

Article

New Application of *cycloSaligenyl* Prodrugs Approach for the Delivery of Fosfoxacin Derivatives in Mycobacteria

Mathilde Munier, Denis Tritsch, Didier Lièvremon, Michel Rohmer  and Catherine Grosdemange-Billiard *

Laboratoire Chimie et Biochimie de Molécules Bioactives, Université de Strasbourg/CNRS, UMR 7177, Institut Le Bel, 4 Rue Blaise Pascal, 67081 Strasbourg, France

* Correspondence: grosdemange@unistra.fr

Abstract: In this work, we implemented for the first time the *cycloSaligenyl* prodrug strategy to increase the bioavailability of fosmidomycin phosphate analogs in bacteria. Here, we report the synthesis of 34 *cycloSaligenyl* prodrugs of fosfoxacin and its derivatives. Among them, fifteen double prodrugs efficiently prevented the growth of the non-pathogenic, fast-growing *Mycobacterium smegmatis*.

Keywords: isoprenoid biosynthesis; *cycloSaligenyl* prodrug; fosfoxacin; deoxyxylulose 5-phosphate reducto-isomerase; *Mycobacterium smegmatis*

1. Introduction

The overuse and misuse of antibiotics, coupled with the absence of new drug development, resulted in a rapid and alarming emergence of microbial resistance. To date, this silent pandemic is an increasingly serious threat to global public health, as recently reported by the World Health Organization, a threat exacerbated by the absence of new drug development [1]. The multidrug- and extensively drug-resistant strains of *Mycobacterium tuberculosis* are prime examples. As these strains are resistant to at least the first line of antitubercular drugs, isoniazid and rifampicin, which received their marketing authorizations in 1952 and 1972, respectively, they are responsible for tuberculosis, which is one of the top ten causes of death worldwide [2,3]. Therefore, there is an urgent need to develop new antitubercular drugs that act differently from the antibiotics currently on the market. In addition, because mycobacteria have a thick lipophilic cell wall, they are naturally resistant to known antibiotics, making the development of new antitubercular drugs a challenge [4].

A potential target is the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), the second enzyme of the 2-C-methyl-D-erythriol 4-phosphate (MEP) pathway, the only source of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) in most pathogenic bacteria. As the MEP pathway is absent in humans, it represents a very attractive target for the development of novel antimicrobials [5]. Fosmidomycin **1a** and its close relative FR-900098 **1b** (Scheme 1), two natural phosphonate compounds [6], were found to have a strong antibacterial activity) acting as potent inhibitors of DXR [7].

Due to its pharmacokinetic properties, moderate oral bioavailability and fast clearance, fosmidomycin cannot, however, be used as a drug [8]. To circumvent these issues, much research has been devoted to improving the efficiency of fosmidomycin derivatives. Within this framework, we synthesized two hydroxamate phosphonic acids **2a** and **2b** [9] and the phosphate analog of fosmidomycin, fosfoxacin **3a**, and the related analogs **3b** and **4a–4b** [10] (Scheme 2). Even if the IC₅₀ values of the *N*-methylated derivatives **2b** and **4b** against *Escherichia coli* and *Mycobacterium smegmatis* DXRs are similar to those of fosmidomycin **1a**, none of those natural and synthetic phosphonates **1–3** and phosphates **2–4** inhibits the growth of *M. smegmatis* cells [10].



Citation: Munier, M.; Tritsch, D.; Lièvremon, D.; Rohmer, M.; Grosdemange-Billiard, C. New Application of *cycloSaligenyl* Prodrugs Approach for the Delivery of Fosfoxacin Derivatives in Mycobacteria. *Molecules* **2023**, *28*, 7713. <https://doi.org/10.3390/molecules28237713>

Academic Editor: Harri Lönnberg

Received: 19 October 2023

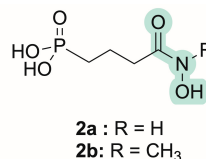
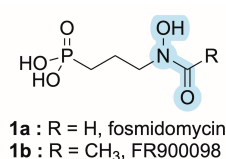
Revised: 15 November 2023

Accepted: 18 November 2023

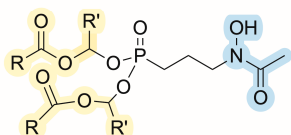
Published: 22 November 2023



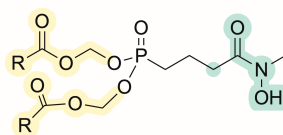
Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).



Acyloxyalkyl and alkoxycarbonyloxyalkyl prodrug series

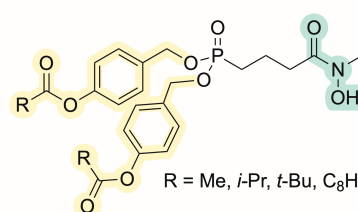


R = *t*Bu, Ph, MeO, *t*BuO, R' = H
R = Me, Et, *t*Bu, Ph, EtO, *t*BuO, R' = CH₃



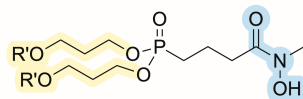
R = *n*-Pr, *t*-Bu, Ph
R = O*i*Pr, POC

Acyloxybenzyl prodrug series

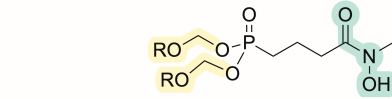


R = Me, *i*-Pr, *t*-Bu, C₈H₁₇, Ph,

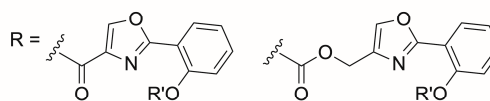
Alkoxyalkyl prodrug series



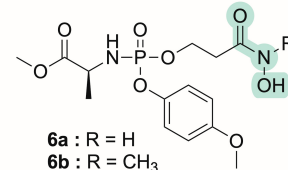
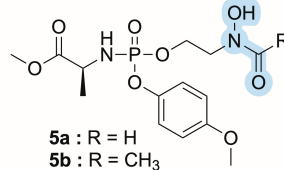
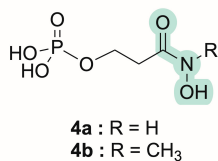
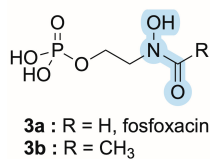
R = C₄H₉, C₈H₁₇, C₁₂H₂₅, C₁₆H₃₃



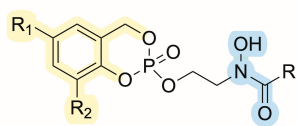
R = R' = H and Bn



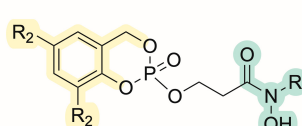
Scheme 1. Natural and synthetic phosphonate DXR inhibitors 1–2 and examples of their prodrugs.



Target molecules



7aa–ag : R = H
7ba–bg : R = CH₃



8ag–ag : R = H
8ba–bg : R = CH₃

R₁ = H, R₂ = H, **a**
R₁ = CH₃, R₂ = H, **b**
R₁ = Cl, R₂ = H, **c**
R₁ = Cl, R₂ = Cl, **d**
R₁ = Br, R₂ = H, **e**
R₁ = CF₃, R₂ = H, **f**
R₁ = OCH₃, R₂ = H, **g**

Scheme 2. Natural and synthetic phosphate DXR inhibitors 3–4, arylphosphoramidate 5–6 and *cyclo*Saligenyl prodrug analogues 7–8.

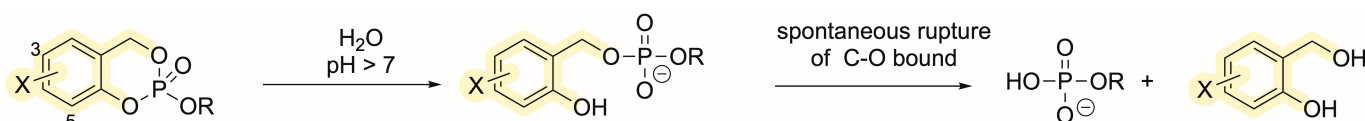
In fact, in contrast to *E. coli*, the mycobacteria lack the transporters allowing the uptake of fosmidomycin derivatives (GlpT and UhpT, the glycerol 3 phosphate and glucose 6 phosphate transporters, respectively) [11]. Besides, these bacteria have a complex, highly lipophilic cell wall, limiting the uptake of diverse chemical compounds as potential antibiotics, rendering the fight against these pathogenic bacteria very difficult. To circumvent the lack of uptake and to increase the bioavailability of phosphonate and phosphate hydrophobic antibiotics, most of the research groups, including ours, focused on prodrug strategies.

The concept of prodrug was introduced in the late 1950s by A Albert and is defined as an inactive pharmaceutical derivative that can be in vivo biotransformed, enzymatically, or chemically into the active parent drug [12].

This strategy is often used to optimize the delivery and the cellular uptake of drugs containing a phosphate or phosphonate group. In fact, such functional groups are negatively charged at physiological pH, a feature restricting their cellular uptake by passive diffusion. Moreover, phosphorylated compounds are rarely developed as potential antibiotics due to their sensitivity towards the hydrolytic activity of the phosphatases. Therefore, the prodrug approach has been adopted to bypass this lack of uptake and to increase the bioavailability of these hydrophilic compounds by (i) masking the charged phosphonate moiety with acyloxymethyl esters, alkoxycarbonyloxymethyl esters, acyloxybenzyl or alkoxyalkyl esters [13,14] (Scheme 1) (ii) replacing the charged phosphate with an aryl phosphoramidate moiety developed by McGuigan to deliver monophosphorylated nucleoside analogs inside the cell (Scheme 2). This method, also called the “ProTide approach” has been largely applied to improve the pharmacological properties of antiviral and anticancer agents [15,16].

The cleavage of these prodrugs is mediated by key endogenous enzymes (esterase, phospholipase, phosphoramidase), which are present in the target microorganism and able to release the parent drug. We have recently reported that the “ProTide” approach may not be suitable for the delivery of fosfoxacin analogs, probably due to the reactivity of the prodrugs and the resulting fast abiotic or enzymatic hydrolysis [17]. Instead of using enzymatic cleavage to release the drugs into the cell from the classically used phosphate masking groups, we investigated the opportunity of using the *cycloSaligenyl* prodrug of fosfoxacin and its derivatives to inhibit the growth of *M. smegmatis*. The *cycloSal* approach, developed by C. Meier for the synthesis of nucleotide prodrugs, improved antiviral activity through the successful intracellular delivery of lipophilic nucleotide derivatives [18,19]. In contrast to the classically used phosphate masking groups, which are cleaved by enzymes, the intracellular cleavage of *cycloSaligenyl* prodrugs is based on a completely pH-driven, chemically efficient, and highly selective hydrolysis mechanism. Moreover, such a masking should also protect the inhibitors against hydrolysis by phosphatases. To our knowledge, the *cycloSal* prodrug approach has never been used to deliver the parent phosphate drug into bacteria.

In this work, we synthesized a series of *cycloSaligenyl* prodrugs of fosfoxacin and its analogs 7 and 8 and tested their growth inhibitory power on *E. coli* and the non-pathogenic, fast-growing *M. smegmatis*. The phosphate parent compounds are expected to be released from the prodrugs at an intracellular pH greater than 7 via a cascade reaction: selective cleavage of the most labile phenyl phosphate ester bond, followed by spontaneous rupture of the benzyl phosphate ester bond releasing the active drug and salicyl alcohol [20] (Scheme 3).



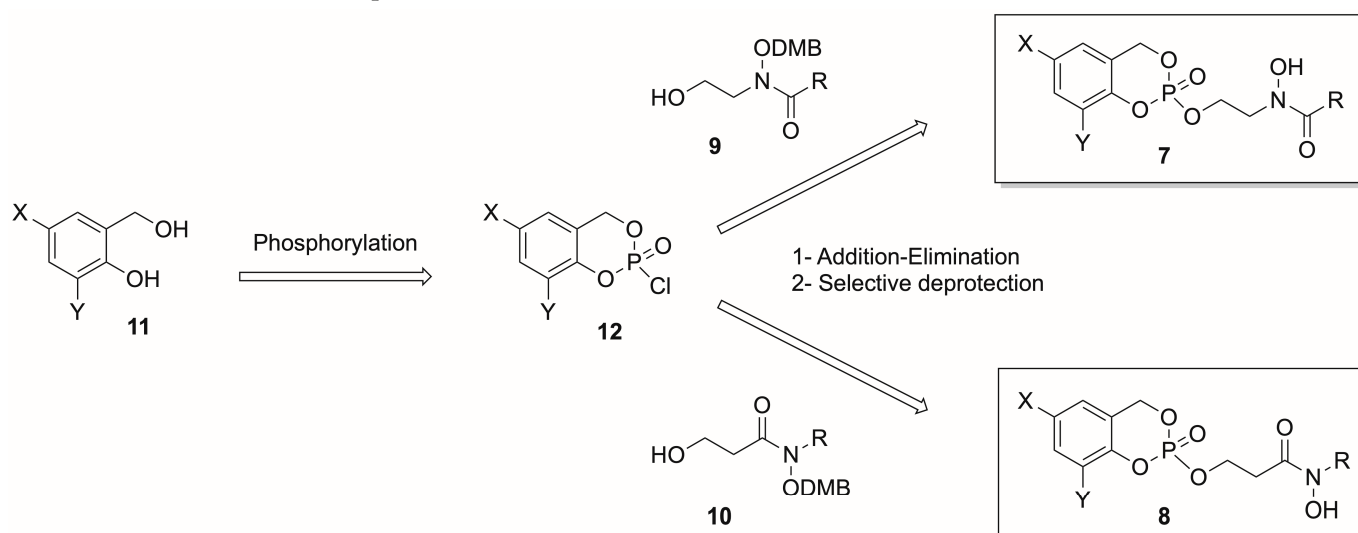
Scheme 3. Hydrolysis mechanism of *cycloSal* group.

As the kinetic hydrolysis being is modulated by the substituent on the aromatic ring at C-3 or C-5 [21], we investigated the influence of electron-withdrawing (Cl, Br, CF₃) and electron-donating (CH₃, OCH₃) substituents on bacterial growth inhibition tests of these *cycloSaligenyl* prodrugs.

2. Results and Discussion

2.1. Chemistry

The strategy to synthesize the *cycloSal* prodrugs **7** and **8** is outlined in Scheme 4. The key step is the addition–elimination of *O*-protected retrohydroxamic and hydroxamic acids **9** and **10** on the *cycloSal*phosphochloridate derivatives **12**, obtained by phosphorylation of the differently substituted salicyl alcohols **11** using phosphorus (V) chemistry (Scheme 4). The choice of the hydroxylamine protecting group is crucial in the synthesis of *cycloSaligenyl* prodrugs, being labile under basic and hydrogenation conditions. Therefore, we choose to protect the hydroxylamine by a 2,4-dimethoxybenzyl (DMB) group, which can be removed in mild conditions (1–2% TFA in DCM, 15 min) [22], allowing the introduction of a masked phosphate moiety at the penultimate step of the prodrug synthesis. All synthetic steps are depicted in Schemes 5–7.

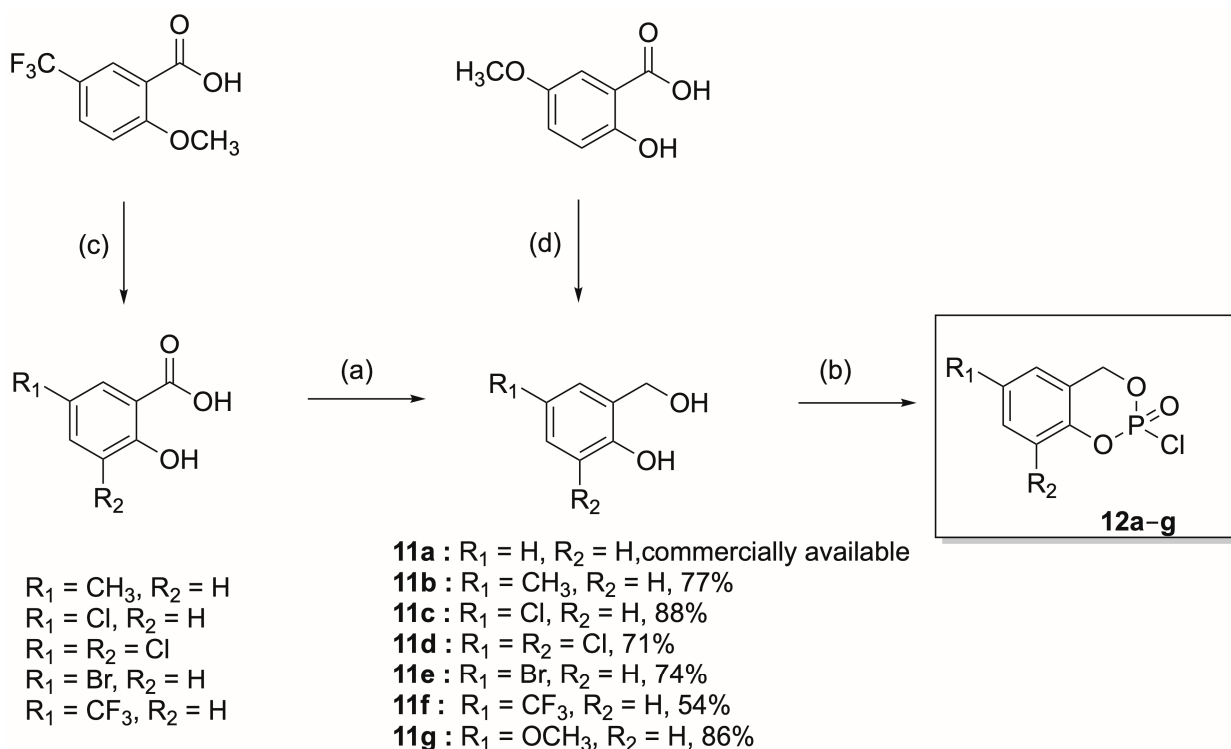


Scheme 4. Synthetic approach of *cycloSaligenyl* prodrugs of fosfoxacin derivatives **7** and **8**.

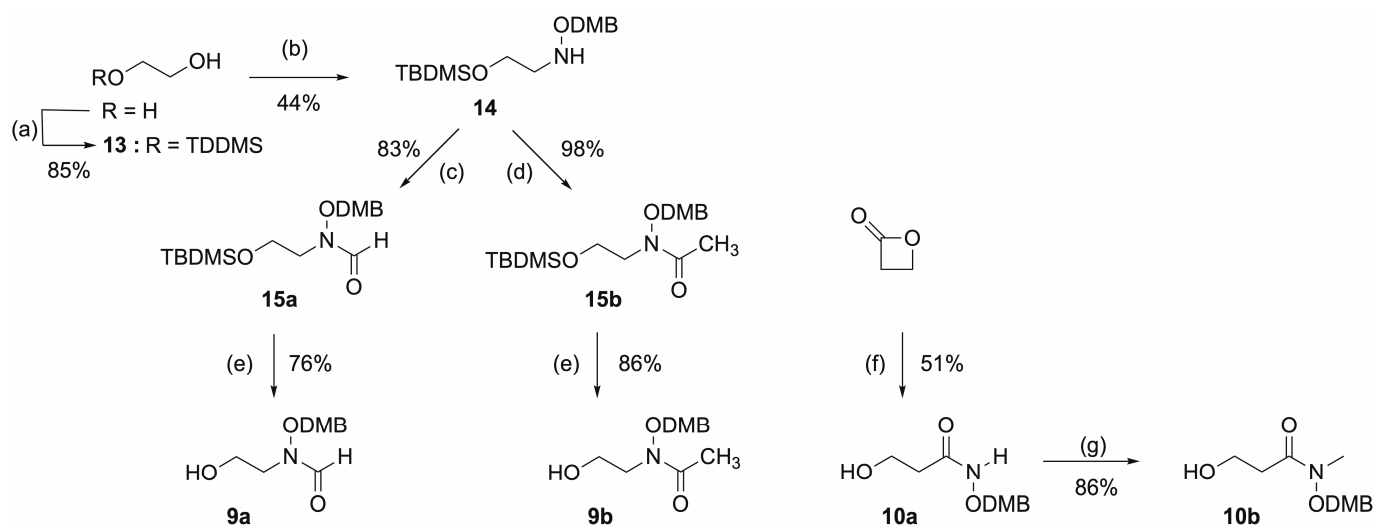
Except for the commercially available saligenol (**11a**), most of the substituted salicyl alcohols (**11b–e**) have been prepared in 71–86% yield by standard reduction methods of commercially available salicylic aldehydes or acids except for the two compounds (**11f–g**). Salicyl alcohol substituted with trifluoromethyl group (**11g**) has been prepared in two steps from the 2-methoxy-5-(trifluoromethyl)benzoic acid. After demethylation using iodocyclohexane in DMF under reflux, the carboxylic acid is immediately reduced with LiAlH₄ into the desired compound **11f** with 54% yield over the two steps [23] (Scheme 5).

The binary system reduction NaBH₄/BF₃·Et₂O affords benzyl alcohol **11g** with an excellent yield, 86%, compared to 28% with LiAlH₄ [24].

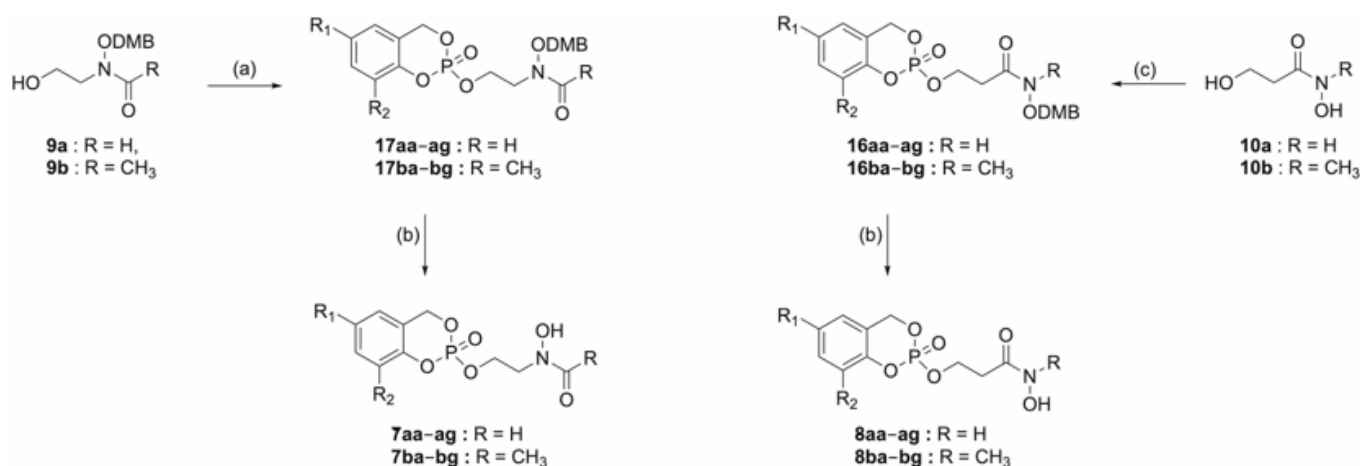
The reaction of a phosphorus oxychloride solution in THF at −78 °C with the salicyl alcohols **11** in the presence of trimethylamine (TEA) led to the non-stable *cycloSal*phosphochloridates **12** (Scheme 5), which were characterized by NMR ¹H and ³¹P. They were directly used in the next reaction, i.e., condensation with the primary alcohol of hydroxamic and retrohydroxamic acids, without purification.



Scheme 5. Synthesis of *CycloSalphosphochloridates* **12a–g**. Reagents and conditions: (a) LiAlH_4 , 0°C to RT; (b) $\text{P}(\text{O})\text{Cl}_3$, TEA, THF, -78°C to RT; (c) iodocyclohexane, DMF, reflux; (d) NaBH_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, reflux; (d) NaBH_4 , THF, 0°C to RT.



Scheme 6. Synthesis of *O*-protected retrohydroxamic and hydroxamic acids **9** and **10**. Reagents and conditions: (a) NaH , TBDMSCl , THF, 0°C to RT; (b) (i) TiF_2O , 2,6-dimethylpyridine, CH_2Cl_2 , -78°C ; (ii) H_2NODMB , CH_2Cl_2 , -78°C to RT; (c) $\text{HCOOH}/\text{Ac}_2\text{O}$ (5:1), THF, RT; (d) Ac_2O , pyridine, RT; (e) $\text{TBAF} \cdot 3(\text{H}_2\text{O})$, THF, RT; (f) (i) H_2NODMB , LiHMDS , THF, -78°C ; (ii) $\text{TBAF} \cdot 3(\text{H}_2\text{O})$, THF, RT; (g) MeI , K_2CO_3 , acetone, reflux.



