Iris Biotech

CYCLIC PEPTIDES

Version: IB3_3

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.

Amino Acids ***Building Blocks*** ***Life Sciences*** ***Drug Delivery*** ***Reagents*** ***Resins*** ***Linkerology®*** ***Click Chemistry***

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-analogues as well as specific linkers for controlled drug delivery and release.

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, ^{t}Bu, Bzl, Acm, Mob, SIT, Phacm, Allocam, Mmt), unusual amino acids, fluorinated derivatives, substituted prolines, arginine analogues

Building Blocks

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

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

Linkerology® and Drug Delivery

Linkers for Solid Phase Peptide Synthesis

Cleavable Linkers

Val-Ala based, Val-Cit based, disulfide-based, Dde-helping hands

Photo-Activatable Linkers

Functionalized Linkers

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

PROTACs

Ligands, linkers & modules

Fullerenes, Poly(2-oxazolines) & Dextrans

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, Maltose, 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 & impurity profiling
- 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

Cyclic Peptides

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.

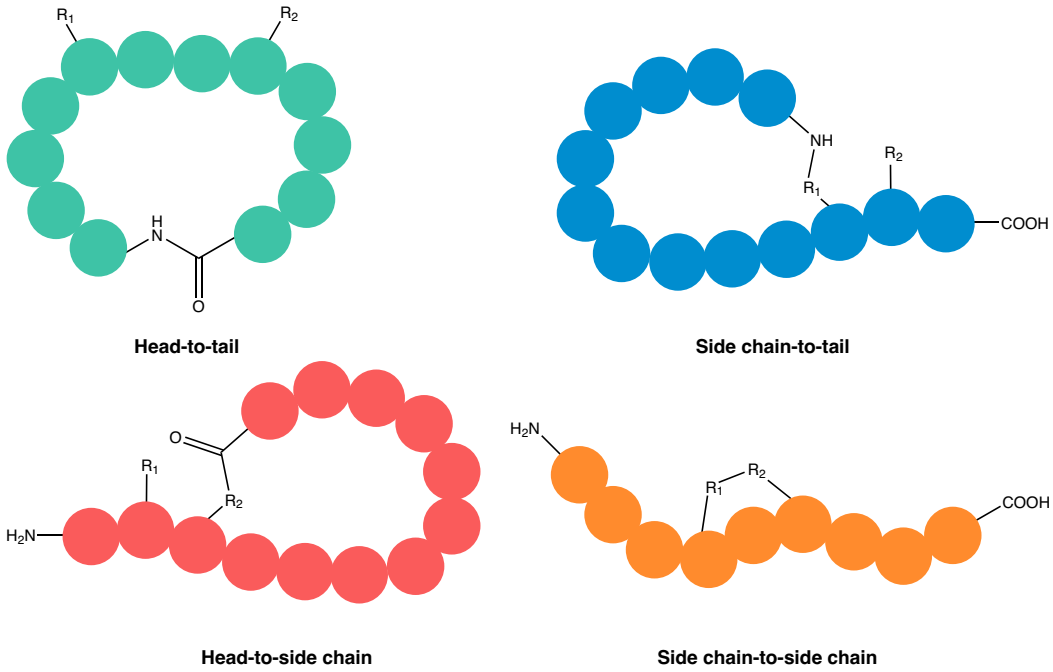

Fig. 1: Categorization of peptide cyclization.

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:

- *Ligation Technologies for the Synthesis of Cyclic Peptides; H. Y. Chow, Y. Zhang, E. Mathesn, X. Li;* ***Chem. Rev.*** *2019;* ***119(17)****: 9971-10001. https://doi.org/10.1021/acs.chemrev.8b00657*
- *Cyclic Peptides as Therapeutic Agents and Biochemical Tools; S. H. Joo;* ***Biomer 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*

In case you can not find the derivative you are looking for, please inquire for a custom synthesis!

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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 Cys protecting group compatible with the chosen combination of sidechain and N-alpha 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 sidechain protected cysteines categorized by their cleavage mechanism and available at Iris Biotech. For a detailed review on cysteine protecting groups, please see *Chem. Soc. Rev.* 2021; *50:* 11098.

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*

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) is used even in bulk productions. It is common to remove Trt using weak acids (e.g. 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 Acm or *t*Bu. Recently, Cys(Trt) has also been shown to be fully deprotected when treated with CuSO4 and cysteamine in aqueous buffered conditions. The trityl 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.

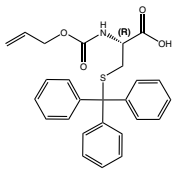
Especially, we are also offering the Smoc-L-Cys(Trt)-OH building block (SAA1110). The Smoc technology allows to replace organic solvents with water during peptide synthesis and thus represents a greener approach for the production of peptides.

Product details

AAA2015 Aloc-L-Cys(Trt)-OH

N-alpha-Allyloxycarbonyl-S-trityl-L-cysteine

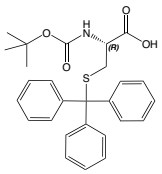
CAS-No. 96865-72-4
Formula $C_{26}H_{25}NO_4S$
Mol. weight 447,55 g/mol



BAA1084 Boc-L-Cys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-L-cysteine

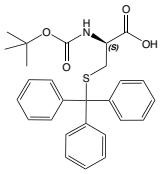
CAS-No. 21947-98-8
Formula $C_{27}H_{29}NO_4S$
Mol. weight 463,59 g/mol



BAA5000 Boc-D-Cys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-D-cysteine

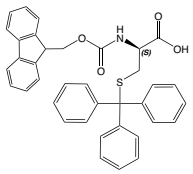
CAS-No. 87494-13-1
Formula $C_{27}H_{29}NO_4S$
Mol. weight 463,59 g/mol



FAA1035 Fmoc-D-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-cysteine

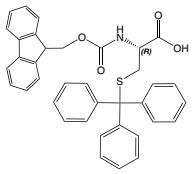
CAS-No. 167015-11-4
Formula $C_{37}H_{31}NO_4S$
Mol. weight 585,71 g/mol



FAA1040 Fmoc-L-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine

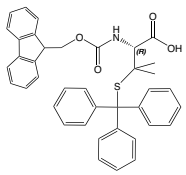
CAS-No. 103213-32-7
Formula $C_{37}H_{31}NO_4S$
Mol. weight 585,71 g/mol



FAA1587 Fmoc-L-Pen(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-penicillamine

CAS-No. 201531-88-6
Formula $C_{39}H_{35}NO_4S$
Mol. weight 613,78 g/mol



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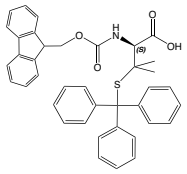
Cyclic Peptides

Product details

FAA1675 Fmoc-D-Pen(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-penicillamine

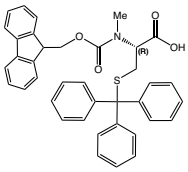
CAS-No. 201532-01-6
Formula $C_{39}H_{35}NO_4S$
Mol. weight 613,78 g/mol



FAA3570 Fmoc-L-MeCys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-trityl-L-cysteine

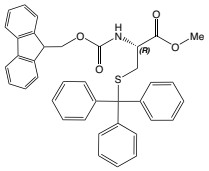
CAS-No. 944797-51-7
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



FAA5670 Fmoc-L-Cys(Trt)-OMe

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine methyl ester

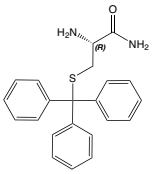
CAS-No. 245088-56-6
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



HAA1560 H-L-Cys(Trt)-NH_2

S-Trityl-L-cysteine amide

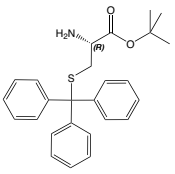
CAS-No. 166737-85-5
Formula $C_{22}H_{22}N_2OS$
Mol. weight 362,49 g/mol



HAA1995 H-L-Cys(Trt)-O*t*Bu*HCl

S-Trityl-L-cysteine *t*-butyl ester hydrochloride

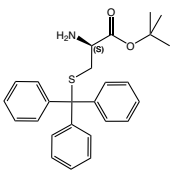
CAS-No. 158009-03-1
Formula $C_{26}H_{29}NO_2S$*HCl
Mol. weight 419,58*36,45 g/mol



HAA2100 H-D-Cys(Trt)-O*t*Bu*HCl

S-Trityl-D-cysteine *t*-butyl ester hydrochloride

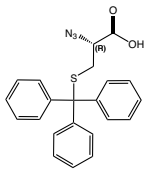
CAS-No. 439089-10-8
Formula $C_{26}H_{29}NO_2S$*HCl
Mol. weight 419,58*36,45 g/mol



HAA2810 N_3-L-Cys(Trt)-OH*CHA

(R)-2-azido-3-(tritylthio)propanoic acid cyclohexylamine

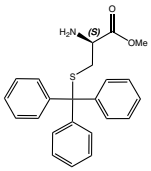
CAS-No.	1286670-90-3
Formula	$C_{22}H_{19}N_3O_2S*C_6H_{13}N$
Mol. weight	389,47*99,17 g/mol



HAA3520 H-D-Cys(Trt)-OMe*HCl

S-trityl-D-cysteine methyl ester hydrochloride

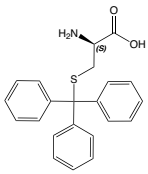
CAS-No.	1020369-32-7
Formula	$C_{23}H_{23}NO_2S*HCl$
Mol. weight	377,50*36,45 g/mol



HAA6120 H-D-Cys(Trt)-OH

S-Trityl-D-cysteine

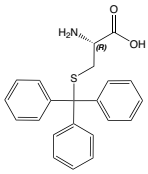
CAS-No.	25840-82-8
Formula	$C_{22}H_{21}NO_2S$
Mol. weight	363,48 g/mol



HAA6160 H-L-Cys(Trt)-OH

S-Trityl-L-cysteine

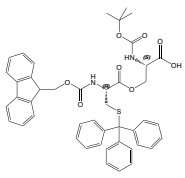
CAS-No.	2799-07-7
Formula	$C_{22}H_{21}NO_2S$
Mol. weight	363,48 g/mol



IAD1040 Boc-L-Ser[Fmoc-L-Cys(Trt)]-OH

O-(N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinyl)-N-(*tert*-butoxycarbonyl)-L-serine

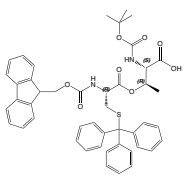
Formula	$C_{45}H_{44}N_2O_8S$
Mol. weight	772,9



IAD2040 Boc-L-Thr[Fmoc-L-Cys(Trt)]-OH

O-(N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-trityl-L-cysteinyl)-N-(*tert*-butoxycarbonyl)-L-threonine

CAS-No.	944283-30-1
Formula	$C_{46}H_{46}N_2O_8S$
Mol. weight	786,93 g/mol



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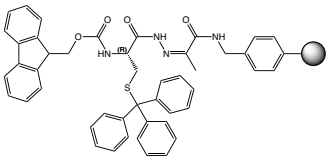
Cyclic Peptides

Product details

PYV1140 Fmoc-L-Cys(Trt)-NHN=Pyv Resin

Fmoc-S-trityl-L-cysteinyl-hydrazono-pyruvyl-amino-methylpolystyrene resin

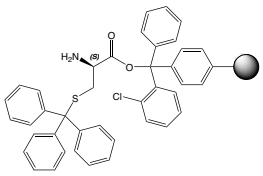
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



RAA1060 H-D-Cys(Trt)-2CT Resin

H-D-Cys(Trt)-2-chlorotrityl resin

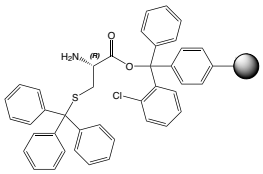
Mesh Size	100-200 mesh
Loading	> 0.4 mmol/g
DVB	1% DVB



RAA1065 H-L-Cys(Trt)-2CT Resin

H-L-Cys(Trt)-2-chlorotrityl resin

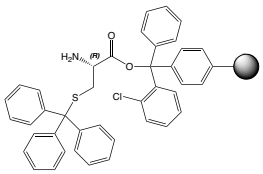
Mesh Size	100-200 mesh
Loading	0.4-1.2 mmol/g
DVB	1% DVB



RAA1066 H-L-Cys(Trt)-2CT Resin

H-L-Cys(Trt)-2-chlorotrityl resin

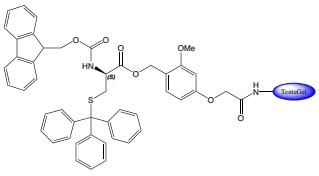
Mesh Size	200-400 mesh
Loading	0.4-1.2 mmol/g
DVB	1% DVB



SAD1106 Fmoc-D-Cys(Trt)-AC TG

Fmoc-D-Cys(Trt)-[3-methoxy-4-hydroxymethyl)phen-oxyacetylamid] TentaGel S

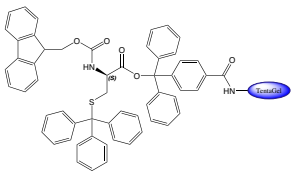
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAD1206 Fmoc-D-Cys(Trt)-Trt TG

Fmoc-D-Cys(Trt)-Trityl TentaGel S

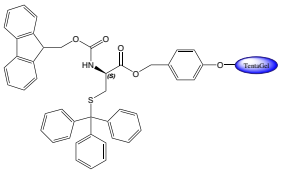
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAD1306 Fmoc-D-Cys(Trt)-Wang TG

Fmoc-D-Cys(Trt)-Wang TentaGel S

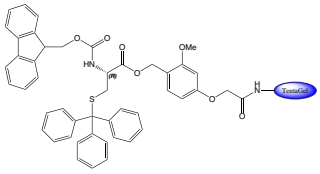
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAL1106 Fmoc-L-Cys(Trt)-AC TG

Fmoc-L-Cys(Trt)-[3-methoxy-4-hydroxymethyl)phen-oxyacetylamid] TentaGel S

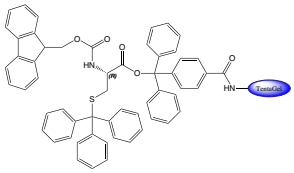
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAL1206 Fmoc-L-Cys(Trt)-Trt TG

Fmoc-L-Cys(Trt)-Trityl TentaGel S

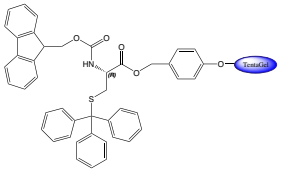
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAL1306 Fmoc-L-Cys(Trt)-Wang TG

Fmoc-L-Cys(Trt)-Wang TentaGel S

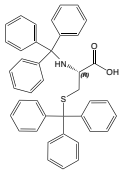
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



TAA1508 Trt-L-Cys(Trt)-OH*DEA

N-alpha-S-Bistrityl-L-cysteine diethylamine

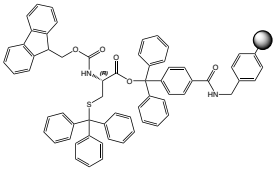
CAS-No.	27486-88-0
Formula	$C_{41}H_{35}NO_2S*C_4H_{11}N$
Mol. weight	678,9 g/mol



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



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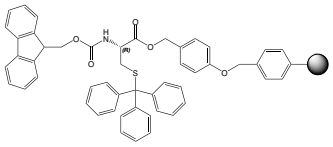
Product details

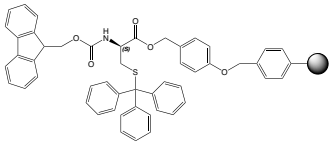
WAA41306 Fmoc-L-Cys(Trt)-Wang Resin

Mesh Size	200-400 mesh
DVB	1% DVB



WAA6118 Fmoc-D-Cys(Trt)-Wang Resin

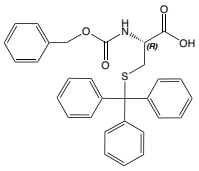
Mesh Size	100-200 mesh
DVB	1% DVB



ZAA1310 Z-L-Cys(Trt)-OH

N-alpha-Benzyloxycarbonyl-S-trityl-L-cysteine

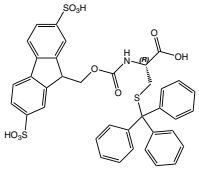
CAS-No.	26311-04-6
Formula	$C_{30}H_{27}NO_4S$
Mol. weight	497,60 g/mol



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 (net)
Formula	$C_{37}H_{29}K_2NO_{10}S_3$
Mol. weight	822,01 g/mol



2.1.2. 4-Methoxytrityl (Mmt)

Mmt represents a very acid-labile Cys protecting group, which can already be cleaved using 1-3% TFA in DCM/TES. The Mmt group displays orthogonality to multiple Cys protecting groups, including *t*Bu, Dpm, *o*Nv, S*t*Bu, and Acm. It is stable to bases, e.g. 30% piperidine in DMF (24 h, 22 °C), very weak acids, e.g. AcOH/TFE/DCM (1:2:7, 30 min) and compatible with standard Fmoc SPPS reagents.

For the targeted synthesis of two disulfide bridges, so far the most commonly applied protecting group combination used to be 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 orthoganality 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.

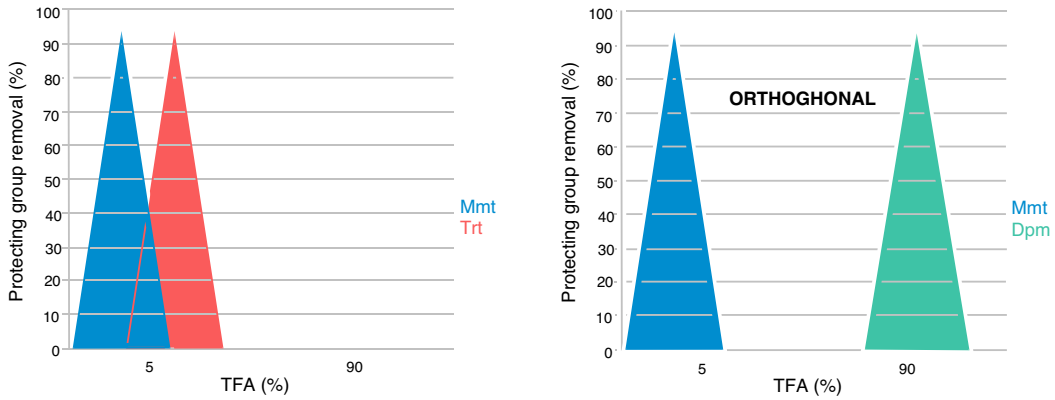


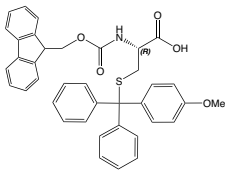
Fig. 2: Orthogonality between Mmt and Trt (left), and Mmt and Dpm (right).

Product details

FAA1030 Fmoc-L-Cys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*p*-methoxytrityl-L-cysteine

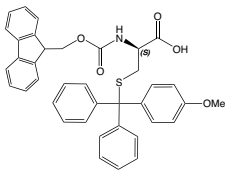
CAS-No.	177582-21-7
Formula	$C_{38}H_{33}NO_5S$
Mol. weight	615,74 g/mol



FAA1614 Fmoc-D-Cys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*p*-methoxytrityl-D-cysteine

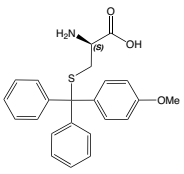
CAS-No.	1198791-73-9
Formula	$C_{38}H_{33}NO_5S$
Mol. weight	615,74 g/mol



HAA3500 H-D-Cys(Mmt)-OH

S-*p*-methoxytrityl-D-cysteine

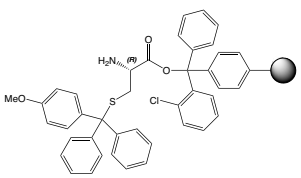
CAS-No.	926935-33-3
Formula	$C_{23}H_{23}NO_3S$
Mol. weight	393,5 g/mol



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



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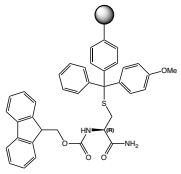
Product details

RAA2620 Fmoc-L-Cys(Mmt resin)-NH_2

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)

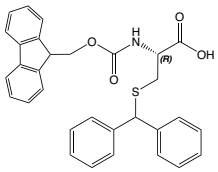
Dpm is stable to low concentrations of TFA cocktails (< 25%) but can be cleaved with higher concentrations. At least 60% TFA up to 90% TFA in DCM (using 2.5% TIS and 2.5% H_2O as scavengers) is required for full removal. Due to its acid lability profile, Dpm is orthogonal to Trt and Mmt. Additionally, Cys racemization is attenuated considerably when using Dpm compared to Trt or Bzl. Furthermore, Dpm is stable towards standard Fmoc SPPS reagents.

Product details

FAA3190 Fmoc-L-Cys(Dpm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenylmethyl-L-cysteine

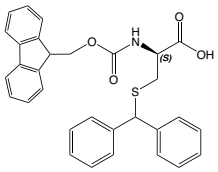
CAS-No.	247595-29-5
Formula	$C_{31}H_{27}NO_4S$
Mol. weight	509,62 g/mol



FAA5650 Fmoc-D-Cys(Dpm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenylmethyl-D-cysteine

Formula	$C_{31}H_{27}NO_4S$
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, Acm, and S*t*Bu in solid-phase peptide synthesis using the Fmoc/*t*Bu 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 S*t*Bu, 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 Ser and Thr.

