SANTIAGO
CUSTOM CHEMICALS

We are a chemistry contract research laboratory

located in Prague, Czech Republic

The Mission of the Santiago Lab

Welcome to our Santiago Lab 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 year 2022, we're opening a brand-new lab dedicated to large-scale projects. 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 collaborate with you.

Šigut

Kryštof Šigut
Founder and CEO Santiago Lab

Welcome to the Santiago Lab

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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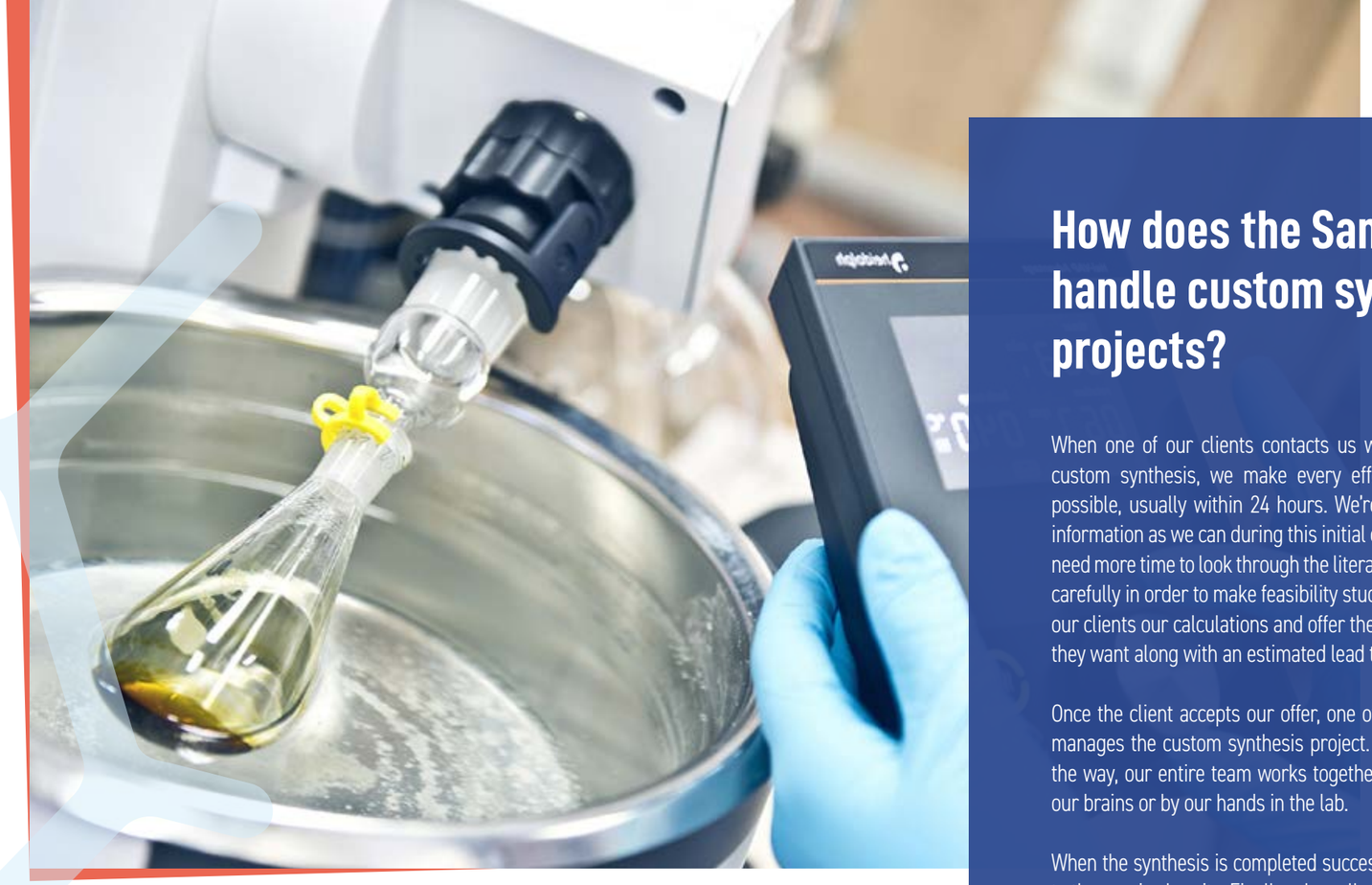
for more info

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



How does the Santiago Lab 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're 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 Santiago Lab, 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.

