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**FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY**
**GEORGE A. OLAH DOCTORAL SCHOOL**

# α-HYDROXYPHOSPHONATES: FROM THEIR SYNTHESIS TO THEIR BIOLOGICAL ACTIVITY

Summary of PhD thesis

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2019

# 1. Introduction

I performed the research work for my PhD thesis under the supervision of *Prof. Dr. György Keglevich*, the head of the *Green Chemical and Organophosphorus Research Group, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics*. Our research focused on the synthesis and reactions of α-hydroxyphosphonates.

α-Hydroxyphosphonates have attracted attention due to their wide range of bioactive effects. Certain derivatives are known as enzyme inhibitors, herbicides and antioxidants, as well as antibiotics and antibacterial agents.

α-Hydroxyphosphonates are usually synthesized by the Pudovik reaction, the addition of dialkyl phosphite to an oxo compound.[1] The advantages of this method are its simplicity, good atom efficiency, and mild reaction conditions in the presence of base catalyst. In the spirit of green chemistry, recent articles targeted the solvent-free synthesis of α-hydroxyphosphonates by avoiding the use of organic solvents during the Pudovik reaction.[2] However, the need for solvents during the work-up and purification was disregarded. In the reported procedures, α-hydroxyphosphonates were purified by a combination of extraction, recrystallization and column chromatography that all consume a considerable amount of solvents. From an industrial point of view, this is a major issue to be handled considering environmental and economic aspects. This recognition was the core idea of my PhD thesis.

Owing to their free hydroxy function, α-hydroxyphosphonates may easily undergo a series of different transformations.[3] Thus, we aimed at examining the reactions of α-hydroxyphosphonates. The main focus was on the elaboration of new synthetic routes starting from α-hydroxyphosphonates to afford new compounds. Another goal was to reconsider transformations already known from the literature from a green chemical point of view to find new alternatives for the synthesis of α-hydroxyphosphonate derivatives.

Despite the fact, that α-hydroxyphosphonates are mainly famous for their bioactivity, their cytotoxicity was hardly investigated. Our goal was to discover the cytotoxic effect of α-hydroxyphosphonates and related derivatives against human cancer cell lines.

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1. Pudovik, A. N.; Zametaeva, G. A. *Izv. Akad. Nauk SSSR Seriya Khimicheskaya*, **1952**, *1952*, 932–939.
2. Olszewski, T. K. *Synthesis*, **2014**, *46*, 403–429.
3. Sobhani, S.; Tashrifi, Z. *Tetrahedron*, **2010**, *66*, 1429–1439.

## 2. Experimental methods

Reaction mixtures were analyzed by thin layer chromatography and $^{31}P$ NMR spectroscopy. New compounds were characterized by $^{31}P$, $^{13}C$ and $^{1}H$ NMR spectroscopy as well as by high resolution mass spectrometry. The structure of a few α-hydroxyphosphonates was determined by single crystal X-ray diffraction measurements.

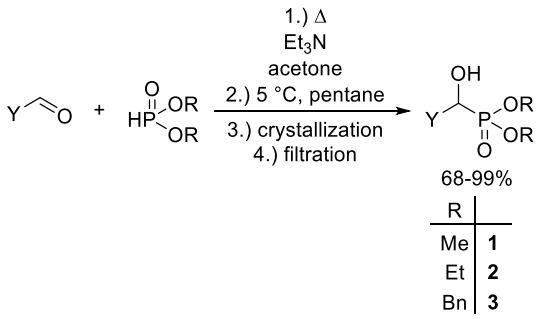
Microwave-assisted reactions were carried out in a CEM Discover (300 W) reactor equipped with a pressure controller.

Quantum chemical calculations were carried out using the Gaussian09 program package by the B3LYP/6-31G(d,p) or B3LYP/6-31++G(d,p) method.

## 3. New scientific results

### 3.1. Synthesis of α-hydroxyphosphonates by a new, green variation of the Pudovik reaction[(1)]

First, we elaborated a new, environmentally friendly variation of the Pudovik reaction to afford α-hydroxyphosphonates. According to our new method, a mixture of a substituted benzaldehyde, a dialkyl phosphite and a catalytic amount of triethylamine was stirred at reflux in a minimal amount of acetone. Then, pentane antisolvent was added to the reaction mixture. On cooling, the desired α-hydroxyphosphonate (**1**–**3**) crystallized and the product could be isolated by a simple filtration, in good yields (68–99%) and in high purity (> 99%) (Scheme 1). The main novelty of this new procedure is the unnecessity of further purification. This way the amount of organic solvents was reduced to the minimum as opposed to the previously reported methods.

