BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

ROLE OF THE SOLVENTS AND ADDITIVES IN THE SYNTHESIS OF BISPHOSPHONIC ACID-BASED DRUG SUBSTANCE

PhD Thesis

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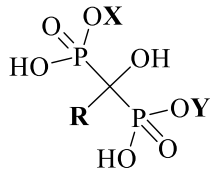
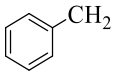
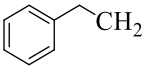
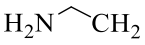
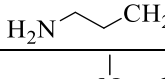
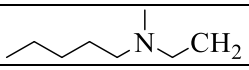
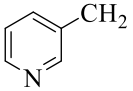
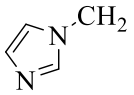
1 INTRODUCTION

I started my PhD work at the Green Chemical and Organophosphorus Research Group of *Prof. Dr. György Keglevich* in 2015, with the supervison of *Prof. Dr. György Keglevich* and *Assoc. Prof. Dr. Alajos Grün*. I became involved in an ongoing research, which is carried out in cooperation with Gedeon Richter Plc., supported by Research Director *Dr. István Greiner* and Head of Department *Sándor Garadnay*. During my work, I investigated the effects of the solvents and P-reagents in the synthesis of α-hydroxymethylene bisphosphonic acid derivatives. My task was to study the mechanism of the reactions, and to optimize and rationalize of the reaction conditions.

There is an increasing interest in the derivatives of α-hydroxy-methylenebisphosphonic acid (dronic acid), as there are many pharmaceutically active ingredients among the compounds, therefore the investigation of their synthesis is an important research area [1, 2].

The structure of bisphosphonic acid derivatives investigated at the Department of Organic Chemistry and Technology of



R	Name	X	Y
CH_3	Etidronate	Na	Na
	Fenidronate	Na	Na
	Benzidronate	Na	Na
	3-Phenylpropidronate	Na	Na
	Pamidronate Pamidronic acid	Na H	H H
	Alendronate	Na	H
	Ibandronate	Na	Na
	Risedronic acid	H	H
	Zoledronic acid	H	H

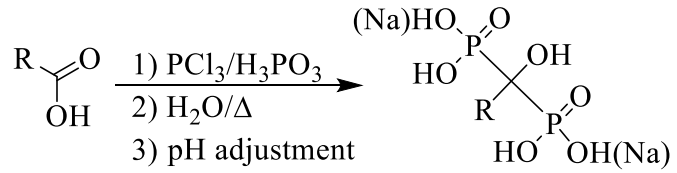
The α-hydroxy-methylenebisphosphonic (dronic) acid derivatives have two phosphonate groups connected to the same carbon atom. The chemical structure of dronic acid derivatives enables them to form a complex with the Ca^{2+} ions, therefore they are able to bind to the bone minerals. The hydroxy group on the central carbon atom increases the affinity to the Ca^{2+} ions. The side chain of the bisphosphonates has also a significant impact on the biological

[1] Hudson, H. R.; Wardle, N. J.; Bligh, S. W. A.; Greiner, I.; Grün, A.; Keglevich, G. *Mini Rev. Med. Chem.*, **2012**, *12*, 313-325.
[2] Russell, R. G. G. *Bone*, **2011**, *49*, 2-19.

activity. The first generation of dronic acid derivatives does not have a nitrogen atom in the C-substituent, while the members of the second and third generation have an aminoalkyl or an *N*-heterocyclic substituent, respectively. These *N*-containing derivatives have a more significant biological effect.

2 LITERATURE

The most common "direct" preparation involves the reaction of the corresponding carboxylic acid or its derivatives (acid chloride, anhydride or ester) with phosphorus trichloride and/or phosphorous acid (or in few instances with phosphoric acid, phosphoryl chloride, phosphorus pentachloride or phosphorus trioxide). The reaction temperature generally ranges from 60 °C to 100 °C, the reaction time is up to 24 hours. Upon the completion of the reaction, the target dronic acid was obtained after hydrolysis and suitable purification (recrystallization, digestion, precipitation) [3].



