Symeres

Making Molecules Matter. Together.

SYNTHETIC CHEMISTRY, ADMESCOPE

Stable isotope-labeled compounds

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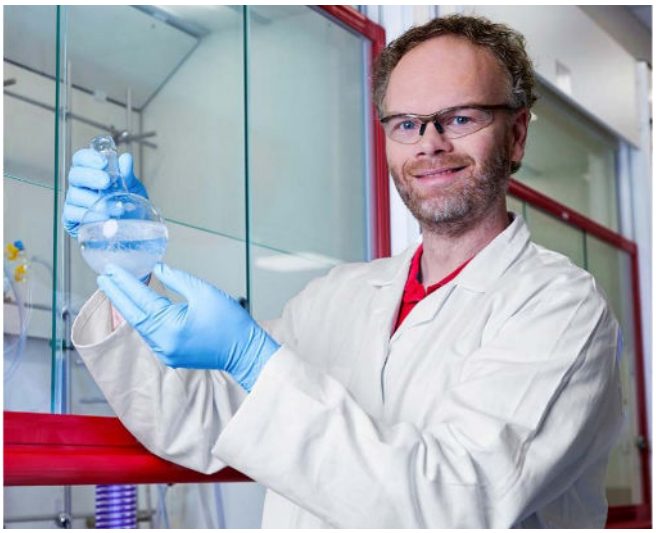
"It is the mark of an educated man to look for precision in each class of things just so far as the nature of the subject admits."
Aristotle

In pharmaceuticals, precision is crucial, requiring researchers to have accurate tools for drug development and an understanding of metabolic pathways. To meet this need, Symeres has adopted stable isotope-labeling techniques to support our customers' research. We use advanced technologies, such as flow chemistry, biocatalysis, and photoredox catalysis, in addition to traditional synthetic methods. Complex custom synthesis is our core business, and we have extensive experience in route scouting, which is essential for synthesizing labeled compounds. Two of our service platforms, Synthetic Chemistry and Admescope, are actively involved in the generation and application of isotopically labeled molecules, respectively. We can discuss with you what labeling you need, make these molecules, and carry out ADME and DMPK studies on the relevant compounds.



Most common isotope labeling

The primary goal of stable isotope labeling in the pharmaceutical industry is to accurately track and quantify molecules in complex biological systems (Figure 1). Deuterium-, carbon-13-, and nitrogen-15-labeled compounds have been effectively used in the analysis of drug metabolites and agrochemicals; reaction mechanism and kinetic studies; the development of sensitive mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy probes; and absorption, distribution, metabolism, and excretion (ADME) studies.[1]

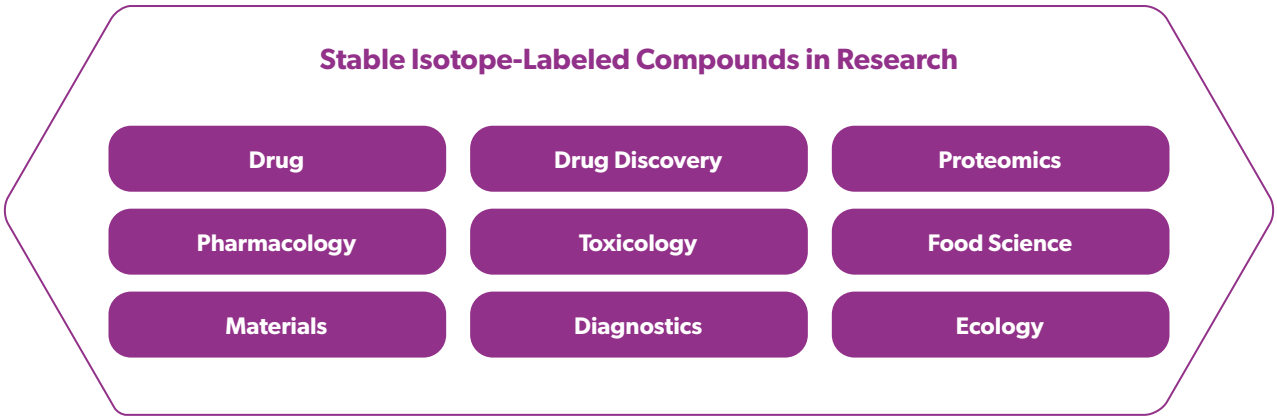


Figure 1. Examples of the application of stable isotope-labeled compounds in different areas of research.[3]

Stable isotopes come in various forms, each serving distinct purposes in pharmaceutical research:

Carbon-13 (^{13}C): Often used to study metabolic pathways and drug metabolism, ^{13}C labeling enables researchers to track the fate of carbon atoms within molecules. By introducing ^{13}C into drug candidates or substrates, scientists can trace metabolic transformations accurately.

Deuterium (^{2}H): ^{2}H labeling finds application in studying drug metabolism, drug–drug interactions, and pharmacokinetics. ^{2}H, a heavy hydrogen isotope, can replace standard hydrogen atoms in organic molecules, altering their physical and chemical properties. This alteration can influence drug stability, metabolic rates, and clearance pathways.

Nitrogen-15 (^{15}N): ^{15}N labeling is instrumental in elucidating protein structures and dynamics. By introducing ^{15}N into amino acids, researchers can perform NMR spectroscopy to study protein folding, interactions, and conformational changes. This information aids in the rational drug design and understanding of drug–protein interactions.