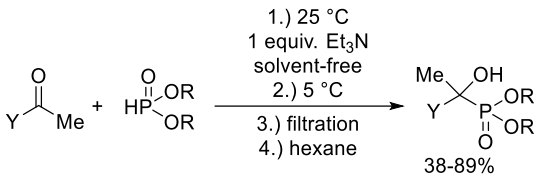



Y = $C_6H_5$ (**a**), 2-$MeC_6H_4$ (**b**), 3-$MeC_6H_4$ (**c**), 4-$MeC_6H_4$ (**d**), 2-$MeOC_6H_4$ (**e**), 3-$MeOC_6H_4$ (**f**), 4-$MeOC_6H_4$ (**g**), 3,4-di$MeOC_6H_3$ (**h**), 3,4,5-tri$MeOC_6H_2$ (**i**), 2-$BnOC_6H_4$ (**j**), 2-$ClC_6H_4$ (**k**), 3-$ClC_6H_4$ (**l**), 4-$ClC_6H_4$ (**m**), 4-$FC_6H_4$ (**n**), 2-$NO_2C_6H_4$ (**o**), 4-$NO_2C_6H_4$ (**p**), 1-naphthyl (**q**), 9-anthranyl (**r**), $C_6H_5CH$=CH (**s**)

**Scheme 1** New, green variation of the Pudovik reaction (**1**–**3**).

### 3.2. Extending the method to the synthesis of α-methyl-α-hydroxyphosphonates

We attempted to extend our new method to the addition of dialkyl phosphites to ketones. However, due to steric hindrance, this reaction was more challenging, and required the use of one equivalent of triethylamine. In the presence of this amount of the catalyst, the acetone solvent also reacted with the >P(O)H reagent. Finally, the synthesis of α-methyl-α-hydroxyphosphonates was performed under solvent-free conditions and the crystallized product was washed with hexane (Scheme 2).[3],[6]




Y = $C_6H_5$ (**a**), 2-$FC_6H_4$ (**t**), 4-$FC_6H_4$ (**n**), 3-$BrC_6H_4$ (**u**), 4-$BrC_6H_4$ (**v**), 4-$NO_2C_6H_4$ (**p**)

**Scheme 2** Synthesis of α-methyl-α-hydroxyphosphonates (**4** and **5**).

### 3.3. Energetics of the triethylamine-catalyzed Pudovik reaction[2]

In the hope of understanding the role of triethylamine in the reaction, and the difference between the reactivity of aldehydes and ketones, the mechanism of the triethylamine-catalyzed Pudovik reaction was investigated by theoretical calculations.

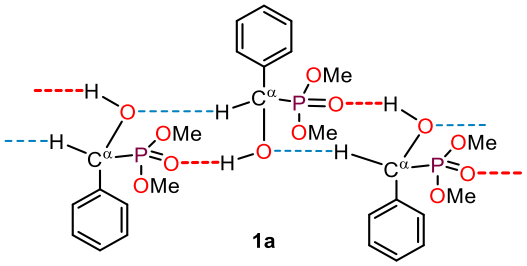
The calculations pointed out that triethylamine is not a base strong enough to deprotonate the dialkyl phosphite. However, it facilitates the proton transfer from the *P*-reagent to the carbonyl function of the oxo compound. This way it reduces the activation enthalpy and catalyzes the reaction. The calculations were in high accordance with the experimental results regarding the reduced reactivity of ketones. It was found that the addition of dialkyl phosphite to a benzaldehyde is more favorable from kinetic as well as from thermodynamic approach.

