Novabiochem®
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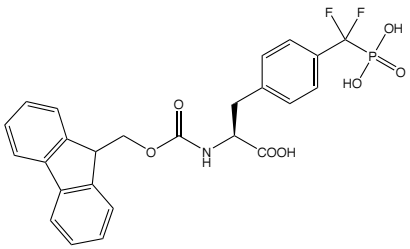
Contents

NEW Building blocks for Fmoc SPPS

NEW Non-hydrolyzable phosphoamino acid

Fmoc-Phe($CF_2PO_3H_2$)-OH (Fmoc-F_2Pmp-OH)



Features & Benefits

- Non-hydrolyzable phosphotyrosine analog
- Compatible with standard Fmoc SPPS methods
- Unprotected side chain obviates need for harsh deprotection conditions

Phosphorylation and de-phosphorylation of key tyrosine residues within cytoplasmic proteins by protein-tyrosine kinases (PTKs) and phosphatases (PTPs), respectively, are key events in the cell signaling pathway. Phosphotyrosine-containing peptides are thus important tools for studying PTPs [1] and the phosphotyrosine-binding SH2 and PTB domains [2] of

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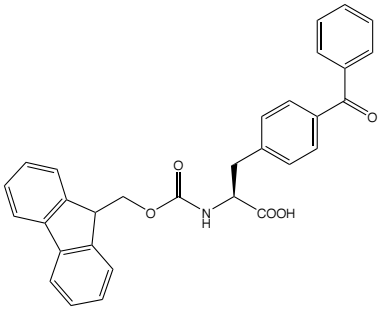
signaling proteins. However, the transient nature of the tyrosine phosphate group in biological systems has led to the development of hydrolytically stable pTyr analogs in which the oxygen of the phenyl phosphate has been replaced by a methylene group such by phosphonomethylphenylalanine (Pmp) [3]. This isostere, whilst overcoming this inherent instability, appears to be a poor substitute for pTyr, as substitution of pTyr by Pmp often leads to a significant reduction in biological activity [4]. Burke and coworkers [see review 5] postulated this effect was due to the lack of the H-bond acceptor phenyl oxygen and incomplete ionization of the phosphonic acid at neutral pH (Pmp, pKa2 7.72 vs pTyr, pKa2 6.22). To overcome these limitations, they developed the pTyr isostere difluorophosphonophenylalanine (F_2Pmp). With a pKa2 of 5.71 it is fully ionized at neutral pH and the methylene fluorine atom can undergo H-bonding. Peptides substituted with F_2Pmp exhibit higher binding affinities to SH2 domains than Pmp analogs [6]. 1000-Fold enhancements in affinities of F_2Pmp-containing peptide compared with those containing Pmp have been observed in assays against PTPs [7]. Furthermore, peptides containing F_2Pmp may also be used as antigens to raise antibodies against phosphoproteins [8].

The first commercially available derivative for the incorporation of F_2Pmp by Fmoc SPPS was Fmoc-F_2Pmp$(OEt)_2$-OH [5]. Whilst coupling of this fully protected compound is straightforward, removal of the two ethyl groups has proven to be highly problematic, as the process requires the use of aggressive reagents such as TMSBr and TMSOTf that causes extensive degradation of peptides. For this reason, the Novabiochem® brand is pleased to introduce Fmoc-F_2Pmp-OH [9]. As the side chain phosphate moiety is unprotected, TFA cleavage generates the desired phosphonopeptide cleanly without the need for deleterious harsh acid treatments. However, lack of phosphate protection does result in sluggish coupling of Fmoc-F_2Pmp-OH and the following amino acid derivative. Therefore, completion of both these coupling reactions should be checked using Kaiser or TNBS tests, and extended or repeat reactions should be performed if necessary. Burke and coworkers report the use of BOP/HOBt/DIPEA for the coupling of Fmoc-F_2Pmp-OH [10].

852288 *NEW*	Fmoc-Phe($CF_2PO_3H_2$)-OH	100 mg
852069	Fmoc-Ser(PO(OBzl)OH)-OH	1 g 5 g
852244	Fmoc-D-Ser(PO(OBzl)OH)-OH	1 g 5 g
852070	Fmoc-Thr(PO(OBzl)OH)-OH	1 g 5 g
852245	Fmoc-D-Thr(PO(OBzl)OH)-OH	1 g 5 g
852071	Fmoc-Tyr(PO(OBzl)OH)-OH	1 g 5 g
852246	Fmoc-D-Tyr(PO(OBzl)OH)-OH	1 g 5 g
852058	Fmoc-Tyr(PO_3H_2)-OH	1 g 5 g
852090	Fmoc-Tyr($PO(NMe_2)_2$)-OH	1 g 5 g

NEW Photoactivatable amino acid derivative

Fmoc-*p*-Bz-Phe-OH (Fmoc-Bpa-OH)



