Final report

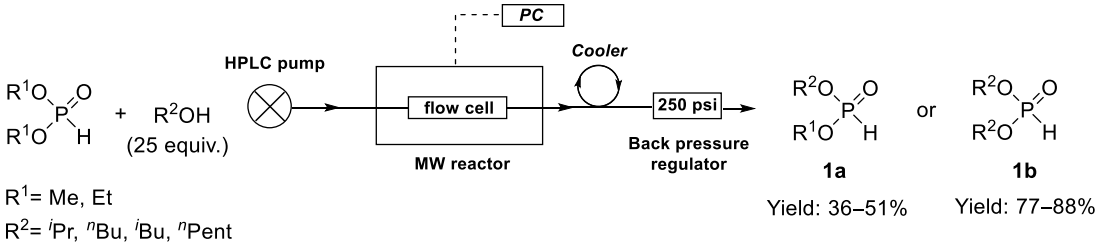
NKFIH – FK 123961

Synthesis of heterocyclic aminophosphonate and aminophosphine oxide derivatives via multicomponent reactions

According to the workplan, we conducted our researches in the field of organophosphorus chemistry and multicomponent synthesis. The main aim of our project was to develop one-pot multicomponent syntheses for the preparation of novel heterocycles containing a phosphonate or a phosphine oxide moiety and the synthesis of *P*-heterocyclic derivatives. All multicomponent reactions were aimed to be optimized through a model reaction in respect of the heating mode, molar ratio of the starting materials, atmosphere, catalyst, temperature, reaction time and solvent applied, and then, the extended preparation of small libraries of structurally-related compounds was also set as a goal. The biological activity, such as *in vitro* cytotoxicity and antibacterial activity of the compounds synthesized, as well as the utilization of some derivatives as phosphine ligands in transition metal complexes were also aimed to be investigated. Cytotoxicity assays used the human lung adenocarcinoma A549 cell line, the mouse fibroblast NIH/3T3 as a healthy cell line and the human promyelocytic leukemia HL-60 cell line. The antibacterial activity of the compounds was investigated on green fluorescent protein (GFP) producing *Bacillus subtilis* (Gram-positive) and *Escherichia coli* (Gram-negative) bacterial cells. Furthermore, we also wished to study the mechanism of the multicomponent reactions by experiments, as well as by quantum chemical calculations.

1.1.) Continuous flow synthesis of dialkyl phosphites

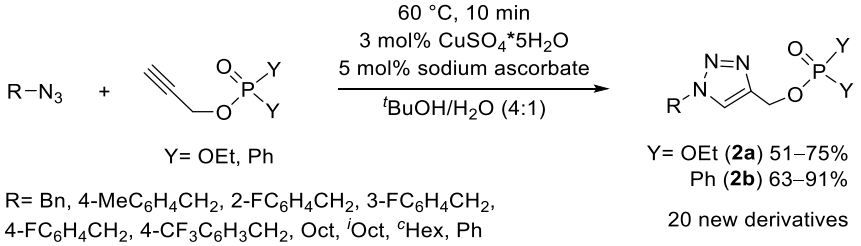
First, a scaled-up microwave (MW)-assisted continuous flow method was developed for the synthesis of various dialkyl phosphites (dialkyl *H*-phosphonates) (**1a**, **1b**) by the catalyst-free alcoholysis of diethyl or dimethyl phosphite applying a MW reactor equipped with a continuous flow cell (Scheme 1) [1,2]. These derivatives serve as important starting materials for most of the multicomponent reactions in this research project. By the optimization of the reaction parameters, the alcoholysis was fine-tuned towards dialkyl phospites with two different (**1a**) or with two identical alkoxy groups (**1b**).



Scheme 1. Continuous flow alcoholysis of dialkyl phosphites

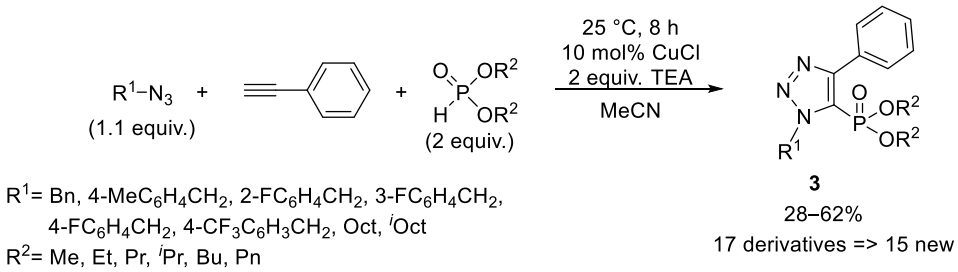
1.2.) Synthesis of triazoles bearing a phosphate, a phosphinate or a phosphonate moiety

A facile and practical method was developed for the synthesis of (1,2,3-triazol-4-yl)methyl diethyl phosphates (**2a**) and (1,2,3-triazol-4-yl)methyl diphenylphosphinates (**2b**) by the copper(I)-catalyzed azide-alkyne cycloaddition of organic azides and diethyl prop-2-ynyl phosphate or prop-2-ynyl phosphinate (Scheme 2) [3]. Our novel approach enabled the simple preparation of 20 new derivatives in good to high yields under mild reaction conditions.



Scheme 2. Synthesis of (1,2,3-triazol-4-yl)methyl diethyl phosphates (**2a**) and (1,2,3-triazol-4-yl)methyl diphenylphosphinates (**2b**) by click reaction

The synthesis of 1,2,3-triazol-5-yl-phosphonates (**3**) was also carried out by the copper(I)-chloride-catalyzed three-component domino reaction of organic azides, phenylacetylene and dialkyl phosphites (Scheme 3) [4,5]. Applying the approach developed, altogether 17 triazol-5-yl-phosphonates (**3**) were synthesized and fully characterized, except two, all of them are new compounds. The biological activity of the derivatives prepared was investigated in antibacterial activity and *in vitro* cytotoxicity assays. None of the synthesized 1,2,3-triazol-5-yl-phosphonates were active against selected Gram-negative bacteria, while the growth of Gram-positive bacteria was somewhat reduced. Several compounds showed low or modest activity against the tested cell lines (A549, NIH/3T3 and HL-60), two of them have the IC_{50} value in 10 micromolar range against HL-60 cells.