R	R ₁	R ₂	cSal	Yield (%)	cSal	Yield (%)	cSal	Yield (%)	Com p8	Yield (%)
H	H	H	17aa	66	7aa	80	16aa	65	8aa	60
H	CH ₃	H	17ab	46	7ab	-	16ab	43	8ab	-
H	Cl	H	17ac	51	7ac	73	16ac	29	8ac	81
H	Cl	Cl	17ad	49	7ad	*	16ad	10	8ad	*
H	Br	H	17ae	37	7ae	-	16ae	11	8ae	-
H	CF ₃	H	17af	52	7afa	-	16af	13	8af	-
H	OCH ₃	H	17ag	64	7ag	-	16ag	18	8a g	-
CH ₃	H	H	17ba	73	7ba	84	16ba	76	8ba	80
CH ₃	CH ₃	H	17bb	36	7bb	-	16bb	75	8bb	83
CH ₃	Cl	H	17bc	56	7bc	68	16bc	86	8bc	44
CH ₃	Cl	Cl	17bd	12	7bd	-	16bd	43	8bd	*
CH ₃	Br	H	17be	51	7be	-	16be	74	8be	-
CH ₃	CF ₃	H	17bf	52	7bf	-	16bf	53	8bf	80
CH ₃	OCH ₃	H	17bg	56	7bg	-	16bg	61	8bg	-

* degradation.

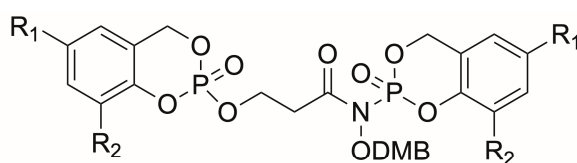
Scheme 7. Synthesis of retrohydroxamic and hydroxamic *cycloSaligenyl* prodrugs **7** and **8**. Reagents and reaction conditions: (a) TEA, DMAP, CH₂Cl₂, −40 °C to RT; (b) 2% TFA, CH₂Cl₂, RT. (c) R = H, pyridine, CH₂Cl₂, −40 °C to RT; R = CH₃, TEA, DMAP, CH₂Cl₂, −40 °C to RT.

The precursor **14** of retrohydroxamic acids **9** was prepared by Woo's method, i.e., activation of alcohol **13** by triflate followed by nucleophilic substitution with the *O*-2,4-dimethoxybenzyl hydroxylamine (Scheme 6). After formylation, compound **15a** was obtained as a mixture of two conformers, *Z* and *E*, in a 30:70 ratio, respectively (determined by NMR spectroscopy), due to the restricted rotation around the C–N bond. Acetylation of **14** led to compound **15b** as the sole *E* conformer. Deprotection of the silylether gave the primary alcohols **9a** and **9b** with the same selectivity as before.

An alternative synthesis has been developed to obtain hydroxamic acids **10**. According to the previously described method, the *O*-protected derivative **10a** was prepared in one step from commercially available β-propiolactone using *O*-2,4-dimethoxybenzyl hydroxylamine in the presence of an excess of LiHMDS (Scheme 6). Compound **10a** was obtained as a mixture of two *Z* and *E* conformers in a 60:40 ratio, respectively [10]. The selective *N*-methylation versus *O*-methylation of **10a** was accomplished under basic conditions with K₂CO₃ and methyl iodide, leading to **10b** as a sole *E* conformer (Scheme 6).

The key coupling step of the *O*-protected retrohydroxamic and hydroxamic acids **9** and **10** with the *cycloSal*phosphochloridate derivatives **12** was carried out in DCM at $-40\text{ }^{\circ}\text{C}$ in the presence of trimethylamine (TEA) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP). In these conditions, the precursors **16b** and **17** of the *cycloSal* prodrugs were obtained in moderate to reasonable yields with the exception of compound **17bd** (Scheme 7).

The coupling of *cycloSal*phosphochloridate with the hydroxamic acid **10a** was performed in the same conditions (TEA/cat. DMAP), yielding the desired precursors **16a** as a mixture of the two *Z* and *E* conformers in a 60:40 ratio along with a by-product. This latter was identified as bis*cycloSal* compound **18**, resulting from the nucleophilic attack of the nitrogen atom of the hydroxamic moiety at the phosphorus atom (Scheme 8). In the presence of an excess of trimethylamine, deprotonation occurs, generating the hydroxamate anion that can react with *cycloSal*phosphochloridate derivatives **12**, leading to the bis(*cycloSal*) compounds in low to modest yield except for **18c** and **18d** isolated in good yields.



18a : $R_1 = \text{H}$, $R_2 = \text{H}$, 20% **18b** : $R_1 = \text{CH}_3$, $R_2 = \text{H}$, 38%
18c : $R_1 = \text{Cl}$, $R_2 = \text{H}$, 84% **18e** : $R_1 = \text{Br}$, $R_2 = \text{H}$, 74%
18f : $R_1 = \text{CF}_3$, $R_2 = \text{H}$, 15% **18g** : $R_1 = \text{OCH}_3$, $R_2 = \text{H}$, 12%

Scheme 8. Bis(*cycloSal*) compounds **18**.

The bis(*cycloSal*) **18d**, substituted with two chlorine atoms could not be obtained because degradation occurred during the purification of silica. To avoid the formation of **18**, an alternative synthesis has been carried out to obtain the compounds **17aa–ag** by replacing TEA with pyridine, a weaker base. The last step is the selective deprotection of the *O*-dimethoxybenzyl group by using 2% or 3% of TFA in DCM [25]. In these conditions, only ten *cycloSal*igenyl prodrugs **7** and **8** were obtained (Scheme 7) and screened for growth inhibition on *E. coli* and *M. smegmatis*. It was not possible to obtain the unprotected bis(*cycloSal*) prodrugs without degradation of the compounds. Accordingly, the antibacterial efficiency of the *O*-protected bis(*cycloSal*) prodrugs **18** has been evaluated.

2.2. Biological Evaluation

The efficacy of the prodrugs in inhibiting the growth of *E. coli* and *M. smegmatis* was evaluated by the paper disk diffusion method at 800 nanomoles. Isoniazid (30 nanomoles) and fosmidomycin (10 nanomoles) were used as reference compounds for positive *M. smegmatis* and *E. coli* growth inhibition. The diameters of the inhibition zone are given with respect to the amount of inhibitor deposited on the disk (Table 1).

Prodrugs **7** and **8** were tested on an *E. coli* culture. among them only the two 5-Cl-*cycloSal* prodrugs (**7ac**, **7bc**) showed growth inhibition in *E. coli*. These two are the only ones to have both an aromatic ring substituted by a halogen and to be retrohydroxamic acids. The growth inhibition induced by prodrugs **7ac** and **7bc** is significantly less effective than the reference compound. In fact, an 80-fold higher amount of prodrugs is required to observe a 2 and 5-fold lower inhibition than fosmidomycin, the most efficient inhibitor of *E. coli* growth (Table 1). This may be due to a degradation of prodrugs **7ac** and **7bc** with the release of the parent molecules, fosfoxacin **3a** and its *N*-acetylated derivative **3b**, respectively, which enter bacteria via glycerol 3-phosphate (GlpT) and/or glucose 6-phosphate (UhpT) transporters. However, compound **7bc** was three and a half times more effective at inhibiting growth in *E. coli* than **7ac**. This result is in accordance with the results observed on *E. coli* DXR for the parent molecules fosfoxacin **3a** and its acetylated analog **3b** [10]. The absence of growth inhibition on *E. coli* of the other prodrugs **7** and **8** seemed to indicate that no release of the drugs occurred outside the bacterial cells in the

incubation medium. To explain the inefficiency of this prodrug series on the *E. coli* strain, various hypotheses can be considered. The rigid aromatic ring of the *cycloSaligenyl* group prevents penetration or at least slows it down considerably. Assuming that the prodrug entered the bacteria, if the release of the parent molecules is too slow, the inhibitor amount will be too low to inhibit the DXR. Since *E. coli* is a fast-growing bacterium, anything that slows down the release of parent inhibitors into bacterial cells should increase the bacterial resistance to these prodrugs.

Table 1. *E. coli* and *M. smegmatis* growth inhibition with *cycloSal* prodrugs **7** and **8** (800 nmoles) and the reference compounds, fosmidomycin (10 nmoles) and isoniazid (30 nmoles).

<i>E. coli</i>		<i>M. smegmatis</i>	
Compound	Diameter (mm)	Compound	Diameter (mm)
Fosmidomycin	40–45	Isoniazide	30–35
7aa	-	7aa	-
7ba	-	7ba	-
8aa	-	8aa	-
8ba	-	8ba	-
8bb	-	8bb	-
7ac	8	7ac	8
7bc	23	7bc	-
8ac	-	8ac	10
8bc	-	8bc	8
8bf	-	8bf	-

Prodrugs **7** and **8** were screened for growth inhibition on *M. smegmatis* strain. Only the 5-Cl-*cycloSal* prodrugs **7ac**, **8ac** and **8bc** displayed a low antibacterial activity and are much less efficient than the antitubercular reference, isoniazid. To induce a 3.5-fold lower inhibition than the reference, 27-fold more amount of prodrugs is required (Table 1). In Mycobacteria, which do not possess the GlpT and UhpT transporters, the *cycloSal* prodrugs enter into the bacteria by passive diffusion to release the active parent compound. We assume that the prodrugs **7** and **8** penetrate the cell but are probably too stable to be chemically hydrolyzed and therefore deliver too low amounts of the DXR inhibitors to observe bacterial growth. The hydrolysis rate of the prodrugs could be controlled by the substituent present at the C-5 position of the salicylic moiety: an electron-withdrawing substituent such as chlorine accelerates the hydrolysis, whereas an electron-donating group stabilizes the phenol ester bond resulting in a decrease of the hydrolysis rate. The 5-Cl-*cycloSal* prodrugs **7ac**, **8ac** and **8bc**, having a lower hydrolytic stability, show the ability to deliver the parent molecules inside the cell. In contrast, the absence of inhibition was observed with the unsubstituted prodrug series (**7aa–8aa**, **7ba–8ba**) and 5-methyl-*cycloSaligenyl* prodrug (**8bb**), which could be correlated with higher hydrolytic stability as compared with the 5-Cl-*cycloSal* prodrugs (Table 1). The lack of inhibition with the 5-CF₃-*cycloSal* prodrug (**8bf**) is unclear and could be due to its inadequate stability or its short half-life resulting in hydrolysis outside the cells to give the phosphohydroxamic acid **2b**, which cannot enter into *M. smegmatis*. Degradation of the prodrug or active compound by various enzymes or expulsion of the inhibitor out of bacteria by efflux pumps may be envisaged to explain the absence or low inhibition in *M. smegmatis* growth with these *cycloSal* prodrugs. Making an assumption that these prodrugs are not lipophilic enough to cross the waxy wall of the mycobacteria, we evaluated the growth inhibition of the double prodrugs. All results are reported in Table 2. Remarkably, the presence of the DMB group greatly enhances the efficiency of the *cycloSal* prodrugs in inhibiting the growth of *M. smegmatis*. Indeed, two compounds of the unsubstituted double prodrug series, **17aa** and **16ba** displayed inhibition

zones (Table 2, entries 1–4), while the *cycloSal* prodrug series were inactive. Compound **16ba** showed nearly the same inhibition as isoniazid but with 27-fold higher amounts of prodrugs. The 5-Cl-*cycloSal* double prodrug series, except for the compound **16bc**, shows a 2 to 3-fold higher inhibition compared to their unprotected analogs, demonstrating that the presence of the DMB-protecting group increases the lipophilicity of the prodrugs, thereby promoting the penetration of the DXR inhibitor into the bacteria. This is in accordance with the work reported in the literature in which the protection of (retro)hydroxamate, e.g., O-linked aryl/alkyl groups, also increases the lipophilicity [26,27]. The 5-CH₃-*cycloSal* double prodrug series (Table 2, entries 5–8) and the 5-OCH₃-*cycloSal* double prodrug series (Table 2, entries 25–28) remain inactive despite the presence of DMB. This is probably due to phosphate release rather than diffusion through the bacterial wall. In fact, these compounds with electron-donating group substituents slow down the rate of drug release, resulting in a very low concentration of the drug, preventing bacterial growth.

Table 2. *M. smegmatis* growth inhibition with double prodrugs **16–17** (800 nmoles).

Entry	R ₁	R ₂	Prodrugs	Prodrugs Inhibition Zone (mm)	Isoniazide Inhibition Zone (mm)
1	H	H	16aa	-	33
2			16ba	26	
3			17aa	19	
4			17ba	-	
5	CH ₃	H	16ab	-	28
6			16bb	-	
7			17ab	-	
8			17bb	-	
9	Cl	H	16ac	-	36
10			16bc	33	
11			17ac	25	
12			17bc	22	
13	Cl	Cl	16ad	-	35
14			16bd	16	
15			17ad	11	
16			17bd	12	
17	Br	H	16ae	8	42
18			16be	31	
19			17ae	20	
20			17be	21	
21	CF ₃	H	16af	-	24
22			16bf	25	
23			17af	19	
24			17bf	17	
25	OCH ₃	H	16ag	-	27
26			16bg	-	
27			17ag	-	
28			17bg	-	

Compared to the isoniazid inhibition zones, the best results were obtained with the 5-halogeno-*cycloSal* double prodrug series (Table 2, entries 10–12 and 17–20) and the 5-CF₃-*cycloSal* double prodrug series (Table 2, entries 21–24) which allow a more efficient release of

the parent compounds due to the presence of the electron-withdrawing substituent in *para* position of the phenolic phosphate ester bond. The loss of activity with the double prodrugs bearing two chlorine atoms at C-3 and C-5 (Table 2, entries 14–16) could be explained by the instability of these compounds and their partial hydrolysis already outside the cell. These mechanisms release the active molecule into the extracellular medium, thereby reducing the concentration of intracellular inhibitors.

It should be noted that for each series, the double prodrugs releasing phosphohydroxamic acid **4a** were inactive (Table 2, entries 3, 11, 15, 23) or only very weakly active (Table 2, entry 19) on *M. smegmatis* growth inhibition. The prodrugs releasing *N*-methylphosphohydroxamic acid **4b** (Table 2, entries 4, 12, 16, 20, 24) displayed the best antimycobacterial activity. These results are not surprising as we previously reported that compound **4a** inhibited the DXR of *M. smegmatis* as well as the fosfoxacin **3a** with IC₅₀ values in the micromolar range. In contrast, the *N*-methylated derivatives **3b** and **4b** were the most effective inhibitors with IC₅₀ values in the nanomolar range.

Bis(*cyclo*Saligenyl) prodrugs **18** were also tested on *E. coli* and *M. smegmatis* strains. As anticipated, none of the compounds was able to inhibit *E. coli* growth, the consequence of a lack of uptake. Concerning *M. smegmatis*, as previously mentioned, the Bis(*cyclo*Saligenyl) prodrugs bearing an electron-withdrawing substituent at C-5 (**18c** and **18e–f**) displayed an antimycobacterial activity, whereas the unsubstituted one (**18a**) or with electron-donating substituents (**18a–b** and **18g**) were inactive (Table 3). A clear correlation was observed between the efficacy of the *M. smegmatis* growth inhibition and the substitution of the saligenyl moiety as well as it was observed with the antiviral *cyclo*Sal pronucleotides developed by C. Meier.

Table 3. *M. smegmatis* growth inhibition with Bis(*cyclo*sal) prodrugs (800 nmoles) and isoniazide (30 nmoles).

Entry	Bis(<i>cyclo</i> sal)	Bis(<i>cyclo</i> sal) Inhibition Zone (mm)	Isoniazide Inhibition Zone (mm)
1	18a	-	35
2	18b	-	35
3	18c	31	35
4	18e	10	35
5	18f	8	24
6	18g	-	24

3. Experimental Section

3.1. Chemistry

3.1.1. General Methods

All non-aqueous reactions were run in dry solvents under an argon atmosphere. Commercial-grade reagents were purchased from Sigma-Aldrich (Burlington, MA, USA) or Acros Organics (Geel, Belgium) and used without further purification. Petroleum ether 40–60 °C (Sigma-Aldrich) was used for purification. Flash chromatography was performed on silica gel 60 (230–400) mesh with the solvent system as indicated. Automated flash chromatography was performed on a Combiflash® Rf™ (Serlabo Technologies, Entraigues-sur-la-Sorgue, France) or on a Puriflash® 215 (Interchim, Montluçon, France). TLC plates were revealed under UV light (254 nm) and/or by spraying with an ethanolic solution of phosphomolybdic acid (20%) or an ethanolic solution of potassium permanganate followed by heating.

The NMR spectra were recorded on a BRUKER Avance 300 (¹H-NMR: 300 MHz; ¹³C-NMR, 75.5 MHz; ³¹P-NMR 121.5 MHz; ¹⁹F-NMR 282.4 MHz) or a BRUKER Avance 400 (¹H-NMR: 400 MHz; ¹³C-NMR, 100.6 MHz; ³¹P-NMR 162 MHz) or a BRUKER Avance 500 (¹H-NMR: 500 MHz; ¹³C-NMR, 125.8 MHz). ¹H-NMR experiments were performed in CDCl₃, D₂O, CD₃OD in CDCl₃ with CHCl₃ (δ = 7.26 ppm), DHO (δ = 4.79 ppm), CD₂HOD

($\delta = 3.31$ ppm) as internal references. ^{13}C -NMR experiments were performed in CDCl_3 with CDCl_3 ($\delta = 77.23$ ppm), CD_2HOD ($\delta = 49.0$ ppm) as internal references. For ^{31}P -NMR reference, the spectrometer had an external reference corresponding to 80% phosphoric acid in D_2O ($\delta = 0$ ppm). The chemical shifts (δ) are expressed in ppm. s, d, t, q, or bs are abbreviations for multiplicity and correspond to singlet, doublet, triplet and quadruplet or broad singlet. J-couplings are exposed in Hz.

Most of the hydroxamate are present as two *Z* and *E* conformers in equilibrium. If only one signal is described, it is common to all conformers. The evaluation of the relative amount of the conformers was made by integration of the CH_2CO or CH_2N or OCH_2DMB proton signals.

Negative or positive-mode electrospray MS was performed on a Bruker Daltonics microTOF spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with an orthogonal electrospray (ESI) interface. Calibration was performed using a solution of 10 mM sodium formate. Sample solutions were introduced into the spectrometer source with a syringe pump (Harvard type 55-1111: Harvard Apparatus Inc., South Natick, MA, USA) with a flow rate of $5\ \mu\text{L min}^{-1}$.

General Procedure A—Reduction of Carboxylic Acid to Alcohol

A solution of carboxylic acid (1 equiv.) in dry THF (9 mL/mmol) at $0\ ^\circ\text{C}$ was treated with a 1 M solution of LiAlH_4 in THF (1.2 mL/mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched by the addition of water. The solvent was evaporated under reduced pressure, and diethyl ether was added. The organic layer was washed with a 10% aqueous solution of HCl. The aqueous layer was then saturated with NaCl and washed several times with diethyl ether. The organic layers were collected, dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness under reduced pressure.

General Procedure B—Synthesis of *cyclo*Salphosphochloridate

A solution of the alcohol **11a–g** (1 equiv.) and triethylamine (2.1 equiv.) in THF (1.9 mL/mmol) was added dropwise to a stirred solution of $\text{P}(\text{O})\text{Cl}_3$ (1.1 equiv.) in THF (1.4 mL/mmol) at $-78\ ^\circ\text{C}$. The reaction mixture was stirred overnight at room temperature. The triethylammonium chloride was filtered, and the solvent was removed under reduced pressure. The crude product was not purified by flash chromatography due to the reactivity of the product.

General Procedure C—Deprotection of Alcohol

The silylether (1 equiv.) in THF (15 mL/mmol) was treated with tetra-*N*-butylammonium fluoride (2 equiv.). The reaction mixture was monitored by TLC (EtOAc). The THF was removed under reduced pressure.

General Procedure D—Synthesis of *cyclo*Salphosphotriester

To a solution of alcohol (1 equiv.), triethylamine (1.1 equiv.), DMAP (0.5 equiv.) in dry DCM (3 mL/mmol) was treated with a solution of *cyclo*Salphosphochloridate **12a–g** (3 equiv.) in DCM (0.80 mL/mmol) at $-40\ ^\circ\text{C}$. The resulting mixture was warmed up to room temperature and stirred overnight. A saturated aqueous solution of NH_4Cl was added, and the aqueous layer was extracted with DCM. The organic layers were collected, dried over anhydrous Na_2SO_4 and filtered, and solvents were removed under reduced pressure.

General Procedure E—Synthesis of *cyclo*Salphosphotriester

The alcohol (1 eq.) was dissolved in anhydrous pyridine (2.8 mL/mmol). The mixture was cooled to $-40\ ^\circ\text{C}$, and the *cyclo*Salphosphochloridate **12a–g** (2 eq.) in toluene (1.1 mL/mmol) was added dropwise. The reaction was stirred to $-40\ ^\circ\text{C}$ for 30 min

and warmed up to room temperature overnight. The pyridine was evaporated under reduced pressure.

General Procedure F—Deprotection of Dimethoxybenzyle

The protected product (1 equiv) was stirred at room temperature in a solution at 2% or 3% of TFA in DCM (2 equiv). The reaction was monitored by TLC (EtOAc). The dichloromethane was removed under reduced pressure, and the mixture was suspended in a minimum of anhydrous methanol, filtered and evaporated under reduced pressure.

2-(Hydroxymethyl)-4-methylphenol (11b). The general procedure A was applied to synthesize the compound **11b** from the corresponding carboxylic acid (1.0 g, 6.57 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 35:65 → EtOAc/petroleum ether, 75:25) to give **11b** as a colorless solid (695 mg, 77%). $R_f = 0.57$ (EtOAc/petroleum ether, 3:7); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.45 (3H, s, CH_3), 5.01 (2H, d, $^4J = 4.7$ Hz, OCH_2Ph), 6.98 (1H, d, $^3J = 8.0$ Hz, CH_{Ar}), 7.04 (1H, s, CH_{Ar}), 7.20 (1H, bdd, $^3J = 8.2$ Hz, $^4J = 1.6$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): 20.6 (CH_3), 64.9 (OCH_2Ph), 116.5 (CH_{Ar}), 124.6 (C_{Ar}), 128.6 (CH_{Ar}), 129.5 (C_{Ar}), 130.1 (CH_{Ar}), 153.9 (C_{ArOH}).

4-Chloro-2-(hydroxymethyl)phenol (11c). The general procedure A was applied to synthesize the compound **11c** from the corresponding carboxylic acid (1.0 g, 5.79 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 20:80 → EtOAc/petroleum ether, 30:70) to give **11c** as a colorless solid (1.32 g, 88%). $R_f = 0.43$ (EtOAc/petroleum ether, 2:8); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 4.83 (2H, s, OCH_2Ph), 6.82 (1H, d, $^3J = 8.6$ Hz, CH_{Ar}), 7.02 (1H, d, $^4J = 2.4$ Hz, CH_{Ar}), 7.20 (1H, dd, $^3J = 8.7$ Hz, $^4J = 2.6$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): 64.4 (OCH_2Ph), 118.2 (CH_{Ar}), 124.9 (C_{Ar}), 126.1 (C_{Ar}), 127.6 (CH_{Ar}), 129.9 (CH_{Ar}), 154.9 (C_{ArOH}).

2,4-Dichloro-6-(hydroxymethyl)phenol (11d). The general procedure A was applied to synthesize the compound **11d** from the corresponding carboxylic acid (2.20 g, 10.6 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 20:80) to give **11d** as a colorless solid (1.45 g, 71%). $R_f = 0.53$ (EtOAc/petroleum ether, 2:8); $^1\text{H-NMR}$ (400 MHz, CDCl_3): 4.77 (2H, s, OCH_2Ph), 7.12 (1H, d, $^4J = 2.4$ Hz, CH_{Ar}), 7.28 (1H, d, $^4J = 2.4$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): 62.4 (OCH_2Ph), 121.2 (C_{Ar}), 125.4 (C_{Ar}), 126.9 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (C_{Ar}), 149.1 (C_{ArOH}).

4-Bromo-2-(hydroxymethyl)phenol (11e). The general procedure A was applied to synthesize the compound **11e** from the corresponding carboxylic acid (1.76 g, 8.10 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 20:80 → EtOAc/petroleum ether, 40:60) to give **11e** as a colorless solid (1.21 g, 74%). $R_f = 0.47$ (EtOAc/petroleum ether, 2:8); $^1\text{H-NMR}$ (500 MHz, CD_3OD): 4.60 (2H, s, OCH_2Ph), 6.68 (1H, d, $^3J = 8.6$ Hz, CH_{Ar}), 7.18 (1H, dd, $^3J = 8.5$ Hz, $^4J = 2.5$ Hz, CH_{Ar}), 7.40 (1H, d, $^4J = 2.5$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (125.8 MHz, CD_3OD): 60.3 (OCH_2Ph), 112.2 (C_{Ar}), 117.6 (CH_{Ar}), 131.5 (CH_{Ar}), 131.6 (C_{Ar}), 131.8 (CH_{Ar}), 155.4 (C_{ArOH}).

