EDITION 2019

Iris BIOTECH GMBH

CUSTOM SYNTHESIS

Fast & efficient from mg to multi-kg
Route Scouting – Process Development – Production

EMPOWERING PEPTIDE INNOVATION

Headquarters:

Iris Biotech GmbH
Adalbert-Zoellner-Str. 1
95615 Marktredwitz, Germany
Phone: +49 9231 97121 - 0
Fax: +49 9231 97121 - 99
Email: info@iris-biotech.de
Internet: www.iris-biotech.de

Office Belgium:

Phone: +49 9231 97121 - 28
Fax: +49 9231 97121 - 99

Distribution Partners:

India:

Sumit Biosciences Pvt Ltd.
D Wing, Krishna Complex
Subhash Road - A, Vile Parle (East)
Mumbai - 400 057, India
Phone: +91 22 6693 8885 / 6
Fax: +91 22 6699 0665
Skype: sumit.bio
Email: sumit_exports@yahoo.com
Internet: www.sumitbiomedical.com
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Japan:

BizCom Japan, Inc.
7F K2 buiding 5-28-1, Higashigotanda, Shinagawa-ku,
Tokyo 141-0022, Japan
Phone: +81 3 6277 3233
Fax: +81 3 6277 3265
Mobile: +81 70 5546 6277
Email: irisbiotech@bizcomjapan.co.jp

USA & Canada:

Peptide Solution LLC
8110 S. Houghton Road, Suite 158 PMB 152
Tucson, AZ 85747, USA
Phone: +1 502 314 1515
Fax: +1 520 422 3333
Email: sales@easypeptide.com
Internet: www.easypeptide.com

Content

1. Introduction, Location & Capabilities

Located in the Business and Industry Park Willstätt (www.biw-gmbh.net), which is a 12 ha chemical production site operating for more than 40 years, we share the infrastructure with over 25 companies and profit from a wide range of professional services.

Being close to the French-German border we have easy access to the major science, business and travel centers of Basel, Strasbourg and Frankfurt.

Efficient energy supply and management, unique services regarding facilities, security and latest telecommunication technology provide us with a very flexible and cost-efficient set-up with outstanding possibilities for expansion and a wide range of capabilities for a chemical company within a vibrating logistics network with an excellent transport connection by road, air and water.

We have all capabilities of a modern chemical laboratory with state-of-the-art reactors and analytical equipment for process control and characterizing intermediates and end products.

There are types of reactions we carry out routinely such as chiral synthesis, enzymatic and other types of optical resolution, and hydrogenation under high pressure. We have specific know-how to work with amphiphilic and hydrophilic compounds, which are difficult to synthesize and purify.

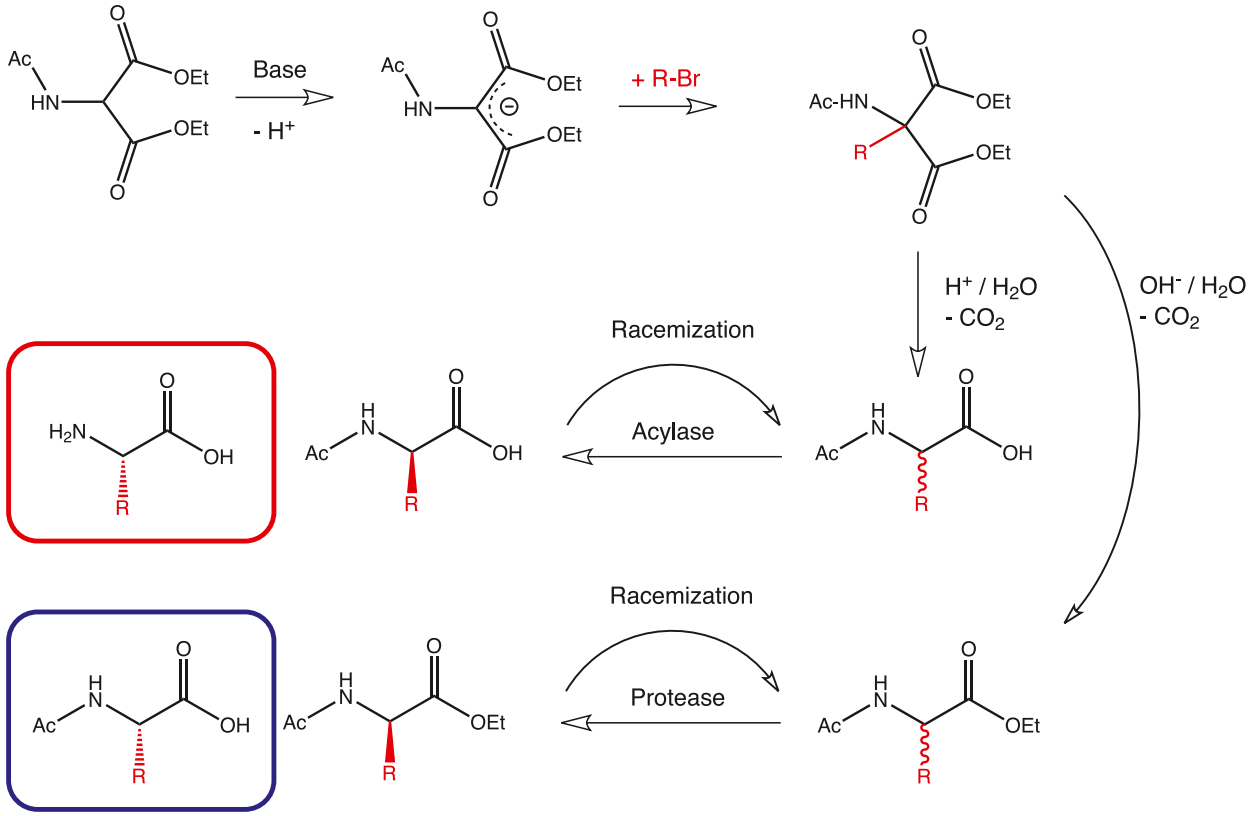
Highly qualified and experienced personnel with profound knowledge in research, process development, production and analytics strive their hardest to bring your order to fast and efficient completion.

The majority of our work goes into projects at gram level followed by scaling up to kg quantities.

2. Single Molecule Platform

a) Unusual α-Amino Acids *via* Acetamidomalonate

The probably most widely used and first approach to unnatural amino acids proceeds *via* alkylation of diethyl acetamidomalonate. This process is daily routine in our laboratories and provides easy access to a large number of analogues in gram scale. Racemic mixtures of both enantiomers are being produced, which need to be separated by enzymatic methods or other separation technologies.



This route is preferred, if both stereoisomers are required in comparable quantities.

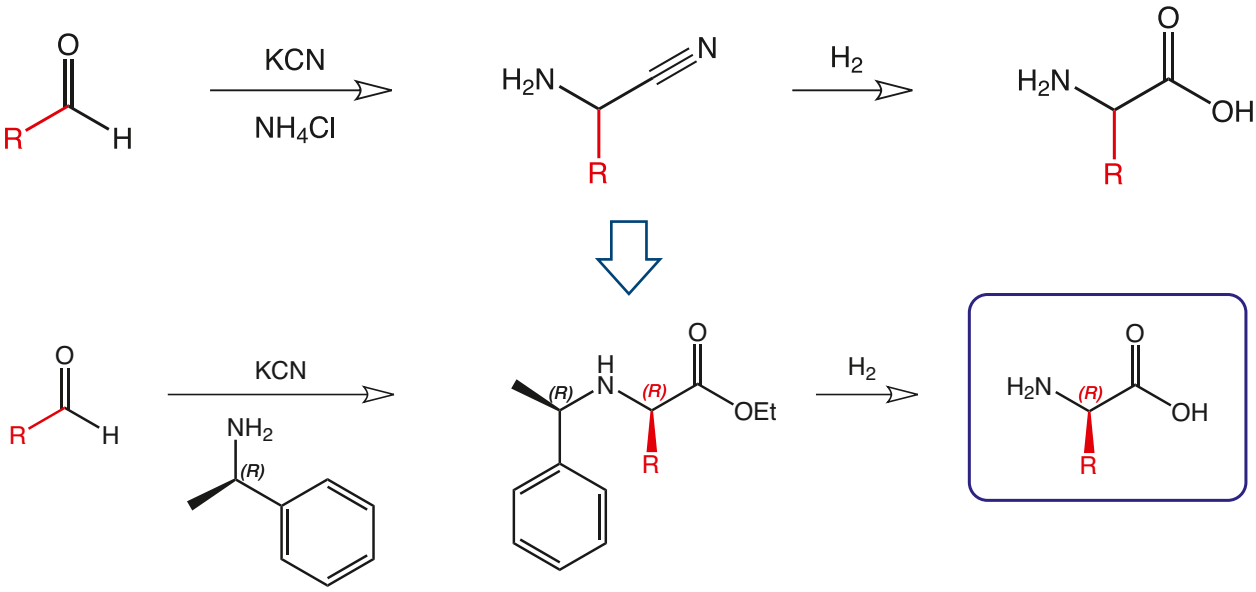
The limitations of this process are:

- the alkylating reagent is not available or very costly.
- only one of the two enantiomers is required. The other enantiomer is “chiral” waste, which needs to be converted into the target compound via racemization.
- available enzymes (acylases and esterases) are not able to separate both isomers.

Typical compounds which are accessible through this process are phenylalanine derivatives and amino acids with certain aliphatic residues carrying additional functional groups.

b) Unusual α-Amino Acids *via* Asymmetric Strecker Synthesis

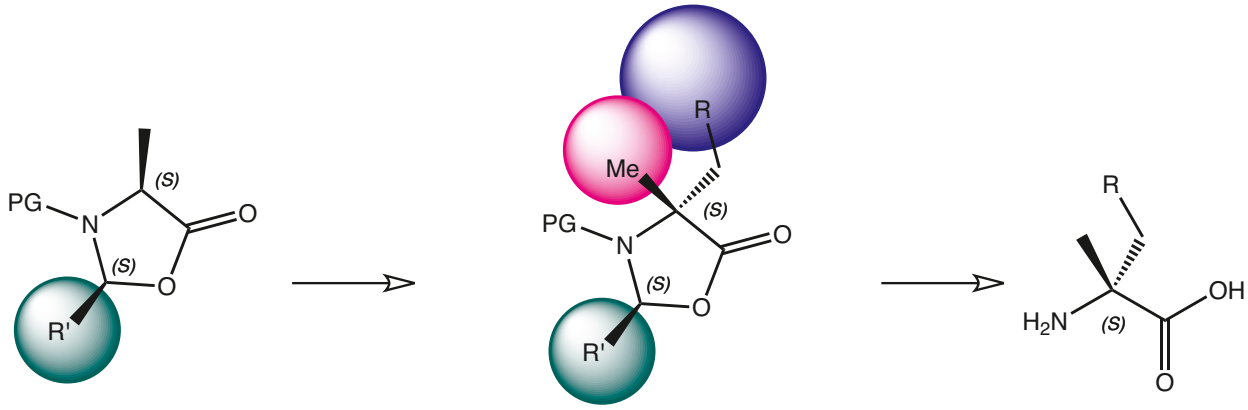
The Strecker synthesis converts aldehydes into amino acids bearing one carbon more than the aldehyde educt. In case a chiral amine is used in the place of ammonium chloride, chiral induction will yield the preferred enantiomer as the mayor project.



