SigutLabs
synthesizing your success

We are a chemistry contract research laboratory

located in Prague, Czech Republic

The Mission of the SigutLabs

Welcome to our SigutLabs brochure. Our laboratory is based on a synergy between our expertise in the chemical business and organic synthesis. We have come a long way as a company since 2018, when our lab was founded with just one chemist. In the past 7 years, we've grown with innovative services like ADC linkers and a dedicated scale-up lab. We've also built a strong presence supporting clients across the globe, including those in Silicon Valley. We want to introduce you to our company and team, as well as our cutting-edge technology and some of our most exciting projects, in this brochure.

We are attempting to build on the legacy of superb Czech chemistry epitomized by Prof. Antonín Holý and his molecule tenofovir in order to put the Czech Republic on the map of global chemistry. I believe you will be intrigued by our work. We are excited to cooperate with you.

Šigut

Kryštof Šigut
Founder and CEO SigutLabs


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Welcome to the SigutLabs

Custom synthesis

Our extensive medicinal and organic chemistry understanding can be helpful to many clients. In that way, we can frequently develop new, easier-to-use synthetic pathways that your lab can use in the future.

We offer expertise in synthetic and medicinal chemistry through collaborative efforts on a wide range of targets:

- ☑ ADC linkers
- ☑ Nucleosides and their phosphates
- ☑ Biologically active compounds
- ☑ Special reagents with unique properties
- ☑ Small libraries of compounds
- ☑ Other sensitive and reactive tool compounds and probes

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We offer custom synthesis of previously reported molecules using described synthetic procedures.

How does the SigutLabs handle custom synthesis projects?

When one of our clients contacts us with a specific request for a custom synthesis, we make every effort to respond as soon as possible, usually within 24 hours. We are trying to provide as much information as we can during this initial communication. But we often need more time to look through the literature and chemical databases carefully in order to make feasibility studies. From there, we can give our clients our calculations and offer the desired amount of products they want along with an estimated lead time.

Once the client accepts our offer, one of our chemists takes on and manages the custom synthesis project. If any problems arise along the way, our entire team works together to find solutions. Either by our brains or by our hands in the lab.

When the synthesis is completed successfully, the product is refined to the required purity. Finally, when all of the analytical data confirms the structure and purity of the product, it is shipped to our client. If necessary, final products are lyophilised before the shipment. Furthermore, to assure the optimal shipment conditions for unstable chemicals, we can ship on dry ice to most destinations globally via DHL. Clients normally receive their product in 24 hours in Europe and 48 hours in the rest of the world, based on our experience.

Contract research

At SigutLabs, we focus on contract research in the fields of organic, bioorganic and medicinal chemistry. Our typical client is a small start-up company with an exciting idea about chemical compounds with unique biological activity but no synthetic lab or personnel to make these molecules. For other clients, we can optimize a critical synthetic step that is preventing them from reaching an industrial scale. Alternatively, we can offer our services to large pharmaceutical companies in need of advanced intermediates for their libraries.

SigutLabs offers the following services:

- ☑ Custom synthesis
- ☑ Scale-up
- ☑ Reaction optimisation
- ☑ Analysis of impurities
- ☑ Chemistry consulting

