letters 2.Vol.12

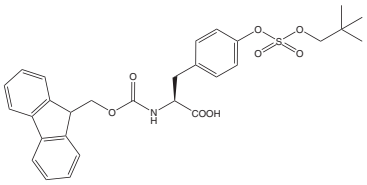
Novabiochem®
NEW • NEW • NEW

- Sulfoamino acid
- Unnatural amino acid
- N-Methylated amino acids
- High-load polar resin

NEW Derivatives for Fmoc SPPS

NEW • Sulfoamino acid

Fmoc-Tyr(SO_3nP)-OH



Features & Benefits

- Building block compatible with standard Fmoc SPPS methods
- Neopentyl sulfate is stable to TFA
- Neopentyl group is removed with NaN_3 or aq. $CH_3CO_2NH_4$

Novabiochem is pleased to offer Fmoc-Tyr(SO_3nP)-OH as an new important tool for the synthesis of sulfotyrosine-containing peptides.

Sulfation of tyrosine is an important post-translational modification that is involved in protein-protein recognition and is found in a number of biologically active peptides such as gastrin II, cholecystokinin, and caerulein [1].

The synthesis of sulfotyrosine-containing peptides is generally regarded as challenging owing to the instability of the sulfo group to acidic conditions. Post-synthetic sulfation [reviewed in 1] or low temperature TFA cleavage [2] have been traditionally used to overcome this limitation. However, the former is technically difficult and not compatible with all amino acid side chains and the latter is only partially effective. More recently, a number of research groups have found that protecting the sulfate stabilizes it during the TFA cleavage, enabling standard reaction conditions to be used without significant loss of the sulfate. The use of three protecting groups have been examined in detail: trichloroethyl (TCE) [3, 4], dichlorovinyl (DCV) [4] and neopentyl (nP) [5, 6].

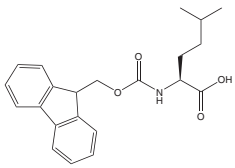
TCE undergoes loss of HCl in the presence of piperidine, and is therefore employed as its elimination product DCV [4]. However, the DCV group is not totally stable to piperidine and so a hindered base such as 2-methylpiperidine should be used for Fmoc removal to avoid premature loss of the protecting group [4]. Its removal is effected by reduction with H_2 and 10% Pd/C [4] or Zn/HCO_2NH_4 [3]. These requirements limit the utility of DCV protection in routine Fmoc SPPS.

The use of nP protection on the otherhand appears to offer considerable promise as the group is stable to piperidine and TFA, making Novabiochem's Fmoc-Tyr(SO_3nP)-OH stable to the standard conditions of Fmoc SPPS. Following TFA-mediated cleavage of the peptide from the resin, the nP can be removed efficiently by treatment of the partially protected peptide with excess NaN_3 in DMF or DMSO at 50 °C [5]. More conveniently, it may also be removed by overnight treatment of the peptide with 1 - 2 M ammonium acetate [6]. However, the yields in this latter approach can be variable and sequence dependent.

Cat.No.	Product	Contents	Price EUR
852347	Fmoc-Tyr(SO_3nP)-OH	1 g	185.00
NEW		5 g	750.00
	Other sulfotyrosine derivatives		
852103	Fmoc-Tyr(SO_3·NnBu_4)-OH	1 g	170.00
		5 g	680.00

NEW • Unnatural amino acids

Fmoc-hLeu-OH

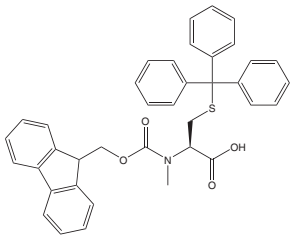


Fmoc-hLeu-OH is the latest addition to our range of side-chain amino-acid homologs.

Cat.No.	Product	Contents	Price EUR
852327	Fmoc-hLeu-OH	1 g	120.00
NEW		5 g	480.00
852267	Fmoc-hArg(Pbf)-OH	1 g	70.00
		5 g	280.00
852266	Fmoc-hCys(Trt)-OH	1 g	195.00
		5 g	775.00
852059	Fmoc-Hse(Trt)-OH	1 g	92.00
		5 g	366.00
852328	Fmoc-hPhe-OH	1 g	50.00
		5 g	195.00

NEW • N-Methylated amino acids

Fmoc-N-Me-Cys(Trt)-OH



Fmoc-N-Me-Asn(Trt)-OH, Fmoc-N-Me-Cys(Trt)-OH, Fmoc-N-Me-Lys(Boc)-OH, Fmoc-N-Me-His(Trt)-OH, Fmoc-N-Me-Met-OH and Fmoc-N-Me-Trp(Boc)-OH are the latest addition to our extensive range of Fmoc-protected *N*-Me amino acids. Introduction of these derivatives is best achieved using HATU/DIPEA. Preactivation times should be kept to a minimum to avoid racemization.

