

Novabiochem®

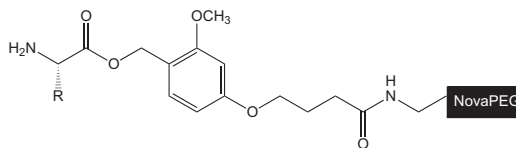
Letters: 2/08

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NEW PEG-based resins for smart peptide synthesis

Pre-loaded HMPB NovaPEG resins



Features & Benefits

- Consist of 100% cross-linked PEG
- Contain no polystyrene or polyacrylamide backbone
- Superior results for difficult or long peptide sequences
- Higher loading than NovaSyn® TG or PEGA resins
- Ideal for synthesis of protected and unprotected peptide acids

Novabiochem's amino acid HMPB NovaPEG resins are the latest additions to our range of NovaPEG resins. They combine the convenience of a pre-loaded support with the versatility of Riniker's [1] HMPB linker and the benefits of the NovaPEG resin, to make them ideal supports for the synthesis of difficult or long peptides by Fmoc SPPS.

These resins are compatible with both batch and continuous-flow methods of synthesis. As they are supplied without Fmoc protection, the second amino acid in the sequence can be coupled without the need for

prior Fmoc removal. Cleavage from these supports can be effected with 95% TFA or 1% TFA to afford peptide acids or protected peptide fragments, respectively. When cleaving NovaPEG resins it is important to use larger volumes of the cleavage cocktail than normally used for polystyrene resin, owing to the excellent swelling properties of these resins.

Unlike other PEG-based polymer supports such as NovaSyn® TG and PEGA resins, which contain either polystyrene or polyacrylamide backbones, NovaPEG resin contains only PEG units [2]. This unique composition confers excellent swelling and mechanical properties on the polymer. The resin beads have similar swelling properties to PEGA resins (Figure 1), but unlike PEGA resins are free flowing beads in the dry state, making them much easier to handle.

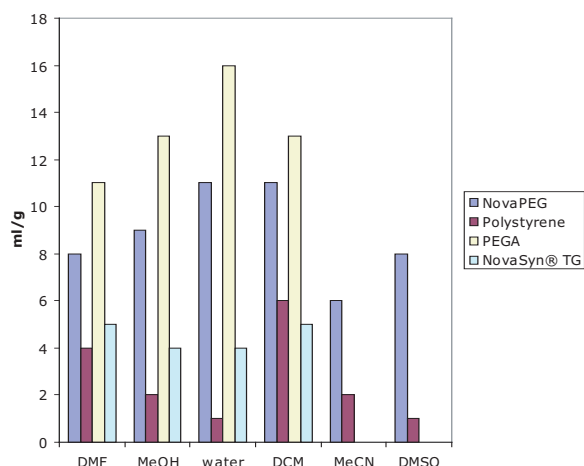


Fig. 1: Swelling properties of NovaPEG and other resins.

The hydrophilic nature of these resins makes them excellent supports for the synthesis of difficult, aggregated peptides and of long peptides and small proteins. In a reported synthesis of Bacuma [2], a 38-residue potential synthetic vaccine, the use of a polystyrene-based support gave an extremely heterogeneous product, whereas NovaPEG Rink Amide resin afforded the target in excellent purity and yield. More remarkable is the result obtained from the synthesis of β -amyloid (1-42) [2]. Using NovaPEG resin, this extremely problematic peptide was obtained in a crude purity of 91% using standard Fmoc SPPS methods.

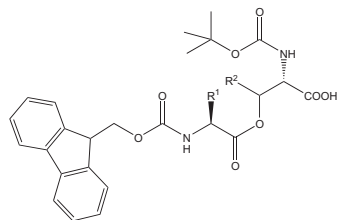
Extraordinary synergies have been observed when NovaPEG resins are used in combination with pseudoproline dipeptides; the syntheses of Rantes [3] and CCL4-L1 [4] could only be achieved by employing a combination of these reagents.

Novabiochem also offers aminomethyl, Rink Amide, FMPB and Wang NovaPEG resins.