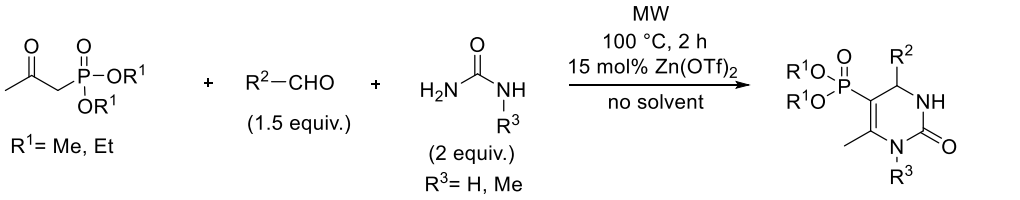


R1= Bn, 4-MeC6H4CH2, 2-FC6H4CH2, 3-FC6H4CH2, 4-FC6H4CH2, 4-CF3C6H3CH2, Oct, iOct
R2= Me, Et, Pr, iPr, Bu, Pn

Scheme 3. Synthesis of 1,2,3-triazol-5-yl-phosphonates by CuCl-catalyzed domino reaction

1.3.) Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates by Biginelli reaction

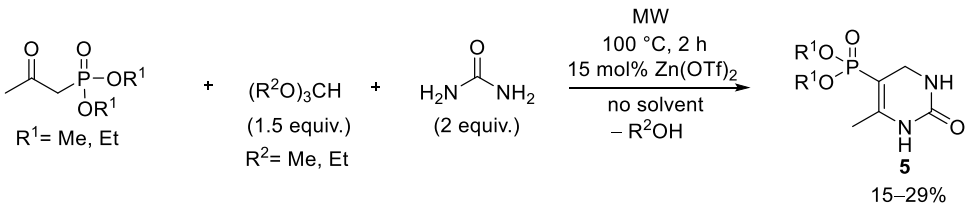
A new, microwave (MW)-assisted method was developed for the synthesis of novel 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates (**4**) by the Biginelli reaction of aldehydes, β-ketophosphonates and urea derivatives under solvent-free conditions (Scheme 4) [6,7]. The 5-diethoxyphosphoryl-4-phenyl-6-styryl-3,4-dihydropyrimidin-2(1*H*)-one, as a new by-product of the condensation, was also isolated and characterized. Our MW-assisted approach made also possible the Biginelli reaction with aliphatic aldehydes, which transformation was previously reported as impossible in the literature. Altogether 26 3,4-dihydropyrimidin-2(1*H*)-one-phosphonates (**4**) were prepared, among them 20 derivatives are new.



R2= Ph, 2-ClC6H4, 3-ClC6H4, 4-ClC6H4, 4-FC6H4, 2-F-4-IC6H3, 3-MeC6H4, 4-HOC6H4, NO2C6H4, 3,4,5-tri(MeO)C6H2, Pr, iBu

Scheme 4. Biginelli reaction of β-ketophosphonates, aromatic or aliphatic aldehydes and urea derivatives

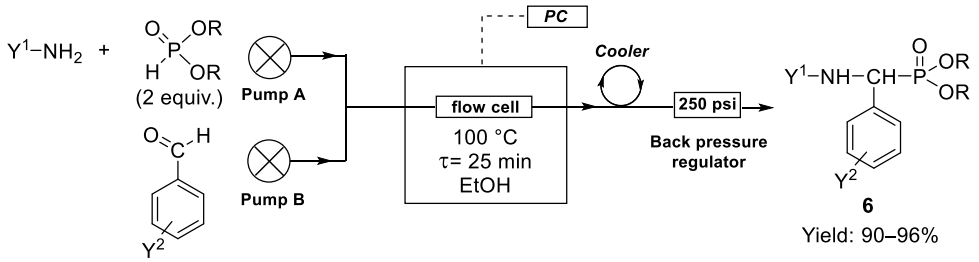
As an extension, the Biginelli reaction was also performed using trialkyl orthoformate instead of aldehydes under the optimized conditions (Scheme 5), however, tt was found that the ortho esters were less reactive in this reaction, since the corresponding dialkyl (6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)phosphonates (**5**) were formed only in low yields.



Scheme 5. Biginelli reaction of β-ketophosphonates, trialkyl orthoformate and urea

1.4.) Special Kabachnik-Fields reaction of 2-formylbenzoic acid, primary amines and dialkyl phosphites or secondary phosphine oxides

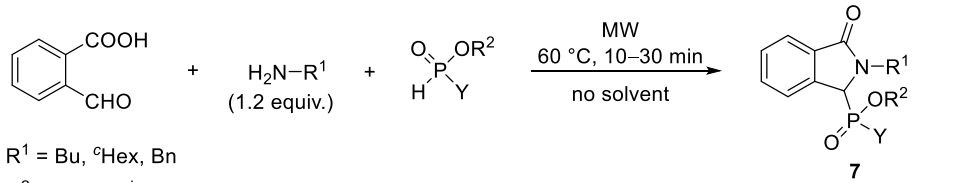
Among our plans was the continuous flow synthesis of heterocyclic phosphorus compounds using a MW reactor equipped with a continuous flow cell. For this purpose, first an efficient, catalyst-free MW-assisted continuous flow method was elaborated for the synthesis of various acyclic α-aryl-α-aminophosphonates (**6**) by Kabachnik-Fields reaction with higher productivity as compared to the batch reactions (Scheme 6) [8]. The Kabachnik-Fields condensation in a flow reactor is a novel approach for the preparation of α-aminophosphonates.



