

Autumn 2023 SPECIAL REPORT

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NUCLEOSYN, CATALOG OF SYNTHETIC LIPIDS

High-quality products developed for:

- Lipid nanoparticles (LNPs) formulation
- Lipidoid nanoparticules formulation

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- Nucleic acids delivery
- Drugs delivery
- Vaccine delivery

HN



The chemistry **you need**

ABOUT NUCLEOSYN CATALOG OF SYNTHETIC LIPIDS CUSTOM SYNTHESIS



About Nucleosyn

Nucleosyn is a company created in 2006 to develop compounds derived from Organic Chemistry dedicated to genomics, (bio)-analysis, vaccines, and diagnostics.

Nucleosyn is the French innovation and R&D subsidiary of the Biosolve Group. Since its creation in 2006, its main objective has been to develop new ranges of innovative products to implement the catalog of reagents and solvents already offered by the group. These specialty products are widely addressed to the private sector (chemical, pharmaceutical, cosmetics, biotechnology industry, biomedical analysis laboratories) and the public domain (hospitals, academic research institutions, CNRS, INSERM, etc.).

Nucleosyn has developed a significant range of DNA & RNA synthesis reagents, stable isotope-labeled molecules and synthetic lipids (used in vaccines as vectorization agents and in LNPs many customized compounds. The company also acquired strong skills and knowledge in the field of custom synthesis, which contributed to building the reputation of Nucleosyn.

Capabilities & Expertise

Nucleosyn provides access to a reliable and sustainable source of DNA & RNA synthesis reagents, stable isotope-labeled molecules, and synthetic lipids that meet your specifications in terms of quality thanks to our chemists and our global supply network. We propose therefore an extensive and detailed catalog. containing most of the synthetic lipids that can be used for the transfection of nucleic acids and for LNPs formulation, including:

- Ionizable lipids
- Cationic lipids
- Helper and PEG lipids
- Cholesterol derivatives
- Isotope-labeled lipids

Nucleosyn has developed its chemistry expertise by undertaking a large number of diverse projects. Custom synthesis of original synthetic lipids bearing exotic functional groups also represents a significant part of the company's research work in the field of synthetic lipids. Nucleosyn's chemists use their expertise and knowledge to devise innovative solutions or improve synthetic pathways to provide a higher-quality end product.



High-quality compounds

Over the years, Nucleosyn has earned a strong reputation for providing high quality compounds. The company is committed to ensuring the purity and identity of the produced molecules.

To demonstrate this, a complete analysis certificate of supplied compounds is provided including all analytical analysis data performed during the manufacturing process (¹H, ¹³C NMR spectra as well as LC-ELSD and LR-MS chromatograms).



Packaging & Shipment

Nucleosyn proposes any packaging size of the compounds, under request, up to multigram quantities in pure form. To ensure long-term stability, compounds are all conditioned in low actinic amber color glassware (for light-sensitive products) and under an argon atmosphere (for air-sensitive products). In addition, they are shipped cold (e.g. dry ice shipping for temperature-sensitive products if necessary with express worldwide delivery). Nucleosyn designs clear identification labels including:

- Usual name of the compound, or specific name under request
- CAS number
- Nucleosyn's catalog number
- Batch number
- LC-ELSD purity of the compound

- Special attention is given to the quality of the analysis performed:
- ¹H, ¹³C NMR spectra, and LR-MS chromatogram free of any residual side impurity signal
- Fine optimization of the LC-ELSD conditions to ensure an unambiguous high-purity determination
- In addition, special care is given to the aspect of the compounds to ensure reproducible experiments and reliable results:
- Clear and free of any foreign matter
- Removal of undesired color





¹H & ¹³C NMR spectra, LC-ELSD & LR-MS chromatograms are attached as well to the certificate of analysis



Catalog of synthetic lipids

Synthetic lipids have numerous desirable properties for applications in nanotechnologies. These compounds are used to prepare liposomes and lipid nanoparticles (LNPs) to encapsulate and deliver active pharmaceutical ingredients, such as nucleic acids, various drugs, vaccines, or even small molecules.

