PSEUDOPROLINE DIPEPTIDES

BACHEM

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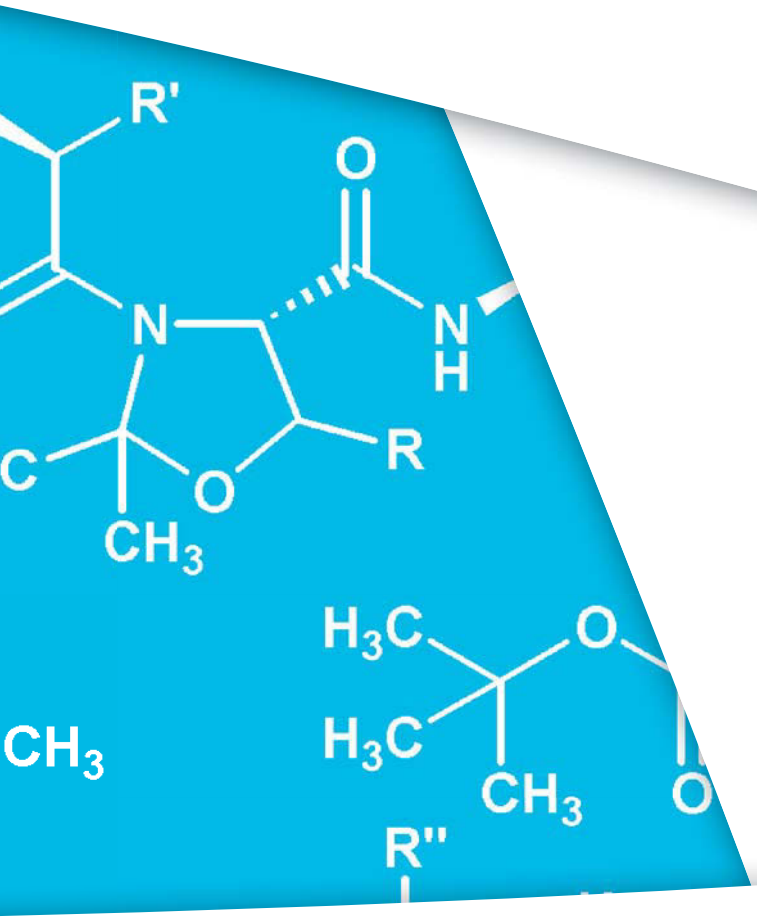


PSEUDOPROLINE AND ISOACYL DIPEPTIDES OFFERED BY BACHEM

The synthesis of very long peptides and “difficult sequences” by chemical means still poses a challenge to the peptide chemist. The difficulties encountered during such syntheses usually are due to the aggregation of the resin-bound peptide. Proline residues disrupt such ordered structures efficiently. Temporary Pro mimics can be readily obtained from Ser and Thr by oxazolidine or from Cys by thiazolidine (“pseudoproline”) formation. Both 2,2-dimethyloxazolidines and -thiazolidines are smoothly cleaved by trifluoroacetic acid and thus suitable for Fmoc-SPPS. Disruption of Ser- and / or Thr-containing aggregates is achieved as well by introducing depsipeptide (“O-acyl isopeptide”) bonds into the peptide backbone. The resulting isopeptide is rearranged yielding the desired sequence in slightly basic solution.

PREFORMED DIPEPTIDES

For facilitating the introduction of oxazolidine or thiazolidine moieties or isopeptide bonds during solid-phase synthesis, protected pseudoproline dipeptides and O-acyl dipeptides have been developed. We offer a broad choice of these versatile building blocks for preventing aggregation during Fmoc-SPPS.

Pseudoproline Dipeptides

Stepwise Fmoc-SPPS may become very difficult or even fail if the resin-bound peptide aggregates. Unfortunately, the predictions of “difficult sequences” based on an assumed propensity of the sequence to form β-sheets are not very reliable, with the exception that such aggregates cannot be formed in the vicinity of proline. The induction of a cis-amide bond by Pro disrupts β-sheets as well as α-helices.

