



Iris
Biotech

CYCLIC PEPTIDES



Version: IB3_4

Empowering Peptide Innovation

With this guiding theme in mind, Iris Biotech's mission is to support researchers by supplying

- innovative technologies,
- rare compounds,
- as well as a broad portfolio on standard consumables,

available in flexible quantities from small scale to bulk quantities. To fulfill our dedication "Empowering Peptide Innovation", we are attending various conferences, symposia, and exhibitions each year. This allows us to remain in direct contact with scientists all over the world, both from academia and industry, to exchange knowledge, and to gather new ideas to tackle your current challenges.

Guided by our dedication to provide

- competent service,
- as well as novel substances and
- latest technologies,

Iris Biotech is your trusted partner for the world of peptides, while having strong expertise in associated disciplines. Thus, our portfolio comprises reagents and tools for the synthesis and modification of peptides, e.g., amino acids, resins and solvents but also for related technologies such as drug delivery, linkerology® and life sciences.

Owed to the growing demand for tailor-made compounds, our portfolio is fine-tuned by our custom synthesis service at Iris Biotech Laboratories. Our skilled scientists offer profound expertise in

- *de novo* route development,
- upscaling towards larger scale production,
- as well as synthesis optimization for increased efficiency.

Examples are the synthesis of rare chiral building blocks, unnatural amino acid derivatives, sophisticated orthogonal protecting groups, heterocycles, building blocks for nucleotides, PEGs and PEG-analogs as well as specific linkers for controlled drug delivery and release.



Amino Acids



Building Blocks



Life Sciences



Drug Delivery



Reagents



Resins



Linkerology®



Click Chemistry

Portfolio Overview

Peptide Synthesis and Modification

(Protected) Amino Acids

Standards such as Fmoc-D/L-AAA and Boc-D/L-AAA, Smoc amino acids for peptide synthesis in water, variety of protecting groups (e.g., Pbf, Trt, ^tBu, Bzl, Acn, Mob, SIT, Phacn, Allocam, Mmt), unusual amino acids, fluorinated derivatives, substituted prolines, arginine analogs

Building Blocks

Amino alcohols, amino aldehydes, diamines and hydrazines, (pseudoproline) dipeptides, polyamines and spermines, fatty acid derivatives, peptide nucleic acids (PNAs)

Reagents

Coupling reagents, solvents and scavengers, protecting groups

Resins

Preloaded resins (e.g., based on Trityl, TCP, TentaGel, Methoxybenzhydryl, Merrifield, PAM, Rink, Wang), scavenger resins, hydrazone resins, poly(acrylamide) resins, Cyclover

Linkerology® and Drug Delivery

Linkers for Solid Phase Peptide Synthesis

Cleavable Linkers

Val-Ala-based, Val-Cit-based, disulfide-based, Dde-helping hands, pH-sensitive linkers

Photo-Activatable Linkers

Functionalized Linkers

Clickable linkers, trifunctional linkers, linkers with maleimide function, cross-linkers, selective N-term acylation and biotinylation, 5HP2O

PROTACs

Ligands, linkers & modules

Fullerenes, Poly(2-oxazolines), Dextrans & Plant-Derived Cholesterol

Superparamagnetic Iron Oxide Nanoparticles

Poly-Amino Acids

Poly-Arg, Poly-Glu, Poly-Lys, Poly-Orn, Poly-Sar

PEGylation

Branched PEGylating reagents, (amino-)PEG-acids, PEG-amines & hydrazides & guanidines, reagents for Click-conjugation, Biotin-PEG-reagents, PEG-thiols, PEG-maleimides, other PEGylating reagents

Life Sciences

Biotinylation Reagents

Carbohydrates

Galactose, Glucose, Mannose, Xylose and others

Drug Metabolites

Peptides

Substrates & Inhibitors

E.g., protein kinase inhibitors, substrates for fusion (Halo/Snap/Clip)-tagged proteins

Natural Products

Dyes and Fluorescent Labels

E.g., ICG, AMC, DAPI

Maillard & Amadori Reaction Products

Large portfolio of derivatives useful as standards for food, pharma and cosmetics industry

Vitamins

Custom Synthesis

Your project requires a compound not listed in our portfolio?
Get in contact and inquire about our custom synthesis capabilities.

Our experienced scientists are excited to accept your synthetic challenge!

In such cases, your request undergoes the following stages:



Step-by-Step Analysis

- Customer's demands

Process Evaluation

- Detailed literature review
- Synthetic possibilities

Strategy Development

- Protocol development
- Method development and validation
- Customized synthesis

Quality Consistency

- Identity confirmation
- Purity verification

Our Service Promise

All our services are based on high standards, transparency & documentation, trust, honesty & confidentiality, as well as the required know-how.

High Standards

- Values: sustainability & responsibility
- State-of-the-art equipment & latest technologies
- High quality standards
- Qualified suppliers & regular audits

Transparency & Documentation

- Talk to our specialists – customer care
- Certificates of analysis & origin
- Impurity profiling
- Safety data sheets
- Analytical and process reports

Trust, Honesty & Confidentiality

- Intergenerational business valuing partnerships
- Meeting the customer's expectations
- Integrity towards our customers

Our Know-How

- One-step reactions & complex multi-step synthesis
- Scalability from mg to kg quantities
- Route scouting





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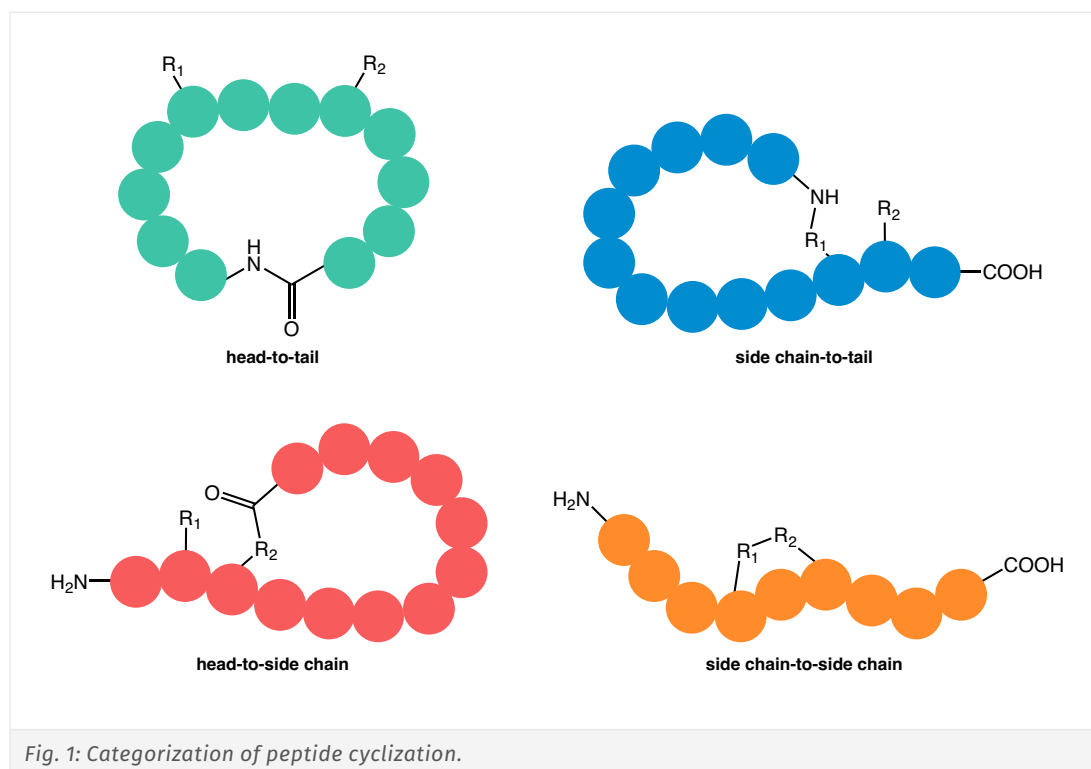
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1. General Introduction

Cyclic peptides have been attracting a lot of attention in recent decades, especially in the area of drug discovery, as more and more naturally occurring cyclic peptides with diverse biological activities, e.g., antibacterial, toxic, immunosuppressive or antitumor activity, have been discovered in all kingdoms of life. Compared to linear peptides, cyclic peptides exhibit a more rigid conformation which is often further increased by additional disulfide bond formation. All together, these bridges allow to form the desired tertiary structure which confers biological activity to the (linear) peptide.

In general, cyclization of peptides results in significantly improved proteolytic stability compared to their linear counterparts. Thus, they are metabolically more stable. Furthermore, the related conformational restriction usually leads to enhanced binding and selectivity as well as increased bioavailability and biological activity as the preorganized ring architecture lowers entropic cost during receptor-binding processes.

Referring to the site of the peptide cyclization reaction, four types can be distinguished: head-to-tail, head-to-side-chain, side-chain-to-tail, and side-chain-to-side-chain cyclization.



Many naturally occurring cyclic peptides are cyclized in the head-to-tail fashion. Within the so-cyclized peptide, the absence of a free N- and C-terminus renders these types of cyclic peptides resistant to hydrolysis by exopeptidases, which further enhances their metabolic stability compared to other types of cyclic peptides.

However, linear precursors without any turn-inducing element typically adopt an extended conformation due to the more stable all-*trans* configuration of the corresponding amide bonds which positions the N- and C-termini far away from each other, rendering them less likely to react intramolecularly. To prevent intermolecular reactions during in solution cyclization attempts, high dilutions are required that lower overall synthetic efficiency. Performing on-resin cyclization allows to achieve a “pseudo dilution” via immobilization of the linear precursor on the solid support.

References:

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- *Cyclic Peptides as Therapeutic Agents and Biochemical Tools*; S. H. Joo; **Biomol Ther (Seoul)** 2012; **20**(1): 19-26. <https://doi.org/10.4062/biomolther.2012.20.1.019>
- *Cyclic peptides: backbone rigidification and capability of mimicking motifs at protein-protein interfaces*; H. Huang, J. Damjanovic, J. Miao, Y.-S. Lin; **Phys. Chem. Chem. Phys** 2021; **23**: 607-616. <https://doi.org/10.1039/D0CP04633G>
- *Cyclic Peptides as Drugs for Intracellular Targets: The Next Frontier in Peptide Therapeutic Development*; L. K. Buckton, M. N. Rahimi, S. R. McAlpine; **Chem. Eur. J.** 2021; **27**(5): 1487-1513. <https://doi.org/10.1002/chem.201905385>


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Any Questions or Suggestions?

We are there for you – simply choose one of the numerous possibilities to get in touch!

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2. Cyclization via Disulfide Bond Formation

Formation of intramolecular disulfide bonds by oxidation of the corresponding free thiol precursors is usually the last step in the synthesis of disulfide-containing peptides and is mainly performed in solution. If only a single disulfide bond is to be formed, any available cysteine protecting group compatible with the chosen combination of side-chain and N- α protecting groups can be used.

In contrast, the formation of multiple disulfide bridges in a targeted way to achieve the desired pairing is a significant challenge, in particular if high purity and good yields are required. It already becomes complex, when two disulfide bridges are present, as the four cysteine residues can form three different bridged derivatives: Cys^I/Cys^{II} & Cys^{III}/Cys^{IV}, Cys^I/Cys^{III} & Cys^{II}/Cys^{IV}, and Cys^I/Cys^{IV} & Cys^{II}/Cys^{III}. Therefore, over the last years, increasingly sophisticated strategies for the protection and subsequent deprotection of cysteine have been developed.

In 1977, Barany and Merrifield described the concept of “orthogonality”, which describes protecting groups that can be chemoselectively removed in the presence of one another without affecting/removing each other when applying defined conditions.

In the following, we present a selection of commonly used, as well as innovative side-chain protected cysteines categorized by their cleavage mechanism and available at Iris Biotech. For a detailed review on cysteine protecting groups, please see *Org. Process Res. Dev.* 2024; **28**(1): 26–45.

References:

- A new amino protecting group removable by reduction. Chemistry of the dithiasuccinoyl (Dts) function; G. Barany, R. B. Merrifield; *J. Am. Chem. Soc.* 1977; **99**(22): 7363–7365. <https://doi.org/10.1021/ja00464a050>
- Cysteine protecting groups: applications in peptide and protein science; R. J. Spears, C. McMahon, V. Chudasama; *Chem. Soc. Rev.* 2021; **50**: 11098. <https://doi.org/10.1039/d1cs00271f>
- Ready to Use Cysteine Thiol Protecting Groups in SPPS, A Practical Overview; A. Chakraborty, S. N. Mthembu, B. G. de la Torre, F. Albericio; *Org. Process Res. Dev.* 2024; **28**(1): 26–45. <https://doi.org/10.1021/acs.oprd.3c00425>
- Cyclic Peptides for Drug Development; X. Ji, A. L. Nielsen, C. Heinis; *Angew. Chem. Int. Ed.* 2024; **63**(3): e202308251. <https://doi.org/10.1002/anie.202308251>
- Native and Engineered Cyclic Disulfide-Rich Peptides as Drug Leads; T. J. Tyler, T. Durek, D. J. Craik; *Molecules* 2023; **28**(7): 3189. <https://doi.org/10.3390/molecules28073189>

2.1. Acid-Labile Protecting Groups

2.1.1. Trityl (Trt)

For the formation of one disulfide bridge, the common building block Fmoc-Cys(Trt)-OH ([FAA1040 on page 79](#)) is used even in bulk productions. It is common to remove Trt using weak acids (e.g., 25% TFA) in the presence of scavengers such as triisopropylsilane (TIS) or triethylsilane (TES) which prevent back-addition of the released Trt cations onto the synthesized peptide during cleavage and isolation. These cleavage conditions render Trt orthogonal to other common protecting groups such as Acn or tBu. Recently, Cys(Trt) has also been shown to be fully deprotected when treated with CuSO₄ and cysteamine in aqueous buffered conditions. The Trt protecting group is compatible with standard Fmoc SPPS reagents.

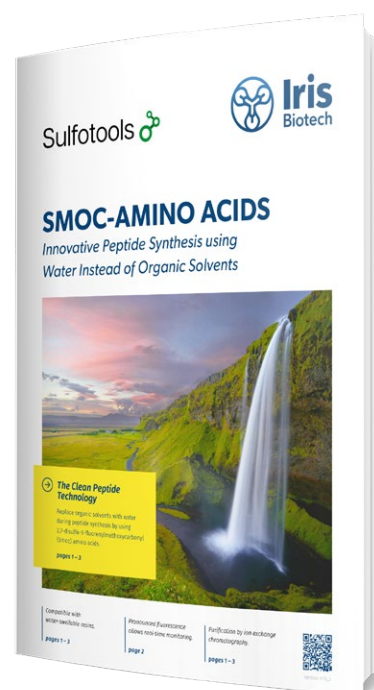
At Iris Biotech we offer side-chain Trt protected cysteine derivatives either with free N-/C-terminus, in combination with other protecting groups, or as preloaded resins.

Especially, we are also offering the Smoc-L-Cys(Trt)-OH building block ([SAA1110 on page 82](#)). The Smoc technology allows to replace organic solvents with water during peptide synthesis and thus represents a greener approach for the production of peptides

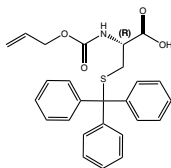
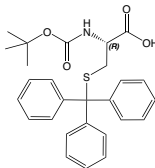
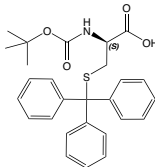
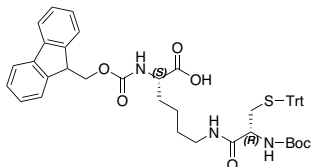
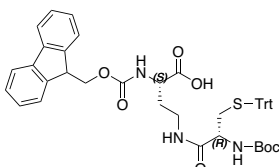
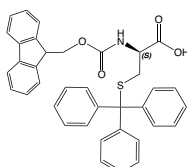


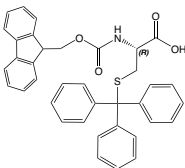
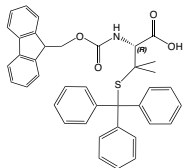
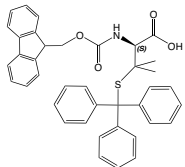
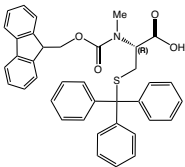
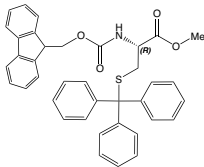
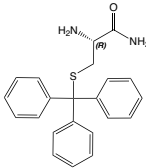
Interested in the Smoc technology?

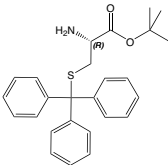
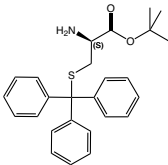
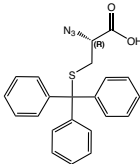
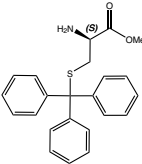
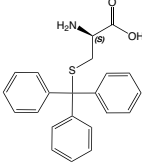
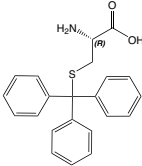
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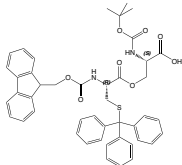
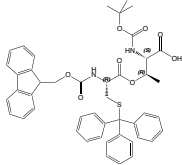
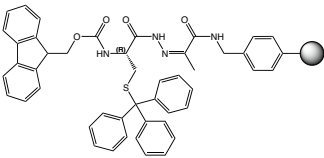
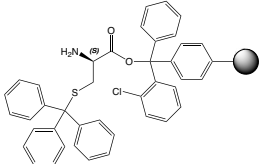
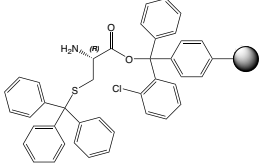
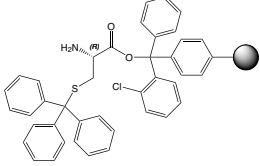


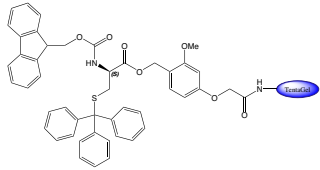
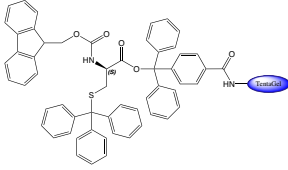
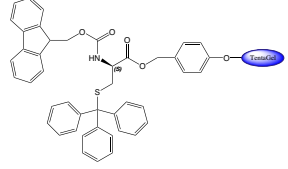
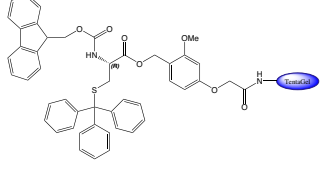
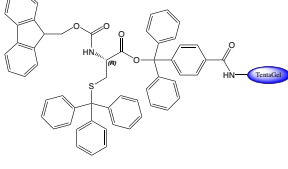
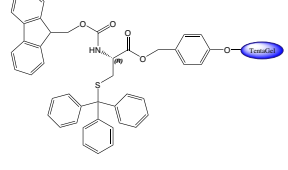
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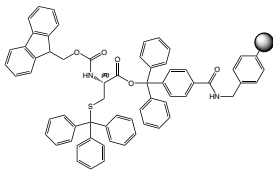
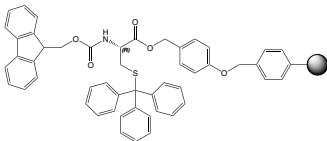
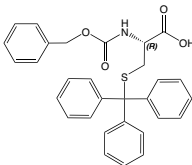
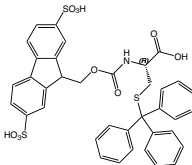
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BAA1084 Boc-L-Cys(Trt)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-trityl-L-cysteine CAS-No. 21947-98-8 Formula $C_{27}H_{29}NO_4S$ Mol. weight 463,59 g/mol		
BAA5000 Boc-D-Cys(Trt)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-trityl-D-cysteine CAS-No. 87494-13-1 Formula $C_{27}H_{29}NO_4S$ Mol. weight 463,59 g/mol		
FAA9315 Fmoc-L-Lys(Boc-Cys(Trt))-OH N2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N6-(N-(<i>tert</i> -butoxycarbonyl)-S-trityl-L-cysteinyl)-L-lysine CAS-No. 587854-43-1 Formula $C_{48}H_{51}N_3O_7S$ Mol. weight 814,01 g/mol		
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Formula	C ₃₇ H ₃₁ NO ₄ S		
Mol. weight	585,71 g/mol		
			
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N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-penicillamine			
CAS-No.	201531-88-6		
Formula	C ₃₉ H ₃₅ NO ₄ S		
Mol. weight	613,78 g/mol		
			
FAA1675	Fmoc-D-Pen(Trt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-penicillamine			
CAS-No.	201532-01-6		
Formula	C ₃₉ H ₃₅ NO ₄ S		
Mol. weight	613,78 g/mol		
			
FAA3570	Fmoc-L-MeCys(Trt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-trityl-L-cysteine			
CAS-No.	944797-51-7		
Formula	C ₃₈ H ₃₃ NO ₄ S		
Mol. weight	599,74 g/mol		
			
FAA5670	Fmoc-L-Cys(Trt)-OMe		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine methyl ester			
CAS-No.	245088-56-6		
Formula	C ₃₈ H ₃₃ NO ₄ S		
Mol. weight	599,74 g/mol		
			
HAA1560	H-L-Cys(Trt)-NH₂		
S-Trityl-L-cysteine amide			
CAS-No.	166737-85-5		
Formula	C ₂₂ H ₂₂ N ₂ O ₂ S		
Mol. weight	362,49 g/mol		
			

		Product details
HAA1995	H-L-Cys(Trt)-OtBu*HCl S-Trityl-L-cysteine t-butyl ester hydrochloride CAS-No. 158009-03-1 Formula $C_{26}H_{29}NO_2S \cdot HCl$ Mol. weight 419,58*36,45 g/mol	 
HAA2100	H-D-Cys(Trt)-OtBu*HCl S-Trityl-D-cysteine t-butyl ester hydrochloride CAS-No. 439089-10-8 Formula $C_{26}H_{29}NO_2S \cdot HCl$ Mol. weight 419,58*36,45 g/mol	 
HAA2810	N₃-L-Cys(Trt)-OH*CHA (R)-2-azido-3-(tritylthio)propanoic acid cyclohexylamine CAS-No. 1286670-90-3 Formula $C_{22}H_{19}N_3O_2S \cdot C_6H_{13}N$ Mol. weight 389,47*99,17 g/mol	 
HAA3520	H-D-Cys(Trt)-OMe*HCl S-trityl-D-cysteine methyl ester hydrochloride CAS-No. 1020369-32-7 Formula $C_{23}H_{23}NO_2S \cdot HCl$ Mol. weight 377,50*36,45 g/mol	 
HAA6120	H-D-Cys(Trt)-OH S-Trityl-D-cysteine CAS-No. 25840-82-8 Formula $C_{22}H_{21}NO_2S$ Mol. weight 363,48 g/mol	 
HAA6160	H-L-Cys(Trt)-OH S-Trityl-L-cysteine CAS-No. 2799-07-7 Formula $C_{22}H_{21}NO_2S$ Mol. weight 363,48 g/mol	 

		Product details
IAD1040	Boc-L-Ser[Fmoc-L-Cys(Trt)]-OH O-(N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteiny)-N-(tert-butoxycarbonyl)-L-serine CAS-No. 944283-13-0 Formula $C_{45}H_{44}N_2O_8S$ Mol. weight 772,9	 
IAD2040	Boc-L-Thr[Fmoc-L-Cys(Trt)]-OH O-(N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteiny)-N-(tert-butoxycarbonyl)-L-threonine CAS-No. 944283-30-1 Formula $C_{46}H_{46}N_2O_8S$ Mol. weight 786,93 g/mol	 
PYV1140	Fmoc-L-Cys(Trt)-NHN=Pyv Resin Fmoc-S-trityl-L-cysteiny-hydrazono-pyruvyl-amino-methylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB	 
RAA1060	H-D-Cys(Trt)-2CT Resin H-D-Cys(Trt)-2-chlorotrityl resin Mesh Size 100-200 mesh Loading > 0.4 mmol/g DVB 1% DVB	 
RAA1065	H-L-Cys(Trt)-2CT Resin H-L-Cys(Trt)-2-chlorotrityl resin Mesh Size 100-200 mesh Loading 0.4-1.2 mmol/g DVB 1% DVB	 
RAA1066	H-L-Cys(Trt)-2CT Resin H-L-Cys(Trt)-2-chlorotrityl resin Mesh Size 200-400 mesh Loading 0.4-1.2 mmol/g DVB 1% DVB	 

			Product details
SAD1106	Fmoc-D-Cys(Trt)-AC TG		
Fmoc-D-Cys(Trt)-[3-methoxy-4-hydroxymethyl]phenoxycetylamid] TentaGel S			
Mesh Size	90 µm		
Loading	0.16-0.26 mmol/g		
SAD1206	Fmoc-D-Cys(Trt)-Trt TG		
Fmoc-D-Cys(Trt)-Trityl TentaGel S			
Mesh Size	90 µm		
Loading	0.15-0.25 mmol/g		
SAD1306	Fmoc-D-Cys(Trt)-Wang TG		
Fmoc-D-Cys(Trt)-Wang TentaGel S			
Mesh Size	90 µm		
Loading	0.16-0.26 mmol/g		
SAL1106	Fmoc-L-Cys(Trt)-AC TG		
Fmoc-L-Cys(Trt)-[3-methoxy-4-hydroxymethyl]phenoxycetylamid] TentaGel S			
Mesh Size	90 µm		
Loading	0.16-0.26 mmol/g		
SAL1206	Fmoc-L-Cys(Trt)-Trt TG		
Fmoc-L-Cys(Trt)-Trityl TentaGel S			
Mesh Size	90 µm		
Loading	0.15-0.25 mmol/g		
SAL1306	Fmoc-L-Cys(Trt)-Wang TG		
Fmoc-L-Cys(Trt)-Wang TentaGel S			
Mesh Size	90 µm		
Loading	0.16-0.26 mmol/g		

		Product details
TCP1130	Fmoc-L-Cys(Trt)-TCP-Resin	 
Fmoc-Cys(Trt)-trityl-carboxyamidomethyl polystyrene		
Mesh Size	200-400 mesh	
Loading	0.3-0.8 mmol/g	
DVB	1% DVB	
WAA41306	Fmoc-L-Cys(Trt)-Wang Resin	 
Fmoc-L-Cysteine(Trityl)-Wang Resin		
Mesh Size	200-400 mesh	
DVB	1% DVB	
WAA6118	Fmoc-D-Cys(Trt)-Wang Resin	
Fmoc-D-Cysteine(Trityl)-Wang Resin		
Mesh Size	100-200 mesh	
DVB	1% DVB	
ZAA1310	Z-L-Cys(Trt)-OH	 
N-alpha-Benzyloxycarbonyl-S-trityl-L-cysteine		
CAS-No.	26311-04-6	
Formula	C ₃₀ H ₂₇ NO ₄ S	
Mol. weight	497,60 g/mol	
SAA1110	Smoc-L-Cys(Trt)-OH	 
N-(((2,7-disulfo-9H-fluoren-9-yl)methoxy)carbo- nyl)-S-trityl-L-cysteine potassium salt		
CAS-No.	2442552-68-1	
Formula	C ₃₇ H ₂₉ K ₂ NO ₁₀ S ₃	
Mol. weight	822,01 g/mol	

2.1.2. 4-Methoxytrityl (Mmt)

Mmt represents a very acid-labile cysteine protecting group, which can already be cleaved using 1-3% TFA in DCM/TES. The Mmt group displays orthogonality to multiple cysteine protecting groups, including tBu, Dpm, oNv, StBu, and AcM. It is stable to bases, e.g., 30% piperidine in DMF (24 h, 22 °C), and compatible with standard Fmoc SPPS reagents.

For the targeted synthesis of two disulfide bridges, a commonly applied protecting group combination is Trt and Mmt. As Mmt can be removed with 1% TFA and Trt requires a higher concentration for removal (ca. 7-10%), in principle, a certain degree of orthogonality is given. However, in large scale syntheses it is necessary to utilize 5% TFA for Mmt removal to achieve complete cleavage. At this concentration, it can be observed that a significant percentage of Trt is already cleaved as well. Therefore, no true orthogonality is provided by this protecting group pair. In such cases, it is best to use the protection pair Mmt and Dpm.

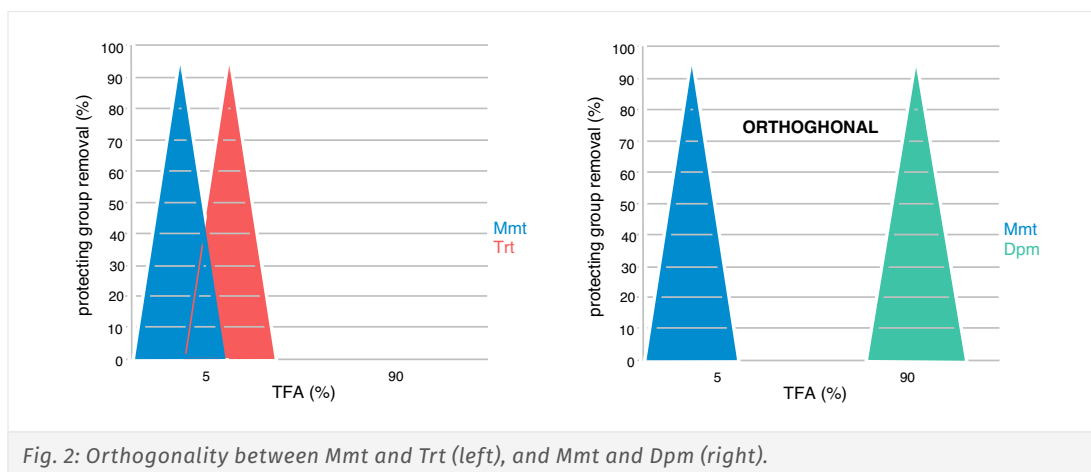
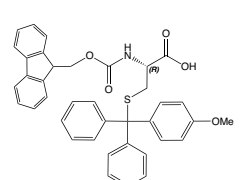
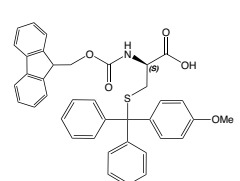
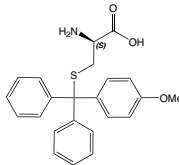
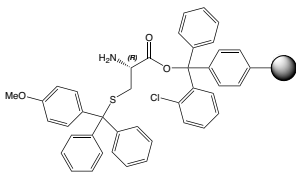
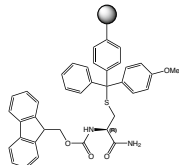


Fig. 2: Orthogonality between Mmt and Trt (left), and Mmt and Dpm (right).

			Product details
FAA1030	Fmoc-L-Cys(Mmt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-p-methoxytrityl-L-cysteine			
CAS-No.	177582-21-7		
Formula	C ₃₈ H ₃₃ NO ₅ S		
Mol. weight	615,74 g/mol		
FAA1614	Fmoc-D-Cys(Mmt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-p-methoxytrityl-D-cysteine			
CAS-No.	1198791-73-9		
Formula	C ₃₈ H ₃₃ NO ₅ S		
Mol. weight	615,74 g/mol		

		Product details
HAA3500	H-D-Cys(Mmt)-OH	
S- <i>p</i> -methoxytrityl-D-cysteine		
CAS-No.	926935-33-3	 
Formula	C ₂₃ H ₂₃ NO ₃ S	
Mol. weight	393,5 g/mol	
RAA1055	H-L-Cys(Mmt)-2CT Resin	
H-L-Cys(Mmt)-2-chlorotrityl resin		
Mesh Size	100-200 mesh	 
Loading	> 0.4 mmol/g	
DVB	1% DVB	
RAA2620	Fmoc-L-Cys(Mmt resin)-NH₂	
Fmoc-L-Cysteine alpha-amide-S-(4-methoxytrityl resin)		
Mesh Size	100-200 mesh	 
Loading	ca. 0.5 mmol/g	
DVB	1% DVB	

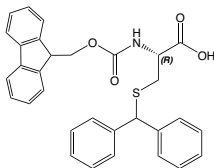
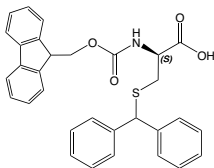
Reference:

- *Synthesis of the very acid-sensitive Fmoc-Cys(Mmt)-OH and its application in solid-phase peptide synthesis; K. Barlos, D. Gatos, O. Hatzi, N. Koch, S. Koutsogianni; Int. J. Pept. Protein Res. 1996; 47: 148-153.*
<https://doi.org/10.1111/j.1399-3011.1996.tb01338.x>

2.1.3. Diphenylmethyl (Dpm, Bzh, Bh)

Dpm is stable to low concentrations of TFA cocktails (< 25%) but can be cleaved with higher concentrations. At least 60% TFA up to 90% TFA in DCM (using 2.5% TIS and 2.5% H₂O as scavengers) is required for full removal. Due to its acid lability profile, Dpm is orthogonal to Trt and Mmt. Additionally, cysteine racemization is attenuated considerably when using Dpm compared to Trt or Bzl. Furthermore, Dpm is stable towards standard Fmoc SPPS reagents.