A lipid nanoparticle (LNP) typically has a spherical shape with an average diameter between 10 nm to 1 µm. Different types of lipids are employed to achieve the desired composition for accurate and efficient delivery of the active ingredients, such as ionizable lipids, cationic lipids, helper lipids, cholesterol derivatives, and branched lipids. Nucleosyn produces and supplies a broad range of synthetic lipids from milligrams to multi-kilos quantities.



Ionizable lipids

Ionizable lipids are bearing an ionizable polar head which is protonated at low pH, but remains neutral under physiological pH. That pH-sensitivity is beneficial for nucleic acids delivery in vivo and improves the biocompatibility of ionizable lipids. Indeed, neutral lipids have fewer interactions with the anionic membrane of blood cells, which contributes to

Tertiary amine polar head

Ionizable amino lipids are used in combination with other lipids for the formation of liposomes, lipid nanoparticles (LNPs), or lipidoid nanoparticles for siRNA, mRNA, small molecules, and vaccine delivery. The tertiary amine polar head is a small amine moiety such as N, N-dimethylamine and the hydrophobic carbon chains can be fully saturated or partially unsaturated.



reducing the toxicity of lipid nanoparticles (LNPs).

These properties make ionizable lipids highly sui-

table for transfection and drug delivery applications.

Nucleosyn provides a broad range of high-quality

ionizable lipids. We certify a complete deprotonation

of the polar head to ensure reproducible experiments

and reliable results.

18:1 DAP (DODAP)

CAS 127512-29-2 4LSC4963

YSK05

CAS 1318793-78-0

4LSC4976



DODMA

CAS 104162-47-2

4LSC4959

CAS 121315-93-3 4LSC4716





Branched lipids

particles (LNPs), in combination with other lipids, for in vivo delivery of anionic substrates. These nanoparticles can be used as well for mRNA, short interfering RNAs, siRNA, or self-amplifying RNA (saRNA) delivery. The hydroxyl groups on the structures allow further derivatization with other functional groups. In addition, branched lipids are also known to be ionizable lipids.

branched lipids. We certify a complete deprotonation of the ionizable sites to ensure reproducible experiments and reliable results.



4LSC4981



are used in combination with other lipids to generate lipid nanoparticles (LNPs). Among these lipids, some of them showed suitable abilities to encapsulate and protect fragile active ingredients of drugs, such as

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Biodegradable lipids

Novel biodegradable lipids are used to prepare well-tolerated *in vivo* lipid nanoparticles (LNPs). In addition, biodegradable lipids are readily eliminated from intracellular compartments thanks to their pKa values within the range of 6.2 – 6.5 which is optimal for *in vivo* applications. Biodegradable lipids can be used for the delivery of siRNA, mRNA, DNA, or even small molecules into cells.





DLin-DMA derivatives

DLin-DMA derivatives incorporate two linoleyl carbon chains as hydrophobic tails. However, the ionizable polar head and the linker can be modulated for various applications. DLin-DMA and other derivatives proved to be key components for the formation of nucleic acid lipid particules (SNALPs), lipid nanoparticules (LNPs) and they are widely used for siRNA, mRNA or DNA delivery.



DLin-MC3-DMA CAS 1224606-06-7 4LSC3133

DI in-DMA

CAS 871258-12-7 4LSC3856

Functionalized polar head

Among the range of ionizable lipids developed for the formulation of lipid nanoparticles (LNPs) for mRNA delivery, exotic polar heads can be envisioned as well, such as an *N*-methylsquaramide moiety in the case of Lipid 29 (4LSC4990) which improves the performance of the corresponding lipid nanoparticles through specific interactions with mRNA.



4LSC4978

Cationic lipids

Cationic lipids bear a positive permanently charged polar head, mostly as a quaternary ammonium salt. Cationic lipids can be used for mRNA delivery in multiple cell types thanks to their charged polar head which facilitates the encapsulation process (LNPs), neutralizes negative charges, and thus facilitates cell uptake.