The aggregation of Ser-, Thr- or Cys-containing peptides during Fmoc-SPPS can thus be efficiently prevented by introducing the Fmoc-protected oxazolidines or thiazolidines, which can be obtained from these amino acids and aldehydes or ketones (Fig. 1). These heterocycles have been ap-

propriately termed pseudoprolines. The pseudoproline approach, originally developed by Manfred Mutter et al. at EPFL Lausanne [1,2], usually employed the Ser and Thr derivatives, as the oxazolidines were cleaved more readily by acids than the thiazolidines [3]. In the meantime, thiazolidine cleavage conditions suitable for standard Fmoc-SPPS have been developed [4]. The incorporation of cysteine pseudoproline derivatives facilitated the synthesis of Cys-rich peptides [5], which will also benefit from milder deprotection conditions. The acid lability of both types of heterocycle can be fine-tuned by the choice of substituents at the 2-position. The isopropylidene group of the oxazolidine (X = O, R', R'' = CH_3) proved to be the best choice for Fmoc-SPPS [3], as the cycle is opened readily yielding Ser (R = H) or Thr (R = CH_3) during the final cleavage with TFA. Both isopropylidene (X = S, R', R'' = CH_3) and benzylidene (X = S, R' = 2,4-Dimethoxyphenyl, R'' = H) derivatives have been used for incorporating cysteine, as the rings can be cleaved by TFA [4]. The main drawback of this approach is the difficult coupling of the following amino acid to the hindered heterocycle. To circumvent this, Fmoc pseudoproline dipeptides were introduced [6] (Fig. 2). The coupling of these building blocks represents the most straightforward method to incorporate pseudoprolines The "preventive" insertion of

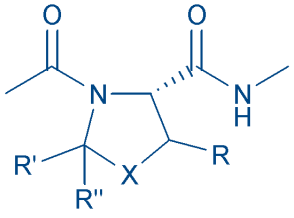


Fig. 1.

R = H, CH_3
X = O, S
R',R'' = H, alkyl, aryl

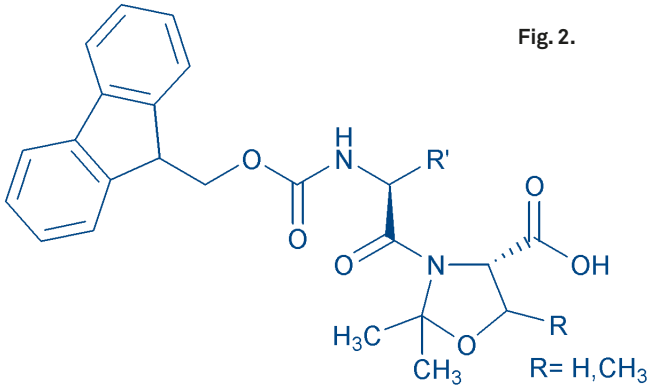
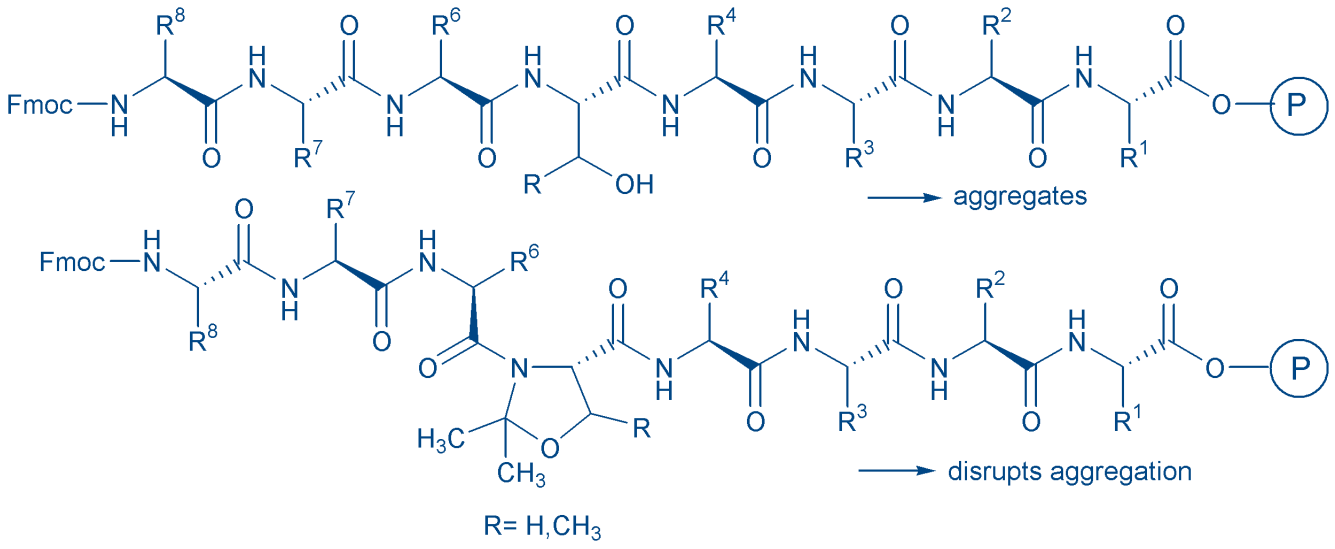