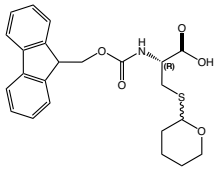
Furthermore, Thp protection leads to improved solubility of the respective Cys-containing protected peptides. Complete Thp deprotection can be carried out with either TFA/TIS/DCM (10:1.5:88.5) within 5 min or with HCl/dioxane (12:88) in 2 h. Additionally, Thp is stable to standard Fmoc SPPS reagents.

Product details

FAA4160 Fmoc-L-Cys(Thp)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-tetrahydro-pyranyl-L-cysteine

CAS-No.	1673576-83-4
Formula	$C_{23}H_{25}NO_5S$
Mol. weight	427,15 g/mol



References:

→ *Tetrahydropyranyl, a nonaromatic acid-labile Cys protecting 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*

2.1.5. *tert*-Butyl (*t*Bu)

Cleavage of *t*Bu 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 choride-sulfoxide in TFA, $Tl(TFA)_3$ or DMSO in TFA (with DMSO acting as an oxidant). If orthogonality to Meb is desired, DMSO/TFA may also be used for deprotection – *t*Bu 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. $PdCl_2$ in a 50 mM Tris or urea buffer at 37 °C was shown to cleave *t*Bu, providing a much milder way to remove the protecting group. *t*Bu is not removed by $[Pd(allyl)Cl]_2$ making it orthogonal to Thz and Acm under those conditions. Besides this, the Cys(*t*Bu) protecting group is stable to oxidation by I_2, stable towards AgOTf/TFA, neat TFA treatment as well as standard Fmoc SPPS reagents.

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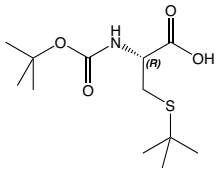
Cyclic Peptides

Product details

BAA1082 Boc-L-Cys(*t*Bu)-OH

N-alpha-*t*-Butyloxycarbonyl-S-*t*-butyl-L-cysteine

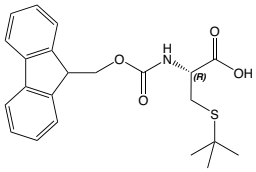
CAS-No.	56976-06-8
Formula	$C_{12}H_{23}NO_4S$
Mol. weight	277,37 g/mol



FAA1716 Fmoc-L-Cys(*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*t*-butyl-L-cysteine

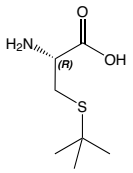
CAS-No.	67436-13-9
Formula	$C_{22}H_{25}NO_4S$
Mol. weight	399,51 g/mol



HAA6150 H-L-Cys(*t*Bu)-OH*HCl

S-*t*-Butyl-L-cysteine hydrochloride

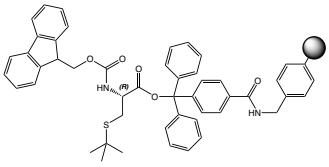
CAS-No.	2481-09-6
Formula	$C_7H_{15}NO_2S$*HCl
Mol. weight	177,26*36,45 g/mol



TCP1120 Fmoc-L-Cys(*t*Bu)-TCP-Resin

Fmoc-Cys(*t*Bu)-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. 4-Methoxybenzyl (Mob)

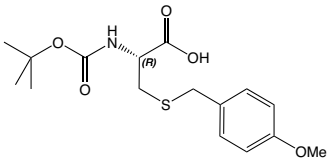
The conditions typically required for full removal of Mob are harsh: neat TFA at 100 °C or HF are reported for deprotection. Mob can also be removed by heavy metal salts, e.g. $Hg(TFA)_2$ or AgOTf in TFA/thioanisole, followed by DTT to obtain the free thiol. $Tl(TFA)_3$ can also be used for deprotection. Besides this, deprotection *via* treatment with $PdCl_2$ in 50 mM Tris or urea buffer at 37 °C is reported. AgOTf cannot cleave Meb, 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-alpha-*t*-Butyloxycarbonyl-S-(4-methoxy-benzyl)-L-cysteine

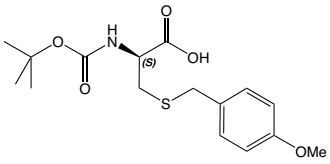
CAS-No. 18942-46-6
Formula $C_{16}H_{23}NO_5S$
Mol. weight 341,43 g/mol



BAA5430 Boc-D-Cys(Mob)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methoxy-benzyl)-D-cysteine

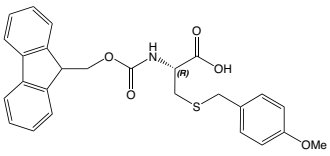
CAS-No. 58290-35-0
Formula $C_{16}H_{23}NO_5S$
Mol. weight 341,43 g/mol



FAA1715 Fmoc-L-Cys(Mob)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine

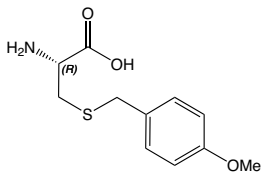
CAS-No. 141892-41-3
Formula $C_{26}H_{25}NO_5S$
Mol. weight 463,55 g/mol



HAA6100 H-L-Cys(Mob)-OH

S-(4-Methoxybenzyl)-L-cysteine

CAS-No. 2544-31-2
Formula $C_{11}H_{15}NO_3S$
Mol. weight 241,3 g/mol



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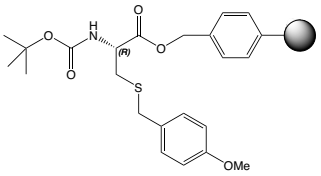
Product details

MAA5220 Boc-L-Cys(Mob)-Merrifield Resin

Boc-L-Cys(4-MeO-Bzl)-Merrifield Resin

Mesh Size	100-200 mesh
Loading	> 0.5 mmol/g
DVB	1% DVB



References:

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

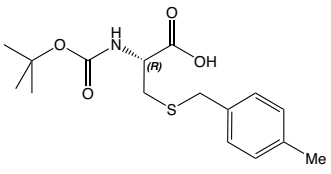
The Meb protecting group is broadly similar to Mob but less labile to TFA. Meb can be removed using HF-anisole (50%, 1 h, 0 °C), $Tl(TFA)_3$ or DMSO/TFA (45 °C). Meb is stable towards AgOTf and orthogonal to Trt, Acm, *t*Bu and S*t*Bu. Consequently, these protecting groups have frequently been used together. 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

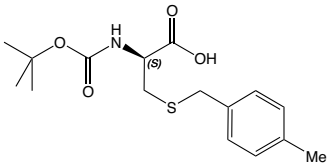
CAS-No.	61925-77-7
Formula	$C_{16}H_{23}NO_4S$
Mol. weight	325,43 g/mol



BAA5420 Boc-D-Cys(MBzl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methyl-benzyl)-D-cysteine

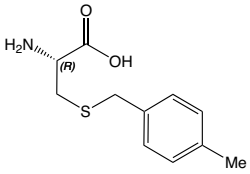
CAS-No.	61925-78-8
Formula	$C_{16}H_{23}NO_4S$
Mol. weight	325,43 g/mol



HAA6090 H-L-Cys(MBzl)-OH

S-(4-Methylbenzyl)-L-cysteine

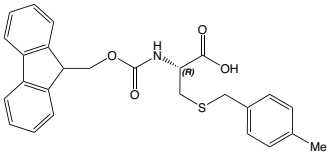
CAS-No.	42294-52-0
Formula	$C_{11}H_{15}NO_2S$
Mol. weight	225,3 g/mol



FAA1714 Fmoc-L-Cys(MBzl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methyl-benzyl)-L-cysteine

CAS-No.	136050-67-4
Formula	$C_{26}H_{25}NO_4S$
Mol. weight	447,53 g/mol



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2.1.8. 4,4'-Dimethoxydiphenylmethyl (Ddm)

This protecting group can be removed using 10% TFA (TFA:DCM:TIS:H_2O 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.

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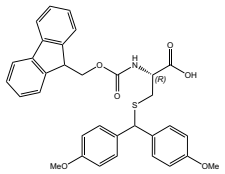
Product details

FAA6940 Fmoc-L-Cys(Ddm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-di(4-methoxyphenyl)methyl-L-cysteine

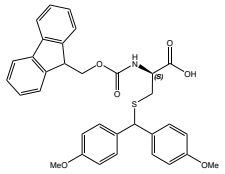
CAS-No.	1403825-56-8
Formula	$C_{33}H_{31}NO_6S$
Mol. weight	569,67 g/mol



FAA6950 Fmoc-D-Cys(Ddm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-di(4-methoxyphenyl)methyl-D-cysteine

Formula	$C_{33}H_{31}NO_6S$
Mol. weight	569,67 g/mol



Reference:

→ *Evaluation of acid-labile S-protecting groups to prevent Cys 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*

2.1.9. 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 more stable than the corresponding oxazolidines of Ser and Thr.

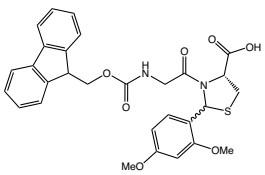
The proline-resembling thiazolidine ring of Cys-pseudoprolines simultaneously protects the side chains and amino group of Cys. Typically, pseudoprolines are incorporated into peptides using dipeptide building blocks. In the case of ψMe,MePro, the protected Cys can be deprotected by TFA within hours. This can be reduced to minutes when using ψH,DmpPro. Complete Cys(ψMe,MePro) 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 pseudoprolines 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

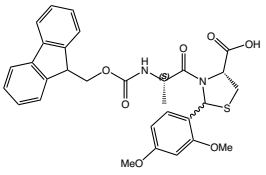
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-glycyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid

CAS-No.	1926163-05-4
Formula	$C_{29}H_{28}N_2O_7S$
Mol. weight	548,61 g/mol



PSI1450 Fmoc-L-Ala-L-Cys[PSI(Dmp,H)pro]-OH

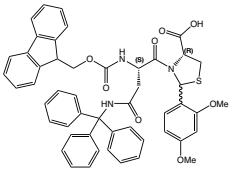
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-alanyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



CAS-No.	2022956-37-0
Formula	$C_{30}H_{30}N_2O_7S$
Mol. weight	562,63 g/mol

PSI1460 Fmoc-L-Asn(Trt)-L-Cys[PSI(Dmp,H)pro]-OH

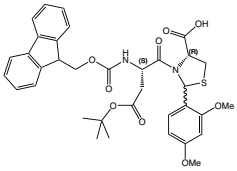
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-beta-trityl-L-asparaginyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{50}H_{45}N_3O_8S$
Mol. weight	847,97 g/mol

PSI1470 Fmoc-L-Asp(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH

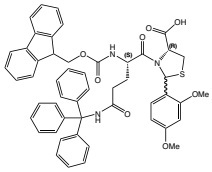
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-beta-*t*-butyl-L-aspartyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



CAS-No.	1359754-16-7
Formula	$C_{35}H_{39}N_2O_9S$
Mol. weight	662,75 g/mol

PSI1480 Fmoc-L-Gln(Trt)-L-Cys[PSI(Dmp,H)pro]-OH

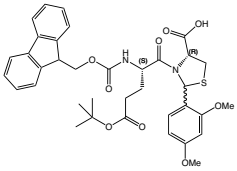
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-gamma-trityl-L-glutaminyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{51}H_{47}N_3O_8S$
Mol. weight	862,00 g/mol

PSI1490 Fmoc-L-Glu(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH

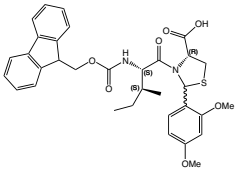
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-gamma-*t*-butyl-L-glutamyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{36}H_{40}N_2O_9S$
Mol. weight	676,78 g/mol

PSI1500 Fmoc-L-Ile-L-Cys[PSI(Dmp,H)pro]-OH

(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-isoleucyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{33}H_{36}N_2O_7S$
Mol. weight	604,71 g/mol

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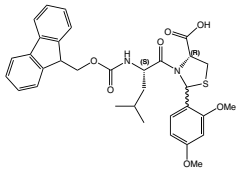
Product details

PSI1510 Fmoc-L-Leu-L-Cys[PSI(Dmp,H)pro]-OH

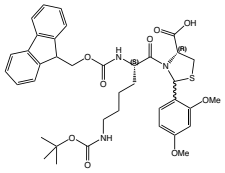
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-leucyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



CAS-No.	1926163-06-5
Formula	$C_{33}H_{36}N_2O_7S$
Mol. weight	604,71 g/mol

PSI1520 Fmoc-L-Lys(Boc)-L-Cys[PSI(Dmp,H)pro]-OH

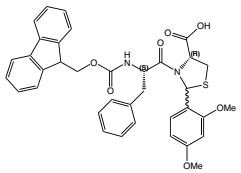
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-*t*-butyloxycarbonyl-L-lysyl)-2-(2,4-dimethoxphenyl) thiazolidine-4-carboxylic acid



CAS-No.	1926163-07-6
Formula	$C_{38}H_{45}N_3O_9S$
Mol. weight	719,84 g/mol

PSI1530 Fmoc-L-Phe-L-Cys[PSI(Dmp,H)pro]-OH

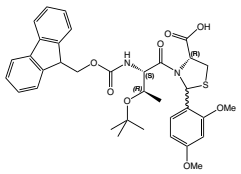
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-phenylalanyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{36}H_{34}N_2O_7S$
Mol. weight	638,73 g/mol

PSI1550 Fmoc-L-Thr(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH

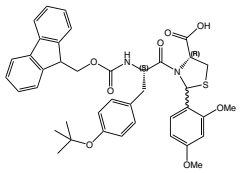
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-O-*t*-butyl-L-threonyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{35}H_{40}N_2O_8S$
Mol. weight	648,77 g/mol

PSI1560 Fmoc-L-Tyr(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH

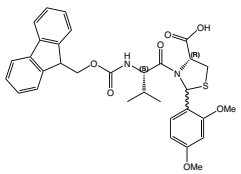
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-O-*t*-butyl-L-thyrosyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



Formula	$C_{40}H_{42}N_2O_8S$
Mol. weight	710,84 g/mol

PSI1570 Fmoc-L-Val-L-Cys[PSI(Dmp,H)pro]-OH

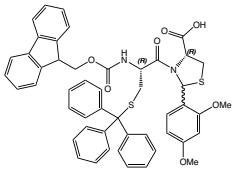
(S)-3-(N-(9-Fluorenylmethyloxycarbonyl)-L-valyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



CAS-No.	1926163-08-7
Formula	$C_{32}H_{34}N_2O_7S$
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-cysteinyl)-2-(2,4-dimethoxphenyl)thiazolidine-4-carboxylic acid



CAS-No.	2022956-75-6
Formula	$C_{49}H_{44}N_2O_7S_2$
Mol. weight	837,01 g/mol

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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 Cys protecting groups, e.g. Trt, *t*Bu, 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, I_2, 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 Tyr and Trp) with Fmoc-Cys(Acm)-OH as building block clearly shows the three expected impurities in significant concentrations in the case of using Acm.

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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 Cys protecting group.

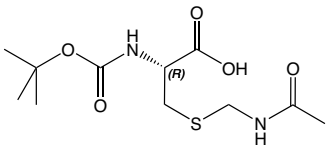
Alternatives to the Acm protecting group are represented by Phacm and Allocam.

Product details

BAA1078 Boc-L-Cys(Acm)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(acetyl-amino-methyl)-L-cysteine

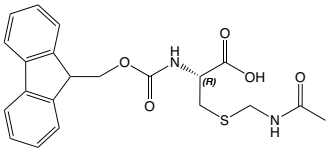
CAS-No.	19746-37-3
Formula	$C_{11}H_{20}N_2O_5S$
Mol. weight	292,36 g/mol



FAA1506 Fmoc-L-Cys(Acm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-cysteine

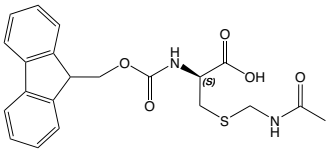
CAS-No.	86060-81-3
Formula	$C_{21}H_{22}N_2O_5S$
Mol. weight	414,48 g/mol



FAA6230 Fmoc-D-Cys(Acm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-cysteine

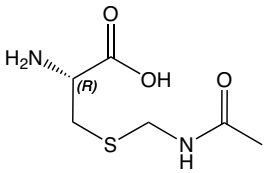
CAS-No.	168300-88-7
Formula	$C_{21}H_{22}N_2O_5S$
Mol. weight	414,48 g/mol



HAA6070 H-L-Cys(Acm)-OH*HCl

S-(Acetyl-aminomethyl)-L-cysteine hydrochloride

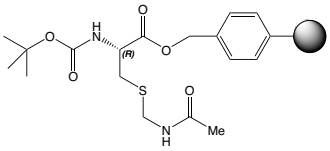
CAS-No.	28798-28-9
Formula	$C_6H_{12}N_2O_3S*HCl$
Mol. weight	192,24*36,45 g/mol



MAA5222 Boc-L-Cys(Acm)-Merrifield Resin

N-alpha-*t*-Butyloxycarbonyl-S-(acetyl-amino-methyl)-L-cysteinyl-Merrifield Resin

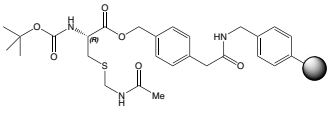
Mesh Size	100-200 mesh
Loading	> 0.5 mmol/g
DVB	1% DVB



PAM5622 Boc-L-Cys(Acm)-PAM Resin

N-alpha-*t*-Butyloxycarbonyl-S-(acetyl-amino-methyl)-L-cysteinyl-PAM Resin

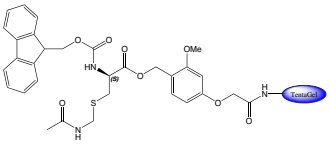
Mesh Size	100-200 mesh
DVB	1% DVB



SAD1107 Fmoc-D-Cys(Acm)-AC TG

Fmoc-D-Cys(S-Acm)-[3-methoxy-4-hydroxymethyl) phenoxyacetylamid] TentaGel S

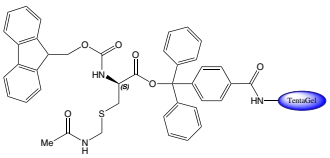
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAD1207 Fmoc-D-Cys(Acm)-Trt TG

Fmoc-D-Cys(S-Acm)-Trityl TentaGel S

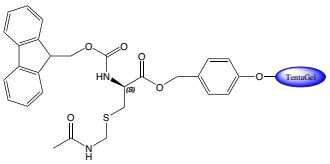
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAD1307 Fmoc-D-Cys(Acm)-Wang TG

Fmoc-D-Cys(S-Acm)-Wang TentaGel S

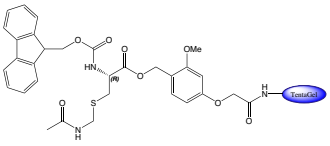
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAL1107 Fmoc-L-Cys(Acm)-AC TG

Fmoc-L-Cys(S-Acm)-[3-methoxy-4-hydroxymethyl) phenoxyacetylamid] TentaGel S

Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



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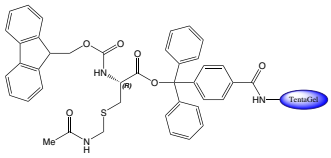
Product details

SAL1207 Fmoc-L-Cys(Acm)-Trt TG

Fmoc-L-Cys(S-Acm)-Trityl TentaGel S

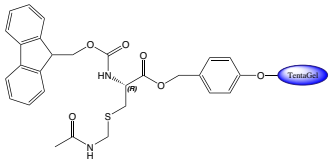
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAL1307 Fmoc-L-Cys(Acm)-Wang TG

Fmoc-L-Cys(S-Acm)-Wang TentaGel S

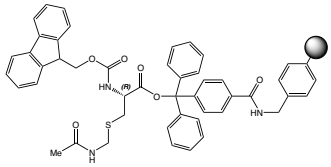
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



TCP1110 Fmoc-L-Cys(Acm)-TCP-Resin

Fmoc-Cys(Acm)-trityl-carboxyamidomethyl polystyrene

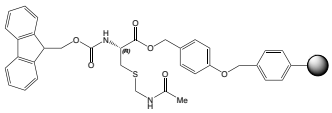
Mesh Size	200-400 mesh
Loading	0.3-0.8 mmol/g
DVB	1% DVB



WAA11307 Fmoc-L-Cys(Acm)-Wang Resin

Fmoc-L-Cys(S-Acm)-Wang Resin

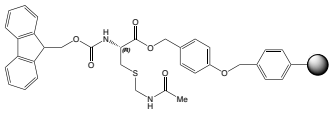
Mesh Size	100-200 mesh
DVB	1% DVB



WAA41307 Fmoc-L-Cys(Acm)-Wang Resin

Fmoc-L-Cys(S-Acm)-Wang Resin

Mesh Size	200-400 mesh
DVB	1% DVB



References:

- → *Palladium-Mediated Direct Disulfide Bond Formation in Proteins Containing S-Acetamidomethyl-cysteine under Aqueous Conditions; S. Laps, H. Sun, G. Kamnesky, A. Brik;* ***Angew. Chem. Int. Ed.*** *2019;* ***58(17)****: 5729-5733. https://doi.org/10.1002/anie.201900988*
- → *Studies on deprotection of cysteine and selenocysteine side-chain protecting groups; K. M. Harris, S. Flemer Jr, R. J. Hondal;* ***J. Pept. Sci.*** *2007;* ***13(2)****: 81-93. https://doi.org/10.1002/psc.795*
- → *p-Nitrobenzyl protection for cysteine and selenocysteine: A more stable alternative to the acetamidomethyl group; M. Muttenthaler, Y. Garcia Ramos, D. Feytens, A. D. de Araujo, P. F. Alewood;* ***Pept. Sci.*** *2010;* ***94(4)****: 423-432. https://doi.org/10.1002/bip.21502*

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.

