Iris Biotech

LINKEROLOGY®

Version: IB6_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

Linkerology®

1. The Concept of Antibody-Drug Conjugation (ADC)

1.1. Technical and Market Background

Conjugating highly potent small molecules to vastly target specific biomolecules, like antibodies, has become a modern and sophisticated approach, particularly in the field of cancer therapy. The list of ADCs in clinics continues to grow, bolstered by the success of two pioneers in this field:

Adcetris® (Seattle Genetics) has been approved in 2011 for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma (ALCL) and reached $476.9 million sales per year in 2018. This drug is composed of a monoclonal antibody targeting CD30 conjugated to four molecules of monomethyl auristatin E *via* a self-immolative linkage (*Fig. 1*). Reduction of interchain disulfide bonds provides reactive cysteine residues, which are then conjugated with maleimide payload linker systems, yielding the final drug compound.

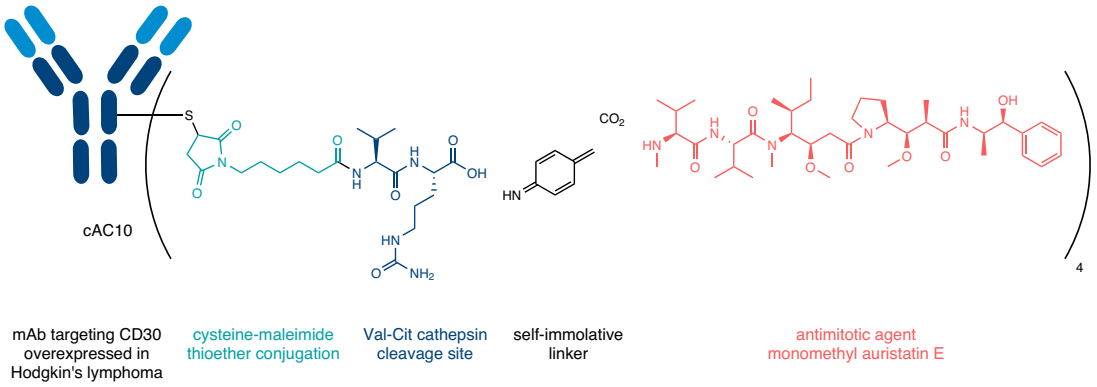

Fig. 1: Composition of Adcetris®, one of the first FDA-approved ADCs.

Kadcyla®, another pioneer in this field, has been approved in 2013 for the treatment of HER-2 positive metastatic breast cancer and reached $981 million sales per year in 2018. In this case, payloads are conjugated to surface accessible lysines resulting in a heterogeneous modification of the core antibody.

Reference:

→ *Antibody-drug conjugates in tumor therapy; B. Sammet, C. Steinkuhler, N. Sewald;* ***Pharm Pat Anal*** *2012; **1**: 65-73. https://doi.org/10.4155/ppa.12.4*

IC_{50}
Inhibitory Concentration
Concentration causing 50% of maximal inhibition of the desired activity.

EC_{50}
Effective Concentration
Concentration causing 50% of maximal response of the desired effect.

ED_{50}
Effective Dose
Dose causing the desired effect in 50% of individuals.

GI_{50}
Growth Inhibition
Concentration causing 50% inhibition of cell proliferation/cell growth.

TC_{50}
Toxic Concentration
Concentration causing a defined toxic effect in 50% of individuals.

TD_{50}
Toxic Dose
Dose causing a defined toxic effect in 50% of individuals.

CC_{50}
Cytotoxic Concentration
Concentration killing 50% of cells.

LC_{50}
Lethal Concentration
Concentration killing 50% of individuals.

LD_{50}
Lethal Dose
Dose killing 50% of individuals.

ADCs – Mode of Action

The typical mode of action of ADCs is shown in Figure 2. An ADC circulates in plasma until it reaches the target cell. The antibody portion of an ADC then nails to a cell-surface antigen that is ideally specific to a cancer cell. Upon binding, the ADC-antigen protein complex becomes internalized into the cancer cell. When the complex is degraded, it releases the cytotoxin which then binds to its target to cause cancer cell apoptosis. The linker between antibody and payload is typically either permanent or cleavable by hydrolases, such as the protease cathepsin B, by glucoronidases or through reductive conditions and the presence of glutathion.

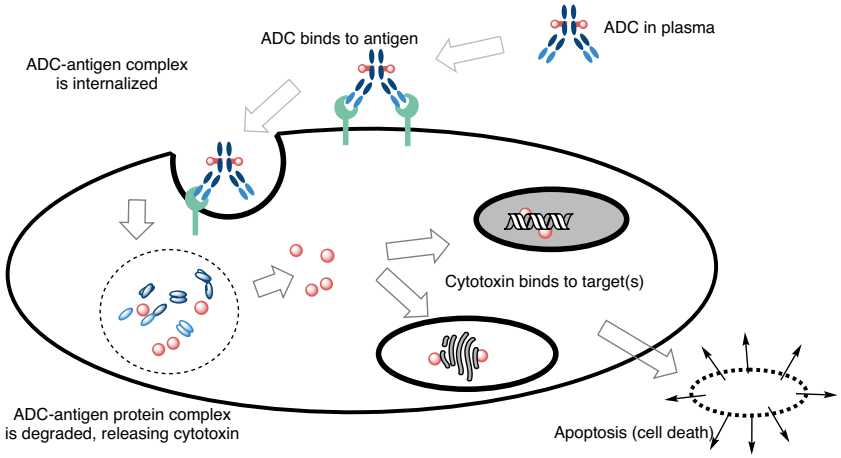

Fig. 2: Mode of action of ADCs.

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This concept is a sophisticated approach combining the high specificity of antibodies with the high potency of (small) drug molecules. The disadvantages of antibodies, like low potency, as well as the drawbacks of small drug molecules, like low specificity accompanied by high toxicity through many side effects, are compensated by the advantages of the other counterpart. A smart synergistic combination of both elements significantly enlarges the narrow therapeutic window of a small drug molecule between minimum (efficacious) and maximum (toxic) dosage (*Fig. 3*). ADC drugs expand the therapeutic window, as they can increase efficacy and decrease toxicity in comparison to traditional chemotherapeutic cancer treatments. Targeted delivery to cancer cells increases the amount of dosed drug reaching the tumor, thus lowering the minimum effective dose (MED). The MTD (maximum, highest tolerable dose without serious side effects) is increased, as less drug compound reaches healthy, non-target tissues. Historically, defining MTD was the primary objective of phase 1 oncology trials. More recently, especially for new targeted drugs (including ADCs), emphasis has been placed on determining the recommended phase 2 dose (RP2D), which better captures chronic toxicities emergent after multiple treatment cycles (e.g., edema, effusion, pneumonitis, ocular toxicities) and certain grade 2 side effects (e.g., diarrhea, mucositis, cytopenia, neuropathy, severe fatigue) that may become intolerable over time. However, interpreting small molecule and ADC doses in clinical trials requires specific interpretation and accurate conversion of the doses to a common unit and expansion of the therapeutic window needs to be discussed individually. An appreciation that ADCs do not significantly enhance the MTDs of their payloads may provide insight into several existing observations in this field, like ADCs that feature a common drug linker often encounter similar MTDs because of payload-associated platform toxicities, independent of the target antigen. This highlights that most off-target adverse events are antibody independent.

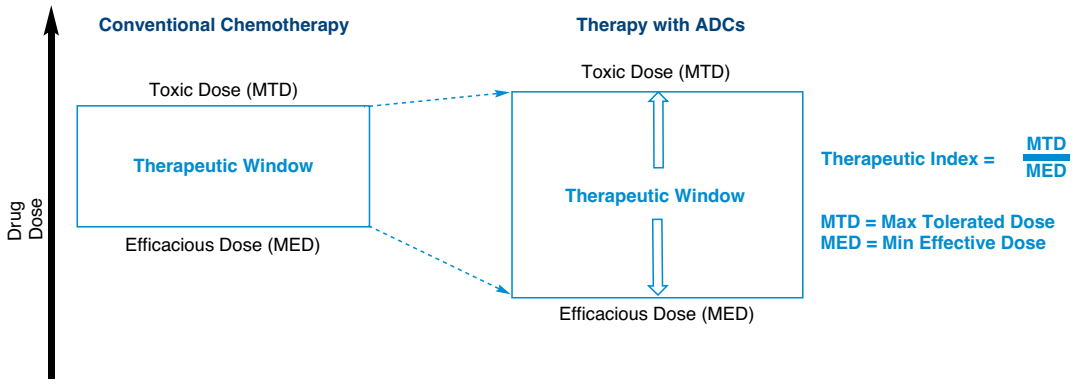

Fig. 3: The therapeutic window is significantly enlarged using ADCs compared to small-molecule drugs.

References:

- *L. Anthony, (2019). ADC Landscape Review 2019 [PowerPoint slides]. Retrieved from http://worldadc-usa.com*
- *Design and Synthesis of Tesirine, a Clinical Antibody-Drug Conjugate Pyrrolobenzodiazepine Dimer Payload; A. C. Tiberghien, J. N. Levy, L. A. Masterson, N. V. Patel, L. R. Adams, S. Corbett, D. G. Williams, J. A. Hartley, P. W. Howard;* ***ACS Med Chem Lett*** *2016;* ***7****: 983-987. https://doi.org/10.1021/acsmedchemlett.6b00062*
- *Recent advances of antibody drug conjugates for clinical applications; P. Zhao, Y. Zhang, W. Li, C. Jeanty, G. Xiang, Y. Dong;* ***Acta Pharmaceutica Sinica B*** *2020;* ***10(9)****: 1589-1600. https://doi.org/10.1016/j.apsb.2020.04.012*
- *The therapeutic window of antibody drug conjugates: A dogma in need of revision; R. Colombo, J. R. Rich;* ***Cancer Cell*** *2022; 40. https://doi.org/10.1016/j.ccell.2022.09.016*
- *Threapeutic index improvement of antibody-drug conjugates; H.-P. Gerber, S. Gangwar, A. Betts;* ***Mabs*** *2023;* ***15(1)****: 2230618. https://doi.org/10.1016/j.ccell.2022.09.016*

	USA	EU & UK	Japan	China
2011	Adcetris			
2012		Adcetris		
2013	Kadcyla	Kadcyla		
2014			Adcetris, Kadcyla	
2015				
2016				
2017	Besponsa, Mylotarc	Besponsa		
2018	Lumoxiti	Mylotarc		
2019	Enhertu, Padcev, Polivy			
2020	Blenrep, Trodelvy	Blenrep, Polivy	Akalux, Enhertu	Adcetris, Kadcyla
2021	Aidixi, Tivak, Zynlonta	Enhertu		Disitamab, Vedotin
2022	Elahere			
2023	Sacituzumab Govitecan			

Fig. 4: Global Approved ADCs (2023).

While initially only small molecules or short peptides have been used as payloads, the panel of conjugates has opened to chelators for radioactive nuclides and larger biomolecules, such as toxic enzymes. Additional variations have been introduced on the antibody side by utilizing antibody fragment combinations or diabodies (*Fig. 5*).

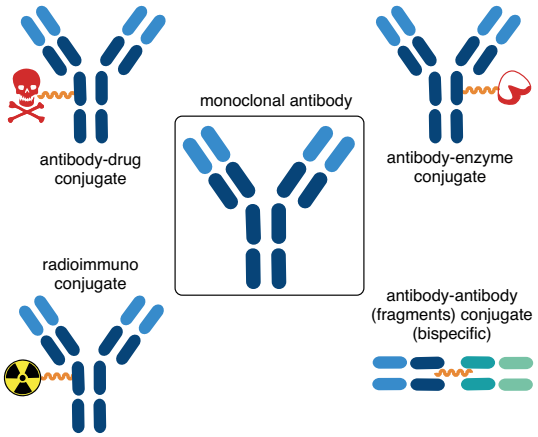

Fig. 5: The concept of antibody-drug conjugation can be extended from conjugations of small cytotoxic molecules to conjugation with chelators for radionuclides, proteins or with antibody fragments.

Points of conjugation are typically the thiol groups of cysteines, the amino functions of lysines or the N-terminus of a monoclonal antibody. Due to the inherent heterogeneity of conjugation to the multiple amines or cysteines found in mAbs, significant research efforts are directed toward the production of discrete, homogeneous ADC products *via* site-specific conjugation. This may involve genetic engineering of the mAb to introduce discrete, available cysteines or non-natural amino acids with an orthogonally reactive functional handle such as an aldehyde, ketone, azido, or alkynyl tag. These site-specific approaches increase the homogeneity of ADCs and enable novel bioorthogonal chemistries which utilize, reactive moieties rather than thiols or amines. This broad diversity of applicable linkers can then be utilized leading to improved design in future generations of ADCs.

References:

→ *Site-specific antibody drug conjugates for cancer therapy; S. Panowski, S. Bhakta, H. Raab, P. Polakis, J. R. Junutula;* ***MAbs*** *2014;* ***6****: 34-45. https://doi.org/10.4161/mabs.27022*

→ *Advances in Precision Oncology: Targeted Thorium-227 Conjugates As a New Modality in Targeted Alpha Therapy; U. B. Hagemann, K. Wickstroem, S. Hammer, R. M. Bjerke, S. Zitzmann-Kolbe, O. B. Ryan, J. Karlsson, A. Scholz, H. Hennekes, D. Mumberg , A. S. Cuthbertson;* ***Cancer Biother Radiopharm*** *2020;* ***35(7)****: 497-510. https://doi.org/10.1089/cbr.2020.3568*

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1.2. Linker Design, Connectivity, Degradability, and Drug-Antibody Ratio (DAR)

Antibody-drug conjugates (ADCs), which combine the specificity, favorable pharmacokinetics, and biodistribution of a monoclonal antibody (mAb) with the cytotoxic potency of a drug are promising new therapeutics for cancer. Along with the development of monoclonal antibodies (mAbs) and cytotoxic drugs, the design of the linker is essential, as it impacts the efficacy and tolerability of ADCs. The linker needs to provide sufficient stability during systemic circulation while providing rapid and efficient release of the cytotoxic drug in its active state inside the tumor cells.

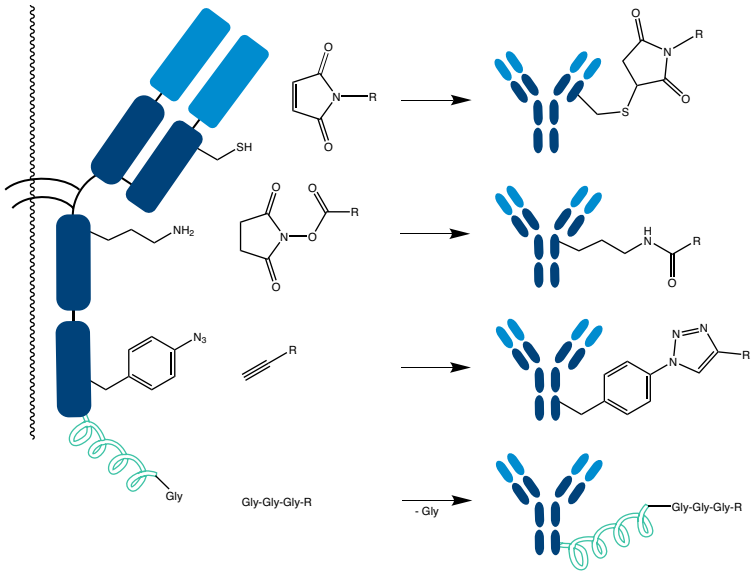

Fig. 6: Thiols form cysteines, amines from lysines, azido functions from non-canonical amino acids and specific sequences accessible on the surface of antibodies can be addressed by different chemical or enzymatical conjugation methodologies.

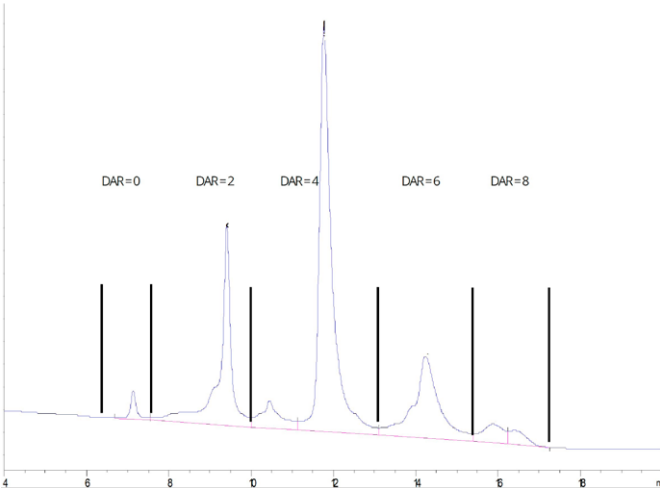

Fig. 7: Drug-antibody ratio (DAR) is an important parameter of an ADC. Low DAR could reduce the antitumor efficacy, while high DAR may affect antibody structure, stability, and antigen binding etc. therefore causing loss of activity. DAR values are also important for the therapeutic index of ADCs. In most ADC drug candidates, the DAR values were maintained at about 2-4. Hence, controlling DAR during ADC preparation is a key procedure. Figure provided by Glycotope.

The type of linkage between payload and biomolecule can basically either be permanent or cleavable under certain well-defined circumstances (*Fig. 6*). As payloads typically are highly cytotoxic, it would be fatal if they were released from their carrier during circulation in plasma. Hence, the linker part should be stable to conditions such as pH, redox potential, presence of proteases in plasma, and all other parameters of plasma. However, after internalization it is favorable that the linker is fragmenting in order to release the drug molecule, ideally in a traceless manner. Conjugations with the antibody can rather easily be achieved using active esters forming amide bonds with lysines, which are usually accessible in a high number on the surface. The resulting conjugate, hence, is rather heterogenic with different numbers of payloads attached at different positions. A more and well-defined drug-antibody ratio (DAR) can be achieved by utilizing the disulfide bridges between heavy and light chains of the antibody.

After reductive cleavage of the disulfide bonds, conjugation chemistry can be performed by different kinds of reactions like conventional maleimides or disulfide bond formation. Heterogeneity can be observed if heavy and light antibody chains do not recombine in the original manner.

A highly accurate and specific DAR with well-defined connectivity can be achieved, if unnatural amino acids, e.g., *p*-azidophenylalanine, can be introduced recombinantly. Click chemistry or other Diels-Alder type reactions can be used to introduce linkers and payloads. In a similar manner, certain peptide fragments can be added, which serve as substrates for ligases in order to conjugate to appropriate linker-payload conjugates.

References:

- *Linker Technologies for Antibody–Drug Conjugates; B. Nolting;* ***Antibody-Drug Conjugates L. Ducry*** *2013;* ***1045****: 71-100. https://doi.org/10.1007/978-1-62703-541-5_5*
- *In Vivo Applications of Bioorthogonal Reactions: Chemistry and Targeting Mechanisms; M. M. A. Mitry, F. Greco, H. M. I. Osborn;* ***Chemistry*** *2023; n/a: e202203942. https://doi.org/10.1002/chem.202203942*

Cleavage Mechanisms

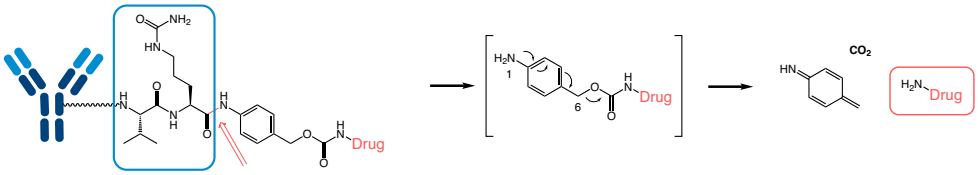

Fig. 8: Valyl-citrullyl dipeptide fragment serves as substrate for cathepsin and suffers cleavage by hydrolysis leading to a 1,6-elimination with fragmentation and traceless release of the drug molecule.

An ADC travels through plasma until it reaches the target cell. After internalization, the complex degrades and releases the payload even with a stable linker. However, release can be accelerated through implementation of moieties which fragmentize under certain conditions. One of the most commonly used spacers is the bifunctional *p*-aminobenzyl alcohol group, which is linked to the peptide through the amino group forming an amide bond, while amine containing cytotoxic drugs are attached through carbamate functionalities to the benzylic hydroxyl group of the linker. The resulting prodrugs are activated upon protease mediated hydrolysis and cleavage of the amide bond of citrulline to the *p*-aminobenzyl fragment, leading to a 1,6-elimination reaction releasing the unmodified drug, carbon dioxide, and remnants of the linker group (*Fig. 8*, *Fig. 9*).

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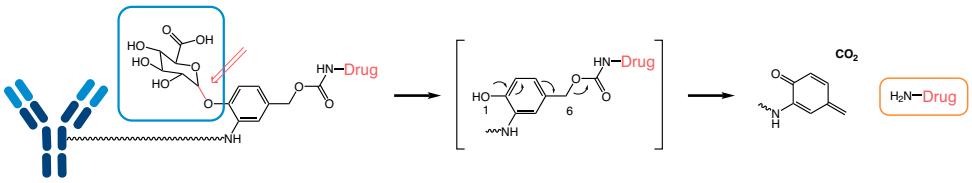


Fig. 9: Glucuronic acid capped p-aminobenzyl will be cleaved by glucuronidases resulting in 1,6-elmination, fragmentation, and traceless release of the drug molecule.

In an extension of the peptide-based linker strategies to provide high ADC stability, β-glucuronic acid-based linkers were developed. Facile release of the active drug is realized through cleavage of the β-glucuronide glycosidic bond by the lysosomal enzyme β-glucuronidase. This enzyme is abundantly present in lysosomes and overexpressed in some tumor types, while its activity outside cells is low. The linker is hydrophilic, stable against circulation, and provides ADCs that are highly active both *in vitro* and *in vivo*.

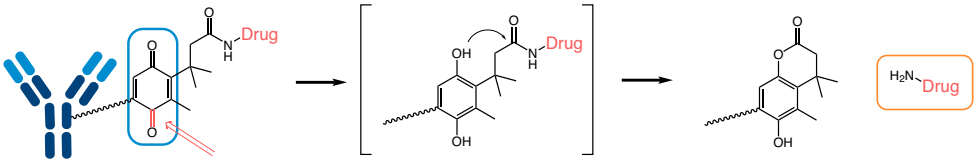


Fig. 10: Chinoidic variations of trimethyl locks are reduced to the corresponding diphenol followed by traceless release of a drug molecule via lacton formation.

Besides hydrolases, the presence of oxidoreductases in the lysosome is being utilized for the design of cleavable linkers. Cytochrome P450 oxidoreductase (CPR), nitroquinone oxidoreductase 1 (NQO1), and cellular reductants such as glutathione (GSH) transform reducible fragments like chinone or disulfide to self-immolative intermediates.

Trimethyl Lock

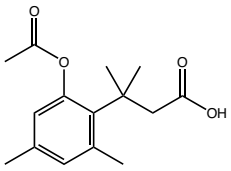
The sterical demand of three closely positioned methyl groups (*Fig. 10*) favors the cleavage of a carbonyl bond by lacton formation. The acidity of the phenol is sufficient to accelerate lactonization at neutral pH and any residue carrying a hydroxyl or amino function will be unlocked, i.e. tracelessly released. The hydroxy group of phenol can be protected and released by a variety of methodologies. This reaction usually requires no elevated temperature. Hence, it will work nicely at physiological conditions.

Product details

RL-2960 Acetyl-Trimethyl-Lock

3-(2-Acetoxy-4,6-dimethylphenyl)-3-methylbutyric acid

CAS-No.	134098-68-3
Formula	$C_{15}H_{20}O_4$
Mol. weight	264,14 g/mol

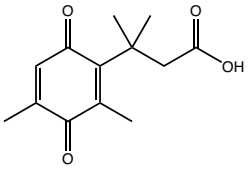


Product details

RL-2950 Fourmethyl-Lock

3-(2,4-dimethyl-3,6-dioxocyclohexa-1,4-dienyl)-3-methylbutanoic acid

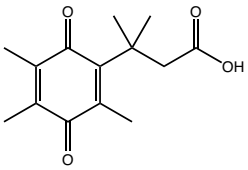
CAS-No.	133544-77-1
Formula	$C_{13}H_{16}O_4$
Mol. weight	236,26 g/mol



RL-2940 Fivemethyl-Lock

3-methyl-3-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanoic acid

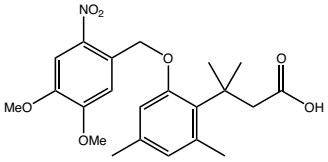
CAS-No.	40662-29-1
Formula	$C_{14}H_{18}O_4$
Mol. weight	250,29 g/mol



RL-2970 Photo-Trimethyl-Lock

3-(2-Nitroveratryl-4,6-dimethylphenyl)-3-methylbutyric acid

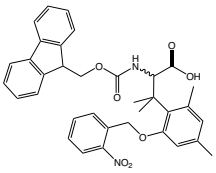
CAS-No.	2095134-25-9
Formula	$C_{22}H_{27}NO_7$
Mol. weight	417,45 g/mol



FAA7190 Fmoc-Spr(oNB)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-beta,beta-dimethyl-(2,4-dimethyl-6-(2-nitrobenzyloxy)phenyl) alanine (rac.)

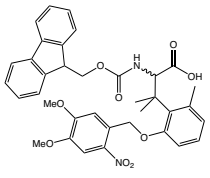
CAS-No.	1032400-98-8
Formula	$C_{35}H_{34}N_2O_7$
Mol. weight	594,66 g/mol



FAA7200 Fmoc-Spr(oNv)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-beta,beta-dimethyl-(2-methyl-6-(2-nitroveratryl)phenyl)alanine (rac.)

CAS-No.	1228829-20-6
Formula	$C_{36}H_{36}N_2O_9$
Mol. weight	640,68 g/mol



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- *Invention of stimulus-responsive peptide-bond-cleaving residue (Spr) and its application to chemical biology tools; A. Shigenaga, J. Yamamoto, T. Kohiki, T. Inokuma, A. Otaka;* ***J Pept Sci*** *2017;* ***23****: 505-513. https://doi.org/10.1002/psc.2961*
- *Trimethyl Lock: A Multifunctional Molecular Tool for Drug Delivery, Cellular Imaging, and Stimuli-Responsive Materials; O. A. Okoh, P. Klahn;* ***ChemBioChem*** *2018;* ***19****: 1668-1694. https://doi.org/10.1002/cbic.201800269*

Disulfide Linkers

Disulfide linkers (*Fig. 11*) are likely first degraded in the lysosome to generate a cysteine-disulfide catabolite followed by disulfide reduction in the cytosol by cellular reductants such as GSH. The kinetics of reduction can be tailored by neighboring one to four methyl groups next to both sulfurs.

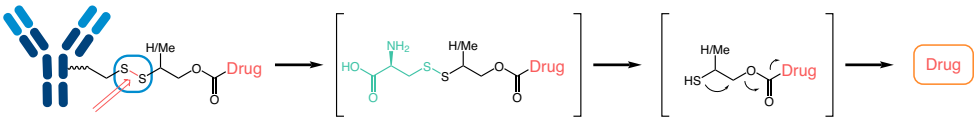

Fig. 11: Mechanism of disulfide bond cleavage in lysosomal compartments.

References:

- *Modulating Therapeutic Activity and Toxicity of Pyrrolobenzodiazepine Antibody-Drug Conjugates with Self-Immolative Disulfide Linkers; T. H. Pillow, M. Schutten, S. F. Yu, R. Ohri, J. Sadowsky, K. A. Poon, W. Solis, F. Zhong, G. Del Rosario, M. A. T. Go, J. Lau, S. Yee, J. He, L. Liu, C. Ng, K. Xu, D. D. Leipold, A. V. Kamath, D. Zhang, L. Masterson, S. J. Gregson, P. W. Howard, F. Fang, J. Chen, J. Gunzner-Toste, K. K. Kozak, S. Spencer, P. Polakis, A. G. Polson, J. A. Flygare, J. R. Junutula;* ***Mol. Cancer. Ther.*** *2017;* ***16****: 871-878. https://doi.org/10.1158/1535-7163.MCT-16-0641*
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Multiple Payloads with one self-immolative Linker

p-Hydroxy- and *p*-amino-benzyl fragments will release payloads by a 1,6-elimination cascade, resulting in chinoide intermediates. Under physiological conditions, they readily add water to reform the aromatic ring structure. In case appropriate carbamate substitutions are also placed on position 2 and 2', a fragmentation will occur in a similar manner as by a 1,4-elimination and release any molecules at these positions (*Fig. 12*).

One of the major challenges related to anticancer chemotherapy is resistance against anticancer drugs. A strategy to revert the resistance of tumor cells is the combined use of different anticancer drugs.

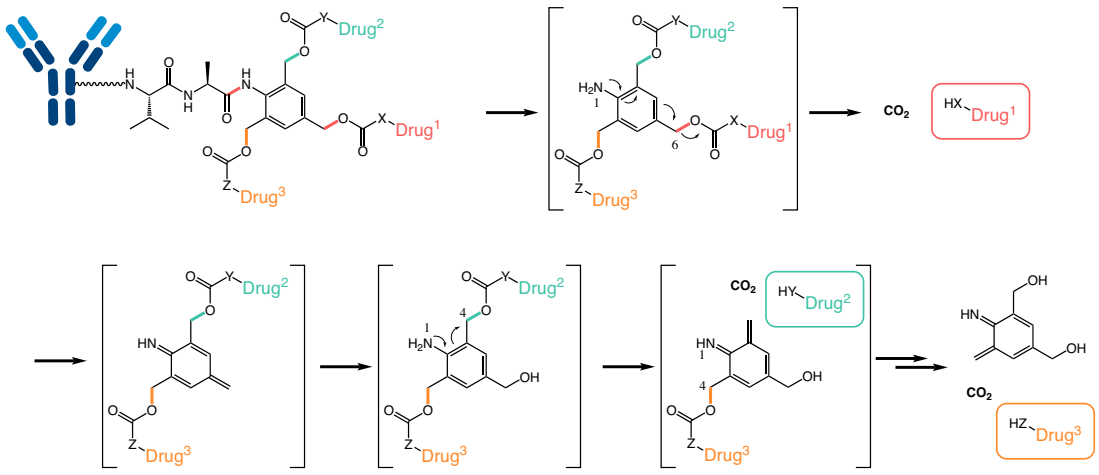

Fig. 12: Mechanism of multiple traceless release.

References:

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- *The azaquinone-methide elimination: comparison study of 1,6- and 1,4-eliminations under physiological conditions; R. Erez, D. Shabat; **Org Biomol Chem** 2008; **6**: 2669-72. https://doi.org/10.1039/b808198k*
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It has been reported that payload release can be supported by introducing a *N,N'*-dimethylethane-1,2-diamine bridge between carbamate and payload. After release of carbon dioxide, it will cyclize and form 1,3-dimethylimidazolidin-2-one and liberate the payload from the linker construction (*Fig. 13*).

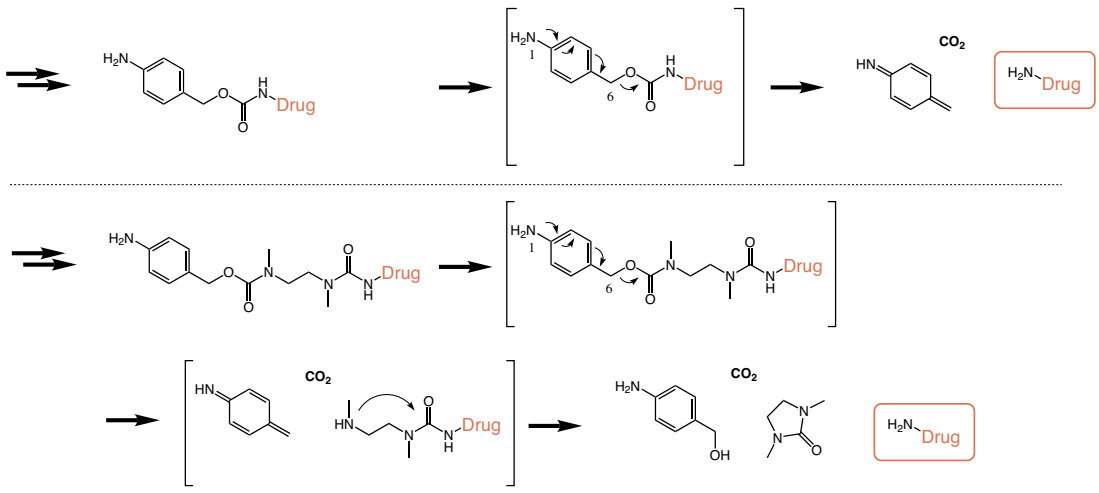

Fig. 13: Mechanism of assisted traceless release by N,N'-dimethylethane-1,2-diamine.

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Besides the benzyl system, other moieties have been used for fragmentation reactions. In *Fig. 14* different methods are summarized, which have been studied and published. PG is the protecting group and LG the leaving group belonging to the payload to be released. X needs to be a strong electron-donating group, such as O, X or NH, in order to initiate the elimination cascade. While the 1,6-elimination of a benzyl system tends to be the most common system, *ortho*-benzyl undergoing a 1,4-elimination can alternatively be used, as well as styrene fragments (1,8-elimination). However, neither naphthalene rings nor biphenyl structures (1,10-elimination) work, even with a strongly donating amino group.

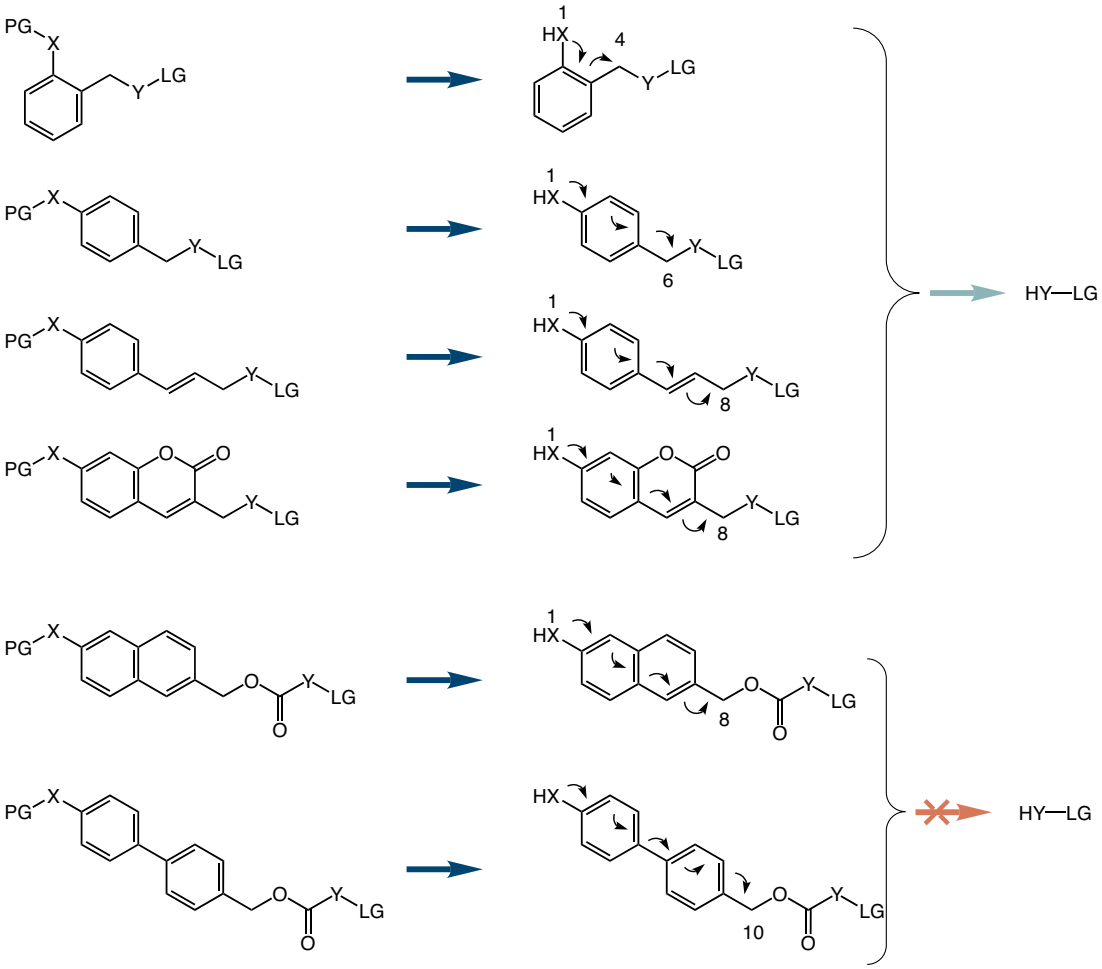

Fig. 14: Possible fragments enabling traceless release of payloads.

References:

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→ *Cleavable linkers in chemical biology; G. Leriche, L. Chisholm, A. Wagner;* ***Bioorg Med Chem*** *2012;* ***20****: 571-82. https://doi.org/10.1016/j.bmc.2011.07.048*

Dioxoborolane Cross-Linker:

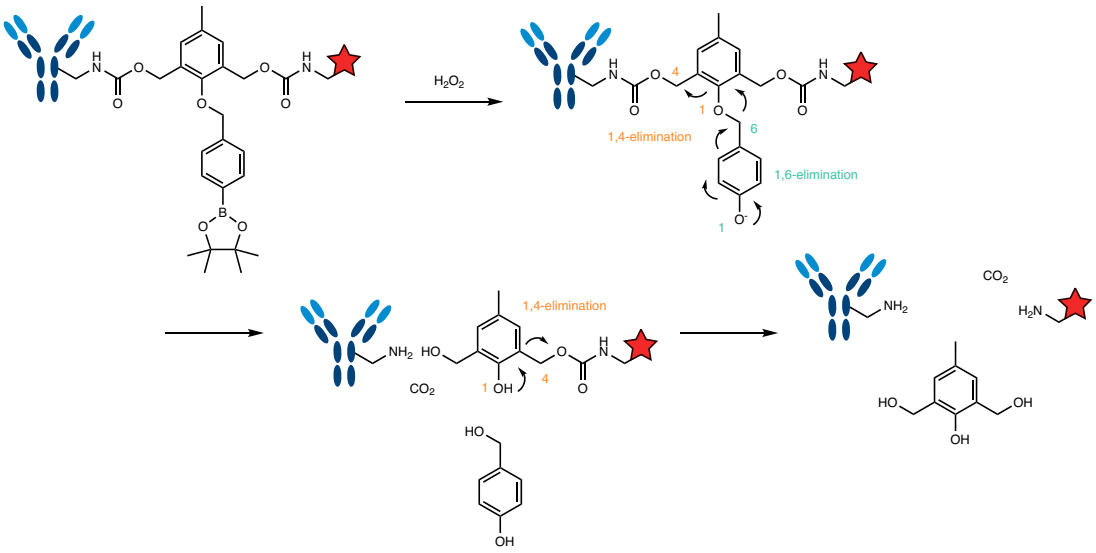


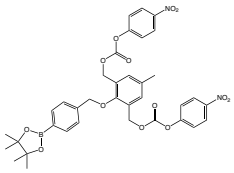
Fig. 15: Tetramethyldioxoborolane cross-linker fragmentize in the presence of H_2O_2.

Tetramethyldioxoborolane linkers are used as cross-linkers or masking protecting groups of alcohols or amines. They release their payloads under mild oxidative conditions, as it is in the presence of H_2O_2. Oxidation initially creates a free phenolate which triggers an initial 1,6-elimination. The second step in this cascade is a 1,4-elimination, followed by a fragmentation under release of the first conjugate. A second 1,4-elimination follows releasing the second conjugated compound. Such moieties are for example being used for the preparation of masked H_2O_2 probes releasing their active fluorophore upon trigger detection. Another application is the generation of liposomes, which disrupt upon H_2O_2 detection and then release the active cargo. Peptides bearing two lysines can be cyclized and masked inactive *via* such a borolane cross-linker. Activity of the bioactive peptide will be restored, if H_2O_2 is present in the tissue environment.

	Product details

RL-4140 TetraMe-Dioxoborolane-(OpNC)$_2$

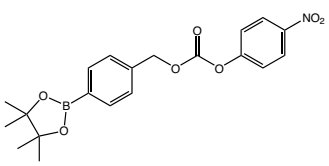
(5-methyl-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)oxy)-1,3-phenylene)bis(methylene) bis(4-nitrophenyl) bis(carbonate)



CAS-No.	1355342-68-5
Formula	$C_{36}H_{35}BN_2O_{13}$
Mol. weight	714,49 g/mol

RL-4130 TetraMe-Dioxoborolane-OpNC

4-Nitrophenyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl carbonate



CAS-No.	1254765-89-3
Formula	$C_{20}H_{22}BNO_7$
Mol. weight	399,21 g/mol

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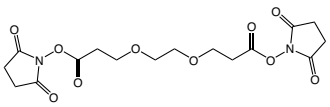
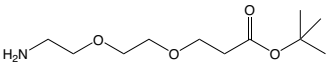
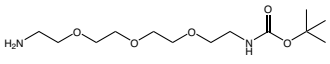
2. Permanent Linkers

2.1. PEG-Based Spacer Molecules

This class of linkers is considered non-cleavable, meaning linker cleavage and payload release do not depend on the differential properties between plasma and cytoplasmic compartments. Instead, the release of the cytotoxic drug is postulated to occur after internalization of the ADC *via* antigen-mediated endocytosis and delivery to lysosomal compartments, where the antibody is degraded to the level of amino acids through intracellular proteolytic degradation. This process releases a drug derivative, formed by the cytotoxic drug, the linker, and the amino acid residue to which the linker was covalently attached.

The following section displays examples of hetero-bifunctional PEG-based spacer molecules. As payloads are quite often rather hydrophobic, PEG fragments help to solubilize the linker-payload conjugate, which is essential to perform successful conjugation to the antibody. It further helps to increase the solubility in physiological media and to improve the pharmacokinetic properties of the whole ADC construct.

Two of the latest approved ADCs, Trodelvy and Zynlonta, were developed with PEG spacers as part of their linkers to improve solubility and stability *in vivo*.

