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# Studies Addressing the Importance of Charge in the Binding of Fosmidomycin-Like Molecules to Deoxyxylulosephosphate Reductoisomerase

Johann Perruchon,[a] Regina Ortmann,[a] Mirko Altenkämper,[a] Katrin Silber,[a] Jochen Wiesner,[b] Hassan Jomaa,[b] Gerhard Klebe,[a] and Martin Schlitzer*[a]

*Fosmidomycin and its homologue FR900098 are inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase, which is part of the mevalonate-independent isoprenoid biosynthetic pathway. Replacement of the phosphonate moiety by uncharged sulfone or sulfonamide partial structures resulted in complete loss of activity. Dropping one of the two negative charges resulted in a marked decrease in activity. Through occupation of a hydrophobic binding site, some activity could be regained, leading to compounds with micromolar activity against cultured malaria parasites.*

## Introduction

Isopentenyldiphosphate (IPP) is the common precursor of a wide variety of isoprenoid compounds. There are two separate pathways that lead to IPP and the isomeric dimethylallyl diphosphate (DMAPP). In humans, isopentenyl diphosphate is synthesized by the well-known mevalonate pathway. In contrast, many pathogenic microorganisms including the causative agents of malaria (*Plasmodium* spp.) and tuberculosis (*Mycobacterium tuberculosis*) use a completely unrelated mevalonate-independent pathway. It is called the 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway, which is also known as the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway, non-mevalonate pathway, or Rohmer pathway. The enzymes of this pathway present valuable targets for the development of specific antimicrobial drugs because their targets are absent in the human host.[1–5] One important step of the DOXP pathway is the reductive isomerization of deoxyxylulosephosphate to methylerythriolphosphate, which is catalyzed by DOXP reductoisomerase (DXR). Fosmidomycin (**1**) and its close homologue FR900098 (**2**) (Figure 1) are well-known inhibitors of DXR.[6] The efficacy of fosmidomycin (**1**) for the treatment of acute, uncomplicated malaria has been proven in several recent clinical trials.[7–9] However, repeated and comparably high doses were required to achieve acceptable cure rates. Apparently, the unfavorable pharmacokinetic profile of fosmidoymcin (**1**) is caused by two molecular features, namely the phosphonate and the hydroxamate moiety. However, the active site of the target enzyme harbors a metal ion, which needs to be complexed to achieve inhibition. Regarding binding site shape and distances and geometries for metal binding, the hydroxamate has proven to best address this issue and remains essential.

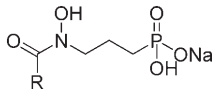



**Figure 1.** Structure of fosmidomycin (**1**, R = H) and FR900098 (**2**, R = $CH_3$).

By considering other moieties of the molecule, it appears necessary to investigate DXR inhibitors with less polar properties to enhance the membrane permeability of this type of agent. This is of particular importance with respect to the development of novel therapeutics for tuberculosis because fosmidomycin is inactive against *M. tuberculosis* at 200 μM although *Mt*DXR is inhibited with an $IC_{50}$ value of 310 nM.[10]

We initiated a study to address the importance of a charged moiety for the binding of fosmidomycin-like molecules to the active site of DXR. The binding mode of fosmidomycin (**1**) to *Ec*DXR has been revealed from the X-ray structure of a DXR–manganese–fosmidomycin complex.[11] It was found that the phosphonate moiety is embedded in a network of hydrogen bonds with the phosphonate oxygen atoms acting as hydrogen bond acceptors and the side chains of Ser186, Ser222, Asn227 and Lys228 as hydrogen bond donors (Figure 2a). Based on these structural data, we embarked into the design of inhibitors in which the charged phosphonate group is replaced by polar moieties that are uncharged at physiological pH, but are still able to engage in hydrogen-bonding networks. Furthermore, analysis of the protein surface of the active site revealed a small region in the vicinity of the phosphonate binding site that was predicted to be able to accommodate small alkyl residues like methyl or ethyl (Figure 3) and thereby add some hydrophobic interactions to the overall binding affinity.

[a] *Dr. J. Perruchon, Dr. R. Ortmann, M. Altenkämper, Dr. K. Silber, Prof. Dr. G. Klebe, Prof. Dr. M. Schlitzer*
*Institut für Pharmazeutische Chemie*
*Philipps-Universität Marburg, Marbacher Weg 6, 35032 Marburg (Germany)*
*Fax: (+49) 6421-282-5953*
*E-mail: schlitzer@staff.uni.marburg.de*

[b] *Dr. J. Wiesner, Priv.-Doz. Dr. H. Jomaa*
*Instiut für Klinische Chemie und Pathobiochemie*
*Universitätsklinikum Gießen und Marburg, Gaffkystraße 11, 35392 Gießen (Germany)*

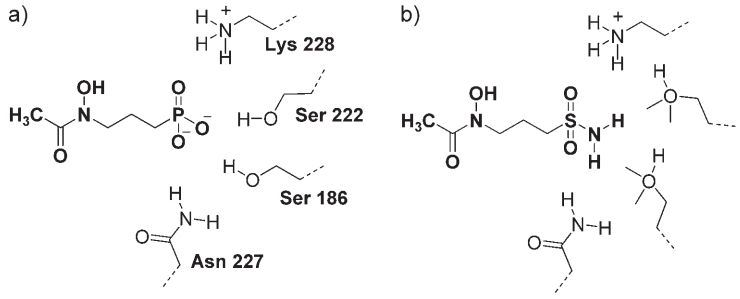



**Figure 2.** a) Schematic representation of the amino acid side chains binding the phosphonate moiety of FR900098. b) Hypothetical binding of a sulfonamide moiety.

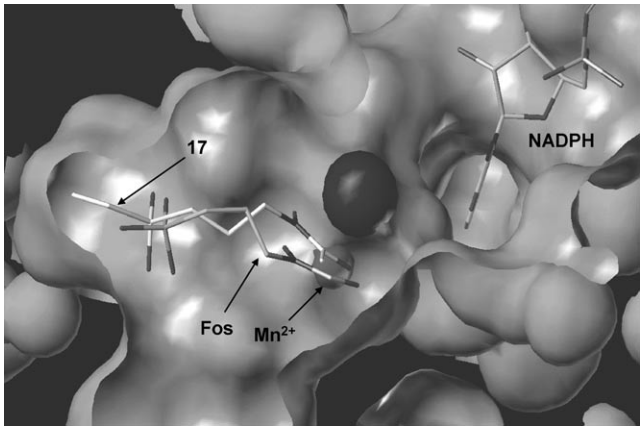



**Figure 3.** Docking solution of the ethyl sulfone derivative **17** superimposed onto the *Ec*DXR–manganese–fosmidomycin structure (Fos = fosmidomycin). NADPH was derived from PDB code: IJVS and minimized into the structure. The terminal methyl group of the ethyl residue of the sulfone compound was placed in a cleft next to the phosphonate binding site.

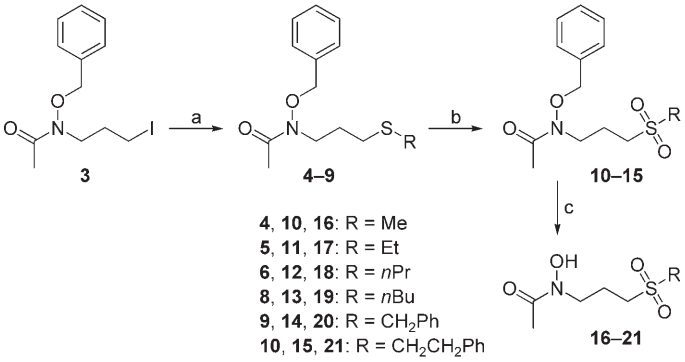
Two functional groups, the sulfone and the sulfonamide moiety were envisioned as potential phosphonate replacements. In the sulfone, the two double-bonded oxygen atoms appeared to be likely to serve most of the hydrogen bonds. The selection of sulfonamides as another possible phosphonate replacement was based on the assumption that the side chain flexibility of Ser186 and Ser222 allows rotation and modifications in the H-bonding network, thus switching the terminal hydroxy groups to serve not only as hydrogen bond donors but also as hydrogen bond acceptors. The predicted interaction of Ser186 and Ser222 with the NH of the sulfonamide moiety is depicted in Figure 2b. Alkyl and arylalkyl residues of different length were added to the sulfone and sulfonamide moiety to explore the presumed extensions of the binding site.

## Results and Discussion

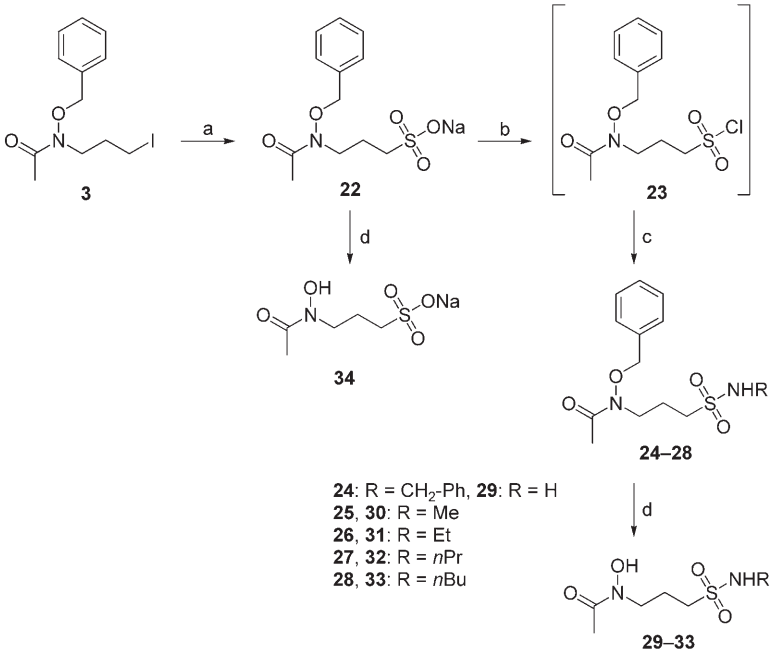
### Chemistry

The synthesis of the sulfones **16**–**21** is displayed in Scheme 1. The preparation of the key intermediate **3** in a one-pot multicomponent reaction has already been published.[12] Reaction of the iodide **3** with the appropriate thiol gave the thioethers **4**–**9**, which were oxidized to the sulfones **10**–**15** by treatment with $(NH_4)_2(Mo_4O_{13})/H_2O_2$. The benzyl protecting group was removed by catalytic hydrogenation to give the sulfones **16**–**21**. The methyl derivatives **4**, **10** and **16** have already been described.[12]

The synthesis of the sulfonamides **29**–**33** and sodium sulfonate **34** is depicted in Scheme 2. Reaction of the key inter-




**Scheme 1.** Reagents and conditions: a) THF, RSH, *n*BuLi; b) $H_2O$/MeOH, [Mo]/$H_2O_2$ (oxidation); c) $H_2$, Pd/C, MeOH.