R= alkyl, aryl, heteroaralkyl

Although the synthesis of dronic acid derivatives is widely discussed in the literature, it can be considered a sort of "black box". They were prepared in many different solvents, but the optimum conditions, and the molar ratios of the P-reagents were not determined. The role of the reagents and the reaction mechanism were not clarified yet. The most commonly used solvents are methanesulfonic acid (MSA), chlorobenzene, sulfolane and toluene, however in many cases the synthesis of dronic acid derivatives was performed in the absence of any solvent. The "direct" synthetic route may be attractive as a consequence of the low price and the easy availability of the reagents, but the reaction has drawbacks as well. The reaction mixtures have a high degree of heterogeneity and are often unstirrable. During the reaction, and the subsequent hydrolysis intensive gas formation may occur. MSA may be considered the best solvent in the synthesis of dronic acid derivatives, as it helps overcome the problems of heterogeneity during the reactions. The data published are misleading and unreliable, as the required type and amount of the P-reagents have not been clarified for long. The role of the P-reactants and the solvents has not been investigated either, and the mechanism has not been

[3] Nagy, D. I., Grün, A., Garadnay, S., Greiner, I., Keglevich, G. Synthesis of Hydroxymethylenebisphosphonic Acid Derivatives in Different Solvents. *Molecules.*, **2016**, *21*, Article No.: 1046.

explored. Moreover, the products prepared were not supplied with adequate criteria for purity. A yield of 30-40% can be considered a good result if it relates to a pure product.

During my research, I focused mainly on the synthesis of α-hydroxymethylene bisphosphonic acids of paramount importance for the pharmaceutical industry, such as pamidronic acid, alendronate, ibandronate, zolderonic acid and risedronic acid. In addition, we also investigated the synthesis of 3-phenylpropidronate. Before my doctoral work, but with my participation, significant results were achieved within the subject by the research group. It has been demonstrated that in MSA the only P-reagent is phosphorus trichloride and phosphorous acid does not participate in the formation of the dronic acids. As part of our research we planned to investigate the effect of solvents and P-reagents. The syntheses of compounds mentioned were studied by using phosphorus phosphorus trichloride and phosphorous acid in sulfolane and in the presence of ionic liquids (ILs) additive. My task was to rationalize and optimize the conditions of the reactions, and to study the mechanisms of the formation of dronic acid derivatives. Until now, there were no comprehensive data on the mechanism of the formation of bisphosphonic acids. Therefore, the literature data were reviewed, and our conceptions were summarized.

3 EXPERIMENTAL METHODS

NMR: ^{31}P, ^{13}C and ^{1}H NMR spectra were obtained on a Bruker AV-300 spectrometer operating at 121.50 MHz, 75.5 MHz and 500 MHz, respectively.

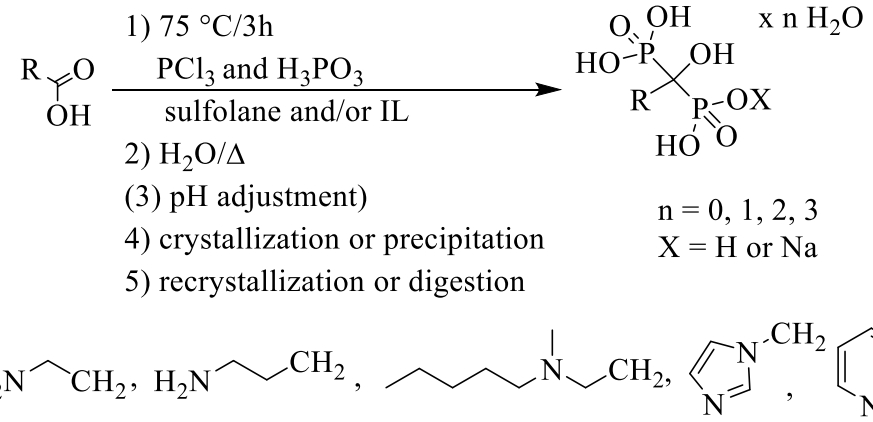
Potentiometric titrator: The dronic derivative content of the samples was determined by potentiometric acid-base titrations on a Mettler DL77 potentiometric titrator. The titration was carried out using 0.1M sodium hydroxide solution. The dronic acid derivative content of the samples can be calculated from the weight of the sample (~0.10 g) and the quantity of sodium hydroxide solution used. The results (yields and purities) were averaged over at least three independent experiments.