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			Product details
FAA3190	Fmoc-L-Cys(Dpm)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenyl-methyl-L-cysteine			
CAS-No.	247595-29-5		
Formula	C ₃₁ H ₂₇ NO ₄ S		
Mol. weight	509,62 g/mol		
FAA5650	Fmoc-D-Cys(Dpm)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenyl-methyl-D-cysteine			
Formula	C ₃₁ H ₂₇ NO ₄ S		
Mol. weight	509,62 g/mol		

Reference:

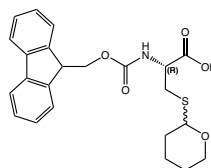
→ *Acid-labile Cys-protecting groups for the Fmoc/tBu strategy: filling the gap*; M. Gongora-Benitez, L. Mendive-Tapia, I. Ramos-Tomillero, A. C. Breman, J. Tulla-Puche, F. Albericio; **Org Lett** 2012; **14**: 54725. <https://doi.org/10.1021/ol3025>

2.1.4. Tetrahydropyranyl (Thp)

Tetrahydropyranyl (Thp) is an S,O-acetal nonaromatic protecting group for cysteine which has been shown to be superior to Trt, Dpm, Acn, and StBu in solid-phase peptide synthesis using the Fmoc/tBu strategy. Thp is stable in mildly acidic conditions (1% TFA in DCM), but its acid-lability is strongly increased in the presence of TIS. Cys(Thp)-protected peptides exist as a diastereomeric mixture; however, once cleaved in concentrated TFA with a scavenger (e.g., 95% TFA, 2.5% TIS in DCM), a single pure product is obtained. Racemization is also decreased compared to Trt, Dpm or StBu, and fewer side products, e.g., C-terminal 3-(1-piperidinyl)alanine adducts, are observed. More recently, Thp has been explored as a protecting group for additional amino acid residues such as serine and threonine.

Furthermore, Thp protection leads to improved solubility of the respective cysteine-containing protected peptides. Complete Thp deprotection can be carried out with either TFA/TIS/DCM (10:1.5:88.5) within 5 min or with HCl/dioxane (12:88) in 2 h. Additionally, Thp is stable to standard Fmoc SPPS reagents.

		Product details
FAA4160	Fmoc-L-Cys(Thp)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-tetrahydropyranyl-L-cysteine		
CAS-No.	1673576-83-4	
Formula	C ₂₃ H ₂₅ NO ₃ S	
Mol. weight	427,15 g/mol	



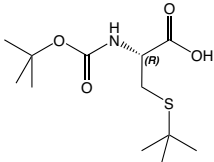
References:

- *Tetrahydropyranyl, a nonaromatic acid-labile Cysteineprotecting group for Fmoc peptide chemistry*; I. Ramos-Tomillero, H. Rodriguez, F. Albericio; **Org Lett** 2015; **17**: 1680-3. <https://doi.org/10.1021/acs.orglett.5b00444>
- *Studies on the Synthesis of Insulin Peptides*; G. F. Holland, L. A. Cohen; **J. Am. Chem. Soc.** 1958; **80(14)**: 3765-3769. <https://doi.org/10.1021/ja01547a075>
- *Understanding Tetrahydropyranyl as a Protecting Group in Peptide Chemistry*; A. Sharma, I. Ramos-Tomillero, A. El-Faham, E. Nicolas, H. Rodriguez, B. G. de la Torre, F. Albericio; **ChemistryOpen** 2017; **6**: 168-177. <https://dx.doi.org/10.1002/open.201600156>

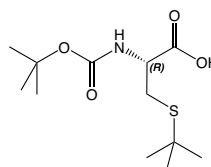
2.1.5. tert-Butyl (tBu)

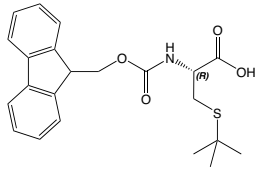
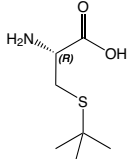
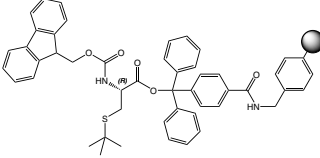
Cleavage of tBu can be achieved with HF using anisole as scavenger and TFA in the presence of 2,2'-dithiobis(5-nitropyridine) (DTNP). To form the disulfide, cleavage may be performed using silyl chloride-sulfoxide in TFA, Ti(TFA)₃ or DMSO in TFA (with DMSO acting as an oxidant). If orthogonality to MeB is desired, DMSO/TFA may also be used for deprotection – tBu is cleaved in DMSO/TFA at room temperature, whilst higher temperatures (45 °C) are required to cleave MeB. The above-mentioned methods of deprotection are rather harsh and often result in the formation of side products and low yields. PdCl₂ in a 50 mM Tris or urea buffer at 37 °C was shown to cleave tBu, providing a much milder way to remove the protecting group. tBu is not removed by [Pd(allyl)Cl]₂ making it orthogonal to Thz and AcM under those conditions. Besides this, the Cys(tBu) protecting group is stable to oxidation by I₂, stable towards AgOTf/TFA, neat TFA treatment as well as standard Fmoc SPPS reagents.

		Product details
BAA1082	Boc-L-Cys(tBu)-OH	
N-alpha-t-Butyloxycarbonyl-S-t-butyl-L-cysteine		
CAS-No.	56976-06-8	
Formula	C ₁₂ H ₂₃ NO ₄ S	
Mol. weight	277,37 g/mol	



The chemical structure shows Boc-L-Cys(tBu)-OH. It consists of a tert-butyl group attached to an oxygen atom, which is part of a carbonyl group (C=O). This carbonyl is connected to a nitrogen atom (NH) via a single bond. The nitrogen atom is further connected to a chiral carbon atom (C) marked with a wedge bond and labeled (R). This chiral carbon is also bonded to a carboxylic acid group (COOH) and a side chain consisting of a methylene group (CH2) and a sulfur atom (S) bonded to a tert-butyl group.



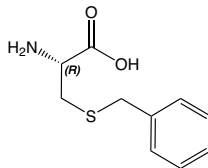
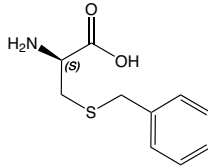
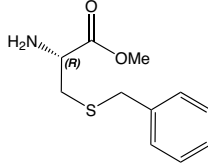
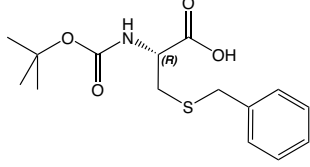
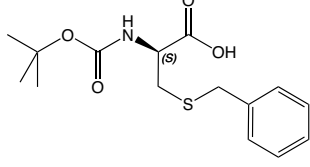
		Product details
FAA1716 Fmoc-L-Cys(tBu)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-t-butyl-L-cysteine CAS-No. 67436-13-9 Formula C ₂₂ H ₂₅ NO ₄ S Mol. weight 399,51 g/mol		
HAA6150 H-L-Cys(tBu)-OH*HCl S-t-Butyl-L-cysteine hydrochloride CAS-No. 2481-09-6 Formula C ₇ H ₁₅ NO ₂ S*HCl Mol. weight 177,26*36,45 g/mol		
TCP1120 Fmoc-L-Cys(tBu)-TCP-Resin Fmoc-Cys(tBu)-trityl-carboxyamidomethyl polystyrene Mesh Size 200-400 mesh Loading 0.3-0.8 mmol/g DVB 1% DVB		

References:

- *Palladium prompted on-demand cysteine chemistry for the synthesis of challenging and uniquely modified proteins*; M. Jbara, S. Laps, M. Morgan, G. Kamnesky, G. Mann, C. Wolberger, A. Brik; **Nat. Commun.** 2018; **9**: 3154. <https://doi.org/10.1038/s41467-018-05628-0>
- *Synthesis of Four-Disulfide Insulin Analogs via Sequential Disulfide Bond Formation*; F. Wu, J. P. Mayer, V. M. Gelfanov, F. Liu, R. D. DiMarchi; **J. Org. Chem.** 2017; **82(7)**: 3506-3512. <https://doi.org/10.1021/acs.joc.6b03078>
- *2,2'-Dithiobis(5-nitropyridine) (DTNP) as an effective and gentle deprotectant for common cysteine protecting groups*; A. L. Schroll, R. J. Hondal, S. Flemer Jr.; **J. Pept. Sci.** 2012; **18(1)**: 1-9. <https://doi.org/10.1002/psc.1403>
- *Tert-Butyl group as thiol protection in peptide synthesis*; J. J. Pastuszak, A. Chimiak; **J. Org. Chem.** 1981; **46(9)**: 1868-1873. <https://doi.org/10.1021/jo00322a024>

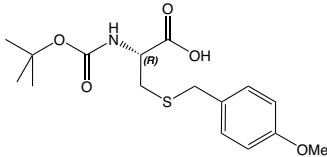
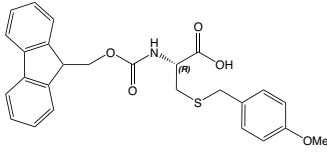
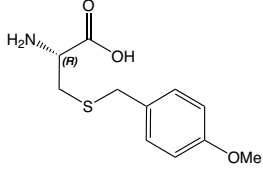
2.1.6 Benzyl (Bzl)

The Bzl group is the most stable acid-labile protecting group. The use of S-Bzl protection for cysteine is suitable for Boc/Bzl-based SPPS. The protecting group can be removed using Na/NH₃ or anhydrous HF in the presence of scavengers at room temperature. Nowadays, it is mainly replaced by more labile benzyl-based protecting groups such as Mob or Meb.

			Product details
HAA1574	H-L-Cys(Bzl)-OH		
S-Benzyl-L-cysteine			
CAS-No.	3054-01-1		
Formula	C ₁₀ H ₁₃ NO ₂ S		
Mol. weight	211,29 g/mol		
			
HAA6110	H-D-Cys(Bzl)-OH		
S-Benzyl-D-cysteine			
CAS-No.	23032-53-3		
Formula	C ₁₀ H ₁₃ NO ₂ S		
Mol. weight	211,29 g/mol		
			
HAA6080	H-L-Cys(Bzl)-OMe*HCl		
S-Benzyl-L-cysteine methyl ester hydrochloride			
CAS-No.	16741-80-3		
Formula	C ₁₁ H ₁₅ NO ₂ S*HCl		
Mol. weight	225,31*36,45 g/mol		
			
BAA1079	Boc-L-Cys(Bzl)-OH		
N-alpha-t-Butyloxycarbonyl-S-benzyl-L-cysteine			
CAS-No.	5068-28-0		
Formula	C ₁₅ H ₂₁ NO ₄ S		
Mol. weight	311,38 g/mol		
			
BAA5410	Boc-D-Cys(Bzl)-OH		
N-alpha-t-Butyloxycarbonyl-S-benzyl-D-cysteine			
CAS-No.	102830-49-9		
Formula	C ₁₅ H ₂₁ NO ₄ S		
Mol. weight	311,38 g/mol		
			

2.1.7. 4-Methoxybenzyl (Mob, 4-MBzl)

The conditions typically required for full removal of Mob are harsh: neat TFA at 100 °C or HF are reported for deprotection. Mob can also be removed by heavy metal salts, e.g., Hg(TFA)₂ or AgOTf in TFA/thio-anisole, followed by DTT to obtain the free thiol. Tl(TFA)₃ can also be used for deprotection. Besides this, deprotection via treatment with PdCl₂ in 50 mM Tris or urea buffer at 37 °C is reported. AgOTf cannot cleave Mob, making Mob and Meb orthogonal under this treatment. The Mob protecting group is stable to HBr, TFA (without scavengers) and standard Fmoc SPPS reagents.

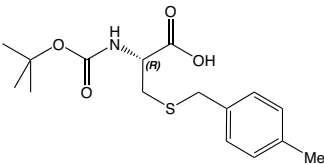
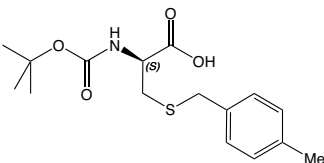
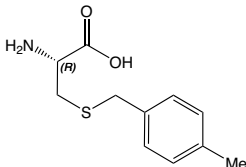
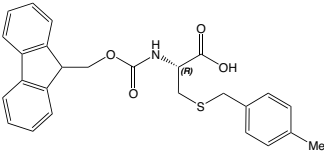
		Product details
BAA1081	Boc-L-Cys(Mob)-OH	
N- α -t-Butyloxycarbonyl-S-(4-methoxy-benzyl)-L-cysteine		
CAS-No.	18942-46-6	
Formula	C ₁₆ H ₂₃ NO ₅ S	
Mol. weight	341,43 g/mol	
		
FAA1715	Fmoc-L-Cys(Mob)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine		
CAS-No.	141892-41-3	
Formula	C ₂₆ H ₂₅ NO ₅ S	
Mol. weight	463,55 g/mol	
		
HAA6100	H-L-Cys(Mob)-OH	
S-(4-Methoxybenzyl)-L-cysteine		
CAS-No.	2544-31-2	
Formula	C ₁₁ H ₁₅ NO ₃ S	
Mol. weight	241,3 g/mol	
		

References:

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2.1.8. Methylbenzyl (Meb, 4-MeBn, 4-MeBzl)

The Meb protecting group is broadly similar to Mob but less labile to TFA. Meb can be removed using HF-anisole (50%, 1 h, 0 °C), $\text{Ti}(\text{TFA})_3$ or DMSO/TFA (45 °C). Meb is stable towards AgOTf and orthogonal to Trt, Acn, tBu and StBu. Consequently, these protecting groups have frequently been used together. Furthermore, Meb is stable towards standard Fmoc and Boc SPPS reagents.

		Product details
BAA1080	Boc-L-Cys(MBzl)-OH	
N-alpha-t-Butyloxycarbonyl-S-(4-methyl-benzyl)-L-cysteine		
CAS-No.	61925-77-7	
Formula	$\text{C}_{16}\text{H}_{23}\text{NO}_4\text{S}$	
Mol. weight	325,43 g/mol	
		
BAA5420	Boc-D-Cys(MBzl)-OH	
N-alpha-t-Butyloxycarbonyl-S-(4-methyl-benzyl)-D-cysteine		
CAS-No.	61925-78-8	
Formula	$\text{C}_{16}\text{H}_{23}\text{NO}_4\text{S}$	
Mol. weight	325,43 g/mol	
		
HAA6090	H-L-Cys(MBzl)-OH	
S-(4-Methylbenzyl)-L-cysteine		
CAS-No.	42294-52-0	
Formula	$\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$	
Mol. weight	225,3 g/mol	
		
FAA1714	Fmoc-L-Cys(MBzl)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methyl-benzyl)-L-cysteine		
CAS-No.	136050-67-4	
Formula	$\text{C}_{26}\text{H}_{25}\text{NO}_4\text{S}$	
Mol. weight	447,53 g/mol	
		

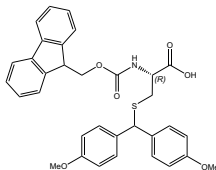
References:

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- Regioselective Formation of Multiple Disulfide Bonds with the Aid of Postsynthetic S-Tritylation; M. Mochizuki, S. Tsuda, K. Tanimura, Y. Nishiuchi; *Org. Lett.* 2015; **17(9)**: 2202-2205. <https://doi.org/10.1021/acs.orglett.5b00786>

2.1.9. 4,4'-Dimethoxydiphenylmethyl (Ddm)

This protecting group can be removed using 10% TFA (TFA:DCM:TIS:H₂O 10:85:2.5:2.5, 1 h, 25 °C). It is recommended as a racemization-suppressing alternative to Trt. Additionally, Ddm can be used as alternative to Mmt, if sterical hindrance of the bulky Mmt group is an issue. Ddm is compatible with standard Fmoc SPPS reagents.

		Product details
FAA6940	Fmoc-L-Cys(Ddm)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-di(4-methoxyphenyl)methyl-L-cysteine		
CAS-No.	1403825-56-8	
Formula	C ₃₃ H ₃₁ NO ₆ S	
Mol. weight	569,67 g/mol	
		

Reference:

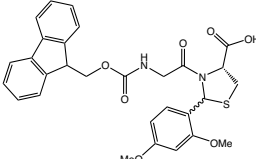
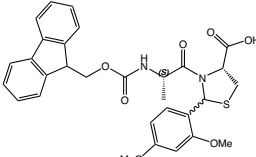
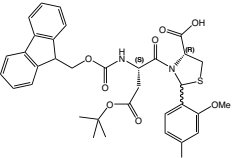
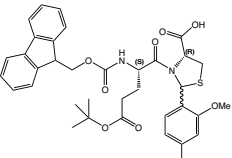
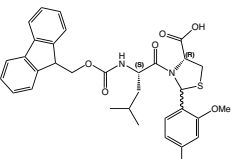
- Evaluation of acid-labile S-protecting groups to prevent cysteine racemization in Fmoc solid-phase peptide synthesis; H. Hibino, Y. Miki, Y. Nishiuchi; *J. Pept. Sci.* 2014; **20(1)**: 30-35. <https://doi.org/10.1002/psc.2585>

2.1.10. Pseudoprolines (ψPro)

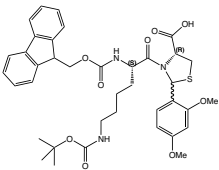
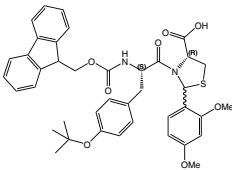
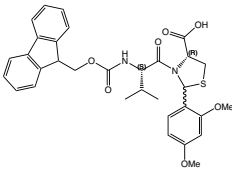
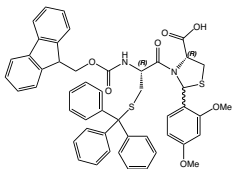
Pseudoprolines have developed as standard building blocks for peptide synthesis in order to disrupt aggregation, reduce aspartimide formation and thus help improving the yield of difficult and long sequences. Cysteine-based pseudoprolines are usually more stable than the corresponding oxazolidines of serine and threonine.

The proline-resembling thiazolidine ring of Cys-pseudoprolines simultaneously protects the side-chains and amino group of cysteine. Typically, pseudoprolines are incorporated into peptides using dipeptide building blocks. In the case of ψ^{Me,Me}Pro, the protected cysteine can be deprotected by TFA within hours.

This can be reduced to minutes when using $\psi^{H,Dmp}Pro$. Complete Cys($\psi^{Me,Me}Pro$) deprotection can alternatively be achieved with TFMSA at 0 °C within 15 min. Furthermore, $\psi^{H,Dmp}Pro$ shows stability to Pd(0) suggesting orthogonality to allyl-based protecting groups. Alternatively, for $\psi^{H,H}Pro$, the group is stable to strong acids. Besides this, in general, the kinetics of deprotection appear to be dependent on the acid and solvent system used. Notably, the use of pseudoproline induces a “kink” within the peptide backbone – similar to proline – which favors peptide macrocyclization.

		Product details
PSI1440 Fmoc-Gly-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-glycyl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 1926163-05-4 Formula C ₂₉ H ₂₈ N ₂ O ₇ S Mol. weight 548,61 g/mol		
PSI1450 Fmoc-L-Ala-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-alanyl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 2022956-37-0 Formula C ₃₀ H ₃₀ N ₂ O ₇ S Mol. weight 562,63 g/mol		
PSI1470 Fmoc-L-Asp(tBu)-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-beta-t-butyl-L-aspartyl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 1359754-16-7 Formula C ₃₅ H ₃₉ N ₂ O ₉ S Mol. weight 662,75 g/mol		
PSI1490 Fmoc-L-Glu(tBu)-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-gamma-t-butyl-L-glutamyl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 2565804-44-4 Formula C ₃₆ H ₄₀ N ₂ O ₉ S Mol. weight 676,78 g/mol		
PSI1510 Fmoc-L-Leu-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-leucyl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 1926163-06-5 Formula C ₃₃ H ₃₆ N ₂ O ₇ S Mol. weight 604,71 g/mol		

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		Product details
PSI1520 Fmoc-L-Lys(Boc)-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-N-epsilon- l-on-t-butyloxycarbonyl-L-lysyl)-2-(2,4-dimethoxyphenyl) thiazolidine-4-carboxylic acid CAS-No. 1926163-07-6 Formula C₃₈H₄₅N₃O₉S Mol. weight 719,84 g/mol		
PSI1560 Fmoc-L-Tyr(tBu)-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-O-t-bu- tyl-L-tyrosyl)-2-(2,4-dimethoxyphenyl)thiazolidi- ne-4-carboxylic acid Formula C₄₀H₄₂N₂O₈S Mol. weight 710,84 g/mol		
PSI1570 Fmoc-L-Val-L-Cys[PSI(Dmp,H)pro]-OH (S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-val- yl)-2-(2,4-dimethoxyphenyl)thiazolidine-4-carboxylic acid CAS-No. 1926163-08-7 Formula C₃₂H₃₄N₂O₇S Mol. weight 590,69 g/mol		
PSI1580 Fmoc-L-Cys(Trt)-L-Cys(Psi(Dmp,H)pro)-OH (R)-3-(N-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cy- steiny)-2-(2,4-dimethoxyphenyl)thiazolidine-4-car- boxylic acid CAS-No. 2022956-75-6 Formula C₄₉H₄₄N₂O₇S₂ Mol. weight 837,01 g/mol		

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- *Synthesis of Cyclogossine B Using a Traceless Pseudoproline Turn-Inducer*; M. S. Y. Wong, K. A. Jiliffe; **Aust. J. Chem.** 2009; **63**(5): 797-801. <https://doi.org/10.1071/CH09643>

2.2. Oxidation-Labile Protecting Group Acetamidomethyl (Acm)

Acm shows stability to commonly used peptide synthesis protocols, can be removed under relatively mild conditions and displays no major racemization problems. The Acm protecting group works orthogonal to a number of other cysteine protecting groups, e.g., Trt, tBu, Meb, Msbh, Mmt, and Dnpe. One deprotection method, for example, is the removal by using transition metal catalysts, such as Pd(II) complexes. Besides, cleavage can be triggered by using 15 eq. DTNP in 97.5% TFA/thioanisole, I₂, or Hg(OAc)₂.

One major disadvantage of the Acm group is the tendency of the cleaved protecting group to alkylate the electron rich aromatic rings of tyrosine and tryptophan. The synthesis of the following model sequence (including tyrosine and tryptophan) with Fmoc-Cys(Acm)-OH as building block clearly shows the three expected impurities in significant concentrations in the case of using Acm.

Target sequence:

Ala – Cys– Phe – Trp – Lys – Tyr – Cys– Val

Side products:

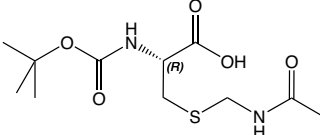
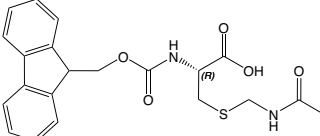
Ala – Cys– Phe – **Trp(Acm)** – Lys – Tyr – Cys– Val

Ala – Cys– Phe – Trp – Lys – **Tyr(Acm)** – Cys– Val

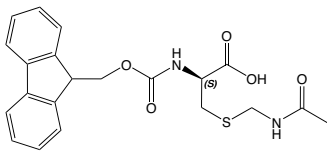
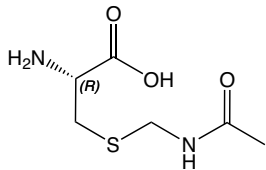
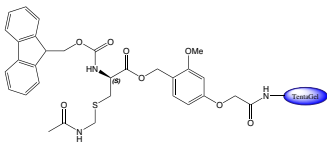
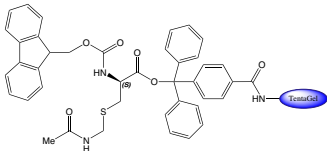
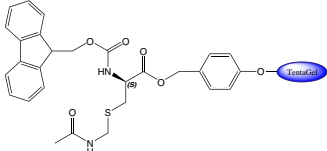
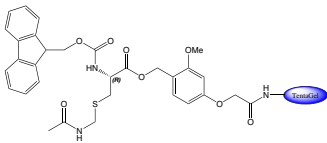
Ala – Cys– Phe – **Trp(Acm)** – Lys – **Tyr(Acm)** – Cys– Val

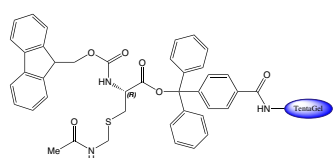
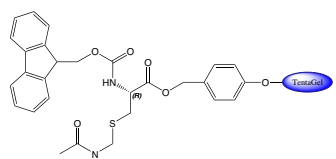
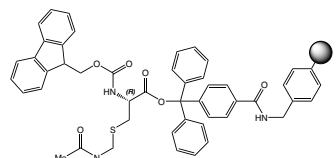
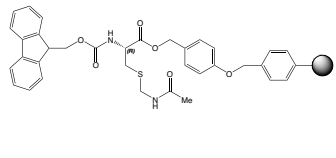
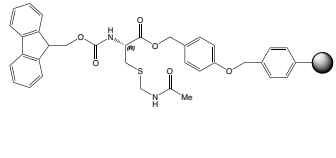
Fig. 3: Side products formed by back-alkylation when using Acm as cysteine protecting group.

Alternatives to the Acm protecting group are represented by Phacm and Allocam.

		Product details
BAA1078 Boc-L-Cys(Acm)-OH N- α -t-Butyloxycarbonyl-S-(acetyl-aminomethyl)-L-cysteine CAS-No. 19746-37-3 Formula C ₁₁ H ₂₀ N ₂ O ₅ S Mol. weight 292,36 g/mol		
FAA1506 Fmoc-L-Cys(Acm)-OH N- α -(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-cysteine CAS-No. 86060-81-3 Formula C ₂₁ H ₂₂ N ₂ O ₅ S Mol. weight 414,48 g/mol		

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			Product details
FAA6230	Fmoc-D-Cys(Acm)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-cysteine CAS-No. 168300-88-7 Formula $C_{21}H_{22}N_2O_3S$ Mol. weight 414,48 g/mol			
HAA6070	H-L-Cys(Acm)-OH*HCl		
S-(Acetyl-aminomethyl)-L-cysteine hydrochloride CAS-No. 28798-28-9 Formula $C_6H_{12}N_2O_3S \cdot HCl$ Mol. weight 192,24*36,45 g/mol			
SAD1107	Fmoc-D-Cys(Acm)-AC TG		
Fmoc-D-Cys(S-Acm)-[3-methoxy-4-hydroxymethyl] phenoxyacetylamid] TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g			
SAD1207	Fmoc-D-Cys(Acm)-Trt TG		
Fmoc-D-Cys(S-Acm)-Trityl TentaGel S Mesh Size 90 µm Loading 0.15-0.25 mmol/g			
SAD1307	Fmoc-D-Cys(Acm)-Wang TG		
Fmoc-D-Cys(S-Acm)-Wang TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g			
SAL1107	Fmoc-L-Cys(Acm)-AC TG		
Fmoc-L-Cys(S-Acm)-[3-methoxy-4-hydroxymethyl] phenoxyacetylamid] TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g			

		Product details
SAL1207	Fmoc-L-Cys(Acm)-Trt TG	
Fmoc-L-Cys(S-Acm)-Trityl TentaGel S		
Mesh Size	90 µm	
Loading	0.15-0.25 mmol/g	
		
SAL1307	Fmoc-L-Cys(Acm)-Wang TG	
Fmoc-L-Cys(S-Acm)-Wang TentaGel S		
Mesh Size	90 µm	
Loading	0.16-0.26 mmol/g	
		
TCP1110	Fmoc-L-Cys(Acm)-TCP-Resin	
Fmoc-Cys(Acm)-trityl-carboxyamidomethyl polystyrene		
Mesh Size	200-400 mesh	
Loading	0.3-0.8 mmol/g	
DVB	1% DVB	
		
WAA11307	Fmoc-L-Cys(Acm)-Wang Resin	
Fmoc-L-Cys(S-Acm)-Wang Resin		
Mesh Size	100-200 mesh	
DVB	1% DVB	
		
WAA41307	Fmoc-L-Cys(Acm)-Wang Resin	
Fmoc-L-Cys(S-Acm)-Wang Resin		
Mesh Size	200-400 mesh	
DVB	1% DVB	
		

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<https://doi.org/10.1002/bip.21502>

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2.3. Base-Labile Protecting Groups

Base-labile protecting groups include 9-fluorenylmethyl (Fm; cleavage with eg. HF:anisole 95:5, 1 h, 0 °C), 2-(2,4-dinitrophenyl)ethyl (Dnpe; cleavage using 50% piperidine in DMF, 30 min), 9-Fluorenylmethoxy-carbonyl (Fmoc; transformation to Fm by treatment with Et₃N). Like all other base-labile protecting groups, they are incompatible with Fmoc SPPS.

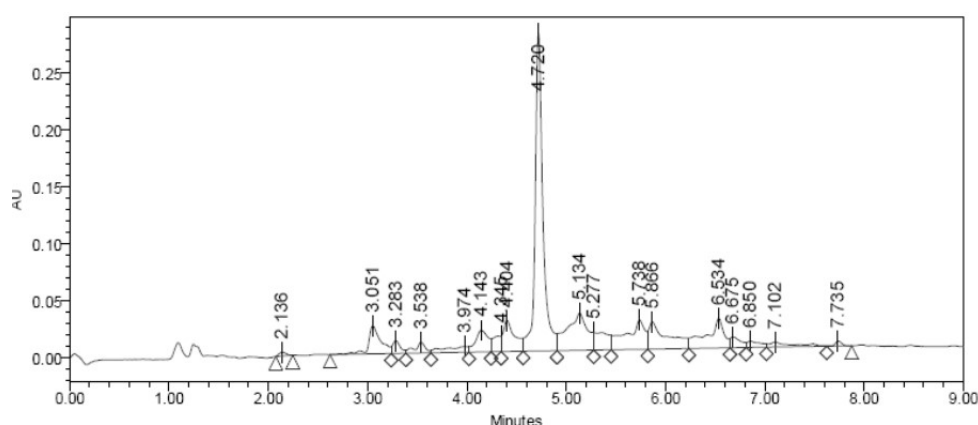
2.4. Enzyme-Labile Protecting Groups

2.4.1. Phenylacetamidomethyl (Phacm)

Phacm shows the same stability and orthogonality as Ac_m and has the additional advantage that it can be deprotected either chemically by I₂/AcOH, or enzymatically by Penicillin G Amidase (PGA). Phacm is stable to standard Fmoc and Boc SPPS reagents.

Through the mild and highly specific conditions when removing Phacm with PGA, no adduct formation occurs and the desired cyclic peptide is being formed in high yield. This also holds true if Phacm is removed chemically with I₂. PGA (penicillin G amidase, penicillin acylase, penicillin amidohydrolase from *E. coli* on acrylic resin, systematic name: penicillin amidohydrolase, E.C. 3.5.1.11) has an active pocket which is very specific for phenylacetic acid (Phac). The most prominent commercial use is hydrolysis of a phenylacetamid bond during production of the penicillin API 6-APA (DeMartin *et al.*, **J. Mol. Catal. B: Enzymatic** 1999; **6**: 437). The high specificity of PGA towards the phenylacetyl moiety makes the use of Phacm very promising as alternative for Ac_m. The principle capability of using PGA for hydrolyzing Phacm and deprotecting cysteine already was discovered by Albericio *et al.* in 1995 using native PGA. Adding co-solvents like acetonitrile helps to improve the solubility of hydrophobic sequences. Water in combination with DMSO (80:20) will make deprotection and cyclization a one-pot reaction, which is usually completed within 16 h to 24 h (37 °C, pH 7).