		Product details
PEG4120 NHS-PEG(2)-NHS 3,6-Dioxaoctandioic acid bissuccinimidyl ester CAS-No. 65869-63-8 Formula $C_{16}H_{20}N_2O_{10}$ Mol. weight 400,34 g/mol		
PEG1365 H_2N-PEG(2)-CO-O*t*Bu 3-(2-(2-Aminoethoxy)ethoxy)propanoic acid *t*-butyl ester CAS-No. 756525-95-8 Formula $C_{11}H_{23}NO_4$ Mol. weight 233,3 g/mol		
PEG6835 Boc-NH-PEG(3)-NH_2*HCl *tert*-butyl (2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)carbamate CAS-No. 101187-40-0 net Formula $C_{13}H_{28}N_2O_5$*HCl Mol. weight 292,38*36,46 g/mol		

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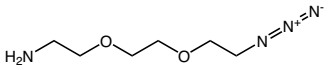
Product details

PEG4980 H_2N-PEG(2)-N_3*TosOH

2-[2-(2-Azidoethoxy)ethoxy]ethanaminium tosylat

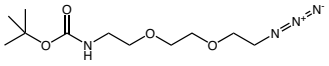
CAS-No.	2173092-98-1
Formula	$C_7H_{14}N_4O_2$*$C_7H_8O_3S$
Mol. weight	174,20*172,20 g/mol



PEG4960 Boc-NH-PEG(2)-N_3

1-(*t*-Butyloxycarbonyl-amino)-3,6-dioxa-8-octaneazide

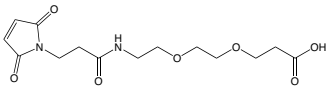
CAS-No.	950683-55-3
Formula	$C_{11}H_{22}N_4O_4$
Mol. weight	274,32 g/mol



PEG1555 mal-PEG(2)-COOH

3-(2-(2-(3-Maleimidopropanamido)ethoxy)ethoxy) propanoic acid

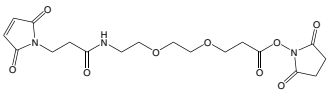
CAS-No.	756525-98-1
Formula	$C_{14}H_{20}N_2O_7$
Mol. weight	328,32 g/mol



PEG1560 mal-PEG(2)-NHS

3-(2-(2-(3-Maleimidopropanamido)ethoxy)ethoxy) propanoic acid succinimidyl ester

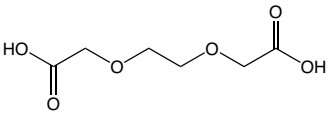
CAS-No.	955094-26-5
Formula	$C_{18}H_{23}N_3O_9$
Mol. weight	425,39 g/mol



PEG2035 DOODA

3,6-Dioxaoctanedioic acid

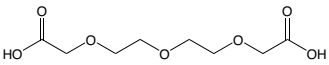
CAS-No.	23243-68-7
Formula	$C_6H_{10}O_6$
Mol. weight	178,14 g/mol



PEG2030 TUDA

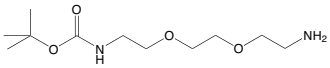
3,6,9-Trioxaundecandioic acid

CAS-No.	13887-98-4
Formula	$C_8H_{14}O_7$
Mol. weight	222,19 g/mol



BNN1016 Boc-DOOA

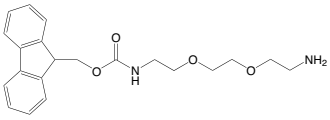
1-(*t*-Butyloxycarbonyl-amino)-3,6-dioxa-8-octaneamine, liq.



CAS-No.	153086-78-3
Formula	$C_{11}H_{24}N_2O_4$
Mol. weight	248,32 g/mol

FNN1007 Fmoc-DOOA*HCl

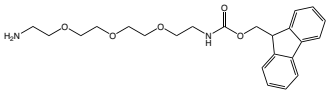
1-(9-Fluorenylmethyloxycarbonyl-amino)-3,6-dioxa-8-octaneamine hydrochloride



CAS-No.	868599-73-9
Formula	$C_{21}H_{26}N_2O_4$*HCl
Mol. weight	370,45*36,45 g/mol

RL-4390 Fmoc-NH-PEG(3)-NH_2*HCl

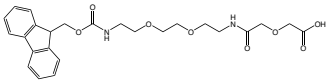
(9H-fluoren-9-yl)methyl (2-(2-(2-(2-aminoethoxy) ethoxy)ethoxy)ethyl)carbamate hydrochloride



CAS-No.	906079-91-2
Formula	$C_{23}H_{30}N_2O_5$*HCl
Mol. weight	414,50*36,45 g/mol

PEG5180 Fmoc-DOOA-DIG-OH

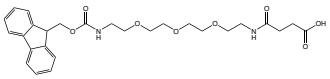
2-(2-(2-(2-((9-Fluorenylmethyloxycarbonyl)amino) ethoxy)ethoxy)ethylamino)-diglycolic acid



CAS-No.	669073-64-7
Formula	$C_{25}H_{30}N_2O_8$
Mol. weight	486,51 g/mol

RL-4400 Fmoc-NH-PEG(3)-NH-Suc-OH

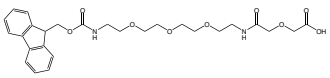
1-(9H-fluoren-9-yl)-3,17-dioxo-2,7,10,13-tetraoxa-4,16-diazaicosan-20-oic acid



CAS-No.	1653992-32-5
Formula	$C_{27}H_{34}N_2O_8$
Mol. weight	514,57 g/mol

RL-4410 Fmoc-NH-PEG(3)-DIG-OH

1-(9H-fluoren-9-yl)-3,17-dioxo-2,7,10,13,19-pentaoxa-4,16-diazahenicosan-21-oic acid



CAS-No.	489427-26-1
Formula	$C_{27}H_{34}N_2O_9$
Mol. weight	530,57 g/mol

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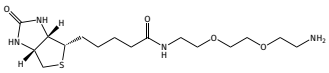
Product details

RL-4060 Biotin-DOOA

Biotinyl-1-amino-3,6-dioxa-8-octanamine

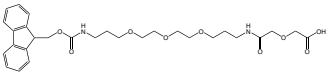
CAS-No. 138529-46-1
Formula $C_{16}H_{30}N_4O_4S$
Mol. weight 374,50 g/mol



FAA5730 Fmoc-TTD-DIG-OH

[N1-(9-Fluorenylmethoxycarbonyl)-1,13-diamino-4,7,10-trioxatridecan-diglycolic acid

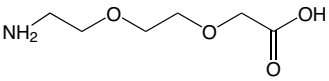
CAS-No. 916585-44-9
Formula $C_{29}H_{38}N_2O_9$
Mol. weight 558,62 g/mol



PEG2420 H-O_2Oc-OH

[2-(2-aminoethoxy)ethoxy]acetic acid

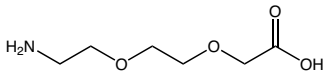
CAS-No. 134978-97-5
Formula $C_6H_{13}NO_4$
Mol. weight 163,17 g/mol



PEG7940 H-O_2Oc-OH*HCl

8-amino-3,6-dioxaoctanoic acid hydrochloride

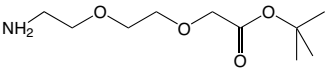
CAS-No. 134979-01-4
Formula $C_6H_{13}NO_4$*HCl
Mol. weight 163,17*36,45 g/mol



PEG2430 H-O_2Oc-O*t*Bu*HCl

[2-(2-aminoethoxy)ethoxy]acetic acid *tert*-butyl ester*HCl

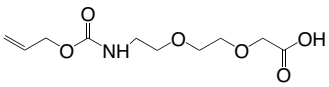
CAS-No. 2098500-69-5
Formula $C_{10}H_{21}NO_4$*HCl
Mol. weight 219,28*36,45 g/mol



AAA1905 Aloc-O_2Oc-OH*DCHA

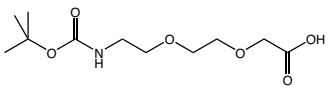
8-(Allyloxycarbonyl-amino)-3,6-dioxaoctanoic acid dicyclohexylamine

CAS-No. 560088-74-6
Formula $C_{10}H_{17}NO_6$*$C_{12}H_{23}N$
Mol. weight 247,11*181,32 g/mol



PEG8080 Boc-O_2Oc-OH

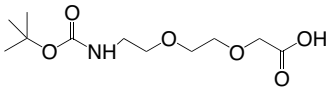
(2-(2-(*t*-Butyloxycarbonylamino)ethoxy)ethoxy)acetic acid



CAS-No.	108466-89-3
Formula	$C_{11}H_{21}NO_6$
Mol. weight	263,29 g/mol

BAA1466 Boc-O_2Oc-OH*DCHA

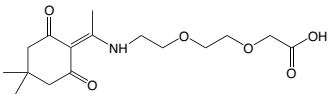
8-(*t*-Butyloxycarbonyl-amino)-3,6-dioxaoctanoic acid dicyclohexylammonium salt



CAS-No.	560088-79-1
Formula	$C_{11}H_{21}NO_6$*$C_{12}H_{23}N$
Mol. weight	263,29*181,32 g/mol

DAA1016 Dde-O_2Oc-OH

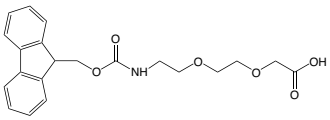
8-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-amino]-3,6-dioxaoctanoic acid, {2-[2-(Dde-amino) ethoxy]ethoxy}acetic acid



CAS-No.	1263045-93-7
Formula	$C_{16}H_{25}NO_6$
Mol. weight	327,37 g/mol

FAA1435 Fmoc-O_2Oc-OH

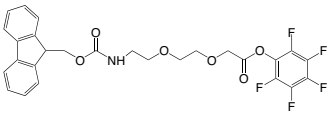
8-(9-Fluorenylmethyloxycarbonyl-amino)-3,6-dioxaoctanoic acid



CAS-No.	166108-71-0
Formula	$C_{21}H_{23}NO_6$
Mol. weight	385,42 g/mol

FAA6020 Fmoc-O_2Oc-PFP

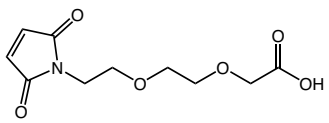
8-(9-Fluorenylmethyloxycarbonyl-amino)-3,6-dioxaoctanoic acid pentafluorophenyl ester



CAS-No.	1263044-39-8
Formula	$C_{27}H_{22}F_5NO_6$
Mol. weight	551,5 g/mol

PEG4870 Mal-O_2Oc-OH

{2-[2-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethoxy] ethoxy}acetic acid



CAS-No.	173323-23-4
Formula	$C_{10}H_{13}NO_6$
Mol. weight	243,21 g/mol

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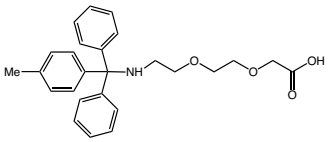
Product details

PEG4650 Mtt-O_2Oc-OH*DEA

N-(4-Methyltrity)-8-amino-3,6-dioxaoctanoic acid diethylamine

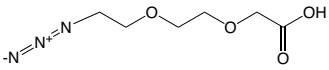
CAS-No.	2098500-66-2
Formula	$C_{26}H_{29}NO_4$*$C_4H_{11}N$
Mol. weight	419,51*73,14 g/mol



PEG2780 N_3-O_2Oc-OH*CHA

[2-(2-azidoethoxy)ethoxy]acetic acid cyclohexylamine salt

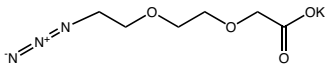
CAS-No.	2098500-94-6
Formula	$C_6H_{11}N_3O_4$*$C_6H_{13}N$
Mol. weight	189,17*99,17 g/mol



PEG7950 N_3-AEEA-OK

Potassium 8-azido-3,6-dioxaoctanoate

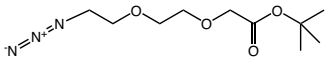
CAS-No.	882518-90-3 net
Formula	$C_6H_{10}KN_3O_4$
Mol. weight	39,10*188,16 g/mol



PEG5390 N_3-O_2Oc-O*t*Bu

8-Azido-3,6-dioxaoctanoic acid *t*-butyl ester

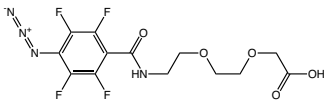
CAS-No.	251564-45-1
Formula	$C_{10}H_{19}N_3O_4$
Mol. weight	245,28 g/mol



PEG5000 N_3-TFBA-O_2Oc

{2-[2-(4-Azido-2,3,5,6-tetrafluorobenzoyl-amino)ethoxy] ethoxy}acetic acid

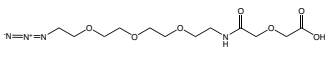
CAS-No.	1993119-45-1
Formula	$C_{13}H_{12}F_4N_4O_5$
Mol. weight	380,25 g/mol



RL-4370 N_3-PEG(3)-NH-DIG-OH

Diglycolic acid PEG3 azide

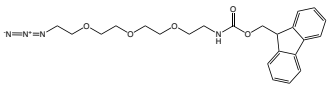
CAS-No.	239081-53-9
Formula	$C_{12}H_{22}N_4O_7$
Mol. weight	334,33 g/mol



Product details

RL-4380 Fmoc-NH-PEG(3)-N_3

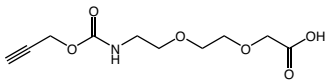
(9H-fluoren-9-yl)methyl (2-(2-(2-(2-azidoethoxy)ethoxy) ethoxy)ethyl)carbamate



CAS-No.	1172605-58-1
Formula	$C_{23}H_{28}N_4O_5$
Mol. weight	440,50 g/mol

PAA1050 Poc-O_2Oc-OH*DCHA

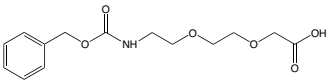
8-(Popargylyloxycarbonyl-amino)-3,6-dioxaoctanoic acid dicyclohexylamine



Formula	$C_{10}H_{15}NO_6$*$C_{12}H_{23}N$
Mol. weight	245,23*181,32 g/mol

ZAA1186 Z-O_2Oc-OH*DCHA

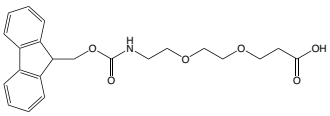
8-(Benzyloxycarbonyl-amino)-3,6-dioxaoctanoic acid dicyclohexylamine



CAS-No.	560088-84-8
Formula	$C_{14}H_{19}NO_6$*$C_{12}H_{23}N$
Mol. weight	297,31*181,32 g/mol

PEG1810 Fmoc-AEEP

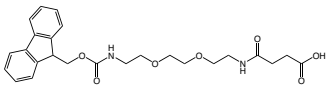
3-(2-(2-(9-Fluorenylmethyloxycarbonyl)aminoethoxy) ethoxy)propanoic acid



CAS-No.	872679-70-4
Formula	$C_{22}H_{25}NO_6$
Mol. weight	399,44 g/mol

PEG4970 Fmoc-Ebes

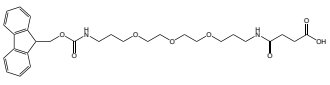
N-[8-(9-Fluorenylmethyloxycarbonyl)amino-3,6-di-oxaoctyl]succinamic acid



CAS-No.	613245-91-3
Formula	$C_{25}H_{30}N_2O_7$
Mol. weight	470,51 g/mol

FAA1568 Fmoc-TTDS-OH

[N1-(9-Fluorenylmethoxycarbonyl)-1,13-diami-no-4,7,10-trioxatridecan-succinamic acid



CAS-No.	172089-14-4
Formula	$C_{29}H_{38}N_2O_8$
Mol. weight	542,63 g/mol

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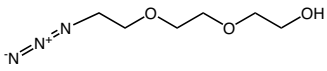
Product details

PEG4900 N_3-EEEt-OH

2-[2-(2-Azidoethoxy)ethoxy]ethanol

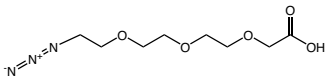
CAS-No.	86520-52-7
Formula	$C_6H_{13}N_3O_3$
Mol. weight	175,19 g/mol



PEG5400 N_3-AEEEA*CHA

11-Azido-3,6,9-trioxaundecanoic acid cyclohexylamine

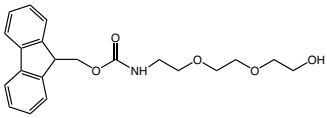
CAS-No.	172531-37-2 net
Formula	$C_8H_{15}N_3O_5$*$C_6H_{13}N$
Mol. weight	233,22*99,17 g/mol



PEG5370 Fmoc-AEEE

2-(2-(2-(9-Fluorenylmethyloxycarbonyl)aminoethoxy) ethoxy)ethanol

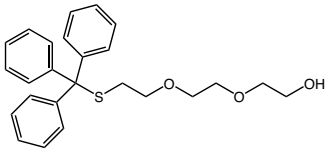
CAS-No.	560088-66-6
Formula	$C_{21}H_{25}NO_5$
Mol. weight	371,43 g/mol



PEG7010 Trt-S-EEE

S-Trityl-2-(2-(2-mercaptoethoxy)ethoxy)ethanol

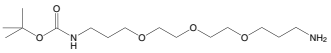
CAS-No.	728033-15-6
Formula	$C_{25}H_{28}O_3S$
Mol. weight	408,55 g/mol



BNN1028 Boc-TOTA

1-(*t*-Butyloxycarbonyl-amino)-4,7,10-trioxa-13-tri-decanamine, liq.

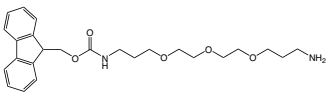
CAS-No.	194920-62-2
Formula	$C_{15}H_{32}N_2O_5$
Mol. weight	320,43 g/mol



FNN1011 Fmoc-TOTA*HCl

1-(9-Fluorenylmethyloxycarbonyl-amino)-4,7,10-tri-oxa-13-tridecanamine hydrochloride

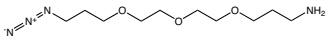
CAS-No.	868599-75-1
Formula	$C_{25}H_{34}N_2O_5$*HCl
Mol. weight	442,56*36,45 g/mol



Product details

BNN1150 N_3-TOTA

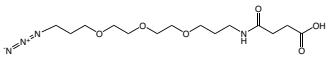
1-Azido-4,7,10-trioxa-13-tridecanamine



CAS-No. 1162336-72-2
Formula $C_{10}H_{22}N_4O_3$
Mol. weight 246,31 g/mol

PEG5170 N_3-TOTA-Suc

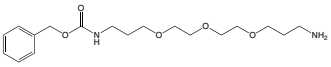
1-Azido-4,7,10-trioxa-13-tridecaneamine succinamic acid



CAS-No. 1993176-74-1
Formula $C_{14}H_{26}N_4O_6$
Mol. weight 346,38 g/mol

PEG1745 Z-TOTA

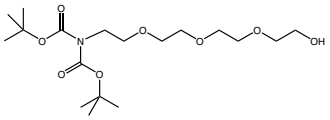
1-Benzyloxycarbonyl-4,7,10-trioxa-13-tridecaneamine



CAS-No. 220156-99-0
Formula $C_{18}H_{30}N_2O_5$
Mol. weight 354,44 g/mol

PEG7860 Boc2-AEEEE

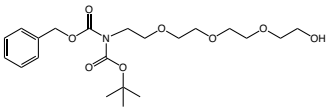
2-(2-(2-(2-(Di-(*t*-butylmethyloxycarbonyl))aminoethoxy) ethoxy)ethoxy)ethanol



CAS-No. 2389064-37-1
Formula $C_{18}H_{35}NO_8$
Mol. weight 393,47 g/mol

PEG5385 Boc,Z-AEEEE

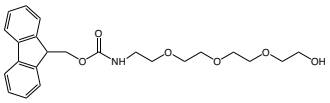
2-(2-(2-(2-(Benzyloxycarbonyl-*tert*-Butylmethyloxycarbonyl)aminoethoxy)ethoxy)ethoxy)ethanol



CAS-No. 2389064-46-2
Formula $C_{21}H_{33}NO_8$
Mol. weight 427,49 g/mol

PEG5380 Fmoc-AEEEE

2-(2-(2-(2-(9-Fluorenylmethyloxycarbonyl)aminoethoxy)ethoxy)ethoxy)ethanol



CAS-No. 868594-41-6
Formula $C_{23}H_{29}NO_6$
Mol. weight 415,48 g/mol

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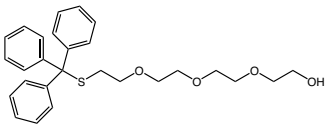
Product details

PEG6730 Trt-S-EEEE

S-Trityl-2-(2-(2-(2-mercaptoethoxy)ethoxy)ethoxy) ethanol

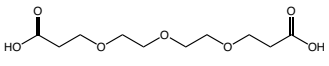
CAS-No. 125607-10-5
Formula $C_{27}H_{32}O_4S$
Mol. weight 452,61 g/mol



PEG4875 HOOC-dPEG™(3)-COOH

Diethyleneglycol-bis(propionic acid)

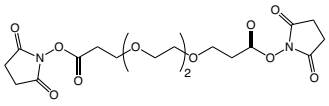
CAS-No. 96517-92-9
Formula $C_{10}H_{18}O_7$
Mol. weight 250,25 g/mol



PEG4130 NHS-PEG(3)-NHS

3,6,9-Trioxaundecandioic acid bissuccinimidyl ester

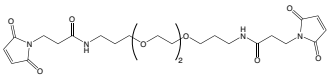
CAS-No. 1314378-16-9
Formula $C_{18}H_{24}N_2O_{11}$
Mol. weight 444,39 g/mol



PEG1485 mal-dPEG(3)-mal

Bis-(1,13-(3-maleimidopropionyl)amido)-4,7,10-trioxatridecane

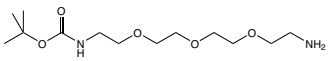
CAS-No. 756525-89-0
Formula $C_{24}H_{34}N_4O_9$
Mol. weight 522,55 g/mol



PEG7870 Boc-NH-PEG(3)-NH_2

1-(*t*-Butyloxycarbonyl)amino-3,6,9-trioxa-undecan-11-amine

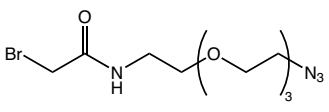
CAS-No. 101187-40-0
Formula $C_{13}H_{28}N_2O_5$
Mol. weight 292,37 g/mol



PEG7190 Bromoacetamido-PEG(3)-N_3

Bromoacetamido-tri(ethylene glycol)-azide

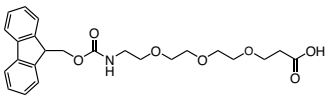
CAS-No. 940005-81-2
Formula $C_{10}H_{19}BrN_4O_4$
Mol. weight 339,19 g/mol



Product details

PEG4370 Fmoc-NH-PEG(3)-COOH

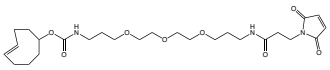
12-(9-Fluorenylmethyloxycarbonylamino)-4,7,10-trioxa-dodecanoic acid



CAS-No.	867062-95-1
Formula	$C_{24}H_{29}NO_7$
Mol. weight	443,49 g/mol

TCO1050 TCO-PEG(3)-mal

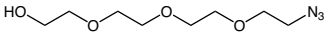
trans-Cyclooctene-PEG(3)-maleimide



CAS-No.	1809356-72-6
Formula	$C_{26}H_{41}N_3O_8$
Mol. weight	523,62 g/mol

PEG3760 N_3-PEG(3)-OH

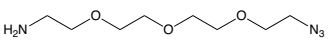
alpha-Azido-omega-hydroxy tetra(ethylene glycol)



CAS-No.	86770-67-4
Formula	$C_8H_{17}N_3O_4$
Mol. weight	219,24 g/mol

PEG3060 H_2N-PEG(3)-N_3

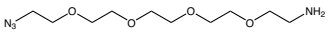
1-Amino-11-azido-3,6,9-trioxaundecane



CAS-No.	134179-38-7
Formula	$C_8H_{18}N_4O_3$
Mol. weight	218,25 g/mol

PEG5320 N_3-PEG(4)-NH_2

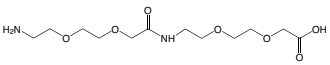
14-Azido-3,6,9,12-tetraoxatetradecan-1-amine



CAS-No.	951671-92-4
Formula	$C_{10}H_{22}N_4O_4$
Mol. weight	262,31 g/mol

PEG1221 H-O_2Oc-O_2Oc-OH

17-Amino-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecan-1-oic acid



CAS-No.	1143516-05-5
Formula	$C_{12}H_{24}N_2O_7$
Mol. weight	308,33 g/mol

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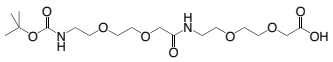
Product details

BAA1485 Boc-O_2Oc-O_2Oc-OH

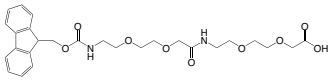
17-(*t*-Butyloxycarbonyl-amino)-9-aza-3,6,12,15-tetraoxa-10-on-heptadecanoic acid



CAS-No.	1069067-08-8
Formula	$C_{17}H_{32}N_2O_9$
Mol. weight	408,45 g/mol

FAA1787 Fmoc-O_2Oc-O_2Oc-OH

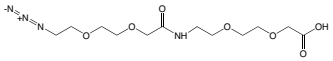
17-(9-Fluorenylmethyloxycarbonyl-amino)-9-aza-3,6,12,15-tetraoxa-10-on-heptadecanoic acid



CAS-No.	560088-89-3
Formula	$C_{27}H_{34}N_2O_9$
Mol. weight	530,58 g/mol

PEG2790 N_3-O_2Oc-O_2Oc-OH

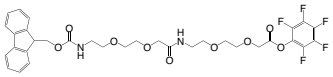
8-(8-Azido-3,6-dioxaoctanoylamido)-3,6-dioxaoctanoic acid



CAS-No.	1254054-60-8
Formula	$C_{12}H_{22}N_4O_7$
Mol. weight	334,33 g/mol

FAA6790 Fmoc-O_2Oc-O_2Oc-PFP

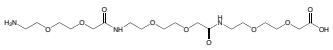
17-(9-Fluorenylmethyloxycarbonyl-amino)-9-aza-3,6,12,15-tetraoxa-10-on-heptadecanoic acid pentafluorophenyl ester



Formula	$C_{33}H_{33}F_5N_2O_9$
Mol. weight	696,61 g/mol

PEG2770 H-O_2Oc-O_2Oc-O_2Oc-OH

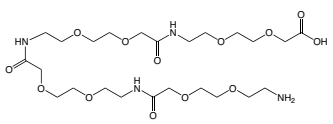
26-amino-10,19-dioxo-3,6,12,15,21,24-hexaoxa-9,18-diazahexacosan-1-oic acid



CAS-No.	2773558-06-6
Formula	$C_{18}H_{35}N_3O_{10}$
Mol. weight	453,48 g/mol

PEG8060 H-O_2Oc-O_2Oc-O_2Oc-O_2Oc-OH

8-amino-3,6-dioxaoctanoic acid tetramer

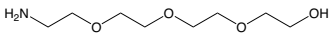


CAS-No.	2773558-66-8
Formula	$C_{24}H_{46}N_4O_{13}$
Mol. weight	598,64 g/mol

Product details

PEG1320 H_2N-PEG(4)-OH

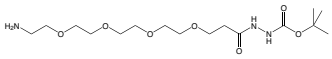
2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)ethanol



CAS-No.	86770-74-3
Formula	$C_8H_{19}NO_4$
Mol. weight	193,24 g/mol

PEG1335 H_2N-dPEG(4)-NHNH-Boc

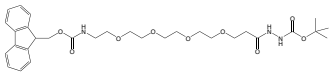
15-Amino-4,7,10,13-tetraoxa-pentadecanoyl-*N'*-(*t*-butyloxycarbonyl)-hydrazid



CAS-No.	1263047-17-1
Formula	$C_{16}H_{33}N_3O_7$
Mol. weight	379,45 g/mol

PEG1805 Fmoc-NH-dPEG(4)-NHNH-Boc

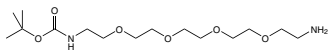
15-(9-Fluorenylmethyloxycarbonyl)amino-4,7,10,13-tetraoxa-pentadecanoyl-*N'*-(*t*-butyloxycarbonyl)hydrazid



CAS-No.	1263044-77-4
Formula	$C_{31}H_{43}N_3O_9$
Mol. weight	601,69 g/mol

PEG7880 Boc-NH-PEG(4)-NH_2

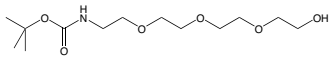
1-(*t*-Butyloxycarbonyl)amino-3,6,9,12-tetraoxatetradecan-14-amine



CAS-No.	811442-84-9
Formula	$C_{15}H_{32}N_2O_6$
Mol. weight	336,42 g/mol

PEG1915 Boc-NH-PEG(4)-OH

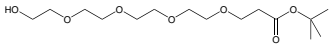
2-(2-(2-(2-(*t*-Butyloxycarbonylamino)ethoxy)ethoxy)ethoxy)ethanol



CAS-No.	106984-09-2
Formula	$C_{13}H_{27}NO_6$
Mol. weight	293,36 g/mol

PEG1535 HO-dPEG(4)-CO-OtBu

15-Hydroxy-4,7,10,13-tetraoxa-pentadecanoic acid *t*-butyl ester



CAS-No.	518044-32-1
Formula	$C_{15}H_{30}O_7$
Mol. weight	322,39 g/mol

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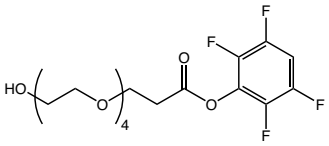
Product details

PEG7220 HO-PEG(4)-TFP

Hydroxy-tetra(ethylene glycol)-propionyl 2,3,5,6-tetrafluorophenyl ester

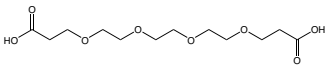
Formula $C_{17}H_{22}F_4O_7$
Mol. weight 414,35 g/mol



PEG4880 HOOC-dPEG™(4)-COOH

Tetraethyleneglycol-bis(propionic acid)

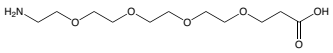
CAS-No. 31127-85-2
Formula $C_{12}H_{22}O_8$
Mol. weight 294,30 g/mol



PEG1370 H_2N-dPEG(4)-COOH

15-Amino-4,7,10,13-tetraoxa-pentadecanoic acid

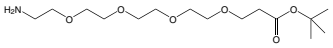
CAS-No. 663921-15-1
Formula $C_{11}H_{23}NO_6$
Mol. weight 265,3 g/mol



PEG1375 H_2N-dPEG(4)-CO-O*t*Bu

15-Amino-4,7,10,13-tetraoxa-pentadecanoic acid *t*-butyl ester

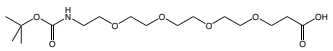
CAS-No. 581065-95-4
Formula $C_{15}H_{31}NO_6$
Mol. weight 321,41 g/mol



PEG1920 Boc-NH-PEG(4)-COOH

15-*t*-Butyloxycarbonylamino-4,7,10,13-tetraoxa-pentadecanoic acid

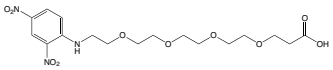
CAS-No. 756525-91-4
Formula $C_{16}H_{31}NO_8$
Mol. weight 365,42 g/mol



PEG2145 Dnp-NH-PEG(4)-COOH

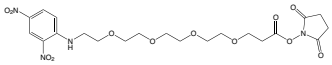
1-(2,4-Dinitrophenylamino)-3,6,9,12-tetraoxapentadecanoic acid

CAS-No. 858126-76-8
Formula $C_{17}H_{25}N_3O_{10}$
Mol. weight 431,39 g/mol



PEG2150 Dnp-NH-PEG(4)-NHS

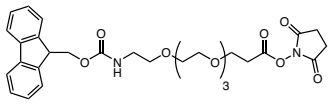
1-(2,4-Dinitrophenylamino)-3,6,9,12-tetraoxapentadecanoic acid succinimidyl ester



CAS-No.	858126-78-0
Formula	$C_{21}H_{28}N_4O_{12}$
Mol. weight	528,47 g/mol

PEG4410 Fmoc-NH-dPEG™(4)-NHS

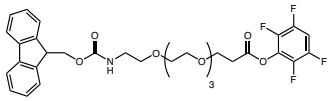
15-(9-Fluorenylmethyloxycarbonyl)amino-4,7,10,13-tetraoxa-pentadecanoic acid succinimidyl ester



CAS-No.	1314378-14-7
Formula	$C_{30}H_{36}N_2O_{10}$
Mol. weight	584,24 g/mol

PEG7810 Fmoc-NH-dPEG™(4)-TFP

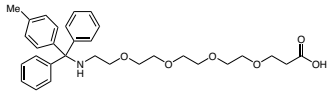
15-(9-Fluorenylmethyloxycarbonyl)amino-4,7,10,13-tetraoxa-pentadecanoic acid (2,3,5,6-tetrafluorophenyl) ester



Formula	$C_{32}H_{33}F_4NO_8$
Mol. weight	635,6 g/mol

PEG2161 Mtt-NH-PEG(4)-COOH*TEA

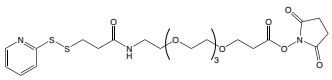
1-(*p*-Methytritylamino)-3,6,9,12-tetraoxapentadecanoic acid triethylamionium salt



CAS-No.	1310680-33-1 (net)
Formula	$C_{31}H_{39}NO_6*C_6H_{15}N$
Mol. weight	$C_{31}H_{39}NO_6*C_6H_{15}N$ g/mol

PEG2230 OPSS-PEG(4)-NHS

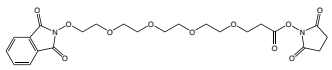
N-[3-(*o*-Pyridyldisulfido)propanoyl]-15-amino-4,7,10,13-tetraoxa-pentadecanoyl succinimidyl ester



CAS-No.	1334177-95-5
Formula	$C_{23}H_{33}N_3O_9S_2$
Mol. weight	559,65 g/mol

PEG5080 Phth-NO-dPEG™(4)-NHS

1-Phthalimidoxy-3,6,9,12-tetraoxapentadecan-15-oic acid succinimdyl ester



Formula	$C_{23}H_{28}N_2O_{11}$
Mol. weight	508,48 g/mol

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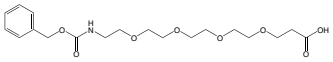
Product details

PEG1495 Z-NH-dPEG(4)-COOH

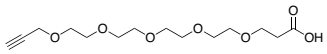
15-Benzyloxycarbonylamino-4,7,10,13-tetraoxa-pentadecanoic acid



CAS-No. 756526-00-8
Formula $C_{19}H_{29}NO_8$
Mol. weight 399,44 g/mol

PEG8170 Propargyl-PEG(5)-COOH

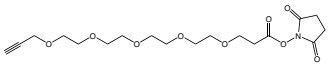
4,7,10,13,16-pentaoxanonadec-18-ynoic acid



CAS-No. 1245823-51-1
Formula $C_{14}H_{24}O_7$
Mol. weight 304,34 g/mol

PEG5410 Alkyne-PEG(4)-NHS

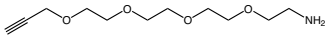
Alkyne-PEG(4)-succinimidyl ester



CAS-No. 1393330-40-9
Formula $C_{18}H_{27}NO_9$
Mol. weight 401,41 g/mol

PEG5430 Alkyne-PEG(4)-NH_2

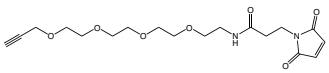
Alkyne-PEG(4)-amine



CAS-No. 1013921-36-2
Formula $C_{11}H_{21}NO_4$
Mol. weight 231,29 g/mol

PEG5440 Alkyne-PEG(4)-mal

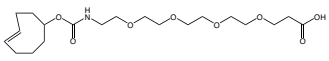
Alkyne-PEG(4)-maleimide



CAS-No. 1609651-90-2
Formula $C_{18}H_{26}N_2O_7$
Mol. weight 382,41 g/mol

TCO1040 TCO-PEG(4)-COOH

trans-Cyclooctene-PEG(4)-Acid

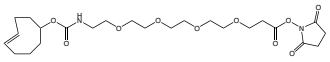


CAS-No. 1802913-21-8
Formula $C_{20}H_{35}NO_8$
Mol. weight 417,49 g/mol

TCO1010 TCO-PEG(4)-NHS

trans-Cyclooctene-PEG(4)-carboxy succinimidyl ester

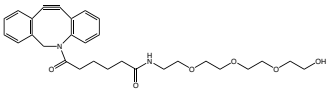
CAS-No. 1621096-79-4
Formula $C_{24}H_{38}N_2O_{10}$
Mol. weight 514,57 g/mol



RL-2510 DBCO-PEG(4)-OH

Dibenzoazacyclooctyne-tetra(ethylene glycol)

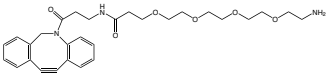
CAS-No. 1416711-60-8
Formula $C_{29}H_{36}N_2O_6$
Mol. weight 508,61 g/mol



RL-2420 DBCO-PEG(4)-NH_2*TFA

Dibenzoazacyclooctyne-tetra(ethylene glycol)-amine trifluoro acetic acid salt

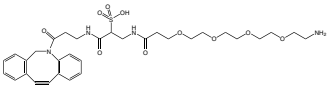
CAS-No. 1255942-08-5 net
Formula $C_{29}H_{37}N_3O_6*C_2F_3HO_2$
Mol. weight 523,62*114,02 g/mol



RL-2421 DBCO-Sulfo-PEG(4)-NH_2

Dibenzoazacyclooctyne-tetra(ethylene glycol)amine

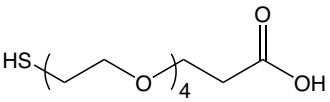
CAS-No. 2055198-05-3
Formula $C_{32}H_{42}N_4O_{10}S$
Mol. weight 674,76 g/mol



PEG1970 HS-dPEG(4)-COOH

15-Mercapto-4,7,10,13-tertaoxa-pentadecanoic acid

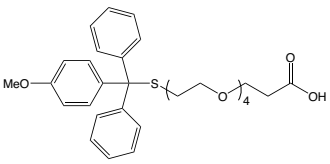
CAS-No. 749247-06-1
Formula $C_{11}H_{22}O_6S$
Mol. weight 282,35 g/mol



PEG1740 Mmt-S-dPEG(4)-COOH

15-(4-Methoxytrityl)thio-4,7,10,13-tertaoxa-pentadecanoic acid

CAS-No. 1263047-31-9
Formula $C_{31}H_{38}O_7S$
Mol. weight 554,69 g/mol



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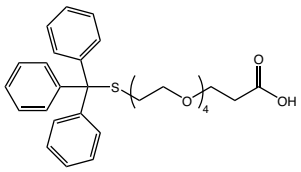
Product details

PEG6710 Trt-S-PEG(4)-COOH*H2O

15-Tritylmercapto-4,7,10,13-tetraoxapentadecanoic acid monohydrate

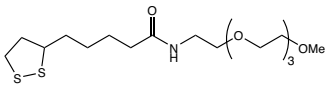
CAS-No. 882847-05-4 net
Formula $C_{30}H_{36}O_6S*H_2O$
Mol. weight 524,67*18,01 g/mol



PEG3590 Lipoamide-dPEG™(4)-OMe

alpha-Lipoamide-omega-methoxy tetra(ethylene glycol)

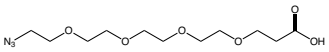
CAS-No. 1334172-66-5
Formula $C_{17}H_{33}NO_5S_2$
Mol. weight 395,58 g/mol



PEG2345 N_3-PEG(4)-COOH

15-Azido-4,7,10,13-tetraoxa-pentadecanoic acid

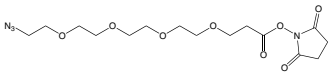
CAS-No. 1257063-35-6
Formula $C_{11}H_{21}N_3O_6$
Mol. weight 291,3 g/mol



PEG1400 N_3-dPEG(4)-NHS

15-Azido-4,7,10,13-tetraoxa-pentadecanoic acid succinimidyl ester

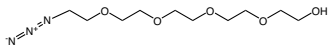
CAS-No. 944251-24-5
Formula $C_{15}H_{24}N_4O_8$
Mol. weight 388,37 g/mol



PEG5300 N_3-PEG(4)-OH

2-(2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethoxy) ethanol

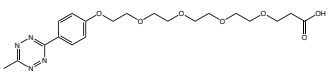
CAS-No. 86770-68-5
Formula $C_{10}H_{21}N_3O_5$
Mol. weight 263,29 g/mol



RL-2310 MeTz-PEG(4)-COOH

Methyltetrazine-PEG(4)-acid

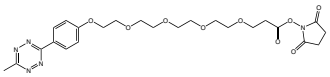
CAS-No. 1802907-91-0
Formula $C_{20}H_{28}N_4O_7$
Mol. weight 436,56 g/mol



RL-2330 MeTz-PEG(4)-NHS

Methyltetrazine-PEG(4)-propanoyl succinimidyl ester

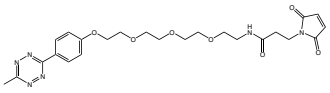
CAS-No. 1802907-92-1
Formula $C_{24}H_{31}N_5O_9$
Mol. weight 533,53 g/mol



RL-2340 MeTz-PEG(4)-mal

Methyltetrazine-PEG(4)-maleimide

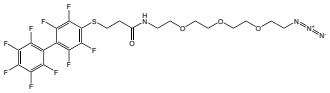
CAS-No. 1802908-02-6
Formula $C_{24}H_{30}N_6O_7$
Mol. weight 514,53 g/mol



RL-4030 PFB-mercaptopropionyl-PEG3-N_3

Perfluorobiphenyl-mercaptopropionyl-PEG(3)-N_3

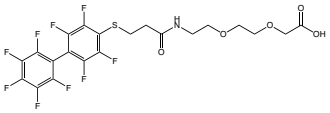
Formula $C_{23}H_{21}F_9N_4O_4S$
Mol. weight 620,49 g/mol