Thermal analysis: The water content of the dronic acid derivative samples was determined with TG and DSC measurements (on SETARAM Labsys TG instrument).

Quantum chemical calculations: Quantum chemical investigations were carried out using the Gaussian09 program package (G09) by B3LYP/6-31G(d,p) methods.

4 NEW SCIENTIFIC RESULTS

During the research, the synthesis of alendronate, ibandronate, zoledronic acid and risedronic acid was investigated in sulfolane.



In the case of alendronate and risedronic acid, similar results were realized in sulfolane (52% and 58%) than before in MSA (67% and 74%) at the Department, while the pure ibandronate and zoledronic acid was synthesized in higher yield in sulfolane (83% and 74%) than in MSA (46% and 53%). In the case of ibandronate, the yield was doubled. It is proved that the combined use of P-reagents (PCl_3 and H_3PO_3) is indispensable in sulfolane for achieving high yields, the use of phosphorus trichloride alone is not enough. In each case, the optimal ratio of the P-reactants was determined. It has been confirmed that the activated species of $(HO)_2P\text{-}O\text{-}PCl_2$ and $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$ react also with the starting carboxylic acid or its chloride in sulfolane.

Results achieved in sulfolane

Dronic acid/dronate	**Reagents**		**Purity**	**Yield**	**Results with 3.2 equiv. PCl_3 in MSA at the Department (Purity / Yield)**
	PCl_3 (equiv.)	**H_3PO_3 (equiv.)**			
Alendronate	3	2	99%	52%	98% / 57%
Ibandronate	3	4	100%	83%	99% / 46%
Zoledronic acid	2	2	100%	74%	99% / 53%
Risedronic acid	2	2	100%	58%	92% / 74%

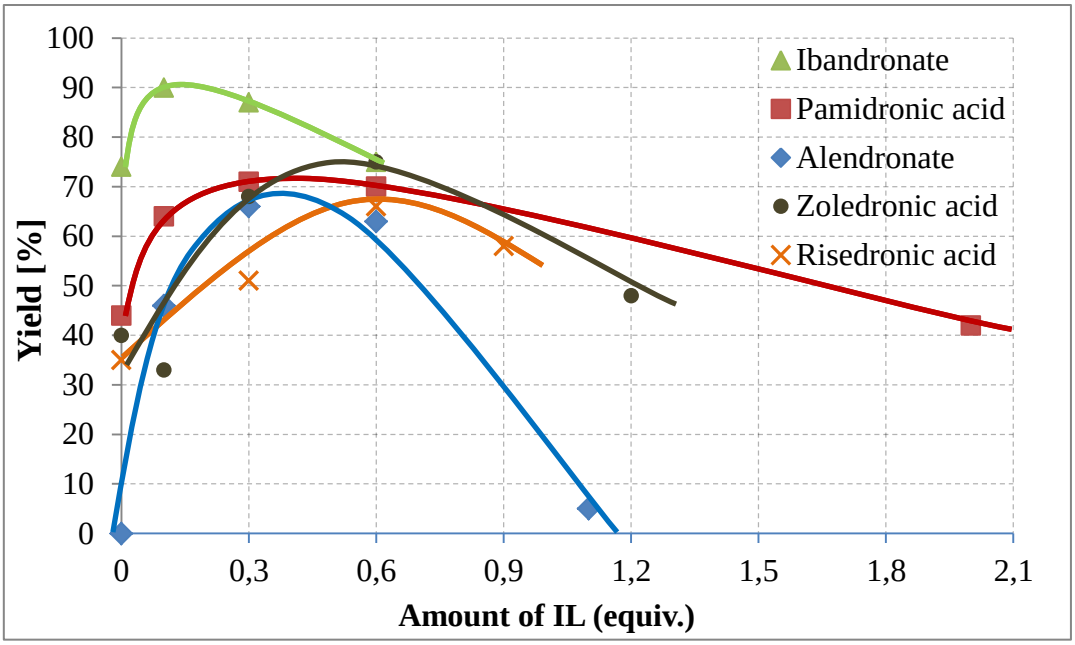
The investigation of the synthesis of dronic acid derivatives in the presence of IL additives was a very important part of my research. The ILs are considered green solvents because of their low vapor pressure, high thermal stability, and their potential that they can be recycled or reused. The preparation of pamidronic acid, alendronate, ibandronate, zoledronic acid and risedronic acid was studied in the presence of IL additives.