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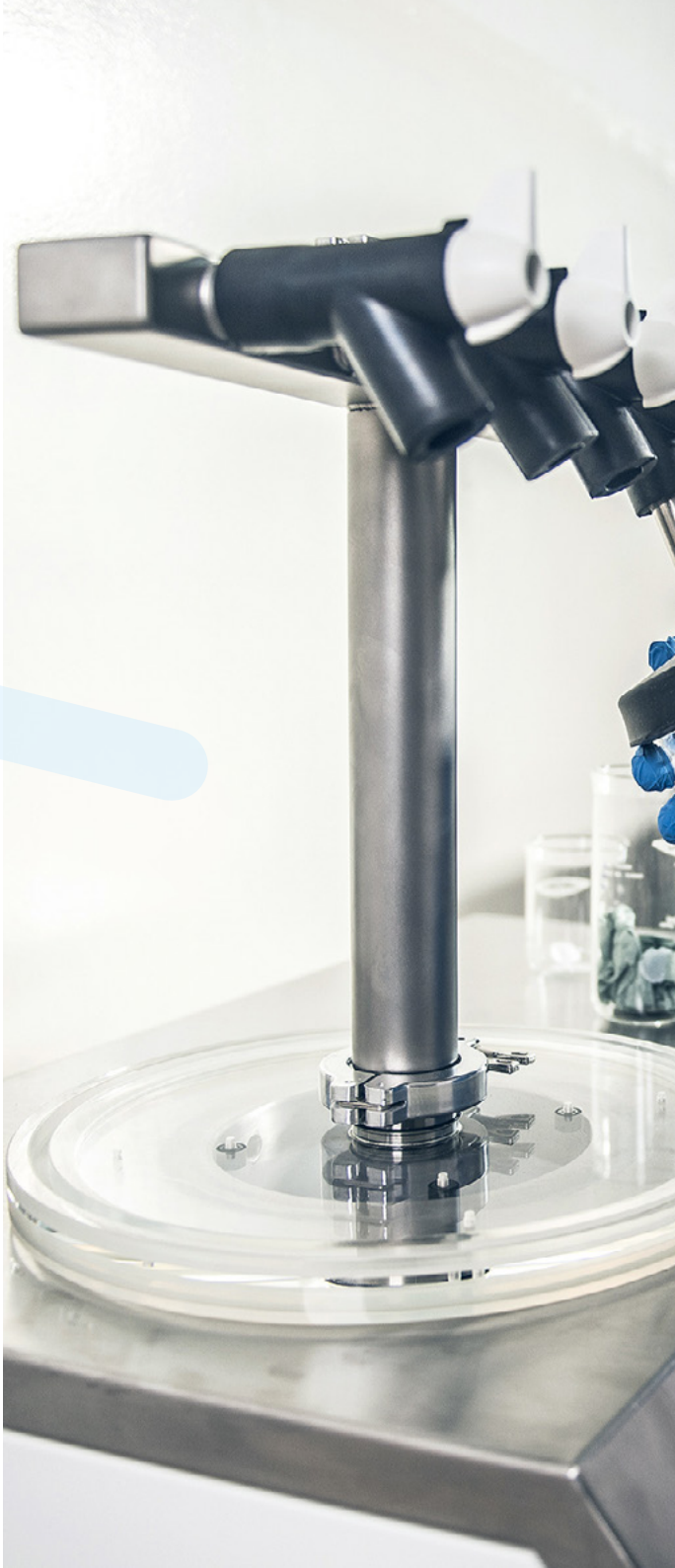

We offer undescribed compounds through developing novel synthetic routes.

Scale-up

We provide custom quantities ranging from 1 mg to 10 kg of the final product. It is not a simple task to scale-up the synthesis of small molecules from the mg scale to hundreds of g or kg. You cannot simply use a larger reaction flask and expect the reaction to behave similarly. Because processes that work well on a small scale in the lab simply do not work on a large scale without significant modifications.

SigutLabs is ready to assist you in scaling up your process or synthesizing your desired products on a large scale.

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From small quantities to larger deliveries.

Our best molecules

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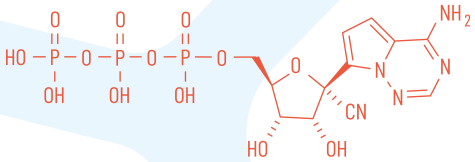
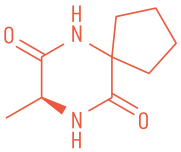


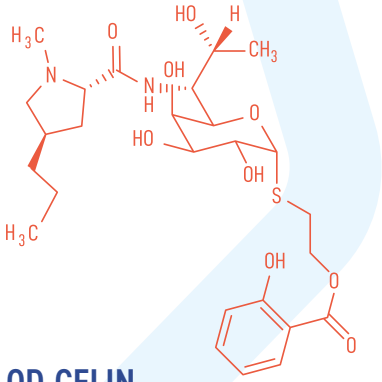
Remdesivir triphosphate (GS-443902)

GS-443902 is the active triphosphate metabolite of Remdesivir with activity against zoonotic feline infectious peritonitis virus (FIPV) and severe acute respiratory syndrome (SARS) virus from the Coronaviridae family.