RL-4040 PFB-mercaptopropionyl-AEEA

Perfluorobiphenyl-mercaptopropionyl-AEEA

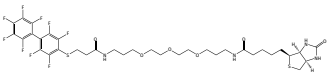
Formula $C_{21}H_{16}F_9NO_5S$
Mol. weight 565,41 g/mol



RL-4050 PFB-mercaptopropionyl-TOTA-Biotin

Perfluorobiphenyl-mercaptopropionyl-TOTA-Biotin

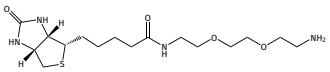
Formula $C_{35}H_{41}F_9N_4O_6S_2$
Mol. weight 848,84 g/mol



RL-4060 Biotin-DOOA

Biotinyl-1-amino-3,6-dioxa-8-octanamine

CAS-No. 138529-46-1
Formula $C_{16}H_{30}N_4O_4S$
Mol. weight 374,50 g/mol



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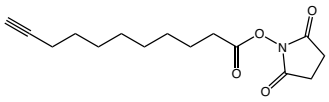
2.2. Hydrophobic Spacer Molecules

Product details

RL-3460 10-Undecynoyl-OSu

10-Undecynoic acid N-hydroxysuccinimide ester

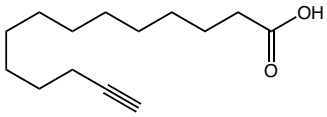
CAS-No. 1006592-57-9
Formula $C_{15}H_{21}NO_4$
Mol. weight 279,34 g/mol



RL-2055 Alkyne-myristic acid

13-Tetradecynoic acid

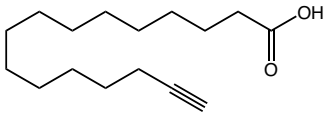
CAS-No. 82909-47-5
Formula $C_{14}H_{24}O_2$
Mol. weight 224,34 g/mol



RL-2060 Alkyne-palmitic acid

15-Hexadecynoic acid

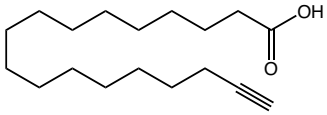
CAS-No. 99208-90-9
Formula $C_{16}H_{28}O_2$
Mol. weight 252,39 g/mol



RL-2065 Alkyne-stearic acid

17-Octadecynoic acid

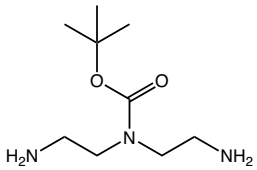
CAS-No. 34450-18-5
Formula $C_{18}H_{32}O_2$
Mol. weight 280,45 g/mol



BNN1330 DETA(HBH)*2HCl

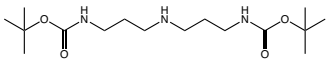
tert-butyl bis(2-aminoethyl)carbamate

CAS-No. 1914917-65-9
Formula $C_9H_{21}N_3O_2$*2HCl
Mol. weight 203,29*72,92 g/mol



BNN1340 DPTA(BHB)*HCl

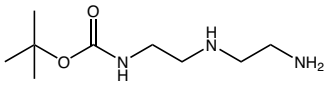
di-*tert*-butyl (azanediylbis(propane-3,1-diyl))dicarbamate



CAS-No.	82409-03-8
Formula	$C_{16}H_{33}N_3O_4$*HCl
Mol. weight	331,46*36,46 g/mol

BNN1350 DETA(BHH*2HCl)

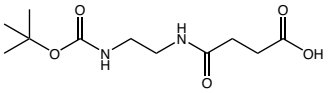
tert-butyl (2-((2-aminoethyl)amino)ethyl)carbamate dihydrochloride



CAS-No.	162279-67-6
Formula	$C_9H_{21}N_3O_2$*2HCl
Mol. weight	203,29*72,92 g/mol

BNN1380 Boc-EDA-Suc-OH

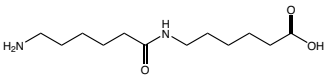
Boc,Succinoyl-ethylenediamine



CAS-No.	891781-87-6
Formula	$C_{11}H_{20}N_2O_5$
Mol. weight	260,29 g/mol

HAA9300 H-Aca-Aca-OH

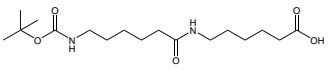
6-(6-Aminohexanamido)hexanoic acid



CAS-No.	2014-58-6
Formula	$C_{12}H_{24}N_2O_3$
Mol. weight	244,34 g/mol

BAA4870 Boc-Aca-Aca-OH

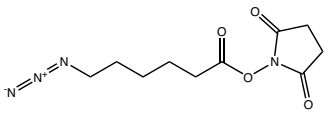
N-Boc-6-(6-Aminohexanamido)hexanoic acid



CAS-No.	14254-45-6
Formula	$C_{17}H_{32}N_2O_5$
Mol. weight	344,45 g/mol

RL-2980 N_3-Aca-OSu

6-Azidocaproic acid N-hydroxysuccinimidyl ester



CAS-No.	866363-70-4
Formula	$C_{10}H_{14}N_4O_4$
Mol. weight	254,24 g/mol

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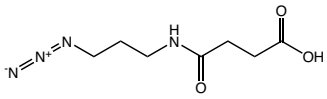
Product details

RL-4350 N_3-DAPr-Suc-OH

Azido-propylenediamine-succinoyl-OH

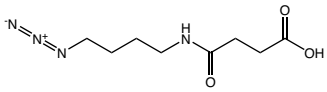
CAS-No.	929894-58-6
Formula	$C_7H_{12}N_4O_3$
Mol. weight	200,20 g/mol



RL-4360 N_3-DABu-Suc-OH

Azido-butylenediamine-succinoyl-OH

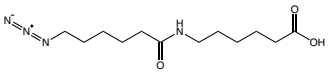
CAS-No.	2226183-50-0
Formula	$C_8H_{14}N_4O_3$
Mol. weight	214,23 g/mol



HAA6990 N_3-Aca-Aca-OH

6-(6-azidohexanamido)hexanoic acid

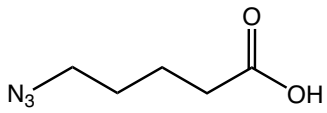
CAS-No.	866363-71-5
Formula	$C_{12}H_{22}N_4O_3$
Mol. weight	270,33 g/mol



AAA1970 N_3-Pen-OH

5-Azido-pentanoic acid

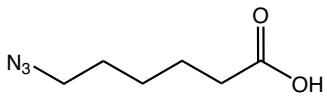
CAS-No.	79583-98-5
Formula	$C_5H_9N_3O_2$
Mol. weight	143,14 g/mol



AAA1960 N_3-Hx-OH

6-Azido-hexanoic acid

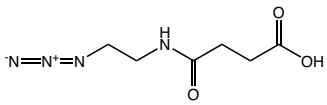
CAS-No.	79598-53-1
Formula	$C_6H_{11}N_3O_2$
Mol. weight	157,17 g/mol



BNN1370 N_3-EDA-Suc-OH

Azido-ethylenediamine-succinoyl-OH

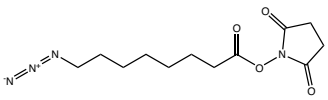
CAS-No.	2225891-73-4
Formula	$C_6H_{10}N_4O_3$
Mol. weight	186,17 g/mol



RL-3480 8-Azido-octanoyl-OSu

8-Azidodooctanoic acid N-hydroxysuccinimide ester

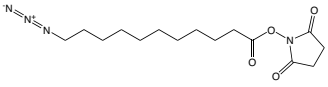
CAS-No. 2576471-56-0
Formula $C_{12}H_{18}N_4O_4$
Mol. weight 282,30 g/mol



RL-3170 11-Azido-undecanoyl-OSu

11-Azidoundecanoic acid N-hydroxysuccinimide ester

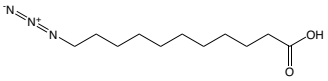
CAS-No. 850080-13-6
Formula $C_{15}H_{24}N_4O_4$
Mol. weight 324,38 g/mol



RL-3200 11-Azidoundecanoic acid

11-Azido-undecanoic acid

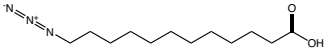
CAS-No. 118162-45-1
Formula $C_{11}H_{21}N_3O_2$
Mol. weight 227,30 g/mol



RL-3210 12-Azidododecanoic acid

12-Azido-dodecanoic acid

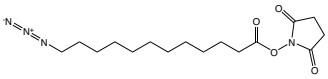
CAS-No. 80667-36-3
Formula $C_{12}H_{23}N_3O_2$
Mol. weight 241,33 g/mol



RL-3220 12-Azido-dodecanoyl-OSu

12-Azidododecanoic acid N-hydroxysuccinimide ester

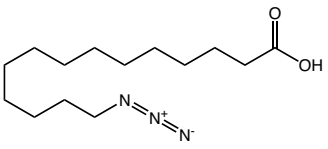
CAS-No. 2489524-00-5
Formula $C_{16}H_{26}N_4O_4$
Mol. weight 338,40 g/mol



RL-3230 14-Azido-myristic acid

14-azidotetradecanoic acid

CAS-No. 176108-61-5
Formula $C_{14}H_{27}N_3O_2$
Mol. weight 269,38 g/mol



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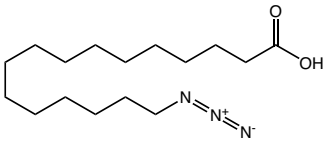
Product details

RL-3240 16-Azido-palmitic acid

16-azidohexadecanoic acid

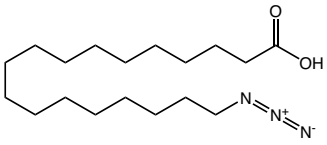
CAS-No. 112668-54-9
Formula $C_{16}H_{31}N_3O_2$
Mol. weight 297,44 g/mol



RL-3250 18-Azido-stearic acid

18-azidooctadecanoic acid

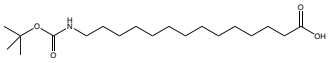
CAS-No. 1529763-58-3
Formula $C_{18}H_{35}N_3O_2$
Mol. weight 325,49 g/mol



BAA4240 14-(Boc-amino)-myristic acid

14-((*t*-Butyloxycarbonyl)amino)tetradecanoic acid

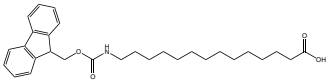
CAS-No. 2307778-46-5
Formula $C_{19}H_{37}NO_4$
Mol. weight 343,51 g/mol



FAA8160 14-(Fmoc-amino)-myristic acid

14-((9-Fluorenylmethyloxycarbonyl)amino)tetradecanoic acid

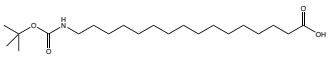
CAS-No. 1931109-55-5
Formula $C_{29}H_{39}NO_4$
Mol. weight 465,63 g/mol



BAA3900 16-(Boc-amino)-palmitic acid

16-((*t*-Butyloxycarbonyl)amino)hexadecanoic acid

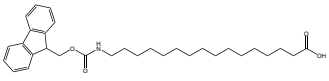
CAS-No. 135747-73-8
Formula $C_{21}H_{41}NO_4$
Mol. weight 371,55 g/mol



FAA7460 16-(Fmoc-amino)-palmitic acid

16-((9-Fluorenylmethyloxycarbonyl)amino)hexadecanoic acid

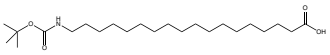
CAS-No. 1356220-22-8
Formula $C_{31}H_{43}NO_4$
Mol. weight 493,68 g/mol



BAA3910 18-(Boc-amino)-stearic acid

18-((*t*-Butyloxycarbonyl)amino)octadecanoic acid

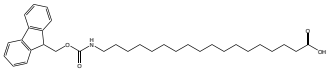
CAS-No. 2389064-45-1
Formula $C_{23}H_{45}NO_4$
Mol. weight 399,61 g/mol



FAA7450 18-(Fmoc-amino)-stearic acid

18-((9-Fluorenylmethyloxycarbonyl)amino)octadecanoic acid

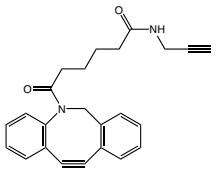
CAS-No. 1199580-37-4
Formula $C_{33}H_{47}NO_4$
Mol. weight 521,73 g/mol



RL-4020 DBCO-C6-Alkyne

N-(propargylamidoadipoyl)-dibenzoazacyclooctyne

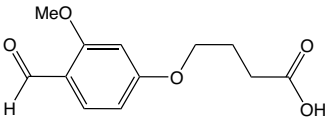
Formula $C_{24}H_{22}N_2O_2$
Mol. weight 370,45 g/mol



RL-1002 FMPB-Linker

4-(4'-Formyl-3'-methoxyphenoxy) butanoic acid

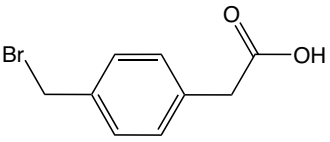
CAS-No. 309964-23-6
Formula $C_{12}H_{14}O_5$
Mol. weight 238,24 g/mol



RL-1008 Br-PAM-Linker

4-Bromomethylphenyl-acetic acid

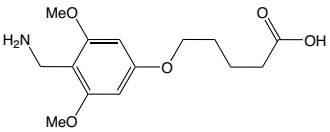
CAS-No. 13737-36-5
Formula $C_9H_9BrO_2$
Mol. weight 229,1 g/mol



RL-1050 H-PAL-Linker

5-[4-Aminomethyl-3,5-dimethoxyphenoxy]-pentanoic acid

Formula $C_{14}H_{21}NO_5$
Mol. weight 283,31 g/mol



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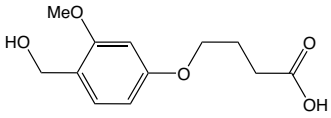
Product details

RL-1114 HMPB-Linker

4-(4-Hydroxymethyl-3-methoxyphenoxy)-butyric acid

CAS-No.	136849-75-7
Formula	$C_{12}H_{16}O_5$
Mol. weight	240,24 g/mol



2.3. Permanent Linkers with Maleimide Function

Michael addition of a thiol to a maleimide is commonly used for numerous bioconjugations. Several commercial constructs like Brentuximab vedotin, Trastuzumab emtansine, and Cimzia contain a thiol-maleimide adduct. However, this reaction is reversible. During the journey of an appropriate thioether containing drug through physiological media, this bond can break, and fragments are released which might contribute to certain unwanted or even toxic reactions.

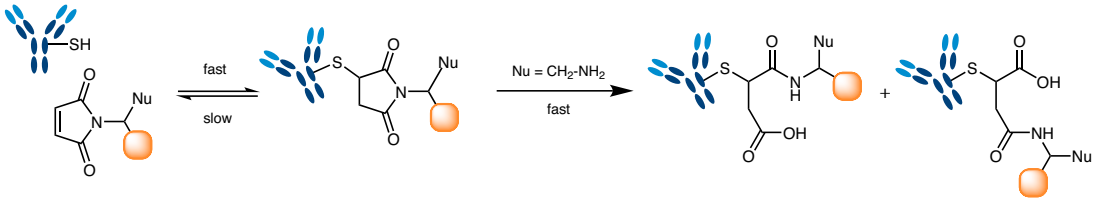


Fig. 16: Maleimides bind reversibly to thiols resulting in thioethers. This linkage turns stable once the maleimide ring is opened through hydrolysis.

However, if the succinimide moiety of a maleimide-thiol conjugate is hydrolyzed, the ring-opened product is fully stabilized towards cleavage (*Fig. 16*). The rates of ring-opening hydrolysis are greatly accelerated by electron withdrawing N-substituents and good nucleophiles in the proximity of the carbonyl functions. Thus, conjugates made with nucleophilic side chains and electron-withdrawing maleimides may be purposefully hydrolyzed to their ring-opened counterparts and ensure good *in vivo* stability.

References:

- *Covalent Modification of Biomolecules through Maleimide-Based Labeling Strategies; K. Renault, J. W. Fredy, P. Y. Renard, C. Sabot;* ***Bioconjug Chem*** *2018;* ***29****: 2497-2513. https://doi.org/10.1021/acs.bioconjchem.8b00252*
- *Optimisation of the dibromomaleimide (DBM) platform for native antibody conjugation by accelerated post-conjugation hydrolysis; M. Morais, J. P. M. Nunes, K. Karu, N. Forte, I. Benni, M. E. B. Smith, S. Caddick, V. Chudasama, J. R. Baker;* ***Org Biomol Chem*** *2017;* ***15****: 2947-2952. https://doi.org/10.1039/c7ob00220c*
- *Use of a next generation maleimide in combination with THIOMAB™ antibody technology delivers a highly stable, potent and near homogeneous THIOMAB™ antibody-drug conjugate (TDC); J. P. M. Nunes, V. Vassileva, E. Robinson, M. Morais, M. E. B. Smith, R. B. Pedley, S. Caddick, J. R. Baker, V. Chudasama;* ***RSC Advances*** *2017;* ***7****: 24828-24832. https://doi.org/10.1039/c7ra04606e*
- *Long-term stabilization of maleimide-thiol conjugates; S. D. Fontaine, R. Reid, L. Robinson, G. W. Ashley, D. V. Santi;* ***Bioconjug Chem*** *2015;* ***26****: 145-52. https://doi.org/10.1021/bc5005262*

→ *Self-hydrolyzing maleimides improve the stability and pharmacological properties of antibody-drug conjugates; R. P. Lyon, J. R. Setter, T. D. Bovee, S. O. Doronina, J. H. Hunter, M. E. Anderson, C. L. Balasubramanian, S. M. Duniho, C. I. Leiske, F. Li, P. D. Senter;* ***Nat Biotechnol*** *2014;* ***32****: 1059-62. https://doi.org/10.1038/nbt.2968*

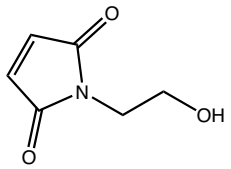
→ *Mild method for succinimide hydrolysis on ADCs: impact on ADC potency, stability, exposure, and efficacy; L. N. Tumey, M. Charati, T. He, E. Sousa, D. Ma, X. Han, T. Clark, J. Casavant, F. Loganzo, F. Barletta, J. Lucas, E. I. Graziani;* ***Bioconjug Chem*** *2014;* ***25****: 1871-80. https://doi.org/10.1021/bc500357n*

Product details

RL-3000 Mal-Et-OH

N-(2-Hydroxyethyl)maleimide

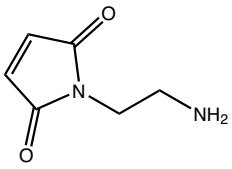
CAS-No.	1585-90-6
Formula	$C_6H_7NO_3$
Mol. weight	141,12 g/mol



RL-2780 Mal-NH_2*HCl

2-Maleimidoethylamine hydrochloride

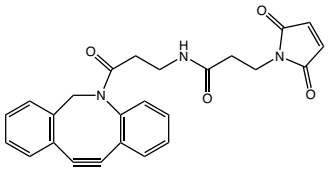
CAS-No.	134272-64-3
Formula	$C_6H_8N_2O_2$*HCl
Mol. weight	140,14*36,45 g/mol



RL-2490 DBCO-mal

Dibenzoazacyclooctyne-maleimide

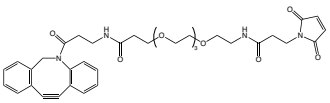
CAS-No.	1395786-30-7
Formula	$C_{25}H_{21}N_3O_4$
Mol. weight	427,45 g/mol



RL-2500 DBCO-PEG(4)-mal

Dibenzoazacyclooctyne-tetra(ethylene glycol)-maleimide

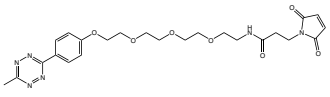
CAS-No.	1480516-75-3
Formula	$C_{36}H_{42}N_4O_9$
Mol. weight	674,74 g/mol



RL-2340 MeTz-PEG(4)-mal

Methyltetrazine-PEG(4)-maleimide

CAS-No.	1802908-02-6
Formula	$C_{24}H_{30}N_6O_7$
Mol. weight	514,53 g/mol



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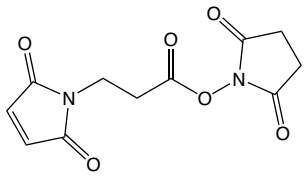
Product details

MAA1020 Mal-beta-Ala-OSu

3-(Maleimido)propionic acid N-succinimidyl ester

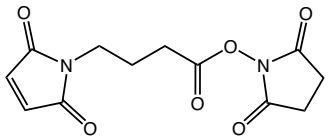
CAS-No. 55750-62-4
Formula $C_{11}H_{10}N_2O_6$
Mol. weight 266,21 g/mol



RL-2640 Mal-Bu-NHS

4-Maleimidobutyric acid-NHS ester

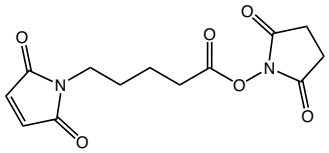
CAS-No. 80307-12-6
Formula $C_{12}H_{12}N_2O_6$
Mol. weight 280,23 g/mol



RL-2670 Mal-Pen-NHS

5-Maleimidopentanoic acid-NHS ester

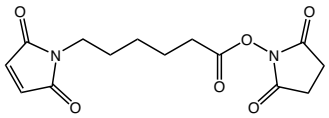
CAS-No. 103750-03-4
Formula $C_{13}H_{14}N_2O_6$
Mol. weight 294,26 g/mol



RL-2660 Mal-Hx-NHS

6-Maleimidohexanoic acid-NHS ester

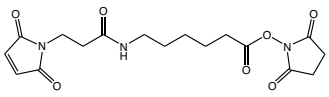
CAS-No. 55750-63-5
Formula $C_{14}H_{16}N_2O_6$
Mol. weight 308,29 g/mol



RL-2690 Mal-PrHx-NHS

6-(3-Maleimidopropionylamino)-hexanoic acid-NHS ester

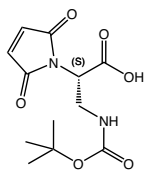
CAS-No. 367927-39-7
Formula $C_{17}H_{21}N_3O_7$
Mol. weight 379,36 g/mol



MAA1040 Mal-L-Dap(Boc)-OH*DCHA

N-alpha-MaleimidoN-beta-*t*-butyloxycarbonyl-L-2,3-diaminopropionic acid dicyclohexylamine

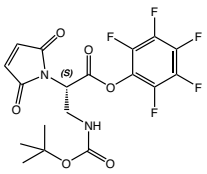
CAS-No. 2004724-16-5
Formula $C_{12}H_{16}N_2O_6*C_{12}H_{23}N$
Mol. weight 284,27*181,32 g/mol



MAA1080 Mal-L-Dap(Boc)-OPfp

N-alpha-MaleimidoN-beta-*t*-butyloxycarbonyl-L-2,3-diaminopropionic acid pentafluorophenolate

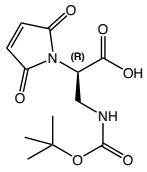
CAS-No.	1887132-90-2
Formula	$C_{18}H_{15}F_5N_2O_6$
Mol. weight	450,31 g/mol



MAA1060 Mal-D-Dap(Boc)-OH*DCHA

N-alpha-MaleimidoN-beta-*t*-butyloxycarbonyl-D-2,3-diaminopropionic acid dicyclohexylamine

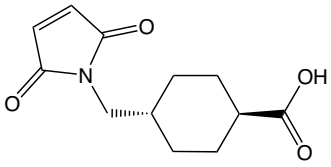
CAS-No.	2382651-11-6 net
Formula	$C_{12}H_{16}N_2O_6$*$C_{12}H_{23}N$
Mol. weight	284,27*181,32 g/mol



MAA5400 Mal-AMCHC-OH

trans-4-(maleimidomethyl)cyclohexane-1-carboxylic acid

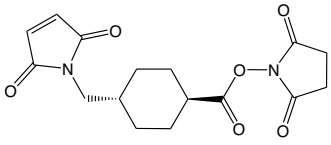
CAS-No.	69907-67-1
Formula	$C_{12}H_{15}NO_4$
Mol. weight	237,25 g/mol



MAA1000 Mal-AMCHC-OSu

trans-N-Succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate

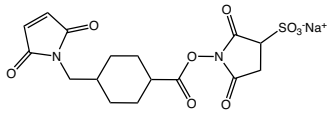
CAS-No.	71875-81-5
Formula	$C_{16}H_{18}N_2O_6$
Mol. weight	334,33 g/mol



MAA1050 Sulfo-SMCC

4-(N-Maleimidomethyl)cyclohexane-1-carboxylic acid 3-sulfo-N-hydroxysuccinimide ester sodium salt (*cis*/*trans* mixture)

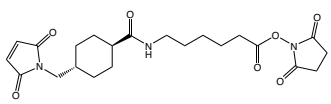
CAS-No.	92921-24-9
Formula	$C_{16}H_{17}N_2NaO_9S$
Mol. weight	436,37 g/mol



RL-2650 Mal-cHxHx-NHS

6-[*trans*-4-(Maleimidomethyl)-cyclohexanoylamino]-hexanoic acid-NHS ester

CAS-No.	125559-00-4
Formula	$C_{22}H_{29}N_3O_7$
Mol. weight	447,48 g/mol



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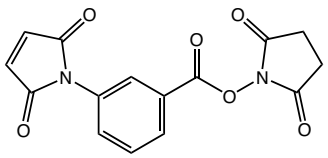
Product details

RL-2600 3-Mal-Bz-NHS

3-Maleimidobenzoic acid-NHS ester

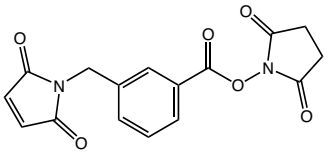
CAS-No. 58626-38-3
Formula $C_{15}H_{10}N_2O_6$
Mol. weight 314,25 g/mol



RL-2610 3-Mal-MBz-NHS

3-(Maleimidomethyl)-benzoic acid-NHS ester

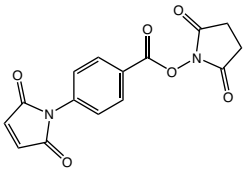
CAS-No. 91574-36-6
Formula $C_{16}H_{12}N_2O_6$
Mol. weight 328,28 g/mol



RL-2620 4-Mal-Bz-NHS

4-Maleimidobenzoic acid-NHS ester

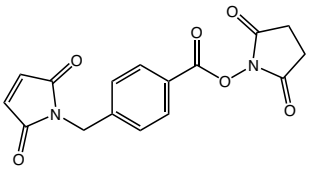
CAS-No. 64191-06-6
Formula $C_{15}H_{10}N_2O_6$
Mol. weight 314,25 g/mol



RL-2630 4-Mal-MBz-NHS

4-(Maleimidomethyl)-benzoic acid-NHS ester

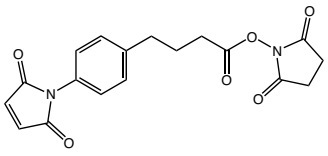
CAS-No. 64987-84-4
Formula $C_{16}H_{12}N_2O_6$
Mol. weight 328,28 g/mol



RL-2680 Mal-PhBu-NHS

4-(4-Maleimidophenyl)-butyric acid-NHS ester

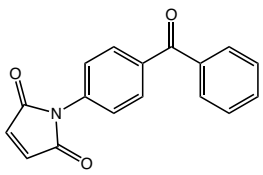
CAS-No. 79886-55-8
Formula $C_{18}H_{16}N_2O_6$
Mol. weight 356,33 g/mol



LS-3350 4-(N-Maleimido)benzophenone

1-(4-Benzoylphenyl)-1H-pyrrole-2,5-dione

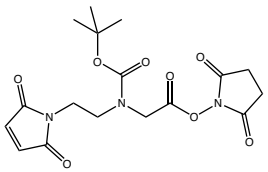
CAS-No. 92944-71-3
Formula $C_{17}H_{11}NO_3$
Mol. weight 277,28 g/mol



RL-3430 MaI-N-Boc-Aeg-NHS

N-(*t*-butoxycarbonyl)-N-(2-(maleinimido)ethyl)glycine N-Hydroxysuccinimidyl ester

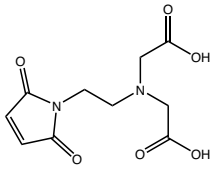
CAS-No.	2576471-29-7
Formula	$C_{17}H_{21}N_3O_8$
Mol. weight	395,37 g/mol



RL-3450 MaI-CH_2CH_2-N-(CH2-COOH)$_2$

2,2'-((2-(maleinimido)ethyl)azanediyl)diacetic acid

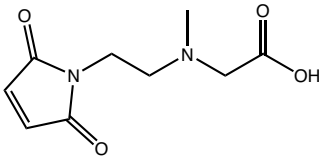
CAS-No.	207612-92-8
Formula	$C_{10}H_{12}N_2O_6$
Mol. weight	256,21 g/mol



RL-3400 MaI-CH_2CH_2-N(Me)-CH2-COOH

N-(2-(maleinimido)ethyl)-N-methylglycine

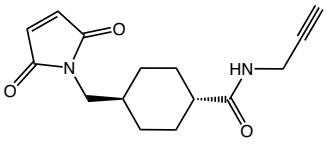
CAS-No.	2576471-52-6
Formula	$C_9H_{12}N_2O_4$
Mol. weight	212,21 g/mol



MAA1100 MaI-AMCHC-N-Propargylamide

trans-4-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)methyl]-N-(prop-2-yn-1-yl)cyclohexane-1-carboxamide

CAS-No.	2027476-42-0
Formula	$C_{15}H_{18}N_2O_3$
Mol. weight	274,32 g/mol



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2.4. Photoactivatable Linkers

Irradiation of diazirines with UV light (ca. 350-360 nm) yields a highly reactive carbene species that can undergo insertions into C–C, C–H, O–H, and X–H (X = heteroatom) bonds of neighboring molecules to irreversibly form a covalent bond (*Fig. 17*). The diazirine moiety is the smallest of all photophores, so introduction of a diazirine-bearing amino acid into a peptide or protein usually does not impair its biological activity. Further, advantages of diazirine crosslinkers are their stability at room temperature and their relative stability against nucleophiles as well as towards both acidic and basic conditions.

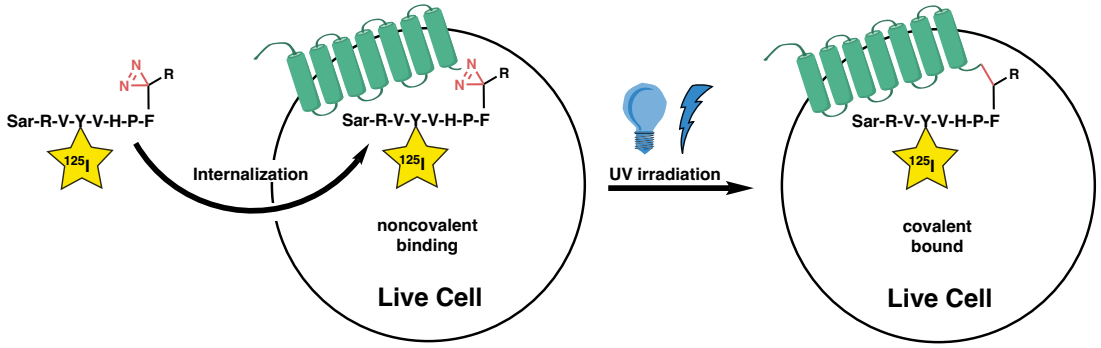

Fig. 17: Use of photo-phenylalanine for the identification of angiotensin-II receptor binding sites; ^{125}I is used as a radiotracer.

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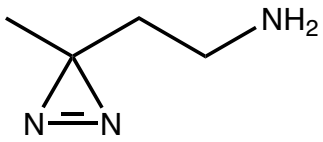
Product details

RL-2910 Photo-Butylamine

2-(3-methyl-3H-diazirin-3-yl)ethan-1-amine hydrochloride

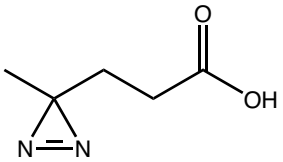
CAS-No.	25055-95-2
Formula	$C_4H_9N_3$*HCl
Mol. weight	99,13*36,45 g/mol



RL-2890 Photo-Pentanoic acid

3-(3-methyl-3H-diazirin-3-yl)propanoic acid

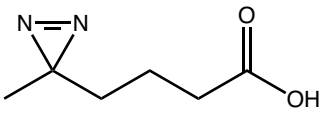
CAS-No.	25055-86-1
Formula	$C_5H_8N_2O_2$
Mol. weight	128,13 g/mol



RL-2900 Photo-Hexanoic acid

4-(3-methyl-3H-diazirin-3-yl)butanoic acid

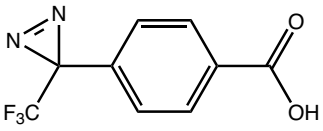
CAS-No.	16297-97-5
Formula	$C_6H_{10}N_2O_2$
Mol. weight	142,16 g/mol



RL-2920 Photo-Benzoic acid

4-[3-(Trifluoromethyl)-3H-diazirin-3-yl]benzoic acid

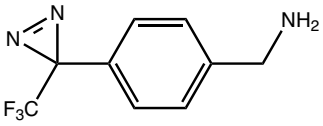
CAS-No.	85559-46-2
Formula	$C_9H_5F_3N_2O_2$
Mol. weight	230,14 g/mol



RL-2930 Photo-Benzylamine*HCl

4-[3-(Trifluoromethyl)-3H-diazirin-3-yl]benzylamine hydrochloride

CAS-No.	1258874-29-1
Formula	$C_9H_8N_3F_3$*HCl
Mol. weight	215,18*36,45 g/mol



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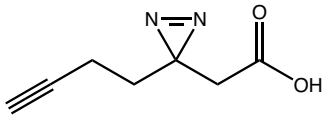
Product details

RL-3410 Photo-Click-Heptanoic acid

2-(3-(but-3-ynyl)-3H-diazirin-3-yl)acetic acid

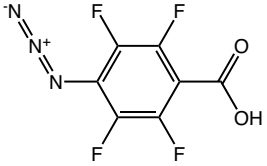
CAS-No.	2049109-24-0
Formula	$C_7H_8N_2O_2$
Mol. weight	152,15 g/mol



RL-2035 ATFB

4-Azido-2,3,5,6-tetrafluorobenzoic acid

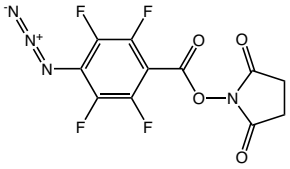
CAS-No.	122590-77-6
Formula	$C_7HF_4N_3O_2$
Mol. weight	235,1 g/mol



RL-2045 ATFB-NHS

N-Succinimidyl 4-azido-2,3,5,6-tetrafluorobenzoate

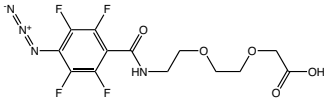
CAS-No.	126695-58-7
Formula	$C_{11}H_4F_4N_4O_4$
Mol. weight	332,17 g/mol



PEG5000 N_3-TFBA-O_2Oc

{2-[2-(4-Azido-2,3,5,6-tetrafluorobenzoyl-amino)ethoxy] ethoxy}acetic acid

CAS-No.	1993119-45-1
Formula	$C_{13}H_{12}F_4N_4O_5$
Mol. weight	380,25 g/mol



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3. Cleavable Linkers

Peptidic bonds are expected to have a high serum stability, as lysosomal proteolytic enzymes show reduced activities in blood due to endogenous inhibitors and the unfavorably high pH value of blood compared to lysosomes. This was confirmed by preclinical *in vivo* studies, which revealed half-lives of seven to ten days for peptide linkers. Release of a drug conjugated *via* a peptidyl linker to monoclonal antibodies (mAb) occurs specifically due to the action of lysosomal proteases (e.g., cathepsin and plasmin). These proteases may be present at elevated levels in certain tumor tissues. Therefore, peptide linkers combine greater systemic stability with rapid enzymatic release of the drug in the target cell. Besides Val-Ala, Val-Cit and Phe-Lys, other sequences have been reported as lysosomally cleavable peptides, like Gly-Phe-Leu-Gly and Ala-Leu-Ala-Leu.

References:

- *Star structure of antibody-targeted HPMA copolymer-bound doxorubicin: a novel type of polymeric conjugate for targeted drug delivery with potent antitumor effect; M. Kovar, J. Strohalm, T. Etrych, K. Ulbrich, B. Rihova;* ***Bioconjug Chem*** *2002;* ***13****: 206-15. https://doi.org/10.1021/bc010063m*
- *Synthesis of a lipophilic daunorubicin derivative and its incorporation into lipidic carriers developed for LDL receptor-mediated tumor therapy; A. J. Versluis, E. T. Rump, P. C. Rensen, T. J. Van Berkel, M. K. Bijsterbosch;* ***Pharm Res*** *1998;* ***15****: 531-7. https://doi.org/10.1023/a:1011917508056*
- *Influence of a peptide linker on biodistribution and metabolism of antibody-conjugated benzyl-EDTA. Comparison of enzymatic digestion in vitro and in vivo; M. Studer, L. A. Kroger, S. J. DeNardo, D. L. Kukis and C. F. Meares;* ***Bioconjug Chem*** *1992;* ***3****: 424-9. https://doi.org/10.1021/bc00017a012*

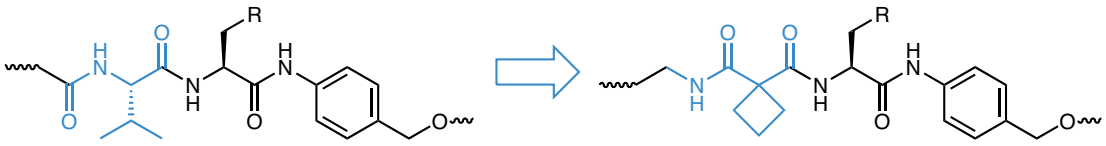

Fig. 18: Cyclobutane-1,1-dicarboxamide can replace valine in dipeptide linker systems, resulting in improved ADC selectivity.

Peptide-based ADC linkers, such as Val-Cit or Val-Ala, that are cleaved by lysosomal proteases have shown sufficient stability in serum and effective payload-release in targeted cells. However, the use of peptide-based linkers limits the ability to modulate protease specificity. Furthermore, if the linker can preferentially be hydrolyzed by tumor-specific proteases only, safety margin may improve. In this context, a cyclobutane-1,1-dicarboxamide-containing linker (*Fig. 18*) replacing valine in other sequences has been invented which is hydrolyzed predominantly by cathepsin B, while the typical valine-citrulline dipeptide linker is rather less. ADCs bearing the nonpeptidic linker are as efficacious and stable *in vivo* as those with the dipeptide linker. Hence, the application of the peptidomimetic linker presents new opportunities for improving the selectivity of ADCs.