Y^1= Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, $PhCH_2$, 4-$MeOPhCH_2$
Y^2= H, 2-Cl, 3-Cl, 4-Cl, 4-OH, 4-Me, 4-MeO

Scheme 6. Continuous flow synthesis of α-aminophosphonates by Kabachnik-Fields reaction

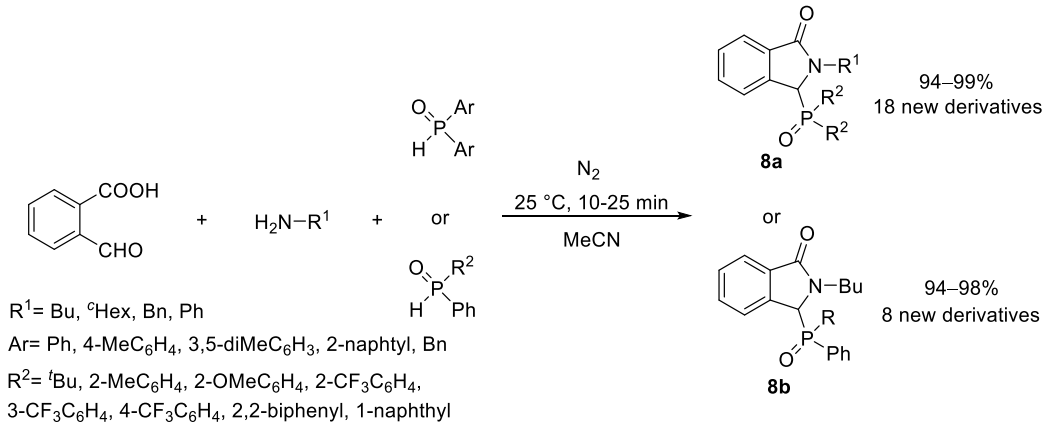
After that, a facile, efficient and catalyst-free method was developed for the batch and continuous flow three-component condensation of 2-formylbenzoic acid, aliphatic primary amines and various dialkyl phosphites (Scheme 7) [9,10]. The batch approach enabled the solvent-free synthesis of the target compounds (**7**) in high yields (70-94%) at low temperature (60 °C) under short reaction times (10-30 min). By the *in situ* FT-IR study on the condensation of 2-formylbenzoic acid, butylamine and diethyl phosphite, the reaction was followed in "real time" and the time-dependent concentration profiles of the reaction components were determined. The novel continuous flow MW-assisted method elaborated is suitable for the synthesis of the corresponding isoindolin-1-one-3-phosphonates (**7**) in a "few g" scale. Altogether 16 derivatives were synthesized, except two, all of them are new compounds.



R^1 = Bu, ^{c}Hex, Bn
R^2 = Me, Et, ^{i}Pr, Bu, Bn
Y = OMe, OEt, O^{i}Pr, OBu, OBn, Ph

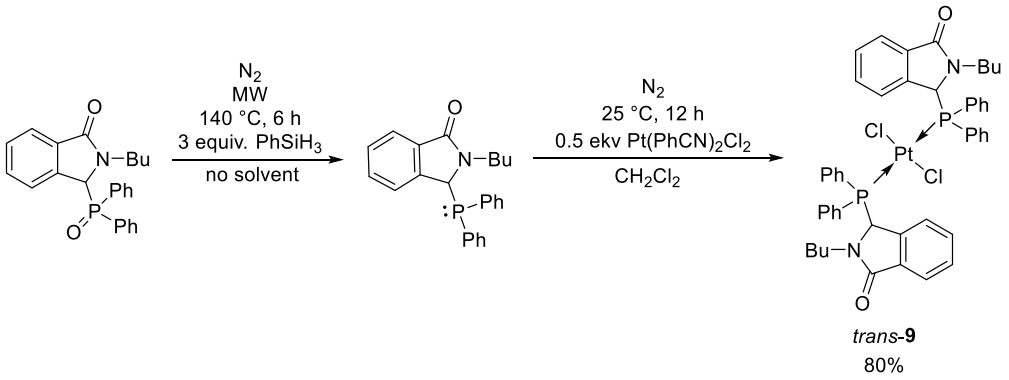
Scheme 7. Condensation of 2-formylbenzoic acid, primary amines and dialkyl phosphites

The one-pot three-component reaction of 2-formylbenzoic acid, primary amines and achiral or chiral secondary phosphine oxides was also investigated (Scheme 8) [11]. The new procedure developed means a promising approach to attain 3-oxoisoindolin-1-ylphosphine oxides bearing same (**8a**) or different (**8b**) substituents on the phosphorus atom, since it applies mild and easily operational conditions (no special reagents, catalysts or additives, no heating). In all 26 new derivatives were synthesized in high to excellent yields and were fully characterized. The biological activity of the compounds prepared was also tested in *in vitro* cytotoxicity and antibacterial assays. Several 3-oxoisoindolin-1-ylphosphine oxides (**8a**) showed modest activity against HL-60 cell line, furthermore, two derivatives incorporating 3,5-dimethylphenyl groups on the phosphorus atom were also active against selected Gram-positive bacteria.



Scheme 8. Special Kabachnik-Fields reaction of 2-formylbenzoic acid, primary amines and secondary phosphine oxides