This route is preferable if the corresponding aldehyde is accessible and if the α-carbon can be obtained in the desired configuration. In such cases this route can be easily up-scaled.

c) C_α-Methyl-Amino Acids *via* Oxazolidin-5-one

C_α-Methyl and C_α-alkyl-amino acids can be produced by a number of platforms, where the (2S,4S)-4- methyl-oxazolidin-5-one scaffold is one of the most popular one. By sophisticated selection of size, nature and optical configuration of the auxiliary side group R, high chemical and optical purity of the resulting C_α-alkyl-amino acids can be achieved. We optimized published procedures and have own proprietary routes, which enable us to supply all kinds of protected α-methyl amino acids in high yield and purity.

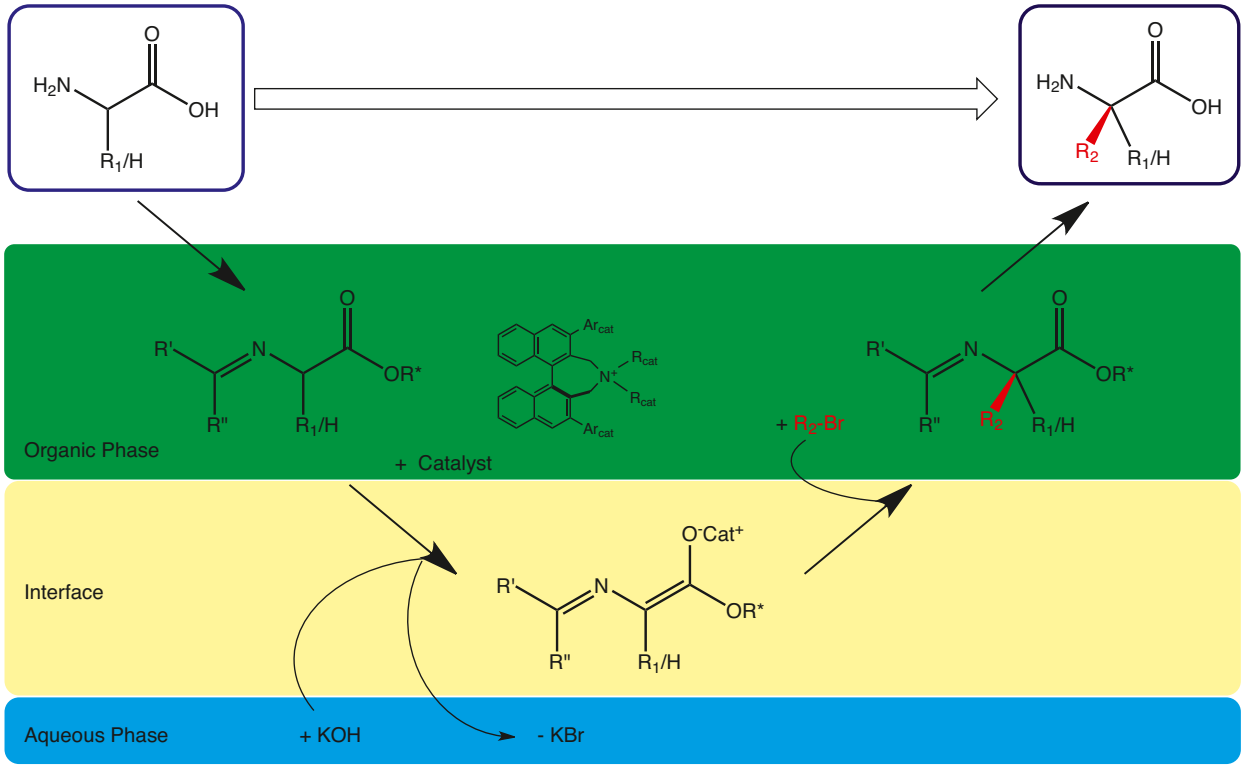


R or S

Such building blocks are being used to build up resistance towards proteolytic digestion of corresponding peptides or to implement certain amide bond conformation.

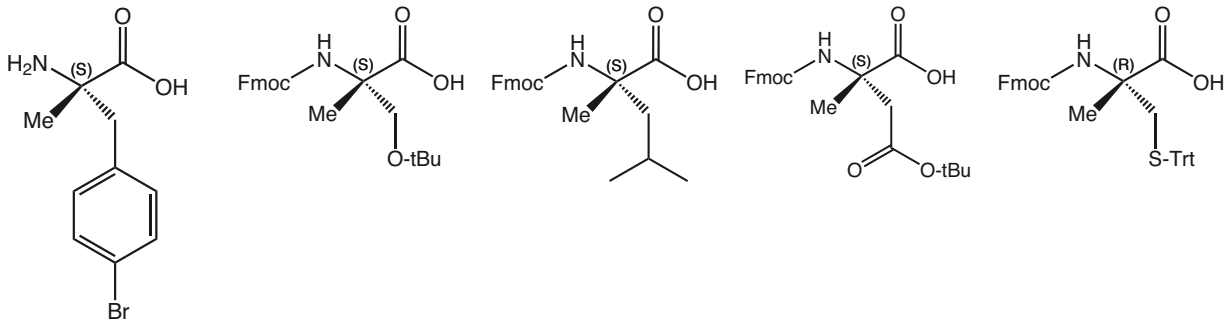
d) C_α-Substituted-Amino Acids *via* Asymmetric Phase Transfer Reaction

Phase-transfer alkylations e.g. with the chiral Maruoka catalyst, provide access to unique mono- and disubstituted amino acids. Typically, such building blocks increase the chemical and metabolic stability of peptides and restrict the conformational freedom of the neighboring amino acid side chains.



Available α-methyl amino acids produced by different technologies:

(S) α-Me-Phe(4-Br)	(S) Fmoc-α-Me-Ser(tBu)	(S) Fmoc-α-Me-Leu	(S) Fmoc-α-Me-Asp(tBu)	(S) Fmoc-α-Me-Cys(Trt)
HAA5350	**FAA4900**	**FAA3045**	**FAA3085**	**FAA4840**



Though rather costly in gram scale synthesis, this process opens up new avenues for designing and economic production of appropriate building blocks in multi-kg and bulk scale. Conventional amino acids can be produced *via* stereoselective alkylation of glycine or alanine without any use of metal. Therefore this method represents a safe and environmentally friendly technology.

References:

- Design and Synthesis of Chiral α,α-Disubstituted Amino Acids and Conformational Study of Their Oligopeptides; M. Tanaka; *Chemical and Pharmaceutical Bulletin* 2007; **55**: 349-358. doi:10.1248/cpb.55.349
- Design of N-Spiro C2-Symmetric Chiral Quaternary Ammonium Bromides as Novel Chiral Phase-Transfer Catalysts: Synthesis and Application to Practical Asymmetric Synthesis of α-Amino Acids; T. Ooi, M. Kameda and K. Maruoka; *Journal of the American Chemical Society* 2003; **125**: 5139-5151. doi:10.1021/ja021244h
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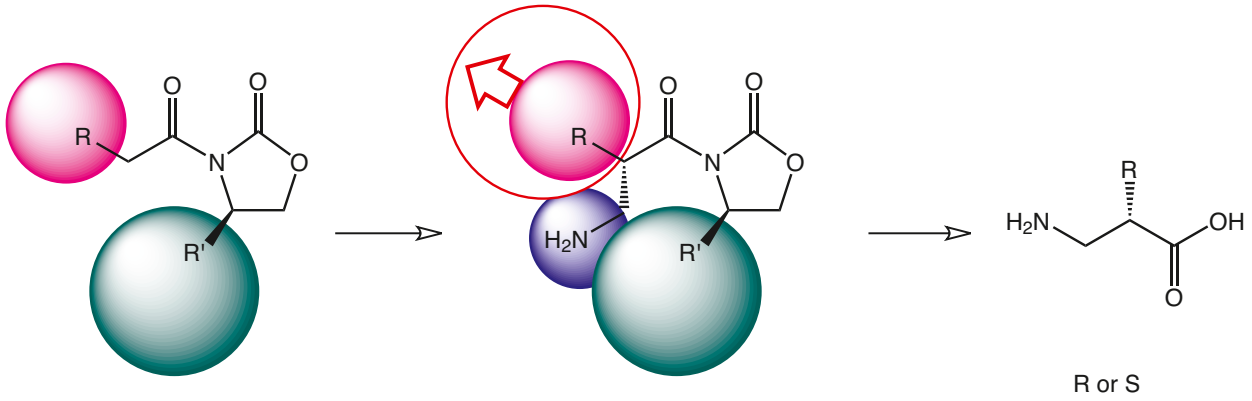
- Concise, Catalytic Asymmetric Synthesis of Tetrahydroisoquinoline- and Dihydroisoquinoline-3-carboxylic Acid Derivatives; T. Ooi, M. Takeuchi and K. Maruoka; *Synthesis* 2001; **2001**: 1716-1718. doi:10.1055/s-2001-16747
- Practical Aspects of Recent Asymmetric Phase-Transfer Catalysis; K. Maruoka; *Organic Process Research & Development* 2008; **12**: 679-697. doi:10.1021/op7002979

e) β²-Amino Acids *via* Oxazolidin-2-one

β²-Amino acids have sparked considerable special interest, not only as diverse structural elements, but also due to the fact that beta-peptide analogues of peptides consisting of natural amino acids form similar 3D structures with enhanced enzymatic and chemical stability. The development of drug discovery platforms based on beta-peptides is likely to offer novel types of drugs addressing to date inaccessible disease targets. Via selected residues R' on position 4 of an oxazolidion-2-one scaffold, a large number of β²-amino acids is accessible for lab scale and bulk synthesis.