Reference:

- *Discovery of Peptidomimetic Antibody-Drug Conjugate Linkers with Enhanced Protease Specificity; B. Wei, J. Gunzner-Toste, H. Yao, T. Wang, J. Wang, Z. Xu, J. Chen, J. Wai, J. Nonomiya, S. P. Tsai, J. Chuh, K. R. Kozak, Y. Liu, S. F. Yu, J. Lau, G. Li, G. D. Phillips, D. Leipold, A. Kamath, D. Su, K. Xu, C. Eigenbrot, S. Steinbacher, R. Ohri, H. Raab, L. R. Staben, G. Zhao, J. A. Flygare, T. H. Pillow, V. Verma, L. A. Masterson, P. W. Howard, B. Safina;* ***J. Med. Chem.*** *2018;* ***61****: 989-1000. https://doi.org/10.1021/acs.jmedchem.7b01430*

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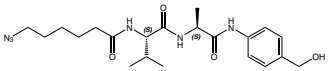
3.1. Valine-Alanine-Based Enzymatically Cleavable Linkers

Product details

ADC1290 6-Azidohexanoyl-Val-Ala-PAB

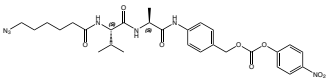
6-azidohexanoyl-valyl-alanyl-(4-aminobenzyl alcohol)



CAS-No. 2706564-30-7
Formula $C_{21}H_{32}N_6O_4$
Mol. weight 432,52 g/mol

ADC1300 6-Azidohexanoyl-Val-Ala-PAB-PNP

6-azidohexanoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



Formula $C_{28}H_{35}N_7O_8$
Mol. weight 597,62 g/mol

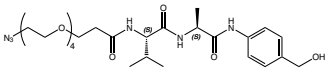
Reference:

→ *NKT cell-dependent glycolipid-peptide vaccines with potent anti-tumour activity; R. J. Anderson, B. J. Compton, C. W. Tang, A. Authier-Hall, C. M. Hayman, G. W. Swinerd, R. Kowalczyk, P. Harris, M. A. Brimble, D. S. Larsen, O. Gasser, R. Weinkove, I. F. Hermans, G. F. Painter;* ***Chem. Sci.*** *2015; **6**: 5120-5127. https://doi.org/10.1039/c4sc03599b*

Product details

ADC1330 Azido-PEG(4)-Val-Ala-PAB

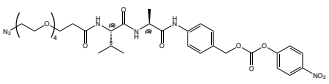
azido-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl alcohol)



Formula $C_{26}H_{42}N_6O_8$
Mol. weight 566,65 g/mol

ADC1340 Azido-PEG(4)-Val-Ala-PAB-PNP

azido-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

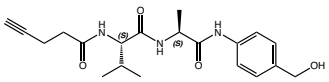


Formula $C_{33}H_{45}N_7O_{12}$
Mol. weight 731,75 g/mol

ADC1310 4-Pentynoyl-Val-Ala-PAB

4-pentynoyl-valyl-alanyl-(4-aminobenzyl alcohol)

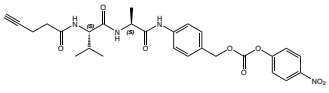
CAS-No.	1956294-75-9
Formula	$C_{20}H_{27}N_3O_4$
Mol. weight	373,45 g/mol



ADC1320 4-Pentynoyl-Val-Ala-PAB-PNP

4-pentynoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	1956294-76-0
Formula	$C_{27}H_{30}N_4O_8$
Mol. weight	538,55 g/mol



Reference:

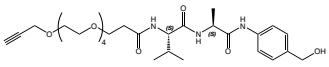
→ *Integrin-Targeting Knottin Peptide-Drug Conjugates Are Potent Inhibitors of Tumor Cell Proliferation; N. Cox, J. R. Kintzing, M. Smith, G. A. Grant, J. R. Cochran;* ***Angew Chem Int Ed*** *2016;* ***55****: 9894-7. https://doi.org/10.1002/anie.201603488*

Product details

ADC1350 Alkyne-PEG(4)-Val-Ala-PAB

propargyl-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl alcohol)

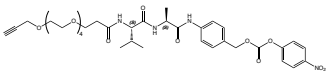
CAS-No.	2348405-90-1
Formula	$C_{29}H_{45}N_3O_9$
Mol. weight	579,68 g/mol



ADC1360 Alkyne-PEG(4)-Val-Ala-PAB-PNP

propargyl-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	2348405-91-2
Formula	$C_{36}H_{48}N_4O_{13}$
Mol. weight	744,79 g/mol



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→ *Exploration of the carmaphycins as payloads in antibody drug conjugate anticancer agents; J. Almaliti, B. Miller, H. Pietraszkiewicz, E. Glukhov, C. B. Naman, T. Kline, J. Hanson, X. Li, S. Zhou, F. A. Valeriote, W. H. Gerwick;* ***Eur J Med Chem*** *2019;* ***161****: 416-432. https://doi.org/10.1016/j.ejmech.2018.10.024*

→ *Design and synthesis of novel dual-cyclic RGD peptides for alphavbeta3 integrin targeting; J. Liu, X. Cheng, X. Tian, D. Guan, J. Ao, Z. Wu, W. Huang, Z. Le;* ***Bioorg Med Chem Lett*** *2019;* ***29****: 896-900. https://doi.org/10.1016/j.bmcl.2019.01.043*

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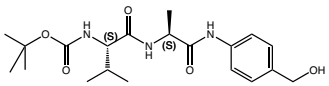
Product details

ADC1040 Boc-Val-Ala-PAB

t-Butyloxycarbonyl-valyl-alanyl-4-aminobenzylalcohol

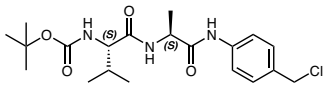
CAS-No. 1884577-99-4
Formula $C_{20}H_{31}N_3O_5$
Mol. weight 393,48 g/mol



ADC1660 Boc-Val-Ala-PAB-Cl

tert-butyloxycarbonyl-valyl-alanyl-4-aminobenzylchloride

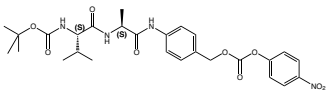
Formula $C_{20}H_{30}ClN_3O_4$
Mol. weight 411,93 g/mol



ADC1050 Boc-Val-Ala-PAB-PNP

t-Butyloxycarbonyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)carbonate

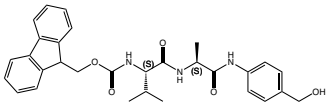
CAS-No. 1884578-00-0
Formula $C_{27}H_{34}N_4O_9$
Mol. weight 558,58 g/mol



ADC1060 Fmoc-Val-Ala-PAB

9-Fluorenylmethyloxycarbonyl-valyl-alanyl-4-aminobenzylalcohol

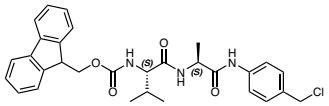
CAS-No. 1394238-91-5
Formula $C_{30}H_{33}N_3O_5$
Mol. weight 515,61 g/mol



ADC1670 Fmoc-Val-Ala-PAB-Cl

9-Fluorenylmethyloxycarbonyl-valyl-alanyl-4-aminobenzylchloride

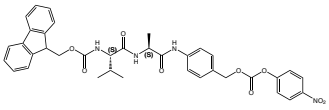
CAS-No. 1491136-17-4
Formula $C_{30}H_{32}ClN_3O_4$
Mol. weight 534,05 g/mol



ADC1070 Fmoc-Val-Ala-PAB-PNP

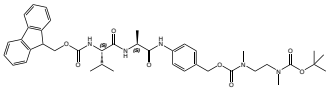
9-Fluorenylmethyloxycarbonyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)carbonate

CAS-No. 1394238-92-6
Formula $C_{37}H_{36}N_4O_9$
Mol. weight 680,71 g/mol



ADC1410 Fmoc-Val-Ala-PAB-NMeCH$_2$CH$_2$NMe-Boc

9-Fluorenylmethyloxycarbonyl-valyl-alanyl-4-aminobenzyloxycarbonyl-((*t*-buytl methyl(2-methylamino)ethyl)carbamate)



CAS-No.	1691196-82-3
Formula	$C_{40}H_{51}N_5O_8$
Mol. weight	729,86 g/mol

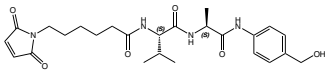
References:

- *Multivalency Increases the Binding Strength of RGD Peptidomimetic-Paclitaxel Conjugates to Integrin alphaV beta3; A. Raposo Moreira Dias, A. Pina, A. Dal Corso, D. Arosio, L. Belvisi, L. Pignataro, M. Caruso and C. Gennari;* ***Chemistry*** *2017;* ***23****: 14410-14415. https://doi.org/10.1002/chem.201703093*
- *Synthesis and biological evaluation of RGD peptidomimetic-paclitaxel conjugates bearing lysosomally cleavable linkers; A. Dal Corso, M. Caruso, L. Belvisi, D. Arosio, U. Piarulli, C. Albanese, F. Gasparri, A. Marsiglio, F. Sola, S. Troiani, B. Valsasina, L. Pignataro, D. Donati, C. Gennari;* ***Chemistry*** *2015;* ***21****: 6921-9. https://doi.org/10.1002/chem.201500158*
- *Elongated multiple electronic cascade and cyclization spacer systems in activatible anticancer prodrugs for enhanced drug release; F. M. de Groot, W. J. Loos, R. Koekkoek, L. W. van Berkom, G. F. Busscher, A. E. Seelen, C. Albrecht, P. de Bruijn, H. W. Scheeren;* ***J Org Chem*** *2001;* ***66****: 8815-30. https://doi.org/10.1021/jo0158884*

Product details

ADC1270 MC-Val-Ala-PAB

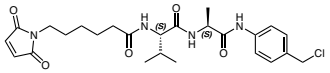
6-maleimidohexanoyl-valyl-alanyl-(4-aminobenzyl alcohol)



CAS-No.	1870916-87-2
Formula	$C_{25}H_{34}N_4O_6$
Mol. weight	486,56 g/mol

ADC1700 MC-Val-Ala-PAB-Cl

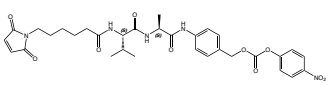
6-Maleimidohexanoyl-valyl-alanyl-(4-aminobenzyl chloride)



Formula	$C_{25}H_{33}ClN_4O_5$
Mol. weight	521,01 g/mol

ADC1280 MC-Val-Ala-PAB-PNP

6-maleimidohexanoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No.	1639939-40-4
Formula	$C_{32}H_{37}N_5O_{10}$
Mol. weight	651,66 g/mol

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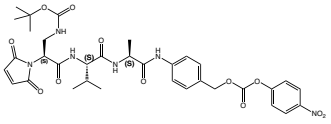
References:

- *Improved Methodology for the Synthesis of a Cathepsin B Cleavable Dipeptide Linker, Widely Used in Antibody-Drug Conjugate Research; D. Mondal, J. Ford, K. G. Pinney;* ***Tetrahedron Lett*** *2018;* ***59****: 3594-3599. https://doi.org/10.1016/j.tetlet.2018.08.021*
- *Next generation maleimides enable the controlled assembly of antibody-drug conjugates via native disulfide bond bridging; F. F. Schumacher, J. P. Nunes, A. Maruani, V. Chudasama, M. E. Smith, K. A. Chester, J. R. Baker, S. Caddick;* ***Org Biomol Chem*** *2014;* ***12****: 7261-9. https://doi.org/10.1039/c4ob01550a*
- *Site-Specific Conjugation of Auristatins onto Engineered scFv Using Second Generation Maleimide to Target HER2-positive Breast Cancer in Vitro; N. Aubrey, E. Allard-Vannier, C. Martin, F. Bryden, S. Letast, C. Colas, Z. Lakhrif, N. Collinet, I. Dimier-Poisson, I. Chourpa, M. C. Viaud-Massuard, N. Joubert;* ***Bioconjug Chem*** *2018;* ***29****: 3516-3521. https://doi.org/10.1021/acs.bioconjchem.8b00668*
- *Impact of cathepsin B-sensitive triggers and hydrophilic linkers on in vitro efficacy of novel site-specific antibody-drug conjugates; F. Bryden, C. Martin, S. Letast, E. Lles, I. Vieitez-Villemin, A. Rousseau, C. Colas, M. Brachet-Botineau, E. Allard-Vannier, C. Larbouret, M. C. Viaud-Massuard, N. Joubert;* ***Org Biomol Chem*** *2018;* ***16****: 1882-1889. https://doi.org/10.1039/c7ob02780j*

Product details

ADC1080 Mal-Dap(Boc)-Val-Ala-PAB-PNP

N-alpha-Maleimido-N-beta-t-butyloxycarbonyl-L-2,3-diaminopropionyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



Formula	$C_{34}H_{40}N_6O_{12}$
Mol. weight	721,71 g/mol

References:

- *Linker Technologies for Antibody–Drug Conjugates; B. Nolting;* ***Antibody-Drug Conjugates L. Ducry*** *2013;* ***1045****: 71-100. https://doi.org/10.1007/978-1-62703-541-5_5*
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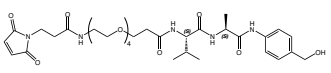
- *In Vivo Antitumor Activity of a Novel Acetazolamide-Cryptophycin Conjugate for the Treatment of Renal Cell Carcinomas; S. Cazzamalli, E. Figueras, L. Petho, A. Borbely, C. Steinkuhler, D. Neri, N. Sewald;* ***ACS Omega*** *2018;* ***3****: 14726-14731. https://doi.org/10.1021/acsomega.8b02350*

Product details

ADC1390 Mal-beta-Ala-PEG(4)-Val-Ala-PAB

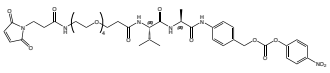
maleimido-beta-alanyl-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl alcohol)



CAS-No.	2417003-93-9
Formula	$C_{33}H_{49}N_5O_{11}$
Mol. weight	691,77 g/mol

ADC1400 Mal-beta-Ala-PEG(4)-Val-Ala-PAB-PNP

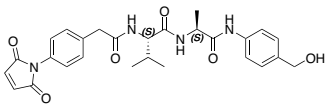
maleimido-beta-alanyl-tetraethyleneglycol-propanoyl-valyl-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No. 2417003-94-0
Formula $C_{40}H_{52}N_6O_{15}$
Mol. weight 856,87 g/mol

ADC1730 Mal-PhAc-Val-Ala-PAB

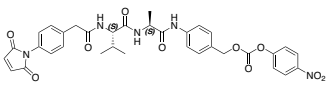
(S)-2-(2-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)acetamido)-N-((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide



Formula $C_{27}H_{30}N_4O_6$
Mol. weight 506,56 g/mol

ADC1740 Mal-PhAc-Val-Ala-PAB-PNP

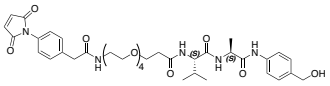
4-((S)-2-((S)-2-(2-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)acetamido)-3-methylbutanamido)propanamido)benzyl (4-nitrophenyl) carbonate



Formula $C_{34}H_{33}N_5O_{10}$
Mol. weight 671,66 g/mol

ADC1770 Mal-PhAc-PEG(4)-Val-Ala-PAB

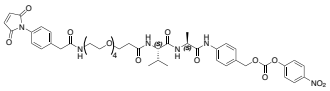
(S)-2-(3-(2-(2-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)acetamido)ethoxy)propanamido)-N-((S)-1-((4-(hydroxymethyl)phenyl)amino)-1-oxopropan-2-yl)-3-methylbutanamide



Formula $C_{32}H_{39}N_5O_8$
Mol. weight 621,69 g/mol

ADC1780 Mal-PhAc-PEG(4)-Val-Ala-PAB-PNP

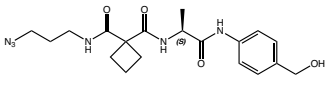
4-((2S,5S)-15-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)-5-isopropyl-2-methyl-4,7,14-trioxo-10-oxa-3,6,13-triazapentadecanamido)benzyl (4-nitrophenyl) carbonate



Formula $C_{39}H_{42}N_6O_{12}$
Mol. weight 786,80 g/mol

ADC1580 Azido-cyclobutane-1,1-dicarboxamide-Ala-PAB

3-azidopropyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl alcohol)



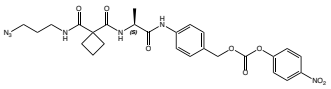
CAS-No. 2576471-45-7
Formula $C_{19}H_{26}N_6O_4$
Mol. weight 402,45 g/mol

back to content ↑

Product details

ADC1590 Azido-cyclobutane-1,1-dicarboxamide-Ala-PAB-PNP

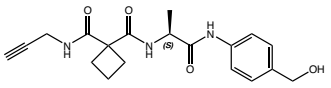
3-azidopropyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No. 2576471-36-6
Formula $C_{26}H_{29}N_7O_8$
Mol. weight 567,55 g/mol

ADC1600 Propargyl-cyclobutane-1,1-dicarboxamide-Ala-PAB

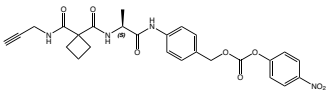
propargyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl alcohol)



CAS-No. 2576471-28-6
Formula $C_{19}H_{23}N_3O_4$
Mol. weight 357,40 g/mol

ADC1610 Propargyl-cyclobutane-1,1-dicarboxamide-Ala-PAB-PNP

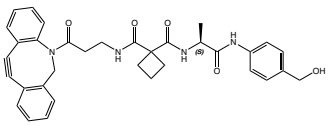
propargyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No. 2576471-42-4
Formula $C_{26}H_{26}N_4O_8$
Mol. weight 522,51 g/mol

ADC1620 DBCO-cyclobutane-1,1-dicarboxamide-Ala-PAB

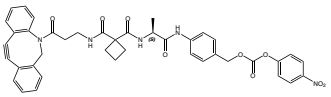
dibenzoazacyclooctyne-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl alcohol)



CAS-No. 2576471-46-8
Formula $C_{34}H_{34}N_4O_5$
Mol. weight 578,66 g/mol

ADC1630 DBCO-cyclobutane-1,1-dicarboxamide-Ala-PAB-PNP

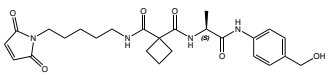
dibenzoazacyclooctyne-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No. 2576471-43-5
Formula $C_{41}H_{37}N_5O_9$
Mol. weight 743,76 g/mol

ADC1560 Mal-cyclobutane-1,1-dicarboxamide-Ala-PAB

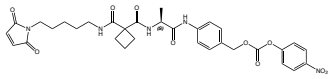
5-maleimidopentyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl alcohol)



CAS-No. 2576471-41-3
Formula $C_{25}H_{32}N_4O_6$
Mol. weight 484,54 g/mol

ADC1570 Mal-cyclobutane-1,1-dicarboxamide-Ala-PAB-PNP

5-maleimidopentyl-cyclobutane-1,1-dicarboxamide-alanyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No.	2576471-35-5
Formula	$C_{32}H_{35}N_5O_{10}$
Mol. weight	649,65 g/mol

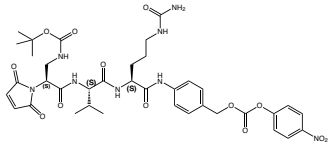
Reference:

→ *Discovery of Peptidomimetic Antibody-Drug Conjugate Linkers with Enhanced Protease Specificity; B. Wei, J. Gunzner-Toste, H. Yao, T. Wang, J. Wang, Z. Xu, J. Chen, J. Wai, J. Nonomiya, S. P. Tsai, J. Chuh, K. R. Kozak, Y. Liu, S. F. Yu, J. Lau, G. Li, G. D. Phillips, D. Leipold, A. Kamath, D. Su, K. Xu, C. Eigenbrot, S. Steinbacher, R. Ohri, H. Raab, L. R. Staben, G. Zhao, J. A. Flygare, T. H. Pillow, V. Verma, L. A. Masterson, P. W. Howard, B. Safina;* ***J. Med. Chem.*** *2018;* ***61****: 989-1000. https://doi.org/10.1021/acs.jmedchem.7b01430*

3.2. Valine-Citrulline-Based Enzymatically Cleavable Linkers

ADC1090 Mal-Dap(Boc)-Val-Cit-PAB-PNP

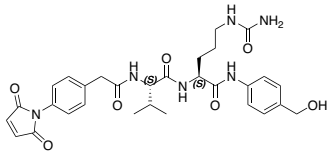
N-alpha-Maleimido-N-beta-*t*-butyloxycarbonyl-L-2,3-diaminopropionyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No.	2281797-57-5
Formula	$C_{37}H_{46}N_8O_{13}$
Mol. weight	810,81 g/mol

ADC1750 Mal-PhAc-Val-Cit-PAB

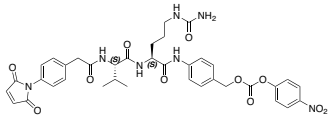
(S)-2-((S)-2-(2-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)acetamido)-3-methylbutanamido)-N-(4-(hydroxymethyl)phenyl)-5-ureidopentanamide



Formula	$C_{30}H_{36}N_6O_7$
Mol. weight	592,65 g/mol

ADC1760 Mal-PhAc-Val-Cit-PAB-PNP

4-((S)-2-((S)-2-(2-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)acetamido)-3-methylbutanamido)-5-ureidopentanamido)benzyl (4-nitrophenyl) carbonate



Formula	$C_{37}H_{39}N_7O_{11}$
Mol. weight	757,76 g/mol

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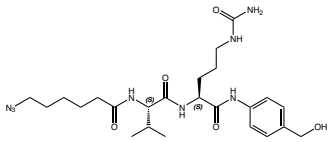
Product details

ADC1120 6-Azidohexanoyl-Val-Cit-PAB

6-azidohexanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

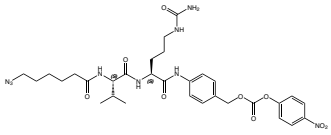
CAS-No.	1613321-02-0
Formula	$C_{24}H_{38}N_8O_5$
Mol. weight	518,61 g/mol



ADC1130 6-Azidohexanoyl-Val-Cit-PAB-PNP

6-azidohexanoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	1613321-01-9
Formula	$C_{31}H_{41}N_9O_9$
Mol. weight	683,71 g/mol



Reference:

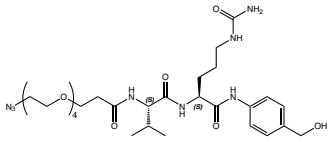
→ *NKT cell-dependent glycolipid-peptide vaccines with potent anti-tumour activity; R. J. Anderson, B. J. Compton, C. W. Tang, A. Authier-Hall, C. M. Hayman, G. W. Swinerd, R. Kowalczyk, P. Harris, M. A. Brimble, D. S. Larsen, O. Gasser, R. Weinkove, I. F. Hermans, G. F. Painter;* ***Chem. Sci.*** *2015; **6**: 5120-5127. https://doi.org/10.1039/c4sc03599b*

Product details

ADC1160 Azido-PEG(4)-Val-Cit-PAB

azido-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

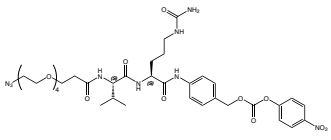
CAS-No.	2055024-64-9
Formula	$C_{29}H_{48}N_8O_9$
Mol. weight	652,74 g/mol



ADC1170 Azido-PEG(4)-Val-Cit-PAB-PNP

azido-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	1869126-60-2
Formula	$C_{36}H_{51}N_9O_{13}$
Mol. weight	817,84 g/mol

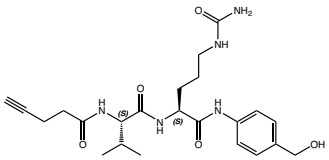


Product details

ADC1140 4-Pentynoyl-Val-Cit-PAB

4-pentynoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

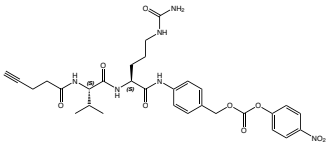
CAS-No. 2708150-97-2
Formula $C_{23}H_{33}N_5O_5$
Mol. weight 459,54 g/mol



ADC1150 4-Pentynoyl-Val-Cit-PAB-PNP

4-pentynoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

Formula $C_{30}H_{36}N_6O_9$
Mol. weight 624,64 g/mol



Reference:

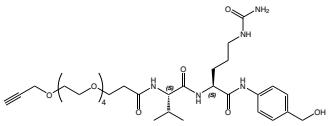
→ *Integrin-Targeting Knottin Peptide–Drug Conjugates Are Potent Inhibitors of Tumor Cell Proliferation. N. Cox, J. R. Kintzing, M. Smith, G. A. Grant, J. R. Cochran;* ***Angew. Chem. Int. Ed.*** *2016;* ***55(34)****: 9894-9897. https://doi.org/10.1002/anie.201603488*

Product details

ADC1180 Alkyne-PEG(5)-Val-Cit-PAB

propargyl-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

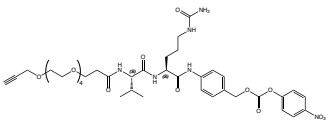
Formula $C_{32}H_{51}N_5O_{10}$
Mol. weight 665,77 g/mol



ADC1190 Alkyne-PEG(5)-Val-Cit-PAB-PNP

propargyl-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

Formula $C_{39}H_{54}N_6O_{14}$
Mol. weight 830,88 g/mol



References:

→ *Exploration of the carmaphycins as payloads in antibody drug conjugate anticancer agents. J. Almaliti, B. Miller, H. Pietraszkiewicz, E. Glukhov, C. B. Naman, T. Kline, J. Hanson, X. Li, S. Zhou, F. A. Valeriote, W. H. Gerwick;* ***Eur J Med Chem.*** *2019;* ***161****: 416-432. https://doi.org/10.1016/j.ejmech.2018.10.024*

→ *Design and synthesis of novel dual-cyclic RGD peptides for avβ3 integrin targeting. J. Liu, X. Cheng, X. Tian, D. Guan, J. Ao, Z. Wu, W. Huang, Z. Le;* ***Bioorg Med Chem Lett.*** *2019;* ***29(7)****: 896-900. https://doi.org/10.1016/j.bmcl.2019.01.043*

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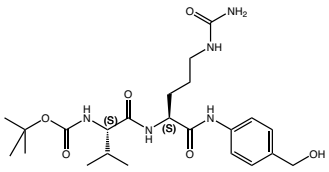
Product details

ADC1020 Boc-Val-Cit-PAB

t-Butyloxycarbonyl-valyl-citrullyl-4-aminobenzylalcohol

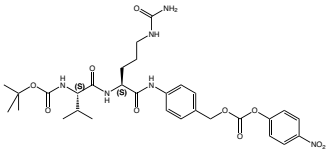
CAS-No. 870487-09-5
Formula $C_{23}H_{37}N_5O_6$
Mol. weight 479,59 g/mol



ADC1010 Boc-Val-Cit-PAB-PNP

t-Butyloxycarbonyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)carbonate

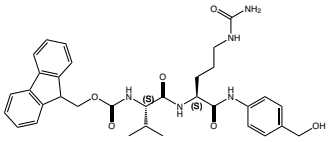
CAS-No. 870487-10-8
Formula $C_{30}H_{40}N_6O_{10}$
Mol. weight 644,67 g/mol



ADC1030 Fmoc-Val-Cit-PAB

9-Fluorenylmethyloxycarbonyl-valyl-citrullyl-4-aminobenzylalcohol

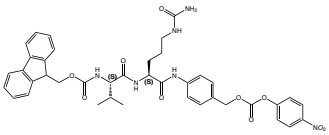
CAS-No. 159858-22-7
Formula $C_{33}H_{39}N_5O_6$
Mol. weight 601,29 g/mol



ADC1000 Fmoc-Val-Cit-PAB-PNP

9-Fluorenylmethyloxycarbonyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)carbonate

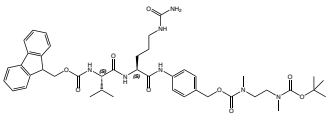
CAS-No. 863971-53-3
Formula $C_{40}H_{42}N_6O_{10}$
Mol. weight 766,80 g/mol



ADC1240 Fmoc-Val-Cit-PAB-NMeCH$_2$CH$_2$NMe-Boc

9-Fluorenylmethyloxycarbonyl-valyl-citrullyl-4-aminobenzyloxycarbonyl-((*t*-buytl methyl(2-methylamino)ethyl)carbamate)

CAS-No. 1802297-96-6
Formula $C_{43}H_{57}N_7O_9$
Mol. weight 815,95 g/mol



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→ *Multivalency Increases the Binding Strength of RGD Peptidomimetic-Paclitaxel Conjugates to Integrin αVβ3. A. R. M. Dias, A. Pina, A. Dal Corso, D. Arosio, L. Belvisi, L. Pignataro, M. Caruso, C. Gennari;* ***Chem. Eur. J.*** *2017;* ***23(58)****: 14410-14415. https://doi.org/10.1002/chem.201703093*

→ *Synthesis and Biological Evaluation of RGD Peptidomimetic–Paclitaxel Conjugates Bearing Lysosomally Cleavable Linkers. A. D. Corso, M. Caruso, L. Belvisi, D. Arosio, U. Piarulli, C. Albanese, F. Gasparri, A. Marsiglio, F. Sola, S. Troiani, B. Valsasina, L. Pignataro, D. Donati, C. Gennari;* ***Chem. Eur. J.*** *2015;* ***21(18)****: 6921-6929. https://doi.org/10.1002/chem.201500158*

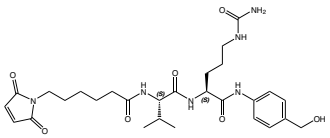
→ *Elongated Multiple Electronic Cascade and Cyclization Spacer Systems in Activatible Anticancer Prodrugs for Enhanced Drug Release. F. M. H. de Groot, W. J. Loos, R. Koekkoek, L. W. A. van Berkom, G. F. Busscher, A. E. Seelen, C. Albrecht, P. Bruijn, H. W. Scheeren;* ***J. Org. Chem.*** *2001;* ***66(26)****: 8815-8830. https://doi.org/10.1021/jo0158884*

Product details

ADC1100 MC-Val-Cit-PAB

6-maleimidohexanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

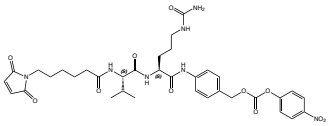
CAS-No.	159857-80-4
Formula	$C_{28}H_{40}N_6O_7$
Mol. weight	572,65 g/mol



ADC1110 MC-Val-Cit-PAB-PNP

6-maleimidohexanoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	159857-81-5
Formula	$C_{35}H_{43}N_7O_{11}$
Mol. weight	737,76 g/mol



Reference:

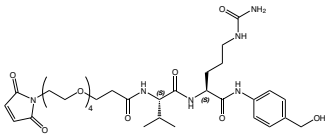
→ *Improved Methodology for the Synthesis of a Cathepsin B Cleavable Dipeptide Linker, Widely Used in Antibody-Drug Conjugate Research. D. Mondal, J. Ford, K. G. Pinney;* ***Tetrahedron Lett.*** *2018;* ***59(40)****: 3594-3599. https://doi.org/10.1016/j.tetlet.2018.08.021*

Product details

ADC1200 Mal-PEG(4)-Val-Cit-PAB

maleimido-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)

CAS-No.	2055041-39-7
Formula	$C_{33}H_{50}N_6O_{11}$
Mol. weight	706,78 g/mol



Reference:

→ *In Vivo Antitumor Activity of a Novel Acetazolamide–Cryptophycin Conjugate for the Treatment of Renal Cell Carcinomas. S. Cazzamalli, E. Figueras, L. Pethő, A. Borbély, C. Steinkühler, D. Neri, N. Sewald;* ***ACS Omega*** *2018;* ***3(11)****: 14726-14731. https://doi.org/10.1021/acsomega.8b02350*

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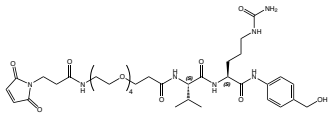
Product details

ADC1220 Mal-beta-Ala-PEG(4)-Val-Cit-PAB

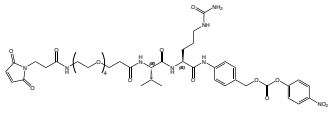
maleimido-beta-alanyl-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl alcohol)



CAS-No.	1949793-41-2
Formula	$C_{36}H_{55}N_7O_{12}$
Mol. weight	777,86 g/mol

ADC1230 Mal-beta-Ala-PEG(4)-Val-Cit-PAB-PNP

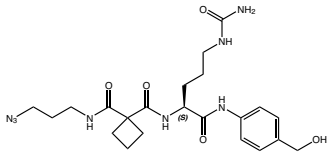
maleimido-beta-alanyl-tetraethyleneglycol-propanoyl-valyl-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No.	2003260-12-4
Formula	$C_{43}H_{58}N_8O_{16}$
Mol. weight	942,96 g/mol

ADC1480 Azido-cyclobutane-1,1-dicarboxamide-Cit-PAB

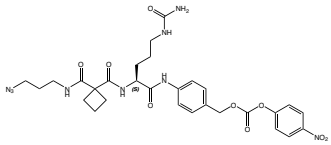
3-azidopropyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl alcohol)



CAS-No.	2576471-33-3
Formula	$C_{22}H_{32}N_8O_5$
Mol. weight	488,54 g/mol

ADC1490 Azido-cyclobutane-1,1-dicarboxamide-Cit-PAB-PNP

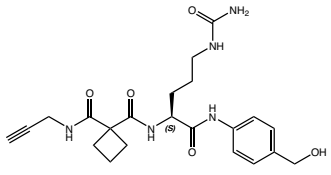
3-azidopropyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate



CAS-No.	2576471-44-6
Formula	$C_{29}H_{35}N_9O_9$
Mol. weight	653,64 g/mol

ADC1500 Propargyl-cyclobutane-1,1-dicarboxamide-Cit-PAB

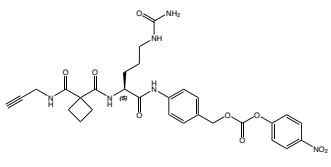
propargyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl alcohol)



CAS-No.	2576471-27-5
Formula	$C_{22}H_{29}N_5O_5$
Mol. weight	443,50 g/mol

ADC1510 Propargyl-cyclobutane-1,1-dicarboxamide-Cit-PAB-PNP

propargyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

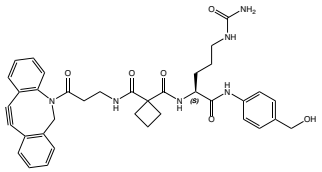


CAS-No.	2576471-40-2
Formula	$C_{29}H_{32}N_6O_9$
Mol. weight	608,60 g/mol

ADC1520 DBCO-cyclobutane-1,1-dicarboxamide-Cit-PAB

dibenzoazacyclooctyne-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl alcohol)

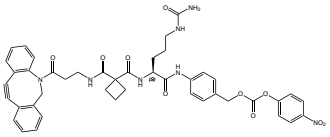
CAS-No.	2576471-51-5
Formula	$C_{37}H_{40}N_6O_6$
Mol. weight	664,75 g/mol



ADC1530 DBCO-cyclobutane-1,1-dicarboxamide-Cit-PAB-PNP

dibenzoazacyclooctyne-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

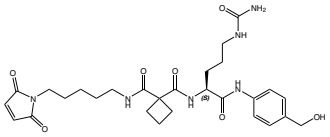
CAS-No.	2576471-34-4
Formula	$C_{44}H_{43}N_7O_{10}$
Mol. weight	829,85 g/mol



ADC1460 Mal-cyclobutane-1,1-dicarboxamide-Cit-PAB

5-maleimidopentyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl alcohol)

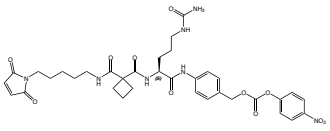
CAS-No.	1799663-03-8
Formula	$C_{28}H_{38}N_6O_7$
Mol. weight	570,64 g/mol



ADC1470 Mal-cyclobutane-1,1-dicarboxamide-Cit-PAB-PNP

5-maleimidopentyl-cyclobutane-1,1-dicarboxamide-citrullyl-(4-aminobenzyl)-(4-nitrophenyl)-carbonate

CAS-No.	2204228-34-0
Formula	$C_{35}H_{41}N_7O_{11}$
Mol. weight	735,74 g/mol



Reference:

→ *Discovery of Peptidomimetic Antibody–Drug Conjugate Linkers with Enhanced Protease Specificity. B. Wei, J. Gunzner-Toste, H. Yao, T. Wang, J. Wang, Z. Xu, J. Chen, J. Wai, J. Nonomiya, S. Ping Tsai, J. Chuh, K. R. Kozak, Y. Liu, S. Yu, J. Lau, G. Li, G. D. Phillips, D. Leipold, A. Kamath, D. Su, K. Xu, C. Eigenbrot, S. Steinbacher, R. Ohri, H. Raab, L. R. Staben, G. Zhao, J. A. Flygare, T. H. Pillow, V. Verma, L. A. Masterson, P. W. Howard, B. Safina;* ***J. Med. Chem.*** *2018;* ***61(3)****: 989-1000. https://doi.org/10.1021/acs.jmedchem.7b01430*

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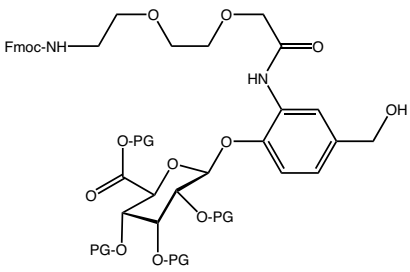
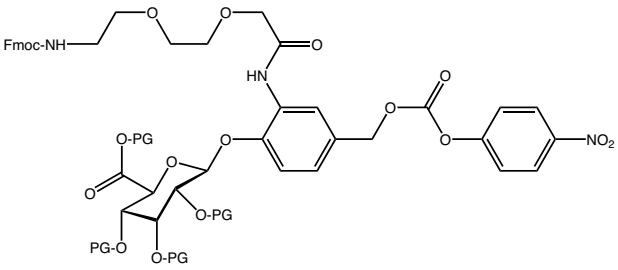
3.3. β-Glucuronide Enzymatically Cleavable Linkers

As an extension of the linkerology® toolbox, the design of linkers with improved stability during systemic circulation is highly desired. As the drug-releasing lysosomal enzyme β-glucuronidase is abundantly present within lysosomes and overexpressed in some tumor types but low outside cells, β-glucuronic acid-based linkers provide the potential for high ADC stability in the systemic circulation and selective intracellular drug release. Especially for ADCs based on highly hydrophobic drugs, the incorporation of the highly hydrophilic β-glucuronides may circumvent the tendency of aggregation. For example, a drug-linker consisting of a β-glucuronide linked to auristatin MMAF was prepared. Rat plasma stability analysis revealed an extrapolated half-life of 81 days, compared with about six days for the corresponding valine-citrulline dipeptide-linked MMAF.

Interested in β-Glucuronide Enzymatically Cleavable Linkers?

Please contact our Custom Synthesis for more details.





References:

- *Expanded Utility of the β-Glucuronide Linker: ADCs That Deliver Phenolic Cytotoxic Agents; S. C. Jeffrey, J. De Brabander, J. Miyamoto, P. D. Senter;* ***ACS Med. Chem. Lett.*** *2010;* ***1****: 277-280. https://doi.org/10.1021/ml100039h*
- *Development and Properties of β-Glucuronide Linkers for Monoclonal Antibody-Drug Conjugates; S. C. Jeffrey, J. B. Andreyka, S. X. Bernhardt, K. M. Kissler, T. Kline, J. S. Lenox, R. F. Moser, M. T. Nguyen, N. M. Okeley, I. J. Stone, X. Zhang, P. D. Senter;* ***Bioconjugate Chem.*** *2006;* ***17****: 831-840. https://doi.org/10.1021/bc0600214*
- *Linker Technologies for Antibody–Drug Conjugates; B. Nolting;* ***Antibody-Drug Conjugates L. Ducry*** *2013;* ***1045****: 71-100. https://doi.org/10.1007/978-1-62703-541-5_5*

3.4. Disulfide-Based (Self-Immolative) Linkers

Another chemically labile linkage extensively exploited in the development of antibody-drug conjugates are disulfides. They are stable at physiological pH and are designed to release the drug upon internalization inside cells. The cytosol provides a significantly more reducing environment compared to the extracellular milieu and the presence of cytoplasmic thiol cofactor, such as reduced glutathione (GSH). Additionally, the intracellular enzyme protein disulfide isomerase, or similar enzymes capable of cleaving disulfide bonds, may also contribute to the preferential cleavage of disulfide bonds inside cells. GSH is reported to be present in cells in the concentration range of 0.5-10 mM, compared with a significantly lower concentration of GSH or cysteine in plasma at approximately 5 µM. This is especially true for tumor cells, where irregular blood flow leads to a hypoxic state, resulting in enhanced activity of reductive enzymes and therefore in even higher glutathione concentrations.

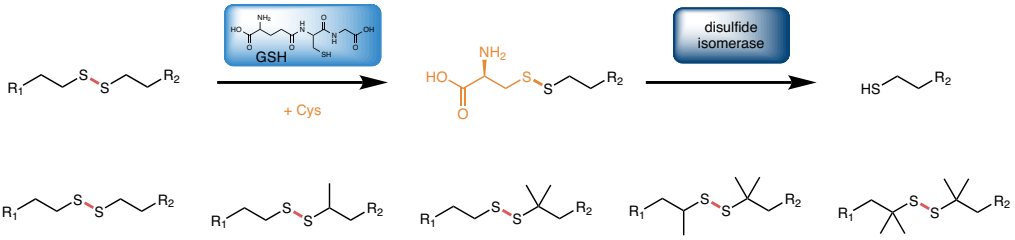


Fig. 19: The stability of disulfide linkers can be finetuned by neighboring methylation.

The stability of disulfide bridges can be fine-tuned by adjacent residues (*Fig. 19*). Methyl groups are bulky enough to have a significant influence on the thermodynamic stability of the disulfide bridge. While one additional methyl group already enhances the stability drastically, two methyl groups make the disulfide bond practically stable towards reductive cleavage. A methylation number of three or four will completely lock the disulfide bridge towards further modifications. As the direct conjugation of cleavable triggers to bioactive agents through disulfide bridges suffers from ineffective cleavage in case of bulky moieties and resulting steric hindrance as well as restricted possibilities for trigger-drug combinations, disulfide based self-immolative linkers (DSILs) provide a robust strategy for selective activation upon disulfide cleavage in the reductive cytoplasmic milieu. Disulfide-based self-immolative linkers benefit of the reversibility of disulfide-bond formation. Upon oxidation, free thiols form less nucleophilic disulfide bonds, preventing self-immolative fragmentation. However, this process can be reversed in the presence of reducing agents, such as GSH. Those specifications allow for sufficient stability in the extracellular milieu but spontaneous self-immolative reaction within the cytosol upon GSH-mediated disulfide cleavage. Variations in the linker's chemical composition (disulfide ethoxycarbonyl (SSE) vs. disulfide benzyloxycarbonyl (SSB)) result in chemically tunable kinetics of the self-immolative cleavage due to different response rates towards GSH, showing higher rates for SSB-based DSILs compared to SSE-based ones (*Fig. 20*). Thus, the choice of the linker allows for fine-tuning of the cleavage speed and payload release.

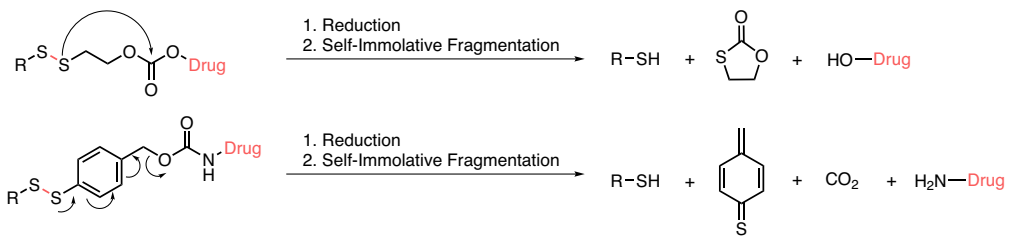


Fig. 20: Disulfide-based self-immolative linkers either based on an intramolecular cyclization cascade mechanism or on a 1,6-elimination.