2-(Hydroxymethyl)-4-(trifluoromethyl)phenol (11f) Step1: Iodocyclohexane (5 mL, 45.4 mmol) was added to a solution of 2-(methoxy)-5-(trifluoromethyl)benzoic acid (1 g, 4.54 mmol) in DMF (5 mL). The mixture was refluxed for 4 h, and then the DMF was evaporated under reduced pressure. The resulting oil was dissolved in DCM (40 mL) and washed with a saturated aqueous solution of NaHCO_3 (2 × 50 mL). The aqueous layer was acidified with a 10% HCl solution until a pH = 2 was obtained. The aqueous layer was then extracted with DCM (3 × 70 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness under reduced pressure. The crude product (1.95 g) was not purified and directly reduced with LiAlH_4 . $R_f = 0.68$ (EtOAc/petroleum ether, 5:5); $^1\text{H-NMR}$ (400 MHz, CD_3OD): 7.05 (1H, d, $^3J = 8.6$ Hz, CH_{Ar}), 7.74 (1H, dd, $^3J = 8.8$ Hz, $^4J = 2.2$ Hz, CH_{Ar}), 8.13 (1H, d, $^4J = 2.0$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (125.8 MHz, CD_3OD): 114.3 (C_{Ar}), 119.5 (CH_{Ar}), 122.5 (q, $^2J_{\text{C-F}} = 32.9$ Hz, C_{ArCF_3}), 125.6 (q, $^1J_{\text{C-F}} = 269.4$ Hz, C_{ArCF_3}), 129.1 (q,

$^3J_{C-F} = 4.0$ Hz, CH_{Ar}), 133.1 (q, $^3J_{C-F} = 3.0$ Hz, CH_{Ar}), 165.9 (C_{Ar}), 172.6 (CO); ^{19}F -NMR (282.4 MHz, CD_3OD): -64.4 .

Step 2: The general procedure A was applied to synthesize the compound **11f** from the freshly prepared carboxylic acid (see step 1) (935 mg, 4.54 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 20:80 $\rightarrow$ EtOAc/petroleum ether, 40:60) to give **11f** as a colorless solid (473 mg, 54%). $R_f = 0.47$ (EtOAc/petroleum ether, 2:8); 1H -NMR (400 MHz, $CDCl_3$): 4.94 (2H, s, OCH_2Ph), 6.96 (1H, d, $^3J = 8.5$ Hz, CH_{Ar}), 7.30 (1H, s, CH_{Ar}), 7.47 (1H, dd, $^3J = 8.5$ Hz, $^4J = 1.9$ Hz, CH_{Ar}), 7.80 (1H, d, $C_{Ar}OH$); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 64.7 (OCH_2Ph), 117.2 (CH_{Ar}), 122.5 (q, $^2J_{C-F} = 33.1$ Hz, $C_{Ar}CF_3$), 124.6 (C_4°), 125.1 (q, $^3J_{C-F} = 3.3$ Hz, CH_{Ar}), 127.0 (q, $^3J_{C-F} = 3.6$ Hz, CH_{Ar}), 159.3 (C_{Ar}); ^{19}F -NMR (282.4 MHz, $CDCl_3$): -62.5 .

2-(Hydroxymethyl)-4-methoxyphenol (11g). To a solution of 2-hydroxy-5-methoxybenzoic acid (3 g, 17.8 mmol), $NaBH_4$ (1.55, 41 mmol) in THF (47 mL) was added a solution of $BF_3 \cdot Et_2O$ (3.3 mL, 26.7 mmol) in THF (12 mL) and refluxed overnight. The reaction mixture was cooled, poured into H_2O (50 mL) and extracted with EtOAc (3×100 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (3×100 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified by automated chromatography (petroleum ether $\rightarrow$ EtOAc/petroleum ether, 5:5) to give a colorless solid (2.18 g, 86%). $R_f = 0.38$ (EtOAc/petroleum ether, 3:7); 1H -NMR (500 MHz, $CDCl_3$): 3.75 (3H, s, OCH_3), 4.81 (2H, s, OCH_2Ph), 6.61 (1H, d, $^4J = 2.9$ Hz, CH_{Ar}), 6.76 (1H, dd, $^3J = 9.0$ Hz, $^4J = 2.7$ Hz, CH_{Ar}), 6.81 (1H, d, $^3J = 8.7$ Hz, CH_{Ar}); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 56.0 (OCH_3), 64.9 (OCH_2Ph), 113.6 (CH_{Ar}), 114.6 (CH_{Ar}), 117.4 (CH_{Ar}), 125.6 (C_{Ar}), 150.0 (C_{Ar}), 153.3 (C_{Ar}).

2-Chloro-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12a). The product was obtained as a colorless oil according to general procedure B. $R_f = 0.91$ (EtOAc/petroleum ether, 5:5); 1H -NMR (400 MHz, $CDCl_3$): 5.44–5.53 (2H, m, OCH_2Ph), 7.11 (2H, dd, $^3J = 7.9$ Hz, $^3J = 7.9$ Hz, CH_{Ar}), 7.23 (1H, dd, $^3J = 7.9$ Hz, $^3J = 7.7$ Hz, CH_{Ar}), 7.37 (1H, dd, $^3J = 7.9$ Hz, $^3J = 7.9$ Hz, CH_{Ar}); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -6.03 .

2-Chloro-6-methyl-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12b). The product was obtained as a slightly yellow oil according to general procedure B. $R_f = 0.93$ (EtOAc/petroleum ether, 5:5); 1H -NMR (400 MHz, $CDCl_3$): 2.34 (3H, s, CH_3), 5.39–5.48 (2H, m, OCH_2Ph), 6.91 (1H, s, CH_{Ar}), 6.98 (1H, d, $^3J = 8.4$ Hz, CH_{Ar}), 7.15 (1H, d, $^3J = 8.4$ Hz, CH_{Ar}); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -5.84 .

2,6-Dichloro-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12c). The product was obtained as a colorless oil according to general procedure B. $R_f = 0.88$ (EtOAc/petroleum ether, 3:7); 1H -NMR (400 MHz, $CDCl_3$): 5.40–5.50 (2H, m, OCH_2Ph), 6.91 (1H, d, $^3J = 8.7$ Hz, CH_{Ar}), 7.13 (1H, d, $^4J = 2.4$ Hz, CH_{Ar}), 7.33–7.36 (1H, m, CH_{Ar}); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -6.66 .

2,6,8-Trichloro-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12d). The product was obtained as a yellow oil according to general procedure B. $R_f = 0.33$ (EtOAc/petroleum ether, 15:85); 1H -NMR (400 MHz, $CDCl_3$): 5.41–5.49 (2H, m, OCH_2Ph), 7.05 (1H, m, CH_{Ar}), 7.46 (1H, s, CH_{Ar}); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -6.81 .

6-Bromo-2-chloro-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12e). The product was obtained as a yellow oil according to general procedure B. 1H -NMR (300 MHz, $CDCl_3$): 5.38–5.54 (2H, m, OCH_2Ph), 7.00 (1H, d, $^3J = 8.7$ Hz, CH_{Ar}), 7.27–7.28 (1H, s, CH_{Ar}), 7.46–7.50 (1H, m, CH_{Ar}); ^{31}P -NMR (121.5 MHz, $CDCl_3$): -6.48 .

2-Chloro-6-(trifluoromethyl)-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12f). The product was obtained as a yellow oil according to general procedure B. 1H -NMR (400 MHz, $CDCl_3$): 5.49–5.58 (2H, m, OCH_2Ph), 7.24 (1H, d, $^3J = 8.6$ Hz, CH_{Ar}), 7.43 (1H, s, CH_{Ar}), 7.66 (1H, d, $^3J = 8.2$ Hz, CH_{Ar}); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -6.99 ; ^{19}F -NMR (282.4 MHz, $CDCl_3$): -63.4 .

2-Chloro-6-methoxy-4H-benzo[d][1,3,2]dioxaphosphinine 2-oxide (12g). The product was obtained as a yellow oil according to general procedure B. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 5.40–5.50 (2H, m, OCH_2Ph), 6.60 (1H, d, $^4J = 3.3$ Hz, CH_{Ar}), 6.87–6.89 (1H, m, CH_{Ar}), 7.03 (1H, d, $^3J = 8.9$ Hz, CH_{Ar}); $^{31}\text{P-NMR}$ (121.5 MHz, CDCl_3): -5.87 .

O-(2,4-Dimethoxybenzyl)hydroxylamine Step 1: *N*-hydroxyphthalimide (5.00 g, 29.6 mmol) and 2,4-dimethoxybenzyl alcohol (4.96 g, 30.4 mmol) were stirred in dichloromethane (220 mL) at 0°C . Triphenyl phosphine (12.2 g, 46.5 mmol) was added, followed by diisopropylazodicarboxylate (9.0 mL, 45.7 mmol). The resulting solution was stirred at room temperature for 24 h. The dichloromethane was removed under reduced pressure, and the resulting oil was recrystallized in boiling ethanol (200 mL) to give colorless crystals (6.32 g, 68%). $R_f = 0.55$ (EtOAc/petroleum ether, 3:7); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.72 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.21 (2H, s, CH_2), 6.39–6.44 (2H, m, Ar-H), 7.31 (1H, d, $^3J = 8.4$ Hz, Ar-H), 7.70–7.79 (4H, m, Ar-H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): 55.4 (OCH_3), 55.7 (OCH_3), 74.5 (CH_2), 98.6–134.3 (CH_{Ar} and C_{Ar}), 160.1 ($\text{H}_3\text{CO-C}_{\text{Ar}}$), 162.4 ($\text{H}_3\text{CO-C}_{\text{Ar}}$), 163.7 (C=O); MS (EI) $^+$: m/z calculated for $\text{C}_{17}\text{H}_{15}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 336.08, found 336.08.

Step 2: *N*-(2,4-dimethoxybenzyloxy)phthalimide previously synthesized (3 g, 9.6 mmol) was stirred in refluxing ethanol (100 mL). *N*-methylhydrazine was added, and the resulting mixture was stirred at reflux for 1 h. The ethanol was removed under reduced pressure, and the ether was added. The mixture was stirred for 30 min. The solid was filtered, and the solvent was removed to give an oil (1.93 g) slightly contaminated by phthalimide. $R_f = 0.52$ (EtOAc/petroleum ether, 5:5); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.66 (2H, s, CH_2), 5.38 (2H, bs, NH_2), 6.44–6.46 (2H, m, Ar-H), 7.22 (1H, d, $^3J = 8.8$ Hz, Ar-H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): 55.5 (OCH_3), 55.7 (OCH_3), 73.1 (CH_2), 98.8–131.8 (CH_{Ar} and C_{Ar}), 159.3 ($\text{H}_3\text{CO-C}_{\text{Ar}}$), 161.3 ($\text{H}_3\text{CO-C}_{\text{Ar}}$).

2-((*t*-Butyldimethylsilyl)oxy)ethan-1-ol (13). Sodium hydride (475 mg, 18.2 mmol) was suspended in THF (36 mL). The resulting mixture was cooled to 0°C , the ethylene glycol (1 mL, 17.7 mmol) was added dropwise, and the mixture was stirred for 1 h. A solution of *t*-butyldimethylsilyl chloride (2.74 g, 18.0 mmol) in THF (8 mL) was added over a period of 10 min. The resulting mixture was stirred for 4 h at room temperature. A saturated aqueous solution of NaHCO_3 (40 mL) was added, and the mixture was extracted with EtOAc (2×40 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (2×40 mL). The collected organic layers were dried over anhydrous Na_2SO_4 , filtered, and solvents were removed under reduced pressure. The crude was purified by flash chromatography (EtOAc/petroleum ether, 2:8) to give the compound **13** as a colorless oil (2.48 g, 80%). $R_f = 0.25$ (EtOAc/petroleum ether, 1:9); $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.08 (6H, s, Si- CH_3), 0.91 (9H, s, Si-*t*-Bu), 1.99 (1H, bs, OH), 3.62–3.65 (2H, m, CH_2OTBDMS), 3.70–3.73 (2H, m, CH_2OH); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): -5.1 (Si- CH_3), 18.5 (C_4° of *t*-Bu), 26.1 (CH_3 of *t*-Bu), 63.9 (CH_2OTBDMS), 64.3 (CH_2OH).

N-(2-((*t*-butyldimethylsilyl)oxy)ethyl)-O-(2,4-dimethoxybenzyl) (14). To a solution of **13** (500 mg, 2.8 mmol) in DCM (35 mL), 2,6-lutidine (0.40 mL, 3.4 mmol) was added. The solution was cooled down to -78°C , and the trifluoromethanesulfonic anhydride (470 μL , 2.8 mmol) was added dropwise. The resulting mixture was stirred at -78°C for 1 h, and *O*-(2,4-dimethoxybenzyl)hydroxylamine (770 mg, 4.2 mmol) in DCM (20 mL) was added dropwise. The solution was stirred at -78°C for 1 h, warmed up to room temperature, and stirred for another 2 h. The reaction mixture was diluted with DCM (30 mL) and washed with a saturated aqueous solution of NH_4Cl (60 mL), a saturated solution of NaHCO_3 (60 mL), water (60 mL) and brine (60 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvents were removed under reduced pressure to give a pale yellow oil. The crude was purified by flash chromatography (petroleum ether $\rightarrow$ EtOAc/petroleum ether, 15:85) to give the product **14** as a colorless oil (424 mg, 44%). $R_f = 0.46$ (EtOAc/petroleum ether, 1:9); $^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.04 (6H, s, Si- CH_3), 0.87 (9H, s, *t*-Bu), 3.03 (2H, t, $^3J = 5.3$ Hz, CH_2N), 3.73 (2H, t, $^3J = 5.3$ Hz, CH_2OTBDMS), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.70

(2H, s, OCH₂DMP), 6.45–6.48 (2H, m, CH_{Ar}), 7.23 (1H, m, CH_{Ar}); ¹³C-NMR (75.5 MHz, CDCl₃): −5.2 (Si-CH₃), 18.5 (C₄^o of *t*Bu), 26.1 (CH₃ of *t*Bu), 53.9 (CH₂N), 55.6 (OCH₃), 55.7 (OCH₃), 59.6 (CH₂OTBDMS), 70.1 (OCH₂DMP), 98.7 (CH_{Ar}), 104.0 (CH_{Ar}), 118.6 (C_{Ar}), 131.5 (CH_{Ar}), 159.1 (C_{Ar}OCH₃), 161.1 (C_{Ar}OCH₃); MS (EI)⁺: *m/z* calculated for C₁₇H₃₁NO₄SiNa [M + Na]⁺ 364.19 found 364.19.

N-(2-((*t*-Butyldimethylsilyl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)formamide (**15a**). A solution of formic acid (1.11 mL, 29.5 mmol) and acetic anhydride (0.56 mL, 5.9 mmol) was stirred at room temperature for 30 min. The solution was then cooled to 0 °C, and a solution of protected hydroxylamine **14** (200 mg, 0.59 mmol) in a minimum of THF was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, allowed to warm up at room temperature, and stirred overnight. The reaction mixture was diluted with EtOAc, and the organic layer was washed twice with water and twice with a 0.1 M aqueous solution of KOH. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 2:8) to give **15a** as a colorless oil (180 mg, 83%) and as a mixture of the two *Z* and *E* conformers in a 30:70 ratio. R_f = 0.43 (EtOAc/petroleum ether, 2:8); ¹H-NMR (300 MHz, CDCl₃): 0.06 (6H, s, Si-CH₃), 0.88 (9H, s, *t*Bu), 3.44–3.83 (10H, m, OCH₂CH₂N and OCH₃), 4.86 (7/10H of 2H, bs, OCH₂DMP), 4.96 (3/10H of 2H, bs, OCH₂DMP), 6.45–6.47 (2H, m, CH_{Ar}), 7.17 (1H, d, ²*J* = 7.0 Hz, CH_{Ar}), 7.92 (3/10H of 1H, bs, CHO), 8.19 (7/10H of 1H, bs, CHO); ¹³C-NMR (75.5 MHz, CDCl₃): −5.2 (Si-CH₃), 18.5 (C₄^o of *t*Bu), 26.1 (CH₃ of *t*Bu), 47.4 (CH₂N), 51.8 (CH₂N), 55.6 (OCH₃), 55.7 (OCH₃), 58.8 (CH₂OTBDMS), 59.3 (CH₂OTBDMS), 71.4 (OCH₂DMP), 72.9 (OCH₂DMP), 98.8 (CH_{Ar}), 104.3 (CH_{Ar}), 115.4 (C_{Ar}), 133.0 (CH_{Ar}), 159.0 (CHO), 159.7 (C_{Ar}OCH₃), 162.2 (C_{Ar}OCH₃), 163.6 (CHO); MS (EI)⁺: *m/z* calculated for C₁₈H₃₁NO₅SiNa [M + Na]⁺ 392.19, found 392.18.

N-(2-((*t*-Butyldimethylsilyl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)acetamide (**15b**). To a solution of *N*-H hydroxylamine **14** (116 mg, 0.34 mmol) in acetic anhydride (4 mL/mmole) was added dropwise pyridine (0.08 mL, 1.02 mmole equiv). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated to dryness under reduced pressure. The product **15b** was obtained without purification as a colorless oil (128 mg, 98%) and as the sole *E* conformer. R_f = 0.29 (EtOAc/petroleum ether, 1:9); ¹H-NMR (300 MHz, CDCl₃): 0.05 (6H, s, Si-CH₃), 0.88 (9H, s, *t*Bu), 2.83 (3H, s, COCH₃), 3.78–3.83 (10H, m, OCH₂CH₂N and OCH₃), 4.83 (2H, s, OCH₂DMP), 6.45–6.48 (2H, m, CH_{Ar}), 7.17 (1H, d, ²*J* = 9.0 Hz, CH_{Ar}); ¹³C-NMR (75.5 MHz, CDCl₃): −5.2 (Si-CH₃), 18.5 (C₄^o of *t*Bu), 22.4 (COCH₃), 26.1 (CH₃ of *t*Bu), 49.1 (CH₂N), 55.5 (OCH₃), 55.6 (OCH₃), 59.6 (CH₂OTBDMS), 71.4 (OCH₂DMP), 98.8 (CH_{Ar}), 104.3 (CH_{Ar}), 115.7 (C_{Ar}), 132.7 (CH_{Ar}), 159.6 (C_{Ar}OCH₃), 162.1 (C_{Ar}OCH₃), 166.6 (COCH₃); MS (EI)⁺: *m/z* calculated for C₁₉H₃₃NO₅SiNa [M + Na]⁺ 406.20, found 406.20.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-hydroxyethyl)formamide (**9a**). The general procedure C was applied to synthesize the compound **9a** from protected alcohol **15a** (200 mg, 0.59 mmol). The crude product was purified by flash chromatography (EtOAc) to give **9a** as a colorless oil (97 mg, 76%) and as a mixture of the two *Z* and *E* conformers in a 30:70 ratio. R_f = 0.37 (EtOAc); ¹H-NMR (500 MHz, CDCl₃): 2.70 (1H, bs, OH), 3.42–3.84 (10H, m, OCH₂CH₂N and OCH₃), 4.87 (7/10H of 2H, bs, OCH₂DMP), 5.02 (3/10H of 2H, bs, OCH₂DMP), 6.45–6.47 (2H, m, CH_{Ar}), 7.17 (1H, d, ²*J* = 8.1 Hz, CH_{Ar}), 7.96 (3/10H of 1H, bs, CHO), 8.22 (7/10H of 1H, bs, CHO); ¹³C-NMR (75.5 MHz, CDCl₃): 48.7 (CH₂N), 53.5 (CH₂N), 55.6 (OCH₃), 55.7 (OCH₃), 60.8 (CH₂OH), 71.5 (OCH₂DMP), 73.2 (OCH₂DMP), 98.8 (CH_{Ar}), 104.6 (CH_{Ar}), 114.9 (C_{Ar}), 132.2 (CH_{Ar}), 159.7 (C_{Ar}OCH₃), 162.4 (C_{Ar}OCH₃), 164.2 (CHO); MS (EI)⁺: *m/z* calculated for C₁₂H₁₇NO₅Na [M + Na]⁺ 278.0999, found 278.0980.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-hydroxyethyl)acetamide (**9b**). The general procedure C was applied to synthesize the compound **9b** from protected alcohol **15b** (200 mg, 0.59 mmol). The crude product was purified by flash chromatography (EtOAc) to give **9b** as a colorless oil (133 mg, 80%) and as the sole *E* conformer. R_f = 0.48 (EtOAc);

$^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.13 (3H, s, COCH_3) 3.80–3.84 (10H, m, $\text{OCH}_2\text{CH}_2\text{N}$ and OCH_3), 4.83 (2H, s, OCH_2DMP), 6.46–6.49 (2H, m, CH_{Ar}), 7.19 (1H, d, $^2J = 9.0$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): 20.4 (COCH_3), 50.4 (CH_2N), 55.6 (OCH_3), 55.7 (OCH_3), 61.8 (CH_2OH), 71.9 (OCH_2DMP), 98.9 (CH_{Ar}), 104.5 (CH_{Ar}), 115.1 (C_{Ar}), 133.0 (CH_{Ar}), 159.7 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.4 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 174.2 (COCH_3); MS (EI) $^+$: m/z calculated for $\text{C}_{13}\text{H}_{19}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 292.12, found 292.12.

N-((2,4-Dimethoxybenzyl)oxy)-3-hydroxypropanamide (**10a**). A stirred suspension of *O*-protected hydroxylamine (3.06 g, 16.7 mmol) in dry THF (4.5 mL/mmol) at -78°C was treated with 1 M solution of LiHMDS (55.5 mL, 55.5 mmol). After 1 h, a solution of β -propiolactone (0.70 mL, 11.1 mmol) in a minimum of THF was added. The resulting solution was stirred overnight at room temperature. The reaction was cooled at -78°C , quenched with a saturated aqueous solution of NH_4Cl , warmed to room temperature and extracted several times with EtOAc. The collected organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated to dryness under reduced pressure. The crude product was dissolved in THF and treated with TBAF(H_2O) $_3$ (1.5 equiv). After total consumption of the starting material, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc $\rightarrow$ EtOAc/MeOH, 90:10) to give the product **10a** (1.45 g, 51%) as a colorless solid and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. $R_f = 0.24$ (EtOAc); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.30 (6/10H of 2H, bs, CH_2CO), 2.63 (4/10H of 2H, bs, CH_2CO), 2.91 (1H, bs, OH), 3.79–3.84 (8H, m, OCH_3 and CH_2OH), 4.80 (4/10H of 2H, bs, OCH_2DMP), 4.91 (6/10H of 2H, bs, OCH_2DMP), 6.44–6.48 (2H, m, CH_{Ar}), 7.22 (1H, m, CH_{Ar}), 8.16 (4/10 of 1H, bs, NH), 8.58 (6/10 of 1H, bs, NH); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): 33.5 (CH_2CO), 35.6 (CH_2CO), 55.5 (OCH_3), 55.6 (OCH_3), 58.1 (CH_2OH), 58.6 (CH_2OH), 73.2 (OCH_2DMP), 74.6 (OCH_2DMP), 98.6 (CH_{Ar}), 104.1 (CH_{Ar}), 114.9 (C_{Ar}), 155.9 (C_{Ar}), 132.8 (CH_{Ar}), 159.5 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 161.8 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.3 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 169.8 (CO), 176.6 (CO); MS (EI) $^+$: m/z calculated for $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 278.10, found 278.10.

