_{38}NO_9P$: calculated C 55.92%, H 7.43%, N 2.72%; found C 55.61%, H 7.47%, N 2.61%.

*6.1.6.8. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(2,5-dimethyl-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9b**).* Yield: 91%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19, 1.20 (2s, 18H, C(CH_3)$_3$), 1.59–1.87 (m, 2H, CH_2), 1.90 (s, 3H, acetyl. CH_3), 2.16–2.35 (m, 7H, PhCH_3 overlapping CH), 2.87–3.01 (m, 1H, CH_2), 3.19–3.64 (m, 3H, CH_2), 5.52–5.70 (m, 4H, OCH_2O), 6.89–7.11 (m, 3H, aromat.), 9.66 (s, 1H, OH). ^{13}C NMR (DMSO-d_6), δ (ppm): 18.9, 20.9 (2s, PhCH_3), 20.6 (acetyl. CH_3), 25.1 ($J_{C,P} = 2.9$ Hz, CH_2), 26.8 (C(CH_3)$_3$), 31.3 (d, $J_{C,P} = 4.2$ Hz, CH_2), 33.7 (d, $J_{C,P} = 136.5$ Hz, PCH), 38.6 (C(CH$_3$)$_3$), 45.7 (NCH_2), 81.8 (OCH_2O), 127.5, 130.5, 130.7 (tert., aromat.), 133.1, 135.0 (quart., aromat.), 136.7 (d, $J_{C,P} = 14.4$ Hz, CH_2C quart., aromat.), 171.4 (C=O, hydroxamate), 176.5 (C=O, ester). IR: 3195 cm^{-1} (O–H),

1758 cm^{-1} (C=O, ester), 1637 cm^{-1} (C=O, hydroxamate), 1236 cm^{-1} (P=O). Anal. Calcd for $C_{26}H_{42}NO_9P$: calculated C 57.45%, H 7.79%, N 2.58%; found C 57.07%, H 7.89%, N 2.58%.

*6.1.6.9. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(3,4-dichloro-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9c**).* Yield: 91%. ^{1}H NMR (DMSO-d_6), δ (ppm): 1.16 (2s, 18H, C(CH_3)$_3$), 1.47–1.87 (m, 2H, CH_2), 1.92 (s, 3H, acetyl. CH_3), 2.26–2.46 (m, 1H, CH), 2.61–3.00 (m, 2H, CH_2), 3.37–3.70 (m, 2H, CH_2), 5.47–5.68 (m, 4H, OCH_2O), 7.19–7.27 (m, 1H, aromat.), 7.49–7.59 (m, 2H, aromat.), 9.69 (s, 1H, OH). ^{13}C NMR (DMSO-d_6), δ (ppm): 20.6 (acetyl. CH$_3$), 25.0 (CH$_2$), 26.8 (C(CH$_3$)$_3$), 32.7 (d, $J_{C,P} = 2.3$ Hz, CH$_2$), 36.7 (d, $J_{C,P} = 145.6$ Hz, PCH), 38.6 (C(CH$_3$)$_3$), 45.6 (NCH$_2$), 81.7 (OCH$_2$O), 129.9, 130.6, 131.4 (tert., aromat.), 129.4, 131.2 (quart., aromat.), 140.2 (d, $J_{C,P} = 12.2$ Hz, CH$_2$$C$ quart., aromat.), 174.7 (C=O, hydroxamate), 176.5 (C=O, ester). IR: 3190 cm^{-1} (O–H), 1749 cm^{-1} (C=O, ester), 1620 cm^{-1} (C=O, hydroxamate), 1240 cm^{-1} (P=O). HRFAB-MS $C_{24}H_{36}Cl_2NO_9P$ $[M+H]^+$: calculated 584.1585; found 584.1587.

*6.1.6.10. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(4-methoxy-benzyl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9d**).* Yield: 91%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.20–1.28 (m, 18H, C(CH_3)$_3$), 1.58–2.36 (m, 6H, acetyl. CH_3 overlapping CH_2, CH), 2.42–2.60 (m, 1H, CH_2), 2.91–3.36 (m, 2H, CH_2), 3.53–3.84 (m, 4H, OCH_3 overlapping CH_2), 5.53–5.80 (m, 4H, OCH_2O), 6.75–6.90 (m, 2H, aromat.), 7.00–7.16 (m, 2H, aromat.). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH$_3$), 23.5 (d, $J_{C,P} = 2.8$ Hz, CH$_2$), 26.9 (2s, C(CH$_3$)$_3$), 33.6 (d, $J_{C,P} = 3.6$ Hz, CH$_2$), 35.7 (d, $J_{C,P} = 136.6$ Hz, PCH), 38.8 (C(CH$_3$)$_3$), 46.0 (d, $J_{C,P} = 3.5$ Hz, NCH$_2$), 55.3 (OCH$_3$), 81.6 (OCH$_2$O), 114.1 (OCCH tert., aromat.), 129.9 (tert., aromat.), 129.3 (d, $J_{C,P} = 17.3$ Hz, quart., aromat.), 158.5 (CH$_3$OC quart., aromat.), 172.8 (C=O, hydroxamate), 176.9 (C=O, ester). IR: 3199 cm^{-1} (O–H), 1753 cm^{-1} (C=O, ester), 1622 cm^{-1} (C=O, hydroxamate), 1246 cm^{-1} (P=O). Anal. Calcd for $C_{25}H_{40}NO_{10}P$: calculated C 55.04%, H 7.39%, N 2.57%; found C 55.28%, H 7.44%, N 2.56%.

