Iris Biotech

Empowering Peptide Innovation

NEW

Peptide Modifier – **Fatty Amino Acids**

Fatty Amino Acids have raised interest recently, as they improve the pharmacokinetic & pharmacologic properties of peptide APIs and other biopharmaceuticals. The most prominent block busters are Liraglutide and Semaglutide. Their lifetime in serum is drastically improved as the fatty acid residue helps to bind temporarily to serum albumin. This conjugation enhances stability towards proteolytic degradation and serves as drug delivery technique.

GLP – 1 (7-37) amide

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly-NH_2

Liraglutide (Victoza®) **$4.4 billion (2018)**

[γ-L-Glutamoyl(N-α-hexadecanoyl)-Lys26, Arg34-GLP-1(7–37)]

H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(γ-Glu-palmitoyl)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH

Semaglutide (Rybelsus®, Ozempic®) **$267 million (2018)**

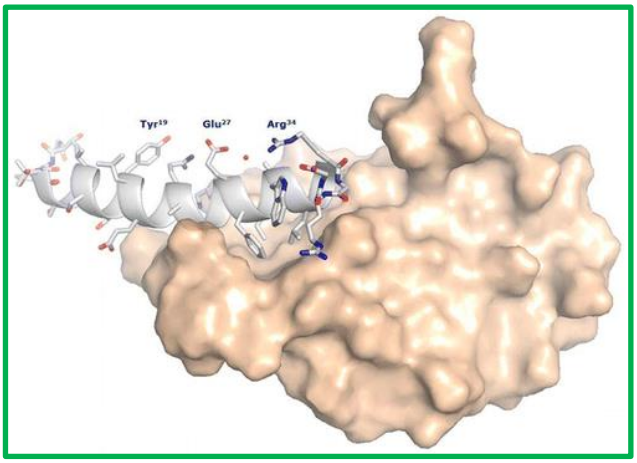
$N^{6.26}$-{18-[N-(17-carboxyheptadecanoyl)-L-γ-glutamyl]-10-oxo-3,6,12,15-tetraoxa-9,18- diazaoctadecanoyl}-[8-(2-amino-2-propanoic acid),34-L-arginine]-GLP-1(7–37)]

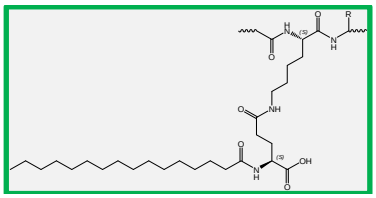
H-His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(C_{18}-diacid-γ-Glu-OEG-OEG)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH

Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide.

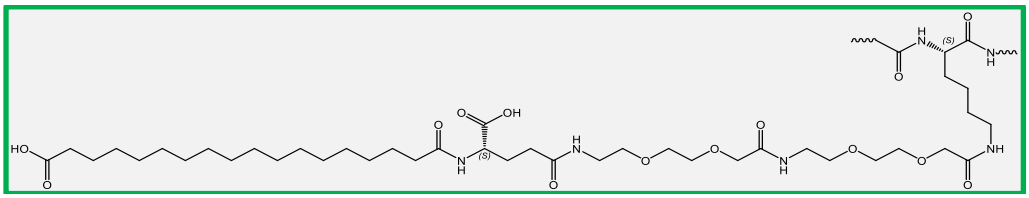
Jesper Lau, Paw Bloch, Lauge Schäffer, Ingrid Pettersson, Jane Spetzler, Jacob Kofoed, Kjeld Madsen, Lotte Bjerre Knudsen, James McGuire, Dorte Bjerre Steensgaard, Holger Martin Strauss, Dorte X. Gram, Sanne Møller Knudsen, Flemming Seier Nielsen, Peter Thygesen, Steffen Reedtz-Runge, Thomas Kruse; *J. Med. Chem.* 2015; **58(18):** 7370-7380. DOI: 10.1021/acs.jmedchem.5b00726