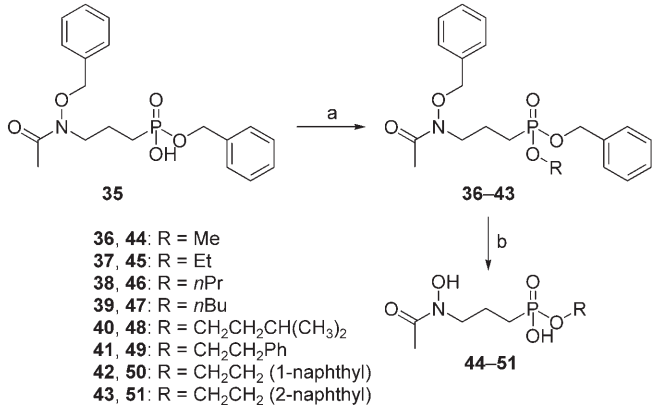



**Scheme 2.** Reagents and conditions: a) $H_2O$/MeOH, $Na_2SO_3$; b) $CH_2Cl_2$, $SOCl_2$; c) $CH_2Cl_2$, $R_2NH_2$; d) $H_2$, Pd/C, MeOH.

mediate **3** with $Na_2SO_3$ gave the sodium sulfonate **22**, which was converted into sulfonyl chloride **23** with thionyl chloride. Treatment with the appropriate amine led to the sulfonamides **24**–**28**. Finally catalytic hydrogenation removed the benzyl protecting group at the hydroxamic acid moiety and yielded the desired sulfones **29**–**33**. Direct hydrogenation of sodium sulfonate **22** gave the unprotected sodium sulfonate **34**. Sodium sulfonates **22** and **34** as well as *N*-methyl sulfonamides **25** and **30** have already been described.[12]

The synthesis of the phosphonic acid monoesters is displayed in Scheme 3. Intermediate **5**, which has benzyl protecting groups at the hydroxamic acid moiety and the phosphonic acid was prepared as described elsewhere.[13] The reaction of **5** with an alkyl halide yielded the fully protected phosphonic acid esters **36**–**43**. Removal of the benzyl protecting groups by catalytic hydrogenation lead to phosphonic acid monoesters **44**–**51**.




**Scheme 3.** Reagents and conditions: a) RI, DMF, $Et_3N$, 60 °C, 6 h or RX, DMPU, $Et_3N$, NaI, 80 °C, 8 h; b) $H_2$, Pd/C, MeOH.

### DOXP reductoisomerase inhibition assay

The assay was performed in a reaction mixture that contained 100 mM Tris-HCl (pH 7.5), 0.2% BSA, 1 mM $MnCl_2$, 1 mM NADPH, 0.3 mM DOXP, and 1 μg mL$^{-1}$ recombinant DOXP reductoisomerase from *E. coli*. The mixture was incubated with a dilution series of the test compounds on a 96-well plate at 37 °C, and the reaction was started by the addition of DOXP. The decrease in absorption was monitored at 340 nm with a microplate reader (details in the Experimental Section below).

### Molecular modeling

The binding site geometry was taken from the protein–ligand complex of fosmidomycin as observed in the crystal structure with bound $Mn^{2+}$ (PDB code: 1ONP). Ligands were docked into the binding pocket by using AutoDock 3.0.[14–16] All ligands exhibited a hydroxamate function to mimic the α-ketohydroxy moiety of the substrate. Both oxygen atoms show nearly the same distance to the metal (*N*-hydroxy: 2.1 Å and carbonyl: 2.4 Å). Based on these structural findings, along with an expected p$K_a$ shift due to the proximity of a metal ion, the hydroxamate function is assumed to be planar and deprotonated. Additionally, most ligands exhibit a second acidic moiety, which is also considered to be deprotonated. The partitioning of the total charge into individual contributions assigned to different atoms was performed by using the AM1 Hamiltonian[17] of the semiempirical package MOPAC 6.0.[18,19]

From the reference crystal structure (PDB code: 1ONP), ligand and solvent molecules were removed, and $Mn^{2+}$ was converted into the better-parameterized $Mg^{2+}$ because both metal ions are interchangeable in active DXR. To suggest a reasonable cofactor binding mode, NADPH coordinates were transferred from PDB code: 1JVS after both protein structures were superimposed, based on $C^{\alpha}$ coordinates. A subsequent minimization of the transferred cofactor with the MAB force field, as implemented in MOLOC[20] revealed no significant movements.

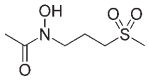
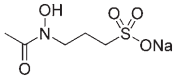
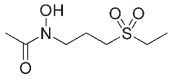
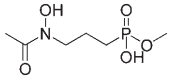
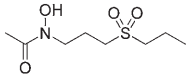
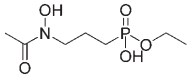
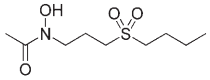
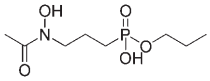
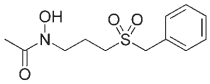
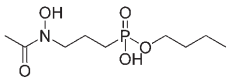
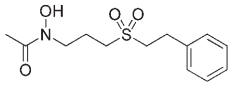
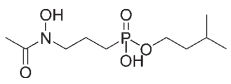
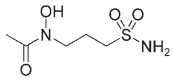
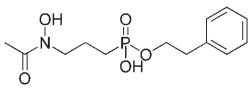
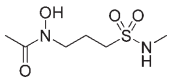
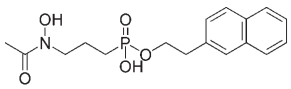
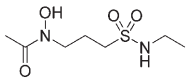
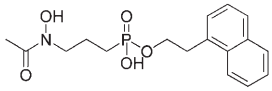
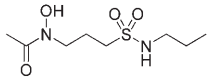
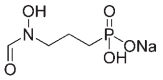
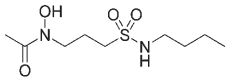
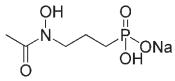
AutoDock 3.0 required the addition of polar hydrogen atoms with the PROTONATE utility in AMBER,[21] and the generated hydrogen-bonding network was visually inspected for internal consistency. AMBER united-atom charges were assigned as defined in the AMBER force field,[22] and solvation parameters were added by using the ADDSOL utility of AutoDock 3.0. Docking runs were performed by using the Lamarckian genetic algorithm as implemented in AutoDock 3.0, by using an initial population of 50 randomly placed individuals, a maximum number of $1.5\times10^6$ energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80 and an elitism value of 1. The generated ligand-docking solutions, which mutually differed by rmsd $\leq$1 Å were clustered together and the lowest docking energy that was found for one entry of a cluster was used as representative. For each ligand, in total 10 solutions were generated. By examining the obtained metal coordination and placement of the phosphonate group one configuration was selected for affinity prediction by visual inspection. The ranking of different ligands based on their predicted affinity to DXR was performed by using the knowledge-based scoring function DrugScore. This protocol was initially validated by docking fosmidomycin back into its original protein crystal structure (PDB code: 1ONP).

### Biological results

As shown in Table 1, neither the sulfone (**16**–**21**) nor the sulfonamide derivatives (**29**–**33**) of FR900098 displayed any significant inhibitory activity against *Ec*DXR at a concentration of 30 μM. Because the activities of a particular compound against DXR form *E. coli* and *P. falciparum* are usually well correlated,[23] we do not expect any significant activity of these compounds against enzyme isoforms of other species. Apparently, the hydrogen-bonding network cannot adjust to the interaction profile that is required to bind to the sulfonamide, with Ser186 and Ser222 remaining in their original orientation resulting in a repulsive interaction with the sulfonamide NH. While this could be a possible explanation for the lack of activity of the sulfonamides, the lack of activity of the sulfone derivatives leads to the conclusion that it is not sufficient for inhibitor binding to serve the hydrogen bonding network. Instead, the negative

**Table 1.** Inhibitory activity of fosmidomycin analogues.

| Compd | Structure | $IC_{50}$ (*Ec*DXR) [μM] | Compd | Structure | $IC_{50}$ (*Ec*DXR) [μM] | $IC_{50}$ (Dd2) [μM][a] |
|---|---|---|---|---|---|---|
| **16** |  | > 30 | **34** |  | 23 | – |
| **17** |  | > 30 | **44** |  | 50 | > 10 |
| **18** |  | > 30 | **45** |  | 23 | > 10 |
| **19** |  | > 30 | **46** |  | 16 | > 10 |
| **20** |  | > 30 | **47** |  | 3.9 | > 10 |
| **21** |  | > 30 | **48** |  | 2.1 | > 10 |
| **29** |  | > 30 | **49** |  | 0.49 | 4.96 |
| **30** |  | > 30 | **50** |  | 1.6 | 5.90 |
| **31** |  | > 30 | **51** |  | 2.4 | 5.69 |
| **32** |  | > 30 | **1** |  | 0.035 | 0.57 |
| **33** |  | > 30 | **2** |  | 0.035 | 0.27 |

[a] $IC_{50}$ values toward the growth of cultured malaria parasites.

charge of the phosphonate is the decisive factor in the binding of fosmidomycin-like molecules. A similar result has been obtained by Proteau and co-workers, who prepared a sulfamic acid ester analogue of fosmidomycin that inhibited *Synechocystis* DXR with a $K_i$ value of 2800 μM.[24] Although undesired, this is an important result that guides compound optimization strategies for the further development of DXR inhibitors.

Based on the knowledge that was obtained with the uncharged molecules, we then focused our attention on inhibitors that bear functional groups that have one negative charge at physiological pH conditions. The sulfonic acid moiety is most similar to the phosphonate with regard to the orientation of three oxygen atoms around the central atom, but it possesses one negative charge less than the phosphonate. The sulfonic acid derivative **34** displayed an $IC_{50}$ value of 23 μM, thus it is approximately 500-fold less active than the corresponding phosphonate derivative, FR900098 (**2**); this clearly shows the importance of the charge for inhibitor binding to DXR.