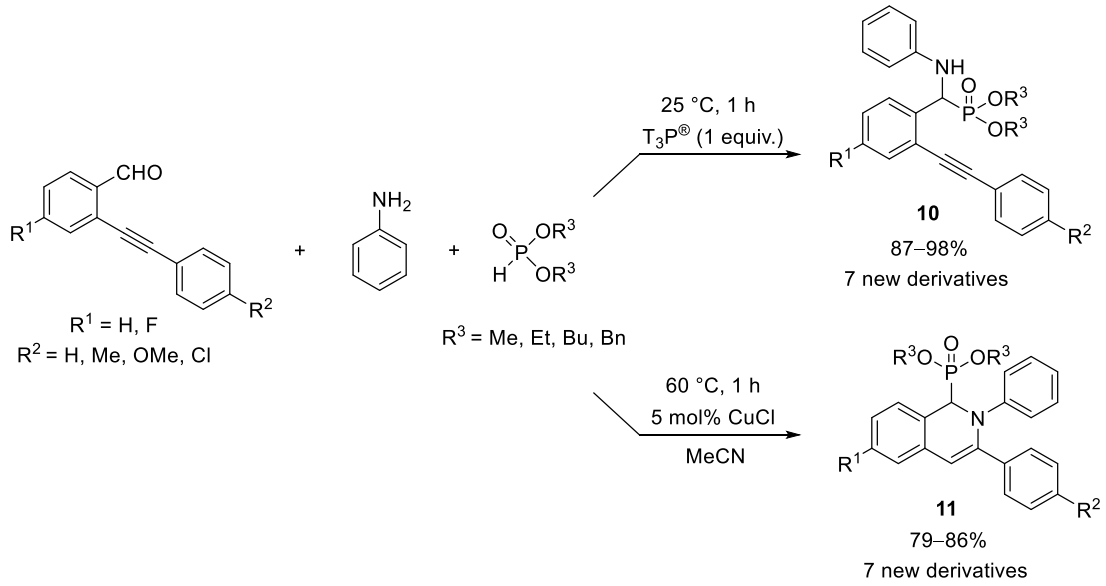
After deoxigenation, one of the 3-oxoisoindolin-1-ylphosphine oxides has been utilized as P-ligand for the synthesis of a monodentate platinum(II) complex [11]. The complex (**9**) was formed in a relative configuration of *trans*, based on platinum-phosphorus coupling constant ($^1J_{Pt\text{-}P}$) in the ^{31}P NMR spectra. The relative orientation of the *trans*-**9** platinum(II) complex was also confirmed by X-ray diffraction measurements.



Scheme 9. Deoxygenation of an (oxoisoindolinyl)phosphine oxide and formation of a platinum(II) complex ((*trans*)-**9**)

1.5.) Special Kabachnik-Fields reaction of 2-alkynylbenzaldehydes, primary amines and dialkyl phosphites or secondary phosphine oxides

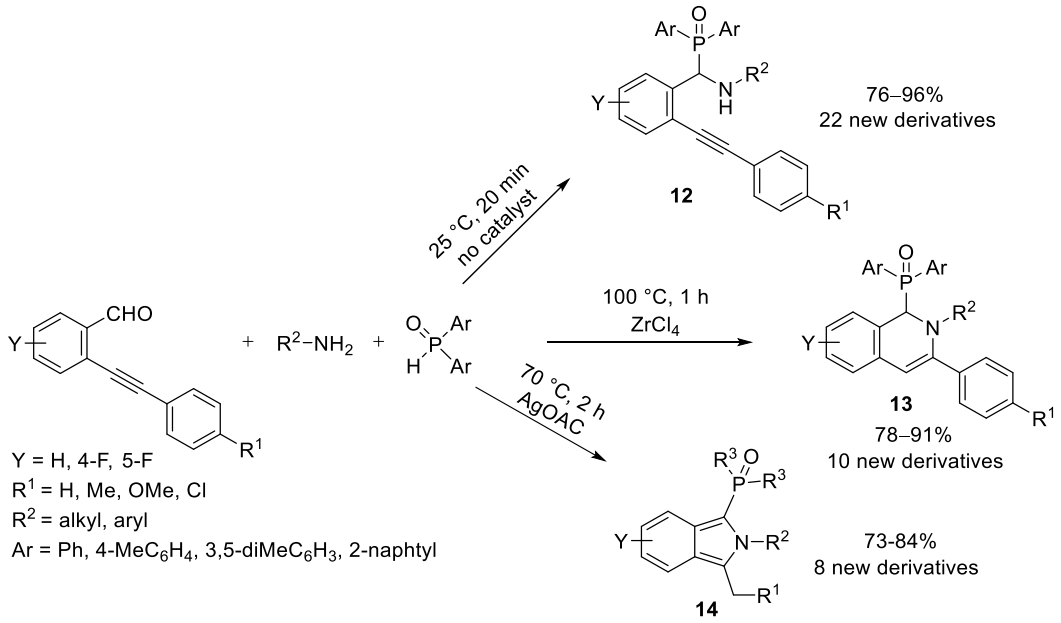
Investigation of the three-component reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites was also performed (Scheme 10) [12]. It was found that two type of compounds were formed according to the catalyst system used. By the propylphosphonic anhydride ($T_3P^®$)-mediated Kabachnik-Fields reaction, α-amino (2-alkynylphenyl)-methylphosphonates (**10**) were obtained selectively in high yields. The method developed has the advantages of the simple operation and mild reaction conditions, and it does not require a chromatographic separation. Moreover, novel 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates (**11**) were prepared by the CuCl-catalyzed condensation at 60 °C for short reaction time (1 h). Our approach is faster and cheaper compared with the literature examples, where the reactions were complete after 4–6 h using more expensive catalysts. Altogether, seven α-amino (2-alkynylphenyl)-methylphosphonates and seven 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates were synthesized in good to high yields. The *in vitro* cyctotoxicity of the products synthesized was studied against A549, NIH/3T3 and HL-60 cell lines, and it was found that compounds with butoxy groups linked in the phosphorus atom showed activity against HL-60 cells (IC_{50}= 4–15 μM).



Scheme 10. Kabachnik-Fields reaction of 2-alkynylbenzaldehydes, aniline and dialkyl phosphites

The three-component reactions of 2-alkynylbenzaldehydes, primary amines and secondary phosphine oxides was also performed (Scheme 11) [13]. After a comprehensive catalytic study, we have found that the reaction could lead to the formation of three types of products (**12**–**14**). Various α-amino (2-alkynylphenyl)-methylphosphine oxides (**12**) were synthesized in the

absence of any catalyst at ambient temperature for short reaction time. Applying zirconium(IV) chloride as a catalyst, 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphine oxides (**13**) can be prepared, however, using silver acetate, 2*H*-isoindol-1-yl-phosphine oxides (**14**) were the main components. Based on the bioactivity tests, all the three-types of products (**12**–**14**) showed promising activity against NIH/3T3 and HL-60 cell lines, however, the most active derivatives were the 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphine oxides (**13**), which had their IC_{50} values in the 8–9 micromolar range against HL-60 cells.