The effect of the P-reagent ratios and the amount of ILs were investigated. The optimal ratio of phosphorus trichloride and phosphorous acid for different dronates were 2:2 or 3:2 equivalents. It is also demonstrated that using of phosphorus trichloride or phosphorous acid alone is not enough for the completion of the reactions in ILs.

Synthesis of dronic acid derivatives in the presence of optimum amount of ILs additives and P-reagents quantity

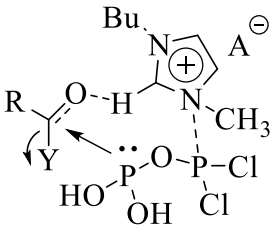
Dronic acid/dronate	**IL (optimal amount)**	**Reagents**		**Purity [%]**	**Yield [%]**
		PCl_3 (equiv.)	**H_3PO_3 (equiv.)**		
Pamidronic acid	[bmim][PF_6] (0.3 equiv.)	2	2	100	71
Alendronate	[bmim][BF_4] (0.3 equiv.)	3	2	98	66
Ibandronate	[bmim][BF_4] (0.1 equiv.)	3	2	99	90
Zoledronic acid	[bmim][BF_4] (0.6 equiv.)	2	2	99	75
Risedronic acid	[bmim][BF_4] (0.6 equiv.)	2	2	100	66

The most effective IL in the case of pamidronic acid was the 1-butyl-3-methylimidazolium hexafluorophosphorate ([bmim][PF_6]), while in the case of the other four dronic acid derivatives studied is the 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]). In the case of bisphosphonic acid derivatives, we found first that the ILs should not be used as a solvent, only as an additive, in amount of 0.1-0.6 equivalents. By the novel method, outstanding yields were reached compared to the previous results realized at the Department. As shown in the following figure, it can be observed for all dronic acid derivatives, the yields follow a curve with a maximum depending on the amount of ILs. The ILs caused the most significant increase on the yield of alendronate. The synthesis of alendronate is not possible at all in the absence of any solvents, while nearly 70% yield was achieved with the use of 0.3 equivalents of [bmim][BF_4] additive, while increasing the amount of IL to 1.1 equivalents inhibited the reaction. Differing from the case of other bisphosphonates, ibandronate could be prepared in high yields (~75%) also the absence of any solvent. In the case of ibandronate, it is required to use the IL additive in the smallest quantity; with applying 0.1 equivalents of [bmim][BF_4], the yield increased to 90%. In the solvent-free synthesis of ibandronate, the hydrochloride or phosphorous acid salt of *N*-methyl-*N*-pentyl-β-alanine ($^{n}PentMeN(CH_2)_2CO_2H{\bullet}HCl$ or $^{n}PentMeN(CH_2)_2CO_2H{\bullet}H_3PO_3$) may also have a positive role in the higher yields, as it may behave as that may act as an IL under the reaction conditions.



Because of the good results achieved in sulfolane and in the presence of IL additive, the synthesis of dronic acid derivatives were investigated in the mixture of sulfolane and IL additive with using of the best P-reagents ratio (2:2 or 3:2), and the optimal amount of the IL additive. In the case of ibandronate, the yield becomes worse, while in the case of risedronic acid it did not change. By contrast, in the synthesis of alendronate and zoledronic acid, the joint use of the ionic liquid additive and sulfolane as the solvent mixture had synergetic effect afforded alendronate and zoledronic acid in a record yield of 80% and 93%, respectively.

It was assumed that the presence of an IL may increase the electrophilic character of the carbonyl group of the carboxylic acid derivatives, thus may facilitate the attack of the nucleophilic P-atom of the activated P-reagents [$(HO)_2$P-O-PCl_2 or $(HO)_2$P-O-PCl-O-$P(OH)_2$] to the carbon atom of the carbonyl function group.