In a second series, we employed the monomethyl (**44**), ethyl (**45**), and propyl (**46**) esters of FR900098 (**2**). It is known that such alkyl esters are biologically stable.[25,26] Therefore, these molecules represent FR900098 derivatives with one negative charge, but they differ from the sulfonic acid derivative in that they have an additional alkyl residue of increasing length. The important finding in this small series is that the activity increases with increasing length of the alkyl residue, which indicates the presence of a lipophilic binding region. Occupation of this region appears to be suited to at least attenuate the effect of the reduced charge. Based on the modeling of the ethylsulfone **17** (Figure 3) it has been anticipated that the methyl ester (**44**) would be the most active compound of this series compared with the larger ethyl (**45**) and propyl (**46**) esters. The methyl group seems to be ideal to address volume and property requirements of the small hydrophobic binding site next to the phosphonate binding site. Surprisingly, in contrast to this prediction, the activity increased with the length of the alkyl residue from 50 μM to 16 μM. Although these values are not impressive, they clearly indicate that there is more to be learned about this enzyme. An additional flexible docking experiment suggested that the methyl group of the methyl ester might fit into the small binding site, which we tried to address already with the small sulfone derivative **17**. However, the

larger propyl side chain of inhibitor **46** is shown in a different binding site, which furthermore appears to be spacious enough to accommodate even larger hydrophobic residues (Figure 4). Indeed, the *n*-butyl (**47**) and the isopentyl (**48**) esters were considerably more active, with $IC_{50}$ values of

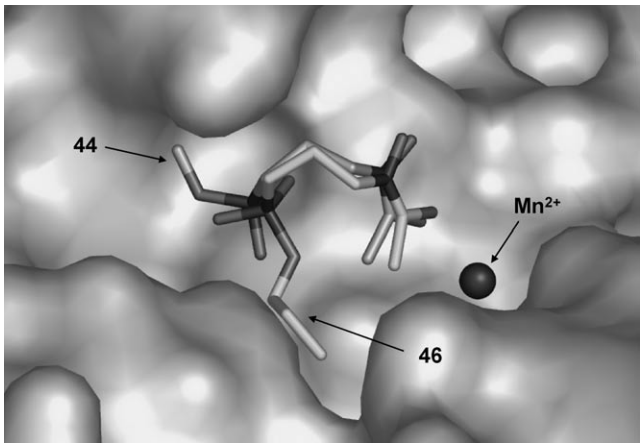



**Figure 4.** Docking solution of the methyl ester **44** and the propyl ester **46** revealed an additional binding site capable of accommodating even larger lipophilic residues.

3.9 μM and 2.1 μM, respectively. However, this higher inhibitory activity against DXR did not translate into measurable antiparasitic activity. The *n*-butyl (**47**) and the isopentyl (**48**) esters did not show any impact on the growth of cultured malaria parasites at 10 μM, as was the case with the other esters **44**–**46**. Encouraged by the increase in activity against the isolated enzyme by enlargement of the ester moiety, we decided to carry this approach further in preparing three different arylethyl monoesters (**49**–**51**). From this series, the 1-naphthyl ethyl (**51**) and the 2-naphthyl ethyl (**50**) ester were as active as the *n*-butyl (**47**) and the isopentyl (**48**) esters, with $IC_{50}$ values of 2.4 μM and 1.6 μM, respectively. In contrast, the phenethyl ester **49** displayed a 3–5-fold more potent activity in the enzyme assay with an $IC_{50}$ value of 0.49 μM. Thus, it could be demonstrated, that the loss of activity that results from dropping one negative charge from the phosphonate moiety can be at least partially compensated through occupation of an additional hydrophobic binding site. In addition, compounds **49** and **50** displayed activity against cultured malaria parasites in the 5 μM range as well as some weak activity against *M. tuberculosis* at a concentration where fosmidomycin is inactive (preliminary data, not shown).

## Conclusions

This study clearly demonstrated the importance of the negative charge for the binding of fosmidomycin-like inhibitors to DXR. Uncharged molecules are virtually inactive whereas derivatives that possess only one instead of two negative charges are markedly less active. Nevertheless, it was shown that it is possible to regain some of the activity that was lost by the reduction of the charge by occupation of hitherto unexploited areas of the enzyme. In addition, these compounds apparently display some better membrane penetration ability. Unfortunately, enzyme inhibitory activity is still too low to obtain significant activity against cultured malaria parasites or mycobacteria. Although undesired, these results guide further attempts to design novel DXR inhibitors in which only transient lipophilic modification of the lead structure is desired because the unmodified phosphonate moiety proved to be clearly essential for high activity. We have reported recently some preliminary results that demonstrate that a prodrug approach that masks the polar phosphonate moiety of FR900098 by appropriate bio-labile moieties is promising.[27]

## Experimental Section

### *General*

IR spectra were recorded on a JASCO FT/IR-410 spectrometer, on a Nicolet 510P FTIR spectrometer, or on a Bruker ALPHA-P FTIR spectrometer (in case of total reflection). $^1H$ and $^{13}C$ NMR spectra were recorded on Jeol Eclipse 400 and Jeol Eclipse 500 spectrometers, and the chemical shifts ($\delta$) were measured relative to residual solvent as an internal reference. Mass spectra were obtained on PE Biosystems API 2000 (ESI MS data), Jeol MStation JMS 700 (FAB spectra), or VG-AutoSpec Micromass (EI MS data) spectrometers. Reactions were monitored by TLC on Alugram SIL G/UV 254 silica gel analytical plates with 250 mm coating. Liquid chromatography was carried out on Merck silica gel 60 (230–240 mesh). Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. The DOXP reductoisomerase inhibition assay was carried out with a SpectraMax 340PC microplate reader (Molecular Devices, Ismaning, Germany).

The preparation and characterization of compounds **4**, **10**, **16**, **22**, **25**, **30**, and **34** have been described previously.[12]

***N*-(Benzyloxy)-*N*-[3-(alkylsulfanyl)propyl]acetamides (4–9):** *N*-(benzyloxy)-N-(3-iodopropyl)acetamide **3**[12] (500 mg, 1.5 mmol, 1.0 equiv) and THF (10 mL) were added to a 25-mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar, and the mixture was cooled to −78 °C. RSNa or RSLi (R = Me, Et, *n*Pr, *n*Bu, Bn, $CH_2$Bn) (2.25 mmol, 1.5 equiv) and THF (10 mL) were added to a second 50-mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar, and the mixture was vigorously stirred for 15 min. The resulting heterogeneous suspension was quickly added dropwise to the solution of acetamide **3**, and the mixture was stirred for 30 min at −78 °C and allowed to stir at room temperature. The reaction was monitored by TLC. After completion of the reaction (1 h), the solvent was removed by evaporation, and the crude *N*-(benzyloxy)-*N*-[3-(alkylthio)propyl]acetamides **4**–**9** were purified by a flash column chromatography (silica gel, $Et_2O$/pentane, 1:2 or 1:3).

***N*-(Benzyloxy)-*N*-[3-(ethylsulfanyl)propyl]acetamide (5)**: Yield: 269 mg (67%), yellowish oil; $R_f = 0.37$ ($Et_2O$/pentane, 2:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta = 7.44$–$7.35$ (m, 5H, Ar), 4.83 (s, 2H, $CH_2ON$), 3.75 (t, $^3J = 6.6$ Hz, 2H, $CH_2N$), 2.55 (t, $^3J = 6.0$ Hz, 2H, $SCH_2$), 2.52 (t, $^3J = 6.0$ Hz, 2H, $SCH_2$), 2.10 (s, 3H, $COCH_3$), 1.92 (m, 2H, $CH_2$), 1.22 ppm (t, $^3J = 5.8$ Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta =$ 172.60 (CO), 134.50 (Cq), 129.18, 128.97, 128.71 (5CH, Ar), 76.75

($OCH_2$), 44.60 (br s, $NCH_2$), 28.84 ($SCH_2$), 26.82 ($SCH_2$), 25.82 ($CH_2$), 20.51 ($COCH_3$), 14.70 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1659 $cm^{-1}$ (C=O)

***N*-(Benzyloxy)-*N*-[3-(*n*-propylsulfanyl)propyl]acetamide (6)**: Yield: 306 mg (72%), yellow oil; $R_f$ = 0.26 ($Et_2O$/pentane, 1:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.43–7.34 (m, 5H, Ar), 4.83 (s, 2H, $CH_2ON$), 3.75 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.47 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.46 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.11 (s, 3H, $COCH_3$), 1.92 (m, 2H, $CH_2$), 1.60 (m, 2H, $CH_2$), 0.98 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.35 (CO), 134.55 (Cq), 129.19, 128.97, 128.72 (5CH, Ar), 76.75 ($OCH_2$), 44.55 (br s, $NCH_2$), 34.12 ($SCH_2$), 29.28 ($SCH_2$), 26.93 ($CH_2$), 22.90 ($CH_2$), 20.51 ($COCH_3$), 13.47 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1660 $cm^{-1}$ (C=O)

***N*-(Benzyloxy)-*N*-[3-(*n*-butylsulfanyl)propyl]acetamide (7)**: Yield: 302 mg (68%), yellow oil; $R_f$ = 0.34 ($Et_2O$/pentane, 1:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.44–7.35 (m, 5H, Ar), 4.83 (s, 2H, $CH_2ON$), 3.75 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.50 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.49 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.10 (s, 3H, $COCH_3$), 1.92 (m, 2H, $CH_2$), 1.55 (m, 2H, $CH_2$), 1.39 (m, 2H, $CH_2$), 0.90 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 174.20 (CO), 134.40 (Cq), 129.18, 128.97, 128.71 (5CH, Ar), 76.74 ($OCH_2$), 44.57 (br s, $NCH_2$), 31.76 ($SCH_2$), 31.02 ($CH_2$), 29.33 ($SCH_2$), 26.91 ($CH_2$), 21.98 ($CH_2$), 20.51 ($COCH_3$), 13.65 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1660 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(benzylsulfanyl)propyl]acetamide (8)**: Yield: 341 mg (69%), yellow oil; $R_f$ = 0.38 ($Et_2O$/pentane, 1:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.42–7.37 (m, 5H, Ar), 7.28 (m, 2H, Ar), 7.20 (m, 3H, Ar), 4.78 (s, 2H, $CH_2ON$), 3.70 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.69 (s, 2H, $SCH_2Ph$), 2.41 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.07 (s, 3H, $COCH_3$), 1.89 ppm (m, 2H, $CH_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 174.35 (CO), 138.25 (Cq), 134.40 (Cq), 129.17, 128.97, 128.82, 128.71, 128.45, 126.94 (10CH, Ar), 76.75 ($OCH_2$), 44.20 (br s, $NCH_2$), 36.12 ($SCH_2$), 28.51 ($SCH_2$), 26.46 ($CH_2$), 20.51 ppm ($COCH_3$); IR (total reflection): $\tilde{\nu}$ = 1658 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(phenethylsulfanyl)propyl]acetamide (9)**: Yield: 345 mg (67%), yellow oil; $R_f$ = 0.39 ($Et_2O$/pentane, 1:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.41–7.37 (m, 5H, Ar), 7.27 (m, 2H, Ar), 7.17 (m, 3H, Ar), 4.79 (s, 2H, $CH_2ON$), 3.70 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.85 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.74 (t, $^3J$ = 6.0 Hz, 2H, $SCH_2$), 2.52 (t, $^3J$ = 5.8 Hz, 2H, $CH_2$), 2.09 (s, 3H, $COCH_3$), 1.90 ppm (m, 2H, $CH_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 174.35 (CO), 140.48 (Cq), 134.40 (Cq), 129.18, 129.08, 128.72, 128.60, 128.44, 126.32 (10CH, Ar), 76.75 ($OCH_2$), 44.20 (br s, $NCH_2$), 36.24 ($SCH_2$), 33.53 ($CH_2$), 29.48 ($SCH_2$), 26.85 ($CH_2$), 20.51 ppm ($COCH_3$); IR (total reflection): $\tilde{\nu}$ = 1660 $cm^{-1}$ (C=O).

