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FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE OLAH DOCTORAL SCHOOL

***N*-Heterocycles containing phosphonate or phosphine oxide moiety and cyclodextrin-based supramolecular systems: synthesis and formulation**

Summary of PhD thesis

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NATIONAL RESEARCH, DEVELOPMENT
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CycloLab Cyclodextrin Research and Development Ltd.

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1. Introduction

One of the key challenges of modern chemical research is the efficient, sustainable, and industrially relevant synthesis of new, high valuable molecules. In drug discovery, materials science, and molecular biology, there is an increasing demand for well-defined, functional small molecules with specific biological activities that can be prepared using modern and environmentally sustainable technologies.

Heterocyclic compounds play a central role in this perspective, especially nitrogen (*N*)-containing heterocycles, which serve as core structures in many natural products, active pharmaceutical ingredients (APIs), and industrially relevant molecules. The introduction of phosphonate or phosphine oxide functionalities into these frameworks, further increases structural diversity and can improve stability as well as biological activity. At the same time, the development of such compounds is increasingly supported by modern, environmentally friendly and sustainable technologies, such as microwave (MW)-assisted syntheses and continuous flow chemistry.

My doctoral research was carried out at the Budapest University of Technology and Economics (BME) at the Department of Organic Chemistry and Technology in the Innovative Pharmaceutical and Chirotechnological Research Group led by Dr. Erika Bálint, and in an industrial environment at CycloLab Cyclodextrin Research and Development Ltd. under the supervision of Dr. Levente Szócs, and later Dr. István Puskás. Working at the boundary of academic and industrial chemical research has strongly shaped the direction of my research projects as well, leading me to develop solutions that may extend beyond scientific curiosity to address industrial relevance and technological feasibility.

At BME, my work focused on the development of MW-assisted multicomponent synthesis of new *N*-heterocycles, including pharmaceutically relevant isoindolinone and benz[*de*]isoquinolinone phosphonates and phosphine oxides, as well as spirooxindole dihydropyridine bisphosphonates (Figure 1). Our aim was to develop preferably solvent-, catalyst-, or additive-free protocols, systematically optimize the reaction conditions, build up diverse molecular libraries, and investigate reaction mechanisms. Another major direction of my PhD research was the development of a scalable, pilot-scale semicontinuous-flow process for the three-step synthesis of capsaicin and related capsaicinoids (Figure 1). To address their limited aqueous solubility, cyclodextrin (CD)-based supramolecular systems were also investigated and the inclusion complex formation with α - and β -CDs highly improved their water solubility and stability (Figure 1).

At CycloLab, a novel oxidized impurity, namely mono-(6-sulfinic acid)-sugammadex related to sugammadex production was synthesized and fully characterized, contributing to pharmaceutical impurity profiling (Figure 1).

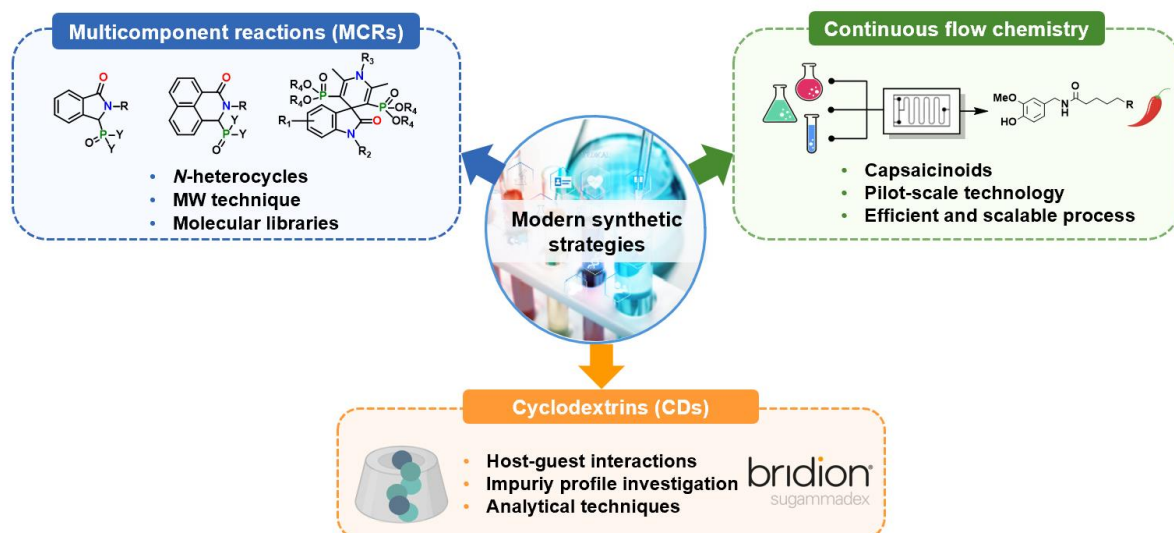


Figure 1. The key objectives of my doctoral research work.

2. Background

Multicomponent reactions (MCRs) have become key tools in modern synthetic chemistry, particularly since the 1990s, when the demand for structurally diverse new chemical entities increased in pharmaceutical research. For example, from the beginning, the Ugi four-component reaction (4-CR)¹ and later the Kabachnik–Fields condensation² enable efficient, atom-economic, one-pot syntheses of complex molecules, including versatile heterocycles together with α -aminophosphonates. In most of the cases, these reactions can be further enhanced by MW irradiation³ and continuous flow technologies⁴, which improve selectivity, shorten reaction times, and support scalability.

