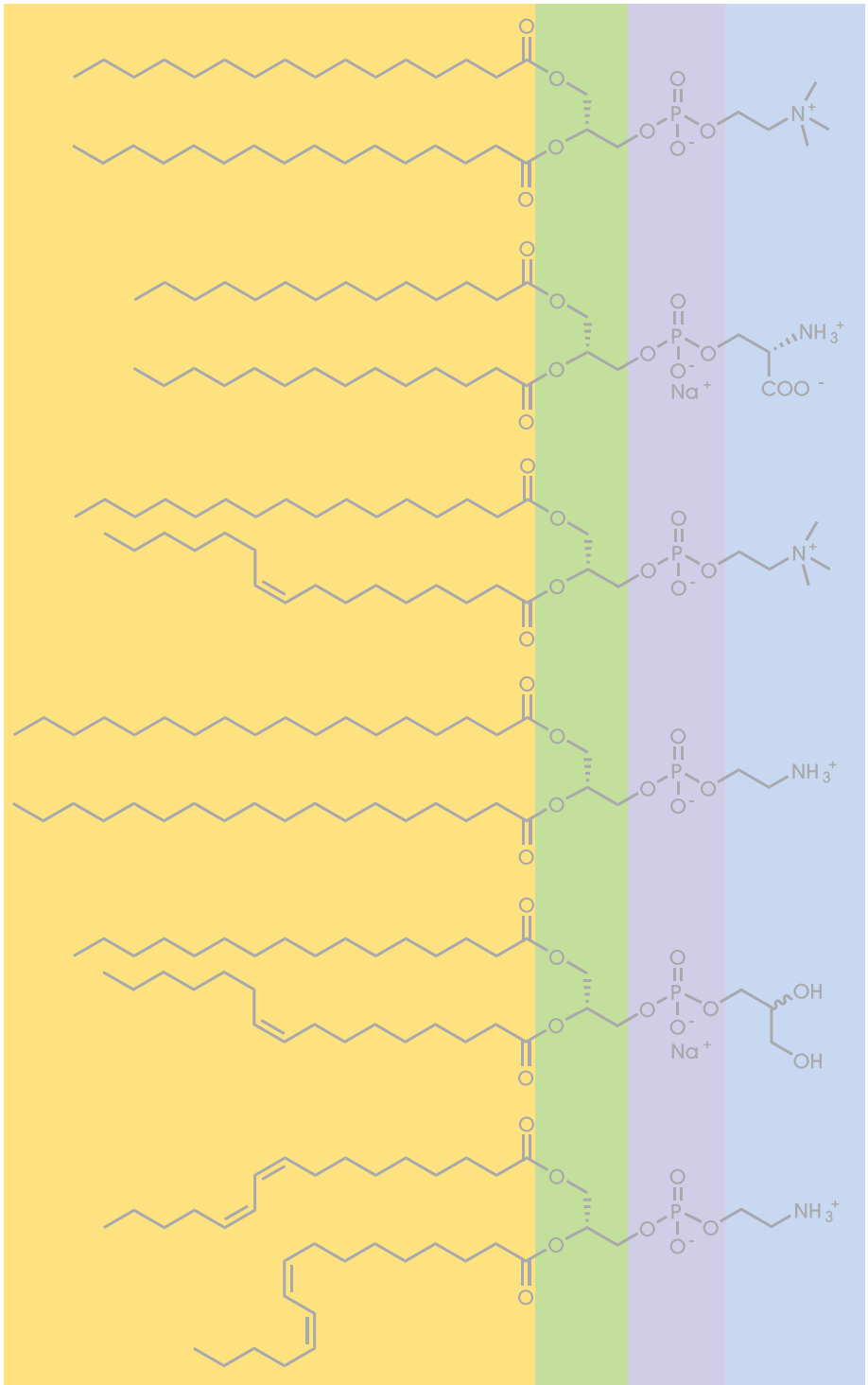
Genzyme Pharmaceuticals

SYNTHETIC PHOSPHOLIPIDS AND OTHER SYNTHETIC LIPIDS

HIGH QUALITY MATERIALS FOR DRUG PRODUCTS



genzyme
Pharmaceuticals

PHOSPHOLIPIDS AT GENZYME PHARMACEUTICALS

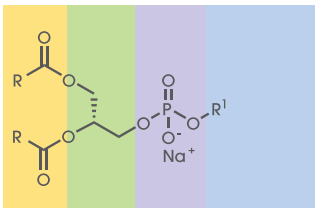
Phospholipids are naturally occurring molecules and as such, are primary constituents of cell membranes.

