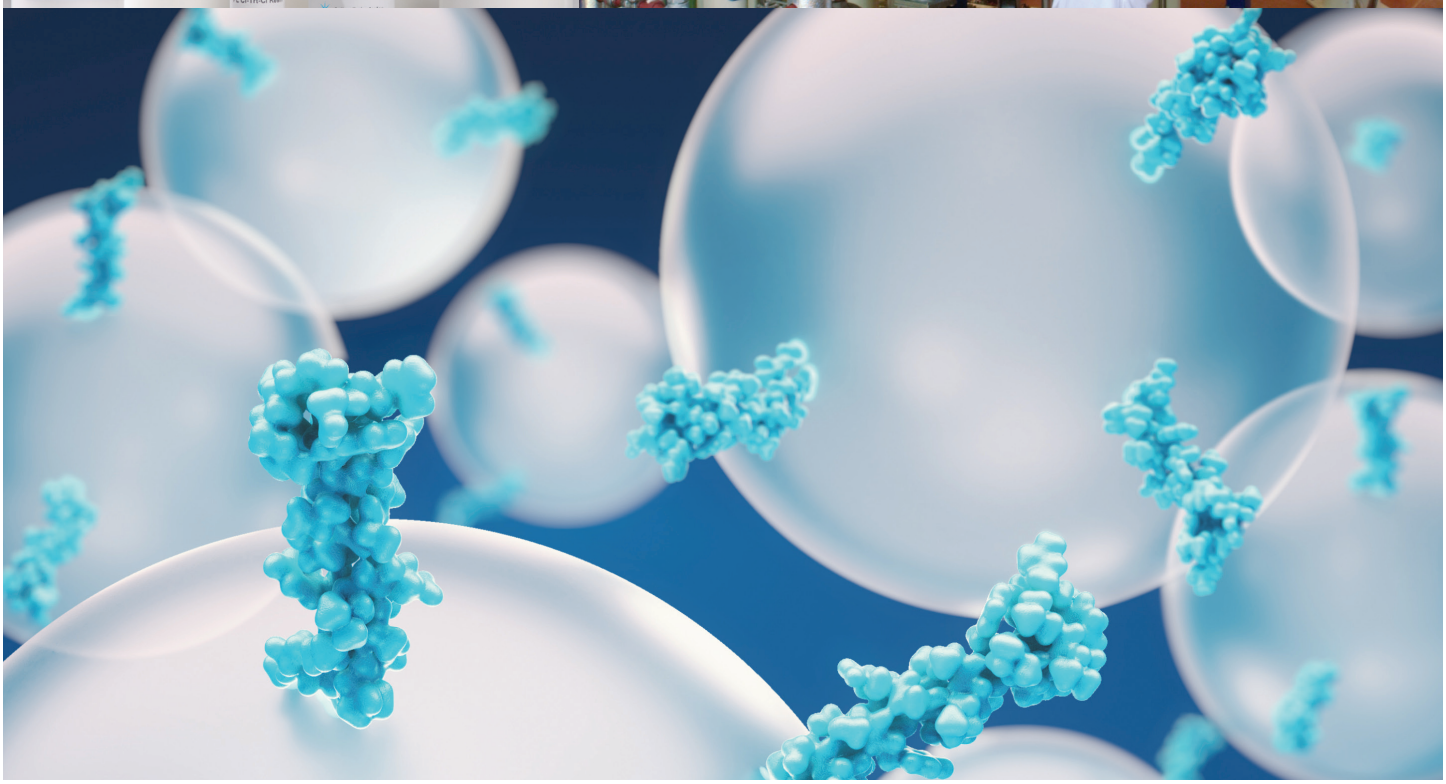
Agilent
Trusted Answers

Production-Scale Peptide Synthesis

Using Agilent StratoSpheres synthesis support resins



The benefits of StratoSpheres resins for peptide synthesis

The StratoSpheres product line encompasses a wide range of polymer resin supports for the development and large-scale manufacture of peptide active pharmaceutical ingredients (APIs).