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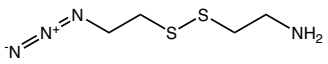
Product details

HNN1090 N_3-Cystamine*HCl

Azido-cystamine hydrochloride

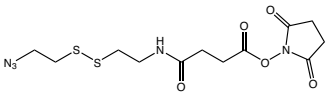
CAS-No. 1807512-40-8 net
Formula $C_4H_{10}N_4S_2$*HCl
Mol. weight 178,28*36,45 g/mol



HAA2255 N_3-Cystamine-Suc-OSu

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

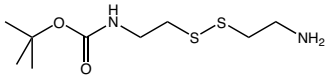
CAS-No. 1987341-40-1
Formula $C_{12}H_{17}N_5O_5S_2$
Mol. weight 375,42 g/mol



BNN1170 Boc-Cystamine

2-(*t*-Butyloxycarbonylamino)ethyldithio-2'-ethylamine

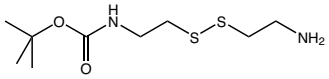
CAS-No. 485800-26-8
Formula $C_9H_{20}N_2O_2S_2$
Mol. weight 252,40 g/mol



BNN1063 Boc-Cystamine*HCl

2-(*t*-Butyloxycarbonylamino)ethyldithio-2'-ethylamine hydrochloride

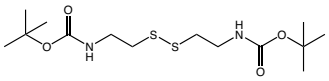
CAS-No. 93790-49-9
Formula $C_9H_{20}N_2O_2S_2$*HCl
Mol. weight 252,40*36,45 g/mol



BNN1360 Di-Boc-Cystamine

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

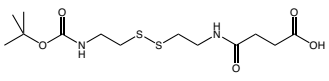
CAS-No. 67385-10-8
Formula $C_{14}H_{28}N_2O_4S_2$
Mol. weight 352,51 g/mol



BAA2180 Boc-Cystamine-Suc-OH

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

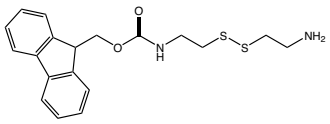
CAS-No. 946849-79-2
Formula $C_{13}H_{24}N_2O_5S_2$
Mol. weight 352,47 g/mol



RL-3370 Fmoc-Cystamine*HCl

2-((9-Fluorenylmethyloxycarbonylamino)ethyl)disulfanyl-(2-aminoethane) hydrochloride

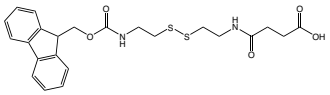
CAS-No.	2893917-85-4
Formula	$C_{19}H_{22}N_2O_2S_2$*HCl
Mol. weight	374,52*36,45 g/mol



RL-3310 Fmoc-Cystamine-Suc

4-(2-((2-(9-Fluorenylmethyloxycarbonylamino)ethyl) disulfanyl)ethylamino)-4-oxobutanoic acid

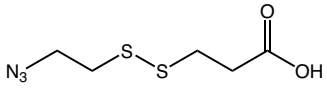
CAS-No.	946849-80-5
Formula	$C_{23}H_{26}N_2O_5S_2$
Mol. weight	474,59 g/mol



RL-4100 Azido-SS-COOH

3-((2-azidoethyl)disulfanyl)propanoic acid

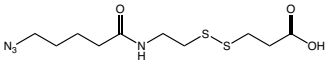
CAS-No.	2228857-32-5
Formula	$C_5H_9N_3O_2S_2$
Mol. weight	207,27 g/mol



RL-3320 Azido-Pen-SS-COOH

3-((2-(5-azidopentanamido)ethyl)disulfanyl)propanoic acid

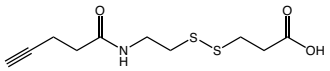
Formula	$C_{10}H_{18}N_4O_3S_2$
Mol. weight	306,40 g/mol



RL-3330 Alkyne-SS-COOH

3-((2-pent-4-ynamidoethyl)disulfanyl)propanoic acid

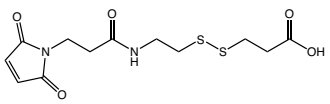
CAS-No.	2279938-29-1
Formula	$C_{10}H_{15}NO_3S_2$
Mol. weight	261,36 g/mol



RL-4090 Mal-SS-COOH

3-((2-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)ethyl)disulfanyl)propanoic acid

CAS-No.	2128735-24-8
Formula	$C_{12}H_{16}N_2O_5S_2$
Mol. weight	332,39 g/mol



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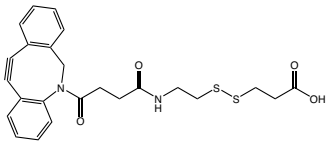
Product details

RL-4110 DBCO-Suc-SS-COOH

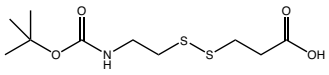
CAS-No. 2749426-25-1
Formula $C_{24}H_{24}N_2O_4S_2$
Mol. weight 468,59 g/mol



RL-2190 Boc-SS-COOH

3-((2-(*tert*-butoxycarbonylamino)ethyl)disulfanyl) propanoic acid

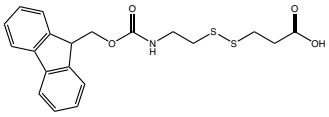
CAS-No. 485800-27-9
Formula $C_{10}H_{19}NO_4S_2$
Mol. weight 281,39 g/mol



RL-2200 Fmoc-SS-COOH

3-((2-(((9H-fluoren-9-yl)methoxy)carbonylamino)ethyl) disulfanyl)propanoic acid

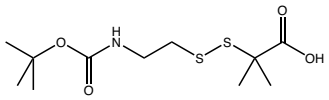
CAS-No. 864235-83-6
Formula $C_{20}H_{21}NO_4S_2$
Mol. weight 403,52 g/mol



RL-2810 Boc-AEDI-OH

2-((2-(*t*-Butyloxycarbonylamino)ethyl)disulfa-nyl)-2-methylpropanoic acid

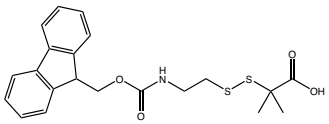
CAS-No. 144700-78-7
Formula $C_{11}H_{21}NO_4S_2$
Mol. weight 295,42 g/mol



RL-2800 Fmoc-AEDI-OH

2-((2-((9-Fluorenylmethyloxycarbonyl)amino)ethyl) disulfanyl)-2-methylpropanoic acid

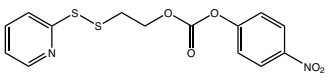
CAS-No. 1823244-38-7
Formula $C_{21}H_{23}NO_4S_2$
Mol. weight 417,54 g/mol



RL-3500 OPSS-OpNC

2-(2-Pyridithio)ethyl-*p*-nitrophenylcarbonate

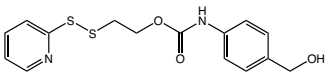
CAS-No. 874302-76-8
Formula $C_{14}H_{12}N_2O_5S_2$
Mol. weight 352,38 g/mol



Product details

RL-3890 OPSS-PAB

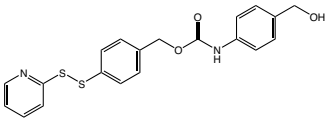
2-(pyridin-2-yldisulfaneyl)ethyl (4-(hydroxymethyl) phenyl)carbamate



CAS-No.	2362536-42-1
Formula	$C_{15}H_{16}N_2O_3S_2$
Mol. weight	336,42 g/mol

RL-3920 OPSS-Bzl-PAB

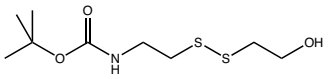
4-(pyridin-2-yldisulfaneyl)benzyl (4-(hydroxymethyl) phenyl)carbamate



Formula	$C_{20}H_{18}N_2O_3S_2$
Mol. weight	398,50 g/mol

RL-3510 Boc-NH-SS-OH

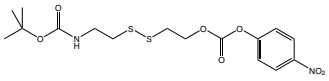
2-((2-(*t*-Butyloxycarbonylamino)ethyl)disulfaneyl) ethan-1-ol



CAS-No.	877864-07-8
Formula	$C_9H_{19}NO_3S_2$
Mol. weight	253,38 g/mol

RL-3520 Boc-NH-SS-OpNC

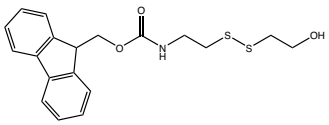
2-((2-(*t*-Butyloxycarbonylamino)ethyl)disulfaneyl) ethan-1-yl *p*-nitrophenylcarbonate



CAS-No.	2040301-00-4
Formula	$C_{16}H_{22}N_2O_7S_2$
Mol. weight	418,48 g/mol

RL-3530 Fmoc-NH-SS-OH

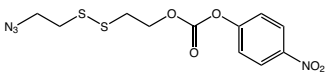
2-((2-((9-Fluorenylmethyloxycarbonyl)amino)ethyl) disulfaneyl)ethan-1-ol



CAS-No.	2576471-39-9
Formula	$C_{19}H_{21}NO_3S_2$
Mol. weight	375,50 g/mol

RL-4150 Azido-SS-OpNC

2-((2-azidoethyl)disulfanyl)ethyl (4-nitrophenyl) carbonate



CAS-No.	2766027-28-3
Formula	$C_{11}H_{12}N_4O_5S_2$
Mol. weight	344,36 g/mol

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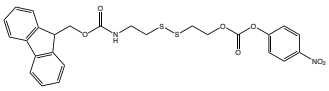
Product details

RL-3540 Fmoc-NH-SS-OpNC

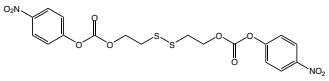
2-((2-((9-Fluorenylmethyloxycarbonyl)amino)ethyl) disulfaneyl)ethan-1-yl *p*-nitrophenylcarbonate



CAS-No.	2576471-53-7
Formula	$C_{26}H_{24}N_2O_7S_2$
Mol. weight	540,61 g/mol

RL-4160 pNCO-SS-OpNC

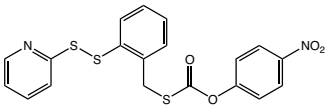
disulfanediylbis(ethane-2,1-diyl) bis(4-nitrophenyl) bis(carbonate)



CAS-No.	1435972-52-3
Formula	$C_{18}H_{16}N_2O_{10}S_2$
Mol. weight	484,45 g/mol

RL-4170 2-OPSS-Bzl-OpNC

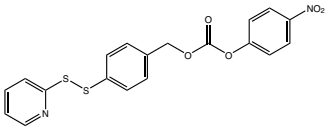
O-(4-nitrophenyl) S-(2-(pyridin-2-yldisulfanyl)benzyl) carbonothioate



CAS-No.	1384425-52-8
Formula	$C_{19}H_{24}N_2O_4S_3$
Mol. weight	430,51 g/mol

RL-3550 OPSS-Bzl-OpNC

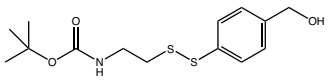
(4-(pyridin-2-yldisulfaneyl)benzyl) *p*-nitrophenylcarbonate



CAS-No.	1151989-04-6
Formula	$C_{19}H_{14}N_2O_5S_2$
Mol. weight	414,45 g/mol

RL-3560 Boc-NH-SS-Bzl-OH

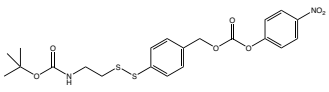
4-((2-(*t*-Butyloxycarbonylamino)ethyl)disulfaneyl) benzylalcohol



CAS-No.	2576471-54-8
Formula	$C_{14}H_{21}NO_3S_2$
Mol. weight	315,45 g/mol

RL-3570 Boc-NH-SS-Bzl-OpNC

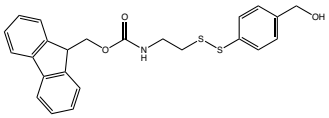
4-((2-(*t*-Butyloxycarbonylamino)ethyl)disulfaneyl) benzyl *p*-nitrophenylcarbonate



CAS-No.	2576471-38-8
Formula	$C_{21}H_{24}N_2O_7S_2$
Mol. weight	480,55 g/mol

RL-3580 Fmoc-NH-SS-Bzl-OH

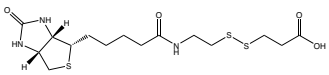
4-((2-((9-Fluorenylmethyloxycarbonyl)amino)ethyl) disulfaneyl)benzylalcohol



CAS-No.	2064282-26-2
Formula	$C_{24}H_{23}NO_3S_2$
Mol. weight	437,57 g/mol

RL-3300 Biotin-SS-COOH

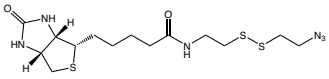
3-((2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl)pentanamido)ethyl)disulfanyl)propanoic acid



CAS-No.	104582-29-8
Formula	$C_{15}H_{25}N_3O_4S_3$
Mol. weight	407,57 g/mol

RL-4120 Biotin-SS-N_3

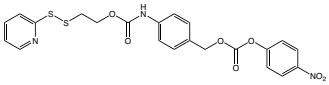
N-(2-((2-azidoethyl)disulfanyl)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



CAS-No.	1620523-64-9
Formula	$C_{14}H_{24}N_6O_2S_3$
Mol. weight	404,57 g/mol

RL-3820 OPSS-PAB-OpNC

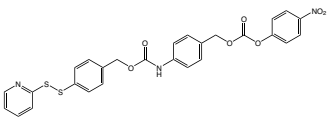
2-(pyridin-2-yldisulfaneyl)ethyl (4-((((4-nitrophenoxy) carbonyl)oxy)methyl)phenyl)carbamate



CAS-No.	2362536-70-5
Formula	$C_{22}H_{19}N_3O_7S_2$
Mol. weight	501,53 g/mol

RL-3850 OPSS-Bzl-PAB-OpNC

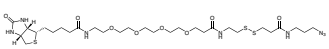
4-(pyridin-2-yldisulfaneyl)benzyl (4-((((4-nitrophenoxy) carbonyl)oxy)methyl)phenyl)carbamate



Formula	$C_{27}H_{21}N_3O_7S_2$
Mol. weight	563,60 g/mol

PEG8100 Biotin-PEG(4)-SS-Azide

N-(2-((3-((3-azidopropyl)amino)-3-oxopropyl)disulfaneyl)ethyl)-1-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxapentadecan-15-amide



CAS-No.	1260247-52-6
Formula	$C_{29}H_{52}N_8O_8S_3$
Mol. weight	736,96 g/mol

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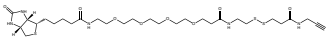
Product details

PEG8110 Biotin-PEG(4)-SS-Alkyne

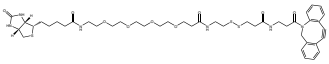
N-(2-((3-oxo-3-(prop-2-ynylamino)propyl)disulfanyl)ethyl)-1-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxapentadecan-15-amide



CAS-No.	1260247-54-8
Formula	$C_{29}H_{49}N_5O_8S_3$
Mol. weight	691,92 g/mol

PEG8120 Biotin-PEG(4)-SS-DBCO

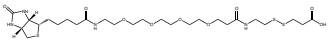
N-(2-((3-(3-(azadibenzocyclooctyn-1-yl)-3-oxopropylamino)-3-oxopropyl)disulfanyl)ethyl)-1-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxapentadecan-15-amide



Formula	$C_{44}H_{60}N_6O_9S_3$
Mol. weight	913,18 g/mol

PEG8090 Biotin-PEG(4)-SS-COOH

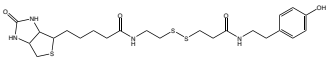
9,25-dioxo-29-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-12,15,18,21-tetraoxa-4,5-dithia-8,24-diazanonacosan-1-oic acid



CAS-No.	1380166-80-2
Formula	$C_{26}H_{46}N_4O_9S_3$
Mol. weight	654,86 g/mol

LS-3570 Biotin-SS-Tyramide

N-(2-((3-(4-hydroxyphenethylamino)-3-oxopropyl)disulfanyl)ethyl)-5-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



CAS-No.	678975-20-7
Formula	$C_{23}H_{34}N_4O_4S_3$
Mol. weight	526,74 g/mol

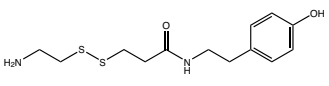
LS-3930 Biotin-PEG(4)-SS-Tyramide

N-(2-((3-(4-hydroxyphenethylamino)-3-oxopropyl)disulfanyl)ethyl)-1-(5-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxapentadecan-15-amide

Formula	$C_{34}H_{55}N_5O_9S_3$
Mol. weight	774,02 g/mol

LS-3960 Tyramide-SS-amine*HCl

3-((2-aminoethyl)disulfanyl)-N-(4-hydroxyphenethyl)propanamide hydrochloride

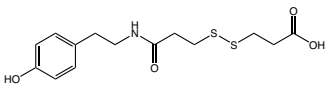


Formula	$C_{13}H_{20}N_2O_2S_2$*HCl
Mol. weight	300,44*36,45 g/mol

LS-4010 Tyramide-SS-COOH

3-((3-(4-hydroxyphenethylamino)-3-oxopropyl)disulfanyl)propanoic acid

Formula	$C_{14}H_{19}NO_4S_2$
Mol. weight	329,43 g/mol



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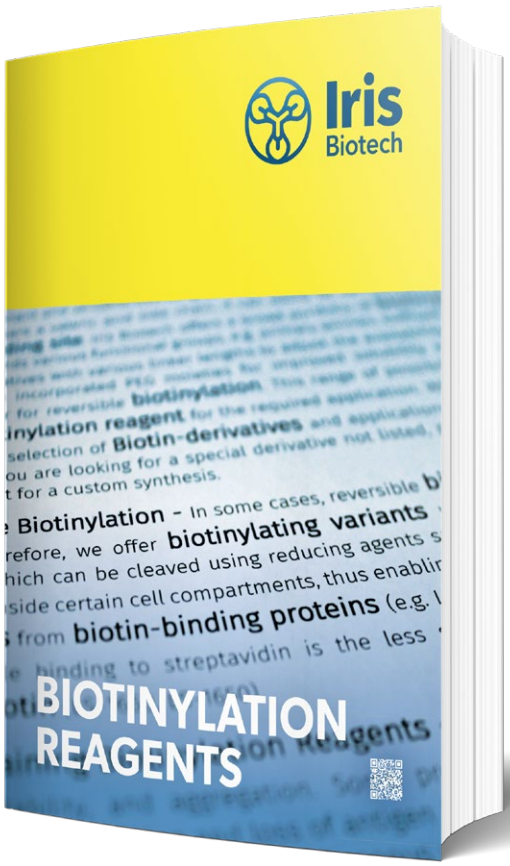

3.5. Dde-Based Linkers

The Dde [N-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-ethyl] protecting group is commonly utilized to protect the sidechain amine groups of lysine, ornithine, 2,4-diaminobutyric acid, and 2,3-diaminopropionic acid. Dde shows orthogonal cleavage conditions to Fmoc (piperidine or DBU) and *t*Bu (TFA) deprotecting protocols and is stable to denaturing washing conditions, while allowing for a mild and selective removal in the presence of other protecting groups using a buffered aqueous solution of hydrazine or hydroxylamine, thus representing a versatile tool for the site-specific modification of peptides. Advantageously, the cleavage can be followed spectrophotometrically since the reaction product of Dde with hydrazine is a chromophoric derivative.

Placing Dde as one terminal group of a linker and a functional group prone for conjugation as the other, or using Dde as the central connective portion of a linker, allows for the creation of new bifunctional linkers that can be selectively and temporarily attached to:

Appropriately modified biomolecules for binding to streptavidin (with terminal biotin) (*Fig. 21* (A)), or conjugation to any solid supports, e.g. *via* Click reaction (*Fig. 21* (B)).

- Solubilizing tags, e.g. hexa-lysine ("helping-hand linkers", *Fig. 21* (C)), oligo-arginine, PEGs (*Fig. 21* (D)) or other hydrophilic groups improving solubility of hydrophobic peptides or other compounds when being attached to either the N-terminus or any lysine side chain within a peptide sequence.
- Dyes and any other conjugate for monitoring, diagnostics, targeting or other purposes.

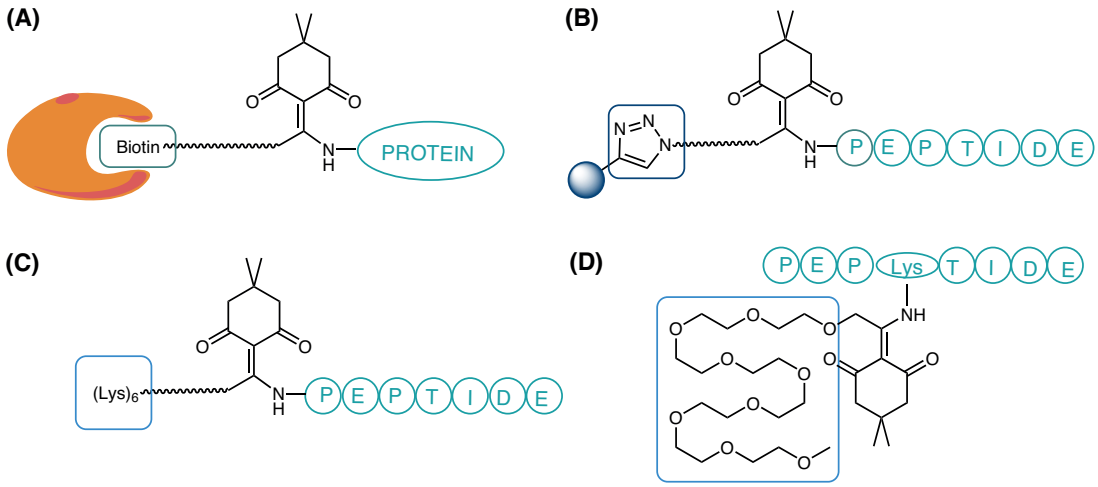

Fig. 21: Dde-based linkers can be utilized for various applications: Attachment of a cleavable biotin tag to proteins for catch-and-release affinity purification over Streptavidin beads (A), reversible labeling or conjugation to other biomolecules, or reversible immobilization on solid supports via Click chemistry (B), temporary attachment of solubilizing tags like oligo-lysine (C) or PEGs (D).

Dde/ivDde linkers are implemented in simple and nearly quantitative steps:

1. Orthogonal deprotection of lysine residues in a peptide or N-terminus or any other amino function of a hydrophobic compound.
2. On-resin incorporation of the linker.
3. Fmoc-SPPS elongation.
4. Cleavage of the peptide from the resin and removal of all side chain protecting groups.
5. The tagged peptide can be separated from truncated sequences.
6. In-solution cleavage using mild aqueous hydrazine to cleave the Dde linker after purification, streptavidin attachment, NCL-based assembly or another reaction step. The cleavage can be monitored spectroscopically as the resulting pyrazole shows a strong absorption at 290 nm.

Dde/ivDde becomes particularly useful for handling and purification of insoluble and aggregation-prone peptides, as any appropriate solubilizing promoting group can be attached to create so-called "helping-hand" linkers that can be removed in a traceless manner (*Fig. 22*).

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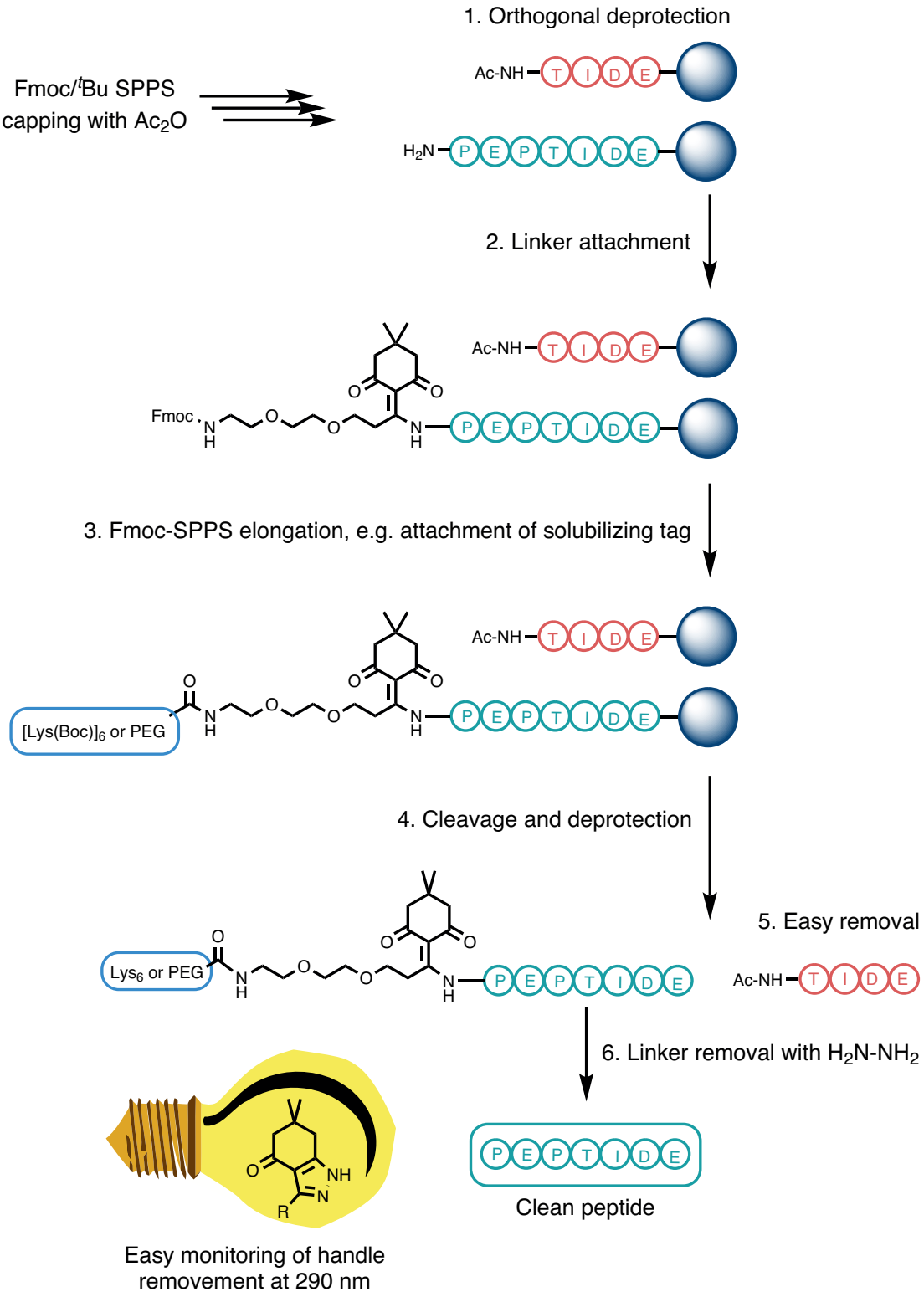

Fig. 22: Dde-based "helping-hand" linkers improve the solubility and allow for the purification of hydrophobic peptides. Removal of the handle can be easily monitored spectroscopically at 290 nm.

Procedure for Removing Helping-Hands from Peptides (adapted from Jacobsen *et al.*, *J Am Chem Soc* 2016):

10 mL of 2 M hydrazine stock solution (pH 7.5) is being prepared as follows:

1. Weigh 5.7 g Guanidinium chloride and 75 mg DTT into 15 mL Falcon tube.
2. Add 1 mL of 1 M NaH2PO4.
3. Add 2 mL of 10 M hydrazine in water.
4. Add 0.5 mL of 12 M HCl.
5. Dissolve solution by thorough vortexing.
6. Adjust pH to 7.5 by adding concentrated HCl.
7. Fill to a final volume of 10 mL with water.
8. Filter solution using 0.2 µm syringe filter.

Cleavage of the helping-hand can be triggered by equivolume addition of 2 M hydrazine stock solution into the solution of the peptide. After adding the hydrazine solution, subtle adjustment may be necessary to achieve a final solution pH of 7.5. The reaction is normally completed within minutes. Deprotection can be monitored spectrophotometrically at 290 nm.

Despite its widespread use, the biotinylation of proteins for subsequent purification *via* Streptavidin beads bears certain hurdles, e.g. concerning the removal of the proteins from the beads due to the strong binding. One possible improvement is represented by the use of appropriately derivatized Dde-linkers. The connection of such a bifunctional linker with a biotin moiety on the one end, and a clickable group (alkyne, e.g. DBCO) or tyramide on the other, allows for the selective attachment to appropriately modified biomolecules, as well as the mild release of captured proteins from the beads after purification (*Fig. 23*).

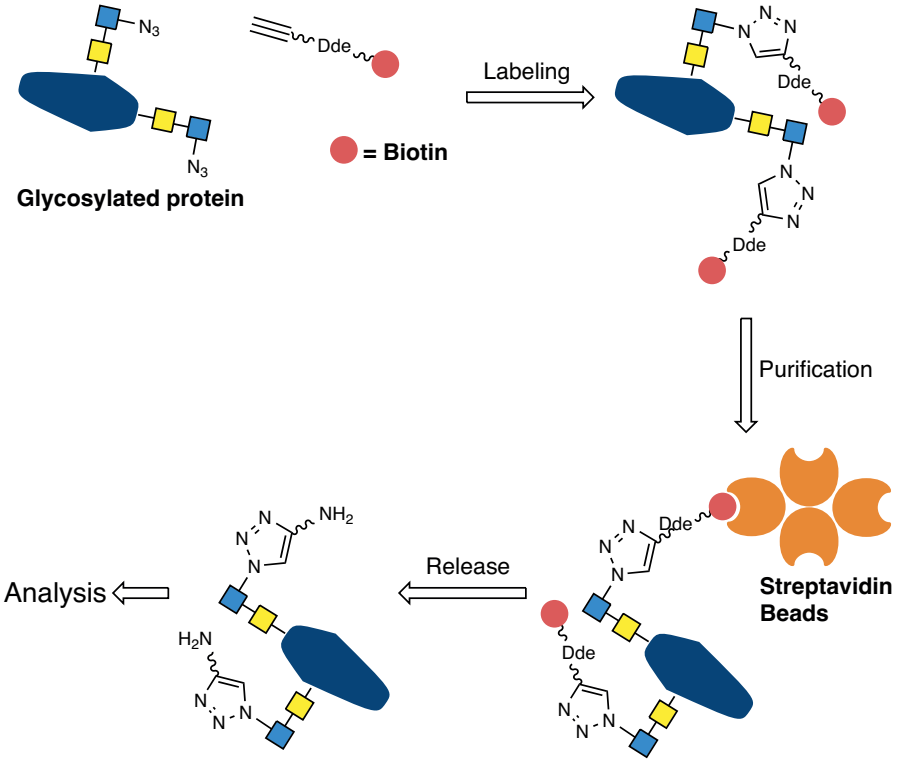

Fig. 23: Biotinylation of an azide-bearing glycoprotein using Click chemistry, followed by purification of the labelled protein over Streptavidin beads, release of the protein by hydrazinolysis of the Dde-group, and analysis of the isolated glycoprotein (adapted from Griffin et al. Mol. Biosys. 2016).

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Aside from the commonly used cleavage solution for Dde consisting of 2% hydrazine monohydrate in H_2O, the following procedure may be used in order to ensure full orthogonality between Dde and Fmoc.

Selective Removal of Dde/ivDde using hydroxylamine (adapted from Díaz-Mochón *et al.*, *Org. Lett.* 2004):

1.25 g (1.80 mmol) of $NH_2OH{\cdot}HCl$ and 0.918 g (1.35 mmol) of Imidazole were suspended in 5 mL NMP, and the mixture sonicated until complete dissolution. This solution can be stirred for at least 2 weeks at -20 °C. Just before reaction, five volumes of this solution were diluted with one volume of alternatively DCM or DMF.

Dde is easy to cleave, but not very robust. Thus, during Fmoc cleavage, Dde might migrate to free lysine ε-amino groups ("scrambling") or, in rare cases, even to the peptide's free amino terminus. Especially during the synthesis of longer peptide sequences, a certain extent of Dde is removed during Fmoc cleavage with piperidine.

The sterically more demanding protecting group ivDde is more stable towards piperidine and does usually not migrate to free lysine amino groups. However, for some sequences, total removal of the robust ivDde is hardly possible - especially near the C-terminus or in aggregating sequences.

A newer group for the orthogonal protecting of amino groups reported in literature is MeDmb (methyl dimethylbarbituric acid). At Iris Biotech, we are also offering the sterically more demanding ivDmb. There is no "one-fits-all" when you are to decide on the protecting group selection for orthogonal lysine side chain protection. When your peptide shows a low tendency for scrambling, Lys(Dde) may be fine. Otherwise, you can switch to more robust ones such as Lys(ivDde) or Lys(ivDmb). If you do not succeed in completely removing the ivDde protecting group, the brand-new ivDmb should be your choice.
For more details on the ivDmb protecting group, see our blog post:

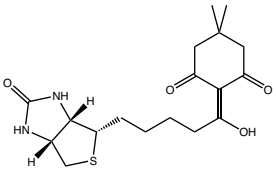
https://www.iris-biotech.de/blog/potm-next-generation-lysine-side-chain-protecting-groups/

References:

- *A novel lysine-protecting procedure for continuous flow solid phase synthesis of branched peptides; B. W. Bycroft, W. C. Chan, S. R. Chhabra, N. D. Hone;* ***Journal of the Chemical Society, Chemical Communications*** *1993: 778-779. https://doi.org/10.1039/c39930000778*
- *An appraisal of new variants of Dde amine protecting group for solid phase peptide synthesis; S. R. Chhabra, B. Hothi, D. J. Evans, P. D. White, B. W. Bycroft, W. C. Chan;* ***Tetrahedron Letters*** *1998;* ***39****: 1603-1606. https://doi.org/10.1016/s0040-4039(97)10828-0*
- *Investigation on the stability of the Dde protecting group used in peptide synthesis: migration to an unprotected lysine; K. Augustyns, W. Kraas, G. Jung;* ***J Pept Res*** *1998;* ***51****: 127-33. https://doi.org/10.1111/j.1399-3011.1998.tb00630.x*
- *Evaluation of ivDde as a quasi-orthogonal protecting group for Fmoc solid-phase peptide synthesis; R. R. Wilhelm, A. Srinivasan, M. A. Schmidt; Peptides for the New Millennium: Proceedings of the 16th American Peptide Symposium June 26–July 1, 1999, Minneapolis, Minnesota, USA 2000: 58-59. https://doi.org/10.1007/0-306-46881-6_19*
- *Synthesis of a chlorothalonil peptide conjugate mimicking protein-bound pesticide residues; H. Hrenn, W. Schwack, W. Seilmeier, H. Wieser;* ***Tetrahedron Lett*** *2003;* ***44****: 1911-1913. https://doi.org/10.1016/S0040-4039(03)00121-7*
- *Reaction of 1,3-dimethyl-5-acetyl-barbituric acid (DAB) with primary amines. Access to intermediates for selectively protected spermidines; E. T. da Silva, E. L. S. Lima;* ***Tetrahedron Lett*** *2003;* ***44****: 3621-3624. https://doi.org/10.1016/S0040-4039(03)00709-3*
- *Scope and Limitations of Barbituric and Thiobarbituric Amino Acid Derivatives as Protecting Groups for Solid-Phase Peptide Synthesis: Towards a Green Protecting Group; S. Ramkisson, H. H. Al-Rasheed, K. A. Dahlous, B. G. De La Torre, A. El-Faham, F. Albericio;* ***ChemistrySelect*** *2021;* ***6****: 6626-6630. https://doi.org/10.1002/slct.202101539*

LS-4020 Biotin-Dde

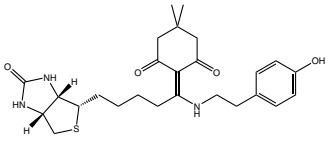
2-(1-hydroxy-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentylidene)-5,5-dimethylcyclohexane-1,3-dione



CAS-No.	194038-08-9
Formula	$C_{18}H_{26}N_2O_4S$
Mol. weight	366,48 g/mol

LS-4000 Biotin-Dde-Tyramide

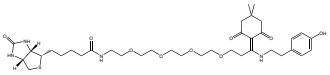
2-(1-(4-hydroxyphenethylamino)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentylidene)-5,5-dimethylcyclohexane-1,3-dione



Formula	$C_{26}H_{35}N_3O_4S$
Mol. weight	485,64 g/mol

PEG8130 Biotin-PEG(4)-Dde-Tyramide

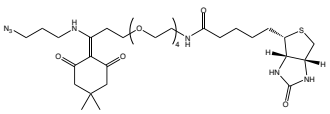
N-(15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-18-(4-hydroxyphenyl)-3,6,9,12-tetraoxa-16-azaoctadecyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



Formula	$C_{34}H_{56}N_4O_9S$
Mol. weight	732,93 g/mol

PEG7960 Biotin-PEG(4)-Dde-N_3

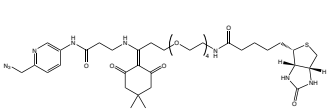
N-(19-azido-15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,6,9,12-tetraoxa-16-azanonadecyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



CAS-No.	1802907-93-2
Formula	$C_{32}H_{53}N_7O_8S$
Mol. weight	695,87 g/mol

PEG7970 Biotin-PEG(4)-Dde-Picolyl-N_3

N-(6-(azidomethyl)pyridin-3-yl)-15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-1-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxa-16-azanonadecan-19-amide



CAS-No.	2055048-42-3
Formula	$C_{38}H_{57}N_9O_9S$
Mol. weight	815,98 g/mol

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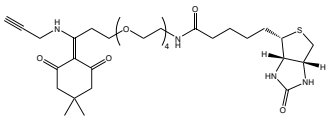
Product details

PEG7980 Biotin-PEG(4)-Dde-Alkyne

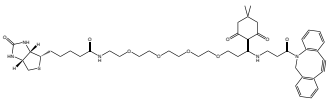
N-(15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,6,9,12-tetraoxa-16-azanonadec-18-ynyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



CAS-No.	1802908-00-4
Formula	$C_{32}H_{50}N_4O_8S$
Mol. weight	650,83 g/mol

PEG8140 Biotin-PEG(4)-Dde-DBCO

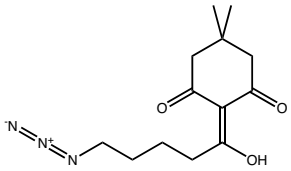
N-(15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-19-oxo-19-(azadibenzocyclooctyn-1-yl)-3,6,9,12-tetraoxa-16-azanonadecyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide



CAS-No.	1807512-43-1
Formula	$C_{47}H_{61}N_5O_9S$
Mol. weight	872,08 g/mol

RL-3280 N_3-Pen-Dde

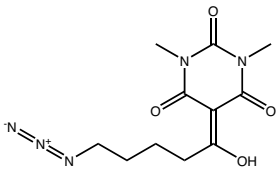
2-(5-azido-1-hydroxypentylidene)-5,5-dimethylcyclohexane-1,3-dione



CAS-No.	1867129-38-1
Formula	$C_{13}H_{19}N_3O_3$
Mol. weight	265,31 g/mol

RL-3290 N_3-Pen-Dtpp

5-(5-azido-1-hydroxypentylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione



CAS-No.	1867129-42-7
Formula	$C_{11}H_{15}N_5O_4$
Mol. weight	281,27 g/mol

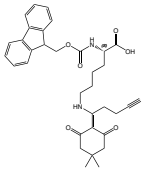
The Dde derived linker might cleave under mildly acidic and even neutral conditions in the one or the other case. The DTPM derived linker is totally stable under acidic conditions as well as to a wide range of chemical treatments, including particularly harsh sodium methoxide-based deacetylation of chemically introduced glycans.