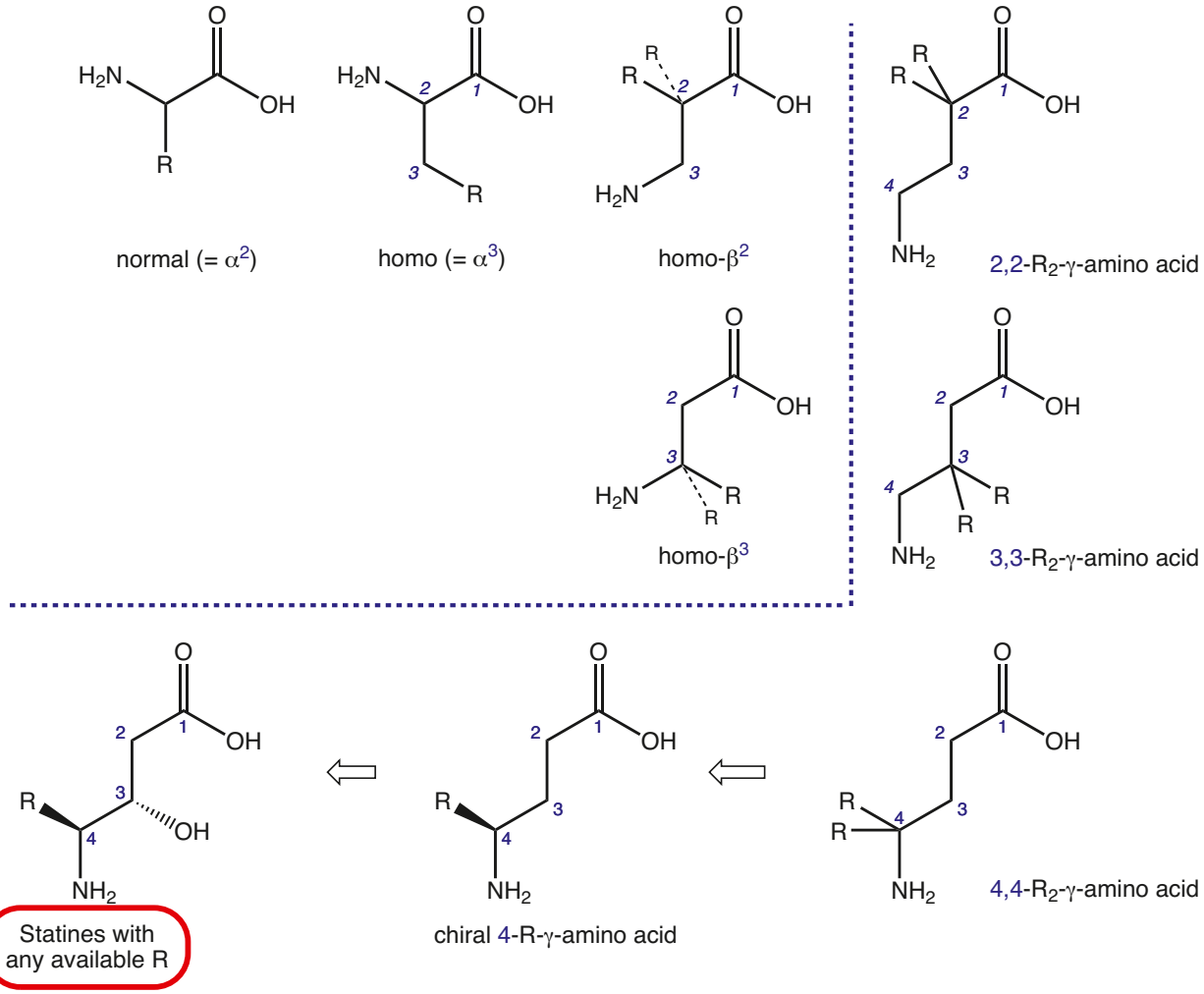


References:

- β-Peptide Foldamers: Robust Helix Formation in a New Family of β-Amino Acid Oligomers; D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell and S. H. Gellman; Journal of the American Chemical Society 1996; 118: 13071-13072. doi:10.1021/ja963290l
- Antibiotics: Non-haemolytic β-amino-acid oligomers; E. A. Porter, X. Wang, H.-S. Lee, B. Weisblum and S. H. Gellman; Nature 2000; 404: 565-565.
- Chimeric (α/β + α)-Peptide Ligands for the BH3-Recognition Cleft of Bcl-xL: Critical Role of the Molecular Scaffold in Protein Surface Recognition; J. D. Sadowsky, M. A. Schmitt, H.-S. Lee, N. Umezawa, S. Wang, Y. Tomita and S. H. Gellman; Journal of the American Chemical Society 2005; 127: 11966-11968. doi:10.1021/ja053678t
- Inhibition of γ-Secretase Activity by Helical β-Peptide Foldamers; Y. Imamura, N. Watanabe, N. Umezawa, T. Iwatsubo, N. Kato, T. Tomita and T. Higuchi; Journal of the American Chemical Society 2009; 131: 7353-7359. doi:10.1021/ja9001458
- De Novo Design of a Monomeric Helical β-Peptide Stabilized by Electrostatic Interactions; R. P. Cheng and W. F. DeGrado; Journal of the American Chemical Society 2001; 123: 5162-5163. doi:10.1021/ja010438e
- Design, machine synthesis, and NMR-solution structure of a β-heptapeptide forming a salt-bridge stabilised 314-helix in methanol and in water; P. I. Arvidsson, M. Rueping and D. Seebach; Chemical Communications 2001: 649-650. doi:10.1039/b101085i

f) Substituted Homo-β- and γ-Amino Acids & Statines

Homologization of natural amino acids results e.g. in homo-β^2, homo-β^3 and γ-amino acids. Several platforms are available to display the whole assortment of homo-amino acids, as well as the higher homologues and double substituted derivatives $\beta^{2,2}$-, $\beta^{3,3}$-, and corresponding γ-amino acids. Via specific templates with tailored residues each conformation can precisely be addressed.



The variation and possibilities become even more diverse with GABA (γ-amino butyric acid) as scaffold. Our platforms allows a large variety of substituted γ-amino butyric acid and Statine analogues.

Our Tool Box	Properties
✔ homo-β^2 amino acids including 2,2-disubstituted analogues	✔ high structural diversity with novel structures
✔ homo-β^3 amino acids including 3,3-disubstituted analogues	✔ superior biological activity
✔ double substituted γ-amino acids on the positions 2,2 or 3,3 or 4,4	✔ tune cell & membrane penetration
✔ chiral 4-substituted γ-amino acids	✔ better chemical stability
✔ Statine analogues with side chains from any accessible residue	✔ enhanced enzymatic stability
	✔ fine tuning of solubility and lipophilicity
	✔ adjusting isoelectric point

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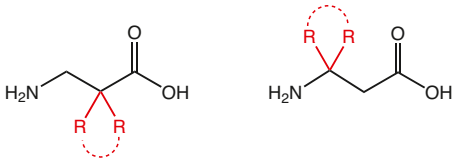
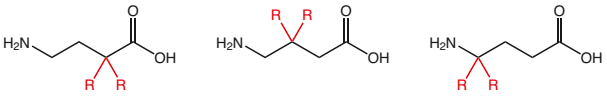
- SDZ PRI 053, an orally bioavailable human immunodeficiency virus type 1 proteinase inhibitor containing the 2- aminobenzylstatine moiety. Billich A, Fricker G, Müller I, Donatsch P, Ettmayer P, Gstach H, Lehr P, Peichl P, Scholz D, Rosenwirth B.; *Antimicrob Agents Chemother.* 1995; **39(7)**: 1406-13.
- Design and synthesis of hydroxyethylene-based peptidomimetic inhibitors of human beta-secretase. Hom RK, Gailunas AF, Mamo S, Fang LY, Tung JS, Walker DE, Davis D, Thorsett ED, Jewett NE, Moon JB, John V.; *J Med Chem.* 2004; **47(1)**: 158-64.
- Molecular basis for selectivity of high affinity peptide antagonists for the gastrin-releasing peptide receptor. Tokita K, Katsuno T, Hocart SJ, Coy DH, Llinares M, Martinez J, Jensen RT. *J Biol Chem.* 2001; **276(39)**: 36652-63.
- Mechanism of Inhibition of beta-site amyloid precursor protein-cleaving enzyme (BACE) by a statine-based peptide. Marcinkeviciene J, Luo Y, Graciani NR, Combs AP, Copeland RA. *J Biol Chem.* 2001; **276(26)**: 23790.

Examples substituted homo-β- and γ-amino acids & statines:

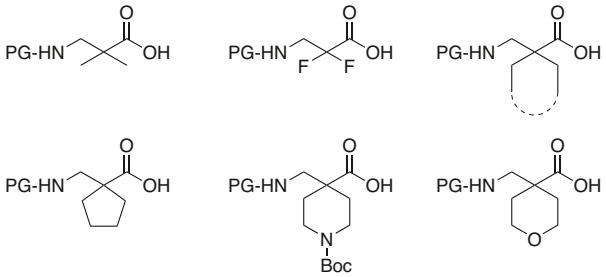
β-Disubstituted Amino Acids



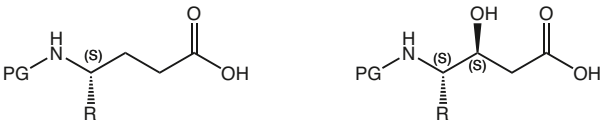
γ-Amino Acids



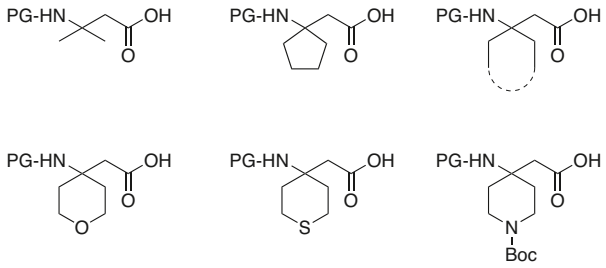
$\beta^{2,2}$ Amino Acids



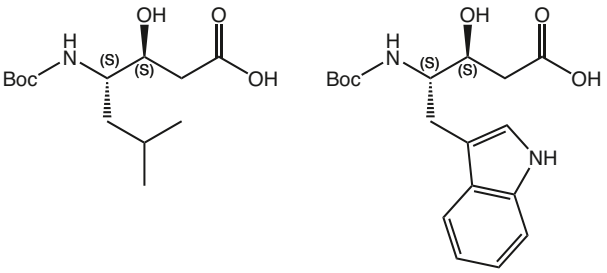
γ-Amino Acids & Statine Analogues



$\beta^{3,3}$ Amino Acids

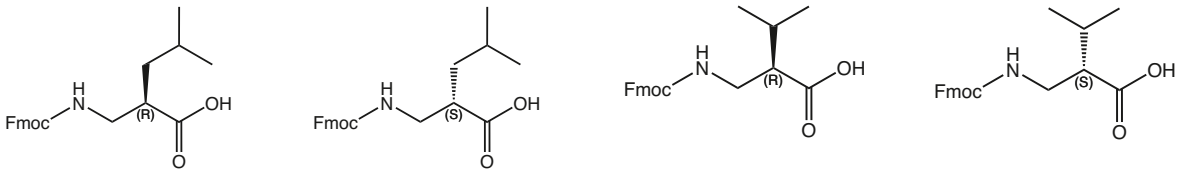


Statine Analogues



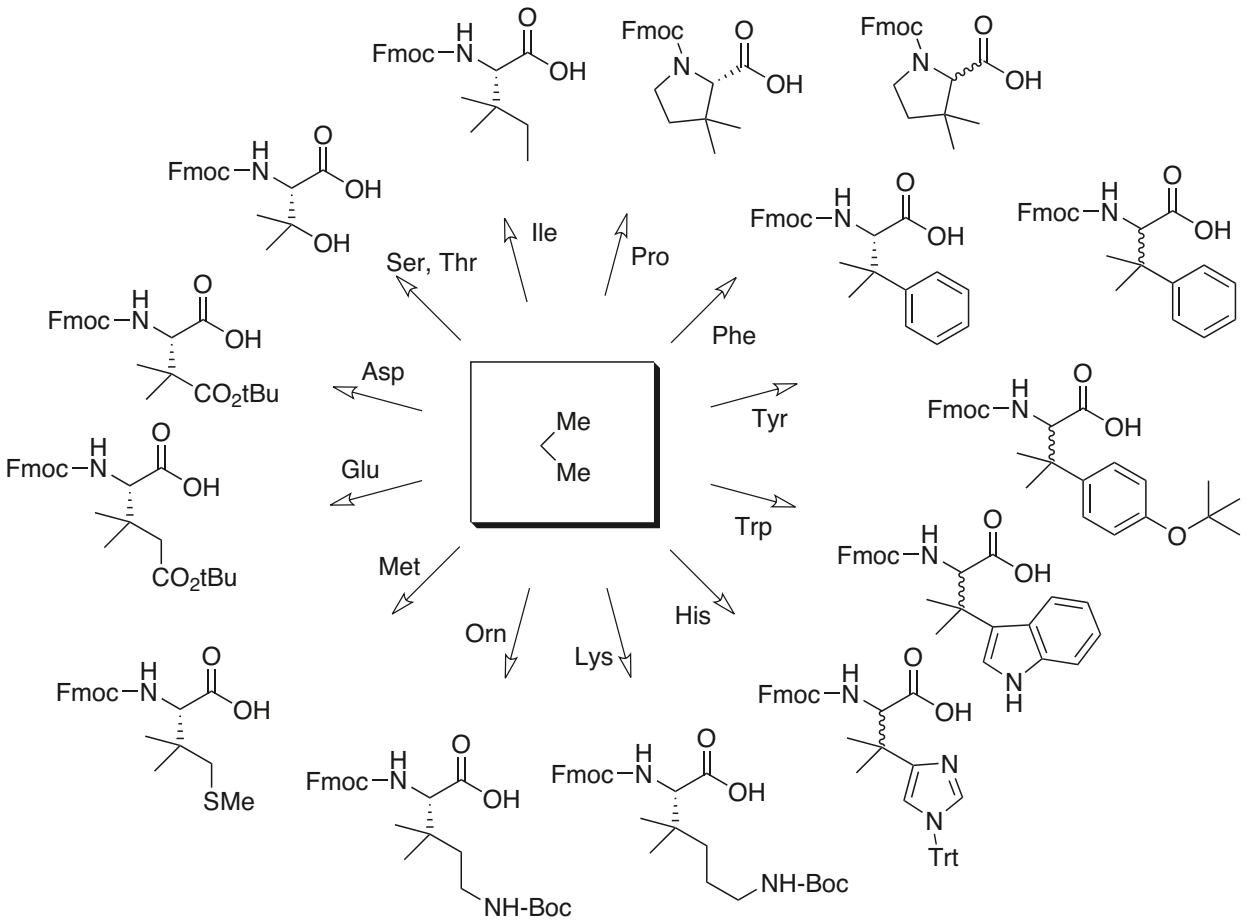
Available as catalogue items:

Fmoc-β²-homo-Leu (R)	Fmoc-β²-homo-Leu (S)	Fmoc-β²-homo-Val (R)	Fmoc-β²-homo-Val (S)
FAA5300	**FAA5310**	**FAA5320**	**FAA5330**



g) β,β-Dimethylated Amino Acids

Structural diversity and stabilization towards chemical and enzymatic degradation are the guiding theme of amino acid derivatization. β,β-Dimethylation of amino acids is smart approach where structure and conformation of the α-carbon is being maintained, while modification occurs at the neighbouring carbon.



With *tert*-leucine and penicillamine there are already β,β-dimethylated amino acids known in the peptide community, however, access to other analogues is very unique and available only through our specific synthesis platform.

References:

- Synthesis and Biological Activity of Analogues of the Antimicrotubule Agent N,beta,beta-Trimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1- isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (HTI-286); A. Zask, G. Birnberg, K. Cheung, J. Kaplan, C. Niu, E. Norton, R. Suayan, A. Yamashita, D. Cole, Z. Tang, G. Krishnamurthy, R. Williamson, G. Khafizova, S. Musto, R. Hernandez, T. Annable, X. Yang, C. Discafani, C. Beyer, L.M. Greenberger, F. Loganzo, S. Ayral-Kaloustian; *J. Med. Chem.* 2004; **47**: 4774-4786.
- Serine as Chiral Educt for the Practical Synthesis of Enantiopure N-Protected beta-Hydroxyvaline; J.E. Dettwiler, W.D. Lubell; *J. Org. Chem.* 2003; **68**: 177-179.
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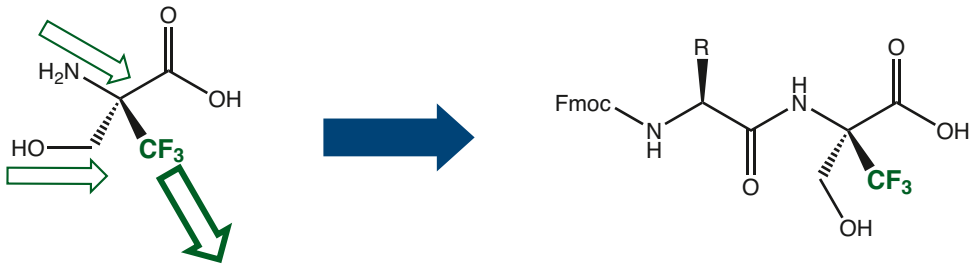
- A General Method for Making Peptide Therapeutics Resistant to Serine Protease Degradation: Application to Dipeptidyl Peptidase IV Substrates; K.R. Heard, W. Wu, Y. Li, P. Zhao, I. Woznica, J.H. Lai, M. Beinborn, D.G. Sanford, M.T. Dimare, A.K. Chiluwal, D.E. Peters, D. Whicher, J.L. Sudmeier, W.W. Bachovchin; *J. Med. Chem.* 2013; **56**: 8339-8351; dx.doi.org/10.1021/jm400423p.

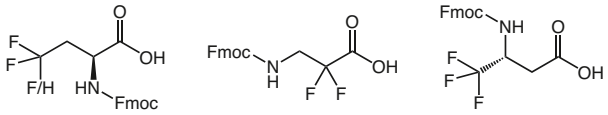
h) Fluorinated Amino Acids

Fluorinated amino acids have gained widespread attention as they may endow peptides and proteins with advantageous biophysical, chemical and biological properties. The unique property of fluorine, i.e. bearing the highest electronegativity of all elements, oozes out to neighboring groups resulting in unique properties of polarity, lipophilicity, acidity/basicity and conformation of the specific side chains and alters properties on stability, folding kinetics and activity of peptides and proteins.

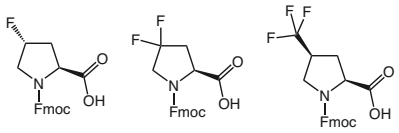


As ultimate consequence α-amino functions in α-trifluoromethyl amino acids or hydroxy functions in corresponding serines do normally not have to be protected during standard SPPS protocols. Due to the high electron withdrawing property of the α-trifluoromethylgroup their nucleophilicity has been drastically be reduced to a level, that acylation will not occur. The drawback is that for forming an amide bond more aggressive acetylating methodologies have to be applied. It is most convenient in such cases to use a dipeptide building block consisting of a normal Fmoc-protected amino acids coupled to the fluorinated building block.

Examples of γ-amino butyric acids



Examples around the proline scaffold

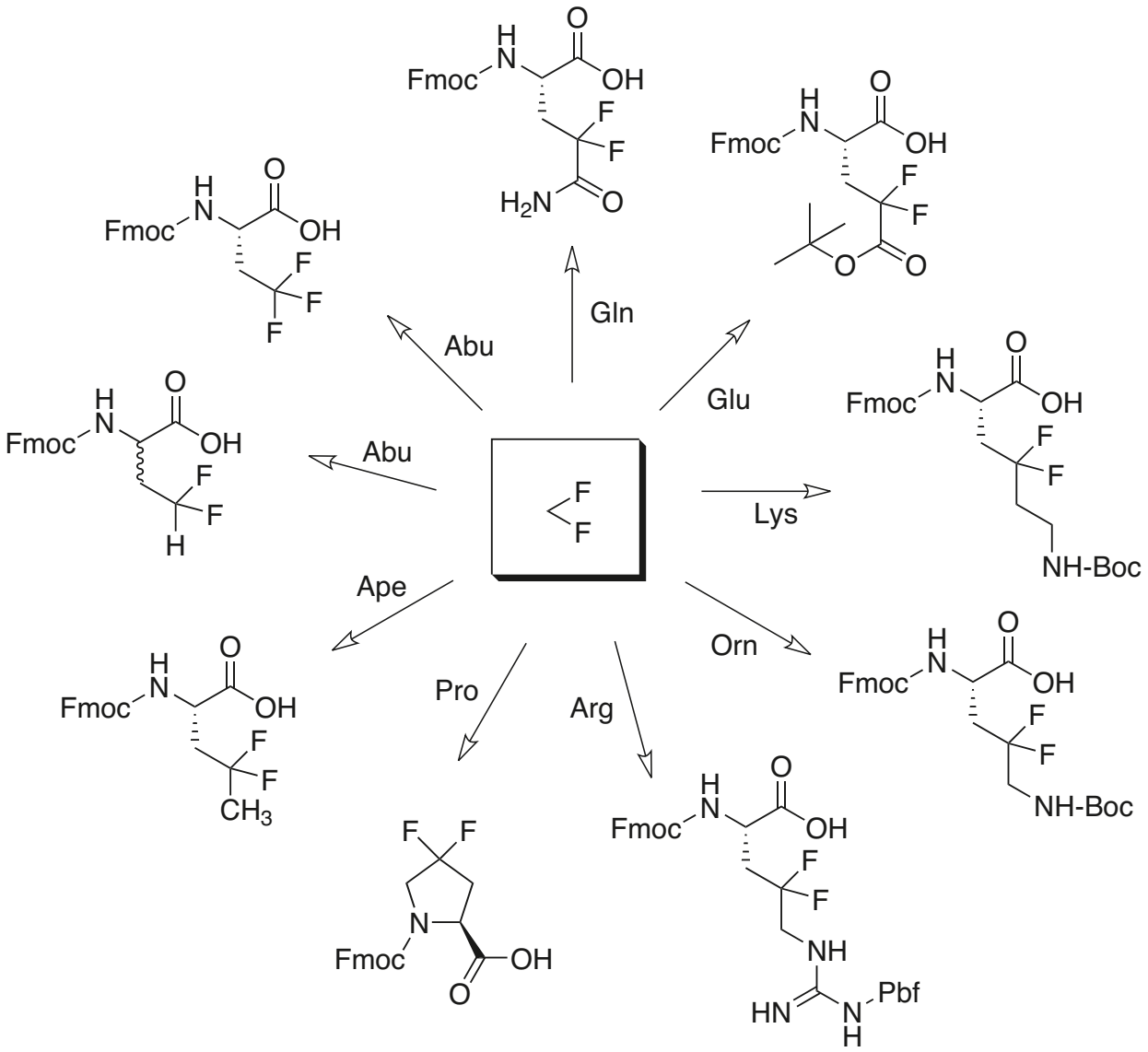


Reference:

- Fluorinated amino acids: compatibility with native protein structures and effects on protein-protein interactions; Salwiczek M, Nyakatura EK, Gerling UI, Ye S, Koksch B.; *Chem. Soc. Rev.* 2012; **41(6)**: 2135-71. doi: 10.1039/c1cs15241f.