ABSTRACT: Liraglutide is an acylated glucagon-like peptide-1 (GLP-1) analogue that binds to serum albumin *in vivo* and is approved for once-daily treatment of diabetes as well as obesity. The aim of the present studies was to design a once weekly GLP-1 analogue by increasing albumin affinity and secure full stability against metabolic degradation. The fatty acid moiety and the linking chemistry to GLP-1 were the key features to secure high albumin affinity and GLP-1 receptor (GLP-1R) potency and in obtaining a prolonged exposure and action of the GLP-1 analogue. Semaglutide was selected as the optimal once weekly candidate. Semaglutide has two amino acid substitutions compared to human GLP-1 (Aib8, Arg34) and is derivatized at lysine 26. The GLP-1R affinity of semaglutide (0.38 ± 0.06 nM) was three-fold decreased compared to liraglutide, whereas the albumin affinity was increased. The plasma half-life was 46.1 h in mini-pigs following i.v. administration, and semaglutide has an MRT of 63.6 h after s.c. dosing to mini-pigs. Semaglutide is currently in phase 3 clinical testing.





Fmoc-Lys(Palm-Glu-OtBu)-OH
FAA3790



Fmoc-Lys(Ggu-Glu(AA-AA))-OH
FAA7640

Building Blocks for Manufacturing Liraglutide and Semaglutide

Available in Large Scale & Including Documentation for GMP Manufacturing of the Peptide APIs

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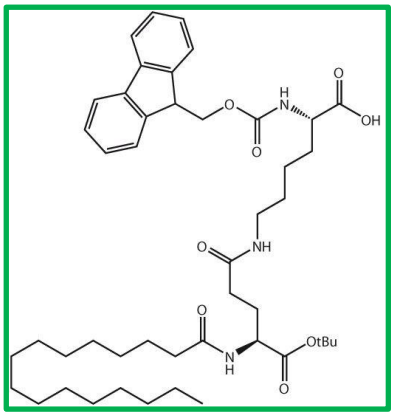
Peptide Half-Life Extension: Divalent, Small-Molecule Albumin Interactions Direct the Systemic Properties of Glucagon-Like Peptide 1 (GLP-1) Analogues.

Esben M. Bech, Manuel C. Martos-Maldonado, Pernille Wismann, Kasper K. Sørensen, Søren Blok van Witteloostuijn, Mikkel B. Thygesen, Niels Vrang, Jacob Jelsing, Søren L. Pedersen, and Knud J. Jensen;
J. Med. Chem., 2017; **60(17):** 7434–7446.
DOI: 10.1021/acs.jmedchem.7b00787.

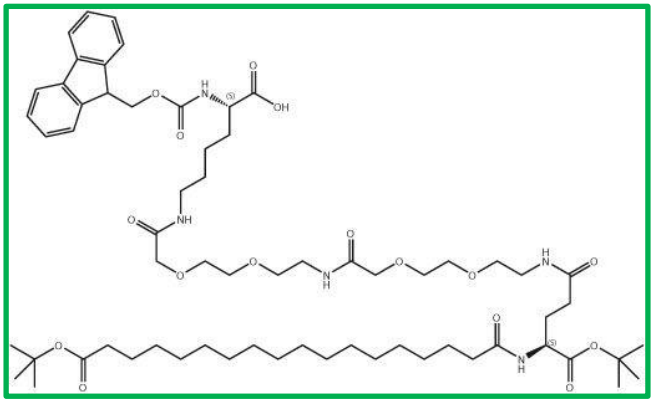
ABSTRACT: Noncovalent binding of biopharmaceuticals to human serum albumin protects against enzymatic degradation and renal clearance. Herein, we investigated the effect of mono- or divalent small-molecule albumin binders for half-life extension of peptides. For proof-of-principle, the clinically relevant glucagon-like peptide 1 (GLP-1) was functionalized with diflunisal, indomethacin, or both. *In vitro*, all GLP-1 analogues had subnanomolar GLP-1 receptor potency. Surface plasmon resonance revealed that both small molecules were able to confer albumin affinity to GLP-1 and indicated that affinity is increased for divalent analogues. In lean mice, the divalent GLP-1 analogues were superior to monovalent analogues with respect to control of glucose homeostasis and suppression of food intake. Importantly, divalent GLP-1 analogues showed efficacy comparable to liraglutide, an antidiabetic GLP-1 analogue that carries a long-chain fatty acid. Finally, pharmacokinetic investigations of a divalent GLP-1 analogue demonstrated a promising gain in circulatory half-life and absorption time compared to its monovalent equivalent.