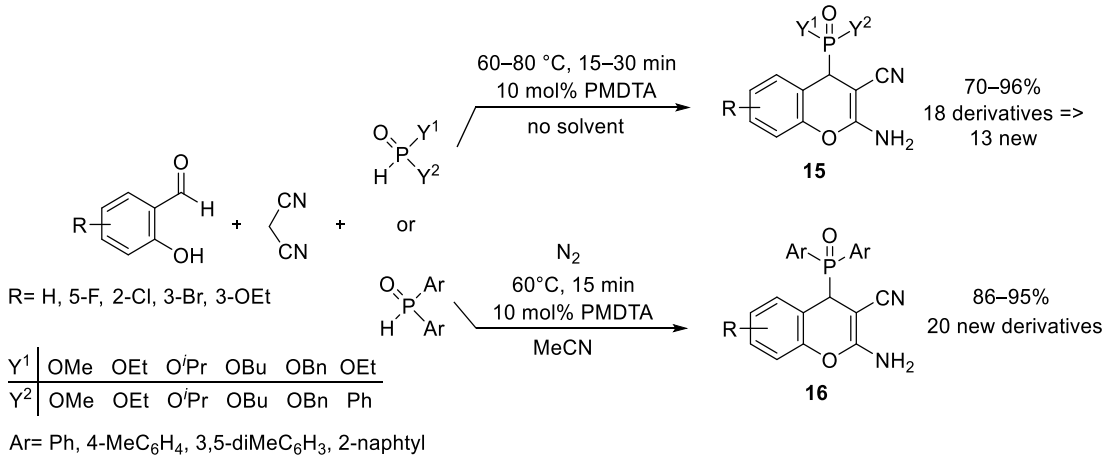


Scheme 11. Three-component reaction of 2-alkynylbenzaldehydes, primary amines and secondary phosphine oxides

1.6.) Three-component reaction of salicylaldehydes, malononitrile and dialkyl phosphites or secondary phosphine oxides

A simple, efficient and fast pentamethyldiethylenetriamine (PMDTA)-catalyzed novel method was elaborated for the preparation of new (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates (**15**) by the domino Knoevenagel–phospha-Michael reaction of salicylaldehydes, malononitrile and dialkyl phosphites under solvent-free conditions (Scheme 12) [14]. The method developed did not require chromatographic separation, since the products could be recovered from the reaction mixture by simple filtration. Our approach made also possible the condensation with secondary phosphine oxides, and this reaction has not been previously reported in the literature. Altogether 18 (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonate derivatives (**15**) and 20 (2-amino-3-cyano-4*H*-chromen-4-yl)phosphine oxides (**16**) were prepared in good to high yields, and fully characterized. The X-Ray structures of five

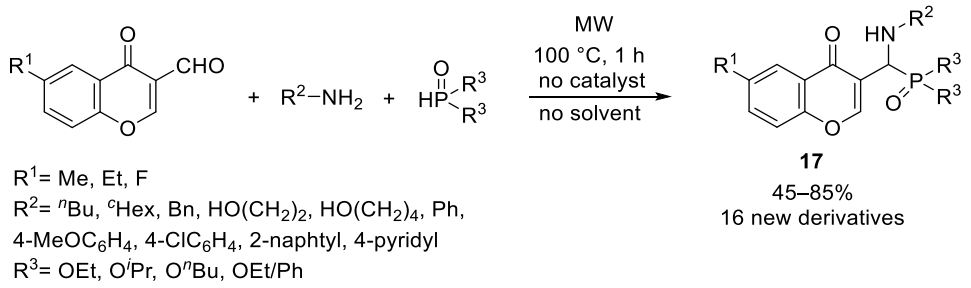
derivatives were also studied. According to the bioactivity studies, several chromenylphosphonates (**15**) showed moderate and promising activities against the tested cell lines, especially the dibenzyl (2-amino-3-cyano-4H-chromen-4-yl)phosphonates, which had their IC_{50} values in the 8–9 micromolar range against NIH/3T3 cell line, and in the 3–7 micromolar range against HL-60 cells. None of the prepared derivatives reduced the growth of Gram-negative bacteria, however, chromenylphosphine oxides containing 3,5-dimethylphenyl groups on the phosphorus atom were active against selected Gram-positive bacteria. Two of the latter derivatives also showed activity in the 10 micromolar range against HL-60 cells.



Scheme 12. PMDTA-catalyzed reaction of salicylaldehydes, malononitrile and dialkyl phosphites or secondary phosphine oxides

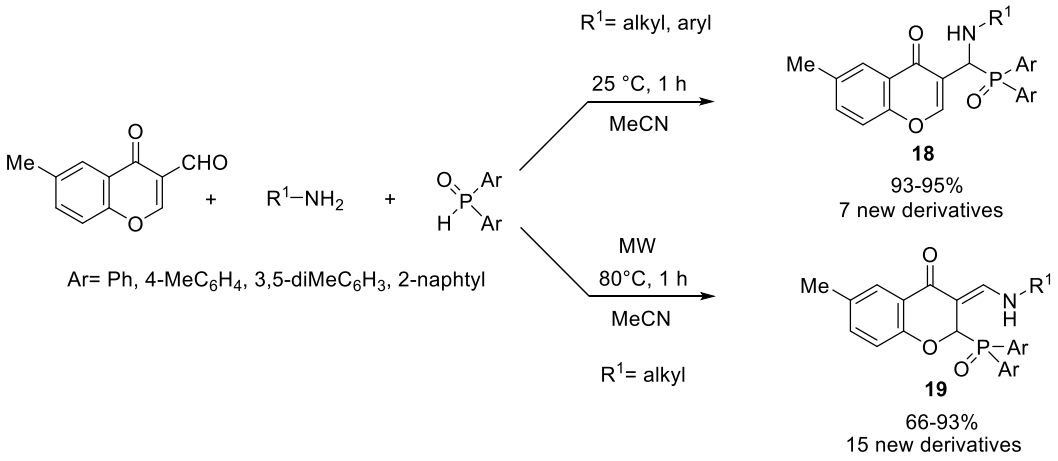
1.7.) Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites or secondary phosphine oxides

A new MW-assisted catalyst- and solvent-free method was developed for the synthesis of dialkyl-((amino)(4-oxo-4*H*-chromen-3-yl)methyl)phosphonates (**17**) by the Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites [15]. This approach has a simple operation and green reaction conditions (no catalyst, no solvent, and short reaction times), and it does not require chromatographic separation. Our method is cheaper, faster and more environmentally friendly compared with other examples in the literature. In all, 16 new dialkyl-((amino)(4-oxo-4*H*-chromen-3-yl)methyl)phosphonates (**17**) were synthesized in good to high yields.



