Received: 31 May 2018 | Accepted: 20 August 2018

DOI: 10.1002/hc.21436

RESEARCH ARTICLE

WILEY Heteroatom Chemistry

Green synthesis and cytotoxic activity of dibenzyl α-hydroxyphosphonates and α-hydroxyphosphonic acids

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Funding information
National Research Development and Innovation Fund, Grant/Award Number: K119202; Chinoin-Sanofi Pharmaceuticals; József Varga Foundation; New National Excellence Program of the Ministry of Human Capacities, Grant/Award Number: ÚNKP-17-4-I-BME-133

Abstract

A series of dibenzyl α-hydroxyphosphonates and the corresponding α-hydroxyphosphonic acids, mostly new compounds, have been synthesized. The dibenzyl α-hydroxyphosphonates have been obtained in the Pudovik reaction of substituted benzaldehydes and dibenzyl phosphite in the presence of triethylamine as the catalyst. The amount of the solvent was minimized during the reaction, and the workup involved crystallization from the reaction mixture. A new protocol was developed to transform the dibenzyl 1-hydroxyphosphonates to the corresponding phosphonic acids by catalytic hydrogenation. The derivatives prepared were screened as potential cytotoxic agents against Mes-Sa human uterine sarcoma cell line.

1 | INTRODUCTION

The continuing interest in α-hydroxyphosphonates is owing to the versatile bioactive effect of a series of compounds containing this scaffold. A number of related derivatives were identified as enzyme inhibitors,[1] pesticides,[2] and antibacterial,[3,4] antimicrobial,[5,6] or antifungal[3] agents, as well as antioxidants,[7,8] which underline their importance in organophosphorus chemistry. The investigation of their cytotoxic effect is still in its infancy, as only one paper reported their effectiveness against human cancer lines.[9]

α-Hydroxyphosphonates are not only in the focus due to their possible use in pharmacology, but they also represent a privileged class in modern synthetic chemistry, as may be starting materials for a number of potentially bioactive compounds. One of the most prominent classes of α-hydroxyphosphonate derivatives is the family of the corresponding α-hydroxyphosphonic acids mainly known as the inhibitors of CD45 tyrosine phosphatase[10] and undecaprenyl diphosphate phosphatase (UPPP).[11] Related molecules were also tested as potential inhibitors of P5C reductase[12] and as possible ligands binding in the pocket of protein Src SH_2.[13]

Contract grant sponsor: National Research Development and Innovation Fund

Contract grant number: K119202

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As for the syntheses of these valuable bioactive compounds, the most frequently applied synthetic strategy to α-hydroxyphosphonates is the nucleophilic addition of dialkyl phosphites to an aldehyde or ketone.[14] Since the so-called Pudovik reaction was first reported using alkali alcoholates as the catalyst to deprotonate the >P(O)H reagent,[15] procedures in the presence of a wide range of base catalysts, using, for example, sodium ethylate in ethanol[16] were published. Organic bases, such as quinine[17,18] and tetramethylguanidine,[19] were also proved to catalyze the Pudovik reaction. The addition was also performed applying organometallic reagents including butyl lithium,[20] lithium diisopropyl amide,[21] and Grignard reagents.[22] Accomplishments applying metal-amido complexes are also known.[23-27] Although the use of base catalysts in the addition of dialkyl phosphite to oxo compounds is more widespread, a few acid-catalyzed procedures were also reported employing Lewis acid-like MoO_2Cl_2,[28] $NbCl_5$,[29] or $Ti(O^iPr)_4$.[30] According to another protocol, the Pudovik reaction was performed on the surface of silica-supported tungstic acid.[31] The appearance of the principles of green chemistry brought about a paradigm shift also in the synthesis of α-hydroxyphosphonates. Recent articles targeted to perform the addition under mild and solvent-free reaction conditions. These methods mainly employed simple and inexpensive oxides/bases/salts as catalysts, including aluminum oxide,[32,33] magnesium oxide,[34-36] barium hydroxide,[37,38] sodium carbonate,[39-41] potassium hydrogen sulfate,[7] and inorganic phosphates,[42,43] as well as triethylamine[44] or piperazine.[45] In a few cases, the components were activated by grinding[41,45] or microwave (MW) irradiation.[39,40,46,47] The new, environmentally friendly protocols emphasize the lack of solvent during the reaction; however, the use of volatile organic compounds could not be eliminated from the workup process, as it comprised intensive use of solvents in operations like extraction, column chromatography, and recrystallization.

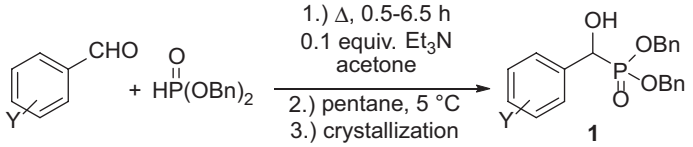
α-Hydroxyphosphonic acids are usually prepared from the corresponding α-hydroxyphosphonates. One synthetic route to α-hydroxyphosphonic acids involves the hydrolysis of α-hydroxyphosphonates in the presence of hydrochloric acid used in an excess.[11] Another widely applied method is the fission of the *C–O* bond of the ester function of α-hydroxyphosphonates using trimethylsilyl bromide, followed by hydrolysis.[48-50] An oxidative method is also known, starting from α-hydroxyalkyl-*H*-phosphinic acids, employing I_2/DMSO as the oxidizing system.[51] In most cases, the main goal was to synthesize a potentially bioactive target molecule, and the method itself represented a secondary issue. As a consequence of this approach, less attention was devoted to find the optimal conditions of the reactions that usually remained excessive regarding temperature, time, and amount of the reagents. A few of the related articles came up with the idea of applying catalytic hydrogenation for the synthesis of α-hydroxyphosphonic acids starting from the corresponding benzyl phosphonates.[52-55] However, in most cases, the removal of the benzyl groups is only one transformation of a multistep synthesis; thus, the catalytic hydrogenation was not studied in detail.

A new and benign method was developed for the synthesis of α-hydroxyphosphonates starting from substituted benzaldehyde and dimethyl or diethyl phosphite by us.[56] Our protocol employed triethylamine as an inexpensive catalyst and targeted to minimize the use of organic solvents during the reaction, as well as the work-up procedure, in contrast to the methods previously described in the literature. The new protocol under discussion allowed the preparation of α-hydroxyphosphonates by a simple crystallization from the reaction mixture eliminating the need for further purification steps.