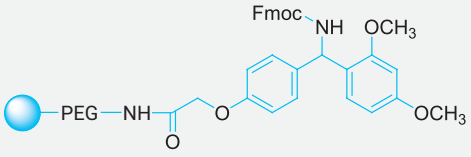
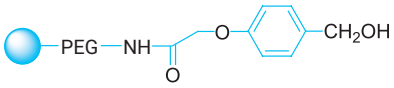
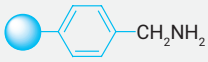
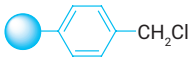
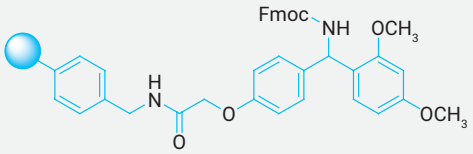
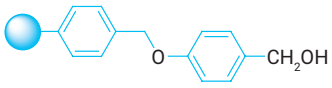
These include resins for Boc and Fmoc chemistries and include chloromethylstyrene (CMS), aminomethylstyrene (AMS), Rink, Wang, and AmphiSpheres (PEG modified polystyrene). StratoSpheres are high-performance, high-quality resins that enable you to make the highest quality APIs. They will decrease your time-to-market and accelerate the manufacturing process.

Manufacturing

Our large-scale resin manufacturing facility means that we have your needs covered from early development, through clinical trials to successful market launch, while providing you with long term security of supply.

- Copolymerization providing superior synthesis performance, better quality, and higher purity peptides.
- ISO 9001 manufacturing processes producing high quality resins, with tight particle size distribution, and high batch-to-batch reproducibility.
- Scale-up to ensure economy of scale, support for quality agreements and audits, and on-time delivery worldwide.

Ordering Guide

Product Name	Description and Structure	Loading	Part Number 100 g	Part Number 1 kg
AmphiSpheres 40 RAM AmphiSpheres 20 RAM	Fmoc Rink Amide (RAM) PEG polystyrene 	0.4 mmol/g 0.7 mmol/g	PL3867-4764 PL3867-4762	PL3867-6764 PL3867-6762
AmphiSpheres 20 HMP	Hydroxymethylphenoxy (HMP or Wang linker) PEG polystyrene 	0.7 mmol/g	PL3863-4762	PL3863-6762
PL-AMS	Aminomethylpolystyrene (AMS) 	0.4 mmol/g 0.6 mmol/g 1.0 mmol/g 2.0 mmol/g		PL1464-6749 PL1464-6769 PL1464-6799 PL1464-6789
PL-CMS	Chloromethylpolystyrene (CMS) or poly(styrene-co-chloromethylstyrene) 	0.4 mmol/g, 0.6 mmol/g and 1.0 mmol/g PL-CMS resin loadings are available upon request		
PL-Rink	Fmoc Rink amide AMS resin 	0.3 mmol/g 0.7 mmol/g	PL1467-4749 PL1467-4799	PL1467-6749 PL1467-6799
PL-Wang	4-Hydroxymethylphenoxymethyl polystyrene 	0.4 mmol/g 0.6 mmol/g 0.9 mmol/g 1.1 mmol/g PL-Wang resin loading is available upon request		PL1463-6749 PL1463-6769 PL1463-6799

Particle Technologies

Product Types

Quality

Our manufacturing techniques, particularly the use of copolymerization, provide the highest quality supports. Agilent is ISO 9001:2015 accredited, and we regularly entertain customer audits and quality inspections.

Capabilities

Agilent has a purpose-built production facility located in the UK.

Particles are produced by copolymerization in multi-kilogram quantities with batches typically up to 100 kg in size. Chemical modification (attachment of appropriate handles, linkers and functional groups) is carried out in our kilolab facilities (20 L glass vessels) from 100 g to 2 kg.