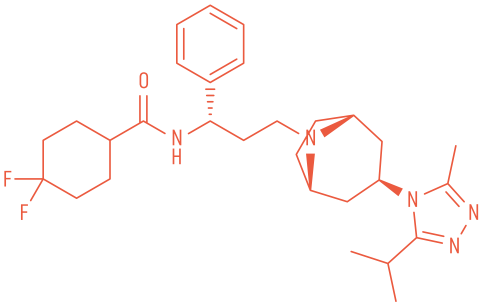
Alaptide

Alaptide stimulates human diploid cells (LEP-19) without causing transformational changes in their morphology. This effect can be used in various areas of regenerative medicine, including burn treatment, skin treatment, and so on.



OD-CELIN

OD-CELIN is a Lincomycin derivative with distinct antibacterial properties against a variety of strains (such as MRSA, Clostridium difficile, Streptococcus pneumoniae etc.)



Maraviroc

Maraviroc is an antagonist of the C-C motif chemokine receptor CCR5, which is involved in the process of HIV cell penetration.

State-of-the-art instruments

LC-MS (Shimadzu LC-MS-2020)

Our company owns and routinely employs a Shimadzu LC-MS system to quickly and effectively analyse reaction mixtures and final products. The instrument has two modes of operation: normal (silica gel, organic solvents) and inverted (C18, water-based mixtures of solvents).

2.5 L stainless steel autoclave

Our stainless steel autoclave is very efficient for performing reactions under a high-pressure.

Lyophilizer (Gregory instruments, model L4-110)

At temperatures as low as -110 °C, this instrument allows for the efficient and safe freeze-drying of sensitive compounds (such as nucleosides). This significantly increases shelf life while also making transportation easier.

Automatic flash chromatography systems (ECOM)

Currently, our company owns four fully automatic flash chromatography systems for purifying reaction mixtures. These systems can purify mg to 20 g of a product and can operate in normal or inverted mode.

ReactoMate ATOM System (Asynt) 20 L glass reactor

A jacketed glass reactor vessel for a large scale reactions.

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Highly experienced team

Our chemists hold PhDs in chemistry from prestigious universities. Years of experience in organic and medicinal chemistry at top international scientific institutions back up their degrees. We provide contract-based projects as well as full-time equivalent chemists.

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Krystof Sigut (CEO & Founder)

Krystof studied organic chemistry at the University of Chemistry and Technology, Prague and gained international experience from the University of Glasgow (United Kingdom).

Dr. Petr Slavik (Head of Research)

Petr studied organic and supramolecular chemistry at the University of Chemistry and Technology, Prague. He did a postdoctoral fellowship at the University of York in the United Kingdom and gained additional international experience at the Tokyo University of Science and Technology in Japan.

Dr. Alessandro Panattoni (Head of Chemistry)

Alessandro studied biochemistry at the Charles University and got international experience from Dublin City University (Ireland) and the University of Oxford (United Kingdom).

Dr. Michal Marz (Senior Research Scientist)

Michal received his Ph.D. from the University of Chemistry and Technology, Prague where he worked on photochemical transformations mediated by flavins.

Dr. Michal Maryska (Senior Research Scientist)

Michal received his Ph.D from the University of Chemistry and Technology, Prague. He was there researching various psychedelic organic compounds. His fellowship at the University of Troms gained him vauable additional international experience (Norway).

Dr. Eva Zahorska (Senior Research Scientist)

Eva received her Ph.D. doctorate at the Helmholtz Institute for Pharmaceutical Research Saarland (Germany). Her research focused on the development of anti-virulence glycomimetic drugs against Pseudomonas aeruginosa.

Case studies

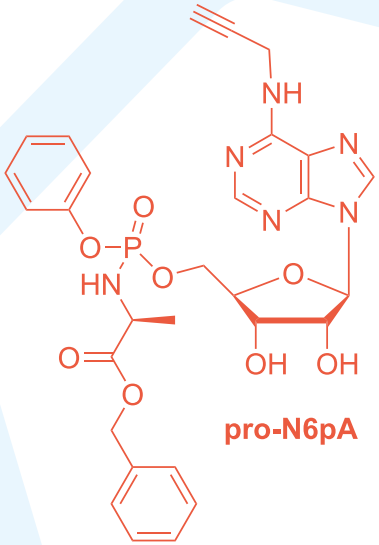
Simplifying AMPylation research: Making pro-N6pA commercially available

AMPylation, a critical protein post-modification process, is gaining significant research interest. Yet, a **major roadblock existed** – the lack of a readily available probe molecule for studying this process. This case study explores how SigutLabs tackled this challenge by making N6-propargyl adenosine phosphoramidate (pro-N6pA) commercially accessible, paving the way for **more efficient AMPylation research.**

Background information

Researchers from the Technical University of Munich and Max Planck Institute of Psychiatry, Munich, Germany recently reported (Nat Commun 11, 517 (2020)) novel N6-propargyl adenosine phosphoramidate (pro-N6pA). This innovative compound offers a simplified approach to identifying proteins undergoing AMPylation, a crucial protein post-translational modification (PTM) involved in the modulation of neurodevelopment and neurodegeneration (Cell Chemical Biology, 27(7), 773-779).