Dimethyl and diethyl α-hydroxyphosphonates are extensively studied compounds; however, the synthesis of the corresponding dibenzyl phosphonates has hardly been investigated, as so far only a few papers reported their synthesis.[57-60] Two dibenzyl α-hydroxyphosphonates were synthesized on the surface of Al_2O_3-KF.[57] Extraction with CH_2Cl_2 afforded the products in low yields of 50%. The same method was used for the preparation of another derivative in a resolution study.[58] In another article,[59] not any detail on the preparation was provided. Finally, reference[60] covers a procedure that involves the use of an exotic V-containing catalyst, and the workup may involve recrystallization or column chromatography to afford the hydroxyphosphonates in yields of 84%-92%. Prompted by the recognition that a green synthetic route toward dibenzyl α-hydroxyphosphonates is still missing from the literature, we aimed at the extension of our method starting from dibenzyl phosphite and substituted benzaldehydes to prepare dibenzyl α-hydroxyphosphonates as new compounds. We also wished to transform the derivatives so obtained to the corresponding α-hydroxyphosphonic acids by hydrogenolytic debenzylation, making thus available two series of potentially cytotoxic compounds. The investigation of the anticancer effect of α-hydroxyphosphonates is a pioneering work, as their cytotoxic activity was studied only in one case, but on other cell lines that we aimed at in our study.[9]

2 | RESULTS AND DISCUSSION

At first, dibenzyl α-hydroxyphosphonates (**1**) were synthesized from substituted benzaldehydes and dibenzyl phosphite by the extension of our method reported previously.[56] An equimolar mixture of the starting components was stirred at reflux in a minimal amount of acetone (1 mL for 11.0 mmol benzaldehyde) in the presence of 10 mol% triethylamine as the catalyst (Scheme 1). The



SCHEME 1 A solvent-economic, green protocol for the synthesis of dibenzyl α-hydroxyphosphonates (**1a**-**i**)

Y = H (**a**), 2-Cl (**b**), 3-Cl (**c**), 4-Cl (**d**), 2-NO_2 (**e**), 4-NO_2 (**f**), 3-Me (**g**), 4-Me (**h**), 2-MeO (**i**)

reaction times depended highly on the substituent in the aromatic ring. The reaction of benzaldehyde and dibenzyl phosphite was completed after 0.5 hours (Table 1, entry 1). Aryl aldehydes with electron-withdrawing chloro and nitro substituents were of similar reactivity, requiring a reaction time of 0.5 hours (Table 1, entries 2-6). However, starting from aryl aldehydes bearing electron-donating substituents, a longer reaction time was necessary. In case of tolualdehydes, completion of the reaction required 5.5 hours (Table 1, entries 7 and 8). 2-Methoxybenzaldehyde revealed the lowest reactivity, as in this case, the amount of the catalyst had to be increased to 20 mol%, and completion of the addition required 6.5 hours (Table 1, entry 9). The workup included the addition of pentane (6 mL), followed by cooling the reaction mixture to 5°C. The product crystallized from the reaction mixture on cooling. The dibenzyl α-hydroxyphosphonates (**1a**-**i**) were obtained by a simple filtration in yields of 88%-99%, in a purity of >99%.

After the synthesis of dibenzyl α-hydroxyphosphonates (**1a**-**i**), we aimed at the preparation of α-hydroxyphosphonic acids (**2a**-**i**) by catalytic hydrogenation of the corresponding benzyl phosphonates under mild conditions, as an alternative route to classical hydrolysis. The hydrogenation reactions were performed using 10% Pd/C (with a catalyst/substrate ratio of 0.05 g/g) in methanol at 25°C and 10 bar (Scheme 2).

In all but one cases, the reactions took place rather easily, and a short reaction time of 5-15 minutes was sufficient (Table 2). With one exception, the α-hydroxyphosphonic acids were obtained in yields of 72%-90% after purification.

In case of dibenzyl 1-hydroxy-1-(4-nitrophenyl) -methylphosphonate (**1f**), in the first 2 minutes the hydrogen uptake was as fast as in the other cases. After 2 minutes, the hydrogen uptake slowed down dramatically and lasted for 2.5 hours. The longer reaction time and higher hydrogen uptake are due to the reduction of the nitro function in the aromatic ring taking place in parallel to the debenzylation. The product so-obtained was 1-(4-aminophenyl)-1-hydroxymethylphosphonic acid (**2j**). It is worthy to mention that interrupting the catalytic hydrogenation, different intermediates could be pointed out from the mixture making use of ^{31}P NMR analysis (Table 3).

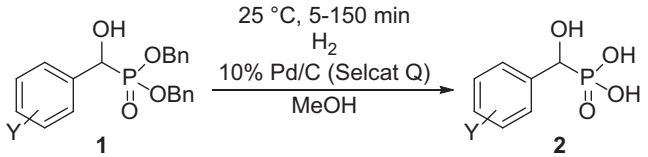
The catalytic debenzylation is a more robust and efficient way for the preparation of α-hydroxyphosphonic acids than the traditional acidic hydrolysis.

All together, nine dibenzyl α-hydroxyphosphonates and eight α-hydroxyphosphonic acids were synthesized. The new derivatives, four α-hydroxyphosphonates (**1b**, **1c**, **1e**, and **1g**) and four α-hydroxyphosphonic acids (**2j**, **2g**-**i**), were fully characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as HRMS data by us. **1a**, **1d**, **1f**, **1h**, and **1i** already known from the literature were identified by ^{31}P NMR chemical shifts and HRMS data. α-Hydroxyphosphonic acids **2a**-**d** were mentioned in the literature; however, their characterization remained incomplete. For this, they were also characterized by us by ^{13}C NMR data. It is noted that a part of the hydroxyphosphonic acids (**2b**, **2c**, **2j**,

TABLE 1 Experimental details for the preparation of dibenzyl α-hydroxyphosphonates (**1a**-**i**)

Entry	Y	Time (h)	Product	Yield (%)
1	H	0.5	**1a**	95
2	2-Cl	0.5	**1b**	93
3	3-Cl	0.5	**1c**	88
4	4-Cl	0.5	**1d**	95
5	2-NO_2	0.5	**1e**	91
6	4-NO_2	0.5	**1f**	99
7	3-Me	5.5	**1g**	88
8	4-Me	5.5	**1h**	94
9	2-MeO	6.5[a]	**1i**	96

[a]In this case, 20 mol% of triethylamine was used.