Peptide Synthesis with Fmoc-Cys(Ac_m)



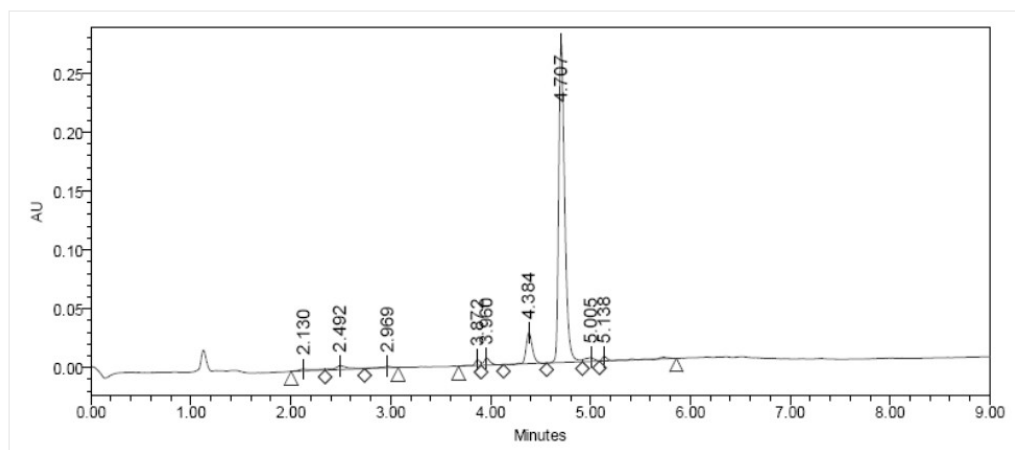
Adduct Formation with Trp and Tyr:

Several impurities present in significant concentration of peptides carrying Tyr(Acm), Trp(Acm).

Orthogonality: Fmoc, Boc

Deprotection: TFA, Npys, I₂, Tl³⁺, Ph₂SO, MeSiCl₃

Peptide Synthesis with Fmoc-Cys(Phacm)



No Adduct Formation:

- clean crude peptide
- clean product and high yield

Orthogonality: same as Acm

Deprotection: same as Acm **and** by hydrolysis in the presence of PGA, water:DMSO (80:20), pH 7, 37 °C, 16-24 h

Fig. 4: Comparison of Fmoc-Cys(Acm) and Fmoc-Cys(Phacm) as building blocks for peptide synthesis.

Isolated in 1997 off the coast of Mozambique from marine species, the cyclothiopeptide thiocoralline has been identified as a potent antitumor agent. Four *N*-methylated amino acids and two of them in *D* configuration mask a DNA bisintercalating chromophore. It has several features that make its structure extremely complex. In particular the high number of cysteines, the presence of consecutive *N*-methyl-amino acids, and a bicyclic structure formed by a disulfide bridge flanked by two thioester moieties, makes it a real challenge for synthetic chemists.

Albericio *et al.* mastered the synthesis by selecting an orchestrated scheme of protecting groups where the key technology was using the phenylacetamidomethyl (Phacm) group, since it can be cleaved under very mild, i.e. aqueous, conditions.

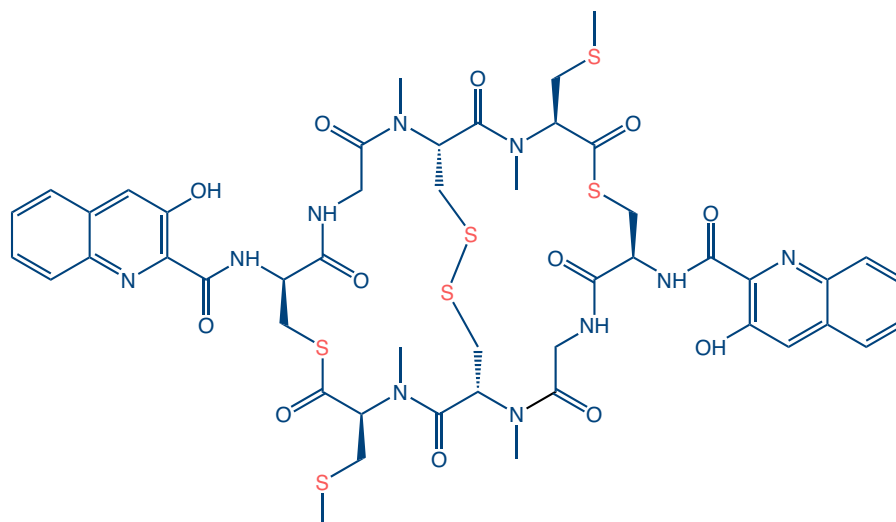
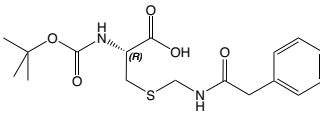
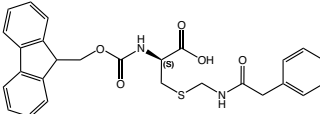
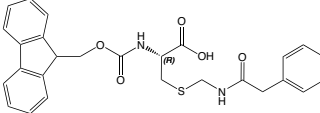


Fig. 5: Chemical structure of the cyclodepsipeptide thiocoraline.

		Product details
BAA6390 Boc-L-Cys(Phacm)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-(Phenylacetylaminomethyl)-L-cysteine CAS-No. 57084-73-8 Formula C ₁₇ H ₂₄ N ₂ O ₅ S Mol. weight 368,45 g/mol		 
FAA3710 Fmoc-D-Cys(Phacm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(phenylacetylaminomethyl)-D-cysteine CAS-No. 1565818-55-4 Formula C ₂₇ H ₂₆ N ₂ O ₅ S Mol. weight 490,57 g/mol		 
FAA6910 Fmoc-L-Cys(Phacm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-Phenylacetylaminomethyl)-L-cysteine CAS-No. 159680-21-4 Formula C ₂₇ H ₂₆ N ₂ O ₅ S Mol. weight 490,57 g/mol		 

References:

- Enzyme-labile protecting groups for the synthesis of natural products: solid-phase synthesis of thiocoraline; J. Tulla-Puche, M. Gongora-Benitez, N. Bayo-Puxan, A. M. Francesch, C. Cuevas, F. Albericio; *Angew. Chem. Int. Ed. Engl.* 2013; **52**: 5726-30. <https://doi.org/10.1002/anie.201301708>
- S-Phenylacetamidomethyl (Phacm): an orthogonal cysteine protecting group for Boc and Fmoc solid-phase peptide synthesis strategies; M. Royo, J. Alsina, E. Giralt, U. Slomczynska, F. Albericio; *J. Chem. Soc., Perkin Trans. 1* 1995; 1095-1102. <https://doi.org/10.1039/p19950001095>

2.5. Palladium-Labile Protecting Groups

2.5.1. Allyloxycarbonyl (Alloc, Aloc)

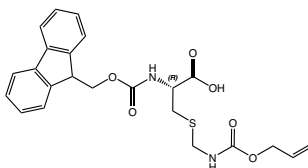
Alloc groups can be deprotected using tributyltin hydride (Bu_3SnH) and a Pd(0) catalyst. Removal can be achieved within 10 min using $\text{PdCl}_2(\text{PPh}_3)_2$ in DCM and AcOH with Bu_3SnH . The Alloc group is stable in TFA/DCM (24 h, 50 °C), but base-labile. Piperidine treatment (30% in DMF, 3 h, 30 °C) of Boc-Cys(Alloc)-OH results in complete removal of the Alloc group. Additionally, under Fmoc conditions, the Alloc group is prone to undergoing $\beta \rightarrow \alpha$ shifts, and intramolecular acylation reactions may also occur. These issues hinder its suitability as a cysteine protecting group. As such, other allyl-based Pd-labile protecting groups, such as Allocam, are recommended instead.

References:

- Allyl-based groups for side-chain protection of amino-acids; A. Loffet, H. X. Zhang; *Int. J. Pept. Prot. Res.* 1993; **42**(4): 346-351. <https://doi.org/10.1111/j.1399-3011.1993.tb00504.x>
- Use of Alloc-amino acids in solid-phase peptide synthesis. Tandem deprotection-coupling reactions using neutral conditions; N. Thieriet, J. Alsina, E. Giralt, F. Guibé, F. Albericio; *Tetrahedron Lett* 1997; **38**: 7275-7278. [https://doi.org/10.1016/s0040-4039\(97\)01690-0](https://doi.org/10.1016/s0040-4039(97)01690-0)

2.5.2. Allyloxycarbonylaminomethyl (Allocam)

The Allocam-protecting group, which is a variant of the Acm protecting group, allows for a palladium-mediated single-step approach using mild reaction conditions and readily available reagents. The Allocam group can be removed using Bu_3SnH and a Pd(0) catalyst in AcOH (10 min, RT). Cys(Allocam) displays stability towards piperidine but is slightly unstable to the acidic conditions used for Boc removal, with ~10% degradation seen following 20 h of treatment with 25% TFA in DCM. Besides this, Allocam is stable to standard Fmoc SPPS reagents.

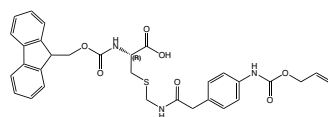
		Product details
FAA7610	Fmoc-L-Cys(Allocam)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((allyloxycarbonylamino)methyl)-L-cysteine		
CAS-No.	232953-09-2	
Formula	C ₂₃ H ₂₄ N ₂ O ₆ S	
Mol. weight	456,51 g/mol	
		

References:

- Direct palladium-mediated on-resin disulfide formation from Allocam protected peptides; T. D. Kondasinghe, H. Y. Saraha, S. B. Odeesho, J. L. Stockdill; **Org Biomol Chem** 2017; **15**: 2914-2918. <https://doi.org/10.1039/c7ob00536a>
- Disulfide Formation Strategies in Peptide Synthesis; T. M. Postma, F. Albericio; **Eur. J. Org. Chem.** 2014; **17**: 3519-3530. <https://doi.org/10.1002/ejoc.201402149>
- Allylic protection of thiols and cysteine: I: The allyloxycarbonylaminoethyl group; A. Malanda Kimbonguila, A. Merzouk, F. Guibé, A. Loffet; **Tetrahedron** 1999; **55**: 6931-6944. [https://doi.org/10.1016/s0040-4020\(99\)00322-1](https://doi.org/10.1016/s0040-4020(99)00322-1)
- Allylic protecting groups and their use in a complex environment part II: Allylic protecting groups and their removal through catalytic palladium π -allyl methodology; F. Guibé; **Tetrahedron** 1998; **54**: 2967-3042. [https://doi.org/10.1016/s0040-4020\(97\)10383-0](https://doi.org/10.1016/s0040-4020(97)10383-0)
- The allyloxycarbonylaminoethyl group: a new allytic protection for the thiol group of cysteine; A. M. Kimbonguila, A. Merzouk, F. Guibé, A. Loffet; **Tetrahedron Lett** 1994; **35**: 9035-9038. [https://doi.org/10.1016/0040-4039\(94\)88420-x](https://doi.org/10.1016/0040-4039(94)88420-x)

2.5.3. (Allyloxycarbonylamino)phenylacetylaminomethyl (Aapam)

Cys(Aapam) represents an Alloc protected Phacm linker as removable side-chain modification for the incorporation of e.g., solubility tags facilitating the preparation of hydrophobic peptides and proteins. The Alloc-Phacm cysteine can easily be introduced in peptides during Fmoc SPPS. The Alloc group can then be removed by using tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄] in the presence of phenylsilane with the Phacm group being completely stable under these conditions. After Alloc-deprotection, further groups can be coupled to the remaining free amine of Phacm, e.g., a solubility tag. The fully synthesized peptide can be cleaved from the resin by using TFA and the solubilized peptide fragments can be assembled by ligation. Finally, the Phacm-linked solubility tag can easily be removed in solution by treatment with PdCl₂ to yield the fully unprotected cysteine side-chain. As the resulting free cysteine can be converted to alanine through desulfurization, the Alloc-Phacm linker can be used as side-chain modification to incorporate solubility tag at the position of cysteine, but also of alanine.

		Product details
FAA5150	Fmoc-L-Cys(Aapam)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((4-(allyloxycarbonylamino)phenylacetylaminomethyl)-L-cysteine		
CAS-No.	1946783-89-6	
Formula	C ₃₁ H ₃₁ N ₃ O ₇ S	
Mol. weight	589,66 g/mol	
		

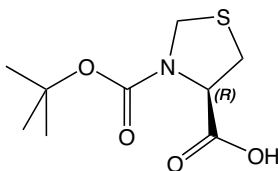
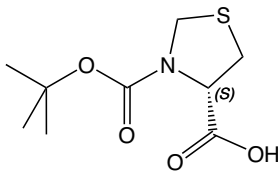
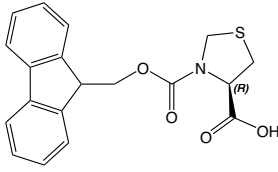
References:

- Palladium Mediated Rapid Deprotection of N-Terminal Cysteine under Native Chemical Ligation Conditions for the Efficient Preparation of Synthetically Challenging Proteins; M. Jbara, S. K. Maity, M. Seenaiyah, A. Brik; *J. Am. Chem. Soc.* 2016; **138**(15): 5069-5075. <https://doi.org/10.1021/jacs.5b13580>
- Palladium-assisted removal of a solubilizing tag from a Cysteine Side Chain to Facilitate Peptide and Protein Synthesis; S. K. Maity, G. Mann, M Jbara, S. Laps, G. Kamnesky, A. Brik; *Org. Lett.* 2016; **18**(12): 3026-3029. <https://doi.org/10.1021/acs.orglett.6b01442>

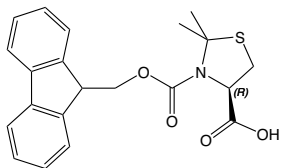
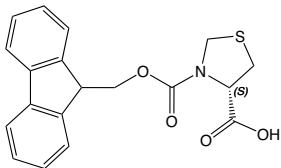
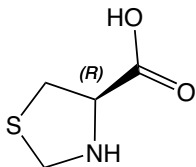
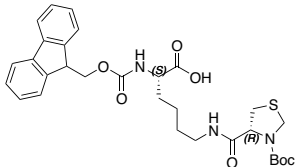
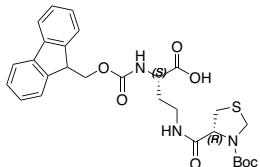
2.6. N-terminal Cysteine Protecting Groups

2.6.1. Thiazolidine (Thz)

The Thz group simultaneously protects the thiol and the amino group of cysteine and can be removed using oxidants such as H_2O_2 and I_2 . Removal will also occur following treatment with iodoacetic acid and benzyl chloride (pH 10–11, RT), or ferric chloride in air (pH 10). Alternatively, deprotection of Thz can be achieved by adjusting the reaction mixture to ca. pH 4 in the presence of a large excess of methoxyamine.

			Product details
BAA1135	Boc-L-Thz-OH		
(R)-N-t-Butyloxycarbonyl-thiazolidine-4-carboxylic acid			
CAS-No.	51077-16-8		
Formula	$C_9H_{15}NO_4S$		
Mol. weight	233,29 g/mol		
			
BAA1186	Boc-D-Thz-OH		
(S)-N-(t-Butyloxycarbonyl)-thiazolidine-4-carboxylic acid			
CAS-No.	63091-82-7		
Formula	$C_9H_{15}NO_4S$		
Mol. weight	233,29 g/mol		
			
FAA1427	Fmoc-L-Thz-OH		
(R)-N-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid			
CAS-No.	133054-21-4		
Formula	$C_{19}H_{17}NO_4S$		
Mol. weight	355,42 g/mol		
			

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			Product details
FAA1437	Fmoc-L-Thz(Me2)-OH		
(R)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid			
CAS-No.	873842-06-9		
Formula	C ₂₁ H ₂₁ NO ₄ S		
Mol. weight	383,46 g/mol		
FAA1495	Fmoc-D-Thz-OH		
(S)-N-alpha-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid			
CAS-No.	198545-89-0		
Formula	C ₁₉ H ₁₇ NO ₄ S		
Mol. weight	355,42 g/mol		
HAA1132	H-L-Thz-OH		
(R)-Thiazolidine-4-carboxylic acid			
CAS-No.	34592-47-7		
Formula	C ₄ H ₇ NO ₂ S		
Mol. weight	133,16 g/mol		
FAA9320	Fmoc-L-Lys(Boc-Thz)-OH		
N2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N6-((R)-3-(tert-butoxycarbonyl)thiazolidine-4-carboxyl)-L-lysine			
Formula	C ₃₀ H ₃₇ N ₃ O ₇ S		
Mol. weight	583,70 g/mol		
FAA9330	Fmoc-L-Dab(Boc-Thz)-OH		
(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((R)-3-(tert-butoxycarbonyl)thiazolidine-4-carboxamido)butanoic acid			
CAS-No.	2968514-54-5		
Formula	C ₂₈ H ₃₃ N ₃ O ₇ S		
Mol. weight	555,65 g/mol		

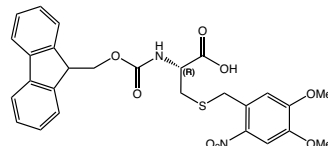
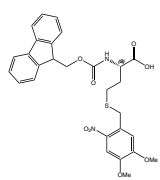
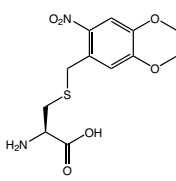
References:

- *The Action of Formaldehyde upon Cysteine*; S. Ratner, H. T. Clarke; **J. Am. Chem. Soc.** 1937; **59(1)**: 200-206.
<https://doi.org/10.1021/ja01280a050>
- *Palladium in the Chemical Synthesis and Modification of Proteins*; M. Ibara, S. Kumar Maity, A. Brik; **Angew. Chem. Int. Ed.** 2017; **56(36)**: 10644-10655. <https://doi.org/10.1002/anie.201702370>

2.7. Photolabile Protecting Groups

2.7.1. 2-Nitroveratryl (oNv)/Dimethoxynitrobenzyl (DMNB)

2-Nitroveratryl (oNv) is a photolabile orthogonal protecting group that is compatible with SPPS protocols and can be cleaved by irradiation with UV light (350 nm, 30 min, aq. media) under ambient conditions. No significant racemization is observed upon incorporation of Cys(oNv) during SPPS using diisopropyl-carbodiimide (DIC) and HOBt activation. Combination with S-pyridinesulfonyl activation allows for rapid *in situ* disulfide bond formation. In order to demonstrate the versatility of this approach, it was applied to the synthesis of a number of model peptides, e.g., oxytocin, α -conotoxin Iml, and human insulin.

		Product details
FAA3970 Fmoc-L-Cys(oNv)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-cysteine CAS-No. 214633-71-3 Formula $C_{27}H_{26}N_2O_8S$ Mol. weight 538,57 g/mol		
FAA8870 Fmoc-L-hCys(oNv)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-homocysteine Formula $C_{28}H_{28}N_2O_8S$ Mol. weight 552,60 g/mol		
HAA9320 H-L-Cys(oNv)-OH S-(4,5-dimethoxy-2-nitrobenzyl)-L-cysteine CAS-No. 214633-68-8 Formula $C_{12}H_{16}N_2O_6S$ Mol. weight 316,33 g/mol		

Reference:

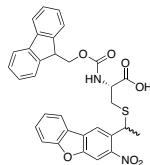
- 2-nitroveratryl as a photocleavable thiol-protecting group for directed disulfide bond formation in the chemical synthesis of insulin; J. A. Karas, D. B. Scanlon, B. E. Forbes, I. Vetter, R. J. Lewis, J. Gardiner, F. Separovic, J. D. Wade, M. A. Hossain; **Chemistry** 2014; **20**: 9549-52. <https://doi.org/10.1002/chem.201403574>
- A method for directed evolution and functional cloning of enzymes; H. Pedersen, S. Hölder, D. P. Sutherlin, U. Schwitter, D. S. King, P. G. Schultz; **PNAS** 1998; **95(18)**: 10523-10528. <https://doi.org/10.1073/pnas.95.18.10523>
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- *Biosynthetic selenoproteins with genetically-encoded photocaged selenocysteines*; R. Rakauskaitė, G. Urbanavičiūtė, A. Rukšėnaitė, Z. Liutkevičiūtė, R. Juškėnas, V. Masevičius, S. Klimašauskas; **Chem. Commun.** 2015; **51**: 8245-8248. <https://doi.org/10.1039/C4CC07910H>

2.7.2. Nitrodibenzofuran (NDBF)

Nitrodibenzofuran (NDBF) is a photocleavable side-chain protecting group that can be removed by photolysis upon irradiation with UV-light (365 nm) or – especially for *in vivo* applications – by two-photon excitation using near infrared light (800 nm). Additionally, NDBF deprotection results in clean conversion to the free thiol without the occurrence of S-to-N shifts. In addition, this cage exhibits a faster UV photolysis rate relative to simple nitrobenzyl PPGs. An example showed that NDBF is photolyzed 16–160 times more efficiently than other nitrobenzyl PPGs. Besides, NDBF is fully compatible with Fmoc SPPS. Additional methoxy-substitution (OMe-NDBF) leads to a higher two-photon photolysis efficiency compared to NDBF.

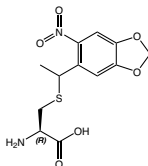
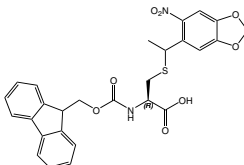
		Product details
FAA8420	Fmoc-L-Cys(NDBF)-OH	
N-alpha-(9-Fluorenylmethyloxycarbo- nyl)-S-(1-(3-nitro-dibenzofuran-2-yl)-ethyl)-L-cysteine		
CAS-No.	1895883-28-9	
Formula	C ₃₂ H ₂₆ N ₂ O ₇ S	
Mol. weight	582,62 g/mol	
		

References:

- *A red shifted two-photon-only caging group for three-dimensional photorelease*; Y. Becker, E. Unger, M. A. H. Fichte, D. A. Gacek, A. Dreuw, J. Wachtveitl, P. J. Walla, A. Heckel; **Chem. Sci.** 2018; **9**: 2797-2902. <https://doi.org/10.1039/c7sc05182d>
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- *The nitrodibenzofuran chromophore: a new caging group for ultra-efficient photolysis in living cells*; A. Momotake, N. Lindegger, E. Niggli, R. J. Barsotti, G. C. R. Ellis-Davies; **Nature Methods** 2006; **3**: 35-40. <https://doi.org/10.1038/NMETH821>
- *Methoxy-Substituted Nitrodibenzofuran-Based Protecting Group with an Improved Two-Photon Action Cross-Section for Thiol Protection in Solid Phase Peptide Synthesis*; T. K. Bader, F. Xu, M. H. Hodny, D. A. Blank, M. D. Distefano; **J. Org. Chem.** 2020; **85**: 1614-1625. <https://doi.org/10.1021/acs.joc.9b02751>

2.7.3. (Methylenedioxy)nitrophenylethyl (MDNPE)

Cys(MDNPE) can be uncaged by irradiation with 365 nm leading to the formation of a ketone as byproduct, which will not undergo undesired reactions with proteins.

		Product details
HAA9270	H-L-Cys(MDNPE)-OH	
1-[4',5'-(methylenedioxy)-2'-nitrophenyl]ethyl]-L-cysteine		
CAS-No.	1551078-43-3	 
Formula	C ₁₂ H ₁₄ N ₂ O ₆ S	
Mol. weight	314,31 g/mol	
FAA7945	Fmoc-L-Cys(MDNPE)-OH	
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl)-L-cysteine		
Formula	C ₂₇ H ₂₄ N ₂ O ₈ S	 
Mol. weight	536,56 g/mol	

References:

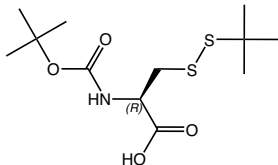
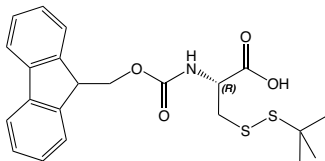
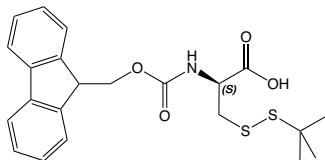
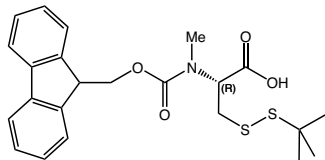
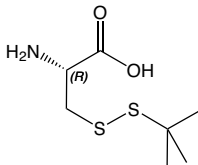
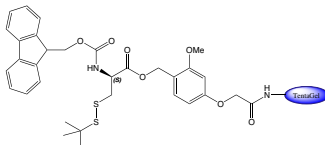
- Genetic Encoding of Photocaged Cysteine Allows Photoactivation of TEV Protease in Live Mammalian Cells; D. P. Nguyen, M. Mahesh, S. J. Elsässer, S. M. Hancock, C. Uttamapinant, J. W. Chin; **J. Am. Chem. Soc.** 2014; **136(6)**: 2240-2243. <https://doi.org/10.1021/ja412191m>
- Spatio-Temporal Photoactivation of Cytotoxic Proteins; R. Cruz-Samperio, R. J. Mart, L. Y. P. Luk, Y.-H. Tsai, A. T. Jones, R. K. Allemann; **ChemBioChem** 2022; **23**: e202200115. <https://doi.org/10.1002/cbic.202200115>

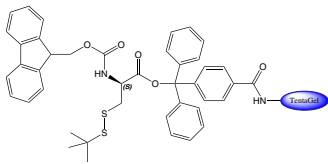
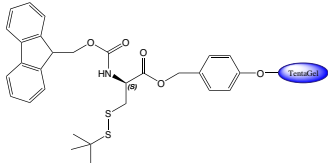
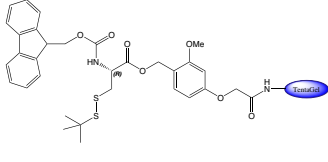
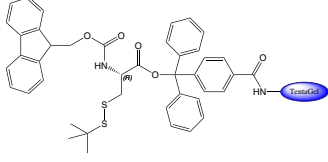
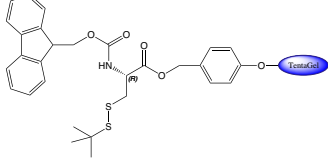
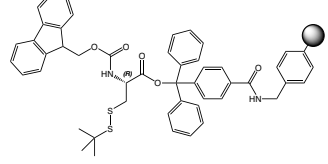
2.8. Reduction-Labile Protecting Groups

2.8.1. *tert*-Butylthio (StBu)

StBu can be removed under organic or aqueous conditions with reducing agents such as thiols, e.g., 2-mercaptoethanol or DTT, or phosphines (e.g., PBU₃, PPh₃, TCEP). The StBu protecting group is stable to acidic conditions (e.g., TFA:thioanisole:phenol, 92:5:2.5 v/v) provided no thiol scavenger is added. If required, 2-methylindole and anisole can be used as alternative scavengers. The StBu protecting group is orthogonal to other protecting groups, such as Trt, Acm, Meb/Mob, tBu, and Allocam. StBu is unstable towards HF and can be applied for both Fmoc and Boc SPPS.

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			Product details
BAA6415	Boc-L-Cys(StBu)-OH		
N-(<i>tert</i> -butoxycarbonyl)-S-(<i>tert</i> -butylthio)-L-cysteine			
CAS-No.	30044-61-2		
Formula	C ₁₂ H ₂₃ NO ₄ S ₂		
Mol. weight	309,44 g/mol		
			
FAA1575	Fmoc-L-Cys(StBu)-OH		
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-(<i>t</i> -butylthio)-L-cysteine			
CAS-No.	73724-43-3		
Formula	C ₂₂ H ₂₅ NO ₄ S ₂		
Mol. weight	431,57 g/mol		
			
FAA1965	Fmoc-D-Cys(StBu)-OH		
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-(<i>t</i> -butylthio)-D-cysteine			
CAS-No.	501326-55-2		
Formula	C ₂₂ H ₂₅ NO ₄ S ₂		
Mol. weight	431,57 g/mol		
			
FAA3340	Fmoc-L-MeCys(S-<i>t</i>Bu)-OH		
N-alpha-(9-Fluorenylmethoxycarbonyl)-N-alpha-methyl-S-(<i>t</i> -butylthio)-L-cysteine			
CAS-No.	1013096-03-1		
Formula	C ₂₃ H ₂₇ NO ₄ S ₂		
Mol. weight	445,59 g/mol		
			
HAA6140	H-L-Cys(StBu)-OH		
S-Thio- <i>t</i> -butyl-L-cysteine			
CAS-No.	30044-51-0		
Formula	C ₇ H ₁₅ NO ₂ S ₂		
Mol. weight	209,32 g/mol		
			
SAD1109	Fmoc-D-Cys(SS-<i>t</i>Bu)-AC TG		
Fmoc-D-Cys(S-S- <i>t</i> Bu)-[3-methoxy-4-hydroxymethyl]phenoxyacetylamid] TentaGel S			
Mesh Size	90 µm		
Loading	0.16-0.26 mmol/g		
			

		Product details
SAD1209	Fmoc-D-Cys(SS-tBu)-Trt TG Fmoc-D-Cys(S-S-tBu)-Trityl TentaGel S Mesh Size 90 µm Loading 0.15-0.25 mmol/g	 
SAD1309	Fmoc-D-Cys(SS-tBu)-Wang TG Fmoc-D-Cys(S-S-tBu)-Wang TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g	 
SAL1109	Fmoc-L-Cys(SS-tBu)-AC TG Fmoc-L-Cys(S-S-tBu)-[3-methoxy-4-hydroxymethyl]phenoxyacetylamid] TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g	 
SAL1209	Fmoc-L-Cys(SS-tBu)-Trt TG Fmoc-L-Cys(S-S-tBu)-Trityl TentaGel S Mesh Size 90 µm Loading 0.15-0.25 mmol/g	 
SAL1309	Fmoc-L-Cys(SS-tBu)-Wang TG Fmoc-L-Cys(S-S-tBu)-Wang TentaGel S Mesh Size 90 µm Loading 0.16-0.26 mmol/g	 
TCP1230	Fmoc-L-Cys(StBu)-TCP-Resin Fmoc-Cys(StBu)-trityl-carboxyamidomethyl polystyrene Mesh Size 200-400 mesh Loading 0.3-0.8 mmol/g DVB 1% DVB	 

[↑ back to content](#)

General Introduction

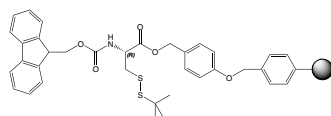
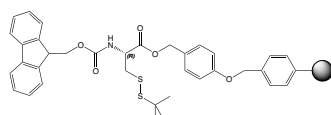
Cyclization via Disulfide Bond Formation

Cleland's Reagent – DTT

Chemoselective Ligation-Mediated Peptide Cyclization

Product Overview

Index

		Product details
WAA11309 Fmoc-L-Cys(SS-tBu)-Wang Resin Fmoc-L-Cys(S-S-tBu)-Wang Resin Mesh Size 100-200 mesh DVB 1% DVB		
		
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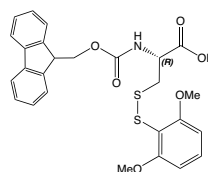
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- *Regioselective Formation of Multiple Disulfide Bonds with the Aid of Postsynthetic S-Tritylation*; M. Mochizuki, S. Tsuda, K. Tanimura, Y. Nishiuchi; **Org. Lett.** 2015; **17(9)**: 2202-2205. <https://doi.org/10.1021/acs.orglett.5b00786>
- *Trimethoxyphenylthio as a Highly Labile Replacement for tert-Butylthio Cysteine Protection in Fmoc Solid Phase Synthesis*; T. M. Postma, M. Giraud, F. Albericio; **Org. Lett.** 2012; **14(21)**: 5468-5471. <https://doi.org/10.1021/ol3025499>
- *S-Alkylmercapto-Gruppen zum Schutz der SH Funktion des Cysteins; I. Synthese und Stabilität einiger S-(Alkylmercapto)cysteine*; U. Weber, P. Hartter; **Hoppe-Seyler's Z. Physiol. Chem.** 1970; **351**: 1384-1388. <https://doi.org/10.1515/bchm2.1970.351.2.1384>

2.8.2. Dimethoxyphenylthio (S-Dmp) and 2,4,6-Trimethoxyphenylthio (S-Tmp)

Both groups can be removed using NMM (0.1 M) with either 20% 2-mercaptoethanol in DMF or 5% DTT in DMF in 5 min. Due to the fast deprotection with nucleophiles, S-Dmp can even be used in automated synthesizers. In contrast, removal of the StBu protecting group using the aforementioned conditions required 3 h of incubation with BME, whereas little to no deprotection of StBu was observed when using DTT. Both the S-Dmp and S-Tmp groups were noted to be compatible to Fmoc removal conditions (20% piperidine in DMF, 4 h).