### 3.4. X-ray diffraction measurements of α-hydroxyphosphonates[3]

The structure of seven α-hydroxyphosphonates (**1a**, **1h**, **3d**, **3l**, **3o**, **4a** and **4p**) was studied by single crystal X-ray diffraction measurements. It was observed that the molecules of α-hydroxyphosphonates form either dimers or chain-like associates in the crystal structure. It was concluded that α-hydroxyphosphonates possessing a hydrogen atom in the position α (**1a**, **1h**, **3d** and **3l**) tend to form chain-like associates. However, α-methyl-α-hydroxyphosphonates (**4a** and **4p**) are inclined to form dimers. The only exception to this role was dibenzyl 1-hydroxy-1-(2-nitrophenyl)-methylphosphonate

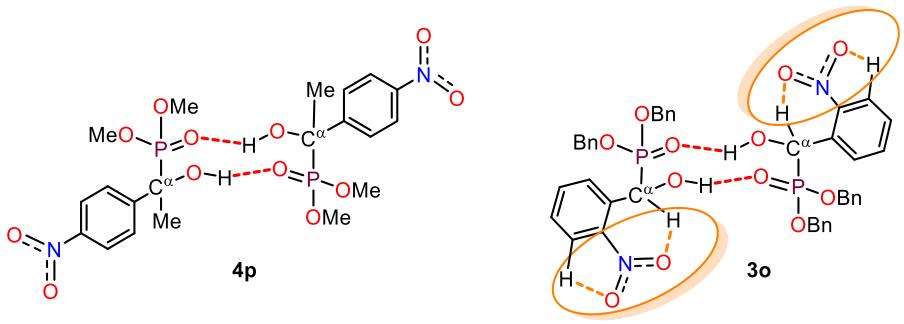
(**3o**). In contrast to our expectations, the molecules of **3o** formed dimers.

It was observed that the formation of chain-like associates requires the presence of two interactions: a *H*-bridge between P=O···H–O functions (Scheme 3, red dashed lines), and a weaker interaction between the α-H atom and the *O* atom of the hydroxy function ($C^{\alpha}$–H···O–$C^{\alpha}$) (Scheme 3, blue dashed lines).




**Scheme 3** The two interactions necessary for the formation of chain-like associates.

In case of α-methyl-α-hydroxyphosphonates (**4a** and **4p**) and dibenzyl 1-hydroxy-1-(2-nitrophenyl)methylphosphonate (**3o**) the secondary interaction ($C^{\alpha}$–H···O–$C^{\alpha}$) does not exist. As the consequence, the molecules of these derivatives (**4a**, **4p** and **3o**) formed dimers.

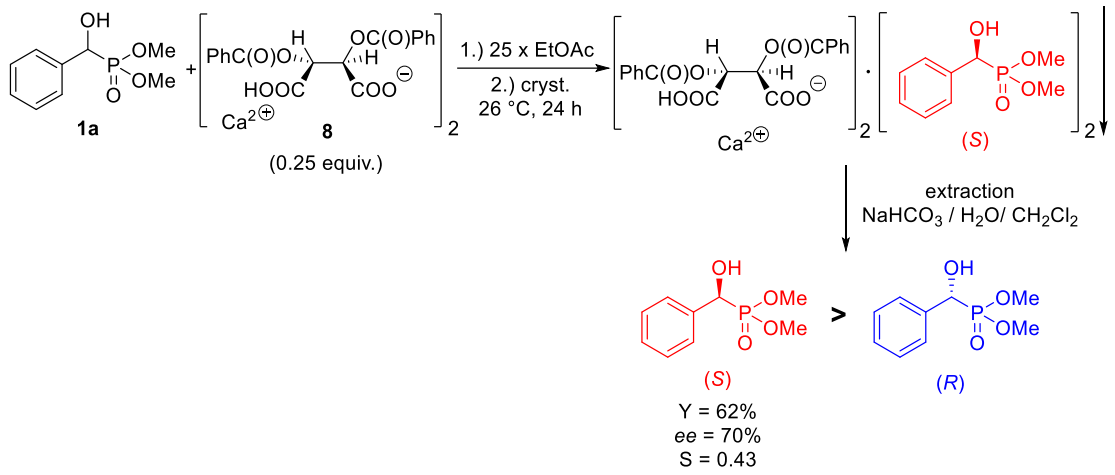



**Scheme 4** The crystal structure of dimer-forming α-hydroxyphosphonates.

### 3.5. Resolution of α-hydroxyphosphonates with tartaric acid derivatives

A new method has been elaborated for the resolution of dimethyl 1-hydroxy-1-phenylmethylphosphonate (**1a**) with tartaric acid derivatives. First, we optimized the conditions of the resolution regarding the type and quantity of the resolution agent and the solvent. The best results were obtained with 0.25 equivalents of acidic Ca salt of *O*,*O*'-dibenzoyl-(*R*,*R*)-tartaric acid ($Ca(H\text{-}DBTA)_2$ (**8**)) agent, in 25x EtOAc referring to the amount of the resolution agent at 26 °C, applying a crystallization time of 24 h.