Fmoc-N-Me-Cys(Trt)-OH has been used as a tool to prepare peptide thioesters. Under acidic conditions, the residue attached to the amino group of *N*-methylcysteine can migrate to the cysteinyl thiol group, resulting in the formation of a peptide thioester (Figure 1) [7, 8]. This *N*- to *S*-migration can be reversed by dissolution of the peptide in pH 8 buffer. Addition of a thiol compound to an acidic solution of the peptide will result in cleavage at the *N*-methylcysteine with formation of a peptide thioester derived from the *N*-terminal fragment.

Fmoc-N-Me-His(Trt)-OH is poorly soluble in DMF or NMP. However, it does dissolve upon activation with HBTU/DIPEA.

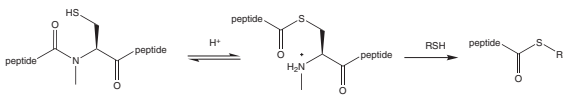


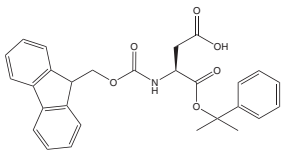
Fig. 1: Formation of peptide thioesters via *N*- to *S*-shift.

Cat.No.	Product	Contents	Price EUR
	NEW N-Methylated amino acids		
852353	Fmoc-N-Me-Asn(Trt)-OH	250 mg	75.00
NEW		1 g	225.00
852348	Fmoc-N-Me-Cys(Trt)-OH	250 mg	160.00
NEW		1 g	480.00
852361	Fmoc-N-Me-Lys(Boc)-OH	250 mg	160.00
NEW		1 g	480.00
852354	Fmoc-N-Me-His(Trt)-OH	250 mg	160.00
NEW		1 g	480.00
852362	Fmoc-N-Me-Met-OH	1 g	69.00
NEW		5 g	269.00
852344	Fmoc-N-Me-Trp(Boc)-OH	250 mg	160.00
NEW		1 g	480.00
852138	Fmoc-MeAla-OH	1 g	69.00
		5 g	269.00
852248	Fmoc-D-N-MeAla-OH	1 g	120.00
		5 g	480.00
852329	Fmoc-N-Me-Asp(OtBu)-OH	250 mg	75.00
		1 g	225.00

852330	Fmoc-N-Me-Glu(OtBu)-OH	250 mg	75.00
		1 g	225.00
852231	Fmoc-MeIle-OH	1 g	69.00
		5 g	269.00
852139	Fmoc-MeLeu-OH	1 g	69.00
		5 g	269.00
852137	Fmoc-MePhe-OH	1 g	69.00
		5 g	269.00
852055	Fmoc-Sar-OH	5 g	48.00
		25 g	169.00
852289	Fmoc-N-Me-Ser(tBu)-OH	250 mg	75.00
		1 g	225.00
		5 g	900.00
852331	Fmoc-N-Me-Thr(tBu)-OH	250 mg	75.00
		1 g	225.00
852332	Fmoc-N-Me-Tyr(tBu)-OH	250 mg	75.00
		1 g	225.00
852230	Fmoc-MeVal-OH	1 g	69.00
		5 g	269.00

NEW • Selectively-protected Asp derivative

Fmoc-Asp-O-2-PhiPr



Features & Benefits

- Tool for on-resin synthesis of Asp-containing cyclic peptides
- PhiPr group selectively removed with 1% TFA in DCM

Fmoc-Asp-O-2-PhiPr is a useful new tool for the on-resin synthesis of C-terminally modified or cyclic peptides. Anchoring of the Asp β-carboxyl to a Wang type resin and subsequent Fmoc synthesis results in a protected resin-bound peptide bearing a selectively protected *C*-terminal carboxyl functionality. Treatment with 1% TFA in DCM unmasks this carboxyl [9], allowing it to be activated and coupled to nucleophiles such as *N*-terminal and side-chain amino groups to make the corresponding cyclic peptide (Figure 2) or added nucleophiles such as amines or thiols to generate the respective *C*-terminal carboxamide or thioester.

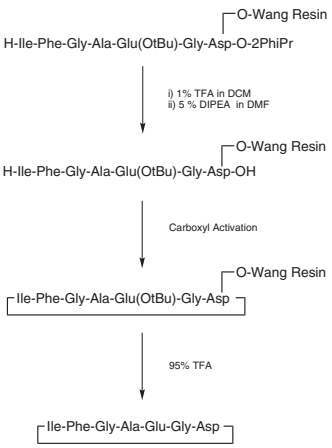


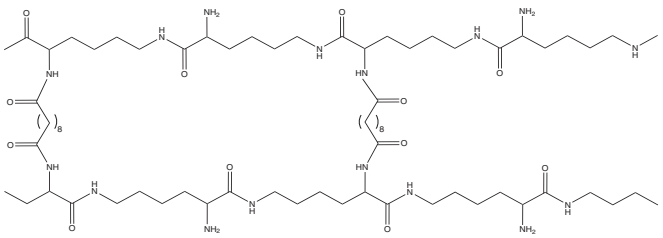
Fig. 2: Synthesis of cyclic peptides using Fmoc-Asp-O-2-PhiPr.