Y= OH, Cl

R =H_2N CH_2, H_2N CH_2, N CH_2, N CH_2, N CH_2

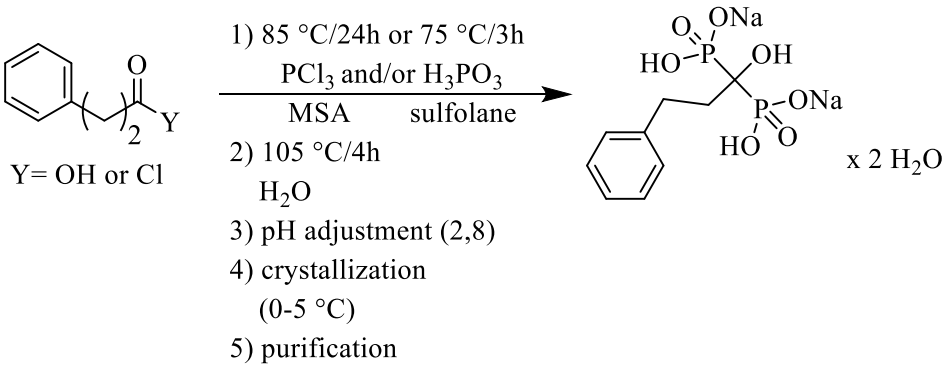
In summary, during the research, the synthesis of bisphosphonic acid derivatives of the highest importance in the pharmaceutical industry were made more efficient. Instead of the average yield of 30-40% in the feasibility discipline of dronic acid derivatives, significantly

higher yields were reached. The pamidronic acid was synthesized in a yield of 72%, the alendronate in a yield of 80%, the ibandronate in a yield of 90%, the zoledronic acid in a yield of 93% and the risedronic acid in a yield of 66%.

To date, the highest yields achieved in different solvents at the Department

Dronic acid derivative	MSA (Purity/Yield)	Sulfolane (Purity/Yield)	IL (Purity/Yield)	Sulfolane + IL (Purity/Yield)
Pamidronic acid	99%/57% [44]	100%/63% [44]	100%/72% [S2]	-
Alendronate	98%/57% [43]	99%/52% [S3]	98%/66% [S3]	100%/80% [S3]
Ibandronate	99%/46% [43]	100%/83% [S4]	99%/90% [S4]	99%/68% [S4]
Zoledronic acid	99%/53% [41]	100%/74% [S5]	99%/75% [S5]	99%/93% [S5]
Risedronic acid	92%/74% [41]	100%/58% [S6]	100%/66% [S6]	100%/67% [S6]

On another line, the preparation of 3-phenylpropidronate was investigated starting from 3-phenylpropionic acid or 3-phenylpropanoic acid chloride in MSA.



Unexpectedly, it was found that 3-phenylpropidronate is not possible to be synthesized only with using phosphorus trichloride alone in MSA, using of phosphorous acid beside phosphorus trichloride is necessary. However, this statement is in complete contradiction with previous experiences. The best yields of 65% and 72% were obtained when the carboxylic acid or carboxylic acid chloride were reacted with 2 equivalents of phosphorus trichloride and 4 equivalents of phosphorous acid. There is no significant effect of the starting material applied on the yields. Based on the results, in the case of 3-phenylpropidronate the activated P-reagents are also the intermediate of $(HO)_2P\text{-}O\text{-}PCl_2$ and $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$ in MSA, as was it previously assumed in the preparation of pamidronic acid in sulfolane. These compounds can react with the carboxylic acid, carboxylic acid chloride or mixed anhydride ($Ph(CH_2)_2C(O)\text{-}O\text{-}S(O)_2Me$) which may form directly in the reaction mixture. The previously assumed intermediate $Cl_2P\text{-}O\text{-}S(O)_2Me$ formed from phosphorus trichloride and MSA "*in situ*" is not too probable as the P-nucleophile against the carbonyl group of the starting compounds.

The synthesis of 3-phenylpropidronate was also carried out starting from 3-phenylpropionic acid or 3-phenylpropanoic acid chloride, phosphorus trichloride and phosphorous acid in sulfolane. The P-reagents were also necessary to use simultaneously. Interestingly, the results are fully comparable with those obtained in MSA. The highest yields (65% starting from 3-phenylpropionic acid and 68% starting from 3-phenylpropanoic acid chloride) were also reached when the phosphorus trichloride and phosphorous acid were used in amount of 2:4 equivalents. The yields obtained do not depend on the solvent and the starting compound, only on the ratio of the reagents, thus the role of mixed anhydride is not significant indeed. It is revealed with quantum chemical calculations that the $-P(OH)_2$ moiety of P-species is more reactive than the $-PCl_2$ unit.

