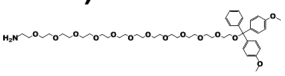
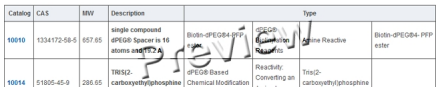
Advantages of Discrete PEG (dPEG™) over conventional alkyl (aliphatic methylene, X-(CH2)n-Y) spacers and linkers



Full Product Listing Page



Catalog	CAS	MW	Description	Type			
10010	1334172-58-5	657.65	single compound dPEG® Spacer is 16 atoms and MW 2 A	Biotin-dPEG®4-PFP ester	dPEG® Based Chemical Modification	Amine Reactive	Biotin-dPEG®4- PFP ester
10014	51805-45-9	286.65	TRIS(2-carboxyethyl)phosphine	dPEG® Based Chemical Modification	Reactivity: Converting an	Tris(2-carboxyethyl)phosphine	

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Broad range of crosslinkers and related products that now contain the discrete polyethylene glycol (dPEG) based spacers are preferred substitutes to aliphatic methylene chain spacers, X-(CH2)n-Y. Alkyl spacers have serious limitations and drawbacks in comparison to dPEG products. Conventional chain spacers have been widely used for many years for the lack of batter alternative.

With dPEG crosslinking products, you now have a set of tools that not only overcomes the drawbacks of the alkyl liners and spacers but also provides many new creative options for your research work with chain spacers.

dPEG linkers are extremely water soluble and hydrophilic, while the alkyl linkers are neither. The water solubility and hydrophilicity of dPEGs gives them a very large range of applications.

In contrast the opposite properties in the alkyl spacers have severely limited their actual and potential uses in biological systems. There are the aliphatic linker containing crosslinkers at the sulfo-NHS esters, which are soluble in water, commercially available. However, when the linkers are attached or crosslinked, the inherent hydrophobicity of the alkyl spacers returns, and all the disadvantages become apparent. The hydrophobic characteristics of the alkyl linkers and spacers are most often manifested through increased aggregation and precipitation in the modified or crosslinked products.

dPEG-containing compounds solve the problem by significantly decreasing and in some cases eliminating aggregation and precipitation. In addition to being water soluble, the dPEG linkers are organic soluble and can be used in organic media when this is desirable. DPEG likes the normal organics used for conventional linkers such as DMF and DMAC, but also especially likes methylene chloride.

Biotinylation reagents along with LC linker (amino caproic acid) are a good illustration of dPEG excellent performance in comparison to its analog.

Sulfo-NHS-LC-biotin is probably the most popular biotinylation currently available on the market. The hydrophilic LC linker is introduced to enhance the binding depth to streptavidin. Once labeled, the LC-biotin will seek hydrophobic regions in the protein and hide in them, making it less available to the streptavidin. At the same time, the hydrophobic LC-biotin labels causes serious agglomeration and precipitation problems.

There is agglomeration data available that compares the sulfo-NHS-LC-biotin with PN 10200, which has the dPEG4 spacer (the length of 2x LC). The data shows that human IgG biotinylated with the sulfo-NHS-LC biotin precipitates within a couple of weeks, while human IgG biotinylated with NHS-dPEG4 biotin (PN 10200) shows no agglomeration on the third week.

The comparison is dramatic. Customers who use MAL-dPEGx-NHS esters (PN10214, 10274, 10284, dPEG = 4,8,12, resp.) in place of the well known and widely used SMCC and related heterobifunctional crosslinkers, have made similar types of observations. In addition the use of

MAL-dPEGx-NHS esters often decrease or eliminate immunogenicity.

Application Note: Because some of our crosslinkers are viscous, we often recommend our customers initially dissolve the compound in an organic solvent rather than water. With peptide synthesis dPEG reagents, as well as with many of the modification reagents, the application is already going into an organic medium, so this property becomes very valuable to the application.

Immunogenicity of d-PEG-linked compounds.

PEG is well known to be non-immunogenic, which makes dPEG-linked compounds non-immunogenic as well. This is a huge advantage of dPEG products. In contrast, the alkyl linkers containing more than two or three methylene groups are highly immunogenic. Oftentimes the alkyl spacer length needs to be shortened to hide its undesirable property.

Even if the goal is a specific immune response, e.g., using a carrier protein conjugated to a peptide with a conventional linker to generate specific antibodies, conventional linkers contribute to a linker dependent response. It is anticipated that such response is eliminated with the use of dPEG linkers.

Control over distance/spacing.

For most applications that involve alkyl spacers it would be desirable to have longer spacers to control the distance of the conjugation species. However, with all inherent issues related to poor solubility, a tendency to exaserbate aggregtion and high immunogenicity, the control over conventional spacer distance remained limited for the last 10-15 years.

dPEG spacer properties impose absolutely no restrictions to increasing the length of the linkers. As already discussed above, the dPEG spacers are extremely water soluble, hydrophilic and non-immunogenic.

The use of the PEG spacer is not new. Yet available reagents are in high MW ranges (2,000 or 3,400, average n about = 45 and 75, respectively) have very long spacers (>250-300 Angstroms), and are complex polymer mixtures.

Now with the advent of the smaller dPEGs, which are single compounds that have spacers in a length range more useful for most applications, the opportunities to optimize length variable for most applications are readily available. There is a variety of different linkers and spacers ranging from dPEG4 to dPEG24, with the option to customize the length to any specific ethylene oxide unit number. You can now select spacer chain lengths from about 20 to 90 A. This option becomes increasingly important as more and more researchers are using modeling to predict the physical requirements of molecules. Also in a variety of other applications it is vital to be confident of working with a single spacer length and not a range of lengths.

Wide dPEG product selection and customization option allows you to find immediate potential solution for your chemical modification needs.

Modification reagents.

Timtec offers modification reagents, dPEGx products, which have no counterparts within alkyl chains. These products are specifically designed to be chemically bonded to a drug, protein or other biological compounds. Modification reagents increase water solubility, decrease immunogenicity and aggregation, as well as potentially decrease toxicity. The dPEGx products are terminated on one end with a methyl group and with amine (NHS ester), sulfhydryl (maleimide) or carbonyl (amine) reactive on the other. These discrete molecular weight products are available in the range from dPEG4 to dPEG24 or from about 200 to over 1000. Product numbers 10211, 10260 and 10262(link to these prducts).

Recently two more products were added PN10305 and PN 10307), which offer the potential to be released (e.g., as a pro-drug) or bonded to functionalities other than just the amine. For example, there are products that can bond to acids, aldehydes, and sulfhydryls. The latter are of growing interest as molecular engineers can introduce the sulfhydryl almost at will using site-directed mutagenesis.

Note: The different physical properties of dPEG-containing crosslinkers and modification reagents are initially perceived to be complicated in use. Many of the lower MW materials are viscous liquids that can be problematic to handle. Technical support is always available to assist our customers in handling products and using solvents and solvent systems efficiently to take full advantage of reagent properties. Contact TimTec with product related questions and for ordering.

Full Product Listing Page