Fig. 2.

such moieties is highly recommended when synthesizing long peptides lacking prolines (Fig. 3). The repeated inclusion of pseudoproline units during the elongation of the peptide will improve the overall coupling efficiency, even if aggregation does not pose a severe problem. A considerable number of syntheses of long or "inaccessible" peptides, which succeeded only due to the insertion of pseudoprolines in appropriate positions, has been published since the introduction of these derivatives [7-9]. Difficult peptides as IAPP [10, 11] or RANTES [12] could be synthesized following standard Fmoc-SPPS protocols after evaluation of the required number and optimal position of the oxazolidine moieties to be inserted. As with Fmoc amino acid derivatives, couplings can be accelerated by microwave irradiation [13-15]. Pseudoproline dipeptides show their high versatility as building blocks not only during the SPPS of long and difficult peptides. When synthesizing short peptides, a distinctly purer crude product may be obtained by incorporating merely a single pseudoproline unit [14]. The heterocycles are left

THE INCORPORATION OF PSEUDOPROLINES FACILITATES CYCLIZATION OF PEPTIDES

Fig. 3.

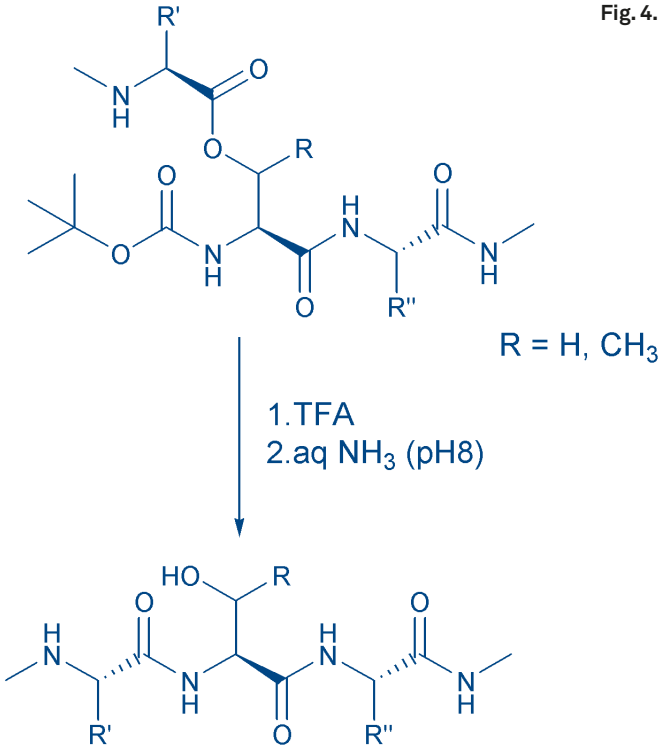


intact when cleaving fully protected peptide fragments from SASRIN or 2-chlorotrityl resin with diluted TFA [16,17] and their presence markedly increases the solubility of the cleavage products. Accordingly, the purification and coupling of the fragments as well as the modification of partially protected peptides in solution are facilitated by insertion of pseudoproline moieties.