Scheme 13. MW-assisted Kabachnik-Fields reaction of 3-formylchromones, primary amines and dialkyl phosphites

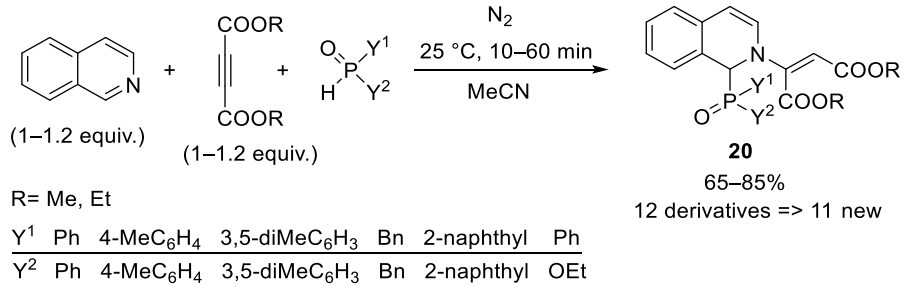
A novel and practical catalyst-free method was elaborated for the synthesis of new chromonyl-substituted α-aminophosphine oxides (**18**) by the Kabachnik-Fields reaction of 6-methyl-3-formylchromone, primary amines and secondary phosphine oxides at ambient temperature with a short reaction time [16]. This is a promising approach to attain these new heterocycles, since it applies mild and easily operational conditions (no special reagents, catalysts or additives, no heating). In addition, we have shown that by carrying out the catalyst-free three-component reaction with aliphatic amines or aminoalcohols at higher temperature (80 °C) under MW irradiation, enamine-type derivatives (**19**) were formed instead of chromonyl-substituted α-aminophosphine oxides (**18**). The methodology was applied for the synthesis of a wide range of phosphinoyl-functionalized 3-(amino)methylene chromanones (**19**), which form a new family of compounds in the literature. In case of aromatic amines, the enamine-type derivatives could be only prepared in the presence of a base, however, this reaction was not complete. Detailed experimental and quantum chemical studies have revealed that the phosphinoyl-functionalized 3-(amino)methylene chromanone derivatives (**19**) could be formed by a ring opening of the chromone ring. This transformation depends on the basicity of the amines used in the synthesis, therefore it can easily take place with aliphatic amines. In case of aromatic amines, an additional base had to be used. Among the compounds synthesized several enamine-type derivatives (**19**) showed modest activity against HL-60 cell line (IC_{50}= 10–16 μM).



Scheme 14. Three-component reaction of 3-formyl-6-methylchromone, primary amines and secondary phosphine oxides

1.8.) Reissert-type reaction of isoquinoline, diakyl acetylenedicarboxylates and secondary phosphine oxides or ethyl phenyl-*H*-phosphinate

An effiecient synthetic method for potentially biological active new 1,2-dihydroisoquiolin-1-ylphosphine oxide derivatives (**20**) was developed by the Reissert-type reaction of isoquinoline, dialkyl acetylenedicarboxylates and secondary phosphine oxides or ethylphenyl-*H*-phosphinate (Scheme 15) [17]. The protocol developed enabled the preparation of the target derivatives (**20**) under mild conditions for a short reaction time. The *in vitro* cytotoxicity on different cell lines and antibacterial effect of the 1,2-dihydroisoquiolin-1-ylphosphine oxides synthesized were also investigated. Based on the IC_{50} values determined, those derivatives which contain large groups (3,5-dimethylphenyl or 2-naphthyl) on the phosphorus atom, showed promising activity against HL-60 cells (IC_{50} values in the 3–5 micromolar range) and against Gram-positive bacteria (IC_{50} values in the 9 micromolar range).

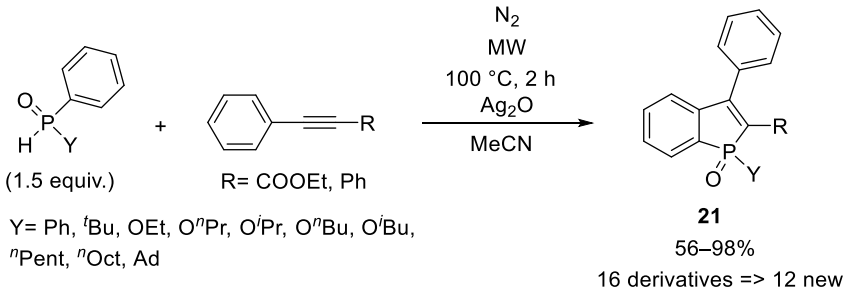


Scheme 15. Reissert-type reaction of isoquinoline, diakyl acetylenedicarboxylates and secondary phosphine oxides or ethyl phenyl-*H*-phosphinate

1.9.) Synthesis of benzo[*b*]phosphole oxides by oxidative cycloaddition

The synthesis of benzo[*b*]phosphole oxides (**21**) by oxidative cycloaddition was also studied (Scheme 16) [18]. The MW-assisted method developed is a practical approach for the

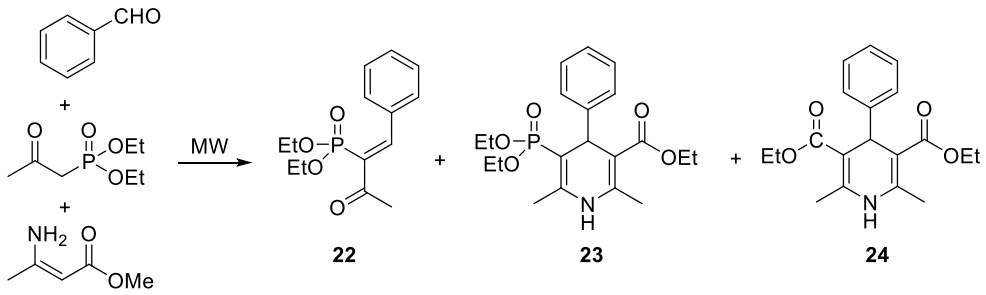
fast and efficient reaction of acetylenes and secondary phosphine oxides or alkyl phenyl-*H*-phosphinates. Altogether, 16 derivatives (**21**) were prepared in good to high yields, among them 12 are new. In order to prove the practical application of the method developed, two scaled-up reactions were performed in a "gram-scale". The target products incorporating reactive phosphinic ester or carboxyl ester groups may offer a route for the further functionalization of these molecules for the realization of better optical properties.