Larger production batches are produced in 50 L, 200 L or 500 L glass lined or hastelloy vessels in batches from 3 kg to 80 kg. Our annual capacity is currently ~ 2 tonnes.

What are StratoSpheres?

These products are specifically designed to provide enabling tools for organic chemists, particularly in the field of high throughput chemistry and drug design and development. The StratoSpheres range is synonymous with quality, at an affordable price.

Why use Polymer Beads?

Since the inception of solid phase synthesis by Bruce Merrifield in 1963, filtration of polymeric particles has proven to be much more efficient than many traditional work-up procedures such as liquid-liquid extraction, re-crystallization or chromatography.

Microporous Particles (1% DVB)

Microporous is the term used to describe very lightly crosslinked polystyrene beads. When dry, the beads are hard and spherical, however most of the functionality is contained within the interior of the particles. In order to gain access to the functional interior, it is necessary to swell the beads. In effect the polymer chains try to dissolve, but the light crosslinking ensures that the material remains in gel form. Once swollen, reagents can readily diffuse into the interior of the beads, and excess reagents or by-products can be washed away.

1% DVB (divinylbenzene) is sufficient to lightly crosslink polystyrene particles. When swollen in solvent, the particles will almost double in diameter (resulting in a six to eight fold increase in volume). Using a poor solvent will cause swollen beads to shrink and inhibit diffusion, meaning washing procedures frequently involve a selection of solvents which will swell and then shrink the beads. If the beads are to be dried, they should be washed in a solvent which causes them to reduce in size.