While phospholipids can be extracted from natural sources, Genzyme Pharmaceuticals' synthetic routes allow for highly purified products with well controlled and consistent batch-to-batch quality, which renders them suitable as pharmaceutical excipients.

Genzyme Pharmaceuticals has extensive experience in the chemical development and GMP manufacture of high quality synthetic phospholipids. These materials are used by biotechnology and pharmaceutical companies as key substances (excipients, critical materials, etc.) in a variety of engineered drug delivery technologies such as liposomes, emulsions, and pulmonary particles. Some phospholipids are also used as Active Pharmaceutical Ingredients (APIs) in drug products.

CHEMISTRY

Phospholipids are similar to triglycerides with the exception that the terminal hydroxyl of the glycerine molecule contains a polar phosphate group instead of a fatty acid. In addition, this phosphate group can be further esterified with polar groups such as ethanolamine, choline or serine (R^1). The polar substitution of the end hydroxyl function in postion 1 of the glycerine backbone, combined with the attachment of fatty acid esters to the other two primary and secondary hydroxyl functions, creates a molecule with a hydrophilic head (the phosphate end) and a hydrophobic tail (the fatty acid groups). These amphiphilic phospholipids can self-assemble to fluid lipid bilayers in an aqueous environment. Genzyme Pharmaceuticals' phospholipids are accessible by multi-step chemical synthesis with some of the final products sharing the same precursors. In this document, the synthesis cascade is presented in four distinct product tiers with increasing chemical complexity. The building blocks of the phospholipid molecule are represented by color.



Fatty acids in yellow, glycerol backbone in green, phosphate group in purple, polar head groups in blue

SYNTHESIS ROUTES FOR VARIOUS PHOSPHOLIPIDS

Tier 1

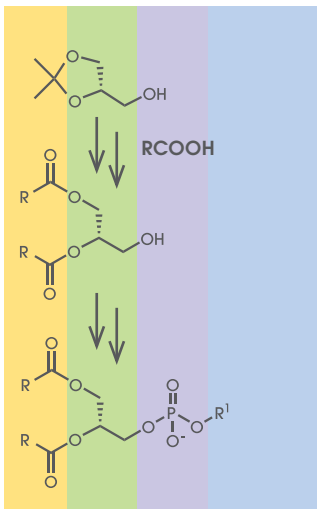
Genzyme Pharmaceuticals' primary large-scale manufacturing process starts with (*S*)-1,2-isopropylideneglycerol ((*S*)-IPG), which is derivatized to 1,2-diacylglycerol, the key process intermediate for the production of a wide variety of phospholipids.

Tier 1 phospholipids (1,2-diacylated) are obtained when the corresponding polar head group is attached via chemical synthesis to 1,2-diacylglycerol.

Many of our *Tier 1* products are used as critical excipients in investigational drug products.