Features & Benefits

- Photoactivatable cross-linker
- Compatible with standard Fmoc SPPS methods

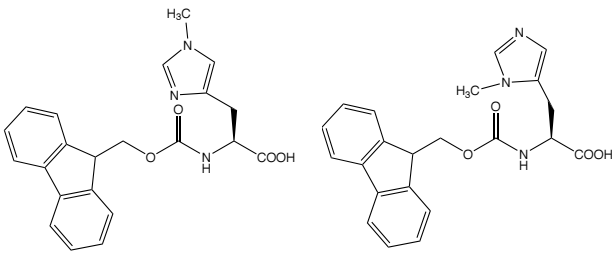
Fmoc-*p*-Bz-Phe-OH-OH is a useful tool for preparing photoactivatable peptide-based affinity probes [11]. On photolysis at 366 nm, Benzoylphenylalanine (Bpa) generates a biradical that has a preference for insertion into C-H bonds, particularly those of Leu, Val and Met side chains.

The derivative can be introduced using standard coupling method such as PyBOP and is stable to conditions used in peptide chain extension. For the cleavage of Bpa containing peptide from the resin, the use of thiols and silanes should be avoided as dithioketal formation and reduction, respectively, have been observed.

852287	Fmoc-*p*-Bz-Phe-OH	1 g
NEW		5 g

NEW Fmoc amino acid derivatives

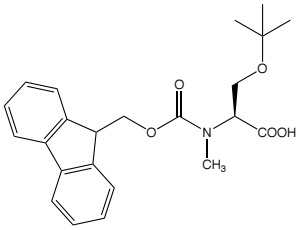
Fmoc-His(1-Me)-OH/Fmoc-His(3-Me)-OH



Fmoc-His(1-Me)-OH and Fmoc-His(3-Me)-OH are building blocks for the introduction of His(1-Me) and His(3-Me) by Fmoc SPPS. They have been coupled using BOP [12], HBTU [13] and HCTU [14] without reports of racemization, despite lacking imidazole protection.

852258	Fmoc-His(1-Me)-OH	250 mg
NEW		1 g
852286	Fmoc-His(3-Me)-OH	250 mg
NEW		1 g

Fmoc-N-Me-Ser(tBu)-OH



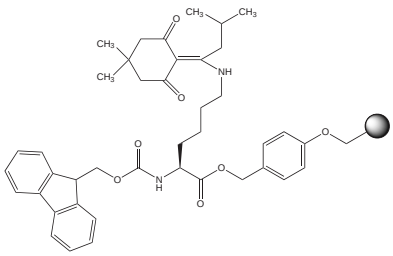
Fmoc-M-Me-Ser(tBu)-OH is the latest addition to our range of N-methylated amino acids.

852289	Fmoc-N-Me-Ser(tBu)-OH	250 mg
NEW		5 g

Novabiochem´s other N-methyl amino acids

852138	Fmoc-MeAla-OH	1 g
		5 g
852248	Fmoc-D-MeAla-OH	1 g
		5 g
852231	Fmoc-MeIle-OH	1 g
		5 g
852139	Fmoc-MeLeu-OH	1 g
		5 g
852137	Fmoc-MePhe-OH	1 g
		5 g
852055	Fmoc-Sar-OH	5 g
		25 g
852230	Fmoc-MeVal-OH	1 g
		5 g

NEW Resin for the synthesis of branched & cyclic peptides



Features & Benefits

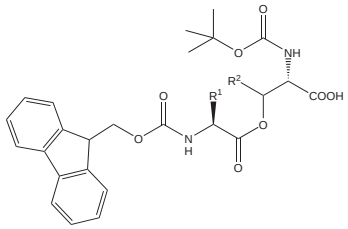
- Allow on-resin synthesis of cyclic peptides
- Ideal for high-throughput synthesis of libraries of cyclic peptides

Fmoc-Lys(ivDde)-Wang resin is a useful tool for the synthesis of branched and cyclic peptides, as peptides carrying a side chain modification on a C-terminal lysine residue. The ε-amino protecting group, ivDde, is stable to piperidine but can easily be removed by treatment with 2% hydrazine in DMF, leaving all other protecting groups intact [15]. This allows selective deprotection of the Lys residue for subsequent side-chain modification.

Removal of ivDde can either be carried out in a batch-wise or continuous flow manner. In the latter case it can be followed spectrophotometrically at the same wavelength used to monitor Fmoc removal, as the reaction-product of ivDde with hydrazine is an chromophoric indazole derivative. It is important to note that, as hydrazine will remove Fmoc, assembly of the peptide backbone must be completed prior to deprotection of the ivDde side chain. The N-terminus of the peptide should be protected with Boc. This can be achieved either by direct incorporation of the N-terminal residue as a Boc protected amino acid or acylation of the free N-terminal amino group with Boc_2O.