*6.1.6.11. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(5,6,7,8-tetrahydronaphthalene-2-yl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9e**).* Yield: 78%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.22–1.27 (m, 18H, C(CH_3)$_3$), 1.74–1.82 (m, 4H, CH_2), 2.06–2.37 (m, 6H, acetyl. CH_3 overlapping CH_2, CH), 2.43–2.58 (m, 1H, CH_2), 2.63–2.87 (m, 4H, CH_2), 2.96–3.42 (m, 2H, CH_2), 3.52–4.19 (m, 1H, CH_2), 5.57–5.79 (m, 4H, OCH_2O), 6.76–7.15 (m, 3H, aromat.), 8.81–9.77 (m, 1H, OH). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH$_3$), 23.1 (d, $J_{C,P} = 4.7$ Hz, CH$_2$), 24.2, 24.5 (CH$_2$), 26.9 (C(CH$_3$)$_3$), 29.1 (d, $J_{C,P} = 4.7$ Hz, CH$_2$), 30.5 (d, $J_{C,P} = 137.1$ Hz, PCH), 32.9, 33.9 (CH$_2$), 39.5 (C(CH$_3$)$_3$), 41.3 (NCH$_2$), 81.6 (OCH$_2$O), 121.1, 124.6, 124.7 (tert., aromat.), 130.9, 132.7, 138.4 (quart., aromat.), 173.3 (C=O, hydroxamate), 177.4 (C=O, ester). IR: 3207 cm^{-1} (O–H), 1753 cm^{-1} (C=O, ester), 1643 cm^{-1} (C=O, hydroxamate), 1238 cm^{-1} (P=O). HRFAB-MS $C_{28}H_{44}NO_9P$ $[M+H]^+$: calculated 570.2834; found 570.2810.

*6.1.6.12. 2,2-Dimethyl-propionic acid [3-(acetyl-hydroxy-amino)-1-(5,6,7,8-tetrahydronaphthalene-1-yl)-propyl]-(2,2-dimethyl-propionyloxymethoxy)-phosphinoyloxymethyl ester (**9f**).* Yield: 93%. ^{1}H NMR ($CDCl_3$), δ (ppm): 1.14–1.31 (m, 18H, C(CH_3)$_3$), 1.51–2.82 (m, 15H, acetyl. CH_3 overlapping CH_2, CH), 2.85–3.45 (m, 2H, CH_2), 3.53–3.89 (m, 1H, CH_2), 5.56–5.79 (m, 4H, OCH_2O), 6.82–7.19 (m, 3H, aromat.), 9.04–9.97 (m, 1H, OH). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.6 (acetyl. CH$_3$), 22.7, 23.3 (CH$_2$), 26.3 (d, $J_{C,P} = 2.8$ Hz, CH$_2$), 26.8, 26.9 (C(CH$_3$)$_3$), 30.0, 31.4 (CH$_2$), 34.9 (d, $J_{C,P} = 144.8$ Hz, PCH), 38.8 (C(CH$_3$)$_3$), 46.0, 46.3 (2s, NCH$_2$), 81.6 (d, $J_{C,P} = 7.2$ Hz, OCH$_2$O), 125.4, 127.0, 128.3 (tert., aromat.), 135.3, 135.8, 138.1 (quart., aromat.), 172.9 (C=O, hydroxamate), 176.9 (C=O, ester). IR: 3190 cm^{-1} (O–H), 1751 cm^{-1} (C=O, ester), 1639 cm^{-1} (C=O, hydroxamate), 1232 cm^{-1} (P=O). Anal. Calcd for $C_{28}H_{44}NO_9P$: calculated C 59.04%, H 7.79%, N 2.46%; found C 59.13%, H 8.06%, N 2.30%.

6.2. Determination of in vitro antimalarial activity

6.2.1. Culture of P. falciparum

The *P. falciparum* 3D7 strain was maintained in continuous culture, according to Trager and Jensen and Das Gupta et al. [14b]. The parasites were grown in human red blood cells (RBCs blood group A positive), RPMI 1640 medium supplemented with 25 mM HEPES, 20 mM sodium bicarbonate, and 0.5% AlbuMAX (Invitrogen, Karlsruhe, Germany) at 5% hematocrit. The flasks were gassed with 90% N_2, 5% O_2, and 5% CO_2 and incubated at 37 °C. The development of the cultures and the percentage of infected RBCs were determined by light microscopy of Giemsa-stained thin smears.

