Kalexsyn Overview 2018

Kalexsyn, Inc.
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What we do

- Custom synthesis of difficult molecules, including heterocycles, steroids, small peptides, beta-lactams, and natural products.
- Process route development to enable scale-up of early stage compounds.
- Process impurity identification and synthesis
- Stable label synthesis
- Medicinal chemistry including SAR analysis and optimization for potency, safety, and pharmacokinetics.

What we deliver

- Experienced medicinal, synthetic and process chemists
- Solutions to challenging chemistry problems
  - Over 99% success rate
  - Time saving
  - Cost saving
  - IP generating
- Clear written and oral communication specific to your needs

Our Capabilities

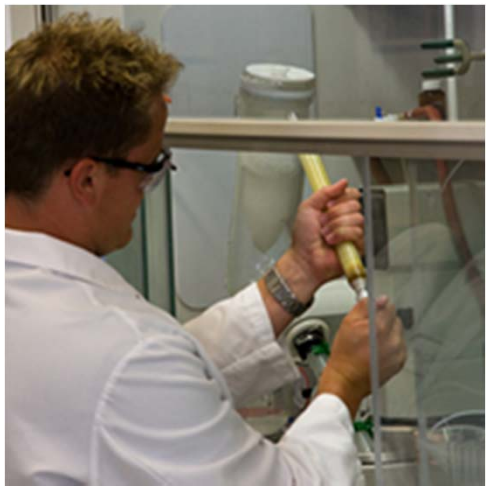
- Medicinal Chemistry, SAR, IP creation
- Custom synthesis of challenging targets
- Stable label compounds (^{2}H, ^{13}C, ^{15}N, ^{18}O) with analytical capabilities for full characterization.
- Schedule II, III, IV, and V controlled substances
- Glucuronides, metabolites, process impurities
- High pressure reactor capability up to 2000psi
- Early API and process improvement chemistry
- Milligrams to hundreds of grams
- FTE Projects tailored to a project's scope
- Fixed Quote Projects

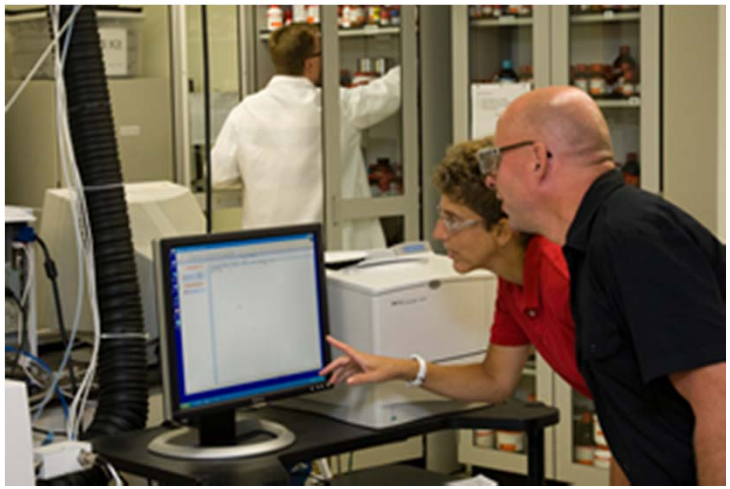
Our strengths

- Provide you with a turn-key, world class chemistry department.
- Understand the importance of protecting intellectual property.
- Provide you with a chemistry solution that does not need constant oversight.
- Provide novel and innovative solutions (patentable) to therapeutic programs.
- Team members with decades of experience working on therapeutic program teams.
- Communication - designed around your needs
- A business designed from a customer's perspective

Our Scientists

- Our chemists and senior advisors have a total of over 1000 publications and patents and have had key roles in the invention and development of several marketed drugs.
- 23 medicinal and process chemists at the bench. ~1:1 ratio of Ph.D. to MS/BS.





Early API

- Milligram to kilo syntheses using up to 50 L glass reactors
- Containment system for High Potency compounds.
- Process route optimization
- Process chemistry re-design
- Process impurity identification and synthesis

Customer-centric

Kalexsyn

- We realize you have other duties. We offer communication and access to data based on your needs.
- We will meet or exceed your in-house quality standards.
- We solve problems in conjunction with you.
- We provide timelines that are aggressive yet obtainable.
- All issues regarding your project are provided to you as soon as available.
- We don’t conduct in-house research. You get our best scientists and our full attention.