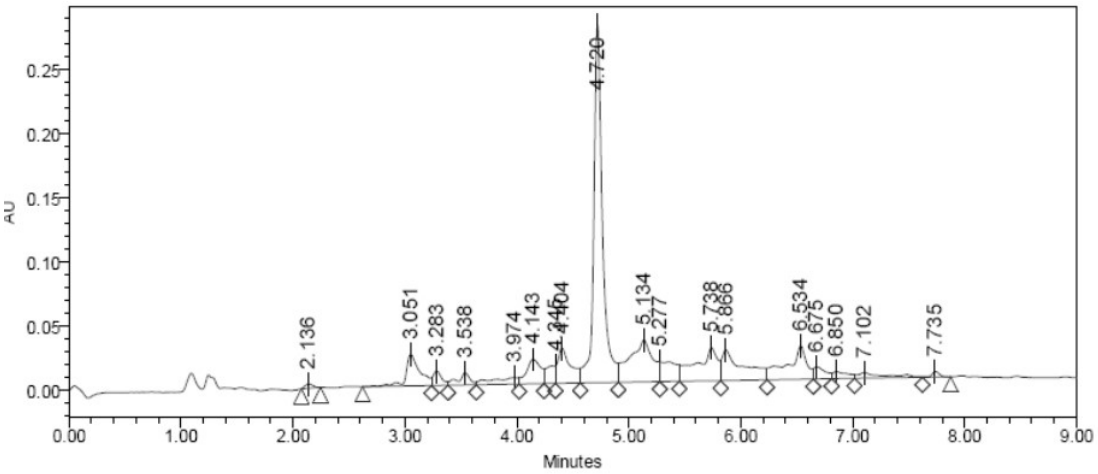
2.4. Enzyme-Labile Protecting Groups

2.4.1. Phenylacetamidomethyl (Phacm)

Phacm shows the same stability and orthogonality as Acm and has the additional advantage that it can be deprotected either chemically by I_2/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 I_2. 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 specifity of PGA towards the phenylacetyl moiety makes the use of Phacm very promising as alternative for Acm. 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(Acm)



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, I_2, Tl^{3+}, Ph_2SO, $MeSiCl_3$

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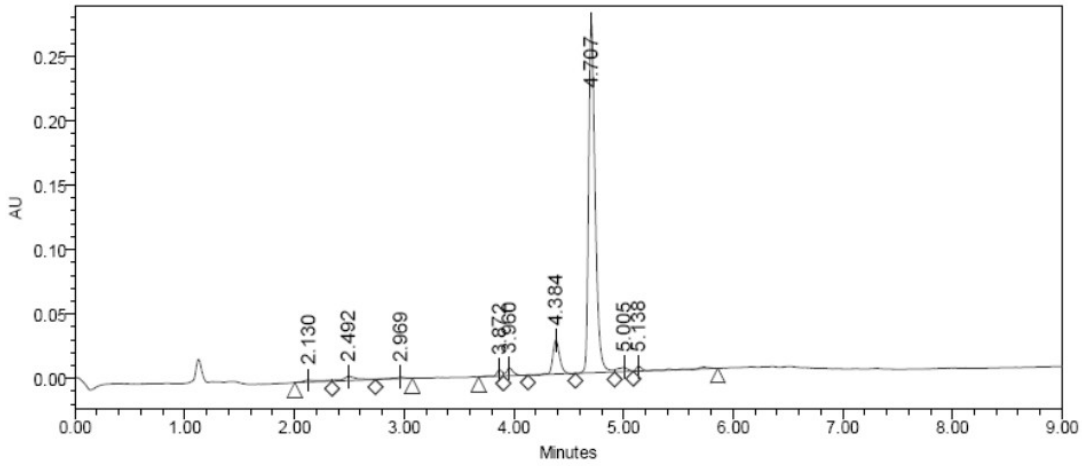
Peptide Synthesis with Fmoc-Cys(Phacm)



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 cyclothiodepsipeptide thiocoraline 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.

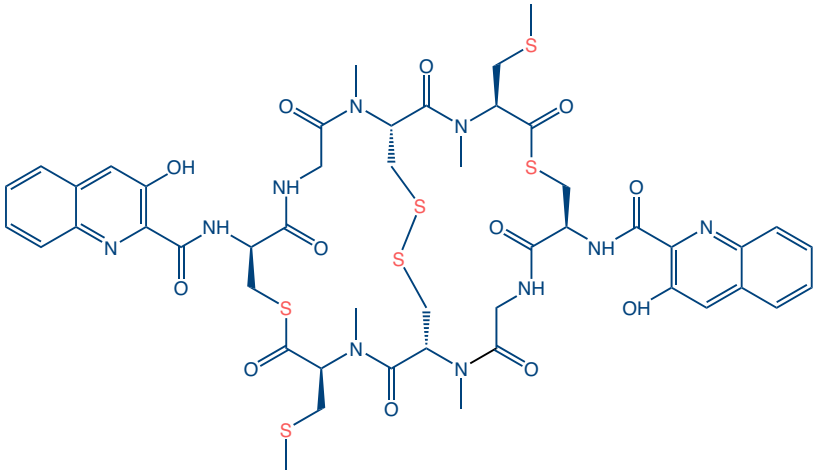
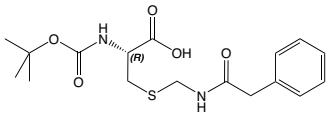


Fig. 5: Chemical structure of the cyclothiodepsipeptide thiocoraline.

BAA6390 Boc-L-Cys(Phacm)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(Phenylacetylamino-methyl)-L-cysteine

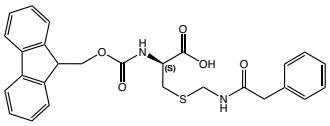
CAS-No.	57084-73-8
Formula	$C_{17}H_{24}N_2O_5S$
Mol. weight	368,45 g/mol



FAA3710 Fmoc-D-Cys(Phacm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(phenylac-etylaminomethyl)-D-cysteine

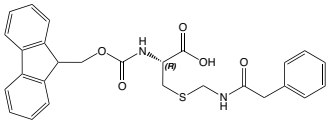
CAS-No.	1565818-55-4
Formula	$C_{27}H_{26}N_2O_5S$
Mol. weight	490,57 g/mol



FAA6910 Fmoc-L-Cys(Phacm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-Phenylace-tylaminomethyl)-L-cysteine

CAS-No.	159680-21-4
Formula	$C_{27}H_{26}N_2O_5S$
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. Slomcyznska, 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 $PdCl_2(PPh_3)_2$ 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 β → α shifts, and intramolecular acylation reactions may also occur. These issues hinder its suitability as a Cys protecting group. As such, other allyl-based Pd-labile protecting groups, such as Allocam, are recommended instead.

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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*

2.5.2. Allyloxycarbonylaminomethyl (Allocam)

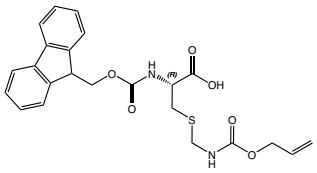
The Allocam-protecting group, which is a variant of the Acm protecting group, allows for a palladium-mediated single-step approach using mild reaction conditions and readily available reagents. The Allocam group can be removed using Bu_3SnH and a Pd(0) catalyst in AcOH (10 min, RT). Cys(Allocam) displays 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-((allyloxy-carbonylamino)methy)-L-cysteine

CAS-No.	232953-09-2
Formula	$C_{23}H_{24}N_2O_6S$
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 allyloxycarbonylaminomethyl 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*

→ *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*

→ *The allyloxycarbonylaminomethyl 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*

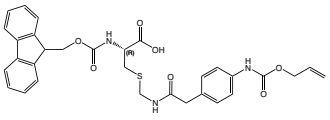
2.5.3. (Allyloxycarbonylamino)phenylacetylaminomethyl (Aapam)

Cys(Aapam) represents an Alloc protected Phacm linker as removable side chain modification for the incorporation of e.g. solubilizing tags facilitating the preparation of hydrophobic peptides and proteins. The Alloc-Phacm Cys can easily be introduced in peptides during Fmoc-solid phase peptide synthesis. The Alloc group can then be removed by using tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] 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 solubilizing 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 solubilizing tag can easily be removed in solution by treatment with $PdCl_2$ 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 solubilizing tags 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	$C_{31}H_{31}N_3O_7S$
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. Seenaiah, 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 Cys 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 Cys 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.

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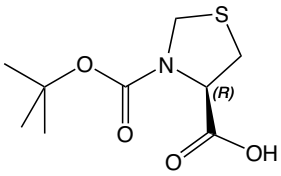
Cyclic Peptides

Product details

BAA1135 Boc-L-Thz-OH

(R)-N-*t*-Butyloxycarbonyl-thiazolidine-4-carboxylic acid

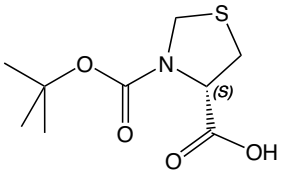
CAS-No.	51077-16-8
Formula	$C_9H_{15}NO_4S$
Mol. weight	233,29 g/mol



BAA1186 Boc-D-Thz-OH

(S)-N-(*t*-Butyloxycarbonyl)-thiazolidine-4-carboxylic acid

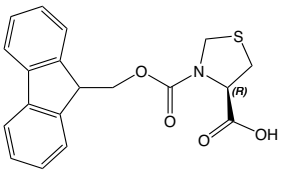
CAS-No.	63091-82-7
Formula	$C_9H_{15}NO_4S$
Mol. weight	233,29 g/mol



FAA1427 Fmoc-L-Thz-OH

(R)-N-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-L-4-carboxylic acid

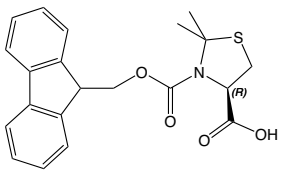
CAS-No.	133054-21-4
Formula	$C_{19}H_{17}NO_4S$
Mol. weight	355,42 g/mol



FAA1437 Fmoc-L-Thz(Me2)-OH

(R)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid

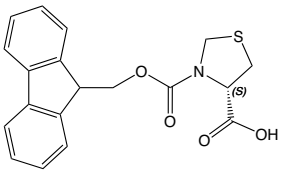
CAS-No.	873842-06-9
Formula	$C_{21}H_{21}NO_4S$
Mol. weight	383,46 g/mol



FAA1495 Fmoc-D-Thz-OH

(S)-N-alpha-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid

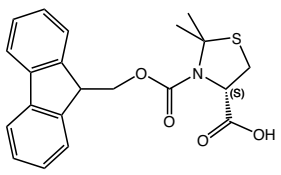
CAS-No.	198545-89-0
Formula	$C_{19}H_{17}NO_4S$
Mol. weight	355,42 g/mol



FAA3160 Fmoc-D-Thz(Me2)-OH

(S)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid

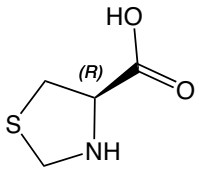
CAS-No.	1932198-36-1
Formula	$C_{21}H_{21}NO_4S$
Mol. weight	383,46 g/mol



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



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→ *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. Jbara, 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 (*o*Nv)

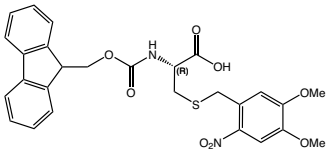
2-Nitroveratryl (*o*Nv) is a photolabile orthogonal protecting group that is compatible with SPPS protocols and can be cleaved by irradiation with UV light (350 nm, 30 min, aq. media) under ambient conditions. No significant racemization is observed upon incorporation of Cys(*o*Nv) during SPPS using diisopropyl-carbodiimide (DIC) and HOBt activation. Combination with S-pyridinesulfenyl 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, alpha-conotoxin ImI, and human insulin.

Product details

FAA3970 Fmoc-L-Cys(*o*Nv)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-cysteine

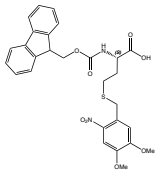
CAS-No.	214633-71-3
Formula	$C_{27}H_{26}N_2O_8S$
Mol. weight	538,57 g/mol



FAA8870 Fmoc-L-hCys(*o*Nv)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-homocysteine

Formula	$C_{28}H_{28}N_2O_8S$
Mol. weight	552,60 g/mol



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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*

2.7.2. Nitrodibenzofuran (NDBF)

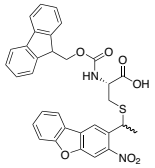
Nitrodibenzofuran (NDBF) is a photocleavable side chain protecting group that can be removed by photolysis upon irradiation with UV-light (365 nm) or – especially for *in vivo* applications – by two-photon excitation using near infrared light (800 nm). Additionally, NDBF deprotection results in clean 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 nitroveratryl derivatives. 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-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



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*

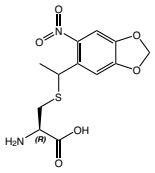
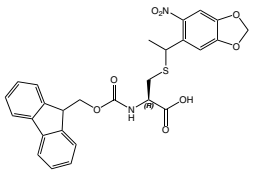
→ *Nitrodibenzofuran: A One- and Two-Photon Sensitive Protecting Group That Is Superior to Brominated Hydroxycoumarin for Thiol Caging in Peptides; M. M. Mahmoodi, D. Abate-Pella, T. J. Pundsack, C. C. Palsuledesai, P. C. Goff, D. A. Blank, M. D. Distefano;* ***J. Am. Chem. Soc.*** *2016;* ***138****: 5848-5859. https://doi.org/10.1021/jacs.5b11759*

→ *The nitrodibenzofuran chromophore: a new caging group for ulta-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 $C_{12}H_{14}N_2O_6S$ 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 $C_{27}H_{24}N_2O_8S$ Mol. weight 536,56 g/mol		

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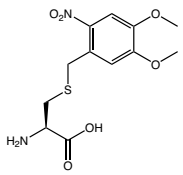
- *Genetic Encoding of Photocaged Cysteine Allows Photoactivation of TEV Protease in Live Mammalian Cells; D. P. Nguyen, M. Mahesh, S. J. Elsässer, S. M. Hancock, C. Uttamapinant, J. W. Chin;* ***J. Am. Chem. Soc.*** *2014;* ***136(6)****: 2240-2243. https://doi.org/10.1021/ja412191m*
- *Spatio-Temporal 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*

2.7.4. Dimethoxynitrobenzyl (DMNB)

This building block permits the incorporation of a photocaged cysteine in a protein. The caging group can be removed by irradiation with UV light leaving the unprotected Cysteine in place.

		Product details
HAA9320 H-L-Cys(DMNB)-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		

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- → *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*
- → *Light Activation of Protein Splicing with a Photocaged Fast Intein; W. Ren, A. Ji. H.-W. Ai;* ***J. Am. Chem. Soc.*** *2015;* ***137(6)****: 2155-2158. https://doi.org/10.1021/ja508597d*
- → *Light-Activation of DNA-Methyltransferases; J. Wolffgramm, B. Buchmuller, S. Palei, A. Muñoz-López, J. Kanne, P. Janning, M. R. Schweiger, D. Summerer;* ***Angew. Chem. Int. Ed.*** *2021;* ***60(24)****: 13507-13512. https://doi.org/10.1002/anie.202103945*
- → *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*

2.8. Reduction-Labile Protecting Groups

2.8.1. *tert*-Butylthio (S*t*Bu)

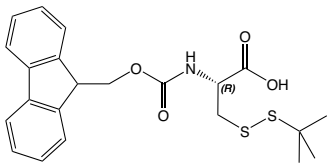
S*t*Bu can be removed under organic or aqueous conditions with reducing agents such as thiols, e.g. 2-mercaptoethanol or DTT, or phosphines (e.g. PBu_3, PPh_3, TCEP). The S*t*Bu protecting group is stable to acidic conditions (e.g. TFA:thioanisole:phenol, 92:2.5:2.5 v/v) provided no thiol scavenger is added. If required, 2-methylindole and anisole can be used as alternative scavengers. The S*t*Bu protecting group is orthogonal to other protecting groups, such as Trt, Acm, Meb/Mob, *t*Bu, and Allocam. S*t*Bu is compatible both with Fmoc and Boc SPPS.

	Product details

FAA1575 Fmoc-L-Cys(S*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butylthio)-L-cysteine

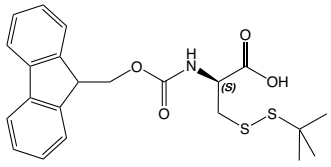
CAS-No.	73724-43-3
Formula	$C_{22}H_{25}NO_4S_2$
Mol. weight	431,57 g/mol



FAA1965 Fmoc-D-Cys(S*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butylthio)-D-cysteine

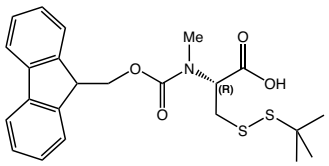
CAS-No.	501326-55-2
Formula	$C_{22}H_{25}NO_4S_2$
Mol. weight	431,57 g/mol



FAA3340 Fmoc-L-MeCys(S-*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-(*t*-butylthio)-L-cysteine

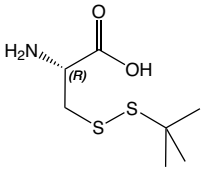
CAS-No.	1013096-03-1
Formula	$C_{23}H_{27}NO_4S_2$
Mol. weight	445,59 g/mol



HAA6140 H-L-Cys(S*t*Bu)-OH

S-Thio-*t*-butyl-L-cysteine

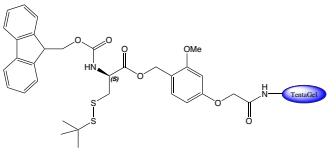
CAS-No.	30044-51-0
Formula	$C_7H_{15}NO_2S_2$
Mol. weight	209,32 g/mol



SAD1109 Fmoc-D-Cys(SS-*t*Bu)-AC TG

Fmoc-D-Cys(S-S-*t*Bu)-[3-methoxy-4-hydroxymethyl) phenoxyacetylamid] TentaGel S

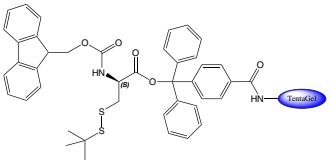
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAD1209 Fmoc-D-Cys(SS-*t*Bu)-Trt TG

Fmoc-D-Cys(S-S-*t*Bu)-Trityl TentaGel S

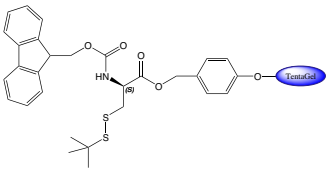
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAD1309 Fmoc-D-Cys(SS-*t*Bu)-Wang TG

Fmoc-D-Cys(S-S-*t*Bu)-Wang TentaGel S

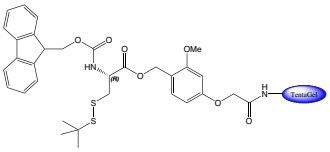
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



SAL1109 Fmoc-L-Cys(SS-*t*Bu)-AC TG

Fmoc-L-Cys(S-S-*t*Bu)-[3-methoxy-4-hydroxymethyl) phenoxyacetylamid] TentaGel S

Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



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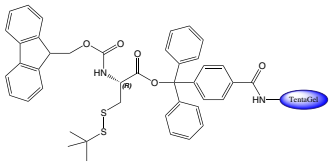
Cyclic Peptides

Product details

SAL1209 Fmoc-L-Cys(SS-*t*Bu)-Trt TG

Fmoc-L-Cys(S-S-*t*Bu)-Trityl TentaGel S

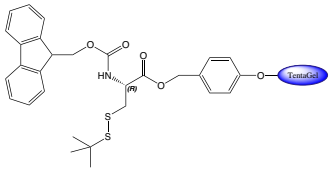
Mesh Size	90 µm
Loading	0.18-0.25 mmol/g



SAL1309 Fmoc-L-Cys(SS-*t*Bu)-Wang TG

Fmoc-L-Cys(S-S-*t*Bu)-Wang TentaGel S

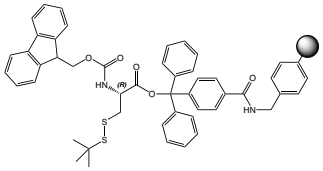
Mesh Size	90 µm
Loading	0.2-0.25 mmol/g



TCP1230 Fmoc-L-Cys(S*t*Bu)-TCP-Resin

Fmoc-Cys(S*t*Bu)-trityl-carboxyamidomethyl polystyrene

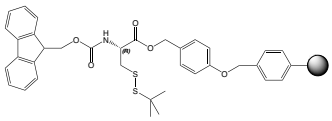
Mesh Size	200-400 mesh
Loading	0.3-0.8 mmol/g
DVB	1% DVB



WAA11309 Fmoc-L-Cys(SS-*t*Bu)-Wang Resin

Fmoc-L-Cys(S-S-*t*Bu)-Wang Resin

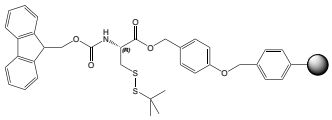
Mesh Size	100-200 mesh
DVB	1% DVB



WAA41309 Fmoc-L-Cys(SS-*t*Bu)-Wang Resin

Fmoc-L-Cys(S-S-*t*Bu)-Wang Resin

Mesh Size	200-400 mesh
DVB	1% DVB



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→ *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)

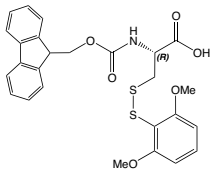
Both groups can be removed using NMM (0.1 M) with either 20% 2-mercaptoethanol in DMF or 5% DTT in DMF in 5 min. Due to the fast deprotection with nucleophiles, S-Dmp can even be used in automated synthesizers. In contrast, removal of the S*t*Bu protecting group using the aforementioned conditions required 3 h of incubation with BME, whereas little to no deprotection of S*t*Bu 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	$C_{26}H_{25}NO_6S_2$
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. https://doi.org/10.1021/ol3025499*

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) 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 S*t*Bu.