Scheme 16. Synthesis of benzo[*b*]phosphole oxides by oxidative cycloaddition

1.10.) Hantzsch reaction of aldehydes, β-ketophosphonates and methyl-3-aminocrotonate

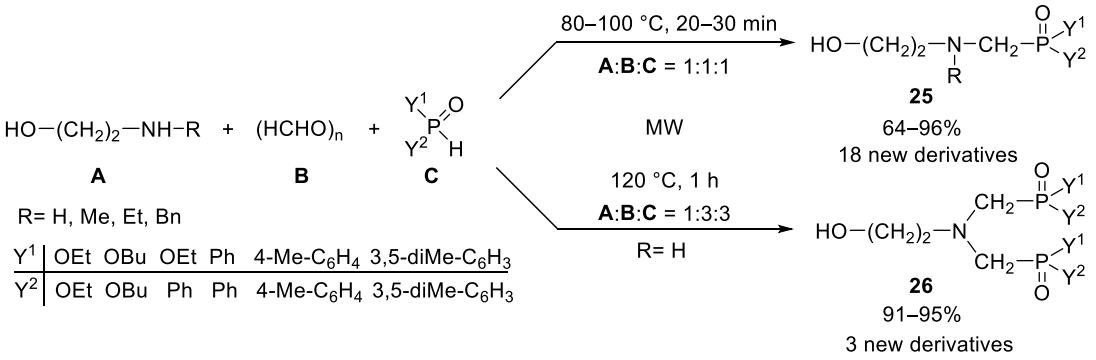
First, the MW-assisted Hantzsch reaction of benzaldehyde, diethyl (2-oxopropyl)phosphonate and methyl-3-aminocrotonate was studied as a model reaction, which was carried out in the absence of any catalyst or by using various acidic or basic catalysts in a solvent or without a solvent. In most cases, the reaction mixtures contained diethyl (*Z*)-(3-oxo-1-phenylbut-1-en-2-yl)phosphonate (**22**) as the Knoevenagel product formed from benzaldehyde and diethyl (2-oxopropyl)phosphonate, the target product (**23**) and the diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**24**). Usually, latter one (**24**) was the major component. For the formation of the target product (**23**), the catalyst- and solvent-free MW-assisted method was the most favourable, however, it was obtained in a low yield (20%). The Hantzsch reaction with dimethyl (2-oxopropyl)phosphonate was similar, and dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**24**) was formed as the main component.



Scheme 17. Hantzsch reaction of aldehydes, β-ketophosphonates and methyl-3-aminocrotonate

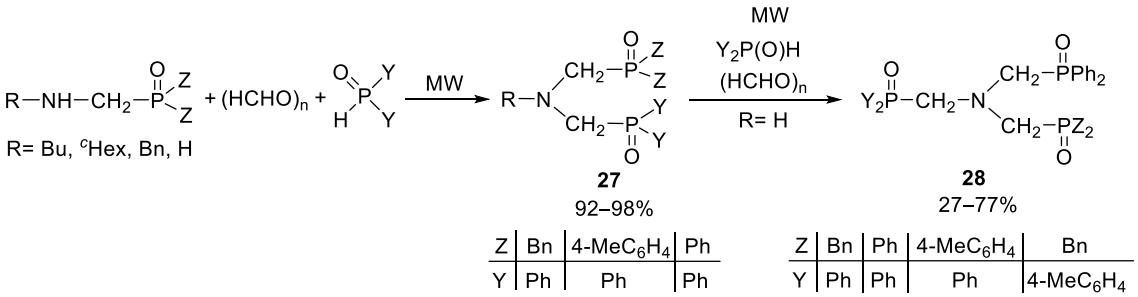
1.11.) Further Kabachnik-Fields reactions

In addition, a novel, catalyst-free and mostly solvent-free MW-assisted method was developed for the preparation of *N*-2-hydroxyethyl-α-aminophosphonates and *N*-2-hydroxyethyl-α-aminophosphine oxides (**25**), as well as *N*,*N*-bis(diarylphosphinoylmethyl)-ethanolamines (**26**) by Kabachnik-Fields condensation of amino alcohols, paraformaldehyde and dialkyl phosphites or diarylphosphine oxides (Scheme 18) [19,20]. Altogether, 21 new derivatives were synthesized in high yields and fully characterized. The crystal structure of two derivatives was also studied by X-ray diffraction analysis.



Scheme 18. Kabachnik-Fields reaction of amino alcohols, paraformaldehyde and dialkyl phosphites or diarylphosphine oxides

Furthermore, an efficient, catalyst-free and MW-assisted method was developed for the synthesis of *N*,*N*-bis(phosphinoylmethyl)amines (**27**) and *N*,*N*,*N*-tris(phosphinoylmethyl)-amines (**28**) bearing different substituents on the phosphorus atoms by the Kabachnik-Fields reaction (Scheme 19) [21,22]. This is a novel approach for the synthesis of the target products. Altogether 13 new derivatives were isolated mostly in high yields and fully characterized.



Scheme 19. MW-assisted Kabachnik-Fields reaction of (aminomethyl)diarylphosphine oxide

The results of the project were also summarized in six further papers [23–28] and five hungarian conference papers [29–33] parts of this research work was also summarized in 3 PhD, 10 MSc and 5 BSc theses.