Pro-N6pA's effectiveness lies in its ability to **enter cells readily** and undergo metabolic activation. Once inside, it transforms into N6pATP, a molecule accepted by AMP-transferases, the enzymes responsible for the AMPylation of proteins.



pro-N6pA

Identifying the issue

SigutLabs was contacted by Dr. Pavel Kielkowski, one of the inventors of the molecule, to inquire about our ability to prepare it on a **larger scale**. At their lab at the TU Munich Munich and later LMU Munich, pro-N6pA was typically prepared on a **milligram (mg) scale** solely for their internal research. This meant that any researcher needing pro-N6pA for their application had to synthesize it themselves.

While the synthesis is well-described with several preparation options available, it remains **time-consuming** and requires a skilled synthetic chemist along with appropriate laboratory equipment for handling sensitive compounds.

Additionally, many scientists from various academic institutions worldwide were contacting Dr. Kielkowski to request pro-N6pA for their studies.

Methodology insight

Equipped with the necessary skills and advanced equipment, SigutLabs' team of experienced chemists tackled the challenge of large-scale pro-N6pA production. Here's how we achieved it:

- ✓ Pathway evaluation: We scrutinized existing and **novel synthetic** pathways for pro-N6pA.
- ✓ Optimization and scale-up: The most promising route was selected and optimized, enabling **multigram** quantities within just two weeks.
- ✓ Exceptional purity: The synthesized pro-N6pA exceeded **99% purity**, verified through advanced analytical techniques including 1H-NMR, 31P-NMR, and LC-MS.

Positive outcome

SigutLabs' collaboration with the Kielkowski Research Group has resulted in the successful large-scale production of pro-N6pA. This accomplishment offers significant benefits to the scientific community:

- ✓ Increased availability: Researchers can now access pro-N6pA readily, eliminating the need for in-house synthesis and **saving valuable time and resources.**
- ✓ Simplified research: Ready-made pro-N6pA facilitates a **quicker start** to AMPylation research projects.
- ✓ Consistent quality: SigutLabs' expertise ensures **consistent quality** and purity of pro-N6pA, leading to reliable research data.

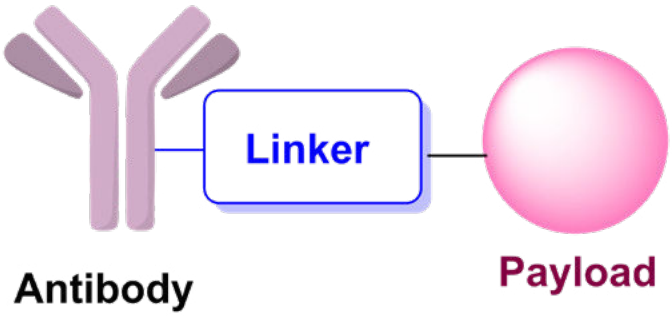
> ***By making pro-N6pA commercially available, we significantly empowered the research community with a key tool for AMPylation studies.***

Unlocking antibody-drug conjugate development through novel linker design

We put innovative chemistry to work for a California startup, helping them streamline their antibody-drug conjugate (ADC) development process. This involved creating **unique linker molecules** custom-designed for their specific needs. By doing this, we **accelerated** their identification of promising lead compounds, significantly impacting their development timeline.

Identifying the issue

Finding the right linker molecule for a new ADC can be challenging. Testing different options to identify suitable linker molecules is time-consuming and expensive. Moreover, many existing linkers may be covered by intellectual property restrictions, **hindering progress**.



Methodology insight

Here is how SigutLabs put its hands to work:

1. Design and synthesis of novel linkers: We began by designing and synthesizing linker molecules specifically for the client's ADC. These linkers were unique and not covered by existing patents, providing the client with greater freedom in their development process.