EXAMPLES

- DPPE
- DPPA, Na
- DPPG, Na
- DPPS, Na

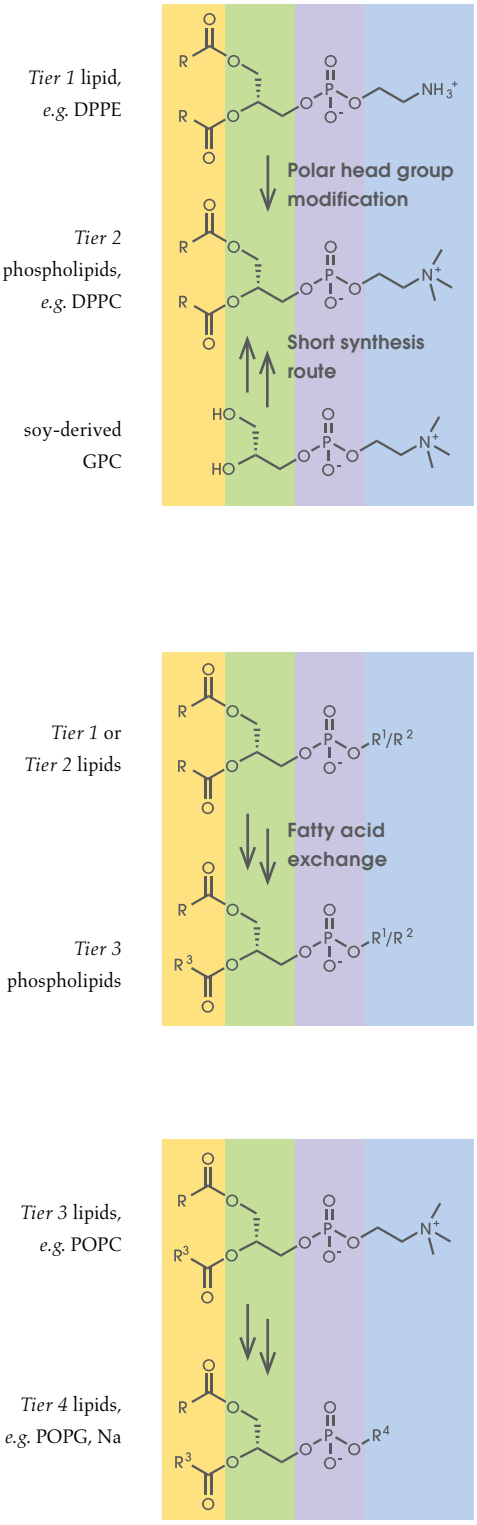


IPG

1,2-diacylglycerol
e.g. DPG

Tier 1
phospholipids
e.g. DPPE

SYNTHESIS ROUTES FOR VARIOUS PHOSPHOLIPIDS *continued*



Tier 2

Tier 2 phospholipids can be obtained by chemically modifying the polar head group of *Tier 1* products, as indicated by the transformation of the R^1 functional group into R^2. *Tier 2* phospholipids are either produced by the "long route" from IPG as shown previously, or via the "short route" from soy-extracted GPC. Genzyme Pharmaceuticals offers products via both routes, differentiated by product number. Note that while the product release specifications for long and short process products are identical, their impurity profiles may differ due to different production processes. Please contact Genzyme Pharmaceuticals for more information on these routes.

EXAMPLES

- DPPC
- DSPC
- PEG'ylated phospholipids

Tier 3

Homogeneous *Tier 1* and *Tier 2* phospholipids can be transformed into *Tier 3* analogues with heterogeneous fatty acids ($R \neq R^3$) via a selective substitution of the fatty acid chain in position 2 of the glycerol moiety. This flexible process allows access to a wide variety of heterogeneous phospholipids via the 2-lyso-phospholipid intermediate (not shown).

EXAMPLE

- POPC

Tier 4

Phosphatidylcholine lipids (*e.g. Tier 3* POPC) can be transformed into *Tier 4* analogues via selective enzymatic reaction.

This produces *Tier 4* phospholipids, the final compounds in the synthesis cascade.

EXAMPLES

- POPG, Na
- POPG, NH_4

OTHER SYNTHETIC LIPIDS

Genzyme Pharmaceuticals offers a variety of other synthetic lipids, some of which can be found in the following product listing. While not listed, sphingolipids are also available. Contact us for more details.

CUSTOM SYNTHESIS OF LIPIDS AND THEIR ANALOGUES

Genzyme Pharmaceuticals also offers custom manufacturing of proprietary phospholipids and lipid-like molecules. In addition, expertise in peptide synthesis makes Genzyme Pharmaceuticals uniquely equipped to produce lipopeptide conjugates. Please inquire for further information.

GMP LIPIDS FOR USE IN CLINICAL AND COMMERCIAL APPLICATIONS

Genzyme Pharmaceuticals routinely manufactures lipids following GMP guidelines and supplies them for use in clinical trials or approved drug products. With adequate notification from the customer of such intended use, Genzyme Pharmaceuticals may release further technical information as regulatory support if appropriate. Please contact us for pricing and availability if you require GMP products.

GMP lipids are packaged in conformance with specifications and materials used in stability studies (see GMP materials and packaging for details) and have product codes prefixed by LP-04-.