As fragments containing a C-terminal proline, fragments with a C-terminal pseudoproline can be coupled with minimal concomitant racemization. Hence pseudoproline dipeptides may establish additional possibilities in convergent peptide synthesis [18]. The incorporation of an oxazolidine moiety greatly facilitates cyclizations of Ser- or Thr-containing peptides, disulfide bridge formations [11], as well as head-to-tail cyclizations [19,20]. The increased tendency to cyclize is due to the presence of a temporary cis-amide bond in the molecule [21,22].

Even though Cys occurs only rarely in peptides and proteins, far less often than Ser and Thr, the incorporation of cysteine pseudoproline is highly attractive due to the peculiar properties of the amino acid. Postma and Albericio showed that on-resin macrocyclization of Cys-containing peptides proceeds more smoothly if Cys(Trt) is replaced by a cysteine pseudoproline [4]. They also observed that cysteine 2,2-dimethylthiazolidines are opened during the final cleavage with TFA/TIS/H_2O (95:2.5:2.5), cleavage duration and temperature depend on the nature of the subsequent amino acid. As their oxazolidine counterparts, cysteine pseudoprolines facilitate end-to-end cyclization [23]. The option of desulfurizing the amino acid may add alanine to the choice of amino acids allowing insertion of a pseudoproline dipeptide [23]. Cysteine derivatives are notorious for their propensity for racemization when activated. Use of the appropriate thiazolidine dipeptides al-

Fig. 4.



lows avoiding this risk, an advantage worth considering when synthesizing multiple disulfide bridge-containing peptides or anchoring cysteine to carriers.
If its thiazolidine ring is left intact, 2,2-dimethylthiazolidin-4-carboxylic acid (Me_2Thz), conveniently introduced as pseudoproline dipeptide, acts as a highly effective cis-proline mimic [16,24,25]. An analog of the cyclopeptide phakellistatin 19 containing three Me_2Thz residues replacing proline, all of them incorporated by coupling pseudoproline dipeptides, showed enhanced activity [26]. For synthesizing peptides containing this proline surrogate the standard TFA-labile lateral protecting groups may have to be replaced by highly acid-labile moieties such as Mtt (His), Trt (Ser) or OPp (Glu) [25].

Isoacyl Dipeptides

A major disadvantage of the pseudoproline approach cannot be left unmentioned: The solubilizing effect of the oxazolidine moiety is lost when deblocking the peptide with TFA. Albeit the quality of the crude product may be vastly improved, further purification will be tedious due to its low solubility.
The N-O shift, a notorious side reaction during HF cleavage, turned out to be the key to the solution of this dilemma. This acid-catalyzed rearrangement involving the hydroxyl moiety of Ser or Thr residues can be smoothly reversed by keeping the peptide in a slightly basic medium (Fig. 4).

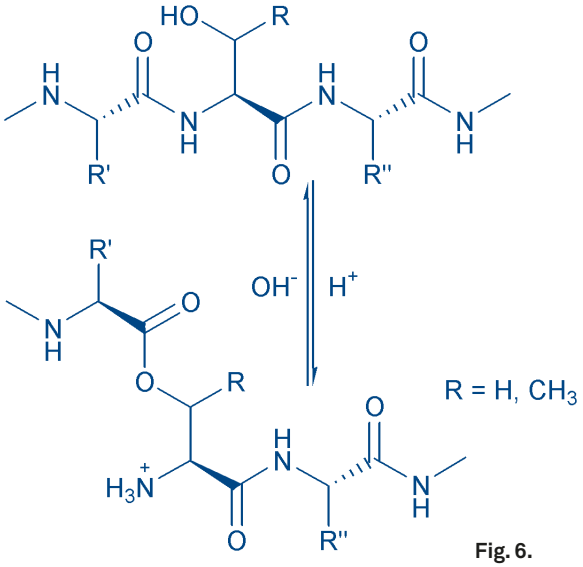


Fig. 6.