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

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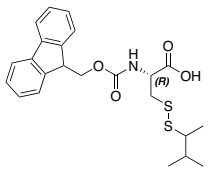
Product details

FAA8495 Fmoc-L-Cys(SIT)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-cysteine

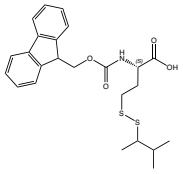
CAS-No.	2545642-31-5
Formula	$C_{23}H_{27}NO_4S_2$
Mol. weight	445,59 g/mol



FAA8865 Fmoc-L-hCys(SIT)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-homocysteine

Formula	$C_{24}H_{29}NO_4S_2$
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-pyridinesulfenyl (Npys)

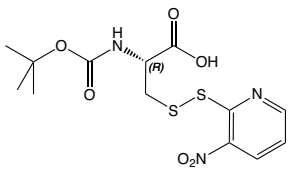
Npys can be removed within 10 min using aliphatic thiols (e.g. 3-mercaptoacetic acid). Besides, deprotection can be triggered at room temperature by tertiary phosphines in the presence of H_2O. Cys(Npys) is stable to strong acids such as TFA (24 h, RT), HF (1 h, RT) and 4 M HCl/dioxane, and is thus suitable 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.

Product details

BAA1860 Boc-L-Cys(Npys)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(3-nitro-2-pyridylthio)-L-cysteine

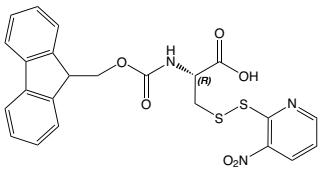
CAS-No.	76880-29-0
Formula	$C_{13}H_{17}N_3O_6S_2$
Mol. weight	375,42 g/mol



FAA1975 Fmoc-L-Cys(Npys)-OH

N-alpha-(9-Fluorenylmethyloxycarbo-
nyl)-S-(3-nitro-2-pyridylthio)-L-cysteine

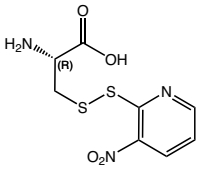
Formula	$C_{23}H_{19}N_3O_6S_2$
Mol. weight	497,54 g/mol



HAA3510 H-L-Cys(Npys)-OH*HCl

S-(3-nitro-2-pyridylthio)-L-cysteine hydrochloride

CAS-No.	108807-66-5
Formula	$C_8H_9N_3O_4S_2$*HCl
Mol. weight	275,30*36,45 g/mol



References:

- → *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. Ménez;* ***J. Immunol. Methods*** *1994;* ***171(1,2)****: 65-71. https://doi.org/10.1016/0022-1759(94)90229-1*
- → *Sulfur protection with the 3-nitro-2-pyridinesulfenyl group in solid-phase peptide synthesis; R. J. Ridge, G. R. Matsueda, E. Haber, R. Matsueda;* ***Int. J. Pept. Prot. Res.*** *1982;* ***19(5)****: 490-498. https://doi.org/10.1111/j.1399-3011.1982.tb02634.x*
- → *3-Nitro-2-pyridinesulfenyl 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 NH_4I/DMS/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.

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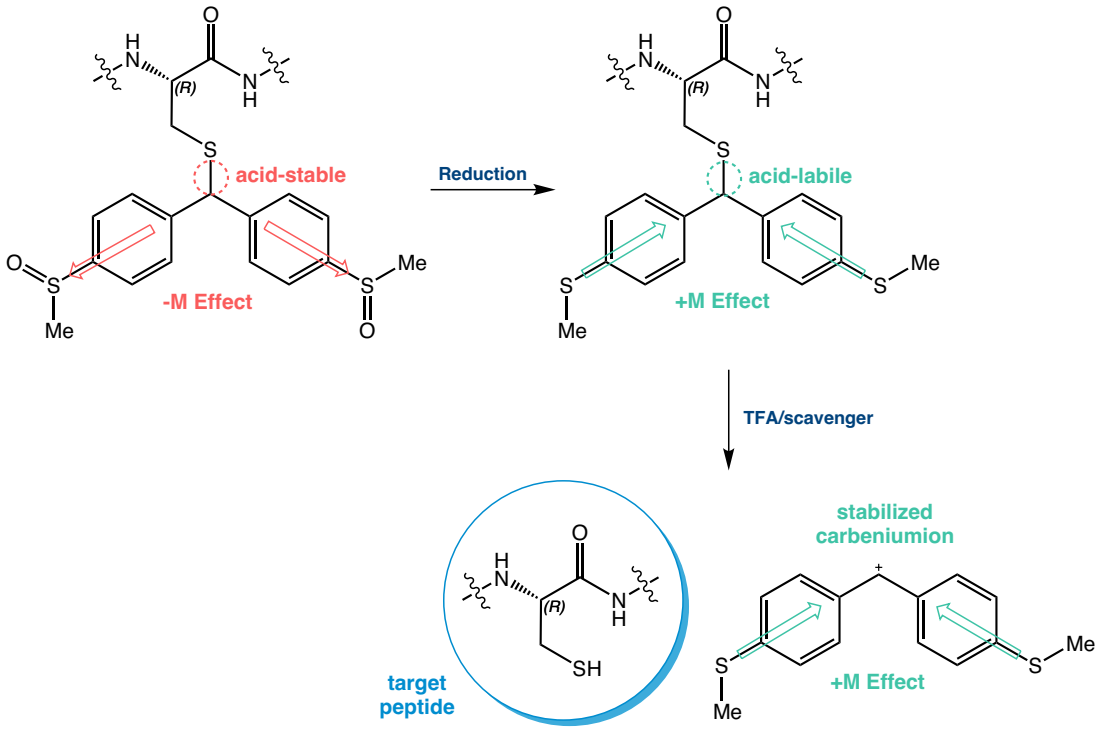


Fig. 6: Cleavage of the Msbh Cysteine protecting group.

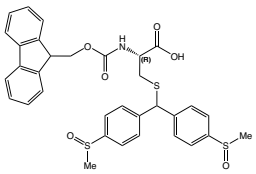
Another suitable application for Msbh-protected cysteine is whenever there is an odd number of cysteines present in a peptide, where all cysteines except one are disulfide-brigded. In such cases, Msbh can be utilized to protect the side chain of the one cysteine that is supposed to remain a free thiol 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

FAA4155 Fmoc-L-Cys(Msbh)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4,4'-di-methylsulfinylbenzhydryl)-L-cysteine

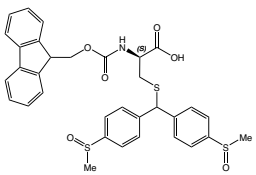
CAS-No.	1584646-97-8
Formula	$C_{33}H_{31}NO_6S_3$
Mol. weight	633,80 g/mol



FAA8150 Fmoc-D-Cys(Msbh)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4,4'-di-methylsulfinylbenzhydryl)-D-cysteine

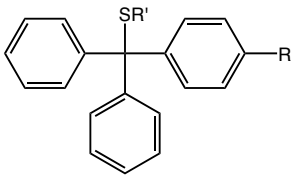
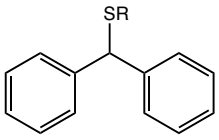
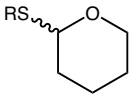
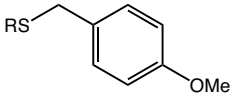
Formula	$C_{33}H_{31}NO_6S_3$
Mol. weight	633,80 g/mol



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*
- *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

Protecting Group	Deprotection	Oxidative Deprotetion	Structure
Mmt (R = OMe) **Trt (R = H)**	R = OMe: > 1% TFA R = H: > 25% TFA	I_2, Tl^{3+}	
Dpm	> 60% TFA	TFA:DMSO: anisole (89:10:1)	
Thp	> 10% TFA	—	
tBu	TFMSA, Hg^{2+}	I_2, Tl^{3+} $Ph_2SO/MeSiCl_3/TFA$	
Mob	TFA/TIS (12 h, 37 °C) $Hg(TFA)_2$ $Tl(TFA)_3$ AgOTf/TFA/thioanisole	—	

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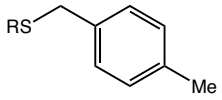
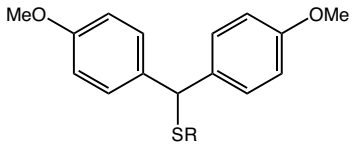
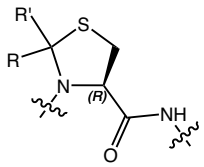
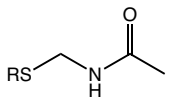
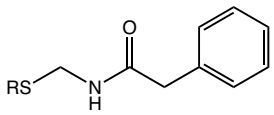
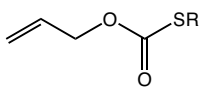
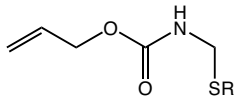
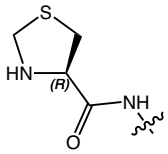
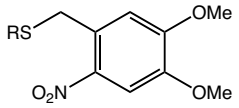
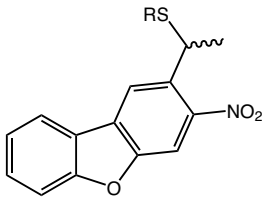
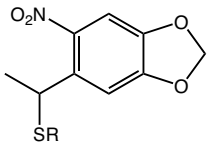
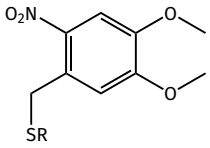
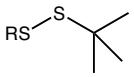
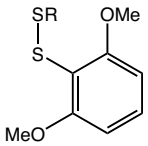
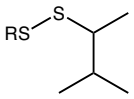
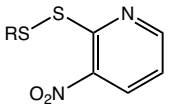
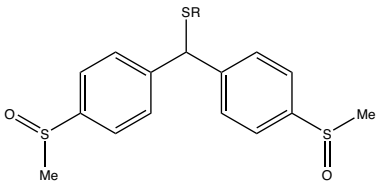
Cyclic Peptides

Protecting Group	Deprotection	Oxidative Deprotetion	Structure
Meb	DMSO/TFA (45 °C) HF/anisole (1 h, 0 °C) $Tl(TFA)_3$	—	
Ddm	TFA:DCM:TIS:H_2O (10:85:2.5:2.5, 1 h, 25 °C)	—	
ψPro	TFA (duration dependent on substitution and sequence)	—	
Acm	I_2/AcOH	I_2, Tl^{3+} $Ph_2SO/MeSiCl_3$	
Phacm	I_2/AcOH; PGA/water	(Immob.) PGA/water & DMSO; $Ph_2SO/MeSiCl_3$	
Alloc	Pd(0) cat./Bu_3SnH/AcOH Piperidine (3 h, 30 °C)	—	
Allocam	Pd(0) cat./Bu_3SnH/AcOH (10 min, RT)	—	
Thz	N-terminal Pd, Cu	H_2O_2, I_2	
***o*Nv**	Photolysis 350 nm	—	
NDBF	Photosysis 365 nm	—	

Protecting Group	Deprotection	Oxidative Deprotetion	Structure
MDNPE	Photolysis 365 nm	—	
DMNB	Photolysis 330-385 nm	—	
StBu	Thiols, Phosphines	—	
S-DMP	0,1% NMM in 5% DTT/ DMF (5 min)	—	
SIT	DTT (5 eq.) in DMF/ DIEA/H_2O (95:2.5:2.5) (3 x 10 min)	—	
Npys	Aliphatic thiols; Tertiary phosphine/ H_2O	—	
Msbh	NH_4I/TMS, TFA	—	

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.

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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 NH_4I/DMS.

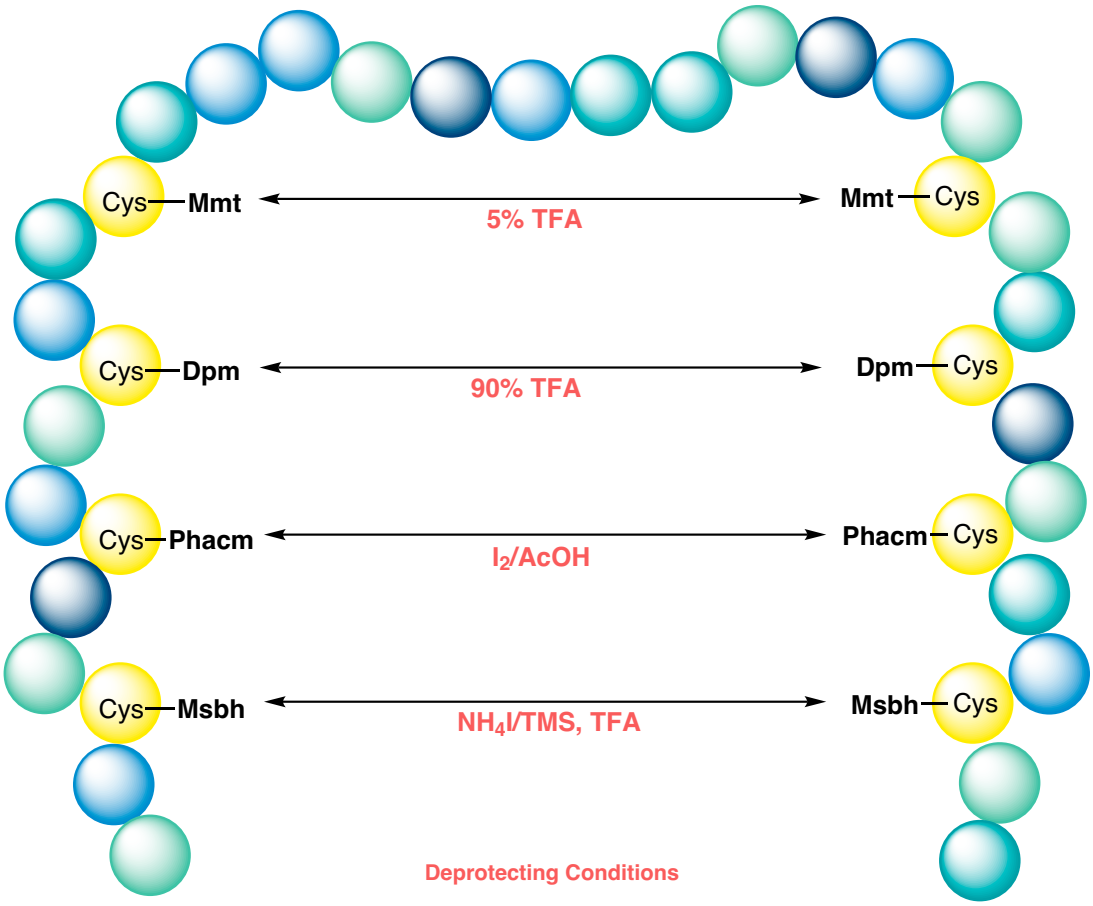

Fig. 7: Consecutive disulfide bond formation via use of orthogonal protecting groups.

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 Cys 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.

# of Disulfide Bridges	Cys 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; $Ph_2SO/MeSiCl_3$
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; $Ph_2SO/MeSiCl_3$
	Fmoc-Cys(Msbh)-OH	NH_4I/TMS, TFA	—
Uneven number of Cys (w/wo derivatization)	Fmoc-Cys(Trt)-OH	> 25% TFA	I_2, Tl^{3+}
	Fmoc-Cys(Msbh)-OH	NH_4I/TMS, TFA	—
	Or:	> 25% TFA	I_2, Tl^{3+}
	Fmoc-Cys(Trt)-OH	Immob. PGA/water	(Immob.) PGA/water & DMSO; $Ph_2SO/MeSiCl_3$
	Fmoc-Cys(Phacm)-OH		
	And several other combinations		

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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).

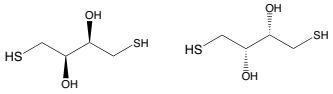
DTT is frequently used to reduce the disulfide bonds of proteins and in order to prevent intramolecular (cyclization) and intermolecular (oligomerisation, polymerization) disulfide bonds from cysteine residues of proteins. However, DTT cannot reduce solvent-inaccessible disulfide bonds, so reduction of disulfide bonds is sometimes carried out under denaturing conditions (e.g., at high temperatures, or in the presence of strong denaturating 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. Rüegg, 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*
- *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*

4. Chemoselective Ligation-Mediated Peptide Cyclization

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

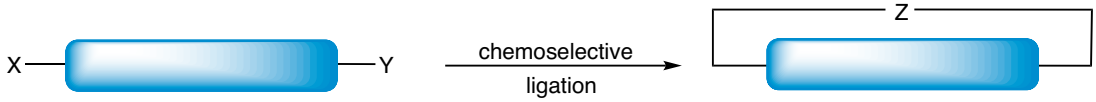


Fig. 8: Intramolecular cyclization.

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. Nonpeptide 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).

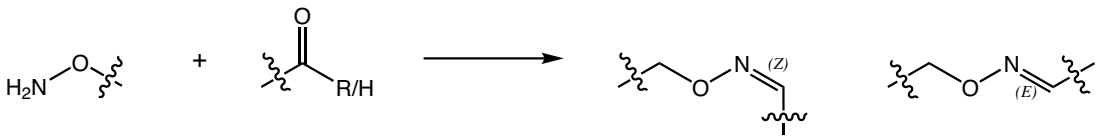


Fig. 9: Schematic illustration of oxime ligation.

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.

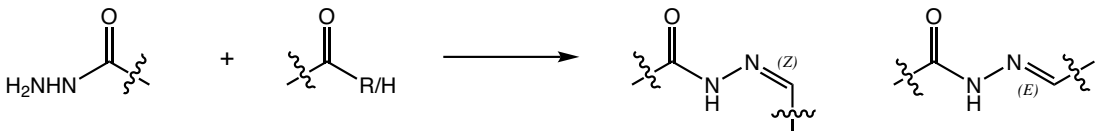


Fig. 10: Schematic illustration of hydrazone ligation.

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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 (aminooxy, 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 aminooxy-containing precursor cause these ligations to be a less attractive strategy when it comes to head-to-tail cyclic peptide synthesis.

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/H_2O/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.

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.

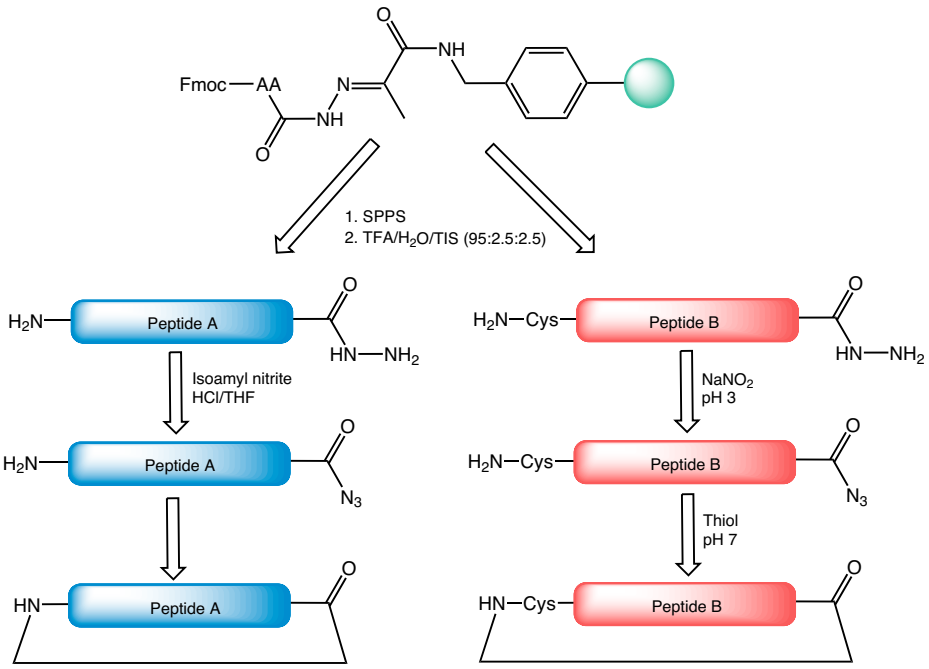


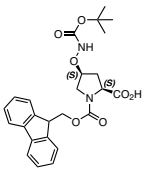
Fig. 11: Formation of cyclic peptides via transformation of peptide hydrazides to their azides.