γ,γ-Difluoro amino acids

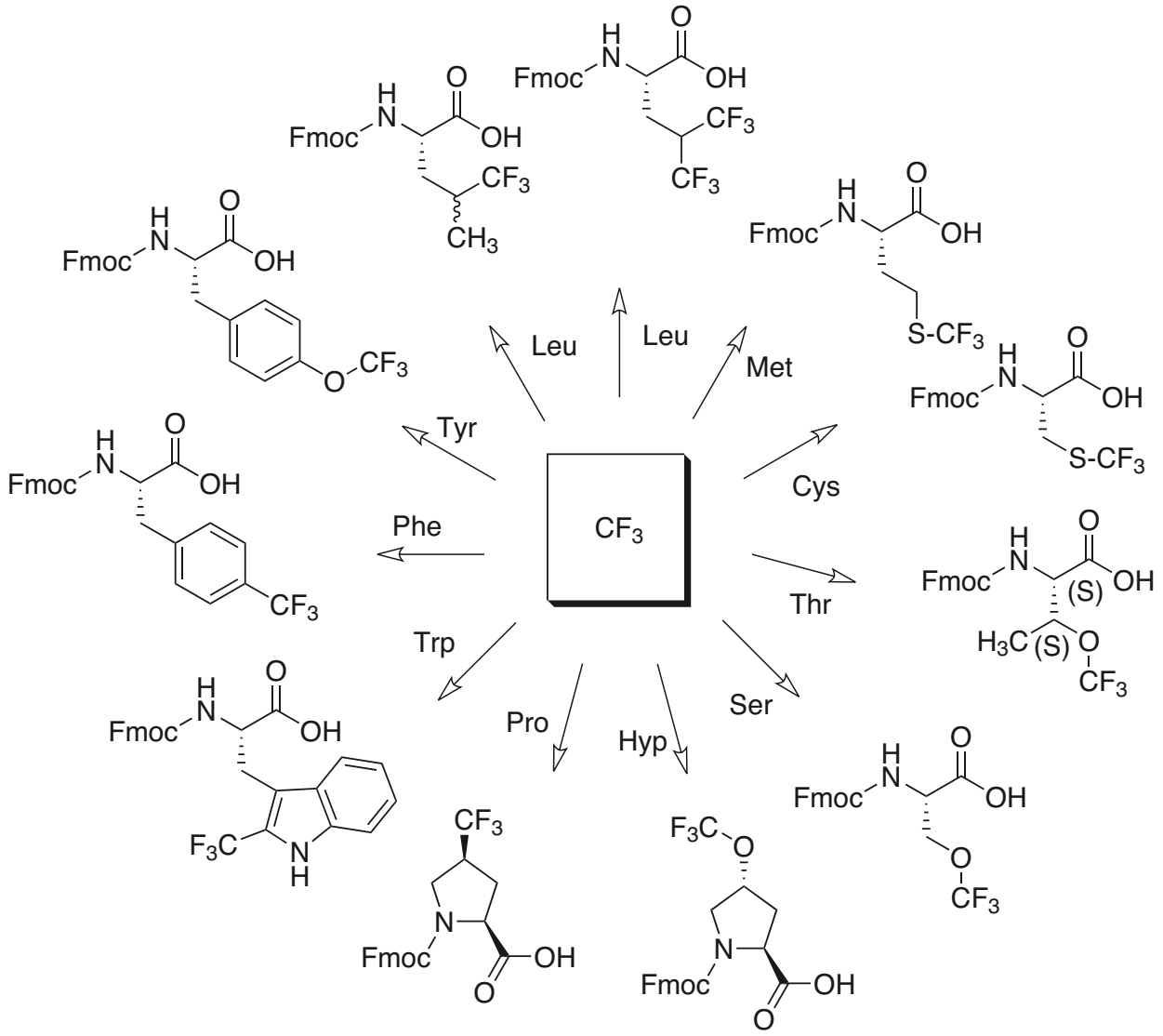
As introduction of Fluorine on the β-position increases the C-H acidity on the α position racemization will happen rather easily. However, if substitution occurs on the β position, even double fluorination results in derivatives, which maintain their optical configuration.



With our platform we are able to provide a large set of γ,γ-difluoro amino acids, which serve to implement structural diversity, polarity, lipophilicity and new conformational and folding moieties into a peptide.

Trifluoromethyl in the side chain of amino acids

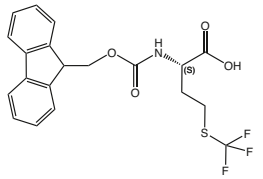
Trifluoromethyl can be attached to aromatic rings of Phe, Trp and Tyr, added to functional groups like thiol, hydroxyl or amine or be formed by replacing hydrogen in methyl groups.



Already available as catalogue item:

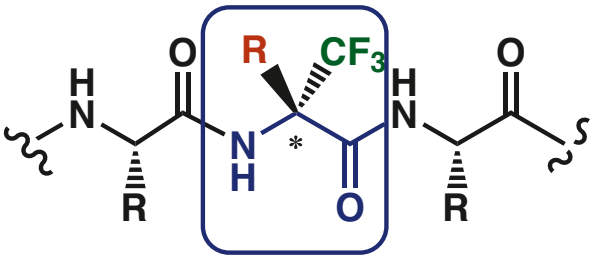
Fmoc-Trifluoromethyl-Methionine

FAA4570

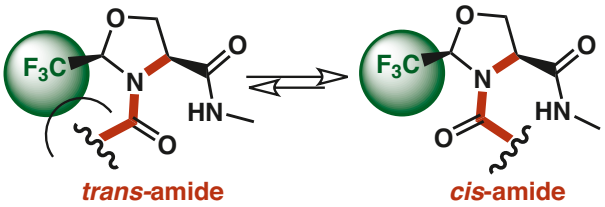


α-Trifluoromethyl amino acids

C_α-Methyl amino acids are characterized that through the increasing sterical requirement at the chiral centre certain conformations are being favoured. This tendency is even stronger with trifluoromethyl groups combined with the strong polarization property of fluorines that can even induce auto-assembly. These amino acids can also be useful as label for ^{19}F-NMR studies.



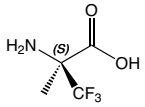
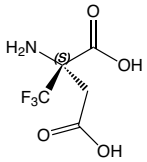
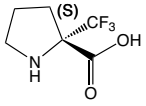
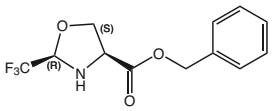
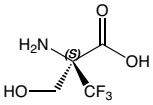
α-substitution induces conformational rigidity combined with higher polarity and lipophilicity



electronic and sterical effects favor cis-amid bond conformation

The incorporation of trifluoromethyl group carrying building blocks into peptides results in increased chemical and thermal stability, increased resistance to degradation by proteases, and enhanced lipophilicity. Appropriate peptides will therefore show a better affinity to lipid membranes and stronger interactions with receptors. Both electronic and steric reasons make a *cis*-amide bond in trifluoromethyl amino acids more favorable, thus the formation of β-turns is induced. In case of synthesis of cyclic peptides, cyclization yields are increased.

Available as catalogue items besides many more

α-Tfm-Ala	α-Tfm-Asp*HCl	α-Tfm-Pro	α-Tfm-PsiPro-OBn	α-Tfm-Ser
HAA1925	**HAA1950**	**HAA1945**	**HAA2765**	**HAA1960**
				

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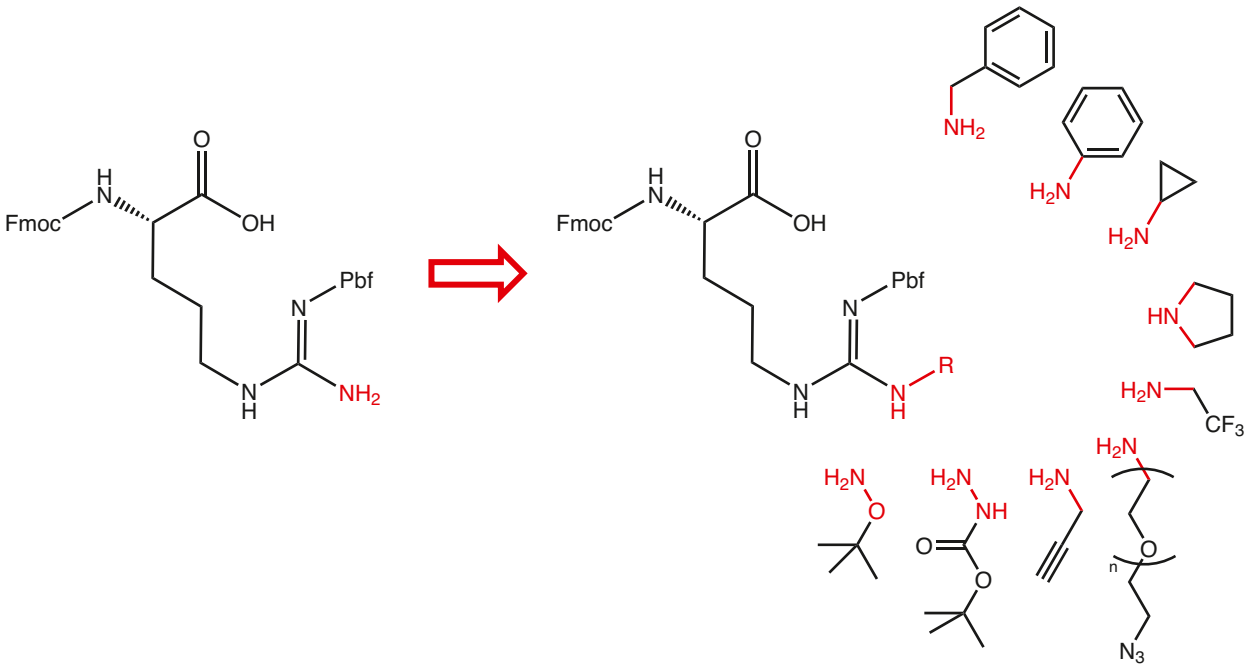
i) Arginine Analogues

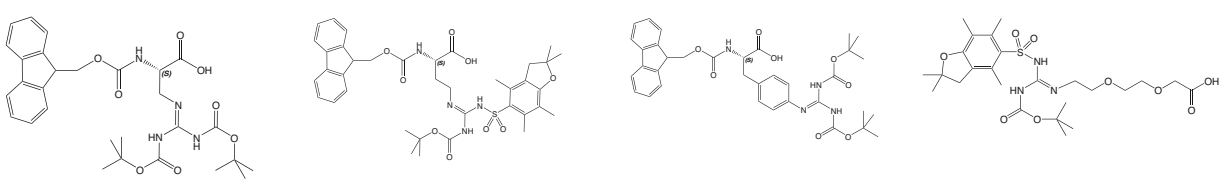
Arginine, a semi-essential amino acid, is included in various important metabolic processes. Normal cell growth is highly dependent on the levels of arginine. The degradation of proteins by trypsin typically happens C-terminally of Lys and Arg. Therefore, altering these amino acids by derivatizing the side chain might have a strong effect on the resistance towards physiological digestion.