		Product details
FAA3180	Fmoc-L-Cys(S-DMP)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2,6-dimethoxythiophenol)-L-cysteine		
CAS-No.	1403834-73-0	
Formula	C ₂₆ H ₂₅ NO ₆ S ₂	
Mol. weight	511,61 g/mol	



Reference:

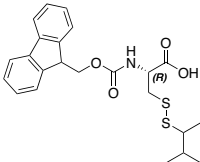
- *Trimethoxyphenylthio as a Highly Labile Replacement for tert-Butylthio Cysteine Protection in Fmoc Solid Phase Synthesis*; T. M. Postma, M. Giraud, F. Albericio; **Org. Lett.** 2012; **14(21)**: 5468-5471.
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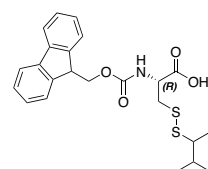
2.8.3. Sec-isoamyl mercaptan (SIT)

The new thiol protecting group sec-isoamyl mercaptan (SIT) expands the toolbox for the synthesis of peptides containing multiple disulfide bridges. The building block Fmoc-L-Cys(SIT)-OH ([FAA8495 on page 77](#)) is fully compatible with Fmoc solid phase peptide synthesis (SPPS), highly stable towards piperidine (basic conditions) and labile towards disulfide reducing agents. The secondary thiol SIT is more stable than primary ones but easier to remove than tertiary thiols such as StBu.

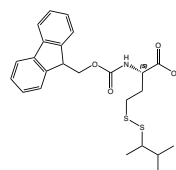
In a comparative study (Chakraborty *et al.*, 2020), the deprotection rate of Fmoc-Cys(StBu)-OH and Fmoc-Cys(SIT)-OH by using DTT as reducing agent was monitored by HPLC for 500 min. After that time, StBu was only partially (60%) removed. In contrast, after already 160 min, SIT was totally removed. Notably, the addition of 5% of water speeds up both reactions: StBu was completely removed within 250 min and SIT in less than 40 minutes. Furthermore, compared to the protecting groups StBu and Trt, SIT shows less racemization.

		Product details
FAA8495	Fmoc-L-Cys(SIT)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-cysteine		
CAS-No.	2545642-31-5	
Formula	C ₂₃ H ₂₇ NO ₄ S ₂	
Mol. weight	445,59 g/mol	





		Product details
FAA8865 Fmoc-L-hCys(SIT)-OH		
N-alpha-(9-Fluorenylmethyloxycarbo- nyl)-S-(sec-isoamyl mercaptan)-L-homocysteine		
Formula	C ₂₄ H ₂₉ NO ₄ S ₂	
Mol. weight	459,62 g/mol	



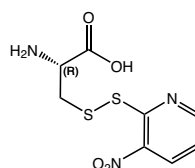
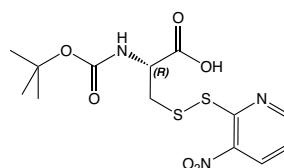
References:

- *Disulfide-Based Protecting Groups for the Cysteine Side Chain*; A. Chakraborty, A. Sharma, F. Albericio, B. G. de la Torre; **Org. Lett.** 2020; **22(24)**: 9644-9647. <https://doi.org/10.1021/acs.orglett.0c03705>
- *olid-Phase Synthesis of an "Inaccessible" hGH-Derived Peptide Using a Pseudoproline Monomer and SIT-Protection for Cysteine*; S. Rao Manne, A. Chakraborty, K. Rustler, T. Bruckdorfer, B. G. de la Torre, F. Albericio; **ACS Omega** 2022; **7(32)**: 28487-28492. <https://doi.org/10.1021/acsomega.2c03261>

2.8.4. 3-Nitro-2-pyridinesulphenyl (Npys)

Npys can be removed within 10 min using aliphatic thiols (e.g., 3-mercaptoacetic acid). Besides, deprotection can be triggered at room temperature by tertiary phosphines in the presence of H_2O . Cys(Npys) is stable to strong acids such as TFA (24 h, RT), HF (1 h, RT) and 4 M HCl/dioxane, and is thus suitable for Boc SPPS. S-Npys is somewhat stable towards aromatic thiols, which can cleave the O-Npys and N-Npys derivatives, enabling a degree of selectivity. The Npys group is not compatible with Fmoc chemistry. Npys is not stable under basic conditions like piperidine.

		Product details
BAA1860	Boc-L-Cys(Npys)-OH	
N-alpha- <i>t</i> -Butyloxycarbonyl-S-(3-nitro-2-pyridylthio)-L-cysteine		
CAS-No.	76880-29-0	
Formula	$C_{13}H_{17}N_3O_6S_2$	
Mol. weight	375,42 g/mol	
HAA3510	H-L-Cys(Npys)-OH*HCl	
S-(3-nitro-2-pyridylthio)-L-cysteine hydrochloride		
CAS-No.	108807-66-5	
Formula	$C_8H_9N_3O_4S_2 \cdot HCl$	
Mol. weight	275,30*36,45 g/mol	

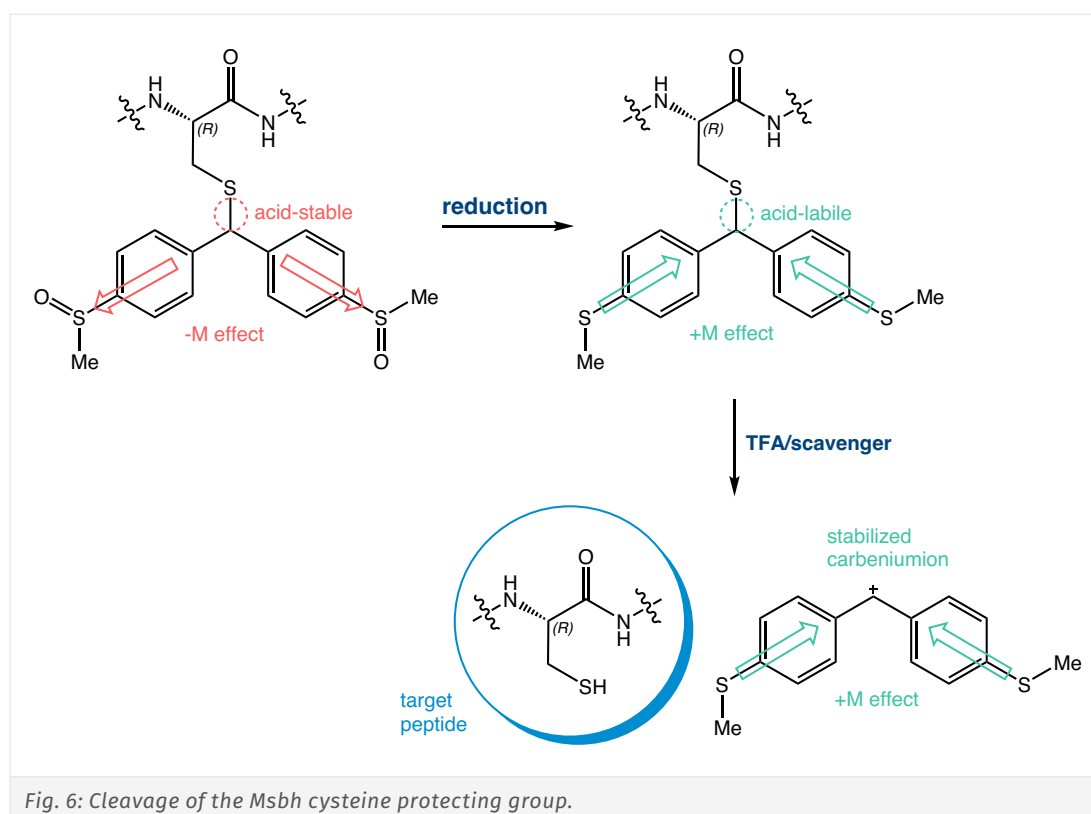


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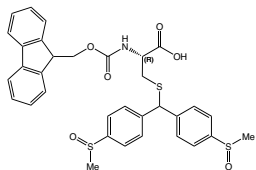
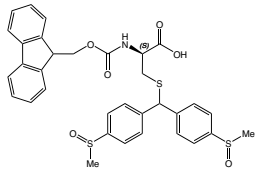
- Boc-Cys(Npys)-OH (BCNP): an appropriate reagent for the identification of T cell epitopes in cystine and/or cysteine-containing proteins; G. Mourier, B. Maillèrea, J. Cottona, M. Hervéa, S. Leroya, M. Léonettia, A. Ménéz; *J. Immunol. Methods* 1994; **171(1,2)**: 65-71. [https://doi.org/10.1016/0022-1759\(94\)90229-1](https://doi.org/10.1016/0022-1759(94)90229-1)
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- 3-Nitro-2-pyridinesulfonyl group: synthesis and applications to peptide chemistry; C. Rentier, K. Fukumoto, A. Taguchi, Y. Hayashi; *J. Pept. Sci.* 2017; **23(7-8)**: 496-504. <https://doi.org/10.1002/psc.2964>

2.9. Safety-Catch Protecting Group 4,4'-Bis(dimethylsulfinyl)benzhydryl (Msbh)

The term “safety-catch protecting group” means that the protecting group is stable/“safe” to a particular set of conditions until the group undergoes a specific reaction. Msbh is stable to acidic (TFA, HF), oxidative (and reductive conditions) until its electron-withdrawing sulfoxide groups are reduced. The formed sulfide renders the bond between the cysteine sulfhydryl group and the benzylic carbon of the Msbh group acid-labile and thus facilitates deprotection using TFA. Both steps can be performed in a one pot reaction using $\text{NH}_4\text{I}/\text{DMS}/\text{TFA}$. The innovative Msbh protecting group is stable to the deprotection conditions of most common cysteine PGs such as Mmt, Trt, Acm, or Phacm. Moreover, it is stable to conditions applied in both Boc and Fmoc chemistry.



Another suitable application for Msbh-protected cysteine is whenever there is an odd number of cysteines present in a peptide, where all cysteines except one are disulfide-brigged. In such cases, Msbh can be utilized to protect the side-chain of the one cysteine that is supposed to remain a free thiol and is therefore deprotected after all disulfide bonds have been installed. The advantage of using Msbh is that it may greatly reduce the risk of disulfide shuffling during deprotection of the last cysteine residue.

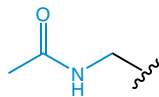
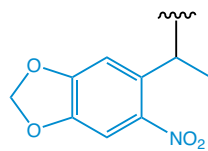
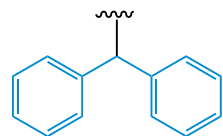
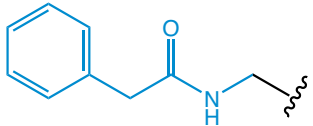
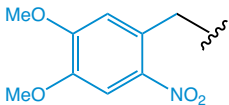
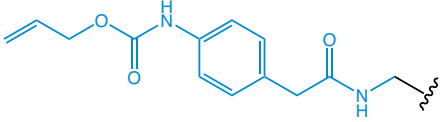
		Product details
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FAA8150 Fmoc-D-Cys(Msbh)-OH N-alpha-(9-Fluorenylmethoxycarbonyl)-S-(4,4'-dimethylsulfinylbenzhydryl)-D-cysteine Formula C ₃₃ H ₃₁ NO ₆ S ₃ Mol. weight 633,80 g/mol		

References:

- Total synthesis of human hepcidin through regioselective disulfide-bond formation by using the safety-catch cysteine protecting group 4,4'-dimethylsulfinylbenzhydryl; Z. Dekan, M. Mobli, M. W. Pennington, E. Fung, E. Nemeth, P. F. Alewood; **Angew. Chem. Int. Ed. Engl.** 2014; **53**: 2931-4. <https://doi.org/10.1002/anie.201310103>
- A new safety-catch protecting group and linker for solid-phase synthesis; S. Thennarasu, C.-F. Liu; **Tetrahedron Lett.** 2010; **51**: 3218-3220. <https://doi.org/10.1016/j.tetlet.2010.04.047>
- A Reductive Acidolysis Final Deprotection Strategy in Solid Phase Peptide Synthesis Based on Safety-Catch Protection; T. Kimura, T. Fukui, S. Tanaka, K. Akaji, Y. Kiso; **Chem. Pharm. Bull.** 1997; **45**: 18-26. <https://doi.org/10.1248/cpb.45.18>
- A safety-catch type of amide protecting group; M. Pátek, M. Lebl; **Tetrahedron Lett.** 1990; **31**: 5209-5212. [https://doi.org/10.1016/s0040-4039\(00\)97844-4](https://doi.org/10.1016/s0040-4039(00)97844-4)
- The p-(methylsulfinyl)benzyl group: a trifluoroacetic acid (TFA)-stable carboxyl-protecting group readily convertible to a TFA-labile group; J. M. Samanen, E. Brandeis; **J. Org. Chem.** 1988; **53**: 561-569. <https://doi.org/10.1021/jo00238a016>
- Solid-Phase Peptide Synthesis Using a Four-Dimensional (Safety-Catch) Protecting Group Scheme; S. Noki, E. Brasil, H. Zhang, T. Bruckdorfer, B. G. de la Torre, F. Albericio; **J. Org. Chem.** 2022, **87(15)**: 9443-9453. <https://doi.org/10.1021/acs.joc.2c01056>

2.10. Summary of Cysteine Protecting Groups available at Iris Biotech

Tab. 1: Overview of cysteine protecting groups and required removal conditions.

Protecting Group	Removal conditions	Remarks	Structure
Acetamido-methyl (Acm)	I ₂ DTNP (2,2'-dithiobis (5-nitropyridine) Tl(III) Hg(II)	- Stable to standard peptide synthesis conditions - Removed under mild conditions with low impact on racemization - Orthogonal to Trt, tBu, Mbzl, Msbh, and Mmt - Caution must be taken when I₂ is applied for the deprotection as iodination of Trp and Tyr might occur	
Methyl-o-nitro-piperonyl (MDNPE)	UV-Light (< 365 nm)	Site-specific covalent protein modification possible	
Diphenylmethyl (Dpm)	60% TFA	- Used in Fmoc and Boc strategy - Dpm is orthogonal to Trt and Mmt - Applied as Bzl replacement	
Phenyl-acetamidomethyl (Phacm)	I ₂ /AcOH	- Environmentally-friendly alternative to Acm - Similar stability and lability to Acm - Deprotection by <i>E. coli</i> penicillin G acylase possible - Orthogonal to Fm, Dnpe, Mbzl - Partially orthogonal to Acm	
4,5-Dimethoxy-2-nitrobenzyl (oNv or DMNB)	UV-light (> 350 nm)	- Stable to Fmoc SPPS conditions - Racemization below 0.5%	
4-(Allyloxycarbonylamino)phenylacetylaminomethyl (Aapam)	Pd/Bu ₃ SnH/ AcOH	Used for side-chain modification by solubilizing tags	

General Introduction

Cyclization via Disulfide Bond Formation

Cleland's Reagent – DTT

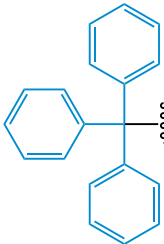
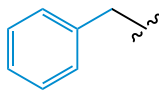
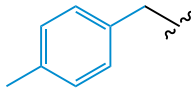
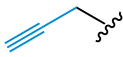
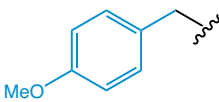
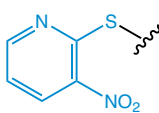
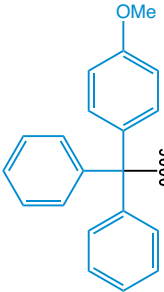
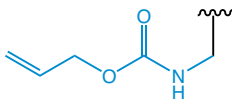
Chemoselective Ligation-Mediated Peptide Cyclization

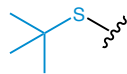
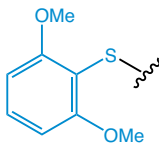
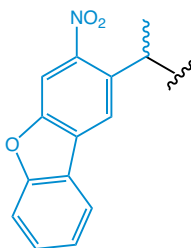
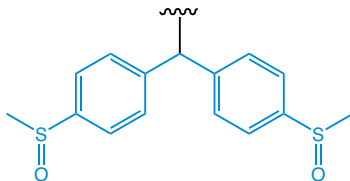
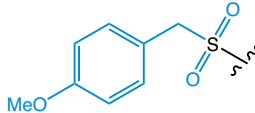
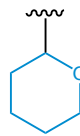
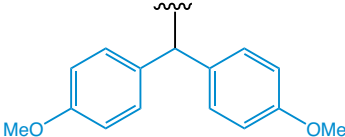
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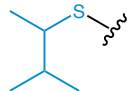
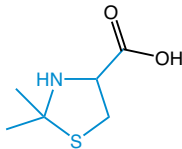
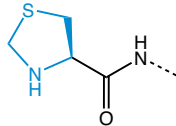
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Cyclic Peptides

Protecting Group	Removal conditions	Remarks	Structure
Trityl (Trt)	25% TFA I ₂	Standard protecting group in Fmoc strategy	
Benzyl (Bn, Bzl)	Na/NH ₃ HF TMSBr/TFA/ thioanisol	Requires harsh deprotection conditions	
4-Methylbenzyl (Mbzl)	HF, MeSiCl ₃ HF/ <i>p</i> -cresol DMSO/TFA (45 min)	- Similar to Mob but less susceptible to TFA - Is orthogonal to Trt, Acn, tBu, and StBu	
Propargyl	[(PhCH ₂ NEt ₃)- 2MoS ₄]	Click conjugation	
4-Methoxybenzyl (Mob)	TFA/TIS Hg(II) Tl(III)	- Standard protecting group in Boc strategy - Full removal requires very harsh conditions - Also compatible with Fmoc strategy - Cys(Mob) might undergo oxidation	
3-Nitro-2-pyridinesulfenyl (Npys)	aliphatic thiols (MAA or BME) tertiary phosphines in water	- Not compatible with Fmoc SPPS but Boc strategy - Not stable towards TBAF - Applied in solid phase disulfide ligation	
4-Methoxytrityl (Mmt)	2% TFA	Orthogonal to tBu, Dpm, oNv, StBu, and Acn	
Allyloxy-carboxylaminomethyl (Allocam)	Pd(0)/Bu ₃ SnH/ AcOH	Orthogonal to tBu, Dpm, oNv, StBu, and Acn	

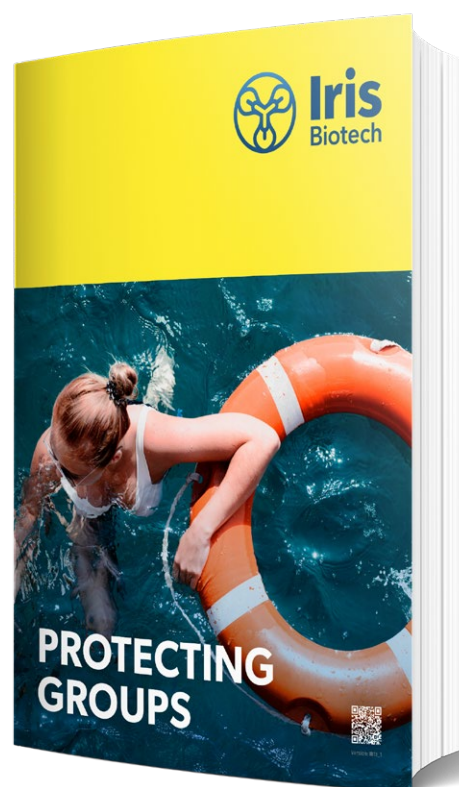
Protecting Group	Removal conditions	Remarks	Structure
<i>tert</i> -Butylthio (S-tBu)	thiols, phosphines	- Compatible with Boc and Fmoc SPPS - Orthogonal to Trt, Acn, Mbzl, Mob, and tBu.	
Dimethoxyphenylthio (S-DMP)	20% BME in DMF 5% DTT in DMF DABDT, DIPEA/H ₂ O/ACN (3:3:94)	- More labile alternative for StBu - Compatible with Fmoc SPPS - Use more TFA-labile resin if selective removal is desired.	
Nitrodibenzofuran (NDBF)	UV-light (> 365 nm)	- Two-photon deprotection is also possible at 800 nm - Compatible with Fmoc strategy - Application in living cells possible	
4,4-Bis(dimethylsulfinyl) benzhydryl (Msbh)	NH ₄ I/DMS/TFA Me ₃ SiCl/Ph ₃ P	- Safety catch protecting group - Stable to Boc and Fmoc strategy	
3-(4-Methoxybenzyl)sulfonyl (SO ₂ Mob)	TFMSA/TFA/ H ₂ O (50:45:5)	Used to provide cysteine sulfonic acid	
Tetrahydropyranyl (THP)	2.5% TFA/TIS/ DCM AgNO ₃	- Selective removal in mild acidic conditions - Better atom economy than Trt - Decreased racemization in comparison with Trt, Dpm or StBu	
<i>tert</i> -Butyl (tBu)	TFMSA, Hg(II)	- Regioselective deprotection in presence of Trt, Acn and Mmt - Not removed by [Pd(allyl)Cl]₂ therefore in might be used as a orthogonal group to Thz and Acn	
4,4'-dimethoxybenzhydryl (Ddm)	TFA/DCM/TIS/ H ₂ O (10:85:2.5:2.5)	Provides lowest suppression rates of racemization in Fmoc SPPS	

Cyclic Peptides

Protecting Group	Removal conditions	Remarks	Structure
Sec-isoamyl mercaptan 3-methyl-2-butanethiol (SIT)	BME in DMF (1:4), 0.1 M DIPEA 20 eq. DTT, ACN/ DIPEA/H ₂ O (95:5:5)	Stable to Fmoc SPPS conditions	
Pseudoproline (thiazolidine)	95% TFA and scavengers	- Incorporation of a kink into the peptide backbone - Reduces aggregation during peptide assembly - In combination with Asp: limits aspartimide formation	
Thiazolidine (Thz)	H ₂ O ₂ , I ₂ Pd(II) and MPAA/TCEP or GSH/ 6 M Gdn · HCl (pH 6.5, 37 °C, 45 min)	- Combined protection of thiol and amino group - Widely used in ligation strategies, but not stable towards NaNO₂ treatment in hydrazide ligation - Pd-mediated deprotection was reported <i>in vivo</i> to provide an α-oxo aldehyde moiety which can be used for bioconjugation	



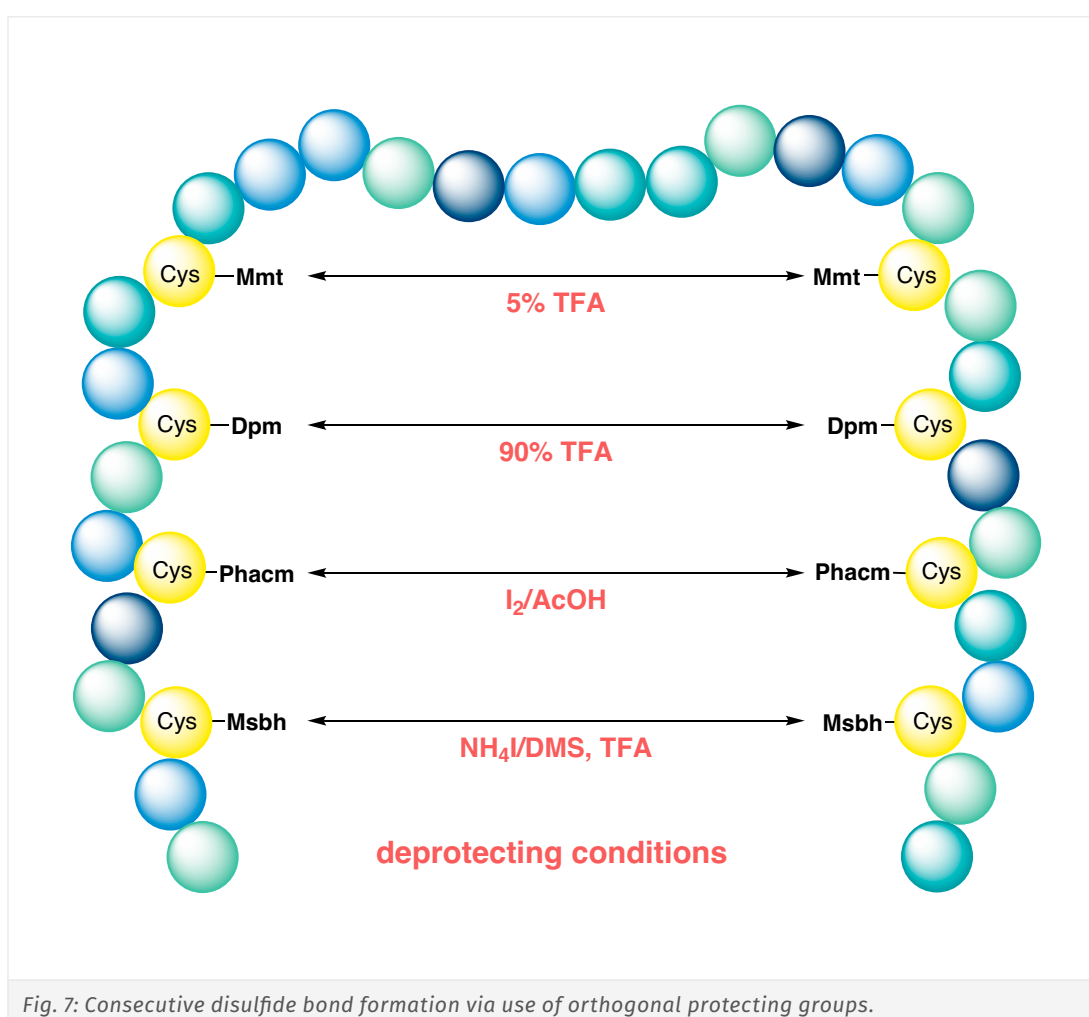
For a detailed overview of protecting groups and deprotection conditions, see our brochure „Protecting Groups“!



2.11. Examples

An advanced combination for the targeted synthesis of peptides with more than one disulfide bridge is as follows:

1. Using Mmt as protecting group and removing it with 5% TFA for construction of the first disulfide bridge. By utilizing a 5% TFA solution instead of 1%, the complete deprotection of all Mmt groups can be ensured.
2. Using Dpm with 90% TFA as deprotection condition for the second disulfide bridge. Through this new combination of protecting groups and cleavage conditions, high purity and yield of the desired double-bridged peptide is the result, which makes this combination useful as the solution of choice from research scale through commercial scale productions.
3. A third disulfide bridge can be introduced by using a pair of Phacm-protected cysteines that can be deprotected either chemically or enzymatically.
4. Tetracystine peptides (four disulfide bridges) may be accessed by utilizing a pair of Msbh-protected cysteines. Msbh is a safety-catch protecting group stable to both Boc- and Fmoc-conditions, that only becomes acid-labile after reductive treatment with $\text{NH}_4\text{I}/\text{DMS}$.



Using some of the above-mentioned protecting groups, another potential sequence for the synthesis of a tetracystine peptide is as follows:

1. The first SS bridge can be designed by using S-DMP as cysteine protection, followed by deprotection with DTT.
2. Then Mmt finds its place for building bridge #2. For cleavage, 5% TFA will work well.
3. The third disulfide bond can successfully be put together applying Dpm and deprotecting it with 90% TFA.
4. Bridge #4 is synthesized using Phacm, while mild removal in water will leave all other bridges intact and maintain the effort done so far with building one of the previous bridges after the other.

Numerous other combinations as suggested above can be applied depending on the individual situation and application. The table below demonstrates how the new arsenal of protecting groups can be applied for different numbers of disulfide bridges or other derivatizations.

Tab. 2: Recommended protection pattern for the subsequent formation of several disulfide bridges.

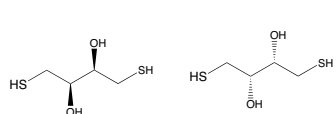
# of Disulfide Bridges	Cysteine Building Blocks to Use	Deprotection Conditions	Oxidative Deprotection
None or 1	Fmoc-Cys(Trt)-OH	> 25% TFA	I ₂ , Tl ³⁺
2	Fmoc-Cys(Mmt)-OH	0.5% to 5% TFA	I ₂ , Tl ³⁺
	Fmoc-Cys(Dpm)-OH	90% TFA	TFA:DMSO:anisole(89:10:1)
3	Fmoc-Cys(Mmt)-OH	0.5% to 5% TFA	I ₂ , Tl ³⁺
	Fmoc-Cys(Dpm)-OH	90% TFA	TFA:DMSO:anisole(89:10:1)
	Fmoc-Cys(Phacm)-OH	I ₂ /AcOH or PGA/water	Immob. PGA/water & DMSO; Ph ₂ SO/MeSiCl ₃
4	Fmoc-Cys(Mmt)-OH	0.5% to 5% TFA	I ₂ , Tl ³⁺
	Fmoc-Cys(Dpm)-OH	90% TFA	TFA:DMSO:anisole(89:10:1)
	Fmoc-Cys(Phacm)-OH	I ₂ /AcOH or PGA/water	Immob. PGA/water & DMSO; Ph ₂ SO/MeSiCl ₃
	Fmoc-Cys(Msbh)-OH	NH ₄ I/TMS, TFA	—
Uneven number of Cys (w/wo derivatization)	Fmoc-Cys(Trt)-OH	> 25% TFA	I ₂ , Tl ³⁺
	Fmoc-Cys(Msbh)-OH	NH ₄ I/TMS, TFA	—
	Or:	> 25% TFA	I ₂ , Tl ³⁺
	Fmoc-Cys(Trt)-OH	Immob. PGA/water	(Immob.) PGA/water &
	Fmoc-Cys(Phacm)-OH		DMSO; Ph ₂ SO/MeSiCl ₃
	And several other combinations		

3. Cleland's Reagent – DTT

Cleland's reagent, also known as DL-Dithiothreitol or DTT, is a water-soluble protective reagent for sulfhydryl groups. It reduces disulfide linkages to free sulfhydryl groups in proteins and enzymes. It is a component of buffers used in protocols for the isolation and purification of proteins.

DTT is a very strong reducing agent due to the property to form a six-membered ring with an internal disulfide bond in oxidized form. The redox potential is -0.33 V at pH 7. The pK_a values of the thiol groups are 9.2 and 10.1, respectively. The reduction of a typical disulfide bond proceeds by two sequential thiol-disulfide exchange reactions. The reducing power of DTT is limited to pH values above 7, since only the negatively charged thiolate form is the reactive agent in opening disulfide bonds. DTT is also used as a reducing agent for thiolated DNA. The terminal sulfurs of thiolated DNA have a tendency to oxidize and form dimers in solution, especially in the presence of oxygen. Dimerization significantly lowers the efficiency of subsequent coupling reactions such as DNA immobilization on gold surfaces in biosensors. Normally, DTT is mixed with a DNA solution and allowed to react, and then is removed by filtration (solid catalyst) or by chromatography (liquid form).

DTT is frequently used to reduce the disulfide bonds of proteins and in order to prevent intramolecular (cyclization) and intermolecular (oligomerisation, polymerization) disulfide bonds from cysteine residues of proteins. However, DTT cannot reduce solvent-inaccessible disulfide bonds, so reduction of disulfide bonds is sometimes carried out under denaturing conditions (e.g., at high temperatures, or in the presence of strong denaturing agents such as 6 M guanidinium chloride, 8 M urea, or 1% sodium dodecyl-sulfate). Conversely, the solvent exposure of different disulfide bonds can be assayed by their speed of reduction in the presence of DTT. DTT can also be used as an oxidizing agent. Its inherent advantage is that effectively no mixed-disulfide species will be formed, which can occur with other agents such as glutathione.