N-((2,4-Dimethoxybenzyl)oxy)-3-hydroxy-*N*-methylpropanamide (**10b**). To a solution of **10a** (267 mg, 1.05 mmol), anhydrous K_2CO_3 (290 mg, 2.1 mmol) in anhydrous acetone (10.5 mL/mmol) was added iodomethane (0.33 mL, 5.25 mmol). The resulting mixture was refluxed overnight. The mixture was filtered, and acetone was removed under reduced pressure. The resulting oil was dissolved in ether. The organic layer was washed with water, and then the aqueous layer was saturated with NaCl and extracted with EtOAc. The organic layers were collected, dried over anhydrous Na_2SO_4 , filtered and evaporated. The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 7:3 $\rightarrow$ EtOAc) to give **10b** as a yellow oil (243 mg, 86%) as a sole *E* conformer. $R_f = 0.44$ (EtOAc/petroleum ether, 7:3); $^1\text{H-NMR}$ (500 MHz, CDCl_3): 2.63 (2H, t, $^3J = 5.6$ Hz, CH_2CO), 3.23 (4H, ds, NCH_3 and OH), 3.79–3.84 (8H, m, OCH_3 and CH_2OH), 4.80 (2H, s, OCH_2DMP), 6.46–6.48 (2H, m, CH_{Ar}), 7.18 (1H, d, $^3J = 8.9$ Hz, CH_{Ar}); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): 33.1 (NCH_3), 34.0 (CH_2CO), 55.6 (OCH_3), 58.8 (CH_2OH), 71.1 (OCH_2DMP), 98.8 (CH_{Ar}), 104.4 (CH_{Ar}), 115.1 (C_{Ar}), 132.9 (CH_{Ar}), 159.67 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.3 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 174.7 (CO); MS (EI) $^+$: m/z calculated for $\text{C}_{13}\text{H}_{19}\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 292.12, found 292.12.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-formamide (**17a**). The general procedure D was applied to synthesize the compound **17aa** from alcohol **9a** (172 mg, 0.67 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 8:2) to give **17aa** as a colorless oil (187 mg, 66%) and as a mixture of the two *Z* and *E* conformers in a 20:80 ratio. $R_f = 0.49$ (EtOAc/cyclohexane, 8:2); $^1\text{H-NMR}$ (400 MHz, CDCl_3): 3.57–3.95 (8H, m, NCH_2 and OCH_3), 4.38 (2H, bs, POCH_2), 4.80 (8/10H of 2H, bs, OCH_2DMP), 4.96 (2/10 of 2H, bs, OCH_2DMP), 5.25–5.39 (2H, m, ArCH_2OP), 6.43–6.45 (2H, m, $\text{CH}_{\text{Ar}}(\text{DMB})$), 7.03 (2H, t, $^3J = 8.2$ Hz, $\text{CH}_{\text{Ar}}(\text{cycloSal})$), 7.11 (2H, m, $\text{CH}_{\text{Ar}}(\text{cycloSal})$ and $\text{CH}_{\text{Ar}}(\text{DMB})$), 7.28 (1H, m, $\text{CH}_{\text{Ar}}(\text{cycloSal})$), 7.87 (2/10H of 1H, bs, CHO), 8.06 (8/10 of 1H, bs, CHO); $^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): 44.6 (d, $^3J_{\text{CP}} = 7.0$ Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 63.9 (d, $^2J_{\text{CP}} = 4.4$ Hz, POCH_2), 69.0 (d, $^2J_{\text{CP}} = 6.9$ Hz, ArCH_2OP), 73.2 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar}}(\text{DMB})$), 104.4 ($\text{CH}_{\text{Ar}}(\text{DMB})$), 114.9 ($\text{C}_{\text{Ar}}(\text{DMB})$), 118.9 (d, $^3J_{\text{CP}} = 8.7$ Hz,

$\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 120.7 (d, $^3J_{\text{CP}} = 8.7$ Hz, $\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 124.5 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 125.4 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 129.9 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 133.1 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 150.1 (d, $^2J_{\text{CP}} = 6.6$ Hz, $\text{C}_{\text{Ar}}\text{OP}$), 159.7 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.4 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 163.7 (CHO); ^{31}P -NMR (162.0 MHz, CDCl_3): -9.89 ; MS (EI) $^+$: m/z calculated for $\text{C}_{19}\text{H}_{22}\text{NO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 446.10, found 446.09.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((6-methyl-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)formamide (**17ab**). The general procedure D was applied to synthesize the compound **17ab** from alcohol **9a** (61 mg, 0.24 mmol). The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 6:4 $\rightarrow$ EtOAc) to give **17ab** as a colorless oil (30 mg, 46%) and as a mixture of two *Z* and *E* conformers in a 20:80 ratio. $R_f = 0.35$ (EtOAc/petroleum ether, 7:3); ^1H -NMR (400 MHz, CDCl_3): 2.30 (3H, s, CH_3Ar), 3.78–3.88 (8H, m, NCH_2 and OCH_3), 4.35–4.38 (2H, bs, POCH_2), 4.80 (8/10H of 2H, bs, OCH_2DMP), 4.97 (2/10 of 2H, bs, OCH_2DMP), 5.20–5.31 (2H, m, ArCH_2OP), 6.42–6.46 (2H, m, $\text{CH}_{\text{Ar}(\text{DMB})}$), 6.83 (1H, bs, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 6.90 (1H, d, $^3J = 8.4$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.07 (1H, d, $^3J = 8.4$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.12–7.15 (1H, m, $\text{CH}_{\text{Ar}(\text{DMB})}$), 7.86 (2/10H of 1H, bs, CHO), 8.07 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, CDCl_3): 20.9 (CH_3Ar), 44.7 (d, $^3J_{\text{CP}} = 5.8$ Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 63.9 (POCH_2), 69.1 (d, $^2J_{\text{C-P}} = 7.0$ Hz, ArCH_2OP), 73.2 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 104.5 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 114.9 ($\text{C}_{\text{Ar}(\text{DMB})}$), 118.7 (d, $^3J_{\text{C-P}} = 7.9$ Hz, $\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 120.3 (d, $^3J_{\text{C-P}} = 8.9$ Hz, $\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 125.7 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 130.4 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 133.1 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 134.2 ($\text{C}_{\text{Ar}}\text{CH}_3$), 148.1 ($\text{C}_{\text{Ar}}\text{OP}$), 159.7 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.4 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 163.8 (CHO); ^{31}P -NMR (162.0 MHz, CDCl_3): -9.7 ; HRMS (EI) $^+$: m/z calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 460.1132, found 460.1116.

N-(2-((6-Chloro-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)formamide (**17ac**). The general procedure D was applied to synthesize compound **17ac** from alcohol **9a** (169 mg, 0.66 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 8:2) to give **17ac** as a colorless oil (155 mg, 51%) and as a mixture of the two *Z* and *E* conformers in a 20:80 ratio. $R_f = 0.51$ (EtOAc/cyclohexane, 8:2); ^1H -NMR (400 MHz, CDCl_3): 3.82–3.88 (8H, m, NCH_2 and OCH_3), 4.39 (2H, bs, POCH_2), 4.80 (8/10H of 2H, bs, OCH_2DMP), 4.96 (2/10 of 2H, bs, OCH_2DMP), 5.18–5.34 (2H, m, ArCH_2OP), 6.43–6.46 (2H, m, $\text{CH}_{\text{Ar}(\text{DMB})}$), 6.94 (1H, d, $^3J = 8.7$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.03 (1H, s, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.12 (1H, d, $^3J = 6.9$ Hz, $\text{CH}_{\text{Ar}(\text{DMB})}$), 7.25 (1H, d, $^3J = 8.8$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.89 (2/10H of 1H, bs, CHO), 8.07 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, CDCl_3): 44.6 (d, $^3J_{\text{CP}} = 6.0$ Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 64.2 (POCH_2), 68.5 (d, $^2J_{\text{CP}} = 6.9$ Hz, ArCH_2OP), 73.2 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 104.5 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 114.9 ($\text{C}_{\text{Ar}(\text{DMB})}$), 120.4 (d, $^3J_{\text{CP}} = 9.5$ Hz, $\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 122.1 (d, $^3J_{\text{CP}} = 10.2$ Hz, $\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 125.4 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 129.7 ($\text{C}_{\text{Ar}}\text{Cl}$), 129.9 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 133.1 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 147.7 (d, $^2J_{\text{CP}} = 6.4$ Hz, $\text{C}_{\text{Ar}}\text{OP}$), 159.7 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 162.4 ($\text{C}_{\text{Ar}}\text{OCH}_3$), 163.7 (CHO); ^{31}P -NMR (162.0 MHz, CDCl_3): -10.4 ; HRMS (EI) $^+$: m/z calculated for $\text{C}_{19}\text{H}_{21}\text{ClNO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 480.0556, found 480.0556.

N-(2-((6,8-Dichloro-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)formamide (**17ad**). The general procedure D was applied to synthesize compound **17ad** from alcohol **9a** (185 mg, 0.73 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 8:2) to give **17ad** as a colorless oil (177 mg, 49%) and as a mixture of two *Z* and *E* conformers in a 20:80 ratio. $R_f = 0.51$ (EtOAc/cyclohexane, 8:2); ^1H -NMR (400 MHz, CDCl_3): 3.82–3.90 (8H, m, NCH_2 and OCH_3), 4.41 (2H, bs, POCH_2), 4.80 (8/10H of 2H, bs, OCH_2DMP), 4.94 (2/10 of 2H, bs, OCH_2DMP), 5.19–5.34 (2H, m, ArCH_2OP), 6.46 (2H, bs, $\text{CH}_{\text{Ar}(\text{DMB})}$), 6.94 (1H, bs, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.14 (1H, m, $\text{CH}_{\text{Ar}(\text{DMB})}$), 7.35 (1H, bs, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.91 (2/10H of 1H, bs, CHO), 8.06 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, CDCl_3): 44.4 (d, $^3J_{\text{CP}} = 6.0$ Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 64.5 (POCH_2), 68.4 (d, $^2J_{\text{CP}} = 6.9$ Hz, ArCH_2OP), 73.2 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 104.5 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 114.8 ($\text{C}_{\text{Ar}(\text{DMB})}$), 123.4 (d, $^3J_{\text{CP}} = 9.5$ Hz, $\text{ClC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 123.7 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 124.9 ($\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 129.6 ($\text{C}_{\text{Ar}}\text{Cl}$), 130.2 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 133.1 ($\text{CH}_{\text{Ar}(\text{DMB})}$), 145.0 ($\text{C}_{\text{Ar}}\text{OP}$),

159.7 ($C_{Ar}OCH_3$), 162.4 ($C_{Ar}OCH_3$), 163.7 (CHO); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -10.9 ; MS (EI) $^+$: m/z calculated for $C_{19}H_{20}Cl_2NO_8PNa$ [$M + Na$] $^+$ 514.02, found 514.02.

N-(2-((6-Bromo-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)formamide (**17ae**). The general procedure D was applied to synthesize compound **17ae** from alcohol **9a** (60 mg, 0.24 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 $\rightarrow$ EtOAc/petroleum ether, 7:3) to give **17ae** as a colorless oil (44 mg, 37%) and as a mixture of the two *Z* and *E* conformers in a 20:80 ratio. R_f = 0.57 (EtOAc/petroleum ether, 7:3); 1H -NMR (400 MHz, $CDCl_3$): 3.76–3.95 (8H, m, NCH_2 and OCH_3), 4.38 (2H, bs, $POCH_2$), 4.80 (8/10H of 2H, bs, OCH_2DMP), 4.95 (2/10 of 2H, bs, OCH_2DMP), 5.22 (1H, dd, 2J = 14.7 Hz, $^3J_{P-H}$ = 18.3 Hz, $ArCH_2OP$), 5.31 (1H, dd, 2J = 14.3 Hz, $^3J_{P-H}$ = 8.0 Hz, $ArCH_2OP$), 6.44–6.46 (2H, m, $CH_{Ar(DMB)}$), 6.89 (1H, d, 3J = 8.7 Hz, $CH_{Ar(cycloSal)}$), 7.11–7.17 (2H, m, $CH_{Ar(DMB)}$ and $CH_{Ar(cycloSal)}$), 7.38 (1H, d, 3J = 8.7 Hz, $CH_{Ar(cycloSal)}$), 7.89 (2/10H of 1H, bs, CHO), 8.06 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 44.5 (d, $^3J_{CP}$ = 6.9 Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 64.1 ($POCH_2$), 64.2 (d, $^2J_{C-P}$ = 4.5 Hz, $POCH_2$), 68.3 (d, $^2J_{C-P}$ = 6.7 Hz, $ArCH_2OP$), 73.2 (OCH_2DMP), 98.8 ($CH_{Ar(DMB)}$), 104.5 ($CH_{Ar(DMB)}$), 114.8 ($C_{Ar(DMB)}$), 117.0 ($C_{Ar}Br$), 120.7 (d, $^3J_{C-P}$ = 8.6 Hz, $CH_{Ar}C_{Ar}OP$), 122.6 (d, $^3J_{C-P}$ = 9.4 Hz, $C_{Ar}CH_2OP$), 128.3 ($CH_{Ar(cycloSal)}$), 132.8 ($CH_{Ar(cycloSal)}$), 133.1 ($CH_{Ar(DMB)}$), 149.3 (d, $^2J_{C-P}$ = 6.5 Hz, $C_{Ar}OP$), 159.7 ($C_{Ar}OCH_3$), 162.4 ($C_{Ar}OCH_3$), 163.7 (CHO); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -10.5 ; HRMS (EI) $^+$: m/z calculated for $C_{19}H_{21}BrNO_8PNa$ [$M + Na$] $^+$ 524.0080, found 524.0138.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((2-oxido-6-(trifluoromethyl)-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)formamide (**17af**). The general procedure D was applied to synthesize the compound **17af** from alcohol **9a** (96 mg, 0.38 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 7:3 $\rightarrow$ EtOAc/cyclohexane, 8:2) to give **17af** as a colorless oil (98 mg, 52%) and as a mixture of two *Z* and *E* conformers in a 20:80 ratio. R_f = 0.50 (EtOAc/cyclohexane, 8:2); 1H -NMR (400 MHz, $CDCl_3$): 3.76–3.94 (8H, m, NCH_2 and OCH_3), 4.42 (2H, bs, $POCH_2$), 4.80 (8/10 of 2H, bs, OCH_2DMP), 4.96 (2/10 of 2H, bs, OCH_2DMP), 5.31 (1H, dd, 2J = 14.4 Hz, $^3J_{P-H}$ = 18.6 Hz, $ArCH_2OP$), 5.40 (1H, dd, 2J = 14.4 Hz, $^3J_{P-H}$ = 8.7 Hz, $ArCH_2OP$), 6.44–6.46 (2H, m, $CH_{Ar(DMB)}$), 7.10–7.13 (2H, m, $CH_{Ar(DMB)}$ and $CH_{Ar(cycloSal)}$), 7.33 (1H, bs, $CH_{Ar(cycloSal)}$), 7.55 (1H, d, 3J = 8.6 Hz, $CH_{Ar(cycloSal)}$), 7.90 (2/10 of 1H, bs, CHO), 8.06 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 44.5 (NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 64.4 ($POCH_2$), 68.6 (d, $^2J_{C-P}$ = 6.8 Hz, $ArCH_2OP$), 73.2 (OCH_2DMP), 98.8 ($CH_{Ar(DMB)}$), 104.5 ($CH_{Ar(DMB)}$), 114.8 ($C_{Ar(DMB)}$), 119.7 (d, $^3J_{C-P}$ = 9.4 Hz, $CH_{Ar}C_{Ar}OP$), 121.3 (d, $^3J_{C-P}$ = 9.1 Hz, $C_{Ar}CH_2OP$), 123.1 ($CH_{Ar(cycloSal)}$), 127.2 ($CH_{Ar(cycloSal)}$), 133.1 ($CH_{Ar(DMB)}$), 152.6 (d, $^2J_{C-P}$ = 6.1 Hz, $C_{Ar}OP$), 159.7 ($C_{Ar}OCH_3$), 162.3 ($C_{Ar}OCH_3$), 163.7 (CHO); ^{31}P -NMR (162.0 MHz, $CDCl_3$): -10.7 ; ^{19}F -NMR (282.4 MHz, $CDCl_3$): -63.2 ; HRMS (EI) $^+$: m/z calculated for $C_{20}H_{21}F_3NO_8PNa$ [$M + Na$] $^+$ 514.0849, found 514.0876.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((6-methoxy-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)formamide (**17ag**). The general procedure D was applied to synthesize compound **17ag** from alcohol **9a** (96 mg, 0.38 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 7:3 $\rightarrow$ EtOAc) to give **17ag** as a colorless oil (110 mg, 64%) and as a mixture of the two *Z* and *E* conformers in a 20:80 ratio. R_f = 0.28 (EtOAc/cyclohexane, 7:3); 1H -NMR (500 MHz, $CDCl_3$): 3.54–3.89 (11H, m, NCH_2 and OCH_3), 4.34 (2H, bs, $POCH_2$), 4.78 (8/10H of 2H, bs, OCH_2DMP), 4.95 (2/10 of 2H, bs, OCH_2DMP), 5.20–5.32 (2H, m, $ArCH_2OP$), 6.41–6.43 (2H, m, $CH_{Ar(DMB)}$), 6.51 (1H, s, $CH_{Ar(cycloSal)}$), 6.78 (1H, d, 3J = 8.6 Hz, $CH_{Ar(cycloSal)}$), 6.92 (1H, d, 3J = 9.2 Hz, $CH_{Ar(cycloSal)}$), 7.10 (1H, m, $CH_{Ar(DMB)}$), 7.84 (2/10H of 1H, bs, CHO), 8.04 (8/10 of 1H, bs, CHO); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 44.7 (d, $^3J_{CP}$ = 6.5 Hz, NCH_2), 55.6 (OCH_3), 55.7 (OCH_3), 55.9 (OCH_3), 63.9 ($POCH_2$), 69.1 (d, $^2J_{C-P}$ = 7.1 Hz, $ArCH_2OP$), 73.2 (OCH_2DMP), 98.8 ($CH_{Ar(DMB)}$), 104.5 ($CH_{Ar(DMB)}$), 110.1 ($CH_{Ar(cycloSal)}$), 114.9 ($C_{Ar(DMB)}$), 115.2 ($CH_{Ar(cycloSal)}$), 119.8 (d, $^3J_{C-P}$ = 8.1 Hz, $CH_{Ar}C_{Ar}OP$), 121.3 ($C_{Ar}CH_2OP$), 133.1 ($CH_{Ar(DMB)}$), 143.9 (d, $^2J_{C-P}$ = 7.3 Hz,

C_{Ar}OP), 156.2 (C_{Ar}OCH₃), 159.7 (C_{Ar}OCH₃), 162.4 (C_{Ar}OCH₃), 163.8 (CHO); ³¹P-NMR (162.0 MHz, CDCl₃): −9.4; HRMS (EI)⁺: *m/z* calculated for C₂₀H₂₄NO₉PNa [M + Na]⁺ 476.1081, found 476.1109.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)acetamide (**17ba**). The general procedure D was applied to synthesize compound **17ba** from alcohol **9b** (190 mg, 0.71 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 8:2) to give **17ba** as a colorless oil (227 mg, 73%) and as the sole *E* conformer. R_f = 0.47 (EtOAc/cyclohexane, 8:2); ¹H-NMR (400 MHz, CDCl₃): 1.99 (3H, s, CH₃CO), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.89–3.98 (2H, m, NCH₂), 4.34–4.41 (2H, m, POCH₂), 4.76 (2H, s, OCH₂DMP), 5.23–5.38 (2H, m, ArCH₂OP), 6.43–6.47 (2H, m, CH_{Ar}(DMB)), 7.01 (2H, t, ³J = 8.6 Hz, CH_{Ar}(cycloSal)), 7.10 (1H, t, ³J = 7.1 Hz, CH_{Ar}(cycloSal)) 7.16 (1H, d, ³J = 8.1 Hz, CH_{Ar}(DMB)), 7.27 (1H, m, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.2 (CH₃CO), 46.1 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 64.4 (d, ²J_{CP} = 5.5 Hz, POCH₂), 68.9 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 71.6 (OCH₂DMP), 98.7 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 115.1 (C_{Ar}(DMB)), 119.0 (d, ³J_{CP} = 9.1 Hz, CH_{Ar}C_{Ar}OP), 120.7 (d, ³J_{CP} = 10.0 Hz, C_{Ar}CH₂OP), 124.4 (CH_{Ar}(cycloSal)), 125.4 (CH_{Ar}(cycloSal)), 129.9 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 150.3 (d, ²J_{CP} = 6.9 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 173.4 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −9.90; MS (EI)⁺: *m/z* calculated for C₂₀H₂₄NO₈PNa [M + Na]⁺ 460.11, found 460.11.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)acetamide (**17bb**). The general procedure D was applied to synthesize compound **17bb** from alcohol **9b** (200 mg, 0.78 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 7:3 → EtOAc) to give **17bb** as a colorless oil (17 mg, 36%) and as the sole *E* conformer. R_f = 0.33 (EtOAc/petroleum ether, 7:3); ¹H-NMR (400 MHz, CDCl₃): 2.00 (3H, s, CH₃CO), 2.29 (3H, s, CH₃Ar), 3.82 (OCH₃), 3.83 (OCH₃), 3.87–3.97 (2H, m, NCH₂), 4.30–4.42 (2H, m, POCH₂), 4.76 (2H, s, OCH₂DMP), 5.18–5.33 (2H, m, ArCH₂OP), 6.43–6.46 (2H, m, CH_{Ar}(DMB)), 6.81 (1H, bs, CH_{Ar}(cycloSal)), 6.89 (1H, d, ³J = 8.3 Hz, CH_{Ar}(cycloSal)), 7.05 (1H, d, ³J = 7.9 Hz, CH_{Ar}(cycloSal)), 7.15 (1H, d, ³J = 7.9 Hz, CH_{Ar}(DMB)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.1 (CH₃CO), 20.8 (CH₃Ar), 46.2 (NCH₂), 55.5 (OCH₃), 55.6 (OCH₃), 64.4 (d, ²J_{C-P} = 5.6 Hz, POCH₂), 69.0 (d, ²J_{C-P} = 7.0 Hz, ArCH₂OP), 71.6 (OCH₂DMP), 98.7 (CH_{Ar}(DMB)), 104.3 (CH_{Ar}(DMB)), 115.1 (C_{Ar}(DMB)), 118.6 (d, ³J_{C-P} = 9.3 Hz, CH_{Ar}C_{Ar}OP), 120.3 (d, ³J_{C-P} = 9.5 Hz, C_{Ar}CH₂OP), 125.6 (CH_{Ar}(cycloSal)), 130.3 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 134.1 (C_{Ar}CH₃), 148.1 (d, ²J_{C-P} = 7.1 Hz, C_{Ar}OP), 159.6 (C_{Ar}OCH₃), 162.2 (C_{Ar}OCH₃), 173.5 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −9.7; HRMS (EI)⁺: *m/z* calculated for C₂₁H₂₆NO₈PNa [M + Na]⁺ 474.1288, found 474.1247.

N-(2-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)acetamide (**17bc**). The general procedure D was applied to synthesize compound **17bc** from alcohol **9b** (180 mg, 0.67 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 8:2) to give **17bc** as a colorless oil (178 mg, 56%) and as the sole *E* conformer. R_f = 0.40 (EtOAc/cyclohexane, 8:2); ¹H-NMR (400 MHz, CDCl₃): 2.00 (3H, s, CH₃CO), 3.83 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.91–3.96 (2H, m, NCH₂), 4.35–4.42 (2H, m, POCH₂), 4.76 (2H, s, OCH₂DMP), 5.16–5.33 (2H, m, ArCH₂OP), 6.44–6.47 (2H, m, CH_{Ar}(DMB)), 6.93 (1H, d, ³J = 8.1 Hz, CH_{Ar}(cycloSal)), 7.00 (1H, d, ⁴J = 2.4 Hz, CH_{Ar}(cycloSal)), 7.15 (1H, d, ³J = 8.0 Hz, CH_{Ar}(DMB)) 7.22 (1H, d, ³J = 8.9 Hz, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.2 (CH₃CO), 45.9 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 64.7 (d, ²J_{CP} = 5.6 Hz, POCH₂), 68.4 (d, ²J_{CP} = 7.2 Hz, ArCH₂OP), 71.7 (OCH₂DMP), 98.8 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 115.1 (C_{Ar}(DMB)), 120.4 (d, ³J_{CP} = 9.1 Hz, CH_{Ar}C_{Ar}OP), 122.3 (d, ³J_{CP} = 9.9 Hz, C_{Ar}CH₂OP), 125.4 (CH_{Ar}(cycloSal)), 129.6 (C_{Ar}Cl), 129.8 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 148.8 (d, ²J_{CP} = 7.0 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 173.4 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −10.4; HRMS (EI)⁺: *m/z* calculated for C₂₀H₂₃ClNO₈PNa [M + Na]⁺ 494.0683, found 494.0683.

N-(2-((6,8-Dichloro-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)acetamide (**17bd**). The general procedure D was applied to synthesize compound **17bd** from alcohol **9b** (214 mg, 0.79 mmol). The crude product was purified by automated flash chromatography (DCM/MeOH, 98:2) to give **17bd** as a colorless oil (15 mg, 12%) and as the sole *E* conformer. *R*_f = 0.32 (DCM/MeOH, 98:2); ¹H-NMR (400 MHz, CDCl₃): 2.02 (3H, s, CH₃CO), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.27–4.45 (2H, m, NCH₂), 4.35–4.42 (2H, m, POCH₂), 4.76 (2H, s, OCH₂DMP), 5.17–5.32 (2H, m, ArCH₂OP), 6.44–6.46 (2H, m, CH_{Ar}(DMB)), 6.92 (1H, CH_{Ar}(cycloSal)), 7.15 (1H, d, ³*J* = 8.3 Hz, CH_{Ar}(DMB)) 7.35 (1H, d, ³*J* = 8.9 Hz, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.1 (CH₃CO), 45.8 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 65.1 (POCH₂), 68.3 (d, ²*J*_{CP} = 7.0 Hz, ArCH₂OP), 71.7 (OCH₂DMP), 98.7 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 115.1 (C_{Ar}(DMB)), 123.4 (d, ³*J*_{CP} = 9.5 Hz, ClC_{Ar}C_{Ar}OP), 123.8 (CH_{Ar}(cycloSal)) 124.9 (d, ³*J*_{CP} = 8.7 Hz, C_{Ar}CH₂OP), 129.5 (C_{Ar}Cl), 130.2 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 145.1 (d, ²*J*_{CP} = 5.9 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.4 (C_{Ar}OCH₃), 173.4 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −10.7; MS (EI)⁺: *m/z* calculated for C₂₀H₂₂Cl₂NO₈PNa [M + Na]⁺ 528.04, found 528.03.