# C	Trival Name	IUPAC Name	Formula
1	Formic acid	Methanoic acid	HCOOH
2	Acetic acid	Ethanoic acid	CH_3COOH
3	Propionic acid	Propanoic acid	CH_3CH_2COOH
4	Butyric acid	Butanoic acid	$CH_3(CH_2)_2COOH$
5	Valeric acid	Pentanoic acid	$CH_3(CH_2)_3COOH$
6	Caproic acid	Hexanoic acid	$CH_3(CH_2)_4COOH$
7	Enanthoic acid	Heptanoic acid	$CH_3(CH_2)_5COOH$
8	Caprylic acid	Octanoic acid	$CH_3(CH_2)_6COOH$
9	Pelargonic acid	Nonanoic acid	$CH_3(CH_2)_7COOH$
10	Capric acid	Decanoic acid	$CH_3(CH_2)_8COOH$
12	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$
14	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$
16	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$
18	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$
20	Arachidic acid	Eicosanoic acid	$CH_3(CH_2)_{18}COOH$
22	Behenic acid	Docosanoic acid	$CH_3(CH_2)_{20}COOH$
24	Lignoceric acid	Tetracosanic acid	$CH_3(CH_2)_{22}COOH$
26	Cerotic acid	Hexacosanoic acid	$CH_3(CH_2)_{24}COOH$
28	Montanic acid	Octacosanoic acid	$CH_3(CH_2)_{26}COOH$
30	Melissic acid	Triacontanoic acid	$CH_3(CH_2)_{28}COOH$
32	Lacceroic acid	Dotriacontanoic acid	$CH_3(CH_2)_{30}COOH$
33	Psyllic acid	Tritriacontanoic acid	$CH_3(CH_2)_{31}COOH$
34	Geddic acid	Tetratriacontanoic acid	$CH_3(CH_2)_{32}COOH$
35	Ceroplastic acid	Pentatriacontanoic acid	$CH_3(CH_2)_{33}COOH$



Available Fatty Acid containing Building Blocks for the Production of **Liraglutide**:

PAA1010	Palm-L-Glu(OSu)-OMe	
PAA1000	Palm-L-Glu(OSu)-OtBu	
PAA1005	Palm-D-Glu(OSu)-OtBu	
PAA1160	Palm-L-Glu-OtBu	
FAA3790	Fmoc-L-Lys(Palm-L-Glu-OtBu)-OH	*main building block*
FAA7760	Fmoc-L-Lys(Palm-D-Glu-OtBu)-OH	*impurity*
FAA7480	Fmoc-D-Lys(Palm-L-Glu-OtBu)-OH	*impurity*
FAA7750	Fmoc-D-Lys(Palm-D-Glu-OtBu)-OH	*impurity*



Available Building Blocks for the Production of **Semaglutide**:

FAA7640	Fmoc-L-Lys(Ggu-L-Glu(AA-AA))-OH
PEG8080	Boc-AEEA
BAA1466	Boc-AEEA*DCHA
BAA1485	Boc-AEEA-AEEA
FAA1435	Fmoc-AEEA
FAA1787	Fmoc-AEEA-AEEA