Cat.No.	Product	Contents	Price EUR
852335	Fmoc-Asp-O-2-PhiPr	1 g	160.00
NEW		5 g	640.00
	Other PhiPr derivatives		
852086	Fmoc-Asp(O-2-PhiPr)-OH	1 g	130.00
		5 g	540.00
852117	Fmoc-Glu-O-2-PhiPr	1 g	160.00
852085	Fmoc-Glu(O-2-PhiPr)-OH	1 g	130.00
		5 g	540.00

NEW High-load polar resins for large scale synthesis

NEW • SpheriTide resins

Features & Benefits



- Loading of base polymer is approximately 3 mmol/g
- Loading of HMPA SpheriTide resin is typically 1.8 - 2.2 mmol/g; Rink Amide SpheriTide 1.0 - 1.3 mmol/g
- Biodegradable - polymer is completely degraded by proteolysis
- Starting materials for resin derived from renewable resources
- Low bed-volume to substitution ratio, means less solvent waste and lower excesses of reagents
- Ideal for research and large scale batch synthesis
- Compatible with a wide range of polar and nonpolar solvents, including MeOH, water, DCM, DMF

SpheriTide resin is a novel hydrophilic, high-load support for both research and large-scale production of peptides that consists of poly-ε-lysine cross-linked with sebacic acid. The loading of the base polymer is 3 mmol/g, which typically provides Rink amide and HMPA functionalized supports of 1.0 - 1.3 mmol/g and 1.8 - 2.2 mmol/g respectively. The resin has a high loading to swelling ratio which helps minimize resin bed volumes, leading to the requirement for lower reagent excesses and reduced volumes of wash solvents. Furthermore, the polar backbone of the polymer allows the resin to swell in a wide range of solvents, including water, DMF, DCM and MeOH.

In traditional polymers formed by free-radical polymerization and post-synthesis functionalization, such as those based on chloromethyl polystyrene, the cross-linking and functionalization tends to cluster. This leads to batch-to-batch irreproducibilty due to inconsistent levels of cross-linking, and introduces pockets of hindrance which ultimately leads to problems with formation of deletion and truncation sequences. With SpheriTide resins. the functionalization is evenly distributed because the structural architecture derived from the polymer ε-lysine, and this leads to better, more uniform reaction kinetics.

A further unique aspect of SpheriTide resins is that the starting materials used in its production are both obtained from renewable biological sources. Poly-ε-lysine is a naturally occurring short-chain polyamide consisting of 25-35 lysine residues linked through their α-carboxyl and ε-amino groups that is produced by bacterial fermentation for use as a food preservative, whereas sebacic acid is made from castor oil for use in the textile industry. SpheriTide is thus one of the first sustainable supports especially designed for peptide synthesis - it is also biodegradable as the polyamide backbone is susceptible to proteolysis.

Cat.No.	Product	Contents	Price EUR
	NEW High-load, polar resin for large scale synthesis		
855149	Rink Amide SpheriTide resin	1 g	70.00
NEW		5 g	275.00
		25 g	995.00
855150	HMPA SpheriTide resin	1 g	54.00
NEW		5 g	216.00
		25 g	864.00

References

1. C. Seibert & T. P. Sakmar (2008) *Biopolymers* (Pept. Sci.), **90**, 459.
2. K. Kitagawa, et al. (2001) *J. Org. Chem.*, **66**, 1.
3. A. Bunschoten, et al. (2009) *Chem. Commun.*, 2999.
4. A. M. Ali & S. D. Taylor (2009) *Angew.Chem. Int. Ed.*, **48**, 2024.
5. L. S. Simpson & T. S. Widlanski (2006) *J. Am. Chem. Soc.*,**128**, 1605.
6. L. S. Simpson, et al. (2009) *Chemistry & Biology*, **16**, 153.
7. H. Hojo, et al. (2007) *Tetrahedron Lett.*, **48**, 25.
8. L. A. Erlich, et al. (2010) *Org. Biomol. Chem.* **8**, 2392.
9. F. Dick, et al. in "Peptides 1996, Proc. of 24th European Peptide Symposium", R. Ramage & R. Epton (Eds.), Mayflower Scientific Ltd., Birmingham, 1998, pp. 339.

For more information please contact our local offices:

France: 0800 699 620
Germany: 0800 6931 000
Italy: 00800 1166 8811
Spain: 00800 1166 8811
Switzerland: 00800 1166 8811
United Kingdom: 0800 622935

For other countries across Europe, please call:
+44 (0) 115 943 0840

For Technical Service contact:
technical@novabiochem.com

MERCK MILLIPORE

www.merckmillipore.com/novabiochem

W.28017.3