N-Heterocycles are fundamental building blocks in medicinal chemistry, as most of the approved small-molecule drugs incorporate at least one *N*-containing ring.⁵ Among them, isoindolinones are particularly valuable structures, present in several approved drugs such as thalidomide, apremilast, and lenalidomide.⁶ Their phosphorus analogues, especially isoindolinone phosphonates, can be prepared in the Kabachnik–Fields reactions followed by cyclization, although many reported methods require solvents, catalysts, or harsh reaction conditions.^{7,8} In contrast, isoindolinone phosphine oxides are rarely described and generally synthesized through multistep procedures.⁹

Benzo[*de*]isoquinolinone derivatives, which are structurally related to 1,8-naphthalimide compounds, have attracted great attention in anticancer research¹⁰ as well as in materials science.¹¹ Compounds such as amonafide and mitonafide have shown notable anticancer activity, although the toxicity has limited their clinical success.¹² Regarding synthetic routes, they mainly rely on the Ugi-type reactions¹³ or cyclization strategies,¹⁴ while phosphorus-containing analogues remain unknown.

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³ Gulati, S.; John, S. E.; Shankaraiah, N. *Beilstein J. Org. Chem.* **2021**, *17* (1), 819–865.

⁴ Carvalho, M. H. R.; de Castro, P. P.; de Oliveira, K. T.; Amarante, G. W. *ChemSusChem* **2025**, *18* (4), e202401840.

⁵ Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. *J. Med. Chem.* **2024**, *67* (14), 11622–11655.

⁶ Jha, M.; Youssef, D.; Sheehy, H.; Jha, A. *Organics* **2025**, *6* (1), 3.

⁷ Reyes-González, M. Á.; Zamudio-Medina, A.; Ramírez-Marroquín, O. A.; Ordonez, M. *Monatshefte Für Chem.-Chem. Mon.* **2014**, *145* (6), 1001–1007.

⁸ Milen, M.; Dancsó, A.; Földesi, T.; Slégel, P.; Volk, B. *Tetrahedron* **2016**, *72* (33), 5091–5099.

⁹ Deniau, E.; Enders, D.; Couture, A.; Grandclaudeon, P. *Tetrahedron Asymmetry* **2005**, *16* (4), 875–881.

¹⁰ Tandon, R.; Luxami, V.; Tandon, N.; Paul, K. *Bioorganic Chem.* **2022**, *121*, 105677.

¹¹ Noirbent, G.; Dumur, F. *Eur. Polym. J.* **2020**, *132*, 109702.

¹² Saez, R.; Craig, J. B.; Kuhn, J. G.; Weiss, G. R.; Koeller, J.; Phillips, J.; Havlin, K.; Harman, G.; Hardy, J.; Melink, T. J. *J. Clin. Oncol.* **1989**, *7* (9), 1351–1358.

¹³ Zhang, J.; Jacobson, A.; Rusche, J. R.; Herlihy, W. *J. Org. Chem.* **1999**, *64* (3), 1074–1076.

¹⁴ Zhang, Y.; Kindelin, P. J.; DeSchepper, D. J.; Zheng, C.; Klumpp, D. A. *Synthesis* **2006**, *2006* (11), 1775–1780.

¹⁵ Chow, L. Q.; Eckhardt, S. G. *J. Clin. Oncol.* **2007**, *25* (7), 884–896.

¹⁶ Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72* (1), 1–42.

¹⁷ Gao, H.; Sun, J.; Yan, C.-G. *J. Org. Chem.* **2014**, *79* (9), 4131–4136.

¹⁸ Szejtli, J. *Akad. Kiadó* **1982**, *25*.

¹⁹ Crini, G.; Aleya, L. *Environ. Sci. Pollut. Res.* **2022**, *29* (1), 167–170.

²⁰ Yang, L. P. H.; Keam, S. J. *Drugs* **2009**, *69* (7), 919–942.

Spirooxindole-dihydropyridines combine two privileged pharmacophores: the oxindole core, found in drugs like sunitinib¹⁵ and the 1,4-dihydropyridine unit present in calcium channel blockers such as amlodipine.¹⁶ Although several MCR-based methods exist in the literature for preparing spirooxindole-dicarboxylates,¹⁷ however, α -aminophosphonate-derived bisphosphonate analogues have not yet been reported.

CDs are cyclic oligosaccharides capable of forming inclusion complexes with hydrophobic molecules, thereby improving solubility and stability.¹⁸ They are widely applied in pharmaceuticals, cosmetics, and food, in which applications their certain derivatives e.g., 2-hydroxypropyl- β -CD (HPBCD) and sulfobutylether- β -CD (SBEB CD) serve as excipients,¹⁹ while sugammadex represents a milestone as a CD-based API.²⁰ CDs are also promising for enhancing the aqueous solubility of poorly soluble compounds, such as capsaicinoids, which bioavailability and stability can be significantly improved through inclusion complexation studies.

3. Experimental methods and equipment

The MW-assisted reactions were carried out in a CEM[®] Discover MW reactor (300 W), equipped with a pressure controller.

In situ FT IR measurements were conducted using a Mettler-Toledo ReactIR 1000 equipment.

For the preparation of different capsaicinoids a Syrris Asia[®] continuous syringe pump, a Syrris Asia[®] heatable reactor and an H-Cube Pro[®] continuous flow hydrogenating reactor developed by ThalesNano Inc. were utilized.

Purifications of compounds were carried out by traditional column chromatography or by flash chromatography using a Combi Flash NextGen 300+ from Teledyne Isco or a Biotage[®] Selekt flash chromatograph with UV/VIS or ELSD detector as visualization and specified eluent systems.