Y = H (**a**), 2-Cl (**b**), 3-Cl (**c**), 4-Cl (**d**), 4-NO_2 (**f**)
3-Me (**g**), 4-Me (**h**), 2-MeO (**i**), 4-NH_2 (**j**)

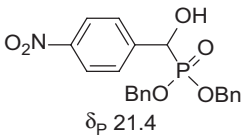
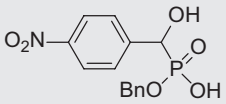
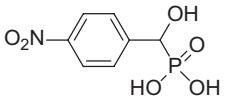
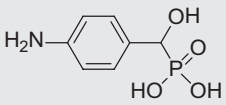
SCHEME 2 Catalytic hydrogenation of dibenzyl α-hydroxyphosphonates (**1a**-**i**)

TABLE 2 Experimental details for the preparation of α-hydroxyphosphonic acids

Entry	Y	Starting HP	Time (min)	Product	Yield (%)
1	H	**1a**	15	**2a**	80
2	2-Cl	**1b**	10	**2b**	85
3	3-Cl	**1c**	5	**2c**	76
4	4-Cl	**1d**	7	**2d**	88
5	4-NO_2	**1f**	150	**2j** (Y = NH_2)	50[a]
6	3-Me	**1g**	9	**2g**	77
7	4-Me	**1h**	9	**2h**	90
8	2-MeO	**1i**	5	**2i**	72

[a]Due to insolubility in methanol, **2j** was purified only by digeration in dichloromethane.

TABLE 3 The course of the catalytic hydrogenation of dibenzyl 1-hydroxy-1-(4-nitrophenyl)-methylphosphonate (**1f**)

	Time (min)		
Components (%)[a]	2	15	150
 δ_P 21.4	12	10	0
 δ_P 17.2 b	51	48	0
 δ_P 16.4	37	29	0
 δ_P 19.2	0	13	100 (Yield: 50%)

[a]Determined on the basis of relative ^{31}P NMR intensities from the crude mixtures (DMSO-d6).
[b]HRMS: $[M - H]^-_{found}$ = 322.04790. $C_{14}H_{13}NO_6P$ requires 322.04860.

and **2g**) could not be identified by MS analysis due to their decomposition under the conditions of the measurements. A few derivatives (**2a**, **2d**, **2h**, and **2i**) appeared as dimers [2M + H].

2.1 | Primary and confirmatory screening assay on 384-well plates

All compounds were dissolved in DMSO and stored at −20°C. To determine growth inhibitory potential, we conducted the cytotoxicity experiments in two steps. As a primary screen, each compound was tested at a final concentration of 20 and 200 μmol/L to exclude nontoxic compounds (Figure 1). Compounds that showed 50% growth inhibition in 200 μmol/L were scored as "hits" and were passed to the second step. As confirmatory cytotoxicity tests, "hit" compounds were tested using a concentration range (extending from 500 μmol/L down to 7.62 nmol/L in 3-fold dilutions) in order to obtain dose-response curves (Figure 2). Via similar screening approaches that were applied here, potent cancer targeting compounds have been identified previously.[61-63]

The primary screen returned 8 compounds showing at least 50% growth inhibition at 200 μmol/L. When 20 μmol/L of the 17 compounds was added to the cell line, none of them could kill at least 50% of the cells.

The cytotoxic compounds were all dibenzyl α-hydroxyphosphonates, while the nontoxic compounds belong all to the group of α-hydroxyphosphonic acids, with

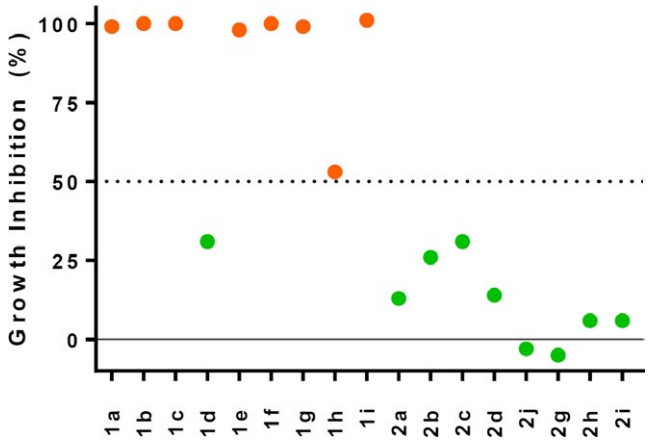


FIGURE 1 Cytotoxicity of the synthesized compounds against Mes-Sa mCherry cell line. Growth inhibition of the compounds at 200 µmol/L concentration in the primary screen

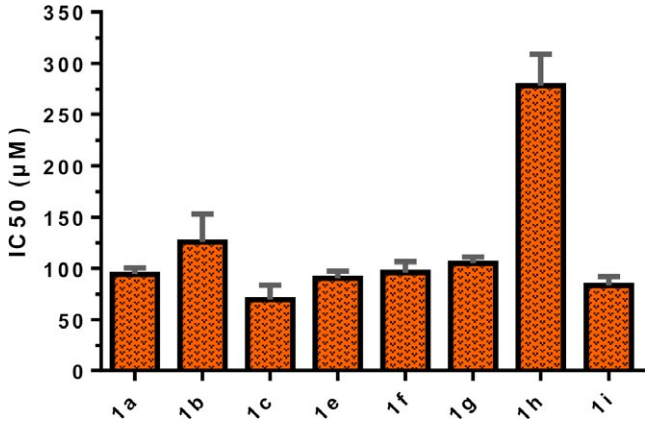


FIGURE 2 IC_{50} values of the compounds exerting at least 50% growth inhibition in the primary screen

the exception of species **1d** that showed only 31% growth inhibition, albeit it belongs to the former group. Interestingly, hydroxyphosphonates **1d** and **1h** having a chloro or a methyl substituent in the para position of the aromatic ring were the least toxic among the dibenzyl α-hydroxyphosphonates, while their ortho- and meta-substituted analogues were more toxic.

During the preliminary cytotoxicity assays, dimethyl and diethyl α-hydroxybenzylphosphonates were also measured in a concentration of 200 µmol/L. None of the more than 25 methyl and ethyl esters showed remarkable cytotoxic effect. Therefore, it is concluded that only the benzyl esters display anticancer effect.

Taken together, dibenzyl α-hydroxyphosphonates show moderate, but significant anticancer cytotoxicity, with the lowest IC_{50} value of 69.5 µmol/L exerted by compound **1c**. As observed, the position of the substituent of the aromatic ring might have a greater impact on the cytotoxicity than the substituents (Cl, NO_2, Me, OMe) themselves. The results obtained on the α-hydroxyphosphonates are promising, as the in vitro cytotoxic activity in general was within the range of the effect (expressed as IC_{50} values) of three well-known chemotherapeutics, which we also tested against the Mes-Sa cell line and which are typically applied to treat uterine sarcoma (doxorubicin, 0.36 µmol/L; carboplatin, 24.8 µmol/L; dacarbazine, 349.8 µmol/L).[64-66] However, the in vivo tolerability of these structures has to be evaluated. Our future aim will be to assess the effects of the α-hydroxyphosphonates on different cancer types and their possible impact on drug resistance, and, moreover, to reveal the possible intracellular targets of these compounds.