		Product details	
RL-1020	DTT (racemic)		
DL-Dithiothreitol			
CAS-No.	3483-12-3		
Formula	$C_4H_{10}O_2S_2$		
Mol. weight	154,25 g/mol		

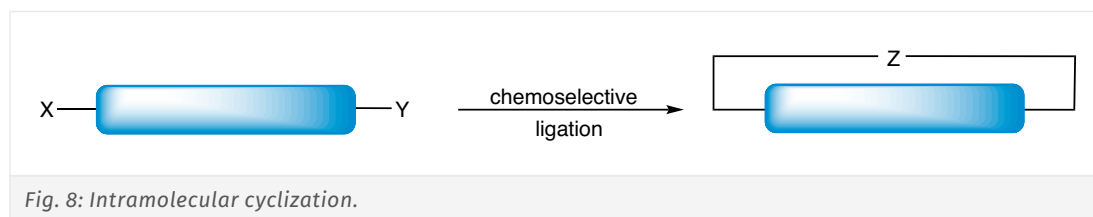
References:

- *Dithiothreitol, a New Protective Reagent for Sh Groups*; W. W. Cleland; **Biochemistry** 1964; **3**: 480-2.
<https://doi.org/10.1021/bi00892a002>
- *Reductive cleavage of cystine disulfides with tributylphosphine*; U. T. Rügge, J. Rudinger; **Enzyme Structure Part E C. H. W. Hirs, N. T. Serge** 1977; **47**: 111-116. [https://doi.org/10.1016/0076-6879\(77\)47012-5](https://doi.org/10.1016/0076-6879(77)47012-5)
- *From production of peptides in milligram amounts for research to multi-tons quantities for drugs of the future*; T. Bruckdorfer, O. Marder, F. Albericio; **Curr Pharm Biotechnol** 2004; **5**: 29-43.
<https://doi.org/10.2174/1389201043489620>

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4. Chemoselective Ligation-Mediated Peptide Cyclization

Within the following chapter, various methods for intramolecular cyclization either creating nonpeptide or peptide linkages are summarized.



The descriptions below should just give an overview about the different technologies available. For a detailed insight on ligation technologies for the synthesis of cyclic peptides, please see the review published by Li *et al.*

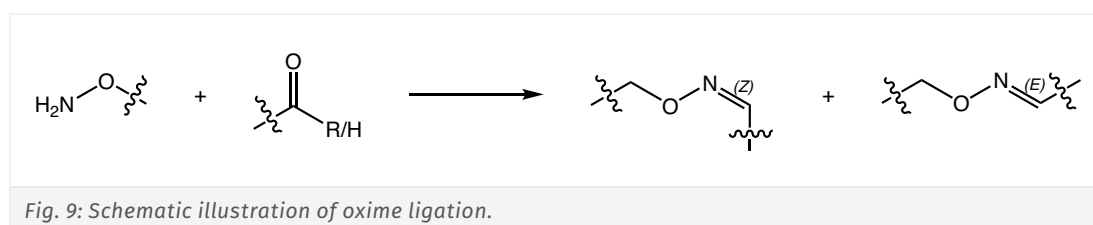
Reference:

→ *Ligation Technologies for the Synthesis of Cyclic Peptides*; H. Y. Chow, Y. Zhang, E. Matheson, X. Li; **Chem. Rev.** 2019; **119**(17): 9971-10001. <https://doi.org/10.1021/acs.chemrev.8b00657>

4.1. Non-Peptide Linkages

4.1.1. Oxime and Hydrazone Ligation

Replacing the primary amino group of an amino acid by an aminooxy moiety leads to an increase in nucleophilicity. Thus, after completion of the peptide synthesis and deprotection of the aminooxy-function, chemoselective reactions with carbonyl compounds (either aldehydes or ketones) under formation of a kinetically stable oxime bond can be performed (= oxime ligation).



In the same manner, hydrazine acids, meaning the amino group of an amino acid replaced by a hydrazide moiety, can undergo hydrazone ligation upon reaction with aldehydes or ketones. Hydrazone linkage is reversible but was found to be stable at physiological pH.

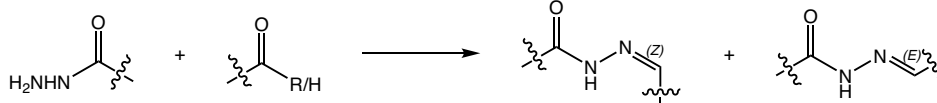


Fig. 10: Schematic illustration of hydrazone ligation.

Both oxime and hydrazone linkage represent good peptidomimetics for amide bonds. The application of oxime and hydrazone ligation for the preparation of head-to-tail cyclic peptides relies on the accessibility of the peptide precursors with reactive groups on N- and C-termini, regardless of the absolute position of the two reactive groups. The oxime and hydrazone ligations are highly chemoselective because the reactive moieties (aminoxy, hydrazide, and aldehyde) are biorthogonal to the side-chain functionalities of the 20 natural amino acids. As typical for intramolecular cyclization reactions, high dilution is required to prevent intermolecular ligations.

The low usage of these ligations for head-to-tail cyclic peptide synthesis is most probably due to the possible hydrolysis of the hydrazine and oxime linkage. The formation of a mixture of products with *E/Z* isomers and the potential side reactions that may occur arising from the instability of the aldehyde or aminoxy-containing precursor cause these ligations to be a less attractive strategy when it comes to head-to-tail cyclic peptide synthesis.

In addition to ligation, another application of hydrazides is their conversion to C-terminal azides with isoamyl nitrite under acidic conditions, and subsequent head-to-tail cyclization forming a native peptide bond.

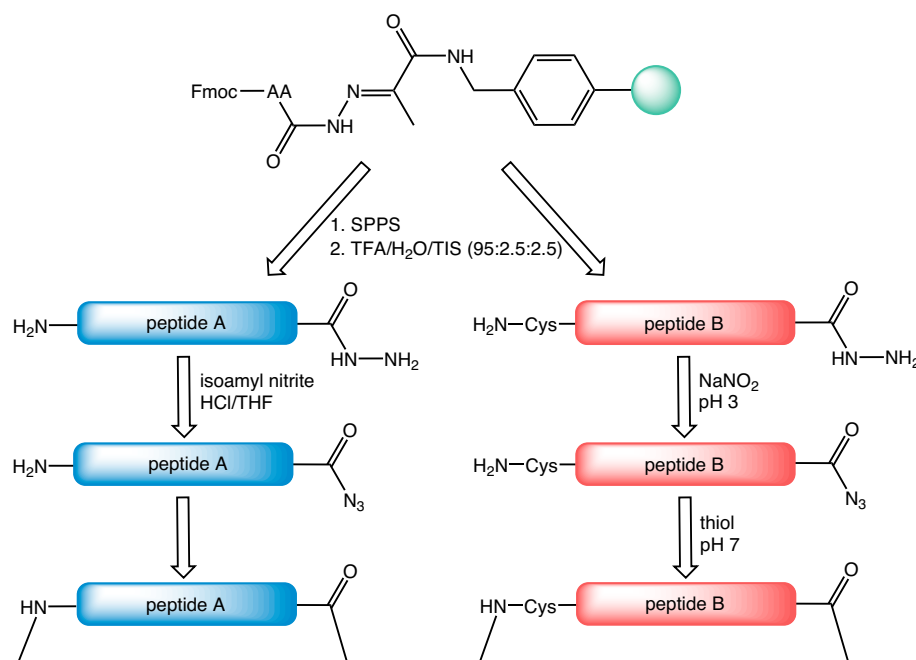
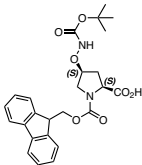
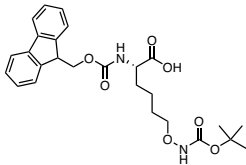
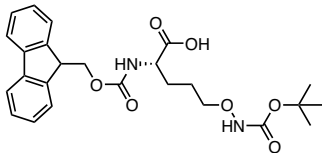
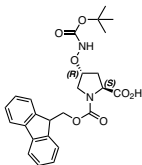
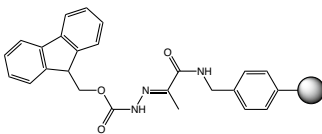


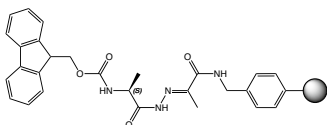
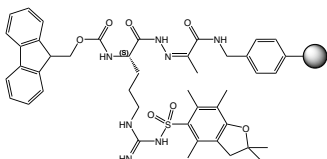
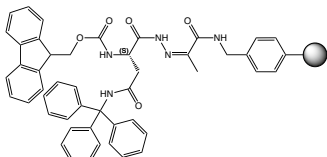
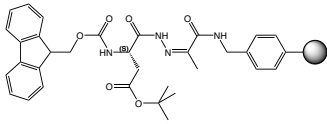
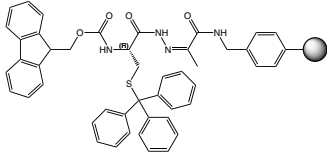
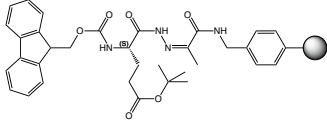
Fig. 11: Formation of cyclic peptides via transformation of peptide hydrazides to their azides.

Besides this, peptide hydrazides can also be converted to peptide thioesters, which are intermediates for application in native chemical ligation (NCL), or used directly as thioester surrogates in NCL.

		Product details
FAA8460	Fmoc-L-cis-Hyp(NHBoc)-OH Fmoc-4-(Boc-aminooxy)-proline (2S,4S) CAS-No. 1015426-31-9 Formula $C_{25}H_{28}N_2O_7$ Mol. weight 468,50 g/mol	 
FAA8450	Fmoc-AAHA(Boc)-OH (S) (S)-2-(Fmoc-amino)-6-(Boc-aminoxy)hexanoic acid CAS-No. 357278-11-6 Formula $C_{26}H_{32}N_2O_7$ Mol. weight 484,54 g/mol	 
FAA8445	Fmoc-Hcan(Boc)-OH (S) (S)-2-(Fmoc-amino)-5-(Boc-aminoxy)pentanoic acid CAS-No. 204844-15-3 Formula $C_{25}H_{30}N_2O_7$ Mol. weight 470,51 g/mol	 
FAA8455	Fmoc-L-trans-Hyp(NHBoc)-OH Fmoc-4-(Boc-aminooxy)-proline (2S,4R) CAS-No. 1015426-45-5 Formula $C_{25}H_{28}N_2O_7$ Mol. weight 468,50 g/mol	 

Besides this, Iris Biotech is offering hydrazone resins for a reliable and convenient method to synthesize peptide hydrazides. The hydrazone linker is completely stable in the course of standard Fmoc SPPS. Linker cleavage occurs with 95% TFA (e.g., TFA/H₂O/TIS, 95:2.5:2.5), which directly affords the desired peptide as a hydrazide. The hydrazone linker tolerates treatment with 5% TFA/DCM, thus permitting selective removal of Mtt and similar acid-labile protecting groups for on-resin side-chain functionalization.

		Product details
PYV1000	Fmoc-NHN=Pyv Resin Fmoc-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB	 

		Product details
PYV1100	Fmoc-L-Ala-NHN=Pyv Resin	
Fmoc-L-alanyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1110	Fmoc-L-Arg(Pbf)-NHN=Pyv Resin	
Fmoc-N'-2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl-L-arginyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1120	Fmoc-L-Asn(Trt)-NHN=Pyv Resin	
Fmoc-N-beta-trityl-L-asparaginyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1130	Fmoc-L-Asp(OtBu)-NHN=Pyv Resin	
Fmoc-L-aspartyl-beta-t-butyl ester-alpha-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1140	Fmoc-L-Cys(Trt)-NHN=Pyv Resin	
Fmoc-S-trityl-L-cysteinyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1150	Fmoc-L-Glu(tBu)-NHN=Pyv Resin	
Fmoc-L-glutamyl-gamma-t-butyl ester-alpha-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		

General Introduction

Cyclization via Disulfide Bond Formation

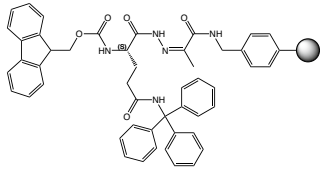
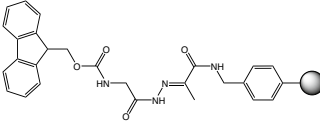
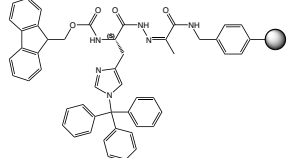
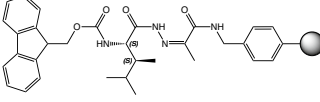
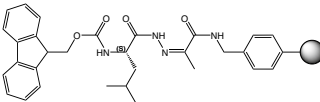
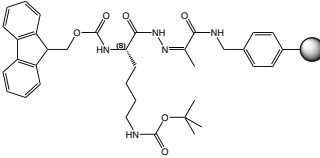
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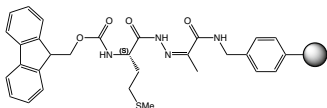
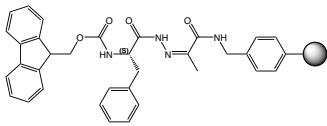
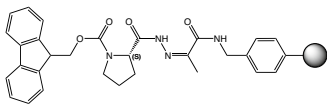
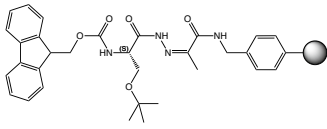
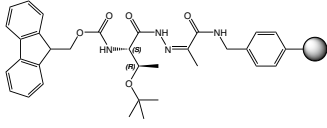
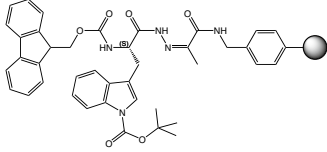
Chemoselective Ligation-Mediated Peptide Cyclization

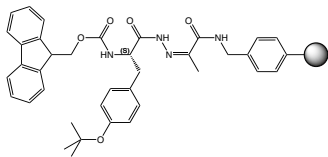
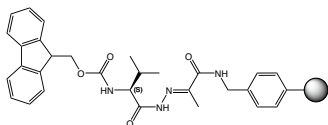
Product Overview

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		Product details
PYV1160 Fmoc-L-Gln(Trt)-NHN=Pyv Resin Fmoc-N-gamma-trityl-L-glutamyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
PYV1170 Fmoc-Gly-NHN=Pyv Resin Fmoc-glycyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
PYV1180 Fmoc-L-His(Trt)-NHN=Pyv Resin Fmoc-N-trityl-L-histidyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
PYV1190 Fmoc-L-Ile-NHN=Pyv Resin Fmoc-L-isoleucyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
PYV1200 Fmoc-L-Leu-NHN=Pyv Resin Fmoc-L-leucyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
PYV1210 Fmoc-L-Lys(Boc)-NHN=Pyv Resin Fmoc-N-epsilon-t-butyloxycarbonyl-L-lysyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		

		Product details
PYV1220	Fmoc-L-Met-NHN=Pyv Resin	
Fmoc-L-methionyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1230	Fmoc-L-Phe-NHN=Pyv Resin	
Fmoc-L-phenylalanyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1240	Fmoc-L-Pro-NHN=Pyv Resin	
Fmoc-L-prolinyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1250	Fmoc-L-Ser(tBu)-NHN=Pyv Resin	
Fmoc-O-t-butyl-L-seryl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1260	Fmoc-L-Thr(tBu)-NHN=Pyv Resin	
Fmoc-O-t-butyl-L-threonyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		
PYV1270	Fmoc-L-Trp(Boc)-NHN=Pyv Resin	
Fmoc-N-t-butyloxycarbonyl-L-tryptophyl-hydrazono-pyruvyl-aminomethylpolystyrene resin		
Mesh Size	100-200 mesh	
Loading	> 0.3 mmol/g	
DVB	1% DVB	
		

		Product details
PYV1280	Fmoc-L-Tyr(tBu)-NHN=Pyv Resin	
Fmoc-O-<i>t</i>-butyl-L-tyrosyl-hydrazono-pyruvyl-amino-methylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
		
PYV1290	Fmoc-L-Val-NHN=Pyv Resin	
Fmoc-L-valyl-hydrazono-pyruvyl-aminomethylpolystyrene resin Mesh Size 100-200 mesh Loading > 0.3 mmol/g DVB 1% DVB		
		

References:

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<https://doi.org/10.1016/j.tet.2015.03.098>
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<https://doi.org/10.1002/cbic.200800281>
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- Oxime Ligation: A Chemoselective Click-Type Reaction for Accessing Multifunctional Biomolecular Constructs; S. Ulrich, D. Boturyn, A. Marra, O. Renaudet, P. Dumy; **Chem. Eur. J.** 2013; **20(1)**: 34-41.
<https://doi.org/10.1002/chem.201302426>

4.1.2. Azide-Alkyne Cycloaddition-Mediated Peptide Cyclization/Click Cyclization

Alkynes and azides can undergo a Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC) to afford 1,4-disubstituted 1,2,3-triazoles. Developed by K. Barry Sharpless and Morton Meldal, this type of chemical transformation was quickly dubbed “Click chemistry”. It has since become a widely used reaction that is orthogonal to many other types of chemical transformations and is used in various kinds of applications. Due to its high thermodynamic driving force, which is usually greater than 20 kcal/mol, the Click reaction rapidly proceeds to completion in almost all cases. CuAAC is highly selective for the 1,4-disubstituted 1,2,3-triazole, whereas ruthenium catalysis affords the 1,5-disubstituted product.

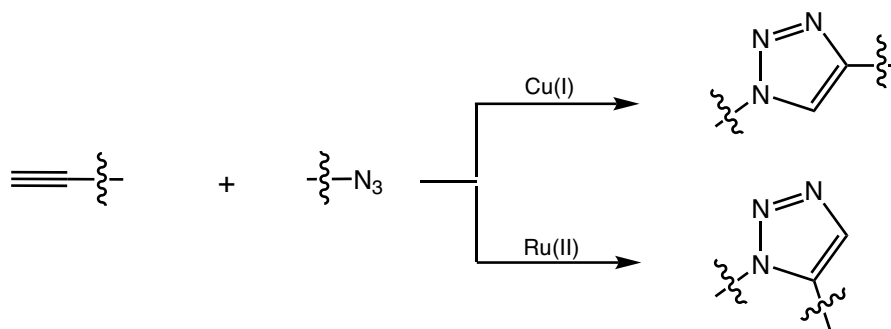


Fig. 12: Schematic illustration of the azide-alkyne-cycloaddition, either Cu(I)- or Ru(II)-catalyzed.

Iris Biotech offers a variety of azido and alkyne amino acids. They can be incorporated into biomolecules by recombinant syntheses, particularly by non-neutral protein translation using the amber-suppression-based orthogonal system, or by chemical reactions. The reaction conditions are fully compatible with SPPS and the reaction could be performed on side-chain unprotected peptides, displaying the high chemoselectivity of the reaction between alkynes and azides.

The resultant 1,4-disubstituted 1,2,3-triazole was found to effectively mimic the native *trans*-amide bond, which provided peptide chemists with another option of amide bond isosteres. In contrast, the 1,5-disubstituted product provided by ruthenium(II) catalysis is a good peptidomimetic of the *cis*-amide bond.

For ease of synthesis, the cyclization of peptides by Click chemistry mainly involves modified side-chains instead of the termini as the introduction of side-chain modified amino acids is very convenient and many building blocks are readily commercially available.

4.1.3. Aziridine Aldehyde-Based Multicomponent Macrocyclization

Yudin and co-workers have developed an Ugi-typed four-component-based macrocyclization. This method involved an aziridine aldehyde, an isocyanide, the N-terminal amino group, and the C-terminal carboxylic acid of a peptide segment.

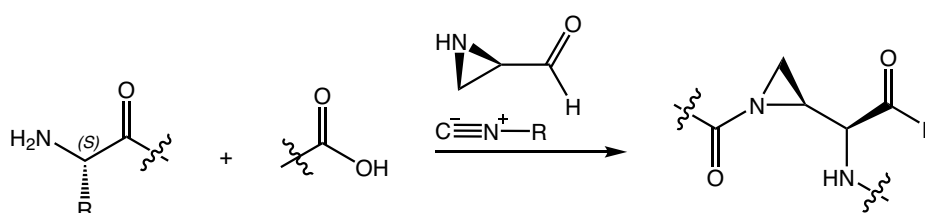


Fig. 13: Schematic illustration of the aziridine aldehyde-based multicomponent macrocyclization.

Reference:

- *Mechanistic investigation of aziridine aldehyde-driven peptide macrocyclization: the imidoanhydride pathway*; S. Zaretsky, J. L. Hickey, J. Tan, D. Pichugin, M. A. St. Denis, S. Ler, B. K. W. Chung, C. C. G. Scully, A. K. Yudin; **Chem. Sci.** 2015; **6**: 5446–5455. <https://doi.org/10.1039/C5SC01958C>

4.1.4. Imine-Mediated Macrocyclization

Baran and co-workers developed a peptide macrocyclization method utilizing the N-terminal amino group and the C-terminal aldehyde of an unprotected linear peptide. Like many other cyclization strategies, this cyclization had to be performed at highly diluted conditions (1 mM). This peptide cyclization started with spontaneous intramolecular imine formation in aqueous media, followed by the nucleophilic attack of the imine to “trap” the cyclic peptide. Depending on the choice of nucleophiles, different moieties at the cyclization site were formed. External nucleophiles such as KCN and NaBH₃CN generated α-aminonitriles or secondary amines at the ring-closure site, respectively, while internal nucleophiles adjacent to the N-terminal amino group, including indole, imidazole, thiol, and selenol, generated heterocycles at the cyclization site.

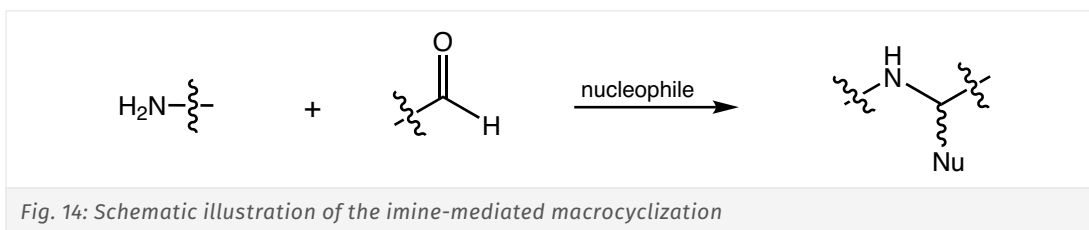


Fig. 14: Schematic illustration of the imine-mediated macrocyclization

The beauty of this cyclization technology is the ability to introduce diverse modifications after cyclization, which enables the generation of an array of analogues derived from the same linear precursors facilitating the synthesis of whole peptide libraries.

Reference:

- *Peptide Macrocyclization Inspired by Non-Ribosomal Imine Natural Products*; L. R. Malins, J. N. deGruyter, K. J. Robbins, P. M. Scola, M. D. Eastgate, M. Reza Ghadiri, P. S. Baran; **J. Am. Chem. Soc.** 2017; **139**(14): 5233–5241. <https://doi.org/10.1021/jacs.7b01624>

4.1.5. Cyanopyridines and Amino thiols for Peptide Cyclization

Cyanopyridine click-like reactions may be used for macrocyclization, stapling, bi- and even tricyclization. The required 1,2-amino thiols can be provided in three ways: a) as N-terminal cysteine (NCys), b) as intra-chain 1,2 amino thiol or c) as 1,3-thiazolidine which can be deprotected later *in situ*. *In vitro*, the reaction is optimally carried out at a pH between 7 and 8. In recombinant proteins, N-terminal cysteines may be provided by the action of TEV protease.

With a 2,6 dicyanopyridine (2,6-DCP) side-chain as bidentate anchor, the formation of bicyclic peptides is rather simple, just two 1,2-amino thiols need to be provided. The cyclization itself will take place within a few minutes in the presence of TCEP (tris-carboxyethylphosphine; LS-3405: <https://www.iris-biotech.de/ls-3405>) as reductant, in a neutral buffer at pH 7.5 and ambient temperature.

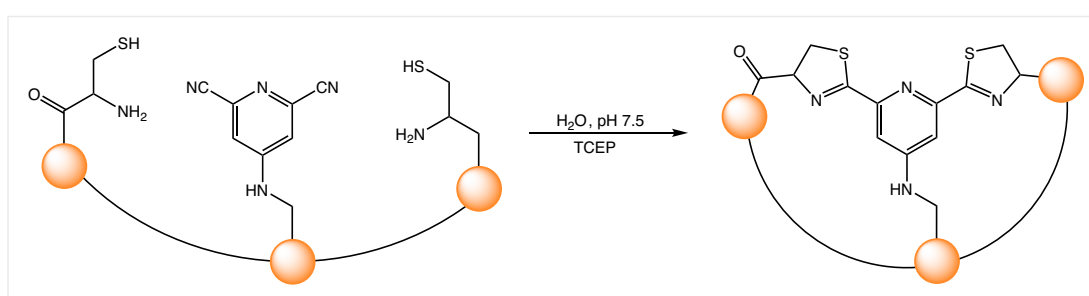
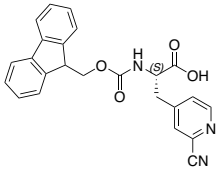
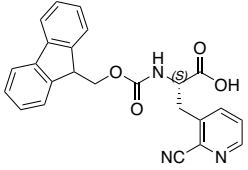
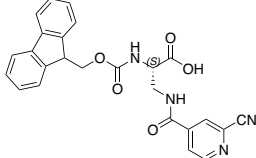
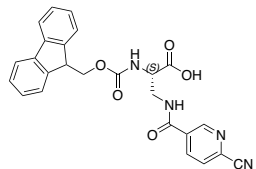
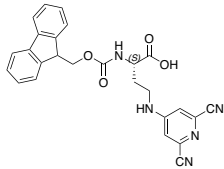
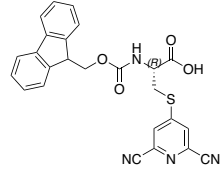


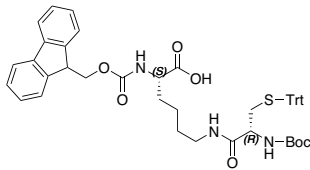
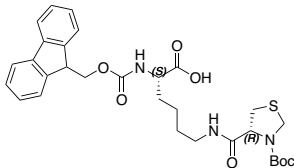
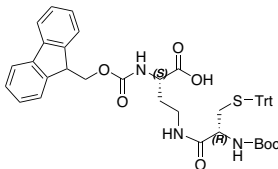
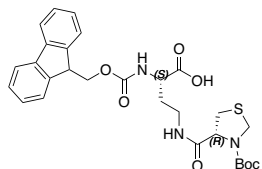
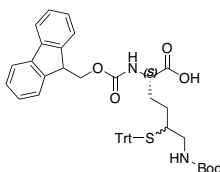
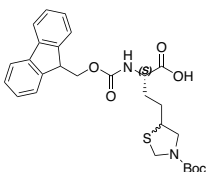
Fig. 15: Example for the synthesis of a bicyclic peptide: When a peptide with an N-terminal cysteine, a C-terminal 1,2-amino thiol and an intra-chain dicyanopyridine (2,6-DCP) is incubated for a few minutes at aqueous neutral conditions, the reaction between the 2,6-DCP and the 1,2 amino thiols will take place quickly. TCEP serves as reduction agent and ensures that the thiols remain in their reduced form.

2,6-Dicyanopyridine may also be used in a non-bound form to make cyclic peptides, when the two 1,2-amino thiols are provided as side-chains, introduced as non-canonical amino acids. For the controlled synthesis of tricyclic peptides, this method even may be combined with the synthesis of bicyclic peptides, when two more 1,2-amino thiols initially are introduced in a protected fashion as 1,3 thiazoles, are deprotected with methoxyamine after the first cyclization and the 2,6-DCP is used to form the thiazoline bridge.

References:

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- Biocompatible and Selective Generation of Bicyclic Peptides; S. Ullrich, J. George, A. Coram, R. Morewood, C. Nitsche; *Angew. Chem Int. Ed.* 2022; **61(43)**: e20228400. <https://doi.org/10.1002/anie.202208400>
- Tobacco Etch Virus protease: A shortcut across biotechnologies; F. Cesaratto, O. Burrone, G. Petris; *J Biotechnol.* 2016; **231(10)**: 239-249. <https://doi.org/10.1016/j.jbiotec.2016.06.012>

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FAA9370	Fmoc-L-3-(2-cyano-4-pyridyl)-alanine (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-cyanopyridin-4-yl)propanoic acid CAS-No. 2245755-79-5 Formula $C_{24}H_{19}N_3O_4$ Mol. weight 413,43 g/mol	 
FAA9375	Fmoc-L-3-(2-cyano-3-pyridyl)-alanine (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-cyanopyridin-3-yl)propanoic acid CAS-No. 2245755-77-3 Formula $C_{24}H_{19}N_3O_4$ Mol. weight 413,43 g/mol	 
FAA9380	Fmoc-L-Dap(2-CINA)-OH (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-cyanoisonicotinamido)propanoic acid Formula $C_{25}H_{20}N_4O_5$ Mol. weight 456,46 g/mol	 
FAA9385	Fmoc-L-Dap(6-CNA)-OH (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-cyanonicotinamido)propanoic acid Formula $C_{25}H_{20}N_4O_5$ Mol. weight 456,46 g/mol	 
FAA9390	Fmoc-L-Dab(2,6-DCP)-OH (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((2,6-dicyanopyridin-4-yl)amino)butanoic acid CAS-No. 2968514-51-2 Formula $C_{26}H_{21}N_5O_4$ Mol. weight 467,49 g/mol	 
FAA9395	Fmoc-L-Cys(2,6-DCP)-OH N-((((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2,6-dicyanopyridin-4-yl)-L-cysteine CAS-No. 2968514-50-1 Formula $C_{25}H_{18}N_4O_4S$ Mol. weight 470,50 g/mol	 

		Product details
FAA9315 Fmoc-L-Lys(Boc-Cys(Trt))-OH N2-(((9H-fluoren-9-yl)methoxy)carbo- nyl)-N6-(N-(<i>tert</i> -butoxycarbonyl)-S-trityl-L-cystei- nyl)-L-lysine CAS-No. 587854-43-1 Formula $C_{48}H_{51}N_3O_7S$ Mol. weight 814,01 g/mol		
FAA9320 Fmoc-L-Lys(Boc-Thz)-OH N2-(((9H-fluoren-9-yl)methoxy)carbo- nyl)-N6-((R)-3-(<i>tert</i> -butoxycarbonyl)thiazolidine-4-car- bonyl)-L-lysine Formula $C_{30}H_{37}N_3O_7S$ Mol. weight 583,70 g/mol		
FAA9325 Fmoc-L-Dab(Boc-Cys(Trt))-OH (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl) amino)-4-((R)-2-(<i>tert</i> -butoxycarbonyl)amino)-3-(tri- tylthio)propanamido)butanoic acid CAS-No. 2968514-52-3 Formula $C_{46}H_{47}N_3O_7S$ Mol. weight 785,96 g/mol		
FAA9330 Fmoc-L-Dab(Boc-Thz)-OH (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl) amino)-4-((R)-3-(<i>tert</i> -butoxycarbonyl)thiazolidi- ne-4-carboxamido)butanoic acid CAS-No. 2968514-54-5 Formula $C_{28}H_{33}N_3O_7S$ Mol. weight 555,65 g/mol		
FAA9335 Fmoc-L-Lys(5-STrt, Boc)-OH (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl) amino)-6-((<i>tert</i> -butoxycarbonyl)amino)-5-(tritylthio) hexanoic acid CAS-No. 1240666-29-8 Formula $C_{45}H_{46}N_2O_6S$ Mol. weight 742,93 g/mol		
FAA9340 Fmoc-L-Lys(4-Thz, Boc)-OH (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl) amino)-4-(3-(<i>tert</i> -butoxycarbonyl)thiazolidin-5-yl) butanoic acid CAS-No. 1240666-28-7 Formula $C_{27}H_{32}N_2O_6S$ Mol. weight 512,62 g/mol		

General Introduction

Cyclization *via* Disulfide Bond Formation

Cleland's Reagent – DTT

Chemoselective Ligation-Mediated Peptide Cyclization

Product Overview

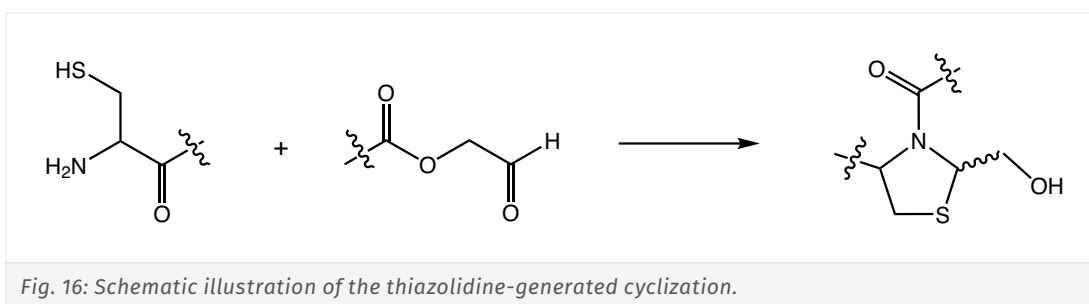
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4.2. Peptide Linkages

4.2.1. Thiazolidine-Generated Cyclization

With this method, cyclic peptides with ring sizes from five to 26 residues were successfully synthesized. Although no limitations for the C-terminal amino acid are reported, all synthesized model peptides reported by Tam *et al.* contained Gly-cysteine at the cyclization sites. The intramolecular cyclization is initiated in a pH 5.5 aqueous solution followed by *O*-to-*N*-acyl transfer at pH 5.9. Heating promotes the *O*-to-*N*-acyl transfer, but as side reactions such as hydrolysis and decomposition are observed. The rate of the cyclization is dependent on the formed ring size – the larger, the faster.