Reference:

→ *Combining triazole ligation and enzymatic glycosylation on solid phase simplifies the synthesis of very long glycoprotein analogues; M. Galibert, V. Piller, F. Piller, V. Aucagne, A. F. Delmas;* ***Chem. Sci.*** *2015; **6**: 3617-3623. https://doi.org/10.1039/c5sc00773a*

FAA8115 Fmoc-L-Lys(Pentynoyl-DIM)-OH

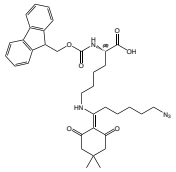
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-[1-(4,4-dimethyl-2,6- dioxocyclohexylidene)pent-4-yn-1-yl]-L-lysine



CAS-No.	2408993-33-7
Formula	$C_{34}H_{38}N_2O_6$
Mol. weight	570,69 g/mol

FAA8145 Fmoc-L-Lys(N_3-Aca-DIM)-OH

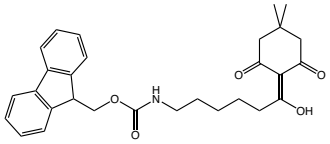
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-[6-azido-1-(4,4-dimethyl-2,6- dioxocyclohexylidene)hexyl]-L-lysine



CAS-No.	2408993-39-3
Formula	$C_{35}H_{43}N_5O_6$
Mol. weight	629,76 g/mol

RL-3260 Fmoc-Aca-DIM

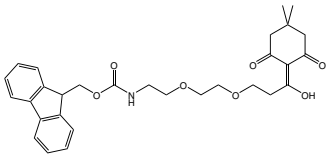
6-((9-Fluorenylmethyl)oxycarbonylamino)-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-hexan-1-ol



CAS-No.	2379561-08-5
Formula	$C_{29}H_{33}NO_5$
Mol. weight	475,58 g/mol

RL-3270 Fmoc-AEEP-DIM

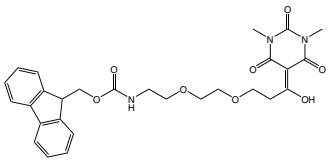
3-(2-(2-(9-Fluorenylmethyl)oxycarbonylaminoethoxy) ethoxy)-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-propan-1-ol



CAS-No.	1988771-96-5
Formula	$C_{30}H_{35}NO_7$
Mol. weight	521,60 g/mol

RL-3470 Fmoc-AEEP-DMB

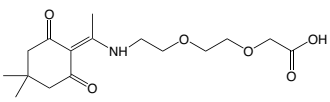
(9-Fluorenylmethyloxycarbonyl)amino-PEG(2)-Dtpp



Formula	$C_{28}H_{31}N_3O_8$
Mol. weight	537,57 g/mol

DAA1016 Dde-O_2Oc-OH

8-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-amino]-3,6-dioxaoctanoic acid, {2-[2-(Dde-amino) ethoxy]ethoxy}acetic acid



CAS-No.	1263045-93-7
Formula	$C_{16}H_{25}NO_6$
Mol. weight	327,37 g/mol

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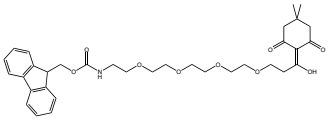
Product details

PEG8150 Fmoc-PEG(4)-Dde

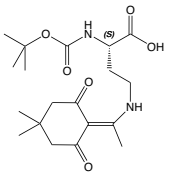
1-(9H-Fluorenylmethyloxycarbonylamino)-15-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,6,9,12-tetraoxapentadecyl-15-ol



CAS-No.	2093409-87-9
Formula	$C_{34}H_{43}NO_9$
Mol. weight	609,71 g/mol

BAA1191 Boc-L-Dab(Dde)-OH

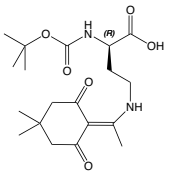
N-alpha-*t*-Butyloxycarbonyl-N-gamma-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-L-2,4-diaminobutyric acid



CAS-No.	1263045-50-6
Formula	$C_{19}H_{30}N_2O_6$
Mol. weight	382,46 g/mol

BAA1171 Boc-D-Dab(Dde)-OH

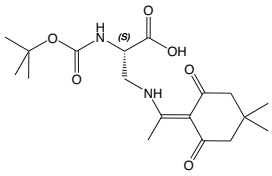
N-alpha-*t*-Butyloxycarbonyl-N-gamma-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-D-2,4-diaminobutyric acid



CAS-No.	1263046-41-8
Formula	$C_{19}H_{30}N_2O_6$
Mol. weight	382,46 g/mol

BAA1193 Boc-L-Dap(Dde)-OH

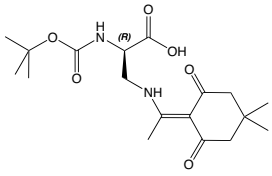
N-alpha-*t*-Butyloxycarbonyl-N-beta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-L-2,3-diaminopropionic acid



CAS-No.	1263045-09-5
Formula	$C_{18}H_{28}N_2O_6$
Mol. weight	368,43 g/mol

BAA1176 Boc-D-Dap(Dde)-OH

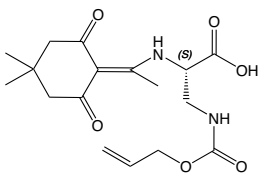
N-alpha-*t*-Butyloxycarbonyl-N-beta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-D-2,3-diaminopropionic acid



Formula	$C_{18}H_{28}N_2O_6$
Mol. weight	368,43 g/mol

DAA1011 Dde-L-Dap(Aloc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-beta-allyloxycarbonyl-L-2,3-diaminopropionic acid

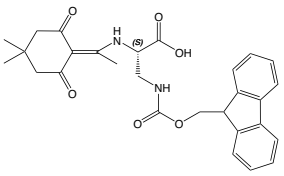


CAS-No.	1263045-89-1 net
Formula	$C_{17}H_{24}N_2O_6$
Mol. weight	352,39 g/mol

DAA1012 Dde-L-Dap(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-beta-(9-fluorenylmethyloxycarbonyl)-L-2,3-di-aminopropionic acid

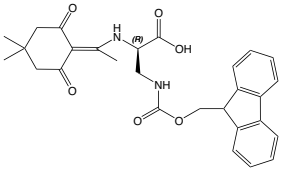
CAS-No. 1263046-98-5
Formula $C_{28}H_{30}N_2O_6$
Mol. weight 490,56 g/mol



DAA1006 Dde-D-Dap(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-beta-(9-fluorenylmethyloxycarbonyl)-D-2,3-di-aminopropionic acid

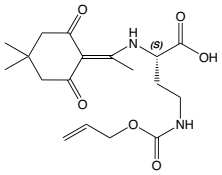
CAS-No. 1263046-87-2
Formula $C_{28}H_{30}N_2O_6$
Mol. weight 490,56 g/mol



DAA1009 Dde-L-Dab(Aloc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-gamma-allyloxycarbonyl-L-2,4-diaminobutyric acid

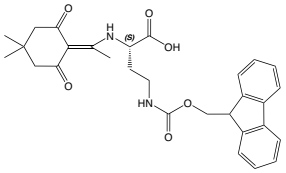
Formula $C_{18}H_{26}N_2O_6$
Mol. weight 366,42 g/mol



DAA1010 Dde-L-Dab(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylide-ne)ethyl-N-gamma-(9-fluorenylmethyloxycarbo-nyl)-L-2,4-diaminobutyric acid

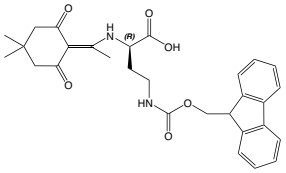
CAS-No. 1263045-85-7
Formula $C_{29}H_{32}N_2O_6$
Mol. weight 504,59 g/mol



DAA1004 Dde-D-Dab(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylide-ne)ethyl-N-gamma-(9-fluorenylmethyloxycarbo-nyl)-D-2,4-diaminobutyric acid

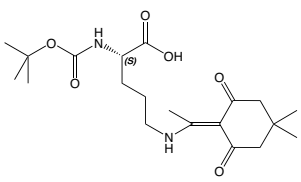
CAS-No. 1263046-84-9
Formula $C_{29}H_{32}N_2O_6$
Mol. weight 504,59 g/mol



BAA1197 Boc-L-Orn(Dde)-OH

N-alpha-*t*-Butyloxycarbonyl-N-delta-[1-(4,4-di-methyl-2,6-dioxocyclohex-1-ylidene)ethyl]-L-ornithine

CAS-No. 1272755-14-2
Formula $C_{20}H_{32}N_2O_6$
Mol. weight 396,49 g/mol



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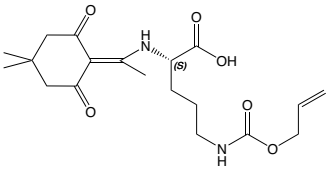
Product details

DAA1001 Dde-L-Orn(Aloc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-delta-allyloxycarbonyl-L-ornithine

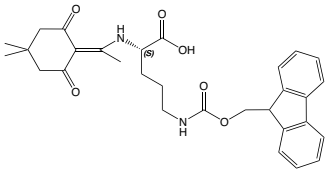
CAS-No. 1423017-98-4
Formula $C_{19}H_{28}N_2O_6$
Mol. weight 380,44 g/mol



DAA1002 Dde-L-Orn(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-delta-(9-fluorenylmethyloxycarbonyl)-L-ornithine

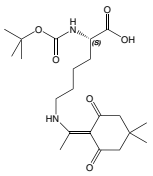
CAS-No. 1423017-87-1
Formula $C_{30}H_{34}N_2O_6$
Mol. weight 518,62 g/mol



BAA1286 Boc-L-Lys(Dde)-OH*DCHA

N-alpha-*t*-Butyloxycarbonyl-N-epsilon-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl-L-lysine dicyclohexylamine

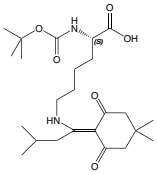
CAS-No. 444795-66-8 net
Formula $C_{21}H_{34}N_2O_6*C_{12}H_{23}N$
Mol. weight 410,51*181,32 g/mol



BAA1287 Boc-L-Lys(ivDde)-OH

N-alpha-*t*-Butyloxycarbonyl-N-epsilon-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-L-lysine

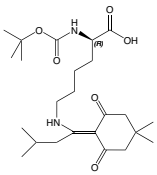
CAS-No. 862847-44-7
Formula $C_{24}H_{40}N_2O_6$
Mol. weight 452,6 g/mol



BAA5010 Boc-D-Lys(ivDde)-OH

N-alpha-*t*-Butyloxycarbonyl-N-epsilon-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-D-lysine

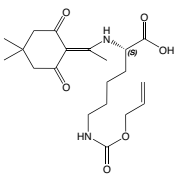
CAS-No. 1301706-85-3
Formula $C_{24}H_{40}N_2O_6$
Mol. weight 452,6 g/mol



DAA1013 Dde-L-Lys(Aloc)-OH*DCHA

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-epsilon-allyloxycarbonyl-L-lysine dicyclohexylamine

CAS-No. 264230-73-1 net
Formula $C_{20}H_{30}N_2O_6*C_{12}H_{23}N$
Mol. weight 394,47*181,32 g/mol

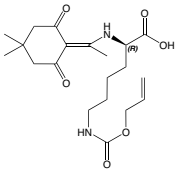


Product details

DAA1007 Dde-D-Lys(Aloc)-OH*DCHA

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-epsilon-allyloxycarbonyl-D-lysine dicyclohexylamine

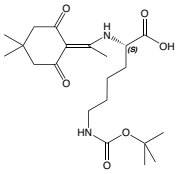
CAS-No.	1272754-85-4 net
Formula	$C_{20}H_{30}N_2O_6*C_{12}H_{23}N$
Mol. weight	394,47*181,32 g/mol



DAA1014 Dde-L-Lys(Boc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-epsilon-*t*-butyloxycarbonyl-L-lysine

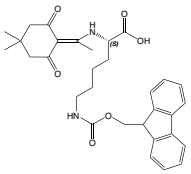
CAS-No.	1189586-14-8
Formula	$C_{21}H_{34}N_2O_6$
Mol. weight	410,51 g/mol



DAA1015 Dde-L-Lys(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-epsilon-(9-fluorenylmethyloxycarbonyl)-L-lysine

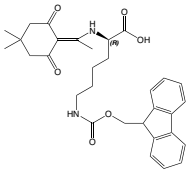
CAS-No.	156648-40-7
Formula	$C_{31}H_{36}N_2O_6$
Mol. weight	532,64 g/mol



DAA1017 Dde-D-Lys(Fmoc)-OH

N-alpha-(4-4-Dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-N-epsilon-(9-fluorenylmethyloxycarbonyl)-D-lysine

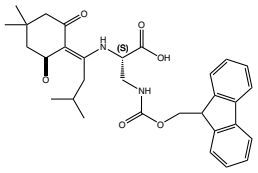
CAS-No.	1301706-71-7
Formula	$C_{31}H_{36}N_2O_6$
Mol. weight	532,64 g/mol



DAA1018 ivDde-L-Dap(Fmoc)-OH

N-alpha-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-N-beta-(9-fluorenylmethyloxycarbonyl)-L-2,3-diaminopropionic acid

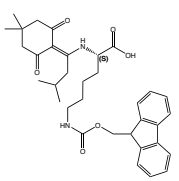
CAS-No.	2389078-71-9
Formula	$C_{31}H_{36}N_2O_6$
Mol. weight	532,63 g/mol



DAA1019 ivDde-L-Lys(Fmoc)-OH

N-alpha-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-N-epsilon-(9-fluorenylmethyloxycarbonyl)-L-lysine

CAS-No.	1446752-60-8
Formula	$C_{34}H_{42}N_2O_6$
Mol. weight	574,71 g/mol



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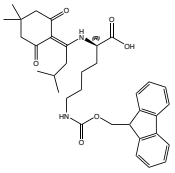
Product details

DAA1030 ivDde-D-Lys(Fmoc)-OH

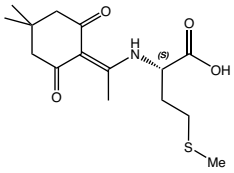
N-alpha-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylide-ne)-3-methylbutyl]-N-epsilon-(9-fluorenylmethyloxy-carbonyl)-D-lysine



CAS-No.	2308529-94-2
Formula	$C_{34}H_{42}N_2O_6$
Mol. weight	574,71 g/mol

DAA1020 Dde-L-Met-OH

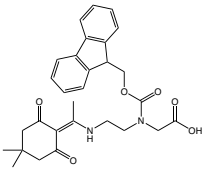
N-?alpha-[1-?(4,?4-?dimethyl-?2,?6-?dioxocyclohexyli-dene?)?ethyl]?-L-methionine



CAS-No.	1435266-87-7
Formula	$C_{15}H_{23}NO_4S$
Mol. weight	313,13 g/mol

FAA8690 Fmoc-Aeg(Dde)-OH

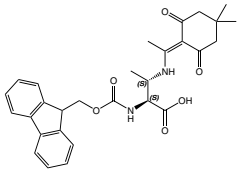
(9-Fluorenylmethyloxycarbonyl)-N-(2-((1-(4,4-di-methyl-2,6-dioxocyclohexylidene)ethyl)amino)ethyl) glycine



Formula	$C_{29}H_{32}N_2O_6$
Mol. weight	504,58 g/mol

FAA8815 Fmoc-L-Abu(3-Dde-amino)-OH (2S,3S)

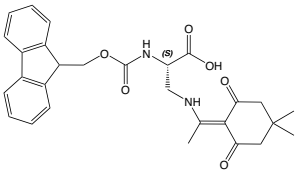
2-(Fmoc-amino)-3-(Dde-amino)butanoic acid (2S,3S)



Formula	$C_{29}H_{32}N_2O_6$
Mol. weight	504,58 g/mol

FAA1462 Fmoc-L-Dap(Dde)-OH

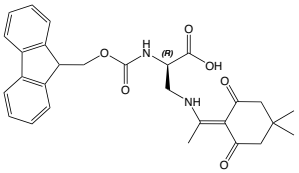
N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-be-ta-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-2,3-diaminopropionic acid



CAS-No.	247127-51-1
Formula	$C_{28}H_{30}N_2O_6$
Mol. weight	490,56 g/mol

FAA1476 Fmoc-D-Dap(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-be-ta-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-D-2,3-diaminopropionic acid

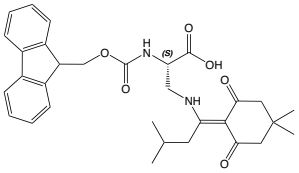


CAS-No.	210830-03-8
Formula	$C_{28}H_{30}N_2O_6$
Mol. weight	490,56 g/mol

FAA1464 Fmoc-L-Dap(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-beta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-L-2,3-diaminopropionic acid

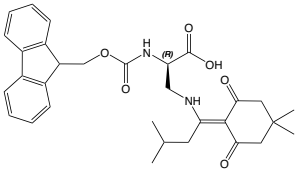
CAS-No.	607366-20-1
Formula	$C_{31}H_{36}N_2O_6$
Mol. weight	532,64 g/mol



FAA1478 Fmoc-D-Dap(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-beta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-D-2,3-diaminopropionic acid

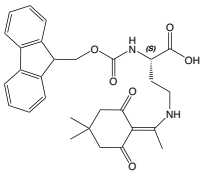
CAS-No.	1228900-15-9
Formula	$C_{31}H_{36}N_2O_6$
Mol. weight	532,64 g/mol



FAA1365 Fmoc-L-Dab(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-gamma-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-L-2,4-diaminobutyric acid

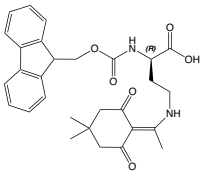
CAS-No.	235788-61-1
Formula	$C_{29}H_{32}N_2O_6$
Mol. weight	504,59 g/mol



FAA1318 Fmoc-D-Dab(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-gamma-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-D-2,4-diaminobutyric acid

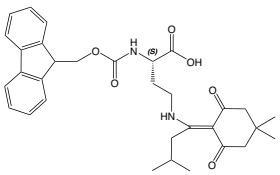
CAS-No.	596797-14-7
Formula	$C_{29}H_{32}N_2O_6$
Mol. weight	504,59 g/mol



FAA1458 Fmoc-L-Dab(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-gamma-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-L-2,4-diaminobutyric acid

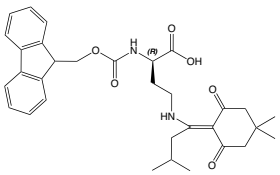
CAS-No.	607366-21-2
Formula	$C_{32}H_{38}N_2O_6$
Mol. weight	546,67 g/mol



FAA1473 Fmoc-D-Dab(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-gamma-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-D-2,4-diaminobutyric acid

CAS-No.	872169-32-9
Formula	$C_{32}H_{38}N_2O_6$
Mol. weight	546,67 g/mol



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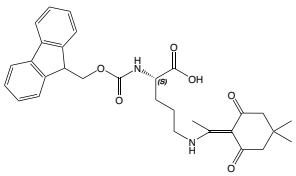
Product details

FAA1502 Fmoc-L-Orn(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-delta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-L-ornithine

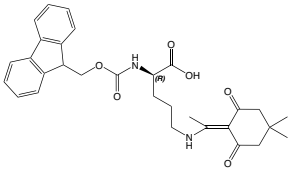
CAS-No. 269062-80-8
Formula $C_{30}H_{34}N_2O_6$
Mol. weight 518,62 g/mol



FAA2090 Fmoc-D-Orn(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-delta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-D-ornithine

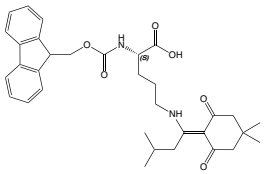
CAS-No. 1419640-31-5
Formula $C_{30}H_{34}N_2O_6$
Mol. weight 518,62 g/mol



FAA1503 Fmoc-L-Orn(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-delta[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-L-ornithine solvate

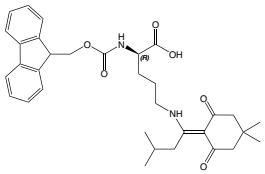
CAS-No. 1198321-33-3
Formula $C_{33}H_{40}N_2O_6$
Mol. weight 560,7 g/mol



FAA1493 Fmoc-D-Orn(ivDde)-OH.solv.

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-delta-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-D-ornithine.solv.

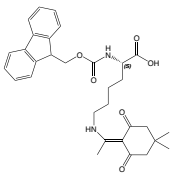
CAS-No. 1272754-86-5
Formula $C_{33}H_{40}N_2O_6$
Mol. weight 560,7 g/mol



FAA1390 Fmoc-L-Lys(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl-L-lysine

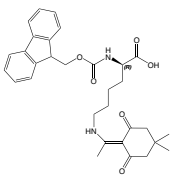
CAS-No. 150629-67-7
Formula $C_{31}H_{36}N_2O_6$
Mol. weight 532,64 g/mol



FAA1486 Fmoc-D-Lys(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-[(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-D-lysine

CAS-No. 333973-51-6
Formula $C_{31}H_{36}N_2O_6$
Mol. weight 532,64 g/mol

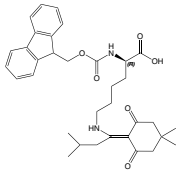


Product details

FAA1488 Fmoc-D-Lys(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-D-lysine

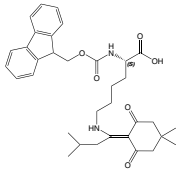
CAS-No. 1272755-33-5
Formula $C_{34}H_{42}N_2O_6$
Mol. weight 574,72 g/mol



FAA1500 Fmoc-L-Lys(ivDde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-epsilon-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl]-L-lysine

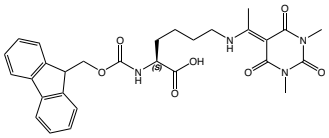
CAS-No. 204777-78-6
Formula $C_{34}H_{42}N_2O_6$
Mol. weight 574,72 g/mol



FAA8840 Fmoc-L-Lys(MeDmb)-OH

(2S)-6-{[1-(1,3-dimethyl-2,4,6-trioxo-1,3-diazinan-5-ylidene)ethyl]amino}-2-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)hexanoic acid

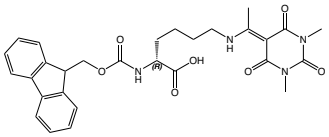
Formula $C_{29}H_{32}N_4O_7$
Mol. weight 548,60 g/mol



FAA8845 Fmoc-D-Lys(MeDmb)-OH

(2R)-6-{[1-(1,3-dimethyl-2,4,6-trioxo-1,3-diazinan-5-ylidene)ethyl]amino}-2-({[(9H-fluoren-9-yl)methoxy]carbonyl}amino)hexanoic acid

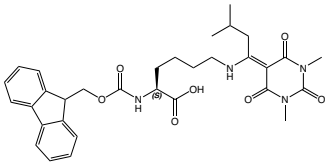
Formula $C_{29}H_{32}N_4O_7$
Mol. weight 548,60 g/mol



FAA7975 Fmoc-L-Lys(ivDmb)-OH

N2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N6-(1-(1,3-dimethyl-2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)-3-methylbutyl)-L-lysine

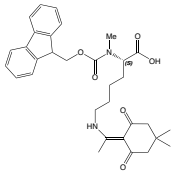
Formula $C_{32}H_{38}N_4O_7$
Mol. weight 590,68 g/mol



FAA1401 Fmoc-L-MeLys(Dde)-OH

N-alpha-(9-Fluorenylmethyloxycarbonyl)-N-alpha-methyl-N-epsilon-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl-L-lysine

CAS-No. 1428229-84-8
Formula $C_{32}H_{38}N_2O_6$
Mol. weight 546,67 g/mol



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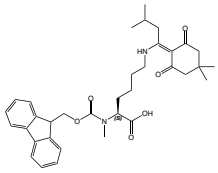
Product details

FAA7935 Fmoc-L-MeLys(ivDde)-OH

N2-(((9H-fluoren-9-yl)methoxy)carbonyl)-N6-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-N2-methyl-L-lysine

CAS-No.	1173996-67-2
Formula	$C_{35}H_{44}N_2O_6$
Mol. weight	588,75 g/mol



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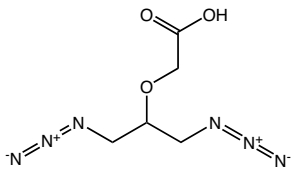
4. Trifunctional Linkers

Product details

AAA2190 DAPOA*DCHA

2-(1,3-diazidopropan-2-yloxy)acetic acid dicyclohexylamine

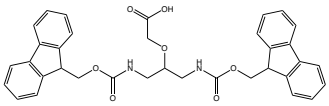
CAS-No. 2389064-43-9 net
Formula $C_5H_8N_6O_3$*$C_{12}H_{23}N$
Mol. weight 200,16*181,32 g/mol



FAA7570 Fmoc2-DAPOA

2-((1,3-bis((9-fluorenylmethyloxycarbonyl)amino)propan-2-yl)oxy)acetic acid

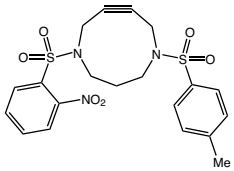
CAS-No. 688350-01-8
Formula $C_{35}H_{32}N_2O_7$
Mol. weight 592,64 g/mol



RL-2710 DACN(Tos,Ns)

N-(*o*-nitrobenzenesulfonyl)-*N'*-(*p*-toluenesulfonyl)-4,8-diazacyclononyne

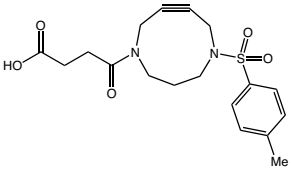
CAS-No. 1797508-58-7
Formula $C_{20}H_{21}N_3O_6S_2$
Mol. weight 463,53 g/mol



RL-2720 DACN(Tos,Suc-OH)

N-succinoyl-*N'*-(*p*-toluenesulfonyl)-4,8-diazacyclononyne

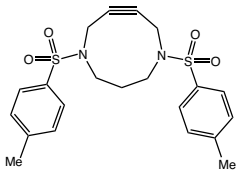
CAS-No. 2109751-68-8
Formula $C_{18}H_{22}N_2O_5S$
Mol. weight 378,44 g/mol



RL-2730 DACN(Tos_2)

N,N'-bis(*p*-toluenesulfonyl)-4,8-diazacyclononyne

CAS-No. 1797508-57-6
Formula $C_{21}H_{24}N_2O_4S_2$
Mol. weight 432,56 g/mol



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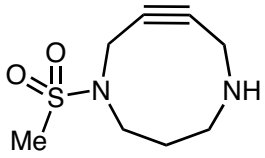
Product details

RL-3600 DACN(Ms)*HCl

N-(Mesyl)-4,8-diazacyclononyne hydrochloride

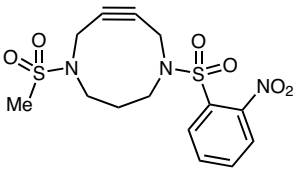
CAS-No. 2331322-16-6
Formula $C_8H_{14}N_2O_2S*HCl$
Mol. weight 202,27*36,46 g/mol



RL-3610 DACN(Ms,Ns)

N-(Mesyl)-*N'*-(2-nosyl)-4,8-diazacyclononyne

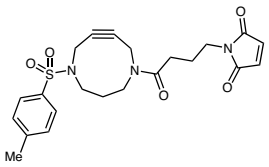
CAS-No. 2411082-25-0
Formula $C_{14}H_{17}N_3O_6S_2$
Mol. weight 387,43 g/mol



RL-3630 DACN(Tos,Mal)

N-(maleimidobutyryl)-*N'*-(*p*-toluenesulfonyl)-4,8-diazacyclononyne

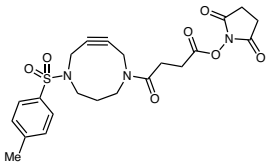
CAS-No. 2411082-28-3
Formula $C_{22}H_{25}N_3O_5S$
Mol. weight 443,52 g/mol



RL-2725 DACN(Tos,Suc-NHS)

N-(succinoyl-NHS ester)-*N'*-(*p*-toluenesulfonyl)-4,8-diazacyclononyne

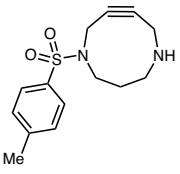
CAS-No. 2411082-26-1
Formula $C_{22}H_{25}N_3O_7S$
Mol. weight 475,52 g/mol



RL-2735 DACN(Tos)*HCl

N-(*p*-toluenesulfonyl)-4,8-diazacyclononyne hydrochloride

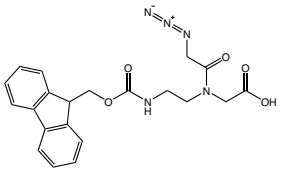
CAS-No. 2331322-18-8
Formula $C_{14}H_{18}N_2O_2S*HCl$
Mol. weight 278,37*36,46 g/mol



HAA9330 N_3-Gly-Aeg(Fmoc)-OH

N-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-N-(2-azidoacetyl)glycine

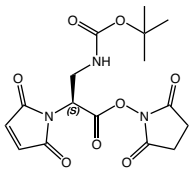
CAS-No. 2606227-07-8
Formula $C_{21}H_{21}N_5O_5$
Mol. weight 423,43 g/mol



MAA1120 MaI-L-Dap(Boc)-OSu

N-alpha-Maleimido-N-beta-Boc-L-2,3-diaminopropionic acid NHS ester

CAS-No.	1703778-79-3
Formula	$C_{16}H_{19}N_3O_8$
Mol. weight	381,34 g/mol



For various functional group conjugation please inquire with our Custom Synthesis Service.

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5. Cross-Linkers for other Bio Applications

5.1. Substrates for Fusion (Halo/Snap/Clip)-Tagged Proteins

Site-specific protein labeling is a versatile tool for studying protein function and interaction in living cells. Various peptide-based protein tags have been developed. Herein, we are focusing on HaloTag®, SNAP-Tag® and CLIP-Tag™, as well as corresponding substrates offered by Iris Biotech. Those labeling systems enable the specific, covalent attachment of in principle any molecule of choice to a protein of interest.

The HaloTag® (*Fig. 24*) is a 33 kDa self-labeling protein tag derived from the haloalkane dehalogenase DhaA from *Rhodococcus rhodochrous*. Its active site reacts in a nucleophilic attack with chloroalkane linker substrates to form an irreversible bond in the case of the mutated enzyme. The chloroalkane linker can easily be functionalized with a label of choice, e.g. with a fluorophore or biotin. For the wild-type enzyme, this intermediate would be hydrolyzed, leading to the regeneration of the enzyme.

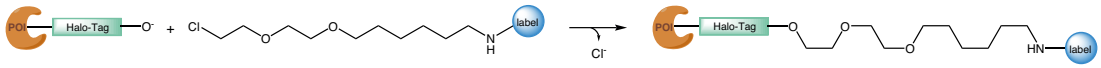


Fig. 24: Schematic illustration of the HaloTag® reaction

The SNAP-tag® (*Fig. 25*) is a 20 kDa self-labeling protein tag based on a modified form of the human O6-alkyl-guanine-DNA-alkyltransferase (hAGT), a DNA repair enzyme. A cysteine residue within the SNAP-tag® undergoes an irreversible reaction with synthetic O6-benzylguanine (BG) derivatives, resulting in a covalent thioether bond. The BG moiety can easily be further functionalized with a label of choice, e.g. fluorophore, biotin, generally without affecting the reaction of the substrate with the SNAP-tag®.

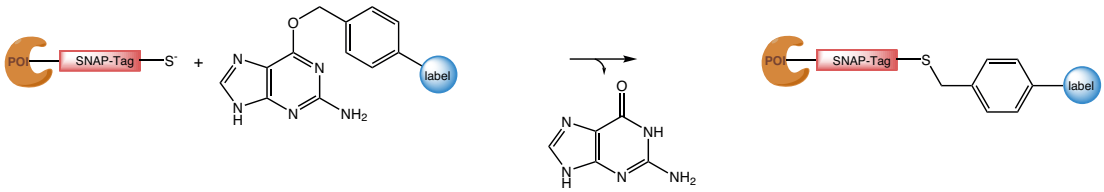


Fig. 25: Schematic illustration of the SNAP-tag® reaction

The CLIP-tag™ (*Fig. 26*) (20 kDa) is a modified version of the SNAP-tag, engineered to react with benzylcytosine (BC) instead of benzylguanine (BG). Thus, properties are similar. CLIP-tag™- and SNAP-tag®-fused proteins can be labeled simultaneously in the same cells.

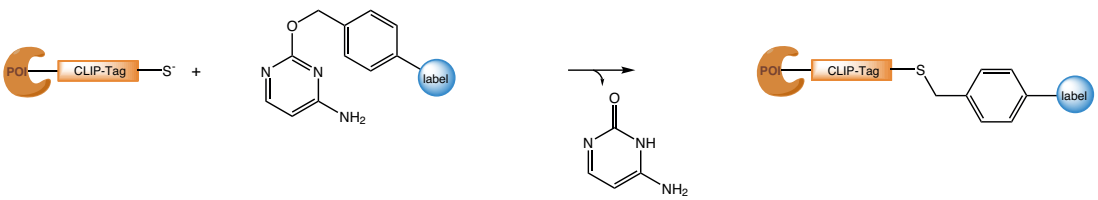


Fig. 26: Schematic illustration of the CLIP-tag™ reaction

Table summarizing main properties of HaloTag®, SNAP-tag® and CLIP-tag™.

	HaloTag	SNAP-tag	CLIP-tag
Origin	Haloalkane dehalogenase *(Rhodococcus rhodochrous)*	Human O6-alkylguanine-DNA-alkyltransferase	Human O6-alkylguanine-DNA-alkyltransferase
Reactivity	Chloroalkane derivatives	O6-benzylguanine derivatives	Benzylcytosine derivatives
Length	297 amino acids	182 amino acids	182 amino acids
Molecular Weight	33.6 kDa	19.4 kDa	19.4 kDa

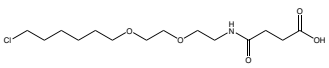
Iris Biotech offers a Biotin- (RL-3860) as well as an ICG-functionalized (RL-3830) SNAP-tag® substrate, as well as the corresponding CLIP-tag™ suitable (RL-3840, RL-3870) derivatives. Biotinylated proteins can for example be selectively isolated based on the high affinity towards avidin representing a useful tool for purification, immobilization, and labeling. Indocyanine green (ICG) is a near-infrared fluorescence imaging dye (absorption maximum 800 nm + slight absorption in the visible range; emission maximum 810 nm) approved by the FDA.

As substrates for the HaloTag® various products are offered, e.g. suitable for further functionalization *via* Click Chemistry.

Product details

RL-3180 Halo-PEG(2)-Suc

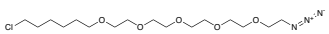
4-((2-(2-((6-chlorohexyl)oxy)ethoxy)ethyl) amino)-4-oxobutanoic acid



CAS-No. **1488363-39-8**
Formula **$C_{14}H_{26}ClNO_5$**
Mol. weight **323,81 g/mol**

RL-3640 Halo-PEG(5)-azide

1-azido-21-chloro-3,6,9,12,15-pentaoxahenicosane



CAS-No. **1261238-21-4**
Formula **$C_{16}H_{32}ClN_3O_5$**
Mol. weight **381,90 g/mol**

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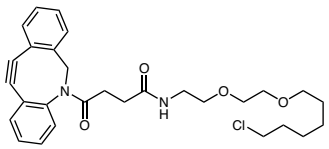
Product details

RL-3670 Halo-DBCO

N-[2-[2-[(6-chlorohexyl)oxy]ethoxy]ethyl]-gamma-oxo-dibenz[b,f]azocine-5(6H)-butanamide

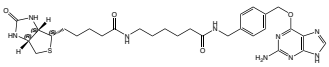
CAS-No. 1808119-16-5
Formula $C_{29}H_{35}ClN_2O_4$
Mol. weight 511,06 g/mol



RL-3860 Biotin-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-6-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl)pentanamido)hexanamide

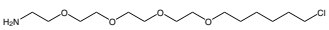
CAS-No. 471918-16-8
Formula $C_{29}H_{39}N_9O_4S$
Mol. weight 609,75 g/mol



RL-3690 Halo-PEG(4)-NH_2*HCl

18-Chloro-3,6,9,12-tetraoxa-octadecan-1-amine hydrochloride

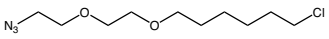
CAS-No. 1261238-20-3
Formula $C_{14}H_{30}ClNO_4$*HCl
Mol. weight 311,85*36,46 g/mol



RL-3700 Halo-PEG(2)-Azide

1-Azido-12-chloro-3,6-dioxadodecane

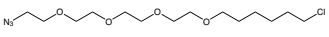
CAS-No. 2568146-55-2
Formula $C_{10}H_{20}ClN_3O_2$
Mol. weight 249,74 g/mol



RL-3710 Halo-PEG(4)-Azide

1-Azido-18-chloro-3,6,9,12-tetraoxaoctadecane

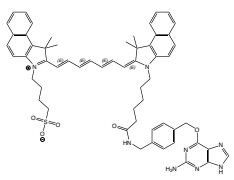
Formula $C_{14}H_{28}ClN_3O_4$
Mol. weight 337,85 g/mol



RL-3830 ICG-SNAP

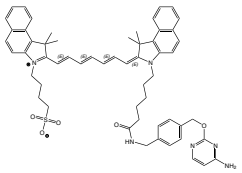
4-(2-((1E,3E,5E,7E)-7-(3-(6-((4-(((2-amino-9H-purin-6-yl) oxy)methyl)benzyl)amino)-6-oxohexyl)-1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)hepta-1,3,5-trien-1-yl)-1,1-dimethyl-1H-benzo[e]indo l-3-ium-3-yl) butane-1-sulfonate

Formula $C_{58}H_{62}N_8O_5S$
Mol. weight 983,25 g/mol



RL-3840 ICG-CLIP

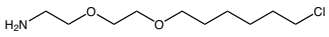
4-(2-((1E,3E,5E,7E)-7-(3-(6-((4-((((4-aminopyrimidin-2-yl) oxy)methyl)benzyl)amino)-6-oxohexyl)-1,1-dimethyl-1,3-dihydro-2H-benzo[e]indol-2-ylidene)hepta-1,3,5-trien-1-yl)-1,1-dimethyl-1H-benzo[e]indo l-3-ium-3-yl) butane-1-sulfonate



Formula	$C_{57}H_{62}N_6O_5S$
Mol. weight	943,22 g/mol

RL-3680 Halo-PEG(2)-NH_2*HCl

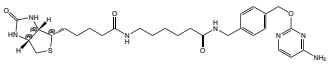
12-Chloro-3,6-dioxa-dodecan-1-amine hydrochloride



CAS-No.	1035373-85-3
Formula	$C_{10}H_{22}ClNO_2$*HCl
Mol. weight	223,74*36,46 g/mol

RL-3870 Biotin-Clip

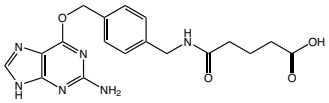
N-(4-(((4-aminopyrimidin-2-yl)oxy)methyl)benzyl)-6-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl)pentanamido)hexanamide



CAS-No.	1004524-73-5
Formula	$C_{28}H_{39}N_7O_4S$
Mol. weight	569,73 g/mol

RL-3835 SNAP-acid

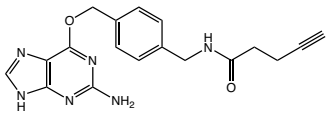
5-((4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl) amino)-5-oxopentanoic acid



CAS-No.	881663-34-9
Formula	$C_{18}H_{20}N_6O_4$
Mol. weight	384,40 g/mol

RL-3930 Alkyne-SNAP

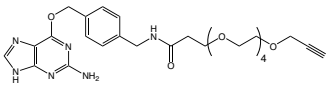
N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl) pent-4-ynamide



CAS-No.	1104822-07-2
Formula	$C_{18}H_{18}N_6O_2$
Mol. weight	350,38 g/mol

RL-3940 Alkyne-PEG(5)-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzy-l)-4,7,10,13,16-pentaoxanonadec-18-ynamide



Formula	$C_{27}H_{36}N_6O_7$
Mol. weight	556,62 g/mol

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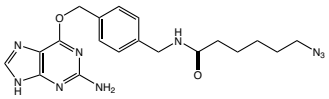
Product details

RL-3950 Azide-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-6-azidohexanamide

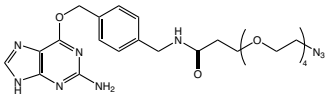
Formula $C_{19}H_{23}N_9O_2$
Mol. weight 409,45 g/mol



RL-3960 Azide-PEG(4)-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-1-azido-3,5,7,9-tetraoxadodecan-12-amide

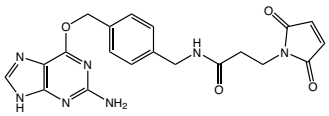
Formula $C_{24}H_{33}N_9O_6$
Mol. weight 543,59 g/mol



RL-3970 Mal-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamide

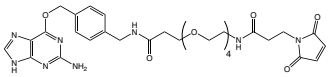
Formula $C_{20}H_{19}N_7O_4$
Mol. weight 421,42 g/mol



RL-3980 Mal-PEG(4)-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-1-(3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamido)-3,6,9,12-tetraoxapentadecan-15-amide

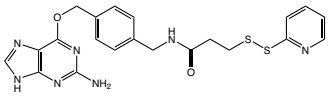
CAS-No. 1151762-31-0
Formula $C_{31}H_{40}N_8O_9$
Mol. weight 668,71 g/mol



RL-3990 OPSS-SNAP

N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-3-(pyridin-2-yldisulfaneyl)propanamide

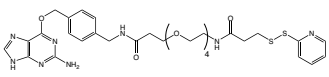
Formula $C_{21}H_{21}N_7O_2S_2$
Mol. weight 467,57 g/mol



RL-4000 OPSS-PEG(4)-SNAP

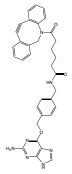
N-(4-(((2-amino-9H-purin-6-yl)oxy)methyl)benzyl)-1-(3-(pyridin-2-yldisulfaneyl)propanamido)-3,6,9,12-tetraoxapentadecan-15-amide

CAS-No. 2278175-10-1
Formula $C_{32}H_{42}N_8O_7S_2$
Mol. weight 714,86 g/mol



RL-4010 DBCO-SNAP

Formula $C_{34}H_{31}N_7O_3$
Mol. weight 585,67 g/mol



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→ *Snap-, CLIP- and Halo-Tag Labelling of Budding Yeast Cells; F. Stagge, G. Y. Mitronova, V. N. Belov, C. A. Wurm, S. Jakobs; PLoS ONE 8(10): e78745. https://doi.org/10.1371/journal.pone.0078745*

5.2. Specific His Tag Acylation

A frequently used tag for protein modification is the so-called His tag. His tags, or polyhistidine tags, comprise a consecutive series of six to ten histidine residues. His tags are widely used for protein purification by immobilized-metal ion affinity chromatography, allowing to extract a protein of interest from thousands of other proteins present in a cell lysate. However, as an inadvertent side-reaction, it is reported that His tagged proteins can undergo N-terminal acylation with gluconolactone (GDL). The discovery of this reaction by Geoghegan and coworkers triggered the inspiration for the development of His tag-based peptide segments for selective acylations. Thus, Jensen *et al.* developed two methods that use poly-His sequences to direct the highly selective acylation of proteins, either at the N-terminus or at a specific Lys residue.

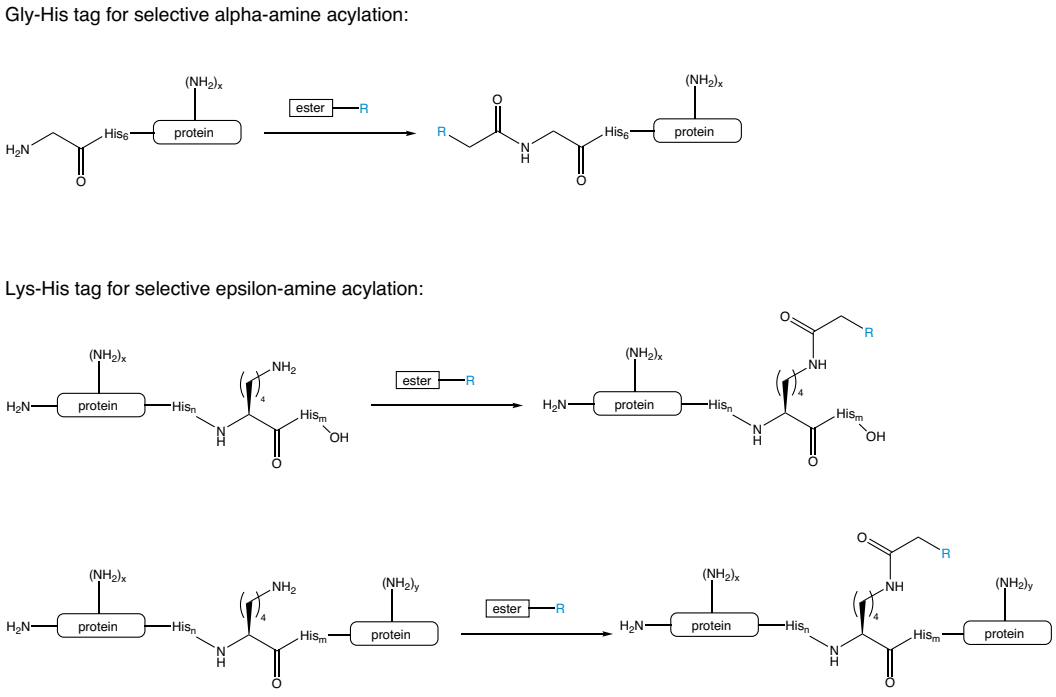


Fig. 27: Schematic illustration of Gly-His tag acylation and Lys-His tag acylation. Functionalized esters can be used for the introduction of the desired moieties, e.g. azides, biotin.