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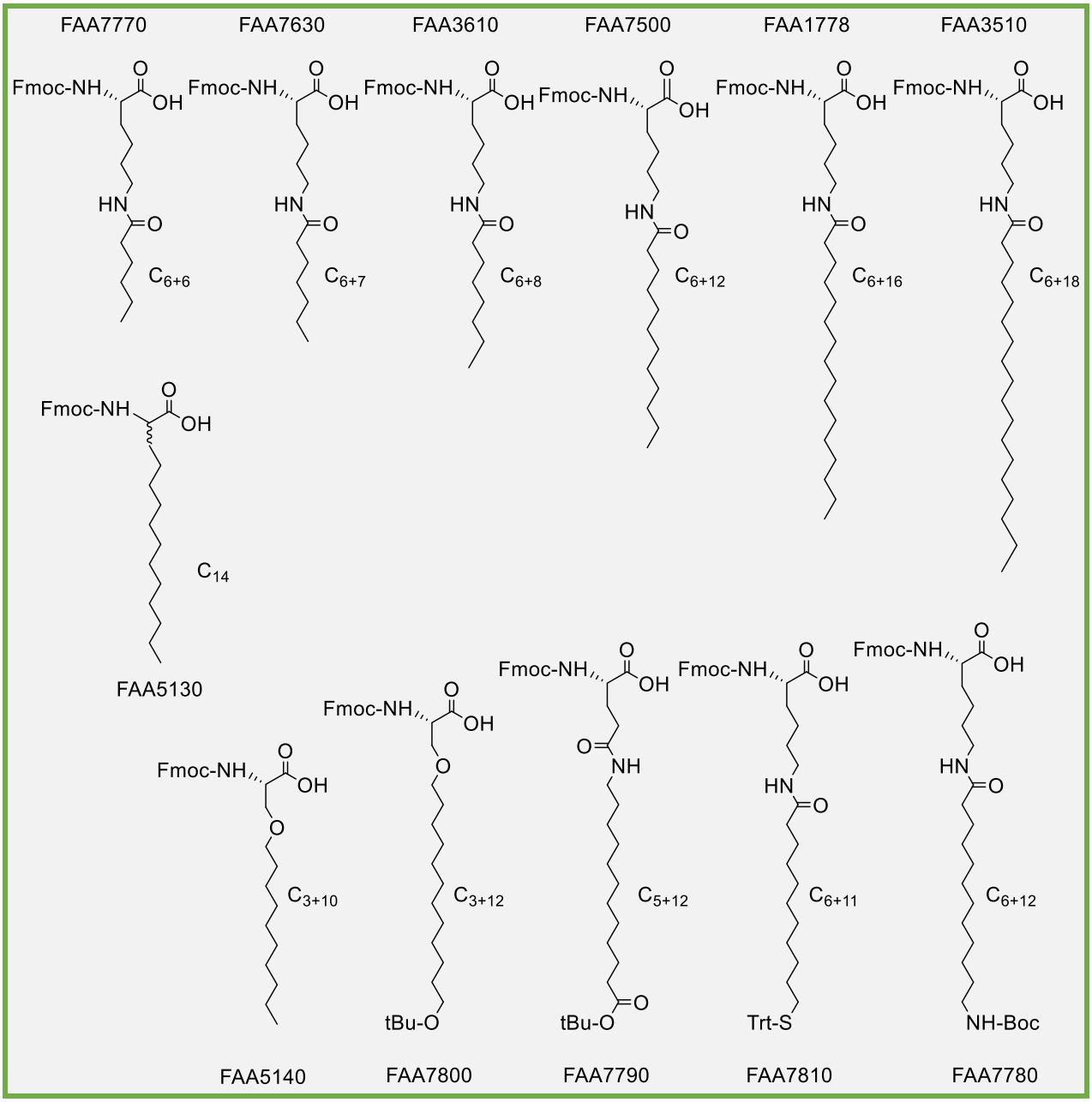
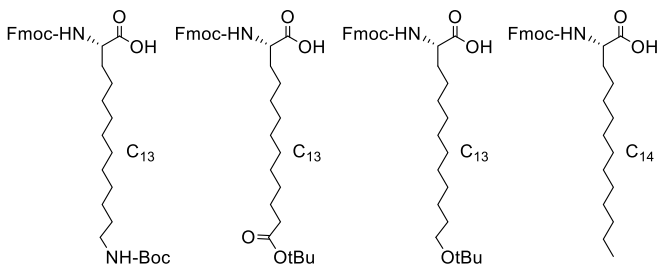
Available Fatty Amino Acids Analogues including Terminal Functionality



- ✓ Conjugates with Asn, Cys, Dap, Dab, Gln, Lys, Ser, give easy access to isostructural analogues.
- ✓ A variety of terminal functional groups can nicely be designed.
- ✓ Production route is a scalable process, up-scaling is easily possible.
- ✓ Longer homologues of norleucine & longer fatty amino acid homologues with different terminal functional groups are in development and can be supplied on custom synthesis basis.