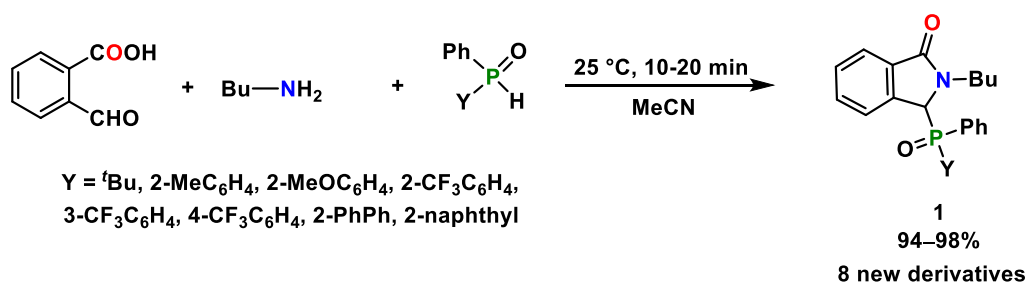
The reactions were followed and monitored by thin-layer chromatography (TLC), gas chromatography (GC), high pressure liquid chromatography (HPLC), and ³¹P NMR spectroscopy. Whenever it was necessary, mass spectrometric detection was also applied, thus, GC-MS or HPLC-MS analyses were performed to support compound identification and reaction monitoring. The products were also characterized by ³¹P, ¹³C, and ¹H NMR spectroscopy, and identified by HRMS data. Whenever required, particularly for detailed structural elucidation and interaction studies, 2D NMR techniques were also applied, including 2D ¹H-¹H and 2D ¹H-¹³C correlation experiments, as well as 2D NOE and ROESY measurements. The stoichiometry of CD complexation with capsaicinoids was investigated by the Job's method of continuous variation.

For the calculations of the experimental design, the preparation of the Pareto chart and 3D surface plot, Statistica[®] software was applied. The quantum chemical calculations were carried out with the Gaussian 16 suite of programs, at the ω B97X-D/def2SVP level of theory.

4. New scientific results

4.1. A new and efficient, catalyst-free synthesis of P-chiral isoindolinone phosphine oxides via Kabachnik–Fields reaction followed by cyclization^[1]

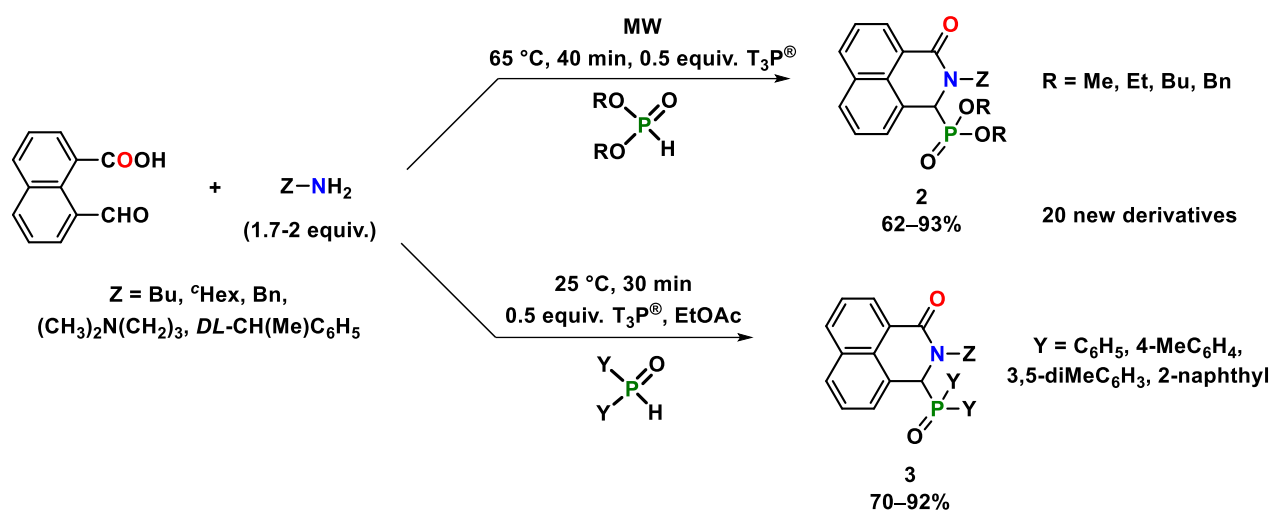
In my first research project, our objective was to design and synthesize P-chiral isoindolinone phosphine oxides (**1**) by incorporating P-chiral secondary phosphine oxides into the Kabachnik–Fields reaction followed by cyclization of 2-formylbenzoic acid and primary amines (Scheme 1). Using this strategy, we successfully prepared eight previously unreported 3-oxoisoindolin-1-ylphosphine oxides (**1**) in excellent yields (94–98%) and with varying degrees of diastereoselectivity. The presence of the stereogenic phosphorus center enabled us to investigate the influence of different P-substituents on reaction efficiency and diastereoselectivity, highlighting that P-chiral units provide an effective means of expanding molecular diversity.



Scheme 1. Three-component reaction of 2-formylbenzoic acid, butylamine and P-chiral phosphine oxides.