N-(2-((6-Bromo-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-((2,4-dimethoxybenzyl)oxy)acetamide (**17be**). The general procedure D was applied to synthesize compound **17be** from alcohol **9b** (60 mg, 0.22 mmol). The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 5:5) to give **17be** as a colorless oil (58 mg, 51%) and as the sole *E* conformer. *R*_f = 0.42 (EtOAc/petroleum ether, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.00 (3H, s, CH₃CO), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃) 3.87–3.99 (2H, m, NCH₂), 4.33–4.43 (2H, m, POCH₂), 4.75 (2H, s, OCH₂DMP), 5.20 (1H, dd, ²*J* = 14.4 Hz, ³*J*_{P-H} = 19.1 Hz, ArCH₂OP), 5.30 (1H, dd, ²*J* = 14.0 Hz, ³*J*_{P-H} = 8.0 Hz, ArCH₂OP), 6.44–6.47 (2H, m, CH_{Ar}(DMB)), 6.87 (1H, d, ³*J* = 8.6 Hz, CH_{Ar}(cycloSal)), 7.14–7.17 (2H, m, CH_{Ar}(DMB) and CH_{Ar}(cycloSal)), 7.37 (1H, d, ³*J* = 9.3 Hz, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.1 (CH₃CO), 45.9 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 64.7 (d, ²*J*_{C-P} = 5.7 Hz, POCH₂), 68.3 (d, ²*J*_{C-P} = 7.0 Hz, ArCH₂OP), 71.7 (OCH₂DMP), 98.8 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 115.0 (C_{Ar}(DMB)), 116.9 (C_{Ar}Br), 120.7 (d, ³*J*_{C-P} = 9.0 Hz, CH_{Ar}C_{Ar}OP), 122.7 (d, ³*J*_{C-P} = 10.1 Hz, C_{Ar}CH₂OP), 128.3 (CH_{Ar}(cycloSal)), 132.8 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 149.4 (d, ²*J*_{C-P} = 7.1 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 173.4 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −10.3; HRMS (EI)⁺: *m/z* calculated for C₂₀H₂₄BrNO₈P [M + H]⁺ 516.0417, found 516.0411.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((2-oxido-6-(trifluoromethyl)-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)acetamide (**17bf**). The general procedure D was applied to synthesize compound **17bf** from alcohol **9b** (98 mg, 0.36 mmol). The crude product was purified by automated flash chromatography EtOAc/cyclohexane, 7:3 → EtOAc) to give **17bf** as a colorless oil (73 mg, 52%) and as the sole *E* conformer. *R*_f = 0.42 (EtOAc/cyclohexane, 8:2); ¹H-NMR (500 MHz, CDCl₃): 1.97 (3H, s, CH₃CO), 3.81 (6H, s, OCH₃), 3.88–3.99 (2H, m, NCH₂), 4.38–4.45 (2H, m, POCH₂), 4.75 (2H, bs, OCH₂DMP), 5.28 (1H, dd, ²*J* = 14.2 Hz, ³*J*_{P-H} = 18.7 Hz, ArCH₂OP), 5.38 (1H, dd, ²*J* = 14.3 Hz, ³*J*_{P-H} = 7.5 Hz, ArCH₂OP), 6.44–6.47 (2H, m, CH_{Ar}(DMB)), 7.08 (1H, d, ³*J* = 8.4 Hz, CH_{Ar}(cycloSal)), 7.15 (1H, d, ³*J* = 7.9 Hz, CH_{Ar}(DMB)), 7.30 (1H, bs, CH_{Ar}(cycloSal)), 7.54 (1H, d, ³*J* = 8.5 Hz, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.1 (CH₃CO), 44.8 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 64.8 (d, ²*J*_{C-P} = 5.6 Hz, POCH₂), 68.5 (d, ²*J*_{C-P} = 6.9 Hz, ArCH₂OP), 71.7 (OCH₂DMP), 98.8 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 115.0 (C_{Ar}(DMB)), 119.6 (d, ³*J*_{C-P} = 9.4 Hz, CH_{Ar}C_{Ar}OP), 121.4 (d, ³*J*_{C-P} = 9.9 Hz, C_{Ar}CH₂OP), 123.9 (q, ³*J*_{C-F} = 2.9 Hz, CH_{Ar}(cycloSal)), 125.8 (q, ¹*J*_{C-F} = 273.4 Hz, C_{Ar}CF₃), 126.7 (q, ²*J*_{C-F} = 32.9 Hz, C_{Ar}CF₃), 127.2 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMB)), 152.7 (d, ²*J*_{C-P} = 6.9 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.4 (C_{Ar}OCH₃), 173.3 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −10.5; ¹⁹F-NMR (282.4 MHz, CDCl₃): −63.2; HRMS (EI)⁺: *m/z* calculated for C₂₁H₂₃F₃NO₈PNa [M + Na]⁺ 528.1006, found 528.1001.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-((6-methoxy-2-oxido-4*H*-benzo[*d*][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)acetamide (**17bg**). The general procedure D was applied to synthesize com-

pound **17bg** from alcohol **9b** (92 mg, 0.36 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 7:3 → EtOAc) to give **17bg** as a colorless oil (94 mg, 56%) and as the sole *E* conformer. *R*_f = 0.27 (EtOAc/cyclohexane, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.00 (3H, s, CH₃CO), 3.76 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.88–3.97 (2H, m, NCH₂), 4.31–4.41 (2H, bs, POCH₂), 4.75 (2H, bs, OCH₂DMP), 5.19–5.33 (2H, m, ArCH₂OP), 6.43–6.46 (2H, m, CH_{Ar}(DMB)), 6.52 (1H, d, ⁴*J* = 2.9 Hz, CH_{Ar}(cycloSal)), 6.79 (1H, dd, ³*J* = 8.9 Hz, ⁴*J* = 2.5 Hz, CH_{Ar}(cycloSal)), 6.92 (1H, d, ³*J* = 9.1 Hz, CH_{Ar}(cycloSal)), 7.16 (1H, d, ³*J* = 8.1 Hz, CH_{Ar}(DMB)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.2 (CH₃CO), 46.1 (NCH₂), 55.6 (OCH₃), 55.7 (OCH₃), 55.9 (OCH₃), 64.4 (d, ²*J*_{C-P} = 5.6 Hz, POCH₂), 69.0 (d, ²*J*_{C-P} = 6.8 Hz, ArCH₂OP), 71.7 (OCH₂DMP), 98.7 (CH_{Ar}(DMB)), 104.4 (CH_{Ar}(DMB)), 110.1 (CH_{Ar}(cycloSal)), 115.1 (CH_{Ar}(cycloSal)), 119.8 (d, ³*J*_{C-P} = 8.8 Hz, CH_{Ar}C_{Ar}OP), 121.1 (d, ³*J*_{C-P} = 9.4 Hz, C_{Ar}CH₂OP), 132.9 (CH_{Ar}(DMB)), 144.0 (d, ²*J*_{C-P} = 6.8 Hz, C_{Ar}OP), 156.1 (C_{Ar}OCH₃), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 173.5 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.7; HRMS (EI)⁺: *m/z* calculated for C₂₁H₂₆NO₉PNa [M + Na]⁺ 490.1237, found 490.1250.

N-((2,4-Dimethoxybenzyl)oxy)-3-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16aa**). The general procedure E was applied to synthesize compound **16aa** from alcohol **10a** (153 mg, 0.60 mmol). The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 8:2) to give **16aa** as a colorless oil (205 mg, 65%) and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. *R*_f = 0.38 (EtOAc/cyclohexane, 9:1); ¹H-NMR (400 MHz, CDCl₃): 2.48 (6/10H of 2H, bs, CH₂CO), 2.83 (4/10H of 2H, bs, CH₂CO), 3.81 (6H, s, OCH₃), 4.40–4.49 (2H, m, POCH₂), 4.77 (4/10 of 2H, bs, OCH₂DMP), 4.85 (6/10 of 2H, bs, OCH₂DMP), 5.34 (2H, m, ArCH₂OP), 6.45 (2H, m, CH_{Ar}(DMP)), 7.05 (2H, m, CH_{Ar}(cycloSal)), 7.11 (1H, pseudo-t, ³*J* = 7.4 Hz, CH_{Ar}(cycloSal)), 7.17 (1H, m, CH_{Ar}(DMP)), 7.29 (1H, pseudo-t, ³*J* = 7.8 Hz, CH_{Ar}(cycloSal)), 7.88 (4/10H of 1H, bs, NH), 8.35 (6/10H of 1H, bs, NH); ¹³C-NMR (125.8 MHz, CDCl₃): 32.5 (d, ³*J*_{C-P} = 5.9 Hz, CH₂CO), 34.6 (d, ³*J*_{C-P} = 5.1 Hz, CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 63.6 (POCH₂), 64.4 (POCH₂), 68.8 (ArCH₂OP), 68.9 (ArCH₂OP), 73.5 (OCH₂DMP), 74.9 (OCH₂DMP), 98.8 (CH_{Ar}(DMP)), 104.2 (CH_{Ar}(DMP)), 104.4 (CH_{Ar}(DMP)), 114.9 (C_{Ar}(DMP)), 115.9 (C_{Ar}(DMP)), 118.9 (d, ³*J*_{C-P} = 9.0 Hz, CH_{Ar}C_{Ar}OP), 120.7 (C_{Ar}CH₂OP), 124.4 (CH_{Ar}(cycloSal)), 124.6 (CH_{Ar}(cycloSal)), 125.5 (CH_{Ar}(cycloSal)), 129.9 (CH_{Ar}(DMP)), 130.0 (CH_{Ar}(DMP)), 132.9 (CH_{Ar}(cycloSal)), 133.1 (CH_{Ar}(cycloSal)), 150.2 (C_{Ar}OP), 159.6 (C_{Ar}OCH₃), 159.7 (C_{Ar}OCH₃), 161.9 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 166.7 (CO), 173. (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.8, −9.9; MS (EI)⁺: *m/z* calculated for C₁₉H₂₂NO₈Pna [M + Na]⁺ 446.10, found 446.10.

N-((2,4-Dimethoxybenzyl)oxy)-3-((6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16ab**). The general procedure E was applied to synthesize compound **16ab** from alcohol **10a** (200 mg, 0.78 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 7:3 → EtOAc) to give **16ab** as a colorless oil (146 mg, 43%) and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. *R*_f = 0.36 (EtOAc/cyclohexane, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.26 (3H, s, CH₃Ar), 2.42–2.51 (6/10 of 2H, m, CH₂CO), 2.80–2.86 (4/10 of 2H, CH₂CO), 3.79 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 4.39–4.45 (2H, m, POCH₂), 4.75 (4/10 of 2H, s, OCH₂DMP), 4.80–4.85 (6/10 of 2H, s, OCH₂DMP), 5.21–5.31 (2H, m, ArCH₂OP), 6.42–6.44 (2H, m, CH_{Ar}(DMP)), 6.82 (1H, s, CH_{Ar}(cycloSal)), 6.90 (1H, d, ³*J* = 8.3 Hz, CH_{Ar}(cycloSal)), 7.05 (1H, d, ³*J* = 8.5 Hz, CH_{Ar}(cycloSal)), 7.13–7.17 (1H, m, CH_{Ar}(DMP)), 7.85 (4/10H of 1H, bs, NH), 8.32 (6/10H of 1H, bs, NH); ¹³C-NMR (125.8 MHz, CDCl₃): 20.9 (CH₃Ar), 32.5 (CH₂CO), 34.7 (CH₂CO), 55.6 (OCH₃), 55.8 (OCH₃), 63.6 (POCH₂), 64.3 (POCH₂), 68.9 (d, ²*J*_{C-P} = 5.3 Hz ArCH₂OP), 69.1 (d, ²*J*_{C-P} = 6.5 Hz ArCH₂OP), 73.5 (OCH₂DMP), 75.0 (OCH₂DMP), 98.8 (CH_{Ar}(DMP)), 104.3 (CH_{Ar}(DMP)), 104.4 (CH_{Ar}(DMP)), 116.0 (C_{Ar}(DMP)), 118.6 (d, ³*J*_{C-P} = 8.8 Hz, CH_{Ar}C_{Ar}OP), 120.3 (C_{Ar}CH₂OP), 125.7 (CH_{Ar}(cycloSal)), 130.4 (CH_{Ar}(cycloSal)), 130.5 (CH_{Ar}(cycloSal)), 132.9 (CH_{Ar}(DMP)), 133.1 (CH_{Ar}(DMP)), 134.3 (C_{Ar}CH₃), 148.0 (C_{Ar}OP), 148.2 (C_{Ar}OP), 159.6 (C_{Ar}OCH₃), 162.0 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 166.8 (C_{Ar}OCH₃), 171.4 (CO), 173.4 (CO);

^{31}P -NMR (162.0 MHz, CDCl_3): -9.3 , -9.5 ; MS (EI) $^+$: m/z calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 460.1132, found 460.1166.

3-((6-Chloro-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-((2,4-dimethoxybenzyl)oxy)propanamide (**16ac**). The general procedure E was applied to synthesize compound **16ac** from alcohol **10a** (200 mg, 0.78 mmol). The crude product was purified by automated flash chromatography (EtOAc) to give **16ac** as a colorless oil (103 mg, 29%) and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. $\text{Rf} = 0.34$ (EtOAc); ^1H -NMR (400 MHz, CDCl_3): 2.49 (6/10 of 2H, m, CH_2CO), 2.83 (4/10 of 2H, CH_2CO), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.42–4.51 (2H, m, POCH_2), 4.78 (4/10 of 2H, s, OCH_2DMP), 4.86 (6/10 of 2H, s, OCH_2DMP), 5.22–5.38 (2H, m, ArCH_2OP), 6.47 (2H, m, $\text{CH}_{\text{Ar(DMP)}}$), 6.98 (1H, pseudo-d, $^3J = 8.7$ Hz, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.05 (1H, t, $^3J = 2.1$ Hz, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.18 (1H, m, $\text{CH}_{\text{Ar(DMP)}}$), 7.24 (1H, bs, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.84 (4/10H of 1H, bs, NH), 8.29 (4/10H of 1H, bs, NH); ^{13}C -NMR (125.8 MHz, CDCl_3): 32.5 (CH_2CO), 34.5 (CH_2CO), 55.6 (OCH_3), 55.8 (OCH_3), 63.8 (POCH_2), 64.6 (POCH_2), 68.3 (ArCH_2OP), 73.6 (OCH_2DMP), 75.0 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar(DMP)}}$), 104.3 ($\text{CH}_{\text{Ar(DMP)}}$), 104.4 ($\text{CH}_{\text{Ar(DMP)}}$), 114.9 ($\text{C}_{\text{Ar(DMP)}}$), 115.9 ($\text{C}_{\text{Ar(DMP)}}$), 120.3 (d, $^3J_{\text{C-P}} = 9.4$ Hz, $\text{CH}_{\text{ArC}_{\text{ArOP}}}$), 122.2 ($\text{C}_{\text{ArCH}_2\text{OP}}$), 125.5 ($\text{CH}_{\text{Ar(cycloSal)}}$), 130.3 ($\text{CH}_{\text{Ar(cycloSal)}}$), 132.9 ($\text{CH}_{\text{Ar(DMP)}}$), 148.7 (C_{ArOP}), 159.7 ($\text{C}_{\text{ArOCH}_3}$), 166.6 ($\text{C}_{\text{ArOCH}_3}$), 173.3 (CO); ^{31}P -NMR (162.0 MHz, CDCl_3): -10.3 , -10.4 ; MS (EI) $^+$: m/z calculated for $\text{C}_{19}\text{H}_{21}\text{ClNO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 480.0586, found 480.0600.

3-((6,8-Dichloro-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-((2,4-dimethoxybenzyl)oxy)propanamide (**16ad**). The general procedure E was applied to synthesize compound **16ad** from alcohol **10a** (250 mg, 0.98 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 9:1) to give **16ad** as a colorless oil (49 mg, 10%) and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. $\text{Rf} = 0.47$ (EtOAc/cyclohexane, 9:1); ^1H -NMR (500 MHz, CDCl_3): 2.50 (6/10 of 2H, m, CH_2CO), 2.83 (4/10 of 2H, CH_2CO), 3.81–3.83 (6H, m, OCH_3), 4.42–4.55 (2H, m, POCH_2), 4.77 (4/10 of 2H, s, OCH_2DMP), 4.84 (6/10 of 2H, s, OCH_2DMP), 5.23–5.37 (2H, m, ArCH_2OP), 6.44 (2H, pseudo-s, $\text{CH}_{\text{Ar(DMP)}}$), 6.97 (1H, s, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.17 (1H, m, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.37 (1H, s, $\text{CH}_{\text{Ar(DMP)}}$), 8.14 (4/10H of 1H, bs, NH), 8.64 (6/10H of 1H, bs, NH); ^{13}C -NMR (125.8 MHz, CDCl_3): 32.4 (CH_2CO), 34.3 (CH_2CO), 55.6 (OCH_3), 55.7 (OCH_3), 64.2 (POCH_2), 65.0 (POCH_2), 68.1 (ArCH_2OP), 68.2 (ArCH_2OP), 73.5 (OCH_2DMP), 74.9 (OCH_2DMP), 98.7 ($\text{CH}_{\text{Ar(DMP)}}$), 104.3 ($\text{CH}_{\text{Ar(DMP)}}$), 104.4 ($\text{CH}_{\text{Ar(DMP)}}$), 114.9 ($\text{C}_{\text{Ar(DMP)}}$), 115.9 ($\text{C}_{\text{Ar(DMP)}}$), 123.5 ($\text{ClC}_{\text{ArC}_{\text{ArOP}}}$), 123.9 ($\text{CH}_{\text{Ar(cycloSal)}}$), 124.0 ($\text{CH}_{\text{Ar(cycloSal)}}$), 124.8 ($\text{C}_{\text{ArCH}_2\text{OP}}$), 129.5 (C_{ArCl}), 129.8 (C_{ArCl}), 130.3 ($\text{CH}_{\text{Ar(cycloSal)}}$), 132.9 ($\text{CH}_{\text{Ar(DMP)}}$), 133.1 ($\text{CH}_{\text{Ar(DMP)}}$), 144.9 (C_{ArOP}), 145.1 (C_{ArOP}), 159.6 ($\text{C}_{\text{ArOCH}_3}$), 159.7 ($\text{C}_{\text{ArOCH}_3}$), 161.9 ($\text{C}_{\text{ArOCH}_3}$), 162.3 ($\text{C}_{\text{ArOCH}_3}$), 166.5 (CO), 173.2 (CO); ^{31}P -NMR (162.0 MHz, CDCl_3): -10.3 , -10.4 ; MS (EI) $^+$: m/z calculated for $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{NO}_8\text{PNa}$ $[\text{M} + \text{Na}]^+$ 492.04, found 492.04.

3-((6-Bromo-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-((2,4-dimethoxybenzyl)oxy)propanamide (**16ae**). The general procedure E was applied to synthesize compound **16ae** from alcohol **10a** (139 mg, 0.54 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 6:4 $\rightarrow$ EtOAc) to give **16ae** as a colorless oil (29 mg, 11%) and as a mixture of two *Z* and *E* conformers in a 60:40 ratio. $\text{Rf} = 0.37$ (EtOAc/cyclohexane, 7:3); ^1H -NMR (500 MHz, CDCl_3): 2.48 (6/10 of 2H, bs, CH_2CO), 2.81 (4/10 of 2H, bs, CH_2CO), 3.81 (6H, s, OCH_3), 4.37–4.54 (2H, m, POCH_2), 4.76 (4/10 of 2H, bs, OCH_2DMP), 4.85 (6/10 of 2H, bs, OCH_2DMP), 5.24 (1H, dd, $^2J = 14.5$ Hz, $^3J_{\text{P-H}} = 18.0$ Hz, ArCH_2OP), 5.34 (1H, dd, $^2J = 14.3$ Hz, $^3J_{\text{P-H}} = 9.5$ Hz, ArCH_2OP), 6.43–6.45 (2H, m, $\text{CH}_{\text{Ar(DMP)}}$), 6.92 (1H, d, $^3J = 8.7$ Hz, $\text{CH}_{\text{Ar(cycloSal)}}$), 7.11–7.19 (2H, m, $\text{CH}_{\text{Ar(DMP)}}$ and $\text{CH}_{\text{Ar(cycloSal)}}$), 7.39 (1H, d, $^3J = 8.2$ Hz, $\text{CH}_{\text{Ar(cycloSal)}}$), 8.11 (4/10 of AH, bs, NH), 8.63 (6/10 of 1H, bs, NH); ^{13}C -NMR (125.8 MHz, CDCl_3): 32.4 (CH_2CO), 34.4 (CH_2CO), 55.6 (OCH_3), 55.7 (OCH_3), 63.8 (POCH_2), 64.7 (POCH_2), 68.1 (d, $^2J_{\text{C-P}} = 6.7$ Hz, ArCH_2OP), 68.2 (d, $^2J_{\text{C-P}} = 6.3$ Hz, ArCH_2OP), 73.5 (OCH_2DMP), 74.6 (OCH_2DMP), 98.8 ($\text{CH}_{\text{Ar(DMP)}}$), 104.3 ($\text{CH}_{\text{Ar(DMP)}}$), 104.4 ($\text{CH}_{\text{Ar(DMP)}}$), 114.9 ($\text{C}_{\text{Ar(DMP)}}$), 116.0 ($\text{C}_{\text{Ar(DMP)}}$), 116.9 (C_{ArBr}), 117.1

(C_{Ar}Br), 120.6 (d, ³J_{C-P} = 9.1 Hz, CH_{Ar}C_{Ar}OP), 122.5 (d, ³J_{C-P} = 9.5 Hz, C_{Ar}CH₂OP), 122.7 (d, ³J_{C-P} = 10.3 Hz, C_{Ar}CH₂OP), 128.3 (CH_{Ar(cycloSal)}), 128.4 (CH_{Ar(cycloSal)}), 132.9–133.1 (CH_{Ar(cycloSal)} and CH_{Ar(DMP)}), 149.2 (d, ²J_{C-P} = 6.4 Hz, C_{Ar}OP), 149.4 (d, ²J_{C-P} = 6.4 Hz, C_{Ar}OP), 159.6 (C_{Ar}OCH₃), 159.7 (C_{Ar}OCH₃), 161.9 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 166.6 (CO), 173.2 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −10.1, −10.2; HRMS (EI)⁺: *m/z* calculated for C₁₉H₂₂BrNO₈PNa [M + Na]⁺ 502.0261, found 502.0331.

N-((2,4-Dimethoxybenzyl)oxy)-3-((2-oxido-6-(trifluoromethyl)-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16af**). The general procedure E was applied to synthesize compound **16af** from alcohol **10a** (152 mg, 0.60 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 3:7 → EtOAc) to give **16af** as a colorless oil (38 mg, 13%) and as a mixture of the two *Z* and *E* conformers in a 60:40 ratio. R_f = 0.33 (EtOAc/cyclohexane, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.47–2.49 (6/10 of 2H, m, CH₂CO), 2.76–2.88 (4/10 of 2H, m, CH₂CO), 3.80 (6H, s, OCH₃), 4.42–4.54 (2H, m, POCH₂), 4.76 (4/10 of 2H, bs, OCH₂DMP), 4.84 (6/10 of 2H, s, OCH₂DMP), 5.27–5.43 (2H, m, ArCH₂OP), 6.24–6.44 (2H, m, CH_{Ar(DMP)}), 7.13–7.16 (2H, m, CH_{Ar(cycloSal)} and CH_{Ar(DMP)}), 7.33 (1H, s, CH_{Ar(cycloSal)}), 7.55 (1H, d, ³J = 6.3 Hz, CH_{Ar(cycloSal)}), 7.83 (4/10 of 1H, bs, NH), 8.28 (6/10 of 1H, bs, NH); ¹³C-NMR (125.8 MHz, CDCl₃): 32.5 (CH₂CO), 34.5 (CH₂CO), 55.6 (OCH₃), 55.8 (OCH₃), 64.0 (POCH₂), 64.7 (POCH₂), 68.3–68.5 (ArCH₂OP), 73.6 (OCH₂DMP), 75.0 (OCH₂DMP), 98.8 (CH_{Ar(DMP)}), 104.3 (CH_{Ar(DMP)}), 104.5 (CH_{Ar(DMP)}), 114.9 (C_{Ar(DMP)}), 115.2 (C_{Ar(DMP)}), 119.6 (d, ³J_{C-P} = 9.5 Hz, CH_{Ar}C_{Ar}OP), 121.4 (C_{Ar}CH₂OP), 123.2 (CH_{Ar(cycloSal)}), 127.4 (CH_{Ar(cycloSal)}), 132.9 (CH_{Ar(DMP)}), 133.1 (CH_{Ar(DMP)}), 152.7 (C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.0 (C_{Ar}OCH₃), 162.4 (C_{Ar}OCH₃), 166.5 (C_{Ar}OCH₃), 171.4 (CO), 173.2 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −10.4, −10.5; ¹⁹F-NMR (282.4 MHz, CDCl₃): −63.2, −63.3; HRMS (EI)⁺: *m/z* calculated for C₂₀H₂₂NO₈P [M + H]⁺ 492.1030, found 492.1011.