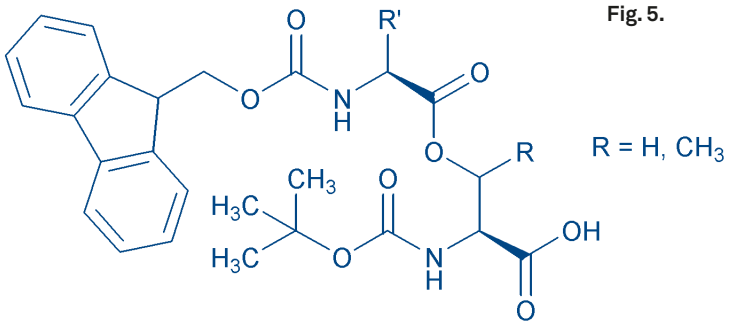


Fig. 5.

As the N-O shift, i.e. O-isoacyl peptide formation, causes a disruption of the secondary structure, it is accompanied by an increase in solubility [27,28]. At first, this type of depsipeptide was obtained by Fmoc-SPPS involving on-resin esterification of the subsequent Fmoc-amino acid to the free hydroxyl moiety of an N-terminal Boc-Ser/Thr followed by elongation of the peptide [29]. Low conversions, concomitant racemization, and diketopiperazine formation during the subsequent SPPS cycle [30] are the main drawbacks of this straightforward approach. The recently introduced Fmoc O-acyl dipeptides help to overcome these problems [31,32] (Fig. 5), though diketopiperazine formation is not affected by the method chosen for introducing the ester bond (incorporation of more base-labile Bsmoc N^{α}-protection at this position helps to reduce the extent of this side-reaction [30,33]).
As pseudoproline dipeptides, O-acyl dipeptides turned out to be versatile building blocks for the synthesis of difficult peptides such as β-amyloid (1-42) [34], which indeed showed an improved solubility and reduced propensity for fibril formation, and insulin, where isoacyl dipeptides were inserted in both A- and B-chain [35]. Peptides containing O-acyl bonds to Ser or Thr may act as soluble prodrugs, hence they have also been termed “switch peptides” [36] (Fig. 6).

β-elimination of O-acyl dipeptides during activation has been described by Coin et al. [37]. If this side reaction poses a problem pseudoproline dipeptides should be incorporated in place of the isoacyl dipeptide to disrupt the aggregated structure.

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PSEUDO-PROLINE DIPEPTIDES

Fmoc-dipeptide building blocks containing Ser- or Thr-derived oxazolidines or Cys-derived thiazolidines (pseudoprolines) proved to be versatile tools for overcoming some intrinsic problems in the field of peptide chemistry. The presence of pseudoprolines within a peptide sequence results in the disruption of β-sheet structures considered as a source of intermolecular aggregation during chain elongation, thus increasing solvation and coupling kinetics in peptide assembly. Therefore, incorporation of pseudoprolines offers new possibilities for accessing large peptides by convergent strategies and chemoselective ligation techniques. Moreover, incorporation of a pseudoproline unit facilitates cyclization of peptides.