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.

FAA8460 Fmoc-L-*cis*-Hyp(NHBoc)-OH

Fmoc-4-(Boc-amino)oxy)-proline (2S,4S)

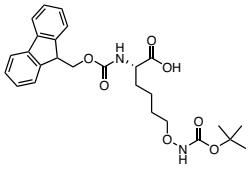
CAS-No.	1015426-31-9
Formula	$C_{25}H_{28}N_2O_7$
Mol. weight	468,50 g/mol



FAA8450 Fmoc-AAHA(Boc)-OH (S)

(S)-2-(Fmoc-amino)-6-(Boc-aminoxy)hexanoic acid

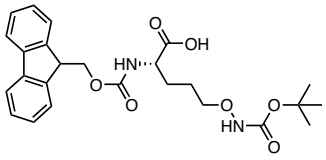
CAS-No.	357278-11-6
Formula	$C_{26}H_{32}N_2O_7$
Mol. weight	484,54 g/mol



FAA8445 Fmoc-Hcan(Boc)-OH (S)

(S)-2-(Fmoc-amino)-5-(Boc-aminoxy)pentanoic acid

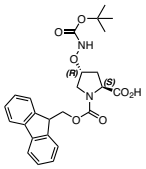
CAS-No.	204844-15-5
Formula	$C_{25}H_{30}N_2O_7$
Mol. weight	470,51 g/mol



FAA8455 Fmoc-L-*trans*-Hyp(NHBoc)-OH

Fmoc-4-(Boc-amino)oxy)-proline (2S,4R)

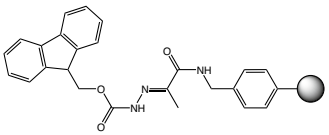
CAS-No.	1015426-45-5
Formula	$C_{25}H_{28}N_2O_7$
Mol. weight	468,50 g/mol



PYV1000 Fmoc-NHN=Pyv Resin

Fmoc-hydrazono-pyruvyl-aminomethylpolystyrene resin

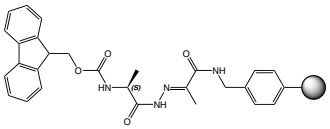
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



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



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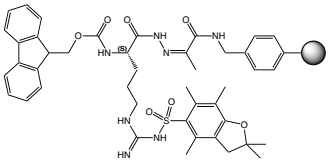
Product details

PYV1110 Fmoc-L-Arg(Pbf)-NHN=Pyv Resin

Fmoc-*N*'-2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl-L-arginyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

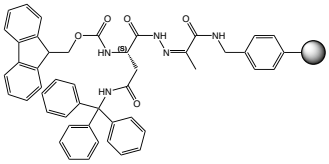
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1120 Fmoc-L-Asn(Trt)-NHN=Pyv Resin

Fmoc-N-beta-trityl-L-asparaginyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

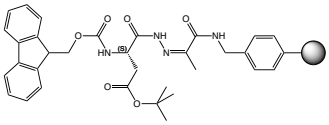
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1130 Fmoc-L-Asp(O*t*Bu)-NHN=Pyv Resin

Fmoc-L-aspartyl-beta-*t*-butyl ester-alpha-hydrazono-pyruvyl-aminomethylpolystyrene resin

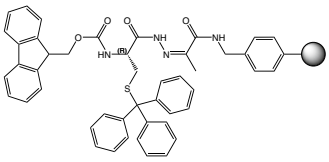
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1140 Fmoc-L-Cys(Trt)-NHN=Pyv Resin

Fmoc-S-trityl-L-cysteinyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

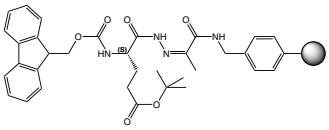
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1150 Fmoc-L-Glu(*t*Bu)-NHN=Pyv Resin

Fmoc-L-glutamyl-gamma-*t*-butyl ester-alpha-hydrazono-pyruvyl-aminomethylpolystyrene resin

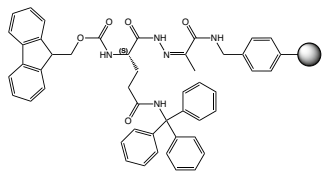
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1160 Fmoc-L-Gln(Trt)-NHN=Pyv Resin

Fmoc-N-gamma-trityl-L-glutaminyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

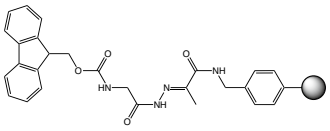
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1170 Fmoc-Gly-NHN=Pyv Resin

Fmoc-glycyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

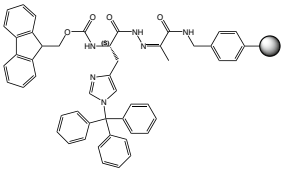
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1180 Fmoc-L-His(Trt)-NHN=Pyv Resin

Fmoc-N-trityl-L-histidyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

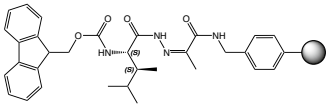
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1190 Fmoc-L-Ile-NHN=Pyv Resin

Fmoc-L-isoleucyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

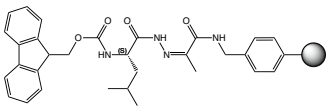
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1200 Fmoc-L-Leu-NHN=Pyv Resin

Fmoc-L-leucyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

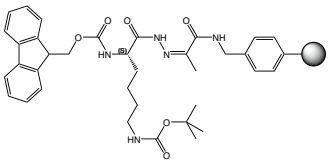
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1210 Fmoc-L-Lys(Boc)-NHN=Pyv Resin

Fmoc-N-epsilon-*t*-butyloxycarbonyl-L-lysyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

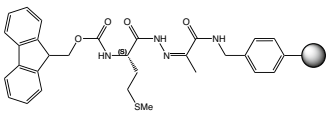
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



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



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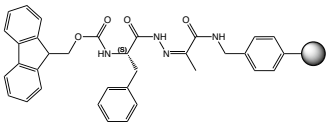
Product details

PYV1230 Fmoc-L-Phe-NHN=Pyv Resin

Fmoc-L-phenylalanyl-hydrazono-pyruvyl-aminomethyl-polystyrene resin

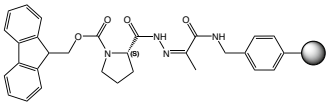
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1240 Fmoc-L-Pro-NHN=Pyv Resin

Fmoc-L-prolinyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

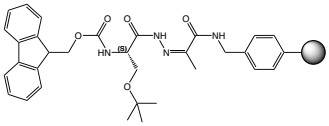
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1250 Fmoc-L-Ser(*t*Bu)-NHN=Pyv Resin

Fmoc-O-*t*-butyl-L-seryl-hydrazono-pyruvyl-amino-methylpolystyrene resin

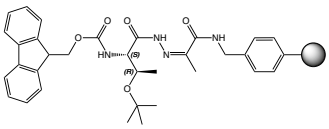
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1260 Fmoc-L-Thr(*t*Bu)-NHN=Pyv Resin

Fmoc-O-*t*-butyl-L-threonyl-hydrazono-pyruvyl-amino-methylpolystyrene resin

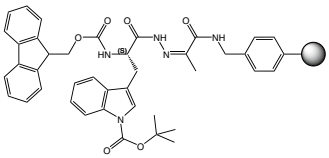
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1270 Fmoc-L-Trp(Boc)-NHN=Pyv Resin

Fmoc-N-*t*-butyloxycarbonyl-L-tryptophyl-hydrazono-pyruvyl-aminomethylpolystyrene resin

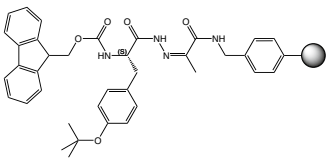
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



PYV1280 Fmoc-L-Tyr(*t*Bu)-NHN=Pyv Resin

Fmoc-O-*t*-butyl-L-tyrosyl-hydrazono-pyruvyl-amino-methylpolystyrene resin

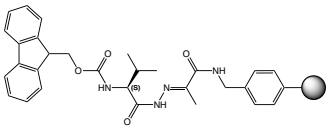
Mesh Size	100-200 mesh
Loading	> 0.3 mmol/g
DVB	1% DVB



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



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- *Facile and efficient chemical synthesis of APET×2, an ASIC-targeting toxin, via hydrazide-based native chemical ligation; S.-J. Li, D.-L. Qu, Y.-H. Wang, Y. He, M. Wen, Q.-X. Guo, J. Shi, Y.-M. Li;* ***Tetrahedron*** *2015;* ***71****: 3363-3366. https://doi.org/10.1016/j.tet.2015.03.098*
- *Chemical synthesis of proteins using peptide hydrazides as thioester surrogates; J.-S. Zheng, S. Tang, Y.-K. Qi, Z.-P. Wang, L. Liu;* ***Nature Protocols*** *2013;* ***8****: 2483. https://doi.org/10.1038/nprot.2013.152*
- *44. Amino-oxy-derivatives. Part I. Some a-amino-oxy-acids and a-amino-oxy-hydrazides. D. Mchale, J. Green, P. Mamalis;* ***J. Chem. Soc.*** *1960; 225-229. https://doi.org/10.1039/JR9600000225*
- *SAR by Oxime-Containing Peptide Libraries: Application to Tsg101 Ligand Optimization; F. Liu, A. G. Stephen, A. A. Waheed, M. J. Aman, E. O. Freed, R. J. Fisher, T. R. Burke;* ***ChemBioChem*** *2008;* ***9(12)****: 2000-2004. https://doi.org/10.1002/cbic.200800281*
- *A Versatile Set of Aminooxy Amino Acids for the Synthesis of Neoglycopeptides; M. R. Carrasco, R. T. Brown;* ***J. Org. Chem.*** *2003;* ***68****: 8853-8858. https://doi.org/10.1021/jo034984x*
- *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-substituted isomer, whereas ruthenium catalysis affords the 1,5-disubstituted regioisomer.

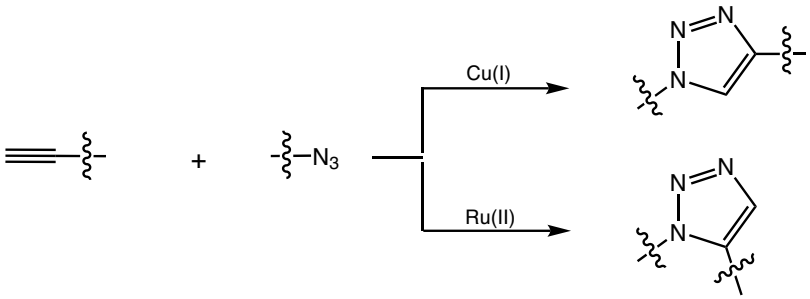

Fig. 12: Schematic illustration of the azide-alkyne-cycloaddition, either Cu(I)- or Ru(II)-catalyzed.

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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.

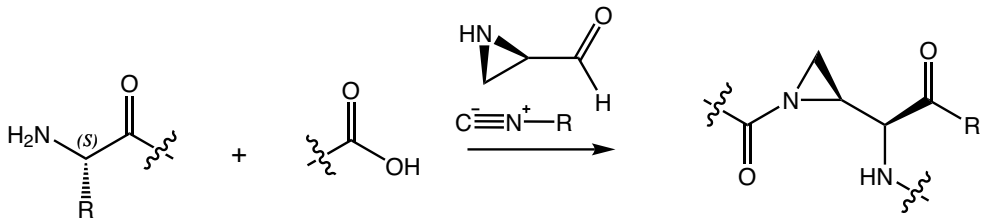

Fig. 13: Schematic illustration of the aziridine aldehyde-based multicomponent macrocyclization.

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 $NaBH_3CN$ 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.

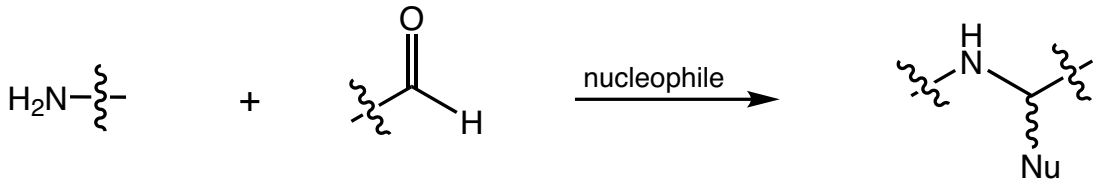

Fig. 14: Schematic illustration of the imine-mediated macrocyclization

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*

4.2. 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-Cys 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.

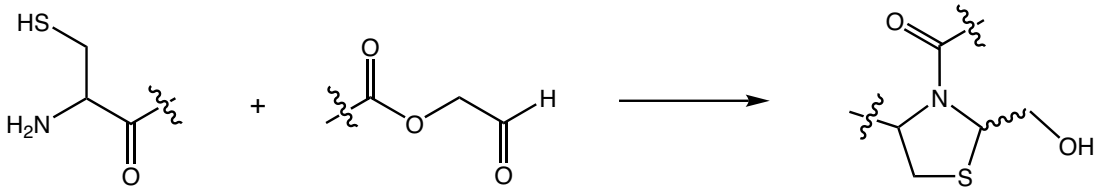

Fig. 15: Schematic illustration of the thiazolidine-generated cyclization.

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*

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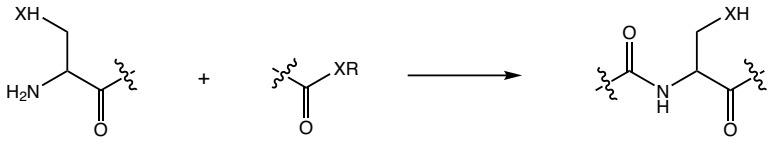
4.2.2. Native Chemical Ligation-Mediated Cyclization

Native chemical ligation (NCL) of unprotected peptide segments involves the reaction between a first peptide fragment alpha-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 Cys can be replaced by Selenocysteine.



X = S or Se

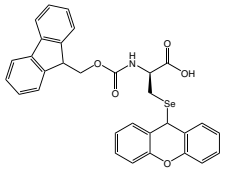
Fig. 16: Schematic illustration of native chemical ligation.

Product details

FAA8600 Fmoc-D-Sec(Xan)-OH

Fmoc-Se-xanthyl-D-selenocysteine

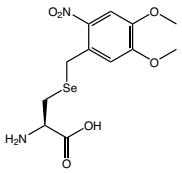
Formula	$C_{31}H_{25}NO_5Se$
Mol. weight	570,49 g/mol



HAA9255 H-L-Sec(DMNB)-OH*TFA

Dimethoxynitrobenzyl selenocysteine TFA salt

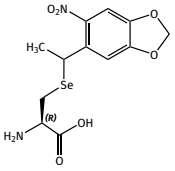
CAS-No.	1644398-13-9
Formula	$C_{12}H_{16}N_2O_6Se*CF_3COOH$
Mol. weight	363,24*114,02 g/mol



HAA9360 H-L-Sec(MDNPE)-OH

Se-(Methyl-*o*-nitropiperonyl)-selenocysteine

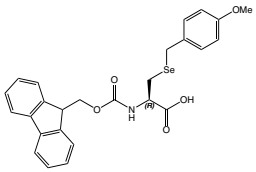
CAS-No.	2235373-47-2
Formula	$C_{12}H_{14}N_2O_6Se$
Mol. weight	361,21 g/mol



FAA8705 Fmoc-L-Sec(Mob)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-Se-(4-methoxybenzyl)-L-selenocysteine

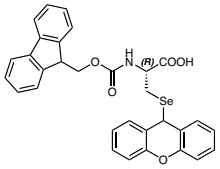
CAS-No.	150308-80-8
Formula	$C_{26}H_{25}NO_5Se$
Mol. weight	510,46 g/mol



FAA8465 Fmoc-L-Sec(Xan)-OH

Fmoc-Se-xanthyl-L-selenocysteine

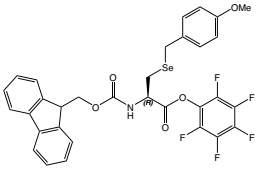
CAS-No.	1639843-35-8
Formula	$C_{31}H_{25}NO_5Se$
Mol. weight	570,49 g/mol



FAA8760 Fmoc-L-Sec(Mob)-OPfp

N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-4-methoxybenzyl selenocysteine pentafluorophenyl ester

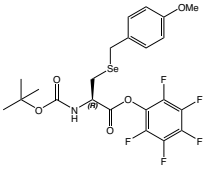
CAS-No.	939431-43-3
Formula	$C_{32}H_{24}F_5NO_5Se$
Mol. weight	676,51 g/mol



BAA4830 Boc-L-Sec(Mob)-OPfp

N-alpha-*tert*-Butoxycarbonyl-4-methoxybenzyl-L-selenocysteine pentafluorophenyl ester

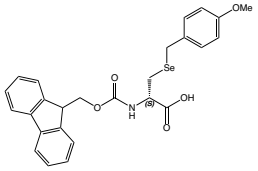
CAS-No.	1257525-48-6
Formula	$C_{22}H_{22}F_5NO_5Se$
Mol. weight	554,38 g/mol



FAA8710 Fmoc-D-Sec(Mob)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-Se-(4-methoxybenzyl)-D-selenocysteine

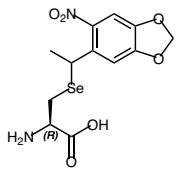
Formula	$C_{26}H_{25}NO_5Se$
Mol. weight	510,46 g/mol



HAA9230 H-L-Sec(MDNPE)*TFA

(2R)-2-amino-3-((1-(6-nitrobenzo[d][1,3]dioxol-5-yl) ethyl)selanyl)propanoic acid trifluoroacetate

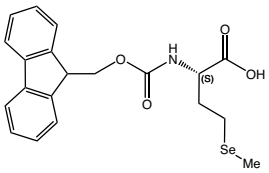
CAS-No.	2235373-48-3
Formula	$C_{12}H_{14}N_2O_6Se*CF_3CO_2H$
Mol. weight	361,22*114,02 g/mol



FAA4205 Fmoc-L-Selenomethionine

N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-selenomethionine

CAS-No.	1217852-49-7
Formula	$C_{20}H_{21}NO_4Se$
Mol. weight	418,35 g/mol



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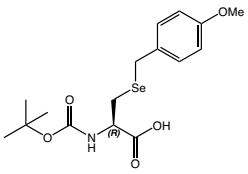
Product details

BAA3760 Boc-L-Sec(Mob)-OH

N-alpha-*t*-Butyloxycarbonyl-Se-(4-methoxybenzyl)-L-selenocysteine

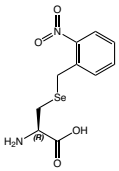
CAS-No.	959415-39-5
Formula	$C_{16}H_{23}NO_5Se$
Mol. weight	388,32 g/mol



HAA9465 H-L-Sec(oNB)-OH*HCl

(R)-2-amino-3-((2-nitrobenzyl)selanyl)propanoic acid

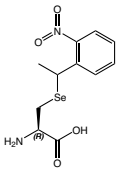
CAS-No.	324582-23-2 net
Formula	$C_{10}H_{12}N_2O_4Se*HCl$
Mol. weight	303,18*36,46 g/mol



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



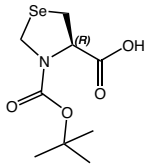
Besides Sec, our portfolio contains a variety of selenazolidine carboxylic acids (Sez derivatives). Sez can be deprotected and converted to Sec by treatment with O-methylhydroxylamine ($MeONH_2$) at pH 4 or by using Cu(II) salts.

Product details

BAA4880 Boc-L-Sez-OH

Boc selenazolidine carboxylic acid

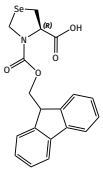
CAS-No.	1841180-44-6
Formula	$C_9H_{15}NO_4Se$
Mol. weight	280,19 g/mol



FAA8860 Fmoc-L-Sez-OH

Fmoc selenazolidine carboxylic acid

CAS-No.	1985651-74-8
Formula	$C_{19}H_{17}NO_4Se$
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.