**Synthesis of the *N*-(benzyloxy)-*N*-[3-(alkylsulfonyl)propyl]acetamide (10–15)**: *N*-(Benzyloxy)-*N*-[3-(alkylbenzylsulfonyl)propyl]acetamide **4–9** (0.99 mmol, 1.0 equiv), $(NH_4)_2(Mo_4O_{13})$ (66.3 mg, 0.1 mmol), $H_2O_2$ (1 mL), and MeOH (7 mL) were added to a 5-mL two-necked round-bottom flask that was equipped with a magnetic stirring bar. The resulting heterogeneous mixture was stirred at room temperature under $N_2$, and the reaction was monitored by TLC. After completion of the reaction (4 h), the solvent was removed by evaporation and the crude *N*-(benzyloxy)-*N*-[3-(*alkyl*sulfonyl)propyl]acetamides **10–15** were purified by column chromatography (silica gel, $Et_2O$/pentane, 5:1).

***N*-(Benzyloxy)-*N*-[3-(ethylsulfonyl)propyl]acetamide (11)**: Yield: 223 mg (75%), whitish solid; $R_f$ = 0.33 ($Et_2O$/pentane, 5:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.40–7.35 (m, 5H, Ar), 4.80 (s, 2H, $CH_2ON$), 3.77 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.66 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.64 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.12 (m, 2H, $CH_2$), 2.08 (s, 3H, $COCH_3$), 1.28 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.81 (CO), 133.92 (Cq), 129.26, 129.12, 128.74 (5CH, Ar), 76.68 ($OCH_2$), 49.09 ($CH_2SO_2$), 47.22 ($CH_2SO_2$), 43.77 (br s, $NCH_2$), 20.32 ($COCH_3$), 19.69 ppm ($CH_2$), 6.46 ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1654 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(*n*-propylsulfonyl)propyl]acetamide (12)**: Yield: 208 mg (67%), whiteish solid; $R_f$ = 0.35 ($Et_2O$/pentane, 5:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.40–7.34 (m, 5H, Ar), 4.81 (s, 2H, $CH_2ON$), 3.77 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.96 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.92 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.16 (m, 2H, $CH_2$), 2.09 (s, 3H, $COCH_3$), 1.84 (m, 2H, $CH_2$), 1.05 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.70 (CO), 134.02 (Cq), 129.31, 129.18, 128.81 (5CH, Ar), 76.69 ($OCH_2$), 54.72 ($CH_2SO_2$), 50.03 ($CH_2SO_2$), 43.79 (br s, $NCH_2$), 19.81 ($COCH_3$), 15.75 ($CH_2$), 13.11 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1649 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(*n*-butylsulfonyl)propyl]acetamide (13)**: Yield: 227 mg (70%), whitish solid; $R_f$ = 0.38 ($Et_2O$/pentane, 5:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.40–7.35 (m, 5H, Ar), 4.82 (s, 2H, $CH_2ON$), 3.79 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.96 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.93 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.17 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.79 (m, 2H, $CH_2$), 1.47 (m, 2H, $CH_2$), 0.95 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.55 (CO), 133.82 (Cq), 129.26, 129.11, 128.77 (5CH, Ar), 76.65 ($OCH_2$), 52.28 ($CH_2SO_2$), 49.50 ($CH_2SO_2$), 43.65 (br s, $NCH_2$), 24.55 ($CH_2$), 22.01 ($CH_2$), 19.82 ($COCH_3$), 13.48 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$ = 1656 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(benzylsulfonyl)propyl]acetamide (14)**: Yield: 257 mg (72%), whitish solid; $R_f$ = 0.43 ($Et_2O$/pentane, 5:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.41–7.32 (m, 10H, Ar), 4.82 (s, 2H, $CH_2ON$), 4.21 (s, 2H, $SO_2CH_2Ph$), 3.74 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 2.87 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.10 (m, 2H, $CH_2$), 2.07 ppm (s, 3H, $COCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.60 (CO), 134.08 (Cq), 130.52, 129.31, 129.29 (5CH, Ar), 129.17 (CH), 129.07 (CH), 128.79 (CH), 127.97 (Cq), 76.68 ($OCH_2$), 59.57 ($CH_2SO_2$), 48.38 ($CH_2SO_2$), 43.75 (br s, $NCH_2$), 20.36 ($COCH_3$), 19.76 ppm ($CH_2$); IR (total reflection): $\tilde{\nu}$ = 1655 $cm^{-1}$ (C=O).

***N*-(Benzyloxy)-*N*-[3-(phenethylsulfonyl)propyl]acetamide (15)**: Yield: 278 mg (75%), whitish solid; $R_f$ = 0.45 ($Et_2O$/pentane, 5:1); $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$ = 7.46–7.21 (m, 15H, Ar), 4.84 (s, 2H, $CH_2ON$), 3.78 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.24 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 3.14 (t, $^3J$ = 8.0 Hz, 2H, $CH_2Ph$), 2.96 (t, $^3J$ = 7.5 Hz, 2H, $SO_2CH_2$), 2.17 (m, 2H, $CH_2$), 2.12 ppm (s, 3H, $COCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$ = 172.48 (CO), 137.39 (Cq), 133.97 (Cq), 129.30, 129.19, 128.92, 128.81, 128.38, 127.10 (10CH, Ar), 76.65 ($OCH_2$), 54.29 ($CH_2SO_2$), 50.50 ($CH_2SO_2$), 43.77 (br s, $NCH_2$), 27.95 ($CH_2$), 20.40 ($COCH_3$), 19.84 ppm ($CH_2$); IR (total reflection): $\tilde{\nu}$ = 1652 $cm^{-1}$ (C=O).

**Synthesis of the *N*-hydroxy-*N*-[3-(alkylsulfonyl)propyl]acetamides (16–21)**: *N*-(benzyloxy)-*N*-[3-(*alkyl*sulfonyl)propyl]acetamides **10–15** (0.85 mmol, 1.0 equiv), pure MeOH (5 mL) and 10% Pd/C (59 mg) were carefully added to a 20 mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar. The heterogeneous mixture was stirred at room temperature under $H_2$, and the reaction was monitored by TLC. After 3 h of stirring, followed by evaporation of the solvent, the crude *N*-hydroxy-*N*-[3-(alkylsulfonyl)propyl]acetamides **16–21** were dissolved in MeOH (3 mL) and filtered through a short pad of celite, which was thoroughly washed with MeOH. The solvent was evaporated under reduced pressure.

***N*-Hydroxy-*N*-[3-(ethylsulfonyl)propyl]acetamide (17)**: Yield: 156 mg (88%), white solid, mp = 83 °C; $^1H$ NMR (400 MHz, [$D_6$]acetone), $\delta$ = 3.66 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.10 (t, $^3J$ = 7.8 Hz,

2H, $SO_2CH_2$), 3.08 (t, $^3J$=7.5 Hz, 2H, $SO_2CH_2$), 2.80 (s, 1H, NOH), 2.01 (m, 2H, $CH_2$), 1.99 (s, 3H, $COCH_3$), 1.22 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, [D$_6$]acetone), $\delta$=174.58 (CO), 49.11 ($SO_2CH_2$), 46.61 ($SO_2CH_2$), 46.24 (br s, $NCH_2$), 19.84 ($CH_2$), 19.78 ($COCH_3$), 5.96 ppm ($CH_3$); IR (total reflection): $\tilde{\nu}$=1608 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_7H_{15}NO_4S$: 209.0722 $[M]^+$, found: 209.0713.

***N*-Hydroxy-*N*-[3-(*n*-propylsulfonyl)propyl]acetamide (18)**: Yield: 152 mg (80%), whitish solid, mp=96 °C; $^1$H NMR (400 MHz, [D$_6$]acetone), $\delta$=3.70 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.04 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 3.03 (t, $^3J$=7.5 Hz, 2H, $SO_2CH_2$), 2.87 (s, 1H, NOH), 2.04 (m, 2H, $CH_2$), 2.02 (s, 3H, $COCH_3$), 1.79 (m, 2H, $CH_2$), 1.05 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, [D$_6$]acetone), $\delta$=174.28 (CO), 53.95 ($SO_2CH_2$), 49.91 ($SO_2CH_2$), 46.23 (br s, $NCH_2$), 19.84 ($CH_2$), 19.78 ($COCH_3$), 15.65 ($CH_2$), 12.52 ppm ($CH_3$); IR (KBr): $\tilde{\nu}$=1613 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_8H_{17}NO_4S$: 223.0878 $[M]^+$, found: 223.0879.

***N*-Hydroxy-*N*-[3-(*n*-butylsulfonyl)propyl]acetamide (19)**: Yield: 186 mg (92%), white solid, mp=103 °C; $^1$H NMR (400 MHz, [D$_6$]acetone), $\delta$=3.71 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.04 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 3.03 (t, $^3J$=7.5 Hz, 2H, $SO_2CH_2$), 2.86 (s, 1H, NOH), 2.04 (m, 2H, $CH_2$), 2.01 (s, 3H, $COCH_3$), 1.76 (m, 2H, $CH_2$), 1.47 (m, 2H, $CH_2$), 0.97 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$).; $^{13}$C NMR (100 MHz, [D$_6$]acetone), $\delta$=174.18 (CO), 52.14 ($SO_2CH_2$), 49.78 ($SO_2CH_2$), 46.34 (br s, $NCH_2$), 23.96 ($CH_2$), 21.63 ($CH_2$), 19.94 ($CH_2$), 19.90 ($COCH_3$), 13.17 ppm ($CH_3$); IR (KBr): $\tilde{\nu}$=1613 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_9H_{19}NO_4S$: 237.1035 $[M]^+$, found: 237.1017.