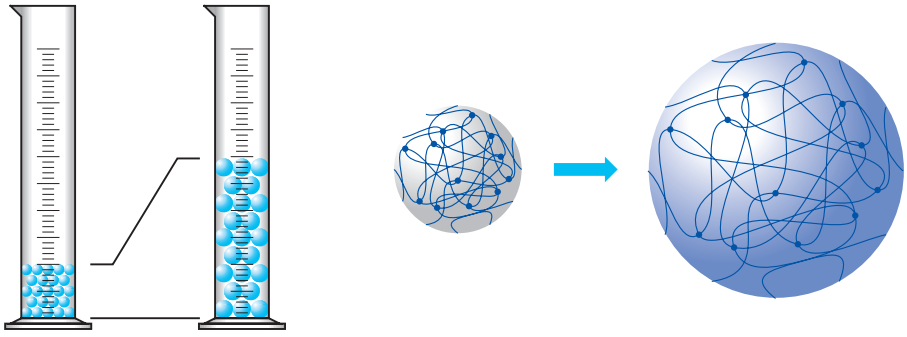


Figure 1. Solvation of microporous particles

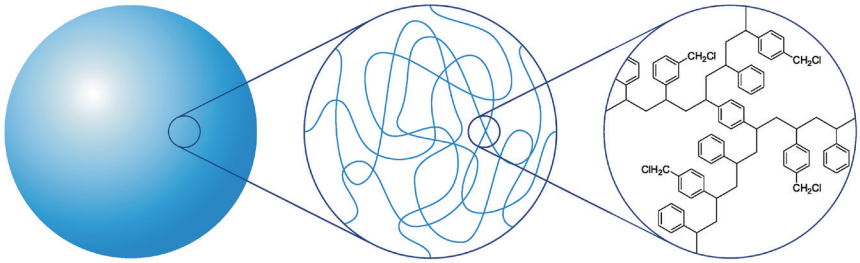


Figure 2. Composition of a microporous particle

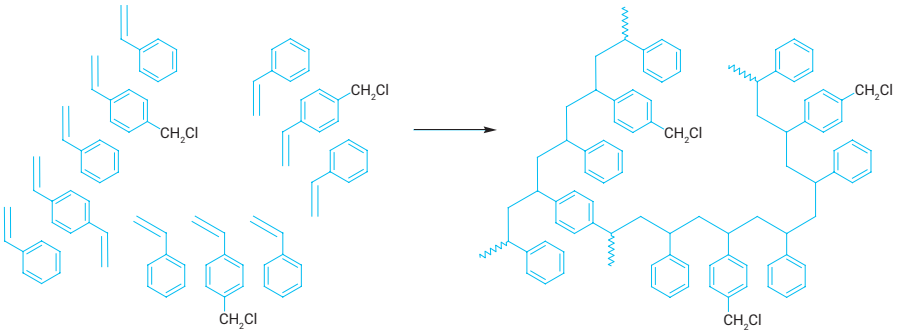


Figure 3. Composition of a microporous particle

Resin Loading

Using proprietary copolymerization techniques, the level of functionality in a polymer can be readily controlled without the problems that other methods of functionalization can bring. The materials obtained by copolymerization show much greater reproducibility and are free from by-products arising from side reactions.

The resin loading (and its swell) determines the concentration of reactive sites. Using a 1.0 mmol/g loading resin to produce a typical peptide, after about 8-10 amino acids have been coupled together, 1 g of peptide per gram of resin will be left. The peptide-resin assembly will begin to behave more like a peptide than polystyrene. If you wish to make a large peptide (20–30 amino acids), it will almost certainly be necessary to start with a resin with a lower loading. Agilent therefore offers a wide choice of resin loadings suitable for peptide synthesis.

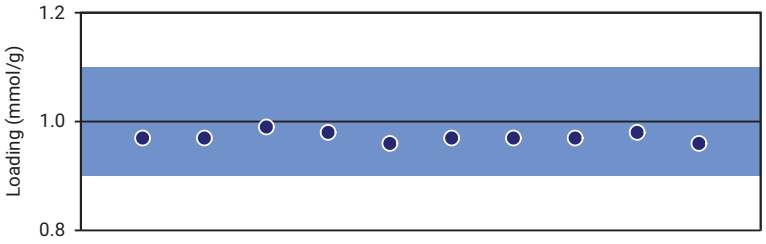


Figure 4. This plot shows the exceptional loading reproducibility of ten batches of PL-CMS 1.0 mmol/g, 75-150 µm manufactured over a period of more than a decade.