References

1. Bálint, E.; Tajti, Á.; Tóth, N.; Keglevich, G. Continuous flow alcoholysis of dialkyl *H*-phosphonates with aliphatic alcohols. *Molecules* **2018**, *23*, 1618. [IF: 3.060], **Independent citation:** 12
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32. Zwillinger-Tripolszky, A.; Tóth, E.; Bálint, E. *Klikk és Dominó reakciók tanulmányozása foszfortartalmú reagensekkel*. In: Ádám, A. A.; Ziegenheim, Sz. (szerk.) I. FKF Szimpózium - Fiatal Kémikusok Fóruma. Magyar Kémikusok Egyesülete, Budapest, 2019, pp. 6-11. (ISBN: 978-615-6018-00-7)
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19 scientific papers with ΣIF: 59.223, 6 conference papers with ΣIF: 6.288, 2 peer-reviewed papers without IF, 5 hungarian conference proceedings, sum of their independent citations: 119, and further 1 paper is under preparation.

List of presentations:

1. Tóth, N.; Tajti, Á.; Bálint, E.; Keglevich, G.: Alcoholysis of dialkyl phosphites in a continuous flow microwave reactor. 15th European Workshop in Phosphorus Chemistry, Uppsala, Sweden, 14-16 March, 2018. (poster presentation)
2. Tripolszky, A.; Bálint, E.; Keglevich, G.: Synthesis of α-aminophosphine oxide derivatives. 15th European Workshop in Phosphorus Chemistry, Uppsala, Sweden, 14-16 March, 2018. (poster presentation)
3. Bálint, E.; Tajti, A.; Tripolszky, A.; Tóth, N.; Keglevich, G.: Microwave-assisted synthesis of α-aminophosphonate and related derivatives. 22th International Conference on Phosphorus Chemistry, Budapest, Hungary, 8-13 July, 2018. (oral presentation)
4. Tripolszky, A.; Tóth, E.; Keglevich, G.; Bálint, E.: Synthesis of triazole derivatives with phosphorus side chain. 22th International Conference on Phosphorus Chemistry, Budapest, Hungary, 8-13 July, 2018. (poster presentation)
5. Tóth, N.; Tajti, Á.; Ladányi-Pára, K.; Bálint, E.; Keglevich, G.: Synthesis of phosphonates in a continuous flow manner. 22th International Conference on Phosphorus Chemistry, Budapest, Hungary, 8-13 July, 2018. (poster presentation)
6. Tóth, N.; Hümpfner, E.; Rávai, B.; Tajti, Á; Keglevich, G.; Bálint, E.: Foszfonát oldalláncot tartalmazó N heterociklusok előállítása multikomponensű reakciókkal. XLI. Kémiai Előadói Napok, Szeged, Magyarország, 2018. október 15-17. (oral presentation)
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9. Tóth, N.; Hümpfner, E.; Rávai, B.; Tajti, Á.; Bálint E.: Kabachnik-Fields- és Biginelli-reakciók tanulmányozása mikrohullámú reaktorban. I. FKF Szimpózium, Fiatal Kémikusok Fóruma, Debrecen, 3-5 April, 2019. (poster presentation)
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11. Tajti, Á.; Tóth, N.; Kalocsai, D.; Szatmári, E.; Keglevich, G.; Bálint, E.: Aminofoszfonátok környezetbarát előállítása Kabachnik-Fields-reakcióval. I. FKF Szimpózium, Fiatal Kémikusok Fóruma, Debrecen, 3-5 April, 2019. (oral presentation)

12. Bálint, E.: Környezetbarát kémia, avagy mit keres a mikrohullám a kémiai laboratóriumokban? ITDK nyilvános ülés, Budapest, Szent Margit Gimnázium, 10 May, 2019. (oral presentation)
13. Bálint, E.: Kabachnik-Fields- és Biginelli-reakciók tanulmányozása – Irodalmi összefoglaló, BME, Szerves Kémia és Technológia Tanszék, Budapest, 17 May, 2019. (oral presentation)
14. Bálint, E.: Kabachnik-Fileds- és Biginelli-reakciók tanulmányozása – Kutatási módszertan előadás, BME, Szerves Kémia és Technológia Tanszék, Budapest, 31 May, 2019. (oral presentation)
15. Bálint, E.: Heterociklusos foszforvegyületek előállítása gyűrűzárással. BME, Új Nemzeti Kiválóság Program Zárókonferencia, Budapest, 19 June, 2019. (oral presentation)
16. Bálint, E.; Tóth, N.; Rávai, B.; Tajti, Á.; Iskandarov, J.; Perdih, F.: Multicomponent syntheses of *N*-heterocycles containing phosphonate or phosphine oxide moiety. 18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubljana, Slovenia, 18-21 September, 2019. (oral presentation)
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21. Rávai, B.; Tóth, N.; Tajti, Á; Bálint, E.: *Izoindolinon-foszfonátok és izoindolinon foszfin oxidok szintézisének tanulmányozása.* XLII. Kémiai Előadói Napok, Szeged, 28-30 Oktober, 2019.
22. Rávai, B.; Tóth, N.; Tajti, Á.; Bálint, E.: Synthesis of isoindolinone phosphonates and isoindolinone phosphine oxides, 15th ChemCYS - Chemistry Conference for Young Scientists, Blankenberge, Belgium, 19-21 February, 2020. (poster presentation)
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24. Rávai, B.: Izoindolinon-foszfin-oxidok előállításának tanulmányozása. BME, Új Nemzeti Kiválóság Program Zárókonferencia, 27 May, 2020. (online oral presentation)
25. Tripolszky, A.: Potenciális bioaktivitással rendelkező 1,2,3-triazolil-5-foszfonátok szintézise dominó reakcióval. BME, Új Nemzeti Kiválóság Program Zárókonferencia, 27 May, 2020. (online oral presentation)
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38. Rávai, B.; Popovics-Tóth, N.; Bálint, E.: Foszfonát- vagy foszfin-oxid szerkezeti egységet tartalmazó izoindolinon- és benz[*de*]izokinolinon-származékok előállítása, Tavaszi Szél Konferencia 2022, Pécs, 2022. május 6-8.
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