N-((2,4-Dimethoxybenzyl)oxy)-3-((6-methoxy-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16ag**). The general procedure E was applied to synthesize compound **16ag** from alcohol **10a** (175 mg, 0.69 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 3:7 → EtOAc) to give **16ag** as a colorless oil (49 mg, 18%) and as a mixture of two *Z* and *E* conformers in a 60:40 ratio. R_f = 0.46 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): 2.48–2.49 (6/10 of 2H, m, CH₂CO), 2.82–2.86 (4/10 of 2H, m, CH₂CO), 3.75 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.40–4.47 (2H, m, POCH₂), 4.77 (4/10 of 2H, bs, OCH₂DMP), 4.85 (6/10 of 2H, s, OCH₂DMP), 5.21–5.33 (2H, m, ArCH₂OP), 6.43–6.46 (2H, m, CH_{Ar(DMP)}), 6.55 (1H, d, ⁴J = 2.8 Hz CH_{Ar(cycloSal)}), 6.80 (1H, dd, ³J = 9.1 Hz, ⁴J = 1.8 Hz, CH_{Ar(DMP)}), 6.96 (1H, d, ³J = 8.9 Hz, CH_{Ar(DMP)}), 7.15–7.20 (1H, m, CH_{Ar(cycloSal)}), 7.91 (4/10 of 1H, bs, NH), 8.40 (6/10 of 1H, bs, NH); ¹³C-NMR (125.8 MHz, CDCl₃): 32.8 (CH₂CO), 34.7 (CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 55.9 (OCH₃), 63.6 (POCH₂), 64.4 (POCH₂), 68.8–69.0 (ArCH₂OP), 73.5 (OCH₂DMP), 75.0 (OCH₂DMP), 98.8 (CH_{Ar(DMP)}), 104.3 (CH_{Ar(DMP)}), 110.2 (CH_{Ar(cycloSal)}), 115.3 (CH_{Ar(cycloSal)}), 116.0 (C_{Ar(DMP)}), 119.7 (d, ³J_{C-P} = 8.8 Hz, CH_{Ar}C_{Ar}OP), 121.3–121.5 (C_{Ar}CH₂OP), 132.9–133.1 (CH_{Ar(DMP)}), 143.8–144.0 (C_{Ar}OP), 156.1 (C_{Ar}OCH₃), 156.3 (C_{Ar}OCH₃), 159.6 (C_{Ar}OCH₃), 162.0 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 166.8 (CO), 171.1 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.3, −9.5; HRMS (EI): *m/z* calculated for C₂₀H₂₄NO₉PNa [M + Na]⁺ 476.1081, found 476.1102.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-methyl-3-((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16ba**). The general procedure D was applied to synthesize compound **16ba** from alcohol **10b** (153 mg, 0.57 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 8:2) to give **16ba** as a colorless oil (148 mg, 76%) and as the sole *E* conformer. R_f = 0.25 (EtOAc/cyclohexane, 8:2); ¹H-NMR (300 MHz, CDCl₃): 2.79–2.92 (2H, m, CH₂CO), 3.18 (3H, s, NCH₃), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.39–4.51 (2H, m, POCH₂), 4.77 (2H, s, OCH₂DMP), 5.27–5.42 (2H, m, ArCH₂OP), 6.47 (2H, m, CH_{Ar(DMP)}), 7.02–7.06 (2H, m, CH_{Ar(cycloSal)}), 7.11 (1H, t, ³J = 7.5 Hz, CH_{Ar(cycloSal)}), 7.17 (1H, d, ³J = 8.9 Hz, CH_{Ar(DMP)}), 7.28 (1H, t, ³J = 7.6 Hz, CH_{Ar(cycloSal)}), ¹³C-NMR (75.5 MHz,

CDCl₃): 32.9 (d, ³J_{C-P} = 7.0 Hz, CH₂CO), 33.3 (NCH₃), 55.6 (OCH₃), 55.7 (OCH₃), 64.4 (d, ²J_{C-P} = 5.3 Hz, POCH₂), 66.7 (d, ²J_{C-P} = 6.8 Hz, ArCH₂OP), 71.3 (OCH₂DMP), 98.8 (CH_{Ar}(DMP)), 104.4 (CH_{Ar}(DMP)), 115.0 (C_{Ar}(DMP)), 118.9 (d, ³J_{C-P} = 9.0 Hz, CH_{Ar}C_{Ar}OP), 120.9 (d, ³J_{C-P} = 9.8 Hz, C_{Ar}CH₂OP), 124.3 (CH_{Ar}(cycloSal)), 125.3 ((CH_{Ar}(cycloSal)), 129.7 (CH_{Ar}(cycloSal)), 132.8 (CH_{Ar}(DMP)), 150.4 (d, ²J_{C-P} = 6.9 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 171.2 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.5; MS (EI)⁺: *m/z* calculated for C₂₀H₂₄NO₈PNa [M + Na]⁺ 460.11, found 460.11.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-methyl-3-((6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**16bb**). The general procedure D was applied to synthesize compound **16bb** from alcohol **10b** (150 mg, 0.56 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 5:5 → EtOAc) to give **16bb** as a colorless oil (190 mg, 75%) and as the sole *E* conformer. R_f = 0.47 (EtOAc/cyclohexane, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.30 (3H, s, CH₃Ar), 2.79–2.92 (2H, m, CH₂CO), 3.18 (3H, s, NCH₃), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.37–4.50 (2H, m, POCH₂), 4.77 (2H, s, OCH₂DMP), 5.23–5.379 (2H, m, ArCH₂OP), 6.45–6.47 (2H, m, CH_{Ar}(DMP)), 6.87 (1H, bs, CH_{Ar}(cycloSal)), 6.91 (1H, d, ³J = 8.5 Hz, CH_{Ar}(DMP)), 7.07 (1H, d, ³J = 8.0 Hz, CH_{Ar}(DMP)), 7.18 (1H, d, ³J = 8.9 Hz, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 20.9 (CH₃Ar), 33.0 (d, ³J_{C-P} = 7.1 Hz, CH₂CO), 33.3 (NCH₃), 55.6 (OCH₃), 55.7 (OCH₃), 64.4 (d, ²J_{C-P} = 5.4 Hz, POCH₂), 68.8 (d, ²J_{C-P} = 6.5 Hz, ArCH₂OP), 71.3 (OCH₂DMP), 98.8 (CH_{Ar}(DMP)), 104.4 (CH_{Ar}(DMP)), 115.0 (C_{Ar}(DMP)), 118.6 (d, ³J_{C-P} = 9.1 Hz, CH_{Ar}C_{Ar}OP), 120.5 (d, ³J_{C-P} = 9.6 Hz, C_{Ar}CH₂OP), 125.7 (CH_{Ar}(cycloSal)), 130.3 (CH_{Ar}(cycloSal)), 133.0 (CH_{Ar}(DMP)), 134.0 (C_{Ar}CH₃), 148.3 (d, ²J_{C-P} = 6.4 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 171.2 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.3; HRMS (EI)⁺: *m/z* calculated for C₂₁H₂₇NO₈P [M + H]⁺ 452.1469, found 452.1508.

3-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-*N*-((2,4-dimethoxybenzyl)oxy)-*N*-methylpropanamide (**16bc**). The general procedure D was applied to synthesize compound **16bc** from alcohol **10b** (195 mg, 0.72 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 9:1) to give **16bc** as a colorless oil (292 mg, 86%) and as the sole *E* conformer. R_f = 0.51 (EtOAc/cyclohexane, 9:1); ¹H-NMR (300 MHz, CDCl₃): 2.78–2.90 (2H, m, CH₂CO), 3.18 (3H, s, NCH₃), 3.82 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 4.39–4.51 (2H, m, POCH₂), 4.77 (2H, s, OCH₂DMP), 5.21–5.39 (2H, m, ArCH₂OP), 6.47 (2H, m, CH_{Ar}(DMP)), 6.97 (1H, d, ³J = 8.9 Hz, CH_{Ar}(cycloSal)), 7.05 (1H, t, ³J = 2.4 Hz, CH_{Ar}(cycloSal)), 7.17 (1H, d, ³J = 8.6 Hz, CH_{Ar}(DMP)), 7.24 (1H, bs, CH_{Ar}(cycloSal)); ¹³C-NMR (75.5 MHz, CDCl₃): 32.9 (d, ³J_{C-P} = 7.3 Hz, CH₂CO), 33.3 (NCH₃), 55.6 (OCH₃), 55.7 (OCH₃), 64.4 (d, ²J_{C-P} = 5.2 Hz, POCH₂), 68.1 (d, ²J_{C-P} = 6.8 Hz, ArCH₂OP), 71.3 (OCH₂DMP), 98.8 (CH_{Ar}(DMP)), 104.5 (CH_{Ar}(DMP)), 115.0 (C_{Ar}(DMP)), 118.9 (d, ³J_{C-P} = 9.0 Hz, CH_{Ar}C_{Ar}OP), 122.3 (d, ³J_{C-P} = 9.1 Hz, C_{Ar}CH₂OP), 125.4 (CH_{Ar}(cycloSal)), 129.5 (C_{Ar}Cl), 129.9 (CH_{Ar}(cycloSal)), 133.0 (CH_{Ar}(DMP)), 148.5 (d, ²J_{C-P} = 6.5 Hz, C_{Ar}OP), 159.7 (C_{Ar}OCH₃), 162.3 (C_{Ar}OCH₃), 171.1 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −10.0; MS (EI)⁺: *m/z* calculated for C₂₀H₂₃ClNO₈PNa [M + Na]⁺ 494.0742, found 494.0626.

3-((6,8-Dichloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-*N*-((2,4-dimethoxybenzyl)oxy)-*N*-methylpropanamide (**16bd**). The general procedure D was applied to synthesize compound **16bd** from alcohol **10b** (241 mg, 0.89 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 8:2) to give **16bd** as a colorless oil (175 mg, 43%) and as the sole *E* conformer. R_f = 0.40 (EtOAc/petroleum ether, 8:2); ¹H-NMR (400 MHz, CDCl₃): 2.84–2.89 (2H, m, CH₂CO), 3.19 (3H, s, NCH₃), 3.82 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 4.41–4.62 (2H, m, POCH₂), 4.78 (2H, s, OCH₂DMP), 5.22–5.39 (2H, m, ArCH₂OP), 6.47 (2H, m, CH_{Ar}(DMP)), 6.97 (1H, d, ³J = 2.3 Hz, CH_{Ar}(cycloSal)), 7.20 (1H, t, ³J = 8.9 Hz, CH_{Ar}(DMP)), 7.38 (1H, bs, CH_{Ar}(cycloSal)); ¹³C-NMR (125.8 MHz, CDCl₃): 32.7 (d, ³J_{C-P} = 6.9 Hz, CH₂CO), 33.1 (NCH₃), 55.4 (OCH₃), 55.5 (OCH₃), 64.7 (d, ²J_{C-P} = 5.5 Hz, POCH₂), 67.9 (d, ²J_{C-P} = 6.9 Hz, ArCH₂OP), 71.2 (OCH₂DMP), 98.6 (CH_{Ar}(DMP)), 104.3 (CH_{Ar}(DMP)), 114.7 (C_{Ar}(DMP)), 123.4 (d, ³J_{C-P} = 9.5 Hz, ClC_{Ar}C_{Ar}OP), 123.7 (CH_{Ar}(cycloSal)), 124.7 (d, ³J_{C-P} = 8.8 Hz, C_{Ar}CH₂OP)

129.3 ($C_{Ar}Cl$), 130.0 ($CH_{Ar(cycloSal)}$), 132.8 ($CH_{Ar(DMP)}$), 145.1 (d, $^2J_{C-P}$ = 5.9 Hz, $C_{Ar}OP$), 159.5 ($C_{Ar}OCH_3$), 162.2 ($C_{Ar}OCH_3$), 171.2 (CO); ^{31}P -NMR (162.0 MHz, $CDCl_3$): −10.5; MS (EI) $^+$: m/z calculated for $C_{20}H_{22}Cl_2NO_8PNa$ [$M + Na$] $^+$ 528.04, found 528.04.

3-((6-Bromo-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-((2,4-dimethoxybenzyl)oxy)-N-methylpropanamide (**16be**). The general procedure D was applied to synthesize compound **16be** from alcohol **10b** (150 mg, 0.56 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 5:5 → EtOAc) to give **16be** as a colorless oil (215 mg, 74%) and as the sole *E* conformer. R_f = 0.47 (EtOAc/cyclohexane, 7:3); 1H -NMR (500 MHz, $CDCl_3$): 2.76–2.91 (2H, m, CH_2CO), 3.18 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.38–4.52 (2H, m, $POCH_2$), 4.77 (2H, s, OCH_2DMP), 5.24 (1H, dd, 2J = 14.2 Hz, $^3J_{P-H}$ = 17.9 Hz, $ArCH_2OP$), 5.36 (1H, dd, 2J = 14.1 Hz, $^3J_{P-H}$ = 8.7 Hz, $ArCH_2OP$), 6.45–6.47 (2H, m, $CH_{Ar(DMP)}$), 6.91 (1H, d, 3J = 8.8 Hz, $CH_{Ar(cycloSal)}$), 7.16–7.20 (2H, m, $CH_{Ar(DMP)}$ and $CH_{Ar(cycloSal)}$), 7.38 (1H, d, 3J = 8.7 Hz, $CH_{Ar(cycloSal)}$); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 32.9 (d, $^3J_{C-P}$ = 7.0 Hz, CH_2CO), 33.3 (NCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 64.5 (d, $^2J_{C-P}$ = 5.2 Hz, $POCH_2$), 68.0 (d, $^2J_{C-P}$ = 6.9 Hz, $ArCH_2OP$), 71.3 (OCH_2DMP), 98.8 ($CH_{Ar(DMP)}$), 104.5 ($CH_{Ar(DMP)}$), 114.9 ($C_{Ar(DMP)}$), 116.8 ($C_{Ar}Br$), 120.7 (d, $^3J_{C-P}$ = 9.2 Hz, $CH_{Ar}C_{Ar}OP$), 122.8 (d, $^3J_{C-P}$ = 9.8 Hz, $C_{Ar}CH_2OP$), 128.3 ($CH_{Ar(cycloSal)}$), 132.8 ($CH_{Ar(cycloSal)}$), 133.0 ($CH_{Ar(DMP)}$), 149.5 (d, $^2J_{C-P}$ = 6.6 Hz, $C_{Ar}OP$), 159.7 ($C_{Ar}OCH_3$), 162.3 ($C_{Ar}OCH_3$), 171.1 (CO); ^{31}P -NMR (162.0 MHz, $CDCl_3$): −10.3; HRMS (EI) $^+$: m/z calculated for $C_{20}H_{23}BrNO_8PNa$ [$M + Na$] $^+$ 538.0237, found 538.0255.

3-((6-((Difluoro- λ^3 -methyl)- λ^2 -fluoranyl)-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-((2,4-dimethoxybenzyl)oxy)-N-methylpropanamide (**16bf**). The general procedure D was applied to synthesize the compound **16bf** from alcohol **10b** (150 mg, 0.56 mmol). The crude product was purified by automated flash chromatography (EtOAc/cyclohexane, 5:5 → EtOAc) to give **16bf** as a colorless oil 149 mg, 53%) and as the sole *E* conformer. R_f = 0.44 (EtOAc/cyclohexane, 7:3); 1H -NMR (500 MHz, $CDCl_3$): 2.78–2.91 (2H, m, CH_2CO), 3.18 (3H, s, NCH_3), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.41–4.54 (2H, m, $POCH_2$), 4.77 (2H, s, OCH_2DMP), 5.33 (1H, dd, 2J = 14.4 Hz, $^3J_{P-H}$ = 18.5 Hz, $ArCH_2OP$), 5.45 (1H, dd, 2J = 14.3 Hz, $^3J_{P-H}$ = 8.4 Hz, $ArCH_2OP$), 6.45–6.47 (2H, m, $CH_{Ar(DMP)}$), 7.14 (1H, d, 3J = 8.7 Hz $CH_{Ar(cycloSal)}$), 7.17 (1H, d, 3J = 8.6 Hz, $CH_{Ar(DMP)}$), 7.35 (1H, s, $CH_{Ar(cycloSal)}$), 7.57 (1H, d, 3J = 8.4 Hz, $CH_{Ar(cycloSal)}$); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 32.9 (d, $^3J_{C-P}$ = 7.0 Hz, CH_2CO), 33.3 (NCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 64.7 (d, $^2J_{C-P}$ = 5.3 Hz, $POCH_2$), 68.3 (d, $^2J_{C-P}$ = 6.7 Hz, $ArCH_2OP$), 71.3 (OCH_2DMP), 98.8 ($CH_{Ar(DMP)}$), 104.7 ($CH_{Ar(DMP)}$), 114.9 ($C_{Ar(DMP)}$), 119.6 (d, $^3J_{C-P}$ = 9.3 Hz, $CH_{Ar}C_{Ar}OP$), 121.5 (d, $^3J_{C-P}$ = 9.7 Hz, $C_{Ar}CH_2OP$), 123.1 (q, $^3J_{C-F}$ = 3.2 Hz, $CH_{Ar(cycloSal)}$), 123.7 (q, $^1J_{C-F}$ = 271.1 Hz, $C_{Ar}CF_3$), 126.8 (q, $^2J_{C-F}$ = 33 Hz, $C_{Ar}CF_3$), 127.2 (q, $^3J_{C-F}$ = 3.6 Hz, $CH_{Ar(cycloSal)}$), 133.0 ($CH_{Ar(DMP)}$), 152.9 (d, $^2J_{C-P}$ = 6.4 Hz, $C_{Ar}OP$), 159.7 ($C_{Ar}OCH_3$), 162.4 ($C_{Ar}OCH_3$), 171.1 (CO); ^{31}P -NMR (121.5 MHz, $CDCl_3$): −10.3; ^{19}F -NMR (282.4 MHz, $CDCl_3$): −63.2; HRMS (EI) $^+$: m/z calculated for $C_{21}H_{23}F_3NO_8PNa$ [$M + Na$] $^+$ 528.1006, found 528.1005.

N-((2,4-Dimethoxybenzyl)oxy)-3-((6-methoxy-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-N-methylpropanamide (**16bg**). The general procedure D was applied to synthesize compound **16bg** from alcohol **10b** (150 mg, 0.56 mmol). The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc) to give **16bg** as a colorless oil (160 mg, 61%) and as the sole *E* conformer. R_f = 0.5 (EtOAc/cyclohexane, 8:2); 1H -NMR (500 MHz, $CDCl_3$): 2.79–2.92 (2H, m, CH_2CO), 3.18 (8/10 of 3H, s, NCH_3), 3.23 (2/10 of 3H, s, NCH_3), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.37–4.50 (2H, m, $POCH_2$), 4.77 (8/10 of 2H, s, OCH_2DMP), 4.80 (2/10 of 2H, s, OCH_2DMP), 5.23–5.37 (2H, m, $ArCH_2OP$), 6.45–6.47 (2H, m, $CH_{Ar(DMP)}$), 6.55 (1H, d, 4J = 2.8 Hz $CH_{Ar(cycloSal)}$), 6.80 (1H, dd, 3J = 8.8 Hz, 4J = 1.9 Hz, $CH_{Ar(cycloSal)}$), 6.95 (1H, d, 3J = 8.9 Hz, $CH_{Ar(DMP)}$), 7.18 (1H, d, 3J = 8.5 Hz, $CH_{Ar(cycloSal)}$); ^{13}C -NMR (125.8 MHz, $CDCl_3$): 32.8 (d, $^3J_{C-P}$ = 7.1 Hz, CH_2CO), 33.1 (NCH_3), 55.4 (OCH_3), 55.5 (OCH_3), 55.8 (OCH_3), 64.4 (d, $^2J_{C-P}$ = 5.4 Hz, $POCH_2$), 68.6 (d, $^2J_{C-P}$ = 6.7 Hz, $ArCH_2OP$), 71.1 (OCH_2DMP), 98.6 ($CH_{Ar(DMP)}$), 104.3 ($CH_{Ar(DMP)}$), 110.1