4.2. Synthesis, mechanistic insights of phosphoryl- and phosphinoyl-substituted benzo[de]isoquinolinones^[2]

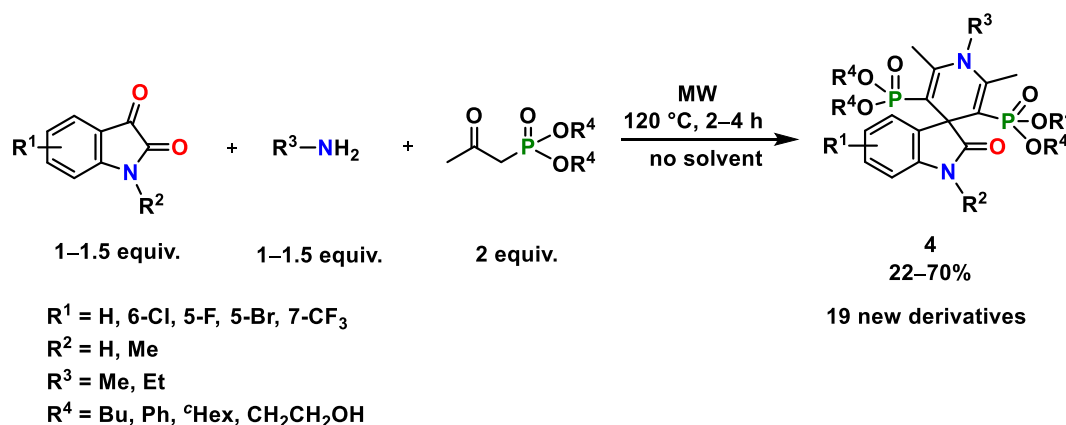
Building on these results, we developed a T₃P[®]-mediated one-pot three-component reaction (3-CR) for the synthesis of phosphoryl- or phosphinoyl-functionalized benzo[de]isoquinolinones (**2,3**) from 1,8-naphthalaldehydic acid, primary amines, and either dialkyl phosphites or secondary phosphine oxides (Scheme 2). The reaction was first optimized through catalyst screening, followed by the application of a statistical experimental design model to identify the key factors affecting reaction efficiency. Mechanistic investigations were performed using *in situ* FT-IR spectroscopy, which provided insight into crucial intermediates operating through two distinct reaction pathways and intermediates. Altogether, 20 new derivatives (**2,3**) were obtained in high to excellent yields.



Scheme 2. Multicomponent synthesis of new phosphoryl- or phosphinoyl-functionalized benzo[de]isoquinolinones.

4.3. A catalyst- and solvent-free MW-assisted multicomponent method for the synthesis of spirooxindole-based dihydropyridine bisphosphonates^[3]

We also investigated the synthesis of spirooxindole dihydropyridine bisphosphonates (**3**) through a MW-assisted, catalyst- and solvent-free MCR applying various isatins, primary amines, and β -ketophosphonates (Scheme 3). This methodology enabled the preparation of 19 previously unreported derivatives (**4**). A plausible reaction mechanism was also proposed and further confirmed by density functional theory (DFT) calculations. Overall, our study offers both practical and theoretical insights into the construction of structurally complex spirocyclic *N*-heterocycles containing multiple phosphorus functionalities.



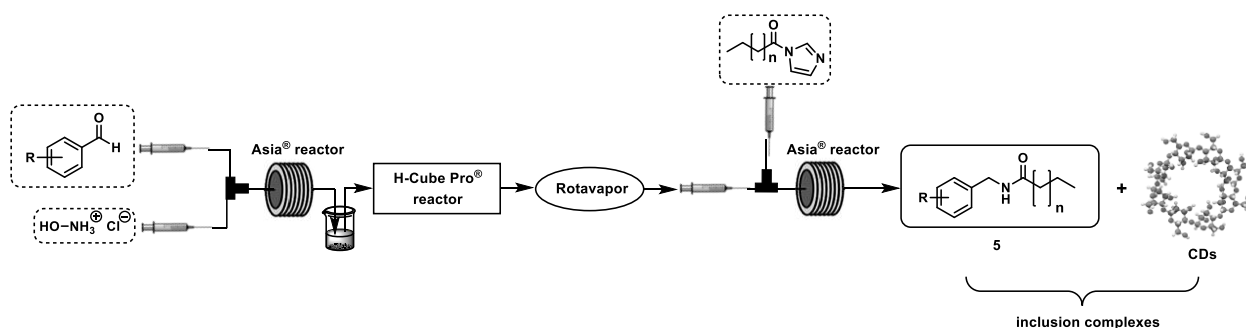
Scheme 3. The MW-assisted, catalyst- and solvent-free MCR of isatins, primary amines, and β -ketophosphonates.

4.4. Pilot-scale semicontinuous flow synthesis of capsaicinoids and their inclusion complexation with cyclodextrins^[4]

Beyond the synthesis of novel *N*-heterocycles, my PhD research also addressed the practical challenges associated with small, lipophilic molecules. In this context, we focused on capsaicinoids,

which are characterized by poor water solubility and the potential to form irritant airborne particles. To overcome these limitations, after their pilot-scale semicontinuous flow synthesis, we studied their CD-based inclusion complexations (Scheme 4).

Initially, a three-step semicontinuous flow process was established, consisting of an oxime formation, a hydrogenation, and an *N*-acylation step, enabling the preparation of capsaicin, dihydrocapsaicin, and nonivamide on a gram-per-hour scale. This approach demonstrated both high productivity and scalability. In the subsequent phase of the work, inclusion complexation studies with α - and β -CD and their derivatives resulted in a significant enhancement of aqueous solubility regarding the capsaicinoids (**5**). The formation and stoichiometry of the complexes were verified by Job's plot analyses, while 2D ROESY NMR spectroscopy provided molecular level evidence of host-guest interactions.



Scheme 4. Schematic illustration of the pilot-scale semicontinuous flow synthesis of different capsaicinoids and their inclusion complexation with CDs.