Applying this method, the (*S*) enantiomer of dimethyl 1-hydroxy-1-phenylmethylphosphonate (**1a**) could be obtained in an enantiomeric excess of 70% and resolvability of 0.43 (Scheme 5).




**Scheme 5** Resolution of dimethyl 1-hydroxy-1-phenylmethylphosphonate (**1a**) with Ca(H-DBTA)$_2$.

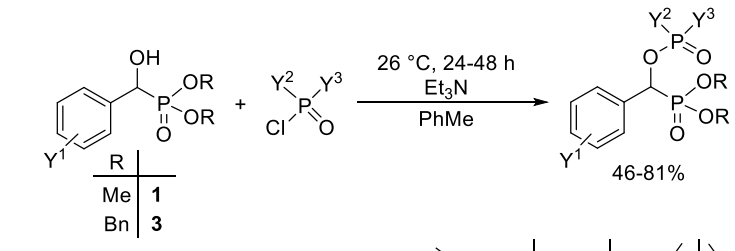
After optimizing the above resolution, the purification of dimethyl 1-hydroxy-1-phenylmethylphosphonate (**1a**) enantiomeric mixtures was investigated. It was found that the enantiomeric mixtures of **1a** could be efficiently purified through the recrystallization of the diastereomer complex (*ee* ≥ 91%), as well as by the recrystallization of an enantiomeric mixture of at least 80% enantiomeric excess (*ee* = 85–99%).

Our new method was successfully extended to the resolution of a series of dimethyl 1-hydroxy-1-arylmethylphosphonates (**1b**, **1e**, **1g**, **1j** and **1k**).

### 3.6. Acylation of α-hydroxyphosphonates with *P*-chlorides[4]

As the reaction of α-hydroxyphosphonates with *P*-chlorides was hardly investigated in the literature,[4] the acylation of dimethyl and dibenzyl 1-hydroxy-1-arylmethylphosphonates was performed with 1-chloro-3-phospholene-1-oxides and diphenylphosphinic chloride to afford new α-phosphinoyloxyphosphonates (**10**–**13**) (Scheme 6).

The phosphinoylation took place at ambient temperature within 24–48 h. After purification, the products (**10**–**13**) were obtained in yields of 46–81%.




| R \ Y$^2$, Y$^3$ | Ph,Ph | | |
|---|---|---|---|
| Me | **10** | **11** | **12** |
| Bn | **13** | — | — |

**Scheme 6** Acylation of α-hydroxyphosphonates (**1** and **3**) with phosphinic chlorides.

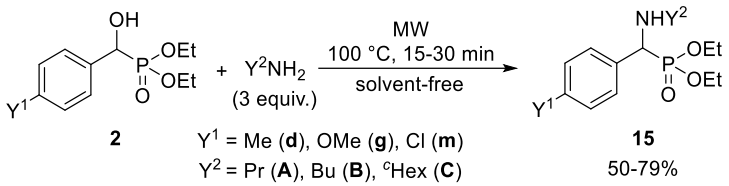
4. Dimukhametov, M. N.; Bayandina, E. V.; Litvinov, I. A.; Alfonsov, V. A. *Russ. Chem. Bull.* **2001**, *50*, 287–291.

The acylation was also attempted with diphenyl phosphoryl chloride. However, the decreased reactivity of this *P* reagent as opposed to the phosphinic chlorides and the moisture sensitivity of the products led to the desired α-phosphoryloxyphosphonates (**14a** and **14m**) in modest (~16%) yields.

### 3.7. Nucleophilic substitution of α-hydroxyphosphonates with primary amines[2]

A new method has been elaborated for the nucleophilic substitution of diethyl 1-hydroxy-1-arylmethylphosphonates with primary amines in our research group.[5]

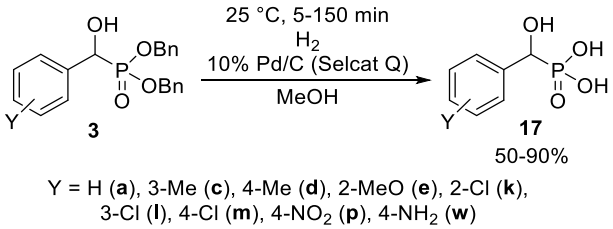
Our research work involved the extension of this method starting from diethyl 1-hydroxy-1-arylmethylphosphonates (**2**). The reactions were carried out under microwave (MW) conditions at 100 °C using 3 equivalents of a primary amine, without the use of any solvent or catalyst (Scheme 7). The nucleophilic substitutions were complete within 15–30 min. This enhanced reactivity was explained by a neighboring group effect that facilitates the reaction.[5] α-Aminophosphonates (**15**) were obtained in yields of 50–79% after purification.