The specialized approach to the synthesis of labeled compounds

The synthesis of stable isotope-labeled compounds necessitates specialized approaches distinct from conventional synthetic routes:

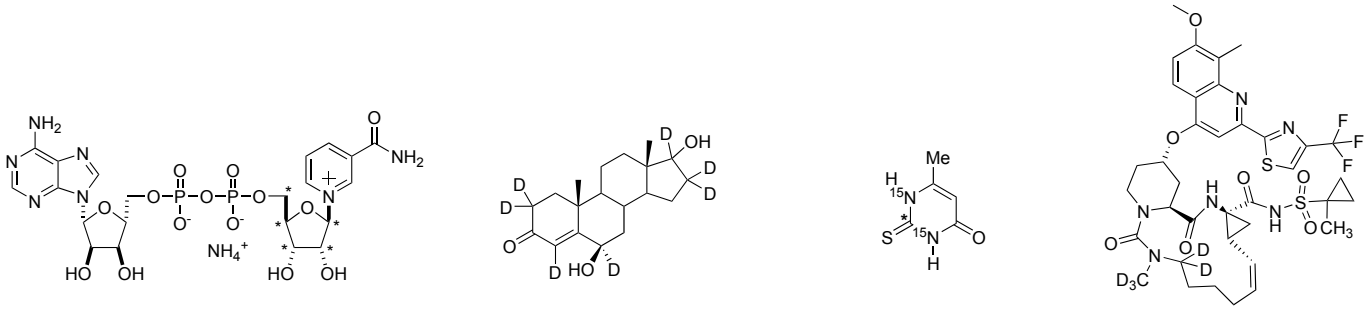
Isotopic enrichment: Incorporating isotopically enriched precursors is essential for achieving high isotopic purity in labeled compounds. This requires customized synthesis routes tailored to specific labeling requirements, often involving specialized chemical reactions and purification techniques.

Optimization for isotopic incorporation: Synthesis routes must be meticulously optimized to maximize isotope incorporation while minimizing costs and synthetic steps. This entails the careful selection of isotope precursors and reaction conditions to ensure efficient labeling and high product yields.

Quality assurance and control: Stringent quality-control measures are imperative to verify isotopic purity and minimize contamination. Analytical techniques such as mass spectrometry and NMR spectroscopy are employed to assess the isotopic composition and purity of labeled compounds, ensuring their suitability for pharmaceutical applications.

The incorporation of isotopes into an organic compound can be performed by employing two main methods, namely, the direct use of isotope-containing commercially available precursors and subsequent synthesis of desired compounds or, in the case of deuterium-containing molecules, the hydrogen/deuterium exchange reaction. Both principles have been successfully utilized at Symeres for the synthesis of various molecules in which one or more stable isotopes were embedded. This has resulted in the delivery of hundreds of compounds to our clients over the past 30+ years.

We offer not only custom synthesis services but also a broad range of stable isotope-labeled compounds (Figure 2) available for purchase (see the catalog at **Chiralix - Symeres** company) allowing you to choose the most suitable approach for your research.



NAD+ $^{13}C_5$ | 6-beta-Hydroxytestosterone-D_7 major | Methylthiouracil-$^{13}C^{15}N_2$ | IDX16320-D_5

Figure 2. Examples of stable isotope-labeled compounds available at Symeres.

ADME/DMPK studies with labeled compounds

From a drug-safety perspective, we offer the correlation of metabolite exposure between human and preclinical species, and thus, identification of metabolites disproportionately found in or unique to humans. This can be done by comparing the *in vivo* metabolite profiles from animal species to *in vitro* human models and characterizing *in vivo* human metabolites from FIH, SAD, MAD, or human ADME studies with cold or radiolabeled compounds against the preclinical animal samples.

If you are interested in synthesis of labeled compounds, please contact Kirill Kulish. Our team aims to ensure the success of your

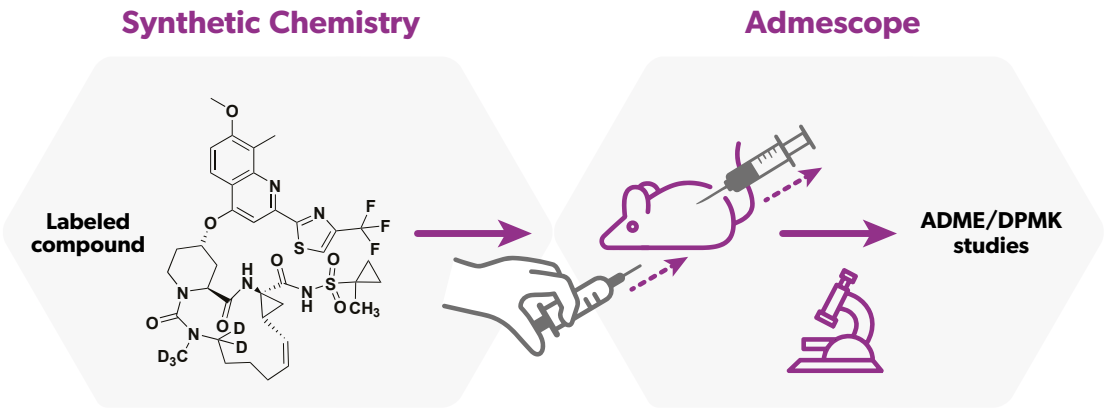


Figure 3. An example of two Symeres' services working together.

By harnessing the capabilities of stable isotopes, pharmaceutical researchers can accelerate drug discovery and development, paving the way for personalized medicine and targeted therapies.

If you are interested in the synthesis of labeled compounds, please contact Kirill Kulish: **kirill.kulish@symeres.com**. Our team aims to ensure the success of your project and will happily assist you.

[1] *Synthesis*, **2013**, *15, 3805–3807; Chem. Res. Toxicol.*, **2008**, *21 (9), 1672–1689; Angew. Chem. Int. Ed.*, **2018**, *57, 1758–1784*

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