4.5. Identification of mono-(6-sulfinic acid)-sugammadex as a cyclodextrin-based oxidative impurity in industrial manufacturing^[5]

Finally, we successfully synthesized and characterized an industrially relevant pharmaceutical impurity associated with the γ -CD-based API, called sugammadex. In this work, a previously unreported mono-(6-sulfinic acid)-sugammadex impurity was synthesized through a multistep synthetic strategy (Figure 2). The structures of all intermediates, as well as the final impurity were confirmed by 1D and 2D NMR spectroscopy, HRMS, and tandem MS analyses. Our work provides a more detailed understanding of the impurity profile of sugammadex, helping to ensure safer and more consistent manufacturing.

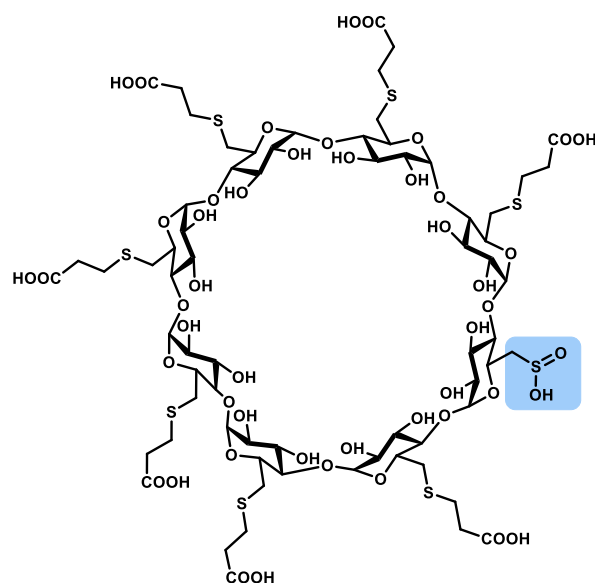


Figure 2. The synthesized target impurity related to sugammadex production.

In conclusion, we synthesized and fully characterized more than 80 novel *N*-heterocyclic compounds containing phosphonate or phosphine oxide moiety by developing broadly applicable and straightforward synthetic methodologies. Our findings have expanded the scope of phosphorus chemistry and MCRs, leading to the establishment of new families of compounds.

Moreover, the comprehensive characterization of a CD-based pharmaceutical impurity, together with detailed inclusion complexation studies, underscores the relevance of synthetic chemistry not only from a scientific perspective, but also in terms of industrial applicability and regulatory considerations.

5. Thesis points

1. I developed an efficient, simple, and catalyst-free multicomponent synthesis for the preparation of new 3-oxoisindolin-1-ylphosphine oxides by the Kabachnik–Fields reaction followed by cyclization of 2-formylbenzoic acid, primary amines and P-chiral secondary phosphine oxides. The condensations proceed efficiently at room temperature, with short reaction times (10-20 min), affording excellent yields (94–98%) and diverse diastereomeric ratios.^[1]
2. I successfully developed a novel, one-pot, three-component method for the synthesis of benzo[*de*]isoquinolinone phosphonates, which enables the efficient, T₃P[®]-mediated preparation of a new family of compounds. The optimization of the model reaction was carried out through investigating different catalysts and an additive together with a statistical experimental design model. Furthermore, I extended the reaction to additional structurally diverse primary amines and dialkyl phosphites. In addition, I provided a mechanistic insight into the reaction, which demonstrated that one plausible reaction pathway is not viable, while the other pathway proceeds via a key intermediate, 3-hydroxy-benzo[*de*]isoquinolinone.^[2]
3. I was the first to establish the T₃P[®]-promoted multicomponent synthesis of benzo[*de*]isoquinolinone phosphine oxides in the reaction of 1,8-naphthalaldehydic acid, primary amines and secondary phosphine oxides at room temperature, in short reaction time (30 min). Using *in situ* FT-IR spectroscopy, I demonstrated the key role of T₃P[®] in the formation of the desired product and identified two different mechanistic pathways by detecting two reaction intermediates. The efficient synthetic protocol afforded 14 new phosphinoyl-substituted benzo[*de*]isoquinolinones.^[2]
4. Using a MW-assisted, catalyst- and solvent-free synthetic method, I prepared a 19-membered new molecular library of spirooxindole dihydropyridine bisphosphonates. Mechanistic studies showed that a key iminophosphonate intermediate was formed and successfully characterized, while DFT calculations also supported the proposed reaction pathway.^[3]
5. I was the first to develop the pilot-scale semiflow synthesis of capsaicin, dihydrocapsaicin and nonivamide using a heatable tube flow reactor and a continuous flow hydrogenation reactor. The process consisted of three consecutive steps, enabling the feasible and scalable semicontinuous flow production of biologically important capsaicinoids.^[4]

6. I demonstrated that inclusion complexation of capsaicin, dihydrocapsaicin and nonivamide with various α - and β -CD derivatives results in a significantly increased water solubility and reduced pungency. Phase solubility studies, Job's plot and 2D ROESY NMR characterizations confirmed that α -CDs form higher stability complexes with linear, flexible nonivamide, while β -CDs encapsulate more effectively branched or unsaturated capsaicin and dihydrocapsaicin.^[4]
7. I successfully prepared and thoroughly characterized a novel mono-(6-sulfinic acid)-sugammadex impurity using multi-step synthetic procedures. I have demonstrated that this compound can potentially form as a significant impurity in the industrial production of sugammadex. I proved that the impurity is formed during perbromination and the subsequent reaction with MPA, where both the PPh_3 and NaOMe/MeOH system can contribute to its formation. Furthermore, I have shown that various inorganic and organic bases facilitate the conversion of the sulfone group to the sulfinic acid function.^[5]

6. Application possibilities

The overall results of my doctoral research have both direct and possible future applications in medicinal chemistry, chemical technology or formulation studies.