Our platform gives access to guanidine substituted arginine derived from any amine, that is commercially accessible.

The following guanidine building blocks and arginine homologues are already available as catalogue items:

Fmoc-Agp(Boc)2-OH	Fmoc-Agb(Pbf,Boc)-OH	Fmoc-Phe(4-guanidino-Boc2)-OH	Boc,Pbf-amidino-AEEA
FAA1772	**FAA6161**	**HAA1739**	**FAA6080**



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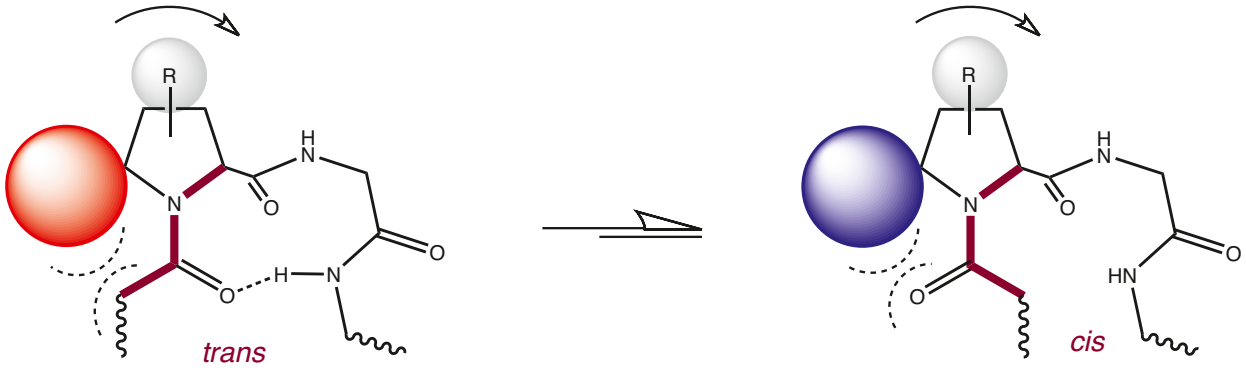
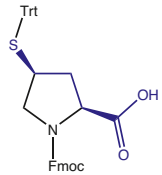
j) Substitutions around the Proline Scaffold

Residues at the pyrrolidine ring of proline induce *cis*- and *trans*-amide bond conformation through steric and/or electronic effects. Additional functional groups rearm proline with properties for three-way-crosslinking or hydrophobic interactions.



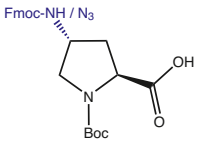
Available as catalogue items besides many more:

Fmoc-Pro(4-STrt)-OH



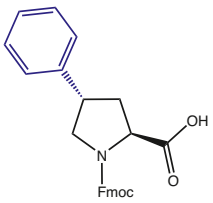
three- functional, homocysteine analogue

Boc-Pro(4-N3)-OH
Boc-Pro-(Fmoc)-OH



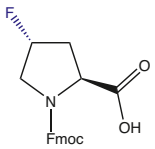
three- functional, cross-linking via amid or click

Fmoc-Pro(4-Ph)-OH



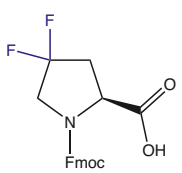
steric & hydrophobic interaction

Fmoc-Pro(4-F)-OH



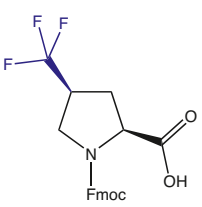
chiral, lipophilic, polar

Fmoc-Pro(4-CF3)-OH



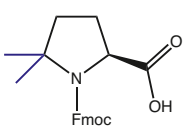
chiral, lipophilic, polar

Fmoc-Pro (4,4-F2)-OH



lipophilic, polar

on demand



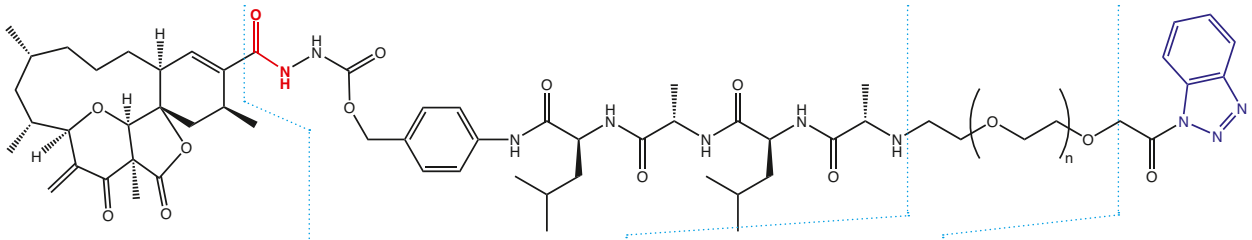
steric interaction inducing *cis*-amid bond formation

k) Customized Linkers

Linker design often becomes a rather complex and specific project, as many parameters define its property.

α-functional group	linking fragment	ω-functional group
amine	shape, lenght	alcohol
Alloc	form (linear, cyclic, branched dendritic)	aldehyde
Boc	homogeneous, mixed blocks, peptidic	azide
Fmoc	nature: hydrophilic, lipophilic, ridged, flexible aliphatic, PEG, poly(amino acids), poly(2-oxazoline), peptides	alkyne
Cbz	reactive side chains or inert	cyclooctyne
carbonyl	stable or cleavable under defined conditions (pH, light, presence of certain enzymes)	tetrazine
carboxyl	homobifunctional	trans-cyclooctene
maleimide	heterobifunctional	norbornene
iodoactetyl	multi functional	biotin
thiol		
lipoic acid		

Example: Enzyme cleavable linker for antibody-drug conjugation



Part 1:

The left side of the molecule carries Okilactomycin, a highly toxic payload (HCT-116 : IC50 = 2 nM), to 4-aminobenzyl group which tracelessly disappears after hydrolysis of the amide bond

Part 2:

The Ala-Leu-Ala-Leu tetramer sequence acts as substrate to catepsin B, which specifically hydrolysis the amide bond to 4- aminobenzyl. Thus this linker specifically degrades in the lysosome, only, and is stable in plasma.

Part 3:

As payload and tetramer is rather hydrophobic the conjugate will suffer from low solubility. In order to equip this compound with sufficient hydrophilicity, PEG or other solubilizing fragments are added.

Part 4:

This conjugate is intended to be attached to nucleophiles, like amino functions of lysines in an antibody. Standard activation with NHS esters will result in low conjugation yields, as NHS ester haydrolysis will be the preferred reaction. Benzotriazol esters are stable at the coupling conditions and will provide high coupling yields.

References:

- N-Fmoc-α-sulfo-β-alanine: a versatile building block for the water solubilisation of chromophores and fluorophores by solid-phase strategy; Romieu A., Bruckdorfer T., Clave G., Grandclaude V., Massif C., and Renard P-Y; *Org. Biomol. Chem.* 2011; **9**: 5337.
- One step synthesis of α-sulfo-β-alanine; Wagner D., Gertner D., Zilkha A.; *Tetrahedron Lett.* 1968; **43**: 4479-4480. DOI: 1016/S0040-4039(01)99165-8
- Postsynthetic Derivatization of Fluorophores with α-Sulfo-β-alanine Dipeptide Linker. Application to the Preparation of Water-Soluble Cyanine and Rhodamine Dyes; Romieu A. *et al.*; *Bioconjugate Chem.* 2008; **19**: 279-289. DOI: 10.1021/bc7003268
- Water solubilization of xanthene dyes by post-synthetic sulfonation in organic media; Romieu A. *et al.*; *Tet.Lett.* 2010; **51**: 3304-3308. DOI: 10.1016/j.tetlet.2010.04.080
- Water-Soluble BODIPY Derivatives; Niu S.L., Ulrich G., Ziessel R., Kiss A., Renard P-Y., Romieu A.; *Org. Lett.* 2009; **11(10)**: 2049-2052. DOI: 10.1021/ol900302n
- A novel heterotrifunctional peptide-based cross-linking reagent for facile access to bioconjugates. Applications to peptide fluorescent labelling and immobilisation; Clave G., *et al.*; *Organic and Biomolecular Chemistry* 2008; **6(17)**: 3065 - 3078. DOI: 10.1039/B807263A
- Negatively Charged, Dye Labeled-Dideoxynucleotides for "Direct-Load" DNA Sequencing, Nampalli S. *et al.*; *Nucleosides, Nucleotides and Nucleic Acids* 2003; **22(5-8)**: 1471 - 1474. DOI: 10.1081/NCN-120023013
- Bioconjugation with Stable Luminescent Lanthanide(III) Chelates Comprising Pyridine Subunits; Hovinen J., Guy P.M.; *Bioconjugate Chem.* 2009; **20(3)**: 404-421; DOI: 10.1021/bc800370s.

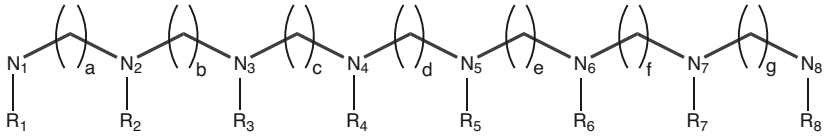
l) Spermines, Spermidines and other Polyamines

Polyamines such as ethylene diamine and its higher homologues are important feedstocks for the chemical industry. Compounds like putrescine, spermidine, and spermine play important roles in both eukaryotic and prokaryotic cells and show many other different biological functions. As cations they bind to DNA, and, in structure, they represent compounds with multiple positive charges with well-defined spaced intervals.