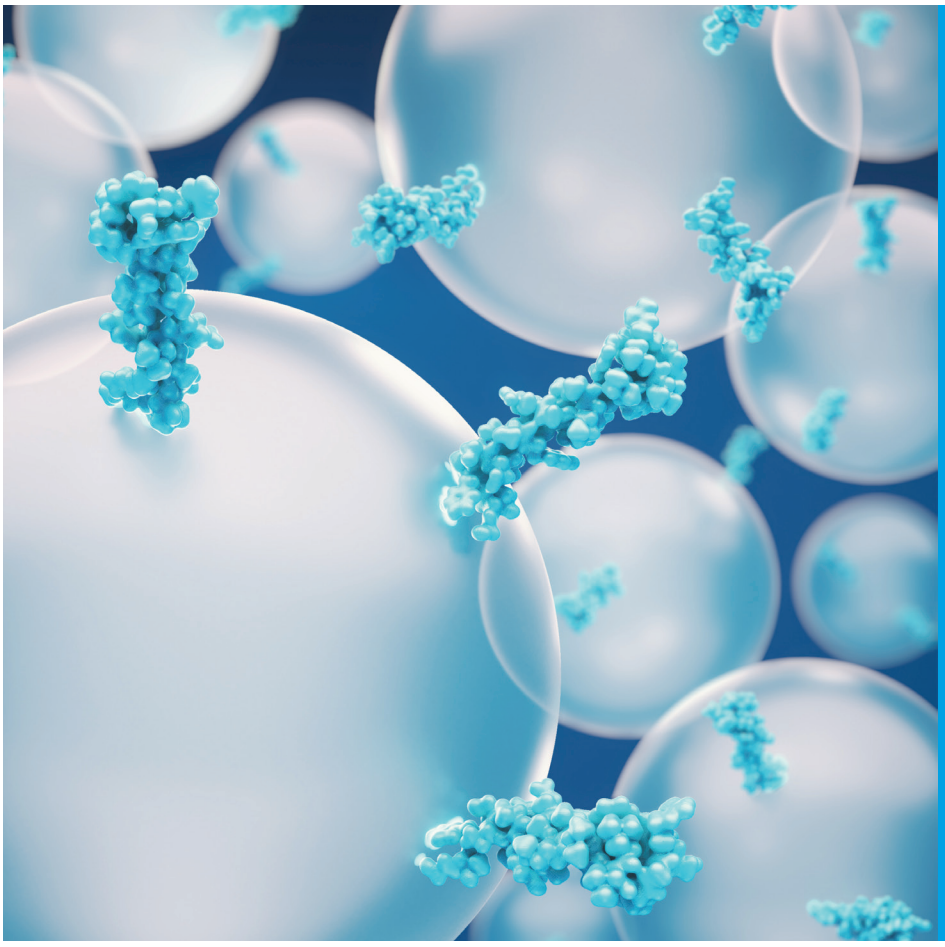
Particle Size

A wide range of particle sizes can be produced using suspension polymerization techniques. The most common size is 75-150 µm (100- 200 mesh) for solid phase peptide synthesis applications.

These beads are somewhat easier to handle than other particle size ranges, and can be readily dispensed using manual, semi-automated or automated techniques commonly employed in high throughput synthesis. The bead sizes are appropriate for repeated swell-shrink cycles that are encountered in solid phase peptide synthesis.

Hydrophobicity

Polystyrene is the most commonly used material for resins and supports. It is particularly easy to handle because it forms glassy beads when dry, and will swell readily in appropriate solvents. The choice of solvent to swell a microporous polystyrene is somewhat limited – the polystyrene backbone is hydrophobic and therefore requires the use of tetrahydrofuran, dichloromethane, toluene and other non-polar solvents. More polar solvents that may be used include dimethylformamide, dimethylacetamide and N-methylpyrrolidone.



Highest Level Reproducibility

Using proprietary copolymerization techniques gives StratoSpheres particles the highest level of reproducibility and exceptional quality.

Reliability

The reproducibility and reliability of StratoSpheres particles are essential for polymer-assisted synthesis.

Description:

PEG modified polystyrene

Application:

Solid Phase Peptide Synthesis

Additional Information:

Agilent manufactures in multi kg quantities. Please enquire for details.

www.agilent.com/chem/stratospheres

AmphiSpheres

Specifically designed for solid phase peptide synthesis, AmphiSpheres amphipathic resin is a key product in the StratoSpheres product family.

As the name suggests, this type of material contains both hydrophobic (polystyrene, PS) and hydrophilic (polyethyleneglycol, PEG) components. This subtly changes the swell characteristics of the material allowing a broader range of solvents to be used. At the same time, the active functionality is located at the end of a PEG chain which helps promote reactivity.

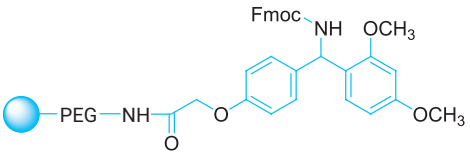
Two versions are available with differing PEG content:

- AmphiSpheres 20 has 20% w/w PEG content and a loading of 0.7 mmol/g.
- AmphiSpheres 40 has 40% w/w PEG content and a loading of 0.4 mmol/g.

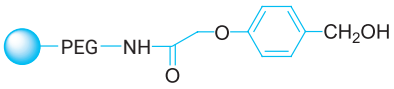
AmphiSpheres 20 contains 20% w/w polyethylene glycol and therefore retains a high loading per gram and has handling characteristics close to that of "glassy" polystyrene. This means that the yield of product is not compromised to the same degree as with larger PEG chains.