First of all, the development of efficient and generally applicable multicomponent synthetic methods of new *N*-heterocyclic compounds containing phosphonate or phosphine oxide moiety enabled the preparation of more than 80 novel compounds, significantly expanding the chemical space of phosphonate- and phosphine oxide-functionalized structures.

Furthermore, the first semicontinuous flow technology for capsaicinoid synthesis demonstrates clear scalability and industrial feasibility in a controllable production of biologically active small molecules.

Cyclodextrin-based inclusion complexation increases the practical utility of poorly soluble compounds by improving their aqueous solubility and stability, which in turn expands their potential applications in pharmaceutical, food, and agricultural formulations. In addition, the synthesis and full analytical characterization of a previously unreported impurity in an API manufacturing contributes directly to pharmaceutical quality control and regulatory compliance.

All in all, I hope that my multidisciplinary PhD research will provide guidance and inspiration for future studies through the development of *N*-heterocycles, additional MCRs and synthetic methods or formulation ideas in the field of supramolecular chemistry.

7. List of publications

7.1. Publications closely related to the dissertation

[1] Popovics-Tóth, N.; **Rávai, B.**; Tajti, Á.; Varga, B.; Bagi, P.; Perdih, F.; Szabó, P. T.; Hackler, L.; Puskás G. L.; Bálint, E. Three-component synthesis, utilization and biological activity of phosphinoyl-functionalized isoindolinones, *Org. Biomol. Chem.* **2021**, *19*, 8754.

DOI: <https://doi.org/10.1039/D1OB01610E> IF: 3.89, **Q1**, IC: 9 (39%)

[2] **Rávai, B.**; Popovics-Tóth, N.; Komka, K.; Csontos, I.; Szokol, B.; Órfi, Z.; Órfi, L.; Bálint, E. Phosphoryl- or phosphinoyl-functionalized benzo[*de*]isoquinolinones: Synthesis, experimental design, mechanism and biological activity, *React. Chem. Eng.* **2024**, *9*, 583.

DOI: <https://doi.org/10.1039/D3RE00489A> IF: 3.10, **Q2**, IC: 0 (100%)

[3] **Rávai, B.**; Németh, Á. S.; Kelemen, Zs.; Bálint, E. Microwave-assisted multicomponent synthesis of spirooxindole dihydropyridine bisphosphonates, *Eur. J. Org. Chem.* **2025**, e202400873.

DOI: <https://doi.org/10.1002/ejoc.202400873> IF: 2.7, **Q2**, IC: 2 (60%)

[4] **Rávai, B.**; Ujj, D. V.; Orosz J. M.; Revenco, E.; Béni, Sz.; Tajti, Á.; Bálint, E. Pilot-scale continuous flow synthesis of capsaicinoids and their formulation with cyclodextrins, *ACS Omega* **2026**, *11*, 4570.

DOI: <https://doi.org/10.1021/acsomega.5c10910> IF: 4.3, **Q1**, IC: 0 (55%)

[5] **Rávai, B.**; Kese, I.; Szakály, P. S.; Herr, D.; Iványi, R.; Bálint, E.; Szócs, L. Mono-(6-sulfinic acid)-Sugammadex: A newly identified cyclodextrin-based oxidative impurity in industrial production, *Carbohydr. Polym.*, **2025**, *362*, 123659.

DOI: <https://doi.org/10.1016/j.carbpol.2025.123659> IF: 12.5, **D1**, IC: 0 (60%) (HAS's highlighted publication in November 2025)

7.2. Other publications broadly related to the dissertation

[6] Tajti, Á.; Tóth, N.; **Rávai, B.**; Csontos, I.; Szabó P.; Bálint, E. Study on the microwave-assisted batch and continuous flow synthesis of *N*-alkyl-isoindolin-1-one-3-phosphonates by a special Kabachnik–Fields condensation, *Molecules* **2020**, *25*, 3307.

DOI: <https://doi.org/10.3390/molecules25143307> IF: 4.411, **Q1**, IC: 15 (30%)

[7] Orosz, J. M.; **Rávai, B.**; Mátravölgyi, B.; Bálint, E. Flow synthesis of capsaicin and capsaicinoid analogues, *ACS Sustainable Chem. Eng.* **2024**, *12*, 7913.

DOI: <https://doi.org/10.1021/acssuschemeng.4c01839> IF: 7.3, **D1**, IC: 5 (10%) (HAS's highlighted publication in June 2024)

[8] Steinsits, D.; **Rávai, B.**; Kelemen, Zs.; Hackler, Jr. L.; Vernyik, V.; Puskás G. L.; Bálint, E. 3,3-Bis(hydroxyaryl)oxindoles and spirooxindoles bearing a xanthene moiety: Synthesis, mechanism, and biological activity, *J. Org. Chem.* **2025**, *90*, 6454.

DOI: <https://doi.org/10.1021/acs.joc.5c00270> IF: 3.6, **Q2**, IC: 2 (30%)

[9] **Rávai, B.**; Orosz J. M.; Péterfi, O.; Galata, D. L.; Bálint, E. Flow chemical laboratory practice for undergraduate students: Synthesis of paracetamol, *J. Flow Chem.* **2023**, *14*, 409.

DOI: <https://doi.org/10.1007/s41981-023-00303-y> IF: 2.0, **Q2**, IC: 2 (50%)

[10] **Rávai, B.**; Orosz, J. M.; Steinsits, D.; Bálint, E. A BME Innovatív Gyógyszeripari és Kirechnológiai Kutatócsoport áramlásos kémia területén végzett kutatásai, *Magyar Kémiai Folyóirat*, **2025**, *131*, 200.