under development

Prices are in EUR, net, EXW Germany

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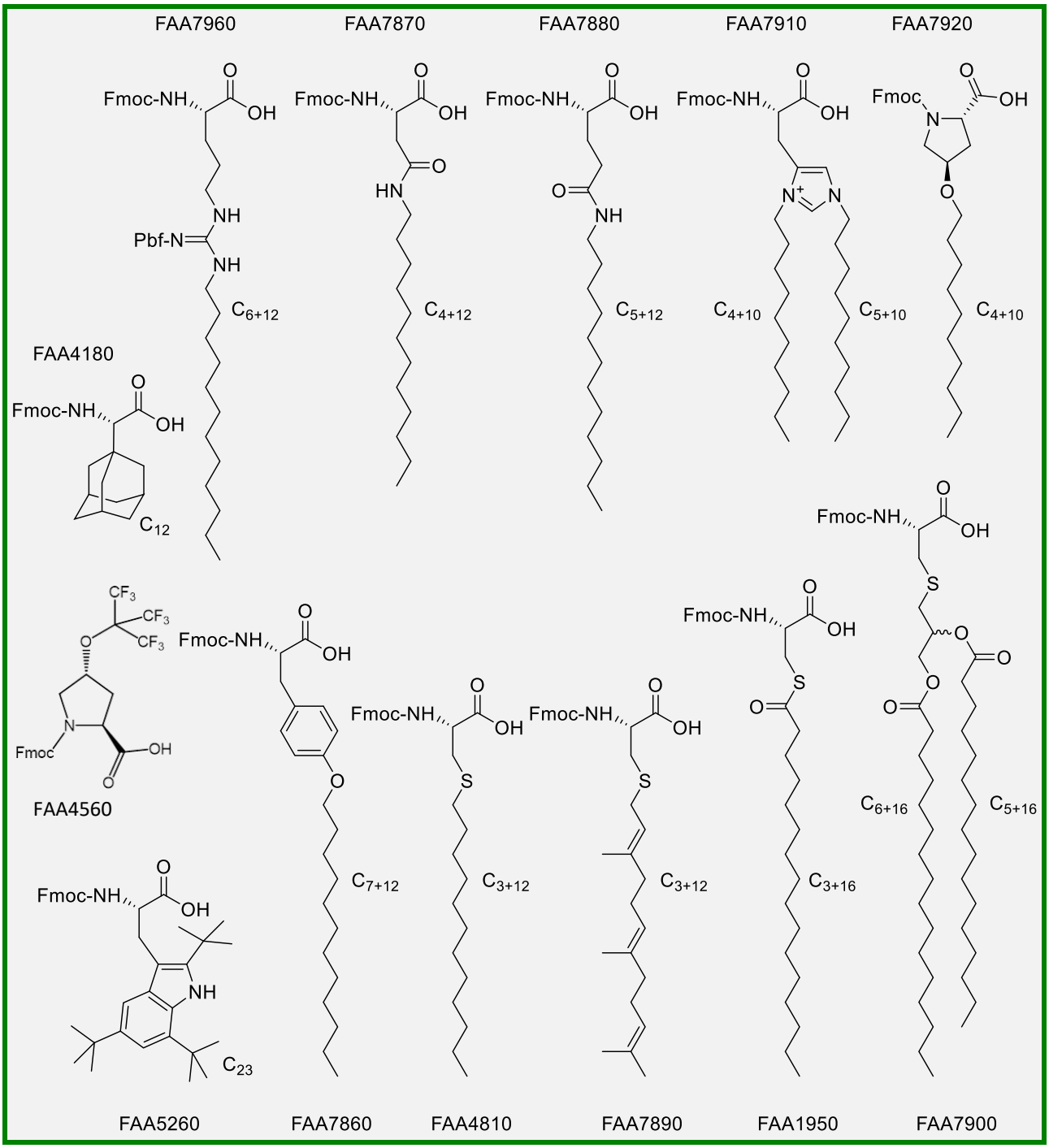
Available Amino Acids Derivatives carrying Long Aliphatic and other Hydrophobic Residues



- ✓ Conjugates with Arg, Asn, Cys, Gln, His, Hyp, Ser, Tyr give easy access to new analogues.
- ✓ Two fatty acid residues can be attached on the same amino acid in some cases.
- ✓ Published applications: antimicrobial peptides, adjuvants, cancer vaccines, novel receptor agonist, cancer imaging, and peptide amphiphiles (PAs) with unusual thermal stability.
- ✓ Production route is a scalable process, up-scaling is easily possible.

➔ Contact us for Custom Synthesis of the Fatty Amino Acid of Your Choice!