***N*-Hydroxy-*N*-[3-(benzylsulfonyl)propyl]acetamide (20)**: Yield: 173 mg (75%), whitish solid, mp=125 °C; $^1$H NMR (400 MHz, MeOH-d$_3$), $\delta$=7.43–7.37 (m, 5H, Ar), 4.40 (s, 2H, $SO_2CH_2Ph$), 3.70 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.01 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 2.80 (s, 1H, NOH), 2.07 (m, 2H, $CH_2$), 2.01 ppm (s, 3H, $COCH_3$); $^{13}$C NMR (100 MHz, MeOH-d$_3$), $\delta$=173.99 (CO), 132.12, 129.86 (5CH, Ar), 129.82 (Cq), 58.43 ($SO_2CH_2$), 48.66 ($SO_2CH_2$), 46.23 (br s, $NCH_2$), 19.33 ($CH_2$), 18.85 ppm ($COCH_3$); IR (KBr): $\tilde{\nu}$=1614 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_{12}H_{17}NO_4S$: 271.0878 $[M]^+$, found: 271.0857.

***N*-Hydroxy-*N*-[3-(phenethylsulfonyl)propyl]acetamide (21)**: Yield: 165 mg (68%), white solid, mp=115 °C; $^1$H NMR (400 MHz, MeOH-d$_3$), $\delta$=7.33–7.18 (m, 5H, Ar), 3.70 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.36 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 3.11 (t, $^3J$=8.0 Hz, 2H, $CH_2Ph$), 3.04 (t, $^3J$=7.5 Hz, 2H, $SO_2CH_2$), 2.50 (s, 1H, NOH), 2.07 (m, 2H, $CH_2$), 2.01 ppm (s, 3H, $COCH_3$); $^{13}$C NMR (100 MHz, MeOH-d$_3$), $\delta$=174.12 (CO), 139.44 (Cq), 129.88, 129.59, 127.93 (5CH, Ar), 55.43 ($SO_2CH_2$), 51.66 ($SO_2CH_2$), 47.93 (br s, $NCH_2$), 28.98 ($CH_2$), 20.66 ($CH_2$), 20.22 ppm ($COCH_3$); IR (KBr): $\tilde{\nu}$=1610 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_{13}H_{19}NO_4S$: 285.1035 $[M]^+$, found: 285.1035.

**3-[Acetyl(benzyloxy)amino]propane-1-sulfonyl chloride (23)**: Sodium 3-[acetyl(benzyloxy)amino]propane-1-sulfonate **22** (800 mg, 2.62 mmol), toluene (10 mL) and $SOCl_2$ (0.262 mL, 1 mL/0.1 mmol of acid) were added successively and dropwise to a 25-mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar. The mixture was heated at reflux, and the reaction was monitored by TLC. After stirring of the mixture for 2 h and evaporation of the solvent and excess $SOCl_2$, crude 3-[acetyl(benzyloxy)amino]propane-1-sulfonyl chloride **23** (498 mg, 62%) was obtained, and was used without further purification in the next step.

***N*-(Benzyloxy)-*N*-[3-(N-alkylsulfamoyl)propyl]acetamide (24–28)**: Crude 3-[acetyl(benzyloxy)amino]propane-1-sulfonyl chloride **23** (498 mg, 1.62 mmol, 1 equiv), $RNH_2$ (R=Bn, Me, Et, *n*Pr, *n*Bu; 4.86 mmol, 3 equiv), and $CH_2Cl_2$ (20 mL) were added to a 20-mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar. The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC. After 12 h of stirring followed by evaporation of the solvent and excess amine, the crude product was dissolved in $Et_2O$ (3 mL) and filtered through a short pad of celite, which was then thoroughly washed with $Et_2O$. Evaporation of the solvent under reduced pressure afforded *N*-(benzyloxy)-*N*-[3-(*N*-alkylsulfamoyl)propyl]acetamides **24–28** in good chemical purity without further purification.

***N*-(Benzyloxy)-*N*-[3-(benzylsulfamoyl)propyl]acetamide (24)**: Yield: 520 mg (53% over two steps, from **22**); pale-yellow solid; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$=7.43–7.30 (m, 10H, Ar), 4.81 (s, 2H, $CH_2ON$), 4.63 (t, $^3J$=5.8 Hz, 1H, NH), 4.26 (d, $^3J$=6.0 Hz, 2H, $SO_2NCH_2Ph$), 3.74 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 2.95 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 2.09 (m, 2H, $CH_2$), 2.08 ppm (s, 3H, $COCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$=172.30 (CO), 137.35 (Cq), 134.09 (Cq), 129.29, 129.15, 128.86, 128.80, 128.07, 127.91 (10CH, Ar), 76.42 ($OCH_2$), 50.67 ($SO_2CH_2$), 47.18 ($NCH_2Ph$), 43.28 (br s, $NCH_2$), 21.65 ($CH_2$), 20.44 ppm ($COCH_3$).

***N*-(Benzyloxy)-*N*-[3-(ethylsulfamoyl)propyl]acetamide (26)**: Yield: 478 mg (59% over two steps, from **22**); pale-yellowish solid; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$=7.42–7.36 (m, 5H, Ar), 4.83 (s, 2H, $CH_2ON$), 4.27 (br t, $^3J$=5.5 Hz, 1H, NH), 3.78 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.12 (dq, $^3J$=5.8 Hz, $^3J$=5.5 Hz, 2H, $SO_2NCH_2$), 2.99 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 2.11 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.18 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$=172.23 (CO), 133.98 (Cq), 129.29, 129.15, 128.80 (5CH, Ar), 76.75 ($OCH_2$), 50.01 ($SO_2CH_2$), 43.92 (br s, $NCH_2$), 38.27 ($SO_2NCH_2$), 21.70 ($CH_2$), 20.44 ($COCH_3$), 15.83 ppm ($CH_3$).

***N*-(Benzyloxy)-*N*-[3-(*n*-propylsulfamoyl)propyl]acetamide (27)**: Yield: 476 mg (56% over two steps, from **22**); pale-yellow solid; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$=7.42–7.37 (m, 5H, Ar), 4.83 (s, 2H, $CH_2ON$), 4.24 (t, $^3J$=6.4 Hz, 1H, NH), 3.78 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.05 (dt, $^3J$=5.8 Hz, $^3J$=6.4 Hz, 2H, $SO_2NCH_2$), 3.03 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 2.11 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.56 (m, 2H, $CH_2$), 0.92 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$=172.23 (CO), 134.09 (Cq), 129.29, 129.16, 128.81 (5 CH Ar), 76.72 ($OCH_2$), 50.02 ($SO_2CH_2$), 44.99 ($SO_2NCH_2$), 42.03 (br s, $NCH_2$), 23.61 ($CH_2$), 21.73 ($CH_2$), 20.44 ($COCH_3$), 11.05 ppm ($CH_3$).

***N*-(Benzyloxy)-*N*-[3-(*n*-butylsulfamoyl)propyl]acetamide (28)**: Yield: 488 mg (55% over two steps, from **22**); pale-yellow solid; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$=7.42–7.36 (m, 5H, Ar), 4.82 (s, 2H, $CH_2ON$), 4.18 (t, $^3J$=6.4 Hz, 1H, NH), 3.78 (t, $^3J$=6.6 Hz, 2H, $CH_2N$), 3.05 (dt, $^3J$=5.8 Hz, $^3J$=6.4 Hz, 2H, $SO_2NCH_2$), 3.03 (t, $^3J$=7.8 Hz, 2H, $SO_2CH_2$), 2.11 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.36 (m, 2H, $CH_2$), 1.35 (m, 2H, $CH_2$), 0.91 ppm (t, $^3J$=5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$=172.10 (CO), 134.07 (Cq), 129.26, 129.11, 128.76 (5CH, Ar), 76.68 ($OCH_2$), 52.55 ($SO_2CH_2$), 49.79 ($SO_2NCH_2$), 42.97 (br s, $NCH_2$), 32.27 ($CH_2$), 21.65 ($CH_2$), 20.40 ($COCH_3$), 19.67 ($CH_2$), 9.40 ppm ($CH_3$).

***N*-Hydroxy-*N*-(3-sulfamoylpropyl) acetamide (29) and *N*-hydroxy-*N*-(3-(*N*-alkylsulfamoyl)propyl)acetamide (30–33)**: *N*-(benzyloxy)-*N*-[3-(N-*alkyl*sulfamoyl)propyl]acetamide **24–28** (0.66 mmol, 1.0 equiv), pure MeOH (5 mL), and, carefully, 10% Pd/C (46 mg) were added to a 20-mL two-necked round-bottom flask that was flushed with inert gas and equipped with a magnetic stirring bar. The heterogeneous mixture was stirred at room temperature under $H_2$, and the reaction was monitored by TLC. After 3 h of stir-

ring followed by evaporation of the solvent, the crude product was dissolved in MeOH (3 mL) and filtered through a short pad of celite, which was then thoroughly washed with MeOH. Evaporation of the solvent under reduced pressure gave *N*-hydroxy-*N*-(3-sulfamoylpropyl)acetamide **29** and *N*-hydroxy-*N*-(3-(*N*-alkylsulfamoyl)-propyl)acetamides **30**–**33**.

***N*-Hydroxy-*N*-(3-sulfamoylpropyl)acetamide (29)**: Yield: 98 mg (76%), yellowish oil; $^1$H NMR (400 MHz, $CD_3OH$), $\delta$ = (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.06 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.10 (s, 3H, $COCH_3$), 2.06 ppm (m, 2H, $CH_2$); $^{13}$C NMR (100 MHz, $CD_3OH$), $\delta$ = 172.40 (CO), 49.13 ($CH_2SO_2$), 44.20 (brs, $NCH_2$), 22.06 ($COCH_3$), 20.84 ppm ($CH_2$).

***N*-Hydroxy-*N*-[3-(ethylsulfamoyl)propyl]acetamide (31)**: Yield: 125 mg (84%), pale-yellow solid, mp = 123 °C; $^1$H NMR (400 MHz, $CD_3OH$), $\delta$ = 3.72 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.07 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 3.02 (m, 2H, $SO_2NCH_2$), 2.09 (s, 3H, $COCH_3$), 2.06 (m, 2H, $CH_2$), 1.16 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OH$), $\delta$ = 172.23 (CO), 50.01 ($SO_2CH_2$), 43.92 (brs, $NCH_2$), 38.27 ($SO_2NCH_2$), 21.70 ($CH_2$), 20.44 ($COCH_3$), 15.83 ppm ($CH_3$); IR (KBr): $\tilde{\nu}$ = 3279 (NH), 1600 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_7H_{16}N_2O_4S$: 224.0831 $[M]^+$, found: 224.00821.