The highly selective and efficient N-terminal acylation of proteins is based on a Gly-His_6 segment (Gly-His tag) complemented by the use of 4-methoxy phenyl esters as finely tuned acylating agents, resulting in stable conjugates. Other acylating agents, e.g. lactons, thioesters, N-hydroxysuccinimide ester were also tested but gave only limited N-terminal acylation or low selectivity.

General Conjugation Protocol:

A 35 µM solution of GH6-protein in 200 mM HEPES buffer at pH 7.5 is incubated with 40 equiv. of azidoacetyl 4-methoxyphenylester for 24 h at 4 °C. The formation of the mono-functionalized product can be observed by ESI-MS and can reach 70% to 90% conversion. A higher conversion rate can be achieved by the addition of two aliquots of 10 equiv. of the acylating agent in the course of the next 48 h.

For the acylation of Lys, Jensen *et al*. developed the peptide sequence His_n-Lys-His_m (Lys-His tag) that directs the acylation of the designated Lys N-epsilon amine under mild conditions and with high selectivity over native Lys residues.

Both methods provide highly selective acylation, yield stable conjugates, and do not require the use of metal ions. In detail, referring to literature, yields for the protein modification with Gly-His are typically 60–80% mono-acylation with 1–5% over-acylation, while for Lys-His it is typically 50–70% monoacylation with 1–8% over-acylation. The Gly-His tag as well as the Lys-His tag maintain the capacity for immobilized metal ion affinity chromatography and have been shown robust for the attachment of azides, fluorophores, and biotin to different proteins, including antibodies.

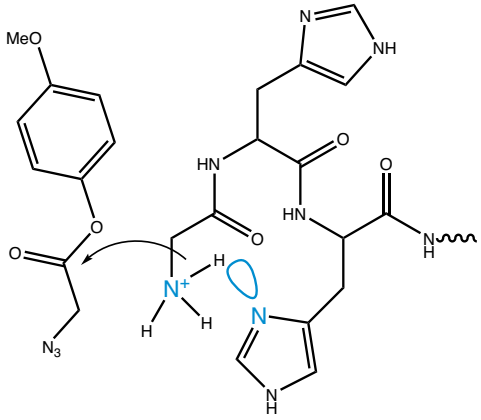


Fig. 28: Imidazole rings of neighboring histidines in a His tag catalyze the acylation of a glycyl N-terminus via a base catalyzed mechanism.

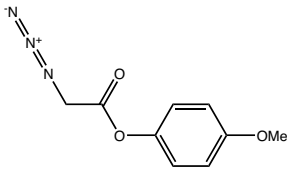
Mechanistic studies indicate that the very high selectivity of the His tag acylation is based on specific base catalysis, in which a His side-chain assists deprotonation during the direct acylation of the Gly α-amine (*Fig. 28*). The ester preferentially reacts with assistance from His side-chain imidazoles since they are not protonated (pK_a ~ 6.0) at the pH of the reaction, in contrast to the N-terminal α-amine (pK_a ~ 7.6-8.0) and Lys side-chains (pK_a ~ 10.5). The presence of the additional five His residues in the His tag may serve to modulate the basicity of the imidazole nitrogen of the catalytic residue. A recent study has shown that the pK_a values of individual His side-chains in a His_6-tag span a range from 4.8-7.5.

Product details

RL-3010 N_3Ac-OPhOMe

4-Methoxyphenyl 2-azidoacetate

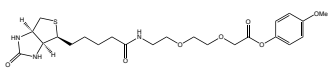
CAS-No.	2546513-31-7
Formula	$C_9H_9N_3O_3$
Mol. weight	207,19 g/mol



RL-3100 Biotin-AEEA-OPhOMe

2-(2-(2-(Biotinamido)ethoxy)ethoxy)acetic acid 4-methoxyphenyl ester

CAS-No.	2546513-67-9
Formula	$C_{23}H_{33}N_3O_7S$
Mol. weight	495,59 g/mol



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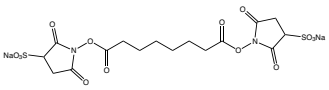
5.3. Bifunctional Protein Cross-Linkage

Product details

RL-2770 BSSS

Bis(sulfosuccinimidyl) suberate sodium salt

CAS-No.	127634-19-9
Formula	$C_{16}H_{18}N_2Na_2O_{14}S_2$
Mol. weight	572,43 g/mol



This molecule (*Fig. 29*) carries amino reactive sulfo-NHS esters on both ends and is a water-soluble, homo-bi functionalprotein cross-linker (spacer length: 11.4 Å). Due to its water solubility, conjugation reactions can conveniently take place at physiological conditions. This 8-atom spacer is non-cleavable and the molecule is not cell membrane permeable. It can be used to prepare antibody-protein conjugates, for crosslinking cell surface proteins, and for covalently binding an antibody to an immobilized Protein A or Protein G resin.

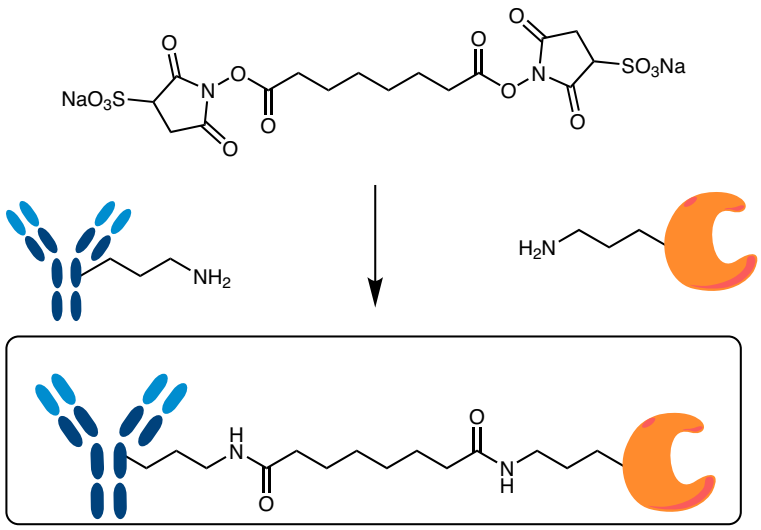


Fig. 29: BSSS can be used for cross-linkage of different biomolecules.

General BSSS Cross-Linking Protocol:

1. Allow vial of BSSS to fully equilibrate to ambient temperature before opening to prevent condensation inside the vial (BSSS is moisture-sensitive).
2. Immediately before use, prepare a 50 mM solution of BSSS, by dissolving 10 mg BSSS in 350 mL of 25 mM sodium phosphate, pH 7.4 (do not use amine containing buffers for the conjugation reaction).
3. Add BSSS solution (20-fold excess cross-linker to protein) to the protein sample so that the final concentration is between 0.5 to 5 mM.
4. Allow the sample to react at room temperature for 45 minutes to 1 hour. Allow slightly longer if reaction must be done on ice (the reaction rate is only slightly slower at low temperatures).
5. Quench any unreacted BSSS with 25 mM to 60 mM Tris and allow to react for 10-15 minutes at room temperature.
6. Desalt sample to remove unreacted BSSS, i.e., by gel filtration, dialysis, etc.

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5.4. Proteolysis Targeting Chimeras (PROTACs®)

Targeted protein degradation (*Fig. 30*) *via* proteolysis-targeting chimeras (PROTACs) is an emerging attempt to cure diseases caused by the irregular expression of certain disease-causing proteins. Such protein degraders act as bifunctional linkers and allow to feed the protein of interest (POI) to the cell's Ubiquitin-Proteasome system, thus, to eliminate the malexpressed proteins. These PROTACs consist of three components: one ligand with high affinity for E3 ubiquitin ligase, another one with high affinity for the protein of interest (POI) and an appropriate cross-linker joining both ligands. This linker can also be used to increase the solubility, if needed, e.g. by incorporation of PEGs. The resulting proximity of both, the recruited POI and the E3 ligase, allows the polyubiquitination of the POI by the E3 associated E2 enzyme. This leads to a labeling of the POI for degradation through the proteasome.

Mode of action:

1. A cross-linker unites the POI ligand and E3 ligase ligand = PROTAC.
2. The three-component PROTAC recruits the POI and the E2-associated E3 ligase *via* the respective ligands = Ternary complex.
3. Several Ubiquitins are added to Lys residues of the POI = Polyubiquitination.
4. The ubiquitinated POI is degraded by the proteasome.

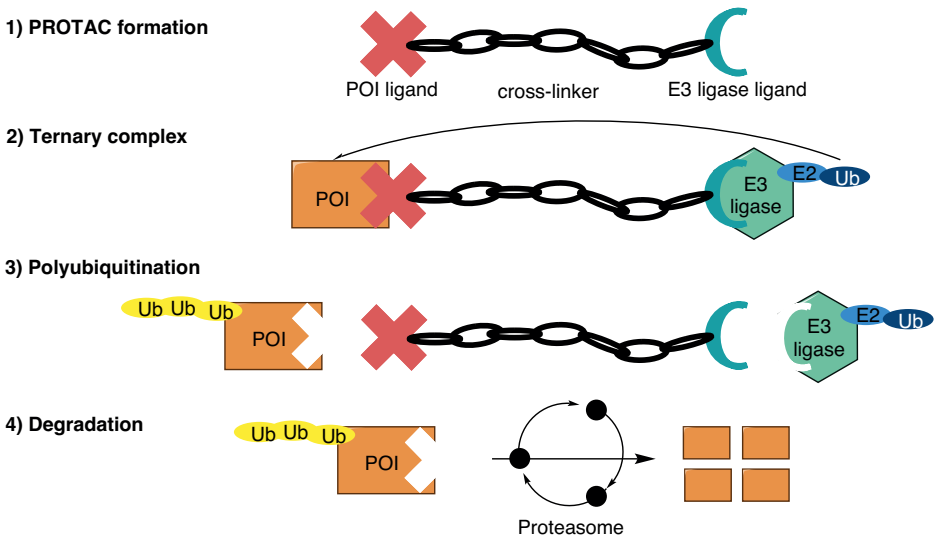

Fig. 30: Targeted protein degradation via proteolysis-targeting chimeras.

To construct a suitable PROTAC, we provide a variety of E3 ubiquitin ligase ligands in combination with linkers of various length and an elective amino-, carboxyl-, click- or thiol-reactive end ("Partial PROTACs").

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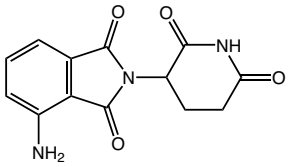
E3-Ligase Ligands & Negative Controls

Product details

PTC1000 Pomalidomide

1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline,

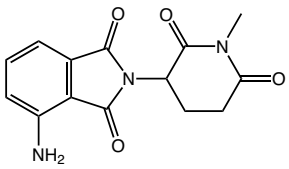
CAS-No.	19171-19-8
Formula	$C_{13}H_{11}N_3O_4$
Mol. weight	273,24 g/mol



PTC1010 N-Methylated pomalidomide

4-Amino-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

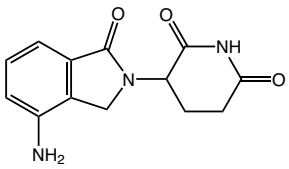
CAS-No.	1352827-50-9
Formula	$C_{14}H_{13}N_3O_4$
Mol. weight	287,27 g/mol



PTC1020 Lenalidomide

1-Oxo-4-amino-2-(2,6-dioxopiperidin-3-yl)isoindole

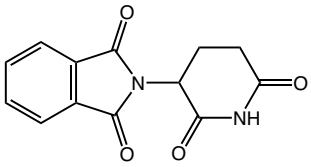
CAS-No.	191732-72-6
Formula	$C_{13}H_{13}N_3O_3$
Mol. weight	259,26 g/mol



PTC1030 (±)-Thalidomide

(±)-2-(2,6-Dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione

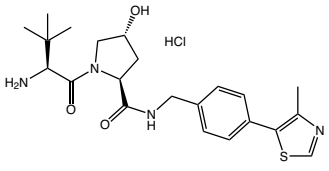
CAS-No.	50-35-1
Formula	$C_{13}H_{10}N_2O_4$
Mol. weight	258,23 g/mol



PTC1040 (S,R,S)-AHPC hydrochloride

(2S,4R)-1-((S)-2-Amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride

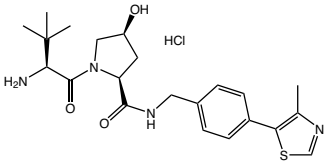
CAS-No.	1448189-80-7
Formula	$C_{22}H_{30}N_4O_3S$*xHCl
Mol. weight	430,56 (free base) g/mol



PTC1050 (S,S,S)-AHPC hydrochloride

(2S,4S)-1-((S)-2-Amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride

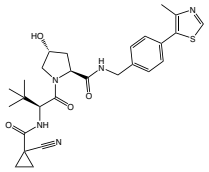
CAS-No.	2115897-23-7
Formula	$C_{22}H_{30}N_4O_3S$*xHCl
Mol. weight	430,56 (free base) g/mol



PTC1060 VH298

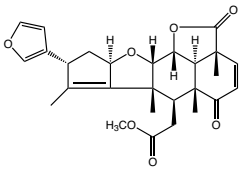
(2S,4R)-1-((S)-2-(1-Cyanocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

CAS-No.	2097381-85-4
Formula	$C_{27}H_{33}N_5O_4S$
Mol. weight	523,65 g/mol



PTC1070 Nimbolide

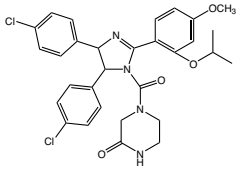
CAS-No.	25990-37-8
Formula	$C_{27}H_{30}O_7$
Mol. weight	466,52 g/mol



PTC1080 Nutlin-3

(±)-4-[4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

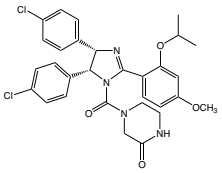
CAS-No.	548472-68-0
Formula	$C_{30}H_{30}Cl_2N_4O_4$
Mol. weight	581,49 g/mol



PTC1090 Nutlin-3a

(-)-4-(4,5-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxyphenyl)-4,5-dihydro-1H-imidazole-1-carbonyl) piperazin-2-one

CAS-No.	675576-98-4
Formula	$C_{30}H_{30}Cl_2N_4O_4$
Mol. weight	581,49 g/mol



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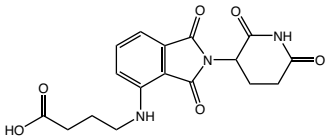
Amino Reactive Partial PROTACs

Product details

PTC1100 Pomalidomide-C3-COOH

4-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)butanoic acid

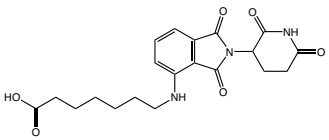
CAS-No. 2225940-47-4
Formula $C_{17}H_{17}N_3O_6$
Mol. weight 359,33 g/mol



PTC1110 Pomalidomide-C6-COOH

7-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)heptanoic acid

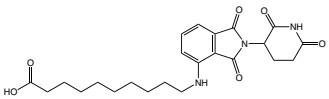
CAS-No. 2225940-50-9
Formula $C_{20}H_{23}N_3O_6$
Mol. weight 401,41 g/mol



PTC1120 Pomalidomide-C9-COOH

10-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)amino)decanoic acid

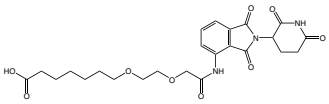
CAS-No. 2243000-24-8
Formula $C_{23}H_{29}N_3O_6$
Mol. weight 443,5 g/mol



PTC1130 Pomalidomide-PEG2-butyl COOH

7-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)amino)-2-oxoethoxy)ethoxy)heptanoic acid

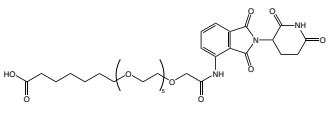
Formula $C_{24}H_{29}N_3O_9$
Mol. weight 503,5 g/mol



PTC1140 Pomalidomide-PEG6-butyl COOH

1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl) amino)-1-oxo-3,6,9,12,15,18-hexaoxapentacosan-25-oic acid

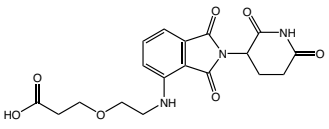
Formula $C_{32}H_{45}N_3O_{13}$
Mol. weight 679,71 g/mol



PTC1150 Pomalidomide-PEG1-COOH

3-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)propanoic acid

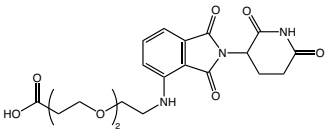
CAS-No.	2139348-60-8
Formula	$C_{18}H_{19}N_3O_7$
Mol. weight	389,36 g/mol



PTC1160 Pomalidomide-PEG2-COOH

3-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanoic acid

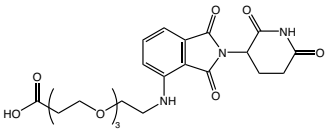
CAS-No.	2140807-17-4
Formula	$C_{20}H_{23}N_3O_8$
Mol. weight	433,42 g/mol



PTC1170 Pomalidomide-PEG3-COOH

3-(2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoic acid

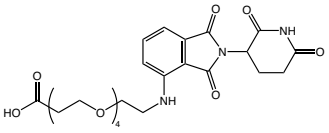
CAS-No.	2138440-82-9
Formula	$C_{22}H_{27}N_3O_9$
Mol. weight	477,46 g/mol



PTC1180 Pomalidomide-PEG4-COOH

1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oic acid

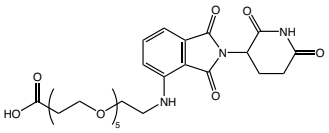
CAS-No.	2138440-81-8
Formula	$C_{24}H_{31}N_3O_{10}$
Mol. weight	521,52 g/mol



PTC1190 Pomalidomide-PEG5-COOH

1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oic acid

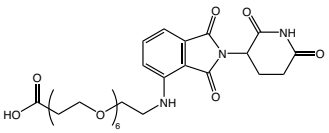
CAS-No.	2139348-63-1
Formula	$C_{26}H_{35}N_3O_{11}$
Mol. weight	565,57 g/mol



PTC1200 Pomalidomide-PEG6-COOH

1-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18-hexaoxahenicosan-21-oic acid

CAS-No.	2225148-49-0
Formula	$C_{28}H_{39}N_3O_{12}$
Mol. weight	609,62 g/mol



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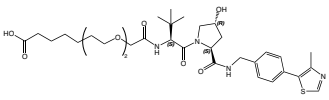
Product details

PTC1220 (S,R,S)-AHPC-PEG2-butyl COOH

(S,R,S)-AHPC-2-2-6-acid,7-(2-(2-(((S)-1-((2S,4R)-4-Hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)heptanoic acid



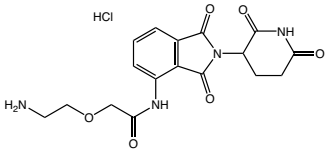
Formula	$C_{33}H_{48}N_4O_8S$
Mol. weight	660,82 g/mol

Carboxy Reactive Partial PROTACs

Product details

PTC1230 Pomalidomide-PEG1-NH_2 hydrochloride

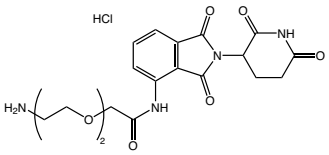
2-(2-Aminoethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide hydrochloride



CAS-No.	2380273-67-4
Formula	$C_{17}H_{18}N_4O_6$*xHCl
Mol. weight	374,35 (free base) g/mol

PTC1240 Pomalidomide-PEG2-NH_2 hydrochloride

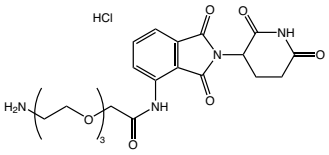
2-(2-(2-Aminoethoxy)ethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide hydrochloride



Formula	$C_{19}H_{22}N_4O_7$*xHCl
Mol. weight	418,40 (free base) g/mol

PTC1250 Pomalidomide-PEG3-NH_2 hydrochloride

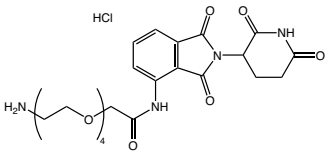
2-(2-(2-(2-Aminoethoxy)ethoxy)ethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide hydrochloride



Formula	$C_{21}H_{26}N_4O_8$*xHCl
Mol. weight	462,45 (free base) g/mol

PTC1260 Pomalidomide-PEG4-NH_2 hydrochloride

14-Amino-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12-tetraoxatetradecanamide hydrochloride

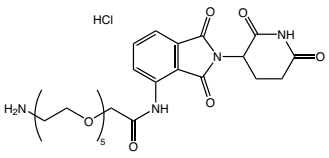


Formula	$C_{23}H_{30}N_4O_9$*xHCl
Mol. weight	506,41 (free base) g/mol

PTC1270 Pomalidomide-PEG5-NH_2 hydrochloride

17-Amino-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15-pentaoxaheptadecanamide hydrochloride

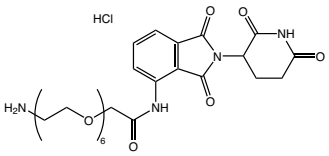
Formula $C_{25}H_{34}N_4O_{10}$*xHCl
Mol. weight 550,56 (free base) g/mol



PTC1280 Pomalidomide-PEG6-NH_2 hydrochloride

20-Amino-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15,18-hexaoxaicosanamide hydrochloride

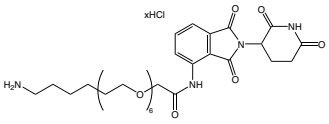
Formula $C_{27}H_{38}N_4O_{11}$*xHCl
Mol. weight 594,61 (free base) g/mol



PTC1300 Pomalidomide-PEG6-butyl-NH_2 hydrochloride

4-Amino-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin

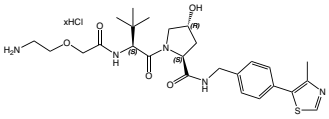
Formula $C_{31}H_{46}N_4O_{11}$*xHCl
Mol. weight 650,72 (free base) g/mol



PTC1310 (S,R,S)-AHPC-PEG1-NH_2 hydrochloride

(2S,4R)-1-((S)-2-(2-(2-Aminoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride

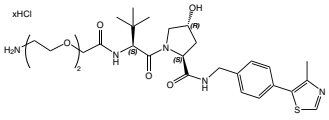
Formula $C_{26}H_{37}N_5O_5S$*xHCl
Mol. weight 531,67 (free base) g/mol



PTC1320 (S,R,S)-AHPC-PEG2-NH_2 hydrochloride

(2S,4R)-1-((S)-2-(2-(2-(2-Aminoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride

CAS-No. 2097973-72-1
Formula $C_{28}H_{41}N_5O_6S$*xHCl
Mol. weight 575,72 (free base) g/mol



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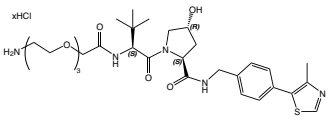
Product details

PTC1330 (S,R,S)-AHPC-PEG3-NH_2 hydrochloride

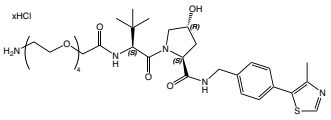
(2S,4R)-1-((S)-14-Amino-2-(*tert*-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride



CAS-No.	2097971-11-2
Formula	$C_{30}H_{45}N_5O_7S$*xHCl
Mol. weight	619,77 (free base) g/mol

PTC1340 (S,R,S)-AHPC-PEG4-NH_2 hydrochloride

(2S,4R)-1-((S)-17-Amino-2-(*tert*-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaheptadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride



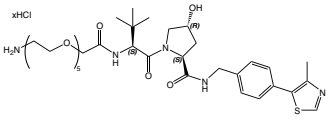
CAS-No.	2010159-57-4
Formula	$C_{32}H_{49}N_5O_8S$*xHCl
Mol. weight	663,83 (free base) g/mol

Click Reactive Partial PROTACs

Product details

PTC1350 (S,R,S)-AHPC-PEG5-NH_2 hydrochloride

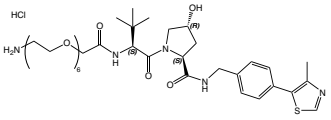
(2S,4R)-1-((S)-20-Amino-2-(*tert*-butyl)-4-oxo-6,9,12,15,18-pentaoxa-3-azaicosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride



Formula	$C_{34}H_{53}N_5O_9S$*xHCl
Mol. weight	707,88 (free base) g/mol

PTC1360 (S,R,S)-AHPC-PEG6-NH_2 hydrochloride

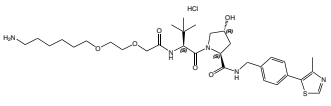
(2S,4R)-1-((S)-23-Amino-2-(*tert*-butyl)-4-oxo-6,9,12,15,18,21-hexaoxa-3-azatricosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride



Formula	$C_{36}H_{57}N_5O_{10}S$*xHCl
Mol. weight	751,93 (free base) g/mol

PTC1370 (S,R,S)-AHPC-PEG2-butyl-NH_2 hydrochloride

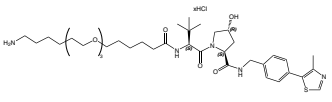
(2S,4R)-1-((S)-2-(2-(2-((6-Aminohexyl)oxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula	$C_{32}H_{49}N_5O_6S$*xHCl
Mol. weight	631,83 (free base) g/mol

PTC1380 (S,R,S)-AHPC-C6-PEG3-butyl-NH_2 hydrochloride

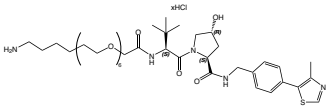
(2S,4R)-1-((S)-22-Amino-2-(*tert*-butyl)-4-oxo-10,13,16-trioxa-3-azadocosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula $C_{38}H_{61}N_5O_7S*xHCl$
Mol. weight 731,99 (free base) g/mol

PTC1390 (S,R,S)-AHPC-PEG6-butyl-NH_2 hydrochloride

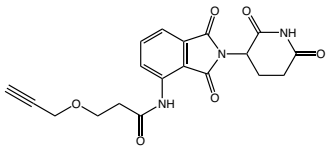
(2S,4R)-1-((S)-27-Amino-2-(*tert*-butyl)-4-oxo-6,9,12,15,18,21-hexaoxa-3-azaheptacosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula $C_{40}H_{65}N_5O_{10}S*xHCl$
Mol. weight 808,04 (free base) g/mol

PTC1400 Pomalidomide-PEG1-Alkyne

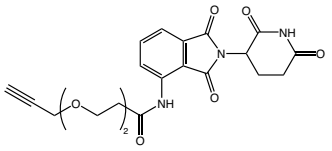
N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(prop-2-yn-1-yloxy)propanamide



Formula $C_{19}H_{17}N_3O_6$
Mol. weight 383,35 g/mol

PTC1410 Pomalidomide-PEG2-Alkyne

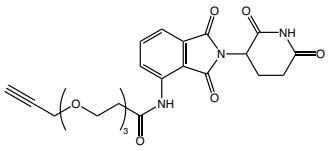
N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(2-(prop-2-yn-1-yloxy)ethoxy)propanamide



Formula $C_{21}H_{21}N_3O_7$
Mol. weight 427,41 g/mol

PTC1420 Pomalidomide-PEG3-Alkyne

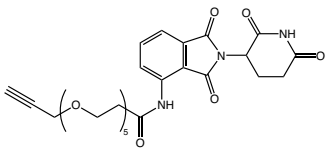
N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy)propanamide



Formula $C_{23}H_{25}N_3O_8$
Mol. weight 471,46 g/mol

PTC1440 Pomalidomide-PEG5-Alkyne

N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-4,7,10,13,16-pentaoxanonadec-18-ynamide



Formula $C_{27}H_{33}N_3O_{10}$
Mol. weight 559,57 g/mol

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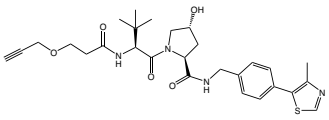
Product details

PTC1460 (S,R,S)-AHPC-PEG1-Alkyne

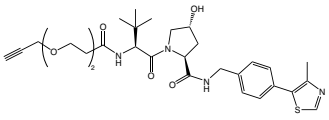
(2S,4R)-1-((S)-3,3-Dimethyl-2-(3-(prop-2-yn-1-yloxy) propanamido)butanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula	$C_{28}H_{36}N_4O_5S$
Mol. weight	540,67 g/mol

PTC1470 (S,R,S)-AHPC-PEG2-Alkyne

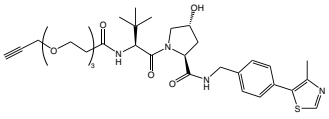
(2S,4R)-1-((S)-3,3-Dimethyl-2-(3-(2-(prop-2-yn-1-yloxy) ethoxy)propanamido)butanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula	$C_{30}H_{40}N_4O_6S$
Mol. weight	584,73 g/mol

PTC1480 (S,R,S)-AHPC-PEG3-Alkyne

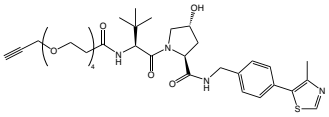
(2S,4R)-1-((S)-2-(*tert*-Butyl)-4-oxo-7,10,13-trioxa-3-azahexadec-15-ynoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



CAS-No.	2374122-30-0
Formula	$C_{32}H_{44}N_4O_7S$
Mol. weight	628,78 g/mol

PTC1490 (S,R,S)-AHPC-PEG4-Alkyne

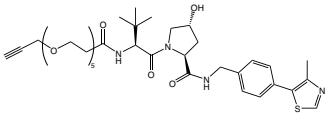
(2S,4R)-1-((S)-2-(*tert*-Butyl)-4-oxo-7,10,13,16-tetraoxa-3-azanonadec-18-ynoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula	$C_{34}H_{48}N_4O_8S$
Mol. weight	672,83 g/mol

PTC1500 (S,R,S)-AHPC-PEG5-Alkyne

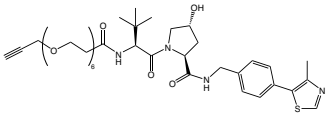
(2S,4R)-1-((S)-2-(*tert*-Butyl)-4-oxo-7,10,13,16,19-pentaoxa-3-azadocos-21-ynoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



Formula	$C_{36}H_{52}N_4O_9S$
Mol. weight	716,88 g/mol

PTC1510 (S,R,S)-AHPC-PEG6-Alkyne

(2S,4R)-1-((S)-2-(*tert*-Butyl)-4-oxo-7,10,13,16,19,22-hexaoxa-3-azapentacos-24-ynoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

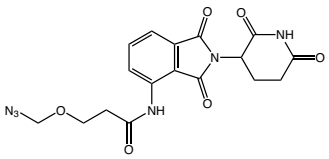


Formula	$C_{38}H_{56}N_4O_{10}S$
Mol. weight	760,94 g/mol

PTC1520 Pomalidomid- PEG1-N_3

2-(2-Azidoethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide

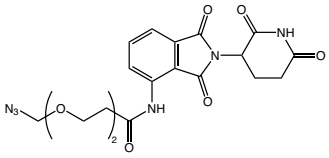
CAS-No.	2133360-04-8
Formula	$C_{17}H_{16}N_6O_6$
Mol. weight	400,35 g/mol



PTC1530 Pomalidomid- PEG2-N_3

2-(2-(2-Azidoethoxy)ethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide

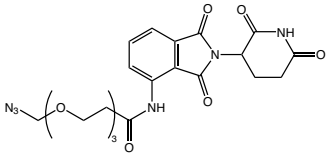
CAS-No.	2267306-14-7
Formula	$C_{19}H_{20}N_6O_7$
Mol. weight	444,4 g/mol



PTC1540 Pomalidomid- PEG3-N_3

2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)acetamide

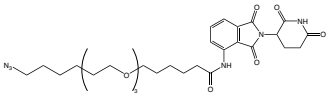
CAS-No.	2267306-15-8
Formula	$C_{21}H_{24}N_6O_8$
Mol. weight	488,45 g/mol



PTC1560 Pomalidomid-C6-PEG3-butyl-N_3

6-(2-(2-((6-Azidohexyl)oxy)ethoxy)ethoxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)hexanamide

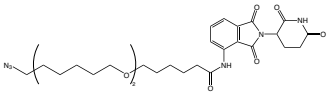
CAS-No.	2300178-66-7
Formula	$C_{29}H_{40}N_6O_8$
Mol. weight	600,66 g/mol



PTC1570 Pomalidomid-C6-PEG1-C3-PEG1-butyl-N_3

6-((5-((6-Azidohexyl)oxy)pentyl)oxy)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)hexanamide

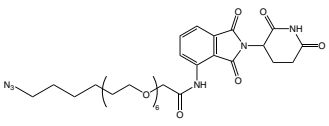
Formula	$C_{30}H_{42}N_6O_7$
Mol. weight	598,69 g/mol



PTC1580 Pomalidomid-PEG6-butyl-N_3

4-azido-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3,6,9,12,15,18-hexaoxatetracosanamide

Formula	$C_{31}H_{44}N_6O_{11}$
Mol. weight	676,71 g/mol



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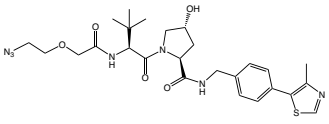
Product details

PTC1590 (S,R,S)-AHPC-PEG1-N_3

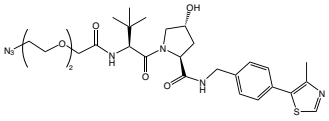
(2S,4R)-1-((S)-2-(2-(2-Azidoethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



CAS-No.	2101200-09-1
Formula	$C_{26}H_{35}N_7O_5S$
Mol. weight	557,67 g/mol

PTC1600 (S,R,S)-AHPC-PEG2-N_3

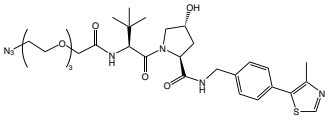
(2S,4R)-1-((S)-2-(2-(2-(2-Azidoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



CAS-No.	2010159-45-0
Formula	$C_{28}H_{39}N_7O_6S$
Mol. weight	601,72 g/mol

PTC1610 (S,R,S)-AHPC-PEG3-N_3

(2S,4R)-1-((S)-14-azido-2-(*tert*-butyl)-4-oxo-6,9,12-trioxa-3-azatetradecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



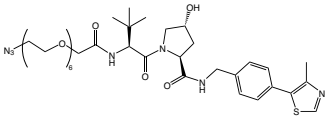
CAS-No.	1797406-80-4
Formula	$C_{30}H_{43}N_7O_7S$
Mol. weight	645,77 g/mol

Thiol Reactive Partial PROTACs

Product details

PTC1640 (S,R,S)-AHPC-PEG6-N_3

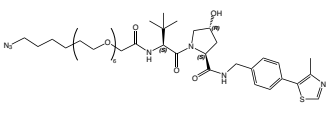
(2S,4R)-1-((S)-23-Azido-2-(*tert*-butyl)-4-oxo-6,9,12,15,18,21-hexaoxa-3-azatricosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide



CAS-No.	2086298-71-5
Formula	$C_{36}H_{55}N_7O_{10}S$
Mol. weight	777,93 g/mol

PTC1680 (S,R,S)-AHPC-PEG6-butyl-N_3

(2S,4R)-1-((S)-27-Azido-2-(*tert*-butyl)-4-oxo-6,9,12,15,18,21-hexaoxa-3-azaheptacosanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

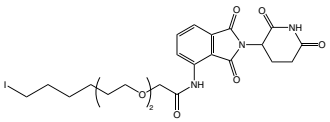


Formula	$C_{40}H_{63}N_7O_{10}S$
Mol. weight	834,03 g/mol

PTC1690 Pomalidomid-PEG2-butyl-I

N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)-2-(2-((6-iodohexyl)oxy)ethoxy)acetamide

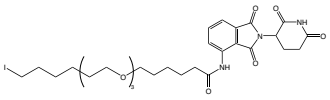
CAS-No.	1835705-72-0
Formula	$C_{23}H_{28}IN_3O_7$
Mol. weight	585,39 g/mol



PTC1700 Pomalidomid-C6-PEG3-butyl-I

N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)-6-(2-(2-((6-iodohexyl)oxy)ethoxy)ethoxy) hexanamide

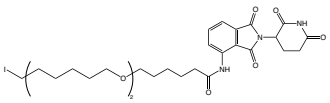
CAS-No.	1835705-70-8
Formula	$C_{29}H_{40}IN_3O_8$
Mol. weight	685,55 g/mol



PTC1710 Pomalidomid-C6-PEG1-C3-PEG1-butyl-I

N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)-6-((5-((6-iodohexyl)oxy)pentyl)oxy)hexana-mide

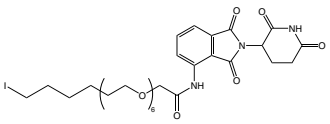
CAS-No.	1835705-76-4
Formula	$C_{30}H_{42}IN_3O_7$
Mol. weight	683,57 g/mol



PTC1720 Pomalidomid-PEG6-butyl-I

N-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindo-lin-4-yl)-24-iodo-3,6,9,12,15,18-hexaoxatetracosanamide

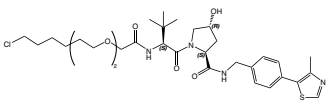
CAS-No.	1835705-74-2
Formula	$C_{31}H_{44}IN_3O_{11}$
Mol. weight	761,6 g/mol



PTC1730 (S,R,S)-AHPC-PEG2-butyl-Cl

(2S,4R)-1-((S)-2-(2-(2-((6-Chlorohexyl)oxy)ethoxy) acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide

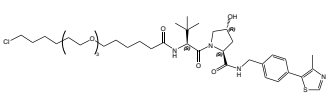
CAS-No.	1835705-57-1
Formula	$C_{32}H_{47}ClN_4O_6S$
Mol. weight	651,26 g/mol



PTC1750 (S,R,S)-AHPC-C6-PEG3-butyl-Cl

(2S,4R)-1-((S)-2-(*tert*-Butyl)-22-chloro-4-oxo-10,13,16-trioxa-3-azadocosanoyl)-4-hydroxy-N-(4-(4-methylthi-azol-5-yl)benzyl)pyrrolidine-2-carboxamide

CAS-No.	1835705-55-9
Formula	$C_{38}H_{59}ClN_4O_7S$
Mol. weight	751,42 g/mol



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In addition to these pre-designed building blocks, we offer custom synthesis of your required ligand-linker combination (*Fig. 31*) or "complete PROTAC". This allows to design a library of slightly different PROTACs in order to find the best combination for your application, as even small changes in ligands and cross-linkers might affect the efficiency of the formation of the ternary complex.

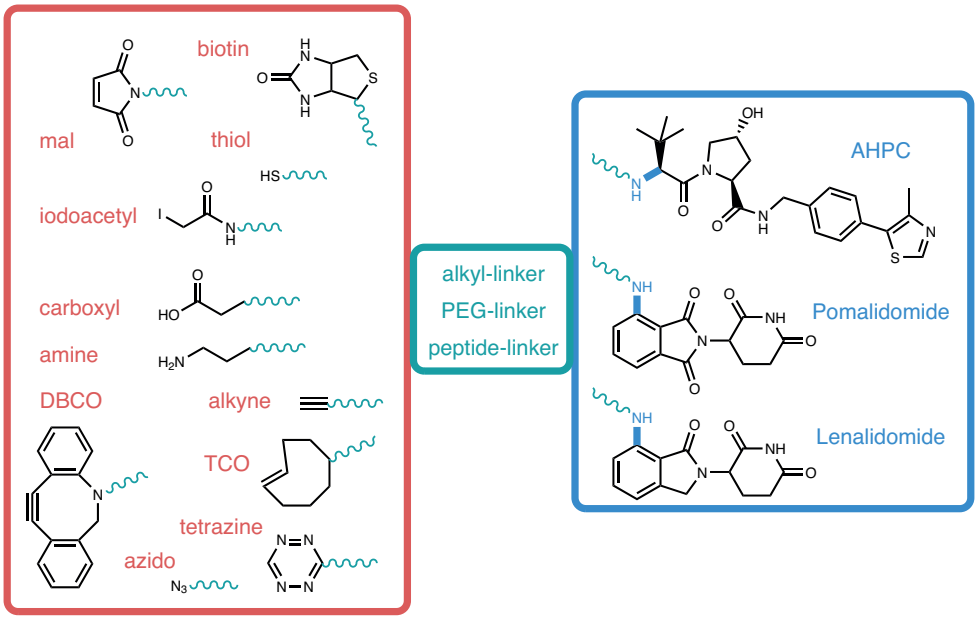

Fig. 31: Possibilities of PROTAC design. Above displayed options for linker constructs can be conjugated to substrates of the protein of interest, in order to create the desired PROTAC®.

Please contact us for Custom Synthesis of the PROTAC® linker fragment of your choice or complete functional PROTAC®.

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5.5. Site-Selective π-Clamp Mediated Cysteine Arylation

For the modification of proteins, cysteine is a suitable choice for bioconjugation because of the high nucleophilicity of its thiol group as well as the low abundance of Cys residues in the majority of naturally occurring proteins (ca. 1.7%). However, conventional chemical cysteine-based conjugation techniques are not site-specific resulting in a multiple labelling mixture at random positions.

In nature, selective reactions in proteins are triggered by the formation of certain microenvironments by three-dimensional secondary structures of the surrounding polypeptide architecture. Inspired by nature, Pentelute *et al.* envisioned a new strategy for site-selective chemistry, the so called "π-clamp" arylation. Cysteine embedded in the four-amino-acid sequence (Phe-Cys-Pro-Phe) tunes up the thiol reactivity for site-selective conjugation with perfluoroaromatic reagents. Thus, the π-clamp allows the selective modification of one cysteine site in a protein containing multiple other endogenous cysteine residues.

