Symeres

Making Molecules Matter. Together.

SYNTHETIC CHEMISTRY, DRUG DISCOVERY

Innovations in Unnatural Amino Acids: Advancing Functional Diversity and Applications

ANA RIOZ, KIRILL KULISH, TOMMI MEULEMANS, RICHARD BLAUW, RUSSELL THOMAS

"The best way to predict the future is to invent it."
Alan Kay

1. Introduction

The synthesis, characterization, and study of the physicochemical properties of small molecules are at the heart of our business. At Symeres, synthesizing unnatural amino acids comes naturally to us. In this white paper, we aim to share our expertise and recent advancements in the custom synthesis and scaleup of unnatural amino acids, with a focus on side-chain modifications, N-functionalization, beta-amino acids, and cyclic variants.

Amino acids are the fundamental building blocks of peptides and proteins, driving essential biological processes.

The incorporation of unnatural amino acids unlocks unparalleled chemical diversity, paving the way for novel functionalities and applications. These modified amino acids are extensively used in drug development, peptide design, and materials science, providing solutions that go beyond the capabilities of their natural counterparts, including improvements to stability, specificity, and immunogenicity.

Our synthetic chemistry teams are comprised of hundreds of highly experienced scientists with interdisciplinary expertise. Equipped with state-of-the-art research tools and advanced technologies, such as flow chemistry, biocatalysis, photochemistry, and chemocatalysis, we are exceptionally positioned to perform a wide range of modifications within amino acid chains. These include both well-established methods from the literature and pioneering innovative approaches. In the main text, we explore the most commonly applied modifications of natural amino acids.

Figure 1. Developability Roadmap

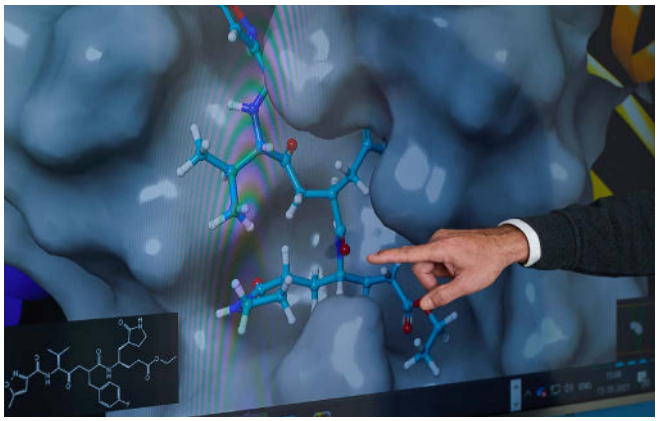
Symeres can provide you with a comprehensive evaluation of the potential of a drug candidate or candidates to be developed into a safe, effective, and marketable medication. The Roadmap typically involves the analysis of various factors, including chemistry; selection of phase/form; chemical and physical properties; formulation; pharmacokinetics; toxicity; and, if required, assistance with planning and authoring your IND/IMPD.

Key topics covered for IND/IMPD filing

Identification and mitigation of potential risks and challenges associated with the development of a new drug candidate are covered by a drug developability assessment. This is essential for the following reasons:

1. determine whether a drug candidate has the critical requisites to progress into drug development;

2. identify potential issues with a drug candidate, such as poor pharmacokinetics, low solubility, or toxicity, and enable researchers to address them early in the drug development process and avoid alterations to timelines and budget at later stages;
3. optimize key properties of the drug candidate to improve study outcomes and potential IP position;
4. provide a robust, homogeneous data and knowledge package, for example, solubility and compound characterization, for successful IND or IMPD filing on a single batch and form.



When's the right moment to contact us?

Our Developability Roadmaps are typically performed early in the drug development process, often just before, or immediately after the clinical candidate selection. They are conducted by multidisciplinary teams of experts, including medicinal chemists, toxicologists, synthetic chemists, analysts, materials and formulation scientists, and regulatory experts.

A systematic, well-thought-out drug developability assessment, such as the Symeres Developability Roadmap, is critical for the efficient development of new drugs. It helps biotech and pharmaceutical companies make informed decisions about which drug candidates to prioritize. It also enables the early identification of potential development risks that should be addressed with the highest priority to avoid delays and unnecessary costs.

Vital components of success

Our Developability Roadmap involves the evaluation of various components related to a drug candidate's ability to be developed into a safe, effective, and marketable medication. The specific components can vary according to the compound, therapeutic indication, and target product profile. However, some common components include the following:

1. **Chemistry:** Whether the current synthetic route is amenable and cost-efficient for scale-up, including sourcing of key raw materials, length and yield of the synthesis, purification methods, chirality, and safety aspects.
2. **Chemical and physical properties:** Assessment of the drug candidate's chemical and physical properties, such as solubility, chemical stability, and experimentally determined pK_a, log*P* and log*D*, as well as ensuring appropriate analytical methods are available for the coming studies.
3. **DMPK:** Assessment of the drug candidate's pharmacokinetic properties, such as *in vivo* absorption, distribution, metabolism, and excretion; DDI potential; as well as nonregulatory rodent and nonrodent pharmacokinetic studies.
4. **Toxicology:** Carrying out non-regulatory genotoxicity studies, cardiac channel electrophysiology, safety pharmacology, and exploratory tox studies.
5. **Form selection:** Investigation of the polymorph landscape, salts, or cocrystals; drug–excipient compatibility; ease of manufacture; and stability is essential. This ensures that the drug can be manufactured consistently and efficiently.
6. **Formulation:** Studying preclinical and toxicology formulations for early phases involves thorough preformulation studies, including excipient compatibility and vehicle screening.
7. **Regulatory considerations:** Assessment of regulatory requirements and guidelines for drug development is necessary to ensure that the drug can be developed in compliance with applicable laws and regulations. This can also be extended to assistance in authoring the Module 3 content of the IND/IMPD.

Symeres services

The Developability Roadmap is composed of data and information from several technical disciplines, including chemistry, materials science, formulation, ADME, and toxicology groups. The majority of these studies are conducted at Symeres, with some specific aspects, such as electrophysiology and in vivo toxicology, conducted under Symeres' control at trusted third parties located in Europe and the USA. The results are reported in a single document containing the relevant data in a format that will greatly facilitate your IND/IMPD filing. We provide more than just data and will work with your team to identify program risks, propose mitigation strategies, and coordinate future activities.

With Symeres managing the entire Developability Roadmap for you, you will save the most important asset – time. We achieve extremely efficient project management and execution via effective communication between our departments. This can be easily tracked by our extensive track record, with over 30 years of experience in the market.

Material quantities and general timelines

We will work with you to tailor a package best suited to your project and target product profile, aiming to minimize both the overall timelines and the material that we prepare. We would recommend that the package be created around a single batch of a defined polymorph and/or salt form to maximize robustness and remove a significant source of interstudy variability.

For further inquiries or collaboration opportunities,
please contact us via: science@symeres.com
www.symeres.com

Symeres