04-12-2212	H-Ala-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2213	H-Arg(Pbf)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2214	H-Asn(Trt)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2215	H-Asp(OtBu)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2216	H-Cys(Trt)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2217	H-Gln(Trt)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2218	H-Glu(OtBu)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2219	H-Gly-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2220	H-His(Trt)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2221	H-Ile-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2222	H-Leu-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2223	H-Lys(Boc)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2224	H-Met-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2225	H-Phe-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2227	H-Ser(tBu)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2228	H-Thr(tBu)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2229	H-Trp(Boc)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2230	H-Tyr(tBu)-HMPB NovaPEG resin	1 g
NEW		5 g
04-12-2231	H-Val-HMPB NovaPEG resin	1 g
NEW		5 g
01-64-0485	NovaPEG amino resin	1 g
		5 g
		25 g
01-64-0474	NovaPEG Wang resin	1 g
		5 g
		25 g
01-64-0478	NovaPEG HMPB resin	1 g
		5 g
01-64-0473	NovaPEG Rink Amide resin	1 g
		5 g
		25 g
01-64-0483	NovaPEG Rink Amide resin LL	1 g
		5 g
01-64-0477	NovaPEG FMPB resin	1 g
		5 g
		25 g

NEW Structure breaking isoacyl dipeptides

Boc-Ser(Fmoc-Asn(Trt))-OH/Boc-Ser(Fmoc-Gln(Trt))-OH
Boc-Thr(Fmoc-Ile)-OH/Fmoc-Thr(Fmoc-Val)-OH



Boc-Ser(Fmoc-Asn(Trt))-OH: R¹ = CH₂CONHTrt; R² = H
Boc-Ser(Fmoc-Gln(Trt))-OH: R¹ = (CH₂)₂CONHTrt; R² = H
Boc-Thr(Fmoc-Val)-OH: R¹ = CH(CH₃)₂; R² = CH₃
Boc-Thr(Fmoc-Ile)-OH: R¹ = CH(CH₃)CHCH₃; R² = CH₃

Features & Benefits

- Improved yields and purities of insoluble aggregated peptides
- Purification can be carried out on soluble depsipeptide prior to conversion to native sequence
- Ideal for synthesis of amyloidogenic peptides
- Routine use provides same benefits as pseudoproline dipeptides

The Novabiochem® brand is pleased to offer Boc-Ser(Fmoc-Asn(Trt))-OH, Boc-Ser(Fmoc-Gln(Trt))-OH, Boc-Thr(Fmoc-Ile)-OH and Boc-Thr(Fmoc-Val)-OH as the latest additions to our range of isoacyl dipeptides.

Isoacyl dipeptides are remarkable new tools for enhancing synthetic efficiency in Fmoc SPPS that consist of a Boc-protected serine or threonine derivative in which the β-hydroxyl group is acylated by an Fmoc-amino acid [5, 6]. They perform the same role, and are used in exactly the same manner, as pseudoproline dipeptides. Substitution of Aaa-Ser or Aaa-Thr in a peptide sequence with an isoacyl dipeptide results in the formation of a depsipeptide analog of the native sequence in which the amide bond between Aaa and Ser or Thr is replaced by an ester linkage. This modification results in a marked change in the conformation of the peptide chain which leads to disruption of aggregation in much the same way as would insertion of a pseudoproline or N-Dmb/Hmb-residue [7 - 9]. However, the real benefits of using isoacyl dipeptides become apparent once the peptide is released from the solid phase. In contrast to pseudoproline dipeptides, the product cleaved when using isoacyl dipeptides is the depsipeptide and not the native peptide sequence (Figure 2). Such depsipeptide analogs of aggregation prone peptides have been found to be more soluble and consequently more easily purified than the highly structured native peptide [7 - 9]. For example, isoacyl β-amyloid has a solubility of 15 mg/ml in water, whereas for the natural peptide it is only 0.14 mg/ml [10]. Once the depsipeptide form is purified, it can be easily converted to the native form

by adjusting the pH to 7.4. Spontaneous O- to N-acyl migration occurs, with formation of an amide bond between the Ser or Thr residue and the next amino acid. This pH controlled switching of the peptide conformation can be very advantageous in the study of amyloidogenic peptides, where the initial aggregation state of the peptide to be used in the assay is often unknown. For instance, a non-aggregated