**Scheme 7** Nucleophilic substitution of α-hydroxyphosphonates (**2**) with primary amines.

### 3.8. Catalytic hydrogenation of dibenzyl 1-hydroxy-1-arylmethylphosphonates[5]

Dibenzyl 1-hydroxy-1-arylmethylphosphonates (**3**) obtained by us were subjected to catalytic hydrogenation to afford α-hydroxyphosphonic acids (**17**). The reactions were carried out in the presence of Pd/C catalyst at 25 °C (Scheme 8).



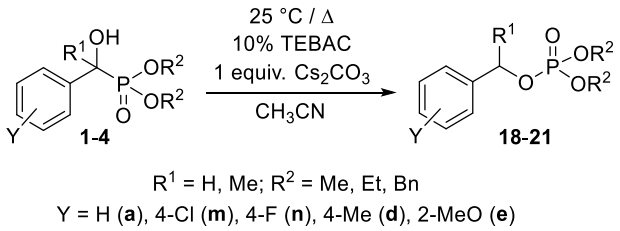

**Scheme 8** Synthesis of α-hydroxyphosphonic acids (**17**) by catalytic hydrogenation.

This procedure is an alternative route for the synthesis of α-hydroxyphosphonic acids (**17**) that are usually prepared *via* the acid-catalyzed hydrolysis of the corresponding methyl or ethyl ester.[6,7]

5. Kiss, N. Z.; Kaszás, A.; Drahos, L.; Mucsi, Z.; Keglevich, G. *Tetrahedron Lett.* **2012**, *53*, 207–209.
6. Forlani, G.; Occhipinti, A.; Berlicki, Ł.; Dziedzioła, G.; Wieczorek, A.; Kafarski, P. *J. Agric. Food Chem.* **2008**, *56*, 3193–3199.
7. Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron*, **2007**, *63*, 6720–6731.

### 3.9. Phospha-Brook rearrangement of α-hydroxyphosphonates

The phospha-Brook rearrangement of α-hydroxyphosphonates (**1a**, **1d**, **1e**, **1m**, **1n**, **2a**, **3a** and **4a**) was performed in the presence of cesium carbonate, under phase-transfer catalytic conditions, in acetonitrile to afford the corresponding benzyl phosphates (**18**–**21**) (Scheme 9).[7]




**Scheme 9** Phospha-Brook rearrangement of α-hydroxyphosphonates (**1**–**4**) to benzyl phosphates (**18**–**21**).

It was concluded that electron-withdrawing substituents in the aromatic ring facilitate the rearrangement, while electron releasing functions slow down the reaction. This observation was supported by quantum chemical calculations. A putative mechanism of the rearrangement was also suggested.

In the presence of cesium carbonate, a "one-pot" accomplishment of the Pudovik reaction and the phospha-Brook rearrangement was also elaborated. Following this way, the synthesis of four benzyl phosphates (**18a**, **18m**, **18d** and **18g**) was also performed from the corresponding substituted benzaldehydes and dimethyl phosphite.

The rearrangement of dimethyl 1-hydroxy-1-phenylmethylphosphonate (**1a**) was also attempted in acetone as the solvent. However, in this case beside the benzyl phosphate (**18a**), a dimethyl (2-hydroxypropane-2-yl)phosphonate (**22**) by-product was also formed in the reaction. The reason for the formation of by-product **22** is the retro-Pudovik reaction that occurred under the conditions of the rearrangement, and resulted in the formation of dimethyl phosphite and benzaldehyde. Cesium carbonate catalyzed the Pudovik reaction between the so-formed dimethyl phosphite and the acetone used as the solvent leading to the formation of compound **22**. This experience is a proof for the reversibility of the Pudovik reaction under basic conditions.