AmphiSpheres 40 contains 40% w/w polyethylene glycol and uses a longer PEG chain than AmphiSpheres 20. The amount of PEG is noticeable in that the material is more difficult to shrink down without becoming sticky. However the increased length of PEG chain can give significantly improved results in the synthesis of "difficult" peptide sequences.

Attachment of the appropriate linker or handle enables the material to be used for the synthesis of peptide acids and peptide amides.



AmphiSpheres RAM for peptide amides



AmphiSpheres HMP for peptide acids

Ordering Information

AmphiSpheres Resin	100 g	1 kg
AmphiSpheres 20 RAM, 0.7 mmol/g 75-150 µm	PL3867-4762	PL3867-6762
AmphiSpheres 20 HMP, 0.7 mmol/g 75-150 µm	PL3863-4762	PL3863-6762
AmphiSpheres 40 RAM, 0.4 mmol/g 75-150 µm	PL3867-4764	PL3867-6764

Description:

Aminomethylpolystyrene

Application:

Synthesis Support

Additional Information:

Agilent manufactures in multi kg quantities. Please enquire for details.

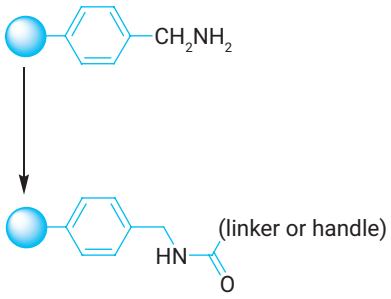
www.agilent.com/chem/stratospheres

PL-AMS Resin

Aminomethylstyrene resin is a particularly versatile material suitable for the attachment of a variety of spacers, handles and linkers (for use in solid phase synthesis).

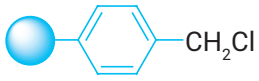
A number of methods exist for preparing aminomethylstyrene, usually by direct aminomethylation of polystyrene or conversion of chloromethyl functionalized particles. PL-AMS is prepared by the latter approach as this enables the copolymerized PL-CMS to be used as a starting material. It is therefore possible for a very wide range of loadings and particle size combinations to be prepared to suit any given application.

The preferred method of attachment of linkers or handles is through an amide bond. We prepare a number of products in this way, including PL-Rink.



Ordering Information

PL-AMS Resin (1% DVB)	1 kg
0.4 mmol/g, 75-150 µm	PL1464-6749
0.6 mmol/g, 75-150 µm	PL1464-6769
1.0 mmol/g, 75-150 µm	PL1464-6799
2.0 mmol/g, 75-150 µm	PL1464-6789



Description:

Chloromethylpolystyrene;
poly(styrene-co-chloromethylstyrene)

Application:

Acid Labile, Synthesis of Acids

Additional Information:

Agilent manufactures in multi kg quantities. Please enquire for details.

www.agilent.com/chem/stratospheres

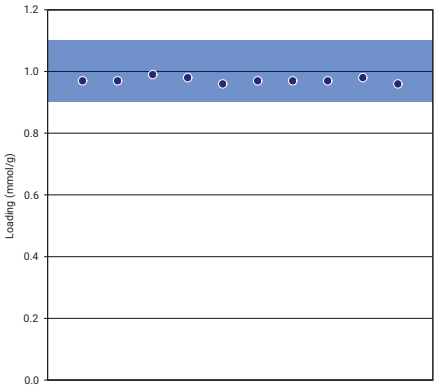


Figure 4. This plot shows the exceptional loading reproducibility of ten batches of PL-CMS 1.0 mmol/g, 75-150 µm manufactured over a period of more than a decade.