Kalexsyn Founders

David C. Zimmermann, Chief Executive Officer

- 23 years experience in the pharmaceutical industry (Upjohn, Pharmacia & Upjohn, and Pharmacia).
- 12 years as a medicinal chemist in various therapeutic areas.
- Research Manager in Medicinal Chemistry at Pharmacia.
- Responsible for negotiations and management of external chemistry CROs.
- Responsible for $16.4 million Pharmacia chemistry budget for Kalamazoo site.
- Developed web and database technologies for chemistry departments.

Robert C. Gadwood, Ph.D., President & CSO

- 17 years experience in the pharmaceutical industry (Upjohn, Pharmacia & Upjohn, and Pharmacia).
- Associate Director of Medicinal Chemistry at Pharmacia with direct responsibility for a group of PhD & non-PhD scientists.
- Chemistry team leader of the Oxazolidinone Antibacterial Team (largest chemistry effort in Pharmacia history).
- Experience in multiple therapeutic areas including infectious diseases, cardiovascular, oncology and dermatology.
- Assistant Professor of Chemistry, Northwestern University.
- Numerous publications and patents.

In-House Analytical

Kalexsyn

400 and 300 MHz NMRs, with auto-samplers and variable temperature

Multiple ion probe H, F, C, N, P etc.

Multiple Agilent 1100 HPLC units

Four CombiFlash Rf systems including ELSD and reverse-phase prep capability.

Polarimeter

FT-IR

Two walk-up LC/MS spectrometers

GC system

KF Titrator

Access to CHN, ROI, LOD, Exact Mass

Cheminformatics

Kalexsyn

- **Symyx Discovery Notebook Software**
  - Electronic Notebook
  - Reaction Database
- **SciFinder**
  - Unlimited searching for every chemist.
- **Access to journals**
  - Access to reprints of all journals through reprint providers.
- **Secure, dedicated Oracle server platforms**
  - Allows creation of proprietary databases.
  - SQL programming capability.
- **Work directly with molecular modeling provider**
  - Former head of computational chemistry at Novartis.
  - In house tools for molecular modeling (PyMol, Autodock)

Experimental Data

Kalexsyn

- Symyx electronic notebook software allows rapid creation of experimental procedures in PDF form directly from the notebook.
- Facile patent preparation.
- Consistent notebook format from scientist to scientist.
- Analytical data generated in PDF form can be incorporated into notebook.

Kalexsyn Laboratories

- Over 20,000 sq ft of lab space.
- Custom designed medicinal chemistry research facility with open lab plan.
- Designed to eliminate exposure (zero-exposure) to scientists.
- 13 linear feet of hood space per chemist.

Working with clients

- Confidential Disclosure Agreement (CDA) and Master Service Agreement (MSA) executed prior to start of work.
- Review Request For Proposal (RFP) and provide you with cost, timetable, decision points, critical issues, options.
  - Provide each RFP with the attention it deserves.
  - Reasonable yet aggressive timelines.
- Quotes on project basis or FTE basis.
  - Complexity of the chemistry
  - Precedence of the chemistry
  - SAR, IP enabling projects on FTE only
  - FTE available on short-term basis

Process Example

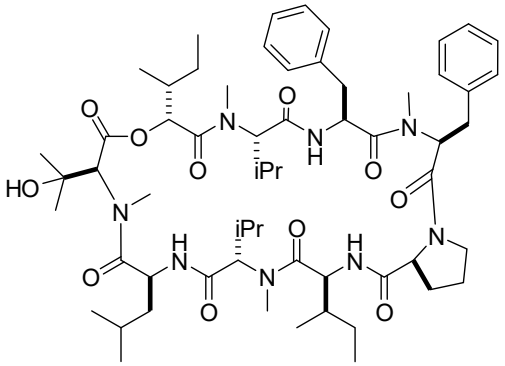
- Multi-national pharma company with a natural product pre-clinical candidate that was initially identified as an isolation from natural sources with great difficulty. An efficient total synthesis would be more profitable and would ensure a steady source of API.
- They had a proposed API synthetic route to the desired compound but it was neither efficient nor scalable.
  - A key Diels-Alder reaction required $LiClO_4$ (explosive) in ether (highly flammable, peroxide former)
  - The synthesis of the dienophile was also not scalable due to an unstable intermediate and high cost of reagents.
- Company had two other CROs try to find a better catalyst for the Diels-Alder reaction and a better synthesis of the dienophile. They both failed.
- Company approached Kalexsyn for a proposal and we worked with our consultant to generate new ideas for the Diels-Alder reaction and dienophile synthesis.