Santiago Lab 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.

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

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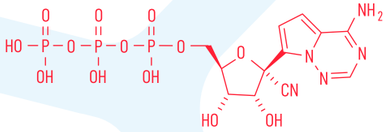
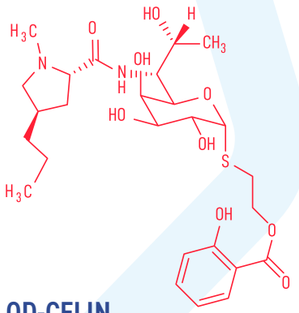
From small quantities to larger deliveries.

Our best molecules



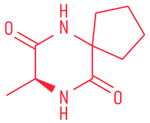
Remdesivir triphosphate (GS-443902)

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.



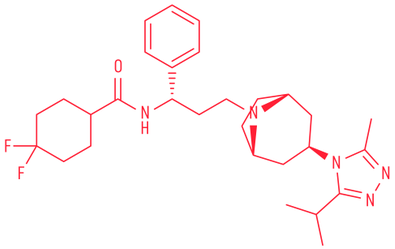
OD-CELIN

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



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.



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)

The 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, the company owns four fully automatic flash chromatography systems for purifying reaction mixtures. These systems can purify mg to 20 g of 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.

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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Kryštof Šigut /CEO and founder/

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

Petr Slavík /Head of Chemistry/

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.

Alessandro Panattoni /scientist/

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

Michal März /scientist/

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

Michal Maryška /scientist/

Michal received his Ph.D. from the University of Chemistry and Technology, Prague. In his research he focused on psychoactive substances and medicinal chemistry. Also, he gained international experience at the University of Tromsø (Norway) and Hanoi University of Science (Vietnam).

Case studies

ANTIVIRAL KIT - AVIROMIX

When a thousands of people worldwide suffered from the lethal coronavirus (COVID-19) in 2020, we came up with an ambitious project to contribute to the global pandemic solution.

Everything began with the question, **"How can we help as a small chemical company?"** First, we considered distributing anti-bacterial solutions, but this plan was thwarted by Good Manufacturing Practice (GMP) for licensed companies only. As a result, we focused our efforts on the area in which we excel, organic synthesis.

When the pandemic started, the search for an effective vaccine began at the same time. Scientists from all over the world have begun to fight a new type of coronavirus. To begin, known potential drugs were repurposed and tested. **Remdesivir, Favipiravir, Chloroquine, Hydroxychloroquine, Azithromycin,** and others were the most promising, with preliminary activity against COVID-19.

We realized it was nearly impossible to find a distributor who provides all of the most promising COVID-19 drug candidates. Furthermore, shipping times ranged from 1 to 4 weeks, which was unacceptable in the midst of a pandemic in which hundreds of people were dying every day.

Our goal was to quickly distribute antiviral sets comprised of the five most potent and promising repurposed drugs. These sets were created to support institutes dealing with the synthesis of new promising drug candidates, virology labs, and microbiology labs.

This set had the following significant advantages:

1. prompt delivery (within 48 h in the EU)
2. all potential drugs at the same time, ready for use
3. detailed supporting documentation for each drug in the set
4. DNA-free
5. easily accessible on our new website

Figure 1: Aviromix

OPTIMIZATION AND SCALE-UP OF THE ANTIBIOTIC SYNTHESIS

The Santiago Lab performed the scale-up synthesis of highly active Clindamycin derivative for the Institute of Microbiology of the Czech Acedemy of Science (Figure 1).

Scaling-up is always tricky. A product can sometimes be easily purified through simple extraction or recrystallization. Unfortunately, during this project, the majority of the intermediates were rich oily mixtures for which all recrystallization attempts failed.