CYSTEINE DERIVATIVES

Fmoc-Ala-Cys(Psi(Me,Me)pro)-OH
NEW
B-4365

Fmoc-Asp(OtBu)-Cys(Psi(Me,Me)pro)-OH NEW
B-4370

Fmoc-Lys(Boc)-Cys(Psi(Me,Me)pro)-OH NEW
B-4375

Fmoc-Ser(tBu)-Cys(Psi(Me,Me)pro)-OH NEW
B-4380

Fmoc-Ala-Cys(Psi(Dmp,H)pro)-OH
NEW
B-4385

Fmoc-Cys(Trt)-Cys(Psi(Dmp,H)pro)-OH
NEW
B-4390

Fmoc-Gly-Cys(Psi(Dmp,H)pro)-OH
NEW
B-4395

Fmoc-Leu-Cys(Psi(Dmp,H)pro)-OH
NEW
B-4400

Fmoc-Lys(Boc)-Cys(Psi(Dmp,H)pro)-OH NEW
B-4405

Fmoc-Val-Cys(Psi(Dmp,H)pro)-OH
NEW
B-4410

SERINE DERIVATIVES

Fmoc-Ala-Ser(Psi(Me,Me)pro)-OH
B-4270

Fmoc-Asn(Trt)-Ser(Psi(Me,Me)pro)-OH
B-4090

Fmoc-Asp(OtBu)-Ser(Psi(Me,Me)pro)-OH
B-4275

Fmoc-Gln(Trt)-Ser(Psi(Me,Me)pro)-OH
B-4100

Fmoc-Glu(OtBu)-Ser(Psi(Me,Me)pro)-OH
B-4285

Fmoc-Gly-Ser(Psi(Me,Me)pro)-OH
B-4055

Fmoc-Ile-Ser(Psi(Me,Me)pro)-OH
B-3910

Fmoc-Leu-Ser(Psi(Me,Me)pro)-OH
B-3540

Fmoc-Lys(Boc)-Ser(Psi(Me,Me)pro)-OH
B-4295

Fmoc-Phe-Ser(Psi(Me,Me)pro)-OH
B-3920

Fmoc-Ser(tBu)-Ser(Psi(Me,Me)pro)-OH
B-3935

Fmoc-Thr(tBu)-Ser(Psi(Me,Me)pro)-OH
B-3915

Fmoc-Trp(Boc)-Ser(Psi(Me,Me)pro)-OH
B-4315

Fmoc-Tyr(tBu)-Ser(Psi(Me,Me)pro)-OH
B-3925

Fmoc-Val-Ser(Psi(Me,Me)pro)-OH
B-4330

THREONINE DERIVATIVES

Fmoc-Ala-Thr(Psi(Me,Me)pro)-OH
B-3535

Fmoc-Asn(Trt)-Thr(Psi(Me,Me)pro)-OH
B-4095

Fmoc-Asp(OtBu)-Thr(Psi(Me,Me)pro)-OH
B-4280

Fmoc-Gln(Trt)-Thr(Psi(Me,Me)pro)-OH
B-4105

Fmoc-Glu(OtBu)-Thr(Psi(Me,Me)pro)-OH
B-4290

Fmoc-Gly-Thr(Psi(Me,Me)pro)-OH
B-4085

Fmoc-Ile-Thr(Psi(Me,Me)pro)-OH
B-3440

Fmoc-Leu-Thr(Psi(Me,Me)pro)-OH
B-3545

Fmoc-Lys(Boc)-Thr(Psi(Me,Me)pro)-OH
B-3930

Fmoc-Phe-Thr(Psi(Me,Me)pro)-OH
B-4300

Fmoc-Ser(tBu)-Thr(Psi(Me,Me)pro)-OH
B-4305

Fmoc-Thr(tBu)-Thr(Psi(Me,Me)pro)-OH
B-4310

Fmoc-Trp(Boc)-Thr(Psi(Me,Me)pro)-OH
B-4320

Fmoc-Tyr(tBu)-Thr(Psi(Me,Me)pro)-OH
B-4325

Fmoc-Val-Thr(Psi(Me,Me)pro)-OH
B-3470

ISOACYL DIPEPTIDES

Isoacyl dipeptides have been developed as building blocks for preventing aggregation of the growing peptide chains during Fmoc-SPPS. As the isopeptide structure is not affected by the final acidolytic cleavage, the solubility of the crude product is improved facilitating the subsequent purification. The depsipeptide will rearrange yielding the desired product in slightly basic solution.