2. Initial screening: Many linkers we produced were conjugated to the antibody and the activity and toxicity of the resulting ADCs were screened. This initial testing phase allowed us to quickly evaluate linker performance before proceeding to more complex stages.

3. Medicinal chemistry optimization: Based on the results of the first screening, we employed medicinal chemistry techniques to refine the linker structure. We considered biological activity and toxicity data to optimize the linker for both efficacy and safety. Screening and optimization processes were iterated until the best candidates were selected.

4. Lead compound and backup development: We synthesized a sufficient quantity of the novel linker molecules following optimization. This enabled the client to develop their lead ADC candidate efficiently and backup leads for further testing.

5. Technology transfer and verification: Once the optimal linker was identified, we transferred the manufacturing knowledge and procedures to a Contract Development and Manufacturing Organization (CDMO) for large-scale cGMP production. We closely monitored and followed CDMO throughout the process to ensure a quick successful outcome.

6. Quality control: Finally, we rigorously analyzed all compounds produced by the CDMO to verify their quality and purity, ensuring the client received compounds suitable for further development.

Positive outcome

Thanks to our innovative approach, the client's ADC development journey got a significant **boost**. Designing novel linkers specifically tailored to their needs not only saved valuable time but also provided greater flexibility compared to using existing, potentially patented, linker technologies. This case study exemplifies the power of our chemistry expertise in facilitating the **efficient and successful** development of ADCs.

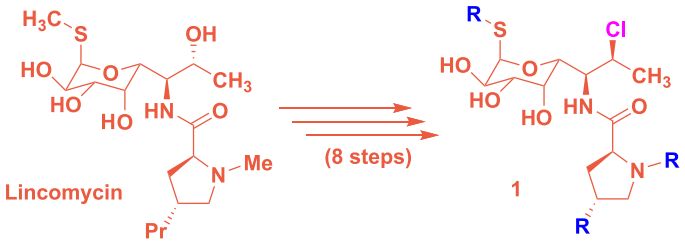
> ***The client's best ADC candidate reached clinical phase 1, with the project still going...***

Overcoming challenges of lincomycin derivative scale-up

The process of scaling up is always very **challenging**. While sometimes products can be easily purified through methods like extraction or recrystallization, in certain cases, intermediates present a unique **set of obstacles**. Such was the scenario in this case where most of the intermediates were rich oily mixtures for which all the attempts of **recrystallization failed**.

Identifying the issue

SigutLabs undertook the scale-up synthesis of a highly active clindamycin derivative for the Institute of Microbiology of the Czech Academy of Science (Figure 1).



The given synthetic procedure was only designed for a **small scale** (100 mg) and contained several **hidden issues**. An illustrative example was the selective oxidation of -SMe moiety to sulfoxide with m-chloroperoxybenzoic acid (mCPBA). According to the given procedure, only 1 eq. of mCPBA was used even though the oxidation of amine nitrogen in the proline part of the lincomycin was also possible. This expected oxidation might significantly **decrease the overall yield** of the whole synthesis during scale-up.

Methodology insight

To address this challenge, we devised an alternative approach consisting of **mild overoxidation** to sulfoxide-N-oxide followed by the selective reduction of N-oxide with sulfoxide moiety preservation. This action reduced the **significant mass losses**. Analyzing the intermediates posed another challenge, as the given procedure only utilized TLC for analysis, leaving a lack of information regarding the mixture composition. Moreover, HPLC and a similar method based on light absorption could not be used due to the very low absorption of the intermediates. However, we successfully overcame this challenge by the use of **LC/MS** as a convenient method for characterizing the crude reaction mixtures (Figure 2).

The last step of the synthesis, the selective chlorination of the secondary hydroxyl group, proved to be even more challenging. The lincomycin derivative molecule contains four secondary hydroxyl moieties which can be subsequently replaced by chlorine atoms. The frequently used chlorination agents ($SOCl_2$, $POCl_3$, PPh_3 + NCS, PPh_3 + CCl_4,...) **lead ultimately to overchlorination** or undesired elimination of HCl from the molecule. Finally, we identified a mixture of DMF and $(COCl)_2$ to serve our purpose as a very mild chlorination reagent.