Furthermore, the given synthetic procedure was only intended for use on a small scale (100 mg) and had several flaws. Some issues arise directly from the scale-up point of view, such as the **need to use much larger volumes of solvents and reagents during the work-up** to completely remove impurities. Other issues were related to unwanted by-products that significantly complicated subsequent steps of the synthesis. Problems that did not exist on a small scale but became serious when reactions were performed on a multigram scale. However, **we were able to modify key steps of the synthesis**, which led to better results and allowed us to prepare the final compound on the desired large scale (20 g).

We were also struggling with the analytical aspect of this project, because the majority of the intermediates were only analyzed by TLC according to the procedure. As a result, we didn't know anything about the composition of the mixture. Furthermore, due to the very low absorption of the intermediates, HPLC and a similar method based on light absorption could not be used. However, we successfully overcame this obstacle by employing LC/MS as a convenient method for characterizing crude reaction mixtures.

In the end, we were able to prepare more than 30 g of desired Clindamycin derivatives in excellent purity using our optimized procedure and delivered it to our client. We recently returned to this project, and in collaboration with the Institute of Microbiology of the Czech Acedemy of Science we are developing even more active, novel antibiotics.

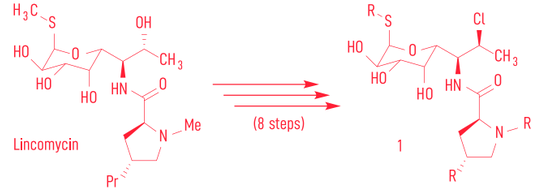


Figure 1: Total synthesis of Clindamycin derivative 1 starting from Lincomycin

Articles

TRIPHOSPHATES OF NUCLEOSIDE-BASED ANTIVIRAL DRUGS

The largest class of antiviral agents based on small molecules is nucleoside analogues. They are now the foundation of chemotherapy for several viral chronic infections, including HIV, hepatitis B and C viruses, and herpes viruses. These medications are made up of chemically modified synthetic nucleosides that mimic their natural counterparts and target viral polymerase, a key enzyme in the virus replication cycle.

The active form of nucleoside analogues is **5'-O-triphosphate (TP)**. Nucleoside triphosphates are used by polymerases to extend nucleic acids during replication, the biosynthesis of DNA, or transcription, the process by which RNA is synthesized. Viral polymerases cannot distinguish between natural nucleotides and the active triphosphate form of synthetic nucleotides. While synthesizing DNA/RNA, these enzymes incorporate the nucleotide analogue within the sequence of the growing strand rather than the natural nucleotide.

Nucleoside triphosphates- mechanism of action

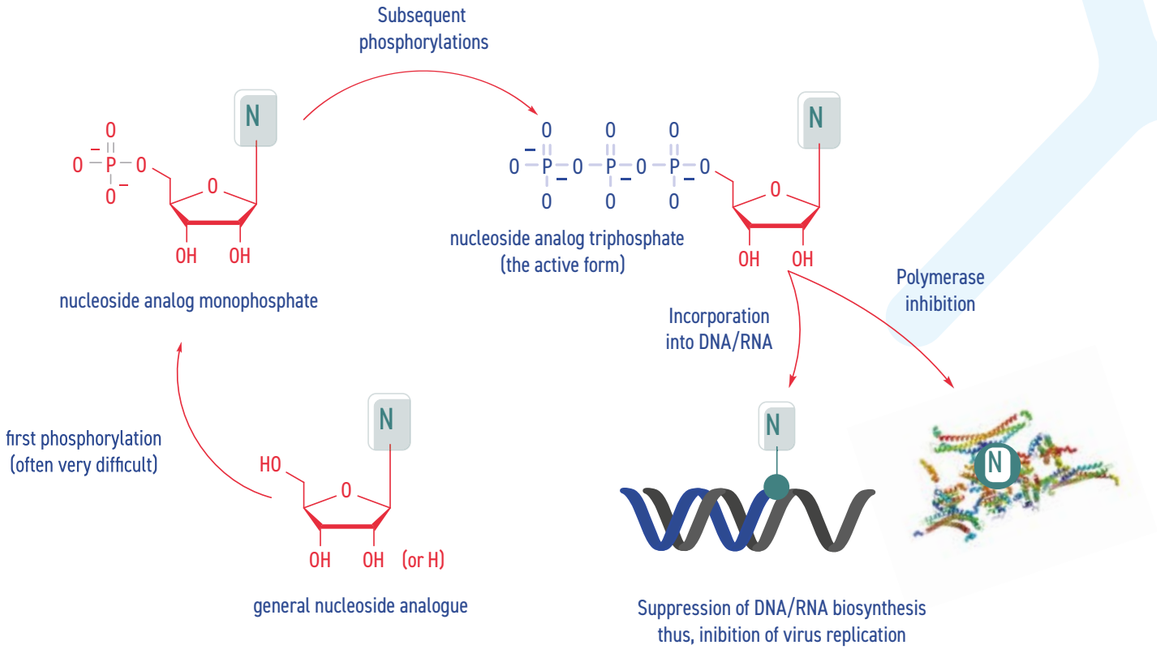
Although several inhibition mechanisms are used, analogues are frequently designed to cause **chain termination**, thereby blocking viral replication once incorporated into the nucleic acid. Alternatively, **nucleoside analogues** can inhibit cellular or viral enzymes involved in nucleoside/tide metabolism without being incorporated into DNA/RNA.