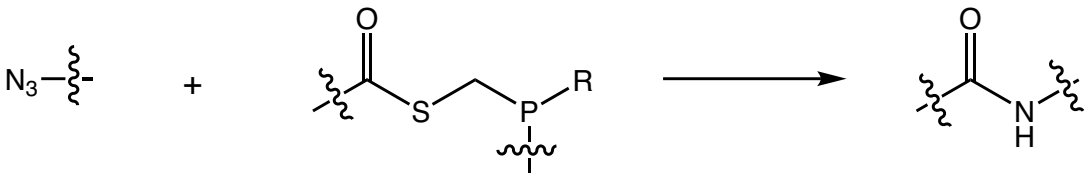


Fig. 17: Schematic illustration of the traceless Staudinger Ligation-Mediated Peptide Cyclization.

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 alpha-ketoacid (KA) and an N-terminal hydroxylamine (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 alpha-ketoacid resins make the approach more convenient, however, noticeable epimerization at the C-terminal residue remains a major drawback.

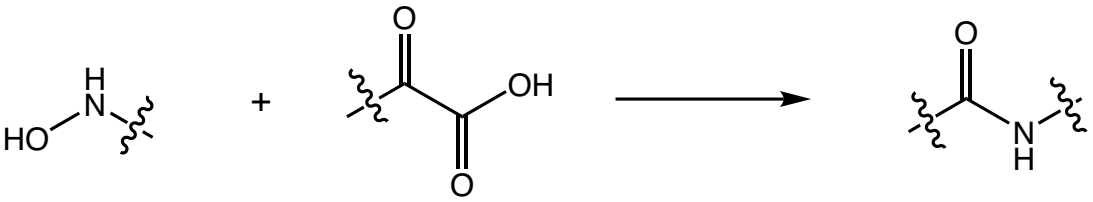


Fig. 18: Schematic illustration of the KAHA ligation.

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References:

→ *Chemoselective Amide Ligations by Decarboxylative Condensations of N-Alkylhydroxylamines and alpha-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 alpha-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 alpha-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-alpha-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 Ser or Thr 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.

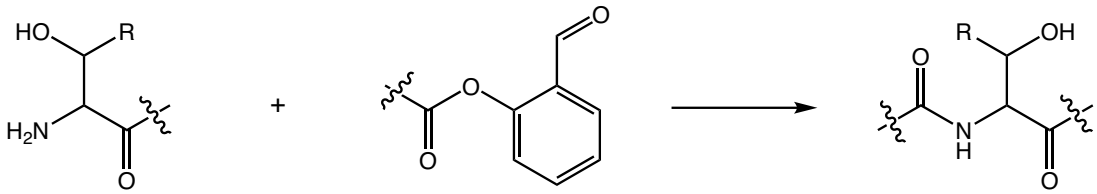


Fig. 19: Schematic illustration of Serine/Threonine Ligation-Mediated Peptide Cyclization.

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*

5. Product Overview

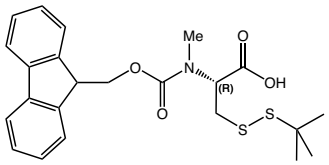
5.1. Cysteine Building Blocks

Product details

FAA3340 Fmoc-L-MeCys(S-*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-(*t*-butylthio)-L-cysteine

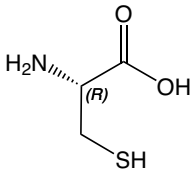
CAS-No.	1013096-03-1
Formula	$C_{23}H_{27}NO_4S_2$
Mol. weight	445,59 g/mol



HAA1080 Cysteine*HCl*H_2O

L-Cysteine Hydrochloride Monohydrate

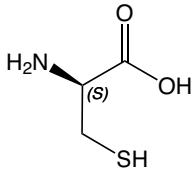
CAS-No.	7048-04-6
Formula	$C_3H_7NO_2S*HCl*H_2O$
Mol. weight	121,2*36,5*18,1 g/mol



HAA1017 H-D-Cys-OH*HCl*H_2O

D-Cysteine Hydrochloride

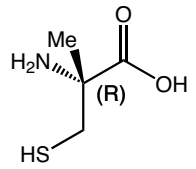
CAS-No.	32443-99-5
Formula	$C_3H_7NO_2S*HCl*H_2O$
Mol. weight	121,2*36,45*18,01 g/mol



HAA2075 H-alpha-Me-L-Cys-OH*HCl

(R)-2-Amino-3-mercapto-2-methylpropionic acid hydrochloride

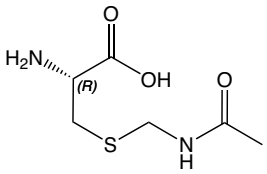
CAS-No.	148766-37-4
Formula	$C_4H_9NO_2S*HCl$
Mol. weight	135,18*36,45 g/mol



HAA6070 H-L-Cys(Acm)-OH*HCl

S-(Acetyl-aminomethyl)-L-cysteine hydrochloride

CAS-No.	28798-28-9
Formula	$C_6H_{12}N_2O_3S*HCl$
Mol. weight	192,24*36,45 g/mol



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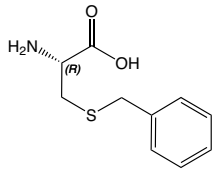
Cyclic Peptides

Product details

HAA1574 H-L-Cys(Bzl)-OH

S-Benzyl-L-cysteine

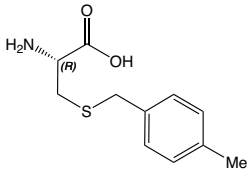
CAS-No.	3054-01-1
Formula	$C_{10}H_{13}NO_2S$
Mol. weight	211,29 g/mol



HAA6090 H-L-Cys(MBzl)-OH

S-(4-Methylbenzyl)-L-cysteine

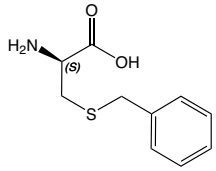
CAS-No.	42294-52-0
Formula	$C_{11}H_{15}NO_2S$
Mol. weight	225,3 g/mol



HAA6110 H-D-Cys(Bzl)-OH

S-Benzyl-D-cysteine

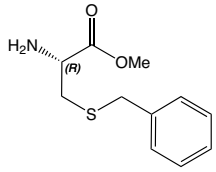
CAS-No.	23032-53-3
Formula	$C_{10}H_{13}NO_2S$
Mol. weight	211,29 g/mol



HAA6080 H-L-Cys(Bzl)-OMe*HCl

S-Benzyl-L-cysteine methyl ester hydrochloride

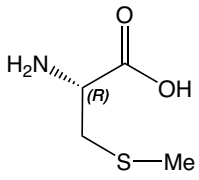
CAS-No.	16741-80-3
Formula	$C_{11}H_{15}NO_2S$*HCl
Mol. weight	225,31*36,45 g/mol



HAA1078 H-L-Cys(Me)-OH*HCl

S-Methyl-L-cysteine hydrochloride

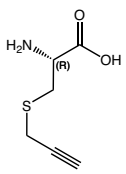
CAS-No.	13331-74-3
Formula	$C_4H_9NO_2S$*HCl
Mol. weight	135,19*36,45 g/mol



HAA2350 H-L-Cys(Propargyl)-OH*HCl

S-Propargyl-L-cysteine hydrochloride

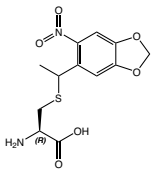
CAS-No.	3262-64-4 net
Formula	$C_6H_9NO_2S$*HCl
Mol. weight	159,21*36,45 g/mol



HAA9270 H-L-Cys(MDNPE)-OH

1-[4',5'-(methylenedioxy)-2'-nitrophenyl]ethyl]-L-cysteine

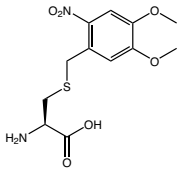
CAS-No.	1551078-43-3
Formula	$C_{12}H_{14}N_2O_6S$
Mol. weight	314,31 g/mol



HAA9320 H-L-Cys(DMNB)-OH

S-(4,5-dimethoxy-2-nitrobenzyl)-L-cysteine

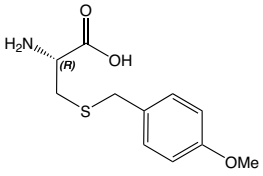
CAS-No.	214633-68-8
Formula	$C_{12}H_{16}N_2O_6S$
Mol. weight	316,33 g/mol



HAA6100 H-L-Cys(Mob)-OH

S-(4-Methoxybenzyl)-L-cysteine

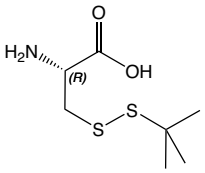
CAS-No.	2544-31-2
Formula	$C_{11}H_{15}NO_3S$
Mol. weight	241,3 g/mol



HAA6140 H-L-Cys(StBu)-OH

S-Thio-*t*-butyl-L-cysteine

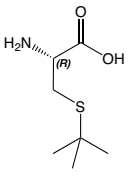
CAS-No.	30044-51-0
Formula	$C_7H_{15}NO_2S_2$
Mol. weight	209,32 g/mol



HAA6150 H-L-Cys(*t*Bu)-OH*HCl

S-*t*-Butyl-L-cysteine hydrochloride

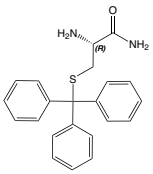
CAS-No.	2481-09-6
Formula	$C_7H_{15}NO_2S$*HCl
Mol. weight	177,26*36,45 g/mol



HAA1560 H-L-Cys(Trt)-NH_2

S-Trityl-L-cysteine amide

CAS-No.	166737-85-5
Formula	$C_{22}H_{22}N_2OS$
Mol. weight	362,49 g/mol



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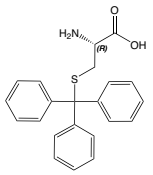
Cyclic Peptides

Product details

HAA6160 H-L-Cys(Trt)-OH

S-Trityl-L-cysteine

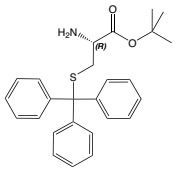
CAS-No. 2799-07-7
Formula $C_{22}H_{21}NO_2S$
Mol. weight 363,48 g/mol



HAA1995 H-L-Cys(Trt)-O*t*Bu*HCl

S-Trityl-L-cysteine *t*-butyl ester hydrochloride

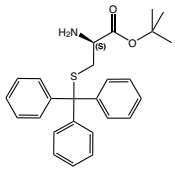
CAS-No. 158009-03-1
Formula $C_{26}H_{29}NO_2S*HCl$
Mol. weight 419,58*36,45 g/mol



HAA2100 H-D-Cys(Trt)-O*t*Bu*HCl

S-Trityl-D-cysteine *t*-butyl ester hydrochloride

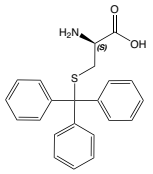
CAS-No. 439089-10-8
Formula $C_{26}H_{29}NO_2S*HCl$
Mol. weight 419,58*36,45 g/mol



HAA6120 H-D-Cys(Trt)-OH

S-Trityl-D-cysteine

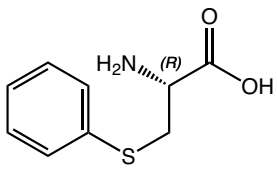
CAS-No. 25840-82-8
Formula $C_{22}H_{21}NO_2S$
Mol. weight 363,48 g/mol



HAA4510 H-L-Cys(Phenyl)-OH

S-Phenyl-L-cysteine

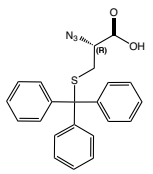
CAS-No. 34317-61-8
Formula $C_9H_{11}NO_2S$
Mol. weight 197,25 g/mol



HAA2810 N_3-L-Cys(Trt)-OH*CHA

(R)-2-azido-3-(tritylthio)propanoic acid cyclohexylamine

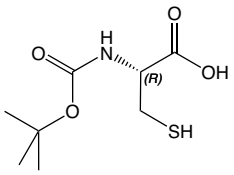
CAS-No. 1286670-90-3
Formula $C_{22}H_{19}N_3O_2S*C_6H_{13}N$
Mol. weight 389,47*99,17 g/mol



BAA1083 Boc-L-Cys-OH

N-alpha-*t*-Butyloxycarbonyl-L-cysteine

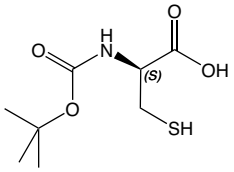
CAS-No.	20887-95-0
Formula	$C_8H_{15}NO_4S$
Mol. weight	221,27 g/mol



BAA1170 Boc-D-Cys-OH

N-alpha-*t*-Butyloxycarbonyl-D-cysteine

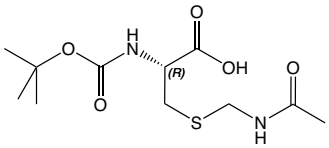
CAS-No.	149270-12-2
Formula	$C_8H_{15}NO_4S$
Mol. weight	221,27 g/mol



BAA1078 Boc-L-Cys(Acm)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(acetyl-amino-methyl)-L-cysteine

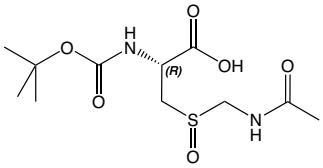
CAS-No.	19746-37-3
Formula	$C_{11}H_{20}N_2O_5S$
Mol. weight	292,36 g/mol



BAA1510 Boc-L-Cys(Acm,O)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(acetyl-amino-methyl)-S-oxo-L-cysteine

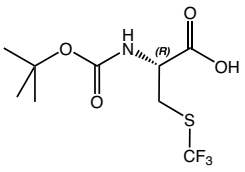
CAS-No.	75893-04-8
Formula	$C_{11}H_{20}N_2O_6S$
Mol. weight	308,35 g/mol



BAA4360 Boc-L-Cys(CF_3)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trifluoromethyl-L-cysteine

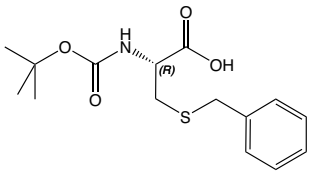
CAS-No.	943926-18-9
Formula	$C_9H_{14}F_3NO_4S$
Mol. weight	289,27 g/mol



BAA1079 Boc-L-Cys(Bzl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-benzyl-L-cysteine

CAS-No.	5068-28-0
Formula	$C_{15}H_{21}NO_4S$
Mol. weight	311,38 g/mol



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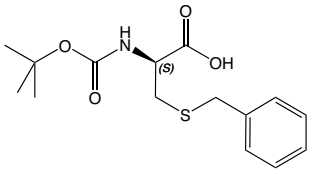
Product details

BAA5410 Boc-D-Cys(Bzl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-benzyl-D-cysteine

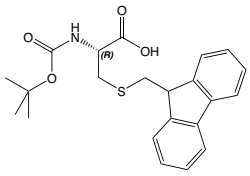
CAS-No. 102830-49-9
Formula $C_{15}H_{21}NO_4S$
Mol. weight 311,38 g/mol



BAA5510 Boc-L-Cys(Fm)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(9-fluorenyl-methyl)-L-cysteineN-alpha-*t*-Butyloxycarbo-nyl-S-(9-fluorenylmethyl)-L-cysteine

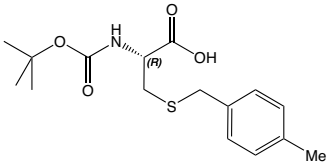
CAS-No. 84888-35-7
Formula $C_{22}H_{25}NO_4S$
Mol. weight 399,51 g/mol



BAA1080 Boc-L-Cys(MBzl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methyl-benzyl)-L-cy-steine

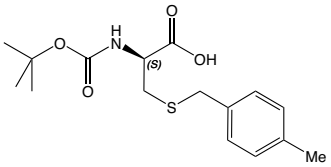
CAS-No. 61925-77-7
Formula $C_{16}H_{23}NO_4S$
Mol. weight 325,43 g/mol



BAA5420 Boc-D-Cys(MBzl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methyl-benzyl)-D-cy-steine

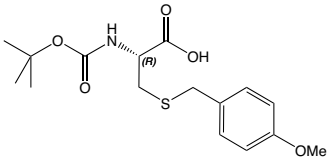
CAS-No. 61925-78-8
Formula $C_{16}H_{23}NO_4S$
Mol. weight 325,43 g/mol



BAA1081 Boc-L-Cys(Mob)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methoxy-benzy-l)-L-cysteine

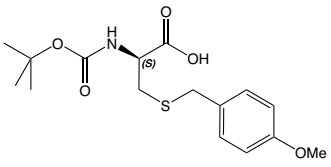
CAS-No. 18942-46-6
Formula $C_{16}H_{23}NO_5S$
Mol. weight 341,43 g/mol



BAA5430 Boc-D-Cys(Mob)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methoxy-benzy-l)-D-cysteine

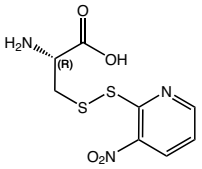
CAS-No. 58290-35-0
Formula $C_{16}H_{23}NO_5S$
Mol. weight 341,43 g/mol



HAA3510 H-L-Cys(Npys)-OH*HCl

S-(3-nitro-2-pyridylthio)-L-cysteine hydrochloride

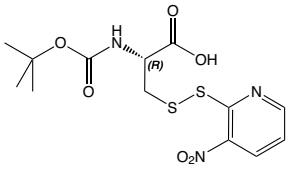
CAS-No. 108807-66-5
Formula $C_8H_9N_3O_4S_2$*HCl
Mol. weight 275,30*36,45 g/mol



BAA1860 Boc-L-Cys(Npys)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(3-nitro-2-pyridylthio)-L-cysteine

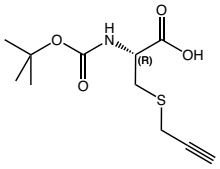
CAS-No. 76880-29-0
Formula $C_{13}H_{17}N_3O_6S_2$
Mol. weight 375,42 g/mol



BAA2250 Boc-L-Cys(Propargyl)-OH*DCHA

N-alpha-*t*-Butyloxycarbonyl-S-propargyl-L-cysteine dicyclohexylamine

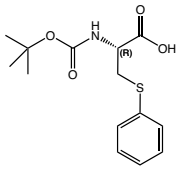
CAS-No. 1260119-25-2 net
Formula $C_{11}H_{17}NO_4S$*$C_{12}H_{23}N$
Mol. weight 259,32*181,32 g/mol



BAA3140 Boc-L-Cys(Ph)-OH

N-alpha-*t*-Butyloxycarbonyl-S-phenyl-L-cysteine

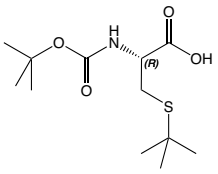
CAS-No. 163705-28-0
Formula $C_{14}H_{19}NO_4S$
Mol. weight 297,37 g/mol



BAA1082 Boc-L-Cys(*t*Bu)-OH

N-alpha-*t*-Butyloxycarbonyl-S-*t*-butyl-L-cysteine

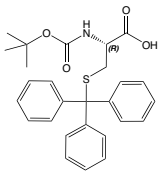
CAS-No. 56976-06-8
Formula $C_{12}H_{23}NO_4S$
Mol. weight 277,37 g/mol



BAA1084 Boc-L-Cys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-L-cysteine

CAS-No. 21947-98-8
Formula $C_{27}H_{29}NO_4S$
Mol. weight 463,59 g/mol



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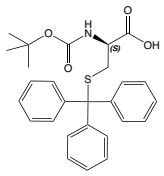
Product details

BAA5000 Boc-D-Cys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-D-cysteine

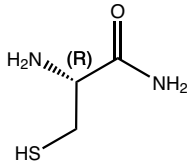
CAS-No. 87494-13-1
Formula $C_{27}H_{29}NO_4S$
Mol. weight 463,59 g/mol



HAA3530 H-L-Cys-NH_2*HCl

L-Cysteine amide hydrochloride

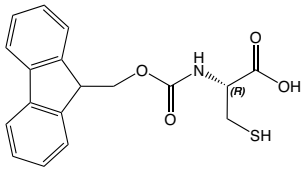
CAS-No. 16359-98-1
Formula $C_3H_8N_2OS$*HCl
Mol. weight 120,17*36,45 g/mol



FAA1362 Fmoc-L-Cys-OH*H_2O

N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-cysteine monohydrat

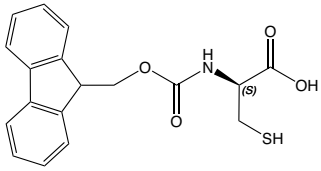
CAS-No. 135248-89-4net
Formula $C_{18}H_{17}NO_4S$*H_2O
Mol. weight 343,40*18,01 g/mol



FAA1470 Fmoc-D-Cys-OH*H_2O

N-alpha-(9-Fluorenylmethyloxycarbonyl)-D-cysteine monohydrat

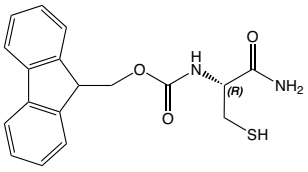
CAS-No. 157355-80-1 net
Formula $C_{18}H_{17}NO_4S$*H_2O
Mol. weight 343,4*18,01 g/mol