SERINE DERIVATIVES

Boc-Ser(Ala-Fmoc)-OH
B-3940

Boc-Ser(Ile-Fmoc)-OH
B-3960

Boc-Ser(Leu-Fmoc)-OH
B-3970

Boc-Ser(Val-Fmoc)-OH
B-3980

THREONINE DERIVATIVES

Boc-Thr(Ala-Fmoc)-OH
B-3945

Boc-Thr(Gly-Fmoc)-OH
B-3955

Boc-Thr(Ile-Fmoc)-OH
B-3965

Boc-Thr(Leu-Fmoc)-OH
B-3975

Boc-Thr(Val-Fmoc)-OH
B-3985

RELATED BUILDING BLOCKS

Reversible N-alkylation of the peptide bond by 2-hydroxy-4-methoxybenzyl (Hmb) or 2,4-dimethoxybenzyl (Dmb) moieties, which both are removed under the conditions of the final TFA cleavage, disrupts aggregation as effectively as the incorporation of a pseudoproline residue. Use of appropriately modified building blocks allows to obtain difficult peptides lacking Ser, Thr and Cys by solid-phase synthesis. Furthermore, the base-catalyzed aspartimide formation of the Asp-Gly motif can be efficiently suppressed by incorporation of HmbGly or DmbGly. Hence, we also offer a range of Dmb and Hmb derivatives and dipeptides.