Nucleosyn provides various high-quality cationic lipids. Specific attention is given to the counter anion of the quaternary ammonium head to ensure a full conversion into the requested one.

Helper lipids

Helper lipids are commonly used to increase the stability *in vivo* and the fluidity of lipid nanoparticles (LNPs). In addition, helper lipids are also known to boost the delivery efficiency of lipid nanoparticles (LNPs). As an example of a helper lipid provided by Nucleosyn, DOPE, with a cone-shape geometry

Phospholipids

Phospholipids can be subdivided into smaller categories like phosphatidic acids and phosphatidylethanolamine derivatives. Phosphatidic acids, including DOPA (4LSC4991 & 4LSC4992), have been used to generate various artificial membranes, such as





favoring the formation of hexagonal II phase, can promote the endosomal release of ONs.

Knowing the selection process of both cationic and helper lipids for innovative lipid nanoparticle formulation, Nucleosyn provides several types of highquality helper lipids.

micelles and liposomes. Phosphatidylethanolamine derivatives, including DOPE (4LSC3291) and DSPC (4LSC3288), are rather used as emulsifiers to assist DNA-liposome complex transport through membranes, or lipid nanoparticles (LNPs) stabilizers.



PEG lipids

PEG lipids as helper lipids include ALC-0159 (4LSC4952) which is a non-ionic surfactant. It contains a PEG chain of 45 to 46 units and has been used in the Pfizer-BioNTech SARS-CoV-2 mRNA vaccine.

ALC-0159 CAS 1849616-42-7 4LSC4952

Cholesterol derivatives

Cholesterol derivatives can be combined with cationic lipids to form cationic liposomes. These liposomes are used as intracellular delivery nanocarriers for nucleic acids, as well Nucleosyn provides high-quality cholesterol as pRNA and siRNA for intratumoral gene delivery. In addition, the incorporation of cholesterol

in lipid nanoparticles (LNPs) improves intracellular delivery and LNP stability in vivo.

derivatives. We certify the absolute configuration of the stereogenic centers.



CAS 166023-21-6 4LSC4986



CAS 191173-82-7 4LSC4985

Isotope-labeled lipids

For many years, Nucleosyn has built its experience in labeling a wide range of molecules. Our expertise allows us to perform the incorporation of isotopic labels at specific positions of the compound, including site-selective and multiple site-selective schemes. Nucleosyn provides custom stable isotope lipids to support dedicated projects, such as therapeutic drug monitoring thanks to mass spectrometry.



[13C,]-DLin-MC3-DMA 4LSC4992



[D,,]-DLin-MC3-DMA CAS 2917653-17-7 4LSC4993



4LSC4994

Custom synthesis

Nucleosyn has also been built around its unique chemistry skills and experience in custom synthesis by using novel chemical synthetic approaches alongside classical methodologies. Taking advantage of its highly trained team of chemists, Nucleosyn has earned a reputation for completing even the most challenging syntheses on time and to full requirement.

Custom synthesis provided by Nucleosyn considers the manufacture of compounds from milli-grams to multi-grams scale synthesis and could be done with a patentability and freedom to operate (FTO) analysis of specialized chemicals and/or a chemical process. Each project is treated with utmost confidentiality if requested (confidentiality agreement).



Linker

Etc...

Hydrophobic tail

To induce the structuration of a stable liposome with good shape and size.

- Fully saturated alkyl chain (lauric, palmitic...)
- Unsaturated chain (linoleic, oleic...)
- Dissymmetric chains
- Customized chain
- Etc...

To bind and then release nucleic acid after cleavage to reduce toxicity.

- Chain length modulation

- Classic functional group (ester, amide, amine,...)
- Exotic functional group

Polar head

To vectorize liposome for targeted release of nucleic acids.

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- Ionizable polar head
- Fixed cationic head
- Phosphorylated unit
- Exotic moiety
- Customized head
- Etc...









Contact us

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