3 | CONCLUSION

In conclusion, two reactions were realized using green methods. At first, the Pudovik reaction of substituted aldehydes and dibenzyl phosphite was performed to obtain dibenzyl α-hydroxyphosphonates (**1a-i**) including four new compounds in a simple way. The main novelty of this protocol is that the excessive use of organic solvents during the workup procedures can be avoided by applying a few mLs of acetone and pentane during the synthesis. The method involves a one-pot synthesis and a crystallization step. The dibenzyl α-hydroxyphosphonates (**1a-i**) were transformed to the corresponding α-hydroxyphosphonic acids (**2a-j**) by catalytic hydrogenation. All of the nine dibenzyl α-hydroxyphosphonates (**1a-i**) and eight α-hydroxyphosphonic acids (**2a-g** and **2j**) were tested against the Mes-Sa uterine sarcoma cell line, and eight of the hydroxyphosphonates showed promising cytotoxic effect.

4 | EXPERIMENTAL

4.1 | General information

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were taken on a Bruker Avance 300 as well as a Bruker DRX 500 instrument. ^{1}H-^{15}N HMBC (heteronuclear multiple bond connectivity) spectrum was measured on a Bruker Avance III HDX 800 instrument; ^{15}N chemical shift is given in parts per million relative to neat nitromethane. The exact mass measurements were performed using a Q-TOF Premier mass spectrometer in positive or negative electrospray mode.

The cytotoxic activity of the compounds was investigated against Mes-Sa, a human uterine sarcoma cell line, purchased from ATCC. Mes-Sa cells were engineered to stably express the mCherry fluorescent protein using a lentiviral system.[61] Mes-Sa mCherry cell line was cultivated in DMEM (Sigma-Aldrich, Hungary) supplemented with 10% fetal bovine serum, 5 mmol/L glutamine, and 50 unit/mL penicillin and streptomycin (Life Technologies), and was kept at 37°C, under 5% CO_2 atmosphere.

4.2 | General procedure for the synthesis of dibenzyl 1-hydroxy-1-phenylmethylphosphonates (1a-i)

A mixture of 11.0 mmol of substituted benzaldehyde (benzaldehyde: 1.2 g, 3-methylbenzaldehyde: 1.3 g, 4-methylbenzaldehyde: 1.3 g, 2-methoxybenzaldehyde: 1.5 g, 2-chlorobenzaldehyde: 1.5 g, 3-chlorobenzaldehyde: 1.5 g, 4-chlorobenzaldehyde: 1.5 g, 2-nitrobenzaldehyde: 1.7 g, 4-nitrobenzaldehyde: 1.7 g), 11.0 mmol (2.4 mL) of dibenzyl phosphite, and 1.1 mmol (153 μL) of triethylamine was stirred in acetone (1.0 mL) at reflux for 0.5-6.5 hours (for details, see Table 1). After adding pentane (6.0 mL), the reaction mixture was cooled to 5 °C. On cooling, the product crystallized from the reaction mixture. A simple filtration afforded products **1a-i** in yields of 88%-99% and in purity of >99% (Table 1).

4.3 | Characterization data for products 1

4.3.1 | Dibenzyl 1-hydroxy-1-phenylmethylphosphonate (1a)

Yield: 95%; δ_P (121.5 MHz, $CDCl_3$) 22.1; $\delta_{P,lit}$ (161.0 MHz, $CDCl_3$)[59] 22.4; Mp: 104-105°C; Mp_{lit}[59]: 117-118; δ_H (500.1 MHz, $CDCl_3$) 4.84-4.99 (4H, m, 2×OCH_2), 5.06 (1H, d, $^2J_{P,H}$ 10.4, PCH), 7.17-7.49 (15H, m, Ar); $[M + H]^+$, found 369.1256. $C_{21}H_{21}O_4P$ requires 369.1250.

4.3.2 | Dibenzyl 1-(2-chlorophenyl)-1-hydroxymethylphosphonate (1b)

Yield: 93%; δ_P (121.5 MHz, $CDCl_3$) 21.9; δ_C (125.8 MHz, $CDCl_3$) 67.2 (d, ^1J 161.2, PCH), 68.4 (d, ^2J 7.2, OCH_2), 68.7 (d, ^2J 7.2, OCH_2), 127.0 (d, ^4J 3.1, C_5), 127.8 and 127.9 ($C_{2'}$), 128.25 and 128.29 ($C_{4'}$), 128.39 and 128.43 ($C_{3'}$), 129.2-129.4 (m, C_3, C_4, C_6), 133.0 (d, ^3J 8.3, C_2), 134.7 (C_1), 136.0 (d, ^3J 5.9, $C_{1'}$); δ_H (500.1 MHz, $CDCl_3$) 4.68-5.23 (5H, m, 2×OCH_2, OH), 5.69 (1H, d, $^2J_{P,H}$ 11.2, PCH), 7.16-7.34 (13H, m, Ar), 7.73-7.80 (1H, m, H_3); $[M + H]^+$, found 403.0869. $C_{21}H_{20}O_4PCl$ requires 403.0860.

4.3.3 | Dibenzyl 1-(3-chlorophenyl)-1-hydroxymethylphosphonate (1c)

Yield: 88%; δ_P (121.5 MHz, $CDCl_3$) 22.3; δ_C (75.5 MHz, $CDCl_3$) 68.5 (d, ^2J 7.4, OCH_2), 68.9 (d, ^2J 7.2, OCH_2), 70.4 (d, ^1J 159.0, PCH), 125.3 (d, ^3J 5.7, C_6), 127.3 (d, ^3J 5.7, C_2), 127.90 and 127.92 ($C_{2'}$), 128.2 (d, ^5J 3.4, C_4)*, 128.44 and 128.48 ($C_{4'}$), 128.51 and 128.55 ($C_{3'}$), 129.4 (d, ^4J 2.7, C_5)*, 134.2 (d, ^4J 3.0, C_3), 135.8 (d, ^3J 5.9, $C_{1'}$), 138.4 (C_1); δ_H (500.1 MHz, $CDCl_3$) 4.76-5.13 (6H, m, 2×OCH_2, PCH, OH), 7.15-7.47 (14H, m, Ar), *may be reversed; $[M + H]^+$, found 403.0881. $C_{21}H_{20}O_4PCl$ requires 403.0860.

4.3.4 | Dibenzyl 1-(4-chlorophenyl)-1-hydroxymethylphosphonate (1d)

Yield: 95%; δ_P (121.5 MHz, $CDCl_3$) 21.7; $\delta_{P,lit}$ (161.0 MHz, $CDCl_3$)[59] 22.4; Mp: 132-133°C; Mp_{lit}[59]: 126-128; $[M + H]^+$, found 403.0869. $C_{21}H_{20}O_4PCl$ requires 403.0860.