### 3.10. Cytotoxicity assays[6]

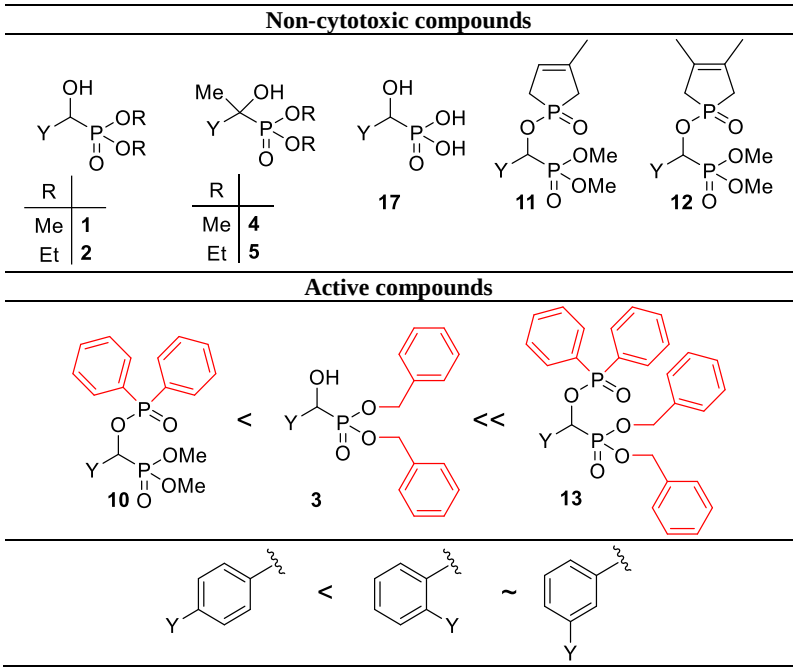
In the frame of a collaboration we had the opportunity to screen fifty-six α-hydroxyphosphonates (**1**–**5**), α-hydroxyphosphonic acids (**17**) and α-phosphinoyloxyphosphonates (**10**–**13**) against human cancer cell lines (Mes-Sa mCh and Mes-Sa/Dx5 mCh uterine sarcoma cell lines, HT-29 rectosigmoid adenocarcinoma, HOP-62 lung adenocarcinoma and MALME-3M metastatic melanoma). First, a

primary screening was performed in a concentration of 200 μM. During the primary screening, dibenzyl 1-hydroxy-1-arylmethylphosphonates (**3**) and α-phosphinoyloxyphosphonates containing the diphenylphosphinoyl moiety (**10** and **13**) were found as bioactive agents. Based on the primary screening, compounds **3**, **10** and **13** were chosen for further investigations and their $IC_{50}$ values were determined. Derivatives possessing both dibenzyl and diphenylphosphinoyl moieties (**13**) showed increased cytotoxicity ($IC_{50}$ ~ 10 μM) against all five cell lines.

The correlation between the substituent in the aromatic ring and the biological activity was also investigated. It was found that in case of our chemical library, the position of the substituent has a higher impact on the cytotoxicity than the type of the functional group. *Para*-substituted derivatives were the least promising agents, while *ortho*- and *meta*-substituted analogues showed higher biological activity. Table 1 summarizes the structure-activity relationships.

These results are so far the most detailed structure-activity observations pertaining to a compound library involving α-hydroxyphosphonates, α-hydroxyphosphonic acids and α-phosphinoyloxyphosphonates.

**Table 1** Structure-activity relationships of the cytotoxicity assays.



## 4. Theses

1. A new, environmentally friendly synthesis of α-hydroxyphosphonates was elaborated starting from substituted benzaldehydes and dialkyl phosphites.[1]

2. It was found by theoretical calculations that triethylamine catalyzes the Pudovik reaction *via* an interaction with the hydrogen atom of dialkyl phosphite.[2]

3. Single crystal X-ray diffraction measurements pointed out that hydroxyphosphonates containing a hydrogen in position α form chain-like associates in their crystal lattice, while the monomers of α-methyl-α-hydroxyphosphonates form dimers.[3]

4. A new procedure was elaborated for the resolution of dimethyl 1-hydroxy-1-phenylmethylphosphonate with the acidic calcium salt of *O*,*O*'-dibenzoyl-(*R*,*R*)-tartaric acid. The resolution of a series of 1-hydroxy-1-arylmethylphosphonates was performed according to this method.