***N*-Hydroxy-*N*-[3-(*n*-propylsulfamoyl)propyl]acetamide (32)**: Yield: 126 mg (80%), pale-yellow solid, mp = 137 °C; $^1$H NMR (400 MHz, $CD_3OH$), $\delta$ = 3.74 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.06 (m, 2H, $SO_2NCH_2$), 3.01 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.11 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.55 (m, 2H, $CH_2$), 0.94 ppm (t, $^3J$ = 5.9 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OH$), $\delta$ = 172.29 (CO), 50.02 ($SO_2CH_2$), 43.99 ($SO_2NCH_2$), 42.03 (brs, $NCH_2$), 23.61 ($CH_2$), 21.73 ($CH_2$), 20.46 ($COCH_3$), 11.0 ppm ($CH_3$); IR (KBr): $\tilde{\nu}$ = 3292 (NH), 1601 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_8H_{18}N_2O_4S$: 238.0987 $[M]^+$, found: 238.0987.

***N*-Hydroxy-*N*-[3-(*n*-butylsulfamoyl)propyl]acetamide (33)**: Yield: 127 mg (76%), pale yellow solid, mp = 138 °C; $^1$H NMR (400 MHz, $CD_3OH$), $\delta$ = 3.78 (t, $^3J$ = 6.6 Hz, 2H, $CH_2N$), 3.05 (m, 2H, $SO_2NCH_2$), 3.02 (t, $^3J$ = 7.8 Hz, 2H, $SO_2CH_2$), 2.11 (m, 2H, $CH_2$), 2.10 (s, 3H, $COCH_3$), 1.52 (m, 2H, $CH_2$), 1.40 (m, 2H, $CH_2$), 0.94 ppm (t, $^3J$ = 5.8 Hz, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OH$), $\delta$ = 172.10 (CO), 52.45 ($SO_2CH_2$), 45.71 ($SO_2NCH_2$), 42.93 (brs, $NCH_2$), 32.27 ($CH_2$), 21.65 ($CH_2$), 20.40 ($COCH_3$), 19.77 ($CH_2$), 9.49 ppm ($CH_3$); IR (KBr): $\tilde{\nu}$ = 3281 (NH), 1600 cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_9H_{20}N_2O_4S$: 252.1144 $[M]^+$, found: 252.1125.

**Synthesis of the [3-(acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester *alkyl* esters (36–40)**: [3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid monobenzyl ester **35** (prepared according to ref. [13] and was used without purification; 3.77 g, 10 mmol, 1.0 equiv) was dissolved in DMF (20 mL) and $Et_3N$ (1.4 mL, 10 mmol, 1.0 equiv) was added. After stirring for 0.5 h the appropriate alkyl iodide (20 mmol, 2.0 equiv) was added, and the mixture was stirred at 60 °C for 6 h. The solvent was removed and the residue was dissolved in $CH_2Cl_2$. The solution was washed with aq $NaHCO_3$, aq $Na_2S_2O_3$ and $H_2O$, and dried ($Na_2SO_4$). After removal of the solvent the residue was purified by column chromatography on silica gel, eluting with $CH_2Cl_2$/MeOH (98:2 or 99:1).

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester methyl ester (36)**: Yield: 665 mg (17%), yellowish oil; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$ = 7.31–7.39 (m, 10H, Ar), 5.06 (d, 2H, $^3J_{H,P}$ = 8.7 Hz, $POCH_2$), 4.79 (s, 2H, $NOCH_2$), 3.68 (t, 2H, $^3J$ = 6.6 Hz, $NCH_2$), 3.64 (d, 2H, $^3J_{H,P}$ = 11.0 Hz, $POCH_3$), 2.08 (s, 3H, $CH_3$), 1.70–1.79 (m, 2H, $CH_2$), 1.87–1.98 ppm (m, 2H, $CH_2$); $^{13}$C NMR (100 MHz, [$D_6$]DMSO), $\delta$ = 172.55 (CO), 136.46 (d, $^3J_{C,P}$ = 5.4 Hz, $POCH_2C$), 134.39 ($NOCH_2C$), 129.30, 129.11, 128.84, 128.73, 128.55, 128.05 (10C, Ar), 76.49 ($NOCH_2$), 67.41 (d, $^2J_{C,P}$ = 7.1 Hz, 2×$POCH_2$), 52.30 (d, $^2J_{C,P}$ = 6.9 Hz, 2×$POCH_3$), 45.37 ($NCH_2$), 23.85 (d, $^1J_{C,P}$ = 142 Hz, $PCH_2$), 20.58 ($COCH_3$), 20.27 ppm (d, $^2J_{C,P}$ = 4.6 Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta$ = 33.84 ppm; IR (liquid film): $\tilde{\nu}$ = 1661 cm$^{-1}$ (C=O). HRMS (FAB) *m/z*: calcd for $C_{20}H_{26}NO_5PH$: 392.1627 $[M+H]^+$, found: 392.1625.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid ethyl ester benzyl ester (37)**: Yield: 284 mg (7%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ = 7.71–7.79 (m, 3H, Ar), 7.61 (s, 1H, Ar), 7.40–7.46 (m, 2H, Ar), 7.23–7.36 (m, 11H, Ar), 4.87–5.05 (m, 2H, $POCH_2Ph$), 4.70 (s, 2H, $NOCH_2$), 4.14–4.31 (m, 2H, $POCH_2CH_2$), 3.59 (brs, 2H, $NCH_2$), 3.07 (t, 2H, $^3J$ = 6.9 Hz, $POCH_2CH_2$), 2.04 (s, 3H, $COCH_3$), 1.64–1.93 ppm (m, 4H, $PCH_2CH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ = 172.66 (CO), 136.56 (d, $^3J_{C,P}$ = 6.1 Hz, $POCH_2C$), 134.43 ($NOCH_2C$), 129.26, 129.08, 128.81, 128.68, 128.46, 127.97 (10CH, Ar), 76.50 ($NOCH_2$), 61.81 (d, $^2J_{C,P}$ = 6.7 Hz, $POCH_2CH_3$), 67.22 (d, $^2J_{C,P}$ = 5.7 Hz, $POCH_2C$), 45.45 ($NCH_2$), 23.33 (d, $^1J_{C,P}$ = 142 Hz, $PCH_2$), 20.55 ($COCH_3$), 20.33 (d, $^2J_{C,P}$ = 4.0 Hz, $PCH_2CH_2$), 16.47 ppm (d, $^3J_{C,P}$ = 5.8 Hz, $POCH_2CH_3$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta$ = 32.48 ppm; IR (liquid film): $\tilde{\nu}$ = 1651 cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{21}H_{28}NO_5P$: 405.1705 $[M]^+$, found: 405.1706.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid propyl ester benzyl ester (38)**: Yield: 336 mg (8%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ = 7.30–7.39 (m, 10H, Ar), 5.05 (d, $^3J_{H,P}$ = 8.9 Hz, 2H, $POCH_2Ph$), 4.79 (s, 2H, $NOCH_2$), 3.84–3.99 (m, 2H, $POCH_2CH_2$), 3.69 (t, $^3J$ = 6.1 Hz, 2H, $NCH_2$), 2.08 (s, 3H, $COCH_3$), 1.89–1.97 (m, 2H, $CH_2$), 1.71–1.78 (m, 2H, $CH_2$), 1.59–1.66 (m, 2H, $CH_2$), 0.90 ppm (t, $^3$J = 7.5 Hz, 3H, $POCH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ = 172.40 (CO), 136.44 (d, $^3J_{C,P}$ = 5.8 Hz, $POCH_2C$), 134.26 ($NOCH_2C$), 129.14, 128.96, 128.68, 128.55, 128.33, 127.84 (10CH, Ar), 76.34 ($NOCH_2$), 67.16 (d, $^2J_{C,P}$ = 7.6 Hz, $POCH_2$), 67.08 (d, $^2J_{C,P}$ = 5.8 Hz, $POCH_2$), 45.42 ($NCH_2$), 9.97 ($CH_2$-$CH_3$), 23.78 (d, $^3J_{C,P}$ = 5.8 Hz, $POCH_2CH_2$), 23.12 (d, $^1J_{C,P}$ = 143 Hz, $PCH_2$), 20.44 (CO-$CH_3$), 20.21 ppm (d, $^2J_{C,P}$ = 5.9 Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta$ = 32.47; IR (liquid film): $\tilde{\nu}$ = 1663 cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{22}H_{30}NO_5PH$: 420.1490 $[M+H]^+$, found: 420.1910.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester butyl ester (39)**: Yield: 477 mg (11%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ = 7.29–7.38 (m, 10H, Ar), 5.05 (d, 2H, $^3J_{H,P}$ = 8.8 Hz, $POCH_2Ph$), 4.78 (s, 2H, $NOCH_2$), 3.88–4.02 (m, 2H, $POCH_2CH_2$), 3.68 (t, 2H, $^3J$ = 6.5 Hz, $NCH_2$), 2.08 (s, 3H, $COCH_3$), 1.88–1.96 (m, 2H, $PCH_2CH_2$), 1.70–1.77 (m, 2H, $PCH_2$), 1.55–1.61 (m, 2H, $POCH_2CH_2$), 1.30–1.37 (m, 2H; $POCH_2CH_2CH_2$), 0.89 ppm (t, $^3J$ = 7.4 Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ = 172.35 (CO), 136.42 (d, $^3J_{C,P}$ = 5.8 Hz, $POCH_2C$), 134.26 ($NOCH_2C$), 129.11, 128.93, 128.66, 128.52, 128.30, 127.82 (10CH, Ar), 76.31 ($NOCH_2$), 67.77 (d, $^2J_{C,P}$ = 6.8 Hz, $POCH_2Ph$), 65.39 (d, $^2J_{C,P}$ = 6.7 Hz, $POCH_2CH_2$), 45.34 ($NCH_2$), 32.41 (d, $^3J_{C,P}$ = 5.7 Hz, $POCH_2CH_2$), 23.10 (d, $^1J_{C,P}$ = 142 Hz, $PCH_2$), 20.41 ($COCH_3$), 20.19 (d, $^2J_{C,P}$ = 4.0 Hz, $PCH_2CH_2$), 18.63 ppm ($POCH_2CH_2CH_2$), 13.52 ($CH_2CH_3$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta$ 032.49. ppm; IR (liquid film): $\tilde{\nu}$ = 1665 cm$^{-1}$ (C=O). HRMS (FAB) *m/z*: calcd for $C_{23}H_{32}NO_5PH$: 434.2096 $[M+H]^+$, found: 434.2104.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester 3-methyl-butyl ester (40)**: Yield: 716 mg (16%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ = 7.29–7.38 (m, 10H, Ar), 5.05 (d, 2H, $^3J_{H,P}$ = 8.7 Hz, $POCH_2Ph$), 4.78 (s, 2H, $NOCH_2$), 3.89–4.05 (m, 2H, $POCH_2CH_2$), 3.68 (t, 2H, $^3J$ = 6.2 Hz, $NCH_2$), 2.08 (s, 3H, $COCH_3$), 1.89–1.96 (m, 2H, $PCH_2$-$CH_2$), 1.61–1.77 (m, 3H, $PCH_2$ + CH), 1.46–1.50 (m, 2H, $POCH_2CH_2$), 0.86–0.87 ppm (m, 6H, 2×$CH_3$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ = 172.45 (CO), 136.43 (d, $^3J_{C,P}$ = 5.8 Hz, $POCH_2C$),

134.26 ($NOCH_2C$), 129.13, 128.95, 128.68, 128.54, 128.33, 127.85 (10 CH, Ar), 76.33 ($NOCH_2$), 67.13 (d, $^2J_{C,P}=5.7$ Hz, ($POCH_2Ph$), 64.16 (d, $^2J_{C,P}=7.5$ Hz, $POCH_2CH_2$), 45.27 ($NCH_2$), 39.08 (d, $^3J_{C,P}=5.7$ Hz, $POCH_2CH_2$), 24.52 ($POCH_2CH_2CH$), 23.12 (d, $^1J_{C,P}=143$ Hz, $PCH_2$), 22.30 (2 C, $2\times CH_3$), 20.42 ($COCH_3$), 20.21 ppm (d, $^2J_{C,P}=4.8$ Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta=32.51$ ppm; IR (liquid film): $\tilde{\nu}=1662$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{24}H_{34}NO_5PH$: 448.2253 $[M+H]^+$, found: 448.2254.