Note: Primary packaging materials/conditions are different from those for non-GMP products bearing codes prefixed by LP-R4-. If you require non-GMP products for Research and Development use, see the following product listing.

GMP MATERIALS AND PACKAGING

Material weights of 2.5 kg or less are packaged in a low-density polyethylene (LDPE) primary pouch, which is then further packaged into an LDPE-lined aluminum pouch; a desiccant sachet is placed between the pouches and the aluminum pouch is then heat sealed.

Shipments of product may be further packed into a plastic drum to provide additional protection during transit.

Material weights of 5 kg or more are packaged in the primary pouch as above and placed in a steel drum.

Primary Packaging Specifications

The products are packed in polyethylene inner-liners of sizes 600x750mm, 750x1,000mm and 800x1,400mm, depending on the packaging volume.

Inner-liners are composed of natural low density polyethylene, manufactured in a controlled environment with a particulate cleanliness level of 10,000 according to the IEST-STD-CC1246D standard.

The polymers used are certified in compliance with the European Commission Directive 2002/72/EC and with the US code of Federal regulation 21 CFR 177.1520.

Secondary Packaging Specifications

The inner-liners are placed in cylindrical steel drums closed with lids, and equipped with a seal and galvanized ring. According to the shipment volume, two sizes of drums are currently in use (20L, 55L).

ANALYTICAL AND REGULATORY CAPABILITIES

Our facility holds a current GMP Certificate and has been inspected by the Swiss Regulatory Agency, the U.S. FDA, numerous customers and Genzyme Corporate Quality Compliance. To date these inspections have resulted in no reported critical observations.

The facility maintains independent, extensive Quality Analysis and Quality Control laboratories fully integrated within Genzyme Corporate Quality. These labs are staffed with highly trained technicians and outfitted with state-of-the-art equipment ensuring the customer seamless support in critical development areas such as:

- Analytical development and validation
- Cleaning validation and stability studies
- Supplier evaluation and qualification
- GMP and manufacturing documentation

LIPIDS FOR USE IN RESEARCH AND DEVELOPMENT

A wide selection of non-GMP products is available from stock for general R&D use only.

R&D lipids are packaged in brown glass bottles with polypropylene screw-caps lined with LDPE and have product codes prefixed with LP-R4- (see following product listing).

PHOSPHOLIPIDS

Please contact Genzyme Pharmaceuticals to place your lipid order.

Abbreviation Product Description	**Item #**	**CAS Number**
Monoglycerols		
Monocaprin 1-Decanoyl-*rac*-glycerol	LP-R4-158	26402-22-2
Monolaurin 1-Lauroyl-*rac*-glycerol	LP-R4-146	142-18-7
Monomyristin 1-Myristoyl-*rac*-glycerol	LP-R4-160	589-68-4
1-Undecanoyl-*rac*-glycerol	LP-R4-159	64633-19-8
Diacylglycerols		
DLG 1,2-Dilauroyl-*sn*-glycerol	LP-R4-063	
DMG 1,2-Dimyristoyl-*sn*-glycerol	LP-R4-027	60562-16-5
DPG 1,2-Dipalmitoyl-*sn*-glycerol	LP-R4-028	30334-71-5
DPyG 1,2-Diphytanoyl-*sn*-glycerol	LP-R4-150	32448-31-0
DSG 1,2-Distearoyl-*sn*-glycerol	LP-R4-029	1429-59-0

Tier 1

Phosphatidic Acids		
DLPA, Na 1,2-Dilauroyl -*sn*-glycero-3-phosphatidic acid, sodium salt	LP-R4-121	108321-06-8
DMPA, Na 1,2-Dimyristoyl-*sn*-glycero-3-phosphatidic acid, sodium salt	LP-R4-024	80724-31-8
DPPA, Na 1,2-Dipalmitoyl-*sn*-glycero-3-phosphatidic acid, sodium salt	LP-R4-025	71065-87-7
DSPA, Na 1,2-Distearoyl-*sn*-glycero-3-phosphatidic acid, sodium salt	LP-R4-026	108321-18-2
Phosphoglycerols		
DLPG, Na 1,2-Dilauroyl-*sn*-glycero-3-phosphoglycerol, sodium salt	LP-R4-079	73548-69-3
DMPG, Na 1,2-Dimyristoyl-*sn*-glycero-3-phosphoglycerol, sodium salt	LP-R4-015	200880-40-6
DMP-*sn*-1-G, NH_4 1,2-Dimyristoyl-*sn*-glycero-3-phospho-*sn*-1-glycerol, amm. salt	LP-R4-040	