5. New α-phosphinoyloxyphosphonates and α-phosphoryloxyphosphonates were synthesized through the acylation of dialkyl 1-hydroxy-1-arylmethylphosphonates with phosphinic and phosphoric chlorides.[4]

6. Our results showed that the microwave-assisted, solvent- and catalyst-free reaction of diethyl 1-hydroxy-1-arylmethylphosphonates and primary amines affords diethyl 1-alkylamino-1-arylmethylphosphonates within surprisingly short reaction times owing to a beneficial neighboring group effect.[2]

7. Dibenzyl 1-hydroxy-1-arylmethylphosphonates were converted to the corresponding α-hydroxyphosphonic acids in a new, benign way by catalytic hydrogenation.[5]

8. A new procedure was elaborated for the rearrangement of dialkyl 1-hydroxy-1-arylmethylphosphonates to benzyl phosphates in the presence of bases, under phase-transfer catalytic conditions.[7]

9. The formation of the corresponding aldehyde and dialkyl phosphite from dimethyl 1-hydroxy-1-phenylmethylphosphonate was observed in the presence of alkali carbonates. The reversibility of the Pudovik reaction was proved by trapping the dialkyl phosphite with another oxo compound.

10. It was found that dibenzyl 1-hydroxy-1-arylmethylphosphonates and α-phosphinoyloxyphosphonates deriving from diphenylphosphinic chloride showed significant cytotoxic effect against human cancer cell lines.[6]

## 5. Application possibilities

During the research work included in my PhD thesis we have synthesized and characterized about 85 derivatives, mainly new compounds. We have broadened the scale of available α-hydroxyphosphonic acid derivatives that may be valuable starting materials towards new, potentially bioactive compounds.

Due to the promising results of the cytotoxicity assays, our chemical library may be of pharmaceutical importance.

## 6. Publications

### 6.1. Full scientific publications related to the PhD thesis

(1). Keglevich, G.; **Rádai, Z.**; Kiss, N. Z. To date the greenest method for the preparation of α-hydroxyphosphonates from substituted benzaldehydes and dialkyl phosphites. *Green Process. Synth.* **2017**, *6*, 197–201. [IF: 0.736]

(2). Kiss, N. Z.; **Rádai, Z.**; Mucsi, Z.; Keglevich G. Synthesis of α-aminophosphonates from α-hydroxyphosphonates; A theoretical study. *Heteroatom Chem.* **2016**, *27*, 260–268. [IF: 1.221, Citations: 3]

(3). **Rádai, Z.**; Kiss, N. Z.; Czugler, M.; Karaghiosoff, K.; Keglevich, G. The typical crystal structure of a few representative α-aryl-α-hydroxyphosphonates. *Acta Crystallogr. C Struct. Chem.* **2019**, *75*, 283–293. [IF: 0.930 (2018)]

(4). **Rádai, Z.**; Hodula, V.; Kiss, N. Z.; Kóti, J.; Keglevich, G. Phosphorylation of (1-aryl-1-hydroxymethyl)phosphonates. *Mendeleev Commun.* **2019**, *29*, 153–154. [IF: 2.010 (2018)]

(5). **Rádai, Z.**; Szeles, P.; Kiss, N. Z.; Hegedűs, L.; Windt, T.; Nagy, V.; Keglevich, G. Green synthesis and cytotoxic activity of dibenzyl α-hydroxyphosphonates and α-hydroxyphosphonic acids. *Heteroatom Chem.* **2018**, *29*, e21436. [IF: 1.011]

(6). **Rádai, Z.**; Windt, T.; Nagy, V.; Füredi, A.; Kiss, N. Z.; Ranđelović, I.; Tóvári, J.; Keglevich, G.; Szakács, G.; Tóth, S. Synthesis and anticancer cytotoxicity with structural context of an α-hydroxyphosphonate based compound library derived from substituted benzaldehydes. *New J. Chem.* **2019**, *43*, 14028–14035. [IF: 3.069 (2018)]

### 6.2. Proceedings related to the PhD theses

(7). Kiss, N. Z.; **Rádai, Z.**; Szabó, R.; Aichi Y.; Laasri, L.; Sebti, S. Synthesis of organophosphates starting from α-hydroxyphosphonates. *Phosphorus, Sulfur Silicon Relat. Elem*. **2019**, *194*, 370–371. [IF: 0.781 (2018)]

(8). Kiss, N. Z.; **Rádai, Z.**; Keglevich, G. Green syntheses of potentially bioactive α-hydroxyphosphonates and related derivatives. *Phosphorus, Sulfur Silicon Relat. Elem*. **2019**, *194*, 1003–1006. [IF: 0.781 (2018)]