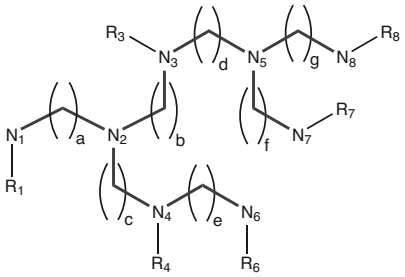
We have technology available to custom manufacture any type of Polyamine with the following parameters:

- ✓ **Polyamines containing any number from 2 to 8 Nitrogens**
- ✓ **Spacers with different numbers of Carbons (a to h)**
- ✓ **Bearing additional residues or protecting groups at any Nitrogen (R1 to R8)**
- ✓ **Linear or branched structures of your choice**
- ✓ **Any cyclic structures**

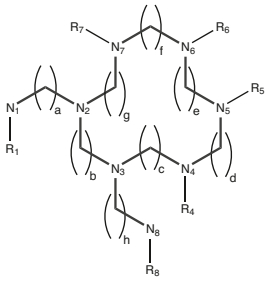
Linear



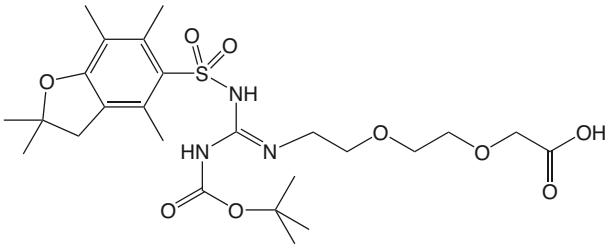
Branched



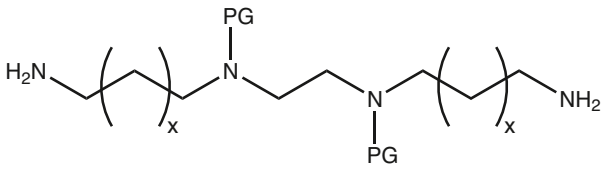
Cyclic

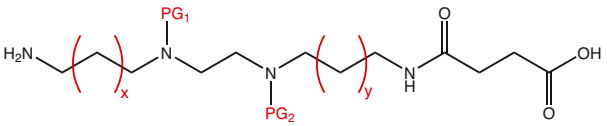


Orthogonal protecting groups, selected different fatty acid residues or other conjugates



Selection of number of nitrogen, adjusting chain length, selection of protecting groups





References:

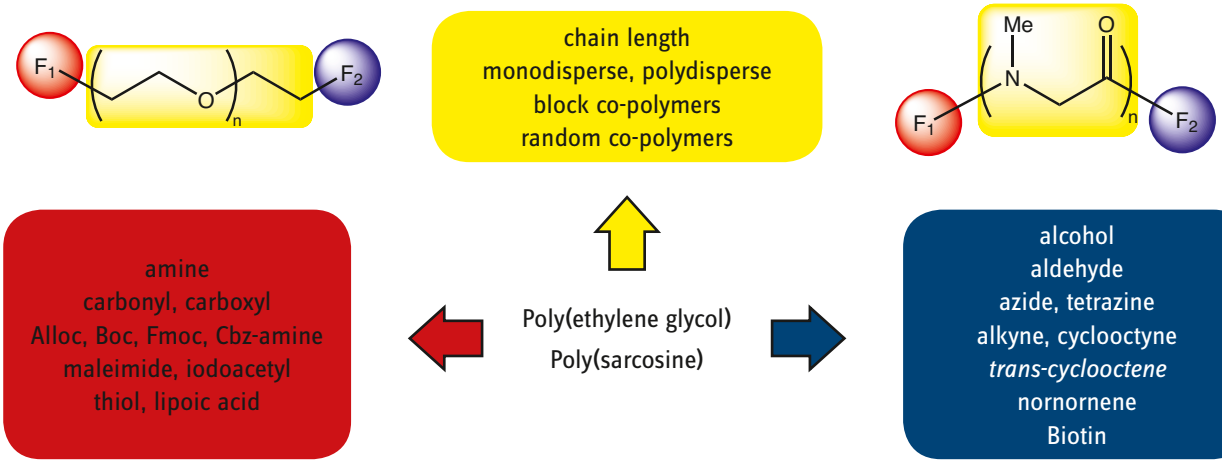
- Uncompetitive Antagonism of AMPA Receptors: Mechanistic Insights from Studies of Polyamine Toxin Derivatives; Trine F. Andersen, Denis B. Tikhonov, Ulrik Bølcho, Konstantin Bolshakov, Jared K. Nelson, Florentina Pluteanu, Ian R. Mellor, Jan Egebjerg, and Kristian Strømgaard; *J. Med. Chem.* 2006; **49**: 5414-5423.
- Deglycobleomycin A6 analogues modified in the methylvalerate moiety; Xiaoqing Cai Paul A. Zaleski, Ali Cagir, Sidney M. Hecht; *Bioorganic & Medicinal Chemistry* 2011; **19**: 3831–3844.

3. The Polymer Program

a) Derivatization of Poly(ethylene glycol) (PEGs) and Poly(sarcosine) (PSR)

Poly(ethylene glycol) (PEGs) and **Polysarcosine (PSR)** are linear bifunctional polymers. Chain length and polydispersity can be varied within a broad range. We have chemical platforms available to attach any possible functional group on each of the two termini. A large variety of homo- and hetero-bifunctional polymers can be supplied.

Among potential alternatives for polymer carriers, polypeptoids in general and polysarcosine (PSR) in particular stand out in terms of safety, synthetic control and versatility. It already has been employed in a number of drug delivery systems, including dendrimers, polymer micelles, polyplexes, protein conjugates, micro- and nanoparticles, polymersomes and nanotubes. A wide range of functional terminal groups can be realized. As PSR is intrinsically heterobifunctional (-COOH, $-NH_2$), the scope of hetero-bifunctional building block design is extensive and easy to realize. Functional polysarcosine offers a great opportunity to create innovation and opportunities in many different fields of applications.



The challenges in polymer chemistry:

For the (custom) synthesis of poly(ethylene glycol)s (PEGs) and other hydrophilic polymers specific know-how is required. The high solubility of such polymers in practically every solvent makes synthesis and particularly purification a challenging task. PEG starting material and PEG product normally display similar solubility. Normal purification technologies like precipitation, crystallization, liquid/liquid extraction or even column chromatography hardly result in good purification results. The second challenge is the absence of good chromophores for UV absorption or fluorescence detection. Product specific analytical methods are required in order to provide accurate and reliable information about impurities, yield and quality in general at each production step.

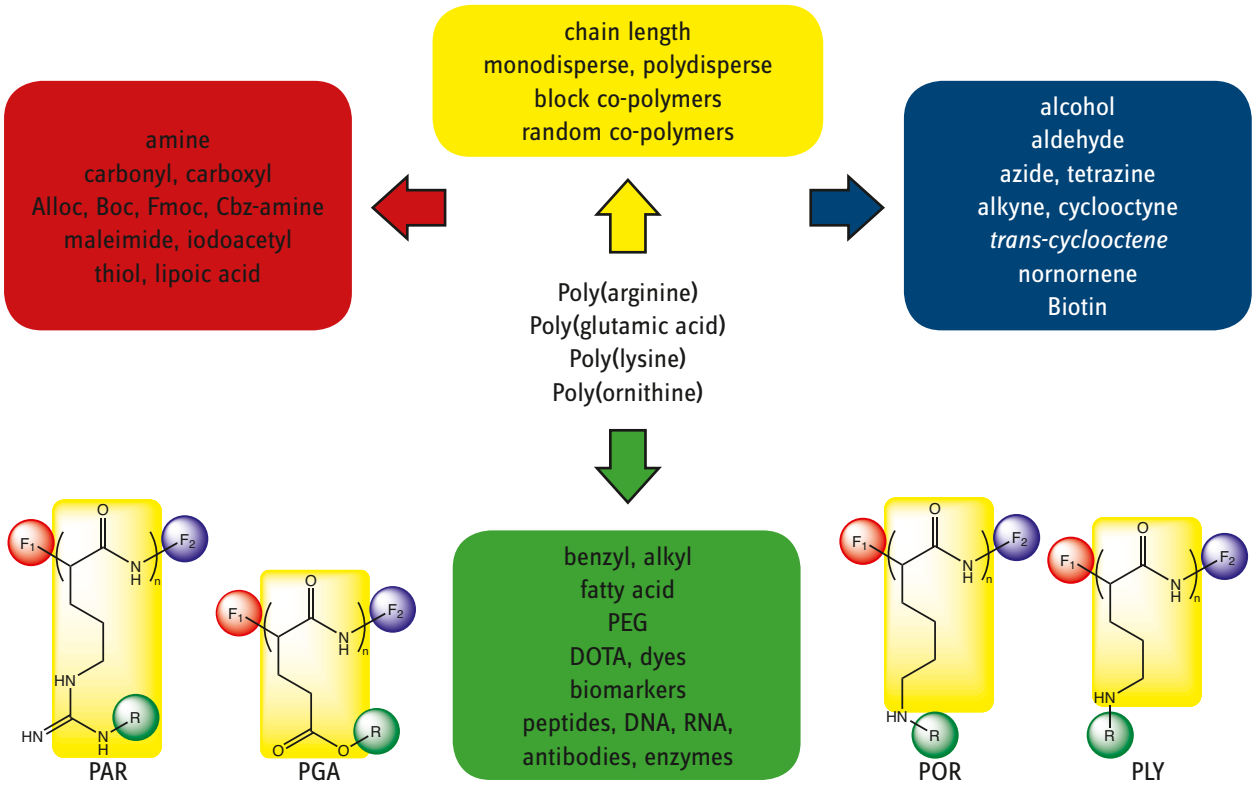
Please provide the following information:

1. Polymer chain length or molecular weight
2. Functionality on head
3. Functionality on tail (pay attention whether it is compatible with the other terminus!)
4. Quantity (grams to kg) and standard custom synthesis or cGMP production

Besides non-GMP custom synthesis, any of our PEG compounds can also be produced in kg quantities according cGMP.

b) Variations of Poly(amino acids) from Arg, Glu, Lys, Orn,

Poly(amino acids) e.g. from **Arg**, **Glu**, **Orn** and **Lys** show the same pallet of diversity as PEGs and PSR enriched by the capability to functionalize the side chain. They gain increasing interest in polymer therapeutics and become a superior alternative as their biodegradability overcomes the limitation of PEG in this aspect. Their inherent side chain functionally expands the field of polymer therapeutics to small molecules and enables in a smart way combination therapy.



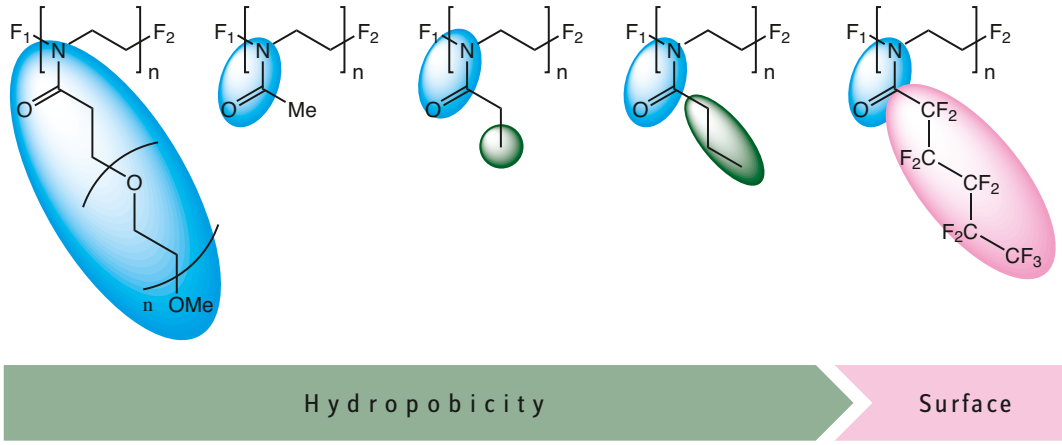
Please provide the following information:

1. Nature of polymer, chain length or molecular weight
2. Random or block-copolymer, functionality of side residues
3. Functionality on head
4. Functionality on tail (pay attention whether it is compatible with the other terminus!)
5. Quantity (grams to kg) and standard custom synthesis or GMP production

Please contact us to define the polymer of your choice.