4.3.5 | Dibenzyl 1-hydroxy-1-(2-nitrophenyl)-methylphosphonate (1e)

Yield: 91%; δ_P (121.5 MHz, $CDCl_3$) 21.1; δ_C (75.5 MHz, $CDCl_3$) 66.0 (d, ^1J 160.0, PCH), 68.7 (d, ^2J 7.5, OCH_2), 69.2 (d, ^2J 7.3, OCH_2), 124.7 (d, ^4J 2.5, C_3), 127.8 and 128.0 ($C_{2'}$), 128.3-128.5 (m, $C_{4'}$, C_4, $C_{3'}$), 129.1 (d, ^3J 4.6, C_6), 132.7 (d, ^2J 1.1, C_1), 133.4 (d, ^4J 3.0, C_5), 135.7 (d, ^3J 5.4, $C_{1'}$), 135.8 (d, ^3J 5.6, $C_{1'}$), 147.4 (d, ^3J 6.1, C_2); δ_H (500.1 MHz, $CDCl_3$) 4.93 (2H, ~d, $^3J_{P,H}$ 8.4, OCH_2) 4.97-5.07 (2H, m, OCH_2), 6.28 (1H, d, $^2J_{P,H}$ 14.3, PCH), 7.13-7.34 (10H, m, 2×CH_2Ph), 7.39-7.44 (1H, m, H_4), 7.57-7.63 (1H, m, H_5), 7.92 (1H, ~d, $^3J_{H,H}$ 7.9, H_6)*, 7.95 (1H, ~d, $^3J_{H,H}$ 8.2, H_3)*, *may be reversed; $[M + H]^+$, found 414.1114. $C_{21}H_{20}NO_6P$ requires 414.1101.

4.3.6 | Dibenzyl 1-hydroxy-1-(4-nitrophenyl)-methylphosphonate (1f)

Yield: 99%; δ_P (121.5 MHz, $CDCl_3$) 20.8; $\delta_{P,lit}$ (161.0 MHz, $CDCl_3$)[59] 20.6; Mp: 104-105°C; Mp_{lit}[59]: 87-88; $[M + H]^+$, found 414.1105. $C_{21}H_{20}NO_6P$ requires 414.1101.

4.3.7 | Dibenzyl 1-hydroxy-1-(3-methylphenyl)methylphosphonate (1g)

Yield: 88%; δ_P (121.5 MHz, $CDCl_3$) 22.3; δ_C (75.5 MHz, $CDCl_3$) 21.4 (CH_3), 68.3 (d, ^2J 7.2, OCH_2), 68.5 (d, ^2J 7.1, OCH_2), 71.1 (d, ^1J 158.7, PCH), 124.3 (d, ^3J 6.0, C_6), 127.8-128.0 (m, $C_{2'}$, C_2), 128.2 (d, ^4J 2.5, C_5)*, 128.28 and 128.31 ($C_{4'}$), 128.4 and 128.5 ($C_{3'}$), 128.9 (d, ^5J 3.2, C_4)*, 136.1 (d, ^3J 6.1, $C_{1'}$), 136.1-136.3 (m, $C_{1'}$, C_1), 137.9 (d, ^4J 2.6, C_3); δ_H (300.1 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 4.83-5.07 (5H, m, 2×OCH_2, PCH), 7.06-7.42 (14H, m, Ar), *may be reversed; $[M + H]^+$, found 383.1409. $C_{22}H_{23}O_4P$ requires 383.1407.

4.3.8 | Dibenzyl 1-hydroxy-1-(4-methylphenyl)methylphosphonate (1h)

Yield: 94%; δ_P (121.5 MHz, $CDCl_3$) 22.4; $\delta_{P,lit}$ (161.0 MHz, $CDCl_3$)[59] 22.4; Mp: 110-111°C; Mp_{lit}[59]: 87-88; $[M + H]^+$, found 383.1392. $C_{22}H_{23}O_4P$ requires 383.1407.

4.3.9 | Dibenzyl 1-hydroxy-1-(2-methoxyphenyl)methylphosphonate (1i)

Yield: 96%; δ_P (121.5 MHz, $CDCl_3$) 22.9; $\delta_{P,lit}$ (161.0 MHz, $CDCl_3$)[59] 22.9; Mp: 91-92°C; Mp_{lit}[59]: 99-101; δ_H (500.1 MHz, $CDCl_3$) 3.58 (1H, br, OH), 3.70 (3H, s, OCH_3), 4.79-4.97 (2H, m, OCH_2) 5.01-5.12 (2H, m, OCH_2), 5.46 (1H, d, $^2J_{P,H}$ 12.1, PCH), 6.84 (1H, ~d, $^3J_{H,H}$ 8.3, H_3), 6.97 (1H, ~t, $^3J_{H,H}$ 7.5, H_5), 7.15-7.20, 7.27-7.37 and 7.46-7.52 (12H, m, Ar); $[M + H]^+$, found 399.1378. $C_{22}H_{23}O_5P$ requires 399.1356.

4.4 | General procedure for the synthesis of 1-hydroxy-1-phenylmethylphosphonic acids (2a-j)

α-Hydroxyphosphonates (4.1 mmol, **1a**: 1.5 g, **1b**: 1.7 g, **1c**: 1.7 g, **1d**: 1.7 g, **1f**: 1.7 g, **1g**: 1.6 g, **1h**: 1.6 g, **1i**: 1.6 g) were hydrogenated in the presence of 10% Pd/C (Selcat Q) (with a catalyst/substrate ratio of 0.05 g/g, 0.08-0.09 g) in methanol (30 mL) in a 80-mL stainless steel autoclave equipped with a magnetic stirrer (stirring speed = 1100 rpm). The hydrogenations took place at 10 bar and 25°C in 5-150 minutes. Then, the catalyst was filtered off, and activated carbon (0.15-0.17 g) was added to the solution. After a 1-h stirring, the absorbent was filtered off, and the organic solvent was evaporated. The crude product so-obtained was dissolved in CH_2Cl_2 (5 mL) and stirred for 15 minutes at reflux. After filtration, α-hydroxyphosphonic acids were obtained in yields of 50%-90%, in a purity of >98.5% (Table 2).

4.5 | Characterization data for products 2

4.5.1 | 1-Hydroxy-1-phenylmethylphosphonic Acid (2a)

Yield: 80%; δ_P (121.5 MHz, D_2O) 19.4; $\delta_{P,lit}$ (121.5 MHz, $CDCl_3$)[58] 22.4; δ_C (125.8 MHz, D_2O) 70.7 (d, ^1J 158.5, PCH), 127.1 (d, ^3J 5.8, C_2), 128.2 (d, ^4J 3.0, C_3), 128.5 (d, ^5J 2.3, C_4), 137.1 (C_1); δ_H (500.1 MHz, D_2O) 4.88 (1H, d, $^2J_{P,H}$ 12.3, PCH), 7.23-7.38 (5H, m, Ar); $[2M + H]^+$, found 377.0545. $C_{14}H_{18}O_8P_2$ requires 377.0550.