5 THESES

1. Efficient and novel methods have been developed which ensure high yield for the synthesis of the bisphosphonic acid derivatives (pamidronic acid, alendronate, ibandronate, zoledronic acid and risedronic acid) in sulfolane and/or in the presence of ionic liquid additive. It has been demonstrated that it is necessary to use both phosphorus trichloride and phosphorous acid as the P-reagents simultaneously in ratios of 2:2 or 3:2. When the P-reagents are applied separately, formation of bisphosphonic acid cannot be observed. [S2-S7]

2. It is confirmed that the activated P-reagents in sulfolane and/or in the presence of ionic liquid additive are the species $(HO)_2P\text{-}O\text{-}PCl_2$ and $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$ which form from phosphorus trichloride and phosphorous acid. They react with the carbonyl group of the starting carboxylic acid and/or the acid chloride which may form ”*in situ*” in the reaction mixture. [S1-S7]

3. It is proved that during the synthesis of bisphosphonic acid derivatives, the ionic liquids should not be used as solvents only in smaller amount as an additive. Depending on the starting carboxylic acid, their optimum amount is between 0.1-0.6 equivalents and depending on the amount of ionic liquid, the yields followed a curve with a maximum. [S2-S7]

4. The syntheses of alendronate and zoledronic acid were developed in the mixture of sulfolane as a solvent and ionic liquid as an additive. It was found that the combined use was beneficial, as it was observed that the yields increased significantly. The use of a catalytic amount of ionic liquid together with sulfolane is synergetic. [S2-S7]

5. Efficient method have been developed for the syntheses of 3-phenylpropidronate in meathanesulfonic acid and in sulfolane which ensures high yields. It is demonstrated that the syntheses of 3-phenylpropidronate is not possible by applying phosphorus trichloride alone in methanesulfonic acid, phosphorous acid should be added to phosphorus trichloride as well. It is assumed in contrast to the previously studied dronate derivatives that instead of the mixed anhydride $[Ph(CH_2)_2C(O)\text{-}O\text{-}S(O)_2Me]$, the 3-phenylpropionic acid or 3-phenylpropionic acid chloride react with the intermediates $(HO)_2P\text{-}O\text{-}PCl_2$ or $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$ in methanesulfonic acid, instead of the previously supposed $Cl_2P\text{-}O\text{-}S(O)_2Me$. [S1]

6. The stable forms of activated P-reagents [$(HO)_2P\text{-}O\text{-}PCl_2$ és $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$] were elucidated by quantum chemical calculations. Calculations revealed that while $(HO)_2P\text{-}O\text{-}PCl_2$ is stable in the neutral form, $(HO)_2P\text{-}O\text{-}PCl\text{-}O\text{-}P(OH)_2$ is dissociated to onium salt [$(HO)_2P\text{-}O\text{-}P^{+}\text{-}O\text{-}P(OH)_2\ Cl^{-}$]. The calculations confirmed that the $-P(OH)_2$ moiety of species $(HO)_2P\text{-}O\text{-}PCl_2$ is more reactive than the $-PCl_2$ unit, therefore the $-P(OH)_2$ moiety attacks to the carbonyl group's carbon atom of 3-phenylpropionic acid or 3-phenylpropionic acid chloride. [S1]

7. A solvent-free, green chemically significant process was developed for the synthesis of ibandronate. When phosphorus trichloride and phosphorous acid are combined, ibandronate can be synthesized in high yield in the absence of any solvent. [S4]

6 APPLICATION POSSIBILITIES

The synthesis of hydroxy-bisphosphonates was already investigated in the second half of the 19th century. The first compound synthesized was etidronic acid in 1865. In the early decades, the bisphosphonates were used as corrosion inhibitor, complexing agent or water softener. Their biological activity was revealed in the middle of 1960s, and etidronic acid was the first that entered in the market at the early 1970s.