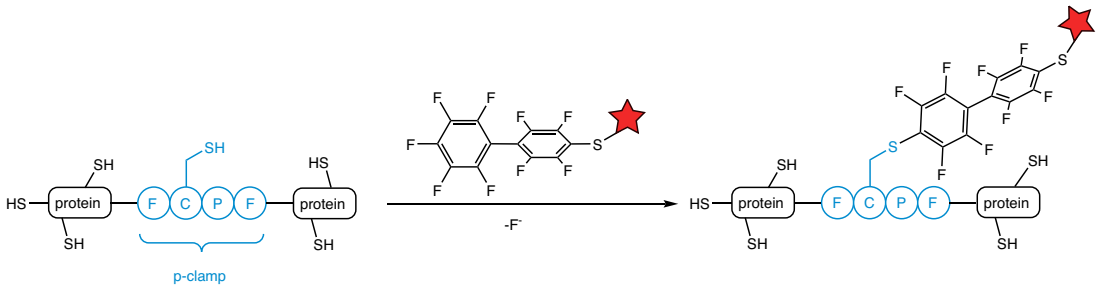

Fig. 32: A cysteine residue inside the π-clamp selectively reacts with perfluorobiphenyl probes in the presence of other competing cysteine residues or thiols.

The reported reaction is site-specific, operational under physiological conditions, enzyme-free, and as efficient as the commonly used azide-alkyne click chemistry. Furthermore, the π-clamp works as part of the N-terminus, the C-terminus, as well as in the middle of a polypeptide chain. Besides, its small size hardly perturbs the target protein's native structure.

In addition to the possibility for site-selective cysteine labeling in any linear peptide, the π-clamp approach should allow for macrocyclization between cysteine thiolates as a last, high-yielding synthetic step either *via* an exogenously added perfluoroaryl-based linker, or by incorporating non-crosslinked perfluoroaryl-based moieties first, followed by their macrocyclization with dithiol reagents.

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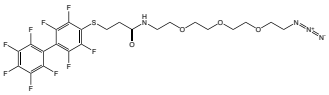
Product details

RL-4030 PFB-mercaptopropionyl-PEG3-N_3

Perfluorobiphenyl-mercaptopropionyl-PEG(3)-N_3

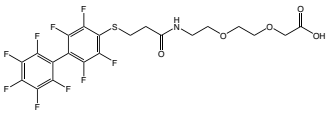
Formula $C_{23}H_{21}F_9N_4O_4S$
Mol. weight 620,49 g/mol



RL-4040 PFB-mercaptopropionyl-AEEA

Perfluorobiphenyl-mercaptopropionyl-AEEA

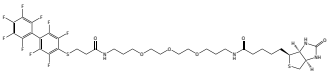
Formula $C_{21}H_{16}F_9NO_5S$
Mol. weight 565,41 g/mol



RL-4050 PFB-mercaptopropionyl-TOTA-Biotin

Perfluorobiphenyl-mercaptopropionyl-TOTA-Biotin

Formula $C_{35}H_{41}F_9N_4O_6S_2$
Mol. weight 848,84 g/mol



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6. Preparing Carriers for Conjugation

Carrier	Conjugation Chemistry	Cleavage Mechanism	Fragmentation for Traceless Release	Cargo Functionality
Biopolymers: • Peptides • Proteins • Antibodies • Single Chain • Nanobodies • Camelides • Oligonucleotides • Aptamers	Thioether formation with maleimide Disulfide bond formation Acylation of amines His tag acylation Click conjugation (CuAAC, SPAAC, IEDDA) Enzyme supported conjugation: • HaloTag® • CLIP-Tag™ • SNAP-Tag® • Sequence dependent conjugation (Sortase, Ligase)	**Enzymatic hydrolysis:** • Val-Ala • Val-Cit • Phe-Lys • Gly-Phe-Leu-Gly • Ala-Leu-Ala-Leu • Cyclobutyl-Ala • Cyclobutyl-Cit • Glucuronic acid	*p*-Aminobenzyl *p*-Hydroxybenzyl *p*-Mercaptobenzyl Oxathiolone Dimethylimidazolidinone	Primary & secondary amines Tertiary amines Alcohols\Phenols Carboxylic acids
Carbon: • Nanotubes • Fullerenes	Nitrene addition *via* photoactivation of perfluoroarylazides			
Metals: • Gold • Silver	Affinity of sulfur to gold and silver	**Reduction:**		
Metal oxide	Chelate formation	**Oxidation:** Tetramethyl-dioxoborolane		
Plastic polymers: • Teflon • Polyethylene • Polystyrene • Latex	Introduction of reactive functional groups by plasma treatment (e.g. ammonia or acrylic acid)			
Silicates	Affinity between silicon and oxygen			

Fig. 33: Conceptual overview of conjugation technologies.

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6.1. Antibodies, Antibody Formats and Proteins by (Cell-free) Recombinant Methodologies

Cell-free protein synthesis, often referred to as *in vitro* translation, is a fast and viable technique which, in comparison to *in vivo* protein synthesis, leads to the production of a target protein in a considerably less laborious way. Cell-free systems are based on lysates derived from *E. coli* or eukaryotic sources and they allow for the synthesis of a broad spectrum of structurally diverse and modified proteins. The path from a DNA template to the protein of interest is reduced to only a few hours of time and additionally, no genetically modified organisms (GMOs) are needed. A variety of proteins, such as certain membrane proteins (e.g. GPCRs), toxins or transcriptional and translational factors, whose synthesis in conventional *in vivo* systems is often associated with difficulties, can be synthesized *in vitro*. Only the target protein is synthesized in cell-free systems, since endogenous mRNA templates are removed during the process of lysate preparation. The open and flexible character of cell-free systems allows the well-tuned adjustment of the reaction environment by supplementing the reaction mixture with co-factors, chaperones, detergents, rare tRNAs and buffers of varying ion composition, depending on the demands of the individual protein. The reaction conditions during protein synthesis significantly impact protein folding, protein activity and functionality.

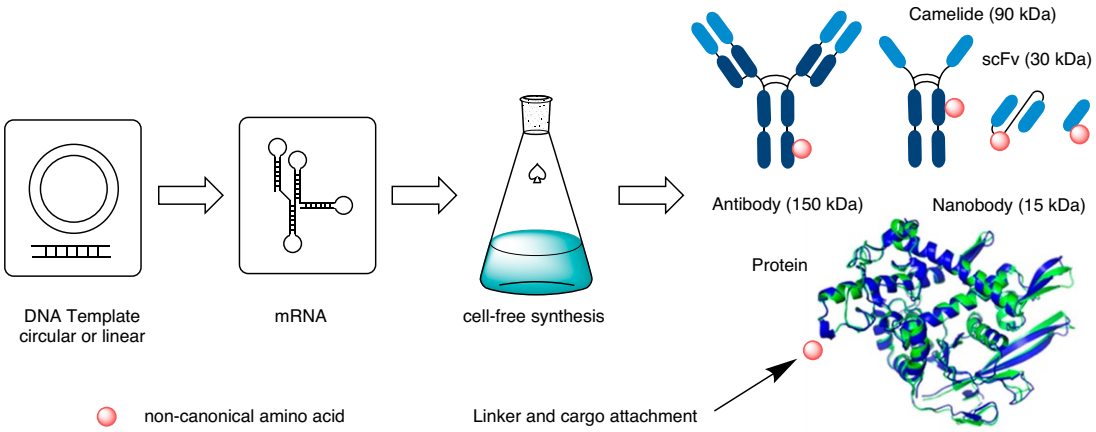

Fig. 34: General principle of cell-free synthesis of biomolecules with position specific introduction of non-canonical amino acids as conjugation point for subsequent Linkerology®.

Cell-free protein synthesis provides a fast access to proteins and antibody formats including introduction of mutations or non-canonical amino acids at defined positions for subsequent conjugation with permanent or self-immolative linkers and payloads. This includes otherwise difficult to synthesize toxic proteins, membrane proteins, labelled proteins, protein-conjugates, and antibody formats.

Do you have a certain bioconjugate in mind?

- *Membrane protein carrying a conjugation function on a specific position.*
- *Antibody, single chain or nanobody decorated with azido or alkyne function for initial linker attachment.*
- *Biomolecule-linker conjugate, ready to load your payload.*
- *Or the final biomolecule-drug-conjugate.*
- *Adaption of your current protein ready for linker attachment.*

Consult with us, we will work out the best solution for you!

You need more details about cell-free protein synthesis?

Watch the recording of our workshop!

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6.2. Aptamers and other Oligonucleotides

Terminal azide bearing nucleotides closely resemble natural nucleotides and are the basis of chemo-enzymatic oligonucleotide labeling. T7 RNA polymerase, poly(A) polymerase and the terminal deoxynucleotidyl transferase (Tdt) tolerate azide and alkyne decorated nucleotides and incorporate them at a defined position. Any mRNA can be site-specifically labeled without special requirements or altered production protocols. By click labeling at the 3'-end the half-life of the mRNA could be modulated, which might be an option for increased mRNA stability.

Feeding living cells with 5-ethynyl uridine (EU) will lead to EU labelled RNA, which further can be modified *via* Click conjugation, e.g. with fluorescent dyes or linkers carrying small molecules, peptides or proteins. Incorporation into DNA can also occur after some incubation time. This is most likely *via* conversion of the EU ribonucleoside into EdU aided by intracellular ribonucleotide reductases.

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With 5-ethynyl-dA-CEP and 5-ethynyl-dU-CEP alkyne moieties can be used under standard conditions for solid phase synthesis of oligonucleotides followed by subsequence Click conjugation.

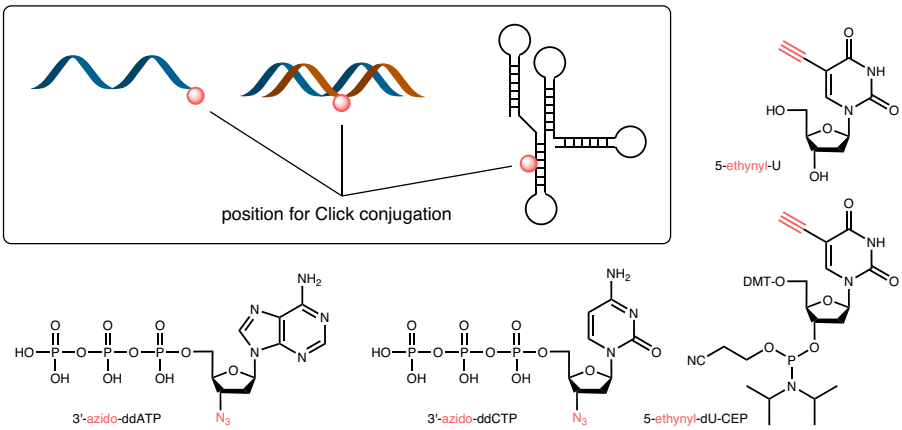

Fig. 35: Alkyne and azido functions can be implemented at specific positions of oligonucleotide sequences by various building blocks.

With partners we have the possibility to provide modified oligonucleotide sequences ready for conjugation with suitable (self-immolative) linkers and payloads.

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6.3. Carbon Compounds

Fullerenes and carbon nanotubes are subject of ongoing research as they possess unique geometrical shapes, as well as appealing photochemical, electrochemical, and physical properties. In addition, they act as efficient radical scavenger and antioxidant, as well as nano carrier for gene and drug delivery. Thus, a wide variety of operations can be considered. There are different options for conjugating linkers and payloads to such type of carriers.

a) Fullerenes carrying phenylbutyric methyl ester (PBM) can be activated by saponification followed by ester or amide formation with appropriate substitutions.

b) Fullerene derivatives with malonic acid moieties can react readily with nucleophiles, e.g. the amino functions of amino acids, amino-PEGs or other linkers and payloads enabling multiple payload decoration on one single fullerene.

c) Perhydroxylated fullerenols are a unique class of water-soluble fullerenes. Their alcohol functions can further be derivatized by ester or ether formation, e.g. *via* Mitsunobo reaction.

d) Fullerenes and carbon nanotubes carrying no functional group can be prepared for conjugation by photoaffinity labeling reagents such as aryl azides. Upon photolysis (258 nm), N_2 is liberated and a stabilized singlet perfluorophenylnitrene is being formed *in situ*, which reacts with neighboring molecules by insertion and addition reactions in moderate to good yields.

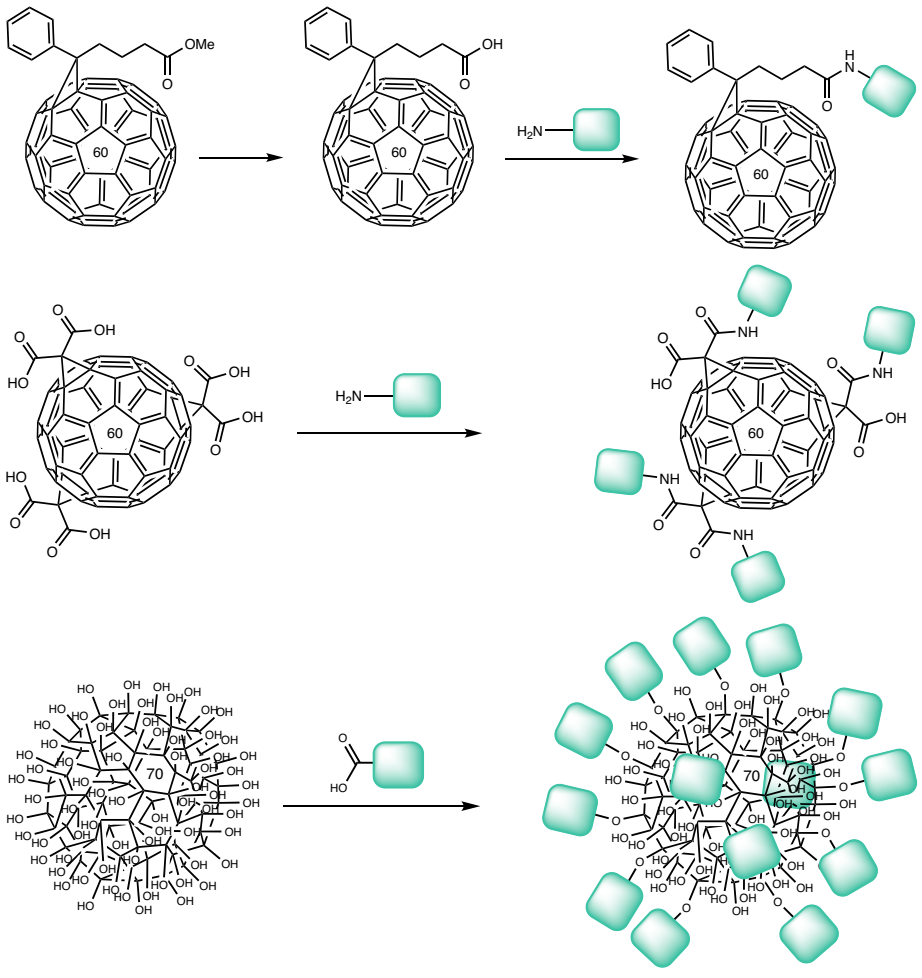

Fig. 36: Pre-derivatized fullerenes allow direct surface conjugation.

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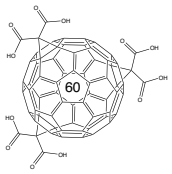
Product details

FLL1070 Fullerene C_{60} (malonic acid)$_n$

Buckminsterfullerene-n-(malonic acid)

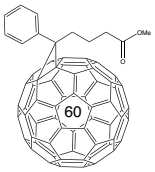
Formula $C_{60}(C_3H_2O_4)n$
Mol. weight 720,66+(102,05)n g/mol



FLL1020 Fullerene C_{60} (PBM)

Fulleren-phenyl-(4-phenylbutyric acid methyl ester)

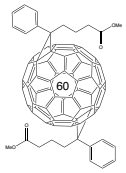
CAS-No. 160848-22-6
Formula $C_{72}H_{14}O_2$
Mol. weight 910,9 g/mol



FLL1010 Fullerene C_{60} (PBM)$_2$

Fulleren-diphenyl-bis(4-phenylbutyric acid methyl ester)

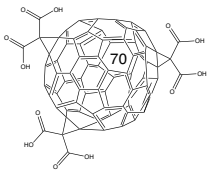
CAS-No. 1048679-01-1
Formula $C_{84}H_{28}O_4$
Mol. weight 1104,14 g/mol



FLL1080 Fullerene C_{70} (malonic acid)$_n$

Buckminsterfullerene-n-(malonic acid)

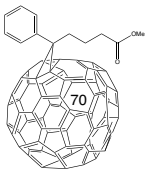
Formula $C_{70}(C_3H_2O_4)n$
Mol. weight 840,77+(102,05)n g/mol



FLL1060 Fullerene C_{70} (PBM)

Fulleren-phenyl-(4-phenylbutyric acid methyl ester)

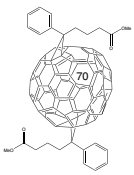
CAS-No. 609771-63-3
Formula $C_{82}H_{14}O_2$
Mol. weight 1031,01 g/mol



FLL1050 Fullerene C_{70} (PBM)$_2$

Fulleren-diphenyl-bis(4-phenylbutyric acid methyl ester)

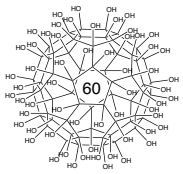
Formula $C_{94}H_{28}O_4$
Mol. weight 1221,25 g/mol



FLL1030 Fullerenol C60

Polyhydroxylated Fullerene

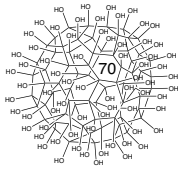
Formula	$C_{60}(OH)n$
Mol. weight	720,66+(17,01)n g/mol



FLL1090 Fullerenol C70

Polyhydroxylated Fullerene

Formula	$C_{70}(OH)n$
Mol. weight	840,77+(17,01)n g/mol



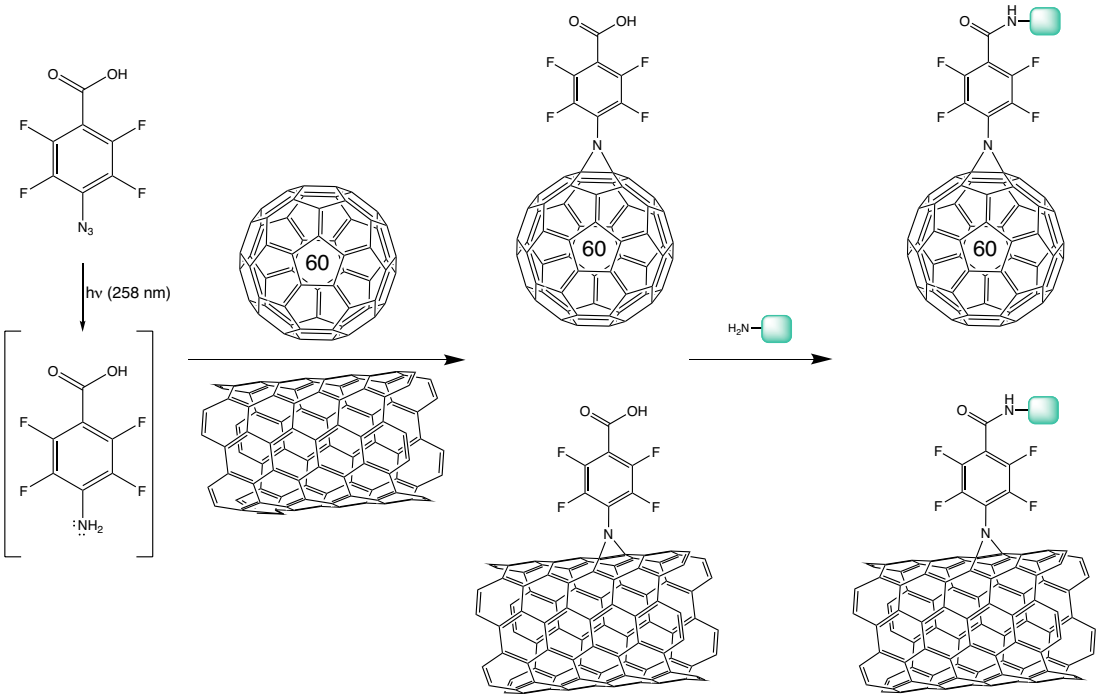


Fig. 37: Carbon nanotubes and fullerenes can be surface decorated with carboxylic acid moieties for subsequent derivatization and linker attachment via photolysis of perfluoroarylazides which form in situ stable and reactive nitrenes.

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6.4. Metals

Nanotechnology and nanobiotechnology using gold or silver particles are broadly diverse, rapidly expanding areas of study in medical diagnostics and therapeutics, sensorics and chemistry. Gold nanoparticles (AuNPs), particularly, have found a wide range of biomedical and environmental monitoring applications (drug delivery, diagnostics, biosensing, bio-imaging, theranostics, and hazardous chemical sensing) due to their excellent optoelectronic and enhanced physico-chemical properties.

Metal particles, however, are not water soluble without further modification. Due to the soft character of gold and sulfur, thiols readily form strong dative bonds to gold and silver surfaces creating a self-assembled monolayer (SAMs), which modifies surfaces for subsequent coupling of proteins, PEGs and other molecules. The formed nanoparticles show excellent stability and can be stored for years.

The bond between gold or silver surface atoms and monothiols is sensitive to reducing agents such as DTT (Cleland's Reagent), while the disulfide lipoic acid moiety (also known as thioctic acid) binds far stronger to metal surfaces and is much more resistant towards removal from the metal surface by DTT, TCEP and similar reagents than monothiols.

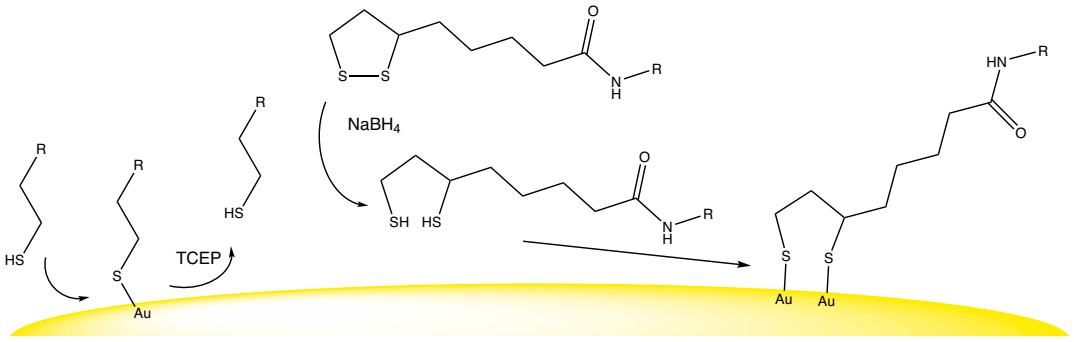

Fig. 38: Thiols react instantly with gold and silver surfaces forming a strong metal-sulfur bond. Lipoic acid requires activation via reduction to the free dithiol and then binds much stronger to the surface as monothiols, which are sensitive to reducing agents.

A variety of protocols exist in the literature for reducing lipoic acid to dihydrolipoic acid (DHLA), which binds instantly to the surface. Typically, tris(2-carboxyethyl)phosphine (TCEP) or sodium borohydride ($NaBH_4$) are being used as reducing agents. In general, TCEP reduction is carried out in water or aqueous buffer (excluding phosphate buffer, in which TCEP is unstable), in three times or greater molar excess to the lipoic acid derivative, using an incubation temperature of 25° C to 50° C, for about 1-2 hours. Each reduction procedure must be optimized for the particular lipoic acid derivative being reduced to the corresponding DHLA derivative.

Lipoamido-PEG-acids and lipoamido-PEG-alcohols can be used as intermediates for further derivatization after attachment to the surface. The density of functional groups on the surface can be tuned by co-coating the bifunctional mercapto- or lipoic-PEG with methoxy-PEG-lipoamides.

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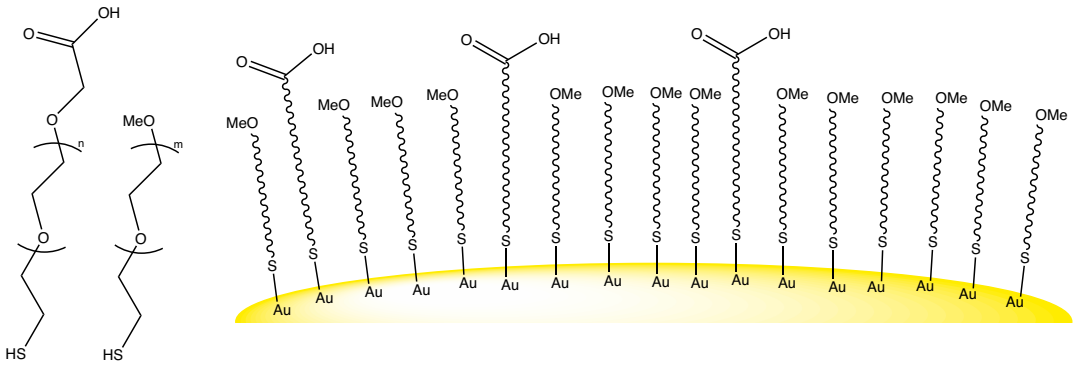

Fig. 39: The density of functional groups can be tuned by co-coating of a PEG-thiol bearing a reactive group such as carboxylic acid with a non-reactive methoxy terminated PEG-thiol.

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- → *Oriented immobilization of antibodies with GST-fused multiple Fc-specific B-domains on a gold surface; T. H. Ha, S. O. Jung, J. M. Lee, K. Y. Lee, Y. Lee, J. S. Park, B. H. Chung;* ***Anal Chem*** *2007;* ***79****: 546-56. https://doi.org/10.1021/ac061639+*
- → *Design of biotin-functionalized luminescent quantum dots; K. Susumu, H. T. Uyeda, I. L. Medintz, H. Mattoussi;* ***J Biomed Biotechnol*** *2007;* ***2007****: 90651. https://doi.org/10.1155/2007/90651*
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6.5. Metal oxides

Nanotechnology and nanobiotechnology using quantum dots, magnetic particles, or metal oxides are broadly diverse, rapidly expanding areas of study in medical diagnostics and therapeutics, sensoric and chemistry. Many metal oxides are not water soluble without further modification.

Compounds containing functional groups which enable noncovalent binding or chelates to oxide surfaces and which carry residues like poly(ethylene glycol) (PEG) or other polymers equip metal oxide nanoparticles with colloidal stability and stealthiness.

Such functional groups are phosphonic acid compounds R–H_2PO_3 which display a strong affinity to metal ionic centers and are characterized by their multidentate binding ability. With appropriate residues the self-assembled monolayer (SAM) and multilayers can be designed. Examples have been published of cerium (CeO_2), iron (γ-Fe_2O_3), aluminum (Al_2O_3), and titanium (TiO_2) oxides of different sizes and morphologies.

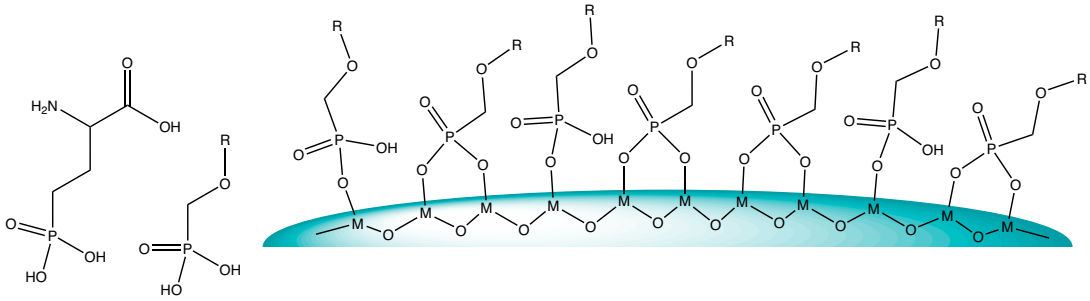

Fig. 40: Metal oxide surfaces form stable bonds with phosphates and phosphonates by multidental, chelating interaction.

References:

→ *Versatile Coating Platform for Metal Oxide Nanoparticles: Applications to Materials and Biological Science; J. F. Berret, A. Graillot; **Langmuir** 2022; **38**: 5323-5338. https://doi.org/10.1021/acs.langmuir.2c00338*

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6.6. Polymeric Surfaces by Plasma Treatment

Plastic polymers, like polyethylene, polystyrene, PTFE, or co-polymers thereof are materials used in many facets of daily life, including tools and devices with biological, human, and pharmacologic applications. A major property of such materials is that they are rather chemically inert to most environmental conditions.

Low pressure plasma treatment offers a new method to decorate such polymers with specific functional groups, such as amines or carboxylic acids, which offer the opportunity to further modify the surface with specific molecules. PEGs, for example, can turn such usually quite hydrophobic surfaces very hydrophilic. Attachments of fluorescent dyes will stain the particles accordingly. Attachment of peptides, proteins, like streptavidin, or antibodies opens the door to numerous biological and pharmacological applications.

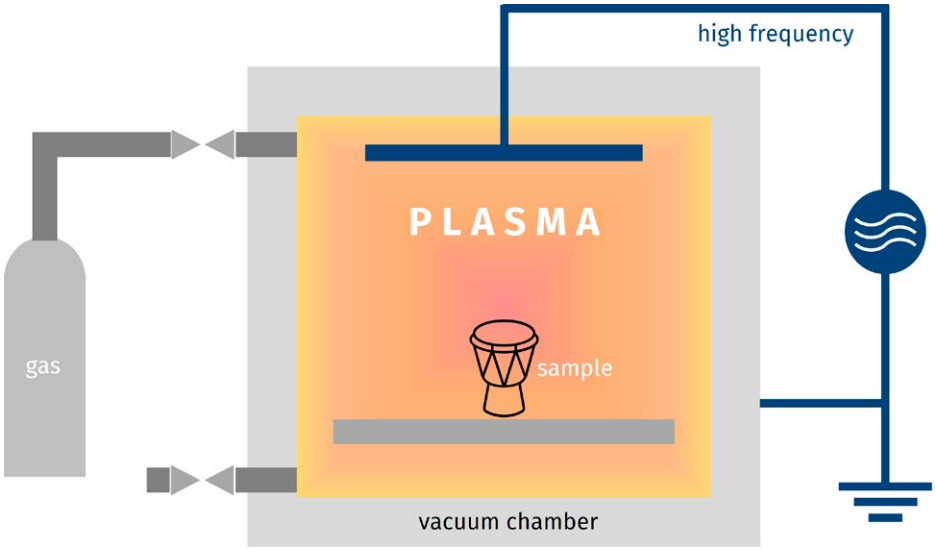

Fig. 41: Plasma chamber for surface coating of samples with functional groups provided by the selected gas.

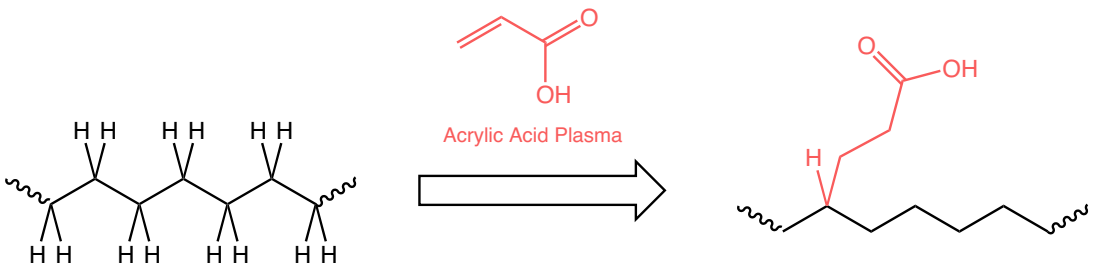

Fig. 42: Introduction of carboxylic acid functions on polyethylene surfaces via acrylic acid plasma treatment.

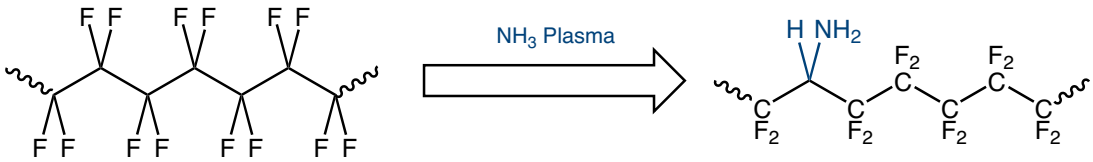

Fig. 43: Introduction of amino functions on PTFE surfaces via ammonia plasma treatment.

One major drawback working on surfaces is analytics, as conventional technologies, like mass spectroscopy, chromatographic purification technologies and other methodologies widely established for small molecules and biologics are not applicable in this case. For surface analytics X-ray photoelectron spectroscopy (XPS) is the method of choice. It is also known as ESCA (Electron Spectroscopy for Chemical Analysis) and is an established method for the analysis of chemical compositions of surfaces. It enables a highly sensitive, quantitative detection of all elements except hydrogen and helium, as well as for the identification of binding and oxidation states on solid surfaces. The method is very sensitive to surfaces, so that even very thin layers can be studied (2 nm to 10 nm depth of information).

The basic principle of XPS is based on the irradiation of a sample surface in vacuum with soft X-rays and analyzing the energy of the emitted photoelectrons. This energy is different from element to element and also depends on the oxidative level of the element. Therefore, analyzing a carbon signal a quantitative determination e.g. between carbon-hydrogen, carbon-nitrogen and carbonyl carbon can be measured. The XPS spectrum results from plotting the number of detected electrons per energy interval against their kinetic energy.

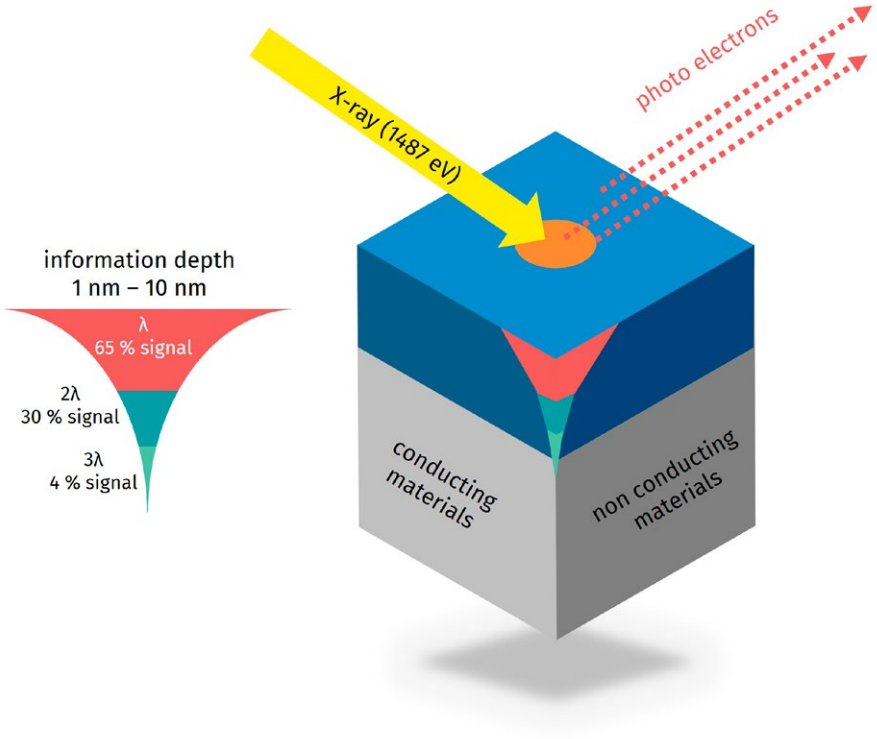

Fig. 44: Principle of X-ray photoelectron spectroscopy and information retrieved by this technique.

Information gained with X-ray photoelectron spectroscopy:

- Detection limit: 0.01 - 1 at%, sub-monolayer
- Detectable elements: Li – U
- Chemical bonding information
- Quantitative information
- Information depth: 1 nm to 10 nm
- Lateral resolution: ca. 30 µm
- Depth profiling
- Imaging/mapping

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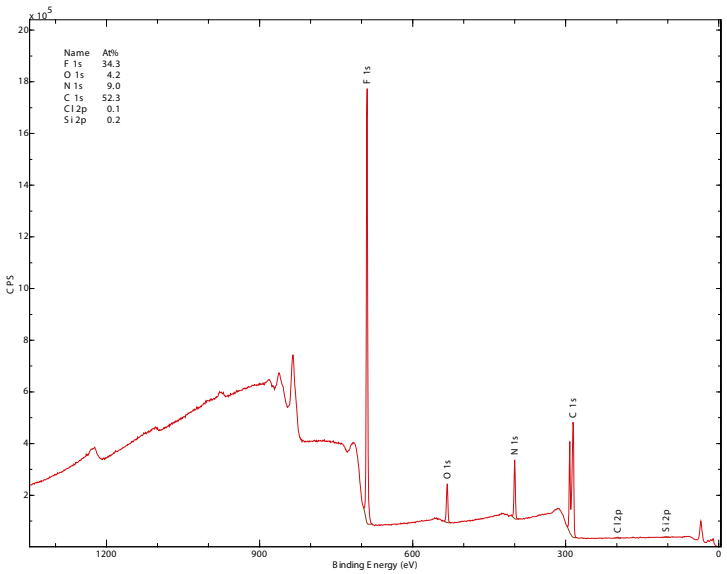

Fig. 45: XPS representing signals of the elements sodium, fluorine, oxygen, nitrogen, calcium, carbon, chlorine, and silicon. The peak area allows quantitative determination of each element.

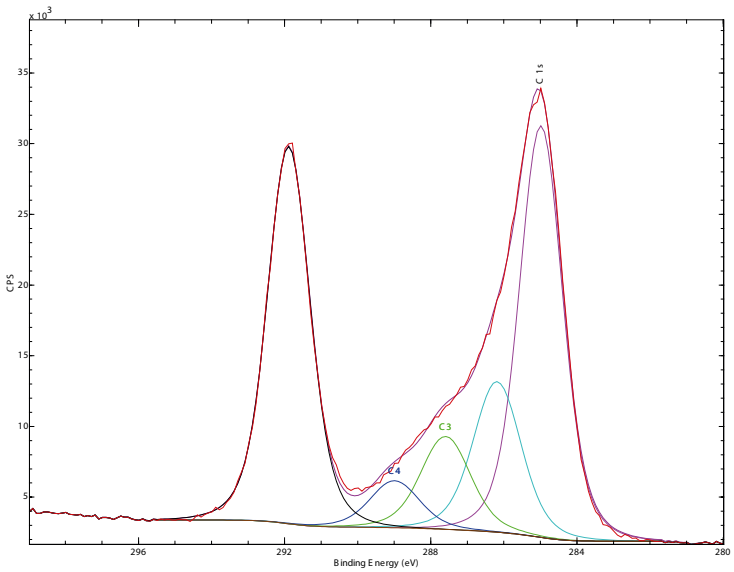

Fig. 46: Expanded XPS spectrum of a carbon signal showing the ratio between C1 (aliphatic carbon), C2 (carbon with single bond to a hetero atom N or O), C3 (carbonyl, amide carbon), C4 (carboxyl, carbonate carbon), and C5 (fluorinated carbon).

Services available from us:

- *Beads of polyethylene, polystyrene, teflon or co-polymers thereof should be surface decorated with permanent or cleavable linkers and loaded with small or biomolecules.*
- *Turning polymer-based surface of devices hydrophilic, biocompatible or non-immunogenic.*
- *Equipping the surface of membranes, devices or other parts made of a certain material with an alternative or orthogonal property.*

Consult with us, we will be happy to carry your application through to market.

References:

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Please find a variety of trimethylsilyl-PEG derivatives in our PEGylation Brochure.

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6.7. Silicates

Glass, quartz and silicates presenting silanol groups at their surface, which can further react with different silane reagents, such as chlorosilanes or alkoxysilanes. It can help to etch the surface prior to coating with acids to remove an outer non-reactive layer and expose silanol groups making them available to form silicon-oxygen-silicon structures and attaching a coating molecule on the surface.

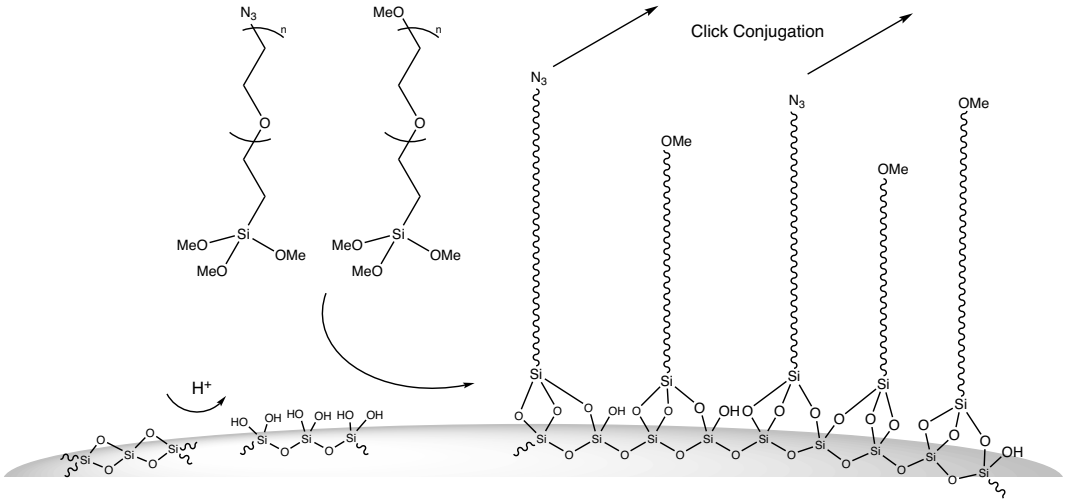

Fig. 47: Silicate-type surfaces eventually require activation by acidic etching prior to reaction with silanizing reagents. Then trimethylsilyl-PEG-azides can conjugate to the surface. The terminal azido functions can then further coupled to Click reactive compounds. The density of functional groups can be diluted and fine-tuned by co-coating with non-reactive methoxy terminated trimethylsilyl-PEG compounds.

References:

→ *Low cost and scalable method for modifying surfaces of hollow particles from hydrophilic to hydrophobic; J. Sharma, G. Polizos, D. Hun, K. Nawaz, R. Sahore;* ***RSC Adv*** *2020;* ***10****: 31065-31069. https://doi.org/10.1039/d0ra06114j*

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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.

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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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