4.5.2 | 1-(2-Chlorophenyl)-1-hydroxymethylphosphonic Acid (2b)

Yield: 85%; δ_P (121.5 MHz, D_2O) 18.5; $\delta_{P,lit}$ (121.5 MHz, D_2O)[12] 16.3; δ_C (75.5 MHz, D_2O) 66.8 (d, ^1J 159.3, PCH), 127.0 (d, ^4J 2.8, C_5), 128.5 (d, ^3J 4.2, C_6), 129.1 (d, ^5J 2.2, C_4)*, 129.2 (d, ^4J 2.9, C_3)*, 132.2 (d, ^3J 8.0, C_2), 135.0 (C_1); δ_H (300.1 MHz, D_2O) 5.38 (1H, d, $^2J_{P,H}$ 12.9, PCH), 7.16-7.39 (3H, m, Ar), 7.51-7.59 (1H, m, H_3); $d_{H,lit}$ (300.1 MHz, D_2O)[12] 4.92 (1H, d, $^2J_{P,H}$ 12.6, PCH), 7.05 (3H, m, ArH), 7.40 (1H, d, $^3J_{H,H}$ 7.5, ArH).

4.5.3 | 1-(3-Chlorophenyl)-1-hydroxymethylphosphonic Acid (2c)

Yield: 76%; δ_P (121.5 MHz, D_2O) 18.2; $\delta_{P,lit}$ (121.5 MHz, D_2O)[12] 20.1; δ_C (75.5 MHz, D_2O) 70.2 (d, ^1J 157.0, PCH), 125.2 (d, ^3J 4.8, C_6)*, 126.7 (d, ^3J 4.9, C_2)*, 127.8 (C_4), 129.7 (C_5), 133.4 (d, ^4J 1.9, C_3), 139.6 (C_1); δ_H (300.1 MHz, D_2O) 4.85 (1H, d, $^2J_{P,H}$ 12.8, PCH), 7.24-7.42 (4H, m, Ar), $\delta_{H,lit}$ (300.1 MHz, D_2O)[12] 4.90 (1H, d, $^2J_{P,H}$ 12.9, PCH), 7.29 (3H, s, ArH), 7.41 (1H, s, ArH).

4.5.4 | 1-(4-Chlorophenyl)-1-hydroxymethylphosphonic Acid (2d)

Yield: 88%; δ_P (121.5 MHz, D_2O) 18.6; $\delta_{P,lit}$ (121.5 MHz, D_2O)[12] 18.9; δ_C (125.8 MHz, D_2O) 70.2 (d, ^1J 158.5, PCH), 128.4 (d, ^4J 2.3, C_3), 128.5 (d, ^3J 5.7, C_2), 133.3 (d, ^2J 3.7, C_1), 136.1 (d, ^5J 2.1, C_4); δ_H (500.1 MHz, D_2O) 4.87 (1H, d, $^2J_{P,H}$ 12.5, PCH), 7.27-7.35 (4H, bs, Ar); $\delta_{H,lit}$ (300.1 MHz, D_2O)[12] 4.75 (1H, d, $^2J_{P,H}$ 12.6, PCH), 7.21 (4H, s, Ar); $[2M - H]^-$, found 442.9659. $C_{14}H_{16}O_8P_2Cl_2$ requires 442.9625.

4.5.5 | 1-(4-Aminophenyl)-1-hydroxymethylphosphonic Acid (2j)

Yield: 50%; δ_P (121.5 MHz, DMSO-d6) 18.4; δ_C (125.8 MHz, DMSO-d6) 70.5 (d, ^1J 158.6, PCH), 126.8 (d, ^4J 2.6, C_3), 127.4 (d, ^3J 5.4, C_2), 127.5 (d, ^2J 1.8, C_1), 140.2 (C_4); δ_H (500.1 MHz, DMSO-d6) 4.66 (1H, d, $^2J_{P,H}$ 13.9, PCH), 7.19-7.42 (4H, m, Ar); δ_N (80.1 MHz, DMSO-d6+TFA): −336.6.

4.5.6 | 1-Hydroxy-1-(3-methylphenyl)-methylphosphonic Acid (2g)

Yield: 77%; δ_P (121.5 MHz, D_2O) 19.8; δ_C (125.8 MHz, D_2O) 20.4 (CH_3), 70.9 (d, ^1J 160.0, PCH), 124.1 (d, ^3J 5.7, C_6), 127.7 (d, ^3J 5.8, C_2), 128.4 (d, ^4J 2.3, C_5)*, 128.7 (C_4)*, 137.4 (C_1), 138.5 (d, ^4J 2.1, C_3); δ_H (500.1 MHz, D_2O) 2.25

(3H, s, CH_3), 4.84 (1H, d, $^2J_{P,H}$ 12.3, PCH), 7.10-7.26 (4H, m, Ar), *may be reversed.

4.5.7 | 1-Hydroxy-1-(4-methylphenyl)-methylphosphonic Acid (2h)

Yield: 90%; δ_P (121.5 MHz, D_2O) 18.8; δ_C (125.8 MHz, D_2O) 20.2 (CH_3), 70.9 (d, ^1J 157.8, PCH), 127.2 (d, ^3J 5.6, C_2), 129.0 (C_3), 134.6 (C_1), 138.3 (d, ^5J 3.1, C_4); δ_H (300.1 MHz, D_2O) 2.25 (3H, s, CH_3), 4.83 (1H, d, $^2J_{P,H}$ 12.0, PCH), 7.13-7.33 (4H, m, Ar); $[2M - H]^{-1}$, found 403.0751. $C_{16}H_{22}O_8P_2$ requires 403.0717.

4.5.8 | 1-Hydroxy-1-(2-methoxyphenyl)-methylphosphonic Acid (2i)

Yield: 72%; δ_P (121.5 MHz, D_2O) 20.2; δ_C (75.5 MHz, D_2O) 55.7 (OCH_3), 64.2 (d, ^1J 161.1, PCH), 111.5 (C_3), 120.9 (d, ^4J 2.6, C_5), 125.4 (C_1), 127.9 (d, ^3J 4.6, C_6) 129.6 (d, ^5J 3.0, C_4), 156.3 (d, ^3J 6.4, C_2); δ_H (500.1 MHz, D_2O) 3.73 (3H, s, OCH_3), 5.33 (1H, d, $^2J_{P,H}$ 12.4, PCH), 6.92-6.99 (2H, m, H_3, H_5), 7.23-7.30 (1H, m, H_4), 7.39-7.44 (1H, m, H_6); $[2M - H]^-$, found 435.0632. $C_{16}H_{22}O_{10}P_2$ requires 435.0616.