Positive outcome

Using these reaction conditions, only traces of overchlorination were observed and ubiquitous elimination was negligible. The final purification process, conducted via reverse column chromatography on multigram scales, yielded the target product with **purity exceeding 90 %** (Figure 3).

> ***In summary, through our optimized procedure, we successfully prepared more than 30 g of the desired lincomycin derivatives with excellent purity.***

Our partners and customers

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We collaborate with and supply custom chemicals to academic research laboratories as well as pharmaceutical companies all over the world.

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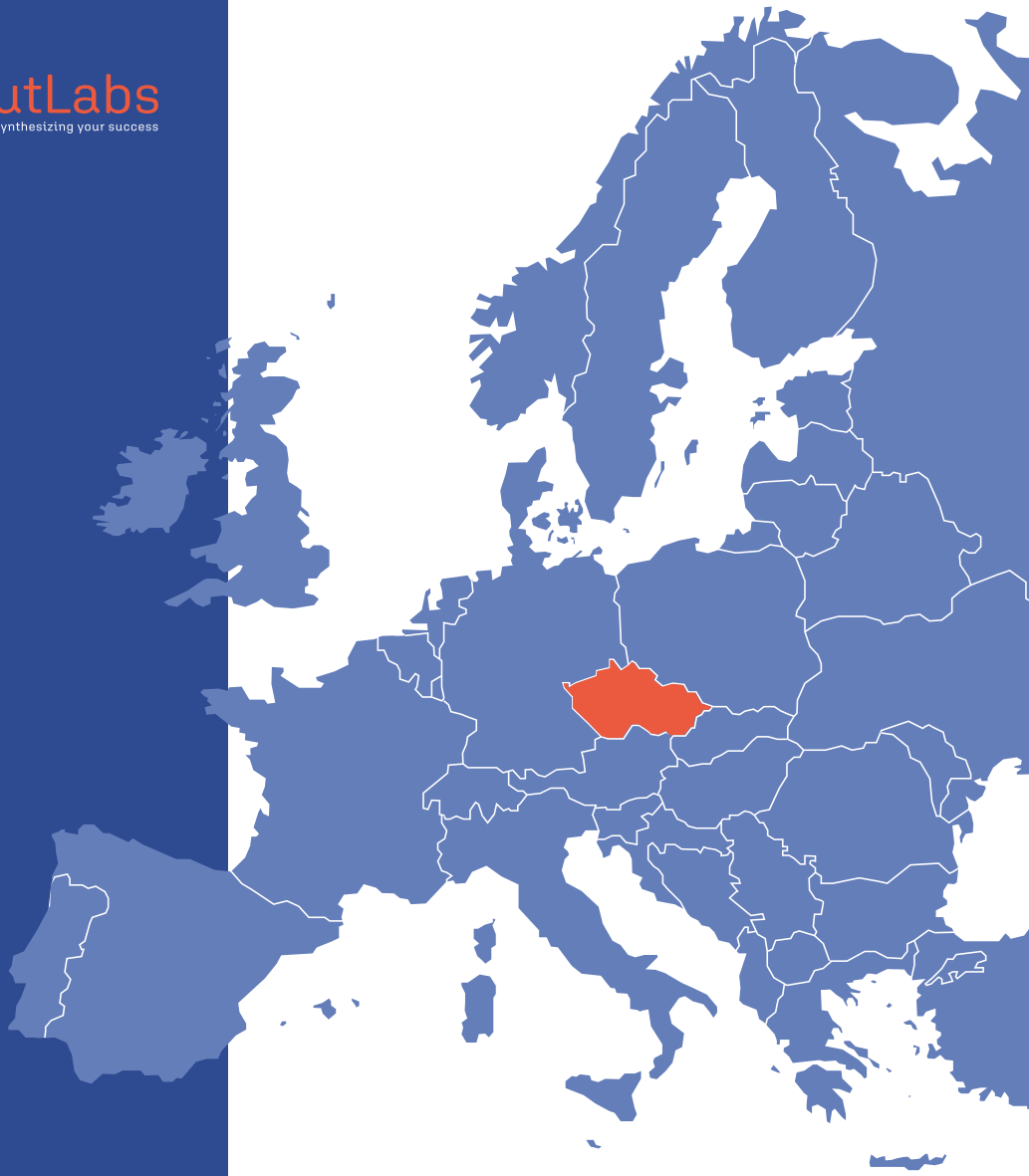

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