(9). **Rádai, Z.**; Kiss, N. Z.; Mucsi, Z.; Keglevich, G. Synthesis of α-hydroxyphosphonates and α-aminophosphonates. *Phosphorus, Sulfur Silicon Relat. Elem*. **2016**, *191*, 1564–1565. [IF: 0.809, Citations: 2]

(10). Grün, A.; **Rádai, Z.**; Nagy, D. I.; Greiner, I.; Keglevich, G. Rational synthesis of α-hydroxyphosphonic derivatives including dronic acids. *Phosphorus, Sulfur Silicon Relat. Elem*. **2019**, *193*, 386–387. [IF: 0.781 (2018)]

(11). Hodula, V.; **Rádai, Z.**; Kiss, N. Z.; Keglevich, G. α-Hidroxifoszfonátok acilezési reakcióinak vizsgálata. Ádám Anna Adél, Ziegenheim Szilveszter (ed.), I. Fiatal Kémikusok Fóruma Konferencia Kiadvány. **2019**, 154–158. ISBN: 978-615-6018-00-7 [IF: –]

### 6.3. Other publications related to the PhD theses

(12). **Rádai, Z.**; Keglevich, G. Synthesis and reactions of α-hydroxyphosphonates. *Molecules* **2018**, *23*, 1439. [IF: 3.060, Citations: 3]

(13). **Rádai, Z.** α-Hydroxyphosphonates as versatile starting materials. *Phosphorus, Sulfur Silicon Relat. Elem*. **2019**, *194*, 425–437. [IF: 0.781 (2018)]

(14). **Rádai, Z.**; Kiss, N. Z.; Keglevich, G. Synthesis of α-hydroxyphosphonates, an important class of bioactive compounds. Keglevich György (ed.), Organophosphorus Chemistry: Novel developments. Berlin/Boston: Walter de Gruyter, **2018**, 91–107. ISBN: 978-3-11-053453-5 [IF: –]

(15). **Rádai, Z.**; Kiss N. Z.; Keglevich, G. Green syntheses of α-hydroxyphosphonates and α-aminophosphonates. Woodrow Phillips (ed.), Chalcogenides: Advances in Research and Application. New York, USA: NOVA Science Publishers, **2018**, 1–25. ISBN: 978-1-53614-372-0 [IF: –]

(16). **Rádai, Z.** α-Hidroxifoszfonátok előállítása, reakciói és biológiai aktivitása. *Magyar Kémiai Folyóirat*, **2019**, *in press* [IF: –]

(17). **Rádai, Z**. Zöld módszerekkel a biológiailag aktív anyagokért: Egy értékes vegyületcsalád előállítása. *Élet és tudomány*, **2018**, *10*, 303–305. [IF: –]

### 6.4. Additional publications

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### 6.5. Oral presentations

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[2]. **Rádai, Z.** Potenciálisan bioaktív foszfinsav és foszfonsav származékok előállítása környezetbarát módszerekkel. *Oláh György Doktori Iskola XV. Konferencia*, Budapest, February 1, **2018**.

[3]. **Rádai, Z.**; Kiss, N. Z.; Hodula, V.; Szabó, R.; Mucsi, Z.; Keglevich, G. Green synthetic routes towards α-hydroxyphosphonates and derivatives. *European Workshop in Phosphorus Chemistry*, Uppsala, Sweden, March 14–16, **2018**.

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[6]. **Rádai, Z.** α-Hidroxifoszfonátok: Zöld szintézis és bioaktivitás. *Akikre büszkék vagyunk – tudományos kiválóságaink*, Budapest, November 21, **2018**.

### 6.6. Poster presentations

[7]. **Rádai, Z.**; Kiss, N. Z.; Mucsi, Z.; Keglevich, G. Synthesis of α-hydroxyphosphonates and α-aminophosphonates. *21st International Conference on Phosphorus Chemistry*, Kazan, Russia, June 5–10, **2016**.

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[10]. **Rádai, Z.**; Hodula, V.; Kiss, N. Z.; Windt, T.; Nagy, V.; Hegedűs, L.; Keglevich, G. Tailoring the structure of α-hydroxyphosphonates to target sarcoma cells. *2nd European Chemistry Conference*, Amsterdam, Netherlands, May 15–16, **2019**.