DMB AND HMB DERIVATIVES AND DIPEPTIDES

Fmoc-Ala-(Dmb)Gly-OH
B-4045

Fmoc-Asp(OtBu)-(Dmb)Gly-OH
B-4035

Fmoc-Asp(OtBu)-(Hmb)Gly-OH
B-3650

Fmoc-D-Asp(OtBu)-(Hmb)Gly-OH
B-3675

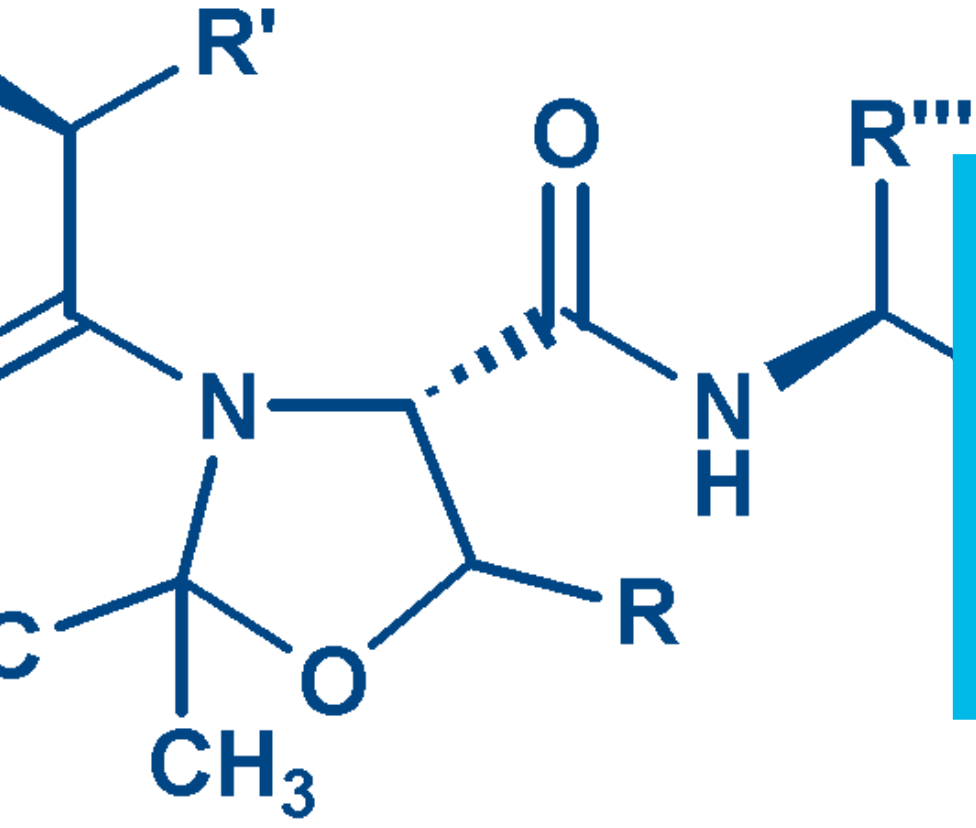
Fmoc-Gly-(Dmb)Gly-OH
B-4040

Fmoc-(Dmb)Ala-OH
B-4175

Fmoc-(Dmb)Gly-OH
B-4170

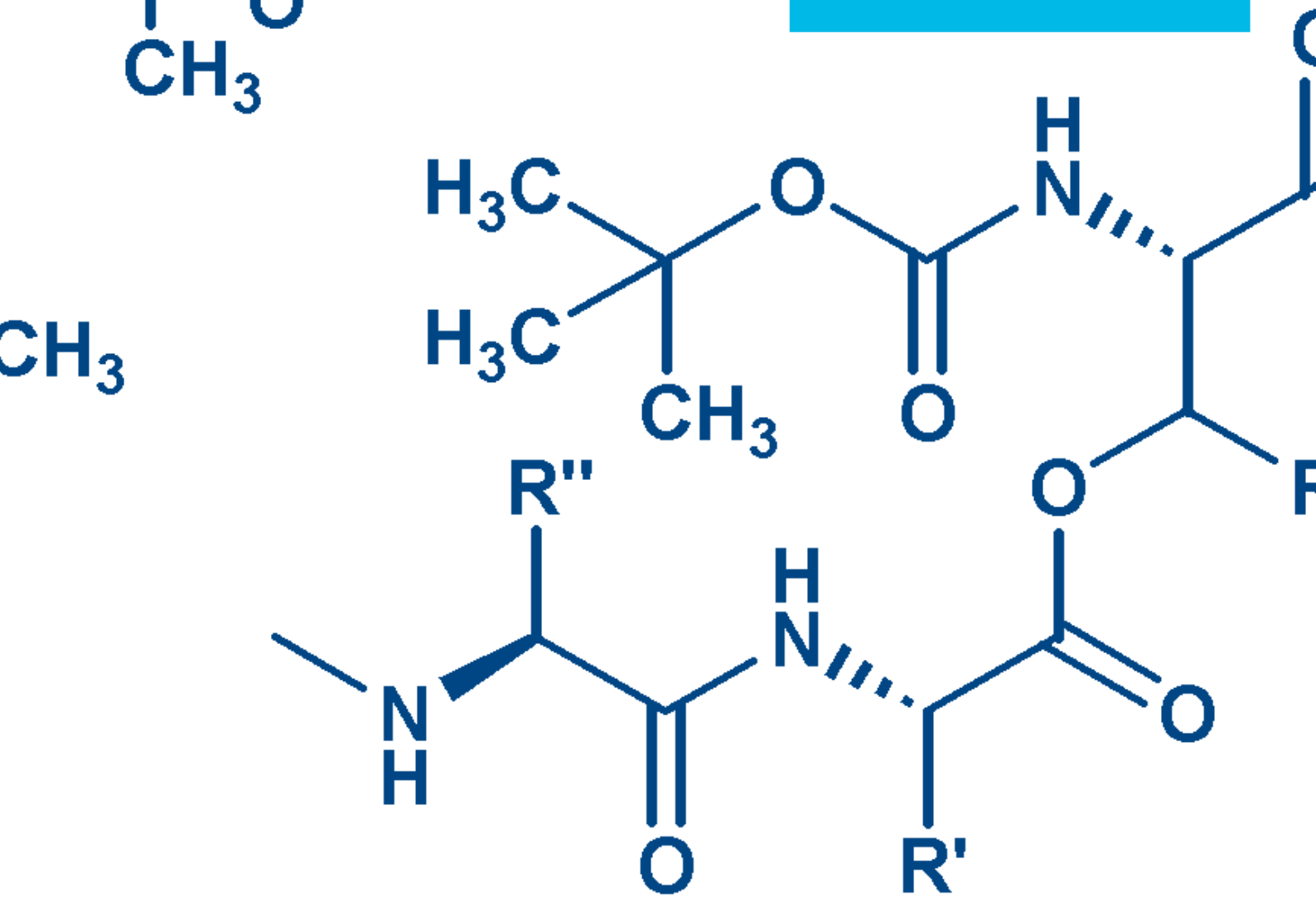
Fmoc-(Dmb)Leu-OH
B-4165

Fmoc-(Hmb)Gly-OH
B-3490



PEPTIDE AGGREGATION

“Difficult sequences”
Incorporation of pseudoprolines offers new possibilities for accessing large peptides by stepwise solid-phase synthesis as well as by convergent strategies. Moreover, incorporation of a pseudoproline unit facilitates cyclization of peptides.



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