Process Example

- Kalexsyn started the project and in one month found conditions for the Diels-Alder reaction. We also found that the starting dienophile supplied by company was impure.
- After eight months, we have given company a new, fully scalable synthesis of high purity dienophile (500 grams) from inexpensive starting material and have completed process development for the overall synthesis of the natural product delivering close to 100 grams of final product.
- The compound we synthesized by this new route is identical in all respects to the authentic natural product.

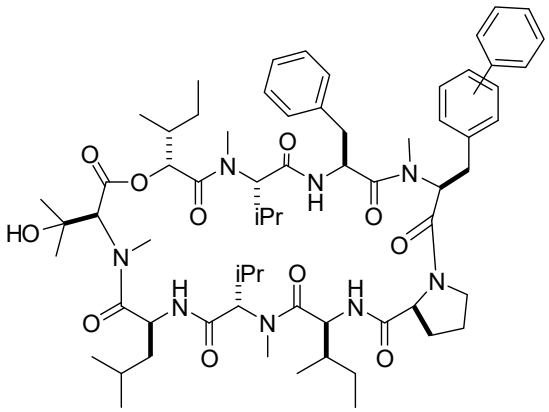
Synthetic Example

- AureoGen Biosciences, Inc. wanted analogs of aureobasidin A that had an improved spectrum of antifungal activity to include *A. fumigatus*.
- Kalexsyn developed an iridium catalyzed borylation and Suzuki arylation that was selective for one phenylalanine residue in the peptide ring.
- Resulting analogs showed good activity against *A. fumigatus* (MIC ~1 µg/mL)
- Aureogen licensed the analogs and the chemistry to Merck (terms undisclosed).



Aureobasidin A

***ACS Med. Chem. Lett.* 2015, *6*, 645.**
US 8,906,848, December 9, 2014.

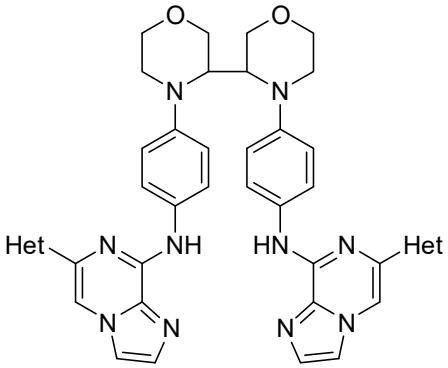


KXN-3833

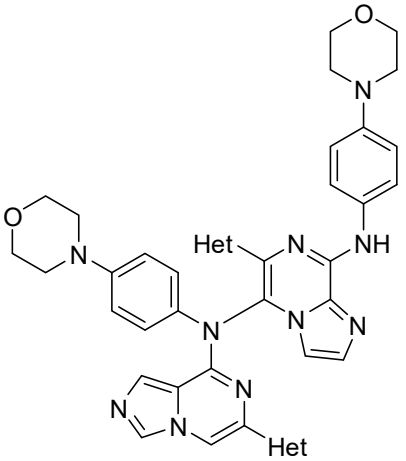
A. Fumigatus MIC ~1 µg/mL

Impurity Example

- A large biotech requested the synthesis of a process impurity which had been identified as **A**.
- After a very lengthy synthesis, Kalexsyn isolated mg quantities of one isomer of **A** and submitted it to the company for testing. It did not match the RT of the impurity, suggesting that the structural assignment of **A** was incorrect.
- Kalexsyn worked with the company's process route to make milligrams of the impurity and determined the structure to actually be **B** based on 2D-NMR studies.
- Kalexsyn developed a de novo synthesis of **B** and prepared 11 grams of **B** in one step from the API. This allowed the company to continue development of their API.