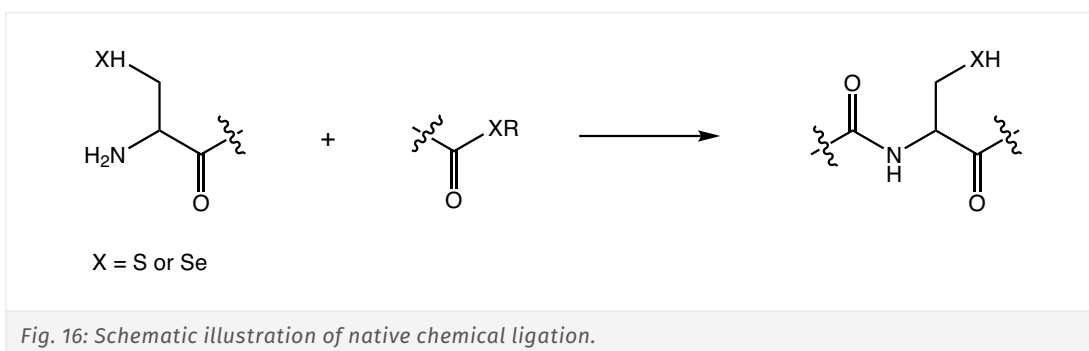


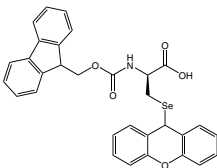
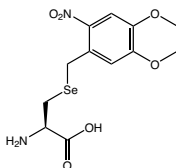
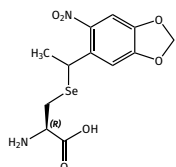
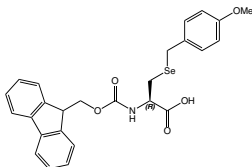
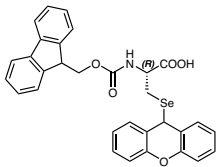
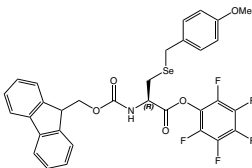
Reference:

→ *Cyclic Peptides from Linear Unprotected Peptide Precursors through Thiazolidine Formation*; P. Botti, T. D. Palinn, J. P. Tam; *J. Am. Chem. Soc.* 1996; **118(42)**: 1018-10024. <https://doi.org/10.1021/ja954278g>

4.2.2. Native Chemical Ligation-Mediated Cyclization

Native chemical ligation (NCL) of unprotected peptide segments involves the reaction between a first peptide fragment α -thioester and a second peptide fragment which carries a cysteine on the N-terminus, to yield a product with a native amide bond at the ligation site. NCL can also be utilized for synthesizing cyclic peptides. As alternative, the N-terminal cysteine can be replaced by selenocysteine.



		Product details
FAA8600	Fmoc-D-Sec(Xan)-OH	
Fmoc-Se-xanthyl-D-selenocysteine		
CAS-No.	2988660-46-2	 
Formula	C ₃₁ H ₂₅ NO ₅ Se	
Mol. weight	570,49 g/mol	
HAA9255	H-L-Sec(oNv)-OH*TFA	
Dimethoxynitrobenzyl selenocysteine TFA salt		
CAS-No.	1644398-13-9	 
Formula	C ₁₂ H ₁₆ N ₂ O ₆ Se*CF ₃ COOH	
Mol. weight	363,24*114,02 g/mol	
HAA9360	H-L-Sec(MDNPE)-OH	
Se-(Methyl-o-nitropiperonyl)-selenocysteine		
CAS-No.	2235373-47-2	 
Formula	C ₁₂ H ₁₄ N ₂ O ₆ Se	
Mol. weight	361,21 g/mol	
FAA8705	Fmoc-L-Sec(Mob)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-Se-(4-methoxybenzyl)-L-selenocysteine		
CAS-No.	150308-80-8	 
Formula	C ₂₆ H ₂₅ NO ₃ Se	
Mol. weight	510,46 g/mol	
FAA8465	Fmoc-L-Sec(Xan)-OH	
Fmoc-Se-xanthyl-L-selenocysteine		
CAS-No.	1639843-35-8	 
Formula	C ₃₁ H ₂₅ NO ₅ Se	
Mol. weight	570,49 g/mol	
FAA8760	Fmoc-L-Sec(Mob)-OPfp	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-4-methoxybenzyl selenocysteine pentafluorophenyl ester		
CAS-No.	939431-43-3	 
Formula	C ₃₂ H ₂₄ F ₅ NO ₃ Se	
Mol. weight	676,51 g/mol	

General Introduction

Cyclization via Disulfide Bond Formation

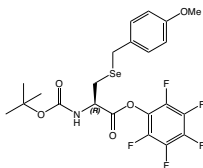
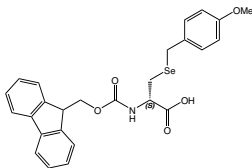
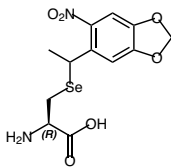
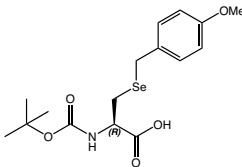
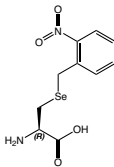
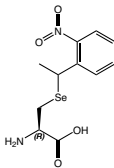
Cleland's Reagent – DTT

Chemoselective Ligation-Mediated Peptide Cyclization

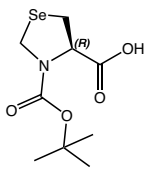
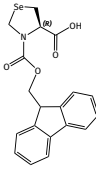
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		Product details
BAA4830	Boc-L-Sec(Mob)-OPfp N- α - <i>tert</i> -Butoxycarbonyl-4-methoxybenzyl-L-selenocysteine pentafluorophenyl ester CAS-No. 1257525-48-6 Formula $C_{22}H_{22}F_5NO_5Se$ Mol. weight 554,38 g/mol	 
FAA8710	Fmoc-D-Sec(Mob)-OH N- α -(9-Fluorenylmethyloxycarbonyl)-Se-(4-methoxybenzyl)-D-selenocysteine CAS-No. 2987041-11-0 Formula $C_{26}H_{25}NO_5Se$ Mol. weight 510,46 g/mol	 
HAA9230	H-L-Sec(MDNPE)*TFA (2R)-2-amino-3-((1-(6-nitrobenzo[d][1,3]dioxol-5-yl)ethyl)selanyl)propanoic acid trifluoroacetate CAS-No. 2235373-48-3 Formula $C_{12}H_{14}N_2O_5Se*CF_3CO_2H$ Mol. weight 361,22*114,02 g/mol	 
BAA3760	Boc-L-Sec(Mob)-OH N- α - <i>t</i> -Butoxycarbonyl-Se-(4-methoxybenzyl)-L-selenocysteine CAS-No. 959415-39-5 Formula $C_{16}H_{23}NO_5Se$ Mol. weight 388,32 g/mol	 
HAA9465	H-L-Sec(oNB)-OH*HCl (R)-2-amino-3-((2-nitrobenzyl)selanyl)propanoic acid CAS-No. 324582-23-2 net Formula $C_{10}H_{12}N_2O_4Se*HCl$ Mol. weight 303,18*36,46 g/mol	 
HAA9475	H-L-Sec(NPE)-OH*HCl (2R)-2-amino-3-((1-(2-nitrophenyl)ethyl)selanyl)propanoic acid Formula $C_{11}H_{14}N_2O_4Se*HCl$ Mol. weight 317,02*36,46 g/mol	 

Besides Sec, our portfolio contains a variety of selenazolidine carboxylic acids (Sez derivatives). Sez can be deprotected and converted to Sec by treatment with *O*-methylhydroxylamine (MeONH₂) at pH 4 or by using Cu(II) salts.

		Product details
BAA4880 Boc-L-Sez-OH Boc selenazolidine carboxylic acid CAS-No. 1841180-44-6 Formula C ₉ H ₁₅ NO ₄ Se Mol. weight 280,19 g/mol		
FAA8860 Fmoc-L-Sez-OH Fmoc selenazolidine carboxylic acid CAS-No. 1985651-74-8 Formula C ₁₉ H ₁₇ NO ₄ Se Mol. weight 402,31 g/mol		

4.2.3. Traceless Staudinger Ligation-Mediated Peptide Cyclization

Staudinger ligation describes the chemoselective reaction between azides and triaryl phosphines or *N*-acylimidazole phosphines to generate an amide. Kleineweischede and Hackenberger first described that this type of reaction can be utilized for the synthesis of cyclic peptides starting from side-chain unprotected linear peptides.

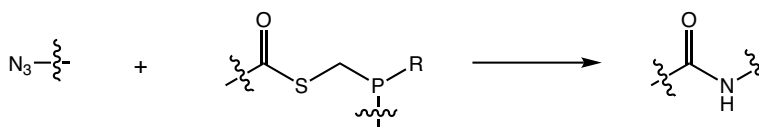


Fig. 17: Schematic illustration of the traceless Staudinger ligation-mediated peptide cyclization.

Reference:

- *Chemoselective Peptide Cyclization by Traceless Staudinger Ligation*; R. Kleineweischede, C. P. R. Hackenberger; *Angew. Chem. Int. Ed.* 2008; **47**(32): 5984-5988. <https://doi.org/10.1002/anie.200801514>

4.2.4. Alpha-Ketoacid Hydroxylamine Ligation-Mediated Peptide Cyclization

The chemoselective reaction between a C-terminal α -ketoacid (KA) and an N-terminal hydroxyl-amine (HA) for the formation of an amide bond at the ligation site is reported for the preparation of head-to-tail cyclic peptides. Eventhough this technology can be used for cyclization at any site within the peptide, it is rarely used, most likely due to the low stability of the free hydroxylamines and the need of temporary protection of the N-terminus during precursor synthesis. Advances like the development of the stable 5-oxaproline as N-terminal hydroxylamine and the protected α -ketoacid resins make the approach more convenient, however, noticeable epimerization at the C-terminal residue remains a major drawback.

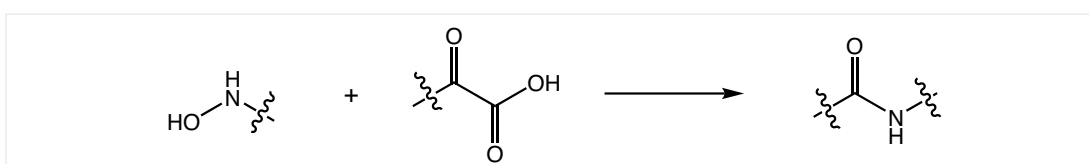


Fig. 18: Schematic illustration of the KAHA ligation.

References:

- Chemoselective Amide Ligations by Decarboxylative Condensations of N-Alkylhydroxylamines and α -Ketoacids; J. W. Bode, R. M. Fox, K. D. Baucom; *Angew. Chem. Int. Ed.* 2006; **45(8)**: 1248-1252.
<https://doi.org/10.1002/anie.200503991>
- Stereoretentive synthesis and chemoselective amide-forming ligations of C-terminal peptide α -ketoacids; L. Ju, A. R. Lippert, J. W. Bode; *J. Am. Chem. Soc.* 2008; **130(13)**: 4253-5. <https://doi.org/10.1021/ja800053t>
- Chemical Protein Synthesis with the α -Ketoacid-Hydroxylamine Ligation; J. W. Bode; *Acc. Chem. Res.* 2017; **50(9)**: 2104-2115. <https://doi.org/10.1021/acs.accounts.7b00277>
- Chemical protein synthesis by chemoselective- α -ketoacid-hydroxylamine (KAHA) ligations with 5-oxaproline; V. R. Pattabiraman, A. O. Ogunkoya, J. W. Bode; *Angew. Chem. Int. Ed. Engl.* 2012; **51(21)**:
<https://doi.org/10.1002/anie.201200907>

4.2.5. Serine/Threonine Ligation-Mediated Peptide Cyclization

Oxazolidine formation via reaction of the 1,2-hydroxy amine bifunctional groups of an N-terminal serine or threonine residue of an unprotected peptide with a C-terminal peptide salicylaldehyde ester and subsequent O-to-N-acyl transfer followed by acidolysis provides the natural peptide Xaa-Ser/Thr linkage at the ligation site.

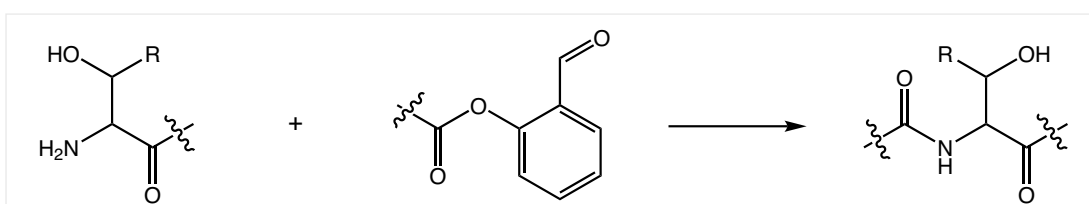


Fig. 19: Schematic illustration of serine/threonine ligation-mediated peptide cyclization.

References:

- *Serine/Threonine Ligation: Origin, Mechanistic Aspects, and Applications*; H. Li, X. Li; **Acc. Chem. Res.** 2018; **51(7)**: 1643-1655. <https://doi.org/10.1021/acs.accounts.8b00151>
- *Protein chemical synthesis by serine and threonine ligation*; Y. Zhang, C. Xu, H. Y. Lam, C. L. Lee, X. Li; **PNAS** 2013; **110(17)**: 6657-6662. <https://doi.org/10.1073/pnas.1221012110>
- *Salicylaldehyde ester-induced chemoselective peptide ligations: enabling generation of natural peptidic linkages at the serine/threonine sites*; X. Li, H. Y. Lam, Y. Zhang, C. K. Chan; **Org. Lett.** 2010; **12(8)**: 1724-7. <https://doi.org/10.1021/ol1003109>

4.3. Enzyme-Mediated Peptide Cyclization

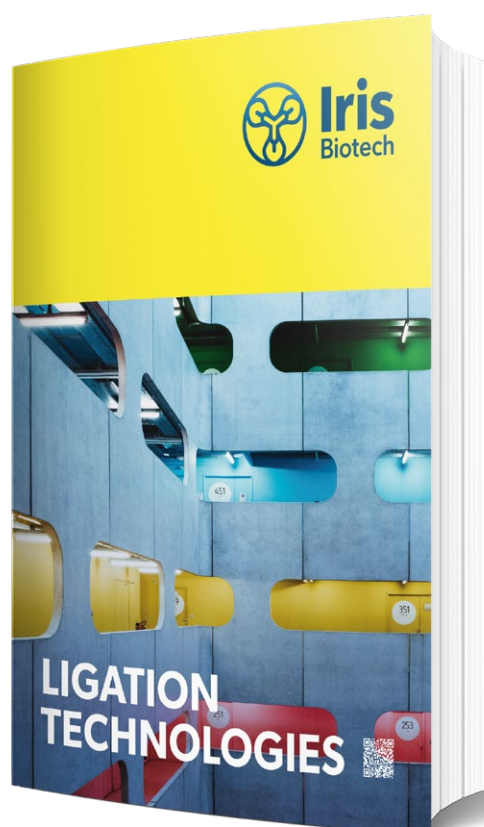
Enzyme-mediated ligation is providing an alternative to chemical synthesis for the cyclization step. Enzyme activities are highly chemoselective. Their nontoxic and catalytic properties are of great value to the pharmaceutical industry in the preparation of cyclic peptide drugs considering purity and cost-effectiveness. Examples include Sortase A, Butelase 1, GmPOPb, and peptiligase.

Reference:

- *Ligation Technologies for the Synthesis of Cyclic Peptides*; H. Y. Chow, Y. Zhang, E. Matheson, X. Li; **Chem. Rev.** 2019; **119(17)**: 9971-10001; <https://doi.org/10.1021/acs.chemrev.8b00657>



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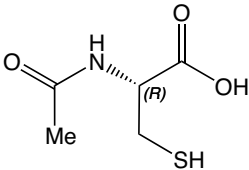
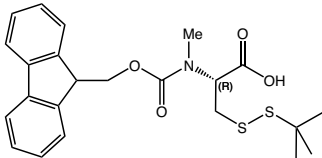
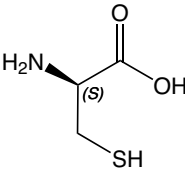
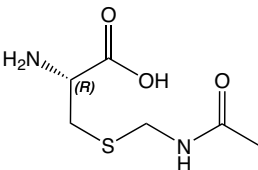
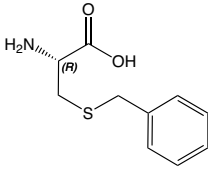
Chemoselective Ligation-Mediated Peptide Cyclization

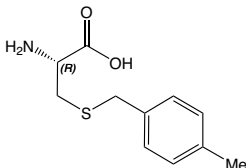
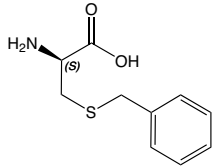
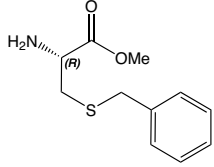
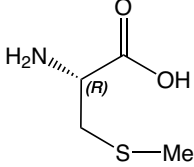
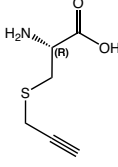
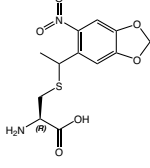
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5. Product Overview

5.1. Cysteine Building Blocks

		Product details
AAA1300 Ac-L-Cys-OH N-alpha-Acetyl-L-cysteine CAS-No. 616-91-1 Formula C ₅ H ₉ NO ₃ S Mol. weight 163,19 g/mol		
FAA3340 Fmoc-L-MeCys(S-tBu)-OH N-alpha-(9-Fluorenylmethoxycarbonyl)-N-alpha-methyl-S-(t-butylthio)-L-cysteine CAS-No. 1013096-03-1 Formula C ₂₃ H ₂₇ NO ₄ S ₂ Mol. weight 445,59 g/mol		
HAA1017 H-D-Cys-OH*HCl*H₂O D-Cysteine hydrochloride monohydrate CAS-No. 32443-99-5 Formula C ₃ H ₇ NO ₂ S*HCl*H ₂ O Mol. weight 121,2*36,45*18,01 g/mol		
HAA6070 H-L-Cys(Acm)-OH*HCl S-(Acetyl-aminomethyl)-L-cysteine hydrochloride CAS-No. 28798-28-9 Formula C ₆ H ₁₂ N ₂ O ₃ S*HCl Mol. weight 192,24*36,45 g/mol		
HAA1574 H-L-Cys(Bzl)-OH S-Benzyl-L-cysteine CAS-No. 3054-01-1 Formula C ₁₀ H ₁₃ NO ₂ S Mol. weight 211,29 g/mol		

		Product details
HAA6090	H-L-Cys(MBzl)-OH S-(4-Methylbenzyl)-L-cysteine CAS-No. 42294-52-0 Formula $C_{11}H_{15}NO_2S$ Mol. weight 225,3 g/mol	 
HAA6110	H-D-Cys(Bzl)-OH S-Benzyl-D-cysteine CAS-No. 23032-53-3 Formula $C_{10}H_{13}NO_2S$ Mol. weight 211,29 g/mol	 
HAA6080	H-L-Cys(Bzl)-OMe*HCl S-Benzyl-L-cysteine methyl ester hydrochloride CAS-No. 16741-80-3 Formula $C_{11}H_{15}NO_2S^*HCl$ Mol. weight 225,31*36,45 g/mol	 
HAA1078	H-L-Cys(Me)-OH*HCl S-Methyl-L-cysteine hydrochloride CAS-No. 13331-74-3 Formula $C_4H_9NO_2S^*HCl$ Mol. weight 135,19*36,45 g/mol	 
HAA2350	H-L-Cys(Propargyl)-OH*HCl S-Propargyl-L-cysteine hydrochloride CAS-No. 3262-64-4 Formula $C_6H_9NO_2S^*HCl$ Mol. weight 159,21*36,45 g/mol	 
HAA9270	H-L-Cys(MDNPE)-OH 1-[4',5'-(methylenedioxy)-2'-nitrophenyl]ethyl]-L-cysteine CAS-No. 1551078-43-3 Formula $C_{12}H_{14}N_2O_6S$ Mol. weight 314,31 g/mol	 

General Introduction

Cyclization via Disulfide Bond Formation

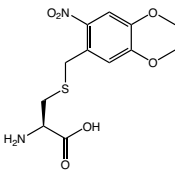
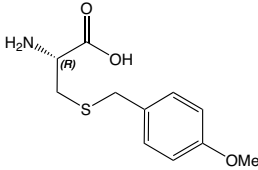
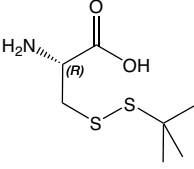
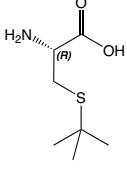
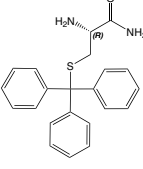
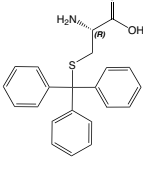
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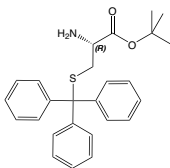
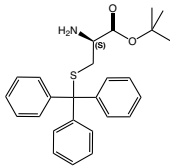
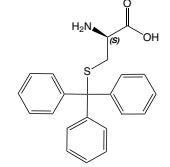
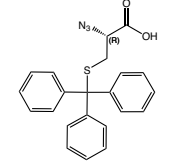
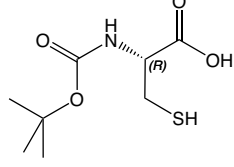
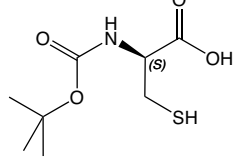
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		Product details
HAA9320	H-L-Cys(oNv)-OH S-(4,5-dimethoxy-2-nitrobenzyl)-L-cysteine CAS-No. 214633-68-8 Formula $C_{12}H_{16}N_2O_6S$ Mol. weight 316,33 g/mol	 
HAA6100	H-L-Cys(Mob)-OH S-(4-Methoxybenzyl)-L-cysteine CAS-No. 2544-31-2 Formula $C_{11}H_{15}NO_3S$ Mol. weight 241,3 g/mol	 
HAA6140	H-L-Cys(StBu)-OH S-Thio-t-butyl-L-cysteine CAS-No. 30044-51-0 Formula $C_7H_{15}NO_2S_2$ Mol. weight 209,32 g/mol	 
HAA6150	H-L-Cys(tBu)-OH*HCl S-t-Butyl-L-cysteine hydrochloride CAS-No. 2481-09-6 Formula $C_7H_{15}NO_2S^*HCl$ Mol. weight 177,26*36,45 g/mol	 
HAA1560	H-L-Cys(Trt)-NH₂ S-Trityl-L-cysteine amide CAS-No. 166737-85-5 Formula $C_{22}H_{22}N_2OS$ Mol. weight 362,49 g/mol	 
HAA6160	H-L-Cys(Trt)-OH S-Trityl-L-cysteine CAS-No. 2799-07-7 Formula $C_{22}H_{21}NO_2S$ Mol. weight 363,48 g/mol	 

		Product details
HAA1995	H-L-Cys(Trt)-OtBu*HCl S-Trityl-L-cysteine t-butyl ester hydrochloride CAS-No. 158009-03-1 Formula $C_{26}H_{29}NO_2S^*HCl$ Mol. weight 419,58*36,45 g/mol	 
HAA2100	H-D-Cys(Trt)-OtBu*HCl S-Trityl-D-cysteine t-butyl ester hydrochloride CAS-No. 439089-10-8 Formula $C_{26}H_{29}NO_2S^*HCl$ Mol. weight 419,58*36,45 g/mol	 
HAA6120	H-D-Cys(Trt)-OH S-Trityl-D-cysteine CAS-No. 25840-82-8 Formula $C_{22}H_{21}NO_2S$ Mol. weight 363,48 g/mol	 
HAA2810	N₃-L-Cys(Trt)-OH*CHA (R)-2-azido-3-(tritylthio)propanoic acid cyclohexylamine CAS-No. 1286670-90-3 Formula $C_{22}H_{19}N_3O_2S^*C_6H_{13}N$ Mol. weight 389,47*99,17 g/mol	 
BAA1083	Boc-L-Cys-OH N-alpha-t-Butyloxycarbonyl-L-cysteine CAS-No. 20887-95-0 Formula $C_8H_{15}NO_4S$ Mol. weight 221,27 g/mol	 
BAA1170	Boc-D-Cys-OH N-alpha-t-Butyloxycarbonyl-D-cysteine CAS-No. 149270-12-2 Formula $C_8H_{15}NO_4S$ Mol. weight 221,27 g/mol	 

General Introduction

Cyclization *via* Disulfide Bond Formation

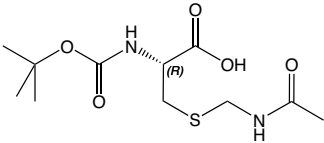
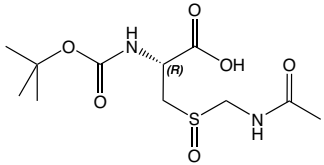
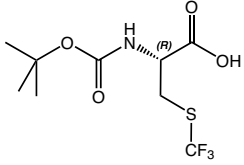
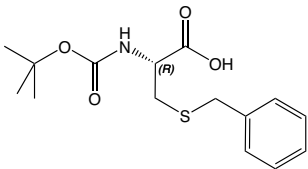
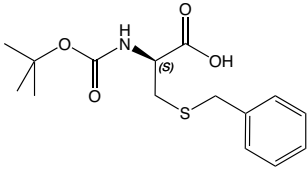
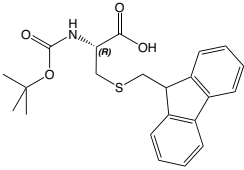
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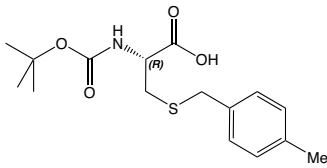
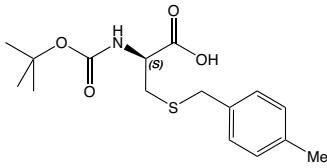
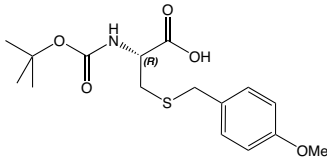
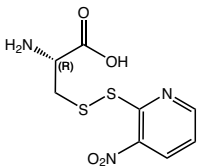
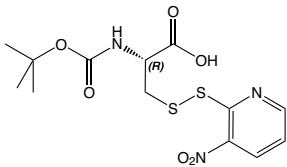
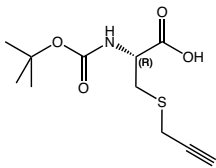
Chemoselective Ligation-Mediated Peptide Cyclization

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		Product details
BAA1078	Boc-L-Cys(Acm)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-(acetyl-amino-methyl)-L-cysteine CAS-No. 19746-37-3 Formula $C_{11}H_{20}N_2O_5S$ Mol. weight 292,36 g/mol	 
BAA1510	Boc-L-Cys(Acm,O)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-(acetyl-amino-methyl)-S-oxo-L-cysteine CAS-No. 75893-04-8 Formula $C_{11}H_{20}N_2O_5S$ Mol. weight 308,35 g/mol	 
BAA4360	Boc-L-Cys(CF₃)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-trifluoromethyl-L-cysteine CAS-No. 943926-18-9 Formula $C_9H_{16}F_3NO_4S$ Mol. weight 289,27 g/mol	 
BAA1079	Boc-L-Cys(Bzl)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-benzyl-L-cysteine CAS-No. 5068-28-0 Formula $C_{15}H_{21}NO_4S$ Mol. weight 311,38 g/mol	 
BAA5410	Boc-D-Cys(Bzl)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-benzyl-D-cysteine CAS-No. 102830-49-9 Formula $C_{15}H_{21}NO_4S$ Mol. weight 311,38 g/mol	 
BAA5510	Boc-L-Cys(Fm)-OH N-alpha- <i>t</i> -Butyloxycarbonyl-S-(9-fluorenyl-methyl)-L-cysteine CAS-No. 84888-35-7 Formula $C_{22}H_{25}NO_4S$ Mol. weight 399,51 g/mol	 

		Product details
BAA1080	Boc-L-Cys(MBzl)-OH	
N-alpha-t-Butyloxycarbonyl-S-(4-methyl-benzyl)-L-cysteine		
CAS-No.	61925-77-7	 
Formula	C ₁₆ H ₂₃ NO ₄ S	
Mol. weight	325,43 g/mol	
BAA5420	Boc-D-Cys(MBzl)-OH	
N-alpha-t-Butyloxycarbonyl-S-(4-methyl-benzyl)-D-cysteine		
CAS-No.	61925-78-8	 
Formula	C ₁₆ H ₂₃ NO ₄ S	
Mol. weight	325,43 g/mol	
BAA1081	Boc-L-Cys(Mob)-OH	
N-alpha-t-Butyloxycarbonyl-S-(4-methoxy-benzyl)-L-cysteine		
CAS-No.	18942-46-6	 
Formula	C ₁₆ H ₂₃ NO ₅ S	
Mol. weight	341,43 g/mol	
HAA3510	H-L-Cys(Npys)-OH*HCl	
S-(3-nitro-2-pyridylthio)-L-cysteine hydrochloride		
CAS-No.	108807-66-5	 
Formula	C ₈ H ₉ N ₃ O ₄ S ₂ *HCl	
Mol. weight	275,30*36,45 g/mol	
BAA1860	Boc-L-Cys(Npys)-OH	
N-alpha-t-Butyloxycarbonyl-S-(3-nitro-2-pyridylthio)-L-cysteine		
CAS-No.	76880-29-0	 
Formula	C ₁₃ H ₁₇ N ₃ O ₆ S ₂	
Mol. weight	375,42 g/mol	
BAA2250	Boc-L-Cys(Propargyl)-OH*DCHA	
N-alpha-t-Butyloxycarbonyl-S-propargyl-L-cysteine dicyclohexylamine		
CAS-No.	1260119-25-2 net	 
Formula	C ₁₁ H ₁₇ NO ₄ S*C ₁₂ H ₂₃ N	
Mol. weight	259,32*181,32 g/mol	

General Introduction

Cyclization via Disulfide Bond Formation

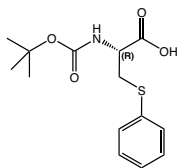
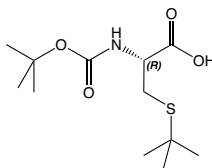
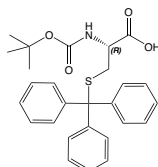
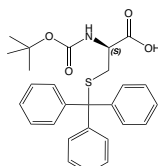
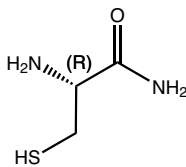
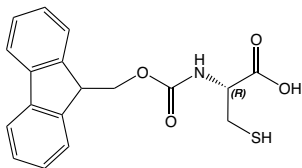
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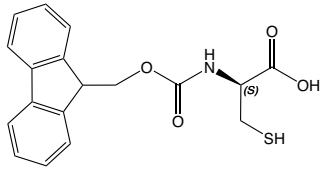
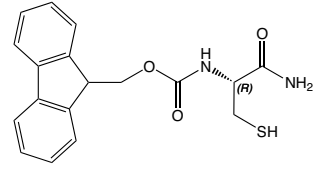
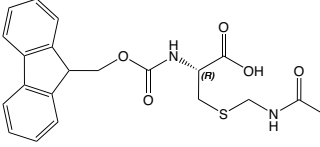
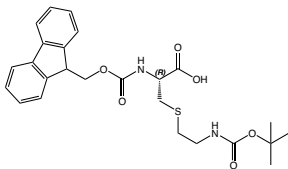
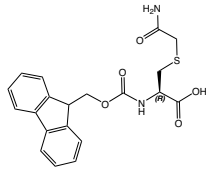
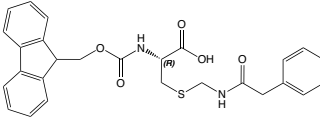
Chemoselective Ligation-Mediated Peptide Cyclization