(CH_{Ar(cycloSal)}), 114.8 (C_{Ar(DMP)}), 114.9 (CH_{Ar(cycloSal)}), 119.6 (d, ³J_{C-P} = 9.2 Hz, CH_{Ar}C_{Ar}OP), 121.4 (d, ³J_{C-P} = 9.6 Hz, C_{Ar}CH₂OP), 132.8 (CH_{Ar(DMP)}), 143.9 (d, ²J_{C-P} = 6.7 Hz, C_{Ar}OP), 155.9 (C_{Ar}OCH₃), 159.5 (C_{Ar}OCH₃), 162.1 (C_{Ar}OCH₃), 171.1 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.3; HRMS (EI)⁺: *m/z* calculated for C₂₁H₂₆NO₉PNa [M + Na]⁺ 490.1237, found 490.1277.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)-3-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**18a**). When general procedure D was applied to synthesize compound 16aa from alcohol **10a** (200 mg, 0.78 mmol), a byproduct **18a** was obtained. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc) to give **18a** as a colorless oil (90 mg, 20%) and as a mixture of two diastereoisomers. R_f = 0.38 (EtOAc/cyclohexane, 5:5); ¹H-NMR (500 MHz, CDCl₃): 2.88 (2H, t, ³J = 6.3 Hz, CH₂CO), 3.78 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.37–4.51 (2H, m, POCH₂), 4.90–4.97 (2H, m, OCH₂DMP), 5.11–5.27 (2H, m, ArCH₂OP), 5.33–5.38 (1H, m, ArCH₂OP), 5.44–5.50 (1H, m, ArCH₂OP) 6.42–6.44 (2H, m, CH_{Ar(DMP)}), 6.88 (5/10 of 1H, d, ³J = 8.4 Hz, CH_{Ar(cycloSal)}), 6.90 (5/10 of 1H, d, ³J = 8.5 Hz, CH_{Ar(cycloSal)}), 6.96 (1H, d, ³J = 7.1 Hz, CH_{Ar(cycloSal)}), 7.03 (2H, t, ³J = 7.5 Hz, CH_{Ar(cycloSal)}), 7.10 (2H, t, ³J = 7.5 Hz, CH_{Ar(cycloSal)}), 7.17 (1H, dd, ³J = 8.9 Hz, ⁴J_{P-H} = 2.0 Hz, CH_{Ar(DMP)}), 7.28 (2H, m, CH_{Ar(cycloSal)}); ¹³C-NMR (125.8 MHz, CDCl₃): 32.9 (d, ³J_{C-P} = 7.1 Hz, CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 63.7 (POCH₂), 68.9 (d, ²J_{C-P} = 6.9 Hz, ArCH₂OP), 69.3 (d, ²J_{C-P} = 7.1 Hz, ArCH₂OP), 69.4 (d, ²J_{C-P} = 7.3 Hz, ArCH₂OP), 71.8 (OCH₂DMP), 98.5 (CH_{Ar(DMP)}), 104.1 (CH_{Ar(DMP)}), 117.6 (C_{Ar(DMP)}), 118.9 (d, ³J_{C-P} = 8.5 Hz, CH_{Ar}C_{Ar}OP), 119.0 (d, ³J_{C-P} = 8.8 Hz, CH_{Ar}C_{Ar}OP), 120.5 (d, ³J_{C-P} = 10.2 Hz, C_{Ar}CH₂OP), 120.8 (d, ³J_{C-P} = 9.8 Hz, C_{Ar}CH₂OP), 124.4 (CH_{Ar(cycloSal)}), 124.7 (CH_{Ar(cycloSal)}), 125.3 (CH_{Ar(cycloSal)}), 125.4 (CH_{Ar(cycloSal)}), 129.9 (CH_{Ar(cycloSal)}), 131.6 (CH_{Ar(DMP)}), 143.0 (d, ²J_{C-P} = 9.5 Hz, C_{Ar}OP), 143.1 (d, ²J_{C-P} = 9.7 Hz, C_{Ar}OP), 150.1 (d, ²J_{C-P} = 7.2 Hz, C_{Ar}OP), 150.3 (d, ²J_{C-P} = 7.6 Hz, C_{Ar}OP), 159.0 (C_{Ar}OCH₃), 161.3 (C_{Ar}OCH₃), 171.4 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.6, −9.7, −18.7; HRMS (EI)⁺: *m/z* calculated for C₂₆H₂₇NO₁₁P₂Na [M + Na]⁺ 614.0952, found 614.0951.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)-3-((6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**18b**). When general procedure D was applied to synthesize compound 16ab from alcohol **10a** (200 mg, 0.78 mmol), a byproduct **18b** was obtained. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc) to give **18b** as a colorless oil (92 mg, 38%) and as a mixture of two diastereoisomers. R_f = 0.72 (EtOAc/petroleum ether, 7:3); ¹H-NMR (500 MHz, CDCl₃): 2.27 (6H, s, CH₃Ar), 2.83 (2H, t, ³J = 6.2 Hz, CH₂CO), 3.76 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 4.33–4.46 (2H, m, POCH₂), 4.88–4.94 (2H, m, OCH₂DMP), 5.05–5.21 (2H, m, ArCH₂OP), 5.29 (1H, d, ²J = 13.9 Hz, ³J_{C-P} = 8.1 Hz, ArCH₂OP), 5.38–5.44 (1H, m, ArCH₂OP) 6.40–6.42 (2H, m, CH_{Ar(DMP)}), 6.72–6.79 (3H, m, CH_{Ar}), 6.88 (5/10 of 1H, d, ³J = 6.0 Hz, CH_{Ar(cycloSal)}), 6.90 (5/10 of 1H, d, ³J = 6.1 Hz, CH_{Ar(cycloSal)}), 7.00–7.05 (2H, m, CH_{Ar}), 7.14 (5/10 of 1H, d, ³J = 7.9 Hz, CH_{Ar}), 7.15 (5/10 of 1H, d, ³J = 7.9 Hz, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 20.8 (CH₃Ar), 20.9 (CH₃Ar), 32.9 (d, ³J_{C-P} = 6.7 Hz, CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 63.6 (POCH₂), 68.9 (d, ²J_{C-P} = 6.6 Hz, ArCH₂OP), 69.4 (d, ²J_{C-P} = 7.3 Hz, ArCH₂OP), 69.5 (d, ²J_{C-P} = 7.1 Hz, ArCH₂OP), 71.8 (OCH₂DMP), 98.5 (CH_{Ar(DMP)}), 104.1 (CH_{Ar(DMP)}), 117.6 (C_{Ar(DMP)}), 118.6 (CH_{Ar}C_{Ar}OP), 120.0 (d, ³J_{C-P} = 10.0 Hz, C_{Ar}CH₂OP), 120.4 (d, ³J_{C-P} = 10.1 Hz, C_{Ar}CH₂OP), 125.5 (CH_{Ar(cycloSal)}), 125.7 (CH_{Ar(cycloSal)}), 130.4 (CH_{Ar(cycloSal)}), 131.5 (CH_{Ar(DMP)}), 134.0 (C_{Ar}CH₃), 134.4 (C_{Ar}CH₃), 143.1 (d, ²J_{C-P} = 9.2 Hz, C_{Ar}OP), 143.2 (d, ²J_{C-P} = 9.7 Hz, C_{Ar}OP), 147.9 (d, ²J_{C-P} = 7.2 Hz, C_{Ar}OP), 148.2 (d, ²J_{C-P} = 5.7 Hz, C_{Ar}OP), 158.9 (C_{Ar}OCH₃), 161.2 (C_{Ar}OCH₃), 171.4 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.4, −9.5, −18.5; HRMS (EI)⁺: *m/z* calculated for C₂₈H₃₁NO₁₁P₂Na [M + Na]⁺ 642.1265, found 642.1335.

N-(6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)-3-((6-chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-*N*-((2,4-dimethoxybenzyl)oxy)propanamide (**18c**). When general procedure D was applied to synthesize compound 16ac from alcohol **10a** (212 mg,

0.78 mmol), a byproduct 18c was obtained. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc) to give **18c** as a colorless oil 3 (24 mg, 84%) and as a mixture of two diastereoisomers. *R*_f = 0.83 (EtOAc); ¹H-NMR (500 MHz, CDCl₃): 2.88 (2H, t, ³*J* = 6.3 Hz, CH₂CO), 3.77 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.35–4.54 (2H, m, POCH₂), 4.87–4.97 (2H, m, OCH₂DMP), 5.03–5.23 (2H, m, ArCH₂OP), 5.27–5.34 (1H, m, ArCH₂OP), 5.38–5.46 (1H, m, ArCH₂OP), 6.43–6.46 (2H, m, CH_{Ar}(DMP)), 6.79 (5/10 of 1H, d, ³*J* = 6.1 Hz, CH_{Ar}(cycloSal)), 6.82 (5/10 of 1H, d, ³*J* = 6.3 Hz, CH_{Ar}(cycloSal)), 6.92–7.02 (3H, m, CH_{Ar}(cycloSal)), 7.14 (1H, dd, ³*J* = 8.8 Hz, ⁴*J* = 2.4 Hz, CH_{Ar}(cycloSal)), 7.19–7.22 (2H, m, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 32.7 (d, ³*J*_{C-P} = 7.0 Hz, CH₂CO), 55.4 (OCH₃), 55.5 (OCH₃), 63.7 (d, ²*J*_{C-P} = 4.1 Hz, POCH₂), 63.7 (d, ²*J*_{C-P} = 4.6 Hz, POCH₂), 68.0 (d, ²*J*_{C-P} = 6.6 Hz, ArCH₂OP), 68.1 (d, ²*J*_{C-P} = 6.6 Hz, ArCH₂OP), 68.6 (d, ²*J*_{C-P} = 7.1 Hz, ArCH₂OP), 68.7 (d, ²*J*_{C-P} = 7.1 Hz, ArCH₂OP), 71.8 (OCH₂DMP), 98.4 (CH_{Ar}(DMP)), 103.9 (CH_{Ar}(DMP)), 117.0 (C_{Ar}(DMP)), 120.1 (CH_{Ar}C_{Ar}OP), 120.2 (CH_{Ar}C_{Ar}OP), 121.7 (d, ³*J*_{C-P} = 9.1 Hz, C_{Ar}CH₂OP), 122.1 (d, ³*J*_{C-P} = 9.0 Hz, C_{Ar}CH₂OP), 125.0 (CH_{Ar}(cycloSal)), 125.2 (CH_{Ar}(cycloSal)), 129.4 (C_{Ar}Cl), 129.5 (C_{Ar}Cl), 129.7 (CH_{Ar}(cycloSal)), 129.8 (CH_{Ar}(cycloSal)), 131.5 (CH_{Ar}(DMP)), 131.6 (CH_{Ar}(DMP)), 142.6 (d, ²*J*_{C-P} = 9.5 Hz, C_{Ar}OP), 142.7 (d, ²*J*_{C-P} = 10.1 Hz, C_{Ar}OP), 148.3 (d, ²*J*_{C-P} = 7.8 Hz, C_{Ar}OP), 148.2 (d, ²*J*_{C-P} = 6.0 Hz, C_{Ar}OP), 158.9 (C_{Ar}OCH₃), 161.3 (C_{Ar}OCH₃); ³¹P-NMR (121.5 MHz, CDCl₃): −10.1, −10.2, −19.4, −19.5; HRMS (EI)⁺: *m/z* calculated for C₂₆H₂₅Cl₂NO₁₁P₂Na [M + Na]⁺ 682.0172, found 682.0168.

N-(6-Bromo-2-oxido-4H-benzo[d][1,3,2]ioxaphosphinin-2-yl)-3-((6-bromo-2-oxido-4H-benzo[d]dioxaphosphinin-2-yl)oxy)-*N*-((2,4-dimethoxybenzyl)oxy)propanamide (**18e**). When general procedure D was applied to synthesize compound **16ae** from alcohol 10a (200 mg, 0.78 mmol), a byproduct **18e** was obtained. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc/petroleum ether, 7:3) to give **18e** as a colorless oil (432 mg, 74%) and as a mixture of two diastereoisomers. *R*_f = 0.34 (EtOAc/petroleum ether, 5:5); ¹H-NMR (400 MHz, CDCl₃): 2.87 (2H, t, ³*J* = 6.1 Hz, CH₂CO), 3.79 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.37–4.51 (2H, m, POCH₂), 4.88–4.96 (2H, m, OCH₂DMP), 5.04–5.22 (2H, m, ArCH₂OP), 5.28–5.33 (1H, m, ArCH₂OP), 5.38–5.45 (1H, m, ArCH₂OP), 6.43–6.46 (2H, m, CH_{Ar}(DMP)), 6.73 (5/10 of 1H, d, ³*J* = 8.3 Hz, CH_{Ar}(cycloSal)), 6.75 (5/10 of 1H, d, ³*J* = 8.1 Hz, CH_{Ar}(cycloSal)), 6.90 (5/10 of 1H, d, ³*J* = 8.1 Hz, CH_{Ar}(cycloSal)), 6.92 (5/10 of 1H, d, ³*J* = 8.3 Hz, CH_{Ar}(cycloSal)), 7.08–7.18 (3H, m, CH_{Ar}(cycloSal) and CH_{Ar}(DMP)), 7.34–7.41 (2H, m, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 32.8 (d, ³*J*_{C-P} = 6.4 Hz, CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 63.8 (d, ²*J*_{C-P} = 4.7 Hz, POCH₂), 63.9 (d, ²*J*_{C-P} = 4.2 Hz, POCH₂), 68.1 (d, ²*J*_{C-P} = 6.7 Hz, ArCH₂OP), 68.2 (d, ²*J*_{C-P} = 6.7 Hz, ArCH₂OP), 68.7 (d, ²*J*_{C-P} = 7.3 Hz, ArCH₂OP), 68.8 (d, ²*J*_{C-P} = 7.6 Hz, ArCH₂OP), 71.9 (OCH₂DMP), 98.6 (CH_{Ar}(DMP)), 104.1 (CH_{Ar}(DMP)), 116.9 (C_{Ar}(DMP)), 117.0 (C_{Ar}(DMP)), 117.2 (C_{Ar}Br), 117.3 (C_{Ar}Br), 120.6 (CH_{Ar}C_{Ar}OP), 120.7 (CH_{Ar}C_{Ar}OP), 122.3 (d, ³*J*_{C-P} = 9.2 Hz, C_{Ar}CH₂OP), 122.7 (d, ³*J*_{C-P} = 9.9 Hz, C_{Ar}CH₂OP), 128.1 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 131.7 (CH_{Ar}), 131.8 (CH_{Ar}), 132.8 (CH_{Ar}), 142.8 (d, ²*J*_{C-P} = 9.7 Hz, C_{Ar}OP), 142.9 (d, ²*J*_{C-P} = 9.7 Hz, C_{Ar}OP), 149.1 (d, ²*J*_{C-P} = 7.2 Hz, C_{Ar}OP), 149.4 (d, ²*J*_{C-P} = 6.7 Hz, C_{Ar}OP), 149.5 (d, ²*J*_{C-P} = 6.7 Hz, C_{Ar}OP), 159.1 (C_{Ar}OCH₃), 161.4 (C_{Ar}OCH₃); ³¹P-NMR (162.0 MHz, CDCl₃): −10.4, −10.5, −19.7, −19.8; HRMS (EI)⁺: *m/z* calculated for C₂₆H₂₆Br₂NO₁₁P₂ [M + H]⁺ 749.9324, found 749.9361.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(2-oxido-6-(trifluoromethyl)-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)-3-((2-oxido-6-(trifluoromethyl)-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**18f**). When general procedure D was applied to synthesize compound **16af** from alcohol 10a (152 mg, 0.60 mmol), a byproduct **18f** was obtained. The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 5:5 → EtOAc/petroleum ether, 7:3) to give **18f** as a colorless oil (59 mg, 15%) and as a mixture of two diastereoisomers. *R*_f = 0.90 (EtOAc/petroleum ether, 7:3); ¹H-NMR (300 MHz, CDCl₃): 2.90 (2H, t, ³*J* = 6.2 Hz, CH₂CO), 3.77 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.20–4.55 (2H, m, POCH₂), 4.88–4.95 (2H, m, OCH₂DMP), 5.13–5.31 (2H, m, ArCH₂OP), 5.39 (1H, d, ²*J* = 14.5 Hz, ³*J* = 7.7 Hz, ArCH₂OP), 5.47–5.54 (1H, m, ArCH₂OP), 6.41–6.50 (2H, m, CH_{Ar}(DMP)), 6.93–6.97 (1H, m, CH_{Ar}), 7.13–7.16 (1H, m, CH_{Ar}), 7.23 (1H, s, CH_{Ar}), 7.28–7.35 (2H, m, CH_{Ar}), 7.45–7.58 (2H,

m, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 32.9 (d, ³J_{C-P} = 8.0 Hz, CH₂CO), 55.5 (OCH₃), 55.7 (OCH₃), 64.1 (d, ²J_{C-P} = 5.6 Hz, POCH₂), 68.4 (d, ²J_{C-P} = 6.6 Hz, ArCH₂OP), 69.0 (d, ²J_{C-P} = 7.1 Hz, ArCH₂OP), 72.0 (OCH₂DMP), 98.6 (CH_{Ar}(DMP)), 104.1 (CH_{Ar}(DMP)), 117.1 (C_{Ar}(DMP)), 119.6 (d, ³J_{C-P} = 3.7 Hz, CH_{Ar}C_{Ar}OP), 119.7 (d, ³J_{C-P} = 3.9 Hz, CH_{Ar}C_{Ar}OP), 121.0 (d, ³J_{C-P} = 10.4 Hz, C_{Ar}CH₂OP), 121.4 (d, ³J_{C-P} = 10.4 Hz, C_{Ar}CH₂OP), 122.8 (CH_{Ar}), 123.1 (CH_{Ar}), 127. (CH_{Ar}), 131.9 (CH_{Ar}(DMP)), 159.1 (C_{Ar}OCH₃), 161.5 (C_{Ar}OCH₃); ³¹P-NMR (121.5 MHz, CDCl₃): −10.4, −10.5, −19.7, −19.8; ¹⁹F-NMR (282.4 MHz, CDCl₃): −63.15, −63.16, −63.20, −63.21; HRMS (EI)⁺: *m/z* calculated for C₂₈H₂₅F₆NO₁₁P₂Na [M + Na]⁺ 750.0699, found 750.0650.

N-((2,4-Dimethoxybenzyl)oxy)-*N*-(6-methoxy-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)-3-((6-methoxy-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**18g**). When general procedure D was applied to synthesize compound **16ag** from alcohol **10a** (175 mg, 0.69 mmol), a byproduct of **18g** was obtained. The crude product was purified by automated flash chromatography (EtOAc/petroleum ether, 3:7 → EtOAc) to give **18g** as a colorless oil (45 mg, 12%) and as a mixture of two diastereoisomers. R_f = 0.60 (EtOAc/petroleum ether, 7:3); ¹H-NMR (300 MHz, CDCl₃): 2.86 (2H, t, ³J = 6.3 Hz, CH₂CO), 3.75 (6H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 4.32–4.49 (2H, m, POCH₂), 4.89–4.98 (2H, m, OCH₂DMP), 5.05–5.20 (2H, m, ArCH₂OP), 5.24–3.34 (1H, m, ArCH₂OP), 5.38–5.46 (1H, m, ArCH₂OP), 6.41–6.45 (3H, m, CH_{Ar}(DMP) and CH_{Ar}), 6.52 (5/10 of 1H, s, CH_{Ar}), 6.53 (5/10 of 1H, s, CH_{Ar}), 6.74–6.84 (3H, m, CH_{Ar}), 6.93–6.98 (1H, m, CH_{Ar}), 7.16 (1H, dd, ³J = 8.8 Hz, ⁴J = 1.5 Hz, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 32.9 (d, ³J_{C-P} = 6.9 Hz, CH₂CO), 55.6 (OCH₃), 55.7 (OCH₃), 55.9 (OCH₃), 63.6 (POCH₂), 63.7 (POCH₂), 68.8 (d, ²J_{C-P} = 6.6 Hz, ArCH₂OP), 69.4 (d, ²J_{C-P} = 6.8 Hz, ArCH₂OP), 69.5 (d, ²J_{C-P} = 6.8 Hz, ArCH₂OP), 71.8 (OCH₂DMP), 98.5 (CH_{Ar}(DMP)), 104.1 (CH_{Ar}(DMP)), 110.1 (CH_{Ar}), 110.2 (CH_{Ar}), 115.0 (CH_{Ar}), 115.1 (CH_{Ar}), 117.6 (C_{Ar}(DMP)), 119.7 (CH_{Ar}C_{Ar}OP), 119.8 (CH_{Ar}C_{Ar}OP), 121.1 (d, ³J_{C-P} = 9.4 Hz, C_{Ar}CH₂OP), 121.4 (d, ³J_{C-P} = 9.4 Hz, C_{Ar}CH₂OP), 131.5 (CH_{Ar}(DMP)), 143.1 (d, ²J_{C-P} = 9.6 Hz, C_{Ar}OP), 143.2 (d, ²J_{C-P} = 9.6 Hz, C_{Ar}OP), 143.7 (d, ²J_{C-P} = 7.3 Hz, C_{Ar}OP), 144.0 (d, ²J_{C-P} = 6.7 Hz, C_{Ar}OP), 156.1 (C_{Ar}OCH₃), 156.3 (C_{Ar}OCH₃), 158.9 (C_{Ar}OCH₃), 161.2 (C_{Ar}OCH₃), 171.4 (CO); ³¹P-NMR (121.5 MHz, CDCl₃): −9.4, −9.5, −18.5; HRMS (EI)⁺: *m/z* calculated for C₂₈H₃₁NO₁₃P₂Na [M + Na]⁺ 674.1163, found 674.1134.

N-Hydroxy-*N*-(2-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)formamide (**7aa**). The general procedure F was applied to synthesize compound **7aa** from *cycloSal* **17aa** (93 mg, 0.22 mmol) and 2% TFA in DCM. The product **7aa** was obtained without purification as an orange oil (48 mg, 80%) and as a mixture of the three *Z*, *E*, and another conformer in a 20:20:60 ratio, respectively. R_f = 0.33 (EtOAc); ¹H-NMR (500 MHz, CD₃OD): 3.57–3.61 (2/10 of 2H, m, NCH₂), 3.76–3.80 (6/10 of 2H, m, NCH₂), 3.85–3.89 (2/10 of 2H, m, NCH₂), 4.35–4.42 (8/10 of 2H, m, POCH₂), 4.48–4.59 (2/10H of 2H, bs, POCH₂), 5.39–5.56 (2H, m, ArCH₂OP), 7.11 (1H, m, CH_{Ar}(*cycloSal*)), 7.22 (2H, m, CH_{Ar}(*cycloSal*)), 7.38 (1H, m, CH_{Ar}(*cycloSal*)), 7.86 (6/10 of 1H, bs, CHO), 7.91 (2/10 of 1H, bs, CHO), 8.19 (2/10 of 1H, bs, CHO); ¹³C-NMR (125.8 MHz, CD₃OD): 47.8 (d, ³J_{CP} = 6.9 Hz, NCH₂), 51.6 (d, ³J_{CP} = 7.2 Hz, NCH₂), 52.0 (d, ³J_{CP} = 8.1 Hz, NCH₂), 62.4 (d, ²J_{CP} = 4.8 Hz, POCH₂), 64.9 (d, ²J_{CP} = 5.6 Hz, POCH₂), 65.2 (d, ²J_{CP} = 5.6 Hz, POCH₂), 70.3 (ArCH₂OP), 70.4 (ArCH₂OP), 70.5 (ArCH₂OP), 119.6 (CH_{Ar}C_{Ar}OP), 119.7 (CH_{Ar}C_{Ar}OP), 119.8 (CH_{Ar}C_{Ar}OP), 122.3 (C_{Ar}CH₂OP), 122.4 (C_{Ar}CH₂OP), 122.5 (C_{Ar}CH₂OP), 125.9 (CH_{Ar}), 126.1 (CH_{Ar}), 126.2 (CH_{Ar}), 126.9 (CH_{Ar}), 127.1 (CH_{Ar}), 127.2 (CH_{Ar}), 131.1 (CH_{Ar}), 131.2 (CH_{Ar}), 131.4 (CH_{Ar}), 151.3 (d, ²J_{CP} = 6.8 Hz, C_{Ar}OP), 166.3 (CHO), 164.9 (CHO); ³¹P-NMR (121.5 MHz, CD₃OD): −10.4; −10.5; −10.6; HRMS (EI)⁺: *m/z* calculated for C₁₀H₁₂NO₆PNa [M + Na]⁺ 296.0294, found 296.0304.

N-(2-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-hydroxyformamide (**7ac**). The general procedure F was applied to synthesize compound **7ac** from *cycloSal* **17ac** (77 mg, 0.17 mmol) and 2% TFA in DCM. The product **7ac** was obtained without purification as an orange oil (38 mg, 73%) and as a mixture of the three *Z*, *E* and another conformer in a 30:40:30 ratio, respectively. R_f = 0.33 (EtOAc); ¹H-NMR (400 MHz, CDCl₃): 3.58 (3/10

of 2H, bs, NCH₂), 3.81 (3/10 of 2H, bs, NCH₂), 3.91 (4/10 of 2H, m, NCH₂), 4.41–4.50 (8/10 of 2H, m, POCH₂), 4.58–4.63 (2/10 of 2H, m, POCH₂), 5.30–5.42 (2H, m, ArCH₂OP), 7.03 (1H, m, CH_{Ar}), 7.10 (1H, d, ⁴J = 2.2 Hz, CH_{Ar}), 7.31 (1H, d, ³J = 8.6 Hz, CH_{Ar}), 7.93 (3/10 of 1H, bs, CHO), 8.07 (1/10 of 1H, bs, CHO), 8.54 (4/10 of 1H, bs, CHO); ¹³C-NMR (125.8 MHz CDCl₃): 46.4 (NCH₂), 63.2 (d, ²J = 6.0 Hz, POCH₂), 64.2 (d, ²J = 6.6 Hz, POCH₂), 68.6 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 68.7 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 69.0 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 120.5 (d, ³J_{CP} = 9.2 Hz, CH_{Ar}C_{Ar}OP), 122.0 (d, ³J_{CP} = 10.1 Hz, C_{Ar}CH₂OP), 125.4 (d, ⁴J = 14.2 Hz CH_{Ar(cycloSal)}), 130.4 (CH_{Ar(cycloSal)}), 148.5 (C_{Ar}OP), 164.8 (CHO); ³¹P-NMR (162.0 MHz, CDCl₃): −6.71, −9.07, −9.63; HRMS (EI)⁺: *m/z* calculated for C₁₀H₁₂ClNO₆PNa [M + Na]⁺ 308.0043, found 308.0085.

N-Hydroxy-*N*-(2-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)acetamide (**7ba**). The general procedure F was applied to synthesize compound **7ba** from *cycloSal* **17ba** (73 mg, 0.17 mmol) and 2% TFA in DCM. The product **7ba** was obtained without purification as an orange oil (41 mg, 84%). R_f = 0.35 (EtOAc); ¹H-NMR (500 MHz, CDCl₃): 1.99 (3H, s, CH₃CO), 3.83–3.94 (2H, m, CH₂N), 4.35–4.40 (2H, m, POCH₂), 5.39–5.51 (2H, m, ArCH₂OP), 7.10 (1H, m, CH_{Ar(cycloSal)}), 7.22 (2H, m, CH_{Ar(cycloSal)}), 7.37 (1H, t, ³J = 7.6 Hz, CH_{Ar(cycloSal)}); ¹³C-NMR (125.8 MHz, CDCl₃): 20.3 (CH₃CO), 48.9 (d, ³J = 6.9 Hz, NCH₂), 65.6 (d, ²J = 6.9 Hz, POCH₂), 70.4 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 119.7 (d, ³J_{CP} = 9.1 Hz, CH_{Ar}C_{Ar}OP), 122.4 (d, ³J_{CP} = 9.9 Hz, C_{Ar}CH₂OP), 124.2 (CH_{Ar}), 125.9 (CH_{Ar}), 126.6 (CH_{Ar}), 127.0 (CH_{Ar}), 130.2 (CH_{Ar}), 131.1 (CH_{Ar}), 151.3 (d, ²J_{CP} = 6.8 Hz, C_{Ar}OP), 172.3 (CO), 174.7 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −8.9, −10.5; HRMS (EI)⁺: *m/z* calculated for C₁₁H₁₄NO₆PNa [M + Na]⁺ 310.0451, found 310.0441.