PL-CMS Resin

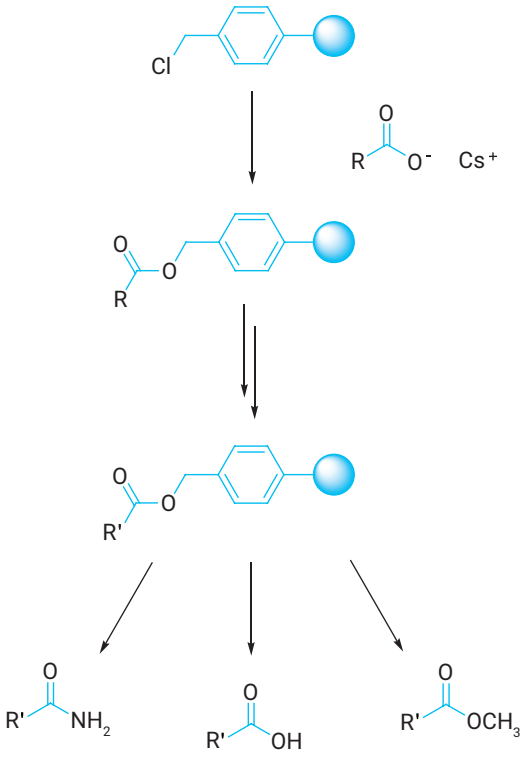
Commonly known as Merrifield resin, PL-CMS is a copolymer support designed for solid phase synthesis of peptides using Boc chemistry.

Boc-amino acids are typically attached to the resin as a cesium salt, although other techniques have also been used. A slight excess of acid is neutralized with cesium carbonate and the activated acid isolated by evaporation. A solution of the activated acid in DMF should be reacted with DMF-swollen PL-CMS at an elevated temperature (e.g. 50 °C) overnight. Cleavage typically requires treatment with very strong acid such as HF or TFMSA.

Other useful techniques for cleavage include saponification or hydrolysis to create free acids, trans-esterification to create methyl esters, or aminolysis to form carboxamides.

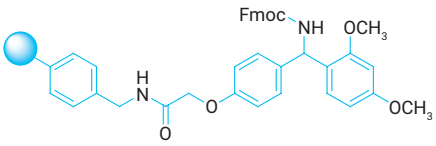
PL-CMS can be used to generate a variety of other supports by the attachment of appropriate linkers, particularly through Williamson ether synthesis.

Note: specialist equipment and training is required to safely perform HF cleavage operations.



Ordering Information

PL-CMS Resin (1% DVB)	**1 kg**
0.4 mmol/g, 0.6 mmol/g and 1.0 mmol/g PL-CMS resin loadings are available upon request	



Description:

Fmoc Rink amide AMS resin

Application:

Solid Phase Peptide Synthesis,
Synthesis of Amides

Additional Information:

Agilent manufactures in multi kg quantities. Please enquire for details.

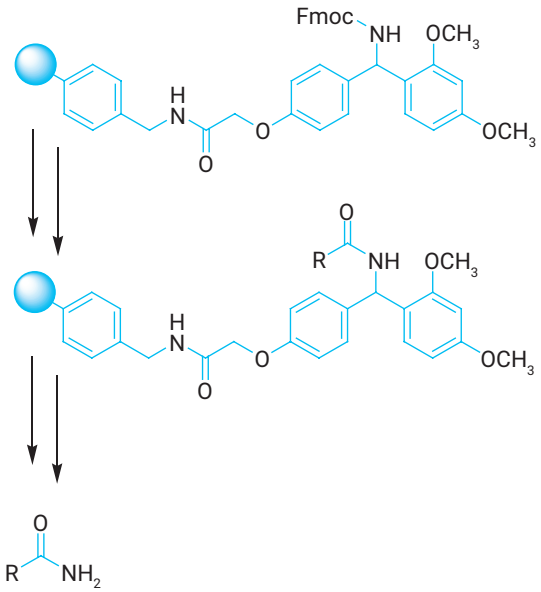
www.agilent.com/chem/stratospheres

PL-Rink Resin

Rink amide resins are often the support of choice for solid phase synthesis of peptide amides using Fmoc chemistry.