DOI: <https://doi.org/10.24100/MKF.2025.02-04.200> IF: –, IC: 0 (33%)

7.3. Short communication broadly related to the dissertation

[11] **Rávai, B.**; Popovics-Tóth, N.; Tajti, Á.; Bálint, E. Synthesis of isoindolinone phosphonates and their related derivatives by multicomponent reaction, *Phosphorus Sulfur Silicon Relat. Elem.* **2022**, *197*, 599.

DOI: <https://doi.org/10.1080/10426507.2021.2012179> IF: 1.3, **Q4**, IC: 3 (70%)

7.4. Conference proceedings

[12] **Rávai, B.**; Kесе, I.; Ürögi, Zs.; Iványi, R.; Szócs, L.; Bálint, E. Synthetic production of impurities of sugammadex through various substitution and oxidation reactions, *XLVII. Chemistry Lectures*, Conference location, time: Szeged, Hungary, 29.10.2024–31.10.2024, Szeged: Szeged Academic Committee, **2024**, 90–95. (ISBN 978-615-6018-28-1).

[13] Bálint, E.; Popovics-Tóth, N.; Tajti, Á.; **Rávai, B.**; Szabó, K. E.; Perdih, F. Microwave-assisted multicomponent syntheses of heterocyclic phosphonates, *Chem. Proc.* **2021**, *3*, 108.

DOI: <https://doi.org/10.3390/ecsoc-24-08548> IC: 2 (33%)

[14] **Rávai, B.**; Tóth, N.; Tajti, Á.; Bálint, E. P-oldalláncot tartalmazó izoindolin gyűrűs származékok előállítása mikrohullámú reaktorban, *XIII. Szent-Györgyi Albert Konferencia*, Konferencia helye, ideje: Budapest, Magyarország, 2019.04.05–2019.04.06., Szent-Györgyi Albert Szakkollégium, **2019**, 38. (ISBN 978-963-313-338-5)

[15] Bálint, E.; Tajti, Á.; Tóth, N.; **Rávai, B.**; Szabó, K.; Javad, I.; Kovács, B. Foszforgánikus vegyületek szintézise multikomponensű reakciókkal, *I. FKF Szimpózium*, Fial Kémikusok Fóruma. Konferencia helye, ideje: Debrecen, Magyarország, 2019.04.03–2019.04.05., Magyar Kémikusok Egyesülete, **2019**, 93–96. (ISBN 978-615-6018-00-7)

[16] Tóth, N.; Hümpfner E.; **Rávai, B.**; Tajti, Á.; Bálint, E. Kabachnik–Fields- és Biginelli reakciók tanulmányozása mikrohullámú reaktorban, *I. FKF Szimpózium*, Fiala Kémikusok Fóruma. Konferencia helye, ideje: Debrecen, Magyarország, 2019.04.03–2019. 04. 05., Magyar Kémikusok Egyesülete, **2019**, 142–147. (ISBN 978-615-6018-00-7)

[17] Tóth, N.; Hümpfner, E.; **Rávai, B.**; Tajti, Á.; Keglevich, G.; Bálint, E. Foszfónát oldalláncot tartalmazó *N*-heterociklusok előállítása multikomponensű reakciókkal, In: Ádám, A. A.; Kocsis, M.; Ziegenheim, Sz. (szerk.) *XLI. Kémiai Előadói Napok*. Konferencia helye, ideje: Szeged, Magyarország, 2018.10.15–2018.10.17. Szeged: Szegedi Akadémiai Bizottság, **2018**, 105–106. (ISBN 978-963-9970-95-3)

7.5. Book chapters

[18] Árvai, Cs.; **Rávai, B.**; Bálint, E.; Mika, L. T. Evaluating Greenness of Solvents. *Encyclopedia of Green Chemistry*; Török, B. Ed.; Elsevier, **2025**, 3, 1–16.

DOI: <https://doi.org/10.1016/B978-0-443-15742-4.00051-X> IC: 0 (50%)

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7.6. Oral presentations closely related to PhD thesis

[1] **Rávai, B.**; Tóth, N.; Tajti, Á.; Bálint, E. *Izoindolinon-foszfónátok és izoindolinon-foszfín-oxidok szintézisének tanulmányozása*, XLII. Kémiai Előadói Napok, Szeged, **2019**. október 28–30.

[2] **Rávai, B.**; Tóth, N.; Tajti, Á.; Bálint, E. *Izoindolinon-foszfónátok és izoindolinon-foszfín-oxidok szintézisének tanulmányozása*, BME VBK Kari Tudományos Diákköri Konferencia, Budapest, **2019**. november 12. (3rd place)

[3] **Rávai, B.**; Tóth, N.; Tajti, Á.; Bálint, E. *Izoindolinon-foszfónátok és izoindolinon-foszfín-oxidok szintézisének tanulmányozása*, 35. Országos Tudományos Diákköri Konferencia (online), Budapest, **2021**. május 17. (1st place)

[4] **Rávai, B.**; Popovics-Tóth, N.; Bálint, E. *Foszfónát vagy foszfín-oxid-oldalláncot tartalmazó izoindolinon- és benz[de]izokinolinon-származékok előállítása*, BME VBK Kari Tudományos Diákköri Konferencia, Budapest, **2021**. november 16. (1st place)

[5] **Rávai, B.**; Popovics-Tóth, N.; Bálint, E. *Foszfónát vagy foszfín-oxid szerkezeti egységet tartalmazó izoindolinon- és benz[de]izokinolinon-származékok előállítása*, XXV. Tavasz szél konferencia, Pécsi Tudományegyetem, Pécs, **2022**. május 6–8.