Even though triphosphates are the active form of antiviral drugs, **direct delivery into cells is impossible because these multicharged molecules cannot pass through lipophilic cell membranes**. Thus, nucleosides or nucleotide prodrugs (generally composed of nucleoside 5'-O-monophosphates (MPs) with lipophilic substituents on the phosphate group) must be used for therapy or in vivo studies. However, the drug's efficacy is dependent on intracellular phosphorylation by kinases to reach the final active form, triphosphate.

Importance of triphosphates

Although synthetic triphosphates cannot be used directly as drugs, their use in biochemical research laboratories is critical. They are used in in vitro experiments to test their affinity to virus-encoded or host polymerases, as well as the enzyme's ability to incorporate the triphosphate into nucleic acids, resulting in suppression of DNA/RNA synthesis via chain termination or other mechanisms.

Furthermore, **when a new virus emerges, it is critical to have an immediate first-line defense available** until vaccines and virus-specific antivirals are developed (as we have seen with COVID-19 and nucleoside drug Remdesivir). In many cases, nucleoside analogues with high antiviral activity or that are already used to treat acute infections caused by medically important RNA and DNA viruses are a first-choice test because their cytotoxicity and pharmacokinetics are well understood. **Having triphosphates of important nucleoside-based drugs on hand allows for rapid in vitro testing of antiviral activity against newly emerging viruses**.



FTE/FFS

At Santiago Lab, we are working on a variety of exciting projects for a wide range of international clients. Depending on the level of complexity, literature precedents, and other factors, **either an FFS (fee for service) or an FTE (full-time equivalent) contract is used**.

Fee for service (FFS)

This type of contract is typically used when a project has some prior literature precedent (either a scientific article or a patent) and no extensive research is required.

An FFS project is typical when a client requests the synthesis of one or more compounds that follow a multistep synthesis based on a patent, and only minor synthetic optimization is required. This is a typical custom synthesis project.

The price quoted before the start of the project is only paid in this type of contract if we successfully prepare and deliver the requested product in the agreed-upon quality.

Full-time Equivalent (FTE)

We use the FTE contract when the project is more difficult, and there is little or no precedent in the literature.

For this type of work, a specific member or members of our team is assigned to this project and is paid for the time spent working on it. Every FTE project begins with a thorough review of the literature and a detailed specification of the requirements with the client.

We can focus on more innovative and challenging research during the FTE contract. This allows us to be much more flexible with the project, specifically designing the chemistry and experiments to meet the needs of the client as they evolve over time.

In comparison to FFS, FTE is typically charged monthly and can be either short-term (one month) or long-term multi-year (more than a year).

Management is critical during the FTE project, so we report the **progress of the research to our client on a weekly basis**. As a result, all of the client's requirements can be met.

Our partners and customers

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

ETH zürich

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

University of Minnesota

University of Turku

University of Chemistry and Technology Prague

ÚOCHB AV ČR IOCB Prague

Brno University of Technology

Université Laval

University of Gdańsk

UKM Universitätsklinikum Münster

香 港 大 學 The University of Hong Kong

Universidade de Aveiro

Charles River Laboratories
Contributing to the Search for Healthier Lives™

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