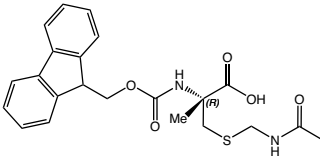
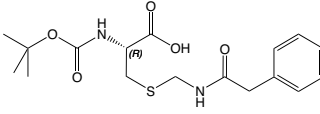
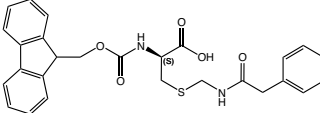
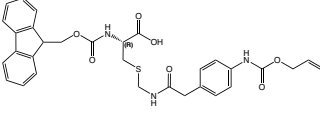
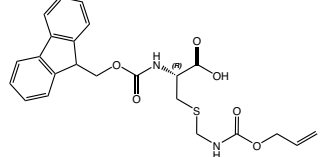
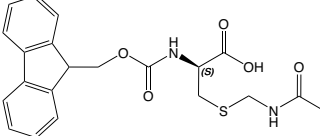
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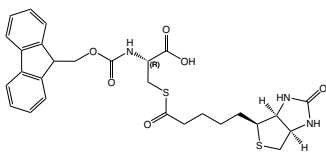
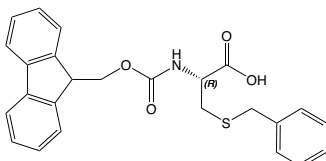
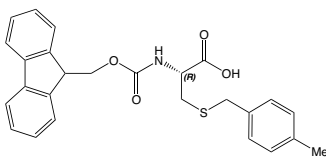
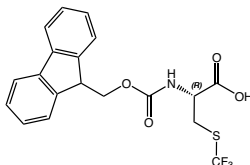
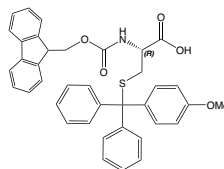
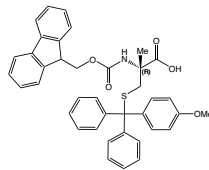
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			Product details
BAA3140	Boc-L-Cys(Ph)-OH		
N-alpha-t-Butyloxycarbonyl-S-phenyl-L-cysteine			
CAS-No.	163705-28-0		
Formula	C ₁₄ H ₁₉ NO ₄ S		
Mol. weight	297,37 g/mol		
			
BAA1082	Boc-L-Cys(tBu)-OH		
N-alpha-t-Butyloxycarbonyl-S-t-butyl-L-cysteine			
CAS-No.	56976-06-8		
Formula	C ₁₂ H ₂₃ NO ₄ S		
Mol. weight	277,37 g/mol		
			
BAA1084	Boc-L-Cys(Trt)-OH		
N-alpha-t-Butyloxycarbonyl-S-trityl-L-cysteine			
CAS-No.	21947-98-8		
Formula	C ₂₇ H ₂₉ NO ₄ S		
Mol. weight	463,59 g/mol		
			
BAA5000	Boc-D-Cys(Trt)-OH		
N-alpha-t-Butyloxycarbonyl-S-trityl-D-cysteine			
CAS-No.	87494-13-1		
Formula	C ₂₇ H ₂₉ NO ₄ S		
Mol. weight	463,59 g/mol		
			
HAA3530	H-L-Cys-NH₂*HCl		
L-Cysteine amide hydrochloride			
CAS-No.	16359-98-1		
Formula	C ₃ H ₈ N ₂ OS*HCl		
Mol. weight	120,17*36,45 g/mol		
			
FAA1362	Fmoc-L-Cys-OH*H₂O		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-cysteine monohydrat			
CAS-No.	135248-89-4		
Formula	C ₁₈ H ₁₇ NO ₄ S*H ₂ O		
Mol. weight	343,40*18,01 g/mol		
			

			Product details
FAA1470	Fmoc-D-Cys-OH*H₂O		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-D-cysteine monohydrat			
CAS-No.	157355-80-1		
Formula	C ₁₈ H ₁₇ NO ₄ S*H ₂ O		
Mol. weight	343,4*18,01 g/mol		
			
FAA1980	Fmoc-L-Cys-NH₂		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-cysteine amide			
CAS-No.	623177-62-8		
Formula	C ₁₈ H ₁₈ N ₂ O ₃ S		
Mol. weight	342,41 g/mol		
			
FAA1506	Fmoc-L-Cys(Acm)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-cysteine			
CAS-No.	86060-81-3		
Formula	C ₂₁ H ₂₂ N ₂ O ₅ S		
Mol. weight	414,48 g/mol		
			
FAA9250	Fmoc-L-Cys(2-Boc-aminoethyl)-OH		
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2-((tert-butoxycarbonyl)amino)ethyl)-L-cysteine			
CAS-No.	2230472-96-2		
Formula	C ₂₅ H ₃₀ N ₂ O ₆ S		
Mol. weight	486,58 g/mol		
			
FAA9090	Fmoc-L-Cys(Cam)-OH		
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2-amino-2-oxoethyl)-L-cysteine			
CAS-No.	1443324-12-6		
Formula	C ₂₀ H ₂₀ N ₂ O ₅ S		
Mol. weight	400,45 g/mol		
			
FAA6910	Fmoc-L-Cys(Phacm)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-Phenylacetylaminomethyl)-L-cysteine			
CAS-No.	159680-21-4		
Formula	C ₂₇ H ₂₆ N ₂ O ₅ S		
Mol. weight	490,57 g/mol		
			

		Product details
FAA6720	Fmoc-L-MeCys(Acm)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-(acetyl-aminomethyl)-L-cysteine		
CAS-No.	481642-19-7	
Formula	C ₂₂ H ₂₄ N ₂ O ₅ S	
Mol. weight	428,5 /mol	
		
BAA6390	Boc-L-Cys(Phacm)-OH	
N-alpha-t-Butyloxycarbonyl-S-(Phenylacetylaminomethyl)-L-cysteine		
CAS-No.	57084-73-8	
Formula	C ₁₇ H ₂₄ N ₂ O ₅ S	
Mol. weight	368,45 g/mol	
		
FAA3710	Fmoc-D-Cys(Phacm)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(phenylacetylaminomethyl)-D-cysteine		
CAS-No.	1565818-55-4	
Formula	C ₂₇ H ₂₆ N ₂ O ₅ S	
Mol. weight	490,57 g/mol	
		
FAA5150	Fmoc-L-Cys(Aapam)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((4-(allyloxycarbonylamino)phenylacetylaminomethyl)-L-cysteine		
CAS-No.	1946783-89-6	
Formula	C ₃₁ H ₃₁ N ₃ O ₇ S	
Mol. weight	589,66 g/mol	
		
FAA7610	Fmoc-L-Cys(Allocam)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((allyloxycarbonylamino)methyl)-L-cysteine		
CAS-No.	232953-09-2	
Formula	C ₂₃ H ₂₄ N ₂ O ₆ S	
Mol. weight	456,51 g/mol	
		
FAA6230	Fmoc-D-Cys(Acm)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-cysteine		
CAS-No.	168300-88-7	
Formula	C ₂₁ H ₂₂ N ₂ O ₅ S	
Mol. weight	414,48 g/mol	
		

		Product details
FAA3720	Fmoc-L-Cys(Biotin)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-biotinyl-L-cysteine		
Formula	C ₂₈ H ₃₁ N ₃ O ₆ S ₂	
Mol. weight	569,69 g/mol	
FAA6270	Fmoc-L-Cys(Bzl)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-benzyl-L-cysteine		
CAS-No.	53298-33-2	
Formula	C ₂₅ H ₂₃ NO ₄ S	
Mol. weight	433,52 g/mol	
FAA1714	Fmoc-L-Cys(MBzl)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-cysteine		
CAS-No.	136050-67-4	
Formula	C ₂₆ H ₂₅ NO ₄ S	
Mol. weight	447,53 g/mol	
FAA8225	Fmoc-L-Cys(CF₃)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trifluoromethyl-L-cysteine		
CAS-No.	1994331-25-7	
Formula	C ₁₉ H ₁₆ F ₃ NO ₄ S	
Mol. weight	411,4 g/mol	
FAA1030	Fmoc-L-Cys(Mmt)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-p-methoxytrityl-L-cysteine		
CAS-No.	177582-21-7	
Formula	C ₃₈ H ₃₃ NO ₅ S	
Mol. weight	615,74 g/mol	
FAA4845	Fmoc-alpha-Me-L-Cys(Mmt)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-(4-methoxytrityl)-L-cysteine		
CAS-No.	1198791-74-0	
Formula	C ₃₉ H ₃₅ NO ₅ S	
Mol. weight	629,76 g/mol	

General Introduction

Cyclization **via** Disulfide Bond Formation

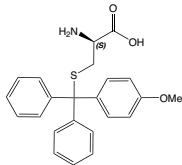
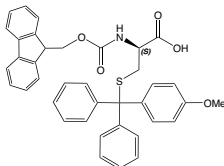
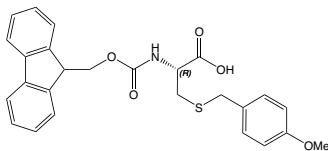
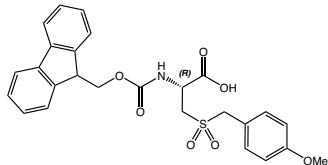
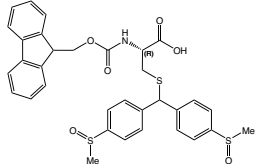
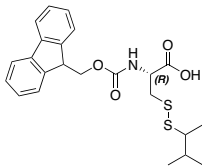
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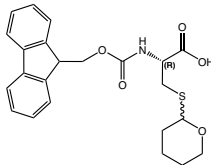
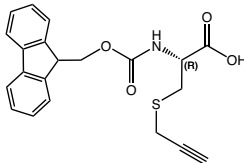
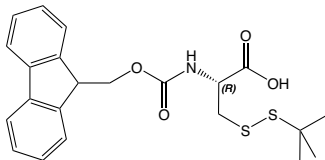
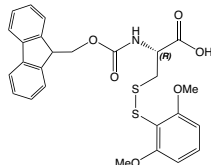
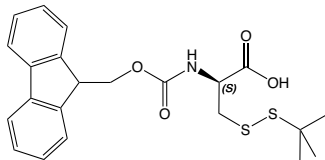
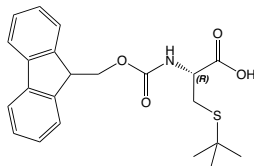
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		Product details
HAA3500	H-D-Cys(Mmt)-OH	
S- <i>p</i> -methoxytrityl-D-cysteine		
CAS-No.	926935-33-3	
Formula	C ₂₃ H ₂₃ NO ₃ S	
Mol. weight	393,5 g/mol	
FAA1614	Fmoc-D-Cys(Mmt)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S- <i>p</i> -methoxytrityl-D-cysteine		
CAS-No.	1198791-73-9	
Formula	C ₃₈ H ₃₃ NO ₅ S	
Mol. weight	615,74 g/mol	
FAA1715	Fmoc-L-Cys(Mob)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine		
CAS-No.	141892-41-3	
Formula	C ₂₆ H ₂₅ NO ₃ S	
Mol. weight	463,55 g/mol	
FAA8410	Fmoc-L-Cys(SO₂Mob)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine-S,S-dioxide		
CAS-No.	2412536-40-2	
Formula	C ₂₆ H ₂₅ NO ₅ S	
Mol. weight	495,55	
FAA4155	Fmoc-L-Cys(Msbh)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S-(4,4'-dimethylsulfinylbenzhydryl)-L-cysteine		
CAS-No.	1584646-97-8	
Formula	C ₃₃ H ₃₁ NO ₆ S ₃	
Mol. weight	633,80 g/mol	
FAA8495	Fmoc-L-Cys(SIT)-OH	
N- α -(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-cysteine		
CAS-No.	2545642-31-5	
Formula	C ₂₃ H ₂₇ NO ₄ S ₂	
Mol. weight	445,59 g/mol	

		Product details
FAA4160	Fmoc-L-Cys(Thp)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-tetrahydro-pyranyl-L-cysteine		
CAS-No.	1673576-83-4	
Formula	C ₂₃ H ₂₅ NO ₃ S	
Mol. weight	427,15 g/mol	
		
FAA3810	Fmoc-L-Cys(Propargyl)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-propargyl-L-cysteine		
CAS-No.	1354752-76-3	
Formula	C ₂₁ H ₁₉ NO ₃ S	
Mol. weight	381,44 g/mol	
		
FAA1575	Fmoc-L-Cys(StBu)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(t-butylthio)-L-cysteine		
CAS-No.	73724-43-3	
Formula	C ₂₂ H ₂₅ NO ₃ S ₂	
Mol. weight	431,57 g/mol	
		
FAA3180	Fmoc-L-Cys(S-DMP)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2,6-dimethoxythiophenyl)-L-cysteine		
CAS-No.	1403834-73-0	
Formula	C ₂₆ H ₂₅ NO ₆ S ₂	
Mol. weight	511,61 g/mol	
		
FAA1965	Fmoc-D-Cys(StBu)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(t-butylthio)-D-cysteine		
CAS-No.	501326-55-2	
Formula	C ₂₂ H ₂₅ NO ₃ S ₂	
Mol. weight	431,57 g/mol	
		
FAA1716	Fmoc-L-Cys(tBu)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-t-butyl-L-cysteine		
CAS-No.	67436-13-9	
Formula	C ₂₂ H ₂₅ NO ₃ S	
Mol. weight	399,51 g/mol	
		

General Introduction

Cyclization via Disulfide Bond Formation

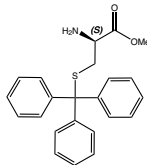
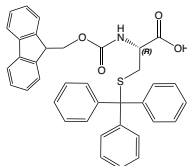
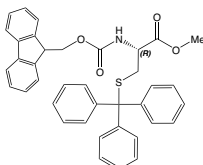
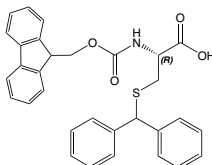
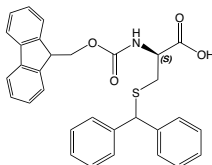
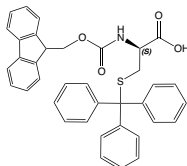
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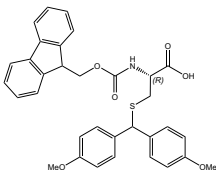
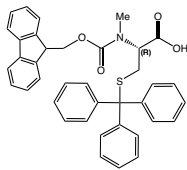
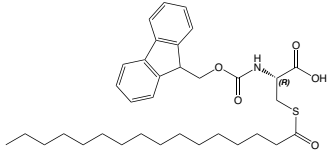
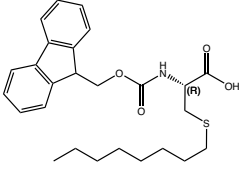
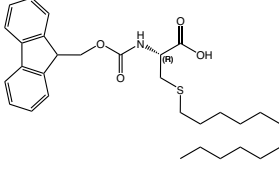
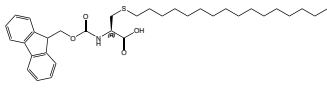
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		Product details
HAA3520	H-D-Cys(Trt)-OMe*HCl S-trityl-D-cysteine methyl ester hydrochloride CAS-No. 1020369-32-7 Formula $C_{23}H_{23}NO_2S^+HCl$ Mol. weight 377,50*36,45 g/mol	 
FAA1040	Fmoc-L-Cys(Trt)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine CAS-No. 103213-32-7 Formula $C_{37}H_{31}NO_4S$ Mol. weight 585,71 g/mol	 
FAA5670	Fmoc-L-Cys(Trt)-OMe N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine methyl ester CAS-No. 245088-56-6 Formula $C_{38}H_{33}NO_4S$ Mol. weight 599,74 g/mol	 
FAA3190	Fmoc-L-Cys(Dpm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenyl-methyl-L-cysteine CAS-No. 247595-29-5 Formula $C_{31}H_{27}NO_4S$ Mol. weight 509,62 g/mol	 
FAA5650	Fmoc-D-Cys(Dpm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenyl-methyl-D-cysteine CAS-No. 2389078-16-2 Formula $C_{31}H_{27}NO_4S$ Mol. weight 509,62 g/mol	 
FAA1035	Fmoc-D-Cys(Trt)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-cysteine CAS-No. 167015-11-4 Formula $C_{37}H_{31}NO_4S$ Mol. weight 585,71 g/mol	 

		Product details
FAA6940	Fmoc-L-Cys(Ddm)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-di(4-methoxyphenyl)methyl-L-cysteine		
CAS-No.	1403825-56-8	 
Formula	C ₃₃ H ₃₁ NO ₆ S	
Mol. weight	569,67 g/mol	
FAA3570	Fmoc-L-MeCys(Trt)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-N-alpha-methyl-S-trityl-L-cysteine		
CAS-No.	944797-51-7	 
Formula	C ₃₈ H ₃₃ NO ₅ S	
Mol. weight	599,74 g/mol	
FAA1950	Fmoc-L-Cys(Palm)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-t-palmitoyl-L-cysteine		
CAS-No.	824955-27-3	 
Formula	C ₃₄ H ₄₇ NO ₅ S	
Mol. weight	581,81 g/mol	
FAA5890	Fmoc-L-Cys(Octyl)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-octyl-L-cysteine		
CAS-No.	210883-65-1	 
Formula	C ₂₆ H ₃₃ NO ₄ S	
Mol. weight	455,61 g/mol	
FAA4810	Fmoc-L-Cys(lauryl)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-dodecyl-L-cysteine		
CAS-No.	1310682-09-7	 
Formula	C ₃₀ H ₄₁ NO ₄ S	
Mol. weight	511,72 g/mol	
FAA8770	Fmoc-L-Cys(palmityl)-OH	
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-hexadecyl-L-cysteine		
CAS-No.	876312-48-0	 
Formula	C ₃₄ H ₄₉ NO ₄ S	
Mol. weight	567,83 g/mol	

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Cyclization **via** Disulfide Bond Formation

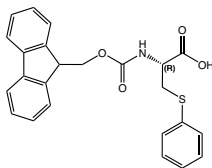
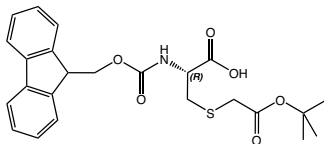
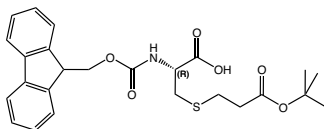
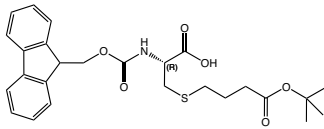
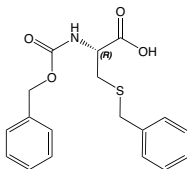
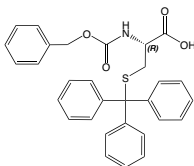
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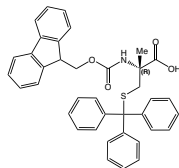
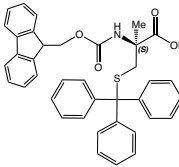
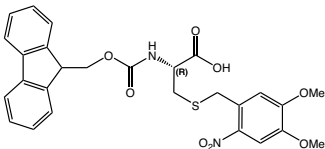
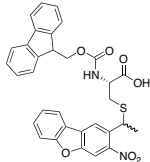
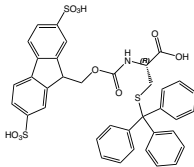
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			Product details
FAA4820	Fmoc-L-Cys(Ph)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-phenyl-L-cysteine			
CAS-No.	488761-06-4		
Formula	C ₂₆ H ₂₁ NO ₄ S		
Mol. weight	419,49 g/mol		
			
FAA4751	Fmoc-L-Cys(Ac-OtBu)-OH*DCHA		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(t-butoxycarbonylmethyl)-L-cysteine dicyclohexylamine			
CAS-No.	269730-62-3 net		
Formula	C ₂₆ H ₂₇ NO ₆ S*C ₁₂ H ₂₃ N		
Mol. weight	457,54*181,32 g/mol		
			
FAA4760	Fmoc-L-Cys(EtCO-OtBu)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(t-butoxycarbonyl-ethyl)-L-cysteine			
CAS-No.	685863-48-3		
Formula	C ₂₅ H ₂₉ NO ₆ S		
Mol. weight	471,57 g/mol		
			
FAA3370	Fmoc-L-Cys(PrCO-OtBu)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(t-butoxycarbonyl-propyl)-L-cysteine			
CAS-No.	102971-73-3		
Formula	C ₂₆ H ₃₁ NO ₆ S		
Mol. weight	485,59 g/mol		
			
ZAA1161	Z-L-Cys(Bzl)-OH		
N-alpha-Benzoyloxycarbonyl-S-benzyl-L-cysteine			
CAS-No.	3257-18-9		
Formula	C ₁₈ H ₁₉ NO ₄ S		
Mol. weight	345,42 g/mol		
			
ZAA1310	Z-L-Cys(Trt)-OH		
N-alpha-Benzoyloxycarbonyl-S-trityl-L-cysteine			
CAS-No.	26311-04-6		
Formula	C ₃₀ H ₂₇ NO ₄ S		
Mol. weight	497,60 g/mol		
			

		Product details
FAA4840	Fmoc-alpha-Me-L-Cys(Trt)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-trityl-L-cysteine CAS-No. 725728-43-8 Formula $C_{38}H_{33}NO_4S$ Mol. weight 599,74 g/mol	 
FAA4850	Fmoc-alpha-Me-D-Cys(Trt)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-trityl-D-cysteine CAS-No. 725728-37-0 Formula $C_{38}H_{33}NO_4S$ Mol. weight 599,74 g/mol	 
FAA3970	Fmoc-L-Cys(oNv)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-cysteine CAS-No. 214633-71-3 Formula $C_{27}H_{26}N_2O_8S$ Mol. weight 538,57 g/mol	 
FAA8420	Fmoc-L-Cys(NDBF)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(1-(3-nitro-dibenzofuran-2-yl)-ethyl)-L-cysteine CAS-No. 1895883-28-9 Formula $C_{32}H_{26}N_2O_7S$ Mol. weight 582,62 g/mol	 
SAA1110	Smoc-L-Cys(Trt)-OH N-(((2,7-disulfo-9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteine potassium salt CAS-No. 2442552-68-1 Formula $C_{37}H_{29}K_2NO_{10}S_3$ Mol. weight 822,01 g/mol	 

General Introduction

 Cyclization **via** Disulfide Bond Formation

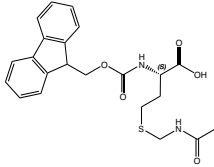
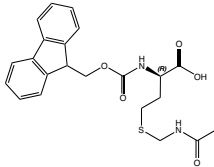
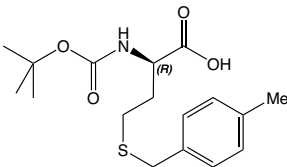
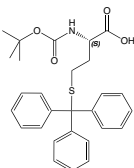
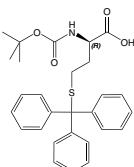
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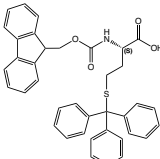
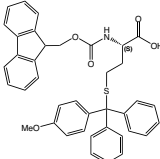
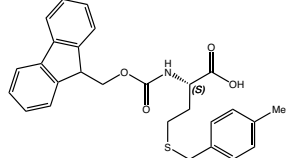
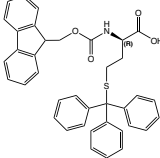
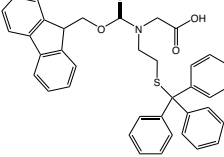
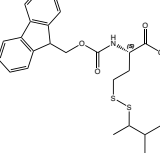
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5.2. Homocysteine Building Blocks

		Product details
FAA8255	Fmoc-L-HCys(Acm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-homocysteine CAS-No. 150281-21-3 Formula $C_{22}H_{24}N_2O_5S$ Mol. weight 428,5 g/mol	 
FAA8260	Fmoc-D-HCys(Acm)-OH N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-homocysteine CAS-No. 2576507-96-3 Formula $C_{22}H_{24}N_2O_5S$ Mol. weight 428,5 g/mol	 
BAA5180	Boc-D-HCys(MBz)-OH N-alpha-t-Butyloxycarbonyl-S-(4-methylbenzyl)-D-homocysteine CAS-No. 214630-13-4 Formula $C_{17}H_{25}NO_4S$ Mol. weight 339,46 g/mol	 
BAA5200	Boc-L-HCys(Trt)-OH N-alpha-t-Butyloxycarbonyl-S-trityl-L-homocysteine CAS-No. 201419-16-1 Formula $C_{28}H_{31}NO_4S$ Mol. weight 477,63 g/mol	 
BAA5190	Boc-D-HCys(Trt)-OH N-alpha-t-Butyloxycarbonyl-S-trityl-D-homocysteine CAS-No. 1301706-43-3 Formula $C_{28}H_{31}NO_4S$ Mol. weight 477,63 g/mol	 

			Product details
FAA1602	Fmoc-L-HCys(Trt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-homocysteine			
CAS-No.	167015-23-8		
Formula	C ₃₈ H ₃₃ NO ₄ S		
Mol. weight	599,76 g/mol		
			
FAA3840	Fmoc-L-HCys(Mmt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxytrityl)-L-homocysteine			
CAS-No.	887644-62-4		
Formula	C ₃₉ H ₃₅ NO ₅ S		
Mol. weight	629,76 g/mol		
			
FAA5680	Fmoc-L-HCys(MBzl)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-homocysteine			
CAS-No.	1821768-91-5		
Formula	C ₂₇ H ₂₇ NO ₄ S		
Mol. weight	461,57 g/mol		
			
FAA6120	Fmoc-D-HCys(Trt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-homocysteine			
CAS-No.	1007840-62-1		
Formula	C ₃₈ H ₃₃ NO ₄ S		
Mol. weight	599,76 g/mol		
			
FAA4830	Fmoc-Nhcys(Trt)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-[2-(tritylthio)ethyl]-glycine			
CAS-No.	882847-27-0		
Formula	C ₃₈ H ₃₃ NO ₄ S		
Mol. weight	599,74 g/mol		
			
FAA8865	Fmoc-L-hCys(SIT)-OH		
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-homocysteine			
Formula	C ₂₄ H ₂₉ NO ₄ S ₂		
Mol. weight	459,62 g/mol		
			

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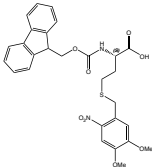
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Cleland's Reagent – DTT

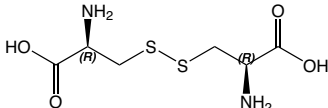
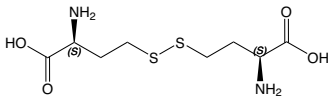
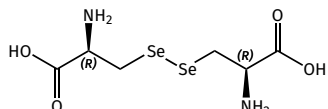
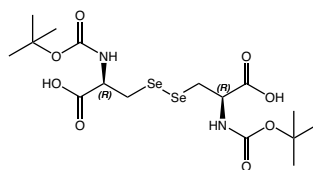
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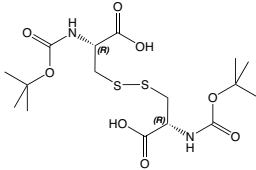
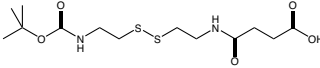
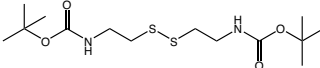
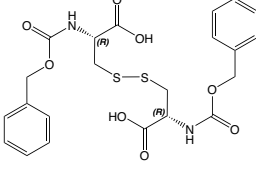
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		Product details
FAA8870	Fmoc-L-hCys(oNv)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-homocysteine		
Formula	C ₂₈ H ₂₈ N ₂ O ₈ S	
Mol. weight	552,60 g/mol	
		

5.3. Cystine Building Blocks

		Product details
HAA1156	(H-L-Cys-OH)₂	
L-Cystine		
CAS-No.	56-89-3	
Formula	C ₆ H ₁₂ N ₂ O ₄ S ₂	
Mol. weight	240,29 g/mol	
		
HAA1157	H-L-HCystine	
L-HomoCystine		
CAS-No.	626-72-2	
Formula	C ₈ H ₁₆ N ₂ O ₄ S ₂	
Mol. weight	268,36 g/mol	
		
HAA9350	(H-L-Sec-OH)₂	
L-Selenocystine, (H-Sec) ₂ , (H-L-Sec) ₂		
CAS-No.	29621-88-3	
Formula	C ₆ H ₁₂ N ₂ O ₄ Se ₂	
Mol. weight	334,11 g/mol	
		
BAA3680	(Boc-L-Sec)₂	
N-alpha-t-Butyloxycarbonyl-L-selenocystine		
CAS-No.	877754-71-7	
Formula	C ₁₆ H ₂₈ N ₂ O ₈ Se ₂	
Mol. weight	534,35 g/mol	
		

		Product details
BAA5390 (Boc-L-Cys-OH)₂ N-alpha,N-alpha'-di-Boc-L-cystine CAS-No. 10389-65-8 Formula C ₁₆ H ₂₈ N ₂ O ₈ S ₂ Mol. weight 440,52 g/mol		
BAA2180 Boc-Cystamine-Suc-OH 4-((2-(2-Butyloxycarbonylaminoethyl)disulfanyl)ethylamino)-4-oxobutanoic acid CAS-No. 946849-79-2 Formula C ₁₃ H ₂₄ N ₂ O ₅ S ₂ Mol. weight 352,47 g/mol		
BNN1360 Di-Boc-Cystamine N,N'-Bis-tert-butoxycarbonyl-cystamine CAS-No. 67385-10-8 Formula C ₁₄ H ₂₈ N ₂ O ₄ S ₂ Mol. weight 352,51 g/mol		
ZAA1190 (Z-L-Cys-OH)₂ N-alpha-Benzoyloxycarbonyl-L-cystine CAS-No. 6968-11-2 Formula C ₂₂ H ₂₄ N ₂ O ₈ S ₂ Mol. weight 508,54 g/mol		

General Introduction

Cyclization **via** Disulfide Bond Formation

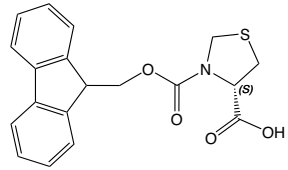
Cleland's Reagent – DTT

Chemoselective Ligation-Mediated Peptide Cyclization

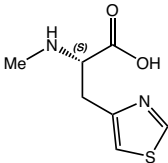
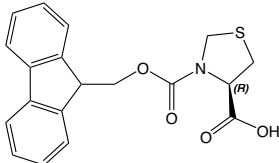
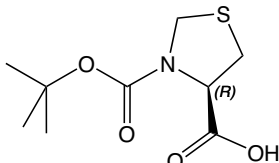
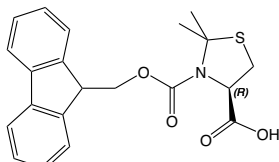
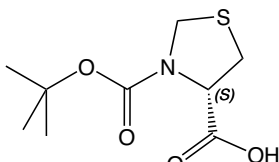
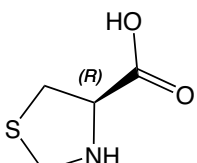
Product Overview

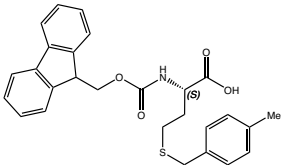
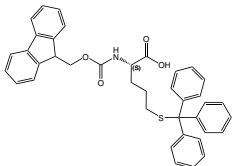
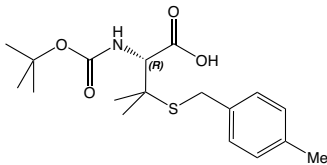
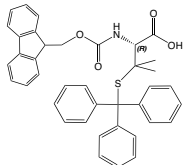
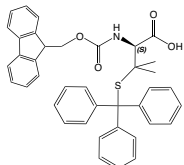
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5.4. Cysteine Protected as Thiazolidine and other Building Blocks

		Product details
FAA1495 Fmoc-D-Thz-OH (S)-N-alpha-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid CAS-No. 198545-89-0 Formula C ₁₉ H ₁₇ NO ₄ S Mol. weight 355,42 g/mol		