4.6 | General procedure for the cytotoxicity assays of compounds 1 and 2

Both primary and confirmatory cytotoxicity tests were conducted using 384-well plates. On day 0, 20 µL of complete medium containing the appropriate number of Mes-Sa mCherry (2500/well) was plated on the 384-well plate using a robotic platform (Hamilton Starlet) and incubated overnight at 37°C with 5% CO_2. Twenty-four hours postseeding, compounds at various concentrations were added to the cells, yielding the final screening concentration. Primary and confirmatory plates were incubated for additional 96 or 144 hours, respectively, and total fluorescence was measured using PerkinElmer EnSpire plate reader by measuring the amount of mCherry (excitation 585 nm/emission 610 nm). These data were imported to a custom program that normalized the data to the positive (100% growth inhibition) and to the negative (0% growth inhibition) controls and calculated the growth inhibition.

ACKNOWLEDGMENTS

The above project was supported by the National Research Development and Innovation Fund (K119202). Z. Rádai is grateful for the fellowship provided by Chinoin-Sanofi Pharmaceuticals and József Varga Foundation. N. Z. Kiss was supported by the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-17-4-I-BME-133). The authors wish to thank Áron Szigetvári (Spectroscopic Research Department, Gedeon Richter Plc.) for providing ^1H-^{15}N HMBC spectral data of **2j**.

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REFERENCES

[1] D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, C. A. Free, W. L. Rogers, S. A. Smith, J. M. DeForrest, R. S. Oehl, E. W. Petrillo Jr., *J. Med. Chem.* **1995**, *38*, 4557.
[2] H. Song, H. Mao, D. Shi, *Chin. J. Chem.* **2010**, *28*, 2020.
[3] A. H. Kategaonkar, R. U. Pokalwar, S. S. Sonar, V. U. Gawali, B. B. Shingate, M. S. Shingare, *Eur. J. Med. Chem.* **2010**, *45*, 1128.
[4] R. U. Pokalwar, R. V. Hangarge, P. V. Maske, M. S. Shingare, *Arkivoc* **2006**, *11*, 196.
[5] G. S. Reddy, C. S. Sundar, S. S. Prasad, E. D. Dadapeer, C. N. Raju, C. S. Reddy, *Der Pharma Chemica* **2012**, *4*, 2208.
[6] S. Sampath, C. N. Raju, C. V. Rao, *Phosphorus Sulfur Silicon* **2016**, *191*, 95.
[7] K. U. M. Rao, C. S. Sundar, S. S. Prasad, C. R. Rani, C. S. Reddy, *Bull. Korean Chem. Soc.* **2011**, *32*, 3343.
[8] K. R. M. Naidu, K. S. Kumar, P. Arulselvan, C. B. Reddy, O. Lasekan, *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 957.
[9] R. M. N. Kalla, H. R. Lee, J. Cao, J. W. Yoo, I. Kim, *New J. Chem.* **2015**, *39*, 3916.
[10] R. F. Frechette, C. Ackerman, S. Beers, R. Look, J. Moore, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2169.
[11] J. Desai, Y. Wang, K. Wang, S. R. Malwal, E. Oldfield, *Chem. Med. Chem.* **2016**, *11*, 2205.
[12] G. Forlani, A. Occhipinti, Ł. Berlicki, G. Dziedzioła, A. Wieczorek, P. Kafarski, *J. Agric. Food Chem.* **2008**, *56*, 3193.
[13] P. Deprez, E. Mandine, D. Gofflo, S. Meunier, D. Lesuisse, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1295.
[14] A. N. Pudovik, G. A. Zametaeva, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1952**, *1952*, 932.
[15] A. N. Pudovik, I. V. Konovalova, *Synthesis* **1979**, *1979*, 81.
[16] G. Keglevich, M. Sipos, D. Takács, I. Greiner, *Heteroatom Chem.* **2007**, *18*, 226.
[17] A. A. Smaardijk, S. Noorda, F. Bolhuis, H. Wynberg, *Tetrahedron Lett.* **1985**, *26*, 493.
[18] H. Wynberg, A. A. Smaardijk, *Tetrahedron Lett.* **1983**, *24*, 5899.
[19] D. Simoni, F. P. Invidiata, M. Manferdini, I. Lampronti, R. Rondanin, M. Roberti, G. P. Pollini, *Tetrahedron Lett.* **1998**, *39*, 7615.
[20] C. Liu, Y. Zhang, Q. Qian, D. Yuan, Y. Yao, *Org. Lett.* **2014**, *16*, 6172.
[21] V. J. Blazis, K. J. Koeller, C. D. Spilling, *J. Org. Chem.* **1995**, *60*, 931.
[22] O. Gawron, C. Grelecki, W. Reilly, J. Sands, *J. Am. Chem. Soc.* **1953**, *75*, 3591.
[23] S. Zhou, Z. Wu, J. Rong, S. Wang, G. Yang, X. Zhu, L. Zhang, *Chem. Eur. J.* **2012**, *18*, 2653.