FAA1980 Fmoc-L-Cys-NH_2

N-alpha-(9-Fluorenylmethyloxycarbonyl)-L-cysteine amide

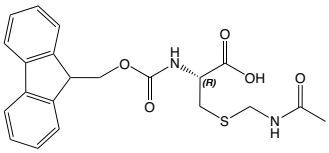
CAS-No. 623177-62-8
Formula $C_{18}H_{18}N_2O_3S$
Mol. weight 342,41 g/mol



FAA1506 Fmoc-L-Cys(Acm)-OH

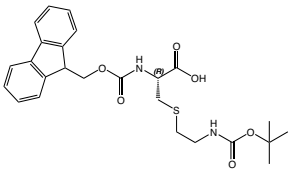
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-cysteine

CAS-No. 86060-81-3
Formula $C_{21}H_{22}N_2O_5S$
Mol. weight 414,48 g/mol



FAA9250 Fmoc-L-Cys(2-Boc-aminoethyl)-OH

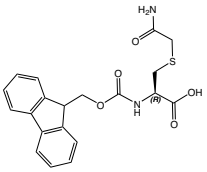
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2-((*tert*-butoxycarbonyl)amino)ethyl)-L-cysteine



CAS-No.	2230472-96-2
Formula	$C_{25}H_{30}N_2O_6S$
Mol. weight	486,58 g/mol

FAA9090 Fmoc-L-Cys(Cam)-OH

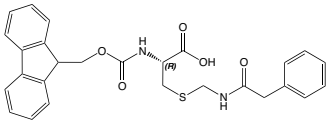
N-(((9H-fluoren-9-yl)methoxy)carbonyl)-S-(2-amino-2-oxoethyl)-L-cysteine



CAS-No.	1443324-12-6
Formula	$C_{20}H_{20}N_2O_5S$
Mol. weight	400,45 g/mol

FAA6910 Fmoc-L-Cys(Phacm)-OH

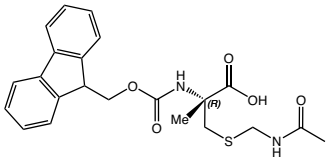
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-Phenylacetylaminomethyl)-L-cysteine



CAS-No.	159680-21-4
Formula	$C_{27}H_{26}N_2O_5S$
Mol. weight	490,57 g/mol

FAA6720 Fmoc-L-MeCys(Acm)-OH

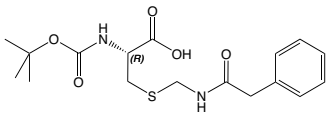
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methal-S-(acetyl-aminomethyl)-L-cysteine



CAS-No.	481642-19-7
Formula	$C_{22}H_{24}N_2O_5S$
Mol. weight	428,5 /mol

BAA6390 Boc-L-Cys(Phacm)-OH

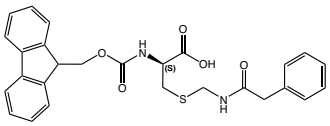
N-alpha-*t*-Butyloxycarbonyl-S-(Phenylacetylaminomethyl)-L-cysteine



CAS-No.	57084-73-8
Formula	$C_{17}H_{24}N_2O_5S$
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	$C_{27}H_{26}N_2O_5S$
Mol. weight	490,57 g/mol

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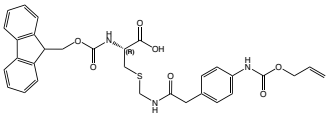
Cyclic Peptides

Product details

FAA5150 Fmoc-L-Cys(Aapam)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((4-(allyloxycarbonylamino)phenylacetylaminomethyl)-L-cysteine

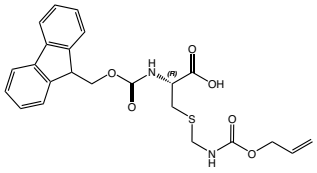
CAS-No. 1946783-89-6
Formula $C_{31}H_{31}N_3O_7S$
Mol. weight 589,66 g/mol



FAA7610 Fmoc-L-Cys(Allocam)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-((allyloxycarbonylamino)methy)-L-cysteine

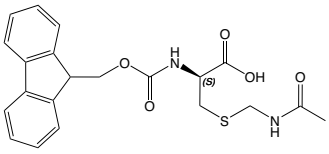
CAS-No. 232953-09-2
Formula $C_{23}H_{24}N_2O_6S$
Mol. weight 456,51 g/mol



FAA6230 Fmoc-D-Cys(Acm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-cysteine

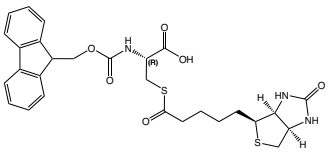
CAS-No. 168300-88-7
Formula $C_{21}H_{22}N_2O_5S$
Mol. weight 414,48 g/mol



FAA3720 Fmoc-L-Cys(Biotin)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-biotinyl-L-cysteine

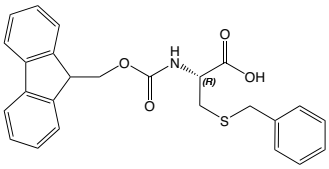
Formula $C_{28}H_{31}N_3O_6S_2$
Mol. weight 569,69 g/mol



FAA6270 Fmoc-L-Cys(Bzl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-benzyl-L-cysteine

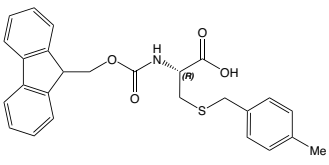
CAS-No. 53298-33-2
Formula $C_{25}H_{23}NO_4S$
Mol. weight 433,52 g/mol



FAA1714 Fmoc-L-Cys(MBzl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-cysteine

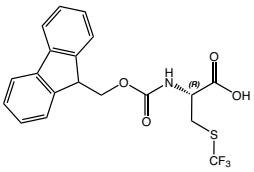
CAS-No. 136050-67-4
Formula $C_{26}H_{25}NO_4S$
Mol. weight 447,53 g/mol



FAA8225 Fmoc-L-Cys(CF_3)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trifluoro-methyl-L-cysteine

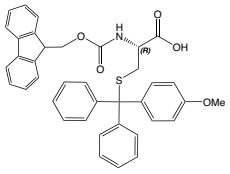
CAS-No.	1994331-25-7
Formula	$C_{19}H_{16}F_3NO_4S$
Mol. weight	411,4 g/mol



FAA1030 Fmoc-L-Cys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*p*-methoxytrityl-L-cysteine

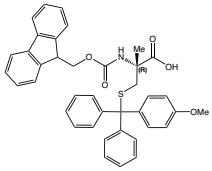
CAS-No.	177582-21-7
Formula	$C_{38}H_{33}NO_5S$
Mol. weight	615,74 g/mol



FAA4845 Fmoc-alpha-Me-L-Cys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-(4-methoxytrityl)-L-cysteine

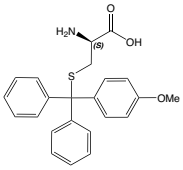
CAS-No.	1198791-74-0
Formula	$C_{39}H_{35}NO_5S$
Mol. weight	629,76 g/mol



HAA3500 H-D-Cys(Mmt)-OH

S-*p*-methoxytrityl-D-cysteine

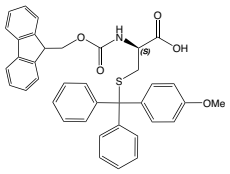
CAS-No.	926935-33-3
Formula	$C_{23}H_{23}NO_3S$
Mol. weight	393,5 g/mol



FAA1614 Fmoc-D-Cys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*p*-methoxytrityl-D-cysteine

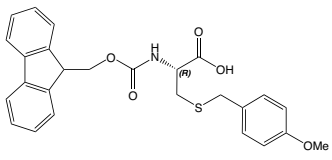
CAS-No.	1198791-73-9
Formula	$C_{38}H_{33}NO_5S$
Mol. weight	615,74 g/mol



FAA1715 Fmoc-L-Cys(Mob)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine

CAS-No.	141892-41-3
Formula	$C_{26}H_{25}NO_5S$
Mol. weight	463,55 g/mol



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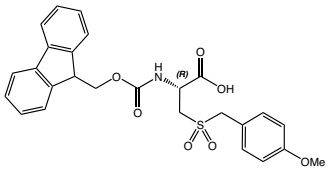
Product details

FAA8410 Fmoc-L-Cys(SO2Mob)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxybenzyl)-L-cysteine-S,S-dioxide

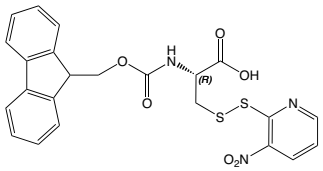
CAS-No.	2412536-40-2
Formula	$C_{26}H_{25}NO_7S$
Mol. weight	495,55



FAA1975 Fmoc-L-Cys(Npys)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(3-nitro-2-pyridylthio)-L-cysteine

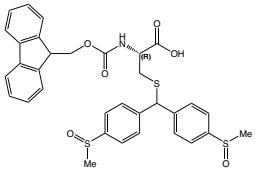
CAS-No.	159700-51-3
Formula	$C_{23}H_{19}N_3O_6S_2$
Mol. weight	497,54 g/mol



FAA4155 Fmoc-L-Cys(Msbh)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4,4'-dimethylsulfinylbenzhydryl)-L-cysteine

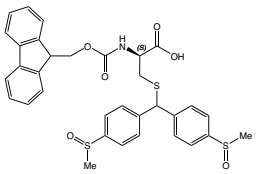
CAS-No.	1584646-97-8
Formula	$C_{33}H_{31}NO_6S_3$
Mol. weight	633,80 g/mol



FAA8150 Fmoc-D-Cys(Msbh)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4,4'-dimethylsulfinylbenzhydryl)-D-cysteine

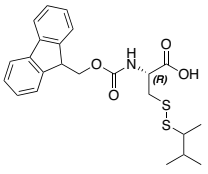
Formula	$C_{33}H_{31}NO_6S_3$
Mol. weight	633,80 g/mol



FAA8495 Fmoc-L-Cys(SIT)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-cysteine

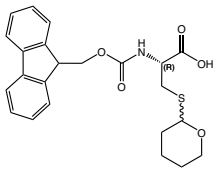
CAS-No.	2545642-31-5
Formula	$C_{23}H_{27}NO_4S_2$
Mol. weight	445,59 g/mol



FAA4160 Fmoc-L-Cys(Thp)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-tetrahydropyranyl-L-cysteine

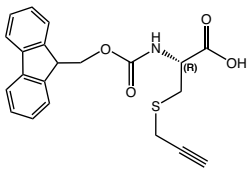
CAS-No.	1673576-83-4
Formula	$C_{23}H_{25}NO_5S$
Mol. weight	427,15 g/mol



FAA3810 Fmoc-L-Cys(Propargyl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-propargyl-L-cysteine

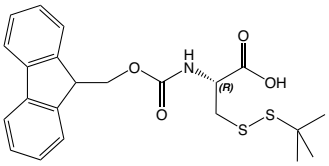
CAS-No.	1354752-76-3
Formula	$C_{21}H_{19}NO_4S$
Mol. weight	381,44 g/mol



FAA1575 Fmoc-L-Cys(S*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butylthio)-L-cysteine

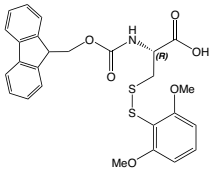
CAS-No.	73724-43-3
Formula	$C_{22}H_{25}NO_4S_2$
Mol. weight	431,57 g/mol



FAA3180 Fmoc-L-Cys(S-DMP)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2,6-dimethoxythiophenol)-L-cysteine

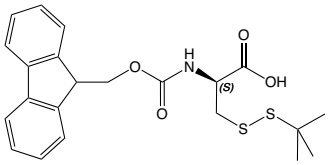
CAS-No.	1403834-73-0
Formula	$C_{26}H_{25}NO_6S_2$
Mol. weight	511,61 g/mol



FAA1965 Fmoc-D-Cys(S*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butylthio)-D-cysteine

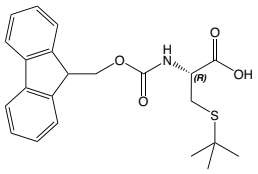
CAS-No.	501326-55-2
Formula	$C_{22}H_{25}NO_4S_2$
Mol. weight	431,57 g/mol



FAA1716 Fmoc-L-Cys(*t*Bu)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*t*-butyl-L-cysteine

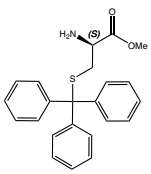
CAS-No.	67436-13-9
Formula	$C_{22}H_{25}NO_4S$
Mol. weight	399,51 g/mol



HAA3520 H-D-Cys(Trt)-OMe*HCl

S-trityl-D-cysteine methyl ester hydrochloride

CAS-No.	1020369-32-7
Formula	$C_{23}H_{23}NO_2S$*HCl
Mol. weight	377,50*36,45 g/mol



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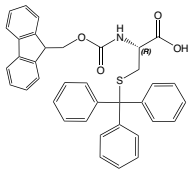
Product details

FAA1040 Fmoc-L-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine

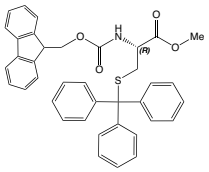
CAS-No. 103213-32-7
Formula $C_{37}H_{31}NO_4S$
Mol. weight 585,71 g/mol



FAA5670 Fmoc-L-Cys(Trt)-OMe

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-cysteine methyl ester

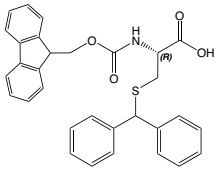
CAS-No. 245088-56-6
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



FAA3190 Fmoc-L-Cys(Dpm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenylmethyl-L-cysteine

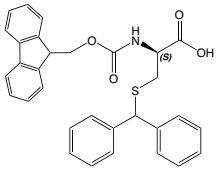
CAS-No. 247595-29-5
Formula $C_{31}H_{27}NO_4S$
Mol. weight 509,62 g/mol



FAA5650 Fmoc-D-Cys(Dpm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-diphenylmethyl-D-cysteine

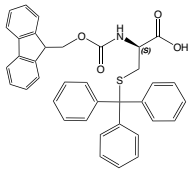
Formula $C_{31}H_{27}NO_4S$
Mol. weight 509,62 g/mol



FAA1035 Fmoc-D-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-cysteine

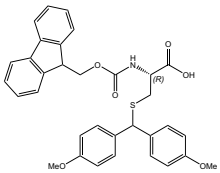
CAS-No. 167015-11-4
Formula $C_{37}H_{31}NO_4S$
Mol. weight 585,71 g/mol



FAA6940 Fmoc-L-Cys(Ddm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-di(4-methoxyphenyl)methyl-L-cysteine

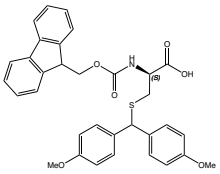
CAS-No. 1403825-56-8
Formula $C_{33}H_{31}NO_6S$
Mol. weight 569,67 g/mol



FAA6950 Fmoc-D-Cys(Ddm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-di(4-methoxyphenyl)methyl-D-cysteine

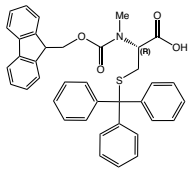
Formula	$C_{33}H_{31}NO_6S$
Mol. weight	569,67 g/mol



FAA3570 Fmoc-L-MeCys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-S-trityl-L-cysteine

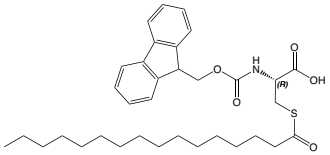
CAS-No.	944797-51-7
Formula	$C_{38}H_{33}NO_4S$
Mol. weight	599,74 g/mol



FAA1950 Fmoc-L-Cys(Palm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-*t*-palmitoyl-L-cysteine

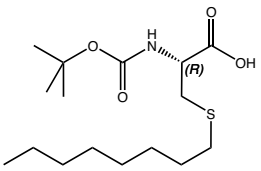
CAS-No.	824955-27-3
Formula	$C_{34}H_{47}NO_5S$
Mol. weight	581,81 g/mol



BAA1520 Boc-L-Cys(Octyl)-OH

N-alpha-*t*-Butyloxycarbonyl-S-octyl-L-cysteine

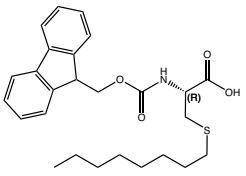
CAS-No.	67194-12-1
Formula	$C_{16}H_{31}NO_4S$
Mol. weight	333,49 g/mol



FAA5890 Fmoc-L-Cys(Octyl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-octyl-L-cysteine

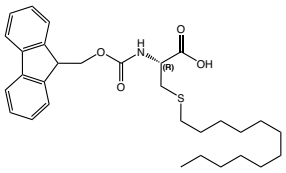
CAS-No.	210883-65-1
Formula	$C_{26}H_{33}NO_4S$
Mol. weight	455,61 g/mol



FAA4810 Fmoc-L-Cys(lauryl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-dodecyl-L-cysteine

CAS-No.	1310682-09-7
Formula	$C_{30}H_{41}NO_4S$
Mol. weight	511,72 g/mol



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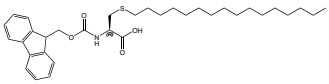
Product details

FAA8770 Fmoc-L-Cys(palmityl)-OH

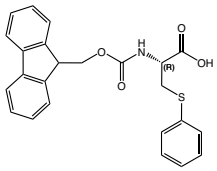
N-alpha-(9-Fluorenylmethoxycarbonyl)-S-hexadecyl-L-cysteine



CAS-No.	876312-48-0
Formula	$C_{34}H_{49}NO_4S$
Mol. weight	567,83 g/mol

FAA4820 Fmoc-L-Cys(Ph)-OH

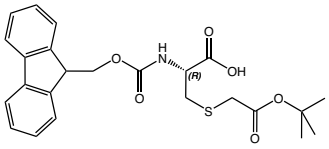
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-phenyl-L-cysteine



CAS-No.	488761-06-4
Formula	$C_{24}H_{21}NO_4S$
Mol. weight	419,49 g/mol

FAA4751 Fmoc-L-Cys(Ac-O*t*Bu)-OH*DCHA

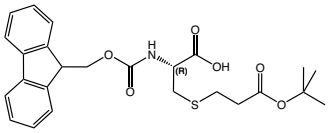
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butoxycarbonylmethyl)-L-cysteine dicyclohexylamine



CAS-No.	269730-62-3 net
Formula	$C_{24}H_{27}NO_6S*C_{12}H_{23}N$
Mol. weight	457,54*181,32 g/mol

FAA4760 Fmoc-L-Cys(EtCO-O*t*Bu)-OH

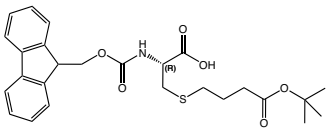
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butoxycarbonylethyl)-L-cysteine



CAS-No.	685863-48-3
Formula	$C_{25}H_{29}NO_6S$
Mol. weight	471,57 g/mol

FAA3370 Fmoc-L-Cys(PrCO-O*t*Bu)-OH

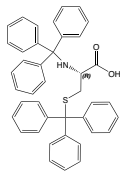
N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(*t*-butoxycarbonylpropyl)-L-cysteine



CAS-No.	102971-73-3
Formula	$C_{26}H_{31}NO_6S$
Mol. weight	485,59 g/mol

TAA1508 Trt-L-Cys(Trt)-OH*DEA

N-alpha-S-Bistrityl-L-cysteine diethylamine

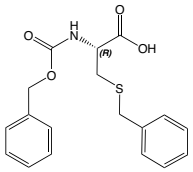


CAS-No.	27486-88-0
Formula	$C_{41}H_{35}NO_2S*C_4H_{11}N$
Mol. weight	678,9 g/mol

ZAA1161 Z-L-Cys(Bzl)-OH

N-alpha-Benzyloxycarbonyl-S-benzyl-L-cysteine

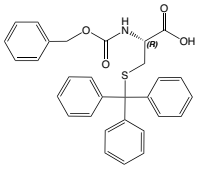
CAS-No. 3257-18-9
Formula $C_{18}H_{19}NO_4S$
Mol. weight 345,42 g/mol



ZAA1310 Z-L-Cys(Trt)-OH

N-alpha-Benzyloxycarbonyl-S-trityl-L-cysteine

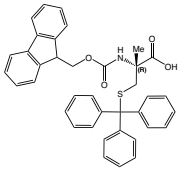
CAS-No. 26311-04-6
Formula $C_{30}H_{27}NO_4S$
Mol. weight 497,60 g/mol



FAA4840 Fmoc-alpha-Me-L-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-trityl-L-cysteine

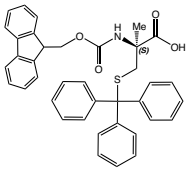
CAS-No. 725728-43-8
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



FAA4850 Fmoc-alpha-Me-D-Cys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-alpha-methyl-S-trityl-D-cysteine

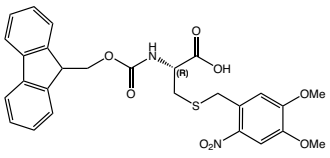
CAS-No. 725728-37-0
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



FAA3970 Fmoc-L-Cys(*o*Nv)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-cysteine