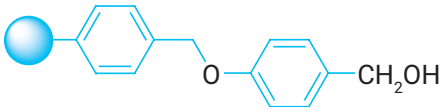
Prior to use, PL-Rink requires the removal of the Fmoc protecting group, which can be accomplished using standard deprotection protocols, eg: 20% piperidine in DMF for 30 min, followed by thorough washing prior to use. This resin is very versatile, as the initial amino acid can be attached using any conventional amide bond forming chemistries (symmetrical anhydrides, active esters etc). This coupling reaction can also be monitored using colorimetric tests such as the Kaiser test.

Following assembly of the protected peptide sequence, the N-terminal Fmoc protection is removed. At the same time, any tert-butyl based side chain protection is removed by cleavage of the peptide amide from the resin using 95% TFA solution.



Ordering Information

PL-Rink Resin (1% DVB)	100 g	1 kg
0.3 mmol/g, 75-150 µm	PL1467-4749	PL1467-6749
0.7 mmol/g, 75-150 µm	PL1467-4799	PL1467-6799



Description:

4-Hydroxymethylphenoxymethyl polystyrene

Application:

Solid Phase Peptide Synthesis, Synthesis of Carboxylic Acids

Additional Information:

Agilent manufactures in multi kg quantities. Please enquire for details.

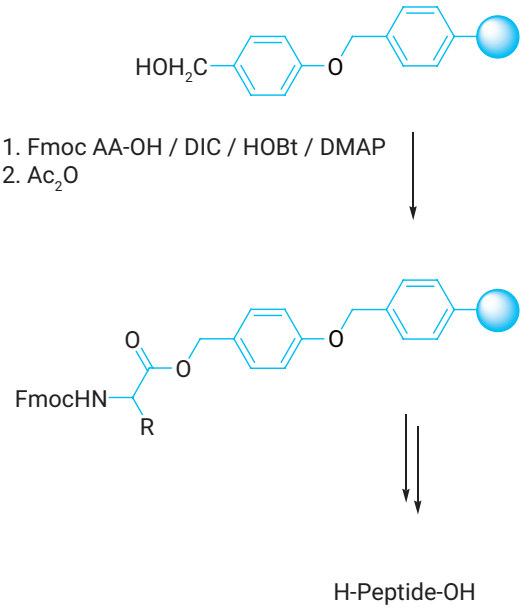
www.agilent.com/chem/stratospheres

PL-Wang Resin

PL-Wang is a 4-alkoxybenzylalcohol functionalized polystyrene, prepared from copolymerized PL-CMS. This support was originally designed for solid phase peptide synthesis using Fmoc protection strategies and is cleaved using ~ 95% TFA. It is also particularly useful for solid phase synthesis of small molecules which have a carboxylic acid functional group. Amino acids and carboxylic acids are attached to this resin through esterification. Care should be taken during the activation procedure to minimize any risk of racemization.

Acidic alcohols, particularly phenols, may also be attached to PL-Wang.

Wang resins have also been converted to carbamate functionalized materials in order to prepare substituted amines.



Ordering Information

PL-Wang Resin (1% DVB)	1 kg
0.4 mmol/g, 75-150 µm	PL1463-6749
0.6 mmol/g, 75-150 µm	PL1463-6769
0.9 mmol/g, 75-150 µm	PL1463-6799
1.1 mmol/g PL-Wang resin loading is available upon request	

Agilent chemistries: providing you confidence and control

Agilent is ISO 9001:2015 accredited and our technologies are widely used in chromatography, life science and pharmaceutical chemistries:

- Superior quality, reliable particles for bead-based assays, chromatography media, supports for peptide synthesis.
- Meticulous end-to-end monitoring of production to ensure the highest consistency and performance.
- More than 45 years of experience in polymer resin manufacturing beginning in Shropshire the UK in 1976.
- Committed to continuous development ahead of the curve with the technology.
- Support for quality agreements and audits, and on-time delivery worldwide.

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