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		Product details
HAA3840	H-L-MeAla(4-Thz)-OH N-alpha-Methyl-beta-(4-thiazolyl)-L-alanine CAS-No. 2131118-50-6 Formula $C_7H_{10}N_2O_2S$ Mol. weight 186,23 g/mol	 
FAA1427	Fmoc-L-Thz-OH (R)-N-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid CAS-No. 133054-21-4 Formula $C_{19}H_{17}NO_4S$ Mol. weight 355,42 g/mol	 
BAA1135	Boc-L-Thz-OH (R)-N-t-Butyloxycarbonyl-thiazolidine-4-carboxylic acid CAS-No. 51077-16-8 Formula $C_9H_{15}NO_4S$ Mol. weight 233,29 g/mol	 
FAA1437	Fmoc-L-Thz(Me2)-OH (R)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid CAS-No. 873842-06-9 Formula $C_{21}H_{21}NO_4S$ Mol. weight 383,46 g/mol	 
BAA1186	Boc-D-Thz-OH (S)-N-(t-Butyloxycarbonyl)-thiazolidine-4-carboxylic acid CAS-No. 63091-82-7 Formula $C_9H_{15}NO_4S$ Mol. weight 233,29 g/mol	 
HAA1132	H-L-Thz-OH (R)-Thiazolidine-4-carboxylic acid CAS-No. 34592-47-7 Formula $C_4H_7NO_2S$ Mol. weight 133,16 g/mol	 

		Product details
FAA5680	Fmoc-L-HCys(MBzl)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-homocysteine		
CAS-No.	1821768-91-5	
Formula	C ₂₇ H ₂₇ NO ₄ S	
Mol. weight	461,57 g/mol	
		
FAA5370	Fmoc-2-amino-5-(tritylthio)-pentanoic acid (S)	
(S)-2-((9-Fluorenylmethyloxycarbonyl)amino)-5-(tritylthio)pentanoic acid		
CAS-No.	1417789-17-3	
Formula	C ₃₉ H ₃₅ NO ₄ S	
Mol. weight	613,76 g/mol	
		
BAA5850	Boc-L-Pen(MBzl)-OH*DCHA	
N-alpha-t-Butyloxycarbonyl-S-(4-methylbenzyl)-L-penicillamine dicyclohexylamine		
CAS-No.	198474-61-2	
Formula	C ₁₈ H ₂₇ NO ₄ S*C ₁₂ H ₂₃ N	
Mol. weight	353,48*181,32 g/mol	
		
FAA1587	Fmoc-L-Pen(Trt)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-penicillamine		
CAS-No.	201531-88-6	
Formula	C ₃₉ H ₃₅ NO ₄ S	
Mol. weight	613,78 g/mol	
		
FAA1675	Fmoc-D-Pen(Trt)-OH	
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-penicillamine		
CAS-No.	201532-01-6	
Formula	C ₃₉ H ₃₅ NO ₄ S	
Mol. weight	613,78 g/mol	
		

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Product code	Product name	Page	Product code	Product name	Page
BAA5390	(Boc-L-Cys-OH) ₂	86	BNN1360	Di-Boc-Cystamine	86
BAA3680	(Boc-L-Sec) ₂	85	RL-1020	DTT (racemic)	48
HAA1156	(H-L-Cys-OH) ₂	85	FAA5370	Fmoc-2-amino-5-(tritylthio)-pentanoic acid (S)	88
HAA9350	(H-L-Sec-OH) ₂	85	FAA8450	Fmoc-AAHA(Boc)-OH (S)	51
ZAA1190	(Z-L-Cys-OH) ₂	86	FAA4850	Fmoc-alpha-Me-D-Cys(Trt)-OH	82
AAA1300	Ac-L-Cys-OH	67	FAA4845	Fmoc-alpha-Me-L-Cys(Mmt)-OH	76
AAA2015	Aloc-L-Cys(Trt)-OH	5	FAA4840	Fmoc-alpha-Me-L-Cys(Trt)-OH	82
BAA2180	Boc-Cystamine-Suc-OH	86	SAD1107	Fmoc-D-Cys(Acm)-AC TG	23
BAA5410	Boc-D-Cys(Bzl)-OH	16, 71	FAA6230	Fmoc-D-Cys(Acm)-OH	23, 75
BAA5420	Boc-D-Cys(MBzl)-OH	18, 72	SAD1207	Fmoc-D-Cys(Acm)-Trt TG	23
BAA5000	Boc-D-Cys(Trt)-OH	5, 73	SAD1307	Fmoc-D-Cys(Acm)-Wang TG	23
BAA1170	Boc-D-Cys-OH	70	FAA5650	Fmoc-D-Cys(Dpm)-OH	13, 79
BAA5180	Boc-D-HCys(MBz)-OH	83	FAA1614	Fmoc-D-Cys(Mmt)-OH	11, 77
BAA5190	Boc-D-HCys(Trt)-OH	83	FAA8150	Fmoc-D-Cys(Msbh)-OH	41
BAA1186	Boc-D-Thz-OH	30, 87	FAA3710	Fmoc-D-Cys(Phacm)-OH	27, 75
BAA1078	Boc-L-Cys(Acm)-OH	22, 71	SAD1109	Fmoc-D-Cys(SS-tBu)-AC TG	35
BAA1510	Boc-L-Cys(Acm,O)-OH	71	SAD1209	Fmoc-D-Cys(SS-tBu)-Trt TG	36
BAA1079	Boc-L-Cys(Bzl)-OH	16, 71	SAD1309	Fmoc-D-Cys(SS-tBu)-Wang TG	36
BAA4360	Boc-L-Cys(CF ₃)-OH	71	FAA1965	Fmoc-D-Cys(SiBu)-OH	35, 78
BAA5510	Boc-L-Cys(Fm)-OH	71	SAD1106	Fmoc-D-Cys(Trt)-AC TG	9
BAA1080	Boc-L-Cys(MBzl)-OH	18, 72	FAA1035	Fmoc-D-Cys(Trt)-OH	5, 79
BAA1081	Boc-L-Cys(Mob)-OH	17, 72	SAD1206	Fmoc-D-Cys(Trt)-Trt TG	9
BAA1860	Boc-L-Cys(Npys)-OH	39, 72	WAA6118	Fmoc-D-Cys(Trt)-Wang Resin	10
BAA3140	Boc-L-Cys(Ph)-OH	73	SAD1306	Fmoc-D-Cys(Trt)-Wang TG	9
BAA6390	Boc-L-Cys(Phacm)-OH	75	FAA1470	Fmoc-D-Cys-OH*H ₂ O	74
BAA2250	Boc-L-Cys(Propargyl)-OH*DCHA	72	FAA8260	Fmoc-D-HCys(Acm)-OH	83
BAA6415	Boc-L-Cys(SiBu)-OH	35	FAA6120	Fmoc-D-HCys(Trt)-OH	84
BAA1082	Boc-L-Cys(tBu)-OH	14, 73	FAA1675	Fmoc-D-Pen(Trt)-OH	6, 88
BAA1084	Boc-L-Cys(Trt)-OH	5, 73	FAA8710	Fmoc-D-Sec(Mob)-OH	63
BAA1083	Boc-L-Cys-OH	70	FAA8600	Fmoc-D-Sec(Xan)-OH	62
BAA5200	Boc-L-HCys(Trt)-OH	83	FAA1495	Fmoc-D-Thz-OH	31, 86
BAA5850	Boc-L-Pen(MBzl)-OH*DCHA	88	PSI1440	Fmoc-Gly-L-Cys[PSI(Dmp,H)pro]-OH	20
BAA3760	Boc-L-Sec(Mob)-OH	63	PYV1170	Fmoc-Gly-NHN=Pyv Resin	53
BAA4830	Boc-L-Sec(Mob)-OPfp	63	FAA8445	Fmoc-Hcan(Boc)-OH (S)	51
IAD1040	Boc-L-Ser[Fmoc-L-Cys(Trt)]-OH	8	FAA9375	Fmoc-L-3-(2-cyano-3-pyridyl)-alanine	59
BAA4880	Boc-L-Sez-OH	64	FAA9370	Fmoc-L-3-(2-cyano-4-pyridyl)-alanine	59
IAD2040	Boc-L-Thr[Fmoc-L-Cys(Trt)]-OH	8	PSI1450	Fmoc-L-Ala-L-Cys[PSI(Dmp,H)pro]-OH	20
BAA1135	Boc-L-Thz-OH	30, 87	PYV1100	Fmoc-L-Ala-NHN=Pyv Resin	52

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PYV1120	Fmoc-L-Asn(Trt)-NHN=Pyv Resin	52	FAA8410	Fmoc-L-Cys(SO ₂ Mob)-OH	77
PYV1130	Fmoc-L-Asp(OtBu)-NHN=Pyv Resin	52	SAL1109	Fmoc-L-Cys(SS-tBu)-AC TG	36
PSI1470	Fmoc-L-Asp(tBu)-L-Cys[PSI(Dmp,H)pro]-OH	20	SAL1209	Fmoc-L-Cys(SS-tBu)-Trt TG	36
FAA8460	Fmoc-L-cis-Hyp(NHBoc)-OH	51	WAA11309	Fmoc-L-Cys(SS-tBu)-Wang Resin	37
FAA9395	Fmoc-L-Cys(2,6-DCP)-OH	59	WAA41309	Fmoc-L-Cys(SS-tBu)-Wang Resin	37
FAA9250	Fmoc-L-Cys(2-Boc-aminoethyl)-OH	74	SAL1309	Fmoc-L-Cys(SS-tBu)-Wang TG	36
FAA5150	Fmoc-L-Cys(Aapam)-OH	29, 75	FAA1575	Fmoc-L-Cys(SiBu)-OH	35, 78
FAA4751	Fmoc-L-Cys(Ac-OtBu)-OH*DCHA	81	TCP1230	Fmoc-L-Cys(SiBu)-TCP-Resin	36
SAL1107	Fmoc-L-Cys(Acm)-AC TG	23	FAA1716	Fmoc-L-Cys(tBu)-OH	15, 78
FAA1506	Fmoc-L-Cys(Acm)-OH	22, 74	TCP1120	Fmoc-L-Cys(tBu)-TCP-Resin	15
TCP1110	Fmoc-L-Cys(Acm)-TCP-Resin	24	FAA4160	Fmoc-L-Cys(Thp)-OH	14, 78
SAL1207	Fmoc-L-Cys(Acm)-Trt TG	24	SAL1106	Fmoc-L-Cys(Trt)-AC TG	9
WAA41307	Fmoc-L-Cys(Acm)-Wang Resin	24	PSI1580	Fmoc-L-Cys(Trt)-L-Cys(Psi(Dmp,H)pro)-OH	21
WAA11307	Fmoc-L-Cys(Acm)-Wang Resin	24	PYV1140	Fmoc-L-Cys(Trt)-NHN=Pyv Resin	8, 52
SAL1307	Fmoc-L-Cys(Acm)-Wang TG	24	FAA1040	Fmoc-L-Cys(Trt)-OH	6, 79
FAA7610	Fmoc-L-Cys(Allocam)-OH	29, 75	FAA5670	Fmoc-L-Cys(Trt)-OMe	6, 79
FAA3720	Fmoc-L-Cys(Biotin)-OH	76	TCP1130	Fmoc-L-Cys(Trt)-TCP-Resin	10
FAA6270	Fmoc-L-Cys(Bzl)-OH	76	SAL1206	Fmoc-L-Cys(Trt)-Trt TG	9
FAA9090	Fmoc-L-Cys(Cam)-OH	74	WAA41306	Fmoc-L-Cys(Trt)-Wang Resin	10
FAA8225	Fmoc-L-Cys(CF ₃)-OH	76	SAL1306	Fmoc-L-Cys(Trt)-Wang TG	9
FAA6940	Fmoc-L-Cys(Ddm)-OH	19, 80	FAA1980	Fmoc-L-Cys-NH ₂	74
FAA3190	Fmoc-L-Cys(Dpm)-OH	13, 79	FAA1362	Fmoc-L-Cys-OH*H ₂ O	73
FAA4760	Fmoc-L-Cys(EtCO-OtBu)-OH	81	FAA9390	Fmoc-L-Dab(2,6-DCP)-OH	59
FAA4810	Fmoc-L-Cys(lauryl)-OH	80	FAA9325	Fmoc-L-Dab(Boc-Cys(Trt))-OH	5, 60
FAA1714	Fmoc-L-Cys(MBzl)-OH	18, 76	FAA9330	Fmoc-L-Dab(Boc-Thz)-OH	31, 60
FAA7945	Fmoc-L-Cys(MDNPE)-OH	34	FAA9380	Fmoc-L-Dap(2-CINA)-OH	59
RAA2620	Fmoc-L-Cys(Mmt resin)-NH ₂	12	FAA9385	Fmoc-L-Dap(6-CNA)-OH	59
FAA1030	Fmoc-L-Cys(Mmt)-OH	11, 76	PYV1160	Fmoc-L-Gln(Trt)-NHN=Pyv Resin	53
FAA1715	Fmoc-L-Cys(Mob)-OH	17, 77	PSI1490	Fmoc-L-Glu(tBu)-L-Cys[PSI(Dmp,H)pro]-OH	20
FAA4155	Fmoc-L-Cys(Msbh)-OH	41, 77	PYV1150	Fmoc-L-Glu(tBu)-NHN=Pyv Resin	52
FAA8420	Fmoc-L-Cys(NDBF)-OH	33, 82	FAA8255	Fmoc-L-HCys(Acm)-OH	83
FAA5890	Fmoc-L-Cys(Octyl)-OH	80	FAA5680	Fmoc-L-HCys(MBzl)-OH	84, 88
FAA3970	Fmoc-L-Cys(oNv)-OH	32, 82	FAA3840	Fmoc-L-HCys(Mmt)-OH	84
FAA1950	Fmoc-L-Cys(Palm)-OH	80	FAA8870	Fmoc-L-hCys(oNv)-OH	32, 85
FAA8770	Fmoc-L-Cys(palmityl)-OH	80	FAA8865	Fmoc-L-hCys(SIT)-OH	39, 84
FAA4820	Fmoc-L-Cys(Ph)-OH	81	FAA1602	Fmoc-L-HCys(Trt)-OH	84
FAA6910	Fmoc-L-Cys(Phacm)-OH	27, 74	PYV1180	Fmoc-L-His(Trt)-NHN=Pyv Resin	53
FAA3370	Fmoc-L-Cys(PrCO-OtBu)-OH	81	PYV1190	Fmoc-L-Ile-NHN=Pyv Resin	53
FAA3810	Fmoc-L-Cys(Propargyl)-OH	78	PSI1510	Fmoc-L-Leu-L-Cys[PSI(Dmp,H)pro]-OH	20
FAA3180	Fmoc-L-Cys(S-DMP)-OH	38, 78	PYV1200	Fmoc-L-Leu-NHN=Pyv Resin	53

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PSI1520	Fmoc-L-Lys(Boc)-L-Cys[PSI(Dmp,H)pro]-OH	21	HAA3510	H-L-Cys(Npys)-OH*HCl	39, 72
PYV1210	Fmoc-L-Lys(Boc)-NHN=Pyv Resin	53	HAA9320	H-L-Cys(oNv)-OH	32, 69
FAA9315	Fmoc-L-Lys(Boc-Cys(Trt))-OH	5, 60	HAA2350	H-L-Cys(Propargyl)-OH*HCl	68
FAA9320	Fmoc-L-Lys(Boc-Thz)-OH	31, 60	HAA6140	H-L-Cys(SiBu)-OH	35, 69
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FAA3570	Fmoc-L-MeCys(Trt)-OH	6, 80	RAA1066	H-L-Cys(Trt)-2CT Resin	8
PYV1220	Fmoc-L-Met-NHN=Pyv Resin	54	HAA1560	H-L-Cys(Trt)-NH ₂	6, 69
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PYV1230	Fmoc-L-Phe-NHN=Pyv Resin	54	HAA1995	H-L-Cys(Trt)-OtBu*HCl	7, 70
PYV1240	Fmoc-L-Pro-NHN=Pyv Resin	54	HAA3530	H-L-Cys-NH ₂ *HCl	73
FAA8705	Fmoc-L-Sec(Mob)-OH	62	HAA1157	H-L-HCystine	85
FAA8760	Fmoc-L-Sec(Mob)-OPfp	62	HAA3840	H-L-MeAla(4-Thz)-OH	87
FAA8465	Fmoc-L-Sec(Xan)-OH	62	HAA9230	H-L-Sec(MDNPE)*TFA	63
PYV1250	Fmoc-L-Ser(tBu)-NHN=Pyv Resin	54	HAA9360	H-L-Sec(MDNPE)-OH	62
FAA8860	Fmoc-L-Sez-OH	64	HAA9475	H-L-Sec(NPE)-OH*HCl	63
PYV1260	Fmoc-L-Thr(tBu)-NHN=Pyv Resin	54	HAA9465	H-L-Sec(oNB)-OH*HCl	63
FAA1437	Fmoc-L-Thz(Me2)-OH	31, 87	HAA9255	H-L-Sec(oNv)-OH*TFA	62
FAA1427	Fmoc-L-Thz-OH	30, 87	HAA1132	H-L-Thz-OH	31, 87
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PYV1270	Fmoc-L-Trp(Boc)-NHN=Pyv Resin	54	SAA1110	Smoc-L-Cys(Trt)-OH	10, 82
PYV1280	Fmoc-L-Tyr(tBu)-NHN=Pyv Resin	55	ZAA1161	Z-L-Cys(Bzl)-OH	81
PSI1570	Fmoc-L-Val-L-Cys[PSI(Dmp,H)pro]-OH	21	ZAA1310	Z-L-Cys(Trt)-OH	10, 81
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HAA1017	H-D-Cys-OH*HCl*H ₂ O	67			
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HAA1574	H-L-Cys(Bzl)-OH	16, 67			
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HAA6090	H-L-Cys(MBzl)-OH	18, 68			
HAA9270	H-L-Cys(MDNPE)-OH	34, 68			
HAA1078	H-L-Cys(Me)-OH*HCl	68			

Notes

Notes

Code of Conduct

As business activity of Iris Biotech GmbH impacts people's lives and health, it must be operated in ethical and correct manner and act with integrity and responsibility. To ensure high ethical standards and fair business practices, Iris Biotech GmbH applies an integrated policy known as its Code of Conduct.

In 2001 Iris Biotech GmbH was founded just at the beginning of the Biotech movement and the first remarkable breakthrough of biotech pharma products. Although the biotech field is rather young compared to other industries we believe on long-term business, a good partnership between our business partners and Iris Biotech GmbH and a good reputation. It is our duty as well as our responsibility to maintain and to extend this over the next generations – based on the principles of an honourable and prudent tradesman which based upon the concept of honourable entrepreneurship.

This Code of Conduct has been developed following the “Voluntary Guidelines for Manufacturers of Fine Chemical Intermediates and Active Ingredients” issued by AIME (Agrochemical & Intermediates Manufacturers in Europe) and the requirements of some of our business associates.

Iris Biotech GmbH commits to hold this Code of Conduct and to include and apply its principles in the management system and the company policies.

Ethics

Iris Biotech GmbH undertakes business in an ethical manner and acts with integrity. All corruption, extortion and embezzlement are prohibited. We do not pay or accept bribes or participate in other illegal inducements in business or government relationships. We conduct our business in compliance with all applicable anti-trust laws. Employees are encouraged to report concerns or illegal activities in the workplace, without threat of reprisal, intimidation or harassment.

Labour

Iris Biotech GmbH is committed to uphold the human rights of workers and to treat them with dignity and respect. Child labour, workplace harassment, discrimination, and harsh and inhumane treatment are prohibited. Iris Biotech GmbH respects the rights of the employees to associate freely, join or not join labour unions, seek representation and join workers' councils. Employees are paid and their working timetable is established according to applicable wage and labour laws. Employees are able to communicate openly with management regarding working conditions without threat of reprisal, intimidation or harassment.

General Policies

Contracts and Secrecy Agreements are binding and the confidential information received is only used for intended purposes. Clear management and organizational structures exist to provide efficient normal working and to address problems quickly. Know-how is protected and intellectual property is respected.

Health and Safety

Iris Biotech GmbH provides a safe and healthy working environment to the employees and protects them from overexposure to chemical and physical hazards. Products are produced, stored and shipped under the guidelines of the relevant chemical and safety legislation. Risks and emergency scenarios are identified and evaluated, and their possible impact is minimized by implementing emergency plans and written procedures. Safety information regarding hazardous materials is available to educate, train and protect workers from hazards. Preventive equipment and facilities maintenance is performed at suitable periods to reduce potential hazards. Employees are regularly trained in health and safety matters and are informed about product properties and risk classification when it is required.

Environment

Iris Biotech GmbH operates in an environmentally responsible and efficient manner, minimizing adverse impacts on the environment. Waste streams are managed to ensure a safe handling, movement, storage, recycling and reuse, before and after being generated. Systems to prevent and mitigate accidental spills and releases to the environment are in place. All required environmental permits and licenses are obtained and their operational and reporting requirements are complied with.

Production and Quality Management

A quality management system following the Good Distribution Practices (GDP rules) of Active Pharmaceutical Ingredients is established covering all the aspects of the worldwide distribution of products. Regular audits are performed to evaluate the efficiency and fulfilling of the quality system. Process controls to provide reproducible product quality are established. There are preventive maintenance procedures to ensure plant reliability and the lowest risk of failure. Staff is trained periodically about GMP and GDP rules. Procedures are established and installations are designed to avoid cross contamination. Batch and analytical records are kept for inspection and audit purposes for suitable periods according guidelines.

Research and Development

Research and development staff education is appropriate to their functional activity and they are trained to develop, optimize and scale-up the processes. Intellectual property is respected and know-how protected. Development of manufacturing processes reflects the principles of the Green Chemistry according to the American Chemical Society Green Chemistry Institute. Animal testing is not used unless alternatives are not scientifically valid or accepted by regulators. If animal testing is carried out, animals are treated so that pain and stress are minimized.

Terms and Conditions of Sales

All orders placed by a buyer are accepted and all contracts are made subject to the terms which shall prevail and be effective notwithstanding any variations or additions contained in any order or other document submitted by the buyer. No modification of these terms shall be binding upon Iris Biotech GmbH unless made in writing by an authorised representative of Iris Biotech GmbH.

Placing of Orders

Every order made by the buyer shall be deemed an offer by the buyer to purchase products from Iris Biotech GmbH and will not be binding on Iris Biotech GmbH until a duly authorised representative of Iris Biotech GmbH has accepted the offer made by the buyer. Iris Biotech GmbH may accept orders from commercial, educational or government organisations, but not from private individuals and Iris Biotech GmbH reserves the right to insist on a written order and/or references from the buyer before proceeding.

There is no minimum order value. At the time of acceptance of an order Iris Biotech GmbH will either arrange prompt despatch from stock or the manufacture/acquisition of material to satisfy the order. In the event of the latter Iris Biotech GmbH will indicate an estimated delivery date. In addition to all its other rights Iris Biotech GmbH reserves the right to refuse the subsequent cancellation of the order if Iris Biotech GmbH expects to deliver the product on or prior to the estimated delivery date. Time shall not be of the essence in respect of delivery of the products. If Iris Biotech GmbH is unable to deliver any products by reason of any circumstances beyond its reasonable control („Force Majeure“) then the period for delivery shall be extended by the time lost due to such Force Majeure. Details of Force Majeure will be forwarded by Iris Biotech GmbH to the buyer as soon as reasonably practicable.

Prices, Quotations and Payments

Prices are subject to change. For the avoidance of doubt, the price advised by Iris Biotech GmbH at the time of the buyer placing the order shall supersede any previous price indications. The buyer must contact the local office of Iris Biotech GmbH before ordering if further information is required. Unless otherwise agreed by the buyer and Iris Biotech GmbH, the price shall be for delivery ex-works. In the event that the buyer requires delivery of the products otherwise than ex-works the buyer should contact the local office of Iris Biotech GmbH in order to detail its requirements. Iris Biotech GmbH shall, at its discretion, arrange the buyer's delivery requirements including, without limitation, transit insurance, the mode of transit (Iris Biotech GmbH reserves the right to vary the mode of transit if any regulations or other relevant considerations so require) and any special packaging requirements (including cylinders). For the avoidance of doubt all costs of delivery and packaging in accordance with the buyer's requests over and above that of delivery in standard packaging ex-works shall be for the buyer's account unless otherwise agreed by both parties. Incoterms 2020 shall apply. Any tax, duty or charge imposed by governmental authority or otherwise and any other applicable taxes, duties or charges shall be for the buyer's account. Iris Biotech GmbH may, on request and where possible, provide quotations for multiple packs or bulk quantities, and non-listed items. Irrespective of the type of request or means of response all quotations must be accepted by the buyer without condition and in writing before an order will be accepted by Iris Biotech GmbH. Unless agreed in writing on different terms, quotations are valid for 30 days from the date thereof. Payment terms are net 30 days from invoice date unless otherwise agreed in writing. Iris Biotech GmbH reserves the right to request advance payment at its discretion. For overseas transactions the buyer shall pay all the banking charges of Iris Biotech GmbH. The buyer shall not

be entitled to withhold or set-off payment for the products for any reason whatsoever. Government/ Corporate Visa and MasterCard (and other such credit cards) may be accepted on approved accounts for payment of the products. Personal credit cards are not acceptable. Failure to comply with the terms of payment of Iris Biotech GmbH shall constitute default without reminder. In these circumstances Iris Biotech GmbH may (without prejudice to any other of its rights under these terms) charge interest to accrue on a daily basis at the rate of 2% per month from the date upon which payment falls due to the actual date of payment (such interest shall be paid monthly). If the buyer shall fail to fulfil the payment terms in respect of any invoice of Iris Biotech GmbH Iris Biotech GmbH may demand payment of all outstanding balances from the buyer whether due or not and/or cancel all outstanding orders and/or decline to make further deliveries or provision of services except upon receipt of cash or satisfactory securities. Until payment by the buyer in full of the price and any other monies due to Iris Biotech GmbH in respect of all other products or services supplied or agreed to be supplied by Iris Biotech GmbH to the buyer (including but without limitation any costs of delivery) the property in the products shall remain vested in Iris Biotech GmbH.

Shipping, Packaging and Returns

The buyer shall inspect goods immediately on receipt and inform Iris Biotech GmbH of any shortage or damage within five days. Quality problems must be notified within ten days of receipt. Goods must not be returned without prior written authorisation of Iris Biotech GmbH. Iris Biotech GmbH shall at its sole discretion replace the defective products (or parts thereof) free of charge or refund the price (or proportionate price) to buyer. Opened or damaged containers cannot be returned by the buyer without the written prior agreement of Iris Biotech GmbH. In the case of agreed damaged containers which cannot be so returned, the buyer assumes responsibility for the safe disposal of such containers in accordance with all applicable laws.

Product Quality, Specifications and Technical Information

Products are analysed in the Quality Control laboratories of Iris Biotech GmbH's production partners by methods and procedures which Iris Biotech GmbH considers appropriate. In the event of any dispute concerning reported discrepancies arising from the buyer's analytical results, determined by the buyer's own analytical procedures, Iris Biotech GmbH reserves the right to rely on the results of own analytical methods of Iris Biotech GmbH. Certificates of Analysis or Certificates of Conformity are available at the discretion of Iris Biotech GmbH for bulk orders but not normally for prepack orders. Iris Biotech GmbH reserves the right to make a charge for such certification. Specifications may change and reasonable variation from any value listed should not form the basis of a dispute. Any supply by Iris Biotech GmbH of bespoke or custom product for a buyer shall be to a specification agreed by both parties in writing. Technical information, provided orally, in writing, or by electronic means by or on behalf of Iris Biotech GmbH, including any descriptions, references, illustrations or diagrams in any catalogue or brochure, is provided for guidance purposes only and is subject to change.

Safety

All chemicals should be handled only by competent, suitably trained persons, familiar with laboratory procedures and potential chemical hazards. The burden of safe use of the products of Iris Biotech GmbH vests in the buyer. The buyer assumes all responsibility for warning his employees, and any persons who might reasonably be expected to come into contact with the products, of all risks to person and property in any way connected with the products and for instructing them in their safe handling and use. The buyer also assumes the responsibility for the safe disposal of all products in accordance with all applicable laws.

Uses, Warranties and Liabilities

All products of Iris Biotech GmbH are intended for laboratory research purposes and unless otherwise stated on product labels, in the catalogue and product information sheet of Iris Biotech GmbH or in other literature furnished to the buyer, are not to be used for any other purposes, including but not limited to use as or as components in drugs for human or animal use, medical devices, cosmetics, food additives, household chemicals, agricultural or horticultural products or pesticides. Iris Biotech GmbH offers no warranty regarding the fitness of any product for a particular purpose and shall not be responsible for any loss or damage whatsoever arising there from. No warranty or representation is given by Iris Biotech GmbH that the products do not infringe any letters patent, trademarks, registered designs or other industrial rights. The buyer further warrants to Iris Biotech GmbH that any use of the products in the United States of America shall not result in the products becoming adulterated or misbranded within the meaning of the Federal Food, Drug and Cosmetic Act (or such equivalent legislation in force in the buyer's jurisdiction) and shall not be materials which may not, under sections 404, 505 or 512 of the Act, be introduced into interstate commerce. The buyer acknowledges that, since the products of Iris Biotech GmbH are intended for research purposes, they may not be on the Toxic Substances Control Act 1976 („TSCA“) inventory. The buyer warrants that it shall ensure that the products are approved for use under the TSCA (or such other equivalent legislation in force in the buyer's jurisdiction), if applicable. The buyer shall be responsible for complying with any legislation or regulations governing the use of the products and their importation into the country of destination (for the avoidance of doubt to include, without limitation, the TSCA and all its amendments, all EINECS, ELINCS and NONS regulations). If any licence or consent of any government or other authority shall be required for the acquisition, carriage or use of the products by the buyer the buyer shall obtain the same at its own expense and if necessary produce evidence of the same to Iris Biotech GmbH on demand. Failure to do so shall not entitle the buyer to withhold or delay payment. Any additional expenses or charges incurred by Iris Biotech GmbH resulting from such failure shall be for the buyer's account. Save for death or personal injury caused by negligence of Iris Biotech GmbH, sole obligation of Iris Biotech GmbH and buyer's exclusive remedy with respect to the products proved to the satisfaction of Iris Biotech GmbH to be defective or products incorrectly supplied shall be to accept the return of said products to Iris Biotech GmbH for refund of the actual purchase price paid by the buyer (or proportionate part thereof), or replacement of the defective product (or part thereof) with alternative product. Iris Biotech GmbH shall have no liability to the buyer under or arising directly or indirectly out of or otherwise in connection with the supply of products by Iris Biotech GmbH to the buyer and/or their re-sale or use by the buyer or for any product, process or services of the buyer which in any way comprises the product in contract tort (including negligence or breach of statutory duty) or otherwise for pure economic loss, loss of profit, business, reputation, depletion of brand, contracts, revenues or anticipated savings or for any special indirect or consequential damage or loss of any nature except as may otherwise be expressly provided for in these terms. All implied warranties, terms and representations in respect of the products (whether implied by statute or otherwise) are excluded to the fullest extent permitted by law. The buyer shall indemnify Iris Biotech GmbH for and against any and all losses, damages and expenses, including legal fees and other costs of defending any action, that Iris Biotech GmbH may sustain or incur as a result of any act or omission by the buyer, its officers, agents or employees, its successors or assignees, its customers or all other third parties, whether direct or indirect, in connection with the use of any product. For the avoidance of doubt and in the event that Iris Biotech GmbH supplies bespoke or custom product to the buyer's design or specification, this indemnity shall extend to include any claim by a third party that the manufacture of the product for the buyer or the use of the product by the buyer infringes the intellectual property rights of any third party.

General

Iris Biotech GmbH shall be entitled to assign or sub-contract all or any of its rights and obligations hereunder. The buyer shall not be entitled to assign, transfer, sub-contract or otherwise delegate any of its rights or obligations hereunder. Any delay or forbearance by Iris Biotech GmbH in exercising any right or remedy under these terms shall not constitute a waiver of such right or remedy. If any provision of these terms is held by any competent authority to be invalid or unenforceable in whole or in part the validity of the other provisions of these terms and the remainder of the provision in question shall not be affected. These terms shall be governed by German Law and the German Courts shall have exclusive jurisdiction for the hearing of any dispute between the parties save in relation to enforcement where the jurisdiction of the German Courts shall be non-exclusive.



Get in Contact



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Distribution Partners

The list contains the current distributors of Iris Biotech in different regions of the world. The latest list of distribution partners and contact details is available at: www.iris-biotech.de/distribution-partner

China:

Chengdu Yoo Technology Co., Ltd.

Japan:

BizCom Japan, Inc.

Shigematsu & Co., Ltd

Cosmo Bio Co., Ltd.

USA & Canada:

Peptide Solutions LLC

India, Bangladesh, Oman, Sri Lanka, United Arab Emirates:

Sumit Biosciences Pvt Ltd.

Empowering Peptide Innovation