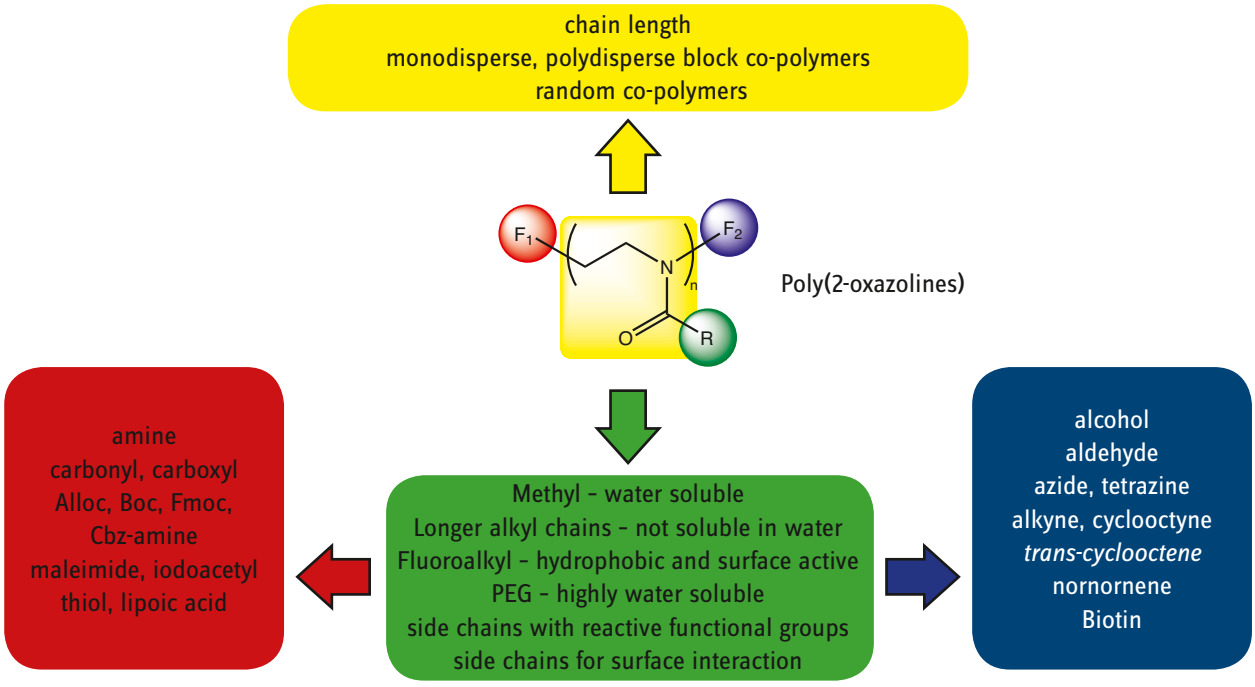
c) Poly(2-oxazolines) (POx) – 2nd generation polymer carriers

A quantum leap in polymer therapeutics came with development of **Poly(2-oxazolines) (POx)**. POx is intrinsically heterobifunctional (-COOH, -NH2), therefore, the scope of the heterofunctional building-block design is extensive and easy to realise. Additionally they offer the possibility to vary the polymer property within a wide range. Through sophisticated choice of side chain residues polymer properties can be fine-tuned to display specific properties of hydrophilicity & hydrophobicity. The carrier molecule can specifically be equipped with properties like thermoresponsivity, low or high viscosity, glass transition temperature, stealth behavior.



Biocompatible, Nontoxic, Antimicrobial, Antifungal, Antifouling!

Very broad variation of Size, Architecture, and Chemical Functionality!



Please provide the following information:

1. Chain length or molecular weight
2. Random or block-copolymer, functionality of side residues
3. Desired physical property (hydro- or lipophilicity, surface activity etc.)
4. Functionality on head
5. Functionality on tail (pay attention, whether it is compatible with the other terminus!)
6. Quantity (grams to kg) and standard custom synthesis or GMP production

4. Development Projects

It can happen that route of synthesis, yield and purity for a specific molecule is uncertain to predict precisely.

However, we have ideas, how to reach the target and need to carry out several trial experiments and research, followed by developing the trials to a robust process, in order to find a suitable route of production.

Typical tasks are:

1. Lab-scale *de-novo* route development as basis for a later competitive, sustainable manufacturing.
2. Optimization or re-designing of an existing synthetic route, in order to increase the efficiency of your processes with a selection of efficient technologies.
3. Finding a patent free approach to your molecule.

More complex questions be worked out on Contract R&D basis. This encompasses developments, which can typically be described as:

Finding the right molecule or polymer for a specific application e.g. in bioconjugation, analytics or material science;

this work typically leads to the development of a sustainable and scalable route of synthesis; and can include production of your compound from lab scale to bulk.

Payment is based on Fee-for-Service on Full Time Equivalent (FTE) and for milestones.

Let us support you and prepare your compound or realize your project in our laboratory according to your requirements.

5. Contract Manufacturing of Lab Samples according to your own Process

Do you have an urgent need of your own compound in gram or kg scale, but currently no lab space or manpower available?

We will implement your process in a professional environment.

As a matter of course, everything concerning your process will be treated as strictly confidential.

Following completion of the project, you will receive a comprehensive documentation from our skilled team of scientists, so you can easily follow and reproduce every step.

6. 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 respect the rights of the employees to associate freely, join or not join labour unions, seek representation and join workers' councils. Employees are paid and their working timetable is established according to applicable wage and labour laws. Employees are able to communicate openly with management regarding working conditions without threat of reprisal, intimidation or harassment.

General Policies

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

Health and Safety

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

Environment

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

Production and Quality Management

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

Research and Development

Research and development staff education is appropriate to their functional activity and they are trained to develop, optimize and scale-up the processes. Intellectual property is respected and know-how protected. Development of manufacturing processes reflects the principles of the Green Chemistry according 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.

7. Terms and Conditions of Sales

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

Placing of Orders

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

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

Prices, Quotations and Payments

Prices are subject to change. For the avoidance of doubt, the price advised by Iris Biotech GmbH at the time of the buyer placing the order shall supersede any previous price indications. The buyer must contact the local office of Iris Biotech GmbH before ordering if further information is required. Unless otherwise agreed by the buyer and Iris Biotech GmbH, the price shall be for delivery ex-works. In the event that the buyer requires delivery of the products otherwise than ex-works the buyer should contact the local office of Iris Biotech GmbH in order to detail its requirements. Iris Biotech GmbH shall, at its discretion, arrange the buyer‘s delivery requirements including, without limitation, transit insurance, the mode of transit (Iris Biotech GmbH reserves the right to vary the mode of transit if any regulations or other relevant considerations so require) and any special packaging requirements (including cylinders). For the avoidance of doubt all costs of delivery and packaging in accordance with the buyer‘s requests over and above that of delivery in standard packaging ex-works shall be for the buyer‘s account unless otherwise agreed by both parties. Incoterms 2010 shall apply. Any tax, duty or charge imposed by governmental authority or otherwise and any other applicable taxes, duties or charges shall be for the buyer‘s account. Iris Biotech GmbH may, on request and where possible, provide quotations for multiple packs or bulk quantities, and non-listed items. Irrespective of the type of request or means of response all quotations must be accepted by the buyer without condition and in writing before an order will be accepted by Iris Biotech GmbH. Unless agreed in writing on different terms, quotations are valid for 30 days from the date thereof. Payment terms are net 30 days from invoice date unless otherwise agreed in writing. Iris Biotech GmbH reserves the right to request advance payment at its discretion. For overseas transactions the buyer shall pay all the banking charges of Iris Biotech GmbH. The buyer shall not be entitled to withhold or set-off payment for the products for any reason whatsoever. Government/Corporate Visa and MasterCard (and other such credit cards) may be accepted on approved accounts for payment of the products. Personal credit cards are not acceptable. Failure to comply with the terms of payment of Iris Biotech GmbH shall constitute default without reminder. In these circumstances Iris Biotech GmbH may (without prejudice to any other of its rights under these terms) charge interest to accrue on a daily basis at the rate of 2% per month from the date upon which payment falls due to the actual date of payment (such interest shall be paid monthly). If the buyer shall fail to fulfil the payment terms in respect of any invoice of Iris Biotech GmbH Iris Biotech GmbH may demand payment of all outstanding balances from the buyer whether due or not and/or cancel all outstanding orders and/or decline to make further deliveries or provision of services except upon receipt of cash or satisfactory securities. Until payment by the buyer in full of the price and any other monies due to Iris Biotech GmbH in respect of all other products or services supplied or agreed to be supplied by Iris Biotech GmbH to the buyer (including but without limitation any costs of delivery) the property in the products shall remain vested in Iris Biotech GmbH.

Shipping, Packaging and Returns

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

Product Quality, Specifications and Technical Information

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

Safety

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

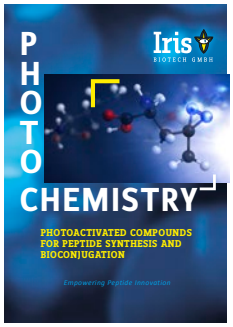
Uses, Warranties and Liabilities

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

General

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

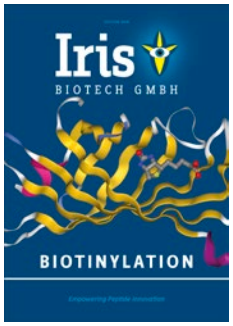
Publications from Iris Biotech:



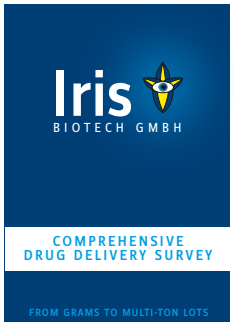
Photochemical transformations are usually orthogonal to classical chemical transformations, a characteristic that renders them a valuable tool for chemists. This booklet describes our whole range of innovative **photoactivated compounds**, as well as their applications.

Our comprehensive **Guideline on Resins** for solid-supported peptide synthesis. Complete with protocols for resin loading and linker cleavage, standard protocols for peptide chemistry, as well as a current product list of our solid supports. It also includes latest resin developments, e.g. SEA and Hydrazon resins, very useful tools for the synthesis of long peptides via native chemical ligation (NCL).

Brochure for **Click Chemistry** containing over 300 different Azido and Alkyne Compounds for drug discovery, drug delivery and diagnostics.



The affinity and specificity of the avidin-biotin interaction have been exploited for numerous applications in immunology, histochemistry and affinity chromatography, to name only a few. This brochure provides a comprehensive overview of all **compounds for biotinylation** in our portfolio.



Our **Comprehensive Drug Delivery Survey** contains the latest state-of-the-art collection of carriers for Polymer Therapeutics available today. More than 900 productsfrom the areas PEGylation, poly (amino acids) and PEG-based multifunctional Dendrimers give the medicinal chemist all options to find the right delivery technology from small drug molecules up to large biopharmaceuticals.

Find in our brochure **Diagnostic Tools** plenty of substrates for reporter enzymes and drug interaction studies, metabolites, glucuronides and inhibitors, inducers, antibody conjugates and cross-linkers, natural products with biological and pharmacological activity, carbohydrates, dyes and fluorescent labels as Tools in Immunology, Diagnostic, Biochemistry and Molecular Biology.

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IRIS BIOTECH GMBH
ADALBERT-ZOELLNER-STR. 1
D-95615 MARKTREDWITZ, GERMANY
PHONE +49 92 31 97121 - 0
FAX +49 92 31 97121 - 99
INFO@IRIS-BIOTECH.DE
WWW.IRIS-BIOTECH.DE