[24] L. Zhao, H. Ding, B. Zhao, C. Lu, Y. Yao, *Polyhedron* **2014**, *83*, 50.
[25] S. Yang, X. Zhu, S. Zhou, S. Wang, Z. Feng, Y. Wei, H. Miao, L. Guo, F. Wang, G. Zhang, X. Gu, X. Mu, *Dalton Trans.* **2014**, *43*, 2521.
[26] H. Miao, S. L. Zhou, S. W. Wang, L. J. Zhang, Y. Wei, S. Yang, F. H. Wang, Z. Chen, Y. Chen, Q. B. Yuan, *Sci. China Chem.* **2013**, *56*, 329.
[27] B. Liu, J. F. Carpentier, Y. Sarazin, *Chem. Eur. J.* **2012**, *18*, 13259.
[28] R. G. de Noronha, P. J. Costa, C. C. Romão, M. J. Calhorda, A. C. Fernandes, *Organometallics* **2009**, *28*, 6206.
[29] V. Thottempudi, K. H. Chung, *Bull. Korean Chem. Soc.* **2008**, *29*, 1781.
[30] X. Zhou, Y. Liu, L. Chang, J. Zhao, D. Shang, X. Liu, L. Lin, X. Feng, *Adv. Synth. Catal.* **2009**, *351*, 2567.
[31] S. Santhisudha, P. Sreelakshimi, S. H. Jayaprakash, B. V. Kumar, C. S. Reddy, *Phosphorus Sulfur Silicon* **2015**, *190*, 1479.
[32] C. Jin, H. He, *Phosphorus Sulfur Silicon* **2011**, *186*, 1397.
[33] S. Sebti, A. Rhihil, A. Saber, M. Laghrissi, S. Boulaajaj, *Tetrahedron Lett.* **1996**, *37*, 3999.
[34] I. Aouani, K. Lahbib, S. Touil, *Med. Chem.* **2015**, *11*, 206.
[35] H. R. Hudson, R. O. Yusuf, R. W. Matthews, *Phosphorus Sulfur Silicon* **2008**, *183*, 1527.
[36] A. R. Sardarian, B. Kaboudin, *Synth. Commun.* **1997**, *27*, 543.
[37] M. Pandi, P. K. Chanani, S. Govindasamy, *Appl. Catal. A: Gen.* **2012**, *441-442*, 119.
[38] K. P. Nandre, J. P. Nandre, V. S. Patil, S. V. Bhosale, *Chem. Biol. Interface* **2012**, *2*, 314.
[39] G. Keglevich, V. R. Tóth, L. Drahos, *Heteroatom Chem.* **2011**, *22*, 15.
[40] B. Kaboudin, R. Nazari, *J. Chem. Res. (S)* **2002**, *2002*, 291.
[41] D. L. Kong, R. D. Liu, G. Z. Li, P. W. Zhang, M. S. Wu, *Asian J. Chem.* **2014**, *26*, 1246.
[42] M. A. Kulkarni, U. P. Lad, U. V. Desai, S. D. Mitragotri, P. P. Wadgaonkar, *C. R. Chimie* **2013**, *16*, 148.
[43] A. Smahi, A. Solhy, R. Tahir, S. Sebti, J. A. Mayoral, J. I. García, J. M. Fraile, M. Zahouily, *Catal. Commun.* **2008**, *9*, 2503.
[44] C. Wang, J. Zhou, X. Lv, J. Wen, H. He, *Phosphorus Sulfur Silicon* **2013**, *188*, 1334.
[45] K. S. Kumar, C. B. Reddy, M. V. N. Reddy, C. R. Rani, C. S. Reddy, *Org. Commun.* **2012**, *5*, 50.
[46] S. Kumari, A. Shekhar, D. D. Pathak, *Chem. Sci. Trans.* **2014**, *3*, 45.
[47] S. S. Prasad, S. H. Jayaprakash, K. U. Rao, N. B. Reddy, P. C. R. Kumar, C. S. Reddy, *Org. Commun.* **2014**, *7*, 98.
[48] N. S. Tulsi, A. M. Downey, C. W. Cairo, *Bioorg. Med. Chem.* **2010**, *18*, 8679.
[49] Q. Long, X. Deng, Y. Gao, H. Xie, H. Peng, H. He, *Phosphorus Sulfur Silicon* **2013**, *188*, 819.
[50] D. M. Cermak, S. C. Cermak, A. B. Deppe, A. L. Durhan, *Ind. Crops Prod.* **2012**, *37*, 394.
[51] D. Albouy, A. Brun, A. Munoz, G. Etemad-Moghadam, *J. Org. Chem.* **1998**, *63*, 7223.
[52] M. Hoffman, *Synthesis* **1998**, *1988*, 62.
[53] K. Schiessl, A. Roller, F. Hammerschmidt, *Org. Biomol. Chem.* **2013**, *11*, 7420.
[54] H. Sun, G. B. Reddy, C. George, E. J. Meuillet, M. Berggren, G. Powis, A. P. Kozikowski, *Tetrahedron Lett.* **2002**, *43*, 2835.
[55] A. E. Wróblewski, I. E. Głowacka, *Tetrahedron* **2005**, *61*, 11930.
[56] G. Keglevich, Z. Rádai, N. Z. Kiss, *Green Process Synth.* **2017**, *6*, 197.
[57] F. Texier-Boullet, M. Lequitte, *Tetrahedron Lett.* **1986**, *27*, 3515.
[58] B. Malinowska, P. Majewska, P. Szatkowski, P. Kafarski, B. Lejczak, *Biocatal. Biotransfor.* **2011**, *29*, 271.
[59] V. D. Pawar, S. Bettigeri, S. S. Weng, J. Q. Kao, C. T. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 6308.
[60] S. S. Weng, G. Y. Lin, H. C. Li, K. C. Yang, T. M. Yang, H. C. Liu, S. H. Sie, *Appl. Organomet. Chem.* **2012**, *26*, 455.
[61] V. F. Pape, S. Tóth, A. Füredi, K. Szebényi, A. Lovrics, P. Szabó, M. Wiese, G. Szakács, *Eur. J. Med. Chem.* **2016**, *117*, 335.
[62] A. Füredi, S. Tóth, K. Szebényi, V. F. Pape, D. Türk, N. Kucsma, L. Cervenak, J. Tóvári, G. Szakács, *Mol. Cancer Ther.* **2017**, *16*, 45.
[63] A. Füredi, K. Szebényi, S. Tóth, M. Cserepes, L. Hámori, V. Nagy, E. Karai, P. Vajdovich, T. Imre, P. Szabó, D. Szüts, J. Tóvári, G. Szakács, *J. Control Release* **2017**, *261*, 287.
[64] I. Judson, J. A. Radford, M. Harris, J. Y. Blay, Q. van Hoesel, A. le Cesne, A. T. van Oosterom, M. J. Clemons, C. Kamby, C. Hermans, J. Whittaker, E. Donato di Paola, J. Verweji, S. Nielsen, *Eur. J. Cancer* **2001**, *37*, 870.
[65] A. N. Fader, D. M. Roque, E. Siegel, N. Búza, P. Hui, O. Abdelghany, S. K. Chambers, A. A. Secord, L. Havrilesky, D. M. O'Malley, F. Backers, N. Nevadunsky, B. Edraki, D. Pikaart, W. Lowery, K. S. ElSahwi, P. Celano, S. Bellone, M. Azodi, B. Litkouhi, E. Ratner, D. A. Silasi, P. E. Schwartz, A. D. Santin, *J. Clin. Oncol.* **2018**, *36*, 2044.
[66] X. García-Del-Muro, A. López-Pousa, J. Maurel, J. Martín, J. Martínez-Trufero, A. Casado, A. Gómez-España, J. Fra, J. Cruz, A. Poveda, A. Meana, C. Pericay, R. Cubedo, J. Rubió, A. De Juan, N. Laínez, J. A. Carrasco, R. de Andrés, J. M. Buesa, *J. Clin. Oncol.* **2011**, *29*, 2528.

How to cite this article: Rádai Z, Szeles P, Kiss NZ, et al. Green synthesis and cytotoxic activity of dibenzyl α-hydroxyphosphonates and α-hydroxyphosphonic acids. *Heteroatom Chem*. 2018;e21436. https://doi.org/10.1002/hc.21436