N-(2-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)ethyl)-*N*-hydroxyacetamide (**7bc**). The general procedure F was applied to synthesize compound **7bc** from *cycloSal* **17bc** (71 mg, 0.15 mmol) 2% TFA in DCM. The product **200c** was obtained without purification as an orange oil (33 mg, 68%). R_f = 0.43 (EtOAc); ¹H-NMR (400 MHz, CDCl₃): 2.12–2.28 (3H, s, CH₃CO), 3.58 (3/10 of 2H, bs, NCH₂), 3.93–4.01 (2H, m, NCH₂), 4.41–4.48 (2H, m, POCH₂), 5.30–5.34 (2H, m, ArCH₂OP), 7.03 (1H, d, ³J = 8.7 Hz CH_{Ar}), 7.10 (1H, d, ⁴J = 2.2 Hz, CH_{Ar}), 7.31 (1H, d, ³J = 8.1 Hz, CH_{Ar}); ¹³C-NMR (125.8 MHz, CDCl₃): 20.6 (CH₃CO), 20.7 (CH₃CO), 47.2 (NCH₂), 65.2 (d, ²J = 6.9 Hz, POCH₂), 68.7 (d, ²J_{CP} = 6.9 Hz, ArCH₂OP), 120.2 (d, ³J_{CP} = 8.0 Hz, CH_{Ar}C_{Ar}OP), 120.5 (d, ³J_{CP} = 8.2 Hz, CH_{Ar}C_{Ar}OP), 122.7 (C_{Ar}CH₂OP), 125.4 (CH_{Ar(cycloSal)}), 125.5 (CH_{Ar(cycloSal)}), 128.7 (C_{Ar}Cl), 129.5 (CH_{Ar(cycloSal)}), 130.4 (CH_{Ar(cycloSal)}); ³¹P-NMR (162.0 MHz, CDCl₃): −6.71; HRMS (EI)⁺: *m/z* calculated for C₁₁H₁₄ClNO₆PNa [M + Na]⁺ 322.0242, found 322.0202.

N-Hydroxy-3-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**8aa**). The general procedure F was applied to synthesize compound **8aa** from *cycloSal* **16aa** (80 mg, 0.19 mmol) and 3% TFA in DCM. The crude product was purified by preparative TLC (MeOH/EtOAc, 5:95 *v/v*) to give **8aa** as a colorless oil (31 mg, 60%) and as a sole *Z* conformer. R_f = 0.39 (EtOAc/methanol, 95:5); ¹H-NMR (400 MHz, CD₃OD): 2.49 (2H, m, CH₂CO), 4.37–4.51 (2H, m, POCH₂), 5.38–5.48 (ArCH₂OP), 7.10 (1H, pseudo-d, ³J = 7.9 Hz, CH_{Ar(cycloSal)}), 7.17–7.23 (2H, m, CH_{Ar(cycloSal)}), 7.37 (1H, pseudo-t, ³J = 7.6 Hz, CH_{Ar}); ¹³C-NMR (125.8 MHz, CD₃OD): 34.8 (d, ³J_{C-P} = 7.5 Hz, CH₂CO), 65.9 (d, ²J_{C-P} = 5.3 Hz, POCH₂), 70.2 (d, ²J_{C-P} = 6.9 Hz, ArCH₂OP), 119.5 (d, ³J_{C-P} = 9.0 Hz, CH_{Ar}C_{Ar}OP), 122.4 (d, ³J_{C-P} = 9.8 Hz, C_{Ar}CH₂OP), 125.9 (CH_{Ar(cycloSal)}), 127.1 (CH_{Ar(cycloSal)}), 131.2 (CH_{Ar(cycloSal)}), 151.3 (d, ²J_{C-P} = 6.8 Hz, C_{Ar}OP), 169.0 (CO); ³¹P-NMR (162 MHz, CD₃OD): −9.3; HRMS (EI)⁺: *m/z* calculated for C₁₀H₁₂NO₆PNa [M + Na]⁺ 296.0294, found 296.0266.

3-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-*N*-hydroxypropanamide (**8ac**). The general procedure F was applied to synthesize compound **8ac** from *cycloSal* **16ac** (93 mg, 0.20 mmol) and 2% TFA in DCM. The product **201c** was obtained without purification as a colorless oil (50 mg, 81%) and as a mixture of two *Z* and *E* conformers in a 60:40 ratio. R_f = 0.18 (EtOAc); ¹H-NMR (500 MHz, CDCl₃): 2.61 (6/10 of 2H, bs, CH₂CO), 2.93 (4/10 of 2H, bs, CH₂CO), 4.42–4.47 (2H, m, POCH₂), 5.24–5.35 (2H, m, ArCH₂OP), 6.97 (1H,

pseudo-d, $^3J = 8.4$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.05 (1H, pseudo-s, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.24 (1H, pseudo-s, $\text{CH}_{\text{Ar}(\text{cycloSal})}$); ^{13}C -NMR (125.8 MHz, CDCl_3): 29.9 (CH_2CO), 64.9 (POCH_2), 68.5 (d, $^2J_{\text{C-P}} = 6.5$ Hz, ArCH_2OP), 123.5 (d, $^3J_{\text{C-P}} = 9.4$ Hz, $\text{ClC}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 124.1 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 124.2 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 124.5 ($\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 125.6 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 130.0 ($\text{C}_{\text{Ar}}\text{Cl}$), 130.3 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 148.5 (d, $^2J_{\text{C-P}} = 5.2$ Hz, $\text{C}_{\text{Ar}}\text{OP}$); ^{31}P -NMR (162.0 MHz, CDCl_3): -10.3 ; HRMS (EI) $^+$: m/z calculated for $\text{C}_{11}\text{H}_{12}\text{ClNO}_6\text{P}$ $[\text{M} + \text{H}]^+$ 308.0085, found 308.0110.

N-Hydroxy-*N*-methyl-3-((2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**8ba**). The general procedure F was applied to synthesize the compound **8ba** from *cycloSal* **16ba** (20 mg, 0.05 mmol) and 2% TFA in DCM. The product **8ba** was obtained without purification as a colorless oil (11 mg, 80%) and as a mixture of two *Z* and *E* conformers in a 30:70 ratio. $R_f = 0.30$ (EtOAc); ^1H -NMR (400 MHz, CDCl_3): 2.76 (30/100H of 2H, bs, CH_2CO), 2.87–3.06 (70/100H of 2H, m, CH_2CO), 3.24 (70/100H of 3H, s, NCH_3), 3.33 (30/100H of 3H, s, NCH_3), 4.43–4.53 (2H, m, POCH_2), 5.30–5.44 (2H, m, ArCH_2OP), 6.84 (1H, bs, OH), 7.05–7.09 (2H, m, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.15 (1H, t, $^3J = 7.6$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.32 (1H, t, $^3J = 7.8$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$); ^{13}C -NMR (125.8 MHz, CDCl_3): 32.3 (CH_2CO), 33.3 (CH_2CO), 36.3 (NCH_3), 64.4 (POCH_2), 65.3 (d, $^2J_{\text{C-P}} = 5.3$ Hz, POCH_2), 69.0 (d, $^2J_{\text{C-P}} = 6.8$ Hz, ArCH_2OP), 118.9 (d, $^3J_{\text{C-P}} = 9.1$ Hz, $\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 120.6 (d, $^3J_{\text{C-P}} = 10.1$ Hz, $\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 124.8 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 125.6 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 130.2 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 150.0 (d, $^2J_{\text{C-P}} = 6.1$ Hz, $\text{C}_{\text{Ar}}\text{OP}$), 170.4 (CO); ^{31}P -NMR (162.0 MHz, CDCl_3): -9.7 ; MS (EI) $^+$: m/z calculated for $\text{C}_{11}\text{H}_{14}\text{NO}_6\text{PNa}$ $[\text{M} + \text{Na}]^+$ 310.043, found 310.043.

N-Hydroxy-*N*-methyl-3-((6-methyl-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**8bb**). The general procedure F was applied to synthesize the compound **8bb** from *cycloSal* **16bb** (20 mg, 44 μmol) in 2% TFA in DCM. The product **202b** was obtained without purification as a colorless oil (11 mg, 83%) and as a mixture of two *Z* and *E* conformers in a 30:70 ratio, respectively. $R_f = 0.24$ (EtOAc); ^1H -NMR (500 MHz, CDCl_3): 2.31 (3H, s, CH_3), 2.77–3.07 (3H, m, CH_2CO and OH), 3.26 (7/10 of 3H, s, NCH_3), 3.34 (3/10 of 3H, s, NCH_3), 4.47 (2H, bs, POCH_2), 5.27–5.39 (2H, m, ArCH_2OP), 6.86 (1H, s, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 6.93–6.96 (1H, m, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.10 (1H, d, $^3J = 8.3$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$); ^{13}C -NMR (125.8 MHz, CDCl_3): 20.9 (CH_3), 33.3 (CH_2CO), 36.2 (NCH_3), 65.6 (d, $^2J_{\text{C-P}} = 6.4$ Hz, POCH_2), 69.3 (d, $^2J_{\text{C-P}} = 6.6$ Hz, ArCH_2OP), 118.6 (d, $^3J_{\text{C-P}} = 8.9$ Hz, $\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 120.1 (d, $^3J_{\text{C-P}} = 9.7$ Hz, $\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 125.8 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 130.6 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 134.6 ($\text{C}_{\text{Ar}}\text{CH}_3$), 147.8 (d, $^2J_{\text{C-P}} = 7.1$ Hz, $\text{C}_{\text{Ar}}\text{OP}$); ^{31}P -NMR (162.0 MHz, CDCl_3): -9.2 ; MS (EI) $^+$: m/z calculated for $\text{C}_{12}\text{H}_{16}\text{NO}_6\text{P}$ $[\text{M} + \text{H}]^+$ 302.0788, found 302.077.

3-((6-Chloro-2-oxido-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)-*N*-hydroxy-*N*-methylpropanamide (**8bc**). The general procedure F was applied to synthesize compound **8bc** from *cycloSal* **16bc** (87 mg, 0.18 mmol) and 2% TFA in DCM. The product **8bcc** was obtained without purification as a colorless oil (25 mg, 44%) and as a mixture of two *Z* and *E* conformers in a 30:70 ratio. $R_f = 0.31$ (EtOAc); ^1H -NMR (500 MHz, CDCl_3): 2.80 (3/10 of 2H, bs, CH_2CO), 2.94–3.09 (7/10 of 2H, bs, CH_2CO), 3.29 (7/10 of 3H, bs, NCH_3), 3.37 (3/10 of 3H, bs, NCH_3), 4.51 (2H, bs, POCH_2), 5.28–5.41 (2H, m, ArCH_2OP), 7.02 (1H, pseudo-d, $^3J = 8.7$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.09 (1H, pseudo-d, $^3J = 2.3$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$), 7.30 (1H, pseudo-d, $^3J = 8.7$ Hz, $\text{CH}_{\text{Ar}(\text{cycloSal})}$); ^{13}C -NMR (125.8 MHz, CDCl_3): 29.9 (CH_2CO), 32.3 (CH_2CO), 36.2 (NCH_3), 36.4 (NCH_3), 64.5 (POCH_2), 65.6 (d, $^2J_{\text{C-P}} = 5.3$ Hz, POCH_2), 68.4 (ArCH_2OP), 68.6 (d, $^2J_{\text{C-P}} = 6.1$ Hz, ArCH_2OP), 120.3 (d, $^3J_{\text{C-P}} = 8.8$ Hz, $\text{CH}_{\text{Ar}}\text{C}_{\text{Ar}}\text{OP}$), 121.9 ($\text{C}_{\text{Ar}}\text{CH}_2\text{OP}$), 125.5 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 130.3 ($\text{CH}_{\text{Ar}(\text{cycloSal})}$), 148.5 ($\text{C}_{\text{Ar}}\text{OP}$); ^{31}P -NMR (162.0 MHz, CDCl_3): -10.2 ; HRMS (EI) $^+$: m/z calculated for $\text{C}_{11}\text{H}_{13}\text{ClNO}_6\text{PNa}$ $[\text{M} + \text{Na}]^+$ 344.0061, found 344.0030.

N-Hydroxy-*N*-methyl-3-((2-oxido-6-(trifluoromethyl)-4*H*-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)propanamide (**8bf**). The general procedure F was applied to synthesize compound **8bf** from *cycloSal* **16bf** (20 mg, 40 μmol) and 2% TFA in DCM. The product **8bf** was obtained without purification as a colorless oil (11 mg, 80%) and as a mixture of two *Z* and *E* conformers in a 40:60 ratio. $R_f = 0.57$ (EtOAc); ^1H -NMR (500 MHz, CDCl_3): 2.77–3.06 (3H, m, CH_2CO

and OH), 3.26 (6/10 of 3H, s, NCH₃), 3.36 (4/10 of 3H, s, NCH₃), 4.63 (2H, m, POCH₂), 5.35–5.49 (2H, m, ArCH₂OP), 7.16–7.20 (1H, m, CH_{Ar(cycloSal)}), 7.38 (1H, s, CH_{Ar(cycloSal)}), 7.61 (1H, d, ³J = 8.5 Hz, CH_{Ar(cycloSal)}); ¹³C-NMR (125.8 MHz, CDCl₃): 31.9 (CH₂CO), 33.3 (CH₂CO), 36.0 (NCH₃), 36.3 (NCH₃), 64.5 (POCH₂), 65.8 (d, ²J_{C-P} = 6.2 Hz, POCH₂), 68.7 (d, ²J_{C-P} = 7.0 Hz, ArCH₂OP), 119.7 (d, ³J_{C-P} = 9.2 Hz, CH_{Ar}C_{Ar}OP), 121.2 (d, ³J_{C-P} = 9.8 Hz, C_{Ar}CH₂OP), 123.2 (CH_{Ar(cycloSal)}), 127.5 (CH_{Ar(cycloSal)}), 152.4 (d, ²J_{C-P} = 7.3 Hz, C_{Ar}OP), 170.3 (CO); ³¹P-NMR (162.0 MHz, CDCl₃): −10.3; ¹⁹F-NMR (282.4 MHz, CDCl₃): −63.3; HRMS (EI)⁺: *m/z* calculated for C₁₂H₁₃F₃NO₆PNa [M + Na]⁺ 378.0325, found 378.0331.

3.2. Bacterial Growth Inhibition

The antimicrobial activity of all *cycloSal* prodrugs (**7** and **8**), double prodrugs (**16** and **17**) and Bis(*cycloSal*) prodrugs (**18**) against *E. coli* and *M. smegmatis*, was determined using the paper disc diffusion method. A bacterial suspension (200 µL, mid-exponential phase) was spread on agar plates (9 cm diameter) using glass beads. Agar plates contained Luria-Bertani medium for *E. coli* and MS medium for *M. smegmatis* [17]. Paper discs (Durieux no. 268, diameter 6 mm) impregnated with a volume ≤ 8 µL of double prodrugs, *cycloSal* prodrugs or Bis(*cycloSal*) prodrugs were placed on petri dishes. Growth inhibition was examined after a 24 h incubation period at 37 °C. Isoniazid (30 nmoles) and fosmidomycin (10 nmoles) are used as reference compounds for *M. smegmatis* and *E. coli*, respectively.

4. Conclusions

The *cycloSal* approach has largely been applied to various nucleosides to improve their biological activity in antiviral and cancer therapy. This technique allows an efficient intracellular nucleotide delivery from the pronucleotides via a specific pH-driven mechanism. Even if the *cycloSal* strategy might be useful to deliver non-nucleotide phosphorylated molecules, it has not been widely used in the past. We implemented this ProTide strategy to synthesize prodrugs of fosfoxacin and its analogs, inhibitors of the DXR. The synthesized prodrugs were shown to prevent the growth of *M. smegmatis*, with the best candidates being prodrugs with an electron-withdrawing substituent on the *cycloSal* moiety and a DMB-protecting group on the hydroxamate. The presence of the DMB, combined with the presence of a *cycloSal* prodrug, appears to increase the molecule lipophilicity and, thus, its penetration into the cell. However, two questions still remain: (i) Is the DMB hydrolyzed or supported by an enzyme to liberate the inhibitor? (ii) are the O-DMB-protected inhibitors of the DXR capable of binding in the DXR active site? Further work is currently in progress in our laboratory to answer these questions. Nevertheless, this first report of the use of *cycloSal*igenyl prodrugs on bacteria provided very interesting candidates. They offer insights and new perspectives for the development of antimycobacterial prodrugs.

Author Contributions: M.M. performed all the syntheses. D.T. performed biological assays. Writing-original draft preparation C.G.-B. Writing-review and editing, M.M., D.T., D.L., M.R. and C.G.-B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Data are contained within the article.

Acknowledgments: M.M. acknowledges financial support from the 'Ministère de la Recherche'. The authors express their gratitude to L. Allouche, B. Vincent and M. Coppe for NMR measurements.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. Antimicrobial Resistance. Key Facts 17 November 2017. Available online: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance> (accessed on 12 July 2023).
2. World Health Organization. Tuberculosis. Key Facts 21 April 2023. Available online: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis> (accessed on 12 July 2023).

3. Sulis, G.; Pa, M. Isoniazid-resistant tuberculosis: A problem we can no longer ignore. *PLoS Med.* **2020**, *17*, e1003023. [[CrossRef](#)] [[PubMed](#)]
4. Mori, G.; Roberto Chiarelli, L.; Riccardi, G.; Pasca, M.R. New prodrugs against tuberculosis. *Drug Discov. Today* **2017**, *22*, 519–525. [[CrossRef](#)] [[PubMed](#)]
5. Rohmer, M.; Grosdemange-Billiard, C.; Seemann, M.; Tritsch, D. Isoprenoid biosynthesis as a novel target for antibacterial and antiparasitic drugs. *Curr. Opin. Investig. Drugs* **2004**, *5*, 154–162. [[PubMed](#)]
6. Katayama, N.; Nozaki, Y.; Harada, S.; Ono, H.; Industries, T.C.J. Fosfadecyn and fosfocytocin, new nucleotide antibiotics produced by bacteria. *Antibiotics* **1990**, *43*, 238–246. [[CrossRef](#)] [[PubMed](#)]
7. Masini, T.; Hirsch, A.K.H. Development of inhibitors of the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway enzymes as potential anti-infective agents. *J. Med. Chem.* **2014**, *57*, 9740–9763. [[CrossRef](#)] [[PubMed](#)]
8. Murakawa, T.; Sakamoto, H.; Fukada, S.; Konishi, T.; Nishida, M. Pharmacokinetics of fosmidomycin, a new phosphonic acid antibiotic. *Antimicrob. Agents Chemother.* **1982**, *21*, 224–230. [[CrossRef](#)] [[PubMed](#)]
9. Kuntz, L.; Tritsch, D.; Grosdemange-Billiard, C.; Hemmerlin, A.; Willem, A.; Bach, T.J.; Rohmer, M. Isoprenoid biosynthesis as a target for antibacterial and antiparasitic drugs: Phosphonohydroxamic acids as inhibitors of deoxyxylulose phosphate reductoisomerase. *Biochem. J.* **2005**, *386*, 127–135. [[CrossRef](#)]
10. Munier, M.; Tritsch, D.; Krebs, F.; Esque, J.; Hemmerlin, A.; Rohmer, M.; Stote, R.H.; Grosdemange-Billiard, C. Synthesis and biological evaluation of phosphate isosters of fosmidomycin and analogs as inhibitors of *Escherichia coli* and *Mycobacterium smegmatis* 1-deoxyxylulose 5-phosphate reductoisomerases. *Bioorg. Med. Chem.* **2017**, *25*, 684–689. [[CrossRef](#)]
11. Brown, A.C.; Parish, T. Dxr is essential in *Mycobacterium tuberculosis* and fosmidomycin resistance is due to a lack of uptake. *BMC Microbiol.* **2008**, *8*, 78. [[CrossRef](#)]
12. Albert, A. Chemical aspects of selective toxicity. *Nature* **1958**, *182*, 421–422. [[CrossRef](#)]
13. Courtens, C.; Risseuw, M.; Caljon, G.; Cos, P.; Van Calenbergh, S. Acyloxybenzyl and Alkoxyalkyl Prodrugs of a Fosmidomycin Surrogate as Antimalarial and Antitubercular Agents. *ACS Med. Chem. Lett.* **2018**, *9*, 986–989. [[CrossRef](#)] [[PubMed](#)]
14. Courtens, C.; van Charante, F.; Quennesson, T.; Risseuw, M.; Cos, P.; Caljon, G.; Coenye, T.; Van Calenbergh, S. Acyloxymethyl and alkoxy carbonyloxymethyl prodrugs of a fosmidomycin surrogate as antimalarial and antibacterial agents. *Eur. J. Med. Chem.* **2023**, *245*, 114924. [[CrossRef](#)] [[PubMed](#)]
15. Mehellou, Y.; Balzarini, J.; McGuigan, C. Aryloxy phosphoramidate triesters: A technology for delivering monophosphorylated nucleosides and sugars into cells. *ChemMedChem* **2009**, *4*, 1779–1791. [[CrossRef](#)] [[PubMed](#)]
16. Slusarczyk, M.; Ferla, S.; Branciale, A.; McGuigan, C. Synthesis and biological evaluation of 6-substituted-5-fluorouridine ProTides. *Bioorg. Med. Chem.* **2018**, *26*, 551–565. [[CrossRef](#)]
17. Munier, M.; Tritsch, D.; Lièvre, D.; Rohmer, M.; Grosdemange-Billiard, C. Synthesis and biological evaluation of aryl phosphoramidate prodrugs of fosfoxacin and its derivatives. *Bioorg. Chem.* **2019**, *89*, 103012. [[CrossRef](#)] [[PubMed](#)]
18. Meier, C.; Lorey, M.; De Clercq, E.; Balzani, J. Cyclic saligenyl phosphotriesters of 2',3'-dideoxy-2',3'-didehydrothymidine (d4T)—A new pro-nucleotide approach. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 99–104. [[CrossRef](#)]
19. Hecker, S.J.; Erion, M.D. Prodrugs of phosphates and phosphonates. *J. Med. Chem.* **2008**, *51*, 2328–2345. [[CrossRef](#)]
20. Meier, C.; Balzarini, J. Application of the cycloSal-prodrug approach for improving the biological potential of phosphorylated biomolecules. *Antiviral Res.* **2006**, *71*, 282–292. [[CrossRef](#)]
21. Meier, C. cycloSal Phosphates as chemical trojan horses for intracellular nucleotide and glycosylmonophosphate delivery—Chemistry meets biology. *Eur. J. Org. Chem.* **2006**, *5*, 1081–1102. [[CrossRef](#)]
22. Ruda, G.F.; Wong, P.E.; Alibu, V.P.; Norval, S.; Read, K.D.; Barrett, M.P.; Gilbert, I.H. Aryl phosphoramidates of 5-phospho erythronohydroxamic acid, a new class of potent trypanocidal compounds. *J. Med. Chem.* **2010**, *53*, 6071–6078. [[CrossRef](#)]
23. Zuo, L.; Yao, S.; Wang, W.; Duan, W. An efficient method for demethylation of aryl methyl ethers. *Tetrahedron Lett.* **2008**, *49*, 4054–4056. [[CrossRef](#)]
24. Cho, S.-D.; Park, Y.-D.; Kim, J.-J.; Falck, J.R.; Yoon, Y.-J. Facile reduction of carboxylic acids, esters, acid chlorides, amides and nitriles to alcohols or amines using NaBH₄/BF₃·Et₂O. *Bull. Korean Chem. Soc.* **2004**, *25*, 407–409. [[CrossRef](#)]
25. Barlaam, B.; Hamon, A.; Maudet, M. New hydroxylamines for the synthesis of hydroxamic acids. *Tetrahedron Lett.* **1998**, *39*, 7865–7868. [[CrossRef](#)]
26. San Jose, G.; Jackson, E.R.; Haymond, A.; Johnny, C.; Edwards, R.L.; Wang, X.; Brothers, R.C.; Edelstein, E.K.; Odom, A.R.; Boshoff, H.I.; et al. Structure—activity relationships of the MEPicides: N-Acyl and O-linked analogs of FR900098 as inhibitors of Dxr from *Mycobacterium tuberculosis* and *Yersinia pestis*. *ACS Infect. Dis.* **2016**, *2*, 923–935. [[CrossRef](#)] [[PubMed](#)]
27. Courtens, C.; Risseuw, M.; Caljon, G.; Maesb, L.; Cosb, P.; Martin, A.; Van Calenbergh, S. Double prodrugs of a fosmidomycin surrogate as antimalarial and antitubercular agents. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1232–1235. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.