- [6] **Rávai, B.;** Popovics-Tóth, N.; Bálint, E. *Foszfónát vagy foszfin-oxid szerkezeti egységet tartalmazó izoindolinon- és benz[de]izokinolinon-származékok előállítása*, 36. Országos Tudományos Diákköri Konferencia, Szeged, **2023**. április 12–15. (3rd place)
- [7] **Rávai, B.;** Popovics-Tóth, N.; Komka, K.; Csontos, I.; Bálint, E. *Új benz[de]izokinolinon gyűrűs vegyületek kísérlettervezési modellen alapuló előállítása; mechanizmus- és biológiai aktivitás vizsgálata*, Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, **2023**. május 31.–június 2.
- [8] **Rávai, B.;** Kese, I.; Ürögi, Zs.; Iványi, R.; Szócs, L.; Bálint, E. *Investigation of the synthesis of Sugammadex impurities through various substitution and oxidation reactions*, XLVII. Kémiai Előadói Napok, Szeged, **2024**. október 29–31.
- [9] **Rávai, B.;** Kese, I.; Iványi, R.; Szócs, L.; Bálint, E. *Mono-(6-szulfínsav)-Sugammadex, mint új ciklodextrin-alapú ipari szennyező szintetikus előállítása*, Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, **2025**. június 23.–június 25.
- [10] **Rávai, B.;** Kese, I.; Szakály, P. S.; Herr, D.; Iványi, R.; Bálint, E.; Puskás, I.; Szócs, L. *Identification and Characterization of Mono-(6-Sulfinic Acid)-Sugammadex: A Novel Oxidative Impurity in Sugammadex Production*, 8th European Cyclodextrin Conference, Budapest, **2025**. szeptember 9–12.
- [11] **Rávai, B.** *From N- and O-heterocycles to Cyclodextrins: Innovative and Green Technologies in Organic Chemistry*, Zechmeister László előadóverseny, MTA Kémiai Biológiai Munkabizottság, Budapest, **2025**. november 21.
- [12] **Rávai, B.** *Nitrogén-heterociklusok és ciklodextrinek a modern szintézisek és alkalmazások területén*, Patonay Tamás-díjas előadás, Heterociklusos és Elemorganikus Kémiai Munkabizottság nyílt ülése, Magyar Kémikusok Egyesülete, Budapest, **2025**. december 12.
- [13] **Rávai, B.** *Nitrogen Heterocycles and Cyclodextrins in Modern Syntheses and Applications*, 3rd Blue Danube PhD Symposium (online), Budapest, **2026**. február 13.

7.7. Poster presentations closely related to PhD thesis

- [1] **Rávai, B.;** Tóth, N.; Tajti, Á.; Bálint, E. *Synthesis of isoindolinone phosphonates and isoindolinone phosphine oxides*, Chemistry Conference for Young Scientists, Blankenberge, Belgium, **2020**. február 19–21.
- [2] **Rávai, B.;** Popovics-Tóth, N.; Tajti, Á.; Bálint, E. *Synthesis of isoindolinone phosphonates and their related derivatives by multicomponent reaction*, 23rd International Conference on Phosphorus Chemistry, Częstochowa, Lengyelország, **2021**. július 5–9.
- [3] **Rávai, B.;** Popovics-Tóth, N.; Bálint, E. *Izoindolinon-foszfónátok és izoindolinon-foszfin-*

oxidok szintézisének tanulmányozása, Vegyészkonferencia, Magyar Kémikusok Egyesülete, Eszterházy Károly Katolikus Egyetem, Eger, **2022.** június 15–17.

[4] **Rávai, B.**; Popovics-Tóth, N.; Bálint, E. *Foszfónát vagy foszfin-oxid szerkezeti egységet tartalmazó benz[de]izokinolinon-származékok előállítása*, Vegyészkonferencia, Magyar Kémikusok Egyesülete, Eszterházy Károly Katolikus Egyetem, Eger, **2022.** június 15–17.

[5] **Rávai, B.**; Ana Chkhetia; Németh Á.; Bálint, E. *Multicomponent reaction of isatins, β -ketophosphonates and primary amines*, 4th George Olah Conference, Budapest University of Technology and Economics, Budapest, **2022.** szeptember 26.

[6] **Rávai, B.**; Németh, Á., S.; Steinsits, D.; Bálint, E. *Izatinalapú spirooxindol-dihidropiridinek és spiroxantének előállítása*, MKE 4. Nemzeti Konferencia, Eger, **2023.** július 10–12.

[7] **Rávai, B.**; Orosz, J. M.; Ujj, D. V.; Szabó, K. E.; Revenco, E., Bálint, E. *Study of the synthesis of capsaicin derivatives, their complexation with cyclodextrins and their biological activity*, 6th European Cyclodextrin Conference, Budapest, **2023.** szeptember 5–8.

[8] **Rávai, B.**; Steinsits, D.; Ujj, D. V.; Szőcs, L.; Bálint, E. *Synthesis of 3,3-disubstituted oxindoles and their conjugation with cyclodextrines*, 9th EuChemS Chemistry Congress, Dublin, Írország, **2024.** július 7–11.

[9] **Rávai, B.**; Kese, I.; Szakály, P. S.; Herr, D.; Iványi, R.; Bálint, E., Puskás, I.; Szőcs, L. *A novel cyclodextrin-based oxidative impurity in industrial manufacturing and further investigations in oxidative transformations*, 30th European Conference on Heterocycles in Chemistry, Budapest, **2025.** augusztus 24–28.

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