**Synthesis of the [3-(acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester arylethyl esters (41–43)**: 3-(Acetylbenzyloxyamino)propyl]phosphonic acid monobenzyl ester **35** (prepared according to[13] and used without purification; 3.77 g, 10 mmol, 1.0 equiv) was dissolved in DMPU (20 mL) and $Et_3N$ (1.4 mL, 10 mmol, 1.0 equiv) was added. After stirring for 0.5 h the appropriate aryl ethyl halide (20 mmol, 2.0 equiv) was added followed by NaI (1.50 g, 10 mmol, 1.0 equiv). The resulting mixture was stirred at 80 °C for 4 h. A further quantity of NaI was added, and the stirring was continued for another 4 h. The mixture was precipitated into hexane (800 mL) at 0 °C, and the hexane solution was removed by decantation. The last step was repeated twice, and the residue was dissolved in $CH_2Cl_2$. The solution was washed with aq $NaHCO_3$, aq $Na_2S_2O_3$, $H_2O$ and dried ($Na_2SO_4$). The solvent was removed and the residue was purified by column chromatography on silica gel by eluting with $CH_2Cl_2$/MeOH (98:2 or 99:1).

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester phenethyl ester (41)**: Prepared from phenethyl iodide without addition of NaI. Yield: 963 mg (20%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta=7.15$–$7.37$ (m, 15 H, Ar), 4.89–5.00 (m, 2 H, $POCH_2Ph$), 4.76 (s, 2 H, $NOCH_2$), 4.05–4.23 (m, 2 H, $POCH_2CH_2Ph$), 3.63 (br s, 2 H, $NCH_2$), 2.88–2.92 (m, 2 H, $POCH_2CH_2Ph$), 2.07 (s, 3 H, $COCH_3$), 1.81–1.90 (m, 2 H, $CH_2$), 1.56–1.71 ppm (m, 2 H, $CH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta=137.22$ (d, $^4J_{C,P}=1.9$ Hz, $POCH_2CH_2C$), 136.34 (d, $^3J_{C,P}=5.5$ Hz, $POCH_2C$), 134.27 ($NOCH_2C$), 129.13, 128.95, 128.67, 128.54, 128.42, 128.33, 127.84, 126.60 (10 CH, Ar), 76.34 ($NOCH_2$), 67.00 (d, $^2J_{C,P}=7.0$ Hz, $POCH_2$), 66.00 (d, $^2J_{C,P}=6.7$ Hz, $POCH_2$), 45.21 ($NCH_2$), 36.93 (d, $^3J_{C,P}=3.8$ Hz, $POCH_2CH_2$), 23.06 (d, $^1J_{C,P}=142$ Hz, $PCH_2$), 20.41 ($COCH_3$), 20.12 ppm (d, $^2J_{C,P}=4.8$ Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta=32.56$; IR (liquid film): $\tilde{\nu}=1667$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{27}H_{32}NO_5PH$: 482.2096 $[M+H]^+$, found: 482.2112.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester 2-naphthalen-2-yl-ethyl ester (42)**: Prepared from 2-(2-naphthyl) ethyl chloride (synthesized according to ref. [19]); yield: 266 mg (5%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta=7.71$–$7.79$ (m, 3 H, Ar), 7.61 (s, 1 H, Ar), 7.40–7.46 (m, 2 H, Ar), 7.23–7.36 (m, 11 H, Ar), 4.87–5.05 (m, 2 H, $POCH_2$), 4.70 (s, 2 H, $NOCH_2$), 4.14–4.31 (m, 2 H, $POCH_2CH_2$), 3.59 (br s, 2 H, $NCH_2$), 3.07 (t, $^3J=6.9$ Hz, 2 H, $POCH_2CH_2$), 2.04 (s, 3 H, $COCH_3$), 1.64–1.93 ppm (m, 4 H, $PCH_2CH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta=136.43$ (d, $^3J_{C,P}=6.2$ Hz, $POCH_2C$), 134.89 (quaternary naphth-C), 134.41 ($NOCH_2C$), 133.59 (quaternary naphth-C), 132.39 (d, $^4J_{C,P}=2.3$ Hz, $POCH_2CH_2C$), 129.28, 129.09, 128.82, 128.71, 128.52, 128.22, 128.05, 127.95, 127.66, 127.62, 127.40, 126.18, 125.67 (17 CH, Ar), 76.39 ($NOCH_2$), 67.17 (d, $^2J_{C,P}=6.9$ Hz, $POCH_2C$), 66.03 (d, $^2J_{C,P}=6.9$ Hz, $POCH_2CH_2$), 45.42 ($NCH_2$), 37.15 (d, $^3J_{C,P}=6.2$ Hz, $POCH_2CH_2$), 23.23 (d, $^1J_{C,P}=142$ Hz, $PCH_2$), 20.56 ($COCH_3$), 20.27 ppm (d, $^2J_{C,P}=3.8$ Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta=32.69$ ppm; IR (liquid film): $\tilde{\nu}=1661$ cm$^{-1}$ (C=O); HRMS (EI) *m/z*: calcd for $C_{31}H_{34}NO_5P$: 531.2175 $[M]^+$, found: 531.2145.

**[3-(Acetyl(benzyloxy)amino)propyl]phosphonic acid benzyl ester 2-naphthalen-1-yl-ethyl ester (43)**: Prepared from 1-naphthyl ethyl bromide. Yield: 478 mg (9%), yellowish oil; $^1$H NMR (500 MHz, $CDCl_3$), $\delta=7.96$–$8.00$ (m, 1 H, Ar), 7.80–7.85 (m, 1 H, Ar), 7.68–7.74 (m, 1 H, Ar), 7.43–7.52 (m, 3 H, Ar), 7.25–7.39 (m, 11 H, Ar), 4.88–5.05 (m, 2 H, $POCH_2Ph$), 4.74 (s, 2 H, $NOCH_2$), 4.14–4.36 (m, 2 H, $POCH_2CH_2Ph$), 3.62 (br s, 2 H, $NCH_2$), 3.33–3.41 (m, 2 H, $POCH_2CH_2Ph$), 2.06 (s, 3 H, $COCH_3$), 1.56–1.89 ppm (m, 2 H, $PCH_2CH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta=137.22$ (d, $^4J_{C,P}=1.9$ Hz, $POCH_2CH_2$), 136.34 (d, $^3J_{C,P}=5.5$ Hz, $POCH_2C$), 134.27 ($NOCH_2C$), 129.13, 128.95, 128.67, 128.54, 128.42, 128.33, 127.84, 126.60 (10 CH, Ar), 76.34 ($NOCH_2$), 67.00 (d, $^2J_{C,P}=7.0$ Hz, $POCH_2$), 66.00 (d, $^2J_{C,P}=6.7$ Hz, $POCH_2CH_2$), 45.21 ($NCH_2$), 36.93 (d, $^3J_{C,P}=3.8$ Hz, $POCH_2CH_2$), 23.06 (d, $^1J_{C,P}=142$ Hz, $PCH_2$), 20.41 ($COCH_3$), 20.12 ppm (d, $^2J_{C,P}=4.8$ Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta=32.71$ ppm; IR (liquid film): $\tilde{\nu}=1670$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{31}H_{34}NO_5PH$: 532.2253 $[M+H]^+$, found: 532.2252.