Abbreviation Product Description	**Item #**	**CAS Number**
Phosphoglycerols *continued*		
DPPG, Na 1,2-Dipalmitoyl-*sn*-glycero-3-phosphoglycerol, sodium salt	LP-R4-016	200880-41-7
DSPG, Na 1,2-Distearoyl-*sn*-glycero-3-phosphoglycerol, sodium salt	LP-R4-017	124011-52-5
DSP-*sn*-1-G, Na 1,2-Distearoyl-*sn*-glycero-3-phospho-*sn*-1-glycerol, sodium salt	LP-R4-035	148553-48-4
Phosphoserines		
DPPS, Na 1,2-Dipalmitoyl-*sn*-glycero-3-phospho-L-serine, sodium salt	LP-R4-081	145849-32-7
Phosphoethanolamines		
DLPE 1,2-Dilauroyl-*sn*-glycero-3-phosphoethanolamine	LP-R4-064	42436-56-6
DMPE 1,2-Dimyristol-*sn*-glycero-3-phosphoethanolamine	LP-R4-018	998-07-2
DOPE 1,2-Dioleoyl-*sn*-glycero-3-phosphoethanolamine	LP-R4-069	4004-05-1
DPPE 1,2-Dipalmitoyl-*sn*-glycero-3-phosphoethanolamine	LP-R4-019	923-61-5
1,3-DPPE 1,3-Dipalmitoyl-*sn*-glycero-2-phosphoethanolamine	LP-R4-167	67303-93-9
DPyPE 1,2-Diphytanoyl-*sn*-glycero-3-phosphoethanolamine	LP-R4-147	201036-16-0
DSPE 1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine	LP-R4-020	1069-79-0

Tier 2

Phosphocholines		
DAPC 1,2-Diarachidoyl-*sn*-glycero-3-phosphocholine	LP-R4-122	61596-53-0
DLPC 1,2-Dilauroyl-*sn*-glycero-3-phosphocholine	LP-R4-101	18194-25-7
DMPC 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine	LP-R4-058	18194-24-6
DOPC 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine	LP-R4-070	4235-95-4
DPPC 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine	LP-R4-057	63-89-8
DPPC 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine, (short route)	LP-R4-108	63-89-8
DPePC, Chloride 1,2-Dipalmitoyl-*sn*-glycero-O-ethyl-3-phosphocholine, chloride	LP-R4-095	328250-18-6

Abbreviation Product Description	Item #	CAS Number
Phosphocholines *continued*		
DPePC, Triflate 1,2-Dipalmitoyl-*sn*-glycero-O-ethyl-3-phosphocholine, triflate (trifluoromethanesulfonate)	LP-R4-102	474945-32-9
DSPC 1,2-Distearoyl-*sn*-glycero-3-phosphocholine	LP-R4-076	816-94-4
MPEGylated (Methoxypolyethyleneglycol-) Phospholipids		
MPEG-2000-DMPE N-(Carbonyl-methoxypolyethyleneglycol-2000)-1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-123	
MPEG-5000-DMPE N-(Carbonyl-methoxypolyethyleneglycol-5000)-1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-077	
MPEG-2000-DPPE N-(Carbonyl-methoxypolyethyleneglycol 2000)-1,2 dipalmitoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-080	205494-72-0
MPEG-5000-DPPE N-(Carbonyl-methoxypolyethyleneglycol 5000)-1,2 dipalmitoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-075	205494-72-0
MPEG-750-DSPE N-(Carbonyl-methoxypolyethyleneglycol 750)-1,2 distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-087	147867-65-0
MPEG-2000-DSPE N-(Carbonyl-methoxypolyethyleneglycol 2000)-1,2 distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-039	147867-65-0
MPEG-5000-DSPE N-(Carbonyl-methoxypolyethyleneglycol 5000)-1,2 distearoyl-*sn*-glycero-3-phosphoethanolamine, sodium salt	LP-R4-092	147867-65-0