In the beginning, the hydroxy-bisphosphonates were used to treat tumor diseases affecting bone tissue. Nowadays, they are considered the best drugs in the treatment of osteoporosis, Paget-disease and tumor-induced hypercalcaemia, but they also have direct anti-cancer (breast, prostate, and kidney) and anti-parasitic effect. They are still used in the treatment of rheumatoid arthritis and osteoarthritis. These are serious chronic illnesses of today. In many cases, the mineral density of the bones decreases, so they become fragile, they can break easily. Osteoporosis affects more than 200 million people worldwide, the number of patients can be estimated from 800 thousands to 1 million in Hungary, two-thirds of whom are women, one-third are men. Worldwide, approximately 9 million fractures are attributable to osteoporosis. The compounds have also shown direct antiparasitic activity, and furthermore they are also useful in the therapy of HIV infection, as they are able to reduce the resistance against the HIV enzyme reverse transcriptase inhibitors. They are used in implant-related bone formation (orthopedics and dentistry), to promote bone fracture healing and also the medical diagnostics.

It can be seen that the dronic acid derivatives are extremely important and useful compounds pharmaceutical point of view, thus, the efficient synthesis methods developed are considered outstanding results. Bisphosphonic acid derivatives can be obtained with higher purity with the applying of syntheses developed, than with the currently used industry processes in MSA. When sulfolane and/or IL are used, sodium methanesulfonate does not form during the pH adjustment of the processing of the reaction mixture, which is difficult to remove. Purification of the crude products are easier, the products can be filtered well.

Cost analysis was performed for zoledronic acid. It is determined whether it is possible to produce 1 kg of zoledronic acid at the lowest cost in MSA in sulfolane or in the presence of ionic liquid additive. The synthesis of zoledronic acid in MSA is the most expensive method, the synthesis of it in sulfolane is the cheapest way. The methods developed in sulfolane and in the presence of IL additive is more environmentally friendly than the current process in MSA. For the reasons illustrated, it is imperative to consider the introduction of the novel processes in industry. A deeper understanding of the mechanism of reactions allows for rational planning of syntheses.

7 PUBLICATIONS

7.1. FULL SCIENTIFIC PUBLICATIONS RELATED TO THE PhD THESIS

[1] Grün, A.; Nagy, D. I.; Németh, O.; Mucsi, Z.; Garadnay, S.; Greiner, I.; Keglevich, G. The Synthesis of 3-Phenylpropidronate Applying Phosphorus Trichloride and Phosphorous Acid in Methanesulfonic Acid. *Curr. Org. Chem.,* **2016**, *20*, 1745-1752. [IF: **1,924**, S-NDI: **80%,** C: **1**]

[2] Grün, A.; Nagy, D. I.; Garadnay, S.; Greiner, I.; Keglevich, G. Efficient synthesis of pamidronic acid using an ionic liquid additive. *Lett. Drug. Des. Discov.,* **2016**, *13*, 475-478. [IF: **1,170**, S-NDI: **90%,** C: **3**]

[3] Nagy, D. I.; Grün, A.; Garadnay, S.; Greiner, I.; Keglevich, G. Investigation of the Effect of Medium in the Preparation of Alendronate; Till Now the Best Synthesis in the Presence of an Ionic Liquid Additive. *Heteroatom Chem.*, **2017**, *28*, Article No.: 21370. [IF:**1,137**, S-NDI: **90%,** C: **1**]

[4] Nagy, D. I.; Grün, A.; Pavela, O.; Garadnay, S.; Greiner, I.; Keglevich, G. Efficient Synthesis of Ibandronate in the Presence of an Ionic Liquid. *Lett. Drug. Des. Discov.,* **2017,** *15*, 713-720. [IF: **0,924**, S-NDI: **60%,** C: **1**]

[5] Nagy, D. I.; Grün, A.; Lévay, K.; Garadnay, S.; Greiner, I.; Keglevich, G. Efficient syntheses of zoledronic acid as an active ingredient of a drug against osteoporosis. *Synth. Commun*., **2018**, *48*, 663-671. [IF: **1,377** (2017), S-NDI: **60%**]

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7.2. REVIEW AND MINI-REVIEW PUBLICATIONS RELATED TO THE PhD THESIS

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7.4. ORAL PRESENTATION

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7.5 POSTER PRESENTATIONS

1 Nagy, D. I.; Grün, A.; Kovács, R.; Garadnay, S.; Greiner, I.; Keglevich, G. α-Hidroxi-metilénbiszfoszfonsavak előállítása, MKE 2. Nemzeti Konferencia, 2015 augusztus 31.- szeptember 2., Hajdúszoboszló, ISBN: 978-963-9970-57-1

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