856186	Fmoc-Lys(ivDde)-Wang resin	1 g
NEW		5 g

NEW Structure breaking isoacyl dipeptides



Boc-Ser(Fmoc-Asp(OtBu))-OH: $R^1 = CH_2COOtBu$; $R^2 = H$
Boc-Thr(Fmoc-Asp(OtBu))-OH: $R^1 = CH_2COOtBu$; $R^2 = CH_3$
Boc-Thr(Fmoc-Arg(Pbf))-OH: $R^1 = (CH_2)_3NHC(=NH)NHPbf$; $R^2 = CH_3$
Boc-Ser(Fmoc-Glu(OtBu))-OH: $R^1 = (CH_2)_2COOtBu$; $R^2 = H$
Boc-Thr(Fmoc-Glu(OtBu))-OH: $R^1 = (CH_2)_2COOtBu$; $R^2 = CH_3$
Boc-Ser(Fmoc-Leu-OH: $R1 = CH_2CH(CH_2CH_3)CH_3$; $R^2 = CH_3$
Boc-Thr(Fmoc-Leu-OH: $R1 = CH_2CH(CH_2CH_3)CH_3$; $R^2 = H$
Boc-Ser(Fmoc-Met)-OH: $R1 = (CH_2)_2SCH_3$; $R^2 = H$
Boc-Thr(Fmoc-Met)-OH: $R1 = (CH_2)_2SCH_3$; $R^2 = CH_3$
Boc-Ser(Fmoc-Val)-OH: $R1 = CH(CH_3)_2$; $R^2 = H$
Boc-Thr(Fmoc-Val)-OH: $R1 = CH(CH_3)_2$; $R^2 = CH_3$

Features & Benefits

- Improved yields and purities of insoluble aggregated peptides
- Purification can be carried out on the soluble depsipeptide prior to conversion to native sequence
- Use of an isoacyl dipeptide at the C-terminus of a peptide prevents epimerization during fragment coupling and cyclization reactions

The Novabiochem® brand is pleased to offer Boc-Ser(Fmoc-Leu)-OH Boc-Thr(Fmoc-Leu)-OH as the latest additions to our range of isoacyl dipeptides [16, 17].

Isoacyl dipeptides are powerful tools for enhancing synthetic efficiency in Fmoc SPPS [18 - 20]. Not only does their use aid the synthesis of difficult sequences, but it enables aggregation prone insoluble peptides to be purified in their soluble depsipeptide form prior to conversion to the native sequence.

An important further application of isoacyl dipeptides is in fragment condensation as their use at the C-terminus of protected peptides enables coupling [21 - 23] and cyclization [24] to be carried out without risk of epimerization.

852262	Boc-Ser(Fmoc-Leu)-OH	1 g
NEW		5 g
852263	Boc-Thr(Fmoc-Leu)-OH	1 g
NEW		5 g
852174	Boc-Ser(Fmoc-Ala)-OH	1 g
		5 g
852249	Boc-Ser(Fmoc-Arg(Pbf)-OH	1 g
		5 g
852257	Boc-Ser(Fmoc-Asn(Trt)-OH	1 g
		5 g
852298	Boc-Ser(Fmoc-Asp(OtBu))-OH	1 g
		5 g
852256	Boc-Ser(Fmoc-Gln(Trt))-OH	1 g
		5 g
852295	Boc-Ser(Fmoc-Glu(OtBu))-OH	1 g
		5 g
852168	Boc-Ser(Fmoc-Gly)-OH	1 g
		5 g
852250	Boc-Ser(Fmoc-Ile)-OH	1 g
		5 g
852293	Boc-Ser(Fmoc-Met)-OH	1 g
		5 g
852169	Boc-Ser(Fmoc-Phe)-OH	1 g
		5 g
852172	Boc-Ser(Fmoc-Ser(tBu))-OH	1 g
		5 g
852173	Boc-Ser(Fmoc-Thr(tBu))-OH	1 g
		5 g
852290	Boc-Ser(Fmoc-Val)-OH	1 g
		5 g
852170	Boc-Thr(Fmoc-Ala)-OH	1 g
		5 g
852294	Boc-Thr(Fmoc-Arg(Pbf))-OH	1 g
		5 g
852297	Boc-Thr(Fmoc-Asp(OtBu))-OH	1 g
		5 g
852296	Boc-Thr(Fmoc-Glu(OtBu))-OH	1 g
		5 g
852171	Boc-Thr(Fmoc-Gly)-OH	1 g
		5 g
852252	Boc-Thr(Fmoc-Ile)-OH	1 g
		5 g
852292	Boc-Thr(Fmoc-Met)-OH	1 g
		5 g
852253	Boc-Thr(Fmoc-Val)-OH	1 g
		5 g

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