Tier 3

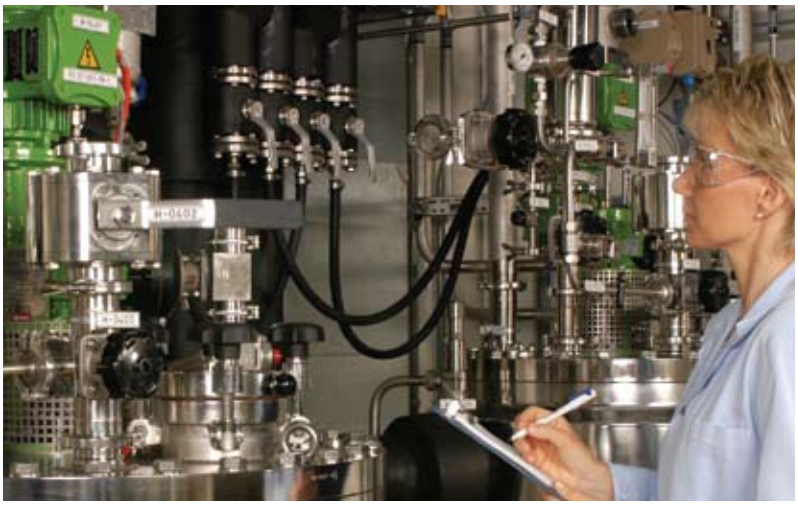
Phospholipids with Heterogeneous Fatty Acid Chains		
PLPC 1-Palmitoyl-2-lauroyl-*sn*-glycero-3-phosphocholine	LP-R4-151	
POPC 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine	LP-R4-031	26853-31-6
POPC 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (short route)	LP-R4-107	26853-31-6
SMPC 1-Stearoyl-2-myristoyl-*sn*-glycero-3-phosphocholine	LP-R4-152	
1,3-POPE 1-Palmitoyl-3-oleoyl-*sn*-glycero-2-phosphoethanolamine	LP-R4-163	884324-34-9

Abbreviation Product Description	**Item #**	**CAS Number**
Tier 4		
Phosphoglycerols with Heterogeneous Fatty Acid Chains		
POPG, Na 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol, sodium salt (short route)	LP-R4-073	202070-86-8
POPG, Na 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol, sodium salt	LP-R4-124	202070-86-8
POPG, NH_4 1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol, amm. salt	LP-R4-074	267228-70-6
Miscellaneous		
Cholesterol, Derivative of		
SCS Sodium cholesteryl sulfate	LP-R4-091	2864-50-8
Cholesterol	CH-0355	57-88-5
2-Lyso-phospholipids		
P-lyso-PC 1-Palmitoyl-2-lyso-*sn*-glycero-3-phosphocholine	LP-R4-078	17364-16-8
P-lyso-PC 1-Palmitoyl-2-lyso-*sn*-glycero-3-phosphocholine (short route)	LP-R4-098	17364-16-8
S-lyso-PC 1-Stearoyl-2-lyso-*sn*-glycero-3-phosphocholine	LP-R4-083	19420-57-6
S-lyso-PC 1-Stearoyl-2-lyso-*sn*-glycero-3-phosphocholine (short route)	LP-R4-113	19420-57-6
Ether Lipids		
1-O-Octadecyl-2-O-methyl-*sn*-glycerol	LP-R4-153	83167-59-3
Cationics		
DODMA Dimethylamino-1,2-dioleyloxy-propane	LP-04-110	104162-47-2
DOTAP Cl 2,3-Dioleoyloxy-propyl-trimethylammoniumchlorid	LP-04-117	132172-61-3
Fatty Acids		
Oliec acid	CH-0098	112-80-1
Palmitic acid	CH-0104	57-10-3
Stearic acid	CH-0129	57-11-4
Myristic acid	CH-0092	544-63-8

CONTACT GENZYME PHARMACEUTICALS FOR SYNTHETIC PHOSPHOLIPIDS

With experience in all stages of method development, scale-up and production, as well as adherence to the most stringent quality systems, Genzyme Pharmaceuticals is a reliable partner for the supply of these additional products and services:

- Amino acid derivatives for peptides and peptidomimetics
- Pseudoproline dipeptides
- Synthetic peptides
- Drug delivery technologies
- Custom development and GMP manufacture



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