6.2.2. Preparation of drug solutions

Twenty micromoles of the respective compounds were dissolved in 400 µl DMSO and further diluted with water/ethanol (50/50) to obtain the particular concentration.

6.2.3. Determination of parasite growth inhibition

The tests were carried out in 96-well microtiter plates under strict aseptic conditions, according to literature. Dilutions of each compound were added to 250 µl of a suspension of *P. falciparum* infected erythrocytes (1.5% hematocrit, 1.5–2% parasitemia). The plates were flushed with a gas mixture consisting of 90% N_2, 5% O_2 and 5% CO_2, closed tightly and incubated at 37 °C for 24 h. Afterwards, 0.1 µCi of 8-[^{3}H]-hypoxanthine was added to each well. The plates were flushed with the above mentioned gas mixture, incubated for additional 24 h at 37 °C and subsequently harvested with a cell harvester system (Inotech, Dottikon, Switzerland).

Infected erythrocytes were washed four times with distilled water before they were analysed for incorporated radioactivity in a multidetector liquid scintillation counter (Wallac, Turku, Finland).

References

[1] J. Wiesner, R. Ortmann, H. Jomaa, M. Schlitzer, Angew. Chem. 115 (2003) 5432−5451.

[2] H. Jomaa, J. Wiesner, S. Sanderbrand, B. Altincicek, C. Weidemeyer, M. Hintz, I. Türbachova, M. Eberl, J. Zeidler, H.K. Lichtenthaler, D. Soldati, E. Beck, Science 285 (1999) 1573−1576.

[3] J. Zeidler, J. Schwender, C. Müller, J. Wiesner, C. Weidemeyer, E. Beck, H. Jomaa, H.K. Lichtentaler, Z. Naturforsch. C. 53 (1999) 980−986.

[4] T. Kuzuyama, S. Takahashi, M. Takagi, H. Seto, Biol. Chem. 275 (2000) 19928−19932.

[5] (a) M.A. Missinou, S. Borrmann, A. Schindler, S. Issifou, A.A. Adegnika, P.B. Matsiegui, R. Binder, B. Lell, J. Wiesner, T. Baranek, H. Jomaa, P.G. Kremsner, Lancet 360 (2002) 1941−1942;
(b) B. Lell, R. Ruangweerayut, J. Wiesner, M.A. Missinou, A. Schindler, T. Baranek, M. Hintz, D. Hutchinson, H. Jomaa, P.G. Kremsner, Antimicrob. Agents Chemother. 47 (2003) 735−738.

[6] (a) T. Tsuchiya, K. Ishibashi, M. Terakawa, M. Nishiyama, N. Itoh, H. Noguchi, Eur. J. Drug Metab. Pharmacokinet. 7 (1982) 59−64;
(b) J. Wiesner, F. Seeber, Expert. Opin. Ther. Targets 9 (2005) 23−44.

[7] (a) T. Kurz, D. Geffken, C. Wackendorf, Z. Naturforsch. 58b (2003) 106−110;
(b) T. Kurz, D. Geffken, C. Wackendorf, Z. Naturforsch. 58b (2003) 457−461.

[8] (a) R. Ortmann, J. Wiesner, A. Reichenberg, D. Henschker, E. Beck, H. Jomaa, M. Schlitzer, Bioorg. Med. Chem. Lett. 13 (2003) 2163−2166;
(b) R. Ortmann, J. Wiesner, A. Reichenberg, D. Henschker, E. Beck, H. Jomaa, M. Schlitzer, Arch. Pharm. Chem. Life Sci. 338 (2005) 305−314.

[9] T. Kurz, D. Geffken, U. Kaula (BioAgency AG), DE 10356410A1 and WO 2005048715, 2005.

[10] T. Haemers, J. Wiesner, S. Van Poecke, J. Goeman, D. Henschker, E. Beck, H. Jomaa, S. Van Calenbergh, Bioorg. Med. Chem. Lett. 16 (2006) 1888−1891.

[11] T. Kurz, K. Schlüter, U. Kaula, B. Bergmann, R.D. Walter, D. Geffken, Bioorg. Med. Chem. 14 (2006) 5121−5135.

[12] C.E. McKenna, P. Shen, J. Org. Chem. 46 (1981) 4573−4576.

[13] H.T. Serafinowska, R.J. Ashton, S. Bailey, M.R. Harnden, S.M. Jackson, D. Sutton, J. Med. Chem. 38 (1995) 1372−1379.

[14] (a) R.E. Desjardins, C.J. Canfield, J.D. Haynes, J.D. Chulay, Antimicrob. Agents Chemother. 16 (1979) 710−718;
(b) R. Das Gupta, T. Krause-Ihle, B. Bergmann, I.B. Müller, A.R. Khomutov, S. Müller, R.D. Walter, K. Lüersen, Antimicrob. Agents Chemother. 49 (2005) 2857−2864;
(c) W. Trager, J.D. Jensen, Science 193 (1976) 673−677.