**Synthesis of the [3-(acetyl(hydroxy)amino)propyl]phosphonic acid monoesters (44–51)**: The [3-(acetyl-(hydroxy)amino)propyl]phosphonic acid benzyl ester alkyl ester **36–43** (0.5 mmol), pure MeOH (5 mL) and 10% Pd/C (20 mg) were carefully added to a 20-mL two-necked round-bottom flask. The heterogeneous mixture was stirred at room temperature under $H_2$, and the reaction was monitored by consumption of $H_2$. After completion of the reaction the catalyst was filtered off, and the solvent was removed.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid monomethyl ester (44)**: Yield: 105 mg (99%), light-red oil; $^1$H NMR (500 MHz, [D$_6$]DMSO), $\delta=3.50$–$3.53$ (m, 5 H, $POCH_3$ + $NCH_2$), 1.97 (s, 3 H, $CH_3$), 1.69–1.75 (m, 2 H, $CH_2$), 1.52–1.59 (m, 2 H, $CH_2$); $^{13}$C NMR (125 MHz, [D$_6$]DMSO), $\delta=170.94$ (CO), 51.49 (d, $^2J_{C,P}=5.0$ Hz, $2\times POCH_3$), 48.20 (d, $^3J_{C,P}=18.2$ Hz, $NCH_2$), 23.30 (d, $^1J_{C,P}=138$ Hz, $PCH_2$), 20.89 ($COCH_3$), 20.80 (d, $^2J_{C,P}=3.0$ Hz, $PCH_2CH_2$); $^{31}$P NMR (202 MHz, [D$_6$]DMSO), $\delta=22.79$; IR (liquid film): $\tilde{\nu}=1621$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_6H_{14}NO_5PH$: 212.0688 $[M+H]^+$, found: 212.0687.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic monoethyl ester (45)**: Yield: 111 mg (99%), light red oil; $^1$H NMR (500 MHz, [D$_6$]DMSO), $\delta=3.87$–$3.95$ (m, 2 H, $POCH_2$), 3.52 (t, 2 H, $^3J=6.9$ Hz, $NCH_2$), 1.97 (s, 3 H, $COCH_3$), 1.65–1.77 (m, 2 H, $CH_2$), 1.52–1.61 (m, 2 H, $CH_2$), 1.20 ppm (t, 3 H, $^3J=7.0$ Hz, $POCH_2CH_3$); $^{13}$C NMR (125 MHz, [D$_6$]DMSO), $\delta=$ 170.28 (CO), 59.81 (d, $^2J_{C,P}=6.1$ Hz, $POCH_2CH_3$), 47.64 ($NCH_2$), 23.18 (d, $^1J_{C,P}=138$ Hz, $PCH_2$), 20.26 ($COCH_3$), 20.09 (d, $^2J_{C,P}=6.3$ Hz, $PCH_2CH_2$), 16.33 ppm (d, $^3J_{C,P}=6.1$ Hz, $POCH_2CH_3$); $^{31}$P NMR (202 MHz, [D$_6$]DMSO), $\delta=29.17$; IR (liquid film): $\tilde{\nu}=1620$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_7H_{16}NO_5PH$: 226.0844 $[M+H]^+$, found: 226.0827.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid mono-*n*-propyl ester (46)**: Yield: 118 mg (99%), light red oil; $^1$H NMR (500 MHz,[D$_6$]DMSO), $\delta=3.74$–$3.78$ (m, 2 H, $POCH_2CH_2$), 3.51 (t, 2 H, $^3J=6.2$ Hz, $NCH_2$), 1.97 (s, 3 H, $C{=}OCH_3$), 1.72 (m, 2 H, $CH_2$), 1.51–1.58 (m, 4 H, $2\times CH_2$), 0.88 ppm (t, 3 H, $^3J=7.4$ Hz, $CH_2CH_3$); $^{13}$C NMR (125 MHz, [D$_6$]DMSO), $\delta=$ 70.84 (CO), 65.79 (d, $^2J_{C,P}=6.6$ Hz, $POCH_2$), 48.17 ($NCH_2$), 24.13 (d, $^3J_{C,P}=6.0$ Hz, $POCH_2CH_2$), 23.95 (d, $^1J_{C,P}=144$ Hz, $PCH_2$), 20.91 ($C{=}OCH_3$), 20.89 ($PCH_2CH_2$), 10.70 ppm ($CH_2H_3$); $^{31}$P NMR (202 MHz, $CDCl_3$), $\delta=26.66$ ppm; IR (liquid film): $\tilde{\nu}=1621$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{22}H_{30}NO_5PH$: 240.1001 $[M+H]^+$, found: 240.1015.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid mono-*n*-butyl ester (47)**: Yield: 125 mg (99%), light-red oil; $^1$H NMR (500 MHz, $CD_3OD$), $\delta=3.96$–$3.99$ (m, 2 H, $POCH_2CH_2$), 3.67 (t, 2 H, $^3J=6.5$ Hz, $NCH_2$), 2.10 (s, 3 H, $COCH_3$), 1.85–1.93 (m, 2 H, $PCH_2CH_2$), 1.61–1.73 (m, 4 H, $POCH_2CH_2$ + $PCH_2$), 1.40–1.35 (m, 2 H, $POCH_2CH_2CH_2$), 0.95 ppm (t, 3 H, $^3J=7.4$ Hz, $CH_2CH_3$); $^{13}$C NMR (125 MHz, $CD_3OD$,

DEPT), $\delta = 173.23$ (CO), 65.22 (d, $^2J_{C,P} = 6.5$ Hz, $POCH_2CH_2$), 48.69 ($NCH_2$), 33.14 (d, $^3J_{C,P} = 6.1$ Hz, $POCH_2CH_2$), 23.50 (d, $^1J_{C,P} = 136$ Hz, $PCH_2$), 20.72 (d, $^2J_{C,P} = 3.2$ Hz, $PCH_2CH_2$), 19.57 ($COCH_3$), 19.23 ($POCH_2CH_2CH_2$), 13.34 ppm ($CH_2CH_3$); $^{31}$P NMR (202 MHz, $CD_3OD$), $\delta = 30.79$ ppm; IR (liquid film): $\tilde{\nu} = 1618$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_9H_{20}NO_5PH$: 254.1157 $[M+H]^+$, found: 254.1161.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid 3-methylbutyl ester (48)**: Yield: 111 mg (83%), light red oil; $^1$H NMR (500 MHz, $CD_3OD$), $\delta = 3.98$–4.02, (m, 2H, $POCH_2CH_2$), 3.66 (t, 2H, $^3J = 6.1$ Hz, $NCH_2$), 2.11 (s, 3H, $COCH_3$), 1.84–1.94 (m, 2H, $PCH_2CH_2$), 1.67–1.80 (m, 3H, $PCH_2$ + CH), 1.52–1.56 (m, 2H, $POCH_2CH_2$), 0.93 ppm (t, 6H, $^3J = 6.6$ H, $2\times CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$, DEPT), $\delta = 173.41$ (CO), 63.81 (d, $^2J_{C,P} = 6.1$ Hz, $POCH_2CH_2$), 48.68 (d, $^3J_{C,P} = 21.5$ Hz, $NCH_2$), 39.75 (d, $^3J_{C,P} = 6.2$ Hz, $POCH_2CH_2$), 24.99 ($POCH_2CH_2CH$), 22.89 (d, $^1J_{C,P} = 136$ Hz, $PCH_2$), 22.06 ($2\times CH_3$), 20.65 (d, $^2J_{C,P} = 3.2$ Hz, $PCH_2CH_2$), 19.50 ($COCH_3$); $^{31}$P NMR (202 MHz, $CD_3OD$), $\delta = 30.60$ ppm; IR (liquid film): $\tilde{\nu} = 1662$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{10}H_{22}NO_5PH$: 268.13143 $[M+H]^+$, found: 268.1333.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid monophenethyl ester (49)**: Yield: 140 mg (93%), light-red oil; $^1$H NMR (500 MHz, $[D_6]$DMSO), $\delta = 7.19$–7.31 (m, 5H, Ar), 4.03–4.08 (m, 2H, $POCH_2$), 3.45–3.50 (m, 2H, $NCH_2$), 2.84–2.90 (m, 2H, $POCH_2CH_2$), 1.97 (s, 3H, $COCH_3$), 1.50–1.70 ppm (m, 4H, $PCH_2CH_2$); $^{13}$C NMR (125 MHz, $[D_6]$DMSO), $\delta = 137.87$ ($POCH_2CH_2C_{Ph}$), 128.81, 128.18, 126.20 (5CH, Ar), 64.46 (d, $^2J_{C,P} = 5.8$ Hz, $POCH_2$), 47.41 ($NCH_2$), 36.37 (d, $^3J_{C,P} = 5.7$ Hz, $POCH_2CH_2$), 23.36 (d, $^1J_{C,P} = 142$ Hz, $PCH_2$), 20.77 ($PCH_2CH_2$), 20.24 ppm ($COCH_3$); $^{31}$P NMR (202 MHz, $[D_6]$DMSO), $\delta =$ 29.25 ppm; IR (liquid film): $\tilde{\nu} = 1615$ cm$^{-1}$ (C=O); HRMS (FAB) *m/z*: calcd for $C_{13}H_{20}NO_5PH$: 302.1157 $[M+H]^+$, found: 302.1104.

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid mono(2-naphthalen-2-yl-ethyl) ester (50)**: Yield: 174 mg (99%), light red oil; $^1$H NMR (500 MHz, $CD_3OD$), $\delta = 7.75$–7.79 (m, 3H, Ar), 7.69 (s, 1H, Ar), 7.34–7.44 (m, 3H, Ar), 4.21–4.26 (m, 2H, $POCH_2CH_2$), 3.56 (t, 2H, $^3J = 6.6$ Hz, $NCH_2$), 3.09 (t, 2H, $^3J = 6.8$ Hz, $POCH_2CH_2$), 2.09 (s, 3H, $COCH_3$), 1.59–1.81 ppm (m, 4H, $PCH_2CH_2$); $^{13}$C NMR (125 MHz, $CD_3OD$), $\delta = 172.54$ (CO), 135.48 (quaternary naphth-C), 133.76 (quaternary naphth-C), 132.51 ($POCH_2CH_2C$), 127.73, 127.29, 127.26, 127.25, 127.20, 125.71, 125.17 (7CH, Ar), 65.32 (d, $^2J_{C,P} = 5.8$ Hz, $POCH_2CH_2$), 36.91 (d, $^3J_{C,P} = 6.7$ Hz, $POCH_2CH_2$), 22.97 (d, $^1J_{C,P} =$ 141 Hz, $PCH_2$), 20.02 ($PCH_2CH_2$), 18.93 ppm ($COCH_3$); $^{31}$P NMR (202 MHz, $[D_6]$DMSO), $\delta = 32.57$ ppm; IR (liquid film): $\tilde{\nu} = 1618$ cm$^{-1}$ (C=O); HRMS (ESI) *m/z*: calcd for $C_{17}H_{22}NO_5PNa$: 374.113331 $[M+H]^+$, found: 374.112219

**[3-(Acetyl(hydroxy)amino)propyl]phosphonic acid mono(2-naphthalen-1-yl-ethyl) ester (50)**: Yield: 149 mg (85%), light-red oil; $^1$H NMR (500 MHz, $[D_6]$DMSO), $\delta = 7.37$–8.13 (m, 7H, CH, Ar), 4.13–4.17 (m, 2H, $POCH_2CH_2Ph$), 3.47 (t, 2H, $^3J = 6.6$ Hz, $NCH_2$), 3.39–3.35 (m, 2H, $POCH_2CH_2Ph$), 1.96 (s, 3H, $COCH_3$), 1.63–1.74 (m, 2H, $CH_2$), 1.49–1.55 ppm (m, 2H, $CH_2$);$^{13}$C NMR ($[D_6]$DMSO, 125 MHz), $\delta =$ 133.77 (quaternary naphth-C), 133.29 (quaternary naphth-C), 131.49 (quaternary naphth-C), 129.33, 129.29, 128.48, 126.88, 125.52, 125.43, 126.97 (7CH, Ar), 66.11 (d, $^2J_{C,P} = 8.6$ Hz, $POCH_2CH_2$), 47.58 ($NCH_2$), 33.45 ($POCH_2CH_2$), 23.26 (d, $^1J_{C,P} = 141$ Hz, $PCH_2$), 20.24 ($COCH_3$), 20.05 ppm ($PCH_2CH_2$); $^{31}$P NMR (202 MHz, $[D_6]$DMSO), $\delta = 28.97$ ppm; IR (liquid film): $\tilde{\nu} = 1620$ cm$^{-1}$; HRMS (ESI) *m/z*: calcd for $C_{17}H_{22}NO_5PH$: 352.1313 $[M+H]^+$, found: 352.1281

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