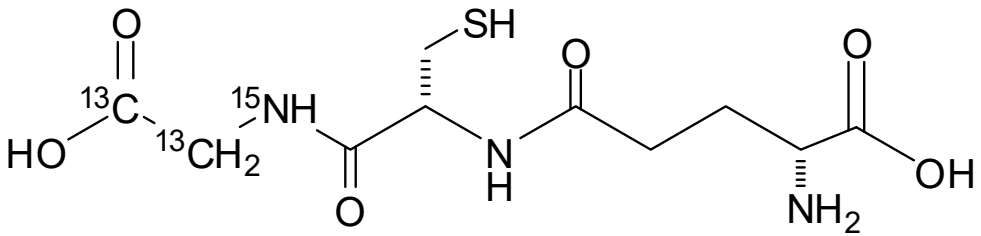


A

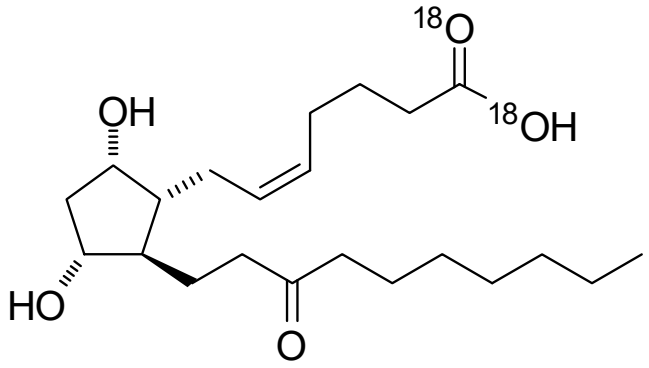


B

Stable Label Projects



Glutathione

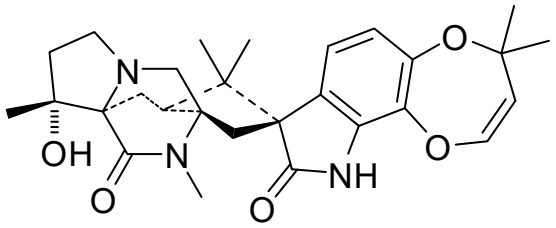


$^{18}O_2$-Unoprostone

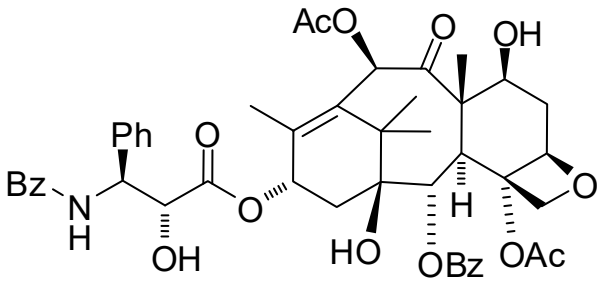
Project Examples

Kalexsyn

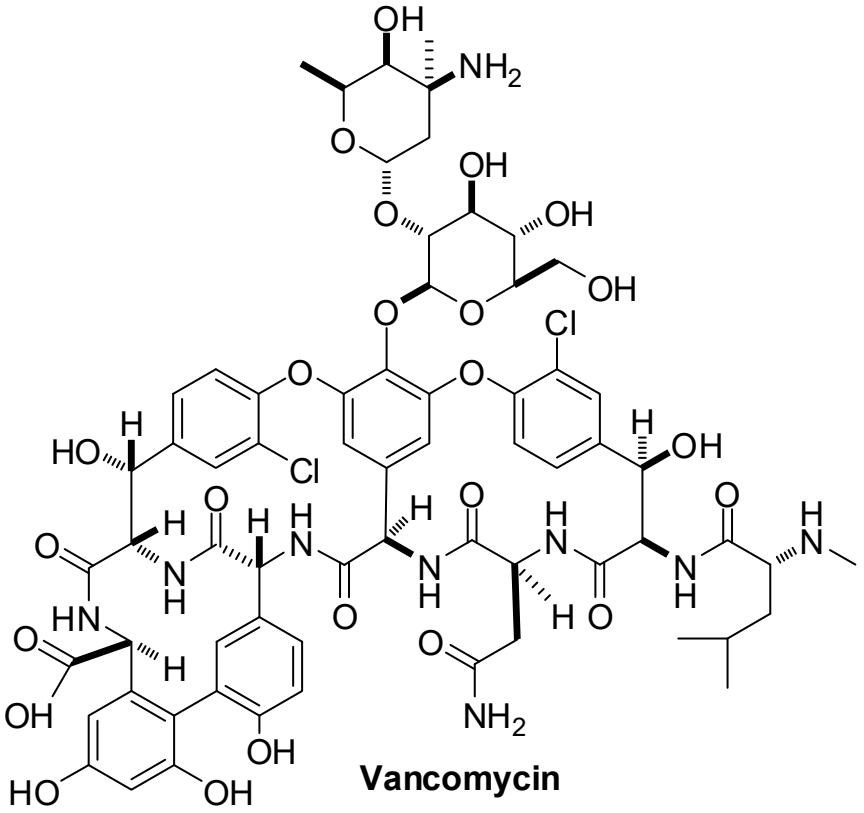
Chemistry Developed for Synthesis and Modification of Complex Natural Products Such As:



Paraherquamide



Paclitaxel

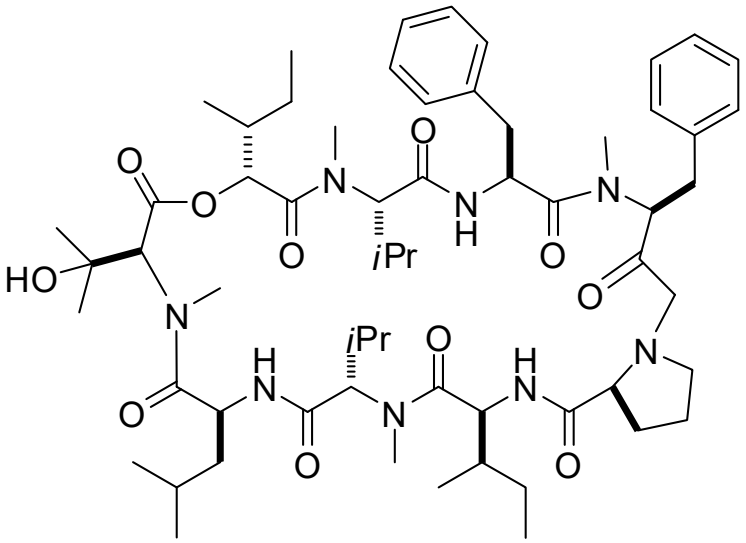


Vancomycin

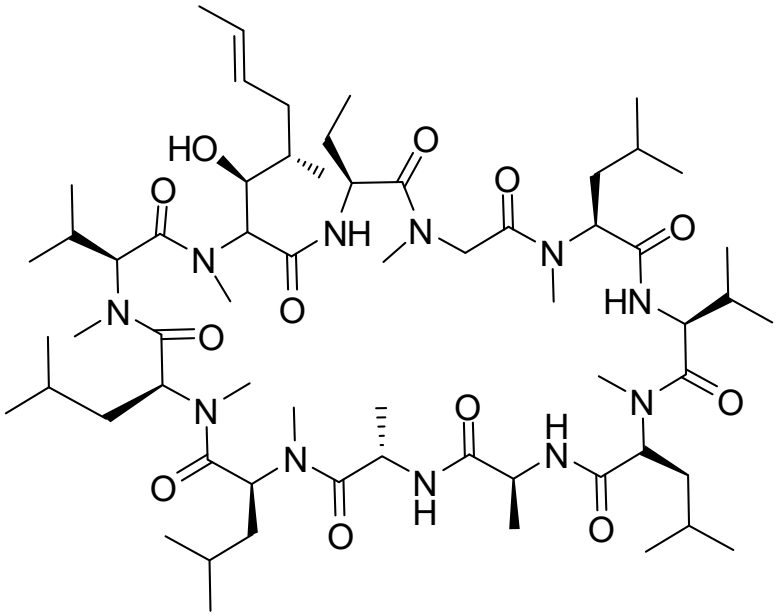
Project Examples

Kalexsyn

Experience With the Chemistry of Macrocyclic Peptide Starting Materials Such As:



Aureobasidin A



Cyclosporin A

Stability and Growth

- Operational since 2003
- Financially stable
- 100% equity owned by Founders
- Operating from a state-of-the-art custom designed laboratory facility
- Global customer base
  - Projects carried out for more than 115 pharmaceutical customers.

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