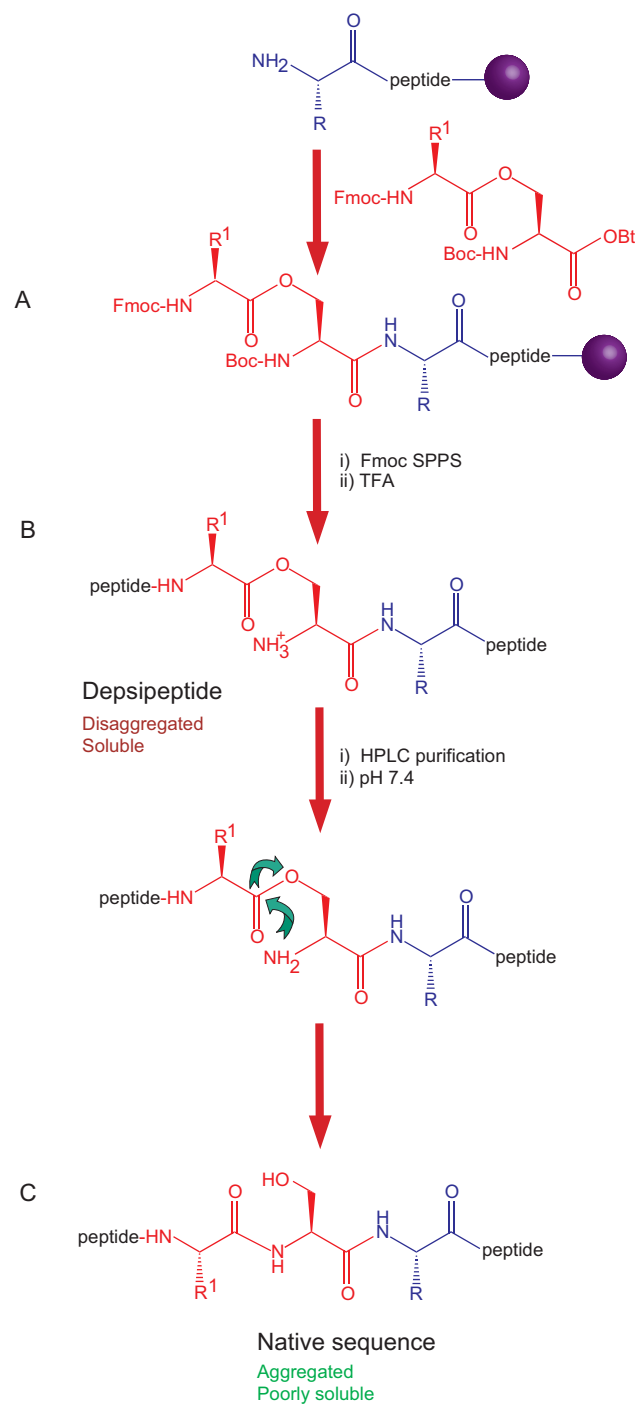


Fig. 2: Principles of peptide synthesis with isoacyl dipeptides, illustrated with Ser. R and R¹ = amino-acid side chains.

depsipeptide can be introduced into a bioassay and the native peptide formed *in situ* under physiological conditions, enabling activity of the native sequence in a non-aggregated state to be determined [11, 12].

Activation of isoacyl dipeptides with base-mediated coupling methods such as HBTU/DIPEA has been shown to cause β -elimination of the Fmoc-amino acid from the serine or threonine side chain [13–14]. This can lead to the formation of peptides omitting serine/threonine or by-products derived from dehydroresidues. Coupling under non-basic conditions using HOBt/DIPCDI in DCM appears to eliminate this problem [13, 14].

05-20-0022 Boc-Ser(Fmoc-Asn(Trt))-OH
NEW

1 g
5 g

05-20-0023 Boc-Ser(Fmoc-Gln(Trt))-OH
NEW

1 g
5 g

05-20-0019 Boc-Thr(Fmoc-Ile)-OH
NEW

1 g
5 g

05-20-0018 Boc-Thr(Fmoc-Val)-OH
NEW

1 g
5 g

05-20-0016 Boc-Ser(Fmoc-Arg(Pbf))-OH

1 g
5 g

05-20-0017 Boc-Ser(Fmoc-Ile)-OH

1 g
5 g

05-20-0015 Boc-Ser(Fmoc-Ala)-OH

1 g
5 g

05-20-0009 Boc-Ser(Fmoc-Gly)-OH

1 g
5 g

05-20-0010 Boc-Ser(Fmoc-Phe)-OH

1 g
5 g

05-20-0013 Boc-Ser(Fmoc-Ser(tBu))-OH

1 g
5 g

05-20-0014 Boc-Ser(Fmoc-Thr(tBu))-OH

1 g
5 g

05-20-0011 Boc-Thr(Fmoc-Ala)-OH

1 g
5 g

05-20-0012 Boc-Thr(Fmoc-Gly)-OH

1 g
5 g

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