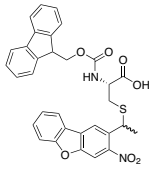
CAS-No. 214633-71-3
Formula $C_{27}H_{26}N_2O_8S$
Mol. weight 538,57 g/mol



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



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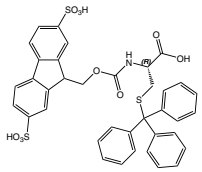
Product details

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 (net)
Formula $C_{37}H_{29}K_2NO_{10}S_3$
Mol. weight 822,01 g/mol



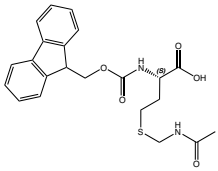
5.2. Homocysteine Building Blocks

Product details

FAA8255 Fmoc-L-HCys(Acm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-L-homocysteine

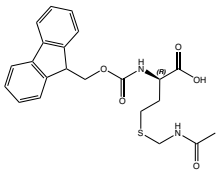
CAS-No. 150281-21-3
Formula $C_{22}H_{24}N_2O_5S$
Mol. weight 428,5 g/mol



FAA8260 Fmoc-D-HCys(Acm)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(acetyl-aminomethyl)-D-homocysteine

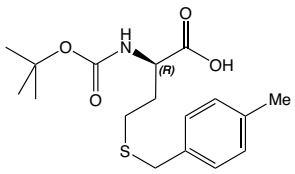
CAS-No. 2576507-96-3
Formula $C_{22}H_{24}N_2O_5S$
Mol. weight 428,5 g/mol



BAA5180 Boc-D-HCys(MBz)-OH

N-alpha-*t*-Butyloxycarbonyl-S-(4-methylbenzyl)-D-homocysteine

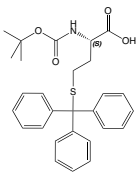
Formula $C_{17}H_{25}NO_4S$
Mol. weight 339,46 g/mol



BAA5200 Boc-L-HCys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-L-homocysteine

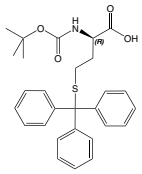
CAS-No. 201419-16-1
Formula $C_{28}H_{31}NO_4S$
Mol. weight 477,63 g/mol



BAA5190 Boc-D-HCys(Trt)-OH

N-alpha-*t*-Butyloxycarbonyl-S-trityl-D-homocysteine

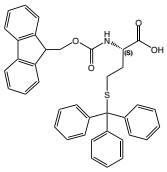
CAS-No. 1301706-43-3
Formula $C_{28}H_{31}NO_4S$
Mol. weight 477,63 g/mol



FAA1602 Fmoc-L-HCys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-homocysteine

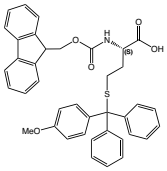
CAS-No. 167015-23-8
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,76 g/mol



FAA3840 Fmoc-L-HCys(Mmt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methoxytrityl)-L-homocysteine

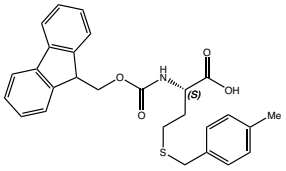
CAS-No. 887644-62-4
Formula $C_{39}H_{35}NO_5S$
Mol. weight 629,76 g/mol



FAA5680 Fmoc-L-HCys(MBzl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-homocysteine

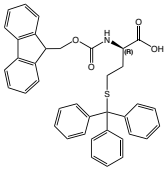
CAS-No. 1821768-91-5
Formula $C_{27}H_{27}NO_4S$
Mol. weight 461,57 g/mol



FAA6120 Fmoc-D-HCys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-homocysteine

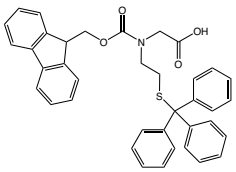
CAS-No. 1007840-62-1
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,76 g/mol



FAA4830 Fmoc-Nhcys(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-[2-(tritylthio)ethyl]-glycine

CAS-No. 882847-27-0
Formula $C_{38}H_{33}NO_4S$
Mol. weight 599,74 g/mol



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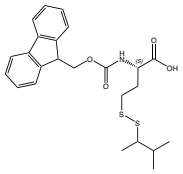
Product details

FAA8865 Fmoc-L-hCys(SIT)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(sec-isoamyl mercaptan)-L-homocysteine

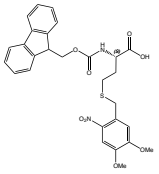
Formula $C_{24}H_{29}NO_4S_2$
Mol. weight 459,62 g/mol



FAA8870 Fmoc-L-hCys(*o*Nv)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(2-nitroveratryl)-L-homocysteine

Formula $C_{28}H_{28}N_2O_8S$
Mol. weight 552,60 g/mol



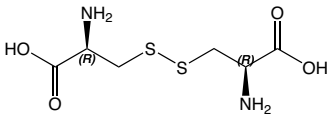
5.3. Cystine Building Blocks

Product details

HAA1156 $(H\text{-}L\text{-}Cys\text{-}OH)_2$

L-Cystine

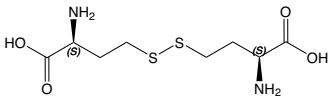
CAS-No. 56-89-3
Formula $C_6H_{12}N_2O_4S_2$
Mol. weight 240,29 g/mol



HAA1157 H-L-HCystine

L-HomoCystine

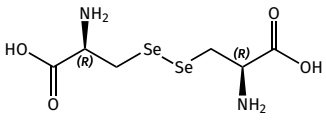
CAS-No. 626-72-2
Formula $C_8H_{16}N_2O_4S_2$
Mol. weight 268,36 g/mol



HAA9350 (H-L-Sec-OH)2

L-Selenocystine, (H-Sec)2, (H-L-Sec)2

CAS-No. 29621-88-3
Formula $C_6H_{12}N_2O_4Se_2$
Mol. weight 334,11 g/mol

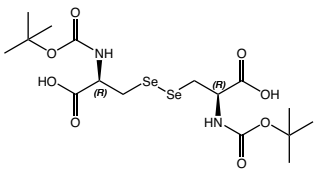


Product details

BAA3680 (Boc-L-Sec)$_2$

N-alpha-*t*-Butyloxycarbonyl-L-selenocystine

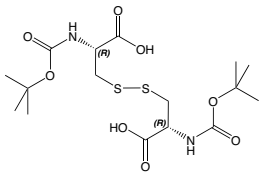
CAS-No. 877754-71-7
Formula $C_{16}H_{28}N_2O_8Se_2$
Mol. weight 534,35 g/mol



BAA5390 (Boc-L-Cys-OH)$_2$

N-alpha,N-alpha'-di-Boc-L-cystine

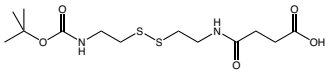
CAS-No. 10389-65-8
Formula $C_{16}H_{28}N_2O_8S_2$
Mol. weight 440,52 g/mol



BAA2180 Boc-Cystamine-Suc-OH

4-(2-((2-*t*-Butyloxycarbonylaminoethyl)disulfanyl) ethylamino)-4-oxobutanoic acid

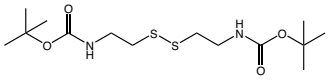
CAS-No. 946849-79-2
Formula $C_{13}H_{24}N_2O_5S_2$
Mol. weight 352,47 g/mol



BNN1360 Di-Boc-Cystamine

N,N'-Bis-*tert*-butoxycarbonyl-cystamine

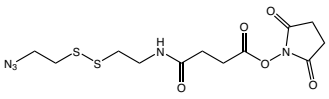
CAS-No. 67385-10-8
Formula $C_{14}H_{28}N_2O_4S_2$
Mol. weight 352,51 g/mol



HAA2255 N_3-Cystamine-Suc-OSu

4-(2-((2-Azidoethyl)disulfanyl)ethylamino)-4-oxobutanoic acid succinimidyl ester

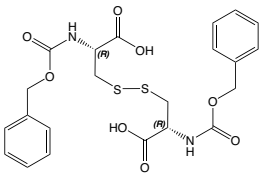
CAS-No. 1987341-40-1
Formula $C_{12}H_{17}N_5O_5S_2$
Mol. weight 375,42 g/mol



ZAA1190 (Z-L-Cys-OH)$_2$

N-alpha-Benzyloxycarbonyl-L-cystine

CAS-No. 6968-11-2
Formula $C_{22}H_{24}N_2O_8S_2$
Mol. weight 508,54 g/mol



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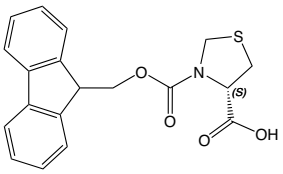
5.4. Cysteine protected as Thiazolidine and other Building Blocks

Product details

FAA1495 Fmoc-D-Thz-OH

(S)-N-alpha-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-4-carboxylic acid

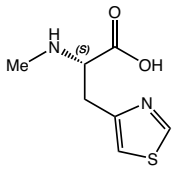
CAS-No.	198545-89-0
Formula	$C_{19}H_{17}NO_4S$
Mol. weight	355,42 g/mol



HAA3840 H-L-MeAla(4-Thz)-OH

N-alpha-Methyl-beta-(4-thiazolyl)-L-alanine

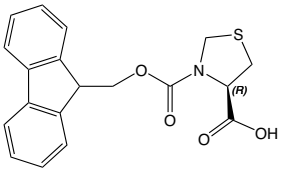
CAS-No.	2131118-50-6
Formula	$C_7H_{10}N_2O_2S$
Mol. weight	186,23 g/mol



FAA1427 Fmoc-L-Thz-OH

(R)-N-(9-Fluorenylmethyloxycarbonyl)-thiazolidine-L-4-carboxylic acid

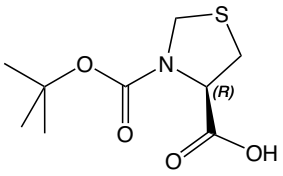
CAS-No.	133054-21-4
Formula	$C_{19}H_{17}NO_4S$
Mol. weight	355,42 g/mol



BAA1135 Boc-L-Thz-OH

(R)-N-*t*-Butyloxycarbonyl-thiazolidine-4-carboxylic acid

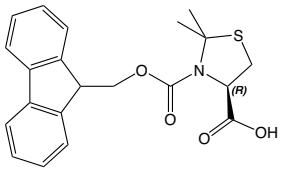
CAS-No.	51077-16-8
Formula	$C_9H_{15}NO_4S$
Mol. weight	233,29 g/mol



FAA1437 Fmoc-L-Thz(Me2)-OH

(R)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid

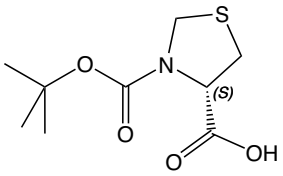
CAS-No.	873842-06-9
Formula	$C_{21}H_{21}NO_4S$
Mol. weight	383,46 g/mol



BAA1186 Boc-D-Thz-OH

(S)-N-(t-Butyloxycarbonyl)-thiazolidine-4-carboxylic acid

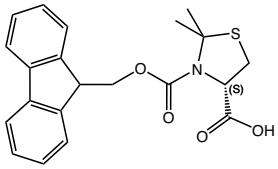
CAS-No.	63091-82-7
Formula	$C_9H_{15}NO_4S$
Mol. weight	233,29 g/mol



FAA3160 Fmoc-D-Thz(Me2)-OH

(S)-N-(9-Fluorenylmethyloxycarbonyl)-2,2-dimethyl-thiazolidine-4-carboxylic acid

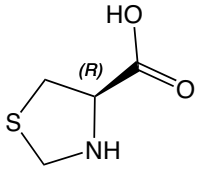
CAS-No.	1932198-36-1
Formula	$C_{21}H_{21}NO_4S$
Mol. weight	383,46 g/mol



HAA1132 H-L-Thz-OH

(R)-Thiazolidine-4-carboxylic acid

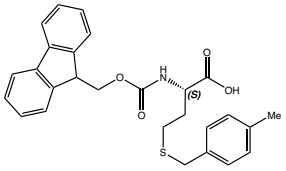
CAS-No.	34592-47-7
Formula	$C_4H_7NO_2S$
Mol. weight	133,16 g/mol



FAA5680 Fmoc-L-HCys(MBzl)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-(4-methylbenzyl)-L-homocysteine

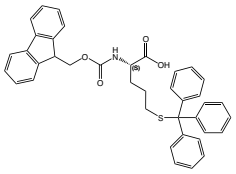
CAS-No.	1821768-91-5
Formula	$C_{27}H_{27}NO_4S$
Mol. weight	461,57 g/mol



FAA5370 Fmoc-2-amino-5-(tritylthio)-pentanoic acid (S)

(S)-2-((9-Fluorenylmethyloxycarbonyl)amino)-5-(tritylthio)pentanoic acid

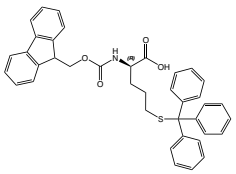
CAS-No.	1417789-17-3
Formula	$C_{39}H_{35}NO_4S$
Mol. weight	613,76 g/mol



FAA7580 Fmoc-2-amino-5-(tritylthio)-pentanoic acid (R)

(R)-2-((9-Fluorenylmethyloxycarbonyl)amino)-5-(tritylthio)pentanoic acid

CAS-No.	1359658-41-5
Formula	$C_{39}H_{35}NO_4S$
Mol. weight	613,76 g/mol



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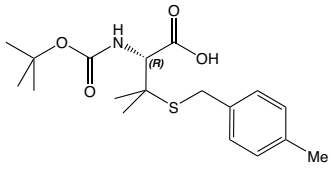
Product details

BAA5850 Boc-L-Pen(MBzl)-OH*DCHA

N-alpha-*t*-Butyloxycarbonyl-S-(4-methylbenzyl)-L-penicillamine dicyclohexylamine

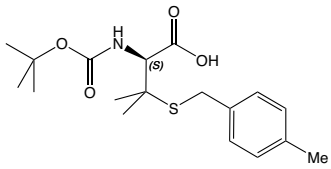
CAS-No. 198474-61-2
Formula $C_{18}H_{27}NO_4S*C_{12}H_{23}N$
Mol. weight 353,48*181,32 g/mol



BAA1361 Boc-D-Pen(MBzl)-OH*DCHA

N-alpha-*t*-Butyloxycarbonyl-S-(4-methylbenzyl)-D-penicillamine dicyclohexylamine

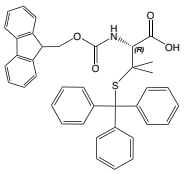
CAS-No. 198470-36-9
Formula $C_{18}H_{27}NO_4S*C_{12}H_{23}N$
Mol. weight 353,48*181,32 g/mol



FAA1587 Fmoc-L-Pen(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-L-penicillamine

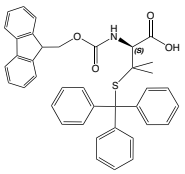
CAS-No. 201531-88-6
Formula $C_{39}H_{35}NO_4S$
Mol. weight 613,78 g/mol



FAA1675 Fmoc-D-Pen(Trt)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-S-trityl-D-penicillamine

CAS-No. 201532-01-6
Formula $C_{39}H_{35}NO_4S$
Mol. weight 613,78 g/mol



Notes

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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 isrespected.

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.

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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 theproduct 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.

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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.

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FAA8445	Fmoc-Hcan(Boc)-OH (S)	48
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PYV1100	Fmoc-L-Ala-NHN=Pyv Resin	48
PYV1110	Fmoc-L-Arg(Pbf)-NHN=Pyv Resin	49
PSI1460	Fmoc-L-Asn(Trt)-L-Cys[PSI(Dmp,H)pro]-OH	18
PYV1120	Fmoc-L-Asn(Trt)-NHN=Pyv Resin	49
PYV1130	Fmoc-L-Asp(O*t*Bu)-NHN=Pyv Resin	49
PSI1470	Fmoc-L-Asp(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH	18
FAA8460	Fmoc-L-*cis*-Hyp(NHBoc)-OH	48
FAA9250	Fmoc-L-Cys(2-Boc-aminoethyl)-OH	68
FAA5150	Fmoc-L-Cys(Aapam)-OH	28, 69
FAA4751	Fmoc-L-Cys(Ac-O*t*Bu)-OH*DCHA	75
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FAA6910	Fmoc-L-Cys(Phacm)-OH	26, 68
FAA3370	Fmoc-L-Cys(PrCO-O*t*Bu)-OH	75
FAA3810	Fmoc-L-Cys(Propargyl)-OH	72
FAA3180	Fmoc-L-Cys(S-DMP)-OH	36, 72
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FAA8410	Fmoc-L-Cys(SO2Mob)-OH	71
SAL1109	Fmoc-L-Cys(SS-*t*Bu)-AC TG	34
SAL1209	Fmoc-L-Cys(SS-*t*Bu)-Trt TG	35
WAA11309	Fmoc-L-Cys(SS-*t*Bu)-Wang Resin	35
WAA41309	Fmoc-L-Cys(SS-*t*Bu)-Wang Resin	35
SAL1309	Fmoc-L-Cys(SS-*t*Bu)-Wang TG	35
FAA1575	Fmoc-L-Cys(S*t*Bu)-OH	33, 72
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FAA1716	Fmoc-L-Cys(*t*Bu)-OH	13, 72
TCP1120	Fmoc-L-Cys(*t*Bu)-TCP-Resin	13
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SAL1106	Fmoc-L-Cys(Trt)-AC TG	8
PSI1580	Fmoc-L-Cys(Trt)-L-Cys(Psi(Dmp,H)pro)-OH	20
PYV1140	Fmoc-L-Cys(Trt)-NHN=Pyv Resin	7, 49
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WAA41306	Fmoc-L-Cys(Trt)-Wang Resin	9
SAL1306	Fmoc-L-Cys(Trt)-Wang TG	8
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FAA1362	Fmoc-L-Cys-OH*H_2O	67
PSI1480	Fmoc-L-Gln(Trt)-L-Cys[PSI(Dmp,H)pro]-OH	18
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PSI1490	Fmoc-L-Glu(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH	18
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PSI1500	Fmoc-L-Ile-L-Cys[PSI(Dmp,H)pro]-OH	18
PYV1190	Fmoc-L-Ile-NHN=Pyv Resin	50
PSI1510	Fmoc-L-Leu-L-Cys[PSI(Dmp,H)pro]-OH	19
PYV1200	Fmoc-L-Leu-NHN=Pyv Resin	50
PSI1520	Fmoc-L-Lys(Boc)-L-Cys[PSI(Dmp,H)pro]-OH	19
PYV1210	Fmoc-L-Lys(Boc)-NHN=Pyv Resin	50
FAA6720	Fmoc-L-MeCys(Acm)-OH	68
FAA3340	Fmoc-L-MeCys(S-*t*Bu)-OH	34, 60
FAA3570	Fmoc-L-MeCys(Trt)-OH	5, 74
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FAA8760	Fmoc-L-Sec(Mob)-OPfp	56
FAA8465	Fmoc-L-Sec(Xan)-OH	56
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FAA8860	Fmoc-L-Sez-OH	57
PSI1550	Fmoc-L-Thr(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH	19
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PYV1270	Fmoc-L-Trp(Boc)-NHN=Pyv Resin	51
PSI1560	Fmoc-L-Tyr(*t*Bu)-L-Cys[PSI(Dmp,H)pro]-OH	19
PYV1280	Fmoc-L-Tyr(*t*Bu)-NHN=Pyv Resin	51
PSI1570	Fmoc-L-Val-L-Cys[PSI(Dmp,H)pro]-OH	19
PYV1290	Fmoc-L-Val-NHN=Pyv Resin	52
FAA4830	Fmoc-Nhcys(Trt)-OH	78
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HAA1574	H-L-Cys(Bzl)-OH	61
HAA6080	H-L-Cys(Bzl)-OMe*HCl	61
HAA9320	H-L-Cys(DMNB)-OH	32, 62
HAA6090	H-L-Cys(MBzl)-OH	16, 61
HAA9270	H-L-Cys(MDNPE)-OH	32, 62
HAA1078	H-L-Cys(Me)-OH*HCl	61
RAA1055	H-L-Cys(Mmt)-2CT Resin	10
HAA6100	H-L-Cys(Mob)-OH	14, 62
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HAA4510	H-L-Cys(Phenyl)-OH	63
HAA2350	H-L-Cys(Propargyl)-OH*HCl	61
HAA6140	H-L-Cys(S*t*Bu)-OH	34, 62
HAA6150	H-L-Cys(*t*Bu)-OH*HCl	13, 62
RAA1065	H-L-Cys(Trt)-2CT Resin	7
RAA1066	H-L-Cys(Trt)-2CT Resin	7
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HAA6160	H-L-Cys(Trt)-OH	6, 63
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HAA9255	H-L-Sec(DMNB)-OH*TFA	55
HAA9230	H-L-Sec(MDNPE)*TFA	56
HAA9360	H-L-Sec(MDNPE)-OH	55
HAA9475	H-L-Sec(NPE)-OH*HCl	57
HAA9465	H-L-Sec(oNB)-OH*HCl	57
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